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CONTENTS

INTRODUCTION

For many years the structural elucidation and synthesis of terpenoids have been a challenge to the organic chemist but only recently has the biological significance of this class of compounds become apparent. Of the many types of terpenoids now known one of the most interesting is the diterpenoid group. Not only has this class been used as a testing ground for the Biogenetic Isoprene Rule but because of the obvious importance of the gibberellins in the promotion of plant growth much research has been directed towards elucidating the biosynthesis and biclogical interconversions of the diterpenoids.

At present there are approximately 300 diterpenes known, the majority of which have been isolated from plant and fungal extracts, although they are occasionally found in animal tissue.

Diterpenoid Biogenesis

Diterpenoids[1,2,3,4], can be regarded as formed from geranylgeranyl (1) or geranyllinalyl (2) pyrophosphates in accordance with the principles of the Biogenetic Isoprene Rule (Scheme I). The majority of diterpenoids have the labdane skeleton (3) in which rings A and B have been formed, however, subsequent cyclisation to tri- and tetracyclic diterpenoids can follow. Structural variations arise from Wagner-Meerwein rearrangements, ring cleavage and ring contraction and/or expansion.

The various basic skeletal types of diterpenoids derive from the cyclisation of a geranylgeraniol (or equivalent) precursor as follows (see Scheme I).

Monocyclic: Vitamin A (4)[5] while a diterpenoid, is not normally derived from geranylgeraniol directly. The animals in which it is found ingest C_{40} carotenoids from higher plants and cleavage of these produce two molecules of Vit. A.

Bicyclic: Next is the unrearranged bicyclic labdane group, a representative member being manool (5), which

presumably results from electrophilic attack of a proton on the C-3, C-4 double bond, attack of the $\Delta^{5,10}$ double bond on the C-4 cation, capture of the electrons of the $\Delta^{8,9}$ double bond by the resulting cation at C-10 and finally loss of a proton from the C-17 methyl group. The stereochemistry (trans) of the decalin system would be predicted if the process is synchronous and involves cyclisations by antiparallel additions. A wide range of oxygenation is found within this group, the terminal side chain carbon atom being frequently oxidised to carboxyl as in labdanolic acid (6). There are approximately 70 members of this group while in the rearranged labdane class there are only 15. The members of this group arise from Wagner-Meerwein rearrangement of the primary labdane to give structures of the type found in clerodin (7) and cascarillin (8) although columbin (9) and its congeners, also members of this group, surprisingly have the A/B cis-fusion. Biosynthetic studies show that pleuromutilin (10) is probably also formed via a precursor with a labdane skeleton.

Tricyclic: Cyclisation of the equivalent of manool (5) or its allylic isomer gives rise to the next group, the

tricyclic diterpenoids which fall into 4 sub-groups, the pimaranes, the rearranged pimaranes, the cassanes and the abietanes. Direct cyclisation of manool produces, via a carbonium ion of the type (11), pimaradiene (12) from which pimaric (13) and isopimaric (14;R=CO_2H) acids are derived. Alternatively the intermediate cation (11) can undergo a series of 1,2 hydride and methyl migrations leading to the carbonium ions (15) and (16). Loss of a proton from C-6 in the former gives rimuene (17) and from C-18 in the latter, dolabradiene (18). One further structural variation in this class involves yet another rearrangement sequence from the hydroxylic cation (19) and affords cassene (20) and its congeners. The final group of tricyclic diterpenoids is formed by rearrangement of pimaradiene (12) to abietadiene (21) from which are derived abietic acid (22) and its congeners, several of which possess a phenolic ring C, for example totarol (23).

Tetracyclic: The tetracyclic diterpenoids[6] have such closely related skeletal structures that their genesis from a common biosynthetic pathway seems very probable. In 1955, Wenkert suggested[7] that the tetracyclic diterpenoids might all derive from tricyclic precursors

of the pimaradiene (12) and isopimaradiene (14;R=CH_3) type by protonation and formation of a carbonium ion at C-8, followed by capture of the electrons of the vinyl group. Loss of a proton would then give directly hibaene (24) from pimaradiene and isohibaene (25) from the C-13 epimeric precursor. Alternatively, rearrangement of the initially produced secondary carbonium ions (26) and (27) could lead to the other known tetracyclic diterpenes (and indeed the pentacyclic hydrocarbon trachylobane (28)). The intermediates in these further transformations (Schemes II and III) can be conveniently summarised by the hydrogen bridged structures (29) and (30) which are in effect face-protonated cyclopropyl cations, and would on opening give rise to the various tetracyclic diterpenes, kaurene (31), isokaurene (32), atisirene (33) and isoatisirene (34) from (29) and phyllocladene (35), isophyllocladene (36), neoatisirene (37) and isoneoatisirene (38) from (30) (or by proton loss trachylobane (28) from (29) and isotrachylobane (39) from (30)).

Certain of these diterpenoids have been found in both enantiomeric forms e.g. both (+)- and (-)-kaurene have

been isolated, although almost all natural derivatives of kaurene are related to (-)-kaurene. Phyllocladene (35) has also been detected in both (+) and (-) forms, but it, together with isophyllocladene (36) and phyllocladanol (40) are the sole representatives of the compounds originating from the cyclisation of isopimaradiene. The other diterpenes which appear to be derived from this type of precursor have not so far been isolated from a natural source although they have been synthesised in anticipation of their discovery in nature.

From the above it can be seen that the tetracyclic diterpenoids fall into three main groups, the largest of which can be further sub-divided into the phyllocladane-kaurane and the rearranged kaurane (gibberellane) classes. Typical examples of each class are 7-hydroxykaurenolide (41) and gibberellic acid (42) with the alkaloid garryfoline (43) a notable member of a group of diterpenoid alkaloids derived from kaurene. The gibberellins are derived from a kaurane precursor by extensive modification. Important among these are contraction of ring B to form a cyclopentane carboxylic acid, oxidation at C-19, loss of the C-10 methyl and lactonization, and oxidative

modification of ring A and the C/D bridgehead position. This suggested biogenesis has been supported by labelling experiments[8] with (1-^{14}C) acetate using the fungus Gibberella fujikuroi. There are approximately 30 compounds in each of these sub-groups, the gibberellins deriving their numbers from the wide range of oxidative modifications. They are now the most widely studied tetracyclic diterpenoids, the interest arising because of their growth controlling function in the higher plants.

The second group contains 12 compounds having the hibane skeleton. Oxygenation at C-17, C-18 and occasionally at C-3 is found in this group, e.g. beyerol (44).

The last of the three groups is the smallest (atisane), having only two non-nitrogenous members, atisirene (33) and isoatisirene (34). Atisirene can be looked on as the parent of another group of diterpene alkaloids, of which atisine (45) is an example. Rearrangement of atisine can, in principle give rise to the third group of diterpene alkaloids, lycoctonine (46) being one of them.

Pentacyclic: Ourisson and his co-workers have isolated[9] several diterpenoids based on the trachylobane skeleton including the pentacyclic hydrocarbon trachylobane (28)

itself, which as mentioned above can be readily incorporated into Wenkert's scheme as can isotracylobane (39) in the isopimaradiene derived series. Indeed, the intermediate hydrogen bridged structures (29) and (30) are in effect protonated trachylobane and isotrachylobane respectively. The latter has not so far been isolated from a natural source but it has been synthesised.

Apart from the majority of diterpenoids which fall so readily into the above biogenetic scheme there exists a small group of diterpenoids arising from cyclisation of geranygeraniol to produce fourteen-membered ring compounds (see below). There are 15 known compounds of this type, among them cembrene (47) the parent hydrocarbon, from which its oxygenated relatives may be derived. A recent example[10] is euphorbiasteroid (48).

In Vivo and Enzymatic Synthesis of Diterpenoids

The aim of the *in vivo* experiment in this field is to study the fate of a precursor (often acetate or mevalonate) through the various steps in its conversion into a gibberellin or other diterpenoid. By this technique it is hoped that eventually a full knowledge of the precursors, intermediates and reactions involved may be attained.

The chief difficulty in this type of investigation is the extremely poor incorporation of labelled acetate or mevalonate into terpenoids by higher plants.[11] Among the reasons for this are (a) the large turnover of diterpenoid in the plant (b) the high level of acetate incorporation into carbohydrate and protein, and (c) the extensive compartmentalization of the enzymes and cofactors required for isoprenoid biosynthesis in green plants, which means that the acetate or mevalonate may not reach the biosynthetic site. However, a few successful studies[12] have been made although the literature still contains conflicting results in several cases.

In order to resolve this problem workers have turned

to cell-free homogenates and several cases of diterpenoid synthesis from labelled mevalonate have now been reported.[13,14,15] Graebe et al. reported[13] the conversion of this precursor into (-)-kaurene (31), (-)-kauren-19-ol (49) and trans-geranylgeraniol (1) in cell-free homogenates of the endosperm nucleus of the seed of Echinocystis macrocarpa Greene. They also found that radioactive kaurene was transformed into gibberellic acid with appreciable ^{14}C incorporation when incubated with F. moniliforme. Another factor indicating the role of (-)-kaurene as a gibberellin precursor is its growth promoting effect on "dwarf-5" and "anther-1" mutants of Zea mays L., identical to that produced by exogenous gibberellins. Kaurenol (49) also displays this activity whereas trans-geranylgeraniol does not, suggesting that the latter is at least not a free intermediate in gibberellin biosynthesis.

More recently Hanson[15] found very low (0.02%) incorporation of specifically labelled pimaradiene (12) into gibberellic acid but Cross reported[16] no incorporation in analogous experiments. The latest results in this field by West[17,18] do not conflict with Hanson's

contention that free (-)-pimara-8(14)-diene may act as an intermediate in kaurene biosynthesis. However, in view of the contradictory results and lack of compelling evidence to substantiate his proposal the intermediacy of pimaradiene in the pathway must remain in doubt. Geranylgeranyl pyrophosphate on the other hand has been successfully metabolised in cell-free extracts from seedlings of Ricinus communis L.[17] into a mixture of five cyclic diterpenes. The products were identified as (+)-hibaene (24), (+)-sandracopimaradiene (50), (-)-kaurene (31), trachylobane (28) and casbene (51), a close relative of the naturally occuring hydrocarbon cembrene (47) (see above). The mechanistic scheme suggested by Wenkert[7] (Schemes II and III) accounts for the biosynthesis of the first four from geranylgeranyl pyrophosphate and the production of the fifth is easily understood by reference to Scheme IV. A different folding of the substrate followed by heterolysis of the pyrophosphate and participation of the double bond distal to the leaving group produces a C-14 carbocyclic ring and an isopropyl cation which can cyclise to the cembrene related product as shown. This work of West supports Ruzicka's contention[19] that

geranylgeraniol or one of its derivatives should be a general precursor of cyclic diterpenes and contrasts with earlier reports[20,21] that only kaurene could be detected. Very similar results[18] were obtained by West using seedlings of Ricinus communis L. and labelled mevalonate.

In the most recent work of Hanson[22] higher levels of incorporation of label are reported and evidence is provided that the alcohol (52) (as its pyrophosphate) acts as a precursor of the tetracyclic diterpenes. Gibberella fujikuroi was grown in the presence of labelled alcohol and the metabolites isolated. The three products were 7-hydroxykaurenolide (53), 7,18-dihydroxykaurenolide (54), and gibberellic acid (55) and the extent of incorporation was respectively 0.54%, 0.45%, and 5.13%. The label appears in the predicted position as shown. No tricyclic diterpenoids of the pimaradiene type were found again, casting doubt on the role of pimaradiene (or related compounds) in the biogenetic scheme.

At the present time the biogenetic pathway from mevalonate to gibberellic acid still poses several

questions, but through these recent labelling studies much has been learned about the nature of the intermediates involved.

In Vitro Synthesis of Diterpenoids:-

Rings A and B:

Investigations in this area have been mainly concerned with the cyclisation of acyclic precursors in a completely stereoselective fashion to form bicyclic systems capable of further stereoselective elaboration to tricyclic diterpenoids and polycyclic triterpenoids. Johnson[23] discussed the difficulties in accomplishing this type of olefinic cyclisation by utilising known techniques and has devised several novel methods of ring closure to surmount the major problems of low yields and trans to cis double bond isomerisation prior to closure.

The role of enzymes in the in vivo cyclisation process is not completely understood. The contention that the enzyme holds the substrate (e.g. geranylgeranyl pyrophosphate (1)) in a single rigidly folded conformation with the olefinic bonds correctly positioned for cyclisation has been challenged by Stork[24] and Eschenmoser[25] independently. Their proposal that all - trans polyolefins such as squalene should have an

intrinsic susceptibility to cyclise stereoselectively to a product having the "natural" trans rings A/B stereochemistry was tested by the cyclisation of trans-desmethylfarnesic ester (56) which did indeed give the predicted product (57) in 70% yield. However, the same product was obtained from the cyclisation of the cis substrate (58). This result was explained by Stork[24] when he isolated a monocyclic product (59) in a similar cyclisation procedure and he concluded that ring closures of cis and trans isomers involve a common intermediate of this monocyclic diene type (59). This contrasts with enzymic cyclisations where no deuterium is incorporated when the reaction is carried out in a deuterium oxide medium,[26] indicating that partially cyclised intermediates are not reprotonated and further cyclised.

The solvolysis[27,28] of trans-5,9-decadienyl p-nitrobenzenesulphonate (60) in buffered formic acid proceeded with significant rate enhancement due to participation of the $\Delta^{5,6}$ olefinic bond and produced a complex mixture of products. After cleavage of the formate esters it was shown that the major product overall (35%)

was the trans monocyclic alcohol (61), and the major bicyclic product the trans decalol (62). The bicyclic fraction which was formed in 12% yield, consisted exclusively of trans-decalin derivatives; no cis products were found in either class.

The solvolysis was repeated with the corresponding cis sulphonate ester (63), and in this case the major product (38%) was the cis monocyclic alcohol (64). The components of the bicyclic fraction (16%) in this case all belonged to the cis-decalin series, the major products being the epimeric alcohols (65).

This was the first report of the stereoselective production of bicyclic material from acyclic substrates according to the predictions of the Stork-Eschenmoser hypothesis. However, because of the low yields of fully cyclised material from the solvolysis of sulphonate esters, and the lack of functionality in ring A (a serious handicap for synthetic application) Johnson examined various other possible substrates.

Because of the ease with which 5-methyl-5-hexenal (66) cyclises completely under very mild conditions, Johnson decided to attempt cyclisations of the trans and

cis dienic acetals (67) and (68). The reactions were conducted in presence of stannic chloride in benzene at 25°. The trans substrate yielded only trans bicyclic material (90%) while the cis dienic acetal also displayed complete stereoselectivity to give only cis decalin products (80%). Degradation and oxidation of the mixtures of products from the two series gave rise to the ketonic double bond isomers (69) and (70) respectively.

Cyclisation of the acyclic trienic acetal (71;R=H) also proceeded with high stereoselectivity, the products (50%) being the mixture of ketonic double bond isomers (72). The rate and yield in this reaction were lower than in the case of the dienic acetals, because of the decreased nucleophilicity of the olefinic bond. In the cyclisation of the trienic acetal (71;R=CH_3) the presence of the trisubstituted $\Delta^{5,6}$ double bond appears to revert the reaction to a faster rate. A higher yield of tricyclic products is also obtained. The cyclisation to tetracyclic structures is merely an extension of this general procedure with tetraenic acetals (73) as the substrates.

This cyclisation technique gives good yields, provides functionality in ring A and has wide applicability in the synthesis of bi- and tri- cyclic systems. The other procedure investigated and developed by Johnson also meets all these requirements and in addition readily gives tetracyclic material.

The substrates for the reaction are monocyclic enols with side chains of the desired lengths and unsaturation for the product required. The reaction is initiated with formic acid and promoted by the allylic nature of the cation produced. It occurs very rapidly in the cold, is highly stereoselective and produces excellent yields.

An example of a bicyclic product is the dimethyloctalol (74) formed[29] in excellent yield from the dienol (75). A quantitative yield of tricyclic material was obtained[30] by formic acid conversion of the trienol (76) into a mixture of four hydrocarbons (77) and an alcohol (78), the reaction again being notably stereoselective. All five products were shown to be in the same stereochemical series by their interconversion and transformation into (±)-fichtelite (79), a natural product of known

relative configuration.

The synthesis of tetracyclic compounds has also been achieved by this cyclisation method. Formic acid treatment of the tetraenol (80) effected cyclisation to a mixture of products, the major component of which has been shown to be the tetracyclic alcohol (81), by its conversion into (±)-D-homo-5β-androstan-17-one.

A parallel investigation of cyclisation reactions has been carried out by van Tamelen[31] utilising acyclic terpenes with terminal epoxides to induce ring closure. The stimulus for a study of this mode of cyclisation came from the verification that squalene 2,3-oxide is an authentic intermediate in the conversion of squalene into lanosterol.

After solving[32,33] the problems associated with the synthesis of terminal epoxides, van Tamelen proceeded to demonstrate the power of this method in cyclisation reactions where a defined stereoisomer is desired. Initially the most suitable reagent for stereoselective cyclisation proved to be BF_3 etherate. This reagent induced the cyclisation of trans-trans-farnesyl acetate terminal epoxide (82) to a mixture of bicyclic diol

monoacetates (83) and (84), the major product (83) being present in 85% yield and having all four asymmetric centres in the relative configuration characteristic of the normal 3-hydroxy A/B ring system of polycyclic terpenoids. The isomer (84) was formed in 15% yield in the above reaction but became the major component when the cyclisation was conducted in 85% phosphoric acid. This provides a possibility of forming the B/C *syn* as well as the B/C *anti* configuration.

With the basic pattern of cyclisation established van Tamelen then extended the ring closure method to the tricyclic case. The epoxide (85), derived from *trans*, *trans*, *trans*-geranylgeraniol, by subjection to $SnCl_4$ in benzene at 0°, provided after work up and chromatographic separation a small amount of tricyclic diol monoacetate (86). Whether or not the reaction proceeds *via* a synchronous pathway is not yet clear. However, no matter the mechanism of the cyclisation, the tricyclic diterpenoid produced has all six asymmetric centres specifically oriented in the manner most commonly found in compounds of natural provenance.

In summary, polycylic products obtained from acyclic polyenes are formed stereoselectively whatever the mode of cyclisation employed. In nearly every case the carbocyclic skeleton formed has the same relative configuration as the more common natural products of that class. This appears to add weight to the Stork-Eschenmoser hypothesis and casts some doubt on the widely held belief that an enzyme acts as a template upon which the substrate must be molded into a certain rigid configuration prior to cyclisation.

Rings C and D:

Various groups have studied the formation of ring C from bicyclic labdanes (see page 4). Edwards[34] investigated the cationic cyclisation of manool (5) in 98-100% formic acid. During 20 min. practically complete conversion into tri- and tetra-cyclic materials was achieved. The tricyclic fraction consisted of a 1:1 mixture of pimara-8(9),15-diene and the corresponding isopimaradiene. The only tetracyclic product was shown to be a formate with a hibane skeleton (87). Of the two possible routes to this product (Scheme V) pathway (b) was deemed improbable as it involved the cyclisation of a cyclo-octyl cation to a 6,4 bicyclic system with the resulting strain and steric interactions. This, according to Edwards, left route (a) as the more likely although it involved an unprecedented C-14 to C-16 hydride shift. Also at this time Wenkert,[35] independently, found the same products but he favoured route (b) to the hibane system. He felt that the solvolytic conversion of the model compound (88) into the (3,2,1) bicyclic system (89) provided a sound analogy and reinforced his conclusions.

More recent studies have shown the latter assignment to be cofrect. Edwards[36] illustrated this first by the cyclisation of manool specifically labelled with two deuterium atoms at C-17. These atoms were found exclusively at C-15 in the tetracyclic formate produced. Involvement of route (a) would have required location of the deuterium atoms on C-14 and C-16. Wenkert[37] verified this result, the cyclisation in formic acid of (14-^{14}C) isomanool (90) furnishing (14-^{14}C)-14α-hibyl formate (91). The work of Oehlaschlager[38] served as a final confirmation of the intermediacy of the cyclo-octyl cation and a 6,4 ring system. He found that C-14 deuterated manool was converted to 14α-hibyl formate with the deuterium label present only at C-14.

Other products have now been reported from the cyclisation of bicyclic alcohols of the manool type. McCreadie and Overton[39] have converted labdadienols into pimara- and rosa- dienes products e.g. (92) and (93) respectively. They and other workers have also reported the presence of additional products, the identity of which remain undetermined but which are probably tri- or tetra-cyclic in nature.

Herz has reported[40] the closure of the fourth ring (D) using compounds with the tricyclic pimarane skeleton as substrates. The cationically induced cyclisations of suitably substituted derivatives of pimaradienes were investigated. In the isopimaric acid series, solvolysis of (94) resulted not only in the desired cyclisation of the two-carbon side chain toward C-8, but also in the concomitant migration of a methyl group and formation of (95).

An analogous methyl migration during the solvolysis of the pimaric acid derivative (96) was not expected since the C-10 methyl and two-carbon side chain are cis and thus the various hydrogen atoms and groups are not favourably orientated to permit concerted reactions. However, the product obtained from this reaction had also undergone methyl migration. The isomerisation of the $\Delta^{8,14}$ double bond to the $\Delta^{8,9}$ position prior to cyclisation, and the intervention of the ion (97) explained his failure to achieve the formation of the hibane skeleton. His sole success to this end was the cyclisation of mesylates of the type (98) with potassium t-butoxide to hibane derivatives (99) which were subsequently transformed into (-)-hibaene (24).

Biogenetic-like Rearrangements of the Tetracyclic Diterpenoids:-

Wenkert's scheme (Schemes II and III) summarises the relationship among the tetra- and penta- cyclic diterpenes and in addition has stimulated numerous attempts to interconvert the members of this class *via* carbonium ion rearrangements. A Glasgow group[41] sought conditions which would convert any one of these diterpenes into an equilibrium mixture containing other members of the same series with the hope of discovering the nature of the intermediate(s) involved. The results obtained by treating the various hydrocarbons with hydrochloric acid in chloroform are summarised in Table I. As the attainment of equilibrium in some cases was very slow the use of more drastic conditions[42] was also examined. Treatment of kaurene (31) with hot formic acid for 30 min. produced three formates (100), (101) and (102), all having the hibane skeleton, but the continued action of the acid gave rise finally to a mixture of hydrocarbons. The most abundant were hibaene (24), isokaurene (32), and isoatiserene (34). Similar prolonged treatment of hibaene with formic acid furnished a mixture of hydrocarbons identical (g.l.c.) to that obtained from kaurene,

suggesting the attainment of thermodynamic equilibrium in these cases.

Recently Coates[43] has succeeded in converting the hibane type system (103) to methyl trachyloban-19-oate (104) and the kaurane derivatives (105) via carbonium ion rearrangements. The transformation of isophyllocladene epoxide (106) by treatment with BF_3 etherate into a neoatiserene (107) system has also been reported,[44] again a carbonium ion rearrangement, is involved.

All the preceeding work had been concerned with the generation of the ion (108), but Coates devised[45] a π-route to the hydrogen-shift isomeric ion (109), which he suspected of being the immediate biogenetic precursor of atiserene and atisine. He subjected the tosylate (110) to buffered formolysis and isolated the sole product (111) after alkaline hydrolysis and chromatographic separation. This tertiary alcohol (111) under more vigorous formolysis suffered a further rearrangement to the formate (112) with the hibane skeleton. Coates deduced that the tertiary isomer was the product of kinetic control under mild conditions, while the thermodynamically more stable secondary ester is formed at

higher temperatures. He also found no crossover rearrangement (12 $\rightleftharpoons$ 16 hydride shift) between (108) and (109) although this occurs readily in absence of the C-13 methyl group (see below) and in the parent bicyclo-octane system under solvolytic[46] conditions.

In this thesis the results of a study of the rearrangements initiated when a carbonium ion is generated at C-16 in a nor-17-kaurane and phyllocladane skeleton are reported. The preliminary investigations were completed[47] before Coates' publication concerning the π-route to the ion (109) (see above). The investigation was undertaken because of the intrinsic interest in the products and mechanism of the rearrangement of the bridged bicyclic moieties and also because of the synthetic utility of the interconversions.

Related Carbonium Ion Rearrangements

There is still much controversy[48] over the existence of non-classical carbonium ions as intermediates in organic cationic reactions. The evidence for non-classical ions has been considerably strengthened recently but is still not conclusive, while the supporters of the theory of a pair of rapidly equilibrating ions have adduced results to support their contention.

In the following discussion and in the rest of this thesis non-classical structures are used only for convenience, the alternative possibility of a pair of rapidly equilibrating classical ions is recognised. Much work[49] has centred on the carbonium ion rearrangements of bridged bicyclic ring systems with the aim of determining the nature of the intermediate ions, but while the primary question is still unresolved, many interesting and novel rearrangements within these systems have been observed.

The 2-bicyclo(2,2,2) octyl and exo-2-bicyclo(3,2,1) octyl systems are connected in carbonium ion reactions through a common mesomeric cation (113). This unsym-

metrical cation is generated when Δ^3-cyclohexanylethyl bromo-benzene-p-sulphonate (114) is solvolysed,[50] the bicyclo products consisting of a 54:46 mixture of 2-bicyclo(2,2,2)octyl acetate (115;X=OAc) and 2-exo-bicyclo (3,2,1)octyl acetate (116;X=OAc). When the brosylates derived from these products (115;X=OBs) and (116;X=OBs) are subjected to acetolysis the same ratio of products arises. This indicates the interversion of the same intermediate ion (113).

Another mode of formation of this intermediate mesomeric ion would be the solvolysis of the bicyclo (3,2,1)octyl-6-toluene-p-sulphonates (117;X=OTs) and (118;X=OTs) if the ion generated (119) were to undergo a 4,6 hydride transfer. Such a 1,3 hydride shift had been well documented[51] in the bicyclo(2,2,1)heptane series but as there had been no report of this in the simple bicyclo(3,2,1)octane system Appleton et al.[46] prepared the exo- and endo-6-tosylates of bicyclo (3,2,1)octane and subjected them to buffered acetolysis at 105° for 18 hours. The products they obtained and the yields in which they were formed (Table II) left little doubt that heterolysis of the tosylates (117;X=OTs)

and (118;X=OTs) is accompanied or followed by 4,6 hydride shift and formation of the mesomeric ion (113). An alternative explanation of the products (115;X=OAc) and (116;X=OAc) could be proton loss from the classical ion (119) or mesomeric ion (120) and formation of tricyclo(3,2,1,$0^{2,7}$)octane (121) with subsequent acid catalysed cyclopropane ring opening to the products. This route to the acetates was shown to be of no more than minor importance as buffered acetolysis of the tricyclic compound (121) led to a markedly different product ratio.

Thus ionisation of (117;X=OTs) and participation of the 4,5-sigma bond will lead to the non-classical ion (120) which can either (a) suffer solvent capture at C-5 or C-6 (equivalent positions) to give the 6-acetate (117;X=OAc) or (b) undergo 4,6-(or 4,5-) hydride shift leading to the bridged species (113) from which (115;X=OAc) and (116;X=OAc) are readily formed. On the other hand solvolysis of (118;X=OTs) led to a prepondenance of product (117;X=OAc) from direct displacement. However, (115;X=OAc) and (116;X=OAc) were again formed presumably <u>via</u> the classical ion (119) and then hydride shift

(perhaps with intervention of ion (120)) to the mesomeric ion (113).

The solvolytic behaviour of the parent bicyclo (3,2,1)octyl-6-tosylates provided an indication of the migrations and rearrangements to be expected when the bicyclic portion is incorporated into a tetracyclic diterpene. In this case the departure from equivalence of certain positions in the substrate and intermediary carbonium ions, which are equivalent in the parent octane, and the effect which rings A and B of the diterpene will exert on the conformational mobility and stability of the bicyclo(3,2,1)octyl moiety would be expected to lead to a wider range of products including a variation in the extent of elimination.

TABLE I

Product composition after acid treatment

Hydrocarbon	Time of isomerisation*		Product composition (%; approx.)		
	a	b		a	b
Hibaene	4 days	21 days	Hibaene	44%	35%
			Kaurene	11	13
			Isokaurene	33	38
			Isoatisirene	11	13
			Atisirene	1	1
Kaurene	2 hr.	14 days	Kaurene	25	23
			Isokaurene	75	71
			Isoatisirene	0	5
			Atisirene	0	1
Isoatisirene	2 hr.	14 days	Kaurene	0	-
			Isokaurene	0	0.5
			Isoatisirene	92	91
			Atisirene	8	8
Trachylobane	15 min.	14 days	Kaurene	1	1
			Isokaurene	3	3
			Isoatisirene	90	90
			Atisirene	6	6

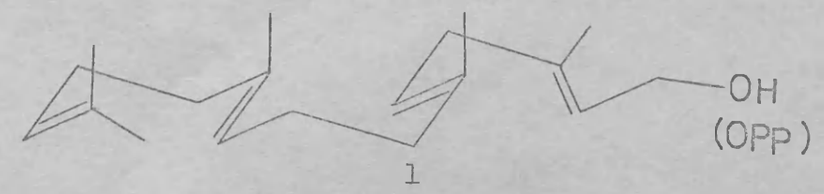
* Only two representative experiments are quoted.

TABLE II

Acetates formed from buffered acetolysis of (117;X=OTs), (118;X=OTs) and (121).

	(117;X=OAc)	(118;X=OAc)	(116;X=OAc)	(115;X=OAc)	(122;X=OAc)
(117;X=OTs)	16%	0	40%	44%	<1%
(118;X=OTs)	60%	0	19%	21%	0
(121)	26%	0	33%	35%	6%

SCHEME I



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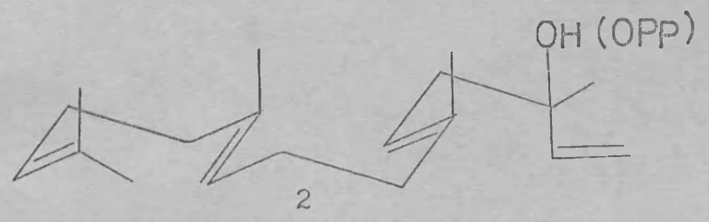

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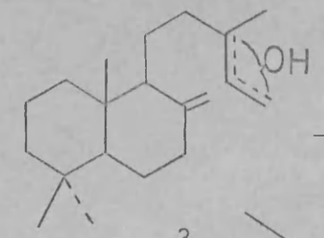

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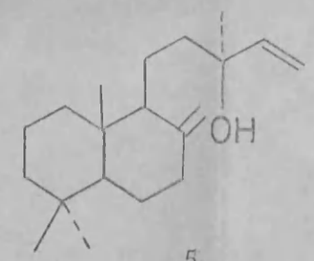

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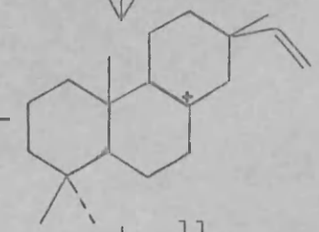
Schemes II & III



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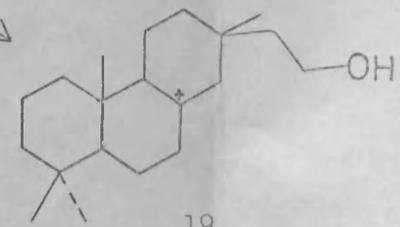

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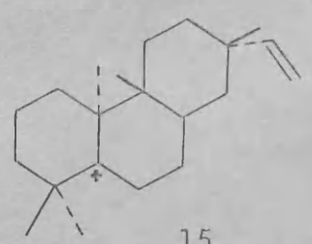

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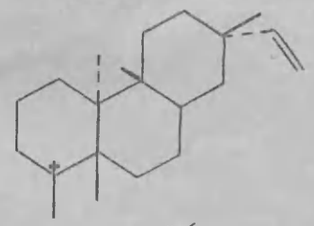

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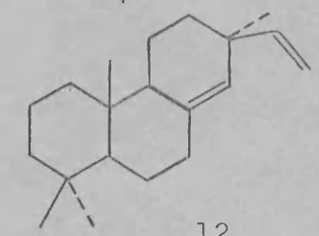

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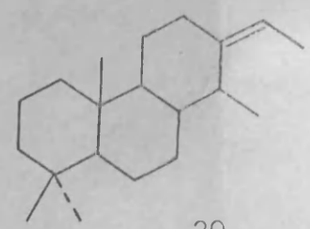

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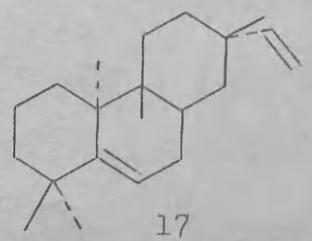

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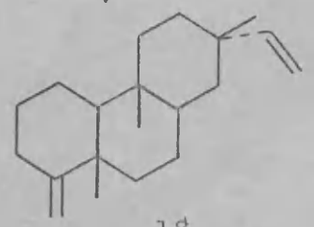

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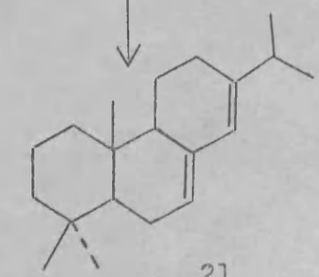

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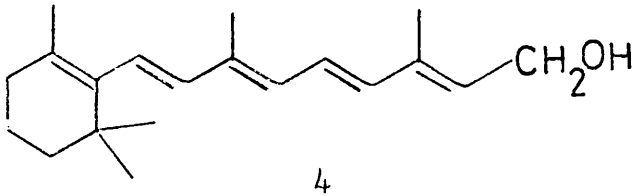
CH2OH

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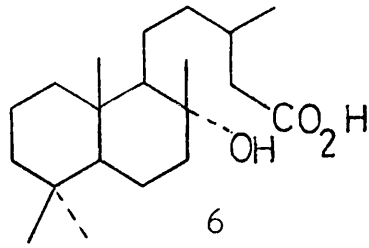
OH
CO2H

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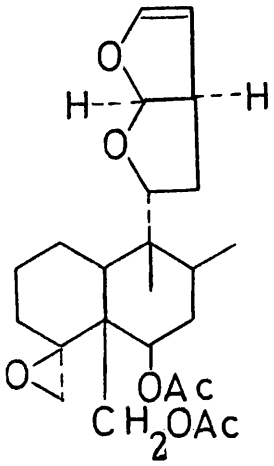
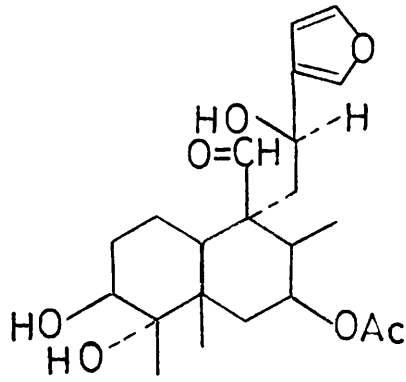
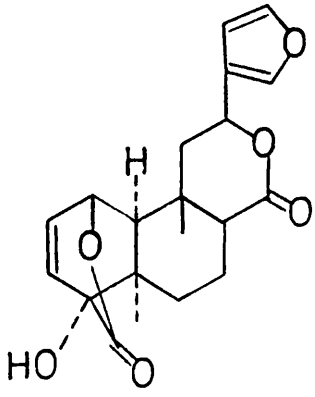

O
H
H
O
O
OAc
CH2OAc

7


O
HO
H
O=CH
HO
HO
OAc

8


O
H
O
O
O
HO
O

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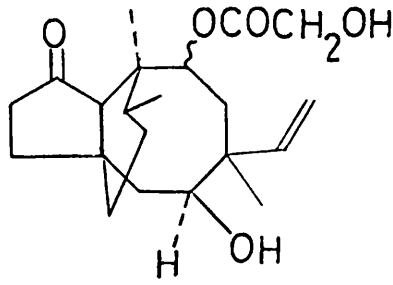
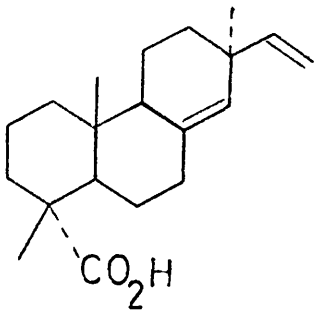

O
OCOCH2OH
H
OH

10



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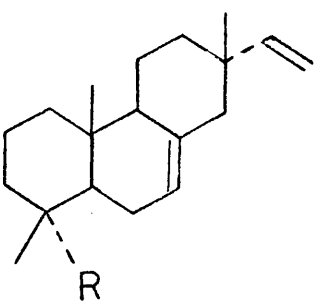

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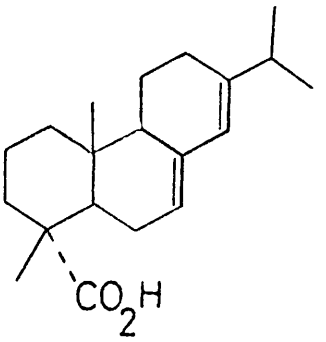

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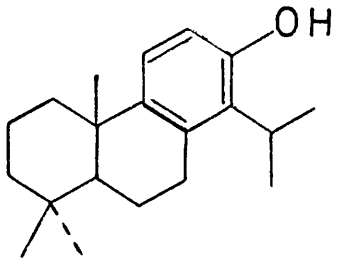

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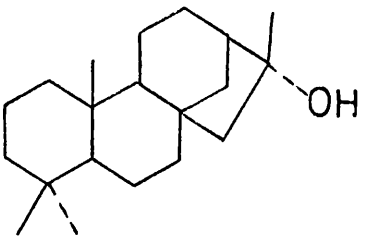

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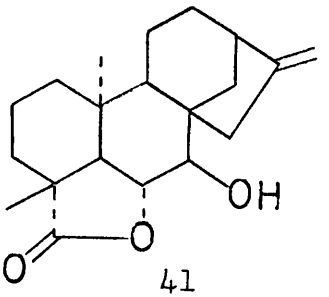

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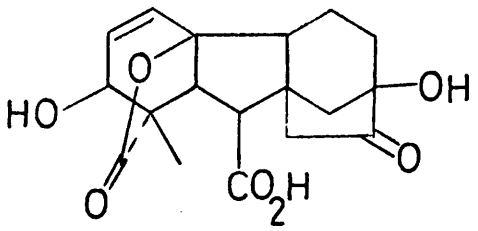

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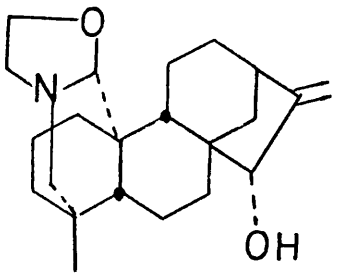

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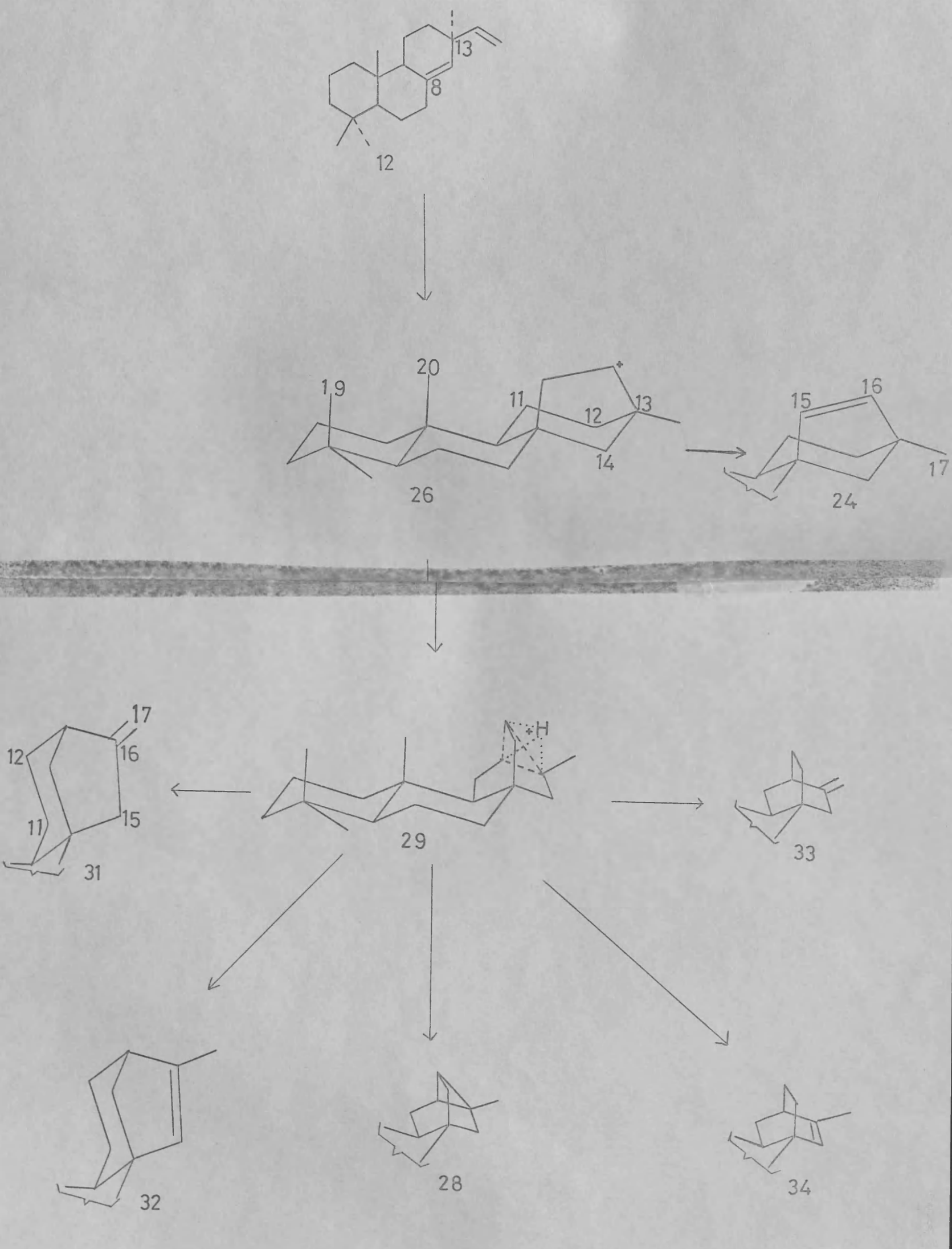
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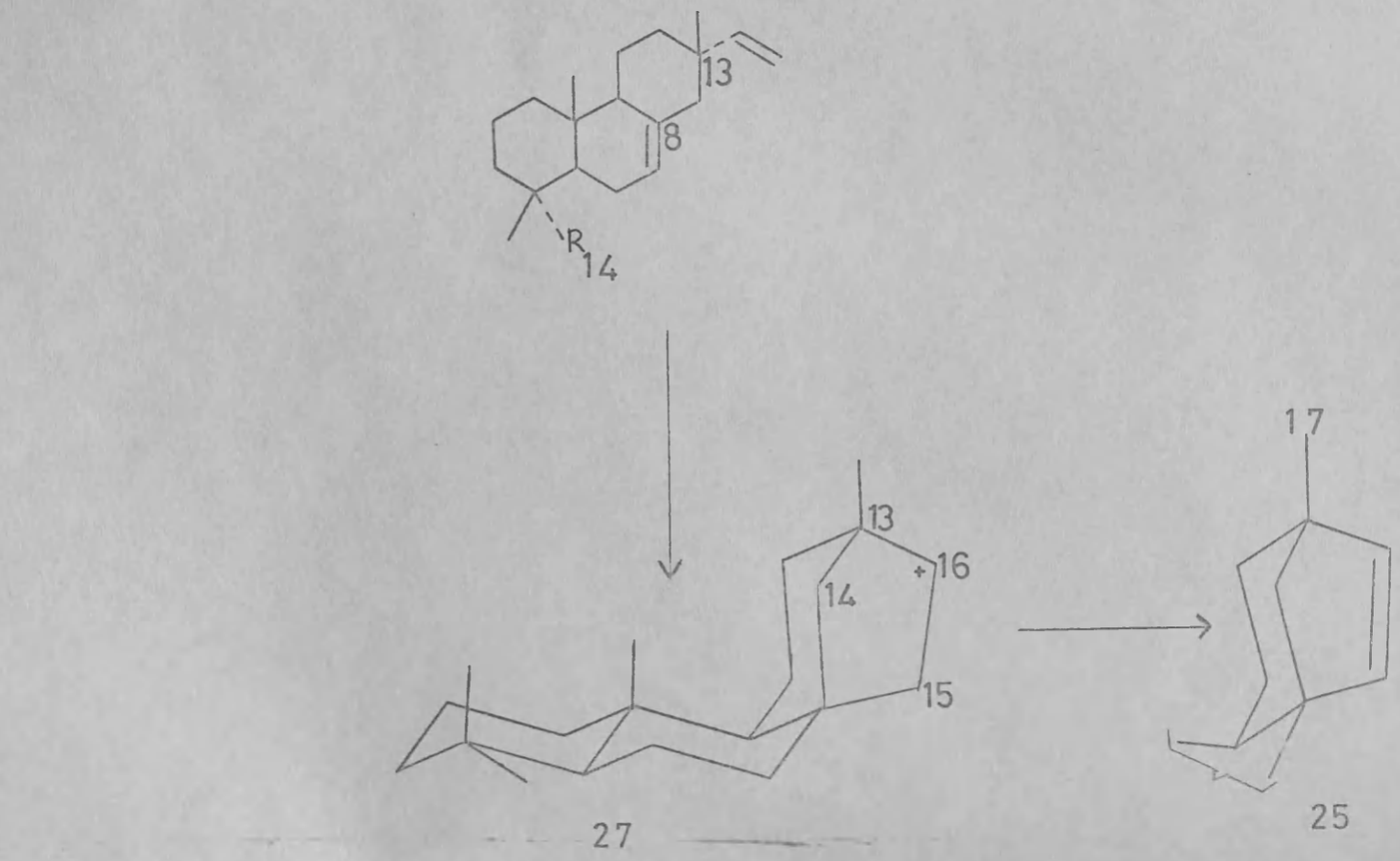
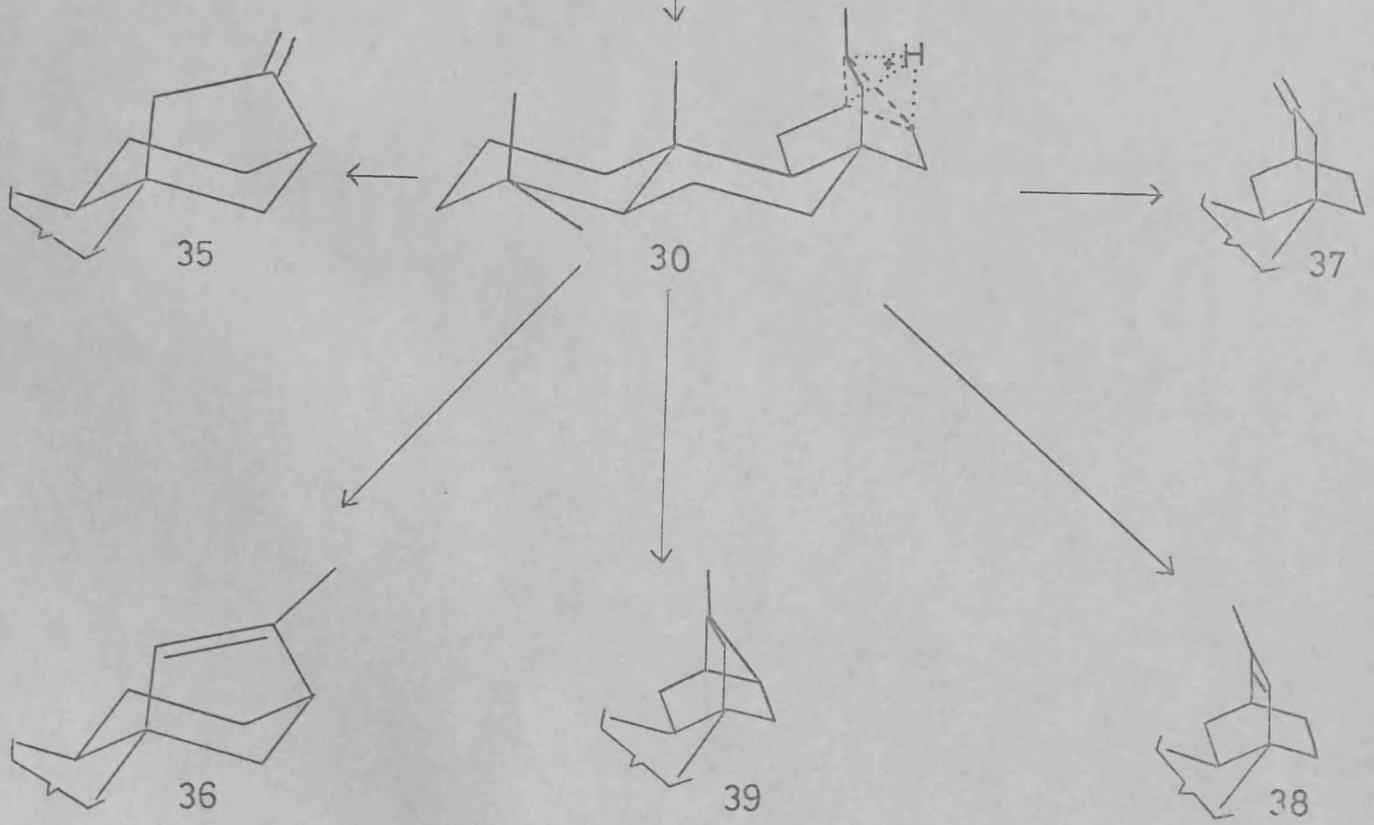
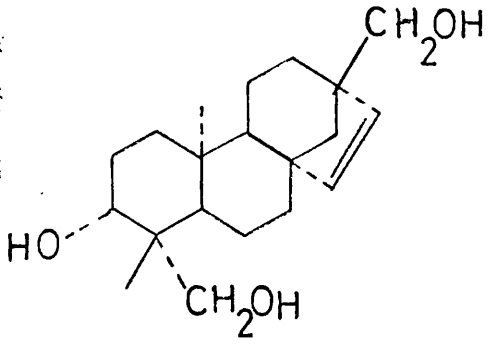
SCHEME III







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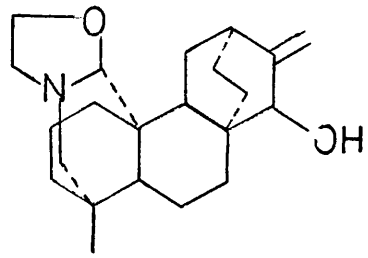

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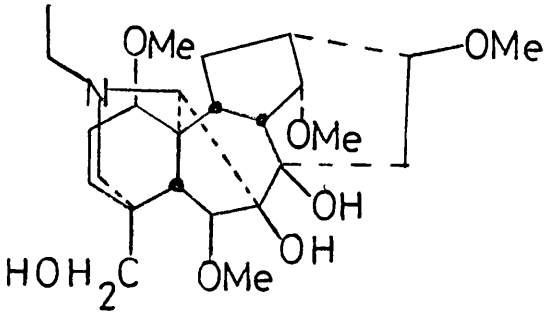

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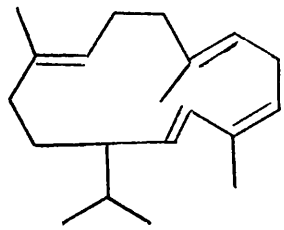

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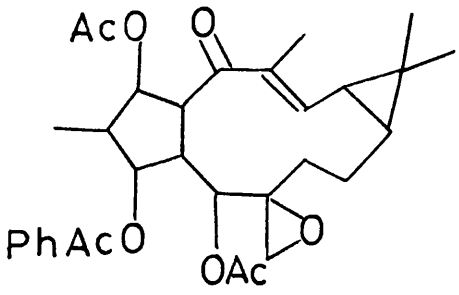

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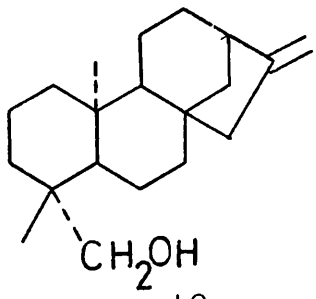

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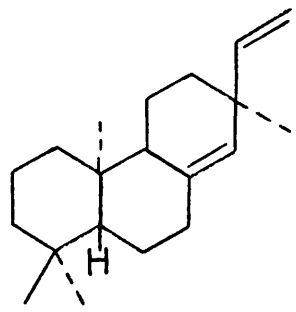

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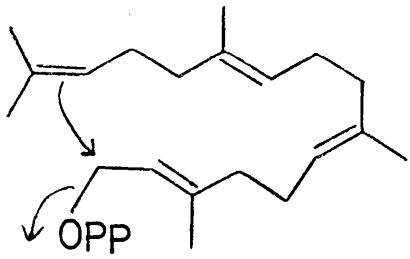

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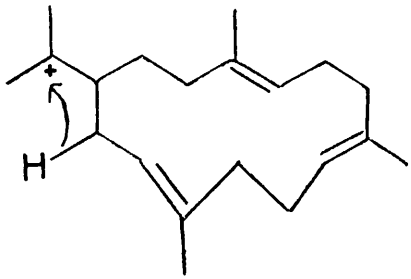

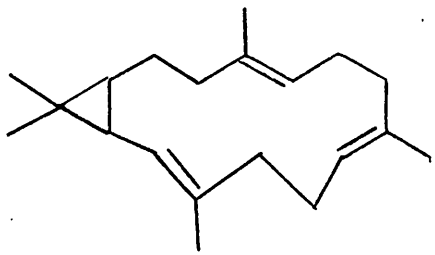

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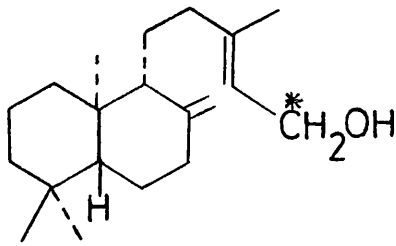

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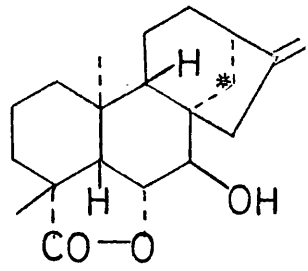

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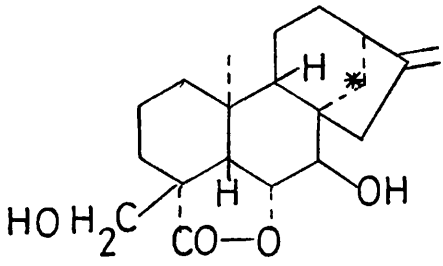

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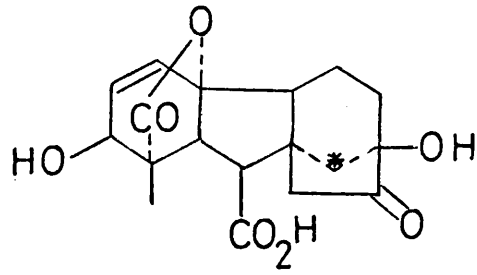

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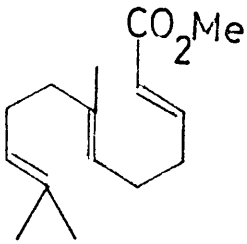

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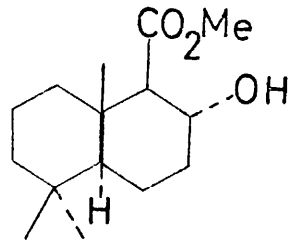

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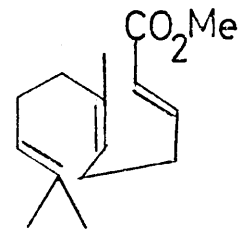

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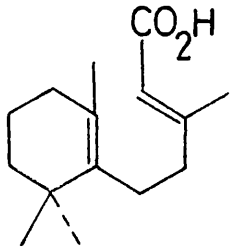

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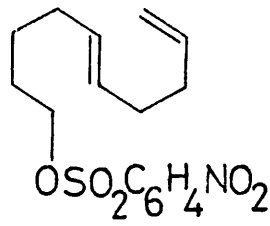

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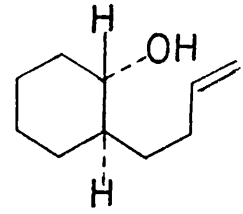

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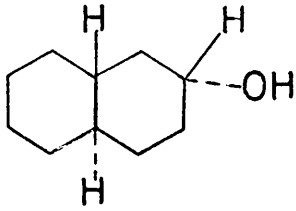

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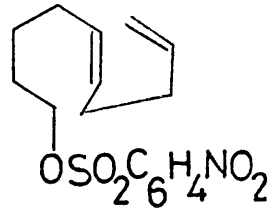

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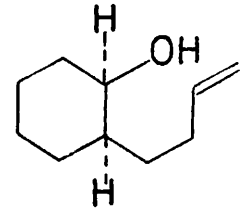

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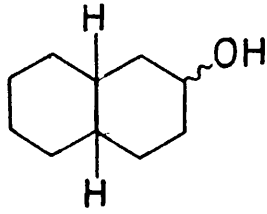

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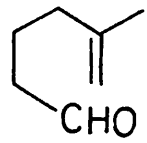

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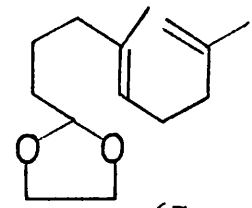

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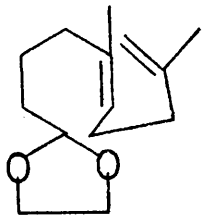

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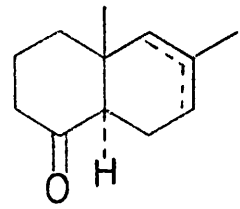

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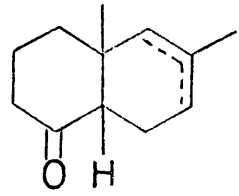

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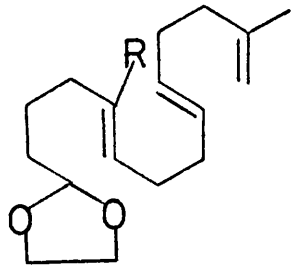

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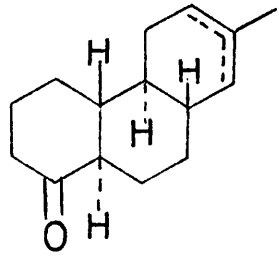

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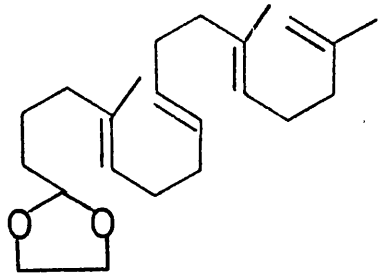

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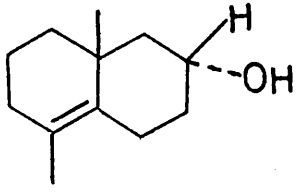

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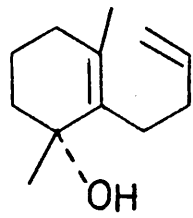

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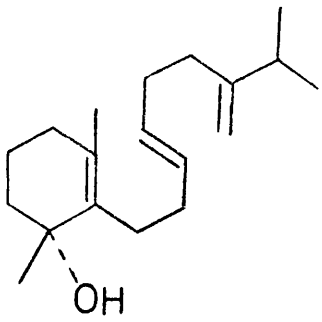

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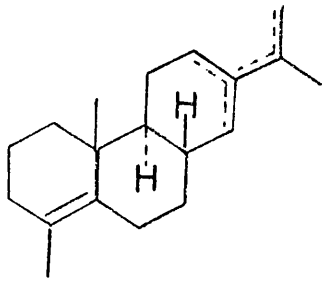

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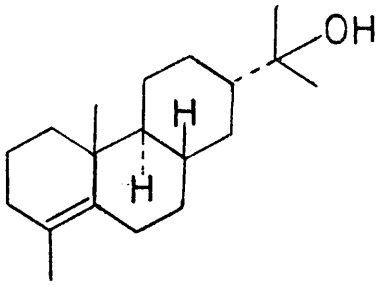

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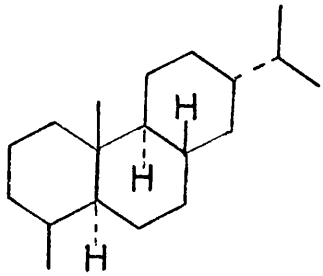

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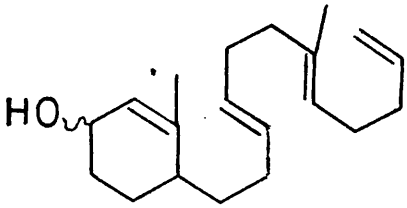

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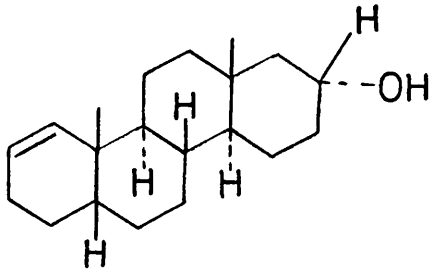

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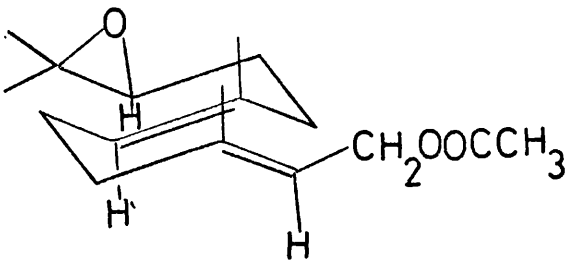
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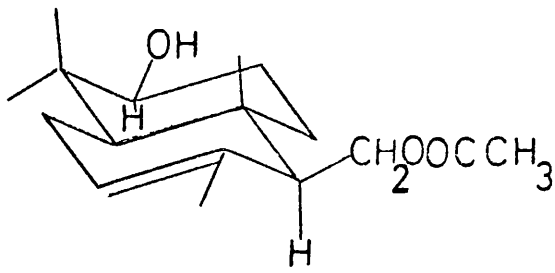
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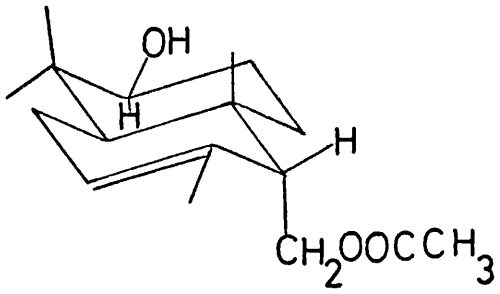
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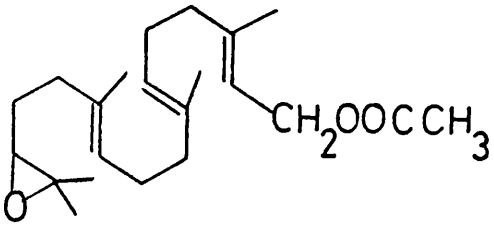
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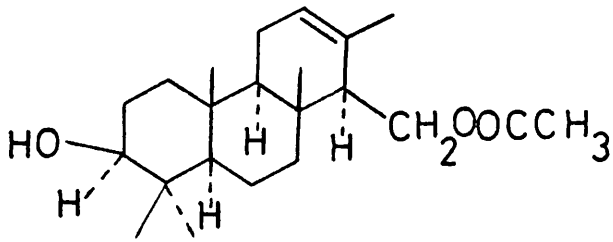
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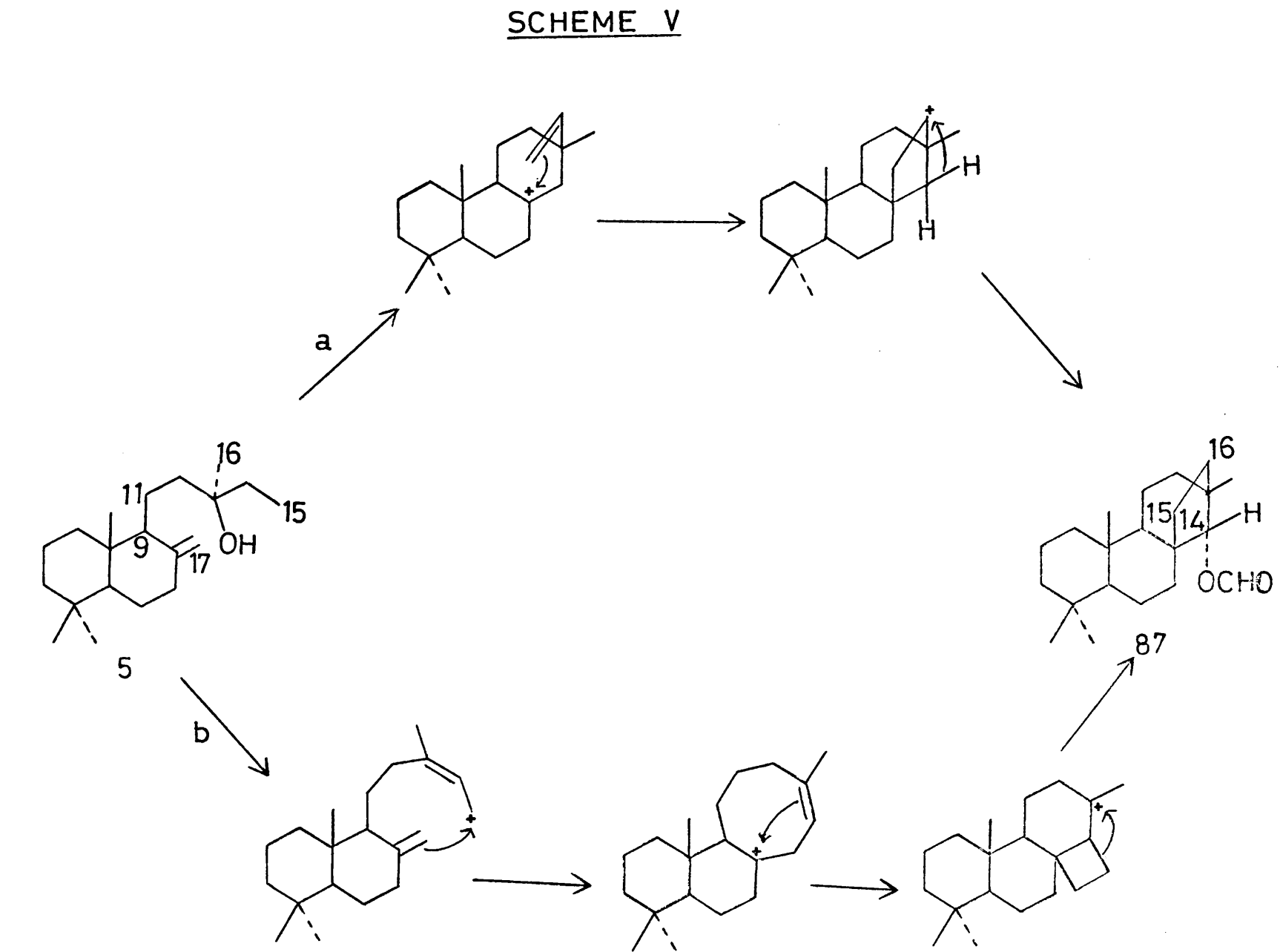
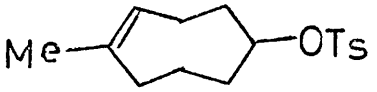
86

SCHEME V





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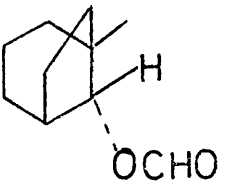

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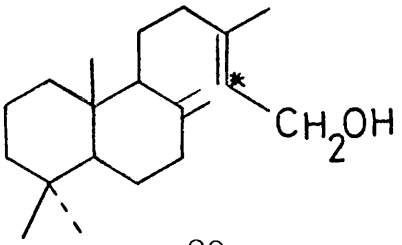

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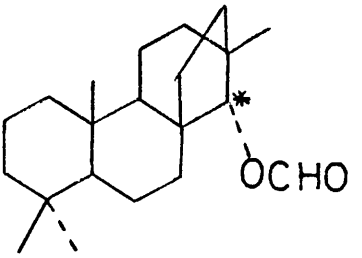

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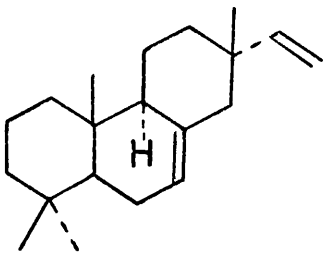

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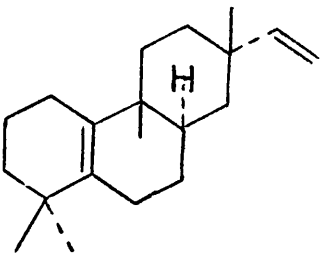

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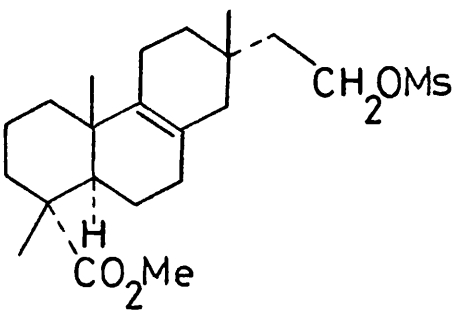

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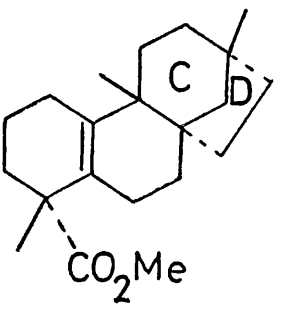

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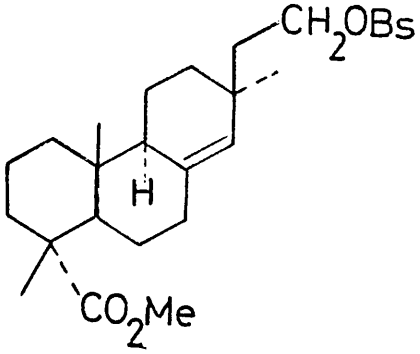

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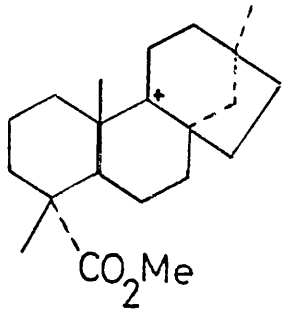

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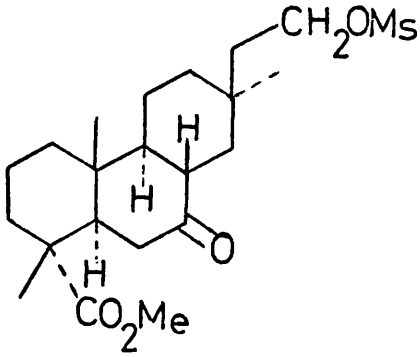

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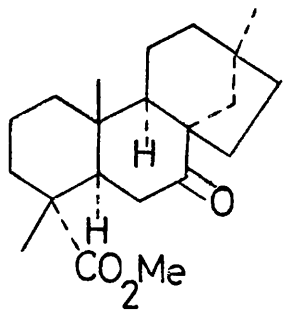

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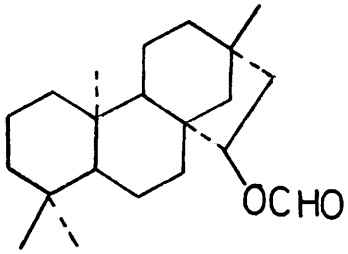

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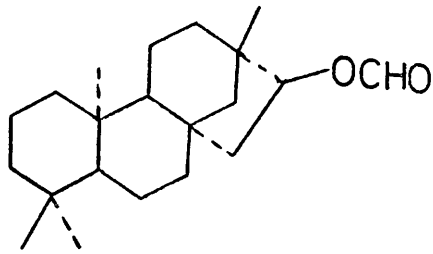

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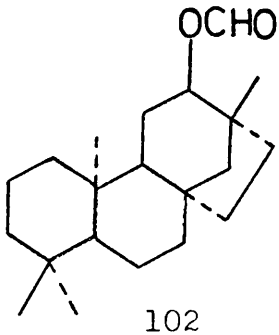

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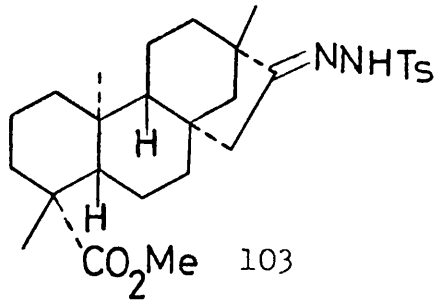

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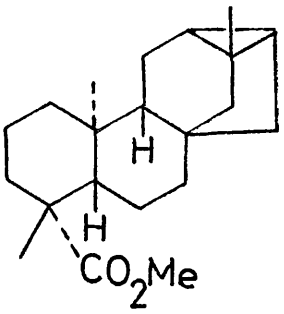

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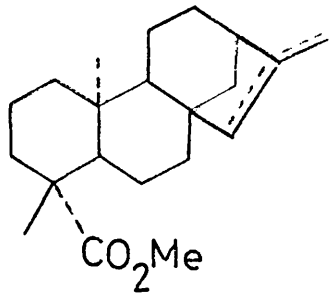

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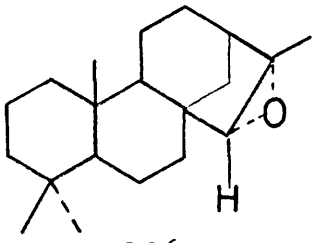

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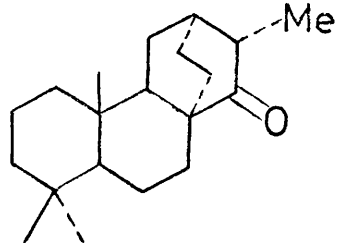

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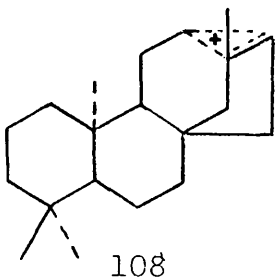

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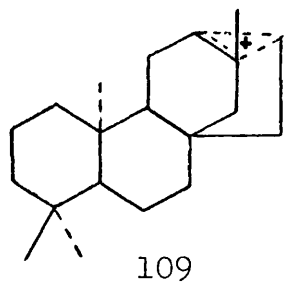

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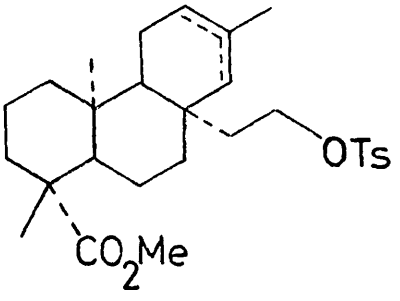

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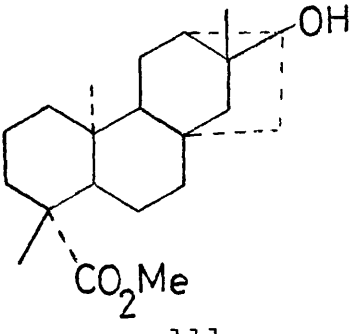

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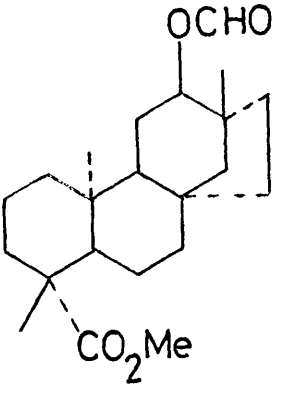

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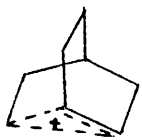

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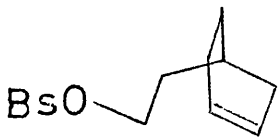

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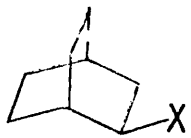

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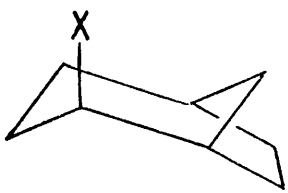

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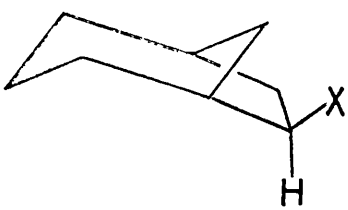

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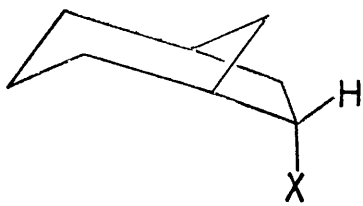

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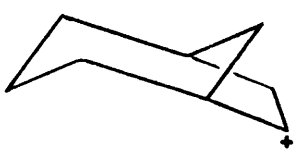

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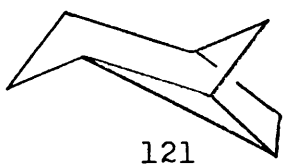

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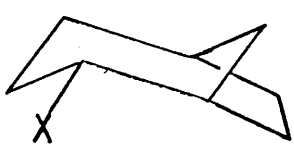


122

CLASSIFIED

The Buffered Acetolyses of the Toluene-p-Sulphonates of exo- and endo-17-Norkauran- and 17-Norphyllocladan-16-ols

An early attempt of Sobti and Dev[52] to interconvert tetracyclic diterpenes via carbonium ions generated by ester solvolysis was only partially successful. Thus solvolysis of the toluene-p-sulphonate of hiban-16β-ol (1) in a buffered solution, lithium carbonate in 66% aqueous dioxan, produced a mixture of hydrocarbons containing hibaene (2), kaurene (3), and isokaurene (4). These products were also obtained in the same proportions by passing the ester (1) over alumina in hexane solution. An analogous rearrangement has also been observed by Ghisalberti and Jefferies[53] on solvolysis of the corresponding ester with a C-18 carbomethoxy substituent. These two groups of workers were seeking products with the atisirene (5) or trachylobane (6) skeletons but it is not surprising that the products they obtained were kaurane derived. In a 16-β-ester of hibane the C_{12}-C_{13} bond is ideally orientated to undergo concerted migration on heterolysis of the substituent. The resulting carbonium ion can then suffer proton loss from either C-17 or C-15 to yield kaurene and isokaurene respectively.

The route to the atisane system would involve a hydride shift from C-12 to C-16 followed by migration of the C_{13}-C_{16} bond to C-12 and proton loss from C-17 or C-14 to produce atisirene and isoatisirene respectively.

An examination of the skeletons of 17-norkaurane and 17-norphyllocladane suggests that their interconversion by generation of a carbonium ion at C-16 should be feasible. This interconversion had been attempted by two groups of workers, but both attempts were abandoned. Surprisingly, according to Briggs,[54] solvolysis of the tosylate or the m-nitrobenzenesulphonate of 17-norphyllocladan-16β-ol (7;X=OTs or X=O-m-NO_2Bs) potassium acetate/acetic acid furnished as the only isolable product 17-norphyllocladan-16-one (8). In these derivatives, however, the leaving group is endo- with respect to the bicyclo(3,2,1)octane system and hence the C_{12}-C_{13} bond is not aligned in the trans-antiparallel orientation, commonly accepted as being most favourable for concerted participation in a reaction. However, Turner and his co-workers[55] found that the epimeric tosylate (9;X=OTs) on buffered acetolysis yielded mainly olefinic material and only traces of acetates. The

olefinic fraction, on the basis of i.r. analysis, appeared to be largely norphyllocladene (10). This group in a final attempt to convert the norphyllocladane into the norkaurane skeleton, carried out the deamination of the amine (obtained by sodium-alcohol reduction of the oxime of 17-norphyllocladan-16-one (8)) in aqueous acetic acid. The resulting mixture was treated with lithium aluminium hydride to convert any acetates to alcohols which were then oxidised to the ketones with chromium trioxide. 17-norphyllocladan-16-one (8) was shown to be the major product contaminated with minor amounts of 17-norphyllocladene (10) and 17-norphyllocladan-15-one (11). A fourth product which was not characterised showed absorption in the i.r. attributed to a six-membered ring ketone. The authors suggested that these last two products might have arisen from hydride shifts. They were presumably implying that a C-15 to C-16 shift accounted for the formation of the C-15 acetate and a C-12 to C-16 shift had given a C-12 acetate. However they did not assign a structure to the latter or the derived ketone. The analogous conversions of norkaurane esters into derivatives of

norphyllocladane had not been attempted.

In this study the toluene-p-sulphonates of exo- and endo-17-norkauran- and 17-norphyllocladan-16-ols (12, 13, 9, 7;allX=OTs) were subjected to buffered acetolysis and the nature and distribution of the products were determined (Tables I and II).

Starting Materials: The tree Cryptomeria japonica D. Don exists[56] in two forms which although morphologically indistinguishable produce different metabolites, notably in one case (-)-kaurene (3) and in the other (+)-phyllocladene (14). These two terpenes were isolated from the foliage of the two chemical varieties by extraction with light petroleum (b.p.60-80°) and provided convenient sources of each free from the other. Purification of each was effected by column chromotography over silica impregnated with silver nitrate and elution with increasing percentages of ethyl acetate in light petroleum (b.p. 60-80°).

These diterpenes were then converted[57] with osmium tetroxide-sodium periodate into the corresponding 17-norketones[54,55,57,58] (15) and (8), which on reduction with lithium aluminium hydride gave mainly endo-nor-

kauranol[58] (13;X=OH) and endo-norphyllocladanol[54] (7;X=OH) respectively. The endo- isomers were expected to be the major products from the reductions since the molecular geometry of the norketones dictates approach of the reagent from the less hindered faces. Reduction of the norketones by sodium in isopropanol gave the same products. Similarly lithium in liquid ammonia also furnished mainly the endo- isomers so the corresponding exo- alcohols were prepared by treating the endo- isomers with sodium n-butoxide in n-butanol to achieve equilibration, the thermodynamically more stable exo- epimers predominating. The resulting exo-, endo- mixtures were separated by preparative thin layer chromatography (t.l.c.). The stereochemistries of the alcohols were readily verified as being those shown by a study of their n.m.r. spectra. The resonances from the carbinol protons had a width of ca. 30 Hz in the endo- compounds but $W_{\frac{1}{2}}$ of 12-14 Hz in the exo- isomers.

These four alcohols were separately converted into the corresponding tosylates by treatment with toluene-p-sulphonyl chloride in pyridine at 0^{o}. Of the four, only the endo-norkauranol tosylate (13;X=OTs) failed to

crystallise and it was therefore purified by preparative t.l.c.

Results: All four tosylates (12, 13, 9, 7;X=OTs) were then individually subjected to treatment with sodium acetate/acetic acid at 100° for 6 hr. As expected, the products from each could be separated readily into hydrocarbon and acetate fractions by elution through short alumina columns in petroleum-ether (b.p. 60-80°). The hydrocarbons were eluted with light petroleum, the acetates with ether.

The compositions of the olefinic fractions were determined by a combination of chromatography over silica gel impregnated with silver nitrate and gas-liquid chromatography (g.l.c.). The norditerpenes (16),[59] (10), and (17) required for comparison were prepared from the alcohols (12;X=OH), (9;X=OH), and (18;X=OH) by elimination of toluene-p-sulphonic acid from the derived tosylates. These norditerpenes did not react when subjected to the acetolysis conditions.

Analysis of the acetate mixtures was more laborious, since separation could not be achieved by either t.l.c. or g.l.c. However, reduction of each mixture with

lithium aluminium hydride gave the corresponding alcohols, which were separated by preparative t.l.c. into fractions consisting of either individual components or mixtures of only two components. These two-component mixtures when oxidised furnished in each case two ketones, separable by t.l.c. The single components were also separately converted into the corresponding ketones.

Seven ketones were obtained in all, and of these, two, 17-norkauran-16-one (15) and 17-norphyllocladan-16-one (8) were already available for direct comparison. An authentic sample of 17-noratisan-16-one[60,61] (enantio-(19)) was required for comparison and its synthesis from (+)-phyllocladene is now described.

Treatment of phyllocladene with osmium tetroxide-sodium periodate produced the norketone (8) which gave the lactone[55,62] (20) when reacted with trifluoracetic acid in the presence of 90% hydrogen peroxide. Reduction of this lactone with lithium aluminium hydride furnished the diol[55] (21). Selective oxidation of the secondary hydroxyl with N-bromoacetamide gave the ketol (22;X=OH) which was cyclised by treating the derived tosylate (22;X=OTs) with potassium t-butoxide in t-butanol.

The product from the cyclisation reaction had identical spectral and physical characteristics to one of the ketones derived from the solvolyses.

The identity of yet another ketone derived from the acetolyses was determined by comparison of its physical and spectral properties with those of 17-noratisan-13-one[60] (23). The 17-noratisan-13-one was prepared from (-)-kaurene by an essentially similar route to that which had been utilised for the preparation of 17-noratisan-16-one from (+)-phyllocladene. Thus norkauran-16-one (15) yielded successively the lactone[62] (24), the diol[62] (25), the ketol (26;X=OH), the tosylate (26;X=OTs), and finally the cyclised product, 17-noratisan-13-one. Difficulties were encountered in converting the diol into the ketol in this case and necessitated a modification of the experimental procedure for this step. (See Experimental Section).

Of the three remaining ketones of undetermined constitution, one was identified by its physical and spectral properties which were identical to those of the well documented[55,59] 17-norphyllocladan-15-one (11). The structures of the two remaining ketones (27) and (28) were inferred from (a) their conversion into 17-norphyllo-

cladane[59] (29) and 17-norkaurane (30), authentic samples of which were obtained for g.l.c. comparison by a modified[63] Wolff-Kishner reduction of the 16-ketones, and (b) their i.r. carbonyl stretching frequencies. Assignment of the oxygen function to C-12 rather than C-11 is made on the basis of the mechanism of the solvolytic rearrangement, which presumably follows the behaviour[46] of the parent bicyclo(3,2,1)octyl system.

The configurations of the hydroxy-groups in the alcohols derived from the acetate fraction are formulated as shown on the basis of the following considerations. The exo- orientation of the functional groups in norkauran-16-ol (12;X=OH) and norphyllocladan-16-ol (9;X=OH) was established by direct comparison with authentic specimens; the physical properties[59] of the norphyllocladan-15-ol (31;X=OH) showed it to be the exo- isomer also. The noratisan-13-ol (18;X=OH) derived from the acetolysis was identical to the major product of reduction of the ketone (23) with lithium aluminium hydride and is therefore probably the α-isomer.

Configurations are assigned to the other three alcohols (32;X=OH), enantio-(33;X=OH), and (34;X=OH)

mainly on the basis of the supposed mechanism for their formation. However, certain spectral evidence supports the latter two assignments. The n.m.r. spectrum of the second displays a multiplet at 6.22τ, $W_{\frac{1}{2}}$ 9 Hz. This suggests that if ring C in this phyllocladane derivative, exists in a chair conformation, as seems likely from models, then the hydroxyl function is indeed β (i.e. axial) and the carbinol proton equatorial (with small couplings to each of its three neighbours). Although there has been some controversy over the conformation of ring C in the kaurane skeleton a Japanese group has shown[64] that the chair arrangement is possible, and indeed should be commonly found in kauranes having no significant steric interference between the C-10 angular methyl group and substituents on the (3,2,1)bicyclic moiety. Thus alcohol (34;X=OH) probably has ring C in a chair (or near chair) conformation and the $W_{\frac{1}{2}}$ of 13 Hz for the n.m.r. resonance at 6.30τ indicates that the hydroxyl group is α (i.e. axial)

Discussion: Acetates: The solvolysis of the tosylate of exo-norkauranol (12;X=OTs) gave six acetates (Table I). In view of the behaviour[46] of the parent bicyclo(3,2,1) octyl system a mechanistic scheme (Scheme) can be

formulated as the major pathway to these products. Ionisation of (12;X=OTs) with participation of the 12,13 σ-bond gives the non-classical ion (35), which can (a) suffer solvent capture at either C-13 or C-16 to give enantio- (9;X=OAc) and (12;X=OAc) respectively; (b) undergo a 12,13 hydride shift which leads to ion (36), from which (32;X=OAc) and enantio- (33;X=OAc) can be derived; or (c) undergo a 12,16 hydride shift leading to the ion (37), which can furnish (18;X=OAc) and (34;X=OAc). The intervention of these bridged ions would explain the stereospecificity of product formation, only one epimer being isolated in each of the six cases. The endo- tosylate (13;X=OTs) furnished the same six acetates. The product distribution appears to indicate that in this case ionisation can lead either directly to the exo-acetate (12;X=OAc) or presumably via a classical C-16 carbonium ion to the mesomeric ion (35) and thence to the six acetates as before (see Scheme).

Analogous considerations probably apply to the solvolysis of the exo- and endo- derivatives of norphyllocladane (9;X=OTs) and (7;X=OTs) as far as acetate products are concerned although in the case of the exo- isomer the

yield of acetate was so low that no estimate could be made of the relative amounts produced. However, in these solvolyses an additional product, the 15-acetate (31;X=OAc) of norphyllocladane, was formed. In the phyllocladane skeleton there is severe steric compression between the C-10 methyl group and the endo- hydrogen atom at C-15. This strain is relieved when C-15 becomes sp^2-hybridised and thus products resulting from a 1,2 hydride shift from C-15 to C-16 on solvolysis of a 16-tosylate are to be expected.

Olefins: The only olefins isolated from reaction of the norkaurane derivatives were 17-norkaur-15-ene (16), 17-norphylloclad-15-ene(enantio-(10)), and 17-noratisir-13-ene (17) (Table II). The latter pair may well be derived from the ions (35) and (37), which are involved in the formation of the corresponding acetates (enantio-(9;X=OAc)) and (18;X=OAc). Significantly, there is considerable interaction between the C-15 methylene and the C-10 methyl group in these two acetates.

In the norphyllocladane series only the Δ^{15} olefin (10) related to the parent system was isolated. Notable here however is the high proportion of the total product

which the olefin constitutes, especially in the case of the exo- form (ca. 80%). Presumably the reduction in the amount of steric interaction between C-15 and C-20 when C-15 becomes sp^2-hybridised is again a major factor. This argument should apply to a similar extent to (7;X=OTs) and (9;X=OTs). However, the formation of a much larger proportion of olefin from the exo- than from the endo- tosylate may reflect the fact that it is the endo- proton attached to C-15 which is strongly compressed against the C-10 methyl group. Loss of this proton as C-15 becomes trigonal may then be especially favoured even although its orientation (trans) with respect to the tosylate function in the exo-ester is analogous to that of its geminal counterpart in the endo- ester. There appears to be at least three possible pathways for formation of (10) from (9;X=OTs). The first (a) direct trans- elimination of toluene-p-sulphonic acid, involves removal of the endo- proton from C-15 and ester function from C-16. However, molecular models reveal that loss of this proton by such a mechanism may not be favoured for two reasons. Elongation of the σ-bond joining the endo- hydrogen atom to C-15 appears to produce even more severe steric interactions with the C-10 methyl

group, and also access to this proton by external base is restricted by steric crowding. A second and perhaps more attractive possibility (b) involving a 1,2 hydride shift from C-15 to C-16 as heterolysis proceeds would form a C-15 cation, which could then either capture solvent (see before) or lose a porton from C-16 to give (10) in which C-15 remains trigonal. (Such a 1,2 hydride shift results when isophyllocladene epoxide is treated with Lewis acids to produce[44,59,62] phyllocladan-15-one, whereas similar treatment of the equivalent derivative of isokaurene gives[62] mainly the allylic secondary alcohol (see later)). However, (c) some other mechanism (e.g. cyclic) could play a major role in the elimination. The work of Froemsdoff[65] on the intervention of a dual mechanism in base-promoted toluene-p-sulphonate eliminations illustrates that cis- elimination is more common than has been believed and may accompany the more usual trans- elimination in a simultaneous process from a single substrate. Treatment of (3-exo-^{2}H) bicyclo (2,2,1)heptyl-2-exo-bromide (38) with potassium t-hexoxide gave the corresponding olefin by exclusive cis- elimination. However, in acyclic systems that allow the stereoelectronic

requirements of both cis- and trans- elimination to be fulfilled, he found that trans- elimination occurs almost exclusively. He suggested that his work on bridged bicyclic compounds and the earlier results of Sicher and Zavada[66] show that cis- eliminations stem from an inability of these systems to adopt a geometry favourable for trans- elimination without creating a prohibitive amount of conformational strain.

In comparison to the bicycloheptyl system less strain is required to align the endo-C-15 proton in a trans-antiparallel arrangement with respect to the exo-C-16 tosylate in (9;X=OTs). However, the difficulty encountered by the external base in extracting the endo-C-15 proton may make the cis- elimination energetically more favourable in this case.

With the aim of resolving the relative importance of these three pathways, the tosylate of 17-norphyllocladan-16-exo-ol specifically labelled with a deuterium atom in the C-16 endo- position was subjected to buffered acetolysis. This labelled compound was prepared from the norketone (8) by reduction with lithium aluminium deuteride in ether. The product consisted of a 9:1

mixture of the endo- and exo- alcohols respectively. The alcohols were separated by preparative t.l.c. The less polar endo- epimer was oxidised by Jones' technique[66] and again reduced with lithium aluminium deuteride. By recycling the endo- alcohol three times sufficient exo-norphyllocladanol deuterated in the C-16 endo- position was obtained. As expected the n.m.r. spectrum of this alcohol displayed three methyl resonances at 9.12, 9.16, and 9.20τ, which are present in the spectrum of the non-deuterated alcohol. The absence of the broad peak at 5.98τ in the former indicated the presence of a deuterium atom in the desired position. Treatment of the deuterated alcohol with toluene-p-sulphonyl chloride in chilled pyridine converted it into the corresponding tosylate, the n.m.r. spectrum of which showed peaks at 7.56, 9.20, and 9.25τ. No resonances attributable to a carbinyl proton is present.

If the elimination of toluene-p-sulphonic acid follows route (a) the norphyllocladene product will have retained the deuterium atom at C-16. Similarly, if route (c), the cis- elimination, is in operation, the deuterium will also be found at C-16 in the product.

However, if a 1,2 hydride shift from C-15 to C-16 is involved (route b), at least a partial loss of deuterium from the molecule would be anticipated.

The norphyllocladene product from the solvolysis was separated from the small acetate fraction by elution through a short alumina column in light petroleum (b.p. 60-80°) and its n.m.r. spectrum recorded. As expected this showed the three methyl resonances at 9.16, 9.20, and 9.27 τ which are also present in the spectrum of the non-deuterated norphyllocladene, however, the broad olefinic peak at 4.23 τ is of lower intensity in the former spectrum and in fact integrates for only one proton. The more or less complete retention of the deuterium atom was even more convincingly confirmed by a study of the mass spectrum of this olefin. The peak corresponding to the molecular ion (m/e 259) from the species $C_{19}H_{29}D$ is at least fifty times more intense than that from its undeuterated analogue, thus indicating the presence of less than 2% of the latter. This result excludes (b), the hydride shift mechanism, as a significant route and taken in conjunction with the arguments discussed above would appear to indicate the intervention

of route (c) as the major product-forming pathway in this elimination.

Syntheses of (-)-Phyllocladene, (-)-Atiserene, and (-)-Neoatisirene

While several tetracyclic diterpenes have been synthesised the products were either racemic in nature or the number of reactions involved in their production rendered the synthetic sequence of little utility as a diterpene source. For example, the synthesis of (+)-phyllocladene (14) reported[55] by Turner et al. employed the Cornforth-Robinson ketone[67] (39) as the starting material. Over twenty steps were required to furnish the α,β -unsaturated aldehyde (40) which had been shown by Briggs and his associates[68] to yield phyllocladene on Wolff-Kishner reduction. Thus a formal stereospecific total synthesis of (+)-phyllocladene was accomplished but no synthesis of or conversion to (-)-phyllocladene has been reported.

The norphyllocladanone (enantio- (8)) derived from the norkauran-16-ol tosylates acetolyses was stirred with methylenetripheylphosphorane in ether under nitrogen.[69] This converted the ketone into a product having physical and spectral properties identical to those of (+)-phyllocladene from C. japonica[56] with the exception of its sign (-) of specific rotation.

Zalkow and Girotra reported[60] a synthesis of (-)-atisirene (5) in 1963. In this study they were attempting a synthesis of the carbon skeleton of atisine, a diterpenoid alkoloid based on the atisane system. This synthesis involved 15 steps from the starting material, maleopimaric acid (41). (±)-Atisirene and (±)-kaurene were prepared by Ireland et al.[61] The key intermediate in this investigation was the readily available aldehyde (42). This aldehyde gave rise to the ketones (43) and (44) which were cyclised by base to furnish the atisirane (45) and kaurane (46) derived moieties respectively. Further transformations led to (±)-atisirene and (±)-kaurene.

(-)-Atisirene (5) prepared from ketone (19) by the Wittig reagent was found to be identical in all respects with (-)-atisirene from Erythroxylon monogynum.[41]

In their study of 1963, Zalkow and Girotra[60] prepared 17-noratisiran-13-one (enantio- (23)) which they later converted[70] to the C_{20} hydrocarbon (+)-neoatisirene with the Wittig reagent. In the present investigation similar treatment of the 17-noratisiran-13-one (23), derived from the solvolyses, furnished (-)-neoatisirene (47) which had the physical and spectral properties

characteristic of its enantiomer.

Thus the solvolyses of the norkauranol tosylates provides a route for the conversion of (-)-kaurene into these three diterpenes. In principle the ketones derived via the nor-tosylates from (+)-phyllocladene could be utilised for the formation of (+)-kaurene, (+)-atisirene, and (+)-neoatisirene. This investigation has therefore provided a novel means of preparing six inaccessible diterpenes namely:- (-)-phyllocladene, (+)-kaurene, (+)- and (-)-neoatisirene and (+)- and (-)-atisirene from readily available precursors ((-)-kaurene and (+)-phyllocladene).

EXPERIMENTAL

General:-

T.l.c. was carried out on Kieselgel G (Merck). Woelm alumina (neutral) was used for column chromatography. G.l.c. analyses were performed with a Perkin-Elmer F11 gas chromatograph (stainless steel column $\frac{1}{16}$ in. X 13 ft.) containing 2½% SE-30 at 190°C; nitrogen gas pressure 17 lb./in.^{2}).

M.p.s. were determined with a Kofler hot-stage apparatus. Specific rotations refer to solutions in chloroform (c 0.5-1, unless otherwise stated) at 20°. Light petroleum refers to the fraction of b.p. 60-80°. I.r. spectra were recorded for solutions in carbon tetrachloride with a Perkin-Elmer 257 grating spectrophotometer, and n.m.r. spectra with Perkin-Elmer R10 and Varian Associates HA-100 spectrometers for dilute solutions in deuterio-chloroform or benzene with tetramethylsilane as internal standard. Microanalyses were performed by Mr. J.M.L. Cameron, Glasgow and his staff.

(-)-Kaurene (3).- Foliage of Cryptomeria japonica was finely ground and extracted with light-petroleum in a Soxhlet apparatus for six hours. The solvent was removed and the residue subjected to chromatographic separation over silica gel impregnated with 10% silver nitrate. Fractions were collected by eluting with increasing percentages of ethyl acetate in light-petroleum. The second component eluted (with ethyl acetate: light petroleum, 2:48) was kaurene which on crystallisation from methanol formed needles, m.p. 50-51°, $[\alpha]_D$ -75° (lit.[56], m.p. 51-52° and $[\alpha]_D$ -78°).

(+)-Phyllocladene (14).- (+)-Phyllocladene was isolated, by the above procedure, from the other "chemical variety" of C. japonica. Crystallisation of the relevant material from methanol gave (+)-phyllocladene, m.p. 98-99°, $[\alpha]_D$ +13°. (lit.[56], m.p. 98.5°, $[\alpha]_D$ +13°).

17-Norkauran-16-one (15).- Kaurene (2.7 g.) was stirred with osmium tetroxide[57] (150 mg.) in a mixture of dioxan (25 ml.) for 10 min. To the rapidly darkening solution was added sodium periodate (6 g.) in portions during 30 min. The stirring was continued for 22 hr. after which the solution was filtered and the white precipitate washed with acetic acid. The filtrate was evaporated *in vacuo* at 40°, and water (100 ml.) added. The evaporation was repeated and the colourless residue taken up in methylene chloride and washed with saturated sodium bicarbonate solution until the evolution of carbon dioxide ceased. The organic layer was then separated, dried over anhydrous magnesium sulphate and the solvent evaporated. The resulting norketone (1.93 g.) crystallised from aqueous methanol as needles, m.p. 116-119° (lit.,[58] 117°), $\nu_{max.}$ 1742 cm.$^{-1}$ τ 8.91, 9.13 and 9.17 (all 3H,s).

The Tosylate (13;X=OTs) of 17-Norkauran-16β-ol.- The ketone (15) (1 g.) was treated with excess of lithium aluminium hydride in refluxing dry ether for 1 hr. Work-up with a saturated aqueous solution of sodium sulphate furnished a mixture of the α- and β-16-ols (ca. 1:5) (952 mg.). These alcohols on preparative t.l.c. (ethyl acetate-light petroleum (3:17)) yielded the β-isomer (806 mg.) as fine needles, m.p. 162-163° (from aqueous ethanol) (lit.,[58] 160-161°), τ 8.95, 9.15, and 9.18 (all 3H,s) and 5.70 (1H,m, width 30Hz). Chilled solutions of this alcohol (13;X=OH) (500 mg.) in dry pyridine (6 ml.) and toluene-p-sulphonyl chloride (650 mg.) in the same solvent (4 ml.) were mixed and kept at 18° for 12 hr. Work-up gave the tosylate (13;X=OTs) as an oil (745 mg.), which showed one spot on t.l.c. (ethyl acetate-light petroleum (1:9)), τ 7.58, 8.97, 9.16 and 9.21 (all 3H,s) 5.21 (1H,m) and 2.40 (4H,q).

The Tosylate (12;X=OTs) of 17-Norkauran-16α-ol.- Sodium (2 g.) was dissolved in n-butanol (40 ml.) and the alcohol (13;X=OH) (200 mg.) was heated in the resulting solution at reflux for 1 hr. Preparative t.l.c. of the products furnished 17-norkauran-16α-ol (12;X=OH) (133 mg.) and starting material (54 mg.). The former gave fine needles, m.p. 159-160° (from aqueous ethanol), τ 8.98, 9.14, and 9.18 (all 3H,s), and 5.92 (1H,m, $W_{\frac{1}{2}}$ 14Hz) (Found: C, 82.7; H, 11.95. $C_{12}H_{32}O$ requires C, 82.55; H, 11.65%). The tosylate was prepared as described for the β-isomer; m.p. 132-133° (from methanol), τ 7.56, 8.98, 9.15, and 9.18 (all 3H,s) 5.35 (1H,m) and 2.41 (4H,q) (Found: C, 72.55; H, 8.85. $C_{26}H_{38}O_3S$ requires C, 72.5; H, 8.9%).

17-Norphyllocladan-16-one (8).- Treatment[57] of (+)-phyllocladene (14) with osmium tetroxide-sodium meta-periodate gave the norketone (8)which yielded needles,

m.p. 99-102° (from methanol) (lit.,[54] 101-102°), $\nu_{max.}$ 1742 cm.,$^{-1}$ τ 9.15 (6H,s) and 9.20 (3H,s).

The Tosylate (7;X=OTs) of 17-Norphyllocladan-16β-ol.- The ketone (8) (1 g.) was reduced with excess of lithium aluminium hydride in refluxing dry ether and the resulting mixture of exo- and endo- alcohols (1:9) (972 mg.) was separated by preparative t.l.c. The β-isomer (7) gave plates, m.p. 150-152° (from ethanol) (lit.,[59] 150-152°), τ 9.10, 9.17, and 9.20 (all 3H,s), and 5.65 (1H,m, width 30 Hz). The corresponding tosylate had m.p. 108-110° (from light petroleum) (lit.,[54] 107-108°), τ 7.58 (3H,s), 9.19 (6H,s), 9.21 (3H,s), 5.11 (1H,m), and 2.53 (4H,q).

The Tosylate (9;X=OTs) of 17-Norphyllocladan-16α-ol.- Equilibration of the endo- alcohol (7;X=OH) with sodium in n-butanol as already described furnished the exo-isomer

(9;X=OH), m.p. 155-156° (from ethanol) (lit.,[59] 156-157°), τ 9.12, 9.16, and 9.20 (all 3H,s) and 5.98 (1H,m, $W_{\frac{1}{2}}$ 12Hz). The corresponding tosylate (9;X=OTs) had m.p. 132-133° (from methanol) (isolated previously[55] as an oil), τ 7.56 (3H,s), 9.20 (6H,s), 9.25 (3H,s), 5.28 (1H,m) and 2.42 (4H,q) (Found: C, 72.55; H, 8.85. $C_{26}H_{38}O_3S$ requires C, 72.5; H, 8.9%).

Buffered Acetolyses.- Each tosylate (1 g.) was heated at 100° for 6 hr. in dry acetic acid (50 ml.) containing sodium acetate (300 mg.). The mixture was then poured into water and extracted with ether three times. The extracts were combined, washed with saturated aqueous sodium hydrogen carbonate and then brine, and dried ($MgSO_4$). Removal of the solvent in vacuo left in each case a colourless oil which ran on analytical t.l.c. (ethyl acetate-light petroleum (1:9)) as two spots, one

of intermediate, the other of very low polarity. These oily products were each separated into olefinic and acetate fractions by chromatography over alumina (Grade I) with first light petroleum and then ether as eluent (for yields see footnote to Table I).

Olefins.- The mixtures of olefins from the norkauranol exo- and endo-tosylates (12;X=OTs) and (13;X=OTs) were separated by preparative t.l.c. on silica gel impregnated with silver nitrate (10%), with ethyl acetate-light petroleum (1:99) as developing solvent. Both substrates gave three olefins (for yields see Table II) identical (g.l.c., n.m.r. spectrum, and m.p.) with authentic samples of 17-norkaur-15-ene, 17-norphylloclad-15-ene, and 17-noratisir-13-ene. The only olefin isolated from the norphyllocladanol tosylates (7;X=OTs) and (9;X=OTs) was 17-norphylloclad-15-ene (10), again identified by

direct comparison with an authentic sample. The authentic samples were prepared by heating the tosylates (9;X=OTs), (12;X=OTs), and (18;X=OTs) in refluxing collidine for 30 min. 17-Norphylloclad-15-ene (10) gave plates, m.p. 71-72° (from aqueous methanol) (lit.,[59] 73°), τ 9.16, 9.20, and 9.27 (all 3H,s), and 4.23br (2H,s). (Found: C, 88.3; H, 11.7. $C_{19}H_{30}$ requires C, 88.3; H, 11.7%). 17-Norkaur-15-ene (16) crystallised on sublimation and had m.p. 33-36°, τ 8.98, 9.17, and 9.21 (all 3H,s), 4.50 (1H,d, J 6HZ), and 4.17 (1H,q, J 6 and 3Hz) (Found: C, 88.35; H, 11.8. $C_{19}H_{30}$ requires C, 88.3; H, 11.7%). 17-Noratisir-13-ene (17) after purification by preparative t.l.c. (SiO_2-$AgNO_3$ as before) and then sublimation had m.p. 41-46°, τ 9.10, 9.14, and 9.21 (all 3H,s), 4.60 (1H,q, J 10 and 4HZ), and 4.04 (1H,m), m/e 258.

Acetates.- The acetate fractions were separately converted into mixtures of alcohols by treatment with excess of lithium aluminium hydride in refluxing dry ether for 1 hr.

The alcohols from both norkauranol tosylates (13;X=OTs) and (12;X=OTs) ran in each case as five spots on t.l.c. (ethyl acetate-light petroleum (1:6) developed twice). Preparative t.l.c. gave five fractions which were treated as follows (in order of increasing polarity: the yields of the alcohols quoted in Table I were estimated from the quantities of each recovered from t.l.c.). Fraction one contained 17-norkauran-12-ol (34;X=OH), m.p. 127-129° (from ethyl acetate-light petroleum), τ 8.84, 9.18, and 9.21 (all 3H,s), and 6.30 (1H,m, $W_{\frac{1}{2}}$ 13 Hz) (Found: C, 82.5; H, 11.5. $C_{19}H_{32}O$ requires C, 82.55; H, 11.65%). Fraction

two gave 17-nor-atisiran-13α-ol (18;X=OH), m.p. 129-130° (from ethyl acetate-light petroleum), τ 9,00, 9.18, and 9.22 (all 3H,s), and 6.10 (1H,m, $W_{\frac{1}{2}}$ 20 Hz) (Found: C, 82.7; H, 11.8%). Fraction three gave 17-norphyllocladan-12-ol (enantio- (33;X=OH)), m.p. 144-146° (from ethyl acetate-light petroleum), τ 9.12, 9.17, and 9.21 (all 3H,s), and 6.22 (1H,m, $W_{\frac{1}{2}}$ 9 Hz) (Found: C 82.35; H, 11.65%). A portion of the fourth fraction after repeated preparative t.l.c. (ethyl acetate-light petroleum (3:17)) gave 17-norphyllocladan-16-ol (enantio- (9;X=OH)), m.p. 153-155° (from ethyl acetate-light petroleum), and 17-noratisiran-16β-ol (32;X=OH), m.p. 171-172° (from the same solvent), τ 9.18 (6H,s), 9.23 (3H,s), and 6.16 (1H,m, $W_{\frac{1}{2}}$ 22 Hz) (Found: C, 82.7; H, 11.7%). The separation process was not completely effective and the ratio of the two alcohols in the mixture was estimated by oxidation of another portion

of fraction four and separation of the resulting ketones by preparative t.l.c. The fifth fraction contained 17-norkauran-16α-ol (12;X=OH), m.p. 159-160° (from ethyl acetate-light petroleum).

The six alcohols were converted into the corresponding ketones with Jones reagent.[71] 17-Norkauran-12-one (28) had, after sublimation, m.p. 120-124° $[\alpha]_D$ -12° (c 0.1), $\nu_{max.}$ 1710 cm.$^{-1}$, τ 9.16 (6H,s) and 9.20 (3H,s) (Found: C, 83.0; H, 11.0. $C_{19}H_{30}O$ requires C, 83.15; H, 11.0%), 17-Noratisiran-13-one (23) had m.p. 123-125° (from methanol) (reported[60] m.p. of enantiomer 126-127°), $[\alpha]_D$ -37°, $\nu_{max.}$ 1725 cm.$^{-1}$, τ 9.14 (3H,s) and 9.21 (6H,s) (Found: C, 82.95; H, 11.25%). 17-Noratisiran-16-one (19) had m.p. 147-148° (from methanol) (reported[60] m.p. of enantiomer 145-146°), $[\alpha]_D$ -173°, $\nu_{max.}$ 1727 cm.$^{-1}$, τ 9.00, 9.15, and 9.18 (all 3H,s) (Found: C, 83.35; H, 11.25%). 17-Norphyllocladan-12-one (enantio- (27)) had,

after sublimation, m.p. 122-124°, $[\alpha]_D$ -51°, $\nu_{max.}$ 1710 cm.$^{-1}$ τ 9.14 (6H,s) and 9.20 (3H,s) (Found: C, 83.15; H, 10.95%). 17-Norphyllocladan-16-one (enantio- (8)) had m.p. 100-101° (from ethyl acetate), $[\alpha]_D$ -70°, $\nu_{max.}$ 1742 cm.$^{-1}$ τ 9.15 (6H,s) and 9.20 (3H,s). 17-Norkauran-16-one (15) had m.p. 113-115° (from methanol), $[\alpha]_D$ -23°, $\nu_{max.}$ 1742 cm.$^{-1}$ τ 8.91, 9.13, and 9.17 (all 3H,s).

The alcohols from the norphyllocladanol tosylates were separated as already described. The alcohols from the endo-substrate were identical in m.p., n.m.r. spectrum, and t.l.c. behaviour with those obtained from the norkauranol tosylates. The derived ketones were also identical in all respects except $[\alpha]_D$ value (similar magnitude but opposite sign in all cases) with those obtained previously. One additional alcohol, the norphyllocladan-15-ol (31:X=OH) was obtained (see Table I)

and had m.p. 124-126° (from aqueous methanol) (lit.,[59] 125-126°). The derived ketone (11) had m.p. 128-130° (from light petroleum) (lit.,[59] 132-133°), $[\alpha]_D$ -31°, $\nu_{max.}$ 1738 cm.,$^{-1}$ τ 9.18 (6H,s) and 9.21 (3H,s). The alcohols from the exo-norphyllocladanol tosylate were identified by their n.m.r. and t.l.c. behaviour and by conversion into the corresponding ketones and comparison of these with authentic samples by i.r. and t.l.c.

Preparation of 17-Noratisiran-16-one (enantio- (19)) from the Norphyllocladan-16-one (8).

The Lactone (20).- Hydrogen peroxide (1.1 ml.; 90%) was added to mixture of trifluoroacetic anhydride (5.3 g.) and methylene chloride (25 ml.) at 0°. After 1 hr. at 0° with stirring and with the exclusion of moisture, this solution was added slowly to a mixture of the norketone (1 g.) and anhydrous disodium hydrogen phosphate in methylene chloride (100 ml.) also at 0°. The reaction was allowed to warm to 20°, after which water was added

and the product (963 mg.) isolated with methylene chloride. Crystallisation from methanol afforded the lactone, m.p. 151-153° (lit.,[55,62] 50-154°).

Reduction of the Lactone (20).- The lactone (947 mg.) was heated in refluxing ether with lithium aluminium hydride for 2 hr. A slurry of sodium sulphate in water was added, and after the evolution of gas had ceased, the ether was dried with anhydrous sodium sulphate. Removal of drying agent and solvent afforded the diol (893 mg.) which crystallised from ether as needles, m.p. 168-171° (lit.,[55] 167-169°).

Oxidation of the Diol (21).- N-Bromoacetamide (1 g.) was added to the diol (806 mg.) in a mixture of acetone (80 ml.), methanol (20 ml.) and water (20 ml.). After 1 hr. in the dark the golden solution was stirred with

isopropanol (50 ml.) for one further hour in the dark. The solvent was then evaporated and the residue dissolved in ether and washed with water. After recovery, the ketol (530 mg.) was crystallised from ethyl acetate and had m.p. 152-155°., $\nu_{max.}$ 1740 cm.,$^{-1}$ τ 9.11, 9.15 and 9.19 (all 3H,s), and 6.25 (2H,m) (Found: C, 77.9; H, 11.05. $C_{19}H_{32}O_2$ requires C, 78.05; H, 11.05%).

The Tosylate (22;X=OTs) of the Ketol (22;X=OH).- Chilled solutions of the ketol (501 mg.) and toluene-p-sulphonyl chloride (610 mg.) in pyridine were mixed and after 5 hr. the derived tosylate was isolated by pouring the reaction into water and extracting with ether. This product (431 mg.) when crystallised from methanol had m.p. 156-157°, $[\alpha]_D$ +10°, τ 7.51, 9.10, 9.13 and 9.19 (all 3H,s), 5.85 (2H,m), and 2.38 (4H,q). (Found: C, 69.95; H, 8.7. $C_{26}H_{38}O_4S$ requires C, 69.95; H, 8.6%).

17-Noratisiran-16-one (enantio- (19)).- The tosylate (243 mg.) in anhydrous benzene (10 ml.) was stirred with potassium t-butoxide (0.26 g.) in t-butyl alcohol (10 ml.) for 2 hr. at 20°. The ketone (enantio- (19)) (153 mg.) was recoved with chloroform and had m.p. 147-148° (from light-petroleum) (lit.,[60] 145-146°), $[\alpha]_D$ +186°, τ 9.00, 9.15, and 9.18 (all 3H,s).

Preparation of 17-Noratisiran-13-one (23) from the Norkauran-16-one (15)

The Lactone (24).- The norketone (537 mg.) when treated with trifluoroacetic acid and hydrogen peroxide (90%), as described above for the norphyllocladanone, furnished the lactone (573 mg.) which crystallised as prisms m.p. 145-7° (from acetone) (lit.,[62] 146-148°).

Reduction of the Lactone.- The lactone (551 mg.) was heated in refluxing ether with lithium aluminium hydride for 2 hr. Work up afforded the diol (522 mg.) which was recrystallised from ether and had m.p. 154-156° (lit.,[62] 155-156°).

Oxidation of the Diol (25).- (The reaction on the kaurene-derived diol was attempted in the way described above for the phyllocladene-derived species. However, in this case a poor yield necessitated a revised mode of oxidation. The conditions which eventually proved successful were as follows). The diol (508 mg.) was dissolved in ethyl acetate (20 ml.) and methanol (6 drops), water (3 drops) and N-bromo-acetamide (625 mg.) were added. The reaction was allowed to stand in the dark at 20°, the formation of the ketol being followed by analytical t.l.c. After 30 min. the reaction had turned a deep golden colour and

t.l.c. revealed that the diol had been completely converted to the ketol. The reaction mixture was directly applied onto 10 preparative t.l.c. plates (20 cm. X 20 cm. X 0.5 mm.) (developing solvent, ethyl acetate-light-petroleum (1:4)). The ketol (438 mg.) isolated, on crystallisation from ethyl acetate gave needles, m.p. 90-92°. $\nu_{max.}$ 1710 cm.,$^{-1}$ τ 8.87 (3H,s), 9.11 (6H,s) and 6.12 (2H,m) (Found: C, 77.9; H, 11.0. $C_{19}H_{32}O_2$ requires C, 78.05; H, 11.05%).

The Tosylate (26;X=OTs) of the Ketol (26;X=OH).- The ketol (427 mg.) was converted to the derived tosylate (648 mg.) as above. Crystallisation of the product yielded needles which had m.p. 140-142° (from methanol). $[\alpha]_D$ +98°, τ 7.55, 8.91, 9.13 and 9.16 (all 3H,s), 5.92 (2H,t), and 2.40 (4H,q). (Found: C, 69.80; H, 8.53. $C_{26}H_{38}O_4S$ requires C, 69.95; H, 8.6%).

17-Noratisiran-13-one (23).- The above tosylate (631 mg.) was cyclised with base, as described above for the preparation of 17-noratisiran-16-one. The resulting ketone (376 mg.) on crystallisation had m.p. 124-125° (from light-petroleum) (reported[60] m.p. of enantiomer 126-127°), $[\alpha]_D$ -42°, τ 9.14, (3H,s) and 9.21 (6H,s).

17-Norkaurane (30).- The norkauranone (50 mg.) was heated in refluxing ethanol (3 ml.) containing hydrazine hydrate (1 ml.) for 30 min. Evaporation of the solvent under vacuum was followed by the addition of sublimed potassium t-butoxide (50 mg.) in dimethyl sulphoxide (4 ml.). After 30 min. of stirring the solution had turned orange, eventually becoming a deep red. Work up by addition of water and extraction with n-pentane and elution of the pentane layer through a short alumina column furnished the 17-norkaurane (32 mg.), m.p. 56-60°

(after sublimation). (Found: C, 87.8; H, 12.65. $C_{19}H_{32}$ requires C, 87.6; H, 12.4%). Reduction of 17-norkauran-12-one (28) under the same conditions gave a product with a g.l.c. retention time identical with that of 17-norkaurane.

17-Norphyllocladane (29).- The hydrocarbon (29)[59] derived as above from the ketone (8) had g.l.c. properties identical with those of the product derived in the same manner from the ketone (27).

(16 -^{2}H)-17-Norphyllocladan-16-ol.- The norketone (8) (302 mg.) was reduced with excess lithium aluminium deuteride in ether for 2 hr. Work up afforded the endo-/exo- mixture of alcohols (ca. 9:1) which were separated by preparative t.l.c. (ethyl acetate-light petroleum

(3:17)) into the two components, the more polar, the exo- isomer (28 mg.) was retained while the endo-alcohol (261 mg.) was oxidised with Jones reagent. The recovered ketone (8) (238 mg.) was reduced by the above procedure and the exo-alcohol (20 mg.) retained. The endo-alcohol was recycled once more to provide a further quantity (13 mg.) of the exo-alcohol. This alcohol (61 mg. in total) had m.p. 155-157°; τ 9.12, 9.16, and 9.20 (all 3H,s), no resonance ca. 6.0 τ.

The Tosylate of (16 -^{2}H)-17-Norphyllocladan-16-ol.- The above alcohol (61 mg.) when treated with a chilled solution of toluene-p-sulphonyl chloride in pyridine was transformed into the corresponding tosylate (82 mg.). This derivative on crystallisation from methanol had m.p. 132-134°, τ 7.56 (3H,s), 9.20 (6H,s), 9.25 (3H,s), and 2.42 (4H,q) no multiplet at 5.28 τ.

Buffered Acetolysis.- The above tosylate (73 mg.) was heated in acetic acid/sodium acetate as described above. The reaction was worked up and the product chromatographed over a short alumina column in light petroleum. Analytical t.l.c. on silica gel-10% silver nitrate (ethyl acetate-light petroleum (1:99)) and g.l.c. of the hydrocarbon fraction showed it to be essentially norphyllocladene. Crystallisation gave plates, m.p. 70-71° (from aqueous methanol), τ 9.16, 9.20, and 9.27 (all 3H,s) and a broad resonance at 4.23 τ (1H,s) (Found: M, 259.2426. $C_{19}H_{29}D$ requires M, 259.2431). Less than 2% $C_{19}H_{30}$ by mass spec.

(-)-Phyllocladene.- The ketone (enantio- (8)) (50 mg.) was treated with freshly prepared[61] methylenetriphenylphosphorane in ether. Work up and chromatography of the product over alumina (Grade I) in light petroleum gave (-)-phyllocladene (enantio- (14)) (21 mg.), which after

sublimation had m.p. 92-96°, $[\alpha]_D$ -12° (Found: C, 87.9; H, 11.8. $C_{20}H_{32}$ requires C, 88.15; H, 11.85%) identical in n.m.r., g.l.c., and t.l.c. (SiO_2-$AgNO_3$) behaviour with (+)-phyllocladene from Cryptomeria japonica.[56]

(-)-Neoatisirene.- 17-Noratisiran-13-one (23) (50 mg.) was converted into (-)-neoatisirene (39) (17 mg.) as described above and had m.p. 73-76° (from methanol), $[\alpha]_D$ -85° (reported[69] for enantiomer: m.p. 75-76°, $[\alpha]_D$ +89°), τ 9.14 (6H,s), 9.19 (3H,s), 5.47 (1H, narrow q), and 5.28br (1H,s) (Found: M, 272.2504. $C_{20}H_{32}$ requires M, 272.2504).

(-)-Atisirene.- 17-Noratisiran-16-one (19) (50 mg.) was converted into (-)-atisirene (33 mg.) as described before; it had m.p. 56-58° (from methanol), $[\alpha]_D$ -36°, identical in all respects with (-)-atisirene from Erythroxylon monogynum.[72]

TABLE I

Approximate composition (%) of acetate fraction* from buffered acetolysis of (12;X=OTs), (13;X=OTs), (9;X=OTs) and (7;X=OTs)

(All X=OAc)	(12;X=OTs)	(13;X=OTs)	(All X=OAc)	(9;X=OTs)	(7;X=OTs)
(12)	30	45	enantio- (12)	†	†
enantio- (9)	5	5	(9)	†	50
(18)	20	15	enantio- (18)	†	10
(32)	25	15	enantio- (32)	†	5
(34)	10	10	enantio- (34)	†	20
enantio- (33)	10	10	(33)	†	5
enantio- (31)	0	0	(31)	†	10

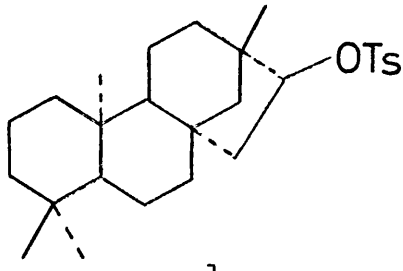
* Total yield of acetates formed from (12;X=OTs), 90%; (13;X=OTs), 85%; (9;X=OTs), 20%; (7;X=OTs), 75%. † Detected but yield not determined. Values accurate to ±3%. All these acetates were stable to the buffered acetolysis conditions.

TABLE II

Approximate composition of olefin* fraction (%)

	(12;X=OTs)	(13;X=OTs)		(9;X=OTs)	(7;X=OTs)
enantio- (10)	20	20	(10)	100	100
(16)	45	55			
(17)	35	25			

* All these olefins were stable to the buffered acetolysis conditions.



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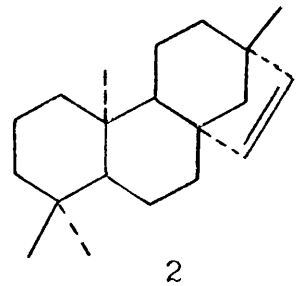

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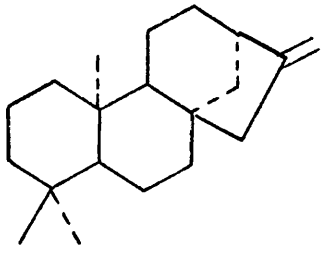

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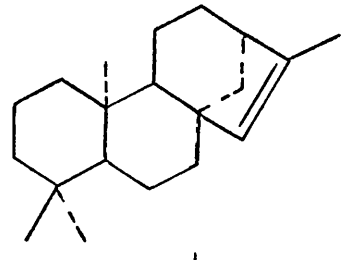

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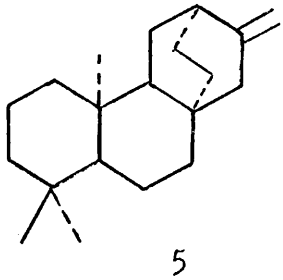

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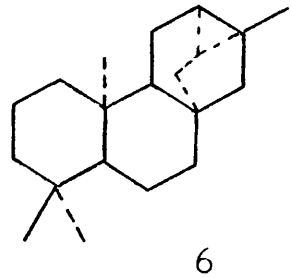

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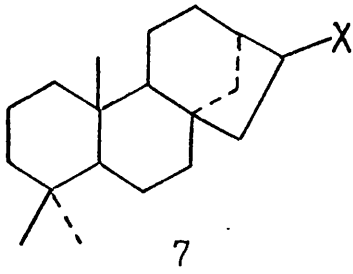

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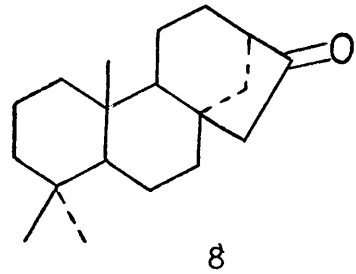

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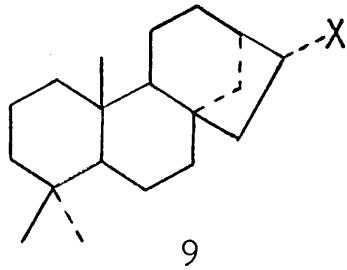

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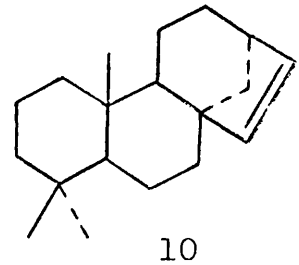

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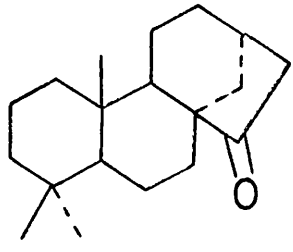

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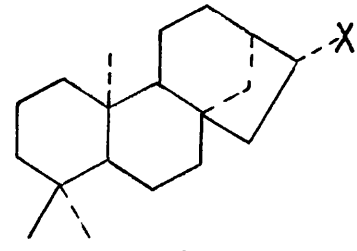

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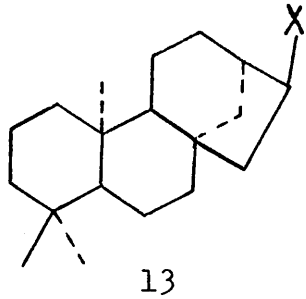

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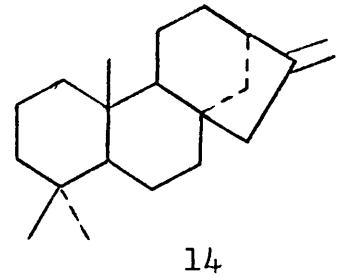

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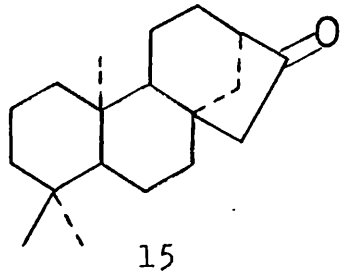

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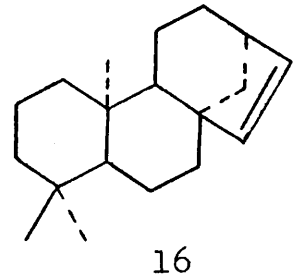

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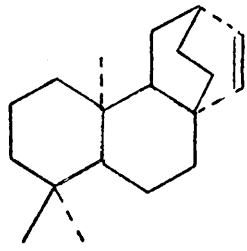

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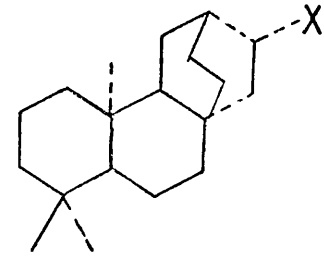

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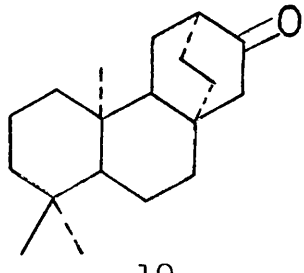

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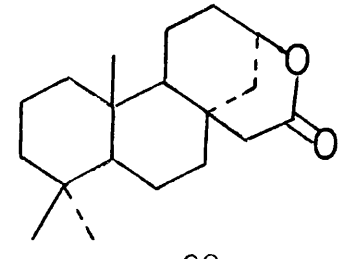

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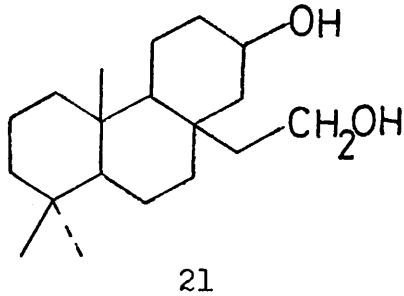

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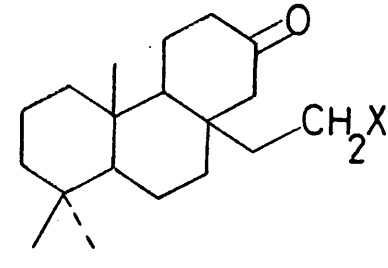

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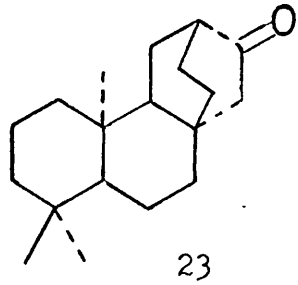

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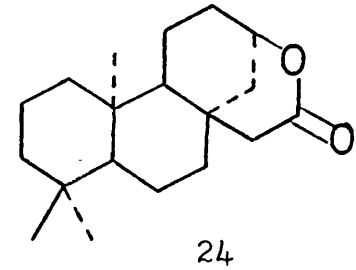

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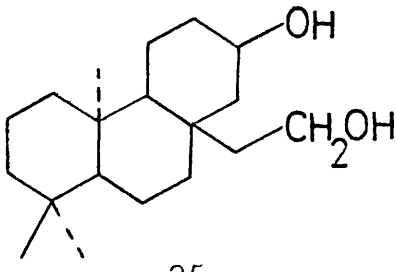

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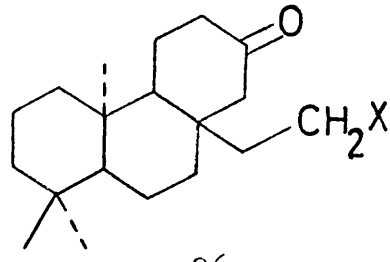

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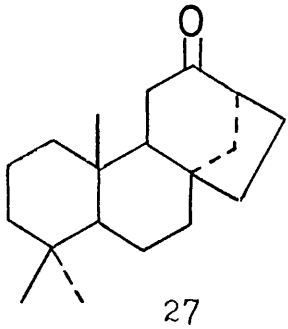

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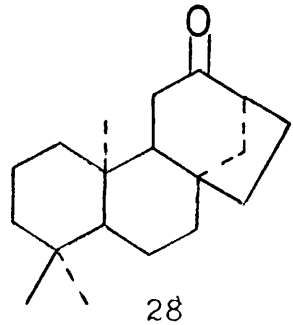

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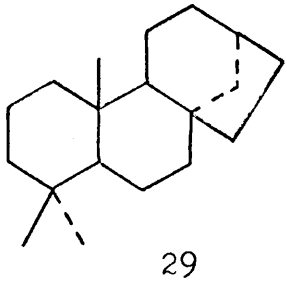

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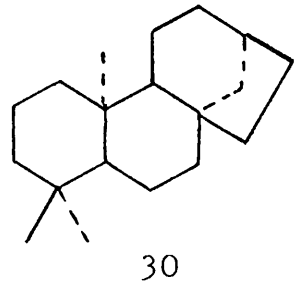

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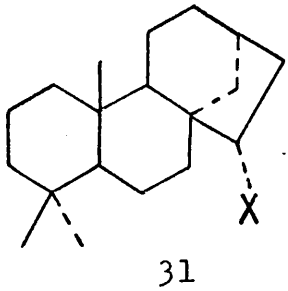

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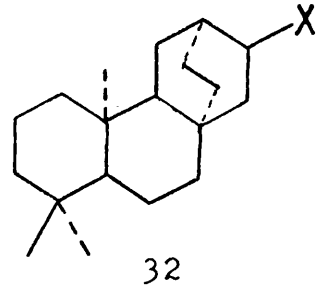

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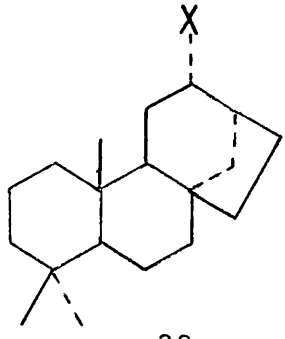

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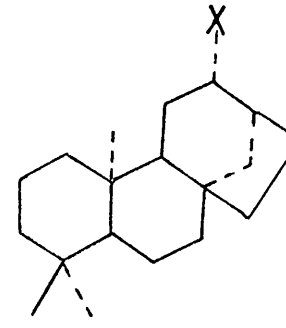

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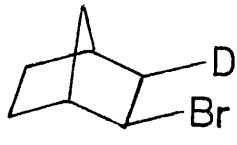

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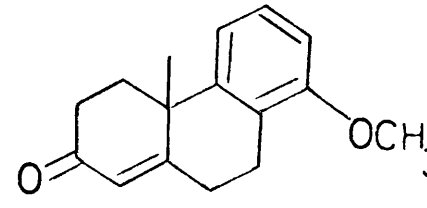

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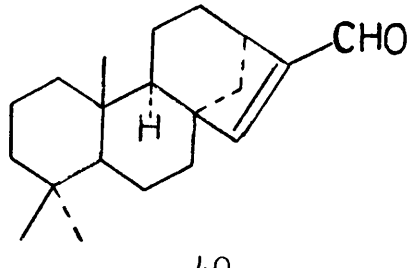

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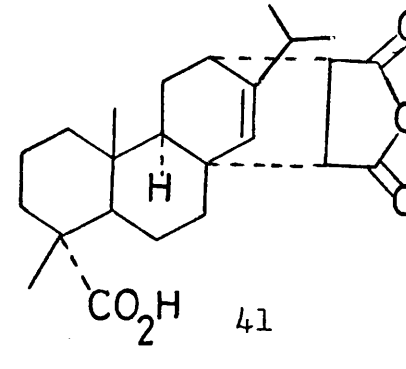

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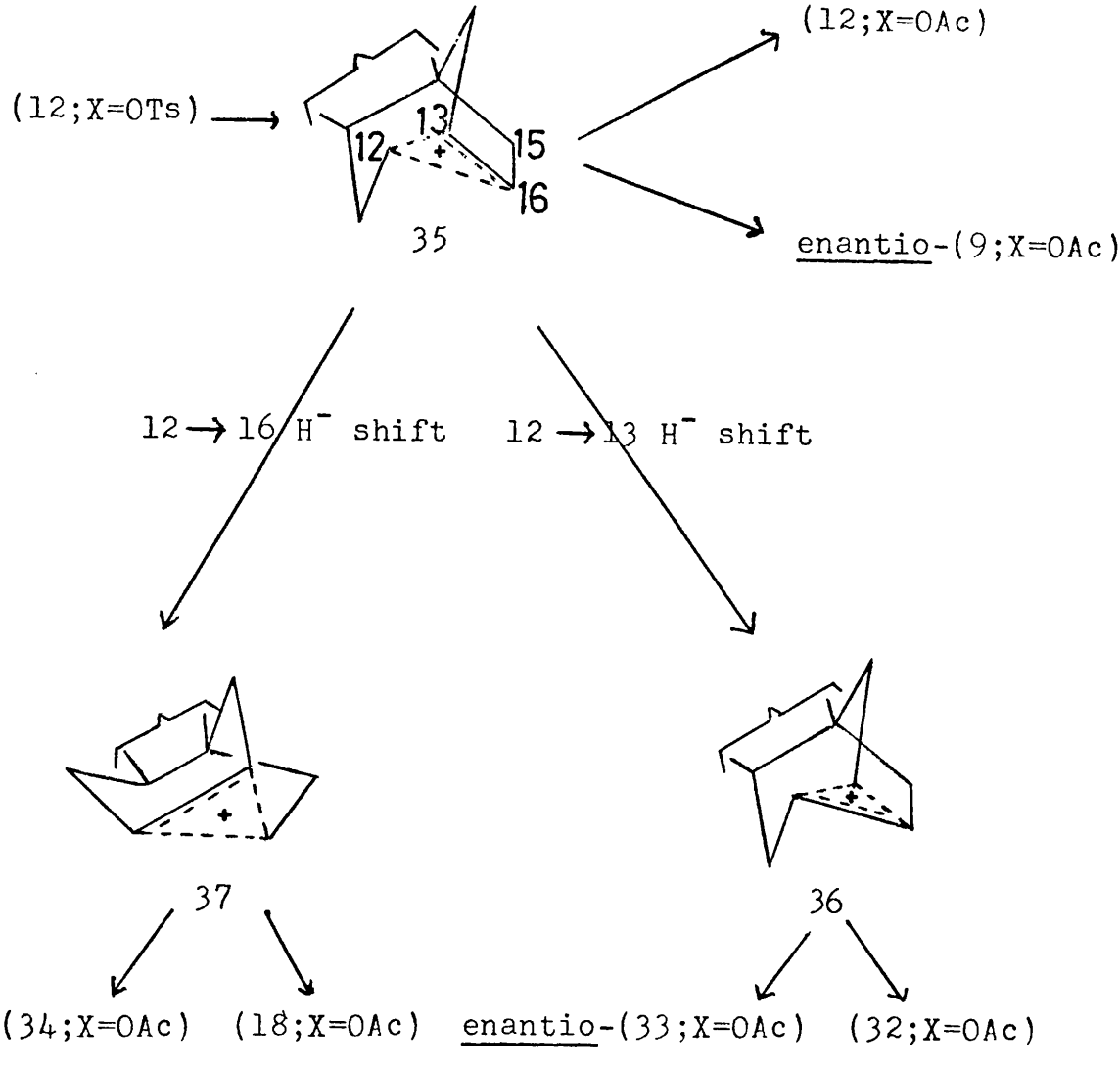
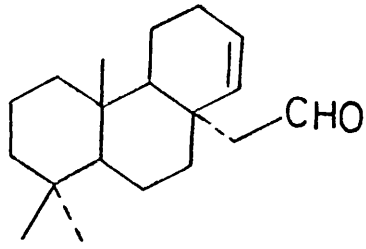

(12;X=OTs)
12
13
15
16
35
(12;X=OAc)
enantio-(9;X=OAc)
12 → 16 H⁻ shift
12 → 13 H⁻ shift
37
36
(34;X=OAc)
(18;X=OAc)
enantio-(33;X=OAc)
(32;X=OAc)

SCHEME



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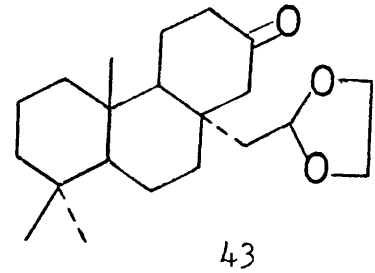

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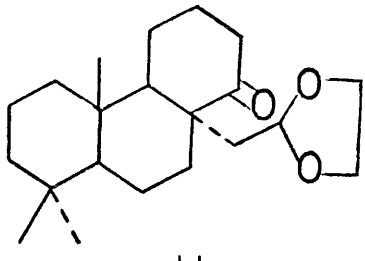

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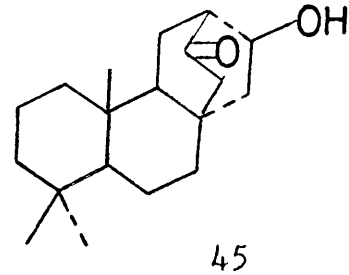

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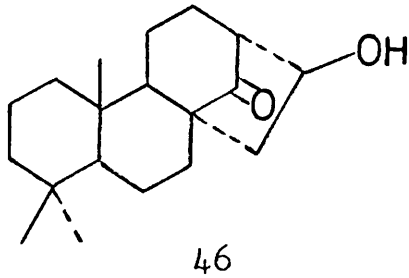

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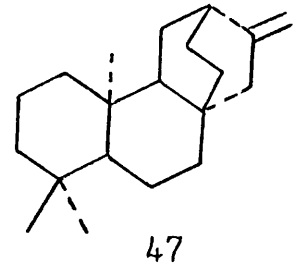


47

CHAPTER II

The Neoatisiranone from Isophyllocladene Epoxide

Several authors have reported the rearrangement of the hibane to the kaurane skeleton on treatment of hibaene epoxide with Lewis acids. In the first of these Kapadi and Dev[73] transformed 15β, 16β-epoxy-ent-hibane (1) with boron trifluoride etherate into ent-kaur-15-en-14β-ol (2). This rearrangement is to be expected in view of the results from the studies of the solvolysis of 16β-hibane esters (see Chapter I). The C-12, C-13 σ bond is ideally orientated to migrate from C-13 to C-16 as the epoxide ring opens with the production of a kaurane skeleton. Proton loss from C-15 of this carbonium ion leads to the product. Treatment of the enantiomeric epoxide, 15α, 16α-epoxyhibane (enantio-(1)) with the same reagent was reported[64] to give a minor amount of the 14α, 15β-diol (3) in addition to kaur-15-en-14α-ol (enantio- (2)), the former being the major product when the reaction was conducted in benzene saturated with water. The sole discrepancy in the various conversions of hibanes into kauranes is the formation[74] of the kaurene derivative (4) from 3α-acetoxy-15β, 16β-epoxy-hibane (5) rather than the expected endocyclic isomer.

This reaction has also been utilised in converting the norhibane into the norkaurane system. Nagata et al.[75] found that treatment of the 13-hydroxy-norhibane epoxide (6) with diethylaluminium chloride gave the corresponding norkauranolone (7).

In contrast to these results no skeletal rearrangement was observed on cleavage of the epoxide derived from isokaurene. Briggs et al.[62] found that treatment of 15α, 16α-epoxykaurane (8) with magnesium bromide etherate gave mainly kaur-16-en-15α-ol (9). In this case, opening of the epoxide ring is accompanied or followed by loss of a proton from C-17 with formation of a C-16, C-17 double bond.

Early attempts[59,62] to rearrange the phyllocladane skeleton involved acid-catalysed opening of the oxirane ring in isophyllocladene epoxide (10). The sole isolable product was 16-epiphyllocladan-15-one (11). The precise reasons for the wide divergence in product type when 15, 16-epoxykaurane and 15,16-epoxyphyllocladane are treated with magnesium bromide etherate are not clear. However, if the assumption is made that rings A, B, and C in both structures exist in all-chair (or near chair) conformations,

examination of molecular models shows that a considerable non-bonded interaction occurs between the 15-hydrogen and the 10-methyl group in 15,16-epoxyphyllocladane (12) but not in 15,16-epoxykaurane (13). Therefore a configurational driving force exists in the phyllocladane series which will favour relief of this non-bonded interaction. Thus in the case of 15,16-epoxyphyllocladane the formation of the ketone (11) by hydride shift[76] (C-15 to C-16) will be especially favoured since this allows C-15 to become trigonal.

We and others[44] have detected the presence of another ketone when 15,16-epoxyphyllocladane is subjected to boron trifluoride etherate. Buchanan and Davis have advanced a structure (14) for this product, mainly on the basis of spectroscopic data. We had come to the same conclusion as to its structure on nearly identical arguments (see below), which are however by no means compelling. This residual uncertainty has been resolved by the synthesis of its enantiomer from (-)-kaurene.

Starting Material: Phyllocladene (15) was isolated from C. japonica as described above (Chapter I). Treatment of this terpene with refluxing glacial acetic acid for

1 hr. furnished a mixture (1:4) of starting material and its endocyclic isomer, isophyllocladene (16). They were separated by preparative t.l.c. over silica gel impregnated with silver nitrate. 15α,16α-Epoxyphyllocladane (12) was prepared by treating isophyllocladene with m-chloroperbenzoic acid in carbon tetrachloride, the reagent attacking only from the less hindered α face of the molecule. Product purification was effected by column chromatography over alumina.

Results: The epoxide in ether was allowed to stand for 10 hr. in the dark in presence of boron trifluoride etherate and work up then afforded an oily residue. Analytical t.l.c. demonstrated the presence of two compounds in this product, the more polar having an identical mobility on t.l.c. to that of the starting epoxide. Preparative t.l.c. separated this mixture into the two components and their i.r. spectra revealed that both were ketones, the less polar having $\nu_{max.}$ 1732 cm.$^{-1}$ and the more polar $\nu_{max.}$ 1714 cm.$^{-1}$ The former was readily identified as 16-epiphyllocladan-15-one (11), its m.p., i.r., and n.m.r. characteristics being identical to those reported.[44,59,62]

The presence of a cyclohexanone in the more polar component was inferred from its i.r. absorption while resonances arising from a secondary and three tertiary methyls were clearly evident in its n.m.r. spectrum. The chemical shift values of methyl groups in carbonyl compounds change according to well defined rules,[77] on going from deuterio-chloroform to benzene as solvent. Therefore n.m.r. spectra of the compound were recorded in various benzene-deuterio-chloroform mixtures (see Table). These results show that only the chemical shift of the resonance attributed to the 17-methyl group alters appreciably, and in fact moves up-field with increasing concentration of benzene. This reinforces the assignment of structure (14) to the more polar product.

Discussion: The most likely mechanistic pathway to this ketone (14) from isophyllocladene epoxide involves in formal terms a fairly complex series of alkyl and hydride shifts, although recent evidence[45,46,78] from studies of the rearrangements of related compounds indicates that non-classical species are probably involved in this transformation. Thus, the non-classical ion (17) proposed by Davis and closely related to the ion (18)

suggested by Wenkert to be of biogenetic significance, may indeed participate in the rearrangement. However, in classical terms the conversion requires; (a) opening of the epoxide ring to give the tertiary ion (19), (b) migration of the σ 12-13 bond to C-16 to furnish the hibane related ion (20), (c) a 1-3 hydride shift from C-12 to C-16 in the latter and (d) rearrangement of the ion (21) produced via migration of the C-13, C-16 σ bond to C-12 to furnish the tertiary carbonium ion (22) which can (e) form the final product by hydride migration from C-14 to C-13 and loss of a boron trifluoride molecule. Because of the complexity of this formal pathway it appeared that more convincing evidence for the structure (14) was required.

The ketone was reduced with lithium aluminium hydride with the aim of dehydrating the resulting alcohol (23) to the known isoneoatisirene (24). Only one alcohol was formed in the reduction, and this is probably the β epimer as hydride attack would be expected to be more facile from the α - face. In its n.m.r. spectrum resonances arising from methyl groups appear at 8.98 τ (d) and 9.16 τ(s). A doublet at 6.95 τ(1H, J, 7 Hz) was observed and must

presumably be assigned to the carbinol proton, which on this basis must suffer a massive amount of shielding. Addition of deuterium oxide caused no change in the spectrum and excluded the possibility that the spin-spin splitting observed for the carbinol proton arose by coupling to the hydroxylic proton. In fact, double irradiation of an overlapping group of protons at 8.14 τ caused the doublet at 6.95 τ to collapse to a singlet and, at the same time, the doublet arising from the secondary methyl group at 8.98 τ also became a singlet and increased in intensity. Thus, it appears probable that the part structure $-CH(OH)-\underset{CH_3}{CH}-C$ is present in this alcohol, and this would be consistent with its derivation from a ketone of constitution (14). However, it is possible that the carbinol proton and the methyl group are each coupled to different protons, both of which have near identical chemical shifts.

In an initial attempt to dehydrate the neoatisiranol (23) it was heated with phosphoryl chloride in pyridine. However, the sole product (g.l.c.) was the olefin (25). This facile rearrangement may be attributed to (a) the

trans- antiparallel relationship of the bond linking the functional group to C-14 and the C-8, C-15 σ bond, and (b) the fact that as the rearrangement proceeds C-8 assumes trigonal character and this reduces the steric congestion associated with the C-10 β methyl group and the bicyclic moiety. However, a study of molecular models reveals that the α hydrogen atom on C-7 is not ideally aligned to undergo concerted elimination. The possibility that the rearrangement may proceed via a C-8 carbonium ion must then be considered. In this case proton loss from C-9 or C-7 might be expected to be of similar probability, the former being more likely on thermodynamic, the latter on kinetic, grounds.

Pelletier has observed[79] an analogous rearrangement when the alcohol (26) is treated with phosphorus tribromide-carbon tetrachloride, although he isolated a product (27) with the $\Delta^{8,9}$ double bond. In his case, migration of the syn- (to the C-10 methyl group) ethano bridge is involved. In this compound (26) the C-8, C-14 bond is trans- antiparallel with respect to the leaving group but now H-9 is ideally orientated to undergo concerted elimination as the C-8, C-14 bond migrates.

Pelletier obtained the same product (27) from solvolysis of the derived tosylate of (26). The β-epoxide (28) also suffered skeletal rearrangement when treated with sulphuric acid to furnish the unsaturated alcohol (29). The corresponding α-epoxide underwent the rearrangement but at a slower rate, as expected from the unfavourable bond orientation in the latter case. However, Pelletier did not observe products arising from C-8, C-9 bond migration to the C-15 position, which would have provided a means of converting the atisine (30) to the aconitine alkaloid skeleton[80,81] (31).

The formulation of the product as (25) in the rearrangement reported here can be substantiated as follows. Its n.m.r. spectrum reveals the presence of one vinyl proton (τ4.83) and significantly a secondary methyl group (τ9.20), while its mass spectrum defines the nature and location of the double bond. Thus the base peak at m/e 148 is produced by a retro-Diels-Alder fission of ring B (25a; arrows), the charge remaining on rings C-D. Confirmatory evidence for the constitution of the olefin (25) comes from its conversion into its tetrasubstituted isomer (32) by exposure to refluxing acetic acid.

It appeared possible that the absence of unrearranged olefin in the product of dehydration with phosphoryl chloride-pyridine could be ascribed to the orientation (cis) of the hydroxy group at C-14 with respect to H-13. Since there is some evidence[82] that phosphorus trichloride-benzene may furnish products of cis- dehydration, the alcohol (23) was subjected to these conditions. Again only the rearranged olefin (25) was formed. A further attempt to effect the desired conversion via pyrolysis of a carbonate[83] of (23) was also unsuccessful. Treatment of the alcohol with ethyl chloroformate in pyridine at -10° and work up gave as the only isolable products the two rearranged olefins (25) and (32) in the ratio 7:3, although the crude product did contain ca. 1% of material which has the same g.l.c. retention time as isoneoatisirene.

In an attempt to convert the ketone (14) directly into isoneoatisirene its tosyl hydrazone was prepared by treatment of the ketone with toluene-p-sulphonyl hydrazine in refluxing ethanol and the crude product was stirred with methyllithium in ether.[84] However, the oily product contained no identifiable diterpenes.

Since convincing evidence for the constitution and stereochemistry of the ketone (14) was not obtained from the experiments discussed above a synthesis of an authentic specimen of the ketone was undertaken to allow direct comparison.

(-)-Kaurene was converted into (-)-neoatisirene *via* the lactone, diol, ketol, ketol tosylate and ketone as described previously (Chapter I). The (-)-neoatisirene was isomerised to the endocyclic species (24) by heating in refluxing glacial acetic acid for 3 hr.[70] Hydroboration[85,86] of this hydrocarbon (*enantio*- (24)) gave mainly one product as expected, the reagent attacking only from the less hindered β face. Oxidation of this alcohol (33) furnished the corresponding ketone (34), which has the 17-methyl group in the more congested α - configuration. This compound on subjection to sodium methoxide in methanol for 90 min. underwent epimerisation at C-16 to give the thermodynamically more stable ketone. This product (*enantio*- (14)) proved to be identical in all but one respect to the ketone (14) obtained from the rearrangement of 15α,16α-phyllocladane epoxide. The sole difference between these two ketones was the sign

of rotation. The synthetic ketone (<u>enantio</u>- (14)) had $[\alpha]_D$ +25°, its optical rotatory dispersion (O.R.D.) curve displaying a positive Cotton effect, whereas the ketone (14) derived from the rearrangement had $[\alpha]_D$ -28°, its O.R.D. curve showing a negative Cotton effect. This synthesis constitutes an unambiguous proof of the constitution and stereochemistry of the ketone (14).

EXPERIMENTAL

(+)-Isophyllocladene (16).- Phyllocladene (1 g.) was isolated as described above from the foliage of C. japonica and treated with refluxing chloroform (100 ml.) and concentrated hydrochloric acid (25 ml.). Analytical t.l.c. and g.l.c. indicated ca. 80% conversion to the endocyclic isomer. Recovery with chloroform followed by preparative t.l.c. of the hydrocarbon mixture over silica gel - silver nitrate (9:1) (ethyl acetate-light petroleum (1:49)) afforded isophyllocladene (840 mg.) which on crystallisation from ethanol had m.p. 110-111° (lit.,[87] 107-109°).

Isophyllocladene epoxide (10).- Isophyllocladene (832 mg.) was dissolved in carbon tetrachloride (100 ml.) and m-chloroperbenzoic acid (1 g.) added. The mixture was allowed to stand in the dark at 20°, the progress of the reaction being followed by analytical t.l.c. After 3 hr.

the reaction was worked up by filtration through an alumina column and elution with carbon tetrachloride and ether - carbon tetrachloride (1:1) to yield 15,16-epoxyphyllocladane (706 mg.) as a white solid. Crystallisation from light petroleum afforded plates, m.p. 92-93° (lit.,[62] 93°) τ 7.03 (1H), 9.11, 9.21, and 9.26 (all 3H,s).

Rearrangement of Isophyllocladene Epoxide.- Isophyllocladene epoxide (10) (500 mg.) was dissolved in anhydrous ether (200 ml.) and boron trifluoride etherate (3 ml.) added. After 10 hr. at 20° the reaction mixture was poured into water (100 ml.). The layers were separated and the aqueous phase extracted with ether (50 ml.). The combined ethereal extracts were washed with brine and dried over anhydrous magnesium sulphate. Evaporation of the solvent afforded an oil (410 mg.) which was

separated into two components by preparative t.l.c. (ethyl acetate-light petroleum (1:49)). The less polar of these after crystallisation from methanol furnished phyllocladan-15-one (11) (261 mg.), m.p. 128-129° (lit.,[59] 127-129°), $\nu_{max.}$ 1732 cm.$^{-1}$ τ 8.98 (3H,d, J, 7Hz), 9.18, 9.20, 9.26 (all 3H,s). The more polar component (same mobility on t.l.c. as isophyllocladene epoxide) crystallised from methanol as colourless plates of the neoatisiran-14-one (14) (123 mg.), m.p. 135-137° (lit.,[44] 137°), $[\alpha]_D$ -28°, O.R.D. $[\alpha]^{trough}_{308}$ - 65 °, $[\alpha]^{peak}_{268}$ + 91 °, $\nu_{max.}$ 1714 cm.$^{-1}$ τ8.92 (3H,s, J, 7Hz), 9.18, 9.24, 9.36 (all 3H,s).

Reduction of the Neoatisiran-14-one (14).- The ketone (14) (107 mg.) was treated with excess lithium aluminium hydride in refluxing ether for 2 hr. Work up and crystallisation of the product from aqueous ethanol

afforded the alcohol (23) (104 mg.), m.p. 156-157° (lit.,[44] 156-158°), $[\alpha]_D$ +11°, τ 6.95 (1H,d, J,6Hz), 8.99 (3H,d, J, 7Hz), 8.99 (3H,s), 9.16 (6H,s).

Dehydration of the Alcohol (23) with Phosphoryl Chloride-Pyridine.- The alcohol (23) (93 mg.) was heated with phosphoryl chloride (2 ml.) in refluxing dry pyridine (10 ml.) for 2 hr. The reaction mixture was cooled and poured into ice-water (40 ml.) and extracted with ether (50 ml.). The organic layer was separated, washed with water and dried. Evaporation of the solvent left as an oily residue (73 mg.) (essentially one product (g.l.c.)) which after preparative t.l.c. on silica gel - silver nitrate (9:1) (ethyl acetate-light petroleum (1:24)) and sublimation afforded colourless plates of the olefin (25), m.p. 103-105°, τ 4.83 (1H,m), 9.20 (3H,d, J, 7Hz), 9.11, 9.14, 9.23 (all 3H,s) (Found: M 272.2499. $C_{20}H_{32}$ requires M 272.2504).

Dehydration of the Alcohol (23) with Phosphorous Trichloride-Benzene.- Using an analogous procedure to that described above for the dehydration with phosphoryl chloride-pyridine the sole product was again the olefin (25).

Treatment of the Alcohol (23) with Ethyl Chloroformate-Pyridine.- Redistilled ethyl chloroformate (1 ml.) was added dropwise to a stirred solution of the alcohol (23) (15 mg.) in pyridine (5 ml.) at -10°. After one hr. at -10° and 12 hr. at 0°, the product (11 mg.) was recovered by pouring into water and extraction with ether. Examination by g.l.c. and t.l.c. (silica gel - silver nitrate) showed the presence of materials with retention times and mobilities identical to the olefin (25) (ca. 70%), its isomer (32) (ca. 30%), and isoneoatisirene (24) (ca. 1%).

The Toluene-p-Sulphonyl Hydrazone of Ketone (14).- The ketone (14) (11 mg.) was treated with excess toluene-p-sulphonyl hydrazine in refluxing ethanol (2 ml.) for 1 hr. Addition of water followed by isolation with ether afforded the product which was dissolved in ether (2 ml.) and excess methyllithium etherate added. The resulting cloudy mixture was stirred for 15 min. at 20°. Isolation of the product with ether followed by analytical t.l.c. (silica gel - silver nitrate) and g.l.c. showed the absence of diterpenes.

Acid Catalysed Isomerisation of the Olefin (25).- The hydrocarbon (25) (32 mg.) was heated in refluxing glacial acetic acid (10 ml.) and the course of the reaction followed by the work up and g.l.c. analysis of aliquots taken every 24 hr. After 7 days, when ca. 75% conversion into the tetra-substituted double bond isomer (32) had

been effected the reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with an aqueous solution of sodium bicarbonate, dried, and the solvent evaporated. The oily residue (25 mg.) was fractionated by preparative g.l.c. and the olefin (32) obtained as an oil, τ 9.18 (3H,d, J, 7Hz), 9.05 (3H,s), 9.11 (6H,s), no olefinic proton(s) (Found: M 272.2507. $C_{20}H_{32}$ requires M 272.2504).

(-)-Isoneoatisirene.- Neoatisirene (35) (256 mg.) was heated in refluxing glacial acetic acid (10 ml.) and the progress of the reaction followed by analysis of aliquots by g.l.c. After 3 hr., conversions into the endocyclic isomer was complete and the reaction mixture was poured into water and extracted with ether. This extract was washed with an aqueous solution of sodium bicarbonate and dried and the solvent evaporated. Preparative t.l.c. of

the oily residue over silica gel - silver nitrate (9:1) (ethyl acetate-light petroleum (1:49)) afforded isoneoatisirene (enantio- (24)) (207 mg.), m.p. 73-75° (from methanol) (lit.,[70] 76-77°).

Hydroboration of Isoneoatisirene.- Boron trifluoride etherate (3.2 ml.) was added to a stirred solution of isoneoatisirene (enantio- (24)) (207 mg.) in ether (20 ml.) under nitrogen. Excess lithium aluminium hydride in ether was then added dropwise and the resulting mixture stirred at 20° for 2 hr. Work up with a saturated aqueous solution of sodium sulphate and evaporation of the solvent left a residue which was redissolved in ethanolic sodium hydroxide (32 ml., 3M). Hydrogen peroxide (25 ml., 30%) was added dropwise under nitrogen to this solution with stirring. After 12 hr. at 20° the product was recovered with chloroform and purified

by preparative t.l.c. The resulting alcohol (33) (198 mg.), on crystallisation from ethanol - water formed colourless needles, m.p. 102-104°, τ 6.37 (1H,m), 8.90 (3H,d, J, 6Hz), 9.06, 9.12, 9.17 (all 3H,s). (Found: C, 82.75; H, 11.7. $C_{20}H_{34}O$ requires C, 82.7; H, 11.8%).

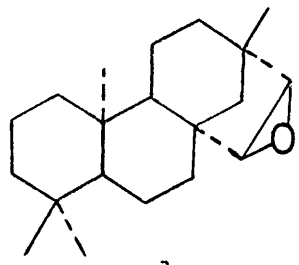
The Ketone (34).- The alcohol (33) (131 mg.) was oxidised by the Jones technique[71] and the crude product (103 mg.) purified by preparative t.l.c. (ethyl acetate-light petroleum (1:49)) and crystallisation from methanol. The ketone (34) obtained had m.p. 128-130°, $\nu_{max.}$ 1709 cm.,$^{-1}$ τ 8.83 (3H,d, J, 7Hz), 9.13, 9.20, 9.37 (all 3H,s) (Found: C, 83.25; H, 11.1. $C_{20}H_{32}O$ requires C, 83.25; H, 11.2%).

The Ketone (enantio- (14)).- The ketone (34) (100 mg.) was heated with sodium hydroxide (250 mg.) in refluxing methanol for 90 min. The product was recovered with chloroform and crystallised from methanol as colourless plates of the ketone (enantio- (14)) (84 mg.), m.p. 135-137°, $[\alpha]_D$ +25° O.R.D. $[\phi]_{309}^{peak}$ + 643°, $[\phi]_{271}^{trough}$ - 925°, $\nu_{max.}$ 1714 cm.,$^{-1}$ (Found: C, 83.15; H, 10.95. $C_{20}H_{32}O$ requires C, 83.25; H, 11.2%), identical n.m.r. and t.l.c. behaviour to that of ketone (14).

TABLE

Solvent	20 Me.	18 Me.	19 Me.	17 Me.
100% Benzene (100 Mc/sec.)	9.36	9.27	9.19	9.03
100% Benzene (60 Mc/sec.)	9.36	9.24	9.16	9.04
50% Benzene (100 Mc/sec.)	9.38	9.23	9.20	8.98
25% Benzene (100 Mc/sec.)	9.38	9.22	9.16	8.93
100% $CDCl_3$ (100 Mc/sec.)	9.36	9.24	9.18	8.92
100% $CDCl_3$ (60 Mc/sec.)	9.32	9.20	9.12	8.82
Reported values	9.36	9.20	9.14	8.95

The Chemical Shifts of C(17), C(18), C(19), and C(20) Methyl Groups of (14) in Various Solvent Systems



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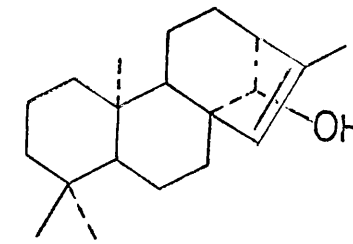

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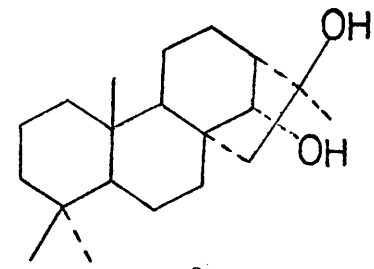

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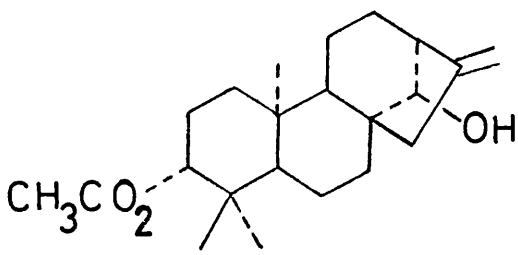

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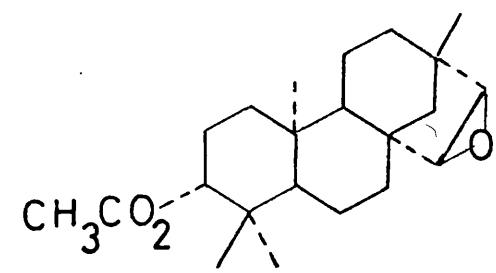

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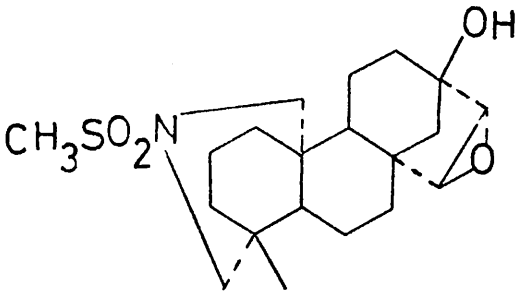

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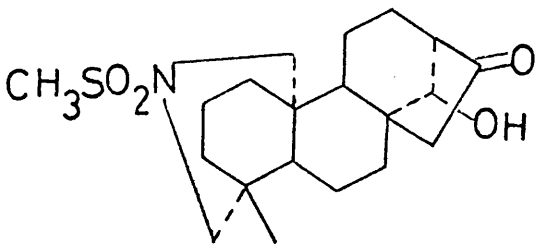

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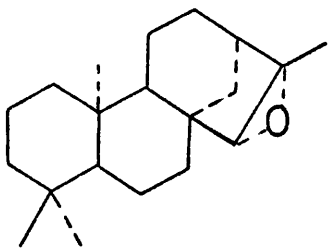

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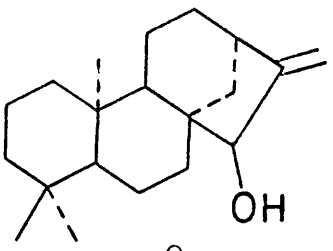

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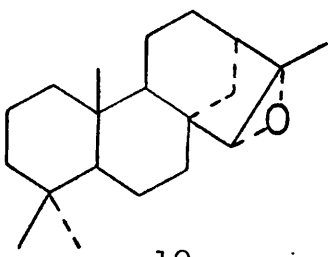

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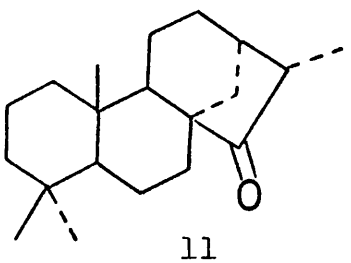

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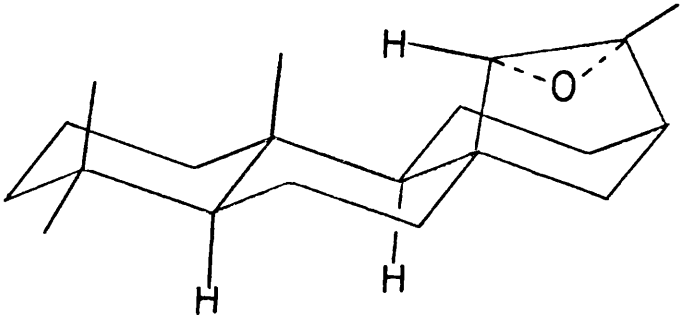

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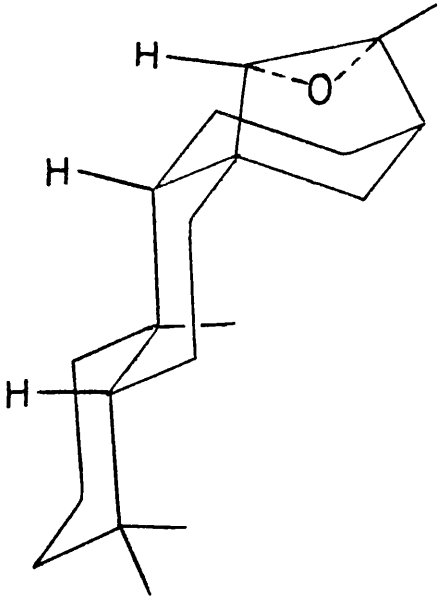

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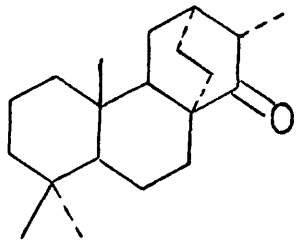

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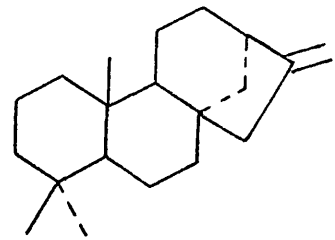

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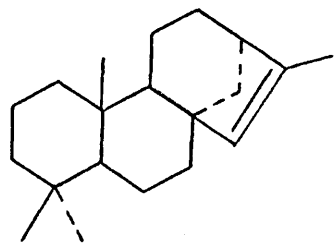

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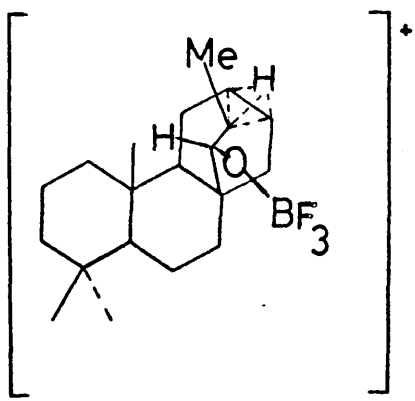

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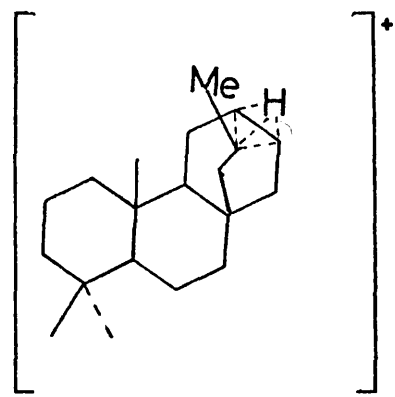

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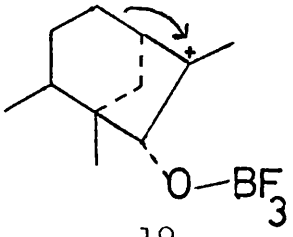

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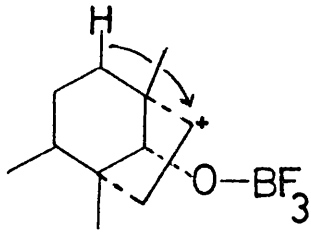

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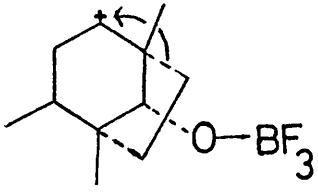

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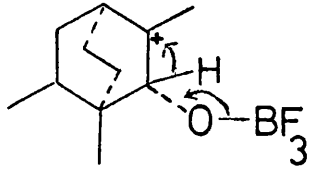

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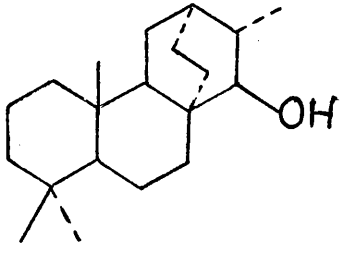

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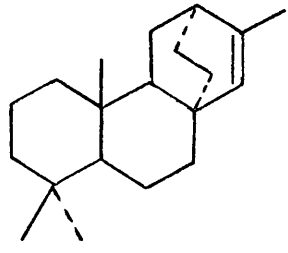

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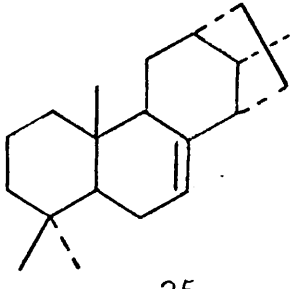

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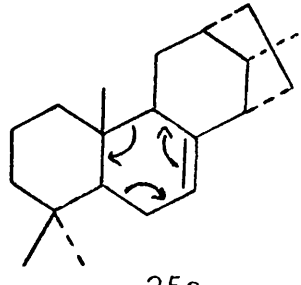

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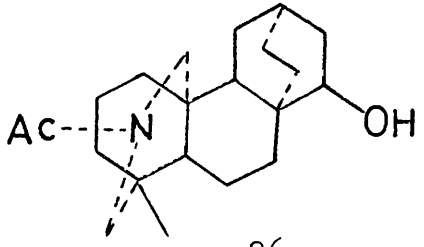

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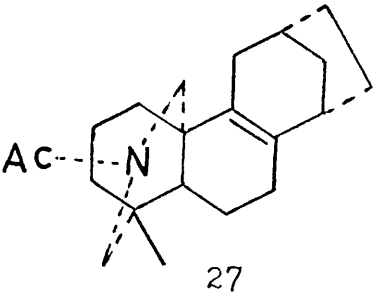

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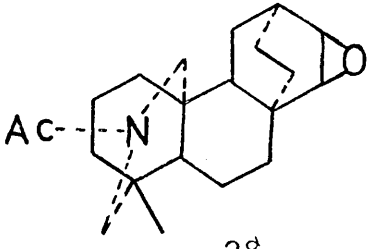

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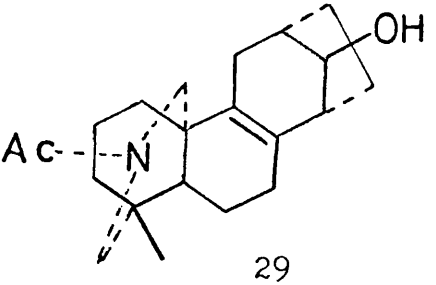

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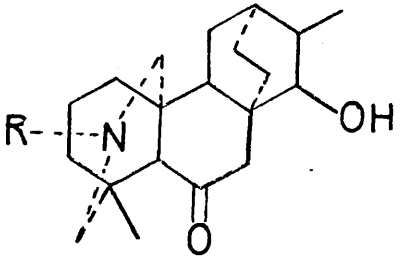

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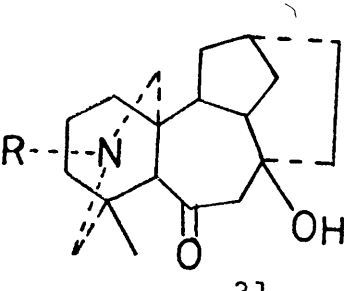

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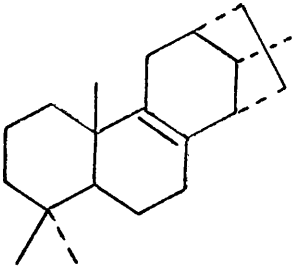

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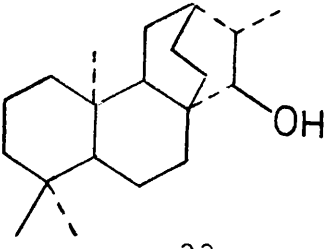

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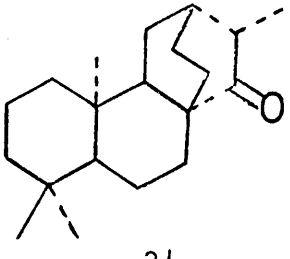

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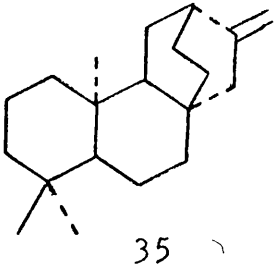

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CHAPTER III

Acid-Catalysed Rearrangement of Phyllocladene

The steviol-isosteviol rearrangement[88] (1 → 2) was the first example of the acid-catalysed conversion of a kaurane derivative into a diterpenoid of a different skeletal class. This reaction was employed by Ireland and co-workers in their synthesis of hibaene[89] (3). Although this rearrangement involves the electronically unfavourable conversion of a tertiary into a secondary carbonium ion, by migration of the C-12, C-13 bond (in 1) to C-16, the availability of electrons from the O-H bond in the substrate and the formation of a carbonyl group in the product renders the reaction viable. Numerous examples of an analogous rearrangement are known in the gibberellin series, e.g. gibberellic acid (4) and allo-gibberic acid (5) in refluxing hydrochloric acid give the rearranged product, gibberic acid (6).[90-92] Nagata and co-workers in their synthetic route to the diterpenoid alkaloids[75] prepared an intermediate possessing the nor-hibaene skeleton (7) which they expected to undergo a similar type of acid-catalysed rearrangement to the nor-kauranone (8). However, they did not attempt this conversion as the rearrangement did not occur when a

model system (9⟶10) was treated with refluxing acid. The authors suggested that the absence of rearranged products could be attributed to the fact that protonation occured preferentially at C-3a. The resulting carbonium ion, which is incapable of rearrangement would be less hindered than that produced by protonation at C-5a. On this basis they predicted protonation of the norhibaene (7) to occur at C-16 rather than C-15. To force carbonium ion formation at C-16 the 16-p-bromobenzenesulphonate (11) was prepared and solvolysed. This did indeed furnish the rearranged product (8).

The acid-catalysed rearrangement of kaurene (12) itself into derivatives of hibaene has been attempted. All the products isolated after treatment of kaurene with refluxing formic acid did in fact possess the hibane skeleton. Apart from starting material, only formates, three in all (13), (14), and (15), were isolable after 30 min. However, prolonged acid treatment resulted in the formation of a mixture of (+)-hibaene (3), (-)-kaurene (12), (-)-isokaurene (16) and (-)-isoatisirene (17). An identical (g.l.c.) mixture of hydrocarbons was also produced by prolonged treatment of hibaene with formic acid. This

suggests that these processes are attaining thermodynamic equilibrium.

In a study[93] which extended this investigation, kaurene, hibaene, atisirene (18), and trachylobane (19), were treated with hydrochloric acid in chloroform. The results (Introduction, Table I) obtained bear out the initial suggestion that the in vitro acid-catalysed rearrangement of the tetracyclic diterpenes is possible, at least in the pimaradiene - derived series. Under the conditions employed, however, the rate of interconversion of distinct skeletal types was so slow as to preclude the attainment of equilibrium among them. Furthermore, although it was impossible from these results to define the nature of the intermediates, it was concluded that since the (iso)atisirene : (iso)kaurene ratio was substantially different, depending on whether the mixture is derived from hibaene or trachylobane there cannot be any unique intermediate (e.g. the hydrogen-bridged ion (20)) in these isomerisations.

As yet no analogous interconversions have been reported in the isopimaradiene - derived series. However, as the acid-catalysed rearrangement of (+)-phyllocladene (21)

would provide isohibaene (22), which is not readily available otherwise, an attempt to effect this interconversion was undertaken.

Starting Material: (+)-Phyllocladene (21) was isolated and purified as previously described (Chapter I) and subjected to treatment with formic acid in refluxing chloroform.

Results: The composition of the resulting product mixture appears to be invariable with the length of reaction time. Thus, the two formates, (23) and (24), obtained after 30 min. were also isolated in the same yield (ca. 85%) after prolonged acid treatment (ca. 4 days). These formates were not readily separable by preparative t.l.c. and they were therefore reduced by lithium aluminium hydride in refluxing ether to the corresponding alcohols which were separated into the two components without difficulty by this technique. The less polar alcohol (25), had in its n.m.r. spectrum, resonances arising from four tertiary methyl groups at 9.10, 9.17, 9.20, and 8.70 τ. The downfield nature of the chemical shift of the last indicates that this methyl group is attached to the carbon atom bearing the hydroxyl function. This

conclusion is substantiated by the lack of resonances attributable to a carbinol proton. This evidence allows the assignment of the constitution (25) to the less polar alcohol. Verification of this and proof of the stereochemistry at C-16 was obtained by comparison of the alcohol with a sample of phyllocladanol (25) isolated from Cryptomeria japonica.[94]

The n.m.r. spectrum of the less polar alcohol displayed resonances from three tertiary methyl groups at 9.10, 9.13, and 9.18 τ, a secondary methyl group at 8.87 τ, and a carbinol proton (broad multiplet) at 5.06 τ. This evidence led to the allocation of the structure (26) to the alcohol and indeed its physical and spectral properties matched those recorded for phyllocladan-15α-ol[55] (26).

Investigation of the hydrocarbon fractions from these reactions by g.l.c. was largely unsuccessful in determining the presence of rearranged skeletal types. The major hydrocarbon from each reaction was isophyllocladene (27), together with a trace of phyllocladene (21).

Discussion: The complete absence of skeletally rearranged products from the acid treatment of phyllocladene is at first sight perhaps surprising. The formation of the isohibane system should be favoured sterically because this would allow a marked reduction in the severe crowding between the C-15 *endo* proton and the C-10 methyl group in phyllocladene. However, this rearrangement would involve a Wagner-Meerwein bond migration which converts the initially formed tertiary ion (28) into the secondary carbonium ion (29), an energetically unfavourable process. Thus the only products isolated from the various formic acid experiments, the formates (23), and (24) and the hydrocarbons (27), and (21) can be regarded as arising from protonation of phyllocladene with generation of the tertiary ion (28). This can either lose a proton from C-17 or C-15 to give rise to phyllocladene and isophyllocladene respectively, or suffer solvent capture at C-16 to form the tertiary formate (23). The secondary formate (24) is presumably derived from the carbonium ion (30), which could be produced either by a C-15 to C-16 hydride shift in (28), or by an elimination reprotonation mechanism *via* isophyllocladene. The former possibility

would also involve the conversion of a tertiary into a secondary carbonium ion, however, in this case the relief in steric compression as C-15 becomes trigonal might make such a transformation energetically favourable. No attempt has been made to seek evidence which might allow a decision as to the pathway(s) involved.

This study did not succeed in providing a simple method for converting phyllocladene into isohibaene, and the failure can not be ascribed to the conditions chosen, formate anion being a poor nucleophile. The type of products obtained would have been expected had a stronger nucleophile been employed, but in this medium of high solvating power rearrangement was anticipated, the intermediate ion(s) being allowed a longer life and hence a greater opportunity to rearrange.

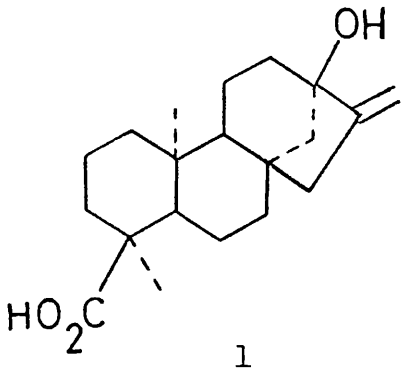
Thus it seems likely that the phyllocladane skeleton is incapable of rearrangement under simple acid treatment although numerous rearrangements of phyllocladene derivatives are now known (e.g. Chapters I and II) under different conditions.

EXPERIMENTAL

Formic Acid Treatment of Phyllocladene.- Phyllocladene (21) (70 mg.) was dissolved in chloroform (1 ml.) and formic acid (5 ml.) added. This mixture was refluxed for 30 min. Evaporation of the solvent left an oily residue (80 mg.) containing two components (t.l.c.), one of very low and the other of intermediate polarity. The low polarity fraction was purified by preparative t.l.c. and shown to be mainly isophyllocladene containing a trace of phyllocladene (g.l.c.). The other fraction could not be resolved into separate components by t.l.c.

Reduction of the Formates.- The formates (68 mg.) were reduced by treatment with lithium aluminium hydride in refluxing ether. Work up afforded a white solid (43 mg.) which was separated by preparative t.l.c. into two components. The less polar alcohol (25) had m.p. 184-185° (lit.,[94] 184-185°) (from methanol), τ 8.70, 9.10, 9.17,

and 9.20 (all 3H,s). The other alcohol (27) had m.p. 112-114° (lit.,[55] 114-115°), τ 9.10, 9.13, and 9.18 (all 3H,s) and 8.87 (3H, d, J = 7Hz), 5.06 (1H,m). The experiment was repeated with phyllocladene (140 mg.) but the reaction time was extended to 4 days. Work up afforded formates (103 mg.) and hydrocarbons (15 mg.). The latter had an identical composition (g.l.c.) to that obtained previously, while the other fraction after reduction to the alcohols (72 mg.) and separation as before yielded (25) (26 mg.) and (27) (21 mg.).



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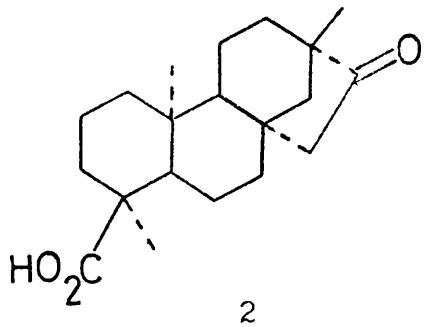

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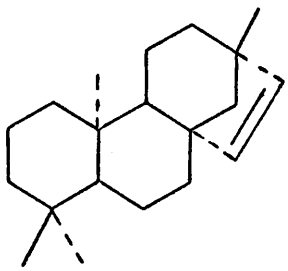

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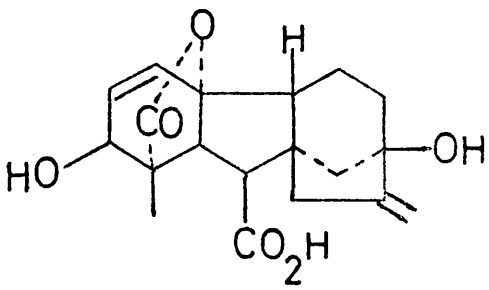

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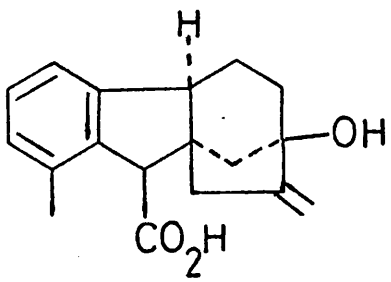

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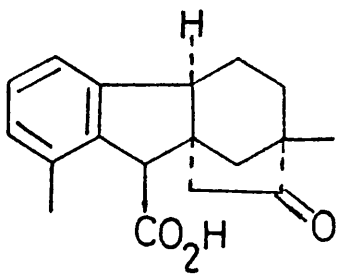

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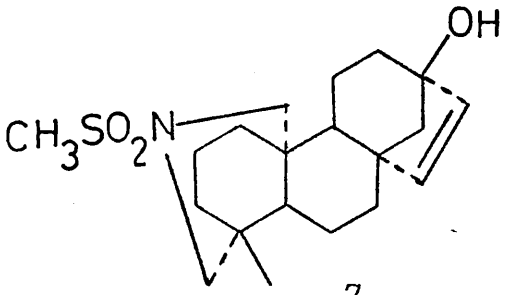

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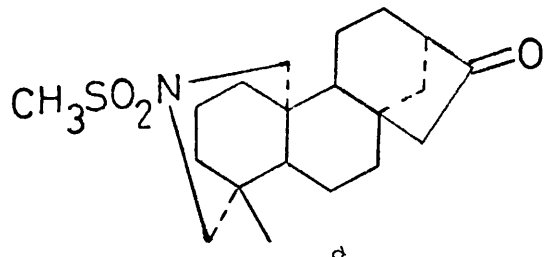

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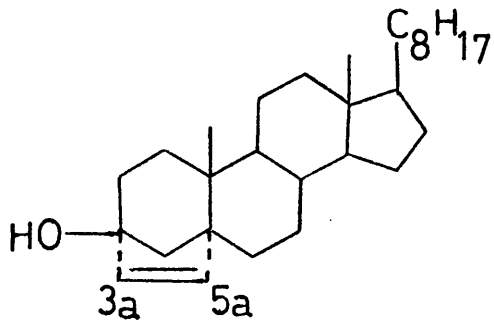

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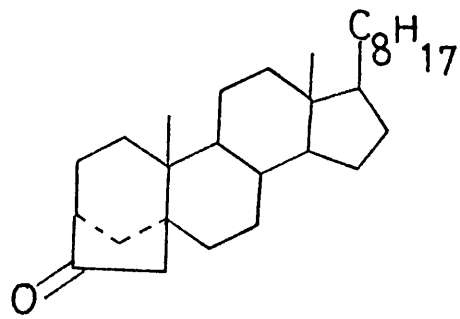

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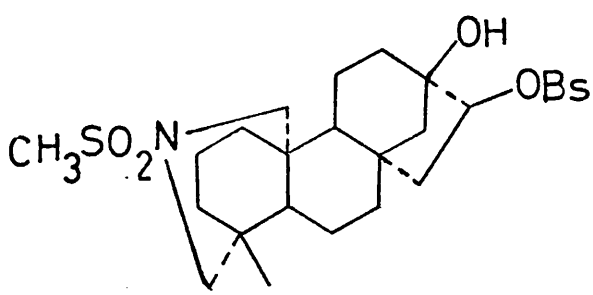

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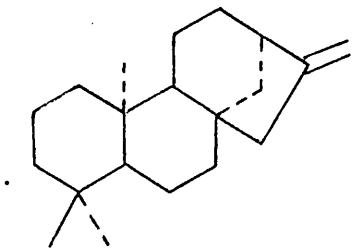

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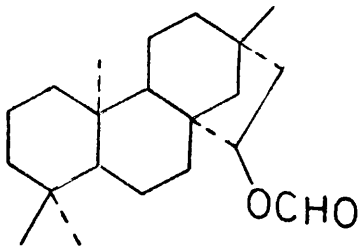

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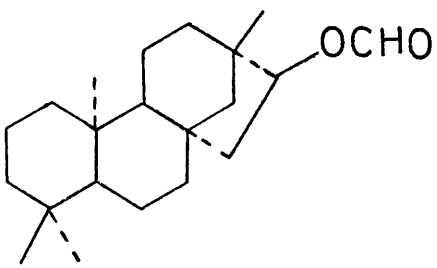

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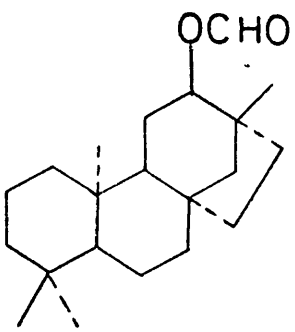

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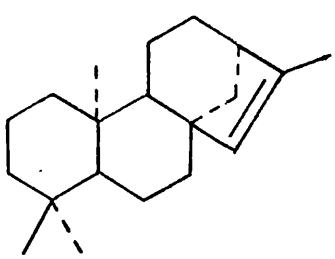

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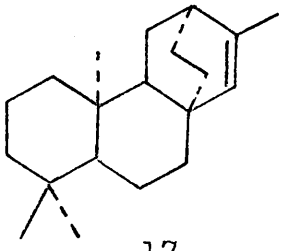

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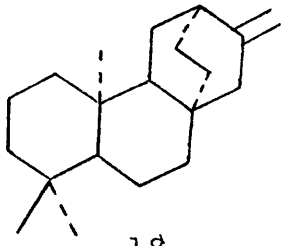

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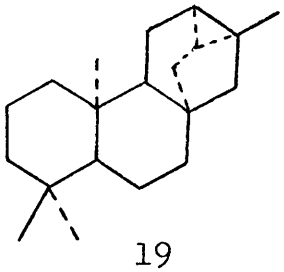

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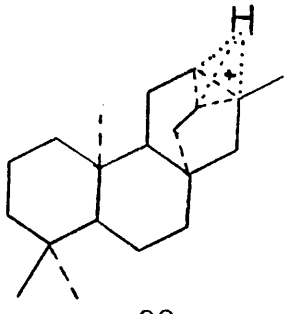

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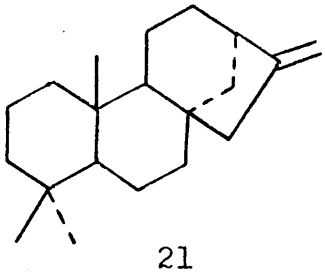

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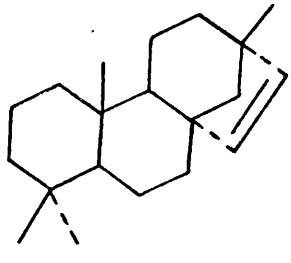

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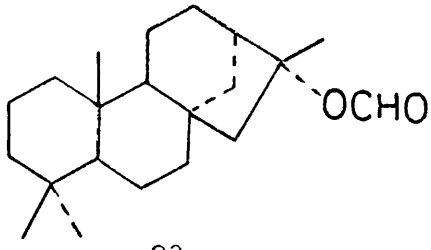

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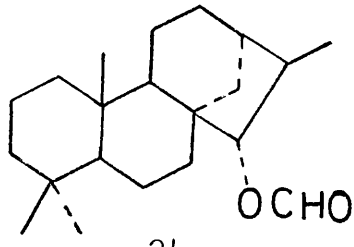

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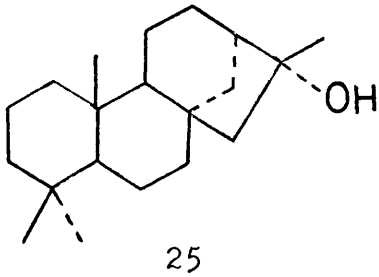

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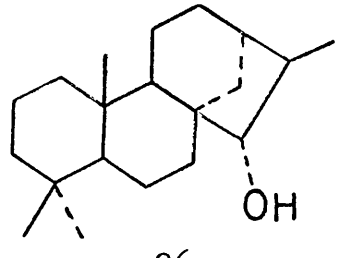

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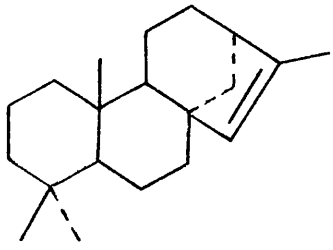

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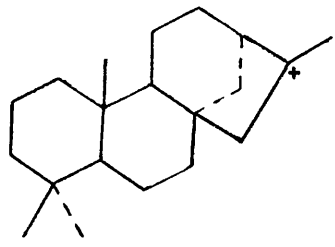

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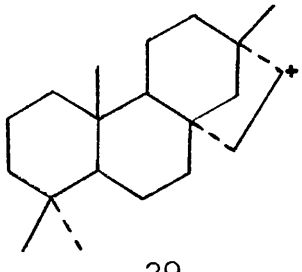

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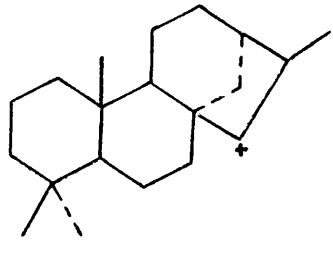

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