CHAPTER-I

INTRODUCTION : BIOMIMETIC TERPENE CYCLISATIONS

ABSTRACT

A brief survey of the biomimetic cyclisation of terpene precursors, in general, is given in this Chapter to present a broad perspective of the current state of the subject and to highlight the mechanistic aspects.

BIOMIMETIC TERPENE CYCLISATIONS

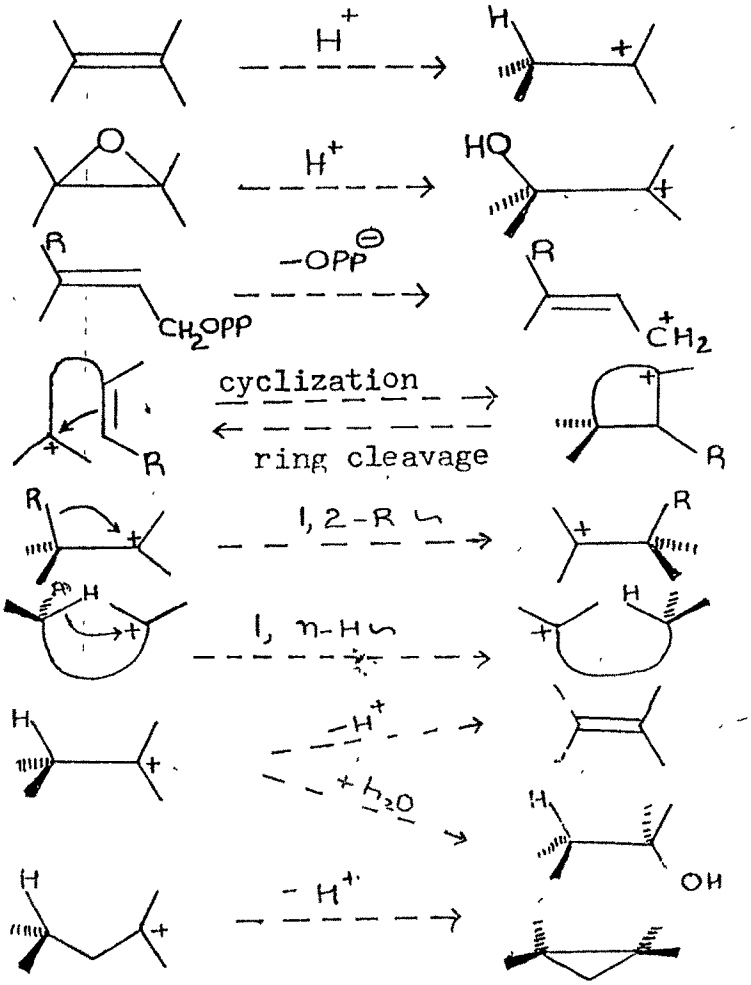
A remarkable characteristic of naturally occuring terpenes is the bewildering array of carbocyclic structures. As of 1970 more than 200 different skelta had been identified (excluding nor metabolites), the structures varying from acyclic chains to hexacyclic ring systems and containing almost all ring sizes from 3 to 14 members[1]. Althougth a considerable number of the 200 are produced by oxidative transformations (eg. ring cleavage) of pre-existing terpenes, a majority neverthless represent primary structures formed in nature through multistep cyclization and rearrangement sequences originating from five basic acyclic precursors.

Efforts directed toward the synthesis of naturally occuring compounds have, almost from the inception of this kind of work followed two kinds of pathways. The first and for many year the major road travelled was that of total synthesis. Thus the steady accretion of knowledge concerning the structural and stereochemical course of such reactions as base-catalyzed condensation, enolate alkylation, and catalytic hydrogenation resulted in the years following the second World War in a series of elegant syntheses of such complex molecules as strychnine, cortisone, chlorophyl, cevine, longifolene, onocerin, germanicol etc. The alternative approach less well explored until recent years has been the path of biogenetic-type synthesis.

It is appropriate at this stage to discuss certain aspects of terpene biogenesis. The term "bio-synthesis" is used to denote the presumably enzyme-mediated processes by which terpenes are formed in a living organism, or an active preparation therefrom and experimental findings obtained with them. The term "biogenesis" refers to the purely hypothetical pathways and mechanisms derived from the consideration of the biogenetic isoprene rule and related theoretical proposals. Since biogenetic theory must, if necessary, be modified to accomodate the results of bio-synthetic investigations, the distinction between the two terms may ultimately disappear.

The biogenetic isoprene rule has afforded a theoretical basis with which biogenetic schemes may be derived to correlate both the structure and stereochemistry of the great majority of the primary terpene skeletons.[2-8]. A fundamental assumption in the original formulation of the biogenetic isoprene rule and its subsequent applications is that individual steps in the proposed scheme should conform to known mechanisms associated with carbonium ion reactions in solution. The notable success of this version of the preceding isoprene rule has evoked a substantial research effort with the aim of simulating biogenetic schemes, or segments therein, by purely chemical means.

The individual steps in biogenetic schemes may be designated as initiating, propagating and terminating. [The biogenesis of certain halogen-containing terpenes recently isolated from marine sources presumably involve Br^+ and Cl^+ initiation.[9-12] Reductive termination, (ie hydride transfer from NADPH) is not shown in the scheme since this termination mode appears to be unique to squalene biogenesis]. There appears two types of initiating reactions: Protonation (of a carbon-carbon double bonds or epoxides), and pyrophosphate ionization. It is reasonable to suppose that the latter step is itself triggered by a proton transfer to a phosphate oxygen.



Dashed arrows are used in the biogenetic pathways in order to stress the hypothetical nature of the schemes.

Although, the specific incorporation of farnesol into the sesquiterpene-derived alkaloid dendrobine[13] and both geranylgeraniol[14] and copalol[15] into the fungal diterpene rosenonolactone has been observed, it neverthless seems unlikely that the alcohols are themselves the substrates for these biosynthetic cyclisations. In the biosynthesis of the tetracyclic diterpene kaurene with soluble enzyme preparations geranylgeranyl and copalyl pyrophosphates were efficiently converted to product; however the corresponding alcohols were completely inactive[16,17].

In most biogenetic schemes several propagation steps are required before termination. An extreme example is the pentacyclic triterpene ketone friedelin the biogenesis of which entails fifteen individual propagating stages. One of the original postulates laid down in the application of the biogenetic isoprene rule to triterpene biogenesis is that such multi step schemes be assumed to proceed uninterrupted to the end product. (ie. termination steps are irreversible)[3-5]. This "non-stop" hypothesis has been verified in triterpene biosynthesis by the absence of tritium loss[18-21] and, albeit negative evidence, in the non-incorporation of various conceivable alcohol intermediates[22-24].

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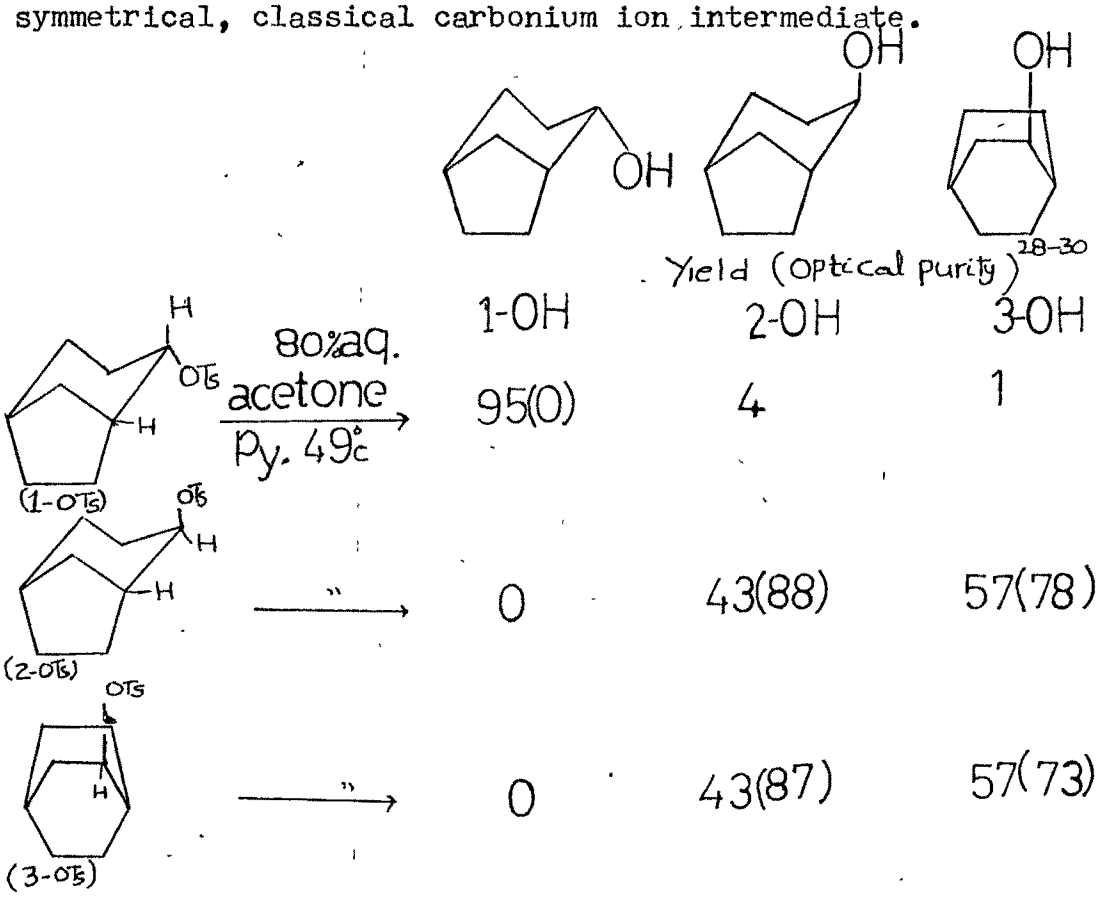
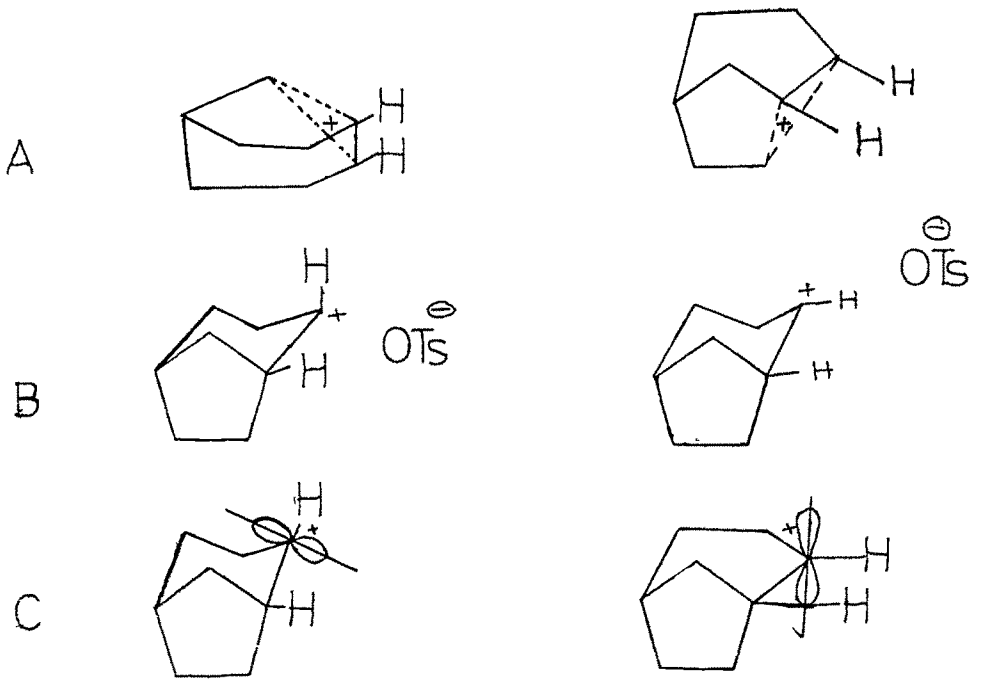
However, the biogenesis of certain sesquiterpenes and most tricyclic and tetracyclic diterpenes require one, and in a few cases two, olefin intermediates. For example, the biogenesis of the bicyclic eudesmane, guaiane, and related sesquiterpenes proceeds through a germacradiene intermediate. Similarly two deprotonation stopping points (germacradiene and bulnesene) evidently intervene between farnesylpyrophosphate and the tricyclic patchoulane sesquiterpenes. In diterpene biosynthesis, the bicyclic copalylpyrophosphate is an established intermediate. Thus, non-stop, single-stop, and evidently double-stop biogenetic schemes obtain in sesqui and diterpene classes.

Since the evolution of terpene biogenetic theory has been influenced by concurrent advances in the understanding of the mechanisms of carbonium ion reactions, it seems appropriate to consider briefly the matter of carbonium ion structure and its relevance of the stereochemistry of rearrangement. Although the question of the existence of σ-bridged non-classical carbonium ions remains unresolved[25-26,27], it is neverthless clear that solvolytic rearrangements of certain rigid structures may take place with a high degree of stereospecificity. Illustrative of this phenomenon are the solvolyses of the endo-and exo-bicyclo [3.2.1] octa-2-yl tosylates 1-OTS and 2-OTS and the related bicyclo [2.2.2]

octan-2-yl tosylate (3-OTs)[28-29,30]. The predominant (95-100%) retention of configuration and structural integrity in the products demonstrates that all three sulphonates undergo S_N-1 type heterolysis and, further, that the solvolyses of 1-OTs and the 2OTs/3-OTs pair proceed, almost exclusively, through different carbonium ion intermediates. Since the product distribution resulting from a free classical bicyclo [3.2.1] octan-2-yl carbonium ion should be independent of the configuration of its antecedent, the need for an alternative structure(s) for the intermediate(s) is apparent. The high optical purity of the bicyclo [2.2.2] octan-2-ol (3-OH) formed from optically active (2-OTs and 3-OTs) similarly indicates that, at most, a minor amount (22-27%) of this product arises from a symmetrical, classical carbonium ion intermediate.



Three different types of structures have been advanced for the carbonium ion intermediates in these, and other[31-33] solvolytic reactions in order to account for stereo selectivity. One is the symmetrically bridged non-classical ion (A), which was favored at the time of Goering and Ficks[28-30]. A second proposal suggests that heterolysis leads to non-interconverting ion pair intermediates (B), differing in the location of the counter ion. The substitution reaction takes place with retention of configuration by exchange of the tosylate counter ion for a solvent molecule, while Wagner-Meerwin rearrangement occurs only to the opposite carbonium ion face. A third explanation invokes conformationally isomeric carbonium ions (C) which undergo preferential rearrangement of the adjacent σ-bond aligned with the p-orbital and nucleophilic attack fast with respect to conformational equilibration. Carbon-Carbon hyperconjugation (vertical stabilization) may have a significant, stabilizing influence upon these conformers and the respective transition states involved in product formation[34,35]. One, or more, of these effects could also contribute to the maintenance of stereospecificity in terpene biosynthesis.



The stereospecific migration of the group anti-parallel to the leaving group observed in the rearrangements of the bicyclo octyl tosylates (1-OTs), (2-OTs) and (3-OTs) is a characteristic common to many carbonium ion rearrangements, and, as mentioned above, is a basic postulate in the biogenetic isoprene rule. It is, neverthless, to be expected that, as the stability of the carbonium ion increases, the tendency towards anti-parallel migration will be diminished. In fact, many rearrangements with overall syn stereochemistry have been reported.

It should be apparent that the realization of a particular rearrangement or sequence of rearrangements, by

chemical means cannot be considered proof that the same transformation takes place in the biosynthesis.

However, for the sake of efficiency it seems likely that the enzymes which mediate terpene biosynthesis would frequently capitalize upon the inherent chemical reactivity of their substrates. This expectation is considered sufficient justification to take the optimistic view that the supposed, biogenetic-type rearrangements of terpenes presented in the following sections may reflect kinetic or thermodynamic phenomena which are relevant to the corresponding step or steps in the biosynthetic process. A demonstrably unfavourable chemical reaction may signal a biosynthetic stage in which enzyme action is crucial to the successful outcome of the biological event. The fact that strong acid catalysis and non-aqueous solvents may be required to bring about a carbonium ion rearrangement does not necessarily detract from the biogenetic significance of the result. While such conditions are admittedly quite unlike the typical intracellular medium, the effective pH of a proton donor group protruding into a highly lipophilic region of an enzyme is a matter for conjecture.

The remarkable ability of a living system to convert an acyclic symmetric hydrocarbon to a tetracyclic, dissymmetric unsaturated alcohol containing 8 asymmetric centers has fascinated the organic chemist and stimulated [illegible] process.

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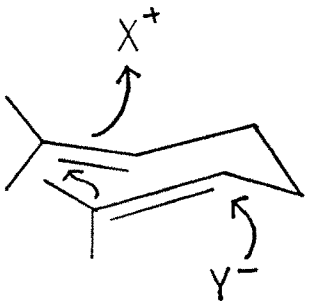
I. Theory of polyene cyclisation :

A fundamental process of terpenoid and steroid biosynthesis is olefin alkylation[36]. This process may in turn be divided into two aspects, the construction of acyclic polyenes, and the conversion of these polyenes into cyclic compounds and it is latter of these processes that we shall be concerned here.

Examples of such cyclization reactions of terpenoid polyenes have been known from the end of the last century[37] but a stereoelectronic theory explaining and predicting the course of these cyclizations was first suggested in 1955. This theory is generally referred to as the Stork-Eschenmoser[38,39] hypothesis and has two basic postulates. First, the formation of a cyclohexane ring by cationic cyclization of a diene, if it is a concerted process, should occur by an anti-parallel addition mechanism. Thus, in the conversion of (4) and (5) the entering electrophile X and the nucleophile Y should be found in the product to have a cis and (atleast initially) diequatorial relationship.



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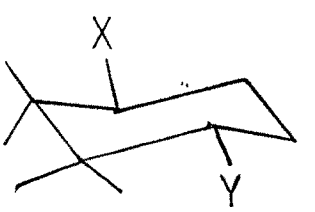

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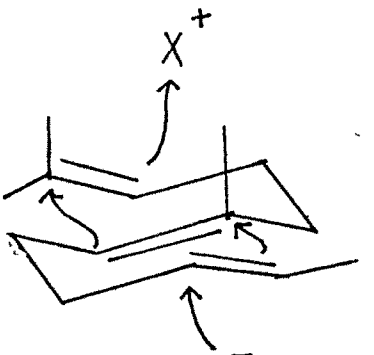
If the nucleophile Y is a π-bond incorporated in an extended trienic chain and if we supply a second nucleophile, Z^-, then the product will be a decalin having a trans-ring junction, as in (6) to (7).



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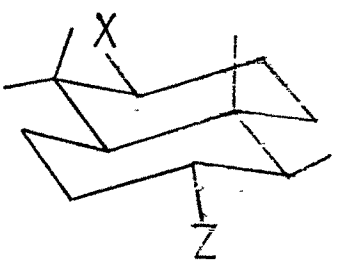

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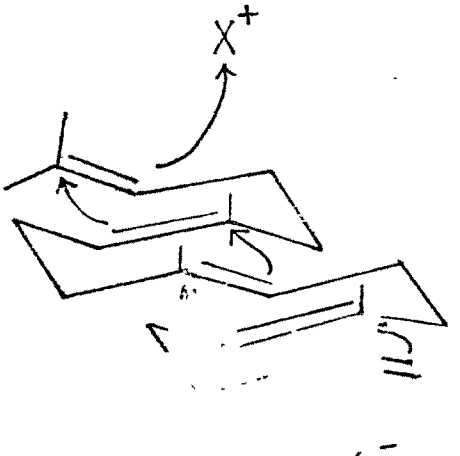
Extension of this postulate to a polyene suggests, that cyclization of a system such as (8) would result in a polycyclic product (9) having the familiar trans-anti-trans-anti-trans-geometry of many of the naturally occuring terpenoids and steroids.



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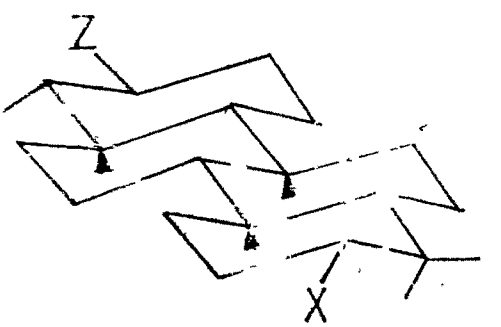

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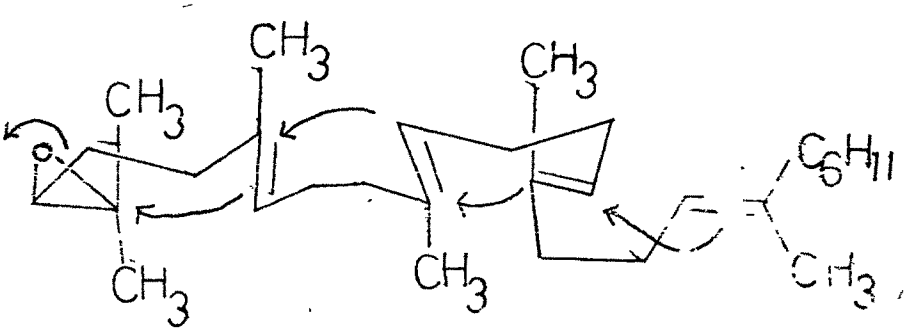
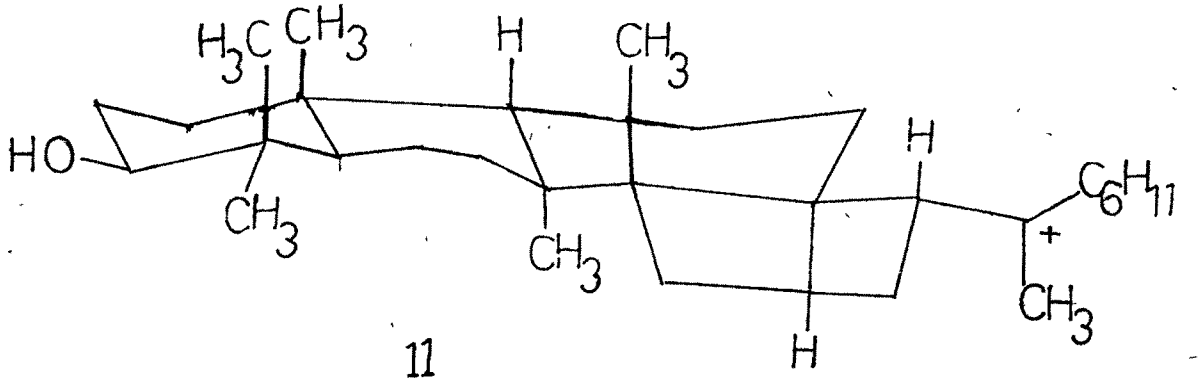
A significant part of the biosynthesis of naturally occuring terpenoids can be accounted for on the basis of a concerted cationic cyclization of an appropriate polyene. This postulate, however, cannot account for one of the most important aspects of the biosynthesis of terpenoids, the formation of lanosterol and cholesterol from squalene. Since these molecules are formed biologically[40] by 1,2 rearrangement of methyl groups from an intermediate tetracyclic product the Stork-Eschenmoser first postulate would lead to the wrong stereochemistry at, inter alia, C-13, 14 of both lanosterol and cholesterol. Thus, the second postulate of this theory is that the principal role of the enzyme in the biological cyclization of polyenes is a conformational one. If the squalene epoxide chain is folded and held as shown in (10) then concerted cyclization will yield an intermediate (11) that upon rearrangement will furnish lanosterol (12).





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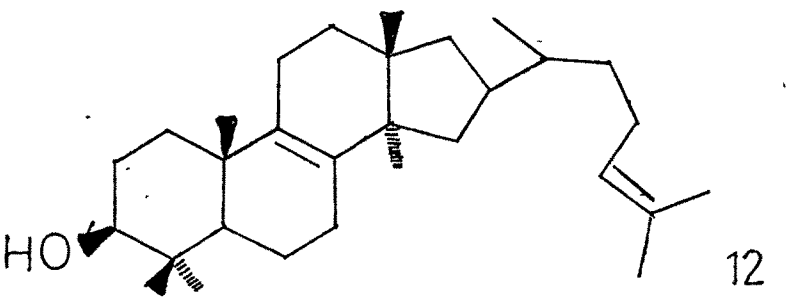

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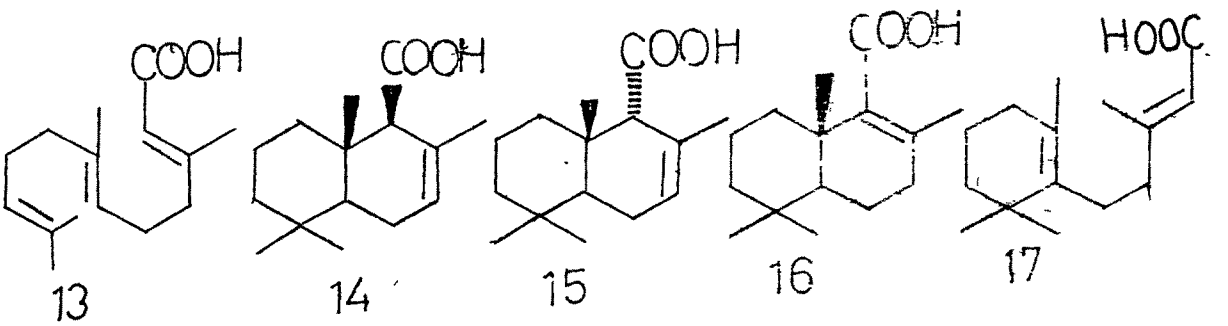
Van Tamelen[41] has proposed a partial alternative to this scheme, on the basis that formation of ring C should proceed in a Markownikow sense to a five membered ring which then undergoes rearrangement.

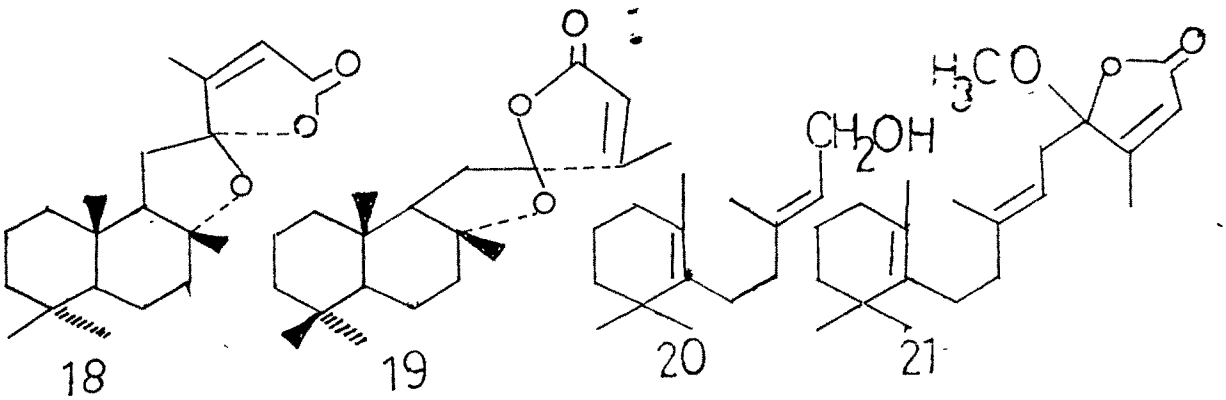
II. Acid-Catalyzed Cyclization :

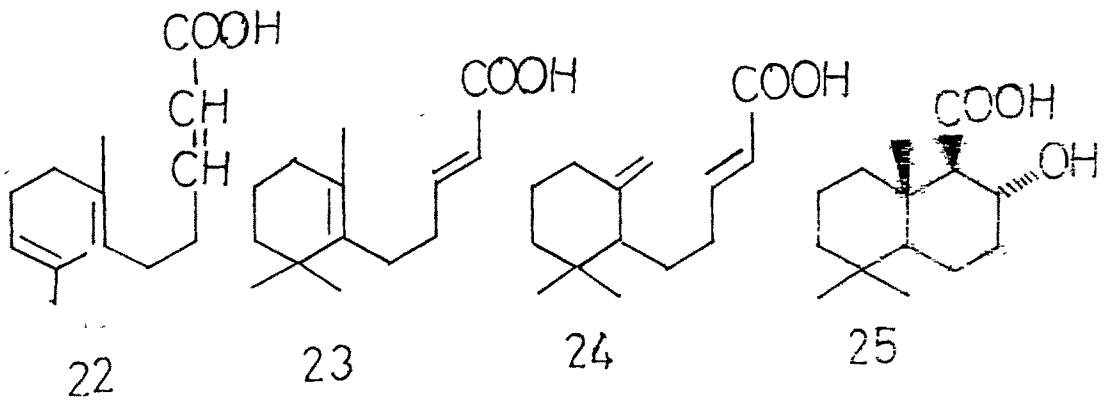
The initial applications of the Stork-Eschenmoser hypothesis to biogenetic type synthesis were disappointing. Stork and Burgstahler[42] investigated the BF_3 catalyzed cyclization of trans-trans-farnesic acid (13). The bicyclic products of this reaction (14), (15) and (16) all contained

a trans-ring junction as predicted. The monocyclic acid (17), however, obtained from farnesic acid by cyclizations under mild conditions, also provided these bicyclic products under more vigorous circumstances. This latter result was unexpected since the theory predicts that cyclization of such a monocyclic olefin should produce a cis-ring junction.



Interestingly this result has been applied to the biogenetic type synthesis of the diterpene lactones α and β-levantenolides[43] (18), (19). Monocyclofarnesol (20) was converted to the butinolide (21). Treatment of the latter with $SnCl_4$ in benzene afforded (18) and (19) in 30o/o and 12o/o yields respectively. The same products were also produced, though in lower yield, from cyclization of an acyclic precursor derived from trans, trans-farnesol[44]. The same type of result as Stork and Burgstahlers was obtained by Eschenmoser[45], who subjected the trans-trans, cis-trans, and trans-cis isomers of desmethyl farnesic acid (22) as well as the monocyclic compounds (23) and (24) to cyclization conditions using su[illegible]ric a[illegible] f[illegible]c ac[illegible]nd in all cases [illegible]tained the tr[illegible]a[illegible] (2[illegible]





Johnson[46] has shown that these results are not caused by interconversion of cis-and trans-fused products under the reaction conditions. The acids (26) and (27) were individually subjected to prolonged tratment with BF_3-etherate and recovered unchanged. The explanation for the lack of stereospecificity in acid catalyzed polyene cyclization must lie in the non-concerted nature of the process. Thus, the cyclizations of farnesic acid and desmethyl farnesic acid must involve intermediate cations of sufficient life time to dictate the formation of the thermodynamically more stable product, the trans-decalin.

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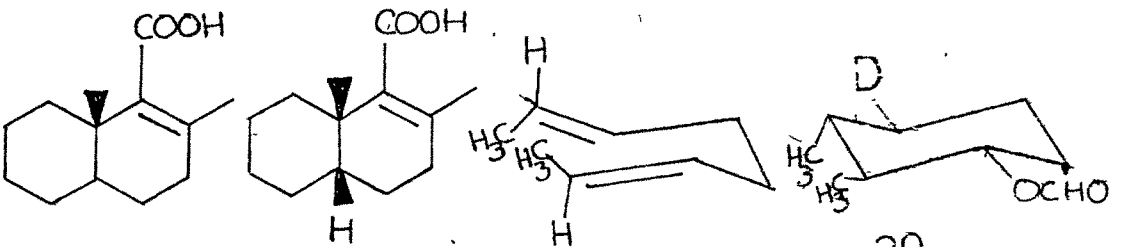
The formation of an intermediate cation can be accounted for interms of the poor nucleophilicity of the double bond conjugated with carboxyl group. Support for this conclusion was adduced by Ulery and Richards[47] who showed that only cyclization product from treatment of diene (28) with deutero formic acid and deuterosulfuric acids was the cyclohexyl formate (29).



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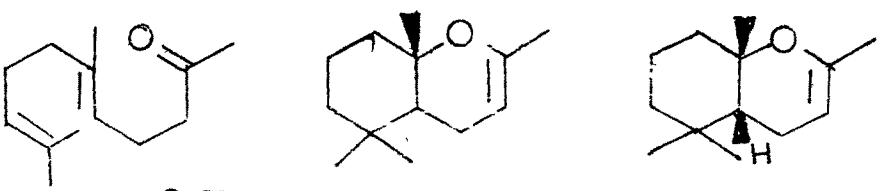
The stereochemistry of this product is in accord with the Stork-Eschenmoser hypothesis. In addition, Kucherov and coworkers[48] have shown that the cis and trans- isomers of geranylacetone (30), lead stereospecifically to the bicyclic ethers (31) and (32) respectively.



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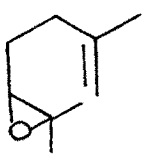
III. Oxidative cyclization :

Although proton acid-catalyzed cyclization of an acyclic terpenoid polyene may in some cases be the *in vivo* pathway for the synthesis of, polycyclic natural prducts, such a process suffers from a serious drawback as a method for biogenetic-type *in vitro* synthesis. A polyenic system may protonate on a variety of olefinic sites and thus be converted to a variegated mixture of cyclized products. Several groups of workers have sought, therefore, to find more specific ways of initiating the cyclization process. These investigations have been aimed at finding not only controlled cyclization methods, but also at finding a biogenetic-type model for the oxidative cyclization pathway common to cholesterol and presumably most triterpene biosynthesis.

The C-3 -OH group of lanosterol, was shown by Bloch and Tchen[49] to arise *in vivo* from molecular oxygen. It appears to be a reasonable assumption that other terpenoids having an oxygen function in the equivalent position are also produced by oxidative cyclization. The problem of biogenetic-type synthesis of these types of systems was centered for some time, therefore, on finding an *in vitro* equivalent of cationic oxygen. One such equivalent can be found in the reactions of peroxy acids. The conversion of

a polyene to an epoxide followed by acid catalyzed opening of the epoxide and synchronous closure of a ring satisfies both the stereochemical and mechanistic requirements of the accepted pathway for biogenesis of lanosterol and, by anology a host of other terpenoids.

The first epoxide cyclization which could directly related to the cyclization of squalene was the BF_3 or $SnCl_4$ catalyzed reaction of geraniolene mono-epoxide[50] (30), under these conditions (30) afforded three products, the bicyclic ether (34) and the cyclohexanols (35) and (36). The ease of cyclization of this acyclic epoxy



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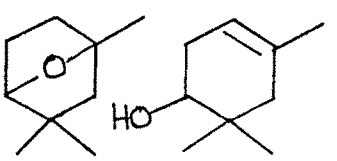

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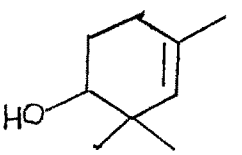

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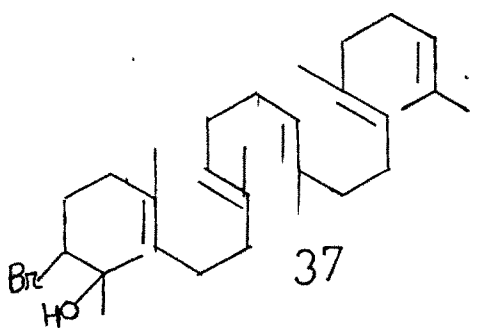
olefin suggested that the reaction could be extended to biogenetic-type synthesis of a variety of C-3 hydroxylated terpenoids. One problem which had to be overcome, however, was that of introducing an epoxide function at the terminal double bond of a polyene system.

Treatment of a polyene such as farnesyl acetate with monoperthallic acid results in a difficultly separable

mixture of terminal and central monoepoxides[51]. A solution to this problem was found by Van Tamelen and coworkers[52,53] who showed that treatment of polyenes with N-bromo-succinimide in an aqueous glyme solution yields primarily a terminal mono-bromohydrin. Thus, squalene is converted by this reagent to the bromohydrin (37) which in turn may be transformed to squalene monoepoxide (38) by treatment with base[53].



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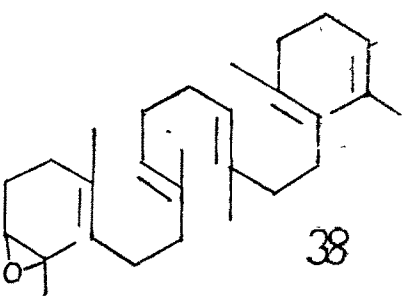

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Application of this oxidation sequence to farnesyl acetate provides the dienic oxide (39), and treatment of this with BF_3-etherate in benzene produces in modest yield the bicyclic diol monoacetates (40) and (41)[54]. The structures and stereochemistry of these cyclization products were demonstrated by conversion to drimenol and epidrimenol respectively and by comparision with authentic samples of the latter two substances. Minor by-products of this cyclization were the bicyclic ether (42) and the dienol (43). The formation of the latter may be accounted for by assuming that a monocyclic product (44) undergoes further

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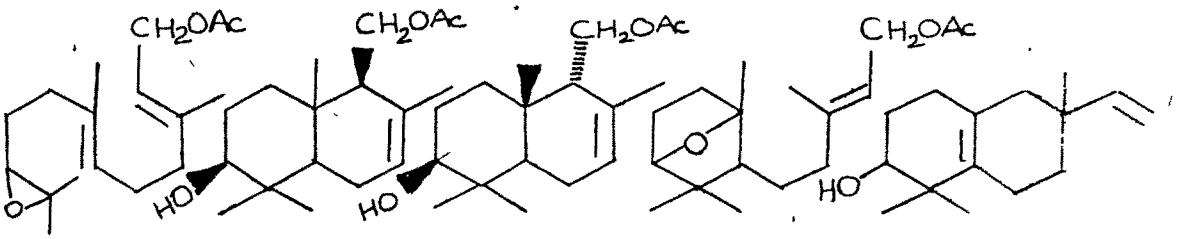
cyclization via the cation (45), a process reminiscent of the pathway of bioformation of ring-C of many diterpenoids.



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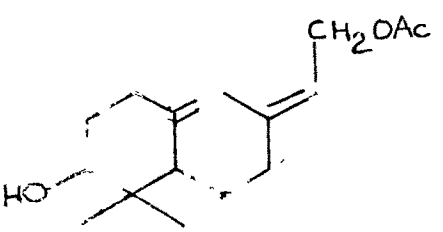
Several monoterpenoid-like compounds have been prepared by employing epoxide cyclization. The unsaturated oxirane (46) obtained from citronellal closes to produce the bicyclic ether (47) as a mixture of stereoisomers[55]. Epoxide (48) affords three products, (49), (50) and (51) upon treatment with BF_3-etherate[56]. Whereas both (49) and (50) arise by opening of the epoxide ring with participation of the double bond, the cycloheptenol (51) is the result of the conversion of the starting material to an intermediate aldehyde (52) which then undergoes cyclization.



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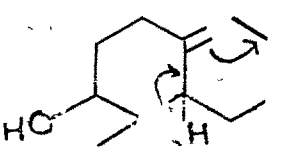

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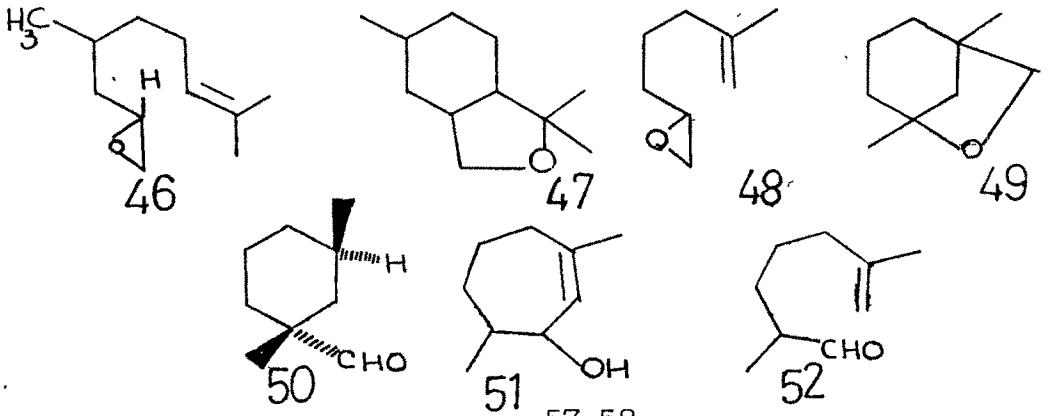
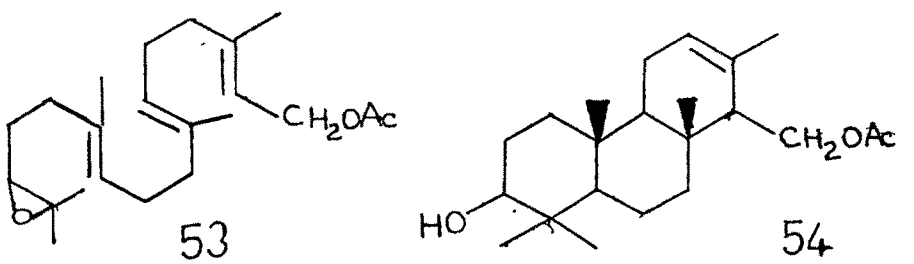
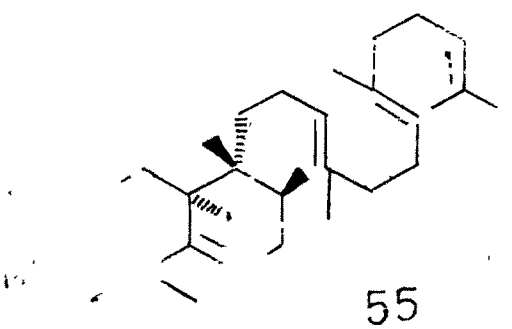


Van Tamelen and coworkers[57,58] have extended these epoxide cyclization to di- and tri-terpene precursers also. For example[57], stannic chloride in benzene catalyzed cyclization of geranyl-geranyl acetate (53) yielded the tricyclic hydroxy acetate (54).



Similar reaction conditions applied[58] to squalene oxide (38) produced the bicyclic alcohol (55) and the two tricyclic alcohols (56) and (57). The formation of both (55) and (56) requires methyl migration of the type suggested for the biosynthesis of lanosterol and other triterpenes from squalene oxide.



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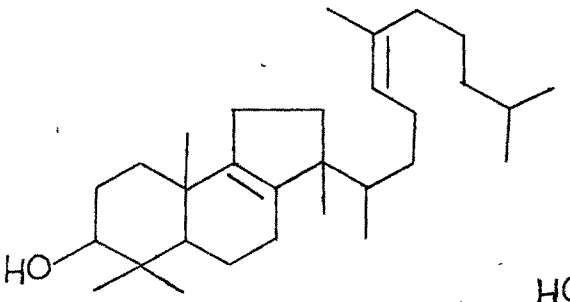

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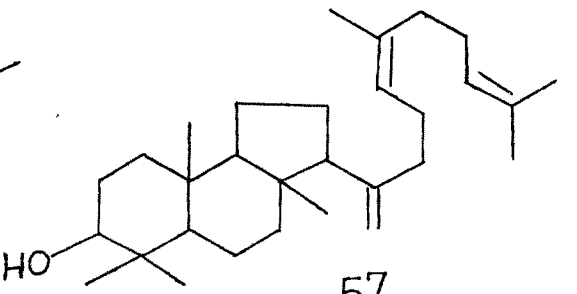

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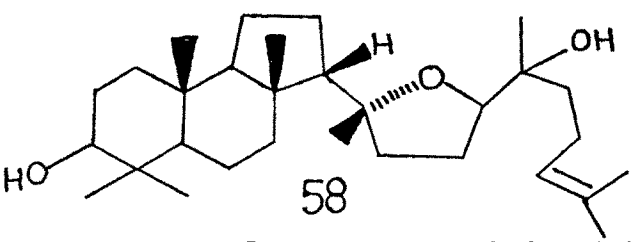
Of particular interest with regard to these non-enzymic cyclization products of squalene oxide is that the naturally occuring triterpenoid malabaricanediol was isolated subsequent to these findings and its structure shown to be (58)[59]. A biogenetic-type synthesis of this substance



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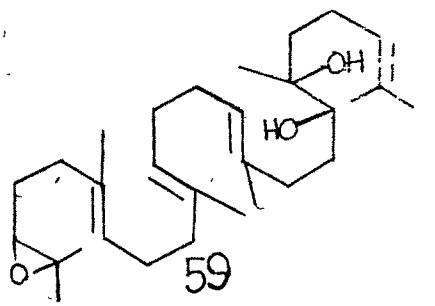


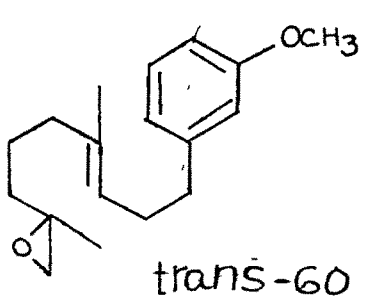
59

from squalene was carried out by Sharples[60]. He converted squalene to the epoxy diol[61](59) and subjected the latter to treatment with picric acid. This protonic acid in contrast to Lewis acid catalysts converted (59) to malabaricanediol without further transformations of the latter to unwanted by-products.

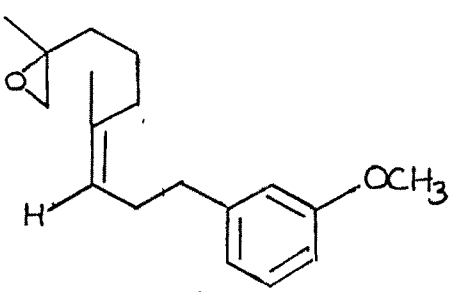
All of the previous examples of epoxy ol . in

been carried out wi' one 'asic type of

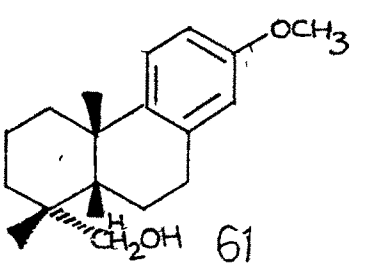
substrate, trans-substituted olefins. In addition the cyclic products have in every case been found to have trans-fused rings. Despite these facts, however, none of these results actually demonstrate whether *in vitro* epoxy olefin cyclization is a stereospecific or stereoselective process. The first such demonstration was supplied by the results of the cyclization reactions of the cis- and trans-isomers of (60)[62]. Each reaction was shown to occur in a stereospecific manner since cis (60) afforded only the cis-tricyclic alcohol (61) and the trans-olefin, trans (60) yielded only the trans isomer (62). The structure and stereochemistry of (62) was proved by oxidation to the known acid (63) while the structure and stereochemistry assigned to (61) was based on spectroscopic evidence.



trans-60



Cis-60



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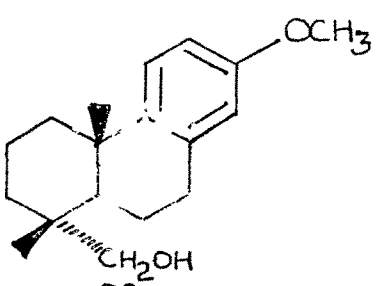

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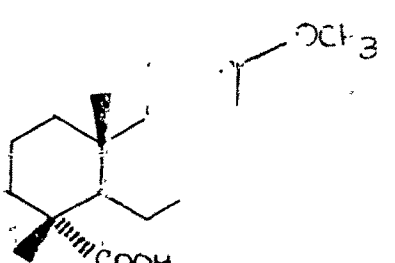

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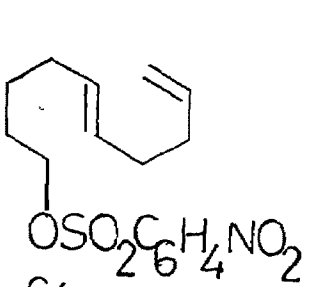
IV. Arene and Alkyl sulphonates, Acetals and Allylic Alcohols :

The epoxide group of the polyenic compounds described above serves two functions in biogenetic type synthesis. It provides an oxygen function at a characteristic location for a variety of terpenoids and steroids, and it serves as a ready source of the cation needed to initiate cyclization. Other oxygenated functional groups may also serve one or both of these purposes. A number of such systems have been investigated. In particular the reactivity of polyenic alkyl acid arene sulfonates, polyenic acetals and polyenic allylic alcohols have been examined. Much of this work has been reviewed previously[63-64].

The cyclization of polyenic arene sulfonates occurs in a stereospecific manner but in low yield. For example, the trans-p-nitro benzene sulfonate (64) upon solvolysis in formic acid affords the trans- decalol (65) as the major bicyclic product[65], but total bicyclic product, all of it possessing trans- ring fusion geometry, was formed in only 12o/o yield. In the corresponding cis-series (66), all of the bicyclic product was characterized by cis-ring fusion but was formed in 16o/o yield only.



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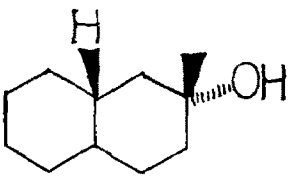

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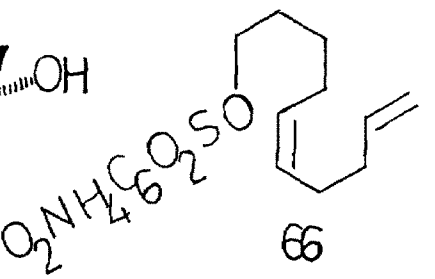

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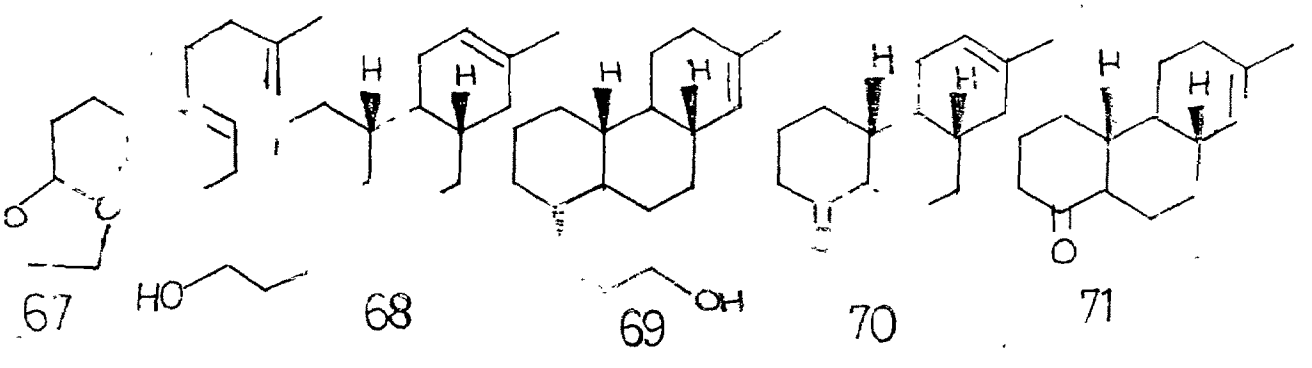
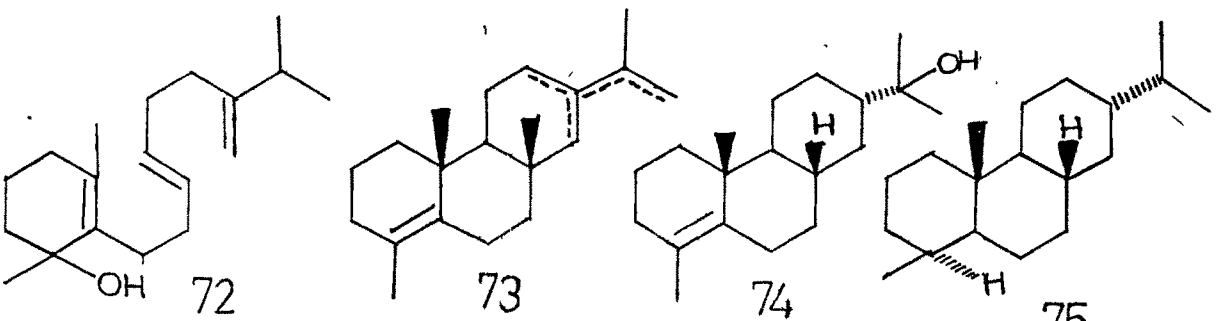
Acid-catalyzed cyclizations of polyenic acetals has proved to be an efficient and stereospecific method for biogenetic type syntheses of potential steroid and terpenoid substances. For example the trienic acetal (67)[66] upon treatment with stannic chloride in benzene solution underwent cyclization to produce a mixtue of products, 87o/o of which is a monohydric alcohol fraction. The latter was shown to consist principally of the tricyclic alcohols (68) and (69). Removal of the ether function by tosylation of hydroxyl group followed by treatment with Zinc and Sodium Iodide converted the mixture to alcohols. The latter were then oxidized to (70) and (71) with Jones reagent. The stereochemistry of these ketones was demonstrated by comparision with known hydrocarbons following Wolff-Kishner reduction.



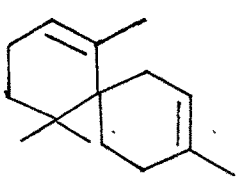
67 68 69 70 71

The most successful of biogenetic-type synthesis systems developed by Johnson has been cyclization of polyenic allylic alcohols. For example, the cyclohexenol (72) is quantitatively transformed by formic acid into a mixture of the hydrocarbons (73) and the alcohol (74)[67]. The stereo- and structural specificity of this cyclization was demonstrated by conversion of the mixture to dl-fichtelite (75) by hydrogenation.



72 73 74 75

Several other terpene syntheses are based on cyclization reactions of allylic alcohols. For examole, monocyclofarnesol, (cis- or trans-) affords α-chamigrene (76) when exposed to iodine in benzene solution.[68]



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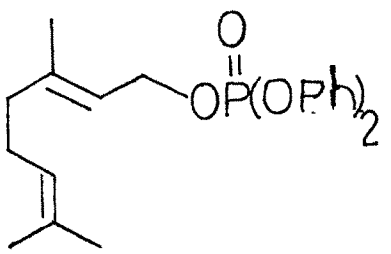
In an experiment closely modelled on the actual biosynthetic pathways for both cyclic and acyclic monoterpenoids, Wood and coworkers[69] found that geranyl and neryl diphenyl phosphates (77) and (78) are converted upon standing to a mixture of 5 terpene hydrocarbons: myrcene (79), cis-β-ocimene (80), trans-β-ocimene (81), limonene (82) and terpinolene (83). The yield of cyclic products is higher in the case of the neryl compound suggesting that cyclization is an anchimerically assisted process. Cyclization of geranyl diphenylphosphate has been suggested to occur only after rearrangement to linaloyl diphenylphosphate (84).



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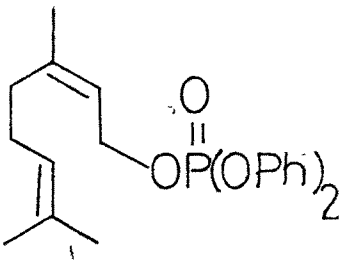

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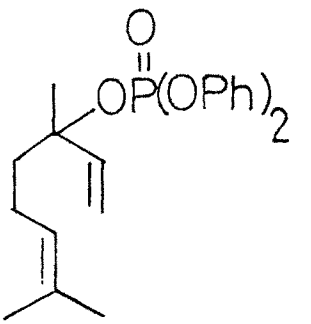

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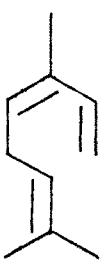

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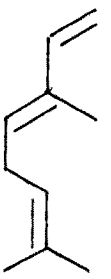

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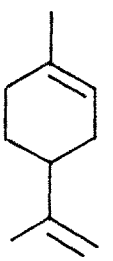

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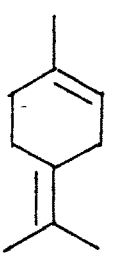
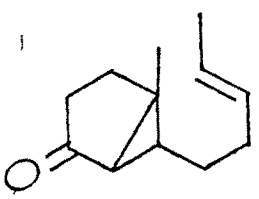


83

V. Cyclopropyl ketones, Enols, and Tertiary Alcohols :

An interesting system employing the cyclization reactions of cyclopropyl ketones for the synthesis of terpenoids and steroids has been developed by Stork and coworkers. For example, the unsaturated cyclopropyl ketone (85) is converted to two bicyclic products (86) and (87), and the cyclohexenone (88) upon treatment with $SnCl_4$ in benzene[70]. Formally these products are all derived from opening of the cyclopropyane ring to a cyclohexyl cation (89) rather than to the alternative cyclopentyl cation (90). The latter might have been expected to be favored because of greater overlap between the orbitals of the bond undergoing cleavage and the carbonyl p-orbitals in the formation of (90) than in the formation of (89)[70].



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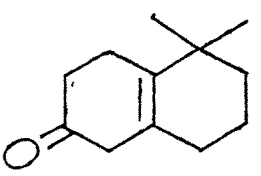

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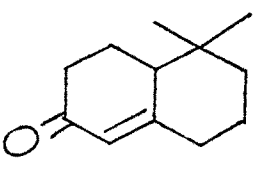

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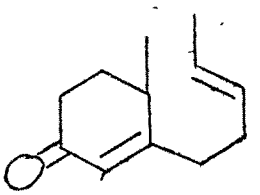

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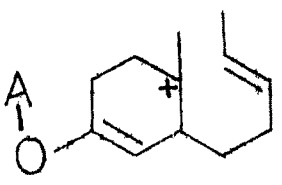

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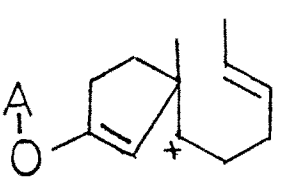

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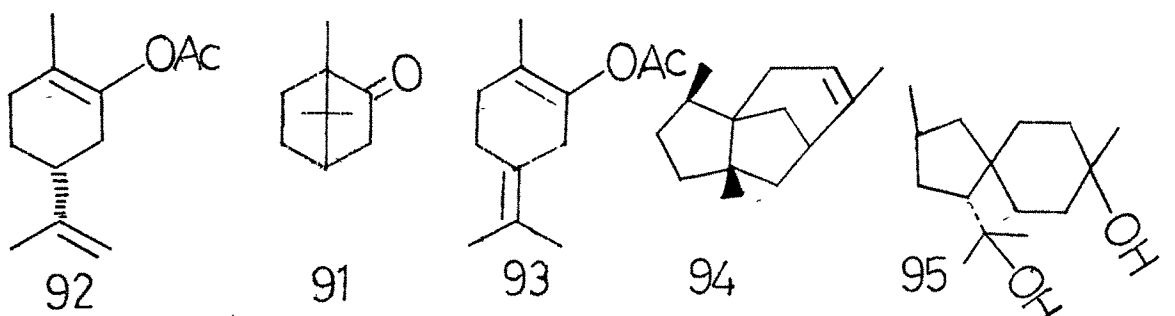
The alkylation of enols by carbonium ions has been used successfully in several biogenetic-type syntheses. A synthesis of camphor (91) by this method was carried out by Money[71]. The mixture of enol acetates obtained from dihydrocarvone was separated and isomer (92) was treated with BF_3-etherate. A 90o/o yield of camphor is obtained in this cyclization. Interestingly the camphor produced this way is racemic despite the fact that optically active dihydrocarvone was employed as the starting material. One explanation offered for this result is that cyclization may occur only after isomerisation of (92) to (93). The latter being symmetric must then yield racemic camphor.



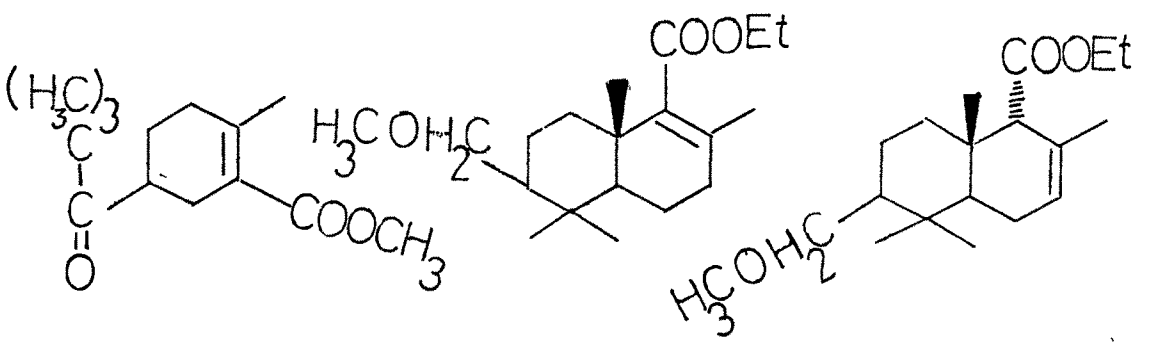
92 91 93 94 95

Several biogenetic-type syntheses of cedrene (94) have also been reported. In one of the Corey syntheses[72] diol (95) produces cedrene when exposed to formic acid .

31

VI. Carbonium ion Catalyzed Cyclization :

An interesting variation of the usual methods by which polyene cyclization is initiated has been investigated by Kucherov and coworkers[73,74]. While most cyclizations have been catalyzed by protonic acids or the more common Lewis acids, these workers have employed carbonium ion catalysts. Thus, for example, treatment of methylgeranate with pivaloyl fluoroborate affords the keto ester (96) in 56o/o yield[73]. Methoxymethyl fluoroborate also serves to initiate cyclization produces the trans-fused ethers (97) and (98) from ethyl cis, trans-farnesate[74]. This cyclization like the proton catalyzed closure of farnesic esters, is a two stage process.



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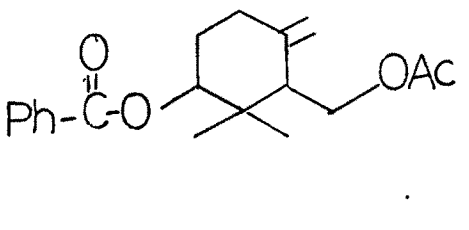
VII. Radical Cyclization :

A contrast to the usual acid catalyzed ionic cyclization of polyenic systems and the assumption[75] that this type of process is truly related to actual biosynthetic pathways is found in the work of Breslow. The latter has investigated the cyclization reactions of polyenes in the presence of radicals. For example, treatment of geranyl acetate with benzoyl peroxide in the presence of cuprous chloride and cupric benzoate produces the cyclized product (99) in yields of 55-60o/o[76]. The process has also been extended to the farnesol series. In particular farnesyl acetate affords 20-30o/o of (100) under similar conditions[77].



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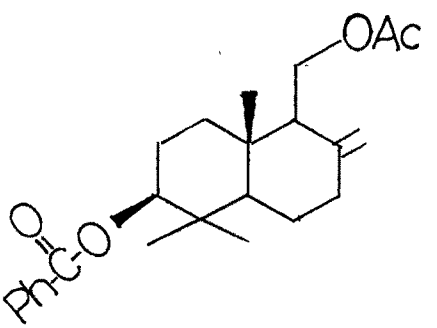

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Concluding remarks :

The structural diversity found in terpene metabolism is mostly elaborated by olefinic cyclizations of five acyclic precursors. There has been recorded very little work relating to biomimetic cyclization of allylic phosphate esters. Although non-enzymic poly olefin terminal epoxide cyclizations are among more fascinating biogenetic like terpenoid synthesis and have received an immense amount of study, another important counterpart of terpene biosynthesis, an allyl phosphate ester cyclization, has never been developed to a useful level due to the lack of a satisfactory reagent to promote a controlled heterolysis of these esters.

In an endeavour to mimic nature in synthesising various acyclic and cyclic terpene hydrocarbons, the present work was undertaken. The foregoing sections describe our efforts towards this goal.

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