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On the Stereochemistry of Biogenetic-Like Olefin Cyclizations

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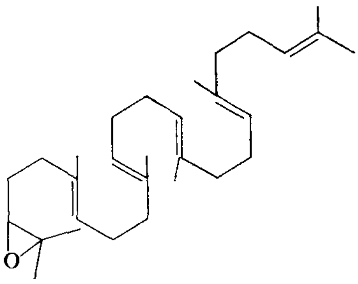
An analysis of the potential involvement of alicyclic cations in biogenetic-like olefin cyclizations is presented. Application of the concepts of conformational analysis and transition state structures to the intramolecular attack of an olefinic double bond on a conformationally rigid cyclohexyl cation leads to the conclusion that such reactions should proceed with high stereoselectivity. A number of examples of cationic olefin cyclizations, including some undertaken specifically to test the theoretical analysis, are reviewed and discussed in relation to the potential involvement of alicyclic cations as intermediates in these cyclizations. This review illustrates some of the problems encountered in attempting to study mechanisms of olefinic cyclizations related to those involved in *in vivo* terpenoid biogenesis. The intervention of cyclohexenyl intermediates is implicated as a major cause of formation of large amounts of *cis* products in cationic olefin cyclizations. The results serve to demonstrate that intrinsic steric factors as well as stereoelectronic factors will favor stereoselective cyclization of polyolefins in enzymatically controlled olefin cyclizations as well as *in vitro* olefinic cyclizations.

INTRODUCTION

The cyclization of an acyclic polyolefin with concomitant rearrangement of polycyclic intermediates is generally conceded to be the key step in the biosynthesis of most classes of cyclic terpenoids (*1–4*). Some of the most impressive examples of this type of biosynthesis involve the acyclic polyolefin squalene. The monoepoxide of this polyolefin (squalene oxide, **1**) has been proved to be a biogenetic precursor of the tetracyclic triterpene lanosterol (**2**) (*5*), of the pentacyclic triterpene β-amyrin (**3**) (*6*), and of the mold metabolite, fusidic acid (**4**) (*7*).

The initial elucidation of the role of squalene in terpenoid biogenesis in 1953 led to extensive studies by organic chemists on the possibility of effecting similar cyclizations in the absence of enzyme control. These studies have now shown conclusively that stereoselective synthesis of polycyclic ring systems can be effected in good yield by nonenzymatic, cationic cyclization of suitable polyolefins (*8, 9*). Of particular interest is the high degree of ring-fusion stereoselectivity observed in these nonenzymatic cyclizations (e.g., **5** → **6**) (*9e*). The basis for this selectivity has not been established although a number of possibilities have been discussed. The first stereorational model for reactions of this type was proposed independently by Stork (*10*) and by Eschenmoser (*11*). These groups proposed that the stereochemistry of polycyclic compounds formed by cationic



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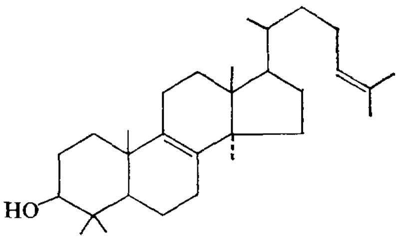

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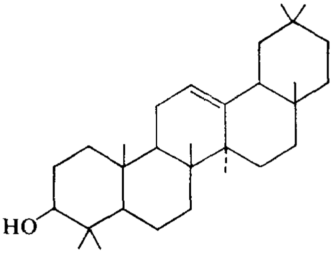

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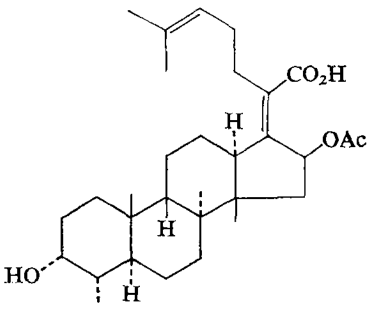
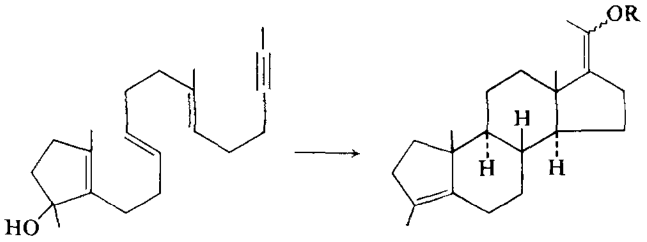


(4)

cyclizations of polyolefins would be governed by the geometry of the double bonds present in the polyolefin. Many examples of this type of behavior have been demonstrated since that time (*8*, *9*, *12*). However, the mechanistic basis for the success of the Stork–Eschenmoser hypothesis has been open to question.



(5) (6)

The stereoselective formation of *trans*-fused ring systems observed in cationic cyclization of polyolefins with *trans*-double bonds can be rationalized by three basic mechanisms. Stork and Eschenmoser (*10*, *11*) suggested a mechanism involving a synchronous reaction in which all bonds involved in the formation of the polycyclic systems are made and broken essentially simultaneously (Fig. 1). Thus, the concerned *trans*-addition to the olefinic bonds ensures that the stereochemistry of the ring fusion formed is the same as the stereochemistry of the olefinic bond.

A second mechanism, which has been preferred by Johnson in rationalizing the results of certain cyclizations of sulfonate esters (*12*), involves the intermediacy of bridged ions (Fig. 2). In this case the stereochemical integrity is preserved by the necessity for "backside" opening of a bridged ion.

The third possible mechanism is one in which classical alicyclic carbonium ions are intermediates (Fig. 3). For this type of mechanism to account for the observed stereoselectivity it would be required (a) that any alicyclic cation involved does not undergo ring inversion before cyclization and (b) that the attack of the olefinic double bond must occur with a high preference for formation of an equatorial C—C bond. It should

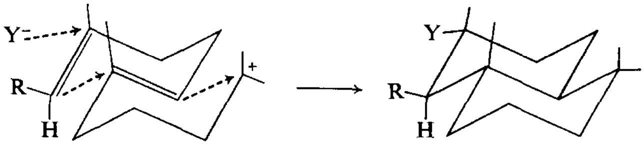


FIG. 1.

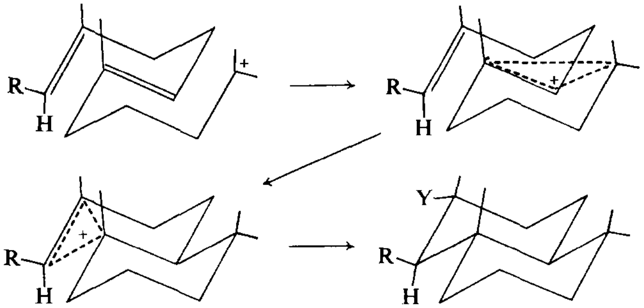


FIG. 2.

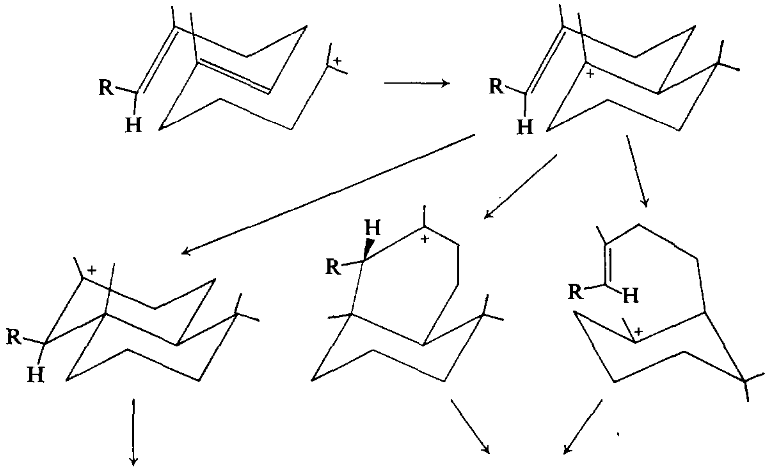


FIG. 3.

be noted that the first two mechanisms involve a stereoelectronic basis for the stereoselectivity of the cyclization. The third mechanism has no such stereoelectronic restraints and stereoselectivity through this mechanism must arise only from considerations of steric and conformational factors.

The possibility of the involvement of short-lived alicyclic cations as shown in Fig. 3 has been discussed for a number of biogenetic-like cyclizations (*8*, *9a*, *9b*, *10*, *11*, *14*). It has often been considered that the attack of a double bond on an alicyclic cation would not be sufficiently selective to account for the observations, although most recent discussions include the possibility of alicyclic cations as intermediates. The observation that attack of solvent and other nucleophiles on intermediates derived from acid treatment of cyclohexanol systems generally gives a mixture of axial and equatorial attack (with axial attack predominating in some cases) (*15*) has been considered evidence against alicyclic cations as intermediates.

In this paper we will present an analysis of the intramolecular attack of a double bond on a cyclohexyl cation (see Fig. 4 below) on the basis of modern concepts of conformational analysis (*16*). This analysis leads to the prediction that such an attack should lead to stereoselective formation of *trans*-fused ring systems. The concept of stereoselective cyclization of alicyclic cations is then discussed in relation to some of the known examples of biogenetic-like olefin cyclizations. In conclusion the relationship of the analysis presented in this paper to the enzymatic biogenesis of polycyclic terpenoids is presented.

THEORETICAL CONSIDERATIONS

The preferred path for a nucleophile to approach a cationic carbon is along a line perpendicular to the plane of the groups on the carbon atom. This line coincides with the axis of the unoccupied *p*-orbital of the carbonium ion. Application of such considerations to the intramolecular attack of a double bond on a substituted cyclohexyl cation is shown in Fig. 4. Two stereoisomeric reaction paths can be envisaged. The double bond can approach from the equatorial side of the cation to form a new bond equatorial to the original ring (**7a** → **8a**) or it can approach from the axial side to form a new axial bond (**7b** → **8b**)[1].

The *trans*-decalin ring system is known to be more stable than the isomeric *cis*-decalin system. The transition states leading to the decalyl cations will be intermediate in geometry between the starting conformations and the products.

In the conformation of 1-methylcyclohexane with an axial methyl group, the hydrogens of the axial methyl group approach the *syn*-axial hydrogens of the ring to within a distance less than the combined van der Waals radii of two hydrogens (*17*). This van der Waals repulsion is a large source of the destabilization of the conformation with the methyl group axial. The C-1 carbon in the *cis*-decalyl cation **8b** is analogous to the axial methyl group in methylcyclohexane. Examination of a model of cation **8b** shows that the bond joining C-1 and C-9 is exactly perpendicular to the plane of the ring. However,

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[1] The cations **7a** and **7b** are assumed to be held conformationally rigid in some manner. The analysis of cases in which conformational isomerization may be involved is discussed below.

the line passing through the cationic carbon of cation **7** perpendicular to the plane of the groups on this carbon is not perpendicular to the plane of the ring. The upper half of this line AE (Fig. 4) is inclined at an angle of about 60° (with respect to the plane of the ring) toward the *syn*-axial hydrogens on the same side of the ring (*18*). Thus, in the cyclization to form the *cis*-decalyl cation **8b**, as C-1 approaches along the line AE to begin bonding with C-9, the hydrogens of C-1 will experience van der Waals repulsion greater than that experienced in the final product as the C-9 carbon is approached to within bonding distance[2]. Likewise, the interactions in the transition state leading to the *trans*-decalyl cation **8a** will be less than in the final product. These considerations suggest that the transition state leading to formation of the *cis*-cation **8b** should be less stable than the transition state leading to the *trans*-decalyl cation **8a** by an amount exceeding the $\Delta G°$ of the final products, and, thus, that the attack of the double bond on the cationic center would be expected to be quite stereoselective. A free energy difference of 2.7 kcal/mole between the two transition states would lead to an isomer ratio of about 99:1 (*19*).

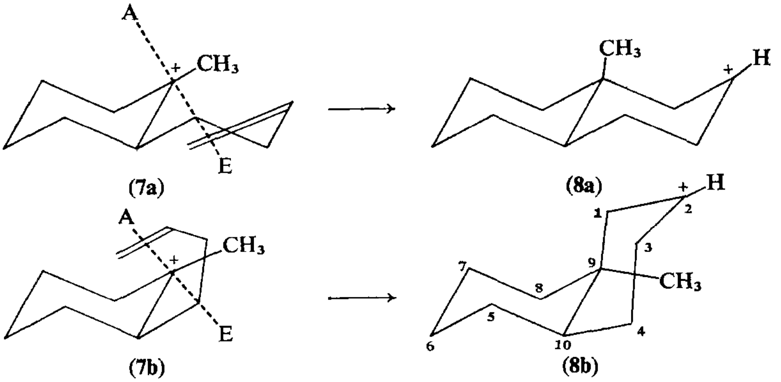
(7a) (8a) (7b) (8b)

FIG. 4.

The above analysis has considered only the remote steric factors involved in the cyclization. The currently popular concepts of torsional strain must also be considered. In a cyclohexyl system with one sp^2-hybridized carbon undergoing bond formation to generate an sp^3-hybridized carbon (**9** → **10**), two torsional strain effects can be envisaged. Based on the structures assigned to other cyclohexyl systems with one sp^2-hybridized carbon (*20*, *21*), the geometry of a cyclohexyl cation can be assumed to be that shown in structure **11** in which the dihedral angle between the substituent R on C-1 and the equatorial substituent on C-2 is slightly greater than 0°. As a new bond is formed by approach from the equatorial side E, the group R must eclipse the equatorial group e, somewhere along the reaction coordinate. For bond formation with approach from the axial side A, the eclipsing is continually decreasing as rehybridization occurs (*20*, *22*). In addition, Cherest and Felkin (*23*) have pointed out that eclipsing of a partially formed equatorial bond with the axial group on C-2 will be greater than

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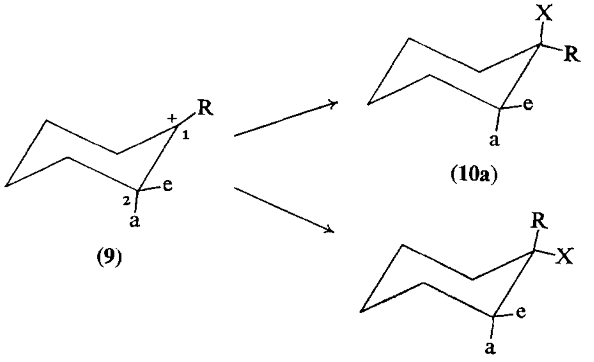
[2] The distance between C-1 and the hydrogens at C-5 and C-7 is about 2.55 Å in cation **8b** (*17*). In cation **7b** the distance from the upper half of line AE to these hydrogens is less than 2.4 Å for any point closer to C-9 than 3.6 Å (18) (C—C bond distance = 1.54 Å).

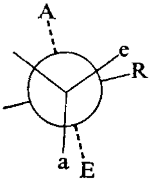
the eclipsing of a partially formed axial bond with the equatorial group at C-2. These two factors are predicted to favor axial bond formation over equatorial bond formation. Cherest and Felkin proposed that in the absence of large remote steric effects, torsional strain will control stereochemistry of bond formation in cyclohexyl systems with one sp^2-hybridized carbon. In the cationic systems we are considering, the magnitude of any torsional strain effect is difficult to evaluate since the extent of bond formation and rehybridization in the transition state cannot be predicted. However, as shown above,



(9)

(10a)

(10e)



(11)

large remote steric factors are predicted to be present and thus are expected to be the controlling factor in predicting stereochemistry.

It should be pointed out that the geometry of the transition state for attack of a carbonium ion on a double bond may be important. The exact geometry cannot be determined. However, if the attack of the double bond on a cationic center involves a

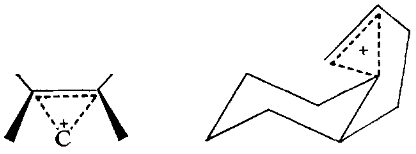
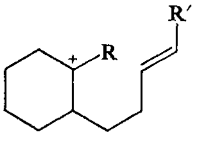


Fig. 5.

transition state with "bridged-ion" character (Fig. 5), such a transition state would further increase the unfavourable steric interactions between the methylene of the double bond and the axial hydrogens at C-5 and C-7 in the case of axial attack. The "bridged-ion" transition state might also be expected to decrease torsional strain of the type proposed by Cherest and Felkin.

It should be pointed out that the specific cases discussed above are not the most favorable cases for stereoselectivity. The addition of substituents to the double bond (e.g., **12**) or the addition of axial substituents to the cyclohexyl ring (e.g., **13**) would be expected to greatly increase the steric interactions in the transition state leading to *cis* products. Thus, these structural features, which are found in many of the cyclizations reported in the literature, are expected to lead to even greater *trans* selectivity.



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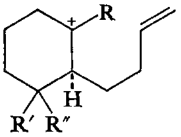
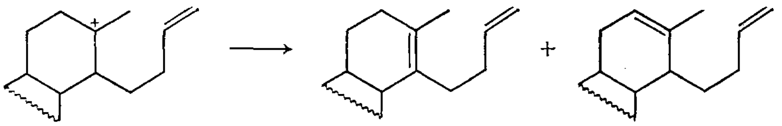


(13)

DISCUSSION

On the basis of the above theoretical analysis and on recent experimental results supporting this analysis (*24*), some of the classical examples of biogenetic-like olefin cyclization will be reviewed and analyzed in terms of the potential involvement of alicyclic cations.



(14) **(15a)** **(15b)**

FIG. 6.

Application of the above theoretical considerations to literature examples of olefinic cyclization is complicated by several factors. It is probable that one mechanism alone cannot account for all of the examples known. For example, Johnson has obtained evidence indicating that bridged-ion intermediates are involved in solvolytic cyclization of sulfonate esters (*12*). More recent results on acetal and allylic alcohol cyclizations suggest that bridged ions are not involved in those cases (*12*). A problem that severely complicates analysis of mechanisms is the possibility of deprotonation reactions leading to olefinic intermediates (Fig. 6). If deprotonation of a cationic intermediate does occur (e.g., **14** → **15**), the possibility of *cis*-fused products being formed by concerted *trans*-addition to the double bond must be considered (*10*). Thus, some or all of the cyclic product could arise from a mechanism not involving attack on a carbonium ion. Another complication that arises in some olefin cyclizations is the possibility of a direct displacement mechanism not involving a symmetrical cation (Fig. 7). With this mechanism stereochemistry of the cyclization is controlled by the stereochemistry of the starting material or intermediate undergoing the displacement.

Before reviewing classical examples of olefinic cyclizations, the results of a study undertaken specifically to avoid the above complications will be presented. In our laboratories we undertook a study of the cyclization of alcohol **16** for this purpose (*24*). Alcohol **16** was selected for several reasons. A cyclization substrate with an equatorial side chain was assured since the alternate conformation is highly destabilized by 1,3-diaxial interactions. The exocyclic allylic alcohol system provided a means for facile initiation of cationic cyclization without complications arising from elimination-reprotonation reactions. The geometries of the starting material and of the cationic intermediate derived from it are the same; thus, reaction must involve attack on a cyclohexyl system with the reactive carbon sp^2-hybridized. Finally, the steric interactions of the exocyclic system are similar to those in the methylsubstituted cyclohexyl system.

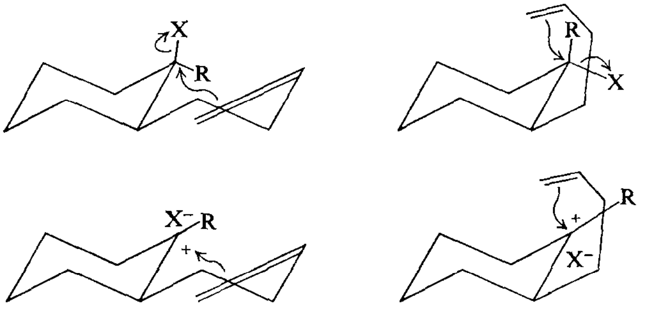
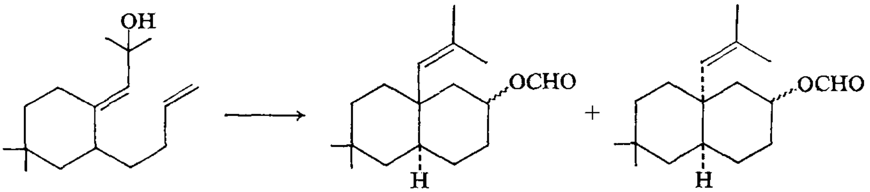
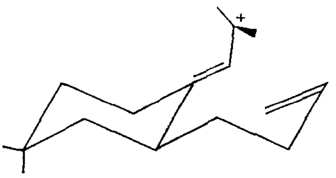


FIG. 7.



(16) (17) (18)

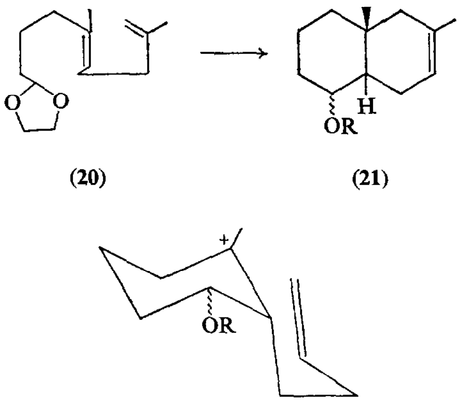


(19)

Cyclization of alcohol **16** at room temperature with formic acid was shown to give a mixture of *trans*-fused products, **17**, and *cis*-fused products, **18**, in a ratio of ~90:10. Thus, in this simplest case, intramolecular attack of a monosubstituted double bond on a conformationally fixed cyclohexyl system with one sp^2-hybridized atom (cation **19**) is shown to be stereoselective for formation of an equatorial bond. This result indicates that steric interactions are more important than torsional interactions and strengthens the prediction that additional substituents on the terminal end of the double bond or axial substituents located at C-3 or C-5 should increase stereoselectivity[3].

On the basis of the results obtained with alcohol **16**, it is possible to rationalize many stereoselective olefin cyclizations on the basis of cationic intermediates. The results do not prove that such a mechanism is the one operating in a particular case, but it does show that cationic intermediates cannot be excluded on the basis of high observed stereoselectivity as originally proposed by early workers in the area (*10*). As discussed below, the results do provide evidence regarding olefinic cyclizations which proceed with low stereoselectivity.

For alicyclic cations to account for the results in stereoselective cyclizations involving *cis* double bonds, a further hypothesis must be made in some cases. It must be considered that conformational inversion of cationic intermediates is slow with respect to the rate of further cyclization (Figs. 3 and 8). Johnson has previously argued that this is not an unreasonable assumption (*12*). Thus, in the cyclization of acetal **20** to form the *cis*-decalin system **21**, cation **22** can form only *cis* products as observed, provided that conformational inversion does not occur before cyclization.



(20) (21)

(22)

FIG. 8.

At this point it becomes possible to consider some of the other reported cyclizations in terms of mechanisms involving alicyclic cations.

One of the early cyclizations studied to test the Stork–Eschenmoser hypothesis was the conversion of olefin **23** (and the *cis*-isomer **24**) into the bicyclic product **25** with strong acid catalysis (*26*, *27*). In this case both isomers gave only *trans*-fused product. Evidence indicating that a monocyclic olefin such as **26** was an intermediate in this cyclization has been presented (*10*, *27*, *28*). The obtention of only *trans*-fused products in the cyclization of olefin **26** shows that concerted *trans*-addition to the double bond is

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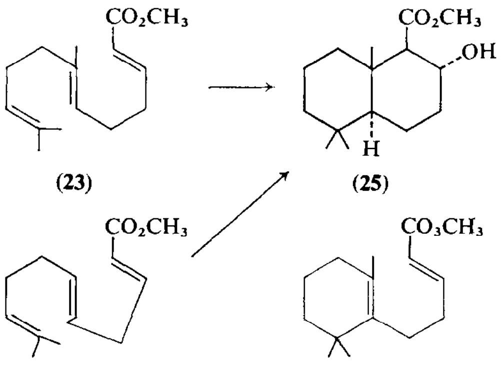
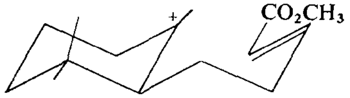
[3] The introduction of a sterically demanding group at the cationic carbon can lead to a case where the "eclipsing" strain becomes a very important consideration. The cyclization of 1-phenyl-2-(3-butenyl)-4,4-dimethylcyclohexanol has been shown to give *cis*-fused products almost exclusively (25).

not occurring in this case. This result is most readily explained through use of an alicyclic cation as an intermediate. This has been suggested previously (*27*, *29*) to be a result of the carbomethoxy group reducing the nucleophilicity of the adjacent double bond so that attack of the double bond is not synchronous with protonation. Protonation of the internal double bond would be expected to lead to the cation **27**, and cyclization of this cation should lead to highly stereoselective equatorial bond formation based on the arguments presented above. The axial substituent on the ring and the substituent on the double bond would lead to severe steric interactions in the transition state resulting from axial approach to form *cis* product.



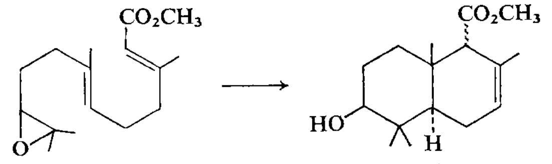
(23) (25)

(24) (26)



(27)

A related cyclization has been studied by van Tamelen and co-workers (*14*) utilizing epoxides **28** and **29** as substrates. In this case cyclization of *trans*-epoxide **28** gave only *trans*-fused products (**30**), and *cis*-epoxide gave *cis*-fused products (**31**). Thus, whereas cyclization of olefins **23** and **24** appears to involve a common intermediate, most logically cation **27**, cyclization of epoxides **28** and **29** cannot involve a common intermediate. If the epoxide cyclization does involve an alicyclic cation mechanism rather than a concerted or bridged-ion mechanism, cyclization of *cis*-epoxide **29** must give a monocyclic cation with an axial side chain and cyclization of *trans*-epoxide **28** a cation with an equatorial side chain similar to cation **27**. Provided that cyclization occurs faster than conformational interconversion of these two cations (as discussed for cation **22** in Fig. 8), this mechanism would account for the observed stereoselectivity with one cation giving only *cis*-fused product and the other cation giving only *trans*-fused product. These examples provide one illustration of the effect of changes in cyclization conditions and/or of the functional group initiating cyclization on the stereochemical course of olefinic cyclizations.



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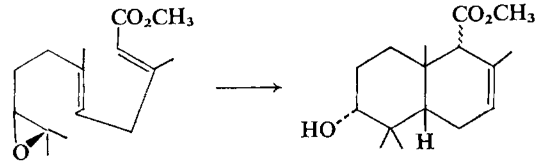


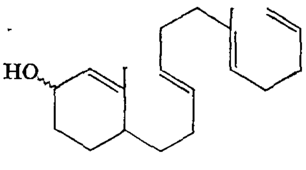
(29) (31)

The cases which must be examined the most critically in light of the conclusions reached above are those in which *cis* products are obtained in much higher proportion than predicted. It is noteworthy that such cases will most often involve substrates where cyclohexenyl intermediates are almost certainly involved. The cyclization of the monocyclic alcohol **32** provides one example of this type (*30*). Cyclization of alcohol **32** in formic acid produced, in addition to the expected product **33**, some of the C, D-*cis* alcohol **34**. The *cis* product **35** was shown to arise from partially cyclized intermediates such as tricyclic olefins **35** and **36** by deuterium incorporation studies. The ratio of *trans* to *cis* products could be varied in this case by changing the cyclization conditions.

Olefinic intermediates have been suggested to be important in the cyclization of 2-(3-butenyl)-1-methylcyclohexanol (**37**) and related compounds by Hibbit and Linstead and later by Johnson and Doshan (*31*). Their studies indicated that acid-catalyzed cyclization led to cyclohexenyl intermediates prior to cyclization. A variety of products was obtained, but methyldecalols could be obtained in ~55% yield. In these studies *cis* products predominated over *trans* products. A mechanistic understanding of this cyclization is complicated by the possibility of conformational inversion of the starting alcohols and of any intermediates involved.

This problem was circumvented in our laboratories by use of alcohol **38** (*32*). Cyclization of this alcohol gave a high yield of bicyclic formates in which the ratio of *cis* to *trans* products was greater than 90:10. Cyclization with deuterioformic acid gave product in which over 86% of the product had incorporated one or more deuterium atoms (49%d_1, 26%d_2, and 11%d_3). This cyclization shows that acid treatment of tertiary cyclohexanols leads to rapid dehydration, and indicates that in this case the predominant pathway for cyclization is concerted protonation–cyclization giving *cis* products (Fig. 9) rather than protonation to the cyclohexyl cation **39**. Thus, this cyclization differs from the example of olefin **26** in the ratio of concerted cyclization to cyclization via a cyclohexyl cation. It might be expected that other examples might exhibit an intermediate ratio for these two reaction pathways.

The above results and the concept of stereoselective attack of olefins on alicyclic cations allow two sets of contrasting cyclization results reported in the literature to be rationalized.



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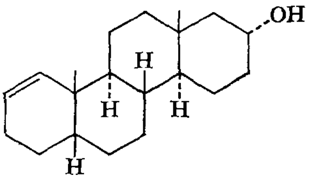

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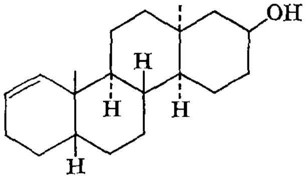

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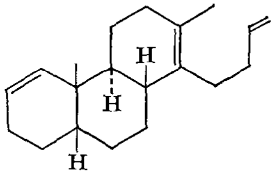

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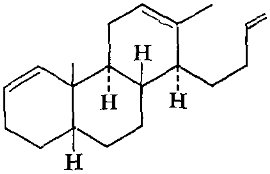

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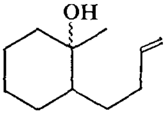

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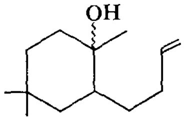

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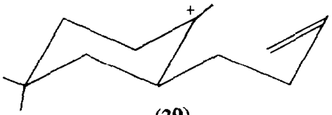

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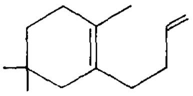

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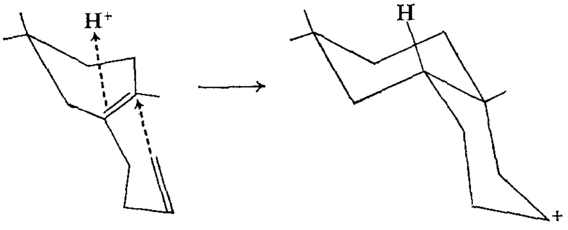

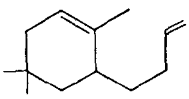

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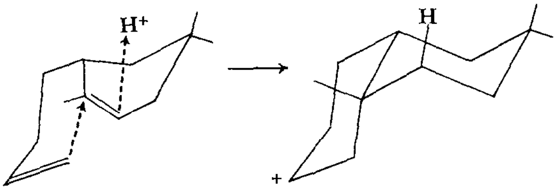
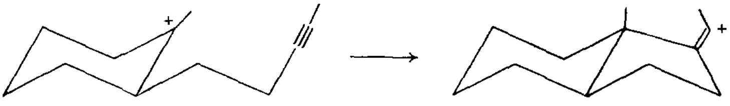
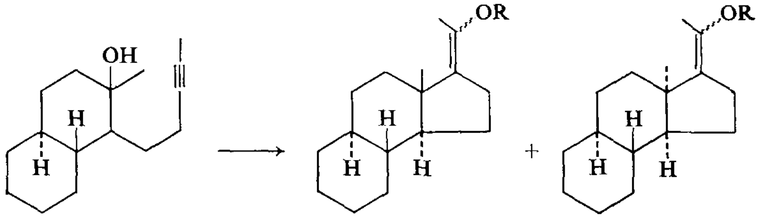


FIG. 9.

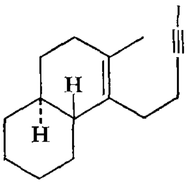
The first case involves formation of five-membered rings. Although not explicitly covered in the theoretical section above, similar steric arguments can be made for stereoselective equatorial attack of the triple bond of a 3-pentenyl side chain on a cyclohexyl cation (**42** → **43**). Lansbury (*33*) has reported that acid-catalyzed cyclization of alcohol **44** forms the tricyclic compounds **45a** and **45b**. The ratio of *trans: cis* products



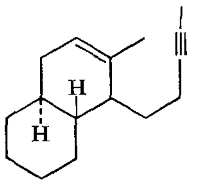
(42) **(43)**



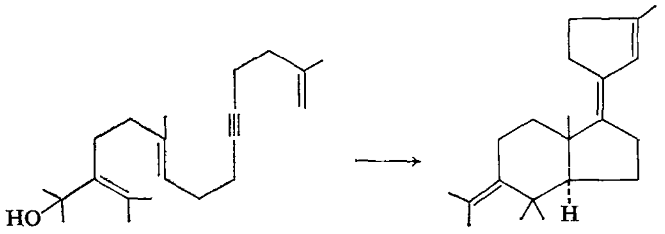
(44) **(45a)** **(45b)**



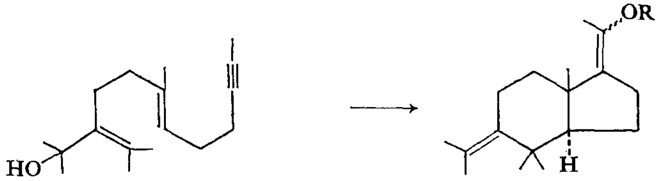
(46a)



(46b)



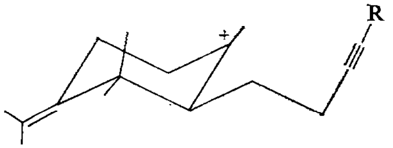
(47) **(48)**



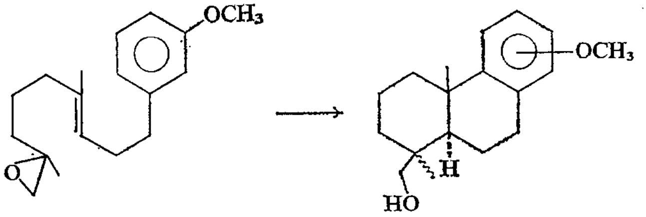
(49) **(50)**

ranged from 80:20 to 60:40 depending upon conditions. The significant fact is that substantial amounts of *cis*-fused products are formed. In contrast, Johnson (*9e*, *34*) reported no evidence for formation of *cis*-fused products in the cyclizations of alcohols **47** and **49**.

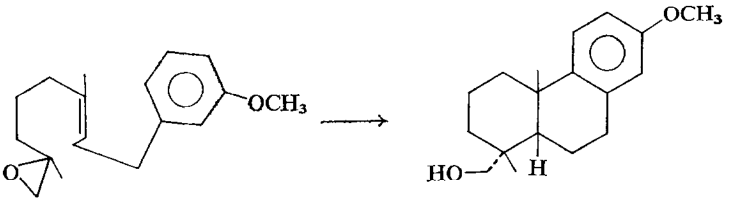
These two sets of results can be readily explained on the basis that some elimination to olefins **46a** and **46b** almost certainly occurs in the cyclization of alcohol **44**. Although reprotonation to the cyclohexyl cation could occur, this cation is predicted to give *trans*-fused products with high selectivity. However, concerted protonation–cyclization of these olefins would give only *cis*-fused products (*10*)[4]. The stereoselective cyclization of alcohols **47** and **49** can then be accounted for by cyclization through cation **51** which, without deprotonation, undergoes stereoselective equatorial attack.



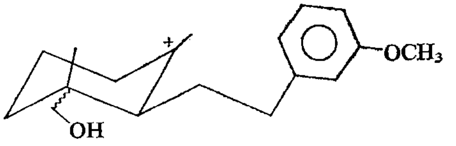
(51)



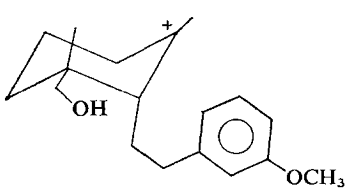
(52) (53)



(54) (55)



(56)



(57)

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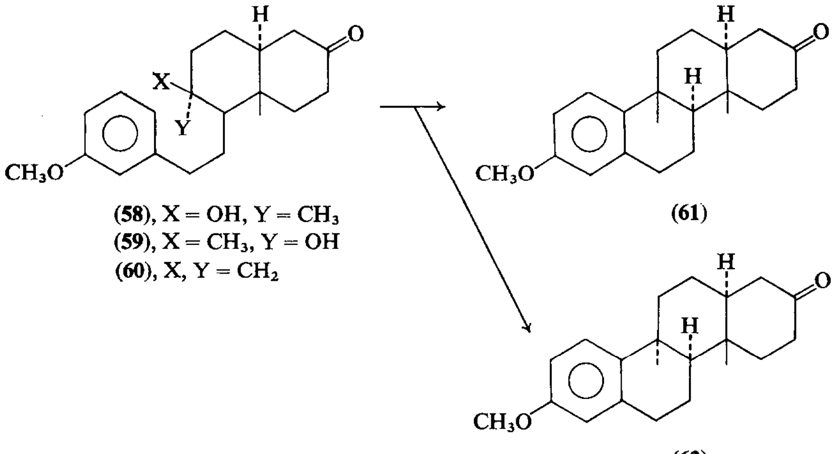
[4] Similar arguments can be used to account for Lansbury's results with 4-chloro-3-pentenyl side chains (35).

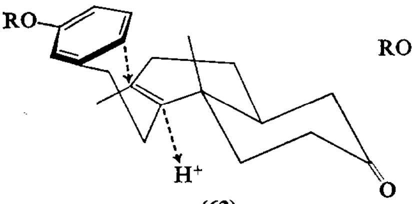
Another case involves cyclizations with aromatic ring systems. Goldsmith (*9a*) reported that cyclization of epoxide **52** gave tricyclic products with *trans*-fused rings only (**53**), and that cyclization of epoxide **54** gave tricyclic material with *cis*-fused rings (**55**). These results would be compatible with alicyclic intermediates such as **56** and **57** in which cyclization is faster than conformational inversion and attack of the aromatic ring on cation **56** is selective for equatorial attack as predicted[5].



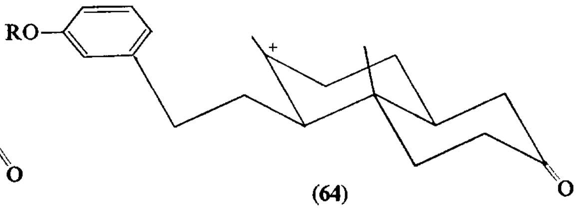
(**58**), X = OH, Y = CH_3
(**59**), X = CH_3, Y = OH
(**60**), X, Y = CH_2

(**61**)

(**62**)



(**63**)



(**64**)

In contrast, Ireland (*36*) has reported that the cyclization of alcohols **58** and **59** and olefin **60** gave tetracyclic products **61** and **62** with a *trans*/*cis* ratio of ~3. Thus, ~25 % of the product was *cis*-fused in a case for which steric arguments would predict high *trans* stereoselectivity. The differences between these two sets of results can be readily

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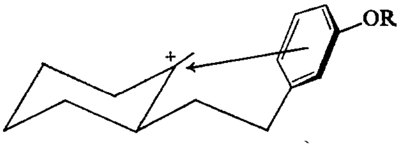
[5] It should be noted that Goldsmith (*9a*) rationalized his results through the use of alicyclic cations, but invoked π-complexing (e.g., i) as a means of insuring conformational stability and stereoselectivity. Our results suggest that such complexing may not be necessary to account for the stereoselectivity, but do not exclude such complexing.



(i)

explained in terms of some formation of cyclic products from olefin **63** by concerted protonation–cyclization rather than only through cation **64** as proposed by Ireland[6, 7].

In the above examples it is seen that *cis*-fused products are formed in large amount only in those cases in which deprotonation to olefinic intermediates is expected and the formation of *cis* products by the concerted mechanism originally postulated by Stork (*10*) is possible[8].

Many studies with allylic alcohols, acetals, and terpene terminal epoxides (e.g., *8a*, *8b*, *9c*, *9e*, *9f*) which have led to stereoselective cyclization can be rationalized by any of the three basic mechanisms and will not be discussed separately. The examples chosen for discussion above were those in which application of the concepts of stereoselective cyclization from alicyclic cation intermediates allow new interpretations of the results.

CONCLUSIONS

The concept of stereoselective equatorial C—C bond formation in the intramolecular attack of a double bond (or similar functional group) on a cyclohexyl cation is supported by both experimental results and theoretical analysis. This conclusion removes the major argument against the potential involvement of alicyclic cations in biogenetic-like olefin cyclizations. Thus, consideration of cationic intermediates in such reactions must not be excluded on the basis of high stereoselectivity. However, more than one mechanism is undoubtedly necessary to account for all examples of biogenetic-like olefin cyclizations. The analysis presented in this paper indicates that concerted protonation–cyclization of cyclohexenyl intermediates may account for cyclization results previously rationalized as occurring through nonselective cyclization of cyclohexyl cations. In particular, the cyclization of methylcyclohexanols appears to lead often to cyclohexenyl intermediates and cyclization to *cis*-fused products.

The results discussed above serve to emphasize again the problems in selecting model substrates for study of olefin cyclizations related to terpenoid biogenesis. Both the means of initiating cationic cyclization and the reaction conditions are important factors in such studies.

The results reviewed above also lead to conclusions with regard to the role of enzyme control in *in vivo* cyclizations. The demonstrated influence of steric factors in favoring stereoselectivity in olefinic cyclizations can be applied to enzymatic reactions. Thus, irrespective of the specific mechanistic details of the cyclization of polyolefins mediated by enzymes, intrinsic steric factors as well as previously recognized stereoelectronic factors favor stereoselectivity. As the extensive work with terpene epoxides by van Tamelen (*8b*, *9c*) has shown, the key enzyme functions for these reactions are prevention of side reactions and specific direction of the reaction through one of several possible conformations and pathways.

[6] A complete analysis of aromatic cyclialkylations has not been attempted at this time because of the complications of conformational mobility, variations in steric factors, and variations in "reactivity" of the aromatic rings.

[7] The results from cyclization of alcohol **16** (see above) contradict Ireland's proposal that torsional strain leads to preferential *cis*-fused ring systems in the absence of very large steric interactions (*36*).

[8] It may also be worthy of note that some of the conditions in which preferential axial attack of solvent on cyclohexyl systems is observed are those where elimination to cyclohexenes is expected (*15*).

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