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Nonenzymic Biogenetic-like Olefinic Cyclizations

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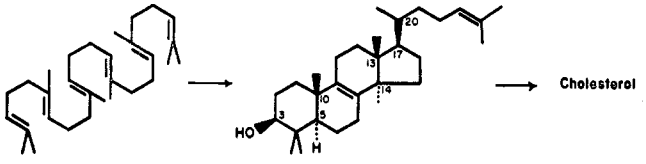
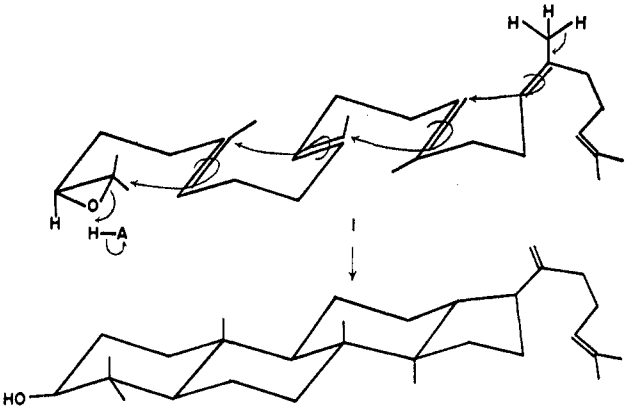
Formolysis of the dienic sulfonate esters **17** and **20** gives bicyclic products which belong exclusively to the *trans*- and *cis*-decalin series, respectively. Although the yield of bicyclization is low, the stereochemical course of the reaction is dictated by the configuration of the substrates according to the Stork–Eschenmoser hypothesis. Acetolysis of the trienic sulfonate ester **23** (R = $SO_2C_6H_4NO_2$) affords tricyclic material **24** in very poor yield, but the process is highly stereoselective. Stannic chloride catalyzed cyclization of the dienic acetals **31** and **32** proceeds in high yield and with high stereoselectivity to give *trans*- and *cis*-decalin derivatives. The all-*trans* trienic acetal **46** (R = H) similarly gives rise exclusively to *trans,anti,trans* tricyclic material in moderate yield. A study of the cyclization of the tetraenic acetal **49** and the optically active dienic acetal **50** is in progress. Allylic cation promoted cyclizations have also given promising results. Thus the dienol **51**, on treatment with formic acid, gives a high yield of bicyclic material **52**. Similarly dienols **53** and **55** both give the *cis*-octalol **54**. The trienol **62** undergoes cyclization in essentially quantitative yield and with high stereoselectivity to give a mixture of the olefins **63** and the alcohol **64** which have been converted into *dl*-fichtelite (**65**). Work is in progress on the preparation and cyclization of the tetraenols **70** and **75**.

One of the most important and exciting achievements of modern chemistry has been the elucidation, in extraordinary detail, of the elaborate pathway by which cholesterol is biologically synthesized from acetate.[1] This accomplishment is without parallel, in view of the magnitude of the structural as well as stereochemical complexities that are implicated.



Of all the stages involved in the biogenesis of cholesterol, there is one transformation which is of outstanding interest, particularly to the organic chemist: namely that in which the open-chain polyolefin, squalene, undergoes (enzyme-catalyzed) polycyclization to produce the tetracyclic substance, lanosterol. Particularly impressive about this process is the fact that this substrate, which has no centers of asymmetry, is thus converted into a product with no less than seven asymmetric centers (at C-3, -5, -10, -13, -14, -17, and -20), and although this product therefore is theoretically capable of existing in 128 different stereochemical forms, only a single isomer is produced in the biosynthesis. This is a truly impressive example of a completely stereoselective process.



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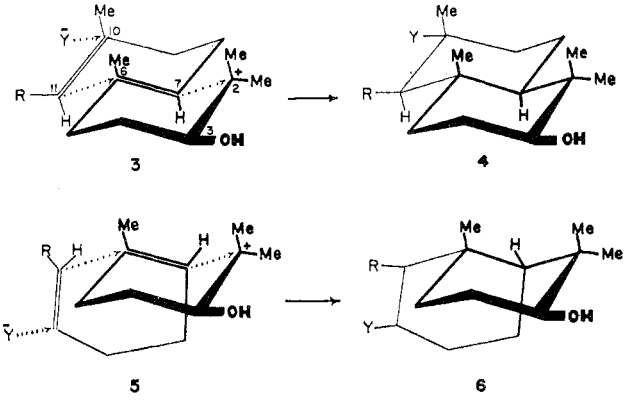
A great many tetra- and pentacyclic triterpenoids are found in the plant world, and many of these substances also appear to be derived biogenetically from squalene. The accompanying formulas depict a way of representing the cyclization of squalene 2,3-oxide (**1**) (which has recently been shown to be an intermediate in the biosynthesis of cholesterol[2]) so as to give

(1) For a recent review see R. B. Clayton, *Quart. Rev.* (London), **19**, 168 (1965).

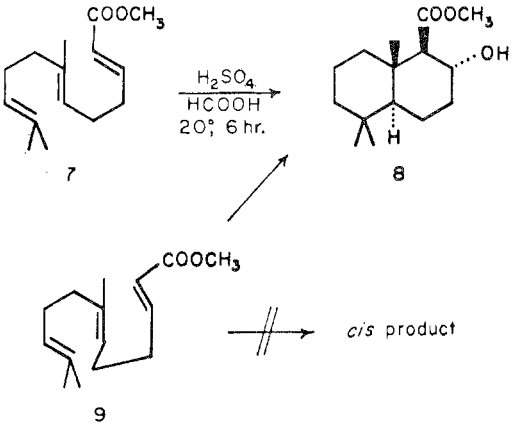
(2) (a) E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *J. Am. Chem. Soc.*, **88**, 4752 (1966); (b) E. J. Corey, W. E. Russey, and P. R. Ortiz de Montellano, *ibid.*, **88**, 4750 (1966).

dammaradienol (**2**), which is found in plants. This transformation (**1** → **2**) is simpler than the squalene to lanosterol conversion which involves some rearrangement of carbon atoms.

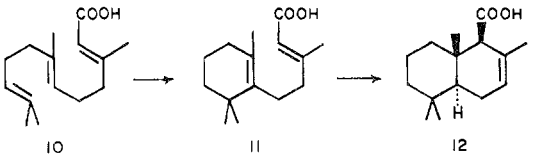
Ever since 1953, when the biosynthetic role of squalene was clearly recognized, organic chemists have been trying to ascertain if squalene or related olefinic systems could be induced to undergo stereoselective cyclization in the absence of enzymes. Such a study has theoretical significance and, if successful, could be of considerable practical importance. The theoretical question to be answered is, how important is the enzyme in directing the course of the cyclization? One popular view is that the enzyme plays an all-important role, *i.e.*, it serves as a template which holds the substrate in a single rigidly folded conformation with the olefinic bonds appropriately juxtaposed for cyclization. There are, on the other hand, some good *a priori* reasons for entertaining the hypothesis that squalene-like (all-*trans*) polyolefins should have an intrinsic susceptibility to cyclize stereoselectively to give a product having "natural" configuration. This concept was set forth independently by Stork[3a] and Eschenmoser[4] in 1955, and the idea may be illustrated as set forth below.



Consider formula **3** which depicts a carbonium ion resulting from protonation of squalene 2,3-oxide followed by opening of the epoxide ring. In essence, the Stork–Eschenmoser hypothesis states that electrophilic attack on the 6,7 olefinic bond by the developing carbonium ion center (at C-2) will be accompanied by a nucleophilic attack by the 10,11 olefinic bond (so as to effect bonding at C-11) in such a way that the addition to the 6,7 olefinic bond is *trans*. If this olefinic bond has *trans* geometry (as in squalene), then the rings of the product **4** will be *trans* fused (most commonly found in nature). The stereochemical course of the process thus resembles the result of the addition of bromine to *trans*-butene-2 which gives *meso*-2,3-dibromobutane. If, in the reaction **3** → **4**, Y^- is an external nucleophile, the process is interrupted at the bicyclic stage, as shown; if, on the other hand, Y^- represents an olefinic bond in the side chain R, the cyclization process continues. A corollary to the Stork–Eschenmoser hypothesis is that if the 6,7 olefinic bond has *cis* geometry, as in formula **5**, then the rings of the cyclization product **6** will be *cis* fused.



With the aim of testing this hypothesis, Eschenmoser[5] examined the acid-catalyzed cyclization of *trans*-desmethylfarnesic ester (**7**) which, gratifyingly, gave the product **8** of "natural" configuration in 60–70% yield. However, the same product was produced when the *cis* substrate **9** was submitted to these cyclization conditions; none of the *cis* product was found.[6] An explanation of these results came from the work of Stork,[3] who proved that boron trifluoride catalyzed cyclization of farnesic acid (**10**) proceeded *via* an isolable intermediary monocyclic diene, **11**, which undergoes further cyclization to give the *trans* bicyclic product **12**. Surely a similar monocyclic diene was involved as a common intermediate in the cyclization of esters **7** and **9**. These cyclizations, therefore, are proceeding by a mechanism which is clearly different from that involved in the enzymic cyclization of squalene which, as shown by Bloch,[7] cannot involve partially cyclized intermediates that are reprotonated, because there was no deuterium incorporation when the enzymic cyclization was carried out in a deuterium oxide medium.



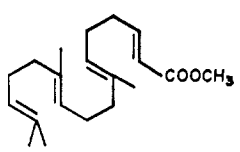
(3) (a) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); (b) P. A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, *Helv. Chim. Acta*, **40**, 2191 (1957).

(4) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *ibid.*, **38**, 1890 (1955).

(5) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *ibid.*, **40**, 1373 (1957).

(6) A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Stadler in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Connor, Ed., J. and A. Churchill, Ltd., London, 1959.

(7) T. T. Tchen and K. Bloch, *J. Am. Chem. Soc.*, **78**, 1516 (1956); *J. Biol. Chem.*, **226**, 931 (1957). However, see footnote 11 of E. E. van Tamelen, J. D. Willett, and R. B. Clayton, *J. Am. Chem. Soc.*, **89**, 3371 (1967), regarding the interpretation of the former work.



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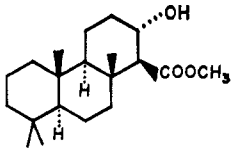
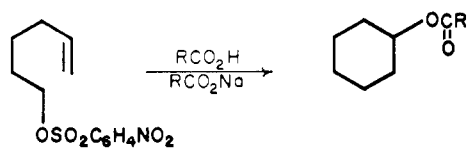


14

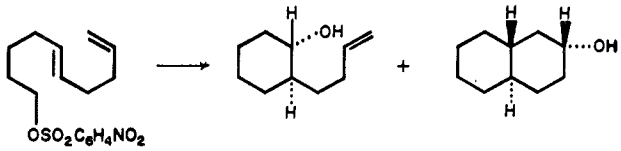
Eschenmoser[6] has also examined the acid-catalyzed cyclization of the trienic ester **13**, which gave the *trans,anti,trans* tricyclic material **14**, but in only 5–10% yield. Eschenmoser states: "Apart from it and from a similarly small amount of bicyclic dihydroxy compound, the main product consists of an intractable oily mixture." He concludes: "It seems that with polyenes of this complexity, acid-catalyzed cyclization ceases to be a useful reaction from the preparative point of view."

Seemingly much of the difficulty that has been encountered in the acid-catalyzed cyclization of systems like **13** or squalene is attributable to the probability that protonation of the substrate occurs rather indiscriminately, initiating, in addition to the desired reaction, a variety of other cyclizations. In addition, the relatively strong acidic conditions generally employed are known to be conducive to deprotonation (hence the production of partially cyclized products) as well as to promoting reactions such as addition to and isomerization of the olefinic bonds. It was with the hope of obviating these difficulties that we initiated, in 1960, a search for a polyolefinic substrate containing an appropriately positioned functional group that could be used to generate a cyclizable cationic center (on carbon) under conditions which would not otherwise affect the olefinic bonds. This requirement appears to be fulfilled, at least in part, by certain polyolefinic epoxides which are being examined by Goldsmith[8] and van Tamelen.[9] Unfortunately limitations in space preclude a review of these most interesting studies. The remainder of the present paper will be confined to consideration of selected aspects of studies of the cyclization of polyolefinic sulfonate esters, acetals, and allylic alcohols.



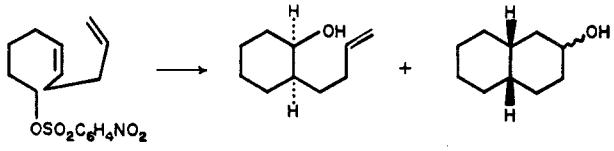
15 16

Cyclization–Solvolysis of Olefinic Sulfonate Esters. The acetolysis[10] or formolysis[11] of 5-hexenyl *p*-nitrobenzenesulfonate (**15**) proceeds with some rate enhancement due to participation of the olefinic bond with concomitant ring formation to produce the corresponding ester **16** of cyclohexanol. In view of this promising cyclization, we were prompted to examine the formolysis of *trans*-5,9-decadienyl *p*-nitrobenzenesulfonate (**17**), which was prepared[11] by a perfectly straightforward method. The solvolysis[11,12] proceeded with significant rate enhancement to produce a rather complex mixture of products which was examined thoroughly. After cleavage of the formate esters it was possible to show that the major component, produced in 35% yield, was the monocyclic *trans* alcohol **18**; none of the *cis* isomer could be detected. The major bicyclic component was *trans,syn*-2-decalol (**19**) ("natural" configuration); moreover, the total bicyclic material (hydrocarbons as well as alcohols), which was formed in about 12% yield, consisted exclusively of *trans*-decalin derivatives; no *cis* product could be found.



17 18 19

Since the formolysis of the *trans* sulfonate ester **17** proceeded stereoselectively to produce only *trans* bicyclic material, it became of special interest to examine the solvolysis of the *cis* isomer **20**. The behavior in this case was very similar to that of the *trans* isomer. A similar mixture of products was produced, but they belonged to the opposite stereochemical series. Thus the major product, formed in 38% yield, was the *cis* monocyclic alcohol **21**; only a trace of *trans* material was found. The total bicyclic material (16% yield) all belonged to the *cis*-decalin series, the alcohol fraction consisting of an epimeric mixture of the *cis*-2-decalols (**22**).



20 21 22

These results of the formolysis of the sulfonate esters **17** and **20** appear to constitute the first example of the stereoselective production of bicyclic material from acyclic substrates according to the predictions of the Stork–Eschenmoser hypothesis. Since the cyclizations of the two isomeric sulfonate esters proceed in exactly the opposite stereochemical sense, the reaction pathways cannot possibly involve a common intermediate; hence we are dealing with a process which is mechanistically quite different from that involved in the cyclization of the dienic acids (**7**, **9**, and **10**). The bicyclization reactions, therefore, must either be concerted processes or involve cationic intermediates which retain the stereochemical integrity of the re-

(8) D. J. Goldsmith and B. C. Clark, Jr., *Tetrahedron Letters*, 1215 (1967), and previous references.

(9) E. E. van Tamelen and R. G. Nadeau, *J. Am. Chem. Soc.*, **89**, 176 (1967), and previous references.

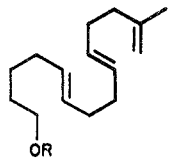
(10) P. D. Bartlett, *Ann.*, **653**, 45 (1962); P. D. Bartlett, W. D. Clossen, and T. J. Cogdell, *J. Am. Chem. Soc.*, **87**, 1308 (1965).

(11) W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jaques, and J. K. Crandall, *ibid.*, **86**, 1959 (1964).

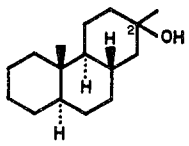
(12) W. S. Johnson and J. K. Crandall, *J. Org. Chem.*, **30**, 1785 (1965).

spective substrates. For reasons which are given elsewhere[12,13] we favor a mechanism involving bridged ion intermediates.

The solvolysis of the trienyl sulfonate ester **23** (R = $SO_2C_6H_4NO_2$) has also been examined.[14] The reaction was performed in acetic acid containing sodium acetate, because the formic acid–sodium formate treatment, which was employed in the aforementioned solvolyses, effected competitive attack on the reactive terminal olefinic bond resulting in addition of solvent or bond migration. The acetolysis product consisted of approximately 20% acyclic, 40% monocyclic, 8–12% bicyclic, and 2.8% tricyclic material. The tricyclic product, after treatment with lithium aluminum hydride to effect cleavage of acetates, was shown to be exclusively the *trans,anti,trans* alcohol **24** (mixture of C-2 epimers). Thus the formation of tricyclic material was highly stereoselective even though the yield was very low.



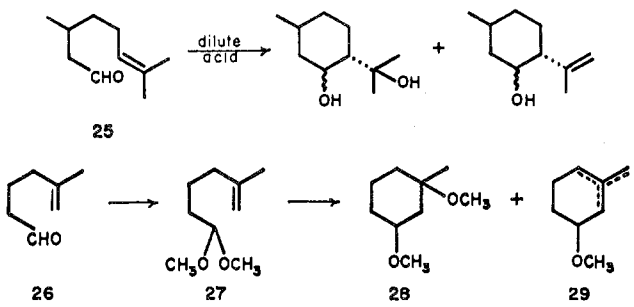
23



24

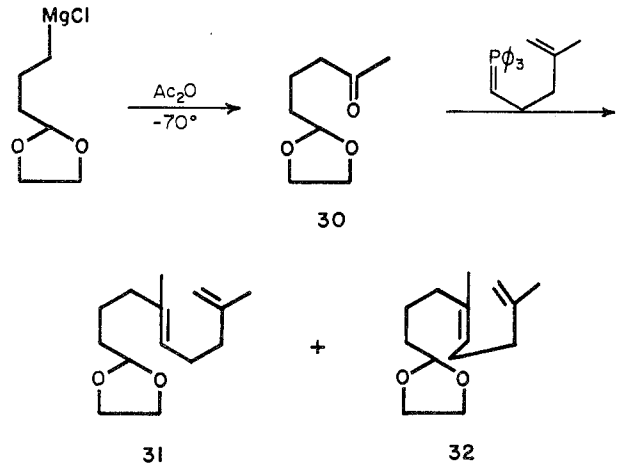
Although the cyclization of sulfonate esters gives the desired stereochemical results, this approach has two major disadvantages: (a) the yields of fully cyclized material are low, and (b) these products are left without any functional group in the first ring, which seriously limits the synthetic utility. With the hope of overcoming these drawbacks, we have been screening a number of other possible substrate candidates. One of these, which shows considerable promise, is the cyclization of olefinic acetals which is considered below.

Cyclization of Olefinic Acetals. The known susceptibility of certain unsaturated aldehydes like citronellal (**25**) to undergo acid-catalyzed cyclization[15] prompted us to explore the possibility of using the aldehydo group to initiate polycyclization of polyolefinic systems. We first considered it essential to ascertain if unsaturated aldehydes having the olefinic bond in the 5 instead of the 6 position would also cyclize readily. The behavior of 5-methyl-5-hexenal (**26**) was therefore studied.[16] When a solution of this aldehyde in methanol containing hydrogen chloride (0.02 *N*) was allowed to stand for 2 hr at 0°, the acetal **27** was formed in quantitative yield. When this same solution was allowed to stand at room temperature, the acetal was completely cyclized, giving a mixture of *cis*- and *trans*-dimethoxymethylcyclohexanes (**28**) and the olefinic ethers



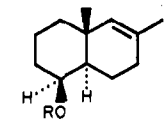
29. The rate of the cyclization process could readily be followed by observing the rate of disappearance of the signal at δ 1.68 ppm (for the C-5 methyl group) in the nmr spectrum of a solution of the acetal **26** in CH_3OD containing hydrogen chloride (0.12 *N*). The half-life for the process was thus estimated to be 8 ± 2 min at 25°. In view of these preliminary results, we turned our attention to the possibility of utilizing acetals instead of aldehydes for the aforementioned objective of producing fused-ring systems from acyclic substrates. In particular we chose to study the *trans* and *cis* dienic acetals **31** and **32**.[17]

A mixture of the two dienic acetals **31** and **32** was prepared by interaction of the acetal ketone **30** with the Wittig reagent from 4-methyl-4-pentenyl bromide, and the components of this mixture were separated by preparative vapor phase chromatography.

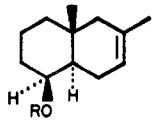


The *trans* dienic acetal **31**, on treatment at 25° with stannic chloride in benzene,[18] underwent a very rapid reaction with the formation of *trans*-bicyclic material in over 90% yield. Spectral analysis (particularly nmr) along with degradation experiments (see below) provided proof that the bicyclic product consisted of the five isomeric substances **33a–37a**. The predominant product (formed in about 60% yield) was the Δ^2 isomer **34a** with a β (axial) side chain (OCH_2CH_2OH). It is of particular interest to note that, when nitromethane was employed instead of benzene as the sol-

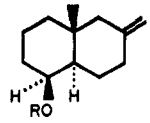
(13) W. S. Johnson, *Trans. N. Y. Acad. Sci.*, in press.
(14) W. S. Johnson and R. B. Kinnel, *J. Am. Chem. Soc.*, **88**, 3861 (1966).
(15) For a short review, see Y. Naves and P. Ochsner, *Helv. Chim. Acta*, **47**, 51 (1964).
(16) H. C. Dunathan and W. S. Johnson, unpublished observations.
(17) W. S. Johnson, A. van der Gen, and J. J. Swoboda, *J. Am. Chem. Soc.*, **89**, 170 (1967).
(18) *Cf.* D. J. Goldsmith, B. C. Clark, Jr., and R. C. Joines, *Tetrahedron Letters*, 1211 (1967).



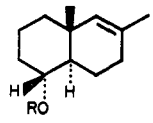
33a (R = CH_2CH_2OH)
33b (R = H)



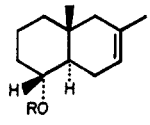
34a
34b



35a
35b

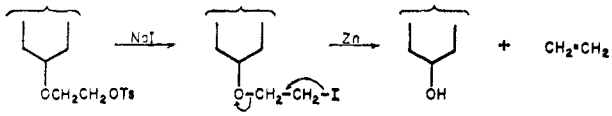


36a
36b

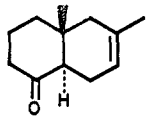


37a
37b

vent for the cyclization, this isomer was obtained in over 80% yield. Except for the substance **35a** with the *exo* double bond, each of these isomers was obtained in a fairly pure state by preparative vapor phase chromatography. The side chain was removed by conversion to the tosylates followed by treatment with zinc and sodium iodide in glyme, giving the secondary alcohols **33b**, **34b**, **36b**, and **37b**.



Oxidation of the two Δ^2 epimers **34b** and **37b** with Jones reagent[19] yielded a single octalone, **38**. Similarly, both Δ^1 epimers **33b** and **36b** yielded a single octalone, **39**. These octalones were converted, by sodium borohydride reduction of their tosylhydrazones,[20] into the *trans*-dimethyloctalins **40** and **41**, respectively, which were identified by comparison with authentic specimens prepared by independent synthesis.



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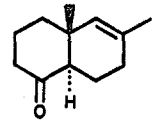

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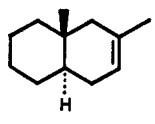

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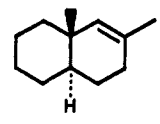
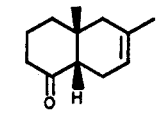


41

The *cis* dienic acetal **32** also readily underwent cyclization to give mainly bicyclic products which were completely different from those found in the *trans* series. The total cyclization mixture was submitted to the degradation and oxidation sequence described above, and the mixture of octalones, obtained in 78% over-all yield, was shown to consist of the Δ^2 isomer **42** and the Δ^1 isomer **43** in a ratio of about 2:1. The structure and configuration of the pure octalones, separated by preparative vapor phase chromatography, were proved by reduction, as described above, to the corresponding hydrocarbons **44** and **45**, respectively. The base-catalyzed interconversion of the *cis*- and *trans*-octalones was also examined. At equilibrium the ratio **42**:**38** was about 1:3, and **43**:**39** about 4:1.



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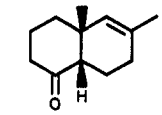

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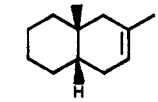

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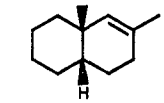
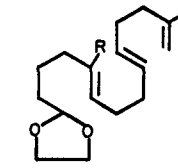


45

Thus an acyclic system had been found which undergoes bicyclization in high yield and with high stereoselectivity according to the predictions of the Stork–Eschenmoser hypothesis. Moreover, the cyclization products have usefully located functional groups. The kinetics of these olefinic acetal cyclizations are quite different from those of the solvolysis of sulfonate esters and are consistent with a mechanism involving initiation by a transition state which resembles a monocyclic classical carbonium ion.[13]



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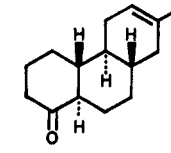

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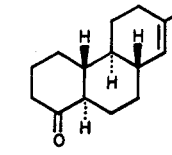


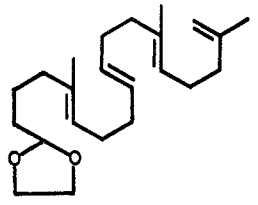
48

The next objective was to examine the possibility of producing a tricyclic product from an acyclic trienic acetal. The acetal **46** (R = H) was easily produced[14] by oxidation of alcohol **23** (R = H) by the Barton method,[21] followed by acid-catalyzed reaction of the resulting aldehyde with ethylene glycol. The trienic acetal **46** (R = H) underwent cyclization[14,22] by the benzene–stannic chloride method much more slowly than the dienic acetals **31** and **32**, because of the lower nucleophilicity of the olefinic bond (di- instead of trisubstituted) involved in the reaction with the acetal function. The crude cyclization mixture was submitted to the degradation–oxidation sequence described above, and in this way the ketones **47** and **48** were pro-

(19) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(20) L. Caglioti and P. Grasselli, *Chem. Ind.* (London), 153 (1964); L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963).
(21) D. H. R. Barton, B. J. Garner, and R. H. Wightman, *J. Chem. Soc.*, 1855 (1964).
(22) W. S. Johnson and A. van der Gen, unpublished observations.

duced as the exclusive tricyclic products in about 50% yield. The configurations of these isomers, which could be separated by vapor phase chromatography,[22] were proved by Wolff–Kishner reduction to the corresponding olefins which were identified by comparison with authentic materials prepared by an independent stereorational synthesis.[14] Thus tricarbocyclic products have been produced in fair yield and with high stereoselectivity from an acyclic substrate. In work that is as yet incomplete,[23] the cyclization of the trienic acetal **46** (R = CH_3) is being examined. This reaction proceeds much more rapidly than the cyclization of the lower homolog **46** (R = H), and the yields of tricyclic material appear to be higher.

In other work that is not yet completed, we have prepared the tetraenic acetal **49**[24] and are examining[25] its cyclization in the hope of obtaining tetracyclic products. We are also studying the cyclization of the acetal **50** derived from *l*-butane-2,3-diol.[26] Preliminary results indicate that this reaction is proceeding with significant asymmetric induction, and in a formal sense the process simulates the results of biocyclizations in that optically active products are formed. Since the absolute configuration of the acetal **50** is known (*R,R*), we feel that, when the absolute configuration of the cyclization product has been ascertained, a clue to the intimate geometry of the transition state for the acetal cyclization reaction may be forthcoming. Thus it is hoped to pin down the reason for the preference for formation of the high-energy cyclization product with an axial side chain, *e.g.*, **34a**.



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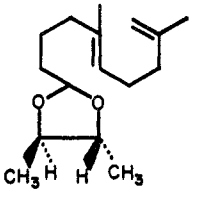
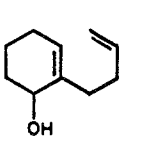


50

Allylic Cation Promoted Cyclizations. A simple example of this type of cyclization is the reaction of the butenylcyclohexenol **51** with formic acid to give the octalol **52** as the major product.[27] The reaction proceeds very rapidly in the cold, it is highly stereoselective, and the yield is high. A possible mechanism of the reaction involves rapid formation of cation A followed by cyclization to give cation B which undergoes preferential equatorial attack by solvent.

Another related case that has been examined is the formic acid promoted cyclization of the isomers **53** and **55** which gave products of nearly identical composition.[27,28] The yield of cyclic material was very



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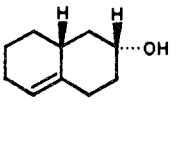

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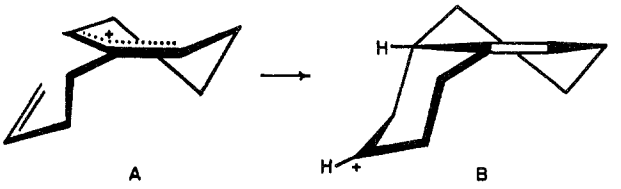
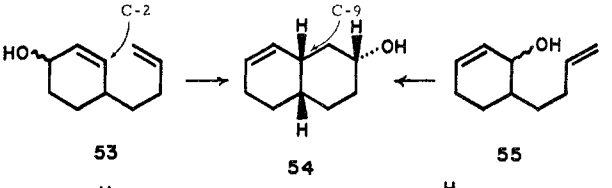
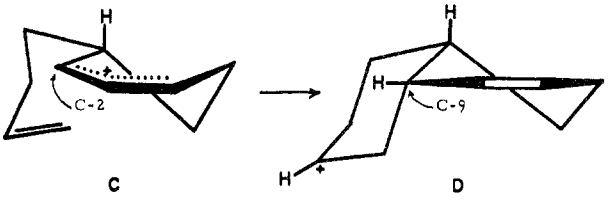


A B

high and the major product was the *cis,syn*-octalol **54**. The process may be envisaged as proceeding *via* cations C → D. The cyclization of the homolog of **53** with a methyl group at C-2 has also been examined.[28,29] The reaction proceeded with very high stereoselectivity to give, in over 90% yield, *cis,syn*-octalol **54** with an angular methyl group in place of the hydrogen at C-9. The ratio of equatorial to axial epimeric alcohols in this case was 97:3, as compared with 84:16 for the system lacking the methyl group. This difference can be rationalized as follows: the substitution of a C-9 methyl in place of H serves to raise the activation energy of axial attack on the cation D, because of the developing 1,3-diaxial interaction between the C-9 substituent and the attacking solvent in the transition state.[28]



53 54 55



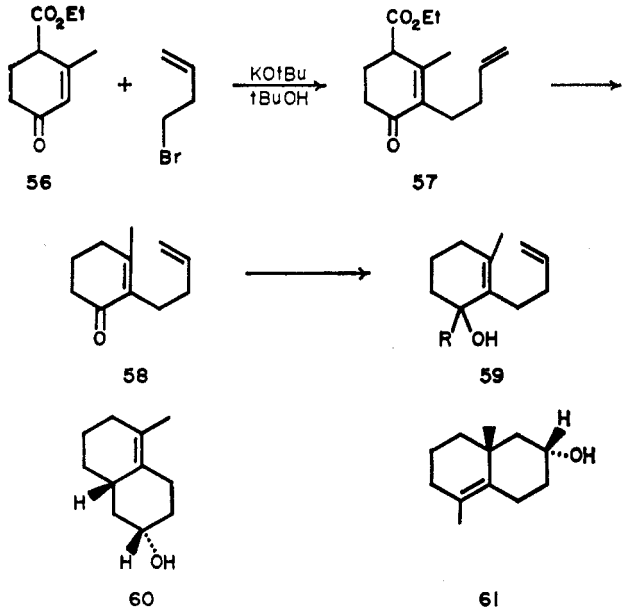
C D

The cyclization of the dienol **59** (R = H) has also been examined.[29] The dienol was prepared by the following steps: (a) alkylation of Hagemann's ester (**56**) with 3-butenyl bromide to give the keto ester **57**, (b) hydrolysis and decarboxylation to afford the dienone **58**, and finally reduction of the dienone with lithium aluminum hydride. The dienol **59** (R = H), on treatment with formic acid, underwent rapid cyclization to give the octalol **60** along with diols derived from the addition of formic acid to the olefinic bond of **60**. There was no evidence of cyclization in the other direction to give the product with an angular methyl group. Marshall[30] in-

(23) W. S. Johnson and V. A. Fung, work in progress.
(24) W. S. Johnson and S. F. Brady, unpublished observations.
(25) W. S. Johnson and K. Wiedhaup, work in progress.
(26) W. S. Johnson, R. D. Stipanovic, and C. A. Harbert, work in progress.
(27) W. S. Johnson, W. H. Lunn, and K. Fitzi, *J. Am. Chem. Soc.*, **86**, 1972 (1964).
(28) W. S. Johnson and K. E. Harding, *J. Org. Chem.*, **32**, 478 (1967).
(29) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Am. Chem. Soc.*, **87**, 5148 (1965).
(30) J. A. Marshall and N. Cohen, *ibid.*, **87**, 2773 (1965); J. A. Marshall, N. Cohen, and A. R. Hochstetler, *ibid.*, **88**, 3408 (1966).

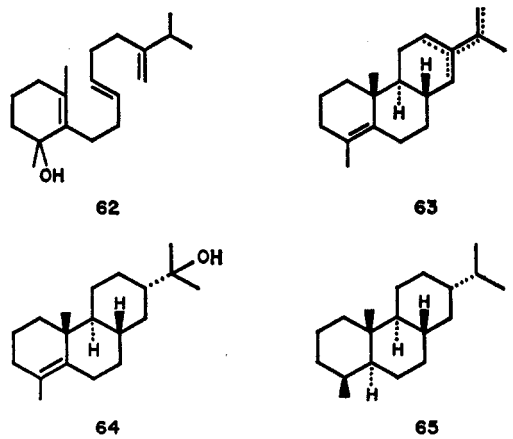
vestigated the cyclization of the dienol **59** (R = CH_3), which was produced by the addition of methyllithium to the dienone **58**. The cyclization proceeded easily to give dimethyloctalol **61** in excellent yield.

The stage was now set for exploring the possibility of producing tricyclic material by allylic cation promoted cyclization. The substrate chosen for this study was the trienol **62** which was prepared by the general approach described above for making the dienol **59** (R = CH_3). In this case Hagemann's ester (**56**) was alkyl-



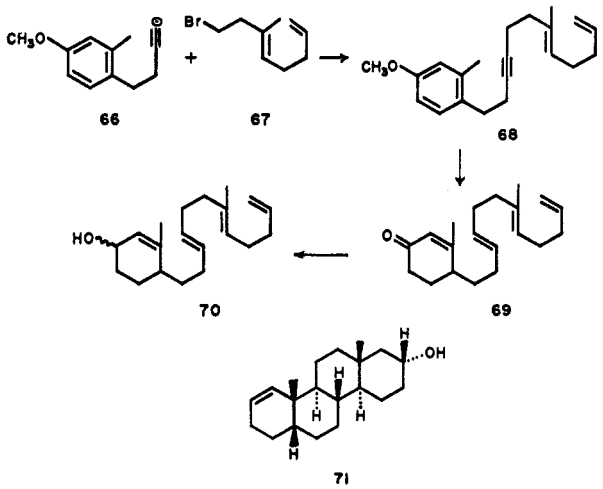
ated with *trans*-1-bromo-7-isopropylocta-3,7-diene.[31]

On shaking with formic acid for 11 min at room temperature, the trienol **62** was converted essentially quantitatively into tricyclic material.[31] The product consisted of a mixture of four hydrocarbons (see **63**) and an alcohol (**64**). These substances were all shown to belong to the same stereochemical series by interconversion experiments and by their transformation into the racemic form of the naturally occurring substance fichtelite (**65**), the configuration of which is known.[32]

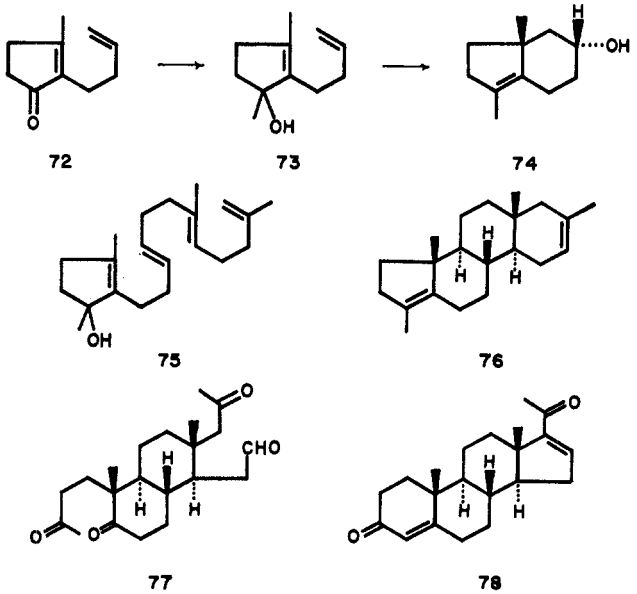


Thus the cyclization of the trienol **62** proceeds essentially quantitatively and with very high stereoselectivity. For the preparation of *dl*-fichtelite, the total crude cyclization product can be treated with phosphorus oxychloride in pyridine (to effect dehydration of the alcohol **64**) and the resulting mixture of dienes hydrogenated over platinum in acetic acid. The resulting mixture contains *dl*-fichtelite which can be separated by preparative vapor phase chromatography in about 50% yield over-all from the trienol **62**.

Currently we are investigating the cyclization of the tetraenol **70**.[33] This substrate was prepared by alkylation of the substituted acetylenic anion **66** with the bromide **67** to give the substance **68** which was converted, *via* Birch reduction, into the tetraenone **69**.



Lithium aluminum hydride reduction of this tetraenone afforded the tetraenol **70**. Formic acid treatment effected cyclization to give a mixture of products, a major component of which was a crystalline alcohol which probably corresponds to the tetracyclic substance **71**, but this point is yet to be proved.[33a]



(31) W. S. Johnson, N. P. Jensen, and J. Hooz, *J. Am. Chem. Soc.*, 88, 3859 (1966).

(32) A. W. Burgstahler and J. N. Marx, *Tetrahedron Letters*, 3333 (1964).

(33) W. S. Johnson and K. E. Harding, work in progress.

(33a) NOTE ADDED IN PROOF. The constitution of this crystalline alcohol has now been established unequivocally by its conversion into *dl*-D-homo-5β-androstan-17-one and comparison with the authentic natural enantiomer synthesized from testosterone.

In another study[34] the dienol **73**, which was produced by the action of methyllithium on the dienone **72**,[35] has been treated with formic acid to give what is almost certainly the bicyclic alcohol **74**. We envisage extending this reaction to the cyclization of the tetraenol **75** which, we hope, will give a significant amount of the tetracyclic diene **76**.[35a] The latter substance, on ozonolysis, would be expected to yield the triketo aldehyde **77** which, by analogy to previous work,[36] should undergo a double intramolecular aldol condensation to give 16-dehydroprogesterone (**78**).

(34) W. S. Johnson and L. A. Dolak, work in progress.
(35) F. B. LaForge, N. Green, and W. A. Gersdorff, *J. Am. Chem. Soc.*, **70**, 3707 (1948).
(35a) NOTE ADDED IN PROOF. M. U. S. Sultanbawa and M. F. Semmelhack have prepared the tetraenol **75** and shown that it gives, on treatment with formic acid, a significant amount of a single crystalline tetracyclic hydrocarbon which we suspect is the substance **76**.
(36) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958); G. Stork, K. N. Khastgir, and A. J. Solo, *ibid.*, **80**, 6457 (1958).

I wish to express my appreciation to my co-workers who are named in the references in connection with their various contributions. These collaborators deserve the major credit for the work from my laboratory that is described in this paper. I wish also to express my thanks to the National Science Foundation, the U. S. Public Health Service, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

The Triplet State: Its Radiative and Nonradiative Properties

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The triplet–singlet radiative transition in aromatic hydrocarbons is the most forbidden electronic transition known for polyatomic molecules. It is thus found that the spin–orbit interaction mechanisms that give the lowest triplet state its radiative properties are sensitive to weak perturbations, *e.g.*, solvent effects, halogen substitution, and lattice vibrations. Explanations are proposed for the observed sensitivity of the mechanisms of these transitions to the different perturbations. In mixed, as well as in pure, aromatic crystals and in some of their derivatives, polarization results indicate that lattice vibrations do not modify the $\pi^* \rightarrow \pi$ phosphorescence mechanisms. On the other hand, a strong coupling between the electronic motion and the lattice motion has been observed in the $\pi^* \rightarrow$ n phosphorescence of the pyrazine crystal in which the intermolecular C—H···N hydrogen bonding constitutes a major part of the lattice energy. The rate of the nonradiative process involving change in multiplicity (intersystem crossing) in compounds having n,π^* and π,π^* states is predicted to be approximately two to three orders of magnitude faster than in compounds having only one of these types of transitions. The importance of the order and the type of the energy levels depends on the validity of the Born–Oppenheimer approximation. The emission decay of pyrazine at very low temperatures (4.2°K) indicates that: (1) intersystem crossing favors the population of one of the triplet sublevels over the others (spin polarization) and (2) spin lattice relaxation between the triplet sublevels is slower than the phosphorescence process.

I. Introduction

The phosphorescence emission of organic molecules in rigid media was first observed[3] in 1895. In 1942, the emission was shown[4] to be electric dipole radiation and in 1944 it was identified[5,6] as radiative intercombination between the lowest triplet state and the ground singlet state. The paramagnetic character of the emitting triplet state was first demonstrated[7] in 1945.

Singlet–triplet transitions are spin forbidden, hence phosphorescence emission requires spin–orbit interaction. In molecules, spin–orbit interactions may have different forms and thus a number of mechanisms can be written down to account for the radiative properties of the $T \rightarrow S$ transition. A large portion of our research efforts during the past few years has been spent on the problem of elucidating these mechanisms and explaining the observed polarization characteristics of the phosphorescence radiation. It is found that, due to the small spin–orbit interactions in organic molecules (0.10–100 cm^{-1} or 0.3–300 cal/mol), the emission mechanism is not unique and is sensitive to rather weak perturbations, *e.g.*, solute–solvent interactions, halogen substitution, and lattice vibrations in certain crystals. These studies are described in more detail in section II.

Until 1961, there was no expression for the intramolecular nonradiative transition probability between

(1) Alfred P. Sloan and Simon Guggenheim Fellow.
(2) Contribution No. 2118.
(3) E. Wiedemann and G. C. Schmidt, *Ann. Physik*, **56**, 201 (1895).
(4) S. Weissman and D. Lipkins, *J. Am. Chem. Soc.*, **64**, 1916 (1942).
(5) G. N. Lewis and M. Kasha, *ibid.*, **66**, 2100 (1944).
(6) A. Terenin, *Acta Physicochim. URSS*, **18**, 210 (1943); *Zh. Fiz. Khim.*, **18**, 1 (1944).
(7) G. N. Lewis and M. Calvin, *J. Am. Chem. Soc.*, **67**, 1232 (1945).
(8) M. Kasha, *Discussions Faraday Soc.*, **9**, 14 (1950).