BIOORGANIC CHEMISTRY 5, 51–98 (1976)

Biomimetic Polyene Cyclizations
A Review

WILLIAM S. JOHNSON

Department of Chemistry, Stanford University, Stanford, California 94305

Received November 17, 1975

It has been shown that certain polyenic substances, having *trans* olefinic bonds in the 1,5 relationship, can be induced to undergo stereospecific, nonenzymic, cationic cyclization to give polycyclic products with the all *trans* ("natural") configuration. These transformations appear to mimic in principle the biogenetic conversion of squalene into polycyclic triterpenoids, e.g., lanosterol. Acetal as well as allylic alcohol functions have proved to be effective initiators for such cyclizations, many of which proceed to a remarkable degree of completion giving mainly totally cyclized products. Thus, it has been possible to convert, in a single step, an open chain tetraenic acetal having no chiral centers, into a tetracyclic product having seven such centers. The process is highly stereoselective giving only two of 64 possible racemates.

Methylacetylenic and also styryl end groups are particularly useful cyclization terminators as they provide a means of realizing five-membered ring formation. Systems with these terminators have been developed for effecting the total synthesis of the steroid nucleus in a single step starting from a substrate containing only one ring.

The mechanism of these biomimetic as well as of the enzymic cyclizations is open to question, but the balance of the evidence is somewhat in favor of a synchronous process.

INTRODUCTION

The strategy for the total synthesis of polycyclic natural products, e.g., steroids and polycyclic triterpenoids, has most generally involved step-by-step annelations, i.e., each new ring is formed one at a time (*1*). The biomimetic approach to total synthesis, on the other hand, entails the formation of a number of rings stereospecifically in a single step via an intramolecular telomerization of an acyclic chain having appositely placed *trans* olefinic bonds. The biomimetic cyclization is analogous to the enzymatic conversion of squalene into polycyclic triterpenoids, e.g., lanosterol, which is the key step in the biogenesis of steroids from acetate as outlined in Fig. 1 (*2*).

In 1955 Stork et al. (*3*) and Eschenmoser et al. (*4*) pointed out that the stereochemical course of the biological cyclization of squalene could be rationalized on stereoelectronic grounds.[1] Their important hypothesis, which immediately stimulated serious biomimetic studies, can be illustrated by considering the cyclization of squalene oxide (**1**), which is a known biogenetic precursor of lanosterol (*5*) and presumably

[1] A comprehensive review of this subject has been published (*6a*).

many plant triterpenoids, e.g., dammaradienol (2). The process may be regarded as involving *trans-anti-parallel* electrophilic additions to the olefinic bonds, in the same stereochemical sense that bromine adds stereospecifically to alkenes. Thus, protonation of the oxygen of squalene oxide (1) generates an incipient cationic center at C-2 that

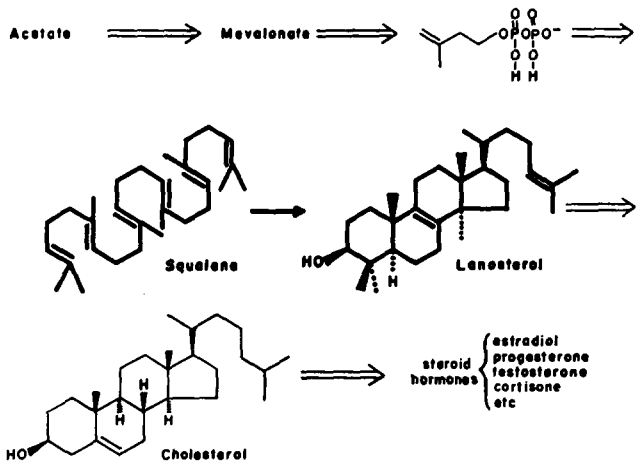
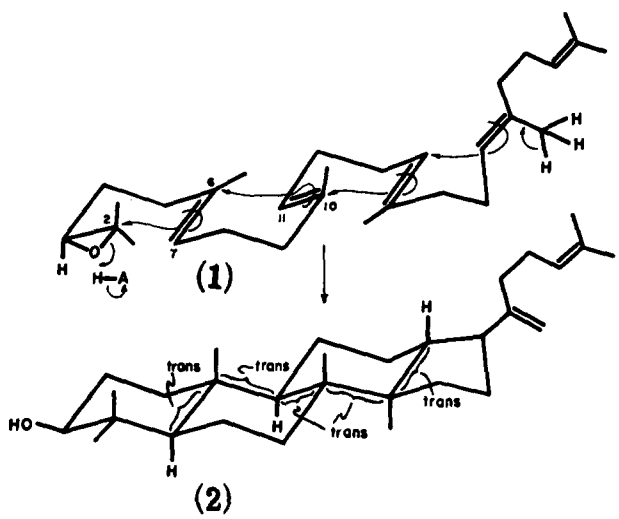


FIG. 1. Flow sheet summary of the biogenesis of steroids from acetate, emphasizing the conversion of squalene to lanosterol.



attacks the 6,7-olefinic bond initiating formation of the 2,7 sigma bond. Concomitantly, the cationic center developing at C-6 starts an electrophilic attack on the 10,11 olefinic bond generating the 6,11 sigma bond, etc. The addition of C-2 and C-11 to the 6,7 olefinic bond occurs in the *trans* manner, yielding the *trans*-fused ring system found in the product (2). Thus, the all-*trans* geometry of the olefinic bonds in squalene results in formation of a *trans,trans,trans,trans,trans* fusion of the four rings in the

product (**2**). A corollary to the hypothesis is that a *cis* olefinic bond will give rise to a *cis*-fused ring system.[1] The general concept of stereoelectronic control of polyene cyclization seems to afford satisfactory rationalization of the course of many biological cyclizations. However, enzymes probably are required not only to promote the occasionally observed non-Markownikoff regio-orientation, but also to induce the preference for boat-like transition states that appear to be involved in the formation of lanosterol.

The first studies directed toward nonenzymic biogenetic-like polyene cyclization involved attempts to initiate cyclization by protonation of the terminal olefinic bond of polyene chains (*3*, *7*, *8*). The results were not promising.[1] Seemingly, much of the difficulty that has been encountered in the acid-catalyzed cyclization of such systems, including 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. Moreover, the relatively strong acidic conditions generally employed are known to be conducive not only to deprotonation (hence, the production of partially cyclized products) but also to promoting reactions such as addition to and isomerization of the olefinic bonds. It was with the hope of obviating these difficulties that we commenced a search, which has been in progress since 1960, for polyolefinic substrates containing an appropriately positioned functional group that could be used to generate a cyclizable cationic center (on carbon) under conditions that would not otherwise affect the olefinic bonds.

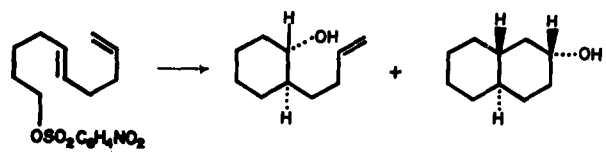
Our own early investigations, which involved a study of the solvolysis of polyenic sulfonate esters, also proved to be unpromising from a synthetic point of view; however, some significant mechanistic results were obtained (see below). From our continuing search for groups that would be more effective than sulfonate esters for initiating cationic polyene cyclizations, two good initiators have emerged to date, namely, the acetal and the allylic alcohol function.

Another effective group for promoting cyclization is the epoxy function, which is the initiator of many enzymic processes. This area has been examined extensively by van Tamelen (*9*). Limitations in space preclude a review of these important studies, which have been in progress for over a decade and have led to total biogenetic type syntheses of a number of complex polycyclic triterpenoids via cyclizations that parallel most closely the biosynthetic pathways. In particular, this work has provided significant evidence regarding the intimate character of the corresponding enzyme-catalyzed reactions. Other important studies that deserve mention are the free radical- and the mercuric ion-initiated cyclizations of Julia (*10*) and the proton- and mercuric ion-initiated cyclizations of Semenovsky (*11*).

The present review is confined mainly to the work from our own laboratory that has been published since the last survey of 1968 (*6a*). For the sake of continuity, brief mention is made of some of the earlier work. In addition, a number of hitherto unpublished results are also disclosed. The major topics that are discussed include the cyclization–solvolysis of sulfonate esters, and cyclizations initiated by the acetal and allylic alcohol functions. Consideration is also given to the participation of styryl and acetylenic functions in polyene cyclizations and their use in the production of five-membered rings. Finally, studies pertaining to the mechanism of polyene cyclizations are reviewed. Brief surveys covering certain limited aspects of this work are on record (*6b*, *c*).

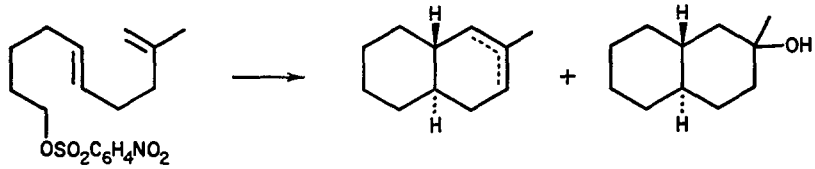
CYCLIZATION–SOLVOLYSIS OF POLYENIC SULFONATE ESTERS

Careful product analyses have been made of the mixtures produced from the solvolysis of acyclic olefinic sulfonate esters designed to produce mono- (*12*), bi- (*13*), and tri-cyclic (*14*) systems.[1] Thus, eleven products were separated and identified from the formolysis of the decadienyl *p*-nitrobenzenesulfonate (**3**). The main component (after cleavage of the formate esters) was the monocyclic *trans* alcohol (**4**), produced in 35% yield. The major bicyclic component was *trans,syn*-2-decalol (**5**) ("natural configuration"). Indeed, all of the bicyclic material (hydrocarbons, as well as alcohols), although formed in only 12% total yield, consisted exclusively of *trans*-decalin derivatives; no *cis* products were found (*13a*). Formolysis of the geometric isomer of (**3**), having a *cis* instead of *trans* internal olefinic bond, gave a similar array of products except that they all belonged to the opposite (*cis*) stereochemical series. In particular, the bicyclic components, formed in 16% yield, all belonged to the *cis*-decalin series (*13b*). Although the yields of bicyclic products were low, the stereospecificity of their formation represented the first example of a system that demonstrably followed the theoretical predictions of Stork and Eschenmoser (see above).



(**3**) (**4**) (**5**)

Acetolysis of the sulfonate ester (**6**), with a methyl substituent on the terminal olefinic bond, showed a slight rate enhancement relative to the parent substrate (**3**). This result has interesting theoretical implications, which are considered below in the section on the mechanism of polyene cyclizations. The bicyclic products, which consisted of mixtures of hydrocarbons (**7**) and the acetates of alcohol (**8**), were produced in 16% yield and belonged exclusively to the *trans*-decalin series (*15*).

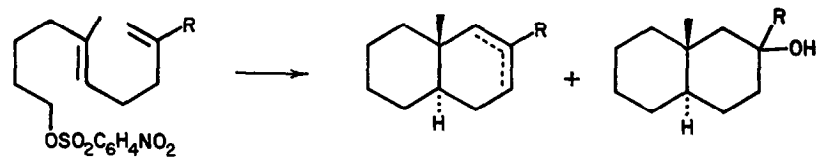


(**6**) (**7**) (**8**)

Solvolysis of appropriately substituted sulfonate esters can lead to products containing an angular methyl group. Thus, acetolysis of substance (**9**) afforded, as the exclusive bicyclic product, the acetate of the CH_3/R *syn* alcohol (**12**), but the yield was only 4% (*16*). Acetolysis of the higher homolog (**10**) gave a mixture of bicyclic hydrocarbons (**11**) in 7.3% yield as well as a 0.5% yield of the acetate of the CH_3/R *anti*-

decalol (**13**) (*17*). Although the yields were again very low, the bicyclic products with angular methyl groups all belonged to the *trans*-decalin stereochemical series.

The solvolysis of olefinic sulfonate esters generally leads to six- instead of five-membered ring formation; however, the latter structure is preferred when the system is so substituted that cyclization can give a tertiary cyclopentylcarbinyl cation (see formula **15**). Thus, formolysis of the ester (**14**) with a terminal isopropylidene group

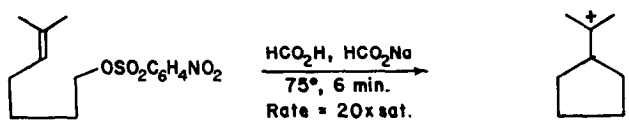


(**9**) R = H
(**10**) R = CH_3

(**11**) R = CH_3

(**12**) R = H
(**13**) R = CH_3

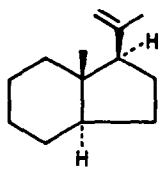
proceeded with a 20-fold rate enhancement relative to the saturated case and gave, in almost quantitative yield, an array of five cyclic products, all derived from the cation (**15**) (*12*).



(**14**) (**15**)

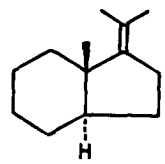
With the aim of extending this encouraging finding to the bicyclic series, the acetolysis of the dienic ester (**16**) was examined carefully (*18*). Unfortunately, the product mixture consisted mainly of five different monocyclic materials derived from the cation (**17**). However, the bicyclic products (**18**), (**19**), and (**20**), although formed in only 7.6% yield, all had the *trans* 6/5 ring system with the angular methyl group, corresponding to the C/D ring system of the steroids.

(**16**) (**17**)



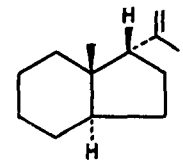
2.2%

(18)



2.9%

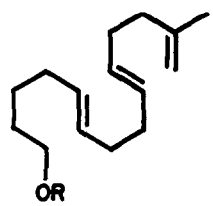
(19)



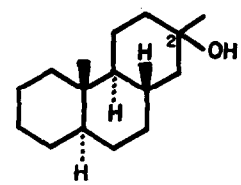
2.5%

(20)

The product from the acetolysis of the trienic sulfonate ester (**21**, R = $SO_2C_6H_4NO_2$), was estimated to consist of 20% acyclic material (**21**, R = Ac), 40% monocyclic, 8–12% bicyclic and 2.8% tricyclic substances (*14*).[1] The tricyclic product, after cleavage of the acetates, was shown to be exclusively the *trans,trans,trans* alcohol (**22**), isolated as a mixture of C-2 epimers. The stereospecificity of the reaction was encouraging, but the low yield was completely unacceptable.



(21)

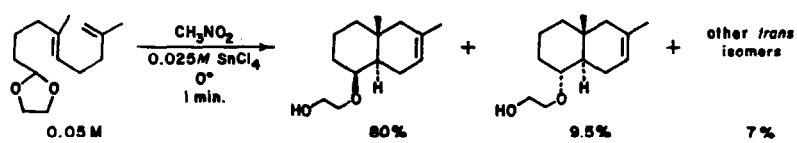


(22)

Thus, the cyclization of polyenic sulfonate esters gives the desired stereochemical results. However, this approach is synthetically useless, because the yields of fully cyclized material are very low.

CYCLIZATION OF POLYENIC ACETALS

After an exhaustive study of the cyclization of the *trans*-dienic acetal (**23**) (*19*),[1] conditions (stannic chloride in nitromethane) were found for its essentially quantitative conversion into *trans*-bicyclic materials, the major product being the substance (**24**). It was also demonstrated that the isomeric form of (**23**) with the *cis* internal olefinic

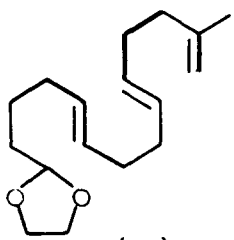


(23) (24) (25)

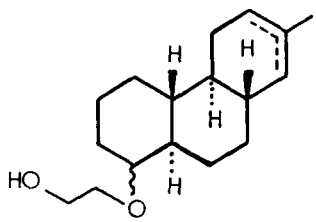
bond, yielded only *cis*-decalin derivatives, in accordance with the theoretical predictions (see above). It is noteworthy that the free aldehyde, corresponding to the acetal (**23**), similarly underwent smooth cyclization to give (>80% yield) a 5:1 ratio of the epimeric octalols corresponding to substances (**24**) and (**25**) but having a hydrogen atom in place of the hydroxyethyl side chain (*20*). The cyclization of polyenic aldehydes has been studied in some detail by Ireland (*21*), particularly in systems containing tetra-substituted olefinic bonds.

Formation of Three Rings

To examine the possibility of forming three rings from trienic acetals, the substance (**26**) was prepared and cyclized with stannic chloride in benzene (*14*).[1] The tricyclic product, which was formed in about 50% yield, was shown to consist of a mixture of isomers (**27**), all of which belonged to the *trans,trans,trans* ("natural") stereochemical series.



(**26**)

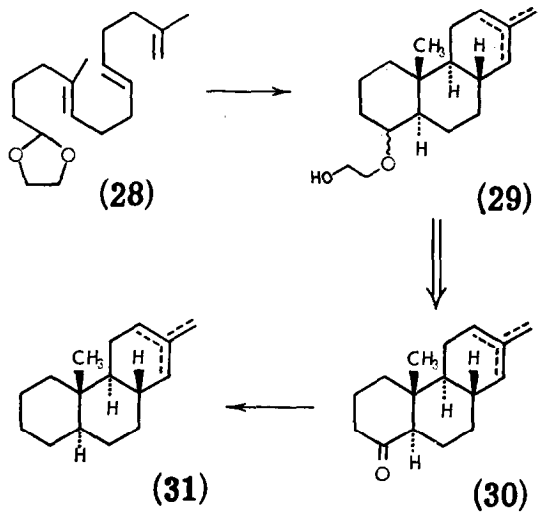


(**27**)

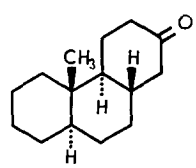
The homologous trienic acetal (**28**) underwent similar cyclization giving all-*trans* tricyclic material (**29**) containing the angular methyl group between rings A and B (*22*). This cyclization reaction was noticeably faster and the yield (62.5%) higher than in the case of the ring closure (**26**) → (**27**), presumably due to the greater nucleophilicity of the tri- as compared with the disubstituted olefinic bond reacting with the acetal residue.

The structure of the product (**29**) was determined by degradation of the side chain to the ketone (**30**), followed by conversion, via Wolff–Kishner reduction, to the hydrocarbon mixture (**31**). This last material was shown to be identical with an authentic specimen produced by reaction of the known ketone (**32**), of established constitution, with methyllithium followed by dehydration.

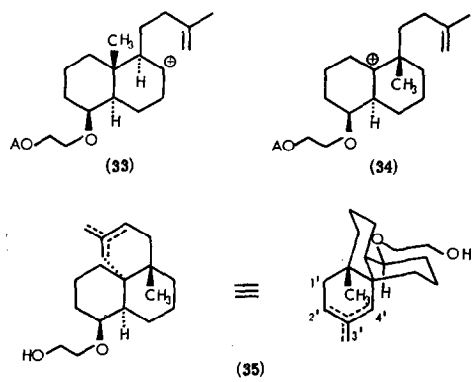
When the acetal (**28**) was treated with stannic chloride in nitromethane (instead of benzene), under the conditions that had been so effective in promoting cyclization of the dienic acetal (**23**), surprisingly, the reaction took an abnormal course. The main product, isolated in 44% yield, proved to be the tricyclic substance (**35**) that appeared to have arisen from the bicyclic cation (**33**) by consecutive suprafacial 1,2-hydride and methyl shifts to give the tertiary cation (**34**) followed by intramolecular reaction with the olefinic bond. The constitution of the product (**35**) was established by single crystal X-ray diffraction analysis of a derivative (*22*).



(28) (29) (30) (31)



(32)

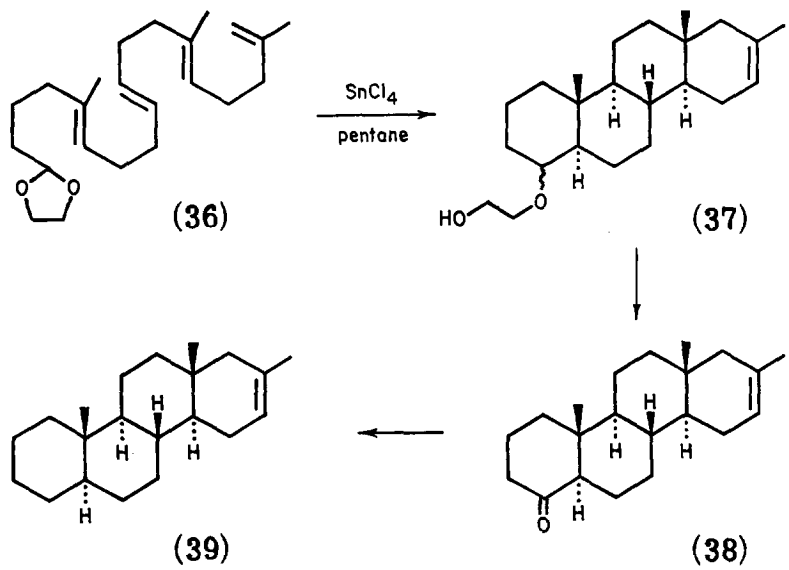


(33) (34) (35)

Formation of Four Rings

To determine if four rings could be produced from an acyclic tetraenic chain in a single step, the cyclization of the tetraenic acetal (**36**) was examined (*23*). This substance, on treatment with stannic chloride in pentane, was converted (30% yield) into a mixture of about equal amounts of two crystalline D-homosteroidal tetracyclic epimers (**37**),

which belonged exclusively to the all-*trans* (natural) stereochemical series. This cyclization, which involves the production of no less than seven asymmetric centers, and in this sense is comparable to the conversion of squalene into lanosterol, is remarkably stereoselective, yielding only two of 64 possible racemates. The constitution of the products (**37**) was established by degradation of the hydroxyethyl side-chain of each



of the two epimers to give the same crystalline 4-keto compound (**38**), which was converted, via Wolff–Kishner reduction, into the hydrocarbon (**39**). This last substance was identified with authentic material prepared from a natural steroid, via several steps involving expansion of ring D.

The cyclization substrate (**36**) was synthesized as aummarized below. The development of the synthon (**41**), required for the right-hand portion of the molecule, was

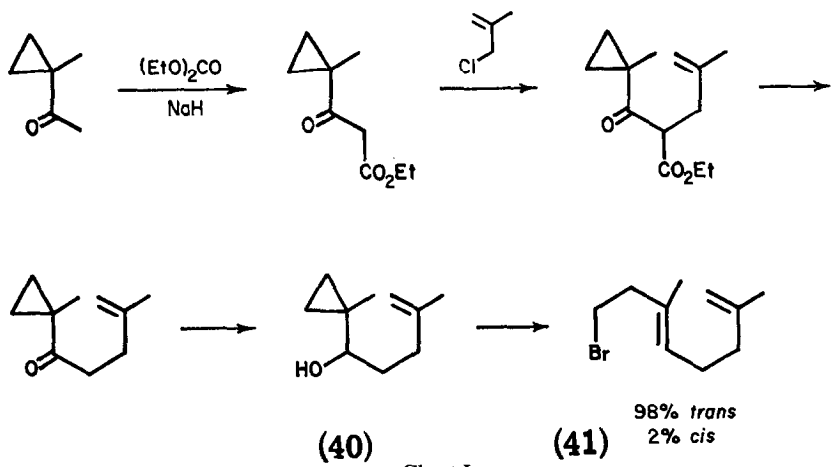


Chart I

effected by the Julia olefin synthesis, which was modified (*24*) to yield the *trans*-trisubstituted olefinic bond (see Chart I). The key step in this stage of the synthesis is the efficient cyclopropylcarbinyl → homoallylic rearrangement, (**40**) → (**41**), which proceeds highly stereoselectively.

The steps of the remainder of the synthesis are summarized in Chart II. The internal *trans*-disubstituted olefinic bond was developed by sodium-in-ammonia reduction of the acetylenic function of substance (**42**) to give the *trans,trans*-trienic alcohol (**43**). Alkylation of sodio acetylacetone with the mesylate of (**43**) gave the β-diketone (**44**, R = H), which was chlorinated giving (**44**, R = Cl), and then deacylated, to yield the chloro ketone (**45**). The *trans*-trisubstituted olefinic bond nearest to the acetal residue was introduced by the stereoselective Cornforth olefin synthesis (*25*).

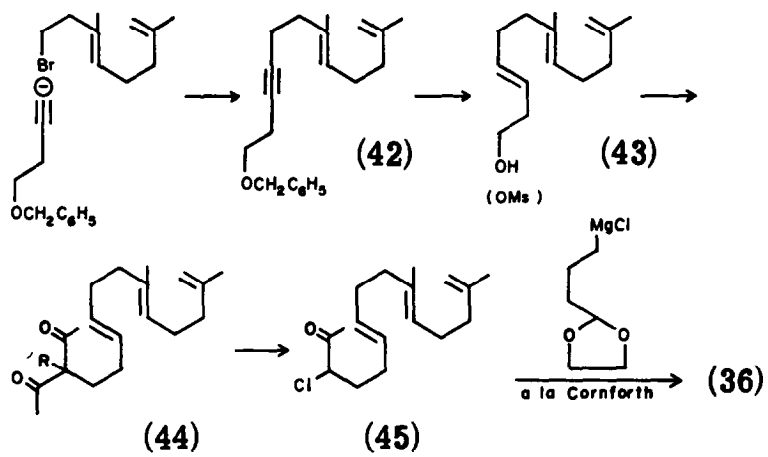
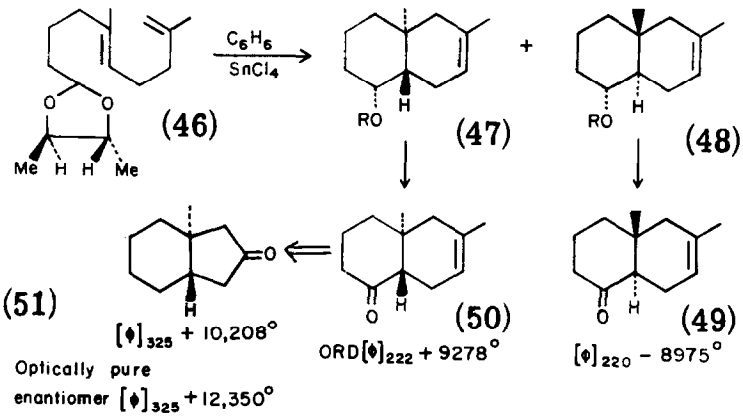


Chart II

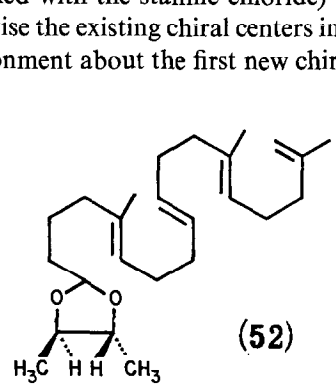
Asymmetric Induction of Cyclizations

It should be emphasized that all of the biomimetic cyclizations described above yielded racemic products, even though only one enantiomeric formula is depicted. For example, the major product from the cyclization of the dienic acetal (**23**) actually consisted of equal amounts of the enantiomer (**24**) and its mirror image (**47**, R = CH_2CH_2OH). The enzymatic cyclizations of squalene, on the other hand, proceed with total asymmetric induction to produce only one enantiomeric form of the polycyclic products. In an effort to simulate this result in a nonenzymic process, we examined the case of the optically active dienic acetal (**46**) derived from (−)-butanediol (*R,R* configuration) (*26*).

Cyclization of acetal (**46**) with stannic chloride in benzene afforded the usual mixture of separable isomers with axial and equatorial side chains. After cleavage of the ether linkage in the side chain, the axial isomer proved to consist of the enantiomer (**47**, R = H) and its mirror image in the ratio 92:8. Thus, an exceedingly high degree of asymmetric induction was realized. The enantiomeric purity and absolute configuration of (**47**, R = H) were determined by oxidation to the ketone (**50**), with the indicated ORD



maximum, and conversion of the latter by a series of steps involving contraction of ring B, into a specimen of the hydrindanone (**51**) with the indicated ORD maximum. The absolute configuration and ORD maximum of the pure enantiomeric form (**51**) are known (*27*). The ketone derived from the equatorial isomer (**48**, R = H) proved to be predominantly in the form of the enantiomer (**49**), i.e., the mirror image of (**50**). The reason for the remarkably high degree of asymmetric induction observed in the cyclization of acetal (**46**) is not clear. Seemingly, there must be considerable rigidity of the acetal residue (complexed with the stannic chloride) in the transition state of the cyclization reaction, otherwise the existing chiral centers in the acetal moiety would not be recognized by the environment about the first new chiral center that is developing.

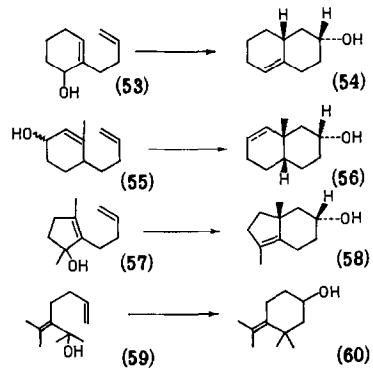


A logical extension of the asymmetric induction study involved the preparation of the optically active tetraenic acetal (**52**). Cyclization with stannic chloride in pentane gave tetracyclic products (cf., formula (**38**)) that were optically active, but the enantiomeric purity has not yet been determined (*28*).

CYCLIZATIONS INITIATED BY ALLYLIC CATIONS

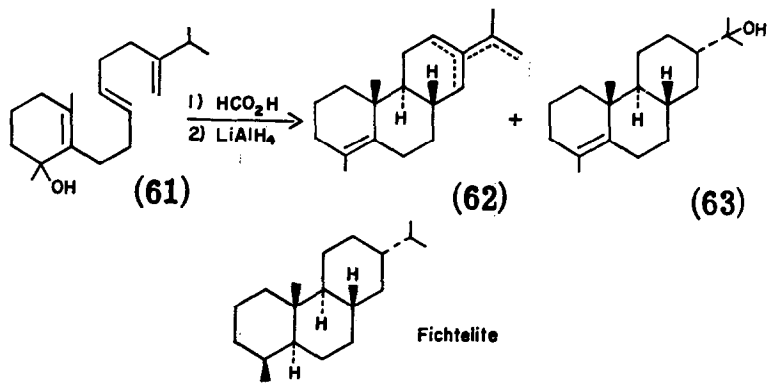
This type of cyclization is exemplified in its simplest form by the following formic acid-promoted single ring closures: the transformations (**53**) → (**54**) (*29*)[1] and (**55**) →

(**56**) (*29, 30*),[1,2] which involve initiation by the cyclohexenyl cation; the transformation (**57**) → (**58**) (*31*),[1] which is promoted by the cyclopentenyl cation; and the transformation (**59**) → (**60**) (*32*), which is induced by the tetramethylallylic cation. Some examples of the use of these various allylic systems to initiate biomimetic cyclizations that produce polycyclic products are given below.

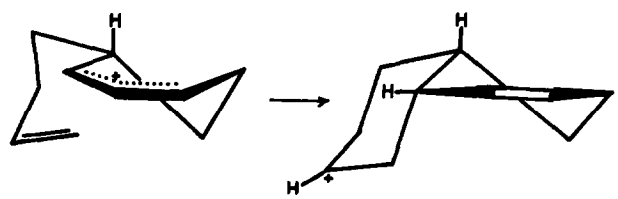


Initiation by the Cyclohexenyl Cation

The formation of two new rings by the cyclohexenyl cation-promoted cyclization is an efficient process. Thus, the trienol (**61**) was quantitatively converted, by the action of cold formic acid, into a mixture of tricyclic products (**62**) and (**63**). The reaction was



[2] The stereospecific formation of the *cis*-fused ring system (**56**) from (**55**) is the expected consequence of the known preference for a cyclohexenyl cation to react with a nucleophile so as to form a pseudo-axial bond as suggested by the following formulas:



stereospecific with respect to the ring fusion (*trans,trans*) as shown by separation and acid-catalyzed interconversion of each of the products, and by the reductive transformation of each of the four hydrocarbons into the racemic form of the natural product fichtelite (**64**) (*33*).[1]

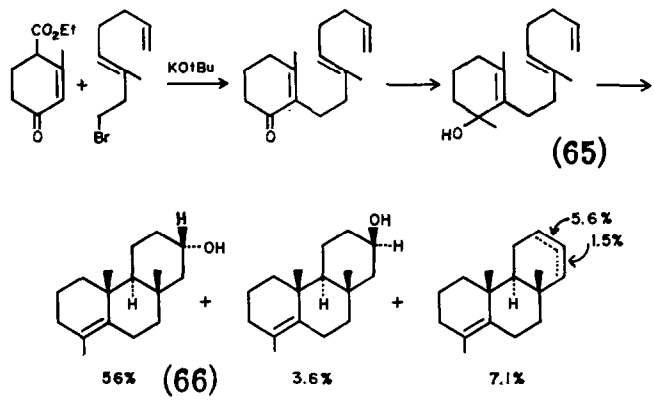


Chart III

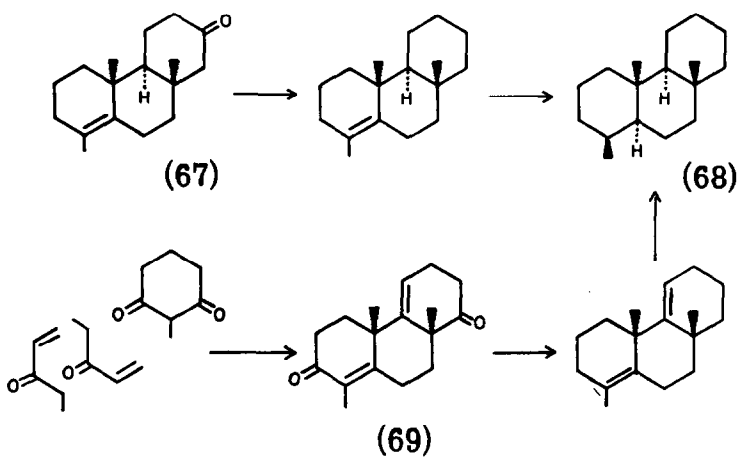
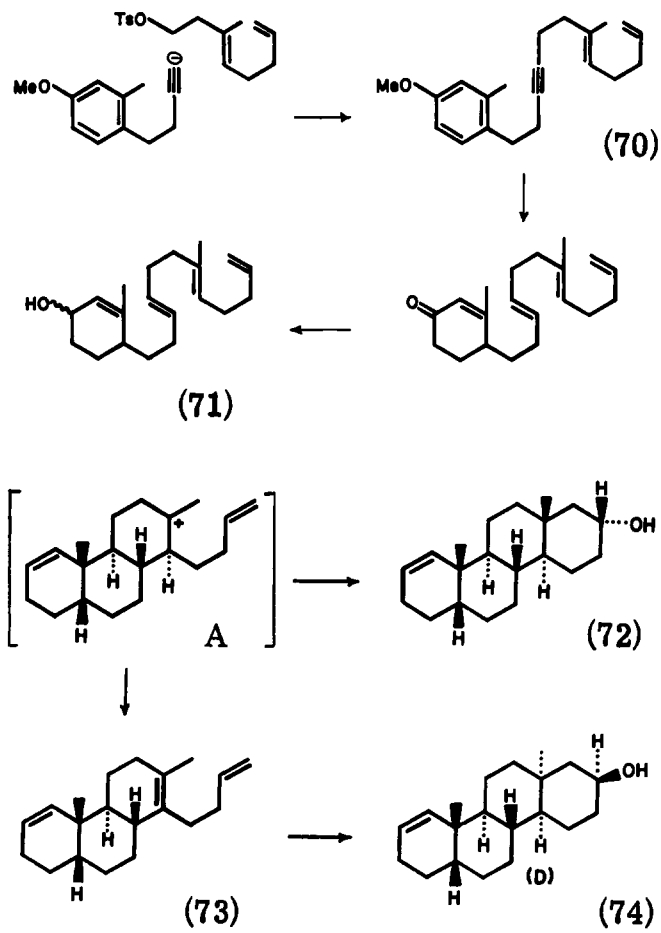


Chart IV

The cyclization of the trienol (**65**) (*34*), which was prepared (see Chart III) by a general method that has previously been reviewed (*6a*), is of interest because it stereospecifically generates tricyclic products like (**66**) having 1,3-diaxial angular methyl groups as they appear in many natural polycyclic triterpenoids, e.g., substance (**2**). The major product (**66**) was shown to have the *trans,trans*-ring fusion by oxidation to the ketone (**67**), which was reductively converted into the trimethylperhydrophenanthrene (**68**) as summarized in Chart IV. This last product was shown to be identical

with authentic material, produced in a stereorational manner from an intermediate (**69**) of known configuration (*35*).

Some examples of cyclohexenyl cation-initiated cyclizations resulting in the production of three new rings follow. When the tetraenol (**71**), prepared via lithium-in-ammonia reduction of (**70**) as shown in the accompanying flow sheet, was treated with formic acid at 25° for 20 min, two crystalline tetracyclic alcohols (**72**) and (**74**) could be isolated in low yield from the mixture after reductive cleavage of the formate esters (*36*). The lack of stereospecificity of the cyclization appeared to violate the theoretical predictions (see above), until it was discovered that cyclization of (**71**) for 1 min gave exclusively the normal product (**72**) (16% yield) along with tricyclic hydrocarbon isomers, mainly (**73**), resulting from deprotonation of the cation A. Treatment of the hydrocarbon fraction with formic acid for 20 min led mainly to the abnormal (C/D *cis*) tetracyclic product (**74**), by a process involving protonation of ring C of (**73**). Thus, both a direct and a stepwise mechanism are involved in the 20-min cyclization reaction (*36*). Cyclization experiments with deuterioformic acid provided confirmation of the dual processes in that there was little deuterium incorporation in the product (**72**);



however, there was approximately one deuterium found in substance (**74**). The failure to observe deuterium incorporation in the cyclization to form (**72**) is reminiscent of the classical negative deuterium incorporation experiment in the enzymatic cyclization of squalene to lanosterol (*37*).

The constitution of the tetracyclic product (**72**) was established by its conversion, via hydrogenation of the olefinic bond followed by oxidation of the alcohol function, into the ketone (**75**). An authentic comparison specimen of this ketone was produced from testosterone according to the scheme outlined in Chart V (*36*).

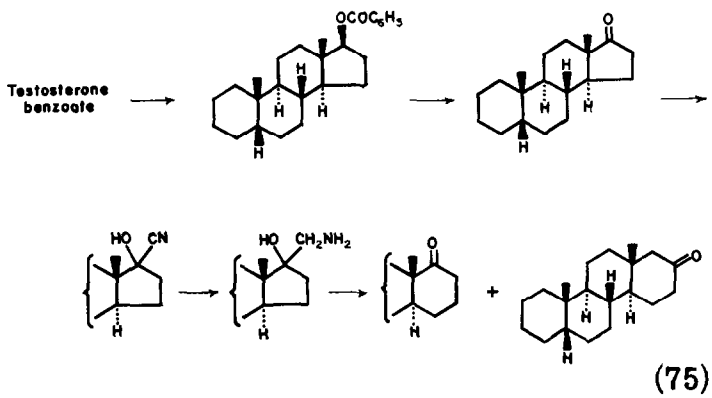
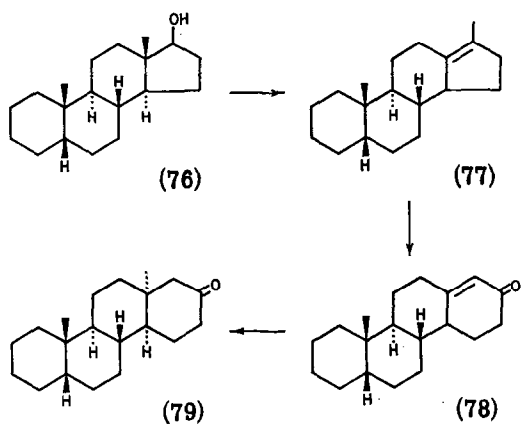


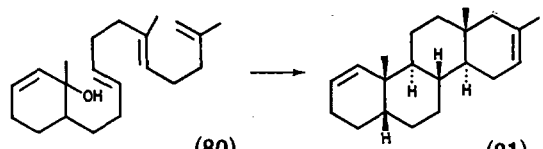
Chart V

The configuration of the abnormal tetracyclic product (**74**) was established by conversion to the ketone (**79**), which was identified with authentic material produced as follows (*36*). Dehydration of 5β-androstan-17β-ol (**76**) afforded the rearranged hydrocarbon (**77**) that was converted, via ozonolysis followed by cyclodehydration, into the unsaturated ketone (**78**). Conjugate addition of methylmagnesium iodide to ketone (**78**) afforded the substance (**79**).



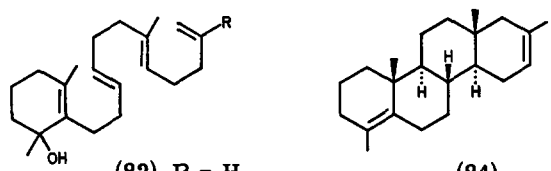
The tendency for the cyclization of the tetraenol (**71**) to stop at the tricyclic stage (**73**), and hence, to produce an abnormal tetracyclic product (**74**), may be associated with inadequate nucleophilicity of the terminal vinyl group for participation in the

direct cyclization. Increased nucleophilicity was expected with a terminal isopropenyl group, and indeed, the substrate (**80**), on treatment with stannic chloride in nitroethane at −78°, underwent cyclization to give a single D-homosteroidal tetracyclic hydrocarbon (**81**) in 60% yield (*38*). The constitution of this substance was established by comparison of the hydrogenation product with authentic material derived from ketone (**75**) via reaction with methyllithium, dehydration, and hydrogenation.



(80) (81)

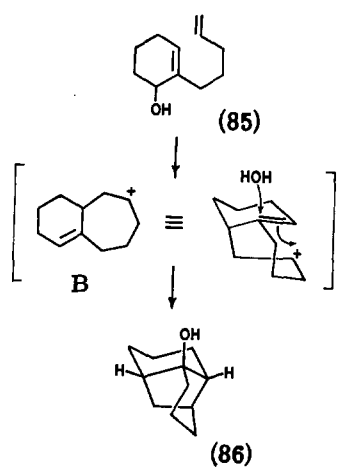
Another more direct comparison of the difference in the effect of a terminal vinyl versus isopropenyl group was observed in the cyclization of the tetraenols (**82**) and (**83**) (*39*). The latter substance was converted in >60% yield, into the tetracyclic hydrocarbon (**84**), while the substrate (**82**) gave a much lower yield of tetracyclic material. The constitution of the product (**84**) was proved by its identity with an authentic specimen produced via a ring D enlargement sequence like that shown in Chart V, but starting from 4-methyltestosterone benzoate.



(**82**) R = H
(**83**) R = CH_3

(**84**)

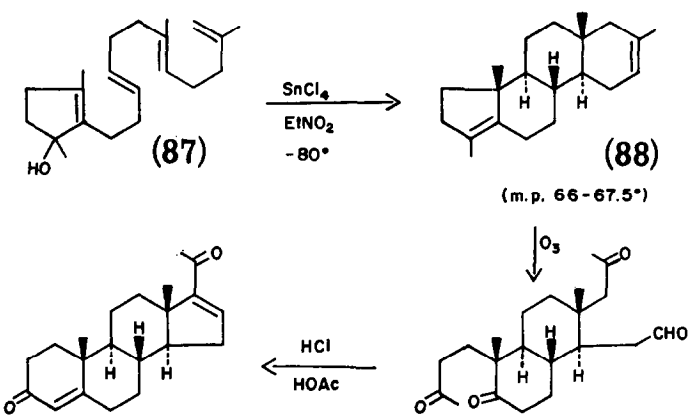
Many additional examples of cyclohexenyl cation-initiated polyene cyclizations are described below in the sections concerning (a) the problem of forming five-membered



rings, and (b) cyclizations involving participation of acetylenic bonds. Moreover, Ireland has employed this initiator in interesting studies aimed at the total synthesis of pentacyclic triterpenoids (*40*). Finally, mention should be made of an unusual example of a cyclohexenyl cation-promoted cyclization, which was observed when the pentenyl-cyclohexenol (**85**) was treated with formic acid (*41*). The major product, isolated after hydrolysis of the formate esters, was not the 6/7 fused-ring bicyclic alcohol expected from attack of a nucleophile on the cation B. Instead, the olefinic bond of the cation B participated in further cyclization to produce a tricyclic bridged-ring system. Thus, the crystalline carbinol (**86**) was isolated in 30% yield, and the constitution was established by single crystal X-ray diffraction analysis (*42*).

Initiation by the Cyclopentenyl Cation

This type of cyclization is exemplified by the cyclization of the tetraenol (**87**), which afforded the crystalline tetracyclic hydrocarbon (**88**) in 70% yield (*31*, *43*). Ozonolysis of substance (**88**) gave, in 65% yield, the triketo aldehyde (**89**) that still retained the five new asymmetric centers that were generated in the cyclization step. Substance (**89**) was finally converted, through a double intramolecular aldol cyclodehydration, into racemic 16,17-dehydroprogesterone (**90**), thereby establishing the stereochemical course of the cyclization step. This represented the first synthesis of a steroid via a biomimetic polyene cyclization.



(87) (88) (m.p. 66-67.5°) (90) (89)

One of the methods used for the synthesis of the substrate (**87**) is summarized in Chart VI.[3] The dienic bromide (**41**) was used to incorporate the *trans*-trisubstituted olefinic bond in the right-hand portion of the molecule. Condensation of this bromide with the lithium salt of the diketal acetylene (**91**) afforded the dienyne (**92**), which was converted, by sodium-in-ammonia reduction to produce the internal disubstituted

[3] This represents a modification (*44*) of a method already described (*43*).

olefinic bond, into the trienic diketal (**93**). The diketone (**94**), produced on acid hydrolysis of the ketal residues, was converted, by aldol cyclodehydration, into the cyclopentenone (**95**), reaction of which with methyllithium afforded the substrate (**87**).

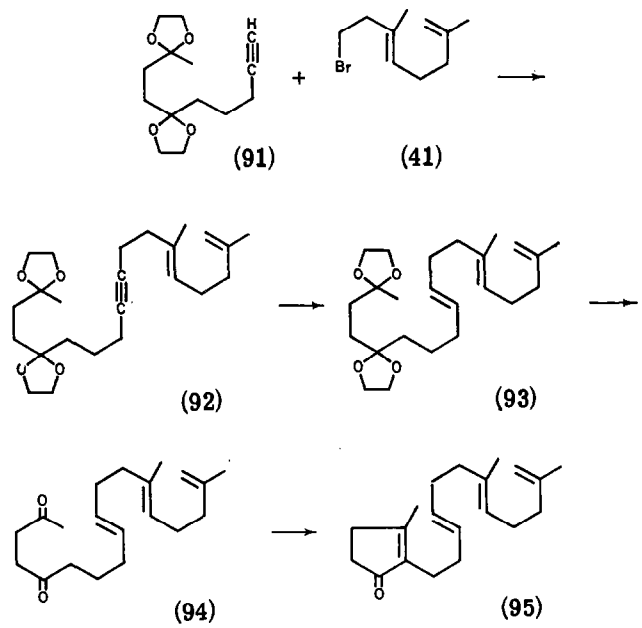


Chart VI

The diketal acetylene (**91**) was produced as depicted in Chart VII. Alkylation of 5-lithio-2-methylfuran with 1,3-dibromopropane gave the bromo compound (**96**), which on ethylene glycolysis was converted directly into the diketal bromide (**97**). This last substance was used to alkylate lithium acetylide, giving (**91**).

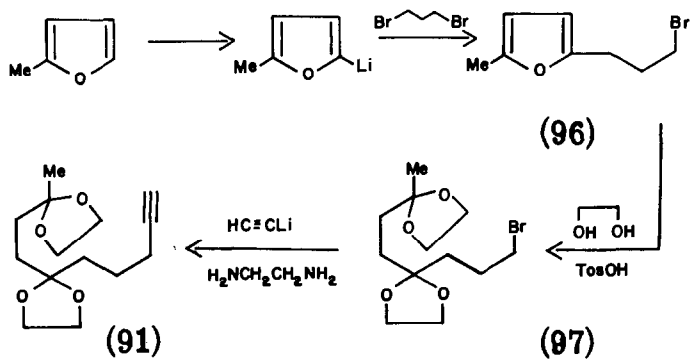
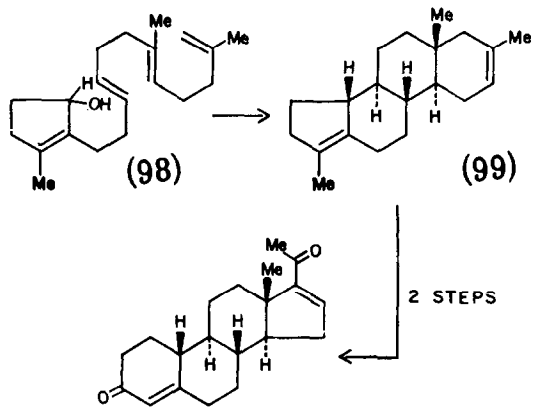


Chart VII

The scheme described above for the synthesis of 16,17-dehydroprogesterone (**90**) has been modified so as to produce the 19-nor steroid (**100**) (*45*). The ketone (**95**), on

reduction with lithium aluminum hydride, was converted into the secondary alcohol (**98**), which underwent regio- as well as stereospecific cyclization in ca. 70% yield (*43*) to give the crystalline tetracyclic substance (**99**). This tetracyclic hydrocarbon was transformed, via the ozonolysis–cyclodehydration sequence (see above) into the 19-nor steroid (**100**).



(100)

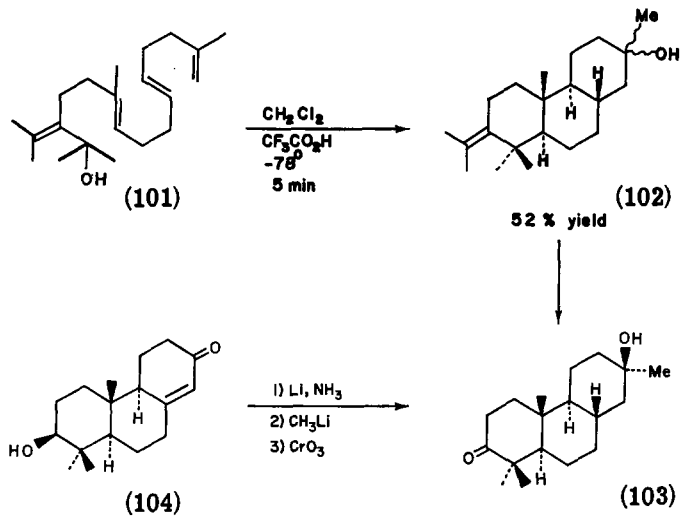
The cyclization of the secondary alcohol (**98**) and the tertiary alcohol (**87**), although formally similar, have been shown to proceed by different mechanisms (*46*). The former cyclizes noticeably more rapidly than the latter substrate. The tertiary alcohol first undergoes a rapid dehydration giving an isolable hydrocarbon containing the cyclopentadiene moiety. This system is reversibly protonated (also a rapid step) by the acid catalyst, giving the cyclopentenyl cation that undergoes cyclization. This sequence was demonstrated by using CF_3CO_2D as the cyclization catalyst which resulted in incorporation of up to six deuterium atoms in ring A of the product (**88**). In contrast, the secondary alcohol (**98**) cyclizes without first undergoing dehydration, there being no deuterium incorporation in the product (**99**) when CF_3CO_2D was employed as the catalyst.

A number of additional examples of cyclopentenyl cation-initiated cyclizations are described below in the section concerning cyclizations involving participation of the acetylenic bond, and in connection with the synthesis of estrone and the mechanism of polyene cyclizations. Ireland has also explored the use of this initiator in studies directed toward pentacyclic triterpenoid synthesis (*40*).

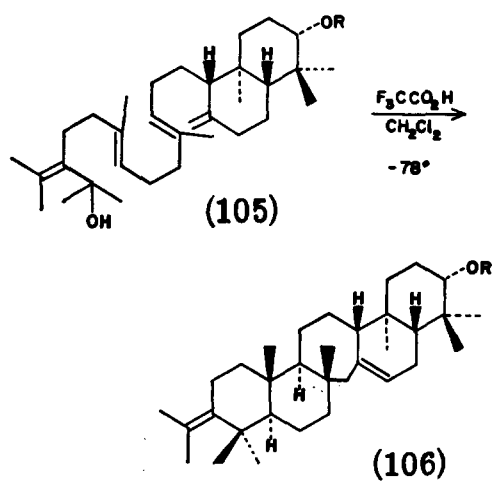
Initiation by the Tetramethylallylic Cation

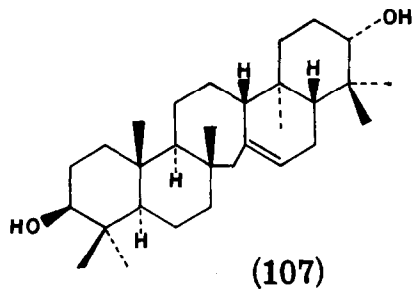
The tetramethyl allylic alcohol function, as incorporated in the substrate (**101**), is an effective cyclization initiator (*47*), and tricyclic material (**102**) is formed rapidly under exceedingly mild conditions. The isopropylidene group can be oxidatively cleaved to the keto group, e.g., ozonolysis of the axial hydroxy epimer of (**102**) gave

the hydroxy ketone (**103**), which was identical with authentic material derived from the unsaturated ketone (**104**) of known configuration. Thus, this type of biomimetic cyclization affords an alternative entry to an important type of natural product structure, with the *gem*-dimethyl group, that is produced by the natural epoxide cyclization initiator (*9*).



Attention is now turned to an example of the use of a tetramethylallylic cation-initiated ring closure to effect the total synthesis of a pentacyclic triterpenoid. The key step involved is the cyclization of the bicyclic tetraenol (**105**), R = $SiMe_2$t-Bu, which resulted in the formation of three new rings including a seven-membered C-ring. The main product (**106**), R = $SiMe_2$t-Bu, could be converted, via selective oxidation of the





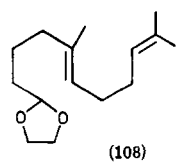
(107)

isopropylidene group followed by reduction and deblocking, into racemic serratenediol (**107**), a pentacyclic triterpenoid with nine asymmetric centers (256 possible racemates) (*48*). The cyclization step proceeded with only slight induction by the asymmetry of the preformed rings D and E. Thus, in addition to substance (**106**), a diastereomer arising from formation of rings A, B, and C in the enantiomeric form depicted in formula (**106**) was produced. This type of stereochemical result was encountered first by van Tamelen in the course of the synthesis of a number of tetra- and pentacyclic triterpenoids via epoxide-initiated cyclizations (*9*).

Other examples of tetramethylallylic cation-promoted cyclizations are described in the following two sections of this review.

THE PROBLEM OF FORMING FIVE-MEMBERED RINGS

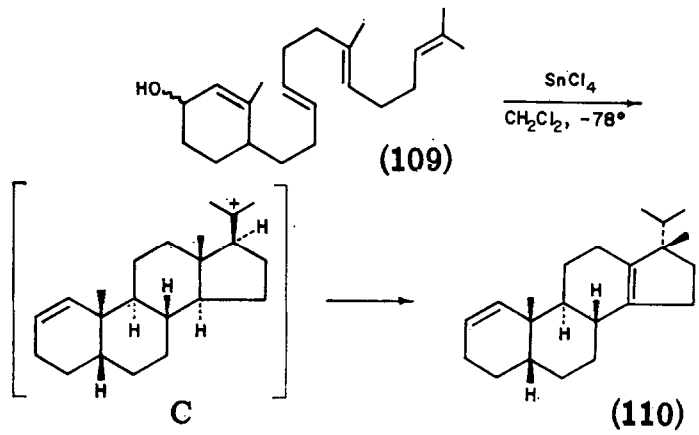
Because the five-membered ring widely occurs in natural products, particularly in the D-ring of steroids, it has been of special interest to search for systems that would result in five-membered ring closure in biomimetic polyene cyclizations.



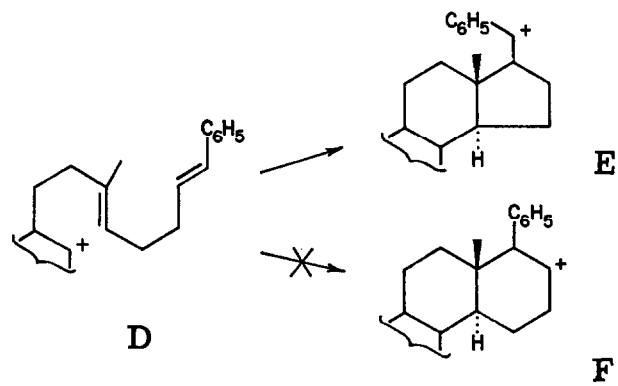
(108)

Since the isopropylidene end group, as incorporated in the sulfonate ester (**16**), led to five-membered ring closure (see above), albeit in poor yield, the corresponding acetal (**108**) was considered to be a promising substrate for obtaining high yields of 6/5 *trans* bicyclic product (*18*). Surprisingly, the substance (**108**) yielded only polymeric material under the same conditions that had given high yields of 6/6 ring closure in the case of the isomeric substance (**23**).

One other system, involving the isopropylidene terminating group, has been examined, namely, the cyclization of the tetraenol (**109**) (*49*). The cyclohexenol initiator as found in the substrate (**109**) is of the type that has been shown (see above, i.e., formulas (**55**) and (**71**)) to yield the *cis* A/B ring fusion.[1,2] Cyclization of substance (**109**) did indeed occur so as to give a five-membered ring D; however, the major product was the tetracyclic hydrocarbon (**110**), evidently produced from the cation

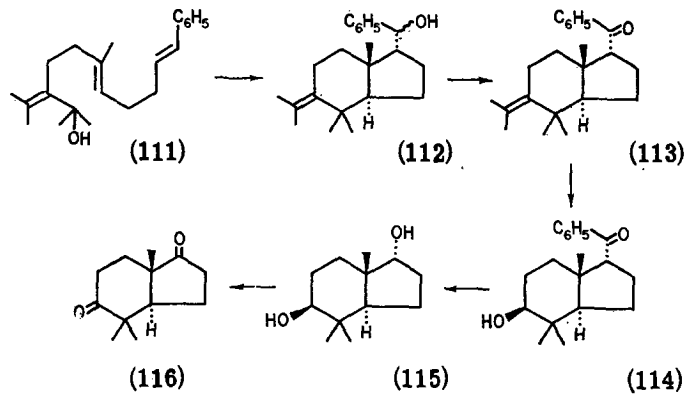


C by a 17α-20 hydride shift followed by a 13β-17β methyl migration and finally the loss of the 14α proton. It has not yet been possible to trap the cation C prior to rearrangement.

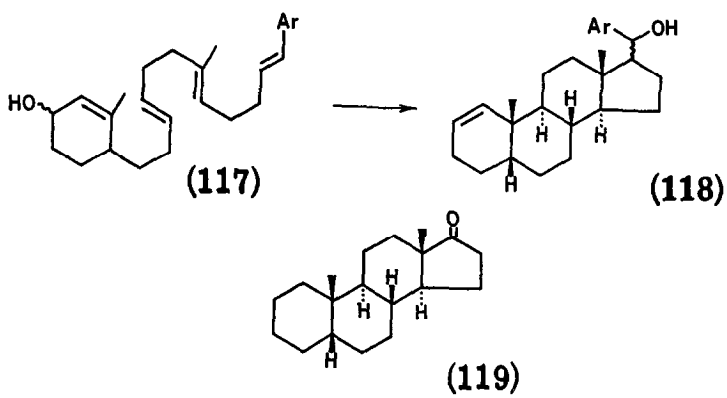


A successful method of inducing five-membered ring closure has been through the use of the styryl terminating group which, when incorporated in a molecule as suggested by partial formula D, participates in cyclization so as to form the resonance-stabilized benzylic cation E in preference to the six-membered ring homobenzylic cation F. Thus, the trienol (**111**) underwent cyclization readily, with trifluoroacetic acid in dichloromethane, to give the bicyclic carbinol (**112**) with the *trans* 6/5 ring system (*50*). The constitution of the carbinol (**112**) was established by oxidation to the ketone (**113**) which, on ozonolysis followed by reduction with sodium borohydride, was converted into the hydroxy ketone (**114**). The acetate of this last substance was submitted to Baeyer–Villager oxidation, then hydrolysis to give the diol (**115**), which on oxidation afforded the known dione (**116**) (*51*).

In addition to leading to five-membered ring formation, the styryl terminator has the advantage that the nucleophilicity of its olefinic bond can be varied by introducing appropriate substituents in the aromatic nucleus. To examine this parameter, the

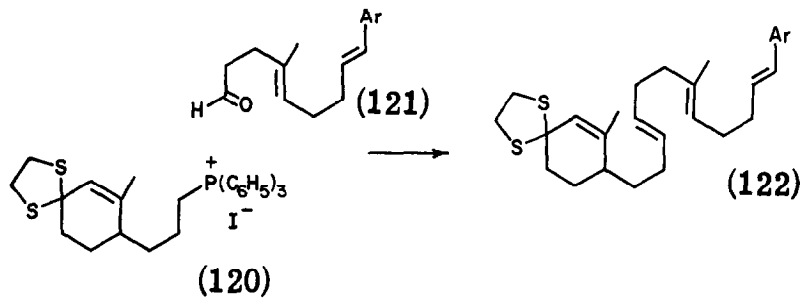


system (**117**) was chosen for study since it also promised to yield, on cyclization, the steroid nucleus, namely, substance (**118**). In the case where Ar = C_6H_5-, cyclization with trifluoroacetic acid in dichloromethane at temperatures of −50° to −25° gave yields of tetracyclic material approaching 70% (*50*). With Ar = *p*-$CH_3C_6H_5$- the yield was increased to 75% (*52*). In the case of Ar = *p*-$CH_3OC_6H_4$- the yields were poor, apparently due to sensitivity of the highly nucleophilic styrene system to the acidic conditions of the cyclization (*53*). The best yield of tetracyclic product (81%) was obtained in the case with Ar = α-naphthyl (*52*).



The structure and configuration of the product (**118**, Ar = C_6H_5) were established by hydrogenation of the 1,2-olefinic bond, oxidation to the 20-keto compound, Baeyer–Villager oxidation followed by hydrolysis of the ester, and finally, oxidation to the known androstanone (**119**) (*50*).

The substrate (**117**) was produced by a method involving, as the convergent step, the Schlosser modification of the Wittig condensation of the phosphonium salt (**120**) with the dienic aldehyde (**121**). A preparation of the phosphonium salt (**120**) is described below in connection with its use in the synthesis of the acetylenic substrate (**154**). One of the methods used for the preparation of the aldehyde (**121**) is illustrated



by the case where Ar = α-naphthyl (*52*) and is outlined in Chart VIII. The *trans* olefinic bonds were developed by a sequence of stereospecific Claisen rearrangements (*54*). Thus the *trans*-disubstituted olefinic bond was formed in the reaction of the allylic alcohol (**124**) with the olefinic ketal (**125**) via the intermediate vinyl ether (**129**) that was not isolated. The *trans*-trisubstituted olefinic bond was produced by reaction of the allylic alcohol (**127**) with methyl orthoacetate, the ketene acetal (**130**) presumably being involved as an intermediate.

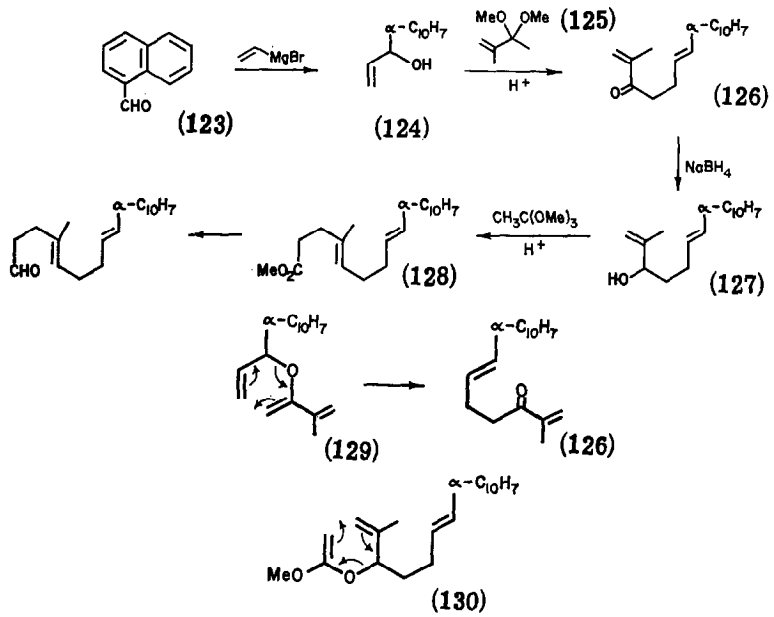


Chart VIII

The problem of forming five-membered rings in biomimetic polyene cyclizations has been solved in principle by the agency of the styrene terminator. This approach, however, still leaves an unsolved problem connected with the efficient conversion of the cyclization products into natural substances. In particular, a high yield method for removal of the aromatic moiety so as to afford a useful product is yet to be developed.

Another effective method of producing five-membered rings in biomimetic polyene cyclizations is through the participation of the acetylenic function. This approach, which leads directly to more useful structures, is considered in the following section.

CYCLIZATIONS INVOLVING PARTICIPATION OF ACETYLENIC BONDS

Acetylenic bonds have been shown to assist the solvolysis of sulfonate esters with concomitant ring formation (*55*). Thus formolysis of the acetylenic *p*-toluenesulfonate (**131**) gave products of both five- and six-membered ring closure as depicted in Chart IX (*55b*).

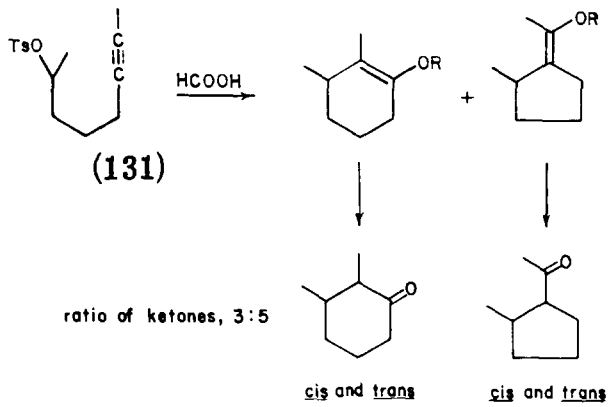
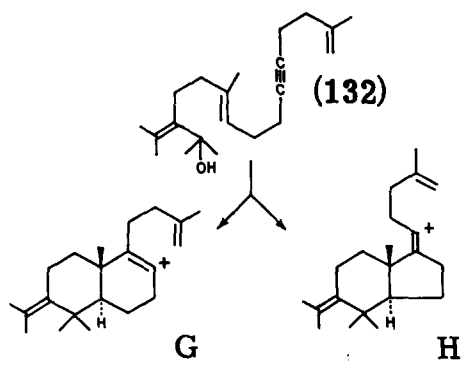


Chart IX

These experiments prompted us to see if acetylenic bonds would participate in biomimetic polyene cyclizations. Our first study involved examination of the cyclization of the trienynol (**132**) which is similar to the tetraenol (**85**) except that the former has an acetylenic bond where the latter has the disubstituted ethylenic bond. According to the precedent cited above, the cyclization of carbinol (**132**) might be expected to proceed via cation G and/or H. If cyclization were to continue further, cation G



would lead to the lanosterol-like A/B/C ring system with an olefinic bond at 8,9. Cation H, on the other hand, would lead to a product having the important *trans*-fused hydrindane ring system.

When the trienynol (**132**) was treated with 2% trifluoroacetic acid in dichloromethane at −70°, the cyclization appeared to proceed entirely via cation H to give the tricyclic hydrocarbon (**133**)[4] in 70% yield (*51*). No product derived from cation G was isolated. The constitution of the hydrocarbon (**133**) was confirmed by oxidative degradation to the dione (**116**). This dione was shown to be identical with authentic material that was synthesized from a *trans*-decalone derivative of known configuration by a scheme involving contraction of ring B shown in Chart X.

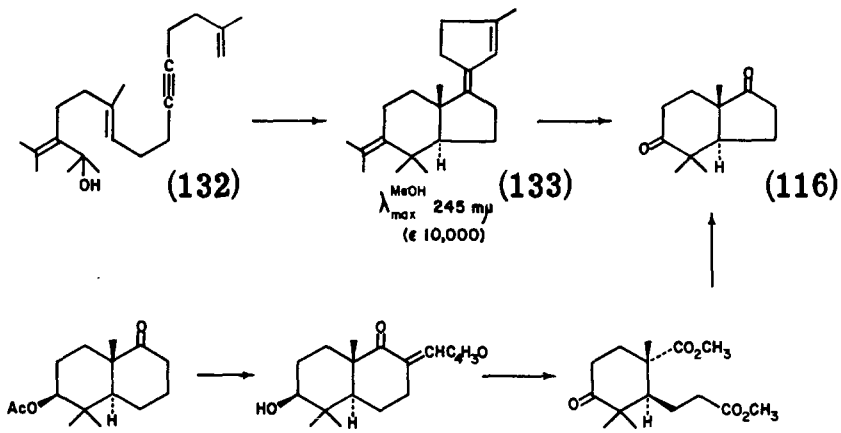


Chart X

Having established the preference for five-membered ring formation in the cyclization of the trienynol (**132**), we turned attention to the simpler system, namely, the dienynol (**134**) (*51*). This substance, upon treatment with formic acid and pentane (two-phase system) for 15 min at 23°, was converted, in over 90% yield, into the enol formate (**135**),[4] the constitution of which was confirmed by oxidation with ruthenium tetroxide to the known trimethylhydrindanedione (**116**). Hydrolysis of the enol formate (**135**) yielded the ketone (**136**) that has all of the structural features of the C/D ring system of progesterone. Lansbury has also developed an approach to this basic type of structure by acid-catalyzed cyclization of acetylenic carbinols, e.g., (**197**) (*56*). His work is considered in more detail below.

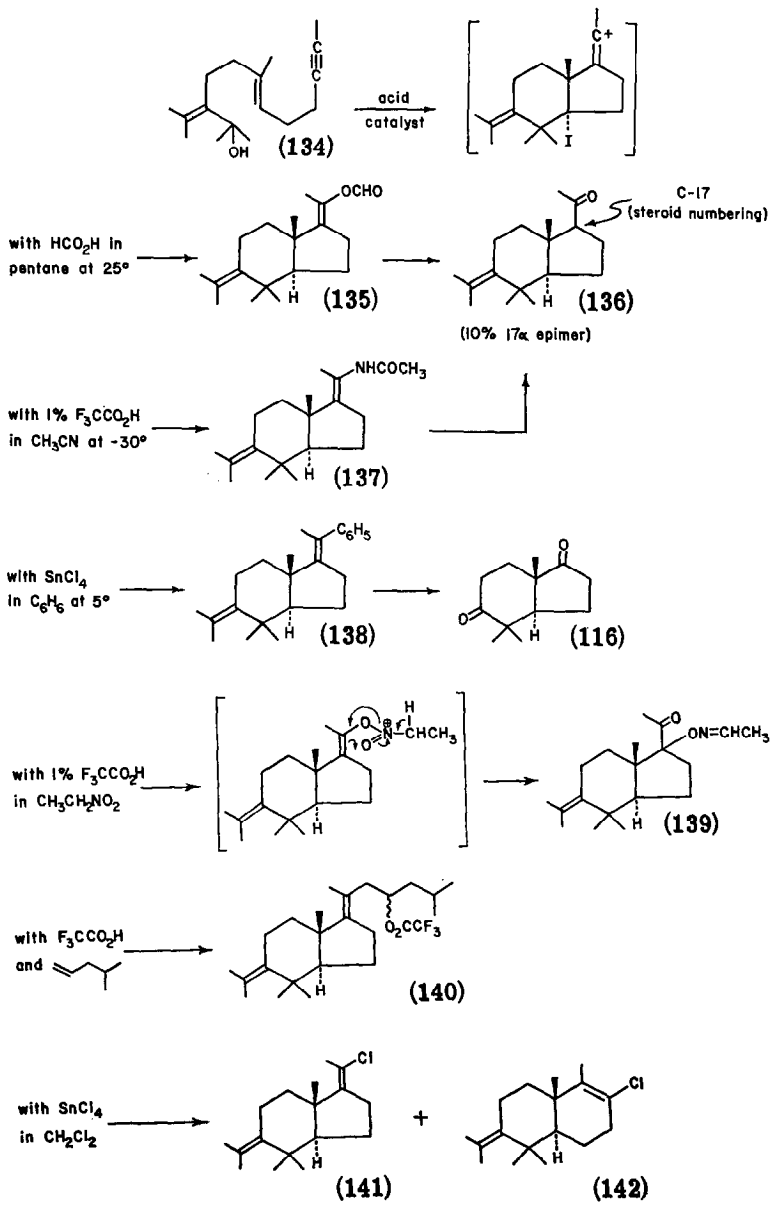
Concerning the Involvement of Vinyl Cation Equivalents

The cyclization of substance (**134**) involves either an intermediate or a transition state having the properties of the vinyl cation I. This cation is a very potent electrophile (see below), and it is especially interesting that such "hot" cations can be generated efficiently under such extremely mild conditions (e.g., with 1% trifluoroacetic acid in

[4] The geometrical configuration about the olefinic bond attached to the five-membered ring is presumed to be as shown (a) on the basis of an assumed preference for *trans* addition to the acetylenic bond, and (b) by analogy to the one example (**167**) in which the configuration was securely established.

dichloromethane at −78°) from a relatively stable ditertiary allylic cation. The energy for this transformation probably is provided by the conversion of an sp^2 to sp^3 bond (affording ca. 40 kcal/mole) and an sp^1 to sp^2 bond (>40 kcal/mole).

The vinyl cation I proved to be exceedingly reactive. Thus, when it was generated in acetonitrile as the solvent, the nitrile reacted as a nucleophile giving, after aqueous work-up, the enamide (**137**),[4] hydrolysis of which afforded the ketone (**136**) (*51*). When stannic chloride in benzene, a system that had been employed successfully for the cyclization of olefinic acetals (see above), was used for the cyclization, the benzene was



trapped by the vinyl cation giving the substance (**138**)[4] (*57*). The constitution of this product was confirmed by oxidative degradation (see above) to the dione (**116**). Trifluoroacetic acid in nitroethane, which was the system of choice for the cyclization of the substrate (**92**) (see above), effected cyclization of (**134**) with capture of the nitroethane giving what proved to be the oximino ether (**139**) (*58*). The structure of an analogous product (**161**) that is described below, was established by degradative experiments. The vinyl cation I also reacted with an alkene, i.e., isohexene to give the alkylation product (**140**)[4] with a cholesterol-like side chain (*57*). The constitution of an analogous product (**164**) described below, was firmly established. Cyclization of (**134**) with stannic chloride in dichloromethane gave a mixture of five- and six-membered ring vinyl chlorides (**141**)[4] and (**142**) (*59*). With trifluoroacetic acid in dichloromethane at −78°, the cyclization proceeded to give exclusively the six-membered ring chloride (**142**) (*60*), the intermediary vinyl cation J evidently abstracting chloride ion from the solvent (see Chart XI). Seemingly, the vinyl cation J is produced by a Wagner–Meerwein rearrangement of cation I. If rearrangement occurred in the opposite sense, via 1,2 shift of the primary rather than the tertiary group, the product would have been an isomer of (**142**) in which the substituents at C-1 and C-2 are interchanged. The structure (**142**) was established by the transformations shown in Chart XI. The conversion to the known diacid (**144**) demonstrated the 6/6 *trans*-fused ring system. The conversion to a carboxylic ester (**143**) with two exchangeable α-hydrogens, showed that the rearrangement had occurred so as to give the isomer with a methyl at C-1 and the chloro at C-2. The alternative ester would have had only one α-hydrogen.

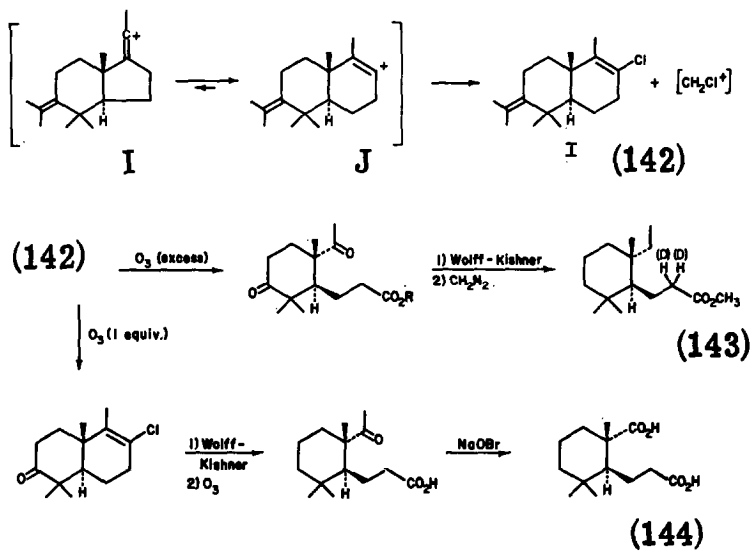


Chart XI

Synthesis of Longifolene

As shown above, vinyl cations generated by participation of acetylenic bonds in biomimetic polyene cyclizations will react with olefinic bonds intermolecularly, e.g.,

(**134**) → (**140**), as well as intramolecularly, e.g., (**132**) → (**133**). Another unusual example of the intramolecular process is described forthwith. This concerns the cyclization of the acetylenic cyclopentenol (**145**) that was expected, a priori, to give rise to the hydroazulenic ketone (**148**) by direct attack of an external nucleophile on the bicyclic vinyl cation K, followed by hydrolysis. The bicyclic substance (**148**) was indeed formed, but only as a by-product. The major product was, instead, the tricyclic carbinol (**146**). The formation of (**146**) may be rationalized by intramolecular reaction of the olefinic bond with the cationic center in K to produce the tricyclic cation L, followed by nucleophilic attack by water in the work-up. The cation L is interesting in that it embodies the unusual feature of destabilization due to the bridgehead olefinic bond, but, on the other hand, the potential stabilizing characteristic of the *7-anti*-norbornenyl cation. Irrespective of the validity of the theoretical considerations, the carbinol (**145**), which was readily prepared by the sequence indicated in Chart XII starting from isopropylidenecyclopentanone, gave the crystalline carbinol (**146**) in

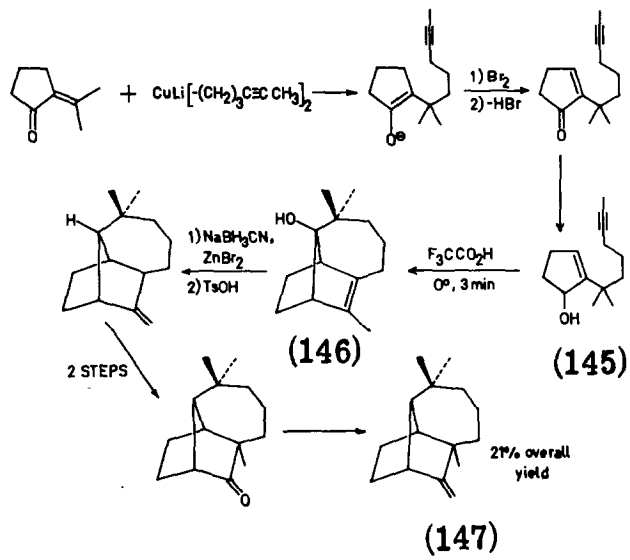
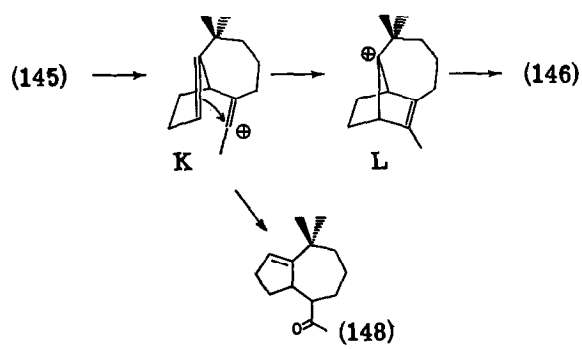


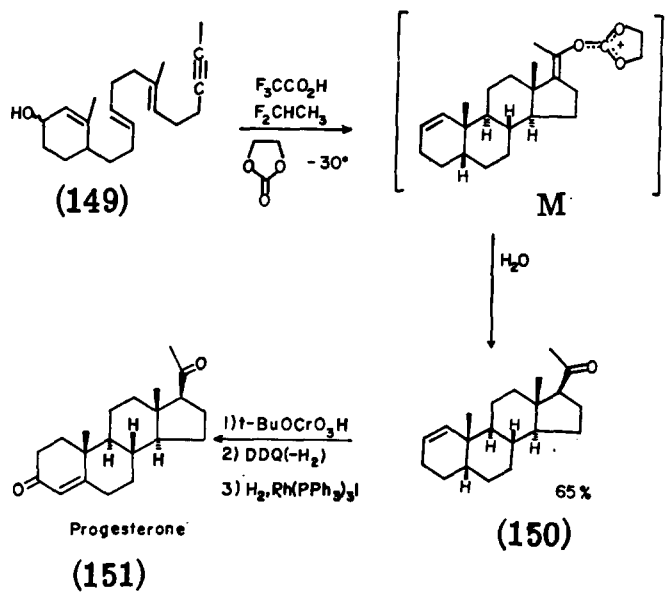
Chart XII



75% yield. The constitution of this bridged ring substance was unequivocally established by its transformation, as indicated in Chart XII, into racemic longifolene (**147**). Thus, a relatively short total synthesis of this natural product was accomplished in 21% overall yield (*61*). One feature of the synthesis that is noteworthy is the hydrogenolysis of the hydroxyl group of carbinol (**146**). Advantage was taken of the known susceptibility of 7-*anti*-norbornenyl substituents to displacement by hydride, probably via the cation L. Thus, the alcohol (**146**), on treatment with sodium cyanoborohydride in the presence of zinc bromide (to assist ionization of the hydroxyl group), afforded the corresponding hydrocarbon in 94% yield. The olefinic bond of this hydrocarbon was readily isomerized, by mild acid treatment, to the more stable exocyclic position.

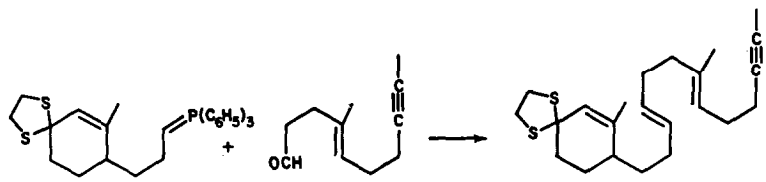
Synthesis of Steroids Including Progesterone, Testosterone, and 19-Norprogesterone

Attention is now turned to the total synthesis of steroids via the application of acetylenic participation in biomimetic polyene cyclizations. The trienynol (**149**) appeared to be a promising substrate for cyclization directly to the steroid nucleus. Indeed, under the indicated conditions, it was converted (65% yield) into the pregnenone (**150**) which, in turn, was readily transformed into progesterone (**151**) (*62*). Ethylene carbonate was added to the cyclization mixture to serve as a nucleophile for the purpose of capturing the vinyl cation, possibly in the form of the stabilized cation M.



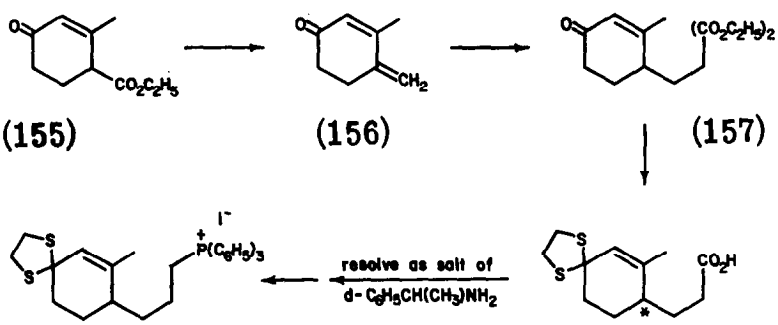
A convergent approach was employed for the synthesis of the cyclization substrate (**149**) (*63*). The key step was the Wittig condensation of the phosphorane (**152**) with the aldehyde (**153**). The Schlosser modification was used in order to obtain the *trans* olefinic bond in the product (**154**). The conversion of substance (**154**) into the substrate

(**149**) involved hydrolysis of the thioketal to the unsaturated ketone, which was reduced with lithium aluminum hydride.



(**152**) (**153**) (**154**)

The phosphonium salt (**120**), required for making the phosphorane (**152**) was prepared from commercially available Hagemann's ester (**155**). Its ethylene ketal was submitted to lithium aluminum hydride reduction, followed by acid hydrolysis (which also effected dehydration) to yield the dienone (**156**). This substance underwent a 1,6-Michael addition with malonic ester, giving the keto diester (**157**), which was converted, by hydrolytic decarboxylation followed by reaction with ethanedithiol, into the thioketal acid (**158**). This acid has an asymmetric center (indicated by the asterisk) and was resolved into the (+) and (−) forms as the salts of optically active α-methylbenzylamine. Use of the (+) form of (**158**) in the remainder of the synthesis led to (+) progesterone, identical with natural material.

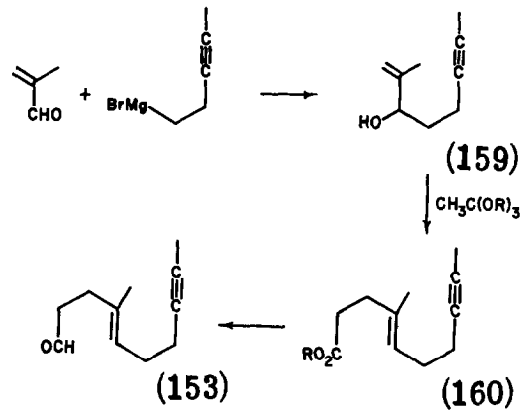


(**155**) (**156**) (**157**)

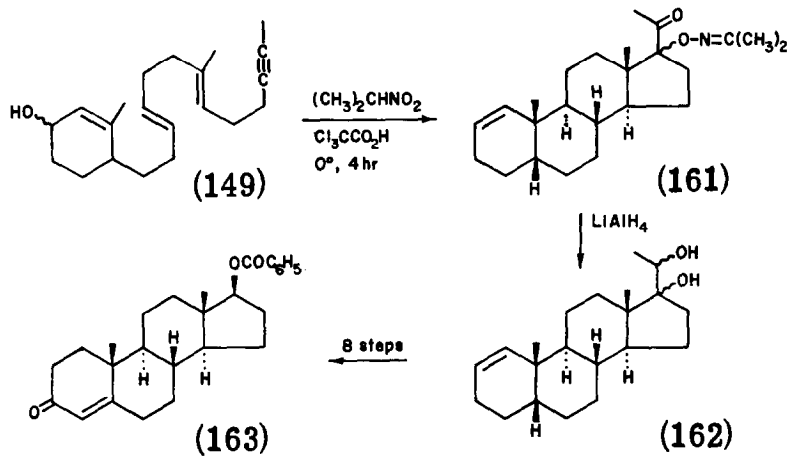
(**120**) (**158**)

The aldehyde (**153**) has been prepared in a variety of ways, one of which involves the addition of 3-pentynylmagnesium bromide to methacrolein. The resulting allylic alcohol (**159**) was heated with ethyl (or methyl) orthoacetate containing 5% propionic acid, which effected the stereospecific orthoacetate Claisen reaction (*54*) involving the intermediacy of a ketene acetal similar to (**130**). The resulting enyne ester (**160**) was obtained in >90% yield, and the olefinic bond was >98% in the *trans* (E) form.

In other cyclization studies, the trienynol (**149**) was treated with trichloroacetic acid in 2-nitropropane giving the oximino ether (**161**) (*58*), analogous to the formation of substance (**139**) (see above). This product was converted by hydrogenolysis with

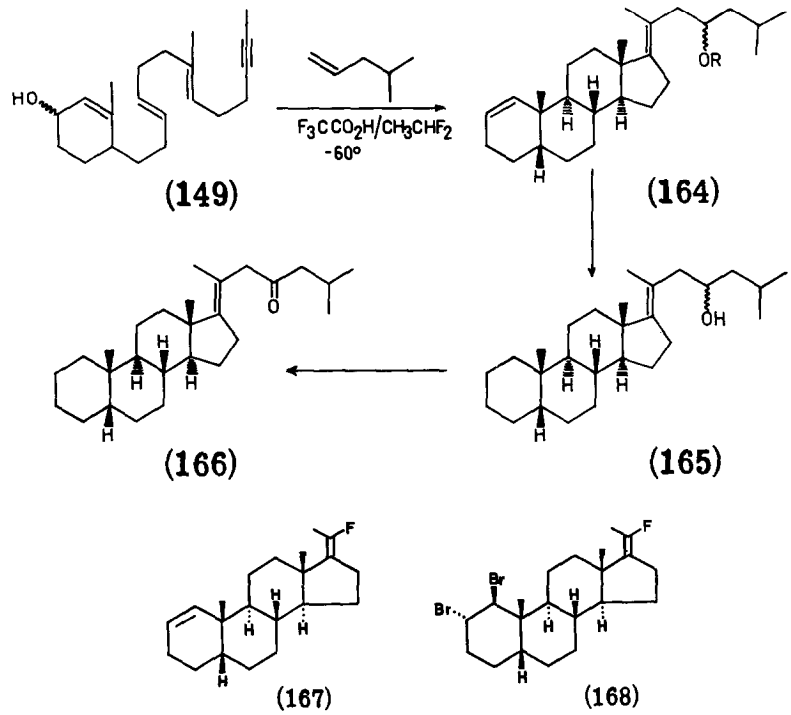


lithium aluminum hydride into the diol (**162**), which was transformed with periodate into the 17-keto compound and thence into testosterone benzoate (**163**) (*64*).



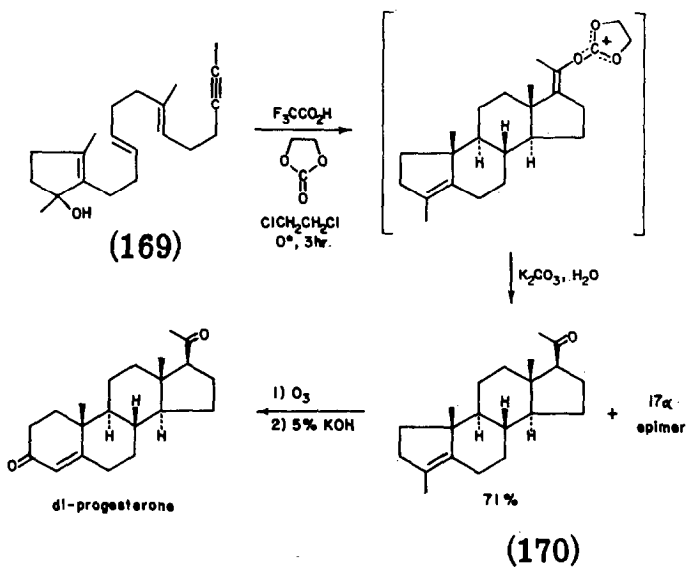
When the trienynol (**149**) was cyclized in the presence of isohexene the product (**164**, R = $COCF_3$),[4] involving capture of the isohexene, was isolated in 30% yield (*65*). This substance was converted into the ketone (**166**) by the following steps: hydride cleavage of the ester to give (**164**, R = H), selective hydrogenation of the olefinic bond in ring A to give product (**165**), and finally, oxidation of the alcohol with Collins reagent. The structure and configuration of the ketone (**166**) were confirmed by comparison with authentic material synthesized from a natural steroid.

In preliminary attempts to effect the aforementioned type of reaction, using boron trifluoride etherate as the catalyst, the major tetracyclic product proved to be the vinyl fluoride (**167**). Thus, it was eventually discovered that cyclization of the substrate (**149**) with boron trifluoride etherate in 1,1-dichloroethylene at –20° afforded the crystalline vinyl fluoride (**167**) in 36% isolated yield. The constitution, including the configuration about the olefinic bond holding the fluorine atom, was proved by single crystal X-ray diffraction analysis of the dibromide (**168**) (*66*).



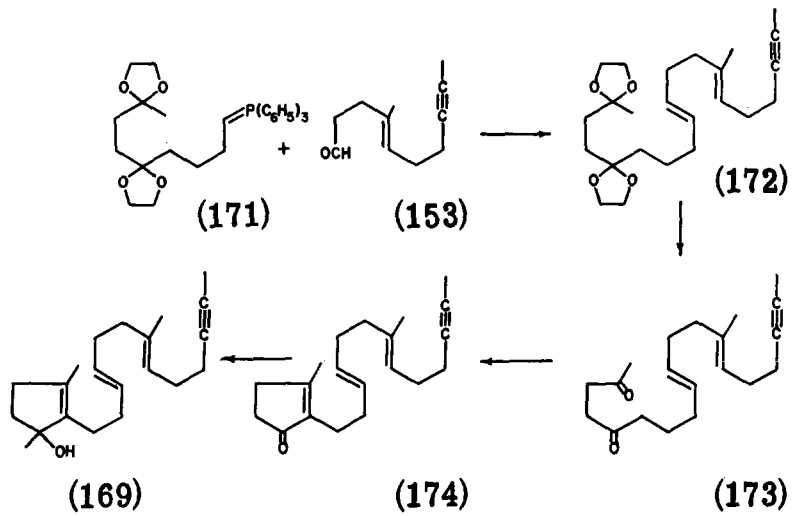
(149) (164) (166) (165) (167) (168)

Another substrate that has proved useful for synthesizing steroids is the cyclopentenol (**169**), which, on cyclization, produced the crystalline ketone (**170**) in 71% yield (*67*). Conversion of this product, via ozonolysis followed by intramolecular aldol condensation (cf. (**93**) → (**94**) → (**95**) above), into the racemic form of progesterone was effected in >80% yield.



(169) (170)

The synthesis of the cyclopentenol (**169**) was effected by the Wittig–Schlosser condensation of the aldehyde (**153**) (prepared as described above) with the phosphorane (**171**). The product (**172**) was hydrolyzed to the diketone (**173**), which in turn was induced to undergo a base-catalyzed cyclodehydration, giving the unsaturated ketone (**174**). Reaction of this last substance with methyllithium gave the cyclization substrate (**169**).



The phosphonium salt (**176**), required for production of the phosphorane (**171**), was prepared from the diketal bromide (**175**), which was in turn synthesized, as shown in Chart XIII, by a scheme similar to that used for preparing the lower homolog (**102**).

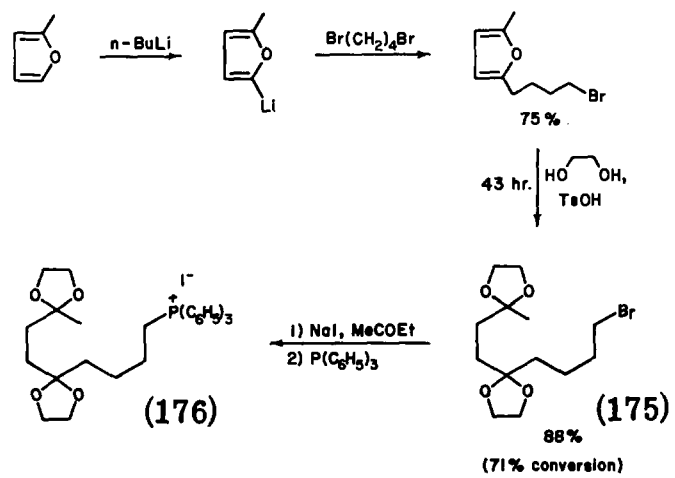
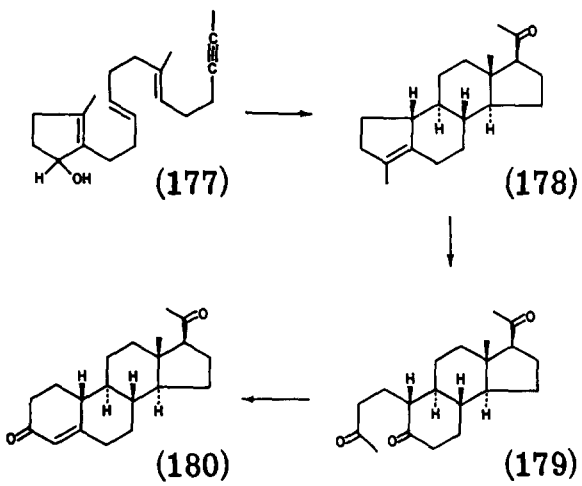


Chart XIII

The scheme for synthesizing progesterone described above has been applied to the synthesis of the 19-nor compound (**180**) (*68*). Thus, reduction of the ketone (**174**) with lithium aluminum hydride afforded the secondary allylic alcohol (**177**). The cyclization of this substrate was regioselective, giving the product (**178**) resulting from ring closure into the secondary allylic position of (**177**), similarly to the conversion of (**98**) into (**99**) (see above). Ozonolysis of the tetracyclic material (**178**) followed by cyclodehydration of the resulting triketone (**179**) gave the racemic form of 19-norprogesterone (**180**), an important structural type in the field of oral contraception.



Synthesis of 11-Substituted Steroids Including 11α-Hydroxyprogesterone

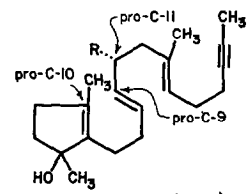
As part of a general study aimed at the total synthesis of 11-substituted steroids, e.g., cortisone, via biomimetic polyene cyclization, we chose to examine the cyclization of the trienynol (**181**, R = CH_3) (*69*) in order to (a) ascertain how the new chiral center at pro-C-11[5] would affect the stereochemical course of the reaction, and (b) determine its potential for use in the synthesis of 11-methylprogesterone. An analysis of the stereochemical problem follows.

Cyclization of substrate (**181**, R = H), without a substituent at pro-C-11[5] is known (see (**169**) → (**170**) above) to be stereospecific giving (71% yield) a single tetracyclic racemic product (**182**, R = H) plus (**183**, R = H),[6] which has been converted into racemic progesterone. The stereochemical course of the cyclization of (**181**, R = H) is the result of initiation of the stereospecific process by equal amounts of backside and frontside attachment of pro-C-9 to pro-C-10 giving (**182**, R = H) and (**183**, R = H), respectively. (Since the substrate (**181**, R = H or CH_3) undergoes facile dehydration prior to cyclization, the chirality of the carbon holding the hydroxyl group is lost and cannot influence the stereochemical course of the cyclization.) The cyclization of the

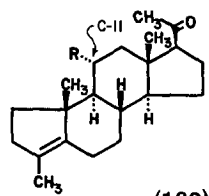
[5] The term "pro-C-11" is meant to refer to that carbon which becomes C-11 (steroid number) in the anticipated product.

[6] Most of the previous formulas containing chiral centers are meant to refer to racemic materials, although only one enantiomer is shown. In the present case the argument refers to the indicated enantiomer only.

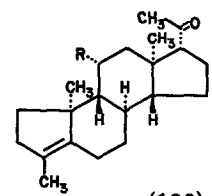
homolog (**181**, R = CH_3) differs in that, because of the chiral center at pro-C-11, it can lead theoretically to two tetracyclic C-11 diastereomers. Thus, the enantiomer with the *R* configuration at pro-C-11, shown in formula (**181**, R = CH_3), could cyclize by a backside attachment of pro-C-9 to pro-C-10, giving the 11-equatorial methyl substance (**182**, R = CH_3) (*R* configuration at C-11 and *R* at C-10); or a frontside attachment giving the 11-axial methyl isomer (**183**, R = CH_3) (*R* at C-11 and *S* at C-10). Since cyclization of the pro-C-11 *S* form of the substrate would give an enantiomeric set of results, it became apparent that the question of how the pro-C-11 chiral center would affect the stereochemical course of the cyclization could be answered by working with racemic materials, and determining the ratio of tetracyclic racemic 11-equatorial (**182** plus enantio-**182**) to 11-axial (**183** plus enantio-**183**) diastereomers. As shown below, the effect of the pro-C-11 chiral center is profound, resulting in apparent total asymmetric induction, so as to produce the 11α-methyl diastereomer (**182**, R = CH_3) as the only detectable tetracyclic product.



(**181**)



(**182**)



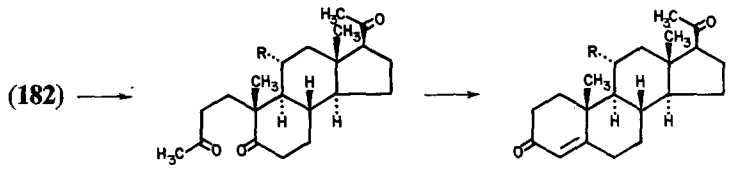
(**183**)

The synthesis of the racemic form of the cyclization substrate (**181**, R = CH_3) was performed by a scheme analogous to that described above for the preparation of the lower homolog (**169**). Thus, the allylic alcohol (**159**) was converted, by reaction with ethyl orthopropionate involving a Claisen rearrangement, into the homolog of compound (**160**, R = C_2H_5) having a methyl group α to the carboethoxy group. This ester was converted into the corresponding aldehyde (**153** with an α methyl substituent), which was employed in the Wittig–Schlosser condensation with the phosphorane (**152**).

Treatment of racemic (**181**, R = CH_3) under the conditions used for the cyclization of the lower homolog (**169**) resulted in only a 16% yield of tetracyclic product. Thus, the rate of cyclization appears to be attenuated by the methyl substituent at pro-C-11, probably because of steric hindrance. Eventually, more vigorous conditions were discovered, i.e., trifluoroacetic acid in trifluoroethanol at 0° for 3 hr, which afforded crystalline racemic (**182**) in over 60% yield. None of the racemic 11β compound (**183**) could be detected.

The constitution of the tetracyclic product (**182**) was established by its conversion, via ozonolysis followed by cyclodehydration of the resulting trione (**184**), into the

racemic form of 11α-methylprogesterone (**185**), the structure of which was established unequivocally by single crystal X-ray diffraction analysis (*66*).



Since cyclization of racemic (**181**, $R = CH_3$) *gives a single diastereomer, it follows that if this substrate were obtained in a pure enantiomeric form, the tetracyclic product would also be enantiomerically pure. Thus, the process involves essentially total asymmetric synthesis induced by the pro-C-11 chiral center.* Indeed, preliminary work has shown that the substrate (**181**, $R = CH_2CH{=}CH_2$), containing an unknown excess of one enantiomer, does indeed cyclize, in over 60% yield, to give an optically active product (*70*).

The synthesis of an 11-oxy steroid via the cyclization of a polyenic substrate having an oxygen substituent at pro-C-11, e.g., substance (**193**), proved to be very difficult. After many failures, we concluded that the resistance to cyclization was probably the result of one or more of the following: (a) steric hindrance due to the substituent at pro-C-11, (b) attenuation of the nucleophilicity of the disubstituted olefinic bond by the inductive effect of the allylic oxygen, and (c) premature destruction of this allylic system by the acidic cyclization catalysts. However, the later success with the cyclization in the pro-C-11 methyl system (see above), prompted reexamination of the pro-C-11-oxy system with the view of exploring the use of the newer and more strenuous cyclization conditions.

The cyclization substrate (**193**) was conveniently prepared by a convergent synthesis, the key step being the addition of the lithium salt of the acetylene (**96**) to aldehyde (**189**) to give the propargylic alcohol (**190**). The preparation of the diketal acetylene (**96**) is described above. The aldehyde (**189**) was prepared as outlined in Chart XIV. Thus,

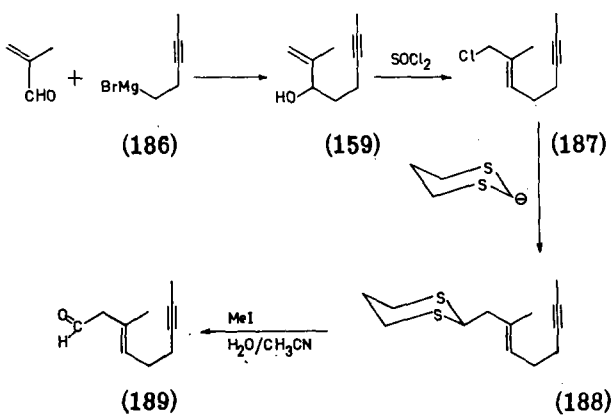
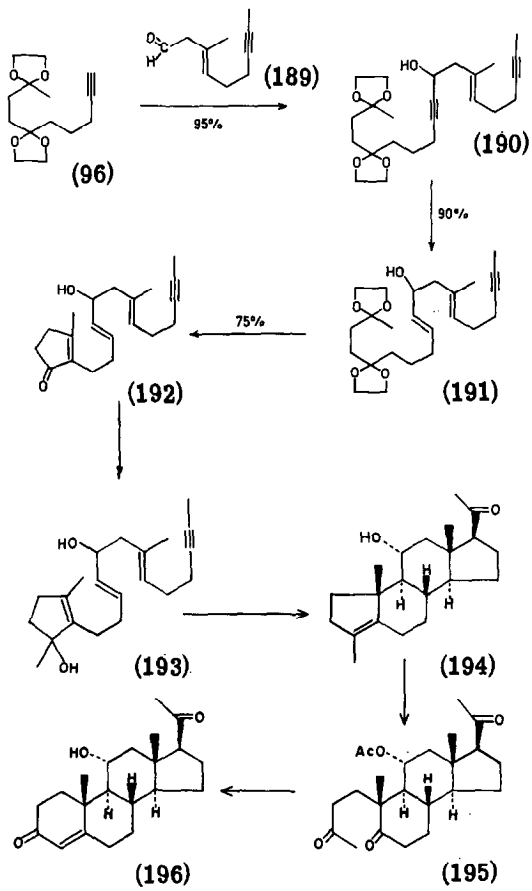


Chart XIV

the enynol (**159**) (produced from the addition of (**186**) to methacrolein) was allowed to interact with thionyl chloride, under conditions known to induce the stereoselective S_Ni' reaction (*43*) to give the allylic chloride (**187**). This chloride, on condensation with the anion of dithiane afforded the thioacetal (**188**), which, on hydrolysis, was converted into the aldehyde (**189**).

Completion of the synthesis involved reduction of the aforementioned propargylic alcohol (**190**) with lithium aluminum hydride to the *trans*-allylic alcohol system (**191**), followed by acid hydrolysis, then cyclodehydration of the resulting 1,4-dione system to afford the hydroxy enone (**192**). Reaction of this last substance with methyllithium gave the substrate (**193**) (*71*).



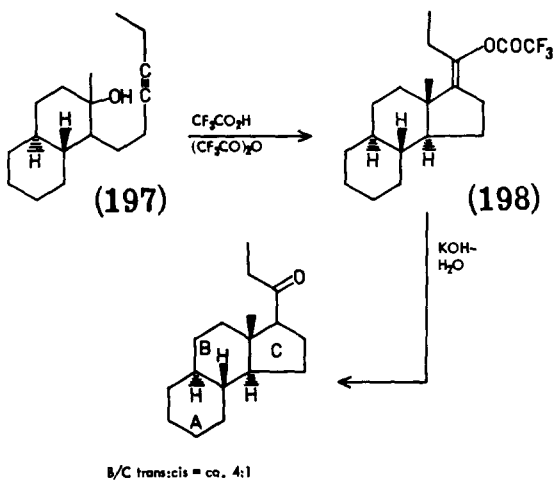
The diol (**193**) proved to be even less susceptible to cyclization than the pro-C-11 methyl analog (see above). However, relatively vigorous conditions were found (*72*), which gave tetracyclic material in 39% yield. The product appeared to consist exclusively of the racemic 11α-substance (**194**) as shown by its conversion, via acetylation followed by ozonolysis, and then, cyclodehydration of the resulting trione (**195**), into the racemic form of 11α-hydroxyprogesterone (**196**), the (+)-enantiomer of which

is a key intermediate in the commercial production of hydrocortisone acetate.[7] The stereospecificity of the cyclization (**193**) → (**194**) is analogous to the behavior described above in the case of the 11-methyl analog, and portends well for obtaining a single optically active cyclization product from an enantiomerically pure substrate.

On the basis of the present state of refinement of the synthesis, racemic 11α-hydroxyprogesterone is obtainable in ca. 15% overall yield in 16 steps from simple compounds. This represents approximately a 7% overall yield in 22 steps of "racemic" hydrocortisone acetate.[7] Our synthesis may be compared with a well-known (*74*) total synthesis, which leads to optically active cortisone in "1% overall yield in 27 steps" (*75*).

The Problem of Regio- and Stereospecific Participation of the Acetylenic Bond

In all of the examples of participation of the acetylenic bond in polyene cyclizations described above, the process has been stereospecific with respect to the developing ring fusion, only *trans* products being produced in accordance with the predictions of the Stork–Eschenmoser hypothesis (*3*, *4*). In contrast, when the acetylenic bond is involved in formation of a single ring such as in the cyclization (**197**) → (**198**), the reaction is generally not stereospecific (*56*). Thus, the product from cyclization of (**197**) after hydrolysis was a mixture of the B/C *trans* ketone (**199**) and its B/C *cis* isomer (not shown) in a ratio of about 4:1.

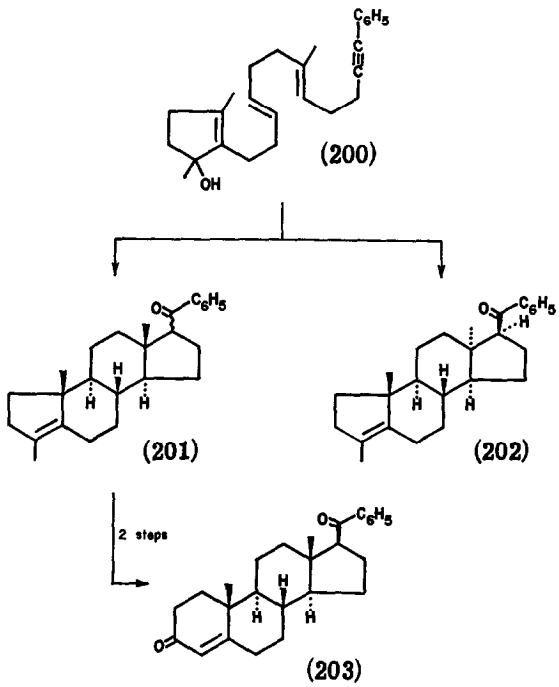


(**199**)

We have encountered one example of participation of an acetylenic bond in polyene cyclizations that is not stereospecific. This case involved the cyclization of the substrate (**200**) with the phenylacetylenic terminator, which it was hoped would give improved yields through its increased nucleophilicity (cf. the case of the styryl terminator

[7] In a personal communication, Dr. Philip F. Beal, III, of the Upjohn Company has indicated that the commercial conversion of (**196**) into hydrocortisone acetate is accomplished in ca. 50% yield according to a simplified and refined version of the published method (*73*).

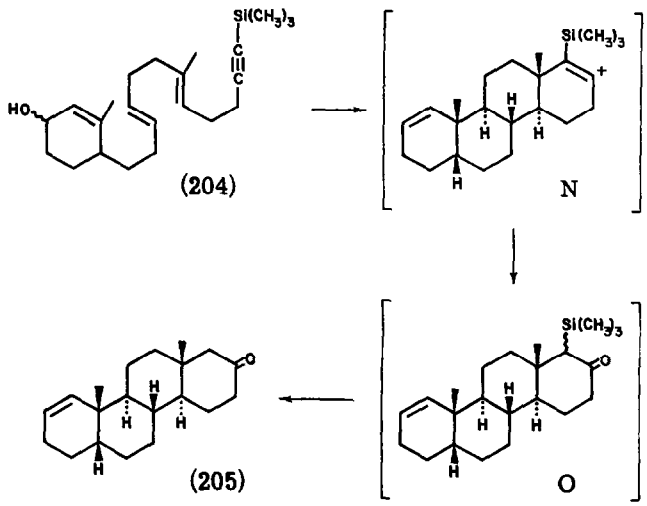
described above). Indeed treatment of substance (**200**) with trifluoroacetic acid in dichloromethane containing ethylene carbonate at −45° for 45 min gave, after basic hydrolysis, about 80% yield of a mixture of three tetracyclic ketones (*76*). About four-fifths of this product was the expected mixture of interconvertible 17α and 17β epimers (**201**) of natural configuration. The rest of the product, quite unexpectedly, proved to be the unnatural C/D *cis* isomer (**202**), the configuration of which was established unequivocally by single crystal X-ray diffraction analysis (*66*). The constitution of the 17β form of the ketone (**201**) was established by the usual conversion, via the ozonolysis-cyclodehydration sequence, into the known (*77*) steroid analog (**203**).



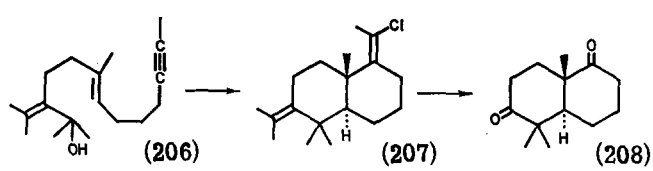
The 4:1 ratio of C/D *trans* (**201**) to C/D *cis* (**202**) products is about the same that would be expected (*56*) from closure of the D ring from a tricyclic intermediate. However, the mild cyclization conditions (see above) compared with those required for the cyclization of substance (**197**), namely a 3:1 mixture of trifluoroacetic acid and its anhydride at about −15° for 2 hr, seemingly preclude the intermediacy of tricyclic material derived from (**200**). The lack of stereospecificity in this case is mystifying.

From the examples cited above it is clear that there is a strong preference for an acetylenic bond that is located in the 5,6-position relative to a developing carbocation center to react so as to form a five-membered ring. A special case in which the six-membered ring is formed to the exclusion of the five has been discovered. This example was encountered in a study of the effect of the trimethylsilylacetylenic group as a terminator of polyene cyclizations (*78*). Thus, the trimethylsilyl substrate (**204**), which was prepared via condensation of the phosphorane (**152**) with the aldehyde analogous to (**153**) (see above) but with a trimethylsilyl in place of the terminal methyl group,

underwent acid-catalyzed cyclization in the presence of ethylene carbonate to give, after treatment with water, the D-homosteroidal ketone (**205**) in 55% yield. There was no evidence for the formation of the product of five-membered ring D closure. The process appears to proceed through the cation N, which is evidently more stable than the alternative cation (from five-membered ring closure) in which the charge is on the carbon holding the trimethylsilyl group. This "beta effect" of charge stabilization by the silyl group has been observed in saturated systems (*79*). The trimethylsilyl ketone O presumably resulting from nucleophilic attack of water on N would be expected to undergo facile hydrolysis to give the ketone (**205**). The structure and configuration of this ketone were established by hydrogenation to the known D-homoandrostanone (**75**) (see above).



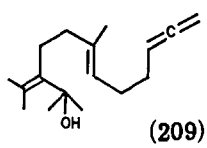
It was not surprising to find that when the acetylenic bond was located in the 6,7-position relative to a developing carbocationic center, that cyclization occurred so as to produce a six-membered ring. Thus, the substrate (**206**), on treatment with stannic chloride in dichloromethane, afforded the 6/6 *trans*-fused system (**207**)[4] as the major product (*80*). The constitution of the product was established by ozonolysis to give the known *trans*-trimethyldecalindione (**208**).



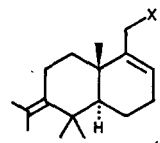
Participation of the Allenic Bond

Finally, the isomeric system (**209**) was examined in order to see if the allene group would participate in polyene cyclizations (*80*). Treatment of (**209**) with stannic chloride in dichloromethane gave, as the major product, the allylic chloride (**210**, X = Cl),

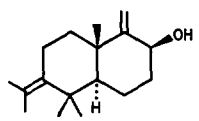
which, on ozonolysis, was degraded to the known dione (**208**), thus, establishing the *trans* 6/6 fused ring system. When trifluoroacetic acid in dichloromethane was used for cyclization, the product, after hydrolysis, consisted of a mixture of (**210**, X = OH) and the isomer (**211**). The structures of these products were proved by interconversion experiments and by oxidative degradation to the known keto diester (**212**).



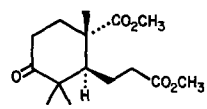
(**209**)



(**210**)



(**211**)



(**212**)

The results of the cyclization of the allenic substance (**209**) are analogous to the behavior found by Bergman (*81*) for the participation of the allenic bond in the solvolysis of sulfonate esters.

CONCERNING THE MECHANISM OF POLYENE CYCLIZATIONS

The question of the mechanism of stereospecific cationic polyene cyclizations, whether enzymic or biomimetic, has been open to debate. On the one hand, the intermediacy of partially cyclized cations (classical or bridged) has been shown to be consistent with the observed stereochemical course of such cyclizations (*82*). On the other hand, a concerted process in which all of the new C—C bonds are formed synchronously represents an equally satisfactory rationalization of the facts. There has been little direct evidence obtained for deciding between the "step-wise" and the "synchronous" mechanisms; however, at the present time the balance (see below) is somewhat in favor of the latter.

It has been demonstrated by deuterium incorporation experiments that certain enzymic (*37*) as well as biomimetic (*36*) polyene cyclizations do not involve partially cyclized olefinic intermediates, which would require reprotonation (and consequent deuterium incorporation) for the cyclization to continue. These findings, however, do not preclude a step-wise process involving cations that do not deprotonate.

Detailed kinetic studies of solvolysis of a series of substituted dienic *p*-nitrobenzenesulfonates (see formula (**3**) above) in both acetic acid (*83*) and in trifluoroethanol (*84*) have shown small but incremental rate enhancements (based on first-order disappearance of starting materials) by substituting methyl groups in place of the vinyl hydrogens of the terminal olefinic bond of substrate (**3**). This apparent second-order anchimeric assistance was also accompanied by small increases in the yields of bicyclic products.

These effects represent a necessary, but not sufficient, condition for a synchronous mechanism. Other evidence consistent with the synchronous process has been obtained in connection with a study of a total synthesis of estrone (**216**) based on a biomimetic polyene cyclization (*85*). This synthesis and the mechanistic considerations are described below.

Synthesis of Estrone

The aforementioned synthesis is shown in Chart XV, the key step being the stereospecific biomimetic cyclization of the secondary allylic alcohol (**213**) to the tetracyclic substance (**214**), which was easily converted, via epoxidation followed by stereospecific boron trifluoride-catalyzed rearrangement of the resulting epoxide (**215**), into the racemic form of estrone (**216**).

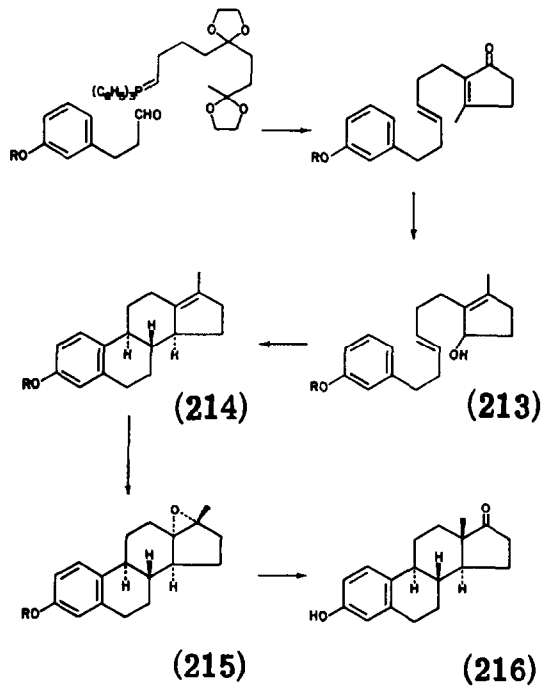
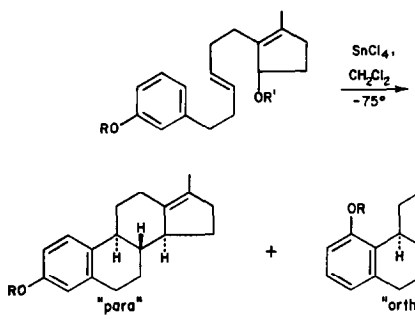


Chart XV

Mechanistic Implications

The Lewis acid-catalyzed cyclization of (**213**) proceeded in quantitative yield, giving in addition the product (**214**), some of the isomer resulting from ring closure *ortho* instead of *para* to the OR group. The *para*/*ortho* ratio varied, depending on the nature of the allylic leaving group as well as the substituent on the oxygen in the aromatic ring (*86*). The results of a study of this effect are summarized in Fig. 2. Particularly

noteworthy is a comparison of the first two cases (Fig. 2) in which the leaving group was changed simply from OH (*para/ortho* ratio 8.4:1) to $OSiMe_3$ (ratio 2.6:1). Thus, the nature of the leaving group is "felt" during the bonding of the aromatic nucleus to the internal olefinic bond. This effect is consistent with a synchronous process. On the other hand, the two different leaving groups could possibly give rise to a different population of conformers of substrate in the ground state, which could be reflected in a difference in product distribution in a step-wise mechanism, provided the activation energies for the cyclizations are low enough so that the Curtin–Hammett principle is not applicable.



R	R'	Ratio para/ortho
Me_3Si	H	8.4
Me_3Si	Me_3Si	2.6
CH_3	H	3.0
C_6H_5CO	H	2.4
C_6H_5CO	C_6H_5CO	1.4

FIG. 2. Effect of substituents on the *para/ortho* ratio in the cyclization of the substrate (**213**).

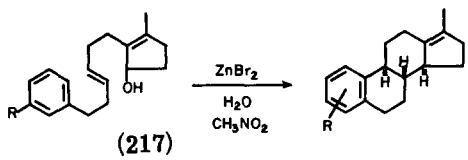
More convincing evidence for a synchronous process was obtained by studying the kinetics of the cyclization of a series of substrates (**217**), with different substituents in the aromatic nucleus (see Fig. 3). The relative rates (measured by monitoring both appearance of products and disappearance of substrates) increase with increasing nucleophilicity of the aromatic nucleus, indicating second-order anchimeric assistance by the aryl group in the heterolysis of the allyl—O bond, but a Hammett plot shows pronounced curvature. The data can be accommodated, however, by the process described in Eq. [1], involving two steps,

$$\text{Substrate (217)} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{intermediate X}] \xrightarrow{k_2} \text{tetracyclic products} \qquad [1]$$

the first being the reversible formation of an unidentified intermediate X, which could be the complex P between substrate (**217**) and zinc bromide. A Hammett plot can be made only from k_2, which is equal to the observed rate when $k_1 \gg k_2$, a condition that is being approached only in those cases with the more electron-withdrawing substituents ($R = CF_3$ and Cl). With the more electron-rich substituents ($R = CH_3$ and OCH_3) it appears that $k_2 \gg k_1$ and $k^{obs} \cong k_1$, consistent with the observed leveling off of the

rates. Using Eq. [1] and the observed rates for cyclization, a relative k_2 for each of the cases shown in Fig. 3 was calculated (*86*). A Hammett plot with these calculated values of k_2 gives a ρ value (–3), which is in the low region for electrophilic aromatic substitutions, suggesting significant participation of the aromatic nucleus in the transition state of the cyclization step.

Other possibilities for intermediate X are the dissociated ion pair Q or the partially cyclized ion R. If the ion R were the intermediate, then the cyclization would not be concerted. However, since no products corresponding to partially cyclized material (derived from R) could be detected, we consider R an unlikely intermediate. Further-

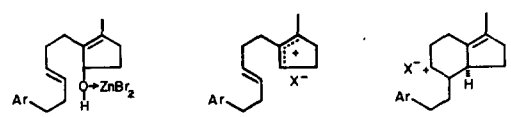


(217)

R	=	CF_3	Cl	H	CH_3	CH_3O
k_{rel}	=	1	3.12	5.90	6.50	6.70
σ	=	0.55	0.23	0	-0.17	-0.27

FIG. 3. Relative rates of cyclization of the substrate (**217**) with different substituents in the aromatic nucleus.

more, there appears to be no precedent for ring opening of such a bicyclic to a monocyclic cation. Finally, if R were the intermediate, the value of ρ for the cyclization would be expected to be larger than –3, consistent with typical electrophilic substitutions. Thus, the dependence of *para/ortho* ratios on the leaving group (see above), the second-order anchimeric assistance in a two-step scheme, the relatively low value of ρ, and the absence of products derived from an intermediate bicyclic cation are most easily accommodated by a mechanism involving the concerted formation of two rings. It should be emphasized, however, that although the evidence points strongly toward a synchronous process in the case of the cyclization (**213**) → (**214**), generalization of this probable mechanistic pathway to other polyene cyclizations awaits experimental verification.



P Q R

CONCLUSION

Acid-catalyzed biomimetic polyene cyclization of acyclic chains is a viable synthetic tool for the stereospecific formation of polycyclic systems. Acetal as well as allylic alcohol functions are useful initiators for these cyclizations. Methyl acetylenic as well

as styryl end groups are particularly useful terminators that can give exclusive five-membered ring formation, and thus, make possible the total synthesis of the steroid nucleus in a single step starting from a one-ring substrate.

The stereochemical course of natural, enzymic polyene cyclizations may to some extent be guided by the same effects that seem to control the nonenzymic processes, i.e., the course of the reaction results from *trans-anti-parallel* electrophilic addition to the olefinic functions according to the prediction of Stork et al. (*3*) and Eschenmoser et al. (*4*).

ACKNOWLEDGMENTS

Special thanks are due to my numerous collaborators who have made many significant contributions to the planning of the research described in this review, and who were entirely responsible for performing the laboratory experiments. I wish also to thank the National Institutes of Health and the National Science Foundation who have afforded the major financial support to our program. In addition, I wish to express my gratitude to Michael E. Garst and Robert C. Ronald for their generous assistance in the editing of the manuscript of this article.

REFERENCES

1. (a) N. ANAND, J. S. BINDRA, AND S. RANGANATHAN, "Art in Organic Synthesis." Holden–Day, San Francisco, 1970; (b) A. A. AKHREM AND Y. A. TITOV, "Total Steroid Synthesis." Plenum Press, New York, 1970; (c) S. E. DANISHEFSKY AND S. DANISHEFSKY, "Progress in Total Synthesis," Vol. 1. Appleton–Century–Crofts, New York, 1971; (d) "The Total Synthesis of Natural Products," Vol. 2 (J. ApSimon, Ed.). Wiley, New York, 1973; (e) K. NAKANISHI, T. GOTO, S. ITO, S. NOTORE, AND S. NOZOE, "Natural Products Chemistry," Vol. 1. Academic Press, New York, 1974; (f) R. T. BLICKENSTAFF, A. C. GHASH, AND G. C. WOLF, "Total Synthesis of Steroids." Academic Press, New York, 1974.
2. R. B. CLAYTON, *Quart. Rev. (London)*, **19**, 168 (1965); L. J. MULHEIRN AND P. J. RAMM, *Chem. Soc. Rev.*, **1**, 259 (1972).
3. (a) G. STORK AND A. W. BURGSTAHLER, *J. Amer. 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, *Helv. Chim. Acta*, **38**, 1890 (1955).
5. (a) E. E. VAN TAMELEN, J. D. WILLETT, R. B. CLAYTON, AND K. E. LORD, *J. Amer. Chem. Soc.*, **88**, 4752 (1966); (b) E. J. COREY, W. E. RUSSEY, AND P. R. ORTIZ DE MONTELLANO, *J. Amer. Chem. Soc.*, **88**, 4750 (1966).
6. (a) W. S. JOHNSON, *Accounts Chem. Res.*, **1**, 1 (1968); (*b*) *Chimia*, **29**, 310 (1975); (c) *Angew. Chemie*, **88**, 33 (1976); *ibid.*, Int. Ed., **15**, 9 (1976).
7. P. A. STADLER, A. NECHVATAL, A. J. FREY, AND A. ESCHENMOSER, *Helv. Chim. Acta*, **40**, 1373 (1957).
8. 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, Eds.). J. and A. Churchill, London, 1959.
9. (a) E. E. VAN TAMELEN, *Accounts Chem. Res.*, **1**, 111 (1968); (b) **8**, 152 (1975).
10. M. JULIA, *Accounts Chem. Res.* **4**, 386 (1971) and later papers.
11. W. A. SMIT, A V. SEMENOVSKY, AND V. F. KUCHEROV, *Tetrahedron Lett.*, 2299 (1964); A. V. SEMENOVSKII, V. A. SMIT, V. F. KUCHEROV, *Izv. Akad. Nauk SSR Ser. Khim.*, 2155 (1970) (*Chem. Abst.*, **74**, 5400 (1971)) and later papers.
12. W. S. JOHNSON AND R. OWYANG, *J. Amer. Chem. Soc.*, **86**, 5593 (1964).
13. (a) W. S. JOHNSON, D. M. BAILEY, R. OWYANG, R. A. BELL, B. JAQUES, AND J. K. CRANDALL, *J. Amer. Chem. Soc.*, **86**, 1959 (1964); (b) W. S. JOHNSON AND J. K. CRANDALL, *J. Org. Chem.*, **30**, 1785 (1965).
14. W. S. JOHNSON AND R. B. KINNEL, *J. Amer. Chem. Soc.*, **88**, 3861 (1966).
15. W. S. JOHNSON, A. S. KATNER, AND G. S. BAYLISS, unpublished observations.

16. W. S. JOHNSON AND F. E. BROT. See Ph.D. dissertation of F.E.B., Stanford University, 1966.
17. W. S. JOHNSON AND J. W. SCOTT. See Ph.D. dissertation of J.W.S., Stanford University, 1966.
18. W. S. JOHNSON AND S. F. BRADY. See Ph.D. dissertation of S.F.B., Stanford University, 1967.
19. (a) W. S. JOHNSON, A. VAN DER GEN, AND J. J. SWOBODA, *J. Amer. Chem. Soc.*, **89**, 170 (1967); (b) A. VAN DER GEN, K. WIEDHAUP, J. J. SWOBODA, H. C. DUNATHAN, AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **95**, 2656 (1973).
20. W. S. JOHNSON AND C. A. HARBERT, unpublished observations.
21. R. E. IRELAND, M. I. DAWSON, J. BORDNER, AND R. E. DICKERSON, *J. Amer. Chem. Soc.*, **92**, 2568 (1970); R. E. IRELAND, C. A. LIPINSKI, C. J. KOWALSKI, J. W. TILLEY, AND D. M. WALBA, *J. Amer. Chem. Soc.*, **96**, 3333 (1974); R. E. IRELAND, M. I. DAWSON, C. J. KOWALSKI, C. A. LIPINSKI, D. R. MARSHALL, J. W. TILLEY, J. BORDNER, AND B. L. TRUS, *J. Org. Chem.*, **40**, 973 (1975).
22. G. D. ABRAMS, W. R. BARTLETT, V. A. FUNG, AND W. S. JOHNSON, *Biorg. Chem.*, **1**, 243 (1971).
23. (a) W. S. JOHNSON, K. WIEDHAUP, S. F. BRADY, AND G. L. OLSON, *J. Amer. Chem. Soc.*, **90**, 5277 (1968); (b) W. S. JOHNSON, K. WIEDHAUP, S. F. BRADY, AND G. L. OLSON, *J. Amer. Chem. Soc.*, **96**, 3979 (1974).
24. S. F. BRADY, M. A. ILTON, AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).
25. J. W. CORNFORTH, R. H. CORNFORTH, AND K. K. MATHEW, *J. Chem. Soc.*, 2539 (1959).
26. W. S. JOHNSON, C. A. HARBERT, AND R. D. STIPANOVIC, *J. Amer. Chem. Soc.*, **90**, 5279 (1968).
27. F. GAUTSCHI, O. JEGER, V. PRELOG, AND R. B. WOODWARD, *Helv. Chim. Acta*, **38**, 296 (1955); C. DJERASSI AND J. E. GURST, *J. Amer. Chem. Soc.*, **86**, 1755 (1964).
28. M. S. KELLOGG AND W. S. JOHNSON, unpublished observations.
29. W. S. JOHNSON, W. H. LUNN, AND K. FITZI, *J. Amer. Chem. Soc.*, **86**, 1972 (1964).
30. W. S. JOHNSON AND K. E. HARDING, *J. Org. Chem.*, **32**, 478 (1967).
31. W. S. JOHNSON, M. F. SEMMELHACK, M. U. S. SULTANBAWA, AND L. A. DOLAK, *J. Amer. Chem. Soc.*, **90**, 2994 (1968).
32. W. S. JOHNSON AND T. K. SCHAAF, unpublished observations. See Ph.D. dissertation of T.K.S., Stanford University, 1969.
33. (a) W. S. JOHNSON, N. P. JENSEN, AND J. HOOZ, *J. Amer. Chem. Soc.*, **88**, 3859 (1966); (b) W. S. JOHNSON, N. P. JENSEN, J. HOOZ, AND E. J. LEOPOLD, *J. Amer. Chem. Soc.*, **90**, 5872 (1968).
34. W. S. JOHNSON AND M. A. ILTON DAWSON, unpublished observations. See Ph.D. dissertation of M.A.I., Stanford University, 1967.
35. R. E. IRELAND AND W. S. JOHNSON et al., *J. Amer. Chem. Soc.*, **92**, 5743 (1970).
36. K. E. HARDING, E. J. LEOPOLD, A. M. HUDRLIK, AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **96**, 2540 (1974).
37. T. T. TCHEN AND K. BLOCK, *J. Amer. Chem. Soc.*, **78**, 1516 (1956); *J. Biol. Chem.*, **226**, 931 (1957).
38. R. L. CARNEY AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **96**, 2549 (1974).
39. W. R. BARTLETT AND W. S. JOHNSON, *Bioorg. Chem.*, **4**, 342 (1975).
40. R. E. IRELAND, P. BEY, K.-F. CHENG, R. J. CZARNY, J.-F. MOSER, AND R. I. TRUST, *J. Org. Chem.*, **40**, 1000 (1975); R. E. IRELAND, T. C. MCKENZIE, AND R. I. TRUST, *J. Org. Chem.*, **40**, 1007 (1975).
41. F. E. BROT, G. D. STELLING, AND W. S. JOHNSON, unpublished observations. See Ph.D. dissertations of F.E.B., Stanford University, 1966, and G.D.S., Stanford University, 1970.
42. G. D. STELLING AND P. G. SIMPSON, unpublished observations. See Ph.D. dissertation of G.D.S., Stanford University, 1970.
43. W. S. JOHNSON, T. -T. LI, C. A. HARBERT, W. R. BARTLETT, T. R. HERRIN, B. STASKUN, AND D. H. RICH, *J. Amer. Chem. Soc.*, **92**, 4461 (1970).
44. B. E. MCCARRY, C. A. HARBERT, B. STASKUN, AND W. S. JOHNSON, unpublished observations.
45. S. J. DAUM, R. L. CLARKE, S. ARCHER, AND W. S. JOHNSON, *Proc. Natl. Acad. Sci.*, **62**, 333 (1969).
46. C. A. HARBERT AND W. S. JOHNSON, unpublished observations.
47. W. S. JOHNSON AND T. K. SCHAAF, *Chem. Commun.*, 611 (1969).
48. G. D. PRESTWICH AND J. N. LABOVITZ, *J. Amer. Chem. Soc.*, **96**, 7103 (1974).
49. K. A. PARKER AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **96**, 2556 (1974).
50. W. S. JOHNSON, L. A. BUNES, AND B. E. RATCLIFFE, unpublished observations. See Ph.D. dissertation of L.A.B., Stanford University, 1974.
51. W. S. JOHNSON, M. B. GRAVESTOCK, R. J. PARRY, R. F. MYERS, T. A. BRYSON, AND D. H. MILES, *J. Amer. Chem. Soc.*, **93**, 4330 (1971).

52. W. S. JOHNSON, J. DOMINGUEZ, AND M. E. GARST, unpublished observations.
53. W. S. JOHNSON AND C. E. WARD, unpublished observations.
54. W. S. JOHNSON, T. J. BROCKSOM, P. LOEW, D. H. RICH, L. WERTHEMANN, R. A. ARNOLD, T.-T. LI, AND D. J. FAULKNER, *J. Amer. Chem. Soc.*, **92**, 4463 (1970).
55. (a) W. D. CLOSSEN AND S. A. ROMAN, *Tetrahedron Lett.*, 6015 (1966); (b) P. E. PETERSON AND R. J. KAMAT, *J. Amer. Chem. Soc.*, **91**, 4521 (1969).
56. P. T. LANSBURY AND G. E. DUBOIS, *Chem. Comm.*, 1107 (1971); P. T. LANSBURY, T. R. DEMMIN, G. E. DUBOIS, AND V. R. HADDON, *J. Amer. Chem. Soc.*, **97**, 394 (1975).
57. M. B. GRAVESTOCK AND W. S. JOHNSON, unpublished observations.
58. D. R. MORTON, M. B. GRAVESTOCK, R. J. PARRY, AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **95**, 4417 (1973).
59. W. S. JOHNSON, M. B. GRAVESTOCK, AND W. G. HAAG, III, unpublished observations.
60. W. S. JOHNSON, M. B. GRAVESTOCK, R. J. PARRY, AND D. A. OKORIE, *J. Amer. Chem. Soc.*, **94**, 8604 (1972).
61. R. A. VOLKMANN, G. C. ANDREWS, AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **97**, 4777 (1975).
62. B. E. MCCARRY, R. L. MARKEZICH, AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **95**, 4416 (1973).
63. R. L. MARKEZICH, W. E. WILLY, B. E. MCCARRY, AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **95**, 4414 (1973).
64. D. R. MORTON AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **95**, 4419 (1973).
65. W. S. JOHNSON AND C. PIETRUSZEWSKI, unpublished observations.
66. A. SHENVI AND K. O. HODGSON, unpublished observations.
67. W. S. JOHNSON, M. B. GRAVESTOCK, AND B. E. MCCARRY, *J. Amer. Chem. Soc.*, **93**, 4332 (1971).
68. W. S. JOHNSON AND W. F. HUFFMAN, unpublished observations.
69. W. S. JOHNSON AND G. E. DUBOIS, *J. Amer. Chem. Soc.*, **98**, 1038 (1976).
70. W. S. JOHNSON, R. MULLER, B. GANEM, AND J. CALZADA, unpublished observations.
71. W. S. JOHNSON, S. ESCHER, AND B. W. METCALF, *J. Amer. Chem. Soc.*, **98**, 1039 (1976).
72. R. S. BRINKMEYER AND W. S. JOHNSON, see (17, footnote 15).
73. J. A. HOGG, P. F. BEAL, A. H. NATHAN, F. H. LINCOLN, W. P. SCHNEIDER, B. J. MAGERLEIN, A. R. HANZE, AND R. W. JACKSON, *J. Amer. Chem. Soc.*, **77**, 4436 (1955).
74. L. VELLUZ, G. NOMINE, AND J. MATHIEU, *Angew. Chem.*, **72**, 725 (1960); L. VELLUZ, G. NOMINE, J. MATHIEU, E. TOROMANOFF, D. BERTIN, R. BUCOURT, AND J. TESSIER, *C. R.*, **250**, 1293 (1960).
75. K. NAKANISHI, T. GOTO, S. ITÔ, S. NATORI, AND S. NOZOE, "Natural Products Chemistry," Vol. 1, pp. 499–500. Academic Press, New York, 1974.
76. W. S. JOHNSON, J. A. KLOEK, AND T. NIEM, unpublished observations.
77. D. F. MORROW, T. P. CULBERTSON, E. L. WITTLE, M. E. BUTLER, AND M. M. CREGER, *J. Med. Chem.*, 7, 537 (1974).
78. D. R. MORTON, R. F. MYERS, T. M. YARNELL, AND W. S. JOHNSON, unpublished observations. See Ph.D. dissertation of T.M.Y., Stanford University, 1975.
79. M. A. COOK, C. EABORN, AND D. R. M. WALTON, *J. Organometal. Chem.*, **24**, 301 (1970); **29**, 389 (1971).
80. H. T. HALL AND W. S. JOHNSON, unpublished observations. See Ph.D. dissertation of H.T.H., Stanford University, 1973.
81. M. H. SEKERA, B.-A. WEISSMAN, AND R. G. BERGMAN, *Chem. Comm.*, 679 (1973).
82. W. S. JOHNSON, *Trans. N.Y. Acad. Sci.*, **29**, 1001 (1967): K. E. HARDING, *Bioorg. Chem.*, **2**, 248 (1973).
83. W. S. JOHNSON AND H. D. DOSHAN, unpublished observations. See Ph.D. dissertation of H.D.D., Stanford University, 1967.
84. G. D. SARGENT, G. D. PRESTWICH, AND W. S. JOHNSON, unpublished observations. See Ph.D. dissertation of G.D.P., Stanford University, 1974.
85. P. A. BARTLETT AND W. S. JOHNSON, *J. Amer. Chem. Soc.*, **95**, 7501 (1973).
86. P. A. BARTLETT, J. I. BRAUMAN, W. S. JOHNSON, AND R. A. VOLKMANN, *J. Amer. Chem. Soc.*, **95**, 7502 (1973).