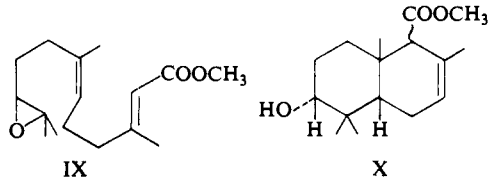
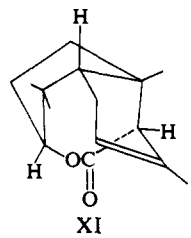
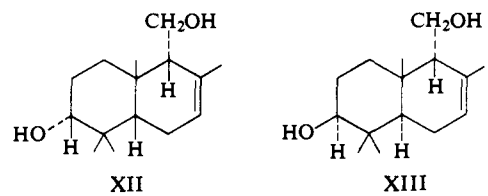
tonation, but can be interpreted in terms of either (a) a completely synchronized cyclization, or (b) a pathway involving an intermediary monocyclic carbonium ion (VIII).

In order to learn more about the intimate stereochemical aspects of the cyclization course, comparable ring closure attempts were made on the *trans,cis*-epoxy ester IX. Under the influence of boron trifluoride etherate in benzene at room temperature, this epoxy ester was converted into a mixture of products, including rearranged acyclic keto ester (~45%), monocyclic hydroxy ester (~10%), and bridged bicyclic ether[3] (~10%) (all yields by vpc). In addition there was formed in small (~3%) yield the bicyclic hydroxy ester X, which, as a component of the original cyclization mixture, was easily transformed by methanolic potassium hydroxide into the





tricyclic lactone XI, mp 107.5–108°. Neither the lactone nor *trans* bicyclic esters IV–V could be detected as components of the original cyclization mixture. The structure (and therefore stereochemistry) of the lactone was suggested by: ir (carbonyl at 5.83 μ), nmr (three-proton resonances at δ 0.92, 0.95, and 1.03 (singlets) and 1.75 (doublet of doublets), one-proton resonances at 2.27 (doublet), 3.78 (broad singlet), and 5.42 (multiplet)), and mass spectroscopy (high-resolution molecular ion at 234.1602 ($C_{15}H_{22}O_2$), base at *m/e* 105, large peak at *m/e* 190). Confirmation of structure was realized by the study of bicyclic diol XII, provided by lithium aluminum hydride reduction of the lactone. The diol of established structure XIII (obtained by hydride reduction of hydroxy ester V)[3] and the stereoisomeric XII possessed complex mass



spectra identical with regard to the appearance (but not intensity) of individual peaks. The yield of carbobicyclic material from IX is low; although to the extent that any is formed, the ring closure of epoxide seems to be stereoselective in the production of *cis*-fused product. This result is in harmony with the concept of cyclization which (1) wholly concerted proceeds with preservation of stereochemical relationships, or (2) involves conformationally "frozen" monocyclic carbonium ions, one type (from IX) giving rise to *cis* product and another type (from III) destined for *trans* fusion.[7]

In regard to formation of the A,B(C) ring system of lanosterol (I), it appears that the biochemical cyclization of squalene oxide is strongly based on organic chemical foundations and that no uncommon enzymic assistance may be needed (1) to produce the temporary 9,10-*cis* stereochemistry considered necessary for further, stereospecific isomerization to I,[4] and (2) to realize stereospecific cyclization without proton exchange from the medium, as observed.[8] Obviously, in A,B ring formation, enzyme action is mandatory (1) to ensure essentially quantitative operation of the squalene oxide cyclization elements which possess purely organic parallels, as outlined, and (2) to block other reaction outlets for starting epoxide, such as isomerization to acyclic ketone and generation of various monocarbocyclic species, as described above and elsewhere.[1,3]

Acknowledgment. The authors are indebted to the National Science Foundation for grant (GP 1937) support.

(7) For the stereoselective cyclization of *trans*- and *cis*-5,9-decadienyl *p*-nitrobenzenesulfonates, see W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jacques, and J. Crandall, *J. Am. Chem. Soc.*, **86**, 1959 (1964); W. S. Johnson and J. Crandall, *ibid.*, **86**, 2085 (1964).
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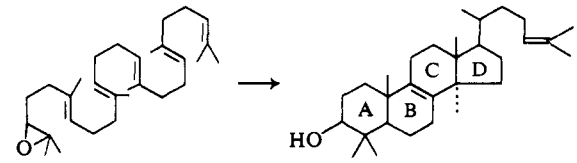
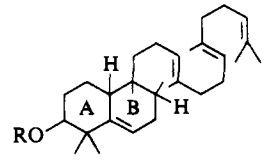
Terpene Terminal Epoxides. Skeletal Rearrangement Accompanying Bicyclization of Squalene 2, 3-Oxide

Sir:

By comparing enzymic and nonenzymic reactivity of a given substrate, it becomes possible to identify qualitatively the role of an enzyme in directing synthetic behavior beyond that normal in the organic chemical sense (see accompanying communication). As part of a program concerned with the bioorganic chemistry of terpenoid terminal epoxides,[1] we describe herein the direct nonenzymic conversion of squalene 2,3-oxide to bicyclic, rearranged product III. Although arrested by the cyclase





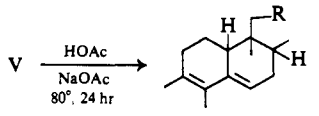
III, R = H
IV, R = $Si(CH_3)_3$
V, R = $SO_2C_6H_4$-*p*-CH_3
IX, R = $COCH_3$

(1) E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

system during biochemical conversion of the oxide to lanosterol (II), the rearrangement finds various parallels in other terpene systems.

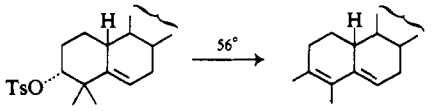
Treatment of squalene 2,3-oxide (I) in benzene at 10° with 0.2 mol of stannic chloride for 10 min produced a complex mixture of cyclization products, including tricyclic materials (25–30%)[2] and rearranged bicyclic alcohol III as the major, single hydroxylic component (*ca.* 20–25% yield), isolated essentially pure by preparative tlc. The nmr spectrum of III revealed four saturated methyls (δ 1.07, 0.85, 0.76), four vinyl methyls (δ 1.58, 3 Me; 1.67, 1 Me), four vinyl protons (δ 5.07, 3 H; 5.38, 1 H), and one equatorial proton on carbon bearing hydroxyl (δ 3.33). The axial nature of the hydroxyl group in III was confirmed by Jones oxidation to the ketone which upon borohydride reduction gave the epimeric alcohol IIIa. The nmr of IIIa showed a quartet centered at δ 3.12 (J_{AX} = 10 and J_{BX} = 4.5 Hz) for the axial proton at C-3.[3]

Initial evidence for the location of the nuclear double bond in III resulted from study of its trimethylsilyl (TMS) ether derivative IV. In the mass spectrum of IV, *m/e* 129 ($Me_3SiO^+C{=}C{-}C{=}C$) was the base peak. Ryhage[4] and Djerassi[5] have observed that the 129 fragmentation of 3-sterol TMS ethers resulted in significant charge retention by the *m/e* 129 fragment only when a Δ^5-olefinic linkage was present. Direct chemical evidence for the presence of the 5,6 double bond was obtained by acetolysis of its tosylate (V), which produced diene VI (38% yield), a



VI, R = farnesyl

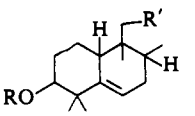
result analogous to the rearrangement of steroidal tosylate VII to diene VIII.[6] Acetolysis of the C-3 epimer of VII



VII VIII

gave only products of ring contraction. Diene VI had $\lambda_{max}^{ethanol}$ (mμ (ε)) 237 (19,350), 243 (19,600), and an inflection at 252 (12,800 [lit. spectrum for VIII: $\lambda_{max}^{ethanol}$ (mμ (ε)) 236 (19,500), 243 (19,900), and an inflection at 252 (12,800)]. The ir, nmr, and mass spectra of VI were also consonant with the assigned structure.

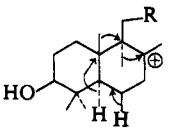
Bicycle III was acetylated, and the side-chain olefinic linkages of the resulting acetate IX were selectively converted to vicinal diols by reaction with 3 equiv of osmium tetroxide in ether–pyridine. Hexol acetate X was converted to aldehyde acetate XI by treatment with sodium periodate in aqueous tetrahydrofuran, and XI was reduced with lithium aluminum hydride to diol XII. Recrystallization of the latter from benzene produced irregular white needles, mp 162–166° (diacetate XIII, mp 74–76°). The mass spectrum of XIII revealed a molecular ion at *m/e* 350 and major fragments at *m/e* 189, 134 (base),



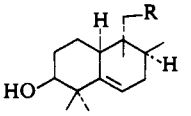
X, R = CH_3CO; R' = $C_{15}H_{31}O_6$
XI, R = CH_3CO; R' = CH_2CHO
XII, R = H; R' = CH_2CH_2OH
XIII, R = CH_3CO; R' = $CH_2CH_2OCOCH_3$

and 119. The prominent *m/e* 134 ion results from retro-Diels–Alder reaction of the cyclohexene ring. The same retro-Diels–Alder fragmentation is characteristic of those di-[7] and triterpene[8] natural products which are structurally analogous to XIII in rings A and B. All four saturated methyl groups were clearly visible in the 100-Mc nmr spectrum of XII (δ 1.10, 1.02, 0.84, 0.79), and the presence of a secondary methyl group (δ 0.79, J = 6.5 Hz) was demonstrated by the double-resonance technique.

Appearance of the unusual structural features of bicycle III (C-3 axial alcohol; the 5,6 double bond; the secondary methyl group) can be nicely interpreted in terms of a series of methyl hydride shifts starting from bicyclic carbonium ion XIV. If the stereochemistry of this carbonium ion conforms to the pattern already established for other terpenoid epoxide cyclizations, and if the methyl hydride shift is stereospecific, then stereochemistry XV for product III follows. There could not be



XIV



XV

isolated from this reaction any nonrearranged bicyclic product, which is the only type secured when terminally functionalized sesquiterpene epoxides (farnesyl acetate, farnesyl ethers, and esters of farnesic acid) are cyclized.

From the foregoing it is evident that yet another major function of squalene oxide cyclase enzymes is prevention of the methyl hydrogen migration phenomenon at the bicyclic level, possibly by enhancing through conformational control, the interaction of nonrearranged carbonium ion (actual or developing) with the neighboring olefinic site, *i.e.*, the biochemically normal process. On the other hand, the rearrangement sequence—superimposed on bi- or higher cyclic systems—must occur during the biosynthesis of various di- and triterpene cases, including rimuene,[7,9] simiarenol,[8] 3β-hydroxyglutinene-(5),[10] alnusenone,[10] and members of the cucurbitacin family.[10]

Acknowledgment. The authors are indebted to the National Science Foundation for grant (GP 1937) support.

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(3) The authors are indebted to Dr. M. Schwartz for the execution and interpretation of this oxidation–reduction sequence.

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