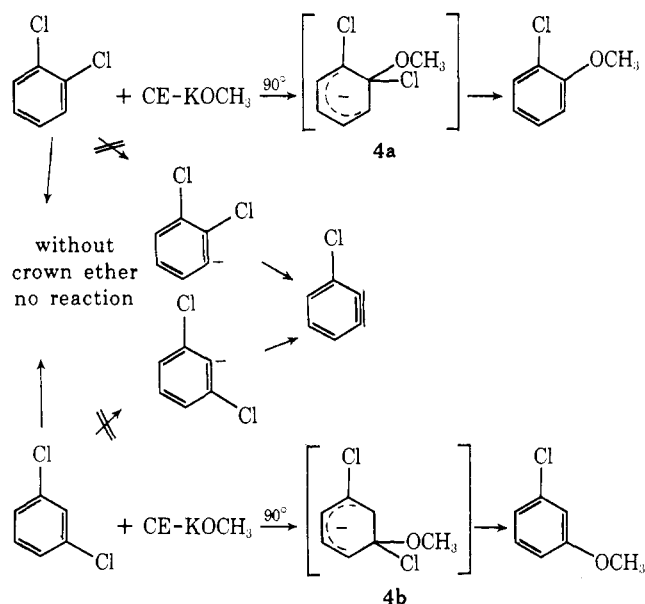


concentration calculated for isomer A-KBr complex and isomer A-KI complex, respectively, are 0.75–0.80 and 0.6–1.0.

Complex 2 can also be used as a base in aprotic solvents. This was demonstrated by reaction of 2 (0.5 *M*) with 2-bromooctane (0.5 *M*) in DMF at 100° for 6 hr. The single 2-octene product was obtained in 75–80% yield, which is nearly quantitative based on bromooctane.<sup>12</sup> Under identical conditions, *n*-Bu<sub>4</sub>Br reacted similarly but slower and thus accounts for a lower yield of 2-octene (60–65%). In refluxing acetone 2 gave a lower yield of 2-octene, and the major product was mesityl oxide from acetone condensation.

We have found a surprising nucleophilic aromatic substitution reaction with the KOH complex 3.<sup>2</sup> It has been determined, however, that only 11% of the anions in toluene solution are actually OH<sup>-</sup>. The predominant anion is OCH<sub>3</sub><sup>-</sup> (89%), which arises from reaction of KOH with CH<sub>3</sub>OH during complex formation.<sup>13,14</sup> This reagent has been used as a strong base in organic solvents and as an anionic polymerization catalyst. Increased chemical reactivity has been reported<sup>2</sup> for the hydroxide ion in the reagent, *e.g.*, in the saponification of hindered esters. We now report enhanced reactivity of the methoxide ion. On heating a 1.0 *M* solution of 3 in *o*-dichlorobenzene at 90° for 16 hr, nucleophilic aromatic substitution occurred and a 40–50% yield of *o*-chloroanisole was obtained as the sole product (Scheme I). No phenols or diphenyl ethers (hydroxide

Scheme I



ion products) or *m*-chloroanisole (benzyne product) were detected. Furthermore, the reaction with *m*-dichlorobenzene gave clean but low conversion to *m*-

(12) Liotta<sup>8</sup> found that the KF-18-crown-6 complex in C<sub>6</sub>H<sub>6</sub> or CH<sub>3</sub>CN exists as a tight ion pair. Consistent with our views on the relative reactivity of ion *vs.* ion pair, the reaction of the KF complex with 2-bromooctane in C<sub>6</sub>H<sub>6</sub> at 90° gave 1- and 2-octene and 2-fluorooctane and was very much slower (*t*<sub>1/2</sub> = 240 hr).

(13) Attempts to prepare a KOH complex without Pedersen's solvent exchange method were unsuccessful. The use of *tert*-butyl alcohol as solvent instead of CH<sub>3</sub>OH during complex formation gave 24% OH<sup>-</sup> in the product due to a reduced equilibrium alkoxide concentration.

(14) Our assay was based on nmr, potentiometric total base titrations (OCH<sub>3</sub><sup>-</sup> + OH<sup>-</sup>), Karl Fischer titrations (OH<sup>-</sup>, H<sub>2</sub>O), and chemical evidence. We thank C. J. Pedersen for preparing a solution of 3 in toluene for our analyses. The titrametric results with this solution were the same as ours.

chloroanisole, perhaps because of reduced stabilization of intermediate 4b relative to 4a. No *o*-chloroanisole was detected, which clearly rules out a benzyne mechanism. Several control reactions were run, and, in the absence of crown ether, no reaction occurred. We have found no previous reference to nucleophilic aromatic substitution reactions of OCH<sub>3</sub><sup>-</sup> with unactivated aromatic halides.

Donnie J. Sam,\* Howard E. Simmons

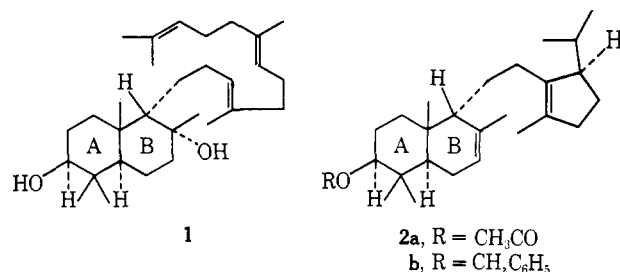
Contribution No. 2113, the Central Research Department  
E. I. du Pont de Nemours and Company  
Wilmington, Delaware 19898

Received December 5, 1973

## Synthesis of Polyenes with Preformed A-B Ring Systems for Cyclization Studies in the Tetracyclic Terpenoid Series

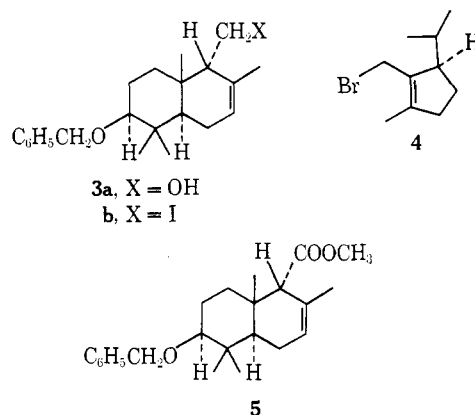
Sir:

As part of a program concerned with the bioorganic chemistry of polycyclic terpenoids, certain polyenes possessing preformed A and B rings came under consideration as potential substrates for enzymic or non-enzymic conversion to tetracyclic systems of the proto-sterol, lanosterol, or other type. Herein we describe stereorational syntheses of polycycles 1 (*dl*) and 2a, sub-



jects of cyclization experiments described in the accompanying communication.

In preparation for a coupling reaction designed to produce system 2, components 3b (*dl*)<sup>1</sup> and 4 (*R*)<sup>2</sup> were



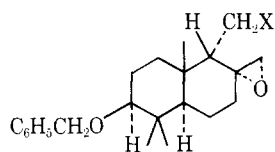
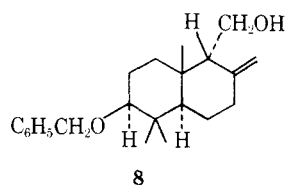
assembled along lines previously followed. Lithium aluminum hydride reduction of the *O*-benzyl *dl*-bicyclic ester 5 produced the expected alcohol 3a, which was

(1) (a) E. E. van Tamelen, M. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966); (b) E. E. van Tamelen and J. P. McCormick, *J. Amer. Chem. Soc.*, **91**, 1847 (1969).

(2) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler-Chauvin, R. J. Anderson, and R. Achini, *J. Amer. Chem. Soc.*, **92**, 7202 (1970).

treated successively with tosyl chloride-pyridine and sodium iodide in acetone to give the tosylate, mp 101–101.5°, and in turn the iodide **3b**, mp 96–97° (51% overall): nmr (CCl<sub>4</sub>)  $\delta$  0.90 (s, 6, -CH<sub>3</sub>), 0.98 (s, 3, -CH<sub>3</sub>), 1.77 (s, 3, C=CCH<sub>3</sub>), 3.13 (d, 2,  $J$  = 4 Hz, -CH<sub>2</sub>I), 4.38 and 4.70 (two d, 2,  $J$  = 12 Hz, ArCH<sub>2</sub>O-), 5.43 (broad m, 1, C=CH), and 7.23 (s, 5, C<sub>6</sub>H<sub>5</sub>). Simultaneous addition of bromide **4** and iodide **3b** (8:1) in ether to a large excess of magnesium in the presence of ethylene dibromide led to a >50% yield of tricyclic benzyl ether **2b** and its A/B antipode (**2Ab**), a mixture separated from other reaction products by preparative tlc (silica gel). After debenzylation (Na-NH<sub>3</sub>) and subsequent acetylation (Ac<sub>2</sub>O-pyridine), the diene acetate mixture was separated by fractional crystallization from MeOH into **2a** and **2Aa** components. The crystalline acetate, mp 108–109°, was 98% pure by vpc;  $M^+$  400; nmr (CDCl<sub>3</sub>)  $\delta$  0.64 (d, 3,  $J$  = 7 Hz, one CH<sub>3</sub> of *i*-Pr), 0.92 (m, 12, CH<sub>3</sub>), 1.66 (m, 6, C=CCH<sub>3</sub>), 2.06 (s, 3, CH<sub>3</sub>-CO<sub>2</sub>-), 2.67 (broad m, 1, C=CCH), 4.50 (broad m, 1, C-3H), and 5.20 (broad m, 1, C=CH). The noncrystalline isomer was purified by preparative tlc (>93% pure):  $M^+$  400; nmr (CDCl<sub>3</sub>)  $\delta$  0.64 (d, 3,  $J$  = 7 Hz, one CH<sub>3</sub> of *i*-Pr), 0.93 (m, 12, -CH<sub>3</sub>), 1.66 (m, 6, C=CCH<sub>3</sub>), 2.06 (s, 3, CH<sub>3</sub>CO<sub>2</sub>-), 2.67 (broad m, 1, C=CCH), 4.50 (broad m, 1, C-3H), 5.20 (broad m, 1, C=CH).<sup>3</sup>

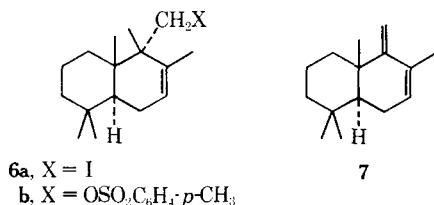
In order to effect the synthesis of diol **1**, modification of the above methodology was called for. On *p*-xylene-sensitized ultraviolet irradiation in *tert*-butyl alcohol-water for 6 hr in a Rayonet reactor,<sup>4</sup> alcohol **3a** was converted to the isomeric homoallylic alcohol **8**,



- 9a**, X = OH  
**b**, X = SO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-*p*-NO<sub>2</sub>  
**c**, X = I  
**d**, X = (CH<sub>2</sub>CH=CCH<sub>3</sub>CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>

which without purification was oxidized in CH<sub>2</sub>Cl<sub>2</sub> with *m*-chloroperbenzoic acid to the noncrystalline  $\alpha$ -epoxide

(3) Despite the presence of allyl-homoallyl halide moieties in intermediates of type **3** and **4**, coupling by other means was not successful. For example, the phosphonium ylide derived from **4** only induced elimination of **6a** or **6b** to diene **7**, which was also produced by the action of tributyl phosphine on **6a**. In similar cases, sulfonium ylide alkylation



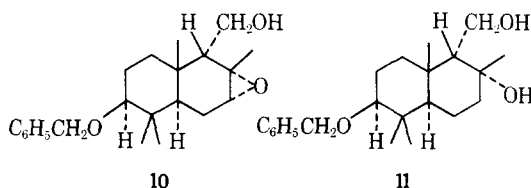
was no more useful. Finally, the Wittig reaction employing aldehyde corresponding to **6a** afforded little of the expected tricyclic triene.

(4) (a) P. J. Kropp and H. J. Krauss, *J. Amer. Chem. Soc.*, **89**, 5199 (1967); (b) J. A. Marshall, *Accounts Chem. Res.*, **2**, 33 (1969).

**9a** (45% overall from **3a**), separated from other oxidation products by basic alumina chromatography: nmr (CCl<sub>4</sub>)  $\delta$  0.83 and 0.99 (2s, 6 H, C-4 CH<sub>3</sub>'s), 1.08 (s, 3 H, C-10 CH<sub>3</sub>), 2.3 (broad s, 1, -OH), 2.57 (AB, 2H,  $J$  = 5 Hz, COCH<sub>2</sub>), 2.90 (dd, 1 H,  $J$  = 3, 10 Hz, C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>OCH<), 3.80 (d, 2H,  $J$  = 6 Hz, -CH<sub>2</sub>OH), 4.50 (AB, 2 H,  $J$  = 11 Hz, ArCH<sub>2</sub>O-), 7.20 (s, 5 H, C<sub>6</sub>H<sub>5</sub>).

Nosylate **9b**, mp 85–86°, on treatment with sodium iodide in acetone for 12 days at room temperature, was transformed to the corresponding iodide **9c**, mp 103–106°, (63%): nmr (CCl<sub>4</sub>)  $\delta$  0.84 and 1.01 (2s, 6 H, C-4 CH<sub>3</sub>'s), 1.10 (s, 3 H, C-10 CH<sub>3</sub>), 2.60 (AB, 2 H,  $J$  = 6 Hz, COCH<sub>2</sub>), 2.92 (dd, 1 H,  $J$  = 4, 10 Hz, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>-OCH<), 3.30 (ABX, 2 H,  $J_{AB}$  = 10 Hz,  $J_{AX}$  = 3 Hz,  $J_{BX}$  = 6 Hz, CH<sub>2</sub>I), 4.50 (AB, 2 H,  $J$  = 11 Hz, ArCH<sub>2</sub>O), 7.20 (s, 5 H, C<sub>6</sub>H<sub>5</sub>). Coupling of the iodide with *trans*-*trans*-farnesyl bromide under the conditions described above for **2** provided, after chromatography on basic alumina, the pure triene epoxide **9d** (20%):  $M^+$  532; nmr (CCl<sub>4</sub>)  $\delta$  0.83 and 1.00 (2s, 6 H, C-4 CH<sub>3</sub>'s), 1.08 (s, 3 H, C-10 CH<sub>3</sub>), 1.59 (s, 9 H, 3C=CCH<sub>3</sub>), 1.66 (s, 3H, C=CCH<sub>3</sub>), 1.98 (broad s, 10 H, 5C=CCH<sub>2</sub>), 2.50 (AB, 2 H,  $J$  = 6 Hz, COCH<sub>2</sub>), 2.87 (dd, 1 H,  $J$  = 3, 10 Hz, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O CH<), 4.9–5.2 (m, 3 H, 3 C=CH), 4.48 (AB, 2 H,  $J$  = 11 Hz, ArCH<sub>2</sub>O), 7.10 (s, 5 H, C<sub>6</sub>H<sub>5</sub>). Reduction with LiAlH<sub>4</sub> gave rise to the expected diol mono-*O*-benzyl ether, which was debenzylated with sodium in liquid ammonia to *dl*-diol **1**, purified by silica gel tlc:  $M^+$  444; nmr (CDCl<sub>3</sub>) 0.76 and 0.98 (2s, 6 H, C-4 CH<sub>3</sub>'s), 1.08 (s, 3 H, C-10 CH<sub>3</sub>), 1.45 (s, 3 H, CH<sub>3</sub>CO), 1.62 (s, 9 H, 3C=CCH<sub>3</sub>), 1.68 (s, 3 H, C=CCH<sub>3</sub>), 2.03 (broad s, 10 H, 5 C=CCH<sub>2</sub>), 3.22 (m, 1 H, HOCH), 5.0–5.25 (m, 3 H, C=CH). LiAlH<sub>4</sub> reduction of **9d** yielded the 8-CH<sub>2</sub>T counterpart of **1**. Attempts to realize a parallel reaction series involving intermediates of the 7,8-oxide types (**10**) were abortive, as were various other coupling variations.

That the epoxide unit in **9a** possesses the  $\alpha$ -configuration is indicated by nmr and chemical comparison with epoxide **10**, obtained by peracid oxidation of **3a**. The



stereochemistry of the epoxide moiety in **10** is revealed by the triplet nature and coupling constant ( $J$  = 2 Hz) of the heterocyclic ring proton, which in the  $\beta$ -series would have been expected to appear as a pair of doublets with  $J$  =  $\sim$ 1–2 and  $\sim$ 7 Hz. Since both **9a** and **10**<sup>5</sup> give rise to the same, single tertiary alcohol **11** on Li-AlH<sub>4</sub> reduction, the stereochemistry of **9a** is established. The configuration at C-8 in diol **1** follows from the foregoing and is corroborated by nmr comparison of **1** with other members of the series. Chemical shift values for substances described herein as well as for other compounds prepared as part of this study reveal that the C-10 methyl is hardly affected by structural variation at C-3 or within the C-9 side chain. On the

(5) This unusual diequatorial opening of a cyclohexene oxide is predated: (a) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1972, p 105; (b) H. H. Appel, C. J. W. Brooks, and K. H. Overton, *J. Chem. Soc.*, 3322 (1959).

other hand, our own and previous data of others<sup>6</sup> reveal that in the presence of a C-8  $\beta$ (axial) substituent the C-10 methyl signal appears at distinctly lower field ( $\Delta = 0.076$ – $0.25$  ppm) than in the presence of the corresponding C-8  $\alpha$ (equatorial) substituent. The identity of the C-10 methyl chemical shifts in **1** and **11** thus indicates like chirality at C-8 in the pair of compounds.

**Acknowledgment.** The authors are grateful to the National Science Foundation (GP 23019) and the National Institutes of Health (GM 10421 and AI05102) for financial assistance. For spectral information, thanks are due Dr. A. Duffield, Dr. L. Durham, and Dr. J. Trudell.

(6) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964.

E. E. van Tamelen,\* A. Grieder, R. G. Lees  
Department of Chemistry, Stanford University  
Stanford, California 94305  
Received December 26, 1973

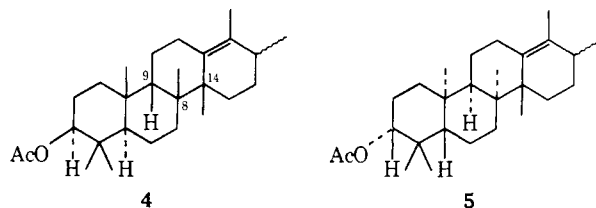
### Cyclization of a Terpenoid Diene with Preformed A–B–D Rings and Its Significance for the Mechanism of Terpenoid Terminal Epoxide Cyclizations

Sir:

In order to illuminate the conformational and mechanistic course of terpenoid terminal epoxide cyclizations, of which enzymic formation of lanosterol is the most notable example, it became of interest to study the further cyclization of tricyclic **1**,<sup>1</sup> which possesses a preformed ring sequence, substitution pattern, and stereochemical arrangement appropriate for conversion *via* tetracycle **2** ( $R = CH_3$ ) to the (pentanor) lanosterol system.<sup>2</sup> Although nonenzymic  $BF_3$  or  $SnCl_4$  catalyzed cyclization of epoxide **3** ( $R = (CH_2)_3CH(CH_3)_2$ ) in  $CH_3NO_2$  generates, presumably through chair-boat-chair folding, 24,25-dihydro- $\Delta^{13(17)}$ -protosterol and 24,25-dihydroparkeol (convertible to 24,25-dihydrolanosterol),<sup>3</sup> laboratory cyclization of **1** or its A–B antipode **1A** under similar conditions provides no detectable amount of cyclopentanohydrophenanthrene-type product. On treatment at room temperature with  $H_2SO_4$ – $CH_3NO_2$ ,  $H_2SO_4$ – $HCO_2H$ , or  $BF_3 \cdot (C_2H_5)_2O$ – $CH_3NO_2$ , the crystalline member of the **1**–**1A** pair generated in up to 75% yield isomer **Y**, mp 141–143.5°; vpc  $R_f = 7.2$  min on 3% OV-17 at 235°; tlc  $R_f = 0.46$  on silica gel; ir ( $CCl_4$ ),  $cm^{-1}$  2950, 2870, 1735, 1465, 1373, 1242, and 1025; nmr ( $CDCl_3$ )  $\delta$  0.90 (m, 9–12,  $CH_3$ ), 0.97 (s, 3,  $CH_3$ ), 1.10 (s, 3,  $CH_3$ ), 1.62 (m, 3–6,  $C=CCH_3$ ), 2.05 (s, 3,  $CH_3CO_2$ ), 2.70 (broad m, 1,  $C=CCH$ ), 4.48 (broad m, 1,  $-OCH$ ); mass spectral (20 eV)  $m/e$  (rel intensity)  $M^+$  400 (3), 149 (100), 136 (45), 121 (8), 107 (4), 93 (2); (70 eV)  $M^+$  400 (3), 189 (2), 161 (1), 149 (100), 136 (34), 121 (18), 107 (11), 93 (9), 81 (6), 69 (6), 43 (11); calcd for  $C_{27}H_{44}O_2$ , 400.3340; found, 400.3352. Ruthenium tetroxide oxidation of **Y**

afforded in high yield a diketone,  $C_{27}H_{44}O_4$ , the nmr and high resolution mass spectra of which revealed, *inter alia*, the presence of one methyl ketone function and the absence of an aldehyde unit; nmr ( $CDCl_3$ )  $\delta$  0.85 (s, 3,  $CH_3$ ), 0.87 (s, 3,  $CH_3$ ), 1.04 (broad, s, 7.5,  $CH_3$ ), 1.10 (s, 4.5,  $CH_3$ ), 2.05 (s, 3,  $CH_3CO_2$ ), 2.13 (s, 3,  $CH_3CO$ ), 4.48 (broad m, 1,  $-OCH$ ); mass spectral (20 eV)  $m/e$  (relative intensity)  $M^+$  432 (<1), 389 (16), 372 (6), 334 (2), 329 (85), 311 (39), 243 (37), 189 (74), 182 (30), 169 (100), 151 (95), 135 (77), 121 (88), 107 (89), 71 (98), 55 (14); high resolution mass spectral (70 eV) 414 (1,  $C_{27}H_{42}O_3$ ), 389 (27,  $C_{25}H_{41}O_3$ ), 372 (8,  $C_{25}H_{40}O_2$ ), 357 (3,  $C_{24}H_{37}O_2$ ), 334 (2,  $C_{21}H_{34}O_3$ ), 329 (92,  $C_{23}H_{37}O$ ), 311 (10,  $C_{23}H_{35}$ ), 189 (35,  $C_{14}H_{21}$ ), 182 (14,  $C_{11}H_{18}O_2$ ), 169 (73,  $C_{10}H_{17}O_2$ ), 71 (52,  $C_4H_7O$ ), 55 (7,  $C_3H_3O$ ), 43 (100,  $C_2H_3O$ ).

Subjection of the noncrystalline **1**–**1A** diastereoisomer to the action of  $BF_3 \cdot (C_2H_5)_2O$ – $CH_3NO_2$  resulted in formation of the closely related isomer **Z**, mp 198–200°. Mass, nmr, and ir spectral studies of **Z** and its  $RuO_4$  oxidation product lead to the conclusion that **Z** is stereoisomeric with **Y**. By reason of detailed analysis of the above and other spectral information, including comparison with mass spectra of  $\Delta^{13(18)}$ -oleanene,<sup>4</sup> isoeuphenyl acetate, and its  $RuO_4$  oxidation product,<sup>5</sup> we propose structures **4**–**5** for cyclization products **Y** and



**Z**, with stereochemical assignments based on the most reasonable conformational course of each cyclization, after which rearrangement (*e.g.*, **6**  $\rightarrow$  **7**  $\rightarrow$  **8**  $\rightarrow$  **4**–**5**) ensues.<sup>6–8</sup>

Quite apart from the nature of products actually formed from **1** and **1A**, nonformation of the protosterol, lanosterol, or parkeol system signifies that tricyclization (*vide supra*) of epoxide **3** does not involve the type of carbonium ion which arises by C-7 portonation of **1** or **1A** and proceeds to **4** or **5**. On the basis of the preferred conformation of starting **1**, this carbonium ion would possess the structure, the stereochemistry, and the initial, most stable conformation portrayed in **9** ( $R$

(4) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 3688 (1963).

(5) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler-Chauvin, R. J. Anderson, and R. S. Achini, *J. Amer. Chem. Soc.*, **92**, 7202 (1970).

(6) Similar acid-promoted ring expansions have been reported: (a) P. de Mayo, "The Higher Terpenoids," Interscience, New York, N. Y., 1959, pp 182–185; (b) M. Uskokovic, M. Gut and R. I. Dorfman, *J. Amer. Chem. Soc.*, **82**, 3668 (1960).

(7) That no epimerization at C-9 occurs during formation of **Y** and **Z** is suggested by the behavior of **1**–**1A** in  $BF_3 \cdot (C_2H_5)_2O$  in  $CHCl_3$ . Under these conditions an equilibrium is established between (*inter alia*) **1** and its 1-isopropyl-3-methylcyclopentene isomer **13** as well as **1A** and the counterpart isomer **13A** (structural assignments based on preservation of nmr signal due to C-7 hydrogen and disappearance of that due to a nonequivalent methyl in the isopropyl side chain of **1**–**1A**), after which cyclization begins. Separate cyclization of isolated **13** or **13A** with  $BF_3 \cdot (C_2H_5)_2O$ – $CH_3NO_2$  gave rise to less than half the yields of **Y** or **Z** secured from **1** or **1A**, thus supporting the belief that **Y** and **Z** are direct products from **1** and **1A**, formed with preservation of AB stereochemistry.

(8) In the 3-desoxy series it was shown that the C-8 tertiary alcohol corresponding to **1**, on treatment with various acids, merely dehydrates to  $\Delta^7$  diene, which then cyclizes to 3-desoxy, **Y**–**Z** counterparts.

(1) E. E. van Tamelen, A. Grieder, and R. G. Lees, *J. Amer. Chem. Soc.*, **96**, 2253 (1974).

(2) "Pentanorlanosterol" is formed by enzymic cyclization of either terminal epoxide **3** ( $R = CH_3$ ) [E. E. van Tamelen and J. H. Freed, *J. Amer. Chem. Soc.*, **92**, 7206 (1970)]; or pentanorsqualene 1,2-oxide [R. J. Anderson, R. P. Hanzlik, K. B. Sharpless, E. E. van Tamelen, and R. B. Clayton, *Chem. Commun.*, 53 (1969)].

(3) E. E. van Tamelen and R. J. Anderson, *J. Amer. Chem. Soc.*, **94**, 8225 (1972).