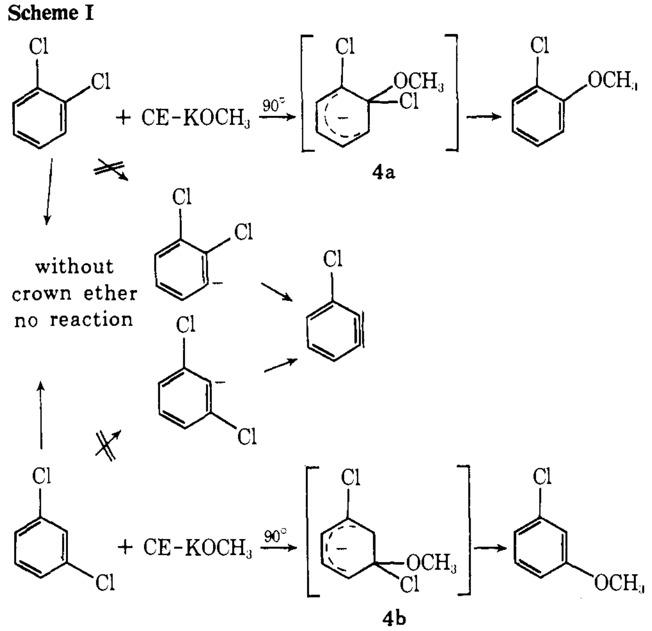
concentration calculated for isomer A–KBr complex and isomer A–KI complex, respectively, are 0.75–0.80 and 0.6–1.0.

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.[12] Under identical conditions, n-Bu_4Br 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**.[2] It has been determined, however, that only 11% of the anions in toluene solution are actually OH^-. The predominant anion is OCH_3^- (89%), which arises from reaction of KOH with CH_3OH during complex formation.[13,14] This reagent has been used as a strong base in organic solvents and as an anionic polymerization catalyst. Increased chemical reactivity has been reported[2] 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*-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_3^- with unactivated aromatic halides.

(12) Liotta[5] found that the KF-18-crown-6 complex in C_6H_6 or CH_3CN 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_6H_6 at 90° gave 1- and 2-octene and 2-fluorooctane and was very much slower ($t_{1/2}$ = 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_3OH during complex formation gave 24% OH^- in the product due to a reduced equilibrium alkoxide concentration.

(14) Our assay was based on nmr, potentiometric total base titrations (OCH_3^- + OH^-), Karl Fischer titrations (OH^-, H_2O), 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.

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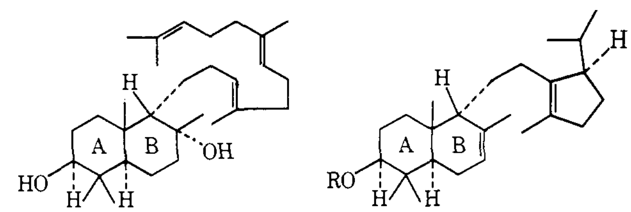
Synthesis of Polyenes with Preformed A–B Ring Systems for Cyclization Studies in the Tetracyclic Terpenoid Series

Sir:

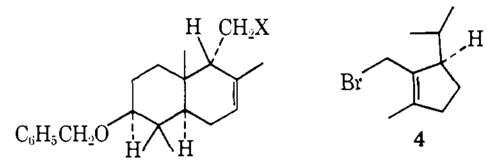
As part of a program concerned with the bioorganic chemistry of polycyclic terpenoids, certain polyenes possessing preformed A and B rings came under consideration as potential substrates for enzymic or nonenzymic conversion to tetracyclic systems of the protosterol, lanosterol, or other type. Herein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



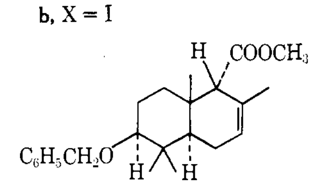
1 **2a**, R = CH_3CO **b**, R = $CH_2C_6H_5$

jects of cyclization experiments described in the accompanying communication.

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



3a, X = OH **b**, X = I **4**



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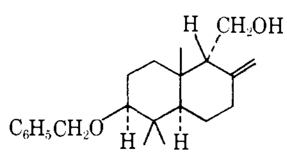
assembled along lines previously followed. Lithium aluminum hydride reduction of the *O*-benzyl *dl*-bicyclic ester **5** produced the expected alcohol **3a**, which was

(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_4) δ 0.90 (s, 6, $-CH_3$), 0.98 (s, 3, $-CH_3$), 1.77 (s, 3, $C{=}CCH_3$), 3.13 (d, 2, J = 4 Hz, $-CH_2I$), 4.38 and 4.70 (two d, 2, J = 12 Hz, $ArCH_2O-$), 5.43 (broad m, 1, $C{=}CH$), and 7.23 (s, 5, C_6H_5). 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 ($Na-NH_3$) and subsequent acetylation (Ac_2O–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 ($CDCl_3$) δ 0.64 (d, 3, J = 7 Hz, one CH_3 of *i*-Pr), 0.92 (m, 12, CH_3), 1.66 (m, 6, $C{=}CCH_3$), 2.06 (s, 3, CH_3CO_2-), 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 ($CDCl_3$) δ 0.64 (d, 3, J = 7 Hz, one CH_3 of *i*-Pr), 0.93 (m, 12, $-CH_3$), 1.66 (m, 6, $C{=}CH_3$), 2.06 (s, 3, CH_3CO_2-), 2.67 (broad m, 1, $C{=}CCH$), 4.50 (broad m, 1, C-3H), 5.20 (broad m, 1, $C{=}CH$).[3]

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,[4] alcohol **3a** was converted to the isomeric homoallylic alcohol **8**,



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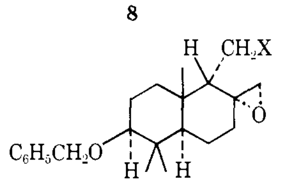
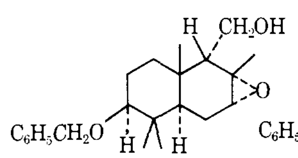


9a, X = OH
b, X = $SO_2C_6H_4$-*p*-NO_2
c, X = I
d, X = $(CH_2CH{=}CCH_3CH_2)_2CH_2CH{=}C(CH_3)_2$

which without purification was oxidized in CH_2Cl_2 with *m*-chloroperbenzoic acid to the noncrystalline α-epoxide **9a** (45% overall from **3a**), separated from other oxidation products by basic alumina chromatography: nmr (CCl_4) δ 0.83 and 0.99 (2s, 6 H, C-4 CH_3's), 1.08 (s, 3 H, C-10 CH_3), 2.3 (broad s, 1, $-OH$), 2.57 (AB, 2H, J = 5 Hz, $COCH_2$), 2.90 (dd, 1 H, J = 3, 10 Hz, $C_6H_5CH_2OCH<$), 3.80 (d, 2H, J = 6 Hz, $-CH_2OH$), 4.50 (AB, 2 H, J = 11 Hz, $ArCH_2O-$), 7.20 (s, 5 H, C_6H_5).

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_4) δ 0.84 and 1.01 (2s, 6 H, C-4 CH_3's), 1.10 (s, 3 H, C-10 CH_3), 2.60 (AB, 2 H, J = 6 Hz, $COCH_2$), 2.92 (dd, 1 H, J = 4, 10 Hz, $C_6H_5CH_2OCH<$), 3.30 (ABX, 2 H, J_{AB} = 10 Hz, J_{AX} = 3 Hz, J_{BX} = 6 Hz, CH_2I), 4.50 (AB, 2 H, J = 11 Hz, $ArCH_2O$), 7.20 (s, 5 H, C_6H_5). 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_4) δ 0.83 and 1.00 (2s, 6 H, C-4 CH_3's), 1.08, (s, 3 H, C-10 CH_3), 1.59 (s, 9 H, $3C{=}CCH_3$), 1.66 (s, 3H, $C{=}CCH_3$), 1.98 (broad s, 10 H, $5C{=}CCH_2$), 2.50 (AB, 2 H, J = 6 Hz, $COCH_2$), 2.87 (dd, 1 H, J = 3, 10 Hz, $C_6H_5CH_2O\,CH<$), 4.9–5.2 (m, 3 H, 3 $C{=}CH$), 4.48 (AB, 2 H, J = 11 Hz, $ArCH_2O$), 7.10 (s, 5 H, C_6H_5). Reduction with $LiAlH_4$ 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 ($CDCl_3$) 0.76 and 0.98 (2s, 6 H, C-4 CH_3's), 1.08 (s, 3 H, C-10 CH_3), 1.45 (s, 3 H, CH_3CO), 1.62 (s, 9 H, $3C{=}CCH_3$), 1.68 (s, 3 H, $C{=}CCH_3$), 2.03 (broad s, 10 H, 5 $C{=}CCH_2$), 3.22 (m, 1 H, $HOCH$), 5.0–5.25 (m, 3 H, $C{=}CH$). $LiAlT_4$ reduction of **9d** yielded the 8-CH_2T 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 α-configuration is indicated by nmr and chemical comparison with epoxide **10**, obtained by peracid oxidation of **3a**. The



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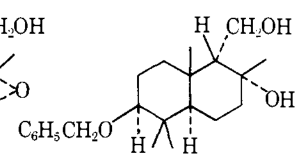

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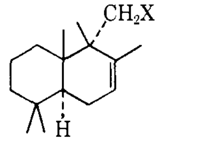
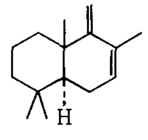
stereochemistry of the epoxide moiety in **10** is revealed by the triplet nature and coupling constant (J = 2 Hz) of the heterocyclic ring proton, which in the β-series would have been expected to appear as a pair of doublets with $J = \sim$1–2 and $\sim$7 Hz. Since both **9a** and **10**[5] give rise to the same, single tertiary alcohol **11** on $LiAlH_4$ 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

(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



6a, X = I
b, X = $OSO_2C_6H_4$-*p*-CH_3



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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).

(5) This unusual diequatorial opening of a cyclohexene oxide is precedented: (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[6] reveal that in the presence of a C-8 β(axial) substituent the C-10 methyl signal appears at distinctly lower field (Δ = 0.076–0.25 ppm) than in the presence of the corresponding C-8 α(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.

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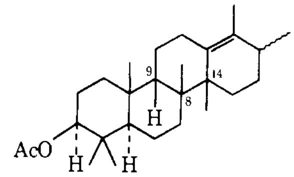
Cyclization of a Terpenoid Diene with Preformed A–B–D Rings and Its Significance for the Mechanism of Terpenoid Terminal Epoxide Cyclizations

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**,[1] 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.[2] 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-dihydo-$\Delta^{13(17)}$-protosterol and 24,-25-dihydroparkeol (convertible to 24,25-dihydrolanosterol),[3] 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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_3-CO–), 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,[4] isoeuphenyl acetate, and its RuO_4 oxidation product,[5] we propose structures **4–5** for cyclization products Y and



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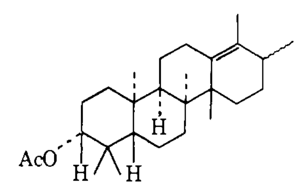

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Z, with stereochemical assignments based on the most reasonable conformational course of each cyclization, after which rearrangement (*e.g.*, 6 → 7 → 8 → 4–5) ensues.[6–8]

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

(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).

(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 dissappearance 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 Δ^7 diene, which then cyclizes to 3-desoxy, Y–Z counterparts.