Direct Sterol Synthesis by the Nonenzymic Cyclization of an Acarbocyclic Monosubstituted Epoxide

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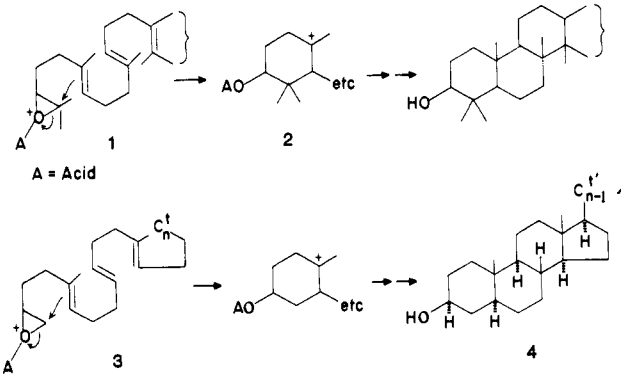
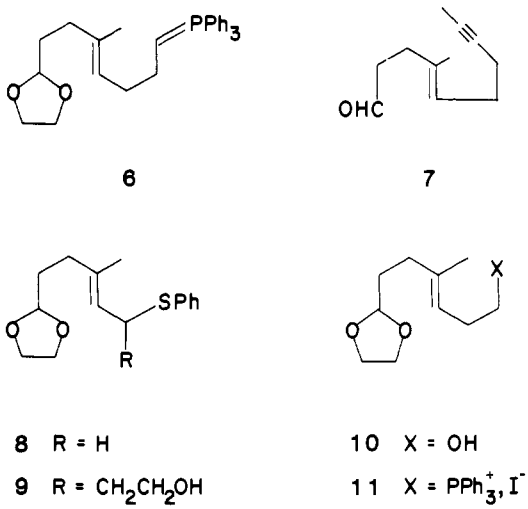
In connection with studies on the bioorganic mechanism of the polycyclization of squalene 1,2-oxide and its analogues (**1**), a high



degree of stereocontrolled neighboring π-bond participation was observed, implying S_N2-type ring opening of the acid-coordinated oxide ring (e.g., **1** → **2**).[1] This behavior suggests that in certain unsaturated epoxide cases, cyclization—even though acid-initiated—could involve "anti-Markovnikov" opening of the oxide unit, with attack of an appropriately sited olefinic bond occurring at the less substituted carbon.[2] Moreover, on this basis a relatively simple acarbocyclic, all-trans polyunsaturated epoxide of structural type **3** (C_n^t = *n*-carbon terminator) would have the potential to generate, directly and in one laboratory operation, the traditional nonaromatic sterol system (**4**). We now report the realization of such a process.[3]

In the construction of the epoxide (**5**) selected for cyclization studies, coupling of two major components, **6** and **7**, was planned



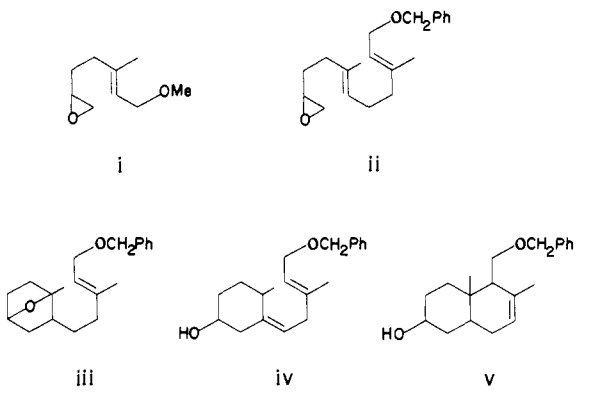
as a key operation. So that the required progenitor of ylide **6** could be obtained, the sulfide **8**[4,6] was converted to its anion (*n*-BuLi, THF, −78 °C), after which reaction with ethylene oxide at 0 °C produced (60%) the alcohol **9**.[7] Reduction with Ca/NH_3(THF, −78 °C) led to (49%) the desulfurized product **10**,[8] successive treatment of which with (a) tosyl chloride (pyridine, 0 °C), (b) NaI (acetone, room temperature), and (c) $(C_6H_5)_3P$ (catalytic amount of EtN(*i*-Pr)$_2$ in C_6H_6, 55 °C in the dark) afforded the phosphonium salt **11**. Schlosser–Wittig coupling of ylide **6** and aldehyde **7**,[9] accomplished by adding C_6H_5Li to **11** in THF/Et_2O at room temperature, then **7** at −78 °C, and finally 1 equiv of C_6H_5Li, yielded (55%) the predominantly all trans polyunsaturated acetal **12** (purified by Florisil hexane/CH_2Cl_2 chromatography).[10] On generation of the parent aldehyde ($HClO_4$, aq THF, room temperature) and its subjection to reaction with $(CH_3)_2S{=}CH_2$[11] (addition of crude aldehyde at −5 °C to reagent prepared by treatment of $Me_3S^+I^-$ with NaH in Me_2SO/THF at −5 °C) the polyunsaturated epoxide **5** was produced in 57% yield.[12]

Cyclization of **5**, symbolized in **13**, is best carried out by

(1) van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 950.

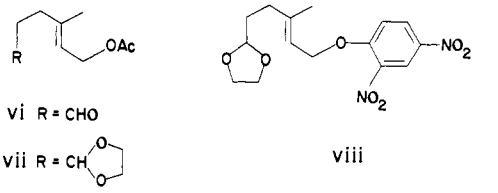
(2) In case **1**, π-bond attack on C-3 ("anti-Markovnikov" opening) presumably is not realizable because attaining essential colinearity of C-3, C-7, and oxygen would require severe bond distortion. See: Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. van Tamelen, E. E.; Pedlar, A. D.; Li, E.; James, D. R. *Ibid.* **1977**, *99*, 6778.

(3) In preliminary work with model compounds, cyclization of epoxides i



and ii (both prepared by means of reactions similar to those employed in the synthesis of oxide **5**) was studied. In the first case, exposure to $SnCl_4$ or $BF_3{\cdot}Et_2O$ under various conditions gave no detectable amounts of cyclization product, a result attributed to the electron-withdrawing character of the methoxyl unit. Accordingly, attention was turned to the higher homologue ii. In this case the NMR spectral character of materials isolated by HPLC after treatment with $SnCl_4$ in CH_2Cl_2 led to the conclusion that bridged oxide iii, cyclohexanol iv, and products of bicyclization v had been formed, with iv predominating. Rather than complete thorough characterization of the aforementioned substances, work on the synthesis and cyclization of oxide **5** was initiated forthwith.

(4) Sulfide **8** may be prepared conveniently by oxidation[5] of geranyl acetate to aldehyde vi; conversion of the latter to acetal vii ($OHCH_2CH_2OH$; *p*-



$CH_3C_6H_4SO_3H$) and thence to DNP ether viii (2,4-$(NO_2)C_6H_3F$; TEA, −80 °C); and finally reaction of vii with thiophenylate ion (C_6H_5SH; NaOH; aq MeOH; reflux). For related work, see: van Tamelen, E. E.; Heyes, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 1252.

(5) van Tamelen, E. E.; Curphey, T. J. *Tetrahedron Lett.* **1962**, 121.

(6) **8**: ^{1}H NMR ($CDCl_3$) δ 1.57 (br s, 3 H, CH_3), 3.53 (d, 2 H, J = 7.6 Hz, SCH_2), 3.88 (m, 4 H, OCH_2CH_2O), 4.80 (tr, 1 H, J = 5 Hz, CH), 5.35 (tr, 1 H, J = 7.6 Hz, vinyl H) 7.1–7.5 (m, 5 H, Ar H).

(7) **9**: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 3.87 (m, 4 H, OCH_2CH_2O), 4.78 (tr, 1 H, J = 5 hz, CH), 5.10 (d, 1 H, J = 10 Hz, vinyl H) 7.15–7.5 (m, 5 H, Ar H); mass spectrum, 308 (M^+), 199, 137, 73.

(8) **10**: ^{1}H NMR ($CDCl_3$) δ 1.63 (d, 3 H, J = 1 Hz, CH_3), 3.62 (tr, 2 H, J = 6.4 Hz, CH_2O), 3.90 (m, 4 Hz, OCH_2CH_2O), 4.84 (tr, 1 H, J = 5 Hz, CH), 5.20 (tr, 1 H, J = 6.7 Hz, vinyl H).

(9) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332. An alternate synthesis developed in this laboratory will be presented elsewhere.

(10) **12**: ^{1}H NMR ($CDCl_3$) δ 1.60 (br s, 6 H, vinyl CH_3), 1.77 (s, 3 H, $\equiv CCH_3$), 3.90 (m, 4 H, OCH_2CH_2O), 4.65 (tr, 1 H, J = 5 Hz, CH), 5.20 (m, 2 H, vinyl H), 5.42 (m, 2 H, vinyl H).

(11) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(12) **5**: ^{1}H NMR ($CDCl_3$) δ 1.60 (br s, 6H, vinyl CH_3), 1.77 (s, 3 H, $\equiv CCH_3$), 5.19 (m, 2 H, vinyl H), 5.42 (m, 2 H, vinyl H).

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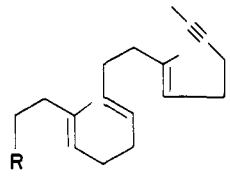
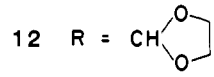
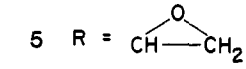
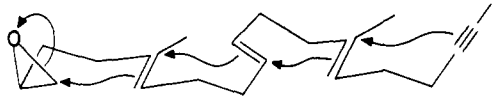


12 R = 

5 R = 



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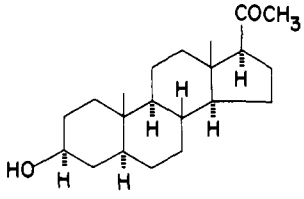

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treatment with $BF_3{\cdot}Et_2O$ and ethylene carbonate in CH_2Cl_2 for 0.33 h at 0 °C.[13] After workup and preliminary chromatography of silica gel, cyclization product was separated and purified by HPLC (monitored by GC). Comparison using the standard criteria, including NMR and mass spectral properties as well as GC retention times, with authentic material indicated the steroidal fraction to be (±)-allopregnanolone (**14**), which assignment was corroborated by radioactivity experiments. The synthetic material was reduced with $NaBT_4$ (MeOH, 0 °C), and the resulting tritium-labeled diol was mixed with authentic, nonradioactive allopregnanediol prepared by $NaBH_4$ reduction under comparable conditions; three recrystallizations from aqueous MeOH sufficed to bring the radioactivity level of the recovered sterol to an immutable value.

Although transformation **13** is of distinct theoretical interest, the yield of (±)-allopregnanolone from oxide **5** so far is modest (~2%). However, in compensation, it should be noted that the cyclization process achieves, in one laboratory operation, generation not only of four new rings but also seven new asymmetric centers—one more than in the biological conversion of squalene oxide to lanosterol—all possessing the proper relative configuration characteristic of normal nonaromatic steroids. Further, in a related polyene cyclization approach that involves use of an epoxide initiator on a preformed A-ring, a yield of naturally occurring nonaromatic steroidal product in excess of 50% has been observed (these studies, which are still in progress, will be described in another publication).[14]

Acknowledgment. We acknowledge financial support from the National Science Foundation (CHE 80-02661).

Registry No. (*u*)-**5**, 81044-08-8; **6**, 81027-73-8; **7**, 41143-17-3; **8**, 81027-74-9; (±)-**9**, 81027-75-0; **10**, 81045-27-4; **11**, 81027-76-1; **12**, 81027-77-2; (±)-**14**, 81076-02-0; vi, 35334-60-2; vii, 35334-61-3; viii, 81027-78-3; geranyl acetate, 105-87-3; 4,12-dimethyl-4,8,12-trien-octadecan-16-ynal, 81027-79-4.

(13) For related examples of ring formation through participation of acetylene bonds in solvolytic processes, see: Peterson, P. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 4521, and also ref 9 herein.

(14) Results obtained by J.-R. Hwu in this laboratory.

Delocalized π Radical Cations of Acetals

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Recent ESR studies have shown that the radical cations of many simple alkanes are σ radicals with extensive spin delocalization through C–C bonds to the axial hydrogens situated in the plane of the extended carbon chain.[1-4] In contrast, we now report cases where positive holes of *saturated* molecules can also be delocalized in π orbitals.

The existence of large angular-dependent β-hydrogen hyperfine couplings associated with oxygen-centered π radicals such as RCH_2O,[5,6] CH_3O,[7] and $(CH_3)_2O^+$[8,9] provides evidence of facile spin-density transfer in these radicals from the oxygen p orbital to the neighboring methylene or methyl group orbital of π symmetry. This observation of efficient hyperconjugation raised the possibility that in a radical cation containing two equivalent oxygen atoms separated by a bridging methylene group, the spin is delocalized in a three-centered [–O–CH_2–O–] π orbital. The examples presented below clearly illustrate this effect and suggest, moreover, that the concept can be extended to include multicentered π orbitals in poly(oxymethylene) systems.

The radical cations were generated in each case by γ irradiation of a solid solution of the parent compound in a Freon matrix, the mechanism occurring by positive charge transfer from the solvent to the solute.[2-4,8-10] As shown in Figure 1, the ESR spectrum of the 1,3-dioxacyclopentane (1,3-dioxolane) radical cation consists of a main triplet with a quintet substructure resulting from hyperfine interaction with two and four equivalent ^1H nuclei, respectively. This pattern is consistent with either a symmetrically delocalized radical cation or a localized species in which the spin is rapidly exchanged between the two oxygen atoms on the ESR timescale. However, an argument based on quantum mechanics (see below) shows unequivocally that the unusually large coupling, $a(2H)$ = 153.0 G, to the hydrogens of the bridging methylene group is characteristic of the symmetrically delocalized radical cation. In fact, a triplet pattern with a hyperfine splitting in the range 135–160 G is a diagnostic feature of the class of radicals described here.

Assuming that each of the two C–H_β bonds in the bridging methylene group of the 1,3-dioxacyclopentane radical cation makes a dihedral angle θ of 30° with the *y* axis of the oxygen p orbitals perpendicular to the O–C–O plane, a coupling of 76 ± 10 G would be expected for the methylene hydrogens from the equation $a_\beta = B_0 + B_2 \cos^2 \theta$, where $B_0 = 0$ and $B_2 = 101 \pm 13$ G,[6] if the unpaired spin population resided on one oxygen atom. On the other hand, if the unpaired electron is distributed between the two oxygen atoms in the 1,3-dioxacyclopentane radical cation such that the coefficients of the oxygen p_y orbitals in the SOMO are equal and have the same sign, the situation governing the admixture of CH_2 group orbitals into the SOMO is closely analogous to that which applies for the cyclohexadienyl radical,[11] and the

(1) (a) Symons, M. C. R.; Smith, I. G. *J. Chem. Res., Synop.* **1979**, 382. (b) Symons, M. C. R. *Chem. Phys. Lett.* **1980**, *69*, 198.
(2) (a) Wang, J. T.; Williams, F. *J. Phys. Chem.* **1980**, *84*, 3156. (b) Wang, J. T.; Williams, F. *Chem. Phys. Lett.* **1981**, *82*, 177.
(3) Shida, T.; Kubodera, H.; Egawa, Y. *Chem. Phys. Lett.* **1981**, *79*, 179.
(4) (a) Iwasaki, M.; Toriyama, K.; Nunome, K. *J. Am. Chem. Soc.* **1981**, *103*, 3591. (b) Toriyama, K.; Nunome, K.; Iwasaki, M. *J. Phys. Chem.* **1981**, *85*, 2149.
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(6) Bernhard, W. A.; Close, D. M.; Hutterman, J.; Zehner, H. *J. Chem. Phys.* **1977**, *67*, 1211.
(7) Iwasaki, M.; Toriyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 1964.
(8) Kubodera, H.; Shida, T.; Shimokoshi, K. *J. Phys. Chem.* **1981**, *85*, 2583.
(9) Wang, J. T.; Williams, F. *J. Am. Chem. Soc.* **1981**, *103*, 6994.
(10) Grimison, A.; Simpson, G. A. *J. Phys. Chem.* **1968**, *72*, 1176 and references therein.
(11) (a) Whiffen, D. H. *Mol. Phys.* **1963**, *6*, 223. (b) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *38*, 773; *39*, 2147.

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