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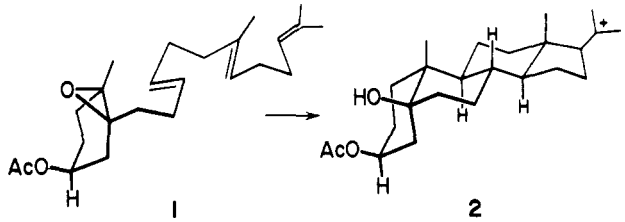
M. Mark Midland,*[16] Deborah C. McDowell
Robert L. Hatch,[17] Alfonso Tramontano
Department of Chemistry, University of California
Riverside, California 92521
Received July 30, 1979

Stereoselective Generation of a Nonaromatic, 3,5-Dioxygenated Steroidal System through Tricyclization of a Polyene Oxide

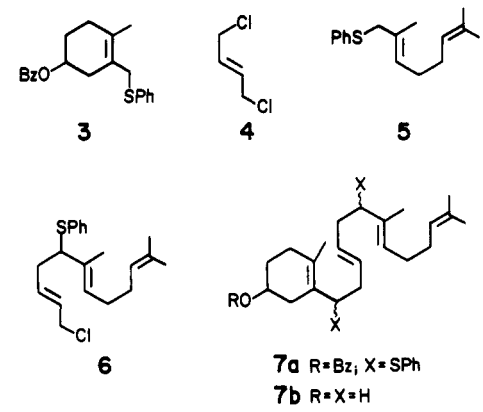
Sir:

Although the biogenetic-type, total synthesis of various naturally occurring polycyclic terpenoids from squalene oxide variants has been achieved,[1] the fabrication of traditional steroids by polycyclization of polyene oxides so far has not been realized.[2] As a preliminary assay, we have now synthesized and studied the behavior of the monocyclic epoxide (±)-**1**,[3] finding that—despite the considerable dissimilarity from squalene oxide and the attendant need to bypass numerous steps parallel to those in the biosynthetic pathway—it undergoes an uncommon tricyclization, giving the A/B cis 3,5-dioxygenated steroidal cation (±)-**2**, the precise result predicted by stereoelectronic theories of epoxide ring opening and polyene cyclization.[4,5]



1 **2**

Epoxide **1** can be readily assembled from building blocks **3**,[6] **4**, and **5**.[7,8] After generation of the anion by treatment of sulfide **5** with BuLi (THF, −78°), alkylation[9] with dichloride **4** (−78 °C room temperature) gave (59%) *trans,trans*-trienyl halide **6**,[10] an oil purified by medium pressure liquid chromatography (MPLC): NMR (100 MHz, $CDCl_3$) δ 1.55 (3 H, br s) and 1.64 (6 H, br s) ($C{=}CCH_3$), 1.87 (4 H, m) and 2.43 (2 H, m) ($C{=}CCH_2$–), 3.60 (1 H, t, J = 8 Hz) (CHS), 4.00

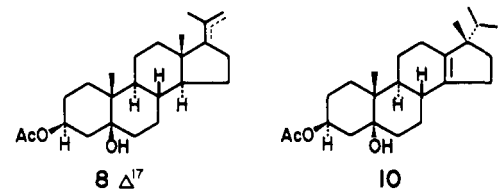


3 **4** **5**

6 **7a** R=Bz; X=SPh
7b R=X=H

(2 H, m) (CH_2Cl), 5.01 (2 H, m) and 5.68 (2 H, m) (C=CH), 7.28 (5 H, m) (C_6H_5–). Trienyl halide **6** was used in turn to alkylate (THF, −78 °C–10°) the BuLi-produced anion of sulfide **3**, thereby generating *trans,trans*-tetraenyl polyether **7a**[10] (59%; 67%, based on consumed **3**): NMR (60 MHz, $CDCl_3$) δ 1.25 (3 H, br s), 1.54 (3 H, br s), and 1.62 (6 H, br s) ($C{=}CCH_3$), 3.51 (2 H, m), 4.16 (1 H, t, J = 8 Hz) (CHS–, CHO–), 4.58 (2 H, s) (CH_2O–), 5.00 (2 H, m) and 5.39 (2 H, m) (C=CH), 6.99–7.51 (15 H, m) (C_6H_5–). Complete benzylic-allylic reduction of **7a** was effected by Li–$EtNH_2$ at −78 °C, thereby providing (76%) tetraenyl alcohol **7b**:[10,11] NMR (60 MHz, $CDCl_3$) δ 1.59 (9 H, br s) and 1.66 (3 H, br s) ($C{=}CCH_3$), 3.87 (1 H, m) (CHO(H)), 4.91–5.53 (4 H, m) (C=CH). Regio- and stereoselective epoxidation of the cyclohexenol moiety in **7b** was achieved through the $Mo(CO)_6$-catalyzed action of t-$C_4H_9O_2H$ (toluene, room temperature),[12] followed by acetylation (Ac_2O–pyridine), giving (67% from **7b**) epoxy acetate **1**:[10,11] NMR (100 MHz, $CDCl_3$) δ 1.29 (3 H, s) ($-OCCH_3$), 1.59 (6 H, br s) and 1.68 (3 H, br s) ($C{=}CCH_3$), 2.01 (3 H, s) ($-OCOCH_3$), 4.62 (1 H, m) (CHOCO–), 5.10 (2 H, m) and 5.39 (2 H, m) (C=CH).

Cyclization of epoxide **1** can be effected, for example, by treatment with 6 equiv of BF_3·Et_2O in CH_2Cl_2 for 2 h at −75 °C, followed by 1 h at −10 to −20 °C. The sole steroidal product (25%) was isolated by preparative TLC ($CH_3CO_2C_2H_5$–C_6H_{14} on silica gel), followed by preparative GC (OV-210 on Chromosorb WAW, 250 °C). Of the three tetracycles which might reasonably derive from cation **2**, viz., **8**–**10**, the **1**-derived substance was identified as (±)-**10** in that



8 Δ^{17}
9 Δ^{20}
10

it was indistinguishable, on the basis of TLC, GC, MS, and IR and NMR spectral comparison, from an authentic sample of **10**, secured by BF_3·Et_2O-induced rearrangement (CH_2Cl_2, −20 to −10 °C) of **8** or **9** from natural sources:[13] NMR (100 MHz, $CDCl_3$) δ 0.74 (3 H, d, J = 7 Hz) and 0.84 (3 H, d, J = 7 Hz) ($CH(CH_3)_2$, 0.94 (3 H, s) and 0.96 (3 H, s) ($-CH_3$), 2.08 (3 H, s) (CH_3CO_2–), 5.23 (1H, m) (CHO–); high resolution MS M^+ ($C_{24}H_{38}O_3$), $M^+ - C_3H_7$, $M^+ - (C_3H_7, H_2O)$, $M^+ - (C_3H_7, H_2O, C_2H_4O_2)$. This structural assignment was corroborated by cocrystallization to a constant radioactivity level per unit mass of a radioactive sample of the Δ^4-3β-ol[14] corresponding to (±)-**10**, admixed with authentic, nonradioactive material, mp 117–119 °C.[15] The constitution of cation **2** follows from the structure and stereochemistry of **10**.

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Application of cyclization mode **1** → **2** involving the use of appropriate terminating groups to selected naturally occurring steroid cases, such as 3β,5β-dihydroxycardenolides as well as 11-oxygenated and Δ^4-3-ketone types, is apparent and planned.

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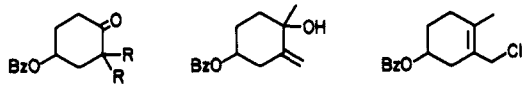
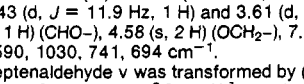
(6) Synthesis: 4-Benzyloxycyclohexanone (i) was transformed into the corresponding α-methylene ketone (ii) by a modification of the method of G.



i R=H *iii* *iv*
ii R,R=CH_2

M. Ksander, J. E. McMurry, and M. Johnson, *J. Org. Chem.*, **42**, 1180 (1977). Treatment with diethyl oxalate and $NaOC_2H_5$ (EtOH, 0 °C to room temp.), gave 63% ethyl-2-oxalyl-4-(phenylmethoxy)cyclohexanone, which without *purification provided ii after successive reactions* (THF, 0 °C) with NaH and gaseous formaldehyde. After conversion (41%) of unisolated ii into tertiary alcohol iii by methyllithium in ether at −78 °C, addition of thionyl chloride to the Li salt of iii (THF, −78 °C) generated allylic halide iv, directly convertible (58% from iii) by lithium thiophenoxide (THF, 0 °C to room temperature) into thioether (±)-**3**: NMR (100 MHz, $CDCl_3$) δ 1.46 (br s, 3 H) ($C{=}CCH_3$), 3.43 (d, J = 11.9 Hz, 1 H) and 3.61 (d, J = 12.3 Hz, 1 H) (CH_2S–), 3.60 (m, 1 H) (CHO–), 4.58 (s, 2 H) (OCH_2–), 7.10–7.49 (m, 10 H) (ArH); IR (neat) 1590, 1030, 741, 694 cm^{-1}.
(7) Synthesis: The heptenaldehyde v was transformed by $(EtO)_2POCH(CH_3)CO_2Et$ [NaH, $(CH_3O)_2(CH_2)_2$, 10–30 °C, 46%] into the trans ester vi, bp 91–95 °C (2 Torr). AlH_3 reduction (Et_2O, −10 to 5 °C, 93%) provided alcohol vii, which, after conversion (*n*-BuLi–*p*-tosyl chloride, THF, 0 °C to



v vi R=CO_2Et
vii R=CH_2OH

room temperature) to unisolated *p*-tosylate and treatment with lithium thiophenoxide (0 °C to room temperature) gave (56%) thioether **5**: NMR (100 MHz, $CDCl_3$) δ 1.57 (s, 3 H), 1.66 (s, 3 H), and 1.73 (d, J = 0.6 Hz, 3 H) ($C{=}CCH_3$), 1.94 (m, 4 H) ($C{=}CCH_2$), 3.49 (s, 2 H) (SCH_2), 5.03 (m, 1 H) and 5.24 (m, 1 H) (C=CH), 7.11–7.44 (m, 5 H) (ArH); IR (neat) 1660, 1580, 736, 688 cm^{-1}.
(8) For an alternative, previous preparation of sulfide **5**, see K. A. Parker and W. S. Johnson, *J. Am. Chem. Soc.*, **96**, 2556 (1974).
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(12) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
(13) The synthesis of sterol derivatives **8** and **9** will be described elsewhere.
(14) Prepared by $NaBT_4$ reduction of the α,β-unsaturated ketone resulting from successive treatment of (±)-**10** with NH_3–methanol, CrO_3–aqueous H_2SO_4–acetone, *p*-TsOH–benzene.
(15) Obtained from the known[16] 20-methylpregna-4,20-dien-3-one by $SnCl_4$-induced ring-D rearrangement followed by $Li(t\text{-}C_4H_9O)_3H$ reduction.
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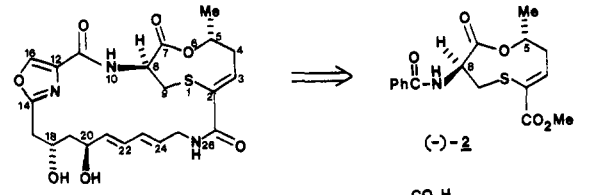
E. E. van Tamelen,* D. G. Loughhead
Department of Chemistry, Stanford University
Stanford, California 94305
Received August, 2, 1979

Studies Directed toward the Total Synthesis of Streptogramin Antibiotics. Enantiospecific Approach to the Nine-Membered Macrocycle of Griseoviridin

Sir:

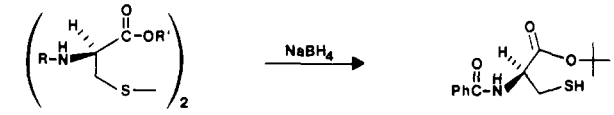
The streptogramin family of antibiotics are broad spectrum acting and are comprised of at least two active compounds, one being mainly peptidic in nature, the other consisting of a 23-membered ring (e.g., griseoviridin, **1**).[1] This class of antibiotics was first discovered in the culture of *Streptomyces graminofaciens*[2] in 1953 and extensive structure elucidation studies have been performed since that time.[3] Recently, the structure of griseoviridin (**1**) was confirmed by X-ray techniques.[4] The most obvious retrosynthetic analysis of **1** requires that it be formed by a convergence scheme comprised of the two fragments, **2** and **3**,[5] and it is the purpose of this report to outline



1 (-)-2 3

our successful stereospecific synthesis of the nine-membered macrocycle **2** in pure enantiomeric form. Inspection of the target antibiotic reveals, in addition to a wide array of functionality, the presence of a rare D-amino acid (C-8) and other chiral centers at C-5, C-18, and C-20. Two of these chiral centers, as well as the lactone and thiovinyl ether linkages, are present in the nine-membered macrocycle **2** which possesses the 5*R*,8*S* configuration.

The stereospecific approach to **2** originates from D-cystine[6] (**4**) which was transformed into the bis *tert*-butyl ester (60% $HClO_4$, *tert*-butyl acetate, 25 °C, 2 days) and treated immediately thereafter with benzoyl chloride in pyridine (0–25 °C, 15 h) to afford the *N*-benzoyl derivative **5** [mp 159–160 °C, $[\alpha]_D$ + 24.4° ($CHCl_3$), 85%].[7] Reduction with sodium borohydride in ethanol gave the (*S*)-cysteine **6** in 82% yield [mp

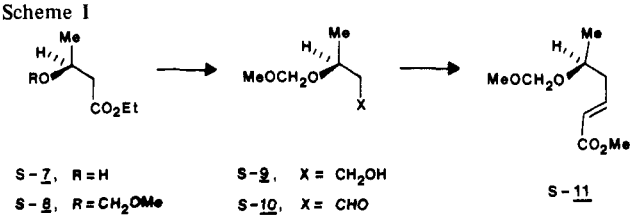


S-(+)-4, R = R' = H
5, R = PhCO, R' = t-Bu

S-(-)-6

95–99 °C, $[\alpha]_D$ −39.6° ($CHCl_3$)].[7] The C-2–C-5 fragment in the nine-membered ring of **2** was stereospecifically constructed as outlined in Scheme I. Ethyl acetoacetate was treated with bakers yeast (28–30 °C, 3 days) to afford the

Scheme I



S-7, R=H S-9, X = CH_2OH S-11
S-8, R=CH_2OMe S-10, X = CHO

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