Synthesis of a Biologically Active Vitamin-D_2 Metabolite

Satish C. Choudhry,* Peter S. Belica, David L. Coffen, Antonino Focella, Hubert Maehr, Percy S. Manchand, Lucia Serico, and Roxana T. Yang

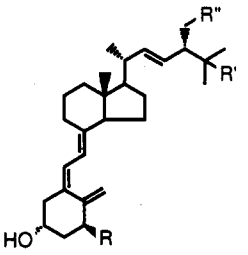
Roche Research Center, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

Received August 18, 1992

The synthesis of 1α,25,28-trihydroxyvitamin-D_2 (1) from vitamin-D_2 is described. Approaches to the upper side-chain synthon via the chiral sulfone **15**, prepared either through the enzymatic resolution of **10** or the opening of the optically pure epoxide **17** with the dianion of methyl phenyl sulfone, are described. A Julia coupling of the sulfone **15** with C-1 hydroxylated aldehyde **7**, obtained from vitamin-D_2, gave the (22*E*)-isomer **24a**, which was deprotected and photoisomerized to give **1**.

Introduction

1α,25,28-Trihydroxyvitamin-D_2 [1,25,28-$(OH)_3$-D_2] **1** has been tentatively identified[1] as an active metabolite of vitamin-D_2. Structure **1** was proven unequivocally by a total synthesis by Batcho[2] in which the two halves of the molecule were prepared in optically pure form and joined at C7–C8 by a Wittig–Horner reaction. This metabolite



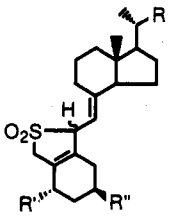
1 R,R',R" = OH 1,25,28 $(OH)_3$ Vitamin-D_2

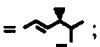
2 R, R', R" = H Vitamin-D_2

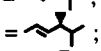
has antiproliferative activity against keratinocytes and sebocytes and has low calcium liability.[3] At 10^{-6} M in vitro, **1** changed the relative number of basal, squamous, and envelope-type keratinocytes[2] from 98:17:15 (control) to 51:26:29. We report herein a novel synthesis of **1** using vitamin-D_2 itself as the starting material. The synthesis (Scheme I) involves three key features: (i) the dissection of the vitamin-D_2 side chain, (ii) C-1 hydroxylation, and (iii) the preparation and introduction of the appropriate upper side chain. The latter was accomplished via a Julia coupling of the aldehyde **7** with the chiral sulfone **15**.

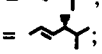
Results and Discussion

Our approach was based on the assumption that aldehyde **7** was readily accessible in large quantities and would be an ideal late-stage intermediate. Aldehyde **7** was prepared from vitamin-D_2 (ergocalciferol, **2**) with some modification of the procedures described by Calverley.[4] Treatment of **2** in CH_2Cl_2 with SO_2 at −10 °C, followed by silylation with *tert*-butyldimethylsilyl chloride, gave **3b** as a free-flowing solid. Cheleotropic extrusion of SO_2 from **3b** followed by hydroxylation at C-1 with selenium dioxide in the presence of 4-methylmorpholine *N*-oxide (NMO), as described by Barton[5] et al., gave a 7:1 ratio of 1α/1β epimeric alcohols, which after filtration to remove polymeric material, was silylated and crystallized to give the (5*E*)-1α-hydroxy derivative, **4c**. Attempts to effect C-1 hydroxylation of the natural (5*Z*) isomer TBDMS (protected **2**) with SeO_2 were unsuccessful. The triene unit in **4c** was again protected with SO_2, and the resulting sulfone was ozonized. Extrusion of SO_2 gave the aldehyde **7**. NMR analysis of crude **7** indicated ca. 10% of the C-20(R) isomer to be present but it could be removed by chromatography.

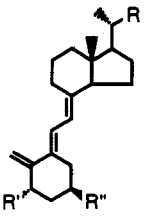


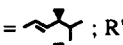
3a R =  ; R' = H; R" = OH

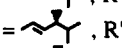
3b R =  ; R' = H; R" = OTBDMS

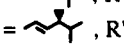
5 R =  ; R', R" = OTBDMS

6 R = CHO; R', R" = OTBDMS



4a R =  ; R' = H, R" = OTBDMS

4b R =  , R' = OH, R" = OTBDMS

4c R =  , R', R" = OTBDMS

7 R = CHO; R', R" = OTBDMS

The first attempt to prepare an optically active C_6 synthon for the side chain was by enzymatic resolution of

(1) (a) Napoli, J. L.; Koszewski, N. J.; Horst, R. L. *Methods in Enzymology*, **1986**, *123*, 127. (b) Koszewski, N. J.; Reinhardt, T. A.; Beitz, D. C.; Napoli, J. L.; Baggiolini, E. G.; Uskokovic, M. R.; Horst, R. L. *Anal. Biochem.* **1987**, *162*, 446.

(2) Batcho, A. D.; Horst, R. L.; Uskokovic, M. R. U.S. Patent, 4,929,609, 1990; *Chem. Abstr.* **1990**, *110*, 95642n.

(3) (a) Holick, M. F.; Uskokovic, M.; Persons, K.; Horst, R.; Baggiolini, E. G.; Truitt, G. A. *Proc. Workshop Vitamin D, 7th (Vitamin D: Mol, Cell. Clin. Endocrinol.)* **1988**, 362. (b) Zhou, J.-Y.; Norman, A. W.; Lubbert, M.; Collins, E. D.; Uskokovic, M. R.; Koeffler, H. P. *Blood* **1989**, *74*, 82. (c) Kistler, A.; Galli, B.; Horst, R.; Truitt, G. A.; Uskokovic, M. R. *Arch. Toxicol.* **1989**, *63*, 394.

(4) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609.

(5) (a) Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819. (b) Andrews, D. R.; Barton, D. H. R.; Cheng, K. P.; Finet, J.-P.; Hesse, R. H.; Johnson, G.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 1637. (c) Hesse, R. H. US 4,772,433, 1988; *Chem. Abstr.* **1988**, *99*, 195277v.

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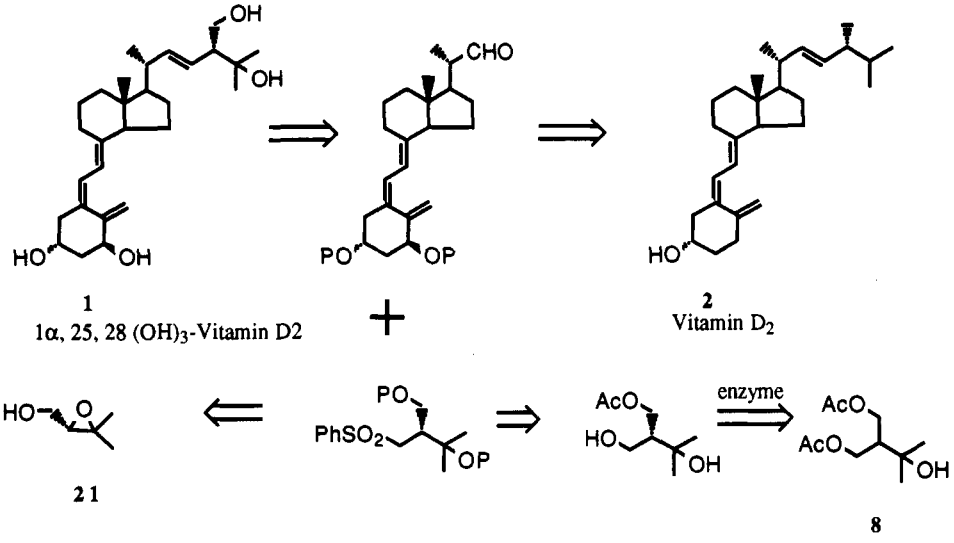
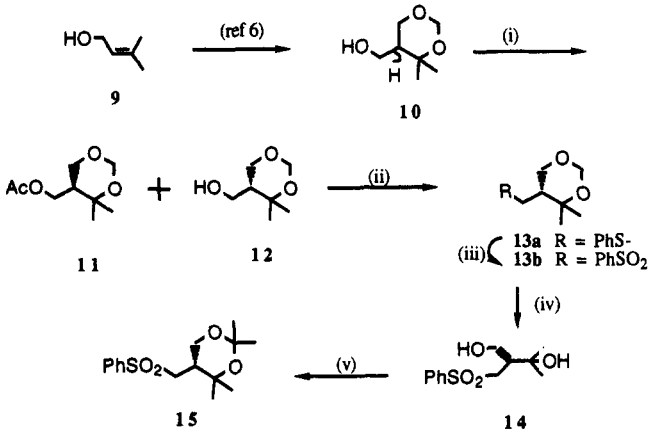
Scheme I

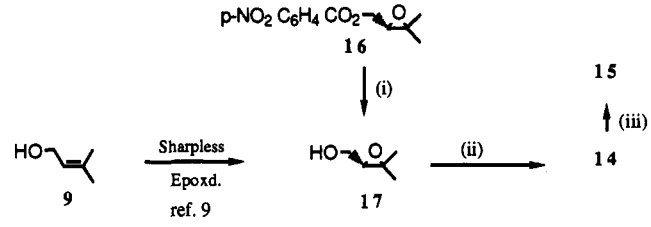


Scheme II[a]



[a] Key: (i) porcine pancratic lipase; (ii) diphenyl disulfide/tri *n*-butylphosphine; (iii) *m*-CPBA/CH_2Cl_2; (iv) boron trichloride/CH_2Cl_2; (v) 2,2-dimethoxypropane/PhH/cat. TsOH.

Scheme III[a]



[a] Key: (i) aqueous NaOH/MeOH; (ii) $CHSO_2Ph^{2-}$ (18)/THF; (iii) 2,2-dimethoxypropane/PhH/cat. TsOH.

a suitable symmetrical compound such as **8** (Scheme I) or its derivative. The preparation of the backbone of **8** is outlined in Scheme II. A Prins reaction between 3-methyl-2-buten-1-ol and formaldehyde provided the known alcohol[6] **10**. Lipase from *P. fluorescenes* showed no selectivity in acetylation toward **10**, but lipase from *Candida cylindracea* and especially porcine pancreatic lipase showed significant selectivity. The L-isomer was acetylated preferentially with concomitant enrichment of the desired *R*-isomer. From 70 g of **10**, we obtained 21 g of unreacted *R*-isomer (**12**) with an enantiomeric purity of better than 95%. The two-step conversion of the hydroxyl group of **12** to the phenylsulfonyl group proceeded uneventfully and provided **13b**. The absolute configuration of **13b** as depicted was established by X-ray crystallographic analysis.

The methylidene acetal in **13b** proved to be extremely acid stable so its use as a protective group slated for eventual removal in the presence of the sensitive triene unit of the vitamin-D system could not be contemplated. Hence, an easily removable protecting group such as disilyl or the acetonide group was sought. Attempts at direct transacetalization of **13b** to **15** with 2,2-dimethoxypropane using a variety of acidic conditions were unsuccessful. However, the methylidene group was easily removed when **13b** was exposed to BCl_3 (1.0 equiv in CH_2Cl_2 at −78 °C) to furnish diol **14** in 30% yield. It appears that Me_2BCl is more promising and gives a better yield (44%) in this conversion. Conversion of the diol to the acetonide worked well using either 2,2-dimethoxypropane or 2-methoxypropene and gave the acetonide sulfone **15** in 70% yield. The reaction using the conventional acetone/copper sulfate method did not occur presumably because of the hindered nature of the diol.

Another approach for the preparation of chiral sulfone **15**, which ultimately proved to be most expeditious, was through the ring opening[7] of epoxide **17** with the dianion of methyl phenyl sulfone,[8] **18** (Scheme III). The known chiral epoxide has been prepared[9] through the Sharpless epoxidation of isoprenyl alcohol **9**. The epoxide is also available commercially as its *p*-nitrobenzoate ester (**16**) which we chose as starting material. Ester **16** was conveniently hydrolyzed by addition of 1 equiv of aqueous sodium hydroxide in methanol. To prevent rearrangement of the epoxy alcohol, the free hydroxyl group was protected as its silyl derivative **19** before being allowed to react with **18**. The reaction, however, was very sluggish and under harsh conditions afforded only the undesired product

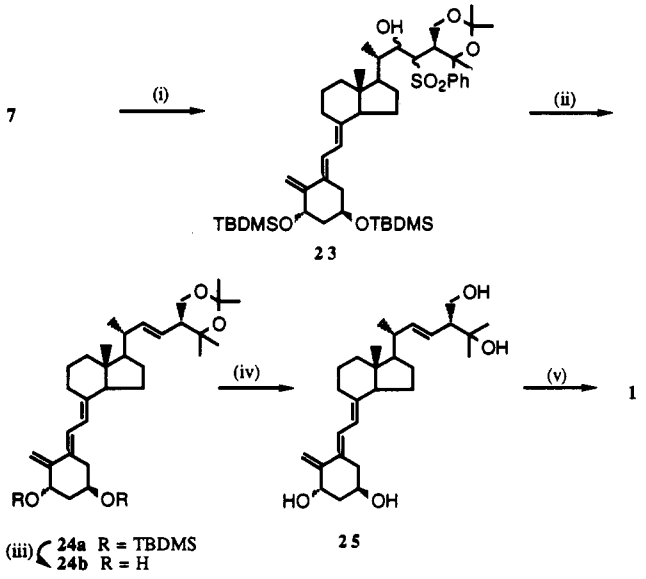
(6) Sagulyants, V. I.; Khaimova, T. G.; Melikyan, V. R.; Pokrovskaya, S. V. *Russ. Chem. Rev.* **1968**, *37*, 17 and references cited therein.

(7) (a) Tachibana, Y.; Yokoyama, S.; Tsuji, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2599. (b) Furst, A.; Labler, L.; Meier, W. *Helv. Chim. Acta* **1982**, *65*, 1499.

(8) (a) White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Kang, M.-c.; Whittle, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6517. (b) Eisch, J. J.; Dua, S. K.; Behrooz, M. *J. Org. Chem.* **1985**, *50*, 3674. (c) Choudhry, S. C.; Serico, L.; Cupano, J. *J. Org. Chem.* **1989**, *54*, 3755.

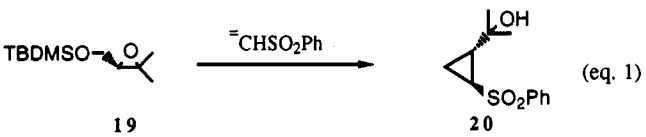
(9) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5766. (b) Suga, T.; Ohta, S.; Ohmoto, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2845.

Scheme IV[a]



[a] Key: (i) 15 + 1 equiv of LDA and then 7; (ii) Na–Hg/MeOH/phosphate buffer; (iii) $(n\text{-Bu})_4N^+F^-$/THF; (iv) Dowex 50W-X4 ion-exchange resin/methanol; (v) 450-W medium-pressure lamp/MeOH.

cyclopropyl derivative **20** as a single isomer which was tentatively assigned the trans configuration as depicted (eq 1). When unprotected **17** was exposed to **18**, the



(eq. 1)

reaction occurred smoothly at room temperature to give the desired sulfone diol **14** with the free hydroxyl group apparently assisting the opening of the epoxide (presumably through lithium coordination[10]). No product resulting from the rearrangement of epoxide **17** prior to its opening was observed.

A Julia coupling[11] of **7** with the anion derived from sulfone **15** (Scheme IV) gave a diastereomeric mixture of hydroxy sulfones **23**, reduction of which with sodium amalgam[12] in the presence of sodium hydrogen phosphate buffer, gave the 22*E* product **24a** in 25% yield. The desilylation of **24a** with tetrabutylammonium fluoride followed by removal of the acetonide group gave **25**, which on photoisomerization gave **1**.

Experimental Section

General Methods. Melting points were determined in capillaries and are uncorrected. Unless otherwise indicated, IR and NMR were determined in $CHCl_3$ and $CDCl_3$, respectively; ^1H NMR spectra were recorded at 200 and/or 400 MHz. Mass spectra (MS) were determined with a direct inlet system with ionization energy of 70 eV; *m/z* values are given with relative intensities in parentheses. TLC plates (silica gel G) were purchased from E. Merck (Darmstadt); spots were visible under short-wavelength UV light and were made visible to the eye by spraying with 10% phosphomolybdic acid in ethanol and heating to 100 °C. Chromatographic purifications were carried out with Fluka silica gel 60 (220–440 mesh unless otherwise stated). All chromatographed products were homogeneous by silica gel TLC.

SO_2-Adduct of 3(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-9,10-secoergosta-5,7(*E*),10(19),22(*E*)-tetraene (3b). A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, Ar inlet, and dry ice condenser was cooled to −25 °C, and SO_2 (130 g) was condensed into it. A solution of 100 g (0.252 mol) of vitamin D_2 (**2**) in CH_2Cl_2 (250 mL) was added. The resulting mixture was stirred at −10 °C for 1.25 h then carefully evaporated at 30 °C. The CH_2Cl_2 was removed at 45 °C using a water aspirator to give a dark brown gel. This was dissolved in CH_2Cl_2 (350 mL) cooled to 5 °C and, with stirring under argon, treated with imidazole (22.5 g, 0.33 mol) and TBDMS chloride (50 g, 0.33 mol). The resulting heterogeneous mixture was stirred at rt overnight and then filtered through Celite. The Celite was washed with CH_2Cl_2 (2 × 250 mL), and the combined washings and filtrate were washed with brine (500 mL), dried ($MgSO_4$), and evaporated to give 140.2 g (97%) of **3b** as a pale yellow solid. Isolation and characterization of the 6*S* and 6*R* isomers have been reported.[4]

TBDMS Ether of 5(*E*)-Vitamin-D_2 (4a). A stirred mixture of **3b** (140.0 g, 0.243 mol) and $NaHCO_3$ (140 g) in 95% EtOH (1.0 L) was boiled under reflux for 1.25 h, and 750 mL of EtOH was removed by distillation (water aspirator). Hexane (1 L) was added and the resulting mixture was stirred at reflux for 15 min, cooled to rt, and filtered. The filter cake was washed with hexane (2 × 200 mL), and the combined filtrate and washings were washed with brine (1.5 L), dried ($MgSO_4$), and evaporated to give 117.2 (94% yield) of **4a** as a pale yellow gum. TLC (25% CH_2Cl_2 in hexane) showed the product at R_f = 0.43. An analytical sample was obtained by flash chromatography over silica gel with 1% EtOAc in hexane as eluent gave **4a** as a gum: $[\alpha]^{25}_D$ +87.7° ($CHCl_3$, *c* = 0.9508); UV (EtOH) λ_{max} 271 (ϵ = 20 600) nm; ^1H NMR δ 0.065 (6 H, s, Me_2Si), 0.57 (3 H, s, CH_3-18), 0.85 (6 H, d, *J* = 7 Hz, CH_3-26 + CH_3-27), 0.89 (9 H, s, *t*-BuSi), 0.91 (3 H, d, *J* = 6 Hz, CH_3-28), 1.02 (3 H, d, *J* = 6 Hz, CH_3-21), 3.84 (1 H, m, CH-3), 4.64 (1 H, s, CH_A-19), 4.93 (CH_B-19), 5.20 (2 H, dd, *J* = 5, 15 Hz, CH-22 + CH-23), 5.90 (1 H, d, *J* = 14 Hz, CH-7), 6.46 (1 H, d, *J* = 14 Hz, CH-6). Anal. Calcd for $C_{34}H_{58}OSi$: C, 79.93; H, 11.44. Found: C, 80.28; H, 12.15.

1(*S*),3(*R*)-Bis(*tert*-butyldimethylsiloxy)-9,10-secoergosta-5(*E*),7(*E*),10(19),22(*E*)-tetraene (4c). A mixture of pulverized SeO_2 (6.296 g, 0.0567 mol) and CH_3OH (600 mL) was boiled under reflux until a solution was obtained (ca. 20 min), and then the solution was cooled to 30 °C and treated with a solution of **4a** (116.0 g, 0.227 mol) followed immediately by NMMO (53.19 g, 0.454 mol). The resulting mixture was stirred at reflux for 5.5 h, cooled to rt, and poured into a mixture of CH_2Cl_2 (1 L) and brine (1.5 L). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (1.5 L). The combined organic extract was washed with 5% $NaHCO_3$ (1.5 L) and 10% brine (2.4 L), dried ($MgSO_4$), and evaporated to give 134 g of a gum. This was chromatographed over 1.5 kg of silica gel with 8.0 L of 2.5% EtOAc in hexane (to remove nonpolar material) followed by 16.0 L of 75% EtOAc in hexane. Evaporation of the appropriate fractions gave 54.9 g of a gum. This was dissolved in CH_2Cl_2 (220 mL), cooled to 10 °C, and treated with imidazole (9.3 g, 0.137 mol) and TBDMSCl (20.6 g, 0.137 mol). The resulting mixture was stirred at rt for 6 h and filtered through Celite, and the filter cake was washed with CH_2Cl_2 (100 mL). The combined filtrate and washings were washed with brine (3 × 100 mL), dried ($MgSO_4$), and evaporated to a semisolid. This was dissolved, with stirring, in ethyl acetate (175 mL), warmed to 70 °C, and diluted with MeOH (220 mL). After being cooled to room temperature, the product (41.56 g) crystallized and was collected by filtration. Recrystallization from EtOAc–MeOH gave 40.42 g (28% overall) of **4c**: mp 115–116 °C (lit.[4] mp 113–114 °C); $[\alpha]^{25}_D$ +62.45 ($CHCl_3$, *c* = 0.9802). The UV, NMR, and MS data agree with those reported.[4]

(6*S*)- and (6*R*)-SO_2 Adducts of 4c (5). A solution of **4c** (50 g) in CH_2Cl_2 (100 mL) was added to SO_2 (100 mL) at −10 °C with stirring. The mixture was stirred for 45 min and evaporated to give 63.8 g of the known[4] sulfone adducts (78:22 mixture of diastereomers) as a foam.

(6*S*)- and (6*R*)-SO_2 Adducts of 1(*S*),3(*R*)-Bis(*tert*-butyldimethylsiloxy)-20(*S*)-formyl-9,10-secopregna-5,7(*E*),10(19)-triene (6). A portion of the above-prepared SO_2 adducts

(10) Marshall, J. A.; Andrews, R. C. *J. Org. Chem.* **1985**, *50*, 1602.
(11) (a) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763. (b) Perlman, K. L.; DeLuca, H. F. *Tetrahedron Lett.* **1992**, 2937. (c) Moriarty, R. M.; Kim, J.; Penmasta, R. *Tetrahedron Lett.* **1992**, 3741.
(12) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(51.1 g, 72.5 mmol) was dissolved in CH_2Cl_2 (380 mL) and MeOH (130 mL). The resulting solution was cooled to −10 °C and, with stirring, treated with O_3 (O_2 pressure = 8 psi) for 40 min, followed by Ar for 10 min. Ph_3P (25 g, 95.4 mmol) was added portionwise at a rate such that the temperature was kept below 0 °C. The mixture was kept at rt for 3 h and then evaporated. The residue was dissolved in ether (150 mL), hexane (150 mL) was added, and the precipitated Ph_3PO was collected by filtration. Evaporation of the filtrate and chromatography of the residue over 480 g of silica gel with an increasing concentration of EtOAc in hexane (1–15%) and collection of the desired fractions gave 33.3 g (78% yield from **5**) of **6** as a colorless solid. The major isomer (6*S*) was obtained as needles: mp 117–118 °C (lit.[4] mp 122–124 °C); $[\alpha]^{25}_D$ +9.21° ($CHCl_3$, c = 1.041). The minor (6*R*, more polar) isomer was obtained as a gum, $[\alpha]^{25}_D$ −18.54° ($CHCl_3$, c = 0.8898).

1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-20(*S*)-formyl-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (7). A solution of **6** (28.85 g, 45.3 mmol) in 95% ethanol (250 mL) was treated with $NaHCO_3$ (28.4 g, 0.34 mol), and the mixture was stirred at reflux for 1.5 h. It was cooled to rt, diluted with EtOAc (100 mL), and filtered through Celite, which was washed with EtOAc. Evaporation of the combined filtrates followed by chromatography of the residue over 258 g of silica gel gave 16.39 g (63%) of **7**: mp 114–116 °C (lit.[4] mp 113–115 °C); $[\alpha]^{25}_D$ +55.20° ($CHCl_3$, c = 1.098). The IR, UV, NMR, and MS data agree with those reported.[4]

(*R*)-4,4-Dimethyl-1,3-dioxane-5-methanol (12). Racemic alcohol **10** (71.25 g, 0.487 mol, 95% pure by GC) was added under Ar to a magnetically stirred suspension of vinyl acetate (850 mL) and lipase (100 g, Sigma Lot 39FO454, type II crude porcine pancreatic lipase) in a 2-L round-bottomed flask. The progress of the transesterification was monitored by GC on a fused-silica capillary column with permethylated β-cyclodextrin as stationary phase (0.32 mm × 25 m) at a temperature gradient of 4 °C/min, 100–200 °C within 50 min, and a H_2 flow rate of 52 cm^3/s. Under these conditions, racemic **10** was resolved with retention times of 34.95 min for desired isomer **11** and 38.33 min for the dextrorotatory enantiomer. After 8.5 h, the reaction was 75% complete and GC showed **12** as a single enantiomer. The separation of **12** from the acetate **11** was achieved by HPLC on a stainless steel column (10 cm × 96 cm) packed with silica gel (40 nm) at a flow rate of 250 mL/min with RI detection and using 1:4 ethyl acetate–hexane followed by 1:1 EtOAc–hexane as eluent. This provided 56.87 g of acetate **11** and 18.58 g (26%) of enantiomerically enriched alcohol **12** as a colorless liquid: $[\alpha]^{25}_D$ −15.95° (c = 1.17%, $CHCl_3$); ^1H NMR δ 1.23, 1.36 (3 H, 3 H, s, s, $(CH_3)_2C$), 1.44 (1 H, br t, OH), 1.95 (1 H, m, CH), 3.52, 3.74 (2 m, 1 H each, CH_2OH), 3.72, 4.09 (2 dd, 1 H each, J_{vic} = 8.9 and 4.3 Hz, J_{gem} = 11.6 Hz, CH_2O), 4.87 (2 H, AB, OCH_2O); MS 145 (<1, M − 1), 131 (4), 101 (5), 81 (3), 71 (17), 69 (11), 59 (100). Anal. Calcd for $C_9H_{16}O_4$: C, 57.51; H, 9.65. Found: C, 57.21; H, 9.96.

4,4-Dimethyl-5-[(phenylthio)methyl]-1,3-dioxane (13a). A mixture of (2.92 g, 20.0 mmol) of **12** (2.92 g, 20.0 mmol) and PhSSPh (5.2 g, 24 mmol) was taken up in dry DMF (20 mL) to which was then added dropwise *n*-Bu3P (4.85 g, 24 mmol). The resulting mixture was stirred at room temperature overnight and then subjected to extractive workup with ether, drying (Na_2SO_4), and evaporation. The crude product was chromatographed on silica gel to give 3.6 g (76% yield) of **13a**, as a thick colorless oil: $[\alpha]^{25}_D$ −85.62° ($CHCl_3$, c = 0.537); ^1H NMR δ 1.25, 1.29 (2 s, 3 H each, $(CH_3)_2C$), 2.00 (1 H, m CH), 2.51, 3.06 (d, d, J_{vic} = 11.4 and 3.1 Hz, J_{gem} = 13.2 Hz, CH_2S), 3.59, 4.19 (2 dd, 1 H each, J_{vic} = 9.9 and 4.3 Hz, J_{gem} = 11.7 Hz, CH_2O), 4.84 (2 H, AB, OCH_2O), 7.21, 7.30, 7.35 (1 H, 2 H, 2 H, C_6H_5). Anal. Calcd for $C_{13}H_{18}SO_2$: C, 65.51; H, 7.61. Found: C, 65.79; H, 7.64.

4,4-Dimethyl-5-[(phenylsulfonyl)methyl]-1,3-dioxane (13b). To a stirred solution of **13a** (27.7 g, 116 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added portionwise a suspension of 85% *m*-CPBA (55 g) in CH_2Cl_2 (600 mL). The mixture was stirred for 0.5 h at 0 °C and then for 24 h at rt, diluted with CH_2Cl_2 (100 mL), and filtered. The filtrate was washed with aqueous 7% NH_3 and then dried (Na_2SO_4), filtered, and evaporated to give 33.04 g of **13b** as a white solid. Chromatography over silica gel column eluting with 3:2:5 EtOAc–CH_2Cl_2–hexane gave 30.55 g (97%) of **13b** as crystalline solid: mp 144–145 °C; $[\alpha]^{25}_D$ −28.30° ($CHCl_3$, c = 0.554); ^1H NMR δ 1.15, 1.16 (2 s, 3 H each, $(CH_3)_2C$), 2.94, 3.02 (2 dd, 1 H each, J_{vic} = 9.8 and 1.8 Hz, J_{gem} = 14.6 Hz, CH_2SO_2), 3.70, 4.20 (2 dd, 1 H each, J_{vic} = 8.9 Hz and 4.2 Hz, J_{gem} 11.9 Hz, CH_2O), 4.83 (2 H, s, OCH_2O), 7.61 (2 H, t, *m*-ArH), 7.70 (1 H, t, *p*-ArH), 7.94 (2 H, d, *o*-ArH). Anal. Calcd for $C_{13}H_{18}SO_4$: C, 57.76; H, 6.71. Found: C, 57.58; H, 6.78.

X-ray Crystallographic Analysis of 13b (with L. J. Todaro and A.-M. Chiu). Crystals of **13b**, $C_{13}H_{18}O_4S$, are orthorhombic, space group $P2_12_12_1$, with a = 7.757 (2) Å, b = 10.734 (5) Å, c = 16.141 (2) Å, Z = 4, d_{calcd} = 1.336 g cm^{-3}, and μ(Cu Kα) = 21.4 cm^{-1}. The structure was solved by a multiple-solution procedure[13] and was refined by full-matrix least-squares methods. By Hamilton's test,[14] the configuration shown corresponds to the absolute configuration.

(*R*)-3-Methyl-2-[(phenylsulfonyl)methyl]-1,3-butanediol (14) from 13b. Bromodimethylborane (2.5 mL, 25.6 mmol) was added dropwise, under Ar, to a solution at −78 °C containing **13b** (3.5 g, 13.0 mmol) and *N,N*-diisopropylethylamine (0.26 mL) in dry CH_2Cl_2 (130 mL). The resulting mixture was stirred for 2.5 h and then transferred via a cannula to a stirred mixture of aqueous saturated $NaHCO_3$ (50 mL) and THF (100 mL). The organic phase was separated, and the aqueous residue was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to furnish a 1:1 mixture of product and starting material. Chromatography of the residue over silica gel and elution with 3:2:5 EtOAc–CH_2Cl_2–hexane gave after concentration of the appropriate fractions 1.48 g (44%) of **14** as a colorless gum: $[\alpha]^{25}_D$ −22.5° ($CHCl_3$, c = 1.042); IR 3625, 3510, 1145 cm^{-1}; UV (EtOH) λ_{max} 216 (ε = 8300) nm; ^1H NMR δ 1.18, 1.28 (2 s, 3 H each, $(CH_3)_2C$), 2.17 (1 H, m, CH), 2.38 (1 H, t, J = 5 Hz, OH), 2.46 (1 H, s, OH), 3.40 (2 H, m, CH_2SO_2), 4.04 (2 H, m, CH_2O), 7.59 (2 H, t, *m*-ArH), 7.68 (1 H, t, *p*-ArH), 7.95 (2 H, d, *o*-ArH); MS m/z 259 (32, M^+ + H). Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.79; H, 7.02. Found: C, 55.46; H, 7.01.

(*S*)-3,3-Dimethyloxiranemethanol (17). A mixture of **16** (5.0 g, 19.9 mmol) and a premixed solution containing MeOH (20 mL) and aqueous 2 N NaOH (20 mL) was stirred at rt for 15 min. Concentration of the mixture gave a slurry which was taken up in CH_2Cl_2 (200 mL), dried ($MgSO_4$), filtered, and evaporated to provide 3.1 g of product as a colorless thick oil. Purification by column chromatography over silica gel with 30%–50% EtOAc–hexane as eluent furnished 1.36 g (40%) of the known epoxide: $[\alpha]^{25}_D$ = −21.8° ($CHCl_3$, c = 1.018) (lit.[9b] $[\alpha]^{25}_D$ = −20.1° ($CHCl_3$, c = 0.42)).

(*S*)-3-Methyl-2-[(phenylsulfonyl)methyl]-1,3-butanediol (14) from 17. To a stirred solution of CH_3SO_2Ph (2.2 g, 14 mmol) and **22** (1.44 g, 14 mmol) in dry THF (80 mL) at 0 °C was added slowly *n*-BuLi (18.5 mL (2.5 N in hexane, 18.5 mmol, 46 mmol) to give a yellow suspension. After the addition was complete, the cold bath was removed and the suspension was allowed to stir at rt overnight to give a pale brown homogeneous solution. The reaction mixture then was quenched with a few drops of H_2O and concentrated. The residue was partitioned between EtOAc and H_2O, dried ($mgSO_4$), filtered, and evaporated. The crude product was chromatographed over silica gel using 20%–30%–50% ethyl acetate–hexane as eluent to give 1.8 g (50% yield) of sulfone diol as a gum $[\alpha]^{25}_D$ −20.96° ($CHCl_3$, c = 0.825). All spectroscopic data were identical to the above sample prepared by the enzymatic method. Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.79; H, 7.02; S, 12.41. Found: C, 55.56; H, 7.14, S, 12.49.

(*S*)-2,2,4,4-Tetramethyl-5-[(phenylsulfonyl)methyl]-1,3-dioxane (15). A solution of **14** (1.8 g, 7.0 mmol) in C_6H_6 (50 mL) was mixed with a 10-fold excess of 2,2-dimethoxypropane (7.3 g). A catalytic amount of *p*-TsOH (20 mg) was added, and the reaction mixture was stirred overnight at rt under Ar. The reaction mixture was taken up in EtOAc (50 mL), washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated. The crude product was chromatographed over silica gel and eluted

(13) (a) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* 1971, *27*, 368. (b) Main, P.; Fiske, S.; Hull, S.; Lssinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. *MULTAN*, 11/82, University of York, England, and University of Louvain, Belgium.

(14) Hamilton, W. C. *Acta Crystallogr.* 1965, *18*, 502.

with 10%–20%–30% EtOAc in hexane to give, after evaporation of appropriate fractions, 1.5 g (72%) of **15** as a crystalline solid: mp 87–89 °C; $[\alpha]^{25}_D$ –31.46 ($CHCl_3$, c = 1.0234); IR ($CHCl_3$) 3625, 3510, 1382, 1372, 1138 cm^{-1}; UV (EtOH) λ_{max} 217 nm (ϵ = 8740); NMR δ 1.15 (3 H, s), 1.18 (3 H, s), 1.38 (6 H, s), 2.17 (1 H, m, –CH(), 3.06 (2 H, m, $-CH_2SO_2$), 3.79 (1 H, dd, J = 8, 12 Hz, $-CH_AO-$), 4.15 (1 H, dd, J = 4.5, 12 Hz, $-CH_BO-$), 7.60 (2 H, t, J = 7.5 Hz, *m*-ArH), 7.69 (1 H, t, J = 7.5 Hz, *p*-ArH), 7.95 (2 H, d, J = 7.5 Hz, *o*-ArH). Anal. Calcd for $C_{15}H_{22}O_4S$: C, 60.38; H, 7.43; S, 10.74. Found: C, 60.20; H, 7.54; S, 10.63.

(1α,3β,5*E*,7*E*)-1,3-Bis[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-25,28-[(1-methylethylidene)bis(oxy)]-23-(phenylsulfonyl)-9,10-secocholesta-5,7,10(19)-trien-22-ol (23). A solution of freshly prepared LDA (from 5.04 mL of a 2.5 M solution of *n*-BuLi in hexane and 1.75 mL of *i*-Pr_2NH in dry THF (20 mL) was added to solution of **15** (2.66 g, 8.91 mmol) in dry THF (20 mL) at –70 °C. The resulting mixture was stirred at –70 °C for 30 min and turned yellow when a solution of **7** (5.94 g, 10.37 mmol) in dry THF (20 mL) was added dropwise. Stirring was continued at –70 °C for an additional 3 h after which 2.0 mL of saturated NH_4Cl solution (20 mL) was added dropwise, and the cooling bath was removed. The mixture was poured into saturated NH_4Cl solution (150 mL) and was extracted with EtOAc (2 × 250 mL). The extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. Chromatography of the residue over 155 g of silica gel packed in hexane and elution with 1% EtOAc in hexane, followed by 10% EtOAc in hexane, gave after concentration of the appropriate fractions 3.10 g (39.9%) of **23** as a gum; IR ($CHCl_3$) 3547, 1145 cm^{-1}; UV (EtOH) λ 210 (ϵ = 21590), 270 (ϵ = 26400) nm: ^1H NMR ($CDCl_3$) δ 0.065 (12 H, s, 2 × Me_2Si), 0.56 (3 H, s, CH_3-18), 0.86 (9 H, s, *t*-BuSi), 0.88 (3 H, s, CH_3), 0.89 (9 H, s, *t*-BuSi), 1.20 (3 H, d, J = 6.5 Hz, CH_3-21), 1.26 (3 H, s, CH_3-26), 1.34 (3 H, s, CH_3-27), 1.39 (3 H, s), 3.29 (1 H, s), 3.43 (1 H, d, J = 9 Hz), 4.05 (1 H, dd, J = 6,13 Hz, CH_A-28), 4.12 (1 H, dd, J = 6,13 Hz, CH_B-28), 4.20 (1 H, br s, CH-3), 4.35 (1 H, br d, J = 7 Hz, CH-23), 4.54 (1 H, br s, CH-1), 4.93 (1 H, s, CH_A-19), 4.99 (1 H, s, CH_B-19), 5.82 (1 H, d, J = 11 Hz, CH-7), 6.45 (1 H, d, J = 11 Hz, CH-6), 7.59 (2 H, t, J = 7 Hz, *m*-ArH), 7.65 (1 H, t, J = 7 Hz, *p*-ArH), 7.96 (2 H, d, J = 7 Hz, *o*-ArH); MS (FAB) 870 (M^+). Anal. Calcd for $C_{49}H_{82}O_7SSi_2$: C, 67.54; H, 9.48; S, 3.68; Si, 6.45. Found: C, 67.54; H, 9.64; S, 3.44; Si, 6.31.

[[(1α,3β,5*E*,7*E*,22*E*)-25,28-[(1-Methylethylidene)bis(oxy)]-9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diyl]bis(oxy)]bis-[(1,1-dimethylethyl)dimethylsilane] (24a). A solution of hydroxysulfone **23** (4.09 g, 4.69 mmol) in MeOH (350 mL) was treated with Na_2HPO_4 (15.43 g) and 5% Na–Hg (13.82 g). The mixture was stirred at room temperature for 6 h and filtered through Celite and the filtrate evaporated. The residue was partitioned between 150 mL of EtOAc (150 mL) and H_2O (75 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated to give 1.92 g of a gum, which was chromatographed over 38 g of silica gel (0–15% EtOAc in hexanes) to give 850 mg after concentration of appropriate fractions (25.4% yield) of **24a**: IR ($CHCl_3$) 1386, 836 cm^{-1}; UV (EtOH) λ_{max} 269 (ϵ = 27 000) nm; ^1H NMR ($CDCl_3$) δ 0.05 (6 H, s, Me_2Si), 0.06 (6 H, s, Me_2Si), 0.58 (3 H, s, CH_3-18), 0.86 (9 H, s, *t*-BuSi), 1.02 (3 H, d, J = 7 Hz, CH_3-21), 1.20 (3 H, s, CH_3-26), 1.23 (3 H, s, CH_3-27), 1.39 (3 H, s), 1.45 (3 H, s), 3.68 (1 H, dd, J = 7, 12 Hz, CH_A-28), 3.80 (1 H, dd, J = 7, 12 Hz, CH_B-28), 4.21 (1 H, s, CH-3), 4.53 (1 H, d, J = 5 Hz, CH-1), 4.94 (1 H, s, CH_A-19), 4.98 (1 H, s, CH_B-19), 5.20 (1 H, dd, J = 6,15 Hz, CH-23), 5.40 (1 H, dd, J = 6,15 Hz, CH-22), 5.81 (1 H, d, J = 12 Hz, CH-7), 6.45 (1 H, d, J = 12 Hz, CH-6); MS (FAB) m/z 712. Anal. Calcd for $C_{43}H_{76}O_4Si_2$: C, 72.41; H, 10.74; Si, 7.88. Found: C, 72.24; H, 10.55; Si, 7.79.

(1a,3b,5*E*,7*E*,22*E*)-25,28-[(1-Methylethylidene)bis(oxy)]-9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diol (24b). A stirred solution of **24a** (830 mg, 1.16 mmol) in THF (30 mL) was treated, under Ar, with 28.0 mL of 1.0 M $Bu_4^+F^-$ in THF (28 mL). The mixture was stirred at rt for 5 h, the solvent was evaporated, and the residue was extracted with EtOAc (100 mL) and brine (50 mL). Extractive workup with EtOAc gave a solid, which was chromatographed (0–50% EtOAc in hexanes) over 30 g of silica gel to give 520 mg (92.2%) of **24b**: mp 127–130 °C; $[\alpha]^{25}_D$ +108.6° (EtOAc, c = 0.638); IR ($CHCl_3$) 3607 cm^{-1}; UV (EtOH) λ_{max} 272 (ϵ = 25 200) nm; ^1H NMR ($CDCl_3$) δ 0.56 (3 H, s, CH_3-18), 1.02 (3 H, d, J = 7 Hz, CH_3-21), 1.20 (3 H, s, CH_3-26), 1.25 (3 H, s, CH_3-27), 1.39 (3 H, s), 1.45 (3 H, s), 3.70 (1 H, dd, J = 6,11, CH_A-28), 3.80 (1 H, dd, CH_B-28), 4.32 (1 H, br s, CH-3), 4.50 (1 H, br s, CH-1), 4.98 (1 H, s, CH_A-19), 5.08 (1 H, s, CH_B-19), 5.13 (1 H, dd, J = 6, 16 Hz, CH-22), 5.40 (1 H, dd, J = 6,16, CH-23), 5.89 (1 H, d, J = 12, CH-7), 6.56 (1 H, d, J = 12 Hz, CH-6); MS m/z 484 (2, M^+). Anal. Calcd for $C_{31}H_{48}O_4$: C, 76.75; H, 10.00. Found: C, 76.47; H, 10.28.

(1a,3b,5*E*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraene-1,3,25,28-tetrol (25). A solution of **24b** (420 mg, 0.866 mmol) in CH_2Cl_2 (28 mL) and MeOH (290 mL) was stirred under Ar with Dowex 50W-X4 ion-exchange resin (11.6 g, H^+ form, prewashed with methanol) for 15 min. Et_3N (2.0 mL) was added, and the mixture was filtered. Evaporation of the filtrate and chromatography of the residue over silica gel (0–100% EtOAc in hexanes) gave 240 mg (62.3%) of **25** as an amorphous solid: $[\alpha]^{25}_D$ +175.9° (CH_3OH, c = 0.1137); IR ($CHCl_3$) 3606 cm^{-1}; UV (EtOH) λ_{max} 272 (ϵ = 14 140) nm; ^1H NMR ($CDCl_3$) δ 0.58 (3 H, s, CH_3-18), 1.04 (3 H, d, J = 6 Hz, CH_3-21), 1.25 (6 H, s, CH_3-25 + CH_3-26), 2.85 (1 H, s, OH), 2.90 (1 H, s, OH), 3.65 (1 H, dd, J = 4,11 Hz, CH_A-28), 3.85 (1 H, dd, J = 4, 11 Hz, CH_B-28), 4.25 (1 H, s, CH-3), 4.50 (1 H, s, CH-1), 4.98 (1 H, s, CH_A-19), 5.13 (1 H, s, CH_B-19), 5.25 (1 H, dd, J = 7, 14 Hz, CH-22), 5.44 (1 H, dd, J = 7, 14 Hz, CH-22), 5.85 (1 H, d, J = 12 Hz, CH-7), 6.60 (1 H, d, J = CH-6);

(1α,3β,5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraene-1,3,25,28-tetrol or 1α,25,28-$(OH)_3$ Vitamin-D_2 (1). A mixture of **25** (33 mg, 0.074 mmol) and 9-acetylanthracene (1.5 mg) in methanol (1 L) was cooled to 0 °C. Ar was passed through the solution, and irradiation was carried out with a 450-W medium-pressure lamp through a uranium filter for 15 min. Evaporation and chromatography of the residue over silica gel gave 28 mg (85%) of **1** as an amorphous solid: $[\alpha]^{25}_D$ +58.9° (CH_3OH, c = 0.537) (lit.[2] $[\alpha]^{25}_D$ +53.5 (EtOH, c = 0.5)); IR ($CHCl_3$) 3608 cm^{-1}; UV (EtOH) λ_{max} 263 (ϵ = 13 540) nm; ^1H NMR ($CDCl_3$) δ 0.56 (3 H, s, CH_3-18), 1.04 (3 H, d, J = 6 Hz, CH_3-21), 1.25 (6 H, s, CH_3-26 + CH_3-27), 2.55 (1 H, t, OH), 3.65 (1 H, dd, J = 6,13 Hz, CH_A-28), 3.74 (1 H, s, OH), 3.83 (1 H, dd, J = 6, 13 Hz, CH_B-28), 4.22 (1 H, br s, CH-3), 4.45 (1 H, br s, CH-1), 4.99 (1 H, s, CH_A-19), 5.20 (1 H, dd, J = 6, 14 Hz, CH-23), 5.32 (1 H, s, CH_B-19), 5.45 (1 H, dd, J = 6,14 Hz, CH-22), 6.02 (1 H, d, J = 12 Hz, CH-7), 6.36 (1 H, d, J = 12 Hz, CH-6); MS m/z 445 (M^+ + H). An analytical sample was prepared by recrystallization from MeOCHO to give a white solid: mp 171–173 °C (lit.[2] mp 173–174 °C). Anal. Calcd for $C_{28}H_{44}O_4$: C, 75.63; H, 9.97. Found: C, 75.46; H, 9.70.

Acknowledgment. The guidance and encouragement of Dr. Milan Uskokovic is greatly appreciated. We are also grateful to L. J. Todaro and A.-M. Chiu for the X-ray crystallographic analysis and other personnel of our Physical Chemistry Department for providing some of the spectroscopic and microanalytical data.

Supplementary Material Available: The details of crystallography, X-ray analysis, and tables of crystallographic data for **13b** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.