heated at reflux for 1 h, cooled, and poured into 40 mL of 10% ammonium chloride saturated with sodium chloride. Extraction with 3 × 20 mL of dichloromethane and concentration of the dried ($MgSO_4$) extracts under vacuum at 42 °C gave a crude product which was subjected to centrifugal chromatography on a 1-mm alumina plate. Elution with dichloromethane–methanol (99:1) at 0.6 mL/min and concentration of fractions 6–23 gave 0.050 mg (88% yield) of (±)-cephalotaxine, mp 122–124 °C (lit.[19,20] mp 115–117, 116–118 °C), which gave IR, NMR and mass spectra that matched those of a sample of natural cephalotaxine.

Acknowledgment. We thank Professor Jon Bordner for an X-ray crystallographic structure of the (2,4-dinitrophenyl)hydrazone of the keto lactam **20**. Dr. Percy Manchand kindly hydrogenated our 3,4-(methylenedioxy)nitrostyrene under high dilution at Hoffmann La-Roche. We are indebted to Dr. Richard Powell, U.S. Department of Agriculture, Northern Regional Research Center, for comparison samples of natural cephalotaxine and cephalotaxinone. Some of the mass spectra were provided by Patricia Matson, Bruce Pitner, Karen LeBoulluec, and Deborah Frasier of our group. The work was supported by Grant R01 12010 from the National Cancer Institute.

Registry No. (±)-**1**, 38848-21-4; **5**, 13838-23-8; (±)-**6**, 58712-01-9; (±)-**6** (acid), 114942-61-9; **7**, 1484-85-1; (±)-**8**, 114942-62-0; (±)-**9**, 114942-63-1; **10**, 6612-99-3; **11**, 10333-13-8; (±)-**11a**, 114942-67-5; (±)-**12**, 114942-64-2; **13**, 114942-65-3; (±)-**14**, 114942-66-4; (±)-**19**, 114942-68-6; (±)-**20**, 114942-69-7; **21**, 114942-70-0; **22**, 114942-71-1; (±)-**22** (4a D-isomer), 114942-72-2; (±)-**24**, 114942-73-3; (±)-**25**, 114942-74-4; (±)-**26**, 114942-75-5; **27**, 114942-76-6; (±)-**30**, 114942-77-7; (±)-**31**, 114942-78-8; (±)-**32**, 114942-79-9; (±)-**33**, 114942-80-2; (±)-**35**, 114942-81-3; (±)-**36**, 114942-82-4; (±)-**37**, 114978-16-4; (±)-**37** (diacetate), 114978-17-5; (±)-**38**, 114956-74-0; (±)-**39**, 114942-83-5; (±)-**40**, 114942-84-6; 2-[(*p*-tolylsulfonyl)oxy]-1-[3,4-(methylenedioxy)phenyl]ethane, 57587-09-4; 4,5,6,7-tetrahydrocyclopenta[*b*]pyran-2(3*H*)-one, 5587-71-3; (±)-2-(2-cyanoethyl)cyclopentanone, 58734-78-4; 2-[3,4-(methylenedioxy)phenyl]ethanol, 6006-82-2.

Supplementary Material Available: X-ray crystallographic data for compounds **13** and **33** (17 pages). Ordering information is given on any current masthead page.

Novel Convergent Synthesis of Side-Chain-Modified Analogues of 1α,25-Dihydroxycholecalciferol and 1α,25-Dihydroxyergocalciferol[1]

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A novel synthetic strategy for the preparation of side-chain-modified analogues of 1α,25-dihydroxycholecalciferol and 1α,25-dihydroxyergocalciferol was developed as a part of the extensive synthetic search for vitamin D analogues of potential anticancer activity. In the methodology developed, the preparation of both series of analogues proceeds conveniently through the partially protected 1α-hydroxyvitamin D C-22 alcohol **5** as the common key intermediate. The 24-dihomo and 25-cyclopentane analogues **1** and **2** of 1α,25-dihydroxycholecalciferol were obtained by alkylation of sulfones **22** and **31**, respectively, with tosylate **6**. Swern oxidation of alcohol **5** afforded 1α-hydroxyvitamin D C-22 aldehyde **7** as a novel useful precursor for side-chain-modified analogues of 1α,25-dihydroxyergocalciferol. As a representative example of this series, the 24*R* analogue **3** was obtained by the condensation of aldehyde **7** with the chiral sulfone **39**. Preliminary studies from this laboratory on human leukemia HL-60 cells reveal **1** as the most active vitamin D analogue to induce the differentiation of human leukemia HL-60 cells with markedly diminished calcemic activity.

Recent discoveries from this[3] and other laboratories[4] of valuable biological activity of 1α-hydroxy analogues of vitamin D modified in the aliphatic side chain have further stimulated our interest in this area. Our extensive studies[5] on the effect of various analogues of 1α,25-dihydroxyvitamin D on differentiation of human leukemia HL-60 cells led us to the conclusion that the elongation of the side chain of (5*Z*,7*E*)-1α-hydroxyvitamin D improves significantly its activity. To further investigate this effect we designed two C-29 homologues with two additional carbon atoms added to the side chain in both aliphatic and alicyclic manner. The novel synthetic strategy developed for the preparation of 24-dihomo analogue **1** (Chart I) and 25-cyclopentane analogue **2** allows also for the more efficient preparation of analogue **3**[6] as well as for further variations of the side chain part of the vitamin D molecule. In our strategy the key vitamin D synthons for the preparation of all side-chain analogues are C-22 vitamin D like compounds **4**–**7**. These, in turn, can be obtained from commercially available steroid **8** by the classical approach.

(1) For a preliminary account of this work, see: Kutner, A.; Perlman, K. L.; Sicinski, R. R.; Phelps, M. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1987**, *28*, 6129.

(2) Present address of: (a) A.K., Institute of pharmaceutical Industry, Rydygiera 8, 01-793 Warszawa, Poland. (b) A.L., Stanford University, Department of Chemistry, Stanford, CA 94305.

(3) (a) Sicinski, R. R.; DeLuca, H. F.; Schnoes, H. K.; Tanaka, Y.; Smith, C. M. *Bioorg. Chem.* **1987**, *15*, 152. (b) Ostrem, V.; Tanaka, Y.; Prahl, J.; DeLuca, H. F.; Ikekawa, N. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2610. (c) Sai, H.; Takatsuto, S.; Ikekawa, N.; Tanaka, Y.; DeLuca, H. F. *Chem. Pharm. Bull.* **1986**, *34*, 4508.

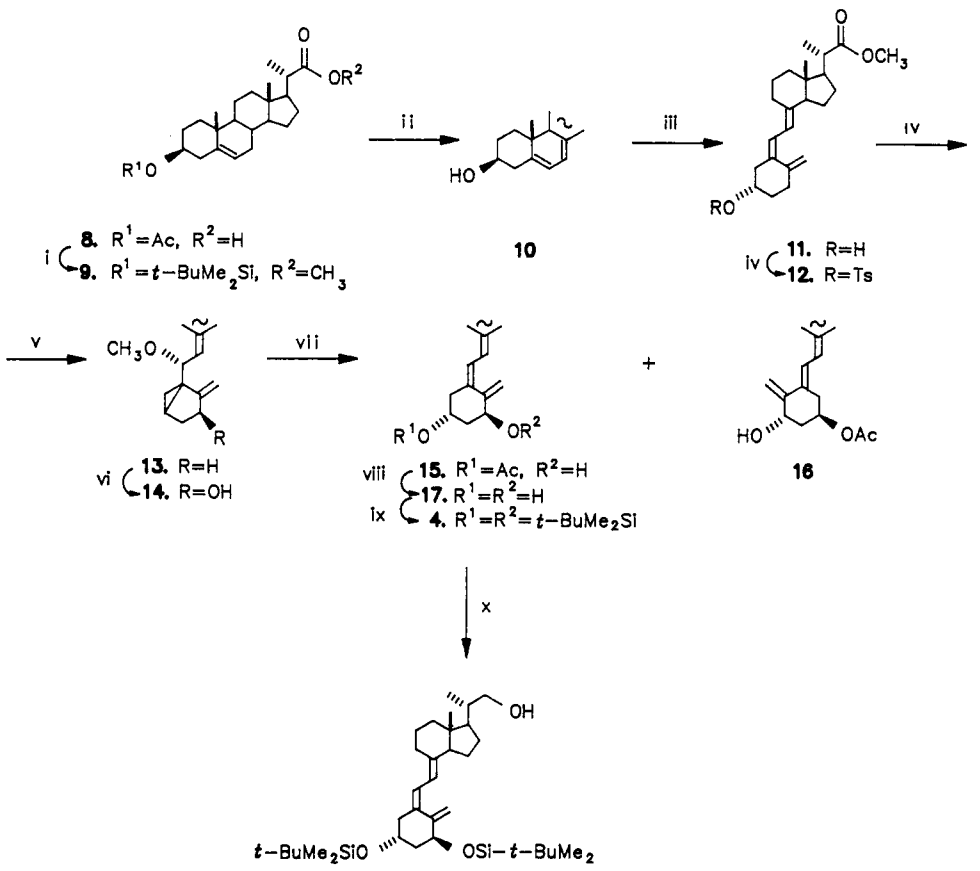
(4) Sai, H.; Takatsuto, S.; Hara, N.; Ikekawa, N. *Chem. Pharm. Bull.* **1985**, *33*, 878.

(5) Ostrem, V. K.; Lau, W. F.; Lee, S. H.; Perlman, K.; Prahl, J.; Schnoes, H. K.; DeLuca, H. F. *J. Biol. Chem.* **1987**, *262*, 14164.

(6) Sicinski, R. R.; Tanaka, Y.; Schnoes, H. K.; DeLuca, H. F. *Bioorg. Chem.* **1985**, *13*, 158.

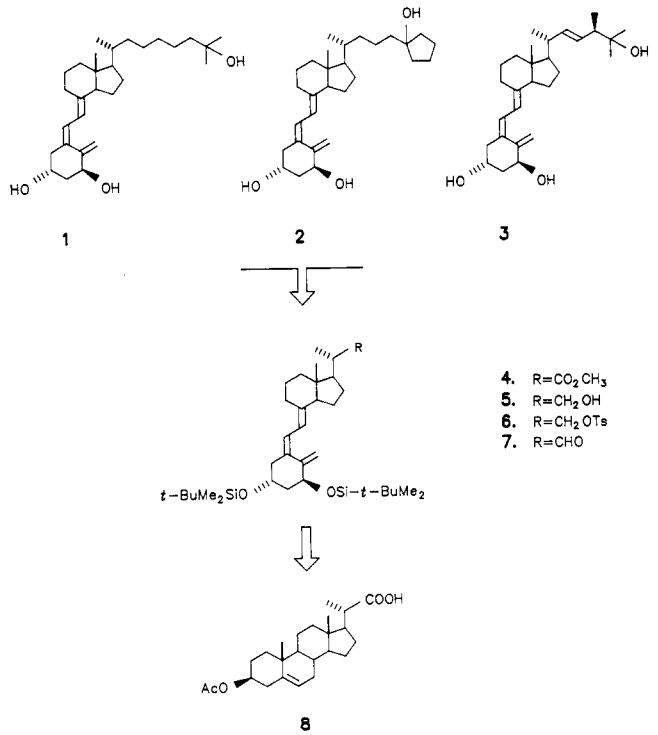
0022-3263/88/1953-3450$01.50/0

Scheme I. Preparation of Diprotected Triol 5[a]



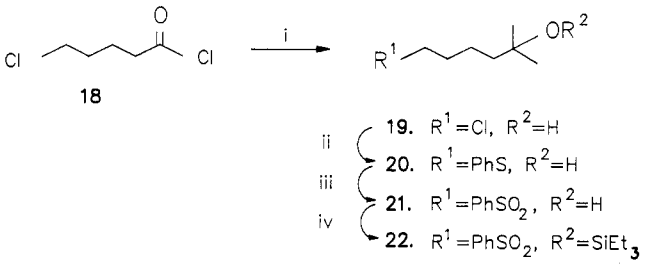
[a] Reagents and conditions: (i) KOH, MeOH; H_2SO_4, MeOH; *t*-$BuMe_2SiCl$, imidazole, DMF; (ii) dibromantin, $KHCO_3$, hexane, Δ; *n*-Bu_4NBr, THF; *n*-Bu_4NF, *s*-collidine; (iii) *hν*, C_6H_6–Et_2O; EtOH, Δ; (iv) *p*-TsCl, py, 4 °C; (v) $KHCO_3$, MeOH, CH_2Cl_2, 55 °C; (vi) *t*-BuOOH, SeO_2, CH_2Cl_2, py; (vii) AcOH, 55 °C; (viii) KOH, MeOH–Et_2O; (ix) *t*-$BuMe_2SiCl$, imidazole, DMF, 55 °C; (x) $LiAlH_4$, THF, 0 °C.

Chart I. Synthetic Strategy



Thus, the 3β-acetoxy-22,23-dinor-5-cholen-24-oic acid (**8**) was converted to the silyl ester **9** (Scheme I). Allylic bromination of **9** and dehydrobromination catalyzed by fluoride ion[7] afforded 5,7-diene **10** in 48% overall yield from **8**. Irradiation of diene **10** and thermolytic [5,7]-sigmatropic hydrogen shift of the resulting previtamin (not shown) provided vitamin D ester **11** in 36% yield.[8] Stereoselective 1α-hydroxylation was accomplished by allylic oxidation of the 3,5-cyclovitamin **13** (obtained by buffered solvolysis of tosylate **12**) with a selenium dioxide and *tert*-butyl hydroperoxide system.[9] Cycloreversion of 1α-

Scheme II. Preparation of Side-Chain Fragment 22[a]



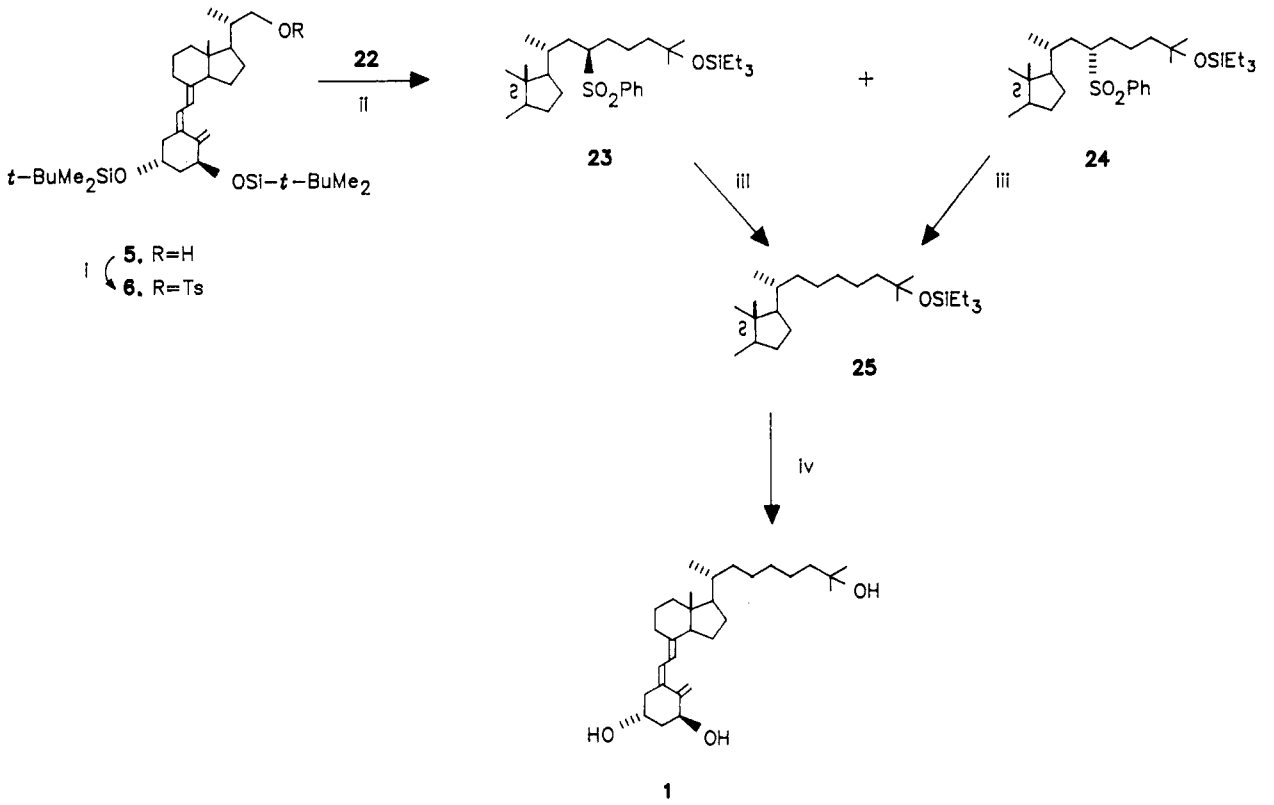
[a] Reagents and conditions: (i) MeMgBr, THF; (ii) PhSH, *t*-BuOK, DMF; (iii) MCPBA, CH_2Cl_2; (iv) Et_3SiCl, imidazole, DMF.

(7) Rappapold, M. P.; Hoogendorf, J.; Pauli, L. F. In *Vitamin D. Chemical Biological and Clinical Endocrinology of Calcium Metabolism*; Walter de Gruyter and Co.: Berlin, 1982; p 1133.

(8) DeLuca, H. F.; Schnoes, H. K.; Lee, S.-H. U.S. Pat. 4512925, 1985; *Chem. Abstr.* **1985**, *103*, 105227c.

(9) (a) Paaren, H.; DeLuca, H. F.; Schnoes, H. K. *J. Org. Chem.* **1980**, *45*, 3253. (b) Esvelt, R. P.; Paaren, H. E.; DeLuca, H. F. *J. Org. Chem.* **1981**, *46*, 456.

Scheme III. Preparation of Vitamin D_3 Analogue 1[a]



[a] Reagents and conditions: (i) *p*-TsCl, py, 5 °C; (ii) LDA, THF, −20 °C; (iii) 5% Na/Hg, Na_2HPO_4, MeOH: (iv) *n*-Bu_4NF, THF, 50 °C.

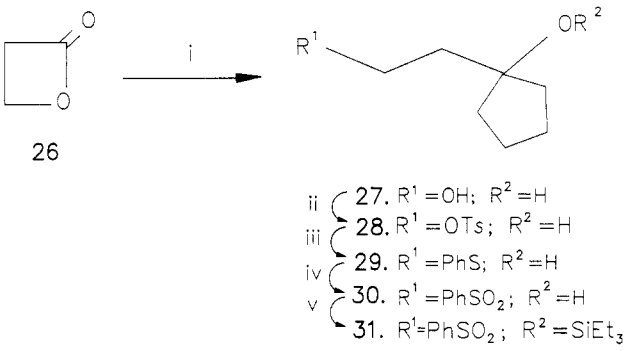
hydroxyvitamin **14** in glacial acetic acid as a proton source and nucleophile gave predominantly acetoxy alcohol **15** (in 19% yield from **11**) with the desired 5*Z*,7*E* geometry of the triene system and 5*E*,7*Z* minor isomer **16** in the ratio of 2.5:1. To improve the overall yield of the hydroxylation sequence (**11**–**15**) ester **16** can be converted to **15** by the known triplet-photosensitized irradiation.[10] After partial hydrolysis of the 3β-acetoxy group in **15**, both 1α- and 3β-hydroxyls in **17** were protected with *tert*-butyldimethylsilyl chloride. Lithium aluminum hydride reduction of protected ester **4** afforded alcohol **5** in an excellent yield.

Our synthesis of the side-chain fragment of analogue **1** started from 5-chlorovaleryl chloride (**18**) as the readily available C-5 synthon (Scheme II). Preparation of the terminal tertiary hydroxyl was easily accomplished by Grignard reaction of **18** with methylmagnesium bromide. Chloride **19** thus obtained was converted to sulfone **21** by the standard method, i.e. **19** was treated with potassium thiophenoxide in alkaline DMF to give sulfide **20**, which in turn was oxidized with 3-chloroperbenzoic acid to afford the sulfone **21** in 67% yield from **18**. Triethylsilyl ether was selected for the protection of the tertiary hydroxyl in sulfone **21**. We anticipated the simultaneous deprotection of all three hydroxyls (1α, 3β, and 25) in the final step of our synthesis of analogue **1**.

The construction of the side-chain part of analogue **1** was accomplished by the alkylation of the protected sulfone **22** with the vitamin D tosylate **6**.[11]

Alkylation of sulfone **22** (Scheme III) and deprotonated with lithium diisopropylamide with tosylate **6** afforded the mixture of C-23 epimeric sulfones **23** and **24** in the ratio of 1:1.8 and 54% yield (based on recovered tosylate **6**). The mixture was unexpectedly easily separated by both thin-layer and high performance liquid chromatography. The absolute configuration of 23*R* and 23*S* was tentatively assigned to sulfones **23** and **24** based on the predominant formation of sterically less hindered sulfone **24** and by the substantial paramagnetic shift of C-18 methyl protons in the ^1H NMR spectrum of sulfone **24** as compared to the chemical shift of the analogous signal in the spectrum of sulfone **23**. Both sulfones gave protected triol **25** by standard desulfonylation with sodium amalgam in a buffered mixture of methanol and tetrahydrofuran followed by a modified nonaqueous workup procedure. As expected, the deprotection of all three hydroxyls in **25** with tetrabutylammonium fluoride afforded triol **1** in a good yield.

Scheme IV. Preparation of Side-Chain Fragment 31[a]



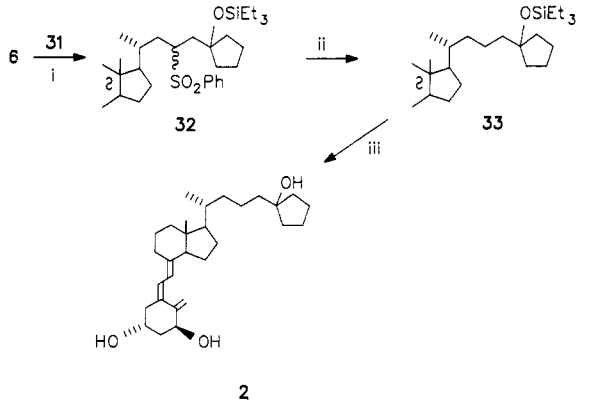
[a] Reagents and conditions: (i) $BrMg(CH_2)_4MgBr$, THF, (ii) *p*-TsCl, py, 4 °C; (iii) PhSH, *t*-BuOK, DMF; (iv) MCPBA, CH_2Cl_2; (v) Et_3SiCl, imidazole, DMF.

Our approach to the alicyclic side-chain fragment **31** (Scheme IV) employed the remarkably facile reaction of bis Grignard reagents with carboxylic acid derivatives.[12]

(10) Gielen, J. W. J.; Koolstra, R. B.; Jacobs, H. J. C.; Havinga, E. *Recl. J. R. Neth. Chem. Soc.* **1980**, *99*, 306.

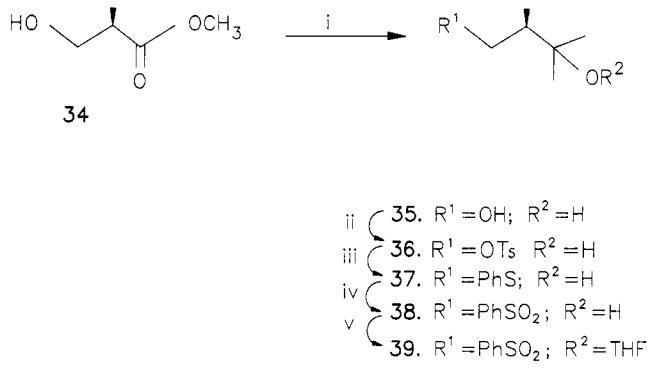
(11) The preparation of a similar bis(triethylsilyl) C-22 tosylate has been reported after our work on **6** was completed. Andres, D. R.; Barton, D. H. R., Hesse, R. H., Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819.

Scheme V. Preparation of Vitamin D_3 Analogue 2[a]



[a] Reagents and conditions: (i) LDA, THF, −20 °C; (ii) 5% Na/Hg, Na_2HPO_4, MeOH; (iii) n-Bu_4NF, THF, 50 °C.

Scheme VI. Preparation of Side-Chain Fragment 39[a]



[a] Reagents and conditions: (i) MeMgBr, THF; (ii) p-TsCl, py, 4 °C; (iii) PhSH, t-BuOK, DMF; (iv) MCPBA, CH_2Cl_2; (v) 2,3-DHF, PPTS, CH_2Cl_2.

In this way diol **27** was obtained by the reaction of β-propiolactone (**26**) with the use of 1,4-bis(bromomagnesio)butane. The protected sulfone **31** was obtained in 74% yield (from **27**) by an analogous reaction sequence as described for sulfone **22**. In analogous fashion, as described for analogue **1**, coupling of tosylate **6** with lithiated sulfone **31**, followed by desulfonylation of **33** with sodium amalgam (Scheme V), afforded, after removal of the protecting groups, the corresponding cyclic analogue **2** in 12% yield (from **6**). The low yield obtained can be attributed to the higher steric hindrance occurring in sulfone **31** as compared with **22**.

For the synthesis of vitamin D_2 analogues, we developed a method based on the use of the new vitamin D C-22 aldehyde **7**. This was obtained in good yield from **5** by Swern oxidation.[13] No protection of the sensitive triene system was necessary under these mild conditions.

Our synthesis of chiral sulfone **39** started from the now available methyl (*R*)-(−)-3-hydroxy-2-methylpropionate (**34**). This was reacted with methylmagnesium bromide to afford diol **35** in good yield (Scheme VI). The protected sulfone **39** was then prepared in 41% yield (from **35**) in the analogous fashion, as described for **22**.

Condensation of aldehyde **7** with deprotonated sulfone **39** (Julia olefination[14]) provided, after desulfonylation of **40**, protected triol **41** with the desired *E* geometry[15] of the side-chain olefin and the retained natural configuration at C-20.[16] Consecutive removal of protective groups of **41** gave triol **3** (Scheme VII).

As an alternative route to D_2 analogues, we also explored the possibility of using vitamin D C-22 carboxylic ester as a precursor. Contrary to numerous reports on acylation of deprotonated sulfones with carboxylic esters,[17] sulfone **39** did not react with ester **4** under various reaction conditions. This might be due to the strong steric hindrance in both reacting species.

In summary, the preparation of the analogues **1**, **2**, and **3** establishes the experimental efficiency and practical utility of a new synthetic strategy involving the coupling of a vitamin D synthon with the appropriate side-chain residue. For the preparation of a series of side-chain-modified vitamin D analogues, this approach has proven to be far more versatile and convenient than previously reported procedures.

Experimental Section

Materials and Methods. Infrared spectra (IR) were obtained on a Nicolet MX-1 FT-IR spectrometer using neat films of oily substances. Ultraviolet (UV) absorption spectra were recorded with a Hitachi Model 60-100 UV–vis spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded at 270 or 400 MHz with Bruker WH-270 or AM-400 FT spectrometers in the solvent noted. Chemical shifts (δ) are reported downfield from internal Me_4Si (δ 0.00) or $CHCl_3$ (δ 7.24). Low- and high-resolution mass spectra were recorded at 70 eV (unless otherwise stated) on a Kratos MS-50 TC instrument equipped with a Kratos DS-55 data system. High resolution data were obtained by peak matching. Samples were introduced into the ion source maintained at 120–250 °C via a direct insertion probe.

Silica gel 60 (Merck, 70–230 or 230–400 mesh) was used for column chromatography. Thin-Layer chromatography (TLC) was performed by using precoated aluminum silica gel sheets with UV indicator from EM Science (Gibbstown, NJ). Solvent systems used: A, chloroform–ethanol 85:15 (v/v); B, hexane–ethyl acetate 1:1; and C, hexane–ethyl acetate 3:1. High performance liquid chromatography (HPLC) was performed on a Waters Associates liquid chromatograph equipped with a Model 6000A solvent delivery system, a Model 6 UK Universal injector, and a Model 450 variable wavelength detector. Zorbax silica (Phenomenex) columns (6.2 mm × 20 cm and 10 mm × 25 cm) were used. Solvent systems: A, 3% 2-propanol in hexane; B, 2% 2-propanol in hexane; C, 6% 2-propanol in hexane; D, 10% 2-propanol in hexane; E, 20% 2-propanol in hexane; F, 2% ethyl acetate in hexane. Silica gel Sep-Pak (Waters Associates) cartridges were used for the prefiltration of HPLC samples.

3β-Acetoxy-22,23-dinor-5-cholenic acid was purcahsed from Steraloids (Wilton, NH). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Other solvents were purified by standard methods. n-Butyllithium in hexanes (Aldrich) was titrated with 1-propanol in the presence of 1,10-phenantroline in THF under argon.

3β-Hydroxy-22,23-dinor-5,7-choladienic Acid Methyl Ester (10). Alkaline hydrolysis of the 3β-acetoxy group of **8** followed by esterification of the carboxylic group and protection of the 3β-hydroxyl with *tert*-butyldimethylsilyl chloride afforded ester **9** in 72% yield. A mixture of 1.0 g (2.1 mmol) of **9**, 0.42 g (1.5 mmol) of dibromantin, and 0.91 g (10 mmol) of anhydrous sodium

(12) (a) Canonne, P.; Bernatchez, M. *J. Org. Chem.* **1987**, *52*, 4025 and references cited therein. (b) Canonne, P.; Foscolos, G. B.; Belanger, D. *J. Org. Chem.* **1980**, *45*, 1828.

(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(14) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4822.

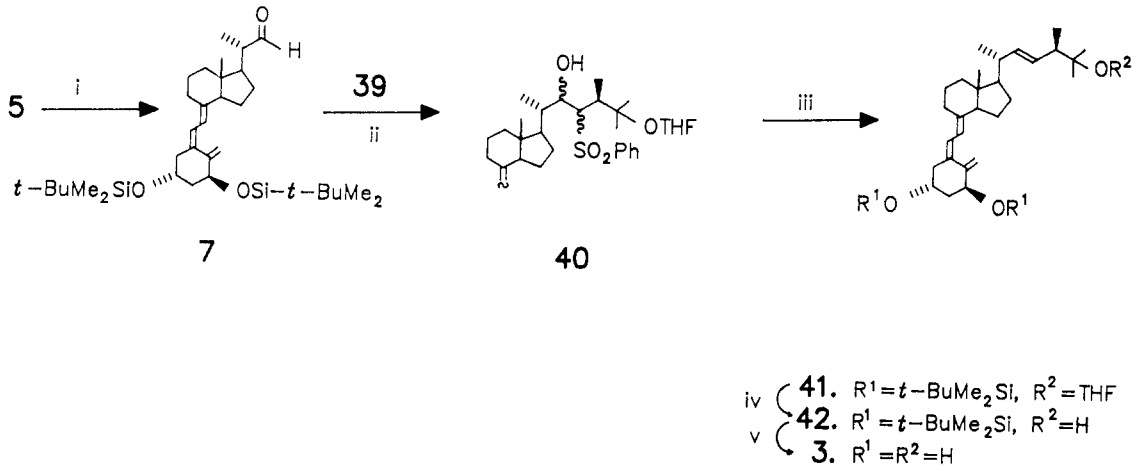
(15) The reductive elimination of α-hydroxy sulfones have been shown to generate exclusively *trans*-olefins. (a) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045 and references cited therein. (b) Morzycki, J. W.; Schnoes, H. K.; DeLuca, H. F. *J. Org. Chem.* **1984**, *49*, 2148.

(16) No epimerization at C-20 has occurred as determined by ^1H NMR. See also: Eyley, S. C.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 727 and 731, and ref 156.

(17) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284 and references cited therein.

(18) DeLuca, H. F.; Schnoes, H. K.; Lee, S.-H.; Phelps, H. E. U.S. Pat. 4 554 106, 1985; *Chem. Abstr.* **1986**, *105*, P608237w.

Scheme VII. Preparation of Vitamin D_2 Analogue 3[a]



[a] Reagents and conditions: (i) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −60 °C; (ii) LDA, THF, −75 °C; (iii) 5% Na/Hg, Na_2HPO_4, MeOH; (iv) PPTS, MeOH; (v) n-Bu_4NF, THF, 55 °C.

bicarbonate in 20 mL of hexane was heated under reflux in a nitrogen atmosphere for 30 min until no **9** was detected (TLC, system C). The precipitate was filtered off and the solution dried down under reduced pressure. To the solution of the residue in 5 mL of anhydrous THF was added 0.06 g (0.19 mmol) of tetrabutylammonium bromide, and the mixture was stirred at room temperature for 30 min under nitrogen. A solution of tetrabutylammonium fluoride (10 mL, 1 M in THF) was then added followed by 0.7 mL of *s*-collidine and the mixture was stirred under nitrogen at room temperature for 1 h. Another 5 mL of tetrabutylammonium fluoride solution was added and stirring was continued for 3 h. To the reaction mixture was added 50 mL of ether, and the organic phase was washed with water, cold 1 N hydrochloric acid, and 10% sodium bicarbonate, and dried ($MgSO_4$). Chromatography on 70–230-mesh silica gel (30 g) with 10% ethyl acetate in hexane gave ester **10** (0.44 g 58%) as a colorless oil. An analytical sample was obtained by HPLC (system A, R_v 77 mL): IR (film) 1737, 1604, 1495, 1082, 1030 cm^{-1}; UV (3% 2-propanol in hexane) λ_{max} 262 nm (ϵ 7000), 272 nm (9800), 282 (10500), 293 (6000); ^1H NMR ($CDCl_3$) δ 0.54 (3 H, s, 18-CH_3), 0.94 (3 H, s, 19-CH_3), 1.22 (3 H, d, J = 6 Hz, 21-CH_3), 3.6 (1 H, m, 3-H), 3.68 (3 H, s, CO_2CH_3), 5.42 (1 H, m, 6-H), 5.58 (1 H, m, 7-H); MS, m/z (relative intensity) 358 (61), 340 (12), 325 (100), 299 (68), 271 (7), 253 (17), 237 (26), 211 (27), 143 (72), 119 (35).

(5*Z*,7*E*)-(3*S*,20*S*)-3-Hydroxy-9,10-seco-5,7,10(19)-pregnatriene-20-carboxylic Acid Methyl Ester (11). A solution of 830 mg (2.3 mmol) of diene **10** in 350 mL of 1:4 (v/v) benzene–ethyl ether was irradiated with stirring under nitrogen in a water-cooled quartz immersion well equipped with a Vycor filter using Hanovia 608A36 medium-pressure UV lamp for 40 min (4 × 10 min). The reaction was monitored by HPLC using 2% 2-propanol in hexane at 265 nm. The solution was dried down under reduced pressure, redissolved in 100 mL of absolute ethanol, and heated under reflux in a nitrogen atmosphere for 3 h. Then the solution was concentrated, redissolved in 1 mL of 10% ethyl acetate in hexane, and chromatographed on 70–230-mesh silica gel (30 g). Ester **11** (298 mg, 36%) was eluted by using a mixture of 15% ethyl acetate in hexane. An analytical sample was obtained by HPLC (system B, R_v 94 mL): IR (film) 1738 cm^{-1}; UV (EtOH) λ_{max} 264 nm, λ_{min} 228 nm; ^1H NMR ($CDCl_3$) δ 0.56 (3 H, s, 18-CH_3), 1.20 (3 H, d, J = 7 Hz, 21-CH_3), 3.66 (3 H, s, CO_2CH_3), 3.95 (1 H, m, 3-H), 4.80 (1 H, d, J = 1.2 Hz, 19*Z*-H), 5.05 (1 H, d, J = 1.2 Hz, 19*E*-H), 6.03 (1 H, d, J = 11 Hz, 7-H), 6.23 (1 H, d, J = 11 Hz, 6-H); MS, m/z (relative intensity) 358 (M^+, 45), 340 (9), 325 (45), 299 (22), 253 (19), 237 (18), 136 (60), 118 (100).

(7*E*)-(3*R*,5*R*,6*R*,20*S*)-6-Methoxy-3,5-cyclo-9,10-seco-7,10(19)-pregnadiene-20-carboxylic Acid Methyl Ester (13). Ester **11** was converted into tosylate **12** by the known method using *p*-toluenesulfonyl chloride in pyridine at 4 °C for 20 h. A solution of 102 mg (0.2 mmol) of **12** in 2 mL of anhyrous dichloromethane was added to a solution of 250 mg of anhydrous potassium bicarbonate in 15 mL of methanol with stirring at 55 °C. The mixture was stirred under nitrogen for 24 h at 55 °C. The solvents were then removed under reduced pressure and the residue extracted with ether. The organic phase was washed with water and dried ($MgSO_4$). Silica gel chromatography, using 20% ethyl acetate in hexane, gave **13** (50 mg, 68%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.54 (3 H, s, 18-CH_3), 0.74 (1 H, m, 3-H), 0.91 (1 H, m, 4-H), 1.20 (3 H, d, J = 7 Hz, 21-CH_3), 3.25 (3 H, s, 6*R*-OCH_3), 3.65 (3 H, s, 22-CO_2CH_3), 4.15 (1 H, d, J = 9 Hz, 6-H), 4.88 (1 H, br s, 19*Z*-H), 5.00 (1 H, d, J = 9 Hz, 7-H), 5.02 (1 H, br s, 19*E*-H); MS, m/z (relative intensity) 372 (M^+, 17), 340 (100), 253 (48), 221 (40), 135 (72).

(5*Z*,7*E*)- and (5*E*,7*E*)-(1*S*,3*R*,20*S*)-1-Hydroxy-3-acetoxy-9,10-seco-5,7,10(19)-pregnatriene-20-carboxylic Acid Methyl Esters (15 and 16). *tert*-Butyl hydroperoxide (112 μL, 3.0 M in toluene) was added to a suspension of 9 mg (0.8 mmol) of selenium dioxide in 2 mL of dry dichloromethane. The mixture was stirred at room temperature under nitrogen until a clear solution was formed. Anhydrous pyridine (12 μL, 0.15 mmol) was then added followed by a solution of 50 mg of ester **13** in 2 mL of dichloromethane. The mixture was stirred under nitrogen for 30 min. Cold 10% sodium bicarbonate (2 mL) was added and the mixture extracted with ether. The organic phase was washed with cold 10% sodium bicarbonate and ice water and dried over anhydrous $MgSO_4$. Silica gel chromatography (10–20% ethyl acetate in hexane) afforded 12.5 mg of alcohol **14**. The product was then immediately dissolved in 0.5 mL of glacial acetic acid and the solution was heated at 55 °C with stirring under nitrogen for 15 min. The reaction mixture was poured over ice, extracted with ether, and washed with ice-cold saturated sodium bicarbonate. The combined ether extracts were washed with water and dried ($MgSO_4$). Analytical samples of (5*Z*,7*E* and 5*E*,7*E* isomers, **15** and **16**, respectively, were obtained by preparative HPLC (system C) in a ratio of 2.5:1. Isomers **15** and **16** were separated by the maleic anhydride procedure worked out in this laboratory[18] to give 6 mg of **15** (20% overall yield from **12**).

15: HPLC, R_v 68 mL; UV (EtOH) λ_{max} 264 nm, λ_{min} 227, A264/A227 = 2.07; ^1H NMR ($CDCl_3$) δ 0.56 (3 H, s, 18-CH_3), 1.20 (3 H, d, J = 6.5 Hz, 21-CH_3), 2.04 (3 H, s, 3β-acetyl), 3.66 (3 H, s, 22-CO_2CH_3), 4.4 (1 H, m, 1-H), 5.2 (1 H, m, 3-H), 5.01 (1 H, br s, 19*E*-H), 5.34 (1 H, br s, 19*Z*-H), 6.01 (1 H, d, J = 10 Hz, 7-H), 6.33 (1 H, d, J = 10 Hz, 6-H); MS, m/z (relative intensity), 416 (M^+, 4), 356 (100), 338 (21), 251 (13), 134 (95).

16: HPLC, R_v 78 mL; UV (EtOH) λ_{max} 267 nm, λ_{min} 227, A267/A227 = 3.51; ^1H NMR ($CDCl_3$) δ 0.56 (3 H, s, 18-CH_3), 1.20 (3 H, d, J = 6.5 Hz, 21-CH_3), 2.04 (3 H, s, 3β-OAc), 3.66 (3 H, s, 22-CO_2CH_3), 4.5 (1 H, m, 1-H), 5.3 (1 H, m, 3-H), 4.99 (1 H, br s, 19*E*-H), 5.13 (1 H, br s, 19*Z*-H), 5.81 (1 H, d, J = 10 Hz, 7-H), 6.56 (1 H, d, J = 10 Hz, 6-H).

(5*Z*,7*E*)-(1*S*,3*R*,20*S*)-1,3-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-5,7,10(19)-pregnatriene-20-carboxylic Acid Methyl Ester (4). To a stirred solution of 100 mg (0.24 mmol) of ester **15** in 10 mL of ethyl ether was added 10 mL of a 0.1 N

solution of KOH in methanol. The solution was stirred at room temperature for 90 min until no starting material was detected by TLC (solvent system B). Dihydroxy ester **17** was isolated by standard extraction procedure (ethyl acetate, saturated NaCl, anhydrous $MgSO_4$) as a colorless oil (86.2 mg, 96%). A mixture of 250 mg (3.6 mmol) of imidazole and 250 mg (1.6 mmol) of *tert*-butyldimethylsilyl chloride in 2 mL of DMF was then added to a stirred solution of 86.2 mg (0.23 mmol) of **17** in 4 mL of DMF. The mixture was stirred for 15 min at 55 °C until no starting material was detected by TLC (system B). The product was isolated with hexane. The organic extract was washed with brine and dried ($MgSO_4$). A hexane solution of the crude product was filtered through a silica gel Sep-Pak cartridge to give **4** (136 mg, 98%) as a colorless oil: IR (film) 2974, 2930, 1736, 1447, 1286, 1258, 1150, 1085 cm^{-1}; UV (hexane) λ_{max} 264 nm, λ_{min} 227, A264/A227 = 1.91; ^1H NMR ($CDCl_3$) δ 0.07 [12 H, s, $Si(CH_3)_2]_2$, 0.55 (3 H, s, 18-CH_3), 0.86 [18 H, s, $C(CH_3)_3$], 1.20 (3 H, d, J = 6.8 Hz, 21-CH_3), 3.65 (3 H, s, OCH_3), 4.18 (1 H, m, 3-H), 4.36 (1 H, m, 1-H), 4.84 (1 H, d, J = 1.2 Hz, 19*Z*-H), 5.16 (1 H, d, J = 1.2 Hz, 19*E*-H), 5.96 (1 H, d, J = 11.2 Hz, 7-H), 6.19 (1 H, d, J = 11.2 Hz, 6-H); MS, m/z (intensities normalized to m/z 248) 602 (M^+, 10), 470 (59), 413 (7), 338 (10), 248 (100).

(5*Z*,7*E*)-(1*S*,3*R*,20*S*)-1,3-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-22,23-dinor-5,7,10(19)-cholatrien-24-ol (5). To a stirred solution of 136.2 mg (0.23 mmol) of ester **4** in 5 mL of anhydrous THF was added 25 mg (0.65 mmol) of lithium aluminum hydride under argon at 0 °C. The suspension was stirred for 15 min at 0 °C and the excess reagent was decomposed by the dropwise addition of 10% H_2O in THF. The suspension was diluted with 10 mL of THF and the stirring was continued for an additional 15 min at room temperature. The product was isolated by the standard extraction procedure with ethyl acetate. Silica gel Sep-Pak filtration in 10% ethyl acetate in hexane gave **5** (118.4 mg, 91%) as a colorless oil: IR (film) 3450, 2952, 2886, 1447, 1258, 1105, 1085, 834 cm^{-1}; UV (EtOH) λ_{max} 264 nm, λ_{min} 227, A264/A227 = 1.57; ^1H NMR ($CDCl_3$) δ 0.00 (12 H, s, $SiCH_3$), 0.53 (3 H, s, 18-CH_3), 0.85 [18 H, s, $SiC(CH_3)_3$], 1.04 (3 H, d, J = 6.4 Hz, 21-CH_3), 3.37 and 3.63 (1 H and 1 H, each m, 22-CH_2), 4.17 (1 H, m, 3-H), 4.35 (1 H, m, 1-H), 4.84 (1 H, br s, 19*Z*-H), 5.16 (1 H, br s, 19*E*-H), 6.00 (1 H, d, J = 12.2 Hz, 7-H), 6.21 (1 H, d, J = 12.2 Hz, 6-H); MS, m/z (intensities normalized to m/z 248), 574 (M^+, 17), 442 (67), 383 (11), 308 (17), 248 (100).

2-Methyl-6-(phenylsulfonyl)-2-[(triethylsilyl)oxy]hexane (22). A solution of 3 g (19.2 mmol) of 5-chlorovaleryl chloride (**18**) in 25 mL of anhydrous THF was added dropwise with vigorous stirring, over 30 min, under argon, to a solution of methylmagnesium bromide (12.9 mL of 3 M in ether) in 25 mL of dry THF at −10 °C. The reaction mixture was allowed to warm up to room temperature within 2 h, then quenched with water, and neutralized with diluted hydrochloric acid. The mixture was extracted with ether and purified by distillation in vacuo to give chloride **19** (2.1 g, 70%) as a colorless liquid. To a stirred solution of 1.32 g (12 mmol) of thiophenol and 1.32 g (11.3 mmol) of potassium *tert*-butoxide was added 1.5 g (10 mmol) of chloride **19** in 5 mL of anhydrous dimethylformamide. The reaction mixture was stirred at room temperature overnight and extracted with dichloromethane. The organic layer was washed with aqueous sodium carbonate and water and dried ($MgSO_4$). Solvents were removed in vacuo and the crude oil was purified by silica gel chromatography with hexane–ethyl acetate to give sulfide **20** (2.2 g, 98%) as a colorless oil. Sulfide **20** (1.01 g, 4.5 mmol) was then dissolved in 40 mL of dry dichloromethane and 2.5 g (11.6 mmol, Aldrich 80-85%) of 3-chloroperbenzoic acid was added in portions with stirring and occasional cooling. The reaction mixture was stirred for 2 h and quenched with 10% sodium bicarbonate. The combined organic extracts were washed with aqueous sodium sulfite and brine and dried over magnesium sulfate. The solvent was removed in vacuo and the crude oil was purified by silica gel flash chromatography using hexane–ethyl acetate to afford sulfone **21** (1.1 g, 97%) as a colorless liquid. Then 1.15 g (7.7 mmol) of triethylsilyl chloride was added to a stirred solution of 1.3 g (5.1 mmol) of sulfone **21** and 1.5 g (22.7 mmol) of imidazole in 50 mL of dry DMF. The reaction mixture was stirred at room temperature for 2 h and diluted with dichloromethane. The mixture was washed with aqueous ammonium chloride and water. The organic layer was dried over sodium sulfate and solvents were removed under reduced pressure. Silica gel flash chromatography with 9:1 hexane–ethyl acetate gave pure protected sulfone **22** (1.8 g, 97%) as a thick colorless oil: IR (film) 3045, 2940, 1440, 1360, 1130, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.52 (6 H, q, J = 6.2 Hz, $SiCH_2$), 0.90 (9 H, t, J = 6.2 Hz, $SiCCH_3$), 1.14 (6 H, s, CH_3), 1.31–1.46 (4 H, m), 1.66–1.74 (2 H, m), 3.08–3.12 (2 H, m, 6-H), 7.57 (2 H, t, J = 6.8 Hz, Ar H, meta), 7.65 (1 H, t, J = 6.8 Hz, Ar H, para), 7.92 (2 H, d, J = 6.8 Hz, Ar H, ortho); MS, m/e (relative intensity) 370 (M^+, 2), 341 (100), 227 (18), 173 (24), 103 (22), 75 (45), 55 (33); exact mass calcd for $C_{19}H_{34}O_3SSi$ 370.1998, found 370.1942.

(5*Z*,7*E*)-(1*S*,3*R*,20*S*)-1,3-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-22,23-dinor-5,7,10(19)-cholatrienol 22-*p*-Toluenesulfonate (6). An ice-cold solution of 42.7 mg (0.22 mmol) of *p*-toluenesulfonyl chloride in 50 μL of dry pyridine was added to a stirred solution of alcohol **5** at 0 °C under nitrogen. The mixture was stirred at 5 °C for 22 h and monitored by TLC (system C). The reaction mixture was poured on ice-cold saturated aqueous $NaHCO_3$ and stirring was continued for another 30 min. The product was extracted with 1:1 (v/v) ethyl ether–hexane. The organic phase was washed with saturated NaCl and dried over $MgSO_4$. Solvents were removed under reduced pressure and pyridine was removed in a stream of nitrogen. Crude product was purified by silica gel Sep-Pak filtration (5% ethyl acetate in hexane) to give pure tosylate **6** (54 mg, 98%): IR (film) 2950, 1580, 1367, 1267, 1189, 1178, 1099, 1085, 835 cm^{-1}; UV (hexane) λ_{max} 263 nm, λ_{min} 236; ^1H NMR ($CDCl_3$) δ 0.00 (12 H, s, $SiCH_3$), 0.43 (3 H, s, 18-CH_3), 0.81 [18 H, s, $SiC(CH_3)_3$], 0.93 (3 H, d, J = 6.8 Hz, 2-CH_3), 2.40 (3 H, s, $ArCH_3$), 3.64 and 3.91 (1 H and 1 H, each m, 22-CH_2), 4.13 (1 H, m, 3-H), 4.31 (1 H, m, 1-H), 4.79 (1 H, br s, 19*Z*-H), 5.13 (1 H, br s, 19*E*-H), 5.94 (1 H, d, J = 12.8 Hz, 7-H), 6.17 (1 H, d, J = 12.8 Hz, 6-H), 7.43 and 7.84 (2 H and 2 H, each m, Ar H); MS, m/z (intensity relative to m/z 248), 728 (6), 596 (30), 556 (7), 464 (7), 424 (44), 367 (19), 292 (23), 248 (100); exact mass calcd for $C_{41}H_{68}O_5Si_2S$ 728.4338, found 728.4326.

Sulfones 23 and 24. Diisopropylamine (9 μL, 64 μM) was added to a stirred solution of *n*-BuLi (48 μL, 1.35 M in hexanes) containing 1,10-phenanthroline as an indicator (red color) at −78 °C under argon. The solution was stirred under argon for 30 min at −77 °C. Then the solution of sulfone **22** (29 mg, 80 μmol) in 100 μL of THF was added followed by another 100 μL of THF used the rinsings. The resulting brown mixture was stirred at −75 °C under argon for 30 min and the cooling bath was replaced with a CCl_4–dry ice bath. After 15 min of stirring at −21 °C, the solution of 11.6 mg (16 μmol) of tosylate **6** was added and the color of the reaction mixture turned back to red. The solution was stirred at −20 to −10 °C for 3.5 h and 1 mL of saturated NH_4Cl was added at −10 °C. The mixture was extracted with hexane and the organic phase was washed with saturated NaCl. The organic extract was filtered through a silica gel Sep-Pak cartridge followed by 20 mL of 10% ethyl acetate in hexane. Preparative HPLC (column 6.2 × 25 cm, system F, R_v 37 mL) provided the unreacted tosylate **6** (3.0 mg). Sulfone **23** (2.1 mg; 19% based on recovered tosylate **6**) was then eluted at R_v 55 mL: IR (film) 3500, 2956, 1440–1301, 1258, 1147, 1086, 1072, 1064 cm^{-1}; UV (hexane) λ_{max} 264 nm, λ_{min} 230, A264/A230 = 1.96; ^1H NMR ($CDCl_3$) δ 0.41 (3 H, s, 18-CH_3), 0.51 (6 H, q, J = 5.7 Hz, $SiCH_2$-), 0.86 and 0.88 [9 H and 9 H, each s, $SiC(CH_3)_3$], 0.90 (9 H, t, J = 8 Hz, $SiCH_2CH_3$), 1.13 (3 H, d, J = 5.8 Hz, 21-CH_3), 1.23 (6 H, s, 26,27-CH_3), 4.17 (1 H, m, 3-H), 4.37 (1 H, m, 1-H), 4.85 (1 H, br s, 19*Z*-H), 5.17 (1 H, br s, 19*E*-H), 5.99 (1 H, d, J = 11.0 Hz, 7-H), 6.21 (1 H, d, J = 10.8 Hz, 6-H), 7.54 (2 H, t, J = 7.3 Hz, Ar H, meta), 7.61 (1 H, t, J = 7.3 Hz, Ar H, para), 7.88 (2 H, d, J = 7.3 Hz, Ar H, ortho); MS, m/z (intensity relative to m/z 794) 926 (M^+, 16), 794 (100), 737 (9), 530 (9), 521 (6), 389 (13), 301 (8).

Sulfone **24** (3.8 mg; 35% based on recovered tosylate **6**) was eluted at R_v 87 mL: IR (film) 3500, 2955, 1440, 1304, 1257, 1148, 1086, 1072, 1064 cm^{-1}; UV (hexane) λ_{max} 264 nm, λ_{min} 229, A264/A229 = 2.06; ^1H NMR ($CDCl_3$) δ 0.49 (3 H, s, 18-CH_3), 0.51 (6 H, q, J = 5.7 Hz, $SiCH_2$-), 0.85 [18 H, s, $SiC(CH_3)_3$], 0.90 (9 H, t, J = 7.9 Hz, $SiCH_2CH_3$), 1.13 (3 H, d, J = 6.2 Hz, 21-CH_3), 1.23 (6 H, s, 26,27-CH_3), 4.16 (1 H, m, 3-H), 4.35 (1 H, m, 1-H), 4.83 (1 H, br s, 19*Z*-H), 5.16 (1 H, br s, 19*E*-H), 5.98 (1 H, d, J = 11.1 Hz, 7-H), 6.20 (1 H, d, J = 11.3 Hz, 6-H), 7.54 (2 H, t, J = 7 Hz, Ar H, meta), 7.61 (1 H, t, J = 7 Hz, Ar H, para), 7.86 (2

H, d, J = 7 Hz, Ar H, ortho); MS, m/z (intensity relative to m/z 794) 926 (19), 794 (100), 737 (11), 530 (28), 521 (14), 389 (33), 301 (14).

24-Dihomo-1,25-dihydroxyvitamin D_3 (1). A saturated solution of Na_2HPO_4 in methanol (0.5 mL) was added to a stirred solution of sulfone **23** (1.80 mg) in 0.5 mL of anhydrous THF followed by 80 mg of powdered anhydrous Na_2HPO_4. The mixture was stirred under argon for 30 min and cooled down to 0 °C. Fresh 5% sodium amalgam (ca. 200 mg) was then added and the mixture was stirred for 3 h at 5 °C monitored by TLC (system C). The mixture was diluted with 3 mL of hexane and stirring was continued for 15 min. The hexane layer was decanted and the methanol layer was washed with hexane (3 × 2 mL). The hexane layer was washed with ice-cold saturated NaCl and filtered through a silica Sep-Pak cartridge to give **25** (1.19 mg, 78%) as a colorless oil. Protected triol **25** was also obtained the same way by the sodium amalgam reduction of sulfone **24**. Ether **25** (1.1 mg) was dissolved in 0.5 mL of anhydrous THF, and to this solution was added tetrabutylammonium fluoride in THF (20 μL, 1 M solution). The mixture was stirred under argon for 50 min at 50 °C. Ether (3 mL) was then added and the organic phase was washed with saturated NaCl. Solvents were removed and the residue was dissolved in 10% 2-propanol in hexane and filtered through silica Sep-Pak. Preparative HPLC (column 6.2 mm × 25 cm, system D, R_v 62 mL) yielded triol 1 (465 μg, 76%): IR (film) 3360, 2927, 1602, 1447, 1376, 1297, 1146, 1106, 1086, 1064 cm^{-1}; UV (10% 2-propanol in hexane) λ_{max} 264 nm, λ_{min} 228, A264/A228 = 1.91; ^1H NMR ($CDCl_3$) δ 0.52 (3 H, s, 18-CH_3), 0.90 (3 H, d, J = 6.4 Hz, 21-CH_3), 1.19 (6 H, s, 26,27-CH_3), 4.22 (1 H, m, 3-H), 4.42 (1 H, m, 1-H), 4.99 (1 H, br s, 19*Z*-H), 5.31 (1 H, br s, 19*E*-H), 6.00 (1 H, d, J = 11.1 Hz, 7-H), 6.36 (1 H, d, J = 11.2 Hz, 6-H); MS, m/z (relative intensity) 444 (M^+, 1.4), 426 (41), 393 (10), 251 (26), 209 (17), 197 (20), 157 (29), 155 (37), 134 (58), 105 (54), 59 (100); exact mass calcd for $C_{29}H_{48}O_3$ 444.3603, found 444.3609.

1-[2-(Phenylsulfonyl)ethyl]-1-[(triethylsilyl)oxy]cyclopentane (31). Diol **27** was prepared from β-propiolactone **26** and 1,4-bis(bromomagnesio)butane by the known method.[12b] Further preparation followed the methods described for sulfide **20**, sulfone **21**, and protected sulfone **22**. Protected sulfone **31** was obtained in 48% overall yield as a thick, colorless oil: IR (film) 3050, 2900, 1440, 1405, 1300, 1230, 1045, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.47 (6 H, q, J = 5.7 Hz, $SiCH_2$), 0.86 (9 H, t, J = 5.7 Hz, CH_3), 1.46–1.57 (4 H, m), 1.63–1.71 (4 H, m), 1.86–1.89 (2 H, m, 1-H), 3.23–3.26 (2 H, m, 2-H), 7.58 (2 H, t, J = 7.3 Hz, Ar H, meta), 7.66 (1 H, t, J = 7.3 Hz, Ar H, para), 7.92 (2 H, d, J = 7.3 Hz, Ar H, ortho); MS m/z (30 eV, relative intensity) 386 (M^+, 0.01), 339 (M^+ – Et, 100), 227 (8), 199 (8), 163 (17), 135 (10), 115 (9), 95 (13), 87 (12), 75 (14); exact mass calcd for $C_{19}H_{32}O_3SSi$ 368.1841, found 368.1936.

26,27-Trimethylene-1,25-dihydroxyvitamin D_3 (2). Analogue **2** was prepared by the same method as described for analogue 1. A mixture of C-23 epimeric sulfones **32** was not separated and directly desulfonylated with 5% sodium amalgam to give ether **33**. Triol **2** was obtained by deprotection of **33**, as described for **25**, as a thick, colorless oil (55 μg, 12% yield from **6**) by preparative HPLC (column, 10 × 25 cm, system D, R_v 94 mL): IR (film) 3360, 2930, 1605, 1442, 1378, 1291, 1145, 1105, 1080, 1062 cm^{-1}; UV (10% 2-propanol in hexane) λ_{max} 264 nm, λ_{min} 228, A264/A228 = 1.71; ^1H NMR (CD_3OD) δ 0.48 (3 H, s, 18-CH_3), 0.87 (3 H, d, J = 6.4 Hz, 21-CH_3), 4.03 (1 H, m, 3-H), 4.25 (1 H, m, 1-H), 4.80 (1 H, br s, 19*Z*-H), 5.19 (1 H, br s, 19*E*-H), 5.98 (1 H, d, J = 11.2 Hz, 7-H), 6.23 (1 H, d, J = 11.1 Hz, 6-H); MS, m/z (relative intensity) 442 (M^+, 5), 424 (43), 406 (38), 388 (7), 373 (7), 298 (6), 285 (12), 269 (20), 251 (24), 134 (100), 85 (28); exact mass calcd for $C_{29}H_{48}O_3$ $C_{29}H_{46}O_3$ 442.3447, found 442.3438.

(3*S*)-2,3-Dimethyl-4-(phenylsulfonyl)-2-[(2′-tetrahydrofuranyl)oxy]butane (39). A solution of 2.11 g (17.9 mmol) of ester **34** in 8 mL of anhydrous THF was added dropwise to a stirred solution of 30 mL (2.7 M in ether) of methylmagnesium bromide under nitrogen at 0 °C. The mixture was stirred at ambient temperature for 2 h and ice-cooled diluted hydrochloric acid was slowly added. The mixture was extracted with ethyl ether and worked up by the standard method to give diol **35** as a colorless oil (1.2 g, 57%). The oil was dissolved in 5 mL of anhydrous pyridine and 2.34 g (12.3 mmol) of *p*-toluenesulfonyl chloride was added with stirring. The mixture was stirred for 16 h at 4 °C and quenched with ice-cold saturated $NaHCO_3$. The suspension was stirred at room temperature for 30 min and worked up by the standard method. Silica gel flash chromatography gave tosylate **36** as a colorless oil (2.14 g, 65%). Sulfone **38** was then obtained as a thick, colorless oil in 51% yield from **36** (by the method described for **21**): $[\alpha]^{22}_D$ +27.9° (*c* 1.3, $CHCl_3$). To a solution of 186 mg of **38** in 1 mL of anhydrous dichloromethane was added 10 mg of pyridinium *p*-toluenesulfonate followed by 0.2 mL of freshly distilled 2,3-dihydrofuran. The mixture was stirred overnight, diluted with dichloromethane, and worked up in the usual way. Silica gel flash chromatography with 20% ethyl acetate in hexane gave protected sulfone **39** (182 mg, 76%) as a colorless oil: IR (film) 2979, 1448, 1305, 1144, 1037, 1006 cm^{-1}; UV (EtOH) λ_{max} 215 nm (ε 7400), λ_{max} 257.5 (550), λ_{max} 263.5 (790), λ_{max} 270.5 (680); ^1H NMR ($CDCl_3$) δ 1.04 (3 H, s, 1-CH_3), 1.10 (3 H, m, 3-CH_3), 1.17 and 1.18 (3 H and 3 H, each s, 2-CH_3), 1.8 (4 H, m, 3′-H, 4′-H), 2.14 (1 H, m, 3-H), 2.8 (1 H, m, 4-CH), 3.6 (1 H, m, 4-CH), 3.8 (2 H, m, 5′-CH_2), 5.3 (1 H, m, 2′-H), 7.6 and 7.9 (5 H, m, Ar H); FAB-MS, m/z (relative to m/z 295), 313 (M^+ + 1, 60), 295 (100), 255 (23), 243 (83); exact mass calcd for $C_{16}H_{24}O_4S$ 312.1395, found 312.1451.

(5*Z*,7*E*)-(1*S*,3*R*,20*S*)-1,3-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-22,23-dinor-5,7,10(19)-cholatrien-24-al (7). A solution of 30 μL (0.34 mmol) of oxalyl chloride in 0.5 mL of dichloromethane was added dropwise to a stirred solution of 50 μL (0.7 mmol) of DMSO in 3 mL of dichloromethane at −60 °C under nitrogen. After the mixture was stirred for 10 min at −60 °C, the solution of 27 mg (0.05 mmol) of alcohol **5** in 1 mL of dichloromethane was slowly added. The mixture was stirred for 30 min at −60 °C and 0.2 mL of triethylamine was added. The product was extracted with ethyl acetate, washed (NaCl), and dried ($MgSO_4$). Silica gel Sep-Pak filtration afforded pure **7** (17 mg, 62%) as a colorless oil: IR (film) 2954, 2929, 2884, 2857, 1727, 1472, 1375, 1256, 1085, 909, 880, 835 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.00 (12 H, s, $SiCH_3$), 0.60 (3 H, s, 18-CH_3), 0.88 [18 H, s, SiC-$(CH_3)_3$], 1.11 (3 H, d, J = 6.9 Hz, 21-CH_3), 4.23 (1 H, m, 3-H), 4.43 (1 H, m, 1-H), 4.93 (1 H, br s, 19*Z*-H), 5.19 (1 H, br s, 19*E*-H), 6.07 (1 H, d, J = 10.0 Hz, 7-H), 6.26 (1 H, d, J = 10.0 Hz, 6-H), 9.54 (1 H, d, J = 3 Hz, 22-H); UV (hexane) λ_{max} 264 nm, λ_{min} 227, A264/A227 = 1.9; MS, m/*z* (intensities relative to m/z 248) 572 (M^+, 13), 440 (53), 383 (11), 308 (14), 248 (100); exact mass calculated for $C_{34}H_{60}O_3Si_2$ 572.4081, found 572.4117.

(24*R*)-1,25-Dihydroxyvitamin D_2 (3). To a solution of *n*-BuLi in hexanes (47 μL, 1.35 M) containing 1,10-phenanthroline as an indicator was added 9.6 μL (0.068 mmol) of diisopropylamine with stirring under argon at −76 °C (red color). After the mixture was stirred for 20 min at −75 °C, the solution of 26.5 mg (0.085 mmol) of sulfone **39** in 0.5 mL of anhydrous THF was added dropwise (brown-red color). The mixture was stirred at −75 °C for 30 min and a solution of 10 mg (0.017 mmol) of aldehyde **7** in 0.7 mL of THF was added. Stirring was continued for 1.5 h and 1 mL of saturated NH_4Cl solution was added (yellow color). The reaction mixture was extracted with ethyl acetate and the organic phase was washed with saturated NaCl. Silica gel flash chromatography with 1% ethyl acetate in hexane afforded 3.6 mg of the unreacted aldehyde **7**. Further elution of the column with 10% ethyl acetate in hexane gave hydroxy sulfone **40** (6.4 mg, 65% based on recovered aldehyde **7**) as a colorless oil. This was used for the next step without further purification. Desulfonylation of **40** with 5% sodium amalgam, as described for **23**, gave protected triol **41** (1.95 mg, 55%). Deprotection of the 25-hydroxy in 1% pyridinium *p*-toluenesulfonate in methanol gave **42** (0.8 mg, 95%). Final deprotection of the 1- and 3-hydroxy of 640 μg of **42**, as described for **25** gave, after HPLC (system D, column 6.2 × 25 cm, R_v 47 mL) triol **3** (337 μg, 81%) as a colorless oil: IR (film) 3411, 1643, 1630, 971 cm^{-1}; UV (EtOH) λ_{max} 264 nm, λ_{min} 229, A264/A229 = 1.57; ^1H NMR ($CDCl_3$) δ 0.54 (3 H, s, 18-CH_3), 0.97 (3 H, d, J = 6.9 Hz, 28-CH_3), 1.01 (3 H, d, J = 6.6 Hz, 21-CH_3), 1.10 and 1.15 (3 H and 3 H, each s, 26-CH_3 and 27-CH_3), 4.21 (1 H, m, 3-H), 4.41 (1 H, m, 1-H), 4.97 (1 H, br s, 19*Z*-H), 5.29 (2 H, m, 22-H and 23-H), 5.31 (1 H, br s, 19*E*-H), 5.99 (1 H, d, J = 11.2 Hz, 7-H), 6.35 (1 H, d, J = 11.2 Hz, 6-H); MS, m/z (relative intensity) 428 (3), 410 (9), 392 (10), 374 (3), 352 (8), 287 (2), 269 (6), 251 (6), 155 (11), 152 (10), 135 (28), 134 (33), 59 (100); exact mass calcd for $C_{28}H_{44}O_3$ 428.3290, found 428.3268.

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Synthesis of Analogues of 1,3-Dihydroxyacetone Phosphate and Glyceraldehyde 3-Phosphate for Use in Studies of Fructose-1,6-diphosphate Aldolase[1]

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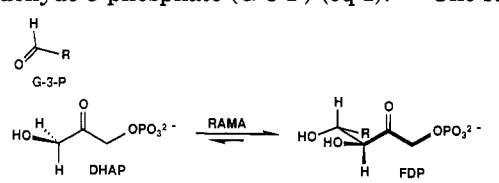
This paper describes the syntheses of five analogues of dihydroxyacetone phosphate (3-azidohydroxyacetone 1-phosphate (**5**), 3-(acetylamino)hydroxyacetone 1-phosphate (**12**), (*R*)-1,3-dihydroxy-2-butanone 1-phosphate (**18**), (±)-1,3-dihydroxy-2-butanone 3-phosphate (**26**), and phosphonomethyl glycolate (**31**)). The syntheses of **18** and **26** are based on a new reaction: that is, the introduction of the phosphate group by reaction of a diazo ketone with dibenzyl phosphate. These methods provide easy access to a number of compounds that are potential substrates for the synthetically useful enzyme aldolase (fructose-1,6-phosphate aldolase from rabbit muscle, EC 4.1.2.13, RAMA) and perhaps for other enzymes of glycolysis. This paper also describes syntheses of 14 aldehydes for examination as substrates for aldolase. When the precursor was available, ozonolysis of vinyl groups proved to be the best route to the corresponding aldehydes.

Introduction

Fructose-1,6-diphosphate aldolases catalyze the reaction of dihydroxyacetone phosphate (DHAP) with D-glyceraldehyde 3-phosphate (G-3-P) (eq 1).[7,8] The stereochem-



(1)

istry of the reaction is that indicated in eq 1; the enzyme removes the *pro-S* hydrogen of DHAP.[9] The enzyme from rabbit muscle (EC 4.1.2.13, RAMA) is commercially available and inexpensive (~$20/500 U, 1 U = 1 μmol of product formed per min with DHAP and G-3-P). It is useful as a catalyst in the synthesis of carbohydrates,[10-17] and its broader applicability in organic synthesis is now being actively developed.[18,19] The conclusions from these studies are (1) aldolase accepts a variety of aldehydes as substrates and (2) it will accept only a few close analogues of DHAP.

As part of a research program designed to explore the substrate specificity of aldolase and to evaluate the utility of its reactions in organic synthesis, we required a number of analogues of the natural substrates.[19] DHAP and G-3-P are relatively sensitive compounds, and syntheses of structural analogues of these substances are not trivial. Here we report synthetic routes to five new analogues of DHAP and 14 analogues of G-3-P. The best synthesis of DHAP analogues is based on a new method to generate

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