that was flash chromatographed (30% EtOAc/hexanes) to give 25-hydroxyvitamin D_2 (**2b**)[6c] (55 mg, 76%), which crystallized from hexane; mp 96–97 °C.

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Registry No. **2a**, 50-14-6; **2b**, 21343-40-8; **3**, 64190-52-9; **4**, 66774-80-9; **5**, 100858-19-3; **6**, 66774-71-8; **7a**, 100858-20-6; **7b**, 100937-69-7; **8**, 100858-21-7; **9a**, 100858-22-8; **9b**, 100937-70-0; **10a**, 100858-23-9; **10b**, 100937-71-1; **11a**, 100858-24-0; **11b**, 100937-72-2; **12**, 100858-25-1; **13**, 100858-26-2; **14**, 100858-27-3; **15**, 100858-28-4; $HC_2(CH_3)_2OMOM$, 17869-83-9; AG 50WX4, 52932-60-2.

Studies on the Synthesis of Side-Chain Hydroxylated Metabolites of Vitamin D. 3. Synthesis of 25-Ketovitamin D_3 and 25-Hydroxyvitamin D_3[1]

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A general method for the synthesis of the principal vitamin D_3 metabolites whether unlabeled or with radiolabeled side chains is described. The synthesis of the key de-*A*,*B*-(ethylenedioxy)cholestanone derivative **7d** is based on the coupling between the iodide **4c** and 3-(trimethylsilyl)-3-buten-2-one (**5b**) via cuprate chemistry. The synthesis of 25-ketovitamin D_3 (a suitable intermediate compound for radiolabeling) was achieved by coupling between **7d** and the *n*-butyllithium-induced carbanion of the phosphine oxide **8c** using Lythgoe's strategy and deprotection. As an example of the utility of this route, 25-hydroxyvitamin D_3 was synthesized.

The principal metabolites of vitamin D_3 (**1a**), 25-hydroxyvitamin D_3 (**1b**), and 1α,25-dihydroxyvitamin D_3 (**1c**) play a role in the vitamin D_3 dependent endocrine system[2] whose importance has stimulated considerable activity in the synthesis of these compound and other analogues.[3] We have been interested for some time in devising a general route to these clinically useful metabolites and their radiolabeled forms for metabolite assays. Our synthetic plan has been centered around the key intermediate compound **7d**, which it was hoped would easily lead to the vitamin D triene system by use of Lythgoe's convergent approach,[3b,4] thus avoiding the low-yielding classical electrocyclic photochemically induced opening of steroidal 5,7-dienes. Furthermore, the side chain of **7d** is suitable for radiolabeling before or after its coupling with the *n*-butyllithium-induced carbanion of phosphine oxide **8c** in the last steps of the synthesis.

The synthesis of **7d** and the application of this compound to the synthesis of 25-hydroxyvitamin D_3 are the subjects of this paper.

Results and Discussion

For this study we started with the triol **2a**,[5] which was selectively protected (*i*-Pr_3SiCl, imidazole, DMF) to give the diol **2b** in 83.3% yield (Chart I). Exposure of **2b** to 1.2 equiv of lead tetraacetate in dichloromethane[6] followed by the addition of an excess of sodium bis(2-methoxyethoxy)aluminum hydride (70% solution in toluene) produced **3a**[7] and **8a** in 96% and 95% yields, respectively. The structural identity of **8a** was established by comparison of its deprotected diol with an authentic sample obtained by deprotection of the corresponding known[5] *tert*-butyldimethylsilyl derivative. Protection of alcohol **3a** (*t*-$BuMe_2SiCl$, imidazole, DMF)[8] afforded **3b** in 93% yield. Side-chain cleavage of **3b** when treated with ozone in $MeOH/CH_2Cl_2$ at −78 °C followed by in situ reduction (−78 → 0 °C) afforded protected alcohol **4a** in 60% yield.[9] The identity of **4a** was established by comparison of its deprotected diol with an authentic sample obtained by direct ozonolysis of vitamin D_2.[10] Alcohol **4a** was then converted to the crystalline iodide **4c** in 86% yield by the well-known two-step sequence (*p*-TsCl, py; NaI, acetone).

The crucial two-step sequence for the generation of **7b** was best achieved (in 65% yield) as follows: (i) Metalation of the iodide **4c** with *tert*-butyllithium in diethyl ether afforded the corresponding lithium salt intermediate, which was treated with Corey's copper reagent[11] ($CuC_2C(CH_3)_2OCH_3$, Et_2O). Slow addition of enone **5b**[12] to the resulting assumed mixed cuprate **6** finally afforded the desired ketone **7a**. All these one-pot reactions were carried

(1) For a preliminary communication describing part of this work, see: Fernandez, B.; Mascareñas, J. L.; Pumar, M. C.; Vila, M. J.; Mouriño, A.; Castedo, L. "Vitamin D: Chemical, Biochemical and Clinical Update"; Norman, A. W., Schaefer, K., Grigoleit, H.-G., Herrath, D. v., Eds.; Walter de Gruyter: Berlin-New York, 1985; p 792.

(2) For general reviews on the subject, see: (a) Norman, A. W. "Vitamin D, The Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979. (b) DeLuca, H. F.; Paaren, H. G.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1.

(3) For general reviews on the synthesis of vitamin D metabolites and analogues, see: (a) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98. (b) *Synform* **1985**, *3*, 43–124. (c) Lythgoe, B. *Chem. Soc. Rev.* **1980**, *9*, 449. (d) Jones, H.; Rasmusson, G. H. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 63.

(4) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovič, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945 and references therein.

(5) (a) Frosch, J. V.; Harrison, I. T.; Lythgoe, B.; Saksana, A. K. *J. Chem. Soc. Perkin Trans. 1*, **1974**, 2005. (b) Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414.

(6) Corey, E. J.; Iguchi, S.; Albright, J. O. B. *Tetrahedron Lett.* **1983**, *24*, 37.

(7) Kocienski, P. J.; Lythgoe, B.; Roberts, D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 834.

(8) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovič, M. R. *Tetrahedron* **1984**, *48*, 2283.

(9) Under the same conditions, the corresponding tetrahydropyranyl derivative afforded the corresponding THP–**4a** compound in 87% yield.

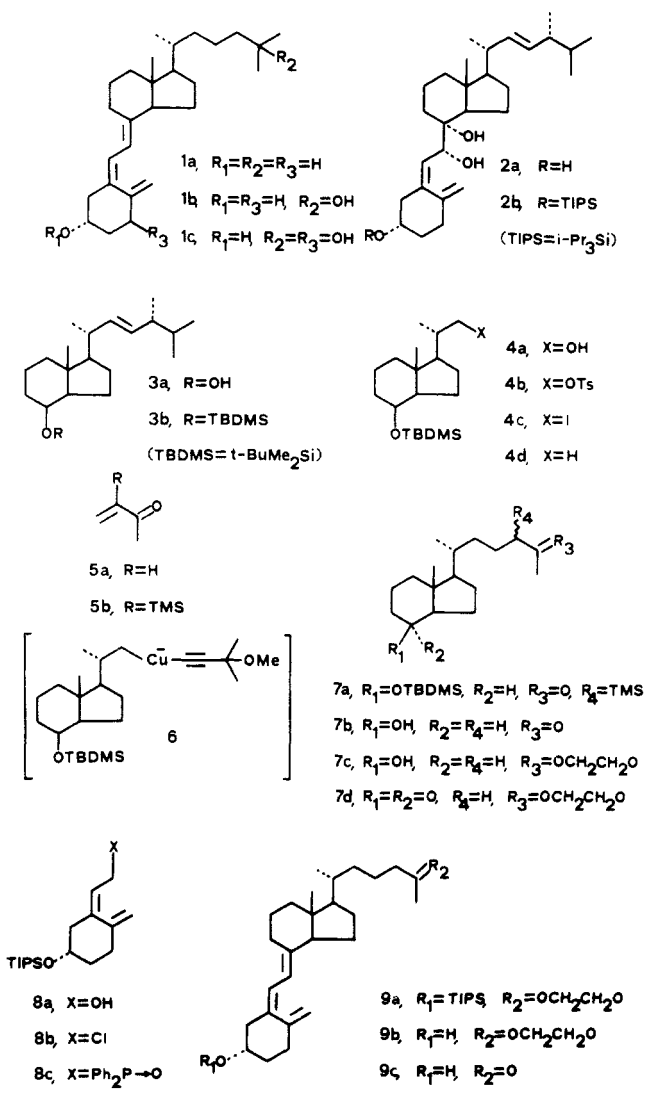
(10) Please see: Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.*, preceding paper in this issue.

(11) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

(12) 3-(Trimethylsilyl)-3-buten-2-one (**5b**) was prepared as per: Boeckman, R. K.; Blum, D. M.; Ganen, B.; Halvey, N. *Org. Synth. 58*, 152.

0022-3263/86/1951-1269$01.50/0

Chart I



out at −80 °C. (ii) One-pot removal of the silyl groups (48% HF/acetonitrile) gave **7b**. The structure assigned to **7b** was confirmed by an alternative route.[13] Ketalization of **7b** with 2,2-ethylenedioxybutane and a trace of *p*-toluenesulfonic acid gave alcohol **7c** (80%), which in turn was oxidized with pyridinium dichromate in dichloromethane to the desired compound **7d** (90%).

Coupling between **7d** and the *n*-butyllithium-induced carbanion of diphenylphosphine oxide **8c**[14] afforded the trienic ketal **9a** (93%), which after deprotection (48% HF, acetonitrile) furnished the ketal **9b** (81%). Deprotection of **9b** (AG 50W-X4 cation-exchange resin)[8] afforded 25-ketovitamin D_3 (**9c**)[15] in 93% yield. This key compound was alternatively obtained directly from **9a** in 79% yield under the same reaction conditions (AG 50W-X4 resin). Finally, 25-ketovitamin D_3 was converted to 25-hydroxyvitamin D_3 (**1b**)[16] in 90% yield by reaction with methyllithium in diethyl ether. The above sequence of reactions (13 steps) afforded 25-hydroxyvitamin D_3 from triol **2a** in a 12% overall yield.

Experimental Section

Materials and Techniques.[17] **3β-*O*-(Triisopropylsilyl)-7,8-dihydroxy-7,8-dihydrovitamin D_2 (2b).** A mixture of the triol **2a** (1.23 g, 2.87 mmol), *i*-Pr_3SiCl (0.64 mL, 3 mmol), and imidazole (0.44 g, 6.5 mmol) in DMF (10 mL) was stirred at room temperature for 10 h. The mixture was poured into water and extracted twice with $CHCl_3$. The organic phase was washed twice with 10% HCl, dried (Na_2SO_4), and concentrated in vacuo to a residue that was flash chromatographed (5% EtOAc/hexanes) to give, after high-vacuum drying, the diol **2b** (1.4 g, 83.3%).

(24*R*,22*E*)-De-*A*,*B*-ergost-22-en-8β-ol (3a) and (*S*,*Z*)-2′-[5-[(Triisopropylsilyl)oxy]-2-methylenecyclohexylidene]-ethanol (8a). $Pb(OAc)_4$ (3.33 g, 7.5 mmol) was added in portions to a −15 °C cooled solution of **2b** (3.6 g, 6.13 mmol) in dry CH_2Cl_2 (70 mL). The resulting mixture was stirred for 15 min at the same temperature and then without the cooling bath for 15 min. Filtration through a short path of Celite–silica gel and washing of the solids with dry CH_2Cl_2 (3 × 10 mL) afforded a colorless solution that was treated at 0 °C with a solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ in toluene (70%, 7.3 mL). The resulting black solution was stirred for 2 h at room temperature. The reaction was quenched by the addition of several pieces of ice. Removal of organic solvents in vacuo afforded a residue that was continuously extracted with refluxing Et_2O for 8 h. The resulting solution was dried (Na_2SO_4) and filtered. Removal of the ether afforded a residue that was flash chromatographed (hexanes, 2–8% EtOAc/hexanes) to give, after high-vacuum drying, **3a**[7] (1.64 g, 96%, colorless oil) and **8a** (1.8 g, 95%, pale yellow oil). Anal. Calcd for $C_{19}H_{34}O$ (**3a**): C, 81.90; H, 12.30. Found: C, 81.66; H, 12.61.

(24*R*,22*E*)-De-*A*,*B*-8β-[(*tert*-butyldimethylsilyl)oxy]-ergost-22-ene (3b). The alcohol **3a** (1.75 g, 6.3 mmol) was stirred with imidazole (1.08 g, 15.8 mmol) and *t*-$BuMe_2SiCl$ (1.4 g, 9.3 mmol) in CH_2Cl_2 (10 mL) and DMF (20 mL) at room temperature for 15 h and then heated at 45 °C for 20 h. *t*-$BuMe_2SiCl$ (0.6 g, 4.0 mmol) and imidazole (0.32 g, 4.6 mmol) were added at room temperature, and the resulting mixture was heated at 80 °C distilling solvent. The remaining solution was stirred at the same temperature for 6 h, allowed to reach room temperature, and poured into ice water. The resulting mixture was extracted twice with ether, and the organic layer was washed with 10% HCl (10 mL) and brine (30 mL), dried (Na_2SO_4), and filtered. Removal of solvents in vacuo afforded a residue that was flash chromatographed (hexanes) to give 2.3 g of **3b** (93%, oil): ^1H NMR δ 5.17 (2 H, m, W = 42 Hz, CH=CH), 4.00 (1 H, m, $^1/_2$ W = 6 Hz, H-8), 0.99 (3 H, d, J = 6.6 Hz, $C_{21}CH_3$ or 28), 0.93 (3 H, s, $C_{18}CH_3$), 0.89 (9 H, s, *t*-BuSi), 0.89 (3 H, d, J = 7.4 Hz, $C_{28}CH_3$ or 21), 0.85 (3 H, d, J = 3.9 Hz, $C_{28}CH_3$ or 27), 0.82 (3 H, d, J = 3.9 Hz, $C_{26}CH_3$ or 27); MS, m/e 392 (M^+).

De-*A*,*B*-8β-[(*tert*-butyldimethylsilyl)oxy]-23,24-dinorcholan-22-ol (4a). A solution of **3b** (2 g, 5.1 mmol) in CH_2Cl_2 (20 mL), MeOH (160 mL), and pyridine (2 mL) was cooled to −78 °C under a gentle flow of N_2 with magnetic stirring (20 min). N_2 was replaced by ozone, which was passed through the solution for 1 h (KI test). The excess of ozone was removed by passing again N_2 (KI test). $NaBH_4$ (1 g) was added in small pieces, and the resulting mixture was allowed to reach room temperature with stirring and a slow flow of N_2. Further portions of $NaBH_4$ (1 g) were added, and the stirring was continued for 12 h at room temperature. Concentration in vacuo followed by the addition of water gave a mixture that was extracted twice with ether, washed twice with water, dried (Na_2SO_4), and filtered. Removal of the ether afforded a residue that was flash chromatographed (5–10% EtOAc/hexanes) to give 1 g of **4a**: white solid, 60%; ^1H NMR δ 4.01 (1 H, m, H-8), 3.64 (1 H, dd, J = 10.5, 3.15 Hz, C*H*HOH), 3.38 (1 H, dd, J = 10.5, 6.8 Hz, CH*H*OH), 1.03 (3 H, d, J = 6.64 Hz, $C_{21}CH_3$), 0.94 (3 H, s, $C_{18}CH_3$), 0.89 (9 H, s, *t*-BuSi); IR (KBr) 3300, 1470, 1250, 1160 cm^{-1}; MS, m/e 311 (M − 15). For identification purposes, a solution of **4a** (25 mg) in acetonitrile

(13) Copper-catalyzed reaction of tosylate **4b** with the Grignard reagent previously used followed by ozonolysis and deprotection afforded **7b** in 20% yield: (a) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc. Perkin Trans. 1* **1977**, 2608. (b) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099.

(14) We recommend the exact reproduction of the experimental procedure described here for the preparation of the allylic chloride **8b**.

(15) This compound has also been obtained by degradation of 25-hydroxyvitamin D_3: Suda, T.; DeLuca, H. F.; Schnoes, H. K.; Tanaka, Y.; Holick, M. F. *Biochemistry* **1970**, *9*, 4777.

(16) Lawson, D. E. M. "Vitamin D"; Academic Press: New York, 1978; pp 22–25.

(17) Please refer to the Experimental Section of the previous paper in this issue.[10]

(6 mL) was stirred with 48% HF (1 mL) at room temperature for 1.5 h. Removal of solvents in vacuo left a residue that was extracted with ether, dried (Na_2SO_4), and filtered. The residue, after removal of the ether, was chromatographed on silica gel (50–80% Et_2O/hexanes) to give de-*A*,*B*-23,24-dinorcholane-22,8β-diol (15.4 mg, 95%), which was identical with an authentic sample obtained by direct ozonolysis–$NaBH_4$ reduction of vitamin D_2.[10]

De-*A*,*B*-8β-[(*tert*-butyldimethylsilyl)oxy]-22-(tosyloxy)-23,24-dinorcholane (4b). A mixture of the protected alcohol **4a** (0.5 g, 1.53 mmol), *p*-toluenesulfonyl chloride (0.4 g, 2 mmol), and pyridine (20 mL) was stirred at 0 °C for 2 h and then left in the refrigerator overnight (16 h). The mixture was poured into a separatory funnel containing ice-cold water. Extraction twice with ether produced an organic phase that was washed with a saturated solution of $CuSO_4$ (4 × 10 mL) and water (20 mL). The organic phase was then dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue on silica gel (2% EtOAc/hexanes) afforded, after crystallization (Et_2O/hexanes), 0.7 g of **4b**: 95%, white crystals, mp 50 °C; ^1H NMR δ 7.79 (2 H, d, *J* = 8.35 Hz, Ar), 7.35 (2 H, d, *J* = 8.35 Hz, Ar), 3.98 (1 H, m, H-8), 3.95 (1 H, dd, *J* = 9.2, 3.06 Hz, C*H*HOTs), 3.8 (1 H, dd, *J* = 9.2, 6.3 Hz, CH*H*OTs), 2.46 (3 H, s, CH_3 Ar), 0.95 (3 H, d, *J* = 6.66 Hz, $C_{21}CH_3$), 0.88 (9 H, s, *t*-BuSi), 0.87 (3 H, s, $C_{18}CH_3$), 0.005 (6 H, s, Me_2Si). Anal. Calcd for $C_{26}H_{44}O_4SSi$: C, 64.95; H, 9.22. Found: C, 64.55; H, 8.98.

De-*A*,*B*-8β-[(*tert*-butyldimethylsilyl)oxy]-23,24-dinor-22-iodocholane (4c). A mixture of **4b** (1 g, 2 mmol), acetone (60 mL, freshly purified by stirring with $KMnO_4$ and distilling from K_2CO_3), and NaI (3 g, 20 mmol) was refluxed with stirring in the dark for 15 h. The resulting mixture was poured into a separatory funnel containing a saturated solution of $NaHCO_3$ (30 mL) and extracted with ether. The resulting organic phase was washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was filtered through a short column of silica gel (hexanes). Removal of solvents in vacuo and crystallization in the refrigerator afforded 0.84 g of iodide **4c**: 94%; mp 41–42 °C; ^1H NMR δ 4.01 (1 H, m, H-8), 3.33 (1 H, dd, *J* = 9.40, 2.15 Hz, C*H*HI), 3.19 (1 H, dd, *J* = 9.40, 4.67 Hz, CH*H*I), 1.0 (3 H, d, *J* = 5.55 Hz, $C_{21}CH_3$), 0.95 (3 H, s, $C_{18}CH_3$), 0.88 (9 H, s, *t*-BuSi), 0.006 (6 H, s, Me_2Si); MS, *m*/*e* 437 (M + 1, 0.2), 436 (M^+, 0.5), 421 (M − 15, 0.2), 228 (100). Anal. Calcd for $C_{19}H_{37}OSiI$: C, 52.28; H, 8.54. Found: C, 52.33; H, 8.66.

De-*A*,*B*-27-norcholestan-8β-ol-25-one (7b). (i) Preparation of a Solution of $CuC_2C(CH_3)_2OCH_3$. A solution of *n*-butyllithium in hexane (1.2 mmol, 0.75 mL) was added to a 0 °C cooled solution of $HC_2C(CH_3)_2OCH_3$ (118 mg, 1.2 mmol, distilled from CaH_2, argon) in Et_2O (1.6 mL). The resulting mixture was stirred for 20 min, after which time CuI was added (240 mg, 1.27 mmol, purified by complexation with Me_2S followed by removal of the Me_2S by heating in vacuo). The resulting suspension was stirred at room temperature for 45 min.

(ii) Metalation of the Iodide 4c. A solution of *tert*-butyllithium in pentane (2.41 mmol, 1.33 mL) was slowly added (40 min) under stirring to a −80 °C cooled solution of **4c** [0.5 g, 1.15 mmol, freshly bulb-to-bulb distilled, bp 145 °C (0.1 mmHg)] in Et_2O (2.3 mL). The stirring was then continued for 1.5 h at the same temperature.

(iii) Preparation of the Mixed Copper Reagent 6 and Coupling Reaction with 5b. The above freshly prepared suspension of copper(I) reagent and washings with Et_2O (3.5 mL) were transferred via cannula and dropwise to the above cooled and freshly prepared carbanion of **4c**. The suspension was stirred at −80 °C for 1 h, after which time a solution of silyl ketone **5b** (190 μL, freshly distilled in vacuo) in Et_2O (2 mL) was slowly added (30 min). The reaction mixture was stirred at the same temperature for 15 min and then poured into a separatory funnel containing a saturated solution of ammonium chloride (20 mL). Extraction with ether afforded an organic phase that was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue of **7a** was subjected as such to deprotection.

(iv) Deprotection of 7a. The above crude residue was dissolved in acetonitrile (10 mL), and the solution was treated with 48% HF (1 mL). After stirring for 3 h, the solution was concentrated in vacuo. Addition of a saturated solution of $NaHCO_3$ and extraction with ether produced an organic phase that was dried (Na_2SO_4) and concentrated in vacuo. The residue was filtered through a short column of silica gel (5% EtOAc/hexanes). Removal of solvents under reduced pressure afforded, after high-vacuum drying, 140 mg of **7b**: 65%, colorless oil; ^1H NMR δ 4.07 (1 H, m, $^1/_2$ *W* = 3 Hz, H-8), 2.38 (2 H, m, CHHCO), 2.13 (3 H, s, CH_3CO), 0.92 (3 H, s, $C_{18}CH_3$), 0.91 (3 H, d, *J* = 6.76 Hz, $C_{21}CH_3$); IR 3610, 1720, 1120 cm^{-1}; MS, *m*/*e* 266 (M^+, 0.2), 251 (M − 15, 0.5), 248 (0.5), 163 (1.5), 135 (8), 111 (56), 97 (16), 95 (18), 94 (17), 93 (19), 91 (12), 83 (10), 82 (17), 81 (34), 79 (29), 77 (15), 71 (19), 69 (22), 68 (18), 67 (50), 58 (21), 57 (31), 56 (10), 55 (100). The structural confirmation of this compound was established by an alternative route.[13]

De-*A*,*B*-25,25-(ethylenedioxy)-27-norcholestan-8β-ol (7c). The keto alcohol **7b** (165 mg, 0.62 mmol) was stirred with 2,2-(ethylenedioxy)butane (6 mL) and a catalytic amount of *p*-toluenesulfonic acid at room temperature for 24 h. The reaction was quenched with a saturated solution of $NaHCO_3$. The mixture was extracted with ether, and the resulting organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the residue (8% EtOAc/hexanes) afforded 150 mg of ketal **7c**: 80%, oil; ^1H NMR δ 4.07 (1 H, br s, C*H*OH), 3.94 (4 H, br s, OCH_2CH_2O), 1.31 (3 H, s, $C_{26}CH_3$), 0.92 (3 H, s, $C_{18}CH_3$), 0.90 (3 H, d, *J* = 6.6 Hz, $C_{21}CH_3$); IR 3400 (br), 1380, 1120 cm^{-1}; MS, *m*/*e* 310 (M^+, 1), 295 (M − 15, 100).

De-*A*,*B*-25,25-(ethylenedioxy)-27-norcholestan-8-one (7d). Pyridinium dichromate (328 mg, 0.87 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate were added to a solution of the protected alcohol **7c** (100 mg, 0.32 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at room temperature for 4.5 h and then diluted with ether. The resulting mixture was filtered through a Celite–silica gel pad, and the filtrate was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was flash chromatographed (8% EtOAc/hexanes) to give 90 mg of **7d**: 90%, colorless oil; ^1H NMR δ 3.94 (4 H, m, OCH_2CH_2O), 1.32 (3 H, s, $C_{26}CH_3$), 0.96 (3 H, d, *J* = 6.01 Hz, $C_{21}CH_3$), 0.63 (3 H, s, $C_{18}CH_3$); IR 3400 (br), 1715, 1120 cm^{-1}; MS, *m*/*e* 308 (M^+, 3), 293 (M − 15, 8), 265 (17), 151 (13), 133 (13), 125 (34), 124 (26), 123 (12), 112 (13), 111 (87), 110 (11), 109 (10), 107 (15), 99 (27), 97 (14), 96 (17), 95 (23), 94 (16), 93 (16), 91 (14), 87 (100), 82 (17), 81 (42), 79 (23); HRMS calcd for $C_{19}H_{32}O_3$ 308.2352, found 308.2251; HRMS calcd for $C_{19}H_{32}O_3 - CH_3$ 293.2117, found 293.2163.

(*S*,*Z*)-[2′-[5-((Triisopropylsilyl)oxy)-2-methylenecyclohexylidene]ethyl]diphenylphosphine Oxide (8c). Commercial *N*-chlorosuccinimide (1 g) was dissolved in CH_2Cl_2 (4 mL) and filtered. Removal of the CH_2Cl_2 in vacuo and high-vacuum drying (P_2O_5) afforded pure material (white crystals, mp 146 °C). A mixture of this *N*-chlorosuccinimide (212.3 mg, 1.59 mmol), CH_2Cl_2 (8 mL), and DMF (5 mL) was stirred at room temperature for 10 min. The resulting solution was cooled to 0 to 5 °C followed by the the slow addition of dimethyl sulfide (0.127 mL, 3.12 mmol). The resulting white precipitate was stirred for 15 min and then cooled to −20 to −25 °C. A solution of the allylic alcohol **8a** (440 mg, 1.42 mmol) in CH_2Cl_2 (2 mL) and washings (CH_2Cl_2 0.5 mL) were added. The resulting suspension was warmed to 0–10 °C (2 h), and the solution was poured into a separatory funnel containing ice-cold brine. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo without heating to a small volume and then diluted with hexane. The solution was washed with brine and concentrated to a small volume as above. Flash chromatography (hexanes), concentration in vacuo without heating, and high-vacuum drying (0.5 min) of the residue furnished 435 mg of the allylic chloride **8b** [94%; R_f (Merck TLC silica gel, 10% EtOAc/hexanes) 0.85, decomposition], which was directly used in the next step: ^1H NMR δ 5.48 (1 H, t, *J* = 7.9 Hz, H-2′), 5.02 (1 H, br s, H-7), 4.86 (1 H, br s, H-7), 4.20 (2 H, m, 2 H-1′), 3.99 (1 H, m, H-5), 1.06 (18 H, s, Me_2CSi).

A solution of *n*-butyllithium in hexane (1.65 mL, 1.6 M, 2.64 mmol) was added to a −5 °C cooled solution of diphenylphosphine (491 mg, 0.46 mL, 2.64 mmol) in THF (8 mL). The resulting mixture was stirred at 0 °C for 30 min. The resulting solution was slowly added to a −60 °C cooled solution of the above allylic chloride **8b** in THF (10 mL). The pale yellow solution was stirred further for 15 min and then quenched by the addition of one drop of water. Removal of the solvents under reduced pressure afforded a residue that was diluted with $CHCl_3$ (60 mL). The solution was

transferred to a separatory funnel and shaken vigorously with 5% H_2O_2 (44 mL) for 4 min. The organic layer was washed twice with 10% Na_2SO_3, dried ($MgSO_4$), and filtered. Removal of the solvent in vacuo left a residue that was dissolved in a small volume of 20% EtOAc/hexanes. Flash chromatography (1.8 × 20 cm, 20–50% EtOAc/hexanes) furnished, after concentration in vacuo and high-vacuum drying (P_2O_5), 422 mg of the phosphine oxide **8c**: 65%; ^{1}H NMR δ 7.4–7.8 (10 H, m, Ar), 5.42 (1 H, m, 1 H-2'), 4.90 (1 H, br s, H-7), 4.66 (1 H, br s, H-7), 3.1–3.8 (3 H, m, 2 H-1', H-5), 1.05 (18 H, s, Me_2CSi); MS m/e 495 (M + 1, 1), 494 (M^+, 4), 449 (100).

25,25-(Ethylenedioxy)-27-norvitamin D_3 Triisopropylsilyl Ether (9a). A solution of *n*-butyllithium in hexane (135 μL, 1.6 M, 0.21 mmol) was added dropwise to a −70 °C cooled solution of the phosphine oxide **8c** (104 mg, 0.21 mmol) in THF (4 mL). The resulting reddish solution was stirred for 30 min followed by the slow addition of the ketone **7d** (50 mg, 0.162 mmol) in THF (1 mL). The resulting solution was stirred for 1 h and then warmed to room temperature (at −35 °C the solution turns orange, at −30 °C yellow, and at 0 °C colorless). Dilution with hexanes and concentration in vacuo afforded a residue that was transferred to a separatory funnel by means of hexanes and EtOAc/hexanes. The organic phase was washed twice with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and filtered. Removal of solvents in vacuo left a residue that was flash chromatographed (1.5 × 5 cm, hexanes–5% EtOAc/hexanes) to give, after concentration in vacuo and high-vacuum drying, 88 mg of **9a**: 93%, viscous colorless oil; ^{1}H NMR δ 6.17 and 6.02 (2 H, AB, J = 11.3 Hz, H-6, H-7), 5.01 (1 H, br s, *Z* H-19), 4.79 (1 H, br d, J = 2.7 Hz, *E*-H-19), 3.95 (4 H, m, OCH_2CH_2O), 1.32 (3 H, s, $C_{26}CH_3$), 1.06 (18 H, d, J = 1.3 Hz), 0.93 (3 H, d, J = 6 Hz, $C_{21}CH_3$), 0.5 (3 H, s, $C_{18}CH_3$); MS, m/e 584 (M^+, 5), 569 (M − 15, 75), 398 (100).

25-Ketovitamin D_3 (9c). An aqueous solution of HF (48%, 4 drops) was added to a solution of the protected vitamin **9a** (38 mg, 0.065 mmol) in acetonitrile (10 mL). The resulting solution was stirred at room temperature in the dark for 3 h. Concentration in vacuo afforded a residue that was diluted with ether (20 mL), transferred to a separatory funnel, and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was flash chromatographed (15% EtOAc/hexanes) to give, after concentration in vacuo and high-vacuum drying, 22 mg of ketal **9b** (81%): MS, m/e 428 (M^+, 3), 413 (M − 15, 2), 410 (M − 18), 43 (100); HRMS calcd for $C_{28}H_{44}O_3$ 428.3292, found 428.3237. A solution of the above hydroxy ketal **9b** (19 mg, 0.044 mmol) in MeOH (10 mL) was stirred with AG 50W-X4 200–400-mesh cation-exchange resin (1.3 g, prewashed with MeOH) at room temperature for 2.5 h in the dark. Filtration and concentration in vacuo afforded a residue that was diluted with $CHCl_3$ and transferred to a separatory funnel and shaken with water. The water phase was further extracted with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (20–40% Et_2O/hexanes) afforded, after removal of solvents under reduced pressure and high-vacuum drying, 16 mg of the desired 25-ketovitamin D_3 (**9c**), 93%. Alternatively, this compound was obtained as follows. A solution of **9a** (30 mg, 0.051 mmol) in MeOH (15 mL) was stirred with AG 50W-X4 resin (1.8 g) at room temperature for 20 h in the dark. Filtration, concentration in vacuo, dilution with EtOAc, washing twice with brine, drying ($MgSO_4$), and concentration in vacuo afforded a residue that was flash chromatographed (5–20% EtOAc/hexanes) to give, after concentration in vacuo and high-vacuum drying, 15 mg of 25-ketovitamin D_3 (**9c**)[15] in 79% yield: ^{1}H NMR δ 6.23 and 6.03 (2 H, AB, J = 11.35 Hz, H-6, H-7), 5.05 (1 H, d, J = 2.60 Hz, *Z*-H-19), 4.81 (1 H, d, J = 2.60 Hz, *E*-H-19), 3.95 (1 H, m, H-3), 2.14 (3 H, s, CH_3CO), 1.25 (s, OH), 0.95 (3 H, d, J = 6.22 Hz, $C_{21}CH_3$), 0.53 (3 H, s, $C_{18}CH_3$); UV (Et_2O) λ_{max} 266 nm (ϵ 18 300), λ_{min} 233 nm; MS, m/e 384 (M^+ 9), 366 (M − 18, 1), 351 (M − 18 − 15, 10), 325 (3), 271 (4), 253 (6), 171 (10), 159 (25), 158 (27), 157 (17), 145 (30), 143 (33), 136 (50), 135 (26), 133 (20), 131 (30), 129 (27), 121 (20), 119 (47), 118 (83), 117 (37), 115 (20), 113 (14), 111 (16), 109 (24), 107 (36), 105 (53), 97 (20), 95 (63), 94 (16), 93 (56), 92 (23), 91 (100).

25-Hydroxyvitamin D_3 (1b). A solution of methyllithium in diethyl ether (0.12 mL, 1.2 M) was added dropwise to a −80 °C cooled solution of 25-ketovitamin D_3 (15 mg, 0.039 mmol) in diethyl ether (4 mL). After stirring for 20 min, the reaction was quenched with water (2 mL). The ether was removed in vacuo, and the residue was diluted with $CHCl_3$ and transferred to a separatory funnel. Addition of water and shaking produced an organic phase that was dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude was flash chromatographed (25% EtOAc/hexanes) to give 14 mg of 25-hydroxyvitamin D_3 (**1b**)[16] in 90% yield.

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Synthesis of Enantiomerically Pure 24-Alkylsterol Side Chains, in Both Enantiomeric Forms, Starting from (*R*)-(+)-Limonene†

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Three couples of enantiomeric synthons corresponding to six 24-alkylsterol side chains, (*R*)- and (*S*)-1-bromo-3,4-dimethylpentane, (*R*)- and (*S*)-1-bromo-3-ethyl-4-methylpentane, and (*R*)- and (*S*)-5-(acetyloxy)-1-bromo-3-(1-methylethyl)pentane, were synthesized from the same chiral intermediate, (*R*)-5-(acyloxy)-3-(1-methylethyl)pentan-1-ol, readily obtainable from (*R*)-(+)-limonene.

The stereospecificity of natural chemoreceptors requires that natural compounds obtained by synthesis have an optical purity as near as possible to 100%. As starting material for the synthesis of such optically pure compounds, natural products like carbohydrates,[1] terpenes,[2] hydroxy acids,[3] and amino acids,[4] which are easily available

† This paper is dedicated to the memory of the late Prof. L. Canonica.

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