Hz, $C_{2'}H$), 4.75 (dd, 1, $C_{3'}H$), 5.33 (d, 1, $J_{3',5'}$ = 0.9 Hz, $C_{5'}H$), 6.22 (d, 1, $C_{1'}H$), 7.98, 8.27 (s, 1, C_2H, C_8H) ppm; MS, m/e 295 (M^+). Anal. Calcd for $C_{11}H_{13}N_5O_3S{\cdot}0.5EtOH$ (335.03): C, 42.02; H, 4.81; N, 20.90; S, 9.55. Found: C, 42.06; H, 4.80; N, 21.38; S, 9.36.

2',3'-*O*-Cyclohexylidene-5'-deoxy-5',5'-bis(isobutylthio)-uridine (23a). Trimethylsilyl triflate (0.31 mL) was added to a solution of **22** (200 mg, 0.6 mmol),[13a] (isobutylthio)trimethylsilane (200 mg, 1.2 mmol), and anhydrous zinc iodide (0.6 mg) in methylene chloride–tetrahydrofuran (1:1, 5 mL). After 1 h at room temperature the mixture was worked up as for **16a** and chromatographed on silica gel using a gradient of 0.5% methanol in methylene chloride, giving 131 mg (45%) of **23a** as a homogeneous foam: λ_{max} (MeOH) 258 nm (ϵ 9800); NMR ($CDCl_3$) 1.00 (m, 12, $CHMe_2$), 1.3–1.9 (m, 12, cyclohexylidene + $CHMe_2$), 2.60 (m, 4, SCH_2), 3.99 (d, 1, $J_{4',5'}$ = 6.4 Hz, $C_{5'}H$), 4.28 (dd, 1, $J_{3',4'}$ = 3.7 Hz, $C_{4'}H$), 4.84 (dd, 1, $J_{1',2'}$ = 3.1 Hz, $J_{2',3'}$ = 6.6 Hz, $C_{2'}H$), 4.95 (dd, 1, $C_{3'}H$), 5.77 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.86 (d, 1, $C_{1'}H$), 7.51 (d, 1, C_6H) ppm; MS, m/e 484 (M^+). Anal. Calcd for $C_{23}H_{36}N_2O_5S_2$ (484.52): C, 57.02; H, 7.44; N, 5.78. Found: C, 56.99; H, 7.40; N. 5.72.

2',3'-*O*-Cyclohexylidene-5'-deoxy-5',5'-bis(methylthio)-uridine (23b). A solution of **22** (190 mg, 0.55 mmol), (methylthio)trimethylsilane (0.18 mL, 1.23 mmol), and anhydrous zinc iodide (0.6 mg) in tetrahydrofuran (5 mL) was stirred at room temperature for 2 h and then partitioned between chloroform and aqueous potassium acetate. The organic phase was washed with water, dried (Na_2SO_4), and evaporated, leaving a residue that was purified by chromatotron chromatography using a gradient of 0–5% methanol in methylene chloride, giving 126 mg (55%) of **23b** as a homogeneous foam: λ_{max} (MeOH) 258 nm (ϵ 10 000); NMR ($CDCl_3$) 1.3–1.8 (m, 10, cyclohexylidene), 2.19, 2.21 (s, 3, SMe), 3.93 (d, 1, $J_{4',5'}$ = 7.1 Hz, $C_{5'}H$), 4.24 (dd, 1, $J_{3',4'}$ = 4.1 Hz, $C_{4'}H$), 4.88 (d, 1, $J_{1',2'}$ = 2.6 Hz, $J_{2',3'}$ = 6.6 Hz, $C_{2'}H$), 5.00 (dd, 1, $C_{3'}H$), 5.76 (d, 1, $C_{1'}H$), 5.76 (d, 1, $J_{5,6}$ = 8.0 Hz, C_5H), 7.40 (d, 1, C_6H), 8.80 (br s, 1, NH) ppm; MS, m/e 400 (M^+). Anal. Calcd for $C_{17}H_{24}N_2O_5S_2{\cdot}H_2O$ (418.51): C, 48.78; H, 6.26; N, 6.69. Found: C, 49.01; H, 5.83; N, 6.32.

1-(2,3-*O*-Cyclohexylidene-5-deoxy-5-(isobutylthio)-β-D-*erythro*-pent-4-enofuranosyl)uracil (24). A solution of **23a** (100 mg, 0.24 mmol) in n acetonitrile (2 mL) was stirred for 2 h at room temperature and at 40 °C for 1 h in the presence of lithium carbonate (103 mg, 1.4 mmol) and mercuric trifluoroacetate (100 mg, 0.24 mmol). TLC showed the presence of some unreacted **23a** together with more polar and less polar products. The mixture was filtered through silica gel, and the filtrate was evaporated to dryness and purified by chromatotron chromatography using a gradient of 0–5% methanol in methylene chloride. The more polar band contained 10 mg (10%) of **22**, while the less polar band gave 36 mg (38%) of **24** as a foam containing a roughly 4:1 mixture of geometric isomers: λ_{max} (MeOH) 256 nm (ϵ 14 300); NMR ($CDCl_3$, major isomer), 0.90 (m, 6, $CHMe_2$e, 1.2–1.8 (m, 10, cyclohexylidene), 1.85 (m, 1, $CHMe_2$), 2.55 (d, 2, J = 7 Hz, SCH_2), 4.98 (dd, 1, $J_{2',3'}$ = 6 Hz, $J_{3',5'}$ = 0.9 Hz, $C_{3'}H$), 5.28 (d, 1, $C_{2'}H$), 5.30 (s, 1, $C_{1'}H$), 5.7 (m, 2, $C_{5'}H$, C_5H), 7.20 (d, 1, $J_{5,6}$ = 8 Hz, C_6H). Anal. Calcd for $C_{19}H_{26}N_2O_5S{\cdot}1.5H_2O$ (421.49): C, 54.13; H. 6.93; N, 6.65. Found: C, 54.39; H, 6.40; N, 6.38.

Studies on the Synthesis of Side-Chain Hydroxylated Metabolites of Vitamin D. 2. Stereocontrolled Synthesis of 25-Hydroxyvitamin D_2[1]

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Received September 24, 1985

An efficient synthesis of 25-hydroxyvitamin D_2 is described. The chiral center at C-24 was introduced by the stereospecific and regioselective displacement of an allylic carbamate by a cuprate. The triene system was assembled by Horner–Wittig coupling of ketone **13** and the anion of phosphine oxide **14**.

The discovery of the fact that vitamin D_3 (**1a**) is metabolized in the living organism to a number of more polar substances that elicit a variety of biological responses has attracted continuing attention to the vitamin D dependent endocrine system during the last two decades.[2] The major metabolites of vitamin D_3 are the 25-hydroxyvitamin D_3 (25-OH-D_3, **1b**) and the 1α,25-dihydroxyvitamin D_3 (1,25-$(OH)_2$-D_3, **1c**), both of which bear a hydroxy group at C-25 that is known to be of great importance with regard to the biological activity of these metabolites.[2] 1,25-$(OH)_2$-D_3 (**1c**) is the most potent metabolite of vitamin D_3 known as regards calcium homeostasis and is considered a true steroid hormone.[2]

Progress in the knowledge of the vitamin D dependent endocrine system owes much to the efforts devoted to the synthesis of vitamin D_3 metabolites and analogues, since considerable amounts of synthetic material are needed to make a complete biological evaluation of every known metabolite. Furthermore, vitamin D_3 analogues (nonnaturally occurring compounds structurally related to vitamin D_3) have been used to characterize the protein receptors and carriers involved in vitamin D_3 metabolism.[3]

Structurally and metabolically related to vitamin D_3 (**1a**) is vitamin D_2 (**2a**), which differs from D_3 only in the nature of the side chain. The metabolism of vitamin D_2 is thought to be identical with that of vitamin D_3,[2,4] in support of which 25-hydroxyvitamin D_2 (25-OH-D_2, **2b**) and 1α,25-hydroxyvitamin D_2 (1,25-$(OH)_2$-D_2, **2c**) have been identified as its major metabolites.[5] Despite its clear relationship with vitamin D_3, the biological significance of vitamin D_2 and its metabolites remains largely unknown[4] due to the scarcity of synthetic metabolites of vitamin D_2, especially of the two major ones, 25-OH-D_2

(1) (a) For previous work with a model system see: Sardina, F. J.; Mouriño, A.; Castedo, L. *Tetrahedron Lett.* **1983**, *24*, 4477–4480. (b) A preliminary account of this work was presented at the Sixth Workshop on Vitamin D, Merano, Italy, 1985. (c) For the sake of consistency and clarity the steroidal numbering is maintained for the secosteroid compounds.

(2) (a) Norman, A. W. "Vitamin D: The Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979. (b) DeLuca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1–65. (c) Jones, H.; Rasmusson, G. H. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 63–121.

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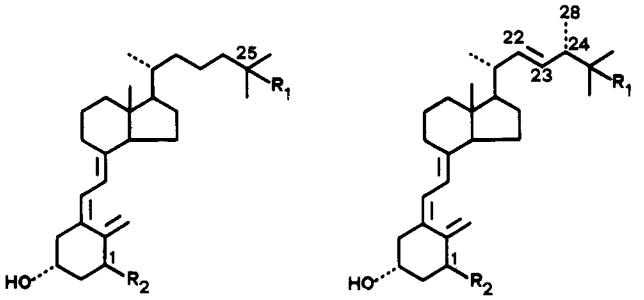
(4) Koshy, K. T. *J. Pharm. Sci.* **1982**, *71*, 137–153.

(5) (a) Jones, G.; Schnoes, H. K.; DeLuca, H. F. *Biochemistry* **1975**, *14*, 1250–1256. (b) Suda, T.; DeLuca, H. F.; Schnoes, H. K.; Blunt, J. W. *Biochemistry* **1969**, *8*, 3515–3520.

0022-3263/86/1951-1264$01.50/0



1a, $R_1=R_2=H$ 2a, $R_1=R_2=H$

1b, $R_1=OH$ $R_2=H$ 2b, $R_1=OH$ $R_2=H$

1c, $R_1=R_2=OH$ 2c, $R_1=R_2=OH$

(**2b**) and 1,25-$(OH)_2$-D_2 (**2c**). The interest in the biological evaluation of these compounds makes them attractive synthetic targets. As a first step in our program to synthesize biologically active metabolites and analogues of vitamin D_2, we have undertaken the synthesis of 25-OH-D_2 (**2b**).

Results and Discussion

The main synthetic problems posed by 25-OH-D_2 are the additional chiral center at C-24 with respect to the vitamin D_3 side chain and the generation of the characteristic triene system. At the time we embarked on this project the available syntheses[6] of 25-OH-D_2 (**2b**) had failed to introduce the chiral C-24 center in a stereodefined way.[7] Moreover, all syntheses published hitherto have made use of the very low-yielding photochemical approach[6,7] to generate the triene moiety of the vitamin. The approach to 25-OH-D_2 (**2b**) presented here overcomes these difficulties. The introduction of the 28-methyl group in a stereoselective fashion[7] takes advantage of the stereospecific syn displacement of primary carbamates by cuprates[8] (Figure 1). The stereochemistry of the newly created C-24 chiral center can be effectively controlled by suitable choice of the configuration of the starting carbamate at C-22. The (22*R*) carbamate yields the natural (24*S*) side chain.[1a] The triene system is generated by the Horner–Wittig coupling method developed by Lythgoe.[9] The materials required for these key steps are the carbamate **10a**, the ketone **13**, and the phosphine oxide **14**.[10] Figure 2 illustrates the synthesis of these compounds. Ozonolysis of vitamin D_2 (**2a**) in absolute methanol at −78 °C followed by reduction with $NaBH_4$ gave the crystalline diol **3**[11] in 85% yield. This procedure is experimentally simpler and gives better yields than the previously used ozonolysis procedures.[11]

The aldehyde **6** has previously been prepared from the diol **3** in three steps:[12] benzoylation, selective hydrolysis of the primary benzoate, and oxidation with Collin's reagent. In our work better results were achieved by Kornblum oxidation[13] of the primary tosylate **5** obtained by selective monotosylation of the diol **3** followed by benzoylation of the free hydroxyl group of the resulting hydroxy tosylate **4**. Thus, reaction of **5** with Me_2SO at 150 °C, using *s*-collidine as base, smoothly gave the aldehyde **6** in 80% yield without epimerization of C-20.[12]

The addition of $LiC{\equiv}CC(CH_3)_2OMOM$ (THF, −78 °C) to the carbonyl group of aldehyde **6** took place without any stereoselection, affording an inseparable 1:1 mixture of **7a** and **7b** (NMR). Since our method for the stereospecific

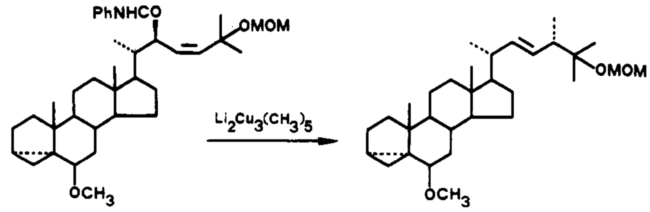


Figure 1.

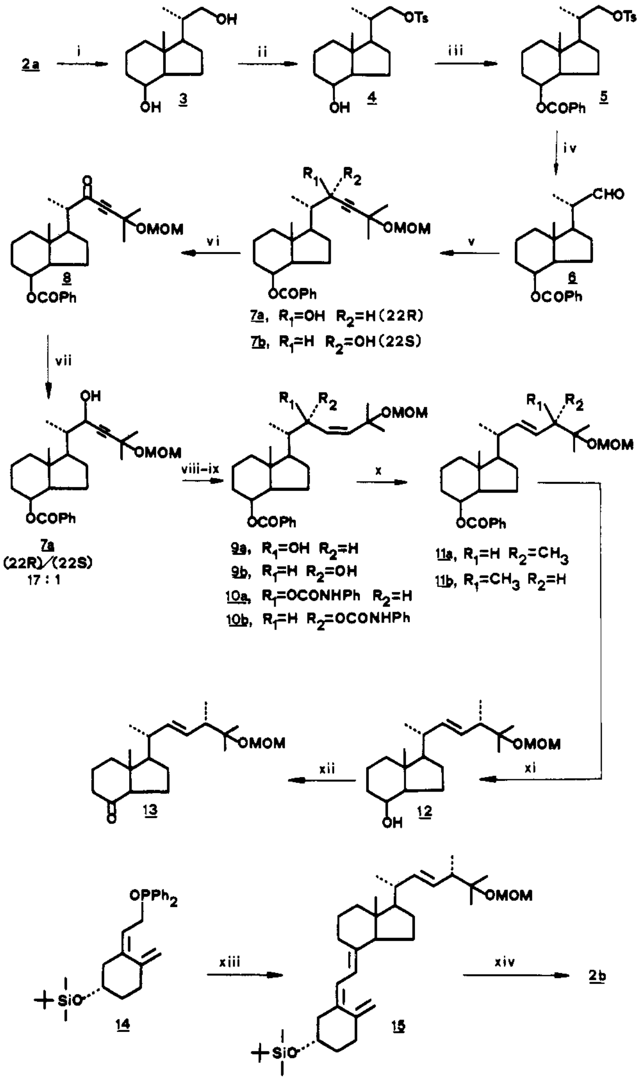


Figure 2. (i) O_3, MeOH–py; $NaBH_4$, 85%. (ii) TsCl, py, 85%. (iii) PhCOCl, py–DMAP, 95%. (iv) Me_2SO, *s*-collidine, 80%. (v) $LiC{\equiv}CC(CH_3)_2OMOM$, THF, 90%. (vi) PDC, CH_2Cl_2, 94%. (vii) $LiAlH_4$-*l*-(−)-*N*-methylephedrine–3,5-dimethylphenol, Et_2O, 94%. (viii) H_2, $Pd/BaSO_4$, quinoline, MeOH; separation, **9a**, 90%, **9b**, 6%. (ix) PhNCO, py–DMAP; **10a**, 95%, **10b**, 96%. (x) $Li_2Cu_3(CH_3)_5$, Et_2O; **11a**, 78%, **11b**, 92%. (xi) $LiAlH_4$, Et_2O, 100%. (xii) PDC, PPTS, CH_2Cl_2, 100%. (xiii) 14 + *n*-BuLi, THF, then 13 94%. (xiv) AG-50WX4, 76%.

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introduction of the 28-methyl group yields the natural (24*S*) configuration only if the (22*R*) carbamate is used as starting material, a method for improving the stereoselectivity of this step was sought. Oxidation of the mixture of **7a,b** with PDC[14] afforded the propargyl ketone **8** in 94% yield [^{13}C NMR, δ 191.13 (C-22)], which was stereoselectively reduced with the complex $LiAlH_4$-*l*-(−)-*N*-methylephedrine-3,5-dimethylphenol developed by Vigneron[15-17] (3 equiv, diethyl ether, −15 °C) to give a 17:1 mixture of **7a** and **7b**, as judged by integration of the H-22 signals in their NMR spectra. The purification of the desired (22*R*) isomer was best carried out at the allylic alcohol stage (**9a,b**). Thus, semihydrogenation of the mixture of **7a,b** over $Pd/BaSO_4$ poisoned with quinoline in methanol, followed by flash chromatography,[18] afforded pure (22*R*) *Z* allylic alcohol **9a** (the more polar isomer) in 71% yield from aldehyde **6**. The ^{13}C NMR spectra of **9a** and **9b** show a marked difference in the chemical shift of C-23: δ 135.39 for **9a** and δ 129.21 for **9b**.[19] An analogous difference has been reported for 22-substituted 23,24-saturated steroids.[20] The required carbamate **10a** was obtained by reaction of **9a** with PhNCO in pyridine using DMAP as catalyst in 95% yield. The ^{13}C NMR spectrum of **10a** shows the signals of the vinylic carbons at δ 128.98 (C-23) and 136.72 (C-24). These same signals appear in the spectrum of **10b**, prepared from **9b** in 96% yield, at δ 122.99 (C-23) and 141.77 (C-24). It is also interesting to note that the methylene protons of the acetal protecting group appear as a nonequivalent AB system in the spectra of alcohols **9a,b** and carbamates **10a,b**.

As in our earlier studies with a model,[1a] the reaction of the (22*R*) allylic carbamate **10a** with $Li_2Cu_3(CH_3)_5$ took place in a stereospecific syn fashion, yielding the benzoate **11a** after 48 h in 78% yield. A less polar byproduct was also detected, probably due to elimination of the oxygenated group at C-25. In order to demonstrate the stereospecificity of the introduction of the 28-methyl group, we subjected the epimeric (22*S*) carbamate **10b** to the syn cuprate displacement to give benzoate **11b** in 92% yield after 4 h. The epimeric benzoates **11a,b** were readily distinguished by their ^{13}C and ^{1}H NMR spectra. The difference in the reactivity of the epimeric carbamates **10a,b** is probably due to the different conformation that the side chains of these molecules must adopt in solution. In this connection, the difference between the chemical shifts of carbons 23 and 24 in the two epimers probably reflects the different steric compression suffered by the reacting (C-24) center.

Interestingly, no attack on the benzoate group has been detected, either during the acetylide coupling[9] or during the complex hydride reduction. This protecting group also resists the conditions of the cuprate displacement (diethyl ether, room temperature), even after 48 h. However, it could be easily and quantitatively removed from **11a,b** by reduction with $LiAlH_4$ in THF at 0 °C. The alcohol **12** thus obtained was oxidized with PDC in CH_2Cl_2 with added PPTS[10] to give ketone **13** quantitatively without epimerization at C-14.

(14) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
(15) (a) Vigneron, J.-P.; Bloy, V. *Tetrahedron Lett.* **1979**, 2683–2686. (b) Vigneron, J.-P.; Jacquet, I. *Tetrahedron* **1976**, *32*, 939–944.
(16) Recently this stereoselective reduction has also been achieved with improved selectivity: Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1984**, *25*, 5981–5984.
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The Horner–Wittig coupling[9] of the phosphine oxide **14**[10] with the ketone **13** yielded the bisprotected form of 25-OH-D_2 (**15**) in a stereoselective fashion in 94% yield. The 7*E*,6*Z* triene was the only product formed, as established by ^{1}H and ^{13}C NMR.

The methoxymethyl and *tert*-butyldimethylsilyl groups were removed simultaneously by treatment of triene **15** with AG 50WX4 ion-exchange resin[21] in deoxygenated methanol at room temperature for 16 h (76% yield). In this way the synthesis of 25-OH-D_2 (**2b**) was completed in 14 steps from vitamin D_2 with an overall yield of 20%.

Experimental Section

General Procedures. NMR spectra were recorded at 250.13 MHz for ^{1}H (δ, Me_4Si, $CDCl_3$) and 62.83 MHz for ^{13}C (δ, $CDCl_3$, carbon multiplicities assigned by INEPT techniques[22]). Melting points are uncorrected. All reactions were performed under an atmosphere of dry, deoxygenated argon, except when otherwise stated. All glassware was dried at 150 °C overnight, assembled hot, and allowed to cool in a stream of dry argon. All transfers of liquid solutions and solvents were performed by syringe techniques or via cannula.[23] All solvents were freshly distilled from the appropriate drying agent before use or stored over 4A molecular sieves.[23] Et_2O and THF were distilled from sodium benzophenone ketyl under argon. CH_2Cl_2 was stirred for 60 h with concentrated sulfuric acid, decanted, washed with water and $NaHCO_3$, dried over $CaCl_2$, filtered, and distilled from P_2O_5. DMF was mixed with benzene (2×) and fractionally distilled. It was further dried by vacuum distillation (2×) from CaH_2 powder with the last distillation onto freshly activated molecular sieves of the type 4A. Me_2SO was vacuum distilled (3×) from CaH_2 powder with the last distillation onto freshly activated molecular sieves of the type 4A. Pyridine was distilled from KOH under nitrogen. Absolute methanol was distilled from Mg turnings. Kugelrohr distillation boiling points (bp) refer to the external air bath temperature.

Ozonolysis of Vitamin D_2. A solution of vitamin D_2 (8.00 g, 20.2 mmol) in absolute methanol (700 mL) and pyridine (7 mL) was placed in an ozonation vessel provided with a magnetic stirring bar. The solution was cooled to −78 °C while purging with N_2. The N_2 flow was stopped, and a stream of ozone was passed until a gray-blue color appeared (2 h and 30 min). The ozone flow was discontinued, and the reaction mixture was purged with N_2 (−78 °C) until no ozone remained in solution (KI test). $NaBH_4$ (2 g) was added in one portion, and the resulting solution was stirred at −78 °C for 20 min while a gentle flow of N_2 was maintained. This operation was repeated twice before the reaction was allowed to reach room temperature overnight. An additional quantity of $NaBH_4$ (1 g) was added at room temperature, and the resulting mixture was stirred for 30 min. The resulting solution was rotary evaporated to a small volume, and the residue was continuously extracted with refluxing ether for 24 h. The ethereal extracts were washed with 5% HCl and H_2O and then dried over Na_2SO_4. Filtration and concentration in vacuo afforded a residue that was flash chromatographed (25% EtOAc/hexanes) to yield diol **3** (5.71 g, 85%). Crystallization from hexane afforded material with melting point 110 °C (lit.[11] mp 109–110 °C).

De-*A*,*B*-23,24-dinor-22-(tosyloxy)cholan-8β-ol (4). A solution of diol **3** (2.60 g, 12.3 mmol) and *p*-TsCl (3.5 g, 18.4 mmol) in pyridine (50 mL) was kept in the refrigerator for 14 h. Addition of ice resulted in a suspension that was extracted with EtOAc/hexanes. The organic extracts were washed with 5% aqueous HCl, H_2O, and saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Removal of solvents in vacuo afforded a residue that was crystallized from hexane to yield 4.2 g of tosylate **4**: 93%; mp 94–95 °C (lit.[10] mp 94–95 °C).

De-*A*,*B*-8β-(benzoyloxy)-23,24-dinor-22-(tosyloxy)cholane (5). Benzoyl chloride (1.15 mL, 9.95 mmol) was added to an

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ice-cooled solution of tosylate 4 (2.80 g, 7.95 mmol) and DMAP (50 mg) in pyridine (25 mL). The resulting solution was kept in the refrigerator for 14 h. Addition of ice resulted in a suspension that was extracted with EtOAc/hexanes. The organic extracts were washed with 5% HCl, H_2O, 5% H_2NOH, and again H_2O. Following drying ($MgSO_4$) and removal of solvents in vacuo, there was obtained a residue that was chromatographed on silica gel (15% EtOAc/hexanes) to give tosyl benzoate **5**, 3.41 g (95%), syrup.

De-*A*,*B*-8β-(benzoyloxy)-23,24-dinorcholan-22-al (6). A solution of benzoate **5** (4.00 g, 8.51 mmol) and *s*-collidine (1.34 g, 11.06 mmol, distilled under vacuum and stored over 4A molecular sieves) in Me_2SO (50 mL, previously heated at 150 °C for 5 min and allowed to come to room temperature under N_2) was heated to 150 °C (oil bath temperature) during 40 min with magnetic stirring. The reaction mixture was allowed to come to room temperature and extracted several times with EtOAc/hexanes (*Caution*! traces of water should be avoided to prevent hydrolysis of the benzoate group.) until TLC showed that no aldehyde remained in the Me_2SO phase. The resulting extracts were washed with brine, dried over Na_2SO_4, and filtered. Removal of solvents in vacuo afforded a residue that was flash chromatographed (7.5% EtOAc/hexanes) and bulb-to-bulb distilled to give the aldehyde **6**:[11] 2.15 g (80%); bp 153–155 °C (0.05 mmHg).

(22*R*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]cholest-23-yn-22-ol (7a) and (22*S*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]cholest-23-yn-22-ol (7b). A solution of *n*-butyllithium in hexane (1.57 mL, 1.42 M) was added dropwise to a −80 °C cooled solution of $HC_2C(CH_3)_2OMOM$ (347 mg, 2.71 mmol) in THF (30 mL). The resulting solution was stirred at 0 °C for 15 min and then cooled back to −80 °C. A solution of aldehyde **6** (500 mg, 1.59 mmol) in THF (15 mL) was slowly added. The reaction mixture was stirred at the same temperature for 30 min. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl, and the resulting mixture was allowed to come to room temperature. The resulting suspension was transferred to a separatory funnel and decanted. The aqueous phase was extracted with ether. The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and filtered. Removal of solvents under reduced pressure afforded a residue that was filtered through a column of silica gel (12% EtOAc/hexanes) to give an 1:1 mixture of **7a** and **7b** (633 mg, 90% combined yield) as a syrup. This mixture was used directly in the next step: ^1H NMR (mixture) δ 8.1–7.3 (5 H, m, Ar), 5.42 (1 H, br s, H-8), 4.90 (2 H, s, OCH_2O), 4.52 ($^1/_2$ H, br d, H-22 of **7a**), 4.49 ($^1/_2$ H, br d, H-22 of **7b**), 3.40 (3 H, s, CH_3O), 1.52 (6 H, s, CH_3-26 and 27); MS, *m/e* 442 (M^+, 1), 381 (5), 380 (7), 362 (12), 285 (100), 259 (32), 258 (40), 243 (15); IR (CCl_4) 3645, 2375, 1720, 1275, 1150, 1070, 1040 cm^{-1}. Anal. Calcd for $C_{27}H_{38}O_5$: C, 73.26; H, 8.67. Found: C, 73.40; H, 8.73.

De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]cholest-23-yn-22-one (8). Pyridinium dichromate (753 mg, 2.0 mmol) was added to a solution of the mixture **7a,b** (633 mg, 1.43 mmol) obtained in the preceding step in CH_2Cl_2 (10 mL). The resulting orange suspension was stirred at room temperature for 24 h. Ether was added and the resulting suspension was filtered through a short column of Celite. The filtrate was washed (5% HCl, H_2O), dried (Na_2SO_4), and filtered. Removal of solvents under reduced pressure afforded a residue which was filtered through a column of silica gel (7.5% EtOAc/hexanes) to afford **8** (594 mg, 94%) as a syrup: ^1H NMR δ 8.07–7.40 (5 H, m, Ar), 5.42 (1 H, br s, H-8), 4.89 (2 H, s, OCH_2O), 3.41 (3 H, s, CH_3O), 2.59 (1 H, m, H-20), 1.60 (6 H, s, CH_3-26 and -27), 1.24 (3 H, d, *J* = 6.6 Hz, CH_3-21), 1.08 (3 H, s, CH_3-18); ^{13}C NMR δ 191.13 (C-22), 166.39 (C-1 Ar), 132.74 (C=O, Bz), 130.83 (C-2 Ar), 129.52 (C-3 Ar), 128.38 (C-4 Ar), 94.01 (C-24), 93.24 (OCH_2O), 82.44 (C-23), 71.73 (C-8), 70.46 (C-25), 55.52 (CH_3O), 52.18 (C-20), 51.54 (C-14), 51.19 (C-17), 42.23 (C-13), 39.86 (C-12), 30.40 (C-9), 29.27 (C-26 and C-27), 26.10 (C-16), 22.79 (C-15), 17.88 (C-11), 16.03 (C-21), 13.80 (C-18); MS, *m/e* 410 (1), 380 (1), 274 (3), 256 (3), 241 (2), 213 (5), 178 (30); IR 2940, 2215, 1720, 1680, 1270, 1150, 1110, 1040 cm^{-1}. Anal. Calcd for $C_{27}H_{36}O_5$: C, 73.59; H, 8.25. Found: C, 73.71; H, 8.29.

Diastereoselective Reduction of Ketone 8. A solution of *l*-(−)-*N*-methylephedrine (183 mg, 1.27 mmol) in Et_2O (6 mL) was added dropwise over 15 min to a solution of $LiAlH_4$ in THF (0.56 mL, 2.29 M). The reaction mixture was stirred for 30 min at room temperature. A solution of 3,5-dimethylphenol (233 mg, 1.91 mmol) in Et_2O (4 mL) was slowly added over 8 min. Stirring was continued for 2 h at room temperature. The resulting reaction mixture was cooled to −15 °C and then a solution of ketone **8** (280 mg, 0.64 mmol) in Et_2O (2.5 mL) was slowly added over 7 min. The resulting solution was stirred at −15 °C for 10 min. The reaction was quenched by the addition of 5% aqueous NaOH. The resulting suspension was extracted with EtOAc/hexanes. The organic extracts were washed (5% HCl, 5% NaOH, H_2O), dried (Na_2SO_4), and filtered. Removal of solvents under reduced pressure afforded a residue that was filtered through a column of silica gel (12% EtOAc/hexanes) to give a 17:1 mixture (NMR ratio) of **7a** and **7b**, 264 mg (94% combined yield). This mixture was subjected directly to the next step: ^{13}C NMR for **7a**, δ 166.50 (C-1 Ar), 132.71 (C=O), 130.89 (C-2 Ar), 129.55 (C-3 Ar), 128.36 (C-4 Ar), 93.04 (OCH_2O), 86.95 (C-24), 85.79 (C-23), 72.05 (C-8), 70.91 (C-25), 65.06 (C-22), 55.36 (CH_3O), 52.01 (C-17), 51.44 (C-14), 41.78 (C-20), 41.71 (C-13), 39.68 (C-12), 30.43 (C-9), 30.10 (C-26, C-27), 26.33 (C-16), 22.49 (C-15), 17.90 (C-11), 13.43 (C-18), 13.12 (C-21).

(22*R*,23*Z*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]cholest-23-en-ol (9a) and (22*S*,23*Z*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]cholest-23-en-22-ol (9b). A solution of the 17:1 mixture of **7a,b** (210 mg, 0.47 mmol) and quinoline (30 mg) in distilled methanol (20 mL) was hydrogenated over Pd/$BaSO_4$ (10%, 20 mg) at 1.8 psi for 8 min. The resulting suspension was filtered through a short column of Celite, and the solvent was removed under reduced pressure to afford a residue that was flash chromatographed (10% EtOAc/hexanes) to give pure **9a** (190 mg, 90%, more polar compound) and pure **9b** (11 mg, 6%, less polar compound) as syrups.

(22*R*)-9a: ^1H NMR δ 8.15–7.4 (5 H, m, Ar), 5.52 (1 H, dd, *J* = 12.4 and 6.7 Hz, H-23), 5.42 (1 H, d, *J* = 12.4 Hz, H-24), 5.41 (1 H, br s, H-8), 4.77 (1 H, d, *J* = 6.9 Hz, OCH_2O), 4.70 (1 H, d, *J* = 6.6 Hz, H-22), 4.69 (1 H, d, *J* = 6.9 Hz, OCH_2O), 3.38 (3 H, s, CH_3O), 1.39 (3 H, s, CH_3-26 or 27), 1.38 (3 H, s, CH_3-26 or 27), 1.04 (3 H, s, CH_3-18), 0.98 (3 H, d, *J* = 6.5 Hz, CH_3-21); ^{13}C NMR δ 166.35 (C-1 Ar), 135.39 (C-23), 134.22 (C-24), 132.52 (C=O), 131.01 (C-2 Ar), 129.48 (C-3 Ar), 128.24 (C-4 Ar), 91.83 (OCH_2O), 76.64 (C-25), 72.12 (C-8), 68.77 (C-22), 55.36 CH_3O), 52.84 (C-17), 51.51 (C-14), 41.63 (C-13), 40.78 (C-20), 39.86 (C-12), 30.48 (C-9), 28.91 (C-26), 28.63 (C-27), 26.38 (C-16), 22.47 (C-15), 17.92 (C-11), 13.32 (C-18), 12.02 (C-21); IR (CCl_4) 3420, 2940, 1715, 1270, 1140, 1110, 1030 cm^{-1}; MS, *m/e* 382 (1), 357 (1), 313 (5), 285 (11), 260 (10), 163 (100). Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.92; H, 9.09. Found: C, 72.67; H, 9.01.

(22*S*)-9b: ^1H NMR δ 8.04–7.39 (5 H, m, Ar), 5.56 (1 H, dd, *J* = 12.5, 6.4 Hz, H-23), 5.49 (1 H, d, *J* = 12.5 Hz, H-24), 5.39 (1 H, br s, H-8), 4.78 (1 H, d, *J* = 7.2 Hz, OCH_2O), 4.73 (1 H, d, *J* = 7.2 Hz, OCH_2O), 4.58 (1 H, dd, *J* = 6.3, 3.7 Hz, H-22), 3.37 (3 H, s, CH_3O), 1.42 (3 H, s, CH_3-26 or 27), 1.38 (3 H, s, CH_3-26 or 27), 1.07 (3 H, s, CH_3-18), 1.01 (3 H, d, *J* = 6.7 Hz, CH_3-21); ^{13}C NMR δ 166.26 (C-1 Ar), 138.81 (C-24), 132.59 (C=O, Bz), 130.87 (C-2 Ar), 129.51 (C-3 Ar), 129.21 (C-23), 128.34 (C-4 Ar), 91.64 (OCH_2O), 77.15 (C-25), 71.94 (C-8), 68.14 (C-22), 55.55 (CH_3O), 53.24 (C-17), 51.26 (C-14), 42.07 (C-13), 40.26 (C-20), 39.72 (C-12), 30.41 (C-9), 28.60 (C-26), 27.61 (C-27), 26.30 (C-16), 22.54 (C-15), 17.80 (C-11), 13.35 (C-18), 12.23 (C-21); IR (CCl_4) 3420, 2940, 1715, 1270, 1140, 1110, 1030 cm^{-1}; MS, *m/e* 382 (1), 357 (1), 313 (5), 285 (11), 260 (10), 163 (100). Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.92; H, 9.09. Found: C, 73.02; H, 8.90.

(22*R*,23*Z*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]-22-[(phenylcarbamoyl)oxy]cholest-23-ene (10a) and (22*S*,23*Z*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]-22-[(phenylcarbamoyl)oxy]cholest-23-ene (10b). An excess of PhNCO was added at 0 °C to a solution of alcohol **9a** (154 mg, 0.35 mmol) and DMAP (20 mg) in pyridine (4 mL). The resulting solution was stirred at 0 °C overnight. A saturated aqueous solution of $NaHCO_3$ was added. The resulting suspension was filtered, and the residue was washed with several portions of EtOAc/hexanes. The filtrate was washed (5% HCl, H_2O, saturated aqueous solution of $CuSO_4$ and H_2O), dried ($MgSO_4$), and filtered. Removal of solvents in vacuo afforded a residue that was chromatographed on silica gel (12% EtOAc/hexanes) to give carbamate **10a** (184 mg, 95%) as a foam. Under identical reaction conditions, alcohol **9b** afforded carbamate **10b** (96%, foam).

(22*R*)-10a: ^{1}H NMR δ 8.1–7.0 (10 H, m, 2 Ar), 6.58 (1 H, br s, NH), 5.98 (1 H, br s, H-22), 5.44 (2 H, m, H-23 and 24), 5.41 (1 H, br s, H-8), 4.82 (1 H, d, J = 7.4 Hz, OCH_2O), 4.75 (1 H, d, J = 7.4 Hz, OCH_2O), 3.38 (3 H, s, CH_3O), 1.49 (3 H, s, CH_3-26 or 27), 1.41 (3 H, s, CH_3-26 or 27), 1.04 (3 H, s, CH_3-18), 1.04 (3 H, d, J = 6.6 Hz, CH_3-21); MS, m/e 385 (1), 243 (1), 201 (1), 163 (10), 119 (50), 105 (100); IR (CCl_4) 3440, 2940, 1735, 1720, 1600, 1440, 1310, 1270, 1140, 1110, 1070, 1040, 940, 920 cm^{-1}. Anal. Calcd for $C_{34}H_{45}NO_6$: C, 72.43; H, 8.06; N, 2.48. Found: C, 72.60; H, 8.13; N, 2.50.

(22*S*)-10b: ^{1}H NMR δ 8.1–7.0 (10 H, m, 2 Ar), 6.63 (1 H, br s, NH), 5.96 (1 H, dd, J = 9.3, 3.5 Hz, H-22), 5.62 (1 H, d, J = 12.4 Hz, H-24), 5.50 (1 H, dd, J = 12.4, 9.5 Hz, H-23), 5.40 (1 H, br s, H-8), 4.77 (1 H, d, J = 7.4 Hz, OCH_2O), 4.72 (1 H, d, J = 7.4 Hz, OCH_2O), 3.35 (3 H, s, CH_3O), 1.42 (6 H, s, CH_3-26 and 27), 1.03 (3 H, s, CH_3-18), 1.06 (3 H, d, J = 6.1 Hz, CH_3-21); MS, m/e 385 (1), 243 (1), 201 (1), 163 (10), 119 (50), 105 (100); IR (CCl_4) 3400, 2940, 1735, 1720, 1600, 1440, 1310, 1270, 1140, 1110, 1070, 1040, 940, 920 cm^{-1}. Anal. Calcd for $C_{34}H_{45}NO_6$: C, 72.43; H, 8.06; N, 2.48. Found: C, 72.58; H, 8.20; N, 2.60.

(22*E*,24*S*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]ergost-22-ene (11a) and (22*E*,24*R*)-De-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]ergost-22-ene (11b). A solution of MeLi–LiBr complex in Et_2O (1.04 mL, 1.56 M) was added dropwise at 0 °C to a suspension of Cu_2I_2 (185 mg, 0.97 mmol; purified by washing with refluxing THF in a Soxhlet under N_2) in Et_2O (10 mL). The resulting yellow suspension became colorless after stirring for 30 min at 0 °C. A solution of carbamate **10a** (180 mg, 0.32 mmol) in Et_2O (4 mL) was added dropwise at the same temperature. The resulting yellow suspension was stirred for 48 h at room temperature in the absence of light. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl, and the resulting suspension was extracted with EtOAc/hexanes. The organic extracts were washed (5% HCl, H_2O, saturated aqueous solution of $NaHCO_3$), dried ($MgSO_4$), and filtered. Removal of solvents under reduced pressure afforded a residue that was flash chromatographed (7.5% EtOAc/hexanes) to give **11a** (112 mg, 78%) as a syrup: ^{1}H NMR δ 8.1–7.4 (5 H, m, Ar), 5.40 (1 H, br s, H-8), 5.30 (1 H, m, J = 15.2, 7.4 Hz, H-22 or 23), 5.25 (1 H, m, J = 15.2, 7.5 Hz, H-23 or 22), 4.71 (2 H, s, OCH_2O), 3.36 (3 H, s, CH_3O), 1.17 (3 H, s, CH_3-26 or 27), 1.13 (3 H, s, CH_3-26 or 27), 1.06 (3 H, s, CH_3-18), 1.03 (3 H, d, J = 6.6 Hz, CH_3-21 or 28), 0.98 (3 H, d, J = 6.9 Hz, CH_3-21 or 28); ^{13}C NMR δ 166.45 (C-1 Ar), 137.00 (C-23), 132.63 (C=O), 130.96 (C-2 Ar), 129.79 (C-22), 129.53 (C-3 Ar), 128.35 (C-4 Ar), 90.84 (OCH_2O), 78.14 (C-25), 72.17 (C-8), 55.00 (CH_3O), 51.64 (C-17 and C-14), 46.52 (C-24), 41.76 (C-13), 39.84 (C-12 and C-20), 30.47 (C-9), 27.38 (C-16), 24.60 (C-26), 23.02 (C-27), 22.60 (C-15), 20.51 (C-21), 17.97 (C-11), 15.06 (C-28), 13.64 (C-18); MS, m/e 410 (1), 380 (1), 352 (5), 288 (12), 284 (20), 258 (30), 102 (100); HRMS, calcd for $C_{20}H_{32}O$ ($C_{28}H_{42}O_4$–benzoic acid–CH_3OH) 288.2453, found 288.2438. Under identical reaction conditions carbamate **10b** gave (in 4 h) benzoate **11b** as a syrup in 92% yield: ^{1}H NMR δ 8.07–7.41 (5 H, m, Ar), 5.41 (1 H, br s, H-8), 5.28 (1 H, m, J = 15.1, 7.4 Hz, H-22 or 23), 5.26 (1 H, m, J = 15.1, 7.6 Hz, H-23 or 22), 4.72 (2 H, s, OCH_2O), 3.37 (3 H, s, CH_3O), 1.17 (3 H, s, CH_3-26 or 27), 1.15 (3 H, s, CH_3-26 or 27), 1.07 (3 H, s, CH_3-18), 1.03 (3 H, d, J = 6.5 Hz, CH_3-21 or 28), 1.00 (3 H, d, J = 6.9 Hz, CH_3-21 or 28); ^{13}C NMR δ 166.48 (C-1 Ar), 137.27 (C-23), 132.64 (C=O), 131.02 (C-2 Ar), 130.00 (C-22), 129.56 (C-3-Ar), 128.34 (C-4-Ar), 90.90 (OCH_2O), 78.10 (C-25), 72.17 (C-8), 55.01 (CH_3O), 51.70 (C-14, C-17), 46.75 (C-24), 41.80 (C-13), 39.84 (C-12, C-20), 30.50 (C-9), 27.65 (C-16), 24.90 (C-26), 22.92 (C-27), 22.65 (C-15), 20.64 (C-21), 17.97 (C-11), 15.26 (C-28), 13.67 (C-18); MS, m/e 410 (1), 380 (1), 352 (5), 288 (12), 284 (20), 258 (30), 102 (100); HRMS, calcd for $C_{20}H_{32}O$ ($C_{28}H_{42}O_4$–benzoic acid–CH_3OH) 288.2453, found 288.2438.

(22*E*,24*S*)-De-*A*,*B*-25-[(methoxymethyl)oxy]ergost-22-en-8β-ol (12). An excess of solid $LiAlH_4$ was added to an ice-cooled solution of benzoate **11a** (100 mg, 0.23 mmol) in Et_2O (5 mL). The resulting suspension was stirred for 1 h at 0 °C. Ice was added, and the resulting mixture was extracted with EtOAc/hexanes. The organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Removal of solvents under reduced pressure afforded a residue that was bulb-to-bulb distilled to give **12** (78 mg, 100%) as a colorless liquid: bp 150 °C (0.1 mmHg); ^{1}H NMR δ 5.30 (1 H, dd, J = 15.3, 7.5 Hz, H-22 or 23), 5.20 (1 H, dd, J = 15.3, 7.8 Hz, H-22 or 23), 4.72 (2 H, s, OCH_2O), 4.08 (1 H, br s, H-8), 3.37 (3 H, s, CH_3O), 1.17 (3 H, s, CH_3-26 or 27), 1.13 (3 H, s, CH_3-26 or 27), 0.97 (9 H, s and d overlapped, CH_3-18, 21, and 28); ^{13}C NMR δ 137.23 (C-23), 129.67 (C-24), 90.88 (OCH_2O), 78.20 (C-25), 69.31 (C-8), 56.47 (C-14), 55.02 (CH_3O), 52.69 (C-17), 46.57 (C-24), 41.73 (C-13), 40.29 (C-12), 39.71 (C-20), 33.56 (C-9), 27.48 (C-16), 24.63 (C-26), 22.96 (C-27), 22.45 (C-15), 20.46 (C-21), 17.36 (C-11), 15.08 (C-28), 13.63 (C-18); MS, m/e 329 (1), 195 (1), 268 (1), 265 (1), 247 (7), 206 (9), 205 (12), 151 (22), 150 (17), 149 (14). Anal. Calcd for $C_{21}H_{38}O_2$: C, 74.57; H, 11.24. Found: C, 74.71; H, 11.02.

(22*E*,24*S*)-De-*A*,*B*-25-[(methoxymethyl)oxy]ergost-22-en-8-one (13). Pyridinium dichromate (240 mg, 0.70 mmol) was added to a solution of alcohol **12** (78 mg, 0.23 mmol) and pyridinium *p*-toluenesulfonate (10 mg) in CH_2Cl_2 (5 mL). The resulting orange suspension was stirred for 24 h at room temperature. Ether was added, and the resulting suspension was filtered through a short column of Celite. The filtrate was washed with a saturated aqueous solution of $CuSO_4$ and H_2O, dried (Na_2SO_4), and filtered. Removal of solvents under reduced pressure afforded a residue that was bulb-to-bulb distilled to give ketone **13** [77 mg (100%); bp 150 °C (0.1 mmHg)] as a colorless liquid: ^{1}H NMR δ 5.32 (1 H, dd, J = 15.3, 7.5 Hz, H-22 or 23), 5.20 (1 H, dd, J = 15.3, 8.0 Hz, H-22 or 23), 4.68 (2 H, s, OCH_2O), 3.34 (3 H, s, CH_3O), 1.14 (3 H, s, CH_3-26 or 27), 1.10 (3 H, s, CH_3-26 or 27), 1.01 (3 H, d, J = 6.6 Hz, CH_3-21 or 28), 0.95 (3 H, d, J = 6.9 Hz, CH_3-21 or 28), 0.62 (3 H, s, CH_3-18); ^{13}C NMR δ 211.75 (C-8), 136.43 (C-23), 130.41 (C-22), 90.90 (OCH_2O), 78.05 (C-25), 61.98 (C-14), 56.51 (C-17), 55.01 (CH_3O), 49.67 (C-13), 46.65 (C-24), 40.85 (C-12), 39.75 (C-20), 38.82 (C-9), 27.57 (C-16), 24.56 (C-26), 23.93 (C-15), 23.07 (C-27), 20.70 (C-21), 18.99 (C-11), 15.04 (C-28), 12.63 (C-18); MS, m/e 278 (14), 233 (3), 215 (3), 179 (5), 151 (16), 134 (17), 103 (100). Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.94; H, 10.80. Found: C, 74.56; H, 10.75.

25-[(Methoxymethyl)oxy]vitamin D_2 *tert*-Butyldimethylsilyl Ether (15). A solution of *n*-butyllithium in hexane (0.12 mL, 2.53 M) was added dropwise to a −70 °C cooled solution of phosphine oxide **14**[15] (141 mg, 0.31 mmol) in THF (8 mL). The resulting red solution was stirred at the same temperature for 30 min. A solution of ketone **13** (70 mg, 0.21 mmol) in THF (2.5 mL) was then added. The resulting solution was stirred for 90 min at −70 °C and became pale orange. The reaction mixture was allowed to come slowly to room temperature (2 h). A drop of H_2O was added, and the solvents were removed under reduced pressure. The residue was redissolved in EtOAc/hexanes, washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and filtered. Removal of solvents under reduced pressure afforded a residue that was chromatographed on silica gel (5% EtOAc/hexanes) to yield 110 mg of triene **15**: 95%, syrup; ^{1}H NMR δ 6.14 (1 H, br d, J = 11.4 Hz, H-6), 5.98 (1 H, br d, J = 11.4 Hz, H-7), 5.27 (2 H, m, H-22 and 23), 4.99 (1 H, br s, *E*-H-19), 4.76 (1 H, br s, *Z*-H-19), 4.71 (2 H, s, OCH_2O), 3.81 (1 H, m, H-3), 3.35 (3 H, s, CH_3O), 2.82 (1 H, br d, J = 12.0 Hz, H-9), 1.16 (3 H, s, CH_3-26 or 27), 1.12 (3 H, s, CH_3-26 or 27), 0.98 (6 H, 2 d, overlapped CH_3-21 and 28), 0.87 (9 H, s, *t*-BuSi), 0.54 (3 H, s, CH_3-18), 0.05 (6 H, s, Me_2Si); ^{13}C NMR δ 145.51 (C-10), 141.28 (C-8), 137.23 (C-23), 136.42 (C-5), 129.75 (C-22), 121.41 (C-6), 117.95 (C-7), 112.07 (C-19), 90.92 (OCH_2O), 78.20 (C-25), 70.53 (C-3), 56.37 (C-14, C-17), 55.05 (CH_3O), 46.84 (C-4), 46.60 (C-24), 45.66 (C-13), 40.45 (C-12), 40.35 (C-20), 36.34 (C-2), 32.68 (C-1), 28.85 (C-9), 27.71 (C-16), 25.82 (*t*-BuSi), 24.66 (C-26), 23.41 (C-15), 23.02 (C-27), 22.18 (C-11), 20.83 (C-21), 18.07 (C-Si), 15.06 (C-28), 12.29 (C-18), −4.65 and −4.69 (Me_2Si).

25-Hydroxyvitamin D_2 (2b). AG-50WX4 ion-exchange resin (1.5 g, prewashed with methanol) was added to a solution of triene **15** (100 mg, 0.18 mmol) in deoxygenated methanol (20 mL). The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was filtered, and the solvents were removed under reduced pressure. The residue was redissolved in EtOAc, washed with brine (three times), dried ($MgSO_4$), and filtered. Removal of solvents under reduced pressure afforded a residue 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.

Acknowledgment. We gratefully acknowledge the financial support of the Comisión Asesora de Investigación Científica (CAICYT) and the generous gift of vitamin D_2 of Hoffmann la Roche (Basel). We thank Dr. Y. Mazur for the physical data of steroidal model systems. F.J.S. thanks the Ministerio de Educación y Ciencia for the grant of a fellowship.

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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Received September 24, 1985

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

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

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