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An Efficient Stereoselective Synthesis of 1α,24(*R*)-Dihydroxyvitamin D_3 by the Dienyne Route.#

Yagamare Fall, Mercedes Torneiro, Luis Castedo, and Antonio Mouriño*

Departamento de Química Orgánica y Sección de Alcaloides del C.S.I.C. 15706 Santiago de Compostela. Spain

FAX 34-81-595012, E-Mail qomourin@usc.es

Abstract: 1α,24(*R*)-Dihydroxyvitamin D_3 (**5e**) was synthesized. The key step in the preparation of the side-chain was opening of the chiral epoxide **10** by the α-anion of the nitrile **9**. The triene system was synthesized by the dienyne route.

INTRODUCTION

Since the discovery that the hormone 1α,25-dihydroxyvitamin D_3 (**1a**) - the physiologically active form of vitamin D_3 (**1b**) - can induce cell differentiation and inhibit the proliferation of malignant cells, there has been great interest in the synthesis of vitamin D analogues as potential drugs for the treatment of malignant tumours and hyperproliferative skin disorders such as psoriasis.[1] Compounds **2**-**5** (Fig. 1) are examples of synthetic analogues of **1a** that exhibit a high cell-differentiation activity/low calcemic action ratio,[2] which has been suggested to be a precondition of the therapeutic utility of a vitamin D analogue.[1] Among these compounds, the analogues 1α,24(*S*)-dihydroxy-26,27-cyclo-22(*E*)-ene-vitamin D_3 (**5d**, Calcipotriol)[2h,2i] and 1α,24(*R*)-dihydroxyvitamin D_3 (**5e**)[2j] are already used clinically for the treatment of psoriasis.

1α,24(*R*)-Dihydroxyvitamin D_3 (**5e**) has previously been synthesized by the classical photochemical ring opening of steroidal $\Delta^{5,7}$-dienes bearing a suitably functionalized side chain,[3] and by the convergent, palladium-catalysed cyclization approach, recently developed by Trost.[2j,4] Here we report an efficient synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 that uses the convergent dienyne approach originally developed by Lythgoe and coworkers[5] and later improved in our laboratory.[6,7] (Scheme 1).

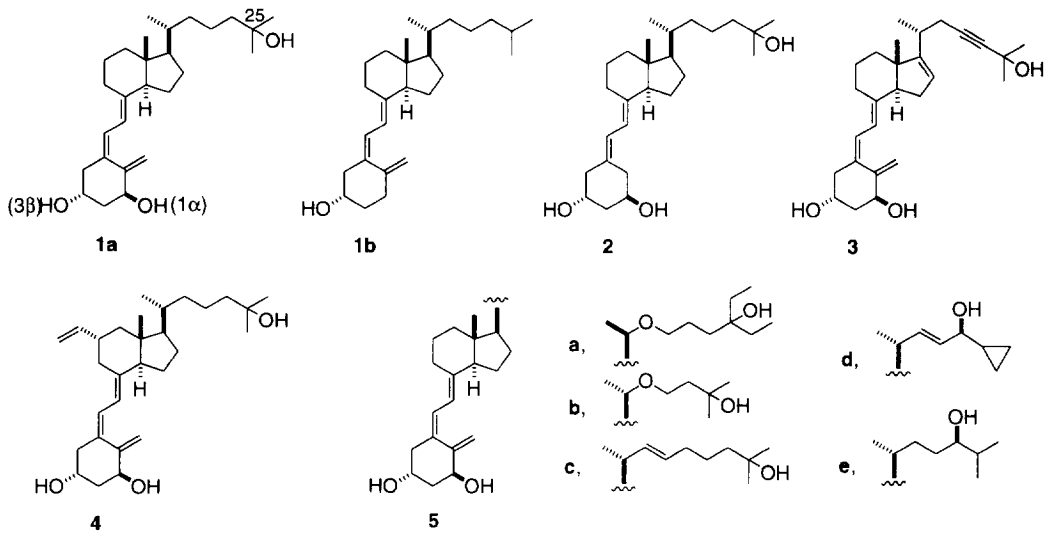
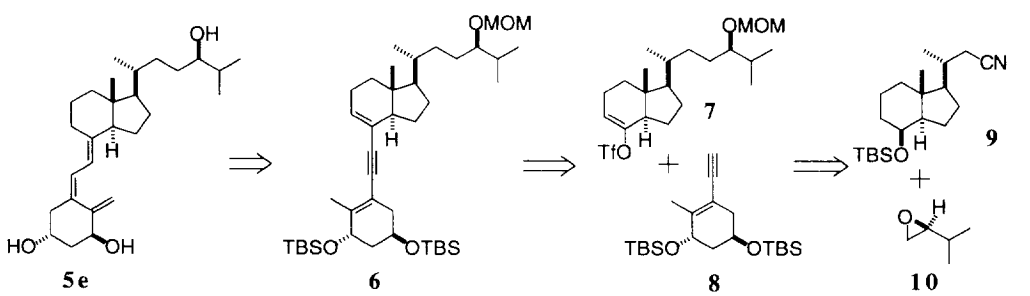


Figure 1. Structures of the hormone 1α,25-$(OH)_2$-D_3, vitamin D_3 and some representative analogues.



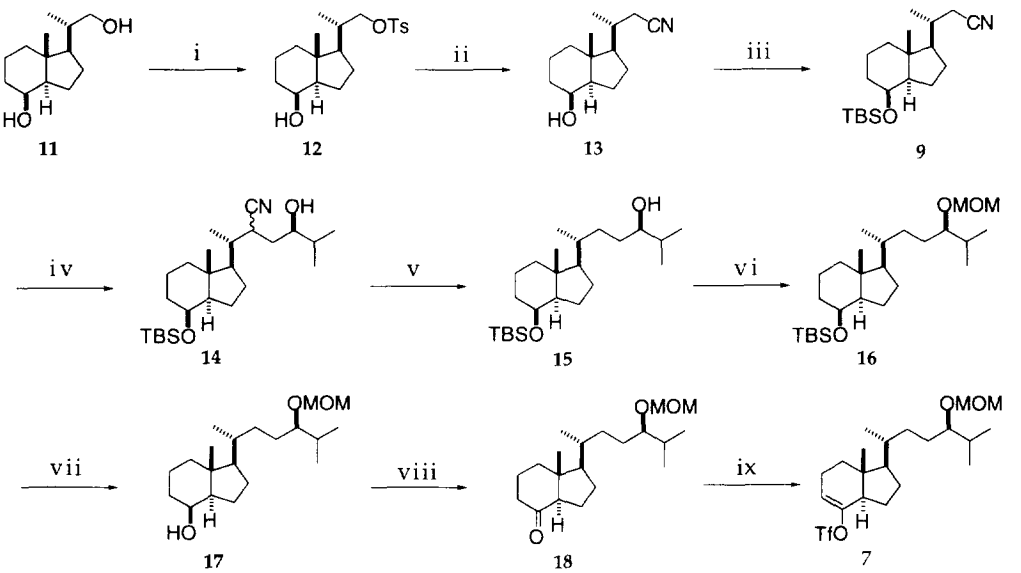
Scheme 1. Retrosynthetic analysis of 1α,24*(R)*-dihydroxyvitamin D_3.

RESULTS AND DISCUSSION

Synthesis of triflate 7 (Scheme 2).

The synthesis starts with the Inhoffen-Lythgoe diol (**11**),[8] which was converted selectively to monotosylate **12**[8,9] in 93% yield by treatment with *p*-toluensulfonyl chloride in the presence of pyridine. Reaction of **12** with sodium cyanide in dimethyl sulfoxide,[10] followed by protection with *tert*-butyldimethylsilyl chloride,[11] afforded nitrile **9**[12] in 89% yield. In the key step, nitrile **9** was deprotonated with lithium diisopropylamide (LDA) in THF at -78 °C and a solution of epoxide **10** (prepared from *L*-valine)[3b] was added to the resulting anion, cleanly affording the hydroxynitrile **14** in 91% yield. Reductive removal of the cyano group of **14** by treatment with potassium in the presence of hexamethylphosphoramide (HMPA) and *tert*-butanol (as

proton source)[13] provided alcohol **15**[12] in 94% yield. Protection of the hydroxyl group of **15** by treatment with chloromethyl methyl ether[14] gave **16** (93%), which was desilylated with tetrabutylammonium fluoride (TBAF) in refluxing THF to afford the alcohol **17** (97%). Oxidation of **17** with pyridinium dichromate (PDC) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane, followed by treatment of the resulting ketone **18** with LDA in THF at -78 °C and trapping of the kinetic enolate with *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$),[15] gave the target vinyl triflate **7** (73%).

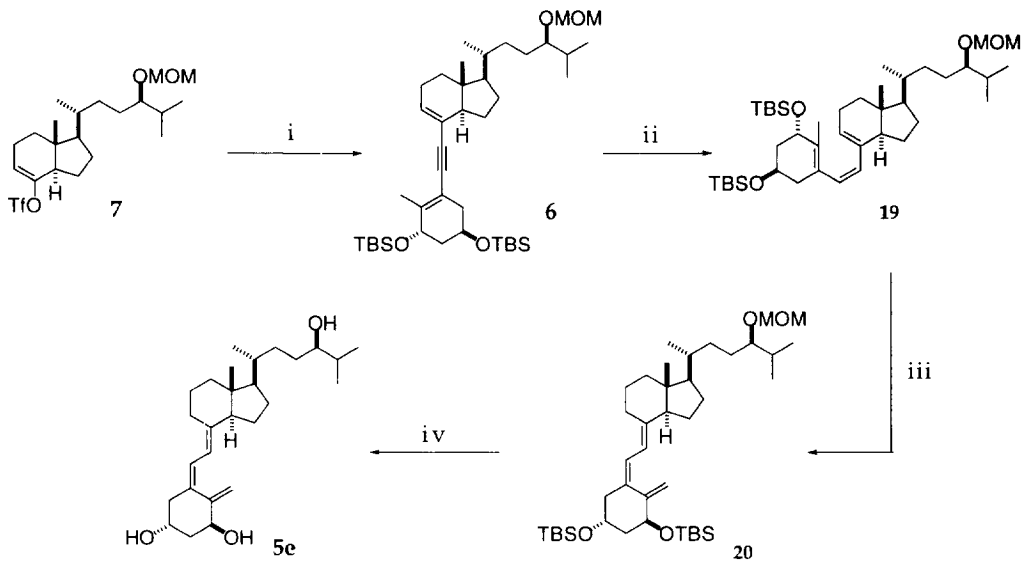


Scheme 2. Reagents: (i) *p*-TsCl (1.1 equiv), py, 0 °C, 12 h (93%); (ii) NaCN, DMSO, 90 °C, 2 h (91%); (iii) *t*-$BuMe_2SiCl$ (TBSCl), imidazole, DMF, 80 °C, 12 h (98%); (iv) LDA, THF, -78 °C, HMPA, epoxide **10**, (91%); (v) *t*-BuOH (2 equiv), HMPA (5 equiv), Et_2O (30 equiv), 0 °C, K in portions (7 equiv), 12 h (94%); (vi) *i*-Pr_2NEt, MOMCl, CH_2Cl_2, 0 °C (93%); (vii) *n*-Bu_4NF, THF, reflux, 18 h (97%); (viii) PDC, CH_2Cl_2, PPTS, rt, 40 h (96%); (ix) LDA, THF, -78 °C, $PhNTf_2$ (76%).

Synthesis of 1α,24*(R)*-dihydroxyvitamin D_3 (Scheme 3).

With triflate **7** in hand, the stage was set for the coupling reaction. Palladium-catalysed cross-coupling between vinyl triflate **7** and enyne **8**[16] afforded dienyne **6** (92%). Partial hydrogenation of **6** under a low (balloon) pressure of H_2 and in the presence of Lindlar palladium catalyst poisoned with quinoline in hexanes, with careful monitoring of the reaction by TLC to avoid overreduction, gave previtamin D **19** (83%). Thermal isomerization of **19** to the protected vitamin **20**, followed by deprotection by successive treatment with TBAF and a cation exchange resin in methanol, and purification by flash chromatography, afforded the desired

1α,24(*R*)-dihydroxyvitamin D_3 (**5e**) (80%).



Scheme 3. Reagents: (i) Enyne **8**, $(Ph_3P)_2PdCl_2$, Et_3N, DMF, 70 °C, 2 h (92%); (ii) H_2, Lindlar catalyst, quinoline, 30 min (83%); (iii) isooctane, 80 °C, 4 h, (94%); (iv) *n*-Bu_4NF, THF, rt, 20 h; then AG 50W-X4, MeOH, rt (80%).

CONCLUSION

1α,24(*R*)-dihydroxyvitamin D_3 (**5e**) was prepared in 13 steps and 27% yield from the Inhoffen-Lythgoe diol (**11**) in an efficient stereoselective synthesis that compares very favourably with other syntheses.[2j] The nitrile approach[17] to the side chain proved an efficient and general method for the synthesis of key intermediates for coupling with enynes containing vitamin D **A**-ring moieties.

EXPERIMENTAL

General. All dry solvents were distilled under argon. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Dichloromethane was distilled from phosphorus pentoxide, and pyridine from KOH. Triethylamine (Merck), *N,N*-diisopropylethylamine (Aldrich), diisopropylamine (Merck) and *tert*-butanol (Merck) were distilled from CaH_2. Dry dimethylformamide (DMF, Merck), hexamethylphosphoramide (HMPA, Aldrich) and dimethylsulfoxide (DMSO, Aldrich) were stored over type 4Å molecular sieves. All reactions were conducted under an argon atmosphere unless otherwise stated. Dry solvents were used for all reactions. Melting points were determined in a capillary tube and are uncorrected. ^1H and ^{13}C

NMR spectra were recorded in $CDCl_3$ in a Bruker WM-250 or AMX 300; chemical shifts are given in δ units with respect to tetramethylsilane as internal standard. In the ^{13}C NMR spectra, carbon types were determined by means of DEPT experiments. IR spectra were recorded in a Perkin Elmer 1420 spectrometer. Mass spectra were measured in a Kratos MS-50 apparatus, using electron impact ionization at 70 eV, unless otherwise stated. Flash chromatography was performed on silica gel by Still's method.[18] Solutions were dried over Na_2SO_4 anhydrous, and concentrated in a rotavapor. TLC was performed on silica gel plates; components were located by illuminating the plates with UV light and/or by treating the plates with phosphomolybdic acid reagent followed by heating.

De-A,B-8β-Hydroxy-23,24-dinorcholane-22-carbonitrile (13). Sodium cyanide (268 mg, 5.46 mmol) was added to a solution of tosylate **12** (1g, 2.7 mmol) in DMSO (35 mL) and heated at 90 °C for 2 h. The mixture was allowed to cool to rt, diluted with water (100 mL) and then extracted with Et_2O (4x50 mL). The ethereal phase was dried and concentrated. Recrystallization of the residue (Et_2O/hexanes) afforded **13** [551 mg, 91%. Rf (40% EtOAc/hexanes): 0.57. White crystals (mp 80-85 °C)]. **^{1}H NMR**: 4.04 (1H, brs, H-8), 2.32 (1H, dd, J_1= 12.7 Hz, J_2=4.0 Hz, CHCN), 2.22 (1H, dd, J_1= 12.7 Hz, J_2=6.7 Hz, CHCN), 1.10 (3H, d, J= 6.6 Hz, CH_3-21), 0.92 (3H, s, CH_3-18). **^{13}C NMR**: 118.83 (CN), 68.75 (CH-8), 55.09, 52.28, 41.78 (C-13), 39.91 (CH_2), 33.38 (CH_2), 32.88, 26.88 (CH_2), 24.46 (CH_2), 22.24 (CH_2), 19.00, 17.15 (CH_2), 13.45. **IR** (KBr) 3554, 2238 cm.$^{-1}$ **LRMS** m/z (I,%): 221 (M^+, 4), 206 (56), 188 (14), 162 (12), 150 (13), 135 (15), 111 (100). **HRMS**: calcd. for $C_{14}H_{23}NO$, 221.1779; found 221,1781. **Anal**: calcd. for $C_{14}H_{23}NO$, C 75.97, H 10.47, N 6.33%; found, C 76.13, H 10.67, N 6.46%.

De-A,B-8β-[(*tert*-Butyldimethylsilyl)oxy]-23,24-dinorcholane-22-carbonitrile (9). Imidazole (433 mg, 6.3 mmol) and TBSCl (542 mg, 3.59 mmol) were successively added to a solution of alcohol **13** (429 mg, 1.9 mmol) in DMF (3.8 mL). The mixture was stirred at 80 °C for 12 h and then cooled to rt and transferred to a separatory funnel containing water (50 mL). The mixture was extracted with hexanes (3x50 mL), and the combined extracts were washed with brine (3x50 mL), then water (3x50 mL), and then dried, filtered and concentrated to a residue, which was flash chromatographed (0-5% hexanes/EtOAc) to give **9** [627 mg, 98%. Rf (40% EtOAc/hexanes): 0.80. Colorless oil]. **^{1}H NMR**: 3.99 (1H, bs, H-8), 2.33 (1H, dd, J_1= 12.6 Hz, J_2= 3.9 Hz, CHCN), 2.21 (1H, dd, J_1= 12.8 Hz, J_2= 6.6 Hz, CHCN), 1.10 (3H, d, J= 6.6 Hz, CH_3-21), 0.91 (3H, s, CH_3-18), 0.86 [9H, s, $SiC(CH_3)_3$], 0.01 [6H, s, $Si(CH_3)_2$]. **^{13}C NMR**: 118.61 (CN), 69.03 (CH-8), 55.18, 52.63, 41.94 (C-13), 40.11 (CH_2), 33.99 (CH_2), 32.85, 26.90 (CH_2), 25.54 [$SiC(\underline{C}H_3)_3$], 24.36 (CH_2), 22.65 (CH_2), 18.94, 17.71(SiC), 17.28 (CH_2), 13.57, -5.09 ($SiCH_3$), -5.46 ($SiCH_3$). **IR** (film): 2246 cm.$^{-1}$ **HRMS** (FAB): calcd. for $C_{20}H_{37}NOSiN$, 358.2542; found, 358.2555.

De-A,B-(24*R*,22ξ)-8β-[(*tert*-Butyldimethylsilyl)oxy]-24-hydroxy-cholestane-22-carbonitrile (14). A solution of *n*-butyllithium in hexanes (2.4 M, 0.441 mL, 1.06 mmol) was added under argon to a stirred solution of diisopropylamine (0.184 mL, 1.30 mmol) in THF (4 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min, then at 0 °C for 30 min, whereupon a solution of nitrile **9** (308 mg, 0.917 mmol) in THF (3 mL) was added. The mixture was cooled to -78 °C and stirred for 1 h. Epoxide **5** [prepared *in situ* from the corresponding tosylate (946 mg, 3.67 mmol) and LDA (3.44 mL) at -78 °C][3b] and HMPA (0.353 mL) were successively added, and the resulting mixture was stirred at -60 °C for 3 h, then at rt for 4 h. Saturated NH_4Cl solution (10 mL) was added. The mixture was extracted with Et_2O (3x20 mL), and the combined organic extracts were dried, filtered and concentrated. The residue was flash chromatographed (5% EtOAc/hexanes) to afford alcohol **14** [52 mg, 91%. Rf (10% EtOAc/hexanes): 0.52. Colorless oil; mixture of diastereoisomers]. **^{1}H NMR**: 3.99 (1H, brs, H-8), 3.43 (1H, m, H-24), 2.97 (1H, m, H-22), 1.02 (3H, d, *J*= 6.6 Hz, CH_3-21), 0.94 (9H, m, CH_3-18, CH_3-26, CH_3-27), 0.88 [9H, s, $SiC(CH_3)_3$], 0.01 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$). **^{13}C NMR**: 121.85 (CN), 73.58 (CH-24), 69.29 (CH-8), 54.65, 52.83, 42.18 (C-13), 40.43 (CH_2), 36.04, 34.40 (CH_2), 34.21 (CH_2), 33.81, 32.32, 27.06 (CH_2), 25.74 [$SiC(\underline{C}H_3)_3$], 22.82 (CH_2), 18.54, 17.94, 17.51 (CH_2), 17.14, 14.12, 13.90, -4.86 ($SiCH_3$), -5.26 ($SiCH_3$). **IR** (film): 3446, 2236 cm.$^{-1}$ **LRMS** m/z (I,%): 406 (M^+-CH_3, 2), 364 (100), 272 (14), 161 (22).

De-A,B-(24*R*)-8β[(*tert*-Butyldimethylsilyl)oxy]-cholestan-24-ol (15). A solution of nitrile **14** (839 mg, 1.99 mmol) in *tert*-butanol (0.400 mL) and Et_2O (2.5 mL) was added to a stirred suspension of potassium (370 mg, excess) in HMPA (2 mL) and Et_2O (2 mL) at 0 °C. The mixture was stirred at 0 °C for 12 h, then at rt until the end of the reaction (monitoring by TLC, ca. 1 h). The excess potassium was removed from the flask, and the mixture was cooled to -78 °C and quenched with cold water (20 mL) under argon. The mixture was allowed to warm to rt, and then extracted with Et_2O (3x20 mL). The organic layers were combined, dried and concentrated. The residue was flash chromatographed (4% EtOAc/hexanes) to give alcohol **15** [740 mg, 94%. Rf (10% EtOAc/hexanes): 0.32. Colorless oil]. **^{1}H NMR**: 4.01 (1H, bs, H-8), 3.30 (1H, m, H-24), 0.93-0.89 (12H, m, CH_3-18, CH_3-21, CH_3-26, CH_3-27), 0.88 [9H, s, $SiC(CH_3)_3$], 0.01 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$). **^{13}C NMR**: 77.00 (CH-24), 69.46 (CH-8), 56.72, 53.04, 42.08 (C-13), 40.69 (CH_2), 35.14, 34.40 (CH_2), 33.46, 31.85 (CH_2), 30.57 (CH_2), 27.27 (CH_2), 25.72 [$SiC(\underline{C}H_3)_3$], 22.99 (CH_2), 18.80, 18.50, 17.92 (SiC), 17.59 (CH_2), 17.10, 13.64, -4.92 ($SiCH_3$), -5.27 ($SiCH_3$). **IR** (film): 3300 cm.$^{-1}$ **LRMS** m/z (I,%): 396 (M+, 0.6), 339 (8), 247 (52), 135 (100). **HRMS**: calcd. for $C_{24}H_{48}O_2Si$, 396.3423; found, 396.3435.

De-A,B-(24*R*)-8β[(*tert*-Butyldimethylsilyl)oxy]-cholestan-24-ol Methoxymethyl ether (16). *N*,*N*-diisopropylethylamine (0.227 mL, 1.3 mmol) and chloromethyl methyl ether[16] (0.102 mL, 1.24) were successively added to a cooled (0 °C) solution of alcohol **15** (112 mg, 0.282 mmol) in CH_2Cl_2 (1.5 mL). The mixture was allowed to warm to rt while stirring overnight, then poured into ice-water and extracted with CH_2Cl_2 (3x10 mL). The organic extracts were combined and washed successively with HCl (5%, 20 ml), saturated Na_2CO_3 solution (20 mL), and brine (20 mL). The organic phase was dried, filtered and concentrated to a residue, which was flash chromatographed (1% EtOAc/hexanes) to afford the ether **16** [115 mg, 93%. Rf (10% EtOAc/hexanes): 0.68. Colorless oil]. **^{1}H NMR**: 4.65 (2H, s, OCH_2O), 3.99 (1H, brs, H-8), 3.39 (3H, s, OCH_3), 3.25 (1H, m, H-24), 0.91-0.88 [21H, m, CH_3-18, CH_3-21, CH_3-26, CH_3-27, $SiC(CH_3)_3$], 0.01 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$). **^{13}C NMR**: 96.16 (OCH_2O), 83.42 (CH-24), 69.52 (CH-8), 56.80, 55.52, 53.09, 42.11 (C-13), 40.73 (CH_2), 35.41, 34.44 (CH_2), 31.36 (CH_2), 31.00, 27.27 (CH_2), 27.06 (CH_2), 25.76 [$SiC(\underline{C}H_3)_3$], 23.03 (CH_2), 18.54, 18.17, 17.96, 17.61 (CH_2), 13.65, -4.90 ($SiCH_3$), -5.25 ($SiCH_3$). **HRMS**: calcd. for $C_{26}H_{52}O_3Si$, 440.3686; found, 440.3687.

De-A,B-(24*R*)-8β–Hydroxy-cholestan-24-ol Methoxymethyl ether (17). A mixture of **16** (590 mg, 1.34 mmol), TBAF (3.7 g, 14.2 mmol) and THF (12 mL) was refluxed for 18 h. The reaction mixture was cooled to rt and poured into brine (50 mL). The mixture was extracted with Et_2O (3x50 mL). The combined organic extracts were dried and filtered, and then concentrated to a residue, which was purified by flash chromatography (4-15% EtOAc/hexanes) to give the deprotected alcohol **17** [423 mg, 97%. Rf (15% EtOAc/hexanes): 0.28. Colorless oil]. **^{1}H NMR**: 4.61 (2H, s, OCH_2O), 4.04 (1H, brs, H-8), 3.36 (3H, s, OCH_3), 3.25 (1H, m, H-24), 0.91 (3H, s, CH_3-18), 0.88 (3H, d, *J*= 6.5 Hz, CH_3-21), 0.874 (3H, d, *J* = 6.8 Hz, CH_3-26), 0.870 (3H, d, *J*=6.8 Hz, CH_3-27). **^{13}C NMR**: 96.10, 83.34, 69.28, 56.59, 55.50, 52.58, 41.79, 40.36, 35.31, 33.56, 31.29, 30.93, 27.07, 26.93, 22.43, 18.42, 18.15, 17.88, 17.34, 13.40. **IR** (film): 3675 cm^{-1}. **HRMS**: calcd. for $C_{20}H_{38}O_3$, 326.2821; found, 326.2819.

De-A,B-(24*R*)-24-[(Methoxymethyl)oxy]-cholestan-8-one (18). PDC (1.13 g, 3.01 mmol) and PPTS (10 mg) were added to a solution of alcohol **17** (356 mg, 1.09 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The reaction mixture was stirred at this temperature for 16 h. More PDC (0.52 g, 1.38 mmol) and PPTS (10 mg) were added and stirring was continued for 24 h at 0 °C. Then Et_2O (20 mL) was added and the resulting suspension was filtered through a short pad of Celite and silica gel. The filtrate was concentrated to a residue, which was purified by flash chromatography (12% EtOAc/hexanes) to give the desired ketone **18** [339 mg, 96%. Rf (15% EtOAc/hexanes): 0.43. Colorless oil]. **^{1}H NMR** (300 MHz): 4.64 (2H, s, OCH_2O), 3.38 (3H, s, OCH_3), 3.25 (1H, m, H-24), 0.95 (3H, d, *J*= 6.0 Hz, CH_3-21), 0.891 (3H, d, *J*= 6.8 Hz, CH_3-26),

0.888 (3H, d, *J*=6.8 Hz, CH_3-27), 0.63 (3H, s, CH_3-18). **^{13}C NMR**: 211.94 (C-8), 96.14 (OCH_2O), 83.26 (CH-24), 61.91, 56.59, 55.55, 49.82 (C-13), 40.86 (CH_2), 38.92 (CH_2), 35.57, 31.34 (CH_2), 30.92, 27.42 (CH_2), 26.89 (CH_2), 23.94 (CH_2), 18.98 (CH_2), 18.59, 18.18, 17.82, 12.37. **HRMS** (FAB): calcd. for $C_{20}H_{36}O_3Na$, 347.2562; found, 347.2553.

De-A,B-(24*R*)-24-[(Methoxymethyl)oxy]-cholest-8-en-8-yl Trifluoromethanesulfonate (7). Lithium diisopropylamide (LDA) was prepared by adding diisopropylamine (0.133 mL, 0.95 mmol) to a solution of *n*-BuLi in hexane (2.25 M, 0.40 mL, 0.90 mmol) and THF (1.5 mL) at -78 °C. After stirring the solution for 10 min at -78 °C, then 20 min at rt, it was again cooled to -78 °C and a solution of ketone **18** (192 mg, 0.592 mmol) in THF (3 mL) was added dropwise *via* cannula. After stirring for 1 h, the enolate solution was warmed to room temperature over a further 1 h and then recooled to -78 °C. A solution of *N*-phenyltriflimide (340 mg, 0.95 mmol) in THF (1 mL) was added and the reaction mixture was allowed to warm to rt overnight. The reaction was then quenched by adding a few drops of MeOH. Concentration of the mixture, followed by purification of the resulting residue by flash chromatography gave triflate **7** [204 mg, 76%. Rf (6% EtOAc /hexanes): 0.37. Colorless oil]. **^{1}H NMR**: 5.56 (1H, q, *J*= 3.4 Hz, H-9), 4.64 (2H, s, OCH_2O), 3.38 (3H, s, OCH_3), 3.26 (1H, m, H-24), 0.94 (3H, d, *J*= 6.3 Hz, CH_3-21), 0.90 (3H, d, *J*= 6.8 Hz, CH_3-26), 0.89 (3H, d, *J*=6.8 Hz, CH_3-27), 0.76 (3H, s, CH_3-18). **^{13}C NMR**: 149.92 (C-8), 118.57 (q, $J_{C\text{-}F}$= 320.4 Hz, CF_3), 115.99 (CH-9), 96.11 (OCH_2O), 83.21 (CH-24), 55.50, 54.17, 50.04, 45.15 (C-13), 36.01, 34.76 (CH_2), 31.29 (CH_2), 30.89, 28.19 (CH_2), 26.85 (CH_2), 23.71 (CH_2), 21.34 (CH_2), 18.45, 18.16, 17.76, 11.15. **LRMS** m/z (I, %): 413 [M^+-$CH(CH_3)_2$, 2], 394 (M^+-$HOCH_2OCH_3$, 10), 381 (14), 327 (11), 295 (23), 263 (43).

(24*R*)-1α-[(*tert*-Butyldimethylsilyl)oxy]-6,7-didehydro-24-[(methoxymethyl)oxy]-previtamin D$_3$ *tert*-Butyldimethylsilyl ether (6). A mixture of enyne **8** (55 mg, 0.14 mmol), triflate **7** (57 mg, 0.125 mmol), Et_3N (0.05 mL, 0.36 mmol), *bis*-triphenylphosphine palladium dichloride (3 mg, 0.0045 mmol, 3.6%) and DMF (1 mL) was heated at 70 °C for 2 h and then cooled to rt. Et_2O (20 mL) was added and the resulting mixture was washed with water (2x20 mL). The aqueous washings were re-extracted with Et_2O (20 mL). The combined organic extracts were dried, filtered and concentrated to a residue, which was purified by flash chromatography (2% EtOAc/hexanes) to afford **6** [79 mg, 92%. Rf (6% EtOAc /hexanes): 0.48. Viscous unstable liquid that must be kept as a cold solution in hexanes in order to avoid its decomposition]. **^{1}H NMR**: 5.96 (1H, m, H-9), 4.65 (2H, s, OCH_2O), 4.18 (1H, m, H-1), 4.08 (1H, m, H-3), 3.39 (3H, s, OCH_3), 3.27 (1H, m, H-24), 1.89 (3H, b s, CH_3-19), 0.94 (3H, d, *J*= 6.3 Hz, CH_3-21), 0.89 [24H, m, CH_3-26, CH_3-27, $2SiCH(C\underline{H}_3)_3$], 0.70 (3H, s, CH_3-18), 0.09 [6H, s, $Si(CH_3)_2$], 0.06 [6H, m, $2Si(C\underline{H}_3)_2$].

^{13}C NMR (CD_2Cl_2): 149.05 (C), 141.74 (C), 135.62 (C), 123.62 (CH), 118.35 (CH), 111.55 (CH_2-19), 96.60 (OCH_2O), 83.70 (CH-24), 72.46 (CH), 68.05 (CH), 56.98, 56.79, 55.77, 46.44 (CH_2), 46.21 (C-13), 45.33 (CH_2), 41.05 (CH_2), 36.71, 31.94 (CH_2), 31.44, 29.30 (CH_2), 28.06 (CH_2), 27.43 (CH_2), 26.04 [2SiC($\underline{C}H_3$)$_3$], 23.96 (CH_2), 22.60 (CH_2), 19.05, 18.52 (2Si$\underline{C}$), 18.40, 18.22, 12.15, -4.57 ($SiCH_3$), -4.60 ($SiCH_3$), -4.70 ($SiCH_3$), -4.92 ($SiCH_3$). **LRMS**, m/z (I,%): 689 (M^++1, 5), 688 (M^+, 8), 558 (10), 557 (24), 556 (47). **HRMS**: calcd. for $C_{41}H_{76}O_4Si_2$, 688.5282; found, 688.5236.

1α,24(*R*)-Dihydroxyvitamin D_3 (5e). A mixture of protected vitamin **20** (68 mg, 0.099 mmol), TBAF (740 mg, 3 mmol) and THF (3 mL) was stirred in the dark for 20 h. The mixture was poured into a saturated solution of NH_4Cl (**^{13}C NMR**: 140.44 (C), 133.31 (CH-9), 122.65 (C), 115.57 (C), 96.16 (OCH_2O), 92.45 (C), 88.17 (C), 83.35 (CH-24), 70.04 (CH), 64.22 (CH), 55.61, 54.68, 50.13, 41.84 (C-13), 41.28 (CH_2), 39.81 (CH_2), 36.30, 35.90 (CH_2), 31.43 (CH_2), 30.96, 27.98 (CH_2), 27.00 (CH_2), 25.86 [SiC($\underline{C}H_3$)$_3$], 25.76 [SiC($\underline{C}H_3$)$_3$], 25.13 (CH_2), 24.14 (CH_2), 19.10, 18.64, 18.26, 18.07 (SiC), 17.96, 11.01, -4.38 ($SiCH_3$), -4.70 ($SiCH_3$), -4.76 ($SiCH_3$), -4.87 ($SiCH_3$). **LRMS** m/z (I,%): 686 (M^+, 1), 672 (2), 671 (3), 643 (2), 611 (3), 555 (76), 554 (100). **HRMS**: calcd. for $C_{41}H_{74}O_4Si_2$, 686.5126; found, 686.5070.

1α-[(*tert*-Butyldimethylsilyl)oxy]-24*R*-[(methoxymethyl)oxy]-previtamin D_3 *tert*-Butyldimethylsilyl ether (19). To a solution of dienyne **6** (53 mg, 0.077 mmol) in hexane (20 mL) was added 0.15 mL of a solution of quinoline in hexane (0.1 mL of quinoline in 20 mL of hexane), followed by Lindlar catalyst (53 mg, Aldrich). After purging the suspension with H_2, the solution was stirred under a slightly positive pressure of H_2 until TLC (6% EtOAc/hexanes) indicated that all the starting material had reacted (monitoring by TLC is a convenient way of avoiding overhydrogenation). After 30 min, all of **6** had been converted to a product with a slightly higher Rf, and the reaction mixture was filtered and concentrated to a residue, which was purified by flash chromatography (2% EtOAc/hexanes) to afford previtamin **19** [44 mg, 83%. Rf (6% EtOAc /hexanes): 0.53. Colorless oil]. This compound slowly converts to the vitamin D form **20** at rt (small peaks corresponding to **20** can be appreciated in the NMR spectra). **^{1}H NMR** (CD_2Cl_2): 5.87 and 5.72 (2H, AB pattern, d, *J*= 12.0 Hz, H-6, H-7), 5.52 (1H, m, H-9), 4.59 (2H, s, OCH_2O), 4.11 (1H, bt, H-1), 4.05 (1H, m, H-3), 3.33 (3H, s, OCH_3), 3.22 (1H, m, H-24), 1.63 (3H, b s, CH_3-19), 0.94 (3H, d, *J*= 6.3 Hz, CH_3-21), 0.86 [21H, m, CH_3-26, CH_3-27, 2SiCH($C\underline{H}_3$)$_3$], 0.68 (3H, s, CH_3-18), 0.08 [6H, s, $Si(CH_3)_2$], 0.03 [6H, m, $Si(CH_3)_2$]. **^{13}C NMR** (CD_2Cl_2): 136.76 (C), 130.98 (C), 130.32 (C), 130.20 (CH), 129.00 (CH), 125.55 (CH), 96.58 (OCH_2O), 83.68 (CH-24), 71.70 (CH), 65.43 (CH), 55.75, 54.85, 51.13, 42.53 (C-13), 42.31 (CH_2), 39.53 (CH_2), 36.71, 36.55 (CH_2), 31.94 (CH_2), 31.41, 28.69 (CH_2), 27.46 (CH_2), 26.09 [SiC($\underline{C}H_3$)$_3$], 26.02 [SiC($\underline{C}H_3$)$_3$], 25.30 (CH_2), 23.88 (CH_2), 18.93, 18.37, 18.17,

17.69, 11.44, -4.19 ($SiCH_3$), -4.51 ($SiCH_3$), -4.60 ($SiCH_3$), -4.75 ($SiCH_3$).

1α-[(*tert*-Butyldimethylsilyl)oxy]-24*R*-[(methoxymethyl)oxy]-vitamin D_3 *tert*-Butyldimethylsilyl ether (20). A solution of previtamin **19** (80 mg, 0.116 mmol) in isooctane (10 mL) was refluxed in the dark for 4 h, and then concentrated to a residue, which was purified by flash chromatography (2% EtOAc/hexanes) to afford **20** [75 mg, 94%. Rf (6% EtOAc/hexanes): 0.53. Colorless oil]. A small amount of the previtamin **19** is observed in the NMR spectra. **^{1}H NMR** (CD_2Cl_2): 6.25 and 6.01 (2H, AB pattern, d, *J*= 11.3 Hz, H-6, H-7), 5.17 (1H, m, H-19*E*), 4.83 (1H, d, *J*= 2.6 Hz, H-19*Z*), 4.59 (2H, s, OCH_2O), 4.37 (1H, dd, J_1=4.0, J_2=6.6 Hz, H-1), 4.18 (1H, m, H-3), 3.33 (3H, s, OCH_3), 3.22 (1H, m, H-24), 0.92 (3H, d, *J*= 5.8 Hz, CH_3-21), 0.86 [24H, m, CH_3-26, CH_3-27, $2SiCH(C\underline{H}_3)_3$], 0.52 (3H, s, CH_3-18), 0.05 15 mL) and extracted with Et_2O (3x10 mL). The combined organic extracts were dried, filtered and concentrated and the residue was dried under vacuum. To the residue dissolved in MeOH (7 mL) was added AG 50W-X4 resin (2 g, prewashed with MeOH). The mixture was stirred overnight at rt in the dark. The resin was filtered out, and the filtrate was concentrated to a residue, which was purified by flash chromatography (50% EtOAc/hexanes) to give **5e**[2j] [33 mg, 80%. Amorphous solid]. **^{1}H NMR** (CD_2Cl_2): 6.34 and 6.00 (2H, AB pattern, d, *J*= 11.3 Hz, H-6, H-7), 5.27 (1H, b s, H-19*E*), 4.94 (1H, b s, H-19*Z*), 4.35 (1H, m, H-1), 4.14 (1H, m, H-3), 3.26 (1H, m, H-24), 0.91 (3H, d, *J*= 6.2 Hz, CH_3-21), 0.88 (3H, d, *J*= 6.8 Hz, CH_3-26), 0.87 (3H, d, *J*= 6.7 Hz, CH_3-27), 0.53 (3H, s, CH_3-18). **^{13}C NMR** (CD_2Cl_2): 148.56 (C), 143.39 (C), 133.97 (C), 125.00 (CH), 117.58 (CH), 111.88 (CH_2-19), 77.30 (CH-24), 71.14 (CH), 67.14 (CH), 56.93, 56.74, 46.26 (C-13), 45.71 (CH_2), 43.35 (CH_2), 40.90 (CH_2), 36.41, 34.01, 32.43 (CH_2), 31.00 (CH_2), 29.40 (CH_2), 28.00 (CH_2), 23.98 (CH_2), 22.62 (CH_2), 19.05, 18.95, 17.35, 12.08. **LRMS**, m/z (I,%): 417 (M^++1, 3), 416 (M^+, 9), 399 (3), 398 (12), 380 (6), 357 (4).

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