The First Synthesis of 24,24-Difluoro-1α-hydroxyvitamin D_3 by Means of Radical Deoxygenation of Alcohols

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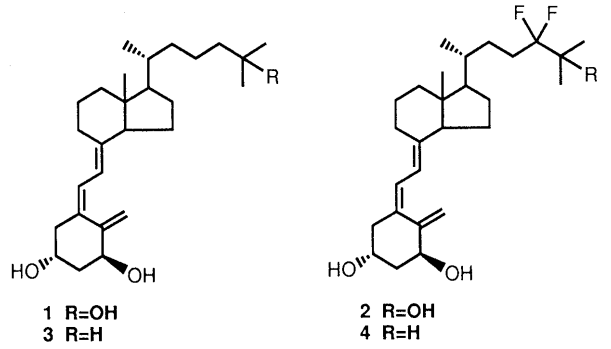
The first synthesis of the title compound 4, a novel analog of 1α-hydroxyvitamin D (α-calcidiol) that might be therapeutically useful, is described. A key feature in the synthesis is the radical deoxygenation of the diol 21, which was prepared according to the previously reported procedure starting from 17. The resulting deoxygenated product 22 with the desired side-chain moiety was finally led to 4 in a conventional manner. Some aspects of the unusual reactivity of 25-OH on radical deoxygenation are also discussed.

Key words 24,24-difluoro-1α-hydroxyvitamin D_3; α-calcidiol; vitamin D analog; radical deoxygenation

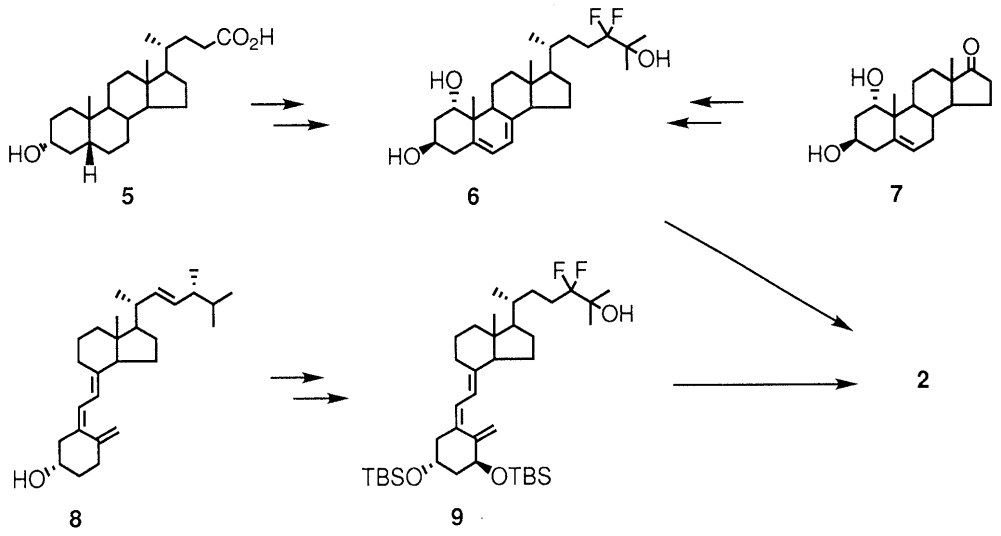
1α,25-Dihydroxyvitamin D_3 (**1**), the hormonally active form of vitamin D_3, mediates intestinal calcium absorption, and bone resorption and mineralization. In addition, **1** has been found to exhibit a variety of biological activities in many tissues and cells since the discovery of the fact that **1** induces cell differentiation and proliferation.[1] This renewed interest has prompted numerous efforts to synthesize a number of vitamin D analogs in order to investigate biological roles of vitamin D and to develop potential therapeutic agents.[2,3] Of the analogs synthesized, those altered in the side-chain are of particular interest, because some of them show higher potency than the parent compound and others show preferential activity on cell differentiation and proliferation over calcium absorption. 24,24-Difluoro-1α,25-dihydroxyvitamin D_3 (**2**)[4-6] is among such compounds, and has proven to be a highly potent vitamin D analog, approximately 5—10 times more active than **1** in *in vivo* vitamin D-responsive systems.[7-11] Thus, the difluoro analog **2** is one of the most potent vitamin D analogs, and might be clinically useful.



1 R=OH, **3** R=H **2** R=OH, **4** R=H

Several vitamin D-related compounds have been clinically used to treat a wide variety of metabolic diseases. Among them, 1α-hydroxyvitamin D_3 (α-calcidiol) (**3**), a synthetic analog of **1**, has been established as a therapeutic agent besides **1**.[12,13] The analog **3** serves as a prodrug, exhibiting activity after hydroxylation at C-25 in the liver to yield **1**. Accordingly, 24,24-difluoro-1α-hydroxy-vitamin D_3 (**4**), the counterpart of **3** for **2**, should also act as **3** does and have potential for therapeutic use as well as **3**. We report here the first synthesis of this novel vitamin D analog **4**.[14]

Initially, the analog **4** was expected to be easily accessible by radical deoxygenation of the 25-OH group in **2** or its derivatives.[15,16] For the synthesis of **2**, we have reported three different routes as shown in Chart 1: firstly, starting with lithocholic acid **5** through an intermediate **6**, secondly, also *via* **6** but starting with 1α-hydroxydehydroepian-



5 **6** **7** **8** **9**

Chart 1

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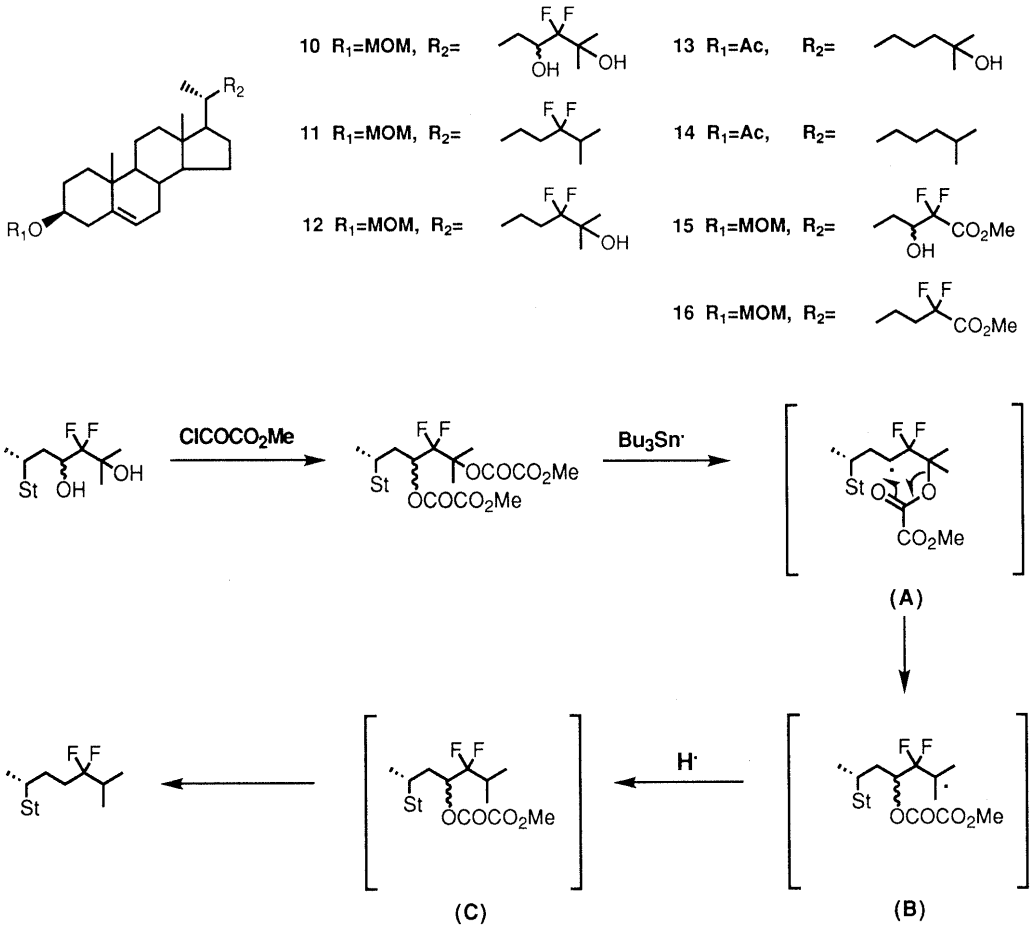
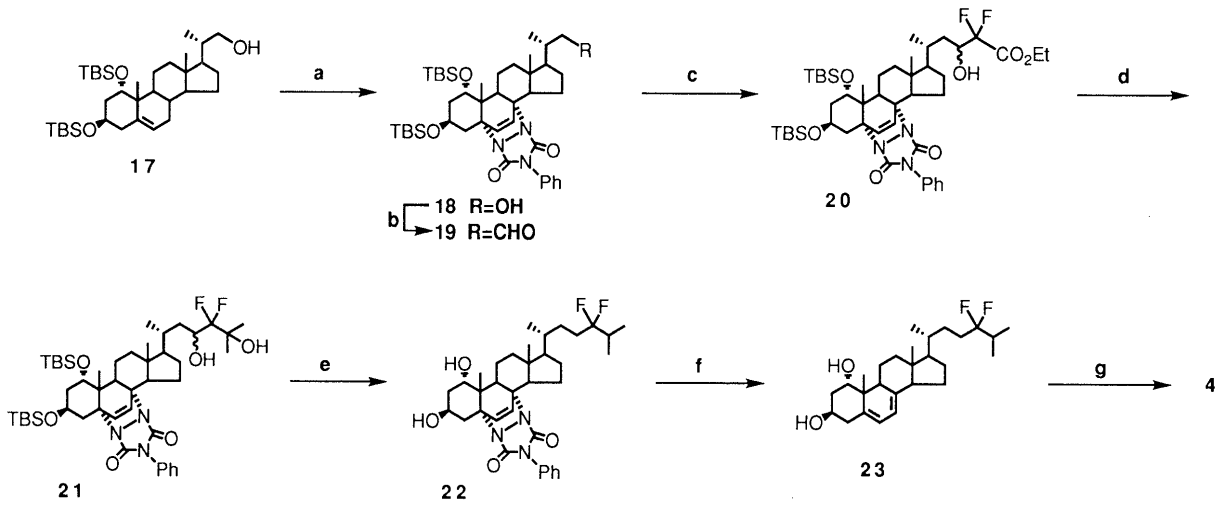


Chart 2

drosterone (**7**), and finally from vitamin D_2 (**8**) through a precursor **9**. The intermediates **6** and/or **9** should be suitable for removal of the 25-OH group. However, all attempts resulted in failure; for example sequential treatment of **9** with methyloxalyl chloride ($ClCOCO_2Me$) and then triphenylstannane-triethylborane[17] gave only a complex mixture. After numerous model studies, we finally found that the desired side-chain moiety can be constructed from the compound bearing hydroxyl groups at both C-23 and C-25; the diol **10** gave **11** in modest yield on treatment with $ClCOCO_2Me$ followed by tributyltin hydride (Bu_3SnH). This reaction is noteworthy. When the 25-monool **12** was subjected to the same conditions, no deoxygenation took place and the alcohol **12** was recovered instead. In contrast, the corresponding 24-H_2 compound **13** was cleanly deoxygenated under the same conditions to give **14** in high yield. Furthermore, the 23-monool **15** also reacted smoothly to furnish the deoxygenated product **16** in high yield. Taking these findings in consideration, one possible explanation for the radical deoxygenation of **10** to **11** could be as follows (Chart 2). Of the two oxalates obtained from **10**, the one at C-23 reacts first and generates a radical intermediate A. Then, the oxalate at C-25 transfers intramolecularly to C-23, yielding another radical intermediate B, which in turn affords the 23-monoester C. Finally, the monoester C reacts again with Bu_3SnH to give the deoxygenated product **11**. Although details of the mechanism remain to be elucidated, this radical deoxygenation is interesting and the procedure may be useful to synthesize *gem*-difluoro compounds.[17]

Successful synthesis of the vitamin D analog **4** is based on the above findings. The requisite diol **21** was prepared from the alcohol **17** according to previously reported procedures (Chart 3).[5] Compound **17** was converted into a 5,7-diene in a usual way and the resulting diene was immediately reacted with 4-phenyl-1,2,4-triazolidine-3,5-dione (PTAD) to give the adduct **18** in 20% yield. We previously used the 5,7-diene directly in the next step, but it was occasionally contaminated with a 4,6-diene, which made purification troublesome. Therefore, the 5,7-diene was protected with PTAD. Sequential treatment of **18** with *p*-toluenesulfonyl chloride (TsCl), potassium cyanide (KCN) and diisobutylaluminum hydride (DIBAL-H) afforded the C_1 elongated aldehyde **19** in 72% overall yield. The Reformatsky reaction of **19** with ethyl bromodifluoroacetate in the presence of activated zinc gave the fluoro-ester **20** in 63% yield as a mixture of diastereoisomers at C-23 in a ratio of 3:2. The diol **21** was obtained from **20** with methylmagnesium bromide in 67% yield.

Removal of the 23- and 25-OH groups in **21** was achieved in the same way as in the model studies. The diol **21** was firstly esterified with $ClCOCO_2Me$ and the resulting ester was subsequently reduced with Bu_3SnH to furnish the deoxygenated product, which was, without purification, deprotected with camphorsulfonic acid (CSA)/MeOH to give the fluoro-diol **22** in 36% yield. The PTAD protective group in **22** was removed by treatment with



a: 1) NBS 2) Bu_4NBr 3) Bu_4NF 4) PTAD b: 1) TsCl-DMAP 2) KCN 3) DIBAL-H c: BrF_2CO_2Et-Zn d: MeMgBr

e: 1) $ClCOCO_2Me$-DMAP 2) Bu_3SnH/AIBN 3) CSA/MeOH f: K_2CO_3-DMSO/Δ g: 1) *hν* 2) Δ/EtOH

Chart 3

K_2CO_3/DMSO to afford the provitamin **23** in 98% yield. Finally, the analog **4** was obtained from the provitamin **23** by conventional thermal and photolytic isomerization.

In preliminary biological evaluation, the vitamin D analog **4** showed higher activity than **2** in intestinal calcium absorption, as expected. The results, including studies on metabolism, will be reported elsewhere.

Experimental

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. Spectral data were recorded on the following instruments: ^{1}H-NMR, JEOL JSX-400; MS, JEOL JMS-D 300; IR, JASCO FT/IR-8000; optical rotations, JASCO DIP-370. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H-NMR. Wakogel C-300 (Wako Pure Chemical Industries Ltd.) and Kieselgel 60 F_{254} (Merck) were used for silica gel flash chromatography and preparative TLC, respectively. HPLC separations were performed on a Waters LC equipped with a 510 HPLC pump and 484 tunable absorbance detector (Waters Associates).

24,24-Difluoro-3β-(methoxymethoxy)cholest-5-ene-23,25-diol (10) A solution of ethyl 24,24-difluoro-23-hydroxy-3β-(methoxymethoxy)homochol-5-en-25-oate (**15**)[19] (290 mg, 0.566 mmol) in tetrahydrofuran (THF, 7.8 ml) was treated with 3 M-MeMgBr/ether (3.9 ml, 11.3 mmol, 20 eq). The mixture was stirred at room temperature for 15 min, poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel flash chromatography (10 g, 15% AcOEt–hexane) to give an inseparable mixture of diastereoisomers of the diol **10** (248 mg, 85%) as colorless needles, mp 142—145 °C (AcOEt–hexane). $[\alpha]_D$ −30.9° (c=0.55, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.70 and 0.72 (3H, s), 1.00 (3H, s), 0.99 and 1.06 (3H, d, J=6.7 Hz), 1.36 (3H, br s), 1.40 (3H, br s), 3.37 (3H, s), 3.42 (1H, tt, J=4.6, 11.3 Hz), 4.06—4.18 (1H, m), 4.69 (2H, s), 5.34—5.38 (1H, m). IR (neat): 3385, 1148, 1105, 1036, 758 cm^{-1}. MS m/z: 436 (M^+ −MOMOH), 421 (M^+ −MOMOH−Me). HR-MS m/z: 436.3167 (M^+ −MOMOH) Calcd for $C_{27}H_{42}F_2O_2$ 436.3135. *Anal.* Calcd for $C_{29}H_{48}F_2O_4$: C, 69.85: H, 9.70. Found: C, 69.61: H, 9.59.

24,24-Difluoro-3β-(methoxymethoxy)cholest-5-en-25-ol (12) A solution of ethyl 24,24-difluoro-3β-(methoxymethoxy)homochol-5-en-25-oate (**16**)[19] (130 mg, 0.262 mmol) in THF (3.5 ml) was treated with 3 M-MeMgBr/ether (1.75 ml, 5.24 mmol, 20 eq). The mixture was stirred at room temperature for 15 min, poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel flash chromatography (10 g, 15% AcOEt–hexane) to give the alcohol **12** (104 mg, 82%) as colorless plates, mp 118—119 °C (hexane). $[\alpha]_D$ −38.4° (c=0.56, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, s), 0.94 (3H, d, J=6.7 Hz), 1.01 (3H, s), 1.36 (6H, br s), 3.37 (3H, s), 3.42 (1H, tt, J=4.6, 11.3 Hz), 4.69 (2H, s), 5.34—5.38 (1H, m). IR (neat): 3449, 1181, 1148, 1107, 758 cm^{-1}. MS m/z: 420 (M^+ −MOMOH), 405 (M^+ −MOMOH−Me). HR-MS m/z: 420.3214 (M^+ −MOMOH) Calcd for $C_{27}H_{42}F_2O$ 420.3189. *Anal.* Calcd for $C_{29}H_{48}F_2O_3$: C, 72.16: H, 10.02. Found: C, 71.89: H, 9.98.

General Procedure for Radical Deoxygenation of Alcohols 10, 12, 13 and 15 Methyl chlorooxalate (3—6 eq) was added to a solution of starting material (0.1—0.5 mmol) and 4-dimethylaminopropylamine (DMAP, 5—10 eq) in CH_2Cl_2 (1—5 ml). The reaction mixture was stirred at room temperature for 15 min, poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated.

A mixture of the resulting oxalate, Bu_3SnH (2—4 eq) and 2,2′-azobisisobutyronitrile (AIBN, 0.5—1 eq) in toluene (1—5 ml) was refluxed for 1 h. The solvent was evaporated off and the residue was purified by silica gel flash chromatography (10 g, 5% AcOEt–hexane) to give the deoxygenated product.

24,24-Difluoro-3β-(methoxymethoxy)cholest-5-ene (11) 36% yield from **10** as colorless scales, mp 89—90 °C (EtOH). $[\alpha]_D$ −34.9° (c=0.51, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.68 (3H, s), 0.93 (3H, d, J=6.7 Hz), 1.00 (6H, d, J=5.8 Hz), 1.01 (3H, s), 3.37 (3H, s), 3.42 (1H, tt, J=4.6, 11.3 Hz), 4.69 (2H, s), 5.33—5.37 (1H, m). IR (neat): 1148, 1107, 1038, 914 cm^{-1}. MS m/z: 404 (M^+ −MOMOH), 389 (M^+ −MOMOH−Me). HR-MS m/z: 404.3245 (M^+ −MOMOH) Calcd for $C_{27}H_{42}F_2$ 404.3255. *Anal.* Calcd for $C_{29}H_{48}F_2O_2$: C, 74.64: H, 10.37. Found: C, 74.52: H, 10.53.

Cholesteryl 3-Acetate (14) 72% yield from 25-hydroxycholesteryl 3-acetate.[20] This was identical with an authentic specimen purchased from Aldrich (mixed melting point, $[\alpha]_D$, ^{1}H-NMR, IR, MS and HR-MS).

Ethyl 24,24-Difluoro-3β-(methoxymethoxy)homochol-5-en-25-oate (16) 80% yield from ethyl 24,24-difluoro-23-hydroxy-3β-(methoxymethoxy)-homochol-5-en-25-oate (**15**).[19] All the data (mp, $[\alpha]_D$, ^{1}H-NMR, IR, MS and HR-MS) of this product were coincident with those reported in the literature.[19]

1α,3β-Bis[(*tert*-butyldimethylsilyl)oxy]-5α,8α-(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)-23,24-bisnorchol-6-en-22-ol (18) A mixture of **17** (4 g, 6.94 mmol), NBS (2.6 g, 14.6 mmol, 2.0 eq), $NaHCO_3$ (4 g, 47.6 mmol, 6.8 eq) and benzoyl peroxide (100 mg, 0.41 mmol, 0.06 eq) in hexane (300 ml) was refluxed for 1 h. The reaction was quenched by the addition of brine and the mixture was extracted with hexane. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The residue was dissolved in THF (100 ml), then Bu_4NBr (300 mg, 0.93 mmol, 0.13 eq) and Et_3N (7 ml, 50.2 mmol, 7.2 eq) were

added to the solution and the mixture was stirred under argon at 0 °C. After 1.5 h, 1.0 M Bu_4NF/THF (30 ml, 30 mmol, 4.3 eq) was added and the whole was stirred under argon at 0 °C for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The brown oily residue was purified by silica gel flash chromatography (100 g, AcOEt–hexane, 1 : 6) to give the 5,7-diene as a pale yellow foam.

This diene was dissolved in AcOEt (30 ml), then PTAD in AcOEt was added to the solution until the red color of PTAD remained, and the solvent was evaporated. The crude product was purified by silica gel flash chromatography (50 g, AcOEt–hexane, 3 : 1—5 : 1) to give the alcohol **18** (800 mg, 20%) as a colorless, viscous oil. $[\alpha]_D$ −5.0° (c=0.77, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.10 (3H, s), 0.13 (3H, s), 0.83 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.92 (3H, s), 1.08 (3H, d, J=6.7 Hz), 2.45 (1H, dd, J=6.7, 12.2 Hz), 2.52—2.59 (2H, m), 3.21—3.26 (1H, m), 3.39 (1H, dd, J=6.9, 10.5 Hz), 3.66 (1H, dd, J=3.1, 10.4 Hz), 3.85 (1H, t, J=2.8 Hz), 4.78 (1H, tt, J=5.4, 10.8 Hz), 6.22 (1H, d, J=8.2 Hz), 6.37 (1H, d, J=8.2 Hz), 7.24—7.47 (5H, m). IR (neat): 3445, 1748, 1696, 1400, 1258 cm^{-1}. MS m/z: 749 (M^+), 692 ($M^+ - t$Bu), 574 (M^+ − PTAD). HR-MS m/z: 574.4244 (M^+ − PTAD) Calcd for $C_{39}H_{62}O_3Si_2$ 574.4234.

1α,3β-Bis[(*tert*-butyldimethylsilyl)oxy]-5α,8α-(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)-24-norchol-6-en-23-al (19) A solution of **18** (556 mg, 0.74 mmol), TsCl (210 mg, 1.1 mmol, 1.5 eq) and DMAP (227 mg, 1.86 mmol, 2.5 eq) in CH_2Cl_2 (10 ml) was stirred overnight at room temperature. The mixture was poured into water and extracted with ether. The combined extracts were successively washed with saturated $CuSO_4$, water and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel flash chromatography (20 g, AcOEt–hexane, 1 : 7) to give the tosylate (622 mg, 93%) as a colorless glass. $[\alpha]_D$ −26.7° (c=1.15, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.12 (3H, s), 0.78 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.91 (3H, s), 1.04 (3H, d, J=6.7 Hz), 2.40 (1H, dd, J=6.7, 12.2 Hz), 2.45 (3H, s), 2.48—2.58 (2H, m), 3.23 (1H, dd, J=4.1, 12.2 Hz), 3.73 (1H, dd, J=6.6, 9.3 Hz), 3.83 (1H, t, J=2.4 Hz), 4.03 (1H, dd, J=3.0, 9.5 Hz), 4.76 (1H, tt, J=5.5, 11.0 Hz), 6.21 (1H, d, J=8.2 Hz), 6.33 (1H, d, J=8.2 Hz), 7.25—7.46 (5H, m), 7.34 (2H, d, J=8.3 Hz), 7.78 (2H, d, J=8.3 Hz). IR (neat): 1750, 1696, 1399, 1177 cm^{-1}. MS m/z: 728 (M^+ − PTAD), 674 (M^+ − PTAD − tBu). HR-MS m/z: 728.4323 (M^+ − PTAD) Calcd for $C_{41}H_{68}O_5SSi_2$ 728.4326.

A mixture of the tosylate (292 mg, 0.32 mmol) and KCN (74 mg, 1.14 mmol. 3.5 eq) in DMSO (10 ml) was heated at 65 °C for 2 h. After having been cooled, the mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel flash chromatography (15 g, AcOEt–hexane, 1 : 7) to give the cyanide (210 mg, 86%) as a white solid, mp 114—115 °C. $[\alpha]_D$ −28.6° (c=0.54, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s), 0.08 (3H, s), 0.10 (3H, s), 0.13 (3H, s), 0.83 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.92 (3H, s), 1.20 (3H, d, J=6.4 Hz), 2.20 (1H, dd, J=7.9, 16.8 Hz), 2.41 (1H, dd, J=3.7, 16.8 Hz), 2.48 (1H, d, J=6.4, 12.2 Hz), 3.24 (1H, dd, J=5.0, 13.9 Hz), 3.85 (1H, t, J=2.6 Hz), 4.77 (1H, tt, J=5.4, 11.0 Hz), 6.23 (1H, d, J=8.2 Hz), 6.35 (1H, d, J=8.2 Hz), 7.25—7.46 (5H, m). IR (neat): 2247, 1750, 1696, 1397, 1256 cm^{-1}. MS m/z: 758 (M^+), 701 ($M^+ - t$Bu), 583 (M^+ − PTAD), 451 (M^+ − PTAD − TBSOH), 394 (M^+ − PTAD − 2TBSOH). HR-MS m/z: 758.4622 (M^+) Calcd for $C_{43}H_{66}N_4O_4Si_2$ 758.4622. *Anal.* Calcd for $C_{43}H_{66}N_4O_4Si_2$: C, 68.03: H, 8.76: N, 7.38. Found: C, 67.75: H, 8.83: N, 7.44.

A 1.5 M DIBAL-H/toluene (0.37 ml, 0.56 mmol, 2.0 eq) solution was added to a stirred solution of the cyanide (210 mg, 0.28 mmol) in CH_2Cl_2 (5 ml) at 0 °C, and the mixture was stirred under argon at 0 °C for 25 min. The reaction was quenched by the addition of saturated NH_4Cl. The mixture was diluted with ether, then $MgSO_4$ was added and the whole was stirred at room temperature for 5 min. The mixture was filtered through Celite and the filtrate was evaporated. The crude product was purified by silica gel flash chromatography (12 g, AcOEt–hexane, 1 : 10—1 : 7) to give the aldehyde **19** (188 mg, 90%) as colorless needles, mp 126—127 °C (AcOEt). $[\alpha]_D$ −33.9° (c=0.74, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s), 0.08 (3H, s), 0.10 (3H, s), 0.13 (3H, s), 0.86 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.93 (3H, s), 1.03 (3H, d, J=6.4 Hz), 1.88 (1H, ddd, J=2.4, 3.0, 10.1 Hz), 2.22 (1H, ddd, J=3.0, 3.7, 9.5 Hz), 2.44—2.59 (5H, m), 3.24 (1H, dd, J=4.0, 14.3 Hz), 3.87 (1H, t, J=2.5 Hz), 4.77 (1H, tt, J=5.5, 11.0 Hz), 6.23 (1H, d, J=8.3 Hz), 6.37 (1H, d, J=8.3 Hz), 7.22—7.47 (5H, m), 9.76 (1H, d, J=2.1 Hz). IR (neat): 1750, 1710, 1696, 1397, 1254 cm^{-1}. MS m/z: 761 (M^+), 704 ($M^+ - t$Bu), 586 (M^+ − PTAD), 454 (M^+ − PTAD − TBSOH), 397 (M^+ − PTAD − TBSOH − tBu), 322 (M^- − PTAD − 2TBSOH). HR-MS m/z: 761.4613 (M^+) Calcd for $C_{43}H_{67}N_3O_5Si_2$ 761.4619. *Anal.* Calcd for $C_{43}H_{67}O_5N_3Si_2$: C, 67.76: H, 8.86: N, 5.51. Found: C, 67.52: H, 8.67: N, 5.36.

Ethyl 24,24-Difluoro-1α,3β-bis[(*tert*-butyldimethylsilyl)oxy]-5α,8α-(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)-23-hydroxyhomochol-6-en-25-oate (20) Ethyl bromodifluoroacetate (48 μl, 383 μmol, 4.0 eq) was added to a suspension of Zn dust (25 mg, 385 μmol, 4.0 eq) in THF (1 ml) and the mixture was refluxed for 10 min. A solution of the aldehyde **19** (73 mg, 96 μmol) in THF (1 ml) was added to the resulting cloudy solution and the refluxing was continued for 10 min. The mixture was poured into 1 M $KHSO_4$ and extracted with AcOEt. The combined extracts were successively washed with 1 M $KHSO_4$ and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel flash chromatography (10 g, AcOEt–hexane, 1 : 10—1 : 8—1 : 7) to give a mixture of diastereoisomers (3 : 2) of the ester **20** (53 mg, 63%) as a colorless, viscous oil. Although the isomers are separable, the mixture was used directly for the next step. ^{1}H-NMR ($CHCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.13 (3H, s), 0.82 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.92 (3H, s), 1.09 (3H, d, J=6.7 Hz), 1.36 and 1.41 (3H, tt, J=1.5, 7.0 Hz), 2.44 (1H, dd, J=6.7, 12.2 Hz), 2.49—2.59 (2H, m), 3.23 (1H, dd, J=5.0, 14.2 Hz), 3.84 (1H, br s), 4.06—4.18 (1H, m), 4.35 and 4.44 (2H, q, J=7.0 Hz), 4.56 (1H, br s), 4.77 (1H, tt, J=5.4, 11.0 Hz), 6.22 (1H, d, J=8.3 Hz), 6.37 (1H, d, J=8.3 Hz), 7.22—7.47 (5H, m). IR (neat): 3411, 1755, 1748, 1682, 1408 cm^{-1}. MS m/z: 710 (M^+ − PTAD), 653 (M^+ − PTAD − tBu), 578 (M^+ − PTAD − TBSOH), 521 (M^+ − PTAD − TBSOH − tBu). HR-MS m/z: 710.4573 (M^+ + PTAD) Calcd for $C_{39}H_{68}F_2O_5Si_2$ 710.4574.

24,24-Difluoro-1α,3β-bis[(*tert*-butyldimethylsilyl)oxy]-5α,8α-(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)cholest-6-ene-23,25-diol (21) A solution of the difluoro ester **20** (63 mg, 71 μmol) in ether (4 ml) was treated with 3.0 M MeMgBr/ether (0.2 ml, 600 μmol, 8.5 eq) at 0 °C, and the mixture was stirred at 0 °C for 30 min then at room temperature for 2 h. It was poured into water and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel flash chromatography (10 g, AcOEt–hexane, 1 : 6–1 : 5) to give a mixture of diastereoisomers of the diol **21** (41 mg, 67%) as a colorless, viscous oil. The mixture was used directly for the next step. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.13 (3H, s), 0.82 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.92 (3H, s), 1.07 (3H, d, J=6.7 Hz), 1.88 (1H, ddd, J=2.4, 3.0, 10.1 Hz), 1.95—2.12 (5H, m), 2.43 (1H, dd, J=6.4, 12.2 Hz), 2.45—2.59 (2H, m), 2.92—2.97 (1H, m), 3.08—3.16 (1H, m), 3.23 (1H, dd, J=5.0, 13.7 Hz), 3.84 (1H, t, J=2.5 Hz), 4.11 (1H, dq, J=10.1, 5.0 Hz), 4.77 (1H, tt, J=5.5, 11.0 Hz), 4.80 (1H, s), 6.21 (1H, d, J=8.3 Hz), 6.37 (1H, d, J=8.3 Hz), 7.24—7.47 (5H, m). IR (neat): 3368, 1748, 1686, 1404 cm^{-1}. MS m/z: 696 (M^+ − PTAD), 639 (M^+ − PTAD − tBu), 564 (M^+ − PTAD − TBSOH), 507 (M^+ − PTAD − TBSOH − tBu). HR-MS m/z: 696.4778 (M^+ − PTAD) Calcd for $C_{39}H_{70}F_2O_4Si_2$ 696.4780.

24,24-Difluoro-5α,8α-(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)-cholest-6-ene-1α,3β-diol (22) A mixture of the diol **21** (80 mg, 92 μmol), DMAP (112 mg, 920 μmol, 10.0 eq) and $ClCOCO_2Me$ (53 μl, 552 μmol, 6.0 eq) in CH_2Cl_2 (5 ml) was allowed to stand at room temperature for 30 min. The mixture was poured into water and extracted with ether. The combined extracts were successively washed with saturated $CuSO_4$, water and brine, dried over $MgSO_4$ and evaporated to give the oxalyl ester as a colorless oil: ^{1}H-NMR δ: 3.84 and 3.91 (3H, s).

A solution of the oxalyl ester and AIBN (8 mg, 49 μmol, 0.5 eq) in toluene (6 ml) was treated with Bu_3SnH (50 μl, 145 μmol, 2.0 eq) and the mixture was refluxed for 30 min. After having been cooled, the mixture was poured into water and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated to give the dideoxy product as a pale yellow oil.

A mixture of the deoxygenated product and CSA (catalytic amount) in 1 : 1 MeOH–$CHCl_3$ (2 ml) was stirred at room temperature overnight. The mixture was concentrated and the residue purified by silica gel preparative TLC (MeOH–$CHCl_3$, 1 : 10) to give **22** (20 mg, 36%) as a colorless, viscous oil. $[\alpha]_D$ −33.6° (c=1.0, $CHCl_3$). ^{1}H-NMR (CD_3OD) δ: 0.94 (3H, s), 1.02 (3H, s), 1.03 (3H, d, J=6.6 Hz), 1.04 (3H, d, J=6.6 Hz), 2.61 (1H, dd, J=5.3, 12.7 Hz), 2.76 (1H, dd, J=7.0, 12.7 Hz), 3.06 (1H, dd, J=5.7, 14.1 Hz), 3.90 (1H, t, J=1.0 Hz), 4.77 (1H, dd, J=5.8, 11.7 Hz), 6.47 (1H, d, J=8.4 Hz), 6.55 (1H, d, J=8.4 Hz),

7.36—7.52 (5H, m). IR (neat): 3420, 1744, 1682, 1412 cm^{-1}. MS *m/z*: 436 ($M^+ - PTAD$), 400 ($M^+ - PTAD - 2H_2O$). HR-MS *m/z*: 436.3159 ($M^+ - PTAD$) Calcd for $C_{27}H_{42}F_2O_2$ 436.3152.

24,24-Difluorocholesta-5,7-diene-1α,3β-diol (23) A mixture of the PTAD adduct **22** (20 mg, 32 μmol) and K_2CO_3 (52 mg, 378 μmol, 12 eq) in DMSO (3 ml) was heated at 110—115 °C for 2 d. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel preparative TLC (AcOEt–hexane, 3 : 1) to give the provitamin **23** (14 mg, 98%) as a colorless, viscous oil. $[\alpha]_D$ −53.3° (c=1.00, $CHCl_3$). UV (EtOH) λ_{max}: 262 (sh), 270 (ε 6100), 281 (10500), 292 (9600) nm. ^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s), 0.95 (3H, s), 0.96 (3H, d, J=6.7 Hz), 1.009 (3H, d, J=7.0 Hz), 1.011 (3H, d, J=7.0 Hz), 3.77 (1H, br s), 4.07 (1H, ddd, J=4.6, 11.3, 16.2 Hz), 5.39 (1H, dt, J=5.5, 2.4 Hz), 5.74 (1H, dd, J=2.4, 5.5 Hz). IR (neat): 3407, 1462, 1379 cm^{-1}. MS *m/z*: 436 (M^+), 418 ($M^+ - H_2O$), 400 ($M^+ - 2H_2O$). HR-MS *m/z*: 436.3153 (M^+) Calcd for $C_{27}H_{42}F_2O_2$ 436.3153.

(5*E*,7*Z*)-24,24-Difluoro-9,10-seco-5,7,10(19)-cholestatriene-1α,3β-diol (24,24-Difluoro-1α-hydroxyvitamin D_3) (4) A solution of the provitamin **23** (10 mg, 20 μmol) in ether (100 ml) was cooled to 0 °C and deoxygenated by bubbling argon through the solution for 40 min. The solution was irradiated with a high-pressure mercury lamp and Vycor filter for 6 min at 0 °C. The solvent was evaporated at below 25 °C and the residue was dissolved in EtOH (100 ml). The solution was refluxed for 1 h, then evaporated. The crude product was purified by HPLC (Lichrosorb Si-60, 25 × 250 mm, 8% isoPrOH–CH_2Cl_2) to give the vitamin D_3 analog **4** (2.6 mg, 26%) as a white solid: $[\alpha]_D$ +75.6° (c=0.15, $CHCl_3$). UV (EtOH) λ_{max}: 264 (ε 18100) nm. ^{1}H-NMR ($CDCl_3$) δ: 0.55 (3H, s), 0.94 (3H, d, J=6.4 Hz), 1.00 (6H, d, J=7.0 Hz), 4.20—4.25 (1H, m), 4.43 (1H, dd, J=4.6, 7.6 Hz), 5.00 (1H, s), 5.33 (1H, t, J=1.7 Hz), 6.02 (1H, d, J=11.5 Hz), 6.38 (1H, d, J=11.5 Hz). IR (neat): 3422, 1645, 1456 cm^{-1}. MS *m/z*: 436 (M^+), 418 ($M^+ - H_2O$), 400 ($M^+ - 2H_2O$), 152, 134. HR-MS *m/z*: 436.3159 (M^+) Calcd for $C_{27}H_{42}F_2O_2$ 436.3153.

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