

The First Synthesis of 24,24-Difluoro-1 α -hydroxyvitamin D₃ by Means of Radical Deoxygenation of Alcohols

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The first synthesis of the title compound **4**, a novel analog of 1 α -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-1 α -hydroxyvitamin D₃; α -calcidiol; vitamin D analog; radical deoxygenation

1 α ,25-Dihydroxyvitamin D₃ (**1**), the hormonally active form of vitamin D₃, 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-1 α ,25-dihydroxyvitamin D₃ (**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.

Several vitamin D-related compounds have been clinically used to treat a wide variety of metabolic diseases. Among them, 1 α -hydroxyvitamin D₃ (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-1 α -hydroxyvitamin D₃ (**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 1 α -hydroxydehydroepian-

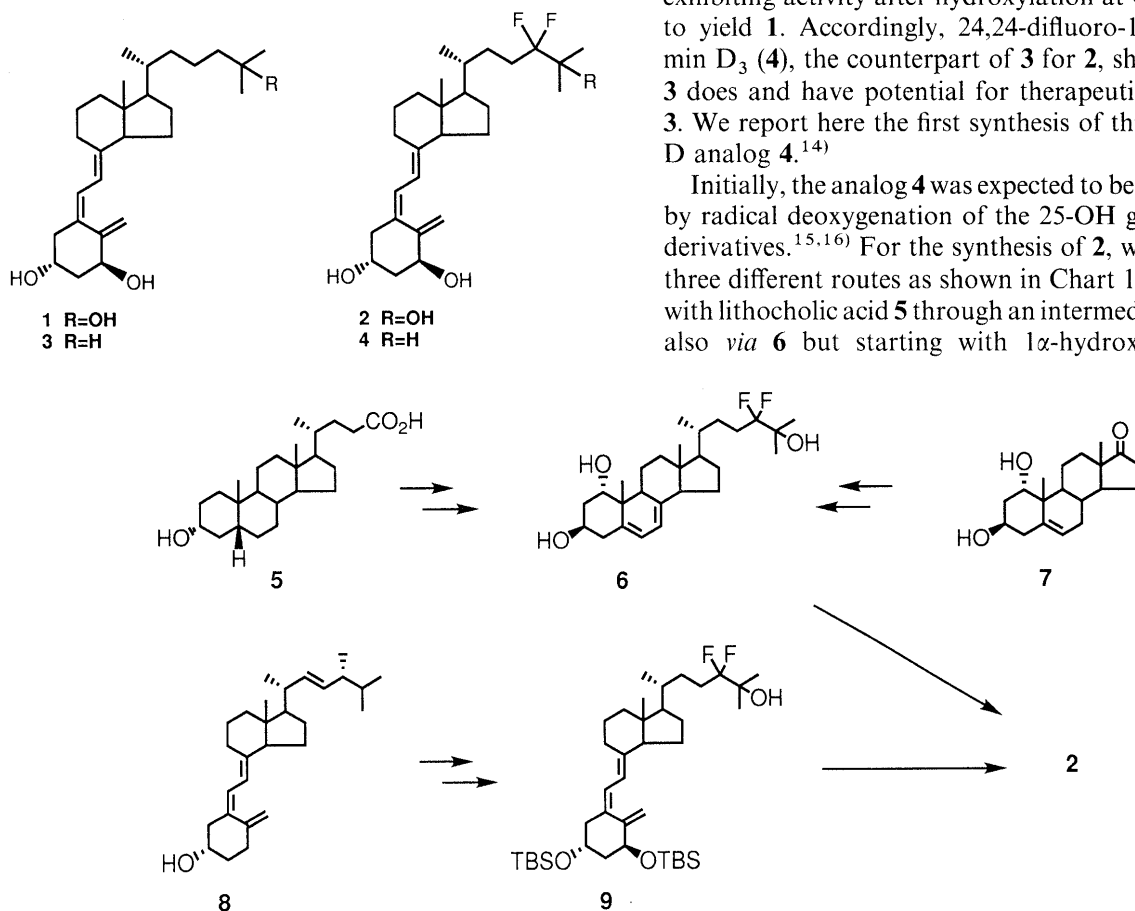


Chart 1

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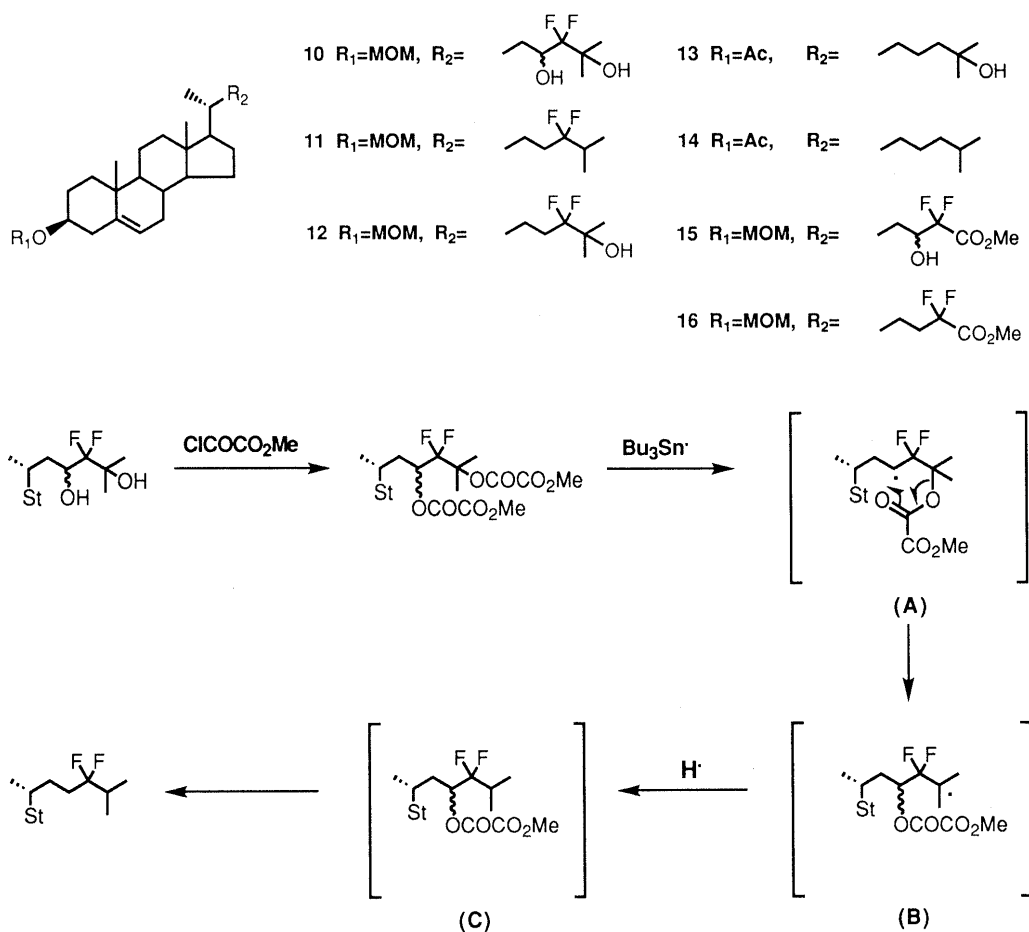


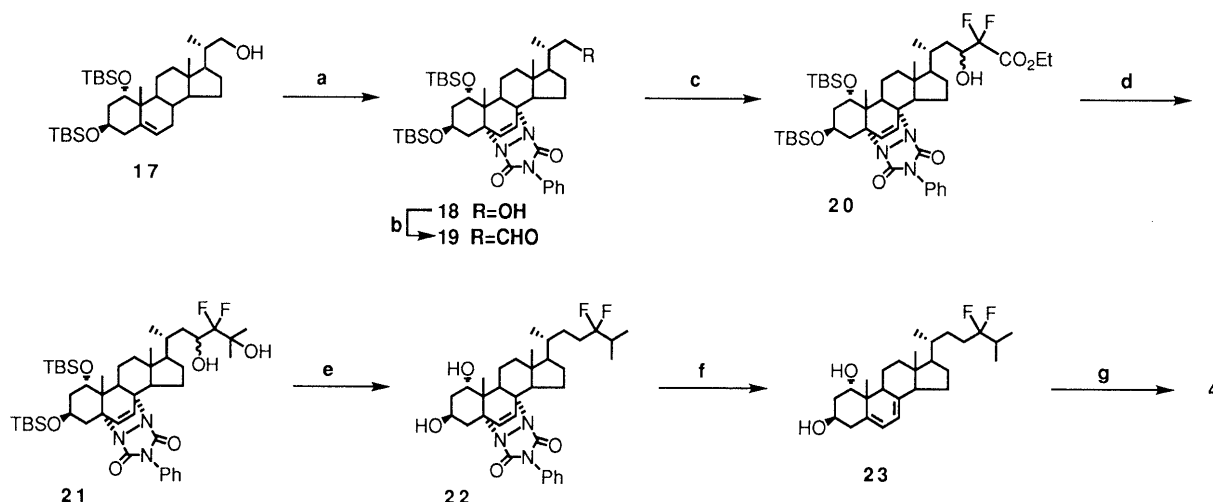
Chart 2

drosterone (7), and finally from vitamin D₂ (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 (ClCOCO₂Me) and then triphenylstannane-triethylborane¹⁷⁾ 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 ClCOCO₂Me followed by tributyltin hydride (Bu₃SnH). 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-H₂ 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 Bu₃SnH 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 C₁ 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 ClCOCO₂Me and the resulting ester was subsequently reduced with Bu₃SnH 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) Bu₄NBr 3) Bu₄NF 4) PTAD b: 1) TsCl-DMAP 2) KCN 3) DIBAL-H c: BrF₂CO₂Et-Zn d: MeMgBr

e: 1) ClCOCO₂Me-DMAP 2) Bu₃SnH/AIBN 3) CSA/MeOH f: K₂CO₃-DMSO/Δ g: 1) hν 2) Δ/EtOH

Chart 3

K₂CO₃/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: ¹H-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 ¹H-NMR. Wakogel C-300 (Wako Pure Chemical Industries Ltd.) and Kieselgel 60 F₂₅₄ (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 MgSO₄ 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). [α]_D –30.9° (*c* = 0.55, CHCl₃). ¹H-NMR (CDCl₃) 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 C₂₇H₄₂F₂O₄ 436.3135. Anal. Calcd for C₂₉H₄₈F₂O₄: 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 MgSO₄ 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). [α]_D –38.4° (*c* = 0.56, CHCl₃). ¹H-NMR (CDCl₃) 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 C₂₇H₄₂F₂O 420.3189. Anal. Calcd for C₂₉H₄₈F₂O₃: 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 CH₂Cl₂ (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 MgSO₄ and evaporated.

A mixture of the resulting oxalate, Bu₃SnH (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). [α]_D –34.9° (*c* = 0.51, CHCl₃). ¹H-NMR (CDCl₃) 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 C₂₇H₄₂F₂ 404.3255. Anal. Calcd for C₂₉H₄₈F₂O₂: 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, [α]_D, ¹H-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, [α]_D, ¹H-NMR, IR, MS and HR-MS) of this product were coincident with those reported in the literature.¹⁹

1α,3β-Bis[(*tert*-butyldimethylsilyloxy)-5α,8α-(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)-23,24-bisnorchole-6-en-22-ol (18) A mixture of **17** (4 g, 6.94 mmol), NBS (2.6 g, 14.6 mmol, 2.0 eq), NaHCO₃ (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 MgSO₄ and evaporated. The residue was dissolved in THF (100 ml), then Bu₄NBr (300 mg, 0.93 mmol, 0.13 eq) and Et₃N (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 Bu₄NF/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 MgSO₄ 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. [α]_D –5.0° (*c* = 0.77, CHCl₃). ¹H-NMR (CDCl₃) 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 C₃₉H₆₂O₃Si₂ 574.4234.

1 α ,3 β -Bis[(*tert*-butyldimethylsilyloxy)-5 α ,8 α -(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 CH₂Cl₂ (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 CuSO₄, water and brine, dried over MgSO₄ 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. [α]_D –26.7° (*c* = 1.15, CHCl₃). ¹H-NMR (CDCl₃) 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 – *t*Bu). HR-MS *m/z*: 728.4323 (M⁺ – PTAD) Calcd for C₄₁H₆₈O₅Si₂ 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 MgSO₄ 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. [α]_D –28.6° (*c* = 0.54, CHCl₃). ¹H-NMR (CDCl₃) 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 C₄₃H₆₆N₄O₄Si₂ 758.4622. Anal. Calcd for C₄₃H₆₆N₄O₄Si₂: 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 CH₂Cl₂ (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 NH₄Cl. The mixture was diluted with ether, then MgSO₄ 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). [α]_D –33.9° (*c* = 0.74, CHCl₃). ¹H-NMR (CDCl₃) 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 – TB-SOH – *t*Bu), 322 (M⁺ – PTAD – 2TBSOH). HR-MS *m/z*: 761.4613 (M⁺) Calcd for C₄₃H₆₇N₃O₅Si₂ 761.4619. Anal. Calcd for C₄₃H₆₇O₅N₃Si₂: C, 67.76; H, 8.86; N, 5.51. Found: C, 67.52; H, 8.67; N, 5.36.

Ethyl 24,24-Difluoro-1 α ,3 β -bis[(*tert*-butyldimethylsilyloxy)-5 α ,8 α -(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)-23-hydroxyhomochol-6-en-25-oate (20) Ethyl bromodifluoroacetate (48 μ l, 383 μ mol, 4.0 eq) was added to a suspension of Zn dust (25 mg, 385 μ mol, 4.0 eq) in THF (1 ml) and the mixture was refluxed for 10 min. A solution of the aldehyde **19** (73 mg, 96 μ mol) 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 KHSO₄ and extracted with AcOEt. The combined extracts were successively washed with 1 M KHSO₄ and brine, dried over MgSO₄ and evaporated. The crude product was purified by silica gel flash chromatography (10 g, AcOEt-hexane, 1:10–1:7) 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. ¹H-NMR (CHCl₃) 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 – *t*Bu), 578 (M⁺ – PTAD – TBSOH), 521 (M⁺ – PTAD – TBSOH – *t*Bu). HR-MS *m/z*: 710.4573 (M⁺ + PTAD) Calcd for C₃₉H₆₈F₂O₅Si₂ 710.4574.

24,24-Difluoro-1 α ,3 β -bis[(*tert*-butyldimethylsilyloxy)-5 α ,8 α -(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 μ mol) in ether (4 ml) was treated with 3.0 M MeMgBr/ether (0.2 ml, 600 μ mol, 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 MgSO₄ 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. ¹H-NMR (CDCl₃) 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 – *t*Bu), 564 (M⁺ – PTAD – TBSOH), 507 (M⁺ – PTAD – TBSOH – *t*Bu). HR-MS *m/z*: 696.4778 (M⁺ – PTAD) Calcd for C₃₉H₇₀F₂O₄Si₂ 696.4780.

24,24-Difluoro-5 α ,8 α -(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl)cholest-6-ene-1 α ,3 β -diol (22) A mixture of the diol **21** (80 mg, 92 μ mol), DMAP (112 mg, 920 μ mol, 10.0 eq) and ClCOCMe (53 μ l, 552 μ mol, 6.0 eq) in CH₂Cl₂ (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 CuSO₄, water and brine, dried over MgSO₄ and evaporated to give the oxalyl ester as a colorless oil: ¹H-NMR δ : 3.84 and 3.91 (3H, s).

A solution of the oxalyl ester and AIBN (8 mg, 49 μ mol, 0.5 eq) in toluene (6 ml) was treated with Bu₃SnH (50 μ l, 145 μ mol, 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 MgSO₄ 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-CHCl₃ (2 ml) was stirred at room temperature overnight. The mixture was concentrated and the residue purified by silica gel preparative TLC (MeOH-CHCl₃, 1:10) to give **22** (20 mg, 36%) as a colorless, viscous oil. [α]_D –33.6° (*c* = 1.0, CHCl₃). ¹H-NMR (CD₃OD) 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 ($\text{M}^+ - \text{PTAD}$), 400 ($\text{M}^+ - \text{PTAD} - 2\text{H}_2\text{O}$). HR-MS m/z : 436.3159 ($\text{M}^+ - \text{PTAD}$) Calcd for $\text{C}_{27}\text{H}_{42}\text{F}_2\text{O}_2$ 436.3152.

24,24-Difluorocholesta-5,7-diene-1 α ,3 β -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 $^\circ\text{C}$ 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. $[\alpha]_{\text{D}}^{25} -53.3^\circ$ ($c=1.00$, CHCl_3). UV (EtOH) λ_{max} : 262 (sh), 270 (ϵ 6100), 281 (10500), 292 (9600) nm. $^1\text{H-NMR}$ (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 ($\text{M}^+ - \text{H}_2\text{O}$), 400 ($\text{M}^+ - 2\text{H}_2\text{O}$). HR-MS m/z : 436.3153 (M^+) Calcd for $\text{C}_{27}\text{H}_{42}\text{F}_2\text{O}_2$ 436.3153.

(5E,7Z)-24,24-Difluoro-9,10-seco-5,7,10(19)-cholestatatriene-1 α ,3 β -diol (24,24-Difluoro-1 α -hydroxyvitamin D_3) (4) A solution of the provitamin **23** (10 mg, 20 μmol) in ether (100 ml) was cooled to 0 $^\circ\text{C}$ 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 $^\circ\text{C}$. The solvent was evaporated at below 25 $^\circ\text{C}$ 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 \times 250 mm, 8% isoPrOH– CH_2Cl_2) to give the vitamin D_3 analog **4** (2.6 mg, 26%) as a white solid: $[\alpha]_{\text{D}}^{25} +75.6^\circ$ ($c=0.15$, CHCl_3). UV (EtOH) λ_{max} : 264 (ϵ 18100) nm. $^1\text{H-NMR}$ (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 ($\text{M}^+ - \text{H}_2\text{O}$), 400 ($\text{M}^+ - 2\text{H}_2\text{O}$), 152, 134. HR-MS m/z : 436.3159 (M^+) Calcd for $\text{C}_{27}\text{H}_{42}\text{F}_2\text{O}_2$ 436.3153.

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