An Improved Synthesis of 24,24-Difluoro-1α,25-dihydroxyvitamin D_3 from Readily Available Vitamin D_2

Kaori ANDO,[1] Fumiaki KOIKE, Fumihiro KONDO, and Hiroaki TAKAYAMA*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan.
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An improved synthesis of a highly potent vitamin D_3 analog, 24,24-difluoro-1α,25-dihydroxyvitamin D_3 (1b) has been accomplished *via* vitamin D_2–SO_2 adducts. The introduction of fluorine atoms was performed by treating the α-keto ester (11) with diethylaminosulfur trifluoride. The total yield was 12.5% from inexpensive vitamin D_2 in 11 steps. This sequence is sufficiently straightforward to be conducted on a gram scale.

Key words 24,24-difluoro-1α,25-dihydroxyvitamin D_3; vitamin D_2–SO_2 adduct; Horner–Emmons reaction; α-keto ester; fluorination

1α,25-Dihydroxyvitamin D_3 (**1a**), the physiologically active form of vitamin D_3, acts as one of the most potent regulators of calcium homeostasis and also induces differentiation in myeloid leukemia cells. The recognition of these important biological activities has stimulated a great deal of interest in the synthesis of vitamin D_3 analogs with the aim of increasing and/or separating the biological activities.[2] In the course of our study of the modification of **1a**, we prepared 24,24-difluoro-1α,25-dihydroxyvitamin D_3 (**1b**),[3] in which the C-24 position is blocked to metabolic hydroxylation by fluorine atoms. The hydroxylation at the C-24 position has been postulated to be a step in the deactivation[4] of **1a**. Indeed, biological tests showed that the 24-difluoro compound **1b** is approximately 4—5 times more active than **1a** in the calcium uptake assay in chick duodenal discs[5] and **1b** has a potency of about 5—10 times that of **1a** in the known *in vivo* vitamin D-responsive systems, including intestinal calcium transport, bone calcium mobilization, calcification of epiphyseal plate cartilage, and elevation of plasma calcium and phosphorus concentrations in the rat.[6] Furthermore, **1b** is 4—7 times more potent than **1a** in inducing phagocytosis and C3 rosette formation of HL-60 cells.[7]

Because 24-difluoro compound **1b** has potential medicinal importance and previous approaches to **1b** follow the classical method, which contains both the low-yielding electrocyclic photochemically induced opening of steroidal 5,7-dienes and a tedious HPLC separation, we attempted to develop a superior approach to **1b**. We have recently reported an improved synthesis of **1b** by using commercially available and inexpensive vitamin D_2 as a starting material.[8] Now we would like to describe the details of our improved synthesis of 24,24-difluoro-1α,25-dihydroxyvitamin D_3 (**1b**).

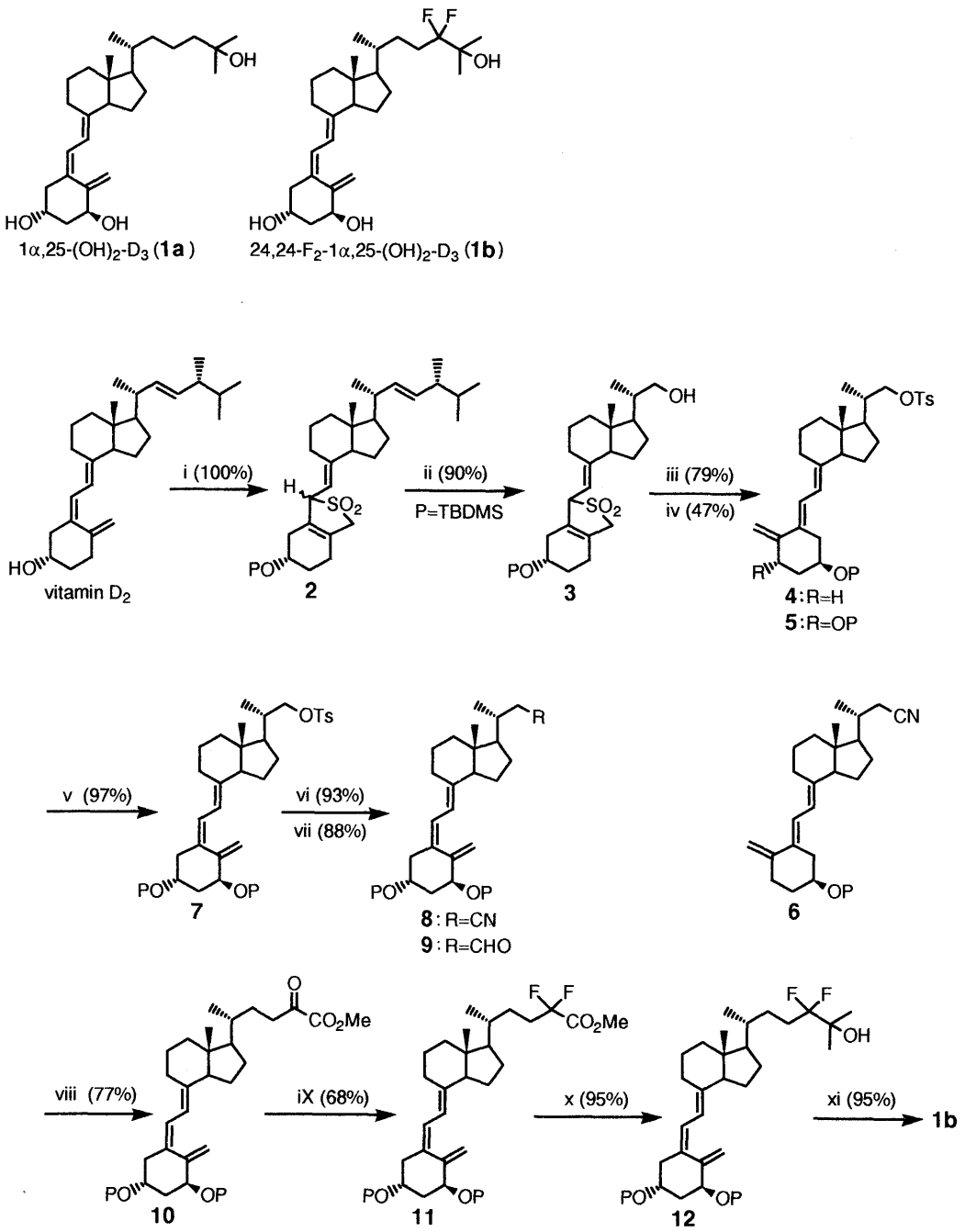
First of all, protection of the labile conjugate triene system of vitamin D_2 was performed by forming its SO_2-adducts. According to our procedure,[9] vitamin D_2 was simply dissolved in liquid sulfur dioxide and the solution was refluxed for 30 min. After evaporation of excess sulfur dioxide and aqueous work-up, the resulting SO_2-adducts were directly silylated with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in *N*,*N*-dimethylformamide (DMF) to give the corresponding 3-*tert*-butyldimethylsilyl ethers **2**[10] as a separable *ca.* 1.2 : 1 mixture in a quantitative yield. For ease of characterization, the major and less polar isomer, (6*S*)-SO_2 adduct (**2a**) was separated by silica gel chromatography. The reaction of **2a** with ozone at −78 °C in 1% pyridine–dichloromethane, followed by the addition of $NaBH_4$ in methanol afforded the C-22 alcohol **3a** in 89% yield. As Hesse *et al.* reported,[11] the strongly electron-withdrawing nature of the SO_2 moiety protected not only the 5(10) double bond but also the 7(8) double bond from ozonolysis. More conveniently, the mixture of SO_2-adducts **2** was treated with ozone and then $NaBH_4$ to give inseparable alcohols **3** (diastereomer ratio *ca.* 1.2 : 1) in 90% yield.

The alcohols **3** were treated with *p*-toluenesulfonyl chloride in pyridine at 5 °C for 16 h or 4-dimethylaminopyridine in dichloromethane for 2 h and the resulting mixture was submitted to the thermal cheletropic extrusion of SO_2 in refluxing ethanol containing $NaHCO_3$ to give the *trans* vitamin D **4** in 79% yield. The selective introduction of a 1α-hydroxyl group into the *trans* vitamin D **4** was performed by Hesse's procedure [SeO_2 (0.7 eq), *N*-methylmorpholine *N*-oxide (NMO) (4 eq) in methanol–CH_2Cl_2, reflux].[12] Silylation of the crude hydroxylation products followed by purification by silica gel chromatography gave the pure bis-TBDMS ether **5** (47% for two steps) along with the unreacted starting material **4** (6%) and the undesired 1β-hydroxylated compound (7%). Attempts to improve the yield of 1α-hydroxylation by using CH_3CN as a solvent or by using the nitrile **6** as a substrate were unsuccessful, giving the corresponding 1α-hydroxylated compound in 30—40% yield.

The *trans* bis-TBDMS ether **5** was photoisomerized to the *cis* isomer **7** under a high-pressure mercury lamp in the presence of anthracene[13] as a triplet sensitizer in 97% yield. The *cis* tosylate **7** is the key vitamin D synthon for the preparation of many side chain analogs of vitamin D.[11,14]

Displacement of the tosyl group with cyanide generated the nitrile **8** (93%), which, on reduction with diisobutylaluminum hydride (DIBAH) gave the aldehyde **9** in 88% yield. Horner–Emmons reaction of the aldehyde **9** with trimethyl ethoxyethyloxyphosphonoacetate which was introduced as acyl anion equivalent by Nakamura,[15] and subsequent acid hydrolysis gave the α-keto ester **10** in 77%

* To whom correspondence should be addressed.



(i) (a) SO_2, reflux (b) TBDMSCl, imidazole, DMF (ii) (a) O_3, 1% pyridine-CH_2Cl_2, -78 °C (b) $NaBH_4$ (iii) (a) TsCl, pyridine, 5 °C (b) EtOH, $NaHCO_3$, reflux (iv) (a) SeO_2-NMO, CH_2Cl_2-MeOH, reflux (b) TBDMSCl, imidazole, DMF (v) $h\nu$-anthracene, Et_3N, toluene, 0 °C (vi) NaCN, DMSO, 90 °C (vii) DIBAH, CH_2Cl_2, -15 °C→0 °C (viii) (a) $(MeO)_2P(O)CH(OEE)CO_2Me$, LDA (b) 0.5 N HCl (ix) DAST, CH_2Cl_2, r.t. (x) MeMgBr, THF, -78 °C→ O °C→ r.t. (xi) Bu_4NF, THF, r.t.

Chart 1

yield.

Introduction of fluorine atoms at the 24-position of **10** was performed by treatment with diethylaminosulfur trifluoride (DAST)[16] in dichloromethane at room temperature to provide the difluoro ester **11** in 68% yield. The use of DAST requires vigorous conditions for most ketones and aldehydes, but fluorination of α-keto esters with DAST is an efficient and mild process, as we[3a] and others[17] have shown. The difluoro ester **11** was treated with excess methylmagnesium bromide to afford the tertiary alcohol **12** in high yield.

After deprotection with Bu_4NF in tetrahydrofuran at room temperature, 24,24-difluoro-1α,25-dihydroxyvitamin D_3 **1b** was obtained as a colorless amorphous powder. The compound **1b** thus obtained showed identical spectroscopic data with the compound **1b** from the electrocyclic photochemically induced opening of the corresponding provitamin.[2a,b] The total yield was 12.5%

from inexpensive vitamin D_2 in 11 steps. This sequence is sufficiently straightforward and practical to be conducted on a gram scale.

The biological activity and metabolism of 24,24-difluoro-1α,25-dihydroxyvitamin D_3 (**1b**) is currently being investigated in detail. The results will be reported elsewhere.

Experimental

Melting points are uncorrected. The ^{1}H-NMR spectra were recorded in $CDCl_3$ at 400 MHz (JEOL JSX-400), and the chemical shifts are expressed in ppm relative to tetramethylsilane (TMS). Column chromatography was performed on silica gel (Wakogel C-300). Other spectral data were recorded on the following instruments: MS, JMS-D 300; IR, JASCO FT/IR-8000; optical rotations, JASCO DIP-370. Tetrahydrofuran (THF) was distilled from sodium/benzophenone just before use. CH_2Cl_2 was distilled from CaH_2 under argon.

(7*E*,22*E*)-3β-(*tert*-Butyldimethylsilyloxy)-9,10-seco-5,7,10(19),22-ergostatetraene SO_2-Adducts (2) A solution of vitamin D_2 (4.00 g, 10.1 mmol) in liquid SO_2 (20 ml) was stirred under reflux for 30 min by using a cold finger condenser and then at room temperature for 30 min. Excess SO_2 was evaporated under reduced pressure. The resulting colorless foam was taken up in AcOEt (80 ml) and the solution was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The obtained solid was dissolved in DMF (32 ml), and treated with imidazole (1.65 g, 24 mmol) and TBDMSCl (1.68 g, 11 mmol). The reaction mixture was stirred at room temperature for 2 h, then AcOEt (120 ml) and H_2O (30 ml) were added. The organic layer was washed with H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was separated by column chromatography using hexane–AcOEt (20 : 1, v/v) as the eluent to provide (6*S*)-**2a** (3.17 g, 55%) and (6*R*)-**2b** (2.62 g, 45%). (6*S*)-**2a**: less polar isomer, colorless needles, mp 116.5—118.2 °C (dec., from CH_2Cl_2–MeOH). ^{1}H-NMR δ: 0.08 (6H, s), 0.66 (3H, s), 0.84 (9H, s), 1.03 (3H, d, J=6.8 Hz), 0.62—2.68 (20H, m), 3.62 (2H, m), 3.98 (1H, m), 4.47 (1H, d, J=10 Hz), 4.68 (1H, d, J=10 Hz), 5.18 (2H, m). MS m/z: 510 (M^+-SO_2), 453 (M^+-SO_2-*tert*-Bu). (6*R*)-**2b**: more polar isomer, colorless needles, mp 120.8—122.1 °C (dec., from CH_2Cl_2–MeOH). ^{1}H-NMR δ: 0.06 (6H, s), 0.57 (3H, s), 0.84 (9H, s), 0.61—2.68 (20H, m), 1.03 (3H, d, J=6.8 Hz), 3.98 (1H, m), 4.58 (1H, d, J=10 Hz), 4.72 (1H, d, J=10 Hz), 5.16 (2H, m). MS m/z: 510 (M^+-SO_2), 453 (M^+-SO_2-*tert*-Bu).

(7*E*,20*S*)-3β-(*tert*-Butyldimethylsilyloxy)-20-hydroxymethyl-9,10-seco-5,7,10(19)-pregnatriene SO_2-Adducts (3) 2a (2.00 g, 3.48 mmol) was treated with ozone in 1% pyridine–CH_2Cl_2 (50 ml) at −78 °C until TLC showed essentially complete consumption of the starting material (*ca.* 20 min). The solution was then purged with argon, and treated with $NaBH_4$ (1.50 g, 40 mmol) in MeOH (10 ml). The mixture was warmed to room temperature, and stirred for 30 min, then the reaction was quenched with brine and the whole was diluted with $CHCl_3$ (50 ml). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography of the residue using hexane–AcOEt (2 : 1) provided **3a** (1.57 g, 89%) as a colorless foamy oil. ^{1}H-NMR δ: 0.05 (3H, s), 0.06 (3H, s), 0.68 (3H, s), 0.88 (9H, s), 1.07 (3H, d, J=6.4 Hz), 1.25—2.26 (19H, m), 2.59 (1H, dd, J=1, 9 Hz), 3.41 (1H, dd, J=6.7, 10.4 Hz), 3.60—3.72 (3H, m), 3.98—4.06 (1H, m), 4.54 (1H, d, J=9.5 Hz), 4.70 (1H, d, J=9.5 Hz). MS m/z: 444 (M^+-SO_2), 387 (M^+-SO_2-*tert*-Bu), 312 (M^+-SO_2-*tert*-$BuMe_2SiOH$). When the mixture of SO_2 adducts **2** was used instead of **2a**, **3a** and **3b** (*ca.* 1.2 : 1) were obtained as an inseparable mixture (90%). **3b**: ^{1}H-NMR δ: 0.60 (3H, s), 1.04 (3H, d, J=6.4 Hz), 4.63 (1H, d, J=9.5 Hz), 4.79 (1H, d, J=9.5 Hz).

(5*E*,7*E*,20*S*)-3β-(*tert*-Butyldimethylsilyloxy)-20-(*p*-tolylsulfonyloxymethyl)-9,10-seco-5,7,10(19)-pregnatriene (4) The mixture of **3a** and **3b** (1.57 g, 3.09 mmol) was dissolved in pyridine (22 ml) and treated with *p*-toluenesulfonyl chloride (1.94 g, 10.2 mmol) at 0 °C. The mixture was stirred for 30 min and then kept in a refrigerator (*ca.* 5 °C) overnight. H_2O (10 ml) was added at 0 °C, and the whole was extracted with AcOEt (3 × 15 ml). The combined extracts were washed with water, 2 N HCl (10 ml), aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The crude oil product was taken up in EtOH (50 ml) and the solution was refluxed in the presence of $NaHCO_3$ (1.26 g, 15 mmol) for 1 h, then concentrated and diluted with CH_2Cl_2 (50 ml). This solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed by using hexane–AcOEt (50 : 1) to give **4** (1.46 g, 79%) as a colorless oil. ^{1}H-NMR δ: 0.060 (3H, s), 0.065 (3H, s), 0.52 (3H, s), 0.88 (9H, s), 1.00 (3H, d, J=6.7 Hz), 1.18—2.03 (14H, m), 2.10—2.20 (1H, m), 2.21—2.30 (1H, m), 2.44—2.50 (1H, m), 2.46 (3H, s), 2.64 (1H, dd, J=13.9, 3.8 Hz), 2.85 (1H, d, J=12.5 Hz), 3.80—3.86 (2H, m), 3.98 (1H, dd, J=3.1, 9.1 Hz), 4.64 (1H, s), 4.93 (1H, s), 5.84 (1H, d, J=11.6 Hz), 6.46 (1H, d, J=11.6 Hz), 7.35 (2H, d, J=8.2 Hz), 7.78 (2H, d, J=8.2 Hz). MS m/z: 598 (M^+), 466 (M^+-*tert*-$BuMe_2SiOH$), 436 (M^+-TsOH). HRMS Calcd for $C_{35}H_{54}O_4SSi$: 598.3509. Found: 598.3472.

(5*E*,7*E*,20*S*)-1α,3β-Bis(*tert*-butyldimethylsilyloxy)-20-(*p*-tolylsulfonyloxymethyl)-9,10-seco-5,7,10(19)-pregnatriene (5) NMO (1.12 g, 8.3 mmol) was stirred in CH_2Cl_2 (15 ml) in the presence of anhydrous $MgSO_4$ for 30 min. This solution was filtered into a flask containing compound **4** (1.24 g, 2.08 mmol) and the mixture was warmed to reflux. To this was added SeO_2 (0.219 g, 2.0 mmol) in MeOH (15 ml), and reflux was continued for a further 3 h. The mixture was cooled, diluted with CH_2Cl_2 (45 ml), washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in DMF (5 ml), and imidazole (0.148 g, 2.2 mmol) and TBDMSCl (1.18 g, 1.0 mmol) were added. The whole was stirred at room temperature for 2 h, and H_2O (15 ml) was added. The mixture was extracted with AcOEt (3 × 15 ml). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4) and concentrated. Column chromatography of the residue using hexane–AcOEt (70 : 1) provided **5** (0.709 g, 47%) as a colorless oil along with **4** (0.0765 g, 6%) and the 1β isomer (0.105 g, 7%). ^{1}H-NMR δ: 0.049 (3H, s), 0.056 (3H, s), 0.060 (3H, s), 0.066 (3H, s), 0.51 (3H, s), 0.86 (9H, s), 0.90 (9H, s), 1.00 (3H, d, J=6.4 Hz), 1.10—1.43 (3H, m), 1.43—1.60 (3H, m), 1.60—1.80 (5H, m), 1.90—2.03 (3H, m), 2.27—2.34 (1H, m), 2.51—2.58 (1H, m), 2.45 (3H, s), 2.83—2.90 (1H, m), 3.81 (1H, dd, J=6.4, 9.1 Hz), 3.98 (1H, dd, J=3.1, 9.1 Hz), 4.18—4.25 (1H, m), 4.50—4.55 (1H, m), 4.94 (1H, s), 4.97 (1H, s), 5.81 (1H, d, J=11.3 Hz), 6.44 (1H, d, J=11.3 Hz), 7.35 (2H, d, J=7.9 Hz), 7.79 (2H, d, J=7.9 Hz). MS m/z: 728 (M^+), 671 (M^+-*tert*-Bu), 596 (M^+-*tert*-$BuMe_2SiOH$), 556 (M^+-TsOH). HRMS Calcd for $C_{41}H_{68}O_5SSi_2$: 728.4324. Found: 728.4384.

(5*Z*,7*E*,20*S*)-1α,3β-Bis(*tert*-butyldimethylsilyloxy)-20-(*p*-tolylsulfonyloxymethyl)-9,10-seco-5,7,10(19)-pregnatriene (7) A solution of **5** (0.930 g, 1.78 mmol), anthracene (0.049 g, 0.73 mmol), and Et_3N (3 drops) in toluene (55 ml) in a Pyrex flask was irradiated with a high-pressure mercury lamp at 0 °C for 20 min. This solution was filtered and concentrated, and the residue was purified by column chromatography using hexane–AcOEt (50 : 1) to give **7** (0.906 g, 97%) as a colorless oil. ^{1}H-NMR δ: 0.047 (3H, s), 0.055 (3H, s), 0.059 (6H, s), 0.49 (3H, s), 0.871 (9H, s), 0.872 (9H, s), 0.99 (3H, d, J=6.7 Hz), 1.10—1.99 (14H, m), 2.21 (1H, dd, J=7, 13 Hz), 2.40—2.49 (1H, m), 2.45 (3H, s), 2.81 (1H, dd, J=4, 12 Hz), 3.80 (1H, dd, J=6.7, 9.5 Hz), 3.98 (1H, dd, J=3.1, 9.5 Hz), 4.15—4.22 (1H, m), 4.36(1H, dd, J=3.7, 6.7 Hz), 4.84 (1H, d, J=2.4 Hz), 5.17 (1H, dd, J=0.9, 2.4 Hz), 6.00 (1H, d, J=11 Hz), 6.21 (1H, d, J=11 Hz), 7.34 (2H, d, J=7.9 Hz), 7.78 (2H, d, J=7.9 Hz). MS m/z: 728 (M^+), 671 (M^+-*tert*-Bu), 596 (M^+-*tert*-$BuMe_2SiOH$), 556 (M^+-TsOH). HRMS Calcd for $C_{41}H_{68}O_5SSi_2$: 728.4324. Found: 728.4384.

(5*Z*,7*E*,20*R*)-1α,3β-Bis(*tert*-butyldimethylsilyloxy)-20-cyanomethyl-9,10-seco-5,7,10(19)-pregnatriene (8) The tosylate **7** (0.320 g, 0.44 mmol) was dissolved in dimethyl sulfoxide (DMSO) (4 ml) and treated with NaCN (0.0314 g, 0.61 mmol). After heating at 90 °C for 1 h, H_2O (5 ml) was added. The mixture was extracted with AcOEt (3 × 15 ml) and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using hexane–AcOEt (100 : 1) to give **8** (0.238 g, 93%) as a colorless foam. ^{1}H-NMR δ: 0.056 (3H, s), 0.059 (3H, s), 0.063 (3H, s), 0.065 (3H, s), 0.55 (3H, s), 0.88 (18H, s), 1.17 (3H, d, J=6.7 Hz), 1.20—1.56 (6H, m), 1.63—2.07 (8H, m), 2.15—2.30 (2H, m), 2.33—2.41 (1H, m), 2.45 (1H, dd, J=13.1, 4.0 Hz), 2.83 (1H, dd, J=4.0, 12 Hz), 4.19 (1H, tt, J=3.6, 7.2 Hz), 4.37 (1H, dd, J=3.7, 6.7 Hz), 4.86 (1H, d, J=2.4 Hz), 5.18 (1H, dd, J=0.9, 2.4 Hz), 6.02 (1H, d, J=11.3 Hz), 6.23 (1H, d, J=11.3 Hz). IR ($CHCl_3$): 2247 cm^{-1}. MS m/z: 583 (M^+), 451 (M^+-*tert*-$BuMe_2SiOH$). HRMS Calcd for $C_{35}H_{61}O_2NSi_2$: 583.4238. Found: 583.4232.

(5*Z*,7*E*,20*R*)-1α,3β-Bis(*tert*-butyldimethylsilyloxy)-20-formylmethyl-9,10-seco-5,7,10(19)-pregnatriene (9) A solution of **8** (0.287 g, 0.491 mmol) in dry CH_2Cl_2 (10 ml) was treated dropwise with diisobutylaluminum hydride (DIBAH) (1 M in hexane) (0.73 ml, 0.73 mmol) at

−15 °C. At 5 min after completion of the addition, the mixture was warmed to 0 °C and stirred for 30 min. After the addition of aqueous NH_4Cl (1 ml) and ether (20 ml), the mixture was stirred for 20 min at 0 °C, dried ($MgSO_4$), filtered through Celite, and concentrated. The residue was purified by column chromatography (hexane–AcOEt) (20 : 1) to give **9** (0.254 g, 88%) as a colorless foam. ^{1}H-NMR δ: 0.059 (6H, s), 0.064 (6H, s), 0.58 (3H, s), 0.88 (18H, s), 1.03 (3H, d, J=6.7 Hz), 1.22—1.44 (3H, m), 1.45—1.59 (2H, m), 1.59—1.74 (2H, m), 1.74—1.82 (1H, m), 1.82—1.93 (2H, m), 1.94—2.11 (3H, m), 2.12—2.27 (3H, m), 2.41—2.52 (2H, m), 2.83 (1H, dd, J=3.7, 11.6 Hz), 4.19 (1H, tt, J=3.7, 7.4 Hz), 4.37 (1H, dd, J=3.7, 6.7 Hz), 4.86 (1H, d, J=2.4 Hz), 5.18 (1H, dd, J=1.2, 2.4 Hz), 6.02 (1H, d, J=11.3 Hz), 6.23 (1H, d, J=11.3 Hz), 9.76 (1H, dd, J=1.2, 3.4 Hz). IR ($CHCl_3$): 1730 cm^{-1}. MS m/z: 586 (M^+), 454 (M^+ − *tert*-$BuMe_2SiOH$), 322 (M^+ − 2*tert*-$BuMe_2SiOH$). HRMS Calcd for $C_{35}H_{62}O_3Si_2$: 586.4234. Found: 586.4213.

(5*Z*,7*E*,20*R*)-1α,3β-Bis(*tert*-butyldimethylsilyloxy)-20-3′-methoxycarbonyl-3′-oxopropyl-9,10-seco-5,7,10(19)-pregnatriene (10) A solution of diisopropylamine (0.040 ml, 0.286 mmol) in THF (1 ml) was treated with BuLi (1.46 M in hexane) (0.196 ml, 0.286 mmol) at 0 °C and the mixture was stirred for 15 min. A solution of trimethyl ethoxyethyloxyphosphonoacetate (71.9 mg, 0.266 mmol) in THF (0.5 ml) was added to the above solution at −40 °C. The mixture was stirred at 0 °C for 20 min, and recooled to −40 °C, then **9** (120 mg, 0.204 mmol) in THF (1 ml) was added dropwise. After warming to room temperature over 1 h, the resulting mixture was treated with aqueous NH_4Cl (10 ml) and extracted with AcOEt (3 × 15 ml). The combined extracts were washed with brine and concentrated. The residue was dissolved in THF (2 ml) and treated with 0.5 N HCl (2 ml). After having been stirred for 30 min at 0 °C, the mixture was extracted with AcOEt (3 × 8 ml) and the combined extracts were washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Column chromatography of the residue using CH_2Cl_2–hexane (1 : 1) gave **10** (104 mg, 77%) as a colorless oil. ^{1}H-NMR δ: 0.058 (6H, s), 0.063 (3H, s), 0.065 (3H, s), 0.53 (3H, s), 0.88 (18H, s), 0.94 (3H, d, J=6.4 Hz), 1.20—2.05 (19H, m), 2.18—2.26 (1H, m), 2.46 (1H, dd, J=3.3, 11 Hz), 2.72—2.95 (2H, m), 3.87 (3H, s), 4.19 (1H, tt, J=3.7, 7.4 Hz), 4.37 (1H, dd, J=3.7, 6.7 Hz), 4.86 (1H, d, J=2.4 Hz), 5.18 (1H, dd, J=0.9, 2.4 Hz), 6.02 (1H, d, J=11.3 Hz), 6.23 (1H, d, J=11.3 Hz). IR ($CHCl_3$): 1734 cm^{-1}. MS m/z: 658 (M^+), 526 (M^+ − *tert*-$BuMe_2SiOH$), 394 (M^+ − 2*tert*-$BuMe_2SiOH$). HRMS Calcd for $C_{38}H_{66}O_5Si_2$: 658.4445. Found: 658.4478.

(5*Z*,7*E*,20*R*)-1α,3β-Bis(*tert*-butyldimethylsilyloxy)-20-3′,3′-difluoro-3′-methoxycarbonylpropyl-9,10-seco-5,7,10(19)-pregnatriene (11) A solution of **10** (34 mg, 0.052 mmol) in dry CH_2Cl_2 (1 ml) was treated with DAST (0.07 ml, 0.52 mmol) at room temperature for 1 h. The reaction was quenched with aqueous $NaHCO_3$ at 0 °C, and the mixture was extracted with AcOEt (3 × 5 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. After column chromatography of the residue using hexane–AcOEt (100 : 1), **11** was obtained as a colorless oil (24 mg, 68%). ^{1}H-NMR δ: 0.059 (6H, s), 0.063 (6H, s), 0.53 (3H, s), 0.88 (18H, s), 0.94 (3H, d, J=6.4 Hz), 1.19—1.40 (4H, m), 1.40—2.26 (15H, m), 2.45 (1H, dd, J=3, 11 Hz), 2.79—2.88 (1H, m), 3.88 (3H, s), 4.19 (1H, tt, J=3.7, 7.3 Hz), 4.37 (1H, dd, J=3.7, 6.7 Hz), 4.86 (1H, d, J=2.4 Hz), 5.18 (1H, d, J=1.8 Hz), 6.02 (1H, d, J=11 Hz), 6.23 (1H, d, J=11 Hz). IR ($CHCl_3$): 1775 cm^{-1}. MS m/z: 680 (M^+), 548 (M^+ − *tert*-$BuMe_2SiOH$), 416 (M^+ − 2*tert*-$BuMe_2SiOH$). HRMS Calcd for $C_{38}H_{66}F_2O_4Si_2$: 680.4464. Found: 680.4488.

(5*Z*,7*E*)-1α,3β-Bis(*tert*-butyldimethylsilyloxy)-24,24-difluoro-9,10-seco-5,7,10(19)-cholestatrien-25-ol (12) A solution of **11** (52 mg, 0.076 mmol) in THF (2 ml) was treated with MeMgBr (3.0 M in Et_2O) (0.33 ml, 0.99 mmol) at −78 °C. Stirring was continued at −78 °C for 30 min, at 0 °C for 30 min, and then at room temperature for 30 min. Aqueous NH_4Cl (5 ml) and AcOEt (5 ml) were added to the mixture and the aqueous layer was extracted with AcOEt (2 × 10 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography of the residue using hexane–AcOEt (10 : 1) gave **12** (49 mg, 95%) as a colorless oil. ^{1}H-NMR δ: 0.059 (6H, s), 0.064 (6H, s), 0.54 (3H, s), 0.88 (18H, s), 0.94 (3H, d, J=6.4 Hz), 1.31 (6H, s), 1.22—2.08 (19H, m), 2.18—2.27 (1H, m), 2.45 (1H, dd, J=3.3, 11 Hz), 2.83 (1H, d, J=12 Hz), 4.20 (1H, tt, J=3.7, 7.4 Hz), 4.37 (1H, dd, J=3.7, 6.4 Hz), 4.87 (1H, d, J=2.4 Hz), 5.18 (1H, dd, J=0.9, 2.4 Hz), 6.02 (1H, d, J=11 Hz), 6.24 (1H, d, J=11 Hz). IR ($CHCl_3$): 3443 cm^{-1}. MS m/z: 680 (M^+), 548 (M^+ − *tert*-$BuMe_2SiOH$), 416 (M^+ − 2*tert*-$BuMe_2SiOH$). HRMS Calcd for $C_{39}H_{70}F_2O_3Si_2$: 680.4828. Found: 680.4796.

(5*Z*,7*E*)-24,24-Difluoro-9,10-seco-5,7,10(19)-cholestatriene-1α,3β,25-triol (24,24-Difluoro-1α,25-dihydroxyvitamin D_3) (1b) A solution of **12** (25 mg, 0.037 mmol) in THF (2 ml) was treated with Bu_4NF (1.0 M in THF) (0.37 ml, 0.37 mmol) overnight under argon at room temperature. Brine (5 ml) was added and aqueous layer was extracted with AcOEt (3 × 5 ml). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude oil was purified by column chromatography using CH_2Cl_2–acetone (6 : 1) to give **1b** (15.8 mg, 95%) as a colorless powder, $[\alpha]_D$ +10.0° (c=0.25, EtOH). UV λ_{max}^{EtOH} nm (ε): 265 (18100). ^{1}H-NMR δ: 0.55 (3H, s), 0.95 (3H, d, J=6.4 Hz), 1.30—2.14 (21H, m), 1.31 (6H, s), 2.31 (1H, dd, J=6.4, 13.1 Hz), 2.60 (1H, dd, J=3.4, 13 Hz), 2.83 (1H, dd, J=3.5, 12 Hz), 4.23 (1H, tt, J=3.2, 6.4 Hz), 4.43 (1H, dd, J=4.3, 7.3 Hz), 5.00 (1H, s), 5.33 (1H, t, J=1.5 Hz), 6.02 (1H, d, J=11.3 Hz), 6.38 (1H, d, J=11.3 Hz). IR ($CHCl_3$): 3690 cm^{-1}. MS m/z: 452 (M^+), 434 (M^+ − H_2O), 416 (M^+ − $2H_2O$). HRMS Calcd for $C_{27}H_{42}F_2O_3$: 452.3099. Found: 452.3097. The sample was pure as judged from ^{1}H-NMR and TLC analysis.

References and Notes

1) Present address: *College of Education, University of the Ryukyus, Nishihara-cho, Okinawa 903-01, Japan.*
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