Synthesis of (1α)-1,25-Dihydroxyvitamin D_3 with a β-Positioned Seven-Carbon Side Chain at C(12)

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Dedicated to Prof. Dr. *Dieter Seebach* on the occasion of his 75th birthday

A convergent synthesis of an analogue of (1α)-1,25-dihydroxyvitamin D_3 (**1b**) with a C_7 side chain at C(12), *i.e.*, of **5** (*Fig.*), is described. A key step of the synthesis is the assembly of the triene system by a Pd^{II}-catalyzed ring closure of an enol triflate ('bottom' fragment) followed by coupling of the resulting Pd^{II} intermediate with an alkenylboronate ('upper' fragment) (*Scheme 2*). The synthetic strategy allows isotopic labelling at the end of the synthesis.

Introduction. – Vitamin D_3[1]) (**1a**; *Fig.*), before eliciting its biological function, must be dihydroxylated to (1α)-1,25-dihydroxyvitamin D_3 (1α,25$(OH)_2D_3$, 1,25D; **1b**), which is considered the hormonally active form of vitamin D_3 [1]. This hormone interacts with the vitamin D nuclear receptor (VDR) [2][3] to form a ligand–VDR complex, which binds to the retinoid X receptor (RXR). The resulting heterodimer interacts with the vitamin D response elements of the DNA to induce important biological functions such as regulation of the mineral metabolism, cell differentiation, cell proliferation, cell growth, apoptosis, and the immune system [1][4]. The fact that the VDR has been found in more than 30 target tissues and cell tumors has led to the consideration that 1α,25$(OH)_2D_3$ is involved in a wider array of biological functions including cancer prevention [1][4][5]. However, the clinical application of 1α,25$(OH)_2D_3$ has been limited by its secondary hypercalcemic effects [6][7]. Efforts to develop vitamin D analogues with strong cell-differentiating ability and low calcemic action have led to the synthesis of more than 3000 vitamin D analogues, but only a few have found clinical applications [8–11]. Most of the vitamin D analogues synthesized to date are modified at the side chain [5][12], some of them with rigid units [13], and others with longer [12][14] or shorter side chains [12][15]. Vitamin D analogues with substituents at the *C* ring [16], *D* ring [17], C(18) [18], triene system [19], or *A* ring [20] or without the *C* or *D* ring or both rings [21] have also been developed (for reviews on the synthesis of vitamin D analogues, see [22]).

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

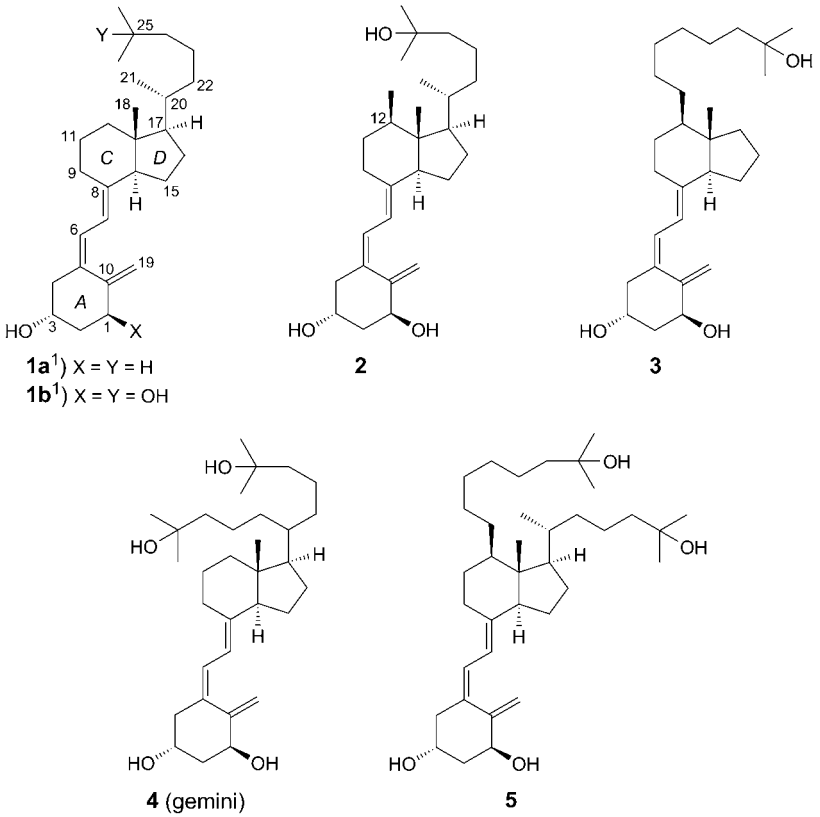
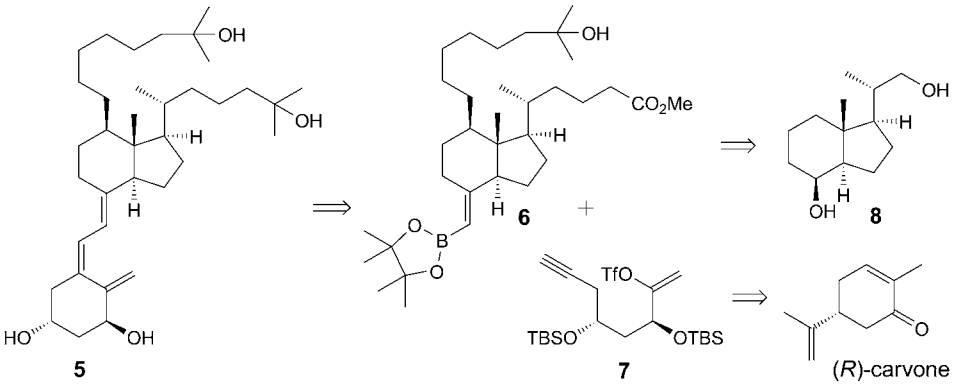


Figure. *Vitamin D_3* (**1a**)*, (1α)-1,25-dihydroxyvitamin D_3* (**1b**)*, and analogues* **2**–**5**

Recently, *Dino Moras* and co-workers published the crystal structure of an engineered ligand-binding domain of the vitamin D receptor (VDR-LBD) that lacks a flexible insertion domain between helices H1 and H3; the mutant VDR bound to $1\alpha,25(OH)_2D_3$ (VDR–1,25D complex) exhibited similar conformation, transactivation ability, and biophysical properties than the wild-type counterpart [23]. The crystal structure of the VDR–1,25D complex shows the H-bonding nature of the interactions between each of the three OH groups of the ligand with the mutant vitamin D receptor (1α-OH with both Ser-237 and Arg-274, 3β-OH with both Tyr-143 and Ser-278, and 25-OH with both His-305 and His-397). We have recently utilized the structural features of *Moras*' crystallographic structure of the VDR–1,25D complex to design active vitamin D analogues [17b][24]. For example, we synthesized the 12β-methyl analogue **2**, which binds strongly to the VDR [16b], and the analogue **3**, which lacks the natural side chain at C(17) and binds significantly to the VDR [16c]. Inspired by the interesting biological profile of compounds **2** and **3** and the potent biological activity of 'gemini' analogue **4**, a vitamin D analogue with two side chains [25], and related compounds [25], we designed and synthesized the new analogue **5**, which possesses the normal side chain of $1\alpha,25(OH)_2D_3$ and a hydroxylated C_7 side chain at C(12).

Results. – The synthetic plan for the synthesis of the target vitamin D_3 analogue **5** is depicted in *Scheme 1* and involves the construction of the triene system by stereoselective Pd-catalyzed cyclization of the enol triflate **7** followed by *Suzuki–Miyaura* coupling of the resulting Pd^{II} intermediate with the cyclic alkenylboronate **6** according to a methodology recently developed in this laboratory [26]. The boronate **6** was constructed in a linear fashion from the *Inhoffen–Lythgoe* diol **8**, which is usually prepared by degradation of vitamin D_2.

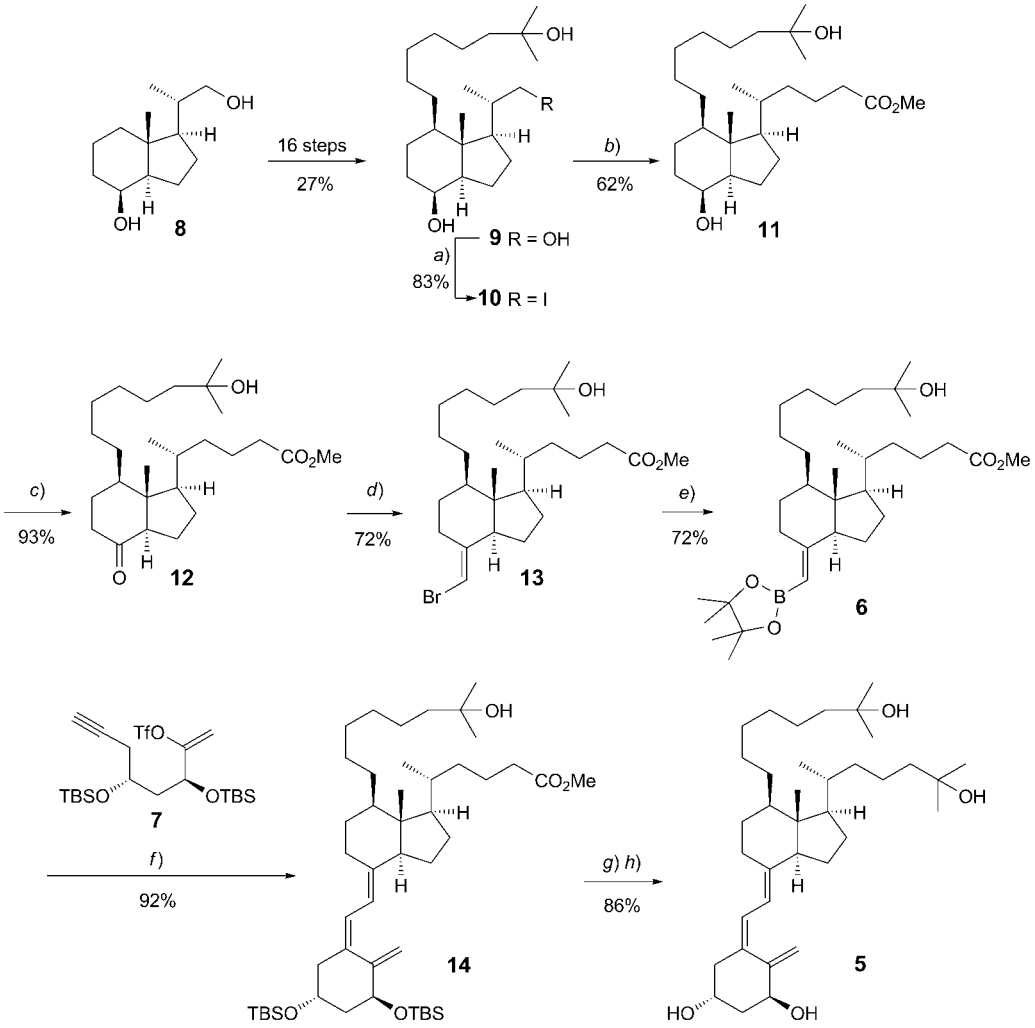
Scheme 1. *Synthetic Plan for the Target (1α)-1,25-Dihydroxyvitamin D_3 Analogue* **5**. TBS = ^{t}BuMe$_2$Si.



The synthesis of the target compound **5** is outlined in *Scheme 2*. The required triol **9** [27] was prepared in 27% overall yield (16 steps) from *Inhoffen–Lythgoe* diol **8** following known methods [28][16b,c]. Transformation of triol **9** into iodo derivative **10** was selectively accomplished with iodine and triphenylphosphine (83% yield). Ni^0-Catalyzed oxidative addition [29] of iodo derivative **10** to methyl acrylate provided methyl ester **11** (62% yield), which was oxidized with *Dess–Martin* periodinane to keto derivative **12** (92%). Conversion of **12** to bromomethylene derivative **13** was accomplished in 72% yield by a *Wittig* reaction with the ylide $Ph_3P{=}CHBr$, generated from $(Ph_3PCH_2Br)Br$ and ^{t}BuOK following a modification of the *Trost* procedure [26]. The upper-fragment cyclic boronate **6** was prepared in 72% yield by *Miyaura* borylation [30] of **13** with bis(pinacolato)diborane (=4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane) in the presence of [1,1′-bis(diphenylphosphino-*κp*)ferrocene]dichloropalladium(II)–dichloromethane complex as the catalyst and tricyclohexylphosphine as ligand. The triene system was installed in 92% yield by treatment of alkenylboronate **6** with an equimolar amount of enol triflate **7** in the presence of a catalytic amount of $[PdCl_2(Ph_3P)_2]$ and K_3PO_4 in H_2O/THF. Finally, treatment of the resulting methyl ester **14** with methylmagnesium bromide followed by removal of the protecting groups gave the desired analogue **5** in 86% yield (20% overall yield from triol **9**, 8 steps).

Conclusions. – An efficient convergent synthesis of **5**, an analogue of (1α)-1,25-dihydroxyvitamin D_3 bearing a C_7 side chain at C(12), was developed. A key step of the synthesis was the Pd-catalyzed assembly of the triene system in the presence of OH and ester functionalities in aqueous medium. The synthetic strategy allows isotopic

Scheme 2. *Synthesis of the Target Analogue* **5**. TBS = ^{t}BuMe$_2$Si.



a) I_2, Ph_3P, 1*H*-imidazole, THF, $-20° \rightarrow$ r.t. *b*) Zn, $NiCl_2 \cdot 6\,H_2O$, py, CH_2=CHCOOMe, r.t. *c*) *Dess–Martin* periodinane, CH_2Cl_2. *d*) (Ph_3PCH_2Br)Br, ^{t}BuOK, toluene, ultrasounds, $-17 \rightarrow 0°$; then **12**. *e*) [$PdCl_2$(dppf)] · CH_2Cl_2, Cy_3P, Pin_2B_2, AcOK, DMSO, 80°. *f*) **7**, [$PdCl_2(Ph_3P)_2$], K_3PO_4, THF, H_2O. *g*) MeMgBr, Et_2O, 0°. *h*) Bu_4NF, THF.

labelling at the end of the synthesis. Biological testing of the new vitamin D analogue is in progress in our laboratory.

We thank the Spanish Ministry of Education and Innovation (projects SAF 2007-67205 and SAF 2010-15291) for financial support and the *Center of Supercomputing of Galicia* (*CESGA*) for allocating computer time. We thank *Dishman-Netherlands BV* for a generous gift of vitamin D_2 used for the preparation of the *Inhoffen–Lythgoe* diol, and Dr. *X. C. González–Avión* and Dr. *X. Pérez* for preliminary experiments.

Experimental Part

General. Pyridinium dichromate (PDC) was prepared following *Corey*'s procedure [31]. $(Ph_3PCH_2Br)Br$ was prepared as reported [32]. Zinc was activated according to *Amarego*'s indications [33]. All reactions involving oxygen- or moisture-sensitive compounds were carried out under Ar. Reaction temp. referred to external bath temp. All solvents were distilled under Ar immediately prior to use: THF and Et_2O from Na/benzophenone, toluene from Na, CH_2Cl_2 from P_2O_5, pyridine from CaH_2, and DMSO from CaH_2 and stored over activated 4 Å molecular sieves. Acetone/dry ice baths were used for reactions at low temperature. Alternatively, acetone baths were cooled with a *CC-100 Cryocool*-immersion cooler, provided with a temp. regulator. Sonications were carried out in a 120–240 W, 35 kHz ultrasonic cleaning bath. Org. extracts were dried over anh. Na_2SO_4 and concentrated with a rotary evaporator at aspirator pressure (20–30 Torr). TLC: aluminium-backed *Merck-60* silica gel plates (0.2 mm thickness); visualization under UV light at 254 nm and by immersion of the plate in a soln. containing either *p*-anisaldehyde (2.5%), acetic acid (1%), and sulfuric acid (3.4%) in 95% ethanol or a soln. of ceric ammonium nitrate (0.5 g) and ammonium molybdate (4.8 g) in H_2O (100 ml) and H_2SO_4 (5.6 ml) followed by heating with a hot gun. Flash column chromatography (FC): *Merck* silica gel (230–400 mesh). IR Spectra: *Bruker* spectrometer, model *IFS-66V* FT-IR; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker-DPX* 250-MHz spectrometer, unless otherwise stated; $CDCl_3$ solns.; chemical shifts δ in ppm downfield from Me_4Si (= 0.0 ppm) with the residual solvent signal at δ(H) 7.26 (*s* in $CDCl_3$) and δ(C) 77.0 (*t* in $CDCl_3$) as internal standard, coupling constants *J* in Hz; distortionless enhancement by polarization transfer (DEPT) for the assignment of C types. Low- and high-resolution (HR) MS: *Micromass Instruments Autospec* (EI) and *Bruker-Microtof* spectrometer (ESI-TOF); in *m*/*z* (rel. %).

*(8β,12β)-12-(7-Hydroxy-7-methyloctyl)-22-iodo-de-*A,B-*23,24-dinorcholan-8-ol* (= *(3*R,*3a*R,*4*R,*7*S,*7a*R*)-Octahydro-3-[(1*S*)-2-iodo-2-methylethyl]-α,α-3a-trimethyl-1*H*-indene-4-heptanol*; **10**). Triphenylphosphine (272 mg, 1.04 mmol) and 1*H*-imidazole (127 mg, 1.86 mmol) were successively added to a soln. of **9** (147 mg, 0.41 mmol) in THF (10 ml). The mixture was cooled to −20°, and I_2 (208 mg, 0.82 mmol) was added in five portions each 15 min. After 15 min, the mixture was removed from the cooling bath and stirred for 30 min at r.t. The reaction was quenched by slow addition of sat. $NaHCO_3$ soln. (15 ml) and sat. $Na_2S_2O_3$ soln. (15 ml). The aq. layer was extracted with AcOEt (3 × 25 ml), the combined org. layer dried and concentrated, and the residue purified by FC (SiO_2 (1 × 8 cm), 10–20% AcOEt/hexanes): **10** (159 mg, 83%). Colorless oil. R_f 0.55 (50% AcOEt/hexanes). IR (film): 3413 (br., OH), 2930*s* (CH), 2860*s* (CH). ^{1}H-NMR (250 MHz): 4.01 (br. *d*, *J* = 1.9, H–C(8)); 3.48 (*dd*, *J* = 2, 9.5, 1 H–C(22)); 2.89 (*dd*, *J* = 9.5, 9.5, 1 H–C(22)); 1.19 (*s*, *Me*$_2$COH); 1.11 (*d*, *J* = 6.7, Me(21)); 0.86 (*s*, Me(18)). ^{13}C-NMR (62.9 MHz): 71 (COH); 68.7 (CH(8)); 56.6 (CH); 53 (CH); 49.4 (CH); 45.4 (C(13)); 43.9 (CH_2); 36.9 (CH); 34 (CH_2); 31.4 (CH_2); 30.1 (CH_2); 29.9 (CH_2); 29.2 (*Me*$_2$COH); 28.2 (CH_2); 24.3 (CH_2); 23.6 (CH_2); 23.5 (Me); 22.2 (CH_2); 20.2 (CH_2); 14.8 (CH_2(22)); 11.3 (Me). EI-MS: 446 (19, $[M - H_2O]^+$), 428 (27, $[M - 2\,H_2O]^+$), 319 (20, $[M - H_2O - I]^+$). HR-EI-MS: 446.2066 ($C_{22}H_{39}IO^+$; calc. 446.2046).

*Methyl (8β,12β)-8-Hydroxy-12-(7-hydroxy-7-methyloctyl)-de-*A,B-*cholan-24-oate* (= *Methyl (δ*R,*1*R,*3a*R,*4*S,*7*R,*7a*R*)-Octahydro-4-hydroxy-7-(7-hydroxy-7-methyloctyl)-δ,7α-dimethyl-1*H*-indene-1-pentanoate*; **11**). Freshly distilled methyl acrylate (330 µl, 3.66 mmol) and $NiCl_2 \cdot 6\,H_2O$ (196 mg, 0.82 mmol) were successively added to a suspension of activated Zn (239 mg, 3.66 mmol) in pyridine (6 ml). The mixture was heated at 60° for 2 h. The red mixture was allowed to warm to r.t., and a soln. of **10** (85 mg, 0.18 mmol) in pyridine (2 ml) was added dropwise *via* cannula. After 20 min, AcOEt (10 ml) was added, and the mixture was filtered through a layer of silica gel. The solids were washed with AcOEt (3 × 15 ml). The resulting filtrate was successively washed with 10% aq. HCl soln. (3 × 30 ml) and sat. $NaHCO_3$ soln. (2 × 30 ml), dried, and concentrated and the residue purified by FC (SiO_2 (1 × 8 cm), 15% AcOEt/hexanes): **11** (48 mg, 62%). Colorless oil. R_f (60% AcOEt/hexanes) 0.50. IR (film): 3429 (br., OH), 2930*s* (CH), 2862*s* (CH), 1740*s* (C=O). ^{1}H-NMR (250 MHz): 3.98 (br. *s*, H–C(8)); 3.66 (*s*, CO_2Me); 1.20 (*s*, *Me*$_2$COH); 0.92 (*d*, *J* = 6.8, Me(21)); 0.82 (*s*, Me(18)). ^{13}C-NMR (62.9 MHz): 174.3 (C(25)); 71 (COH); 69.2 (CH(8)); 57.4 (CH); 53.7 (CH); 51.5 (Me); 49.9 (CH); 45.4 (C(13)); 44 (CH_2); 34.5 (CH_2); 34 (CH_2); 33.3 (CH_2); 32.9 (CH); 31.3 (CH_2); 30.2 (CH_2); 30 (CH_2); 29.2 (2 Me); 28.2 (CH_2);

24.3 (CH_2); 24 (CH_2); 23.5 (CH_2); 22.6 (CH_2); 22.2 (Me); 20.9 (CH_2); 11.3 (Me). EI-MS: 406 (13, $[M-H_2O]^+$), 388 (47, $[M-2\,H_2O]^+$). HR-EI-MS: 406.3432 ($C_{26}H_{46}O_3^+$; calc. 406.3447).

*Methyl (12β)-12-(7-Hydroxy-7-methyloctyl)-8-oxo-de-*A,B-*cholan-24-oate* (= *Methyl (*δR,*1*R,*3a*R,*7*R,*7a*R*)-Octahydro-7-(7-hydroxy-7-methyloctyl)-δ,7α-dimethyl-4-oxo-1*H-*indene-1-pentanoate*; **12**). *Dess–Martin* periodinane (120 mg, 0.283 mmol) was added to a soln. of **11** (93 mg, 0.218 mmol) in CH_2Cl_2 (6 ml). The mixture was stirred for 1 h in the absence of light. The mixture was filtered through a layer of silica gel. The solids were washed with AcOEt (3 × 15 ml), and the resulting filtrate was concentrated. The residue was purified by FC (SiO_2 (1.5 × 5 cm), 20% AcOEt/hexanes): **12** (86 mg, 93%). Colorless oil. R_f (45% AcOEt/hexanes) 0.25. IR (film): 3508 (br., OH), 2956*s* (CH), 2931*s* (CH), 2860*s* (CH), 1739*s* (C=O), 1717*s* (C=O). ^{1}H-NMR (250 MHz): 3.65 (*s*, CO_2Me); 1.20 (*s*, *Me*$_2$COH); 0.94 (*d*, *J* = 6.8, Me(21)); 0.57 (*s*, Me(18)). ^{13}C-NMR (62.9 MHz): 212.5 (C(8)); 174.1 (C(25)); 71 (COH); 62.2 (CH); 56.9 (CH); 52.4 (C(13)); 51.5 (MeO); 49 (CH); 43.9 (CH_2); 40.4 (CH_2); 34.3 (CH_2); 33 (CH); 32.6 (CH_2); 30.8 (CH_2); 30.1 (CH_2); 29.9 (CH_2); 29.6 (CH_2); 29.2 (*Me*$_2$COH); 28.2 (CH_2); 24.3 (CH_2); 23.9 (CH_2); 21.8 (Me); 21.2 (CH_2); 19.3 (CH_2); 10.1 (Me). EI-MS: 404 (71, $[M-H_2O]^+$), 386 (7, $[M-2\,H_2O]^+$). HR-EI-MS: 404.3284 ($C_{26}H_{44}O_3^+$; calc. (404.3290).

*Methyl (8*E*,12β)-8-(Bromomethylene)-12-(7-hydroxy-7-methyloctyl)-de-*A,B-*cholan-24-oate* (= *Methyl (*δR,*1*R,*3a*R,*4*E,*7*R,*7a*R*)-4-(Bromomethylene)octahydro-7-(7-hydroxy-7-methyloctyl)-δ,7α-dimethyl-1*H-*indene-1-pentanoate*; **13**). A suspension of (Ph_3PCH_2Br)Br (544 mg, 1.25 mmol) in toluene (9 ml) was prepared by sonication for 30 min. After cooling to −17°, 1M ^{t}BuOK in THF (1.23 ml, 1.23 mmol) was added, and the resulting mixture was stirred for 3 h. A soln. of **12** (66 mg, 0.156 mmol) in toluene (6 ml) previously cooled to 0° was added *via* cannula. The mixture was stirred for 2 h at −17° and 3 h at r.t. The reaction was quenched by addition of sat. NH_4Cl soln. (1 ml), and the mixture was filtered through a layer of silica gel. The solids were washed with AcOEt (3 × 15 ml), and the filtrate was concentrated. The residue was purified by FC (SiO_2 (2 × 6 cm), 15% AcOEt/hexanes): **13** (56 mg, 72%). Colorless oil. R_f (40% AcOEt/hexanes) 0.51. IR (film): 3457 (br., OH), 3084*w* (=CH), 2954*s* (CH), 2931*s* (CH), 2861*s* (CH), 1741*s* (C=O), 1632*w* (C=C). ^{1}H-NMR (250 MHz): 5.61 (*s*, H–C(7)); 3.65 (*s*, CO_2Me); 1.20 (*s*, *Me*$_2$COH); 0.92 (*d*, *J* = 6.8, Me(21)); 0.46 (*s*, Me(18)). ^{13}C-NMR (62.9 MHz): 174.2 (C(25)); 144.8 (C(8)); 97 (CH(7)); 71 (COH); 56.7 (CH); 56.1 (CH); 51.5 (MeO); 49.5 (CH); 48.8 (C(13)); 44 (CH_2); 34.4 (CH_2); 33.6 (CH); 32.6 (CH_2); 31.2 (CH_2); 31 (CH_2); 30.2 (CH_2); 30 (CH_2); 29.2 (*Me*$_2$COH); 28.3 (CH_2); 28.1 (CH_2); 24.3 (CH_2); 23.9 (CH_2); 22.3 (CH_2); 21.9 (Me); 21.3 (CH_2); 9.6 (Me). EI-MS: 480 (4, $[M-H_2O]^+$), 401 (100, $[M-H_2O-Br]^+$). HR-EI-MS: 480.2596 ($C_{27}H_{45}BrO_2^+$; calc. 480.2306).

*Methyl (8*E*,12β)-12-(7-Hydroxy-7-methyloctyl)-8-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-methylene]-de-*A,B-*cholan-24-oate* (= *Methyl (*δR,*1*R,*3a*S,*4*E,*7*R,*7a*R*)-Octahydro-7-(7-hydroxy-7-methyloctyl)-δ,7α-dimethyl-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene]-1*H-*indene-1-pentanoate*; **6**). Cy_3P (2 mg, 0.007 mmol) and $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (3 mg, 0.003 mmol) were dissolved in DMSO (2 ml), and the mixture was stirred for 25 min. A soln. of **13** (56 mg, 0.112 mmol) in DMSO (2 ml), KOAc (33 mg, 0.336 mmol), and Pin_2B_2 (57 mg, 0.224 mmol) were successively added. The mixture was heated to 80° for 3 h and then cooled to r.t. The reaction was quenched by addition of H_2O (15 ml). The aq. layer was extracted with AcOEt (4 × 25 ml), the combined org. layer dried and concentrated, and the residue purified by FC (SiO_2 (2 × 5 cm), 10–15% AcOEt/hexanes): **6** (44 mg, 72%). Colorless oil. R_f (40% AcOEt/hexanes) 0.48. IR (film): 3515 (br., OH), 2931*s* (CH), 2861*s* (CH), 1742*s* (C=O), 1640*s* (C=C). ^{1}H-NMR (250 MHz): 4.88 (*s*, H–C(7)); 3.65 (*s*, CO_2Me); 1.25 (*s*, 2 Me_2COB); 1.20 (*s*, *Me*$_2$COH); 0.92 (*d*, *J* = 6.8, Me(21)); 0.45 (*s*, Me(18)). ^{13}C-NMR (62.9 MHz): 174.3 (C(25)); 166 (C(8)); 82.5 (COB); 71 (COH); 58.8 (CH); 57.1 (CH); 51.4 (MeO); 50 (CH); 49.4 (C(13)); 44 (CH_2); 34.5 (CH_2); 33.6 (CH); 33.2 (CH_2); 32.6 (CH_2); 31.3 (CH_2); 30.2 (CH_2); 30.1 (CH_2); 30 (CH_2); 29.2 (*Me*$_2$COH); 28.2 (CH_2); 24.9 (1 *Me*$_2$COB); 24.8 (1 *Me*$_2$COB); 24.3 (CH_2); 24 (CH_2); 22.6 (CH_2); 21.9 (CH_3); 21.1 (CH_2); 9.8 (CH_3). EI-MS: 546 (3, *M*), 528 (13, $[M-H_2O]^+$), 399 (100, $[M-C_6H_{16}BO_3]^+$). HR-EI-MS: 546.4464 ($C_{33}H_{59}BO_5^+$; calc. 546.4456).

*(1α,12β)-3-*O*-[(*tert*-Butyl)dimethylsilyl]-1-{[(*tert*-Butyl)dimethylsilyl]oxy}-12-(7-hydroxy-7-methyloctyl)-24-(methoxycarbonyl)-25,26,27-trinorvitamin D_3* (= *Methyl (*δR,*1*R,*3a*S,*4*E,*7*R,*7a*R*)-4-{(2*Z*)-2-{(3*S*,5*R*)-3,5-bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2-methylenecyclohexylidene}ethylidene}octahydro-7-(7-hydroxy-7-methyloctyl)-δ,7α-dimethyl-1*H-*indene-1-pentanoate*; **14**). A 2M aq. K_3PO_4 soln.

(0.9 ml, 1.8 mmol) and $[PdCl_2(PPh_3)_2]$ (2 mg, 0.003 mmol) were successively added to a soln. of **6** (36 mg, 0.066 mmol) and **7** (40 mg, 0.077 mmol) in THF (2 ml). The mixture protected from light was vigorously stirred for 1 h. Then H_2O (1 ml) was added, and the aq. layer was extracted with AcOEt (3 × 10 ml). The combined org. layer was dried and concentrated and the residue purified by FC (SiO_2 (2 × 6 cm), 8% AcOEt/hexanes): **14** (48 mg, 92%). Colorless oil. R_f (30% AcOEt/hexanes) 0.54. ^{1}H-NMR (250 MHz): 6.21 (*d*, *J* = 11.2, H–C(6)); 6.00 (*d*, *J* = 11.2, H–C(7)); 5.18 (*s*, 1 H–C(19)); 4.85 (*s*, 1 H–C(19)); 4.37 (*m*, H–C(1)); 4.19 (*m*, H–C(3)); 3.65 (*s*, CO_2Me); 1.21 (*s*, Me_2COH); 0.98 – 0.77 (*m*, Me(21), 2 Me_3CSi); 0.44 (*s*, Me(18)); 0.05 (overlapped *s*, 2 Me_2Si). ^{13}C-NMR (62.9 MHz): 174.3 (C(25)); 148.4 (C); 140.7 (C); 134.9 (C); 123.2 (CH); 117.7 (CH); 111 (CH_2); 71.8 (CH); 71.1 (COH); 67.5 (CH); 57.2 (CH); 56.9 (CH); 51.4 (MeO); 50.1 (CH); 49.1 (C(13)); 45.9 (CH_2); 44.8 (CH_2); 44 (CH_2); 34.5 (CH_2); 33.7 (CH); 32.6 (CH_2); 31.4 (CH_2); 30.2 (CH_2); 30 (CH_2); 29.7 (CH_2); 29.2 (*Me*$_2$COH); 28.8 (CH_2); 28.2 (CH_2); 25.8 (2 *Me*$_3$CSi); 24.4 (CH_2); 24 (CH_2); 22.4 (CH_2); 21.9 (Me); 21.4 (CH_2); 18.2 (CSi); 18.1 (CSi); 9.7 (Me); – 4.7 (1 Me_2Si); – 4.8 (1 MeSi); – 5.1 (1 MeSi).

(1α,12β)-1,25-Dihydroxy-12-(7-hydroxy-7-methyloctyl)vitamin D$_3$ (=*(1*R,*3*S,*5*Z*)-4-Methylene-5-{(2*E*)-2-{(*1*R,*3a*S,*7*R,*7a*R)-octahydro-1-{(*1*R)-5-hydroxy-1,5-dimethylhexyl}-7-(7-hydroxy-7-methyloctyl)-7α-methyl-4*H*-inden-4-ylidene}ethylidene}cyclohexane-1,3-diol*; **5**). A 3M MeMgBr soln. in Et_2O (102 µl, 0.306 mmol) was added dropwise to a cooled (– 78°) soln. of **14** (40 mg, 0.051 mmol) in Et_2O (4 ml). After 15 min, the cooling bath was removed, and the mixture was stirred at r.t. for 1 h in the absence of light. The reaction was quenched at 0° by slow addition of sat. NH_4Cl soln. (10 ml). The aq. layer was extracted with ^{t}BuOMe (3 × 10 ml). The combined org. layer was dried and concentrated to give a colorless oil (39 mg, 0.049 mmol; R_f (30% AcOEt/hexanes) 0.25. ^{1}H-NMR (250 MHz, CD_2Cl_2): 6.25 (*d*, *J* = 11.2, H–C(6)); 6.02 (*d*, *J* = 11.2, H–C(7)); 5.19 (*s*, 1 H–C(19)); 4.85 (*s*, 1 H–C(19)); 4.41 (*m*, H–C(1)); 4.16 (*m*, H–C(3)); 1.17 (*s*, 2 *Me*$_2$COH); 0.96 – 0.83 (*m*, Me(21), 2 Me_3CSi); 0.47 (*s*, Me(18)); 0.05 (*m*, 2 Me_2Si). This colorless oil was dissolved in THF (4 ml) and treated with 1M Bu_4N in THF (600 µl, 0.6 mmol). After stirring for 20 h in the dark, the reaction was quenched by addition of sat. NH_4Cl soln. (15 ml). The aq. layer was extracted with AcOEt (3 × 15 ml), the combined org. layer dried and concentrated, and the residue purified by FC (SiO_2 (2 × 6 cm), 60 – 90% AcOEt/hexanes): **5** (25 mg, 86%). White foam. R_f (90% AcOEt/hexanes) 0.18. IR ($CHCl_3$): 3366 (br., OH), 2928*s* (CH), 2856*s* (CH), 1648*w* (C=C). ^{1}H-NMR (400 MHz, CD_2Cl_2): 6.34 (*d*, *J* = 11.3, H–C(6)); 6.00 (*d*, *J* = 11.3, H–C(7)); 5.29 (*s*, 1 H–C(19)); 4.95 (*s*, 1 H–C(19)); 4.37 (*dd*, *J* = 4.4, 7.5, H–C(1)); 4.15 (*ddd*, *J* = 3.6, 3.6, 10.3, H–C(3)); 2.81 (*dd*, *J* = 3.8, 13.4, H–C(9)); 2.55 (*dd*, *J* = 3.3, 13.4, 1 H–C(4)); 2.26 (*dd*, *J* = 6.6, 13.4, 1 H–C(4)); 1.16 (overlapped s, *Me*$_2$COH, Me(26)/Me(27)); 0.93 (*d*, *J* = 6.8, Me(21)); 0.48 (*s*, Me(18)). ^{13}C-NMR (100 MHz, CD_2Cl_2): 148.6 (C(10)); 143.4 (C(8)); 133.9 (C(5)); 125.2 (CH(6)); 117.4 (CH(7)); 111.9 (CH_2(19)); 71.3 (COH, C(25)); 71.3 (CH(1)); 67.3 (CH(3)); 57.9 (CH); 57.7 (CH); 50.7 (CH); 49.9 (C(13)); 45.9 (CH_2(4)); 45 (CH_2); 44.6 (CH_2); 43.5 (CH_2); 34.4 (CH); 34.1 (CH_2); 32 (CH_2); 30.8 (CH_2); 30.6 (CH_2); 30.3 (CH_2); 30 (CH_2); 29.6 (*Me*$_2$COH); 29.6 (Me(26), Me(27)); 28.8 (CH_2); 24.9 (CH_2); 23.8 (CH_2); 23.1 (CH_2); 22.3 (Me(21)); 21.9 (CH_2); 10.2 (Me(18)). ESI-TOF-MS: 581 (100, $[M + Na]^+$), 541 (0.3, $[M - OH]^+$), 523 (24, $[M - OH - H_2O]^+$). HR-ESI-TOF-MS: 581.4538 ($C_{36}H_{62}NaO_4^+$; calc. 581.4540).

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Received August 8, 2012