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Novel synthesis of 1α,25-dihydroxy-19-norvitamin D from 25-hydroxyvitamin D

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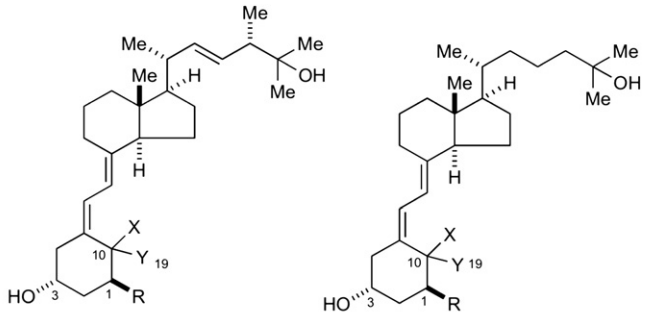
ABSTRACT

19-Norvitamin D analogs **3a** and **3b** were synthesized from 25-hydroxyvitamin D, obtained via a bioconversion method. The synthetic route features a highly regio- and stereoselective hydroboration reaction to afford 25-hydroxy-3,5-cyclopropyl-vitamin D derivatives **12** having olefin at the C1–10-position.

1. Introduction

1α,25-Dihydroxyvitamin D_2 (**1a**) and D_3 (**1b**) (Fig. 1), which are active forms of vitamins D_2 and D_3, respectively, show various significant biological activities, being involved in the regulation of calcium and phosphorus homeostasis, bone mineralization, proliferation and differentiation of various types of cells, and immune regulation.[1] Numerous structure–activity relationship studies have been conducted with the aim of separation and/or enhancement of these characteristic biological activities. In 1990s, 19-nor derivatives **3a** and **3b** were reported by DeLuca et al. to show highly potent cell differentiation-inducing activity with very low calcium mobilization.[2,3] Currently, the 19-nor analog of **1a**, i.e., paricalcitol (**3a**), is available for the treatment and prevention of secondary hyperparathyroidism associated with chronic renal failure.[2]



1a: X, Y = CH_2, R = OH
2a: X, Y = CH_2, R = H
3a: X = Y = H, R = OH (Paricalcitol)

1b: X, Y = CH_2, R = OH
2b: X, Y = CH_2, R = H
3b: X = Y = H, R = OH

Figure 1. Structures of 1α,25-dihydroxyvitamin D_2 (**1a**) and D_3 (**1b**), and their analogs **2** and **3**.

The 19-nor type vitamin D analog **3b** was first synthesized via **2b**, and since then, various attempts have been made to improve the synthetic method. Some efficient syntheses have been reported based upon a strategy of coupling A-ring and CD-ring synthons by the use of Wittig–Horner reaction, Suzuki–Miyaura coupling reaction, and Julia-type olefination reaction.[4,5] These methods allow the preparation of a variety of 19-norvitamin D analogs, but nevertheless, many reaction steps are required for the preparation of the A-ring and 25-hydroxylated CD-ring synthons. Although a shorter direct synthesis of 19-norvitamin D_3 **3b** from **2b** was developed, efficient introduction of the two hydroxyl groups at C1 and 25 remained an issue.[3–6]

We have recently developed a practical synthesis of 25-hydroxyvitamin D_2 (**2a**) and D_3 (**2b**) from the corresponding vitamin D by means of a bioconversion method.[7] In this paper, we wish to report a novel direct synthesis of 1α,25-dihydroxy-19-norvitamin D (**3a**) and (**3b**) from 25-hydroxyvitamin D analogs **2**.

2. Results and discussions

At the outset, we chose the 10-keto **6** as a key intermediate (Scheme 1). A 3,5-cyclovitamin D_2 derivative **4a** was obtained from **2a** by tosylation and solvolysis with methanol, followed by methoxymethyl ether formation at the C25 hydroxyl group. Regioselective dihydroxylation of the C10–19 olefin of **4a** with OsO_4, followed by oxidative cleavage of the resulting glycol with sodium periodinate gave 10-keto-3,5-cyclovitamin D_2 **6a** in 29% yield from **2a** (five steps). Vitamin D_3 derivative **6b** was similarly obtained from **2b** in five steps in 38% yield.

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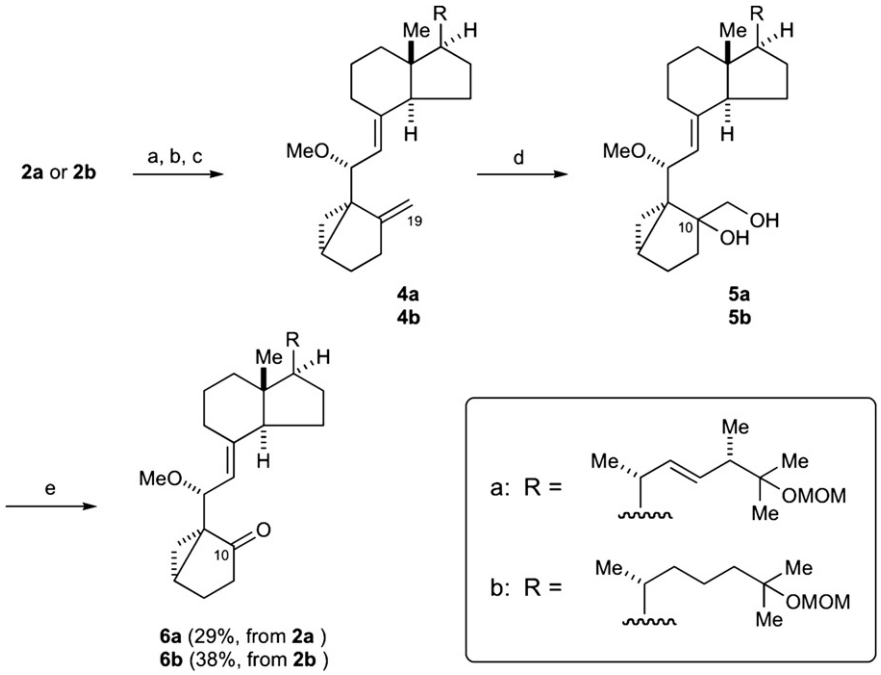
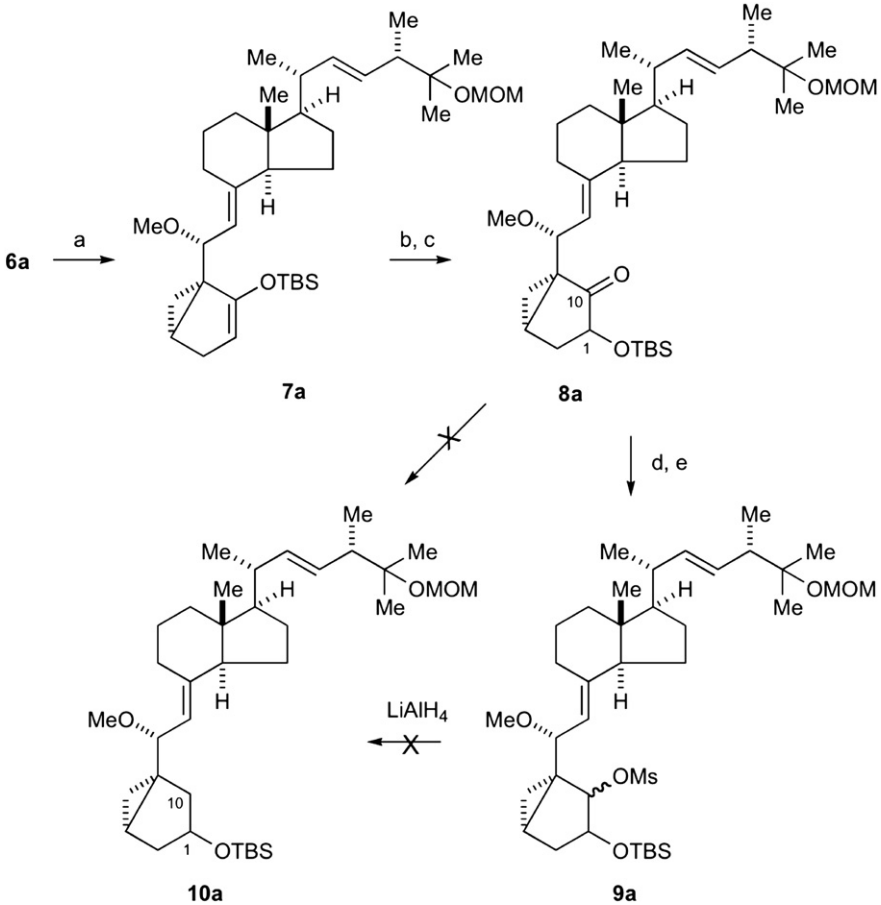
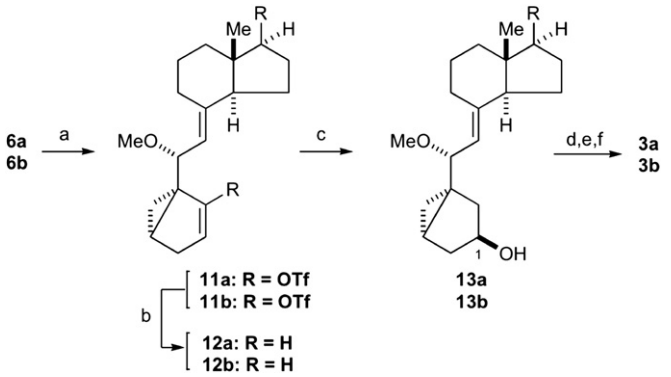


Scheme 1. Synthesis of 10-keto **6** from **2** by oxidation at C19. (a) *p*-TsCl (5.1 equiv), Py, rt; (b) MeOH, $NaHCO_3$ (27 equiv), 55 °C; (c) MOMCl (4.7 equiv), DIPEA (9.6 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt; (d) OsO_4 (1.0 equiv), pyridine; (e) $NaIO_4$ (3.0 equiv), MeOH, 0 °C (**6a**: 29%, from **2a**, **6b**: 38% from **2b**).

Introduction of a hydroxyl group at C1 and reduction at C10 were examined with **6a** (Scheme 2). Rubottom oxidation conditions were successfully applied to the ketone **6a** to generate α-hydroxylated ketone **8a** as a single diastereomer in 66% yield from **6a**.[8] Reduction of the carbonyl group of **8a** to methylene **10a** was examined via mesylate **9a**, but $LiAlH_4$ was unreactive with **9a**. Direct transformation of **8a**



Scheme 2. Oxidation at C1 and investigation of reduction at C10. (a) TBSOTf (2.5 equiv), 2,6-lutidine (4 equiv), DME, 0 °C; (b) *m*-CPBA (1 equiv), CH_2Cl_2, 0 °C; (c) TBSOTf (1.2 equiv), 2,6-lutidine (3 equiv), CH_2Cl_2, 0 °C, 66% (three steps); (d) $NaBH_4$ (4 equiv), EtOH, 0 °C, 58%; (e) MsCl (7 equiv), Et_3N (10 equiv), CH_2Cl_2, 0 °C.



Scheme 3. Synthesis of **3a** and **3b**. (a) LiHMDS (2.5 equiv), Tf_2NPh (2.5 equiv), DME, −75 °C; (b) $Pd(OAc)_2$ (0.1 equiv), *n*-Ph_3P (0.2 equiv), *n*-Bu_3N (3.0 equiv), HCO_2H (2.0 equiv), DMF, 60 °C (**12a**: 49%, two steps, **12b**: 32% two steps); (c) 9-BBN (2.5 equiv), THF, rt, then, 3 mol/L NaOH/30% H_2O_2(1/1), rt (**13a**: 39%, **13b**: 29%); (d) AcOH, 60 °C; (e) 10% KOH aq, EtOH, 0 °C; (f) CSA (2.5 equiv), THF/MeOH, 0 °C (**3a**: 31%, three steps, **3b**: 37% three steps).

into **10a** under a variety of Wolff–Kishner reaction conditions was also unsuccessful.[9]

Thus, conversion of **6a**–**13a** was attempted by applying hydroboration reaction to the olefin **12a** (Scheme 3). Reaction of ketone **6a** with lithium hexamethyldisilazide and *N*-phenyltrifluoromethanesulfonimide in DME gave vinyl triflate **11a**.[10] Reduction of **11a** to the corresponding alkene **12a**[10] was conducted in 49% yield (two steps) with formic acid and tri-*n*-butylamine in the presence of catalytic amounts of palladium diacetate (10 mol %) and triphenylphosphine (20 mol %). Regio- and stereoselective hydroboration reaction of **12a** was conducted with the bulky reagent 9-BBN at room temperature, affording the 1α-hydroxy-3,5-cyclovitamin D_2 derivative **13a** exclusively in 39% yield after oxidation with H_2O_2 and sodium hydroxide.[11] Cycloreversion of **13a** with acetic acid followed by hydrolysis of the resulting acetate with potassium hydroxide in ethanol gave a diol. Finally, the methoxymethyl ether group at C25 was deprotected with camphor sulfonic acid in THF/MeOH to give 1α,25-dihydroxy-19-norvitamin D_2 (**3a**) in 31% yield from **13a**. The vitamin D_3 analog **3b** was synthesized from **6b** in six steps in 4% yield.

The present synthetic route was successfully applied to **2a** without protecting the hydroxyl group at C25 (Scheme 4). Every reaction proceeded similarly to that in the 25-protected case, and paricalcitol (**3a**) was obtained efficiently obtained in nine steps with 3% overall yield.

3. Conclusions

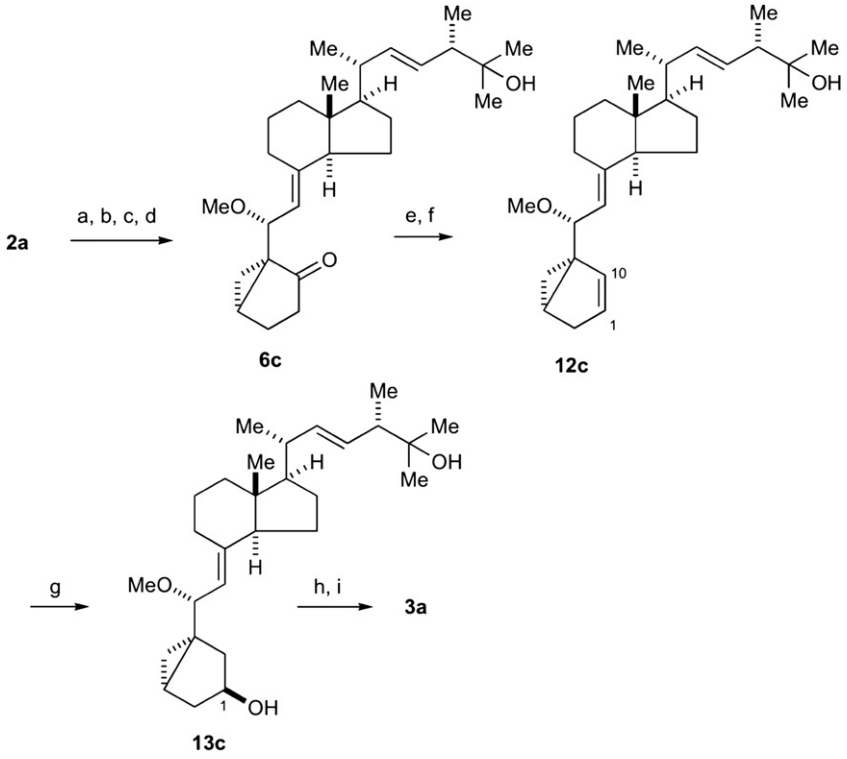
In conclusion we have succeeded in developing a novel direct synthesis of C1 hydroxylated 19-norvitamin D analogs from the corresponding 25-hydroxyvitamin D precursors in a highly regio- and stereoselective manner. The key step is a hydroboration reaction of alkene **12**, which is expected to be a useful synthetic intermediate for a variety of new vitamin D analogs.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on BURKER AVANCE 500 instrument. Mass spectra were recorded on Agilent Technologies Ion Trap LC/MS 6320 spectrometer and JEOL JMS-T100X spectrometer with ESI-MS mode using methanol as solvent. Preparative chromatography was performed using Silica gel 60 N (spherical, neutral, particle size 63–2 mm, Kanto Chemical Co., Inc., Japan) or preparative TLC (silica gel 60 F2541.05744, Merck).

*4.1.1. 6-Methoxy-25-methoxymethyloxy-3,5-cyclovitamin D2 (**4a**).* To a solution of **2a** (2.90 g, 7.0 mmol) in pyridine (40.0 mL) was added *p*-toluenesulfonyl chloride (6.80 g, 35.7 mmol) at 0 °C. After being



Scheme 4. Synthesis of **3a** from **2a**. (a) *p*-TsCl (5.0 equiv), Py rt; (b) MeOH, $NaHCO_3$ (27 equiv), 70 °C; (c) OsO_4 (0.9 equiv), Py; (d) $NaIO_4$ (3.0 equiv), MeOH, 0 °C, 52% (four steps); (e) LiHMDS (2.5 equiv), Tf_2NPh (2.5 equiv), DME, −75 °C; (f) $Pd(OAc)_2$ (0.1 equiv), *n*-Ph_3P (0.2 equiv), *n*-Bu_3N (3.0 equiv), HCO_2H (2.0 equiv), DMF, 60 °C, 22% (two steps); (g) 9-BBN (2.5 equiv), THF, rt, then, 3 mol/L NaOH/30% H_2O_2(1/1), rt; (h) AcOH, 55 °C; (i) 10% KOH aq, EtOH, rt, 25% (three steps).

stirred for 17 h at room temperature, the solution was adjusted to 0 °C and quenched with water (30 mL). The solution was concentrated, added water (50 mL) and extracted with ethyl acetate (50 mL×three times). The organic layer was washed with water, 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, yielding crude 25-hydroxyvitamin D_2 tosylate (3.98 g). Crude tosylate (2.53 g, 4.5 mmol) and sodium hydrogencarbonate (10.3 g, 122.5 mmol) in methanol (100 mL) was stirred for 9 h at 55 °C. After cooling, the reaction mixture was filtered through a pad of Celite. The filtrates were concentrated in vacuo, added water (50 mL) and extracted with ethyl acetate (80 mL×two times). The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The filtrates were concentrated in vacuo to give crude 25-hydroxy-3,5-cyclovitamin D_2 (1.89 g). To a solution of crude 25-hydroxy-3,5-cyclovitamin D_2 (1.62 g, 3.8 mmol) in dichloromethane (30 mL) was added diisopropylethylamine (6.3 mL, 36.4 mmol), methoxymethyl chloride (1.35 mL, 17.9 mmol), and *N*,*N*-dimethylaminopyridine (44.6 mg, 0.36 mmol) at 0 °C. The reaction mixture was stirred for 6 h at room temperature, and concentrated in vacuo. To the residue was added water (15 mL) and extracted with ethyl acetate (30 mL×three times). The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give crude **4a** (1.69 g) as a brown amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.35 (dd, 1H, *J*=8 and 15 Hz, H23), 5.27 (dd, 1H, *J*=8 and 15 Hz, H22), 5.03 (d, 1H, *J*=12 Hz, H7), 5.01 (br s, 1H, H19a), 4.84 (br s, 1H, H19b), 4.70 (s, 2H, MOM–CH_2), 4.17 (d, 1H, *J*=9 Hz, H6), 3.33 (s, 3H, MOM–CH_3), 3.23 (s, 3H, OMe), 2.68 (m, 1H, H9a), 2.21 (m, 2H), 2.12–1.99 (m, 4H), 1.77–1.25 (m, 11H), 1.17 (s, 3H, H26), 1.13 (s, 3H, H27), 1.03 (d, 3H, *J*=7 Hz, H21), 0.99 (d, 3H, *J*=7 Hz, H28), 0.94 (dd, 1H, *J*=5 and 8 Hz, H4a), 0.75 (t, 1H, *J*=5 Hz, H4b), 0.58 (s, 3H, H18); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 153.41 (C10), 144.84 (C8), 138.46 (C22), 131.24 (C23), 120.33 (C7), 104.36 (C19), 91.93 (MOM–CH_2), 79.44 (C6), 79.15 (C25), 57.80 (C17), 57.13 (C14), 56.14 (OMe), 55.46 (MOM–CH_3), 48.11 (C24), 46.58 (C13), 41.85 (C20), 41.59 (C12), 36.70 (C5), 31.24 (C1), 30.44 (C9), 28.97 (C16), 26.38 (C2), 25.73 (C3), 25.21 (C26), 24.72 (C11), 23.60 (C27), 23.19 (C15), 21.47 (C21), 17.31 (C4), 15.68 (C28), 12.73 (C18); ESI-MS *m*/*z*=493.52 $[M+Na]^+$, 505.72 $[M+Cl]^-$; HRMS calcd for $C_{31}H_{50}O_5Na$ 493.3657, found 493.3623.

*4.1.2. 10,19-Dihydro-6-methoxy-25-methoxymethyloxy-3,5-cyclovitamin D2 (**5a**).* To a solution of crude **4a** (1.05 g, 2.2 mmol) in pyridine (7 mL) was added dropwise a pyridine (3 mL) solution of osmium tetraoxide (0.53 g, 2.1 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The solution was adjusted to 0 °C and 40 mL of 10% $NaHSO_3$ was added, and the mixture was stirred for 2 h at room temperature. The reaction mixture was extracted with ethyl acetate (50 mL×three times), and the organic layer was washed with water, 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give crude **5a** (1.04 g) as a brown amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.36 (dd, 1H, *J*=8 and 15 Hz, H23), 5.27 (dd, 1H, *J*=8 and 15 Hz, H22), 4.89 (d, 1H, *J*=9 Hz, H6), 4.70 (s, 2H, MOM–CH_2), 4.58 (d, 1H, *J*=9 Hz, H7), 3.65 (d, 1H, *J*=11 Hz, H19a), 3.58 (d, 1H, *J*=11 Hz, H19b), 3.34 (s, 3H, MOM–CH_3), 3.20 (s, 3H, OMe), 2.71 (m, 1H, H9a), 2.20 (m, 1H, H24), 2.03 (m, 4H), 1.73 (m, 3H), 1.63 (dd, 1H, *J*=7 and 12 Hz, H2b), 1.56–1.30 (m, 9H), 1.17 (s, 3H, H26), 1.13 (s, 3H, H27), 1.03 (d, 3H, *J*=7 Hz, H21), 0.99 (d, 3H, *J*=7 Hz, H28), 0.60 (s, 3H, H18), 0.50 (dd, 1H, *J*=5 and 8 Hz, H4a), 0.38 (t, 1H, *J*=5 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 146.78 (C8), 138.42 (C22), 131.29 (C23), 119.22 (C7), 91.94 (MOM–CH_2), 85.06 (C10), 79.45 (C25), 78.75 (C6), 68.34 (C19), 57.77 (C17), 57.04 (C14), 55.89 (OMe), 55.47 (MOM–CH_3),48.53 (C24), 48.11 (C13), 41.84 (C20), 41.42 (C12), 36.49 (C5), 33.77 (C1), 30.19 (C9), 28.93 (C16), 25.27 (C2), 25.20 (C26), 24.44 (C11), 23.61 (C27), 23.30 (C15), 21.45 (C21), 21.37 (C3), 15.67 (C28), 12.89 (C18), 11.86 (C4); ESI-MS *m*/*z*=527.56 $[M+Na]^+$, 539.63 $[M+Cl]^-$; HRMS calcd for $C_{31}H_{52}O_5Na$ 527.3712, found 527.3672.

*4.1.3. 10,19-Dihydro-6-methoxy-25-methoxymethyloxy-3,5-cyclovitamin D 3 (**5b**).* As described for **5a**, **2b** (1.07 g, 2.7 mmol) was converted into crude **5b** (1.08 g) as a brown amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 4.90 (d, 1H, *J*=9 Hz, H6), 4.68 (s, 2H, MOM–CH_2), 4.58 (d, 1H, *J*=9 Hz, H7), 3.65 (d, 1H, *J*=11 Hz, H19a), 3.58 (d, 1H, *J*=11 Hz, H19b), 3.33 (s, 3H, MOM–CH_3), 3.20 (s, 3H, OMe), 2.70 (m, 1H, H9a), 2.18 (m, 3H), 1.93 (m, 1H, H16a), 1.70(m, 2H), 1.63 (dd, 1H, *J*=7 and 12 Hz, H2b), 1.58–1.20 (m, 15H), 1.20 (s, 6H, H26 and H27), 1.07 (m, 1H, H22b), 0.96 (d, 3H, *J*=6 Hz, H21), 0.59 (s, 3H, H18), 0.51 (dd, 1H, *J*=5 and 8 Hz, H4a), 0.38 (t, 1H, *J*=5 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 146.88 (C8), 119.17 (C7), 92.01 (MOM–CH_2), 85.07 (C10), 78.76 (C6), 77.65 (C25), 68.34 (C19), 58.01 (C17), 56.99 (C14), 55.89 (OMe), 55.45 (MOM–CH_3), 46.64 (C13), 43.38 (C24), 41.59 (C12), 37.67 (C22), 37.46 (C20), 36.48 (C5), 33.76 (C1), 30.20 (C9), 28.70 (C16), 26.81 (C26), 26.73 (C27), 25.27 (C2), 24.46 (C11), 23.34 (C15), 21.62 (C23), 21.33 (C3), 19.38 (C21), 12.61 (C18), 11.85 (C4); ESI-MS *m*/*z*=515.47$[M+Na]^+$, 527.50$[M+Cl]^-$; HRMS calcd for $C_{30}H_{52}O_5Na$ 515.3712, found 515.3705.

*4.1.4. 10-Keto-6-methoxy-25-methoxymethyloxy-3,5-cyclovitamin D2 (**6a**).* To a solution of crude **5a** (1.03 g, 2.0 mmol) in methanol (10 mL) was added dropwise an aqueous solution (9 mL) of sodium periodate (1.32 g, 6.1 mmol) at 0 °C, and the mixture was stirred for 2 h at 0 °C. The reaction mixture was added saturated $NaHCO_3$ (10 mL), concentrated, diluted with water (80 mL), and extracted with ethyl acetate (50 mL×three times). The organic layer was then washed with water, 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel 60 N 18.5 g, *n*-hexane/ethyl acetate=6/1) to give **6a** (312.6 mg, combined five-step yield of 29% from 25-hydroxyvitamin D_2 (**2a**)) as a slightly yellow oil. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.35 (dd, 1H, *J*=8 and 15 Hz, H23), 5.27 (dd, 1H, *J*=8 and 15 Hz, H22), 4.70 (s, 2H, MOM–CH_2), 4.65 (d, 1H, *J*=9 Hz, H6), 4.61 (d, 1H, *J*=9 Hz, H7), 3.33 (s, 3H, MOM–CH_3), 3.18 (s, 3H, OMe), 2.69 (m, 1H, H9a), 2.20 (m, 3H), 2.03 (m, 6H), 1.74 (m, 3H), 1.56–1.23 (m, 7H), 1.17 (s, 3H, H26), 1.13 (s, 3H, H27), 1.03 (d, 3H, *J*=7 Hz, H21), 1.03 (m, 1H, H4b), 0.99 (d, 3H, *J*=7 Hz, H28), 0.57(s, 3H, H18); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 216.72 (C10), 146.83 (C8), 138.43 (C22), 131.29 (C23), 118.32 (C7), 91.90 (MOM–CH_2), 79.46 (C25), 74.69 (C6), 57.76 (C17), 57.07 (C14), 56.47 (OMe), 55.47 (MOM–CH_3), 48.11 (C24), 46.57 (C13), 41.98 (C5), 41.84 (C20), 41.44 (C12), 33.93 (C1), 30.35 (C9), 28.93 (C16), 25.78 (C3), 25.20 (C26), 24.58 (C11), 23.61 (C27), 23.15 (C15), 22.50 (C2), 21.45 (C21), 17.97 (C4), 15.67 (C28), 12.74 (C18); ESI-MS *m*/*z*=495.33$[M+Na]^+$, 507.41$[M+Cl]^-$; HRMS calcd for $C_{30}H_{48}O_4Na$ 495.3450, found 495.3489.

*4.1.5. 10-Keto-6-methoxy-25-methoxymethyloxy-3,5-cyclovitamin D3 (**6b**).* As described for **6a**, crude **5b** (1.08 g, 2.2 mmol) was converted into **6b** (453.8 mg, 38% from 25-hydroxyvitamin D_3 (**2b**)) as a brown oil. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 4.68 (s, 2H, MOM–CH_2), 4.65 (d, 1H, *J*=9 Hz, H6), 4.62 (d, 1H, *J*=9 Hz, H7), 3.33 (s, 3H, MOM–CH_3), 3.18 (s, 3H, OMe), 2.63 (m, 1H, H9a), 2.19 (m, 2H), 2.06 (m, 4H), 1.95 (m, 2H), 1.72 (m, 2H), 1.55–1.23 (m, 13H), 1.20 (s, 6H, H26 and H27), 1.03 (m, 2H), 0.96 (d, 3H, *J*=6 Hz, H21), 0.57 (s, 3H, H18); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 216.71 (C10), 146.89 (C8), 118.22 (C7), 91.97 (MOM–CH_2), 77.62 (C25), 74.70 (C6), 57.96 (C17), 56.99 (C14), 56.45 (OMe), 55.41 (MOM–CH_3), 46.64 (C13), 43.34 (C24), 41.95 (C5), 41.57 (C12), 37.64 (C22), 37.42 (C20), 33.90 (C1), 30.32 (C9), 28.68 (C16), 26.77 (C26), 26.69 (C27), 25.73 (C3),

24.57 (C11), 23.16 (C15), 22.47 (C2), 21.58 (C23), 19.35 (C21), 17.97 (C4), 12.42 (C18); ESI-MS m/z=483.40[M+Na]$^+$, 495.51[M+Cl]$^-$; HRMS calcd for $C_{29}H_{48}O_4Na$ 483.3450, found 483.3442.

*4.1.6. 25-Hydroxy-10-keto-6-methoxy-3,5-cyclovitamin D_2 (**6c**).* As described for **6a**, **2a** (518 mg, 1.3 mmol) was converted into **6c** (279.0 mg, 52% from 25-hydroxyvitamin D_2 (**2a**)) as a brown oil. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.35 (dd, 1H, J=8 and 15 Hz, H23), 5.27 (dd, 1H, J=8 and 15 Hz, H22), 4.65 (d, 1H, J=10 Hz, H6), 4.61 (d, 1H, J=10 Hz, H7), 3.18 (s, 3H, OMe), 2.67 (m, 1H, H9a), 2.20 (m, 2H), 2.03 (m, 7H), 1.71 (m, 3H), 1.59–1.17 (m, 7H), 1.13 (s, 3H, H26), 1.09 (s, 3H, H27), 1.06 (t, 1H, J=5 Hz, H4b), 1.04 (d, 3H, J=7 Hz, H21), 0.99 (d, 3H, J=7 Hz, H28), 0.57 (s, 3H, H18); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 216.73 (C10), 146.85 (C8), 138.33 (C22), 131.55 (C23), 118.31 (C7), 74.69 (C6), 73.36 (C25), 57.77 (C17), 57.08 (C14), 56.47 (OMe), 49.20 (C24), 46.57 (C13), 41.98 (C5), 41.84 (C20), 41.44 (C12), 33.93 (C1), 30.35 (C9), 28.93 (C16), 28.32 (C26), 26.13 (C27), 25.77 (C3), 24.59 (C11), 23.15 (C15), 22.50 (C2), 21.45 (C21), 17.98 (C4), 15.68 (C28), 12.74 (C18); ESI-MS m/z=451.4 [M+Na]$^+$, 463.4 [M+Cl]$^-$; HRMS calcd for $C_{28}H_{44}O_3Na$ 451.3188, found 451.3184.

*4.1.7. 6-Methoxy-25-methoxymethyloxy-10-triflate-3,5-cyclovitamin D_2 (**11a**).* To a solution of **6a** (150 mg, 0.32 mmol) in dimethoxyethane (3.5 mL) was added dropwise a dimethoxyethane (1.5 mL) solution of lithium hexamethyldisilazide (1.6 M in THF, 495 μL, 0.79 mmol) at −75 °C. The mixture was stirred for 1 h at −75 to −70 °C. To this reaction mixture was added *N*-phenylbis(trifluoromethanesulfonimide) (284 mg, 0.79 mmol), and the resulting mixture was stirred at −75 to 15 °C for 15 h. The reaction mixture was concentrated, diluted with water (5 mL), and extracted with ethyl acetate (10 mL×three times). The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give crude **11a** (290.8 mg) as a brown amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.36 (dd, 1H, J=8 and 15 Hz, H23), 5.32 (d, 1H, J=2 Hz, H1), 5.28 (dd, 1H, J=8 and 15 Hz, H22), 4.70 (s, 2H, MOM–CH_2), 4.65 (d, 1H, J=10 Hz, H7), 4.37 (d, 1H, J=10 Hz, H6), 3.44 (s, 3H, MOM–CH_3), 3.23 (s, 3H, OMe), 2.60 (m, 2H), 2.35 (dd, 1H, J=2 and 17 Hz, H2b), 2.20 (m, 1H, H24), 2.03 (m, 3H), 1.75 (m, 4H), 1.45 (m, 3H), 1.35 (m, 3H), 1.17 (s, 3H, H26), 1.13 (s, 3H, H27), 1.09 (dd, 1H, J=5 and 8 Hz, H4a), 1.04 (d, 3H, J=7 Hz, H21), 0.99 (d, 3H, J=7 Hz, H28), 0.57 (s, 3H, H18), 0.53 (t, 1H, J=5 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 153.88 (C10), 147.23 (C8), 138.37 (C22), 131.28 (C23), 118.09 (C7), 114.97 (C1), 91.91 (MOM-CH_2), 79.43 (C25), 76.51 (C6), 57.73 (C17), 57.03 (C14), 56.44 (OMe), 55.44 (MOM–CH_3), 48.08 (C24), 46.52 (C13), 41.80 (C20), 41.36 (C12), 36.90 (C5), 31.02 (C2), 30.31 (C9), 28.88 (C16), 25.16 (C26), 24.73 (C11), 23.58 (C27), 23.08 (C15), 21.41 (C21), 20.08 (C4), 18.55 (C3), 15.63 (C28), 12.65 (C18); ESI-MS m/z=627.35 [M+Na]$^+$; HRMS calcd for $C_{31}H_{47}F_3O_6SiNa$ 627.2943, found 627.2970.

*4.1.8. 6-Methoxy-25-methoxymethyloxy-10-triflate-3,5-cyclovitamin D_3 (**11b**).* As described for **11a**, **6b** (315.9 mg, 0.68 mmol) was converted into crude **11b** (733.9 mg) as a brown amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.33 (d, 1H, J=2 Hz, H1), 4.68 (s, 2H, MOM–CH_2), 4.66 (d, 1H, J=9 Hz, H7), 4.37 (d, 1H, J=9 Hz, H6), 3.33 (s, 3H, MOM–CH_3), 3.24 (s, 3H, OMe), 2.59 (m, 2H), 2.34 (dd, 1H, J=2 and 17 Hz, H2b), 2.02 (m, 2H), 1.93 (m, 1H, H16a), 1.74 (m, 3H), 1.51–1.25 (m, 12H), 1.20 (s, 6H, H26 and H27), 1.09 (dd, 1H, J=4 and 8 Hz, H4a), 1.07 (m, 1H, H22b), 0.96 (d, 3H, J=6 Hz, H21), 0.56 (s, 3H, H18), 0.52 (t, 1H, J=4 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 153.92 (C10), 147.33 (C8), 118.10 (C7), 115.01 (C1), 92.01 (MOM–CH_2), 77.64 (C25), 76.57 (C6), 58.00 (C17), 57.02 (C14), 56.47 (OMe), 55.44 (MOM–CH_3), 46.66 (C13), 43.38 (C24), 41.56 (C12), 37.67 (C22), 37.47 (C20), 36.94 (C5), 31.06 (C2), 30.35 (C9), 28.70 (C16), 26.80 (C26), 26.73 (C27), 24.79 (C11), 23.16 (C15), 21.62 (C23), 20.13 (C4), 19.38 (C21), 18.59 (C3), 12.40 (C18); ESI-MS m/z=615.37[M+Na]$^+$; HRMS calcd for $C_{30}H_{47}F_3O_6SiNa$ 615.2943, found 615.2990.

*4.1.9. 6-Methoxy-25-methoxymethyloxy-1,10-olefin-3,5-cyclovitamin D_2 (**12a**).* To a solution of crude **11a** (0.32 mmol), triphenylphosphine (16.8 mg, 0.063 mmol), and palladium diacetate (7.1 mg, 0.031 mmol) in DMF (4 mL) was added dropwise tributylamine (227 mL, 0.95 mmol) and formic acid (24 mL, 0.63 mmol) at room temperature, and the resulting mixture was stirred at 60 °C for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL×three times). The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel 60 N 4.0 g, *n*-hexane/acetone=50/1) to give **12a** (71.6 mg, 49% from **6a**) as a slightly yellow oil. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.90 (td, 1H, J=2 and 5 Hz, H10), 5.39 (brd, 1H, J=4 Hz, H1), 5.35 (dd, 1H, J=8 and 15 Hz, H23), 5.27 (dd, 1H, J=8 and 15 Hz, H22), 4.87 (d, 1H, J=10 Hz, H7), 4.70 (s, 2H, MOM–CH_2), 3.97 (d, 1H, J=10 Hz, H6), 3.33 (s, 3H, MOM–CH_3), 3.25 (s, 3H, OMe), 2.61 (dd, 1H, J=5 and 13 Hz, H9a), 2.54 (m, 1H, H2a), 2.27 (brd, 1H, J=18 Hz, H2b), 2.20 (m, 1H, H24), 2.03 (m, 3H), 1.72 (m, 2H), 1.47 (m, 4H), 1.34 (m, 4H), 1.17 (s, 3H, H26), 1.13(s, 3H, H27), 1.03 (m, 1H, H4a), 1.03 (d, 3H, J=7 Hz, H21), 0.98 (d, 3H, J=7 Hz, H28), 0.55 (s, 3H, H18), 0.16 (t, 1H, J=4 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 144.29 (C8), 138.44 (C22), 135.37 (C10), 131.20 (C23), 128.95 (C1), 121.04 (C7), 91.90 (MOM–CH_2), 80.18 (C6), 79.43 (C25), 57.77 (C17), 57.05 (C14), 56.09 (OMe), 55.43 (MOM–CH_3), 48.08 (C24), 46.61 (C13), 41.83 (C20), 41.61 (C12), 41.28 (C5), 36.91 (C2), 30.50 (C9), 28.95 (C16), 25.16 (C26), 25.13 (C11), 23.56 (C27), 23.04 (C15), 22.48 (C4), 21.42 (C21), 19.98 (C3), 15.63 (C28), 12.48 (C18); ESI-MS m/z=479.38[M+Na]$^+$; HRMS calcd for $C_{30}H_{48}O_3Na$ 479.3501, found 479.3517.

*4.1.10. 6-Methoxy-25-methoxymethyloxy-1,10-olefin-3,5-cyclovitamin D_3 (**12b**).* As described for **12a**, crude **11b** (0.68 mmol) was converted into **12b** (98.7 mg, 32% from **6b**) as a slightly yellow amorphous after column chromatography (silica gel 60 N 7.5 g, *n*-hexane/ethyl acetate=60/1–6/1). ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.90 (td, 1H, J=2 and 5 Hz, H10), 5.39 (brd, 1H, J=5 Hz, H1), 4.87 (d, 1H, J=9 Hz, H7), 4.67 (s, 2H, MOM–CH_2), 3.97 (d, 1H, J=9 Hz, H6), 3.33 (s, 3H, MOM–CH_3), 3.25 (s, 3H, OMe), 2.61 (dd, 1H, J=4 and 11 Hz, H9a), 2.54 (m, 1H, H2a), 2.27 (brd, 1H, J=17 Hz, H2b), 2.01 (m, 2H), 1.92 (m, 1H, H16a), 1.70 (m, 2H), 1.51–1.22 (m, 12H), 1.23 (s, 6H, H26 and H27), 1.03 (m, 1H, H22b), 1.03 (dd, 1H, J=4 and 8 Hz, H4a), 0.96 (d, 3H, J=6 Hz, H21), 0.58 (s, 3H, H18), 0.16 (t, 1H, J=4 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 144.38 (C8), 135.38 (C10), 128.95 (C1), 121.00 (C7), 91.97 (MOM–CH_2), 80.20 (C6), 77.62 (C25), 58.01 (C17), 57.01 (C14), 56.10 (OMe), 55.42 (MOM–CH_3), 46.71 (C13), 43.35 (C24), 41.78 (C12), 41.29 (C5), 37.67 (C2), 37.46 (C20), 36.92 (C22), 30.51 (C9), 28.74 (C16), 26.77 (C26), 26.70 (C27), 25.16 (C11), 23.09 (C15), 22.49 (C4), 21.59 (C23), 19.97 (C3), 19.38 (C21), 12.20 (C18); ESI-MS m/z=467.45[M+Na]$^+$; HRMS calcd for $C_{29}H_{48}O_5Na$ 467.3501, found 467.3453.

*4.1.11. 25-Hydroxy-6-methoxy-1,10-olefin-3,5-cyclovitamin D_2 (**12c**).* As described for **11a** and **12a**, **6c** (100 mg, 0.23 mmol) was converted into **12c** (20.8 mg, 22% from **6c**) as a slightly yellow amorphous after purification by preparative TLC (*n*-hexane/acetone=3/1). ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.90 (td, 1H, J=2 and 5 Hz, H10), 5.39 (brd, 1H, J=5 Hz, H1), 5.35 (dd, 1H, J=8 and 15 Hz, H23), 5.27 (dd, 1H, J=8 and 15 Hz, H22), 4.87 (d, 1H, J=10 Hz, H7), 3.97 (d, 1H, J=10 Hz, H6), 3.25 (s, 3H, OMe), 2.61 (dd, 1H, J=4 and 11 Hz, H9a), 2.54 (m, 1H, H2a), 2.27 (brd, 1H, J=17 Hz, H2b), 2.04 (m, 4H), 1.72 (m, 4H), 1.48 (m, 3H), 1.34 (m, 3H), 1.13 (s, 3H, H26), 1.09 (s, 3H, H27), 1.03 (m, 1H, H4a), 1.03 (d, 3H,

J=7 Hz, H21), 0.99 (d, 3H, *J*=7 Hz, H28), 0.55 (s, 3H, H18), 0.16 (t, 1H, *J*=4 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 144.35 (C8), 138.39 (C22), 135.41 (C10), 131.50 (C23), 128.99 (C1), 121.07 (C7), 80.22 (C6), 73.36 (C25), 57.82 (C17), 57.10 (C14), 56.13 (OMe), 49.22 (C24), 46.65 (C13), 41.86 (C20), 41.66 (C12), 41.32 (C5), 36.95 (C2), 30.54 (C9), 28.99 (C16), 28.33 (C26), 26.12 (C27), 25.17 (C11), 23.08 (C15), 22.52 (C4), 21.47 (C21), 20.01 (C3), 15.69 (C28), 12.52 (C18); ESI-MS *m*/*z*=435.38[M+Na]$^+$, 447.43[M+Cl]$^-$; HRMS calcd for $C_{28}H_{44}O_2Na$ 435.3239, found 435.3223.

*4.1.12. 1α-Hydroxy-25-methoxymethyloxy-3,5-cyclovitamin D$_2$ (**13a**).* To a solution of **12a** (44.9 mg, 0.098 mmol) in THF (1 mL) was added dropwise 9-borabicyclo[3.3.1]nonane 0.5 M in THF (490 μL, 0.25 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. To the resulting mixture was added water (300 μL), 30% H_2O_2 (300 μL) and 3 M NaOH (300 μL) at 0 °C, and the mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL×three times). The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (*n*-hexane/acetone=3/1) to give **13a** (18.0 mg, 39%) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.36 (dd, 1H, *J*=8 and 15 Hz, H23), 5.28 (dd, 1H, *J*=8 and 15 Hz, H22), 4.94 (d, 1H, *J*=9 Hz, H7), 4.70 (s, 2H, MOM–CH_2), 3.92 (m, 1H, H1), 3.89 (d, 1H, *J*=9 Hz, H6), 3.34 (s, 3H, MOM–CH_3), 3.21 (s, 3H, OMe), 2.64 (m, 1H, H9a), 2.20 (m, 1H, H24), 2.03 (m, 4H), 1.78–1.28 (m, 12H), 1.17 (m, 1H, H3), 1.17 (s, 3H, H26), 1.13 (s, 3H, H27), 1.04 (d, 3H, *J*=7 Hz, H21), 0.99 (d, 3H, *J*=7 Hz, H28), 0.62 (s, 3H, H18), 0.55 (dd, 1H, *J*=4 and 8 Hz, H4a), 0.33 (t, 1H, *J*=4 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 144.86 (C8), 138.47 (C22), 131.24 (C23), 120.41 (C7), 91.94 (MOM–CH_2), 81.19 (C6), 79.45 (C25), 71.26 (C1), 57.76 (C17), 57.18 (C14), 56.20 (OMe), 55.46 (MOM–CH_3), 48.11 (C24), 46.58 (C13), 41.87 (C20), 41.61 (C12), 37.90 (C10), 37.31 (C2), 31.56 (C5), 30.53 (C9), 29.01 (C16), 25.20 (C26), 25.01 (C11), 23.60 (C27), 23.15 (C15), 21.48 (C21), 19.49 (C3), 15.67 (C28), 14.80 (C4), 12.83 (C18); ESI-MS *m*/*z*=497.34[M+Na]$^+$, 509.35[M+Cl]$^-$.

*4.1.13. 1α-Hydroxy-25-methoxymethyloxy-3,5-cyclovitamin D$_3$ (**13b**).* As described for **13a**, **12b** (33 mg, 0.074 mmol) was converted into **13b** (10.0 mg, 29%) as a colorless oil after purification by preparative TLC (*n*-hexane/ethyl acetate=3/1). ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 4.95 (d, 1H, *J*=9 Hz, H7), 4.69 (s, 2H, MOM–CH_2), 3.93 (m, 1H, H1), 3.89 (d, 1H, *J*=9 Hz, H6), 3.33 (s, 3H, MOM–CH_3), 3.21 (s, 3H, OMe), 2.63 (m, 1H, H9a), 2.04 (m, 4H), 1.93 (m, 1H, H16a), 1.75 (dd, 1H, *J*=8 and 13 Hz, H10b), 1.71–1.24 (m, 14H), 1.20 (s, 6H, H26 and H27), 1.13 (m, 1H, H3), 1.05 (m, 1H, H22b), 0.97 (d, 3H, *J*=7 Hz, H21), 0.62 (s, 3H, H18), 0.55 (dd, 1H, *J*=5 and 9 Hz, H4a), 0.38 (t, 1H, *J*=5 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 144.92 (C8), 120.33 (C7), 91.97 (MOM–CH_2), 81.20 (C6), 77.62 (C25), 71.24 (C1), 58.01 (C17), 57.10 (C14), 56.17 (OMe), 55.41 (MOM–CH_3), 46.67 (C13), 43.35 (C24), 41.75 (C12), 37.85 (C10), 37.67 (C2), 37.46 (C20), 37.27 (C22), 31.53 (C5), 30.52 (C9), 28.76 (C16), 26.77 (C26), 26.70 (C27), 25.00 (C11), 23.16 (C15), 21.60 (C23), 19.46 (C3), 19.39 (C21), 14.79 (C4), 12.52 (C18); ESI-MS *m*/*z*=485.43[M+Na]$^+$, 497.30[M+Cl]$^-$; HRMS calcd for $C_{29}H_{50}O_4Na$ 485.3606, found 485.3572.

*4.1.14. 1α,25-Dihydroxy-3,5-cyclovitamin D$_2$ (**13c**).* As described for **13a**, **12c** (19.8 mg, 0.048 mmol) was converted into crude **13c** (86.1 mg) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 5.35 (dd, 1H, *J*=8 and 15 Hz, H23), 5.27 (dd, 1H, *J*=8 and 15 Hz, H22), 4.94 (d, 1H, *J*=9 Hz, H7), 3.92 (m, 1H, H1), 3.89 (d, 1H, *J*=9 Hz, H6), 3.21 (s, 3H, OMe), 2.64 (m, 1H, H9a), 2.11–1.99 (m, 6H), 1.83–1.26 (m, 10H), 1.13 (m, 1H, H3), 1.13 (s, 3H, H26), 1.09 (s, 3H, H27), 1.04 (d, 3H, *J*=7 Hz, H21), 0.99 (d, 3H, *J*=7 Hz, H28), 0.62 (s, 3H, H18), 0.55 (dd, 1H, *J*=4 and 8 Hz, H4a), 0.37 (t, 1H, *J*=4 Hz, H4b); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 144.87 (C8), 138.38 (C22), 131.51 (C23), 120.41 (C7), 81.19 (C6), 73.35 (C25), 71.27 (C1), 57.82 (C17), 57.19 (C14), 56.20 (OMe), 49.00 (C24), 46.59 (C13), 41.86 (C20), 41.62 (C12), 37.91 (C10), 37.31 (C2), 31.56 (C5), 30.54 (C9), 29.00 (C16), 28.33 (C26), 26.12 (C27), 25.01 (C11), 23.15 (C15), 21.48 (C21), 19.49 (C3), 15.69 (C28), 14.80 (C4), 12.83 (C18); ESI-MS *m*/*z*=453.37[M+Na]$^+$, 465.61[M+Cl]$^-$; HRMS calcd for $C_{28}H_{46}O_3Na$ 453.3344, found 453.3300.

*4.1.15. 1α,25-Dihydroxy-19-norvitamin D$_2$, Paricalcitol (**3a**).* A solution of **13a** (17.1 mg, 0.036 mmol) in acetic acid (0.4 mL) was stirred for 20 min at 60 °C. This solution was diluted with ice and saturated $NaHCO_3$ (10 mL), and extracted with ethyl acetate (5 mL×three times). The organic layer was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. To the residue (17.3 mg) was added a 10% KOH–ethanol solution (0.5 mL) at 0 °C, and stirred for 1 h. The reaction mixture was concentrated, diluted with water (5 mL), and extracted with ethyl acetate (5 mL×three times). The organic layer was then washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, to give crude 1α-hydroxy-25-methoxymethyloxy-19-norvitamin D_2 (15.2 mg) as a colorless amorphous. To a solution of the crude (3.9 mg, 8.5 μmol) in a mixed solution (1:3) (0.5 mL) of THF and methanol was added camphor sulfonic acid (5.8 mg, 0.025 mmol) at 0 °C and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (5 mL×three times). The organic layer was then washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (chloroform/methanol=10/1) to give paricalcitol (**3a**) (1.2 mg, 31% from **13a**) as a white powder. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 6.21 (d, 1H, *J*=11 Hz, H6), 5.88 (d, 1H, *J*=11 Hz, H7), 5.35 (dd, 1H, *J*=8 and 15 Hz, H23), 5.27 (dd, 1H, *J*=8 and 15 Hz, H22), 4.04 (m, 1H, H1), 3.98 (m, 1H, H3), 2.84 (brd, 1H, *J*=11 Hz, H9a), 2.59 (brd, 1H, *J*=13 Hz, H4a), 2.41 (brd, 1H, *J*=13 Hz, H10a), 2.21 (dd, 1H, *J*=8 and 13 Hz, H4b), 2.16 (dd, 1H, *J*=7 and 13 Hz, H10b), 2.04 (m, 4H), 1.84 (m, 1H, H2a), 1.76 (m, 2H), 1.67 (m, 2H), 1.55 (m, 3H), 1.35 (m, 3H), 1.13 (s, 3H, H26), 1.09 (s, 3H, H27), 1.04 (d, 3H, *J*=7 Hz, H21), 0.99 (d, 3H, *J*=7 Hz, H28), 0.58 (s, 3H, H18); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm) 142.07 (C8), 138.46 (C22), 133.98 (C5), 131.45 (C23), 123.47 (C6), 117.22 (C7), 73.37 (C25), 68.04 (C1), 67.76 (C3), 57.84 (C17), 57.63 (C14), 49.10 (C24), 46.75 (C13), 45.46 (C10), 42.74 (C2), 41.90 (C20), 41.82 (C12), 37.69 (C4), 29.87 (C9), 29.02 (C16), 28.33 (C26), 26.12 (C27), 24.55 (C11), 23.30 (C15), 21.49(C21), 15.70 (C28), 12.75(C18); ESI-MS *m*/*z*=439.32[M+Na]$^+$, 452.53[M+Cl]$^-$; HRMS calcd for $C_{27}H_{44}O_3Na$ 439.3188, found 439.3199.

*4.1.16. 1α,25-Dihydroxy-19-norvitamin D$_2$, paricalcitol (**3a**) from **13c**.* As described for **3a**, crude **13c** (0.016 mmol) was converted into paricalcitol **3a** (1.7 mg, 25% from **12c**) as a white powder after purification by preparative TLC (chloroform/methanol=10/1).

*4.1.17. 1α,25-Dihydroxy-19-norvitamin D$_3$ (**3b**).* As described for **3a**, **13b** (9.5 mg, 0.020 mmol) was converted into 1α,25-dihydroxy-19-norvitamin D_3 (**3b**) (3.0 mg, 37% from **13b**) as a white powder after purification by preparative TLC (chloroform/methanol=10/1). ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 6.21 (d, 1H, *J*=11 Hz, H6), 5.88 (d, 1H, *J*=11 Hz, H7), 4.03 (m, 1H, H1), 3.98 (m, 1H, H3), 2.83 (m, 1H, H9a), 2.59 (dd, 1H, *J*=4 and 13 Hz, H4a), 2.41 (dd, 1H, *J*=4 and 13 Hz, H10a), 2.20 (dd, 1H, *J*=7 and 13 Hz, H4b), 2.16 (dd, 1H, *J*=6 and 13 Hz, H10b), 2.02 (m, 2H), 1.93 (m, 1H, H16a), 1.83 (m, 1H, H2a), 1.77 (m, 1H, H2b), 1.72–1.23 (m, 14H), 1.17 (s, 6H, H26 and H27), 1.07 (m, 1H, H22b), 0.96 (d, 3H, *J*=6 Hz, H21), 0.57 (s, 3H, H18); ^{13}C NMR

(125 MHz, CD_3OD) δ (ppm) 142.15 (C8), 133.93 (C5), 123.49 (C6), 117.19 (C7), 71.53 (C25), 68.04 (C1), 67.75 (C3), 58.06 (C17), 57.57 (C14), 48.54 (C13), 45.45 (C10 or C24), 43.35 (C10 or C24), 42.74 (C2), 41.98 (C12), 37.81 (C4 or C22), 37.70 (C4 or C22), 37.52 (C20), 29.88 (C9), 29.31 (C26), 29.18 (C27), 28.81 (C16), 24.57 (C11), 23.34 (C15), 21.96 (C23), 19.43 (C21), 19.46 (C18); ESI-MS m/z (%)=427.38$[M+Na]^+$, 439.39$[M+Cl]^-$; HRMS calcd for $C_{26}H_{44}O_5Na$ 427.3188, found 427.3148.

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