Supporting Information

A Concise and Efficient Route to 2α-(ω-Hydroxyalkoxy)-1α,25-dihydroxyvitamin D_3: Remarkably High Affinity to Vitamin D Receptor

Atsushi Kittaka, Yoshitomo Suhara, Hitoshi Takayanagi, Toshie Fujishima, Masaaki Kurihara,

and Hiroaki Takayama*

Experimental detail and spectroscopic characterization of compounds **5-10** (represented by n = 1) and **1a-c** (represented by **1b**).

Methyl 4,6-*O*-Benzylidene-3-*O*-(3-hydroxypropyl)-α-D-altropyranoside (5). The known epoxide **4** (2.52 g, 9.54 mmol) was suspended in 1,3-propanediol (65 mL) and KO^tBu (3.53 g, 31.5 mmol) was added. The mixture was heated at 110 °C for 14 h. After cooling, the mixture was partitioned between CH_2Cl_2 (400 mL) and saturated aqueous NH_4Cl (200 mL), and the aqueous layer was extracted by CH_2Cl_2 (2 X 200 mL). The organic extracts were combined and dried over Na_2SO_4. Silica gel column chromatography (10 - 66% EtOAc in hexane) gave diol **5** (3.06 g, 94%) as a colorless oil: $[\alpha]_D^{19.5}$ +90.7 (c 3.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75-1.91 (2H, m), 2.42 (1H, d, *J* = 5.8 Hz), 3.40 (3H, s), 3.70-3.81 (6H, m), 4.01-4.09 (3H, m), 4.29-4.34 (2H, m), 4.61 (1H, s), 5.56 (1H, s), 7.36-7.38 (3H, m), 7.47-7.50 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 55.3, 59.0, 62.8, 69.3, 69.6, 72.4, 76.5, 77.3, 101.8, 102.5, 126.2, 128.3, 129.1, 137.6; MS m/z 340 $(M)^+$; HRMS calcd for $C_{17}H_{24}O_7$ $(M)^+$ 340.1522, Found 340.1523.

Methyl 4,6-*O*-Benzylidene-3-*O*-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]-α-D-altropyranoside (6). A mixture of diol **5** (3.06 g, 8.98 mmol), imidazole (1.53 g, 22.5 mmol), and TBDMSCl (1.62 g, 10.8 mmol) in DMF (30 mL) was stirred at rt for 3 h. The mixture was partitioned between EtOAc (500 mL) and H_2O (150 mL), and the organic layer was washed with H_2O and brine (150 mL each) and dried over Na_2SO_4. Silica gel column chromatography (10 - 33% EtOAc in hexane) afforded **6** (3.74 g, 92%) as a colorless oil: $[\alpha]_D^{20}$ +68.8 (c 3.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 and 0.03 (6H, each as s), 0.87 (9H, s), 1.78-1.82 (2H, m), 1.93 (1H, br), 3.39 (3H, s), 3.65-3.80 (6H, m), 3.95 (1H, dd, *J* = 2.7 and 8.8 Hz), 3.99-4.00 (1H, m), 4.26-4.33 (2H, m), 4.89 (1H, s), 5.55 (1H, s), 7.34-7.37 (3H, m), 7.47-7.49 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 18.3, 25.9, 33.3, 55.5, 58.6, 60.2, 68.5, 69.4, 70.0, 76.4, 76.9, 102.0, 102.3, 126.0, 126.2, 128.2, 129.0, 137.7; MS m/z 454 $(M)^+$; HRMS calcd for $C_{23}H_{38}O_7Si$ $(M)^+$ 454.2387, Found 454.2387.

Methyl 4-*O*-Benzoyl-6-bromo-3-*O*-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]-6-deoxy-α-D-altropyranoside (7). To the CCl_4 (53 mL) solution of **6** (2.42 g, 5.31 mmol) were added NBS (1.04 g, 5.84 mmol) and $BaCO_3$ (586.8 mg, 2.97 mmol), and the mixture was refluxed for 40 min. After cooling, EtOAc (50 mL) was added and the insoluble materials were filtered off. The filtrate was diluted with EtOAc (350 mL) and this was washed with 0.1M aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, H_2O, and brine (50 mL each), and dried over Na_2SO_4. Silica gel column chromatography (10 - 20% EtOAc in hexane) afforded bromide **7** (2.09 g, 74%) as a colorless oil: $[\alpha]_D^{19.5}$ +46.0 (c 4.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.04 and -0.03 (6H, each as s), 0.83 (9H, s), 1.67-1.73 (2H, m), 2.52 (1H, br), 3.50 (3H, s), 3.55-3.70 (6H, m), 3.73 (1H, dd, *J* = 4.0 and 7.3 Hz), 3.97 (1H, dd, *J* = 3.3 and 7.3 Hz), 4.35 (1H, dt, *J* = 3.7 and 7.0 Hz), 4.70 (1H, d, *J* = 3.3 Hz), 5.45 (1H, dd, *J* = 4.0 and 7.0 Hz), 7.43-7.47 (2H, m), 7.57-7.58 (1H, m), 8.03-8.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5, 18.2, 25.9, 32.7, 32.9, 55.9, 60.0, 67.9, 69.3, 69.8, 69.9, 76.9, 102.7, 128.5, 129.5, 129.8, 133.3, 165.7; FTIR (neat) 1725 cm^{-1};MS m/z 475 and 477 $(M-{}^tBu)^+$; HRMS calcd for $C_{19}H_{28}{}^{79}BrO_7Si$ $(M-{}^tBu)^+$ 475.0787, Found 475.0786.

Methyl 6-Bromo-3-*O*-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]-6-deoxy-α-D-altropyranoside (8). Bromide **7** was dissolved in MeOH (50 mL) and the 28% solution of NaOMe in MeOH (50 μL) was added. The solution was stirred at rt overnight, and silica gel (20 g) was added. The mixture was concentrated *in vacuo*, and the residue was applied on silica gel column chromatography (10 - 33% EtOAc in hexane) to yield diol **8** (1.62 g, 96%) as a colorless oil: $[\alpha]_D^{24.5}$ +75.1 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 1.73-1.85 (2H, m), 2.05 (1H, br), 3.00 (1H, d, *J* = 8.8 Hz), 3.43 (3H, s), 3.54 (1H, dd, *J* = 7.3 and 10.6 Hz), 3.59 (1H, t, *J* = 4.6 Hz), 3.63 (1H, ddd, *J* = 5.5, 7.3 and 9.2 Hz), 3.69-3.82 (5H, m), 3.93-3.98 (2H, m), 4.62 (1H, d, *J* = 2.2 Hz); MS m/z 397 and 399 $(M-OMe)^+$; HRMS calcd for $C_{15}H_{30}{}^{79}BrO_5Si$ $(M)^+$ 397.1046, Found 397.1039.

Methyl 6-Bromo-2,4-bis-(*O*-*tert*-butyldimethylsilyl)-3-*O*-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]-6-deoxy-α-D-altropyranoside (9). A mixture of diol **8** (1.84 g, 4.29 mmol), imidazole (1.17 g, 17.2 mmol), and TBDMSCl (1.94 g, 12.9 mmol) in DMF (30 mL) was stirred at rt overnight. Conventional workup followed by silica gel column chromatography (10% EtOAc in hexane) afforded **9** (2.66 g, 94%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04, 0.08, 0.09 and 0.11 (18H, each as s), 0.89 and 0.90 (27H, each as s), 1.78-1.81 (2H, m), 3.37 (3H, s), 3.40 (1H, m), 3.48 (1H, dd, *J* = 7.3 and 10.6 Hz), 3.55 (1H, dt, *J* = 6.2 and 8.8 Hz), 3.64-3.72 (4H, m), 3.92-3.96 (2H, m), 4.12-4.16 (1H, m), 4.48 (1H, br); MS m/z 658 and 656 $(M)^+$; HRMS calcd for $C_{24}H_{52}{}^{79}BrO_6Si_3$ $(M-{}^tBu)^+$ 599.2256, Found 599.2250.

Methyl 6-Bromo-4-(*O* -*tert*-butyldimethylsilyl)-3-*O*-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]-6-deoxy-α-D-altropyranoside (10). To the THF (25 mL) solution of **9** (2.78 g, 4.23 mmol) was added 1M solution of Bu_4NF in THF (1.06 mL, 1.06 mmol), and the solution was stirred at rt for 2.5 h. Silica gel (10 g) was added and the mixture was concentrated *in vacuo*, and the residue was applied on silica gel column chromatography (1 - 20% EtOAc in hexane) to obtain alcohol **10** (1.16 g, 51%) as a colorless oil along with recovered **9** (647.1 mg, 23%). Further elution from the column with 50% EtOAc in hexane gave a mixture of diols (277.3 mg, 15%), which was recycled to **9** (422.3 mg, 99%) by the procedure described for silylation of **8**. The recovered **9** and reproduced **9** were combined (1.07 g, 1.63 mmol) and desilylated again by the same procedure described above to yield (482.7 mg, 55%) of **10**. Overall yield of **10** was 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05, 0.11 and 0.12 (12H, each as s), 0.89 and 0.90 (18H, each as s), 1.79 (2H, ddd, *J* = 2.6, 6.2 and 12.8 Hz), 2.06 (1H, s), 3.42 (3H, s), 3.48-3.50 (1H, m), 3.52 (1H, dd, *J* = 6.2 and 10.8 Hz), 3.61-3.68 (3H, m), 3.69-3.73 (2H, m), 3.93 (1H, br), 3.96 (1H, dd, *J* = 3.3 and 8.1 Hz), 4.11-4.15 (1H, m), 4.59 (1H, d, *J* = 2.2 Hz); MS m/z 544 and 542 $(M)^+$; HRMS calcd for $C_{18}H_{38}{}^{79}BrO_6Si_2$ $(M-{}^tBu)^+$ 485.1390, Found 485.1402.

2α-(3-Hydroxypropoxy)-1α,25-dihydroxyvitamin D_3 (1b). Enyne **16** (219.3 mg, 0.394 mmol) and bromoolefin **17** (129.6 mg, 0.363 mmol) were dissolved in toluene (5 mL), and Et_3N (5 mL) and $(Ph_3P)_4Pd$ (125.8 mg, 0.109 mmol) were added. The mixture was stirred at rt for 5 min, and then heated at 120 °C for 90 min. The suspension was diluted with EtOAc (10 mL) and filtered through a silica gel pad. The filtrate and washings (EtOAc) of the pad were combined and concentrated *in vacuo*. Silica gel column chromatography (0 - 6% EtOAc in hexane) gave the coupling product **18** (156.6 mg, 52%) as a colorless oil, which was used without any further purification. To the THF (3 mL) solution of **18** (156.6 mg, 0.188 mmol) was added 1M solution of Bu_4NF in THF (0.94 mL, 0.94 mmol), and the mixture was stirred at rt for 4 days. The solution was concentrated to *ca*. 0.5 mL *in vacuo*, and the residue was purified by a preparative TLC plate (silica gel, 10% MeOH in CH_2Cl_2). This TLC purification was performed two times to obtain **1b** (56.3 mg, 61%) as a white powder. Further purification of **1b** for VDR binding assay was conducted by reversed-phase recycle HPLC (YMC-Pack ODS column, 20 X 150 mm, 9.9 mL/min, $CH_3CN:H_2O$ = 6:4).

Spectroscopic Data for **1a-c**.

Compound **1a**

UV (MeOH) λ_{max} 269 nm. Selected data of ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s), 0.93 (3H, d, J = 6.6 Hz), 1.21 (6H, s), 1.83~1.89 (1H, m), 1.96~2.01 (2H, m), 2.23 (1H, dd, *J* = 9.5 and 13.0 Hz), 2.67 (1H, dd, *J* = 4.8 and 13.0 Hz), 2.81~2.84 (1H, m), 3.38 (1H, dd, *J* = 3.3 and 8.1 Hz), 3.72 (1H, ddd, *J* = 2.7, 4.8, and 9.5 Hz), 3.77~3.84 (4H, m), 4.07 (1H, ddd, *J* = 4.8, 7.9, and 9.5 Hz), 4.43 (1H, d, *J* = 3.4 Hz), 5.10 (1H, d, *J* = 1.7 Hz), 5.38 (1H, d, *J* = 1.7 Hz), 6.01 (1H, d, *J* = 11.1 Hz), 6.43 (1H, d, *J* = 11.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.8, 22.2, 23.5, 27.7, 29.1, 29.2, 29.4, 36.1, 36.4, 40.5, 41.2, 44.4, 45.9, 56.4, 56.6, 62.0, 68.6, 71.1, 71.4, 72.5, 85.0, 116.6, 117.1, 125.6, 131.4, 143.7, 144.1; MS m/z 476 $(M)^+$, 458 $(M - H_2O)^+$, 440 $(M - 2H_2O)^+$; HRMS calcd for $C_{29}H_{48}O_5$ $(M)^+$ 476.3503, Found 476.3527.

Compound **1b**

$[\alpha]_D^{24.5}$ +46.4 (c 0.55, $CHCl_3$). UV (MeOH) λ_{max} 267 nm. Selected data of ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s), 0.93 (3H, d, *J* = 6.4 Hz), 1.21 (6H, s), 2.24 (1H, dd, *J* = 9.2 and 13.4 Hz), 2.69 (1H, dd, *J* = 4.4 and 13.4 Hz), 2.81~2.83 (1H, m), 3.38 (1H, dd, *J* = 3.2 and 7.5 Hz), 3.75~3.91 (5H, m), 4.03~4.08 (1H, m), 4.44 (1H, br d, *J* = 2.8 Hz), 5.10 (1H, d, *J* = 1.8 Hz), 5.39 (1H, br s), 6.01 (1H, d, *J* = 11.3 Hz), 6.42 (1H, d, *J* = 11.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.8, 22.2, 23.5, 27.7, 29.1, 29.2, 29.4, 31.9, 36.1, 36.4, 40.5, 41.0, 44.4, 45.9, 56.4, 56.6, 61.2, 68.4, 68.5, 71.1, 71.9, 84.5, 116.1, 117.1, 125.5, 131.5, 143.6, 144.3; MS m/z 490 $(M)^+$, 472 $(M - H_2O)^+$, 454 $(M - 2H_2O)^+$; HRMS calcd for $C_{30}H_{50}O_5$ $(M)^+$ 490.3660, Found 490.3638.

Compound **1c**

UV (MeOH) λ_{max} 267 nm. Selected data of ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s), 0.93 (3H, d, *J* = 6.4 Hz), 1.21 (6H, s), 2.23 (1H, dd, *J* = 9.3 and 13.3 Hz), 2.68 (1H, dd, *J* = 4.6 and 13.3 Hz), 2.81~2.84 (1H, m), 3.35 (1H, dd, *J* = 3.2 and 7.6 Hz), 3.61 (1H, dt, *J* = 6.0 and 9.5 Hz), 3.68~3.77 (4H, m), 4.05 (1H, ddd, *J* = 4.6, 7.6, and 8.6 Hz), 4.42 (1H, d, *J* = 3.0 Hz), 5.10 (1H, d, *J* = 2.1 Hz), 5.39 (1H, br), 6.02 (1H, d, *J* = 11.3 Hz), 6.42 (1H, d, *J* = 11.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.8, 22.2, 23.5, 26.9, 27.6, 29.1, 29.2, 29.4, 29.7, 36.1, 36.4, 40.5, 40.8, 44.4, 45.9, 56.4, 56.5, 62.6, 68.2, 70.0, 71.1, 71.8, 84.6, 116.2, 117.1, 125.5, 131.5, 143.6, 144.2; MS m/z 504 $(M)^+$, 486 $(M - H_2O)^+$, 468 $(M - 2H_2O)^+$; HRMS calcd for $C_{31}H_{52}O_5$ $(M)^+$ 504.3817, Found 504.3823.

Charts of VDR binding assay for **1a-c** (on the next page).

VDR binding assay for **1a**-**c**.