Supplementary Material for Organic & Biomolecular Chemistry

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Synthesis, biological activity, and conformational analysis of CD-ring modified *trans*-decalin 1α,25-dihydroxyvitamin D analogs

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General Methods.

All air sensitive reactions were run under Ar or N_2 atmosphere and reagents were added through septa using oven dried syringes. Et_2O and THF were distilled from benzophenone ketyl prior to use. *N*,*N*-Diisopropylethylamine (DIPEA), Et_3N, CH_3CN and HMPA were distilled from CaH_2, and CH_2Cl_2 was distilled from P_2O_5. TLC were run on glass plates precoated with silica gel (Merck, UV 254). Flash and column chromatography was performed on silica gel (Merck, 230-400 mesh) and HPLC separations were performed on Bio-Sil D 90-10, 10-μm columns (Bio-Rad) of 1 × 25 cm and 2.2 × 25 cm. [α]D values are given in 10^{-1} deg cm^2 g^{-1}. Chemical shifts d_H are reported in ppm relative to CDCl3 (7.26 ppm), C_6D_6 (7.16 ppm), or CD_3OD (3.34 ppm) as an internal reference. *J* values are given in Hz. Chemical shifts d_C are reported in ppm relative to CDCl3 (77.16 ppm), C_6D_6 (128.06 ppm), or CD_3OD (49.86 ppm) as an internal reference. Mass spectra (EI) were recorded at 70 eV.

((8a*S*)-8a-Methyl-3,4,6,7,8,8a-hexahydro-1(2*H*)-naphthylidene)acetonitrile (12).

To a suspension of sodium amide (9.5 g, 244 mmol) in dry THF (250 cm^3) was added a solution of diethyl (cyanomethyl)phosphonate (43.2 g, 244 mmol) in dry THF (250 cm^3) at rt. After stirring for 6 h, a solution of **11** (10.1 g, 62 mmol) in dry THF (250 cm^3) was added. The reaction mixture was stirred at rt for 12 h and the reaction was quenched with water. The aqueous layer was extracted with Et_2O, the combined organic layers were washed with a saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The light-red residue was purified by flash chromatography (cyclohexane–EtOAc, 50:1) to give an inseparable *E*:*Z* 6:1 mixture of cyanide **12** (10.9 g, 96%) as an oil: R_f (cyclohexane–EtOAc, 5:1) 0.54; $[\alpha]^{20}_D$ –68.0 (c 0.74 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2935, 2863, 2215, 1610, 1436, 1271, 1143, 1067 and 819; d_H(500 MHz; $CDCl_3$) 5.45 (*Z*) and 5.41 (*E*) (1

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H, m), 5.15 (*Z*) (t, *J* 1.2) and 5.13 (*E*) (d, *J* 1.5) (1 H), 2.96 (1 H, m), 2.46 (1 H, ddt, *J* 1.6, 5.0 and 13.9), 2.33 (1 H, m), 2.1 (1 H, m), 1.95 (3 H, m), 1.67 (4 H, m), 1.38 (1 H, qt, *J* 4.4 and 13.4), 1.26 (3 H, s); d_C(50 MHz; $CDCl_3$) 175.5, 122.7, 117.8, 91.2, 42.3, 34.9, 32.1, 30.6, 27.5, 27, 25.2, 19; *m/z* (EI) 187 (M^+), 172, 145, 133, 91, 77, 66 and 41; *m/z* (ESI) 210 (M + Na) and 188 (M + H).

((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)acetonitrile (13) and ((1*S*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)acetonitrile (14).

To a stirred solution of cyanide **12** (*E*:*Z* 6:1 mixture, 8.1 g, 42.7 mmol) in dry methanol (900 cm^3) were added magnesium turnings (41.6 g, 1.73 mol) at rt. The vigorous exothermic reaction was controlled by occasionally immerging the reaction flask in a dry ice-isopropanol bath (–20 °C). After stirring the reaction mixture at rt for 18 h, the magnesium salts were dissolved by the addtion of a 2 M HCl aqueous solution. The aqueous layer was extracted with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The colorless residue was purified by flash chromatography to give a 10:1 mixture of **13** and **14**, respectively (7.4 g, 92%), which was separated by HPLC (cyclohexane–EtOAc, 50:1) to afford **13** as a white semi-solid, and **14** as an oil. Data of **13**: R_f (cyclohexane–EtOAc, 5:1) 0.51; ν_{max}(neat)/cm^{-1} 2935, 2861, 2245, 1610, 1443, 1342, 1216, 1144 and 1069; d_H(500 MHz; $CDCl_3$) 5.33 (1 H, m), 2.49 (1 H, dd, *J* 16.6 and 3.7), 2.14 (1 H, m), 2.07 (1 H, dd, *J* 16.6 and 10.4), 2.00 (1 H, m), 1.91 (3 H, m), 1.81 (1 H, m), 1.70–1.45 (4 H, m), 1.45 (1 H, qd, *J* 13.0 and 3.6), 1.31 (2 H, m) and 0.96 (3 H, s); d_C(50 MHz; $CDCl_3$) 142.4, 121.2, 120.1, 46.2, 37.5, 28.2, 27.7, 27.2, 25.7, 25.3, 19.2, 18.8 and 18.4; *m/z* (EI) 189 (M^+), 172, 149, 144, 131, 105, 91, 77, 65 and 41; *m/z* (ESI) 212 (M + Na) and 190 (M + H). Data of **14**: d_H(500 MHz; $CDCl_3$) 5.49 (1 H, m), 2.56 (1 H, dd, *J* 16.9

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and 6.0), 2.25 (1 H, dd, *J* 17.4 and 9.5), 2.23 (1 H, m), 2.00 (2 H, m), 1.91 (2 H, m), 1.87 (1 H, m), 1.79 (1 H, br d, *J* 14.1), 1.57 (5 H, m), 1.37 (2 H, m) and 1.22 (3H, s).

(2*S*)-2-((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)propionitrile (15a) and (2*R*)-2-((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)propionitrile (15b).

To a solution of *i*-Pr_2NH (4.49 g, 44.4 mmol) in dry THF (30 cm^3) at –20 °C was dropwise added *n*-BuLi (2.5 M solution in hexanes, 16.3 cm^3, 40.7 mmol). The reaction mixture was stirred for 30 min, then cooled to –78 °C and a solution of cyanide **13** (7.0 g, 37 mmol) in dry THF (25 cm^3) was dropwise added. After stirring for 1 h, a solution of MeI (16.0 g, 113 mmol) in dry THF (10 cm^3) was dropwise added. The reaction mixture was stirred for 3 h, then allowed to warm to –20 °C and quenched by the addition of Et_2O and water. The aqueous layer was extracted with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The red residue was purified by flash chromatography (cyclohexane–EtOAc, 40:1) followed by HPLC (cyclohexane–EtOAc, 200:1) to afford a 5:1 mixture of **15a** and **15b**, respectively (7.0 g, 93%), used as such in the following step. An analytical sample of both isomers was obtained by careful HPLC separation. Data of **15a**: R_f (cyclohexane–EtOAc, 5:1) 0.51; $[\alpha]^{20}_D$ +138.0 (c 0.84 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2930, 2861, 2236, 1659 and 1444; d_H(500 MHz; $CDCl_3$) 5.34 (1 H, m), 2.90 (1 H, br q, *J* 7.3), 2.20 (1 H, m), 2.00 (1 H, m), 1.95–1.80 (3 H, m), 1.80–1.50 (3 H, m), 1.32 (3 H, d, *J* 7.3), 1.20 (2 H, m) and 1.16 (3 H, s); d_H(50 MHz; $CDCl_3$) 143.1, 122.8, 120.8, 65.9, 52.7, 37.6, 32.8, 27.4, 25.7, 24.7, 24.4, 19.6, 19.4 and 19.0; *m/z* (EI) 203 (M^+); *m/z* (ESI) 242 (M + K), 226 (M + Na) and 204 (M + H). Data of **15b**: R_f (cyclohexane–EtOAc, 5:1) 0.52; d_H(500 MHz; $CDCl_3$) 5.34 (1 H, m), 2.90 (1 H, qd, *J* 7.2 and

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3.1), 2.20 (1 H, m), 2.00 (1 H, m), 1.95–1.80 (3 H, m), 1.80–1.50 (3 H, m), 1.32 (3 H, d, *J* 7.3), 1.20 (2 H, m) and 1.04 (3 H, s).

(2*S*)-2-((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)propan-1-ol (16a) and (2*R*)-2-((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)propan-1-ol (16b).

To a solution of nitriles **15a** and **15b** (ratio 5:1, 6.5 g, 32 mmol) in a mixture of dry *n*-hexane (100 cm^3) and dry Et_2O (12 cm^3) was dropwise added DIBALH (1.5 M solution in toluene, 42.7 cm^3, 9.1 g, 64 mmol) at –78 °C. After stirring for 4 h, the reaction mixture was allowed to warm to 0 °C, was quenched with Et_2O and a 0.25 M oxalic acid aqueous solution (pH 2-3), and further stirred at rt for 1 h. The aqueous layer was extracted with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The colorless residue was purified by flash chromatography (cyclohexane–EtOAc, 50:1) to give a mixture of the corresponding aldehydes (5.3 g, 80%): R_f (cyclohexane–EtOAc, 5:1) 0.59.

The mixture of aldehydes was treated again with DIBALH according to the above procedure. The crude mixture was purified by flash chromatography (cyclohexane–EtOAc, 5:1), followed by HPLC (cyclohexane–EtOAc, 6:1) to afford alcohols **16a** (3.4 g, 64%) and **16b** (0.85 g, 16%). Data of **16a**: R_f (cyclohexane–EtOAc, 4:1) 0.26; $[\alpha]^{20}_D$ +116.0 (c 1.15 in $CHCl_3$); Found: C, 80.6; H, 11.75. Calc. for $C_{14}H_{24}O$: C, 80.7; H, 11.6%; ν_{max}(neat)/cm^{-1} 3352, 2927, 2858, 1658, 1442, 1373, 1215, 1032 and 758; d_H(500 MHz; $CDCl_3$) 5.27 (1 H, s), 3.81 (1 H, dd, *J* 10.3 and 3.5), 3.29 (1 H, dd, *J* 10.2 and 9.9), 2.11 (1 H, m), 1.91 (5 H, m), 1.77 (1 H, m), 1.63–1.50 (4 H, m), 1.30 (2 H, m), 1.15 (2 H, m), 1.06 (3 H, s) and 1.02 (3 H, d, *J* 6.9); d_C(50 MHz; $CDCl_3$) 146.2, 120.9, 67.6, 55.5, 40.2, 38.9, 35.7, 34.7, 29.9, 27.2, 24.2, 21.6, 21.0 and 20.5; *m/z* (EI) 208 (M^+), 192, 181, 169, 156, 149, 135, 121, 109, 93, 79, 67, 55

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and 41; *m/z* (ESI) 226 (M + NH_4), 209 (M + H) and 191 (M + H – H_2O). Data of **16b**: R_f (cyclohexane–EtOAc, 4:1) 0.28; $[\alpha]^{20}_D$ +121.0 (c 0.98 in $CHCl_3$); Found: C, 80.6; H, 11.7. Calc. for $C_{14}H_{24}O$: C, 80.7; H, 11.6%; ν_{max}(neat)/cm^{-1} 3364, 2923, 2858, 1654, 1442, 1382, 1032 and 808; d_H(500 MHz; $CDCl_3$) 5.28 (1 H, s), 3.39 and 3.37 (AB of ABX: 1 H, dd, *J* 10.4 and 7.5, and 1 H, dd, *J* 10.4 and 6.8), 2.13 (1 H, m), 1.94 (6 H, m), 1.81 (2 H, m), 1.64–1.38 (5 H, m), 1.23 (3 H, m), 1.05 (3 H, s) and 0.86 (3 H, d, *J* 7.0); d_C(50 MHz; $CDCl_3$) 146.2, 119.5, 68.6, 48.5, 38.6, 37.7, 33.8, 33.4, 28.1, 25.9, 23.5, 20.4, 19.2 and 13.6; *m/z* (EI) 208 (M^+), 192, 181, 169, 156, 149, 135, 121, 109, 93, 79, 67, 55 and 41; *m/z* (ESI) 226 (M + NH_4) and 209 (M + H).

(2*S*)-2-((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)propyl *N*-((1*S*)-1-(1-naphthyl)ethyl)carbamate (17).

To the solution of alcohol **16b** (50 mg, 0.24 mmol) in CH_2Cl_2 (3 cm^3) was added (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate (50 mg). A solution of TMSOTf (0.002 cm^3) in CH_2Cl_2 (0.1 cm^3) was added and the resulting mixture was stirred at rt for 40 min. The solvent was removed under reduced pressure to yield a residue, which was purified by HPLC (isooctane–EtOAc, 6:1) to afford **17** (94 mg, 97%) as a solid. This was crystallised from *n*-hexane–acetone to give needles, which were recrystalised from *n*-pentane to give the crystals for X-ray analysis of **17**: mp 124-125 °C (from *n*-pentane); R_f (isooctane–EtOAc, 4:1) 0.27; $[\alpha]^{20}_D$ +53.0 (c 0.66 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3299, 2925, 2856, 1682, 1538, 1454, 1378, 1330, 1291, 1252, 1110, 1061, 1012, 981, 798 and 779; d_H(500 MHz; $CDCl_3$) 8.14 (1 H, br s), 7.87 (1 H, d, *J* 8.0), 7.79 (1 H, d, *J* 8.0), 7.56–7.44 (4 H, m), 5.67 (1 H, br s), 5.26 (1 H, s), 4.95 (1 H, br s), 3.89 (1 H, m), 3.79 (1 H, m), 2.11 (2 H, m), 1.95–1.72 (5 H, m), 1.66 (3 H, d, *J* 5.7), 1.50–1.44 (4 H, m), 1.19 (3 H, m), 1.01 (3 H, br s) and 0.84 (3 H, br s); d_C(APT; 125 MHz;

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$CDCl_3$) 155.8 (C), 144.9 (C), 138.9 (C), 133.9 (C), 130.9 (C), 128.8 (CH), 128.2 (CH), 126.4 (CH), 125.7 (CH), 125.2 (CH), 123.3 (CH), 122.2 (CH), 119.5 (CH), 69.8 (CH_2), 48.3 (CH), 46.5 (CH), 38.5 (C), 37.5 (CH_2), 33.3 (CH_2), 30.7 (CH_3), 27.9 (CH_2), 25.8 (CH_2), 23.2 (CH_2), 21.7 (CH_3), 20.2 (CH_3), 19.0 (CH_2) and 13.5 (CH_3); *m/z* (EI) 405 (M^+, 10%), 215 (35), 190 (60), 156 (55), 148 (100), 127 (30), 91 (40) and 67 (45).

(2*S*)-2-((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)propyl *p*-toluenesulfonate (18a).

To a solution of alcohol **16a** (0.87 g, 4.2 mmol) in dry pyridine (40 cm^3) was added *p*-toluenesulfonyl chloride (2.4 g, 12.6 mmol) at 0 °C and the reaction mixture was stirred overnight. The reaction was quenched with Et_2O and water, and the aqueous layer was extracted with Et_2O. The organic layers were combined, washed with brine and water (3 ×), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The red residue was purified by flash chromatography (cyclohexane–EtOAc, 10:1), followed by HPLC with cyclohexane–EtOAc 40:1 as eluent to give tosylate **18a** (1.39 g, 92%): R_f (cyclohexane–EtOAc, 5:1) 0.52; $[\alpha]^{20}_D$ +78.0 (c 0.97 in $CHCl_3$); Found: C, 69.4; H, 8.7. Calc. for $C_{21}H_{30}O_3S$: C, 69.6; H, 8.3%; ν_{max}(neat)/cm^{-1} 2927, 2859, 1598, 1443, 1361, 1188, 1176, 1097 and 957; d_H(500 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.2), 7.34 (2 H, d, *J* 8.2), 5.25 (1 H, s), 4.19 (1 H, dd, *J* 9.5 and 3.5), 3.68 (1 H, dd, *J* 9.6 and 9.6), 2.44 (3 H, s), 2.07 (2 H, m), 1.90 (3 H, m), 1.74 (2 H, m), 1.58 (1 H, m), 1.49 (2 H, m), 1.26–1.10 (4 H, m), 0.95 (3 H, d, *J* 6.9) and 0.91 (3 H, s); d_C(50 MHz; $CDCl_3$) 144.5, 143.9, 133.1, 129.6, 127.7, 119.7, 74.1, 53.5, 38.4, 37.2, 33.1, 31.0, 27.8, 25.1, 22.5, 21.5, 19.8, 19.2 and 18.9; *m/z* (EI) 362 (M^+), 314, 287, 257, 221, 220, 190, 149, 109, 91 and 55; *m/z* (ESI) 380 (M + NH_4).

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(2*R*)-2-((1*R*,8a*R*)-8a-Methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthyl)propyl *p*-toluenesulfonate (18b).

Alcohol **16b** was treated with *p*-toluenesulfonyl chloride as described above for **16a** to give tosylate **18b** (91%): R_f (cyclohexane–EtOAc, 5:1) 0.53; $[\alpha]^{20}_D$ +52 (*c* 0.9, $CHCl_3$); Found: C, 69.5; H, 8.5. Calc. for $C_{21}H_{30}O_3S$: C, 69.6; H, 8.3%; ν_{max}(neat)/cm^{-1} 2928, 2857, 1598, 1442, 1361, 1188, 1177, 1098 and 962; d_H(500 MHz; $CDCl_3$) 7.77 (2 H, d, *J* 8.2), 7.33 (2 H, d, *J* 8.0), 5.25 (1 H, s), 3.76 (2 H, m), 2.44 (3 H, s), 2.12 (1 H, dd, *J* 13.9 and 7.2), 2.05 (1 H, dd, *J* 13.9 and 3.6 Hz), 1.26 (1 H, m), 1.20–1.04 (3 H, m), 0.98 (3 H, s), 0.82 (3 H, d, *J* 7.0); d_C(50 MHz; $CDCl_3$) 144.5, 133.1, 129.6, 127.7, 119.6, 75.3, 47.8, 38.3, 37.2, 33.4, 30.7, 27.8, 25.8, 22.5, 21.5, 20, 19 and 13.1; *m/z* (EI) 362 (M^+), 321, 301, 276, 257, 221, 210, 190, 149, 109, 91, 67 and 55; *m/z* (ESI) 380 (M + NH_4).

(2*S*)-2-((1*R*,4a*S*,5*S*,8a*R*)-5-Hydroxy-8a-methyldecahydro-1-naphthyl)propyl *p*-toluenesulfonate (19a) and (2*S*)-2-((1*R*,4a*R*,5*R*,8a*R*)-5-Hydroxy-8a-methyldecahydro-1-naphthyl)propyl *p*-toluenesulfonate (20a).

A solution of alkene **18a** (1.37 g, 3.8 mmol) in dry THF (25 cm^3) was dropwise added to borane-tetrahydrofuran complex (1.0 M solution in THF, 9.5 cm^3, 9.5 mmol) at –20 °C. The reaction mixture was kept at –20 °C overnight, cooled to –30 °C, and carefully quenched (2 drops/min) with a 2 M NaOH aqueous solution. A 35% H_2O_2 aqueous solution was added, the reaction mixture was stirred at rt for 30 min, and poured into an ice-cold mixture of Et_2O and a $Na_2S_2O_3$ aqueous solution. The aqueous layer was extracted with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The colorless residue was purified by flash chromatography (cyclohexane–Et_2O, 3:1), followed by HPLC (cyclohexane–Et_2O, 4:1) to give an inseparable 2:1 mixture of

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alcohols **19a** and **20a**, respectively (1.18 g, 82%). Data of the mixture of **19a** and **20a**: ν_{max}(neat)/cm^{-1} 2927, 2859, 1598, 1443, 1361, 1188, 1176, 1097 and 957; *m/z* (EI) 380 (M^+), 351, 313, 283, 259, 235, 193, 166, 149, 111, 91 and 55; *m/z* (ESI) 403 (M + Na) and 398 (M + NH_4). Data of **19a**: R_f (cyclohexane–EtOAc 2:1) 0.24; d_H(500 MHz; $CDCl_3$) 7.77 (2 H, d, *J* 8.2), 7.34 (2 H, d, *J* 8.0), 4.11 (1 H, t, *J* 10.0), 3.84 (1 H, td, *J* 10.8 and 4.7), 3.63 (1 H, m), 2.44 (3 H, s), 2.10–0.85 (15 H), 0.94 (3 H, d, *J* 6.8) and 0.85 (3 H, s). Data of **20a**: R_f (cyclohexane–EtOAc 2:1) 0.25; d_H(500 MHz; $CDCl_3$) 7.77 (2 H, d, *J* 8.2), 7.34 (2 H, d, *J* 8.0), 4.11 (1 H, t, *J* 10.0), 3.63 (1 H, m), 3.37 (1 H, td, *J* 10.5 and 4.5), 2.44 (3 H, s), 2.10–0.85 (15 H), 0.93 (3 H, d, *J* 6.8) and 0.70 (3 H, s).

(2*R*)-2-((1*R*,4a*S*,5*S*,8a*R*)-5-Hydroxy-8a-methyldecahydro-1-naphthyl)propyl *p*-toluenesulfonate (19b) and (2*R*)-2-((1*R*,4a*R*,5*R*,8a*R*)-5-Hydroxy-8a-methyldecahydro-1-naphthyl)propyl *p*-toluenesulfonate (20b).

Hydroboration of alkene **18b** as described above for **18a** gave an inseparable 2:1 mixture of alcohols **19b** and **20b**, respectively (82%). Data of the mixture of **19b** and **20b**: ν_{max}(neat)/cm^{-1} 3419, 2931, 2864, 1448, 1377, 1216, 1052, 1019 and 972; *m/z* (EI) 380 (M^+), 371, 348, 311, 300, 258, 229, 193, 175, 149, 111, 91 and 55; *m/z* (ESI) 403 (M + Na) and 398 (M + NH_4). Data of **19b**: R_f (cyclohexane–EtOAc 2:1) 0.24; partial d_H(500 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.0), 7.36 (2 H, d, *J* 8.0), 3.75 (3 H, m), 2.45 (3 H, s), 0.91 (3 H, s) and 0.75 (3 H, d, *J* 7.0). Data of **20b**: R_f (cyclohexane–EtOAc 2:1) 0.25; partial d_H(500 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.0), 7.36 (2 H, d, *J* 8.0), 3.75 (2 H, m), 3.38 (1 H, td, *J* 10.6 and 4.6), 2.44 (3 H, s), 0.76 (3 H, s) and 0.77 (3 H, d, *J* 7.2).

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(6*R*)-2-Methyl-6-((1*R*,4a*S*,8a*R*)-8a-methyl-5-oxodecahydro-1-naphthyl)heptan-2-ol (25a) and (6*R*)-2-Methyl-6-((1*R*,4a*R*,8a*R*)-8a-methyl-5-oxodecahydro-1-naphthyl)heptan-2-ol (10a).

To a solution of a 2:1 mixture of tosylates **19a** and **20a** (1.3 g, 3.4 mmol) in dry acetone (6 cm^3) was added a solution of sodium iodide (12.8 g, 86 mmol) in dry acetone (60 cm^3). Upon heating at 60 °C overnight a white precipitate was formed. The reaction mixture was poured into Et_2O–water, the aqueous layer was extracted with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The yellow residue was purified by flash chromatography (cyclohexane–Et_2O, 9:1) to give an inseparable 2:1 mixture of the corresponding iodides (1.07 g, 93%). Data of the mixture of isomers: R_f (cyclohexane–EtOAc, 4:1) 0.23; *m/z* (ESI) 319 (M – H_2O + H). Data of the major isomer: d_H(500 MHz; $CDCl_3$) 3.88 (1 H, td, *J* 10.7 and 4.8), 3.42 (1 H, m), 2.77 (1 H, m), 1.11 (3 H, d, *J* 6.9) and 0.99 (3 H, s). Data of the minor isomer: d_H(500 MHz; $CDCl_3$) 3.42 (1 H, m), 3.13 (1 H, m), 2.77 (1 H, m), 1.11 (3 H, d, *J* 6.9) and 0.83 (3 H, s).

To a solution of anhydrous $NiCl_2$ (1.2 g, 9.2 mmol) in dry pyridine (60 cm^3) was added zinc powder (3.1 g, 47.7 mmol) followed by ethyl acrylate (5.1 cm^3, 4.74 g, 47.4 mmol). After stirring at 65 °C for 45 min, the red reaction mixture was cooled to 20 °C, and a solution of the above mixture of iodides (1.06 g, 3.16 mmol) in dry pyridine (10 cm^3) was added. The reaction mixture was stirred at rt for 90 min, poured into cold Et_2O–water, and brought to pH 5 (disappearance of the red color) by the careful addition of a 2 M HCl aqueous solution. The aqueous layer was extracted with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The colorless residue was purified by flash chromatography (cyclohexane–Et_2O, 9:1 to 8:2) to afford an inseparable 2:1 mixture of esters **21a** and **22a**, respectively (0.84 g, 86%): R_f (cyclohexane–EtOAc, 2:1)

Supplementary data

0.38–0.36.

To a solution of a 2:1 mixture of esters **21a** and **22a** (0.8 g, 2.58 mmol) in dry THF (40 cm^3) at –5 °C was added methylmagnesium bromide (3 M solution in Et_2O, 21.5 cm^3, 64.5 mmol). The reaction mixture was stirred at rt for 1 h and was then poured into a cold mixture of Et_2O and a saturated NH_4Cl aqueous solution. The aqueous layer was extracted with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The colorless residue was purified by flash chromatography (cyclohexane–Et_2O, 8:2 to 7:3) to give an inseparable 2:1 mixture of diols **23a** and **24a**, respectively (0.71 g, 93%): R_f (cyclohexane–EtOAc, 2:1) 0.28.

To a solution of a 2:1 mixture of diols **23a** and **24a** (0.7 g, 2.37 mmol) in dry CH_2Cl_2 (40 cm^3) at rt was added pyridinium dichromate (0.89 g, 2.37 mmol). After stirring at rt overnight, the reaction mixture was loaded onto a silica gel column and eluted with cyclohexane–Et_2O (8:2 to 7:3). The crude product was further purified by HPLC (cyclohexane–Et_2O, 85:15) to give *cis*-ketone **25a** (407 mg) and *trans*-ketone **10a** (205 mg, total yield 88%). Data of **25a**: R_f (cyclohexane–EtOAc, 2:1) 0.36; $[\alpha]^{20}_D$ +4.3 (c 1.02 in $CHCl_3$); Found: C, 75.9; H, 11.65. Calc. for $C_{19}H_{34}O_2$: C, 77.5; H, 11.6%; ν_{max}(neat)/cm^{-1} 3418, 2937, 2867, 1698, 1452, 1379 and 1150; d_H(500 MHz; $CDCl_3$) 2.33 (1 H, m), 2.18 (1 H, m), 2.02 (3 H, m), 1.73 (2 H, m), 1.61 (1 H, m), 1.16 (6 H, s), 1.07 (3 H, s) and 0.83 (3 H, d, *J* 6.9); d_C(125 MHz; $CDCl_3$) 212.6, 70.7, 65.6, 58.1, 44.6, 44.0, 42.0, 41.3, 36.5, 32.6, 30.4, 29.0, 26.7, 24.0, 22.9, 22.5, 21.4, 20.7, 20.5 and 20.3; *m/z* (EI) 294 (M^+), 277, 276, 243, 221, 191, 178, 165, 149, 147, 111, 98, 69, 59 and 43; *m/z* (ESI) 317 (M + Na), 312 (M + NH_4), 295 (M + H) and 277 (M + H – H_2O). Data of **10a**: R_f (cyclohexane–EtOAc, 2:1) 0.34; $[\alpha]^{20}_D$ +24.0 (c 0.86 in $CHCl_3$); Found: C, 77.35; H, 11.6. Calc. for $C_{19}H_{34}O_2$: C, 77.5; H, 11.6.; ν_{max}(neat)/cm^{-1} 3434, 2936, 2856, 1707, 1447, 1376, 1219, 1159, 936 and 733; d_H(500 MHz; $CDCl_3$) 2.29 (2 H, dd, *J* 9.5

Supplementary data

and 4.9), 2.13 (1 H, dd, *J* 12.2 and 2.9 Hz), 2.01 (2 H, m), 1.84 (2 H, m), 1.74 (1 H, m), 1.59 (1 H, m), 1.19 (6 H, s), 0.92 (3 H, d, *J* 6.9) and 0.74 (3 H, s); d_C(125 MHz; $CDCl_3$) 213.0, 70.8, 65.7, 59.7, 54.7, 44.0, 41.0, 37.3, 32.7, 31.2, 29.1, 29.0, 26.7, 25.4, 23.0, 22.2, 21.4, 21.3, 20.7 and 14.0; *m/z* (EI) 294 (M^+), 279, 276, 243, 221, 191, 178, 165, 147, 125, 111, 98, 81, 59 and 43; *m/z* (ESI) 611 (2M + Na), 317 (M + Na), 295 (M + H) and 277 (M + H – H_2O).

(6*S*)-2-Methyl-6-((1*R*,4a*S*,8a*R*)-8a-methyl-5-oxodecahydro-1-naphthyl)heptan-2-ol (25b) and (6*S*)-2-Methyl-6-((1*R*,4a*R*,8a*R*)-8a-methyl-5-oxodecahydro-1-naphthyl)heptan-2-ol (10b).

Obtained from the mixture of tosylates **19b** and **20b**, as described for the preparation of **25a** and **10a**, in 3 steps:

Esters **21b** and **22b** were obtained, via the corresponding iodides (86%), as an inseparable 2:1 mixture from the mixture of tosylates **19b** and **20b**, respectively (84%), as described for the preparation of **21a** and **22a**: R_f (cyclohexane–EtOAc, 2:1) 0.39–0.33.

Diols **23b** and **24b** were obtained as an inseparable 2:1 mixture from the mixture of esters **21b** and **22b**, respectively (91%), as described for the preparation of **23a** and **24a**: R_f (cyclohexane–EtOAc, 2:1) 0.23–0.16.

Ketones **25b** and **10b** were obtained by oxidation of the mixture of diols **23b** and **24b** with pyridinium dichromate as described for the preparation of **25a** and **10a**. The isomers were separated by HPLC (cyclohexane–Et_2O, 85:15) to give *cis*-ketone **25b** and *trans*-ketone **10b** in a 2:1 ratio, respectively (total yield 86%). Data of **25b**: R_f (cyclohexane–EtOAc 2:1) 0.36; $[\alpha]^{20}_D$ +26.0 (c 1.45 in $CHCl_3$); Found: C, 77.5; H, 11.8. Calc. for $C_{19}H_{34}O_2$: C, 77.5; H, 11.6.; ν_{max}(neat)/cm^{-1} 3426, 2938, 2868, 1698, 1469, 1452, 1381, 1236, 1154, 912 and 733; d_H(500 MHz; $CDCl_3$) 2.37 (1 H, m), 2.25 (1 H, m), 2.05 (3 H, m), 1.80 (2 H, m), 1.70 (1 H, m), 1.20

Supplementary data

(6 H, s), 1.13 (3 H, s), 0.77 (3 H, d, *J* 6.9); d_C(125 MHz; $CDCl_3$) 212.5, 70.8, 58.2, 44.0, 43.0, 42.0, 41.0, 38.8, 36.3, 30.3, 29.0, 29.0, 24.3, 22.4, 21.8, 21.5, 20.7, 20.3 and 15.8; *m/z* (EI) 294 (M^+), 280, 276, 243, 221, 205, 192, 178, 165, 149, 147, 121, 111, 98, 67, 55 and 43; *m/z* (ESI) 317 (M + Na), 312 (M + NH_4), 295 (M + H) and 277 (M + H – H_2O). Data of **10b**: R_f (cyclohexane–EtOAc, 2:1) 0.28; $[\alpha]^{20}_D$ –9.0 (c 1.24 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3434, 2936, 2856, 1707, 1447, 1376, 1219, 1159, 936 and 733; d_H(500 MHz; $CDCl_3$) 2.29 (2 H, dd, *J* 4.9 and 9.5), 2.13 (1 H, dd, *J* 3.0 and 12.7), 2.01 (2 H, m), 1.88–1.74 (3 H, m), 1.58 (4 H, m), 1.23 (6 H, s), 0.77 (3 H, d, *J* 6.9) and 0.75 (3 H, s); d_C(125 MHz; $CDCl_3$) 212.0, 69.9, 58.9, 51.1, 43.1, 43.0, 40.2, 38.0, 36.6, 29.9, 28.4, 28.3, 24.4, 21.4, 21.4, 20.7, 19.9, 15.7 and 13.3; *m/z* (EI) 294 (M^+) 277, 276, 243, 221, 197, 179, 165, 147, 137,125, 111, 95, 81, 67, 59 and 43; *m/z* (ESI) 611 (2M + Na), 317 (M + Na), 295 (M + H) and 277 (M + H – H_2O).

(6*R*)-2-Methyl-6-((1*R*,4a*R*,8a*R*)-8a-methyl-5-oxodecahydro-1-naphthyl)-2-(triethylsilyloxy)heptane (26a).

To a solution of imidazole (6 g, 88.4 mmol) and chlorotriethylsilane (3.33 g, 22.1 mmol) in dry CH_2Cl_2 (30 cm^3) was added alcohol **10a** (0.65 g, 2.21 mmol) in dry CH_2Cl_2 (10 cm^3) at rt. After stirring for 3 h, the reaction mixture was loaded onto a silica gel column and eluted with cyclohexane–Et_2O (95:5 to 85:15) to give silyl ether **26a** (0.795 g, 88%): R_f (cyclohexane–EtOAc, 4:1) 0.58; $[\alpha]^{20}_D$ +5.0 (c 1.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3408, 2951, 2873, 1712, 1458, 1381, 1364, 1235, 1158, 1085, 1041 and 742; d_H(500 MHz; $CDCl_3$) 2.29 (2 H, dd, *J* 9.3 and 4.6), 2.13 (1 H, dd, *J* 12.2 and 2.8), 2.04 (1 H, m), 1.98 (1 H, m), 1.84 (2 H, m), 1.72 (1 H, m), 1.59 (1 H, m), 1.40 (4 H, m), 1.31 (4 H, m), 1.17 (6 H, s), 0.93 (3 H, d, *J* 7.9), 0.92 (9 H, t, *J* 7.9), 0.74 (3 H, s) and 0.54 (6 H, q, *J* 7.9); d_C(125 MHz; $CDCl_3$) 213.5, 73.4, 60.0, 54.9, 45.4, 44.3, 41.3, 37.6, 33.0, 31.5, 29.9, 25.7, 23.3, 22.5, 21.7, 21.6, 21.0, 14.2, 7.2 (3)

Supplementary data

and 6.8 (3); *m/z* (EI) 408 (M^+), 405, 379, 350, 335, 280, 259, 227, 203, 173, 149, 103, 75 and 55; *m/z* (ESI) 447 (M + K), 432 (M + Na) and 409 (M + H).

(6*S*)-2-Methyl-6-((1*R*,4a*R*,8a*R*)-8a-methyl-5-oxodecahydro-1-naphthyl)-2-(triethylsilyloxy)heptane (26b).

Reaction of alcohol **10b** with chlorotriethylsilane as described above for **10a** gave silyl ether **26b** (84%): R_f (cyclohexane–EtOAc, 4:1) 0.56; $[\alpha]^{20}_D$ –10.0 (c 0.95 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3408, 2937, 2873, 1713, 1456, 1382, 1363, 1235, 1157, 1043 and 742; d_H(500 MHz; $CDCl_3$) 2.31 (2 H, dd, *J* 5.2 and 9.7), 2.15 (1 H, dd, *J* 2.9 and 12.2), 2.01 (1 H, m), 1.97 (1 H, m), 1.84 (2 H, m), 1.77 (1 H, m), 1.61 (2 H, m), 1.43–1.27 (8 H, m), 1.20 (3 H, s), 1.19 (3 H, s), 0.95 (9 H, t, *J* 7.9), 0.77 (3 H, d, *J* 6.9), 0.75 (3 H, s) and 0.57 (6 H, q, *J* 7.9); d_C(125 MHz; $CDCl_3$) 213.5, 73.4, 60.1, 51.9, 45.3, 44.1, 41.3, 39.1, 37.6, 31.0, 30.1, 30.0, 25.5, 22.5, 22.5, 21.8, 21.0, 16.9, 14.3, 7.2 (3) and 6.9 (3); *m/z* (EI) 408 (M^+), 405, 379, 350, 295, 280, 259, 227, 203, 173, 149, 115, 103, 75 and 55; *m/z* (ESI) 447 (M + K), 431 (M + Na) and 409 (M + H).

Coupling Reaction of Ketones 26a and 26b with Phosphine Oxides 27 and 28 – General Procedure.

To a solution of A-ring phosphine oxide **27** (**28**) (0.67 mmol) in dry THF (7.5 cm^3) was dropwise added *n*-BuLi (2.5 M solution in hexanes, 0.24 cm^3, 0.60 mmol) at –78 °C under Ar. The formed dark red solution was stirred at –78 °C for 1 h and a solution of ketone **26a** (**26b**) (0.17 mmol) in dry THF (2.5 cm^3) was dropwise added. The red solution was stirred at –78 °C for 2 h and was then allowed to warm to rt. The reaction mixture was loaded onto a silica gel column, the reaction product was eluted (*n*-hexane–EtOAc, 5:1) and further purified by HPLC to give the protected 1,25-D_3 analog.

Supplementary data

Desilylation of the Protected 1,25-D_3 Analogs using TBAF– General Procedure.

To a solution of the protected 1,25-D_3 analog (0.14 mmol) in THF (4 cm^3) was added tetrabutylammonium fluoride (TBAF, 1 M solution in THF, 2.1 cm^3, 2.1 mmol). The reaction mixture was stirred at rt for 12 h and then loaded onto a silica gel column. The reaction product was eluted (*n*-pentane–acetone, 1:1) and further purified by HPLC to give the 1,25-D_3 analog.

(1*R*,3*S*)-5-[(*Z*,2*E*)-2-[(1*R*,4a*R*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5(6*H*)-naphthylidene]ethylidene]-4-methylidenecyclohexane-1,3-diol (2at).

Ketone **26a** was coupled with phosphine oxide **27** according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–EtOAc, 35:1) to give protected **2at** (58%), which was consequently deprotected using TBAF according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–acetone, 6:4) to give **2at** (CY 10012, 57% from **26a**): R_f (CH_2Cl_2–MeOH, 9:1) 0.33; λ_{max}(EtOH)/nm 264; ν_{max}(neat)/cm^{-1} 3416, 2931, 2861, 1448, 1377, 1215, 1156, 1046, 957 and 758; d_H(500 MHz; $CDCl_3$) 6.37 (1 H, d, *J* 11.0), 5.98 (1 H, d, *J* 11.0), 5.33 (1 H, br s), 5.00 (1 H, br s), 4.44 (1 H, m), 4.22 (1 H, m), 2.86 (1 H, m), 2.61 (1 H, m), 2.31 (1 H, dd, *J* 13.0 and 6.4), 2.01 (1 H, m), 1.93 (2 H, m), 1.83 (1 H, m), 1.72 (4 H, m), 1.45 (4 H, m), 1.36 (2 H, m), 1.25 (6 H, m), 1.20 (6 H, s), 1.11 (3 H, m), 0.90 (3 H, d, *J* 7.0), 0.88 (2 H, m) and 0.67 (3 H, s); d_H(500 MHz; CD_3OD) 6.31 (1 H, d, *J* 11.0), 6.05 (1 H, d, *J* 11.0), 5.30 (1 H, d, *J* 1.0), 4.90 (1 H, br s), 4.36 (1 H, t, *J* 5.8), 4.13 (1 H, m), 2.91 (1 H, br d, *J* 12.0), 2.52 (1 H, dd, *J* 3.4 and 13.3), 2.26 (1 H, dd, *J* 6.9 and 13.3), 1.94 (1 H, br d, *J* 13.0), 1.89 (2 H, t, *J* 5.6), 1.87–1.67 (5 H, m), 1.53–1.08 (14 H, m),

Supplementary data

1.16 (6 H, s), 0.93 (3 H, d, *J* 6.9), 0.71 (3 H, s); *m/z* (EI) 430 (M^+) 412, 394, 376, 344, 327, 299, 283, 260, 245, 215, 190, 175, 152, 135, 134, 81 and 43; *m/z* (ESI) 453 (M + Na), 448 (M + NH_4) and 413 (M + H – H_2O).

(1*R*,3*R*)-5-[(*Z*,2*E*)-2-[(1*R*,4a*R*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5(6*H*)-naphthylidene]ethylidene]cyclohexane-1,3-diol (2ar).

Ketone **26a** was coupled with phosphine oxide **28** according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–EtOAc, 35:1) to give protected **2ar** (55%), which was consequently deprotected using TBAF according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–acetone, 6:4) to give **2ar** (CY 10010, 49% from **26a**): R_f (CH_2Cl_2–MeOH, 9:1) 0.33; λ_{max}(EtOH)/nm 264; ν_{max}(neat)/cm^{-1} 3416, 2931, 2861, 1448, 1377, 1215, 1156, 1046, 957 and 758; d_H(500 MHz; $CDCl_3$) 6.30 (1 H, d, *J* 11.0), 5.83 (1 H, d, *J* 11.0), 4.10 (1 H, m), 4.03 (1 H, m), 2.84 (1 H, m), 2.75 (1 H, dd, 1H, *J* 13.0 and 4.0), 2.48 (1 H, m), 2.21 (2 H, m), 1.98–1.80 (6 H, m), 1.80–1.65 (6 H, m), 1.45 (5 H, m), 1.37 (2 H, m), 1.29 (3 H, m), 1.20 (6 H, s), 1.12 (3 H, m), 0.91 (3 H, d, *J* 6.8), 0.88 (2 H, m) and 0.67 (3 H, s); d_H(500 MHz; CD_3OD) 6.31 (1 H, d, *J* 11.0), 6.06 (1 H, d, *J* 11.0), 5.30 (1 H, br s), 4.90 (1 H, s), 4.36 (1 H, t, *J* 5.9), 4.12 (1 H, m), 2.91 (1 H, br d, *J* 12.0), 2.52 (1 H, dd, *J* 3.5 and 13.3), 2.26 (1 H, dd, *J* 7.0 and 13.3), 1.94–1.67 (5 H, m), 1.89 (2 H, t, *J* 5.6), 1.53–1.13 (14 H, m), 1.18 (6 H, s), 0.79 (3 H, d, *J* 6.9) and 0.71 (3 H, s); *m/z* (EI) 430 (M^+) 412, 394, 376, 352, 327, 299, 283, 260, 245, 225, 215, 190, 175, 152, 135, 134, 81 and 49; *m/z* (ESI) 453 (M + Na), 448 (M + NH_4) and 413 (M + H – H_2O).

(1*R*,3*S*)-5-[(*Z*,2*E*)-2-[(1*R*,4a*R*,8a*R*)-1-((1*S*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5(6*H*)-naphthylidene]ethylidene]-4-methylidenecyclohexane-

Supplementary data

1,3-diol (2bt) and (1*R*,3*R*)-5-[(*Z*,2*E*)-2-[(1*R*,4a*R*,8a*R*)-1-((1*S*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5(6*H*)-naphthylidene]ethylidene]cyclohexane-1,3-diol (2br).

These analogs were obtained from ketone **26b** via coupling with phosphine oxide **27** and **28**, respectively, according to the above general procedure, followed by deprotection using TBAF. Data of **2bt** (CY 943): λ_{max}(EtOH)/nm 264; d_H(500 MHz; $CDCl_3$) 6.37 (1 H, d, *J* 11.0), 5.98 (1 H, d, *J* 11.0), 5.34 (1 H, br s), 5.00 (1 H, br s), 4.43 (1 H, m), 4.20 (1 H, m), 2.87 (1 H, m), 2.60 (1 H, m), 2.30 (1 H, m), 2.00 (1 H, m), 1.95 (1 H, m), 1.89 (1 H, m), 1.83 (1 H, m), 1.80–1.68 (4 H, m), 1.45 (4 H, m), 1.40–1.23 (7 H, m), 1.22 (6 H, s), 1.12 (4 H, m), 0.86 (2 H, m), 0.76 (3 H, d, *J* 7.0) and 0.68 (3 H, s). Data of **2br** (CY 941): λ_{max}(EtOH)/nm 261, 251 and 243; d_H(500 MHz; $CDCl_3$) 6.30 (1 H, d, *J* 11.0), 5.80 (1 H, d, *J* 11.0), 4.10 (1 H, m), 4.00 (1 H, m), 2.84 (1 H, m), 2.74 (1 H, dd, *J* 13.0 and 4.0 Hz), 2.48 (1 H, m), 2.22 (2 H, m), 1.94 (1 H, m), 1.87 (2 H, m), 1.79 (3 H, m), 1.68 (2 H, m), 1.50–1.40 (5 H, m), 1.40–1.24 (8 H, m), 1.22 (6 H, s), 1.15 (2 H, m), 0.86 (2 H, m), 0.76 (3 H, d, *J* 6.9) and 0.67 (3 H, s).

(6*R*)-6-[(1*R*,3a*R*,7a*R*)-4-(Trifluoromethanesulfonyloxy)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yl)]-2-methyl-2-(triethylsilyloxy)heptane (29a).

To a solution of alcohol **9a** (0.320 g, 1.14 mmol) and DMAP (0.278 g, 2.28 mmol) in dry CH_2Cl_2 (10 cm^3) was added chlorotriethylsilane (0.290 cm^3, 1.70 mmol), and the mixture was stirred at rt for 12 h. After removal of the solvent under reduced pressure, the residue was chromatographed (isooctane–EtOAc, 15:1) to give the corresponding triethylsilyl ether (0.430 g, 96%).

To the solution of *i*-Pr_2NH (0.12 cm^3, 0.88 mmol) in dry THF (2 cm^3) at 0 ºC was dropwise added *n*-BuLi (1.6 M solution in hexanes, 0.34 cm^3, 0.85 mmol). The mixture was stirred at 0

Supplementary data

ºC for 20 min, then cooled to –78 °C, and a solution of the **9a** derived silyl ether (210 mg, 0.53 mmol) in dry THF (0.5 cm^3) was dropwise added. The reaction mixture was stirred at –78 °C for 45 min, allowed to warm to rt over a period of 2 h, cooled again to –78 °C, and a solution of *N*-phenyltrifluoromethanesulfonimide (286 mg, 0.80 mmol) in dry THF (0.5 cm^3) was dropwise added. The reaction mixture was stirred at –78 °C for 10 min, allowed to warm to rt over a period of 4 h, and Et_2O (5 cm^3) was added. The solution was passed through a short pad of silica gel, which was rinsed with *n*-hexane–EtOAc 4:1 (20 cm^3). Concentration under reduced pressure left a residue, which was purified by HPLC (isooctane–EtOAc, 40:1) to give enol triflate **29a** (258 mg, 92%) as a colorless oil: R_f (isooctane–EtOAc, 5:1) 0.89; $[\alpha]^{20}_D$ +16.8 (c 1.045 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2960, 2874, 1460, 1418, 1379, 1246, 1209, 1145, 1099, 1044, 1012, 963, 936, 900, 874, 742, 725 and 609; d_H(500 MHz; C_6D_6) 5.29 (1 H, br.s), 2.30 (1 H, m), 1.85–0.95 (16 H, m), 1.27 (6 H, s), 1.12 (9 H, t, *J* 8.0), 0.91 (3 H, d, *J* 6.0), 0.71 (6 H, q, *J* 8.0) and 0.56 (3 H, s); d_C(DEPT; 50 MHz; C_6D_6) 150.0 (C), 116.2 (CH), 73.6 (C), 54.4 (CH), 50.2 (CH), 45.8 (CH_2), 45.2 (C), 36.6 (CH_2), 36.2 (CH), 34.8 (CH_2), 30.2 (CH_3), 30.0 (CH_3), 28.4 (CH_2), 23.8 (CH_2), 21.7 (CH_2), 21.2 (CH_2), 18.7 (CH_3), 11.2 (CH_3), 7.4 (CH_3) and 7.2 (CH_2); *m/z* (EI) 511 (M^+, 0.2%), 497 (4), 281 (2), 245 (2), 235 (2), 173 (25), 135 (15), 103 (50) and 75 (100).

(6*R*)-2-Methyl-6-[(1*R*,4a*R*,8a*R*)-5-(trifluoromethanesulfonyloxy)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-1-naphthyl]-2-(triethylsilyloxy)heptane (30a).

Obtained by reaction of ketone **26a** with *N*-phenyltrifluoromethanesulfonimide as described above for the preparation of **29a**. The crude product was purified by HPLC (cyclohexane–EtOAc, 200:1) to afford, next to recovered **26a** (6%), enol triflate **30a** (81%): R_f (cyclohexane–EtOAc, 5:1) 0.70; $[\alpha]^{20}_D$ +24.0 (c 0.86 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3418, 2954,

Supplementary data

2875, 1684, 1457, 1417, 1381, 1240, 1209, 1144, 1057 and 872; d_H(500 MHz; $CDCl_3$) 5.66 (1 H, d, *J* 3.2), 2.21 (3 H, m), 1.90 (2 H, m), 1.78–1.71 (2 H, m), 1.18 (6 H, s), 1.07 (1 H, dd, *J* 2.9 and 12.0), 0.94 (9 H, t, *J* 7.9), 0.90 (3 H, d, *J* 6.9), 0.85 (3 H, s), 0.56 (6 H, q, *J* 7.8); d_C(50 MHz; $CDCl_3$) 150.6, 116.4, 73.2, 65.6, 53.0, 48.7, 45.2, 38.7, 32.8, 32.6, 31.0, 29.7, 29.6, 26.0, 23.0, 21.7, 21.3 (2), 21.1, 12.4, 6.9 (3) and 6.6 (3); *m/z* (EI) 540 (M^+), 525, 511, 473, 427, 379, 346, 335, 293, 259, 235, 203, 173, 149, 135, 103, 75, 69 and 55; *m/z* (ESI) 563 (M + Na).

Coupling Reaction of Enol Triflates 29a and 30a with A-Ring Intermediates 31 and 32 – General Procedure.

To a solution of enol triflate **29a** (**30a**) (0.5 mmol) and A-ring synthon **31** (**32**) (0.5 mmol) in a mixture of Et_2NH (2.5 cm^3) and CH_3CN (5 cm^3) were added CuI (10 mg, 0.05 mmol) and bis(triphenylphosphine)palladium(II) acetate ($Pd(PPh_3)_2(OAc)_2$, 37.5 mg, 0.05 mmol). The reaction mixture was stirred at rt for 1 h and diluted with *n*-pentane–EtOAc 99:1 (25 cm^3). The solution was passed through a short pad of silica gel, which was rinsed with *n*-pentane–EtOAc 99:1 (250 cm^3). Concentration under reduced pressure left a residue, which was purified by HPLC to give the protected 1,25-D_3 analog.

(1*R*,3*S*)-5-[(1*R*,3a*R*,7a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl]ethynyl-4-methylcyclohex-4-ene-1,3-diol (5at).

Enol triflate **29a** was coupled with A-ring synthon **31** according to the above general procedure. The crude product was purified by HPLC (*n*-pentane–EtOAc, 99:1) to give the protected 1,25-D_3 analog **33at** (86%), which was consequently deprotected using TBAF according to the above general procedure. The crude product was purified by HPLC (*n*-

Supplementary data

pentane–acetone, 5:3) to give **5at** (GAO 315, 90%): R_f (isooctane–acetone, 1:1) 0.54; $[\alpha]^{20}_D$ –28.9 (c 0.353 in $CHCl_3$); λ_{max}(EtOH)/nm 287 and 272; ν_{max}(KBr)/cm^{-1} 3380, 2951, 2870, 1650, 1469, 1377, 1218, 1153, 1108, 1046, 955, 910, 845 and 708; d_H(500 MHz; CD_3OD) 5.91 (1 H, m), 4.16 (1 H, m), 4.02 (1 H, m), 2.44 (1 H, dd, *J* 16.7 and 4.2), 2.23 (3 H, m), 2.15–1.90 (3 H, m), 1.94 (3 H, s), 1.81 (1 H, m), 1.70 (1 H, ddd, *J* 13.0, 10.8 and 4.7), 1.53–0.90 (12 H, m), 1.17 (6 H, s), 0.99 (3 H, d, *J* 6.5) and 0.73 (3 H, s); d_C(DEPT; 125 MHz; CD_3OD) 140.8 (C), 134.0 (CH), 124.0 (C), 117.1 (C), 93.9 (C), 88.8 (C), 71.5 (C), 69.7 (CH), 64.0 (CH), 56.1 (CH), 51.4 (CH), 45.3 (CH_2), 43.0 (C), 41.1 (CH_2), 40.1 (CH_2), 37.7 (CH_2), 37.5 (CH), 37.2 (CH_2), 29.3 (CH_3), 29.1 (CH_3), 29.0 (CH_2), 26.0 (CH_2), 25.4 (CH_2), 21.9 (CH_2), 19.2 (CH_3), 19.1 (CH_3) and 11.4 (CH_3); *m/z* (EI) 414 (M^+, 4%), 396 (10), 378 (10), 311 (6), 283 (10), 239 (6), 183 (10), 145 (12), 115 (20), 81 (30) and 58 (100).

(1*R*,3*S*)-5-[(1*R*,3a*R*,7a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl]ethynylcyclohex-4-ene-1,3-diol (5ar).

Enol triflate **29a** was coupled with A-ring synthon **32** according to the above general procedure to give the protected 1,25-D_3 analog **33ar**. The crude product was deprotected using TBAF according to the above general procedure. The product was purified by HPLC (*n*-hexane–acetone, 1:1) to give **5ar** (GAO 205, 92% from **29a**) as a white powder: R_f (isooctane–acetone, 1:1) 0.42; mp 62–63 °C (decomp.); $[\alpha]^{20}_D$ –12.5 (c 0.368 in $CHCl_3$); λ_{max}(MeOH)/nm 281 and 267; ν_{max}(KBr)/cm^{-1} 3398, 2928, 2870, 1636, 1458, 1376, 1276, 1048, 978 and 935; d_H(500 MHz; CD_3OD) 5.95 (1 H, m), 5.91 (1 H, m), 4.36 (1 H, m), 4.06 (1 H, m), 2.42 (1 H, dd, *J* 17.2 and 4.6), 2.24 (2 H, m), 2.10–1.05 (21 H, m), 1.17 (6 H, s), 0.99 (1 H, d, *J* 6.5) and 0.72 (3 H, s); *m/z* (EI) 400 (M^+, 2%), 382 (4), 367 (5), 364 (3), 297 (4), 269 (6), 223 (3), 211 (4), 199 (6), 165 (8), 149 (22), 81 (28), 57 (80) and 43 (100).

Supplementary data

(1*R*,3*S*)-5-[(1*R*,4a*R*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5-naphthyl]ethynyl-4-methylcyclohex-4-ene-1,3-diol (6at).

Enol triflate **30a** was coupled with A-ring synthon **31** according to the above general procedure. The crude product was purified by HPLC (cyclohexane–EtOAc, 200:1) to give the protected 1,25-D_3 analog **34at** (92%), which was consequently deprotected using TBAF according to the above general procedure. The crude product was purified by HPLC (CH_2Cl_2–MeOH, 98:2) to give **6at** (IM 902, 91%): R_f (CH_2Cl_2–MeOH, 9:1) 0.32; $[\alpha]^{20}_D$ –51.0 (c 1.5 in $CHCl_3$); λ_{max}(EtOH)/nm 283, 269 and 259; ν_{max}(neat)/cm^{-1} 3414, 2930, 2854, 2281, 1448, 1363, 1215, 1154, 1103, 1047, 957 and 759; d_H(500 MHz; $CDCl_3$) 6.09 (1 H, d, *J* 3.0), 4.26 (1 H, s), 4.12 (1 H, m), 2.56 (1 H, m), 2.17 (2 H, m), 2.0 (3 H, m), 1.88 (2 H, m), 1.78 (2 H, m), 1.21 (6 H, s), 0.90 (3 H, d, *J* 6.9) and 0.79 (3 H, s); d_C(50 MHz; $CDCl_3$) 139.2, 134.3, 123.6, 116.0, 93.5, 88.0, 70.9, 69.1, 63.1, 53.5, 47.5, 44.1, 39.9, 39.0, 36.4, 33.4, 32.9, 30.4, 29.1, 29.0, 26.8, 25.2, 23.5, 22.8, 21.4 (2), 18.7 and 12.1; *m/z* (EI) 428 (M^+), 419, 410, 392, 353, 317, 293, 221, 199, 183, 173, 159, 142, 105, 103, 75 and 43.

(1*R*,3*S*)-5-[(1*R*,4a*R*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5-naphthyl]ethynylcyclohex-4-ene-1,3-diol (6ar).

Enol triflate **30a** was coupled with A-ring synthon **32** according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–Et_2O, 97:3) to give the protected 1,25-D_3 analog **34ar** (91%), which was consequently deprotected using TBAF according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–acetone, 7:3) to give **6ar** (GAO 183, 96%) as a white powder: R_f (*n*-hexane–acetone, 2:1) 0.27; mp 58–60 °C (decomp.); $[\alpha]^{20}_D$ –38.0 (c 0.469 in $CHCl_3$); λ_{max}(EtOH)/nm 282 and

Supplementary data

268; ν_{max}(KBr)/cm^{-1} 3382, 2930, 2860, 1618, 1461, 1444, 1368, 1217, 1150, 1083, 1044, 972, 933, 911 and 822; d_H(500 MHz; CD_3OD) 6.02 (1 H, br d, *J* 3.2), 5.95 (1 H, t, *J* 1.8), 4.36 (1 H, m), 4.07 (1 H, m), 2.42 (1 H, dd, *J* 17.3 and 4.5), 2.18 (2 H, m), 2.06–0.90 (19 H, m), 1.17 (6 H, s), 1.04 (1 H, dd, *J* 12.2 and 3.5), 0.93 (3 H, d, *J* 6.9) and 0.81 (3 H, s); d_C(DEPT; 50 MHz; CD_3OD) 136.1 (CH), 135.2 (CH), 125.8 (C), 123.4 (C), 91.0 (2C), 72.3 (C), 66.3 (CH), 65.2 (CH), 56.0 (CH), 50.0 (CH), 46.1 (CH_2), 40.6 (CH_2), 40.1 (CH_2), 38.7 (C), 35.7 (CH_2), 35.3 (CH_2), 32.7 (CH), 30.0 (CH_3), 29.1 (CH_2), 27.5 (CH_2), 25.5 (CH_2), 25.2 (CH_2), 24.0 (CH_2), 22.8 (CH_3) and 13.6 (CH_3); *m/z* (EI) 414 (M^+, 0.1%), 396 (0.5), 381 (2), 312 (3), 297 (0.5), 283 (1), 267 (2), 225 (3), 187 (2), 168 (4), 133 (8), 105 (12), 91 (18) and 58 (100).

Semi-Hydrogenation and Hydrogenation of the Yne-Diene Type Derivatives – General Procedure.

A mixture of the ynediene **33** or **34** (0.029 mmol), Lindlar catalyst (0.02 g), and quinoline (2% solution in *n*-pentane, 0.1 cm^3) in EtOAc (2 cm^3) was stirred under a H_2 atmosphere at rt. The reaction was carefully monitored by TLC for disappearance of the starting material. The reaction mixture was then passed through a pad of silica gel and concentrated under reduced pressure to yield the semi-hydrogenated derivative. In the absence of quinoline in the reaction mixture the procedure gave the corresponding derivative with fully hydrogenated triple bond.

(1*R*,3*S*)-5-[(*Z*)-2-[(1*R*,3a*R*,7a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl]ethenyl]cyclohex-4-ene-1,3-diol (3ar).

Ynediene **33ar** was hydrogenated using Lindlar catalyst in the presence of quinoline according to the above general procedure. The crude product was purified by HPLC (0.2% EtOAc in *n*-hexane) to give protected **3ar** (86%), which was consequently deprotected using

Supplementary data

TBAF according to the above general procedure. The crude product was purified by HPLC (*n*-pentane–acetone, 5:3) to give **3ar** (GAO 306, 93%): R_f (isooctane–acetone, 1:1) 0.38; $[\alpha]^{20}_D$ +50.3 (c 0.628 in $CHCl_3$); λ_{max}(EtOH)/nm 259; ν_{max}(KBr)/cm^{-1} 3381, 2926, 2872, 1634, 1469, 1377, 1217, 1149, 1044, 974 and 939; d_H(500 MHz; CD_3OD) 5.87 (1 H, d, *J* 12.3), 5.75 (1 H, d, *J* 12.3), 5.70 (1 H, br s), 5.40 (1 H, br s), 4.36 (1 H, m), 4.00 (1 H, m), 2.54 (1 H, dd, *J* 17.0 and 4.6), 2.30–1.05 (21 H, m), 1.17 (6 H, s), 0.99 (3 H, d, *J* 6.5) and 0.77 (3 H, s); d_C(DEPT; 125 MHz; CD_3OD) 138.0 (C), 137.6 (C), 131.5 (CH), 131.1 (CH), 130.0 (CH), 126.5 (CH), 71.5 (C), 66.1 (CH), 65.1 (CH), 55.8 (CH), 52.3 (CH), 45.3 (CH_2), 43.3 (C), 40.6 (CH_2), 38.6 (CH_2), 37.8 (CH_2), 37.5 (CH), 37.5 (CH_2), 29.4 (CH_2), 29.3 (CH_3), 29.1 (CH_3), 25.6 (CH_2), 24.6 (CH_2), 21.9 (CH_2), 19.3 (CH_3) and 11.9 (CH_3); *m/z* (EI) 402 (M^+, 3%), 384 (4), 366 (4), 351 (4), 299 (2), 273 (8), 237 (12), 213 (10), 183 (10), 143 (20), 131 (20), 81 (35) and 58 (100).

(1*R*,3*S*)-5-[(*Z*)-2-[(1*R*,4a*R*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5-naphthyl]ethenyl]-4-methylcyclohex-4-ene-1,3-diol (4at) and (1*R*,3*S*)-5-[2-[(1*R*,4a*S*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5-naphthyl]ethyl]-4-methylcyclohex-4-ene-1,3-diol (8at).

Triol **6at** was hydrogenated using Lindlar catalyst in the presence of quinoline according to the above general procedure. The reaction mixture was stirred for 45 min. The crude product was purified by flash chromatography (CH_2Cl_2–MeOH, 97:3), followed by HPLC (CH_2Cl_2–MeOH, 98:2) to afford the previtamin **4at** (IM 9053, 54%), and the saturated derivative **8at** (IM 9102, 34%). Data of **4at**: R_f (CH_2Cl_2–MeOH, 9:1) 0.32; $[\alpha]^{20}_D$ –51.0 (c 1.5 in $CHCl_3$); λ_{max}(EtOH)/nm 283, 269 and 259; ν_{max}(neat)/cm^{-1} 3414, 2930, 2854, 1448, 1363, 1215, 1154, 1103, 1047, 957 and 759; d_H(500 MHz; $CDCl_3$) 5.98 (1 H, d, *J* 11.9), 5.85 (1 H, d, *J* 11.9),

Supplementary data

5.46 (1 H, s), 4.19 (1 H, s), 4.03 (1 H, m), 2.44 (1 H, d, *J* 16.1), 2.07 (4 H, m), 1.93 (1 H, d, *J* 5.6), 1.85 (2 H, m), 1.78 (3 H, s), 1.21 (6 H, s), 1.02 (1 H, d, *J* 9.7), 0.89 (3 H, d, *J* 6.9) and 0.82 (3 H, s); *m/z* (EI) 430 (M^+), 412, 394, 379, 376, 351, 336, 305, 291, 283, 265, 237, 227, 209, 195, 174, 156, 141, 134, 131, 105, 91, 81, 75, 59 and 43. Data of **8at**: R_f (CH_2Cl_2–MeOH, 9:1) 0.32; $[\alpha]^{20}_D$ –36.0 (c 0.8 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3412, 2928, 2853, 1449, 1378, 1215, 1157, 1044, 909 and 757; d_H(500 MHz; $CDCl_3$) 5.33 (1 H, m), 4.14 (1 H, m), 4.08 (1 H, m), 2.34 (1 H, dd, *J* 5.1 and 16.5), 2.02 (5 H, m), 1.86 (3 H, m), 1.75 (3 H, s), 1.58 (4 H, m), 1.21 (6 H, s), 1.00 (1 H, dd, *J* 3.2 and 12.9), 0.89 (3 H, d, *J* 6.9) and 0.77 (3 H, s); d_C(50 MHz; $CDCl_3$) 138.2, 132.5, 127.1, 120.3, 70.9, 70.9, 64.1, 53.7, 48.4, 44.2, 40.7, 39.0 36.8, 33.9, 32.9, 32.6, 30.6, 29.1, 29.0, 27.2, 23.5, 23.1, 22.7, 21.7, 21.4, 15.8 and 12.5; *m/z* (EI) 432 (M^+) 414, 396, 378, 363, 343, 341, 325, 301, 285, 277, 273, 259, 199, 161, 140, 105, 95, 55 and 43.

(1*R*,3*S*)-5-[(*Z*)-2-[(1*R*,4a*R*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5-naphthyl]ethenyl]cyclohex-4-ene-1,3-diol (4ar).

Ynediene **34ar** was hydrogenated using Lindlar catalyst in the presence of quinoline according to the above general procedure to give protected **4ar**. The crude product was deprotected using TBAF according to the above general procedure. The product was purified by HPLC (*n*-hexane–acetone, 7:3) to give **4ar** (GAO 182, 83% from **34ar**) as a white powder: R_f (*n*-hexane–acetone, 2:1) 0.28; mp 137–139 °C; $[\alpha]^{20}_D$ +11.0 (c 0.371 in $CHCl_3$); λ_{max}(MeOH)/nm 248, 220 and 206; ν_{max}(KBr)/cm^{-1} 3410, 2932, 2856, 1633, 1465, 1378, 1217, 1156, 1083, 1044, 978, 939, 828 and 756; d_H(500 MHz; CD_3OD) 5.91 (1 H, d, *J* 12.2), 5.76 (1 H, d, *J* 12.2), 5.70 (1 H, br d, *J* 1.8), 5.39 (1 H, br d, *J* 2.0), 4.85 (3 H, s), 4.36 (1 H, m), 3.99 (1 H, m), 2.51 (1 H, dd, *J* 17.1 and 4.5), 2.25–1.05 (22 H, m), 1.29 (6 H, s), 0.93 (3

Supplementary data

H, d, *J* 6.9) and 0.91 (3 H, s); d_C(DEPT; 50 MHz; CD_3OD) 139.9 (C), 138.5 (C), 133.9 (CH), 132.3 (CH), 131.2 (CH), 127.2 (CH), 72.3 (C), 67.0 (CH), 66.0 (CH), 56.1 (CH), 51.5 (CH), 46.1 (CH_2), 41.5 (CH_2), 39.9 (CH_2), 38.8 (C), 36.0 (CH_2), 35.3 (CH_2), 32.7 (CH), 30.0 ($2CH_3$), 29.3 (CH_2), 27.0 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 24.0 (CH_2), 22.8 (CH_3) and 14.3 (CH_3); *m/z* (EI) 416 (M^+, 2%), 398 (2), 311 (2), 281 (2), 267 (4), 223 (6), 213 (8), 160 (8), 131 (10), 105 (16), 91 (30), 69 (40), 58 (70) and 43 (100).

(1*R*,3*S*)-5-[2-[(1*R*,3a*S*,7a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl]ethyl]-4-methylcyclohex-4-ene-1,3-diol (7at).

Ynediene **33at** was hydrogenated using Lindlar catalyst in the absence of quinoline according to the above general procedure. The crude product was purified by HPLC (0.1% EtOAc in *n*-pentane) to give protected **7at**, which was consequently deprotected using TBAF according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–acetone, 5:3) to give **7at** (GAO 320, 66% from **33at**): R_f (isooctane–acetone, 1:1) 0.52; $[\alpha]^{20}_D$ –54.9 (c 0.35 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3354, 2946, 2872, 1469, 1377, 1218, 1156, 1044, 941, 911 and 850; d_H(500 MHz; CD_3OD) 5.26 (1 H, m), 4.03 (1 H, m), 3.97 (1 H, m), 1.72 (3 H, s), 2.35–1.00 (28 H, m), 1.17 (6 H, s), 0.98 (3 H, d, *J* 6.5) and 0.71 (3 H, s); d_C(DEPT; 125 MHz; CD_3OD) 139.9 (C), 133.3 (C), 128.7 (C), 120.8 (CH), 71.5 (C), 71.5 (CH), 64.7 (CH), 55.9 (CH), 52.2 (CH), 45.3 (CH_2), 43.5 (C), 41.9 (CH_2), 40.2 (CH_2), 37.8 (CH_2), 37.7 (CH_2), 37.6 (CH), 34.3 (CH_2), 34.3 (CH_2), 29.4 (CH_2), 29.3 (CH_3), 29.1 (CH_3), 25.5 (CH_2), 24.1 (CH_2), 21.9 (CH_2), 19.3 (CH_3), 16.3 (CH_3) and 11.6 (CH_3); *m/z* (EI) 400 (3%, M – 18), 382 (6), 367 (5), 364 (4), 348 (2), 282 (5), 245 (12), 243 (6), 203 (8), 147 (28), 85 (55) and 58 (100).

(1*R*,3*S*)-5-[2-[(1*R*,3a*S*,7a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-7a-methyl-

Supplementary data

2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl]ethyl]cyclohex-4-ene-1,3-diol (7ar).

Protected previtamin **3ar** was hydrogenated using Lindlar catalyst in the absence of quinoline according to the above general procedure. The crude product was purified by HPLC (0.1% EtOAc in *n*-pentane) to give protected **7ar**, which was consequently deprotected using TBAF according to the above general procedure. The crude product was purified by HPLC (*n*-hexane–acetone, 5:3) to give **7ar** (GAO 305, 81% from **3ar**): R_f (isooctane–acetone, 1:1) 0.39; $[\alpha]^{20}_D$ –53.0 (c 0.474 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3354, 2946, 2872, 1469, 1377, 1218, 1156, 1064, 941, 911, 850 and 696; d_H(500 MHz; CD_3OD) 5.48 (1 H, br.s), 5.24 (1 H, br.s), 4.27 (1 H, m), 4.06 (1 H, m), 2.24 (1 H, dd, *J* 17.1 and 4.3), 2.10–1.05 (24 H, m), 1.16 (6 H, s), 0.98 (3 H, d, *J* 6.5) and 0.71 (3 H, s); d_C(DEPT; 125 MHz; CD_3OD) 140.6 (C), 139.7 (C), 124.1 (CH), 121.0 (CH), 71.7 (C), 66.3 (CH), 65.1 (CH), 56.1 (CH), 52.3 (CH), 45.5 (CH_2), 43.6 (C), 40.9 (CH_2), 38.9 (CH_2), 38.0 ($2CH_2$), 37.9 (CH_2), 37.7 (CH), 34.6 (CH_2), 29.6 (CH_2), 29.4 (CH_3), 29.3 (CH_3), 25.6 (CH_2), 24.2 (CH_2), 22.1 (CH_2), 19.5 (CH_3) and 11.8 (CH_3); *m/z* (EI) 404 (M^+), 386 (10%), 368 (4), 353 (4), 327 (4), 273 (5), 245 (15), 213 (6), 187 (12), 147 (40), 81 (70) and 58 (100).

(1*R*,3*S*)-5-[2-[(1*R*,4a*S*,8a*R*)-1-((1*R*)-5-Hydroxy-1,5-dimethylhexyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydro-5-naphthyl]ethyl]cyclohex-4-ene-1,3-diol (8ar).

Ynediene **34ar** was hydrogenated using Lindlar catalyst in the absence of quinoline according to the above general procedure to give protected **8ar**. The crude product was deprotected using TBAF according to the above general procedure. The product was purified by HPLC (*n*-hexane–acetone, 7:3) to give **8ar** (GAO 181, 81% from **34ar**) as a white powder: R_f (*n*-hexane–acetone, 2:1) 0.28; mp 140–142 °C; $[\alpha]^{20}_D$ –67.8 (c 0.36 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3367, 2930, 2860, 1664, 1467, 1448, 1378, 1356, 1216, 1156, 1083, 1049, 972, 936, 910 and

Supplementary data

829; d_H(500 MHz; CD_3OD) 5.48 (1 H, m), 5.35 (1 H, m), 4.28 (1 H, m), 4.04 (1 H, m), 2.26 (1 H, dd, *J* 4.9 and 16.9), 2.20–0.85 (26 H, m), 1.17 (6 H, s), 0.92 (3 H, d, *J* 6.9) and 0.82 (3 H, s); d_C(DEPT; 50 MHz; CD_3OD) 141.3 (C), 140.1 (C), 124.7 (CH), 122.7 (CH), 72.3 (C), 67.0 (CH), 65.8 (CH), 56.3 (CH), 50.5 (CH), 46.1 (CH_2), 41.6 (CH_2), 39.6 (CH_2), 39.0 (CH_2), 39.0 (C), 36.3 (CH_2), 35.3 (CH_2), 35.2 (CH_2), 32.8 (CH), 30.0 ($2CH_3$), 29.4 (CH_2), 25.7 (CH_2), 25.2 (CH_2), 24.7 (CH_2), 23.9 (CH_2), 22.8 (CH_3) and 14.0 (CH_3); *m/z* (EI) 418 (M^+, 0.5%), 400 (3), 382 (2), 258 (4), 213 (3), 133 (8), 105 (15), 91 (30) and 58 (100).

X-ray crystal structure analysis of compound 17.

Table 4. Relevant torsion angles (°) of the side chain of **17**.

Torsion angle	Molecule A	Molecule B	Molecule C	Molecule D
C(18)-C(13)-C(17)-C(19)	74.7	70.6	72.1	75.8
C(13)-C(17)-C(20)-C(21)	95.2	92.8	91.0	97.3
C(13)-C(17)-C(20)-C(22)	-141.2	-143.5	-146.4	-140.2
C(17)-C(20)-C(22)-O(23)	65.3	172.4	177.9	68.0
C(21)-C(20)-C(22)-O(23)	-166.8	-60.7	-54.5	-163.5
C(20)-C(22)-O(23)-C(24)	155.3	110.5	106.3	154.6
C(22)-O(23)-C(24)-O(25)	5.6	1.2	5.6	4.8
C(22)-O(23)-C(24)-N(26)	-174.2	-178.4	-174.8	-174.2
O(23)-C(24)-N(26)-C(27)	175.2	172.1	175.3	179.7
O(25)-C(24)-N(26)-C(27)	-4.6	-7.5	-5.1	0.7
C(24)-N(26)-C(27)-C(28)	-99.9	-78.7	-82.4	-101.8
C(24)-N(26)-C(27)-C(38)	136.6	157.9	153.8	133.3
N(26)-C(27)-C(28)-C(29)	-59.6	-18.8	-24.1	-64.0

Supplementary data

C(38)-C(27)-C(28)-C(29)	63.2	102.2	98.7	58.8

Table 5. Geometry of the intermolecular hydrogen bonds in the crystal structure of **17**.

D-H----A [position]	H----A (Å)	D----A (Å)	D-H----A (°)
N(26A)-H(26A)----O(25B) [-1-x, -½+y, -1-z]	2.17	3.010	164
N(26B)-H(26B)----O(25A)	2.13	2.977	170
N(26C)-H(26C)----O(25D) [-1-x, -½+y, -1-z]	2.08	2.929	173
N(26D)-H(26D)----O(25C)	2.23	3.075	168