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Synthesis of 5-hydroxy-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one – precursor of putative bioisosteric colchicine analogues

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General information

All reaction temperatures correspond to internal temperatures unless otherwise noted. Solvents for the reactions, extraction and chromatography were technical grade and distilled from indicated drying agents: petroleum ether 40–60^{o}C, acetone, ethyl acetate, methylene chloride and 1,2-dichloroethane (P_2O_5); ethanol and tetrahydrofuran (sodium); isopropanol and methanol (magnesium); *tert*-butanol (CaO); DMF (CaH_2). DMSO was distilled under vacuum. Flash and column chromatography were performed on silica gel Acros (40–60 μm). Reaction control was carried out by thin-layer chromatography on "Silufol-UV254" plates. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on spectrometer Bruker Avance 400 (Varian) in $CDCl_3$ at 400 and 100 MHz correspondingly. Spectra are referenced to residual chloroform (δ 7.26 ppm ^{1}H; δ 77.0 ppm ^{13}C). Elemental analysis was performed on CNH analyser "Vario Micro Cube". Infrared spectra (IR) were registered on Fourier Transform IR spectrometer IR-200 (Thermo Nicolet) in KBr and reported in cm^{-1}. Electron impact mass spectra were obtained with typical voltage of 70 eV. Melting points (uncorrected) were determined in open capillary tubes.

***rac*-3-[4-(Benzyloxy)-3-methoxyphenyl]cyclohexanone** (**4**). A mixture of 1-(benzyloxy)-4-bromo-2-methoxybenzene **3** (9.709 g, 33.13 mmol) in THF (20 ml) and magnesium turnings (0.795 g, 33.13 mmol) activated by iodine (0.05 mg) and 1,2-dibromoethane (2 ml) was refluxed under argon atmosphere until complete dissolving of magnesium. Then a solution of $CuBr{\cdot}Me_2S$ (0.342 g, 1.66 mmol) and hexamethylphosphoramide (11.85 g, 66.17 mmol) in 20 ml THF was injected via syringe at room temperature. The reaction mixture was cooled to –78^{o}C and a solution of 2-cyclohexenone (3.16 g, 32.96 mmol) and Me_3SiCl (4.20 ml, 33.20 mmol) in THF (10 ml) was added dropwise (30 min). The mixture was stirred at –78^{o}C for 3 hours and then for 10 hours at room temperature, diluted with Et_3N (20 ml) and petroleum ether (200 ml) and washed with water (5×80 ml). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum. Chromatography of the residue [1:7, then 1:5 EtOAc/petroleum ether (40–70^{o}C)] gave product **4** (yellowish oil; 2.046 g; yield 20%).

^{1}H NMR (δ): 1.74–1.88 (2H, m), 2.07–2.19 (2H, m), 2.34–2.47 (2H, m), 2.52 (1H, dd, *J*=13.9, 11.6 Hz, H$^{2\text{-}Cy}$), 2.60 (1H, ddd, *J*=13.9, 4.3, 2.0 Hz, H$^{2\text{-}Cy}$), 2.97 (1H, tt, *J*=11.6, 3.7 Hz, H$^{3\text{-}Cy}$), 3.91 (3H, s, OCH_3), 5.15 (2H, s, OCH_2Ph), 6.71 (1H, dd, *J*=8.1, 2.2 Hz, H$^{6\text{-}Ar}$), 6.77 (1H, d, *J*=2.2 Hz, H$^{2\text{-}Ar}$), 6.86 (1H, d, *J*=8.1 Hz, H$^{5\text{-}Ar}$), 7.31–7.52 (5H, m).

^{13}C NMR (δ): 25.46; 32.88; 41.19; 44.38; 49.24 ($C^{3\text{-}Cy}$); 56.07 (OCH_3); 71.15 ($O\underline{C}H_2Ph$); 110.73; 114.20; 118.28; 127.27; 127.82; 128.54; 137.27; 137.71; 146.94; 149.70; 211.14 (C=O).

IR (cm^{-1}): 3060; 3033; 3006; 2954; 2937; 2866; 2831; 1711; 1603; 1589; 1516; 1468; 1452; 1421; 1385; 1313; 1265; 1244; 1221; 1142; 1030; 1009.

MS m/z (% rel. int.): 310 (10, M^+), 219 (4, $M-PhCH_2$), 91 (100, $PhCH_2$).

***rac-trans*-5-[4-(benzyloxy)-3-methoxyphenyl]-1-oxaspiro[2.5]octane (5**). A solution of NaH (0.037 g, 60% dispersion in mineral oil, 0.93 mmol) and Me_3SOI (0.169 g, 0.77 mmol) in DMSO (1.4 ml) was stirred till the termination of the gas bubbles release (~15 min), then ketone **4** (0.238 g, 0.767 mmol) in DMSO (0.7 ml) was added and the mixture was stirred at room temperature for 1 hour and at 55°C for 1.5 hours. The resulting solution was poured into iced water (35 ml), extracted with methylene chloride (3×15 ml) and washed with brine. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum. Chromatography of the residue [1:3, EtOAc/petroleum ether (40–70°C)] gave product **5** (yellowish oil; 0.216 g; yield 87%).

^{1}H NMR (δ): 1.29–1.56 (4H, m), 1.74–2.05 (6H, m), 2.67 (1H, d, *J*=4.7 Hz, $H^{2\text{-}oxirane}$), 2.71 (1H, d, *J*=4.7 Hz, $H^{2\text{-}oxirane}$), 2.91 (1H, tt, *J*=12.4, 3.5 Hz, $H^{3\text{-}Cy}$), 3.90 (3H, s, OCH_3), 5.14 (2H, s, OCH_2), 6.71 (1H, dd, *J*=8.3, 1.8 Hz, $H^{6\text{-}Ar}$), 6.79 (1H, d, *J*=1.8 Hz, $H^{2\text{-}Ar}$), 6.84 (1H, d, *J*=8.3 Hz, $H^{5\text{-}Ar}$), 7.31–7.51 (5H, m).

^{13}C NMR (δ): 23.86; 32.48; 32.91; 41.28; 41.50; 53.98 ($C^{2\text{-}oxirane}$); 56.03 (OCH_3); 58.59 ($C^{3\text{-}oxirane}$); 71.19 ($O\underline{C}H_2Ph$); 111.08; 114.20; 118.29; 127.28; 127.76; 128.51; 137.44; 139.77; 146.57; 149.55.

IR (cm^{-1}): 3058; 3031; 2921; 2856; 1602; 1589; 1515; 1463; 1458; 1421; 1387; 1267; 1251; 1232; 1218; 1139; 1037; 1014.

***rac-cis*-[3-[4-(Benzyloxy)-3-methoxyphenyl]cyclohexanecarbaldehyde** (**6**) A solution of the oxirane **5** (0.146 g, 0.451 mmol) in benzene (2 ml) and $BF_3{\bullet}Et_2O$ (0.033 ml, 0.266 mmol) was stirred for 15 min, then poured into iced water (15 ml) and extracted with benzene (3×20 ml). The organic layer was dried over Na_2SO_4 and evaporated in vacuum. Chromatography of the residue [1:5, then 1:3, EtOAc/petroleum ether (40–70°C)] gave sequentially products **6'** (white solid; 0.018 g; yield 13%) and **6** (yellowish oil; 0.041 g; yield 28%).

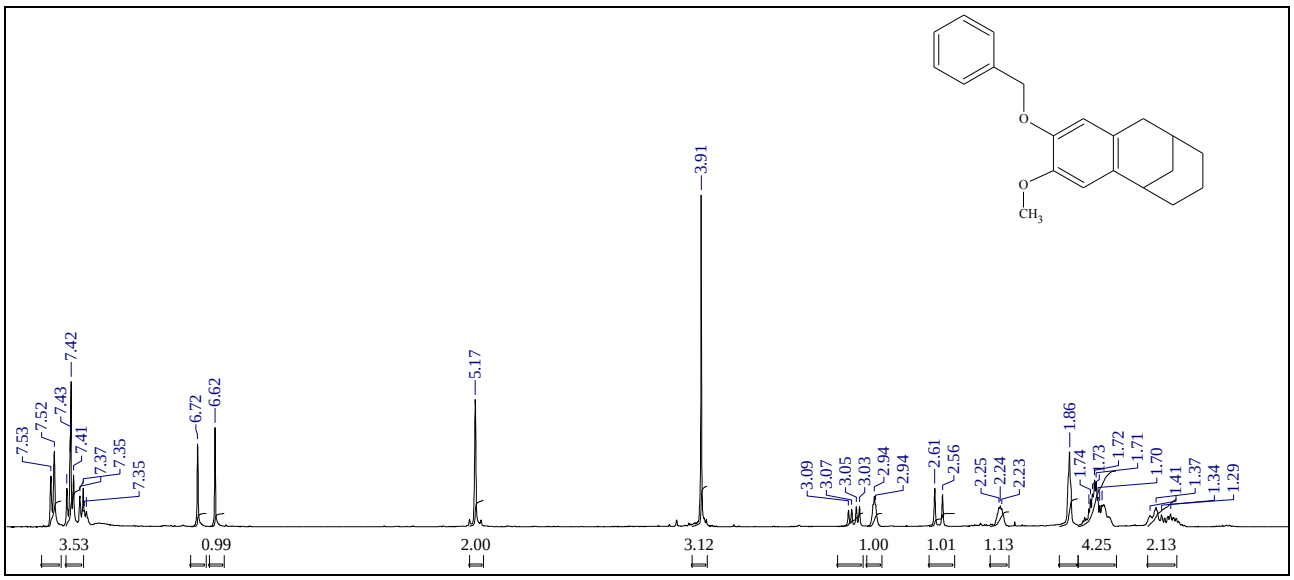
^{1}H NMR (δ): 1.30–1.52 (4H, m), 1.97–2.10 (3H, m), 2.20 (1H, d, *J*=13.4 Hz), 2.44 (1H, ttd, *J*=13.4, 3.6, 1.0 Hz, $H^{3\text{-}Cy}$), 2.59 (1H, tt, *J*=11.9, 3.3 Hz, $H^{1\text{-}Cy}$), 3.95 (3H, s, OCH_3), 5.19 (2H, s, $OC\underline{H}_2Ph$), 6.76 (1H, dd, *J*=8.2, 2.0 Hz, $H^{6\text{-}Ar}$), 6.82 (1H, d, *J*=2.0 Hz, $H^{2\text{-}Ar}$), 6.88 (1H, d, *J*=8.2 Hz, $H^{5\text{-}Ar}$), 7.25–7.54 (5H, m), 9.67 (1H, d, *J*=1.3 Hz, HC=O).

^{13}C NMR (δ): 25.60; 25.65; 33.63; 33.89; 43.01; 50.81; 56.04 (OCH_3); 71.17 (OCH_2Ph); 110.82; 114.17; 118.49; 127.29; 127.78; 128.53; 137.42; 139.89; 146.67; 149.59; 204.09 (C=O).

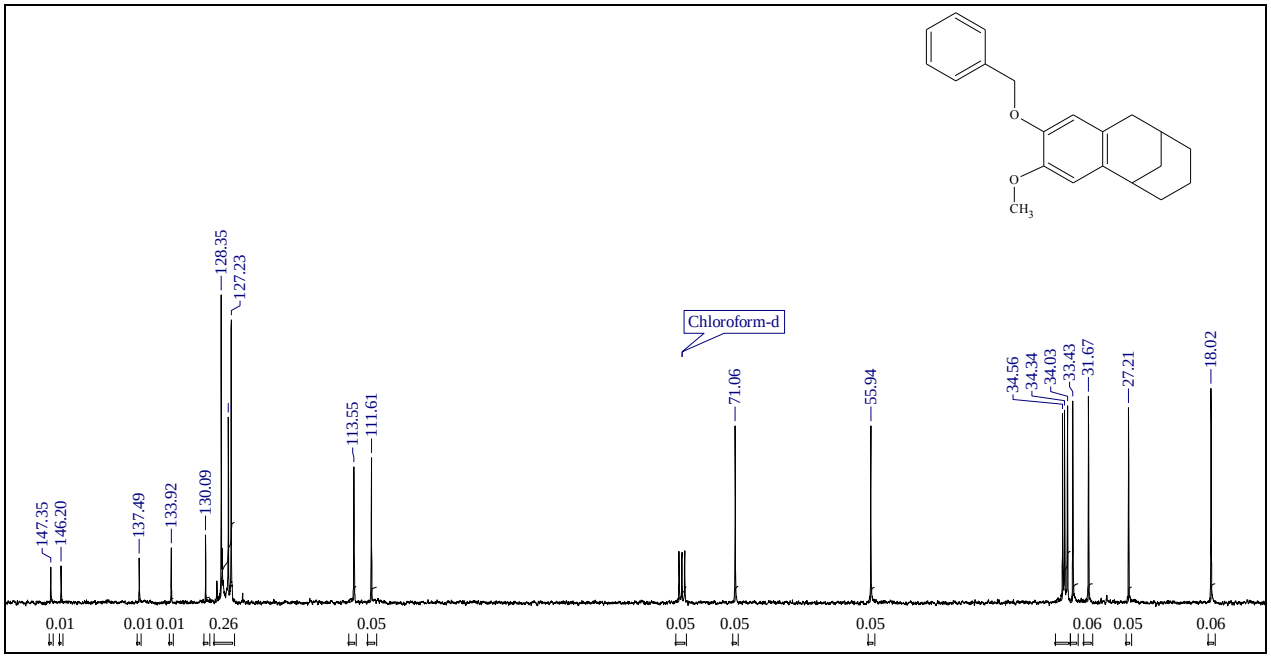
Spectral data for ***rac*-5-(benzyloxy)-4-methoxy-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene** (**6'**): ^{1}H NMR (δ): 1.23–1.41 (2H, m), 1.64–1.75 (4H, m), 1.86 (2H, m), 2.24 (1H, m, H^9), 2.58 (1H, d, *J*=17.4 Hz, H^8), 2.94 (1H, m, H^1), 3.06 (1H, dd, *J*=7.2, 17.4 Hz, H^8), 3.91 (3H, s, OCH_3), 5.17 (2H, s, $OC\underline{H}_2Ph$) 6.62 (1H, s, H^6), 6.72 (1H, s, H^3), 7.36 (1H, d, *J*=7.1 Hz), 7.42 (2H, m, *J*=7.3, 7.1 Hz), 7.53 (2H, d, *J*=7.3 Hz).

^{13}C NMR (δ): 18.02; 27.21; 31.67; 33.43; 34.03; 34.34; 34.56; 55.94 (OCH_3); 71.06 (OCH_2Ph); 111.61; 113.55; 127.22; 127.55; 128.32; 130.09; 133.92; 137.49; 146.20; 147.35.

Found, %: C 81.52; H 7.93. Anal Calcd for $C_{21}H_{24}O_2$, %: C 81.78; H 7.84.



^{1}H NMR spectra of compound **6'**.



^{13}C NMR spectra of compound **6'**.

***rac-cis*-3-[4-(Benzyloxy)-3-methoxyphenyl]cyclohexanecarboxylic acid** (**7**).

1. A mixture of aldehyde **6** (0.115 g, 0.355 mmol) in DMF (3 ml) and Oxone® (0.218 g, 0.710 mmol) was stirred at room temperature overnight (12 hours). The standard isolation procedure was carried out, but the target compound was not detected.

2. To a stirred solution of $AgNO_3$ (0.161 g, 0.948 mmol) in an ice-cooled distilled water (5 ml) was added 0.95 ml 2N NaOH followed by a solution of aldehyde **6** (0.102 g, 0.315 mmol) in a mixture of ethanol (1.4 ml), isopropanol (1.4 ml) and methylene chloride (1.4 ml). The resulting mixture was stirred at room temperature for 1.5 hours, acidified to pH=1 by adding 20% HCl and extracted by CH_2Cl_2 (3×10 ml). The combined organic layers were filtered, dried over Na_2SO_4 and evaporated in vacuum. Chromatography of the residue [1:5, then 1:3, EtOAc/petroleum ether (40–70^{o}C)] gave product **7** (yellowish solid; 0.011 g; yield 10%).

3. To a cooled solution of aldehyde **6** (0.099 g, 0.306 mmol) in a mixture of acetone (3 ml), *tert*-butanol (3 ml) and phosphate buffer pH 6.8 (1 ml) was added dropwise a solution of $KMnO_4$ (0.102 g, 0.643 mmol) in water (1.3 ml). The mixture was stirred at room temperature for 1.5 hours, diluted with a saturated solution of Na_2SO_3 (5 ml), acidified to pH=2 by adding 20% HCl and extracted by ethyl acetate (3×10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated in vacuum. Chromatography of the residue [1:5, then 1:3, EtOAc/petroleum ether (40–70°C)] gave product **7** (yellowish solid, m.p. 61–63°C; 0.032 g; yield 31%).

^{1}H NMR (δ): 1.29 (1H, m), 1.44–180 (4H, m), 1.92 (1H, m), 2.23 (1H, m), 2.34 (1H, m), 2.78 (1H, tt, *J*=11.6, 3.3 Hz, $H^{3\text{-}Cy}$), 2.91 (1H, m, $H^{1\text{-}Cy}$), 3.93 (3H, s, OCH_3), 5.16 (2H, s, OCH_2Ph), 6.74 (1H, dd, *J*=8.2, 1.7 Hz, $H^{6\text{-}Ar}$), 6.82 (1H, d, *J*=1.7 Hz, $H^{2\text{-}Ar}$), 6.86 (1H, d, *J*=8.2 Hz, $H^{5\text{-}Ar}$), 7.26–7.54 (5H, m), 11.0 (1H, br s., CO_2H).

^{13}C NMR (δ): 25.78; 28.40; 33.64; 36.32; 43.12; 43.52; 56.03 (OCH_3); 71.21 (OCH_2Ph); 110.84; 114.18; 118.54; 127.30; 127.76; 128.52; 137.42; 139.90; 146.61; 149.56; 181.82 (COOH).

IR (cm^{-1}): 1028; 1080; 1140; 1221; 1254; 1331; 1381; 1419; 1454; 1514; 1589; 1604; 1699; 2856; 2929; 2999; 3032; 3062; 3402.

MS m/z (% rel. int.): 340 (11, M^+), 294 (2, $M-H_2CO_2$), 203 (21, $M-H_2CO_2-PhCH_2$), 91 (100, $PhCH_2$).

***rac*-5-(Benzyloxy)-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one** (**8**). To a cooled solution of trifluoroacetic anhydride (0.105 ml, 0.752 mmol) in 1,2-dichloroethane (2 ml) was added dropwise a solution of acid **7** (0.128 g, 0.376 mmol) in 1,2-dichloroethane (1 ml). The resulting mixture was stirred 24 hours at room temperature and evaporated in vacuum. Chromatography of the residue [1:7, then 1:3, EtOAc/petroleum ether (40–70°C)] gave product **8** (white solid, m.p. 72–74°C; 0.036 g; yield 30%).

^{1}H NMR (δ): 1.23–1.29 (1H, m), 1.47 (1H, m), 1.66–1.75 (2H, m), 1.84 (1H, dt, *J*=13.0, 4.0 Hz), 1.89 (1H, m), 1.97 (1H, dt, *J*=13.0, 2.5 Hz), 2.34 (1H, dt, *J*=13.9, 3.0 Hz), 2.68 (1H, m, H^1), 3.09 (1H, m, H^9), 3.93 (3H, s, OCH_3), 5.18 (2H, d, *J*=1.5 Hz, OCH_2), 6.68 (1H, s, H^3), 7.30–7.41 (3H, m), 7.48 (2H, d, *J*=7.3 Hz), 7.63 (1H, s, H^6).

^{13}C NMR (δ): 18.02; 29.30; 30.65; 34.15; 35.16; 42.62; 56.08 (OCH_3); 70.85 (OCH_2Ph); 109.83; 109.93; 127.52, 127.59; 127.97; 128.56; 136.72; 142.54; 147.13; 154.45; 200.80 (C=O).

For the X-ray analysis data see the text.

***rac*-5-Hydroxy-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one** (**2,** R=H). The mixture of compound **8** (0.036 g, 0.112 mmol) and 5% palladium on carbon (0.015 g) in methanol (2 ml) was treated with hydrogen gas at atmospheric pressure during 1 hour. The catalyst was filtered off and the residue was evaporated under reduced pressure to give pure product **2**, R=H (colorless oil; 0.024 g; yield 92%).

^{1}H NMR (δ): 1.26 (1H, m), 1.47 (1H, m), 1.66–1.75 (2H, m), 1.84 (1H, dt, *J*=13.1, 4.0 Hz), 1.90 (1H, m), 1.97 (1H, dt, *J*=13.1, 2.7 Hz), 2.35 (1H, m), 2.69 (1H, m, H^1), 3.09 (1H, m, H^9), 3.98 (3H, s, OCH_3), 5.56 (1H, s, OH), 6.66 (1H, s, H^3), 7.59 (1H, s, H^6).

^{13}C NMR (δ): 17.97; 29.34; 30.83; 34.13; 35.19; 42.67; 56.04 (OCH_3); 109.07; 111.54; 128.28; 141.43; 144.41; 151.48; 200.94 (C=O).

Found, %: C 72.45; H 6.89. Anal Calcd for $C_{14}H_{16}O_3$, %: C 72.39; H 6.94.