Total Synthesis of Herbertenolide by Stereospecific Formation of Quaternary Centers in a Crystalline Ketone

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Experimental Section.

General: Tetrahydrofuran (THF) was distilled over sodium-benzophenone ketyl. Diisopropylamine was distilled over CaH_2 . Commercial reagents of the highest purity available were used without further purification. ^1H and ^{13}C NMR spectra were obtained with a Bruker ARX500 or Avance500 spectrometer in CDCl_3 . IR spectra were obtained with a Perkin-Elmer spectrometer either in KBr disks or as neat oils. High resolution mass spectra were obtained by electron ionization. Melting points were uncorrected. All reactions were carried out in oven-dried glass ware under argon atmosphere.

Trans-2-(2-Methoxy-5-methylphenyl)cyclohexanol (5). A 50 mL round bottom flask equipped with a magnetic stirring bar was charged with 2-bromo-4-methylanisole (**4**) (0.735 mL, 5.10 mmol) and THF (8 mL). After cooling to -78°C, *n*-butyllithium (3.25 mL, 5.20 mmol, 1.6M in hexanes) was added dropwise. The reaction mixture was stirred at -78°C for 1h. Cyclohexene oxide (0.257 mL, 2.55 mmol) was added, followed immediately by BF₃·OEt₂ (0.485 mL, 3.82 mmol). After stirring at -78°C for 1.5h, reaction was quenched with saturated NaHCO₃ and warmed to r.t. Product was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with cold 10% NaOH and brine. After drying over MgSO₄, solvent was removed *in vacuo*. Purification by column chromatography (15% EtOAc/hexanes) afforded cyclohexanol **5** (0.546g, 98%) as a viscous, colorless oil. ¹H NMR: δ 1.20-1.60 (m, 4H), 1.70-1.90 (m, 4H), 2.12-2.20 (m, 1H), 2.29 (s, 3H), 2.90-3.00 (m, 1H), 3.71-3.73 (m, 1H), 3.80 (s, 3H), 6.79 (d, 1H, J = 8.3 Hz), 6.99 (dd, 1H, J = 8.3 Hz, 2.1 Hz), 7.05 (d, 1H, J = 2.1 Hz). ¹³C NMR: δ 20.63, 25.11, 26.16, 32.33, 35.14, 55.64, 73.98, 110.82, 127.66, 128.02, 130.09, 131.15, 155.62. IR (neat): 3444, 2997, 2930, 2855, 1504, 1463, 1447, 1250, 1233, 1133, 1064, 1037, 862, 804 cm⁻¹. EI HRMS: calculated for C₁₄H₂₀O₂ 220.1463, found 220.1462.

2-(2-Methoxy-5-methylphenyl)cyclohexanone (6). To a 50 mL round bottom flask equipped with a magnetic stirring bar were added oxalyl chloride (0.238 mL, 2.73 mmol) and CH₂Cl₂ (8 mL). After cooling to -78°C, dimethyl sulfoxide (0.387 mL, 5.46 mmol) in 1.6 mL of CH₂Cl₂ was added dropwise. After 2 min of stirring, cyclohexanol **5** (0.546 g, 2.48 mmol) in 4 mL of CH₂Cl₂ was added over 5 min. The reaction mixture was stirred at -78°C for 15 min. Triethylamine (1.73 mL, 12.4 mmol) was then added and the resulting mixture was stirred for an additional 5 min at -78°C, followed by warming to r.t. slowly. Water (20 mL) was added to the reaction mixture and product was extracted with 20 mL of CH₂Cl₂. The combined organic layer was washed sequentially with 1% HCl (1 × 50 mL), saturated NaHCO₃ (1 × 50 mL), and brine. After drying over MgSO₄ and evaporation of solvent, the crude ketone was purified by column chromatography (10% EtOAc/hexanes) to give 0.530g (98%) of **6** as a light yellow oil. ¹H NMR: δ 1.59-1.81 (m, 2H), 1.99-2.04 (m, 2H), 2.10-2.25 (m, 2H), 2.28 (s, 3H), 2.49-2.53 (m, 2H), 3.74 (s, 3H), 3.89 (dd, 1H, J = 12.7, 5.4 Hz), 6.77 (d, 1H, J = 8.3 Hz), 6.91 (d, 1H, J = 2.0 Hz), 7.03 (dd, 1H, J = 8.2, 2.0 Hz). ¹³C NMR: δ 20.57, 25.58, 27.39, 33.29, 42.18, 50.94, 55.49, 110.46, 127.51, 128.17, 129.42, 129.48, 154.71, 210.02. IR (neat): 2935, 2861, 1714, 1612, 1589, 1504, 1449, 1354, 1317, 1289, 1248, 1197, 1126, 1066, 1034, 882, 838, 806, 732, 706 cm⁻¹. EI HRMS: calculated for C₁₄H₁₈O₂ 218.1307, found 218.1310.

2-(2-Methoxy-5-methylphenyl)-2-methylcyclohexanone (6a). In a 25 mL round bottom flask equipped with a magnetic stirring bar, sodium hydride (0.110 g, 4.58 mmol) was added to 5 mL of dimethoxyethane (DME). Cyclohexanone **6** (1.00g, 4.59 mmol) in 5 mL of DME was then added dropwise with stirring. The mixture was refluxed for 1h. Methyl iodide (0.517 mL, 9.17 mmol) was added and the reaction mixture was allowed to reflux for 1h. After cooling to r.t., the mixture was poured into 5 mL of water and the product was extracted with ether (3 × 10 mL). The combined organic layer was washed with brine, dried over MgSO₄ and concentrated. Purification by column chromatography (15% EtOAc/hexanes) followed by recrystallization from hexanes afforded 0.227 g of unreacted **6** and 0.515 g (63%, based on recovered starting material) of **6a** as a crystalline solid. m.p. 82-83°C. ¹H NMR: δ 1.28 (s, 3H), 1.55-1.65 (m, 2H), 1.70-1.80 (m, 2H), 1.90-2.00 (m, 1H), 2.20-2.30 (m, 1H), 2.33 (s, 3H), 2.38-2.50 (m, 1H), 2.52-2.60 (m, 1H),

3.69 (s, 3H), 6.77 (d, $J = 8.2$ Hz), 7.03 (dd, $J = 8.2, 2.0$ Hz), 7.13 (d, $J = 2.0$ Hz). ^{13}C NMR: δ 20.77, 21.75, 24.57, 28.65, 39.10, 39.98, 51.96, 55.13, 111.52, 127.16, 128.00, 130.00, 133.14, 154.30, 214.52. IR (KBr): 2963, 2938, 2863, 2834, 1704, 1505, 1465, 1456, 1442, 1292, 1248, 1235, 1027, 810, 773, 708 cm^{-1} . EI HRMS: calculated for $\text{C}_{15}\text{H}_{20}\text{O}_2$ 232.1463, found 232.1468.

2-(2-Methoxy-5-methylphenyl)-2,6-dimethylcyclohexanone (7). A 50 mL round bottom flask equipped with a magnetic stirring bar was charged with diisopropylamine (0.542 mL, 3.86 mmol) and THF (5 mL). After cooling to -78°C , *n*-butyllithium (3.76 mL, 3.69 mmol) was added dropwise, and the resulting mixture was stirred at -78°C for 30 min. Cyclohexanone **6a** (0.815g, 3.51 mmol) in 5 mL of THF was added dropwise, and reaction was allowed to come to r.t. After stirring at r.t. for 1h, reaction mixture was cooled to 0°C , and methyl iodide (0.241 mL, 3.86 mmol) was added dropwise. The reaction mixture was allowed to come to r.t. and was stirred for 18h at r.t. Water (10 mL) was added and product was extracted with ether (3×10 mL). The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated. The crude product was purified by column chromatography (5% EtOAc/hexanes) to give **7** (0.821 g, 95%) as an amorphous solid and a mixture of diastereomers (diastereomeric ratio $\sim 11:1$). Spectroscopic data are given for major isomer: ^1H NMR: δ 0.97 (d, 3H, $J = 6.4$ Hz), 1.22 (s, 3H), 1.29-1.35 (m, 1H), 1.50-1.60 (m, 2H), 1.70-1.90 (m, 2H), 2.34 (s, 3H), 2.45-2.55 (m, 1H), 2.56-2.65 (m, 1H), 3.66 (s, 3H), 6.75 (d, 1H, $J = 8.2$ Hz), 7.03 (dd, 1H, $J = 8.2$ Hz, 2.0 Hz), 7.16 (d, 1H, $J = 2.0$ Hz). ^{13}C NMR: δ 14.86, 20.84, 21.70, 25.24, 38.80, 40.37, 41.63, 52.46, 55.18, 111.28, 127.26, 127.96, 130.13, 132.82, 154.44, 215.98. IR (neat): 2966, 2930, 2861, 1715, 1500, 1458, 1369, 1292, 1251, 1238, 1031, 807 cm^{-1} . EI HRMS: calculated for $\text{C}_{16}\text{H}_{22}\text{O}_2$ 246.1620, found 246.1626.

Trans-3-(2-methoxy-5-methylphenyl)-1,3-dimethyl-2-oxocyclohexanecarboxylic acid methyl ester (3). In a 25 mL round bottom flask equipped with a magnetic stirring bar, diisopropylamine (0.478 mL, 3.41 mmol) was added to 5 mL of ether. After cooling to -78°C in a dry ice-acetone bath, *n*-butyllithium (3.13 mmol, 2.08 mL, 1.5M in hexanes) was added dropwise. The reaction mixture was stirred at -78°C for 1h. Cyclohexanone **7** (0.700g, 2.84 mmol) in 5 mL of ether was added dropwise. After stirring for an additional 30 min at -78°C , the reaction mixture was warmed to 0°C and stirred for 1h. The reaction mixture was then re-cooled to -78°C and methyl cyanofomate (0.316 mL, 3.98 mmol) was added dropwise. After stirring for 30 min at -78°C and 18h at r.t., saturated NH_4Cl (10 mL) was added and the product was extracted with ether (3×5 mL). The combined organic layer was washed with brine, dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAc/hexanes) to give **3** (0.626 g, 72%) as a white crystalline solid. m.p. $96-97^\circ\text{C}$. ^1H NMR: δ 1.40 (s, 3H), 1.46 (s, 3H), 1.60-1.70 (m, 1H), 1.70-1.80 (m, 1H), 1.80-1.95 (m, 2H), 2.22-2.30 (m, 1H), 2.30 (s, 3H), 2.45-2.55 (m, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 6.75 (d, 1H, $J = 8.2$ Hz), 7.02 (dd, 1H, $J = 8.2, 2.0$ Hz), 7.09 (d, 1H, $J = 2.0$ Hz). ^{13}C NMR: δ 19.47, 20.84, 23.75, 23.76, 36.11, 39.68, 51.24, 52.28, 55.06, 56.08, 111.17, 126.98, 127.94, 129.66, 135.32, 153.36, 174.05, 209.84. IR (KBr): 2975, 2948, 2921, 1732, 1711, 1498, 1463, 1450, 1240, 1206, 1185, 1132, 1030, 1006, 984, 816 cm^{-1} . HRMS: Calculated for $\text{C}_{18}\text{H}_{24}\text{O}_4$ 304.1675, found 304.1673.

***Trans*-2-(2-Methoxy-5-methylphenyl)-1,2-dimethylcyclopentanecarboxylic acid methyl ester (2).** Ground powder of crystalline **3** (45 mg, 0.148 mmol) was placed in between two microscope slides and cooled with an ice bath. The sample was irradiated with a medium pressure Hanovia mercury arc lamp with a 310nm filter for 12h. Crude product was washed off with CH₂Cl₂ and purified by preparative tlc (5% EtOAc/ hexanes). Ester **2** was obtained as a lightly yellow oil in 63% yield (8 mg, 0.029 mmol) based on unreacted starting material (31 mg, 0.102 mmol). ¹H NMR: δ 0.85 (s, 3H), 1.44 (s, 3H), 1.65-2.00 (m, 4H), 2.27 (s, 3H), 2.40-2.52 (m, 2H), 3.65 (s, 3H), 3.73 (s, 3H), 6.70 (d, 1H, J = 8.2 Hz), 6.98 (dd, 1H, J = 8.2 Hz, 1.5 Hz), 7.03 (d, 1H, J = 2.0 Hz). ¹³C NMR: δ 19.99, 20.80, 23.02, 25.15, 39.56, 51.10, 53.41, 53.61, 54.52, 110.51, 127.44, 128.86, 129.12, 135.23, 155.31, 178.06. IR (neat): 2946, 2927, 1725, 1500, 1462, 1376, 1293, 1254, 1178, 1158, 1090, 1032, 805, 758, 724 cm⁻¹. EI HRMS: calculated for C₁₇H₂₄O₃ 276.1725, found 276.1729.

Herbertenolide (1). Ester **2** (8 mg, 0.0290 mmol) was dissolved in CH₂Cl₂ (3 mL) in a 25 mL round bottom flask equipped with a magnetic stirring bar and cooled to 0°C. Boron tribromide (0.200 mL, 1M in CH₂Cl₂) was then added dropwise with stirring. After stirring for 1h, the mixture was allowed to come to r.t. and continued to stir for 18h. The reaction was quenched with saturated NH₄Cl (5 mL) and the product was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated to give a brown residue. The crude lactone **1** was purified by preparative tlc (5% EtOAc/hexanes) and 4 mg (60%) of **1** was obtained as a white solid (crystallized from ether). m.p. 52-53°C. ¹H NMR: δ 0.93 (s, 3H), 1.13 (s, 3H), 1.70-1.80 (m, 1H), 1.85-2.05 (m, 4H), 2.15-2.25 (m, 1H), 2.33 (s, 3H), 6.89 (d, 1H, J = 1.8 Hz), 6.93 (d, 1H, J = 8.2 Hz), 7.02 (dd, 1H, J = 8.2 Hz, 1.8 Hz). ¹³C NMR: 19.78, 19.88, 20.89, 25.35, 29.03, 29.65, 47.07, 50.80, 115.82, 125.28, 128.02, 133.02, 134.06, 149.62, 173.60. IR (film): 2967, 2926, 1777, 1489, 1460, 1445, 1377, 1267, 1206, 1192, 1082, 1047, 928, 816 cm⁻¹. EI HRMS: calculated for C₁₅H₁₈O₂ 230.1307, found 230.1308.

Page S6: ^1H NMR Spectrum of *trans*-2-(2-Methoxy-5-methylphenyl)cyclohexanol (**5**)

Page S7: ¹H NMR Spectrum of 2-(2-Methoxy-5-methylphenyl)cyclohexanone (6)

Page S8: ¹H NMR Spectrum of 2-(2-Methoxy-5-methylphenyl)-2-methylcyclohexanone (**6a**)

Page S9: ¹H NMR Spectrum of 2-(2-Methoxy-5-methylphenyl)-2,6-dimethylcyclohexanone (7)

Page S10: ^1H NMR Spectrum of *trans*-3-(2-Methoxy-5-methylphenyl)-1,3-dimethyl-2-oxocyclohexanecarboxylic acid methyl ester
(3)

Page S11: ¹H NMR Spectrum of *trans*-2-(2-Methoxy-5-methylphenyl)-1,2-dimethylcyclopentanecarboxylic acid methyl ester (**2**)

Page S12: ¹H NMR Spectrum of (±)-herbertenolide (1).