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Supporting information for

A concise synthesis of herbertenolide

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1. General information

Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. Non-aqueous reaction were conducted under an inert atmosphere of argon in flame-dried glassware. Anhydrous solvent were treated as follow: tetrahydrofuran and diethyl ether were distilled from sodium under argon atmosphere, dichcloromethane and toluene was distilled distilled from calciumhydride under argon atmosphere. Anhydrous chloroform, acetonitrile, 1,2-dichloroethane, methanol and ethyl acetate were commercial available (Adamas, SafeDry, with molecular sieves). Thin layer chromatography was conducted on Merck 60 F254 pre-coated silica gel plates. Column chromatography was carried out by normal silica gel (40-60 µm, 200-400 mesh, Silicycle P60). NMR data including ¹H NMR and ¹³C NMR spectra were recorded on Bruker AVANCE III 500MHz. The chemical shifts (δ) for ¹H and ¹³C are given in ppm relative to residual signals of the solvents (CHCl₃ @ 7.26 ppm ¹H NMR, 77.16 ppm ¹³C NMR). Coupling constants are given in Hz. Low mass spectra were measured on a Shimadzu LCMS-2010EV mass spectrometer (ESI). High resolution mass spectra were obtained from IonSpec 4.7 Tesla FTMS mass spectrometer (MALDI), Bruker APEXIII 7.0 TESLA FTMS (ESI). Chiral HPLC analyses were performed on Waters 2487 Series using Daicel Chiralpak (AD-H, OD-H, IC and IB-3) column with hexane/iPrOH as the eluent. Optical rotations were measured on a Anton Paar MCP 300 polarimeter and are reported as follows: $\left[\alpha\right]_{D}^{25.0}$ (c in g per 100 mL, solvent).

2. Total synthesis of (±)-herbertenolide



To a solution of 2-bromo-4-methylanisole **10** (5.63 g, 28.0 mmol, 1.4 equiv.) in freshly distilled anhydrous THF 50 mL was added *n*-BuLi (12.0 mL, 2.5 M in Hexanes, 30.0 mmol, 1.5 equiv.) dropwise at -78 °C under argon atomosphere. After stirring at this temperature for 1 h, cyclohexene oxide **9** (1.96 g, 20.0 mmol, 1.0 equiv.) in 20 mL THF was added dropwise, followed by BF₃·Et₂O (3.81 mL, 30.0 mmol, 1.5 equiv.) immediately. The resulting mixture was stirred at -78 °C until all cyclohexene oxide **9** were consumed completely as judged by TLC. The reaction mixture was quenched with saturated NaHCO₃ and warmed to room temperature, extracted with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na₂SO₄ and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/30, v/v) to give cyclohexanol **11** (4.09 g, 93%) as a colorless oil.

¹**H NMR (500 MHz, CDCl₃):** δ 7.05 (d, *J* = 2.2 Hz, 1H), 7.00 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 3.77-3.70 (m, 1H), 3.00-2.94 (m, 1H), 2.29 (s, 3H), 2.16-2.11 (m, 1H), 1.86-1.72 (m, 4H), 1.55-1.35 (m, 4H).

¹³C NMR (126 MHz, CDCl₃): δ 155.86, 131.39, 130.30, 128.23, 127.84, 111.09, 74.15, 55.85, 35.37, 32.53, 26.37, 25.32, 20.80.

HRMS (EI) exact mass calcd for C₁₄H₂₀O₂: m/z 220.1463 [M]⁺, found: m/z 220.1462.



To a suspension of cyclohexanol **11** (2.20 g, 10.0 mmol, 1.0 equiv.) and silica gel (4.32 g) in anhydrous CH_2CI_2 100 mL was added pyridinium chlorochromate (4.32 g, 20.0 mmol, 2.0 equiv.) portionwise at 0 °C. The reaction mixture was warmed up to room temperature and stirred until all cyclohexanol **11** consumed completely as judged by TLC. The reaction mixture was filtrated with Celatom and washed with CH_2CI_2 . The combined filtrate were washed with water and brine, dried with anhydrous Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/50, v/v) to obtain cyclohexanone **12** (1.98 g, 91%) as a light yellow oil.

¹**H NMR (500 MHz, CDCl₃):** δ 7.05 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 3.91 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.76 (s, 3H), 2.59-2.47 (m, 2H), 2.30 (s, 3H), 2.24-2.14 (m, 2H), 2.09-2.00 (m, 2H), 1.87-1.77 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 210.08, 154.89, 129.61, 129.58, 128.32, 127.70, 110.63, 55.64, 51.12, 42.34, 33.46, 27.56, 25.75, 20.73.

HRMS (EI) exact mass calcd for C₁₄H₁₈O₂: m/z 218.1307 [M]⁺, found: m/z 218.1309.



To a suspension of NaH (300 mg, 60% dispersion in mineral oil, 7.5 mmol, 1.5 equiv.) in freshly distilled anhydrous THF 10 mL was added cyclohexanone **12** (1.09 g, 5.0 mmol, 1.0 equiv.) in 10 mL THF dropwise at room temperature under argon atomosphere. Then the mixture was warmed to reflux and stirred at this temperature for 1 h. Iodomethane (1.42 g, 10.0 mmol, 2.0 equiv.) in 5 mL THF was added dropwise. The resulting mixture was stirred at this temperature until the ratio of cyclohexanone **12** didn't change anymore after the addition of iodomethane (710 mg, 5.0 mmol, 1.0 equiv.) as judged by TLC. The reaction mixture was quenched with water, extracted with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na₂SO₄ and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/50, v/v) followed by recrystallization from hexanes afforded 368 mg of unreacted cyclohexanone **12** and 499 mg (43% yield, 65%, based on recovered starting material) of cyclohexanone (±)-**13** as a crystalline solid. m.p. 81~82 °C.

¹**H NMR (500 MHz, CDCl₃):** δ 7.13 (d, *J* = 2.1 Hz, 1H), 7.03 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 3.69 (s, 3H), 2.57-2.51 (m, 1H), 2.46-2.39 (m, 1H), 2.33 (s, 3H), 2.28-2.23 (m, 1H), 1.96-1.90 (m, 1H), 1.80-1.71 (m, 2H), 1.66-1.56 (m, 2H), 1.28 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 214.61, 154.53, 133.39, 130.22, 128.21, 127.37, 111.78, 55.35, 52.18, 40.21, 39.33, 28.86, 24.79, 21.98, 20.97.

HRMS (EI) exact mass calcd for $C_{15}H_{20}O_2$: m/z 232.1463 [M]⁺, found: m/z 232.1465.



To a solution of cyclohexanone (\pm)-13 (1.16 g, 5.0 mmol, 1.0 equiv.) in freshly distilled anhydrous THF 10 mL was added lithium diisopropylamide (5.0 mL, 2.0 M in THF/Hexane, 10.0 mmol, 2.0 equiv.) dropwise at -78 °C under argon atomosphere. The reaction mixture was warmed up to room temperature and stirred for 30 min. The mixture was cooled down to 0 °C, iodomethane (1.42 g, 10.0 mmol, 2.0 equiv.) in 5 mL THF was added dropwise. The resulting mixture was stirred at this temperature until all cyclohexanone (\pm)-13 were consumed completely as judged by TLC. The reaction mixture was quenched with water, extracted with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na₂SO₄ and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/100, v/v) to afford cyclohexanone (\pm)-14 (1.13 g, 92%) as an amorphous solid.

¹**H NMR (500 MHz, CDCl₃):** δ 7.16 (d, *J* = 2.1 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 3.66 (s, 3H), 2.65-2.60 (m, 1H), 2.55-2.49 (m, 1H), 2.34 (s, 3H), 1.92-1.85 (m, 1H), 1.81-1.73 (m, 1H), 1.59-1.52 (m, 2H), 1.36-1.26 (m, 1H), 1.22 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 216.12, 154.61, 132.99, 130.29, 128.12, 127.42, 111.46, 55.34, 52.63, 41.80, 40.54, 38.96, 25.41, 21.87, 21.01, 15.02.

HRMS (EI) exact mass calcd for C₁₆H₂₂O₂: m/z 246.1620 [M]⁺, found: m/z 246.1624.



To a solution of cyclohexanone (\pm)-14 (1.23 g, 5.0 mmol, 1.0 equiv.) in THF 10 mL was added formaldehyde (8.0 mL, 37% wt. in water, 100.0 mmol, 20.0 equiv.) and KOH (28.0 mL, 10% w/v in MeOH, 50.0 mmol, 10.0 equiv.) at room temperature. Then the reaction mixture was warmed to 60 °C and stirred at this temperature until the ratio of cyclohexanone (\pm)-14 didn't change anymore after the addition of formaldehyde (4.0 mL, 37% wt. in water, 50.0 mmol, 10.0 equiv.) as judged by TLC. The reaction mixture was quenched with water, extracted with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na₂SO₄ and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/100 to 1/50, v/v) to give 617 mg of unreacted cyclohexanone (\pm)-14 and compound (\pm)-15 (major) 410 mg, (\pm)-15a (minor) 135 mg (40% yield in total, 90%, based on recovered starting material) as colourless oil.

(±)-15 major

¹**H NMR (500 MHz, CDCI₃):** 7.14 (d, *J* = 2.2 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 3.71 (s, 3H), 3.62-3.57 (m, 1H), 3.44-3.38 (m, 1H), 2.68-2.63 (m, 1H), 2.53-2.47 (m, 1H), 2.32 (s, 3H), 1.93-1.80 (m, 2H), 1.75-1.67 (m, 1H), 1.64-1.53 (m, 2H), 1.33 (s, 3H), 0.93 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 219.02, 154.46, 133.40, 129.91, 128.24, 126.44, 110.81, 70.57, 54.97, 51.52, 51.06, 39.49, 36.86, 25.69, 21.40, 21.01, 18.34.

HRMS (EI) exact mass calcd for $C_{17}H_{24}O_3$: m/z 276.1725 [M]⁺, found: m/z 276.1727.



(±)-15a minor

¹**H NMR (500 MHz, CDCl₃):** δ 7.09 (d, *J* = 2.1 Hz, 1H), 7.03 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 3.77 (s, 3H), 3.71-3.66 (m, 1H), 3.43-3.35 (m, 2H), 2.30 (s, 3H), 2.20-2.13 (m, 1H), 2.05-1.96 (m, 1H), 1.93-1.86 (m, 1H), 1.78-1.72 (m, 1H), 1.65-1.55 (m, 2H), 1.53 (s, 3H), 1.35 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 222.26, 152.90, 135.68, 129.98, 128.27, 127.27, 111.34, 71.21, 55.32, 50.78, 48.19, 39.32, 33.64, 24.33, 24.15, 20.98, 18.11.

HRMS (EI) exact mass calcd for $C_{17}H_{24}O_3$: m/z 276.1725 [M]⁺, found: m/z 276.1723.



To a solution of compound (\pm)-**15** (276 mg, 1.0 mmol, 1.0 equiv.) in CH₂Cl₂ 10 mL was added NaHCO₃ (420 mg, 5.0 mmol, 5.0 equiv.) in one portion followed by Dess-Martin periodinane (848 mg, 2.0 mmol,

2.0 equiv.) portionwise within 5 min at 0 °C. The resulting mixture was stirred at this temperature until all compound (\pm)-15 were consumed completely as judged by TLC. The reaction mixture was washed with saturated NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried with anhydrous Na₂SO₄ and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/20, v/v) to afford aldehyde (\pm)-8 as a colorless oil (268 mg, 98%).

¹**H NMR (500 MHz, CDCl₃):** δ 9.37 (d, *J* = 1.2 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 7.04 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 3.77 (s, 3H), 2.47-2.42 (m, 1H), 2.30 (s, 3H), 2.26-2.19 (m, 1H), 1.82-1.70 (m, 3H), 1.62-1.57 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 211.24, 200.26, 153.01, 135.24, 130.08, 128.28, 127.17, 111.27, 62.55, 55.41, 51.00, 39.47, 31.58, 22.54, 21.59, 20.98, 19.23.

HRMS (EI) exact mass calcd for C₁₇H₂₂O₃: m/z 274.1569 [M]⁺, found: m/z 274.1567.



To a solution of aldehyde (\pm)-8 (137 mg, 0.5 mmol, 1.0 equiv.) in EtOAc 10 mL was added H₂O₂ (300 μ L, 30 wt % in H₂O, 1.5 mmol, 3.0 equiv.) in one portion at room temperature. The resulting mixture was stirred at this temperature until all aldehyde (\pm)-8 were consumed completely as judged by TLC. Remove the solvent under vacuo pressure. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/20 to 1/5, v/v) to deliver carboxylic acid (\pm)-16 as a colorless oil (96 mg, 73%).

¹**H NMR (500 MHz, CDCl₃):** δ 7.04 (d, *J* = 2.1 Hz, 1H), 6.99 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 3.68 (s, 3H), 2.58-2.44 (m, 2H), 2.28 (s, 3H), 2.01-1.88 (m, 2H), 1.86-1.75 (m, 2H), 1.48 (s, 3H), 0.87 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 184.33, 155.09, 135.32, 129.29, 128.90, 127.66, 110.31, 53.94, 53.70, 53.27, 39.95, 39.79, 25.33, 22.88, 20.97, 20.13.

HRMS (EI) exact mass calcd for $C_{16}H_{22}O_3$: m/z 262.1569 [M]⁺, found: m/z 262.1571.



To a solution of carboxylic acid (\pm)-**16** (52.3 mg, 0.2 mmol, 1.0 equiv.) in CH₂Cl₂ 5 mL was added BBr₃ (1.0 mL, 1.0 mmol, 1.0 M in CH₂Cl₂, 5.0 equiv.) dropwise at room temperature. The resulting mixture was stirred at this temperature until all carboxylic acid (\pm)-**16** were consumed completely as judged by TLC. The reaction mixture was quenched with saturated NH₄Cl and extracted with CH₂Cl₂. The combined organic layers were dried with anhydrous Na₂SO₄ and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/100, v/v) to afford (\pm)-herbertenolide (**1**) as a white amorphous solid (32.4 mg, 71%).

¹**H NMR (500 MHz, CDCl₃):** δ 7.02 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 2.33 (s, 3H), 2.24-2.16 (m, 1H), 2.05-1.87 (m, 4H), 1.80-1.74 (m, 1H), 1.12 (s, 3H), 0.93 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 173.77, 149.75, 134.22, 133.16, 128.17, 125.44, 115.97, 50.95, 47.22, 29.79, 29.17, 25.51, 21.06, 20.03, 19.93.

HRMS (EI) exact mass calcd for $C_{15}H_{18}O_2$: m/z 230.1307 [M]⁺, found: m/z 230.1309.



Figure S1. Comparison of ¹H NMR spectrum for herbertenolide (1) of this work and previously reported route.

3. Asymmetric synthesis of chiral cyclohexanone 13



Sc(OTf)₃ (1.23 g, 2.5 mmol, 0.05 equiv.) and L1 (1.55 g, 2.5 mmol, 0.05 equiv.) in anhydrous *i*-PrOH (250 mL) was stirred at room temperature under argon atomosphere for 0.5 h. Benzofuranone **17** (8.1 g, 50.0 mmol, 1.0 equiv.), 4 Å molecular sieve (2.0 g) and methyl vinyl ketone (MVK) (8.1 mL, 100.0 mmol, 2.0 equiv.) were added sequently. The resulting mixture was stirred at room temperature until Benzofuranone **17** were consumed completely as judged by TLC. The reaction mixture was filtrated with Celatom and washed with EtOAc. The combined filtrate were removed under vacuum. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/70 to 1/30, v/v) to obtain benzofuranone **18** as a colorless oil (9.71 g, 84%).

 $[\alpha]_D^{25.0} = -80.07 \ (c \ 0.280, \text{CHCl}_3).$

Enantiomeric excess was found to be 92% by chiral HPLC (ChiralPak OD-H column, hexane/i-PrOH = 98:2, 214 nm, 0.7 mL/min, $t_{major} = 15.28$ min, $t_{minor} = 16.35$ min).

¹**H NMR (500 MHz, CDCl₃):** δ 7.07 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 2.33 (s, 3H), 2.32-2.26 (m, 1H), 2.18-2.10 (m, 2H), 2.08-2.01 (m, 1H), 1.99 (s, 3H), 1.47 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 206.96, 180.26, 150.60, 134.29, 131.17, 129.35, 123.69, 110.49, 46.62, 38.70, 32.48, 30.02, 24.43, 21.21.

HRMS (ESI): exact mass calcd for $C_{14}H_{16}O_3Na$: m/z 255.0997 [M+Na]⁺, found: m/z 255.0996.



To a suspension of NaH (1.5 g, 60% dispersion in mineral oil, 37.5 mmol, 1.5 equiv.) in freshly distilled anhydrous THF 130 mL was added benzofuranone **18** (5.8 g, 25.0 mmol, 1.0 equiv.) in 20 mL THF dropwise at room temperature under argon atomosphere. Then the mixture was warmed to 60 °C and stirred at this temperature until benzofuranone **18** were consumed completely as judged by TLC. Quenched the reaction with H₂O in ice bath. The THF was removed under vacuum. The residue was made acidic to a pH of 1 with 6 N HCl. Diluted the mixture with H₂O, extracted with EtOAc and washed with water and brine. The combined organic layers were dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/40 to 1/10, v/v) to afford hemiketal **19** as a white crystalline solid (4.68 g, 81%). m.p. 105~106 °C.

 $[\alpha]_D^{25.0} = -102.69 \ (c \ 0.115, \text{CHCl}_3).$

Enantiomeric excess was found to be 92% by chiral HPLC (ChiralPak AD-H column, hexane/i-PrOH = 80:20, 214 nm, 0.7 mL/min, $t_{major} = 8.45$ min, $t_{minor} = 9.93$ min); the enantiomeric excess of hemiketal **19** could be improved to 99% after once recrystallization with Et₂O/hexane.

¹**H NMR (500 MHz, CDCl₃):** δ 6.96 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 3.28 (s, 1H), 2.89 (q, *J* = 16.5 Hz, 2H), 2.31 (s, 3H), 2.24-2.17 (m, 1H), 2.07-1.98 (m, 1H), 1.95-1.84 (m, 2H), 1.49 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 208.20, 154.45, 133.29, 131.56, 129.39, 123.84, 110.01, 109.74, 47.84, 47.74, 35.69, 35.49, 21.23, 21.06.

HRMS (ESI): exact mass calcd for C₁₄H₁₇O₃: m/z 233.1178 [M+H]⁺, found: m/z 233.1179.



To a solution of hemiketal **19** (218 mg, 1.0 mmol, 1.0 equiv.) in MeOH (5 mL) and CH_2Cl_2 (5 mL), TMSCHN₂ (2.0 M in Hexane, 2.5 mL, 5.0 mmol, 5.0 equiv.) was added dropwise within 30 min at room temperature. The resulting mixture was stirred at room temperature until hemiketal **19** were consumed completely as judged by TLC. The solvent was removed under vacuum. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/20, v/v) to give cyclohexenone **20** as a white amorphous solid (220 mg, 85%).

 $[\alpha]_D^{25.0} = -24.46 \ (c \ 0.148, \text{CHCl}_3).$

¹**H NMR (500 MHz, CDCl₃):** δ 7.05 (d, *J* = 2.2 Hz, 1H), 7.02 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.79 (d, *J* = 2.2 Hz, 1H), 5.43 (d, *J* = 1.3 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.76-2.68 (m, 1H), 2.61-2.52 (m, 1H), 2.34-2.27 (m, 1H), 2.28 (s, 3H), 1.65-1.60 (m, 1H), 1.51 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 203.04, 175.45, 154.75, 133.75, 129.91, 128.37, 128.31, 112.16, 101.00, 55.62, 55.58, 47.37, 33.44, 26.52, 21.34, 20.91.

HRMS (EI): exact mass calcd for C₁₆H₂₀O₃: m/z 260.1412 [M]⁺, found: m/z 260.1413.



To a solution of cyclohexenone **20** (52.0 mg, 0.2 mmol, 1.0 equiv.) in MeOH (2 mL) was added 10% Pd/C (wet, 20 mg) and TFA (2 μ L, 0.02 mmol, 0.1 equiv.). The mixture was hydrogenated at 45 °C under 1 atm H₂ atomosphere until cyclohexenone **20** were consumed completely as judged by TLC. After filtration through Celite pad and removal of the solvent, the residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/100, v/v) to afford chiral cyclohexanone **13** as a white crystalline solid (43.2 mg, 93%). m.p. 82~83 °C.

 $[\alpha]_D^{25.0} = -32.69 \ (c \ 0.305, \text{CHCl}_3).$

Enantiomeric excess was found to be 99% by chiral HPLC (ChiralPak OD-H column, hexane/i-PrOH = 99:1, 214 nm, 0.7 mL/min, $t_{major} = 15.20$ min, $t_{minor} = 12.11$ min)

¹**H NMR (500 MHz, CDCl₃):** δ 7.13 (d, *J* = 2.1 Hz, 1H), 7.03 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 3.69 (s, 3H), 2.57-2.51 (m, 1H), 2.46-2.39 (m, 1H), 2.33 (s, 3H), 2.28-2.23 (m, 1H), 1.96-1.90 (m, 1H), 1.80-1.71 (m, 2H), 1.66-1.56 (m, 2H), 1.28 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 214.61, 154.53, 133.39, 130.22, 128.21, 127.37, 111.78, 55.35, 52.18, 40.21, 39.33, 28.86, 24.79, 21.98, 20.97.

HRMS (EI) exact mass calcd for C₁₅H₂₀O₂: m/z 232.1463 [M]⁺, found: m/z 232.1465.

4. ¹H & ¹³C NMR spectrum for the total synthesis of (±)-herbertenolide





































5. ¹H & ¹³C NMR spectrum for the asymmetric synthesis of chiral cyclohexanone 13



S28











6. HPLC spectrum for the asymmetric synthesis of chiral cyclohexanone 13



HPLC Report

No.	PeakNo	ID. Name	R.	Time	PeakHe i ght	PeakArea	Conc	
1	1		15.	740	521902.6	10789674.8	50.0512	
2	2		16.	707	482283.0	10767611.9	49.9488	
Tota	1				1004185.6	21557286.7	100.0000	

HPLC Report



HPLC Report

Sample Name:YSY-I-28-2 AD-H 8020 214 0.7 Re

Recording Time:2019.05.15 15:13



No.	PeakNo	ID. Name	R. Time	PeakHe ight	PeakArea	Conc	
1	1		8.490	325800.3	6632153.1	50.7546	
2	2		9.940	184416.0	6434948.8	49.2454	
Tota	1			510216.3	13067101.9	100.0000	

HPLC Report



No.	PeakNo	ID. Name	R. Time	PeakHe ight	PeakArea	Conc	
1	1		8.448	187423.5	4123695.6	96.0153	
2	2		9.932	5569.8	171136.9	3.9847	
Tota	1			192993.3	4294832.4	100.0000	

NOTE: The enantiomeric excess of hemiketal **19** could be improved to 99% after once recrystallization.



HPLC Report

No.	PeakNo	ID. Name	R. Time	PeakHe i ght	PeakArea	Conc		
1	1		8.240	1090769.4	21971187.1	99.9792		
2	2		9.620	411.5	4565.9	0.0208		
Tota	L			1091181.0	21975753.0	100.0000		
No.	1	DName	Mi	(ug)	MO(ug)	Cm(ug/m3)	Cc(mg/m3)	



	Retention Time	Peak Area	Peak Height	% Peak Area
1	12.088	56402670	2346324	49.82
2	15.383	56808064	1873422	50.18



		i calli i ca	i can neight	/or call rea
1	12.113	55723	2373	0.08
2	15.201	66694405	2092038	99.92

7. X-ray single crystal diffraction data of hemiketal 19



Figure S2. Crystal structure of hemiketal 19

Experimental

A suitable crystal was selected and measured on a XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer. The crystal was kept at 172.97(13) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation.

Crystal structure determination of hemiketal 19

Crystal Data for C₁₄H₁₆O₃ (M =232.27 g/mol): orthorhombic, space group P2₁2₁2₁ (no. 19), a = 7.30150(10) Å, b = 11.6303(2) Å, c = 28.2622(3) Å, V = 2399.99(6) Å³, Z = 8, T = 172.97(13) K, μ (CuK α) = 0.727 mm⁻¹, Dcalc = 1.286 g/cm³, 54055 reflections measured (8.22° ≤ 2 Θ ≤ 134.15°), 4292 unique (R_{int} = 0.1048, R_{sigma} = 0.0310) which were used in all calculations. The final R_1 was 0.0311 (I > 2 σ (I)) and wR_2 was 0.0793 (all data).

Identification code	exp_2527
Empirical formula	$C_{14}H_{16}O_3$
Formula weight	232.27
Temperature/K	172.97(13)
Crystal system	orthorhombic

Table S1. Crystal data and structure refinement for hemiketal 19

Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	7.30150(10)
b/Å	11.6303(2)
c/Å	28.2622(3)
α/°	90
β/°	90
$\gamma/^{\circ}$	90
Volume/Å ³	2399.99(6)
Z	8
$\rho_{calc}g/cm^3$	1.286
µ/mm ⁻¹	0.727
F(000)	992.0
Crystal size/mm ³	$0.39 \times 0.32 \times 0.28$
Radiation	$CuK\alpha$ ($\lambda = 1.54184$)
2Θ range for data collection/°	8.22 to 134.15
Index ranges	$-8 \le h \le 8, -13 \le k \le 13, -33 \le l \le 33$
Reflections collected	54055
Independent reflections	4292 [$R_{int} = 0.1048, R_{sigma} = 0.0310$]
Data/restraints/parameters	4292/0/314
Goodness-of-fit on F ²	1.044
Final R indexes $[I \ge 2\sigma(I)]$	$R_1 = 0.0311, wR_2 = 0.0787$
Final R indexes [all data]	$R_1 = 0.0320, wR_2 = 0.0793$
Largest diff. peak/hole / e Å ⁻³	0.21/-0.13
Flack parameter	0.10(8)

Table S2. Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for hemiketal **19**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{II} tensor

Atom	x	У	Z	U(eq)	
O1	2106(2)	8996.6(13)	2815.2(5)	29.1(3)	
O2	748(2)	8976.6(13)	2072.1(5)	28.4(3)	
O3	3997(2)	6086.9(15)	2885.2(6)	41.7(4)	
C1	886(3)	9490.8(18)	3122.6(7)	27.2(4)	
C2	1301(3)	10361(2)	3441.6(8)	34.3(5)	
C3	-107(4)	10740(2)	3735.9(7)	35.8(6)	
C4	-1874(4)	10301(2)	3711.5(8)	34.6(5)	
C5	-2235(3)	9441.7(19)	3376.6(7)	30.7(5)	
C6	-853(3)	9032.9(18)	3090.2(7)	25.4(4)	
C7	-845(3)	8086.7(18)	2723.3(6)	23.9(4)	
C8	-818(3)	6886.1(19)	2959.7(7)	28.5(5)	
C9	1021(3)	6588.6(19)	3181.3(7)	32.5(5)	
C10	2542(3)	6584.9(18)	2826.1(8)	29.8(5)	
C11	2171(3)	7253.7(19)	2377.9(7)	26.8(5)	
C12	1030(3)	8320.0(18)	2476.2(6)	23.3(4)	

C13	-2482(3)	8149(2)	2390.0(8)	32.1(5)
C14	-3357(5)	10721(3)	4039.6(11)	57.4(8)
O4	6034.0(19)	4530.8(13)	3413.6(4)	26.7(3)
O5	6675.5(18)	5854.7(12)	4002.8(5)	24.6(3)
O6	9541(2)	3653.8(18)	4760.5(6)	47.1(5
C15	5087(3)	6420.6(18)	4134.7(7)	22.6(4)
C16	4898(3)	7601.6(19)	4154.6(7)	27.1(5)
C17	3197(3)	8024.5(19)	4287.3(7)	26.8(4)
C18	1731(3)	7312.1(19)	4398.2(6)	23.1(4)
C19	1997(3)	6118.5(18)	4381.2(6)	21.9(4)
C20	3680(3)	5680.5(17)	4243.5(6)	20.6(4)
C21	4334(3)	4456.1(18)	4177.5(7)	21.7(4)
C22	4698(3)	3877(2)	4660.0(7)	29.4(5)
C23	6472(3)	4277(2)	4891.4(7)	36.0(5)
C24	8081(3)	3938(2)	4595.0(8)	29.5(5)
C25	7766(3)	3934.6(19)	4065.4(7)	25.8(4)
C26	6175(3)	4670.8(17)	3907.5(7)	21.7(4)
C27	3003(3)	3703.0(19)	3898.7(8)	29.7(5)
C28	-112(3)	7803(2)	4518.9(8)	31.5(5)

Table S3. Anisotropic Displacement Parameters (Å2×103) for hemiketal 19. The Anisotropicdisplacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$

Atom	U11	U22	U33	U23	U13	U12
01	27.9(8)	27.9(8)	31.7(7)	-0.2(6)	-3.0(6)	-5.0(6)
O2	28.1(7)	31.0(8)	26.1(7)	12.4(6)	4.0(6)	-0.9(7)
O3	42.5(10)	37.3(9)	45.4(9)	5.9(8)	-13.5(8)	8.0(8)
C1	33.1(11)	24.4(11)	24.0(9)	3.5(8)	-2.4(9)	-1.5(9)
C2	43.1(14)	26.3(12)	33.7(11)	1.1(9)	-13.8(10)	-4.6(10)
C3	59.9(15)	20.6(12)	26.9(10)	-0.2(8)	-6.5(10)	2.8(11)
C4	52.0(15)	22.2(12)	29.6(10)	3.3(9)	3.7(10)	5.3(10)
C5	38.4(12)	24.9(11)	28.6(10)	5.9(9)	3.2(9)	-0.6(10)
C6	33.1(11)	20.5(10)	22.7(9)	4.0(8)	-0.8(8)	-1.1(9)
C7	28.2(11)	23.1(11)	20.3(9)	2.5(8)	1.0(8)	-3.9(9)
C8	38.2(12)	21.8(11)	25.5(9)	2.5(8)	3.3(9)	-6.9(9)
C9	50.6(14)	22.5(11)	24.4(9)	5.8(8)	-6.3(10)	-2.0(10)
C10	38.3(13)	20.4(11)	30.7(10)	0.3(9)	-11.0(9)	-1.6(9)
C11	29.9(11)	26.8(12)	23.8(9)	1.8(8)	-0.8(9)	0.9(9)
C12	26.4(10)	22.5(10)	21.1(8)	3.1(8)	-1.4(8)	-3.0(8)
C13	30.6(12)	36.0(13)	29.8(10)	1.0(9)	-1.0(9)	-6.3(10)
C14	80(2)	35.6(15)	56.9(16)	-9.7(13)	26.3(16)	-1.4(14)
O4	26.7(8)	33.5(8)	20.0(6)	0.8(6)	1.3(6)	8.9(6)
O5	21.3(7)	20.7(7)	31.8(7)	1.6(6)	5.1(6)	-0.3(6)
O6	31.4(9)	66.1(13)	43.7(9)	27.7(9)	-7.7(7)	-1.3(8)

C15	23.7(10)	22.3(11)	21.7(9)	1.2(8)	2.5(8)	0.3(8)
C16	30.1(11)	20.5(11)	30.7(10)	2.2(8)	2.4(9)	-4.3(9)
C17	33.5(11)	19.5(11)	27.6(9)	0.8(8)	-0.4(9)	1.3(9)
C18	25.2(10)	26.1(11)	18.1(9)	-2.5(7)	-2.1(8)	3.5(8)
C19	22.7(10)	23.2(11)	19.9(9)	-0.6(8)	-0.3(7)	-2.4(8)
C20	23.4(10)	21.3(10)	16.9(8)	1.0(7)	0.3(7)	-1.3(8)
C21	21.0(10)	20.4(10)	23.6(9)	1.2(8)	1.6(8)	0.9(8)
C22	30.5(11)	28.7(12)	28.9(10)	10.8(9)	8.2(9)	4.5(9)
C23	42.7(13)	42.6(14)	22.7(10)	6.5(9)	-1.8(9)	4.9(11)
C24	27.2(11)	27.7(12)	33.6(11)	11.4(9)	-5.7(9)	-3.1(9)
C25	21.8(10)	26.9(11)	28.6(10)	2.7(8)	1.3(8)	3.6(9)
C26	23.1(10)	20.5(10)	21.6(9)	1.8(7)	0.5(8)	0.6(8)
C27	26.1(11)	23.6(11)	39.5(11)	-5.6(9)	1.6(9)	-1.3(9)
C28	28.7(11)	31.8(13)	33.9(11)	-3.9(9)	0.1(9)	4.5(10)

Table S4.Bond Lengths for hemiketal 19

Atom	Atom	Length/Å	Atom	Atom	Length/Å
01	C1	1.370(3)	O4	C26	1.409(2)
01	C12	1.468(2)	O5	C15	1.385(2)
O2	C12	1.389(2)	05	C26	1.450(2)
O3	C10	1.221(3)	O6	C24	1.210(3)
C1	C2	1.389(3)	C15	C16	1.382(3)
C1	C6	1.380(3)	C15	C20	1.375(3)
C2	C3	1.393(3)	C16	C17	1.388(3)
C3	C4	1.390(4)	C17	C18	1.389(3)
C4	C5	1.401(3)	C18	C19	1.403(3)
C4	C14	1.507(4)	C18	C28	1.501(3)
C5	C6	1.378(3)	C19	C20	1.386(3)
C6	C7	1.512(3)	C20	C21	1.514(3)
C7	C8	1.548(3)	C21	C22	1.544(3)
C7	C12	1.560(3)	C21	C26	1.566(3)
C7	C13	1.524(3)	C21	C27	1.527(3)
C8	C9	1.522(3)	C22	C23	1.523(3)
C9	C10	1.497(3)	C23	C24	1.496(3)
C10	C11	1.511(3)	C24	C25	1.514(3)
C11	C12	1.520(3)	C25	C26	1.510(3)

Table S5.	Bond Angles for hemiketal 19
Lable Det	

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	O1	C12	106.91(15)	C15	O5	C26	106.87(15)
O1	C1	C2	125.1(2)	C16	C15	O5	124.53(19)
01	C1	C6	113.20(18)	C20	C15	05	112.85(17)

C6	C1	C2	121.7(2)	C20	C15	C16	122.6(2)
C1	C2	C3	117.2(2)	C15	C16	C17	116.9(2)
C4	C3	C2	122.6(2)	C16	C17	C18	122.6(2)
C3	C4	C5	118.0(2)	C17	C18	C19	118.39(19)
C3	C4	C14	121.2(2)	C17	C18	C28	121.0(2)
C5	C4	C14	120.8(2)	C19	C18	C28	120.60(19)
C6	C5	C4	120.3(2)	C20	C19	C18	119.77(19)
C1	C6	C7	108.82(18)	C15	C20	C19	119.66(19)
C5	C6	C1	120.1(2)	C15	C20	C21	109.01(17)
C5	C6	C7	131.1(2)	C19	C20	C21	131.32(18)
C6	C7	C8	111.13(15)	C20	C21	C22	110.84(16)
C6	C7	C12	100.60(16)	C20	C21	C26	100.43(15)
C6	C7	C13	112.71(18)	C20	C21	C27	113.73(17)
C8	C7	C12	109.83(17)	C22	C21	C26	110.63(16)
C13	C7	C8	108.63(17)	C27	C21	C22	108.36(18)
C13	C7	C12	113.78(15)	C27	C21	C26	112.73(16)
C9	C8	C7	113.19(18)	C23	C22	C21	113.11(18)
C10	C9	C8	112.29(17)	C24	C23	C22	110.30(18)
O3	C10	C9	123.7(2)	O6	C24	C23	123.2(2)
O3	C10	C11	121.0(2)	O6	C24	C25	121.0(2)
C9	C10	C11	115.32(19)	C23	C24	C25	115.75(17)
C10	C11	C12	111.41(17)	C26	C25	C24	114.06(17)
01	C12	C7	105.70(15)	O4	C26	O5	108.19(15)
01	C12	C11	105.26(16)	O4	C26	C21	113.68(16)
O2	C12	01	108.73(16)	O4	C26	C25	106.46(16)
O2	C12	C7	109.50(16)	05	C26	C21	106.10(15)
O2	C12	C11	112.30(16)	O5	C26	C25	106.84(16)
C11	C12	C7	114.90(17)	C25	C26	C21	115.20(16)

Table S6. Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for hemiketal **19**

Atom	x	у	z	U(eq)
H2	1738.64	9137.41	1952.64	43
H2A	2468.61	10677.51	3458.13	41
H3	147.37	11308.9	3957.52	43
H5	-3412.96	9145.8	3347.46	37
H8A	-1755.91	6860.31	3202.55	34
H8B	-1118.08	6309.52	2724.12	34
H9A	1297.99	7143.37	3427.41	39
H9B	941.29	5835.98	3327.76	39
H11A	1528.86	6765.7	2154.44	32
H11B	3325.39	7479.65	2235.59	32

H13A	-3580.53	7968.76	2561.3	48
H13B	-2322.35	7606.61	2137.25	48
H13C	-2575.07	8910.73	2261.39	48
H14A	-2811.11	11113.16	4303.04	86
H14B	-4054.74	10077.12	4152.43	86
H14C	-4148.95	11239.01	3872.3	86
H4	5254.85	4971.38	3309.68	40
H16	5866.75	8090.46	4082.52	33
H17	3031.26	8816.48	4302.48	32
H19	1048.23	5622.78	4461.92	26
H22A	3683.89	4042.21	4870.88	35
H22B	4749.78	3050.61	4615.68	35
H23A	6449.76	5105.73	4928.34	43
H23B	6581.93	3934.76	5203.16	43
H25A	8869.21	4204.4	3909.72	31
H25B	7551.74	3149.93	3963.07	31
H27A	1959.29	3527.58	4092.11	45
H27B	3603.71	3002.08	3808.5	45
H27C	2610.26	4105.88	3620.13	45
H28A	-120.59	8041.97	4844.09	47
H28B	-1037.3	7229.02	4470.36	47
H28C	-356.85	8453.74	4319.46	47