

Supporting information

A Concise Total Synthesis of (\pm)-Cipadonoid B from Synthetic Azedaralide

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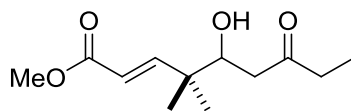
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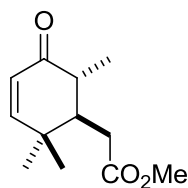
General Experimental

¹H and ¹³C NMR spectra were recorded with a Bruker AV300 (300.13 MHz; 75.47 MHz), AV400 (400.13 MHz; 100.62 MHz), DRX500 (500.13 MHz; 125.77 MHz), in deuteriochloroform (CDCl₃). Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. Low resolution electrospray ionisation mass spectrometry measurements (LRESIMS) were recorded in positive ionization mode on a Bruker Esquire HCT (High Capacity 3D ion trap) instrument with a Bruker ESI source. High resolution electron impact ionisation (HREIMS) accurate mass measurements were recorded on a Finnigan MAT 900XL-TRAP (EI 70 eV) using perfluorokerosene-H as reference calibrant. High resolution electrospray ionisation (HRESIMS) accurate mass measurements were recorded in positive mode on a Bruker MicrOTOF-Q (quadrupole – Time of Flight) instrument with a Bruker ESI source using sodium formate as reference calibrant. GC/MS data were recorded on a Shimadzu GC-17A VR.3, mass spectrometer. Column chromatography was performed using distilled solvents either on silica gel (Flash Silica gel 230 – 400 mesh) or using a Biotage Isolera One (MPLC) with samples loaded onto a HP-SIL SNAP flash cartridge. Dichloromethane (DCM), toluene and xylenes were freshly distilled from calcium hydride before use. Melting points were determined on a Stuart SMP11 Melting Point apparatus and are uncorrected. Fine chemicals were purchased from the Aldrich Chem. Co. All compounds synthesised here-in were conducted in the racemic series.



(E)-Methyl 4,4-dimethyl-5-hydroxy-7-oxonon-2-enoate (8)

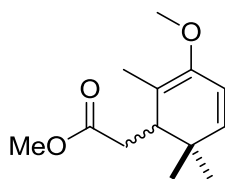
A stirring solution of (*E*)-methyl 4,4-dimethyl-5-oxopent-2-enoate (5.78 g, 37.0 mmol) in freshly distilled DCM (185 mL) was cooled to -78 °C under argon. A solution of TiCl₄ (20.35 mL, 40.7 mmol, 2M in DCM) was added dropwise, followed by the addition of 2-(*tert*-butyldimethylsilyloxy)but-1-ene (7.18 g, 38.5 mmol) via cannula to the dark red solution. The resultant mixture was stirred for 30 min. at -78 °C and quenched by the addition of sat. NH₄Cl (50 mL). The biphasic mixture was allowed to warm to r.t. and the separated aqueous layer extracted with diethyl ether (3 x 100 mL). The combined organic layer was successively washed with sat. NaHCO₃, water and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to afford (*E*)-methyl 5-hydroxy-4,4-dimethyl-7-oxonon-2-enoate (4.00 g, 47%) as a colourless oil. ¹H NMR (500 MHz CDCl₃): δ = 6.95 (d, *J* = 16.1 Hz, 1H), 5.77 (d, *J* = 16.1 Hz, 1H), 3.84 (dt, *J* = 10.4, 2.2 Hz, 1H), 3.68 (s, 3H), 3.17 (d, *J* = 3.2 Hz, 1H), 2.48 – 2.34 (m, 4H), 1.04 (s, 3H), 1.03 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 212.2, 167.1, 154.7, 119.3, 73.4, 51.5, 43.9, 40.8, 36.8, 23.0, 22.1, 7.4; LRMS (ESI) Calculated: (M+Na⁺): 251.13 Found: 251.09; HRMS (ESI) Calculated for C₁₂H₂₀O₄Na⁺: 251.1259, Found: 251.1247.



Methyl 2-(2,2,6-trimethyl-5-oxocyclohex-3-enyl)acetate (9)

Anhydrous toluene (15 mL) was added to potassium hydride (30% w/w in mineral oil, ~ 6.7 mL), the suspension briefly stirred, then left to settle for 10 min. The supernatant was removed via syringe, and quenched with wet THF. This process was repeated twice and then the remaining solid dried under reduced pressure, to give a free flowing powder (2.00 g, 49.87 mmol). (*E*)-Methyl 5-hydroxy-4,4-dimethyl-7-oxonon-2-enoate **8** (2.00 g, 9.51 mmol) in anhydrous toluene (40 mL) was added dropwise via cannula to a stirring suspension of the washed potassium hydride (2.00 g, 49.87 mmol) in toluene (400 mL) under an atmosphere of argon at 0 °C. The suspension was stirred at 0 °C for 15 min., then allowed to warm to r.t. and stirred for further 30 min. The reaction was quenched by the dropwise addition of a

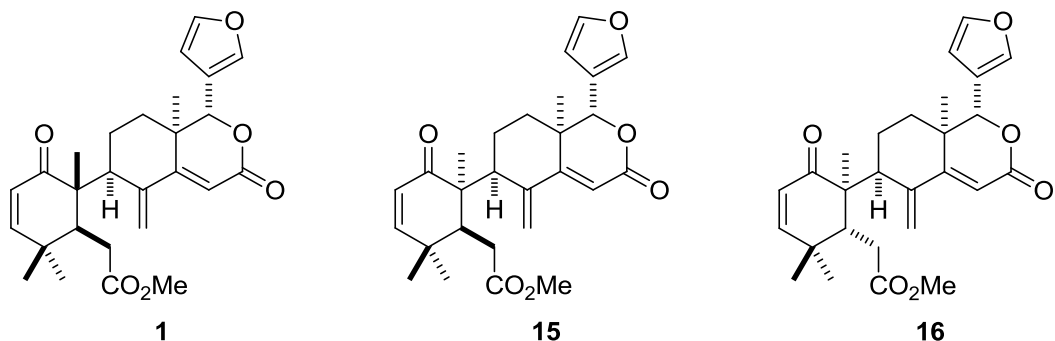
solution of acetic acid (3 mL) in toluene (20 mL), to attain a neutral pH, followed by water (50 mL). The layers were separated and the aqueous phase extracted with DCM (3 x 150 mL). The organic layers were combined, washed with sat. NaHCO₃, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a crude yellow oil. Column chromatography (petroleum ether/ethyl acetate, 4:1) provided methyl 2-(2,2,6-trimethyl-5-oxocyclohex-3-enyl)acetate as a clear oil (0.85 g, 46 %) as a mixture of diastereomers (22:78, syn:anti). The product was placed in the freezer overnight, and the resultant crystals separated from the oil, washed with petroleum ether and dried to give the pure *anti* isomer. ¹H NMR (500 MHz CDCl₃): δ = 6.57 (d, *J* = 12.6 Hz, 1H), 5.85 (d, *J* = 12.6 Hz, 1H), 3.67 (s, 3H), 2.60 – 2.10 (m, 4H), 1.13 (s, 3H), 1.08 (d, *J* = 7.7 Hz, 3H), 1.01 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 200.8, 173.7, 158.9, 125.9, 51.9, 46.3, 43.3, 42.0, 36.6, 28.0, 20.3, 11.8; LRMS (ESI) Calculated: (M+Na⁺): 233.12 Found: 233.10; HRMS (ESI) Calculated for C₁₂H₁₈O₃Na⁺: 233.1154, Found: 233.1144.



Methyl 2-(3-methoxy-2,6,6-trimethylcyclohexa-2,4-dien-1-yl)acetate (11)

To a solution of the cyclohex-2-enone **9** (169 mg, 0.8 mmol) in freshly distilled DCM (8 mL), in a sealed tube under argon was added 2,6-di-*tert*-butyl-4-methylpyridine (660 mg, 3.2 mmol), and methyl trifluoromethanesulfonate (376 μL, 3.4 mmol). The resultant mixture was stirred at 90 °C for 4 hours. The reaction vessel was allowed to cool to room temperature and diluted with ethyl acetate (75 mL) and washed with water (50 mL), sat. NaHCO₃ solution (50 mL) and brine. The organic phase was dried with Na₂CO₃, filtered and concentrated *in vacuo* to give a clear oil (0.97 g). The oil was purified by column chromatography (1:10 → 1:4 ethyl acetate:petroleum spirit) to give the titled compound (128 mg, 71 %) as a clear oil. 2,6-Di-*tert*-butyl-4-methylpyridine was also recovered. ¹H NMR (300 MHz CDCl₃): δ = 5.78 (d, *J* = 9.9 Hz, 1H), 5.37 (d, *J* = 9.9 Hz, 1H), 3.63 (s, 3H), 3.49 (s, 3H), 2.47 (dd, *J* = 7.5, 14.8 Hz, 1H), 2.26 (t, *J* = 6.5 Hz, 1H), 2.13 (dd, *J* = 5.7, 15.0 Hz, 1 H), 1.66 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 174.4, 146.6, 137.2, 119.9, 116.6, 57.4, 51.6, 47.2, 35.0, 32.9, 26.4, 24.5, 14.7; GC/MS *m/z* (%) 224.2 (M⁺, 13.0%), 152.2 (13.5), 151.1 (100), 149.1 (34.5), 136.2 (35.8), 135.2 (11.6), 121.1 (12.5), 119.2 (12.7), 105.2 (11.9), 91.1

(32.7), 79.1 (14.3), 77.1 (19.7), 43.1 (11.1), 41.1 (22.5); **HRMS** (EI) Calculated for C₁₃H₂₀O₃: 224.1412, Found: 224.1415



A solution of methyl 2-(3-methoxy-2,6,6-trimethylcyclohexa-2,4-dien-1-yl)acetate **11** (284 mg, 1.27 mmol), azedaralide **2** (82.5 mg, 0.32 mmol) and a crystal of *p*-toluenesulfonic acid in dry xylenes (3.1 mL) was stirred for 4 hours at 180 °C in a sealed tube under argon. Following cooling to room temperature, the reaction mixture was diluted with DCM (50 mL) and washed with saturated NaHCO₃ solution, brine, dried over Na₂SO₃ and concentrated to give a yellow oil. Purification using MPLC (1:4 ethyl acetate:petroleum spirit), gave **1** (28.8 mg, 20.1 %), **15** (6.3 mg, 4.4 %) and **16** (21.7 mg, 15.1 %).

Compound **1** (±)-Cipadonoid B: white amorphous solid

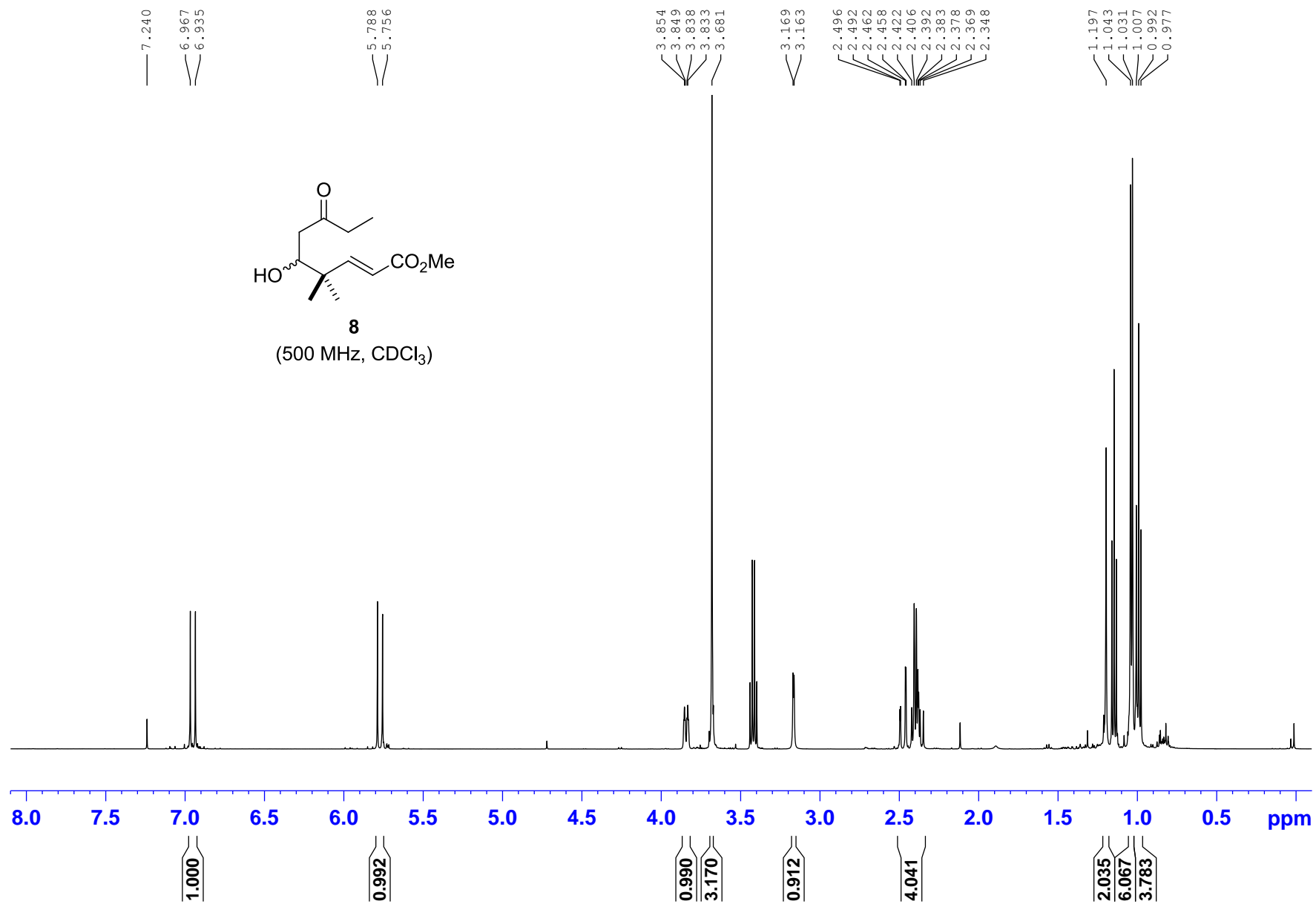
¹H NMR (500 MHz CDCl₃): δ = 7.43 (m, 1H), 7.37 (m, 1H), 6.67 (d, *J* = 10.0 Hz, 1H), 6.39 (d, *J* = 1.5 Hz, 1H), 6.00 (s, 1H), 5.91 (d, *J* = 10.5 Hz, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 5.29 (s, 1H), 5.01 (s, 1H), 3.69 (s, 3H), 2.83 (dd, *J* = 6.0, 4.5 Hz, 1H), 2.43 (m, 3H), 2.04 (dq, *J* = 15.5, 3.0 Hz, 1H), 1.74 (m, 1H), 1.38 (td, *J* = 14.0, 4.5 Hz, 1H), 1.11 (s, 9H), 1.06 (dt, *J* = 13.5, 4.5 Hz, 1H), 0.97 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): 203.5, 174.1, 166.2, 166.0, 159.1, 143.4, 142.7, 141.1, 127.0, 121.4, 120.4, 111.6, 110.1, 79.9, 52.1, 50.7, 47.6, 43.6, 39.3, 37.1, 31.7, 30.2, 29.5, 24.0, 21.1, 21.0, 18.5; **LRMS** (ESI) Calculated: (M+Na⁺): 475.21, Found: 475.20; **HRMS** (ESI) Calculated for C₂₇H₃₂O₆Na⁺: 475.2091, Found: 475.2089.

Compound **15**: slightly yellow oil

¹H NMR (500 MHz CDCl₃): δ = 7.50 (m, 1H), 7.41 (m, 1H), 6.47 (d, *J* = 10.5 Hz, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 5.94 (s, 1H), 5.83 (d, *J* = 10.0 Hz, 1H), 5.25 (s, 1H), 5.18 (s, 1H), 4.71 (s, 1H), 3.70 (s, 3H), 3.14 (t, *J* = 5.5 Hz, 1H), 2.68 (dd, *J* =

16.5, 4.5 Hz, 1H), 2.54 (m, 2H), 1.88 (m, 1H), 1.81 (m, 1H), 1.73 (m, 1H), 1.29 (ddd, $J = 13.5, 6.5, 3.5$ Hz, 1H), 1.20 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 202.2, 173.8, 166.5, 164.9, 155.4, 143.2, 143.1, 141.2, 124.5, 120.7, 120.1, 113.1, 110.0, 79.9, 54.7, 52.2, 48.5, 43.5, 39.5, 37.4, 32.7, 31.4, 31.0, 23.0, 22.0, 18.7, 17.6$; **LRMS** (ESI) Calculated: ($\text{M}+\text{Na}^+$): 475.21, Found: 475.20; **HRMS** (ESI) Calculated for $\text{C}_{27}\text{H}_{32}\text{O}_6\text{Na}^+$: 475.2091, Found: 475.2094.

Compound **16**: colourless crystals (MeOH); mp 195 – 196 °C; $^1\text{H NMR}$ (500 MHz CDCl_3 : $\delta = 7.51$ (m, 1H), 7.39 (t, $J = 1.5$ Hz, 1H), 6.59 (d, $J = 10.0$ Hz, 1H), 6.46 (m, 1H), 5.82 (d, $J = 10.0$ Hz, 1H), 5.74 (s, 1H), 5.49 (s, 1H), 5.42 (d, $J = 1.5$ Hz, 1H), 5.39 (s, 1H), 3.69 (s, 3H), 2.92 (dd, $J = 8.1, 3.0$ Hz, 1H), 2.63 (dd, $J = 6.3, 3.3$ Hz, 1H), 2.45 (dd, $J = 8.5, 17.0$ Hz, 1H), 2.37 (dd, $J = 17.0, 2.5$ Hz, 1H), 2.19 (td, $J = 13.0, 4.0$ Hz, 1H), 1.99 (dq, $J = 4.2, 14.7$ Hz, 1H), 1.69 (m, 1H), 1.19 (s, 3H), 1.13 (dt, $J = 4.2, 13.5$ Hz, 1H), 1.07 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 203.1, 174.5, 166.2, 165.6, 158.8, 143.4, 142.7, 141.2, 127.8, 122.0, 120.4, 112.3, 110.2, 79.9, 52.1, 47.0, 44.1, 39.6, 37.0, 31.7, 29.4, 29.3, 24.4, 22.1, 19.4, 18.4; **LRMS** (ESI) Calculated: ($\text{M}+\text{Na}^+$): 475.21 Found: 475.20; **HRMS** (ESI) Calculated for $\text{C}_{27}\text{H}_{33}\text{O}_6^+$: 453.2272, Found: 453.2272.



— 212.33

— 167.08

— 154.74

— 119.25

77.25
77.00
76.74
73.37

— 51.45

— 43.91

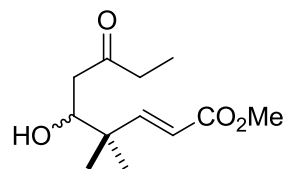
— 40.77

— 36.77

— 29.59

23.03
22.06

— 7.42



8

(125 MHz, CDCl₃)

