

Biomimetic Synthesis of the Bisindole Framework Present in Sciodole, an alkaloid from *Tricholoma Sciodes*

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**Electronic Supplementary
Information**

CONTENTS

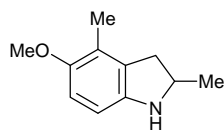
	Page
General Experimental	1
Experimental Procedures	2
^1H NMR spectrum of 10	8
^{13}C NMR spectrum of 10	9
^1H NMR spectrum of 13	10
^{13}C NMR spectrum of 13	11
^1H NMR spectrum of 14	12
^{13}C NMR spectrum of 14	13
NOESY spectrum of 14	14
^1H NMR spectrum of 16	15
^{13}C NMR spectrum of 16	16
^1H NMR spectrum of 11	17
^{13}C NMR spectrum of 11	18
NOESY spectrum of 11	19
^1H NMR spectrum of 17	20
^{13}C NMR spectrum of 17	21
NOESY spectrum of 17	22

Experimental

General

All reactions were carried out in flame or oven dried glassware under a dry nitrogen atmosphere unless otherwise stated. Tetrahydrofuran and diethyl ether were dried over sodium wire. Dichloromethane, pyridine and triethylamine were dried over calcium hydride. Ethanol and methanol were dried over magnesium ethoxide and methoxide respectively. All solvents were distilled prior to use. Flash chromatography was carried out using 0.063-0.1 mm silica gel with the desired solvent. Thin layer chromatography (TLC) was performed using UV fluorescence and/or staining with: vanillin in methanolic sulfuric acid, a solution of ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid, iodine or a solution of potassium permanganate and potassium carbonate in aqueous sodium hydroxide. High resolution mass spectra were recorded at a nominal resolution of 5000 to 10000. Infrared spectra were obtained using a Perkin-Elmer Spectrum One Fourier Transform IR spectrometer with a universal attenuated total reflectance (ATR) attachment installed. Absorption maxima are expressed as wavenumber (cm^{-1}). NMR spectra were recorded on either a Bruker DRX300 spectrometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei or using a Bruker DRX400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. All chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (^1H) and CDCl_3 (^{13}C). ^1H NMR data is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets; dt, doublet of triplets; sep, septet), coupling constant (J Hz) and assignment. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

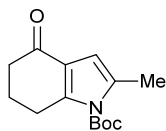
5-Methoxy-2,4-dimethylindoline (**10**)



A sealed tube was charged with a solution of 5-methoxy-2,4-dimethylindole¹ (1.000 g, 5.71 mmol) and phenyldimethylsilane (1.75 mL, 11.42 mmol) in degassed and dry dichloromethane (15 mL) was added *tris*-(pentafluorophenyl)borane (146 mg, 0.29 mmol, 5 mol%), resulting in the evolution of gas which was subsequently allowed to vent under a stream of nitrogen. Once complete, the reaction was sealed under nitrogen and heated to 50 °C. After 24 hours, the reaction was quenched by the slow addition of triethylamine (1 mL) before being diluted with dichloromethane (20 mL). The organic phase was washed with water (3 × 20 mL) and then brine (20 mL) before being dried over sodium sulfate and concentrated *in vacuo*. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:4) to afford the *title compound* **10** (855 mg, 4.82 mmol, 84%) as a dark orange oil; ν_{max} (neat)/cm⁻¹ 3361, 2958, 2831, 1606, 1477, 1437, 1376, 1288, 1236, 1096, 1003, 796, 732; δ_{H} (400 MHz, CDCl₃) 6.56 (1 H, d, *J* 8.4, ArH), 6.42 (1 H, d, *J* 8.3, ArH), 4.02-3.94 (1 H, m, CH), 3.76 (3 H, s, OMe), 3.32 (1 H, br s, NH), 3.10 (1 H, dd, *J* 15.2, 8.4, $\frac{1}{2}$ CH₂), 2.56 (1 H, dd, *J* 15.7, 8.2, $\frac{1}{2}$ CH₂), 2.11 (3 H, s, Me), 1.30 (3 H, d, *J* 6.3, Me); δ_{C} (100 MHz, CDCl₃) 151.7 (C), 144.4 (C), 130.2 (C), 123.7 (C), 109.6 (CH), 106.5 (CH), 56.5 (OMe), 55.5 (CH), 37.3 (CH₂), 22.5 (Me), 12.6 (Me); HRMS (ESI) found: 178.1225 [C₁₁H₁₅NO + H]⁺ requires: 178.1226.

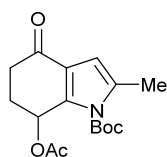
¹ J. A. Homer and J. Sperry, *ARKIVOC*, **2018**, *iv*, 6.

tert-Butyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole-1-carboxylate (**13**)



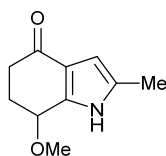
To a stirred solution of 2-methyl-4,5,6,7-tetrahydroindol-4-one (860 mg, 5.76 mmol) in dichloromethane (50 mL) was added di-*tert*-butyl dicarbonate (2.481 g, 11.37 mmol), 4-dimethylaminopyridine (378 mg, 3.09 mmol) and triethylamine (1.16 mL, 8.32 mmol). The resulting reaction mixture was stirred at room temperature for 1 hour. After this time, water (50 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 25 mL). The organic phases were combined, washed with brine (50 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting crude was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (3:7) to afford the *title compound* **13** (1.225 g, 4.91 mmol, 85%) as a yellow solid, m.p. 90 – 91 °C; ν_{max} (neat)/cm⁻¹ 2961, 2924, 2160, 1739, 1666, 1547, 1430, 1387, 1368, 1300, 1258, 1170, 1133, 1100, 993, 841, 818, 775; δ_{H} (400 MHz, CDCl₃) 6.25 (1 H, s, ArH), 3.05 (2 H, t, *J* 5.8, CH₂), 2.44 (2 H, m, CH₂), 2.37 (3 H, s, Me), 2.14-2.08 (2 H, m, CH₂), 1.61 (9 H, s, Boc, 3 × Me); δ_{C} (100 MHz, (CDCl₃) 195.0 (C), 149.7 (C), 145.6 (C), 132.8 (C), 122.6 (C), 107.3 (CH), 85.1 (C), 37.6 (CH₂), 28.2 (Boc, 3 × Me), 25.5 (CH₂), 23.8 (CH₂), 16.2 (Me); HRMS (ESI) found: 272.1261 [C₁₄H₁₉NO₃ + Na]⁺ requires: 272.1257.

tert-Butyl-7-acetoxy-2-methyl-4-oxo-4,5,6,7-tetrahydroindole-1-carboxylate (**14**)



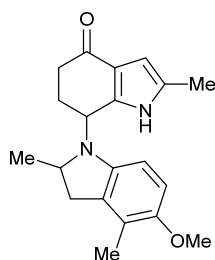
To a stirred solution of **13** (200 mg, 0.80 mmol) in toluene (20 mL) was added lead(IV) acetate (622 mg, 1.40 mmol). The resulting solution stirred at 80 °C for 16 hours. After this time the reaction was cooled to room temperature and quenched by the addition of water (20 mL). The phases were partitioned and the aqueous phase was then extracted with dichloromethane (3 × 10 mL). The organic phases were combined, washed with brine (40 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (3:7) to afford the *title compound* **14** (165 mg, 0.54 mmol, 67%) as a yellow oil; ν_{max} (neat)/cm⁻¹ 2978, 1738, 1673, 1541, 1433, 1392, 1369, 1335, 1312, 1258, 1230, 1167, 1136, 1100, 1028, 1016, 997, 954, 935, 814, 771; δ_{H} (400 MHz, CDCl₃) 6.38 (1 H, app t, *J* 3.4, CHOAc), 6.30 (1 H, s, ArH), 2.75-2.66 (1 H, m, $\frac{1}{2}$ CH₂), 2.46-2.37 (5 H, m, 2 × $\frac{1}{2}$ CH₂ + Me), 2.34-2.26 (1 H, m, $\frac{1}{2}$ CH₂), 2.06 (3 H, s, OAc), 1.59 (9 H, s, Boc, 3 × Me); δ_{C} (100 MHz, CDCl₃) 194.6 (C), 170.4 (C), 149.0 (C), 138.8 (C), 135.1 (C), 124.7 (C), 107.5 (CH), 85.9 (C), 64.4 (CH), 33.3 (CH₂), 29.1 (CH₂), 28.0 (Boc, 3 × Me), 21.2 (Me), 16.3 (Me); HRMS (ESI) found: 330.1309 [C₁₆H₂₁NO₅ + Na]⁺ requires: 330.1312.

7-Methoxy-2-methyl-4,5,6,7-tetrahydroindol-4-one (**16**)



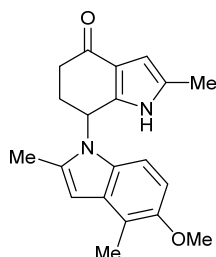
To a stirred solution of **10** (12.7 mg, 0.07 mmol) and **14** (20 mg, 0.07 mmol) in THF (1 mL) was added freshly prepared sodium methoxide (9.7 mg, 0.18 mmol). The resulting solution was allowed to stir at room temperature for 30 minutes. After this time the reaction was quenched by the slow addition of aqueous ammonium chloride (5 mL, saturated). The resulting aqueous phase was extracted with dichloromethane (3×5 mL). The organic fractions were then combined, washed with brine (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (3:7) to afford the *title compound* **16** (4 mg, 0.02 mmol, 35%) as an off-white solid, m.p. 140 – 143°C; ν_{max} (neat)/cm⁻¹ 3200, 3160, 2919, 2850, 1632, 1586, 1480, 1373, 1196, 1179, 1090, 984, 840, 812, 764, 721; δ_{H} (300 MHz, CDCl₃) 8.31 (1 H, s, NH), 6.19 (1 H, m, ArH), 4.55 (1 H, dd, J 8.6, 4.4, CHOMe), 3.49 (3 H, s, OMe), 2.71-2.62 (1 H, m, $\frac{1}{2}$ CH₂). 2.49-2.38 (2 H, m, $2 \times \frac{1}{2}$ CH₂), 2.26 (3 H, d, J 1.1, Me), 2.09-1.97 (1 H, m, $\frac{1}{2}$ CH₂); δ_{C} (75 MHz, CDCl₃) 193.5 (C), 141.9 (C), 130.1 (C), 120.7 (C), 103.3 (CH), 72.7 (CH), 56.3 (OMe), 35.9 (CH₂), 29.7 (CH₂), 13.0 (Me); HRMS (ESI) found: 202.0832 [C₁₀H₁₃NO₂ + Na]⁺ requires: 202.0838.

7-(5-Methoxy-2,4-dimethylindolin-1-yl)-2-methyl-1,5,6,7-tetrahydroindol-4-one (**11**)



To a stirred solution of **10** (173 mg, 0.98 mmol) and **14** (100 mg, 0.33 mmol) in THF (2.5 mL) was added freshly prepared sodium methoxide (8.8 mg, 0.16 mmol). The resulting solution was allowed to stir at room temperature for 30 minutes. Five additional portions of sodium methoxide (8.8 mg, 0.16 mmol) were added at 30 minute intervals. After this time the reaction was allowed to stir for additional 3 hours before being quenched by the slow addition of aqueous ammonium chloride (10 mL, saturated). The resulting aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were then combined, washed with brine (20 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (3:7) to afford indoline **11** (42 mg, 0.13 mmol, 40%) as a dark brown solid comprising an inseparable 2:1 mixture of diastereomers, m.p. 187 – 189 °C; ν_{max} (neat)/cm⁻¹ 3106, 2931, 1626, 1590, 1475, 1432, 1378, 1360, 1342, 1281, 1244, 1179, 1097, 980, 944, 843, 799, 730; Major diastereomer - δ_{H} (300 MHz, CDCl₃) 8.39 (1 H, br s, NH), 6.37 (1 H, d, *J* 8.5, ArH), 6.26 (1 H, m, ArH), 5.47 (1 H, d, *J* 8.4, ArH), 4.54 (1 H, dd, *J* 11.1, 4.8, CHN), 3.84-3.78 (1 H, m, CH), 3.69 (3 H, s, OMe), 3.22-3.11 (1 H, m, $\frac{1}{2}$ CH₂), 2.67-2.32 (4 H, m, 2 × $\frac{1}{2}$ CH₂ + CH₂), 2.22 (3 H, d, *J* 0.6, Me), 2.10-1.98 (4 H, m, Me + $\frac{1}{2}$ CH₂), 1.46 (3 H, d, *J* 6.0, Me); δ_{C} (100 MHz, (CDCl₃) 193.4 (C), 151.7 (C), 143.6 (C), 142.6 (C), 130.5 (C), 129.9 (C), 123.6 (C), 120.3 (C), 109.1 (CH), 107.6 (CH), 103.8 (CH), 58.5 (CH), 56.3 (OMe), 51.4 (CH), 37.8 (CH₂), 36.7 (CH₂), 22.5 (CH₂), 20.7 (Me), 13.0 (Me), 12.4 (Me); Minor diastereomer - δ_{H} (300 MHz, CDCl₃) 8.30 (1 H, br s, NH), 6.53 (1 H, d, *J* 8.5, ArH), 6.22 (1 H, m, ArH), 6.13 (1 H, br d, *J* 7.5, ArH), 4.80 (1 H, dd, *J* 10.8, 4.6, CHN), 3.99-3.89 (1 H, m, CH), 3.74 (3 H, s, OMe), 3.11-3.22 (1 H, m, $\frac{1}{2}$ CH₂), 2.67-2.32 (4 H, m, 2 × $\frac{1}{2}$ CH₂ + CH₂), 2.21 (3 H, d, *J* 0.6, Me), 2.10-1.98 (4 H, m, Me + $\frac{1}{2}$ CH₂), 1.11 (3 H, d, *J* 6.2, Me); δ_{C} (100 MHz, (CDCl₃) 193.2 (C), 151.4 (C), 144.0 (C), 129.8 (C), 129.4 (C), 124.1 (C), 120.7 (C), 109.3 (CH), 104.4 (CH), 103.6 (CH), 57.9 (CH), 56.4 (OMe), 51.6 (CH), 38.2 (CH₂), 36.9 (CH₂), 26.5 (CH₂), 21.6 (Me), 14.3 (Me), 12.5 (Me), 1 × C not observed; HRMS (ESI) found: 347.1724 [C₂₀H₂₄N₂O₂ + Na]⁺ requires: 347.1730.

5-Methoxy-2,2',4-trimethyl-1',5',6',7'-tetrahydro-4'H-[1,7'-biindol]-4'-one (**17**)



To a stirred solution of **11** (40 mg, 0.12 mmol) in dichloromethane (2 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (28.0 mg, 0.12 mmol). The resulting solution was warmed to 40 °C and allowed to stir for 3 hours. After this time the reaction was diluted with DCM (10 mL) and the organic phase was washed with NaHCO₃ (5 × 10 mL) until aqueous washings were colourless. The solvent was then removed *in vacuo* and the resulting crude was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:1) to afford the *title compound* **17** (22.2 mg, 0.07 mmol, 56%) as a light brown solid, m.p. 219 – 221 °C; ν_{max} (neat)/cm⁻¹ 3092, 2939, 1625, 1592, 1480, 1443, 1425, 1366, 1341, 1268, 1226, 1165, 1126, 1101, 1007, 848, 790, 778, 765, 743, 711; δ_{H} (300 MHz, CDCl₃) 8.09 (1 H, br s, NH), 6.68-6.60 (1 H, m, ArH), 6.34-6.28 (3 H, 3 × ArH), 5.67-5.60 (1 H, m, CH), 3.90-3.74 (3 H, m, OMe), 2.73-2.49 (6 H, m, Me + CH₂ + ½CH₂), 2.37 (3 H, s, Me), 2.22-2.06 (4 H, m, Me + ½CH₂); δ_{C} (100 MHz, (CDCl₃) 192.8 (C), 151.5 (C), 140.4 (C), 137.1 (C), 130.6 (C), 130.2 (C), 130.1 (C), 121.5 (C), 116.8 (C), 108.9 (CH), 108.0 (CH), 103.9 (CH), 100.2 (CH), 57.4 (OMe), 50.1 (CH), 37.8 (CH₂), 30.4 (CH₂), 13.5 (Me), 13.0 (Me), 12.0 (Me); HRMS (ESI) found: 345.1568 [C₂₀H₂₂N₂O₂ + Na]⁺ requires: 345.1573.

