Total Synthesis of Panepophenanthrin.

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Supporting information.

General experimental details:

All solvents and reagents were purified by standard techniques reported in Perrin, D.D.; Amarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 2mmHg.

All experiments were carried out under inert atmosphere unless otherwise stated.

¹H NMR spectra were recorded at 400 and 500 MHz using, Bruker DPX400, Bruker AM500 and Bruker AMX500 instruments. For ¹H spectra recorded in CDCl₃, CD₃OD, chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Proton assignments are supported by ¹H-¹H COSY where necessary. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate). Coupling constants (*J*) are reported in Hertz to the nearest 0.5Hz.

¹³C NMR spectra were recorded at 100.6 and 125.8 MHz using Bruker DPX400, Bruker AM500 and Bruker AMX500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ¹³C-¹H (HMQC and HMBC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak.

Flash column chromatography was carried out using SorbsilTM C60 (40-63 mm, 230-40 mesh) silica gel or Florisil (100-200 mesh). Thin layer chromatography was carried out on glass plates pre-coated with Merck silica gel 60 F₂₅₄ which were visualised by quenching of u.v. fluorescence or by staining with 10% w/v ammonium molybdate in 2M sulphuric acid or 1% w/v potassium permanganate in aqueous alkaline solution followed by heat, as appropriate.

Melting points were recorded using a Cambridge Instruments GallenTM III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded either as a thin film between NaCl plates or as a KBr disc (as indicated) on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Absorption maxima are reported in wavenumbers (cm⁻¹) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad.

Low resolution mass spectra were recorded on V. G. Micromass ZAB 1F and V. G. Masslab instruments as appropriate with modes of ionisation being indicated as CI,

EI, ES or APCI with only molecular ions, molecular ion fragments and major peaks being reported. High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer.

Experimental Procedures.

TES-Protected Dimer ()-8.

To a round-bottomed flask fitted with a water condenser was added bromoxone ()-6¹ (1.1 g, 3.4 mmol) dissolved in 20 mL of degassed toluene. Vinyl stannane 4² (1.60 g, 4.3 mmol,) was added and the mixture was heated to 110°C. In a separate flask, Pd₂dba₃ (320 mg, 0.34 mmol), and AsPh₃ (330 mg, 1.08 mmol) were stirred in 10 mL of degassed toluene for 20 minutes. The catalyst solution was then added to the above reaction drop-wise over 10 minutes and the reaction mixture was stirred for an additional 1 h at 110°C. The solvent was removed by rotary evaporation. The crude product was subjected to silica gel chromatography (1% methanol in Chloroform) to afford two products: the monomer ()-7 and the dimer ()-8. But upon standing overnight, ()-7 was transformed into ()-8. Finally ()-8 was obtained in 75% overall yield (827 mg) as a white powder.

Data for ()-7: ¹H NMR (400 MHz, MeOD) δ_H 0.63 (6H, q, *J* 8.0), 0.98 (9H, t, *J* 8.0), 1.30 (3H, br s), 1.31 (3H, br s), 3.49 (1H, br dd, *J* 3.7, 1.1), 3.74 (1H, m, *J* 3.7, 1.1, 2.5), 4.62 (1H, br d, *J* 5.0), 6.32 (1H, d, *J* 16.2), 6.44 (1H, d, *J* 16.2), 6.63 (1H, br dd, *J* 5.0, 2.5); ¹³C (MeOD, 100.6 MHz) δ_C 4.8, 7.0, 28.70, 28.74, 55.2, 58.8, 64.1, 71.4, 120.7, 134.3, 139.7, 143.4, 195.2.

¹ Block, O.; Klein, G.; Altenbach, H.; Brauer, D. J. *J. Org. Chem.* **2000**, 65, 716.

² Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, 55, 1857.

Data for ()-8: mp = 90 °C; $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3435, 1691, 1599; ^1H NMR (500 MHz, CDCl_3) δ_{H} 0.66 (12H, q, J 7.9), 0.99 (9H, t, J 7.9), 1.00 (9H, t, J 7.9), 1.19 (3H, s), 1.23 (3H, s), 1.37 (3H, s), 1.44 (3H, s), 2.10 (1H, d, J 11.8), 2.53 (1H, br d, J 11.8), 3.29 (1H, br s), 3.41-3.46 (3H, m), 3.47 (1H, d, J 4.5), 3.73 (1H, br t, J 4.5), 4.52 (1H, d, J 3.5), 4.58 (1H, d, J 3.5), 5.68 (1H, d, J 16.5), 6.13 (1H, d, J 16.5), 6.81 (1H, dd, J 5.6, 2.5); ^{13}C (CDCl_3 , 125.7 MHz) δ_{C} 4.9, 5.1, 6.8, 6.9, 25.5, 29.6, 30.2, 32.2, 48.3, 49.6, 54.5, 55.3, 55.4, 56.0, 56.2, 59.6, 65.7, 68.7, 71.3, 78.6, 101.4, 129.6, 138.5, 138.7, 141.9, 194.9; m/z (ES-) 647 (100%, M-1); HRMS (ES-) Calculated for $\text{C}_{34}\text{H}_{55}\text{O}_8\text{Si}_2$ ($[\text{M}-\text{H}]^-$): 647.3457. Found: 647.3436.

Panepophenanthrin ()-1.³

Panepophenanthrin (±)-1

To a 25 mL round-bottomed flask containing methanol (5mL), was added ()-8 (199mg, 0.31 mmol), the solution was allowed to stir for 5 minutes. NH_4F (45.5mg, 1.23mmol) was then added and the mixture allowed to stir until the reaction had completed (approx 2h). The solvent was removed under reduced pressure and the crude mixture subjected to silica gel chromatography (3% methanol in chloroform) to give the title compound as a white solid (110mg, 85%). R_f = 0.3 (9:1 CHCl_3 :MeOH); mp = 81 °C; $\nu_{\max}/\text{cm}^{-1}$ (KBr) 3435, 1672, 1600; ^1H NMR (500 MHz, MeOD) δ_{H} 1.17 (3H, s), 1.20 (3H, s), 1.35 (3H, s), 1.45 (3H, s), 2.04 (1H, br d, J 10.0), 2.34 (1H, m, J 10.0, 3.0, 2.0), 3.32 (1H, d, J 4.1), 3.35 (1H, dd, J 5.1, 2.0), 3.42 (1H, d, J 4.1), 3.50 (1H, br t, J 3.5), 3.83 (1H, br t, J 3.5), 4.35 (1H, br t, J 2.2), 4.55 (1H, br t, J 2.2), 5.68 (1H, d, J 16.2), 5.98 (1H, d, J 16.2), 6.82 (1H, dd, J 5.1, 3.0); ^{13}C (MeOD, 125.7

³ Sekizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod.* **2002**, 65, 1491.

MHz) δ_C 26.2, 29.5, 30.3, 32.3, 50.0, 51.2, 55.1, 55.6, 57.1, 57.2, 57.3, 60.7, 66.3, 69.0, 71.8, 79.2, 102.6, 129.2, 138.8, 139.9, 143.1, 196.2; HRMS (ES-) Calculated for $C_{22}H_{27}O_8$ ($[M-H]^-$): 419.1704. Found: 419.1706.

Comparison of the 1H NMR of Natural and Synthetic Panepophenanthrin 1.

Comparison of the ^{13}C NMR of Natural and Synthetic Panepophenanthrin 1.