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Total Synthesis of the Ubiquitin-Activating Enzyme Inhibitor (+)-Panepophenanthrin

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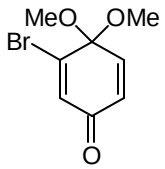
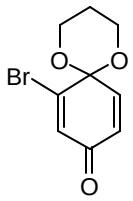
General Information: ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a 75.0 MHz spectrometer (with complete proton decoupling) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, d 7.24; ^{13}C, d 77.23). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet,) and coupling constants. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Low and high-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. HRTOFMS spectra were obtained with Micromass LCT spectrometer by Ms. Qing Liao (Department of Chemistry and Chemical Biology, Harvard University). X-ray crystal structures were obtained by Dr. Emil Lobkovsky (Department of Chemistry and Chemical Biology, Cornell University). Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are recorded as $[\alpha]_D$ (concentration in grams/100 mL solvent). Chiral HPLC analysis was performed on an Agilent 1100 series (CHIRALCEL OD, Column No. OD00CE-AI015). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbent Incorporated). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. All reagents were used as supplied by Sigma-Aldrich, Fluka, and Strem Chemicals. Methylene chloride, toluene, hexane, and benzene and 1,2-dichloroethane were distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Ph_3COOH[S1] was prepared from trityl alcohol according to literature procedures. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

[S1] D. E. Bissing, C. A. Matuszac, W. E. McEwen, *J. Am. Chem. Soc.* **1964**, *86*, 3824.



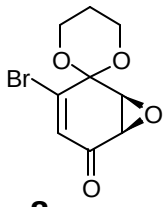
10

Dimethoxy ketal 10. Compound **9** (10.10 g, 50 mmol) was dissolved in 100 mL MeOH and cooled to 0°C, $PhI(OAc)_2$ (17.71 g, 55 mmol) was added over 10 min and the reaction was stirred at rt for a further 30 min. The reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification on silica gel (25 % EtOAc in hexane) provided 10.48 g (45 mmol, 90 %) of dimethoxy ketal **10** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) 6.86 (d, 1H, J = 1.6 Hz), 6.84 (d, 1H, J = 10.8 Hz), 6.46 (dd, 1H, J = 2.0, 10.0 Hz), 3.28 (s, 6H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 182.8, 146.7, 144.0, 135.9, 131.9, 94.9, 51.4; IR (thin film) νmax 3057, 2938, 2834, 1674, 1603, 1457, 1278, 1091, 954 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_8H_{10}BrO_3$: 232.9813, found: 232.9828 .



11

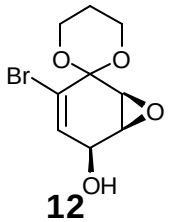
Cyclic ketal 11. A mixture of **10** (4.34 g, 18.7 mmol), and 1,3-propanediol (5.69 g, 74.8 mmol) were placed in a round-bottomed flask and dissolved in 150 mL anhydrous DME. To this solution was added $BF_3.Et_2O$ (2.4 mL, 19.6 mmol) dropwise at rt over 0.5 h, and the reaction was stirred for a further 2 h at rt. The reaction was quenched by addition of 100 mL Et_2O, and extracted with an additional 100 mL Et_2O. The combined organic layers were washed with sat. $NaHCO_3$, sat. brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by recrystallization (hexanes : EtOAc = 10:1) provided 3.42 g (14.0 mmol, 75 %) of cyclic ketal **11** as a yellow solid. mp 99-100°C; ^1H NMR (400 MHz, $CDCl_3$) 7.66 (d, 1H, J = 10.4 Hz), 6.50 (d, 1H, J = 1.6 Hz), 6.25 (q, 1H, J = 10.4 Hz), 4.20 (m, 2H), 4.09 (m, 2H), 2.33 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 182.6, 147.1, 138.4, 132.8, 127.0, 89.5, 61.5, 24.6; IR (thin film) νmax 3046, 2980, 2880, 1675, 1608, 1284, 1115, 1009, 952 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_9H_9BrO_3$: 243.9735, found: 243.9747.



8

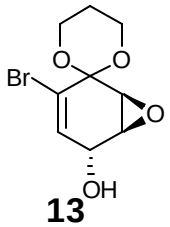
Monoepoxide 8. Ph_3COOH (5.50 g, 19.9 mmol) was dissolved in 50 mL toluene, and (16.0 mL, 16.0 mmol) of 1.0 M NaHMDS in THF was added at rt. After 20 min, (1.87 g, 7.95 mmol) *L*-DIPT in 10 mL toluene was added, the reaction mixture was stirred for 30 min at rt, and then cooled to –78 °C, cyclic ketal **11** (1.94 g, 7.95 mmol) in 20 mL toluene was added dropwise and the reaction mixture was stirred at –55 °C for 48 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20 % EtOAc in hexane) provided 1.73 g (6.65 mmol, 85 %) of monoepoxide **8** as a white solid, mp 145-146°C; ^1H NMR (400 MHz, $CDCl_3$) 6.43 (d, 1H, J = 2.0 Hz), 4.32 (m, 2H), 4.27 (d, 1H, J = 3.6 Hz), 4.20 (m, 2H), 3.54 (q, 1H, J = 8.0 Hz), 2.28 (m, 1H), 1.68 (m, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 189.1, 146.2, 130.0, 92.2, 61.4, 61.2, 52.8, 51.5, 24.1; IR (thin film) νmax 3058, 2962, 2873, 1690, 1623, 1290, 1246, 1138, 1105 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_9H_{10}BrO_4$: 260.9762 ,

found: 260.9726; $[\alpha]_D^{23}$ = +210° (c = 0.65 $CHCl_3$). The ee was determined to be 92-95% using a Regis chiral HPLC column (R,R) whelk-O1 (25 cm × 4.0 mm (20% isopropanol in hexane, retention time 10.28 min (major enantiomer) and 12.51 min (minor enantiomer)).



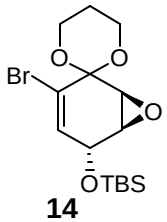
12

Syn epoxy alcohol 12. Enone **8** (1.48 g, 5.69 mmol) was dissolved in 50 mL anhydrous THF and the reaction mixture was cooled to –78 °C. 1.0 M Super-Hydride in THF (6.5 mL, 6.5 mmol) was added dropwise at –78 °C and the reaction was stirred for 1h before being quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (50 % EtOAc in hexane) provided 1.47 g (5.61 mmol, 98 %) of **12** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 6.08 (q, 1H, *J* = 2.0, 2.8 Hz), 4.43 (dt, 1H, *J* = 3.2, 11.6 Hz), 4.27 (m, 2H), 4.19 (m, 2H), 4.13 (m, 2H), 3.63 (m, 1H), 2.24 (m, 1H), 2.07 (d, 1H, *J* =12 Hz), 1.59 (dt, 1H, *J* = 3.2, 16.0 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 131.7, 124.4, 65.9, 61.4, 61.1, 54.3, 50.9, 24.2; IR (thin film) νmax 3412, 2973, 2931, 2880, 1654, 1428, 1142, 1042 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_9H_{12}BrO_4$: 262.9919, found: 262.9934.; $[\alpha]_D^{23}$ = +43° (c = 0.9, $CHCl_3$).



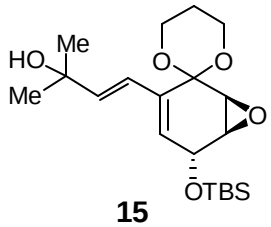
13

Anti epoxy alcohol 13. Ph_3P (900 mg, 3.44 mmol) was dissolved in 10 mL anhydrous THF, and DIAD (678 uL, 3.44 mmol) was added dropwise at rt. The reaction was stirred at rt for 30 min at which time a white precipitate had formed. The mixture was cooled to –50 °C, and alcohol **12** (694 mg, 2.65 mmol) in 5 mL THF was added. After stirring at –50 °C for 20 min, 4-nitrobenzoic acid (575 mg, 3.44 mmol) in 5 ml THF was added. The mixture was stirred at –50 °C for 30 min, slowly warmed to rt, and then stirred for a further 1 h at rt. The reaction mixture was concentrated *in vacuo*, and purified on silica gel (20 % EtOAc in hexane) to afford the 4-nitrobenzoate intermediate. The crude ester was dissolved in 25 mL MeOH, and 2.8 mL (2.8 mmol) of 1.0 M NaOMe in MeOH was added at rt. The reaction was stirred at rt for 30 m, then quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (50 % EtOAc in hexane) provided 555 mg (2.12 mmol, 80 %) of **13** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 6.26 (q, 1H, *J* = 2.0, 5.2 Hz), 4.39 (q, 1H, *J* = 4.8, 9.6 Hz), 4.24 (m, 3H), 4.11 (m, 2H), 3.98 (dd, 1H, *J* = 0.8, 3.6 Hz), 3.48 (m, 1H), 2.35 (d, 1H, *J* = 10.0 Hz), 2.22 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 131.1, 126.3, 127.6, 92.2, 63.9, 61.8, 60.4, 54.5, 24.0; IR (thin film) νmax 3412, 2973, 2931, 2880, 1654, 1428, 1142, 1042 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_9H_{12}BrO_4$: 262.9841, found: 262.9884.; $[\alpha]_D^{23}$ = +30° (c = 1.0, $CHCl_3$).



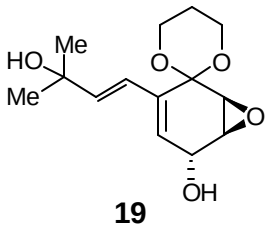
14

Silyl ether 14. TBSCl (496 mg, 3.28 mmol), imidazole (220 mg, 3.28 mmol), and **13** (570 mg, 2.19 mmol) were dissolved in 10 mL anhydrous DMF, and stirred at rt for 10h. The reaction was quenched by addition of pH 7 buffer and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (10 % EtOAc in hexane) provided 728 mg (1.94 mmol, 90 %) of **14** as a white solid. mp 94-95°C ^{1}H NMR (400 MHz, $CDCl_3$) 6.06 (q, 1H, *J* = 4.4 Hz), 4.32 (m, 2H), 4.27 (d, 1H, *J* = 3.6 Hz), 4.20 (m, 2H), 3.54 (q, 1H, *J* = 8.0 Hz), 2.28 (m, 1H), 1.68 (m, 1H); 0.89 (s, 9H), 0.11 (d, 6H, *J* = 4.0 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 131.4, 125.1, 91.8, 64.8, 61.7, 60.5, 56.0, 49.9, 25.7, 24.3, 18.1, -4.6, -4.7; IR (thin film) νmax 2929, 2857, 1471, 1258, 1144, 1117 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{15}H_{26}BrO_4Si$: 377.0783 , found: 377.0767; $[\alpha]_D^{23}$ = -11° (c = 0.9 $CHCl_3$).



15

Diene 15. Vinyl bromide **14** (400 mg, 1.06 mmol), $Pd(OAc)_2$ (23 mg, 0.10 mmol), and Ag_2CO_3 (585 mg, 2.12 mmol) were placed in a 10 mL flame-dried Schlenk tube. To this mixture was added 2 mL anhydrous DMF, followed by 2-methyl-3-buten-2-ol (660 µL, 6.36 mmol). The reaction mixture was stirred at 90°C for 16 h, then filtered through a small Isolute HM-N Column,[S2] and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (50 % EtOAc in hexane) provided 322 mg (0.85 mmol, 80%) of **15** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) 6.32 (d, 1H, *J* = 16 Hz), 6.17 (d, 1H, *J* = 16 Hz), 5.71 (m, 1H), 4.48 (d, 1H, *J* = 4.0 Hz), 4.29 (m, 2H), 4.02 (m, 3H), 3.35 (m, 1H), 2.20 (m, 1H), 1.52 (s, 1H), 1.51 (d, 1H, *J* = 16 Hz), 1.34 (s, 6H), 0.89 (s, 9H), 0.11 (d, 6H, *J* = 4.0 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ139.5, 134.1, 124.2, 122.5, 93.1, 71.0, 63.4, 61.4, 60.2, 56.3, 48.8, 29.6, 29.5, 25.7, 24.7, 18.1, -4.6, -4.7; IR (thin film) νmax 3437, 2958, 2930, 1669, 1470, 1387, 1254, 1131, 1073 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{20}H_{35}O_5Si$: 382.2254, found: 382.2212; $[\alpha]_D^{23}$ = -10° (c = 2.8, $CHCl_3$).

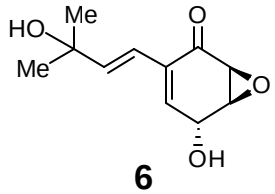


19

***Dienol 19*. 15 (**170 mg, 0.44 mmol) was dissolved in 5 mL THF and 0.530 mL (0.53 mmol) TBAF (1.0 M in THF) was added at 0°C. After stirring for 3 h at rt, the reaction mixture was concentrated *in vacuo*. Purification on silica gel (25 % EtOAc in CH_2Cl_2) provided 118 mg (0.44 mmol, 98 %) of **19** as a colorless oil . ^{1}H NMR (400 MHz, $CDCl_3$) 6.32 (d, 1H, *J* = 16 Hz), 6.17 (d, 1H, *J* = 16 Hz), 5.91 (dd, 1H, *J* = 1.2, 4.8 Hz), 4.42 (q, 1H, *J* = 4.8, 9.6 Hz), 4.32 (m, 2H), 4.03 (m, 3H), 3.47 (m, 1H), 2.79 (d, 1H, , *J* = 10.0 Hz), 2.20 (m, 1H), 1.54 (d, 1H, *J* = 13.6 Hz), 1.32 (s, 3H), 1.29 (s, 3H); ^{13}C

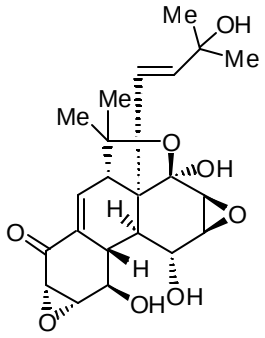
[S2] ISOLUTE HM-N, PART No. 800-0100-CM. Argonaut Technologies (www.argotech.com).

NMR (75.0 MHz, $CDCl_3$) δ 140.1, 136.0, 123.1, 122.0, 93.6, 71.0, 62.8, 61.4, 60.1, 54.5, 48.2, 29.5, 29.4, 24.7; IR (thin film) νmax 3402, 2969, 2928, 1430, 1261, 1128, 1042 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{14}H_{21}O_5$: 269.1389, found: 269.1367; $[\alpha]_D^{23}$ = +29° (c = 0.3, $CHCl_3$).



6

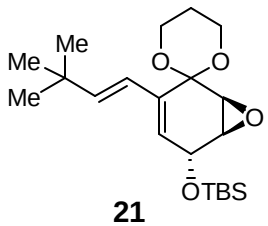
Dienol Monomer 6. Dienol **19** (24 mg, 0.09 mmol) was dissolved in 0.8 mL CH_3CN-CH_2Cl_2 (1:1) and 0.2 mL HCl (1.0 M) was added at 0 °C. After stirring for 2 h at rt, the reaction mixture was treated with sat. aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with pH 7 buffer, brine, and dried over Na_2SO_4 and $KHCO_3$ for 2 h. The solution was filtered, and concentrated in *vacuo*. The crude product (17.8 mg, 0.086 mmol, 95%) was used directly without purification in the next step. ^1H NMR (400 MHz, $CDCl_3$) 6.62 (dd, 1H, *J* = 2.4, 6.0 Hz), 6.42 (d, 1H, *J* = 16.0 Hz), 6.30 (d, 1H, *J* = 16.0 Hz), 4.61 (d, 1H, *J* = 5.2 Hz), 3.73 (m, 1H), 3.48 (dd, 1H, *J* = 1.2, 3.6 Hz), 1.30 (s, 3H), 1.28 (s, 3H); CIHRMS $[M]^+$ $C_{11}H_{14}O_4$: 210.0892, found: 210.0919.



1

Panepophenanthrin 1. Crude monomer **6** (17.8 mg, 0.086 mmol) was concentrated and placed under argon at rt for 24 h. Purification on silica gel ($CHCl_3$: MeOH= 20 : 1) provided 14 mg (0.034 mmol, 80%) of **1** as a white solid. mp 144.5-146 °C (Natural 144-146 °C). ^1H NMR (400 MHz, CD_3OD) 6.80 (dd, 1H, *J* = 3.2, 5.2 Hz), 5.99 (d, 1H, *J* = 16.0 Hz), 5.66 (d, 1H, *J* = 16.0 Hz), 4.54 (s, 1H), 4.34 (s, 1H), 3.82 (br t, 1H, *J* = 3.6, 3.6 Hz), 3.48 (br t, 1H, *J* = 3.2, 3.2 Hz), 3.41 (d, 1H, *J* = 4.0 Hz), 3.34 (dd, 1H, *J* = 1.6, 4.8 Hz), 3.31 (d, 1H, *J* = 2.4 Hz), 2.31 (d, 1H, *J* = 10.0 Hz), 2.01 (d, 1H, *J* = 7.6 Hz), 1.44 (s, 3H), 1.33 (s, 3H), 1.20(s, 3H), 1.17(s, 3H); ^{13}C NMR (75.0 MHz, CD_3OD) δ 196.5, 143.1, 140.1, 138.9, 129.4, 102.8, 79.2, 71.8, 69.0, 66.2, 60.6, 57.4, 57.2, 57.1, 55.6, 55.1, 51.2, 50.0, 32.2, 30.2, 29.4, 26.1; IR (thin film) νmax 3392, 2973, 2930, 2537, 1684, 1599, 1368, 1146, 1016 cm^{-1}; HRTOFMS $[M+Na]^+$ calculated for $C_{22}H_{28}NaO_8$: 443.1682, found: 443.1678; $[\alpha]_D^{23}$ = + 147.5° (c = 1.0, MeOH). (Natural: $[\alpha]_D^{23}$ = + 149.8° (c = 1.0, MeOH)).

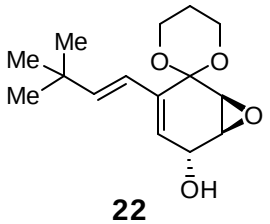
Synthetic and natural panepophenanthrin gave the same R_f value in the following three solvent systems: R_f = 0.45 ($CHCl_3$: MeOH = 5:1), R_f = 0.55 (CH_2Cl_2 : MeOH = 5:1), R_f = 0.42 (EtOAc : MeOH = 10:1).



21

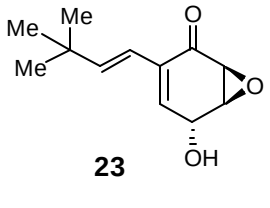
Epoxy diene 21. **14** (86 mg, 0.23 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), and Ag_2CO_3 (126 mg, 0.46 mmol) were placed in a 10 mL

flame-dried glass reactor.[S3] To this mixture was added 2 mL dry DMF, followed by 3,3-dimethylbutene (240 uL, 1.84 mmol), and the vial was sealed with a crimped cap. The reaction mixture was stirred at 90 °C for 24 h, then filtered through a small Isolute HM-N Column[S2], and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (25 % EtOAc in hexane) provided 63 mg (0.16 mmol, 70%) of **21** as a white solid. mp 102-103°C; ^{1}H NMR (400 MHz, $CDCl_3$) 6.04 (d, 1H, *J* = 16 Hz), 6.01 (d, 1H, *J* = 16 Hz), 5.65 (q, 1H, *J* = 2.4, 4.4 Hz), 4.48 (d, 1H, *J* =4.0 Hz), 4.29 (m, 2H), 4.01 (m, 3H), 3.35 (m, 1H), 2.20 (m, 1H), 1.51 (d, 1H, *J* = 16 Hz), 1.03 (s, 9H), 0.89(s, 9H), 0.11(d, 6H, *J* = 4.0 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 143.4, 134.9, 122.6, 120.5, 93.2, 76.6, 63.6, 61.3, 60.2, 56.4, 48.9, 33.3, 29.4, 25.8, 24.8, 18.1, -4.5, -4.6; IR (thin film) νmax 2955, 2860, 1472, 1387, 1258, 1131, 1073 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{21}H_{37}O_4Si$: 381.2461, found: 381.2448; $[\alpha]_D^{23}$ = -1.0° (c = 0.9, $CHCl_3$).



22

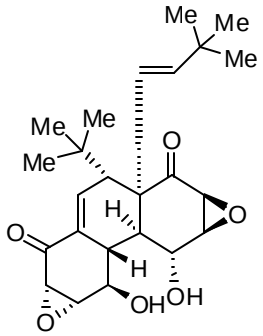
Epoxy diene 22. Diene **21** (50 mg, 0.13 mmol) was dissolved in 1.5 mL THF and 0.160 mL (0.16 mmol) TBAF (1.0 M in THF) was added at 0°C. After stirring for 3 h at rt, the reaction mixture was concentrated *in vacuo*. Purification on silica gel (25 % EtOAc in hexanes) provided 33 mg (0.12 mmol, 96 %) of **22** as a white solid. mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 6.06 (s, 2H), 5.87 (dd, 1H, *J* = 4.8, 6.8 Hz), 4.44 (q, 1H, *J* =8.8, 13.6 Hz), 4.29 (m, 2H), 4.02 (m, 3H), 3.48 (dd, 1H, *J* = 3.6, 5.2 Hz), 2.18 (m, 1H), 1.70 (d, 1H, *J* = 5.6 Hz), 1.56 (d, 1H, *J* = 14.6 Hz), 1.03 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 144.3, 137.4, 121.4, 120.9, 93.7, 76.6, 63.0, 61.4, 60.1, 54.4, 48.4, 33.4, 29.4, 24.8; IR (thin film) νmax 3407, 2959, 2868, 1462, 1386, 1265, 1131, 1043 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_{15}H_{22}O_4$: 266.1518, found: 266.1507; $[\alpha]_D^{23}$ = +10.0° (c = 0.4, $CHCl_3$).



23

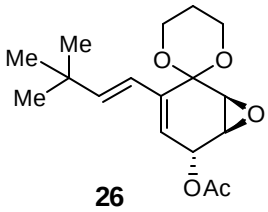
Monomer 23. **22** (24 mg, 0.09 mmol) was dissolved in 0.8 mL CH_3CN-CH_2Cl_2 (1:1) and 0.2 mL HCl (1.0 M) was added at 0 °C. After stirring for 3 h at rt, the reaction mixture was treated with sat. aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with pH 7 buffer, and brine, and dried over Na_2SO_4 and $KHCO_3$ for 2 h. Then the solution was filtered, and concentrated in *vacuo*. The crude product (18.0 mg, 0.084 mmol, 95%) was used directly without purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) 6.53 (dd, 1H, *J* = 0.8, 2.8 Hz), 6.23 (d, 1H, *J* = 16.0 Hz), 6.02 (d, 1H, *J* = 16.0 Hz), 4.71 (q, 1H, *J* =5.6, 8.8 Hz), 3.77 (q, 1H, *J* =1.2, 2.4 Hz), 3.51 (m, 1H), 2.18 (d, 1H, *J* = 13.2 Hz), 1.01 (s, 9H); CIHRMS $[M]^+$ calculated for $C_{12}H_{16}O_3$: 208.1099, found: 208.1102.

[S3] DISCOVER MICROWAVE VIAL, Cat. No. 908035. (CEM Corporation, www.cem.com)



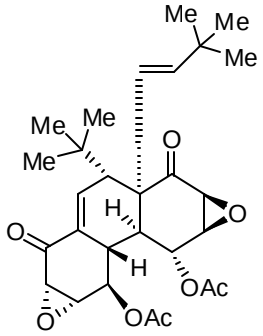
24

Dimer 24. Crude monomer **23** (18.0 mg, 0.084 mmol) was concentrated and stayed under argon at rt for 24 h. Purification on silica gel (CH_2Cl_2 : EtOAc = 2:1) provided 14 mg (0.034 mmol, 80%) of **24** as a white solid. mp 125-127 ^oC. ^1H NMR (400 MHz, $CDCl_3$) 6.82 (dd, 1H, *J* = 2.4, 4.8 Hz), 5.55 (d, 1H, *J* = 16.8 Hz), 5.28 (d, 1H, *J* = 17.2 Hz), 4.65 (s, 1H), 4.13 (d, 1H, *J* = 8.8 Hz), 3.50 (d, 1H, *J* = 3.2 Hz), 3.36 (d, 1H, *J* = 3.2 Hz), 3.29 (d, 1H, *J* = 3.2 Hz), 3.10 (dd, 1H, *J* = 2.8, 4.8 Hz), 2.73 (m, 1H), 2.56 (br t, 1H, *J* = 4.8, 10.0 Hz), 2.45 (s, 1H), 2.24 (s, 1H), 0.99 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 203.4, 194.7, 143.9, 140.8, 131.8, 125.7, 71.2, 67.7, 61.7, 57.9, 55.0, 54.1, 53.3, 50.2, 48.6, 44.8, 35.5, 33.7, 30.8, 28.7; IR (thin film) νmax 3453, 2958, 1699, 1639, 1466, 1365, 1265, 1052 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{25}H_{32}O_6$: 417.2277, found: 417.2270; $[\alpha]_D^{23}$ = +88.0^o (c = 0.2, $CHCl_3$).



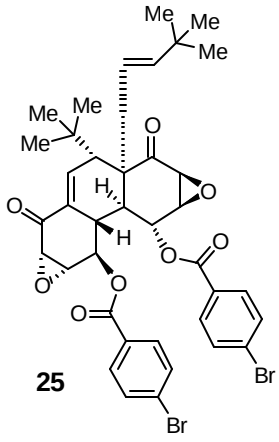
26

Acetate 26. **22** (24 mg, 0.09 mmol), and DMAP (2.0 mg, 0.02 mmol) were dissolved in anhydrous CH_2Cl_2. 1,3-diisopropyl carbodiimide (14.0 μL, 0.10 mmol) was added to this reaction mixture, and followed by acetic acid (6.0 μL, 0.10 mmol). The reaction was stirred at rt for 30 m. Purification on silica gel (hexane : EtOAc = 5:1) provided 25 mg (0.082 mmol, 91%) of **26** as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) 6.06 (s, 2H), 5.80 (dd, 1H, *J* = 2.0, 4.8 Hz), 5.70 (d, 1H, *J* =4.4 Hz), 4.29 (m, 2H), 4.04 (m, 3H), 3.42 (br t, 1H, *J* = 2.0, 3.6 Hz), 2.20 (m, 1H), 2.08 (s, 3H), 1.55 (d, 1H, *J* = 12.0 Hz), 1.02 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.5, 144.6, 138.6, 119.8, 117.1, 93.1, 64.5, 61.4, 60.1, 52.8, 48.2, 33.4, 29.3, 24.7, 20.9; IR (thin film) νmax 2958, 2868, 1739, 1457, 1368, 1265, 1230, 1132, 1045 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_{17}H_{24}O_5$: 308.1624, found: 308.1655; $[\alpha]_D^{23}$ = -9.5^o (c = 1.0, $CHCl_3$).



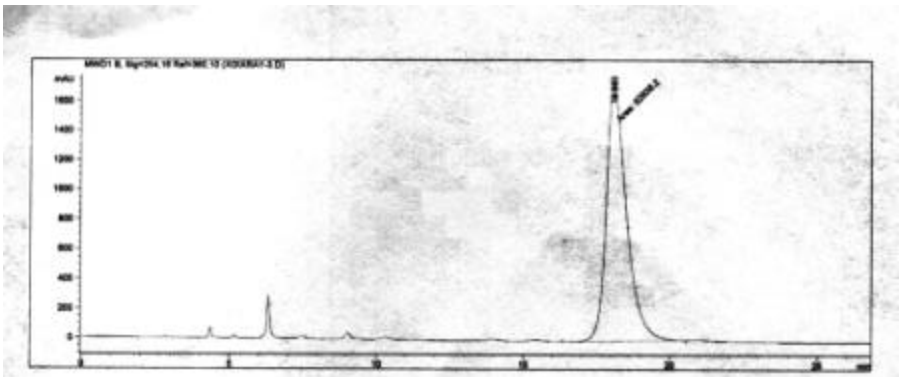
28

***Bis-acetate dimer 28*.** Prepared from **26** in 90% yield according to the procedures reported for monomer **23** and dimer **24**. ^1H NMR (400 MHz, $CDCl_3$) 6.79 (dd, 1H, *J* = 2.0, 5.6 Hz), 5.85 (s, 1H), 5.73 (d, 1H, *J* = 16.8 Hz), 5.38 (d, 1H, *J* = 6.8 Hz), 5.12 (d, 1H, *J* = 16.8 Hz), 3.55 (d, 1H, *J* = 2.4 Hz), 3.51 (s, 1H), 3.44 (d, 1H, *J* = 3.6 Hz), 3.34 (d, 1H, *J* = 3.6 Hz), 2.95 (m, 2H), 2.58 (d, 1H, *J* = 9.2 Hz), 2.17 (s, 3H), 2.08 (s, 3H), 0.97(s, 9H), 0.95(s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.9, 142.7, 142.5, 126.0, 77.4, 71.0, 68.0, 58.5, 55.0, 54.0, 53.2, 50.1, 47.3, 41.5, 35.0, 33.5, 31.0, 28.8, 21.0, 20.9; IR (thin film) νmax 2959, 2869, 1742, 1707, 1652, 1464, 1368, 1235, 1036 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_{28}H_{36}O_8$: 500.2410, found: 500.2398; $[\alpha]_D^{23}$ = -11.0^o (c = 0.1, $CHCl_3$).

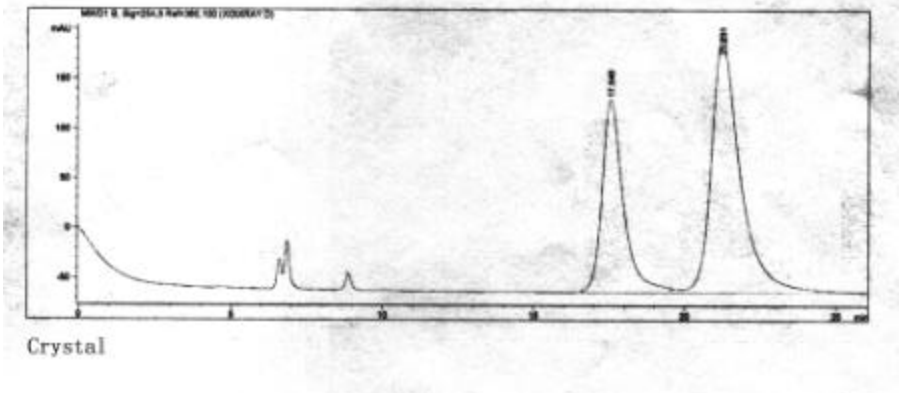


25

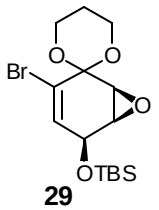
4-Bromobenzoate dimer 25. Dimer **24** (23 mg, 0.055 mmol), 4-bromobenzoic acid (25 mg, 0.12 mmol), and DMAP (2.0 mg, 0.011 mmol) were dissolved in anhydrous CH_2Cl_2. DIC (20 μL, 0.12 mmol) was added to this mixture and the reaction was stirred at rt for 2 h. Purification on silica gel (hexane : EtOAc = 10:1) provided 38 mg (0.049 mmol, 90%) of **25** as a white solid. mp 123-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.84 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 2H, *J* = 4.4 Hz), 7.53 (q, 4H, *J* = 8.4, 16.0 Hz), 6.82 (dd, 1H, *J* = 2.8, 5.6 Hz), 6.12 (s, 1H), 6.02 (s, 1H), 5.97 (d, 1H, *J* = 16.8 Hz), 5.27 (d, 1H, *J* = 16.8 Hz), 3.93 (s, 1H), 3.88 (s, 1H), 3.72 (d, 1H, *J* = 4.0 Hz), 3.54 (d, 1H, *J* = 3.6 Hz), 3.08 (d, 1H, *J* = 9.6 Hz), 2.97 (d, 1H, *J* = 5.2 Hz), 2.76 (d, 1H, *J* = 9.6 Hz), 0.98(s, 9H), 0.80(s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 194.3, 165.3, 164.8, 143.3, 142.9, 134.4, 132.0, 131.9, 131.5, 131.3, 129.1, 129.0, 127.9, 127.8, 125.7, 77.4, 69.5, 68.7, 57.4, 56.9, 56.2, 55.8, 53.7, 51.7, 42.2, 34.2, 33.3, 30.5, 29.1, 28.9; IR (thin film) νmax 2959, 2855, 1717, 1628, 1590, 1484, 1365, 1262, 1098, 1012 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{38}H_{39}Br_2O_8$: 781.0933, found: 781.0940 ; $[\alpha]_D^{23}$ = +76.0° (c = 0.2, $CHCl_3$). The ee of crystal was determined to be 27% and the ee of the condensed solution was determined to be 100% using a Regis chiral HPLC column (R,R) whelk-O1 (25 cm × 4.0 mm (20% isopropanol in hexane, retention time 18.08 min (major enantiomer) and 21.22 min (minor enantiomer)).



Condensed Solution

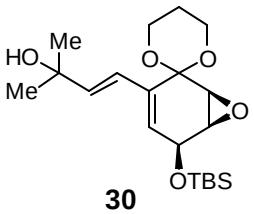


Crystal



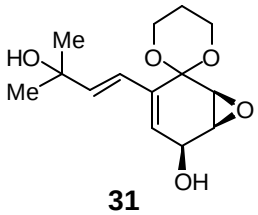
29

Prepared from **12** in 90% yield according to the procedures reported for **14**. mp 77-78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 5.93 (q, 1H, *J* = 2.4 Hz), 4.58 (q, 1H, *J* = 2.4 Hz), 4.27 (m, 2H), 4.18 (m, 2H), 3.98 (d, 1H, *J* = 4.0 Hz), 3.44 (m, 1H), 2.22 (m, 1H), 1.56 (m, 1H); 0.89 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 132.5, 122.7, 92.3, 67.0, 61.3, 60.8, 53.9, 49.1, 25.5 24.1, 17.9, -4.8, -4.9; IR (thin film) νmax 2954, 2857, 1471, 1383, 1140, 1097 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{15}H_{26}BrO_4Si$: 377.0783 , found: 377.0825; $[\alpha]_D^{23}$ = +32^o (c = 2.0 $CHCl_3$).



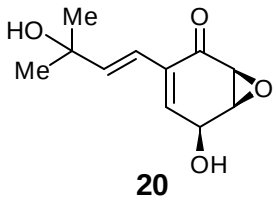
30

Prepared from **29** in 80% yield according to the procedures reported for **15**.^{1}H NMR (400 MHz, $CDCl_3$) 6.29 (d, 1H, *J* = 16 Hz), 6.13 (d, 1H, *J* = 16 Hz), 5.57 (d, 1H, *J* = 2.0 Hz), 4.65 (s, 1H), 4.28 (m, 2H), 4.02 (m, 3H), 3.43 (m, 1H), 2.18 (m, 1H), 1.53 (d, 1H, *J* = 16 Hz), 1.33 (s, 6H), 0.91(s, 9H), 0.12(s, 6H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 139.1, 134.5, 125.6, 122.1, 93.8, 70.9, 66.1, 61.1, 60.5, 54.3, 48.7, 29.5, 29.4, 25.7, 24.7, 18.1, -4.6, -4.7; IR (thin film) νmax 3446, 2957, 2857, 1472, 1387, 1254, 1131, 1073 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{20}H_{35}O_5Si$: 383.2254, found: 383.2242; $[\alpha]_D^{23}$ = +14^o (c = 0.6, $CHCl_3$)..



31

Prepared from **30** in 95% yield according to the procedures reported for **19**. ^{1}H NMR (400 MHz, $CDCl_3$) 6.29 (d, 1H, *J* = 16 Hz), 6.16 (d, 1H, *J* = 16 Hz), 5.71 (d, 1H, *J* = 2.0 Hz), 4.49 (s, 1H), 4.31 (m, 2H), 4.16 (dd, 1H, *J* = 1.6, 4.0 Hz) 4.06 (m, 2H), 3.60 (m, 1H), 2.22 (m, 1H), 1.53 (d, 1H, *J* = 13.6 Hz), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 139.9, 135.3, 124.3, 121.8, 93.2, 71.0, 64.7, 61.1, 60.7, 54.6, 50.2, 29.5, 29.4, 24.6; IR (thin film) νmax 3398, 2971, 2876, 1372, 1271, 1128, 1000 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_{14}H_{20}O_5$: 268.1311, found: 268.1294; $[\alpha]_D^{23}$ = -6.0^o (c = 1.25, $CHCl_3$).



20

Prepared from **31** in 91% yield according to the procedures reported for **6**. ^{1}H NMR (400 MHz, $CDCl_3$) 6.40 (d, 1H, *J* = 16.0 Hz), 6.38 (d, 1H, *J* = 2.4 Hz), 6.20 (d, 1H, *J* = 16.0 Hz), 4.70 (dd, 1H, *J* = 2.4, 8.0 Hz), 3.82 (m, 1H), 3.52 (d, 1H, *J* = 4.0 Hz), 2.66 (d, 1H, *J* = 14.4 Hz), 1.33 (s, 3H), 1.32 (s, 3H); IR (thin film) νmax 3369, 2973, 2928, 1682, 1376, 1232, 1147, 1041 cm^{-1}; CIHRMS $[M+H]^+$ $C_{11}H_{15}O_4$: 211.0971, found: 211.0975. $[\alpha]_D^{23}$ = -106^o (c = 0.6, $CHCl_3$).

NMR data (in CD_3OD) comparison of natural and synthetic panepophenanthrin

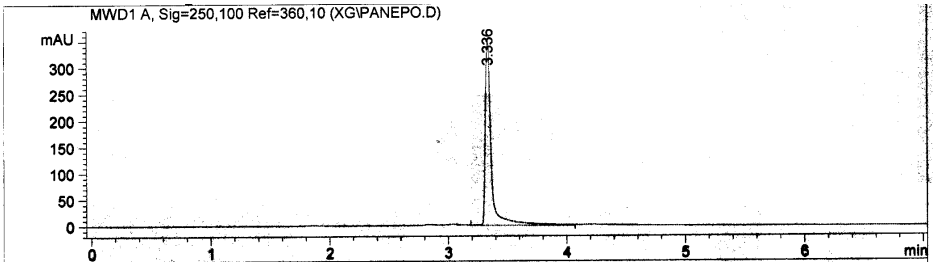
^{1}H NMR (Hz)		^{13}C NMR (Hz)	
Natural (500 MHz)	Synthetic (400 MHz)	Natural (100 MHz)	Synthetic (75.0 MHz)
6.81 (dd, 3.0, 5.0)	6.80 (dd, 3.2, 5.2)	196.2	196.5
5.99 (d, 16.0)	5.99 (d, 16.0)	143.0	143.1
5.68 (d, 16.0)	5.66 (d, 16.0)	139.9	140.1
4.55 (br t, 2.0, 2.0)	4.54 (s)	138.8	138.9
4.35 (br t, 2.0, 2.0)	4.34 (s)	129.2	129.4
3.84 (br t, 4.0, 4.0)	3.82 (br t, 3.6, 3.6)	102.6	102.8
3.50 (br t, 4.0, 4.0)	3.48 (br t, 3.2, 3.2)	79.2	79.2
3.42 (d, 4.0)	3.41 (d, 4.0)	71.8	71.8
3.35 (dd, 2.0, 5.0)	3.34 (dd, 1.6, 4.8)	69.0	69.0
3.32 (d, 4.0)	3.31 (d, 2.4)	66.2	66.2
2.33 (m, 10.0, 2.0, 2.0, 2.0)	2.31 (d, 10.0)	60.7	60.6
2.03 (br d, 10.0, 2.0)	2.01 (d, 7.6)	57.3	57.4
1.45 (s)	1.44 (s)	57.2	57.2
1.35 (s)	1.33 (s)	57.1	57.1
1.20 (s)	1.20 (s)	55.6	55.6
1.17 (s)	1.17 (s)	55.1	55.1
		51.2	51.2
		50.0	50.0
		32.3	32.2
		30.3	30.2
		29.4	29.4
		26.1	26.1

$[a]_D$ of Natural and synthetic panepophenanthrin:

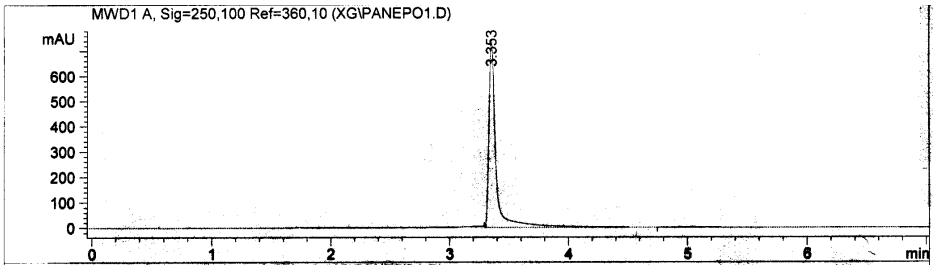
	Natural panepophenanthrin	Synthetic panepophenanthrin
$[a]_D$	$+149.8^o$ (*c* 1.0, MeOH)	$+147.5^o$ (*c* 1.0, MeOH)

HPLC data of natural and synthetic panepophenanthrin[a]

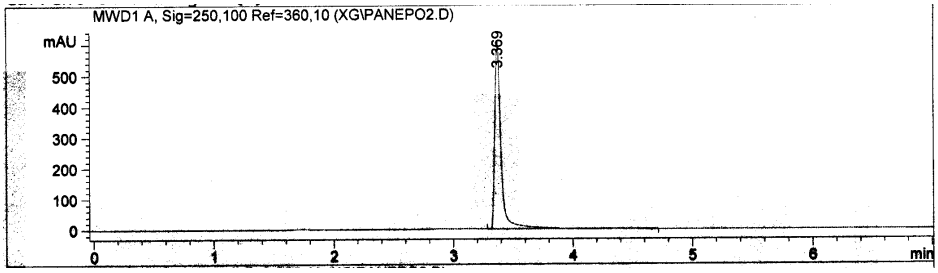
Natural:



Synthetic:

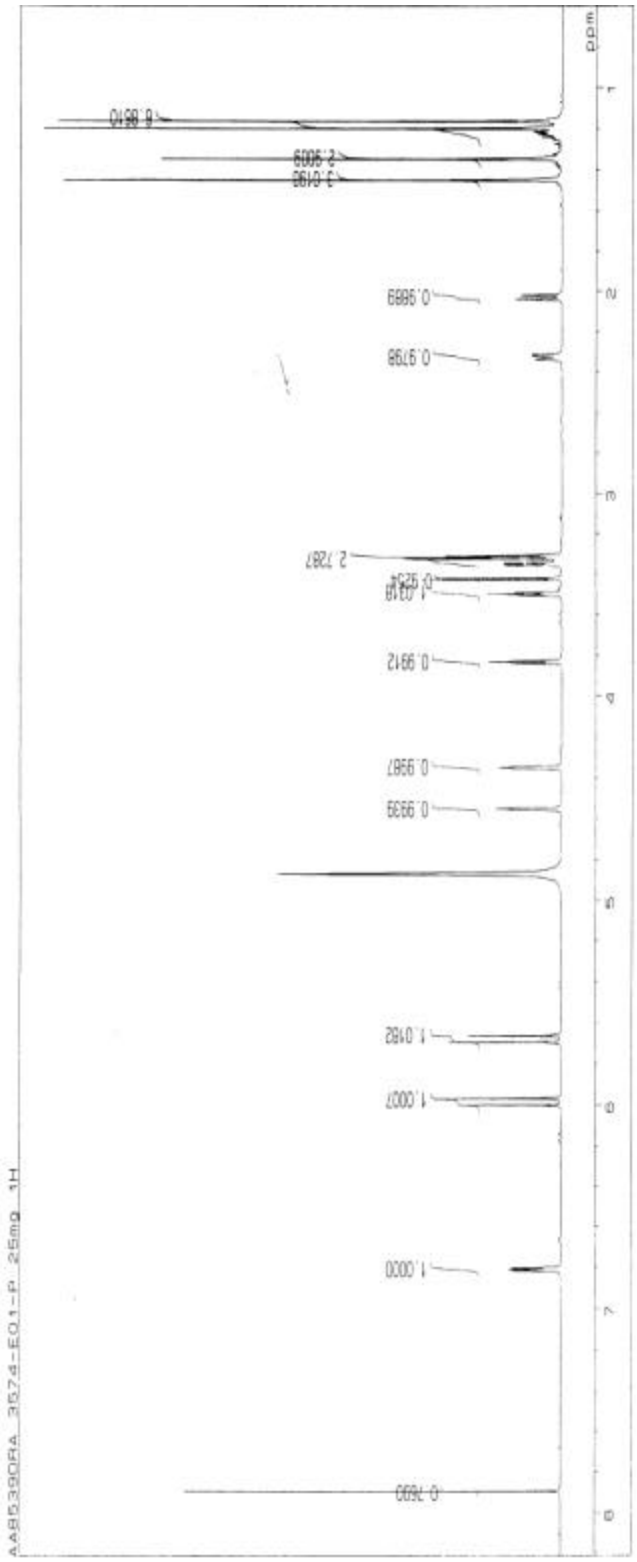


Natural+Synthetic:

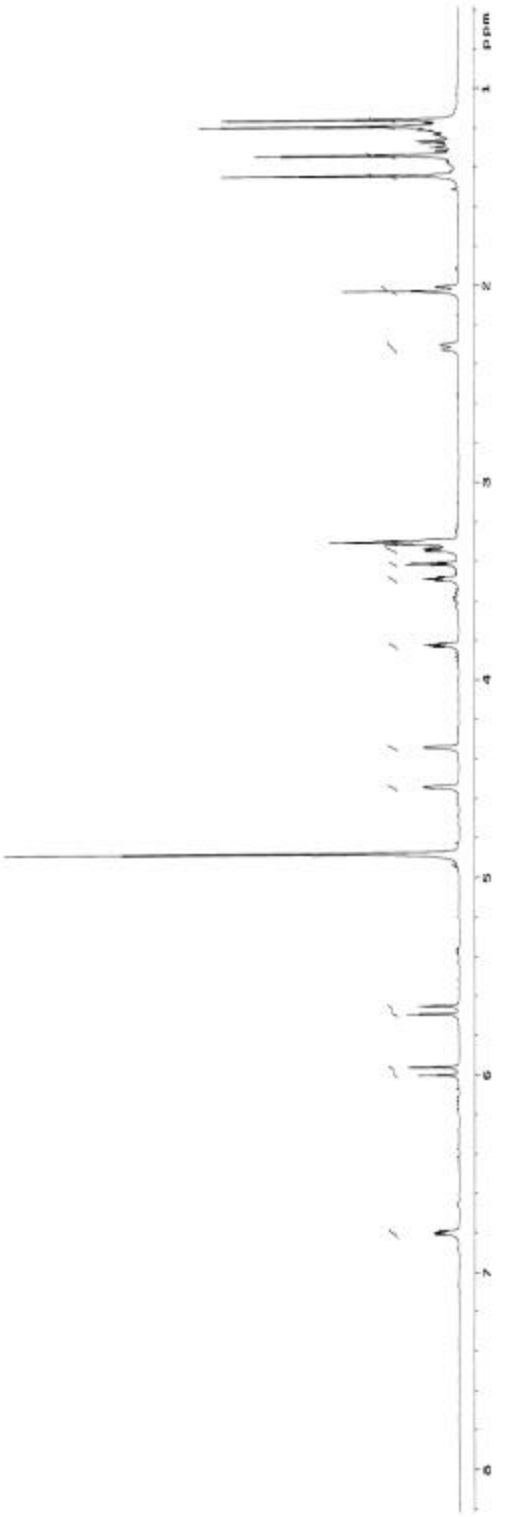


Sample Name	r_t (min)
Natural panepophenanthrin	3.336
Synthetic panepophenanthrin	3.353
Natural and synthetic panepophenanthrin (co-injection)	3.369

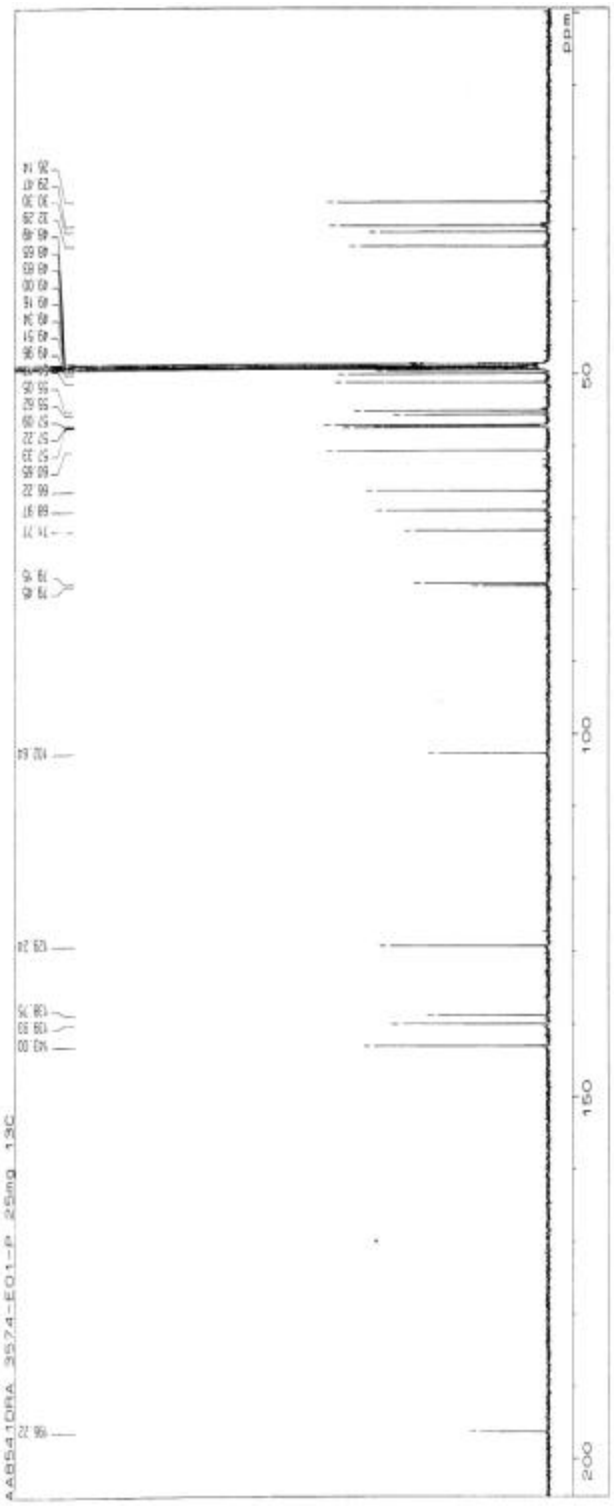
[a] Experimental condition:
Column: Agilent Zorbax SB-C18 (4.6mm ID x 7.5cm) 3.5μL
Eluent: 100% MeCN
Detector wavelength: 250 nm
Flow rate: 0.5 mL/min.



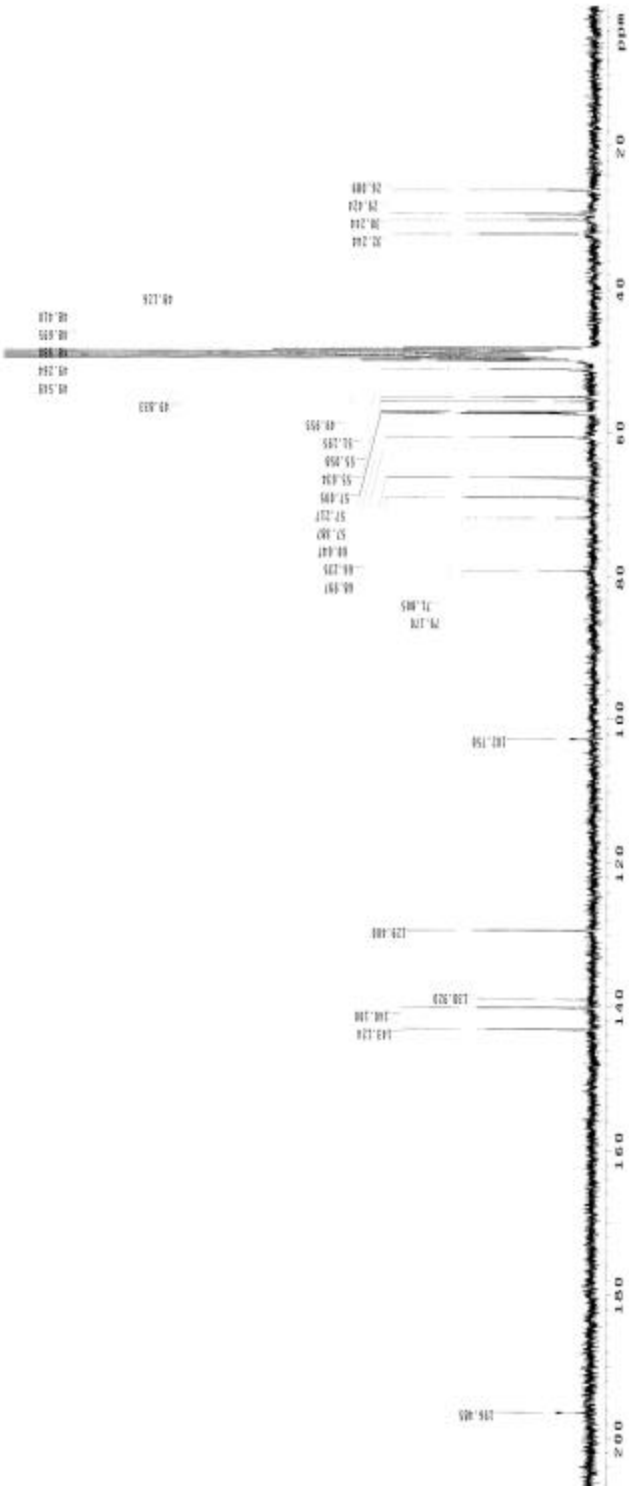
^{1}H NMR (500 MHz, CD_3OD) of natural panepophenanthrin



^{1}H NMR (400 MHz, CD_3OD) of synthetic panepophenanthrin

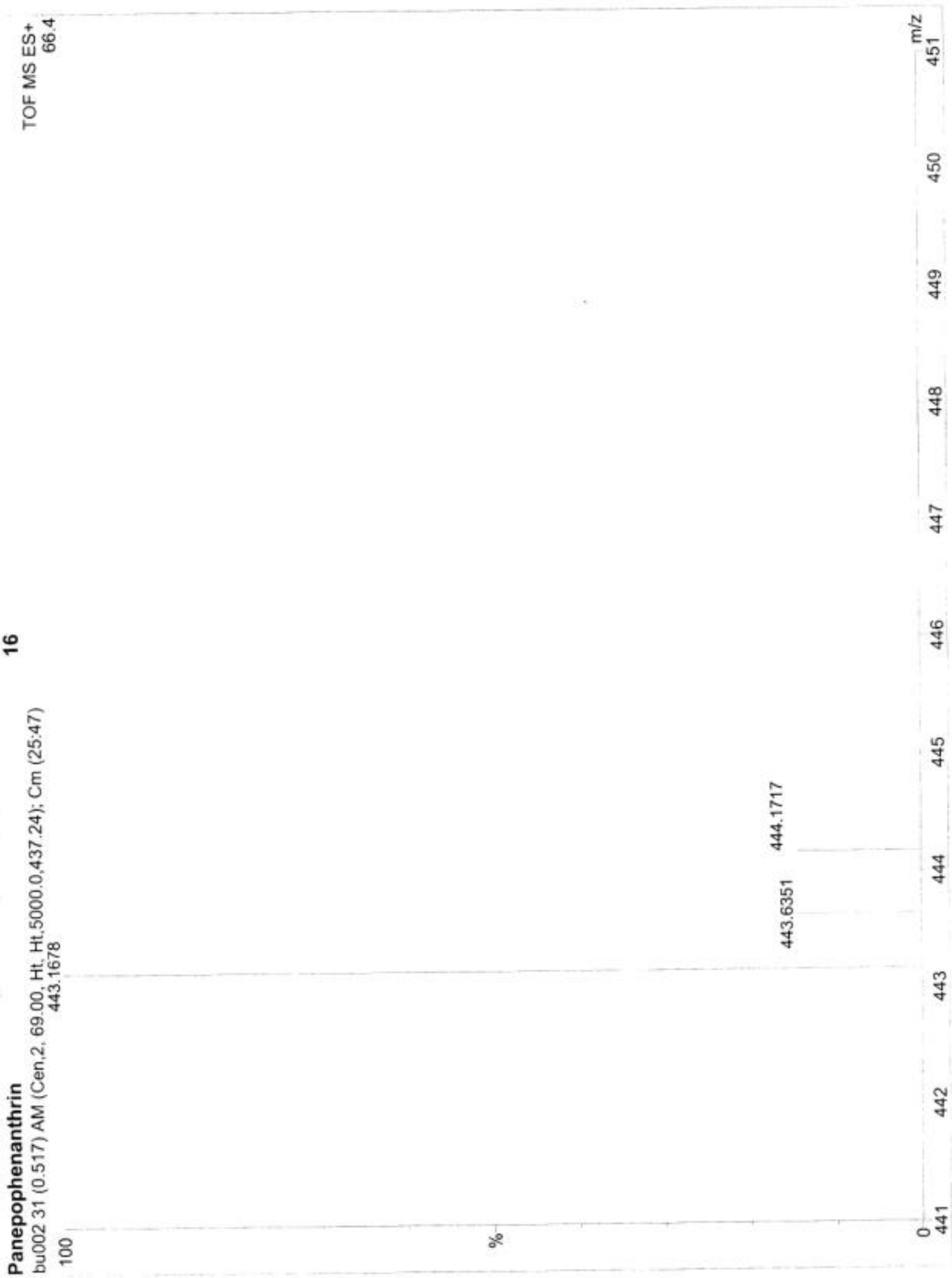


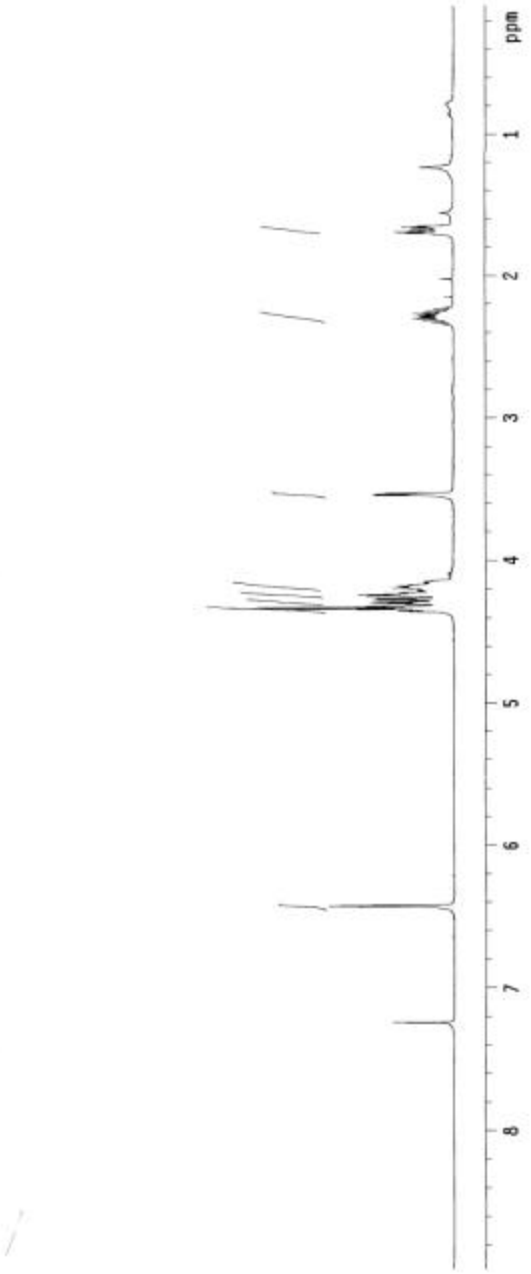
^{13}C NMR (125 MHz, CD_3OD)
of natural panepophenanthrin



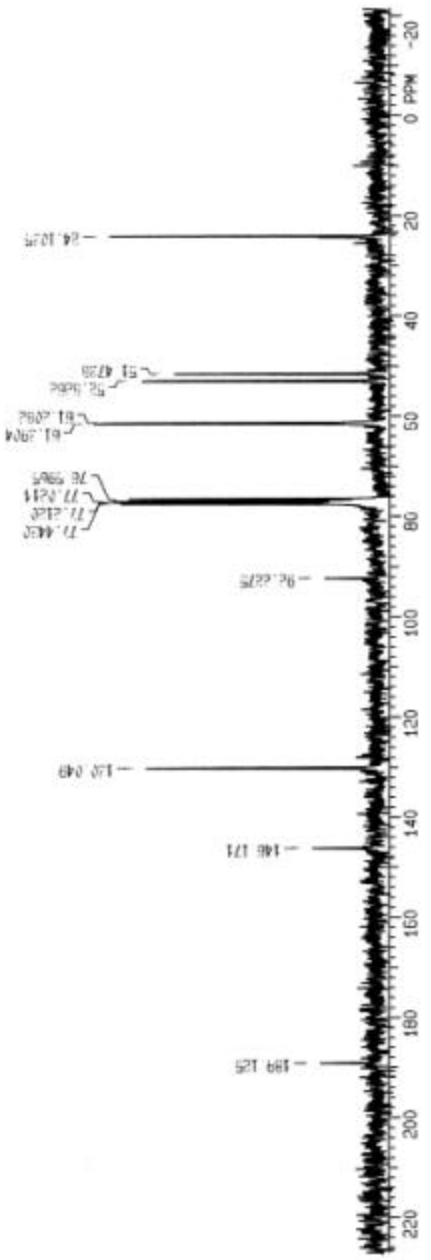
^{13}C NMR (75 MHz, CD_3OD)
of synthetic panepophenanthrin

HRTOFMS of synthetic panepophenanthrin:

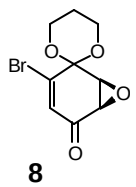




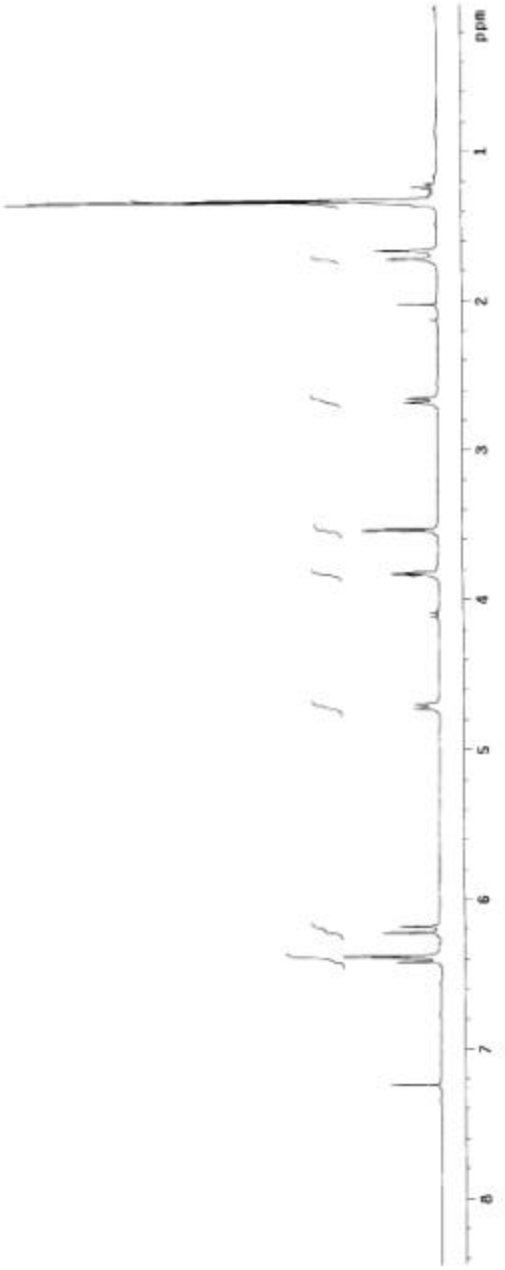
^{1}H NMR (400 MHz, $CDCl_3$)



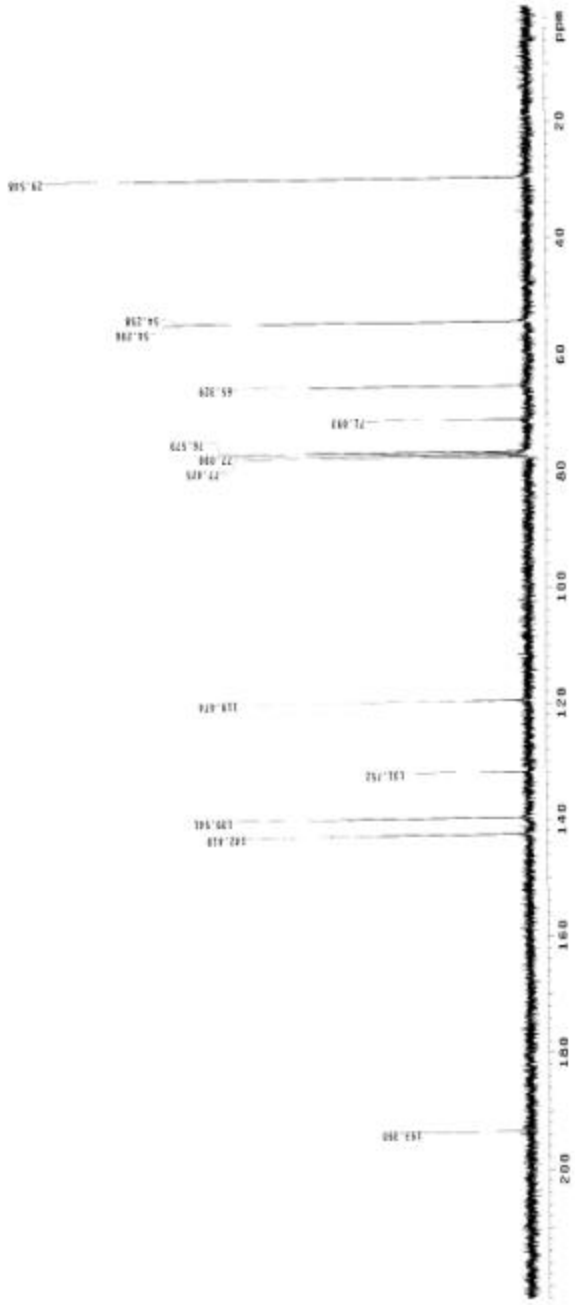
^{13}C NMR (75 MHz, $CDCl_3$)



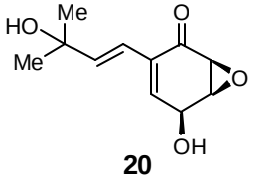
8



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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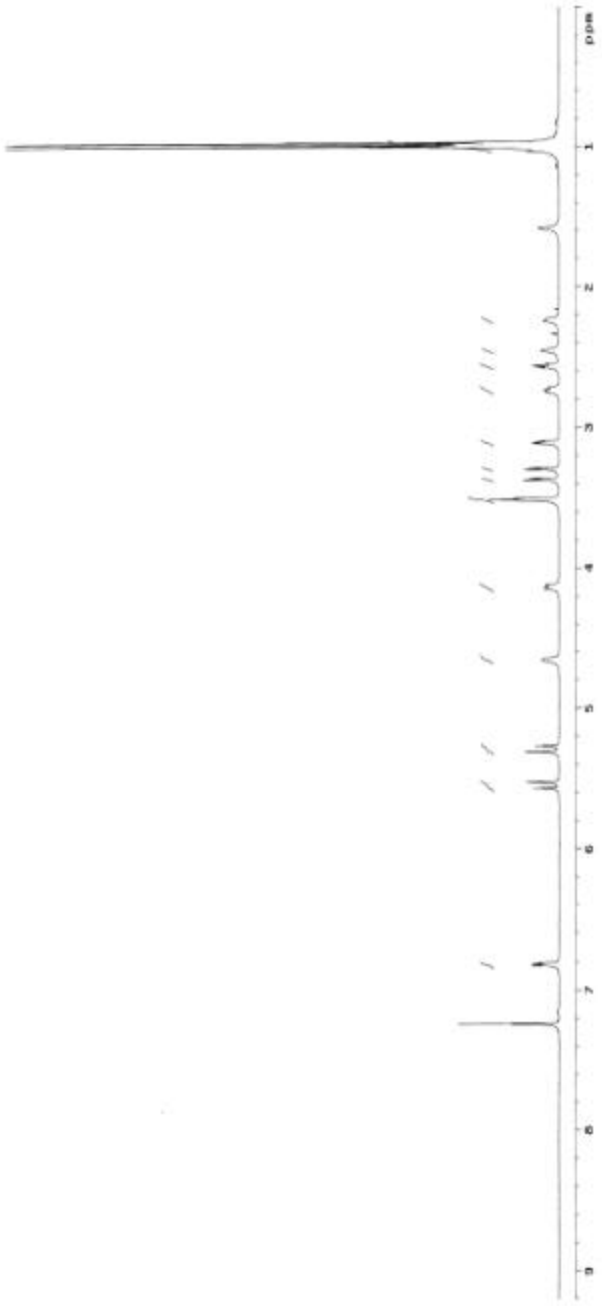
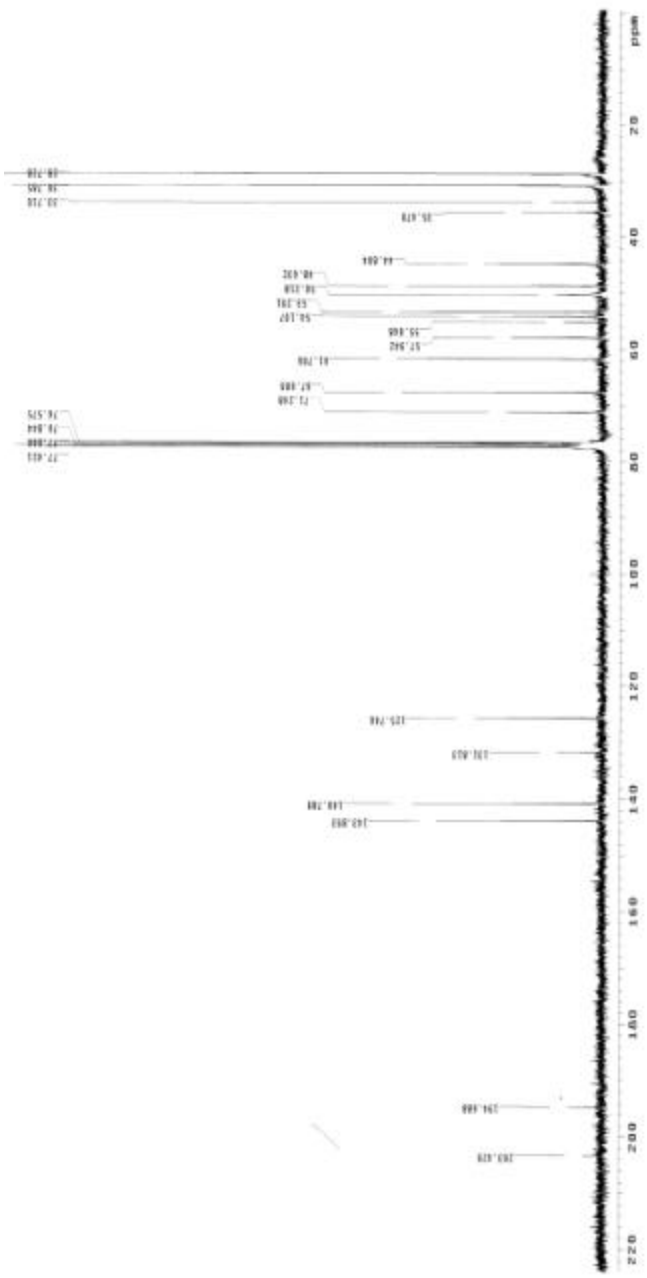
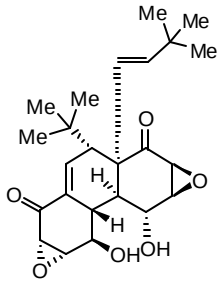


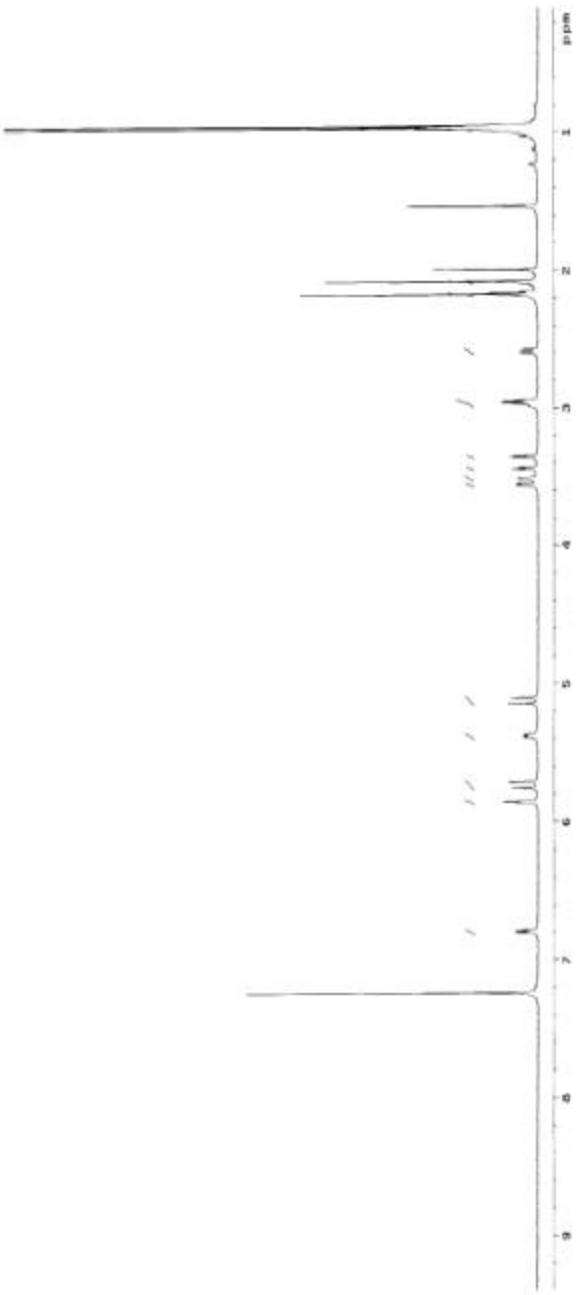
^{1}H NMR (400 MHz, $CDCl_3$)



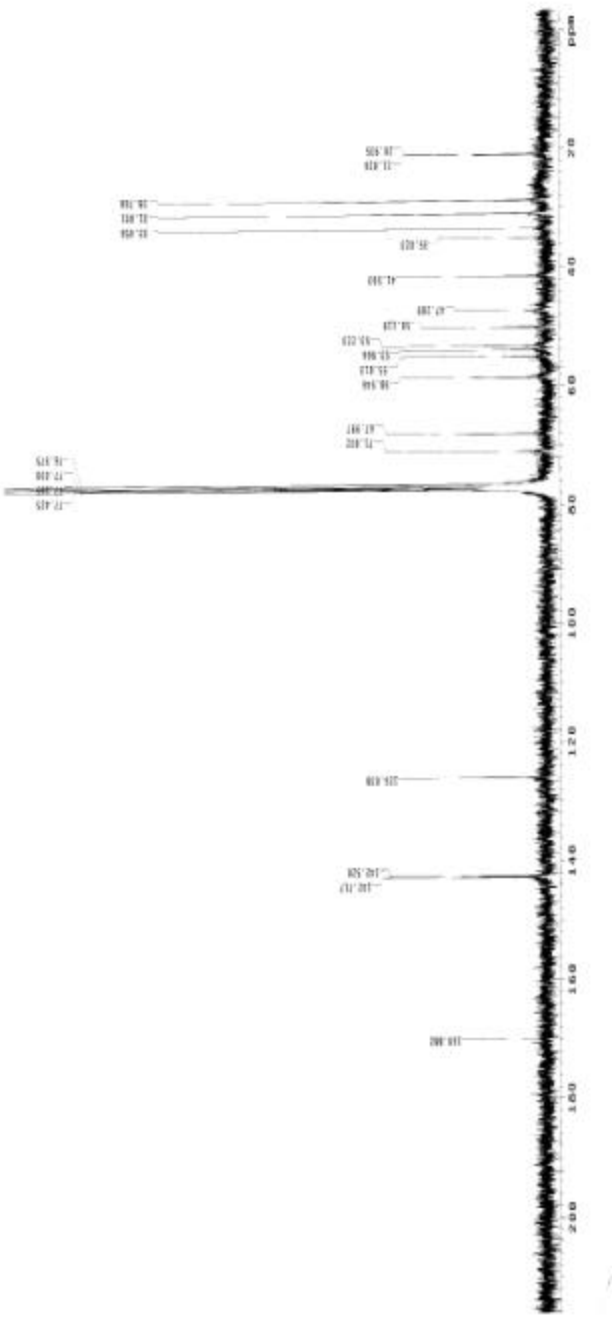
^{13}C NMR (75 MHz, $CDCl_3$)



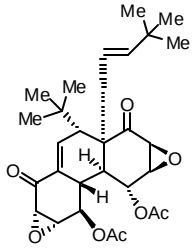
24



^{1}H NMR (400 MHz, $CDCl_3$)

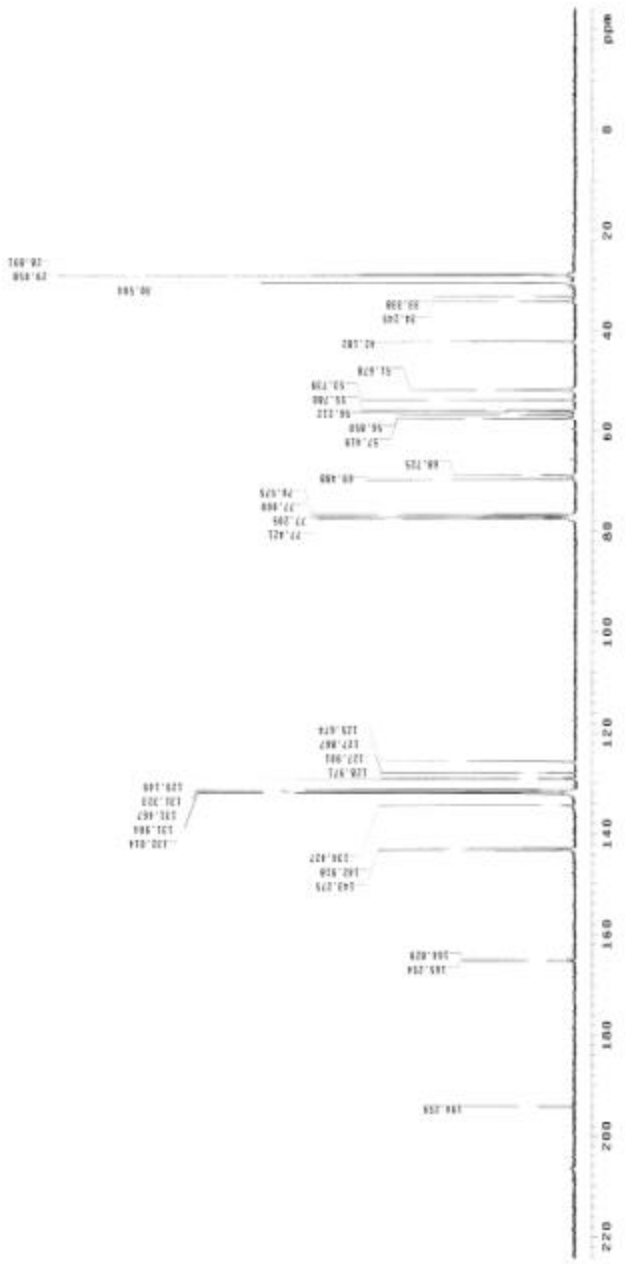


^{13}C NMR (75 MHz, $CDCl_3$)

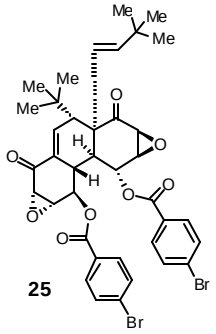


28

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



25

Computations: All calculations were performed with Spartan '02, Wavefunction Inc., Irvine, CA, 2002. Structures described in Figure 3 were optimized with both B3LYP/6-31G* and AM1 theory but frequency analysis could only be performed at the semiempirical level because of molecular size. Values for ΔE are DFT energy differences relative to two molecules of monomer. Estimated ΔG values combine DFT energetics and semiempirical free energy changes. Only a single conformation is included and thus free energy changes must be considered approximate.

Table 1 Dimerization Route to Panepophenanthrin

Structure	AM1 E (kcal/mol)	rel. E (kcal/mol)	B3LYP/6-31G*//AM1	E rel DFT	G° (kcal/mol)
monomer	-105.73		-728.37929		124.00627
monomer x 2	-211.47	0.00	-1456.75857	0.00	248.01254
open dimer	-212.25	-0.78	-1456.76604	-4.69	267.80166
tethered 2+4 TS	-174.92	36.55	-1456.73232	16.47	269.43175
panepophenanthrin	-236.26	-24.78	-1456.79544	-23.14	273.07747
untethered 2+4TS	-176.97	34.50	-1456.74129	10.84	267.9501
untethered product	-222.26	-10.79	-1456.77712	-11.64	271.63584

Structure	B3LYP/6-31G* opt	rel. E (kcal/mol)
monomer	-728.39395	
monomer x 2	-1456.78790	0.00
open dimer	-1456.79514	-4.54
tethered 2+4 TS	-1456.75957	17.77
panepophenanthrin	-1456.82320	-22.14
untethered 2+4TS	-1456.78002	4.94
untethered product	-1456.80601	-11.36

Optimized Structures from Calculations

Monomer 6 B3LYP/6-31G* optimized geometry

Energy -728.3939495 hartrees

Coordinates (Angstroms)

	ATOM	X	Y	Z
1	C	1.018289	-0.388698	0.058266
2	C	1.642053	0.686070	-0.470351
3	H	1.048746	1.479148	-0.920202
4	C	3.123174	0.938872	-0.467186
5	H	3.418430	1.213464	-1.494142
6	C	1.810920	-1.484391	0.690524
7	C	3.302761	-1.461598	0.510802
8	H	3.847643	-2.136545	1.168362

9	C	3.949759	-0.267119	-0.060172
10	H	4.984438	-0.052588	0.217090
11	O	3.362217	2.038216	0.419863
12	H	4.202397	2.449507	0.162067
13	O	3.767495	-1.431556	-0.858263
14	O	1.287529	-2.370016	1.350303
15	C	-0.444659	-0.562070	0.090263
16	H	-0.776591	-1.594698	0.148935
17	C	-1.340338	0.434855	0.098723
18	H	-0.997999	1.470357	0.119238
19	C	-2.849645	0.309242	0.135525
20	C	-3.457184	1.022625	-1.079905
21	H	-3.104903	2.058004	-1.132579
22	H	-4.548457	1.038258	-0.988430
23	H	-3.185566	0.510829	-2.008657
24	C	-3.352922	-1.136076	0.224329
25	H	-2.956178	-1.640395	1.113434
26	H	-3.062424	-1.722032	-0.654343
27	H	-4.444998	-1.133999	0.293741
28	O	-3.326688	1.061347	1.271729
29	H	-2.917300	0.670988	2.061037

Hemiacetal tethered Dimer B3LYP/6-31G* geometry; starting with lowest conformation

Energy = -1456.7951379

		Coordinates (Angstroms)		
ATOM		X	Y	Z
1	C	-3.193318	1.268740	-1.137589
2	C	2.527402	-1.094791	0.169776
3	C	-1.425019	2.090596	0.445095
4	C	-0.338711	2.004872	-0.334950
5	C	-2.749655	1.545045	0.109057
6	C	3.710281	-1.570809	0.594667
7	H	3.747045	-2.536995	1.094690
8	H	-2.578162	1.523343	-1.998266
9	H	-1.339168	2.490057	1.450849
10	H	-0.413618	1.542744	-1.318239
11	C	-3.576637	1.114823	1.273692
12	C	-5.036522	0.875310	1.040210
13	H	-5.588157	0.521298	1.908904
14	C	5.046943	-0.903482	0.466212
15	H	5.360013	-0.547889	1.462980
16	C	2.404458	0.253151	-0.553692
17	C	3.757181	0.847973	-0.960397

18	H	3.738971	1.359279	-1.921031
19	C	5.025172	0.292568	-0.472219
20	H	5.923407	0.409354	-1.083008
21	O	-3.083616	0.881862	2.373139
22	C	-4.414456	0.432480	-1.428901
23	H	-4.868442	0.756618	-2.372529
24	C	-5.459017	0.515771	-0.331917
25	H	-6.320245	-0.141696	-0.456334
26	O	-4.034205	-0.927497	-1.636301
27	H	-3.521847	-1.212012	-0.848803
28	O	-5.734534	1.807925	0.192643
29	O	5.956748	-1.903068	-0.005661
30	H	6.856812	-1.583630	0.164769
31	O	4.499143	1.510666	0.067998
32	O	1.728759	0.094028	-1.791812
33	H	1.069151	-0.611114	-1.682816
34	O	1.719431	1.070281	0.378660
35	C	1.081884	2.355725	0.067095
36	C	1.178968	3.114760	1.393425
37	H	0.774824	2.515628	2.213871
38	H	0.634227	4.063112	1.342927
39	H	2.230608	3.319843	1.612252
40	C	1.762778	3.165623	-1.045681
41	H	2.811627	3.357974	-0.802923
42	H	1.252823	4.131796	-1.133827
43	H	1.698898	2.662704	-2.013844
44	C	1.325856	-1.924109	0.374786
45	H	1.558054	-2.951260	0.655277
46	C	0.032221	-1.580572	0.235691
47	H	-0.243896	-0.554610	0.007746
48	C	-1.153729	-2.526172	0.362492
49	C	-1.437235	-3.206114	-0.985854
50	H	-1.616192	-2.456763	-1.763777
51	H	-2.330865	-3.835466	-0.908633
52	H	-0.589191	-3.828715	-1.285925
53	C	-0.983785	-3.566347	1.479045
54	H	-0.804002	-3.077197	2.443052
55	H	-0.143608	-4.240135	1.281058
56	H	-1.893870	-4.168731	1.558472
57	O	-2.346231	-1.749390	0.633765
58	H	-2.195755	-1.197382	1.420634

Hemiacetal tethered 4+2 transition state B3LYP/6-31G* geometry

Energy = -1456.7595690

Coordinates (Angstroms)

	ATOM	X	Y	Z
1	C	-0.278980	-2.069695	-0.839016
2	C	-0.755216	0.257713	0.898965
3	C	-0.197920	0.138140	-1.922308
4	C	-1.407259	0.468310	-1.367806
5	C	0.382621	-1.126079	-1.653971
6	C	-0.620205	-1.135667	1.072164
7	H	0.352054	-1.467847	1.423506
8	H	-1.358620	-2.130303	-0.937173
9	H	0.439129	0.879145	-2.395050
10	H	-2.096068	-0.331810	-1.130564
11	C	1.783724	-1.332703	-2.084329
12	C	2.546954	-2.463726	-1.446750
13	H	3.504962	-2.683357	-1.913358
14	C	-1.730129	-1.943858	1.731610
15	H	-1.721296	-2.980466	1.375966
16	C	-2.089354	0.971713	1.121079
17	C	-3.298304	0.042105	1.220852
18	H	-4.204064	0.564216	1.528571
19	C	-3.124441	-1.375983	1.551180
20	H	-3.896627	-1.896634	2.117067
21	O	2.333622	-0.647534	-2.938844
22	C	0.314831	-3.435803	-0.562305
23	H	0.041782	-3.745481	0.458513
24	C	1.826860	-3.491358	-0.680094
25	H	2.261448	-4.491377	-0.613218
26	O	-0.267849	-4.338984	-1.510793
27	H	-0.145931	-5.242873	-1.178581
28	O	2.562936	-2.480107	0.005441
29	O	-1.478290	-2.055924	3.138205
30	H	-1.419147	-1.147771	3.482195
31	O	-3.516485	-0.977169	0.226849
32	O	-2.012244	1.608005	2.395362
33	H	-2.485212	2.451446	2.294058
34	O	-2.325135	2.034737	0.205430
35	C	-2.039876	1.828820	-1.227602
36	C	-3.393582	1.872097	-1.954980
37	H	-4.035878	1.045790	-1.635074
38	H	-3.247042	1.794642	-3.037836
39	H	-3.906014	2.815945	-1.739936
40	C	-1.150541	2.993845	-1.661621
41	H	-0.185022	2.969733	-1.150932
42	H	-1.643130	3.941500	-1.422229
43	H	-0.975014	2.962909	-2.742419

44	C	0.414803	1.131895	0.954234
45	H	0.204771	2.192371	1.057056
46	C	1.700968	0.746546	0.866539
47	H	1.964895	-0.302482	0.752387
48	C	2.878841	1.701788	0.924486
49	C	3.940543	1.146239	1.892841
50	H	3.521469	1.022345	2.899639
51	H	4.787628	1.837432	1.950643
52	H	4.305959	0.167377	1.562653
53	C	3.476593	1.900085	-0.476296
54	H	2.744682	2.386499	-1.127507
55	H	3.757778	0.945534	-0.930730
56	H	4.364968	2.538268	-0.414026
57	O	2.476813	3.012406	1.345565
58	H	2.113242	2.925392	2.242294

Untethered 4+2 transition state B3LYP/6-31G* optimized geometry

Energy = -1456.806010

Coordinates (Angstroms)

ATOM		X	Y	Z
1	C	2.162837	0.100143	0.506364
2	C	-0.135969	0.819670	-0.617931
3	C	0.139830	0.431883	1.843151
4	C	-0.214943	1.492965	0.850544
5	C	1.277132	-0.261195	1.684536
6	C	1.309215	0.154998	-0.811663
7	H	1.123736	-0.878784	-1.105894
8	H	2.547361	1.111574	0.687997
9	H	-0.536341	0.170088	2.651643
10	H	0.596844	2.229264	0.836693
11	C	1.545372	-1.413226	2.580790
12	C	2.344973	-2.529458	1.973617
13	H	2.523841	-3.389267	2.615562
14	C	2.100183	0.729274	-2.009844
15	H	3.139680	0.379724	-1.958874
16	C	-0.342859	1.978065	-1.619751
17	C	0.804981	2.912724	-1.856637
18	H	0.556915	3.849209	-2.349916
19	C	2.099962	2.244907	-2.091172
20	H	2.816005	2.708037	-2.773318
21	O	1.118335	-1.505835	3.721300
22	C	3.435546	-0.772721	0.415298

23	H	3.812655	-0.780582	-0.616404
24	C	3.248658	-2.215561	0.854176
25	H	4.116304	-2.864176	0.704294
26	O	4.399234	-0.154189	1.274517
27	H	5.222790	-0.666322	1.231710
28	O	1.998380	-2.844402	0.599498
29	O	1.479807	0.197096	-3.185568
30	H	1.931240	0.556212	-3.966177
31	O	1.867243	2.969854	-0.889079
32	O	-1.370303	2.150642	-2.254927
33	O	-1.627110	3.428117	0.337346
34	C	-1.470767	2.334308	1.256632
35	C	-1.161741	3.018025	2.598965
36	H	-0.263143	3.637572	2.511793
37	H	-1.007086	2.293514	3.404105
38	H	-1.997607	3.669184	2.872114
39	C	-2.788369	1.554617	1.364351
40	H	-3.107518	1.163191	0.394692
41	H	-3.570856	2.223471	1.737580
42	H	-2.708903	0.707591	2.054466
43	C	-1.244482	-0.200161	-0.851150
44	H	-2.107428	0.207718	-1.367588
45	C	-1.233927	-1.495299	-0.521483
46	H	-0.373834	-1.945814	-0.029636
47	C	-2.349082	-2.497520	-0.764519
48	C	-3.624345	-1.896632	-1.367199
49	H	-4.036980	-1.113049	-0.720316
50	H	-4.377923	-2.683813	-1.466248
51	H	-3.445368	-1.461341	-2.356065
52	C	-1.824360	-3.643747	-1.638854
53	H	-0.919968	-4.075949	-1.198847
54	H	-1.588422	-3.285288	-2.645823
55	H	-2.582115	-4.431742	-1.708580
56	O	-2.665866	-3.123228	0.498948
57	H	-2.910793	-2.411841	1.112350
58	H	-2.130650	3.117505	-0.431570

Untethered 4+2 dimer B3LYP/6-31G* optimization

Energy = -1456.8060103

	Coordinates (Angstroms)		
ATOM	X	Y	Z

1	C	2.162837	0.100143	0.506364
2	C	-0.135969	0.819670	-0.617931
3	C	0.139830	0.431883	1.843151
4	C	-0.214943	1.492965	0.850544
5	C	1.277132	-0.261195	1.684536
6	C	1.309215	0.154998	-0.811663
7	H	1.123736	-0.878784	-1.105894
8	H	2.547361	1.111574	0.687997
9	H	-0.536341	0.170088	2.651643
10	H	0.596844	2.229264	0.836693
11	C	1.545372	-1.413226	2.580790
12	C	2.344973	-2.529458	1.973617
13	H	2.523841	-3.389267	2.615562
14	C	2.100183	0.729274	-2.009844
15	H	3.139680	0.379724	-1.958874
16	C	-0.342859	1.978065	-1.619751
17	C	0.804981	2.912724	-1.856637
18	H	0.556915	3.849209	-2.349916
19	C	2.099962	2.244907	-2.091172
20	H	2.816005	2.708037	-2.773318
21	O	1.118335	-1.505835	3.721300
22	C	3.435546	-0.772721	0.415298
23	H	3.812655	-0.780582	-0.616404
24	C	3.248658	-2.215561	0.854176
25	H	4.116304	-2.864176	0.704294
26	O	4.399234	-0.154189	1.274517
27	H	5.222790	-0.666322	1.231710
28	O	1.998380	-2.844402	0.599498
29	O	1.479807	0.197096	-3.185568
30	H	1.931240	0.556212	-3.966177
31	O	1.867243	2.969854	-0.889079
32	O	-1.370303	2.150642	-2.254927
33	O	-1.627110	3.428117	0.337346
34	C	-1.470767	2.334308	1.256632
35	C	-1.161741	3.018025	2.598965
36	H	-0.263143	3.637572	2.511793
37	H	-1.007086	2.293514	3.404105
38	H	-1.997607	3.669184	2.872114
39	C	-2.788369	1.554617	1.364351
40	H	-3.107518	1.163191	0.394692
41	H	-3.570856	2.223471	1.737580
42	H	-2.708903	0.707591	2.054466
43	C	-1.244482	-0.200161	-0.851150
44	H	-2.107428	0.207718	-1.367588
45	C	-1.233927	-1.495299	-0.521483
46	H	-0.373834	-1.945814	-0.029636

47	C	-2.349082	-2.497520	-0.764519
48	C	-3.624345	-1.896632	-1.367199
49	H	-4.036980	-1.113049	-0.720316
50	H	-4.377923	-2.683813	-1.466248
51	H	-3.445368	-1.461341	-2.356065
52	C	-1.824360	-3.643747	-1.638854
53	H	-0.919968	-4.075949	-1.198847
54	H	-1.588422	-3.285288	-2.645823
55	H	-2.582115	-4.431742	-1.708580
56	O	-2.665866	-3.123228	0.498948
57	H	-2.910793	-2.411841	1.112350
58	H	-2.130650	3.117505	-0.431570

Panepophenanthrin B3LYP/6-31G* geometry

Energy = -1456.8231976

Coordinates (Angstroms)

ATOM		X	Y	Z
1	C	0.267407	-2.027212	0.175906
2	C	-0.888304	0.247146	0.414262
3	C	-1.003696	-0.978653	-1.747978
4	C	-1.789982	-0.172581	-0.766882
5	C	-0.029475	-1.800404	-1.308550
6	C	-0.436880	-1.025802	1.166918
7	H	0.297817	-0.721290	1.919926
8	H	-0.145584	-3.026845	0.387495
9	H	-1.212755	-0.947145	-2.815229
10	H	-2.547669	-0.846221	-0.346222
11	C	0.698182	-2.634474	-2.307591
12	C	2.043961	-3.172446	-1.894092
13	H	2.418208	-3.991384	-2.506113
14	C	-1.525821	-1.768386	1.979081
15	H	-2.070441	-2.461948	1.315919
16	C	-1.854151	1.215944	1.172508
17	C	-2.767046	0.536435	2.186629
18	H	-3.227445	1.245864	2.873936
19	C	-2.575623	-0.862817	2.601626
20	H	-2.899580	-1.175201	3.594395
21	O	0.276372	-2.864206	-3.431010
22	C	1.758575	-2.190691	0.525233
23	H	2.235546	-1.214093	0.662257
24	C	2.561661	-2.941226	-0.530424
25	H	3.306830	-3.636571	-0.139115
26	O	1.769999	-2.921415	1.767817

27	H	2.555176	-2.659545	2.272290
28	O	3.010346	-2.130839	-1.616381
29	O	-0.917344	-2.491878	3.041904
30	H	-0.046973	-2.807864	2.731548
31	O	-3.642925	-0.487356	1.709318
32	O	-1.233859	2.213927	1.928126
33	H	-0.633692	2.687177	1.327211
34	O	-2.620741	1.835371	0.129136
35	C	-2.585743	1.107602	-1.133593
36	C	-4.029439	0.776358	-1.526913
37	H	-4.515425	0.196425	-0.737624
38	H	-4.053088	0.197080	-2.458375
39	H	-4.601014	1.697017	-1.683322
40	C	-1.956309	2.023327	-2.192111
41	H	-0.965610	2.376245	-1.897496
42	H	-2.591580	2.904201	-2.332300
43	H	-1.871954	1.512202	-3.158284
44	C	0.373061	0.974487	-0.066844
45	H	0.506122	1.044089	-1.140758
46	C	1.358610	1.410867	0.724992
47	H	1.274012	1.326849	1.807816
48	C	2.699751	1.959367	0.282977
49	C	2.851372	3.425461	0.725975
50	H	3.862668	3.789603	0.502289
51	H	2.685068	3.519854	1.803964
52	H	2.139062	4.072903	0.202456
53	C	2.972540	1.801736	-1.217243
54	H	3.981288	2.165499	-1.450103
55	H	2.271534	2.386929	-1.822797
56	H	2.908380	0.750460	-1.513998
57	O	3.630762	1.139314	1.030096
58	H	4.525835	1.418753	0.777341

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