Electronic Supporting Information

Design, Synthesis and Biological Evaluation of a Macrocyclic Discodermolide/Dictyostatin Hybrid

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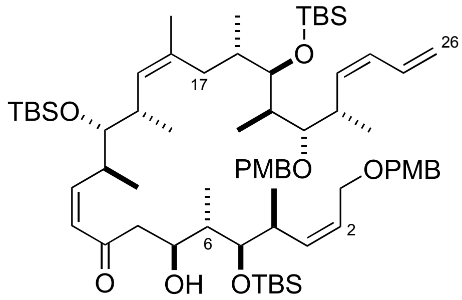
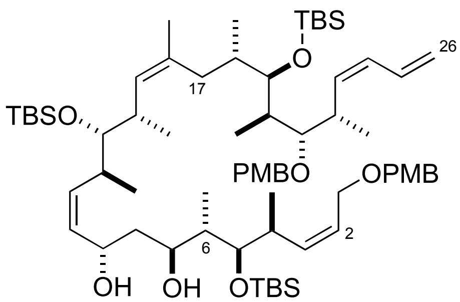
General Experimental Details

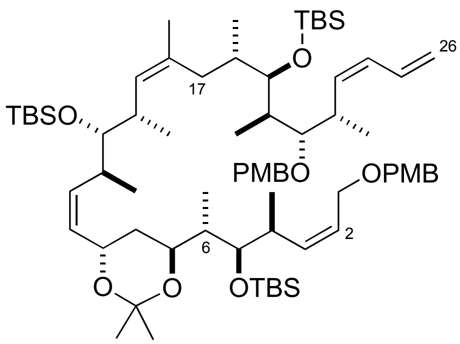
Thin layer chromatography was carried out on commercial glass backed silica gel 60 F254 plates. Visualization of chromatograms was accomplished using ultraviolet light (254 nm) and/or heating the plate after staining with either a solution of 20% ceric ammonium molybdate w/v in H_2O or 20% potassium permanganate w/v in H_2O. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 589 nm (sodium D line) and concentrations (c) are reported in g/100 mL. Infrared (IR) spectra were recorded on a Perkin-Elmer 1620 FT-IR spectrophotometer with internal calibration. Only selected, characteristic IR absorption data, in wavenumbers (cm^{-1}) are provided for each compound. NMR spectra were recorded using deuteriobenzene (C_6D_6) or deuteriomethanol (CD_3OD) as the solvent. Chemical shifts (δ) are given in parts per million (ppm) from tetramethylsilane (δ = 0) and were measured relative to the signal of the solvent in which the sample was analyzed (C_6D_6: δ 7.15, ^{1}H NMR; δ 128.0, ^{13}C NMR; CD_3OD: δ 4.78, ^{1}H NMR; δ 49.0, ^{13}C NMR). Coupling constants (J values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: number of protons, multiplicity (br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet), coupling constant and proton assignment where applicable.



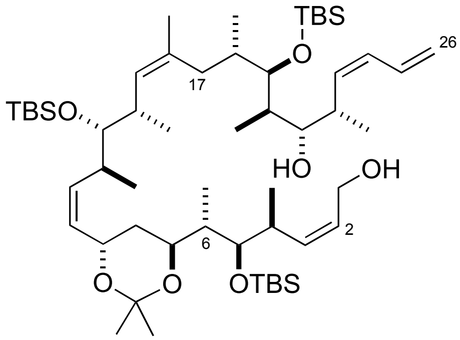
Aldol Adduct **10**: ***R**$_f$* 0.59 (20% EtOAc / hexane); **[α]$_D^{20}$** +61.6 (*c* = 0.02, MeOH); **IR** (Thin Film) ν_{max} = 3396 (*br*, OH), 2961 (m), 1613 (m), 1514 (s), 1457 (m), 1301 (m); **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.34 (2H, d, *J* = 8.6 Hz, ArH), 7.29 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (2H, d, *J* = 8.6 Hz, ArH), 6.82 (2H, d, *J* = 8.8 Hz, ArH), 6.73 (1H, *app* dt, *J* = 17.0, 11.0 Hz, C_{25}-H), 6.32 (1H, dd, *J* = 9.7, 11.4 Hz, C_{11}-H), 6.13 (1H, *app* t, *J* = 11.1 Hz, C_{24}-H), 5.98 (1H, d, *J* = 11.6 Hz, C_{10}-H), 5.74 (1H, *app* t, *J* = 10.7 Hz, C_{23}-H), 5.70 - 5.60 (2H, m, C_2-H + C_3-H), 5.28 (1H, d, *J* = 16.8 Hz, C_{26}-H_xH_y), 5.15 (1H, d, *J* = 9.5 Hz, C_{26}-H_xH_y), 4.97 (1H, d, *J* = 10.3 Hz, C_{15}-H), 4.61 and 4.57 (2H, AB system, *J* = 10.6 Hz, OCH_2Ar), 4.43 and 4.40 (2H, AB system, *J* = 11.6 Hz, OCH_2Ar), 4.35 - 4.27 (1H, m, C_7-H), 4.14 (1H, dd, *J* = 5.2, 11.7 Hz, C_1-H_xH_y), 4.05 (1H, dd, *J* = 5.0, 11.8 Hz, C_1-H_xH_y), 3.97 - 3.89 (2H, m, C_5-H + C_{12}-H), 3.67 (1H, d, *J* = 2.9 Hz, C_{19}-H), 3.63 (1H, *app* t , *J* = 4.1 Hz, OH), 3.49 (1H, dd, *J* = 2.8, 8.0 Hz, C_{13}-H), 3.38 (1H, dd, *J* = 3.8, 7.4 Hz, C_{21}-H), 3.34 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.14 - 3.10 (1H, m, C_{22}-H), 2.86 - 2.81 (1H, m, C_4-H), 2.62 - 2.59 (1H, dd, *J* = 2.1, 17.1 Hz, C_8-H_xH_y), 2.60 – 2.52 (1H, m, C_{14}-H), 2.40 (1H, dd, *J* = 9.3, 17.4 Hz, C_8-H_xH_y), 2.22 (1H, *app* t, *J* = 12.5 Hz, C_{17}-H_xH_y), 2.06 - 2.02 (1H, m, C_{20}-H), 1.97 - 1.92 (2H, m, C_6-H + C_{18}-H), 1.81 (1H, d, *J* = 11.4 Hz, C_{17}-H_xH_y), 1.68 (3H, s, C_{16}-CH_3), 1.28 (3H, d, *J* = 6.8 Hz, C_{20}-CH_3), 1.17 (6H, d, *J* = 6.1 Hz, C_{12}-CH_3 + C_{22}-CH_3), 1.10 – 0.92 (33H, C_4-CH_3 + C_6-CH_3 + C_{14}-CH_3 + 3 x $SiC(CH_3)_3$), 0.88 (3H, d, *J* = 7.1 Hz, C_6-CH_3), 0.21 (3H, s, $Si(CH_3)$), 0.20 (3H, s, $Si(CH_3)$), 0.18 (3H, s, $Si(CH_3)$), 0.17 (3H, s, $Si(CH_3)$), 0.16 (3H, s, $Si(CH_3)$), 0.10 (3H, s, $Si(CH_3)$); **^{13}C NMR** (125MHz, C_6D_6) δ = 201.2, 159.6, 159.5 (2C), 151.3, 137.5, 135.4, 134.7, 132.7, 132.5, 131.3, 131.1, 130.8, 129.4, 129.2 (2C), 127.2, 125.9, 125.4, 117.7, 113.9 (2C), 84.7, 80.8, 77.8, 76.9, 75.2, 74.9, 72.1 (d, *J* = 6.1 Hz), 69.3, 65.9, 65.8, 54.5, 50.9, 48.6, 44.8, 40.4, 38.5, 37.8, 37.1, 36.9, 36.5, 35.9, 35.6, 35.5, 30.2, 26.4, 26.3, 26.1, 26.0, 25.9, 22.9, 18.7, 18.6, 18.5, 18.3, 17.9, 17.8, 17.6, 14.8, 11.8, 11.0, –3.1, –3.3, –3.5, –3.9, –4.0, –4.2; **HRMS** (ES^+) Calcd for $C_{68}H_{116}O_9Si_3Na$ $[M+Na]^+$ 1183.7819, found 1183.7786.



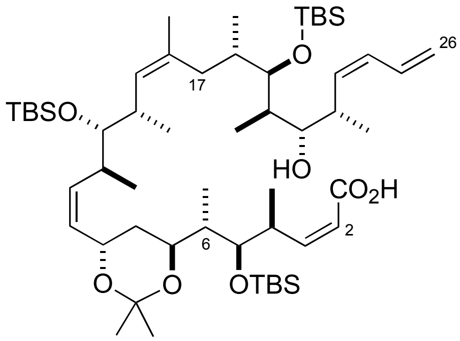
1,3-*anti* diol **11**: ***R****f* 0.32 (20% EtOAc / hexane); **[α]**$_D^{20}$ +49.7 (*c* = 0.68, $CHCl_3$); **IR** (Thin Film) ν_{max} = 3477 (*br*, OH), 2957 (s), 2930 (s), 2856 (s), 1614 (m), 1515 (s), 1462 (s), 1375 (m); **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.32 (2H, d, *J* = 8.6 Hz, ArH), 7.30 (2H, d, *J* = 8.6 Hz, ArH), 6.84 (4H, *app* t, *J* = 11.4 Hz, ArH), 6.73 (1H, *app* dt, *J* = 16.8, 10.4 Hz, C_{25}-H), 6.11 (1H, *app* t, *J* = 11.0 Hz, C_{24}-H), 5.71 (1H, *app* t, *J* = 10.6 Hz, C_2-H), 5.69 (1H, *app* t, *J* = 11.2 Hz, C_{23}-H), 5.66 – 5.64 (2H, m, C_{10}-H + C_{11}-H), 5.57 (1H, *app* t, *J* = 10.4 Hz, C_3-H), 5.26 (1H, d, *J* = 16.9 Hz, C_{26}-H_xH_y), 5.19 (1H, d, *J* = 10.3 Hz, C_{15}-H), 5.13 (1H, d, *J* = 10.1 Hz, C_{26}-H_xH_y), 4.91 (1H, *br* s, C_9-H), 4.60 and 4.54 (2H, AB system, *J* = 10.6 Hz, OCH_2Ar), 4.47 and 4.41 (2H, AB system, *J* = 11.5 Hz, OCH_2Ar), 4.17 and 4.04 (2H, dd AB system, *J* = 10.1, 12.2 Hz, C_1-H_2), 4.10 (1H, *app* t, *J* = 8.5 Hz, C_7-H), 3.80 (1H, dd, *J* = 3.4, 6.4 Hz, C_5-H), 3.65 (1H, *app* t, *J* = 4.6 Hz, C_{19}-H), 3.46 (1H, *br* s, OH), 3.41 (1H, dd, *J* = 4.6, 6.3 Hz, C_{13}-H), 3.36 (1H, dd, *J* = 4.2, 6.8 Hz, C_{21}-H), 3.33 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.16 - 3.09 (1H, m, C_{22}-H), 3.03 – 2.96 (1H, m, C_{12}-H), 2.90 - 2.82 (1H, m, C_4-H), 2.74 - 2.67 (1H, m, C_{14}-H), 2.58 (1H, *br* s, OH), 2.32 (1H, *app* t, *J* = 12.5 Hz, C_{17}-H_xH_y), 2.08 – 1.98 (3H, m, C_6-H + C_{18}-H + C_{20}-H), 1.91 - 1.86 (2H, m, C_8-H_xH_y + C_{17}-H_xH_y), 1.77 - 1.72 (1H, m, C_8-H_xH_y), 1.73 (3H, s, C_{16}-CH_3), 1.26 (3H, d, *J* = 6.9 Hz, C_{20}-CH_3), 1.17 (3H, d, *J* = 6.9 Hz, C_{12}-CH_3), 1.15 (3H, d, *J* = 6.5 Hz, C_{22}-CH_3), 1.13 (3H, d, *J* = 6.6 Hz, C_{14}-CH_3), 1.12 (3H, d, *J* = 6.9 Hz, C_4-CH_3), 1.09 (9H, s, $SiC(CH_3)_3$), 1.05 (9H, s, $SiC(CH_3)_3$), 1.00 (9H, s, $Si(CH_3)_3$), 0.97 (3H, d, *J* = 6.1 Hz, C_6-CH_3), 0.94 (3H, d, *J* = 7.3 Hz, C_{20}-CH_3), 0.21 (3H, s, $SiCH_3$), 0.19 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$), 0.15 (6H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 159.5 (2C), 151.8, 137.3, 134.7, 134.1, 132.8, 132.5, 132.1, 131.6, 131.3, 130.8, 129.4, 129.3, 128.3, 127.3, 125.8, 117.7, 113.9 (2C), 84.6, 80.9, 79.1, 77.6, 75.1, 72.2, 71.2, 65.9 (2C), 54.6 (2C), 44.1, 41.3, 40.4, 37.5, 37.1, 36.6, 36.5, 35.6, 35.5, 26.4, 26.3, 26.1, 23.1, 18.7, 18.6, 18.5, 18.2, 17.7, 17.5, 14.7, 14.2, 11.1, 1.2, –3.1, –3.2, –3.9 (2C), –4.3; **HRMS** (ES$^+$) Calcd for $C_{68}H_{118}O_9Si_3Na$ $[M+Na]^+$ 1185.7976 found 11858.7975.



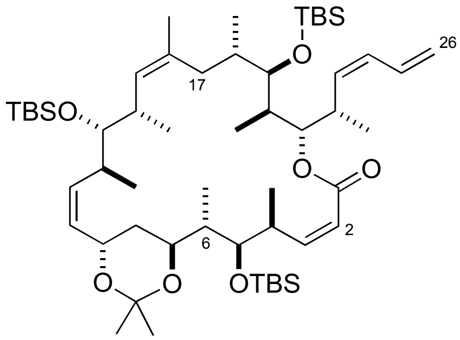
Acetonide **14**: ***R**$_f$* 0.53 (10% EtOAc / hexane); **[α]$_D^{20}$** +35.8 (*c* = 0.15, $CHCl_3$); **IR** (Thin film) ν_{max} = 2956 (s), 2929 (s), 2857 (s), 1726 (w), 1613 (m), 1514 (s), 1462 (s); **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.31 (2H, d, *J* = 8.5 Hz, ArH), 7.29)2H, d, *J* = 8.9 Hz, ArH), 6.85 (2H, d, *J* = 8.4 Hz, ArH), 6.82 (2H, d, *J* = 8.4 Hz, ArH), 6.71 (1H, *app* dt, *J* = 16.8, 10.6 Hz, C_{25}-H), 6.11 (1H, *app* t, *J* = 11.0 Hz, C_{24}-H), 5.83 (1H, *app* t, *J* = 11.9 Hz, C_{11}-H), 5.72 – 5.66 (2H, m, C_2-H + C_{23}-H), 5.63 – 5.57 (2H, m, C_{10}-H + C_3-H), 5.26 (1H, d, *J* = 16.6 Hz, C_{26}-H_xH_y), 5.13 (1H, d, *J* = 10.0 Hz, C_{26}-H_xH_y), 5.09 (1H, d, *J* = 10.2 Hz, C_{15}-H), 4.73 (1H, *br app* q, *J* = 8.3 Hz, C_9-H), 4.59 and 4.54 (2H, AB system, *J* = 10.5 Hz, OCH_2Ar), 4.43 (2H, s, OCH_2Ar), 4.18 – 4.13 (2H, m, C_1-H_xH_y + C_1-H_xH_y), 4.03 (1H, *app* dt, *J* = 6.0, 9.3 Hz, C_7-H), 3.96 (1H, dd, *J* = 2.6, 10.0 Hz, C_5-H), 3.62 (1H, *app* t, *J* = 4.1 Hz, C_{19}-H), 3.38 – 3.34 (2H, m, C_{21}-H + C_{13}-H), 3.35 (3H, s, $ArOCH_3$), 3.32 (3H, s, $ArOCH_3$), 3.14 – 3.08 (1H, m, C_{22}-H), 2.92 – 2.84 (2H, m, C_{12}-H + C_4-H), 2.66 – 2.59 (1H, m, C_{14}-H), 2.26 (1H, *app* t, *J* = 10.5 Hz, C_{17}-H_xH_y), 2.04 – 2.00 (3H, m, C_6-H + C_{18}-H + C_{20}-H), 1.87 – 1.80 (2H, m, C_8-H_xH_y + C_{17}-H_xH_y), 1.75 – 1.69 (1H, C_8-H_xH_y), 1.72 (3H, s, C_{16}-CH_3), 1.47 (3H, s, $C(CH_3)$), 1.45 (3H, s, $C(CH_3)$), 1.25 (3H, d, *J* = 6.8 Hz, C_{18}-CH_3), 1.19 (3H, d, *J* = 7.0 Hz, C_4-CH_3), 1.15 (3H, d, *J* = 6.8 Hz, C_{22}-CH_3), 1.13 (3H, d, *J* = 6.4 Hz, C_{12}-CH_3), 1.10 (3H, d, *J* = 6.6 Hz, C_{14}-CH_3), 1.08 (9H, s, $SiC(CH_3)_3$), 1.04 (18H, s, 2 x $SiC(CH_3)_3$), 0.99 – 0.95 (6H, m, C_6-CH_3 + C_{20}-CH_3), 0.22 (3H, s, $Si(CH_3)$), 0.20 (3H, s, $Si(CH_3)$, 0.18 (3H, s, $Si(CH_3)$), 0.15 (6H, s, $Si(CH_3)_2$), 0.14 (3H, s, $Si(CH_3)$); **^{13}C NMR** (125 MHz, C_6D_6), δ = 159.7, 137.2, 135.9, 134.8, 132.6, 132.5, 131.6, 131.5, 131.3, 130.7, 129.6, 129.5, 129.4, 125.7, 117.9, 114.1 (2C), 100.3, 84.8, 81.5, 78.0, 75.9, 75.5, 72.3, 67.9, 66.4, 63.5, 54.8 (2C), 46.7, 40.6, 38.8, 38.0, 37.3, 36.7, 35.9, 35.8, 35.7, 26.6, 26.5, 26.4, 25.8, 25.4, 23.2, 19.1, 19.0, 18.9, 18.7, 18.5, 18.4, 15.3, 11.0, 10.6, -2.8, -3.0, -3.1, -3.4, -3.7, -4.1; **HRMS** (ES^+) Calcd for $C_{71}H_{122}O_9Si_3Na$ $[M+Na]^+$ 1225.8289 found 1225.8245.



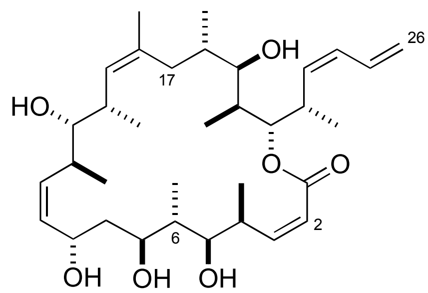
Alcohol **12**: ***R**$_f$* 0.20 (20% EtOAc / hexane); **[α]$_D^{20}$** +18.4 (*c* = 0.13, $CHCl_3$); **IR** (Thin film) ν_{max} = 3418 (*br* w), 2957 (s), 2930 (s), 2856 (s), 1729 (m), 1515 (m), 1462 (s), 1376 (s); **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.65 (1H, *app* dt, *J* = 16.9 , 10.9 Hz, C_{25}-H), 6.06 (1H, *app* t, *J* = 10.9 Hz, C_{24}-H), 5.91 (1H, *app* t, *J* = 10.4 Hz, C_{11}-H), 5.65 (1H, dd, *J* = 8.0, 10.9 Hz, C_{10}-H), 5.57 (1H, *app* dt, *J* = 11.0, 6.9 Hz, C_2-H), 5.43 (1H, *app* t, *J* = 10.4 Hz, C_3-H), 5.21 (1H, *app* t, *J* = 10.5 Hz, C_{23}-H), 5.17 (1H, d, *J* = 17.6 Hz, C_{26}-H_xH_y), 5.12 (1H, d, *J* = 10.1 Hz, C_{15}-H), 5.06 (1H, d, *J* = 10.2 Hz, C_{26}-H_xH_y), 4.75 (1H, *app* q, *J* = 7.5 Hz, C_9-H), 4.19 – 4.13 (2H, m, C_1-H_xH_y + C_7-H), 3.99 (1H, *br* dd, *J* = 5.8, 11.7 Hz, C_1-H_xH_y), 3.79 – 3.75 (2H, m, C_5-H + C_{19}-H), 3.38 – 3.34 (2H, C_{13}-H + C_{21}-H), 3.00 – 2.88 (2H, m, C_4-H + C_{12}-H), 2.84 – 2.79 (1H, m, C_{22}-H), 2.70 – 2.65 (1H, m, C_{14}-H), 2.44 (1H, *app* t, *J* = 12.4 Hz, C_{17}-H_xH_y), 2.13 – 2.06 (2H, m, C_{18}-H + C_6-H), 1.92 – 1.84 (3H, m, C_8-H_xH_y + C_{17}-H_xH_y + C_{20}-H), 1.83 – 1.82 (1H, m, C_8-H_xH_y), 1.80 (3H, s, C_{16}-CH_3), 1.51 (3H, s, C(CH_3)), 1.48 (3H, s, C(CH_3)), 1.20 (3H, d, *J* = 7.0 Hz, C_{12}-CH_3), 1.14 (3H, d, *J* = 6.7 Hz, C_{14}-CH_3), 1.12 (3H, d, *J* = 6.9 Hz, C_{20}-CH_3), 1.08 (9H, s, SiC(CH_3)$_3$), 1.06 (3H, d, *J* = 7.0 Hz, C_4-CH_3), 1.041 (9H, s, SiC(CH_3)$_3$), 1.036 (9H, s, SiC(CH_3)$_3$), 1.01 (3H, d, *J* = 7.2 Hz, C_6-CH_3), 0.98 (3H, d, *J* = 6.7 Hz, C_{18}-CH_3), 0.87 (3H, d, *J* = 6.8 Hz, C_{22}-CH_3), 0.21 (3H, s, Si(CH_3)), 0.20 (3H, s, Si(CH_3)), 0.19 (3H, s, Si(CH_3)), 0.15 (3H, s, Si(CH_3)), 0.14 (3H, s, Si(CH_3)), 0.13 (3H, s, Si(CH_3)); **^{13}C NMR** (125 MHz, C_6D_6) δ = 136.9, 135.7, 134.7, 132.8, 132.5, 131.5, 131.3, 130.8, 118.5, 100.5, 81.5, 79.1, 77.5, 76.0, 67.7, 63.7, 58.5, 44.8, 39.1, 38.2, 37.8, 37.7, 37.3, 36.6, 36.0, 35.1, 26.6, 26.5, 26.4, 25.6, 25.4, 23.4, 19.5, 18.8 (2C), 18.5, 17.3, 14.2, 14.0, 11.8, 10.0, -3.0, -3.1 (2C), -3.4, -3.5, -3.8; **HRMS** (ES^+) Calcd for $C_{55}H_{106}O_9Si_3Na$ $[M+Na]^+$ 985.7139 found 985.7126.



Seco-acid **13**: ***R****f* 0.42 (20% EtOAc / hexane); **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.60 (1H, *app* dt, *J* = 16.6, 10.5 Hz, C_{25}-H), 6.11 (1H, dd, *J* = 10.2, 11.4 Hz, C_3-H), 6.06 (1H, *app* t, *J* = 10.2 Hz, C_{11}-H), 6.02 (1H, *app* t, *J* = 10.5 Hz, C_{24}-H), 5.82 (1H, d, *J* = 11.5 Hz, C_2-H), 5.70 (1H, dd, *J*, = 8.2, 10.7 Hz, C_{10}-H), 5.16 (1H, dd, *J* = 0.9, 16.7 Hz, C_{26}-H_xH_y), 5.09 – 5.03 (3H, m, C_{15}-H + C_{23}-H + C_{26}-H_xH_y), 4.68 (1H, *br app* q, *J* = 8.3 Hz, C_9-H), 4.32 (1H, *app* dt, *J* = 9.5, 5.9 Hz, C_7-H), 3.96 (1H, dd, *J* = 3.5, 7.4 Hz, C_5-H), 3.88 – 3.84 (2H, m, C_4-H + C_{19}-H), 3.43 (1H, *br* dd, *J* = 1.2, 5.1 Hz, C_{21}-H), 3.30 (1H, dd, *J* = 1.3, 8.6 Hz, C_{13}-H), 2.92 (1H, *br app* quin., *J* = 7.0 Hz, C_{12}-H), 2.82 – 2.75 (1H, m, C_{22}-H), 2.66 – 2.58 (1H, m, C_{14}-H), 2.53 (1H, t, *app* t, *J* = 12.4 Hz, C_{17}-H_xH_y), 2.18 (1H, *app* sex., *J* = 6.8 Hz, C_6-H), 2.14 – 2.09 (1H, m, C_{18}-H), 2.02 – 1.90 (2H, m, C_8-H_xH_y + C_{20}-H), 1.85 (3H, s, C_{16}-CH_3), 1.83 – 1.76 (2H, m, C_8-H_xH_y + C_{17}-H_xH_y), 1.52 (3H, s, C(CH_3)), 1.49 (3H, s, C(CH_3)), 1.21 (3H, d, *J* = 7.0 Hz, C_{12}-CH_3), 1.20 (3H, d, *J* = 6.9 Hz, C_6-CH_3), 1.15 (3H, d, *J* = 7.9 Hz, C_{14}-CH_3), 1.12 (3H, d, *J* = 6.9 Hz, C_{20}-CH_3), 1.10 (9H, s, SiC(CH_3)$_3$), 1.05 (9H, SiC(CH_3)$_3$), 1.03 (3H, d, *J* = 7.8 Hz, C_4-CH_3), 1.01 (9H, s, SiC(CH_3)$_3$), 0.96 (3H, d, *J* = 6.6 Hz, C_{18}-CH_3), 0.78 (3H, d, *J* = 6.6 Hz, C_{22}-CH_3), 0.26 (3H, s, Si(CH_3)), 0.23 (3H, s, Si(CH_3)), 0.20 (3H, s, Si(CH_3)), 0.14 (3H, s, Si(CH_3)), 0.13 (3H, s, Si(CH_3)), 0.06 (3H, s, Si(CH_3)); **^{13}C NMR** (125 MHz, C_6D_6) δ = 170.0, 168.1, 156.4, 135.2, 134.1, 133.1, 132.2, 131.7, 131.2, 130.8, 127.5, 118.9, 100.4, 81.7, 78.8, 76.7, 76.4, 66.6, 63.5, 60.0, 43.8, 38.8, 38.3, 37.8, 37.1, 36.3, 35.3, 34.6, 34.3, 30.2, 26.6, 26.5, 26.4, 25.4 (2C), 23.2, 20.5, 20.4, 19.6, 18.9, 18.8, 18.7, 16.9, 14.2, 14.0, 13.0, 10.2, 9.9, 1.4, -2.7, -2.9, -3.1, -3.4, -3.6; **HRMS** (ES^+) Calcd for $C_{55}H_{104}O_8Si_3Na$ $[M+Na]^+$ 999.6931 found 999.6934.



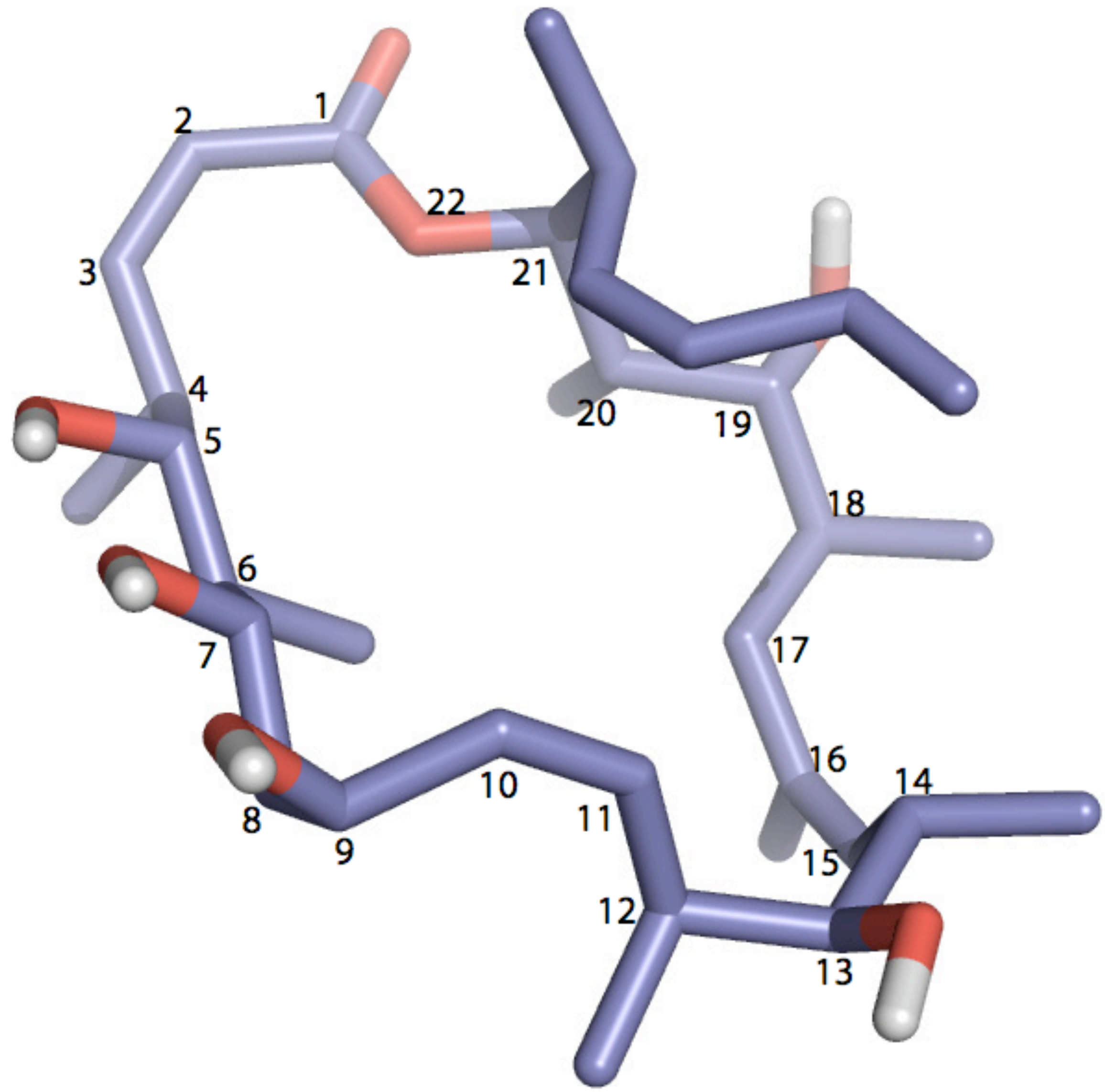
Macrocycle **15**: $\boldsymbol{R_f}$ 0.32 (5% EtOAc / hexane); $[\boldsymbol{\alpha}]_D^{20}$ +40.9 (*c* = 0.11, $CHCl_3$); **IR** (Thin film) ν_{max} = 2959 (s), 2928 (s), 2857 (s), 1721 (s, C=O), 1462 (s), 1380 (m); **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.67 (1H, *app* dt, *J* = 16.8 , 10.6 Hz, C_{25}-$\underline{H}$), 6.13 (1H, *app* t, *J* = 12.0 Hz, C_3-$\underline{H}$), 6.11 (1H, *app* t, *J* = 10.7 Hz, C_{11}-$\underline{H}$), 5.93 (1H, *app* t, *J* = 11.3 Hz, C_{24}-$\underline{H}$), 5.72 (1H, d, *J* = 11.4 Hz, C_2-$\underline{H}$), 5.68 (1H, *app* t, *J* = 10.3 Hz, C_{10}-$\underline{H}$), 5.13 – 5.05 (4H, m, C_{21}-$\underline{H}$ + C_{23}-$\underline{H}$ + C_{26}-$\underline{H}_xH_y$ + C_{26}-$H_x\underline{H}_y$), 4.99 (1H, d, *J* = 9.3 Hz, C_{15}-$\underline{H}$), 4.72 (1H, *br* q, *J* = 9.2 Hz, C_9-$\underline{H}$), 4.51 – 4.45 (1H, m, C_7-$\underline{H}$), 4.02 (1H, *app* quin, *J* = 7.6 Hz, C_4-$\underline{H}$), 3.75 (1H, d, *J* = 10.0 Hz, C_5-$\underline{H}$), 3.39 (1H, d, *J* = 10.2 Hz, C_{19}-$\underline{H}$), 3.28 (1H, d, *J* = 9.1 Hz, C_{13}-$\underline{H}$), 3.00 – 2.92 (2H, m, C_{12}-$\underline{H}$ + C_{22}-$\underline{H}$), 2.69 (1H, *app* t, *J* = 13.0 Hz, C_{17}-$\underline{H}_xH_y$), 2.66 – 2.52 (2H, m, C_{14}-$\underline{H}$ + C_{18}-$\underline{H}$), 2.30 – 2.25 (1H, m, C_6-$\underline{H}$), 2.15 – 2.09 (1H, m, C_{20}-$\underline{H}$), 1.99 – 1.94 (1H, m, C_8-$\underline{H}_xH_y$), 1.97 (3H, s, C_{16}-$C\underline{H}_3$), 1.79 (1H, d, *J* = 12.5 Hz, C_{17}-$H_x\underline{H}_y$), 1.71 – 1.66 (1H, m, C_8-$H_x\underline{H}_y$), 1.50 (3H, s, $C(C\underline{H}_3)$), 1.49 (3H, s, $C(C\underline{H}_3)$), 1.29 (3H, d, *J* = 6.8 Hz, C_6-$C\underline{H}_3$), 1.17 (3H, d, *J* = 7.3 Hz, C_{12}-$C\underline{H}_3$), 1.14 (3H, d, *J* = 6.9 Hz, C_{14}-$C\underline{H}_3$), 1.13 – 1.10 (3H + 9H, m, C_{20}-$C\underline{H}_3$ + $SiC(C\underline{H}_3)_3$), 1.04 (9H, s, $SiC(C\underline{H}_3)_3$), 1.01 (9H, s, $SiC(C\underline{H}_3)_3$), 0.97 (3H, d, *J* = 6.7 Hz, C_{18}-$C\underline{H}_3$), 0.92 (3H, d, *J* = 6.6 Hz, C_4-$C\underline{H}_3$), 0.75 (3H, d, *J* = 6.5 Hz, C_{22}-$C\underline{H}_3$), 0.27 (3H, s, $Si(C\underline{H}_3)$), 0.26 (3H, s, $Si(C\underline{H}_3)$), 0.18 (3H, s, $Si(C\underline{H}_3)$), 0.12 (3H, s, $Si(C\underline{H}_3)$), 0.10 (3H, s, $Si(C\underline{H}_3)$), 0.04 (3H, s, $Si(C\underline{H}_3)$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 165.5, 159.0, 134.8, 133.5, 132.9, 131.6, 131.5, 130.5, 130.3, 127.5, 125.8, 119.0, 117.8, 100.6, 81.4, 78.0, 77.8, 76.1, 65.8, 63.7, 60.0, 41.8, 39.3, 38.8, 38.1, 36.2, 34.8, 34.6, 34.3, 32.6, 32.4, 30.4, 26.5 (2C), 26.4, 25.3, 24.9, 22.7, 22.6, 21.3, 20.2, 18.9, 18.8, 17.0, 14.2, 11.4, 10.9, 10.7, 10.0, -2.2, -2.4, -2.7, -2.9, -3.0, -3.1; **HRMS** (ES^+) Calcd for $C_{55}H_{102}O_7Si_3Na$ $[M+Na]^+$ 981.6826, found 981.6866.



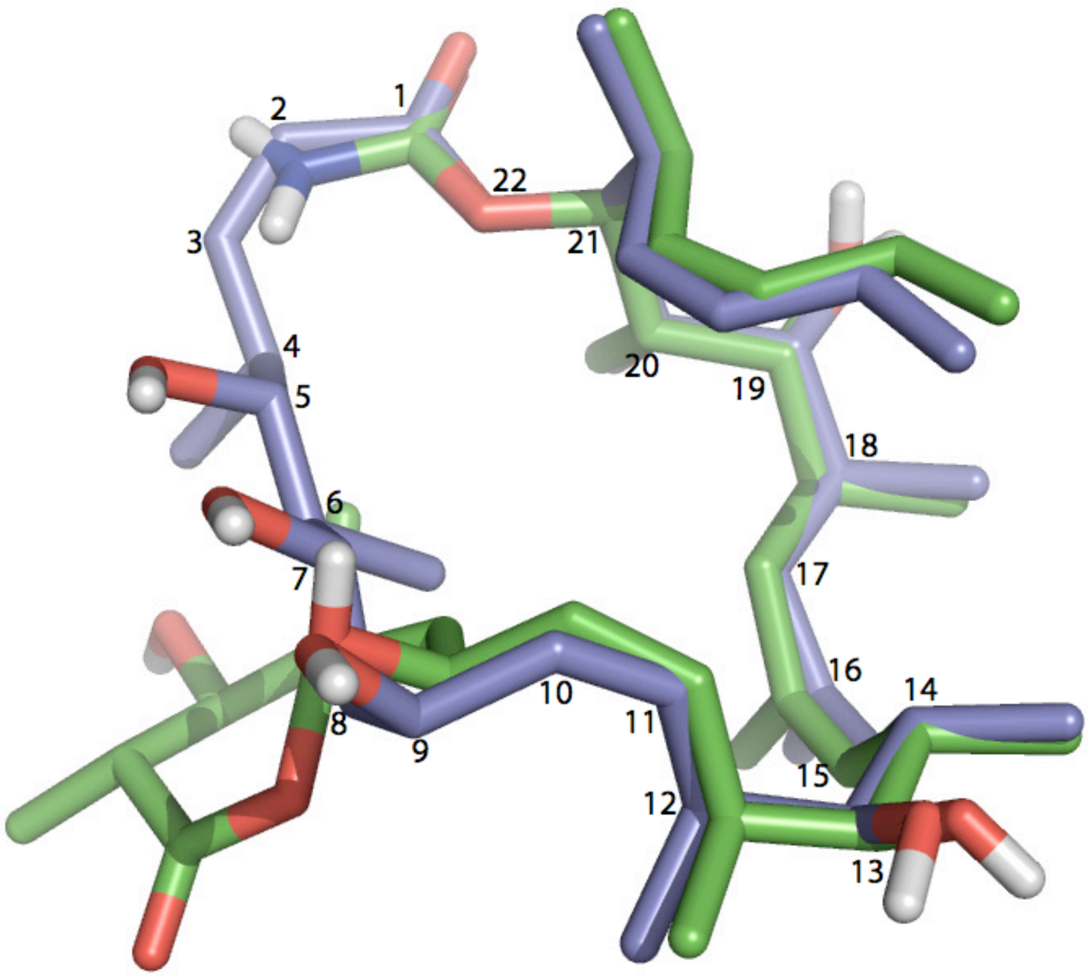
Macrocyclic Discodermolide **3**: ***R*$_f$** 0.39 (100% EtOAc); **R$_t$** 28 min (10% IPA / hexane); **[α]$_D^{20}$** +71.6 (*c* = 0.27); **IR** (Thin film) v_{max} = 3385 (*br*, s, OH), 2963 (s), 2929 (s), 2873 (s), 1713 (s, C=O), 1640 (m), 1454 (s), 1413 (m), 1379 (m); **^{1}H NMR** (700 MHz, CD_3OD) δ = 6.62 (1H, *app* dt, *J* = 17.0, 10.6 Hz, C_{25}-$\underline{H}$), 6.08 (1H, *app* t, *J* = 10.9 Hz, C_3-$\underline{H}$), 5.98 (1H, *app* t, *J* = 10.9 Hz, C_{24}-$\underline{H}$), 5.65 (1H, d, *J* = 11.8 Hz, C_2-$\underline{H}$), 5.57 (1H, dd, *J* = 9.0, 10.9 Hz, C_{11}-$\underline{H}$), 5.30 (1H, *app* t, *J* = 10.1 Hz, C_{10}-$\underline{H}$), 5.19 (1H, *br app* t, *J* = 9.0 Hz, C_{23}-$\underline{H}$), 5.16 (1H, d, *J* = 17.0 Hz, C_{26}-$\underline{H}_xH_y$), 5.08 (1H, d, *J* = 10.1 Hz, C_{26}-$H_x\underline{H}_y$), 4.88 (1H, *br* d, *J* = 4.9 Hz, C_{21}-$\underline{H}$), 4.83 (1H, d, *J* = 10.2 Hz, C_{15}-$\underline{H}$), 4.50 (1H, *br* d, *J* = 8.3 Hz, C_9-$\underline{H}$), 4.12 (1H, *br* dd, *J* = 3.9, 9.7 Hz, C_7-$\underline{H}$), 3.55 (1H, *br* s, C_4-$\underline{H}$), 3.37 – 3.32 (1H, m, C_5-$\underline{H}$), 3.07 – 3.02 (2H, m, C_{13}-$\underline{H}$ + C_{22}-$\underline{H}$), 2.98 (1H, *br* s, C_{19}-$\underline{H}$), 2.56 (1H, *app* quin., *J* = 7.7 Hz, C_{12}-$\underline{H}$), 2.40 – 2.35 (1H, m, C_{14}-$\underline{H}$), 2.32 (1H, *br* s, C_{17}-$\underline{H}_xH_y$), 2.11 (1H, *br* s, C_{18}-$\underline{H}$), 1.96 – 1.91 (1H, m, C_{20}-$\underline{H}$), 1.78 (1H, *app* sex., *J* = 7.2 Hz, C_6-$\underline{H}$), 1.65 (3H, s, C_{16}-$C\underline{H}_3$), 1.53 (1H, d, *J* = 12.6 Hz, C_{17}-$H_x\underline{H}_y$), 1.36 (1H, ddd, *J* = 2.6, 11.4, 13.8 Hz, C_8-$\underline{H}_xH_y$), 1.24 (1H, dd, *J* = 2.9, 10.7 Hz, C_8-$H_x\underline{H}_y$), 1.05 (3H, d, *J* = 7.2 Hz, C_{12}-$C\underline{H}_3$), 0.97 (3H, d, *J* = 6.8 Hz, C_{20}-$C\underline{H}_3$), 0.95 (3H, d, *J* = 6.8 Hz, C_4-$C\underline{H}_3$), 0.93 (3H, d, *J* = 6.8 Hz, C_{14}-$C\underline{H}_3$), 0.91 (3H, d, *J* = 6.8 Hz, C_{22}-$C\underline{H}_3$), 0.84 (3H, d, *J* = 7.0 Hz, C_6-$C\underline{H}_3$), 0.64 (3H, d, *J* = 6.3 Hz, C_{18}-$C\underline{H}_3$); **^{13}C NMR** (175 MHz, CD_3OD) δ = 173.0 (C_1), 167.6 (C_{16}), 135.3 (C_{10}), 134.5 (C_{23}), 133.6 (C_{25}), 131.4 (C_{24}), 131.3 (C_{15}), 131.0 (C_{11}), 119.6 (C_2), 118.4 (C_{26}), 80.8 (C_{13}), 78.6 (C_5), 78.1 (C_{21}), 77.0 (C_{19}), 68.2 (C_7), 65.1 (C_9), 43.4 (C_6), 38.6 (C_{17}), 38.4 (C_8), 38.3 (C_{14} + C_{20}), 37.2 (C_4), 35.8 (C_{12}), 35.5 (C_{22}), 32.8 (C_{18}), 23.2 (C_{16}-$\underline{C}H_3$), 19.9 (C_{12}-$\underline{C}H_3$), 19.3 (C_{22}-$\underline{C}H_3$), 17.8 (C_{14}-$\underline{C}H_3$), 12.8 (C_4-$\underline{C}H_3$), 12.0 (C_6-$\underline{C}H_3$), 11.7 (C_{18}-$\underline{C}H_3$), 10.1 (C_{20}-$\underline{C}H_3$); **HRMS** (ES^+) Calcd for $C_{34}H_{56}O_7Na$ $[M+Na]^+$ 599.3918, found 599.3923.

Molecular Modelling

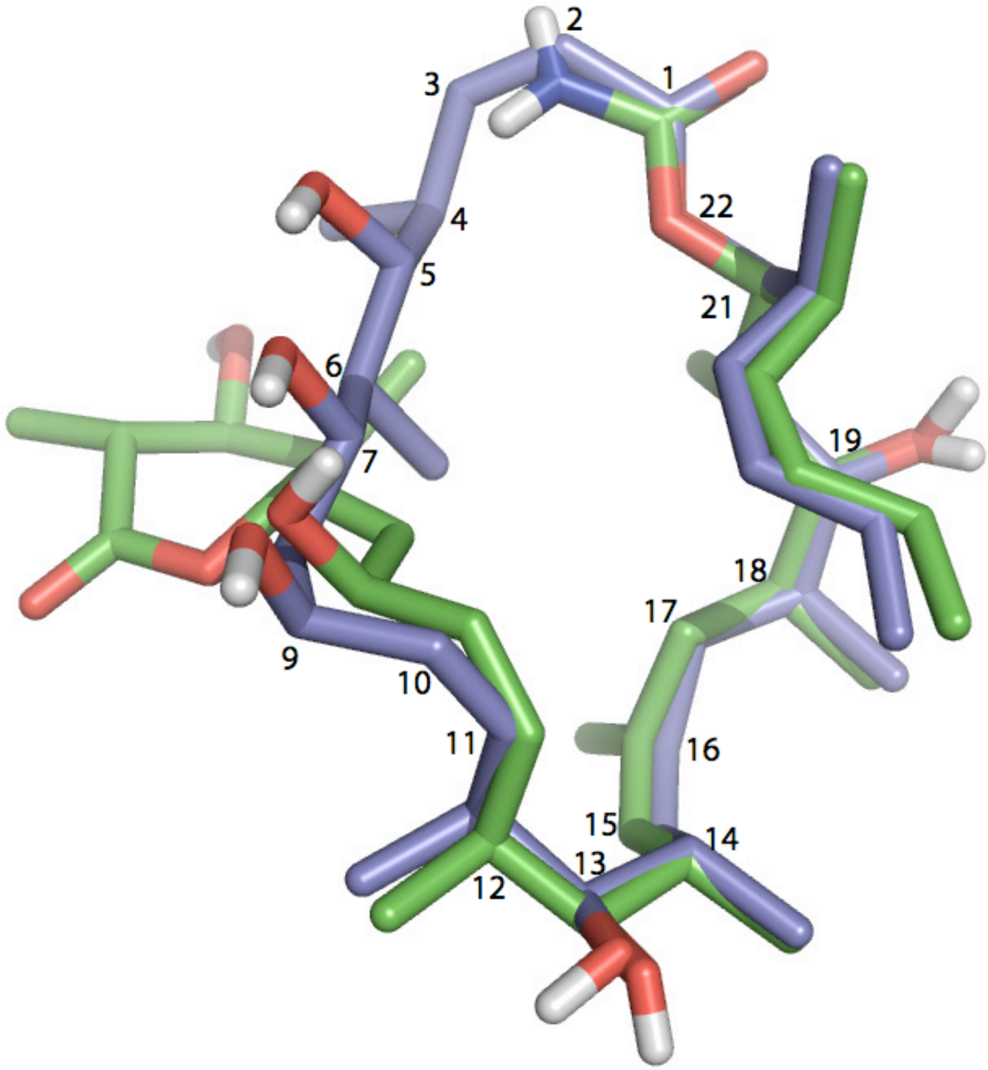
The following low energy structures were obtained using Macromodel (Version 8.0),[a] a 10,000 step Monte Carlo conformational search, with the MM2* force field and a Born/surface area (GB/SA) water solvent model.[b]



Hybrid **3** global minimum structure.



Overlay of the global minimum energy of hybrid **3** with the X-ray structure of discodermolide **1**.



Alternative view of overlay of the global minimum energy of hybrid **3** and the X-ray structure of discodermolide **1**.

Comparison of experimental and molecular modelling predicted $^3J_{H,H}$ coupling constants. $^3J_{H,H}$ coupling constants were calculated using the modified form of the Karplus equation by Altana *et al.*[c] Boltzmann average values were then calculated from all conformations at 298K.

Proton Number	Experimental/Hz		Predicted/Hz
13-14	**10.1**		8.8
17up-18	**small**	(small)	3.2
17down-18	**12.6**		12.3
18-19	**2.9**		3.3
19-20	**8.8**		9.9
20-21	**3.2**		2.6
21-22	**7.8**		11.4
4--5	**4.2**		4.1
5--6	**8.3**		9.4
6--7	**5.7**		3.8
7--8up	**11**		11.7
7--8down	**2.2**		2.6
8up--9	**10.6**		4.6
8down--9	**small**	(small)	2.0
12--13	**small**	(small)	2.0
Average Error /ppm			**1.77** **(assuming small J values are ~ 2Hz)**

[a]F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.

[b] W. C. Still, A. Tempczyk, R. C. Hawley and T. Hendrickson, *J. Am. Chem. Soc.*, 1990, **112**, 6127.

[c] C. A. G. Haasnoot, F. A. M. De Leeuw and C. Altona, *Tetrahedron*, 1980, **36**, 2783.