Using Equilibrium Isotope Effects to Detect Intramolecular OH/OH Hydrogen Bonds: Structural and Solvent Effects

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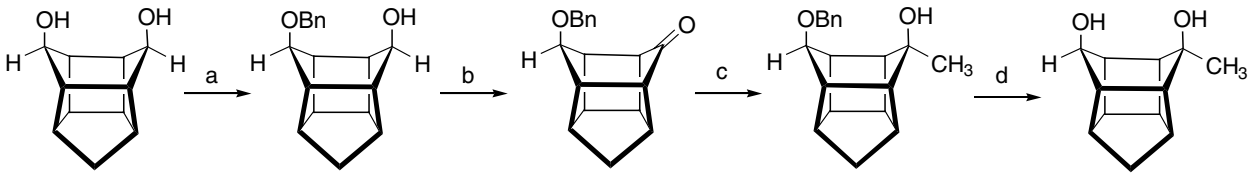
SUPPLEMENTARY MATERIAL

Preparation of alcohol **7** and diols **10**, **11**, and **13**



3 **7** **7a** **7b** **13**

(a) **Monobenzyl ether 7.** Cage diol **3** (750 mg, 4.2 mmol) was dissolved in a 2:1 mixture of THF and DMF (27 mL total) and cooled to 0 °C. NaH (300 mg of a 60% oil dispersion, 7.5 mmol) was added in portions. A catalytic amount of imidazole (10 mg) was added to the

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resulting suspension which was allowed to stir at 0 °C for an additional 30 minutes. Benzyl bromide (622 μL, 5.2 mmol) was added *via* syringe and the reaction was brought to room temperature and stirred for five hours. The reaction was again cooled to 0 °C and quenched by dilution with diethyl ether (50 mL) and slow addition of saturated aqueous ammonium chloride (50 mL). The organic layer was separated and washed with brine (50 mL). The aqueous phases were reextracted once with additional ether (50 mL). The combined organics were dried over magnesium sulfate, filtered, and evaporated. The residue was purified with silica gel flash chromatography (2.5 x 10 cm CH_2Cl_2 slurry pack, eluting with pure CH_2Cl_2 (100 mL) then with 30% EtOAc/ CH_2Cl_2) to yield a white solid, mp 78-80 °C (1.09 g, 96%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.00 ppm (1H, d, J = 11 Hz); 1.60 (1H, d, J = 11 Hz); 2.20-2.35 (3H, m); 2.40-2.55 (3H, m); 2.60 (1H, m); 2.75 (1H, m); 3.60 (1H, t, J = 4 Hz); 3.63 (1H, m); 4.51 (2H, s); 5.65 (1H, d, J = 12 Hz); 7.15-7.30 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 34.98 ppm, 36.09, 39.14, 39.77, 40.37, 43.16, 43.30, 43.37, 46.34, 72.41, 72.62, 79.67, 128.27 (2C), 128.39, 128.95 (2C), 137.51; IR (KBr pellet) ν 3366, 2955, 2861, 1481, 1114, 720 cm^{-1}; Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C,80.53; H, 7.68.

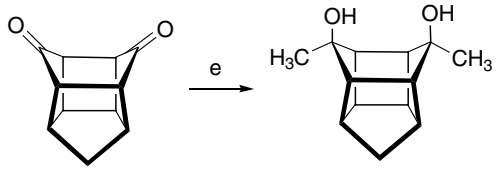
(b) **Monobenzyl ether ketone 7a:** Monobenzyl ether **7** (307 mg, 1.14 mmol) was dissolved in acetone (11 mL) and cooled to 0 °C. Jones reagent (650 μL of a 1.96 M aq. H_2CrO_4 solution) was added dropwise and the mixture was stirred at 0 °C for 4 hr. The flask contents were diluted with ethyl acetate (20 mL) and residual Cr(VI) was quenched with the addition of saturated aqueous sodium thiosulfate. The organic layer was washed with saturated sodium bicarbonate (20 mL) and brine (20 mL). The aqueous phases were reextracted once with ethyl acetate (30 mL). The organic phases were pooled and dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was purified with silica gel flash chromatography (2.5 x 5 cm CH_2Cl_2 slurry pack, eluting with 50% EtOAc/ CH_2Cl_2) to yield a white solid, mp 83-85 °C (274 mg, 90%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.45 ppm (1H, d, J = 11 Hz); 1.82 (1H, d, J = 11 Hz); 2.37 (1H, m); 2.47 (1H, m); 2.55 (2H, br. s); 2.80 (1H, br. s); 2.85 (1H, m); 3.03 (1H, m);

3.77 (1H, t, J = 4 Hz); 4.43 (2H, AB q, J = 12 Hz); 7.15-7.40 (5H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 36.96 ppm, 38.29, 40.40, 40.47, 40.95, 41.72, 44.24, 49.83, 51.18, 71.47, 78.10, 127.50, 127.64 (2C), 128.27 (2C), 137.92, 216.24; IR (KBr pellet) ν 2955, 2861, 1731, 1130, 697 cm^{-1}; Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C,81.19; H, 7.08.

(c) **Methyl Cage Monobenzyl Ether 7b:** Ketone **7a** (635 mg, 2.38 mmol) was dissolved in THF (20 mL) and cooled to 0 °C in a flask maintained under a nitrogen atmosphere. Methyl magnesium chloride (4.0 mL of a 3.0 M solution in THF, 12 mmol) was added dropwise via syringe. The flask was then moved to a 70 °C oil bath, fit with spiral coil condenser, and refluxed for 2 hr under a nitrogen atmosphere. The flask was then cooled in an ice bath and quenched by dilution with diethyl ether (50 mL), followed by slow addition of saturated aqueous ammonium chloride (50 mL). The aqueous phase was removed and reextracted with hexane (50 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil that was purified with silica gel flash chromatography (2.5 x 10 cm CH_2Cl_2 slurry pack, eluting with pure CH_2Cl_2 (100 mL) then with 20-40% EtOAc/ CH_2Cl_2(80 mL each)) to yield an oil (658 mg, 98%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.08 ppm (1H, d, J = 11 Hz); 1.10 (3H, s); 1.57 (1H, d, J = 11 Hz); 2.05 (1H, m); 2.35 (1H, m); 2.40 (2H, br. s); 2.50 (3H, m); 2.80 (1H, m); 3.60 (1H, t, J = 3 Hz); 4.52 (2H, s); 6.5 (1H br. s); 7.20-7.40 (5H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.81 ppm, 34.27, 35.56, 37.91, 40.55, 43.02, 43.50, 43.92, 44.27, 51.16, 71.95, 74.75, 79.13, 127.51 (2C), 127.71, 128.14, 128.31 (2C), 136.75; IR (film) ν 3371, 2962, 2861, 1148, 1069, 699 cm^{-1}; HRMS (EI, M+H$^+$) Calcd for $C_{19}H_{22}O_2$: 283.1698. Found: 283.1701.

(d) **Methyl Cage Diol 13:** Methyl cage monobenzyl ether **7b** (625 mg, 2.21 mmol) was dissolved in ethyl acetate (50 mL). Pd-C (20 mg) was added and the flask was fit with a balloon containing hydrogen gas. After 2.5 hr the suspension was filtered through a short plug of silica gel, rinsing with ethyl acetate. This solution was concentrated to an oil that was purified with silica gel flash chromatography (2.5 x 10 cm CH_2Cl_2 slurry pack, eluting with 50-70% EtOAc/

CH_2Cl_2(80 mL each)) to yield a white crystalline powder, mp 118-119 °C (402 mg, 95%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.09 ppm (1H, d, J = 11 Hz); 1.17 (3H, s); 1.61 (1H, d, J = 11 Hz); 2.10 (1H, m); 2.32 (1H, m); 2.39-2.45 (3H, m); 2.55 (2H, sept.); 2.67 (1H, m); 3.81 (1H, t, J = 3 Hz); 5.59 (2H, br. s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 27.96 ppm, 34.73, 38.82, 39.01, 41.06, 43.75, 44.07, 44.97, 46.89, 51.20, 72.10, 76.43; IR (10 mM CH_2Cl_2) ν 3587, 3364, 3058, 2965, 1250, 1125 cm^{-1}; HRMS (EI, M^+) Calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1152.



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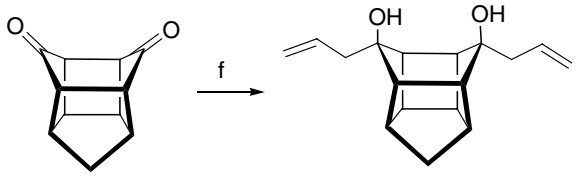
(e) Dimethyl cage diol **10**. Pentacyclo[5.4.0.0^{2,6}.0.^{3,10}.0^{5,9}]undecane-8,11-dione (Aldrich, 1.53 g, 8.78 mmol) was dissolved in methyl magnesium bromide (20 mL of a 3.0 M solution in diethyl ether, 60 mmol, 6.8 equiv.) with stirring at room temperature. The flask was then moved to a 70 °C oil bath, fit with spiral coil condenser, and refluxed for 3 hr under a nitrogen atmosphere. The flask was then cooled in an ice bath and quenched by dilution with diethyl ether (50 mL), followed by slow addition of saturated aqueous ammonium chloride (50 mL). The aqueous phase was removed and reextracted with diethyl ether (50 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil that was purified with silica gel flash chromatography (5 x 10 cm, 10% EtOAc/CH_2Cl_2 slurry pack, eluting with 10% EtOAc/CH_2Cl_2 (200 mL), 25% EtOAc/CH_2Cl_2 (200 mL), 50% EtOAc/CH_2Cl_2 (200 mL), 50% EtOAc/$CHCl_3$ (200 mL), and finally, 20/40/40% MeOH/EtOAc/$CHCl_3$ (200 mL). The fractions containing product were evaporated to yield a white powder, mp 111-114 °C (1.39 g, 76%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.02 ppm (1H, dt, J = 10.5 Hz, J = 1.8 Hz); 1.04 (3H, s); 1.48 (1H, dt, J = 10.5 Hz, J = 1.5 Hz); 1.96 (2H, br t, J = 2.3 Hz); 2.27 (2H, m); 2.33 (2H, m); 2.45 (2H, m); 6.89 (2H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 28.72 ppm, 34.50, 39.84, 44.53,

45.11, 52.70, 75.37; IR (KBr disk) ν 3102 (br), 2968, 2862, 1170 cm^{-1}; HRMS (EI+) Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1306.



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(f) Diallyl cage diol **11**. Pentacyclo[5.4.0.$0^{2,6}$.0.^{3,10}.$0^{5,9}$]undecane-8,11-dione (Aldrich, 3.3 g, 18.9 mmol) was dissolved in allyl magnesium bromide (76 mL of a 1.0 M solution in diethyl ether, 76 mmol) with stirring at room temperature. The flask was then moved to a 40 °C oil bath, fit with spiral coil condenser, and refluxed for 2 hr under a nitrogen atmosphere. The flask was then cooled in an ice bath and quenched by dilution with diethyl ether (200 mL), followed by slow addition of saturated aqueous ammonium chloride (200 mL). The aqueous phase was removed and re-extracted with diethyl ether (2 x 50 mL). The combined organics were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil that was purified with silica gel flash chromatography (5 x 20 cm, 10% hexane slurry pack, eluting with 25% EtOAc/hexane (360 mL) and then 33% EtOAc/hexane (400 mL). The fractions containing product were evaporated to yield a white powder, mp 70-71 °C (3.6 g, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.14 ppm (1H, dt, J = 11 Hz, J = 1.8 Hz); 1.58 (1H, dt, J = 11 Hz, J = 1.8 Hz); 2.14-2.24 (6H, m); 2.44-2.46 (2H, m); 2.49-2.50 (2H, m); 2.57-2.61 (2H, m); 5.10 (2H, br. s); 5.12-5.21 (4H, m); 5.91-6.01 (2H, m); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 34.34 ppm, 40.37 (2C), 43.23 (2C), 44.46 (2C), 44.49 (2C), 49.59 (2C), 77.71 (2C), 118.25 (2C), 134.22 (2C); IR (KBr disk) ν 3131 (br), 2957, 2862, 1640, 1479, 1283, 1159, 1051, 910 cm^{-1}; HRMS (EI, $M+H^+$) Calcd for $C_{17}H_{23}O_2$: 259.1698. Found: 259.1698.