An Experimental and Theoretical Study of a Bicyclic Acetal Equilibrium

Andrew P Dominey and Jonathan M Goodman*

*Department of Chemistry, Lensfield Road, Cambridge,
CB2 1EW, UK*

J.M.Goodman@ch.cam.ac.uk

Supporting Information

General Experimental Details

THF was distilled from Na/benzophenone ketyl. Hexane, CH_2Cl_2 and MeOH were distilled from CaH_2. Saturated NH_4Cl was diluted with aqueous ammonia to *ca.* pH 9 and all other reagents were used as received. All reactions were performed under argon in oven-dried glassware at room temperature, except where indicated. Organic extracts were dried with $MgSO_4$ and concentrated at reduced pressure. Flash column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh) and thin layer chromatography (TLC) was performed with Merck Kieselgel 60 F_{254} plates. Optical rotations were measured at ambient temperature and IR spectra were taken using thin films on NaCl plates.

(2*R*)-1,2-*O*-Isopropylidenehept-6-en-1,2,3-triols (5). To a stirred suspension of Mg turnings (2.3 g, 95 mmol) and a few crystals of I_2 in THF (15 cm^3) was added 4-bromobutene (4.5 cm^3, 6.0 g, 44 mmol) in THF (2 × 5 cm^3). Refluxing began spontaneously and the solution was cooled briefly in ice. The Grignard reagent was allowed to form at room temperature for 0.5 h, when the solution was cooled to *ca.* -10 °C (ice-acetone) and (*R*)-2,3-*O*-isopropylideneglyceraldehyde **4** (2.283 g, 17.54 mmol) was added carefully in THF (3 × 5 cm^3). The reaction was quenched after 3.5 h by the addition of aqueous NH_4Cl-NH_4OH (20 cm^3), which was extracted with ether. The combined organic extracts were washed with brine (2 × *ca.* 0.3 volume), dried, filtered and concentrated. Flash column chromatography (SiO_2, 1:2 EtOAc-hexane) gave the inseparable alcohols **5** (2.852 g, 87%). ***Syn*-5** (minor diastereomer) had R_f = 0.26 (1:2 EtOAc-hexane); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.79 (m, 1H), 5.06-4.92 (m, 2H), 4.02-3.84 (m, 3H), 3.48 (m, 1H), 2.37 (d, 1H, *J* = 5.0 Hz), 2.30-2.03 (m, 2H), 1.60-1.36 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.0, 115.0, 109.3, 79.1, 71.5, 66.1, 32.8, 29.6, 26.6, 25.2. ***Anti*-5** (major diastereomer) had R_f = 0.26 (1:2 EtOAc-hexane); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.80 (m, 1H), 5.01 (m, 2H), 4.03-3.85 (m, 3H), 3.75 (m, 1H), 2.34-2.08 (m, 2H), 2.21 (d, 1H, *J* = 3.6 Hz), 1.56-1.34 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.0, 115.1, 109.0, 78.6, 70.2, 64.7, 31.8, 29.9, 26.5, 25.3.

(4’*R*,5*S*)-5-[2,2-Dimethyl-(1,3)-dioxolan-4-yl]tetrahydrofuran-2-ols (6) and (4’*R*,5*R*)-5-[2,2-dimethyl-(1,3)-dioxolan-4-yl]tetrahydrofuran-2-ols (7). A solution of alkenes **5** (324 mg, 1.74 mmol) was ozonised at -78 °C in CH_2Cl_2 (*ca.* 10 cm^3). The reaction was quenched by the addition of PPh_3 (1.378 g, 5.25 mmol) and allowed to warm to room temperature. After 2.5 h, the solution was concentrated and flash column chromatography (SiO_2, 1:1 EtOAc-hexane) afforded *anti* and *syn* lactols **6** and **7** (*ca.* 2 : 1, 309 mg, 94%) as mixtures of anomers. **6** had R_f = 0.23 (1:1 EtOAc-hexane); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.54 (m, $1H_{[major]}$), 5.45 (m, $1H_{[minor]}$), 4.24-3.99 (m, 6H), 3.84-3.76 (m, 2H), 3.41 (d, 1H, *J* = 5.8 Hz), 3.06 (d, 1H, *J* = 2.2 Hz), 2.22-1.77 (m, 8H), 1.44 (s, $3H_{[major]}$), 1.41 (s, $3H_{[major]}$), 1.35 (s, $3H_{[minor]}$), 1.34 (s, $3H_{[minor]}$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 109.4, 98.8, 79.1, 77.2, 66.8, 32.5, 26.4, 25.2, 24.9 (major anomer), 109.6, 98.7, 80.6, 78.1, 67.0, 34.0, 26.5, 25.4, 25.0 (minor anomer). **7** had R_f = 0.17 (1:1 EtOAc-hexane); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.60 (br d, $1H_{[minor]}$, *J* = 3.2 Hz), 5.47 (br s, $1H_{[major]}$), 4.23-3.95 (m, 6H), 3.83-3.66 (m, 2H), 3.33 (br s, 1H), 3.01 (br s, 1H), 2.18-1.75 (m, 8H), 1.44 (s, $3H_{[major]}$), 1.42 (s, $3H_{[major]}$), 1.37 (s, $3H_{[minor]}$), 1.35 (s, $3H_{[minor]}$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 109.8, 98.7, 78.8, 78.2, 66.1, 34.1, 26.4, 25.4, 24.9 (major anomer), 109.8, 99.0, 79.7, 77.2, 66.0, 32.9, 26.4, 25.5, 24.9 (minor anomer).

(1*R*,2*S*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-2-ol (ent-1) and (1*R*,4*R*,5*S*)-2,8-dioxabicyclo[3.2.1]octan-4-ol (ent-2). Concentrated HCl (0.100 cm^3 of 31-33%, 0.9 mmol) was added to a solution of lactols **6** (112 mg, 0.60 mmol) in THF (5 cm^3). The reaction was quenched after 20.5 h by pouring into saturated aqueous $NaHCO_3$ (2 cm^3) and water (2 cm^3), which were extracted with EtOAc (12 × *ca.* 4 cm^3). The combined organic extracts were dried, filtered and concentrated to yield inseparable bicyclic acetals **ent-1** and **ent-2** (*ca.* 2 : 1, 166 mg, 85%). **ent-1** and **ent-2** had R_f = 0.23 (19:1 EtOAc-hexane); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.51 (s, $1H_{[\mathbf{8}]}$), 5.44 (d, $1H_{[\mathbf{9}]}$, *J* = 3.9 Hz), 4.44 (br s, $2H_{[\mathbf{8},\,\mathbf{9}]}$), 3.98-3.77 (m, $3H_{[\mathbf{8},\,\mathbf{9}],}$), 3.71-3.64 (m, $2H_{[\mathbf{8},\,\mathbf{9}]}$), 3.28 (s, $1H_{[\mathbf{9}]}$), 2.58 (d, 1H, *J* = 9.8 Hz), 2.18-1.56 (m, $8H_{[\mathbf{8},\,\mathbf{9}]}$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 101.8, 77.3, 67.0, 66.4, 27.5, 23.4 (**ent-1**), 99.9, 79.0, 68.0, 64.5, 28.3, 24.9 (**ent-2**).

Example procedure for bicyclic acetal equilibration. CF_3SO_3H in $CDCl_3$ (0.050 cm^3 of a 0.020 cm^3 in 1.00 cm^3 solution, 0.01 mmol) was added to a solution of bicyclic acetals **ent-1** and **ent-2** (14 mg, 0.1 mmol) in $CDCl_3$ (0.75 cm^3) and the reaction was monitored by ^1H NMR at intervals.

(1*R*,2*S*,5*R*)-2-Methoxy-6,8-dioxabicyclo[3.2.1]octane (8) and (1*R*,4*R*,5*S*)-4-methoxy-2,8-dioxabicyclo[3.2.1]octane (9). KH (437 mg of a 35 wt.% mineral oil dispersion, 3.81 mmol) was washed with hexane (3 × 1 cm^3) and rinsed with THF (1 cm^3). It was then suspended in THF (2 cm^3) and cooled to 0 °C, when bicyclic acetal mixture **ent-1** and **ent-2** (92 mg, 0.71 mmol) was added in THF (2 × 2 cm^3). The reaction was stirred for 0.5 h before MeI (0.220 cm^3, 3.54 mmol) was added. After 23 h, the reaction was poured into aqueous NH_4Cl-NH_4OH (6 cm^3), which was extracted with Et_2O (3 × *ca.* 4 cm^3), then EtOAc (3 × *ca.* 4 cm^3) and $CHCl_3$ (3 × *ca.* 4 cm^3). The combined organic extracts were dried, filtered, concentrated and flash column chromatography (SiO_2, 1:1 EtOAc-hexane) gave methylated bicyclic acetals **8** (27 mg, 26%) and **9** (15 mg, 15%). **8** had $R_f = 0.20$ (1:1 EtOAc-hexane); $[\alpha]_D$ -106.5 ($c = 2.00$, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.51 (s, 1H), 4.58 (br d, 1H, $J = 4.8$ Hz), 3.79 (m, 2H), 3.41 (s, 3H), 3.16 (br s, 1H), 1.90-1.73 (m, 3H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 101.7, 75.7, 74.2, 66.3, 56.4, 27.9, 19.8; HRMS (FAB) calcd. for $C_7H_{13}O_3$ 145.0865, found 145.0859 (MH^+). **9** had $R_f = 0.24$ (19:1 EtOAc-hexane); $[\alpha]_D$ +13.4 ($c = 0.85$, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.46 (d, 1H, $J = 4.2$ Hz), 4.58 (d, 1H, $J = 6.5$ Hz), 3.86 (m, 2H), 3.44 (s, 3H), 2.87 (s, 1H), 2.17-1.97 (m, 3H), 1.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 99.5, 76.8, 75.4, 60.5, 56.6, 28.5, 24.9; HRMS (EI) calcd. for $C_7H_{12}O_3$ 144.0786, found 144.0782 (M^+); m/z (rel. intensity) 144 (5, M^+), 85 (53), 58 (100).

(2*R*,3*S*)-1,2-*O*-Isopropylidene-3-methoxyhept-6-en-1,2-diol (10) and (2*R*,3*R*)-1,2-*O*-isopropylidene-3-methoxyhept-6-en-1,2-diol (11). KH (1.096 g of a 35 wt.% mineral oil dispersion, 9.56 mmol) was washed with hexane (2 × 3 cm^3) and rinsed with THF (3 cm^3). It was then suspended in THF (5 cm^3) and cooled to 0 °C. The inseparable alcohol mixture **5** (327 mg, 1.76 mmol) was added in THF (3 + 2 cm^3) and the mixture was left to stir for 0.5 h, when MeI (0.27 cm^3, 616 mg, 4.34 mmol) was added and the reaction was allowed to warm to room temperature. It was quenched after 22.5 h by pouring into aqueous NH_4Cl-NH_4OH (30 cm^3), which was extracted with Et_2O (3 × 10 cm^3). The combined organic extracts were washed with brine (2 × 15 cm^3), dried, filtered, concentrated and flash column chromatography (SiO_2, 1:9 EtOAc-hexane) afforded *anti* and *syn* methyl ethers **10** and **11** (*ca.* 2 : 1, 327 mg, 93%). **10** had R_f = 0.27 (1:7 EtOAc-hexane); $[\alpha]_D^{20}$ +9.6 (*c* = 1.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 5.81 (m, 1H), 5.07-4.93 (m, 2H), 4.02 (m, 2H), 3.84 (m, 1H), 3.41 (s, 3H), 3.25 (m, 1H), 2.16 (m, 2H), 1.58 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.4, 114.7, 109.0, 80.6, 77.5, 66.3, 58.6, 30.1, 29.1, 26.5, 25.3; IR 1641 cm^{-1} (w); HRMS (EI) calcd. for $C_{10}H_{17}O_3$ 185.1178, found 185.1182 (M^+ - Me); m/z (rel. intensity) 185 (35, M^+ - Me), 149 (66), 143 (100), 101 (49), 67 (64), 57 (73). **11** had R_f = 0.23 (1:7 EtOAc-hexane); $[\alpha]_D^{20}$ +28.2 (*c* = 2.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 5.76 (m, 1H), 5.04-4.91 (m, 2H), 4.11 (dd, 1H, *J* = 13.9, 6.6 Hz), 3.93 (dd, 1H, *J* = 8.1, 6.5 Hz), 3.61 (app t, 1H, *J* = 7.8 Hz), 3.43 (s, 3H), 3.17 (dd, 1H, *J* = 12.1, 6.3 Hz), 2.14 (m, 2H), 1.63-1.21 (m, 2H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.2, 114.9, 109.2, 81.2, 77.9, 65.8, 58.6, 29.7, 29.5, 26.5, 25.3; IR 1641 cm^{-1} (w); HRMS (CI) calcd. for $C_{10}H_{17}O_3$

185.1178, found 185.1184 (M^+ - Me); m/z (rel. intensity) 185 (8, M^+ - Me), 101 (37), 67 (33), 44 (100).

(2*R*,3*S*)-3-methoxyhept-6-en-1,2-diol (12). To a stirred solution of acetonide **10** (39 mg, 0.19 mmol) in MeOH (5 cm^3) was added a solution of HCl in Et_2O (0.010 cm^3 of 1.0 mol dm^{-3}, 10 μmol). Additional HCl in Et_2O solution (0.010 cm^3 of 1.0 mol dm^{-3}, 10 μmol) was added after 16.5 h and the reaction was heated to reflux. After a further 1.5 h, the reaction was concentrated to yield **12** (30 mg, 96%). R_f = 0.20 (4:1 EtOAc-hexane); $[\alpha]_D^{20}$ +15.8 (*c* = 2.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.79 (m, 1H), 5.06-4.93 (m, 2H), 3.72-3.63 (m, 3H), 3.53 (d, 1H, *J* = 4.1 Hz), 3.38-3.36 (m, 4H), 3.24 (m, 1H), 2.25-2.00 (m, 2H), 1.73-1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.2, 115.1, 82.1, 72.4, 63.4, 58.4, 29.4, 29.1; IR 3382 cm^{-1} (br), 1640 cm^{-1} (m); HRMS (FAB) calcd. for $C_8H_{17}O_3$ 161.1178, found 161.1192 (MH^+).

(1*R*,2*S*,5*R*)-2-Methoxy-6,8-dioxabicyclo[3.2.1]octane (8). A solution of diol **12** in CH_2Cl_2 (*ca.* 5 cm^3) was ozonised at -78 °C. The reaction was quenched by the addition of PPh_3 (206 mg, 0.79 mmol) and it was allowed to warm to room temperature. After 22 h, the solution was concentrated and flash column chromatography (SiO_2, 19:1 EtOAc-hexane) yielded an intermediate hemiacetal (24 mg). This product was dissolved directly in THF (5 cm^3) and a few 4 Å molecular sieves were added, together with a solution of HCl in Et_2O (1.2 cm^3 of 1.0 mol dm^{-3}, 1.2 mmol). After 24 h the reaction was filtered through celite and concentrated. Flash column chromatography (SiO_2, 1:1 EtOAc-hexane) gave bicyclic acetal **8** (13 mg, 50%), identical (*R*$_f$, ^{1}H NMR, ^{13}C NMR) with the sample prepared previously.

(2*R*,3*R*)-3-methoxyhept-6-en-1,2-diol (13). To a stirred solution of acetonide **11** (122 mg, 0.61 mmol) in MeOH (4 cm^3) was added a solution of HCl in Et_2O (2.0 cm^3 of 1.0 mol dm^{-3}, 2.0 mmol). After 6 h the reaction was concentrated and flash column chromatography (SiO_2, 19:1 EtOAc-hexane) afforded diol **13** (93 mg, 95%). R_f = 0.27 (19:1 EtOAc-hexane); $[\alpha]_D^{20}$ -17.5 (*c* = 2.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.78 (m, 1H), 5.05-4.92 (m, 2H), 3.66-3.60 (m, 3H), 3.38 (s, 3H), 3.24-3.20 (m, 1H), 3.10 (br d, 1H, *J* = 1.3 Hz), 2.51 (br s, 1H), 2.11 (m, 2H), 1.74-1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.1, 114.9, 81.1, 72.9, 63.9, 58.1, 29.3, 29.0; IR 3394 cm^{-1} (br), 1640 cm^{-1} (m); HRMS (CI) calcd. for $C_8H_{17}O_3$ 161.1178, found 161.1178 (MH^+); m/z (rel. intensity) 178 (69, M + H_3N^+), 161 (100, MH^+), 129 (39, M^+ - OMe), 99 (82, M^+ - $HOCHCH_2OH$).

(1*R*,2*R*,5*R*)-2-Methoxy-6,8-dioxabicyclo[3.2.1]octane (14). A solution of diol **13** in CH_2Cl_2 (*ca.* 10 cm^3) was ozonised at -78 °C. The reaction was quenched by the addition of PPh_3 (370 mg, 1.41 mmol) and allowed to warm to room temperature. After 17 h, the solution was concentrated, the crude was taken up in THF (5 cm^3) and a solution of HCl in Et_2O (1.0 cm^3 of 1.0 mol dm^{-3}, 1.0 mmol) was added. The reaction was concentrated after 16.75 h and flash column chromatography (SiO_2, 1:3 EtOAc-hexane) gave bicyclic acetal **14** (25 mg, 38%). R_f = 0.29 (1:4 EtOAc-hexane); $[\alpha]_D^{20}$ -66.1 (*c* = 1.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46 (s, 1H), 4.48 (br app t, 1H, *J* = 3.8 Hz), 4.10 (d, 1H, *J* = 7.4 Hz), 3.69 (dd, 1H, *J* = 7.1, 5.4 Hz), 3.49

(m, 1H), 3.36 (s, 3H), 1.97 (m, 1H), 1.74 (dd, 1H, *J* = 13.2, 6.0 Hz), 1.67-1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 100.8, 74.9, 73.5, 64.9, 56.2, 30.7, 22.4; HRMS (EI) calcd. for $C_7H_{12}O_3$ 144.0786, found 144.0788 (MH^+); m/z (rel. intensity) 144 (3, MH^+), 101 (100), 71 (40), 58 (95).