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Metal Hydride Reduction of Bicyclo[2.2.2]octan-2-ones. Preparation and Stereochemistry of 5-Substituted Bicyclo[2.2.2]octan-2-ols

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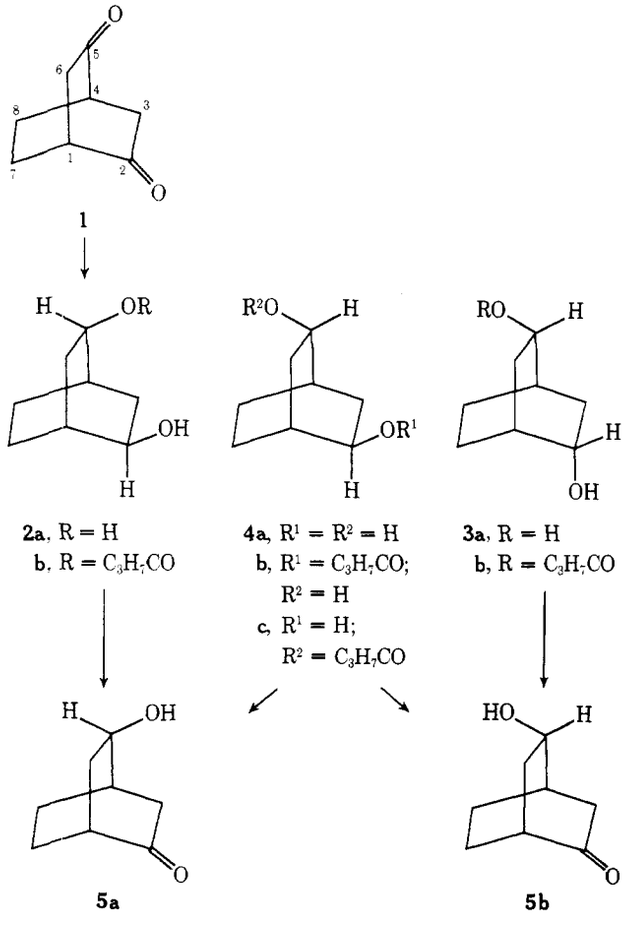
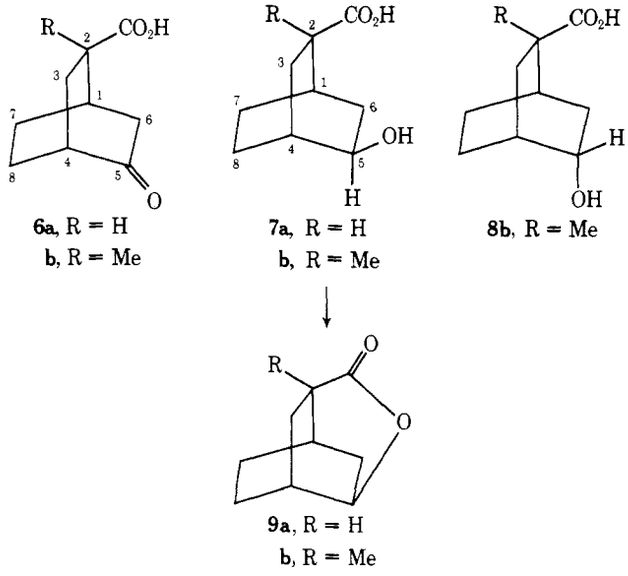
We have examined the metal hydride reduction of a number of 5-substituted bicyclo[2.2.2]octan-2-ones in order to prepare compounds of known relative geometry at the 2,5 position which were required as template molecules for enzyme mimetic studies. Bicyclo[2.2.2]octane-2,5-dione (**1**), prepared by a modification of the method of Guha and Krishnamurthy,[1] was treated with sodium borohydride at room temperature to give a mixture (70–80%) of diols. One isomer could be separated by thin layer chromatography on silica gel, but more satisfactory separation was achieved by either short path column chromatography on alumina[2] or high-pressure liquid chromatography on Porasil. The three diols **2a, 3a,** and **4a** were eluted in that order. The diol **4a** was readily recognized to have the syn-anti configuration of the OH groups, since on partial oxidation it gave two 5-hydroxybicyclo[2.2.2]octan-2-ones and partial esterification with butyryl chloride gave two monobutyrates. The other two isomers each gave a single, different 5-hydroxybicyclo[2.2.2]octan-2-one on oxidation, and each isomer also gave a single, different monobutyrate. The stereoisomers **2a** and **3a** were distinguished from the ^{13}C NMR spectra,[3] and by the ^1H NMR spectra of their respective monobutyrates, taken in the presence of $Eu(DPM)_3$.

The ^1H NMR spectrum of **2b** in $CDCl_3$ with 0.1 equiv of $Eu(DPM)_3$ showed the C-7, C-8 bridge protons appearing in the same region as the β-CH_2 protons of the *n*-butyryl group, these protons thus experiencing only a small downfield shift. By contrast, under the same conditions the C-7, C-8 bridge protons in **3b** were all shifted further downfield, the protons syn to the OH group being more deshielded than those syn to the ester group.[4] The chemical shift of the other protons in the spectra of **2b** and **3b** were also in accord with the stereochemical assignment.

Reduction of **1** with lithium aluminum hydride gave essentially the same composition of diols, but reduction with lithium tri-*tert*-butoxyaluminum hydride gave a mixture comprised almost exclusively of the isomers **3a** and **4a.**

In contrast, reduction of the keto acid **6a** with sodium borohydride gave only one isomer, the known syn alcohol **7a.**[5] However, when the 2-methyl derivative **6b** was reduced under the same conditions, besides the predominant syn isomer **7b,** some of the anti isomer **8b** was also obtained. The assigned stereochemistry of these isomers was confirmed by the conversion of **7a** and **7b** into the respective lactones **9a** and **9b.**





The lack of stereoselective control in the reduction of **1** suggests that there is little preference for the approach of the borohydride to the first ketone group.[6,7] The smaller amount of **2a** compared to **4a** may indicate that the formation of the OH syn to the second ketone group assists in directing the borohydride from that side of the molecule.[8] The syn carboxylic acid group of **6a** presumably shields the ketone function from attack on that side, allowing exclusive formation of **7a.** We suspect that the lower stereoselectivity found in the reduction of **6b** is caused by increased steric shielding from the C-7,8 bridge on the ketone owing to the interaction with the C-2 methyl group, which forces these carbons closer to the C-5,6 bridge.

Experimental Section

^1H NMR spectra ($CDCl_3$) were recorded on either a Varian T-60 or HA-100 spectrometer using Me_4Si as internal standard and are reported in δ units. ^{13}C NMR spectra ($CDCl_3$) were recorded on a

Varian CFT-20 spectrometer with Me_4Si as internal standard and are reported in parts per million. IR spectra were recorded on a Unicam SP-200 spectrophotometer. Mass spectra were taken on either an AEI-MS 9 or MS 12 spectrometer at 70 eV. Aluminium oxide for chromatography was Merck PF_{254} (type E) and Kieselgel was Merck (0.05–0.2 mesh).

Reduction of Bicyclo[2.2.2]octa-2,5-dione. The dione **1** (1.40 g, 10 mmol) was dissolved in ethanol (300 ml), the solution was stirred at room temperature, and sodium borohydride (2.85 g, 7.5 mmol) was added. After 3 h the clear solution was acidified with 20% HCl (100 ml) and then neutralized with Na_2CO_3. The solvent was removed by evaporation and the residual white solid was heated under reduced pressure whereupon a mixture of the diols (1.0 g) sublimed. The mixture was preadsorbed on Kieselgel (100 g), added to a column of Kieselgel (1000 g), and eluted with a mixture of $CHCl_3$–EtOH (9:1 v/v). Compound **2a** (100 mg) eluted first followed by a mixture of **3a** and **4a** (600 mg). The latter mixture was preadsorbed on alumina (15 g), added to a column of alumina (150 g), and eluted with $CHCl_3$–petroleum ether (9:1 v/v). Compound **3a** (300 mg) was eluted first followed by **4a** (150 mg).

Compound **2a:** mass spectrum *m/e* 142 (16%, M^+), 124 (66%, $M^+ - H_2O$); IR (KBr) 3320 (b), 2920, 2858, 1445, 1360 cm^{-1}; ^1H NMR δ 4.0 (m, 2 H), 2.2–1.0 (m, 12 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.85. Found: C, 67.76; H, 9.79.

Compound **3a:** mass spectrum *m/e* 142 (20%, M^+), 124 (40%, $M^+ - H_2O$); IR (KBr) 3280 (b), 2920, 2858, 1440, 1362 cm^{-1}; ^1H NMR δ 4.0 (m, 2 H), 2.2–1.0 (m, 12 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.85. Found: C, 67.70; H, 10.10.

Compound **4a:** mass spectrum *m/e* 142 (1%, M^+), 124 (100%, $M^+ - H_2O$); IR (KBr) 3280 (b), 2920, 2858, 1440, 1365 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.85. Found: C, 67.45; H, 10.09.

A more efficient separation of the mixture of the three diols could be effected by high-pressure liquid–liquid chromatography on Porasil (4.0 ft × 0.375 in.) using MeOH–$CHCl_3$ (3:97 v/v) as eluent. Under these conditions 1.0 g of the mixture gave 100 mg of **2a,** 300 mg of **3a,** and 400 mg of **4a.**

Esterification of 2a, 3a and 4a. The diol (100 mg, 0.7 mmol) was dissolved in dry THF (10 ml) and butyryl chloride (80 mg, 0.74 mmol) was added. The solution was stirred for ca 2 h, the reaction being monitored by TLC (SiO_2) and worked up when the diester was detected (R_f ~0.9, Et_2O). The solvent was removed under reduced pressure and the residue was extracted with ether. Removal of the ether gave an oil which on preparative TLC (SiO_2, Et_2O) gave the monoester (ca. 125 mg, 80%).

Compound **2b:** mass spectrum *m/e* 212 (1%, M^+), 194 (55%, $M^+ - H_2O$); ^1H NMR δ 5.0 (m, 1 H), 4.0 (m, 1 H), 2.6–0.8 (m, 17 H).

Compound **3b:** mass spectrum *m/e* 212 (2%, M^+), 194 (100%, $M^+ - H_2O$); ^1H NMR δ 5.0 (m, 1 H), 4.0 (m, 1 H), 3.0–1.0 (m, 17 H).

Compound **4b,c:** These compounds were distinct on TLC but were not separated from each other. The mixture had mass spectrum *m/e* 212 (1%, M^+), 194 (100%, $M^+ - H_2O$); ^1H NMR δ 5.0 (m, 1 H), 4.0 (m, 1 H), 1.0–3.0 (m, 17 H).

Oxidation of the Diols to the Monoketones. The diol **4a** (100 mg, 0.07 mol) was dissolved in acetone (1.5 ml) and Jones reagent (0.01 N) was added dropwise, the reaction mixture being monitored by TLC (Al_2O_3; Et_2O–$CHCl_3$, 3:2 v/v) after each addition. After complete disappearance of the starting material the reaction mixture was separated by TLC, using the above conditions. TLC showed two compounds, the monoketones **5a** and **5b.** The mixture of **5a,b** had mass spectrum *m/e* 140 (M^+), 122 ($M^+ - H_2O$); IR ($CDCl_3$) 3600, 3400, 2900, and 1740 cm^{-1}. Oxidation of the mixture of monoketones with Jones reagent gave the diketone **1.** Similar oxidation of **2a** gave only the monoketone **5a** (TLC), and oxidation of **3a** gave only the monoketone **5b** (TLC). Both **5a** and **5b** were separately converted into **1** by further oxidation.

Reduction of the Keto Acids 6a and 6b. The keto acid (9.5 g, 52.2 mmol) was dissolved in ethanol (150 ml), the solution was made alkaline with 10% NaOH solution, sodium borohydride (6.0 g, 15.8 mmol) was added in several portions, and the mixture was refluxed for 3 h. The solution was neutralized with 10% HCl solution, the ethanol was removed under reduced pressure, and the residual mixture was extracted with chloroform. The chloroform solution was dried ($MgSo_4$) and the solvent removed by evaporation to give the corresponding alcohols (**6a** → **7a; 6b** → **7b** + **8b**).

Compound **7a:** 8.1 g, 85%; mp 143–144 °C (lit.[5] 143–144 °C); mass spectrum *m/e* 170.0951 ($C_9H_{14}O_3$ requires 170.0943); ^1H NMR δ 8.40 (s, 2 H, OH, CO_2H), 3.85 (m, 1 H, H-5), 2.8–1.6 (m, 11 H); ^{13}C NMR 180.04 (CO_2H), 68.46 (C-5), 41.47 (C-2), 33.68 (C-6), 31.16 (C-4), 28.55 (C-1), 25.01 (C-7), 22.80 (C-8), 21.28 ppm (C-3).

Compound **7b** (recrystallization from acetone): 66%; mp 167–168 °C; mass spectrum *m/e* 184.1087 ($C_{10}H_{16}O_3$ requires 184.1099), 93 (100%); IR ($CHCl_3$) 3500, 1710 cm^{-1}; ^1H NMR δ 6.50 (s, 2 H, OH, CO_2H), 3.85 (m, 1 H, H-5), 2.8–1.6 (m, 11 H), 1.30 (s, 3 H, CH_3); ^{13}C NMR 182.78 (CO_2H), 68.29 (C-5), 43.44 (C-2), 35.80 (C-6), 33.43, 32.53 (C-1, 4), 30.01 (C-3), 26.28 (Me), 22.76 (C-8), 20.07 ppm (C-7).

Compound **8b** (separated from **7b** by conversion of **7b** to the lactone **9b** (see below): 9%; mp 182–183 °C; mass spectrum *m/e* 184.1089 ($C_{10}H_{16}O_3$ requires 184.1099), 93 (100%); IR ($CHCl_3$) 3500, 1710 cm^{-1}; ^1H NMR δ 6.50 (s, 2 H, OH, CO_2H), 3.85 (m, 1 H, H-5), 2.8–1.6 (m, 11 H), 1.30 (s, 3 H, CH_3); ^{13}C NMR 181.80 (CO_2H), 68.00 (C-5), 42.76 (C-2), 35.53 (C-6), 34.31 (C-3), 33.11, 32.78 (C-1,4), 26.28 (Me), 20.91 (C-7), 17.61 ppm (C-8).

Lactonization of 7a and 7b. The alcohol (300 mg, 176 mmol) was dissolved in dry toluene (benzene for **7b**) (30 ml), a small amount of *p*-toluenesulfonic acid (ca. 10 mg) was added, and the mixture was heated to reflux under N_2 for 2 h. Ether (20 ml) was then added to the cooled solution, and the mixture was then extracted with 10% aqueous $NaHCO_3$ (2 × 5 ml), and then washed with water until the washings were neutral. The organic layer was dried ($MgSO_4$) and evaporation of the solvent gave the lactone.

Compound **9a** (purified by sublimation (13 mm), recrystallization from petroleum ether–benzene): 80 mg, 37%; mp 205–206 °C (lit.[5] 204.5–205.5 °C); mass spectrum *m/e* 152.0843 ($C_9H_{12}O_2$ requires 152.0837); IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 4.5 (m, 1 H, H-5), 3.2–1.6 (m, 11 H); ^{13}C NMR 77.97 (C-2), 40.93 (C-5), 35.26 (C-3), 28.12 (C-6), 26.36 (C-4), 23.78 (C-1), 21.87, 21.52 ppm (C-7,8).

Compound **9b** (purified by sublimation): 195 mg, 71%; mp 124–125 °C; mass spectrum *m/e* 166.0994 ($C_{10}H_{14}O_2$ requires 166.0992); IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 4.65 (m, 1 H, H-2), 3.2–1.6 (m, 11 H), 1.2 (s, 3 H, Me); ^{13}C NMR 76.67 (C-2), 43.00 (C-5), 35.39, 34.95 (C-3,6), 30.69 (C-4), 27.01 (C-1), 21.59 (C-8), 20.51 (C-7), 18.12 ppm (Me).

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Registry No.—**1,** 57346-05-1; **2a,** 57378-53-7; **2b,** 60662-00-2; **3a,** 57378-52-6; **3b,** 60687-03-8; **4a,** 57346-04-0; **4b,** 60687-04-9; **4c,** 60687-05-0; **5a,** 60662-01-3; **5b,** 60687-06-1; **6a,** 49826-60-0; **6b,** 57346-07-3; **7a,** 41977-18-8; **7b,** 38347-91-0; **8b,** 57378-54-8; **9a,** 49826-59-7; **9b,** 38348-92-1; butyryl chloride, 141-75-3.

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(4) It is well known that $Eu(DPM)_3$ binds more readily to hydroxyl than to ester functions. See J. K. M. Sanders and D. H. Williams, *J. Am. Chem. Soc.*, **93,** 641 (1971); F. Bohlman and J. Jacob, *Chem. Ber.*, **108,** 2809 (1975).
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(6) Each ketone group in **1** is flanked on one side by a two-carbon methylene bridge and on the other by a bridge consisting of a methylene group and a remote carbonyl group. The steric shielding provided by these bridges would appear to be very similar.
(7) See E. C. Ashby and S. A. Noding, *J. Am. Chem. Soc.*, **98,** 2010 (1976).
(8) However, compound **4a** can be obtained from either the monoketone **5a** or **5b** whereas **2a** can only arise from **5a,** so that without any steric preference twice as much of **4a** should be obtained as **2a** (or **3a**). That there is some direction of the second reduction is supported by the finding that with the more hindered reducing agent no **2a** was formed.

Oxidation of 1,3-Dihydrobenzo[*c*]selenaphene (2-Selenaindan) to 2,2′-Diformyldibenzyl Diselenide

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As part of the development of an alternate synthesis of selenobiotin (Figure 1),[1] we wished to explore the possibilities of α-alkylation of selenoxides lacking β hydrogen: whether they would be stable, and if they would react similarly to