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STEREOSPECIFIC SOLID STATE SODIUM BOROHYDRIDE REDUCTIONS OF CAGE DIKETONES

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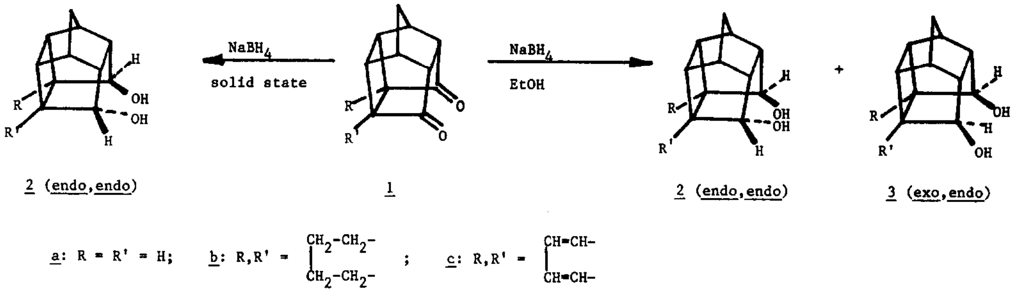
Abstract: Solid state reductions of carbonyl groups in three cage diketones, **1a–1c**, have been performed by using sodium borohydride, and the results thereby obtained have been compared with the corresponding reductions performed in ethanol solution. In each case, the solid state reduction proceeds stereospecifically; hydride transfer occurs exclusively at the exo face of the carbonyl group. In contrast, the corresponding homogeneous (solution-phase) reductions display only moderate stereoselectivity.

Introduction. Relatively few solid-solid organic reactions have been reported.[1-5] Recently, Toda and coworkers[6] have reported that solid state $NaBH_4$ reductions of ketones afford the corresponding alcohols with a high degree of regio- and enantioselectivity. Pursuant to this report and to our continuing interests in the synthesis and chemistry of novel, substituted pentacyclo[$5.4.0.0^{2,6}.0^{3,10}.0^{5,9}$]undecanes,[7] we turned our attention to the corresponding solid state $NaBH_4$ promoted reductions of three cage diketones, **1a–1c** (Scheme 1).

Results and Discussion. Cookson and coworkers[8] reported that $NaBH_4$ reduction of pentacyclic cage diketone **1a**, when performed in ethanol solution, afforded a mixture of the corresponding endo,endo and exo,endo diols, **2a** and **3a**, respectively (product ratio **2a**:**3a** = 38:62). In contrast to these results, we find that the corresponding solid state $NaBH_4$ reduction of **1a** affords exclusively the corresponding endo,endo diol, **2a**, in quantitative yield. Thus, an intimate mixture of finely powdered **1a** and $NaBH_4$ under argon was agitated at room temperature for one week. Workup of the reaction mixture afforded **2a**, whose structure was established by comparison of its ^1H and ^{13}C NMR spectra with those of authentic material.[8,9]

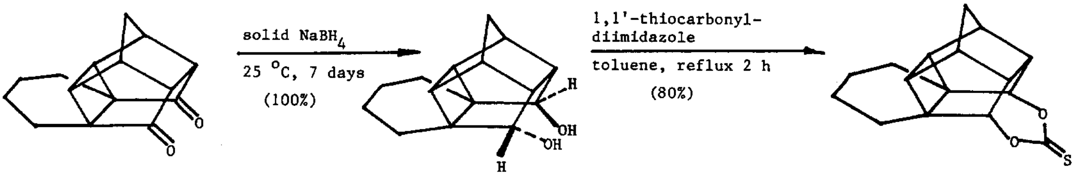
Similarly, the corresponding solid state $NaBH_4$ reductions of cage diketones **1b**[10] and **1c**[10] resulted in stereospecific formation of the corresponding endo,endo diols, **2b** and **2c**, each in essentially quantitative yield. Workup of the reaction mixture afforded **2b** (or **2c**) in essentially quantitative yield. Catalytic hydrogenation of a solution of **2c** in ethyl acetate, performed by using hydrogen over palladized charcoal catalyst, afforded material that was identical in all respects with the material, **2b**, that had been synthesized previously via solid state $NaBH_4$ reduction of **1b**.

Scheme 1



The proton noise-decoupled ^{13}C NMR spectrum of **2b** thereby obtained consists of only eight signals; this observation requires that **2b** contain a twofold symmetry element. In fact, two cage diol structures are consistent with the ^{13}C NMR spectral evidence, i.e., endo,endo diol **2b** and the corresponding exo,exo diol. The fact that the product of solid state $NaBH_4$ reduction of **1b** exclusively affords endo,endo diol **2b** was demonstrated unequivocally by converting this material to the corresponding cyclic thiocarbonate ester (i.e., **4**, Scheme 2).[11]

Scheme 2



We also attempted acid-promoted intramolecular dehydration of **2b**, a process which is expected to afford the corresponding heptacyclic cage ether, **5** (Scheme 2). However, this approach proved to be unsuccessful; only decomposition of **2b** resulted from these attempts (see the Experimental Section). This result is noteworthy in view of the relative ease with which **2a**[12] and other substituted pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-endo,endo-8,11-diols[13] are known to undergo acid-promoted intramolecular dehydration to form the corresponding, substituted 12-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane in high yield.

We have also investigated the reductions of **1b** and of **1c** in solution by using ethanolic $NaBH_4$. Whereas the corresponding solid state reduction of **1b** afforded **2b** exclusively, the reduction of **1b** when perfomed in solution displayed only moderate stereoselectivity; a mixture of endo,endo and exo,endo diols (**2b** and **3b**) was thereby produced (product ratio: **2b:3b** = 77:22). Similarly, reduction of **1c** with ethanolic $NaBH_4$ led to an intractable mixture of diols, **2c** and **3c**. Catalytic hydrogenation of a solution of this mixture of **2c** and **3c** in EtOAc, performed by using hydrogen over palladized charcoal catalyst, afforded a mixture of **2b** and **3b** (product ratio 72:25), the components of which were separated and characterized (see Experimental Section).

Summary and Conclusions. The foregoing results obtained for $NaBH_4$ promoted reductions of **1a–1c** are summarized in Table 1. We conclude that $NaBH_4$ promoted solid state reductions of cage diketones, which we find to occur stereospecifically in each of the three cases studied, offers a convenient and essentially quantitative route for synthesizing the corresponding endo,endo cage diols.

Table 1. Product ratios of diols formed via reduction of cage diketones **1a–1c** performed by using $NaBH_4$ in ethanol solution and in the solid state

	Product Ratio, endo,endo : exo,endo	
Reactant	Ethanolic $NaBH_4$	Solid State $NaBH_4$
1a	38:62	100:0
1b	78:22	100:0
1c	74:26	100:0

Experimental Section

Melting points are uncorrected. High-resolution mass spectra were obtained by the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE 68588.

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-endo-8-endo-11-diol (2a). Cage diketone **1a** (87 mg, 0.50 mmol) and $NaBH_4$ (400 mg, excess) were ground together under an argon atmosphere into a fine powder, thereby producing an intimate solid mixture. The resulting powdery mixture was agitated under argon at room temperature for 7 days. Water (15 mL) then was added, and the resulting mixture was extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo to afford pure endo,endo diol, **2a** (89 mg, 100%), as a colorless microcrystalline solid: mp 275-276 °C (lit^8 mp 276-276.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (AB, J_{AB} = 10.3 Hz, 1 H), 1.58 (AB, J_{AB} = 10.3 Hz, 1 H), 2.05-2.36 (m, 4 H), 2.40-2.69 (m, 4 H), 3.76 (s, 2 H), 5.63 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 34.33 (t), 38.17 (d), 39.73 (d), 42.85 (d), 45.38 (d), 71.63 (d).

Hexacyclo[7.4.2.0.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadecane-endo-2-endo-8-diol (2b). Reduction of solid **1b**^{10} (114 mg, 5.0 mmol) with $NaBH_4$ (400 mg, excess) was performed as described above. Workup of the reaction mixture afforded pure **2b** (116 mg, 100%) as a colorless microcrystalline solid: mp 115.0-115.5 °C; IR (film) 3170 (s), 2938 (s), 2868 (s), 1164 (s), 1275 (s), 1184 (m), 1127 (s), 1078 (s), 1014 (m), 982 cm^{-1} (w); ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 10.2 Hz, 1 H), 1.26-1.40 (m, 2 H), 1.50-2.00 (m, 7 H), 2.14-2.48 (m, 6 H), 3.32 (s, 2 H), 5.76 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.31 (t), 26.84 (t), 34.75 (t) 41.41 (d), 42.61 (d), 45.28 (s), 45.85 (d), 76.02 (d). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54 H, 8.67. Found: C, 77.88; H, 8.87.

Hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadecane-endo-2-endo-8-diol Cyclic Thiocarbonate Ester (4). A solution of diol **2b** (116 mg, 0.500 mmol) and 1,1'-thiocarbonyldiimidazole (90 mg, 0.50 mmol) in dry toluene (15 mL) under argon was refluxed fo 2 h. The reaction mixture was allowed to cool to room temperature and then was concentrated in vacuo. The residue was dissolved in $CHCl_3$ (50 mL), and the resulting solution was washed successively with water (30 mL), 10% aqueous HCl (2 x 30 mL), water (30 mL), saturated aqueous $NaHCO_3$ solution (2 x 30 mL), and water (30 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica by eluting with 25% $CHCl_3$-hexane Pure **4** (110 mg, 80%) was thereby obtained as a colorless microcrystalline solid: mp

239-240 °C; IR (KBr) 2934 (s), 2869 (s), 1412 (s), 1281 (s), 1249 (s), 1220 (s), 1108 (s), 1050 (s), 1014 (s), 704 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.25 (d, *J* = 10.9 Hz, 1 H), 1.46-2.18 (complex m, 9 H), 2.42 (s, 4 H), 2.93 (s, 2 H), 4.07 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.56 (t), 25.64 (r), 36.27 (t), 41.53 (d), 42.40 (d), 45.49 (d), 45.74 (s), 88.59 (d), 192.76 (s); mass spectrum (70 eV), *m/e* (relative intensity) 274 (molecular ion, 43.9), 214 (16.9), 186 (9.3), 155 (10,9), 131 (32.6), 115 (32.7), 105 (21.0), 91 (100.0), 78 (25.5), 65 (30.2). Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.02; H, 6.61. Found: C, 69.85; H, 6.71.

Hexacyclo[7.4.2.0.$0^{1,9}$.$0^{3,7}$.$0^{4,14}$.$0^{6,15}$]pentadeca-9,12-diene-*endo*-2-*endo*-8-diol (2c). An intimate mixture of cage diketone **1c**[10] (112 mg, 5.0 mmol) and $NaBH_4$ (400 mg, excess) were reacted under argon in the manner described above for the corresponding reduction of **1a**. Workup of the reaction mixture as described above afforded pure **2c** (114 mg, 100%) as a colorless gummy semisolid; IR (film) 3200 (s), 2962 (s), 2874 (m), 1588 (w), 1478 (m), 1273 (m), 1131 (s), 1082 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.88 (*AB*, J_{AB} = 10.6 Hz, 1 H), 1.51 (*AB*, J_{AB} = 10.6 Hz, 1 H), 2.25-2.60 (m, 4 H), 2.75 (s, 2 H), 3.54 (s, 2 H), 5.36-5.50 (m, 2 H), 5.65-6.05 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 32.14 (t), 42.19 (d), 45.61 (d), 47.11 (s), 53.84 (d), 75.56 (d), 123.70 (d), 128.09 (d). Anal. Calcd for $C_{15}H_{20}O_2$: M_r 228.1150. Found (high-resolution mass spectrometry): M_r 228.1152.

A solution of **2c** (114 mg, 5.0 mmol) in EtOAc (20 mL) was reduced with H_2 gas (20 psig) over 5% palladized charcoal catalyst in a Parr shaker apparatus at room temperature during 3 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue (114 mg, 98%) was obtained as a colorless microcrystalline solid: mp 115.0-115.5 °C, (mixture mp with authentic **2b** was undepressed).

Reduction of 1b with Ethanolic Sodium Borohydride. To a solution of **1b**[10] (114 mg, 5.0 mmol) in EtOH (10 mL) was added $NaBH_4$ (100 mg, 25 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, and water (20 mL) was added to the residue. The resulting mixture was extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (30 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The residue, a mixture of diols **2b** and **3b** (116 mg, 100%), was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane mixed solvent. *Endo,endo* diol **2b** (89 mg, 78%) was thereby obtained as a colorless microcrystalline solid: mp 115.0-115.5 °C. Further elution of the chromatography column by using 70% EtOAc-hexane as eluent afforded the corresponding *exo,endo* diol, **3b** (25 mg, 22%) as a colorless microcrystalline solid: mp 185 °C; IR (KBr) 3340 (s), 2953 (s), 1313 (w), 1170 (w), 1080 (m), 1057 (s), 985 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.0-2.6 (complex m, 17 H), 2.73 (s, 1 H), 3.50 (s, 1 H), 4.65 (s, 1 H); ^{13}C NMR (CD_3OD) δ 19.94 (2 C, t), 25.13 (t), 27.07 (t), 36.51 (t), 43.28 (d), 43.70 (d), 44.02 (d), 46.48 (d), 46.88 (s), 48.27 (d), 50.16 (d), 50.73 (s), 76.58 (d), 78.62 (d). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54; H, 8.67. Found: C, 77.84; H, 8.69.

Reduction of 1c with Ethanolic Sodium Borohydride. To a solution of **1c**[10] (112 mg, 0.5 mmol) in ethanol (10 mL) was added $NaBH_4$ (100 mg, 2.5 mmol), and the resulting mixture was stirred at room temperature for 2 h. Workup of the reaction mixture was performed in the manner described for the corresponding reduction of **1b** with ethanolic $NaBH_4$. An intractable mixture of diols **2c** and **3c** (114 mg, 100%) was thereby obtained; ^{13}C NMR ($CDCl_3$) δ 32.12 (t), 32.57 (t), 42.18 (d), 42.45 (d), 45.57 (d), 46.07 (d), 47.07 (s), 47.54 (s), 49.18 (d), 49.47 (d), 53.30 (d), 53.83 (d), 54.25 (d), 73.84 (d), 73.93 (d), 75.45 (d), 121.75 (d), 123.68 (d), 124.31 (d), 125.75 (d), 127.33 (d), 128.09 (d).

The mixture of diols **2c** and **3c** thereby obtained (114 mg, 5.0 mmol) was reduced with H_2 gas (20 psig) over 5% palladized charcoal catalyst by using the procedure described above for the corresponding reduction of **2c**. The resulting mixture of diols **2b** and **3b** was purified via column chromatography on silica gel, thereby affording pure **2b** (83 mg, 72%, mp 115.0-115.5 °C) and pure **3b** (29 mg, 25%, mp 185 °C).

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