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Regioselectivity in the Reduction of Cyclic Enediones with $NaBH_4/CeCl_3$

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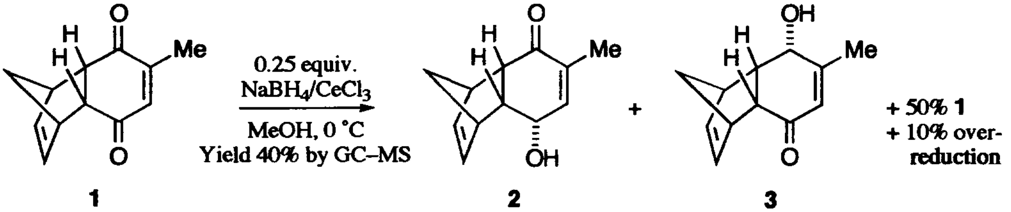
Abstract: Reductions of cyclic enediones by sodium borohydride proceed with markedly different regiochemical preferences with and without cerium(III) chloride. In the presence of $CeCl_3$, reductions appear to be controlled by two phenomena: the accessibility toward axial addition, in common with reactions without $CeCl_3$, and accessibility for complexation by the Lewis acid.

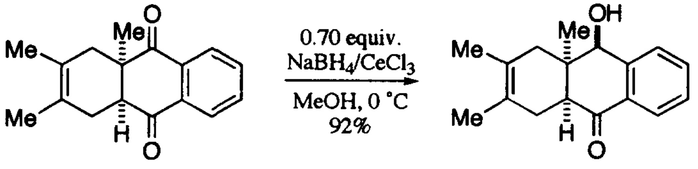
We recently showed that 1,2-reductions of cyclic enediones by $NaBH_4$ in methanol and Li(O-*t*-Bu)$_3$AlH in THF follow the same stereo- and regiochemical course.[1,2] Reduction occurs by axial addition of hydride, and accessibility of the carbonyls then far outweighs electronic contributions in determining regioselectivity. The result is that reduction of the seemingly more hindered carbonyl can proceed stereospecifically in excellent yield. We report herein that in some instances regioselectivity can be effectively reversed by the use of $NaBH_4/CeCl_3$.[3]

The reaction of enedione **1** with $NaBH_4/CeCl_3$ in methanol at 0 °C proceeded[4,5] with a regiochemical preference opposite to that of $NaBH_4$ without the $CeCl_3$, although over-reduction made this reaction synthetically unattractive.[6] Nevertheless, in the presence of $CeCl_3$, $NaBH_4$ produced the monoalcohols **2** and **3** in a 3:1 ratio, respectively, whereas without $CeCl_3$ **2** and **3** were produced in a 1:5 ratio, respectively.[1]

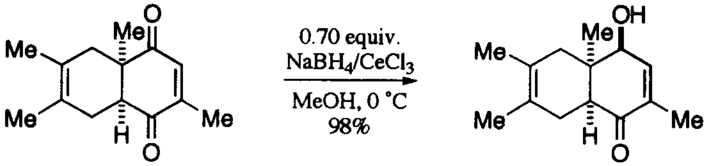


1 **2** **3**

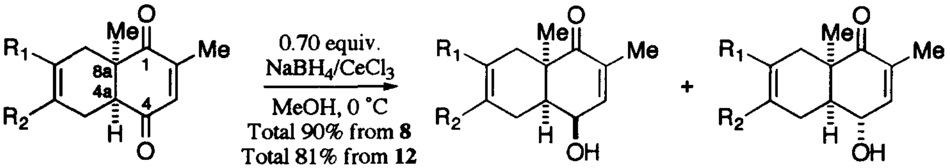
On the other hand, the reduction of enedione **4** proceeded in the same regiochemical sense with or without $CeCl_3$, yielding monoalcohol **5** in very good yield (regioselectivity ≥ 95%). When the controlling features of enediones **1** and **4** were combined in enedione **6**, a single monoalcohol product **7** was produced stereo- and regiospecifically with $NaBH_4/CeCl_3$. ($NaBH_4$ reduction of **6** without $CeCl_3$ gives **7** and another monoalcohol.[1]) Opposition of the controlling features led to mixtures of three monoalcohols, but with a modest preference for products with regiochemistry opposite to that for $NaBH_4$ alone. With $NaBH_4/CeCl_3$, enedione **8** provided monoalcohols **9**, **10**, and **11** in a 1.7:1:1 ratio, respectively, with a regioselectivity of 73% in favor of reduction of the C-4 alcohol, but $NaBH_4$ alone had given only **11**.[1] Also, a 1:1 mixture of isomers **12** gave **13**, **14**, and **15** in a 1.7:1:1.2 ratio, respectively, and therefore 69% regioselectivity in favor of **13** and **14**.



4 **5**



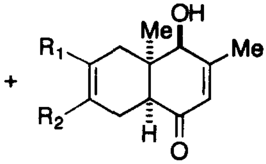
6 **7**



8 R_1 = Me, R_2 = Me
12 R_1 = H, R_2 = Me *and* R_1 = Me, R_2 = H (1:1)

9 R_1 = Me, R_2 = Me
13 R_1 = H, R_2 = Me *and* R_1 = Me, R_2 = H (1:1)

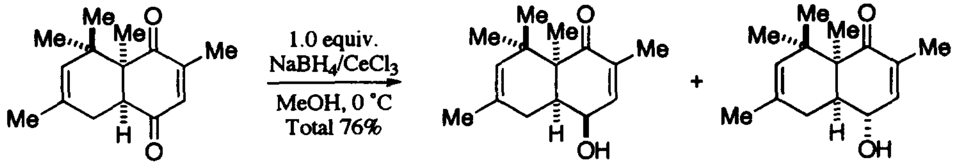
10 R_1 = Me, R_2 = Me
14 R_1 = H, R_2 = Me *and* R_1 = Me, R_2 = H (1:1)



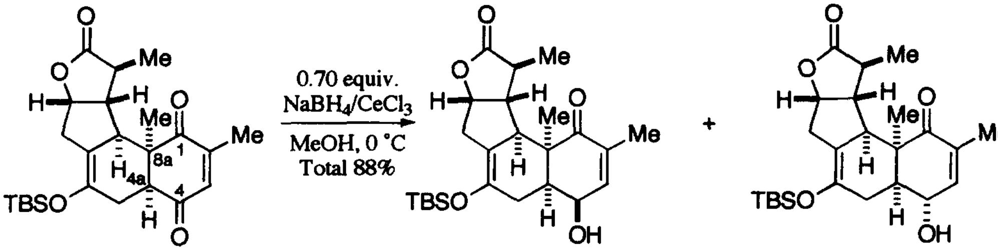
11 R_1 = Me, R_2 = Me
15 R_1 = H, R_2 = Me *and* R_1 = Me, R_2 = H (1:1)

From the above reactions it is not clear how the addition of $CeCl_3$ enhances the role of the vinylic methyl, relative to reductions without $CeCl_3$ in which the electronic effect of this methyl was dominated by the steric influences from other regions of the substrate molecules.[1] It is known that the $CeCl_3$ behaves as a Lewis acid and complexes with the carbonyl oxygen to enhance 1,2-reduction over 1,4-reduction.[7] Regioselectivity might reasonably be attributed to selective complexation, and the following examples suggest that this is determined by hindrance rather than a difference in basicity between the two carbonyls. In enedione **16**, the region around the C-1 carbonyl is more encumbered than in **8** or **12**, but the basicity of C-4 cannot be significantly different. However, monoreduction of **16** with $NaBH_4/CeCl_3$ was regiospecific, albeit with little stereoselectivity, giving epimers **17** and **18** in a 2.8:1 ratio. (A minor amount of over-reduced material was also obtained.) Similarly, reduction of the tetracyclic enedione **19** with $NaBH_4/CeCl_3$ yielded **20** and **21** (in a 1.5:1

ratio, but nevertheless with 100% regioselectivity) with no over-reduced product, whereas reduction at C-1 was the only reaction observed with $NaBH_4$ alone.[1]



16 **17** **18**



19 **20** **21**

Conjugate and diol-forming reductions were not important processes with $NaBH_4/CeCl_3$, except with enedione **1**. In general, by using approximately 0.7 molar equivalents of $NaBH_4$, very good yields of monoalcohol were obtained. In spite of the poor stereochemical control, which has been noted before in reductions with $NaBH_4/CeCl_3$,[7] the regioselectivity afforded by this reductive process may still make this a useful alternative to other methods.

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References and Notes

1 Liu, C.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 3683–3687.

2 Regioselectivity in the reactions of enediones toward lithium acetylide was previously examined by: Liotta, D.; Saindane, M.; Sunay, U.; Jamison, W. C. L.; Grossman, J.; Phillips, P. *J. Org. Chem.* **1985**, *50*, 3243–3245. For some examples of selectivity in synthetic applications: (a) Das, J.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308–3319. (b) Kienzle, F.; Stadlweiser, J.; Rank, W.; Schönholzer, P. *Helv. Chim. Acta* **1990**, *73*, 1108–1138. (c) Nampalli, S.; Bhide, R. S.; Nakai, H. *Synth. Commun.* **1992**, *22*, 1165–1177. (d) Khan, N.; Larsen, L.; Sutherland, J. K. *Tetrahedron* **1993**, *49*, 8233–8240.

3 The reduction of 4-oxoisophorone by $NaBH_4/CeCl_3$ was an isolated example reported by: Ishihara, M.; Tsuneya, T.; Shiota, H.; Shiga, M.; Nakatsu, K. *J. Org. Chem.* **1986**, *51*, 491–495.

4 Typical procedure: To a solution of **8** (0.177 g, 0.811 mmol) and $CeCl_3{\cdot}7H_2O$ (0.302 g, 0.811 mmol) in methanol (8.0 mL) at 0 °C was added $NaBH_4$ (22.3 mg, 0.560 mmol) in portions over 4 min. The mixture was stirred for 2 min before it was poured into 40 mL of a dilute NH_4Cl solution. This was extracted with ethyl acetate. The combined organic extracts were washed with H_2O and a saturated NaCl solution, then

dried over anhydrous $MgSO_4$ and concentrated under vacuum. Flash chromatography provided **9**, **10**, and **11** in a total yield of 90%.

5 For the physical and spectroscopic data for **1** – **8**, **12**, and **15** see reference 1.

Important characterization data for **9**: colorless crystals, mp 67.5–69 °C; IR (Nujol) 3404, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.40 (1H, br s), 4.92 (1H, m, C-4H), 2.63 (1H, d, J = 17.1 Hz), 2.42 (1H, m, C-4aH), 1.79 (3H, t, J = 1.8 Hz), 1.62 (3H, br s), 1.56 (3H, br s), 1.18 (3H, s, C-8aMe, saturation gave 9% NOE at δ 4.92 and 5% at δ 2.42); ^{13}C NMR ($CDCl_3$, 75 MHz, number of attached hydrogens from APT and/or heteronuclear correlation in parentheses) δ 202.2 (0), 142.4 (1), 133.7 (0), 124.3 (0), 123.2 (0), 67.7 (1), 46.2 (1), 45.9 (0), 39.8 (2), 29.2 (2), 24.2 (3), 18.8 (3), 18.7 (3), 16.0 (3).

10: viscous liquid; IR (film) 3434, 1658 cm^{-1}; ^{1}H NMR δ 6.59 (1H, br s), 4.26 (1H, m), 1.78 (3H, t, J = 1.7 Hz), 1.65 (3H, br s), 1.61 (3H, br s), 1.16 (3H, s); ^{13}C NMR δ 203.4 (0), 146.1 (1), 132.7 (0), 123.9 (0), 122.2 (0), 67.4 (1), 47.7 (1), 44.5 (0), 37.5 (2), 29.9 (2), 20.0 (3), 19.1 (3), 18.9 (3), 16.1 (3).

Monoalcohols **13**, **14**, and **15** were each 1:1 isomers so the spectra were complex. For **13**: ^{1}H NMR δ 6.41; for **14**: ^{1}H NMR δ 6.59; for **15**: ^{1}H NMR δ 5.88.

17: colorless oil; IR (film) 3454, 1682 cm^{-1}; ^{1}H NMR δ 6.31 (1H, narrow m), 5.25 (1H, narrow m), 4.80 (1H, m, C-4H), 2.75 (1H, m, C-4aH), 2.08 (1H, dd, J = 7.0, 18.5 Hz), 1.88 (1H, dd, J = 9.1, 18.5 Hz), 1.76 (3H, t, J = 2.0 Hz), 1.59 (3H, d, J = 0.8 Hz), 1.34 (3H, s), 1.23 (3H, s, C-8aMe, saturation gave 11% NOE at δ 4.80, 3% at δ 2.75, and 1.5% at δ 0.94), 0.94 (3H, s); ^{13}C NMR δ 203.2 (0), 140.0 (1), 135.0 (0), 132.7 (1), 128.4 (0), 68.1 (1), 50.5 (0), 43.7 (1), 37.4 (0), 28.14 (2), 28.08 (3), 25.1 (3), 23.3 (3), 17.2 (3), 16.4 (3).

18: colorless solid, mp 89–91 °C; IR (CCl_4) 3465, 1664 cm^{-1}; ^{1}H NMR δ 6.60 (1H, br s), 5.07 (1H, br s), 4.32 (1H, m), 1.80 (3H, t, J = 2.1 Hz), 1.69 (3H, br s), 1.18 (3H, s), 0.91 (3H, s), 0.79 (3H, s); ^{13}C NMR δ 202.6 (0), 145.9 (1), 136.7 (0), 131.5 (1), 127.2 (0), 68.0 (1), 50.2 (1), 48.4 (0), 36.3 (0), 28.9 (3), 27.8 (2), 26.5 (3), 23.7 (3), 21.7 (3), 16.3 (3).

20: white solid, mp 148.5–150 °C; IR (CCl_4) 3463, 1769, 1711, 1677 cm^{-1}; ^{1}H NMR δ 6.37 (1H, br s), 5.10 (1H, apparent q, J = 5.9 Hz), 4.96 (1H, m, C-4H, saturation gave 7% NOE at δ 6.60, 7% at δ 2.56, and 1% at δ 1.30), 3.32 (1H, apparent q, J = 6.8 Hz), 3.00 (1H, dd, J = 7.0, 18.0 Hz), 2.56 (1H, m, C-4aH), 1.75 (3H, dd, J = 1.6, 2.0 Hz), 1.31 (3H, d, J = 9.4 Hz), 1.30 (3H, s, C-8aMe), 0.89 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR δ 202.1 (0), 180.2 (0), 142.1 (1), 140.9 (0), 133.9 (0), 116.5 (0), 82.6 (1), 67.6 (1), 54.4 (1), 49.4 (1), 49.0 (1), 48.4 (0), 43.6 (1), 34.5 (2), 28.6 (2), 25.7 (3C, 3), 21.8 (3), 18.0 (0), 15.8 (3), 15.1 (3), –3.8 (3), –4.1 (3).

21: white solid, mp 150–151.5 °C; IR (CCl_4) 3456, 1770, 1710, 1667 cm^{-1}; ^{1}H NMR δ 6.54 (1H, narrow m), 4.98 (1H, m), 4.24 (1H, m), 3.05 (1H, dd, J = 7.2, 16.4 Hz), 2.56 (1H, m), 1.81 (3H, t, J = 1.4 Hz), 1.43 (3H, s), 1.21 (3H, d, J = 7.5 Hz), 0.92 (9H, s), 0.10 (3H, s), 0.08 (3H, s); ^{13}C NMR δ 202.0 (0), 180.0 (0), 142.2 (1), 140.0 (0), 134.9 (0), 116.8 (0), 81.7 (1), 67.3 (1), 52.0 (1), 49.9 (1), 48.5 (1), 45.9 (0), 42.2 (1), 33.3 (2), 30.9 (2), 25.6 (4C, 3), 25.5 (3), 18.0 (0), 16.1 (3), –3.9 (3), –4.1 (3).

6 "Over-reduction" refers to formation of diols and/or 1,4-reduction. Double reduction of the Diels–Alder adduct of cyclopentadiene and 1,4-benzoquinone to the corresponding cis-diol by $NaBH_4/CeCl_3$ was exploited synthetically by: Trost, B. M.; Tometzki, G. B. *J. Org. Chem.* **1988**, *53*, 915–917.

7 Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68, and references therein.

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