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Neighbouring Group Directed Protonation in the Birch Reduction of Styrene Double Bonds

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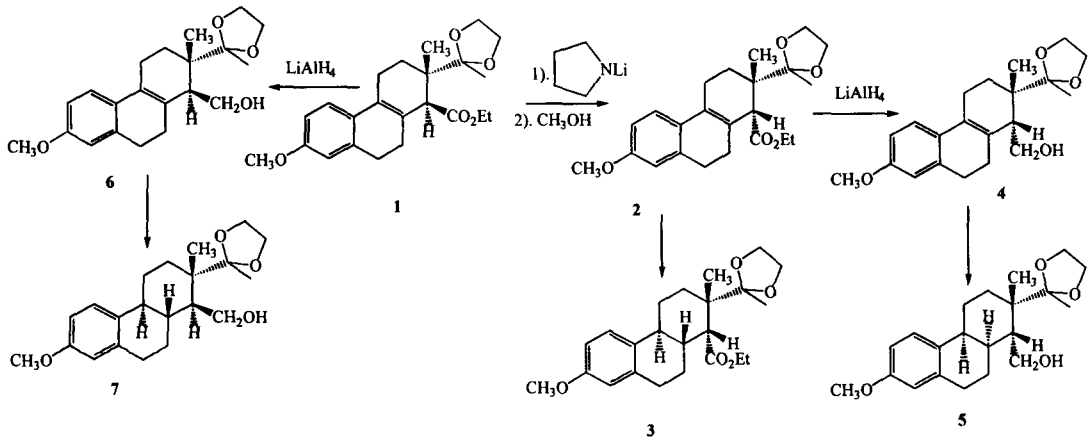
Abstract A neighbouring hydroxyl group mediates a diastereoselective protonation in the Birch reduction of styrene double bonds. © 1997 Elsevier Science Ltd.

Birch reduction has been generally applied in the conversion of functionalized aromatic rings to cyclohexenones and related cyclohexane derivatives.[1] A selective reduction of the double bond in styrene derivatives can furthermore often be achieved in a controlled Birch reduction.[1b,2] In the cases of highly substituted double bond, its reduction often proceeds in a *trans* manner and thus provides an important alternative to the transition metal catalyzed *cis* hydrogenation.[1b,2] We now report a pronounced effect of a neighbouring hydroxyl group upon the rate and the stereochemical outcome of the Birch reduction of several styrene derivatives. Since the Birch reduction of styrenes and metal-ammonia reduction of α,β-unsaturated ketones are mechanistically related,[1,3] it can be expected that this "neighbouring hydroxyl group effect" will also provide the means to establish the desired configuration at the β-carbon in metal-ammonia reductions of α,β-unsaturated ketones[3] and similar unsaturated systems.

The rate enhancement in Birch reductions by neighbouring hydroxyl groups and hydroxyl-mediated proton addition to the more hindered face of aromatic rings during the reduction have been reported.[1,4] However, such effects during the reduction of the styrene double bond have not been observed to the best of our knowledge.

Treatment of racemic 14β-ester **1**[5,6] (Scheme 1) with sodium in NH_3/THF at -40 °C for 20 minutes afforded a complicated mixture from which no significant amount of a pure reduced product could be isolated. Epimerization of **1** gave a quantitative yield of the 14α-ester **2**, whose structure was determined by X-ray crystallography and spectroscopy.[7] Birch reduction of **2** gave an improved product distribution (Table 1, entry 1). The major product, **3** (70 % yield), possessed the β-H(8), α-H(9) configuration[6] (Scheme 1) as established

by quantitative homonuclear *noe* differential spectroscopy.[8] Birch reduction of alcohol **4**, obtained by LAH reduction of **2**, afforded **5** (71 % yield), possessing the α-H(8), α-H(9) configuration as shown by X-ray crystallography and spectroscopy[9] (Scheme 1; Table 1, entry 2).



Scheme 1

Table 1. Birch reduction of various substrates and product distributions[a]

Entry	Substrate	t(m)	Conv.(%)	Product distribution[b]				
				α-H(8) α-H(9)	α-H(8) β-H(9)	β-H(8) α-H(9)	β-H(8) β-H(9)	red/overred.[c]
1	**2**	20	92			70		85/15
2	**4**	4	100	71				85/12
3	**6**	4	100	0	0	100	0	100/0

a. A representative reaction procedure: To a solution of the substrate (0.58 mmol) in THF (5.0 mL) and NH_3 (11 mL) was added Na (4 mmol) portionwise to sustain a blue solution at -40 °C for the required time. Distribution between a saturated solution of NH_4Cl and diethyl ether followed by evaporation of the organic extracts gave the crude product. b. Determined by integration of the ^1H NMR spectra of the crude products. c. Ratio of products with only the C(8)=C(9) double bond reduced (red.) and products with both this double bond and the aromatic ring reduced (overred.).

The α-face in compounds **1**, **2** and **4** is screened by the bulky ketal grouping, while the β-face is blocked by the C(13) methyl group. In compound **1**, the β-face is furthermore partially screened by the ester

group; this explains the complex mixture of products obtained on reduction of **1** and resulting from both α- and β-protonation at C(8) as well as from extensive aromatic ring reduction. The C(14) ester group in **2** is likely *pseudoaxial* (as it is in the crystal[7]) and its influence, combined with that of the ketal group, causes a relatively slow, but reasonably efficient protonation from the β-face at C(8). Compared to the reduction of **2**, that of alcohol **4** is significantly faster (see entries 1 and 2 in Table 1) and the major product has the α-H(8) configuration. This is clearly best explained by an intramolecular proton donation by the α-CH_2OH grouping.[10,11]

This postulate is strongly supported by the results of the Na/NH_3 reduction of alcohol **6**, obtained by LAH treatment of ester **1**. In contrast to the slow and nonselective Birch reduction of **1**, alcohol **6** gave a quantitative yield of **7** in a very fast reaction (Scheme 1, Table 1, entry 3). The stereochemistry of **7** was established by X-ray crystallography and spectroscopy.[12] Since the two substrates, **1** and **6**, possess identical stereochemistry, the pronounced difference in both the rate and the selectivity of the two reductions is best explained by the beneficial presence of the hydroxyl group.

In conclusion, the results obtained with the two alcohols, **4** and **6**, show that the direction of the first protonation during the Birch reduction of the styrene double bond can be controlled by a suitably situated hydroxyl group, while a comparison with the results obtained with ester **1** and **2** leaves no doubt that this hydroxyl group causes a marked acceleration of the reduction.

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References:

1. For general review of the Birch reduction see: a). Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron Asym.*, **1996**, *7*, 317. b). Mander, L. N. in "*Comprehensive Organic Synthesis*", Trost, B. M. and Flemming I. (Ed), Pergamon, **1991**, *Vol. 8*, page 489. c). Rabideau, P. W.; Marcinow, Z., *Org. React.*, **1992**, *42*, 1.

2. Siemann, Hans-J. Droescher, P.; Undeutsch, B.; Schwartz, S., *Steroids*, **1995**, *60*, 308.

3. It has been cogently argued that the direction of the first protonation (at the β-carbon) in the metal-ammonia reduction of α,β-unsaturated ketones is determined by the geometry of that lowest energy transition state which allows a favourable orbital overlap of the intermediate radical anion (or dianion) (Stork, G.; Darling, S. D., *J. Am.*

Chem. Soc., **1964,** *86* 1761). Since higher energy stereoelectronically allowed transition states are always possible (axial rather than equatorial substituent, distorted 1,3-diaxial interaction, a twisted-boat *etc.*), it is possible that a β-configuration opposite to that normally observed could be obtained using an intramolecular protonation by a strategically placed hydroxyl group.

4. a). Cotsaris, E.; Paddon-Row, M. N., *J. Chem. Soc., Chem. Commun.*, **1982**, 1206. b). Cotsaris, E.; Paddon-Row, M. N., *J. Chem. Soc., perkin Trans. 2*, **1984**, 1487.

5. Lin, Z. Ph.D. Thesis, **1996**, University of New Brunswick, Canada.

6. Steroid numbering.

7. ^{1}H NMR (ppm): 7.17 (d, 1H), 6.70 (dd, 1H), 6.67 (d, 1H), 4.08 (q, 2H), 3.78 - 3.97 (m, 4H), 3.78 (s, 3H), 2.88 (s, 1H), 2.69 (m, 2H), 2.50 - 2.10 (m, 4H), 1.62 (m, 2H), 1.35 (s, 3H), 1.12(t, 3H), 1.02 (s, 3H). IR (cm^{-1}): 1717(vs). M.p. 78.0 - 78.5 °C. HRMS: M^+ found: 386.2107; Calcd. for $C_{23}H_{30}O_5$: 386.2093.

8. Irradiation of β-H(8) in **3** showed an enhancement on the methyl group at C(1) (6.8 %) and no *noe* effect on H(9), while the irradiation of α-H(9) showed no *noe* effect on this methyl group.

9. ^{1}H NMR (ppm): 7.03 (d, 1H), 6.70 (dd, 1H), 6.58 (d, 1H), 4.08 - 4.04, 3.80 -3.76 (m, 2H), 3.96 - 3.92, 3.73 - 3.53 (m, 4H), 3.75 (s, 3H), 2.76 (m, 2H), 2.81 (m, 1H), 2.52 (m, 1H), 2.03 (m, 1H), 1.89 (m, 2H), 1.62 - 1.63 (m, 4H), 1.38, 1.22 (s, 3H), 1.16, 1.12 (s, 3H). ^{13}C NMR: 157.5, 137.2, 133.2, 130.5, 113.1, 112.3, 69.4, 63.7, 62.6, 62.0, 56.1, 47.7, 44.8, 35.9, 33.9, 33.3, 31.7, 28.0, 25.9, 19.6, 14.9. IR (cm^{-1}): 3300, 1151, 1053. M.p. 147.8 - 149.2 °C. HRMS: M^+ found: 346.2147; Calcd. for $C_{21}H_{30}O_4$: 346.2144.

10. Not surprisingly, the Birch reduction of the TBDMS derivative of **4** gave exclusively compounds with β-H(8) configuration in a slow reaction yielding considerable amount of overreduction products.

11. The observed α-protonation at C(9)[6] during the reduction of **2** and **4** is best explained by a "product development control" at the transition state and the conformational dominance by the bulky ketal group. In the reduction of ester **2**, α-protonation at C(9) leads to the more stable B/C *trans* product with an equatorial ketal group, while the B/C *cis* product **5** with an equatorial ketal group (as shown by X-ray diffraction) is formed by α-protonation at C(9) in the reduction of alcohol **4** (β-Protonation at C(9) in the reduction of **4** would give a B/C *trans* product with an axial ketal group.)

12. ^{1}H NMR (ppm): 7.18 (d, 1H), 6.69 (dd, 1H), 6.62 (d, 1H), 4.07 - 4.02, 3.86 - 3.77 (m, 4H), 3.947 (m, 2H), 3.758 (s, 3H), 3.208 (dt, 1H), 2.855 - 2.818 (m, 2H), 2.311 - 2.216 (m, 3H), 1.902 - 1.853 (m, 1H), 1.617 - 1.545 (m, 2H), 1.473 - 1.352 (m, 2H), 1.38 (m, 1H), 1.384 (s, 3H), 0.922 (s, 3H). IR (cm^{-1}): 3472. M.p. 111.2 - 112.5 °C. HRMS: M^+ found: 346.2141, 10 %; Calcd. for $C_{21}H_{30}O_4$: 346.2144.

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