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High 1,6 Diastereoselectivity in the Hydride Reduction of an Acyclic Ketone Substrate via Bicyclic Chelation Control

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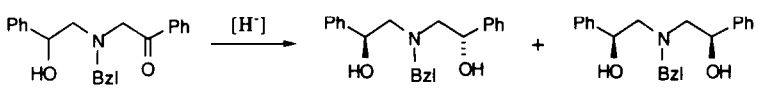
Summary: Reduction of acyclic ε-hydroxy ketone **3** with *R*-Alpine-Hydride® in methylene chloride provided a strong preponderance of the *anti* diastereomer of **4** (*anti*:*syn* = 12:1). This impressive 1,6 stereoselectivity is attributed to bicyclic chelation control of hydride addition. Copyright © 1996 Elsevier Science Ltd

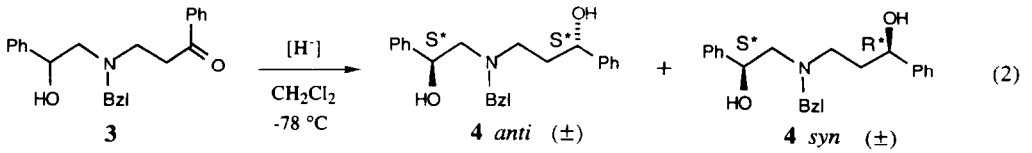
A major challenge in synthetic organic chemistry is the control of stereochemistry between remote sites in conformationally flexible systems. Thus, there are relatively few examples of asymmetric induction in acyclic molecules with stereocenters at a distance of 1,5 or greater, especially in the absence of perturbation by other stereogenic features.[1,2] Recently, we reported high 1,5 diastereoselectivity, *anti*:*syn* = 10:1 or 13:1, in the reduction of acyclic δ-hydroxy ketone **1** with *R*-Alpine-Hydride® or $Zn(BH_4)_2$, respectively (eq 1).[3] To account for these remarkable results, we proposed a model involving chelation control via a bicyclic metal complex.[3,4] In our continuing studies of such bicyclic chelation-based acyclic stereocontrol, we have now attained high 1,6 *anti* diastereoselectivity in the *R*-Alpine-Hydride® reduction of ε-hydroxy ketone **3**.



(1)

1 Bzl = benzyl *anti* (*dl*) **2** *syn* (*meso*) **2**

ε-Hydroxy ketone **3**, readily prepared by reacting 2-(benzylamino)-1-phenylethanol and 3-chloropropiophenone in the presence of diisopropylethylamine (THF solvent; 65% yield) (eq 2), was reduced in CH_2Cl_2 at -78 °C to furnish a mixture of isomeric 1,6-diols **4**. Depending on the hydride reducing agent, we obtained the following *anti*:*syn* ratios of **4**: 2:1 with $LiBH_4$ (77%), 7.5:1 with $Zn(BH_4)_2$ (83%), and 12:1 with *R*-Alpine-Hydride® (83%).[5] The 12:1 stereoselectivity for 1,6 reduction of an acyclic substrate is certainly impressive! Also, the $Zn(BH_4)_2$ result is quite respectable, as well. It is noteworthy that these reductions of **4** proceeded much more rapidly and in higher yield than the corresponding reductions of **1**.[3]



(2)

The diastereomeric ratios for **4** were nicely quantitated by 400-MHz proton NMR ($CDCl_3$) (Fig.1). There were two different pairs of doublets for the aliphatic benzylic protons ("AB quartets") centered at δ 3.74 (*anti*) and δ 3.71 (*syn*), with no overlap of the signals due to a large chemical shift difference between the pair of doublets for the *anti* isomer, Δδ(*anti*) = 0.40 ppm (J = 13.2 Hz), and a small difference between the pair of doublets for the *syn* isomer, Δδ(*syn*) = 0.11 ppm (J = 13.2 Hz).

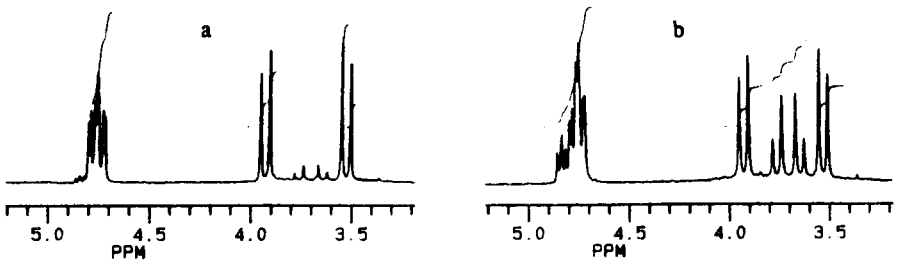
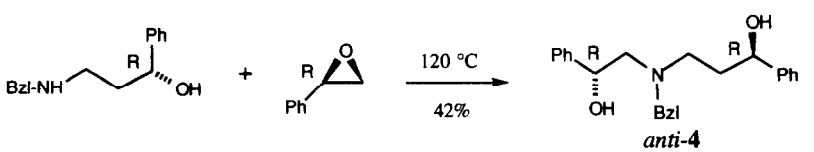


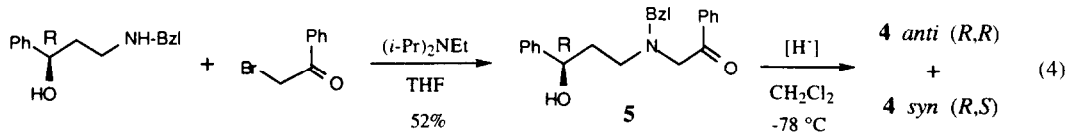
Figure 1. ^1H NMR spectra of diols **4**: (a) *R*-Alpine-Hydride reduction, *anti*:*syn* = 12:1; (b) $LiBH_4$, *anti*:*syn* = 2:1.

For unambiguous assignment of the benzyl resonances, we synthesized an authentic sample of the *anti* (*R*,*R*) isomer of **4** by means of (*R*)-styrene oxide (eq 3).



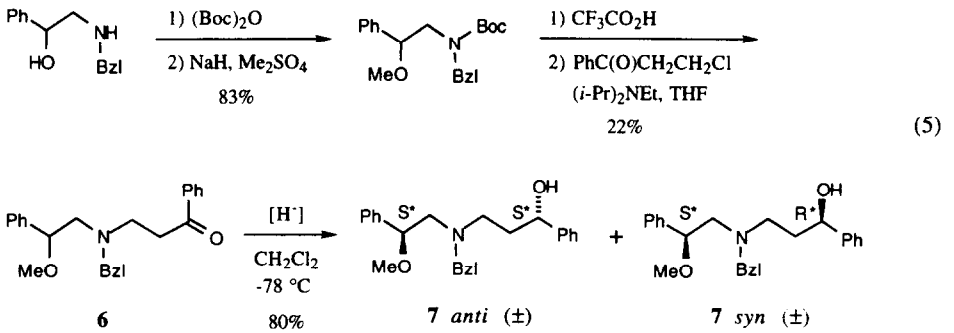
(3)

Hydroxy ketone **5** (*R* enantiomer only) was prepared and reduced with *R*-Alpine-Hydride® or $Zn(BH_4)_2$ in CH_2Cl_2 at -78 °C to give 1,6-diols **4** in 75% or 72% yield, respectively (eq 4). For this "reversed" 1,6 acyclic system, the *anti*:*syn* ratios of 5:1 and 3:1, respectively, are significant but unremarkable. Still, where 1,6 acyclic stereocontrol is concerned, a 5:1 ratio is meaningful. Comparing the two results, with **3** and **5**, it seems that the degree of 1,6 diastereoselectivity is dependent on the distance between the hydroxyl and amine groups, with the β-hydroxy amine arrangement being preferred over the γ-hydroxy amine.

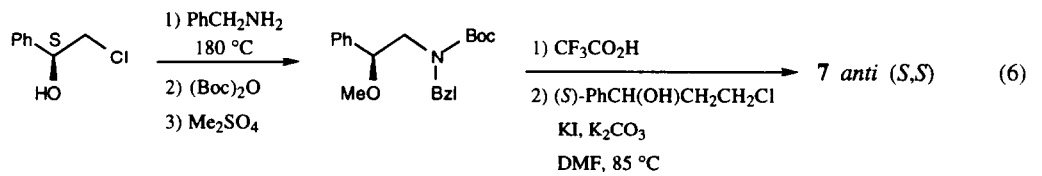


(4)

To evaluate the importance of a free hydroxyl, we prepared methoxy amino ketone **6**, in a Boc protection sequence, and subjected it to *R*-Alpine-Hydride® at -78 °C in CH_2Cl_2 (eq 5). Methoxy amino alcohols **7** were isolated in 80% yield as a 4:1 mixture of *anti* and *syn* isomers,[6] and the isomer assignment was established by the synthesis of an authentic sample of *anti*-(*S*,*S*)-**7** (eq 6). Clearly, methylation of the hydroxyl group in **3** caused some loss in stereoselectivity (*anti*:*syn* = 12:1 for **3** → **4**).

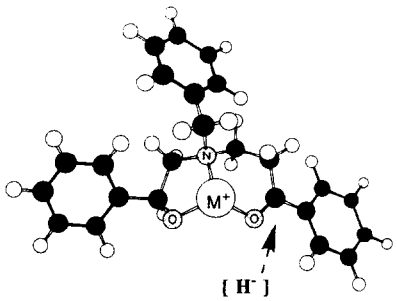


(5)



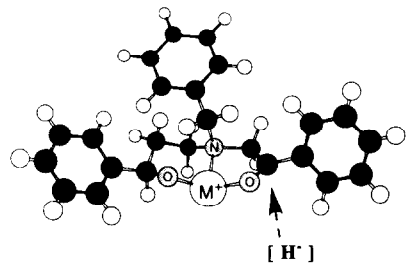
(6)

We propose a 5,6-bicyclic chelate structure, such as in model **8**, to rationalize the high 1,6 acyclic diastereocontrol in the reduction of **3**. The lithium or zinc ion would be complexed with the hydroxyl, amine, and ketone groups of **3** to establish a conformationally rigid architecture, and the hydride species would attack the carbonyl in the 6-membered ring from an axial direction to allow an equatorial phenyl ring to develop in the transition state. This leads to the major *anti* 1,6-diol product. If one considers the 5,6-bicyclic chelate model as being critical for 1,6 diastereoselectivity, then the methoxy group in **6** is reasonably effective as a ligand for lithium in this reaction, albeit not as effective as a hydroxyl. In the reduction of **5**, the hydroxyl, amine, and ketone groups would complex with the lithium ion to give a related 6,5-bicyclic chelate, **9**, which would undergo hydride attack at the carbonyl in the 5-membered ring from the less hindered face, as shown, leading to the preferred *anti* diol. This direction of addition is opposite to that obtained for the 1,5 diastereoselective reduction of **1**.[3]



8

5,6-Bicyclic Chelate Complex



9

6,5-Bicyclic Chelate Complex

High *anti* stereocontrol (>10:1) between remote 1,6 stereocenters was achieved in the reduction of hydroxy amino ketone **3** with *R*-Alpine-Hydride®. The distance between the hydroxyl and amino groups had a greater effect on the diastereoselectivity than the distance between the ketone and amino groups (cf. reduction of **3** and **5**). A methoxy group (viz. **6**) diminished, but did not destroy, the *anti* stereocontrol. It is reasonable to suggest that bicyclic chelation control is responsible for the extraordinary 1,6 acyclic stereocontrol.

Acknowledgment. We thank Dr. Michael Costanzo for helpful discussions and graphics for **8** and **9**.

References and Notes

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4. For related examples of bicyclic chelation control, see: (a) Carey, J. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3935. (b) Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Ibid.* **1993**, *34*, 8387. (c) Ref. 2a. (d) Ref. 2k.
5. Typical reduction procedure: To a solution of **3** (0.067 mmol) in dry CH_2Cl_2 (3 mL) at -78 °C was added dropwise *R*-Alpine-Hydride® (0.5 M in THF, 0.14 mmol) via syringe. The mixture was stirred at -78 °C for 3 h, quenched with water, allowed to warm to room temperature, and extracted with ethyl acetate. The organic layer was washed with water, then brine, and dried (Na_2SO_4). The volatiles were removed in vacuo and the residue was separated by preparative TLC (EtOAc-hexane, 1:4) to give **4**, as a mixture of *anti* and *syn* diols.
6. The *anti:syn* ratio of product **7** was determined by intergrating the two sets of AB quartets for the products in the 400-MHz ^1H NMR spectrum ($CDCl_3$). Both AB quartets centered around δ 3.75 but had no overlapping of peaks due to the variation in the chemical shift difference between the pair of doublets in the AB quartets for the two isomers (*anti* isomer: Δδ = 0.28 ppm, J = 13.3 Hz; *syn* isomer: Δδ = 0.57 ppm, J = 13.2 Hz).

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