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Remote Acyclic Diastereocontrol Involving a Bicyclic Metal Chelate. High 1,5 Asymmetric Induction in the Hydride Reduction of δ-Hydroxy Ketones

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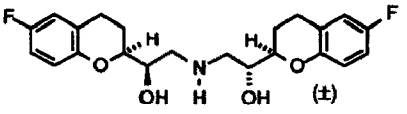
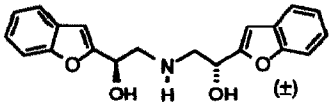
Summary: A variety of reducing agents was explored to effect stereoselective reduction of acyclic δ-hydroxy ketone **3a**; *R*-Alpine-Hydride provided high *anti* stereoselectivity (*anti*:*syn* = 7:1). Reduction of **3b** in CH_2Cl_2 with *R*-Alpine-Hydride or $Zn(BH_4)_2$ afforded impressive *anti* stereoselectivity: 10:1 and 13:1, respectively. The stereochemical outcome is attributed to a bicyclic metal-chelate species (viz. **10**).

Stereochemical control in reactions of acyclic molecules has attracted a great deal of attention. Enormous advances have been made in the generation of new proximal (1,2 and 1,3) stereogenic centers with a high level of asymmetric induction;[1,2] however, remote (>1,3) stereocontrol still poses a challenging problem.[3] As a continuation of our interest in stereocontrol with nonrigid systems,[4,5] we report herein an example of high 1,5 diastereoselectivity in the reduction of acyclic δ-hydroxy ketones.



1 (nebivolol)



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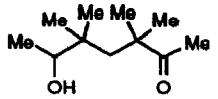

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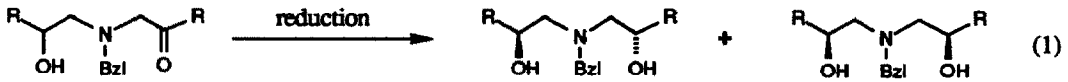
In a medicinal chemistry project, we had occasion to conduct the synthesis of nebivolol (**1**)[6] analogue **2**. The key step for the synthesis of **2** is the stereoselective reduction of racemic δ-hydroxy ketone **3a**[7] to racemic *anti*-diol **4a** (eq 1). Examples of high asymmetric induction by a singular, remote stereogenic center bearing a hydroxyl group in nucleophilic addition to hydroxy ketones are rare.[8] Maier et al.[9] reported that the reduction of δ-hydroxy ketone **6** with $LiAlH_4$ in Et_2O provided the corresponding 1,5 diols with a *anti*:*syn* ratio of just 55:45. At the outset, we hoped that the diastereoselectivity might be improved for the reduction of **3a** with $LiAlH_4$ because of the amine nitrogen,[10] which could cooperate with the hydroxyl to direct hydride delivery. Unfortunately, no induction (**4a**:**5a** = 1:1) was observed when **3a** was reduced with $LiAlH_4$, and the bulkier $LiAlH(O\text{-}t\text{-}Bu)_3$ also showed no selectivity (Table I).[11] In an attempt to achieve an excess of *anti* (**4a**) over *syn* (**5a**) diols, we studied 14 additional reducing agents (Table I). Interestingly, only *R*-Alpine-Hydride® (**7**,



(1)

3a or **3b**

a: R = 2-benzofuranyl
b: R = phenyl

(±)
4a or **4b**

(meso)
5a or **5b**

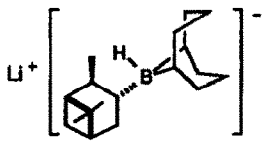
entry 16)[12] was able to afford a useful level of diastereoselectivity (**4a**:**5a** = 7:1; 43% yield of purified **4a**, mp 103-104 °C, C/H/N analysis), although no enantioselectivity was found.[13]

Table I. Reduction of δ-Hydroxy Ketone **3a** to Diols **4a** and **5a**[a]

entry	reagent	solvent	**4a**:**5a**	entry	reagent	solvent	**4a**:**5a**
1[b]	$Pd(OH)_2$, H_2	MeOH	1:1[c]	9	DIBAL	CH_2Cl_2	1:1[d]
2[e]	$NaBH_4$	MeOH	1:1[d]	10	BH_3•THF	THF	1:1[f]
3[e]	$NaBH_4/CeCl_3$	MeOH	1:1[d]	11	BH_3•pyridine	THF	1:1[f]
4	$NaBH(OAc)_3$	THF	1:1[d]	12	BH_3•Me_2S	THF	1:1[f]
5	Red-Al	CH_2Cl_2	1:1[f]	13	**8**	THF	1:1[f]
6	K-Selectride	THF	1:1[f]	14	**9**	THF	2:1[d]
7	$LiAlH_4$	Et_2O	1:1[d]	15	$Zn(BH_4)_2$	Et_2O	2.5:1[d]
8	$LiAlH(O\text{-}t\text{-}Bu)_3$	THF	1:1[f]	16	**7**[g]	THF	7:1[d]

(a) Reactions were conducted at -78 °C, then slowly warmed to 23 °C over 18 h, unless otherwise indicated. (b) At 23 °C for 2 h. (c) The N-debenzylated products were obtained; the ratio was determined by ^{13}C NMR. (d) The ratio was determined by ^1H NMR. (e) At 5 °C for 2 h. (f) The ratio was estimated by TLC. (g) At -98 °C with slow warming to 23 °C over 18 h.

As shown in Table I, $Zn(BH_4)_2$ (entry 15) and lithium thexyl-(*R*)-limonylborohydride (**9**; entry 14), exhibit modest 1,5 asymmetric induction. None of the reducing agents produced more *syn* diols **5a** than *anti* diols **4a**. NB-Enantride™ (**8**), which is structurally similar to *S*-Alpine-Hydride® and reported to be much more effective for the asymmetric reduction of ketones,[14] is ineffective in our case (entry 13). These results suggest the intermediacy of a metal-chelate with external hydride delivery, as discussed by Baker et al. for the $LiEt_3BH$ reduction of a δ-hydroxy ketone (actually a 1,3 asymmetric induction).[15] Thus, we reasoned that the stereoselectivity might be enhanced by changing conditions to favor a rigid chelate species, for example, by using a less coordinating solvent and by lowering the reaction temperature.



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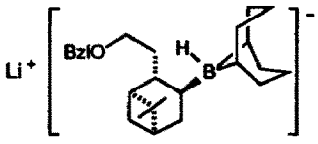

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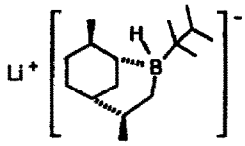


9

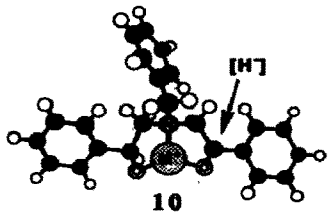
In follow-up studies we used **3b**,[7] a simpler, more readily available δ-hydroxy ketone, as the reaction substrate (Table II).[11,16] Thus, the following observations were realized with Alpine-Hydride. (1) When **3b** was reduced with **7** under the conditions used for **3a**, a similar diastereoselectivity was achieved (entry 1). (2) The 1,5 asymmetric induction is independent of Alpine-Hydride chirality, as the *R* and *S* forms furnished the same ratio of **4b**:**5b** (entries 1 and 2). (3) The *anti*:*syn* selectivity increases as temperature decreases (entries 3-5). (4) The hydride anion structure plays an important role: cf. *R*-Alpine-Hydride (**7**) and $LiBH_4$ (entries 7 and 11; also see data in Table I). (5) Replacement of THF by noncoordinating CH_2Cl_2 significantly enhances 1,5 diastereoselectivity (entries 6 and 7). Similar trends were seen with $Zn(BH_4)_2$ (entries 8-10), particularly

the remarkable solvent effect. Indeed, reduction of **3b** with $Zn(BH_4)_2$ in CH_2Cl_2 at -78 °C produced the *anti* and *syn* diols with excellent *anti* selectivity (*anti*:*syn* = 13:1, entry 10).

Table II. Reduction of δ-Hydroxy Ketone **3b** to Diols **4b** and **5b**

entry	reagent	temp (°C)	time (h)	solvent	4b:5b[a]	yield (%)[b]
1	*R*-Alpine-Hydride	-98 → 0	16	THF	6:1	57
2	*S*-Alpine-Hydride	-98 → 0	16	THF	6:1	62
3	*R*-Alpine-Hydride	-78	5.5	THF	6:1	17
4	*R*-Alpine-Hydride	-40	5	THF	4:1	37
5	*R*-Alpine-Hydride	0	2	THF	3:1	62
6	*R*-Alpine-Hydride	-40	5	CH_2Cl_2	6:1	40
7[c]	*R*-Alpine-Hydride	-78	26	CH_2Cl_2	10:1	40
8	$Zn(BH_4)_2$	0	2	THF	2:1	
9	$Zn(BH_4)_2$	-40	5	THF	4:1	
10	$Zn(BH_4)_2$	-78	26	CH_2Cl_2	13:1	47
11	$LiBH_4$	-78	26	CH_2Cl_2	5:1	

(a) Determined by ^1H NMR. (b) Isolated yield of mixture from preparative TLC. (c) $LiEt_3BH$ gave an 8:1 ratio (55%).



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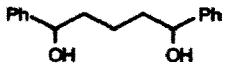

12

To rationalize the results, we propose a 5,5 bicyclic structure such as **10**, in which the lithium or zinc ion is complexed with the hydroxyl, amine, and ketone groups in **3a** or **3b**. In the conformationally rigid array, endo attack by the hydride species is sterically unfavored; attack is preferred from the less hindered exo side, leading to the *anti* diols. Thus, when the reaction is performed in THF, this good donor solvent competes with the groups in **3** for complexation of the metal center and diminishes or inhibits chelate formation. On the other hand, the relatively noncoordinating CH_2Cl_2 enhances chelate involvement. The lack of stereoselectivity with NB-enantride (**8**) may be attributed to the presence of a coordinating ether group in the reagent itself, which could inhibit formation of the chelation complex (**10**).

To determine the influence of the amine nitrogen, δ-hydroxy ketone **11**[17] was reduced at -78 °C in THF with *R*-Alpine-Hydride or $Zn(BH_4)_2$, and the *anti*:*syn* ratio for 1,5-diols **12** was estimated by ^{13}C NMR (relative intensities of the methylene carbons). The nearly 1:1 ratio obtained for either reduction here underscores the importance of the amine nitrogen in **3a** and **3b** for achieving high 1,5 asymmetric induction.

We have presented an interesting example of high 1,5 asymmetric induction in an acyclic system, which involves hydride reduction of a prochiral ketone (sp^2 center) five atoms removed from an existing stereocenter bearing a hydroxyl group. The hydroxyl and intrachain nitrogen cooperate via a metal chelate to direct hydride addition. Such "bicyclic chelation control" is unusual and intriguing,[18] and one could explore for high 1,6 and

1,7 acyclic diastereoselection in the reduction of homologous hydroxy ketones, via 5,6, 6,6, and 5,7 bicyclic complexes. Further studies on this novel type of remote acyclic stereocontrol are in progress.

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11. Products **4a/5a** or **4b/5b** were isolated as a mixture and diastereomeric ratios were determined by proton NMR in $CDCl_3$ (300 or 400 MHz). The diastereotopic benzyl protons of the *anti* isomers appear as two doublets (**4a**: δ 3.75 and 3.92, J = 13.7 Hz; **4b**: δ 3.66 and 3.94, J = 13.5 Hz), whereas the two protons in the *syn* isomers appear as a singlet (**5a**: δ 3.79; **5b**: δ 3.77).
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16. Typical reduction procedure: To a solution of **3b** (0.22 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added dropwise *R*-Alpine-Hydride (0.46 mmol, 0.5 M in THF) via syringe over 35 min. The mixture was stirred at -78 °C for 26 h and quenched with water. The mixture was extracted (CH_2Cl_2) and the organic layer was washed (water; brine) and dried (Na_2SO_4). The volatiles were removed *in vacuo* and the residue was separated by preparative TLC (EtOAc-hexanes, 1:2.5) to give **4b** and **5b**, as a mixture.
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