Remote Stereocontrol by utilizing Intramolecular Carbonyl Reduction with Boranes

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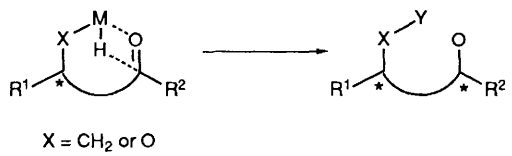
A simple and efficient method for the remote (1,4- and/or 1,5-) stereocontrol was realized by utilizing an intramolecular carbonyl reduction with $ThexBH_2$ (Thex = 1,1,2-trimethylpropyl).

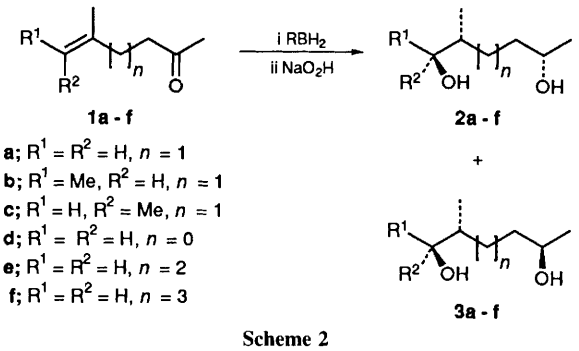
Stereoselective carbonyl reduction reactions directed by neighbouring stereogenic centres are of great interest as an efficient method in the synthesis of polyhydroxylated natural products such as macrolide and polyether antibiotics. While there have been several reports of useful methods for relative 1,2- and 1,3-asymmetric induction in directed carbonyl reduction reactions,[1] an efficient and reliable method for 1,4- or more remote stereocontrol in carbonyl reduction is not well developed.[2] As shown in Scheme 1, a high level of asymmetric induction is expected if the reducing agent is incorporated in a reactant and the reduction proceeds through an intramolecularly constrained cyclic transition state. Here we report our results which demonstrate the potential of the approach in such stereocontrol.

Reaction of 5-methylhex-5-en-2-one **1a** with BH_3 (1.0 equiv.) in tetrahydrofuran (THF; 0.25 mol dm^{-3}) at temperatures from −85 to 20 °C followed by treatment of the reaction mixture with alkaline hydrogen peroxide gave a 2.4 : 1 mixture of the 1,4-*syn*-1,5-diol **2a** and 1,4-*anti*-1,5-diol **3a** in 87% yield (Scheme 2). Assuming that the intervention of an intermol-

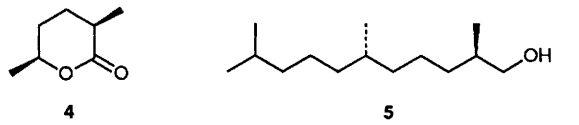


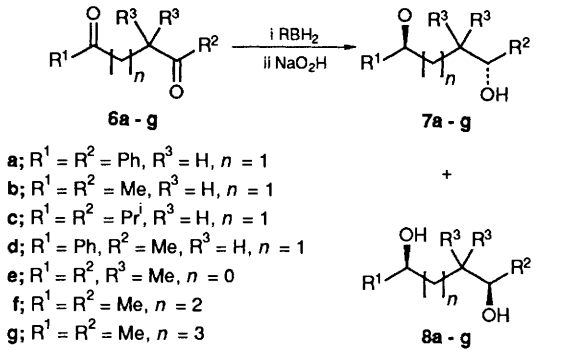
X = CH_2 or O

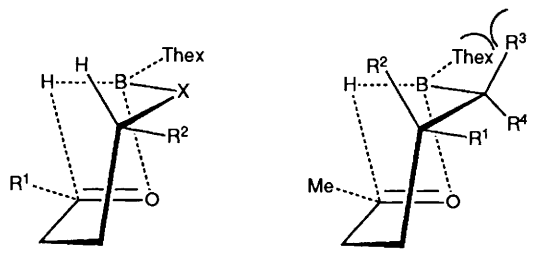
Scheme 1



Scheme 2







Scheme 3

Table 1 Reaction of enone **1** and diketone **6** with $ThexBH_2$[a]

Entry	Substrate	Products	Yield[b] (%)	2 : 3 or 7 : 8[c]
1	**1a**	**2a, 3a**	84	15 : 1
2[d]			91	11 : 1
3[e]			87	2.4 : 1
4	**1b**	**2b, 3b**	78	19 : 1
5[f]			83	4.1 : 1
6	**1c**	**2c, 3c**	32	1 : 8.5
7[f]			100	3.0 : 1
8	**1d**	**2d, 3d**	49	2.5 : 1[g]
9	**1e**	**2e, 3e**	86	6.6 : 1
10	**1f**	**2f, 3f**	57	1.2 : 1[g]
11	**6a**	**7a, 8a**[h]	59	47 : 1
12	**6b**	**7b, 8b**[i]	92	11 : 1
13[d]			100	8.1 : 1
14[f]			93	1.4 : 1
15	**6c**	**7c, 8c**[h]	78	8.1 : 1
16	**6d**	**7d, 8d**	89	17 : 1[g]
17	**6e**	**7e, 8e**[j]	39	6.1 : 1
18	**6f**	**7f, 8f**	44	1 : 1
19	**6g**	**7g, 8g**	18	1 : 1

[a] Unless otherwise noted, reactions were performed by employing 1.0 equiv. of $ThexBH_2$ in THF (0.02 mol dm^{-3}) at temperatures from −85 to 20 °C. [b] Combined yields of stereoisomers. [c] Ratios were determined by ^{13}C NMR analyses. [d] 0.25 mol dm^{-3} in THF. [e] BH_3 in THF (0.25 mol dm^{-3}) was employed. [f] BH_3 in THF (0.02 mol dm^{-3}) was employed. [g] Relative stereochemistry of the major product was not determined. [h] Stereochemistry was determined by ^1H NMR analysis of the acetonide derivative. [i] Ref. 7. [j] Ref. 8.

ecular reduction reduced the stereoselectivity, we turned our attention to thexylborane ($ThexBH_2$) which has been frequently employed in intramolecular hydroborations.[3] Reaction of **1a** with $ThexBH_2$ (1.0 equiv.) in THF (0.25 mol dm^{-3}) and the similar reaction under more dilute conditions (0.02 mol dm^{-3}) provided the two diastereoisomeric diols with even greater selectivity. Both reactions proceeded with excellent yields, giving **2a** and **3a** in ratios of 11 : 1 and 15 : 1, respectively (Table 1).

The relative stereochemistry of **2a** was determined by converting a 11 : 1 mixture of **2a** and **3a** to *cis*-2-methyl-5-hexanolide **4**,[4] sex pheromone of male *Xylocopa hirutissima*, in 32% overall yield by the following reaction sequence: (i) 3,4-dihydro-2*H*-pyran (DHP), TsOH (Ts = *p*-$MeC_6H_4SO_2$), (ii) Ac_2O, pyridine (Py), (iii) TsOH, MeOH, (iv) Jones CrO_3, (v) K_2CO_3, MeOH and (vi) HCl (1 mol dm^{-3}).

Reaction of *Z*-enone **1b** with $ThexBH_2$ also proceeded with a high 1,4-*syn* selectivity to give **2b**† as a major product (entry 4). In contrast to this, *E*-enone **1c**, a geometrical isomer of **1b**, exhibited an opposite 1,4-*anti* stereoselectivity in the reaction with $ThexBH_2$ to afford an 8.5 : 1 mixture of **3c**† and **2c** (entry 6). It should be noted that reaction of **1c** with BH_3 proceeded with a moderate 1,4-*syn* selectivity (**2c** : **3c** = 3.0 : 1, entry 7).

A high level of 1,5-asymmetric induction (6.6 : 1) was observed in the reaction of the homologous enone **1e** (n = 2) (entry 9). Conversion of the major product to *rel*-(6*R*,2*S*)-2,6,10-trimethylundecanol **5**, an epimer of the side chain alcohol of α-tocopherol,[5]‡ clearly showed the stereoselective formation of **2d**. As shown in entries 9 and 10, degrees of 1,3- and 1,6-stereocontrol were low.

We found that reduction of 1,4-diketone **6** (n = 1) with $ThexBH_2$ is also stereoselective (Scheme 3). Thus, for example, treatment of **6a** with $ThexBH_2$ (1.1 equiv.) in THF (0.02 mol dm^{-3}) at temperatures from −85 to 20 °C gave a 47 : 1 mixture of *meso* (or *anti*) **7a** and (±) (or *syn*) **8a**. As shown in Table 1, a high 1,4-*anti* selectivity was observed in reactions of both symmetrical and unsymmetrical 1,4-diketones. However, *meso* selectivity was reduced in the reaction of 1,3-diketone **6e**; reactions of 1,5-diketone **6f** and 1,6-diketone **6g** were nonstereoselective.

† The relative stereochemistries of **2b** and **3c** were determined by comparing their ^{13}C NMR spectra with that of a mixture of authentic samples prepared from a 15 : 1 mixture of **2a** and **3a**. Reaction of 5-tetrahydropyranyloxy-2-methylheptanal, prepared from this mixture in four steps, with MeMgI followed by removal of the THP group gave a 52 : 41 : 4 : 3 mixture of **2b**, **2c**, **3b** and **3c**.

‡ 50% overall yield; (i) Bu^tPh_2SiCl, Et_3N, *N*,*N*-dimethyl-4-aminopyridine, (ii) TsCl, Py, (iii) $[Me_2CH(CH_2)_3]_2CuLi$, (iv) Bu_4NF.

High levels of asymmetric induction as well as the effect of concentration upon selectivities observed in the present hydroboration–reduction of enones and reduction of diketones (see entries 12 and 13) support an intramolecular mechanism for these reactions. Formation of 8-hydroxy-7-methyloctan-2-one (18%) as a by-product in the reaction of **1f** suggests that the alkene is more reactive than a carbonyl group under the present reaction conditions and, therefore, the reaction of the enone most probably proceeds through an intermolecular hydroboration at the first step followed by intramolecular carbonyl reduction.

It is reasonable to assume that the local geometry of the transition state in the intramolecular carbonyl reduction is similar to the staggered transition state that was proposed in the intermolecular reaction based on *ab initio* calculations.[5] Then, with the exception of the reaction of **1c** with $ThexBH_2$, selectivities observed in both hydroboration–reduction of enones and reduction of diketones are rationalized by the cyclic transition state **9** in which R^2 takes a pseudo-equatorial position. The 1,4-*anti* selectivity observed in the reaction of **1c** with $ThexBH_2$, but not with BH_3, may be the result of an unfavourable *gauche* interaction between the methyl group (R^3) and the sterically demanding thexyl group in transition state **10** which forces the reaction to proceed rather through pseudo-diaxial transition state **11**.

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