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Stereocontrolled 1,4-Asymmetric Reduction of Cyclic Hemiketals. Synthesis of Both *anti*- and *syn*-1,4-Diols, and Their Transformations into *trans*- and *cis*-2,5-Disubstituted Tetrahydrofurans

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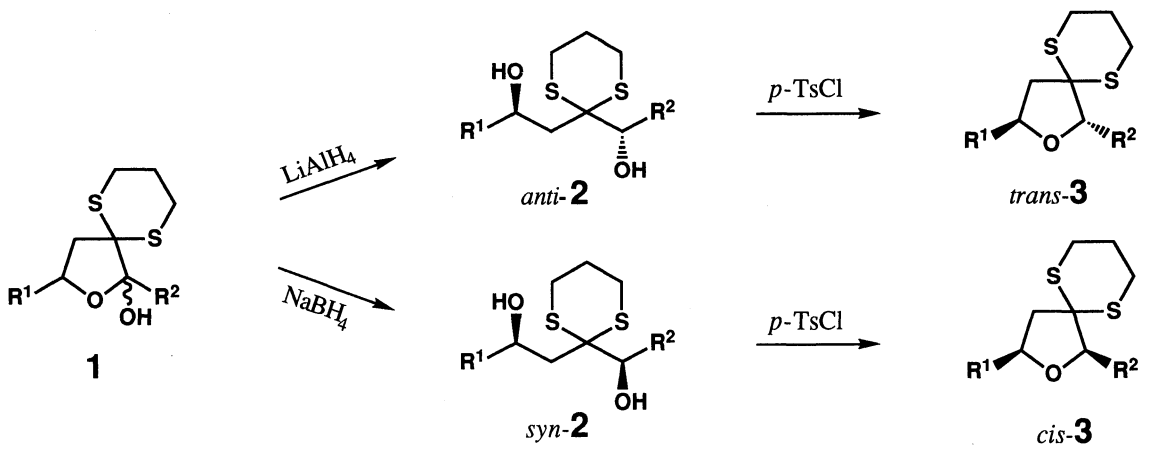
Reduction of dithioacetal-functionalized cyclic hemiketals with $LiAlH_4$ in THF and $NaBH_4$ in ethanol gave the corresponding *anti*- and *syn*-1,4-diols with excellent stereoselectivity, respectively. The *anti*- and *syn*-1,4-diols were easily transformed into *trans*- and *cis*-2,5-disubstituted tetrahydrofurans with complete stereospecificity by the one-step cyclodehydration with *p*-TsCl in pyridine, respectively.

Stereocontrolled construction of 1,n-diol structures is an important and prominent problem in recent organic synthesis. The most typical and fundamental strategy is the 1,n-asymmetric induction based on the nucleophilic addition of organometallics or hydrides to chiral n-hydroxy carbonyl derivatives. This type of methodology has been widely developed in recent years producing highly stereocontrolled 1,2- and 1,3-asymmetric induction.[1)] However, 1,4-asymmetric induction has been still difficult mainly because of the difficulty in controlling the remote chiral center in the chelation-controlled transition states.[1,2)] Recently, Tsuchihashi *et al.* reported a new approach for the 1,4-asymmetric induction based on nucleophilic addition of methyllithium to lactols and showed promise in synthesizing 1,4-*syn* diols with high stereoselectivity.[3)] However, up to now, no method for the stereocontrolled synthesis of 1,4-diol skeletons has emerged to the level that would allow general access to both *anti* and *syn* stereoisomers. In this paper, we wish to report a novel and efficient strategy to synthesize each of the two 1,4-diol configurational isomers with a high degree of stereochemical control based on stereoselective hydride addition to the cyclic hemiketal **1** (Scheme 1). Furthermore, we will also demonstrate that chiral *anti*- and *syn*-1,4-diols obtained by this method are easily transformed into optically active *trans*- and *cis*-2,5-



Scheme 1.

Table 1. Stereocontrolled Reduction of Cyclic Hemiketals **1** to *anti*-**2** with $LiAlH_4$ in THF[a)]

Entry	Hemiketal	R^1	R^2	Temp/ °C	Yield/ %[b)]	Stereoselectivity[c)] *anti*-**2** : *syn*-**2**
1	**1a**	Me	Ph	-78	39	13.3 : 1[d)]
2	**1a**	Me	Ph	0	65	5.5 : 1
3	**1a**	Me	Ph	-78	66	94.6 : 1
4	**1b**	Me	*n*-Pr	-78	78	4.7 : 1
5	**1c**	*n*-C_6H_{13}	*n*-Pr	-78	75	13.3 : 1
6	**1d**	Ph	Ph	-78	53	>99.0 : 1

a) The reactions were carried out with 2 equiv. of $LiAlH_4$ for 7-10 h. b) Yield of isolated isomeric mixture after silica-gel column chromatography. c) Determined by 400 MHz ^1H NMR analysis. d) Reduction in ether.

disubstituted tetrahydrofurans without epimerization by the one-step cyclodehydration process, respectively.[4)]

Although several metal hydride reagents such as DIBAL-H and $Zn(BH_4)_2$ were inert towards the cyclic hemiketal **1a**, we have found that the reduction of **1a** with $LiAlH_4$ afforded the corresponding 1,4-diol **2** in good yield with high preference to *anti* selectivity (Table 1). $LiAlH_4$-reduction of **1a** in ether at -78 °C or in THF at 0 °C gave *anti*-**2a** with high stereoselectivity (Entries 1,2), while a superior result (95:1) was realized for the reduction in THF at -78 °C (Entry 3). The high *anti* preference of the $LiAlH_4$-reduction was further demonstrated by the reduction with several different cyclic hemiketals **1b-d** to give *anti*-**2b-d** with the results summarized in Table 1.[2)] In marked contrast, the reduction of a series of cyclic hemiketals **1a-d** with $NaBH_4$ in ethanol at 0 °C showed good opposite selectivity without exception leading to the formation of *syn*-**2a-d**. The results are summarized in Table 2. Stereochemistry of the diol **2** could be easily determined after their transformations into the tetrahydrofuran derivative **3** by the stereoselective one-step cyclodehydration (Scheme 1).[2)] The treatment of the isomeric mixture of *anti*-**2** and *syn*-**2** with 5 equiv. of *p*-TsCl in pyridine at room temperature for 48 h cleanly gave the mixture of tetrahydrofurans, *trans*-**3** and *cis*-**3**, while exactly maintaining the isomeric ratio (*anti* : *syn* = *trans* : *cis*). The relative stereochemistry of these tetrahydrofurans was assigned based on the NOE-measurement of the ring protons.

The present stereoselective 1,4-asymmetric reduction was further demonstrated by reducing the chiral cyclic hemiketals **4** and **5** (Scheme 2).[5)] The $LiAlH_4$-reduction of these cyclic hemiketals in THF at -78 °C afforded

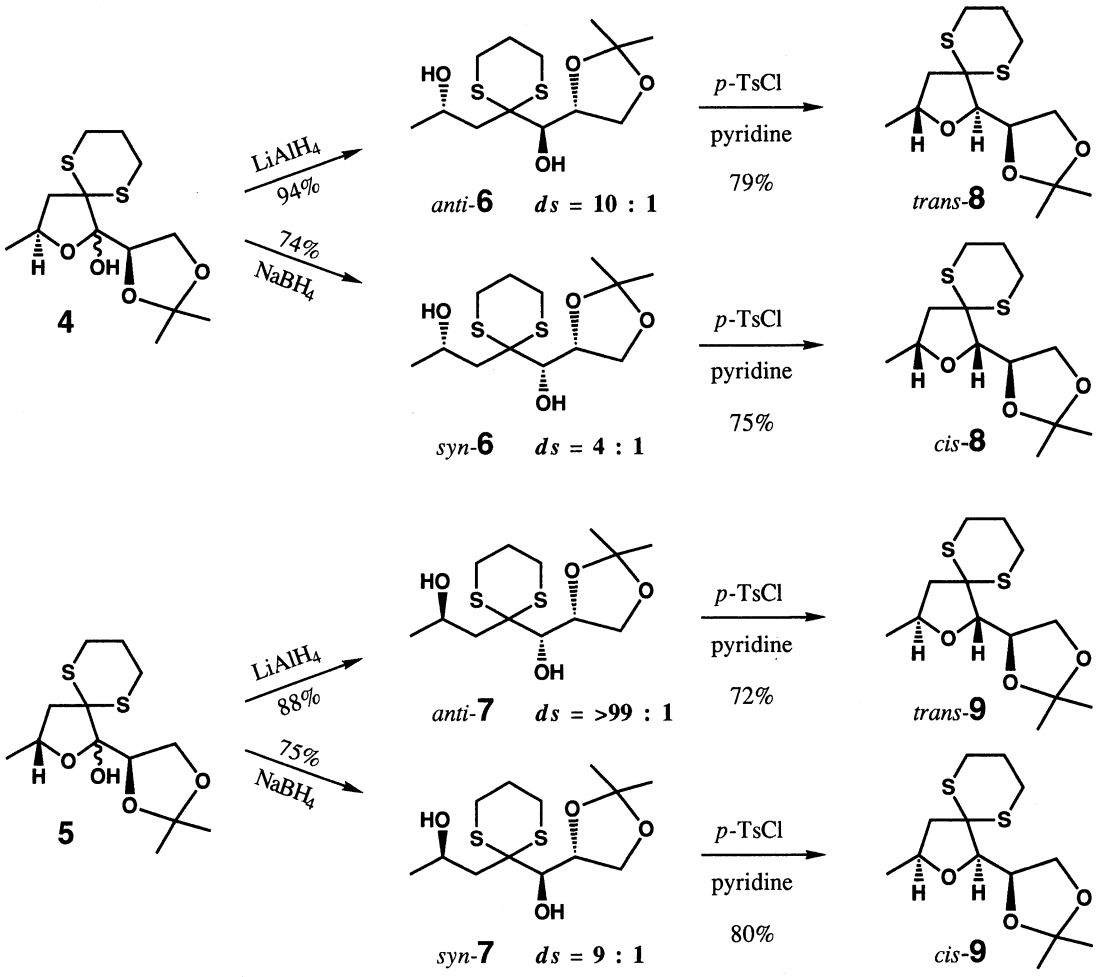
Table 2. Stereocontrolled Reduction of Cyclic Hemiketals **1** to *syn*-**2** with $NaBH_4$ in Ethanol[a)]

Entry	Hemiketal	R^1	R^2	Temp/ °C	Yield/ %[b)]	Stereoselectivity[c)] *syn*-**2** : *anti*-**2**
1	**1a**	Me	Ph	r.t.	91	1.2 : 1
2	**1a**	Me	Ph	-40	68	2.7 : 1
3	**1a**	Me	Ph	0	98	3.5 : 1
4	**1b**	Me	*n*-Pr	0	95	5.4 : 1
5	**1c**	*n*-C_6H_{13}	*n*-Pr	0	64	3.2 : 1
6	**1d**	Ph	Ph	0	75	3.0 : 1

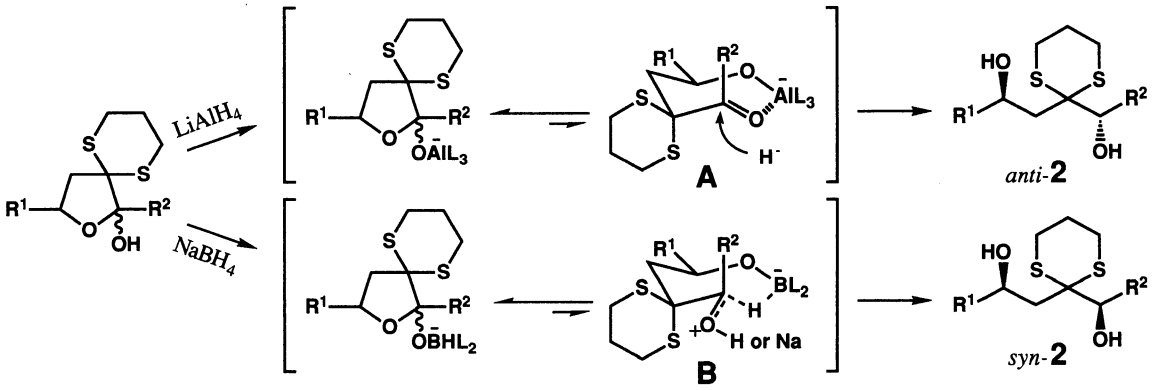
a) The reactions were carried out with 2 equiv. of $NaBH_4$ for 7-10 h. b) Yield of isolated isomeric mixture after silica-gel column chromatography. c) Determined by 400 MHz ^1H NMR analysis.

anti-**6**,**7** in good yields with excellent selectivities of 10:1 and >99:1, respectively.[6] On the other hand, the $NaBH_4$-reduction of **4** and **5** showed good *syn* preference to give *syn*-**6**,**7** in good yields with selectivities of 4:1 and 9:1, respectively. We have already found that the 1,2-asymmetric reduction of a similar type of chiral α,β-dialkoxy 1,3-dithian-2-yl ketones without any other chiral center with $LiAlH_4$ and $NaBH_4$ shows high *syn* and low *anti* selectivity, respectively.[7] The cyclic hemiketals **4** and **5** are thus regarded as a "*mismatched substrate*" and "*matched substrate*", respectively in either $LiAlH_4$- and $NaBH_4$-reductions. It is generally believed that 1,n-asymmetric induction is more effective than 1,m(m>n)-asymmetric induction. However, remarkably, the stereochemical courses are predominantly controlled by the 1,4-asymmetric induction rather than the 1,2-asymmetric induction. This indicates a high reliability of the present 1,4-asymmetric reduction with the cyclic hemiketals **1**. The optically active 1,4-diols, *anti*-**6**,**7** and *syn*-**6**,**7**, could be easily transformed into the corresponding optically active tetrahydrofurans, *trans*-**8**,**9** and *cis*-**8**,**9**, by the cyclodehydration process in good yield without epimerization, respectively (Scheme 2).[4]

The stereochemical courses of the present reductions would be rationalized based on the two different types of transition states illustrated in Scheme 3. We hypothesized that the putative ligand exchange of the hydride reagents precedes the actual reduction step. In the $LiAlH_4$-reduction, the ligand exchange is presumed to lead to the formation of the seven-membered transition state **A** where the attack of a hydride should occurs preferentially



Scheme 2.



Scheme 3.

from the peripheral side leading to the formation of *anti* products.[8] On the other hand, the $NaBH_4$-reduction is presumed to proceed *via* the seven-membered transition state **B** which involves intramolecular hydride delivery[9] as well as carbonyl activation by a proton or Na^+ leading to the formation of *syn* products. In the latter case, the 1,2-interaction between the dithioacetal group and R^2 that occurred on the other transition state should destabilize the transition state to a high extent when compared with the favored transition state **B**.

Further study on synthetic applications of the methodology as well as scope and limitation are now in progress.

References

1) For reviews, see: E. L. Eliel, "Asymmetric Synthesis," ed by J. D. Morrison, Academic, New York (1983), Vol. 2, pp. 125-156; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984); G. J. McGarvey, M. Kimura, T. Oh, and J. M. Williams, *J. Carbohydr. Chem.*, **3**, 125 (1984); T. Oishi and T. Nakata, *Acc. Chem. Res.*, **17**, 338 (1984); S. Masamune, W. Choy, J. S. Peterson, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, **24**, 1 (1985); J. Jurczack, S. Pikul, and T. Bauer, *Tetrahedron* , **42**, 447 (1986).

2) We have recently reported a new type of 1,4-asymmetric induction based on the alkylation of achiral aldehydes with chiral 1,3-dithianyl anions giving *anti*-**2** selectively, and the transformation of *anti*-**2** into *trans*-**3** by the stereoselective one-step cyclodehydration process: H. Chikashita, H. Yasuda, Y. Kimura, and K. Itoh, *Chem. Lett.*, **1992**, 195.

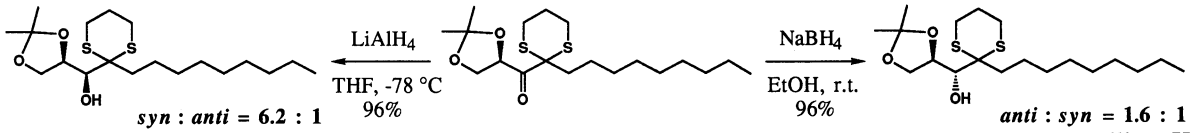
3) K. Tomooka, T. Okinaga, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 6335 (1987); K Tomooka, K. Matsuzawa, K. Suzuki, and G. Tsuchihashi, *ibid.*, **28**, 6339 (1987).

4) We have already shown that the present type of cyclization proceeds without racemization: See Ref. 2.

5) Chiral cyclic hemiketal **4** was easily prepared as the optically pure form by acylation of the dianion of (*S*)-1-(1,3-dithian-2-yl)-2-propanol with ethyl 1,2-*O*-isopropylidene-D-glycerate. Chiral cyclic hemiketal **5** was prepared by a similar method with (*R*)-1-(1,3-dithian-2-yl)-2-propanol which was obtained with the (*S*)-form by its improved Mitsunobu-inversion: H. Chikashita, E. Kittaka, Y. Kimura, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 833 (1989).

6) Stereochemistry of the diols **6** and **7** could be easily determined by 400 MHz ^1H NMR analysis based on their 2,3-stereochemistry: See Ref. 7.

7) For example, 1,2-asymmetric reduction of the following ketone with $LiAlH_4$ and $NaBH_4$ showed the opposite selectivity with the results shown below. See also: H. Chikashita, T. Nikaya, H. Uemura, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 2121 (1989).



8) A similar mechanism have been recently postulated for the alkylation of lactols with organometallics: K. Tomooka, T. Okinaga, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **30**, 1563 (1989).

9) A six membered type of similar transition state was proposed for the reduction with $Me_4NBH(OAc)_3$: D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, **110**, 3560 (1988).

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