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A New Stereocontrolled Route to *trans*-2,5-Disubstituted Tetrahydrofurans

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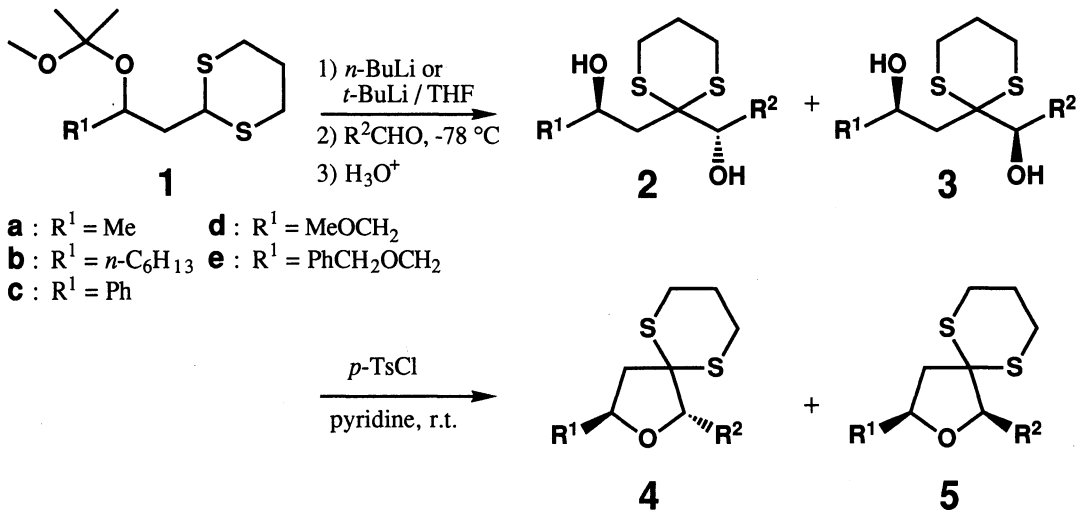
An effective new route for the stereocontrolled synthesis of *trans*-2,5-disubstituted tetrahydrofurans was described, which involved a new type of 1,4-asymmetric induction based on the addition of originally designed dithianyl anion to aldehydes and a stereocontrolled cyclodehydration of the resulting 1,4-diols.

Development of a methodology for the stereocontrolled construction of substituted tetrahydrofurans continues to receive significant attention in connection with the synthesis of polyether antibiotics and other natural products containing oxacyclic units. Among many notable methodologies,[1] one noteworthy example for the stereoselective construction of 2,5-disubstituted tetrahydrofurans is the cyclization of a hydroxy epoxide with the relative stereochemistry predetermined, as demonstrated by Kishi.[2] An alternative route may be achieved by the stereoselective direct cyclodehydration of a 1,4-diol, but such an approach has not so far been generally employed[3] because of difficulties of stereoselective facile synthesis of 1,4-diols[4] and problems on the discrimination between two secondary hydroxyl groups in a 1,4-diol molecule at the cyclization stage.[5] Here we wish to report our initial results of a new strategy via this process which is promising for the stereoselective construction of the especially troublesome *trans*-2,5-disubstituted tetrahydrofurans. Thus, the method can be realized by a new type of 1,4-asymmetric induction based on hydroxyalkylation of the dithianyl anion derived from **1** with aldehydes, followed by the highly stereoselective one-step cyclodehydration of the resulting 1,4-*anti* diols **2** to *trans*-tetrahydrofurans **4** as shown in Scheme 1.



Scheme 1.

Table 1. Stereocontrolled Synthesis of *trans*-2,5-Disubstituted Tetrahydrofurans **4**

			Preparation of 1,4-diols[a]		Cyclization of 1,4-diols[d]	
Entry	Substrate	Aldehyde	Yield[b]/ %	**2/3** (*anti/syn*)[c]	Yield[e]/ %	**4/5** (*trans/cis*)[c]
1	**1a**	*n*-C_3H_7CHO	82	86 / 14	58	86 / 14
2	**1a**	*n*-$C_9H_{19}CHO$	70	81 / 19	44	81 / 19
3	**1a**	*i*-C_3H_7CHO	72	80 / 20	63	80 / 20
4	**1a**	*t*-C_4H_9CHO	79	81 / 19	84	81 / 19
5	**1a**	*c*-$C_6H_{11}CHO$	75	80 / 20	68	80 / 20
6	**1b**	*t*-C_4H_9CHO	34	>99 / 1	66	>99 / 1
7	**1c**	*t*-C_4H_9CHO	50	97 / 3	60	97 / 3
8	**1d**	*t*-C_4H_9CHO	81	80 / 20	81	80 / 20
9	**1e**	*t*-C_4H_9CHO	48	85 / 15	-	-

a) All the reactions were carried out by metalation of **1** (2 mmol) with *n*-BuLi or *t*-BuLi (2.2 mmol) in THF (5 ml) at -30 °C (1 h) - 0 °C (3 h) followed by the reaction with aldehydes (2.2 mmol) at -78 °C for 3 h. b) Total isolated yield of unseparable mixture of **2** and **3** by midium pressure liquid chromatography (MPLC) on silica gel. c) Isomeric ratio was determined by 400 MHz ^{1}H NMR analysis. d) All the reactions were carried out on 2-mmol scale with 5 equiv. of *p*-TsCl in pyridine (5 ml) at room temperature for 24 h. e) Isolated yield of isomeric mixture of **4** and **5** by silica-gel MPLC.

Employing the simple procedure with dianion[6] of 1-(1,3-dithian-2-yl)-2-hydroxypropane (non-protected **1a**) and aldehydes showed almost no stereoselection. So we investigated the efficiency of protecting the OH site of this alcohol and found that the anion of 1-methyl-1-methoxyethyl (MMOE) ether **1a**[7] in THF was the most effective for stereoselective hydroxyalkylation with aldehydes to 1,4-*anti* diols **2** with the respective results summarized in Table 1 (Entries 1-5). The stereoselectivity was influenced by the nature of the alkoxyl group. Tetrahydropyranyloxy, tetrahydrofuranyloxy and *tert*-butyldimethylsilyloxy groups appeared to induce lower selectivity than MMOEO-group. Noteworthy is that these groups induced the selectivity to some extent but remarkably the methoxymethyloxy group showed almost no effect on the stereoselection. In the reaction with **1a**, the addition of HMPA extinguished the selectivity to high extent. On the other hand, the similar reaction of pivalaldehyde using anions of **1b** and **1c** showed very high stereoselectivity as shown in Table 1 (Entries 6 and 7). Considering these facts, as illustrated in Fig. 1, the origin of the stereoselectivity on the present 1,4-asymmetric induction may be attributable to the steric bulkiness of both the substituent R^1 (a *versus* b) and the MMOE group (A *versus* B) in the five-membered chelating transition state structure. It should be noted that the stereoselectivity attained with **1e** was higher than that observed with **1d** (Entries 8 and 9), suggesting also an importance of the steric effect induced by R^1. The relatively lower selectivity of the reactions of **1d** and **1e** when compared with that of **1b** and **1c** may be due to a participation of the chelation effect between Li^+ and an oxygen of methoxy and benzyloxy groups.

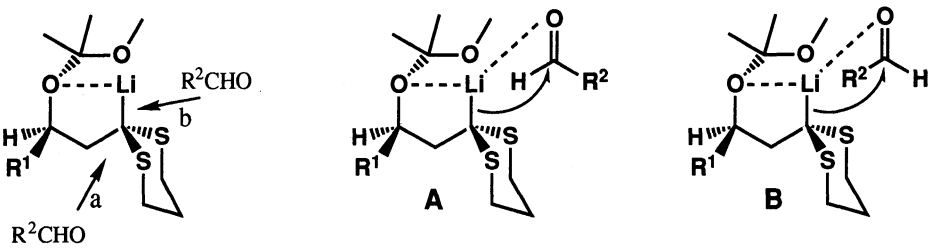
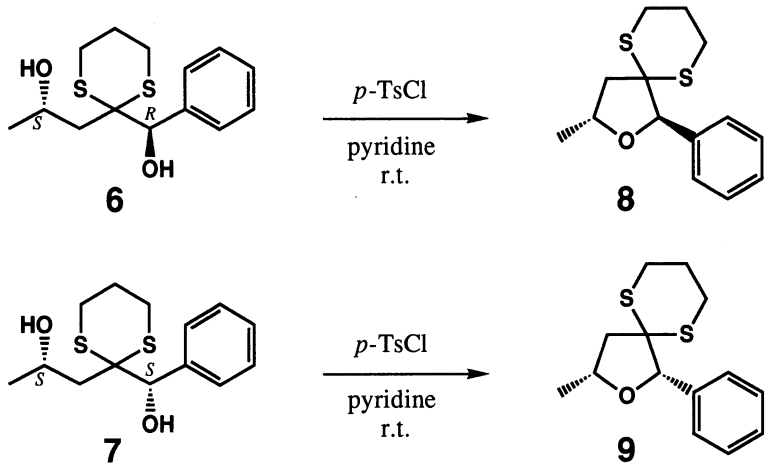


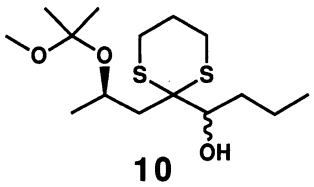
Fig. 1.

Treatment of an isomeric mixture of **2** and **3** with 5 equiv. of *p*-TsCl in pyridine at room temperature cleanly and stereoselectively gave a mixture of **4** and **5** in good yields (Table 1). The stereochemistry of **4** and **5** was assigned based on the chemical shift[8] of C_5-CH_3 and C_5-H together with NOE-measurement by 400 MHz ^{1}H NMR. The most significant feature is that diastereomeric ratios (**2/3**) of 1,4-diols are exactly transferred to the isomeric ratios (**4/5**) of the cyclization products. Stereoselectivities of this reaction were further investigated by the individual treatment of the optically active diastereoisomers **6** and **7** under the reaction conditions, which were prepared from optically pure (*S*)-**1a**[6] and benzaldehyde as an easily separable mixture (Scheme 2).[9]



Scheme 2.

The reactions of **6** and **7** gave only the corresponding optically active **8** and **9**, respectively, without loss of optical activity as shown in Scheme 2.[10] These results show that these cyclizations proceeded with the absolute stereospecificity (no epimerization) and that the absolute discrimination of two secondary hydroxyl groups of a 1,4-diol (no racemization) was made for either *anti* or *syn* diol.[11] On the other hand, no tosylation of partially protected racemic diol **10** (isomeric mixture) occurred under the conditions, indicating an importance of the



existence of dithioacetal group in a 1,4-diol molecule for the discrimination of two secondary hydroxyl groups in the cyclization. Thus, the present stereoselective cyclodehydration should proceed via the mechanism of chemoselective tosylation at the hydroxyl group more distant from the dithioacetal group, followed by SN2-type intramolecular cyclization with complete inversion of configuration at the tosyloxylated carbon.

In summary, we have presented a novel route which provides a convenient, efficient, and overall stereocontrolled synthesis of *trans*-2,5-disubstituted tetrahydrofurans. The dithioacetal group could be efficiently utilized for natural product synthesis because of its easy conversion to a variety of functionalities. Applications to natural product synthesis as well as development of the efficient procedure for the opposite stereoselection to prepare *cis*-2,5-disubstituted tetrahydrofurans are now under investigation.

References

1) For recent papers, see: J. E. Semple and M. M. Joullie, *Heterocycles*, **14**, 1825 (1980); D. R. Williams, Y. Harigaya, J. L. Moore, and A. D'sa, *J. Am. Chem. Soc.*, **106**, 2641 (1984); P. C. Ting and P. A. Bartlett, *ibid.*, **106**, 2668 (1984); M. J. Kurth and M. J. Rodrigues, *ibid.*, **109**, 7577 (1987); R. L. Mulholland, Jr. and A. I. Chamberlin, *J. Org. Chem.*, **53**, 1082 (1988); M. F. Semmelhack and N. Zhang, *ibid.*, **54**, 4483 (1989).

2) T. Fukiya, B. Vransic, D. P. Negri, and Y. Kishi, *Tetrahedron Lett.*, **1987**, 2741; T. Nakata and Y Kishi, *ibid.*, **1978**, 2745.

3) As an exception, stereospecific cyclodehydration of 1,4-diols has been efficiently utilized for the synthesis of highly substituted tetrahydrofurans: D. R. Williams, J. G. Phillips, and B. A. Barner, *J. Am. Chem. Soc.*, **103**, 7398 (1981); D. R. Williams and J. G. Phillips, *Tetrahedron*, **42**, 3013 (1986).

4) 1,4-Asymmetric induction by nucleophilic additions to chiral alkoxy aldehydes would be a convenient, useful, and standard route for the stereoselective construction of 1,4-diols, but an efficiently controlled method based on this methodology is rare: M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, and R. Steinbach, *Angew. Chem., Int. Ed. Engl.*, **22**, 989 (1983).

5) Although cyclodehydration processes of 1,n-diols to the corresponding cyclic ethers have been previously reported, these procedures are not exempted from these problems: J. C. Martin, J. A. Franz, and R. J. Arhart, *J. Am Chem. Soc.*, **96**, 4604 (1974); A. Molnar, K. Felfoldi, and M. Martok, *Tetrahedron*, **37**, 2149 (1981); D. Kotkar, S. W. Mahajan, and A. K. Mandal, and P. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1749.

6) H. Chikashita, E. Kittaka, Y. Kimura, and Y. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 833 (1989).

7) MMOE ethers **1** can be easily and quantitatively prepared by $POCl_3$-catalyzed addition of the 1-(1,3-dithian-2-yl)-2-alkanol to 2-methoxypropene: A. F. Klug, K. G. Untch, and J. H. Friend, *J. Am. Chem. Soc.*, **94**, 7827 (1972).

8) In the present type of tetrahydrofurans, literature data indicate that the C_5-CH_3 doublet for *trans* isomers generally resonates at higher field and in contrary the C_5-H multiplet for *trans* isomers resonates at lower field, than those of *cis* isomers.

9) We have examined the reaction of **1a** with aromatic aldehydes such as benzaldehyde or furfural under several different reaction conditions to improve the stereoselectivity (roughly 1:1), but have not obtained any satisfactory results yet.

10) The optical purities were determined to be >98% ee, by 400 MHz ^1H NMR chiral shift study with (+)-Eu(hfc)$_3$.

11) Specific rotations (in chloroform) of compounds prepared in the present study are as follows: **6**, $[\alpha]^{24}_D$ -30.8° (c 1.9); **7**, $[\alpha]^{24}_D$ +20.0° (c 2.4); **8**, $[\alpha]^{22}_D$ +5.53° (c 1.8); **9**, $[\alpha]^{22}_D$ -59.7° (c 1.5).

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