CHEMISTRY LETTERS, pp. 1003-1004, 1990.

Diastereo-Differentiating Isomerization of Meso 3,4-Epoxycyclopentanone Ketal to a Chiral 4-Hydroxy-2-cyclopentenone Ketal

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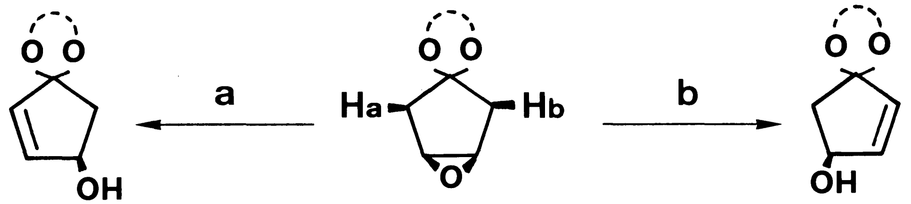
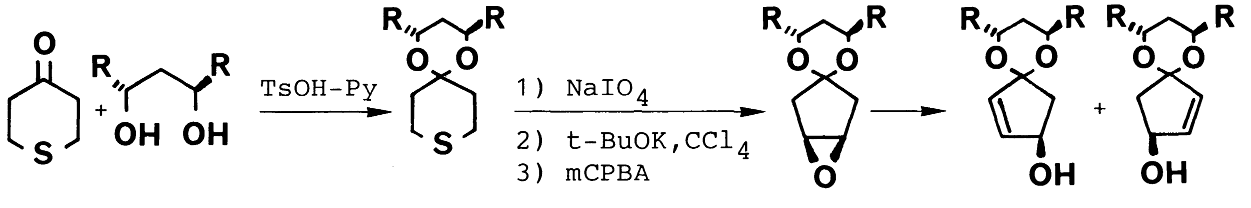
A new type diastereo-differentiating isomerization of meso 3,4-epoxycyclopentanone carrying a chiral diol as ketal to give 4-hydroxy-2-cyclopentenone ketals was demonstrated in a ratio of up to 87.7 to 12.3.

Isomerizations of meso 3,4-epoxycyclopentanone ketal(**1**) provide chiral 4-hydroxy-2-cyclopentenone ketal(**2**) by treatment of strong base. When optically active diol was incorporated in a ketal moiety of **1** as a chiral auxiliary, diastereo-differentiating isomerization could be possible in giving **2** as an optically active state. In a substrate **1**, the isomerization could be induced by the attack of base to β syn protons(H_a and H_b in the figure), which were located close to the chiral ketal moiety.$^{1)}$



2a **1** **2b**

This report deals with a new type diastereo-differentiating reaction designed based on the strategy mentioned above. As for chiral auxiliaries, we employed optically pure (2*R*,4*R*)-2,4-pentanediol(PD) and (3*S*,5*S*)-2,6-dimethyl-3,5-heptanediol(DMHD) which was recently developed as a bulky analogue of PD.$^{2)}$ The substrates(**3** and **4**) were prepared from 4-thianone as shown in Scheme 1.$^{3)}$



R=Me,i-Pr

3:R=Me **4**:R=i-Pr **5**:R=Me **7**:R=i-Pr **6**:R=Me **8**:R=i-Pr

Scheme 1.

Isomerization of 3 and 4 proceeded in the presence of 2.5 molar equivalent of various lithium amides at 0 °C. The results are shown in Table 1.

Table 1. Isomerization of 3 and 4 with Lithium Amides

Entry	Substrate	Base	Solvent	**5** / **6**[a)]	Yield/%
1	3	$\mathrm{LiNEt_2}$	Ether	84.1 / 15.9	46.4
2	**3**	$\mathrm{LiNEt_2}$	Ether+HMPA	84.6 / 15.4	36.8
3	**3**	$\mathrm{LiNEt_2}$	Hexane	72.6 / 27.4	34.3
4	**3**	$\mathrm{LiN}(i\text{-}\mathrm{Pr})_2$	Ether	62.4 / 37.6	12.8
5	**3**	$\mathrm{LiN}(i\text{-}\mathrm{Pr})_2$	Ether+HMPA	84.4 / 15.6	9.1
6	**3**	LiTMP[b]	Ether	62.0 / 38.0	9.6
				7 / **8**[a)]	
7	**4**	$\mathrm{LiNEt_2}$	Ether	87.7 / 12.3	80.7

a) The diastereomer ratios, **5**/**6** and **7**/**8**, were determined by capillary GLC analysis(silicone OV-1, 25 m, 0.25 mm i.d.).
b) TMP=2,2,6,6-tetramethylpiperidide

Isomerization of 3 with $\mathrm{LiNEt_2}$/ether system gave a mixture of diastereomers(**5** and 6) in an appreciable ratio with a moderate yield(Entry 1).[4)] The use of a mixture of ether and HMPA as a solvent did not positively enhance both diastereomer ratio and yield(Entry 2). The use of nonpolar solvent such as hexane was unfavorable(Entry 3). The uses of reagents carrying bulky alkyl group resulted in a decrease of yield without increasing diastereomer ratio(Entries 4-6).

Isomerization of **4** under the conditions of Entry 1 gave a mixture of diastereomers(**7** and 8) in the highest ratio and excellent chemical yield(Entry 7).[4)] These results showed that bulkiness of the chiral auxiliary in the substrate played key role to increase the diastereomer ratio as well as chemical yield.

The present results not only offered a new type diastereo-differentiating reaction but gave carbonyl protected 4-hydroxy-2-cyclopentenone: a synthon for the synthesis of natural products such as prostaglandins. The results also emphasized the efficiency of DMHD as a chiral auxiliary.

References
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4) Configuration of hydroxylic carbon in both 5 and **7** was determined to be *R* by chemical correlation with (+)-(*R*)-4-(*t*-butyldimethylsilyloxy)-2-cyclopentenone. M. Kitamura, I. Kasahara, K. Manabe, R. Noyori, and H. Takaya, J. Org. Chem., **53**, 708(1988).

(Received March 29, 1990)