

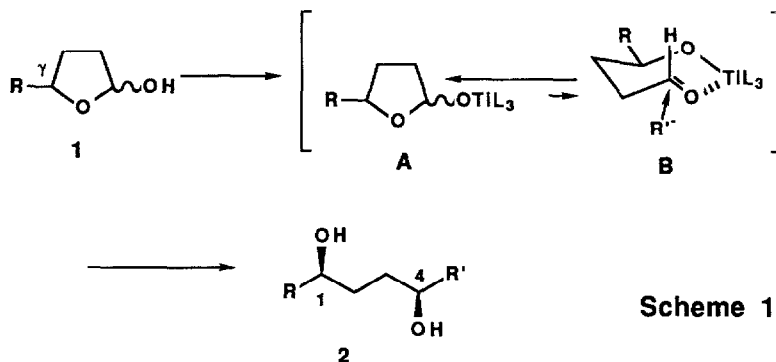
### Lactols in Stereoselection 3. Highly *anti*-Cram Selective 1,2-Asymmetric Induction

Katsuhiko Tomooka<sup>†</sup>, Tatsuyuki Okinaga, Keisuke Suzuki\*, and late Gen-ichi Tsuchihashi  
Department of Chemistry, Keio University, Hiyoshi, Yokohama 223, Japan

*Summary:* Nucleophilic addition of  $\text{MeTi}(\text{O-}i\text{Pr})_3$  to  $\alpha$ -chiral lactols proceeds in highly diastereoselective manner. The sense of the diastereofacial selection is *anti*-Cram-type, which provides a new and useful method for 1,2-asymmetric induction.

Since the pioneering work by Cram *et al.*,<sup>1)</sup> much interests have been paid to the stereoselectivity in the nucleophilic addition to chiral carbonyl compounds. Numerous data have been accumulated for a number of different categories, e.g. chelation-controlled, nonchelation-controlled, and so on.<sup>2)</sup>

Recently, we reported a unique behavior of chiral  $\gamma$ - and  $\delta$ -lactols as a sort of "template" in the related asymmetric induction.<sup>3)</sup> Nucleophilic attack to these latent hydroxy aldehydes, such as 1, proceeds in highly diastereoselective manner, particularly by the use of organotitanium reagents,<sup>4)</sup> which offers a new opportunity for remote (1,4-, and 1,5-) stereocontrol. Our postulate for this process is schematically shown for the case of the 1,4-asymmetric induction with  $\gamma$ -lactol 1 with the  $\gamma$ -chirality (Scheme 1). The seven-membered Ti-chelate of type B, disposing the substituent R pseudo-equatorial,



is the reactive intermediate that undergoes the nucleophilic attack from the peripheral side to establish the 1,4-*syn* relationship in the diol 2.

With this postulate in mind, we examined the reactions of the lactols possessing the  $\alpha$ -chirality in order to see the sense and the degree of the 1,2-asymmetric induction. In this communication, we wish to describe a prominent outcome of this attempt, that is, the realization of highly *anti*-Cram stereoselection on this "lactol template".<sup>5)</sup>

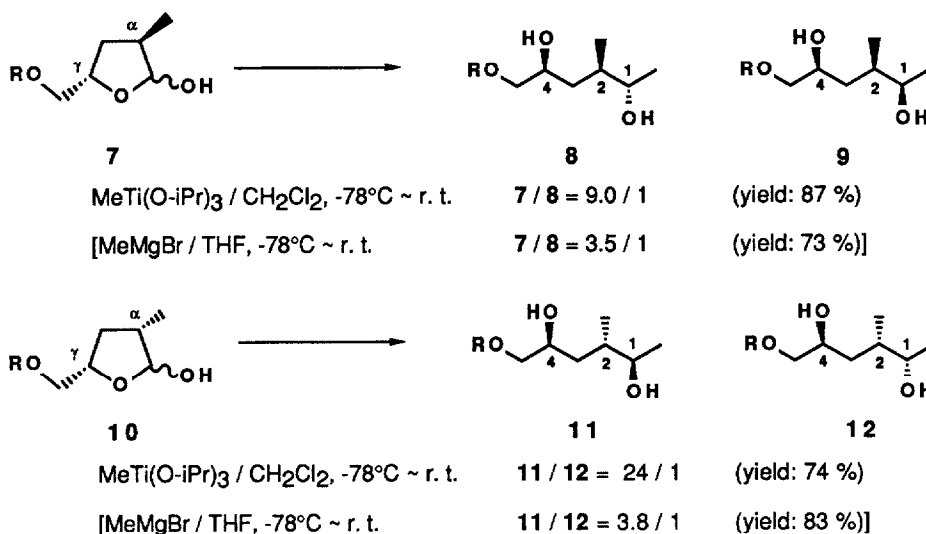
<sup>†</sup>Present address: Department of Chemical Technology, Tokyo Institute of Technology, Meguro, Tokyo 152



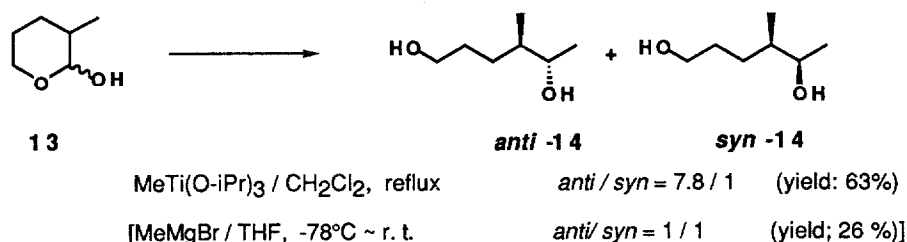
the methyl group and a bulky ligand L on the metal.<sup>10</sup> The model serves quite well for predicting the sense of this diastereoselective reaction,<sup>11, 12</sup> although quite primitive, ignoring many pertinent factors, e.g. the coordination angle, the aggregation state, and so on.

To gain further insight, we performed the reaction of  $\alpha,\gamma$ -disubstituted lactols **7**, **10**.<sup>13</sup> The  $\alpha$ -substituent drives the reaction to 1,2-*anti* direction, while the  $\gamma$ -substituent to 1,4-*syn* direction (Cf. Scheme 1). Therefore, these two substituent effects are expected to be cooperative in **10**, whereas contradict each other in **7** based on the model. The results of these attempts turned out to be consistent with this modelling.<sup>14</sup> Namely, the reaction of **10** led to a highly selective formation of **11**, while the selectivity was lower in the case of **7**. That the selectivity of **11** / **12** still holds a high level (9.0 / 1) suggests that the effect of  $\alpha$ -chirality is far more influential than the effect of the  $\gamma$ -chirality.

**Scheme 2** (R- = t-BuPh<sub>2</sub>Si-)



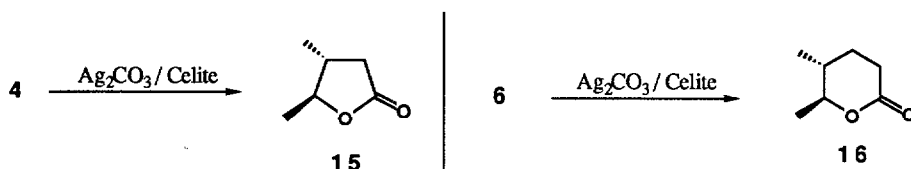
The homologous  $\delta$ -lactol **13** also underwent the *anti*-selective addition, although the selectivity was lower in comparison with the  $\gamma$ -lactol cases.<sup>5,6</sup> The reactivity of  $\delta$ -lactol **13** toward the methylating agents were substantially lower than that of the  $\gamma$ -lactols, and the addition reaction began to proceed above 0°C. Interestingly, the reaction under reflux was the condition of choice to gain better selectivity, and substantial decrease of the ratio was observed by lowering the reaction temperature [14: *anti*/*syn* = 4.4/1 (0°C), *anti*/*syn* = 3.0/1 (-78°C ~ 0°C)]. The reason for this unexpected tendency is not clear.



**Acknowledgments:** Generous supports from the Kurata Science Foundation and from the Ministry of Education, Science and Culture (Grant-in-Aid No. 63740297) are gratefully acknowledged.

### References and Notes

- 1) D. J. Cram and F. A. A. Elfafez, *J. Am. Chem. Soc.*, **74**, 5828 (1954).
- 2) E. L. Eliel, in "Asymmetric Synthesis," Vol. 2A, J. D. Morrison, Ed., Academic, New York, 1983, pp 125-155.
- 3) K. Tomooka, T. Okinaga, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 6335 (1987).
- 4) Review: M. T. Reetz, "Organotitanium Reagents in Organic Synthesis," Springer, Berlin, 1986.
- 5) For a successful example in the *anti*-Cram stereoselection, K. Maruoka, T. Itoh, and H. Yamamoto, *J. Am. Chem. Soc.*, **107**, 4573 (1985), and the references cited therein.
- 6) Capillary GLC: PEG 20M, 50 m.
- 7) Stereostructures of **4** and **14** was determined by the correlation to  $\gamma$ -lactone **15** and  $\delta$ -lactone **16**. For the  $^1\text{H}$  NMR data of **15** and **16**; see  
 15: S. Byström, H.-E. Högberg, and T. Norin, *Tetrahedron*, **37**, 2249 (1981).  
 16: E. Cooke, T. C. Paradellis, and J. T. Edward, *Can. J. Chem.*, **60**, 29 (1982).



- 8)  $\text{MeTi}(\text{O}-i\text{Pr})_3$ : K. Clauß, *Liebigs Ann. Chem.*, **711**, 19 (1968). The reagent prepared *in situ* from  $(i\text{PrO})_3\text{TiCl}$  and  $\text{MeLi}$  in  $\text{Et}_2\text{O}$  gave comparable results. It should be noted, however, that the selectivity lowered (*anti* / *syn* = 7 / 1) when the reagent was prepared *in situ* from  $(i\text{PrO})_3\text{TiCl}$  and  $\text{Me}_2\text{Zn}$  in  $\text{CH}_2\text{Cl}_2$  [M. T. Reetz, R. Steinbach, J. Westermann, and R. Peter, *Angew. Chem., Int. Ed. Engl.*, **19**, 1011 (1980).], presumably due to the interference by the coexisting Lewis acid, *i.e.*,  $\text{ZnCl}_2$ .
- 9) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, **1968**, 2199; N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, **1**, 61 (1977).
- 10) Recently, Reissig *et al.* suggested the involvement of seven-membered chelate species in their addition reaction to  $\alpha$ -chiral aldehydes with a  $\gamma$ -ester function; T. Kunz and H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, **27**, 268 (1988).
- 11) Seven-membered chelate species are recently invoked in explaining some stereoselective reactions. See ref. 10 and the references cited therein. For the example where the direct evidence for such a species is obtained: T. Poll, J. O. Metter, and G. Helmchen, *Angew. Chem., Int. Ed. Engl.*, **24**, 112 (1985).
- 12) That the addition reactions occur after the formation of alkoxide of lactols are verified by the gas volumetric measurements of the methane produced. The results indicated that the alkoxide formation is generally complete below  $-50^\circ\text{C}$ , while the addition occurs at higher temperatures.
- 13) These isomeric lactones were prepared from the nor-methyl lactone by methylation (LDA,  $\text{MeI}$  / THF-HMPA,  $-78^\circ\text{C}$ ; 7/10 = 11/1), separation (silica-gel TLC) and half-reduction of each isomer (DIBAL / toluene,  $-78^\circ\text{C}$ ). The stereostructures were determined at the stage of the methylated lactones by NOE study (400 MHz NMR).
- 14) The structures of **8** and **11** were determined by correlating them to **4** by the following transformations [(1)  $\text{EtOCH}=\text{CH}_2$ , PPTS, (2) TBAF, (3) PPTS /  $\text{MeOH}$ , (4)  $\text{NaIO}_4$ , (5)  $\text{LiAlH}_4$ ].

(Received in Japan 12 November 1988)