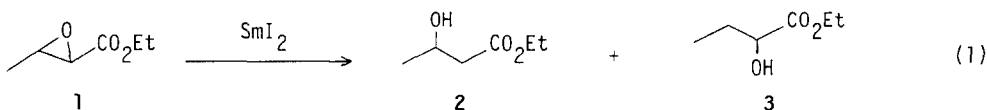


SmI<sub>2</sub>-INDUCED HIGHLY REGIOSELECTIVE REDUCTION OF  
α,β-EPOXY ESTERS AND γ,δ-EPOXY-α,β-UNSATURATED ESTERS.  
AN EFFICIENT ROUTE TO OPTICALLY ACTIVE β-HYDROXY AND δ-HYDROXY ESTERS<sup>1)</sup>

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Summary: α,β-Epoxy esters were rapidly reduced at room temperature to yield β-hydroxy esters with retention of the configurations at the β-carbon atoms by using SmI<sub>2</sub>-THF-HMPA system in the presence of N,N-dimethylaminoethanol (DMAE). The conditions were successfully applied to the synthesis of vinyllogous δ-hydroxy esters.

Esters having a hydroxyl function at their α-, β-, γ-, or δ-position not only constitute an important class of natural products but also serve as useful intermediates in organic synthesis. As one of our synthetic efforts in this field,<sup>2)</sup> we have recently reported a highly regioselective conversion of α,β-epoxy esters to α-hydroxy esters.<sup>3)</sup> On the other hand, however, there have been few examples for the reductive cleavage of α,β-epoxy esters at their α-site to afford β-hydroxy esters with appreciable selectivity,<sup>4)</sup> though a number of methods have been developed for the regioselective reduction of α,β-epoxy ketones.<sup>5)</sup> In connection with our recent interest in the use of SmI<sub>2</sub> in organic synthesis,<sup>6)</sup> the reduction of α,β-epoxy esters by this reagent was investigated (eq 1). In this paper are described a highly regioselective synthesis of β-hydroxy esters from α,β-epoxy esters and of δ-hydroxy-β,γ-unsaturated esters from γ,δ-epoxy-α,β-unsaturated esters, respectively.



As preliminary experiments, ethyl 2,3-epoxybutyrate (1) was reduced under various conditions. As can be seen in Table 1, it was revealed that (i) addition of HMPA highly accelerated the electron transfer process,<sup>7)</sup> completing the reaction instantaneously, (ii) the presence of a proton source much improved the chemical yield, and (iii) addition of a strong chelating agent such as tetramethylethylenediamine (TMEDA) or DMAE was crucial to attain high regioselectivity. Thus, the best result was obtained when HMPA (5 eq) and DMAE (2 eq) were used as additives (Run 6).

Under the optimized conditions, a variety of α,β-epoxy esters were reduced rapidly to afford the desired β-hydroxy esters with excellent selectivity in satisfactory yields. The results are listed in Table 2. As a particular case, octyl 2,3-epoxypropionate caused substantial side reactions such as transesterification and the formation of the undesired β-hydroxy ester (The first example in Table 2). In all cases studied, the major by-products were saturated esters (E.g., see footnote e in Table 2).

Table 1. Effect of Additives on the Reduction of the  $\alpha,\beta$ -Epoxy Ester (1) by  $\text{SmI}_2^{\text{a)}$ 

Run	Additive	Reaction time (min)	Yield (%) <sup>b)</sup>	Product ratio <sup>c)</sup> 2 : 3
1	none	60	5	
2	HMPA (5eq)	1	19	
3	HMPA + 2-PrOH (5eq) (2eq)	1	34	10 : 1
4	DMAE (5eq)	30	60	20 : 1
5	HMPA + TMEDA + 2-PrOH (5eq) (2eq) (2eq)	1	46	200 : 1
6	HMPA + DMAE (5eq) (2eq)	1	68	> 200 : 1

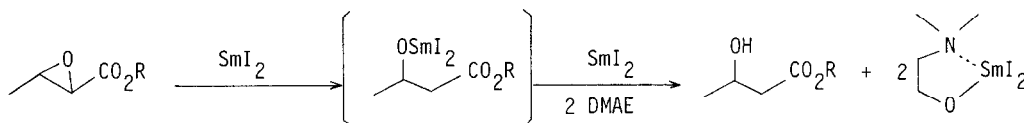
a) The reactions were carried out by using the epoxy ester (1) (0.12 mmol) and a  $\text{SmI}_2$ -THF solution (0.1 mol  $\text{dm}^{-3}$ , 3 ml) at room temperature with or without additives. b) Isolated yield. c) Determined by  $^1\text{H}$  NMR (400 MHz) analysis.

Table 2. Regioselective Reduction of  $\alpha,\beta$ -Epoxy Esters by Using  $\text{SmI}_2$ -HMPA-DMAE<sup>a)</sup>

Substrate	Reaction time (min)	Product	Yield (%) <sup>b)</sup>	Ratio ( $\beta$ -OH : $\alpha$ -OH) <sup>c)</sup>
	1		50 <sup>d)</sup>	17 : 1
	1		62 <sup>e)</sup>	> 200 : 1
	1		62	> 200 : 1
	1		68	> 200 : 1
	1		76	> 200 : 1

a) The reactions were carried out by using the epoxy esters (0.2 mmol), HMPA (1 mmol), DMAE (0.4 mmol), and a  $\text{SmI}_2$ -THF solution (0.1 mol  $\text{dm}^{-3}$ , 4.5 ml) at room temperature. b) Isolated yield. c) Determined by  $^1\text{H}$  NMR (400 MHz) analysis. d) 1-Octanol was also isolated in 25% yield as a by-product. e) Octyl 2-methylpropionate was also isolated in 35% yield. f) A mixture of the stereoisomers (1 : 1.7). g) A mixture of the stereoisomers (1 : 3.8).

The mechanism of the reaction is not clear, but from the analogy with the reduction of  $\alpha$ -haloesters by  $\text{SmI}_2$ <sup>8)</sup> and with the alkali metal reduction of an  $\alpha,\beta$ -epoxy ester,<sup>4)</sup> it seems to be plausible that the initial electron transfer occurs at  $\alpha$ -carbon atom to leave an ester-stabilized radical as shown below.



DMAE plays an important role in the reaction, i.e., it works not only as a nice proton source but also as an efficient chelating agent to remove the Lewis acidic  $\text{Sm(III)}$  species from the reaction system, which tends to open up the starting oxirane ring in non-regioselective way with the formation of the undesired  $\alpha$ -hydroxy derivative.

In agreement with the above mechanistic view, an optically pure  $\alpha,\beta$ -epoxy ester (**4**)<sup>9</sup> was converted to the  $\beta$ -hydroxy ester (**5**) with complete retention of the configuration at  $\beta$ -carbon atom.<sup>10)</sup> Therefore, the combination of the present method with the Sharpless process<sup>9)</sup> is considered to provide an efficient route to optically active  $\beta$ -hydroxy esters, especially for the ones having tert-hydroxyl group on the asymmetric carbon, such as **A**, which does not seem to be easily accessible by the conventional aldol approach.<sup>11)</sup>

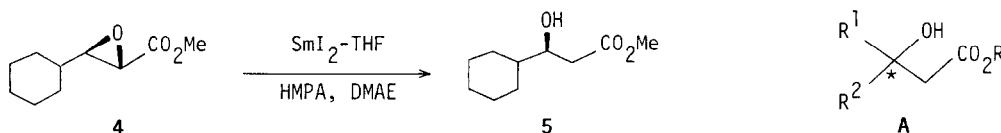


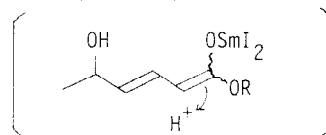
Table 3. Regio- and Stereoselective Reduction of  $\gamma,\delta$ -Epoxy- $\alpha,\beta$ -unsaturated Esters by Using  $\text{SmI}_2$ -HMPA-DMAE System<sup>a)</sup>

Substrate	Reaction time (min)	Product	Yield (%) <sup>b)</sup>	Ratio ( $\delta$ -OH : $\alpha$ -OH) <sup>c)</sup>
	1		73	> 200 : 1
	1		74	> 200 : 1
	1		80	> 200 : 1
	1		90	> 200 : 1

a) The reactions were carried out by using the epoxy esters (0.7 mmol), HMPA (0.7 ml), DMAE (1.4 mmol), and a  $\text{SmI}_2$ -THF solution (0.1 mol  $\text{dm}^{-3}$ , 15 ml) at room temperature. b) Isolated yield. c) Determined by <sup>1</sup>H NMR (400 MHz) analysis.

The optimized reaction conditions for the conversion of  $\alpha,\beta$ -epoxy esters to  $\beta$ -hydroxy esters were successfully applied to the reduction of the vinylogous epoxy esters yielding  $\delta$ -hydroxy- $\beta,\gamma$ -unsaturated esters with exclusive E geometry<sup>12,13</sup> (Table 3).

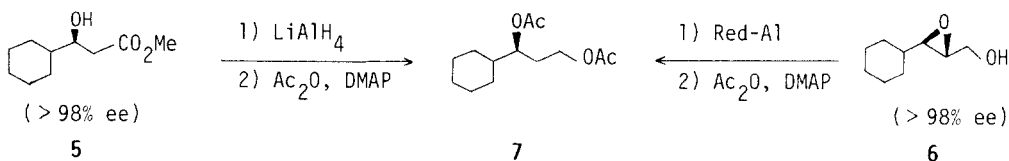
The reaction seems to proceed through successive two-electron transfer process generating a conjugated enolate followed by regioselective protonation at  $\alpha$ -carbon atom.



The products, thus obtained, are considered to serve as potentially useful intermediates in organic synthesis.

### References and Notes

- 1) Presented at the 53rd National Meeting of the Chemical Society of Japan, Nagoya, Oct 1986.
- 2) For the synthesis of  $\gamma$ - and  $\delta$ -lactones: See K.Otsubo, J.Inanaga, and M.Yamaguchi, *Tetrahedron Lett.*, **27**, 5763 (1986); K.Otsubo, K.Kawamura, J.Inanaga, and M.Yamaguchi, *Chem. Lett.*, in press.
- 3) K.Otsubo, J.Inanaga, and M.Yamaguchi, the preceding paper.
- 4) While the present study was in progress, alkali metal reduction of a variety of epoxides, including one example of  $\alpha,\beta$ -epoxy ester, has been reported: See E.Bartmann, *Angew. Chem. Int. Ed. Engl.*, **25**, 653 (1986).
- 5) G.A.Molander and G.Hahn, *J. Org. Chem.*, **51**, 2596 (1986) and references cited therein.
- 6) For a recent review: See H.B.Kagan and J.L.Namy, *Tetrahedron*, **42**, 6573 (1986).
- 7) For the remarkable effect of HMPA in other  $\text{SmI}_2$ -promoted reactions: See J.Inanaga, M.Ishikawa, and M.Yamaguchi, *Chem. Lett.*, in press, and reference 2.
- 8) G.A.Molander and G.Hahn, *J. Org. Chem.*, **51**, 1135 (1986).
- 9) Prepared from the corresponding allylic alcohol according to the Sharpless process: See J.M.Chong and K.B.Sharpless, *Tetrahedron Lett.*, **26**, 4683 (1985).
- 10) According to the following scheme, the hydroxy ester (**5**) and the epoxy alcohol (**6**) were reduced and acetylated to give the corresponding diacetates (**7**) and their optical purities were determined by  $^1\text{H}$  NMR (400 MHz) analyses with a chiral shift reagent, tris[3-(heptafluoropropyl)hydroxymethylene]-d-camphorato]europium(III), by comparing with the dl-diacetate (**7**).



- 11) For a review: See C.H.Heathcock, "Asymmetric Synthesis," ed by J.D.Morrison, Academic Press, Orlando, Florida (1984), Vol 3, p 111.
- 12) Quite recently, the same conversion has been achieved by using  $\text{SmI}_2$  in the absence of HMPA and DMAE at low temperature (below  $-90^\circ\text{C}$ ): See G.A.Molander, B.E.La Belle, and G.Hahn, *J. Org. Chem.*, **51**, 5259 (1986).
- 13) Palladium-catalyzed stereospecific hydrogenolysis of (E)-4,5-epoxy-4-methyl-2-alkenoates with ammonium formate has also been reported recently: See I.Shimizu, M.Oshima, M.Nisar, and J.Tsuji, *Chem. Lett.*, 1775 (1986).

(Received in Japan 16 June 1987)