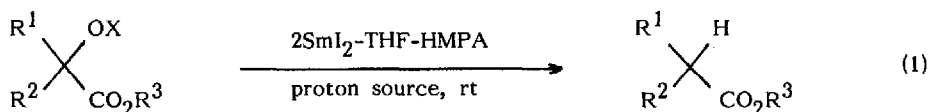


A HIGHLY EFFICIENT DEOXYGENATION OF  $\alpha$ -OXYGENATED ESTERS  
VIA  $\text{SmI}_2$ -INDUCED ELECTRON TRANSFER PROCESS<sup>1)</sup>

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Summary: A variety of  $\alpha$ -oxygenated esters, such as  $\alpha$ -acetoxy-,  $\alpha$ -methoxy-,  $\alpha$ -OTHP, and  $\alpha$ -hydroxy esters were easily reduced at room temperature to give the corresponding saturated esters in good to excellent yields with the aid of an efficient electron transfer system,  $\text{SmI}_2$ -THF-HMPA. The method was successfully applied to the direct conversion of (R,R)-tartrates to (R)-malates.

Although a number of reducing agents are available for the reductive elimination of  $\alpha$ -oxygen functionalities of ketones,<sup>2)</sup> the reduction of  $\alpha$ -oxygenated esters to the corresponding saturated esters is not an easy task.<sup>3)</sup> In this communication, we report the first general method for such transformations by using an efficient electron transfer system,  $\text{SmI}_2$ -THF-HMPA.<sup>1,4)</sup> (eq. 1)



X = Ac, Me, THP, H

The reactions were carried out at room temperature by using 2.5-3.0 molar equivalents of  $\text{SmI}_2$ -THF solution<sup>5)</sup> in the presence of HMPA<sup>6)</sup> and appropriate proton sources. As shown in Table 1,  $\alpha$ -acetoxy esters were cleanly deacetoxyated within a few minutes. The reduction of  $\alpha$ -methoxy derivatives also proceeded smoothly to give the saturated esters in good yields regardless of the substitution pattern of methoxyl groups.

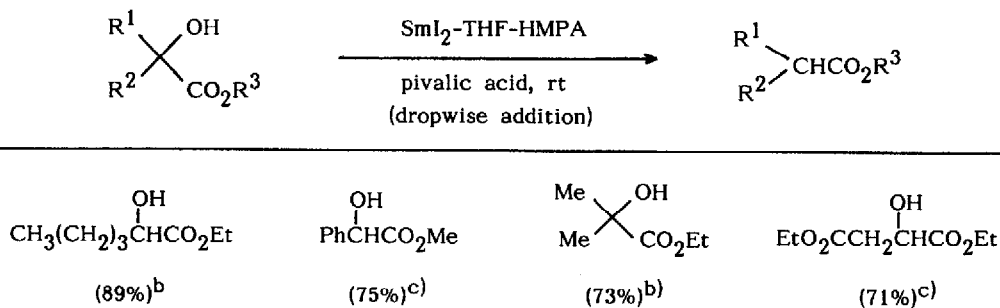
Interestingly, when a diastereomeric mixture (ca. 1:2) of  $\alpha$ -OTHP esters was subjected to the above conditions, the reaction rate was rapidly decreased during 1-2 h and after 6 h the reduction product was obtained in 57% yield together with the recovered THP ether (40%) which was found to be a single isomer by <sup>1</sup>H NMR analysis. The fact that samarium diiodide did differentiate the two stereoisomers seems to indicate that the activation of ester carbonyl by proper coordination of substrates to samarium is very important for the smooth electron transfer.<sup>7)</sup> The reduction of sterically crowded *Q*-*t*-butyldimethylsilyl ethers proceeded only very slowly<sup>8)</sup> and simple esters did not undergo reduction with  $\text{SmI}_2$  under the present conditions.

The direct dehydroxylation of  $\alpha$ -hydroxy esters was also carried out. In this case, however, the reaction conditions used for the reduction of acetoxy or methoxy esters were not effective,<sup>9)</sup> and it was found that the use of much acidic proton source such as carboxylic acids was preferable. Thus, pivalic acid was used with the devised addition procedure (see footnote a in Table 2) to minimize the consumption of  $\text{SmI}_2$  by the acid. (Table 2)

Table 1. Deoxygenation of  $\alpha$ -Acetoxy and  $\alpha$ -Methoxy Esters at Room Temperature<sup>a)</sup>

Run	$\alpha$ -Oxygenated ester	Proton source	Reaction time	Rproduct	Yield(%) <sup>b)</sup>
1	$\text{CH}_3(\text{CH}_2)_4\overset{\text{OAc}}{\text{C}}\text{HCO}_2\text{Me}$	MeOH	< 5 min	$\text{CH}_3(\text{CH}_2)_5\text{CO}_2\text{Me}$	> 95 <sup>c)</sup>
2	$\text{Ph}\overset{\text{OAc}}{\text{C}}\text{HCO}_2\text{Me}$	MeOH	1 min	$\text{PhCH}_2\text{CO}_2\text{Me}$	96
3	$\text{Me}\overset{\text{OAc}}{\text{C}}(\text{Me})\text{CO}_2\text{Et}$	EtOH	< 5 min	$\text{Me}\overset{\text{Me}}{\text{C}}\text{HCO}_2\text{Et}$	> 95 <sup>c)</sup>
4	$\text{MeOCH}_2\text{CO}_2\text{C}_8\text{H}_{17}$	$\text{C}_8\text{H}_{17}\text{OH}$	3 h	$\text{CH}_3\text{CO}_2\text{C}_8\text{H}_{17}$	73
5	$\text{CH}_3(\text{CH}_2)_3\overset{\text{OMe}}{\text{C}}\text{HCO}_2\text{Me}$	MeOH	12 h	$\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{Me}$	85 <sup>c)</sup>
6	$\text{Ph}\overset{\text{OMe}}{\text{C}}\text{HCO}_2\text{Me}$	MeOH	3 h	$\text{PhCH}_2\text{CO}_2\text{Me}$	89
7	$\text{Ph}\overset{\text{OMe}}{\text{C}}(\text{Me})\text{CO}_2\text{Me}$	MeOH	12 h	$\text{Ph}\overset{\text{Me}}{\text{C}}\text{HCO}_2\text{Me}$	95

a) A  $\text{SmI}_2$ -THF solution ( $0.1 \text{ mol dm}^{-3}$ , 5-6 ml) was added to a mixture of  $\alpha$ -oxygenated esters (0.2 mmol), proton sources (0.24 mmol), and HMPA (0.3 ml) at 20-22°C under nitrogen. b) Isolated yield unless otherwise stated. c) GLC yield.

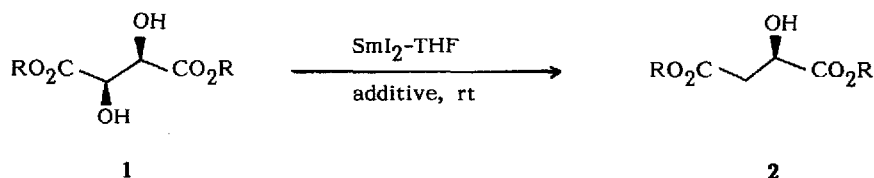
Table 2. Dehydroxylation of  $\alpha$ -Hydroxy Esters<sup>a)</sup>

a) A solution of pivalic acid (0.5 mmol) in THF (3 ml) was added dropwise to a mixture of hydroxy esters (0.2 mmol), HMPA (0.3 ml), and a  $\text{SmI}_2$ -THF solution ( $0.1 \text{ mol dm}^{-3}$ , 6 ml) over 1-2 h at 20-22°C and the mixture was stirred for additional 1-2 h under nitrogen. b) GLC yield. c) Isolated yield.

The present dehydroxylation conditions were applied to the direct conversion of (R,R)-tartrates (**1**) (natural) to (R)-malates (**2**) (unnatural).<sup>10)</sup> However, the yield of **2** was low and a substantial amount of succinate was isolated (15%) as the result of overreduction, indicating that the substrate is fairly susceptible to this reduction conditions probably because of the  $\alpha$ -diol structure. (Entry 1 in Table 3) Therefore, other additives and/or proton sources were examined precisely, some of the examples being shown in Table 3.

Thus, ethylene glycol was found to give the best result which seems to be ascribable to the suitable acidity and the strong coordinating ability of ethylene glycol to samarium ion, and under the conditions, optically pure (R)-diisopropyl malate<sup>11,12)</sup> and (R)-diethyl malate<sup>12)</sup> were obtained almost quantitatively<sup>13)</sup> and in 72% yield,<sup>14)</sup> respectively.

Table 3. One-Step Conversion of (R,R)-Tartrates (**1**) to (R)-Malates (**2**)<sup>a)</sup>



Entry	Tartrate(R)	Additive	Reaction Time	Yield(%) <sup>b)</sup>
1	<i>i</i> -Pr	HMPA, pivalic acid	3 min	32
2	<i>i</i> -Pr	<i>i</i> -PrOH	24 h	51
3	<i>i</i> -Pr	HOCH <sub>2</sub> CH <sub>2</sub> OH	1 h	99 <sup>c)</sup>
4	<i>i</i> -Pr	HOCH <sub>2</sub> CCH <sub>2</sub> OMe	12 h	9
5	<i>i</i> -Pr	HOCH(Me)CH(Me)OH	10 min	60
6	Et	HOCH <sub>2</sub> CH <sub>2</sub> OH	20 min	72 <sup>c)</sup>

a) The reactions were carried out at 0.6 mmol scale. For a typical experiment, see ref. 11.

b) Determined by <sup>1</sup>H NMR (400 MHz) analysis unless otherwise stated.

c) Isolated yield.

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 63540403) from the Ministry of Education, Science, and Culture, Japan.

#### References and Notes

- 1) Lanthanides in Organic Synthesis. 21. Presented at the 56th National Meeting of the Chemical Society of Japan, Tokyo, April, 1988.
- 2) For example, see G. A. Molander and G. Hahn, *J. Org. Chem.*, **51**, 1135 (1986) and references cited therein.
- 3) For the regioselective C-O bond-cleavage of  $\alpha,\beta$ -epoxy esters to yield  $\beta$ -hydroxy esters, see a) K. Otsubo, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **28**, 4437 (1987); b) M. Miyashita,

M. Hoshino, T. Suzuki, and A. Yoshikoshi, *Chem. Lett.*, **507** (1988). The reaction of  $\alpha$ -alkoxyacid chlorides by  $\text{SmI}_2$  has been reported to cause decarbonylation: M. Sasaki, J. Collin, and H. B. Kagan, *Tetrahedron Lett.*, **29**, 4847 (1988).

- 4) For other electron transfer reactions with this system, see ref. 3a; J. Inanaga, M. Ishikawa, and M. Yamaguchi, *Chem. Lett.*, 1485 (1987); K. Otsubo, K. Kawamura, J. Inanaga, and M. Yamaguchi, *ibid.*, 1487 (1987); K. Otsubo, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 5763 (1986); Y. Handa, J. Inanaga, and M. Yamaguchi, *J. Chem. Soc., Chem. Commun.*, in the press.
- 5) P. Girard, J. L. Namy, and H. B. Kagan, *J. Am. Chem. Soc.*, **102**, 2693 (1980). A THF solution of  $\text{SmI}_2$  used in this study was prepared from Sm and diiodomethane in place of diiodoethane.
- 6) In the absence of HMPA, almost no desired reduction or very slow reaction was observed even after prolonged reaction time (24 h).
- 7) The reaction seems to proceed through successive two electron transfer to the ester carbonyl followed by  $\beta$ -elimination of the resulting  $\beta$ -oxygen-substituted carbanion to afford the corresponding ester enolate, which may be protonated to yield the final product. The formation of a chelate structure might be crucial for the initial electron transfer.
- 8) For instance, the reduction of methyl *O*-(*t*-butyldimethylsilyl)mandelate at room temperature for 20 h gave the saturated ester in 13% yield.
- 9) For example, when the reduction of ethyl 2-hydroxyhexanoate was conducted in the presence of ethanol, the saturated ester was obtained only in 33% yield.
- 10) Three methods have been reported for the conversion of **1** into **2**, where tin hydride reduction of the appropriate intermediates was adopted as a key reaction. For the reduction of monobromo derivatives, see a) E. J. Corey, A. Marfat, and D. J. Hoover, *Tetrahedron Lett.*, **22**, 1587 (1981); b) E. Hungerbuler, D. Seebach, and D. Wasmuth, *Helv. Chim. Acta*, **64**, 1467 (1981). For the reduction of thionocarbonate derivative, see c) M. Alpegiani and S. Hanessian, *J. Org. Chem.*, **52**, 278 (1987). Total steps and overall yield obtained by these methods: (a; 4 steps, 56%), (b; 3 steps, 47%), and (c; 2 steps, 67%).
- 11) To a mixture of (R,R)-diisopropyl tartrate (148 mg, 0.63 mmol) and a  $\text{SmI}_2$ -THF solution (0.1 mol  $\text{dm}^{-3}$ , 19 ml) was added dropwise a solution of ethylene glycol (0.5 ml) in THF (19 ml) during 30 min at room temperature. After stirring for additional 30 min, the reaction mixture was exposed to air to quench excess  $\text{SmI}_2$ . Ethylene glycol (0.57 ml), silica gel (ca. 3 g), and hexane (10 ml) were added and the mixture was stirred for 10 min; chromatographic purification (silica gel, hexane/ethyl acetate = 3/1) gave (R)-diisopropyl malate (137 mg, 99%) as an oil.
- 12) The optical purity was determined to be >99% ee by  $^1\text{H}$  NMR (400 MHz) analysis of its acetate with a chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), by comparing with the corresponding *dl*-malate.
- 13) The yield was decreased by increasing the experimental scale, e.g., at 10 mmol scale, 70% yield of the malate was obtained with some recovery of starting tartrate (15%).
- 14) The lower yield of the diethyl ester than that of the diisopropyl ester is due to the partial transesterification.

(Received in Japan 8 March 1989)