Highly Stereoselective Synthesis of Both Enantiomers of 2-Methyl-3-Hydroxythioesters by Asymmetric Aldol Reactions Using Similar Types of Chiral Sources Derived from *L*-Proline

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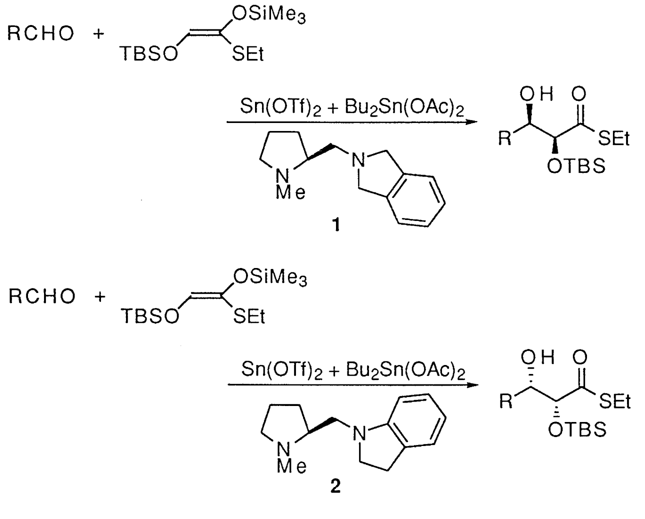
Both enantiomers of 2-methyl-3-hydroxythioesters have been synthesized in chiral tin(II) Lewis acid-mediated aldol reactions of silyl enolate **3** with aldehydes, by simply choosing similar types of chiral sources, **4** and **5**, derived from *L*-proline.

Optically active α-methyl-β-hydroxy units are often observed in various important natural and unnatural products, and development of efficient methods for the preparation of these units has been strongly desired.[1] Particularly, a recent requirement is a new reaction for preparing both enantiomers of the above units, because the biological activities of the compounds containing the units have been shown to be quite different between enantiomers in some cases.[2] While several protocols have already been reported, asymmetric aldol reactions of enolate components derived from propionate derivatives with aldehydes provide one of the most prospective routes for this preparation.[3] However, according to conventional methods, both enantiomers of the chiral sources are required as precursors, auxiliaries, or catalysts. Both enantiomers of the sources are often hard to obtain (for example, alkaloids, amino acids, sugars, etc.), and this limits the synthesis of both enantiomers. In this paper, we describe a solution to this problem, a new method for the preparation of both enantiomers of α-methyl-β-hydroxy units by using similar types of chiral sources.

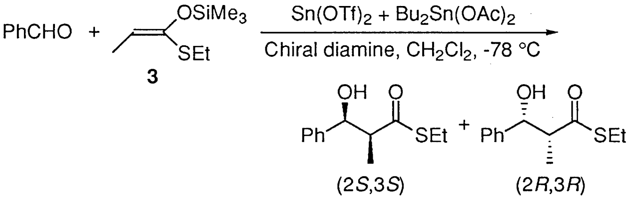
Recently, we reported a new route for the preparation of both enantiomers of optically active 2,3-dihydroxythioester derivatives by using similar types of chiral sources,[4] based on "chiral Lewis acid-controlled synthesis."[5] This route is based on the tin(II)-mediated asymmetric aldol reactions of (*Z*)-1-ethylthio-1-trimethylsiloxy-2-*t*-butyldimethylsiloxyethene with aldehydes, and both enantiomers of the aldol adducts were obtained selectively by choosing chiral ligand **1** or **2** (Scheme 1). First, we performed the reaction of (*Z*)-1-ethylthio-1-trimethylsiloxypropene (**3**) with benzaldehyde in the presence of tin(II) triflate, chiral diamine **2**, and dibutyltin diacetate ($Bu_2Sn(OAc)_2$). The reaction proceeded smoothly at -78 °C in dichloromethane to afford the corresponding adduct including the α-methyl-β-hydroxy unit in a high yield with a high *syn*-selectivity. However, the enantiomeric excess of the *syn*-adduct was low. The high diastereoselectivity and rather low enantioselectivity indicated that in order to improve the selectivity, development of a chiral ligand with increased enantiofacial selectivity of an aldehyde was necessary. We designed and synthesized several chiral ligands and found that chiral ligand **4**[6] was suitable for our purpose.

In the presence of tin(II) triflate, chiral diamine **4**, and $Bu_2Sn(OAc)_2$, silyl enolate **3** was treated with benzaldehyde at -78 °C in dichloromethane. The reaction proceeded smoothly to afford the corresponding adduct in a high yield with an excellent *syn*-selectivity. The enantiomeric excess of the *syn*-adduct was 82% with a 2*R*, 3*R* absolute configuration. On the other hand, when chiral diamine **1** was used, the *syn*-adduct was obtained in a 66% ee with a 2*S*, 3*S* absolute configuration. Higher 2*S*, 3*S* selectivity was observed when chiral diamine **5** was used.[7] These results are summarized in Table 1.



Scheme 1. Synthesis of both enantiomers of 2,3-dihydroxythioester derivatives.

Table 1. Effect of chiral diamines



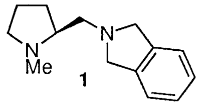
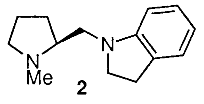
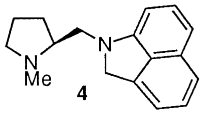
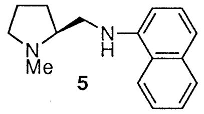
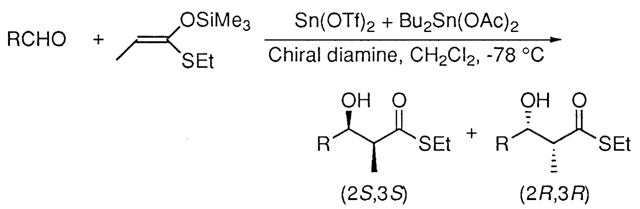
Chiral diamine	Yield/%	*syn*/*anti*	2*S*,3*S*/2*R*,3*R* (ee/%)
 **1**	98	99/ 1	83.0/17.0 (66)
 **2**	90	93/ 7	35.0/65.0 (30)
 **4**	80	>99/ 1	9.0/91.0 (82)
 **5**	85	>99/ 1	>99.5/<0.5 (>99)

Table 2. Synthesis of both enantiomers of 2-methyl-3-hydroxythioesters



Aldehyde	Chiral diamine	Yield/%	*syn*/*anti*	2*S*,3*S*/2*R*,3*R* (ee/%)
Ph	**4**	80	>99/ 1	9.0/91.0 (82)
	5	85	>99/ 1	>99.5/<0.5 (>99)[a]
CH_3CH_2	**4**	67	>99/ 1	4.5/95.5 (91)[b]
	5	85	>99/ 1	>99.5/<0.5 (>99)[a,b]
$CH_3(CH_2)_6$	**4**	75	>99/ 1	4.5/95.5 (91)[b]
	5	90	>99/ 1	>99.5/<0.5 (>99)[a,b]
c-C_6H_{11}	**4**	75	>99/ 1	4.0/96.0 (92)[b]
	5	90	>99/ 1	>99.5/<0.5 (>99)[a,b]
(*E*)-$CH_3CH=CH$	**4**	69	>99/ 1	10.0/90.0 (80)[b]
	5	92	>99/ 1	>99.5/<0.5 (>99)[a,b]
(*E*)-PhCH=CH	**4**	79	>99/ 1	9.5/90.5 (81)[b]
	5	91	>99/ 1	>99.5/<0.5 (>99)[a,b]
2-furyl	**4**	83	>99/ 1	8.0/92.0 (84)
	5	93	>99/ 1	>99.5/<0.5 (>99)[a]

[a] Ref. 7. [b] 2*S*,3*R*/2*R*,3*S*.

We then tested several aldehydes, including aromatic, aliphatic, α,β-unsaturated, and heterocyclic aldehydes (Table 2). In every case, 2-methyl-3-hydroxythioesters with a 2*R*, 3*R* absolute configuration were obtained in high selectivities by using chiral ligand **4**. Since *syn*-adducts with the reverse absolute configuration (2*S*, 3*S*) were obtained in high diastereo- and enantioselectivities,[7] both enantiomers of *syn*-2-methyl-3-hydroxythioesters were prepared according to the present method, by using similar types of chiral ligands, **4** and **5**.

A typical experimental procedure is described for the reaction of **3** with benzaldehyde. To a suspension of tin(II) triflate (0.4 mmol) in dichloromethane (0.5 ml) were added chiral diamine **4** (0.48 mmol) in dichloromethane (0.5 ml) and dibutyltin diacetate (0.44 mmol) in dichloromethane (0.5 ml) successively at room temperature. The mixture was then cooled to -78 °C and dichloromethane solutions (0.5 ml each) of **3** (0.4 mmol) and benzaldehyde (0.27 mmol) were successively added. The mixture was stirred for 20 h, and saturated aq. $NaHCO_3$ was then added to quench the reaction. After a usual work up, the crude product was chromatographed on silica gel to give S-ethyl 3-hydroxy-2-methyl-3-phenylpropanethioate. The diastereomers were separated and the optical purity was determined by HPLC using a chiral column (Daicel Chiralpak AS, hexane-*i*-PrOH = 19/1).

In summary, we have developed an efficient method for the preparation of both enantiomers of optically active 2-methyl-3-hydroxythioesters. According to this method, both enantiomers can be prepared from the same materials by simply choosing chiral ligands, **4** and **5**, which are prepared from L-proline. In addition to the synthetic utility of the present method, the similarity of the chiral ligands having naphthalene rings is noted. Further studies to clarify the origin of the unique selectivities in the transition states[8] as well as to develop more efficient ligands are now in progress.

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References and Notes

1 For recent example, A. B. Smith, III, S. M. Condon, J. A. McCauley, J. L. Leazer, Jr., J. M. Leahy, and R. E. Maleczka, Jr., *J. Am. Chem. Soc.*, **117**, 5407 (1995); I. Paterson, K.-S. Yeung, R. A. Ward, J. G. Cumming, and J. D. Smith, *J. Am. Chem. Soc.*, **116**, 9391 (1994); Y. Mori, M. Asai, J. Kawade, A. Okumura, and H. Furukawa, *Tetrahedron Lett.*, **35**, 6503 (1994).

2 For example, S. C. Stinson, *Chem. Eng. News*, Sept 27, 38 (1993), and references cited therein.

3 T. Mukaiyama and S. Kobayashi, "Organic Reactions," ed by L. A. Paquetee et al., John Wiley & Sons, New York (1994), Vol. 46, p. 1; C. Gennari, "Asymmetric Synthesis with Enol Ethers," in "Comprehensive Organic Synthesis," ed by B. M. Trost, I. Fleming, Pergamon Press, Oxford (1991), Vol. 2, p. 629.

4 S. Kobayashi and M. Horibe, *J. Am. Chem. Soc.*, **116**, 9805 (1994).

5 This means the syntheses of *both individual* diastereomers or enantiomers from the same starting materials *by designing chiral Lewis acids.* Cf. S. Kobayashi and T. Hayashi, *J. Org. Chem.*, **60**, 1098 (1995); S. Kobayashi, M. Horibe, and M. Matsumura, *Synlett*, **1995**, 675.

6 Chiral ligand **4** was prepared from Boc-proline and benz[*cd*]indoline according to the standard procedure; DCC coupling afforded an amide, which was reduced via two steps (BH_3 and then $LiAlH_4$) to give the desired ligand (**4**) as an oil.

7 S. Kobayashi, H. Uchiro, Y. Fujishita, I. Shiina, and T. Mukaiyama, *J. Am. Chem. Soc.*, **113**, 4247 (1991).

8 Similar transition states as shown in Ref. 4 is postulated. Details will be reported in due course.