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An Efficient Method for the Preparation of Chiral Synthons Starting from Racemic Compounds by Way of Asymmetric Synthesis

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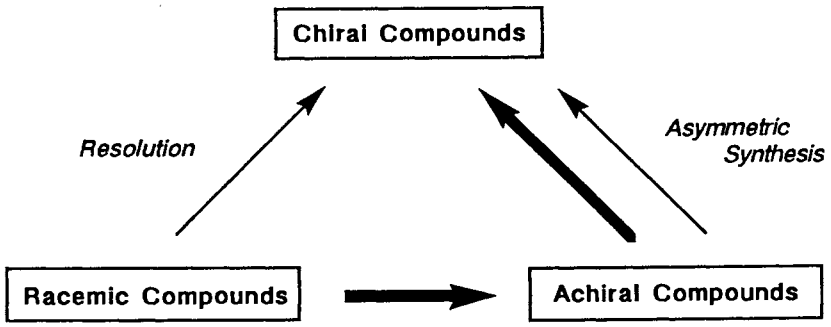
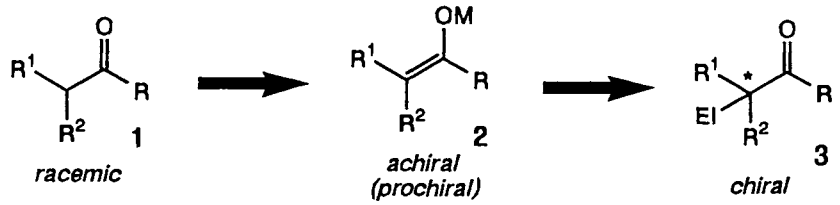
Optically active α-alkoxy-α-methyl-β-hydroxy ester derivatives are prepared starting from racemic α-alkoxy propionic acid ester derivatives by way of asymmetric aldol reaction of the corresponding achiral intermediates. (-)-2-C-Methyl-D-threono-1,4-lactone is conveniently synthesized by using this methodology.

Optical resolution and kinetic resolution are among the most popular and general methods for the preparation of chiral compounds from racemic compounds.[1] In these processes, however, the yield of one enantiomer is less than 50% and the enantiomeric excess is affected by the extent of conversion.[2]

In this communication, we would like to report an efficient method for the synthesis of chiral compounds from racemic compounds via achiral intermediates by use of an asymmetric reaction as a key step (Scheme 1). According to this procedure, 100% yields and 100% ees can be theoretically attained starting from racemic compounds.



Scheme 1.



Scheme 2.

The present strategy is shown in Scheme 2. Starting materials **1**, racemic carbonyl compounds, are converted to the corresponding achiral enolates **2**, which in turn react with achiral electrophiles in enantioselective manners to give the chiral carbonyl compounds **3**. Although some reactions according to this line have already been reported, the yields and enantiomeric excesses were not satisfactory in most cases.[3)]

In order to embody this strategy, S-ethyl 2-benzyloxypropanethioate was chosen as a model racemic compound and was treated with LDA in THF at -78 °C and then chlorotrimethylsilane (TMSCl) to give the corresponding silyl enolate **4a** (R^2=SEt).[4)] Asymmetric aldol reaction of **4** with benzaldehyde was performed in the presence of tin(II) triflate, (S)-1-methyl-2-[(pyrrolidin-1-yl)methyl]pyrrolidine and dibutyltin diacetate in dichloromethane.[5)] The reaction proceeded at -78 °C to afford the corresponding aldol-type adduct in high diastereo- and enantioselectivities (syn/anti=2/98, anti aldol=97% ee), however yield was not satisfactory (58%).

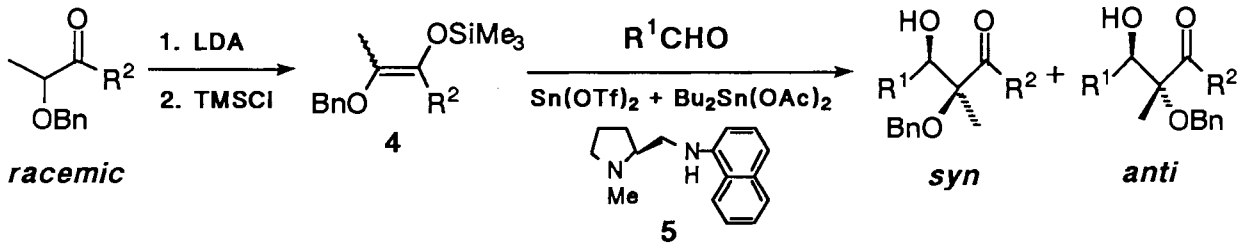


Table 1. Yields and Selectivities in the Aldol Reaction

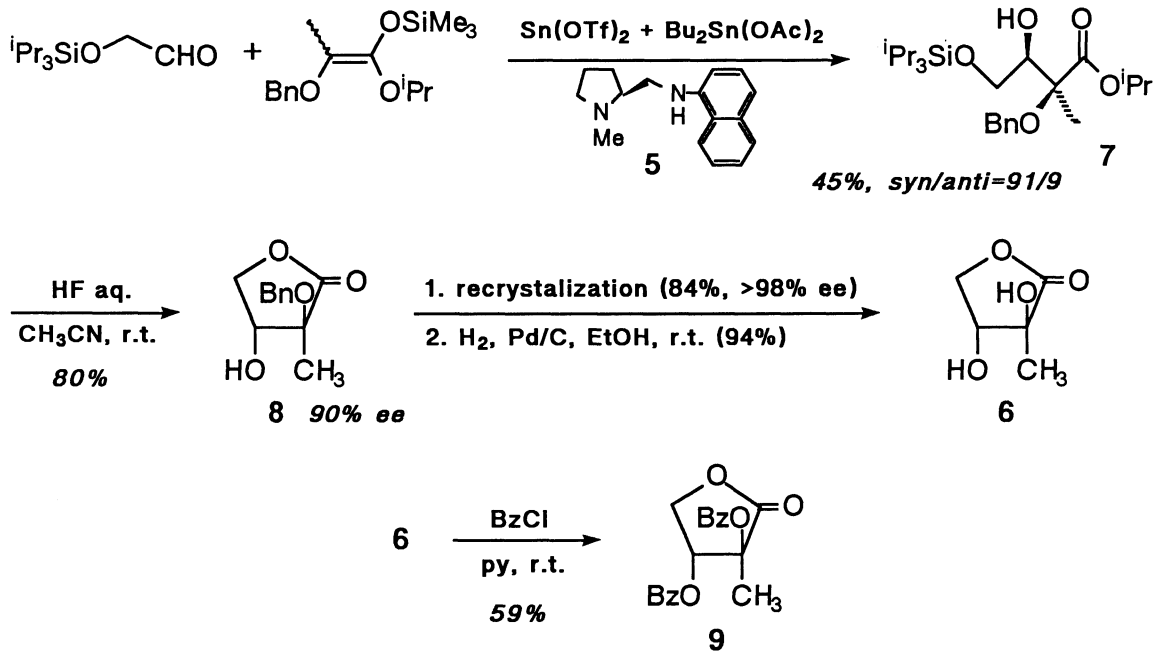
R^1	R^2	Yield / %	syn / anti	ee / % (syn)
Ph	SEt [a)]	58 [b)]	2 / 98	97 [c)]
Ph	OMe [d)]	87	67 / 33	90
Ph	OEt [e)]	quant.	81 / 19	80
Ph	O^{i}Pr [f)]	89	96 / 4	83
Ph	OPh [g)]	81	98 / 2	96
CH_3CH=CH	OMe [d)]	quant.	81 / 19	88
CH_3CH=CH	O^{i}Pr [f)]	79	96 / 4	88
CH_3CH=CH	OPh [g)]	50	88 / 12	94
PhCH=Ch	O^{i}Pr [f)]	85	97 / 3	87
n-C_6H_{13}	O^{i}Pr [f)]	70	98 / 2	87
c-C_6H_{11}	OMe [d)]	65	83 / 17	94
c-C_6H_{11}	O^{i}Pr [f)]	52	97 / 3	97

a) E/Z=12/88. b) (S)-1-Methyl-2-[(pyrrolidin-1-yl)methyl]pyrrolidine was employed instead of 5. c) Enantiomeric excess of the anti adduct. d) E/Z=59/41. e) E/Z=64/36. f) E/Z=71/29. f) E/Z=58/42.

After examination of some reaction factors, use of ketene silyl acetals instead of **4a** was found to be quite effective to improve the yield. Several examples are shown in Table 1. Enolization and trapping by TMSCl proceeded in almost quantitative yields in every case, and the ketene silyl acetals thus obtained were used without further purification. The yields and selectivities shown in Table 1 are those of the asymmetric aldol reaction. In every case, syn aldol-type adducts are predominantly obtained in high yields with high ees.

A typical experimental procedure is described for the reaction of racemic phenyl 2-benzyloxypropionate with benzaldehyde; phenyl 2-benzyloxypropionate was converted to the corresponding silyl enolate according to the conventional method (1. LDA/THF, -78 °C, 2. TMSCl, -78 °C to r.t., almost quantitative yield). The silyl enolate thus obtained was pure enough to use in the successive reaction without distillation. To a solution of tin(II) triflate (0.4 mmol) and (S)-1-methyl-2-[(N-naphthylamino)methyl]pyrrolidine (5, 0.48 mmol) in dichloromethane (1 ml) was added dibutyltin diacetate (0.44 mmol) in dichloromethane (1 ml) at room temperature. The mixture was stirred for 30 min and then cooled to -78 °C. Dichloromethane solutions (0.5 ml each) of the silyl enol ether (0.4 mmol) and benzaldehyde (0.27 mmol) were successively added. The reaction mixture was further stirred for 20 h, and quenched with aqueous sodium hydrogen carbonate. After usual work up, phenyl 2-benzyloxy-2-methyl-3-hydroxy-3-phenylpropionate was obtained in 81% yield (syn/anti=98/2). The enantiomeric excess of the syn isomer (96% ee) was determined by HPLC analysis using Daicel Chiralcel OD.

Next, in order to demonstrate the utility of this methodology, total synthesis of (-)-2-C-Methyl-D-threono-1,4-lactone (6) was tried (Scheme 3). The reaction of triisopropylsiloxyacetaldehyde with the silyl enol ether **4** (R^2=O^{i}Pr) was carried out in the presence of tin(II) triflate, chiral diamine 5 and dibutyltin diacetate to give the



Scheme 3.

corresponding aldol-type adduct **7** in 45% yield with a syn/anti ratio of 91/9. The enantiomeric excess of the major syn isomer was determined to be 90%ee by HPLC analysis using Daicel Chiralcel OD after derivation to the lactone **8**. First recrystarization of **8** in benzene/hexane system gave optically pure lactone **8**, followed by deprotection of benzyl group to give (-)-2-C-Methyl-D-threono-1,4-lactone (**6**).[6] The optical purity of this synthetic sample was confirmed after derivation to the dibenzoate **9** using HPLC analysis (Daicel Chiralcel OD).[7]

Thus, a efficient method for the synthesis of optically active compounds starting from racemic compounds via achiral intermediates are demonstrated by using the asymmetric aldol reaction of the silyl enol ethers with achiral aldehydes.

Further investigations to apply this concept to other reactions as well as to utilize this reaction for the synthesis of several natural products are now in progress.

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4) E/Z=12/88. The ratio and the geometry were determined by ^{1}H NMR and NOESY spectrum, respectively.

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

6) $[\alpha]_D^{28}$ -18 ° (c 0.4, H_2O) (lit. $[\alpha]_D^{28}$ -11 ° (c 0.5, H_2O)[8]). Possibility of racemization of the compound **6** obtained in the literature was pointed out by Teresa et al.[9]

7) $[\alpha]_D^{23}$ -126 ° (c 0.47, acetone) (lit. $[\alpha]_D^{22}$ -57 ° (c 1.9, acetone)[8])

8) A. Ishizu, B. Lindberg, and O. Theander, *Acta. Chem. Scand.*, **21**, 424 (1967).

9) J. P. Teresa, J. C. H. Aubanell, A. S. Feliciano, and J. M. M. Corral, *Tetrahedron Lett.*, **21**, 1359 (1980).

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