Pergamon

Tetrahedron Letters 42 (2001) 6303–6306

TETRAHEDRON LETTERS

Enantioselective synthesis of β-hydroxy-α-methyl-α-methylthio esters as precursors of *anti-vic*-hydroxymethyl units

Isamu Shiina* and Ryoutarou Ibuka

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

Received 23 May 2001; revised 13 June 2001; accepted 6 July 2001

Abstract—A new method for the synthesis of optically active *anti-vic*-hydroxymethyl units that correspond to *anti*-aldol derivatives is developed by way of successive enantioselective aldol and diastereoselective desulfurization reactions.

Stereoselective aldol reactions are frequently employed for the syntheses of complicated natural and unnatural oxygenated products since *syn-vic*-hydroxymethyl units that correspond to *syn*-aldol derivatives are now prepared easily by Mukaiyama–Evans type aldol reactions via chiral boron enolates.[1] Chiral diamine-coordinated tin(II) enolates[2] and other metal enolates having chiral auxiliaries[3] were also successfully utilized for the enantioselective synthesis of aldol units. Then, chiral Lewis acid-mediated aldol reactions of enol silyl ethers or ketene silyl acetals with aldehydes were developed as powerful tools for the synthesis of optically active aldol units.[4] In the above synthesis, the corresponding *syn*-aldol units were obtained in good yields with high diastereo- and enantioselectivities when the reactions of silyl nucleophiles prepared from propanoic acid derivatives with aldehydes were carried out in the presence of chiral Lewis acids including such metals as tin(II),[5] boron and titanium(IV), etc.[4]

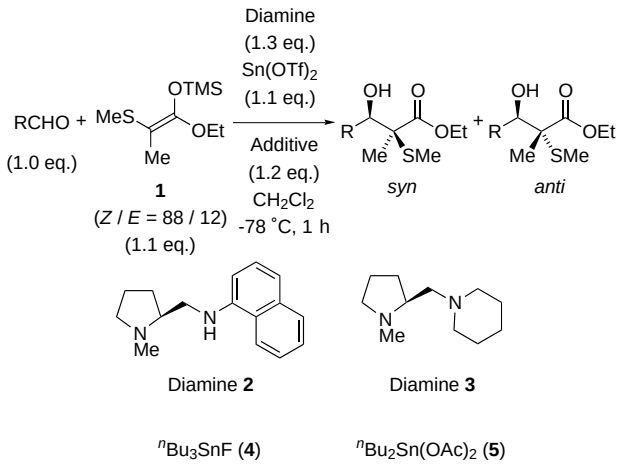
A unique method for the preparation of *syn*- or *anti*-1,2-diol units by asymmetric aldol reaction of enol silyl ethers derived from *S*-ethyl (*t*-butyldimethylsiloxy)ethanethioate and *S*-ethyl benzyloxyethanethioate with achiral aldehydes using chiral tin(II) Lewis acids was reported from our laboratory in 1991.[6] In 1992, this method was further developed into the reaction of silyl nucleophiles derived from alkyl 2-benzyloxypropanoate and *S*-ethyl 2-benzyloxypropanethioate with achiral aldehydes, and the corresponding *syn*- or *anti*-aldol units possessing chiral quaternary centers at the C2-position were obtained in high yields with high diastereo- and enantioselectivities.[7] These methods were successfully applied to the stereoselective syntheses of natural and unnatural polyoxy compounds such as monosaccharides,[8] leinamycin,[9] paclitaxel (Taxol®),[10] cephalosporolide D[11] and khafrefungin.[12]

The construction of several optically active synthetic intermediates by asymmetric aldol reaction was thus realized. However, there have not been many reports that practically provided *anti*-aldol units and methods for stereoselective synthesis of *anti-vic*-hydroxymethyl units that correspond to *anti*-aldol derivatives still needed to be improved. The following are some examples that provided *anti*-aldol derivatives. Masamune et al. obtained *anti*-aldols preferentially by using ketene silyl acetals, achiral aldehydes and a catalytic amount of chiral boron Lewis acid in 1992.[13] Then in 1997, Masamune and Abiko et al. further developed diastereoselective asymmetric aldol reaction by utilizing boron enolate derived from (2*S*,1*R*)-1-phenyl-2-{benzyl[(2,4,6 - trimethylphenyl)sulfonyl]amino}propyl propanoate.[14] Kobayashi et al. recently reported *anti*-selective catalytic asymmetric aldol reaction of ketene silyl acetal with achiral aldehydes by using a chiral zirconium(IV) complex prepared from $Zr(O^tBu)_4$ and (*R*)-3,3′-diiodo-1,1′-bi-2-naphthol in situ.[15]

Ketene silyl acetals derived from *S*-ethyl *t*-butylthioethanethioate[16] and ethyl 1,3-dithiolane-2-carboxylate[17] are useful nucleophiles since alkylthio groups are easily converted to other functionalities. A

* Corresponding author. Fax: (+81)-3-3260-5553; e-mail: shiina@ch.kagu.sut.ac.jp

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01238-2



Scheme 1. Asymmetric aldol reaction using chiral tin(II) Lewis acid.

method for the synthesis of optically active *syn*- and *anti*-aldol units was then introduced in 1998 by Kiyooka et al. by way of successive asymmetric aldol and desulfurization reactions.[18] In this protocol, *syn*- or *anti*-aldols that possessed methylthio groups at the C2-position were prepared by the asymmetric aldol reaction of 1-ethoxy-1-trimethylsiloxy-2-methylthio-1-propene (**1**) with achiral aldehydes by promoting a chiral boron Lewis acid. Further, both *syn*- and *anti*-desulfurizated aldol units were obtained from the above aldols in high enantiopurity.

On the other hand, preparation of optically active 2-alkylthio-substituted aldols by using ketene silyl acetals derived from 2-alkylthiopropanoic acid was also planned as our strategy for stereoselective syntheses of aldol units having chiral quaternary centers at the C2-position by using tin(II) Lewis acids.[7] It was assumed that *anti*-aldol units would be produced more efficiently if enantio- and diastereoselective aldol and diastereoselective desulfurization reactions were successively performed. Here, we would like to describe a sequential methodology for the stereoselective synthesis of *anti-vic*-hydroxymethyl units that correspond to *anti*-aldol derivatives by combining enantioselective aldol and diastereoselective desulfurization reactions.

First, a regioisomeric mixture of **1**[18] ($Z/E=88/12$) was prepared from ethyl 2-methylthiopropanoate by treating it with LDA and chlorotrimethylsilane. Asymmetric aldol reaction of the mixed ketene silyl acetal **1** with benzaldehyde in the presence of tri-*n*-butyltin fluoride (**4**) and tin(II) trifluoromethanesulfonate coordinated with chiral diamine **2** at −78°C gave the corresponding *syn*-aldol adduct with high diastereo- and enantioselectivities (see Scheme 1, Table 1, entry 1). The use of di-*n*-butyltin diacetate (**5**) as an additive increased the yield to 83% and stereoselectivities were slightly higher than those using **4** (entries 1 and 2). The combination of **5** and chiral diamine **3** was not found suitable for the present method as shown in entries 3 and 6. When 3-phenylpropanal, an aliphatic aldehyde, was used as a substrate, the desired *syn*-aldol was obtained in good yield with high stereoselectivities by the promotion of tin(II) trifluoromethanesulfonate coordinated with chiral diamine **2** in the coexistence of **4** (entry 4).

Examples of the optically active *syn*-aldols prepared by the present protocol are listed in Table 2. The reaction

Table 1. Reaction conditions and stereoselectivities of the asymmetric aldol reaction

Entry	RCHO	Diamine	Additive	Yield (%)	*syn*/*anti*	Ee (%)[a]
1	PhCHO	**2**	**4**	68	95/5	92
2	PhCHO	**2**	**5**	83	97/3	95
3	PhCHO	**3**	**5**	38	80/20	44
4	$Ph(CH_2)_2CHO$	**2**	**4**	55	92/8	92
5	$Ph(CH_2)_2CHO$	**2**	**5**	66	90/10	65
6	$Ph(CH_2)_2CHO$	**3**	**5**	Trace	–	–

[a] Ee of *syn*-aldol.

Table 2. Stereoselective synthesis of aldols that possess asymmetric quaternary centers at the C2-position

Entry	RCHO	Additive	Yield (%)	*syn*/*anti*	Ee (%)[a]
1	PhCHO	**5**	83	97/3	95
2	4-$MeOC_6H_4CHO$	**5**	83	99/1	92
3	4-MeC_6H_4CHO	**5**	86	99/1	91
4	4-ClC_6H_4CHO	**5**	87	97/3	90
5	(*E*)-$CH_3CH{=}CHCHO$	**5**	74	96/4	95
6[b]	(*E*)-$PhCH{=}CHCHO$	**5**	85	95/5	90
7	$PhCH_2CH_2CHO$	**4**	55	92/8	92
8[c]	$CH_3(CH_2)_6CHO$	**4**	52	91/9	92
9[c]	*c*-$C_6H_{11}CHO$	**4**	65	91/9	95

[a] Ee of *syn*-aldol.
[b] 1.2 equiv. of **1**, 1.4 equiv. of diamine **2**, 1.2 equiv. of $Sn(OTf)_2$ and 1.3 equiv. of additive **5** were used.
[c] 1.5 equiv. of **1**, 1.7 equiv. of diamine **2**, 1.5 equiv. of $Sn(OTf)_2$ and 1.6 equiv. of additive **4** were used.

of **1** with aromatic aldehydes (entries 1–4) and α,β-unsaturated aldehydes (entries 5 and 6) proceeded smoothly at −78°C in the presence of chiral tin(II) Lewis acid to give the corresponding aldols in good yields with high stereoselectivities. In the cases of using aliphatic aldehydes, the chemical yields were generally moderate. However, *syn*-aldols here were obtained with high diastereo- and enantioselectivities, as shown in entries 7–9.

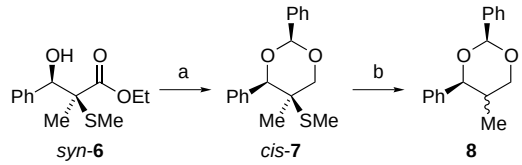
A typical experimental procedure is described for the synthesis of ethyl (2*S*,3*R*)-3-hydroxy-2-methyl-2-methylthio-3-phenylpropanoate (*syn*-**6**);[18] to tin(II) trifluoromethanesulfonate (101 mg, 0.242 mmol) were added a solution of chiral diamine **2** (69.1 mg, 0.288 mmol) in dichloromethane (0.5 mL) and a solution of **5** (91.5 mg, 0.261 mmol) in dichloromethane (0.5 mL) at room temperature. After the reaction mixture was stirred for 5 min at the same temperature, a solution of the mixed ketene silyl acetal **1** ($Z/E=88/12$, 52.6 mg, 0.239 mmol) in dichloromethane (0.5 mL) and a solution of benzaldehyde (22.5 mg, 0.212 mmol) in dichloromethane (0.5 mL) were successively added to the clear solution at −78°C. The reaction mixture was stirred for 1 h at −78°C and saturated aqueous sodium hydrogencarbonate was added. Then, the mixture was filtered through a short pad of Celite with dichloromethane and the filtrate was extracted with dichloromethane. The organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (hexane/AcOEt = 5/1) to afford *syn*-**6** (43.0 mg, 80%) and *anti*-**6** (1.5 mg, 2.8%) as colorless oils. *syn*-**6**: $[\alpha]_D^{24}=+38.0°$ (*c* 1.05, $CHCl_3$); HPLC (CHIRALCEL AD, *i*-PrOH/hexane = 1/19, flow rate = 1.0 mL/min): $t_R=8.8$ min (2.6%), $t_R=9.9$ min (97.4%).

Next, stereoselective desulfurization of the derivatives of aldol adducts to give *anti*-aldol units was studied. Although several attempted reductions of *syn*- and *anti*-aldols **6** and their linear derivatives gave poor stereoselectivities, desulfurization of *cis*-stereoisomer of benzylideneacetal **7** with Raney nickel (W5) afforded *trans*-**8** with good diastereoselectivity (*cis*/*trans* = 11/89) in which the desired *anti*-*vic*-hydroxymethyl unit was contained (Scheme 2). On the other hand, reduction of *trans*-**7**, which was prepared from *anti*-**6**, scarcely took place under the same conditions. Therefore, asymmetric aldol reaction of **1** with aldehydes to give *syn*-aldols preferentially was proved appropriate for the production of *anti*-aldol units according to this sequential aldol-desulfurization methodology.

The stereoselectivity in hydrogenation step was assumed to be determined by the direction of hydrogen approach to the six-membered free radical intermediate generated by desulfurization with Raney nickel in the transition state (Fig. 1). The transition state giving *trans*-**8** which corresponds to the *anti*-aldol unit seems more stable than that of giving *cis*-**8** because of the repulsion between functionalities at the C4- and C5-positions of *cis*-**8**. Calculated energy difference between stable ts-A and unstable ts-B is ca. 0.9 kcal/mol in UHF/6-31G**//UHF/3-21G level.[19]

Furthermore, it was found that the desulfurization of 4-methoxybenzylidene derivatives, i.e. *cis*-**9** prepared from aromatic *syn*-aldols, gave desirable *trans*-**10** predominantly by treating it with Raney nickel (W5) as illustrated in Scheme 3.

As shown in Scheme 4, aliphatic *anti*-aldol units are also available from the optically active aldol adducts containing methylthio groups at the C2-position. Compound *trans*-**12** was produced in good yield with complete stereoselectivity by ways of successive reduction of



Scheme 2. Transformation of the aldols to cyclic compounds. (a) (1) $LiBH_4$, CH_2Cl_2, rt, quant. (from *syn*-**6**), 89% (from *anti*-**6**); (2) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, quant. (for *cis*-**7**), 84% (for *trans*-**7**); (b) Raney Ni (W5), EtOH, reflux, 67%, *cis*-**8**/*trans*-**8** = 11/89 (from *cis*-**7**), trace (from *trans*-**7**).

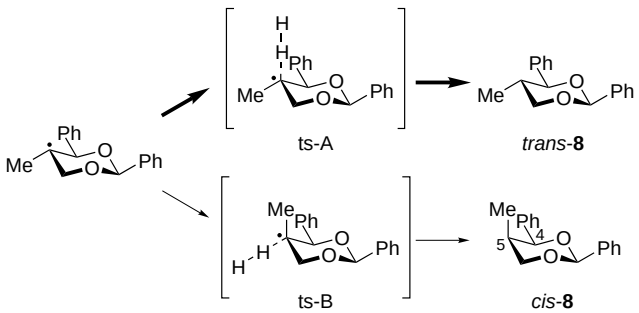
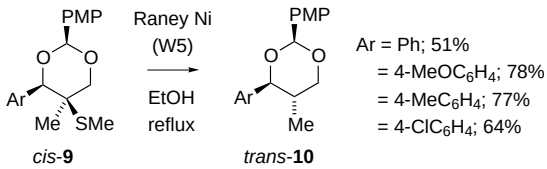
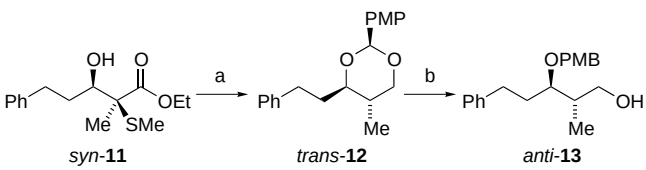


Figure 1. Assumed pathway to give desulfurizated compounds.



Scheme 3. Stereoselective desulfurization of 4-methoxybenzylidene derivatives.



Scheme 4. Stereoselective synthesis of *anti*-*vic*-hydroxymethyl units. (a) (1) $LiBH_4$, CH_2Cl_2, rt, 94%; (2) $PMPCH(OMe)_2$, CSA, CH_2Cl_2, rt, 89%; (3) Raney Ni (W5), EtOH, reflux, 73%, *cis*/*trans* = 0/100; (b) DIBAL, CH_2Cl_2, rt, 80%.

syn-**11**, formation of 4-methoxybenzylidene acetal, and successful desulfurization. Thus obtained *trans*-**12** can easily be transformed to the desired *anti*-*vic*-hydroxymethyl unit **13** which corresponds to the *anti*-aldol derivative by the known reductive cleavage.

The distinctive features of this synthetic protocol are to construct optically active *syn*-aldol adducts having asymmetric quaternary centers at the C2-position first, and then to produce *anti*-*vic*-hydroxymethyl units by successive desulfurization of the derivatives of aldol adducts. The present method is expected to be quite useful for the preparation of *anti*-aldol units which are otherwise not easily obtained from propanoic acid derivatives. It could also be employed for the stereoselective syntheses of polyketides having these functionalities. Our programs for applying these utilities to the total syntheses of natural products are now in progress.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

References

1. (a) Mukaiyama, T.; Inoue, T. *Chem. Lett*. **1976**, 559–562; (b) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Chem. Lett*. **1977**, 153–154; (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 174–178; (d) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127–2129.
2. (a) Iwasawa, N.; Mukaiyama, T. *Chem. Lett*. **1982**, 1441–1444; (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381–1390; (c) Mukaiyama, T.; Kobayashi, S. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 46, pp. 1–103.
3. Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Rathke, M. W.; Weipert, P.; Paterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp. 181–319.
4. (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp. 997–1065; (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389.
5. (a) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett*. **1990**, 129–132; (b) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc*. **1991**, *113*, 4247–4252; (c) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761–1772.
6. (a) Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett*. **1990**, 1019–1022; (b) Mukaiyama, T.; Shiina, I.; Kobayashi, S. *Chem. Lett*. **1991**, 1901–1904; (c) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn*. **1994**, *67*, 1708–1716; See also: (d) Kobayashi, S.; Kawasuji, T. *Tetrahedron Lett*. **1994**, *35*, 3329–3332; (e) Kobayashi, S.; Horibe, M. *Chem. Eur. J*. **1997**, *3*, 1472–1481.
7. (a) Kobayashi, S.; Shiina, I.; Izumi, J.; Mukaiyama, T. *Chem. Lett*. **1992**, 373–376; (b) Mukaiyama, T.; Shiina, I.; Izumi, J.; Kobayashi, S. *Heterocycles* **1993**, *35*, 719–724.
8. (a) Mukaiyama, T.; Shiina, I.; Kobayashi, S. *Chem. Lett*. **1990**, 2201–2204; (b) Mukaiyama, T.; Anan, H.; Shiina, I.; Kobayashi, S. *Bull. Soc. Chim. Fr*. **1993**, *130*, 388–394; See also: (c) Kobayashi, S.; Onozawa, S.; Mukaiyama, T. *Chem. Lett*. **1992**, 2419–2422; (d) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911–913.
9. (a) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc*. **1993**, *115*, 8451–8452; (b) Fukuyama, T.; Kanda, Y. *J. Synth. Org. Chem. Jpn*. **1994**, *52*, 888–899.
10. (a) Mukaiyama, T.; Shiina, I.; Sakata, K.; Emura, T.; Seto, K.; Saitoh, M. *Chem. Lett*. **1995**, 179–180; (b) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J*. **1999**, *5*, 121–161.
11. (a) Shiina, I.; Fukuda, Y.; Ishii, T.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett*. **1998**, 831–832; (b) Shiina, I.; Fujisawa, H.; Ishii, T.; Fukuda, Y. *Heterocycles* **2000**, *52*, 1105–1123.
12. Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc*. **2001**, *123*, 1372–1375.
13. Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett*. **1992**, *33*, 1729–1732.
14. (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc*. **1997**, *119*, 2586–2587; (b) Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem*. **1997**, *62*, 8978–8979.
15. Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc*. **2000**, *122*, 5403–5404.
16. Kobayashi, S.; Horibe, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2565–2569.
17. Kiyooka, S.; Hena, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2181–2184.
18. (a) Hena, M. A.; Terauchi, S.; Kim, C.-S.; Horiike, M.; Kiyooka, S. *Tetrahedron: Asymmetry* **1998**, *9*, 1883–1890. For other Kiyooka's approaches to the constructing aldol units stereoselectively, see: (b) Kiyooka, S.; Hena, M. A. *J. Org. Chem*. **1999**, *64*, 5511–5523; (c) Kiyooka, S.; Shahid, K. A.; Hena, M. A. *Tetrahedron Lett*. **1999**, *40*, 6447–6449; (d) Kiyooka, S.; Shahid, K. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1537–1542; (e) Kiyooka, S.; Shahid, K. A. *Tetrahedron Lett*. **2000**, *41*, 2633–2637.
19. There are the imaginary frequencies of ts-A at −2157 cm^{-1} and of ts-B at −2126 cm^{-1}. In ROHF/cc-pVTZ//ROHF/3-21G level, the difference is ca. 1.2 kcal/mol (−3211 and −3151 cm^{-1}). All calculations were performed with the program package *SPARTAN* 5.0.3 of Wavefunction, Inc. (http://www.wavefun.com) or *TITAN* 1.0.1 of Schrödinger, Inc. (http://www.schrodinger.com) and Wavefunction, Inc.