ENANTIOSELECTIVE SYNTHESIS OF THE α-HYDROXY-α-METHYL-β-HYDROXY UNITS VIA ASYMMETRIC ALDOL REACTION#

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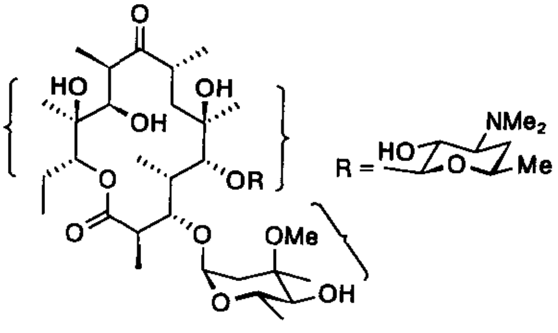
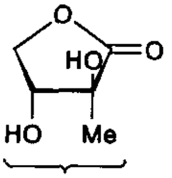
Abstract — The α-hydroxy-α-methyl-β-hydroxy units are enantioselectively prepared by way of asymmetric aldol reactions between both achiral β,β-disubstituted silyl enolates and aldehydes. (-)-2-*C*-Methyl-D-threono-1,4-lactone is conveniently synthesized by using this reaction.

The α-hydroxy-α-methyl-β-hydroxy units are often included in a series of pyrrolizidine alkaloids, especially in 11- or 12-membered pyrrolizidine dilactones, which have attracted much attention due to their potential hepatotoxic, carcinogetic, and mutagenic properties.[1] These units are also often observed in biologically active macloride antibiotics such as erythromycin, roxithromycin, clarithromycin, etc.[2] or γ-valerolactone or δ-butyrolactone derivatives including branched sugars such as (-)-2-*C*-methyl-D-threono-1,4-lactone (1).[3]



Erythromycin A



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Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

For the synthesis of these units, rather complicated multistage transformations have often been required in conventional methods, and to develop a new methodology for the stereoselective constructions of these successive asymmetric centers including quaternary carbons is strongly required.[4] In this paper, we would like to describe efficient and general synthesis of α-hydroxy-α-methyl-β-hydroxy units as optically active forms by way of asymmetric aldol reactions of β,β-disubstituted silyl enolates with aldehydes. A total synthesis of (-)-2-*C*-methyl-D-threono-1,4-lactone by using this methodology is also described.[5] We have already reported highly diastereo- and enantioselective aldol reaction of the silyl enol ether derived from *S*-ethyl propanethioate with aldehydes by using a chiral tin(II) Lewis acid consisting of tin(II) triflate, a chiral diamine and a tin(IV) compound.[6] First, the silyl enol ether of *S*-ethyl 2-benzyloxypropanethioate (**2**, E / Z = 12 / 88)[7] was applied to the above reaction system; for example, asymmetric aldol reaction of **2** with benzaldehyde was carried out in the presence of tin(II) triflate, (S)-1-methyl-2-[(pyrrolidin-1-yl)methyl]pyrrolidine (**3**) and dibutyltin diacetate in dichloromethane. 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), but the yield was not satisfactory (58%). When (S)-1-methyl-2-[(*N*-naphthylamino)methyl]pyrrolidine (**4**) was used instead of **3**, lower yield and lower selectivities were observed (40% yield, syn/anti=54/46, syn aldol=16%ee, anti aldol=84%ee). Then the reactions of the silyl enolate derived from phenyl 2-benzyloxypropionate (**5**) with aldehydes were tried in the presence of tin (II) triflate, chiral diamine (**3**) and dibutyltin diacetate. Benzaldehyde quite smoothly reacted with **5** to give the corresponding adduct in excellent selectivities (72% yield, syn/anti=11/89, anti aldol=95%ee). Interestingly, when chiral diamine (**4**) was employed instead of **3**, reverse diastereoselectivity was observed and syn adduct was obtained in high yield with high selectivities. In the reaction of aromatic aldehydes, the diastereoselectivity could be controlled by choosing the chiral ligand as shown in Table 1. While anti adducts were predominantly obtained by using chiral diamine (**3**), syn adducts were obtained by using chiral diamine (**4**) under almost same conditions. On the other hand, syn adducts were preferentially produced in the reactions of aliphatic or α,β-unsaturated aldehydes when chiral diamine (**4**) was employed (see Table 2), but the reactions did not proceed when chiral diamine (**3**) was used. Next, effects of ester groups on yields, diastereo- and enantioselectivities were examined (Table 3). High enantiomeric excess was observed when the silyl enolate derived from methyl 2-benzyloxypropionate (**6a**) was treated with benzaldehyde, but diastereoselectivity was moderate (Entry 1). In the reactions of the silyl enolates derived from the ethyl or isopropyl esters (**6b** or **6c**), good yields and selectivities were attained. In particular, the silyl enolate of the isopropyl ester (**6c**) worked well in the reactions with aliphatic or α,β-unsaturated aldehydes.

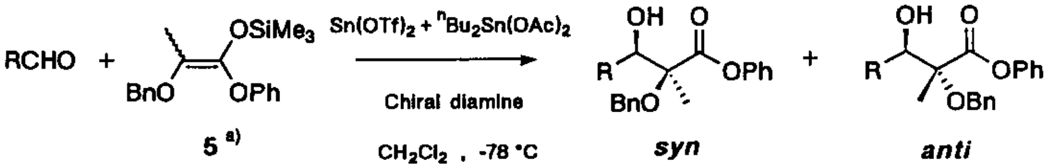
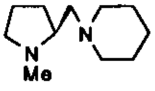


Table 1. Reaction of 5 with Aromatic Aldehydes

Entry	Aldehyde	Chiral diamine	Yield / %	syn / anti [b]	ee / % [c]
1	PhCHO	3	72	11 / 89	95
2	PhCHO	4	81	98 / 2	96
3	*p*-MePhCHO	3	44	8 / 92	95
4	*p*-MePhCHO	4	38	88 / 12	80
5	*p*-NO_2PhCHO	3	50	26 / 74	73
6	*p*-NO_2PhCHO	4	44	91 / 9	81

a) E / Z = 58 / 42. b) Determined by ^{1}H-nmr. c) Ee's of the major diastereomers.

Chiral diamine



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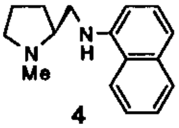

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Table 2. Reaction of 5 with α,β-Unsaturated or Aliphatic Aldehydes by Using Chiral Diamine (4)

Entry	Aldehyde	Yield / %	syn / anti [a]	ee / % [b]
1	(E)-$CH_3CH{=}CHCHO$	50	88 / 12	94
2	(E)-PhCH=CHCHO	53	86 / 14	93
3	EtCHO	41	51 / 49	67
4	c-$C_6H_{11}CHO$	15	94 / 6	92

a) Determined by ^{1}H-nmr. b) Ee's of the syn diastereomers.

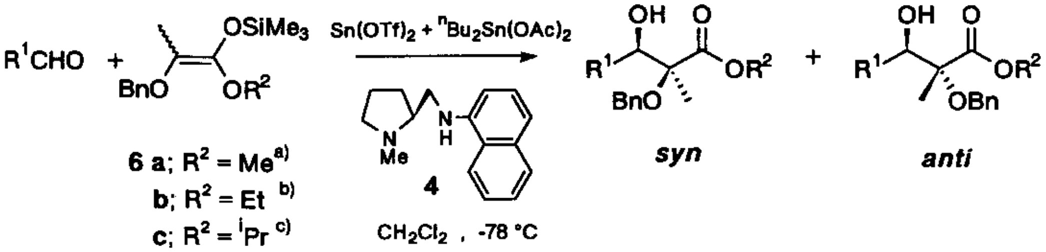


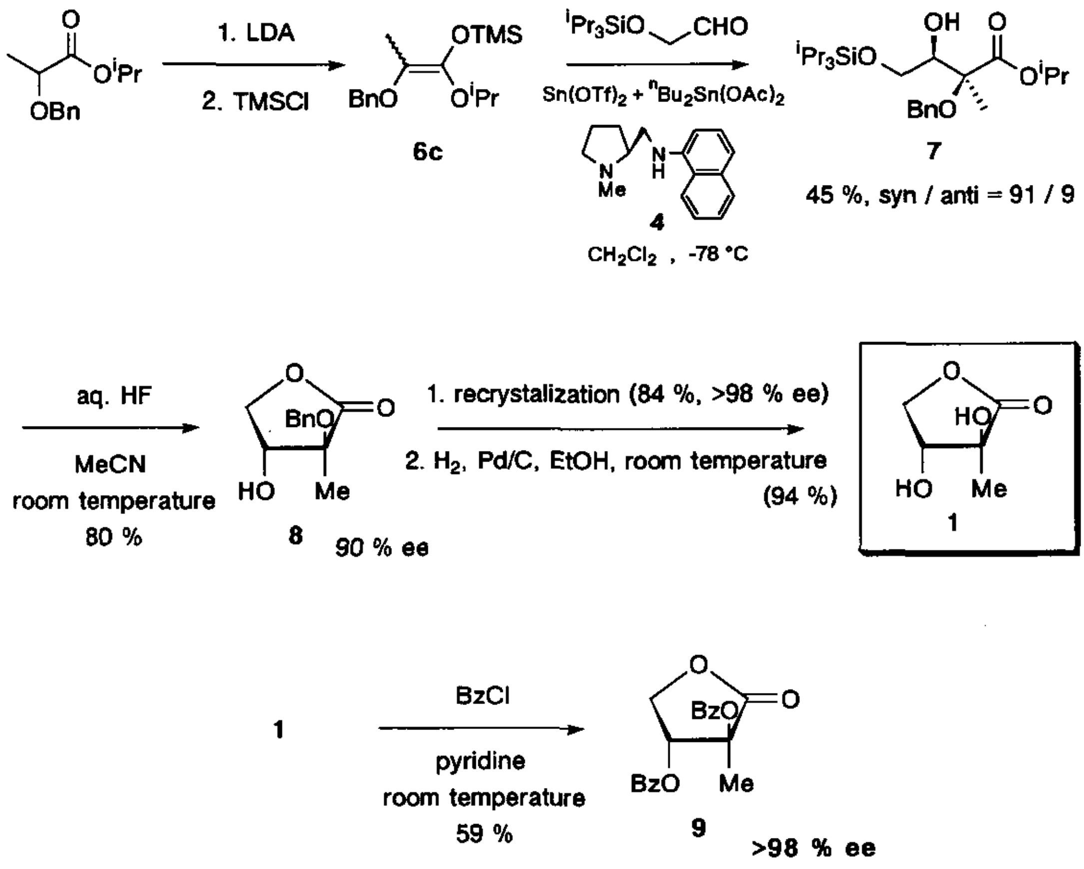
Table 3. Reaction of 6a-c with Various Aldehydes

Entry	Aldehyde	Silyl enolate	Yield / %	syn / anti [d)]	ee / % [e)]
1	PhCHO	**6a**	87	67 / 33	90
2	PhCHO	**6b**	quant.	81 / 19	80
3	PhCHO	**6c**	89	96 / 4	83
4	(E)-CH_3CH=CHCHO	**6a**	quant.	81 / 19	88
5	(E)-CH_3CH=CHCHO	**6c**	79	96 / 4	88
6	(E)-PhCH=CHCHO	**6c**	85	97 / 3	87
7	n-$C_6H_{13}CHO$	**6c**	70	98 / 2	87
8	c-$C_6H_{11}CHO$	**6a**	65	83 / 17	94
9	c-$C_6H_{11}CHO$	**6c**	52	97 / 3	97

a) E / Z = 59 / 41. b) E / Z = 64 / 36. c) E / Z = 71/ 29. d) Determined by ^1H-nmr.
e) Ee's of the major diastereomers.

Then the catalytic asymmetric aldol reaction using 20 mol% of tin (II) triflate and chiral diamine was studied. According to the standard procedure shown in the previous paper,[8] a mixture of **6c** and benzaldehyde was slowly added to the propionitrile solution of the chiral catalyst for over 4 h. The reaction proceeded smoothly to afford the corresponding adduct in 60% yield with high diastereoselectivity (syn/anti=90/10). The enantiomeric excess of the syn adduct was proved to be 96%ee, determine by hplc analysis.

Finally, in order to demonstrate the utility of this reaction, total synthesis of (-)-2-*C*-methyl-D-threono-1,4-lactone (**1**) was tried (Scheme 1). The reaction of triisopropylsiloxyacetaldehyde with the silyl enolate (**6c**) was carried out in the presence of tin(II) triflate, chiral diamine (**4**) and dibutyltin diacetate, and the corresponding aldol-type adduct (**7**) was obtained 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**). *t*-Butyldimethylsiloxyacetaldehyde or *t*-butyldiphenylsiloxyacetaldehyde did not give better results (Table 4). Recrystarization of **8** in benzene/hexane system gave optically pure lactone (**8**), and (-)-2-*C*-methyl-D-threono-1,4-lactone (**1**) was obtained after deprotection of benzyl group.[9] The optical purity of this synthetic sample was confirmed to be >98%ee as its dibenzoate (**9**) using hplc analysis (Daicel Chiralcel OD).[10]



Scheme 1.

Table 4. Reaction of 6a, c with Alkylsiloxyacetaldehydes by Using of Chiral Diamine (4)

Entry	Aldehyde	Silyl enolate	Yield / %	syn / anti [a)]	ee / % [b)]
1	$^{t}BuMe_2SiOCH_2CHO$	6a	30	68 / 32	62
2	$^{t}BuMe_2SiOCH_2CHO$	6c	40	72 / 28	66
3	$^{i}Pr_3SiOCH_2CHO$	6c	45	91 / 9	90
4	$^{t}BuPh_2SiOCH_2CHO$	6c	46	81 / 19	19

a) Determined by ^{1}H-nmr. b) Ee's of the syn diastereomers.

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9. $[\alpha]_D^{28}$ -18 ° (c 0.4, H_2O) (lit.,[3] $[\alpha]_D^{28}$ -11 ° (c 0.5, H_2O)). Possibility of racemization of the compound (**1**) obtained in the literature was pointed out by Teresa *et al.*[11]
10. $[\alpha]_D^{23}$ -126 ° (c 0.47, acetone) (lit.,[3] $[\alpha]_D^{22}$ -57 ° (c 1.9, acetone)).
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