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ENANTIOSELECTIVE SYNTHESIS OF β-HYDROXY-α-METHYL CARBONYL COMPOUNDS BY ALDOL REACTION[1,2]

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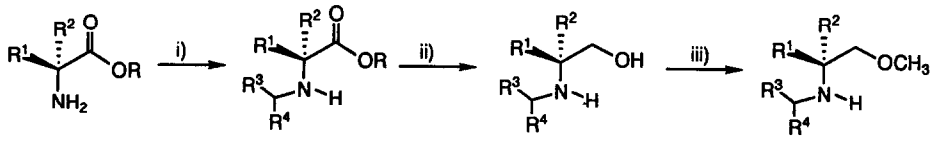
The enantioselective aldol reactions of ketone lithium enolates with aldehydes mediated chiral lithium amides were extensively investigated. The chiral amino ethers **4a-4l** and diamines **16a,b** were prepared from α-amino acids. The reaction conditions and the substituent effects of chiral lithium amides were examined using **4a-4l** and **16a,b** in the aldol reaction of lithium enolate of 2,2-dimethyl-3-pentanone (**17a**) with benzaldehyde. When the lithium amide from **4b** or **4c** was used, **18a** was obtained in 92-93% yield and 68% enantiomeric excess. Reactions of various ketones **17a-17d** with aldehydes afforded the β-hydroxy-α-methyl carbonyl compounds **18a-18k** in 40-95% yield and 10-77% enantiomeric excess. The best result of 77% enantiomeric excess was realized in the aldol reaction of **17a** with 1-naphthaldehyde using the chiral lithium amide from **4b**. The aldols **18l-18k** were easily converted to the carboxylic acid derivatives **19a-19c** of 40-60% enantiomeric excess.

One of the most important subjects in modern synthetic organic chemistry is the stereoselection on acyclic systems and numerous investigations have been concerned with this problem. Among them, the stereoselection of aldol reaction has been studied most extensively[3] since this reaction directly affords β-hydroxy-α-methyl carbonyl compounds (aldols) which are very useful synthons for natural product synthesis. When the aldol reaction is used for the natural product synthesis, it is necessary to obtain the optically active aldols and to this end both relative and absolute configurations of the aldols should be controlled. Although there are many successful reports on diastereoselective aldol reactions[3] to obtain optically active aldols, only a few reports on enantioselective ones have been known.[3-9] Mukaiyama and co-workers[4] used L-proline derived chiral diamines to stannous triflate mediated aldol reaction. Masamune and co-workers[5] and Paterson and co-workers[6] investigated chirally modified boron triflate mediated enantioselective aldol reactions. Ito and co-workers[7] used the chiral gold complex to the aldol reaction of aldehydes with isocyanoacetates. Regan and Staunton[8] reported the enantioselective synthesis of mellein methyl ether using the chiral lithium amides derived from α-phenylethylamine and the Germann group[9] investigated the enantioselective addition of the carboxylic acid dianion to benzaldehyde in the presence of the chiral lithium amides. However, in the case of the aldol reaction of ketone lithium enolates with aldehydes, a typical aldol reaction, the asymmetric inductions are usually low (less than 30%ee).[3] We have already reported[2] our preliminary results on the enantioselective aldol reaction of lithium enolate from 2,2-dimethyl-3-pentanone with benzaldehyde using chiral lithium amide as a chiral auxiliary.[10] In this paper we now describe the details of our results.

A series of chiral amino ethers and diamines necessary for the systematic investigation of the substituent effects of chiral auxiliaries were derived from readily available α-amino acids. Chiral amino ethers were prepared according to the method developed earlier[11] (Scheme I). α-Amino acids **1**(R=H) or



1 2 3 4

a : R^1=R^3=R^4=CH_3, R^2=H

b : R^1=$(CH_3)_2CH$, R^2=H, R^3=R^4=CH_3

c : R^1=H, R^2=C_6H_5, R^3=R^4=CH_3

d : R^1=$C_6H_5CH_2$, R^2=H, R^3=R^4=CH_3

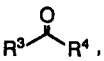
e : R^1=$(CH_3)_2CH$, R^2=H, R^3,R^4=-$(CH_2)_5$-

f : R^1=$(CH_3)_2CH$, R^2=H, R^3=R^4=C_2H_5

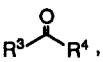
g : R^1=$(CH_3)_2CH$, R^2=R^4=H, R^3=C_6H_5

h : R^1=$(CH_3)_2CH$, R^2=R^4=H, R^3=c-C_6H_{11}

i : R^1=$(CH_3)_2CH$, R^2=R^4=H, R^3=$(CH_3)_3C$

Reagents when R=H i)  , $NaBH_3CN$, CH_3OH, ii)$LiAlH_4$, THF

iii) NaH, CH_3I, THF

when R=CH_3 i)  , $NaBH_3CN$, CH_3OH, CH_3CO_2H

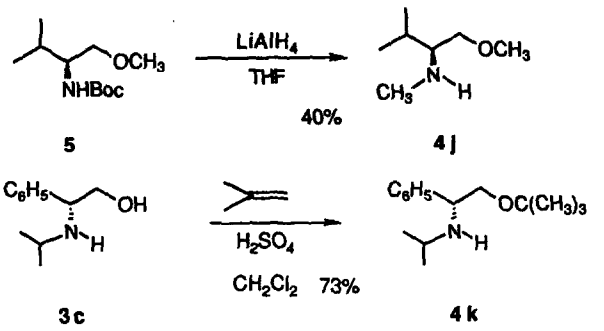
ii) $LiAlH_4$, ether iii) NaH, CH_3I, THF

Scheme I

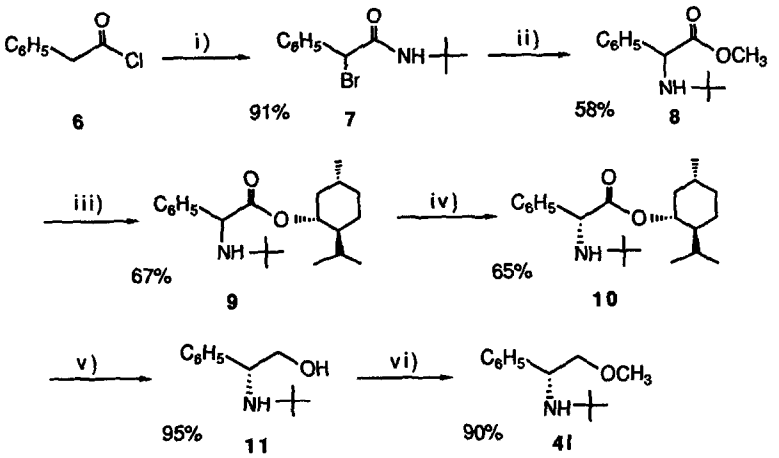
Table I Preparation of Chiral Amino Ethers

entry	R^1	R^2	R^3	R^4	R	compd suffix	isolated yield % 1→2	2→3	3→4
1	CH_3	H	CH_3	CH_3	H	**a**	56	70	53
2	$(CH_3)_2CH$	H	CH_3	CH_3	H	**b**	74	91	82
3	H	C_6H_5	CH_3	CH_3	H	**c**	76	84	81
4	$C_6H_5CH_2$	H	CH_3	CH_3	H	**d**	86	77	87
5	$(CH_3)_2CH$	H	-$(CH_2)_5$-		H	**e**	86	81	85
6	$(CH_3)_2CH$	H	C_2H_5	C_2H_5	CH_3	**f**	97	86	61
7	$(CH_3)_2CH$	H	C_6H_5	H	CH_3	**g**	90	90	74
8	$(CH_3)_2CH$	H	c-C_6H_{11}	H	CH_3	**h**	82	82	77
9	$(CH_3)_2CH$	H	$(CH_3)_3C$	H	CH_3	**i**	67	87	85

esters **1**(R=CH_3) were reductively N-alkylated by the treatment of the suitable ketones or aldehydes with sodium cyanoborohydride to give the N-alkylated derivatives **2**.[12,13] Reduction to amino alcohols **3** with lithium aluminum hydride, followed by O-methylation with methyl iodide-sodium hydride in tetrahydrofuran afforded the required amino ethers **4**. The yields of each steps were summarized in Table I. The N-methyl and O-t-butyl derivatives, **4j** and **4k**, were also prepared by reduction of the t-butylurethane **5**[14] and by O-t-butylation of the alcohol **3c**, respectively (Scheme II). Since the optically active N-t-butyl α-amino acid is not available from optically active α-amino acid, the N-t-butyl



Scheme II

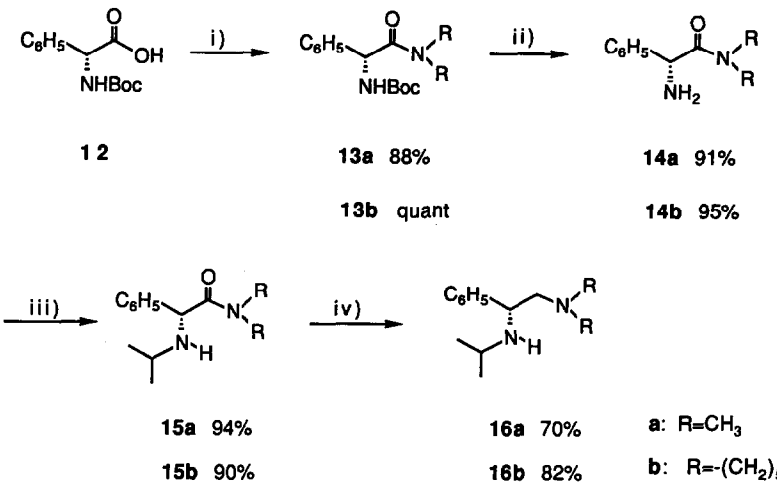


Reagents i) a) Br_2, CCl_4 b) $(CH_3)_3CNH_2$, CH_2Cl_2
ii) a) $(CH_3)_3COK$, $(CH_3)_3COH$ b) $SOCl_2$, CH_3OH
iii) L-menthol, $(CH_3)_3COK$, benzene
iv) a) $(COOH)_2$, ether b) recrystallization c) NaOH
v) $LiAlH_4$, ether vi) NaH, CH_3I, THF

Scheme III

derivative **4l** was prepared through optical resolution (Scheme III). Phenylacetyl chloride (**6**) was brominated and condensed with t-butylamine.[15] Treatment of bromoamide **7** with potassium t-butoxide in t-butanol[16] afforded the N-t-butyl α-amino acid potassium salt which was then converted to the methyl ester **8** by the action of thionyl chloride in methanol. The ester exchange reaction of **8** using L-menthol and an equimolar amount of potassium t-butoxide in benzene proceeded smoothly to give the menthyl ester **9**. The optical resolution of **9** was performed by repetitive recrystallizations of its oxalate from ethanol. The optical purity of less soluble isomer **10** was determined to be over 99% by 400MHz ^{1}H-NMR

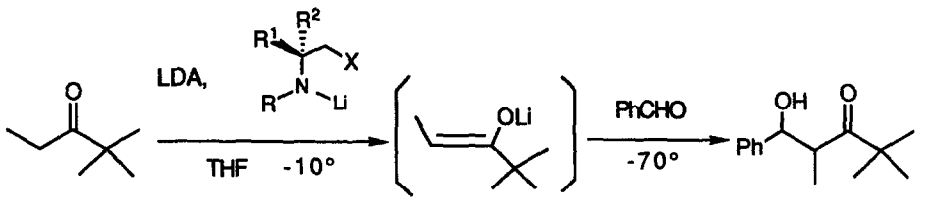
analysis and the absolute configuration was tentatively assigned to be (R) from the result obtained by the following aldol reaction (see below). The optically resolved **10** was easily converted to the desired amino ether **4l** by reduction and O-methylation. Chiral diamines **16a** and **16b** were prepared as shown in Scheme IV. N-t-Butoxycarbonyl-D-α-phenylglycine (**12**) was condensed with dimethylamine or piperidine using diethyl phosphorocyanidate (DEPC) and triethylamine in dimethylformamide.[17] Acid hydrolysis of the t-butoxycarbonyl group gave the primary amines **14** which were then converted to the N-isopropyl derivatives **15**. Subsequent reduction of the amide function afforded the desired diamines **16a** and **16b**.



Reagents i) R_2NH, DEPC, $(C_2H_5)_3N$, DMF ii) CF_3CO_2H
iii) $(CH_3)_2CO$, $NaBH_3CN$, CH_3OH, CH_3CO_2H iv) $LiAlH_4$, THF

Scheme IV

Since the aldol reaction of 2,2-dimethyl-3-pentanone (**17a**) with benzaldehyde by use of lithium diisopropylamide (LDA) was known to give erythro-aldol **18a** diastereoselectively,[18] the reaction conditions and the substituent effects of chiral auxiliaries were investigated using this reaction (Scheme V). The reaction was performed by allowing the enolate solution to react with benzaldehyde at -70°C for 5 min. The enantiomeric excess of the product **18a** was easily determined by HPLC on a chiral stationary phase column and the absolute configuration of the major isomer was tentatively assigned from the chiral recognition mechanism and the order of elution from the chiral column.[19,20] Furthermore, this assignment was confirmed by ^{1}H-NMR analysis of its (R)-α-methoxy-α-trifluoromethylphenylacetic acid ((R)-MTPA) ester and chemical correlation to the known compound (see below). The results are summarized in Table II. The aldol reaction using 1.2 equiv of the chiral lithium amide from **4b** instead of LDA, afforded the erythro-aldol **18a** in 90% yield but the enantiomeric excess of **18a** was only 18%ee. However, when this reaction was performed by a combination of 1.2 equiv of LDA and equimolar amount of the chiral lithium amide from **4b**, the 93% chemical yield and 68%ee were realized. Probably, LDA acts as a strong base and the chiral lithium amide acts as a chiral auxiliary under reaction conditions, and the



17a 18a

Scheme V

Table II. Aldol Reaction of 2,2-Dimethyl-3-pentanone with Benzaldehyde Using Various Chiral Lithium Amides.

entry	chiral lithium amide[a]	isolated yield %	%ee[b]	config[c]
1	**4a**	85	45	S, S
2[d]	**4b**	90	18	S, S
3	**4b**	93	68	S, S
4[e]	**4b**	92	47	S, S
5[f]	**4b**	88	33	S, S
6	**4c**	92	68	R, R
7	**4d**	80	44	S, S
8	**4e**	89	57	S, S
9	**4f**	90	35	S, S
10	**4g**	86	19	S, S
11	**4h**	92	50	S, S
12	**4i**	93	12	S, S
13	**4j**	77	5	S, S
14	**4k**	85	54	R, R
15	**4l**	97	65	R, R
16	**16a**	87	28	R, R
17	**16b**	84	30	R, R
18	g)	80	66	R, R

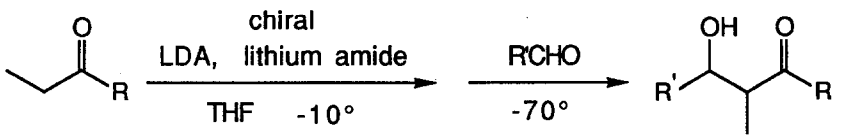
a) The chiral lithium amides were smoothly produced from the corresponding **4** and **16**, by treatment with equimolar amounts of n-butyllithium. b) The enantiomeric excess was determined by HPLC analysis. c) See ref. 20. d) LDA was not used. e) The enolate was formed at room temperature. f) The enolate was formed at -70°C. g) The chiral lithium amide derived from (S)-N-isopropyl-α-phenylethylamine[8] was used.

chiral lithium amide from **4b** is a more effective chiral ligand than the chiral amine **4b** itself. Both lowering and raising the enolate formation temperature caused decrease of enantiomeric excess.

Substituent effects of the chiral lithium amide were summarized as follows; as for the substituents attached to the chiral carbon atom (R^1, R^2), the combination of isopropyl-hydrogen or hydrogen-phenyl groups gave the best result (68%ee) and the use of methyl or benzyl groups were less effective. Furthermore these substituents determined the absolute configuration of the product. When the chiral

lithium amides of which R^1 was alkyl group and R^2 was hydrogen were used, the (S, S)-**18a** was obtained as the major isomer, while when R^1 was hydrogen and R^2 was phenyl group, the (R, R)-**18a** was predominant. On the contrary, the chiral amino ether **4l** which was prepared through optical resolution would be (R) configuration because the (R, R)-**18a** was obtained as the major product. The N-substituent strongly affected the enantiomeric excess and the use of bulky groups (isopropyl, cyclohexyl, cyclohexylmethyl, and t-butyl) gave the enantiomeric excess up to 50%ee. Among them, the isopropyl group showed the highest value. A striking decrease of the enantiomeric excess was observed when the N-3-pentyl, neopentyl, benzyl, and methyl groups were employed. The substituent X which would be expected to chelate to the lithium atom intramolecularly, and the methoxy group turned out to be the most effective but the amino function reduced the asymmetric efficiency. Interestingly, when the chiral lithium amide derived from (S)-N-isopropyl-α-phenylethylamine[8] was used, in this case X was hydrogen and it can not chelate to the lithium atom, the enantiomeric excess was 66%ee which was almost the same as that when X was the methoxy group. From the above results, we concluded the chiral lithium amides derived from **4b** and **4c** were the most effective chiral auxiliaries.

We next turned our attention to the generality of this reaction. We investigated the aldol reaction of the various ethyl ketones with aldehydes in the presence of the chiral lithium amides from **4b** and **4c** (Scheme VI). The enantiomeric excess of the each products **18** was determined by HPLC analysis or by ^{1}H-NMR analysis. The results are shown in Table III. Several noteworthy features are apparent from the Table III. The aldol reaction of 2,2-dimethyl-3-pentanone (**17a**) with various aldehydes afforded mainly erythro-aldol **18a** - **18f**.[21] When aromatic aldehydes were used, the aldols **18a** and **18b** were obtained in good chemical yield and high enantiomeric excess. Especially, in the case of 1-naphthaldehyde, the best result of 77%ee was realized. The use of 3-phenylpropanal, 2-methylpropanal and cyclohexanecarbaldehyde afforded the aldols **18c**-**18e** of 40-63%ee, among which the chiral lithium amide from **4c** gave slightly better results. When 2,2-dimethylpropanal was used, both the chemical yield and the enantiomeric excess decreased probably due to its steric hinderance. The aldol reaction of 3-pentanone or 2-methyl-3-pentanone and 1-naphthaldehyde afforded the aldols **18g** and **18h** as the mixture of diastereomers (erythro : threo ≅ 1 : 2) and the enantiomeric excesses of erythro isomers were always higher than those of threo isomers, but these were below 42%ee. The use of the ketones **17a** and **17d** having bulky substituents gave predominantly erythro-aldols **18b** and **18j**, respectively, with higher enantiomeric excess (60-70%ee). From the above results, it is obvious that the use of ketones having bulky substituents is essential to obtain good stereoselectivity.



17 **18**

Scheme VI

The absolute configurations of the major aldols obtained by the reaction using the chiral lithium amide from **4b** were confirmed as the following way. Since the ^{1}H-NMR analysis of the MTPA ester has

Table III Aldol Reaction of the Various Ethyl Ketones with Aldehydes in the Presence of the Chiral Lithium Amides

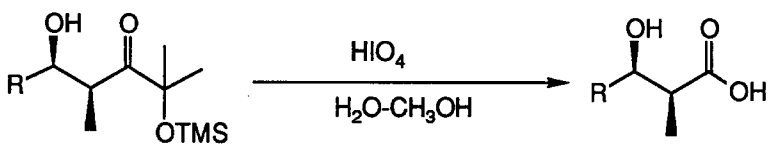
entry	R	ketone	R'	product	chiral lithium amide[a]	isolated yield %	ratio[b] erythro : threo	%ee of erythro isomer(config)[d]	%ee of threo isomer(config)[d]
1	$(CH_3)_3C$	**17a**	C_6H_5	**18a**	**4b**	93	c)	68[b](S, S)	
2	$(CH_3)_3C$	**17a**	C_6H_5	**18a**	**4c**	92	c)	68[b](R, R)	
3	$(CH_3)_3C$	**17a**	1-$C_{10}H_7$	**18b**	**4b**	85	97 : 3	77[b](S, S)	21[b](S, R)
4	$(CH_3)_3C$	**17a**	1-$C_{10}H_7$	**18b**	**4c**	84	96 : 4	72[b](R, R)	18[b](R, S)
5	$(CH_3)_3C$	**17a**	$C_6H_5CH_2CH_2$	**18c**	**4b**	92	c)	41[e](S, R)	
6	$(CH_3)_3C$	**17a**	$C_6H_5CH_2CH_2$	**18c**	**4c**	91	c)	43[e](R, S)	
7	$(CH_3)_3C$	**17a**	$(CH_3)_2CH$	**18d**	**4b**	80	c)	48[e](S, R)	
8	$(CH_3)_3C$	**17a**	$(CH_3)_2CH$	**18d**	**4c**	79	c)	58[e](R, S)	
9	$(CH_3)_3C$	**17a**	c-C_6H_{11}	**18e**	**4b**	74	c)	45[e](S, R)	
10	$(CH_3)_3C$	**17a**	c-C_6H_{11}	**18e**	**4c**	93	c)	63[e](R, S)	
11	$(CH_3)_3C$	**17a**	$(CH_3)_3C$	**18f**	**4b**	48	c)	33[f](S, S)	
12	$(CH_3)_3C$	**17a**	$(CH_3)_3C$	**18f**	**4c**	72	c)	37[f](R, R)	
13	C_2H_5	**17b**	1-$C_{10}H_7$	**18g**	**4b**	73	35 : 65	10[b](S, S)	9[b](S, R)
14	C_2H_5	**17b**	1-$C_{10}H_7$	**18g**	**4c**	91	30 : 70	15[b](R, R)	3[b](R, S)
15	$(CH_3)_2CH$	**17c**	1-$C_{10}H_7$	**18h**	**4b**	85	30 : 70	42[b](S, S)	26[b](S, R)
16	$(CH_3)_2CH$	**17c**	1-$C_{10}H_7$	**18h**	**4c**	85	31 : 69	34[b](R, R)	20[b](R, S)
17	$TMSO(CH_3)_2C$	**17d**	C_6H_5	**18i**	**4b**	69	c)	39[g](S, S)	
18	$TMSO(CH_3)_2C$	**17d**	1-$C_{10}H_7$	**18j**	**4b**	53	c)	62[b](S, S)	
19	$TMSO(CH_3)_2C$	**17d**	1-$C_{10}H_7$	**18j**	**4c**	56	c)	60[b](R, R)	
20	$TMSO(CH_3)_2C$	**17d**	$(CH_3)_2CH$	**18k**	**4b**	43	c)	40[g](S, R)	

a) *The chiral lithium amides were generated from* **4b** and **4c**, respectively, by treatment with equimolar amounts of n-butyllithium. b) Determined by HPLC analysis. c) Only erythro isomer was obtained. d) See ref. 20. e) Determined by ^{1}H-NMR analysis of the corresponding methoxy methyl ether in the presence of Eu(hfc)$_3$. f) Determined by ^{1}H-NMR analysis of the corresponding acetyl ester in the presence of Eu(hfc)$_3$. g) Determined by ^{1}H-NMR *analysis of corresponding* (R)-MTPA *ester.*

Table IV ^{1}H-NMR Chemical Shifts for the α-Methyl Resonances of the (R)-MTPA Esters Derived from Aldols (18)

	δ, ppm	
starting aldol	major	minor
18a	1.25	1.05
18b	1.35	1.30
18d	1.02	0.95
18l	1.21	1.05
18k	1.03	0.98

been known to the useful method for assigning the absolute configurations of chiral alcohols,[22] the aldols (**18a**, **18b**, **18d**, **18l**, and **18k**) were converted to the corresponding (R)-MTPA esters and the ^{1}H-NMR spectra of them were measured. As shown in Table IV, the signals due to α-methyl group of major isomers appear consistently at lower field than those of minor isomers. From the known relationship between prefered conformation of MTPA esters and their ^{1}H-NMR chemical shifts,[22] these results indicated that the configurations of the β-hydroxy group of the major aldols are (S) for **18a**, **18b**, and **18l** and (R) for **18d** and **18k**. On the other hand, the erythro relative configurations of these aldols were already determined by their ^{1}H- or ^{13}C-NMR spectra.[21] Accordingly, the absolute configurations of the major aldols should be (S, S) for **18a**, **18b**, and **18l** and (S, R) for **18d** and **18k**. Furthermore, the aldols **18l**-**18k** were converted to the β-hydroxy-α-methyl carboxylic acids **19a**-**19c** by the method reported by Heathcock and co-workers[18](Scheme VII). When the aldols **18** were treated with periodic acid in aqueous methanol, the carboxylic acids **19** were obtained in good yield. By the comparison of the specific rotations of **19a** and **19c**, respectively, with the reported ones,[23] the absolute configurations of them were unambiguously determined to (S, S) for **19a** and (S, R) for **19c**. In addition, this operation, that is, the enantioselective aldol reaction and subsequent chemical transformation make possible to prepare synthetically useful β-hydroxy-α-methyl carboxylic acid derivatives of 40-60%ee. Consequently, by utilizing the ^{1}H-NMR analysis of MTPA esters and the chemical correlation to the known compounds, the absolute configurations of the major aldols (**18a**, **18b**, **18d**, **18l**, and **18k**) which were obtained by



18i	R=C_6H_5	**19a**	R=C_6H_5	85%
18j	R=1-$C_{10}H_7$	**19b**	R=1-$C_{10}H_7$	quant.
18k	R=$(CH_3)_2CH$	**19c**	R=$(CH_3)_2CH$	94%

Scheme VII

using the chiral lithium amide from **4b** were determined. When the chiral lithium amide from **4c** was used, the HPLC and ^{1}H-NMR spectra cleanly indicated that the major isomers were the enantiomers of those obtained by using **4b**. Although, the absolute configurations of the other aldols (**18c, 18e-18h**) were not rigorously determined, we assigned them as shown in Table III by comparison of the HPLC or ^{1}H-NMR spectra with those of **18a** and **18d**.

Thus, we provided the enantioselective aldol reaction of ketone lithium enolates with aldehydes using chiral lithium amides as chiral auxiliaries. This method represents following characteristic features; i) chiral auxiliaries are easily prepared from readily available α-amino acids; ii) chemical yields are fairly good; iii) when ketones having bulky substituents are used, aldols are obtained in 40-77%ee; iv) both antipodes of β-hydroxy-α-methyl carbonyl compounds can be prepared. At present, the precise mechanism of this reaction is unknown since the structure of lithium enolates and that of chiral lithium amides in addition to the aggregations of them are not fully understood.[24] However, this method which affords the β-hydroxy-α-methyl carbonyl compounds in high optical purity would promise the efficient enantioselective synthesis.

EXPERIMENTAL

Melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrophotomer using nujol mull or as films. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL PMX-60, FX-100, or GSX-400 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. HPLC was carried out with an Erma Optical Works ERC-8710 high-pressure liquid chromatograph. Ether was distilled from lithium aluminum hydride and tetrahydrofuran was distilled from benzophenone ketyl. Dimethylformamide was dried over molecular sieves (4A). Silica gel (BW-820MH or BW-200, purchased from Fuji-Davison) was used for column chromatography. All reactions involving organometallic reagents were conducted under an argon atmosphere.

General Procedure for the Preparation of Chiral Amino Alcohols 3. (1) From Amino Acid. N-Isopropyl or N-cyclohexyl amino acids were prepared by the method reported by Ohfune and co-workers.[12] N-Alkyl amino acid **2**(R=H) (0.1 mol) was added in small portions to an ice-cold suspension of lithium aluminum hydride (5.69 g, 0.15 mol) in tetrahydrofuran (400 mL) and the mixture was stirred at room temperature for 5-8 h. Ethyl acetate (6 mL), 10% aqueous sodium hydroxide (6 mL), and water (18 mL) was successively added dropwise in an ice-bath, and the mixture was stirred at room temperature for several hours. After filtration, the precipitates were washed with ether. The organic layer was dried over sodium sulfate, and concentrated in vacuo. The residue was purified by distillation or recrystallization.

(S)-2-Isopropylaminopropan-1-ol (3a): A colorless oil, bp 70-72°C/16mmHg; $[\alpha]^{25}_D$+34.6°(c1, MeOH); IR 3250, 1170, 1140, 1080, 1050 cm^{-1}; ^{1}H-NMR δ 1.03(d, J=6Hz), 1.07(d, J=6Hz)(9H), 2.28(2H, br s), 2.6-3.1(2H, m), 3.2-3.6(2H, m). Oxalate; mp 129-131°C (EtOH). Anal. Calcd for $C_8H_{17}NO_5$: C, 46.37; H, 8.27; N, 6.76. Found C, 46.24; H, 8.07; N, 6.87.

(S)-2-Isopropylamino-3-methylbutan-1-ol (3b): A colorless oil, bp 76.5-77.5°C/9mmHg; $[\alpha]^{24}_D$-3.3°(c1, EtOH); IR 3350, 2960, 1465, 1380, 1175, 1140, 1050 cm^{-1}; ^{1}H-NMR δ 0.88(3H, d, J=6Hz), 0.95(3H, d, J=6Hz), 1.01(3H, d, J=6Hz), 1.07(3H, d, J=6Hz), 1.4-2.1(3H, m), 2.44(1H, dq, J=6Hz), 2.89(1H, dq, J=6Hz), 3.20(1H, dd, J=6 and 10Hz), 3.52(1H, dd, J=6 and 10Hz). Oxalate; mp 190.5-191.5°C (EtOH). Anal. Calcd for $C_{10}H_{21}NO_5$: C, 51.05; H, 9.00; N, 5.95. Found C, 50.83; H, 9.00; N, 5.91.

(R)-2-Isopropylamino-2-phenylethanol (3c): A colorless solid, mp 68.5-71°C(n-hexane); $[\alpha]^{24}_D$-63.7°(c1, EtOH); IR 3250, 1600, 1170, 1135, 1060, 1040, 700 cm^{-1}; ^{1}H-NMR δ 1.02(3H, d, J=6Hz), 1.07(3H, d, J=6Hz), 1.8-2.5(2H, br s), 2.5-3.0(1H, m), 3.5-4.1(3H, m), 7.40(5H, s). Oxalate; mp 177.5-179°C(EtOH). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found C, 57.73; H, 6.96; N, 5.22.

(S)-2-Isopropylamino-3-phenylpropan-1-ol (3d): A colorless solid, mp 61-62°C(n-hexane); $[\alpha]^{24}_D$-4.0°(c1, MeOH); IR 3300, 1135, 1035, 695 cm^{-1}; ^{1}H-NMR δ 0.98(3H, d, J=7Hz), 1.03(3H, d, J=7Hz), 1.98(2H, br s), 2.7-3.2(4H, m), 3.3-3.8(2H, m), 7.38(5H, s). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found C, 74.33; H, 10.16; N, 7.51.

(S)-2-Cyclohexylamino-3-methylbutan-1-ol (3e): A colorless oil, bp 110-120°C/5mmHg; $[\alpha]^{26}_D$-3.2°(c1, MeOH); IR 3350, 2930, 1445, 1360, 1110, 1050 cm^{-1}; ^{1}H-NMR δ 0.86(d, J=6Hz), 0.93(d, J=6Hz), 0.86-2.1(m)(19H), 2.3-2.8(2H, m), 3.1-3.6(2H, m). Oxalate; mp 174-175°C(decomp)(EtOH). Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.15; N, 5.09. Found C, 56.67; H, 9.48; N, 5.36.

(2) From Amino Acid Methyl Ester. (2-1) Reductive Alkylation. To a solution of L-valine methyl ester (**1b**, R=Me) (6.55 g, 50 mmol) in dry methanol (100 mL) was added sodium cyanoborohydride (3.14 g, 50 mmol) and the aldehyde or ketone (60 mmol), and the pH of the mixture was adjusted to ca. 6 by adding acetic acid. The solution was stirred at room temperature for 2-3 h. If the reaction did not proceed completely, another 60 mmol of the carbonyl compound was added and the mixture was stirred overnight. The solution was cooled with ice-methanol, then added 40% aqueous potassium carbonate (200 mL) and extracted with ether. The organic layer was washed twice with saturated aqueous sodium chloride and dried over sodium sulfate. Concentration in vacuo gave the residue, which was purified by column chromatography on silica gel using either n-hexane-ethyl acetate (15:1-40:1) or n-hexane-ether (30:1) as an eluent.

Methyl (S)-3-Methyl-2-(3-pentylamino)butanoate (2f): A colorless oil, bp 83-86°C/5mmHg; $[\alpha]^{27}_D$+31.0°(c1, MeOH); IR 3320, 2950, 1730, 1450, 1380, 1230, 1190, 1160 cm^{-1}; ^{1}H-NMR δ 0.8-1.0(12H, m), 1.2-1.6(5H, m), 1.7-1.9(1H, m), 2.1-2.3(1H, m), 3.03(1H, d, J=9Hz), 3.70(3H, s). Oxalate; mp 93.5-95°C(EtOH-ether). Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found C, 53.43; H, 8.51; N, 4.84.

Methyl (S)-2-Benzylamino-3-methylbutanoate (2g): A colorless oil, bp 115-120°C/2mmHg(Kugelrohr); $[\alpha]^{27}_D$-50.2°(c1, MeOH); IR 3300, 2950, 1730, 1460, 1365, 1200, 1150, 700 cm^{-1}; ^{1}H-NMR δ 0.95(3H, d, J=6Hz), 0.96(3H, d, J=6Hz), 1.70(1H, br s), 1.7-2.1(1H, m), 3.03(1H, d, J=6Hz), 3.59(1H, d, J=13Hz), 3.72(3H, s), 3.83(1H, d, J=13Hz), 7.30(5H, s). Oxalate; mp 140-142°C(AcOEt). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.86; H, 6.80; N, 4.50. Found C, 57.75; H, 6.83; N, 4.45.

Methyl (S)-2-Cyclohexylmethylamino-3-methylbutanoate (2h): A colorless oil, bp 110-118°C/3mmHg(Kugelrohr); $[\alpha]^{26}_D$-11.9°(c1, MeOH); IR 3300, 2920, 1735, 1465, 1360, 1200, 1160 cm^{-1}; ^{1}H-NMR δ 0.92(d, J=7Hz), 0.95(d, J=7Hz), 0.5-2.0(m)(19H), 2.1-2.5(2H, m), 2.93(1H, d, J=6Hz), 3.71(3H, s). Oxalate; mp 146-147.5°C(AcOEt). Anal. Calcd for $C_{15}H_{27}NO_6$: C, 56.76; H, 8.58; N, 4.41. Found C, 56.42; H, 8.30; N, 4.26.

Methyl (S)-3-Methyl-2-neopentylaminobutanoate (2i): A colorless oil, bp 100-110°C/22mmHg(Kugelrohr); $[\alpha]^{25}_D$-12.1°(c1, MeOH); IR 3350, 2960, 1735, 1465, 1360, 1200, 1150 cm^{-1}; ^{1}H-NMR δ 0.88(s), 0.92(d, J=7Hz), 0.95(d, J=7Hz)(15H), 1.38(1H br s), 1.7-1.9(1H, m), 2.03(1H, d, J=11Hz), 2.37(1H, d, J=11Hz), 2.87(1H, d, J=6Hz), 3.70(3H, s). Oxalate; mp 119-120°C(AcOEt). Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found C, 53.34; H, 8.94; N, 5.11.

(2-2) Reduction with Lithium Aluminum Hydride. The solution of **2**(R=Me) (40 mmol) in ether (50 mL) was added dropwise to an ice-cold suspension of lithium aluminum hydride (2.28 g, 60 mmol) in ether (70 mL) and the mixture was stirred at room temperature for 1 h. The workup procedure was the same as previously described.

(S)-3-Methyl-2-(3-pentylamino)butan-1-ol (3f): A colorless oil, bp 105-110°C/5mmHg(Kugelrohr); $[\alpha]^{25}_D$+38.5°(c1, $CHCl_3$); IR 3330, 2950, 1450, 1375, 1140, 1050 cm^{-1}; ^{1}H-NMR δ 0.8-1.0(12H, m), 1.2-2.2(7H, m), 2.3-2.6(2H, m), 3.27(1H, dd, J=6 and 10Hz), 3.47(1H, dd, J=5 and 10Hz). Anal. Calcd for $C_{10}H_{23}NO$: C, 69.31; H, 13.38; N, 8.08. Found C, 69.23; H, 13.28; N, 8.22.

(S)-2-Benzylamino-3-methylbutan-1-ol (3g): A colorless oil, bp 105-110°C/0.3mmHg(Kugelrohr); $[\alpha]^{26}_D$+1.6°(c1, MeOH); IR 3350, 2960, 1455, 1390, 1370, 1105, 1045, 700 cm^{-1}; ^{1}H-NMR δ 0.94(6H, t, J=7Hz), 1.6-2.3(3H, m), 2.4-2.6(1H, m), 3.36(1H, dd, J=7 and 11Hz), 3.65(1H, dd, J=4 and 11Hz), 3.79(2H, s), 7.30(5H, s). Oxalate; mp 174-175.5°C(EtOH). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found C, 59.25; H, 7.28; N, 4.96.

(S)-2-Cyclohexylmethylamino-3-methylbutan-1-ol (3h): A colorless oil, bp 99-99.5°C/0.5mmHg; $[\alpha]^{27}_D$+12.9°(c1, MeOH); IR 3350, 2930, 1450, 1390, 1370, 1115, 1060 cm^{-1}; ^{1}H-NMR δ 0.92(t, J=7Hz), 0.6-1.9(m)(18H), 2.05(2H, br s), 2.3-2.6(3H, m), 3.30(1H, dd, J=7 and 10Hz), 3.59(1H, dd, J=4 and 10Hz). Oxalate; mp 166.5-167.5°C(EtOH). Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.41; N, 4.84. Found C, 58.37; H, 9.50; N, 4.83.

(S)-3-Methyl-2-neopentylaminobutan-1-ol (3i): A colorless oil, bp 95-100°C/4mmHg(Kugelrohr); $[\alpha]^{27}_D$+19.6°(c1, MeOH); IR 3360, 2950, 1470, 1380, 1360, 1110, 1045 cm^{-1}; ^{1}H-NMR δ 0.93(15H, s and t, J=7Hz), 1.6-2.1(3H, m), 2.24(d, J=12Hz), 2.2-2,4(m), 2.45(d, J=12Hz)(3H), 3.26(1H, dd, J=7 and 11Hz), 3.57(1H, dd, J=4 and 11Hz). Oxalate; mp 190-191.5°C(decomp)(EtOH). Anal. Calcd for $C_{12}H_{25}NO_5$: C, 54.73; H, 9.57; N, 5.32. Found C, 54.57; H, 9.80; N, 5.46.

General Procedure for the Preparation of Chiral Amino Ethers 4. To an ice-cold suspension of sodium hydride (4.80 g, 60% oil suspension, 0.12 mol)(n-hexane washed) in tetrahydrofuran (70 mL) was added dropwise the amino alcohol **3** (0.1 mol) in tetrahydrofuran (130 mL) and the mixture was stirred at room temperature for 1 h. Methyl iodide (21.3 g, 0.15 mol) in

tetrahydrofuran (100 mL) was added dropwise in an ice-bath, and stirred at room temperature for 1-4 h. Saturated aqueous sodium chloride (150 mL) was slowly added to the ice-cold reaction mixture and the organic layer was separated. The aqueous layer was extracted with ether. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. In the case of **4a**, the solvent was removed at atmospheric pressure using a Widmer column. The residue was purified by distillation.

(S)-2-Isopropylamino-1-methoxypropane (4a): A colorless oil, bp 71-76°C/54-58mmHg(Kugelrohr); $[\alpha]^{22}_D$+29.7°(c1, MeOH); IR 3300, 2970, 1450, 1380, 1340, 1170, 1160, 1120 cm^{-1}; ^{1}H-NMR δ 1.03(d, J=6Hz), 1.07(d, J=6Hz)(9H), 1.37(1H, br s), 2.7-3.1(2H, m), 3.1-3.4(m), 3.17(s)(5H). Oxalate; mp 124-126°C(EtOH-ether). Anal. Calcd for $C_9H_{19}NO_5$: C, 48.85; H, 8.66; N, 6.33. Found C, 48.60; H, 8.60; N, 6.07.

(S)-2-Isopropylamino-1-methoxy-3-methylbutane (4b): A colorless oil, bp 78.5-79.5°C/43mmHg; $[\alpha]^{22}_D$-6.0°(c1, EtOH); IR 3320, 2960, 1460, 1380, 1175, 1120 cm^{-1}; ^{1}H-NMR δ 0.92(d, J=8Hz), 1.05(d, J=8Hz)(12H), 1.12(1H br s), 1.6-2.0(1H, m), 2.4-3.0(2H, m), 3.1-3.5(m), 3.35(s)(5H). Oxalate; mp 143.5-146°C(EtOH-ether). Anal. Calcd for $C_{11}H_{23}NO_5$: C, 52.99; H, 9.30; N, 5.62. Found C, 52.95; H, 9.40; N, 5.68.

(R)-2-Isopropylamino-1-methoxy-2-phenylethane (4c): A colorless oil, bp 74-75°C/3mmHg; $[\alpha]^{24}_D$-69.7°(c1, EtOH); IR 3300, 2950, 1450, 1380, 1360, 1195, 1120, 700 cm^{-1}; ^{1}H-NMR δ 0.97(3H, d, J=6Hz), 1.02(3H, d, J=6Hz), 1.70(1H, br s), 2.5-2.9(1H, m), 3.33(3H, s), 3.33-3.5(2H, m), 3.9-4.1(1H, m), 7.30(5H, s). Oxalate; mp 169-172°C(decomp) (EtOH). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found C, 59.12; H, 7.40; N, 4.83.

(S)-2-Isopropylamino-1-methoxy-3-phenylpropane (4d): A colorless oil, bp 105-110°C/2mmHg(Kugelrohr); $[\alpha]^{21}_D$+11.5°(c1, MeOH); IR 3300, 2960, 1500, 1450, 1380, 1180, 1125, 705 cm^{-1}; ^{1}H-NMR δ 0.98(3H, d, J=7Hz), 1.03(3H, d, J=7Hz), 1.27(1H, br s), 2.7-3.1(4H, m), 3.3-3.5(2H, m), 3.50(3H, s), 7.30(5H, s). Oxalate; mp 153.5-155°C(EtOH). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found C, 60.81; H, 7.82; N, 4.68.

(S)-2-Cyclohexylamino-1-methoxy-3-methylbutane (4e): A colorless oil, bp 100-103.5°C/7mmHg; $[\alpha]^{26}_D$-6.6°(c1, MeOH); IR 3320, 2930, 1445, 1360, 1185, 1110 cm^{-1}; ^{1}H-NMR δ 0.82(d, J=6Hz), 0.8-1.8(m)(18H), 2.1-2.5(2H, m), 2.9-3.2(m), 3.02(s)(5H). Oxalate; mp 140-141°C(EtOH-ether). Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.41; N, 4.84. Found C, 57.74; H, 9.32; N, 4.91.

(S)-1-Methoxy-3-methyl-2-(3-pentylamino)butane (4f): A colorless oil, bp 76-78°C/8mmHg; $[\alpha]^{22}_D$-5.1°(c1, MeOH); IR 3300, 2980, 1450, 1360, 1180, 1100 cm^{-1}; ^{1}H-NMR δ 0.91(12H, t, J=6Hz), 1.2-1.9(6H, m), 2.0-2.6(2H, m), 3.2-3.4(m), 3.30(s)(5H). Oxalate; mp 85.5-87°C(EtOH-ether). Anal. Calcd for $C_{13}H_{27}NO_5$: C, 56.30; H, 9.81; N, 5.05. Found C, 56.16; H, 9.95; N, 4.97.

(S)-2-Benzylamino-1-methoxy-3-methylbutane (4g): A colorless oil, bp 86.5-87°C/0.7mmHg; $[\alpha]^{25}_D$-5.9°(c1, MeOH); IR 3320, 2950, 1450, 1380, 1360, 1200, 1120 cm^{-1}; ^{1}H-NMR δ 0.91(3H, d, J=7Hz), 0.94(3H, d, J=7Hz), 1.63(1H, s), 1.7-2.1(1H, m), 2.5-2.6(1H, m), 3.2-3.5(m), 3.31(s)(5H), 3.79(2H, s), 7.29(5H, s). Oxalate; mp 118-119°C(AcOEt). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found C, 60.24; H, 7.56; N, 4.77.

(S)-2-Cyclohexylmethylamino-1-methoxy-3-methylbutane (4h): A colorless oil,

bp 79-82°C/0.7mmHg; $[\alpha]^{25}_D$+9.0°(c1, MeOH); IR 3320, 2950, 1450, 1385, 1365, 1200, 1120 cm^{-1}; ^{1}H-NMR δ 0.88(d, J=7Hz), 0.92(d, J=7Hz), 0.7-1.9(m)(19H), 2.3-2.5(3H, m), 3.1-3.5(m), 3.32(s)(5H). Oxalate; mp 122.5-125°C(AcOEt). Anal. Calcd for $C_{15}H_{29}NO_5$: C, 59.38; H, 9.64; N, 4.62. Found C, 59.57; H, 9.64; N, 4.73.

(S)-1-Methoxy-3-methyl-2-neopentylaminobutane (4i): A colorless oil, bp 75-80°C/4mmHg(Kugelrohr); $[\alpha]^{24}_D$+15.2°(c1, MeOH); IR 3350, 2950, 1465, 1395, 1360, 1200, 1110 cm^{-1}; ^{1}H-NMR δ 0.88(s), 0.88-1.0(m)(15H), 1.18(1H, s), 1.5-2.0(1H, m), 2.2-2.5(3H, m), 3.2-3.4(m), 3.30(s)(5H). Oxalate; mp 122.5-123°C (AcOEt). Anal. Calcd for $C_{13}H_{27}NO_5$: C, 56.30; H, 9.81; N, 5.05. Found C, 55.98; H, 9.46; N, 5.08.

(S)-1-Methoxy-3-methyl-2-methylaminobutane (4j). To an ice-cold solution of (S)-2-amino-1-methoxy-3-methylbutane[14] (5.51 g, 47 mmol) in dioxane (60 mL)-water (40 mL) was added 1N aqueous sodium hydroxide (47 mL) and di-t-butyl dicarbonate (10.78 g, 49 mmol) in dioxane (20 mL). The solution was stirred at room temperature for 2.5 h. Dioxane was removed in vacuo and the pH of the residue was adjusted to 3 by adding 1N hydrochloric acid in an ice-bath and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and concentrated in vacuo. The residue was distilled under reduced pressure (61-64.5°C/0.3mmHg). Almost pure **5** (8.08 g, 79 %) was obtained as a colorless oil. To an ice-cold suspension of lithium aluminum hydride (2.83 g, 75 mmol) in tetrahydrofuran (60 mL) was added dropwise a solution of **5** (8.08 g, 37 mmol) in tetrahydrofuran (40 mL) and the mixture was stirred at room temperature for 4 h. The workup procedure was the same as above described. The solvent was removed at atmospheric pressure using a Widmer column. The residue was purified by distillation followed by recrystallization of its oxalate (3.25 g, 40%): mp 97-98°C(EtOH-ether). Anal. Calcd for $C_9H_{19}NO_5$: C, 48.86; H, 8.66; N, 6.33. Found C, 48.88; H, 8.46; N, 6.26. The amine **4j**, a colorless oil, bp 90-97°C/95mmHg(Kugelrohr); $[\alpha]^{25}_D$+18.5°(c1, MeOH); IR 3350, 2960, 1460, 1385, 1370, 1200, 1110 cm^{-1}; ^{1}H-NMR δ 0.87(3H, d, J=7Hz), 0.92(3H, d, J=7Hz), 1.40(1H, s), 1.5-2.0(1H, m), 2.1-2.6(m), 2.42(s)(4H), 3.1-3.6(m), 3.33(s)(5H).

(R)-1-t-Butoxy-2-isopropylamino-2-phenylethane (4k). To an ice-cold solution of **3c** (355 mg, 2 mmol) in methylene chloride (4 mL) was added isobutylene (2 mL) and sulfuric acid (0.02 mL). The reaction flask was stoppered and the mixture was stirred at room temperature for 2 days. Sulfuric acid (0.1 mL) was added to the mixture and stirred for 4 h. After the mixture was cooled with ice, triethylamine (0.65 mL) was added and the mixture was concentrated in vacuo. Water (10 mL) was added to the residue. The solution was made basic with 10% aqueous sodium hydroxide, and extracted with ether. The organic layer was dried over sodium sulfate, and concentrated in vacuo. The residue was purified by distillation to give **4k** (341 mg, 79%): A colorless oil, bp 68-69°C/1mmHg; $[\alpha]^{25}_D$ -53.2°(c1, EtOH); IR 3330, 1470, 1370, 1200, 1080, 705 cm^{-1}; ^{1}H-NMR δ 0.98(3H, d, J=6Hz), 1.06(3H, d, J=6Hz), 1.17(9H, s), 1.77(1H, br s), 2.5-2.9(1H, m), 3.3-3.5(2H, m), 4.00(1H, dd, J=4 and 8Hz), 7.4-7.7(5H, m). Oxalate; mp 135-136.5°C(EtOH-ether). Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found C, 62.83; H, 8.10; N, 4.27.

2-Bromo-N-t-butyl-2-phenylethanamide (7). This bromoamide was prepared by the method reported by Baumgarten and co-workers.[15] mp 133-135°C(lit.[15] 128-130°C).

Methyl 2-t-Butylamino-2-phenylethanoate (8). The bromoamide **7** (27.03 g, 0.1 mol) was suspended in t-butanol (300 mL). Potassium t-butoxide (24.69 g, 0.22 mol) was added in one

portion and the mixture was cooled with ice-bath to prevent the temperature did not exceed above 40°C. When the temperature began to drop, the cooling bath was removed and the mixture was stirred for 30 min. Ether-methanol (2 : 1) (750 mL) was added to the mixture and the precipitates were removed by filtration. Concentration of the filtrate gave the residue which was triturated with 300 mL of ether. The N-t-butyl α-amino acid potassium salt (15.79 g, 64%) was obtained as a colorless solid which was used for the next step without further purification. To a suspension of the salt (13.32 g, 54 mmol) in methanol (200 mL) was added dropwise thionyl chloride (37 mL, 510 mmol) in an ice-methanol bath. The mixture was refluxed for 4.5 h and concentrated in vacuo. The residue was cooled with ice-methanol, then added 40% aqueous potassium carbonate (160 mL) and extracted with ether. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over sodium sulfate. Removal of the solvent gave almost pure **8** (10.92 g, 91%) which was used for the next step without further purification. The analytical sample was prepared by distillation under reduced pressure: A colorless oil, bp 95-100°C/0.25mmHg(Kugelrohr); IR 3330, 2960, 1735, 1450, 1365, 1210, 1170, 730, 700 cm^{-1}; ^{1}H-NMR δ 1.08(9H, s), 1.98(1H, s), 3.65(3H, s), 4.45(1H, s), 7.1-7.4(5H, m). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found C, 70.23; H, 8.64; N, 6.21.

L-Menthyl (R)-2-t-Butylamino-2-phenylethanoate (10). To a solution of the methyl ester **8** (10.92 g, 49.4 mmol) and L-menthol (8.48 g, 54.4 mmol) in benzene (300 mL) was added potassium t-butoxide (5.54 g, 49.5 mmol). The Dean-Stark apparatus packed with 5A molecular sieves was attached to the flask and the mixture was refluxed for 1 h. Water (300 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with benzene and the combined organic layer was washed with water and saturated aqueous sodium chloride. The solution was dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel using n-hexane-benzene-ethyl acetate (25:25:1) as an eluent to give the racemic menthyl ester **9** (11.34 g, 67%). Oxalic acid (6.46 g, 71.8 mmol) dissolved in methanol (20 mL) was added to the solution of the amino ester **9** (24.76 g, 71.8 mmol) in ether (400 mL). Removal of the solvent gave the oxalate of **9** (31.23 g) which was recrystallized from ethanol nine times. The optically resolved menthyl ester **10** was obtained as a colorless solid (10.19 g, 65%) which was converted to the free amino ester by the usual way: A colorless oil; $[\alpha]^{25}_D$-117.9°(c1, MeOH); IR 3330, 2970, 1730, 1455, 1365, 1240, 1170, 730, 700 cm^{-1}; ^{1}H-NMR δ 0.39(3H, d, J=7Hz), 0.62(3H, d, J=7Hz), 0.90(d, J=6Hz), 1.11(s), 0.8-1.3(m)(17H). 1.46-1.48(1H, m), 1.6-1.7(2H, m), 1.73(1H, br,s), 1.98-2.01(1H, m), 4.39(1H, s), 4.58(1H, dt, J=4 and 11Hz), 7.2-7.4(5H, m). Oxalate; mp 175.5-176.5°C(EtOH). Anal. Calcd for $C_{27}H_{37}NO_6$: C, 66.18; H, 8.56; N, 3.22. Found C, 66.07; H, 8.47; N, 3.22.

(R)-2-t-Butylamino-2-phenylethanol (11). To an ice-cold suspension of lithium aluminum hydride (1.15 g, 30 mmol) in ether (35 mL) was added dropwise the menthyl ester **10** (6.98 g, 20 mmol) in ether (20 mL). The mixture was stirred at room temperature for 1 h. The workup procedure was the same as previously described. The crude product was purified by column chromatography on silica gel using chloroform-methanol (50:1) as an eluent to give the alcohol **11** (3.82 g, 99%): A colorless solid, mp 54-56°C(n-hexane); $[\alpha]^{25}_D$-48.1°(c1, MeOH); IR 3250, 1600, 1380, 1225, 1080, 1050, 705 cm^{-1}; ^{1}H-NMR δ 1.04(9H, s), 2.15(2H, br s), 3.26(1H, t, J=10Hz), 3.56(1H, dd, J=5 and 10Hz), 3.85(1H, dd, J=5 and 10Hz), 7.27(5H, s). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found C, 74.37; H, 10.13; N, 7.11.

(R)-2-t-Butylamino-1-methoxy-2-phenylethane (4l). This chiral amino ether was obtained by the same procedure for the methylation of the alcohol **3** as above described: A colorless oil, bp 100-105°C/2mmHg; $[\alpha]^{25}_D$-52.3°(c1, MeOH); IR 3350, 2970, 1605, 1450, 1390, 1365, 1230, 1125, 705 cm^{-1}; ^{1}H-NMR δ 0.99 (9H, s), 1.64(1H, br s), 3.2-3.33(m), 3.33(s)(5H), 4.05(1H, dd, J=6 and 8Hz), 7.2-7.4(5H, m). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found C, 75.25; H, 10.17; N, 6.72.

(R)-2-(t-Butoxycarbonylamino)-N,N-dimethyl-2-phenylethanamide (13a) and 1-[(R)-2-(t-Butoxycarbonylamino)-2-phenylethanoyl]piperidine (13b). To an ice-cold solution of **12** (12.55 g, 50 mmol) in dimethylformamide (100 mL) was added dimethylamine hydrochloride or piperidine (60 mmol), diethyl phosphorocyanidate (9.78 g, 60 mmol) in dimethylformamide (25 mL), and triethylamine (12.23 g, 120 mmol for **13a**, 6.06 g, 60 mmol for **13b**) in dimethylformamide (25 mL). The mixture was stirred in an ice-bath for 1 h and at room temperature overnight. After dilution with ethyl acetate-benzene (2:1) (1200 mL), the organic layer was successively washed with 10% aqueous citric acid, water, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, and dried over sodium sulfate. Removal of the solvent gave almost pure **13** which was used for the next step without further purification. The analytical samples were prepared by recrystallization from n-hexane. **13a**: A colorless solid, mp 109-110.5°C(n-hexane); $[\alpha]^{27}_D$-164.1°(c1, MeOH); IR 3420, 1710, 1640, 1400, 1170 cm^{-1}; ^{1}H-NMR δ 1.42(9H, s), 2.90(3H, s), 2.98(3H, s), 5.57(1H, d, J=8Hz), 6.07(1H, d, J=8Hz), 7.37(5H, s). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.72; H, 7.97; N, 10.07. Found C, 64.71; H, 8.09; N, 9.94. **13b**: A colorless solid, mp 95.5-98°C(n-hexane); $[\alpha]^{22}_D$-123.9°(c1, MeOH); IR 3430, 1705, 1630, 1165 cm^{-1}; ^{1}H-NMR δ 1.2-1.7(m), 1.40(s)(15H), 3.1-3.8(4H, m), 5.53(1H, d, J=8Hz), 6.10(1H, d, J=8Hz), 7.33(5H, s). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found C, 67.62; H, 8.32; N, 8.65.

(R)-2-Isopropylamino-N,N-dimethyl-2-phenylethanamide (15a) and 1-((R)-2-Isopropylamino-2-phenylethanoyl)piperidine (15b). The t-butylurethane **13** (50 mmol) was dissolved in trifluoroacetic acid (100 mL) in an ice-bath and the mixture was stirred for 30 min. After concentration in vacuo, benzene was added to the residue, and evaporated in vacuo. This workup using benzene was repeated three times. Water (100 mL) was added to the residue and the solution was made basic with 10% aqueous sodium hydroxide. The solution was salted out with sodium chloride and extracted with ether, and the organic layer was dried over sodium sulfate. Removal of the solvent gave **14** which was used for the next step without further purification. N-Isopropyl derivatives **15** were obtained by the same procedure for the reductive alkylation of L-valine methyl ester (**1b**, R=Me) as above described. **15a**: A colorless solid, mp 102-103°C(n-hexane); $[\alpha]^{27}_D$-145.2°(c1, MeOH); IR 3330, 1635, 1180, 1135 cm^{-1}; ^{1}H-NMR δ 1.07(6H, d, J=6Hz), 2.4-2.8(m), 2.65(s)(2H), 2.97(6H, s), 4.63(1H, s), 7.33(5H, s). Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found C, 71.16; H, 9.07; N, 12.61. **15b**: A colorless solid, mp 87.5-89°C(AcOEt); $[\alpha]^{23}_D$-93.8°(c1, MeOH); IR 3320, 1620, 1300, 1265, 1225, 1140 cm^{-1}; ^{1}H-NMR δ 0.9-1.7(m), 1.06(d, J=6Hz)(12H), 2.50(1H, s), 2.59(1H, q, J=6Hz), 3.1-3.8(4H, m), 4.58(1H, s), 7.27(5H, s). Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.80; H, 9.29; N, 10.76. Found C, 73.81; H, 9.04; N, 10.71.

(R)-N-Isopropyl-N',N'-dimethyl-1-phenylethane-1,2-diamine (16a) and 1-((R)-2-Isopropylamino-2-phenylethyl)piperidine (16b). A solution of **15** (15 mmol) in

tetrahydrofuran (25 mL) was added dropwise to an ice-cold suspension of lithium aluminum hydride (1.14 g, 30 mmol) in tetrahydrofuran (50 mL) and the mixture was stirred at room temperature for 3-6 h. The workup procedure was the same as described above. The crude **16** was purified by distillation. **16a**: A colorless oil, bp 92-93°C/0.6mmHg(Kugelrohr); $[\alpha]^{26}_D$-74.9°(c1, MeOH); IR 3300, 2950, 1450, 1360, 1170, 700 cm^{-1}; ^{1}H-NMR δ 0.97(3H, d, J=6Hz), 1.02(3H, d, J=6Hz), 1.9-2.1(2H, m), 2.25(6H, s), 2.4-2.8(2H, m), 3.77(1H, dd, J=4 and 10Hz), 7.1-7.4(5H, m). Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58. Found C, 75.48; H, 10.99; N, 13.32. **16b**: A colorless oil, bp 82-90°C/0.5mmHg; $[\alpha]^{27}_D$-74.4°(c1, MeOH); IR 3300, 2930, 1450, 1380, 1155, 700 cm^{-1}; ^{1}H-NMR δ 0.98(3H, d, J=6Hz), 1.03(3H, d, J=6Hz), 1.3-1.8(6H, m), 2.1-2.9(8H, m), 3.82(1H, dd, J=5 and 8Hz), 7.1-7.4(5H, m). Anal. Calcd for $C_{16}H_{26}N_2$: C, 77.99; H, 10.64; N, 11.37. Found C, 77.87; H, 10.83; N, 11.39.

General Procedure for the Enantioselective Aldol Reaction. To a solution of diisopropylamine (121 mg, 1.2 mmol) and **4** or **16** (1.2 mmol) in tetrahydrofuran (8 mL) was added 2.4 mmol of n-butyllithium (1.6M in n-hexane) at -10°C. After 30 min, the ketone **17** (1.0 mmol) in tetrahydrofuran (2 mL) was added dropwise over 5 min. The mixture was stirred at -10°C for 30 min then cooled to -70°C and the aldehyde (1.1 mmol) was added in one portion. After 5 min, saturated aqueous ammonium chloride (2 mL) was added and the mixture was warmed to room temperature. Water (20 mL) was added, and the mixture was extracted with ether. The organic layer was washed with 10% aqueous citric acid, water, and saturated aqueous sodium chloride and dried over sodium sulfate. After concentration in vacuo, the residue was purified by column chromatography on silica gel using n-hexane-ethyl acetate (15:1), n-hexane-ether (10:1-20:1), benzene-ethyl acetate (50:1) or n-hexane-benzene-ethyl acetate (25:25:1-30:10:1) as an eluent. The results are summarized in Tables II and III.

***erythro*-1-Hydroxy-2,4,4-trimethyl-1-phenylpentan-3-one (18a)**: The IR and ^{1}H-NMR spectra of this material were in agreement with those of the authentic sample prepared by the reported procedure.[18]

***erythro*-1-Hydroxy-2,4,4-trimethyl-1-(1-naphthyl)pentan-3-one (18b)**: A colorless oil; IR 3450, 2970, 1690, 1480, 1370, 990 cm^{-1}; ^{1}H-NMR δ 1.04(3H, d, J=7Hz), 1.18(9H, s), 3.3-3.4(1H, m), 4.18(1H, s), 5.72(1H, d, J=2Hz), 7.4-8.0(7H, m). Anal. Calcd for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found C, 80.10; H, 8.27.

***erythro*-5-Hydroxy-2,2,4-trimethyl-7-phenylheptan-3-one (18c)**: A colorless oil; IR 3450, 2970, 1690, 1480, 1370, 990 cm^{-1}; ^{1}H-NMR δ 1.13(3H, d, J=7Hz), 1.14(9H, s), 1.5-2.2(2H, m), 2.5-3.2(3H, m), 3.37(1H, s), 3.6-3.9(1H, m), 7.24(5H, s). ^{13}C-NMR δ 11.17, 26.03, 32.35, 35.92, 43.12, 44.99, 70.96, 125.84, 128.41, 141.87, 222.14. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found C, 77.08; H, 10:00.

***erythro*-5-Hydroxy-2,2,4,6,-tetramethylheptan-3-one (18d)**: A colorless oil; IR 3470, 2950, 1680, 1480, 1370, 980 cm^{-1}; ^{1}H-NMR δ 0.87(3H, d, J=7Hz), 1.02(3H, d, J=7Hz), 1.07(3H, d, J=7Hz), 1.18(9H, s), 1.5-1.8(1H, m), 3.1-3.4(3H, m). ^{13}C-NMR δ 10.59, 19.01, 19.36, 26.03, 30.60, 39.72, 45.22, 76.76, 222.49. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found C, 70.77; H, 11.86.

***erythro*-1-Cyclohexyl-1-hydroxy-2,4,4-trimethylpentan-3-one (18e)**: A colorless oil; IR 3470, 2920, 1690, 1480, 1360, 980 cm^{-1}; ^{1}H-NMR δ 1.05(d, J=7Hz), 1.16(s), 0.8-

2.3(m)(23H), 3.1-3.4(2H, m), 3.50(1H, s). ^{13}C-NMR δ 10.56, 26.00, 25.84, 26.04, 26.40, 29.00, 29.65, 39.17, 39.99, 45.23, 75.46, 222.65. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found C, 74.56; H, 11.77.

***erythro*-5-Hydroxy-2,2,4,6,6-pentamethylheptan-3-one (18f)**: A colorless oil; IR 3500, 2960, 1690, 1480, 1360, 990 cm^{-1}; ^{1}H-NMR δ 0.96(9H, s), 1.09(3H, d, J=7Hz), 1.16(9H, s), 3.23(1H, s), 3.28(1H, s), 3.36(1H, q, J=7Hz). ^{13}C-NMR δ 11.93, 26.15, 27.15, 35.80, 39.02, 45.05, 77.57, 222.43. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found C, 72.12; H, 12.28.

***erythro*-1-Hydroxy-2-methyl-1-(1-naphthyl)pentan-3-one (*erythro*-18g)**: A colorless oil; IR 3430, 2930, 1700, 1450, 1375, 975 cm^{-1}; ^{1}H-NMR δ 1.03(6H, t and d, J=7 and 8Hz), 2.15(2H, q, J=8Hz), 2.8-3.3(2H, m), 5.84(1H, d, J=3Hz), 7.1-8.0(7H, m). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found C, 79.40; H, 7.59.

***threo*-1-Hydroxy-2-methyl-1-(1-naphthyl)pentan-3-one (*threo*-18g)**: A colorless oil; IR 3430, 2930, 1705, 1450, 1370, 975 cm^{-1}; ^{1}H-NMR δ 0.94(3H, d, J=7Hz), 1.00(3H, t, J=7Hz), 2.40(2H, q, J=7Hz), 3.0-3.5(2H, m), 5.49(1H, d, J=8Hz), 7.4-8.0(6H, m), 8.1-8.3(1H, m). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found C, 79.10; H, 7.42.

***erythro*- and *threo*-1-Hydroxy-2,4-dimethyl-1-(1-naphthyl)pentan-3-one (18h)**: A colorless oil; IR 3450, 2970, 1700, 1460, 1365, 1010 cm^{-1}; ^{1}H-NMR δ 0.87(d, J=7Hz), 1.00(d, J=7Hz), 1.04(d, J=7Hz), 1.07(d, J=7Hz), 1.09(d, J=7Hz), 1.10(d, J=7Hz)(9H), 2.4-2.9(1H, m), 3.0-3.7(2H, m), 5.54(0.7H, d, J=6Hz threo isomer), 5.81(0.3H, d, J=3Hz erythro isomer), 7.5-8.2(7H, m). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found C, 79.49; H, 8.12.

***erythro*-1-Hydroxy-2,4-dimethyl-4-trimethylsilyloxy-1-phenylpentan-3-one (18i)**: The IR and ^{1}H-NMR spectra of this material were in agreement with those of the authentic sample prepared by the reported procedure.[18]

***erythro*-1-Hydroxy-2,4-dimethyl-4-trimethylsilyloxy-1-(1-naphthyl)pentan-3-one (18j)**: A colorless oil; IR 3480, 2950, 1695, 1455, 1375, 1250, 845 cm^{-1}; ^{1}H-NMR δ 0.18(9H,s), 1.04(3H, d, J=7Hz), 1.33(3H, s), 1.40(3H, s), 3.48(1H, br s), 3.7-4.3(1H, m), 5.81(1H, d, J=3Hz), 7.4-8.2(7H, m). Anal. Calcd for $C_{20}H_{28}O_3Si$: C, 69.72; H, 8.19. Found C, 69.52; H, 8.25.

***erythro*-5-Hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one (18k)**: The IR and ^{1}H-NMR spectra of this material were in agreement with those of reported ones.[18]

Determination of Enantiomeric Excesses of Aldols 18.

(1) HPLC Method. Each aldol (1-10 mg) was dissolved in isopropanol (0.1 mL), and 1 μL of them was subject to HPLC using a Bakerbond^{TM} (DNBPG) chiral column (RP-7103-0) (i.d. 4.6x250 mm, purchased from J.T. Baker Chemical Co.). The retention times are summarized in Table V.

(2) ^{1}H-NMR Method (2-1) Application of Chiral Shift Reagent i) Preparation of Methoxy Methyl Ether of Aldols. The aldols **18** (0.2 mmol) was dissolved in methylene chloride (1 mL). N,N-Diisopropylethylamine (0.07 mL, 0.4 mmol), chloromethyl methyl ether (0.03 mL, 0.4 mmol) was added and the solution was stirred at room temperature for 2 h. Water (15 mL) was added and extracted with ether. The organic layer was washed with 1N hydrochloric acid, water, and saturated aqueous sodium chloride and dried over sodium sulfate. After concentration in vacuo, the residue was purified by column chromatography on silica gel using either n-hexane-ethyl acetate (50:1) or

Table V HPLC of Aldols 18 Using a Bakerbond™ (DNBPG) Chiral Column[a]

				t_r, min			
			mobile[b]	erythro isomer		threo isomer	
compd	R	R'	phase	(S, S)[c]	(R, R)[c]	(S, R)[c]	(R, S)[c]
18a	$(CH_3)_3C$	C_6H_5	A	10.98	11.65		
18b	$(CH_3)_3C$	1-$C_{10}H_7$	B	9.52	11.83	13.08	14.27
18g	C_2H_5	1-$C_{10}H_7$	B	22.05	23.62	29.35	32.70
18h	$(CH_3)_2CH$	1-$C_{10}H_7$	B	16.18	18.40	21.32	23.75
18j	$TMSO(CH_3)_2C$	1-$C_{10}H_7$	B	9.88	11.80		

a) Flow rate, 1.0 mL/min; chart speed, 2 or 5mm/min; detector UV 254nm. b) n-Hexane-isopropanol (A 200:1; B 100:1). c) See ref. 20.

n-hexane-ether (15:1-20:1) as an eluent to give the corresponding methoxy methyl ether of aldols.

ii) Preparation of Acetyl Ester of Aldol. The aldol **18f** (50 mg, 0.25 mmol) was dissolved in pyridine (1 mL). Acetic anhydride (0.05 mL, 0.5 mmol), 4-dimethylaminopyridine (31 mg, 0.25 mmol) was added and the solution was stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate (15 mL), and washed with 5% hydrochloric acid twice, saturated aqueous sodium bicarbonate, and water. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatograpy on silica gel using n-hexane-ether (20:1) as an eluent to give the acetyl ester of aldol.

iii) ^{1}H-NMR Measurement. The methoxy methyl ether or acetyl ester of the aldol (10-30 mg) was dissolved in deuteriochloroform and chiral shift reagent $Eu(hfc)_3$ (10-20 mg) was added. ^{1}H-NMR was measured (JEOL FX-100 spectrometer) and the enantiomeric excess was determined from the ratio of integration of the corresponding peaks.

(2-2) Application of (R)-MTPA Ester To a solution of the aldol **18** (0.2 mmol) in methylene chloride (2 mL) was added (R)-MTPA (70 mg, 0.3 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol). Dicyclohexylcarbodiimide (62 mg, 0.3 mmol) dissolved in methylene chloride (0.5 mL) was added in an ice-bath and the solution was stirred for 1 h and then stirred at room temperature overnight. After dilution with ethyl acetate, the insoluble material was removed by filtration. The filtrate was washed with 10% citric acid, water, saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride and dried over sodium sulfate. Removal of the solvent gave the residue which was purified by column chromatography on silica gel using n-hexane-ethyl acetate (15:1-30:1) as an eluent. The ^{1}H-NMR spectrum of the (R)-MTPA ester thus obtained was measured (JEOL GSX-400 or FX-100 spectrometer) and the enantiomeric excess was determined.

General Procedure for the Preparation of β-Hydroxy-α-methyl Carboxylic Acids 19. To a solution of aldols **18i-18k** (0.5 mmol) in methanol (10 mL) was added 5.2 mL of periodic acid (0.54 M in water) and the mixture was stirred at room temperature overnight. After concentration in vacuo, water (5 mL) was added to the residue. The solution was salted out with sodium chloride and extracted with ether, and the organic layer was dried over sodium sulfate. Removal of the solvent gave the residue which was purified by column chromatography on silica gel using chloroform-methanol (25:1) or chloroform-isopropanol (50:1) as an eluent.

***erythro*-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (19a)**: The IR and ^{1}H-NMR spectra of this material were in agreement with those of authentic sample prepared by the reported procedure.[18] The acid obtained from the aldol **18l** of 39%ee showed the following specific rotation: $[\alpha]^{22}_D$-11.0°(c1, $CHCl_3$).

Methyl *erythro*-3-Hydroxy-2-methyl-3-(1-naphthyl)propanoate (Methyl ester of 19b): To identify the product, the crude acid (IR 3550, 1710 cm^{-1}) was converted to the methyl ester by the action of trimethylsilyldiazomethane in 20% methanol-benzene.[25] The methyl ester showed the following properties: A colorless oil; IR 3450, 2950, 1725, 1455, 1350, 1170 cm^{-1}; ^{1}H-NMR δ 1.07(3H, d, J=7Hz), 2.70(1H, br s), 2.7-3.2(1H, m), 3.68(3H, s), 5.92(1H, d, J=3Hz), 7.3-8.1(7H, m). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found C, 73.65; H, 6.63.

***erythro*-3-Hydroxy-2,4-dimethylpentanoic Acid (19c)**: The IR and ^{1}H-NMR spectra of this material were in agreement with those of reported ones.[18] The acid obtaiend from the aldol **18k** of 40%ee showed the following specific rotation: $[\alpha]^{22.5}_D$-3.5°(c1.4, $CHCl_3$).

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