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Chiral Environment Specifically Induced by Metal Ion: Asymmetric α-Alkylation of α-Amino Esters Using Pyridoxal Derivatives Having a Chiral Ionophore Function

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Abstract: Stereoselective alkylation of aldimines, prepared from α-amino esters and pyridoxal models having an ionophoric side-chain composed of a chiral glycerol structure, proceeded in the presence of Li^+ or Na^+ to afford α,α-dialkyl amino esters after acidic hydrolysis. Both the structure of the side chain and the metal ion were found to be in relation with the stereoselectivity, affording the highest stereoselectivity when the side-chain having a 2-naphthylmethoxy group and a methoxy group at the respective 3'- and 2'-positions was employed in the presence of Na^+.

Keywords: Amino acids and derivatives; Alkylation; Asymmetric reactions; Pyridines

Introduction

The utility of α,α-dialkyl amino acids in medicinal and biochemical application has been receiving a great deal of attention because of the following characteristic properties: some of them are known as an enzyme-inhibitor[1] or a component of biologically active natural products.[2] The conformation of the peptides, in particular, those containing α,α-dialkyl amino acids, is reported to be stereochemically constrained.[3] Therefore, much effort has been paid to the development of the synthesis of α,α-dialkyl amino acids particularly in an enantioselective manner.[4]

Since a pyridoxal-pyridoxamine coenzyme system is closely involved in the biosynthetic and metabolic reactions of amino acids in a biological system, a number of examples mimicking the reactions have been reported.[5] It occurred to us that the pyridoxal-pyridoxamine system would be applicable to the synthesis of unnatural amino acids employing reactions which are not involved in a biological system as well. As such an example, we reported the Li^+ ion specific α-alkylation of an imino ester, easily obtainable from an α-amino ester and a pyridoxal model **1** as designed to have an ionophore function at C-3 as shown in Fig. 1.[6] In this reaction, the electron-withdrawing property of the pyridine ring not only accelerated the formation of the aldimine from the respective α-amino ester and pyridoxal model, but also activated the α-position as expected. In addition, the conformation of the imino-ester moiety was found to be restricted by the chelation of Li^+ with the ethoxyethoxy group at C-3 as shown, which prompted us to apply this methodology to asymmetric synthesis of α,α-dialkyl amino esters **2** by introducing chirality at this position (Fig. 1).

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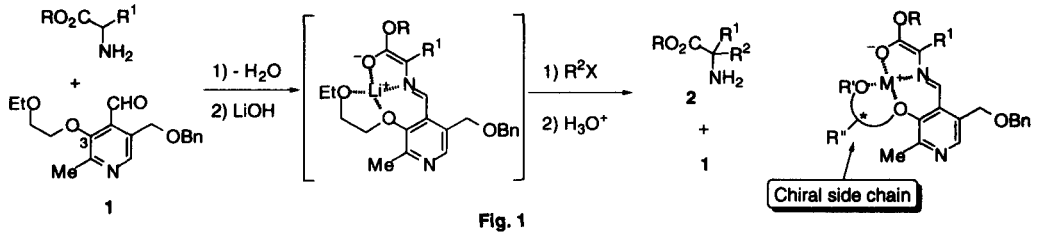
Expecting the side chain to have diverse stereoselectivities depending on its structure and the metal ion, we selected optically active glycerol as a basic skeleton of the side chain. Herein we describe synthesis of the chiral pyridoxal model compounds and their application to the asymmetric α-alkylation of α-amino esters.[7]



1 Fig. 1

Results and Discussion

Synthesis of the Model Compounds 10 Pyridoxal models having a chiral side chain at C-3 were synthesized as shown in Scheme 1. The side-chain fragments were prepared from optically active epoxide **3**. The substituents R^3 were easily introduced by nucleophilic cleavage of the epoxide as summarized in Table 1. Subsequent alkylation of **4** with R^4X furnished the desired products **5**. Deprotection with a fluoride ion and bromination afforded the side-chain fragments **7**.

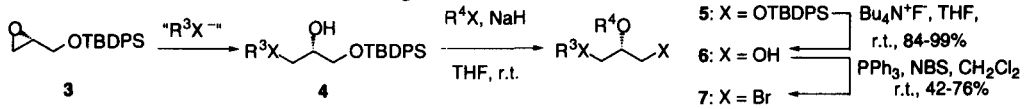
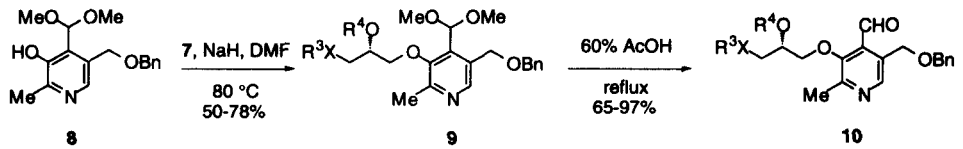
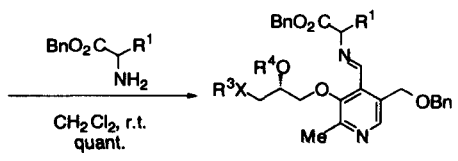


Table 1 Nucleophilic epoxide cleavage of **3** and *O*-alkylation of **4**

R^3X	Reagents	Product **4**	Yield (%)	R^4X	Product **5**	Yield (%)
BnO	BnOH, tropylium BF_4^-	**a**	67	MeI	**a**	86
BnS	BnSH, MeONa, MeOH	**b**	93	MeI	**b**	91
MeO	MeOH, tropylium BF_4^-	**c**	69	BnBr	**c**	99
1-NaphCH_2O	1-NaphCH_2OH, tropylium BF_4^-	**d**	68	MeI	**d**	97
2-NaphCH_2O	2-NaphCH_2OH, tropylium BF_4^-	**e**	74	MeI	**e**	97



8 9 10



11

Compd.	R^1	R^3X	R^4
Aa	Me	BnO	Me
Ab	Me	BnS	Me
Ac	Me	MeO	Bn
Ad	Me	1-NaphCH_2O	Me
Ae	Me	2-NaphCH_2O	Me
Be	Bn	2-NaphCH_2O	Me
Ce	H	2-NaphCH_2O	Me

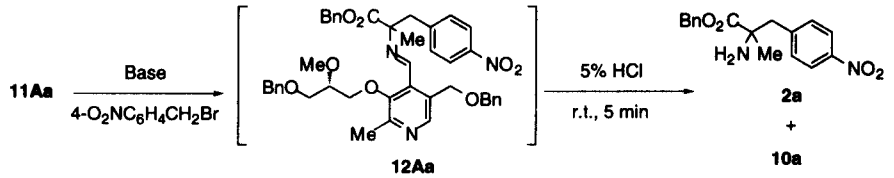
Naph = Naphthyl

Scheme 1

Coupling reactions of **7** with pyridoxal fragment **8** and deprotection by treatment with acid gave the desired pyridoxal derivatives **10**. Aldimines **11** were easily obtained in almost quantitative yields only by mixing pyridoxal derivatives **10** and amino esters in methylene chloride and were used for alkylation without purification.

Alkylation of Aldimines At first, *p*-nitrobenzylation of aldimine **11Aa** prepared from the model compound **10a** and L-Ala-OBn was examined under various conditions, and the results are shown in Table 2. Differently from the reaction of the ethoxyethoxy derivative **1** reported previously,[6] the reaction under a two-phase system did not afford satisfactory results (runs 1-3). However a sodium ion was suggested to be the most suitable. The reaction with LDA or NaH as a base was found to be effective. The stereoselectivity was suggested to depend on the metal ion as expected and the reaction with NaH stereoselectively gave *R*-**2a** (runs 4 and 5).

Table 2 *p*-Nitrobenzylation of aldimine **11Aa**

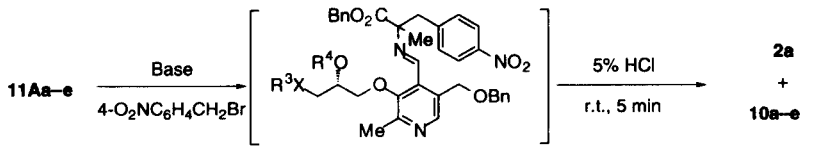


Run	Reaction Conditions				Amino Ester **2a**		
	Base	Solvent	Temp. (°C)	Time (h)	Isolated Yield (%)	*ee* (%)	Config.
1	LiOH	CH_2Cl_2	0	5	trace	–	–
2	NaOH	CH_2Cl_2	0	5	32	26	*R*
3	KOH	CH_2Cl_2	0	5	trace	–	–
4	LDA	THF	-78 → 0	12	59	8	*S*
5	NaH	THF	-78 → 0	12	57	58	*R*

a Yields were based on L-Ala-OBn.

We next examined the *p*-nitrobenzylation of aldimines **11Ab-e** prepared from L-Ala-OBn and model compounds **10b-e** by employing NaH and LDA, respectively, and the results are summarized in Table 3. Substitution of the benzyloxy group of **11Aa** with a benzylthio group slightly increased the stereoselectivity in both cases of employing NaH and LDA as a base (runs 1 and 2 vs. runs 3 and 4). The stereoselectivity of the reaction of the aldimine **11Ac** having a reversed substituent pattern of the side chain of **11Aa** decreased with NaH (run 1 vs. run 5), but increased when LDA was employed as a base (run 2 vs. run 6). Expecting more effective shielding by the aromatic ring, aldimines **11Ad** and **e** having 1- and 2-naphthylmethyl groups, respectively, were also examined. Consequently, in the reaction with NaH, the stereoselectivity was somewhat lowered by replacing the benzyl group of **11Aa** with a 1-naphthylmethyl group (run 1 vs. run 7), but was largely improved by replacing with a 2-naphthylmethyl group (run 1 vs. run 9). In the reaction with LDA, similar effect on the stereoselectivity was not observed and the yields decreased in both cases (runs 8 and 10).

Table 3 *p*-Nitrobenzylation of aldimines **11Aa-e** with NaH or LDA as a base

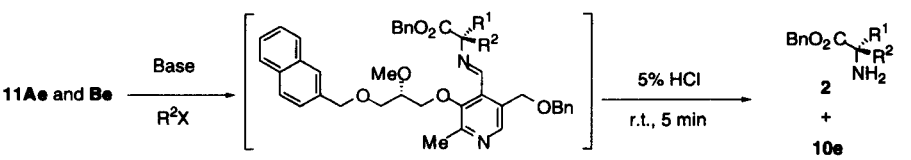


12Aa–e

Run	Aldimine 11A			Base	Amino Ester 2a		
	Compound	R^3X	R^4		Isolated Yield (%)[a]	*ee* (%)	Config.
1	**a**	BnO	Me	NaH	57	58	*R*
2	**a**	BnO	Me	LDA	59	8	*S*
3	**b**	BnS	Me	NaH	61	64	*R*
4	**b**	BnS	Me	LDA	61	22	*S*
5	**c**	MeO	Bn	NaH	74	18	*S*
6	**c**	MeO	Bn	LDA	49	48	*S*
7	**d**	1-NaphCH_2O	Me	NaH	50	38	*R*
8	**d**	1-NaphCH_2O	Me	LDA	44	0	–
9	**e**	2-NaphCH_2O	Me	NaH	61	83	*R*
10	**e**	2-NaphCH_2O	Me	LDA	34	22	*R*

a Yields were based on L-Ala-OBn.

Table 4 Alkylation of aldimines **11Ae** and **Be**



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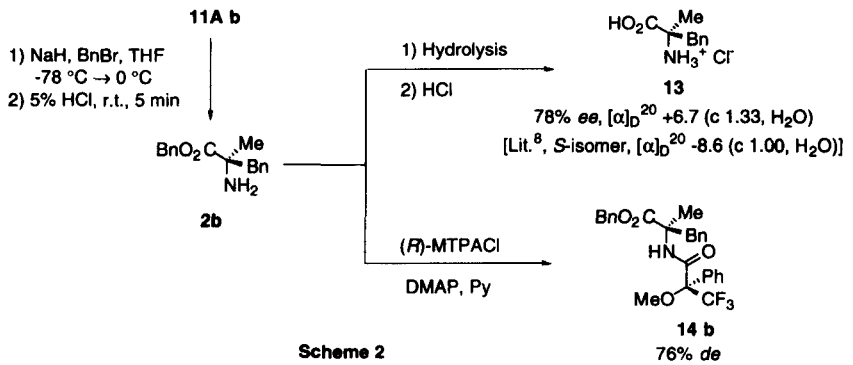
Run	Aldimine 11		R^2X	Base	Amino Ester 2			
	Compound	R^1			Product	Isolated Yield (%)[a]	*ee* (%)	Config.
1	**Ae**	Me	BnBr	LDA	**2b**	34	26	*R*
2	**Ae**	Me	BnBr	NaH	**2b**	58	86	*R*
3	**Ae**	Me	BnBr	NaHMDS	**2b**	42	83	*R*
4	**Ae**	Me	BnBr	KH	**2b**	28	7	*R*
5	**Ae**	Me	$BrCH_2CO_2Et$	NaH	**2c**	73	78	*R*
6	**Ae**	Me	CH_2=$CHCH_2Br$	NaH	**2d**	48	17	*R*
7	**Be**	Bn	MeI	NaH	**2b**	51	82	*S*

a Yields were based on L-Ala-OBn (runs 1-7) and L-Phe-OBn (run 7).

Focusing on the model compound **10e**, we further examined the reaction and the results are shown in Table 4. As is obvious from runs 1-4, Li^+ and K^+ as an alkali metal ion lowered the stereoselectivity, but the reaction with NaHMDS was as stereoselective as that with NaH. These results show that a sodium ion, not the kind of base anion, plays an important role in the stereoselectivity. Alkylation with ethyl bromoacetate also smoothly took place to afford **2c** with similar stereoselectivity (run 5), while that with allyl bromide was

poorly stereoselective (run 6). Although the reason is not clear, this unexpectedly low stereoselectivity of the latter allylation could be attributable to its S_N2' character. It is also interesting that the methylation of aldimine **11Be** prepared from **10e** and L-Phe-OBn afforded an enantiomer *S*-**2b** in good *ee*, suggesting that both enantiomers would be stereoselectively obtained from the same chiral auxiliary.

The stereochemistries of the products **2** were assigned as follows. The amino ester **2b** obtained by benzylation of the aldimine **11Ab** was derived to the known amino acid **13** by hydrolysis, the $[\alpha]_D$ value of which was compared with the literature value of the *S*-isomer,[8] showing that the product **2b** has an *R*-configuration with 78% *ee*. The *de* value obtained from ^1H and ^{19}F NMR spectra of the corresponding MTPA amide **14b** also agreed well with it and was 76% *de*. Therefore, the *ee* values of the other alkylated products, **2a**, **c** and **d**, were also obtained from ^1H and ^{19}F NMR spectra of their MTPA amide derivatives **14**. The stereochemistries were tentatively assigned by comparison of their ^1H NMR data with that of **14b**: the chemical shifts for the α-methyl hydrogens of the main isomers obtained from the aldimine **11Ae** appeared at higher field than those of the minor isomers (Table 5 in Experimental Section).[9]



Scheme 2

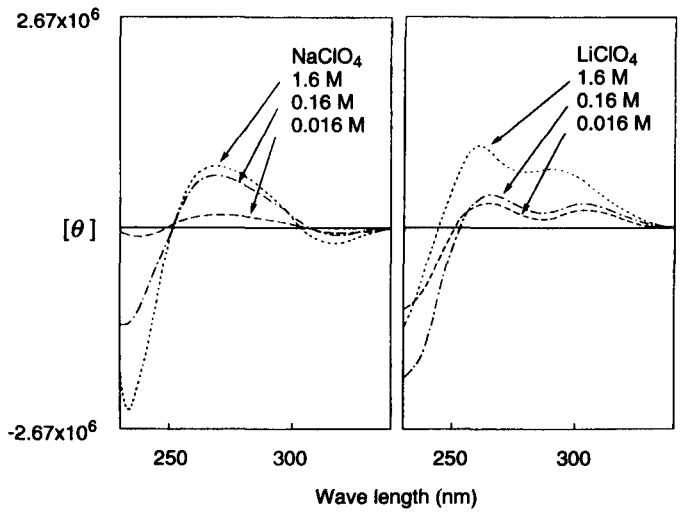


Fig. 2 CD spectra for **11Ce** (0.16 mM in MeCN) measured in the presence of Na^+ or Li^+

As regards the mechanism for this stereoselective alkylation, it is obvious that the metal ion plays a considerable role. We studied CD analysis of the aldimine **11Ce**, which was prepared from **10e** and Gly-OBn and, accordingly, has chirality only on the side chain. The aldimine **11Ce** showed no significant CD spectrum in the absence of a metal ion, while the addition of a metal ion caused CD absorption depending on the concentration of the metal ion as shown in Fig. 2. These findings strongly suggest that the chiral side chain does not have a certain conformation without a metal ion but can construct chiral environment depending on the kind of metal ion and its concentration.

As for the reaction of **11Ae** with Na^+ which afforded better stereoselectivity than with Li^+, we would like to propose a possible transition state as shown in Fig. 3 from the following experimental results. In a previous paper, we showed that the conformation of the imino ester moiety is restricted in the direction of the C-3 position to capture Li^+.[6] This conformational restriction in the same direction appears to be true in the case of the chiral aldimine **11Ae** with Na^+ as well. The fact that the terminal substituent of the side chain (R^3) is important for the stereoselectivity suggests that the 3'-oxygen would be involved for the formation of the chelation structure and, consequently, the terminal naphthyl group could effectively shield one of the two diastereomeric enolate faces. Although, taking account of these facts, two possible transition states, **A** for *re*-face selectivity and **B** for *si*-face selectivity, would be proposed, the steric repulsion between the 2'-methoxy group and the methyl group on the pyridine ring in the transition state **B** and/or the additional coordination of the 2'-oxygen in the transition state **A** could favor the transition state **A**, which appears to afford the major isomer.

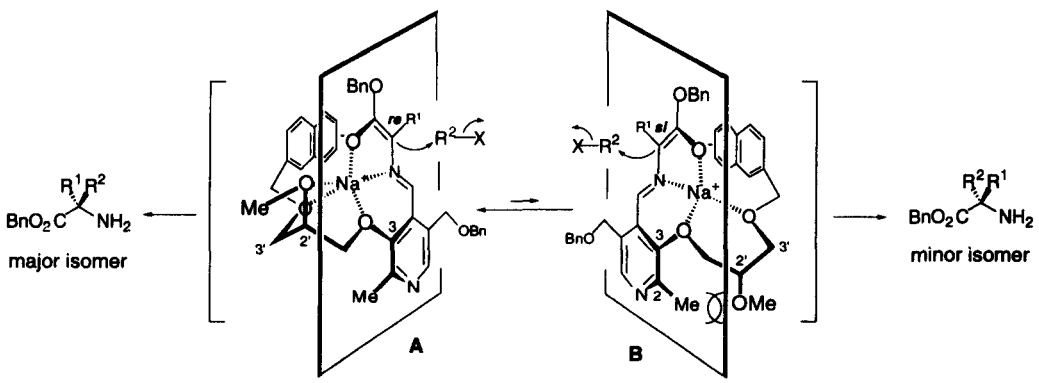


Fig. 3 Possible transition states **A** and **B** for the α-alkylation of the aldimine **11Ae** with Na^+

In conclusion, we have shown the asymmetric α-alkylation of an amino ester by using pyridoxal model compounds having a chiral ionophore side chain. Despite the fact that the only one chiral center is on a flexible, linear side chain and is also far from the reaction center, the chirality is shown to be effectively transferred by forming a chiral metal-chelation structure in our model system. Further applications involving

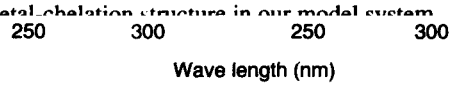


Fig. 2 CD spectra for **11Ce** (0.16 mM in MeCN) measured in the presence of Na^+ or Li^+

Experimental

General. Melting points (mps) were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared spectra were measured on a JASCO FT/IR-200 Fourier-transfer infrared spectrometer. ^{1}H-NMR spectra were measured on a JEOL GX-500 (500 MHz), Hitachi R-250HT (250 MHz), or a Varian VXR-200 (200 MHz) spectrometer and tetramethylsilane (TMS) was used as an internal standard. ^{13}C NMR spectra were measured on a Varian VXR-200 (50.3 MHz) with $CDCl_3$ as an internal standard (77.0 ppm). 19F NMR spectra were taken on a Varian VXR-200 (180 MHz) with hexafluorobenzene (-162.9 ppm) as an internal standard. Low and High resolution mass spectra (EI-MS and HR-MS) were obtained by use of a JEOL D-300 mass spectrometer. $[\alpha]_D$ values were obtained on a JASCO DIP-370 polarimeter. CD spectra were taken on a JASCO J-720W spectropolarimeter For silica gel and aminopropylsilica gel column chromatography, E. Merck Kieselgel 60 (0.063-0.200 mm) and Fuji Silysia Chemical Ltd. NH-DM1020 (100-200 mesh) were used, respectively. The starting materials **3**[10] and **8**[6] were prepared according to the literature.

(*S*)-3-Benzyloxy-1-(*t*-butyldiphenylsiloxy)-2-propanol (4a)

Compound **4a** was prepared according to the procedure reported by Thompson *et al.* as follows.[11] A mixture of epoxide **3** (1.00 g, 3.21 mmol), benzyl alcohol (1.00 ml, 9.62 mmol) and tropylium tetrafluoroborate (40 mg, 0.22 mmol) was stirred and heated at 70 °C for 3 h. The reaction mixture was cooled, dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution and worked up as usual. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 10) to afford the title compound **4a**[11, 12] (902 mg, 67%) as a colorless oil.

The compounds **4c-e** were prepared from the corresponding alcohol by the same procedure as described above.

(*S*)-1-(*t*-Butyldiphenylsiloxy)-3-methoxy-2-propanol (4c), 69% yield, $[\alpha]_D^{26}$ -0.33 (c 5.23, $CHCl_3$). IR (KBr): 3455, 1589, 1488 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.07 (9H, s, *t*-Bu), 3.36 (3H, s, OMe), 3.40-3.48 (2H, m, 3-H), 3.67-3.82 (2H, m, 1-H), 3.90 (1H, m, 2-H), 7.32-7.55 (6H, m, aromatic H), 7.62-7.75 (4H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 26.8, 59.1, 64.8, 70.6, 73.5, 127.7, 129.8, 133.1, 135.5. EI-MS *m/z* (%): 287 (M^+-*t*-Bu, 2.5), 91 (Bzl^+, 100). HRMS Calcd for $C_{16}H_{19}O_3Si$ (M^+-*t*-Bu): 287.1104, Found: 287.1106.

(*S*)-1-(*t*-Butyldiphenylsiloxy)-3-(1-naphthylmethoxy)-2-propanol (4d), 68% yield, $[\alpha]_D^{22}$ +1.7 (c 1.18, $CHCl_3$). IR (KBr): 3454, 1598, 1589, 1510 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.04 (9H, s, *t*-Bu), 3.60-3.66 (2H, m, 3-H), 3.69 (2H, d, J = 6.1 Hz, 1-H), 3.89 (1H, m, 2-H), 4.98 (2H, s, NaphCH_2), 7.28-7.62 (14H, m, aromatic H), 7.78-7.90 (2H, m, aromatic H), 8.06 (1H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 26.8, 64.7, 70.8, 70.9, 71.9, 123.9, 125.1, 125.8, 126.2, 126.5, 127.7, 128.5, 128.7, 129.7, 131.7, 133.1, 133.4, 133.7, 135.5. EI-MS *m/z* (%): 412 (M^+-*t*-BuH, 0.2), 141 ($NaphCH_2^+$, 100). HRMS Calcd for $C_{26}H_{24}O_3Si$ (M^+-*t*-BuH): 412.1495, Found: 412.1513.

(*S*)-1-(*t*-Butyldiphenylsiloxy)-3-(2-naphthylmethoxy)-2-propanol (4e), 74% yield, $[\alpha]_D^{23}$ -2.0 (c 2.12, $CHCl_3$). IR (KBr): 3460, 1602, 1587, 1509 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.03 (9H, s, *t*-Bu), 3.50-3.66 (2H, m, 3-H), 3.71 (2H, d, J = 6.5 Hz, 1-H), 3.93 (1H, m, 2-H), 4.68 (2H, s, NaphCH_2) 7.37-7.89 (17H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 26.8, 64.8, 70.8, 70.9, 73.5, 125.7, 125.9, 126.1, 126.5, 127.7, 127.7, 127.9,

128.2, 129.8, 130.0, 133.1, 133.2, 135.5, 135.5. EI-MS *m/z* (%): 412 (M^+-*t*-BuH, <0.1), 141 ($NaphCH_2^+$, 100). HRMS Calcd for $C_{26}H_{24}O_3Si$ (M^+-*t*-BuH): 412.1495, Found: 412.1489.

(*R*)-1-Benzylthio-3-(*t*-butyldiphenylsiloxy)-2-propanol (4b)

To a stirred solution of sodium methoxide in methanol, which had been prepared by dissolving Na (221 mg, 9.61 mg-atom) in methanol (10.0 ml), was added benzyl mercaptan (0.45 ml, 3.85 mmol). After 10 min stirring, a solution of **3** (1.00 g, 3.21 mmol) in benzene (5 ml) was added to the reaction mixture and the whole was stirred at room temperature for 15 min. The solvent was evaporated off under reduced pressure and the resultant residue was partitioned between ether and water. The organic phase was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel column chromatography (ethyl acetate : hexane = 1 : 10) afforded the title compound (1.31 g, 93%) as a colorless oil. $[\alpha]_D^{26}$ -10.0 (c 1.43, $CHCl_3$). IR (KBr): 3464, 1600, 1589 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (9H, s, *t*-Bu), 2.53 (1H, dd, *J* = 7.1, 13.9 Hz, 1-H), 2.60 (1H, dd, *J* = 5.1, 13.9 Hz, 1-H), 3.65 (2H, d, *J* = 5.1 Hz, 3-H), 3.71 (2H, s, benzylic H), 3.78 (1H, m, 2-H), 7.20-7.30 (5H, m, aromatic H), 7.32-7.45 (6H, m, aromatic H) 7.60-7.66 (4H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 26.8, 34.5, 36.4, 66.4, 70.5, 127.0, 127.7, 128.5, 128.8, 129.8, 132.9, 135.5, 138.0. EI-MS *m/z* (%): 379 (M^+-*t*-Bu, 4.2), 91 (Bzl^+, 100). HRMS Calcd for $C_{22}H_{23}O_2SSi$ (M^+-*t*-Bu): 379.1188, Found: 379.1193.

(*S*)-3-Benzyloxy-1-(*t*-butyldiphenylsiloxy)-2-methoxypropane (5a)

To a stirred THF (30 ml) suspension of NaH (60% in oil, 3.81 g, 95.3 mmol), which had been washed with pentane three times and dried under vacuum, was added dropwise a solution of **4a** (36.4 g, 86.7 mmol) in THF (200 ml) under ice-cooling, then the whole was stirred at room temperature for 1 h. Methyl iodide (6.48 ml, 104 mmol) was added dropwise to the reaction mixture under stirring at 0 °C and stirring was continued for 4 h at room temperature. The reaction mixture was poured into water, concentrated under vacuum and extracted with ethyl acetate. The ethyl acetate layer was worked up as usual and the residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 10) to give the title compound **5a** (32.5 g, 86%) as a colorless oil. $[\alpha]_D^{26}$ -7.1 (c 1.00, $CHCl_3$). IR (KBr): 1589, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (9H, s, *t*-Bu), 3.40 (3H, s, OMe), 3.47 (1H, m, 2-H), 3.58 (1H, dd, *J* = 6.3, 9.8 Hz, 3-H), 3.65 (1H, dd, *J* = 4.2, 9.8 Hz, 3-H), 3.74 (2H, d, *J* = 6.3 Hz, 1-H), 4.53, 4.57 (2H, AB q, *J* = 12.6 Hz, benzylic H), 7.25-7.48 (11H, m, aromatic H), 7.61-7.72 (4H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.1, 26.7, 58.0, 62.7, 69.7, 73.4, 80.9, 127.4, 127.6 (2C), 128.3, 129.6, 133.4, 135.5, 138.2. EI-MS *m/z* (%): 377 (M^+-*t*-Bu, 2.4), 91 (Bzl^+, 100). HRMS Calcd for $C_{23}H_{25}O_3Si$ (M^+-*t*-Bu): 377.1573, Found: 377.1574.

The compounds **5b-e** were prepared by the same method as described above.

(*R*)-1-Benzylthio-3-(*t*-butyldiphenylsiloxy)-2-methoxypropane (5b), 91% yield, $[\alpha]_D^{25}$ +4.5 (c 1.10, $CHCl_3$). IR (KBr): 1601, 1589, 1493 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.02 (9H, s, *t*-Bu), 2.58 (1H, dd, *J* = 6.9, 14.4 Hz, 1-H), 2.65 (1H, dd, *J* = 5.5, 14.4 Hz, 1-H), 3.33 (3H, s, OMe), 3.60-3.80 (3H, m, 2- and 3-H), 3.72 (2H, s, benzylic H), 7.18-7.46 (11H, m, aromatic H), 7.60-7.70 (4H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.1, 26.8, 32.6, 37.0, 58.0, 64.2, 81.5, 126.9, 127.6, 128.4, 128.9, 129.6, 133.3, 135.5, 138.4. EI-MS *m/z* (%): 393 (M^+-*t*-Bu, 12), 91 (Bzl^+, 100). HRMS Calcd for $C_{23}H_{25}O_2SSi$ (M^+-*t*-Bu): 393.1345, Found: 393.1362.

(*S*)-2-Benzyloxy-1-(*t*-butyldiphenylsiloxy)-3-methoxypropane (5c), 99% yield, $[\alpha]_D^{25}$ -11.3 (c 1.34, $CHCl_3$). IR (KBr): 1589, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.04 (9H, s, *t*-Bu), 3.37 (3H, s, OMe), 3.45-3.75 (3H, m, 2- and 3-H), 3.77 (2H, d, *J* = 6.1 Hz, 1-H), 4.63 (2H, s, benzylic H), 7.20-7.45 (11H, m, aromatic H), 7.62-7.72 (4H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.1, 26.8, 59.1, 63.4, 72.0, 72.6, 78.5, 127.3, 127.5, 127.6, 128.2, 129.6, 133.4, 135.5, 138.6. EI-MS *m/z* (%): 377 (M^+-*t*-Bu, 0.5), 91 (Bzl^+, 100). HRMS Calcd for $C_{23}H_{25}O_3Si$ (M^+-*t*-Bu): 377.1573, Found: 377.1571.

(*S*)-1-(*t*-Butyldiphenylsiloxy)-2-methoxy-3-(1-naphthylmethoxy)propane (5d), 97% yield, $[\alpha]_D^{26}$ +4.7 (c 5.09, $CHCl_3$). IR (KBr): 1598, 1589, 1511 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00 (9H, s, *t*-Bu), 3.36 (3H, s, OMe), 3.38-3.76 (5H, m, 1-, 2- and 3-H), 4.98, 5.00 (2H, AB q, *J* = 12.2 Hz, $NaphCH_2$), 7.26-7.68 (14H, m, aromatic H), 7.78-7.90 (2H, m, aromatic H), 8.09 (1H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 26.8, 58.0, 62.8, 69.8, 72.0, 81.0, 124.1, 125.1, 125.7, 126.1, 126.4, 127.6, 128.4, 128.5, 129.6, 131.7, 133.4, 133.5, 133.7, 135.6. EI-MS *m/z* (%): 427 (M^+-*t*-Bu, 1.22), 141 ($NaphCH_2^+$, 100). HRMS Calcd for $C_{27}H_{27}O_3Si$ (M^+-*t*-Bu): 427.1729, Found: 427.1732.

(*S*)-1-(*t*-Butyldiphenylsiloxy)-2-methoxy-3-(2-naphthylmethoxy)propane (5e), 97% yield, $[\alpha]_D^{24}$ -2.7 (c 2.17, $CHCl_3$). IR (KBr): 1602, 1587, 1508 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.01 (9H, s, *t*-Bu), 3.40 (3H, s, OMe), 3.49, 3.59 (each 1H, m, 3-H), 3.68 (1H, m, 2-H), 3.77 (2H, d, *J* = 6.4 Hz, 1-H), 4.67, 4.73 (2H, AB q, *J* = 13.5 Hz, $NaphCH_2$), 7.26-7.90 (17H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 26.8, 58.0, 62.8, 69.8, 73.5, 81.0, 125.7 (2C), 126.0, 126.4, 127.6 (2C), 127.9, 128.1, 129.6, 132.9, 133.2, 133.4, 135.6, 135.8. EI-MS *m/z* (%): 427 (M^+-*t*-Bu, 1.0), 141 ($NaphCH_2^+$, 100). HRMS Calcd for $C_{27}H_{27}O_3Si$ (M^+-*t*-Bu): 427.1729, Found: 427.1737.

(*R*)-3-Benzyloxy-2-methoxy-1-propanol (6a)

To a stirred solution of **5a** (31.0 g, 71.4 mmol) in THF (200 ml) was added a THF solution of tetrabutylammonium fluoride (1 M, 71.4 ml, 71.4 mmol) at room temperature, then the whole was stirred for 10 h at the same temperature. After concentration under vacuum, the residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 3) to afford the title compound **6a** (13.1 g, 94%) as a colorless oil. $[\alpha]_D^{26}$ +21.4 (c 1.00, $CHCl_3$). IR (KBr): 3437, 1604, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.45 (1H, m, 2-H), 3.47 (3H, s, OMe), 3.55-3.61 (2H, m, 3-H), 3.64, 3.76 (each 1H, m, 1-H), 3.53, 3.54 (2H, AB q, *J* = 6.8 Hz, benzylic H), 7.21-7.38 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 57.7, 62.1, 69.4, 73.4, 80.1, 127.5, 127.6, 128.3, 137.8. EI-MS *m/z* (%): 196 (M^+, 4.8), 91 (Bzl^+, 100). HRMS Calcd for $C_{11}H_{16}O_3$ (M^+): 196.1099, Found: 196.1100.

The compounds **6b-e** were prepared by the same method as described above.

(*R*)-3-Benzylthio-2-methoxy-1-propanol (6b), 95% yield, $[\alpha]_D^{25}$ +39.5 (c 1.07, $CHCl_3$). IR (KBr): 3447, 1601, 1494 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.52 (1H, dd, *J* = 7.6, 12.4 Hz, 3-H), 2.61 (1H, dd, *J* = 6.2, 12.4 Hz, 3-H), 3.25 (1H, m, 2-H), 3.37 (3H, s, OMe), 3.56 (1H, m, 1-H), 3.74 (1H, m, 1-H), 3.75 (2H, s, benzylic H), 7.20-7.35 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 30.8, 36.8, 57.3, 62.9, 80.8, 127.0, 128.4, 128.8, 138.0. EI-MS *m/z* (%): 212 (M^+, 5.8), 91 (Bzl^+, 100). HRMS Calcd for $C_{11}H_{16}O_2S$ (M^+): 212.0868, Found: 212.0866.

(*R*)-2-Benzyloxy-3-methoxy-1-propanol (6c), 84% yield, $[\alpha]_D^{25}$ +26.4 (c 1.22, $CHCl_3$). IR (KBr): 3447, 1602, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.39 (3H, s, OMe), 3.4-3.8 (5H, m, 1-, 2- and 3-H), 4.64, 4.66 (2H,

AB q, J = 11.1 Hz, benzylic H), 7.28-7.40 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 59.2, 62.5, 72.0, 72.7, 77.8, 127.7 (2C), 128.3, 138.1. EI-MS *m/z* (%): 196 (M^+, 2.5), 91 (Bzl^+, 100). HRMS Calcd for $C_{11}H_{16}O_3$ (M^+): 196.1099, Found: 196.1109.

(*R*)-2-Methoxy-3-(1-naphthylmethoxy)-1-propanol (6d), 96% yield, $[\alpha]_D^{22}$ +13.27 (c 4.85, $CHCl_3$). IR (KBr): 3440, 1597, 1511 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.44 (3H, s, OMe), 3.56-3.78 (5H, m, 1-, 2- and 3-H), 3.96, 4.00 (2H, AB q, J = 10.1 Hz, $NaphCH_2$), 7.36-7.59 (4H, m, aromatic H), 7.77-7.96 (2H, m, aromatic H), 8.08 (1H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 57.8, 62.3, 69.4, 72.0, 80.1, 123.9, 125.1, 125.8, 126.2, 126.5, 128.5, 128.7, 131.6, 133.2, 133.7. EI-MS *m/z* (%): 246 (M^+, 31), 141 ($NaphCH_2^+$, 100). HRMS Calcd for $C_{15}H_{18}O_3$ (M^+): 246.1256, Found: 246.1257.

(*R*)-2-Methoxy-3-(2-naphthylmethoxy)-1-propanol (6e), 99% yield, colorless crystals, mp 39-40 °C (ethyl acetate-hexane). $[\alpha]_D^{23}$ +19.9 (c 1.24, $CHCl_3$). IR (KBr): 3429, 1602, 1508 (aromatic) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.48 (3H, s, OMe), 3.49 (1H, m, 2-H), 3.62 (2H, d, J = 5.3 Hz, 3-H), 3.64-3.80 (2H, m, 1-H), 4.72 (2H, s, $NaphCH_2$) 7.42-7.52 (3H, m, aromatic H), 7.75-7.88 (4H, m, aromatic H). ^{13}C NMR (50.3 MHz) δ: 57.8, 62.4, 69.5, 73.6, 80.1, 125.6, 125.9, 126.1, 126.5, 127.6, 127.8, 128.2, 133.0, 133.2, 135.3. EI-MS *m/z* (%): 246 (M^+, 34), 141 ($NaphCH_2^+$, 100). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.94; H, 7.32.

(*S*)-3-Benzyloxy-1-bromo-2-methoxypropane (7a)

To a stirred solution of **6a** (7.10 g, 36.2 mmol) in CH_2Cl_2 (100 ml) were added triphenylphosphine (11.4 g, 43.5 mmol) and NBS (9.67 g, 54.3 mmol) in one portion at room temperature, then stirring was continued for 5 min at the same temperature. A saturated $NaHCO_3$ solution (100 ml) was added to the reaction mixture and the whole was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated $NaHCO_3$ solution and worked up as usual. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 3) to afford the title compound **7a** (5.70 g, 61%) as a colorless oil. $[\alpha]_D^{22}$ +5.3 (c 1.50, $CHCl_3$). IR (KBr): 1592, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.45 (3H, s, OMe), 3.45-3.65 (5H, m, 1-, 2- and 3-H), 4.57 (2H, s, benzylic H), 7.25-7.40 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 31.8, 57.8, 69.6, 73.4, 79.2, 127.6, 127.7, 128.3, 137.8. EI-MS *m/z* (%): 260 (M^++2, 7.4), 258 (M^+, 7.4), 91 (Bzl^+, 100). HRMS Calcd for $C_{11}H_{15}O_2{}^{79}Br$ (M^+): 258.0256, Found: 258.0256.

The compounds **7b-e** were prepared by the same method as described above.

(*S*)-3-Benzylthio-1-bromo-2-methoxypropane (7b), 42% yield, $[\alpha]_D^{20}$ +18.3 (c 3.71, $CHCl_3$). IR (KBr): 1601, 1494 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.65 (2H, d, J = 6.0 Hz, 3-H), 3.35 (1H, m, 2-H), 3.36 (3H, s, OMe), 3.50 (2H, d, J = 4.8 Hz, 1-H), 3.76 (2H, s, benzylic H), 7.20-7.38 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 33.2, 33.4, 37.0, 57.6, 79.8, 127.1, 128.5, 128.9, 138.1. EI-MS *m/z* (%): 276 (M^++2, 6.3), 274 (M^+, 6.2), 91 (Bzl^+, 100). HRMS Calcd for $C_{11}H_{15}OS^{79}Br$ (M^+): 274.0025, Found: 274.0020.

(*S*)-2-Benzyloxy-1-bromo-3-methoxypropane (7c), 63% yield, $[\alpha]_D^{24}$ +1.66 (c 1.08, $CHCl_3$). IR (KBr): 1586, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.39 (3H, s, OMe), 3.4-3.6 (4H, m, 1- and 3-H), 3.72 (1H, m, 2-H), 4.62, 4.68 (2H, AB q, J = 11.8 Hz, benzylic H), 7.23-7.42 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 32.1, 59.3, 72.1, 72.6, 76.9, 127.8 (2C), 128.4, 137.8. EI-MS *m/z* (%): 260 (M^++2, 2.9), 258 (M^+, 2.9), 91 (Bzl^+, 100). HRMS Calcd for $C_{11}H_{15}O_2{}^{79}Br$ (M^+): 258.0256, Found: 258.0255.

(*S*)-1-Bromo-2-methoxy-3-(1-naphthylmethoxy)propane (7d), 57% yield, $[\alpha]_D^{23}$ +7.0 (c 3.91, $CHCl_3$). IR (KBr): 1597, 1510 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.42 (3H, s, OMe), 3.42-3.59 (3H, m, 1- and 2-H), 3.62-3.72 (2H, m, 3-H), 4.98, 5.00 (2H, AB q, J = 10.1 Hz, NaphCH_2), 7.39-7.58 (4H, m, aromatic H), 7.79-7.88 (2H, m, aromatic H), 8.12 (1H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 32.0, 57.8, 69.6, 72.1, 79.1, 124.1, 125.1, 125.8, 126.2, 126.6, 128.5, 128.8, 131.7, 133.3, 133.7. EI-MS *m/z* (%): 310 (M^++2, 7.9), 308 (M^+, 8.2), 141 (NaphCH_2^+, 100). HRMS Calcd for $C_{15}H_{17}O_2{}^{79}Br$ (M^+): 308.0413, Found: 308.0418.

(*S*)-1-Bromo-2-methoxy-3-(2-naphthylmethoxy)propane (7e), 76% yield, $[\alpha]_D^{20}$ +8.93 (c 1.01, $CHCl_3$). IR (KBr): 1602, 1508 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.45 (3H, s, OMe), 3.39-3.73 (5H, m, 1-, 2- and 3-H), 4.73 (2H, s, NaphCH_2), 7.42-7.53 (3H, m, aromatic H), 7.73-7.89 (4H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 31.7, 57.8, 69.6, 73.6, 79.2, 125.6, 125.9, 126.1, 126.5, 127.6, 127.8, 128.2, 133.0, 133.2, 135.3. EI-MS *m/z* (%): 310 (M^++2, 11), 308 (M^+, 11), 141 (NaphCH_2^+, 100). HRMS Calcd for $C_{15}H_{17}O_2{}^{79}Br$ (M^+): 308.0413 , Found: 308.0415.

(*S*)-3-(3-Benzyloxy-2-methoxypropoxy)-5-(benzyloxymethyl)-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (9a)

To a stirred DMF (5 ml) suspension of NaH (60% in oil, 251 mg, 6.28 mmol), which had been washed with pentane three times and dried under vacuum, was added a solution of **8** (1.46 g, 4.83 mmol) in DMF (10 ml) at room temperature, then the whole was stirred at the same temperature for 1 h. Subsequent to the addition of a solution of **7a** (1.50 g, 5.79 mmol), the reaction mixture was stirred at 80 °C for 4 h, then extracted with ether and water. The combined ethereal layer was washed with 1 M NaOH solution and worked up as usual. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 1) to give the title compound **9a** (1.81 g, 78%) as a colorless oil. $[\alpha]_D^{25}$ +3.3 (c 1.08, MeOH). IR (KBr): 1586, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.54 (3H, s, 2-Me), 3.36, 3.37, 3.56 (each 3H, s, OMe), 3.64-3.80 (3H, m, side chain 2- and 3-H), 3.84-4.00 (2H, m, side chain 1-H), 3.58, 3.58, 4.84 (each 2H, s, benzylic H and 5-CH_2), 5.64 (1H, s, $CH(OMe)_2$), 7.26-7.98 (10H, m, aromatic H), 8.62 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 55.6, 55.7, 58.1, 66.9, 68.6, 72.4, 73.5, 73.9, 79.1, 101.4, 127.4, 127.6, 127.6, 127.7, 128.2, 128.3, 131.3, 136.7, 137.7, 138.3, 145.3, 150.5, 151.7. EI-MS *m/z* (%): 481 (M^+, <0.1), 450 (M^+-OMe, 4.5), 91 (Bzl^+, 100). HRMS Calcd for $C_{27}H_{32}NO_5$ (M^+-OMe): 450.2281, Found: 450.2283.

The compounds **9b-e** were prepared by the same method as described above.

(*R*)-5-(Benzyloxymethyl)-3-(3-benzylthio-2-methoxypropoxy)-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (9b), 64% yield, $[\alpha]_D^{22}$ +20.2 (c 1.04, MeOH). IR (KBr): 1601, 1494 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.50 (3H, s, 2-Me), 2.73 (2H, d, J = 6.2 Hz, side chain 3-H), 3.38, 3.39, 3.44 (each 3H, s, OMe), 3.55 (1H, m, side chain 2-H), 3.80, 4.59, 4.83 (each 2H, s, benzylic H and 5-CH_2), 3.82-3.92 (2H, m, side chain 1-H), 5.62 (1H, s, $CH(OMe)_2$), 7.22-7.40 (10H, m, aromatic H), 8.54 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 31.2, 37.0, 55.7, 55.7, 57.8, 66.9, 72.4, 74.6, 79.6, 101.3, 127.0, 127.4, 127.6, 128.2, 128.4, 128.8, 131.3, 136.7, 138.0, 138.3, 145.3, 150.3, 151.6. EI-MS *m/z* (%): 497 (M^+, 0.1), 91 (Bzl^+, 100). HRMS Calcd for $C_{28}H_{35}NO_5S$ (M^+): 497.2236, Found: 497.2239.

(*S*)-3-(2-Benzyloxy-3-methoxypropoxy)-5-(benzyloxymethyl)-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (9c), 61% yield, $[\alpha]_D^{24}$ -12.1 (c 1.16, MeOH). IR (KBr): 1588, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.53 (3H, s, 2-Me), 3.32, 3.36, 3.42 (each 3H, s, OMe), 3.63-3.69 (2H, m, side chain 3-H), 3.80-

4.00 (3H, m, side chain 1- and 2-H), 4.58, 4.78, 4.84 (each 2H, s, benzylic H and 5-CH_2), 5.83 (1H, s, $CH(OMe)_2$), 7.20-7.43 (10H, m, aromatic H), 8.53 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 55.7, 55.8, 59.2, 67.0, 71.5, 72.4, 72.5, 74.0, 76.6, 101.4, 127.5, 127.6 (2C), 127.7, 128.3, 128.3, 131.4, 136.8, 138.1, 138.4, 145.4, 150.4, 151.8. EI-MS *m/z* (%): 482 (M^++H, <0.1), 481 (M^+, <0.1), 91 (Bzl^+, 100). HRMS Calcd for $C_{28}H_{35}NO_6$ (M^+): 481.2464, Found: 481.2466.

(*S*)-5-(Benzyloxymethyl)-3-[2-methoxy-3-(1-naphthylmethoxy)propoxy]-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (9d), 50% yield, $[\alpha]_D^{24}$ +1.9 (c 3.70, MeOH). IR (KBr): 1597, 1510 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.46 (3H, s, 2-Me), 3.28, 3.30, 3.52 (each 3H, s, OMe), 3.68-3.80 (3H, m, side chain 2-H and 3-H), 3.81-3.94 (2H, m, side chain 1-H), 4.58, 4.84, 5.04 (each 2H, s, benzylic H, 5-CH_2 and NaphCH_2), 5.62 (1H, s, $CH(OMe)_2$), 7.18-7.56 (9H, m, aromatic H), 7.76-7.90 (2H, m, aromatic H), 8.11 (1H, m, aromatic H), 8.54 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 55.7, 55.8, 58.2, 67.0, 68.7, 72.1, 72.5, 74.0, 79.2, 101.4, 123.9, 125.1, 125.8, 126.2, 126.5, 127.5, 127.6, 128.3, 128.5, 128.8, 131.4, 131.6, 133.2, 133.7, 136.8, 138.3, 145.2, 150.5, 151.7. EI-MS *m/z* (%): 531 (M^+, 0.3), 141 (NaphCH_2^+, 100). HRMS Calcd for $C_{32}H_{37}NO_6$ (M^+): 531.2621, Found: 531.2641.

(*S*)-5-(Benzyloxymethyl)-3-[2-methoxy-3-(2-naphthylmethoxy)propoxy]-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (9e), 72% yield, $[\alpha]_D^{22}$ +4.8 (c 3.10, MeOH). IR (KBr): 1602, 1509 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.52 (3H, s, 2-Me), 3.33, 3.34, 3.56 (each 3H, s, OMe), 3.65-3.81 (3H, m, side chain 2-H and 3-H), 3.81-3.98 (2H, m, side chain 1-H), 4.58, 4.76, 4.84 (each 2H, s, benzylic H, 5-CH_2 and NaphCH_2), 5.65 (1H, s, $CH(OMe)_2$), 7.23-7.57 (8H, m, aromatic H), 7.76-7.85 (4H, m, aromatic H), 8.53 (1H, s. 6-H). ^{13}C NMR ($CDCl_3$) δ: 19.2, 55.7, 55.7, 58.2, 66.9, 68.6, 72.4, 73.6, 73.9, 79.2, 101.4, 125.6, 125.9, 126.1, 126.5, 127.4, 127.6 (2C), 127.7, 128.1, 128.2, 131.4, 132.9, 133.1, 135.2, 136.8, 138.3, 145.3, 150.5, 151.7. EI-MS *m/z* (%): 531 (M^+, 0.4), 141 (NaphCH_2^+, 100). HRMS Calcd for $C_{32}H_{37}NO_6$ (M^+): 531.2621, Found: 531.2643.

(*S*)-3-(3-Benzyloxy-2-methoxypropoxy)-5-(benzyloxymethyl)-2-methylpyridine-4-carbaldehyde (10a)

A solution of **9a** (1.58 g, 3.28 mmol) in acetic acid-water (3 : 2, 25 ml) was stirred at 100 °C for 12 h. Subsequent to the neutralization with saturated $NaHCO_3$ solution, the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was worked up as usual and the resultant residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 1) to give the title compound **10a** (929 mg, 65%) as a colorless oil. $[\alpha]_D^{23}$ +6.2 (c 1.19, $CHCl_3$). IR (KBr): 1699, 1600, 1494 cm^{-1}. ^1H NMR ($CDCl_3$)δ: 2.58 (3H, s, 2-Me), 3.48 (3H, s, OMe), 3.60-3.74 (3H, m, side chain 2- and 3-H), 3.98-4.14 (2H, m, side chain 1-H), 4.56, 4.64, 4.84 (each 2H, s, benzylic H and 5-CH_2), 7.26-7.40 (10H, m, aromatic H), 8.62 (1H, s, 6-H), 10.56 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 19.1, 57.9, 67.3, 68.0, 73.0, 73.5, 75.2, 78.9, 127.2, 127.6 (2C), 127.7, 128.3 (2C), 131.3, 131.8, 137.6, 137.7, 144.4, 153.9, 154.3, 192.3. EI-MS *m/z* (%): 435 (M^+, 0.1), 91 (Bzl^+, 100). HRMS Calcd for $C_{26}H_{29}NO_5$ (M^+): 435.2043, Found: 435.2040.

The compounds **10b-e** were prepared by the same method as described above.

(*R*)-5-(Benzyloxymethyl)-3-(3-benzylthio-2-methoxypropoxy)-2-methylpyridine-4-carbaldehyde (10b), 81% yield, $[\alpha]_D^{22}$ +26.5 (c 1.27, $CHCl_3$). IR (KBr): 1700, 1601, 1494 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.58 (3H, s, 2-Me), 2.63-2.70 (2H, m, side chain 3-H), 3.38 (3H, s, OMe), 3.50 (1H, m, side chain 2-H), 3.78, 4.64, 4.85 (each 2H, s, benzylic H and 5-CH_2), 3.92-4.07 (2H, m, side chain 1-H), 7.20-7.40 (10H, m, aromatic H),

8.60 (1H, s, 6-H), 10.53 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 19.2, 30.8, 36.9, 57.5, 67.3, 73.0, 75.9, 79.4, 127.1, 127.6, 127.6, 128.3, 128.4, 128.8, 131.2, 131.8, 137.7, 137.9, 144.4, 153.9, 154.1, 192.2. EI-MS *m/z* (%): 451 (M^+, 0.2), 91 (Bzl^+, 100). HRMS Calcd for $C_{26}H_{29}NO_4S$ (M^+): 451.1815, Found: 451.1815.

(*S*)-3-(2-Benzyloxy-3-methoxypropoxy)-5-(benzyloxymethyl)-2-methylpyridine-4-carbaldehyde (10c), 77% yield, $[\alpha]_D^{24}$ -9.35 (c 1.20, $CHCl_3$). IR (KBr): 1699, 1585, 1496 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.59 (3H, s, 2-Me), 3.39 (3H, s, OMe), 3.62 (2H, d, *J* = 6.3 Hz, side chain 3-H), 3.94 (1H, m, side chain 2-H), 4.02-4.08 (2H, m, side chain 1-H), 4.63, 4.72, 4.83 (each 2H, s, benzylic H and 5-CH_2), 7.25-7.43 (10H, m, aromatic H), 8.61 (1H, s, 6-H), 10.56 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 19.0, 59.1, 67.3, 71.2, 72.3, 73.0, 75.3, 76.4, 127.6, (2C), 127.69, 127.81, 128.29 (2C), 131.25, 131.83, 137.68, 137.77, 144.43, 154.0, 154.2, 192.2. EI-MS *m/z* (%): 435 (M^+, 0.2), 91 (Bzl^+, 100). HRMS Calcd for $C_{26}H_{29}NO_5$ (M^+): 435.2043, Found: 435.2043.

(*S*)-5-(Benzyloxymethyl)-3-[2-methoxy-3-(1-naphthylmethoxy)propoxy]-2-methylpyridine-4-carbaldehyde (10d), 97% yield, $[\alpha]_D^{22}$ +4.4 (c 5.20, $CHCl_3$). IR (KBr): 1697, 1597, 1510, 1497 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.48 (3H, s, 2-Me), 3.46 (3H, s, OMe), 3.62-3.74 (3H, m, side chain 2- and 3-H), 3.92-4.06 (2H, m, side chain 1-H), 4.64, 4.84 (each 2H, s, benzylic H and 5-CH_2), 5.00, 5.04 (2H, AB q, *J* = 11.7 Hz, NaphCH_2), 7.28-7.34 (9H, m, aromatic H), 7.76-7.88 (2H, m, aromatic H), 8.11 (1H, m, aromatic H), 8.60 (1H, s, 6-H), 10.52 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 19.1, 57.7, 67.2, 67.8, 71.9, 72.9, 75.1, 78.9, 123.7, 124.9, 125.7, 126.0, 126.5, 127.5, 127.6, 128.2, 128.4, 128.7, 131.1, 131.5, 131.6, 133.0, 133.5, 137.7, 144.2, 153.8, 154.2, 192.2. EI-MS *m/z* (%): 485 (M^+, 1.2), 141 (NaphCH_2^+, 100). HRMS Calcd for $C_{30}H_{31}NO_5$ (M^+): 485.2202, Found: 485.2202.

(*S*)-5-(Benzyloxymethyl)-3-[2-methoxy-3-(2-naphthylmethoxy)propoxy]-2-methylpyridine-4-carbaldehyde (10e), 87% yield, $[\alpha]_D^{25}$ +13.2 (c 1.45, $CHCl_3$). IR (KBr): 1696, 1602, 1508, 1497 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.56 (3H, s, 2-Me), 3.45 (3H, s, OMe), 3.60-3.79 (3H, m, side chain 2- and 3-H), 3.97-4.18 (2H, m, side chain 1-H), 4.60, 4.71, 4.82 (each 2H, s, benzylic H and 5-CH_2 and NaphCH_2), 7.23-7.58 (8H, m, aromatic H), 7.76-7.92 (4H, m, aromatic H), 8.61 (1H, s, 6-H), 10.58 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 19.1, 57.9, 67.3, 68.0, 73.0, 73.6, 75.1, 78.9, 125.6, 125.9, 126.1, 126.5, 127.6 (2C), 127.7, 127.7, 128.2, 128.3, 131.3, 131.8, 132.9, 133.1, 135.0, 137.7, 144.4, 153.9, 154.3, 192.3. EI-MS *m/z* (%): 485 (M^+, 1.0), 141 (NaphCH_2^+, 100). HRMS Calcd for $C_{30}H_{31}NO_5$ (M^+): 485.2202, Found: 485.2210.

Alkylation of Aldimines

Aldimines **11** were prepared from pyridoxal model compound **10** (0.20 mmol) and amino ester (0.20 mmol) according to the same procedure as reported previously.[6] ^{1}H NMR analysis of **11** showed that **11** were pure enough and the reaction had proceeded in almost quantitative yields. ^{1}H NMR data for **11** measured in $CDCl_3$ are as follows: **11Aa** δ: 1.49 (3H, d, *J* = 6.8 Hz, α-Me), 2.54 (3H, s, 2-Me), 3.47 (3H, s, OMe), 3.58-3.67 (3H, m, side chain 2- and 3-H), 3.86-3.98 (2H, m, side chain 1-H), 4.10 (1H, q, *J* = 6.8 Hz, α-H), 4.49, 4.54 (each 2H, s, benzylic H), 4.78-4.85 (2H, AB type, 5-CH_2), 5.13-5.17 (2H, AB type, CO_2Bn), 7.20-7.41 (15H, m, aromatic H), 8.54 (1H, s, 6-H), 8.69 (1H, s, imine H); **11Ab** δ: 1.51 (3H, d, *J* = 6.8 Hz, α-Me), 2.52 (3H, s, 2-Me), 2.65 (2H, d, J = 6.7 Hz, side chain 3-H), 3.38 (3H, s, OMe), 3.44 (1H, m, side chain 2- H), 3.74, 4.49 (each 2H, s, benzylic H), 3.85 (2H, d, *J* = 4.7 Hz, side chain 1-H), 4.17 (1H, q, *J* = 6.8 Hz, α-H), 4.76-4.85 (2H, AB type, 5-CH_2), 5.11-5.18 (2H, AB type, CO_2Bn), 7.11-7.40 (15H, m, aromatic H), 8.53

(1H, s, 6-H), 8.67 (1H, s, imine H); **11Ac** δ: 1.40 (3H, d, J = 6.9 Hz, α-Me), 2.55 (3H, s, 2-Me), 3.38 (3H, s, OMe), 3.63 (2H, d, J = 4.5 Hz, side chain 3-H), 3.80-3.99 (3H, m, side chain 1- and 2-H), 4.16 (1H, q, J = 6.9 Hz, α-H), 4.51 (2H, s, benzylic H), 4.70-4.72 (2H, AB type, 5-CH_2), 5.11 (2H, s, CO_2Bn), 7.18-7.39 (15H, m, aromatic H), 8.52 (1H, s, 6-H), 8.63 (1H, s, imine H); **11Ad** δ: 1.41 (3H, d, J = 6.6 Hz, α-Me), 2.46 (3H, s, 2-Me), 3.44 (3H, s, OMe), 3.61 (1H, m, side chain 2-H), 3.68 (2H, d, J = 4.7 Hz, side chain 3-H), 3.78-3.92 (2H, m, side chain 1-H), 4.01 (1H, q, J = 6.6 Hz, α-H), 4.49 (2H, s, benzylic H), 4.76-4.82 (2H, AB type, 5-CH_2), 4.98 (2H, s, NaphCH_2), 5.10 (2H, s, CO_2Bn), 7.22-7.54 (14H, m, aromatic H), 7.78-7.83 (2H, m, aromatic H), 8.10 (1H, m, aromatic H), 8.51 (1H, s, 6-H), 8.60 (1H, s, imine H); **11Ae** δ: 1.46 (3H, d, J = 6.9 Hz, α-Me), 2.50 (3H, s, 2-Me), 3.45 (3H, s, OMe), 3.56-3.70 (3H, m, side chain 2- and 3-H), 3.91-4.10 (2H, m, side chain 1-H), 4.13 (1H, q, J = 6.9 Hz, α-H), 4.51, 4.70, 4.81 (each 2H, s, benzylic H, NaphCH_2 and 5-CH_2), 5.11-5.13 (2H, AB type, CO_2Bn), 7.21-7.59 (13H, m, aromatic H), 7.73-7.91 (4H, m, aromatic H), 8.52 (1H, s, 6-H), 8.62 (1H, s, imine H); **11Be** δ: 2.50 (3H, s, 2-Me), 3.05-3.33 (2H, AB in ABX, β-H), 3.41 (3H, s, OMe), 3.52-3.60 (4H, m, side chain 1- and 3-H), 3.77 (1H, m, side chain 2-H), 4.16 (1H, dd, J = 5.1, 8.9 Hz, α-H), 4.49 (2H, s, benzylic H), 4.68-4.70, 4.74-4.78 (each 2H, AB type, 5-CH_2 and NaphCH_2), 5.11 (2H, s, CO_2Bn), 6.98 (1H, m, aromatic H), 7.01-7.15 (3H, m, aromatic H), 7.23-7.35 (10H, m, aromatic H), 7.43-7.49 (3H, m, aromatic H), 7.75-7.84 (5H, m, aromatic H), 8.40 (1H, s, 6-H), 8.55 (1H, s, imine H); **11Ce** δ: 2.51 (3H, s, 2-Me), 3.44 (3H, s, OMe), 3.66-3.74 (3H, m, side chain 2- and 3-H), 3.92-4.03 (2H, m, side chain 1-H), 4.36 (2H, s, α-H), 4.50, 4.68, 4.78 (each 2H, s, benzylic H, NaphCH_2 and 5-CH_2), 5.10 (2H, s, CO_2Bn), 7.23-7.59 (13H, m, aromatic H), 7.75-7.92 (4H, m, aromatic H), 8.55 (1H, s, 6-H), 8.61 (1H, s, imine H). The aldimines **11** were immediately used for alkylation without purification.

To a stirred solution of LDA (0.24 mmol) or a suspension of NaH (60% in oil, 12 mg, 0.30 mmol) in THF (0.5 ml) was added a THF solution (0.5 ml) of the aldimine **11** at -78 °C and the whole was stirred at -45 °C for 5 min. Alkyl halide (0.24 mmol) was added to the reaction mixture at -78 °C and stirring was continued at the same temperature for 10 h. The reaction mixture was gradually warmed to 0 °C, diluted with ethyl acetate (10 ml) and vigorously stirred with 5% HCl at room temperature for 5 min. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were worked up as usual and the resultant residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 2) to give the pyridoxal model compound **10**. The aqueous phase was neutralized with sodium bicarbonate and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by aminopropylsilica gel column chromatography (ethyl acetate : hexane = 1 : 2) to afford α-alkylated amino ester **2**. The structures of amino esters **2a-d** were identified by comparison of their spectral properties with those of racemic compounds reported previously.[6] The optical purity was determined by derivatizing these amino esters with (*R*)-MTPACl to the corresponding MTPA amide as follows.

Preparation of MTPA Amide

To a solution of amino ester **2** (0.010 mmol) in dry pyridine (0.1 ml) containing a catalytic amount of DMAP were added (*R*)-MTPACl (2.2 μl, 0.012 mmol) and the whole was stirred at room temperature for 2 h. After being diluted with ethyl acetate, the reaction mixture was washed successively with saturated $NaHCO_3$ solution, 5% HCl, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the

amide **14** in almost quantitative yield. The optical purities of **2** were obtained by ^{1}H and ^{19}F NMR analyses of **14** (Table 5).

Table 5 Chemical shifts (ppm) for α-CH_3 (δ_H) and CF_3 (δ_F) groups of **14**

	14a	**14b**	**14c**	**14d**
α-CH_3	1.69 (1.76)	1.66 (1.72)	1.65 (1.69)	1.62 (1.64)
CF_3	-69.0 (-69.4)	-69.4 (-69.8)	-70.1 (-69.9)	-69.9 (-70.2)

Values in the parentheses are for *S*-isomers.

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