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Asymmetric synthesis of β-amino-α-hydroxyphosphinic acid derivatives through hydrophosphinylation of α-amino aldehydes

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Abstract—The diastereoselective synthesis of β-amino-α-hydroxyphosphinates was achieved by hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes with ethyl ethylphosphinate catalyzed by (*S*)-ALB. The hydrophosphinylation using ethyl phosphinate afforded both *syn*- and *anti*-β-amino-α-hydroxy-*H*-phosphinates with high diastereoselectivities by tuning the chirality of ALB.

The β-amino-α-hydroxyphosphinic acids **1** serve as the key intermediates for the synthesis of potent inhibitors of human renin and HIV protease (Fig. 1).[1,2] Stereogenic carbon–phosphorus bond formation processes are of great interest in the stereoselective synthetic sequences of the β-amino alcohol moiety by the reaction of α-amino aldehydes with phosphinic nucleophiles, since the stereochemistry of β-amino alcohol is known to be an important factor to get potent inhibitory active compounds. Although β-amino-α-hydroxyphosphinic acid derivatives were obtained by the reaction of *N*-Boc-α-amino aldehydes with methyl ethylphosphinate (HPO(OMe)(Et)) in the presence of TMSCl and an amine, diastereoselectivity was not observed.[1] Our special interest is in developing concise and highly diastereoselective synthesis of both β-amino-α-hydroxy-phosphinic acids (**1**/X=alkyl) and β-amino-α-hydroxy-*H*-phosphinic acids (**1**/X=H). We examined the chiral AlLi-bis(binaphthoxide) (ALB)[3]-catalyzed hydrophosphinylayion of α-amino aldehydes employing two types of phosphinic nucleophile, alkyl alkylphosphinate (HPO(OR)(R)) and alkyl phosphinate (H_2PO_2R), in extension of our previous work on catalytic asymmetric hydrophosphinylation of aldehydes.[4] The reaction of ethyl ethylphosphinate[5] with *N*,*N*-dibenzyl-α-amino aldehydes[6] afforded *anti*-β-amino-α-hydroxyphosphinates in a highly diastereoselective manner. Furthermore, chiral ALB-catalyzed hydrophosphinylation employing ethyl phosphinate,[7] generated from anhydrous phosphinic acid and triethyl orthoformate in situ, proceeded with a high level of diastereofacial selectivity. The stereochemical outcome of the reaction can be controlled in either *anti*- or *syn*-selective manner by tuning the chirality of ALB.[8] We wish to describe full details in this paper (Scheme 1).

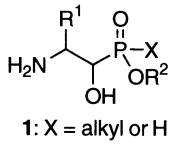
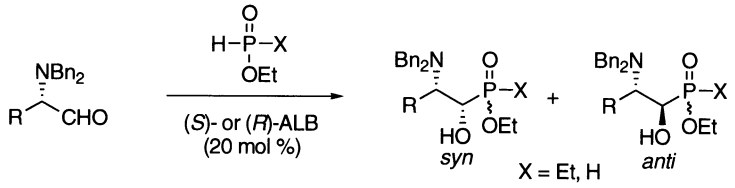


Figure 1.

First, we examined the hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehyde **2a** with ethyl ethylphosphinate in the presence of (*R*)-ALB (20 mol%), generated from (*R*)-binaphthol, in THF at −40°C for 12 h (Table 1). The reaction was found to be sluggish, giving adducts *syn*-**3** and *anti*-**3** only in 4% yield (entry 1). The ^{31}P NMR spectrum of



Scheme 1.

Keywords: diastereoselection; phosphinic acids and derivatives.
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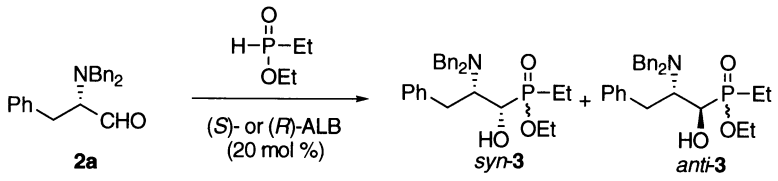
Table 1. Hydrophosphinylation of **2a** with ethyl ethylphosphinate in the presence of ALB

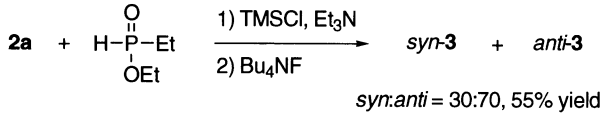


Entry[a]	ALB	Temperature (°C)	*syn*/*anti*[b]	Yield (%)[c]
1	(*R*)-ALB	−40	43:57	4
2	(*R*)-ALB	0	43:57	55
3	(*S*)-ALB	0	11:89	51

[a] All reactions were carried out for 12 h.
[b] Determined by ^{31}P NMR analysis of crude products.
[c] Combined yields of *syn*- and *anti*-isomers.

the crude products revealed that the diastereoselectivity was poor (*syn*/*anti*=43:57). When the reaction was carried out at 0°C, the chemical yield was raised to 55%, but resulting in the same diastereoselectivity (entry 2).[9] On the other hand, employing (*S*)-ALB gave adduct **3** with *anti*-selectivity (*syn*/*anti*=11:89) in 51% yield (entry 3). These results indicated that the combination of (*S*)-ALB and **2a** was suitably matched for inducing diastereofacial selectivity. The hydrophosphinylation products *syn*-**3** and *anti*-**3** were obtained as a 1:1 mixture of isomers arising from the chirality of the phosphinate group, respectively. Only in the case of *syn*-**3**, these diastereomers, *syn*-**3-A** and *syn*-**3-B**, were separated by silica gel column chromatography.

In view of the level of selectivity, ALB-catalyzed hydrophosphinylation was confirmed to be more advantageous over the existing conventional method; that is, hydrophosphinylation of **2a** using 1.5 equiv. of both Et_3N and TMSCl, followed by desilylation with Bu_4NF afforded **3** with modest selectivity (*syn*/*anti*=30:70) in 55% yield (Scheme 2). The stereochemistry of the major diastereomer



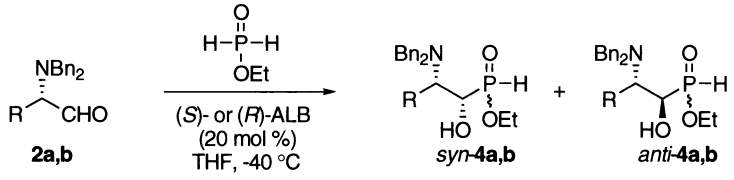
Scheme 2.

was estimated to be *anti* by considering the Felkin–Anh transition state.[10]

We next examined hydrophosphinylation of **2a**,**b** employing ethyl phosphinate for the synthesis of β-amino-α-hydroxy-*H*-phosphinates in a highly diastereoselective manner (Table 2). In these cases, ethyl phosphinate is expected to be readily activated by ALB showing increased nucleophilicity due to the low pK_a value in comparison with ethyl ethylphosphinate.

As we expected, ethyl phosphinate could be activated by the catalyst even at −40°C affording the corresponding hydrophosphinylation products in moderate yields.[11] An intriguing result was revealed upon analyzing the diastereoselectivities of the products. Performing the reaction of **2a** in the presence of (*R*)-ALB gave rise to high *syn*-selectivity (*syn*-**4a**/*anti*-**4a**=87:13) (entry 1). On the other hand, the reaction of **2a** by the use of (*S*)-ALB instead of (*R*)-ALB proceeded with inversed stereoselection to afford *anti*-**4a** in a ratio of 6:94 (entry 2). Also, when the reaction of **2b** was carried out with (*R*)- or (*S*)-ALB, either *syn*-**4b** or *anti*-**4b** could be obtained in high stereoselectivity (entries 3 and 4). In the above-mentioned cases, diastereofacial selectivity was found to be controlled predominantly by the chirality of the asymmetric catalyst rather than that of the α-amino aldehydes. As observed in Table 2, the diastereoselectivity

Table 2. Hydrophosphinylation of **2a**,**b** with ethyl phosphinate in the presence of ALB



Entry[a]	Substrate	ALB	*syn*/*anti*	Yield (%)[b]
1	**2a**	(*R*)-ALB	87:13	66
2	**2a**	(*S*)-ALB	6:94	56
3	**2b**	(*R*)-ALB	94:6	54
4	**2b**	(*S*)-ALB	2:98	71

[a] All reactions were carried out for 12 h at −40°C.
[b] Combined yields of *syn*- and *anti*-isomers.

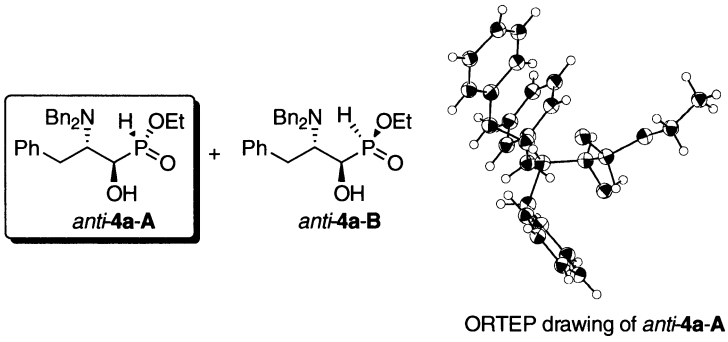
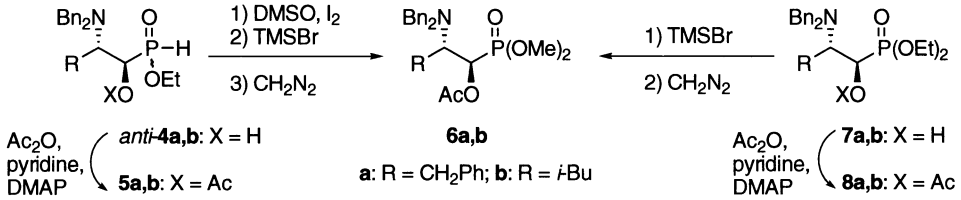


Figure 2.



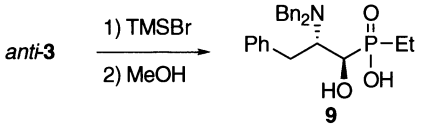
Scheme 3.

of the hydrophosphinylation with (*S*)-ALB is generally higher than that with (*R*)-ALB.

The high diastereoselectivity of the hydrophosphinylation catalyzed by ALB would be accounted for by the kinetically controlled process: treatment of *anti*-**4a** with ethyl phosphinate in the presence of (*R*)-ALB at −40°C formed none of *syn*-isomer that would be expected from a reversible process. Although the exact reason for high selectivities in (*R*)-ALB-catalyzed hydrophosphinylation using ethyl phosphinate in comparison with ethyl ethylphosphinate remains unclear, it seems likely to be associated with a steric disposition for phosphinic nucleophile.

The products *anti*-**4a**,**b** and *syn*-**4a**,**b** were obtained as a 1:1 mixture of diastereoisomers arising from the chirality of the phosphinate group. The diastereomerically pure *anti*-**4a-A** (mp: 149–150°C) was isolated from the mixture (*anti*-**4a-A** and *anti*-**4a-B**) upon recrystallization from ethyl acetate.[12] The relative stereochemistry of *anti*-**4a-A** was confirmed unambiguously by X-ray crystallographic analysis (Fig. 2).

The stereochemistry of *anti*-**4a**,**b** was also confirmed after converting to β-amino-α-acetoxyphosphonate **6a**,**b** through sequential acetylation, oxidation,[13] deesterification[14] and methyl esterification (Scheme 3). The ^{1}H NMR spectra of **6a**,**b** were identical with those of the authentic specimens derived from the known β-amino-α-hydroxyphosphonate **7a**,**b**[10,15] through acetylation and deesterification followed by methyl esterification. The optical purity of **6a** derived from *anti*-**4a** was determined to be 99% ee by HPLC



Scheme 4.

analysis on a chiral phase (DAICEL CHIRALPAK OD column, hexane/EtOH=20:1). Therefore, it was proved that no racemization of *N*,*N*-dibenzyl-α-amino aldehydes took place during the hydrophosphinylation.

Finally, the ethyl ester of *anti*-**3** could be easily removed by treatment with TMSBr followed by methanolysis to give β-amino-α-hydroxyphosphinic acid **9** in 92% yield (Scheme 4) The product **9** was obtained as a single product due to the loss of asymmetric character of phosphorus atom by the rapid transfer of the acidic proton between the phosphoryl (P=O) and the acidic (P–OH) sites.[13]

In conclusion, we have developed a diastereoselective synthesis of β-amino-α-hydroxyphosphinates through hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes with ethyl ethylphosphinate catalyzed by (*S*)-ALB. Moreover, applying ethyl phosphinate to the hydrophosphinylation afforded both *syn*- and *anti*-β-amino-α-hydroxy-*H*-phosphinates selectively by tuning the chirality of ALB. The present methodology would be widely applicable to the synthesis of protease inhibitors.

1. Experimental

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. IR spectra were recorded on a JASCO FTIR-620. Mass spectra were measured on a Finnigan TSQ-700 or a VG Auto Spec E. Elemental analysis were recorded on an Elemental Vavio EL. NMR spectra were obtained on either a Bruker DPX400 NMR spectrometer operating or a Varian Mercury-300BB instrument operating at 400 (or 300) MHz for ^{1}H, 100 (or 75.5) MHz for ^{13}C, and 162 MHz for ^{31}P. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to $CHCl_3$ (δ=7.26) for $CDCl_3$

solution or CH_3OH (δ=3.30) for CD_3OD solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ or CD_3OD are reported relative to the $CDCl_3$ resonance (δ=77.0) and CD_3OD resonance (δ=49.0), respectively. The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ=0) with broad-band ^1H decoupling. The aldehydes **2a**,**b** were prepared in enantiomerically pure forms from the corresponding L-amino acids according to the literature methods and used without purification.[6] All reactions were conducted under nitrogen.

1.1. The procedure for the hydrophosphinylation of 2a with ethyl ethylphosphinate in the presence of (*R*)-ALB

To a solution of ethyl ethylphosphinate (732 mg, 6.0 mmol) in THF (4 mL) was added 0.1 M THF solution of (*R*)-ALB (8.0 mL, 0.8 mmol), prepared from (*R*)-BINOL (458 mg, 1.6 mmol) and $LiAlH_4$ (30.4 mg, 0.8 mmol) in situ according to Shibasaki's method,[3] and a solution of **2a** (4.0 mmol) in THF (8 mL) at 0°C under stirring. After stirring for 12 h at the same temperature, the mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=1:1 to $CHCl_3$/MeOH=20:1) to give *syn*-**3-A** (142 mg, 8%), *syn*-**3-B** (338 mg, 19%) and *anti*-**3** (513 mg, 28%).

1.1.1. Ethyl (1*S*,2*S*)-2-(dibenzylamino)-1-hydroxy-3-phenylpropyl(ethyl)phosphinate (*syn*-3-A). Oil; $[\alpha]_D^{23}$=+24.2 (*c* 0.84, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.04 (15H, m), 5.09 (1H, d, *J*=15.8 Hz), 4.19–4.06 (2H, m), 3.77 (2H, d, *J*=12.6 Hz), 3.66 (1H, dd, *J*=5.4, 10.7 Hz), 3.50–3.33 (3H, m), 2.98 (1H, dd, *J*=10.5, 14.4 Hz), 1.55–1.14 (2H, m), 1.35 (3H, t, *J*=7.0 Hz), 0.87 (3H, td, *J*=7.8, 17.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 58.76; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.0, 138.0, 129.6, 129.3, 128.6, 128.5, 127.4, 126.5, 66.4 (d, J_{PC}=110.6 Hz), 60.3 (d, J_{PC}=6.3 Hz), 58.6, 58.5, 53.3, 34.9, 16.5 (d, J_{PC}=93.9 Hz), 16.3 (d, J_{PC}=5.2 Hz), 5.4 (d, J_{PC}=5.8 Hz); IR (neat) 3240, 1029 cm^{-1}; EIMS *m*/*z* 360 (M^+-CH_2Ph). High resolution MS calcd for $C_{20}H_{27}NO_3P$ (M^+-CH_2Ph): 360.1728. Found: 360.1722.

1.1.2. Ethyl (1*S*,2*S*)-2-(dibenzylamino)-1-hydroxy-3-phenylpropyl(ethyl)phosphinate (*syn*-3-B). Mp 102–104°C; $[\alpha]_D^{24}$=+35.9 (*c* 0.93, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.04 (15H, m), 4.94 (1H, d, *J*=17.0 Hz), 3.82–3.66 (4H, m), 3.55–3.45 (3H, m), 3.34–3.30 (1H, m), 3.01 (1H, dd, *J*=10.7, 14.8 Hz), 1.93–1.71 (2H, m), 1.17 (3H, td, *J*=7.8, 17.9 Hz), 1.03 (3H, t, *J*=7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 55.80; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.2, 138.1, 129.6, 129.3, 128.6, 128.4, 127.4, 126.5, 66.6 (d, J_{PC}=111.7 Hz), 61.0 (d, J_{PC}=7.5 Hz), 58.4, 53.3 (2 carbons), 35.0, 19.4 (d, J_{PC}=91.6 Hz), 16.6 (d, J_{PC}=5.8 Hz), 5.3 (d, J_{PC}=5.2 Hz); IR (KBr) 3167, 1029 cm^{-1}; EIMS *m*/*z* 452 (MH^+). Anal. Calcd for $C_{27}H_{34}NO_3P$: C, 71.82; H, 7.59. Found: C, 71.68; H, 7.59.

1.1.3. Ethyl (1*R*,2*S*)-2-(dibenzylamino)-1-hydroxy-3-phenylpropyl(ethyl)phosphinate (*anti*-3). This compound was obtained as a mixture of diastereomers in a ratio of 1:1. Mp 110–113°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.06 (15H, m), 4.26–4.10 (1H, m), 4.09–3.98 (2H, m), 3.89 (1H, d, *J*=14.1 Hz), 3.83 (1H, d, *J*=14.1 Hz), 3.70 (1H, d, *J*=14.1 Hz), 3.58 (1H, d, *J*=14.1 Hz), 3.40–3.36 (1H, m), 3.12–3.07 (2H, m), 1.84–1.59 (2H, m), 1.23 (1.5H, t, *J*=7.0 Hz), 1.19 (1.5H, t, *J*=7.0 Hz), 1.16 (1.5H, td, *J*=7.7, 17.4 Hz), 1.06 (1.5H, td, *J*=7.8, 17.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 54.61, 54.39; IR (KBr) 3261, 1045 cm^{-1}; EIMS *m*/*z* 360 (M^+-CH_2Ph). Anal. Calcd for $C_{27}H_{34}NO_3P$: C, 71.82; H, 7.59. Found: C, 71.41; H, 7.57.

1.2. The procedure for the hydrophosphinylation of 2a with ethyl ethylphosphinate in the presence of TMSCl and Et_3N

To a solution of ethyl ethylphosphinate (732 mg, 6.0 mmol) in CH_2Cl_2 (21 mL) was added TMSCl (0.76 mL, 6.0 mmol) and Et_3N (0.83 mL, 6.0 mmol) at 0°C and the mixture was stirred for 0.5 h at the same temperature. To this solution was added a solution of **2a** (4 mmol) in THF (4 mL) at 0°C and the mixture was stirred for 12 h at the same temperature. The mixture was poured into cold H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue. To a solution of the residue in THF (8 mL) was added 1 M THF solution of Bu_4NF (4.8 mL, 4.8 mmol) at 0°C. After stirring for 1 h at the same temperature, the mixture was poured into cold H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=1:1 to $CHCl_3$/MeOH=20:1) to give a mixture of *syn*-**3-A**, *syn*-**3-B** and *anti*-**3** (992 mg, 55%).

1.3. General procedure for the hydrophosphinylation of 2a,b with ethyl phosphinate in the presence of (*R*)-ALB

A mixture of anhydrous phosphinic acid (396 mg, 6.0 mmol) and triethyl orthoformate (3.0 mL, 18.0 mmol) was stirred for 1.5 h at room temperature. To this solution was added 4 mL of THF and 0.1 M THF solution of (*R*)-ALB (8.0 mL, 0.8 mmol), prepared from (*R*)-BINOL (458 mg, 1.6 mmol) and $LiAlH_4$ (30.4 mg, 0.8 mmol) in situ, and a solution of **2a**,**b** (4.0 mmol) in THF (8 mL) at −40°C under stirring. After stirring for 12 h at the same temperature, the mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=1:1 to AcOEt) to give *syn*-**4a**,**b** and *anti*-**4a**,**b**.

1.3.1. Ethyl (1*S*,2*S*)-(dibenzylamino)-1-hydroxy-3-phenylpropylphosphinate (*syn*-4a). This compound was obtained as a mixture of diastereomers in a ratio of 1:1. One of the diastereisomers is crystallized in another oily diastereisomer. Yield (987 mg, 58%); ^1H NMR (400 MHz, CD_3OD) δ 7.44–7.16 (15H, m), 7.15 (0.5H, d, *J*=561.7 Hz), 7.03 (0.5H, d, *J*=560.3 Hz), 4.28–4.18 (2H, m), 4.14–4.04 (2H, m), 3.89 (0.5H, m), 3.77–3.54 (3H, m), 3.42–3.36 (0.5H, m), 3.26–3.07 (1.5H, m), 2.88–2.83 (0.5H, m), 1.30 (3H, t, *J*=7.0 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 44.42, 40.09; IR (KBr) 3221, 1190 cm^{-1};

FABMS *m/z* 424 (MH^+). Anal. Calcd for $C_{25}H_{30}NO_3P$: C, 70.90; H, 7.14. Found: C, 71.08; H, 7.10.

1.3.2. Ethyl (1*R*,2*S*)-(dibenzylamino)-1-hydroxy-3-phenylpropylphosphinate (*anti*-4a). This compound was obtained as a mixture of diastereomers in a ratio of 1:1. One of the diastereisomers is crystallized in another oily diastereisomer. Yield (131 mg, 8%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.27–7.08 (15H, m), 6.68 (0.5H, d, J=549.5 Hz), 6.53 (0.5H, d, J=558.0 Hz), 4.42–4.34 (1H, m), 4.28–3.95 (2H, m), 3.91 (1H, d, J=12.3 Hz), 3.86 (1H, d, J=14.0 Hz), 3.78–3.70 (0.5 H, m), 3.60 (1H, d, J=14.3 Hz), 3.52 (1H, d, J=14.1 Hz), 3.49–3.44 (0.5H, m), 3.20–3.11 (1.5H, m), 2.99 (0.5H, dd, J=4.6, 14.3 Hz), 1.28 (1.5H, t, J=7.1 Hz), 1.18 (1.5H, t, J=7.0 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 40.66, 38.40; IR (KBr) 3267, 1197 cm^{-1}; FABMS *m/z* 424 (MH^+). Anal. Calcd for $C_{25}H_{30}NO_3P$: C, 70.90; H, 7.14. Found: C, 70.83; H, 7.12.

1.3.3. Ethyl (1*S*,2*S*)-(dibenzylamino)-1-hydroxy-4-methylpentylphosphinate (*syn*-4b). This compound was obtained as a mixture of diastereomers in a ratio of 1:1. Yield (788 mg, 51%); An oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.39–7.24 (10H, m), 7.12 (0.5H, d, J=558.6 Hz), 7.03 (0.5H, d, J=555.5 Hz), 4.27–4.17 (1H, m), 4.15–4.01 (2H, m), 3.79–3.53 (4H, m), 3.31–3.25 (0.5H, m), 3.17–3.12 (0.5H, m), 1.80–1.60 (2H, m), 1.39 (1.5H, t, J=7.1 Hz), 1.29 (1.5H, t, J=7.0 Hz), 1.23–1.19 (1H, m), 0.93 (1.5H, t, J=6.6 Hz), 0.85 (1.5H, d, J=6.5 Hz), 0.82 (1.5H, d, J=6.1 Hz), 0.79 (1.5H, d, J=6.5 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 43.64, 41.92; IR (neat) 3255, 1189 cm^{-1}; EIMS *m/z* 296 (M^+−HP(O)OEt). High resolution MS calcd for $C_{20}H_{26}NO$ (M^+−HP(O)OEt): 296.2014. Found: 296.2002.

1.3.4. Ethyl (1*R*,2*S*)-(dibenzylamino)-1-hydroxy-4-methylpentylphosphinate (*anti*-4b). This compound was obtained as a mixture of diastereomer in a ratio of 1:1. Yield (44 mg, 3%); An oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.38–7.24 (10H, m), 6.97 (0.5H, d with small splits, J=540.3 Hz), 6.94 (0.5H, d, J=542.3 Hz), 4.45–4.38 (1H, m), 4.24–4.10 (2H, m), 3.95 (2H, d, J=13.6 Hz), 3.47 (2H, d, J=13.6 Hz), 3.22–3.16 (1H, m), 1.97–1.88 (2H, m), 1.39 (1.5H, t, J=7.0 Hz), 1.33 (1.5H, t, J=7.0 Hz), 1.29–1.24 (1H, m), 0.94 (3H, d, J=6.7 Hz), 0.53 (1.5H, d, J=6.2 Hz), 0.51 (1.5H, d, J=6.3 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 40.32, 39.00; IR (neat) 3277, 1203 cm^{-1}; FABMS *m/z* 390 (MH^+). High resolution MS calcd for $C_{22}H_{32}NO_3P$ (MH^+): 390.2198. Found: 390.2175.

1.3.5. Ethyl (1*R*,2*S*)-(dibenzylamino)-1-hydroxy-3-phenylpropylphosphinate (*anti*-4a-A). This compound was obtained by recrystallization of *anti*-**4a** from EtOAc. Mp 149–150°C; $[\alpha]_D^{25}$=+13.7 (*c* 0.80, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.17–7.08 (15H, m), 6.68 (1H, d, J=549.5 Hz), 4.38–4.32 (1H, m), 4.11–3.98 (2H, m), 3.86 (2H, d, J=14.0 Hz), 3.52 (2H, d, J=14.1 Hz), 3.49–3.44 (1H, m), 3.12 (1H, dd, J=9.7, 14.3 Hz), 2.99 (1H, dd, J=4.6, 14.3 Hz), 1.28 (3H, t, J=7.1 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 40.66; ^{13}C NMR (100 MHz, CD_3OD) δ 141.4, 140.8, 131.0, 130.0, 129.1, 127.9, 127.1, 68.6 (d, J_{PC}=109.3 Hz), 64.5 (d, J_{PC}=7.9 Hz), 60.3 (d, J_{PC}=8.0 Hz), 55.3 (2 carbons), 34.4, 16.7 (d, J_{PC}=5.9 Hz); IR (KBr) 3271, 1197 cm^{-1}; FABMS *m/z* 424 (MH^+). Anal. Calcd for $C_{25}H_{30}NO_3P$: C, 70.90; H, 7.14. Found: C, 70.91; H, 7.17.

1.4. Crystal data for compound *anti*-4a-A

X-Ray crystal data of *anti*-**4a-A** were collected by Mac-Science MXC18 diffractometer. The structure was solved by a direct method using SIR92[16] and refined with a full matrix least-squares method. Molecular formula=$C_{25}H_{30}NO_3P$, M_r=423.50, Orthorhombic, space group=$P2_12_12_1$, a=16.725 (4) Å, b=12.170 (2) Å, c=11.434 (3) Å, V=2327.2 (9) Å^3, T=298 K, Z=4, D_x=1.208 mg m^{-3}, (Mo Kα)=0.71073 Å, μ=1.375 mm^{-1}, R=0.083 over 2658 independent reflections. Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC-160271. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

1.4.1. (1*R*,2*S*)-2-(Dibenzylamino)-1-[ethoxy(oxido)phosphino]-3-phenylpropyl acetate (5a). To a stirred solution of *anti*-**4a** (701 mg, 1.5 mmol) in CH_2Cl_2 (4.5 mL) was added Ac_2O (0.50 mL, 4.5 mmol), pyridine (0.38 mL, 4.7 mmol) and DMAP (18 mg, 0.15 mmol) at 0°C and the mixture was stirred for 3 h at room temperature. The mixture was poured into cold water and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=3:1 to 1:1) to give **5a** (650 mg, 93%). This compound was obtained as a mixture of diastereomer in a ratio of 1:1. An oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.25–7.13 (15H, m), 6.86 (0.5H, d with small splits, J=583.7 Hz), 6.70 (0.5H, d with small splits, J=579.8 Hz), 5.53–5.51 (1H, m), 4.08–3.97 (2H, m), 3.76 (1H, d, J=13.7 Hz), 3.75 (1H, d, J=13.7 Hz), 3.72–3.60 (1H, m), 3.56 (1H, d, J=13.7 Hz), 3.52 (1H, d, J=13.7 Hz), 3.25–3.18 (1H, m), 2.99–2.88 (1H, m), 2.03 (1.5H, s), 1.98 (1.5H, s), 1.21 (1.5H, t, J=7.0 Hz), 1.20 (1.5H, t, J=7.1 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 33.12, 32.96; IR (neat) 1748, 1219 cm^{-1}; EIMS *m/z* 374 (M^+−CH_2Ph). High resolution MS calcd for $C_{20}H_{25}NO_4P$ (M^+−CH_2Ph): 374.1521. Found: 374.1529.

1.4.2. (1*R*,2*S*)-2-(Dibenzylamino)-1-[ethoxy(oxido)phosphino]-4-methylpentyl acetate (5b). The compound **5b** was prepared from **4b** (1.56 g, 4.0 mmol) in an analogous manner to that for preparation of **5a**. Purification of the residue by column chromatography (hexane/EtOAc=3:1 to 1:1) gave **5b** (1.64 g, 95%). This compound was obtained as a mixture of diastereomers in a ratio of 1:1. An oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.36–7.25 (10H, m), 7.13 (0.5H, d with small splits, J=577.3 Hz), 7.02 (0.5H, d with small splits, J=569.9 Hz), 5.61–5.59 (1H, m), 4.23–4.09 (2H, m), 3.87 (1H, d, J=6.1 Hz), 3.83 (1H, d, J=6.1 Hz), 3.45–3.37 (3H, m), 2.20 (1.5H, s), 2.19 (1.5H, s), 1.97–1.93 (2H, m), 1.35 (1.5H, t, J=6.9 Hz), 1.32 (1.5H, t, J=7.0 Hz), 0.98 (1.5H, d, J=6.6 Hz), 0.97 (1.5H, d, J=6.6 Hz), 0.57 (1.5H, d, J=6.4 Hz), 0.56 (1.5H, d,

J=6.4 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 33.29, 32.58; IR (neat) 1747, 1219 cm^{-1}; EIMS m/z 432 (MH^+). High resolution MS calcd for $C_{24}H_{35}NO_4P$ (MH^+): 432.2303. Found: 432.2299.

1.4.3. (1*R*,2*S*)-2-(Dibenzylamino)-1-(dimethoxyphosphoryl)-3-phenylpropyl acetate (6a). A solution of **5a** (564 mg, 1.21 mmol), DMSO (0.1 mL, 1.45 mmol) and iodine (30 mg, 0.12 mmol) in THF (4 mL) was stirred for 5 h at 60°C. The mixture was evaporated to give a residue. To a stirred solution of the residue in CH_2Cl_2 (4 mL) was added TMSBr (0.4 mL, 3.03 mmol) and stirred for 12 h at room temperature. After the mixture was concentrated, the residue was dissolved in MeOH (4 mL) and stirred for 2 h at room temperature. Evaporation of the mixture gave a residue. To a stirred solution of the CH_2N_2 in Et_2O (25 mL), prepared from 70 % *N*-nitroso-*N*-methylurea (713 mg, 4.84 mmol), was added a solution of the residue in Et_2O/MeOH=10:1 (6.6 mL) at 0°C and the solution was stirred for 30 min at the same temperature. After decomposition of excess CH_2N_2 with AcOH (0.05 mL), the mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=2:1 to EtOAc) to give **6a** (63 mg, 11%). An oil; $[\alpha]_D^{25}$=+7.0 (c 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.01 (15H, m), 5.88 (1H, d with small splits, J=13.2 Hz), 3.84 (2H, d, J=13.8 Hz), 3.75 (3H, d, J=10.8 Hz), 3.65 (3H, d, J=10.6 Hz), 3.56–3.50 (1H, m), 3.31 (2H, d, J=13.8 Hz), 3.22 (1H, dd, J=3.4, 14.7 Hz), 3.01 (1H, dd, J=10.9, 14.7 Hz), 2.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 139.7, 138.7, 129.5, 128.7, 128.0, 126.8, 125.9, 65.5 (d, J_{PC}=162.2 Hz), 60.3, 58.0 (d, J_{PC}=5.7 Hz), 53.2 (d, J_{PC}=10.2 Hz), 53.1 (d, J_{PC}=10.7 Hz), 33.4, 21.0, 14.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.56; IR (neat) 1748, 1222 cm^{-1}; EIMS m/z 482 (MH^+). High resolution MS calcd for $C_{27}H_{31}NO_5P$ (M^+−H): 480.1939. Found: 480.1944.

1.4.4. (1*R*,2*S*)-2-(Dibenzylamino)-1-(dimethoxyphosphoryl)-4-methylpentyl acetate (6b). The compound **6b** was prepared from **5b** (1.70 g, 4.0 mmol) in an analogous manner to that for preparation of **6a**. Purification of the residue by column chromatography (hexane:EtOAc=3:1 to 1:1) gave **6b** (126 mg, 7%). An oil; $[\alpha]_D^{25}$=−35.0 (c 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.21 (10H, m), 5.86 (1H, d, J=13.8 Hz), 3.82 (2H, d, J=13.4 Hz), 3.74 (3H, d, J=10.7 Hz), 3.67 (3H, d, J=10.6 Hz), 3.24 (2H, d, J=13.4 Hz), 3.21–3.18 (1H, m), 2.15 (3H, s), 1.99–1.88 (1H, m), 1.81–1.74 (1H, m), 1.45–1.38 (1H, m), 0.93 (3H, d, J=6.8 Hz), 0.43 (3H, d, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 139.4, 129.2, 128.1, 127.0, 126.8, 65.5 (d, J_{PC}=161.5 Hz), 54.0 (d, J_{PC}= 5.9 Hz), 53.3, 53.0 (d, J_{PC}=6.5 Hz), 52.9 (d, J_{PC}=7.2 Hz), 36.3, 24.0, 20.9, 20.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.94; IR (neat) 1748, 1223 cm^{-1}; EIMS m/z 448 (MH^+). High resolution MS calcd for $C_{24}H_{35}NO_5P$ (MH^+): 448.2252. Found: 448.2208.

1.4.5. (1*R*,2*S*)-2-(Dibenzylamino)-1-(diethoxyphosphoryl)-3-phenylpropyl acetate (8a). To a stirred solution of **7a** (7.81 g, 19.2 mmol) in CH_2Cl_2 (58 mL) was added Ac_2O (7.5 mL, 57.6 mmol), pyridine (4.6 mL, 59.5 mmol) and DMAP (234 mg, 1.9 mmol) at 0°C and the mixture was stirred for 3 h at room temperature. The mixture was poured into cold water and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=4:1 to 2:1) to give **8a** (7.31 g, 75%). An oil; $[\alpha]_D^{26}$=+4.3 (c 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–6.99 (15H, m), 5.89 (1H, d with small splits, J=13.3 Hz), 4.14–4.06 (4H, m), 3.99–3.93 (1H, m), 3.86 (2H, d, J=13.9 Hz), 3.57–3.52 (1H, m), 3.30 (2H, d, J=13.9 Hz), 3.00 (1H, dd, J=11.2, 14.7 Hz), 2.20 (3H, s), 1.30 (3H, t, J=7.1 Hz), 1.22 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 139.8, 138.9, 129.6, 128.7, 128.0, 126.8, 125.9, 65.3 (d, J_{PC}=162.6 Hz), 62.7 (d, J_{PC}=5.3 Hz, 2 carbons), 58.0 (d, J_{PC}=6.0 Hz), 53.1 (2 carbons), 33.5, 21.1, 16.4 (d, J_{PC}=5.7 Hz), 16.3 (d, J_{PC}=5.7 Hz), 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.13; IR (neat) 1749, 1222 cm^{-1}; EIMS m/z 510 (MH^+). High resolution MS calcd for $C_{29}H_{36}NO_5P$ (M^+): 509.2331. Found: 509.2349.

1.4.6. (1*R*,2*S*)-2-(Dibenzylamino)-1-(diethoxyphosphoryl)-4-methylpentyl acetate (8b). The compound **8b** was prepared from **7b** (1.23 g, 2.8 mmol) in an analogous manner to that for preparation of **8a**. Purification of the residue by column chromatography (hexane/EtOAc=3:1 to 1:1) gave **8b** (929 mg, 70%). An oil; $[\alpha]_D^{26}$=−37.7 (c 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (10H, m), 5.85 (1H, d, J=13.6 Hz), 4.15–4.06 (4H, m), 4.02–3.94 (1H, m), 3.82 (2H, d, J=13.4 Hz), 3.24 (2H, d, J=13.4 Hz), 2.15 (3H, s), 1.99–1.89 (1H, m), 1.81–1.74 (1H, m), 1.51–1.44 (1H, m), 1.30 (3H, t, J=7.1 Hz), 1.24 (3H, t, J=7.1 Hz), 0.93 (3H, d, J=6.8 Hz), 0.42 (3H, d, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 139.6, 129.4, 129.2, 128.1, 127.0, 65.8 (d, J_{PC}=162.3 Hz), 62.6 (2 carbons, d, J_{PC}=6.9 Hz), 54.1 (d, J_{PC}=5.7 Hz), 53.2, 36.3, 24.2, 24.0, 21.0, 20.8, 20.6, 16.5 (d, J_{PC}=5.8 Hz), 16.4 (d, J_{PC}=6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.51; IR (neat) 1749, 1224 cm^{-1}; EIMS m/z 476 (MH^+). High resolution MS calcd for $C_{26}H_{38}NO_5P$ (M^+): 475.2487. Found: 475.2473.

1.4.7. (1*R*,2*S*)-2-(Dibenzylamino)-1-(dimethoxyphosphoryl)-3-phenylpropyl acetate (6a). To a stirred solution of **8a** (1.22 g, 2.4 mmol) in CH_2Cl_2 (8 mL) was added TMSBr (1.7 mL, 9.6 mmol) and stirred for 12 h at room temperature. After the mixture was concentrated, the residue was dissolved in MeOH (11 mL) and stirred for 2 h at room temperature. Evaporation of the mixture gave a residue. To a stirred solution of the CH_2N_2 in Et_2O (54 mL), prepared from 70% *N*-nitroso-*N*-methylurea (1.40 g, 9.6 mmol), was added a solution of the residue in Et_2O/MeOH=10:1 (14.9 mL) at 0°C and the solution was stirred for 30 min at the same temperature. After decomposition of excess CH_2N_2 with AcOH (0.1 mL), the mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=2:1 to EtOAc) to give **6a** (702 mg, 61%). $[\alpha]_D^{25}$=+7.9 (c 0.96, $CHCl_3$). The ^{1}H NMR spectrum was identical with that of the authentic sample prepared from *anti*-**4a**.

1.4.8. (1*R*,2*S*)-2-(Dibenzylamino)-1-(dimethoxyphosphoryl)-4-methylpentyl acetate (6b). The compound **6b** was prepared from **8b** (784 mg, 1.7 mmol) in an analogous manner to that for preparation of **6a**. Purification of the residue by column chromatography (hexane/EtOAc=3:1–1:1) gave **6b** (406 mg, 55%). $[\alpha]_D^{25}=-36.9$ (*c* 0.70, $CHCl_3$). The ^1H NMR spectrum was identical with that of the authentic sample prepared from *anti*-**4b**.

1.4.9. (1*R*,2*S*)-2-(Dibenzylamino)-1-hydroxy-3-phenylpropyl(ethyl)phosphinic acid (9). To a stirred solution of *anti*-**3** (187 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) was added TMSBr (0.11 mL, 0.82 mmol) at 0°C and the mixture was stirred for 12 h at room temperature. After the mixture was concentrated, the residue was dissolved in MeOH (1 mL) and stirred for 1 h at room temperature. Evaporation of the solvent gave **9** (161 mg, 93%). Amorphous; $[\alpha]_D^{25}=+23.2$ (*c* 0.69, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 7.61–6.89 (15H, m), 4.97–4.88 (1H, m), 4.56–4.46 (1H, m), 4.42 (1H, dd, *J*=5.3, 9.4 Hz), 4.32–4.21 (1H, m), 4.15–4.06 (1H, m), 4.05–3.97 (1H, m), 3.58 (1H, dd, *J*=4.5, 15.8 Hz), 3.51 (1H, dd, *J*=7.2, 15.8 Hz), 1.83–1.70 (1H, m), 1.50–1.37 (1H, m), 1.01 (3H, td, *J*=7.7, 18.2 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 56.02; ^{13}C NMR (100 MHz, CD_3OD) δ 138.7, 132.2, 131.7, 131.2, 131.1, 130.6, 130.3, 130.2, 128.6, 65.4 (d, J_{PC}=108.3 Hz), 65.2 (d, J_{PC}=5.5 Hz), 56.8, 55.8, 31.8 (d, J_{PC}=7.5 Hz), 19.3 (d, J_{PC}=90.9 Hz), 5.1 (d, J_{PC}=5.8 Hz); IR (KBr) 3208, 1149 cm^{-1}. FABMS *m*/*z* 424 (MH^+). High resolution MS calcd for $C_{25}H_{31}NO_3P$ (MH^+): 424.2041. Found: 424.2035.

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References

1. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, Jr., E. W. *J. Med. Chem.* **1995**, *38*, 4557.
2. Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625.
3. (a) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926. (b) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104. (c) Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666 and references cited therein.
4. Yamagishi, T.; Yokomatsu, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1999**, *55*, 12125.
5. Froestl, W.; Mickel, S. J.; Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maître, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313.
6. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
7. Fitch, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 61.
8. Preliminary communication of this work: Yamagishi, T.; Suemune, K.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **2001**, *42*, 5033.
9. ^{31}P NMR spectroscopic analysis has been successfully applied to determine the diastereomeric excess of chiral phosphonate derivatives. See: (a) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527. (b) Hammerschmidt, F.; Li, Y.-F. *Tetrahedron* **1994**, *50*, 10253. (c) Kozlowski, J. K.; Rath, N. P.; Spilling, C. D. *Tetrahedron* **1995**, *51*, 6385.
10. In our earlier study, the reaction of **2a** with diethyl *t*-butyldimethylsilylphosphite gave *anti*-β-amino-α-hydroxyphosphonate with modest selectivity (*syn*/*anti*=1:2.8). See: Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1401.
11. The moderate yield of products might be due to partial hydrolysis of the ethyl phosphinate functionality during the work up.
12. We confirmed that the ratio of *anti*-**4a-B** to *anti*-**4a-A** was not changed after refluxing a solution of *anti*-**4a** in ethyl acetate for 4 h. Thus, there was no possibility of epimerization from *anti*-**4a-B** to *anti*-**4a-A** in the recrystallization.
13. Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1995**, *60*, 6656.
14. McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, *18*, 155.
15. Yamagishi, T. PhD Thesis, Tokyo University of Pharmacy and Life Science, 1997.
16. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Olidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435.