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A chemo-enzymatic synthesis of optically active 1,1-diethoxyethyl(aminomethyl)phosphinates: useful chiral building blocks for phosphinyl dipeptide isosteres

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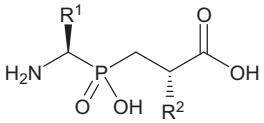
ABSTRACT

The kinetic resolution of 1,1-diethoxyethyl(hydroxymethyl)phosphinate possessing chirality at the phosphorus atom was achieved via a lipase-catalyzed acylation. The product was transformed into the corresponding imine, which in turn is a useful starting material for the preparation of phosphinyl dipeptide isosteres.

1. Introduction

Several studies have demonstrated that the synthesis of peptides with phosphinyl dipeptide isosteres can be a very effective approach for the development of highly potent and selective inhibitors of various aspartic proteases and Zn metalloproteases (Fig. 1).[1] Phosphinyl dipeptide isosteres contain the metabolically stable phosphinic moiety, $NH_2XaaΨ[P(O)OHCH_2]XaaOH$, which mimics the transition state for the tetrahedral geometry of a scissile peptide bond during enzymatic hydrolysis. Although the stereochemistry of phosphinyl dipeptide isosteres affect their biological activities,[2] the number of methods for preparing phosphinyl dipeptide isosteres in a highly stereocontrolled manner are rare.[3]



phosphinyl dipeptide isosteres

Figure 1.

Recent reports demonstrated that racemic phosphinyl dipeptide isosteres could be efficiently prepared in a protected form and in a highly diastereoselective manner starting from ethyl 1,1-diethoxyethyl(aminomethyl)phosphinate **1**[4,5] (Scheme 1). In our method, the α-substituent (R^1) of the phosphinyl dipeptide isosteres was introduced via a stereoselective alkylation of the phosphorus-stabilized carbanion generated from **1**.[4] The β′-substituent (R^2) was also stereoselectively incorporated via the alkylation of the lithium enolates generated from **4**,[5] which was prepared by the stereospecific Michael reaction of stereodefined *H*-phosphinate **3**, readily available from **2**, with an acrylate derivative (Scheme 1). We have proven that two stereogenic centers at the α- and β′-positions are highly controlled under the influence of the phosphorus chirality.[4,5] This means that the asymmetric synthesis of phosphinyl dipeptide isosteres would be feasible through the same sequence utilizing optically active 1,1-diethoxyethyl(aminomethyl)phosphinate **1**.

In our studies on the asymmetric synthesis of phosphinyl dipeptide isosteres, we have previously elucidated that optically active (R_P)-**1**, leading to phosphinyl dipeptide isosteres possessing a definite absolute configuration, could be prepared from (*S*)-phenylethylamine (*S*)-**6** as shown in Scheme 2.[6] However, this method requires the careful separation of diastereomeric intermediates (S,R_P)-**7** and (S,S_P)-**7** by silica gel column chromatography and was thus unsuitable for a larger scale synthesis of (R_P)-**1**.

In order to develop a more facile method applicable to a larger scale synthesis of optically active 1,1-diethoxyethyl(aminomethyl)phosphinate **1**, we examined a chemo-enzymatic route as shown in Scheme 3, in which the lipase-catalyzed acyl transfer reaction of hydroxymethylphosphinate derivative **8** was applied as a key reaction and the resulting optically active alcohols were chemically transformed into the target aminomethylphosphinates. Although the lipase-catalyzed acyl transfer reaction has been utilized as a concise and elegant method to prepare optically active secondary and primary alcohol derivatives bearing an asymmetric center at the carbon atom,[7] this approach has rarely been applied to obtain optically active hydroxymethylphosphinate derivatives.[8,9] However, a highly efficient resolution of **8** is feasible, since several reports by Kielbasinski et al. have shown that some lipases catalyze the acylation of a primary hydroxy group as discriminating

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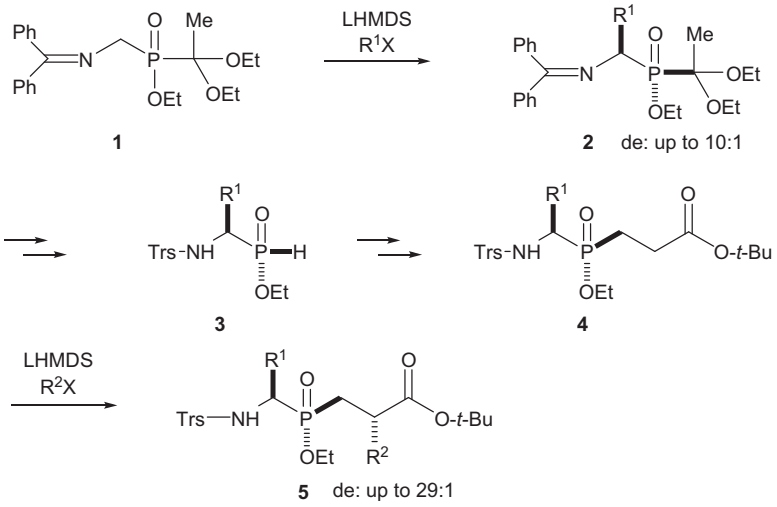
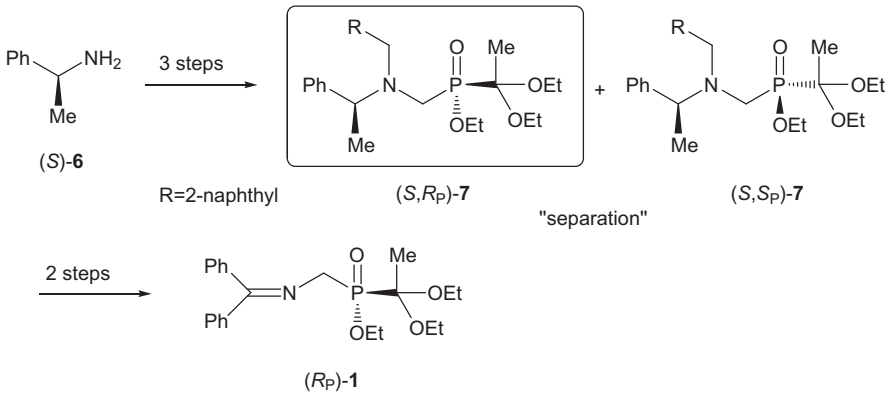
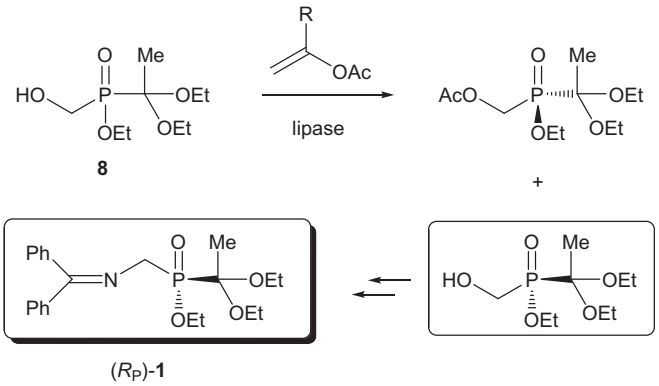


Scheme 1. Stereocontrolled synthesis of phosphinyl dipeptide isosteres.



Scheme 2.

asymmetric environment of the remote phosphorus chirality.[8] Herein, we fully describe the details of our results (Scheme 3).

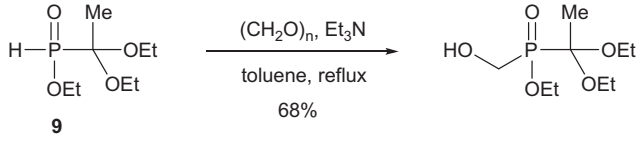


Scheme 3. Chemo-enzymatic strategy for the synthesis of optically active 1,1-diethoxyethyl(aminomethyl)phosphinate (R_p)-**1**.

2. Results and discussion

2.1. Acyl transfer reaction of racemic substrate 8

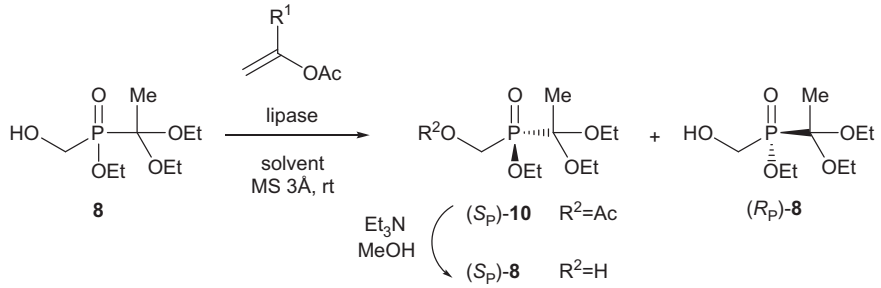
The requisite starting material **8** was readily prepared by the addition of 1,1-diethoxyethyl-*H*-phosphinate **9**[10] to paraformaldehyde in the presence of Et_3N according to the procedure in the literature[8b] (Scheme 4).



Scheme 4.

Acyl transfer reactions of **8** were examined under several conditions and the results are shown in Table 1. First, **8** was acylated with vinyl acetate as an acyl donor in the presence of lipase AK (*Pseudomonas fluorescens*) and molecular sieves 3 Å (MS 3 Å) in *i*-Pr_2O (0.012 M solution of **8**) at room temperature according to the procedure of Shioji et al.[9a] We expected the reaction would proceed efficiently by adding MS 3 Å because the water contents in the reaction system were found to affect the activity of lipase.[11] The reaction reached near to 50% conversion after 8 h as evidenced by TLC monitoring, giving acetate (S_P)-**10** and alcohol (R_P)-**8** in 49% and 31% yields, respectively (entry 1). These compounds could be easily isolated by silica gel column chromatography. The acetyl group of (S_P)-**10** was removed by treatment with Et_3N in MeOH to afford alcohol (S_P)-**8**. While the enantiomeric purity of (S_P)-**8** was modest (70% ee), (R_P)-**8** showed excellent enantiomeric purity (99% ee). From these data, the enantiomeric ratio (E)[12] was

Table 1
Lipase-catalyzed acylation of **8**[a]



Entry	Solvent	Lipase	Time (h)	R^1	Yield % (ee%)[b] of (S_P)-**15**	Yield % (ee%)[b] of (R_P)-**8**	*E* value[c]
1	*i*-Pr_2O	AK	8	H	49 (70)	31 (99)	28
2	CPME	AK	9	H	51 (77)	38 (74)	17
3	*c*-Hexane	AK	6	H	41 (89)	46 (87)	49
4	Hexane	AK	7	H	54 (77)	32 (99)	39
5	Hexane	PS	9	H	27 (47)	62 (76)	6
6	Hexane	AK	19	Me	50 (88)	40 (99)	82

[a] All reactions were carried out in a 0.012 M solution of **8**.
[b] Determined by ^{1}H NMR (300 MHz, $CDCl_3$) analysis of the corresponding (*R*)- and (*S*)-MTPA esters.
[c] Determined by Sih's equation.[12]

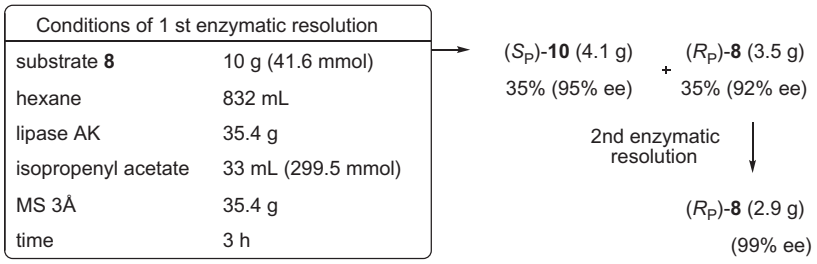
determined to be 28. In an attempt to improve the *E* value, the solvent effect on the enantioselectivity was examined. This survey revealed that employing nonpolar solvents led to relatively good results (entries 2–4). Although the *E*-value decreased in the case of *c*-pentylmethylether (CPME),[13] a replaceable solvent for THF, employing *c*-hexane and hexane improved the selectivity up to *E* = 49 and *E* = 39, respectively. Using lipase AK was crucial for high enantioselectivity, as a reaction employing lipase PS (*Pseudomonas cepacia*) resulted in low selectivity (entry 5). In some lipase-catalyzed resolutions, the acetaldehyde generated from the vinyl acetate is known to disturb reactions by forming Schiff bases[14] with the enzymes or forming hemiacetals with the substrate alcohols.[15] In order to avoid these undesired reactions, isopropenyl acetate was employed next in place of vinyl acetate as an acyl donor for the lipase AK-catalyzed acylation (entry 6). We expected that relatively unreactive acetone was formed and the undesired reaction would be suppressed. While the reaction proceeded slowly, the desired (S_P)-**10** and (R_P)-**8** were obtained in 50% and 40% yields, respectively, after 19 h. The *E* value of this reaction was determined to be 82 and these conditions were found to yield the best results.

2.2. A larger scale synthesis of (R_p)-8

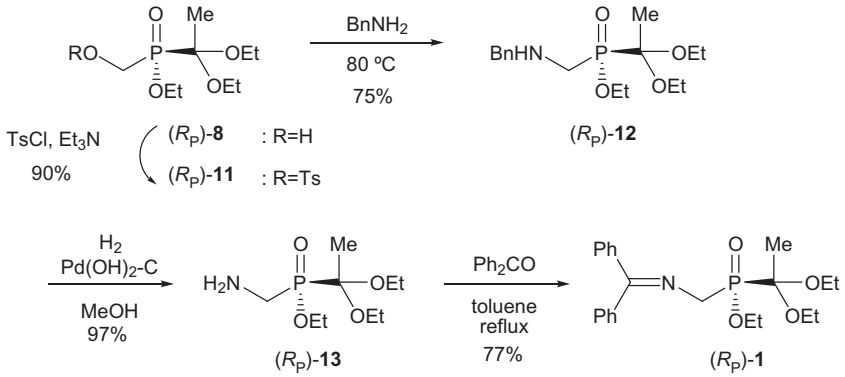
Having established good conditions for the lipase AK-catalyzed acylation of **8** and the substrate specificity on a small scale, we next focused our attention onto the resolution of **8** on a larger scale. For these studies, reducing the volume of the solvent used was highly desirable from an economic point of view and ease of reaction. We found that the substrate concentration could be increased to a 0.05 M solution of **8** without a significant loss of enantiomeric purity of yield for (S_P)-**10** and (R_P)-**8** on a 10 g scale. When the reaction was carried out at a substrate concentration of 0.1 M, the acylation proceeded rapidly to give acetate (S_P)-**15** in 67% yield after 3 h. A typical protocol is shown in Scheme 5. In this protocol, 10 g of **8** were acylated with isopropenyl acetate (33 mL) in hexane (899 mL) in the presence of lipase AK (35.4 g) and MS 3 Å (35.4 g) to give 4.1 g of (S_P)-**15** (35% yield, 95% ee) and 3.5 g of (R_P)-**8** (35% yield, 92% ee), respectively. The enantiomeric purity of (R_P)-**8** was increased to 99% ee by an enzymatic double resolution under the same conditions. Thus, using this protocol, we obtained 2.9 g of (R_P)-**8** with high enantiomeric excess from racemic **8** (10 g).

2.3. Transformation of (R_P)-8 to the target compound

To convert alcohol (R_P)-**8** into the required imine (R_P)-**1**, tosylate (R_P)-**11** was prepared under conventional conditions (Scheme 6). When the nucleophilic substitution of (R_P)-**11** was performed with NaN_3 in DMF at 90 °C, the desired azide was obtained in poor yield (25%). However, the treatment of (R_P)-**11** with benzylamine at 90 °C in solvent-free conditions gave (R_P)-**12** in 75% yield. Thus, the preparation of (R_P)-**1** was accomplished from (R_P)-**12** by the sequential removal of the benzyl group and the formation of an imine with benzophenone. The absolute configuration of (R_P)-**1** was verified by comparison of the specific rotation with the



Scheme 5.



Scheme 6.

reported value.[6] At this stage, based on these results, the absolute configuration of alcohol (R_P)-**8** was deduced. This sequence was also applied to the synthesis of (S_P)-**1** from (S_P)-**8** (see Section 4).

3. Conclusion

In conclusion, we have developed a new and practical method to prepare optically active aminomethylphosphinate (R_P)-**1**, a useful chiral building block for phosphinyl dipeptide isosteres, via the lipase AK-catalyzed kinetic resolution of hydroxymethylphosphinate **8** bearing P-chirality. This method was applicable on a 10 g scale resolution, resolving the issues of our previous methodology. The practical preparation of optically active phosphinyl dipeptide isostere derivatives is ongoing.

4. Experimental

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FTIR-620. Mass spectra were measured on Micromass LCT and Micromass Autospec by electrospray ionization. NMR spectra were obtained on Bruker DPX400 NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C. ^{31}P NMR spectra were obtained on Varian Mercury-300BB instrument operating at 122 MHz. The chemical shift data for each signal on ^{1}H NMR (400 MHz) are expressed as relative ppm from $CHCl_3$ (δ 7.26) or CH_3OH (δ 3.30). The chemical shifts of ^{13}C are reported relative to $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ = 0) with broadband ^{1}H decoupling. Optical rotations were measured with a JASCO P1030 digital polarimeter. Column chromatography was carried out using 63–210 μm Silica Gel 60N (Kanto Chemical Co., Inc.).

4.1. Ethyl 1,1-diethoxyethyl(hydroxymethyl)phosphinate 8

A solution of **9** (7.04 g, 33.5 mmol), Et_3N (2.33 mL, 167.6 mmol) and paraformaldehyde (5.03 g, 167.6 mmol) in toluene (67.0 mL) was stirred for 8 h at 100 °C. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/AcOEt = 1:1 to AcOEt) to give **8** (5.47 g, 68%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.22 (2H, dq, J = 7.1, 7.1 Hz), 4.02 (2H, d, J = 14.7 Hz), 3.91 (2H, dd, J = 3.4, 14.7 Hz), 3.74–3.59 (4H, m), 1.53 (3H, d, J = 11.0 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.18 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.7 (d, J_{CP} = 136.0 Hz), 62.3 (d, J_{CP} = 7.5 Hz), 58.5 (d, J_{CP} = 4.8 Hz), 58.1 (d, J_{CP} = 93.1 Hz), 57.8 (d, J_{CP} = 6.9 Hz), 20.3 (d, J_{CP} = 11.1 Hz), 16.7 (d, J_{CP} = 5.2 Hz), 15.5, 15.3; ^{31}P NMR (122 MHz, $CDCl_3$) δ: 42.87; IR (neat) 3156, 1151, 1037 cm^{-1}; MS m/z 263 (MNa^+); HRMS Calcd for $C_9H_{21}O_5PNa$: 263.1024 (MNa^+). Found: 263.1013.

4.2. (S_P)-Ethyl acetoxymethyl(1,1-diethoxyethyl)phosphinate (S_P)-10 and (R_P)-ethyl hydroxymethyl(1,1-diethoxyethyl)-phosphinate (R_P)-8

To a suspension of MS 3 Å (850 mg) in hexane (85 mL) were added **8** (240 mg, 1 mmol), lipase AK (850 mg), and vinyl acetate (0.72 mL, 7.2 mmol) and stirred for 7 h at room temperature. The mixture was filtered through a pad of Celite and the filtrate was concentrated to give a residue, which was purified by column chromatography (hexane/AcOEt = 1:1 to AcOEt) to give (S_P)-**10** (155.5 mg, 54%, 77% ee) and (R_P)-**8** (79.4 mg, 32%, 99% ee).

(S_P)-**10**: A colorless oil; $[\alpha]_D^{20} = +6.1$ (c 1.2, $CHCl_3$) for a sample of 77% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.47 (1H, dd, J = 7.2, 14.3 Hz), 4.36 (1H, d, J = 7.2, 14.3 Hz), 4.21 (2H, dq, J = 7.1, 7.1 Hz), 3.74–3.60 (4H, m), 2.09 (3H, s), 1.51 (3H, d, J = 11.5 Hz), 1.31 (3H, t, J = 7.1 Hz), 1.17 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1(d, J_{CP} = 7.0 Hz), 101.1 (d, J_{CP} = 145.4 Hz), 62.3 (d, J_{CP} = 7.2 Hz), 58.4 (d, J_{CP} = 5.4 Hz), 58.0 (d, J_{CP} = 7.3 Hz), 57.9 (d, J_{CP} = 100.1 Hz), 20.7, 20.4 (d, J_{CP} = 12.1 Hz), 16.7 (d, J_{CP} = 5.0 Hz), 15.5, 15.3; ^{31}P NMR (122 MHz, $CDCl_3$) δ: 38.35; IR (neat) 1753, 1158, 1038 cm^{-1}; MS m/z 305 (MNa^+); HRMS Calcd for $C_{11}H_{23}O_6PNa$: 305.1130 (MNa^+). Found: 305.1132.

(R_P)-**8**: A colorless oil; $[\alpha]_D^{20} = -11.8$ (c 0.4, $CHCl_3$) for a sample of 99% ee; the ^{1}H NMR spectrum of was identical to that of **9**.

4.3. (S_P)-Ethyl hydroxymethyl(1,1-diethoxyethyl)phosphinate (S_P)-8

To a solution of (S_P)-**10** (61.5 mg, 0.22 mmol) in MeOH (5.4 mL) was added Et_3N (1.1 mL, 7.85 mL) and stirred for 12 h at room temperature. The mixture was concentrated to give a residue, which was purified by column chromatography (hexane/AcOEt = 3:1 to AcOEt) to give (S_P)-**8** (48.3 mg, 92%). The ^{1}H NMR spectrum was identical to that of **8**.

4.4. The (*R*)-MTPA ester of (R_P)-8

To a stirred suspension of (*R*)-MTPA (26.8 mg, 0.125 mmol), DCC (25.8 mg, 0.125 mmol), and DMAP (1.5 mg, 0.012 mmol) in CH_2Cl_2 (0.35 mL) was added a solution of (R_P)-**8** (15 mg, 0.062 mmol) in CH_2Cl_2 (0.7 mL) and stirred at room temperature until the starting material disappeared by TLC monitoring. The mixture was poured into 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 filtered through

a pad of silica gel (AcOEt) and the filtrate was concentrated to give (*R*)-MTPA ester of (R_P)-**8** as a white oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55–7.38 (5H, m), 4.74 (1H, dd, J = 5.7, 14.2 Hz), 4.64 (1H, dd, J = 4.5,14.2 Hz), 4.22–4.15 (2H, m), 3.74–3.57 (7H, m), 1.43 (3H, d, J = 11.8 Hz), 1.28 (3H, t, J = 7.1 Hz), 1.16 (6H, t, J = 7.0 Hz); ^{31}P NMR (122 MHz, $CDCl_3$) δ: 37.66.

4.5. The (*S*)-MTPA ester of (R_P)-8

This compound was prepared from (*S*)-MTPA (26.8 mg, 0.125 mmol) in an analogous manner to that for the (*R*)-MTPA ester of (R_P)-**8** and was obtained as a white oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55–7.39 (5H, m), 4.83 (1H, dd, J = 6.9, 14.1 Hz), 4.52 (1H, dd, J = 3.8,14.1 Hz), 4.23–4.11 (2H, m), 3.78–3.16 (7H, m), 1.46 (3H, d, J = 11.7 Hz), 1.28 (3H, t, J = 7.1 Hz), 1.17 (6H, t, J = 7.0 Hz); ^{31}P NMR (122 MHz, $CDCl_3$) δ: 36.83.

4.6. A larger scale synthesis of (R_P)-8

To a suspension of MS 3 Å (35.4 g) in hexane (832 mL) were added **8** (10 g, 41.6 mmol), lipase AK (35.4 g), and isopropenyl acetate (33 mL, 299.5 mmol) and stirred for 3 h at room temperature. The mixture was filtered through a pad of Celite and the filtrate was concentrated to give a residue, which was purified by column chromatography (hexane/AcOEt = 1:1 to AcOEt) to give (S_P)-**10** (4.1 g, 35%, 95% ee) and (R_P)-**8** (3.5 g, 35%, 92% ee). To a suspension of the obtained (R_P)-**8** (3.5 g, 14.6 mmol) and MS 3 Å (12.4 g) in hexane (292 mL) was added lipase AK (12.4 g), isopropenyl acetate (11.4 mL, 105.1 mmol) and then stirred for 2 h at room temperature as a 2nd enzymatic resolution. Purification in an analogous manner to that of the aforementioned 1st enzymatic resolution gave (R_P)-**8** (2.9 g, 99% ee).

4.7. (R_P)-[(1,1-Diethoxyethyl)(ethoxy)phosphoryl]methyl 4-methylbenzenesulfonate (R_P)-11

To a solution of (R_P)-**8** (480 mg, 2 mmol) in CH_2Cl_2 (9.6 mL) were added Et_3N (0.42 mL, 2.4 mmol), DMAP (24.4 mg, 0.2 mmol) and TsCl (475.6 mg, 2.4 mmol) and the mixture was stirred for 3.5 h at room temperature. The mixture was then poured into 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 purified by column chromatography (hexane/AcOEt = 10:1 to hexane/AcOEt = 1:1) to give (R_P)-**11** (710.3 mg, 90%) as a colorless oil; $[\alpha]_D^{20} = -17.7$ (*c* 0.6, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 4.30 (2H, dd, J = 4.5, 13.0 Hz), 4.21–4.14 (2H, m), 3.73–3.54 (4H, m), 2.43 (3H, s), 1.49 (3H, d, J = 11.7 Hz), 1.30 (3H, t, J = 7.0 Hz), 1.15 (3H, t, J = 6.6 Hz), 1.13 (3H, t, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.5–128.4 (aromatic), 101.0 (d, J_{CP} = 149.9 Hz), 62.7 (d, J_{CP} = 7.5 Hz), 61.9 (d, J_{CP} = 95.3 Hz), 58.6 (d, J_{CP} = 5.6 Hz), 58.1 (d, J_{CP} = 7.7 Hz), 21.8, 20.5 (d, J_{CP} = 11.9 Hz), 16.6 (d, J_{CP} = 4.8 Hz), 15.4, 15.3; ^{31}P NMR (122 MHz, $CDCl_3$) δ: 35.89; IR (neat) 1370, 1180, 1034 cm^{-1}; MS *m/z* 417 (MNa^+); HRMS Calcd for $C_{16}H_{27}O_7PSNa$: 417.1113 (MNa^+). Found: 417.1112.

4.8. (S_P)-[(1,1-Diethoxyethyl)(ethoxy)phosphoryl]methyl 4-methyl benzenesulfonate (S_P)-11

This compound was prepared from (S_P)-**8** with 95% ee (5.30 g, 22.1 mmol) in an analogous manner to that for (R_P)-**11**. Purification of the residue by column chromatography (hexane/AcOEt = 10:1 to hexane/AcOEt = 1:1) gave (S_P)-**11** (8.44 g, 97%) as a colorless oil; $[\alpha]_D^{20} = +16.9$ (*c* 0.2, $CHCl_3$); The ^{1}H NMR spectrum was identical to that of (R_P)-**11**.

4.9. (R_P)-Ethyl (benzylamino)methyl(1,1-diethoxyethyl)-phosphinate (R_P)-12

A solution of (R_P)-**11** (154.4 mg, 0.39 mmol) in benzylamine (0.39 mL, 3.57 mmol) was stirred for 4 h at 80 °C, followed by cooling to room temperature. The mixture was poured into 2 M NaOH and extracted with AcOEt. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by column chromatography (hexane/AcOEt = 1:1 to AcOEt) to give (R_P)-**12** (96.8 mg, 75%). $[\alpha]_D^{20} = -20.8$ (*c* 0.7, $CHCl_3$); the ^{1}H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[6]

4.10. (S_P)-Ethyl (benzylamino)methyl(1,1-diethoxyethyl)-phosphinate (S_P)-12

This compound was prepared from (S_P)-**11** (8.44 g, 21.4 mmol) in an analogous manner to that for (R_P)-**12**. Purification of the residue by column chromatography (hexane/AcOEt = 1:1 to AcOEt) gave (S_P)-**12** (5.47 g, 78%), $[\alpha]_D^{20} = +20.0$ (*c* 0.2, $CHCl_3$); the ^{1}H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[6]

4.11. (R_P)-Ethyl aminomethyl(1,1-diethoxyethyl)phosphinate (R_P)-13

To a solution of (R_P)-**12** (19.5 g, 59.1 mmol) in MeOH (592 mL) was added 20% $Pd(OH)_2$–C (1.83 g) and stirred for 6 h at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue. To a solution of the residue in CH_2Cl_2 (648 mL) was added Et_3N (13.4 mL, 13 mmol) and the mixture was stirred for 30 min at room temperature. To the mixture was added Et_2O (194 mL) and the resulting crystal was removed by filtration. The filtrate was concentrated to give (R_P)-**13** (13.7 g, 97%). $[\alpha]_D^{20} = -21.8$ (*c* 0.7, $CHCl_3$); the ^{1}H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[6]

4.12. (S_P)-Ethyl aminomethyl (1,1-diethoxyethyl)phosphinate (S_P)-13

This compound was prepared from (S_P)-**12** (5.47 g, 16.6 mmol) in an analogous manner to that for (R_P)-**13**. Purification of the residue gave (S_P)-**13** (3.8 g, 96%); $[\alpha]_D^{20} = +20.8$ (*c* 0.2, $CHCl_3$); the ^{1}H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[6]

4.13. (R_P)-Ethyl 1,1-diethoxyethyl{[(diphenylmethylene)-amino]methyl}phosphinate (R_P)-1

A suspension of (R_P)-**13** (4 g, 8.4 mmol) and benzophenone (3.36 g, 18.4 mmol) in toluene (43 mL) was heated at reflux for 12 h with the azeotropic removal of water in a Dean-Stark trap. The mixture was cooled to room temperature and concentrated to give a residue, which was purified by flash column chromatography ($CHCl_3$) to give (R_P)-**1** (5.2 g, 77%); $[\alpha]_D^{20} = -17.2$ (*c* 0.8, $CHCl_3$); the ^{1}H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[6]

4.14. (S_P)-Ethyl 1,1-diethoxyethyl{[(diphenylmethylene)-amino]methyl}phosphinate (S_P)-1

This compound was prepared from (S_P)-**13** (3.8 g, 15.9 mmol) in an analogous manner to that for (R_P)-**1**. Purification of the residue by column chromatography ($CHCl_3$) gave (S_P)-**1** (4.6 g, 72%);

$[\alpha]_D^{20} = +17.4$ (c 0.2, $CHCl_3$); the ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[6]

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