Pergamon

Tetrahedron 54 (1998) 9341–9356

TETRAHEDRON

Enzymatic Desymmetrization of Prochiral 2-Benzyl-1,3-propanediol Derivatives: A Practical Chemoenzymatic Synthesis of Novel Phosphorylated Tyrosine Analogues

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Received 15 May 1998; accepted 11 June 1998

Abstract: (Phosphonomethyl)phenylalanine (Pmp) and (phosphonodifluoromethyl)phenylalanine (F_2Pmp) as well as their β-amino acid congeners were prepared as a protecting variant amenable to the peptide synthesis from readily available 2-benzyl-1,3-propandiols possessing either a diethylphosphonomethyl- or diethylphosphonodifluoromethyl functionality at the *para*-position *via* the lipase-catalyzed desymmetrization.

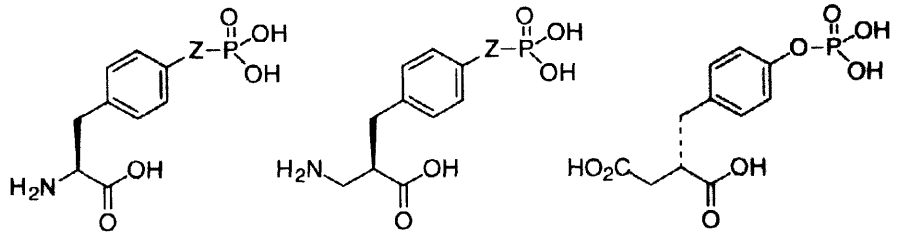
Keywords: amino acids and derivatives; asymmetric synthesis; enzymes and enzymatic reaction; phosphonic acid and derivatives

INTRODUCTION

Phosphorylated tyrosine (*p*Tyr) residues play an important role in protein-tyrosine kinase (PTKs) cellular signaling cascades,[1] since they constitute a key recognition motif for the protein-protein associations mediated by *src*-homology 2 (SH2) domains. A strategy based on interruption of interaction between PTKs with key signaling proteins may hold therapeutic potential for the treatment of diseases mediated by this class of enzymes. The SH2-related peptidmimetic ligands incorporating *p*Tyr is of potential value for the strategy.[2] To protect enzymatic hydrolysis of the phosphate ester function and to increase the ligand affinity to the targeting proteins, various chemical modifications of *p*Tyr have been carried out in recent years.[3] With a rich history of nonhydrolyzable phosphonate saving as a bioisostertic replacement for phosphate,[4] the chemical modifications lead to development of *p*Tyr analogues such as (phosphonomethyl)phenylalanine (Pmp)[5] and the difluoromethylene analogue (F_2Pmp).[6] The chemical modifications of *p*Tyr have been also devoted to synthesis of *p*Tyr analogues modified at the α-amino acid residue.[7] The α carboxymethyl analogue **3** of *p*Tyr was found to be a very useful component of SH2-related peptidmimetic ligands.[7]

While extensive efforts have been devoted to stereoselective synthesis of protecting variants of Pmp[8] and F_2Pmp[9] in recent years, methodology which allows ease of access to a variety of *p*Tyr analogues modified at the α-amino acid residue has not been reported.

0040-4020/98/$19.00
PII: S0040-4020(98)00586-9

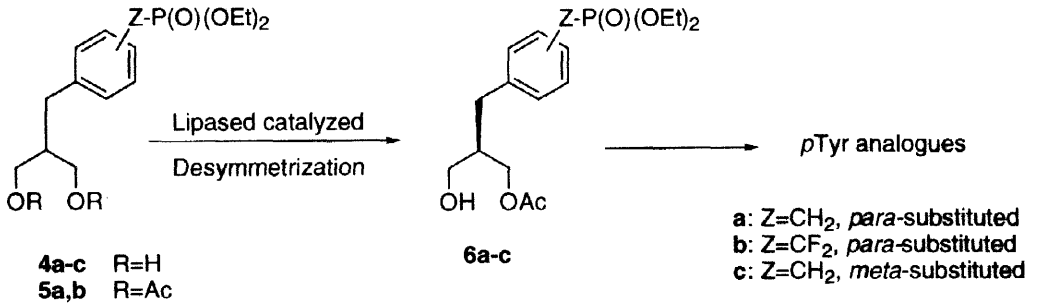


pTyr: Z=O
Pmp: Z=CH_2
F_2Pmp: Z=CF_2

1: Z=CH_2
2: Z=CF_2

3

We have been interested in the synthesis of Pmp and F_2Pmp as well as in synthesis of novel *p*Tyr analogues such as **1** and **2**, which are recognized to be the analogous compounds of Pmp and F_2Pmp with a β-amino acid structure, from readily available phosphonate synthons of high enantiomeric purity. In this paper, we describes lipase-catalyzed desymmetrization of prochiral 2-benzyl-1,3-propanediols **4a-c** and the diacetates **5a,b** giving the phosphonate containing chiral synthons **6a-c** and *ent*-**6a,b**,[10,11] which were successively converted to the targeting *p*Tyr analogues as a protecting variant amenable to automated solid-phase peptide synthesis.



4a-c R=H
5a,b R=Ac

6a-c

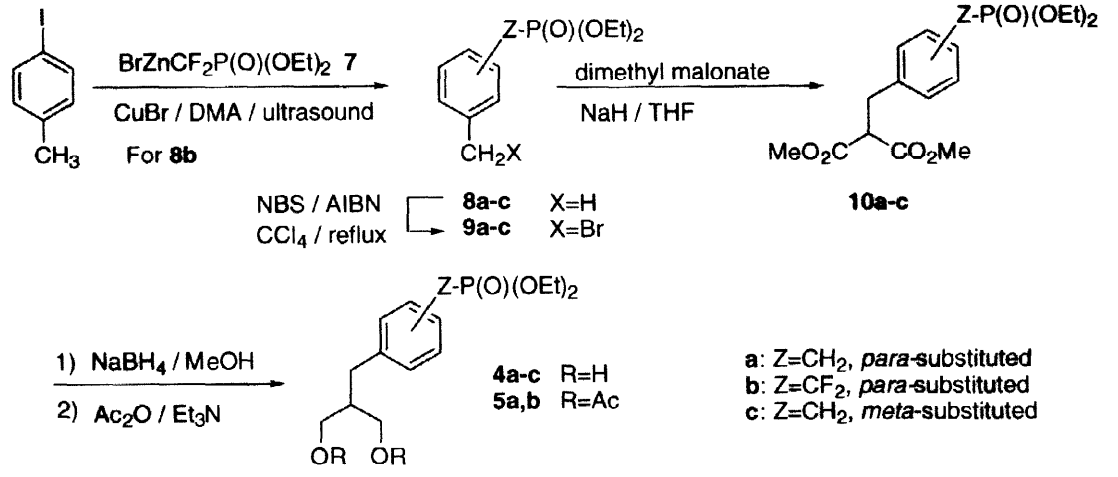
a: Z=CH_2, *para*-substituted
b: Z=CF_2, *para*-substituted
c: Z=CH_2, *meta*-substituted

RESULTS

Lipase-catalyzed desymmetrization of prochiral 2-benzyl-1,3-propanediols 4a-c and the corresponding diacetates 5a,b

The requisite diols **4a-c** and the corresponding diacetates **5a,b** were prepared as summarized in Scheme 1. The known phosphonates **8a,c**,[12] prepared by Arbuzov reaction of the corresponding bromides and triethyl phosphite, were brominated by treatment with NBS in the presence of AIBN to give the bromides **9a,c** in good yields. The difluoromethylene analogue **9b** was prepared from 4-iodotoluene. According to the method reported previously,[13] the zinc reagent **7**, prepared from diethyl bromodifluoromethylphosphonate and zinc powder in dimethylacetamide (DMA), was treated with 4-iodotoluene in the presence of a stoichiometric amount of CuBr under ultrasound irradiation to give **8b** in 80% yield. NBS-mediated bromination of **8b** gave **9b** in good yield.[14] The bromides **9a-c** were coupled with dimethyl malonate in the usual manner to give **10a-c**. The reduction of **10a-c** with excess amounts of $NaBH_4$ in MeOH gave diols **4a-c** in 64-90% yields. The alcohols **4a,b** were respectively acetylated to give **5a,b**.

Scheme 1



The transesterification reaction of diols **4a-c** with vinyl acetate was carried out in THF in the presence of lipase PS from *Pseudomonas cepacia* [15] at room temperature to give the mono acetates **6a-c** (Eq. 1). The results are summarized in Table 1.

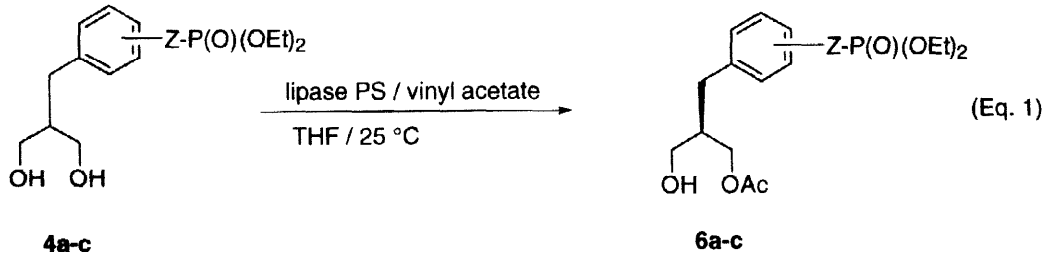


Table 1. Lipase PS-catalyzed transesterification of **4a-c** to give **6a-c**

Entry	Conditions[a]	Z-P(O)(OEt)$_2$		6			
	vinyl acetate (equiv.)	Z	positioning		Yield (%)	Ee (%)	$[\alpha]_D$[b]
1	1.0	CH_2	*para*	**6a**	66	96[c]	
2	2.0	CH_2	*para*	**6a**	97	99[c]	+16.2 (c 1.0)
3	1.0	CF_2	*para*	**6b**	74	95[d]	
4	2.0	CF_2	*para*	**6b**	82	99[d]	+17.0 (c 1.0)
5	1.0	CH_2	*meta*	**6c**	84	85[e]	
6	2.0	CH_2	*meta*	**6c**	87	85[e]	+13.5 (c 1.1)

[a] All reactions were carried out in THF on 10 mmol scale. [b] Measured in MeOH. [c] Determined by HPLC analysis on Chiralcel OD (Daicel). [d] Determined by ^{1}H NMR analysis of the corresponding MTPA esters derived from (+)- and (−)-MTPA. [e] Determined by HPLC analysis on Chiralpak AS (Daicel).

As expected, all reactions gave the desired optically active mono-acetates **6a-c** with *R*-configuration[16,17] in good yield. In the case of the transesterification reaction of **4a** and **4b**, the yield and the enantiomeric purity of the products **6a** and **6b** were found to be slightly dependent upon the amounts of vinyl acetate used. Excellent

enantioselectivity (>99% *ee*) with high chemical yield was obtained, when the reaction was carried out in the presence of 2 equiv. of vinyl acetate (entries 1,3 *vs* 2,4). The enantioselectivity for the transesterification of **4c** under the conditions was determined to be 85% *ee* and it was verified that the diethoxyphophorylmethyl functionality at the *meta*-position unfavorably affects the enantiodiscrimination (entries 5,6 *vs* 2).

In an effort to obtain enantiomeric isomers (*ent*-**6a,b**) of **6a,b**, another versatile chiral synthons for the preparation of novel *p*Tyr analogues, lipase-catalyzed enantioselective hydrolysis of diacetates **5a** and **5b** was carried out (Eq. 2 and Table 2). When the hydrolysis of **5a** was carried out in the presence of lipase PS in a phosphate buffer (pH 7.0, KH_2PO_4 / K_2HPO_4) containing 30% THF, the hydrolysis required prolonged reaction time (>120 h) to give *ent*-**6a** with a low enantioselectivity (40% *ee*) in low yield (entry 1). However, the hydrolysis of **5a** completed within 4 h in a phosphate buffer (pH 7.0, KH_2PO_4 / K_2HPO_4) containing 30% *i*-Pr_2O to give *ent*-**6a** of 98% *ee* in 63% yield, along with an over-hydrolysis product **4a**[18] (entry 2). Using the same conditions, *ent*-**6b** of 95% *ee* was obtained in 65% yield (entry 3).

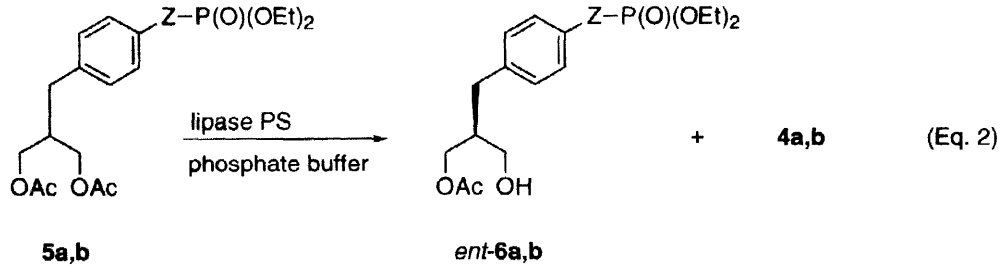


Table 2. Lipase-PS catalyzed enantioselective hydrolysis of diacetates **5a,b**

Entry	Z	Buffer conditions[a]	Time(h)	Product	Yield(%)	Ee(%)	$[\alpha]_D$[b]
1	CH_2	A	120	*ent*-**6a**	35[c]	40[d]	ND[e]
2	CH_2	B	4	*ent*-**6a**	63	98[d]	−16.2 (c 1.0)
3	CF_2	B	4	*ent*-**6b**	65	95[f]	−14.6 (c 1.1)

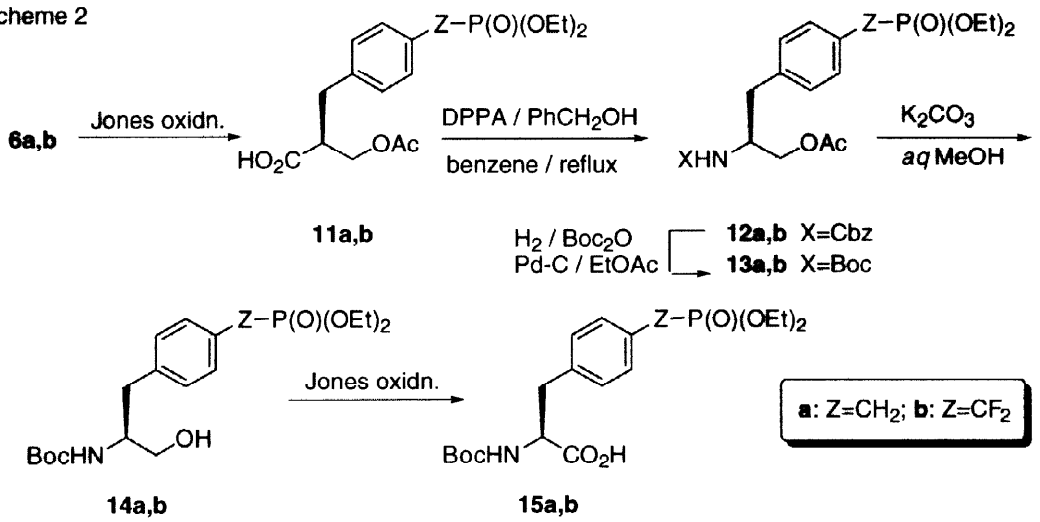
[a] All reactions were carried out at room temperature; condition A: 0.1 M phosphate buffer (pH 7.0, KH_2PO_4/K_2HPO_4):THF=70:30, condition B: 0.1 M phosphate buffer (pH 7.0, KH_2PO_4/K_2HPO_4):*i*-Pr_2O=70:30. [b] Measured in MeOH at 25 °C. [c] Based on NMR analysis. [d] Determined by HPLC analysis (Chiralcel OD, Daicel). [e] Not determined. [f] Determined by ^1H NMR analysis of the corresponding MTPA esters derived from (+)- and (−)-MTPA.

Stereoselective synthesis of N-Boc-Pmp and N-Boc-F_2Pmp derivatives

With chiral synthons **6a-c** and *ent*-**6a,b** in hand, the transformations of **6a,b** to *N*-Boc-Pmp$(OEt)_2$-OH **15a** and *N*-Boc-F_2Pmp$(OEt)_2$-OH **15b** were next examined (Scheme 2). Oxidation of **6a,b** with Jones reagent, followed by Curtius rearrangement[19] [diphenylphosphoryl azide (DPPA), $PhCH_2OH$, refluxing benzene] of the resulting carboxylate **11a,b** gave *N*-Cbz aminoacetates **12a,b** (**12a**: 52% yield for 2 steps; **12b**: 52% yield for 2 steps). Catalytic hydrogenation of **12a** and **12b** over 10% Pd-C in EtOAc in the presence of Boc_2O gave the *N*-Boc aminoacetates **13a** and **13b** in 88% and 83% yield, respectively.[20,21] Hydrolysis of the acetates gave *N*-Boc aminoalcohols **14a,b**, which were oxidized with Jones reagent to give *N*-Boc-Pmp$(OEt)_2$-OH **15a** ($[\alpha]_D^{25}$ +24.0

(c 0.97, EtOAc)) and *N*-Boc-F_2Pmp$(OEt)_2$-OH **15b** ($[\alpha]_D^{25}$ +8.43 (c 0.88, MeOH)) in 75% and 83% yield, respectively. The specific rotations of **15a** and **15b** thus obtained were identical to those reported by Roques[8a] and Burke,[9b] respectively. At this stage, the absolute configuration of phosphonate chiral synthons **6a,b** was unambiguously established to be *R* and it was confirmed that no racemization takes place during these transformations.[22]

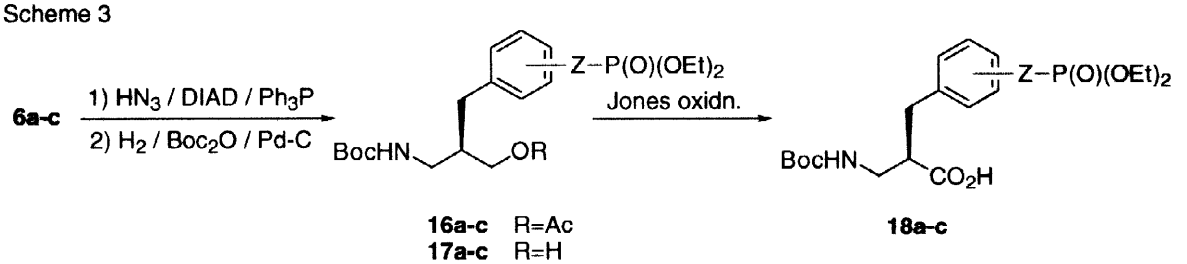
Scheme 2



Efficient conversion of 6a-c to novel pTyr analogues 18a-c with a β-amino acid structrue

β-Amino acids have recently received significant attention, since the discovery of the remarkable helical and enzymatic stability associated with β-peptides.[23] Keeping these characteristic features of β-amino acids in mind, we envisioned that incorporation of *p*Tyr analogues having a β-amino acid structure into SH2-related peptidemimetic ligands might be useful to find novel SH2-ligands with significant biological activities. Accordingly, phosphonate chiral synthons **6a-c** prepared in the previous section were transformed toward *p*Tyr analogues **18a-c** with a β-amino acid structure (Scheme 3).

Scheme 3



a: Z=CH_2; *para*-substituted; **b**: Z=CF_2; *para*-substituted; **c**: Z=CH_2; *meta*-substituted

Reaction of **6a-c** with hydorazoic acid under the Mitsunobu conditions,[24] followed by hydrogenation over 10% Pd-C in the presence of Boc_2O in EtOAc,[20] gave *N*-Boc aminoacetates **16a-c** in good overall yields (**16a**: 98%; **16b**: 68%; **16c**: 86%). After hydrolysis of the acetates with potassium carbonate in aqueous MeOH, the

resulting *N*-Boc aminoalcohols **17a-c** were oxidized with Jones reagent to give **18a-c** in good yields (**18a**: 91%; **18b**:89%; **18c**: 84%). Using these synthetic sequences, novel *p*Tyr analogues **18a-c** with a β-amino acid structure, amenable to automatic solid-phase peptide synthesis, were obtained in multi-gram quantities.

CONCLUSION

In conclusion, we have developed a facile method for the preparation of protecting derivatives of Pmp and F_2Pmp, hydrolytically stable *p*Tyr analogues, from readily available 2-benzyl-1,3-propanediols **4a-c** through chemoenzymatic sequences. The methodology was also applicable to an enantioselective synthesis of novel *p*Tyr analogues **18a-c** having a β-amino acid structure.

EXPERIMENTAL

General. All reactions were carried out under nitrogen atmosphere, unless otherwise specified. All NMR data were recorded in $CDCl_3$ unless otherwise specified on Bruker AM 400 or DPX 400. ^{1}H NMR data were collected by operating at 400 MHz. The chemical shift data for each signal are given in units of δ relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26). ^{13}C- (100 MHz) and ^{31}P NMR (162 MHz) were taken with broad-band ^{1}H decoupling. The chemical shifts of ^{13}C are reported relative to $CDCl_3$ (δ 77.0). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4. ^{19}F NMR (376 MHz) spectra were measured using benzotrifluoride (BTF) as an internal reference. IR spectra were recorded as film or KBr disc on a Perkin-Elmer 1710 FTIR spectrometer. Mass spectra were measured on a Hitachi M-80 or a VG Auto Spec spectrometer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Lipase PS was purchased from Amano Pharmaceutical Co., Ltd.

General procedure of NBS-mediated bromination of 8a-c. The mixture of **8a**,[12a] **8b**,[13] or **8c** (50 mmol)[12b] and NBS (8.9 g, 50 mmol) in CCl_4 (100 mL) containing AIBN (164 mg, 1 mmol) was heated at 90 ℃ for 3h. After being cooled to -15 °C, the precipitates were filtered. The filtrate was washed with brine and concentrated to give crude **9a-c** as oils, which are contaminated with an inseparatable mixture (7-10%) of **8a-c** and the corresponding α,α-dibromides. These oils were used for the next reactions without purification.

4-(Diethoxyphosphorylmethyl)benzyl bromide 9a. An analytical sample was obtained by column chromatography on silica gel (hexane:EtOAc=6:1). ^{1}H NMR δ 7.31-7.23 (4H, m), 4.44 (2H, s), 4.04-3.94 (4H, m), 3.11 (2H, d, J = 21.8 Hz), 1.22 (3H, d, J = 7.0 Hz), 1.21 (3H, d, J = 7.0 Hz); ^{13}C NMR δ 136.3 (d, J_{PC} = 3.2 Hz), 131.9 (d, J_{PC} = 9.2 Hz), 130.1 (d, J_{PC} = 6.3 Hz), 129.1 (d, J_{PC} = 2.4 Hz), 62.1 (d, J_{PC} = 6.7 Hz), 33.4 (d, J_{PC} = 138.3 Hz), 33.1, 16.2 (d, J_{PC} = 5.8 Hz); ^{31}P NMR δ 25.70; IR (film) 1230 cm^{-1}; EIMS *m/z* 322 (M^+, ^{81}Br), 320 (M^+, ^{79}Br).

4-{(Diethoxyphosphoryl)(difluoro)methyl}benzyl bromide 9b. An analytical sample was obtained by column chromatography on silica gel (hexane:EtOAc=15:1 to 9:1). ^{1}H NMR δ 7.59 (2H, d, J = 7.9 Hz), 7.48 (2H, d, J = 7.9 Hz), 4.49 (2H, s), 4.27-4.11 (4H, m), 1.32 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 140.4, 132.6 (dt, J_{PC} = 13.8, J_{FC} = 22.0 Hz), 129.0, 126.7-126.6 (m), 117.8 (dt, J_{PC} = 218.3 Hz, J_{PC} = 263.3 Hz), 64.8 (d, J_{PC} = 6.7 Hz), 32.1, 16.2 (d, J_{PC} = 5.5 Hz); ^{19}F NMR δ -45.8 (d, J_{PF} = 115.6 Hz); ^{31}P NMR δ 7.30 (t, J_{FP} = 115.2 Hz); IR (film) 1272 cm^{-1}; EIMS *m/z* 358 (M^+, ^{81}Br), 356 (M^+, ^{79}Br). The spectral data were identical to those reported by Solas *et al.*[9c]

3-(Diethoxyphosphorylmethyl)benzyl bromide 9c. An analytical sample was obtained by column chromatography on silica gel (hexane:EtOAc=6:1). ^{1}H NMR δ 7.31-7.20 (4H, m), 4.45 (2H, s), 4.05-3.95 (4H, m), 3.12 (2H, d, J = 21.7 Hz), 1.23 (6H, t, J = 7.0 Hz); ^{13}C NMR δ 138.0 (d, J_{PC} = 2.9 Hz), 132.3 (d, J_{PC} = 9.2 Hz), 130.4 (d, J_{PC} = 6.5 Hz), 129.8 (d, J_{PC} = 6.4 Hz), 128.9 (d, J_{PC} = 2.9 Hz), 127.5 (d, J_{PC} = 3.3 Hz), 62.1 (d, J_{PC} = 6.7 Hz), 33.5 (d, J_{PC} = 138.3 Hz), 33.2, 16.3 (d, J_{PC} = 6.0 Hz); ^{31}P NMR δ 25.61; EIMS *m/z* 322 (M^+, ^{81}Br). 320 (M^+, ^{79}Br).

General procedure for the synthesis of dimethyl 2-benzylmalonates 10a-c. To a stirred suspension of NaH (2.16 g of a 60% suspension in mineral oil, 90 mmol; prewashed with hexane) in THF (60 mL) was added a solution of dimethyl malonate (11.9 g, 90 mmol) in THF (120 mL) over 30 min under ice cooling. After being stirred for 30 min at room temperature, a solution of crude **9a-c** (60 mmol) in THF (120 mL) was added over 30 min. The mixture was stirred for 2 h at room temperature. The reaction was quenched with *sat.* NH_4Cl (30 mL) and the organic layer was separated. The separated aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a crude material, which was purified by column chromatography on silica gel. The yield and physical data of **10a-c** are listed below:

Dimethyl 2-[(4-diethoxyphosphorylmethyl)benzyl]malonate 10a. Obtained as an oil in 76% yield after column chromatography on silica gel (hexane:EtOAc = 4:1 to 1:1). ^{1}H NMR δ 7.20 (2H, dd, J = 2.4, 8.0 Hz), 7.13 (2H, d, J = 8.0 Hz), 4.05-3.91 (4H, m), 3.68 (6H, s), 3.64 (1H, t, J = 7.8 Hz), 3.18 (2H, d, J = 7.8 Hz), 3.10 (2H, d, J = 21.6 Hz), 1.22 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 169.0, 136.3 (d, J_{PC} = 3.7 Hz), 130.0 (d, J_{PC} = 9.4 Hz), 129.9 (d, J_{PC} = 6.5 Hz), 128.8 (d, J_{PC} = 2.8 Hz), 62.0 (d, J_{PC} = 6.8 Hz), 53.4, 52.4, 34.2, 33.2 (d, J_{PC} = 138.2 Hz), 16.2 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 27.6, IR (film) 1714, 1230 cm^{-1}; MS *m/z* 372 (M^+); Anal. Calcd for $C_{17}H_{25}O_7P$: C, 54.84; H, 6.77. Found: C, 54.99; H, 6.84.

Dimethyl 2-{4-[(Diethoxyphosphoryl)(difluoro)methyl]benzyl}malonate 10b. Obtained as crystals (mp 60-61 °C) in 71% yield after column chromatography on silica gel (hexane:EtOAc = 6:1 to 2:1). ^{1}H NMR δ 7.53 (2H, d, J = 7.8 Hz), 7.28 (2H, d, J = 8.0 Hz), 4.24-4.07 (4H, m), 3.69 (6H, s), 3.66 (1H, t, J = 7.8 Hz), 3.25 (2H, d, J = 7.8 Hz), 1.29 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 168.8, 140.7, 131.1 (dt, J_{PC} = 13.7 Hz, J_{PC} = 22.0 Hz), 128.8, 126.4, 117.9 (dt, J_{PC} = 218.5 Hz, J_{FC} = 263.1 Hz), 64.6 (d, J_{PC} = 6.8 Hz), 53.1, 52.5, 34.3, 16.2 (d, J_{PC} = 5.4 Hz); ^{19}F NMR δ -45.5 (d, J_{PF} = 116.3 Hz); ^{31}P NMR δ 7.52 (t, J_{FP} = 116.7 Hz), IR (film) 1737, 1271 cm^{-1}; EIMS *m/z* 408 (M^+). Anal. Calcd for $C_{17}H_{23}F_2O_7P$: C, 50.00; H, 5.68. Found: C, 50.02; H, 5.93.

Dimethyl 2-[(3-diethoxyphosphorylmethyl)benzyl]malonate 10c. Obtained as an oil in 56% yield after column chromatography on silica gel (hexane:EtOAc = 3:1 to 1:1). ^{1}H NMR δ 7.23-7.06 (4H, m), 4.05-3.92 (4H, m), 3.69 (6H, s), 3.65 (1H, t, J=7.7 Hz), 3.19 (2H, d, J = 7.8 Hz), 3.10 (2H, d, J = 21.6 Hz), 1.23 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 169.0, 137.9 (d, J_{PC} = 3.0 Hz), 131.8 (d, J_{PC} = 9.2 Hz), 130.1 (d, J_{PC} = 6.5 Hz), 128.6 (d, J_{PC}= 2.9 Hz), 128.2 (d, J_{PC} = 6.4 Hz), 127.2 (d, J_{PC} = 3.4 Hz), 62.0 (d, J_{PC} = 6.7 Hz), 53.4, 52.4, 34.5, 33.5 (d, J_{PC} = 138.0 Hz), 16.2 (d, J_{PC} = 5.8 Hz); ^{31}P NMR δ 27.50; IR (film) 1737, 1246 cm^{-1}; EIMS *m/z* 372 (M^+). Anal. Calcd for $C_{17}H_{25}O_7P$: C, 54.84; H, 6.77. Found: C, 54.40; H, 6.88.

Genral procedure for the preparation of 2-benzylpropanediol derivatives 4a-c. To a stirred solution of diesters **10a-c** (30 mmol) in MeOH (120 mL) was added $NaBH_4$ (6.81 g, 180 mmol) under ice-cooling. The mixture was stirred at room temperature for 2 h. The volatile component of the mixture was evaporated. The residue was portioned into water and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$. The

combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a crude material, which was purified by column chromatography on silica gel to give **4a-c**. The yield and physical data are as follows:

Diethyl {4-[3-hydroxy-2-(hydroxymethyl)propyl]phenyl}methylphosphonate 4a. Obtained as crystals (mp 83-87 °C) in 79% yield after column chromatography on silica gel ($CHCl_3$:MeOH = 200:1 to 100:1). ^1H NMR δ 7.17 (2H, d, J = 7.8 Hz), 7.10 (2H, d, J= 7.8 Hz), 4.05-3.91 (4H, m), 3.69 (2H, broad d, J = 10.6 Hz), 3.56 (2H, dd, J = 6.9, 10.6 Hz), 3.08 (2H, d, J = 21.5 Hz), 2.89 (2H, broad s), 2.55 (2H, d, J = 7.5 Hz), 2.02-1.90 (1H, m), 2.02-1.90 (1H, m), 1.21 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 138.9 (d, J_{PC} = 3.8 Hz), 129.7 (d, J_{PC} = 6.6 Hz), 129.2 (d, J_{PC} = 2.8 Hz), 128.7 (d, J_{PC} = 9.2 Hz), 64.7, 62.2 (d, J_{PC} = 6.7 Hz), 43.8, 33.8, 32.6 (d, J_{PC} = 138.2 Hz), 16.3 (d, J_{PC} = 6.0 Hz); ^{31}P NMR δ 28.20; IR (KBr) 3401, 1229 cm^{-1}; EIMS *m/z* 316 (M^+). Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.95; H, 7.97. Found: C, 56.45; H, 7.78.

Diethyl difluoro{4-[3-hydroxy-2-(hydroxymethyl)propyl]phenyl}methylphosphonate 4b. Obtained as an oil in 64% yield after column chromatography on silica gel ($CHCl_3$:MeOH = 300:1 to 200:1). ^1H NMR δ 7.53 (2H, d, J = 7.7 Hz), 7.28 (2H, d, J = 7.7 Hz), 4.24-4.09 (4H, m), 3.76 (2H, dd, J = 3.9, 10.7 Hz), 3.63 (2H, dd, J = 6.6, 10.7 Hz), 2.66 (2H, d, J = 7.5 Hz), 2.62 (2H, broad s), 2.07-1.98 (1H, m), 1.31 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 143.4, 130.0 (dt, J_{PC} = 13.8 Hz, J_{FC} = 22.0 Hz), 129.1, 126.1 (m), 118.0 (dt, J_{PC} = 219.9 Hz, J_{FC} = 262.8 Hz), 64.9 (d, J_{PC} =6.6 Hz), 64.3, 43.7, 33.9, 16.2 (d, J_{PC} =5.0 Hz); ^{19}F NMR δ -45.1 (d, J_{PF} = 117.6 Hz); ^{31}P NMR δ 6.18 (t, J_{FP} = 117.6 Hz); IR (film) 3408, 1262 cm^{-1}; EIMS *m/z* 352 (M^+). Anal. Calcd for $C_{15}H_{23}F_2O_5P$: C, 51.14; H, 6.58. Found: C, 50.91; H, 6.63.

Diethyl {3-[3-hydroxy-2-(hydroxymethyl)propyl]phenyl}methylphosphonate 4c. Obtained as an oil in 90% yield after column chromatography on silica gel ($CHCl_3$:MeOH = 200:1 to 100:1). ^1H NMR δ 7.26-7.07 (4H, m), 4.03-3.92 (4H, m), 3.76 (1H, dd, J = 3.9, 10.8 Hz), 3.62 (1H, dd, J = 6.5, 10.8 Hz), 3.12 (2H, d, J = 21.6 Hz), 2.83 (1H, broad s), 2.64 (2H, d, J = 7.6 Hz), 2.04-1.95 (1H, m), 1.75 (1H, broad s), 1.24 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 140.6, 130.9 (d, J_{PC} = 8.9 Hz), 130.5 (d, J_{PC} = 5.6 Hz), 128.4, 127.7 (d, J_{PC} = 2.7 Hz), 127.2 (d, J_{PC} = 6.1 Hz), 63.8, 62.3 (d, J_{PC} = 6.7 Hz), 44.0, 33.9, 33.4 (d, J_{PC} = 137.9 Hz), 16.2 (d, J_{PC} = 5.4 Hz); ^{31}P NMR δ 28.09; IR (film) 3402, 1236 cm^{-1}; EIMS *m/z* 317 (M^++1). Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.95; H, 7.97. Found: C, 56.46; H, 7.83.

3-(Acetyloxy)-2-{4-[(diethoxyphosphoryl)methyl]benzyl}propyl acetate 5a. Diol **4a** (4.7 g, 15 mmol) was treated with Ac_2O (4.6 g, 45 mmol), Et_3N (4.6 g, 45 mmol), and *N,N*-dimethylaminopyridine (366 mg, 3mmol) at room temperature for 2 h. The mixture was diluted with 1N HCl and extracted with ether. The extracts were washed with *sat.* $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc=1:1) to give **5a** (5.5 g, 92%) as an oil. ^1H NMR δ 7.22 (2H, dd, J = 2.4, 8.0 Hz), 7.09 (2H, d, J = 8.0 Hz), 4.14-3.95 (8H, m), 3.11 (2H, d, J = 21.5 Hz), 2.66 (2H, d, J = 7.2 Hz), 2.34-2.25 (1H, m), 2.05 (6H, s), 1.23 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 170.7, 137.1 (d, J_{PC} = 3.6 Hz), 129.8 (d, J_{PC} = 6.5 Hz), 129.5 (d, J_{PC} = 9.1 Hz), 129.0 (d, J_{PC} = 2.5 Hz), 63.5, 61.9 (d, J_{PC} = 6.7 Hz), 38.9, 34.0, 33.1 (d, J_{PC} = 138.2 Hz), 20.6, 16.2 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 27.60; IR (film) 1739, 1230 cm^{-1}; EIMS *m/z* 400 (M^+). Anal. Calcd for $C_{19}H_{29}O_7P$: C, 56.99; H, 7.30. Found: C, 56.72; H, 7.26.

3-(Acetyloxy)-2-{4-[(diethoxyphosphoryl)(difluoro)methyl]benzyl}propyl acetate 5b. Obtained as an oil in 84% yield by diacetylation of **4b** in an analogous manner to that for the preparation of **5a**. ^1H NMR δ 7.55 (2H, d, J = 7.7 Hz), 7.25 (2H, d, J = 7.7 Hz), 4.28-4.10 (4H, m), 4.07 (2H, dd, J = 5.3, 11.2 Hz), 4.00 (2H, dd, J = 6.1, 11.2 Hz), 2.74 (2H, d, J = 7.4 Hz), 2.43-2.29 (1H, m), 2.05 (6H, s), 1.31 (6H, t, J = 7.1

Hz); ^{13}C NMR δ 170.5, 141.6, 130.5 (dt, J_{PC} = 13.8, J_{FC} = 22.2 Hz), 128.8, 126.2 (t, J_{FC} = 5.6 Hz), 117.8 (dt, J_{PC} = 218.6, J_{FC} = 263.0 Hz), 64.5 (d, J_{PC} = 6.7 Hz), 63.3, 38.7, 34.2, 20.5, 16.0 (d, J_{PC} = 5.4 Hz); ^{19}F NMR δ –45.3 (d, J_{PF} = 116.7 Hz); ^{31}P NMR δ 7.46 (t, J_{FP} = 116.7 Hz); IR (film)1741, 1231, 1043, 1020 cm^{-1}; EIMS *m/z* 436 (M^+). Anal. Calcd for $C_{19}H_{27}F_2O_7P$: C, 52.30; H, 6.24. Found: C, 52.34; H, 6.12.

General procedure for lipase PS-catalyzed acetylation of 4a-c. A mixture of substrate (10 mmol), vinyl acetate (1.7 g, 20 mmol) and lipase PS (1 g per 1 g of the substrate) in THF (50 mL) was stirred at 25 ℃ for 2 h. The reaction was terminated by filtering off the enzyme. After removal of the filtrate *in vacuo*, the residue was purified by column chromatography on silica gel to give the mono-acetate **6a-c** as oils. The yields and specific rotations are summarized in Table 1. The physical data of **6a-c** are as follows:

(2*R*)-2-[(4-Diethoxyphosphorylmethyl)benzyl]-3-hydroxypropyl acetate 6a. Obtained after column chromatography on silica gel (hexane:EtOAc = 1:2 to 1:4). ^{1}H NMR δ 7.21 (2H, dd, *J* = 2.4, 8.0 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 4.15 (1H, dd, *J* = 4.7, 11.3 Hz), 4.05 (1H, dd, *J* = 6.4, 11.3 Hz), 4.03-3.95 (4H, m), 3.52 (1H, dd, *J* = 4.8, 11.1 Hz), 3.45 (1H, dd, *J* = 6.1, 11.1 Hz), 3.11 (2H, d, *J*= 21.5 Hz), 2.66 (1H, dd, *J* = 7.4, 13.4 Hz), 2.59 (1H, dd, *J* = 7.6, 13.7 Hz), 2.20 (1H, broad s), 2.14-2.05 (1H. m), 2.07 (3H, s), 1.23 (6H, t, *J* = 7.1 Hz); ^{13}C NMR δ 171.5, 138.0, 129.8 (d, J_{PC} = 6.2 Hz), 129.4 (d, J_{PC} = 9.1 Hz), 129.2, 64.0, 62.1 (d, J_{PC} = 6.6 Hz), 61.9, 42.3, 33.9, 32.6, 20.8, 16.3 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 27.85; IR (film) 1737, 1244 cm^{-1}; EIMS *m/z* 358 (M^+). Anal. Calcd for $C_{17}H_{27}O_6P$: C, 56.98; H, 7.59. Found: C, 56.89; H, 7.73. The enantiomeric purity of **6a** was determined by HPLC analysis on a chiral phase [Chiralcel OD (Daicel), hexane:EtOH=90:10, flow rate=0.5 ml/min, UV detector (254 nm), Rt=21.8 min and 24.1 min for **6a** and the corresponding enantiomer, respectively].

(2*R*)-2-{4-[(Diethoxyphosphoryl)(difluoro)methyl]benzyl}-3-hydroxypropyl acetate 6b. Obtained after column chromatography on silica gel (hexane:EtOAc = 1:1 to 1:2). ^{1}H NMR δ 7.54 (2H, d, *J* = 7.8 Hz), 7.27 (2H, d, *J* = 7.8 Hz), 4.26-4.04 (6H, m), 3.58 (1H, dd, *J* = 4.5, 11.2 Hz), 3.49 (1H, dd, *J* = 6.4, 11.2 Hz), 2.74 (1H, dd, *J* = 7.6, 13.7 Hz), 2.66 (1H, dd, *J* = 7.5, 13.7 Hz), 2.17-2.09 (1H, m), 2.08 (3H, s), 1.31 (6H, t, *J* = 7.1 Hz); ^{13}C NMR δ 171.3, 142.6, 130.2 (dt, J_{PC} = 13.9 Hz, J_{FC} = 22.2 Hz), 129.0, 126.2-126.1 (m), 117.9 (dt, J_{PC} = 219.5 Hz, J_{FC} = 263.0 Hz), 64.7 (d, J_{PC} = 6.8 Hz), 63.8, 61.3, 42.0, 33.9, 20.9, 16.1 (d, J_{PC} = 5.4 Hz); ^{19}F NMR δ –45.3 (d, J_{PF} = 117.5 Hz); ^{31}P NMR δ 7.59 (t, J_{FP} = 117.5 Hz); IR (film) 3452, 1739, 1261 cm^{-1}; EIMS *m/z* 394 (M^+). Anal. Calcd for $C_{17}H_{25}F_2O_6P$: C, 51.78; H, 6.39. Found: C, 51.84; H, 6.57. The enantiomeric purity of **6b** was determined by NMR (300 MHz) analysis of the corresponding MTPA esters derived from (+)- and (–)-MTPA.

(2*R*)-2-[(3-Diethoxyphosphorylmethyl)benzyl]-3-hydroxypropyl acetate 6c. Obtained after column chromatography on silica gel (hexane:EtOAc = 1:2 to 1:4). ^{1}H NMR δ 7.26-7.05 (4H, m), 4.20-3.91 (6H, m), 3.56 (1H, dd, *J* = 4.6 Hz), 3.46 (1H, dd, *J* = 5.9, 11.3 Hz), 3.11 (2H, d, *J* = 21.6 Hz), 2.66 (1H, dd, *J* = 7.7, 13.7 Hz), 2.63 (1H, dd, *J* = 7.2, 13.7 Hz), 2.17-2.07 (1H, m), 2.07 (3H, s), 1.23 (3H, t, *J* = 7.0 Hz), 1.22 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 171.3, 139.7 (d, J_{PC} = 2.9 Hz), 131.3 (d, J_{PC} = 9.2 Hz), 130.5 (d, J_{PC} = 6.4 Hz), 128.4 (d, J_{PC} = 2.4 Hz), 127.5 (d, J_{PC} = 3.5 Hz), 127.4 (d, J_{PC} = 6.6 Hz), 64.1, 62.0 (m), 61.3, 42.1, 34.0, 33.4 (d, J_{PC} = 137.9 Hz), 20.7, 16.2 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 27.81; IR (film) 3398, 1738, 1240 cm^{-1}; EIMS *m/z* 358 (M^+). Anal. Calcd for $C_{17}H_{27}O_6P$: C, 56.98; H, 7.59. Found: 56.56; H, 7.55. The enantiomeric purity of **6c** was determined by HPLC analysis on a chiral phase [Chiralpak AS (Daicel),

hexane:EtOH=92:8, flow rate=0.5 ml/min, UV detector (254 nm), Rt=20.4 min and 21.8 min for **6c** and the corresponding enantiomer, respectively].

Lipase PS-catalyzed enantioselective hydrolysis of diacetates 5a,b. Diacetate **5a** (400 mg, 1mmol) or **5b** (436 mg, 1mmol) was suspended in a 70:30 mixture (10 mL) of 0.1 M phosphate buffer (pH 7.0, KH_2PO_4 / K_2HPO_4) and *i*-Pr_2O. The mixture was treated with lipase PS (400 mg for **5a**; 436 mg for **5b**) at room temperature. The reaction was monitored by pH meter, and the medium was manually adjusted to pH 7.0 by adding the buffer. After being stirred for 4 h, the reaction was terminated by filtration of the lipase. The filtrate was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a residue. Purification by column chromatography on silica gel gave *ent*-**6a** (227 mg, 63%) and *ent*-**6b** (256 mg, 65%) as oils, respectively. The physical data were identical to those of **6a** and **6b** except the specific rotation (Table 2).

(2*S*)-3-Acetyloxy-2-{4-[(diethoxyphosphoryl)methyl]benzyl}propanoic acid 11a. To a solution of **6a** (3.58 g, 10 mmol) in acetone (25 mL) was added Jones reagent (10 mL) under ice-cooling. The mixture was stirred at room temperature for 4 h. The reaction was quenched with 2-propanol (5 mL) and the mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude **11a** (3.83 g) as an oil. This was used for the next reaction without purification. An analytical sample was obtained by column chromatography on silica gel (hexane:EtOAc=1:2 to 1:4). $[\alpha]_D^{25}$ +3.07 (c 1.0, MeOH), ^{1}H NMR δ 7.19 (2H, dd, J = 2.3, 8.2 Hz), 7.15 (2H, d, J = 8.2 Hz), 4.22 (2H, d, J = 6.0 Hz), 4.06-3.89 (4H, m), 3.74-2.82 (3H, m), 3.11 (2H, dd, J = 1.7, 21.7 Hz), 2.04 (3H, s), 1.22 (3H, t, J = 7.0 Hz), 1.20 (3H, t, J = 7.0 Hz), ^{13}C NMR δ 175.1, 170.6, 136.8 (d, J_{PC} = 3.8 Hz), 129.7 (d, J_{PC} = 6.4 Hz), 129.2 (d, J_{PC} = 9.4 Hz), 128.9 (d, J_{PC} = 2.6 Hz), 63.7, 62.4 (t, J_{PC} = 5.7 Hz), 46.0, 34.0, 32.8 (d, J_{PC} = 138.4 Hz), 20.5, 16.0 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 28.29; IR (film) 1741, 1240 cm^{-1}; EIMS *m/z* 372 (M^+). Anal. Calcd for $C_{17}H_{25}O_7P$: C, 54.84; H, 6.77. Found: C, 54.71; H, 6.94.

(2*S*)-3-Acetyloxy-2-{4-[(diethoxyphosphoryl)(difluoro)methyl]benzyl}propanoic acid 11b. This compound was prepared as an oil from **6b** in an analogous manner to that for the preparation of **11a** and used for the next reaction without purification. An analytical sample was obtained by column chromatography on silica gel (hexane:EtOAc=1:1). $[\alpha]_D^{25}$ –5.37 (c 1.0, MeOH). ^{1}H NMR δ 7.95 (1H, broad s), 7.53 (2H, d, J = 7.7 Hz), 7.28 (2H, d, J = 7.7 Hz), 4.29-3.96 (6H, m), 3.10-2.99 (2H, m), 2.88 (1H, dd, J = 6.0, 12.5 Hz), 2.03 (3H, s), 1.29 (3H, t, J = 7.0 Hz), 1.28 (3H, t, J = 7.0 Hz); ^{13}C NMR δ 175.1, 170.6, 141.1, 130.9-130.2 (m), 128.9, 126.2, 117.7 (dt, J_{PC} = 220.5 Hz, J_{FC} = 263.2 Hz), 64.9 (d, J_{PC} = 6.6 Hz), 63.5, 45.7, 34.0, 20.4, 16.0; ^{19}F NMR δ –45.6 (d, J_{PF} = 117.5 Hz); ^{31}P NMR δ 7.36 (t, J_{FP} = 118.4 Hz); IR (film) 1746, 1245 cm^{-1}; EIMS *m/z* 408 (M^+). High resolution MS *m/z* calcd for $C_{17}H_{23}F_2O_7P$ (M^+): 408.1149. Found: 408.1132.

(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-{4-[(diethoxyphosphoryl)methyl]phenyl}propyl acetate 12a. A solution of crude **11a** (4.0 g, *ca.* 10 mmol) and Et_3N (1.39 mL, 10 mmol) in benzene (50 mL) was treated with DPPA (2.75 g, 10 mmol) at room temperature for 30 min. After addition of benzyl alcohol (1.03 mL, 10 mmol), the mixture was heated under reflux for 24 h. After being cooled to room temperature, the reaction was quenched with 5% aqueous citric acid. The organic layer was separated and washed with brine. The extracts were dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 1:2 to 1:4) to give **12a** (2.48 g, 52% from **6a**) as an oil. $[\alpha]_D^{25}$ –16.3 (c 1.3, MeOH), ^{1}H NMR δ 7.38-7.29 (5H, m), 7.22 (2H, dd, J = 2.2, 7.6 Hz), 7.16 (2H, d, J = 7.6 Hz), 5.06 (1H, J = 12.2 Hz),

4.91 (1H, d, J = 8.0 Hz), 4.06-3.95 (6H, m), 3.10 (2H, d, J = 21.6 Hz), 2.86 (1H, dd, J = 5.5, 13.6 Hz), 2.79 (1H, dd, J = 7.5, 13.6 Hz), 2.05 (9H, s), 1.23 (6H, t, J = 7.1 Hz). ^{13}C NMR δ 170.6, 155.6, 136.2, 135.5, 129.8 (d, J_{PC} = 5.9 Hz), 129.2 (d, J_{PC} = 2.2 Hz), 128.3, 127.9, 66.5, 65.6, 64.7, 61.9 (d, J_{PC} = 6.5 Hz), 51.1, 37.2, 36.9, 33.1 (d, J_{PC} = 138.0 Hz), 20.6, 16.2 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 27.55; IR (film) 3260, 1740, 1718, 1232 cm^{-1}; EIMS *m/z* 477 (M^+). High resolution MS *m/z* calcd for $C_{24}H_{32}NO_7P$ (M^+): 477.1916. Found: 477.1932.

(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-{4-[(diethoxyphosphoryl)(difluoro)methyl]phenyl}propyl acetate 12b. Obtained in 52% yield from **6b** in an analogous manner to that for the preparation of **12a** after column chromatography on silica gel (hexane:EtOAc=3:1 to 2:1). Yield: 52% from **6b**; an oil; $[\alpha]_D^{25}$ -15.1 (c 1.0, MeOH); ^{1}H NMR δ 7.55 (2H, d, J = 7.6 Hz), 7.39-7.26 (7H, m), 5.07 (1H, s), 4.96 (1H, d, J = 8.6 Hz), 4.25-4.03 (6H, m), 2.95-2.80 (2H, m), 2.05 (3H, s), 1.30 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 170.7, 155.6, 140.1, 136.2, 131.1-131.8 (m), 129.2, 128.4, 128.1, 127.9, 126.4, 117.9 (dt, J_{FC} = 219.1 Hz, J_{PC} = 261.5 Hz), 66.7, 65.7, 64.7 (d, J_{PC} = 6.7 Hz), 51.0, 37.5, 20.6, 16.2 (d, J_{PC} = 5.4 Hz), 15.2; ^{19}F NMR δ -45.4 (d, J_{FP}= 116.6 Hz), ^{31}P NMR δ 7.50 (t, J_{FP} = 116.6 Hz); IR (film) 3308, 1743, 1721, 1537, 1261, 1044 cm^{-1}; MS *m/z* 513 (M^+). High resolution MS *m/z* calcd for $C_{24}H_{30}F_2NO_7P$: 513.1728. Found: 513.1720.

(2*S*)-2-[*tert*-Butoxycarbonyl)amino]-3-{4-[(diethoxyphosphoryl)methyl]phenyl}propyl acetate 13a. A solution of **12a** (955 mg, 2.0 mmol) and Boc_2O (524 mg, 2.4 mmol) in EtOAc (20 mL) was hydrogenated over 10% Pd-C (100 mg) for 12 h at room temperature under atmospheric pressure. The catalyst was removed through Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 2:1 to 1:1) to give **13a** (779 mg, 88%). Mp 77-80 °C; $[\alpha]_D^{25}$ -5.51 (c 1.5, MeOH); ^{1}H NMR δ 7.22 (2H, dd, J = 2.4, 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 4.65 (1H, broad d, J = 6.9 Hz), 4.06-3.95 (7H, m), 3.11 (2H, d, J = 21.6 Hz), 2.84 (1H, dd, J = 5.8, 13.6 Hz), 2.76 (1H, dd, J = 7.4, 13.6 Hz), 2.08 (3H, s), 1.41 (9H, s), 1.23 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 170.8, 155.1, 135.1 (d, J_{PC} = 3.7 Hz), 129.9 (d, J_{PC} = 6.4 Hz), 129.3 (d, J_{PC} = 2.4 Hz), 79.5, 65.0, 62.0 (d, J_{PC} = 6.6 Hz), 50.5, 37.4, 33.3 (d, J_{PC} = 138.2 Hz), 28.3, 20.8, 16.3 (d, J_{PC} = 5.8 Hz); ^{31}P NMR δ 27.57; IR (film) 1742, 1713, 1240 cm^{-1}; EIMS *m/z* 443 (M^+). Anal. Calcd for $C_{21}H_{34}NO_7P$: C, 56.88; H, 7.73; N, 3.16. Found: C, 56.60; H, 7.65; N, 3.26.

(2*S*)-2-[*tert*-Butoxycarbonyl)amino]-3-{4-[(diethoxyphosphoryl)(difluoro)methyl]phenyl}propyl acetate 13b. This compounds was prepared in 83% yield from **12b** in an analogous manner to that for the preparation of **13a**. An oil; $[\alpha]_D^{25}$ –9.03 (c 0.9, MeOH); ^{1}H NMR δ 7.55 (2H, d, J = 7.8 Hz), 7.28 (2H, d, J = 7.8 Hz), 5.07 (broad s), 4.26-4.05 (5H, m), 4.06-4.01 (2H, m), 2.90-2.81 (2H, m), 2.08 (3H, s), 1.40 (9H, s), 1.30 (6H, t with small splits, J = 7.1 Hz); ^{13}C NMR δ 170.4, 154.9, 140.3, 131.0-130.2 (m), 129.0, 128.1, 127.6, 117.7 (dt, J_{FC} = 278.8 Hz, J_{PC} = 217.5 Hz), 79.0, 64.8, 64.4 (d, J_{PC} = 6.6 Hz), 50.2, 37.2, 27.9, 20.3, 15.9 (d, J = 5.3 Hz); ^{19}F NMR δ –45.3 (d, J_{PF} = 116.6 Hz), ^{31}P NMR δ 7.36 (d, J_{FP} = 116.6 Hz); IR (film) 3328, 1744, 1712, 1261, 1044 cm^{-1}; EIMS *m/z* 479 (M^+); High resolution MS *m/z* calcd for $C_{21}H_{32}F_2NO_7P$: 479.1884. Found: 479.1873.

Diethyl [(4-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxypropyl}phenyl)methyl]phsphonate 14a. A solution of **13a** (444 mg, 1 mmol) in 90% MeOH (10 mL) was treated with K_2CO_3 (for 1 h. The volatile component of the mixture was evaporated, and the residue was portioned into water and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$. The combined extracts were washed with brine, dried ($MgSO_4$),

and concentrated. The residue was purified by column chromatography on silica gel (hexane:EtOAc=1:4) to give **14a** (307 mg, 77%) as an oil. $[\alpha]_D^{25}$ -14.9 (c 0.9, MeOH); ^{1}H NMR δ 7.22 (2H, dd, J = 2.3, 8.0 Hz), 7.16 (2H, d, J = 8.0 Hz), 4.83 (1H, d, J = 5.7 Hz), 4.06-3.93 (4H, m), 3.84 (1H, broad s), 3.65-3.60 (1H, m), 3.55-3.49 (1H, m), 3.11 (2H, d, J = 21.6 Hz), 2.82 (2H, t, J = 6.1 Hz), 1.41 (9H, s), 1.23 (3H, t with small splits, J = 7.1 Hz), ^{13}C NMR δ 155.8, 136.9, 129.6 (d, J_{PC} = 9.2 Hz), 129.4 (d, J_{PC} = 2.5 Hz), 129.1 (d, J_{PC} = 9.2 Hz), 79.1, 63.1, 62.1 (d, J_{PC} = 6.7 Hz), 53.5, 36.8, 33.0 (d, J_{PC} = 138.3 Hz), 28.2, 16.2 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 27.86; IR (film) 3344, 1709, 1247 cm^{-1}; EIMS *m/z* 401 (M^+). High resolution MS *m/z* calcd for $C_{19}H_{32}NO_6P$ (M^+): 401.1967. Found: 401.1953.

Diethyl [(4-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxypropyl}phenyl)(difluoro)methyl]phsphonate 14b. This compound was prepared as an oil from **13b** in an analogous manner to that for the preparation of **14a**. Yield: 64%; $[\alpha]_D^{25}$ –13.2 (c 1.1, MeOH); ^{1}H NMR δ 7.54 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 4.80 (1H, broad d, J = 7.1 Hz), 4.25-4.09 (4H, m), 3.84 (1H, broad s), 3.66 (1H, dd, J = 3.7, 10.9 Hz), 3.55 (1H, dd, J = 5.0, 10.9 Hz), 2.89 (2H, d, J = 6.7 Hz), 1.40 (9H, s), 1.31 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 155.8, 141.4, 130.2 (dt, J_{PC} = 13.8 Hz, J_{FC} = 22.1 Hz), 129.4, 126.1, 118.0 (dt, J_{PC} = 219.3 Hz, J_{FC} = 262.7 Hz), 79.2, 64.7 (d, J_{PC} = 6.7 Hz), 63.0, 53.3, 37.0, 28.2, 16.1 (d, J_{PC} = 5.3 Hz); ^{19}F NMR δ -45.22 (d, J_{PF} = 116.9 Hz); ^{31}P NMR δ 6.78 (t, J_{FP} = 116.9 Hz); IR (film) 3441, 3330, 1708, 1261 cm^{-1}; EIMS *m/z* 437 (M^+). Anal. Calcd for $C_{19}H_{30}F_2NO_6P$: C, 52.17; H, 6.93; N, 3.20. Found: C, 51.88; H, 6.86; N, 3.33.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-{4-[(diethoxyphosphoryl)methyl]phenyl}propanoic acid 15a. A solution of **14a** (602 mg, 1.5 mmol) in acetone (30 mL) was added Jones reagent (3 mL) under ice-cooling. The mixture was stirred at room temperature for 1 h. The reaction was quenched with 2-propanol (5 mL). The mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$:MeOH=20:1) to give **15a** (471 mg, 75%) as amorphous powder. $[\alpha]_D^{25}$ +24.0 (c 0.97, EtOAc), *lit.*,[8a] $[\alpha]_D^{25}$ +26.2 (c 1.0, EtOAc); ^{1}H NMR δ 7.19 (2H, broad d, J = 7.9 Hz), 7.12 (2H, broad d, J = 7.9 Hz), 5.08 (2H, broad d, J = 7.9 Hz), 4.59-4.53 (1H, m), 4.02-3.87 (4H, m), 3.24-3.04 (2H, m), 1.40 (9H, s), 1.20 (3H, t with small splits, J = 7.0 Hz), 1.17 (3H, t, J = 7.0 Hz); ^{13}C NMR δ 173.1, 154.9, 134.9 (d, J_{PC} = 3.4 Hz), 129.2–129.1 (m), 79.2, 62.3 (d, J_{PC} = 3.2 Hz), 53.9, 37.1, 32.7 (d, J_{PC} = 137.4 Hz), 28.0, 16.0 (d, J_{PC} = 9.2 Hz); ^{31}P NMR δ 28.8; IR (film) 3700-2080, 1714, 1168, 1054, 1025 cm^{-1}; EIMS *m/z* 416 (M^++1), 359 (M^+–*tert*-Bu). High resolution MS *m/z* calcd for $C_{15}H_{22}NO_7P$ (M^+–*tert*-Bu): 359.1134. Found: 359.1138.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-{4-[(diethoxyphosphoryl)(difluoro)methyl]phenyl}propanoic acid 15b. Prepared by Jones oxidation of **14b** in an analogous manner to that for the preparation of **15a**. Yield: 83%. $[\alpha]_D^{25}$ +8.43 (c 0.88, MeOH), *lit.*,[9b] $[\alpha]_D^{25}$ +8.06 (c 1.08, MeOH); ^{1}H NMR δ 7.53 (2H, d, J = 7.7 Hz), 5.08 (1H, d, J = 7.5 Hz), 4.65-4.55 (1H, m), 3.23 (1H, dd, J = 5.3, 13.5 Hz), 3.12 (1H, dd, J = 5.4, 13.5 Hz), 1.42 (9H, s), 1.33-1.25 (6H, m); ^{13}C NMR δ 173.4, 155.2, 139.5, 131.5-130.4 (m), 129.5, 126.0, 117.8 (dt, J_{PC} = 219.1 Hz, J_{FC} = 261.5 Hz), 79.8, 63.6 (d, J_{PC} = 6.7 Hz), 53.9, 37.6, 28.1, 16.0 (d, J_{PC} = 5.3 Hz); ^{19}F NMR δ –45.6 (d, J_{PF} = 117.9 Hz); ^{31}P NMR δ 6.67 (t, J_{FP} = 117.9 Hz); IR (film) 1714, 1260 cm^{-1}; EIMS *m/z* 452 (M^++1), 395 (M^+–*tert*-Bu). High resolution MS *m/z* calcd for $C_{15}H_{20}F_2NO_7P$ (M^+–*tert*-Bu): 395.0945. Found: 395.0940.

(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-{4-(diethoxyphosphoryl)methyl]benzyl}propyl acetate 16a. To a stirred solution of **6a** (3.58 g, 10 mmol) and Ph_3P (3.15 g, 12 mmol) in THF (100 mL) was

successively added HN_3 [30 mL of benzene solution of HN_3 prepared from NaN_3 (3.00 g, 46 mmol) and 50% H_2SO_4 (20 mL) in benzene (60 mL)] and diisopropyl azodicarboxylate (2.4 mL, 12 mmol) at -35 °C. The mixture was stirred at the same temperature for 30 min, and allowed to warm to room temperature. After being stirred for 2 h, the volatile component of the mixture was evaporated. The residue was dissolved in ether (30 mL), and cooled at -40 °C for 1 h. The precipitate was filtered and the filtrate was evaporated to give an azide (5.6 g), which was used for the next reaction without purification. A solution of the azide and Boc_2O (2.26 g, 12 mmol) in EtOAc (100 mL) was hydrogenated over 10% Pd-C (250 mg) for 2 h at room temperature under atmospheric pressure. The catalyst was removed through Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 2:1 to 1:2) to give **16a** (4.48 g, 98%) as an oil. $[\alpha]_D^{25}$ +4.54 (c 1.0, MeOH); ^{1}H NMR δ 7.12 (2H, dd, J = 2.3, 8.0 Hz), 7.05 (2H, d, J = 8.0 Hz), 4.87 (1H, broad s), 4.01 (1H, dd, J = 4.5, 11.2 Hz), 3.98-3.90 (4H, m), 3.84 (1H, dd, J = 5.4, 11.2 Hz), 3.19-3.10 (1H, m), 3.05 (2H, d, J = 21.5 Hz), 3.04-2.97 (1H, m), 2.60 (3H, s), 1.38 (9H, s), 1.18 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 170.9, 155.9, 137.6 (d, J_{PC} = 2.9 Hz), 129.8 (d, J_{PC} = 6.5 Hz), 129.4 (d, J_{PC} = 9.1 Hz), 129.0, 79.0, 63.9, 61.9 (d, J_{PC} = 6.5 Hz), 41.4, 40.1, 34.9, 33.2 (d, J_{PC} = 138.1 Hz), 28.2, 20.7, 16.2 (d, J_{PC} = 5.7 Hz); ^{31}P NMR δ 26.16; IR (film) 1738, 1712, 1246 cm^{-1}; EIMS *m/z* 458 (M^++1). Anal. Calcd for $C_{22}H_{36}NO_7P$: C, 57.76; H, 7.93; N, 3.06. Found: C, 57.40; H, 7.99; N, 3.11.

(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-{4-(diethoxyphosphoryl)(difluoro)methyl]benzyl}propyl acetate 16b. This compound was prepared in 68% yield from **6b** in an analogous manner to that for the preparation of **16a**. An oil; $[\alpha]_D^{25}$ +2.99 (c 1.0, MeOH); ^{1}H NMR δ 7.54 (2H, d, J = 7.8 Hz), 4.77 (1H, broad s), 4.25-4.07 (5H, m), 3.92-3.88 (1H, m), 3.25-3.17 (1H, m), 3.10-3.02 (1H, m), 2.71 (1H, dd, J = 6.3, 14.1 Hz), 2.63 (1H, dd, J = 8.9, 14.1 Hz), 2.22-2.12 (1H, m), 2.06 (3H, s), 1.43 (9H, s), 1.30 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 170.9, 155.9, 142.2, 130.7-130.1 (m), 128.9, 128.3, 126.2, 117.9 (dt, J_{PC} = 218.9 Hz, J_{PC} = 263.1 Hz), 79.0, 64.5 (d, J_{PC} = 6.7 Hz), 63.7, 41.3, 40.0, 35.1, 28.1, 20.6, 16.1 (d, J_{PC} = 5.1 Hz); ^{19}F NMR δ -45.3 (d, J_{PF} = 117.0 Hz); ^{31}P NMR δ 7.56 (t, J_{FP} = 117.0 Hz); IR (film) 3343, 1739, 1713, 1262 cm^{-1}; EIMS *m/z* 494 (M^++1). Anal. Calcd for $C_{22}H_{34}F_2NO_7P$: C, 53.55; H, 6.94; N, 2.84. Found: C, 53.36; H, 6.84; N, 2.95.

(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-{3-(diethoxyphosphoryl)methyl]benzyl}propyl acetate 16c. This compound was prepared in 86% yield from **6c** in an analogous manner to that for the preparation of **16a**. An oil; $[\alpha]_D^{25}$ +1.99 (c 1.0, MeOH); ^{1}H NMR δ 7.26-7.02 (4H, m), 4.80 (1H, broad s), 4.13-3.88 (6H, m), 3.21-3.01 (2H, m), 3.10 (2H, d, J = 21.6 Hz), 2.64 (1H, dd, J = 6.5, 13.8 Hz), 2.57 (1H, dd, J = 8.3, 13.8 Hz), 2.17-2.08 (1H, m), 2.05 (3H, s), 1.42 (9H, s), 1.22 (6H, t, J = 7.1 Hz); ^{13}C NMR δ 170.9, 155.8, 139.2 (d, J_{PC} = 2.7 Hz), 131.5 (d, J_{PC} = 9.1 Hz), 130.2 (d, J_{PC} = 6.5 Hz), 128.4, 127.5 (d, J_{PC} = 6.4 Hz), 127.3, 78.8, 63.8, 61.8 (d, J_{PC} = 6.7 Hz), 41.2, 40.0, 35.1, 33.3 (d, J_{PC} = 137.9 Hz), 28.1, 20.6, 16.1 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 27.6; IR (film) 3303, 1738, 1713, 1245 cm^{-1}; EIMS *m/z* 457 (M^+). Anal. Calcd for $C_{22}H_{36}NO_7P$: C, 57.76; H, 7.93; N, 3.06. Found: C, 57.79; H, 7.88; 3.13.

Diethyl [{4-[(2*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)propyl]phenyl}-methyl]phosphonate 17a. A solution of **16a** (4.57 g, 10 mmol) in 5% aqueous MeOH (100 mL) was treated with K_2CO_3 (2.76 g, 20 mmol) at 25 °C for 1 h. The solvent was evaporated and the residue was portioned between water and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc

= 1:2 to 1:4) to give **17a** (3.8 g, 92%) as an oil. $[\alpha]_D^{25}$ –9.59 (c 1.0, MeOH); ^{1}H NMR δ 7.14 (2H, dd, *J* = 2.3, 8.0 Hz), 7.06 (2H, d, *J* = 8.0 Hz), 5.18 (1H, broad s), 4.00-3.87 (4H, m), 3.53-3.46 (1H, m), 3.35-3.28 (1H, m), 3.19-3.13 (1H, m), 3.04 (2H, d, *J* = 21.4 Hz), 3.06-2.98 (1H, m), 2.54 (1H, dd, *J* = 7.7, 13.5 Hz), 2.44 (1H, dd, *J* = 7.2, 13.5 Hz), 1.81 (1H, broad s), 1.37 (9H, s), 1.17 (6H, t, *J* = 7.1 Hz); ^{13}C NMR δ 157.2, 138.6 (d, J_{PC} = 3.2 Hz), 129.6 (d, J_{PC} = 6.8 Hz), 129.0 (d, J_{PC} = 1.9 Hz), 128.9 (d, J_{PC} = 9.3 Hz), 79.3, 62.0 (d, J_{PC} = 7.0 Hz), 61.7, 43.1, 40.6, 34.8, 33.0 (d, J_{PC} = 138.3 Hz), 28.2, 16.1 (d, J_{PC} = 5.8 Hz); ^{31}P NMR δ 26.43; IR (film) 3369, 1710, 1251 cm^{-1}; EIMS *m/z* 416 (M^++1). Anal. Calcd for $C_{20}H_{34}NO_6P$: C, 57.82; H, 8.25; N, 3.37. Found: C, 57.48; H, 8.14; N, 3.39.

Diethyl [{4-[(2*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)propyl]phenyl}-(difluoro)methyl]phosphonate 17b. This compound was prepared in 88% yield from **16b** in an analogous manner to that for the preparation of **17a**. An oil; $[\alpha]_D^{25}$ -8.42 (c 1.0, MeOH); ^{1}H NMR δ 7.52 (2H, d, *J* = 7.6 Hz), 7.25 (2H, d, *J* = 7.6 Hz), 4.84 (1H, broad s), 4.25-4.09 (4H, m), 3.59-3.40 (2H, m), 3.41-3.32 (1H, m), 3.23-3.08 (2H, m), 2.68 (1H, dd, *J* = 7.7, 13.7 Hz), 2.55 (1H, dd, *J* = 7.5, 13.7 Hz), 1.87 (1H, m), 1.44 (9H, s), 1.30 (6H, t, *J* = 6.7 Hz); ^{13}C NMR δ 157.4, 143.1, 130.5-130.0 (m), 129.0, 128.4 (d, J_{PC} = 12.4 Hz), 126.2 (m), 118.0 (dt, J_{PC} = 219.1 Hz, J_{FC} = 263.1 Hz), 79.7, 64.7 (d, J_{PC} = 6.7 Hz), 61.4, 43.2, 40.5, 35.0, 28.2, 16.2 (d, J_{PC} = 5.4 Hz); ^{19}F NMR δ -45.2 (d, J_{PF} = 117.1 Hz); ^{31}P NMR δ 7.59 (t, J_{FP} = 117.1 Hz); IR (film) 1690, 1262 cm^{-1}; EIMS *m/z* 452 (M^++1). Anal. Calcd for $C_{20}H_{32}F_2NO_6P$: C, 53.21; H, 7.14; N, 3.10. Found: C, 53.45; H, 7.17; N, 3.17.

Diethyl [{3-[(2*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)propyl]phenyl}-methyl]phosphonate 17c. This compound was prepared in 84% yield from **16c** in an analogous manner to that for the preparation of **17a**. An oil; $[\alpha]_D^{25}$ -8.84 (c 1.0, MeOH); ^{1}H NMR δ 7.26-7.04 (4H, m), 4.90 (1H, broad s), 4.06-3.92 (4H, m), 3.57-3.53 (1H, m), 3.27-3.21 (1H, m), 3.11 (2H, d, *J* = 21.6 Hz), 3.07-3.01 (1H, m), 2.62 (1H, dd, *J* = 7.4, 13.6 Hz), 2.49 (1H, dd, *J* = 7.9, 13.6 Hz), 1.92-1.83 (1H, m), 1.44 (9H, s), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR δ 157.3, 140.2 (d, J_{PC} = 2.5 Hz), 131.3 (d, J_{PC} = 6.3 Hz), 128.4 (d, J_{PC} = 2.2 Hz), 127.5 (d, J_{PC} = 3.1 Hz), 127.3 (d, J_{PC} = 6.6 Hz), 79.3, 62.0 (d, *J* = 6.7 Hz), 61.7, 43.2, 40.4, 35.0, 33.4 (d, J_{PC} = 137.8 Hz), 28.2, 16.2 (d, J_{PC} = 5.8 Hz); ^{31}P NMR δ 27.88; IR (film) 3371, 1709, 1246 cm^{-1}; EIMS *m/z* 415 (M^+). High resolution MS *m/z* calcd for $C_{20}H_{34}NO_6P$ (M^+): 415.2124. Found: 415.2105.

(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-{4-[(diethoxyphosphoryl)methyl]benzyl}propanoic acid 18a. To a solution of **17a** (2.63 g, 6.3 mmol) in acetone (126 mL) was added Jones reagent (13 mL) under ice-cooling. After being stirred for 40 min at room temperature, the reaction was quenched with 2-propanol. The mixture was diluted in water, and extracted with ether. The extracts were washed brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel ($CHCl_3$:MeOH=500:1 to 200:1) to give **18a** (2.46 g, 91%) as amorphous powder. $[\alpha]_D^{25}$ +2.04 (0.98, MeOH); ^{1}H NMR δ 7.18 (2H, broad d, *J* = 8.2 Hz), 7.14 (2H, d, *J* = 8.2 Hz), 5.03 (1H, broad s), 4.05-3.89 (4H, m), 3.43-3.33 (1H, m), 3.29-3.16 (1H, m), 3.11 (2H, d, *J* = 21.6 Hz), 3.00-2.81 (2H, m), 1.42 (9H, s), 1.22 (6H, t, *J* = 5.9 Hz); ^{13}C NMR δ 176.8, 155.9, 137.2, 129.8 (d, J_{PC} = 6.4 Hz), 129.1, 80.9, 62.4 (d, J_{PC} = 7.1 Hz), 47.1, 41.1, 35.4, 33.1 (d, J_{PC} = 138.2 Hz), 28.3, 16.2 (d, J_{PC} = 5.9 Hz); ^{31}P NMR δ 28.68; IR (film) 1714, 1251 cm^{-1}; EIMS *m/z* 430 (M^++1), 429 (M^+). High resolution MS *m/z* calcd for $C_{16}H_{24}NO_7P$ (M^+–*tert*-Bu): 373.1290. Found: 373.1290.

(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-{4-[(diethoxyphosphoryl)(difluoro)methyl]benzyl}-propanoic acid 18b. Obtained in 89% yield by Jones oxidation of **17b** in an analogous manner to that for the

preparation of **18a** after column chromatography on silica gel (hexane:EtOAc = 1:1 to 1:4). An oil; $[\alpha]_D^{25}$ +2.04 (c 1.07, MeOH); ^{1}H NMR δ 7.53 (2H, d, J = 7.9 Hz), 7.29 (2H, d, J = 7.9 Hz), 5.02 (1H, m); 4.25-4.07 (4H, m), 3.43-2.73 (5H, m), 1.47 (9H, s), 1.30 (6H, t, J = 7.0 Hz); ^{13}C NMR δ 177.0, 155.9, 141.5, 132.1 (d, J_{PC} = 10.2 Hz), 130.9-130.3 (m), 129.0, 126.4, 117.9 (dt, J_{PC} = 219.4 Hz, J_{FC}= 263.0 Hz), 79.5, 64.9, 46.9, 41.4, 35.3, 28.3, 16.2 (d, J_{PC} = 5.4 Hz); ^{31}P NMR δ 7.48 (t, J_{FP} = 117.8 Hz); IR (film) 1713, 1261 cm^{-1}; EIMS *m/z* 466 (M^++1). High resolution MS *m/z* calcd for $C_{18}H_{26}F_2NO_7P(M^+-C_2H_4)$: 437.1415. Found: 437.1425.

(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-{3-[(diethoxyphosphoryl)methyl]benzyl}propanoic acid 18c. Obtained in 84% yield by Jones oxidation of **17c** in an analogous manner to that for the preparation of **18a** after column chromatography on silica gel ($CHCl_3$:MeOH=500:1 to 200:1). An oil; $[\alpha]_D^{25}$ +0.60 (c 1.01, MeOH); ^{1}H NMR δ 7.26-7.08 (4H, m), 5.12 (broad s), 4.05-3.90 (4H, m), 3.40-3.31 (1H, m), 3.28-3.18 (1H, m), 3.11 (2H, d, J = 21.7 Hz), 2.98-2.79 (3H, m), 1.40 (9H, s), 1.20 (6H, t, J = 7.0 Hz); ^{13}C NMR δ 176.3, 155.7, 138.7 (d, J_{PC} = 2.5 Hz), 130.9 (d, J_{PC} = 9.3 Hz), 130.2 (d, J_{PC} = 6.3 Hz), 128.4, 127.7 (d, J_{PC} = 6.3 Hz), 127.5, 79.0, 62.3 (d, J_{PC} = 6.2 Hz), 46.9, 41.1, 35.4, 33.2 (d, J_{PC} = 138.2 Hz), 28.1, 16.0 (d, J_{PC} = 5.8 Hz); ^{31}P NMR δ 28.04; IR (film) 1714, 1249 cm^{-1}; EIMS *m/z* 430 (M^++1), 429 (M^+). High resolution MS *m/z* calcd for $C_{16}H_{24}NO_7P$: (M^+–*tert*-Bu): 373.1290. Found: 373.1311.

ACKNOWLEDGMENT

This work was supported in part by Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports and Culture of Japan.

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