



Lipase-Catalyzed Enantioselective Acylation of Prochiral 2-(ω -Phosphono)alkyl-1,3-Propanediols: Application to the Enantioselective Synthesis of ω -Phosphono- α -Amino Acids

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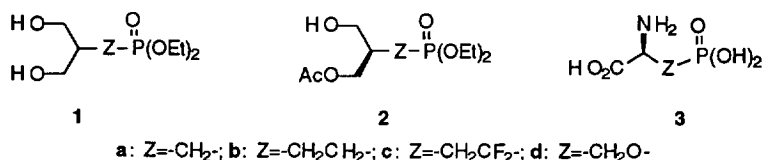
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Abstract: Lipase PS catalyzed acetylation of prochiral 2-(ω -phosphono)alkyl-1,3-propanediols **1a-c** was found to proceed with high enantioselectivity. The applications of phosphonic chirons **2a-c** thus obtained were illustrated by the stereocontrolled synthesis of ω -phosphono- α -amino acids such as L-AP-3, L-AP-4, and N-Boc-L-F₂Pab(OEt)₂-OH.

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INTRODUCTION

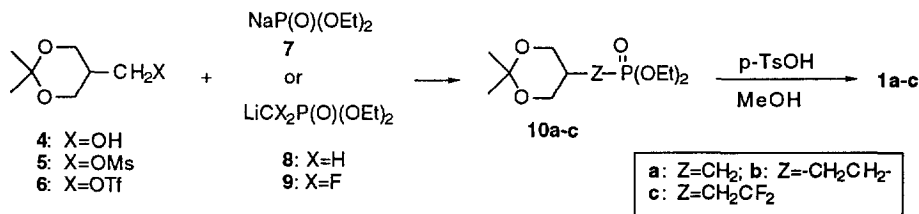
The phosphonic acids are an important class of compounds which exhibit a variety of biologically interesting properties.¹ Chiral non-racemic ω -phosphono- α -amino acids such as L-2-amino-3-phosphonopropanoic acid (L-AP-3) **3a** and L-2-amino-4-phosphonobutyric acid (L-AP-4) **3b** are known to show potent selective antagonist activities against glutamate receptors as well as to show antiviral activity.^{2,3} The difluoromethylene phosphonate analogue **3c** for phosphoserine (pSer) **3d** is a useful component for the synthesis of phosphatase resistant phosphonopeptides in studying signal transduction.⁴ Therefore the asymmetric synthesis of these phosphonate molecules has been intensely studied subject in recent years.^{3,4} Our interest in this area centers on the development of versatile phosphonic chirons such as **2a-c** which would not only be useful for an enantiocontrolled synthesis of these ω -phosphono- α -amino acids in both L- and D-forms but also be valuable on synthesizing chiral phosphonate analogues of naturally occurring biological phosphates. For these purpose, asymmetrization of prochiral 2-(ω -phosphono)alkyl-1,3-propanediols **1a-c** through transesterification with lipase seems to be one of the most promising methods. However, to the best of our knowledge, these protocols have never been applied to the enantioselective synthesis of chiral phosphonate derivatives **2a-c**, while asymmetrization protocols of 2-substituted 1,3-propanediols with lipases have been applied to synthesizing a variety of chiral non-racemic compounds of biological interest.⁵ In this paper, we disclose lipase-catalyzed enantioselective acylation of **1a-c** giving the chirons **2a-c** with high enantiomeric purity, in addition to their application to the enantioselective synthesis of ω -phosphono- α -amino acids **3a-c**.



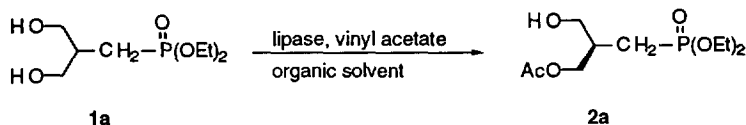
RESULTS AND DISCUSSION

Requisite 2-(phosphono)alkyl-1,3-propanediols **1a-c** were prepared efficiently from readily available isopropylidene-2-hydroxymethyl-1,3-propanediol **4**⁶ (Scheme 1). Michaelis-Becker reaction of the methanesulfonate **5** with **7** [NaH, HP(O)(OEt)₂, DMF, 80 °C] gave the phosphonate **10a** in 96% yield. The homologous phosphonate **10b** and its α,α -difluoro-substituted analogue **10c** were prepared from the triflate **6** through coupling reactions with the corresponding phosphorus-stabilized carbanions **8** and **9** in 70 and 65% yield, respectively, according to the method of Berkowitz⁷ [THF, HMPA, -78 °C]. Deprotection of the acetones **10a-c** in an usual manner [MeOH, *p*-TsOH] gave **1a-c** in virtually quantitative yields.

Scheme 1



First, the lipase-catalyzed transesterification of **1a** with vinyl acetate was examined in several representative organic solvents by using various commercially available lipases. Among the lipases examined,⁸ lipase PS from *Pseudomonas ceparia* and lipase AK from *Pseudomonas fluorescense* were found to catalyze the transesterification reaction. The results are summarized in Table 1. When the transesterification reaction was carried out in the presence of lipase AK in *i*-Pr₂O at 25 °C, the desired mono-acetate **2a** of modest enantiomeric purity (70%) was obtained in good yield (entry 1). The enantioselectivity significantly increased to 98% *ee*, upon conducting the reaction with lipase PS under the same conditions (entry 2). While the reaction proceeded with a low enantioselectivity in hexane and a considerable amount of diacetate was detected (entry 8), THF, *t*-BuOMe, and benzene were also found to be useful solvents for lipase PS-catalyzed transesterification reaction with a high degree of enantioselectivity (entries 4 and 6-7). It was also found that the reaction temperature strongly affects the enantioselectivity; substantial decrease in enantioselectivity was observed upon conducting the reaction at 37 °C (entries 3 and 5).

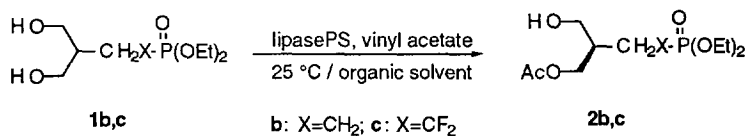
Table 1. Lipase-catalyzed transesterification of 2-(diethylphosphonomethyl)-1,3-propanediol **1a.**

Entry ^a	Lipase	Solvent	Temp.(°C)	Time(min)	Yield(%)	Ee(%) ^b
1	lipase AK	<i>i</i> -Pr ₂ O	25	90	98	70
2	lipase PS	<i>i</i> -Pr ₂ O	25	120	92	98
3	lipase PS	<i>i</i> -Pr ₂ O	37	150	88	83
4	lipase PS	THF	25	150	98	98
5	lipase PS	THF	37	150	90	78
6	lipase PS	<i>t</i> -BuOMe	25	120	92	97
7	lipase PS	benzene	25	120	94	98
8	lipase PS	hexane	25	90	72	79

^aAll reactions were carried out on 1 g scale in the presence of 1.0 equiv. of vinyl acetate and 1 g of lipase.

^bDetermined by HPLC analysis on a chiral phase (Daicel Chiralpak AS).

Having established efficient conditions for the asymmetrization of **1a** with lipase PS, next, our attentions were focused on the transesterification reaction of the homologous phosphonate **1b** and the α,α -difluoro-substituted analogues **1c** to examine how the asymmetric recognition with lipase PS is affected by the distance between the phosphonate group and the prochiral center as well as the fluorine atoms in the molecules (Table 2). As compared with the transesterification reaction of **1a**, the enantioselectivity of the transesterification reaction on homologues phosphonate **1b** was found to decrease slightly under the same conditions (entries 1,2 vs. entries 1,2 in Table 1). It is noteworthy that the transesterification reactions of fluorinated phosphono-1,3-propanediol **1c** were much faster than those of the non-fluorinated analogue **1b** and generally proceeded with higher enantioselectivities (entries 1,2 vs. 3-6). Excellent results regarding with enantioselectivity and yield were obtained by the use of THF or *i*-Pr₂O (entries 3 and 4).

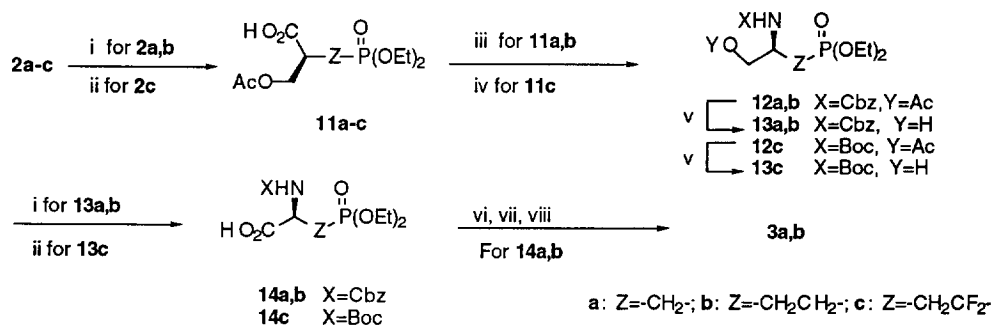
Table 2. Lipase PS-catalyzed transesterification reaction of **1b,c.**

Entry	Substrate	Solvent	Time(min)	Product	Yield(%)	Ee(%)
1	1b	<i>i</i> -Pr ₂ O	150	2b	83	91 ^a
2	1b	THF	240	2b	85	93 ^a
3	1c	<i>i</i> -Pr ₂ O	40	2c	98	98 ^b
4	1c	THF	60	2c	98	98 ^b
5	1c	<i>t</i> -BuOMe	50	2c	98	93 ^b
6	1c	benzene	60	2c	99	96 ^b

^a Determined by HPLC analysis on Daicel Chiralpak AS. ^b Determined by HPLC analysis of the corresponding Mosher esters.

To establish the absolute configuration of the phosphonic chirons **2a-c** as well as to demonstrate their synthetic utility, the chemical transformations towards the known ω -phosphono- α -amino acids **3** were carried out (Scheme 2). Oxidation of **2a,b** with Jones reagent as usual gave acetoxy acids **11a,b** in 65 and 73% yield, respectively. The alcohol **2c** was converted to **11c** in 60% yield through Ru-catalyzed oxidation.⁹ Curtius rearrangement [DPPA, PhCH₂OH or *t*-BuOH]¹⁰ of **11a-c** gave the carbamates **12a-c** [**12a**: 52% yield; **12b**: 71% yield; **12c**: 42% yield].¹¹ The enantiomeric purity of **12a**, **12b**, and **12c** was determined to be >95, 96, and 94% *ee* by HPLC and ¹H NMR analyses of the corresponding Mosher esters. Transformation of **12a-c** into **13a-c** was effective on treatment with Et₃N in MeOH at room temperature. Jones oxidation of **13a** and **13b** gave the acids **14a** and **14b**, a protect form of L-AP-3 and L-AP-4, in 65% and 70% yield, respectively. Hydrogenolysis [H₂ / 10% Pd-C / MeOH] of **14a** and **14b**, followed by acid hydrolysis in an usual manner, gave **3a** [mp 224-226 °C (dec.), [α]_D²⁵ +58.9 (c 1.0, 1N NaOH)] and **3b** [mp 145-146 °C, [α]_D²⁵ +26.0 (c 1.0, 6N HCl)]. The chiroptical comparison with the authentic L-AP-3^{3a} and L-AP-4^{3b,c} clearly reveals that **3a** and **3b** should be the assigned stereochemistry. Then, the absolute configurations of **2a** and **2b** were determined to be *R* at this stage. Ru-catalyzed oxidation of **13c** as reported by Otaka and Burke^{4b} gave N-Boc-L-F₂Pab(OEt)₂-OH **14c**, [mp 112-113 °C, [α]_D²⁵ -10.0 (c 1.1, MeOH)], a phosphoserine mimic bearing protecting groups amenable to automated solid peptide synthesis.⁴ Physical data of **14c** are consistent with the reported one in all respects. Therefore, the absolute configuration of **2c** was established as *R*.

Scheme 2 Transformations of **2a-c** to ω -phosphono- α -amino acids

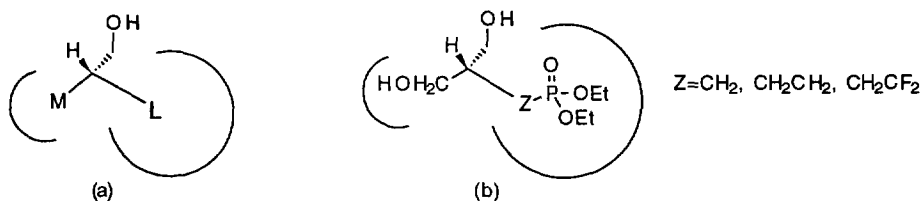


^a Key: i) Jones oxidation; ii) RuCl₃, NaIO₄ in CCl₄-CH₃CN-H₂O; iii) DPPA, Et₃N, PhCH₂OH, Δ ; iv) DPPA, Et₃N, *t*-BuOH, Δ ; v) Et₃N, MeOH, RT; vi) H₂, 10%Pd-C, MeOH; vii) 6N HCl, Δ ; viii) propylene oxide

The stereochemical preference for the lipase PS-catalyzed transesterification of 2-(ω -phosphono)alkyl-1,3-propanediols **2a-c** is consistent with the predictions based on an empirical rule for enantiodiscrimination of chiral primary alcohols with lipases from *Pseudomonas ceparia*, which is recently proposed by Kazlauskas.¹² In the Kazlauskas model, two distinct lipophilic pockets are estimated to exist in the lipase active site which bind the large (L) and medium (M) substituents of the chiral primary alcohols, then, the lipase catalyzes the reaction in favor of the chirality as shown in Fig. 1-a. Taking the ω -phosphonoalkyl groups of **1a-c** to be the large substituent, but the hydroxymethyl group to be the medium substituent, the *pro-R* hydroxymethyl group of **1a-c** would be acylated preferentially from this model (Fig. 1-b). The stereochemical outcome of lipase PS-catalyzed acetylation of **1a-c** agrees with these predictions. The results obtained in this study also suggest that the L pocket is large enough to bind the substituents having the tetrahedral diethylphosphono functionality without the

significant loss of the capability of the enantiodiscrimination. Moreover, the finding obtained from the transesterification reaction of the fluorinated phosphonate **2c** as shown in Table 2 reveals that the introducing the fluorine atoms at the α -position of the phosphonate increases the binding affinity to the L pocket, probably due to the increased lipophilicity arising from the fluorine atoms.

Fig. 1. Predictions for the preferred enantiodiscrimination of chiral primary alcohols with lipases from *Pseudomonas ceparia*



In conclusion, we have developed efficient asymmetric protocols for **1a-c** yielding phosphonic chirons **2a-c** and have demonstrated their synthetic applications to ω -phosphono- α -amino acids **3**. Further applications of phosphonic chirons **2a-c** to the asymmetric synthesis of biologically interesting phosphonate molecules are in due course.

EXPERIMENTAL

General. Melting points are uncorrected. Unless specified otherwise, all reactions were carried out under nitrogen atmosphere. ^1H NMR spectra (300 MHz) were recorded for solution in CDCl_3 as indicated. The chemical shifts (ppm) were reported relative to TMS (0 ppm) or CHCl_3 (7.26 ppm) as an internal reference for solution in CDCl_3 . ^{13}C NMR spectra (75 or 100 MHz) was taken for solution in CDCl_3 or D_2O as indicated. The chemical shifts (ppm) were reported relative to CDCl_3 (77.0 ppm) for solution in CDCl_3 or to acetone- d_6 (29.8 and 206.5 ppm) for solution in D_2O as an internal standard. ^{31}P NMR spectra (160 MHz) was recorded in CDCl_3 using 85% H_3PO_4 as an external standard with broad-band ^1H -decoupling.

2,2-Dimethyl-5-(diethylphosphono)methyl-1,3-dioxane 10a. To a stirred suspension of NaH [1.61 g, 40.3 mmol] in DMF (7 mL) was added diethyl phosphite (5.18 mL, 40.3 mmol) dropwise at 0 °C. The mixture was stirred for 30 min at same temperature and allow to stand at 60 °C for 30 min. After cooled to 0 °C, a solution of the methansulfonate **5⁶** (4.52 g, 20.2 mmol) in DMF (23 mL) was added dropwise. After being stirred at 60 °C for 14 h, the reaction was quenched by addition of *sat.* NH_4Cl . The mixture was extracted with Et_2O . The combined extracts were washed with brine, dried over MgSO_4 , and concentrated to give an oil. Purification by column chromatography (silica gel, hexane-EtOAc=1:1) gave **10a** (5.2 g, 96% yield) as an oil; ^1H NMR (CDCl_3) δ 4.16-4.04 (4H, m), 4.0 (1H, dd, $J=11.9, 4.3$ Hz), 3.66 (1H, dd, $J=11.9, 7.6$ Hz), 2.26-2.10 (1H, m), 1.75 (2H, dd, $J=18.8, 6.8$ Hz), 1.42 (6H, s), 1.33 (6H, t, $J=7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 97.8, 64.6 (d, $J=15.0$ Hz), 61.5 (d, $J=6.4$ Hz), 29.3 (d, $J=3.1$ Hz), 25.2 (d, $J=142.0$ Hz), 25.0, 22.5, 16.3 (d,

$J=5.6$ Hz); ^{31}P NMR (CDCl_3) δ 29.9; IR (neat) 1260, 1028 cm^{-1} ; EIMS m/z 267 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{11}\text{H}_{23}\text{O}_5\text{P}$: C, 49.61; H, 8.71. Found: C, 49.21; H, 8.63.

2,2-Dimethyl-5-(trifluoromethanesulfonyloxy)methyl-1,3-dioxane 6. To a cooled (-40 °C) solution of the alcohol **4**⁶ (1.44 g, 9.9 mmol) and pyridine (0.96 mL, 11.9 mmol) in CH_2Cl_2 (50 mL) was added triflic anhydride (1.99 mL, 11.9 mmol), dropwise, *via* syringe. The mixture was stirred at this temperature for 30 min and diluted with Et_2O . The precipitate was filtered and the filtrate was evaporated to give the crude triflate **6** (2.5 g, 90%) as an unstable oil, which was immediately used for the next coupling reaction. ^1H NMR (CDCl_3) δ 4.75 (2H, d, $J=7.4$ Hz), 4.12 (2H, dd with small splits, $J=11.4$, 3.4 Hz), 3.78 (2H, dd with small splits, $J=11.4$, 3.3 Hz), 2.05-1.96 (1H, m), 1.47 (3H, s), 1.39 (3H, s).

2,2-Dimethyl-5-(2'-diethylphosphono)ethyl-1,3-dioxane 10b. To a cooled (-78 °C) solution of *n*-butyllithium (10.8 mL of 1.6 M solution in hexane) in THF (30 mL) was added HMPA (3.0 mL, 17.23 mmol). The mixture was stirred for 10 min, then, a solution of diethyl methylphosphonate (2.52 mL, 17.23 mmol) in THF (15 mL) was added. After being stirred for 20 min at this temperature, a solution of the triflate **6** (1.71 g, 6.15 mmol) in THF (15 mL) was added dropwise. After 1 h, the reaction was quenched by adding aqueous NH_4Cl and Et_2O . The aqueous layer was further extracted with Et_2O and combined extracts were washed with brine, dried (MgSO_4), and concentrated to give a residue. Purification by column chromatography on silica gel (hexane: $\text{EtOAc}=2:1$ to $1:1$) gave **10b** (1.21 g) in 70 % yield: an oil; ^1H NMR (CDCl_3) δ 4.16-4.03 (4H, m), 3.89 (2H, dd, $J=12.5$, 4.5 Hz), 3.56 (2H, dd, $J=12.5$, 8.6 Hz), 1.86-1.50 (5H, m), 1.41 (3H, s), 1.40 (3H, s), 1.32 (6H, t, $J=7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 97.9, 64.1 (2 carbons), 61.6 (d, $J=6.8$ Hz), 34.6 (d, $J=15.5$ Hz), 26.1, 23.0 (d, $J=141.0$ Hz), 21.6 (m), 16.4 (d, $J=5.7$ Hz); ^{31}P NMR (CDCl_3) δ 31.2; IR (neat) 1241, 1057 cm^{-1} ; EIMS m/z 281 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{12}\text{H}_{25}\text{O}_5\text{P}$: C, 51.42; H, 8.99. Found: C, 50.91; H, 9.07.

2,2-Dimethyl-5-(2',2'-difluoro-2'-diethylphosphono)ethyl-1,3-dioxane 10c. To a solution of diisopropylamine (3.78 mL, 27 mmol) in THF (40 mL) was added *n*-butyllithium (20.7 mL of a 1.6 M solution in hexane) at 0 °C. The resulting solution was stirred for 20 min at 0 °C, then HMPA (4.7 mL, 27 mmol) was added. The mixture was stirred for 5 min, then, cooled to -78 °C. To this solution was added a cooled (-78 °C) solution of diethyl α,α -difluoromethylphosphonate¹³ (5.07 g, 27 mmol) in THF (20 mL) dropwise over 30 min *via* syringe pump. After being stirred for an additional 20 min, a cooled (-78 °C) solution of the triflate **6** (2.5 g, 9 mmol) in THF (20 mL) was added during 30 min *via* syringe pump. After 1 h at -78 °C, the reaction was quenched by adding aqueous NH_4Cl and Et_2O . The aqueous layer was further extracted with Et_2O and the combined extracts were washed with brine, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography on silica gel (hexane: $\text{EtOAc}=4:1$ to $1:1$) to give **10c** (1.85 g) in 65% yield: an oil; ^1H NMR (CDCl_3) δ 4.30 (2H, q, $J=7.1$ Hz), 4.26 (2H, q, $J=7.2$ Hz), 3.98 (2H, dd, $J=11.8$, 4.3 Hz), 3.65 (2H, dd, $J=11.8$, 7.7 Hz), 2.38-2.23 (1H, m), 2.08 (1H, tdd, $J=21.0$, 6.4, 4.6 Hz), 1.42 (6H, s), 1.39 (6H, t, $J=7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 121.5 (dt, $J=260.3$, 216.5 Hz), 98.5, 64.8 (4 carbons), 33.1 (dt, $J=20.7$, 14.6 Hz), 28.5, 25.4, 22.5, 16.4 (d, $J=4.5$ Hz); ^{31}P NMR (CDCl_3) δ 6.57 (t, $J=107.0$ Hz); IR (neat) 1266, 1026 cm^{-1} ; EIMS m/z 317 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{12}\text{H}_{23}\text{O}_5\text{PF}_2$: C, 45.57; H, 7.33. Found: C, 45.37; H, 7.53.

General procedure for hydrolysis of 10a-c to diols 1a-c. A solution of **10a-c** (5 mmol) and *p*-TsOH·H₂O (95 mg, 0.5 mmol) in MeOH (50 mL) was stirred at room temperature until **10a-c** disappeared on TLC (2-3 h). The reaction was quenched by addition of solid NaHCO₃. The mixture was diluted with Et₂O and the precipitate was filtered. The filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel to give **1a-c** as oils. The elution solvent, yield, and physical data for **1a-c** are as follows.

2-(Diethylphosphono)methyl-1,3-propanediol 1a. Elution with CHCl₃:MeOH (50:1 to 20:1); Yield: 96%; ¹H NMR (CDCl₃) δ 4.18-4.04 (4H, m), 3.75 (4H, d, *J*=4.9 Hz), 2.9 (2H, broad s), 2.19-2.05 (1H, m), 1.89 (2H, dd, *J*=18.7, 6.7 Hz), 1.35 (6H, t, *J*=7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 64.3 (d, *J*=9.6 Hz), 61.9 (2 carbons, d, *J*=6.9 Hz), 37.9, 24.3 (d, *J*=140.5 Hz), 16.3 (d, *J*=5.7 Hz); ³¹P NMR (CDCl₃) δ 32.4; IR (neat) 3398, 1219, 1029 cm⁻¹; EIMS *m/z* 227 (M⁺+1). Anal. Calcd for C₈H₁₉O₃P: C, 42.47; H, 8.47. Found: C, 42.54; H, 8.38.

2-(2'-Diethylphosphono)ethyl-1,3-propanediol 1b. Elution with CHCl₃:MeOH (100:1 to 50:1); Yield: 92%; an oil; ¹H NMR CDCl₃) δ 4.12-3.99 (4H, m), 3.78-3.66 (4H, m), 3.66-3.56 (2H, m), 1.84-1.76 (5H, m), 1.29 (6H, t, *J*=7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 64.0 (2 carbons), 61.8 (d, *J*=6.2 Hz), 42.7 (d, *J*=14.0 Hz), 23.0 (d, *J*=140.0 Hz), 20.3 (d, *J*=4.2 Hz), 16.4 (d, *J*=5.5 Hz); ³¹P NMR (CDCl₃) δ 32.7; IR (neat) 3380, 1217, 1029 cm⁻¹; EIMS *m/z* 241 (M⁺+1). Anal. Calcd for C₉H₂₁O₃P: C, 45.00; H, 8.81. Found: C, 44.91; H, 8.79.

2-(2',2'-difluoro-2'-diethylphosphono)ethyl-1,3-propanediol 1c. Elution with hexane:EtOAc (1:1 to 0:1); Yield: 86%; ¹H NMR (CDCl₃) δ 4.23-4.13 (4H, m), 3.84 (2H, broad s), 3.76 (1H, broad d, *J*=10.8 Hz), 3.58 (2H, m), 2.17-1.92 (3H, m), 1.30 (3H, t, *J*=7.1 Hz), 1.29 (3H, t, *J*=7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 123.4 (dt, *J*=216.6, 259.8 Hz), 66.7 (d, *J*=6.9 Hz), 65.8, 37.8 (d, *J*=5.6 Hz), 33.2 (dt, *J*=20.4, 14.6 Hz), 17.9 (d, *J*=5.2 Hz); ³¹P NMR (CDCl₃) δ 6.85 (t, *J*=109.3 Hz); IR (neat) 3402, 1258, 1029 cm⁻¹; EIMS *m/z* 277 (M⁺+1). Anal. Calcd for C₉H₁₉O₃F₂P: C, 39.13; H, 6.93. Found: C, 38.75; H, 7.15.

General procedure for lipase-catalyzed transesterification reaction of 1a-c with vinyl acetate. A mixture of substrate (1 g), vinyl acetate (1.0 equiv. to the subst.) and lipase PS or AK (1 g) in the appropriate solvent (15 mL) was stirred at 25 or 37 °C for the period as indicated in Table 1 and 2. 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 **2a-c** as oils. Yields of the transesterification reaction are summarized in Table 1 and 2. Elution solvent, physical data and the enantiomeric determination for **2a-c** are as follows.

Diethyl (2R)-3-Acetoxy-2-hydroxymethylpropylphosphonate 2a. Elution with CHCl₃; [α]_D²⁵+6.42 (c 1.0, MeOH) for a sample of 98% *ee*; ¹H NMR (CDCl₃) δ 4.19-4.01 (6H, m), 3.7-3.59 (2H, m), 3.16 (broad t, *J*=6.8 Hz), 2.27-2.19 (1H, m), 2.06 (3H, s), 1.90-1.65 (2H, m), 1.32 (6H, t, *J*=7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.1, 64.7 (d, *J*=14.2 Hz), 62.5 (d, *J*=7.6 Hz), 61.9 (d, *J*=6.3 Hz), 35.9, 24.7 (d, *J*=141.3 Hz), 20.8, 16.3 (d, *J*=5.6 Hz); ³¹P NMR (CDCl₃) δ 31.2; IR (neat) 3398, 1740, 1245, 1039 cm⁻¹; EIMS *m/z* 269 (M⁺+1). Anal. Calcd for C₁₀H₂₁O₆P: C, 44.77; H, 7.89. Found: C, 44.55; H, 7.86. The enantiomeric purity of **2a** was determined by HPLC analysis on a chiral phase [Chiralpak AS (Daicel), hexane:EtOH=9:1, flow rate=0.5 ml/min, RI detector, **2a**: Rt=15.2 min, *ent-2a*: Rt=16.7 min].

Diethyl (3R)-4-Acetoxy-3-hydroxymethylbutylphosphonate 2b. Elution with CHCl₃:MeOH (200:1 to 100:1); [α]_D²⁵-1.48 (c 1.2, MeOH) for a sample of 93% *ee*; ¹H NMR (CDCl₃) δ 4.18-4.05 (6H, m), 3.60 (1H, dd, *J*=11.3, 4.9 Hz), 3.56 (1H, *J*=11.3, 5.6 Hz), 2.06 (3H, s), 1.91-1.61 (6H, m), 1.32 (t, *J*=7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 64.1, 61.6 (3 carbons), 40.7 (d, *J*=11.4 Hz), 22.9 (d, *J*=140.7 Hz), 20.8, 20.7 (d, *J*=4.1 Hz), 16.4 (d, *J*=5.4 Hz); ³¹P NMR (CDCl₃) δ 31.9; IR (neat) 3329, 1737, 1240, 1029 cm⁻¹; EIMS *m/z* 283 (M⁺+1). Anal. Calcd for C₁₁H₂₃O₆P: C, 46.80; H, 8.21. Found: C, 47.15; H, 8.24. The enantiomeric purity of **2b** was determined by HPLC analysis [Chiralpak AS (Daicel), hexane:EtOH=20:1, flow rate=0.5 ml/min, RI detector, **2b**: Rt=14.7 min, *ent-2b*: Rt=18.3 min].

Diethyl (3R)-4-Acetoxy-2,2-difluoro-3-hydroxymethylbutylphosphonate 2c. Elution with CHCl₃; [α]_D²⁵+2.14 (c 1.0, MeOH) for a sample of 98% *ee*; ¹H NMR (CDCl₃) δ 4.26-4.20 (5H, m), 4.16 (1H, dd, *J*=11.3, 6.3 Hz), 3.66 (1H, dd, *J*=11.2, 4.5 Hz), 3.58 (1H, dd, *J*=11.2, 5.8 Hz), 2.42-2.10 (3H, m), 2.08 (3H, s), 1.38 (6H, t, *J*=7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 120.7 (dt, *J*=258.8, 214.9 Hz), 64.6 (d, *J*=6.8 Hz), 64.0, 61.9, 34.2, 31.6 (dt, *J*=20.5, 15.0 Hz), 20.7, 16.2 (d, *J*=4.7 Hz); ³¹P NMR (CDCl₃) δ 6.55 (t, *J*=106.1 Hz); IR (neat) 3449, 1741, 1250, 1029 cm⁻¹; EIMS *m/z* 319 (M⁺+1). Anal. Calcd for C₁₁H₂₁O₆F₂P: C, 41.52; H, 6.65. Found: C, 41.67; H, 6.65. The enantiomeric purity of **2c** was determined by HPLC analysis on a chiral phase after converting to (*R*)- and (*S*)-Mosher esters [Chiralpak AS (Daicel), hexane:EtOH=30:1, flow rate=0.5 ml/min, RI detector, (*R*)-Mosher ester of **2c**: Rt=17.8 min, (*R*)-Mosher ester of *ent-2c*: Rt=19.5 min].

(2R)-2-Acetoxyethyl-3-diethylphosphonopropionic acid 11a. To a solution of alcohol **2a** (300 mg, 1.2 mmol) in acetone (4.0 mL) was added Jones reagent (0.8 mL) with ice-cooling and the mixture was stirred for 6 h at 20 °C. After the excess of Jones reagent was destroyed with isopropyl alcohol, the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried (MgSO₄), and evaporated to give the crude oil. Purification by column chromatography on silica gel (CHCl₃:MeOH=80:1) gave **11a** (220 mg, 65%) as an oil; [α]_D²⁵+9.64 (c 1.1, MeOH); ¹H NMR (CDCl₃) δ 4.32 (1H, dd, *J*=11.1, 5.2 Hz), 4.26 (1H, dd, *J*=11.1, 6.1 Hz), 4.16-4.02 (4H, m), 3.05-2.96 (1H, m), 2.29 (1H, ddd, *J*=7.4, 15.6, 18.5 Hz), 2.01 (3H, s), 1.98 (1H, ddd, *J*=6.3, 15.6, 18.5 Hz), 1.29 (6H, t, *J*=7.1 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 174.6 (d, *J*=11.2 Hz), 171.1, 64.5 (d, *J*=10.1 Hz), 62.6 (with a small split), 39.2, 23.9 (d, *J*=144.6 Hz), 21.3 (d, *J*=3.7 Hz), 20.6, 16.1; ³¹P NMR (CDCl₃) δ 28.9. IR (neat) 1742, 1240, 1029 cm⁻¹; EIMS *m/z* 283 (M⁺+1). Anal. Calcd for C₁₀H₁₉O₇P: C, 42.56; H, 6.79. Found: C, 42.16; H, 6.67.

(2S)-2-Acethoxymethyl-4-diethylphosphonobutric acid 11b. Under the similar conditions described as above, **2b** (1.8 g, 6.38 mmol) gave **11b** (1.36 g, 73%) after column chromatography on silica gel (CHCl₃:MeOH=100:1); an oil; [α]_D²⁵-2.02 (c 1.1, MeOH); ¹H NMR (CDCl₃) δ 4.27 (1H, dd, *J*=11.1, 7.2 Hz), 4.21 (1H, dd, *J*=11.1, 5.9 Hz), 4.18-4.05 (4H, m), 2.86-2.76 (1H, m), 2.05 (3H, s), 2.0-1.8 (4H, m), 1.32 (6H, t, *J*=7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 175.1, 171.5, 64.1, 62.2 (d, *J*=6.2 Hz), 44.6 (d, *J*=16.5 Hz), 22.8 (d, *J*=142.3 Hz), 21.3 (d, *J*=3.7 Hz), 20.6, 16.1 (d, *J*=6.0 Hz); ³¹P NMR (CDCl₃) δ 31.6; IR (neat) 2984, 1741, 1235, 1027 cm⁻¹; EIMS *m/z* 297 (M⁺+1). Anal. Calcd for C₁₁H₂₁O₇P: C, 44.60; H, 7.15. Found: C, 44.76; H, 7.69.

(2S)-2-Acetoxyethyl-4,4-difluoro-4-diethylphosphonobutyric acid 11c. A solution of **2c** (944 mg, 2.97 mmol) in CCl_4 (4 mL), CH_3CN (4 mL), and water (6 mL) was treated with NaIO_4 (2.6 g, 12.2 mmol) and $\text{RuCl}_3 \cdot n\text{-H}_2\text{O}$ (6.6 mg) for 4 h at 25 °C. After the excess oxidant was destroyed with isopropyl alcohol, the mixture was extracted with CHCl_3 . The combined extracts were dried over MgSO_4 and evaporated. The residue was chromatographed on silica gel (CHCl_3 : MeOH =200:1) to give **11c** (581 mg, 60%) as an oil; $[\alpha]_D^{25} +7.90$ (c 1.1, MeOH); $^1\text{H NMR}$ (CDCl_3) δ 4.39-4.24 (6H, m), 3.25-3.15 (1H, m), 2.80-2.58 (1H, m), 2.40-2.20 (1H, m), 2.07 (3H, s), 1.39 (6H, t, $J=7.1$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 176.1, 171.7, 120.3 (dt, $J=261.0$, 218.0 Hz), 65.5 (d, $J=6.5$ Hz), 64.5, 38.0, 32.1 (dt, $J=15.9$, 21.1 Hz), 20.7, 16.3 ($J=5.2$ Hz); $^{31}\text{P NMR}$ (CDCl_3) δ 5.83 (t, $J=106.9$ Hz); IR (neat) 2989, 1746, 1246, 1028 cm^{-1} ; EIMS m/z 333 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{11}\text{H}_{19}\text{O}_7\text{F}_2\text{P}$: C, 39.89; H, 5.76. Found: C, 39.62; H, 5.81.

Diethyl (2R)-3-Acethoxy-2-(benzyloxycarbonyl)aminopropylphosphonate 12a. A solution of **11a** (905 mg, 3.21 mmol) and Et_3N (0.49 mL, 3.53 mmol) in toluene (10 mL) was treated with diphenylphosphoryl azide (DPPA) (0.76 mL, 3.53 mmol) for 30 min at 25 °C. After heating under reflux for 30 min, benzyl alcohol (0.37 mL, 3.53 mmol) was added. The mixture was heated under reflux for a further 4 h, then cooled to 25 °C. Aqueous KHSO_4 was added and the mixture was extracted with CHCl_3 . The combined extracts were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane: EtOAc =2:1 to 0:1) to give **12a** (644 mg, 52%) as an oil. $[\alpha]_D^{25} -3.06$ (c 1.0, MeOH); $^1\text{H NMR}$ (CDCl_3) δ 7.40-7.27 (5H, m), 5.47 (1H, broad d, $J=8.6$ Hz), 5.10 (2H, s), 4.33-4.01 (7H, m), 2.15-1.94 (2H, m), 2.05 (3H, s), 1.31 (3H, t, $J=6.9$ Hz), 1.30 (3H, t, $J=7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.5, 156.4, 137.0, 129.1, 128.7, 66.9, 65.8 (d, $J=9.2$ Hz), 62.2 (d, $J=6.5$ Hz), 62.0 (d, $J=6.7$ Hz), 46.1, 27.6 (d, $J=141.0$ Hz), 20.6, 16.3 (d, $J=6.1$ Hz); $^{31}\text{P NMR}$ (160 MHz, CDCl_3) δ 27.1; IR (neat) 3035, 1719, 1234, 1027 cm^{-1} ; EIMS m/z 388 ($\text{M}^+ + 1$), 387 (M^+); High resolution MS m/z calcd $\text{C}_{17}\text{H}_{26}\text{NO}_7\text{P}$ (M^+): 387.1447. Found: 387.1445.

Diethyl (2S)-4-Acethoxy-3-(benzyloxycarbonyl)aminobutylphosphonate 12b. Under the similar conditions described as above, **11b** (950 mg, 3.21 mmol) gave **12b** (911 mg, 71%) as an oil after chromatography on silica gel (hexane: EtOAc =1:1 to 0:1); $[\alpha]_D^{25} -1.78$ (c 1.5, MeOH); $^1\text{H NMR}$ (CDCl_3) δ 7.40-7.28 (5H, m), 5.10 (2H, s), 4.98 (1H, broad d, $J=9.0$ Hz), 4.16-4.01 (6H, m), 4.0-3.86 (1H, m), 2.04 (3H, s), 1.92-1.70 (4H, m), 1.32 (3H, t, $J=7.1$ Hz), 1.31 (3H, t, $J=7.1$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.6, 157.0, 137.1, 129.1, 128.7, 128.6, 66.9, 66.0, 61.9 (d, $J=5.0$ Hz), 50.7 (d, $J=18.0$ Hz), 24.7 (d, $J=3.6$ Hz), 22.1 (d, $J=143.0$ Hz), 20.6, 16.3 (d, $J=6.0$ Hz); $^{31}\text{P NMR}$ (CDCl_3) δ 31.0; IR (neat) 3063, 1718, 1245, 1028 cm^{-1} ; EIMS m/z 402 ($\text{M}^+ + 1$), 401 (M^+); High resolution MS m/z calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_7\text{P}$ (M^+): 401.1603. Found: 401.1601. Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_7\text{P}$: C, 53.86; H, 7.07; N, 3.49. Found: C, 53.28, H, 7.37, N, 3.78.

Diethyl (3S)-4-Acethoxy-3(*t*-butoxycarbonyl)amino-2,2-difluorobutylphosphonate 12c. A solution of **11c** (1 g, 3.01 mmol) and Et_3N (0.46 mL) in 2-methyl-2-propanol (10 mL) was treated with DPPA (0.71 mL) for 30 min at 25 °C. After heating under reflux for 4 h, the mixture was cooled to 25 °C, then quenched with *sat.* KHSO_4 . The mixture was extracted with CHCl_3 . The combined organic extracts were washed with brine, dried (MgSO_4), and concentrated *in vacuo*. An oily residue was chromatographed on silica gel

(hexane:EtOAc=4:1 to 2:1) to yield **12c** (507.5 mg, 42%) as an oil: $[\alpha]_D^{25}$ -2.53 (c 1.5, MeOH), $^1\text{H NMR}$ (CDCl_3) δ 4.89 (1H, broad d, $J=7.1$ Hz), 4.36-4.04 (7H, m), 2.43-2.21 (2H, m), 2.07 (3H, s), 1.43 (9H, s), 1.37 (6H, t, $J=7.1$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 171.7, 155.7, 120.6 (dt, $J_{\text{PC}}=216.0$ Hz, $J_{\text{PF}}=261.1$ Hz), 80.2, 66.3, 65.1 (d, $J=9.4$ Hz), 44.7, 35.9-34.5 (m), 28.4, 20.8, 16.4 (d, $J=4.6$ Hz); $^{31}\text{P NMR}$ (CDCl_3) δ 6.06 (t, $J_{\text{PF}}=104.6$ Hz); EIMS m/z 404 ($M^+ + 1$); IR (neat) 1710, 1246, 1026 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_7\text{F}_2\text{P}$: C, 44.67; H, 7.00; N, 3.47. Found: C, 44.47; H, 7.02; N, 3.56.

General procedure for preparation of hydroxycarbamate 13a-c. A solution of **12a-c** (2 mmol) in MeOH (6 mL) was treated with Et_3N (0.42 mL, 3 mmol) at room temperature until the starting acetate almost disappeared on TLC (8-15 h). Volatile component was removed *in vacuo* and the residue was chromatographed on silica gel to give **13a-c** as oils. Yield, elution solvent, physical data, and the enantiomeric determination for **13a-c** are as follows.

Diethyl (2R)-2-(Benzyloxycarbonyl)amino-3-hydroxypropylphosphonate 13a. Yield: 72% (88% based on recovered **12a**); Elution with CHCl_3 :MeOH (100:1); $[\alpha]_D^{25}$ -9.19 (c 1.9, MeOH); $^1\text{H NMR}$ (CDCl_3) δ 7.4-7.28 (5H, m), 5.63 (1H, broad d, $J=5.8$ Hz), 5.1 (2H, s), 4.19-3.92 (5H, m), 3.90-3.78 (1H, m), 3.77-3.63 (1H, m), 3.53 (1H, m), 2.30-2.01 (2H, m), 1.32 (3H, t, $J=7.1$ Hz), 1.29 (3H, t, $J=7.3$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.9, 137.2, 126.2, 128.8 (2 carbons), 67.0, 64.6 (d, $J=7.1$ Hz), 62.3 (d, $J=5.2$ Hz), 48.9, 27.6 (d, $J=138.7$ Hz), 16.3 (d, $J=5.5$ Hz); $^{31}\text{P NMR}$ (CDCl_3) δ 29.02; IR (neat) 3329, 3065, 1718, 1230, 1026 cm^{-1} ; EIMS m/z 346 ($M^+ + 1$); 345 (M^+). High resolution MS m/z calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_6\text{P}$ (M^+): 345.1341. Found: 345.1323. The enantiomeric purity of **13a** was determined by HPLC on a chiral phase after converting (*R*)- and (*S*)-Mosher esters [Chiralcel OD (Daicel), hexane:EtOH=10:1, flow rate=0.5 ml/min, RI detector, (*S*)-Mosher ester of **13a**: $R_t=19.5$ min, (*S*)-Mosher ester of *ent*-**13a**: $R_t=20.8$ min].

Diethyl (2S)-3-(Benzyloxycarbonyl)amino-4-hydroxybutylphosphonate 13b. Yield: 74% (92% based on recovered **12b**); Elution with CHCl_3 :MeOH (100:1); $[\alpha]_D^{25}$ -1.91 (c 0.94, MeOH); $^1\text{H NMR}$ (CDCl_3) δ 7.4-7.29 (5H, m), 5.49 (1H, broad d, $J=5.0$ Hz), 5.09 (2H, s), 4.12-3.97 (4H, m), 3.75-3.57 (3H, m), 3.15-3.05 (1H, m), 1.92-1.62 (4H, m), 1.33-1.21 (6H, m); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.5, 136.4, 128.3, 127.9, 66.5, 64.0, 61.7 (d, $J=6.3$ Hz), 53.1 (d, $J=17.6$ Hz), 24.1, 21.9 (d, $J=141.3$ Hz), 16.2; $^{31}\text{P NMR}$ (CDCl_3) δ 32.3; IR (neat) 3324, 3064, 1718, 1240, 1028 cm^{-1} ; EIMS m/z 360 ($M^+ + 1$), 359 (M^+); High resolution MS m/z calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_6\text{P}$ (M^+): 359.1498. Found: 359.1523. The enantiomeric purity of **13b** was determined by HPLC on a chiral phase after converting (*R*)- and (*S*)-Mosher esters [Chiralcel OD (Daicel), hexane:EtOH=10:1, flow rate=0.5 ml/min, RI detector, (*R*)-Mosher ester of **13b**: $R_t=19.2$ min, (*R*)-Mosher ester of *ent*-**13b**: $R_t=20.8$ min].

Diethyl (3S)-3-(*t*-Butoxycarbonyl)amino-2,2-difluoro-4-hydroxybutylphosphonate 13c. Yield: 67% (88% based on recovered **12c**); Elution with hexane:EtOAc (2:1 to 1:1); an oil; $[\alpha]_D^{25}$ -4.41 (c 0.5, MeOH); $^1\text{H NMR}$ (CDCl_3) δ 5.28 (1H, d, $J=8.3$ Hz), 4.29-4.11 (5H, m), 3.91 (1H, dd, $J=11.9, 4.2$ Hz), 3.73-3.65 (1H, m), 2.42-2.15 (2H, m), 1.36 (9H, s), 1.31 (6H, t, $J=7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 155.5, 120.1 (dt, $J=259.4, 215.3$ Hz), 79.4, 64.6, 61.2, 47.0, 35.5-34.0 (m), 28.2 (3 carbons), 16.2 (d, $J=5.2$ Hz); $^{31}\text{P NMR}$ (CDCl_3) δ 6.4 (t, $J=106.9$ Hz), IR (neat) 3413, 2982, 1698, 1296, 1028 cm^{-1} ; EIMS m/z 362 ($M^+ + 1$). High resolution MS m/z calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_5\text{F}_2\text{P}$ ($M^+ - \text{CH}_2\text{OH}$): 330.1283. Found: 330.1292. The enantiomeric purity of **13c** was determined by HPLC after converting (*R*)- and (*S*)-Mosher esters [Fine pack (Jasco),

hexane:EtOAc=3:2, flow rate=0.5 ml/min, UV detector (254 nm), (*R*)-Mosher ester of **13c**: Rt=20.7 min, (*R*)-Mosher ester of *ent*-**13c**: Rt=21.8 min].

(2S)-2-(Benzyloxycarbonyl)amino-3-diethylphosphonopropionic acid 14a. Using the procedure for **11a**, alcohol **13a** (1.03 g, 3 mmol) was oxidized with Jones reagent in acetone to give **14a** (700 mg, 65%) after column chromatography on silica gel (CHCl₃:MeOH=200:1). an oil; $[\alpha]_D^{25}$ -9.01 (c 0.5, MeOH); ¹H NMR (CDCl₃) δ 10.1 (1H, broad s), 7.39-7.27 (5H, m), 6.10 (1H, d, *J*=7.1 Hz), 5.13 (1H, d, *J*=12.2 Hz), 5.08 (1H, d, *J*=12.4 Hz), 4.57 (1H, ddd, *J*=28.0, 12.6, 5.7 Hz), 4.15-3.98 (4H, m), 2.61-2.40 (2H, m), 1.35-1.20 (6H, m); ¹³C NMR (75 MHz, CDCl₃) δ 172.9 (d, *J*=7.0 Hz), 156.7, 137.0, 129.3, 128.9, 128.8, 67.3, 63.0 (d, *J*=6.5 Hz), 62.8 (d, *J*=6.9 Hz), 49.7, 27.9 (d, *J*=141.9 Hz), 16.3 (m); ³¹P NMR (CDCl₃) δ 27.3; IR (neat) 3325, 2984, 1723, 1241, 1029 cm⁻¹; EIMS *m/z* 359 (M⁺). High resolution MS *m/z* calcd for C₁₅H₂₂NO₇P: 359.1134. Found: 359.1126.

(2S)-2-(Benzyloxycarbonyl)amino-4-diethylphosphonobutyric acid 14b. Using the procedure for **11a**, alcohol **13b** (1.07 g, 3 mmol) was oxidized with Jones reagent in acetone to give **14b** (785 mg, 70%) after column chromatography on silica gel (CHCl₃:MeOH=200:1): an oil; $[\alpha]_D^{25}$ +0.48 (c 1.1, MeOH); ¹H NMR (300 MHz, CDCl₃) δ ¹³C NMR (75 MHz, CDCl₃) δ 174.1, 156.9, 138.0, 129.1, 128.8, 128.7, 67.2, 62.5 (d, *J*=6.6 Hz), 53.9 (d, *J*=18.5 Hz), 25.5, 21.3 (d, *J*=142.6 Hz), 16.3; ³¹P NMR (160 MHz, CDCl₃) δ 32.4; IR (neat) 3315, 2984, 1719, 1218, 1028 cm⁻¹; EIMS *m/z* 374 (M⁺+1) 373 (M⁺); High resolution MS *m/z* calcd for C₁₆H₂₄NO₇P: 359.1134. Found: 359.1126.

(2S)-2-(*t*-Butoxycarbonyl)amino)-3,3-difluoro-4-diethylphosphonobutyric acid 14c. Using the procedure for **11c**, the alcohol **13c** (361 mg, 1 mmol) was oxidized with RuCl₃·nH₂O·NaIO₄ in CCl₄-CH₃CN-H₂O to give **14c** (176 mg, 47%) as a colorless crystal after column chromatography on silica gel (CHCl₃:MeOH=200:1): mp 112-114 °C, lit.^{4b} mp 112-114 °C; $[\alpha]_D^{25}$ -10.0 (c 1.1, MeOH, MeOH), lit.^{4b} $[\alpha]_D^{25}$ -10.8 (c 2.2, MeOH); ¹H NMR (CDCl₃) δ 5.43 (1H, broad d, *J*=7.9 Hz), 4.67-4.54 (1H, m), 4.30 (2H, q, *J*=7.0 Hz), 4.28 (2H, q, *J*=7.1 Hz), 2.85-2.55 (2H, m), 1.44 (9H, s), 1.38 (6H, t, *J*=7.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 174.6, 156.4, 124-115 (m), 81.0, 65.5, 65.4, 48.7, 35.5-35.3 (m), 28.4, 16.42, 16.38; ³¹P NMR (CDCl₃) δ 5.66 (t, *J*_{PF}=105.7 Hz); IR (neat) 3360, 2985, 1719, 1255, 1023 cm⁻¹; EIMS *m/z* 376 (M⁺+1); High resolution MS *m/z* calcd. for C₁₂H₂₃NO₅F₂P (M⁺-COOH): 330.1286. Found: 330.1194. The ¹H and ¹³C NMR data are in agreement with those of the authentic sample reported by Berkowitz^{4a} and Burke.^{4b}

(2S)-2-Amino-4-phosphonobutyric acid 3a. A solution of **14a** (740 mg, 2.06 mmol) in MeOH (7.4 mL) was hydrogenated over 10% Pd-C (74 mg) for 12 h at room temperature under atmospheric pressure. The catalyst was removed through Celite, and the filtrate was concentrated *in vacuo*. The crystalline residue was heated at reflux in 6N HCl (10 mL) for 24 h. After cooling to room temperature, the mixture was concentrated *in vacuo*, diluted with EtOH (15 mL), and treated with propylene oxide (2.5 mL). The resulting suspension was heated at 50 °C for 2 h before being concentrated to give a white solid. Recrystallization from 50% EtOH/H₂O gave **3a** (111 mg, 32%). mp 224-226 °C (dec.), lit.^{3a} mp 224-226 °C (dec.); $[\alpha]_{365}^{25}$ +58.9 (c 1.0, 1 N NaOH), $[\alpha]_D^{25}$ +12.6 (c 0.75, 1 N NaOH); lit.^{3a} $[\alpha]_{365}^{25}$ +61.8 (c 2.0, 1 N NaOH); lit.^{3a} $[\alpha]_D^{25}$ +13.8 (c 2, 1 N NaOH); ¹³C NMR (75 MHz, D₂O) δ 173.1 (d, *J*=13.7 Hz), 50.3, 28.6 (d, *J*=130.8 Hz); IR (KBr) 3162, 1703, 1280,

1091 cm^{-1} . Anal. Calcd for $\text{C}_3\text{H}_8\text{NO}_3\text{P}(\text{H}_2\text{O})$: C, 19.26; H, 5.39; N, 7.49. Found: C, 19.00; H, 5.09; N, 8.05. The ^{13}C NMR data are in agreement with those of the authentic sample reported by Smith.^{3a}

(2S)-2-Amino-4-phosphonobutyric acid 3b Under the similar conditions described as above, **14b** (746 mg, 2 mmol) gave **3b** (128 mg, 35%). mp 145-146 °C; $[\alpha]_D^{25} +26.0$ (c 1.0, 6N HCl), lit.^{3c} $[\alpha]_D +29$ (6N HCl); ^{13}C NMR (75 MHz, D_2O) δ 173.7, 54.5-53.2 (m), 24.9, 23.8 (d, $J=133.4$ Hz); IR (KBr) 3422, 3161, 1636, 1281, 1067 cm^{-1} ; ESI MS m/z 184 (MH^+). Anal. Calcd for $\text{C}_4\text{H}_{10}\text{NO}_3\text{P}(\text{H}_2\text{O})$: C, 23.89, H, 6.01, N, 6.97. Found: C, 23.71; H, 5.98; N, 6.46.

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