A Facile Synthesis of Novel Chiral Phosphonoacetates Bearing a Stereogenic Phosphorus Atom

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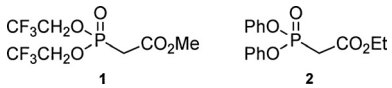
Received September 6, 2004; accepted October 23, 2004

Novel chiral phosphonoacetates bearing a stereogenic phosphorus atom were successfully synthesized by enzyme-catalyzed kinetic resolution of racemic phosphonoacetates.

Key words chiral phosphonoacetate; stereogenic phosphorus atom; kinetic resolution; enzymatic hydrolysis; porcine liver esterase; Horner–Wadsworth–Emmons reagent

Asymmetric Horner–Wadsworth–Emmons (HWE) reaction of prochiral cyclic ketones is of current interest.[1—4] Several useful chiral HWE reagents such as phosphonates,[5—9] phosphonoamides,[10] and phosphonoamidates[11] have been developed for the synthesis of olefins possessing an axis of chirality. However, most of these reagents are restricted to the compounds with non-stereogenic phosphorus atom. Although Motoyoshiya *et al*. reported geometrical selectivity of HWE reactions of aldehydes with racemic phosphonoacetates,[12] the asymmetric HWE reaction of *P*-stereogenic phosphonoacetates has never been established. Herein we describe a facile synthesis of novel chiral phosphonoacetates bearing a stereogenic phosphorus atom utilizing the enzyme-catalyzed kinetic resolution of racemic phosphonoacetates derived from two kinds of *Z*-selective HWE reagents, methyl bis(2,2,2-trifluoroehtyl)phosphonoacetate (Still's reagent, **1**)[13] and ethyl diphenylphosphonoacetate (**2**).[14]

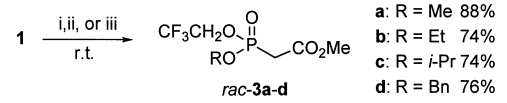


1 2

Fig. 1. *Z*-Selective HWE Reagents

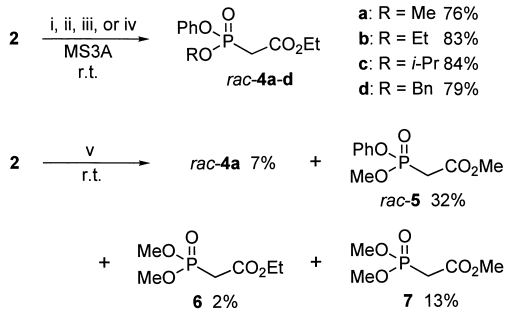
Recently, we reported a new and efficient stereoselective HWE reaction of aldehydes and ketones with bis(2,2,2-trifluoroehtyl)phosphonoacetic acid and found oxophilicity of a phosphorus atom of phosphonoacetate **1**.[15,16] That is to say, the phosphonate moiety of **1** was found to be more easily hydrolyzed than the ester moiety of **1** under aqueous alkaline conditions. Thus, the phosphonoacetic acid was readily prepared by enzymatic hydrolysis of **1** with porcine liver esterase (PLE). Although attempts to hydrolyze the ester moiety of **1** under aqueous alkaline conditions were unsuccessful, reactions of **1** with various alcohols in the presence of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the corresponding phosphonoacetate *rac*-**3a**—**d** as the major product (Chart 1). The similar transformation of **2** using various alcohols gave *rac*-**4a—d** as shown in Chart 2. Attempts to hydrolyze **2** under aqueous alkaline conditions were also unsuccessful, though phosphonoacetates **4a** and **5**—**7** were obtained (Chart 2). It can be concluded that the high oxophilicity of phosphorus atoms of these HWE reagents **1** and **2** appears to be necessary for *Z*-selective HWE reaction with aldehydes.[17—19]

The phosphonoacetates *rac*-**3a**—**d** were subjected to enzymatic hydrolysis utilizing PLE (Sigma, E-2884), as follows. Phosphonoacetates *rac*-**3a**—**d** were dissolved in 1/15 M phosphate buffer solution (pH 7.4) and acetone (9 : 1). After addition of PLE (800 units/mmol), the mixture was stirred at room temperature for the appropriate time. The reaction mixture was treated with 10% HCl and then extracted with AcOEt. After evaporation of the extraction *in vacuo*, the residue was purified on a silica gel column with $CHCl_3$–MeOH as eluent to give the corresponding carboxylic acid **8** and unreacted ester **3**. The enantiomeric excess of resolution product **8** was determined by means of HPLC analysis with chiral-stationary-phase (CSP) after methylation with (trimethylsilyl)diazomethane ($TMSCHN_2$).[20] Unreacted resolution compound **3** was also subjected to HPLC analysis with CSP. As the result of enzymatic kinetic resolution, novel *P*-stereogenic phosphonoacetates (*S*)-**3a** [>99% ee, 43% yield, colorless oil, $[\alpha]_D^{19}$ −6.2° (*c*=1.00, MeOH)], and (*R*)-**8a** (82% ee, 53% yield, white powder) were successfully obtained (Table 1, entry 1). The biochemical stereoselectivity factor of this reaction is excellent (E>52).[21,22] Recrystalliza-



(i) ROH (R = Me, Et), Et_3N (1 mol eq), (ii) *i*-PrOH, DBU (1 mol eq), (iii) BnOH (1 mol eq), DBU (1 mol eq), THF.

Chart 1



(i) MeOH (5 mol eq), DBU (1 mol eq), THF, (ii) EtOH (10 mol eq), DBU (1 mol eq), THF, (iii) *i*-PrOH; DBU (1 mol eq), (iv) BnOH (1 mol eq), DBU (1 mol eq), THF, (v) 1N NaOH (1 mol eq) – MeOH (1 : 1).

Chart 2

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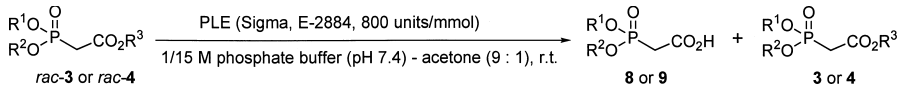
Table 1. PLE-Catalyzed Kinetic Resolution of *rac*-Phosphonoacetates **3** and **4**



Entry	R^1	R^2	R^3	Reaction time	**8** or **9**		**3** or **4**		$E^{e)}$
					Yield (%)	Ee (%)[a,b]	Recovery (%)	Ee (%)[b]	
1	CF_3CH_2	Me	Me	30 min	53 (**8a**)	82 (*R*)	43 (**3a**)	>99 (*S*)	>52
2	CF_3CH_2	Et	Me	15 min	60 (**8b**)	46	27 (**3b**)	84	7
3	CF_3CH_2	*i*-Pr	Me	15 min	29 (**8c**)	29[a,c]	68 (**3c**)	13[c]	2
4	CF_3CH_2	Bn	Me	2 h	72 (**8d**)	12	21 (**3d**)	37	2
5	Ph	Me	Et	30 h	52 (**9a**)	77	42 (**4a**)	>99	>39
6	Ph	Et	Et	7 d	53 (**9b**)	73	46 (**4b**)	86	17
7	Ph	*i*-Pr	Et	7 d	14 (**9c**)	6[a,d]	84 (**4c**)	2[d]	1
8	Ph	Bn	Et	7 d	39 (**9d**)	31	55 (**4d**)	17	2

a) HPLC analysis after methylation with $TMSCHN_2$. *b*) HPLC analysis (CHIRALCEL OD, *n*-hexane/2-propanol). *c*) HPLC analysis (CHIRALPAK AS-H, *n*-hexane/2-propanol). *d*) HPLC analysis (CHIRALPAK AD-H, *n*-hexane/2-propanol). *e*) E=biochemical stereoselectivity factor, see ref. 21 and 22.

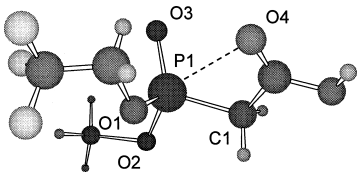


Fig. 2. Computer-Generated Drawing of (*R*)-**8a**

Selected distances (Å): P(1)–O(1) 1.590(3), P(1)–O(2) 1.562(3), P(1)–O(3) 1.467(3), P(1)–C(1) 1.785(3), P(1)–O(4) 2.966(3).

tion of (*R*)-**8a** (82% ee) from *n*-hexane–Et_2O gave (*R*)-**8a** in an enantiomerically pure form [colorless plates, mp 63.0—64.0 °C, $[\alpha]_D^{21}$ +5.8° (*c*=1.00, MeOH)]. The absolute configuration of (*R*)-**8a** was explicitly determined by its X-ray crystallographic analysis as shown in Fig. 2.[23] The interesting feature of the structure is the existence of intramolecular sub-van der Waals contacts in (*R*)-**8a**. The P(1)···O(4) distance [2.966(3) Å, 87% of Σr_{vdW}] is shorter than the sum of their van der Waals radii [3.42 Å; r_{vdW}(P)=1.90 Å, r_{vdW}(O)=1.52 Å].[24,25] The enantioselectivity in the PLE-catalyzed hydrolysis of **3a** may be explained in accordance with the Jones active-site model by regarding the trifluoroethoxy group as accommodating a large hydrophobic zone (H_L), the methoxy group a small hydrophobic zone (H_S), and phosphoryl oxygen a back polar zone (P_B) of the PLE active-site in the same manner as that proposed by Kiełbasiński *et al*. concerning a PLE-catalyzed hydrolysis of phosphinylacetates, phosphonylacetaets, and sulfinylacetates.[26—29]

Subsequently, we investigated the PLE-catalyzed kinetic resolution of *rac*-**4** and found it to work well for *rac*-**4a**. Novel *P*-stereogenic phosphonoacetates **4a** [>99% ee, 42% yield, colorless oil, $[\alpha]_D^{21}$ −10.2° (*c*=1.00, MeOH)], and **9a** (77% ee, 52% yield, colorless oil) were successfully obtained (E>39) as shown in Table 1 (entry 5). Unfortunately, the absolute configurations of oily chiral compounds **4a** and **9a** were not determined. For the preparation of *P*-stereogenic HWE reagents, the E values of *rac*-**3b**—**d** and *rac*-**4b**—**d** were insufficient.

In summary, racemic phosphonoacetates **3** and **4** were readily prepared from *Z*-selective HWE reagents **1** and **2**, respectively, by alcoholysis with various alcohols in the presence of triethylamine or DBU. PLE-catalyzed kinetic resolution of *rac*-**3a** and *rac*-**4a** proceeded in a highly effective manner to give the novel *P*-stereogenic phosphonoacetates. Further work that explores applications of these *P*-stereogenic phosphonoacetates as chiral HWE reagents is currently underway.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-420 IR Fourier transform spectrometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on JEOL JNM-AL400 and JEOL JNM-AL300 spectrometers, respectively. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. Electron impact (EI)-MS were recorded on a JEOL JMS SX-102A spectrometer. Elementary combustion analyses were performed using a Yanaco CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5-mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N; 63—210 μm or Nacalai Tesque 75SL-II-PREP; 75 μm]. The usual workup refers to washing an organic portion with brine, drying it over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. Anhydrous THF, CH_2Cl_2, MeOH, and *i*-PrOH were commercially obtained from Kanto Chemical. Anhydrous EtOH and BnOH were commercially obtained from Wako Pure Chemical Industry and Aldrich, respectively. All reagents were used as purchased.

Typical Procedure for the Preparation of Phosphonoacetates *rac*-3 Triethylamine (1.05 ml, 7.56 mmol) was added to a solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**) (1.60 ml, 7.56 mmol) in anhydrous MeOH (40 ml) at 0 °C under argon. After being stirred at room temperature for 30 min, the reaction mixture was treated with 10% HCl, concentrated *in vacuo*, and then extracted with AcOEt (60 ml×3). The extract was washed with brine (15 ml) and dried over anhydrous $MgSO_4$. The organic layer was evaporated *in vacuo* to afford an oily residue, which was purified by chromatography on silica gel (Kanto Chemical 60N) column [$CHCl_3$/MeOH (20 : 1)] to give *rac*-**3a** (1.67 g, 88%) and methyl dimethylphosphonoacetate (**7**) (0.10 g, 7%) as a colorless oil.

Methyl Methyl(2,2,2-trifluoroethyl)phosphonoacetate (*rac*-**3a**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.07 (2H, d, $^2J_{H,P}$=21.5 Hz), 3.77 (3H, s), 3.84 (3H, d, $^3J_{H,P}$=11.7 Hz), 4.43 (1H, dquint, $^2J_{H,H}$=12.2 Hz, $^3J_{H,F}$=$^3J_{H,P}$=8.3 Hz), 4.51 (1H, dquint, $^2J_{H,H}$=12.2 Hz, $^3J_{H,F}$=$^3J_{H,P}$=8.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 33.6 (d, $^1J_{C,P}$=140.8 Hz), 52.9 (s), 53.1 (d, $^2J_{C,P}$=6.9 Hz), 62.9 (qd, $^2J_{C,F}$=37.7 Hz, $^2J_{C,P}$=5.3 Hz), 122.8 (qd, $^1J_{C,F}$=277.4 Hz, $^3J_{C,P}$=8.1 Hz), 165.7 (d, $^2J_{C,P}$=5.0 Hz); IR (neat) 2964, 1743, 1264, 1174, 1094, 1041 cm^{-1}; EI-MS Calcd for $C_6H_{10}O_5F_3P$ MW 250.0218, Found *m/z* 250.0216 (M^+); *Anal.* Calcd for $C_6H_{10}O_5F_3P$: C, 28.81; H, 4.03. Found: C, 28.85; H, 3.98%.

Methyl Ethyl(2,2,2-trifluoroethyl)phosphonoacetate (*rac*-**3b**): Colorless

oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.37 (3H, t, $^3J_{H,H}$=7.1 Hz), 3.06 (2H, d, $^2J_{H,P}$=21.3 Hz), 3.76 (3H, s), 4.14—4.30 (2H, m), 4.35—4.56 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 16.2 (d, $^3J_{C,P}$=6.2 Hz), 34.0 (d, $^1J_{C,P}$=140.8 Hz), 52.8 (s), 62.8 (qd, $^2J_{C,F}$=37.6 Hz, $^2J_{C,P}$=5.0 Hz), 68.2 (d, $^2J_{C,P}$=6.9 Hz), 122.8 (qd, $^1J_{C,F}$=277.8 Hz, $^3J_{C,P}$=8.4 Hz), 165.8 (d, $^2J_{C,P}$=5.0 Hz); IR (neat) 2989, 1744, 1263, 1172, 1093, 1035 cm^{-1}; EI-MS Calcd for $C_7H_{12}F_3O_5P$ MW 264.0374, Found *m/z* 264.0356 (M^+); *Anal.* Calcd for $C_7H_{12}F_3O_5P$: C, 31.83; H, 4.58. Found: C, 31.85; H, 4.49%.

Methyl Isopropyl(2,2,2-trifluoroethyl)phosphonoacetate (*rac*-**3c**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, d, $^3J_{H,H}$=6.4 Hz), 1.37 (3H, d, $^3J_{H,H}$=6.6 Hz), 3.04 (2H, d, $^2J_{H,P}$=21.5 Hz), 3.76 (3H, s), 4.34—4.54 (2H, m), 4.77—4.90 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 23.76 (d, $^3J_{C,P}$=4.4 Hz) or 23.77 (d, $^3J_{C,P}$=5.6 Hz), 23.84 (d, $^3J_{C,P}$=5.0 Hz) or 23.83 (d, $^3J_{C,P}$=6.2 Hz), 34.4 (d, $^1J_{C,P}$=140.8 Hz), 52.8 (s), 62.7 (qd, $^2J_{C,F}$=37.4 Hz, $^2J_{C,P}$=5.0 Hz), 72.8 (d, $^2J_{C,P}$=7.5 Hz), 122.8 (qd, $^1J_{C,F}$=277.8 Hz, $^3J_{C,P}$=8.6 Hz), 165.9 (d, $^2J_{C,P}$=5.0 Hz); IR (neat) 2986, 1745, 1263, 1173, 1090, 1009 cm^{-1}; EI-MS Calcd for $C_8H_{13}F_3O_5P$ 277.0453, Found *m/z* 277.0439 (M^+-H); *Anal.* Calcd for $C_8H_{14}F_3O_5P$: C, 34.54; H, 5.07. Found: C, 34.48; H, 4.92%.

Methyl Benzyl(2,2,2-trifluoroethyl)phosphonoacetate (*rac*-**3d**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.06 (2H, d, $^2J_{H,P}$=21.2 Hz), 3.73 (3H, s), 4.25—4.45 (2H, m), 5.13 (1H, dd, $^2J_{H,H}$=11.6 Hz, $^3J_{H,P}$=8.5 Hz), 5.18 (1H, dd, $^2J_{H,H}$=11.6 Hz, $^3J_{H,P}$=10.0 Hz), 7.34—7.43 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 34.1 (d, $^1J_{C,P}$=140.8 Hz), 52.8 (s), 62.7 (qd, $^2J_{C,F}$=37.7 Hz, $^2J_{C,P}$=5.3 Hz), 68.4 (d, $^2J_{C,P}$=6.9 Hz), 122.7 (qd, $^1J_{C,F}$=277.8 Hz, $^3J_{C,P}$=8.1 Hz), 128.2 (s), 128.8 (s), 128.9 (s), 135.3 (d, $^3J_{C,P}$=6.2 Hz), 165.6 (d, $^2J_{C,P}$=5.0 Hz); IR (neat) 2959, 1743, 1498, 1265, 1173, 1093, 1013, 698 cm^{-1}; EI-MS Calcd for $C_{12}H_{14}F_3O_5P$ MW 326.0531, Found *m/z* 326.0533 (M^+); *Anal.* Calcd for $C_{12}H_{14}F_3O_5P$: C, 44.18; H, 4.33. Found: C, 44.18; H, 4.25%.

Typical Procedure for the Preparation of Phosphonoacetates *rac*-4 Anhydrous MeOH (0.79 ml, 19.51 mmol) and DBU (0.58 ml, 3.90 mmol) were added to a solution of ethyl diphenylphosphonoacetate (**2**) (1.25 g, 3.90 mmol) and molecular sieves 3A (1.2 g) in anhydrous THF (30 ml) at room temperature under argon. After being stirred at room temperature for 3 h, the reaction mixture was treated with 5% HCl and then extracted with AcOEt (70 ml×3). The extract was washed with brine (20 ml) and dried over anhydrous $MgSO_4$. The organic layer was evaporated *in vacuo* to afford an oily residue, which was purified by chromatography on silica gel (Kanto Chemical 60N) column [*n*-hexane/AcOEt (1 : 1 to 1 : 2)] to give *rac*-**4a** (768 mg, 76%) and trace amount of ethyl dimethylphosphonoacetate (**6**) as a colorless oil.

Ethyl Methylphenylphosphonoacetate (*rac*-**4a**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, $^3J_{H,H}$=7.1 Hz), 3.12 (2H, d, $^2J_{H,P}$=21.7 Hz), 3.89 (3H, d, $^3J_{H,P}$=11.2 Hz), 4.22 (2H, q, $^3J_{H,H}$=7.1 Hz), 7.16—7.28 (3H, m), 7.32—7.38 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1 (s), 33.7 (d, $^1J_{C,P}$=136.4 Hz), 53.8 (d, $^2J_{C,P}$=6.2 Hz), 61.9 (s), 120.5 (d, $^3J_{C,P}$=4.4 Hz), 125.3 (d, $^5J_{C,P}$=1.3 Hz), 129.8 (s), 150.1 (d, $^2J_{C,P}$=8.7 Hz), 165.2 (d, $^2J_{C,P}$=5.6 Hz); IR (neat) 2984, 1736, 1592, 1490, 1279, 1203, 1118, 1042, 768, 691 cm^{-1}; EI-MS Calcd for $C_{11}H_{15}O_5P$ MW 258.0657, Found *m/z* 258.0654 (M^+); *Anal.* Calcd for $C_{11}H_{15}O_5P$: C, 51.17; H, 5.86. Found: C, 50.88; H, 5.92%.

Ethyl Ethylphenylphosphonoacetate (*rac*-**4b**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, $^3J_{H,H}$=7.1 Hz), 1.34 (3H, t, $^3J_{H,H}$=7.1 Hz), 3.10 (2H, d, $^2J_{H,P}$=21.7 Hz), 4.17—4.36 (4H, m), 7.15—7.28 (3H, m), 7.31—7.38 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1 (s), 16.3 (d, $^3J_{C,P}$=6.2 Hz), 34.2 (d, $^1J_{C,P}$=136.4 Hz), 61.8 (s), 63.7 (d, $^2J_{C,P}$=6.2 Hz), 120.6 (d, $^3J_{C,P}$=4.4 Hz), 125.3 (d, $^5J_{C,P}$=1.2 Hz), 129.8 (s), 150.1 (d, $^2J_{C,P}$=8.1 Hz), 165.3 (d, $^2J_{C,P}$=6.2 Hz); IR (neat) 2984, 1738, 1593, 1490, 1277, 1204, 1117, 1036, 768, 691 cm^{-1}; EI-MS Calcd for $C_{12}H_{17}O_5P$ MW 272.0814, Found *m/z* 272.0815 (M^+); *Anal.* Calcd for $C_{12}H_{17}O_5P$: C, 52.94; H, 6.29. Found: C, 52.66; H, 6.34%.

Ethyl Isopropylphenylphosphonoacetate (*rac*-**4c**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25—1.31 (6H, m), 1.38 (3H, d, $^3J_{H,H}$=6.1 Hz), 3.08 (2H, d, $^2J_{H,P}$=21.5 Hz), 4.21 (2H, q, $^3J_{H,H}$=7.2 Hz), 4.82—4.95 (1H, m), 7.15—7.28 (3H, m), 7.31—7.37 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1 (s), 23.79 (d, $^3J_{C,P}$=5.0 Hz), 23.85 (d, $^3J_{C,P}$=3.1 Hz), 34.7 (d, $^1J_{C,P}$=136.4 Hz), 61.7 (s), 72.9 (d, $^2J_{C,P}$=6.9 Hz), 120.7 (d, $^3J_{C,P}$=4.4 Hz), 125.2 (d, $^5J_{C,P}$=1.2 Hz), 129.7 (s), 150.2 (d, $^2J_{C,P}$=8.1 Hz), 165.4 (d, $^2J_{C,P}$=6.2 Hz); IR (neat) 2982, 1739, 1593, 1491, 1277, 1205, 1118, 999, 768, 691 cm^{-1}; EI-MS Calcd for $C_{13}H_{19}O_5P$ MW 286.0970, Found *m/z* 286.0961 (M^+); *Anal.* Calcd for $C_{13}H_{19}O_5P$: C, 54.54; H, 6.69. Found: C, 54.62; H, 6.59%.

Ethyl Benzylphenylphosphonoacetate (*rac*-**4d**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24 (3H, t, $^3J_{H,H}$=7.1 Hz), 3.12 (2H, d, $^2J_{H,P}$=21.5 Hz), 4.18 (2H, q, $^3J_{H,H}$=7.1 Hz), 5.19 (1H, dd, $^2J_{H,H}$=11.7 Hz, $^3J_{H,P}$=8.3 Hz), 5.24 (1H, dd, $^2J_{H,H}$=11.7 Hz, $^3J_{H,P}$=8.8 Hz), 7.15—7.23 (3H, m), 7.28—7.39 (7H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.0 (s), 34.3 (d, $^1J_{C,P}$=136.4 Hz), 61.8 (s), 68.8 (d, $^2J_{C,P}$=6.9 Hz), 120.6 (d, $^3J_{C,P}$=4.4 Hz), 125.3 (d, $^5J_{C,P}$=1.3 Hz), 128.0 (s), 128.6 (s), 129.8 (s), 135.5 (d, $^3J_{C,P}$=6.9 Hz), 150.0 (d, $^2J_{C,P}$=8.1 Hz), 165.2 (d, $^2J_{C,P}$=6.2 Hz); IR (neat) 2983, 1737, 1592, 1490, 1278, 1203, 1117, 1024, 767, 740, 692 cm^{-1}; EI-MS Calcd for $C_{17}H_{19}O_5P$ MW 334.0970, Found *m/z* 334.0962 (M^+); *Anal.* Calcd for $C_{17}H_{19}O_5P$: C, 61.08; H, 5.73. Found: C, 61.01; H, 5.80%.

Methanolysis of Ethyl Diphenylphosphonoacetate (2) To a solution of ethyl diphenylphosphonoacetate (**2**) (122 mg, 0.38 mmol) in MeOH (0.38 ml) was added aqueous 1 N NaOH (0.38 ml) at 0 °C. After being stirred at room temperature for 40 min, the reaction mixture was treated with 5% HCl and then extracted with AcOEt (15 ml×5). The extract was submitted to the usual workup to give an oily residue, which was purified by column chromatography on silica gel (Kanto Chemical N60) [*n*-hexane/AcOEt (1 : 1 to 1 : 2) to $CHCl_3$/MeOH (20 : 1)] to afford *rac*-**4a** (6.5 mg, 7%), *rac*-**5** (30.0 mg, 32%), **6** (1.8 mg, 2%), and **7** (9.0 mg, 13%).

Methyl Methylphenylphosphonoacetate (*rac*-**5**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.13 (2H, d, $^2J_{H,P}$=21.7 Hz), 3.76 (3H, s), 3.89 (3H, d, $^3J_{H,P}$=11.5 Hz), 7.16—7.28 (3H, m), 7.31—7.39 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 33.4 (d, $^1J_{C,P}$=137.0 Hz), 52.8 (s), 53.8 (d, $^2J_{C,P}$=6.9 Hz), 120.5 (d, $^3J_{C,P}$=4.4 Hz), 125.4 (d, $^5J_{C,P}$=1.3 Hz), 129.8 (s), 150.0 (d, $^2J_{C,P}$=8.1 Hz), 165.2 (d, $^2J_{C,P}$=6.2 Hz) ; IR (neat) 2956, 1741, 1592, 1490, 1279, 1203, 1042, 768, 691 cm^{-1}; EI-MS Calcd for $C_{11}H_{15}O_5P$ MW 244.0501, Found *m/z* 244.0501 (M^+); *Anal.* Calcd for $C_{11}H_{15}O_5P$: C, 49.19; H, 5.37. Found: C, 49.04; H, 5.22%.

Ethyl Dimethylphosphonoacetate (**6**):[30] Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.29 (3H, t, $^3J_{H,H}$=7.1 Hz), 2.98 (2H, d, $^2J_{H,P}$=21.5 Hz), 3.82 (6H, d, $^3J_{H,P}$=11.2 Hz), 4.21 (2H, q, $^3J_{H,H}$=7.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1 (s), 33.4 (d, $^1J_{C,P}$=135.1 Hz), 53.2 (d, $^2J_{C,P}$=6.2 Hz), 61.7 (s), 165.7 (d, $^2J_{C,P}$=5.6 Hz).

Methyl Dimethylphosphonoacetate (**7**):[31] Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.00 (2H, d, $^2J_{H,P}$=21.7 Hz), 3.76 (3H, s), 3.82 (6H, d, $^3J_{H,P}$=11.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 33.2 (d, $^1J_{C,P}$=135.1 Hz), 52.7 (s), 53.2 (d, $^2J_{C,P}$=6.2 Hz), 166.1 (d, $^2J_{C,P}$=6.2 Hz).

Typical Procedure for PLE-Catalyzed Kinetic Resolution of Phosphonoacetates PLE (Sigma; E-2884, 224 units, 800 units/mmol) was added to a stirred solution of methyl methyl(2,2,2-trifluoroethyl)phosphonoacetate (*rac*-**3a**) (70 mg, 0.28 mmol) in 1/15 M phosphate buffer (pH 7.4, 9 ml) and acetone (1 ml) at room temperature. After being stirred at room temperature for 30 min, the reaction mixture was treated with 10% HCl (10 ml) and then extracted with AcOEt (40 ml×5). The extract was washed with brine (20 ml) and dried over anhydrous $MgSO_4$. The organic layer was evaporated *in vacuo* to afford an oily residue, which was purified by chromatography on silica gel (Nacalai Tesque 75SL-II-PREP) column [$CHCl_3$/MeOH (20 : 1)] to give (*S*)-**3a** (30.2 mg, 43%, >99% ee) as colorless oil and (*R*)-**8a** (35.0 mg, 53%) as a white powder. To the solution of (*R*)-**8a** in MeOH (1 ml) and benzene (3.5 ml) was added an excess amount of $TMSCHN_2$ (2.0 mol/l solution in *n*-hexane, *ca.* 0.3 ml, *ca.* 0.6 mmol). After being stirred at room temperature for 30 min, the reaction mixture was evaporated *in vacuo* to afford a crude product, which was purified by chromatography on a silica gel (Kanto Chemical 60N) column [$CHCl_3$/MeOH (20 : 1)], giving (*R*)-**3a** (35.2 mg, 95%, 82% ee) as a colorless oil. Recrystallization of (*R*)-**8a** (82% ee) from *n*-hexane–Et_2O gave (*R*)-**8a** as an enantiomerically pure form.

(*R*)-Methyl(2,2,2-trifluoroethyl)phosphonoacetic Acid [(*R*)-**8a**] (>99% ee): Colorless plates, mp 63.0—64.0 °C (Et_2O–*n*-hexane); $[\alpha]_D^{21}$ +5.8° (*c*=1.00, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.10 (2H, d, $^2J_{H,P}$=21.5 Hz), 3.85 (3H, d, $^3J_{H,P}$=11.5 Hz), 4.44 (1H, dquint, $^2J_{H,H}$=12.3 Hz, $^3J_{H,F}$=$^3J_{H,P}$=8.3 Hz), 4.60 (1H, dquint, $^2J_{H,H}$=12.3 Hz, $^3J_{H,F}$=$^3J_{H,P}$=8.3 Hz), 8.43 (1H, bs); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 33.4 (d, $^1J_{C,P}$=142.0 Hz), 53.5 (d, $^2J_{C,P}$=6.9 Hz), 63.3 (qd, $^2J_{C,F}$=37.7 Hz, $^2J_{C,P}$=5.3 Hz), 122.8 (qd, $^1J_{C,F}$=277.4 Hz, $^3J_{C,P}$=8.1 Hz), 167.4 (d, $^2J_{C,P}$=4.4 Hz); IR (KBr) 2981, 2685, 2579, 1726, 1305, 1293, 1226, 1166, 1105, 1047 cm^{-1}; EI-MS Calcd for $C_5H_8F_3O_5P$ MW 236.0061, Found *m/z* 236.0038 (M^+); *Anal.* Calcd for $C_5H_8F_3O_5P$: C, 25.44; H, 3.42. Found: C, 25.54; H, 3.26%.

(*R*)-Methyl Methyl(2,2,2-trifluoroethyl)phosphonoacetate [(*R*)-**3a**] (>99% ee): Colorless oil; $[\alpha]_D^{20}$ +6.3° (*c*=1.00, MeOH); *Anal.* Calcd for $C_6H_{10}F_3O_5P$: C, 28.81; H, 4.03. Found: C, 28.89; H, 3.96%.

(*R*)-Methyl Methyl(2,2,2-trifluoroethyl)phosphonoacetate [(*R*)-**3a**] (82% ee): Colorless oil; $[\alpha]_D^{25}$ +6.0° (*c*=0.50, MeOH); *Anal.* Calcd for $C_6H_{10}F_3O_5P$: C, 28.81; H, 4.03. Found: C, 28.92; H, 4.01%.

(*S*)-Methyl Methyl(2,2,2-trifluoroethyl)phosphonoacetate [(*S*)-**3a**] (>99% ee): Colorless oil; $[\alpha]_D^{19}$ −6.2° (*c*=1.00, MeOH); *Anal.* Calcd for $C_6H_{10}O_5F_3P$: C, 28.81; H, 4.03. Found: C, 28.86; H, 3.78%.

(−)-Ethyl Methylphenylphosphonoacetate [(−)-**4a**] (>99% ee): Colorless oil; $[\alpha]_D^{21}$ −10.2° (*c*=1.00, MeOH); *Anal.* Calcd for $C_{11}H_{15}O_5P$: C, 51.17; H, 5.86. Found: C, 51.35; H, 5.85%.

HPLC analyses were performed using a JASCO PU-980 apparatus equipped with a JASCO UN/VIS detector, using the following columns. CHIRALCEL OD (Daicel Chemical Industries, 0.46 cm i.d.×25 cm), eluent: *n*-hexane/2-propanol=5/1, flow rate: 1.0 ml/min, detection: 220 nm, t_R of (*R*)-(+)-**3a**: 8.57 min, (*S*)-(−)-**3a**: 10.18 min, (+)-**3b**: 5.71 min, (−)-**3b**: 7.04 min. CHIRALCEL OD (Daicel Chemical Industries, 0.46 cm i.d. ×25 cm), eluent: *n*-hexane/2-propanol=9/1, flow rate: 1.0 ml/min, detection: 254 nm, t_R of (−)-**4a**: 12.86 min, (+)-**4a**: 18.39 min.

Acknowledgement This work was partially supported by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science.

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