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Stereocontrolled Synthesis of Hydroxymethylene Phosphonate Analogues of Phosphorylated Tyrosine and Their Conversion to Monofluoromethylene Phosphonate Analogues

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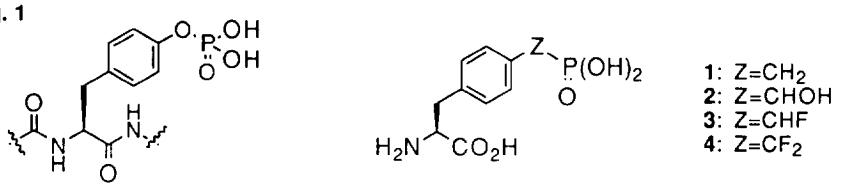
Abstract: A stereocontrolled synthesis of protected variants **13** and **15** of HPmp **2**, a mimic of phosphorylated tyrosine, was achieved through either chiral-auxiliary assisted or chiral heterobimetal catalyzed stereoselective hydrophosphonylation of 4-formyl-L-phenylalanine derivative **7**. Fluorination of HPmp derivatives **13** and **15** thus obtained was carried out to give FPmp derivatives **16** and **17**.

INTRODUCTION

Phosphorylated tyrosine (pTyr) 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 (**Fig. 1**). Non-hydrolyzable pTyr mimics are potentially valuable tools for studying these signaling phenomena.[2] Several protected variants of (phosphonomethyl)phenylalanine (Pmp) **1** have been prepared stereoselectively and incorporated to SH2 related peptide.[3] However, the Pmp-containing peptides were found to be less potent than the parent pTyr containing peptides in binding to SH2 domains.[4] The decreased affinity of Pmp-containing peptides have been thought to be due either to a higher pKa_2 of Pmp-phosphonate relative to pTyr-phosphate or to loss of hydrogen bonding between the phosphate ester oxygen and

the SH2 domain.[5,6] Then, (phosphonohydroxymethyl)phenylalanine (HPmp) **2**, (phosphonofluoromethyl)phenylalanine (FPmp) **3** and (phosphonodifluoromethyl)phenylalanine (F_2Pmp) **4**[7] are proposed by Burke as the more suitable mimics of pTyr;[8,9,10] the hydroxyl- and fluoro-functionality of these substituted Pmp analogues are estimated to serve a dual purpose both as the hydrogen bonding mediator and as a group lowering the pKa_2 of the phosphonates. The substituted Pmp analogues **2-4** have been already incorporated to SH2 related peptides for elucidating the binding affinity to C-terminal SH2 domains of phosphatidylinositol (PI) 3-kinase.[9] While the SH2 related peptide including F_2Pmp are shown to be the most potent in binding to the SH2 domains, HPmp and FPmp containing peptides still preserve the moderate binding affinity.[9] The lower relative affinity of HPmp peptide to the SH2 domain are supposed to attribute mainly the steric effect of the hydroxyl substituent.[9] However, the steric effects arising from the hydroxyl configuration of HPmp-peptides are not clear to date, since the stereo-defined HPmp are not readily available.[8] Moreover, the binding affinity of SH2 related peptides incorporating HPmp or FPmp to other SH2 domains of Src and Grb2 is not elucidated.[9] It is suggested that the modification of the pTyr structures affords one way of altering ligand affinity and inter-SH2 domain specificity.[11] Then, it would be useful to examine the structure-activity relationships of the SH2 related peptides incorporating HPmp and FPmp of the different configurations at the CHOH and CHF stereogenic centers for designing an SH2 domain inhibitor with selective binding activity to a variety of SH2 domains.[12] Therefore, we have interested in the development of methods for stereocontrolled synthesis of HPmp derivatives, which would be also useful for the stereoselective synthesis of FPmp derivatives. In this paper we report an efficient stereocontrolled synthesis of a protective variant of HPmp, in addition to the detailed study of fluorination of HPmp derivatives having defined stereochemistry.

Fig. 1



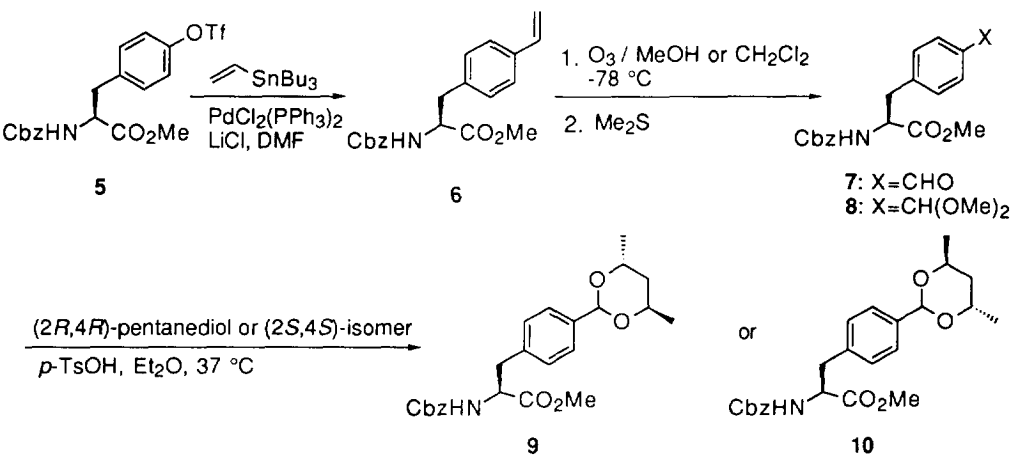
RESULTS AND DISCUSSION

Stereoselective synthesis of HPmp derivatives 13 and 15 using chiral auxiliary assisted hydrophosphonylation.

One of our synthetic strategy for a stereoselective synthesis of HPmp **2** is based on the protocol using stereoselective carbon-phosphorus bond formation by the Lewis acid mediated stereoselective cleavage of homo-chiral dioxane acetals such as **9** and **10** with phosphite as shown in **Schemes 2** and **3**, which methodology has been recently developed by us for the enantioselective synthesis of α-hydroxyphosphonates.[13] Taking advantage of the chirality on the dioxanes, the hydroxyl functionality of HPmp derivatives could be controlled as either *S*- or *R*-configuration. The requisite homo-chiral dioxane acetals **9** and **10** were prepared from methyl *N*-Cbz-L-tyrosinate through 4-step reaction sequence as shown in **Scheme 1**.

Treatment of methyl *N*-Cbz-L-tyrosinate with *N*-phenyltriflimide in the presence of *i*-Pr_2NEt in CH_2Cl_2 under the conditions of Petrakis[14] gave the triflate **5**, mp 72-74 °C, $[\alpha]_D^{20}$+35.2 (c 1.0, $CHCl_3$)] in 96% yield. Palladium-catalyzed coupling reaction of the triflate **5** with tri-*n*-butylvinylstannane in the presence of $PdCl_2(PPh_3)_2$ (2.0 mol%) and LiCl (7.2 equiv.) in DMF at 90 °C gave the vinylphenylalanine **6**, mp 50-52 °C, $[\alpha]_D^{20}$+52.1(c 1.0, $CHCl_3$), in 83% yield.[15] Ozonolysis [1: O_3, MeOH, -78°C; 2: Me_2S] of **6**, followed by dimethyl acetalization [MeOH, $CH(OMe)_3$, *cat.* NH_4NO_3] in one-pot gave the dimethyl acetal **8**, $[\alpha]_D^{20}$+42.7 (c 1.0, $CHCl_3$), as an oil in 85% yield. Alternatively, the aldehyde **7** was prepared by ozonolysis of **6** in CH_2Cl_2. Transacetalization of **8** with (2*R*,4*R*)-pentanediol or the (2*S*,4*S*)-isomer in refluxing ether containing a catalytic amount of *p*-TsOH gave the homo-chiral dioxane acetals **9** [an oil, $[\alpha]_D^{20}$ +44.2 (c 1.0, $CHCl_3$)] and **10** [mp 56-58 °C; $[\alpha]_D^{20}$ +30.0 (c 1.0, $CHCl_3$)] in 95% and 98% yield, respectively.

Scheme 1

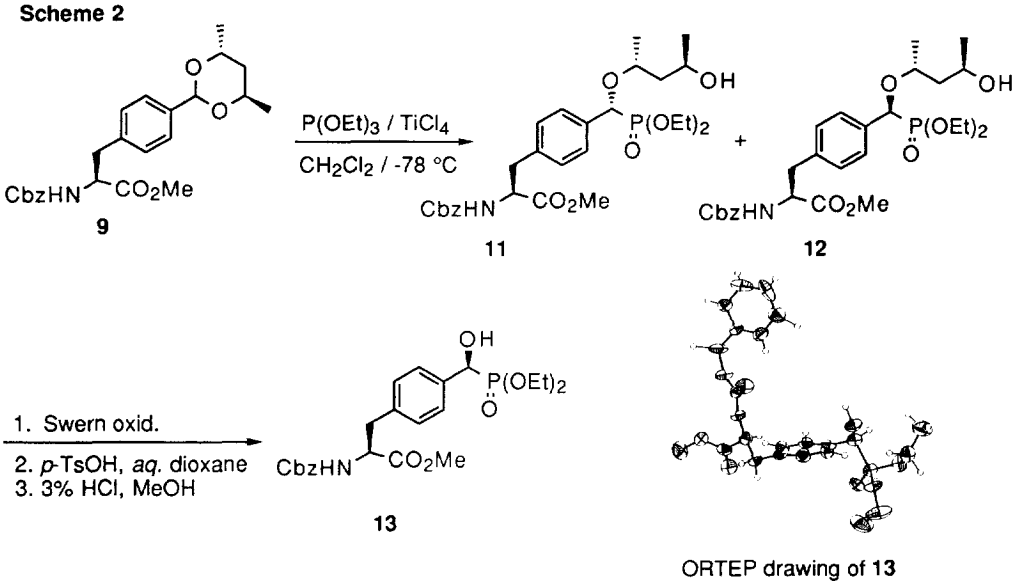


Having established an efficient method for preparation of homo-chiral dioxane acetals **9** and **10**, next, our attention was focused on Lewis acid mediated stereoselective ring-opening reaction of these dioxane acetals with triethyl phosphite. Treatment of the acetal **9** with $TiCl_4$ (2.0 eqiv.) in CH_2Cl_2 in the presence of $(EtO)_3P$ (1.2 equiv.) at -78 °C for 2 h according to the method described previously[13] gave a mixture of diastereomers **11** and **12** in a ratio of 3:97 in 84% yield.[16] The major diastereomer **12** was easily isolated as an oil in diastereomerically pure form (>98% *de*) after column chromatography on silica gel. The relative configuration of **12** was initially assigned on the basis of the mechanistic grounds[13] and confirmed after its conversion to the α-hydroxyphosphonate **13**, mp 88-89 °C; $[\alpha]_D^{20}$ +16.2 (c 1.0, $CHCl_3$), in 83% yield in an usual manner [1. Swern oxidn.; 2. *p*-TsOH / *aq.* dioxane / 90 °C; 3. 3% HCl-MeOH].[13,17] X-ray crystallographic analysis of **13** clearly established the relative configuration (**Scheme 2**).

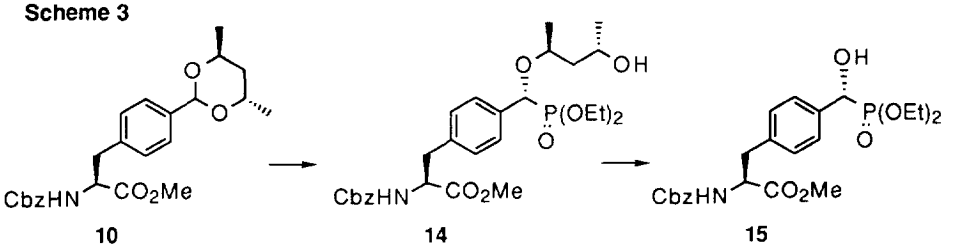
To obtain another HPmp derivative **15**, a series of the reactions under exactly the same conditions described as above were followed starting with the chiral acetal **10** (**Scheme 3**). The reactions worked well to give **14** [90% yield; an oil; $[\alpha]_D^{20}$+77.1 (c 1.0, $CHCl_3$)], and **15** [81% yield; mp 95-97 °C; $[\alpha]_D^{20}$+56.7 (c 0.9, $CHCl_3$)], respectively. The diastereoselectivity for the hydrophosphonylation of **10** giving **14** was determined as

92% *de*[16] and was high enough for the isolation of diastereomerically pure **15** (>95% *de*) after purification of **14** and subsequent removal of the chiral auxiliary. Thus, the present chiral-acetal mediated hydrophosphonylations were found to be a useful method for the synthesis of both α-hydroxyphosphonates **13** and **15** in a stereocontrolled manner.

Scheme 2



Scheme 3



Though diastereomeric α-hydoxyphosphonates **13** and **15** thus obtained are almost identical on NMR spectra (^{1}H, ^{13}C, and ^{31}P) and could not be distinguished by these spectroscopic means, these diastereomers were found to obviously differ in the HPLC-mobility on a chiral phase (Chiralpak AS, hexane: EtOH=5:1, flow rate=0.5 mL/min, UV detector: 254 nm); the α-hydroxyphosphonate **15** (Rt=22.0 min) was elute faster than the corresponding isomer **13** (Rt=25.7 min) under the HPLC conditions.

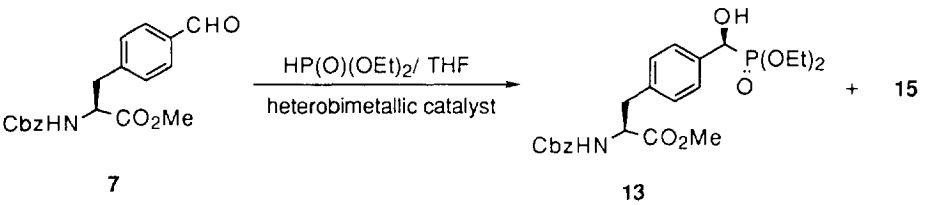
Stereoselective synthesis of 13 through catalytic asymmetric hydrophosphonylation of the aldehyde 7 with heterobimetallic catalysts.

After the establishment of methods for the stereocontrolled synthesis of **13** and **15** as well as for analyzing these diastereomers, next, we briefly examined diastereoselective synthesis of **13** through catalytic asymmetric

hydrophosphonylation of the aldehyde **7** with heterobimetallic asymmetric catalysts such as **La-Li-(*R*)-BINOL**[18] and **Al-Li-(*R*)-BINOL**[19] (**Scheme 4**). These catalysts have been recently proved to be good promoters for asymmetric hydrophosphonylation of prochiral aromatic aldehydes. The catalytic asymmetric hydrophosphonylation with **La-Li-(*R*)-BINOL** have been independently developed by us[20a] and Spilling.[20b] Subsequently, an improved method for the reaction using **Al-Li-(*R*)-BINOL** as a heterobimetallic catalyst was recently disclosed by Shibasaki.[19]

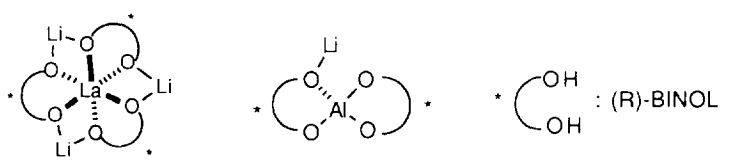
Treatment of the aldehyde **7** with diethyl phosphite in the presence of **La-Li-(*R*)-BINOL** (20 mol %) in THF at -40 °C as described previously gave the α-hydroxyphosphonates **13** and **15** in a ratio of 75:25 in good yield. The diastereomeric ratio slightly improved to 80:20, upon conducting the reaction with **Al-Li-(*R*)-BINOL** in THF at 0 °C.[21] Although these two catalysts work well, the diastereoselectivies were found to be low as compared with those of chiral-acetal mediated hydrophosphonylation.

Scheme 4



7 **13**

Heterobimetallic catalyst	Temp.(°C)	Yield of **13** and **15**	Ratio (**13**:**15**)
La-Li-(*R*)-BINOL	-40	97%	75:25
Al-Li-(*R*)-BINOL	0	84%	80:20



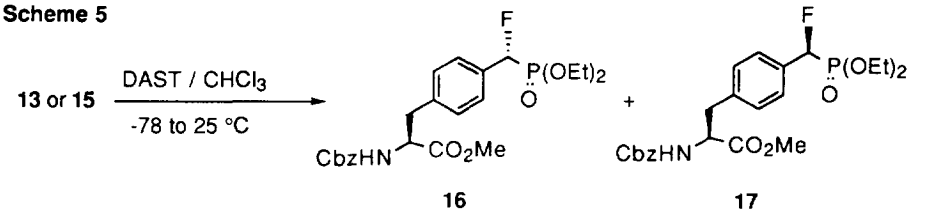
La-Li-(*R*)-BINOL **Al-Li-(*R*)-BINOL**

Conversion of 13 and 15 to FPmp derivatives.

Burke and co-workers have reported that fluorination of a racemic HPmp derivative with (diethylamino)sulfur trifluoride (DAST) proceed in an S_N2 manner as determined by ^1H NMR analysis of the resulting FPmp derivative.[8] However the fluorination of HPmp derivatives has not been extensively studied. With HPmp derivatives **13** and **15** of defined stereochemistry in hand, then, we examined the fluorination of individual diastereomers with DAST in details (**Scheme 5**). Treatment of **13** and **15** with DAST in $CHCl_3$ as reported by Burke gave the corresponding mono-fluorinated derivatives in good yields. The relative configuration of FPmp derivatives derived from **13** and **15** were initially assigned as **16** and **17**, respectively, on the basis of

no evidence of multiple diastereomers as judged by NMR (^1H, ^{13}C and ^{31}P) analyses as well as on the basis of the report of Burke.[8] However, careful analysis of the ^{19}F NMR spectra reveals that two diastereomers **16** and **17** are actually produced in ratios of 60:40 and 44:56 from the fluorination of HPmp derivatives **13** and **15**, respectively.[22] Thus, fluorination of **13** and **15** with DAST under the conditions proved to involve S_N1 pathway.

Scheme 5



To confirm the stereochemical course for the fluorination of α-hydroxyphosphonates in more details, fluorination of optically active α-hydroxyphosphonate derivatives **19a,b** (88% *ee*) having a simple alkyl side chain, prepared from the corresponding chiral acetal **18**, was examined by the use of DAST or 1,1,2,3,3,3-hexafluoropropyldiethylamine (PPDA) as a fluorinating reagent.[23] The data reported in Table 1 show that enantiomeric purity of **20** obtained is very low suggesting that the fluorination of **19** with DAST or PPDA involve an S_N1 reaction pathway.[22] The finding obtained with PPDA (entry 3) are especially sharp contrast to the fluorination of ethyl mandelate which is suggested to proceed in an S_N2 manner under the same conditions.[23b]

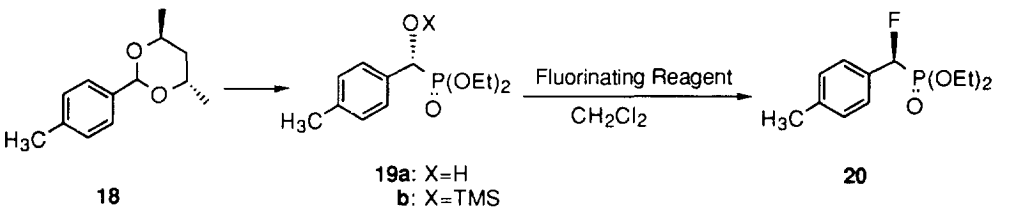


Table 1. Fluorination of Optically Active α-Hydroxyphosphonate Derivatives **19a** and **19b**

Entry	Substrate	Reagent	Temp. (°C)	Yield(%)	Ee(%) of **20**[a]
1	**19a**	DAST	–78	81	8
2	**19b**	DAST	0	81	5
3	**19a**	PPDA	0	49	3

[a] Determined by ^1H-NMR (300 MHz) analysis using (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating reagent.

In conclusion we have developed an efficient method for stereocontrolled synthesis of a protected derivative of HPmp **2**. We believe that the present synthesis is the first representative for stereocontrolled synthesis of

protective variants of HPmp **2** as pTyr mimics and should be useful for elucidating biological effects of the CHOH stereogenic center in binding to SH2 domains. Furthermore we have confirmed that fluorination of α-hydroxybenzylphosphonates **13** and **15** with DAST includes an S_N1 pathway, which are previously believed to proceed in an S_N2 manner.[8]

EXPERIMENTAL

General. All reactions were carried out under nitrogen atmosphere, unless stated otherwise. NMR spectra were recorded at 300 or 400 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ (7.26 ppm) as internal references. ^{13}C NMR(75 or 100 MHz) and ^{31}P NMR (160 MHz) were taken in $CDCl_3$ using $CDCl_3$ (77.0 ppm) as internal standard and 85% H_3PO_4 as an external standard, respectively, with broad-band ^1H decoupling. ^{19}F NMR spectra (376 MHz) was measured in $CDCl_3$ using benzotrifluoride (BTF) as an internal standard.

Methyl 4-[(Trifluoromethyl)sulfonyloxy]-N-Cbz-L-phenylalaninate (5). To a stirred mixture of *N*-Cbz-L-tyrosine methyl ester (2.10 g, 6.40 mmol) , $(i\text{-Pr})_2EtN$ (1.11 mL, 6.40 mmol) in CH_2Cl_2 (18 mL) was added N-phenyltriflimide (2.84 g, 7.96 mmol) at 0 °C. The mixture was stirred at room temperature for 18 h, concentrated, and partitionated between EtOAc and H_2O. The organic phase was dried (Na_2SO_4) and evaporated to give an oil. Purification by flash chromatography (SiO_2, hexane:EtOAc=4:1) gave **5** (2.83 g, 96%): mp 72-74 °C; $[\alpha]_D^{20}$ +35.2 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (5H, m), 7.21-7.14 (4H, m), 5.28 (1H, broad d, *J*=7.5 Hz), 5.11 (1H, d, *J*=12.3 Hz), 5.07 (1H, d, *J*=12.3 Hz), 4.66 (1H, dd, *J*=6.3, 13.9 Hz), 3.71 (3H, s), 3.19 (1H, dd, *J*=5.8, 13.9 Hz), 3.08 (1H, dd, *J*=6.3, 13.9 Hz); IR(KBr) 3343, 1752, 1695, 1539, 1416, 1144 cm^{-1}; MS *m/z* 461 (M^+). Anal. calcd for $C_{19}H_{18}F_3NO_7S$: C, 49.46; H, 3.93; N, 3.04. Found: C, 49.33; H, 3.70; N, 2.98.

Methyl (2S)-N-Cbz-2-Amino-3-(4'-vinylphenyl)propinonate (6). A suspension of triflate **5** (2.90 g, 6.29 mmol), LiCl (1.92 g, 45.3 mmol), $PdCl_2(PPh_3)_2$ (88.3 mg, 0.126 mmol), and tri-*n*-butylvinylstannane (1.83 mL, 6.29 mmol) in DMF (70 mL) was stirred at 90 °C for 24 h. The mixture was poured into cold water, and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give an oil. Chromatography on silica gel (hexane: EtoAc=4:1) gave **6** (1.77 g, 83%): mp 50-52 °C; $[\alpha]_D^{20}$+52.1(c 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (7H, m), 7.06 (2H, d, *J*=8.1 Hz), 6.69 (1H, dd, *J*=10.9, 17.6 Hz), 5.72 (1H, d, *J*=17.6 Hz), 5.25-5.22 (2H, m), 5.12 (1H, d, *J*=12.4 Hz), 5.08 (1H, d, *J*=12.4 Hz), 4.67 (1H, dd, *J*=6.3, 14.2 Hz), 3.73 (3H, s), 3.14 (1H, dd, *J*=5.6, 14.2 Hz), 3.07 (1H, dd, *J*=6.3, 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 155.6, 136.4, 135.3, 129.4, 128.5, 128.1, 128.0, 126.4, 113.7, 66.9, 54.7, 52.3, 37.9; IR (KBr) 3319, 1739, 1691, 1539 cm^{-1}. MS *m/z* 339 (M^+). Anal. calcd for $C_{20}H_{21}NO_4$: C, 70.72; H, 6.24, N, 4.13. Found: C, 71.17; H, 5.93; N, 4.12.

Ozonolysis of 6 (method A: in MeOH). A stream of ozone was bubbled into a solution of **6** (2.04 g, 6.01 mmol) in MeOH (13 mL) at -78 °C until the color of the solution was turned pale blue (2 h). After removal of excess ozone by dry nitrogen gas, the resultant mixture was treated with dimethyl sulfide (0.7 mL) at -78° C for 30 min and warmed up to room temperature. Then, trimethyl orthoformate (0.72 mL, 6.61 mmol) and NH_4NO_3 (15 mg, 0.19 mmol) were added successively. After being stirred for 18 h, the reaction was quenched with solid $NaHCO_3$. The filtrates was evaporated to give an oily residue, which was purified by chromatography on silica gel (hexane:EtOAc=4:1) to give **8** (1.97 g, 85%): an oil; $[\alpha]_D^{20}$ +42.7 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (7H, m), 7.10 (2H, d, *J*=8.2 Hz), 5.36 (1H, s), 5.23 (1H, broad d, *J*=8.0 Hz), 5.11 (1H, d, *J*=12.4 Hz), 5.07 (1H, d, *J*=12.4 Hz), 4.66 (1H, dd, *J*=6.0, 14.0 Hz), 3.71 (3H, s), 3.31 (6H, s), 3.14 (1H, dd, *J*=5.3, 14.1 Hz), 3.08 (1H, dd, *J*=6.0, 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 155.6, 137.0, 136.2, 135.9, 129.1, 128.5, 128.2, 128.0, 127.0, 102.9, 67.0, 54.7, 52.7, 52.3, 37.9; IR (neat) 3334, 2952, 1731, 1519 cm^{-1}; MS *m/z* 386 (M^+-1), 387 (M^+). High resolution MS calcd for $C_{21}H_{25}NO_6(M^+)$: 387.1682. Found: 387.1701. ***(Method B: in CH_2Cl_2).*** Ozonolysis of **6** (1.36 g) was carried out in CH_2Cl_2 (12 mL) as above. Then, the mixture was treated with dimethyl sulfide (0.41 mL) at -78 °C for 30 min and warmed up to room temperature during 3 h. Usual work up gave the residue which was chromatographed on silica gel (hexane:EtOAc=2:1) to give the aldehyde **7** (508 mg, 37.2%): mp 59-61 °C; $[\alpha]_D^{20}$ +49.4 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.97 (1H, s), 7.78 (2H, d, *J*=8.2 Hz), 7.38-7.29 (5H, m), 7.27 (2H, d, *J*=8.2 Hz), 5.27 (1H, broad d, *J*=8.0 Hz), 5.12 (1H, d, *J*=12.3 Hz), 5.06 (1H, d, *J*=12.3 Hz), 4.71 (1H, dd, *J*=6.2, 13.6 Hz), 3.73 (3H, s), 3.25 (1H, dd, *J*=5.5, 13.6 Hz), 3.13 (1H, dd, *J*=6.2, 13.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 171.5, 155.5, 143.0, 136.0, 135.3, 130.0, 129.9, 128.5, 128.2, 128.1, 67.0, 54.5, 52.5, 38.4; IR (KBr) 3336, 1753, 1696, 1537 cm^{-1}; MS *m/z* 342 (M^++1). Anal. calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C,66.57; H, 5.68; N, 4.09.

Transacetalization of 8 with (2R,4R)-pentanediol or the (2S,4S)-isomer. A solution of **8** (2.57 g, 6.64 mmol), (2*R*,4*R*)-pentanediol (760 mg, 7.30 mmo), and *p*-TsOH (125 mg, 0.66 mmol) in Et_2O (13 mL) was heated under reflux for 5 h. The mixture was poured into *sat.* $NaHCO_3$, and extracted with Et_2O. The combined organic extracts were washed with brine, and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed on silica gel (hexane:EtOAc=4:1) to give **9** (2.69 g, 95%); an oil; $[\alpha]_D^{20}$+44.2 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J*=8.2 Hz), 7.36-7.31 (5H, m), 7.09 (2H, d, *J*=8.2 Hz), 5.80 (1H, s), 5.14 (1H, broad d, *J*=8.2 Hz), 5.09 (2H, s), 4.64 (1H, dd, *J*=5.8, 13.9 Hz), 4.46 (1H, dq, *J*=6.7, 6.7 Hz), 4.18 (1H, dqd, *J*=2.4, 6.0, 11.8 Hz), 3.71 (3H, s), 3.13 (1H, dd, *J*=5.8, 13.9 Hz), 3.08 (1H, dd, *J*=5.9, 13.9 Hz), 2.02-1.94 (1H, m), 1.48 (3H, d, *J*=7.0 Hz), 1.46-1.41 (1H, m), 1.28 (3H, d, *J*=6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 155.6, 138.1, 136.2, 136.0, 129.9, 129.2, 128.5, 128.1, 128.0, 126.6, 93.7, 68.6, 68.1, 66.9, 54.7, 52.3, 37.7, 36.7, 21.9, 17.2; IR(neat) 3346, 2974, 1728, 1536 cm^{-1}; MS *m/z* 427 (M^+); High-resolution MS calcd for $C_{24}H_{29}NO_6$ (M^+): 427.1995. Found: 427.1989. Transacetalization of **8** with (2*S*,4*S*)-pentanediol under the same conditions as above gave **10** in 98% yield; mp 56-58 °C; $[\alpha]_D^{20}$ +30.0, (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J*=8.2 Hz), 7.38-7.29 (5H, m), 7.09 (2H, d, *J*=8.2 Hz), 5.80 (1H, s), 5.15 (1H, broad d, *J*=8.1 Hz), 5.09 (2H, s), 4.64 (1H, dd, *J*=5.8, 13.9 Hz), 4.46 (1H, dq, *J*=6.7, 6.7 Hz), 4.18 (1H, dqd, *J*=2.3, 6.0, 11.9 Hz), 3.71 (3H, s), 3.13 (1H, dd, *J*=5.8, 13.9 Hz), 3.08 (1H,

dd, *J*=5.9, 13.9 Hz), 2.05-1.94 (1H, m), 1.48 (3H, d, *J*=7.0 Hz), 1.46-1.42 (1H, m), 1.29 (3H, d, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 155.6, 138.1, 136.2, 136.0, 129.2, 128.4, 128.1, 128.0, 126.5, 93.7, 68.6, 68.1, 66.9, 54.6, 52.3, 37.7, 36.7, 21.9, 17.2; IR (KBr) 3317, 2966, 1734, 1701, 1541 cm^{-1}; MS *m/z* 426 (M^+-1). Anal. calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.37; H, 6.70; N, 3.53.

TiCl$_4$-mediated hydrophosphonylation of 9 and 10 with (EtO)$_3$P. To a stirred mixture of **9** (1.75 g, 4.10 mmol) and $(EtO)_3P$ (0.84 mL, 4.92 mmol) in CH_2Cl_2 (16.4 mL) was added $TiCl_4$ (1.09 mL, 8.20 mmol) at -78 °C. The mixture was stirred at the same temperature for 2 h. Water was added to quench the reaction and the resulting mixture was extracted with $CHCl_3$. The combined organic extracts were washed (brine), dried ($MgSO_4$) and concentrated to give a residue. Purification by chromatography on silica gel (hexane:EtOAc=1:1 to 1:20) gave **12** (1.95 g, 84%) as an oil; $[\alpha]_D^{20}$–10.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.32 (7H, m), 7.11 (2H, d, *J*=8.0 Hz), 5.28 (1H, broad d, *J*=8.0 Hz), 5.09 (2H, s), 4.68-4.63 (1H, m), 4.66 (1H, d, *J*=17.1 Hz), 4.14-4.02 (4H, m), 4.01-3.85 (2H, m), 3.70 (3H, s), 3.13 (1H, dd, *J*=5.8, 14.3 Hz), 3.08 (1H, dd, *J*=6.2, 14.3 Hz), 1.58 (1H, ddd, *J*=2.5, 7.9, 14.3 Hz), 1.48 (1H, ddd, *J*=3.6, 9.9, 14.3 Hz), 1.26 (3H, t, *J*=7.1 Hz), 1.20 (3H, d, *J*=6.2 Hz), 1.17 (3H, t, *J*=7.1 Hz), 1.09 (3H, d, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8, 155.6, 136.3, 136.2, 134.0, 129.4, 128.9 (2 carbons), 128.5, 128.2, 128.1, 75.4 (d, $^1J_{PC}$=171.1 Hz), 71.8 (d, $^3J_{PC}$=13.6 Hz), 67.0, 63.8, 63.2 (d, $^2J_{PC}$=7.1 Hz), 62.8 (d, $^2J_{PC}$=7.1 Hz), 54.8, 52.3, 45.4, 38.0, 23.6, 18.6, 16.4, 16.3; ^{31}P NMR (160 MHz, $CDCl_3$) δ 19.17 (20.4 for the isomer **11**); IR (neat) 3356, 2969, 1728, 1536, 1246 cm^{-1}; MS *m/z* 566 (M^++1); High-resolution MS calcd for $C_{28}H_{40}NO_9P$ (M^+) 565.2441. Found: 565.2473. By exactly the same procedure as above, the acetal **10** was transformed to **14** as an oil in 90% yield: $[\alpha]_D^{20}$+77.1 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (7H, m), 7.12 (2H, d, *J*=7.9 Hz), 5.28 (1H, broad d, *J*=8.2 Hz), 5.07 (2H, s), 4.68-4.64 (2H, m), 4.13-3.86 (6H, m), 3.71 (3H, s), 3.15 (1H, dd, *J*=5.3, 13.8 Hz), 3.05 (1H, dd, J=6.2, 13.8 Hz), 1.62-1.56 (1H, m), 1.52-1.46 (1H, m), 1.26 (3H, t, *J*=7.1 Hz), 1.21 (3H, d, *J*=6.2 Hz), 1.17 (3H, t, *J*=7.1 Hz), 1.09 (3H, d, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 155.5, 136.3, 136.1, 133.7, 129.2, 128.6 (2 carbons), 128.2, 128.0, 127.9, 75.2 (d, $^1J_{PC}$=170.7 Hz), 71.8 (d, $^3J_{PC}$=12.9 Hz), 66.7, 63.6, 62.9 (d, $^2J_{PC}$=7.0 Hz), 62.6 (d, $^2J_{PC}$=6.8 Hz), 54.8, 52.1, 45.4, 37.9, 23.4, 18.5, 16.2 (d, $^3J_{PC}$=5.1 Hz), 16.1 (d, $^3J_{PC}$=5.0 Hz). ^{31}P NMR (160 MHz, $CDCl_3$) δ 19.14 (20.35 for the isomer), IR (neat) 3344, 2949, 1724, 1220 cm^{-1}; MS *m/z* 566 (M^++1). Anal. calcd for $C_{28}H_{40}NO_9P$: C, 59.46; H, 7.13; N, 2.48. Found: C, 59.23; H, 7.24; N, 2.36.

Removal of the chiral auxiliary of 12 and 14. The Swern reagent in CH_2Cl_2 (13 mL) was prepared from DMSO (0.87 mL, 12.3 mmol) and oxalyl chroride (0.91 mL, 10.5 mmol) according to the method of Swern.[24] A solution of **12** (2.57 g, 4.55 mmol) in CH_2Cl_2 (10 mL) was treated with the Swern reagent at –78 °C for 10 min. After being stirred at -20 °C for 1 h, Et_3N (3.87 mL, 27.8 mmol) was added. The mixture was stirred for 30 min and warmed up to room temperature. After being stirred for 6 h, the reaction was quenched with sat. $KHSO_4$. Usual work up give a residue which was dissolved in a mixture of 1,4-dioxane (60 mL) and H_2O (30 mL). The solution was heated at 90 °C for 12 h in the presence of *p*-TsOH (778 mg, 4.1 mmol). The dioxane was removed *in vacuo* and the residue was extracted with $CHCl_3$. After combined organic extracts were evaporated, the residue was treated with 3% HCl-MeOH (45 mL), prepared from MeOH (45 mL) and AcCl (2.25 mL), at room

temperature for 1.5 h.[17] Volatile components were removed *in vacuo*, the residue was made basic with *sat* $NaHCO_3$, and extracted with EtOAc. Separated organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give an oil. Purification by chromatography on silica gel (hexane:EtOAc=1:1 to 1:5) gave **13** (1.8 g, 83%): mp 88-89 °C; $[\alpha]_D^{20}$+16.2 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (7H, m), 7.10 (2H, d, *J*=8.0 Hz), 5.27 (1H, broad d, *J*=8.0 Hz), 5.08 (2H, s), 4.98 (1H, dd, *J*=5.3, 10.9 Hz), 4.64 (1H, dd, *J*=6.1, 13.8 Hz), 4.06-3.99 (4H, m), 3.69 (3H, s), 3.14 (1H, dd, *J*=5.6, 13.8 Hz), 3.06 (1H, dd, *J*=6.1, 13.8 Hz), 1.24 (3H, t, *J*=7.1 Hz), 1.19 (3H, t, *J*=7.1 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 155.6, 136.2, 135.7, 135.4, 129.2, 128.5, 128.2, 128.1, 127.3 (2 carbons), 70.6 (d, $^1J_{PC}$=158.8 Hz), 67.0, 63.3 (d, $^2J_{PC}$=6.6 Hz), 63.1 (d, $^2J_{PC}$=7.0 Hz), 54.8, 52.3, 37.9, 16.3; ^{31}P NMR (160 MHz, $CDCl_3$) δ 21.03; IR(KBr) 3351, 3247, 1733, 1712, 1533, 1262 cm^{-1}; MS *m/z* 480 (M^++1). Anal. calcd for $C_{23}H_{30}N\ O_8P$: C, 57.61; H, 6.31; N, 2.92. Found: C, 57.20; H, 6.45; N, 3.11. By exactly the same procedure as above, **14** was transformed to **15** in 81% yield. **15**: mp 95-97 °C; $[\alpha]_D^{20}$+56.7 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (7H, m), 7.10 (2H, d, *J*=8.0 Hz), 5.27 (1H, broad d, *J*=8.0 Hz), 5.08 (2H, s), 4.97 (1H, dd, *J*=5.2, 10.5 Hz), 4.64 (1H, dd, *J*=6.2, 13.8 Hz), 4.06-3.99 (4H, m), 3.69 (3H, s), 3.13 (1H, dd, *J*=5.8, 13.8 Hz), 3.07 (1H, dd, *J*=6.2, 13.8 Hz), 1.24 (3H, t, *J*=7.1 Hz), 1.19 (3H, t, *J*=7.1 Hz);) ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8; 155.6, 136.2, 135.7, 135.4, 129.2, 128.5, 128.2, 128.1, 127.3 (2 carbons), 70.6 (d, $^1J_{PC}$=158.7 Hz), 67.0, 63.3 (d, $^2J_{PC}$=7.3 Hz), 63.1 (d, $^2J_{PC}$=7.3 Hz), 54.8, 52.3, 37.9, 16.3; ^{31}P NMR (160 MHz, $CDCl_3$) δ 21.04; IR (KBr) 3371, 3248, 1739, 1696, 1519, 1267 cm^{-1}; MS *m/z* 479 (M^+). Anal. calcd for $C_{23}H_{30}NO_8P$: C, 57.61; H, 6.31; N, 2.92. Found: C, 57.77; H, 6.22; N, 2.86.

X-ray crystallographic analysis of 13. X-ray crystal data of **13** were collected by Mac-Science MXC 18 diffarectmeters. The structure was solved by direct methods using SHELXS86 (Sheldrik, 1986) and refined with a full matrix least-squares method. Crystal Data of **13**: $C_{23}H_{30}NO_8P$, Mr=479.00, orthorhombic, space group $P2_12_12_1$, a=9.162(2)Å, b=33.083(7)Å, c=8.029(2)Å, V=2434(1)Å^3, T=288K, Z=4, Dx=1.31 gcm^{-1}, (Cu-Kα)=1.54178Å, μ=13.05 cm^{-1}, R=0.065 over 1437 independent reflections.

La-Li-(R)-BINOL mediated hydrophosphonylation of the aldehyde 7. To a stirred mixture of aldehyde **7** (341 mg, 1 mmol) and diethyl phosphite (0.15 mL, 1.2 mmol) in THF (2.3 mL) was added 4 mL of **La-Li-(*R*)-BINOL** in THF, prepared from lithium (*R*)-binaphthoxide and $LaCl_3$•$7H_2O$ according to the method of Shibasaki,[18] over 5 min at -40 °C. The mixture was stirred for 45 h, then water was added to quench the reaction. Biphase-mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give an oily residue. Purification by flash chromatography (SiO_2, hexane/EtOAc=2:1 to 1:20) gave a mixture of **13** and **15** (465.2 mg, 97%) in a ratio of 75:25 as determined by HPLC (Chiralpak AS, hexane:EtOH=5:1).

Al-Li-(R)-BINOL mediated hydrophosphonylation of the aldehyde 7. A solution of **Al-Li-(*R*)-BINOL** complex in THF (3.0 mL) was prepared from $LiAlH_4$ (11.4 mg, 0.3 mmol) and (*R*)-BINOL (171 mg, 0.6 mmol) according to the method of Shibasaki.[19] To this solution was added diethyl phosphite (0.23 mL, 1.8 mmol) and **7** (512 mg, 1.5 mmol) successively at -40 °C. After being stirred at -40 °C for 2 h, and at 0 °C for 16

h, the reaction mixture was treated with 1N HCl and extracted with Et_2O. Work-up and purification as usual gave a mixture of **13** and **15** (604 mg, 84%) in ratio of 80:20 as determined by HPLC (Chiralpak AS, hexane:EtOH=5:1).

Fluorination of 13 and 15 with DAST. α-Hydroxyphosphonate **13** (976 mg, 2.04 mmol) in $CHCl_3$ (13 mL) was added dropwise with stirring to a solution of DAST (0.40 mL, 3.06 mmol) in $CHCl_3$ (1.2 mL) cooled to –78 °C during 30 min. The mixture was stirred for 10 min and warmed up to room temperature. After being stirred for 20 min, the mixture was poured into ice-cooled brine and extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to give the crude product. Purification by chromatography (SiO_2, hexane/EtOAc=1:1 to 1:2) gave a mixture of **16** and **17** (847 mg, 87% yield) as an oil in ratio of 60:40. $[\alpha]_D^{20}$ +40.0 (c 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (7H, m), 7.14 (2H, d, *J*=7.8 Hz), 5.65 (1H, dd, *J*=7.7, 44.8 Hz), 5.24 (1H, broad d, *J*=7.8 Hz), 5.09 (2H, s), 4.66 (1H, dd, *J*=5.9, 13.8 Hz), 4.15-3.99 (4H, m), 3.70 (3H, s), 3.18-3.05 (2H, m), 1.26 (3H, t, *J*=6.8 Hz), 1.25 (3H, t, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 155.5, 136.9, 136.1, 129.4, 128.5, 128.2, 128.1, 127.1, 127.0 (2 carbons), 89.7 (dd, $^1J_{FC}$=184.3 Hz, $^1J_{PC}$=169.9 Hz), 67.0, 63.7 (d, $^2J_{PC}$=6.6 Hz), 63.3 (d, $^2J_{PC}$=6.4 Hz), 54.7, 52.3, 38.0, 16.3; ^{31}P NMR (160 MHz, $CDCl_3$) δ 14.89 (d, $^2J_{PF}$=84.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –137.71 (0.60F, dd, $^2J_{PF}$=84.3 Hz, $^1J_{HF}$=44.8 Hz,), –137.75 (0.40F, dd, $^2J_{PF}$=84.3 Hz, $^1J_{HF}$=44.8 Hz). IR (neat) 3284, 2987, 1713, 1257 cm^{-1}; MS *m/z* 481 (M^+), Anal. calcd for $C_{23}H_{29}FNO_7P$: C, 57.37; H, 6.07; N, 2.91. Foumd: C, 57.04; H, 6.14; N, 3.04. Fluorination of **15** with DAST by exactly the same procedure as above gave a mixture of **16** and **17** in ratio of 44:56 in 77% yield. The physical data were almost identical with those of a sample obtained from **13** except for specific rotation and ^{19}F NMR spectrum: $[\alpha]_D^{20}$ +32.1 (c 1.0, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.71 (0.44F, dd, $^2J_{PF}$=84.3 Hz, $^1J_{HF}$=44.8 Hz), –137.75 (0.56F, dd, $^2J_{PF}$=84.3 Hz, $^1J_{HF}$=44.8 Hz).

Preparation of optically active α-hydroxy-4-methylbenzylphosphonate (19a). To a mixture of $TiCl_4$ (2.19 mL, 16.5 mmol) and Ti(O-*i*-Pr)$_4$ (1.64 mL, 5.5 mmol) in CH_2Cl_2 (22 mL) cooled to -78 °C was successively added triethyl phosphite (2.26 mL, 13.2 mmol) and CH_2Cl_2 (22 mL) solution of chiral acetal **18**[25] (2.26 g, 11 mmol), prepared from *p*-tolualdehyde and (2*S*,4*S*)-pentanediol as usual. After being stirred at same temperature for 2 h, the reaction was quenched with H_2O. The mixture was extracted with $CHCl_3$. The combined organic extracts were washed (brine), dried ($MgSO_4$), and evaporated to give an oil which was oxidized with DMSO (2.11 mL, 29.7 mmol), oxalyl chloride (2.21 mL, 25.3 mmo), and Et_3N (9.35 mL, 67.1 mmol) as in the case of oxidation of **12**. An usual work up gave an oil which was dissolved in 75% *aq.* dioxane (220 mL) containing *p*-TsOH (1.88 g, 9.9 mmol). After the mixture was heated at 90 °C for 12 h, the dioxane was removed *in vacuo* and the residue was extracted with $CHCl_3$. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give an oil. Purification by chromatography on silica gel (hexane:EtOAc=2:1 to 1:5) gave **19a**[20a] (1.50 g, 53% yield, 88% *ee* determined by NMR analysis of the corresponding Mosher esters): mp 93-94 °C; $[\alpha]_D^{20}$+33.9 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d with small splits, *J*=8.0 Hz), 7.17 (2H, d, *J*=8.0 Hz), 4.97 (1H, d, *J*=10.5 Hz), 4.10-3.92 (4H, m), 2.34 (3H, d, *J*=1.8 Hz), 1.27 (3H, t, *J*=7.1 Hz), 1.22 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 133.4, 129.0, 127.0 (2 carbons),

70.8 (d, $1J_{PC}$158.9 Hz), 63.2 (d, $^2J_{PC}$=7.3 Hz), 63.0 (d, $^2J_{PC}$=7.4 Hz), 21.2, 16.40 (d, $^3J_{PC}$=5.7 Hz), 16.35 (d, $^3J_{PC}$=4.7 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 21.32; IR (KBr) 3261, 1232 cm^{-1}; MS *m/z* 258 (M^+). Anal. calcd for $C_{12}H_{19}O_4P$: C, 55.81; H, 7.42. Found: C, 55.82; H, 7.43.

Diethyl α-Fluoro-4-methylbenzylphosphonate (20). (Method A) α-Hydroxyphosphonate **19a** (206 mg, 0.8 mmol) was treated with DAST (0.16 mL, 1.2 mmol) in CH_2Cl_2 (5.8 mL) at -78 °C for 1.5 h. Work up as for the fluorination of **13** gave **20** (169 mg, 81%). The physical data except for specific rotation, $[\alpha]_D^{20}$ -2.95 (c 1.0, $CHCl_3$), were identical with those of authentic sample reported by Blackburn.[26] ***(Method B)*** α-Hydroxyphosphonate **19a** (516 mg, 2 mmol) was silylated with TMSCl (0.36 mL, 2.8 mmol) and Et_3N (0.56 mL, 4 mmol) in THF (7 mL) at 25 °C for 4 h. The resulting mixture was filtrated to give α-siloxyphosphonate **19b**. Without purification, a solution of **19b** in CH_2Cl_2 (13.3 mL) was added to DAST (0.4 mL, 3.0 mmol) in CH_2Cl_2 (1.3 mL) at -78 °C. The mixture was stirred at the same temperature for 30 min and at 0 °C for 12 h. Usual work-up gave **20** (419 mg, 81%). The physical data was identical with those of authentic sample prepared by method A. ***(Method C)*** A solution of PPDA (443 mg, 1.04 mmol; 50% in $Et_2NCF{=}CFCF_3$) in CH_2Cl_2 (2 mL) was added dropwise into a solution of **19a** (206 mg, 0.8 mmol) in CH_2Cl_2 (1.2 mL) at -78 °C. The mixture was warmed up to 0 °C. After being stirred at the same temperature for 12 h, the reaction was quenched with *sat.* $NaHCO_3$. An oily product was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane:EtOAc=3:1) to give **20** (102 mg, 49%). The physical data except for specific rotation, $[\alpha]_D^{20}$ -2.27 (c 1.1, $CHCl_3$), were identical with those of authentic sample prepared by method A.

Determination of the enantiomeric purity of 20. A solution of **20** (5 mg) and(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (>9.3 mg) in $CDCl_3$ (4 mL) was analyzed by ^{1}H NMR (300 MHz) spectroscopy. Signals due to benzylic protons of **20** and its enantiomer appeared separately at δ 5.52 and 5.54 as a double of doublet ($^2J_{PH}$=7.2 Hz, $^2J_{FH}$=45 Hz). The enantiomeric excess was determined by the relative ratio of integral area for these signals.

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