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Enantioselective Synthesis of *threo*-α,β-Dihydroxyphosphonates by Asymmetric Dihydroxylation of 1(*E*)-Alkenylphosphonates with AD-*mix* Reagents

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Abstract: Asymmetric dihydroxylation (AD) of 1(*E*)-alkenylphosphonates with an AD-*mix* -α or -β reagent was examined to give a series of optically active *threo*-α,β-dihydroxyphosphonates. Good enantioselectivity (>88% *ee*) was observed in the AD reaction of 1(*E*)-alkenylphosphonates with conjugated aromatic substituents. The steric effects of the ester functionality in the course of the dihydroxylation were also evaluated. Enantioselectivity and yield were significantly improved when the AD reaction was carried out with dimethyl phosphonate instead of diethyl phosphonate. © 1997 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The synthesis of chiral α-substituted phosphonic acids has been an important area of research, particularly in connection with the search for a biologically active surrogate for the corresponding carboxylic acids and phosphoric acids esters.[1] Among the various α-substituted phosphonic acids, α-hydroxyphosphonic acid derivatives are phosphorus compounds attracting increased interest in medicinal chemistry. Interesting inhibitory activities towards renin and HIV protease have been observed upon incorporation of β-amino-α-hydroxyphosphonic acids[2] or the related phosphinic acids[3] to a peptidic framework as a transition-state mimic of the hydrolysis of dipeptide. Moreover, α-hydroxyphosphonic acids have been proved to act as a hydrolytically stable mimic of phosphoric acid esters; some benzylic α-hydroxyphosphonic acid derivatives are shown to possess potential inhibitory activities towards EPSP synthase[4] and tyrosine-specific protein kinase.[5] Alternatively, α-hydroxyphosphonates may represent an interesting chiron for the preparation of the parental α-aminophosphonic acids.[6]

Several strategies have been recently developed for the stereoselective synthesis of α-hydroxyphosphonic acid derivatives. Currently available routes to these compounds include addition of non-racemic phosphorus reagents to aldehydes[7] and the use of chiral catalysts to discriminate the enantioface of aldehydes during the addition of phosphorus reagents to aldehydes.[8] Enantioselective reduction of α-ketophosphonates with chiral reductants[9] as well as enantioselctive hydroxylation of phosphonate-stabilized carbanions with chiral oxidants[10] are alternative routes to chiral α-hydroxyphosphonates. Enzymatic resolution of a racemic mixture of α-hydroxyphosphonates[11] as well as [2,3]-Wittig sigmatropic rearrangement of α-allyloxyphosphonates[12] have been reported for the synthesis of stereodefined α-hydroxyphosphonate derivatives.

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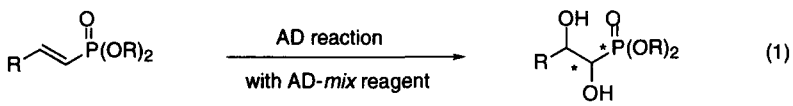
As a part of our ongoing program to develop a new method for the stereoselctive synthesis of α-hydroxyphosphonate derivatives, we have pursued asymmetric dihydroxylation (AD) of 1(*E*)-alkenylphosphonates with an AD-*mix*-α or -β reagent, a commercially available dihydroxy reagent premixed by cinchona alkaloid ligands $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, an osmium source, and a re-oxidant, developed by Sharpless[13] (Eq. 1). The method would be useful for asymmetric synthesis of α,β-dihydroxyphosphonate derivatives from readily available 1-alkenylphosphonates as well as for establishment of effects of the phosphonate functional group in the course of the dihydroxylation. The synthesis and utility of α,β-dihydroxyphosphonate derivatives for the synthesis of biologically interesting phosphonates have been recently disclosed by us[6c,e] and other workers.[14] Preliminary results of AD reaction of 1(*E*)-alkenylphosphonates are communicated.[15] In this paper we describe a full account of these experiments.



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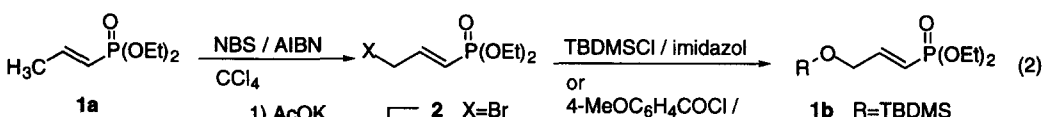
RESULTS AND DISCUSSION

AD reaction of 1(E)-Alkenylphosphonates with AD-mix-α and -β Reagents.

A series of 1(*E*)-alkenylphosphonates **1a-k** used in this study were prepared by three distinct methods as follows. The diethyl 1-alkenylphosphonates **1b,c** possessing an oxygen functionality at the γ-position were derivatized from the known phosphonate **1a**[16] according to Eq. 2. Treatment of **1a** with NBS in refluxing CCl_4 in the presence of AIBN gave the bromide **2** in 60% yield. Acetoxylation of **2** with potassium acetate in refluxing 2-butanone, followed by hydrolysis, gave **3** in 52% yield. The hydroxyl group in **3** was protected with either *t*-butyldimethylsily (TBDMS) or 4-methoxybenzoyl to give **1b** and **1c** in 92% and 48% yield, respectively. The diethyl 1(*E*)-alkenylphosphonates **1d** with a long alkyl substituent and **1e-j** with conjugated aromatic substituents were synthesized by Horner-Emmons-Wadsworth reaction of the corresponding aldehydes in good yields[17] (Eq. 3). Alternatively, dimethyl 1-alkenylphosphonate **1k** was obtained by Pd-catalyzed cross-coupling reaction of (*E*)-β-iodostyrene and dimethyl phosphite according to the method of Hirao[18] (Eq. 4).



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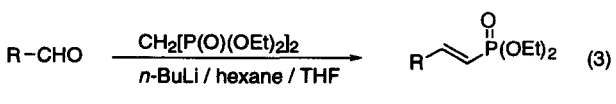

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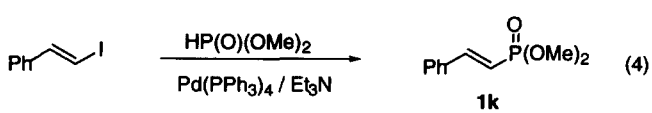
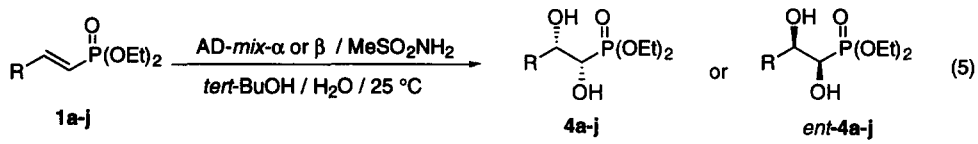


(4)

d: R = *n*-C_7H_{15}; **e**: R = Ph;
f: R = 4-$MeOC_6H_4$; **g**: R = 3-$MeOC_6H_4$;
h: R = 4-ClC_6H_4; **i**: R =1-naphthyl;
j: R=2-fury

First, AD reaction of a series of diethyl 1(*E*)-alkenylphosphonates **1a-j** with an AD-*mix*-α or -β reagent was carried out at 25 °C in 50% *tert*-BuOH in the presence of $CH_3SO_2NH_2$ (1.0 equiv.) and additional potassium osmate (0.8 mol%) according to the conditions reported by Sharpless[13a] (Eq. 5). The results are summarized in Table 1. While the rate of the dihydroxylation under the conditions was rather slow, the desired dihydroxylation products **4a** and **4c-j** were obtained in modest to good yield upon treatment of **1a** and **4c-j** with an AD-*mix*-α reagent for 48 h. The enantiomeric diols *ent*-**4b,d,e,f** were also obtained by the reaction with an AD-*mix*-β reagent. Enantiomeric purity of these products was established by either HPLC analysis on a chiral stationary phase or NMR (^1H and ^{31}P) analysis of the corresponding bis-MTPA esters derived from (+)- and (–)-MTPA.



1a-j **4a-j** *ent*-**4a-j**

Table 1 Asymmetric dihydroxylation of diethyl 1(*E*)-alkenylphosphonates **1a-j** with AD-*mix*-α or -β reagent

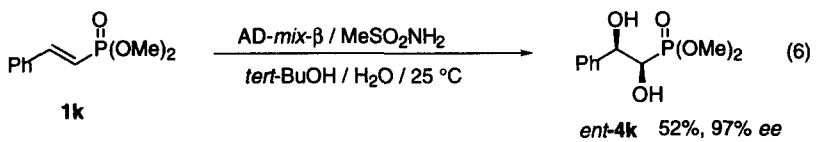
Entry[a]	Substrate	Reagent	Dihydroxylation products			
			R	Yield (%)	Ee (%)	$[\alpha]_D$ [b]
1	**1a**	AD-*mix*-α	Me (**4a**)	48	33[d]	+3.73
2	**1b**	AD-*mix*-β	$TBDMSOCH_2$ (*ent*-**4b**)	65	38[d]	–8.25
3	**1c**	AD-*mix*-α	4-$MeOC_6H_4CO_2CH_2$ (**4c**)	10	97[e]	+3.87
4	**1d**	AD-*mix*-α	*n*-C_7H_{15} (**4d**)[c]	46	84[e]	–0.82
5	**1d**	AD-*mix*-β	*n*-C_7H_{15} (*ent*-**4d**)[c]	63	84[e]	+1.81
6	**1e**	AD-*mix*-α	Ph (**4e**)	42	91[f]	+33.7
7	**1e**	AD-*mix*-β	Ph (*ent*-**4e**)	45	92[f]	–30.8
8	**1f**	AD-*mix*-α	4-$MeOC_6H_4$ (**4f**)	71	95[f]	+28.8
9	**1f**	AD-*mix*-β	4-$MeOC_6H_4$ (*ent*-**4f**)	69	98[f]	–31.6
10	**1g**	AD-*mix*-α	3-$MeOC_6H_4$ (**4g**)	67	96[f]	+32.7
11	**1h**	AD-*mix*-α	4-ClC_6H_4 (**4h**)	65	98[f]	+33.4
12	**1i**	AD-*mix*-α	1-naphthyl (**4i**)	80	93[e]	+63.2
13	**1j**	AD-*mix*-α	2-furyl (**4j**)	17	88[f]	+14.7

[a] All reactions were carried out for 48 h. [b] Measured in MeOH at 20 °C. [c] Stereochemistry was estimated tentatively by an analogy. [d] Determined by NMR analysis of the corresponding bis-MTPA esters derived from (+)- and (–)-MTPA. [e] Determined by HPLC analysis on Chiralcel OD (Daicel). [f] Determined by HPLC analysis on Chiralpak AS (Daicel).

From data reported in Table 1, it was verified that enantioselectivity was highly dependent upon the nature of substituents at the β-position of the substrates. A high level (>88% *ee*) of enantioselectivity was generally attained, when the reaction was conducted with 1(*E*)-alkenylphosphonates conjugated to the aromatic ring (entries 6-13). Similar aromatic substituents effects were also observed with AD reaction of aliphatic phosphonate **1c** possessing a 4-methoxybenzoyloxy group, whereas the yield was very low (entry 2 *vs.* 3). The aromatic substituent effects are consistent with many precedents reported in literature.[13b,19] It shoud be noted that the

enantioselectivity (91-92% *ee*) achieved for the AD reaction of ethyl (*E*)-2-phenylethenyphosphonate **1e** was lower than that (96-97% *ee*) for ethyl cinnamate under the same conditions as reported by Sharpless.[13a] The unfavorable effects of the phosphonate functional group on the AD reaction of aliphatic phosphonate **1d** are more pronounced; enantioselectivity for the AD reaction of **1d** was determined to be 84% *ee* (entries 4 and 5), while very high enantioselectivity (96-99% *ee*) has been reported for the closely related ethyl 1(*E*)-hexenylcarboxylate by Sharpless.[13a] The decreasing enantioselectivity may be ascribed to steric effects arising from the tetrahedral phosphonate functional group.

To clarify the steric effect of the ester substituent on the enantioselectivity, we next briefly examined AD reaction of dimethyl phosphonate **1k** (Eq. 6). The reaction of **1k** with an AD-*mix*-β reagent under exactly the same conditions as above gave the dihydroxylation product *ent*-**4k** in 52% yield. Enantiomeric excess of *ent*-**4k** was determined to be 97%. This experiment reveals that AD reaction of dimethyl 1(*E*)-alkenylphosphonate with AD-*mix*-β proceeds to bring about asymmetric induction more effectively than that of diethyl 1(*E*)-alkenylphosphonate (*vide supra*).



1k *ent*-**4k** 52%, 97% *ee* (6)

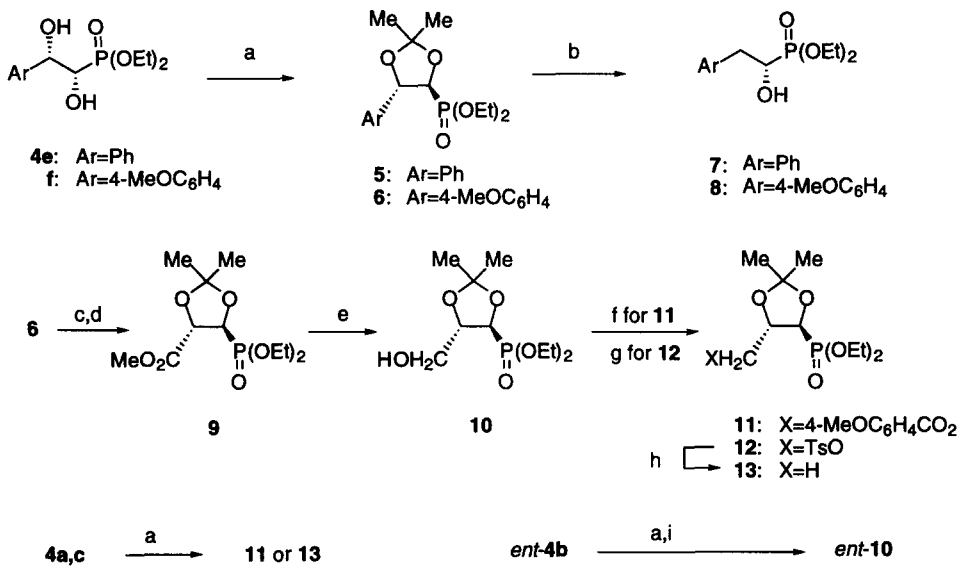
Determination of absolute configuration of dihydroxylation products 4 and ent-4.

The chemical transformations summarized in Scheme 1 were carried out in order to unequivocally establish the absolute configuration of α,β-dihydroxyphosphonates obtained. Treatment of **4e** and **4f** with 2,2-dimethoxypropane in the presence of camphorsulfonic acid gave the acetonides **5** and **6** in good yields. The dihedral angles between HCCP were estimated with the lowest energy conformation of **5** and the corresponding *cis*-isomer produced by MOPAC calculations.[15,20] On the basis of these considerations and the phosphorus version of Karplus equations,[21] a large vicinal proton-phosphorus coupling constant ($^3J_{PH}$= 17.2 Hz) is expected for **6**, while a small coupling constant ($^3J_{PH}$ = 1.7 Hz) is assumed for the *cis*-isomer. Careful analysis of ^{1}H NMR spectrum of **5** and **6** established the *vicinal* coupling constant to be 10.1 and 9.8 Hz, respectively, suggesting their *trans* relative stereochemistry. Hydrogenolysis of **5** and **6** over $Pd(OH)_2$ in MeOH gave α-hydroxyphosphonates **7** and **8**, whose absolute configuration was deduced to be *S* by ^{31}P NMR ($CDCl_3$) analysis of their (*R*)-MTPA esters according to the method of Hammerschmidt.[22] The major signals due to (*R*)-MTPA esters of **7** and **8** were observed at δ 18.37 and 19.19 ppm, while the minor signals arising from the enantiomers appeared at 17.92 and 18.45 ppm, respectively. On the basis of the arguments presented by Hammerschmidt, the ^{31}P NMR signals at lower field in the spectra are assigned with *S*-configuration. Therefore, at this stage, the absolute configuration of **4e** and **4f** was unambigously established as 1*S*,2*S*. Furthermore, the configuration of other dihydroxylation products **4g-k** correlate to that of **4e** and **4f** with their CD spectra: all α,β-dihydroxyphosphonates **4e-j** with 1*S*,2*S*-configuration showed a positive cotton effect at 230–210 nm, whereas 1*R*,2*R* isomers *ent*-**4e,f,k** exhibited a negative cotton effect at these wavelengths.[8b,9c]

Assignment of the absolute configuration of **4a,c** and *ent*-**4b** was made by the chemical correlations to **4f** of the established absolute configuration. Oxidative degradation of the *p*-methoxyphenyl group in **6** with $RuCl_3$-

$NaIO_4$ under the conditions of Martín,[23] followed by esterification with CH_2N_2 gave the methyl ester **9** in 95% yield. Treatment of **9** with $NaBH_4$ in MeOH selectively reduced the methyl ester to give alcohol **10**, $[\alpha]_D^{20}$ −15.5 (c 1.0, MeOH), in 80% yield. The alcohol **10** was acylated with 4-methoxybenzoyl chloride to give **11**. Alternatively, radical-mediated deoxygenation of **10** *via* the tosylate **12** gave the acetonide **13**, $[\alpha]_D^{20}$ −1.8 (c 1.0, MeOH), in 51% yield (2 steps). The sign of optical rotation for the acetonides **11** and **13**, respectively derived from **4c** and **4a**, was identical to those of the authentic specimen from **4f**. Therefore, absolute configuration of **4a** and **4c** was established as 1*S*,2*S*. Furthermore, absolute configuration of *ent*-**10** derived from *ent*-**4b** was confirmed by the chiroptical comparison with the authentic specimen **10** from **4f**. These experiments reveal that absolute configuration of *ent*-**4b** should be 1*R*,2*R*.

Scheme 1



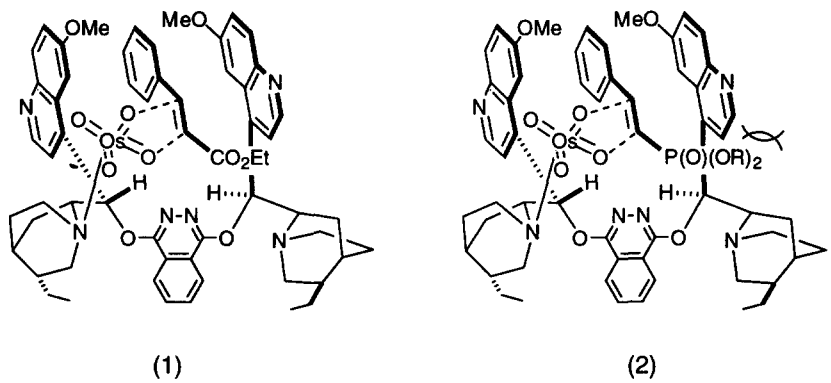
Reagent and conditions: (a) $Me_2C(OMe)_2$, camphorsulfonic acid; (b) H_2, $Pd(OH)_2$, MeOH; (c) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O; (d) CH_2N_2, ether; (e) $NaBH_4$, MeOH; (f) 4-$MeOC_6H_4COCl$, pyridine; (g) TsCl, pyridine; (h) *n*-Bu_3SnH, NaI; (i) Bu_4NF, THF

Mechanistic Consideration.

In order to rationalize the high enantioselectivity observed in asymmetric dihydroxylation using the bis-cinchona alkaloid class of ligands, Sharpless and Corey have proposed different working models of the chiral architecture provided by the ligand.[24,25] In Corey's model,[25] a U-shaped chiral pocket composed by the methoxyquinoline, quinuqulidine binding OsO_4, and phthalazine in the ligand is assumed to install the substrate as shown in Fig. 1. Subsequently, concerted [2+3] cycloaddition of osmium tetraoxide to the double bond occurs to bring about asymmetric dihydroxylation as the observed stereochemistry. The π-π stacking face-to-face

interaction between aromatic rings in the substrate and the methoxyquinoline ring in the ligand is proposed to account for an increased enantioselectivity for conjugated aromatic olefins.

We applied Corey's model to rationalize the unfavorable steric effects of the phosphonate as mentioned in the previous section.[26] Fig. 1-(1) and -(2) show a possible transition state for the dihydroxylation of ethyl (*E*)-cinnamate and 1(*E*)-alkenylphosphonates installed into the U-shaped pocket, respectively. We assume that a steric intercation between the tetrahedral phosphonate functional group and one of the methoxyquinolines in the ligand might be more severe than that for planar carboethoxy functional group; therefore, unfavorable effects of the phosphonate functional group are significant on 1(*E*)-alkenylphosphonates not conjugated with aromatic substituents. The π-π stacking face-to-face stablization with the conjugated aromatic substituents may be assumed to overcome the unfavored steric effects of the phosphonate functional group; thereby, high enantioselectivity was obtained with 1(*E*)-alkenylphosphonates of conjugated aromatic rings. The steric effect of the phosphonate functional group was partially ascertained by the observation of an increased enantioselectivity on AD reaction of **1k** possessing dimethyl phosphonate rather than diethyl phosphonate as shown in Eq. 6.



(1) (2)

Fig. 1 (1) A transition state for osmylation of ethyl cinnamate with OsO_4 • $(DHQD)_2PHAL$ ligand complex of AD-*mix*-β; (2) Possible steric interactions between the phosphonate functional group and the OsO_4•ligand complex.

CONCLUSION

In conclusion we have developed a facile method for enantioselective synthesis of *threo*-α,β-dihydroxyphosphonates by an application of asymmetric dihydroxylation of 1(*E*)-alkenylphosphonates with AD-*mix* reagents. During the studies, effects of the phosphonate functional group as well as conjugated aromatic rings in the course of the dihydroxylation were clarified. Study on synthetic uses of optically active *threo*-α,β-dihydroxyphosphonates for the synthesis of biologically interesting phosphonate molecules are in progress and will be the subject of future reports.

EXPERIMENTAL

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. IR spectra were recorded on a Perkin-Elmer

1710 FTIR spectrometer. Mass spectra were measured on a Hitachi M-80 or a VG Auto Spec spectrometer at 70 eV. NMR spectra were obtained on either a Bruker AM 400 or a Varian Gemini 300 instrument operating at 400 (or 300) MHz for ^{1}H, 100 (or 75.5) MHz for ^{13}C, and 162 MHz for ^{31}P. Spectra were referenced internally using either the residual solvent resonance for ^{1}H and ^{13}C, or $SiMe_4$ (δ=0), and externally for ^{31}P using 85% H_3PO_4 as zero ppm. *J* Values are given in Hz. AD-*mix*-α and -β reagents were purchased from Aldrich. All MTPA esters described in this paper were prepared according to our documented procedure and analyzed without purification.[8h]

Diethyl 3-bromo-1(*E*)-propenylphosphonate 2. A solution of **1a**[16] (8.90 g, 50 mmol) and NBS (12.5 g, 70 mmol) in CCl_4 (100 mL) was heated at 90 °C for 2 h in the presence of AIBN (821 mg, 5 mmol). The mixture was cooled to 0 °C. The precipitate was filtered and the filtrate was diluted with $CHCl_3$. The solution was successively washed with *sat.* Na_2SO_3, *sat.* $NaHCO_3$, and brine. Concentration of the solvent, followed by bulb-to-bulb distillation (bath temp: 120 °C; 0.1 mmHg) gave **2** (6.17 g, 48%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89-6.72 (1H, m), 5.99-5.86 (1H, m), 4.09 (4H, dq, *J* = 7.2, 7.2 Hz), 3.99 (2H, dd, *J* = 1.3, 8.0 Hz), 1.33 (6H, t, *J* = 7.2 Hz). The data was identical to that of the authentic sample reported in literature.[27]

Diethyl 3-hydroxy-1(*E*)-propenylphosphonate 3. A mixture of **2** (5.14 g, 20 mmol) and potassium acetate (3.92 g, 40 mmol) in 2-butanone (100 mL) was heated under reflux for 14 h. The resulting precipitate was filtered. The filtrate was evaporated to leave a residue which was treated with 1 N NaOH (20 mL) in MeOH (100 mL) at room temperature for 1 h. The volatile component of the mixture was removed *in vacuo* and the residue was extracted with EtOAc. The extracts were dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane : EtOAc = 1 : 1) gave **3** (2.02 g, 52%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91-6.76 (1H, m), 6.06-5.91 (1H, m), 4.32-4.26 (2H, m), 4.05 (4H, dq, *J* = 7.2, 7.2 Hz), 1.30 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7 (d, J_{PC} = 5.2 Hz), 114.1 (d, J_{PC} = 189.0 Hz), 62.1, 61.7 (2 carbons, d, J_{PC} = 5.6 Hz), 16.1 (2 carbons, d, J_{PC} = 6.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.7; IR (neat) 3450, 1265 cm^{-1}; EIMS *m/z* 195 (MH^+). Anal. Calcd for $C_7H_{14}O_4P$: C, 43.28; H, 7.79. Found: C, 43.23; H, 7.61.

Diethyl 3-*tert*-butyldimethylsiloxy-1(*E*)-propenylphosphonate 1b. To a stirred solution of **3** (1.94 g, 10 mmol) in DMF (15 mL) was added successively TBDMSCl (1.66 g, 11.0 mmol) and imidazol (1.36 g, 20 mmol) at room temperature. After being stirred for 18 h at the same temperature, the reaction was quenched by the addition of water. The mixture was extracted with EtOAc. The extracts were washed with *sat.* citric acid and brine, dried ($MgSO_4$) and evaporated to leave a residue. Purification by column chromatography on silica gel (hexane : EtOAc = 2 : 1) gave **1b** (2.82 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91-6.76 (1H, m), 6.07-5.92 (1H, m), 4.32-4.29 (2H, m), 4.07 (4H, dq, *J* = 7.1, 7.1 Hz), 1.32 (6H, t, *J* = 7.1 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7 (d, J_{PC} = 6.5 Hz), 114.7 (d, J_{PC} = 189.0 Hz), 62.7 (d, J_{PC} = 21.6 Hz), 61.6 (2 carbons, d, J_{PC} = 5.6 Hz), 25.7, 18.3, 16.3 (2 carbons, d, J_{PC} = 6.3 Hz), -5.50; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.24; IR (neat) 1251 cm^{-1}; EIMS *m/z* 308 (MH^+), 251 (M^+–*t*-Bu). Anal. Calcd for $C_{13}H_{29}O_4PSi$: C, 50.62; H, 9.49. Found: C, 50.12; H, 9.23.

Diethyl 3-(4-methyoxybenzoyl)oxy-1(*E*)-propenylphosphonate 1c. To a stirred solution of 4-methoxybenzoyl chloride (4.98 g, 29.2 mmol) in CH_2Cl_2 (6 mL) containing pyridine (2.1 mL, 25.4 mmol) and 4-dimethylaminopyridine (155 mg, 1.27 mmol) was added a solution of **3** (2.26 g, 12.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred at room temperature for 12 h and portioned between $CHCl_3$ and *sat.* $KHSO_4$. The extracts were washed with brine, dried ($MgSO_4$) and evaporated to leave a residue. Purification by silica gel column chromatograpy (hexane : EtOAc = 1 :1) gave **1c** (1.85 g, 45%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, *J* = 9.0 Hz), 6.93 (2H, d, *J* = 9.0 Hz), 6.89-6.81 (1H, m), 5.99 (1H, tdd, *J* = 2.0, 17.2, 19.1 Hz), 4.96-4.93 (4H, m), 4.13-4.06 (4H, m), 3.87 (3H, s), 1.33 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 163.7, 145.8 (d, J_{PC} = 5.9 Hz), 131.8, 121.9, 118.0 (d, J_{PC} = 189.4 Hz), 113.8, 63.5 (d, J_{PC} = 23.3 Hz), 61.9 (2 carbons, d, J_{PC} = 5.1 Hz), 55.4, 16.3 (2 carbons, d, J_{PC} = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.13; IR (neat) 1717, 1258 cm^{-1}; EIMS *m/z* 328 (M^+).

General procedure for the synthesis of diethyl 1(*E*)-alkenylphosphonates 1d-j by Horner-Emmons-Wadsworth reaction. To a stirred suspension of tetraethyl methylenediphosphonate (8.64 g, 30 mmol) in hexane

(100 mL) was added *n*-buthyllithium in hexane (19.0 mL of 1.3 M solution, 30 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature. The mixture was cooled to 0 °C and a solution of an aldehyde (30 mmol) in THF (20 mL) was added. After being stirred for 10 min at 0 °C, the mixture was heated at 80 °C for 3 h. The reaction was quenched by the addition of water (100 mL). The mixture was extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purifed by column chromatography on silica gel (hexane : EtOAc = 1 : 1) to give **1d-j** as oils. The yield and the physical data of **1d-j** were follows:

Diethy (*E*)-1-nonenylphosphonates 1d.[28] Yield: 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, tdd, *J* = 6.3, 17.1, 22.0 Hz), 5.60 (1H, dd, *J* = 17.1, 21.2 Hz), 4.09-4.00 (4H, m), 2.21-2.16 (2H, m), 1.44-1.40 (2H, m), 1.31-1.25 (8H, m), 1.29 (6H, t, *J* = 7.1 Hz), 0.85 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (d, J_{PC} = 3.3 Hz), 116.7 (d, J_{PC} = 187.8 Hz), 61.5 (2 carbons, d, J_{PC} = 5.5 Hz), 34.2, 34.0, 31.6, 28.9, 27.7, 22.5, 16.3 (2 carbons, d, J_{PC} = 5.9 Hz), 14.0; ^{31}P NMR (162 MHz, $CDCl_3$) 18.69; IR (neat) 1248 cm^{-1}; EIMS m/z 263 (MH^+).

Diethyl (*E*)-1-phenylethenylphosphonate 1e. Yield: 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (6H, m), 6.25 (1H, dd, *J* = 17.6, 17.6 Hz), 4.15 (2H, t, *J* = 7.2 Hz), 4.10 (2H, t, *J* = 7.1 Hz), 1.35 (6H, t, *J* = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.26; IR (neat) 1245 cm^{-1}; EIMS *m/z* 241 (MH^+). The data were identical to the reported values.[17a]

Diethyl (*E*)-2-(4-methoxyphenyl)ethenylphosphonate 1f. Yield: 51%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 9.0 Hz), 7.37 (1H, dd, *J* = 17.0, 22.0 Hz), 6.85 (2H, d, *J* = 9.0 Hz), 6.04 (1H, dd, *J* = 17.0, 17.0 Hz), 4.25 (4H, dq, *J* = 7.0, 8.0 Hz), 3.76 (3H, s), 1.28 (6H, t, *J* = 7.0 Hz). Anal. Calcd for $C_{13}H_{19}O_5P$: C, 57.77; H, 7.08. Found: C, 57.60; H, 6.81. The NMR data were identical to the reported values.[17a]

Diethyl (*E*)-2-(3-methoxyphenyl)ethenylphosphonate 1g. Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.35 (1H, m), 7.23-7.20 (1H, m), 7.04-6.87 (3H, m), 6.18 (1H, dd, *J* = 17.6, 17.6 Hz), 4.09-4.03 (4H, m), 3.76 (3H, s), 1.29 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 149.0 (d, J_{PC} = 6.7 Hz), 136.6, 130.3, 120.8, 116.4, 114.6 (d, J_{PC} = 190.1 Hz), 113.0, 62.3 (2 carbons, d, J_{PC} = 5.4 Hz), 55.7, 16.8 (2 carbons, d, J_{PC} = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.61; IR (neat) 1243 cm^{-1}; EIMS *m/z* 270 (M^+); High resolution MS calcd for $C_{13}H_{19}O_4P$: 270.1021. Found: 270.1034.

Diethyl (*E*)-2-(4-chlorophenyl)ethenylphosphonate 1h. Yield: 58%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.33 (5H, m), 6.23 (1H, dd, *J* = 17.3, 17.3 Hz), 4.18-4.08 (4H, m), 1.35 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.2 (d, J_{PC} = 5.9 Hz), 136.1, 133.3, 129.0, 128.9, 114.7 (d, J_{PC} = 191.8 Hz), 61.9 (2 carbons, d, J_{PC} = 4.3 Hz), 16.4 (2 carbons, d, J_{PC} = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.15; IR (neat) 1248 cm^{-1}; EIMS *m/z* 274 (M^+); Anal. Calcd for $C_{12}H_{16}ClO_3P$: C, 52.47; H, 5.87. Found: C, 52.16; H, 6.14.

Diethy (*E*)-2-(1-naphthyl)ethenyphosphonate 1i. Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.28 (1H, m), 8.20-8.18 (1H, m), 7.90-7.87 (1H, m), 7.74-7.72 (1H, m), 7.58-7.47 (3H, m), 6.37 (1H, dd, *J* = 14.9 Hz, 17.3 Hz), 4.23-4.16 (4H, m), 1.39 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.8 (d, J_{PC} = 7.0 MHz), 133.5, 132.4, 131.0, 130.4, 128.6, 126.8, 126.2, 125.3, 124.7, 123.2, 117.2 (d, J_{PC} = 189.2 Hz), 61.9 (2 carbons, d, J_{PC} = 5.6 Hz), 16.4 (2 carbons, d, J_{PC} = 6.2 Hz), ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.05; IR (neat) 1242 cm^{-1}; EIMS *m/z* 290 (M^+). High resolution MS calcd for $C_{16}H_{19}O_3P$ (M^+): 290.1072. Found: 290.1071.

Diethyl (*E*)-2-(2-furyl)ethenylphosphonate 1j. Yield: 68%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 1.8 Hz), 7.25 (1H, dd, *J* = 17.5, 22.5 Hz), 6.55 (1H, d, *J* = 3.4 Hz), 6.45 (1H, dd, *J* = 1.8, 3.4 Hz), 6.11 (1H, dd, *J* = 17.5, 17.5 Hz), 4.17-4.03 (4H, m), 1.34 (6H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8 (d, J_{PC} = 25.6 Hz), 114.3, 135.0 (d, J_{PC} = 7.6 Hz), 113.7, 111.9, 110.0 (d, J_{PC} = 192.8 Hz), 61.6 (2 carbons, d, J_{PC} = 5.4 Hz), 16.2 (2 carbons, J_{PC} = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.92; IR (neat) 1625, 1246 cm^{-1}; EIMS *m/z* 231 (MH^+).

Cross-coupling reaction of (*E*)-β-iodostyrene and dimethyl phosphite. A mixtue of (*E*)-β-iodostyrene (1.84 g, 8.0 mmol), dimethyl phosphite (0.81 mL, 8.80 mmol), and triethylamine (2.23 mL, 16.0 mmol) was heated at 70 °C under stirring for 3 h. The reaction was quenched by the addition of *sat.* $KHSO_4$. The mixture was extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), evaporated *in vacuo* to leave a residue. Purification by column chromatography on silca gel (hexane : EtOAc = 2 : 1 to 1 : 20) gave **1k** (555 mg, 33%) as an oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.51-7.34 (6H, m), 6.43 (1H, dd, J = 14.2, 14.2 Hz), 4.47 (6H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6 (d, J_{PC} = 6.5 Hz), 134.6, 130.4, 128.9, 127.7, 112.5 (d, J_{PC} = 192.3 Hz), 52.4 (2 carbons, d, J_{PC} = 5.6 Hz), ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.09; IR (neat) 1248 cm^{-1}; EIMS *m/z* 212 (M^+). Anal. Calcd for $C_{10}H_{13}O_3P$: C, 56.60; H, 6.18. Found: C, 56.66; H, 6.16.

General procedure for AD reaction of 1(*E*)-alkenylphosphonates 1a-k with AD-*mix*-α or -β reagent. To a stirred suspension of AD-*mix*-α or -β reagent (2.80 g) in a 50% aqueous *tert*-BuOH (20 mL) was added potassium osmate dihydrate (6.0 mg, 0.8 mol%) at room temperature. The mixture was stirred at room temperature until two clear phases were produced. To this solution was added $CH_3SO_2NH_2$ (190 mg, 2.0 mmol). The solution was cooled to 0 °C and treated with 1(*E*)-alkenylphosphonate **1a-k** (2.0 mmol). After being stirred at 2 h at 0 °C, the mixure was gradually warmed to 25 °C and stirred for 48 h. Na_2SO_3 (6.00 g) was added and the mixture was stirred at room temperature for 1 h to quench the reaction. The mixure was extracted with EtOAc. The extracts were washed with a small amount of brine, dried ($MgSO_4$), and concentrated to give a residue. Purification by column chromatography on silica gel (EtOAc : Et_2O = 1 : 1) gave 1,2-dihydroxyphosphonates **4a-k**. Yield and physical data of **4a-k** were as follows.

Diethyl (1*S*,2*S*)-1,2-dihydroxypropylphosphonate 4a. Obtained as an oil by the reaction with AD-*mix*-α reagent in 48% yield: $[\alpha]_D^{20}$ +3.73 (c 1.0, MeOH) for a sample of 33% *ee*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.9 (d, J_{PC} = 159.3 Hz), 66.6 (d, J_{PC} = 3.3 Hz), 63.0 (d, J_{PC} = 6.8 Hz), 62.6 (d, J_{PC} = 7.2 Hz), 19.2 (d, J_{PC} = 9.5 Hz), 16.3 (2 carbons, d. J_{PC} = 4.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.30; IR(neat) 3371, 1218 cm^{-1}, EIMS *m/z* 213 (MH^+). High resolution MS calcd for $C_7H_{18}O_3P(MH^+)$: 213.0891. Found: 213.0903.

Diethyl (1*R*,2*R*)-3-*tert*-butyldimethylsiloxy-1,2-dihydroxypropylphosphonate *ent*-4b. Obtained as an oil with AD-*mix*-β reagent in 65% yield: $[\alpha]_D^{20}$–8.3 (c 1.0, MeOH) for a sample of 38% *ee*; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30-4.12 (4H, m), 4.08-3.97 (2H, m), 3.74 (2H, d, J = 5.2 Hz), 3.35-3.10 (2H, m, OH), 1.36 (3H, t, J = 5.2 Hz), 1.35 (3H, t, J = 7.2 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.1, 67.6 (d, J_{PC} = 162.5 Hz), 63.2 (d, J_{PC} = 5.5 Hz), 63.1 (d, J_{PC} = 6.2 Hz), 62.6 (d, J_{PC} = 6.8 Hz), 25.8, 18.2, 16.4 (d, J_{PC} = 5.0 Hz), 16.3 (d, J_{PC} = 5.6 Hz), –5.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.08; IR (neat) 3343, 1219 cm^{-1}; EIMS *m/z* 285 (M^+-*tert*-Bu). Anal. Calcd for $C_{13}H_{31}O_6PSi$: C, 45.59; H, 9.13. Found: C, 45.11; H, 9.17.

Diethyl (1*S*,2*S*)-1,2-dihydroxy-3-(4-methoxybenzoyloxy)propylphosphonate 4c. Obtained as an oil by the reaction with AD-*mix*-α reagent in 10% yield. $[\alpha]_D^{20}$+3.87 (c 0.8, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, J = 8.9 Hz), 6.92 (2H, d, J = 8.9 Hz), 4.45 (2H, d, J = 6.3 Hz), 4.37-4.30 (1H, m), 4.28-4.16 (4H, m), 4.03-3.99 (1H, m), 3.86 (3H, s), 1.36 (6H, t, J = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.1, 163.4, 131.7, 122.1, 113.6, 68.7, 68.5 (d, J_{PC} = 162.6 Hz), 64.2 (d, J_{PC} = 13.4 Hz), 63.4 (d, J_{PC} = 6.9 Hz), 63.0 (d, J_{PC} = 7.0 Hz), 55.4, 16.4 (2 carbons, d, J_{PC} = 5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.49; IR (neat) 3334, 1714, 1259 cm^{-1}; EIMS *m/z* 363 (MH^+). Anal. Calcd for $C_{15}H_{23}O_8P$: C, 49.72; H, 6.40. Found: 49.90; H, 6.53.

Diethyl (1*S*,2*S*)-1,2-dihydroxynonylphosphonate 4d. Obtained as an oil by the reaction with AD-*mix*-α reagent in 46% yield. The physical data was identical to that for *ent*-**4d** except for the specific rotation: $[\alpha]_D^{20}$ –0.82 (c 1.0, MeOH).

Diethyl (1*R*,2*R*)-1,2-dihydroxynonylphosphonate *ent*-4d. Obtained as an oil by the reaction with AD-*mix*-β reagant in 63% yield: $[\alpha]_D^{20}$ +1.81 (c 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 4.22-4.12 (4H, m), 3.93-3.89 (1H, m), 3.76 (1H, dt, J = 2.3, 9.3 Hz), 1.67-1.52 (2H, m), 1.33 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.28-1.25 (10H, m), 0.86 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.4 (d, J_{PC} = 159.1 Hz), 70.3, 63.2 (d, J_{PC} = 6.9 Hz), 62.6 (d, J_{PC} = 7.3 Hz), 32.9 (d, J_{PC} = 11.5 Hz), 31.7, 29.4, 29.2, 25.6, 22.6, 16.4 (2 carbons, d, J_{PC} = 3.5 Hz), 14.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.93; EIMS *m/z* 297 (MH^+).

Diethyl (1*S*,2*S*)-1,2-dihydroxy-2-phenylethylphosphonate 4e. Obtained as an oil by the reaction with AD-*mix*-α reagent in 42% yield: $[\alpha]_D^{20}$ +33.7 (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.20 (5H, m), 5.12 (1H, dd, J = 4.0, 8.0 Hz), 4.22-4.10 (4H, m), 4.04 (1H, ddd, J = 3.1, 8.4, 8.4 Hz), 3.97 (1H, t, J = 4.0 Hz), 3.70-3.50 (1H, m), 1.34 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 128.3, 127.8, 126.5, 72.3

(d, J_{PC} = 7.3 Hz), 72.1 (d, J_{PC} = 159.1 Hz), 63.4 (d, J_{PC} = 7.0 Hz), 62.7 (d, J_{PC} = 7.3 Hz), 16.4 (d, J_{PC} = 5.0 Hz), 16.3 (d, J_{PC} = 5.4 Hz), ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.47; IR (neat) 3338, 1218 cm^{-1}; MS *m/z* 275 (MH^+). Anal. Calcd for $C_{12}H_{19}O_5P$: C, 52.55; H, 6.98. Found: C, 52.26; H, 7.08.

Diethy (1*R*,2*R*)-1,2-dihydroxy-2-phenylethylphosphonate *ent*-4e. Obtained as an oil by the reaction with AD-*mix*-β reagent in 45% yield: The physical data was identical to that of **4e** except for the specific rotation: $[\alpha]_D^{20}$ –30.8 (c 1.0, MeOH).

Diethyl (1*S*,2*S*)-1,2-dihydroxy-2-(4-methoxyphenyl)ethylphosphonate 4f. Obtained as an oil by the reaction with AD-*mix*-α reagent in 71% yield: $[\alpha]_D^{20}$ +28.8 (c 1.0, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 6.8 Hz), 6.88 (2H, d, *J* = 6.8 Hz), 5.08-5.02 (1H, m), 4.20-4.09 (4H, m), 3.99 (1H, ddd, *J* = 3.5, 8.2, 8.2 Hz), 3.94-3.88 (1H, m), 3.79 (3H, s), 3.75-3.67 (1H, m), 1.32 (3H, t, *J* = 6.8 Hz), 1.27 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 132.3, 127.9, 113.4, 72.2 (d, J_{PC} = 159.0 Hz), 72.1 (d, J_{PC} = 4.7 Hz), 62.8 (d, J_{PC} = 6.3 Hz), 62.7 (d, J_{PC} = 7.3 Hz), 55.1, 16.1 (2 carbons, d, J_{PC} = 3.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.56; EIMS *m/z* 304 (M^+). Anal. Calcd for $C_{13}H_{21}O_6P$: C, 51.31; H, 6.96. Found: C, 50.79; H, 6.90.

Diethyl (1*R*,2*R*)-1,2-dihydroxy-2-(4-methoxyphenyl)ethylphosphonate *ent*-4f. Obtained as an oil by the reaction with AD-*mix*-β reagent in 69% yield: The physical data were identical to those of **4f** except for the specific rotation: $[\alpha]_D^{20}$ –31.6 (c 1.0, MeOH).

Diethyl (1*S*, 2*S*)-1,2-dihydroxy-2-(3-methoxyphenyl)ethylphosphonate 4g. Obtained as an oil by the reaction with AD-*mix*-α reagent in 67% yield: $[\alpha]_D^{20}$+32.7 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.24 (1H, m), 7.00-6.97 (2H, m), 6.85-6.81 (1H, m), 5.10 (1H, dd, *J* = 4.3, 7.3 Hz), 4.23-4.13 (4H, m), 4.03 (1H, ddd, *J* = 2.8, 8.6, 8.6 Hz), 1.34 (3H, t, *J* = 7.0 Hz), 1.30 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.6, 141.8, 129.2, 118.7, 113.4, 112.1, 72.22 (d, J_{PC} = 3.4 Hz), 72.18 (d, J_{PC} = 159.4 Hz), 63.4 (d, J_{PC} = 6.7 Hz), 62.7 (d, J_{PC} = 7.1 Hz), 55.2, 16.3 (2 carbons, d, J_{PC} = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.92; IR (neat) 3357, 1225 cm^{-1}; EIMS *m/z* 304 (M^+). High resolution MS calcd for $C_{13}H_{21}O_6P$: 304.1076. Found: 304.1068.

Diethyl (1*S*,2*S*)-1,2-dihydroxy-2-(4-chlorophenyl)ethylphosphonate 4h. Obtained as an oil by the reaction with AD-*mix*-α reagent in 65% yield: $[\alpha]_D^{20}$ +33.4 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 8.7 Hz), 7.32 (2H, d, *J* = 8.7 Hz), 5.07 (1H, dd, *J* = 4.2, 7.6 Hz), 4.22-4.11 (4H, m), 3.98 (1H, ddd, *J* = 3.2, 8.7, 8.7 Hz), 1.34 (3H, t, *J* = 7.0 Hz), 1.28 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9, 133.2, 128.1, 72.2 (d, J_{PC} = 160.2 Hz), 72.1 (d, J_{PC} = 4.8 Hz), 63.2 (d, J_{PC} = 6.9 Hz), 62.6 (d, J_{PC} = 7.3 Hz), 16.1 (2 carbons, d, J_{PC} = 5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.69; IR (neat) 3406, 1216 cm^{-1}; EIMS *m/z* 309 (MH^+). High resolution MS calcd for $C_{12}H_{16}O_4PCl$ (M^+–H_2O): 290.0475. Found: 290.0450.

Diethyl (1*S*,2*S*)-1,2-dihydroxy-2-(1-naphthyl)ethylphosphonate 4i. Obtained as an oil by the reaction with AD-*mix*-α reagent in 80% yield: $[\alpha]_D^{20}$ +63.2 (c 1.06, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.88 (2H, m), 7.83-7.77 (2H, m), 7.55-7.47 (3H, m), 6.02-5.96 (1H, m), 4.32-4.22 (4H, m), 4.19 (1H, dd, *J* = 7.1, 7.7 Hz), 1.42 (3H, t, *J* = 7.1 Hz), 1.34 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.5, 133.7, 129.9, 129.0, 128.2, 126.1, 125.3, 125.2, 124.4, 122.4, 70.6 (d, J_{PC} = 159.9 Hz), 68.2, 63.6 (d, J_{PC} = 6.7 Hz), 62.6 (d, J_{PC} = 7.5 Hz), 16.32 (d, J_{PC} = 4.8 Hz), 16.25 (d, J_{PC} = 4.8 Hz); IR (neat) 3336, 1221 cm^{-1}; EIMS *m/z* 324 (M^+). High resolution MS cacld for $C_{16}H_{21}O_5P$: 324.1127. Found: 324.1127.

Diethyl (1*S*,2*S*)-2-(2-furyl)-1,2-dihydroxyethylphosphonate 4j. Obtained as an unstable oil by the reaction with AD-*mix*-α reagent in 17% yield. $[\alpha]_D^{20}$ +14.7 (c 1.0, MeOH) for a sample of 88% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, d, *J* = 1.8 Hz), 6.40 (1H, d, *J* = 3.2 Hz), 6.33 (1H, dd, *J* = 1.8, 3.2 Hz), 5.06 (1H, dd, *J* = 4.5, 4.5 Hz), 4.24 (1H, dd, *J* = 4.1, 8.9 Hz), 4.18-4.09 (4H, m), 1.30 (3H, t, *J* = 7.1 Hz), 1.28 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9 (d, J_{PC} = 13.0 Hz), 142.0, 110.3, 107.8, 70.0 (d, J_{PC} = 161.6 Hz), 67.2 (d, J_{PC} = 4.6 Hz), 63.3 (d, J_{PC} = 6.7 Hz), 62.9 (d, J_{PC} = 7.3 Hz), 16.3 (2 carbons, d, J_{PC} = 4.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.94; IR (neat) 3353, 1256 cm^{-1}; EIMS *m/z* 265 (MH^+).

Dimethyl (1*R*,2*R*)-1,2-dihydroxy-2-phenylethylphosphonate 4k. Obtained as an oil by the reaction with AD-*mix*-β reagent in 52% yield: $[\alpha]_D^{20}$ –42.0 (c 1.0, MeOH) for a sample of 97% *ee* determined by HPLC analysis on

Chiralpak AS (hexane : EtOH=8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (5H, m), 5.12-5.11 (1H, m), 4.08 (1H, ddd, J = 3.1, 8.5, 8.5 Hz), 3.80 (3H, d, J = 10.7 Hz), 3.76 (3H, d, J = 10.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 128.3, 127.9, 126.5, 72.3 (d, J_{PC} = 3.1 Hz), 72.1 (d, J_{PC} = 159.5 Hz), 53.9 (d, J_{PC} = 6.9 Hz), 53.0 (d, J_{PC} = 7.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.69; IR (neat) 3351, 1216 cm^{-1}; EIMS m/z 247 (MH^+). Anal. Calcd for $C_{10}H_{15}O_5P$: C, 48.78; H, 6.14. Found: C, 48.76; H, 6.31.

(4*S*,5*S*)-4-Diethylphosphono-5-phenyl-2,2-dimethyl-1,3-dioxolane 5. A mixture of **4e** (548 mg, 2.00 mmol), 2,2-dimethoxypropane (832 mg, 8.0 mmol) and camphorsulfonic acid (23.2 mg) in benzene (4 mL) was heated under reflux for 2 h. After dilution with ether, the resulting solution was washed with *sat.* $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Column chromatography of the residue on silica gel eluted with hexane-EtOAc (1:1) gave **5** (534 mg, 85%) as an oil: $[\alpha]_D^{20}$ +13.4 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.25 (5H, m), 5.24 (1H, dd, J = 9.1, 10.6 Hz), 4.20-4.00 (4H, m), 4.03 (1H, dd, J = 2.3, 9.1 Hz), 1.57 (3H, s), 1.56 (3H, s), 1.24 (3H, t, J = 5.5 Hz), 1.22 (3H, t, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 128.5, 128.3, 127.1, 113.3 (d, J_{CP} = 11.0 Hz), 79.6, 79.1 (d, J_{PC} = 89.9 Hz), 62.9 (d, J_{PC} = 6.8 Hz), 62.7 (d, J_{PC} = 6.9 Hz), 26.7, 26.2, 16.3 (d, J_{PC} = 6.0 Hz), 16.2 (d, J_{PC} = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.90; IR (neat) 1258 cm^{-1}; EIMS *m/z* 299 (M^+–CH_3). Anal. Calcd for $C_{15}H_{23}O_5P$:C, 57.31; H, 7.38. Found: C, 56.84; H, 7.29.

(4*S*,5*S*)-4-Diethylphosphono-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane 6. This compound was obtained from **4f** (585 mg, 2 mmol) in an analogous method to that for the preparation of **5**. An oil; $[\alpha]_D^{20}$ +6.87 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, d, J = 8.8 Hz), 6.89 (2H, d, J = 8.8 Hz), 5.20 (1H, dd, J = 9.8, 9.8 Hz), 4.20-4.00 (4H, m), 3.99 (1H, dd, J = 2.4, 9.1 Hz), 3.80 (3H, s), 1.56 (3H, s), 1.55 (3H, s), 1.24 (3H, dd, J = 7.0, 7.1 Hz), 1.21 (3H, dd, J = 7.0, 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 128.8, 128.4, 113.8, 111.0 (d, J_{CP} = 12.3 Hz), 79.3 (d, J_{PC} = 4.6 Hz), 77.7 (d, J_{PC} = 170.9 Hz), 62.8 (d, J_{PC} = 6.1 Hz), 62.7 (d, J_{PC} = 6.6 Hz), 55.2, 26.8, 26.2, 16.3 (d, J_{PC} = 5.0 Hz), 16.2 (d, J_{PC} = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.00; EIMS m/z 329 (M^+-CH_3). Anal. Calcd for $C_{13}H_{21}O_5P$: C, 55.80; H, 7.32. Found: 55.69; H, 7.25.

Diethyl (*S*)-1-hydroxy-2-phenylethylphosphonate 7. A solution of **5** (314 mg, 1.0 mmol) in MeOH (10 mL) was hydrogenated at room temperature for 48 h over 20% $Pd(OH)_2$-C (45 mg) under atmospheric pressure. The catalyst was removed through a pad of Celite, and the filtrate was concentrated. Column chromatography of the residue on silica gel eluted with hexane : EtOAc (1 : 1) to EtOAc gave **7** (103 mg, 40%). Mp 59-61 °C; $[\alpha]_D^{20}$ +21.2 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (5H, m), 4.20 (2H, q, J = 7.2 Hz), 4.16 (2H, q J = 7.2 Hz), 4.14-4.08 (1H, m), 3.14 (1H, ddd, J = 3.4, 6.9, 14.3 Hz), 2.94 (1H, ddd, J = 10.2, 10.2, 14.3 Hz), 1.35 (3H, d, J = 7.1 Hz), 1.33 (3H, d, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 129.3, 128.2, 126.4, 68.7 (d, J_{PC} = 161.5 Hz), 62.6 (d, J_{PC} = 5.6 Hz), 62.5 (d, J_{PC} = 6.6 Hz), 37.6, 16.4 (d, J_{PC} = 3.9 Hz), 16.3 (d, J_{PC} = 3.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.58; IR (KBr) 3233, 1239 cm^{-1}; EIMS *m/z* 258 (M^+). High-resolution MS calcd for $C_{12}H_{17}O_3P$ (M^+–H_2O): 240.0915. Found: 240.0939.

Diethyl (*S*)-1-hydroxy-2-(4-methoxyphenyl)ethylphosphonate 8. A solution of **6** (344 mg, 1.0 mmol) in MeOH (10 mL) was hydrogenated at room temperature for 48 h over 20% $Pd(OH)_2$-C (45 mg) under under 4 kg/cm^2 pressure of hydrogen for 10 h. Workup as usual gave **8** (86 mg, 30%) as an oil; $[\alpha]_D^{20}$ +17.4 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.19 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.5 Hz), 4.30-4.10 (4H, m), 4.10-4.00 (1H, m), 3.79 (3H, s), 3.06 (1H, ddd, J = 3.3, 6.7, 14.3 Hz), 2.88 (1H, ddd, J = 10.2, 10.2, 14.4 Hz), 2.60-2.50 (1H, m), 1.35 (3H, t, J = 7.0 Hz), 1.33 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 130.3, 129.3, 113.9, 69.0 (d, J_{PC} = 161.2 Hz), 62.6 (2 carbons, d, J_{PC} = 6.8 Hz), 55.2, 36.8, 16.5 (2 carbons); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.70; IR (neat) 3294, 1249 cm^{-1}; EIMS *m/z* 288 (M^+). High-resolution MS calcd for $C_{13}H_{19}O_4P$ (M^+–H_2O): 270.0624. Found: 270.0635.

(4*S*,5*S*)-4-Diethylphosphono-5-methoxycarbonyl-2,2-dimethyl-1,3-dioxolane 9. To a stirred solution of **6** (608 mg, 2.00 mmol) in CCl_4 (4 mL), CH_3CN (4 mL), and H_2O (6 mL) was added $NaIO_4$ (5.99 g, 28.0 mmol) and $RuCl_3$•H_2O (8.00 mg, 0.04 mmol), successively, under ice-cooling. The mixture was stirred for 5 min at the same temperature, and then gradually warmed to room temperature. After being stirred for 12 h at room temperature, the

mixture was portioned between Et_2O and H_2O. The extracts were washed with brine, dried ($MeSO_4$), and evaporated to leave a residue which was treated with an ethereal solution (9 mL) of CH_2N_2 (prepared from 515 mg of *N*-methyl-*N*-nitrosourea) at 0 °C for 3 h. The solvent was evaporated. Purification of the residue by column chromatography on silica gel (EtOAc : Et_2O = 1 : 1) gave **9** (562 mg, 95%) as an oil. $[\alpha]_D^{20}$ –26.3 (c 1.0, $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, dd, *J* = 7.6, 13.7 Hz), 4.48 (1H, dd, *J* = 1.2, 7.6 Hz), 4.30-4.10 (4H, m), 3.81 (3H, s), 1.52 (3H, s), 1.44 (3H, s), 1.35 (3H, t, *J* = 7.0 Hz), 1.34 (3H, t, *J* = 7.0 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (d, J_{PC} = 7.2 Hz), 113.4 (d, J_{PC} = 9.7 Hz), 75.7, 73.5 (d, J_{PC} = 175.8 Hz), 63.2 (2 carbons, d, J_{PC} = 7.7 Hz), 52.6, 26.2, 25.4, 16.41 (d, J_{PC} = 5.8 Hz), 16.35 (d, J_{PC} = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.00; IR (neat) 1754, 1256 cm^{-1}; EIMS *m/z* 297 (MH^+). Anal. Calcd for $C_{11}H_{21}O_7P$: C, 44.59; H, 7.15. Found: C, 44.07; H, 7.07.

(4*S*, 5*S*)-4-Diethylphosphono-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane 10. To a solution of **9** (296 mg, 1.00 mmol) in MeOH (3 mL) was added $NaBH_4$ (102 mg, 3.00 mmol) at 0 °C. The mixture was stirred for 30 min under ice-cooling, and gradually warmed to room temperature. After being stirred for 1 h at room temperature, the volatile component of the mixture was evaporated. Water was added and the mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. Purification of the residue by silica gel column chromatography eluted with EtOAc : Et_2O (1 : 1) gave **10** (214 mg, 80%) as an oil. $[\alpha]_D^{20}$-15.5 (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 4.40-4.30 (1H, m), 4.30-4.15 (4H, m), 4.09 (1H, dd, *J* = 2.5, 9.4 Hz), 3.90 (1H, ddd, *J* = 3.7, 3.9, 12.1 Hz), 3.74 (1H, ddd, *J* = 3.3, 9.0, 12.1 Hz), 2.37 (1H, dd, *J* = 3.7, 9.0 Hz), 1.46 (3H, s), 1.44 (3H, s), 1.37 (3H, t, *J* = 7.1 Hz), 1.36 (3H, t, *J* = 7.1 Hz), ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.70; IR (neat) 3407, 1240 cm^{-1}; EIMS *m/z* 269 (MH^+). Anal. Calcd for $C_{10}H_{21}O_6P$: C, 44.77; H, 7.89. Found: C, 44.75; H, 7.89.

(4*S*,5*S*)-4-Diethylphosphono-5-(4-methoxybenzoyloxy)methyl-2,2-dimethyl-1.3-dioxolane 11. (method A) To a stirred solution of 4-methoxybenzoyl chloride (510 mg, 2.99 mmol) in CH_2Cl_2 (1 mL) containing pyridine (0.21 mL, 2.6 mmol) and 4-dimethylaminopyridine (16 mg, 0.13 mmol) was added a solution of **10** (350 mg, 1.3 mmol) in CH_2Cl_2 (2.9 mL) at 0 °C. The mixture was stirred at room temperature for 12 h and portioned between $CHCl_3$ and water. The extracts were washed with brine, dried ($MgSO_4$) and evaporated to leave a residue. Purification by column chromatograpy on silica gel (hexane : EtOAc = 3 : 1) gave **11** (519 mg, 99%) as an oil. $[\alpha]_D^{20}$ –12.2 (c 1.7, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (2H, d, *J* = 9.0 Hz), 6.92 (2H, d, *J* = 9.0 Hz), 4.71-4.66 (1H, m), 4.65-4.56 (1H, m), 4.34 (1H, dd, *J* = 4.8, 12.1 Hz), 4.28-4.18 (4H, m), 4.16 (1H, dd, *J* = 1.9, 9.1 Hz), 3.87 (3H, s). 1.49 (3H, s), 1.44 (3H, s), 1.36 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 165.8, 163.5, 131.7, 122.0, 113.6, 111.7 (d, J_{PC} = 10.3 Hz), 75.9 (d, J_{PC} = 4.1 Hz), 71.8 (d, J_{PC} = 173.9 Hz), 63.0 (2 carbons, d, J_{PC} = 7.3 Hz), 55.4, 26.6, 26.2, 16.43 (d, J_{PC} = 5.0 Hz), 16.37 (d, J_{PC} = 4.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.16; IR (neat) 1715, 1256 cm^{-1}; EIMS *m/z* 402 (M^+). **(method B)** A mixture of **4c** (195 mg, 0.54 mmol), 2,2-dimethoxypropane (0.27 mL, 2.16 mmol) and camphorsulfonic acid (11.6 mg, 0.05 mmol) in benzene (4 mL) was heated under reflux for 2 h. Work-up as usual, followed by column chromatography as above gave **11** (200 mg, 92%). The spectroscopic data including the specific rotation, $[\alpha]_D^{20}$ –14.7 (c 1.0, MeOH), were identical to those of the authentic sample prepared by the method A.

(4*S*,5*S*)-4-Diethylphosphono-5-methyl-2,2-dimethyl-1,3-dioxolane 13. (method A) A solution of **10** (386 mg, 1.44 mmol) in CH_2Cl_2 (3 mL) containing pyridine (0.14 mL, 1.73 mmol) and 4-dimethylaminopyridine (17 mg, 0.14 mmol) was treated with *p*-TsCl (330 mg, 1.73 mmol) at room temperature for 3 h. The mixture was poured onto cold water and extracted with ether. The extracts were washed brine, dried ($MgSO_4$), and evaporated to leave the tosylate. Without purification, the tosylate was treated with *n*-Bu_3SnH (0.38 mL, 1.42 mmol) and NaI (354 mg, 2.30 mmol) in refluxing DME (5 mL). After being cooled, the mixture was poured onto cold water and extracted with ether. The extracts were washed brine, dried ($MgSO_4$), and evaporated to leave a residue. Purification of the residue by column chromatography on silica gel (hexane : EtOAc = 1 : 1 to 1 : 2) gave **13** (184.5 mg, 51% for 2-step) as an oil. $[\alpha]_D^{20}$ –1.8 (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 4.39-4.31 (1H, m), 4.26-4.16 (4H, m), 3.70 (1H, dd, *J* =2.9, 9.2 Hz), 1.43 (6H, s), 1.40 (3H, d, *J* = 6.0 Hz), 1.36 (3H, t, *J* = 7.0 Hz), 1.35 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 110.2 (d, J_{PC} = 11.3 Hz), 77.8, 74.5 (d, J_{PC} = 160.0 MHz), 62.6 (2 carbons, d, J_{PC} = 4.6 Hz),

26.7, 25.9, 17.9 (d, J_{PC} = 3.0 Hz), 16.3 (d, J_{PC} = 5.4 Hz), 16.2 (d, J_{PC} = 4.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.15; IR (neat) 1256 cm^{-1}; EIMS *m/z* 251 (M^+–1). High resolution MS *m/z* calcd for $C_{10}H_{20}O_5P$ (M^+–1): 251.1072. Found: 251.1034. **(method B)** A mixture of **4a** (424 mg, 2.00 mmol), 2,2-dimethoxypropane (832 mg, 8.0 mmol) and camphorsulfonic acid (23.2 mg) in benzene (4 mL) was heated under reflux for 2 h. After dilution with ether, the resulting solution was washed with *sat.* $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Purification of the residue as above gave **13** (428 mg, 85%) as an oil. The spectroscopic data including the specific rotation, $[\alpha]_D^{20}$ –2.0 (c 1.0, MeOH), were identical to those of the authentic sample prepared by the method A.

(4*R*,5*R*)-4-Diethylphosphono-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane *ent*-10. A mixture of *ent*-**4b** (348 mg, 1.00 mmol), 2,2-dimethoxypropane (416 mg, 4.0 mmol) and camphorsulfonic acid (11.6 mg, 0.05 mmol) in benzene (3 mL) was heated under reflux for 2 h. Workup as usual gave the corresponding acetonide. Without purification, the acetonide was treated with teterabutylammonium fluoride (1.1 mL of 1.0 M solution in THF) in THF (2 mL) at room temperature for 2 h. The mixure was portioned between Et_2O and H_2O. The extracts were washed with brine, dried ($MgSO_4$), concentrated. Purification of the residue by column chromatography on silica gel (EtOAc : Et_2O = 1 : 1) gave *ent*-**10** (198 mg, 74%) as an oil. The physical data were identical to those of **10** except for the specific rotation: $[\alpha]_D^{20}$ +6.14 (c 1.0, MeOH).

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26. Non-bonding interaction between the diethylphosphonate functional group and the ligand seems to be not severe, when 1(*E*)-alkenylphosphonates are installed into the ligand as in a model proposed by Sharpless.[24] However, at this stage it is difficult to determine which models actually work for the AD reaction of 1(*E*)-alkenylphosphonates.
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