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Asymmetric Dihydroxylation of 1-Acyloxy-2(*E*)-Alkenylphosphonates with AD-*mix* Reagents. Effects of 1-Acyloxy Functional Groups on the Asymmetric Dihydroxylation

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Abstract: Asymmetric dihydroxylation (AD) of a racemic mixture of 1-acyloxy-2(*E*)-alkenylphosphonates with AD-*mix*-α or -β reagents was examined. The kinetic rate of dihydroxylation was highly dependent upon the configuration of the 1-acyloxy functional group as well as the nature of substituents at the 3-position. The reaction of a racemic mixture of diethyl (*E*)-3-phenyl-1-acetyloxy-2-propenylphosphonate with an AD-*mix*-β reagent preferentially dihydroxylated the *R*-enantiomer to leave an unreacted *S*-enantiomer of high enantiomeric purity. Double diastereoselection of the resolved diethyl 3-phenyl-1-acetyloxy-2(*E*)-propenylphosphonate in dihydroxylation was also examined.

INTRODUCTION

The asymmetric dihydroxylation (AD) of olefins provides a powerful tool to create optically active vicinal diols.[1] The osmium tetraoxide-cinchona alkaloid system developed by Sharpless has been applied to asymmetric dihydroxylation of a wide range of possible substrates.[1] In a preceding paper,[2] we have illustrated that AD reaction of 1(*E*)-alkenylphosphonates with an AD-*mix*-α or -β reagent, a commercially available dihydroxy reagent comprising of cinchona alkaloid ligands $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, an osmium source, and a re-oxidant,[1] possesses high potential for the enantioselective synthesis of *threo*-α,β-dihydroxyphosphonates, a new class of compounds with broad application from the medicinal point of view.[3] Moreover, the influence of the phosphonate functional group attached to the double bond in the course of dihydroxylation was clarified.[2] The purpose of this paper is to describe the AD reaction of 2(*E*)-alkenylphosphonates with or without an oxygen functionality at the 1-position as an extension of the previous work[2] (Eq. 1 and 2). Evaluation of the degree of asymmetric induction for 2(*E*)-alkenylphosphonates would be valuable to clarify the influence of the phosphonate functional group in the transition state of the AD reaction, as compared with the asymmetric induction of 1(*E*)-alkenylphosphonates under the same conditions described in the preceding paper (Eq. 1).[2] Moreover, the AD-reaction for 2(*E*)-alkenylphosphonates possessing an oxygen functionality at the 1-position would be a useful method to resolve a racemic mixture of 1-hydroxy-2(*E*)-alkenylphosphonate derivatives, a class of compounds which is difficult to prepare in high enantiomeric purity by the existing method,[4] when the kinetic ratio of the dihydroxylation is altered by the configuration at the 1-position (Eq. 2).[5,6]

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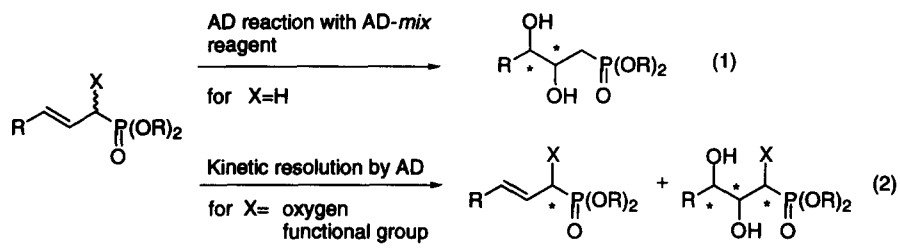
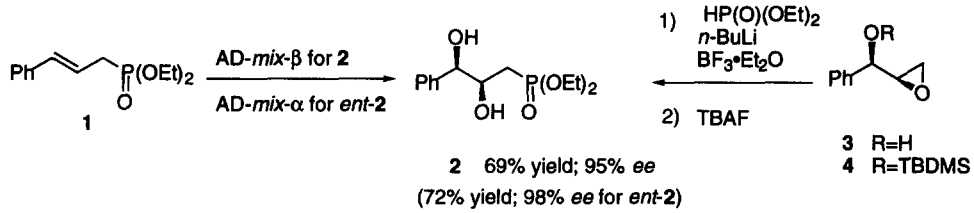


RESULTS AND DISCUSSION

AD reaction of 3-phenyl-2(E)-propenylphosphonate 1 with AD-mix reagents

AD reaction of **1**[7] with AD-*mix*-β was first examined under exactly the same conditions as for 1(*E*)-alkenylphosphonates.[2] The reaction provided the desired dihydroxylation product **2** with 95% enantiomeric excess (*ee*) in 69% yield as expected. AD reaction with AD-*mix*-α gave an enantiomeric isomer (*ent*-**2**) of **2** in comparative yield (72%) and enantiomeric purity (98% *ee*). The absolute configuration of **2** was readily confirmed by chiroptical comparison with the authentic sample derived from the known epoxy alcohol **3**[8] *via* **4** by the established methods.[9]



Since AD reaction of diethyl (*E*)-2-phenylethenylphosphonate under the same conditions proceeded in 91-92% *ee* with modest yield (42-45%) as reported in the preceeding paper,[2] the results obtained with **1** clearly show that AD reaction of 2(*E*)-alkenylphosphonates with AD-*mix* reagents occurs more favorably than that of 1(*E*)-alkenylphosphonates. We assumed that the high enantioselectivity achieved with AD reaction for **1** might be arise from the lower steric influence of the phosphonate functional group that is located in the open space of the front part of the U-shaped pocket proposed by Corey[6] (Fig. 1-(1) *vs* -(2)).

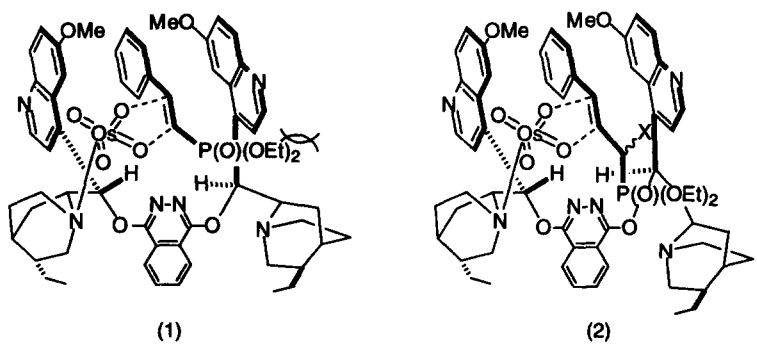
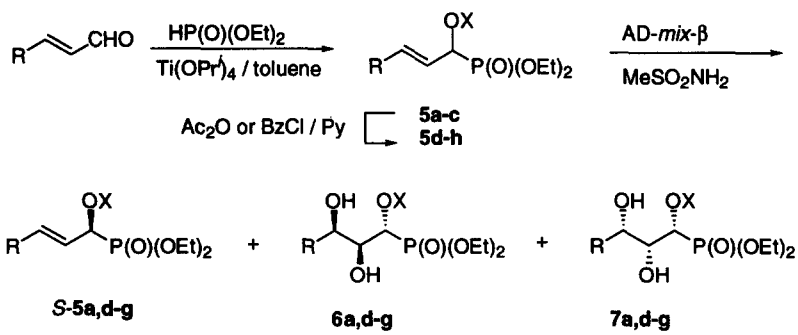


Fig. 1 Comparison with transition states for AD reaction of diethyl (*E*)-2-phenylethenylphosphonate (1) and diethyl (*E*)-3-phenyl-2-propenenylphosphonate (2, X=H) in the ligand of AD-*mix*-β.

AD reaction of a racemic mixture of 2(E)-alkenylphosphonates possessing an oxygen functionality at the 1-position with AD-mix reagents

Having established the features of AD reaction of diethyl 3-phenyl-2(*E*)-propenylphosphonate **1**, our attention was focused on AD reaction of a racemic mixture of 2(*E*)-alkenylphosphonates possessing an oxygen functionality at the 1-position. In the transition state for these reactions, a steric interaction between the oxygen functionality incorporated into the substrate and the methoxyquinoline in the ligand might be altered depending on the configuration of the oxygen functionality (Fig. 1-(2), X=oxygen functionality); therefore, the resulting difference in kinetic rate of dihydroxylation would allow us to resolve the racemates. Keeping these consideration in mind, AD reaction of a series of 2(*E*)-alkenylphosphonates **5a** and **5d-g**, prepared from the corresponding alkenylaldehydes as shown in Scheme 1,[10] was examined. The results are summarized in Table 1.

Scheme 1



a: R = Ph, X = H; **b**: R =4-MeOC$_6$H$_4$, X =H; **c**: R =X =H; **d**: R = Ph, X = Ac
e: R =Ph, X= Bz; **f**: R = 4-MeOC$_6$H$_4$, X =Ac; **g**: R = H, X = Ac; **h** : R = H, X = Bz

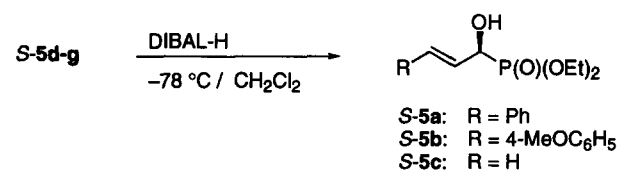
While no difference in the kinetic rate of the dihydroxylation was observed with 1-hydroxy derivative **5a** (entry 1), a moderate difference in the kinetic ratio was accomplished as expected when an acetyloxy or benzoyloxy group was positioned at the 1-position instead of a hydroxy group. Dihydroxylation of the acetate **5d** with AD-*mix*-β reagent in the presence of $MeSO_2NH_2$ occurred preferentially for the *R* enantiomer at 0 °C to leave the unreacted *S* enantiomer (*S*-**5d**) and an inseparable mixture of dihydroxylation products **6d** and **7d**[11] (entry 2). When the reaction was terminated at the conversion of 65%, *S*-**5d** of 99% *ee* was isolated in 35% yield. A moderate rate difference (k_{rel} = 15.6) was observed for this reaction. While it was verified that the kinetic rate difference (k_{rel} = 4.9) significantly decreased upon using AD-*mix*-α under the same conditions, *R*-**5d** of high enantiomeric purity (99% *ee*) was isolated from this reaction (entry 3). The benzoyloxy group at the 1-position in the substrate was proved to be less effective than an acetyloxy group for the kinetic resolution; the k_{rel} for the AD reaction of the benzoate **5e** with either AD-*mix*-α or -β reagent was estimated to be small (entries 4-6). The terminal substituent seems to be an important factor for obtaining a large k_{rel} (entries 2 *vs* 7-9). A very small k_{rel} (1.6) was observed for the reaction of **5h** (entry 9), whereas a moderate k_{rel} (10.7) was observed for AD reaction of 4-methoxyphenyl derivative **5f** (entry 6).

Table 1 Asymmetric dihydroxylation of a racemic mixture of 2(*E*)-alkenylphosphonates **5a,d-h** with AD-*mix*-β or -α reagent

Entry[a]	Substrate (R, X)	AD-*mix*	Time (h)	Conv.[b] (%)	Unreacted **5** config.	yield (%)	*ee* (%)	Yield of diol[c] (%)	k_{rel}[d]
1	**5a** (R=Ph, X=H)	β	10	67	*rac*-**5a**	33	0	13	—
2	**5d** (R=Ph, X=Ac)	β	6	65	*S*-**5d**	35	99[e]	56	15.6
3	**5d** (R=Ph, X=Ac)	α	6	87	*R*-**5d**	13	99[e]	54	4.9
4	**5e** (R=Ph, X=Bz)	β	6	40	*S*-**5e**	60	42[e]	26	6.6
5	**5e** (R=Ph, X=Bz)	β	8	87	*S*-**5e**	13	98[e]	54	4.4
6	**5e** (R=Ph, X=Bz)	α	6	50	*R*-**5e**	50	49*e*	35	4.6
7	**5f** (R=4-MeOPh, X=Ac)	β	6	64	*S*-**5f**	36	94[f]	57	10.7
8	**5g** (R=H, X=Ac)	β	6	56	*S*-**5g**	44	61[f]	52	5.1
9	**5h** (R=H, X=Bz)	β	10	81	*S*-**5h**	19	38[f]	67	1.6

[a] All reactions were carried out at 0 °C on 2 mmol scale. [b] Based on consumption of the racemate. [c] Referred to combined yield of inseparable mixture of **6a,d-g** and **7a,d-g** (*ent*-**6d,e** and *ent*-**7d,e** for entry 3 and 6) (ref. 11). [d] Calculated by the equation reported by Sharpless (ref. 12). [e] Determined by HPLC analysis on Chiralpak AS (Daicel). [f] Determined by NMR (^{31}P and ^{1}H) analysis after converting the corresponding MTPA esters.

The resolved *S*-**5d-g** was converted to the parental 1-hydroxy-2-alkenylphosphonates *S*-**5a-c** by reductive deacylation with DIBAL-H, whose absolute configuration was confirmed by ^{31}P NMR analysis of the corresponding (*R*)-MTPA esters according to the method of Hammerschmidt[13a] (see experimental section).



Double diastereoselection in the dihydroxylation of R-5d

The kinetic behavior observed for the AD reaction of a racemic mixture of **5d** with AD-*mix*-β reagent in the preceding section is apparently due to the double diastereoselection[14] arising from a matched pair between *R*-**5d** and the $(DHQD)_2PHAL$ ligand•OsO_4 complex in the transition state of the dihydroxylation shown in Fig. 1-(2). This fact suggests that asymmetric dihydroxylation of the resolved *R*-**5d** with AD-*mix*-β would be a useful method for preparation of poly-oxygenated phosphonates in a highly diastereoselective manner, which are a class of compounds of interest in glyco-mimetic chemistry.[15]

In order to examine the double diastereoselection in detail, *R*-**5d** of high enantiomeric purity (>99% *ee*) prepared in the preceding section, was submitted to the representative dihydroxylation reactions, and the dihydroxlation products **8** were isolated as the triacetates **9**[11] (Eq. 3 and Table 2).

Initial studies were conducted by the use of quinuclidine as a nonchiral amine ligand for acceleration of the dihydroxylation under the conditions developed by Warren.[16] The reaction preferentially afforded *anti*-**9** in a low yield with a modest diastereoselectivity (81:19) (entry 1). The diastereoselectivity steadily increased to 99:1 upon conducting the dihydroxylation with an AD-*mix*-β reagent as expected, and diastereomerically pure *anti*-**9** was

isolated in 49% yield (entry 2). The reversal of the diastereoselection with modest diastereoselectivity (*anti*-**9**:*syn*-**9** = 11:89) was observed when the dihydroxylation was conducted with an AD-*mix*-α reagent under the same conditions (entry 3). From this reaction diastereomerically pure *syn*-**9** was isolated in 28% yield.

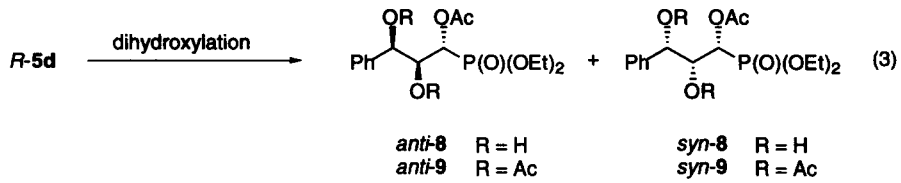
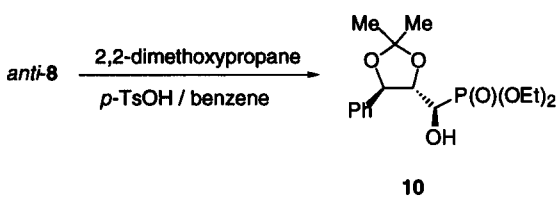


Table 2. Double diastereoselection in the dihydroxylation of *R*-**5d**

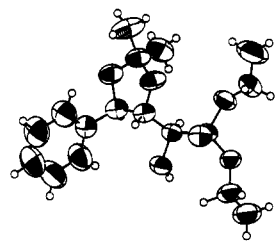
Entry	Dihydroxylation conditions	Time (h)	Isolated yield	Ratio of *anti*-**9** / *syn*-**9**[a]
1	$K_2OsO_4 \cdot 2H_2O$, quinuclidine K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$ in *aq.* 50% *tert*-BuOH at 20 °C[b]	9	22	81:19
2	AD-*mix*-β, $MeSO_2NH_2$ in *aq.* 50% *tert*-BuOH at 0 °C	42	49	99:1
3	AD-*mix*-α, $MeSO_2NH_2$ in *aq.* 50% *tert*-BuOH at 0 °C	42	28	11:89

[a] Determined by ^{31}P-NMR ($CDCl_3$) analysis. [b] Modified conditions for racemic dihydroxylation developed by Warren (ref. 16).

To unequivocally confirm the relative stereochemistry of *anti*-**9** and *syn*-**9** obtained as above, the nearly pure *anti*-**8** was isolated in a low yield[11] from the reaction mixture with AD-*mix*-β and transformed to the acetonide **10** in the usual manner.[17] X-ray crystallographic analysis of **10** clearly established its relative stereochemistry. At this statge, absolute stereochemistry of *anti*-**9** and *syn*-**9** was determined to be 1*R*,2*S*,3*R* and 1*R*,2*R*,3*S*, respectively. The results are in good agreement with the stereochemistry predicted from the mechanistic aspects of the AD reaction of 2(*E*)-alkenylphosphonates with AD-*mix* reagents (Fig. 1).



10



ORTEP drawing of **10**

CONCLUSION

In conclusion, we have shown that kinetic resolution of 1-acetyloxy-2(*E*)-alkenylphosphonates with AD-*mix* reagent is a useful method for obtaining 1-hydroxy-2(*E*)-alkenylphosphonate derivatives with high enantiomeric purity, which are a class of compounds difficult to obtain in a highly enantioselective manner by the

previous methods.[4] Moreover, we have shown that the AD-reaction of the optically active 1-acetyloxy-2(*E*)-alkenylphosphonate derivatives provides poly-oxygenated phosphonates with high diastereoselectivity, which are potentially useful chiral phosphonates in glyco-mimetic chemistry.[15]

EXPERIMENTAL[18]

Diethyl (2*S*,3*R*)-2,3-dihydroxy-3-phenylpropylphosphonate 2. General procedure for AD-reaction of 1(*E*)-alkenylphosphonates described in the preceding paper[2] was applied to **1**[7] giving **2** by the use of AD-*mix*-β reagent. Yield: 69%; mp 63-64 °C; $[\alpha]_D^{20}$ –7.0 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (5H, m), 4.55 (1H, d, *J* = 6.3 Hz), 4.17-4.01 (5H, m), 1.94-1.80 (2H, m), 1.31 (3H, t, *J* = 7.1 Hz), 1.29 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 128.4, 128.0, 127.0, 77.6 (d, J_{PC} = 17.8 Hz), 70.9 (d, J_{PC}=5.4 Hz), 62.0 (2 carbons, d, J_{PC} = 6.2 Hz), 29.5 (d, J_{PC} = 140.4 Hz), 16.3 (2 carbons, d, J_{PC} = 5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.90; IR (KBr) 3364, 1220 cm^{-1}; EIMS *m/z* 289 (MH^+), 271 (M^+–OH). Anal. Calcd for $C_{13}H_{21}O_5P$: C, 54.15; H, 7.35. Found: C, 53.99; H, 7.34.

Diethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropylphosphonate *ent*-2. This compound was obtained by the reaction with AD-*mix*-α reagent as crystals (mp 63-64 °C) in 71% yield. The physical data were identical to those of **2** except for the specific rotation: $[\alpha]_D^{20}$ +7.1 (c 1.0, MeOH).

(1*R*,2*R*)-1-*tert*-Butyldimethylsiloxy-2,3-epoxy-1-phenylpropane 4. A solution of **3**[8] (3.00g, 20.0 mmol) in DMF (30 mL) was treated with TBDMSCl (3.32 g, 22 mmol) and imidazol (2.72 g, 40.0 mmol) at room temperature for 15 h. Water was added to quench the reaction. The mixture was extracted with ether, and the extrats were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane : EtOAc = 20 : 1) to give **4** (4.80 g, 91%) as an oil. $[\alpha]_D^{20}$ –21.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.27 (5H, m), 4.38 (1H, d, *J* = 6.3 Hz), 3.10 (1H, ddd, *J* = 3.0, 4.4, 6.3 Hz), 2.80-2.75 (1H, m), 2.71-2.65 (1H, m), 0.93 (9H, s), 0.12 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 128.3, 127.7, 126.2, 76.8, 56.9, 45.2, 25.8, 18.3, -4.5, -5.0; EIMS *m/z* 207 (M^+-*tert*-Bu).

Preparation of 2 from siloxyepoxide 4. To a stirred solution of diethyl phosphite (4.15 g, 30 mmol) in THF (30 mL) was added *n*-BuLi (18.8 mL of 1.6 M solution in hexane) at –78 °C. After being stirred at the same temparature for 15 min, a solution of **4** (2.64 g, 10 mmol) in THF (5 mL) and BF_3•Et_2O (4.92 mL, 40 mmol) was successively added. The mixture was stirred at -78 °C for 2 h and quenched with *sat.* NH_4Cl. The volatile component (THF) of the mixture was evaporated and the residue was extracted with ether. The organic extracts were concentrated to leave an oil which was dissolved in THF (10 mL). The solution was treated with tetra-*n*-butylamonium fluoride (10 mL of 1.0 M solution in THF) at room temperature for 1 h. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1) to give **2** (662 mg, 23%). The physical data including the specific rotation, $[\alpha]_D^{20}$ –7.1 (c 0.7, MeOH), were identical to those of **2** prepared from **1** with AD-*mix*-β reagent.

Diethyl 1-hydroxy-3-phenyl-2(*E*)-propenenyphosphonate 5a. A solution of diethyl phosphite (10.3 mL, 80 mmol) in toluene (60 mL) was treated with $Ti(OPr^i)_4$ (4.76 mL, 16.0 mmol) at 0 °C for 30 min under stirring. To this mixure, a solution of *trans*-cinnamaldehyde (10.1 mL, 80 mmol) in toluene (60 mL) was added. After being stirred at 0 °C for 12 h, the reaction was quenched with 1 N HCl. The mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a semi-solid. Recrystallization from hexane containing EtOAc gave **5a** (13.8 g, 64%). Mp 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.20 (5H, m), 6.78 (1H, ddd, *J* = 1.5, 4.9, 13.1 Hz), 6.33 (1H, ddd, *J* = 5.3, 6.0, 13.1 Hz), 4.67 (1H, dd, *J* = 6.0, 12.7 Hz), 4.25-4.13 (4H, m), 1.32 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 133.3 (d, J_{PC} = 13.2 Hz), 129.4, 128.7, 127.4. 124.6 (d, J_{PC} = 4.2 Hz), 70.0 (d, J_{PC} = 161.1 Hz), 63.6 (d, J_{PC} = 6.5 Hz), 63.5 (d, J_{PC} = 7.4 Hz), 16.6 (2 carbons, d, J_{PC} = 5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.26; IR (KBr) 3259, 1227 cm^{-1}; EIMS *m/z* 270 (M^+). Anal. Calcd for $C_{13}H_{19}O_4P$: C, 57.77; H, 7.09. Found: C, 58.02; H, 7.15.

Diethyl 1-hydroxy-3-(4-methoxyphenyl)-2(*E*)-propenylphosphonate 5b. Prepared in 80% yield from *trans*-4-methoxycinnamaldehyde (5.8 g, 36 mmol), diethyl phosphite (5.2 mL, 40 mmol) and $Ti(OPr^i)_4$ (2.16 mL, 7.2 mmo) by an analogous method to that for the synthesis of **5a**. Mp 66-67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, J = 8.7 Hz), 6.85 (2H, d, J = 8.7 Hz), 6.71 (1H, dd, J = 4.6, 15.9 Hz), 6.18 (1H, ddd, J = 5.6, 6.6, 15.9 Hz), 4.62 (1H, ddd, J = 1.4, 6.6, 12.2 Hz), 4.22-4.15 (4H, m), 3.81 (3H, s), 1.33 (6H, t with small splits, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 132.0 (d, J_{PC} = 13.5 Hz), 129.2, 127.8, 121.6, 113.9, 69.6 (d, J_{PC} = 161.7 Hz), 63.1 (d, J_{PC} = 6.7 Hz), 63.0 (d, J_{PC} = 7.3 Hz), 55.2, 16.4 (2 carbons, d, J_{PC} = 5.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.42; IR 3267, 1254 cm^{-1}; EIMS *m/z* 300 (M^+). Anal. Calcd for $C_{14}H_{21}O_5P$: C, 55.99; H, 7.05. Found: C, 55.91; H, 7.05.

Diethyl 1-hydroxy-2-propenylphosphonate 5c. Prepared from acrolein (2.67 mL, 40 mmol), diethyl phosphite (5.15 mL, 40.0 mmol) and $Ti(OPr^i)_4$ (2.38 mL, 8.0 mmol) in 65% by an analogus method to that for the synthesis of **5a**. Purification was achieved by column chromatography on silica gel (hexane : EtOAc = 1 : 1 to EtOAc). An oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02-5.93 (1H, m), 5.47 (1H, dddd, J = 1.5, 1.5, 5.1, 17.2 Hz), 5.28 (1H, ddd, J = 1.8, 1.8, 10.6 Hz), 4.51-4.45 (1H, m), 4.19-4.10 (4H, m), 1.30 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8 (d, J_{PC} = 2.9 Hz), 116.9 (d, J_{PC} = 12.1 Hz), 69.5 (d, J_{PC} = 160.1 Hz), 63.1 (d, J_{PC} = 7.3 Hz), 62.9 (d, J_{PC} = 7.3 Hz), 16.4 (2 carbons, d, J_{PC} = 5.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.40; IR (neat) 3297, 1238 cm^{-1}; EIMS *m/z* 195 (MH^+). Anal. Calcd for $C_7H_{15}O_4P$: C, 43.30; H, 7.79. Found: C, 43.20; H, 7.68.

Diethyl 1-acetyloxy-3-phenyl-2(*E*)-propenylphosphonate 5d. A solution of **5a** (2.70 g, 10.0 mmol) in CH_2Cl_2 (20 mL) containing pyridine (2.43 mL, 30.0 mmol) and 4-dimethylaminopyridine (122 mg, 1.0 mmol) was treated with Ac_2O (2.77 mL, 25 mmol) at room temperature for 3 h. The reaction mixture was treated with *sat.* $KHSO_4$ and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1 to 1 : 20) to give **5d** (2.76 g, 89%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.27 (5H, m), 6.75 (1H, dd, J = 4.1, 15.9 Hz), 6.25 (1H, ddd, J = 5.8, 7.5, 15.9 Hz), 5.84 (1H, ddd, J = 1.3, 7.5, 14.1 Hz), 4.23-4.13 (4H, m), 2.18 (3H, s), 1.33 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (d, J_{PC} = 7.8 Hz), 135.7, 135.1 (d, J_{PC} = 12.5 Hz), 128.6, 128.3, 126.7, 120.1 (d, J_{PC} = 4.2 Hz), 69.4 (d, J_{PC} = 171.3 Hz), 63.3 (d, J_{PC} = 8.5 Hz), 63.2 (d, J_{PC} = 8.0 Hz), 20.8, 16.4 (d, J_{PC} = 5.9 Hz), 16.3 (d, J_{PC} = 6.2 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 17.63; IR (neat) 1748, 1223 cm^{-1}; EIMS *m/z* 312 (M^+). Anal. Calcd for $C_{15}H_{21}O_5P$: C, 57.69; H, 6.78. Found: C, 57.26; H, 6.77.

Diethyl 1-benzoyloxy-3-phenyl-2(*E*)-propenylphosphonate 5e. A solution of **5a** (2.70 g, 10.0 mmol) in CH_2Cl_2 (20 mL) containing pyridine (2.43 mL, 30.0 mmol) and 4-dimethylaminopyridine (122 mg, 1.0 mmol) was treated with benzoyl chloride (3.00 mL, 25 mmol) at room temperature for 3 h. Workup and purification as above gave **5e** (3.48 g, 93%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.12 (2H, m), 7.63-7.58 (1H, m), 7.50-7.46 (2H, m), 7.44-7.40 (2H, m), 7.34-7.24 (3H, m), 6.84 (1H, dd, J = 4.3, 15.9 Hz), 6.38 (1H, ddd, J = 5.8, 7.3, 15.9 Hz), 6.11 (1H, ddd, J = 1.3, 7.3, 14.0 Hz), 4.25-4.20 (4H, m), 1.32 (6H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (d, J_{PC} = 7.7 Hz), 135.8, 135.2 (d, J_{PC} = 12.5 Hz), 133.5, 129.9, 129.4, 128.6, 128.5, 128.4, 126.8, 120.3 (d, J_{PC} = 4.2 Hz), 69.9 (d, J_{PC} = 171.1 Hz), 63.4 (d, J_{PC} = 7.3 Hz), 63.2 (d, J_{PC} = 6.3 Hz), 16.5 (d, J_{PC} = 6.4 Hz), 16.4 (d, J_{PC} = 7.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.46; IR (neat) 1729, 1257 cm^{-1}; EIMS *m/z* 374 (M^+). Anal. Calcd for $C_{20}H_{23}O_5P$: C, 64.16; H, 6.19. Found: C, 64.17; H, 6.17.

Diethyl 1-acetyloxy-3-(4-methoxyphenyl)-2(*E*)-propenylphosphonate 5f. Prepared as an oil in 95% yield from **5b** (3.0 g, 10 mmol) by an analogous method to that for the preparation of **5d.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, J = 8.7 Hz), 6.85 (2H, d, J = 8.7 Hz), 6.70 (1H, dd, J = 4.0, 15.9 Hz), 6.10 (1H, ddd, J = 5.9, 7.8, 15.9 Hz), 5.81 (1H, ddd, J =1.1, 7.8, 13.5 Hz), 4.21-4.14 (4H, m), 3.81 (3H, s), 2.16 (3H, s), 1.33 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (d, J_{PC} = 8.1 Hz), 159.9, 135.1 (d, J_{PC} = 13.0 Hz), 128.5, 128.1, 117.8 (d, J_{PC} = 3.6 Hz), 114.0, 69.6 (d, J_{PC} = 172.2 Hz), 63.22 (d, J_{PC} = 7.3 Hz), 63.16 (d, J_{PC} = 6.5 Hz), 55.3, 20.9, 16.5 (d, J_{PC} = 6.4 Hz), 16.4 (d, J_{PC} = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.89; IR (neat) 1746, 1223 cm^{-1}; EIMS *m/z* 342 (M^+). Anal. Calcd for $C_{16}H_{23}O_6P$: C, 56.13; H, 6.77. Found: C, 55.90; H, 6.81.

Diethyl 1-acetyloxy-2-propenylphosphonate 5g. Prepared as an oil in 86% yield from **5c** (1.16 g, 6.00 mmol) by an analogous method to that for the preparation of **5d**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98-5.89 (1H, m), 5.69 (1H, ddd, J = 1.1, 6.1, 14.8 Hz), 5.42 (1H, ddd, J = 1.1, 4.5, 17.2 Hz), 5.37-5.33 (1H, m), 4.21-4.12 (4H, m), 2.16 (3H, s), 1.33 (3H, t, J = 7.0 Hz), 1.32 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (d, J_{PC} = 7.7 Hz), 129.3 (d, J_{PC} = 4.1 Hz), 118.9 (d, J_{PC} = 11.7 Hz), 69.2 (d, J_{PC} = 168.8 Hz), 63.1 (d, J_{PC} = 6.6 Hz), 62.9 (d, J_{PC} = 6.2 Hz), 20.5, 16.2 (d, J_{PC} = 6.1 Hz), 16.1 (d, J_{PC} = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.38; IR (neat) 1753, 1225 cm^{-1}; EIMS m/z 237 (MH^+). Anal. Calcd for $C_9H_{17}O_5P$: C, 45.76; H, 7.25. Found: C, 45.61; H, 7.30.

Diethyl 1-benzoyloxy-2-propenenylphosphonate 5h. Prepared in 52% yield from **5c** (1.47 g, 7.60 mmol) by an analogous method to that for the preparation of **5e**. An oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.10 (2H, m), 7.62-7.58 (1H, m), 7.49-7.45 (2H, m), 6.12-6.02 (1H, m), 5.96 (1H, dddd, J = 1.5, 1.5, 6.0, 14.8 Hz), 5.51 (1H, dddd, J = 1.2, 1.2, 4.6, 17.1 Hz), 5.41-5.37 (1H, m), 4.24-4.18 (4H, m), 1.32 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8 (d, J_{PC} = 7.7 Hz), 133.4, 129.8, 129.3 (d, J_{PC} = 4.1 Hz), 129.2, 128.5, 119.1 (d, J_{PC} = 11.2 Hz), 69.6 (d, J_{PC} = 169.1 Hz), 63.4 (d, J_{PC} = 6.7 Hz), 63.1 (d, J_{PC} = 6.3 Hz), 16.4 (d, J_{PC} = 5.6 Hz), 16.3 (d, J_{PC} = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.21; IR (neat) 1733, 1262 cm^{-1}; EIMS m/z 299 (MH^+). Anal. Calcd for $C_{14}H_{19}O_5P$: C, 56.37; H, 6.42. Found: C, 56.52; H, 6.50.

General procedure for kinetic resolution of 5a and 5d-g with AD-*mix* reagents. To a stirred suspension of AD-*mix*-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 2(*E*)-alkenylphosphonate **5a** or **5d-g** (2.0 mmol). The mixture was stirred at 0 °C for the indicated period in Table 1. Na_2SO_3 (6.00 g) was added and the mixture was stirred at room temperature for 1 h to quench the reaction. The mixture 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 (hexane:EtOAc=1:1 to 1:2) gave unreacted *S*-**5d-g** and inseparable mixture of **6d-g** and **7d-g** as oils. The same procedure was applied for resolution of **5d** giving *R*-**5d** with AD-*mix*-α reagent. The yield of *S*-**5d-g** (*R*-**5d**) and the combined yield of **6d-g** and **7d-g** (*ent*-**6d** and *ent*-**7d**) are shown in Table 1. The physical data of **6d-g** and **7d-g** (*ent*-**6d** and *ent*-**7d**) were not steadily collected because it was difficult to isolate these compounds as a pure state.[11] The spectroscopic data of *S*-**5d-g** and *R*-**5d** were identical to those of the corresponding racemates except for the specific rotation; *S*-**5d** of 99% *ee*: $[\alpha]_D^{20}$ -38.2 (c 1.0, $CHCl_3$); *R*-**5d** of 99% *ee*: $[\alpha]_D^{20}$ +39.9 (c 1.0, $CHCl_3$); *S*-**5e** of 98% *ee*: $[\alpha]_D^{20}$ +23.5 (c 0.9, $CHCl_3$); *R*-**5e** of 49% ee: $[\alpha]_D^{20}$ –11.6 (c 1.1, $CHCl_3$); *S*-**5f** of 94% *ee*: $[\alpha]_D^{20}$ –35.7 (c 1.0, $CHCl_3$); *S*-**5g** of 61% *ee*: $[\alpha]_D^{20}$ +9.25 (c 1.1, $CHCl_3$); *S*-**5h** of 38% *ee*: $[\alpha]_D^{20}$ +16.5 (c 1.0, $CHCl_3$).

General procedure for the reductive deacylation of *S*-5d-g. To a stirred solution of *S*-**5d-g** (0.43 mmol) in CH_2Cl_2 (1.5 mL) was added a 0.95 M solution of DIBAL-H in hexane (1.14 mL, 1.08 mmol for the acetates *S*-**5d,f,g**; 1.69 mL, 1.61 mmol for the benzoates *S*-**5e,h**) at –78 °C. After being stirred for 2 h at the same temperature, the mixture was portioned between EtOAc and *sat.* NH_4Cl. The resulting gel was filtered and the filtrates were extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to leave a residue. Purification of the residue as for the racemates **5a-c** gave *S*-**5a-c**.

Diethyl (*S*)-1-hydroxy-3-phenyl-2(*E*)-propenylphosphonates *S*-5a. 49% yield, mp 105-106 °C, $[\alpha]_D^{20}$ -13.4 (c 0.9, $CHCl_3$) for a sample (99% *ee*) derived from *S*-**5d**; 21% yield, mp 94-95 °C, $[\alpha]_D^{20}$ -3.47 (c 0.6, $CHCl_3$) for a sample (42% *ee*) derived from *S*-**5e**. The other physical data were identical to those of the racemate **5a**.

Diethyl (*S*)-1-hydroxy-3-(4-methoxyphenyl)-2(*E*)-propenylphosphonate *S*-5b. 44% yield, mp 63-65 °C, $[\alpha]_D^{20}$ –8.55 (c 0.6, $CHCl_3$) for a sample (94% *ee*) derived from *S*-**5f**. The other physical data were identical to those of the racemate **5b**.

Diethyl (*S*)-1-hydroxy-2-propenylphosphonate *S*-5c. 63% yield, an oil, $[\alpha]_D^{20}$ +9.61 (c 1.0, $CHCl_3$) for a sample (61% *ee*) derived from *S*-**5g**; 44% yield, an oil, $[\alpha]_D^{20}$ +8.22 (c 0.6, $CHCl_3$) for a sample (38% *ee*) derived from *S*-**5h**. The other physical data were identical those of the racemate **5c**.

Detemination of absolute configuration of *S*-5a-c. The alcohols ***S*-5a-c** were converted to the corresponding (*R*)-MTPA esters according to our documented procedure,[10b] and were analyzed without purification by ^{31}P NMR spectroscopy. In their ^{31}P NMR spectrum ($CDCl_3$), the major signals due to (*R*)-MTPA esters of ***S*-5a**, ***S*-5b** and ***S*-5c** were observed at δ 15.97, 16.20, and 15.78 ppm, while the minor signals arising from the enantiomers appeared at 15.61, 15.86, and 15.39 ppm, respectively. On the basis of the arguments presented by Hammerschmidt,[13a] the ^{31}P NMR signals at lower field in the spectra are assigned with *S*-configuration.

Dihydroxylation of *R*-5d. (method A) A dihydroxylation reagent in an *aqueous* 50% *tert*-BuOH (10 mL) was prepared from potassium ferricyanide (980 mg, 3.0 mmol), potassium carbonate (415 mg, 3.0 mmol), potassium (III) osmate dihydrate (37 mg, 0.01 mmol), quinuclidine (3.9 mg, 0.035 mmol) and methanesulfonamide (95.1 mg, 1 mmol) by the method of Warren[16] with minor modification. The mixure was treated with ***R*-5d** (312 mg, 1 mmol) for 9h at 20 °C. 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. Acetylation of the residue with Ac_2O (0.55 mL, 5.0 mmol) in CH_2Cl_2 (2 mL) in the presence of pyridine (0.49 mL, 6.00 mmol) and 4-dimethylaminopyridine (12.2 mg, 0.10 mmol), followed by an usual work-up gave a mixure of *anti*-**9** and *syn*-**9**. The triacetate *anti*-**9** (92 mg, 22%) was isolated from the mixture by column chromatography on silica gel (hexane:EtOAc=1:1 to 1:5). **(method B)** A solution of AD-*mix*-β or -α reagent (1.4 g), potassium (III) osmate dihydrate (3.0 mg, 0.8 mol %), and methanesulfonamide (95 mg, 1 mmol) in an *aqueous* 50% *tert*-BuOH (10 mL) was cooled to 0 °C. The resulting suspension was treated with ***R*-5d** (312 mg, 1.0 mmol) at 0 °C for 42h. Work-up and the acetylation as above gave a mixture of *anti*-**9** and *syn*-**9**. The *anti*-**9** (211 mg, 49%) was isolated from the mixture obtained with AD-*mix*-β, whereas the *syn*-**9** (120 mg, 28%) was obtaind for the reaction with AD-*mix*-α.

Diethyl (1*R*,2*R*,3*S*)-1,2,3-triacetyloxy-3-phenylpropylphosphonate *syn*-9. An oil; $[\alpha]_D^{20}$ +57.5 (c 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (5H, m), 5.91 (1H, d, *J* = 6.5 Hz), 5.75 (1H, ddd, *J* = 4.6, 4.6, 6.5 Hz), 5.26 (1H, dd, *J* = 4.6, 12.1 Hz), 4.16-4.06 (4H, m), 2.14 (3H, s), 2.07 (3H, s), 2.04 (3H, s), 1.31 (3H, t, *J* = 7.0 Hz), 1.29 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.1, 168.9 (d, J_{PC} = 2.7 Hz), 135.7, 128.8, 128.6, 127.1, 74.0 (d, J_{PC} = 9.4 Hz), 71.4 (d, J_{PC} = 3.5 Hz), 66.2 (d, J_{PC} = 169.2 Hz), 63.1 (d, J_{PC} = 7.2 Hz), 63.0 (d, J_{PC} = 6.8 Hz), 20.8, 20.4 (2 carbons), 16.2 (d, J_{PC} = 4.0 Hz), 16.1 (d, J_{PC} = 4.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.18; IR (neat) 1745, 1210 cm^{-1}; EIMS *m/z* 431 (MH^+). Anal. Calcd for $C_{19}H_{27}O_9P$: C, 53.02; H, 6.32. Found: C, 53.07; H, 6.44.

Diethyl (1*R*,2*S*,3*R*)-1,2,3-triacetyloxy-3-phenylpropylphosphonate *anti*-9. Mp. 45-47 °C; $[\alpha]_D^{20}$ −16.7 (c 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (5H, m), 6.11 (1H, d, *J* = 4.3 Hz), 5.67 (1H, ddd, *J* = 4.3, 8.4, 13.0 Hz), 5.38 (1H, dd, *J* = 8.4, 8.4 Hz), 4.21-4.05 (4H, m), 2.09 (6H, s), 1.97 (3H, s), 1.34 (3H, t, *J* = 7.1 Hz), 1.29 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 168.9, 168.7, 135.8, 128.4, 128.3, 126.8, 72.3 (d, J_{PC} = 7.9 Hz), 71.2, 65.0 (d, J_{PC} = 167.5 Hz), 62.9 (2 carbons, d, J_{PC} = 6.1 Hz), 20.7, 20.3 (2 carbons), 16.2 (d, J_{PC} = 5.6 Hz), 16.1 (d, J_{PC} = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.12; IR (KBr) 1750, 1216 cm^{-1}; EIMS *m/z* 431 (MH^+). Anal. Calcd for $C_{19}H_{27}O_9P$: C, 53.02; H, 6.32. Found: C, 53.40; H, 6.41.

(4*S*,5*R*,1'*R*)-4-[1'-(diethylphosphono)hydroxymethyl]-5-phenyl-2,2-dimethyl-1,3-dioxolane 10. Diol *anti*-**8** (593 mg) with 80% purity[11] was isolated from the dihydroxylation products of ***R*-5d** with AD-*mix*-β by column chromatography on silica gel (hexane:EtOAc=1:1 to 1:2). A mixture of the diol *anti*-**8**, 2,2-dimethoxypropane (1.35 mL, 11.0 mmol) and camphorsulfonic acid (23.2 mg) in benzene (10 mL) was heated under reflux for 12 h. After being cooled, the mixture was portioned between EtOAc and *sat.* $NaHCO_3$. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to leave a residue. Column chromatography on silica gel (hexane:EtOAc = 1:1) gave **10** (200 mg). Mp 116-118 °C; $[\alpha]_D^{20}$ +27.6 (c 0.95, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (2H, m), 7.37-7.28 (3H, m), 5.21 (1H, d, *J* = 7.7 Hz), 4.29-4.20 (1H, m), 4.17-4.00 (5H, m), 1.54 (3H, s), 1.52 (3H, s), 1.29 (3H, t, *J* = 7.2 Hz), 1.24 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.4, 128.2, 128.1, 127.4, 109.8, 82.5, 80.2 (d, J_{PC} = 7.0 Hz), 68.5 (d, J_{PC} = 158.8 Hz), 62.8 (d, J_{PC} = 6.0 Hz), 62.7 (d, J_{PC} = 6.4 Hz), 27.3, 27.0,

16.3 (2 carbons, d, J_{PC} = 4.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.47; IR (KBr) 3217, 1259 cm^{-1}; EIMS *m/z* 343 (M^+–1), 329 (M^+–CH_3). X-ray crystal data of **10** were collected by Mac-Science MXC 18 diffarectometers. The structure was solved by direct methods using SIR 92 (Giacovazzo, 1994)[19] and refined with a full matrix least-squares method. Crystal Data of **10:** $C_{16}H_{25}O_6P$, Mr=344.30, orthorhombic, space group $P2_12_12_1$, a=16.729(4)Å, b=20.550(5)Å, c=5.436(2)Å, V=1868.8(9)Å^3, T=294K, Z=4, Dx=1.223 gcm^{-3}, (Cu-Kα)=1.54178Å, μ=15.189 cm^{-1}, R=0.043 over 1817 independent reflections.

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