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Enzymatic synthesis of optically active α-chloro-δ-hydroxy-β-ketoalkanephosphonates and reactions thereof ☆

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Abstract—A novel and enzymatic approach to α-chloro-δ-hydroxy-β-ketoalkanephosphonates was developed via enantioselective *CALB*-catalyzed acetylation and *CRL*-catalyzed hydrolysis. The resultant optically active compounds provide, via Horner–Wadsworth–Emmons (HWE) reaction, chiral α,β-unsaturated ketones that are building block with potential application in organic synthesis.

1. Introduction

Enzymes represent some of the most sophisticated and elegant machinery known for carrying out selective and highly specific chemical reactions. They have been extensively utilized in the synthesis of chiral pharmaceutics.[2]

The most common synthetic application of phosphonates is their use in the Horner–Wadsworth–Emmons (HWE) reaction for preparing α,β-unsaturated carbonyl compounds.[3] We are interested in using enzymes, especially lipase to synthesize potential biological active β-ketoalkanephosphonates since such chirons could lead directly to chiral α,β-unsaturated ketones. The existing practical routes to chiral β-ketophosphonates are mainly focused on the Michaelis–Arbuzov synthesis[4] and the acylation of alkylphosphonates.[5] Another interesting approach to chiral γ-hydroxy-β-ketophosphonates is based on chiral allene oxide starting from trimethylsilyl-1-alkye.[6] Our group has also exploited the Baker's yeast-mediated enantioreduction of ketones to prepare some optically active γ-hydroxy-β-ketophosphonates and δ-hydroxy-β-ketophosphonates.[7] We also used *Candia Antartic* lipase B (*CALB*) and crude *Candia Rugosa* lipase (*CRL*) to resolve hydroxyphophonates and aminophosphonates to obtain the corresponding chiral compounds.[8] As an extension of our studies on enzymatic reactions of hydroxyphosphonates, we, herein, report a convenient synthesis of optically active α-chloro-δ-hydroxy-β-ketoalkanephosphonates via *CALB* and crude *CRL* catalyzed kinetic resolutions.

2. Results and discussion

The racemic α-chloro-δ-hydroxy-β-ketoalkanephosphonates were easily prepared by reacting the carbanion ion derived from α-chloro-β-ketopropanephosphonate with aldehydes[9] (Scheme 1 and Table 1).

It is well known that the utility of lipases to resolve alcohols and related compounds is of great importance, and we wish to exploit such hydrolases to prepare some interesting and valuable molecules. *CALB*, a kind of hydrolases, could efficiently resolve a lot of secondary alcohols bearing medium groups which were less than the propyl moiety (Fig. 2).[10] Recently, we described *CALB* catalyzed enantioselective acetylation of α- or β-hydroxyalkanephosphonates and δ-hydroxy-β-ketoalkanephosphonates bearing methyl, ethyl or vinyl group. Meanwhile all of those substrates gave excellent results.[8] It was therefore interest to examine the structural effect on the enantioselectivity of *CALB*-catalyzed acetylation of δ-hydroxy-β-ketoalkanephosphonates containing a bulky chlorine atom at α-position. However, our study indicated that there is no significant steric hindrance of chlorine atom on enantioselectivity.

For example, the racemic **1a-c** was subjected to *CALB*-catalyzed acetylation in benzene using vinyl acetate as an acetylating reagent to provide unreacted **2a-c** in 42–45%

☆ Studies on organophosphorus compounds 130. For part 129, see Ref. 1.

Keywords: Horner–Wadsworth–Emmons (HWE) reaction; α-Chloro-δ-hydroxy-β-ketoalkanephosphonates; *Candia Antartic* lipase B (*CALB*); Crude *Candia Rugosa* lipase (*CRL*); Acetylation; Hydrolysis; α,β-Unsaturated ketones.

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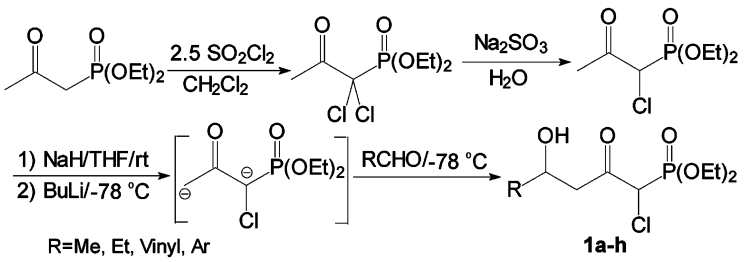


Scheme 1.

Table 1. Preparation of α-chloro-δ-hydroxy-β-ketoalkanephosphonates **1**

Entry	R	Yield (%)	Entry	R	Yield (%)	Entry	R	Yield (%)
1a	Me	86	**1d**	C_6H_5	75	**1g**	2,4-$Cl_2C_6H_3$	83
1b	Et	90	**1e**	4-$MeOC_6H_4$	80	**1h**	2-Furyl	85
1c	Vinyl	88	**1f**	4-FC_6H_4	81			

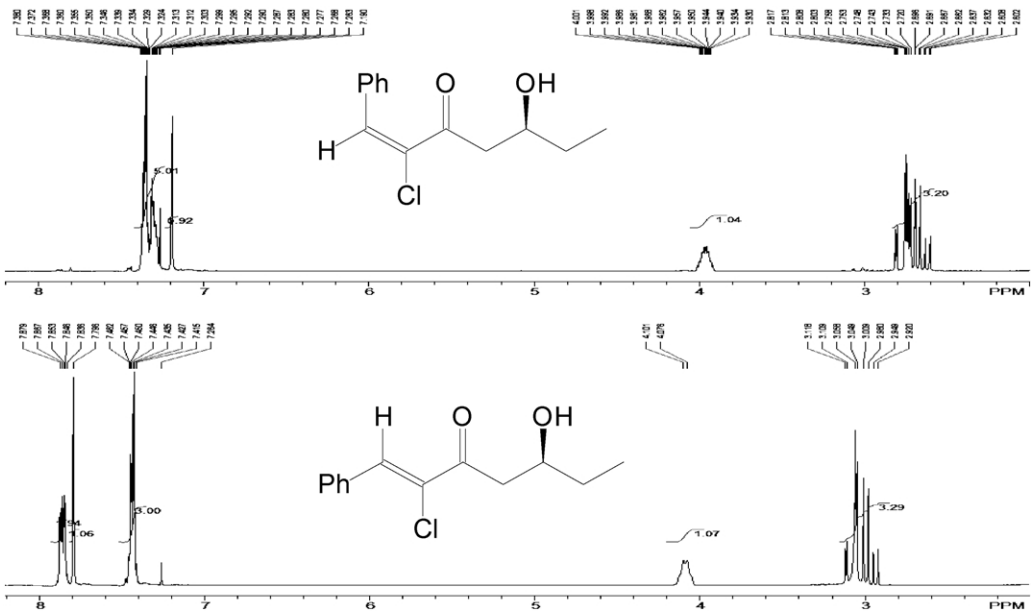
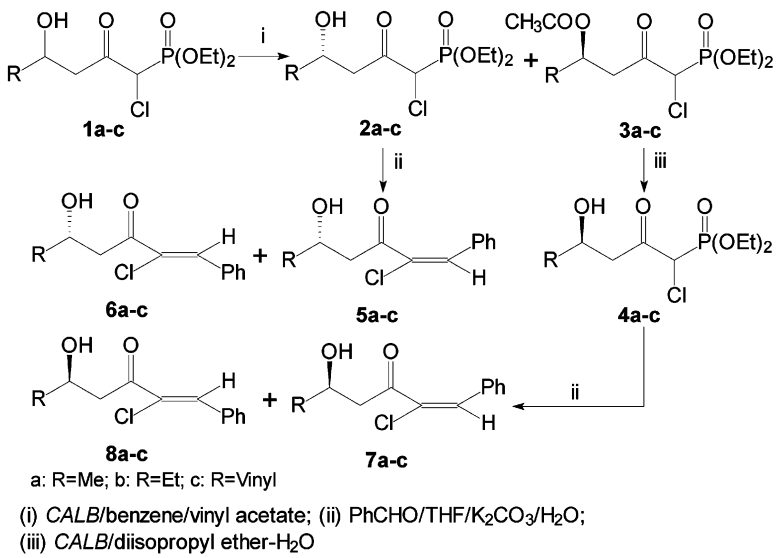


Figure 1. ^{1}H NMR spectrum of *E* and *Z* isomers **5b** and **6b**.

yields and acetylated products **3a**-**c** in 45–50% yields. Since the enantiomers were not resolved under HPLC conditions using a column with chiral stationary phase, the enantiomeric excess of the products **2** and **3** were not obtained directly. To solve this problem, derivatization of compounds **2** and **3** were conducted. The conversion of compounds **2** into α,β-unsaturated ketones through HWE reaction was reported using a DBU/LiBr system.[11] However, it took a long reaction time and provided low yields, and even racemization of the chiral alcohols **2a**-**c**. We then treated compounds **2** with PhCHO, THF, H_2O and KCO_3, which gave a mixture of chiral α,β-unsaturated ketones **5a**-**c** and **6a**-**c** in good yields. The *E* and *Z* isomers were separated by careful TLC and determined through steric hindrance and ^{1}H NMR spectrum (Fig. 1). The enantiomeric excess of compounds **5** and **6** that were determined readily by chiral HPLC analysis were higher than 98%. Similar procedure was applied to determine the ee values of products **3** after the acetyl group was removed. Enzymatic hydrolysis was necessary since chemical hydrolysis caused unavoidable elimination to form olefins. In order to increase the yields of hydrolysis, a system of diisopropyl ether saturated with H_2O was used. As this enzymatic process may enhance the ee values of the hydrolyzed products **3a**-**c**, the ee values of their products **7a**-**c** and **8a**-**c** were also excellent as shown in Scheme 2 and Table 2.

The results obtained indicated that (4*R*)-**1** and (4*R*)-**3** were preferentially acetylated to esters or hydrolysis to alcohols catalyzed by *CALB*, and that is in accordance with the general rule[13] predicted for *CALB* catalyzed resolutions (Fig. 2).

It is noteworthy to state our unsuccessful trials to resolve α-chloro-δ-hydroxy-δ-aryl-β-ketoalkanephosphonates (**1d**-**h**) by use of *CALB*-catalyzed acetylation. It may be rationalized by the large size of aryl group that is unsuitable as medium group as shown in Figure 2 in



Scheme 2.

Table 2. *CALB*-catalyzed enantioselective acetylation of **2a-c** and subsequent derivatization

Entry	R	Yield (%)			**5** (%)		**6** (%)		**7** (%)		**8** (%)		E^a
		2	**3**	**4**	Yield	ee[b]	Yield	ee[b]	Yield	ee[b]	Yield	ee[b]	
a	Me	42	44	85	15	99	75	99	14	99	71	99	>200
b	Et	43	45	87	18	99	77	99	16	99	73	99	>200
c	Vinyl	45	46	90	20	99	74	99	19	99	70	99	>200

[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[12]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK OD, *n*-hexane/isopropyl alcohol=8/2–9/1.

this enzyme system. In contrast with crude *CRL* enantioselective hydrolysis the butyrylation products of β-hydroxy-β-arylethanephosphonates and δ-hydroxy-δ-aryl-β-ketoalkanephosphonates in diisopropyl ether pre-equilibrated with 1.2 M aqueous $MgCl_2$ to prepare optically active β-hydroxy-β-arylethanephosphonates and δ-hydroxy-δ-aryl-β-ketoalkanephosphonates.[8a,c]

Intrigued by the satisfactory results obtained, and taking into the structure similarity, we wish to resolve those α-chloro-δ-hydroxy-δ-aryl-β-ketoalkanephosphonates via *CRL*-catalyzed hydrolysis in diisopropyl ether. Direct butyrylation of **1d-h** using DCC/butyric acid system afforded the butyryl derivatives (**9d-h**) in 75–80% yields. They could be enantioselectively hydrolyzed to corresponding (*R*)-alcohols in diisopropyl ether preequilibrated with 1.2 M aqueous $MgCl_2$. Based on the same reason, the (*R*) alcohols **11d-h** were converted to the corresponding HWE products. When the HWE reaction were done, a problem appeared, if equal substrates and PhCHO was used in THF, the reaction time was extended over 10 h and the yields dropped below 50%, as well as ee values of the products were below 50%. The reasons maybe as follows (Scheme 3). In order to solve this problem, the equal PhCHO and H_2O were used as solvents. And the reaction was completed in 1.5 h and the yields were over 80%. Also because of the presence of α-chlorine atom, the HWE products have *E* and *Z* isomers that could be isolated by careful TLC and determined by steric hindrance and ^1H NMR spectrum (Scheme 4 and Table 3).

The absolute configuration of compounds **10d-h** and **11d-h** were determined through the corresponding δ-hydroxy-β-ketoalkanephosphonates.[8a]

It is a pity that the (*S*)-substrates **10d-h** could not be directly applied to HWE reactions due to the unstability. Because those compounds converted into their γ,δ-unsaturated ketones reaction in the base condition (Scheme 4). And we are now being engaged in enzymatic hydrolysis of those butyryl derivatives **10d-h** to corresponding alcohols.

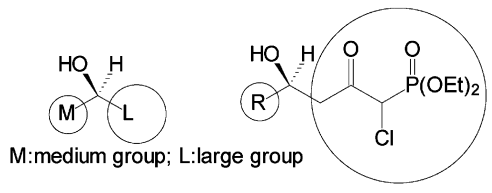
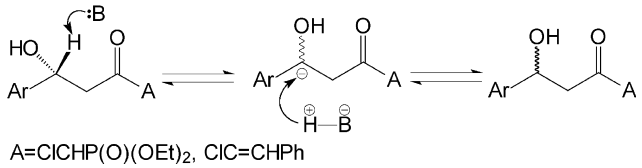


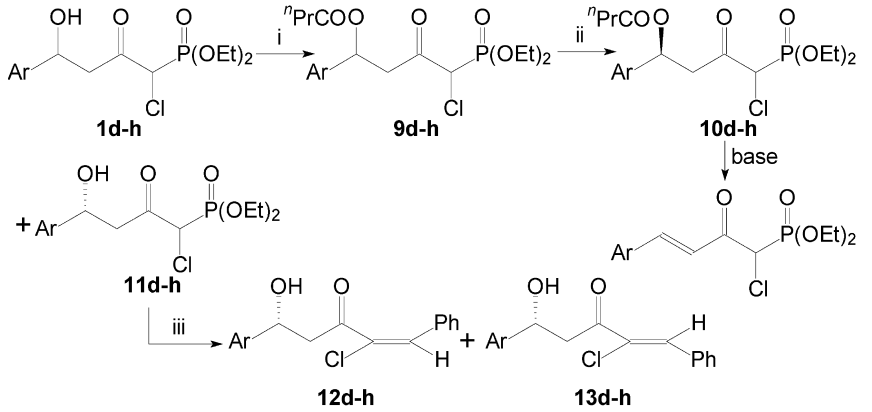
Figure 2. Configuration of the preferential enantiomer of hydroxyalkanephosphonate acetylation catalyzed by *CALB*.

3. Conclusion

In summary, a number of α-chloro-δ-hydroxy-β-ketoalkanephosphonates was successfully resolved by a *CALB*-catalyzed acetylation and a *CRL*-catalyzed hydrolysis. The high optically active α-chloro-δ-hydroxy-β-ketoalkanephosphonates exhibits potential biological and synthetic application.



Scheme 3.



Scheme 4.

Table 3. *CRL*-Catalyzed enantioselective hydrolysis of **9d-h**

Entry	Ar	Yield (%)			**12** (%)		**13** (%)		E^a
		9	**10**	**11**	Yield	ee[b]	Yield	ee[b]	
d	C_6H_5	84	43	40	23	96	66	96	>100
e	4-$MeOC_6H_4$	82	44	39	22	98	67	>99	>100
f	4-FC_6H_4	79	46	41	19	>99	70	>99	>100
g	2,4-$Cl_2C_6H_4$	80	42	41	21	99	65	99	>100
h	2-C_4H_3O	85	45	41	19	92	71	91	>90

[a] *E*, the enantiomeric ratio, were roughly calculated based on the yields of **10d-h** and the ee values of **12d-h**.
[b] The ee values were determined by the chiral HPLC (CHIRALPAK OD and AD, *n*-hexane/isopropyl alcohol=8/2–9/1).

4. Experiment

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard); ^{31}P NMR spectra were taken on the same spectrometer using 80% phosphorus acid as external standard.

CALB (Novozym 435) is a gift from Novo Norvodisk Co. *CRL* (901units/mg) was purchased from Sigma Chemical Co.

The chiral liquid chromatography system: Waters 515 HPLC pump; UV Waters 2487 Dual λ Absorbance Detector, 254 nm; Penelson Network chromatography interface NCI 900, Turbohrom Navigator data station software; CHIRALPAK AD, OD, AS column and dimensions: 0.46 cm×25 cm; the flow rate: 0.7 mL/min; eluent: hexane:isopropanol=9:1—8:2 (v/v).

4.1. General procedure for the preparation of α-chloro-δ-hydroxy-β-ketoalkanephosphonates (1a-h)

To a suspension of sodium hydride (80%, 0.54 g, 18 mmol) in dry THF (8 mL) was added diethyl 1-chloro-2-oxopropylphophonate[14] (3.43 g, 15 mmo) under nitrogen. After 30 min at rt, butyllithium (11.3 mL, in hexane 1.6 M, 18 mmol) was added at −45 to −30 °C. The mixture was kept at this temperature for 1 h, then cooled to −78 °C, and aldehydes (18 mmol) was added at −78 °C. After the mixture was stirred for 1 h at low temperature, saturated NH_4Cl (30 mL) was added and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined extracts was dried and evaporated in vacuum. The residue was subjected to flash chromatography to furnish the racemic α-chloro-δ-hydroxy-β-ketoalkanephosphonates **1a-h**. The yields are listed in Table 1.

4.2. General procedure for CALB-catalyzed acetylation of racemic α-chloro-δ-hydroxy-β-ketoalkanephosphonates (1a-c)

To a stirred solution of hydroxyalkanephosphonate (1 mmol) in benzene (10 mL) was added vinyl acetate (2 mL). The reaction was started by addition of *CALB* (100 mg). The mixture was maintained at 30 °C. When the reaction proceeded to certain conversion (within 50 h), the enzyme was filtered, and washed with ethyl acetate (15 mL). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to

furnish hydroxyalkanephosphonates and their acetates. The yields are listed in Table 2.

4.2.1. (4*S*) Diethyl 1-chloro-2-oxo-4-hydroxypentylphosphonate (2a). Colorless oil; $[\alpha]_D^{20}=+22.4$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3420, 2982, 2934, 1729, 1256, 978 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.64 (1H, dd, *J*=9.6, 17.7 Hz, ClC*H*P(O)), 4.32–4.20 (4H, m, OCH_2CH_3), 4.18–4.09 (1H, m, HOC*H*CH_2), 3.04–2.85 (2H, m, CHCH_2CO), 1.41–1.34 (6H, m, OCH_2CH_3), 1.26–1.23 (3H, m, CHCH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.90, 12.80; *m/z* (EI) 272 (1, M^+), 237 (2), 193(29), 186 (100), 165 (83), 159 (71), 137 (24), 130 (45), 109 (29), 81 (14), 43 (12%); HRMS (EI): M^+, found: 272.0563. $C_9H_{18}ClO_5P$ requires 272.0580.

4.2.2. (4*R*) Diethyl 1-chloro-2-oxo-4-acetyloxypentylphosphonate (3a). Colorless oil; $[\alpha]_D^{20}=+6.7$ (*c* 1.5, $CHCl_3$). [Found: C, 41.98; H, 6.34. $C_{11}H_{20}ClO_6P$ requires C, 41.98; H, 6.41]. ν_{max} (liquid film) 2987, 2937, 1741, 1247, 1023, 979 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.35–5.27 (1H, m, OC*H*CH_2CO), 4.54 (1H, d, *J*=17.7 Hz, ClC*H*P(O)), 4.30–4.19 (4H, m, OCH_2CH_3), 3.30–2.89 (2H, m, CHCH_2-CO), 2.01 (3H, d, *J*=2.7 Hz, COCH_3), 1.43–1.33 (6H, m, OCH_2CH_3), 1.31–1.23 (3H, m, CHCH_3); δ^{31}P (120 MHz, $CDCl_3$) 15.31, 15.15; *m/z* (EI) 315 (1, M^++1), 254 (10), 219 (8), 186 (38), 159 (21), 130 (13), 81 (17), 69 (91), 65 (22), 43 (100%).

4.2.3. (4*S*) Diethyl 1-chloro-2-oxo-4-hydroxyhexylphosphonate (2b). Colorless oil; $[\alpha]_D^{20}=+19.4$ (*c* 1.6, $CHCl_3$). [Found: C, 41.90; H, 7.03. $C_{10}H_{20}ClO_5P$ requires C, 41.73; H, 7.14]. ν_{max} (liquid film) 3422, 2979, 2936, 1729, 1257, 1024, 980 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.64 (1H, dd, *J*=9.9, 17.7 Hz, ClC*H*P(O)), 4.31–4.20 (4H, m, OCH_2CH_3), 4.05–3.99 (1H, m, HOC*H*CH_2), 3.04–2.86 (2H, m, CHCH_2CO), 2.81 (1H, s, O*H*), 1.58–1.49 (2H, m, CHCH_2CH$_3$), 1.41–1.26 (6H, m, OCH_2CH_3), 0.97 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); δ^{31}P (120 MHz, $CDCl_3$) 12.93, 12.84; *m/z* (EI) 286 (1, M^+), 257 (23), 193 (26), 186 (100), 173 (12), 159 (62), 130 (28), 123 (7), 109 (7), 81 (6%).

4.2.4. (4*R*) Diethyl 1-chloro-2-oxo-4-acetyloxypentylphosphonate (3b). Colorless oil; $[\alpha]_D^{20}=+10.3$ (*c* 1.7, $CHCl_3$). [Found: C, 43.90; H, 6.87. $C_{12}H_{22}ClO_6P$ requires C, 43.85; H, 6.75]. ν_{max} (liquid film) 2977, 2938, 1741, 1373, 1244, 1023, 978 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.26–5.16 (1H, m, OC*H*CH_2CO), 4.57 (1H, dd, *J*=9.3, 17.7 Hz, ClC*H*P(O)), 4.30–4.19 (4H, m, OCH_2CH_3), 3.17–2.94 (2H, m, CHCH_2CO), 2.03 (3H, d, *J*=2.4 Hz, COCH_3), 1.68–1.61 (2H, m, CHCH_2CH$_3$), 1.40–1.25 (6H, m, OCH_2CH_3), 1.31–1.23 (3H, m, CHCH_3) 0.92 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); δ^{31}P (120 MHz, $CDCl_3$) 12.85, 12.70; *m/z* (EI) 328 (1, M^++1), 268 (15), 233 (22), 213 (12), 186 (100), 177 (11), 159(53), 130 (24), 83 (24), 43 (20%).

4.2.5. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-5-hexenylphosphonate (2c). Colorless oil; $[\alpha]_D^{20}=+11.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3362, 2985, 1721, 1248, 1049, 1024, 977 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.89–5.83 (1H, m, C*H*=CH_2), 5.36–5.13 (1H, m, CH=CH_2), 4.71–4.60 (2H, m, ClC*H*P(O), HOC*H*CH_2), 4.31–4.20 (4H, m, OCH_2CH_3), 3.16–2.93 (2H, m, CHCH_2CO), 1.40–1.34 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.77, 12.73; *m/z* (EI) 284 (1, M^+), 249 (19), 228 (15), 203 (22), 193 (52), 186 (100), 159 (67), 130 (69), 109 (37), 81 (58), 65 (43), 57 (48), 43 (80%); HRMS (EI): M^+, found: 284.0613. $C_{10}H_{18}ClO_5P$ requires 284.0580.

4.2.6. (4*S*) Diethyl 1-chloro-2-oxo-4-acetyloxyhexenylphosphonate (3c). Colorless oil; $[\alpha]_D^{20}=-2.6$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2988, 2939, 1743, 1240, 1023, 983 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.92–5.79 (1H, m, C*H*=CH_2), 5.73–5.65 (1H, m, OC*H*CH_2CO), 5.37–5.21 (CH=CH_2), 4.54 (1H, d, *J*=17.7 Hz, ClC*H*P(O)), 4.29–4.23 (4H, m, OCH_2CH_3), 3.40–3.06 (2H, m, CHCH_2CO), 2.05 (3H, d, *J*=2.4 Hz, COCH_3), 1.41–1.26 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 15.16, 15.04; *m/z* (EI) 291 (3, M^+-Cl), 249 (9), 231 (16), 203 (28), 186 (34), 175 (36), 159(31), 130 (18), 109 (15), 81 (100), 65 (22), 43 (73%); HRMS (EI): M^+-Cl, found: 291.1024. $C_{12}H_{20}O_6P$ requires 291.0998.

4.3. General procedure for *CALB*-catalyzed hydrolysis of 1-chloro-2-oxo-4-acetyloxy-phosphonates (3a-c)

To a stirred diisopropyl ether presaturated with water (4 mL) was added a mixture of the acetylated phosphonates **3a-c** and 100 mg *CALB*. The solution was stirred at room temperature until the starting material nearly disappeared (24–48 h or so). After filtration and washing with 15 mL ethyl acetate, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the hydrolyzed products of which yields are listed in Table 2.

4.3.1. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxypentylphosphonate (4a). Colorless oil; $[\alpha]_D^{20}=-23.0$ (*c* 1.0, $CHCl_3$). **4a** is the enantiomer of **2a**, its spectroscopic data are identical to **2a** as expected. ν_{max} (liquid film) 3419, 2982, 2935, 1728, 1254, 1025, 979 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.63 (1H, dd, *J*=9.3, 17.4 Hz, ClC*H*P(O)), 4.32–4.20 (4H, m, OCH_2CH_3), 4.19–4.10 (1H, m, HOC*H*CH_2), 3.05–2.85 (2H, m, CHCH_2CO), 1.43–1.35 (6H, m, OCH_2CH_3), 1.28–1.23 (3H, m, CHCH_3); δ^{31}P (120 MHz, $CDCl_3$) 13.37, 13.25; *m/z* (EI) 272 (2, M^+), 193(22), 186 (82), 165 (100), 159 (55), 137 (31), 130 (38), 109 (40), 81 (20), 69 (28%).

4.3.2. (4*S*) Diethyl 1-chloro-2-oxo-4-hydroxyhexylphosphonate (4b). Colorless oil; $[\alpha]_D^{20}=-19.2$ (*c* 1.3, $CHCl_3$). **4b** is the enantiomer of **2b**, its spectroscopic data are identical to **2b** as expected. ν_{max} (liquid film) 3420, 2979, 2936, 1729, 1255, 1024, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.63 (1H, dd, *J*=9.9, 17.7 Hz, ClC*H*P(O)), 4.30–4.20 (4H, m, OCH_2CH_3), 4.04–3.99 (1H, m, HOC*H*CH_2), 3.04–2.83 (2H, m, CHCH_2CO), 2.80 (1H, s, O*H*), 1.57–1.50 (2H, m, CHCH_2CH$_3$), 1.41–1.33 (6H, m, OCH_2CH_3), 0.97 (3H, t, *J*=7.2 Hz, $CHCH_2CH_3$); δ^{31}P (120 MHz, $CDCl_3$) 13.40, 13.21; *m/z* (EI) 286 (1, M^+), 257 (26), 229 (9), 193 (25), 186 (100), 173 (12), 159 (66), 130 (37), 123 (10), 109 (10), 83 (15%).

4.3.3. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-5-hexenylphosphonate (4c). Colorless oil; $[\alpha]_D^{20}=-11.2$ (*c* 1.2, $CHCl_3$). **4c** is the enantiomer of **2c**, its spectroscopic data are identical to **2c** as expected. ν_{max} (liquid film) 3362,

2985, 1721, 1248, 1049, 1024, 977 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.94–5.83 (1H, m, C*H*═CH_2), 5.33 (1H, d, *J*=16.8 Hz, CH═CH_2), 5.15 (1H, d, *J*=10.5 Hz, CH═CH_2), 4.71–4.60 (2H, m, ClC*H*P(O), HOC*H*CH_2), 4.31–4.20 (4H, m, OCH_2CH_3), 3.16–2.93 (2H, m, CHCH_2-CO), 1.40–1.34 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 13.23, 13.17; *m*/*z* (EI) 284 (1, M^+), 242 (22), 231 (23), 203 (22), 199 (84), 186 (100), 179 (39), 171 (35), 159 (66), 143 (56), 130 (55), 109 (21), 81 (56), 43 (34%).

4.4. General procedure for HWE reactions of the chiral α-chloro-δ-hydroxy-β-ketoalkanephosphonates (3a-c) with benzaldehyde

Substrates **3a**-**c** (50 mg), K_2CO_3 (200 mg), H_2O (1 mL), THF (1 mL) and benzaldehyde (0.2 mL) was added in a flask, after the mixture was stirred 2 h, ethyl acetate (5 mL) and brine (5 mL) was added. The aqueous layer was extracted with ethyl acetate (3×5 mL). Dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the products. The eluting solvents were ethyl acetate and *n*-hexane (1:10–1:8) and the yields are listed in Table 2.

4.4.1. (5*S*,1*E*) 1-Phenyl-2-chloro-1-hexen-3-one (5a). Colorless oil; $[\alpha]_D^{20}$=+36.0 (*c* 0.6, $CHCl_3$). ν_{max} (liquid film) 3420, 2966, 2928, 2855, 1699, 1376, 1080, 1052, 959, 749, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 7.18 (1H, s, PhC*H*═C), 4.25–4.19 (1H, m, HOC*H*CH_2), 2.84–2.64 (2H, m, CHCH_2CO), 1.14 (3H, d, *J*=6.3 Hz, HOCHCH_3); *m*/*z* (EI) 224 (18, M^+), 189 (23), 179 (18), 165 (45), 145 (42), 137 (41), 131 (100), 115 (37), 109 (73%); HRMS (EI): M^+, found: 224.0592. $C_{12}H_{13}ClO_2$ requires 224.0604.

4.4.2. (5*S*,1*Z*) 1-Phenyl-2-chloro-1-hexen-3-one (6a). Colorless oil; $[\alpha]_D^{20}$=+22.2 (*c* 1.0, $CHCl_3$). [Found: C, 64.40; H, 6.10. $C_{12}H_{13}ClO_2$ requires C, 64.15; H, 5.83]. ν_{max} (liquid film) 3441, 2966, 2931, 2879, 1683, 1596, 1158, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.80 (1H, s, PhC*H*═C), 7.45–7.43 (3H, m, C_6H_5), 4.38–4.32 (1H, m, HOC*H*CH_2), 3.12–2.93 (2H, m, CHCH_2CO), 1.30 (3H, d, *J*=6.0 Hz, HOCHCH_3); *m*/*z* (EI) 224 (20, M^+), 189 (19), 165 (32), 145 (32), 137 (25), 131 (69), 115 (30), 102 (59), 77 (20), 43 (100%).

4.4.3. (5*R*,1*E*) 1-Phenyl-2-chloro-1-hexen-3-one (7a). Colorless oil; $[\alpha]_D^{20}$=−35.8 (*c* 0.8, $CHCl_3$). **7a** is the enantiomer of **5a**, its spectroscopic data are identical to **5a** as expected. ν_{max} (liquid film) 3407, 2966, 2923, 2852, 1684, 1596, 1448, 1164, 1080, 757, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.27 (5H, m, C_6H_5), 7.18 (1H, s, PhC*H*═C), 4.25–4.19 (1H, m, HOC*H*CH_2), 2.81–2.64 (2H, m, CHCH_2CO), 1.14 (3H, d, *J*=6.9 Hz, HOCHCH_3); *m*/*z* (EI) 224 (29, M^+), 206 (62), 205 (61), 189 (28), 179 (20), 165 (51), 145 (37), 137 (38), 131 (88), 115 (30), 102 (74), 77 (22), 69 (100%).

4.4.4. (5*R*,1*Z*) 1-Phenyl-2-chloro-1-hexen-3-one (8a). Colorless oil; $[\alpha]_D^{20}$=−21.8 (*c* 1.0, $CHCl_3$). **8a** is the enantiomer of **6a**, its spectroscopic data are identical to **6a** as expected. ν_{max} (liquid film) 3421, 2971, 2930, 2879, 1684, 1597, 1164, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.79 (1H, s, PhC*H*═C), 7.45–7.43 (3H, m, C_6H_5), 4.37–4.33 (1H, m, HOC*H*CH_2), 3.12–2.93 (3H, m, CHCH_2CO, O*H*), 1.30 (3H, d, *J*=7.5 Hz, HOCHCH_3); *m*/*z* (EI) 224 (21, M^+), 206 (34), 189 (22), 165 (38), 145 (33), 137 (34), 131 (74), 115 (39), 102 (88), 75 (32), 43 (100) 41 (72%).

4.4.5. (5*S*,1*E*) 1-Phenyl-2-chloro-1-hepten-3-one (5b). Colorless oil; $[\alpha]_D^{20}$=+46.0 (*c* 0.6, $CHCl_3$). [Found: C, 65.69; H, 6.53. $C_{13}H_{15}ClO_2$ requires C, 65.41; H, 6.33]. ν_{max} (liquid film) 3426, 2966, 2929, 1700, 1079, 979, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 7.19 (1H, s, PhC*H*═C), 3.99–3.94 (1H, m, HOC*H*CH_2), 2.82–2.60 (2H, m, CHCH_2CO), 1.50–1.33 (2H, m, CHCH_2CH_3), 0.87 (3H, t, *J*=6.9 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (14, M^+), 203 (30), 179 (18), 165 (100), 145 (53), 137 (43), 131 (73), 115 (28), 102 (60), 77 (11), 57(21%).

4.4.6. (5*S*,1*Z*) 1-Phenyl-2-chloro-1-hepten-3-one (6b). Colorless oil; $[\alpha]_D^{20}$=+35.3 (*c* 1.0, $CHCl_3$). [Found: C, 65.63; H, 6.58. $C_{13}H_{15}ClO_2$ requires C, 65.41; H, 6.33]. ν_{max} (liquid film) 3426, 2966, 2929, 1700, 1079, 979, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.80 (1H, s, PhC*H*═C), 7.46–7.42 (3H, m, C_6H_5), 4.16–4.04 (1H, m, HOC*H*CH_2), 3.12–2.92 (2H, m, CHCH_2CO), 1.67–1.55 (2H, m, CHCH_2CH_3), 1.01 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (15, M^+), 203 (31), 179 (16), 165 (100), 145 (54), 137 (40), 131 (63), 115 (23), 102 (50), 77 (9), 57 (22%).

4.4.7. (5*R*,1*E*) 1-Phenyl-2-chloro-1-hepten-3-one (7b). Colorless oil; $[\alpha]_D^{20}$=−45.5 (*c* 0.4, $CHCl_3$). **7b** is the enantiomer of **5b**, its spectroscopic data are identical to **5b** as expected. ν_{max} (liquid film) 3447, 2966, 2934, 1681, 1596, 1158, 979, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.27 (5H, m, C_6H_5), 7.19 (1H, s, PhC*H*═C), 3.97–3.94 (1H, m, HOC*H*CH_2), 2.81–2.60 (3H, m, CHCH_2CO, O*H*), 1.47–1.28 (2H, m, CHCH_2CH_3), 0.86 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (16, M^+), 220 (39), 203 (29), 179 (14), 165 (100), 145 (50), 137 (41), 131 (65), 115 (22), 102 (61), 83 (48), 77 (16), 57(32%).

4.4.8. (5*R*,1*Z*) 1-Phenyl-2-chloro-1-hepten-3-one (8b). Colorless oil; $[\alpha]_D^{20}$=−36.1 (*c* 0.7, $CHCl_3$). **8b** is the enantiomer of **6b**, its spectroscopic data are identical to **6b** as expected. ν_{max} (liquid film) 3450, 2966, 2935, 1684, 1596, 1159, 979, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.80 (1H, s, PhC*H*═C), 7.46–7.41 (3H, m, C_6H_5), 4.18–4.09 (1H, m, HOC*H*CH_2), 3.12–2.92 (3H, m, CHCH_2CO, O*H*), 1.65–1.53 (2H, m, CHCH_2-CH_3), 1.01 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (13, M^+), 220 (86), 205 (28), 185 (34), 165 (92), 145 (43), 137 (40), 131 (56), 115 (29), 102 (79), 83 (100), 77 (20), 55 (34%).

4.4.9. (5*R*,1*E*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (5c). Colorless oil; $[\alpha]_D^{20}$=+19.0 (*c* 0.4, $CHCl_3$). [Found: C, 65.85; H, 5.84. $C_{13}H_{13}ClO_2$ requires C, 65.97; H, 5.54]. ν_{max} (liquid film) 3424, 3027, 2926, 1698, 929, 751, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45–7.26 (5H, m, C_6H_5), 7.20 (1H, s, PhC*H*═C), 5.85–5.74 (1H, m, C*H*═CH_2), 5.28–5.10 (2H, m, CH═CH_2), 4.72–4.58 (1H, m,

HOC*H*CH_2), 2.87–2.80 (2H, m, CHCH_2CO), 2.71 (1H, s, O*H*); *m*/*z* (EI) 236 (3, M^+), 201 (17), 179 (19), 165 (38), 145 (67), 137 (39), 131 (77), 115 (48), 102 (100), 77 (31), 57 (82%).

4.4.10. (5*R*,1*Z*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (6c). Colorless oil; $[\alpha]_D^{20}=+15.5$ (*c* 0.7, $CHCl_3$). [Found: C, 65.84; H, 5.80. $C_{13}H_{13}ClO_2$ requires C, 65.97; H, 5.54]. ν_{max} (liquid film) 3448, 3027, 2925, 1683, 1596, 1156, 928, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.89–7.86 (2H, m, C_6H_5), 7.81 (1H, s, PhC*H*=C), 7.47–7.43 (3H, m, C_6H_5), 6.01–5.91 (1H, m, C*H*=CH_2), 5.41–5.18 (2H, m, CH=CH_2), 4.81–4.70 (1H, m, HOC*H*CH_2), 3.19–3.08 (2H, m, CHCH_2CO), 3.08 (1H, s, O*H*); *m*/*z* (EI) 236 (9, M^+), 201 (37), 179 (30), 165 (66), 145 (100), 137 (49), 131 (88), 115 (44), 102 (76), 77 (14), 57 (16%).

4.4.11. (5*S*,1*E*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (7c). Colorless oil; $[\alpha]_D^{20}=-19.0$ (*c* 0.4, $CHCl_3$). **7c** is the enantiomer of **5c**, its spectroscopic data are identical to **5c** as expected. ν_{max} (liquid film) 3420, 3025, 2932, 1699, 1088, 929, 753, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.28 (5H, m, C_6H_5), 7.21 (1H, s, PhC*H*=C), 5.86–5.75 (1H, m, C*H*=CH_2), 5.25 (1H, d, *J*=16.8 Hz, CH=CH_2), 5.12 (1H, d, *J*=10.5 Hz, CH=CH_2), 4.71–4.58 (1H, m, HOC*H*CH_2), 2.84–2.74 (3H, m, CHCH_2CO, O*H*); *m*/*z* (EI) 236 (8, M^+), 201 (31), 179 (25), 165 (62), 145 (93), 137 (52), 131 (96), 115 (51), 102 (100), 77 (25), 57 (42%).

4.4.12. (5*S*,1*Z*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (8c). Colorless oil; $[\alpha]_D^{20}=-15.5$ (*c* 0.5, $CHCl_3$). **8c** is the enantiomer of **6c**, its spectroscopic data are identical to **6c** as expected. ν_{max} (liquid film) 3456, 3057, 2926, 1684, 1596, 1448, 1156, 928, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.89–7.86 (2H, m, C_6H_5), 7.81 (1H, s, PhC*H*=C), 7.47–7.42 (3H, m, C_6H_5), 6.01–5.90 (1H, m, C*H*=CH_2), 5.36 (1H, d, *J*=15.3 Hz, CH=CH_2), 5.20 (1H, d, *J*=10.2 Hz, CH=CH_2), 4.80–4.71 (1H, m, HOC*H*CH_2), 3.15–3.07 (3H, m, CHCH_2CO, O*H*), 3.08 (1H, s, O*H*); *m*/*z* (EI) 236 (9, M^+), 201 (34), 180 (25), 165 (65), 145 (100), 137 (53), 131 (98), 115 (47), 102 (97), 91 (21), 77 (28), 57 (59%).

4.5. General procedure for the preparation of diethyl 1-chloro-2-oxo-4-butyryloxy-4-arybutylphosphonates (9d-h)

In a 25 mL flask was added substrates **1d-h** (1 mmol), *n*-butyric acid (0.11 mL, 1.2 mmol), DCC (248 mg, 1.2 mmol) and CH_2Cl_2 (10 mL). The mixture was cooled to −10 °C using ice-salt bath and DMAP (5 mg) was introduced. After the starting material was almost consumed at −10~0 °C (about 1–2 h), diethyl ether (10 mL) was added and the precipitate was filtered off. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the corresponding butyryl derivatives of which yields are listed in Table 3.

4.6. General procedure of *CRL*-catalyzed enantioselective hydrolysis of (9d-h)

Substrates **9d-h** (100 mg) and *CRL* (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 48 h at 30 °C, and filtered off the *CRL* that could be reused and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford unreacted esters **10d-h** and the hydrolyzed alcohols **11d-h**. The yields are listed in Table 3.

4.6.1. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-phenylbutylphosphonate (10d). Colorless oil; $[\alpha]_D^{20}=-3.1$ (*c* 1.2, $CHCl_3$). [Found: C, 53.54; H, 6.54. $C_{18}H_{26}ClO_6P$ requires C, 53.41; H, 6.47]. ν_{max} (liquid film) 3036, 2970, 2936, 2877, 1739, 1262, 1023, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48–7.27 (5H, m, C_6H_5), 6.24–6.18 (1H, m, PhC*H*CH_2), 4.51 (1H, dd, *J*=17.4 Hz, ClC*H*P(O)), 4.30–4.10 (4H, m, OC$H_2$$CH_3$), 3.59–3.17 (2H, m, CHC$H_2$-CO), 2.33–2.25 (2H, m, COC$H_2$$CH_2CH_3$), 1.68–1.59 (2H, m, $COCH_2$CH_2CH_3), 1.43–1.26 (6H, m, OCH_2CH_3), 0.90 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.14; *m*/*z* (EI) 316 (1, $M^+-{}^n$PrCOOH), 290 (23), 205 (7), 187 (26), 174 (100), 152 (23), 131 (34), 125 (42), 108 (16), 97 (22), 80 (17%).

4.6.2. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-phenylbutylphosphonate (11d). Colorless oil; $[\alpha]_D^{20}=+38.0$ (*c* 1.4, $CHCl_3$). [Found: C, 49.98; H, 6.25. $C_{14}H_{20}ClO_5P$ requires C, 50.23, H, 6.02]. ν_{max} (liquid film) 3403, 2986, 2914, 1729, 1255, 1023, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.27 (5H, m, C_6H_5), 5.25–5.17 (1H, m, HOC*H*CH_2), 4.63 (1H, dd, *J*=17.7 Hz, ClC*H*P(O)), 4.28–4.11 (4H, m, OC$H_2$$CH_3$), 3.39–3.07 (3H, m, O*H*, CHCH_2CO), 1.44–1.24 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.29; *m*/*z* (EI) 317 (1, M^+-OH), 299 (44), 228 (25), 193 (85), 186 (46), 159 (49), 131 (64), 105 (100), 77 (57), 65 (100%).

4.6.3. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(4-methoxyphenyl) butylphosphonate (10e). Colorless oil; $[\alpha]_D^{20}=-15.9$ (*c* 0.9, $CHCl_3$). [Found: C, 52.24; H, 6.51. $C_{19}H_{28}ClO_7P$ requires C, 52.48; H, 6.49]. ν_{max} (liquid film) 2970, 2937, 2914, 2841, 1738, 1595, 1513, 1257, 1020, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, *J*=8.7 Hz, C_6H_4), 6.93 (2H, d, *J*=8.4 Hz, C_6H_4), 6.20–6.10 (1H, m, ArC*H*CH_2), 4.58 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.29–4.09 (4H, m, OC$H_2$$CH_3$), 3.86 (3H, s, OCH_3), 3.65–3.19 (2H, m, CHCH_2CO), 2.32–2.22 (2H, m, COC$H_2$$CH_2CH_3$), 1.68–1.58 (2H, m, $COCH_2$CH_2CH_3), 1.44–1.26 (6H, m, OCH_2CH_3), 0.94 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 13.57; *m*/*z* (EI) 346 (8, $M^+-{}^n$PrCOOH), 329 (10), 311 (9), 255 (6), 208 (6), 190 (12), 161 (100), 135 (62), 109 (7%).

4.6.4. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(4-methoxyphenyl) butylphosphonate (11e). Colorless oil; $[\alpha]_D^{20}=+37.1$ (*c* 0.9, $CHCl_3$). [Found: C, 49.42; H, 6.17. $C_{15}H_{22}ClO_6P$ requires C, 49.39; H, 6.08]. ν_{max} (liquid film) 3404, 2986, 2913, 1730, 1613, 1515, 1247, 1095 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, *J*=8.4 Hz, C_6H_4), 6.89 (2H, d, *J*=8.4 Hz, C_6H_4), 5.21–5.13 (1H, m, HOC*H*CH2), 4.62 (1H, dd, *J*=18.3 Hz, ClC*H*P(O)), 4.29–4.11 (4H, m, OC$H_2$$CH_3$), 3.81 (3H, s, OCH_3), 3.40–3.08 (2H, m, CHCH_2CO), 1.41–1.24 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.29; *m*/*z* (EI) 346 (1, M^+-H_2O), 329 (12), 228 (9), 193 (33), 161 (29), 135 (100), 109 (18), 77 (16), 65 (10%).

4.6.5. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(4-flurophenyl) butylphosphonate (10f). Colorless oil; $[\alpha]_D^{20}=-15.9$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2970, 2938, 2878, 1739, 1512, 1234, 1024, 983 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37 (2H, t, *J*=7.2 Hz, C_6H_4), 7.02 (2H, t, *J*=8.4 Hz, C_6H_4), 6.22–6.18 (1H, m, ArC*H*CH_2), 4.54 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.30–4.11 (4H, m, OC$H_2$$CH_3$), 3.66–3.19 (2H, m, CHC$H_2$CO), 2.36–2.23 (2H, m, COC$H_2$$CH_2CH_3$), 1.71–1.60 (2H, m, $COCH_2$CH_2-CH_3), 1.40–1.24 (6H, m, OCH_2CH_3), 0.98 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 12.62, 12.48; *m*/*z* (EI) 422 (1, M^+), 351 (24), 334 (14), 317 (37), 299 (26), 286 (24), 243 (22), 179 (34), 149 (69), 123 (100), 71 (73), 43 (87%); HRMS (EI): M^+, found: 422.1084. $C_{18}H_{25}ClO_6FP$ requires 422.1061.

4.6.6. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(4-fluorophenyl) butylphosphonate (11f). Colorless oil; $[\alpha]_D^{20}=+28.7$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3394, 2987, 2914, 1730, 1511, 1255, 1224, 1023, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (2H, t, *J*=7.8 Hz, C_6H_4), 7.04 (2H, d, *J*=7.8 Hz, C_6H_4), 5.22–5.16 (1H, m, HOC*H*CH2), 4.62 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.29–4.17 (4H, m, OC$H_2$$CH_3$), 3.66–3.05 (2H, m, CHC$H_2$CO), 1.44–1.26 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.27; *m*/*z* (EI) 352 (1, M^+), 329 (12), 317 (38), 243 (6), 228 (19), 193 (66), 186 (32), 179 (38), 159 (33), 123 (100), 109 (24), 97 (42), 65 (10%); HRMS (EI): M^+, found: 352.0602. $C_{14}H_{19}ClFO_5P$ requires 352.0643.

4.6.7. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(2,4-dichlorophenyl) butylphosphonate (10g). Colorless oil; $[\alpha]_D^{20}=-3.5$ (*c* 1.5, $CHCl_3$). [Found: C, 45.47; H, 4.84. $C_{18}H_{24}Cl_3O_6P$ requires C, 45.64; H, 5.11]. ν_{max} (liquid film) 2971, 2937, 2877, 1743, 1264, 1023, 980 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.23 (3H, m, C_6H_3), 6.48–6.44 (1H, m, ArC*H*CH_2), 4.53 (1H, d, *J*=18.0 Hz, ClC*H*P(O)), 4.27–4.18 (4H, m, OC$H_2$$CH_3$), 3.58–3.26 (2H, m, CHC$H_2$-CO), 2.34–2.28 (2H, m, COC$H_2$$CH_2CH_3$), 1.71–1.60 (2H, m, $COCH_2$C$H_2$$CH_3$), 1.40–1.26 (6H, m, OCH_2CH_3), 0.92 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 12.97, 12.94; *m*/*z* (EI) 472 (1, M^+), 401 (42), 367 (68), 349 (48), 321 (22), 293 (27), 199 (100), 186 (49), 173 (56), 159 (36), 71 (82), 43 (62%).

4.6.8. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(2,4-dichlorophenyl) butylphosphonate (11g). Colorless oil; $[\alpha]_D^{20}=+38.4$ (*c* 0.5, $CHCl_3$). [Found: C, 41.81; H, 4.61. $C_{14}H_{18}Cl_3O_5P$ requires C, 41.66; H, 4.49]. ν_{max} (liquid film) 3308, 2985, 2900, 1735, 1245, 1023, 967 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.60 (1H, d, *J*=8.4 Hz, C_6H_3), 7.36–7.28 (2H, m, C_6H_3), 5.52–5.49 (1H, m, HOC*H*CH_2), 4.63 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.30–4.11 (4H, m, OC$H_2$$CH_3$), 3.29–3.06 (2H, m, CHC$H_2$CO), 1.43–1.24 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.74, 12.69; *m*/*z* (EI) 384 (1, M^+-H_2O), 367 (16), 228 (37), 193 (100), 186 (45), 175 (43), 159 (39), 123 (100), 130 (32), 111 (34), 81 (19), 65 (17%).

4.6.9. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(2-furyl) butylphosphonate (10h). Colorless oil; $[\alpha]_D^{20}=-38.7$ (*c* 1.8, $CHCl_3$). [Found: C, 48.38; H, 6.31. $C_{16}H_{24}Cl_3O_7P$ requires C, 48.68; H, 6.13. ν_{max} (liquid film) 2970, 2937, 1733, 1607, 1264, 1021, 977 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38 (1H, s, C_4H_3O), 6.34–6.33 (3H, m, C_4H_3O, ArC*H*CH_2), 4.59 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.30–4.22 (4H, m, OC$H_2$$CH_3$), 3.77–3.31 (2H, m, CHC$H_2$CO), 2.36–2.25 (2H, m, COC$H_2$$CH_2CH_3$), 1.68–1.61 (2H, m, $COCH_2$C$H_2$$CH_3$), 1.41–1.34 (6H, m, OCH_2CH_3), 0.95 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 12.28, 12.14; *m*/*z* (EI) 359 (1, M^+-Cl), 323 (13), 306 (9), 289 (17), 271 (16), 218 (15), 179 (20), 121 (100), 94 (60), 81 (26), 65 (57%).

4.6.10. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(2-furyl) butylphosphonate (11h). Colorless oil; $[\alpha]_D^{20}=+27.2$ (*c* 1.3, $CHCl_3$). [Found: C, 44.35; H, 5.59. $C_{12}H_{18}ClO_6P$ requires C, 44.39; H, 5.59]. ν_{max} (liquid film) 3337, 2991, 2906, 1733, 1243, 1043, 1019, 740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (1H, s, C_4H_3O), 6.33–6.28 (2H, m, C_4H_3O), 5.24–5.18 (1H, m, HOC*H*CH_2), 4.64 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.28–4.10 (4H, m, OC$H_2$$CH_3$), 3.49–3.16 (2H, m, CHC$H_2$CO), 1.39–1.33 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.25, 12.10; *m*/*z* (EI) 307 (8, M^+-OH), 290 (61), 272 (17), 261 (12), 218 (22), 193 (36), 186 (55), 179 (87), 159 (63), 149 (83), 130 (66), 121 (100), 109 (45), 98 (88), 65 (38%).

4.7. General procedure for HWE reactions of the chiral α-chloro-δ-hydroxy-β-ketoalkanephosphonates (11d-h) with benzaldehyde

Substrates **11d-h** (50 mg), K_2CO_3 (200 mg), H_2O (0.5 mL) and benzaldehyde (0.5 mL) were added in a flask, after the mixture was stirred 2 h, ethyl acetate (5 mL) and brine (5 mL) was added. The aqueous layer was extracted with ethyl acetate (3×5 mL). Dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the products. The eluting solvents were ethyl acetate and *n*-hexane (1:10–1:8) and the yields are listed in Table 3.

4.7.1. (5*R*,1*E*) 1-Chloro-1,5-diphenyl-5-hydroxy-1-penten-3-one (12d). Colorless oil; $[\alpha]_D^{20}=+51.8$ (*c* 0.6, $CHCl_3$). ν_{max} (liquid film) 3506, 3031, 2910, 1684, 1596, 1448, 1152, 759, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (10H, m, Ar-*H*), 7.18 (1H, s, PhC*H*=C), 5.17 (1H, dd, *J*=8.4 Hz, HOC*H*CH2), 3.10–2.95 (3H, m, O*H*, CHCH_2-CO); *m*/*z* (EI) 286 (1, M^+), 268 (7), 251 (14), 205 (12), 179 (26), 145 (33), 131 (34), 105 (100), 77 (52), 43 (26%); HRMS (EI): M^+, found: 286.0769. $C_{17}H_{15}ClO_2$ requires 286.0761.

4.7.2. (5*R*,1*Z*) 1-Chloro-1,5-diphenyl-5-hydroxy-1-penten-3-one (13d). Colorless oil; $[\alpha]_D^{20}=+51.3$ (*c* 0.9, $CHCl_3$). [Found: C, 71.13; H, 5.56. $C_{17}H_{15}ClO_2$ requires C, 71.21; H, 5.27]. ν_{max} (liquid film) 3501, 3036, 2911, 1683, 1604, 1152, 1124, 759, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.86–7.83 (2H, m, C_6H_5), 7.78 (1H, s, PhC*H*=C), 7.44–7.30 (8H, m, $2C_6H_5$), 5.27 (1H, dd, *J*=8.4 Hz, HOC*H*CH_2), 3.40 (1H, s, O*H*), 3.31–3.27 (2H, m, CHCH_2-CO); *m*/*z* (EI) 286 (4, M^+), 251 (20), 180 (8), 165 (12), 145 (27), 131 (25), 115 (21), 105 (100), 77 (54), 51 (22%).

4.7.3. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-methoxyphenyl)-1-penten-3-one (12e). Colorless oil;

$[\alpha]_D^{20}$=+47.0 (*c* 0.4, $CHCl_3$). ν_{max} (liquid film) 3497, 2910, 2838, 1686, 1599, 1513, 1251, 1174, 1033, 832, 758, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.28 (5H, m, C_6H_5), 7.27 (1H, s, PhC*H*=C), 7.20 (2H, d, *J*=8.7 Hz, C_6H_4), 6.85 (2H, d, *J*=8.4 Hz, C_6H_4), 5.12 (1H, dd, *J*=8.4 Hz, HOC*H*CH_2), 3.80 (3H, s, OCH_3), 3.04–2.98 (2H, m, CHCH_2CO); *m/z* (EI) 316 (3, M^+), 298 (4), 281 (5), 179 (26), 145 (25), 135 (100), 109 (10), 102 (20), 77 (25), 43 (13%); HRMS (EI): M^+-H_2O, found: 298.0740. $C_{18}H_{15}ClO_2$ requires 298.0761.

4.7.4. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-methoxyphenyl)-1-penten-3-one (13e). Colorless oil; $[\alpha]_D^{20}$=+39.5 (*c* 0.7, $CHCl_3$). [Found: C, 68.00; H, 5.45. $C_{18}H_{17}ClO_3$ requires C, 68.25; H, 5.41]. ν_{max} (liquid film) 3485, 3060, 2910, 2837, 1687, 1611, 1514, 1249, 1176, 1034, 833 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.87–7.83 (2H, m, C_6H_5), 7.78 (1H, s, PhC*H*=C), 7.45–7.37 (3H, m, C_6H_5), 7.33 (2H, d, *J*=9.0 Hz, C_6H_4), 6.91 (2H, d, *J*=9.0 Hz, C_6H_4), 5.23 (1H, dd, *J*=8.7 Hz, HOC*H*CH_2), 3.80 (3H, s, OCH_3), 3.31–3.26 (2H, m, CHCH_2CO); *m/z* (EI) 316 (3, M^+), 298 (33), 263 (26), 179 (48), 161 (49), 145 (29), 135 (100), 115 (13), 102 (28), 77 (20%).

4.7.5. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-fluorophenyl)-1-penten-3-one (12f). Colorless oil; $[\alpha]_D^{20}$=+60.1 (*c* 0.3, $CHCl_3$). ν_{max} (liquid film) 3484, 2909, 1685, 1604, 1510, 1156, 1126, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45–7.23 (9H, m, Ar-*H*), 7.19 (1H, s, PhC*H*=C), 5.16 (1H, dd, *J*=8.1 Hz, HOC*H*CH_2), 3.10–2.94 (2H, m, CHCH_2CO); *m/z* (EI) 304 (3, M^+), 286 (27), 268 (29), 251 (30), 205 (18), 179 (100), 145 (85), 123 (24), 102 (16), 77 (10%); HRMS (EI): M^+, found: 304.0670. $C_{17}H_{14}ClO_2F$ requires 304.0666.

4.7.6. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-fluorophenyl)-1-penten-3-one (13f). Colorless oil; $[\alpha]_D^{20}$=+66.0 (*c* 0.6, $CHCl_3$). [Found: C, 67.00; H, 4.63. $C_{17}H_{14}ClO_2F$ requires C, 67.00; H, 4.63]. ν_{max} (liquid film) 3481, 3062, 2924, 1683, 1604, 1511, 1224, 1155, 1124, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.86–7.83 (2H, m, C_6H_5), 7.78 (1H, s, PhC*H*=C), 7.44–7.30 (5H, m, C_6H_4, C_6H_5), 7.05 (2H, d, *J*=8.7 Hz, C_6H_4), 5.25 (1H, dd, *J*=7.8 Hz, HOC*H*CH_2), 3.44 (1H, s, O*H*), 3.31–3.24 (2H, m, CHCH_2CO); *m/z* (EI) 304 (4, M^+), 286 (8), 269 (17), 251 (13), 179 (13), 145 (48), 131 (35), 123 (100), 115 (77), 97 (28), 77 (47%).

4.7.7. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(2,4-dichlorophenyl)-1-penten-3-one (12g). Colorless oil; $[\alpha]_D^{20}$=+80.0 (*c* 0.3, $CHCl_3$). ν_{max} (liquid film) 3497, 3069, 2924, 1685, 1593, 1382, 1153, 1124, 823, 777, 756, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (1H, d, *J*=7.8 Hz, C_6H_3), 7.49–7.20 (7H, m, C_6H_3, C_6H_5), 6.99 (1H, s, PhC*H*=C), 5.46 (1H, dd, *J*=9.3 Hz, HOC*H*CH_2), 3.44 (1H, d, *J*=3.6 Hz, O*H*), 3.20–2.78 (2H, m, CHCH_2CO); *m/z* (EI) 354 (5, M^+), 319 (10), 205 (22), 175 (93), 173 (100), 145 (72), 131 (35), 111 (55), 102 (50), 77 (23), 43 (42%); HRMS (EI): M^+, found: 353.9961. $C_{17}H_{13}Cl_3O_2$ requires 353.9981.

4.7.8. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(2,4-dichlorophenyl)-1-penten-3-one (13g). Colorless oil; $[\alpha]_D^{20}$=+80.0 (*c* 0.3, $CHCl_3$). [Found: C, 57.59; H, 3.98. $C_{17}H_{13}Cl_3O_2$ requires C, 57.41; H, 3.68]. ν_{max} (liquid film) 3493, 3028, 2926, 2855, 1735, 1684, 1593, 1153, 1124, 757, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, C_6H_5), 7.81 (1H, s, PhC*H*=C), 7.64 (1H, d, *J*=7.8 Hz, C_6H_3), 7.45–7.43 (3H, m, C_6H_5), 7.37–7.26 (2H, m, C_6H_3), 5.57 (1H, d, *J*=9.3 Hz, HOC*H*CH_2), 3.66 (1H, d, *J*=3.6 Hz, O*H*), 3.42–3.03 (2H, m, CHCH_2CO); *m/z* (EI) 354 (10, M^+), 319 (26), 283 (19), 248 (10), 175 (93), 174 (100), 145 (64), 131 (22), 111 (38), 102 (35), 75 (17%).

4.7.9. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(2-furyl)-1-penten-3-one (13h). Colorless oil; $[\alpha]_D^{20}$=+37.1 (*c* 0.8, $CHCl_3$). [Found: C, 65.33; H, 5.04. $C_{15}H_{13}ClO_3$ requires C, 65.11; H, 4.74]. ν_{max} (liquid film) 3483, 2922, 1687, 1607, 1154, 1128, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.26 (6H, m, C_6H_5, C_4H_3O), 7.20 (1H, s, PhC*H*=C), 6.32–6.21 (2H, m, C_4H_3O), 5.20 (1H, t, *J*=4.2 Hz, HOC*H*CH_2), 3.29–3.01 (2H, m, CHCH_2CO), 2.98 (1H, d, *J*=3.9 Hz, O*H*); *m/z* (EI) 276 (18, M^+), 258 (8), 241 (48), 170 (34), 165 (22), 145 (34), 131 (60), 110 (100), 102 (51), 97 (69), 95 (50), 65 (12), 41 (24%).

4.7.10. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(2-furyl)-1-penten-3-one (13h). Colorless oil; $[\alpha]_D^{20}$=+30.5 (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3482, 3028, 2922, 1689, 1607,1575, 1156, 1129, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.82 (1H, s, PhC*H*=C), 7.45–7.39 (4H, m, C_6H_5, C_4H_3O), 6.37–6.33 (2H, m, C_4H_3O), 5.30 (1H, d, *J*=8.7 Hz, HOC*H*CH_2), 3.57–3.33 (3H, m, CHCH_2CO, O*H*); *m/z* (EI) 276 (18, M^+), 258 (11), 241 (49), 170 (34), 145 (34), 131 (61), 110 (100), 102 (53), 97 (22), 95 (54), 77 (15), 41 (31%); HRMS (EI): M^+, found: 276.0555. $C_{15}H_{13}ClO_3$ requires 276.0553.

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References and notes

1. Xu, C.; Zhang, Y.; Yuan, C. *Eur. J. Org. Chem.* **2004**. in press.
2. (a) Anderson, B. A.; Hansen, M. M.; Harkeness, A. R. *J. Am. Chem. Soc.* **1995**, *117*, 12358–12359. (b) Patel, R. N. *Enzyme Microb. Technol.* **1993**, *58*, 1672–1675. (c) Collin, A. N.; Sheldrake, G. N.; Crosby, J. *Chiral in industry II*; Wiley: New York, 1997; pp 245–260.
3. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
4. (a) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696. (b) Flack, J. R.; Abdali, A.; Wittenberger, S. J. *J. Chem. Soc. Chem. Commun.* **1990**, 953–955. (c) Kerdesky, F. A. J.; Schmift, S. P.; Brooks, D. W. *J. Org. Chem.* **1993**, *58*, 3516–3520.
5. (a) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733. (b) Karanewsky, D. S.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1991**, *56*, 3744–3747. (c) Altenbach, H. J.; Holzapfel, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 67–78. (d) Narkunan, K.; Nagarajan, M. *J. Org. Chem.* **1994**, *59*, 6386–6390. (e) Kojina, K.; Saito, S. *Synthesis* **1992**, 949–950. (f) Koskinen, A. M. P.; Krische, M. J. *Synlett*

1990, 665–666. (g) Berkowitz, D. B.; Eggen, M.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666–4675.
6. Kabat, M. M. *Tetrahedron Lett.* **1993**, *34*, 8543–8544.
7. (a) Yuan, C. Y.; Wang, K.; Li, Z. Y. *Heteroat. Chem.* **2001**, *12*, 551–556. (b) Yuan, C. Y.; Wang, K.; Li, Z. Y. *Heteroat. Chem.* **2002**, *13*, 153–156. (c) Wang, K.; Li, J. F.; Yuan, C. Y.; Li, Z. Y. *Chin. J. Chem.* **2002**, *20*, 1379–1387.
8. (a) Zhang, Y. H.; Xu, C. F.; Li, J. F.; Yuan, C. Y. *Tetrahedron: Asymmetry* **2003**, *14*, 63–70. (b) Zhang, Y. H.; Yuan, C. Y.; Li, Z. Y. *Tetrahedron* **2002**, *58*, 2973–2978. (c) Zhang, Y. H.; Li, Z. Y.; Yuan, C. Y. *Tetradedron Lett.* **2002**, *43*, 3247–3249. (d) Yuan, C. Y.; Xu, C. F.; Zhang, Y. H. *Tetrahedron* **2003**, *59*, 6095–6102.
9. Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn* **1989**, *62*, 860–868.
10. Shuji, K.; Norihiko, N.; Hiroyuki, S.; Otohiko, T. *Bull. Chem. Soc. Jpn* **1989**, *62*, 171–179.
11. (a) Orrenius, C.; Oehrner, N.; Rottiui, D.; Mattson, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1217–1220. (b) Rotticu, D.; Halffner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal. B* **1998**, *5*, 267–272.
12. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Shi, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
13. (a) Orrenius, C.; Oehrner, N.; Rottiui, D.; Mattson, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1217–1220. (b) Rotticu, D.; Halffner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal. B* **1998**, *5*, 267–272.
14. (a) Pudowik, A. N. *Zh. Obshch. Khim.* **1956**, *26*, 2238–2242. (b) Haelters, J. P.; Corbel, B.; Sturtz, G. *Phosphorus Sulfur* **1988**, *37*, 65–86.