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Enzymatic synthesis of optically active δ-hydroxy-β-ketoalkanephosphonates†

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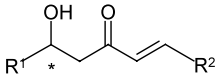
Abstract—A novel and enantioselective approach to δ-hydroxy-β-ketoalkanephosphonates has been developed via CALB-catalyzed enantioselective acetylation and CRL-catalyzed enantioselective hydrolysis.

1. Introduction

Undoubtedly, the most common synthetic application of phosphonates is their use in the Horner–Wadsworth–Emmons (HWE) reaction for preparing α,β-unsaturated carbonyl compounds from condensation of an aldehyde or ketone.[1] Synthesis of non-racemic β-ketophosphonates has aroused great interest during the past decades since such chirons could lead directly to chiral enones. The existing practical routes leading to non-racemic β-ketophosphonates were mainly focused on the Michaelis–Arbuzov synthesis[2] and the acylation of alkylphosphonates.[3] Another interesting approach to chiral γ-hydroxy-β-ketophosphonates was based on Sharpless epoxidation for access to the aldehyde.[4] Our group has also exploited baker's yeast-mediated enantioreduction for preparing some optically active γ-hydroxy-β-ketophosphonates and δ-hydroxy-β-ketophosphonates.[5] Continuing our studies on enzymatic reactions of hydroxyalkanephosphonates, we report the convenient synthesis of optically active δ-hydroxy-β-ketoalkanephosphonates via *Candida antarctica* lipase B- and crude *Candida rugosa* lipase-catalyzed kinetic resolutions. Those chirons, subjected to HWE reaction, would provide the molecules **1** bearing multi functionalities which could find many applications in synthetic organic chemistry. Additionally, many natural products such as yashabushiketol were found to have such a structural unit.[6] Herein, we wish to report a facile enzymatic approach to chiral δ-hydroxy-β-ketoalkanephosphonates and their chemical conversion to **1** via HWE reactions.



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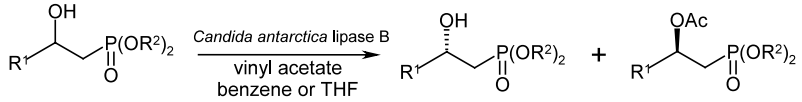
2. Results and discussion

The racemic δ-hydroxy-β-ketoalkanephosphonates could be easily prepared by reacting the carbanion derived from β-ketopropanephosphonates with an aldehyde as previously described.[7] It is known that the utility of lipases for the efficient resolution of alcohols and related compounds is of great importance in organic synthesis, and we wish to exploit such hydro-



R1=Me, Et, vinyl; R2=Me, Et; E up to >100

Scheme 1.

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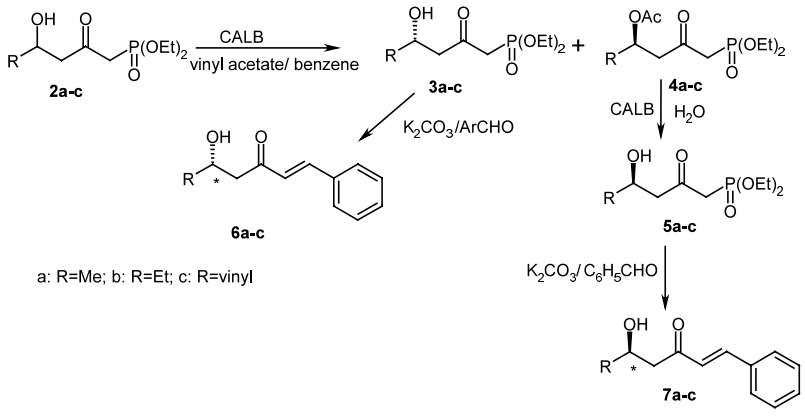
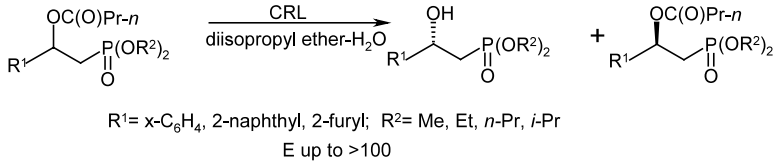


Scheme 2.



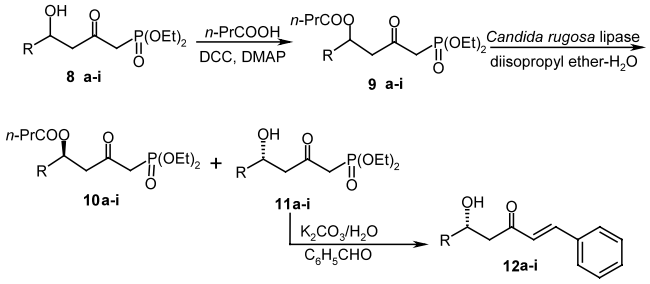
Scheme 3.

lases for the convenient preparation of these interesting alcohols. *C. antarctica* lipase B could efficiently resolve a lot of secondary alcohols bearing a medium sized group less than the propyl moiety.[8] Recently, we reported *C. antarctica* lipase B-catalyzed enantioselective acetylation of hydroxyalkanephosphonates bearing methyl, ethyl or vinyl group as the medium group (Scheme 1).[9]

Herein, the scope of this method is extended, which leads to the formation of chiral δ-hydroxy-β-ketobutanephosphonates (Scheme 2).

Under our reaction conditions, the racemic **2a–c**, subjected to CALB-catalyzed acetylation in benzene, provided unreacted **3a–c** in 35–42% yield and acetylated products **4a–c** in 48–51% yield. Unfortunately, the enantiomeric excess of the unreacted alcohols **3a–c** could not be determined by chiral HPLC after many trials. Mosher's method (especially **3c**) is not applicable here due to the elimination to olefin by a base in the course of synthesis, which may cause partial racemization. We try to convert those racemic compounds to the corresponding enones. Tsuge Otohiko had reported the HWE reactions of these racemic compounds using DBU/LiBr system.[7] However, we found it took a long time and caused racemization under our reaction conditions. Treated with benzaldehyde using K_2CO_3/H_2O system, **3a–c** gave chiral enones **6a–c** with 95–99% enantiomeric excess. It can be inferred that the ee of **3a–c** is even higher. As to the acetylated products, further enzymatic hydrolysis is necessary since chemical hydrolysis caused unavoidable elimination to olefins. As this enzymatic process may enhance the enantiomeric excess of the hydrolyzed **5a–c**, the ee of their HWE products **7a–c** is excellent as shown in Table 1.

We have also developed *C. rugosa* lipase-catalyzed enantioselective hydrolysis in water-equilibrated diiso-



Scheme 4.

Table 1. CALB-catalyzed enantioselective acetylation of **2a–c**

R	Yield of **3a–c** (%)	ee of **6a–c** (%)[b]	Yield of **4a–c** (%)	Yield of **5a–c** (%)	Yield of **7a–c** (%)	ee of **7a–c**[b] (%)	E[a]
Me	40	99.1	48	70	86	98	>25
Et	42	95	45	65	79	95	>19
Vinyl	35	95	51	63	85	97.1	>17

[a] E, the enantiomeric ratio, was roughly calculated based on the yields of **3a–c**, **4a–c** and the ee of **6a–c**.
[b] Ee values were determined by chiral HPLC.

Table 2. *C. rugosa* lipase-catalyzed enantioselective hydrolysis of **11a–i**

Entry	R	Yield of **9a–i** (%)	Yield of **11a–i** (%)	Yield of **12a–i** (%)	ee of **12a–i**[b] (%)	E[a]
1	C_6H_5	69	35	69	98.7	>100
2	4-FC_6H_4	70	38	84	95.9	>87
3	4-MeC_6H_4	73	37	81	100	>100
4	4-$MeOC_6H_4$	69	32	92	96.8	>92
5	4-ClC_6H_4	68	34	78	99.4	>100
6	2-BrC_6H_4	74	36	86	98.0	>100
7	2-ClC_6H_4	73	38	90	97.0	>100
8	2,4-Di-ClC_6H_3	71	39	85	97.5	>100
9	2-Furyl	65	31	95	85.9	>19

[a] E, the enantiomeric ratio, was roughly calculated based on the yields of **11a–i** and the ee of **12a–i**.
[b] Ee values were determined by chiral HPLC.

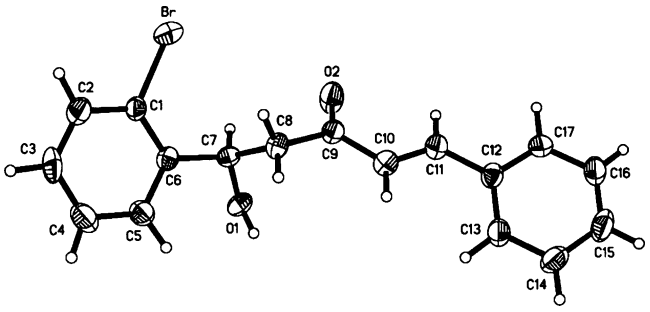


Figure 1. X-Ray structure of compound **12f**.

propyl ether for preparing enantiomerically pure 2-hydroxy-2-aryethanephosphonates (Scheme 3).[10]

Intrigued by the satisfactory results obtained, and taking into account the structure similarity, we wished to resolve those δ-hydroxy-β-ketoalkanephosphonates bearing aryl group via CRL-catalyzed hydrolysis in diisopropyl ether (Scheme 4 and Table 2).

Direct butyrylation of **10a–i** using DCC/butyric acid system afforded the butyryl derivatives **9a–i** in 65–85% yield. They could be enantioselectively hydrolyzed to the corresponding (*R*)-alcohols in water-equilibrated diisopropyl ether. In contrast with CALB, the catalytic preference of CRL toward hydrolysis of the esters of the secondary alcohols could not be accurately predicted. We determined the absolute configuration of the hydrolyzed alcohols according to the X-ray structure of compound **12f** (Fig. 1) since it bears a bromine atom at the 2-position of the phenyl ring. It showed that it was of the (*R*)-configuration.

It is a pity that the unreacted (*S*)-substrates (**10a–i**) could not be directly applied to HWE reactions and we are now engaged in enzymatic hydrolysis of these butyryl derivatives.

3. Conclusion

In summary, the ready access to racemic starting material coupled with their efficient and simple enzymatic resolution here reported makes the preparation of optically active δ-hydroxy-β-ketoalkanephosphonates with high ee more convenient. Consequently, optimization of this method and its application in synthetic organic chemistry are currently undergoing in our laboratory.

4. Experimental

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. The melting point was not corrected.

CALB (Novozym 435) was a gift from Novo Norvodisk Co. *C. rugosa* lipase (901 units/mg) was purchased from Sigma Chemical Co. The racemic δ-hydroxy-β-ketoalkanephosphonates were prepared according to literature.[7]

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; column dimensions: 0.46×25 cm; flow rate: 0.7 mL/min; eluent: hexane:isopropanol = 9:1–8:2 (v/v).

4.1. General procedure for CALB-catalyzed acetylation of racemic δ-hydroxy-β-ketoalkanephosphonates 2a–c

To a stirred solution of hydroxyalkanephosphonate (1 mmol) in benzene (15 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, washed with acetone (5 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 1.

4.1.1. (4*S*)-Diethyl 4-hydroxy-2-oxo-pentylphosphonate 3a. Colorless oil; $[\alpha]_D^{18} = +33.2$ (*c* 1.2, $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$): δ 4.18–4.28 (5H, m, CHOH+ $P(OCH_2CH_3)_2$), 3.10–3.18 (2H, dd, $J=1.5$, 23 Hz, CH_2P), 2.75–2.87 (3H, m, $CH(OH)CH_2CO$), 1.34–1.39 (6H, t, $J=6.9$ Hz, $P(OCH_2CH_3)_2$), 1.22–1.24 (3H, d, $J=6.45$ Hz, CH_3CHOH); ^{31}P NMR (120 MHz, $CDCl_3$): δ 17.76; IR (film): 3404, 2980, 1714, 1446, 1394, 1372, 1249, 1164, 1026, 973 cm^{-1}; EIMS (m/z): 239 (M^++1) (2.06), 237 (2.55), 221 (21.64), 179 (27.28), 165 (88.38), 91 (100), 69 (81.22), 43 (80.12).

4.1.2. (4*R*)-Diethyl 4-acetyloxy-2-oxo-pentylphosphonate 4a. Colorless oil; $[\alpha]_D^{18}=+4.0$ (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.27–5.34 (1H, m, $CHCH_2COCH_2P$), 4.14–4.21 (4H, m, $P(OCH_2CH_3)_2$), 3.07–3.16 (2H, dd, $J=2.1$, 22.8 Hz, CH_2P), 2.81–3.03 (2H, m, $CHCH_2COCH_2P$), 2.01 (3H, s, CH_3CO), 1.34–1.39 (6H, t, $J=7.2$ Hz, $P(OCH_2CH_3)_2$), 1.29–1.31 (2H, d, $J=6.3$ Hz, CH_3CHCH_2CO); ^{31}P NMR (120 MHz, $CDCl_3$): δ 17.76; IR (film): 2986, 1739, 1371, 1284, 1025, 966, 792 cm^{-1}; EIMS (m/z): 237 (11.27), 221 (53.54), 197 (22.93), 179 (77.45), 151 (61.17), 123 (93.50), 69 (80.27), 43 (100).

4.1.3. (4*S*)-4-Diethyl 4-hydroxy-2-oxo-hexylphosphonate 3b. Colorless oil; $[\alpha]_D^{18}=+40$ (c 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.11–4.21 (4H, m, $P(OCH_2CH_3)_2$), 399–4.11 (1H, m, CHOH), 3.11–3.19 (2H, dd, $J=1.5$, 23 Hz, CH_2P), 2.91 (1H, br, s, OH), 2.67–2.85 (2H, m, $CH(OH)CH_2CO$), 1.48–1.55 (2H, m, CH_3CH_2CHOH), 1.33–1.38 (3H, t, $J=7.2$ Hz, $P(OCH_2CH_3)_2$), 0.94–0.99 (3H, t, $J=7.2$ Hz, CH_3CH_2CHOH); IR (film): 3412, 2981, 1715, 1250, 1026, 975 cm^{-1}; EIMS (m/z): 234 ($M-H_2O$) (6.38), 223 (100), 195 (39.21), 179 (45.19), 167 (34.84), 151 (26.17), 123 (61.79). HRMS calcd for $C_{10}H_{19}O_4P$ ($M-H_2O$): 234.10210. Found: 234.10578.

4.1.4. (4*R*)-Diethyl 4-acetyloxy-2-oxo-hexylphosphonate 4b. Colorless oil; $[\alpha]_D^{18}=+11.5$ (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.17–5.21 (1H, m, $CHCH_2COCH_2P$), 4.10–4.19 (4H, m, $P(OCH_2CH_3)_2$), 3.06–3.18 (2H, m, $CHCH_2COCH_2P$), 2.87–2.89 (2H, d, $J=6.3$ Hz, CH_2P), 2.06 (3H, s, CH_3CO), 1.60–1.66 (2H, m, $CH_3CH_2CHCH_2CO$), 1.30–1.36 (6H, m, $P(OCH_2CH_3)_2$), 0.88–0.93 (3H, t, $J=7.5$ Hz, $CH_3CH_2CHCH_2CO$); IR (film): 2979, 1737, 1373, 1249, 1026 cm^{-1}; EIMS (m/z): 251 (8.96), 234 (56.52), 223 (27.78), 179 (100), 151 (55.66), 123 (83.78), 109 (34.75), 43 (57.06). HRMS calcd for $C_{12}H_{23}O_6P$: 294.12323. Found: 294.12583.

4.1.5. (4*R*)-Diethyl 4-hydroxy-2-oxo-5-hexenylphosphonate 3c. Colorless oil; $[\alpha]_D^{18}=+17.5$ (c 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.30–5.35 (1H, m, $CH_2=CH$), 5.13–5.35 (2H, 2dd, $CH_2=CH$), 4.589–4.612 (1H, m, CHOH), 4.137–4.212 (4H, m, $P(OCH_2CH_3)_2$), 3.123–3.199 (2H, d, $J=23$ Hz, CH_2P), 2.85–2.87 (2H, d, $J=5.4$ Hz, $CHOHCH_2CO$), 1.338–1.38 (6H, t, $J=7.2$ Hz, $P(OCH_2CH_3)_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 17.72; IR (film): 3402, 1714, 1647, 1395, 1246, 1024, 973 cm^{-1}; EIMS (m/z): 250 (M^+) (2.52), 233 (3.15), 194 (85.49), 179 (70.33), 151 (47.51), 125 (100), 97 (62.14). Anal. calcd for $C_{10}H_{19}O_5P$: C, 48.00; H, 7.65. Found: C, 47.79; H, 7.89.

4.1.6. (4*S*)-Diethyl 4-acetyloxy-2-oxo-5-hexenylphosphonate 4c. Colorless oil; $[\alpha]_D^{18}=-1.3$ (c 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.78–5.89 (1H, m, $CH_2=CH$), 5.64–5.70 (1H, m, $CH_2=CH-CH$), 5.18–5.33 (2H, m, $CH_2=CH$), 4.10–4.20 (4H, m, $P(OCH_2CH_3)_2$), 3.06–3.15 (2H, dd, $J=2.1$, 22.7 Hz, CH_2P), 2.97–3.02 (2H, m, CH_2COCH_2P), 2.04 (3H, s, CH_3CO), 1.32–1.36 (6H, t, $J=6.9$ Hz, $P(OCH_2CH_3)_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 17.36; IR (film): 2987, 1741, 1623, 1592, 1372, 1244, 1025, 971 cm^{-1}; EIMS (m/z): 293 (M^++1) (5.10), 233 (100), 203 (26.98), 179 (27.30), 123 (44.98), 94 (71.38). Anal. calcd for $C_{12}H_{21}O_6P$: C, 49.30; H, 7.24. Found: C, 49.41; H, 7.10.

4.2. General procedure for CALB-catalyzed hydrolysis of 4-acetyloxy-2-oxo-phosphonates

To a stirred water-saturated diisopropyl ether (4 mL) was added a mixture of the acetylated phosphonates and 300 mg CALB. The solution was stirred at room temperature until the starting material nearly disappeared (3 days or so). After filtration and washing with 5 mL $CHCl_3$, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the hydrolyzed products of whose yields are listed in Table 1.

4.3. General procedure for HWE reactions of the chiral δ-hydroxy-β-ketoalkanephosphonates

To substrates (40 mg) was added K_2CO_3 (300 mg), H_2O (0.6 mL) and benzaldehyde (0.6 mL), the mixture was stirred and ethyl acetate (5 mL) and water (5 mL) was added after the starting material disappeared (generally within 5 h) as monitored by TLC. The aqueous phase was extracted with ethyl acetate (2×5 mL). Dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography. The yields of the reaction products are listed in Table 1.

4.3.1. (5*S*,1*E*)-5-Hydroxy-1-phenyl-1-hexen-3-one 6a. Pale yellow oil; ee 99.1%; $[\alpha]_D^{15}=+41$ (c 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.28, 7.62 (6H, m, Ar–H+ArCH), 6.74 (1H, d, $J=16.5$ Hz, ArCH=CH), 4.30–4.40 (1H, m, CHOH), 2.64–2.95 (3H, OH+ CH_2CO), 1.284 (3H, d, $J=6.6$ Hz, CH_3CHOH); IR (film): 3430, 1703, 1609, 1246, 1174 cm^{-1}; EIMS (m/z): 190 (M^+) (4.71), 145 (13.24), 131 (100), 103 (84.90), 43 (76.13), 102 (27.54). HRMS calcd for $C_{12}H_{14}O_2$: 190.0994. Found: 190.0991.

4.3.2. (5*S*,1*E*)-5-Hydroxy-1-phenyl-1-hepten-3-one 6b. Colorless oil; ee 95%; $[\alpha]_D^{25}=+50.7$ (c 1.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.60 (6H, m, Ar–H+ ArCH), 6.74 (1H, d, $J=16.2$ Hz, ArCH=CH), 4.05–4.13 (1H, m, CHOH), 2.73–2.94 (2H, m, CH_2CO), 1.51–1.64 (2H, m, CH_3CH_2CHOH), 1.03 (3H, t, $J=7.2$ Hz, CH_3CH_2CHOH); IR (film): 3447, 2966, 2932, 1716, 1685, 1652, 1608, 977, 750, 714, 690 cm^{-1}; EIMS (m/z): 204 (M^+) (3.32), 186 (6.81), 146 (19.04), 131 (100), 103

(34.12), 77 (18.37). HRMS calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1106.

4.3.3. (5*R*,1*E*)-5-Hydroxy-1-phenyl-1,6-heptadien-3-one 6c. Colorless oil; $[\alpha]_D^{16}=+33$ (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.62 (6H, m, Ar–H+ArCH), 6.75 (1H, d, $J=16.2$ Hz, ArCH=CH), 5.89–6.00 (1H, m, CH_2=CH–CHOH), 5.16–5.39 (2H, 2d, $J=17.1$, 17.4 Hz, CH_2=CH–CHOH), 4.69–4.70 (1H, m, CHOH), 3.32 (1H, s, OH), 2.85–2.98 (2H, m, CH_2=CH–CHOHCH_2); IR (film): 3437, 1733, 1678, 1646, 1601, 1513, 1256, 1174 cm^{-1}; EIMS (*m*/*z*): 202 (M^+) (1.32), 145 (20.38), 131 (100), 103 (60.55), 78 (28.65). HRMS calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0971.

4.4. General procedure for the preparation of diethyl 4-butyryloxyl-4-aryl-2-oxo-butylphosphonates

In a 25 mL bottle was added substrates (1 mmol), *n*-butyric acid (106 mg, 1.2 mmol) and DCC (248 mg, 1.2 mmol), methylene chloride (10 mL), the mixture was cooled to 0°C and DMAP (10 mg) was added. After the starting material was consumed, 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 2.

4.4.1. Diethyl 4-butyryloxy-2-oxo-4-phenylbutylphosphonate 9a. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–7.39 (5H, m, ArH), 6.18 (1H, dd, $J=8.4$ Hz, ArCH), 4.02–4.14 (4H, m, P (OCH_2CH_3)$_2$), 3.02–3.28 (4H, m, CH_2COCH_2), 2.24 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.56–1.71 (2H, m, $COCH_2CH_2CH_3$), 1.24–1.33 (6H, m, P (OCH_2CH_3)$_2$), 0.87 (3H, t, $J=6.9$ Hz, $COCH_2CH_2CH_3$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.36; IR (film): 3462, 2972, 2936, 2978, 1735, 1255, 1025, 973 cm^{-1}; EIMS (*m*/*z*): 370 (M^+) (0.62), 352 (5.16), 299 (100.00), 253 (11.86), 195 (13.61), 179 (33.79), 144 (56.14), 131 (42.48), 105 (79.68), 77 (17.41). HRMS calcd for $C_{18}H_{27}O_6P$: 370.1545. Found: 370.1512.

4.4.2. Diethyl 4-butyryloxy-2-oxo-4-(4-fluorophenyl)-butylphosphonate 9b. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.38 (2H, m, ArH), 7.02–7.13 (2H, m, ArH), 6.17 (1H, dd, $J=5.7$ Hz, ArCH), 4.05–4.22 (4H, m, P(OCH_2CH_3)$_2$), 3.05–3.37 (2H, m, ArCHCH_2), 3.09 (2H, d, $J=22.8$ Hz, CH_2P), 2.30 (2H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$), 1.57–1.69 (2H, m, $CH_3CH_2CH_2CO$), 1.25–1.43 (6H, m, P(OCH_2CH_3)$_2$), 0.92 (3H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.19; IR (film): 3462, 2982, 2937, 2878, 1733, 1511, 1234, 1029, 974 cm^{-1}; EIMS (*m*/*z*): 388 (M+) (0.86), 317 (100), 300 (8.47), 271 (9.47), 179 (26.70), 162 (25.09), 149 (37.12), 123 (69.89), 109 (12.941). HRMS calcd for $C_{18}H_{26}FO_6P$: 388.1451. Found: 388.1472.

4.4.3. Diethyl 4-butyryloxy-2-oxo-4-(4-methylphenyl)-butylphosphonate 9c. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (2H, d, $J=8.1$ Hz, ArH), 7.15 (2H, d, $J=7.8$ Hz, ArH), 6.18 (1H, dd, $J=8.4$ Hz, ArCH), 4.04–4.21 (4H, m, P(OCH_2CH_3)$_2$), 3.30 (1H, dd, $J=8.4$ Hz, ArCHCH$_2$), 3.09 (2H, d, $J=22.8$ Hz, CH_2P), 3.05–3.13 (1H, m, ArCHCH$_2$), 2.33 (3H, ArCH_3), 2.26 (2H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$), 1.58–1.65 (2H, m, $CH_3CH_2CH_2CO$), 1.27–1.36 (6H, m, P(OCH_2CH_3)$_2$), 0.91 (3H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.48; IR (film): 2981, 2935, 1734, 1502, 1254, 1026, 973 cm^{-1}; EIMS (*m*/*z*): 384 (M^+) (2.12), 366 (5.10), 313 (100), 296 (12.49), 179 (29.64), 158 (81.12), 145 (60.17), 119 (83.73), 91 (20.98), 77 (2.99). HRMS calcd for $C_{19}H_{29}O_6P$: 384.1702. Found: 384.1707.

4.4.4. Diethyl 4-butyryloxy-2-oxo-4-(4-methoxylphenyl)-butylphosphonate 9d. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (2H, d, $J=6.6$ Hz, ArH), 6.85 (2H, d, $J=6.6$ Hz, ArH), 6.181 (1H, dd, $J=8.4$ Hz, ArCH), 4.08–4.17 (4H, m, P(OCH_2CH_3)$_2$), 3.76 (3H, ArOCH_3), 3.08–3.31 (2H, m, ArCHCH_2), 3.08 (2H, d, $J=21.6$ Hz, CH_2P), 2.280 (2H, t, $J=7.5$ Hz, $CH_3CH_2CH_2CO$), 1.59–1.70 (2H, m, $CH_3CH_2CH_2CO$), 1.24–1.37 (6H, m, P(OCH_2CH_3)$_2$), 0.94 (3H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.51; IR (film): 2981, 2937, 2842, 1727, 1599, 1254, 1175, 1027, 974 cm^{-1}; EIMS (*m*/*z*): 400 (M^+) (1.55), 329 (33.09), 312 (19.02), 283 (7.55), 174 (57.14), 161 (100), 135 (39.74). HRMS calcd for $C_{19}H_{29}O_7P$: 400.1651. Found: 400.1689.

4.4.5. Diethyl 4-butyryloxy-2-oxo-4-(4-chlorophenyl)-butylphosphonate 9e. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (4H, s, ArH), 6.159 (1H, dd, $J=6.9$ Hz, ArCH), 4.04–4.20 (4H, m, P(OCH_2CH_3)$_2$), 3.24–3.30 (1H, m, ArCHCH_2), 3.08 (2H, d, $J=23.1$ Hz, CH_2P), 3.11–3.14 (1H, m, ArCHCH_2), 2.28 (2H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$), 1.57–1.67 (2H, m, $CH_3CH_2CH_2CO$), 1.26–1.36 (6H, m, P(OCH_2CH_3)$_2$), 0.90 (3H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.144; IR (film): 2984, 2933, 2910, 1689, 1610, 1253, 1048, 1026, 974 cm^{-1}; EIMS (*m*/*z*): 333 (4.53), 317 (100), 287 (11.27), 178 (31.63), 165 (43.73), 137 (11.40), 102 (13.84). HRMS calcd for $C_{14}H_{19}ClO_5P$ (M–COPr-*n*): 333.0659. Found: 333.0675.

4.4.6. Diethyl 4-butyryloxy-2-oxo-4-(2-bromophenyl)-butylphosphonate 9f. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (1H, dd, $^3J_{H-H}=7.8$ Hz, $^4J_{H-H}=1.2$ Hz, ArH), 7.36 (1H, dd, $^3J_{H-H}=7.8$ Hz, $^4J_{H-H}=2.1$ Hz, ArH), 7.30 (1H, dt, $^3J_{H-H}=7.5$ Hz, $^4J_{H-H}=1.2$ Hz, ArH), 7.15 (1H, dt, $^3J_{H-H}=7.8$ Hz, $^4J_{H-H}=1.8$ Hz, ArH), 6.46 (1H, dd, $J=7.5$ Hz, ArCH), 4.09–4.20 (4H, m, P(OCH_2CH_3)$_2$), 3.04–3.24 (4H, m, ArCHCH_2 $COCH_2$), 2.34 (2H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$), 1.58–1.71 (2H, m, $CH_3CH_2CH_2CO$), 1.24–1.364 (6H, m, P(OCH_2CH_3)$_2$), 0.934 (3H, t, $J=7.5$ Hz, $CH_3CH_2CH_2CO$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.61; EIMS (*m*/*z*): 449 (M^++1) (1.62), 364 (43.49), 363 (39.32), 362 (42.80), 361 (50.15), 281 (100), 253 (20.81), 43 (38.14); IR (film): 2970, 2936, 2877, 1743, 1726, 1257, 1027, 971 cm^{-1}.

4.4.7. Diethyl 4-butyryloxy-2-oxo-4-(2-chlorophenyl)-butylphosphonate 9g. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.39 (4H, m, ArH), 6.51 (1H, dd, $J=8.1$ Hz, ArCH), 4.10–4.21 (4H, m, P(OCH_2CH_3)$_2$), 3.37 (2H, d, $J=23.1$ Hz, CH_2P), 3.09–3.19 (2H, m, ArCHCH_2), 2.32 (2H, t, $J=7.8$ Hz, $CH_3CH_2CH_2CO$), 1.61–1.68 (2H, m, $CH_3CH_2CH_2CO$), 1.26–1.37 (6H, m, P(OCH_2CH_3)$_2$), 0.93 (3H, t, $J=7.2$ Hz, $CH_3CH_2CH_2$-CO); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.27; IR (film): 3466, 2981, 2912, 2877, 1726, 1255, 1026, 973 cm^{-1}; EIMS (m/z): 405 (M^++1) (1.02), 333 (13.35), 317 (81.00), 281 (100.00), 253 (28.06), 225 (27.04), 179 (18.38), 165 (31.42), 139 (22.44), 76 (3.82). HRMS calcd for $C_{18}H_{26}ClO_6P$: 404.1156. Found: 404.1174.

4.4.8. Diethyl 4-butyryloxy-2-oxo-4-(2,4-dichlorophenyl)-butylphosphonate 9h. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.44 (3H, m, ArH), 6.430 (1H, dd, $J=8.7$ Hz, ArCH), 4.06–4.21 (4H, m, P(OCH_2CH_3)$_2$), 3.34 (2H, d, $J=22.8$ Hz, CH_2P), 3.07–3.17 (2H, m, ArCHCH_2), 2.29 (2H, t, $J=7.5$ Hz, $CH_3CH_2CH_2CO$), 1.59–1.66 (2H, m, $CH_3CH_2CH_2CO$), 1.32 (6H, t, $J=6.9$ Hz, P(OCH_2CH_3)$_2$), 0.92 (3H, t, $J=7.5$ Hz, $CH_3CH_2CH_2CO$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.27; IR (film): 2980, 2936, 2877, 1742, 1724, 1255, 1048, 1026, 971 cm^{-1}; EIMS (m/z): 420 (1.05), 367 (12.88), 315 (100.00), 287 (16.46), 259 (16.71), 199 (27.33), 179 (14.74), 136 (13.80), 123 (7.58), 109 (10.43), 78 (2.24). HRMS calcd for $C_{18}H_{25}Cl_2O_6P$: 438.0766. Found: 438.0798.

4.4.9. Diethyl 4-butyryloxy-2-oxo-4-(2-furyl)-butylphosphonate 9i. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.38 (1H, m, ArH), 6.27–6.39 (3H, ArH, ArCH), 4.09–4.19 (4H, m, P(OCH_2CH_3)$_2$), 3.22–3.43 (2H, m, ArCHCH_2), 3.12 (2H, d, $J=22.8$ Hz, CH_2P), 2.25 (2H, t, $J=7.5$ Hz, $CH_3CH_2CH_2CO$), 1.58–1.67 (2H, m, $CH_3CH_2CH_2CO$), 1.30–1.36 (6H, m, P(OCH_2CH_3)$_2$), 0.90 (3H, t, $J=7.2$ Hz, $CH_3CH_2CH_2CO$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.26; IR (film): 2980, 1737, 1253, 1024, 973 cm^{-1}; EIMS (m/z): 360 (M^+) (3.01), 289 (100.00), 273 (13.20), 193 (12.04), 179 (67.55), 151 (38.89), 123 (39.46), 109 (17.59), 71 (15.64), 65 (12.57). HRMS calcd for $C_{16}H_{25}O_7P$: 360.1338. Found: 360.1319.

4.5. General procedure of CRL-catalyzed enantioselective hydrolysis for the preparation of optical active δ-hydroxy-β-ketoalkanephosphonates

To 1.2 M aqueous $MgCl_2$–saturated diisopropyl ether (4 mL) were added substrates (100 mg), and the reaction was started by adding crude CRL (100 mg). When the mixture was stirred about 48 h, filtered off the enzymes and washed with 5 mL ethyl acetate. The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford unreacted esters and the hydrolyzed alcohols of which the yields are listed in Table 2.

4.5.1. (4*R*)-Diethyl 4-hydroxy-2-oxo-4-phenylbutylphosphonate 11a. Colorless oil; $[\alpha]_D^{27}=+41.6$ (c 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.43 (5H, m, ArH), 5.20 (1H, dd, $J=9.0$ Hz, ArCH), 4.10–4.20 (4H, m, P (OCH_2CH_3)$_2$), 3.01–3.20 (4H, m, CH_2COCH_2), 1.27–1.38 (6H, m, P (OCH_2CH_3)$_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.67; IR (film): 3381, 2985, 1716, 1394, 1251, 1047, 1025, 969 cm^{-1}; EIMS (m/z): 300 (M^+) (3.63), 283 (58.26), 195 (74.06), 167 (46.28), 152 (52.86), 139 (50.42), 125 (100.00), 105 (86.79), 97 (68.07), 77 (79.56).

4.5.2. (4*R*)-Diethyl 4-hydroxy-2-oxo-4-(4-fluorophenyl)-butylphosphonate 11b. Colorless oil; $[\alpha]_D^{27}=+42.7$ (c 1.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.37 (2H, m, ArH), 3.99–7.05 (2H, m, ArH), 5.164 (1H, dd, $J=8.4$ Hz, ArCH), 4.08–4.18 (4H, m, P (OCH_2CH_3)$_2$), 3.14 (2H, d, $^2J_{P-H}=23.1$ Hz, CH_2P), 2.93–3.13 (2H, m, CHCH_2), 1.330 (6H, t, $J=7.2$ Hz, P(OCH_2CH_3)$_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.50; IR (film): 3375, 2987, 2912, 1716, 1511, 1223, 1026, 973 cm^{-1}; EIMS (m/z): 318 (M^+) (2.50), 301 (100.00), 179 (16.81), 152 (19.33), 123 (47.73), 109 (15.36), 97 (39.25), 77 (8.92). Anal. calcd for $C_{14}H_{20}FO_5P$: C, 52.83; H, 6.33. Found: C, 52.43; H, 6.16.

4.5.3. (4*R*)-Diethyl 4-hydroxy-2-oxo-4-(4-methylphenyl)-butylphosphonate 11c. Colorless oil; $[\alpha]_D^{27}=+38.9$ (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (2H, d, $J=7.8$ Hz, ArH), 7.22 (2H, d, $J=7.8$ Hz, ArH), 5.16 (1H, dd, $J=9.0$ Hz, ArCH), 4.106–4.21 (4H, m, P (OCH_2CH_3)$_2$), 2.88–3.19 (4H, m, CH_2COCH_2), 2.33 (3H, s, CH_3Ar), 1.31–1.37 (6H, m, P(OCH_2CH_3)$_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.86; IR (film): 3379, 2985, 2912, 1716, 1394, 1253, 1025, 968 cm^{-1}; EIMS (m/z): 314 (M^+) (32.90), 194 (87.27), 167 (57.74), 152 (68.87), 125 (100.00), 119 (99.84), 97 (49.34), 91 (72.38), 77 (34.26). HRMS calcd for $C_{15}H_{23}O_5P$: 314.1283. Found: 314.1282.

4.5.4. (4*R*)-Diethyl 4-hydroxy-2-oxo-4-(4-methoxylphenyl)butylphosphonate 11d. Colorless oil; $[\alpha]_D^{27}=+40.1$ (c 1.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.302 (2H, d, $J=9.3$ Hz, ArH), 6.89 (2H, d, $J=9.0$ Hz, ArH), 5.15 (1H, dd, $J=7.5$ Hz, ArCH), 4.13–4.20 (4H, m, P (OCH_2CH_3)$_2$), 3.81 (3H, s, OCH_3), 3.15 (2H, d, $^2J_{P-H}=$ 22.8 Hz, CH_2P), 2.99–3.08 (2H, m, CHCH_2), 1.35 (6H, t, $J=7.2$ Hz, P(OCH_2CH_3)$_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.62; IR (film): 3384, 2985, 2935, 2910, 1714, 1514, 1249, 1029, 972 cm^{-1}; EIMS (m/z): 330 (M^+) (0.49), 194 (11.02), 152 (20.63), 136 (63.88), 135 (100.00), 125 (37.77), 109 (23.21), 97 (30.75), 77 (34.99), 65 (22.76).

4.5.5. (4*R*)-Diethyl 4-hydroxy-2-oxo-4-(4-chlorophenyl)-butylphosphonate 11e. Colorless oil; $[\alpha]_D^{27}=+41.2$ (c 1.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (4H, s, ArH), 5.16 (1H, dd, $J=8.7$ Hz, ArCH), 4.10–4.18 (4H, m, P (OCH_2CH_3)$_2$), 2.97–3.18 (4H, m, CH_2COCH_2), 1.30–1.35 (6H, m, P(OCH_2CH_3)$_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.58; IR (film): 3371, 2985, 1716, 1248, 1025, 972 cm^{-1}; EIMS (m/z): 334 (M^+) (1.00), 317 (100.00), 195 (36.13), 179 (19.49), 152 (12.25), 139 (22.26), 125 (17.97), 97 (14.54), 77 (12.49).

4.5.6. (4*R*)-Diethyl 4-hydroxy-2-oxo-4-(2-bromophenyl)-butylphosphonate 11f. Colorless oil; $[\alpha]_D^{25}=+69.2$ (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.633 (1H, dd, $^3J_{H-H}=7.8$ Hz, $^4J_{H-H}=1.5$ Hz, ArH), 7.542 (1H, dd, $^3J_{H-H}=7.8$ Hz, $^4J_{H-H}=1.2$ Hz, ArH), 7.34 (1H, dt, $^3J_{H-H}=7.2$ Hz, $^4J_{H-H}=0.6$ Hz, ArH), 7.13 (1H, dt, $^3J_{H-H}=7.5$ Hz, $^4J_{H-H}=1.8$ Hz, ArH), 5.49 (1H, dd, $J=9.3$ Hz, ArCH), 4.10–4.20 (4H, m, $P(OCH_2CH_3)_2$), 2.80–3.22 (4H, m, $ArCHCH_2COCH_2$), 1.31–1.37 (6H, m, $P(OCH_2CH_3)_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.56; IR (film): 3371, 2985, 1716, 1248, 1025, 972 cm^{-1}; EIMS (*m*/*z*): 379 (M^+) (2.81), 362 (36.21), 300 (12.92), 281 (18.47), 194 (93.81), 185 (72.57), 167 (48.02), 152 (17.97), 125 (100.00), 97 (64.29), 77 (66.83). Anal. calcd for $C_{14}H_{20}BrO_5P$: C, 44.35; H, 5.32. Found: C, 44.41; H, 5.50.

4.5.7. (4*R*)-Diethyl 4-hydroxy-2-oxo-4-(2-chlorophenyl)-butylphosphonate 11g. Colorless oil; $[\alpha]_D^{25}=+74.7$ (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (1H, d, $J=5.4$ Hz, ArH), 7.23–7.36 (3H, m, ArH), 5.559 (1H, dd, $J=9.9$ Hz, ArCH), 4.12–4.22 (4H, m, $P(OCH_2CH_3)_2$), 2.85–3.23 (4H, m, CH_2COCH_2), 1.32–1.38 (6H, m, $P(OCH_2CH_3)_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.56; IR (film): 3360, 2985, 2933, 2911, 1718, 1248, 1047, 1027, 972 cm^{-1}; EIMS (*m*/*z*): 334 (M^+) (0.21), 317 (35.85), 281 (9.19), 195 (100.00), 152 (25.58), 139 (53.71), 125 (25.58), 97 (21.03), 77 (16.30). Anal. calcd for $C_{14}H_{20}ClO_5P$: C, 50.23; H, 6.02. Found: C, 50.44; H, 6.27.

4.5.8. Diethyl 4-hydroxy-2-oxo-4-(2,4-dichlorophenyl)-butylphosphonate 11h. Colorless oil; $[\alpha]_D^{25}=+68.7$ (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, d, $J=8.7$ Hz, ArH), 7.27–7.34 (2H, m, ArH), 5.49 (1H, dd, $J=7.8$ Hz, ArCH), 4.11–4.18 (4H, m, $P(OCH_2CH_3)_2$), 3.18 (2H, d, $^2J_{P-H}=23.1$ Hz, CH_2P), 2.80–3.05 (2H, m, $CHCH_2$), 1.34 (6H, dt, $^3J_{H-H}=6.9$ Hz, $^4J_{P-H}=0.9$ Hz, $P(OCH_2CH_3)_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.56; IR (film): 3360, 2985, 2933, 2911, 1718, 1248, 1047, 1027, 972 cm^{-1}; EIMS (*m*/*z*): 334 (M^+) (0.21), 317 (35.85), 281 (9.19), 195 (100.00), 152 (25.58), 139 (53.71), 125 (25.58), 97 (21.03), 77 (16.30). Anal. calcd for $C_{14}H_{19}Cl_2O_5P$: C, 45.55; H, 5.19. Found: C, 45.52; H, 5.32.

4.5.9. Diethyl 4-hydroxy-2-oxo-4-(2-furyl)-butylphosphonate 11i. Colorless oil; $[\alpha]_D^{25}=+28.1$ (*c* 1.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (1H, dd, $^3J_{H-H}=28.2$ Hz, $^4J_{H-H}=0.6$ Hz), 6.30–6.35 (2H, m, ArH), 5.21 (1H, d, $J=9.0$ Hz, ArCH), 4.13–4.22 (4H, m, $P(OCH_2CH_3)_2$), 3.09–3.25 (4H, m, CH_2COCH_2), 1.33–1.39 (6H, m, $P(OCH_2CH_3)_2$); ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.76; IR (film): 3366, 2986, 2912, 1718, 1247, 1024, 973 cm^{-1}; EIMS (*m*/*z*): 290 (M^+) (8.02), 273 (100.00), 244 (11.02), 195 (28.75), 179 (14.81), 152 (12.49), 121 (19.88), 97 (25.43), 65 (8.54). Anal. calcd for $C_{12}H_{19}O_6P$: C, 49.66; H, 6.60. Found: C, 49.60; H, 6.75.

4.6. HWE reactions of diethyl 4-hydroxy-2-oxo-4-(2-aryl)-butylphosphonate

The procedures are similar with that of the aliphatic counterparts. The yields of these reactions are listed in Table 2.

4.6.1. (5*R*,1*E*)-5-Hydroxy-1,5-diphenyl-1-penten-3-one 12a. Colorless oil; $[\alpha]_D^{27}=+67.1$ (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.59 (3H, m, ArH, ArCH=), 7. 29–7.44 (8H, m, ArH), 6.73 (1H, d, $J=16.2$ Hz, ArCH=CHCO), 5.27 (1H, t, $J=6.3$ Hz, ArCH), 3.09 (2H, dd, $J=7.2$ Hz, $CHCH_2CO$); IR (film): 3445, 2971, 2937, 1662, 1625, 1492, 1091, 1014, 977, 831 cm^{-1}; EIMS (*m*/*z*): 252 (M^+) (3.43), 160 (9.86), 145 (37.10), 131 (100.00), 120 (27.81), 105 (65.19), 103 (61.98), 77 (75.26), 51 (33.15).

4.6.2. (5*R*,1*E*)-5-Hydroxy-5-(4-fluorophenyl)-1-phenyl-1-penten-3-one 12b. Colorless solid; mp 108–109°C; $[\alpha]_D^{27}=+59.9$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.60 (8H, m, ArH, ArCH=), 7.06 (2H, t, $J=8.1$ Hz, ArH), 6.74 (1H, d, $J=16.2$ Hz, ArCH=CHCO), 5.25 (1H, s, ArCH), 3.07 (2H, dd, $J=12.0$ Hz, $CHCH_2CO$); IR (film): 3401, 2925, 1646, 1602, 1222, 982, 749, 692 cm^{-1}; EIMS (*m*/*z*): 270 (M^+) (3.27), 233 (7.71), 145 (69.57), 131 (100.00), 123 (85.33), 103 (93.75), 95 (49.78), 91 (9.98), 77 (58.16), 65 (2.97). HRMS calcd for $C_{15}H_{15}FO_2$: 270.10561. Found: 270.10963.

4.6.3. (5*R*,1*E*)-5-Hydroxy-5-(4-methylphenyl)-1-phenyl-1-penten-3-one 12c. White solid; mp 105–107°C; $[\alpha]_D^{27}=+79.6$ (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.03–7.77 (10H, m, ArH, ArCH), 6.74 (1H, d, $J=16.2$ Hz, ArCH=CHCO), 5.24 (1H, dd, $J=7.5$ Hz, ArCH), 3.08–3.11 (2H, m, $CHCH_2CO$), 2.40 (3H, s, CH_3Ar); IR (film): 3456, 3024, 1647, 1448, 1183, 979, 812, 747, 693 cm^{-1}; EIMS (*m*/*z*): 266 (M^+) (2.20), 247 (11.07), 233 (17.21), 145 (79.69), 131 (88.37), 119 (100.00), 103 (91.35), 91 (88.47), 77 (47.83), 65 (21.82). Anal. calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.97; H, 6.92.

4.6.4. (5*R*,1*E*)-5-Hydroxy-5-(4-methoxyphenyl)-1-phenyl-1-penten-3-one 12d. White powder; mp 116–117°C; $[\alpha]_D^{27}=+51.0$ (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.52–7.60 (3H, m, ArH, ArCH), 7.40–7.42 (3H, m, ArH), 7.35 (2H, d, $J=8.4$ Hz, ArH), 6.91 (2H, d, $J=9.0$ Hz, ArH), 6.74 (1H, d, $J=16.2$ Hz, ArCH=CHCO), 5.20–5.23 (1H, m, ArCH), 3.18 (3H, s, OCH_3), 3.07–3.10 (2H, m, $CHCH_2CO$); IR (film): 3509, 3055, 3025, 2938, 2839, 1645, 1514, 1247, 1181, 1035, 980, 838, 817, 748 cm^{-1}; EIMS (*m*/*z*): 282 (M^+) (2.24), 264 (8.17), 145 (47.88), 135 (100.00), 103 (66.44), 92 (14.96), 77 (60.40), 65 (11.84). Anal. calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.74; H, 6.92.

4.6.5. (5*R*,1*E*)-5-Hydroxy-5-(4-chlorophenyl)-1-phenyl-1-penten-3-one 12e. Colorless solid; mp 130–131°C; $[\alpha]_D^{27}=+58.6$ (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.60 (10H, m, ArH, ArCH=), 6.73 (1H, d, $J=16.2$ Hz, ArCH=CHCO), 5.21–5.29 (1H, m,

ArCH), 3.05–3.11 (2H, m, $CHCH_2CO$); IR (film): 3393, 3026, 2928, 1648, 1608, 981, 749, 694 cm^{-1}; EIMS (m/z): 268 (7.80), 233 (12.78), 145 (47.88), 145 (72.70), 139 (61.43), 131 (100.00), 115 (11.27), 111 (26.54), 91 (9.86), 77 (96.64), 63 (11.59). HRMS calcd for $C_{17}H_{15}ClO_2$: 286.0761. Found: 286.0780.

4.6.6. (5*R*,1*E*)-5-Hydroxy-5-(2-bromophenyl)-1-phenyl-1-penten-3-one 12f. Colorless solid; mp 86–87°C; $[\alpha]_D^{27}=+121.2$ (c 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.13–7.71 (10H, m, ArH, ArCH=), 6.75 (1H, d, $J=15.9$ Hz, ArCH=CHCO), 5.55 (1H, dd, $J=9.6$ Hz, ArCH), 3.30 (1H, dd, $J=17.4$ Hz, $CHCH_2CO$), 2.87 (1H, dd, $J=17.4$ Hz, $CHCH_2CO$); IR (film): 3458, 3062, 3028, 2910, 1654, 1608, 1176, 1095, 1068, 1023, 977, 753, 689 cm^{-1}; EIMS (m/z): 313 (2.24), 251 (56.01), 233 (16.10), 185 (47.86), 145 (50.26), 131 (100.00), 103 (83.75), 91 (14.54), 77 (76.53), 65 (5.14). Anal. calcd for $C_{17}H_{15}BrO_2$: C, 61.64; H, 4.56. Found: C, 61.65; H, 4.80.

4.6.7. (5*R*,1*E*)-5-Hydroxy-5-(2-chlorophenyl)-1-phenyl-1-penten-3-one 12g. Colorless oil; mp 108–109°C; $[\alpha]_D^{27}=+68.9$ (c 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.72 (10H, m, ArH, ArCH=), 6.75 (1H, d, $J=16.5$ Hz, ArCH=CHCO), 5.62 (1H, dd, $J=9.6$ Hz, ArCH), 3.29 (1H, dd, $J=17.1$ Hz, $CHCH_2CO$), 2.90 (1H, dd, $J=17.4$ Hz, $CHCH_2CO$); IR (film): 3238, 3059, 2926, 1678, 1606, 1351, 1107, 977, 753, 692 cm^{-1}; EIMS (m/z): 286 (M^+) (0.72), 251 (64.56), 233 (24.20), 154 (15.95), 145 (37.40), 139 (45.94), 131 (100.00), 115 (19.21), 103 (72.43), 77 (77.53), 65 (4.71). Anal. calcd for $C_{17}H_{15}ClO_2$: C, 71.21; H, 5.27. Found: C, 70.83; H, 5.36.

4.6.8. (5*R*,1*E*)-5-Hydroxy-5-(2,4-dichlorophenyl)-1-phenyl-1-penten-3-one 12h. Colorless solid; mp >210°C (decomposition); $[\alpha]_D^{27}=+92.0$ (c 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.27–7.66 (9H, m, ArH, ArCH=), 6.74 (1H, d, $J=15.9$ Hz, ArCH=CHCO), 5.55 (1H, dd, $J=9.6$ Hz, ArCH), 3.25 (1H, dd, $J=17.7$ Hz, $CHCH_2CO$), 2.86 (1H, dd, $J=18.0$ Hz, $CHCH_2CO$); IR (film): 3274, 3084, 3029, 1677, 1604, 1101, 988, 980, 748, 691 cm^{-1}; EIMS (m/z): 303 (3.78), 267 (12.07), 173 (100.00), 145 (91.13), 131 (85.82), 111 (18.49), 103 (92.33), 85 (5.80), 77 (46.85). Anal. calcd for $C_{17}H_{14}Cl_2O_2$: C, 63.57; H, 4.39. Found: C, 63.19; H, 4.44.

4.6.9. (5*R*,1*E*)-5-Hydroxy-5-(2-furyl)-1-phenyl-1-penten-3-one 12i. Pale yellow oil; $[\alpha]_D^{27}=+33.7$ (c 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.55–7.64 (3H, m, ArH, ArCH=), 7.40–7.42 (4H, m, ArH), 6.76 (1H, d, $J=16.2$ Hz, ArCH=CHCO), 6.34 (2H, d, $J=7.8$ Hz, ArH), 5.29 (1H, d, $J=6.9$ Hz, ArCH), 3.15–3.35 (2H, m, $CHCH_2CO$); IR (film): 3430, 3120, 3084, 2923, 1653, 1609, 1181, 1012, 979, 748, 691 cm^{-1}; EIMS (m/z): 242 (M^+) (10.84), 205 (27.24), 145 (27.72), 131 (100.00), 110 (91.33), 103 (66.33), 97 (22.53), 91 (19.11), 77 (51.33), 65 (8.66). HRMS calcd for $C_{15}H_{14}O_3$: 242.0943. Found: 242.0908.

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