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The synthesis of 1-hydroxy phosphonates of high enantiomeric excess using sequential asymmetric reactions: titanium alkoxide-catalyzed P–C bond formation and kinetic resolution

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Abstract—Titanium alkoxide-catalyzed asymmetric phosphonylation of aldehydes yields hydroxy phosphonates in moderate to good enantiomeric excess (e.e.s $\sim$70%). The hydroxy phosphonates were acetylated and the acetates were subjected to enzyme-catalyzed kinetic resolution. The non-racemic acetates **2** (predominantly (*R*)-enantiomer) were hydrolyzed with an (*R*)-enantiomer-selective lipase, resulting predominantly in the hydrolysis of the (*R*)-isomer (at 85% conversion) to give the alcohols **3** with high e.e. Alternatively, hydrolysis of the minor enantiomeric (*S*)-acetate to approximately 20% conversion left the enriched (*R*)-configured acetate with improved e.e. (>90%). The moderate enantioselectivities obtained in the catalytic P–C bond formation are enhanced during the enzymatic hydrolysis. Furthermore, availability of the non-racemic phosphonates permits the use of less selective enzymes, resulting in higher yields in comparison with the standard resolution of racemic materials.

1. Introduction

A major emphasis in the development of new organic reactions is the control of absolute stereochemistry via chiral catalysts. While there are some truly outstanding systems, many others fall short of the desired levels of enantioselectivity when applied to a wide range of substrates.[1]

For almost ten years there has been an interest in the asymmetric synthesis of hydroxy phosphonates,[2] precipitated not only by their biological activity,[3] but also because they are attractive precursors to other α- and γ-substituted phosphonates.[4] Hammerschmidt et al. have investigated enzymatic routes to hydroxy phosphonates extensively,[5] while ourselves and others have studied asymmetric catalysis.[6] Both methods have attained varying levels of success, but a general, reproducible, high yielding and highly selective method is still unavailable.

In 1982, Sih et al. reported a set of equations for describing the course of an enantioselective enzyme-catalyzed hydrolysis.[7a] The substrate–enzyme combination reacting under a given set of conditions is characterized by the enantioselectivity ratio, *E*, which is related to the ratio of the rates for the fast and slow reacting enantiomers. In general for successful resolutions, an *E* of >100 is required. However, it was shown that enzymes with low *E* values could still be useful by cycling the materials through multiple enzymatic hydrolysis reactions, where each cycle leads to an increase in e.e.[7] It appeared evident from these recycling experiments that enzymatic hydrolysis of non-racemic substrates would allow the use of less selective enzymes and result in higher conversion and selectivity when compared to a similar resolution of racemic materials. Thus, it was proposed that an additional enzyme-mediated resolution could be used to enhance the e.e. of the non-racemic 1-hydroxy phosphonates formed by asymmetric catalysis.

Although it has been recognized[8] that the coupling of two asymmetric reactions[9] or an asymmetric reaction and a resolution[10] can lead to the efficient formation of compounds with high e.e., this combination of techniques has not been widely applied. We report herein that a combination of asymmetric catalysis and enzyme-catalyzed kinetic resolution (Scheme 1) leads to the first reliable, high yielding synthesis of 1-hydroxy phosphonates with high enantiopurity.

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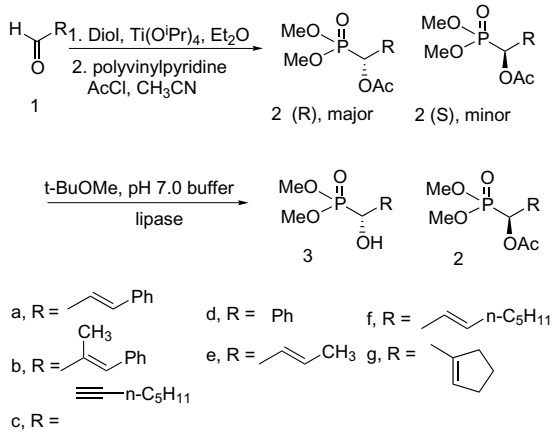


Scheme 1.

2. Results and discussion

An initial screening was used to identify an optimal enzyme system for each phosphonate. Racemic hydroxy phosphonates[11] were acetylated with AcCl/polyvinylpyridine in CH_3CN (>90% yield). A bank of 33 lipase enzymes was screened with the acetate derivatives **2** for enantioselective hydrolysis. The screening was performed on a 0.1 mmol ($\approx$25 mg) sample in 7 mL vials with 16 units of enzyme. Three to five samples of each reaction were taken over a 64 hour period and the results derived directly from HPLC analysis on the crude samples. The data obtained from HPLC were plotted over a graph of the theoretical reaction profiles[7] to estimate values of E and reaction rates (Fig. 1). Enzyme systems exhibiting good enantioselectivities and good reaction rates were used to treat the non-racemic substrates. The amount of enzyme used was adjusted to achieve complete reaction in a reasonable period of time, but no further effort was made to optimize the reaction conditions. While it would have been more efficient to combine asymmetric catalysis with an enantioselective enzyme-catalyzed acetylation, an efficient enzyme system for acylating 1-hydroxy phosphonates was not found.[12]

The non-racemic hydroxy phosphonates were prepared in 70–95% isolated yields and e.e.s of 60–77% by the titanium alkoxide-catalyzed addition of dimethyl phosphite to the aldehyde (Scheme 1) using either cyclohexanediol or dimethyl tartrate as the chiral ligands.[6a,13] It was expected that reaction of the non-racemic acetates **2** ((*R*)-predominant) with an (*R*)-enantiomer-selective lipase would result predominantly in the hydrolysis of the (*R*)-isomer (at 85% conv.) to give the alcohols **3** with high e.e. A 0.1 mmol sample of acetate **2a** ((*R*)-enantiomer, 65% e.e.) was treated with lipase from *Pseudomonas* sp. The reaction (Fig. 2) was followed by HPLC. The data points[14] follow closely to the theoretical prediction. In a similar preparative scale hydrolysis of acetate **2a** (73% e.e.), the reaction was stopped at 80% conversion to give, after chromatographic separation, the hydroxy phosphonate **3a** in 99% e.e. The acetates **2b**, **2c**, and **2d** were treated similarly (Table 1) to give hydroxy phosphonates in e.e. of 92–99%.

Since enzymes are selective for a single enantiomer it was necessary to examine cases where the minor isomer was hydrolyzed preferentially. It was expected that hydrolysis of the (*S*)-acetate (approx. 20% conv.) would leave the enriched (*R*)-acetate with improved e.e.

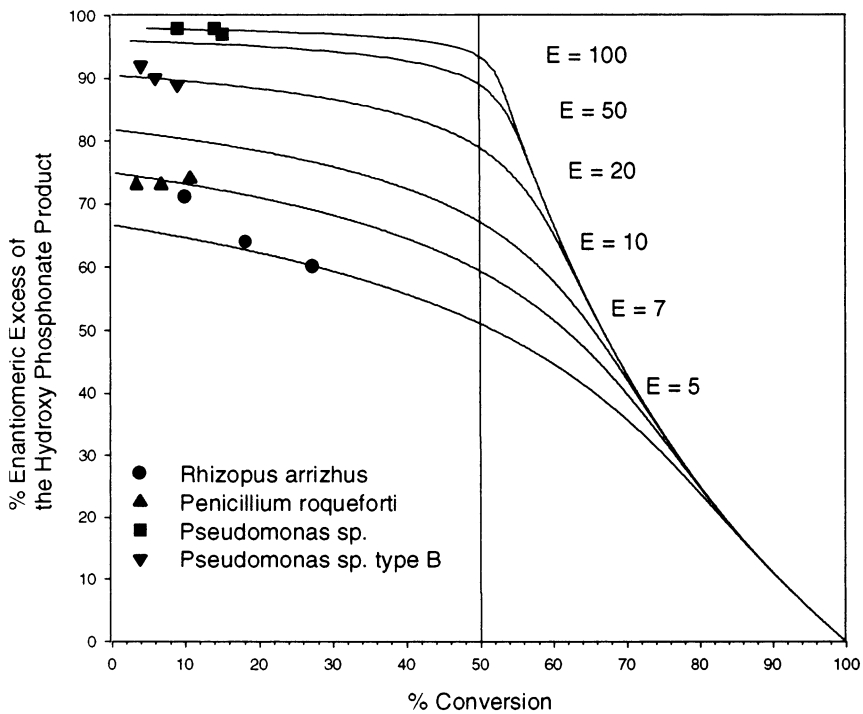


Figure 1. A comparison of the theoretically derived curves and experimental data points for enzyme-catalyzed kinetic resolution of racemic acetoxy phosphonate **2a** with four enzymes.

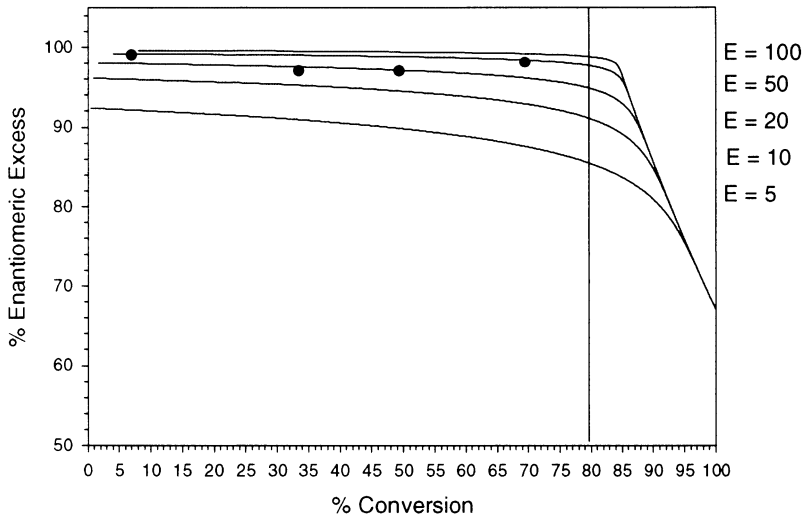
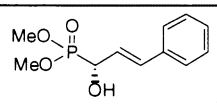
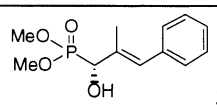
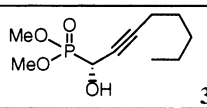
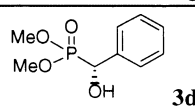


Figure 2. Theoretical and experimental data for an enzyme-catalyzed kinetic resolution of non-racemic acetoxy phosphonate **2a** (65% e.e. (*R*)) with an enzyme selective for the major (*R*)-enantiomer.

Table 1. Hydrolysis of the major enantiomer

Product	Enzyme E, Config	Initial e.e. (config)	% Yield (e.e.)
 **3a**	*Pseudomonas sp.* E = 100, *R*	73% (*R*)	68 (>99)
 **3b**	Lipase PSCII E = 20, *R*	77% (*R*)	75 (>99)
 **3c**	Lipase AY E = 20, *R*	49% (*R*)	59 (92)
 **3d**	Pseudomonas *sp.* type B E = 19, *R*	70% (*R*)	72 (>99)

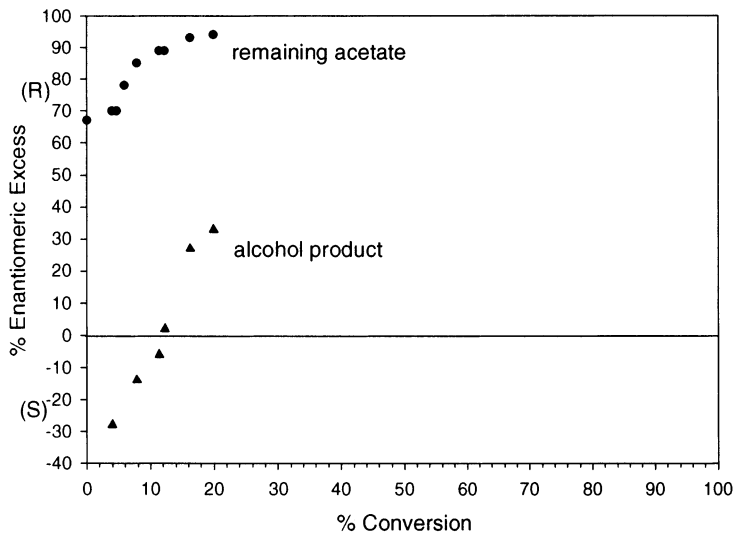
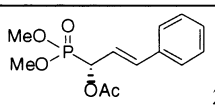
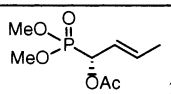
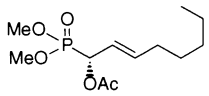
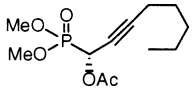
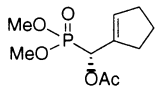


Figure 3. Experimental data for an enzyme-catalyzed kinetic resolution of non-racemic acetoxy phosphonate **2a** (67% e.e. (*R*)) with an enzyme selective for the minor (*S*)-enantiomer.

Table 2. Hydrolysis of the minor enantiomer

Product	Enzyme E, Config	Initial e.e. (config)	% Yield (e.e.)
 **2a**	*Rhizopus arrizhus* E = 6, *S*	73% (*R*)	70 (91)
 **2e**	F-AP15 E = 20, *S*	64% (*R*)	79 (97)
 **2f**	F-AP15 E = 11, *S*	69% (*R*)	74 (95)
 **2c**	*Rhizopus arrizhus* (E = 15, *S*)	49% (*R*)	74 (90)
 **2g**	F-AP15 E = 22, *S*	42% (*R*)	72 (79)

(>90%). A sample of acetate **2a** (67% e.e.) was treated with lipase from *Penicillium roqueforte* ($E=7$). The e.e. (from HPLC) for both the acetoxy phosphonate **2a** and the hydroxy phosphonate **3b** were plotted against conversion (Fig. 3). The graph clearly shows the expected enhancement in the e.e. of the acetate **2a**. On a preparative scale, the acetate **2a** (73% e.e.) was treated with a more active lipase (from *Rhizopus arrizhus*), and reaction stopped at 20% conversion. Separation of the acetate **2a** and alcohol **3a** by chromatography gave the acetoxy phosphonate in 70% yield and greatly improved enantiopurity (91%). Other examples (Table 2) proved equally successful with the more selective enzymes (e.g. **2e**) giving the higher e.e.

In summary, in this synthesis of 1-hydroxy phosphonates, the moderate enantioselectivities encountered in the catalytic P–C bond formation are enhanced by the enzymatic hydrolysis. Furthermore, the availability of the non-racemic phosphonates allows for the use of less selective enzymes and results in higher yields than those achieved with the standard resolutions of racemic materials.

3. Experimental

3.1. General experimental procedures

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian XL-300, a Varian UNITY-*plus* 300 or a Bruker ARX-500 spectrometer in $CDCl_3$. ^{1}H NMR spectra are referenced to internal tetramethylsilane (TMS, $\delta=0.00$), ^{13}C NMR spectra to the center line of $CDCl_3$ (77.23 ppm) and ^{31}P NMR spectra to external 85% H_3PO_4. Coupling constants, J, are reported in Hz. Infrared spectra were recorded on a Perkin–Elmer Model 1600 FT-IR spectrometer. Enantiomer ratios were measured by chiral stationary-phase HPLC on a Regis (*S*,*S*)-Whelk-O 1 column or a Daicel Chiralpak AS column. Optical rotations were determined using a Rudolf Research Autopol III automatic polarimeter set at 589 nm. Mass spectral analyses were performed using a JEOL MStation (JMS-700) mass spectrometer. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA. The enzymes were purchased from Fluka chemical Co (basic and extended lipase kits: *Aspergillus niger*, *Candida antartica*, *Candida cylindracea*, *Mucor miehei*, *Pseudomonas cepacia*, *Pseudomonas fluorescens*, *Rhizopus arrihzus*, *Rhizopus niveus*, hog pancreas, *Aspergillus oryzae*, *Candida lipolytica*, *Mucor javanicus*, *Penicillium roqueforti*, *Pseudomonas fluorescens* (purified), *Rhizomucor miehei*, wheat germ, *Chromobacterium viscosum*, *Pseudomonas* sp., and *Pseudomonas* sp., type B). Additional enzymes were generously donated by Amano Co. ltd., USA (lipases F-AP15, R, A, G, M, AY, AK, PS, CHE, and PGE, Newlase F, and immobilized lipases PS-CI, PS-CII, PS-DI).

The racemic hydroxy phosphonates were prepared by reacting dimethyl phosphite with an aldehyde using either triethylamine[11] or titanium *iso*-propoxide as catalyst. Non-racemic hydroxy phosphonates were prepared by the titanium alkoxide-catalyzed addition of dimethyl phosphite to the aldehyde using either cyclohexanediol[6a] or dimethyl tartrate as the chiral ligands.[13]

3.2. Preparation of (±)-hydroxy phosphonates

Distilled $Ti(O^iPr)_4$ (20 mol%) was added to a solution of dimethyl phosphite (2 equiv.) in freshly distilled CH_2Cl_2 at 0°C. The solution was stirred for 30 min, then the aldehyde (1 equiv.) was added. When the reaction was complete, as indicated by TLC (SiO_2, EtOAc:hexane, 50:50), the mixture was diluted further with CH_2Cl_2 and washed with H_2O. The layers were

separated and the H_2O layer was re-extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with H_2O, dried ($MgSO_4$) and evaporated in vacuo to give the crude hydroxy phosphonates. Purification by column chromatography (SiO_2, gradient EtOAc:hexanes, 50:50 to 100% EtOAc) gave the pure α-hydroxy phosphonates.

3.3. General procedures for the preparation of the non-racemic hydroxy phosphonates

Method A:[6a] To a solution of anhydrous (1*S*,2*S*)-*trans* 1,2-cyclohexanediol (49.9 mg, 430 μmol) in freshly distilled Et_2O (3.5 mL) was added distilled $Ti(O^iPr)_4$ (116 μL, 391 μmol). The mixture was stirred for 30 min to insure complete complexation (diol dissolves). The aldehyde (2 mmol) was added, followed by distilled dimethyl phosphite (216 μL, 2.4 mmol). The flask was placed in a freezer (approx. −15°C). When the reaction was complete, as indicated by TLC (SiO_2, EtOAc:hexane, 50:50), the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with deionized H_2O (60 mL). The CH_2Cl_2 layer was collected and the aqueous layer was extracted further with CH_2Cl_2 (50 mL). The extracts were combined and washed with deionized H_2O (50 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by column chromatography (SiO_2, gradient EtOAc:hexanes, 1:1 to 100% EtOAc) gave the pure α-hydroxy phosphonates.

Method B:[13] To a solution of dimethyl-L-tartrate (20 mol%) in freshly distilled diethyl ether (total conc. = 0.06 M) was added distilled $Ti(O^iPr)_4$ (20 mol%). The mixture was stirred at −15°C for 30 minutes to ensure complete complexation. The aldehyde (40 mmol) was added and the mixture was stirred for an additional 15 minutes. Dimethyl phosphite (80 mmol) was added and the reaction mixture was placed in the freezer (approx. −15°C). After the reaction was complete, as indicated by TLC (SiO_2, EtOAc:hexane, 1:1), the reaction mixture was treated with deionized H_2O and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give crude product. Purification by column chromatography (SiO_2, gradient EtOAc:hexanes, 1:1 to 100% EtOAc) gave the pure α-hydroxy phosphonates.

3.4. (±)-Dimethyl (1-hydroxy-3-phenyl-2*E*-propenyl) phosphonate 3a[6,11,15]

89% yield, mp 101°C; literature[1] 101°C; ^{1}H NMR ($CDCl_3$) δ 7.42–7.38 (m, 2H), 7.34–7.22 (m, 3H), 6.80 (ddd, J_{HH} = 15.6, 1.5 Hz, J_{HP} = 4.9 Hz, 1H), 6.35 (ddd, J_{HH} = 15.9, 6.2 Hz, J_{HP} = 5.6 Hz, 1H), 4.73 (ddd, J_{HH} = 12.9, 1.6, J_{HP} = 6.2 Hz, 1H), 3.85 (d, J_{HP} = 10.3 Hz, 3H), 3.81 (d, J_{HP} = 10.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 136.1 (d, J_{CP} = 2.9 Hz), 132.2 (d, J_{CP} = 13 Hz), 128.4, 127.8, 126.5, 123.5 (d, J_{CP} = 4.3 Hz), 69.2 (d, J_{CP} = 161 Hz), 53.9 (d, J_{CP} = 7.1 Hz), 53.7 (d, J_{CP} = 7.4 Hz); ^{31}P NMR ($CDCl_3$) δ 23.8.

3.5. (±)–Dimethyl (1-hydroxy-2-methyl-3-phenyl-2*E*-propenyl) phosphonate 3b[6d]

87% yield, mp 73–75°C; ^{1}H NMR ($CDCl_3$) δ 7.38–7.22 (m, 5H), 6.68 (dd, J_{HH} = 1.3, J_{HP} = 5.0 Hz, 1H), 4.57 (d, J_{HP} = 12.8 Hz, 1H), 3.84 (d, J_{HP} = 10.5 Hz, 3H), 3.83 (d, J_{HP} = 10.4 Hz, 3H), 2.03 (dd, J_{HP} = 3.0, J_{HH} = 1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.0, 133.3 (d, J_{CP} = 4.7 Hz), 129.2 (d, J_{CP} = 2.7 Hz), 128.5 (d, J_{CP} = 12 Hz), 128.3, 127.0, 74.0 (d, J_{CP} = 156 Hz), 54.1 (d, J_{CP} = 6.8 Hz), 53.8 (d, J_{CP} = 7.3 Hz), 15.62 (d, J = 2.2 Hz); ^{31}P NMR ($CDCl_3$) δ 24.6.

3.6. (±)-Dimethyl (1-hydroxy-2*E*-butenyl) phosphonate 3e[5]

89% yield, pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 1H), 5.62 (m, 1H), 4.45 (m, 1H), 3.85 (d, J_{HP} = 10.4 Hz, 3H), 3.84 (d, J_{HP} = 10.4 Hz, 3H), 1.76 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.9 (d, J = 14 Hz), 125.5, 69.0 (d, J = 162 Hz), 53.6 (d, J = 7.2 Hz), 53.5 (d, J = 7.2 Hz), 18.1; ^{31}P NMR ($CDCl_3$) δ 24.8.

3.7. (±)-Dimethyl (1-hydroxy-2*E*-octenyl) phosphonate 3f[4a]

84% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.88–5.76 (m, 1H), 5.58–5.48 (m, 1H), 4.40–4.34 (m, 1H), 3.74 (d, J_{HP} = 9.6 Hz, 3H), 3.74 (d, J_{HP} = 10.6 Hz, 3H), 3.36 (brd s, 1H), 2.06–1.98 (m, 1H), 1.36–1.19 (2m, 6H), 0.81 (t, J_{HH} = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.8 (d, J_{CP} = 13.3 Hz), 123.8 (d, J_{CP} = 3.7 Hz), 69.3 (d, J_{CP} = 161 Hz), 53.7 (d, J_{CP} = 7.0 Hz), 53.6 (d, J_{CP} = 7.2 Hz), 32.4, 31.4, 28.6 (d, J_{CP} = 2.8 Hz), 22.6, 14.1; ^{31}P NMR ($CDCl_3$) δ 24.8.

3.8. (±)-Dimethyl (1-hydroxy-oct-2-ynyl) phosphonate 3c[4a]

82% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.69 (m, 1H), 3.89 (d, J_{HP} = 10.2 Hz, 3H), 3.88 (d, J_{HP} = 10.5 Hz, 3H), 2.25 (m, 2H), 1.53 (m, 2H), 1.42–1.27 (m, 4H), 0.90 (t, J_{HH} = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 89.4 (d, J_{CP} = 11.5 Hz), 74.1, 58.8 (d, J_{CP} = 171.2 Hz), 54.4 (d, J_{CP} = 7.1 Hz), 54.2 (d, J_{CP} = 7.0 Hz), 30.9, 28.0 (d, J_{CP} = 2.6 Hz), 22.1, 18.8 (d, J_{CP} = 2.6 Hz), 13.9; ^{31}P NMR ($CDCl_3$) δ 20.6.

3.9. (±)-Dimethyl (phenylhydroxymethyl) phosphonate 3d[5,6,11]

93% yield, mp 102°C; literature[1] 102–103°C; ^{1}H NMR ($CDCl_3$) δ 7.50–7.27 (m, 2H), 7.40–7.25 (m, 3H), 5.06 (d, J_{HP} = 11.2 Hz, 1H), 3.70 (d, J_{HP} = 10.5 Hz, 3H), 3.67 (d, J_{HP} = 10.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 136.5 (d, J_{CP} = 1.8 Hz), 128.5 (d, J_{CP} = 2.6 Hz), 128.3 (d, J_{CP} = 3.2 Hz), 127.2 (d, J_{CP} = 5.8 Hz), 70.8 (d, J_{CP} = 159 Hz), 54.1 (d, J_{CP} = 7.0 Hz), 54.0 (d, J_{CP} = 7.5 Hz); ^{31}P NMR ($CDCl_3$) δ 24.3.

3.10. (±)-Dimethyl [(1-cyclopentenyl)-hydroxymethyl] phosphonate 3g

65% yield, pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.87 (m, 1H), 4.64 (d, J_{HP} = 12.7 Hz, 1H), 3.80 (d, J_{HP} = 10.4 Hz,

3H), 3.79 (d, $J_{HP}=10.4$ Hz, 3H), 2.55–2.33 (m, 4H), 1.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 139.5 (d, $J_{CP}=3.1$ Hz), 128.9 (d, $J_{CP}=11.5$ Hz), 67.9 (d, $J_{CP}=160$ Hz), 53.61 (d, $J_{CP}=8.0$ Hz), 53.60 (d, $J_{CP}=8.0$ Hz), 32.6 (d, $J_{CP}=11.6$ Hz), 32.5 (d, $J_{CP}=11.5$ Hz), 23.4; ^{31}P NMR ($CDCl_3$) δ 24.5.

3.11. General procedure for the acetylation of α-hydroxy phosphonates

To a cooled (ice bath), stirred suspension of poly (4-vinyl) pyridine (1.2 equiv.) in dry CH_3CN (10 mL) was added acetyl chloride (2.0 equiv.) followed by hydroxy phosphonate. The suspension was stirred at room temperature until the reaction was complete, as indicated by TLC (SiO_2, EtOAc). The reaction was filtered to remove the polymer and the solvent was removed in vacuo. The residue was adsorbed onto SiO_2 and filtered through a short plug of SiO_2 eluting with EtOAc to give, after evaporation of the solvent in vacuo, the pure acetates.

3.12. Dimethyl (1-acetoxy-3-phenyl-2*E*-propenyl) phosphonate 2a

99% yield, colorless oil; IR (NaCl neat) 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.23 (m, 5H), 6.76 (ddd, $J_{HH}=16$, 1.1, $J_{HP}=4.2$ Hz, 1H), 6.30–6.20 (ddd, $J_{HH}=16$, 6.2, $J_{HP}=5.3$ Hz, 1H), 5.89 (ddd, $J_{HH}=7.5$, 1.1, $J_{HP}=13.9$ Hz, 1H), 3.82 (d, $J_{HP}=10.7$ Hz, 3H), 3.80 (d, $J_{HP}=10.6$ Hz, 3H) 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0 (d, $J_{CP}=7.7$ Hz), 135.4, 135.3 (d, $J_{CP}=12.9$ Hz), 128.5, 128.4, 126.8, 119.6 (d, $J_{CP}=4.6$ Hz), 70.0 (d, $J_{CP}=170$ Hz), 53.8 (d, $J_{CP}=6.5$ Hz), 53.7 (d, $J_{CP}=6.9$ Hz), 20.9; ^{31}P NMR ($CDCl_3$) δ 20.7.

3.13. Dimethyl (1-acetoxy-2-methyl-3-phenyl-2*E*-propenyl) phosphonate 2b

98% yield, colorless oil; IR (NaCl neat) 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.21 (m, 5H), 6.77 (d, $J_{HP}=4.8$ Hz, 1H), 5.71 (dd, $J_{HH}=0.9$, $J_{HP}=14.2$ Hz, 1H), 3.85 (d, $J_{HP}=10.7$ Hz, 3H), 3.81 (d, $J_{HP}=10.7$ Hz, 3H) 2.19 (s, 3H), 2.05 (dd, $J_{HH}=1.38$, $J_{HP}=3.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2 (d, $J_{CP}=8.8$ Hz), 136.5 (d, $J_{CP}=2.5$ Hz), 130.5 (d, $J_{CP}=4.2$ Hz), 130.4 (d, $J_{CP}=11.6$ Hz), 129.1, 129.0, 128.3, 127.2, 73.2 (d, $J_{CP}=168$ Hz), 54.1 (d, $J_{CP}=7.1$ Hz), 54.0 (d, $J_{CP}=6.5$ Hz), 21.1, 15.82 (d, $J_{CP}=2.3$ Hz); ^{31}P NMR ($CDCl_3$) δ 20.8.

3.14. Dimethyl (1-acetoxy-2*E*-butenyl) phosphonate 2e

96% yield, pale yellow oil. IR (NaCl neat) 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00–5.87 (m, 1H), 5.69–5.51 (m, 2H), 3.81 (d, $J_{HP}=10.7$ Hz, 3H), 3.79 (d, $J_{HP}=10.7$ Hz, 3H), 2.14 (s, 3H), 1.76 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.1 (d, $J_{CP}=7.9$ Hz), 133.3 (d, $J_{CP}=12.9$ Hz), 121.9 (d, $J_{CP}=4.0$ Hz), 68.9 (d, $J_{CP}=170$ Hz), 53.8 (d, $J_{CP}=7.0$ Hz), 53.7 (d, $J_{CP}=6.5$ Hz), 20.9, 18.1 (d, $J_{CP}=1.5$ Hz); ^{31}P NMR ($CDCl_3$) δ 21.3.

3.15. Dimethyl (1-acetoxy-2*E*-octenyl) phosphonate 2f

91% yield, pale yellow oil. IR (NaCl neat) 1751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.97–5.85 (m, 1H), 5.69–5.63 (m, 1H), 5.57–5.47 (m, 1H), 3.81 (d, $J_{HP}=10.7$ Hz), 3.78 (d, $J_{HP}=10.6$ Hz), 2.14 (s, 3H), 2.13–2.09 (m, 2H), 1.42–1.26 (2m, 6H), 0.88 (t, $J_{HH}=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2 (d, $J_{CP}=8.0$ Hz), 138.6 (d, $J_{CP}=12.6$ Hz), 120.6 (d, $J_{CP}=4.0$ Hz), 69.2 (d, $J_{CP}=170$ Hz), 53.9 (d, $J_{CP}=7.0$ Hz), 53.8 (d, $J_{CP}=6.4$ Hz), 32.6, 31.5, 28.6, 22.7, 21.2, 14.3; ^{31}P NMR ($CDCl_3$) δ 21.4.

3.16. Dimethyl (1-acetoxy-2-octynyl) phosphonate 2c

90% yield, pale yellow oil. IR (NaCl neat) 1756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (dt, $J_{HH}=2.3$, $J_{HP}=16.2$ Hz, 1H), 3.90 (d, $J_{HP}=10.7$ Hz, 3H), 3.86 (d, $J_{HP}=10.7$ Hz, 3H), 2.28–2.20 (m, 2H), 2.16 (s, 3H), 1.60–1.45 (m, 2H), 1.40–1.28 (m, 4H), 0.89 (t, $J_{HH}=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0 (d, $J_{CP}=7.8$ Hz), 90.4 (d, $J_{CP}=9.3$ Hz), 71.2 (d, $J_{CP}=6.1$ Hz), 58.8 (d, $J_{CP}=177$ Hz), 54.6 (d, $J_{CP}=8.0$ Hz), 54.5 (d, $J_{CP}=6.3$ Hz), 31.2, 28.1, 22.3, 20.9, 19.1, 14.2; ^{31}P NMR ($CDCl_3$) δ 17.1.

3.17. Dimethyl phenyl(acetoxy)methyl phosphonate 3d

90% yield, colorless oil; ^1H NMR ($CDCl_3$) δ 7.50–7.46 (m, 2H), 7.40–7.30 (m, 3H), 6.17 (d, $J_{HP}=13.5$ Hz, 1H), 3.75 (d, $J_{HP}=10.7$ Hz, 3H), 3.64 (d, $J_{HP}=10.6$ Hz, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0 (d, $J_{CP}=8.7$ Hz), 133.1 (d, $J_{CP}=1.9$ Hz), 128.4 (d, $J_{CP}=2.8$ Hz), 128.1 (d, $J_{CP}=2.2$ Hz), 127.4 (d, $J_{CP}=5.7$ Hz), 69.7 (d, $J_{CP}=169$ Hz), 53.9 (d, $J_{CP}=7.1$ Hz), 53.8 (d, $J_{CP}=7.4$ Hz), 20.5; ^{31}P NMR ($CDCl_3$) δ 20.5.

3.18. Dimethyl [(1-cyclopentenyl)acetoxymethyl] phosphonate 2g

93% yield, pale yellow oil; IR (NaCl neat) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88–5.82 (m, 2H), 3.82 (d, $J_{HP}=10.6$ Hz, 3H), 3.78 (d, $J_{HP}=10.7$ Hz, 3H), 2.50–2.34 (m, 4H), 2.15 (s, 3H), 1.97–1.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 169.30 (d, $J_{HP}=8.0$ Hz), 136.0 (d, $J_{CP}=4.1$ Hz), 131.1 (d, $J_{CP}=10.6$ Hz), 67.8 (d, $J_{CP}=169$ Hz), 53.9 (d, $J_{CP}=7.0$ Hz), 53.7 (d, $J_{CP}=6.5$ Hz), 33.0 (d, $J_{CP}=2.5$ Hz), 32.7 (d, $J_{CP}=2.2$ Hz), 23.3, 21.0; ^{31}P NMR ($CDCl_3$) δ 20.6.

3.19. Lipase activity screen on racemic hydroxy phosphonates

The lipase enzymes were weighed into 7 mL vials and dissolved in pH 7.0 phosphate buffer (1.8 mL). Stock solutions of the racemic acetates were prepared by dissolution in *t*-butyl methyl ether (0.25 M). To each vial was added a sample of the acetate solution (0.4 ml). The vials were shaken and the pH was adjusted to 7.0 with either aqueous 1 M NaOH or 1 M K_2PO_4 solution. The vials were agitated on a rotating shaker, and aliquots were removed by dipping the tip of a glass pipette into the solution and allowing a small amount of the organic phase to be drawn up. The aliquots were diluted with EtOH and analyzed directly by HPLC.

Table 3. Preparative scale reaction conditions and results

Compd.	Amount (mg)	Enzyme (Units/mg)	Amount mg (Units)	Yield mg (%)	E.e. (%)	$[\alpha]_D$, conc. solvent (at 20°C in EtOH)
3a	500	*Pseudomonas* sp. (1500)	30 (45,000)	290 (68)	99	+38.5, $c=1$ {+23.0, $c=1$, $CHCl_3$, Ref. 14}
3b	270	Lipase PSCII (30)	200 (6000)	175 (75)	99	+4.0, $c=0.5$
3c	350	Lipase AY (42)	250 (10,500)	175 (59)	92	+25.9, $c=1$
3d	250	*Pseudomonas* sp. type B (160)	15 (2400)	150 (72)	99	+39.4, $c=1$
2a	505	*Rhizopus arrizhus* (0.002)	350 (0.7)	300 (70)	90	+58.2, $c=1$
2c	500	*Rhizopus arrizhus* (0.002)	868 (1.74)	302 (74)	90	+42.1, $c=1$
2e	331	F-AP15 (150)	300 (45,000)	213 (79)	97	+29.3, $c=1$
2f	250	F-AP15 (150)	300 (45,000)	157 (74)	95	+23.4, $c=2.0$
2g	258	F-AP15 (150)	300 (45,000)	155 (72)	79	+16.0, $c=1$

The e.e.s of the hydroxy and acetoxy phosphonate products were determined by HPLC; compounds **2a** and **3a** on a Whelk-O column with EtOH:hexanes, 1:4 (1 mL/min) detected at 254 nm; **3b** on a Whelk-O column with EtOH:hexanes, 1:9 (1 mL/min) detected at 254 nm; **2c**, **2e**, **3c**, and **3g** on a Spherisorb silica column in tandem with a ChiralPak AS column with ^{i}PrOH:hexanes, 1:4 (1 mL/min) detected at 205 nm; **2f** on a ChiralPak AS column with EtOH:hexanes, 1:9 (0.5 mL/min) detected at 205 nm; and **3d** on a Whelk-O column with EtOH:hexanes, 1:9 (1 mL/min) detected at 210 nm. The enantiomers of acetate **2g** were not separable by HPLC on either the ChiralPak AS or Whelk-O columns. The acetate was hydrolyzed using the non-selective lipase from wheat germ and the e.e. of the product hydroxy phosphonate was determined by ^{31}P NMR spectroscopy using quinine as the shift reagent.[16]

3.20. Kinetic resolution of non-racemic acetoxy phosphonates

A solution of the acetates (200–500 mg) in *t*-BuOMe (2–3 mL) was added to a solution of the enzyme (300–1500 U) in pH 7.0 phosphate buffer (2–3 mL) (see Table 1 for quantities). The mixture was agitated on a rotating shaker at room temperature (40°C for Amano enzymes) and the conversion and % e.e. were monitored by HPLC. When approximately 80% of the acetate (or 20–25% for *S* selective enzymes) had been hydrolyzed the reaction mixture was extracted with CH_2Cl_2 (5×20 mL). The combined CH_2Cl_2 extracts were dried and evaporated in vacuo. The products were isolated by column chromatography (SiO_2, EtOAc) and the e.e. was re-determined by HPLC (Table 3).

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