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Determination of the Enantiomeric Purity and Absolute Configuration of α-Hydroxy Phosphonates

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Abstract: The absolute configuration of α-hydroxy phosphonates was determined by NMR spectroscopy of the O-methyl mandelate ester derivatives. The O-methyl mandelate ester diastereoisomers are distinguishable by their ^{1}H and ^{31}P NMR spectra and the observed chemical shifts allow assignment of the absolute configuration of the phosphonate C-1. The crystal structure of (1R) dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-3-phenyl-2*E*-propenyl phosphonate was determined by X-ray diffraction. The enatiomers were separable by HPLC on a chiral stationery phase and therefore the enantiomeric purity of the hydroxy phosphonates could accurately be determined.

INTRODUCTION

α-Hydroxy phosphonates and phosphonic acids have become increasingly important for their biological activity[1] and as convenient intermediates in the synthesis of other α, and γ substituted phosphonates.[2,3] The absolute configuration at the α-position in substituted phosphonic acids has been shown to be important for biological activity.[4] Accordingly, several methods have been reported for the synthesis of optically active α-hydroxy phosphonates.[5] We recently began to explore methods for the asymmetric synthesis of α-hydroxy phosphonates and required a reliable method for the determination of enantiomeric purity and absolute configuration.[6] Previously reported methods for the determination of the enantiomeric purity of α-hydroxy phosphonates include the formation of Mosher esters,[5c,d,l] phosphonodidepsipeptides,[7] and chiral ammonium salts (of the phosphonic acids),[8] whereas the absolute configuration has been elucidated by X-ray diffraction,[2a,5e] chemical correlation and comparison of optical rotations,[5a,c,e,i,l] Horeau's method,[5c] circular dichroism,[5e,k,l] and most recently by ^{31}P NMR spectroscopy of the Mosher ester derivatives.[9]

In 1986, Trost *et al* reported[10] three mild procedures for the formation of the O-methyl mandelate esters of chiral alcohols. The ^{1}H NMR shifts of the diastereoisomeric O-methyl mandelates were easily distinguished, and were consistent for a given diastereoisomer. The observed upfield shifts for the protons in a given diastereoisomer was attributed to the shielding effect of the mandelate phenyl ring and was used to assign the absolute configuration of the hydroxyl bearing carbon. Trost recently extended this method of assigning

absolute configuration to chiral amines via O-methyl mandelate amide formation.[11] Our approach to α-hydroxy phosphonates has been to use a combination of methods, employing HPLC for rapid accurate analysis of the enantiomeric purity, and O-methyl mandelate ester formation for assigning absolute configuration. Where possible, the absolute configuration has been correlated with X-ray diffraction studies.

RESULTS AND DISCUSSION

The diastereoisomeric (R) O-methyl mandelates of three representative racemic α-hydroxy phosphonates were prepared. (R)-O-Methyl mandelic acid was converted to the corresponding acid chloride by reaction with dimethylchloroiminium chloride in acetonitrile.[10] Addition of the α-hydroxy phosphonates **1**, **2** and **3** in pyridine solution yielded the O-methyl mandelate ester diastereomers **4**, **5** and **6**, respectively. In all three examples, the O-methyl mandelate diastereoisomers were cleanly separated by chromatography on silica gel into the less polar isomers **4a**, **5a**, and **6a** and the more polar isomers **4b**, **5b**, and **6b**.[12]

Scheme 1. Preparation of the O-Methyl Mandelate Esters

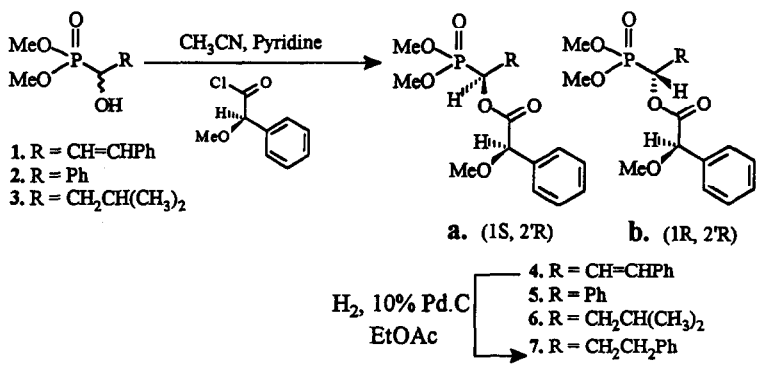


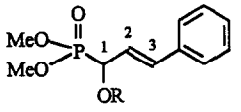
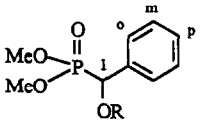
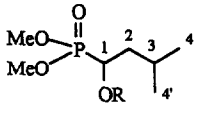
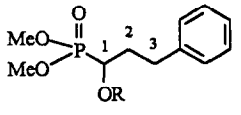
Table 1. ^{31}P NMR shifts of the α-Hydroxy Phosphonates and Their O-Methyl Mandelate Derivatives

Parent alcohol (#), δ ppm	less polar mandelate (#), δ ppm	more polar mandelate (#), δ ppm	Δ,δ (ppm) δ(b) - δ(a)
(1) 24.4	(4a) 19.62	(4b) 19.82	0.20
(2) 24.3	(5a) 18.97	(5b) 19.29	0.32
(3) 28.3	(6a) 22.48	(6b) 23.10	0.62
---	(7a) 22.15	(7b) 22.75	0.60

Both the ^{31}P (Table 1) and ^{1}H NMR (Table 2) spectra revealed some significant differences between the diastereoisomers. The less polar isomers (**4a-6a**) showed upfield shifts for the diastereotopic phosphonate methoxy protons of 0.20 to 0.38 ppm from the parent alcohols. The chemical shift difference for the two methoxy signals had increased to between 0.12 to 0.16 ppm from 0.04 ppm for the corresponding alcohol. The more polar isomer (**4b-6b**) showed an upfield shift of up to 0.57 ppm for protons on the hydrocarbon moiety.

In comparison, the phosphonate methoxy signals had shifted by only 0.03-0.07 ppm with the difference between the two doublets remaining as 0.04 ppm. The ^{31}P NMR signals of the less polar isomer were 0.21-0.62 ppm upfield of the more polar isomer (Table 1).

Table 2. Selected ^{1}H NMR shifts of the α-Hydroxy Phosphonates and Their O-Methyl Mandelate Derivatives

Phosphonate	Proton	Parent Alcohol	less polar Mandelate (a)		more polar Mandelate (b)	
		δ	δ	Δδ	δ	Δδ
 1, R=H; 4, R= O-methylmandelate	MeO	3.85	**3.59**	**0.26**	3.78	0.07
	MeO'	3.81	**3.43**	**0.38**	3.74	0.07
	C(1)-H	4.70	5.88	-1.18	5.93	-1.23
	C(2)-H	6.35	6.24	0.11	**6.11**	**0.23**
	C(3)-H	6.80	6.71	0.09	**6.24**	**0.56**
 2, R = H; 5, R = O-methylmandelate	MeO	3.66	**3.46**	**0.20**	3.63	0.03
	MeO'	3.62	**3.34**	**0.28**	3.60	0.02
	C(1)-H	5.05	6.17	-1.12	6.18	-1.13
	o-H	7.48	7.48	0.0	7.41	0.07
	m,p-H	7.37	7.38	-0.01	7.33(p)	0.04
					7.22(m)	**0.15**
 3, R = H; 6, R = O-methylmandelate	MeO	3.82	**3.53**	**0.29**	3.75	0.07
	MeO'	3.79	**3.41**	**0.38**	3.72	0.07
	C(1)-H	4.0	5.40	-1.40	5.35	-1.35
	C(2)-H	1.95	1.82	0.13	1.73	0.22
	C(3)-H	1.73	1.6	0.13	1.49	0.24
		1.47		-0.13	1.04	0.43
	C(4)-H	0.97	0.92	0.05	**0.68**	**0.29**
	C(4)-H'	0.92	0.88	0.05	**0.65**	**0.27**
 7, R = O-methylmandelate	MeO	--	**3.53**	--	3.74	--
	MeO'	--	**3.40**	--	3.71	--
	C(1)-H	--	5.30	--	5.24	--
	C(2)-H	--	2.16	--	**2.18**	--
	C(3)-H	--	2.62	--	**2.05**	--
	C(3)-H'				**1.99**	--

NMR spectra were recorded in $CDCl_3$; Δδ refers to the chemical shift difference between the parent alchol and the mandelate derivative; +Δδ = upfield shift; -Δδ = downfield shift

The more polar O-methyl mandelate diastereoisomer **4b** of the cinnamyl hydroxy phosphonate was a colorless crystalline solid, mp 87-88 °C. Slow diffusion of hexane into ethyl acetate solution of **4b** gave crystals suitable for X-ray diffraction analysis. The structure (Figure 1) showed that the configuration was

(1R,2'R) and that the mandelate adopted a conformation (in solid) that placed the phenyl ring over the cinnamyl olefinic protons. Examination of the solution ^{1}H NMR spectrum of the mandelate **4b** (Table 2) showed a downfield shift of 0.56 ppm for the C-3 proton of ppm relative the parent alcohol. This suggested the predominant solution conformation was similar to that observed in the solid, and that the phenyl group was exerting shielding effect on the C-3 proton (Scheme 2).

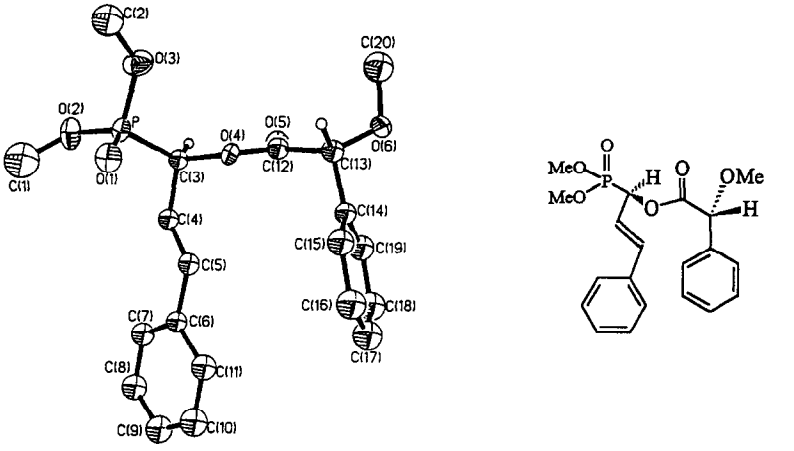
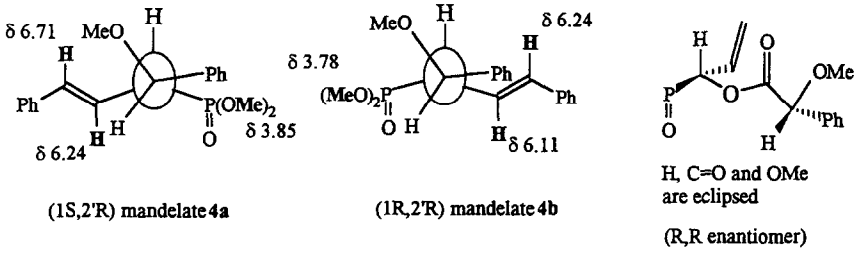


Figure 1: The molecular structure (projection plot) of O-methyl mandelate **4b** shown with 50% probability ellipsoids. Due to the lack of observed reflections, positional and isotropic thermal parameters were refined for the hydrogens atoms on the asymmetric carbon atoms, C3 [C(1)] and C13 [C(2')].

Scheme 2. The Shielding Effect of the Mandelate Phenyl Group

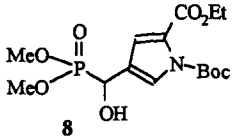


Extended Newman projections viewed along the C(1)-O_2C-C bond

In contrast, the solution ^{1}H NMR spectrum of the (1S,2'R) diastereoisomer **4a** showed a downfield shift of 0.26 and 0.38 ppm for the O-methyl protons relative the parent alcohol. Therefore, α-hydroxy phosphonates appeared to follow the model outlined by Trost for determining absolute configuration of chiral alcohols via O-methyl mandelate ester formation.[10] In addition, there is the advantage of ^{31}P NMR, which also shows predictable shielding effects by the O-methyl mandelate phenyl group. In order to verify this model for hydroxyphosphonates, we prepared (R) O-methyl mandelates from the enantiomerically pure phosphonates (1S) **2**, and (1R) **3**.[6] In addition, the O-methyl mandelates **4a** and **4b** were reduced with hydrogen over 10% palladium on carbon (Scheme 1) to give **7a** and **7b**, respectively. In all cases the less polar isomers (**4a-7a**) had the 1S. 2'R configuration and showed shielding of the phosphonate methyl protons in the ^{1}H NMR spectrum,

and exhibited the higher field signal in the ^{31}P NMR spectrum. Consequently, the more polar isomer (**4b-7b**) had the 1R,2'R configuration and showed shielding of the protons in the hydrocarbon moiety in the ^{1}H NMR spectrum.

While the O-methyl mandelate esters were easily separated, allowed assignment of absolute configuration based upon the shielding effect of the phenyl group, and were useful for an assessment of enantiomeric purity (to the limits of NMR spectroscopy), we were interested in developing a fast, direct, and more accurate method of determining enantiomeric purity and turned our attention to HPLC. Three chiral stationary phases were identified for the direct analysis of α-hydroxy phosphonates,[13] and the ChiralPak AS column was selected for further investigation based upon large retention time differences in the test compound (phosphonate 1). In addition to phosphonates **1-3**, phosphonates **8-10** were prepared and examined by HPLC.



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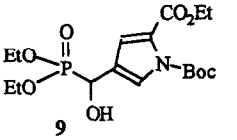

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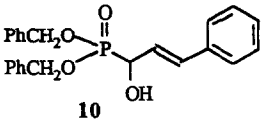

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In all cases the enantiomers were separated with baseline resolution using hexane/ethanol mixtures. The phosphonates **1-3**, and **9** had been prepared enantiomerically enriched[6] and the absolute configurations assigned by X-ray crystallography of precursors (**1** and **3**),[14] by comparison with known compounds (**2**),[5e] or from the NMR spectra of the O-methyl mandelate ester (**1, 2, 3** and **9**). The order of elution was determined as the R enantiomer followed by the S enantiomer.

Table 3. HPLC Data for ChiralPak AS Column

Phosphonate	Solvent System,	flow rate	Detection System	Retention times (R/S) (mins.)	Retention Difference (mins.)
1	EtOH/hexane, 2:8	1 ml/min	254 nm	8.7 and 13.8	5.1
2	EtOH/hexane, 2:8	1 ml/min	254 nm	6.1 and 6.6	0.5
3	EtOH/hexane, 1:9	0.75 mL/min	differential refractometer	7.3 and 7.7	0.4
7	EtOH/hexane, 1:9	1.2 mL/min	254 nm	12.6 and 13.4	0.8
8	EtOH/hexane, 1:9	1.2 mL/min	254 nm	7.6 and 8.4	0.8
9	EtOH/hexane, 2:8	1 mL/min	254 nm	9.9 and 12.8	2.9

In Summary, the mandelate ester derivatives of α-hydroxy phosphonates are useful for determining the absolute configuration at C-1, and for an assessment of enantiomeric purity, whereas HPLC on a chiral stationary phase provides a fast accurate method of determining enantiomeric purity.

EXPERIMENTAL

General Comments. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian XL-300 spectrometer at 300, 121, and 75 MHz, respectively. The ^{1}H chemical shifts are reported in ppm downfield from Me_4Si. The ^{31}P chemical shifts are reported in ppm relative to external H_3PO_4. The ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were recorded on an Autopol III polarimeter (Rudolph Research) under standard conditions. Mass spectra were determined on a Varian Mat 331A spectrometer and microanalyses were performed by Atlantic Microlab Inc. THF was distilled from sodium-benzophenone ketyl, acetonitrile and CH_2Cl_2 were distilled from CaH_2, and the reactions were performed under argon. Racemic phosphonates **1-3** and **8-10** were prepared by addition dimethylphosphite to the aldehydes (10 mol% Et_3N, neat liquids, or CH_2Cl_2 solution).[15] Scalemic Phosphonates **1, 2, and 3** were prepared according to the previously published procedure.[6]

General Procedure for Racemic Hydroxy Phosphonate Formation

A modification of the procedure by Baraldi *et. al.*[15] was used. To a solution of the aldehyde (3.7 mmol) and dialkylphosphite (3.7 mmol) in CH_2Cl_2 (4 mL) was added triethylamine (0.37 mmol). The solution was stirred at room temperature until t.l.c. indicated consumption of the aldehyde. The solution was washed twice with 1M aq. HCl, once with water, dried, and evaporated *in vacuo*. The residue was chromatographed (SiO_2, EtOAc) or recrystallized (EtOAc, hexanes) to yield the pure phosphonate.

Dimethyl 1-hydroxy-3-phenyl-2*E*-propenyl phosphonate 1[16] m.p. 101 °C (EtOAc, hexanes), literature[16] 101 °C; ^{1}H NMR δ 7.42-7.38 (m, 2H), 7.34-7.22 (m, 3H), 6.80 (ddd, 1H, J_{HH} = 15.9 and 1.5 Hz, $^{4}J_{HP}$ = 4.9 Hz), 6.35 (ddd, 1H, J_{HH} = 15.9 and 6.2 Hz, $^{3}J_{HP}$ 5.3 Hz), 4.70 (m, 1H), 4.15 (m, 1H, OH), 3.85 (d, 3H, $^{3}J_{HP}$ = 10.3 Hz), 3.81 (d, 3H, $^{3}J_{HP}$ = 10.3 Hz); ^{13}C NMR δ 136.1 (d, $^{4}J_{CP}$ = 2.9 Hz), 132.4 (d, $^{3}J_{CP}$ = 13.1 Hz), 128.4, 127.8, 126.5, 123.5 (d $^{2}J_{CP}$ = 4.3 Hz) 69.2 (d, $^{1}J_{CP}$ = 160.8 Hz), 53.9 (d, $^{2}J_{CP}$ = 7.1 Hz), 53.7 (d, $^{2}J_{CP}$ = 7.4 Hz); ^{31}P NMR δ 24.4.

Dimethyl phenylhydroxymethyl phosphonate 2[16] m.p.102 °C (EtOAc, hexanes), literature[16] 102-103 °C; ^{1}H NMR δ 7.55-7.45 (m, 2H), 7.40-7.25 (m, 3H), 5.20 (brd s, 1H, OH), 5.05 (d, 1H, $^{2}J_{HP}$ = 11.5 Hz), 3.65 (d, 1H, $^{3}J_{HP}$ = 10.5 Hz), 3.62 (d, 1H, $^{3}J_{HP}$ = 10.5 Hz); ^{13}C NMR δ 136.4, 128.3, 128.2, 126.9, 70.7 (d, $^{1}J_{CP}$ = 157.9 Hz), 53.9 (d, $^{2}J_{CP}$ = 7.1 Hz), 53.7 (d, $^{2}J_{CP}$ = 7.1 Hz); ^{31}P NMR δ 24.3.

Dimethyl 1-hydroxy-3-methyl-butyl phosphonate 3[6d] m.p. 52-54 °C (EtOAc, hexanes); IR (NaCl) 3314, 2956 cm^{-1}; ^{1}H NMR δ 4.0 (m, 1H), 3.82 (d, 3H, $^{3}J_{HP}$ = 10.3 Hz), 3.79 (d, 3H, $^{3}J_{HP}$ = 10.3 Hz), 1.95 (m, 1H), 1.73 (m, 1H), 1.47 (m, 1H), 0.97 (d, 3H, J_{HH} = 6.6 Hz), 0.92 (d, 3H, J_{HH} = 6.6 Hz); ^{13}C NMR δ 65.6 (d, $^{1}J_{CP}$ = 158.5 Hz), 53.25 (d, $^{2}J_{CP}$ = 5.9 Hz), 53.13 (d, $^{2}J_{CP}$ = 5.9 Hz), 39.9, 24.0 (d, $^{2}J_{CP}$ = 13.9 Hz), 23.4, 21.0; ^{31}P NMR δ 28.3. Anal. calcd. for $C_7H_{17}O_4P$; C, 42.86; H, 8.73. Found; C, 42.72, H, 8.79.

Dimethyl 1-[4-(1-*tert*-butoxycarbonyl-2-ethoxycarbonyl-*1H*-pyrrolyl)]-1-hydroxymethyl phosphonate 8 an oil, IR (NaCl, neat) 3280, 2981, 1754, 1724, cm^{-1}; ^1H NMR δ 7.43 (m, 1H), 6.94 (m, 1H), 4.93 (d, 1H, $^2J_{HP}$ = 10 Hz), 4.29 (q, 2H, J_{HH} = 7.2 Hz), 4.14 (brd s, 1H, OH), 3.80 (d, 3H, $^3J_{HP}$ = 10.3 Hz), 3.77 (d, 3H, $^3J_{HP}$ = 10.3 Hz), 1.57 (s, 9H), 1.33 (t, 3H, J_{HH} = 7.2 Hz); ^{13}C NMR δ 160.5, 147.9, 125.9, 124.5 (d, $^2J_{CP}$ = 9.8 Hz), 120.8, 119.2, 85.0, 64.6 (d, $^1J_{CP}$ = 167 Hz), 60.9, 53.8 (multiple peaks), 27.7, 14.3; ^{31}P NMR δ 23.0. Anal. calcd. for $C_{15}H_{24}NO_8P$; C, 47.75; H, 6.41. Found; C, 47.65, H, 6.41.

Diethyl 1-[4-(1-*tert*-butoxycarbonyl-2-ethoxycarbonyl-*1H*-pyrrolyl)]-1-hydroxymethyl phosphonate 9[1d] an oil, IR (NaCl) IR (NaCl, neat) 3291, 2983, 1753, 1724 cm^{-1}; ^1H NMR δ 7.42 (m, 1H), 6.94 (m, 1H), 4.89 (dd, 1H, J_{HH} = 5.2 Hz, $^2J_{HP}$ = 9.6 Hz), 4.29 (q, 2H, J_{HH} = 7.2 Hz), 4.13 (m, 4H), 1.57 (s, 9H), 1.32 (m, 9H); ^{13}C NMR δ 160.5, 147.9, 125.7, 124.6 (d, $^2J_{CP}$ = 9.5 Hz), 121.1, 119.4 (m), 84.9, 64.8 (d, $^1J_{CP}$ = 165 Hz), 63.2 (m) 27.7, 16.6, 16.5, 14.3; ^{31}P NMR δ 20.8. Anal. calcd. for $C_{17}H_{28}NO_8P$; C, 50.37; H, 6.96. Found; C, 50.17, H, 6.97.

Dibenzyl 1-hydroxy-3-phenyl-2*E*-propenyl phosphonate 10[6c] m.p. 147-148 °C (EtOAc); IR (KBr) 3231, 3010, 2957 cm^{-1}; ^1H NMR δ 7.3-7.1 (m, 15H), 6.63 (ddd, 1H, J_{HH} = 15.8 and 1.2 Hz, $^4J_{HP}$ = 4.8 Hz), 6.20 (ddd, 1H, J_{HH} = 16.0 and 5.6 Hz, $^3J_{HP}$ 5.6 Hz), 5.02 (m, 4H), 4.61 (ddd, 1H, J_{HH} = 6.1 and 1.4 Hz, $^2J_{HP}$ 12.3 Hz), 4.10 (brd s, 1H, OH), ; ^{13}C NMR δ 136.1, 136.0, 132.8 (d, $^3J_{CP}$ = 13.2 Hz), 128.4-126.6 (multiple peaks), 123.2 (d $^2J_{CP}$ = 4.7 Hz) 69.8 (d, $^1J_{CP}$ = 159 Hz), 68.6 (d, $^2J_{CP}$ = 7.0 Hz), 68.5 (d, $^2J_{CP}$ = 7.1 Hz); ^{31}P NMR δ 22.5. Anal. calcd. for $C_{23}H_{23}O_4P$; C, 70.04; H, 5.88. Found; C, 70.05; H, 5.89.

General Procedure for O-Methyl Mandelate Ester Formation. To a solution of DMF (0.19 mL, 2.5 mmol, 1.4 equiv.) in acetonitrile (5.4 mL) at 0 °C was added oxalyl chloride (0.16 mL, 1.8 mmol, 1 equiv.), which resulted in the formation of a white precipitate. O-Methyl mandelic acid (0.3 g, 1.8 mmol, 1 equiv.) in acetonitrile (1 mL) was added and the precipitate slowly redissolved. After 20 mins the α-hydroxy phosphonate (1 equiv.) in pyridine (0.3 mL, 2 equiv.) was added. The resulting solution was stirred for an additional 2 hours, and then it was diluted with Et_2O, washed once with water, twice with saturated aq. $CuSO_4$, dried, and evaporated *in vacuo*.

(1S) and (1R) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-3-phenyl-2*E*-propenyl phosphonate (4a and 4b). Column chromatography (SiO_2, EtOAc/hexanes, gradient 2:1 to 100:0) yielded a less polar isomer (1S) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-3-phenyl-2*E*-propenyl phosphonate (**4a**), an oil, $[\alpha]_D$ -67.0 (c=1.74, $CHCl_3$); IR (NaCl, neat) 3028, 2956, 2853, 1759, 1032 cm^{-1}; ^1H NMR δ 7.5-7.2 (m, 10H), 6.71 (dd, 1H, J_{HH} = 16 Hz, $^4J_{HP}$ = 4.1 Hz), 6.24 (ddd, 1H, J_{HH} = 15.8 and 7.4 Hz, $^3J_{HP}$ = 6 Hz), 5.88 (ddd, 1H, J_{HH} = 7.4 and 1 Hz, $^2J_{HP}$ = 13.5 Hz), 4.89 (s, 1H), 3.59 (d, 3H, $^3J_{HP}$ = 11.6 Hz), 3.45 (d, 3H, $^3J_{HP}$ = 11.6 Hz), 3.43 (s, 3H); ^{13}C NMR 169.0, 135.7, 135.5, 135.4, 128.8, 128.6, 128.5, 128.4, 127.3, 126.8, 119.2, 82.3, 69.5 (d, $^1J_{CP}$ = 169 Hz), 57.4, 53.5, 53.4; ^{31}P NMR δ 19.62. Anal. calcd. for $C_{20}H_{23}O_6P$; C, 61.54; H, 5.94. Found; C, 61.33, H, 5.89. A more polar isomer (1R) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-3-phenyl-2*E*-propenyl phosphonate (**4b**), mp = 87-88 °C (EtOAc, hexanes); $[\alpha]_D$ 3.8 (c=1.07, $CHCl_3$); IR (KCl) 3028, 2956, 1753, 1254, 1115, 1017 cm^{-1}; ^1H NMR δ 7.5-7.4 (m, 2H), 7.4-7.3 (m, 3H), 7.4-7.3 (m, 3H), 7.3-

7.2 (m, 2H), 6.24 (dd, 1H, J_{HH} = 16.3 Hz, $^4J_{HP}$ = 4.6 Hz), 6.11 (ddd, 1H, J_{HH} = 15.9 and 5.8 Hz, $^3J_{HP}$ = 4.6 Hz), 5.93 (ddd, 1H, J_{HH} = 6.1 and 1.1 Hz, $^2J_{HP}$ = 14.9 Hz), 4.93 (s, 1H), 3.78 (d, 3H, $^3J_{HP}$ = 11 Hz), 3.74 (d, 3H, $^3J_{HP}$ = 11 Hz), 3.45 (s, 3H), ^{13}C NMR δ 168.9, 135.41, 135.37, 133.9 (d, $^3J_{CP}$ = 12 Hz), 128.9, 128.8, 128.6, 128.4, 128.2, 127.3, 126.6, 126.5, 118.9 (d, $^2J_{CP}$ = 4.8 Hz), 82.4, 69.0 (d, $^1J_{CP}$ = 168 Hz), 57.4, 53.9 (d, $^2J_{CP}$ = 6.9 Hz), 53.8 (d, $^2J_{CP}$ = 6.9 Hz) ^{31}P NMR δ 19.82. Anal. calcd. for $C_{20}H_{23}O_6P$; C, 61.54; H, 5.94. Found; C, 61.67, H, 5.95.

(1S) and (1R) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-1-phenylmethyl phosphonate (5a and 5b). Column chromatography (SiO_2, EtOAc/hexanes, gradient 2:1 to 100:0) yielded a less polar isomer (1S) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-1-phenylmethyl phosphonate (**5a**) an oil; $[\alpha]_D$ -56.8 (c=1.09, $CHCl_3$); IR (NaCl, neat) 3020, 2955, 1760, 1455, 1031 cm^{-1}; ^{1}H NMR δ 7.55-7.40 (m, 1H), 7.40-7.30 (m, 6H), 6.17 (d, 1H, $^2J_{HP}$ = 12.9 Hz), 4.88 (s, 1H), 3.46 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 3.40 (s, 3H), 3.38 (d, 3H, $^3J_{HP}$ = 10.8 Hz); ^{13}C NMR δ 168.8, 135.6, 132.6, 128.8, 128.7, 128.5, 128.48, 128.6, 127.7, 127.6, 127.3, 82.4, 70.5 (d, $^1J_{CP}$ = 168 Hz), 62.5, 53.6 (d, $^2J_{CP}$ = 6.9 Hz), 53.4 (d, $^2J_{CP}$ = 6.4 Hz); ^{31}P NMR δ 18.97; MS (DIP/EI) 121 (100), 105 (28), 91 (29), 77 (49). Anal. calcd. for $C_{18}H_{21}O_6P$; C, 59.34; H, 5.81. Found; C, 59.11, H, 5.76. A more polar isomer (1R) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-1-phenylmethyl phosphonate (**5b**), an oil; $[\alpha]_D$ -1.5 (c=1.12, $CHCl_3$); IR (NaCl, neat) 3020, 2596, 1761, 1455, 1264 cm^{-1}; ^{1}H NMR δ 7.45-7.35 (m, 2H), 7.35-7.30 (m, 3H), 7.30-7.10 (m, 5H), 6.18 (d, 1H, $^2J_{HP}$ = 13.2 Hz), 4.93 (s, 1H), 3.63 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 3.60 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 3.43 (s 3H); ^{13}C NMR δ 168.9, 135.4, 132.4, 128.8, 128.5, 128.3, 128.2, 127.3, 127.2, 127.1, 82.5, 70.5 (d, $^1J_{CP}$ = 168 Hz), 57.4, 53.8 (d, $^2J_{CP}$ = 7 Hz), 53.7 (d, $^2J_{CP}$ = 7 Hz); ^{31}P NMR δ 19.28; MS (DIP/EI) 364 (M+, 6), 121 (100), 109 (21), 105 (26). Anal. calcd. for $C_{18}H_{21}O_6P$. $0.25H_2O$; C, 58.62; H, 5.88. Found; C, 58.72, H, 5.88.

(1S) and (1R) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy)]-3-methyl-butyl phosphonate (6a and 6b) Column chromatography (SiO_2, EtOAc/hexanes, gradient 2:1 to 100:0) yielded a less polar isomer (1S) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy)]-3-methyl-butyl phosphonate (**6a**), an oil; $[\alpha]_D$ -14.3 (c=1.15, $CHCl_3$); IR (NaCl, neat) 2957, 1755, 1455, 1266, 1167, 1031 cm^{-1}; ^{1}H NMR δ 7.5-7.4 (m, 2H), 7.4-7.3 (m, 3H), 5.40 (m, 1H), 4.81 (s, 1H), 3.53 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 3.42 (s, 3H), 3.41 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 1.90-1.78 (m, 1H), 1.68-1.52 (m, 2H), 0.92 (d, 3H, J_{HH} = 6.3 Hz), 0.88 (d, 3H, J_{HH} = 6.3 Hz); ^{13}C NMR δ 169.5, 135.5, 128.7, 128.5, 128.4, 128.3, 127.3, 82.3, 66.5 (d, $^1J_{CP}$ = 165 Hz), 57.3, 53.0 (d, $^2J_{CP}$ = 6.4 Hz), 52.8 (d, $^2J_{CP}$ = 6.4 Hz), 37.7, 24.5 (d, $^2J_{CP}$ = 13 Hz), 23.1, 21.1; ^{31}P NMR δ 22.48; MS (DIP/EI) 121 (100), 109 (17), 105 (19), 77 (24). Anal. calcd. for $C_{16}H_{25}O_6P$; C, 55.81; H, 7.32. Found; C, 55.57, H, 7.29. A more polar isomer (1R) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy)]-3-methyl-butyl phosphonate (**6b**),an oil; $[\alpha]_D$ -73.9 (c=1.23, $CHCl_3$); IR (NaCl, neat) 2957, 1756, 1456, 1167, 1029 cm^{-1}; ^{1}H NMR δ 7.5-7.4 (m, 2H), 7.4-7.3 (m, 3H), 5.35 (m, 1H), 4.82 (s, 1H), 3.75 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 3.72 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 3.42 (s, 3H), 1.81-1.66 (m, 1H), 1.54-1.42 (m, 1H), 1.10-0.9 (m, 1H), 0.68 (d, 3H, J_{HH} = 6.6 Hz), 0.65 (d, 3H, J_{HH} = 6.3 Hz); ^{13}C NMR δ 169.6, 135.7, 128.7, 128.4, 127.1, 82.3, 66.3 (d, $^2J_{CP}$ = 165 Hz), 57.3, 53.2 (d, $^2J_{CP}$ = 6.7 Hz), 37.6, 24.0 (d, $^2J_{CP}$ = 13 Hz), 22.9, 20.7; ^{31}P NMR δ 23.1; MS (DIP/EI) 121 (100), 109 (27), 105 (24), 91 (21), 77 (41). Anal. calcd. for $C_{16}H_{25}O_6P$; C, 55.81; H, 7.32. Found; C, 55.79, H, 7.34.

(1S) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy)]-3-phenylpropanyl phosphonate 7a The unsaturated phosphonate **4a** (33 mg) was dissolved in ethyl acetate (2 mL) and 10% palladium on carbon (5 mg) was added. The suspension was stirred under an atmosphere of hydrogen for 14 hours. The reaction flask was purged with argon for 30 minutes and then the catalyst was removed by filtration, and the resulting solution evaporated *in vacuo*. Column chromatography (SiO_2, EtOAc/hexanes, gradient 2:1 to 100:0) yielded a less polar isomer (1S) dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-3-phenylpropanyl phosphonate **7a**, an oil; IR (NaCl, neat) 2950, 1760, 1255, 1040 cm^{-1}; ^1H NMR δ 7.48-7.44 (m, 2H), 7.38-7.30 (m, 3H), 7.28-7.23 (m, 2H), 7.21-7.16 (m, 1H), 7.10-7.06 (m, 2H), 5.30 (m, 1H), 4.74 (s, 1H), 3.54 (d, 3H, $^3J_{HP}$ = 11 Hz), 3.42 (s, 3H), 3.41 (d, 3H, $^3J_{HP}$ = 11 Hz), 2.70-2.54 (m, 2H), 2.24-2.08 (m, 2H); ^{13}C NMR δ 158.0, 140.1, 135.5, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 82.3, 67.7 (d, $^1J_{CP}$ = 165 Hz), 57.4, 53.1 (d, $^2J_{CP}$ = 7.2 Hz), 53.0 (d, $^2J_{CP}$ = 7.2 Hz), 31.9 (d, $^3J_{CP}$ = 13.2 Hz), 30.9; ^{31}P NMR δ 22.15. Anal. calcd. for $C_{20}H_{25}O_6P$. $0.25H_2O$, C, 60.53; H, 6.48. Found; C, 60.53, H, 6.37.

(1R) Dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-3-phenylpropanyl phosphonate 7b. The unsaturated phosphonate **4b** was hydrogenated as described above. Column chromatography (SiO_2, EtOAc/hexanes, gradient 2:1 to 100:0) yielded a less polar isomer (1R) dimethyl 1-[(2'R)-2'-methoxy-2'-phenylacetoxy]-3-phenylpropanyl phosphonate **7b**, an oil; IR (NaCl, neat) 2950, 1755, 1452, 1255, 1032 cm^{-1}; ^1H NMR δ 7.53-7.48 (m, 2H), 7.42-7.32 (m, 3H), 7.21-7.10 (m, 3H), 6.85-6.80 (m, 2H), 5.24 (m, 1H), 4.87 (s, 1H), 3.74 (d, 3H, $^3J_{HP}$ = 11 Hz), 3.71 (d, 3H, $^3J_{HP}$ = 10.5 Hz), 3.44 (s, 3H), 2.24-2.13 (m, 2H), 2.10-2.01 (m, 1H), 2.01-1.93 (m, 1H); ^{13}C NMR δ 169.6, 139.9, 135.8, 128.9, 128.7, 128.3, 128.2, 126.0, 82.2, 67.2 (d, $^1J_{CP}$ = 165 Hz), 57.4, 53.4 (d, $^2J_{CP}$ = 6.2 Hz), 53.2 (d, $^2J_{CP}$ = 6.2 Hz), 31.3, 31.2; ^{31}P NMR δ 22.75. Anal. calcd. for $C_{20}H_{25}O_6P$. $0.25H_2O$; C, 60.53; H, 6.48. Found; C, 60.69, H, 6.50.

X-Ray Structure Determination. Clear, colorless crystals of (1R) Dimethyl 1-[(2'R)-2'-methoxy-(phenylacetyloxy)]-phenyl-2*E*-propenyl phosphonate **4b** suitable for X-ray analysis were obtained by slow diffusion of hexanes into ethylacetate at room temperature. Details for the crystal structure determination are given in Table 4. Bond distances and bond angles are reported in Table 5 and Table 6 respectively. Data reduction, structure solution and refinement were carried out using SHEXTL-plus.[17] Direct methods were used for the structure solution. The structure solution and successful refinement were carried out in the space group $P2_1$. Full matrix least-squares refinement was carried out by minimizing $\omega(Fo-Fc)^2$. Due to the lack of observed data, only P and O atoms were refined anisotropically, where as C atoms were refined isotropically to convergence. All hydrogen atoms except H(3) and H(13) were included at their calculated positions. H(3) and (H13) were refined isotropically. Roger's η test was used for absolute structure detremination and [η=1(2)]. The crystal data have been deposited at the Cambridge Crystallographic Data Center.[18]

Table 4. Summary of the crystal structure determination

Crystal data

$C_{20}H_{23}O_6P$
$M_r = 390.4$
Monoclinic
$P2_1$
$a = 5.673\ (2)\ (9)$ Å
$b = 10.006\ (4)\ (4)$ Å
$c = 17.981\ (7)$ Å
$\beta = 90.02\ (3)\ (6)°$
$V = 1036.9\ (7)$ Å^3
$Z = 2$
$D_m = 1.250$ Mg/m^3
$F(000) = 412$

MoKα radiation
$\lambda = 0.71073$ Å
$2\theta = 3\text{-}60°$
$\mu' = 0.164$ mm^{-1}
$T = 298$ K
colorless, rectangular plates
0.3 x 0.2 x 0.2 mm

Data collection

Siemens *R3m/V* diffractometer
$\theta\text{-}2\theta$ scans
Absorption correction: none
4916 measured reflections
4784 independent reflections
1210 observed reflections [$F > 4.0s(F)$]

$R_{int} = 0.0263$
$\theta_{max} = 30°$
$h = -8$ to 8
$k = -14$to 14
$l = 0$ to 25
3 standard reflections measured for every 50 reflections

Refinement

Final $R = 0.0904$
$wR = 0.\ 0673$
$S = 1.87$
1138 reflections
112 parameters
All H-atom parameters fixed
$w = 1/[\sigma^2(F) + 0.0025F^2]^{1/2}$

$(\Delta/\sigma)_{max} = 0.317$
$\Delta\rho_{max} = 0.80$ e Å^{-3}
$\Delta\rho_{min} = 0.62$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 5. Bond Lengths (Å)

P-O(1)	1.458 (10)	P-O(2)	1.550 (8)
P-O(3)	1.573 (12)	P-C(3)	1.786 (10)
O(2)-C(1)	1.306 (21)	O(3)-C(2)	1.399 (16)
O(4)-C(3)	1.458 (11)	O(4)-C(12)	1.355 (14)
O(5)-C(12)	1.181 (15)	O(6)-C(13)	1.410 (17)
O(6)-C(20)	1.380 (21)	C(3)-C(4)	1.506 (19)
C(4)-C(5)	1.291 (20)	C(5)-C(6)	1.462 (20)
C(6)-C(7)	1.384 (16)	C(6)-C(11)	1.403 (20)
C(7)-C(8)	1.391 (23)	C(8)-C(9)	1.352 (24)
C(9)-C(10)	1.351 (19)	C(10)-C(11)	1.369 (24)
C(12)-C(13)	1.531 (16)	C(13)-C(14)	1.469 (23)
C(14)-C(15)	1.398 (20)	C(14)-C(19)	1.390 (17)
C(15)-C(16)	1.365 (23)	C(16)-C(17)	1.378 (18)
C(17)-C(18)	1.334 (22)	C(18)-C(19)	1.389 (24)

Table 6. Bond Angles (°)

O(1)-P-O(2)	115.0 (6)	O(1)-P-O(3)	116.9 (5)
O(2)-P-O(3)	103.6 (6)	O(1)-P-C(3)	115.4 (6)
O(2)-P-C(3)	102.6 (4)	O(3)-P-C(3)	101.3 (6)
P-O(2)-C(1)	126.9 (12)	P-O(3)-C(2)	119.1 (10)
C(3)-O(4)-C(12)	116.5 (8)	C(13)-O(6)-C(20)	111.6 (10)
P-C(3)-O(4)	106.0 (6)	P-C(3)-C(4)	112.8 (8)
O(4)-C(3)-C(4)	111.1 (11)	C(3)-C(4)-C(5)	125.6 (10)
C(4)-C(5)-C(6)	127.1 (11)	C(5)-C(6)-C(7)	123.7 (13)
C(5)-C(6)-C(11)	118.4 (10)	C(7)-C(6)-C(11)	117.9 (13)
C(6)-C(7)-C(8)	119.3 (13)	C(7)-C(8)-C(9)	120.2 (12)
C(8)-C(9)-C(10)	122.5 (17)	C(9)-C(10)-C(11)	118.1 (15)
C(6)-C(11)-C(10)	122.0 (11)	O(4)-C(12)-O(5)	124.2 (10)
O(4)-C(12)-C(13)	108.8 (10)	O(5)-C(12)-C(13)	126.8 (11)
O(6)-C(13)-C(12)	111.4 (11)	O(6)-C(13)-C(14)	108.1 (10)
C(12)-C(13)-C(14)	107.5 (11)	C(13)-C(14)-C(15)	121.9 (10)
C(13)-C(14)-C(19)	121.7 (12)	C(15)-C(14)-C(19)	116.4 (14)
C(14)-C(15)-C(16)	120.9 (12)	C(15)-C(16)-C(17)	121.7 (14)
C(16)-C(17)-C(18)	118.3 (16)	C(17)-C(18)-C(19)	121.7 (13)
C(14)-C(19)-C(18)	121.0 (14)		

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12. We have recently shown that the mandelate ester can be cleaved to give the optically pure hydroxy phosphonate by ethanolysis using $Ti(O^iPr)_4$ in refluxing ethanol, therefore providing a method of resolution. The diethyl phosphonate must be used since $Ti(O^iPr)_4$ was also found to catalyze exchange of the phosphonate ester, Kozlowski, J.K.; and Spilling, C.D. unpublished results.
13. Suitable columns were initially identified by sending racemic samples of dimethyl (1-hydroxy-3-phenyl-2*E*-propenyl) phosphonate (**1**) to Chiral Technologies, Exton, PA; and Regis, Morton Grove, IL. The Chiral Technologies Chiralcel OF and ChiralPak AS columns, and the Regis Whelk-O1 column were found to separate the enantiomers with baseline resolution. The following data were provided:
Chiralcel OF, 8:2, hexane:^{i}PrOH, 1 mL/min, 254 nm, retention times of 23.2 and 30.4 mins
ChiralPak AS, 8:2, hexane:^{i}PrOH, 1 mL/min, 254 nm, retention times of 16.4 and 34.9 mins
Whelk-O1, 9:1, hexane:EtOH, 1 mL/min, 254 nm, retention times of 11.9 and 15.5 mins
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