Enzymes in Organic Chemistry, 11:[1] Hydrolase-Catalyzed Resolution of α- and β-Hydroxyphosphonates and Synthesis of Chiral, Non-Racemic β-Aminophosphonic Acids

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Abstract: The enantioselective acylation of racemic diisopropyl α- and β-hydroxyphosphonates by hydrolases in *t*-butyl methyl ether with isopropenyl acetate as acyl donor is limited by the narrow substrate specificity of the enzymes. High enantiomeric excesses (up to 99%) were obtained for the acetates of (*S*)-diisopropyl 1-hydroxy-(2-thienyl)methyl-, 1-hydroxyethyl- and 1-hydroxyhexylphosphonate and (*R*)-diisopropyl 2-hydroxypropylphosphonate. The hydrolysis of a variety of β-chloroacetoxyphosphonates by the lipase from *Candida cylindracea* and protease subtilisin in a biphasic system gives (*S*)-β-hydroxyphosphonates (ee 51–92%) enantioselectively. (*S*)-2-Phenyl-2-hydroxyethyl- and (*S*)-3-methyl-2-hydroxybutylphosphonates (ee 96% and 99%, respectively) were transformed into (*R*)-2-aminophosphonic acids of the same ee.

Keywords: aminophosphonic acids; enantioselectivity; hydrolases; hydroxyphosphonates; kinetic resolution

Introduction

Hydrolytic enzymes are the most widely used biocatalysts in organic chemistry.[2] In continuation of our work on α-acyloxyphosphonates[1] we decided to search for hydrolases kinetically resolving also β-acyloxyphosphonates and esterifying α- and β-hydroxyphosphonates in an organic medium enantioselectively. Furthermore, we wanted to focus on the determination of the absolute configuration and the enantiomeric excess of chiral, non-racemic β-hydroxyphosphonates as well as their transformation into β-aminophosphonic acids as structural analogues of β-amino acids. Recent reports by others[3,4] on lipase-catalyzed acylation of α- and β-hydroxyphosphonates underscore the relevance of such organophosphorus compounds. In one case, part of the assigned configurations have had to be revised.[3]

Results and Discussion

Enantioselective Acetylation of α-Hydroxyphosphonates

The lipase- and protease-catalyzed enantioselective hydrolysis of α-acetoxy- and especially α-chloroacetoxyphosphonates in a biphasic system (phosphate buffer/organic solvent) is a well established method for the preparation of chiral, non-racemic α-hydroxyphosphonates of high enantiomeric excesses.[1] We reasoned that kinetic acetylation of α-hydroxyphosphonates in an organic solvent using isopropenyl acetate as acyl donor would be an attractive alternative, as the preparation of acetates for kinetic resolution by chemical means could be omitted. The required α-hydroxyphosphonates (±)-**3a**–**f**, except **1a**[5b], were prepared by an improved procedure using a substoichiometric quantity of *n*-BuLi at −78 °C instead of phosphazene P_1-*t*-Bu as base[5] (Scheme 1). Thus, the reaction time could be reduced from 16–18 h to one hour. We were primarily interested in diisopropyl phosphonates for synthetic reasons. The isopropyl group is more stable than the ethyl or methyl group when hydroxyphosphonates are transformed into other α-substituted phosphonates by substitution reactions. 36 hydrolases (each 200 mg) were screened with substrates (±)-**3a** and (±)-**3b** (each 100 mg) in a mixture of *t*-butyl methyl ether (4 mL) and isopropenyl acetate (1 mL) at room temperature for 24 h or in combination with 48 h at 40 °C (Scheme 2).

Only lipases SAM II[6] (*Pseudomonas* sp. lipase) and SP 526 (fungal lipase) esterified (±)-**3a** giving the corresponding acetate in 34% yield with an ee of 28% and 77%, respectively. Hydroxyphosphonate (±)-**3b** was accepted as substrate by a number of lipases and proteases. The most promising ones in terms of ee were

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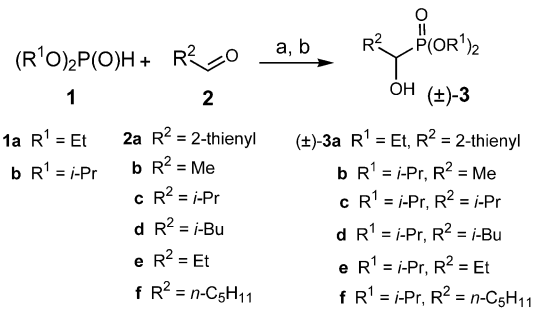
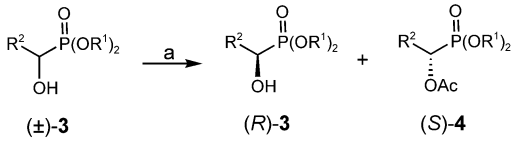


Scheme 1. Preparation of α-hydroxyphosphonates (±)-**3**. a) **1** and 0.16 equiv. of *n*-BuLi, THF, −78 °C, 30 min, then **2**, 1 h; b) H_2SO_4. (±)-**3a**: 70%, (±)-**3b**: 75%, (±)-**3c**: 75%, (±)-**3d**: 74%, (±)-**3e**: 76%, (±)-**3f**: 90%.



Scheme 2. Hydrolase-catalyzed acetylation of α-hydroxyphosphonates. a) Lipase or protease, isopropenyl acetate, *t*-BuOMe.

used to esterify (±)-**3b** on a 1 mmol scale at 40 °C for 24 h. When the conversion was about 50% (TLC), the mixture was filtered through Celite, concentrated under vacuum, and ester **4** and alcohol **3** were separated by flash chromatography. The ester was hydrolyzed chemically.[5] The ee and configuration of the chiral, non-racemic α-hydroxyphosphonates **3** were determined as reported. The data are collected in Table 1. α-Hydroxyphosphonate (S)-**3b** is acetylated preferentially (ee 99–100%) by lipases Novozym 435 (immobilized lipase B from *Candida antarctica*), SAM II, SP 524 (lipase from *Aspergillus niger*) and AK (lipase from *Pseudomonas* sp.). Yuan et al. who used only Novozym 435 in combination with vinyl acetate found that α-hydroxyphosphonates with a small group (R^2 = Me, Et, vinyl) were resolved (ee >95%). Beside **3a**,**b** only **3f** was esterified and gave acetate (*S*)-**4f** with high enantioselectivity. Surprisingly, neither lipases AP 6 (from *Aspergillus niger*) and FAP 15 (from *Rhizopus oryzae*) nor protease Chirazyme P-2 (alkaline endoprotease of serine type), which kinetically resolve a large number of α-hydroxyphosphonates in a biphasic system, catalyze the reverse process in an organic medium.[5,7]

Enantioselective Acetylation of β-Hydroxyphosphonates

Chiral, non-racemic β-hydroxyphosphonates were prepared from β-ketophosphonates using homogenous catalytic hydrogenation[8,9] on a chiral catalyst, CBS reduction,[10] *Saccharomyces cerevisiae*[11] and *Geotrichum candidum*.[3] Furthermore, chiral non-racemic β-hydroxyphosphonates were obtained by kinetic resolution of racemic β-hydroxyphosphonates through Sharpless epoxidation[12] or lipase-catalyzed acetylation[3,4,13] and a rare example of the enantioselective hydrolysis[14] of a β-acetoxyphosphonate.

The biological importance of β-hydroxyphosphonates is demonstrated with three examples. Certain γ-amino-β-hydroxyphosphonic acids are statin analogue renin inhibitors.[15] The (*R*)-3-(*N*-formyl-*N*-hydroxyamino)- and (*R*)-(*N*-acetyl-*N*-hydroxyamino)-2-hydroxypropylphosphonic acids are cell wall active antibiotics produced by *Streptomyces rubellomurinus*.[16] The former was found to be an efficient inhibitor of the 1-deoxy-D-xylulose-5-phosphate reductoisomerase in the alternative non-mevalonate pathway for terpenoid biosynthesis.[17] Phosphonothrixin, a new herbicidal antibiotic, is a homochiral β-hydroxyphosphonic acid.[18]

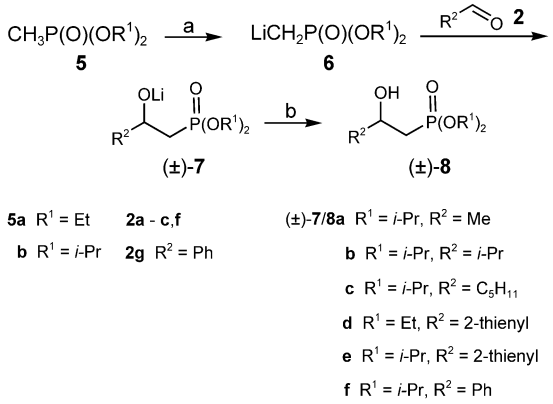
We prepared β-hydroxyphosphonates (±)-**8a**–**f** with the diisopropyl esters predominating (Scheme 3). Metallation of methylphosphonates **5** with *n*- or *s*-BuLi gave lithiomethylphosphonates **6a**,**b** to which aldehydes **2** were added.[19] Work up and purification furnished phosphonates (±)-**8a**–**f**.

β-Hydroxyphosphonates (±)-**8a** and (±)-**8d** were used as standard substrates for screening our collection of hydrolases in the same way as for the α-hydroxyphosphonates for acetylation with isopropenyl acetate

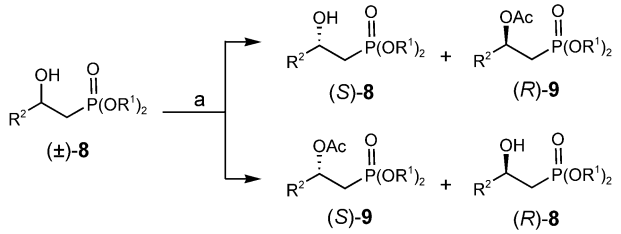
Table 1. Enantioselective acetylation of (±)-**3** with lipases with isopropenyl acetate as acyl donor.

Compound (1 mmol)	Enzyme	[mg]	Isolated alcohol				Isolated ester		Alcohol[a]	
			Yield [%]	Conf.	ee[b] [%]	$[\alpha]_D^{20}$ (*c*)[c]	Yield [%]	$[\alpha]_D^{20}$ (*c*)[c]	Conf.	ee[b] [%]
(±)-**3b**	Novozym	100	62	*R*	62/55	−6.1 (1.2)	36	+24.7 (1.5)	S	98/99
(±)-**3b**	SAM II	15	53	*R*	59/60	−3.0 (1.4)	32	+24.5 (1.6)	*S*	89/90
(±)-**3b**	AK	70	53	*R*	70/68	−4.3 (1.5)	27	+24.7 (1.3)	*S*	95/97
(±)-**3b**	SP 524	30	30	*R*	55/56	−3.2 (1.4)	42	+22.0 (1.0)	*S*	93/95
(±)-**3e**	SAM II	40	44	*R*	77/78	−13.7 (1.6)	45	+36.8 (1.8)	*S*	100/99

[a] Alcohol obtained by chemical hydrolysis of ester.
[b] Determined by ^{1}H NMR/^{31}P NMR spectroscopy of Mosher esters.
[c] Measured in acetone, concentration rounded to the nearest tenth

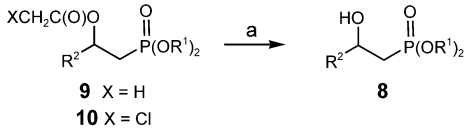


Scheme 3. Preparation of β-hydroxyphosphonates (±)-**8**. a) BuLi/THF, −78 °C; b) AcOH; (±)-**8a**: 78%, (±)-**8b**: 88%, (±)-**8c**: 69%, (±)-**8d**: 91%, (±)-**8e**: 87%, (±)-**8f**: 92%.

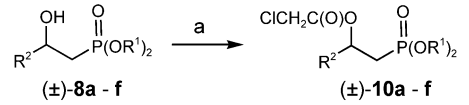


Scheme 4. Hydrolase-catalyzed acetylation of β-hydroxyphosphonates. a) Lipase or protease, isopropenyl acetate, *t*-BuOMe.

as acyl donor. While (±)-**8d** was not esterified, (±)-**8a** was enantioselectively esterified by one protease (ChiroCLEC™-BL, which is cross-linked crystalline subtilisin) and 5 lipases, SP 524, SAM II, Novozym 435, PS and AK (Scheme 4). Then 1 mmol quantities of (±)-**8a** were resolved with the protease and the three lipases giving the best ee. In general, the alcohols **8** and the esters **9** have similar polarities, which might cause trouble when the two have to be separated. The esters **9** were hydrolyzed chemically[5] with triethylamine in a mixture of methanol/water at room temperature (Scheme 5, Table 2).



Scheme 5. Chemical hydrolyses of chiral, non-racemic β-acetoxyphosphonates **9**. a) MeOH, H_2O, Et_3N.



Scheme 6. Synthesis of β-chloroacetoxyphosphonates (±)-**10**. a) Chloroacetic anhydride, CH_2Cl_2, pyridine, 0 °C; (±)-**10a**: 67%, (±)-**10b**: 95%, (±)-**10c**: 83%, (±)-**10d**: 91%, (±)-**10e**: 86%, (±)-**10f**: 98%.

Table 2 shows that lipases gave β-hydroxyphosphonate (*S*)-**8a** and ester (*R*)-**9a** of high ee (94–97%), but the protease acetylated preferentially (*R*)-**8a**. None of the other diisopropyl β-hydroxyphosphonates was acetylated significantly. Yuan et al. who used only Novozym 435 as hydrolase for the enantioselective esterification of β-hydroxyphosphonates found that its substrate specificity is high and that it acetylates only diethyl β-hydroxyphosphonates with chains of up to 4 carbon atoms.[4]

As we did not find a hydrolase with a broad substrate specificity for acetylation of β-hydroxyphosphonates, we decided to prepare β-chloroacetoxyphosphonates (±)-**10a–f** for studying enantioselective hydrolysis (Scheme 6).[20] Using (±)-**10e** as substrate, our collection of enzymes was screened for hydrolases kinetically resolving it in a biphasic system (Scheme 7). The best enzymes were selected for hydrolysis of 1 mmol of racemic substrates **10a–f** in the same way as α-acyloxyphosphonates.[5] When the conversion had reached 45% using an autotitrator, the reaction was stopped and worked up.

The β-chloroacetoxyphosphonates and β-hydroxyphosphonates were separated and the esters were hydrolyzed under mild conditions (Scheme 5). The

Table 2. Enantioselective esterification of β-hydroxyphosphonate (±)-**8a**.

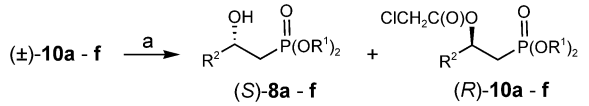
Compound (1 mmol)	Enzyme	mg	Isolated alcohol				Isolated ester		Alcohol[a]	
			Yield [%]	Conf.	ee[b] [%]	$[\alpha]_D^{20}$ (*c*)[c]	Yield [%]	$[\alpha]_D^{20}$ (*c*)[a]	Conf.	ee[b] [%]
(±)-**8a**	Novozym[d]	20	35	*S*	63/67	+7.2 (1.3)	26	+11.1 (1.8)	*R*	97/94
(±)-**8a**	SAM II	50	49	*S*	59/58	+6.3 (1.3)	34	+12.8 (1.7)	*R*	94/95
(±)-**8a**	SP 524	50	39	*S*	47/43	+8.0 (1.2)	23	+10.1 (1.7)	*R*	97/94
(±)-**8a**	ChiroCLEC-BL	20	42	*R*	56/57	−8.4 (1.3)	26	−12.5 (1.0)	*S*	94/91

[a] Alcohol obtained by chemical hydrolysis of ester.
[b] Determined by ^{1}H NMR/^{31}P NMR spectroscopy of Mosher esters.
[c] Measured in acetone, concentration rounded to the nearest tenth.

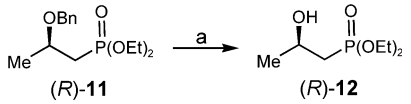
Table 3. Enantioselective hydrolysis of chloroacetates (±)-**10** in a biphasic system.

Substrate	Enzyme	mg[a]	Time [h]	Conv. [%]	Alcohol				Ester		Alcohol obtained from ester by chemical hydrolysis			
					Yield [%]	$[\alpha]_D^{20}$ (*c*)[b]	ee[c] [%]	Conf.	Yield [%]	$[\alpha]_D^{20}$ (*c*)[b]	Yield [%]	$[\alpha]_D^{20}$ (*c*)[b]	ee [%]	Conf.
(±)-**10a**	Subtilisin	1.1	4.1	45	33	+4.2 (1.0)	51	*S*	38	−76.9 (1.4)	59	–	74	*R*
(±)-**10b**	ChiroCLEC-BL	2.0	15	45	34	+11.0 (1.0)	75	*S*	40	−47.6 (1.6)	60	–	60	*R*
(±)-**10c**	CCL	40	15.4	45	29	+23.7 (0.3)	92	*S*	41	+7.4 (1.0)	55	−9 (1.5)	68	*R*
(±)-**10d**	Subtilisin	2.6	0.3	50	49	+7.4 (1.1)	71	*S*	52	−1.0 (1.2)	–	−16 (0.9)	66	*R*
(±)-**10e**	CCL	16.5	11.5	45	36	+4.8 (0.8)	93	*S*	55	+12.4 (0.8)	83	−4.4 (0.8)	65	*R*
(±)-**10f**	Chirazyme P-2	34	2	45	12	+22.6 (1.8)	87	*S*	34	−62.6 (0.9)	96	−20.1 (0.9)	71	*R*
(±)-**10f**	CCL	34	5	45	21	+33.5 (1.0)	83	*S*	37	−37.9 (1.0)	90	−27.6 (1.1)	64	*R*

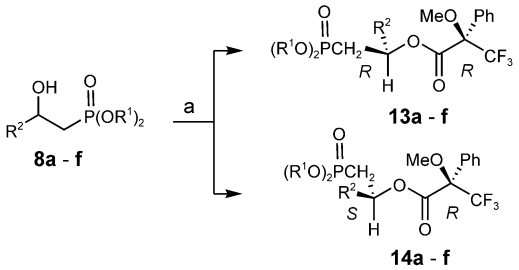
[a] Quantity of enzyme.
[b] Measured in acetone, concentration rounded to the nearest tenth.
[c] Determined by NMR spectroscopy of Mosher esters.



Scheme 7. Enantioselective hydrolysis of chloroacetates (±)-**10a–f**. a) Lipase or protease, biphasic system (phosphate buffer pH 7.0/*t*-BuOMe/hexane).



Scheme 8. Correlation of configuration of (+)-**8a** with that of (*S*)-(+)-**12**. a) Pd (10%)/C, H_2.



Scheme 9. Synthesis of (*R*)-Mosher esters from β-hydroxyphosphonates **8**. a) (*S*)-MTPA-Cl, pyridine, CH_2Cl_2, 18 h; H_2O.

results are collected in Table 3. The absolute configurations and the ee were determined by ^1H and ^{31}P NMR spectroscopy of the Mosher esters. This point will be dealt with carefully, as wrong assignments have been made. The absolute configuration of (+)-**8a** was assumed to be (*S*), as the corresponding diethyl ester prepared from 2-benzyloxypropylphosphonate (*R*)-**11** by palladium-catalyzed deprotection gave levorotatory (*R*)-**12** (Scheme 8). The absolute configuration of (*R*)-**11** is secure as it was prepared from (*R*)-isobutyl lactate

Table 4. Chemical shift differences of phosphorus and methoxy resonances of Mosher esters **13** and **14**.

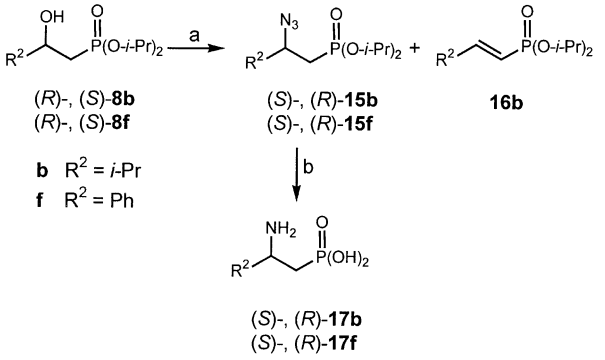
Mosher Esters **13/14**	Chemical shifts δ (ppm)		Δδ[a]
	(*S*) ($^1H/^{31}P$)	(*R*) ($^1H/^{31}P$)	
a	3.52/24.12	3.53/24.20	0.01/0.08
b	3.49/24.99	3.56/25.30	0.07/0.31
c	3.51/24.41	3.55/24.50	0.04/0.09
d	3.41/24.70	3.51/24.82	0.10/0.12
e	3.39/22.43	3.51/22.63	0.12/0.20
f	3.41/23.18	3.54/23.43	0.13/0.25

[a] $\Delta\delta = \delta(R) - \delta(S)$.

by the same sequence as the dideuterated species except using $LiAlH_4$ instead of $LiAlD_4$.[21] This assignment is in agreement with Noyori's assignment of (*R*) configuration to levorotatory dimethyl 2-hydroxypropylphosphonate.[8] Therefore the reduction of diethyl 2-oxopropylphosphonate by baker's yeast gives (*S*)-, but not (*R*)-**12** previously assigned by analogy.[11] Noyori et al. determined the absolute configurations of their dimethyl 2-hydroxyphosphonates by a modified Mosher's method using (*R*)- and (*S*)-MTPA esters.

Diastereomeric (*R*)-Mosher esters **13** and **14** obtained from (*S*)-MTPA-Cl and (*R*)- and (*S*)-**8** are drawn in the generally accepted conformation model with the trifluoromethyl group and the carbinyl hydrogen being eclipsed with the carbonyl oxygen.[22,23] The phosphorus atom in the (*R*)-MTPA ester **14** is shielded by the phenyl group when the β-hydroxyphosphonate has (*S*)-configuration relative to the phosphorus in diastereomer **13**. Consequently, the phosphorus of Mosher ester **14** will resonate at higher field than that of Mosher ester **13** (Table 4). The methoxy group of the Mosher group of **13** is deshielded by the phosphonate group relative to the methoxy group of **14**. The signal of the methoxy group of

14 will therefore be upfield in the ^{1}H NMR spectrum relative to the signal of **13**. The shift differences are larger (0.08 – 0.25 ppm) for the phosphorus signal than the methoxy signals (0.01 – 0.13 ppm). The shift differences are smallest for 2-hydroxypropylphosphonate **8a**, nevertheless the configuration is assigned correctly. Noyori et al. found that dimethyl 2-hydroxy-2-phenylethylphosphonate prepared from (*R*)-styrene oxide is levorotatory. We find that levorotatory diisopropyl phosphonate **8f** has also (*R*)-configuration. Wrong absolute configurations have been assigned to (+)-**8f** in ref.[10], to (+)-**8a** and very likely also to diethyl 2-(2-pyridyl)-2-hydroxyethylphosphonate in ref.[3]



Scheme 10. Conversion of chiral, non-racemic β-hydroxyphosphonates **8** to β-aminophosphonic acids. a) Ph_3P, DIAD, HN_3; b) Ph_3P, H_2O; 6 M HCl, reflux; Dowex 1, AcO^-.

Synthesis of Chiral, Non-Racemic 2-Aminophosphonic Acids

β-Aminophosphonic acids are structural analogues of β-amino acids which have attracted much interest in recent years. 2-Amino-3-phosphonopropionic acid[24] and 2-amino-1-hydroxyethylphosphonic acid[25] are naturally occurring β-aminophosphonic acids. Substituted β-aminodiphosphonic acids are pyrophosphate analogues which inhibit osteoclastic bone resorption, one is used as a therapeutic.[26] β-Amino-α-hydroxyphosphonic acid derivatives are transition state analogue inhibitors of human rennin.[27] Racemic β-aminophosphonic acids are prepared by a variety of methods, especially reductive amination of β-ketophosphonates.[28] Chiral, non-racemic β-aminophosphonic acids were prepared from chiral 2-aminoalcohols[29] or by diastereoselective addition[30] of lithiated methylphosphonic acid esters to (*S*)-sulfinimines.

We show on two representative examples that chiral, non-racemic β-hydroxyphosphonates can be transformed into β-aminophosphonic acids using the Mitsunobu reaction, previously used to transform an enantiopure β-hydroxy-α-silyloxyethylphosphonate[31] into the corresponding β-azidophosphonates (Scheme 10, Table 5).

Chiral, non-racemic β-hydroxyphosphonates **8b** and **8f** with ee 50 – 98% prepared by hydrolase-catalyzed resolution of the corresponding racemic chloroacetates on a preparative scale (5 – 8 mmol), were treated with Ph_3P/DIAD/HN_3. In the case of the benzylic hydroxy group, azides **15f** were formed rapidly. In the case of the sterically more hindered alcohol **8b** elimination was an alternative to substitution resulting in inseparable mixtures of azide **15b** and olefin **16b**, which were used directly for the next step. Reduction of the azides to the amines was achieved in two steps: first Staudinger reaction and then hydrolysis of the iminophosphorane, followed by removal of the isopropyl protecting groups with hot 6 M hydrochloric acid, and purification by ion exchange chromatography furnished chiral, non-racemic β-aminophosphonic acids **17b** and **17f**.[7] Their

Table 5. Conversion of β-hydroxyphosphonates **8** to β-aminophosphonic acids **17**.

Alcohol **8** ee [%][a]	Azide **15**			β-Aminophosphonic acid **17**			
	Yield [%]	Conf.	$[\alpha]_D^{20}$ (*c*)[b]	Yield [%]	$[\alpha]_D^{20}$ (*c*)[c]	Conf.	ee [%][d]
(*R*)-**8b** 98	66[f]	*S*	− 0.5 (1.2)	58	+ 13.4 (0.6)	*S*	99
(*S*)-**8b** 65	82[e]	*R*	+ 2.6 (1.3)	77	− 8.2 (0.6)	*R*	68
(*R*)-**8f** 50	90	*S*	+ 34.9 (2.1)	93	− 9.4 (0.7)	*S*	44
(*S*)-**8f** 95	73	*R*	− 68.8 (1.3)	79	+ 13.2 (0.7)	*R*	96

[a] Determined by NMR spectroscopy of Mosher ester.
[b] Measured in acetone, concentration rounded to the nearest tenth.
[c] Measured in 1 M NaOH, concentration rounded to the nearest tenth.
[d] Determined by HPLC on chiral stationary phase.
[e] Mixture of azide **15b** and olefin **16b** (82 : 18).
[f] Mixture of azide **15b** and olefin **16b** (83 : 17).

racemic counterparts have been prepared by reductive amination.[28] The enantiomeric excesses of their *N*-2,4-dinitrophenyl derivatives were determined by enantioselective HPLC on chiral, stationary phase based on *O*-9-*t*-butylcarbamoylquinine as chiral selector CSP II[33] and agreed (Table 5) with the ee of the starting β-hydroxyphosphonates. The (*R*)-enantiomers of the derivatives of the β-aminophosphonic acids were stronger retained than the (*S*)-enantiomers.

Conclusion

We have demonstrated that the esterification of diisopropyl α- and β-hydroxyphosphonates by hydrolases with isopropenyl acetate as acyl donor in organic solvents is of limited value for the preparation of chiral, non-racemic β-hydroxyphosphonates, although the ee for compounds acting as substrates are high. The alternative, the enantioselective hydrolysis of β-chloroacetoxyphosphonates in a biphasic system gives chiral, non-racemic β-hydroxyphosphonates with ee up to 94% at a conversion of 45%. Their ee and absolute configuration can be determined easily by NMR spectroscopy, preferably ^{31}P NMR, of the Mosher esters. Two chiral, non-racemic β-hydroxyphosphonates were converted to β-aminophosphonic acids *via* their azides with clean inversion of configuration by the Mitsunobu reaction.

Experimental Section

General Remarks

All starting materials and enzymes were obtained form commercial suppliers and were generally used without further purification. ^{1}H and ^{13}C NMR (*J* modulated) spectra were recorded in $CDCl_3$ unless otherwise given, using residual $CHCl_3$ ($\delta = 7.24$) for calibration of ^{1}H NMR spectra and $CDCl_3$ for calibration of ^{13}C NMR spectra ($\delta = 77.00$) on a Bruker AM 400 WB spectrometer at 400.13 and 100.61 MHz, respectively. ^{31}P NMR spectra were recorded on the same spectrometer at 161.97 MHz using H_3PO_4 (85%) as external standard. In order to get undistorted ^{31}P signal intensities for an accurate integration, adequate relaxation times were used without irradiation during this period to avoid NOE enhancements. Chemical shifts (δ) are given in ppm. IR spectra were run on a Perkin-Elmer 1600 FT-IR spectrometer; liquid samples were measured as films between NaCl plates or on a silicon disc.[34] Optical rotations were measured at 20 °C on a Perkin-Elmer 351 polarimeter in a 1 dm cell. TLC was carried on 0.25 mm thick Merck plates, silica gel 60 F_{254}. Flash chromatography was performed with Merck silica gel 60 (230–240 mesh). Spots were visualized by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24} \cdot 4\,H_2O$ (24.0 g) and of $Ce(SO_4)_2 \cdot 4\,H_2O$ (1.0 g) in 10% H_2SO_4 in water (500 mL), followed by heating with a hot-air gun. Melting points were determined on a Reichert Thermovar instrument and were uncorrected. A Metrohm 702 SM Titrino instrument was used as an autotitrator. (*S*)-(+)-α-(Trifluoromethyl)phenylacetyl chloride {JPS Chimie; $[\alpha]_D^{20}$: +126.5 (*c* 5.2, CCl_4), ee >99.5%} was used for derivatization of α- and β-hydroxyphosphonates. Enzymes (lyophilized preparations of lipases and proteases) were stored at +4 °C and were used as supplied.

Enzymes used: Acylase I (from porcine kidney), Pen-G amidase, chymotrypsin A_4 (from bovine pancreas), PPL (from bovine pancreas), Chirazyme® L-9 (from *Aspergillus niger*, Boehringer Mannheim), Chirazyme® P-2 (alkaline endoprotease, Boehringer Mannheim), CCL (lipase from *Candida cylindracea*), protease papain (from *Carica papaya*), subtilisin (from *Bacillus subtilis*), protease ChiroCLEC™-BL (cross-linked microcrystalline subtilisin), pronase (from *Streptomyces griseus*), lipases from Amano: SAM I (from *Pseudomonas fluorescens)* and II (from *Pseudomonas* sp.), AP 6 (from *Aspergillus niger*), F-AP 15 (from *Rhizopus oryzae*), D 20 (from *Rhizopus delemar*), GC 4 (from *Geotrichum candidum*); PS (from *Pseudomonas* sp.), M 10 *(*from *Mucor javanicus*), G 50 (from *Penicillium camembertii*), N (from *Rhizopus niveus*), R 10 (from *Penicillium roqueforti*), AK (from *Pseudomonas fluorescens*), proteases from Amano: M (*from Aspergillus*), B (from *Penicillium*), A (from *Aspergillus*), S (from *Bacillus*), N (from *Bacillus*), acid protease II (from *Rhizopus*), proleather (from *Bacillus*), prozyme 6 (from *Aspergillus*); lipases from Novo Nordisk: 523 (from *Humicola*), SP 524 (from *Mucor*), SP 525 (lipase B from *Candida antarctica*), SP 526 (lipase A from *Candida antarctica*), Novozym 435 (immobilized CAL B, from *Candida antarctica*).

Preparation of α-Hydroxyphosphonates (±)-3a–f, except 1a (General Procedure A)

To a stirred solution of diethyl phosphite (1.38 g, 2.58 mL, 20 mmol) or diisopropyl phosphite (3.23 g, 3.26 mL, 20 mmol) in dry diethyl ether (30 mL) *n*-BuLi (2 mL of a 1.6 M solution in hexane) was added dropwise at −78 °C. After 30 min a solution of the aldehyde (22 mmol) in dry diethyl ether (5 mL) was added and stirring was continued for 1 h. Concentrated H_2SO_4 (3.5 mmol) was added and stirring was continued 10 min. The reaction mixture was concentrated. The residue was taken up in water (10 mL) and extracted three times with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography and if appropriate also by bulb-to-bulb distillation. The spectroscopic data are identical with those reported.[5a] (±)-**1a** was prepared by a literature procedure.[5b]

Preparation of β-Hydroxyphosphonates (±)-8a–f (General Procedure B)

To a stirred solution of diethyl methylphosphonate (1.52 g, 1.46 mL, 10 mmol) or diisopropyl methylphosphonate[35] (1.80 g, 1.85 mL, 10 mmol) in dry THF (20 mL) *s*-BuLi (10 mL of a 1.3 M solution in cyclohexane) or *n*-BuLi (7.5 mL of a 1.6 M solution in hexane) was added dropwise at −78 °C under argon. After 30 min a solution of the aldehyde 2 (12 mmol) in dry THF (5 mL) was added and stirring was continued for 1 h. Acetic acid (0.69 mL, 12 mmol) was added and stirring was continued for 15 min. The reaction mixture

was concentrated under vacuum. The residue was taken up in water (10 mL) and extracted three times with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography and if appropriate also by bulb-to-bulb distillation.

Preparation of β-Chloroacetoxyphosphonates (±)-10 (General Procedure C)

Under argon at 0 °C, a solution of chloroacetic anhydride (90%, 1.34 g, 7.84 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a solution of β-hydroxyphosphonate (±)-**8** (5 mmol) and dry pyridine (1.25 mL) in dry CH_2Cl_2 (20 mL). After stirring for 1 h (TLC: hexane/ethyl acetate, 1:4), the mixture was diluted with H_2O (10 mL) and stirring was continued for 10 min. After addition of concentrated hydrochloric acid (1 mL) the organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with H_2O (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography.

Enzymatic Hydrolysis of Chloroacetates (±)-10 (General Procedure D)

Chloroacetates (±)-**10a–f** (1 mmol) were hydrolyzed enzymatically in a biphasic system (17 mL of a 50 mM phosphate buffer pH 7.0/4 mL of a mixture of hexane/*t*-butyl methyl ether, 1:1) by lipases or proteases (Table 3) as described in the literature except that the reaction mixture was extracted directly after acidification.[36]

Hydrolysis of Chloroacetates (±)-10b, f on a Preparative Scale

Chloroacetate (±)-**10b** (1.846 g, 5.61 mmol) was hydrolyzed in a biphasic system [50 mL of a 50 mM phosphate buffer pH 7.0/20 mL of mixture of hexane/*t*-butyl methyl ether, 1:1; 0.40 g of lipase from *C. cylindracea* (CCL); conversion: 49% by consumption of base] to yield β-hydroxyphosphonate (*S*)-**8b** {0.252 g (18%), $[\alpha]_D^{20}$: +9.9 (*c* 1.0, acetone), ee 65%}, a mixture (0.264 g) of (*S*)-**8b** and ester (*R*)-**10b**, and (*R*)-**10b** {0.423 g (23%), $[\alpha]_D^{20}$: −2.5 (*c* 0.88, acetone)} which gave β-hydroxyphosphonate (*R*)-**8b** {0.306 g (94%), $[\alpha]_D^{20}$: −14.8 (*c* 1.15, acetone), ee 98%} on chemical hydrolysis by General Procedure E.

Similarly, chloroacetate (±)-**10f** (2.722 g, 7.5 mmol) was hydrolyzed in a biphasic system [50 mL of a 50 mM phosphate buffer pH 7.0/20 mL of mixture of hexane/*t*-butyl methyl ether, 1:1; 48 mg of protease P-2 (alkaline endoprotease); conversion: 35% by consumption of base] to yield β-hydroxyphosphonate (*S*)-**8f** {0.56 g (26%), $[\alpha]_D^{20}$: +37.5 (*c* 0.55, acetone), ee 95%} and (*R*)-**10b** {1.349 g (50%), $[\alpha]_D^{20}$: −31.0 (*c* 0.775, acetone)} which gave β-hydroxyphosphonate (*R*)-**8f** {1.01 g (95%), $[\alpha]_D^{20}$: −22.9. (*c* 2.0, acetone), $[\alpha]_D^{20}$: −15.2 (*c* 0.825, $CHCl_3$)[10] ee 50%} on chemical hydrolysis by General Procedure E.

Chemical Hydrolysis of Esters 4, 9 and 10 (General Procedure E)

A solution of ester (0.5 mmol) in MeOH (5 mL), triethylamine (1 mL) and water (1 mL) was stirred at room temperature until all the ester was hydrolyzed (up to 18 h; TLC: CH_2Cl_2/ethyl acetate, 1:1). The solvent was removed under vacuum. The residue was purified by flash chromatography.

Preparation of Mosher Esters 13 and 14 from β-Hydroxyphosphonates 8 (General Procedure F)

A solution of β-hydroxyphosphonate **8** (0.05 mmol), (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-(+)-MTPA-Cl] (0.158 mmol, 0.2 mL of a 0.79 M solution of (*S*)-(+)-MTPA-Cl in dry CH_2Cl_2), dry pyridine (1 mL) and CH_2Cl_2 (0.5 mL) was stirred under argon for 18 h at room temperature (TLC: hexane/ethyl acetate, 1:2). After addition of water (0.5 mL) the solvent was removed under reduced pressure. The residue was diluted with hydrochloric acid (2 M, 5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate, 1:2).

Preparation of β-Aminophosphonic Acids 17 (General Procedure G)

A solution of azide **15** (1 mmol) and triphenylphosphane (1.16 mmol) in a mixture of dry THF (8 mL) and water (0.8 mL) was stirred for 3 h at room temperature and 16 h at 50 °C (TLC: CH_2Cl_2/ethyl acetate, 1:2) and concentrated under reduced pressure. Hydrochloric acid (10 mL, 6 M) was added to the residue and the mixture was refluxed for 5 h. The cooled reaction mixture was diluted with water (15 mL), extracted with diethyl ether to remove triphenylphosphane oxide, and concentrated under reduced pressure. The residue was purified by ion exchange chromatography (Dowex 1X8, 100–200 mesh, acetate form, column: Ø 1.5 cm × 74 cm). Fractions containing product {TLC (2-propanol/water/concentrated ammonia, 6:3:1) or PC[37]} were pooled and concentrated under reduced pressure to give the respective β-aminophosphonic acid.

(±)-Diisopropyl 2-Hydroxypropylphosphonate [(±)-3a]

This hydroxyphosphonate was prepared by General Procedure B using acetaldehyde (10 mmol), diisopropyl methylphosphonate and *n*-BuLi. Flash chromatography (ethyl acetate, R_f = 0.35) gave (±)-**3a**[19c] as a colorless oil; yield: 1.75 g (78%). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.19 (dd, *J* = 2.5, 6.3 Hz, 3H, CH_3), 1.25 [d, *J* = 6.1 Hz, 3H, OCH(C<u>H</u>$_3$)$_2$], 1.26 [d, *J* = 6.1 Hz, 6H, OCH(C<u>H</u>$_3$)$_2$], 1.27 [d, *J* = 6.1 Hz, 3H, OCH(C<u>H</u>$_3$)$_2$], 1.79 (AB part of ABMX system, J_{AB} = 15.2 Hz, J_{AP} = 18.7 Hz, J_{AH} = 3.0 Hz, J_{BP} = 17.2 Hz, J_{BH} = 8.8 Hz, 2H, CH_2P), 3.61 (s, 1H, OH), 4.09 (m, 1H, C<u>H</u>OH), 4.65 [m, 2H, OC<u>H</u>(CH$_3$)$_2$]; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.97 [d, *J* = 5.4 Hz, OCH(<u>C</u>H$_3$)$_2$], 23.98 [d, *J* = 3.1 Hz, OCH(<u>C</u>H$_3$)$_2$], 23.99 [d, *J* =

4.6 Hz, 2C, OCH($\underline{C}H_3)_2$], 24.22 (d, $J = 18.4$ Hz, $\underline{C}H_3COH$), 36.37 (d, $J = 138.4$ Hz, CH_2P), 62.90 (d, $J = 6.1$ Hz, CHOH), 70.51 [d, $J = 6.9$ Hz, O$\underline{C}H(CH_3)_2$], 70.57 [d, $J = 6.9$ Hz, O$\underline{C}H(CH_3)_2$].

(±)-Diisopropyl 2-Hydroxy-3-methybutylphosphonate [(±)-3b]

This hydroxyphosphonate was prepared by General Procedure B using isobutyraldehyde (10 mmol), diisopropyl methylphosphonate and *n*-BuLi. Flash chromatography (EtOAc, $R_f = 0.35$) gave (±)-**3b**[19d] as a colorless oil; yield: 1.75 g (78%). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 6.3$ Hz, 3H, CH_3), 0.90 (d, $J = 7.1$ Hz, 3H, CH_3), 1.296 [d, $J = 6.1$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.302 [d, $J = 6.3$ Hz, 6H, OCH($C\underline{H}_3)_2$], 1.31 [d, $J = 6.1$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.69 [m, 1H, C$\underline{H}(CH_3)_2$], 1.80 (m, 2H, CH_2P), 3.59 (br. s, 1H, OH), 3.71 (ddt, $J = 2.0, 5.3, 11.1$ Hz, 1H, C$\underline{H}$OH), 4.70 [m, 2H, OC$\underline{H}(CH_3)_2$]; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 17.56$ (CH_3), 17.94 (CH_3), 23.98 [d, $J = 3.8$ Hz, OCH($\underline{C}H_3)_2$], 24.00 [d, $J = 3.8$ Hz, OCH($\underline{C}H_3)_2$], 24.03 [d, $J = 3.8$ Hz, 2C, OCH($\underline{C}H_3)_2$], 31.32 (d, $J = 140.0$ Hz, CH_2P), 34.08 (d, $J = 16.8$ Hz, $\underline{C}$HCCP), 62.90 (d, $J = 6.1$ Hz, CHOH), 70.51 [d, $J = 6.9$ Hz, 2C, O$\underline{C}H(CH_3)_2$], 70.57 (d, $J = 6.9$ Hz, CHOH).

(±)-Diisopropyl 2-Hydroxyheptylphosphonate [(±)-3c]

This hydroxyphosphonate was prepared by General Procedure B using hexanal (10 mmol), diisopropyl methylphosphonate and *n*-BuLi. Flash chromatography (ethyl acetate/CH_2Cl_2, 2:1, $R_f = 0.40$) followed by bulb-to-bulb distillation (95 °C/16 Torr) afforded (±)-**3c** as a colorless oil; yield: 1.94 g (69%). IR (Si): $\tilde{\nu} = 3388, 2932, 1226, 987$ cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.84$ [t, $J = 6.8$ Hz, 3H, $C\underline{H}_3(CH_2)_4$], 1.26 (m, 5H, CH_2), 1.27 [d, $J = 5.8$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.28 [m, $J = 6.1$ Hz, 6H, OCH($C\underline{H}_3)_2$], 1.29 [d, $J = 6.1$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.40 (m, 2H, CH_2), 1.52 (m, 1H, CH_2), 1.82 (AB part of ABMX system, $J_{AB} = 15.2$ Hz, $J_{AP} = 19.2$ Hz, $J_{AH} = 2.3$ Hz, $J_{BP} = 15.2$ Hz, $J_{BH} = 9.6$ Hz, 2H, CH_2P), 3.33 (s, 1H, OH), 3.91 (m, 1H, C$\underline{H}$OH), 4.68 [m, 2H, OC$\underline{H}(CH_3)_2$]; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.99$ (CH_3), 22.57 (CH_2), 23.99 [d, $J = 4.6$ Hz, OCH($\underline{C}H_3)_2$], 24.01 [d, $J = 3.8$ Hz, OCH($\underline{C}H_3)_2$], 24.04 [d, $J = 5.4$ Hz, OCH($\underline{C}H_3)_2$], 24.05 [d, $J = 3.8$ Hz, OCH($\underline{C}H_3)_2$], 25.06 (d, $J = 1.5$ Hz, CH_2), 31.69 (CH_2), 34.64 (d, $J = 138.4$ Hz, CH_2P), 38.15 (d, $J = 16.8$ Hz, C-3), 66.57 (d, $J = 6.1$ Hz, CHOH), 70.53 [d, $J = 5.4$ Hz, O$\underline{C}H(CH_3)_2$], 70.54 [d, $J = 5.4$, $\underline{C}H(CH_3)_2$]; anal. calcd. (%) for $C_{13}H_{29}O_4P$: C 55.70, H 10.42; found: C 55.43, H 10.27.

(±)-Diethyl 2-Hydroxy-2-(2-thienyl)ethylphosphonate [(±)-3d]

This hydroxyphosphonate was prepared by General Procedure B using thiophene-2-carbaldehyde (20 mmol), diisopropyl methylphosphonate and *s*-BuLi. Flash chromatography (hexane/ethyl acetate, 1:2, $R_f = 0.35$) gave (±)-**3d**[19b] as a yellow oil; yield: 4.81 g (91%). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$), 1.31 (t, $J = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$), 2.30 (m, 2H, CH_2P), 4.09 (m, 5H, OCH_2, OH), 5.33 (m, 1H, C$\underline{H}$OH), 6.93 (dd, $J = 3.5, 4.9$ Hz, 1H, H_{arom}), 6.96 (dd, $J = 1.3, 3.5$ Hz, 1H, H_{arom}), 7.22 (dd, $J = 1.3, 4.9$ Hz, 1H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 16.32$ (d, $J = 6.1$ Hz, $OCH_2\underline{C}H_3$), 16.38 (d, $J = 5.4$ Hz, $OCH_2\underline{C}H_3$), 36.05 (d, $J = 136.9$ Hz, PCH_2), 61.97 (d, $J = 6.1$ Hz, O$\underline{C}H_2CH_3$), 62.16 (d, $J = 6.1$ Hz, O$\underline{C}H_2CH_3$), 65.20 (d, $J = 3.8$ Hz, CHOH), 123.40 (HC_{arom}), 124.70 (HC_{arom}), 126.60 (HC_{arom}), 147.47 (d, $J = 19.1$ Hz, C_{arom}).

(±)-Diisopropyl 2-Hydroxy-2-(2-thienyl)ethylphosphonate [(±)-3e]

This hydroxyphosphonate was prepared by General Procedure B using thiophene-2-carbaldehyde (10 mmol), diisopropyl methylphosphonate and *s*-BuLi. Flash chromatography (hexane/ethyl acetate, 1:2, $R_f = 0.44$) gave (±)-**3e** as a yellow solid; yield: 2.54 g (87%), mp 66 °C (hexane). IR (Si): $\tilde{\nu} = 3321, 2979, 1386, 1224, 993$ cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.28$ [d, $J = 6.1$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.31 [d, $J = 6.1$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.32 [d, $J = 6.1$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.33 [d, $J = 6.3$ Hz, 3H, OCH($C\underline{H}_3)_2$], 2.25 (m, 2H, CH_2P), 4.28 (d, $J = 2.5$ Hz, 1H, OH), 4.71 [m, 2H, C$\underline{H}(CH_3)_2$], 5.31 (m, 1H, C$\underline{H}$OH), 6.94 (m, 2H, H_{arom}), 7.22 (dd, $J = 1.5$, 5.0 Hz, 1H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.89$ [d, $J = 4.6$ Hz, OCH($\underline{C}H_3)_2$], 23.99 [d, $J = 4.6$ Hz, OCH($CH_3)_2$], 24.04 [d, $J = 5.4$ Hz, OCH($C\underline{H}_3)_2$], 24.05 [d, $J = 3.1$ Hz, OCH($C\underline{H}_3)_2$], 37.24 (d, $J = 137.7$ Hz, CH_2P), 65.36 (d, $J = 4.6$ Hz, $\underline{C}$HOH), 70.90 [d, $J = 6.9$ Hz, O$\underline{C}H(CH_3)_2$], 71.06 [d, $J = 6.1$ Hz, O$\underline{C}H(CH_3)_2$], 123.24 (HC_{arom}), 124.62 (HC_{arom}), 126.55 (HC_{arom}), 147.49 (d, $J = 19.9$ Hz, C_{arom}); anal. calcd. (%) for $C_{12}H_{21}O_4PS$: C 49.30, H 7.24; found: C 49.16, H 7.06.

(±)-Diisopropyl 2-Hydroxy-2-phenylethylphosphonate [(±)-3f]

This hydroxyphosphonate was prepared by General Procedure B using freshly distilled benzaldehyde (10 mmol), diisopropyl methylphosphonate and *n*-BuLi. Flash chromatography (hexane/ethyl acetate, 1:2, $R_f = 0.30$) gave (±)-**3f** as a solid; yield: 2.64 g (92%); mp 69–70 °C (hexane). IR (Si): $\tilde{\nu} = 3350, 2979, 1386, 1222, 993$ cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.26$ [d, $J = 6.3$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.30 [d, $J = 6.3$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.34 [d, $J = 6.3$ Hz, 3H, OCH($C\underline{H}_3)_2$], 1.35 [d, $J = 6.3$ Hz, 3H, OCH($C\underline{H}_3)_2$], 2.13 (m, 2H, CH_2P), 4.12 (d, $J = 2.0$ Hz, 1H, OH), 4.68 [m, 1H, OC$\underline{H}(CH_3)_2$], 4.76 [m, 1H, OC$\underline{H}(CH_3)_2$], 5.06 (m, 1H, C$\underline{H}$OH), 7.25 (m, 1H, H_{arom}), 7.34 (m, 4H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.89$ [d, $J = 4.6$ Hz, OCH($\underline{C}H_3)_2$], 24.00 [d, $J = 3.8$ Hz, OCH($\underline{C}H_3)_2$], 24.05 [d, $J = 3.8$ Hz, OCH($\underline{C}H_3)_2$], 37.19 (d, $J = 136.9$ Hz, CH_2P), 68.81 (d, $J = 4.6$ Hz, CHOH), 70.76 [d, $J = 6.8$ Hz, O$\underline{C}H(CH_3)_2$], 70.87 [d, $J = 6.2$ Hz, O$\underline{C}H(CH_3)_2$], 125.48 (2C, HC_{arom}), 127.59 (HC_{arom}), 128.46 (2C, HC_{arom}), 143.53 (d, $J = 16.8$ Hz, C_{arom}); anal. calcd. (%) for $C_{14}H_{23}O_4P$: C 58.73, H 8.09; found: C 59.00, H 7.83.

(±)-Diisopropyl 2-Chloroacetoxypropylphosphonate [(±)-10a]

This chloroacetate was prepared from hydroxyphosphonate (±)-**3a** (5 mmol) by General Procedure C. Flash chromatography (hexane/ethyl acetate, 1:4, $R_f = 0.43$) gave (±)-**10a** as a colorless liquid; yield: 1.01 g (67%). IR (Si): $\tilde{\nu} = 2980$, 2937, 1758, 1245, 1179, 1140, 1107, 982 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.29$ [d, $J = 6.3$ Hz, 6H, $OCH(C\underline{H}_3)_2$], 1.30 [d, $J = 6.3$ Hz, 6H, $OCH(C\underline{H}_3)_2$], 1.38 (d, $J = 6.3$ Hz, 3H, CH_3), 2.04 (AB part of ABMX system, $J_{AB} = 15.2$ Hz, $J_{AH} = 6.1$ Hz, $J_{AP} = 19.2$ Hz, $J_{BP} = 19.0$ Hz, $J_{BH} = 7.1$ Hz, 2H, PCH_2), 4.01 (AB system, $J = 15.2$ Hz, 2H, CH_2Cl), 4.68 [m, 2H, $OC\underline{H}(CH_3)_2$], 5.25 (dsext, $J = 6.6$, 9.4 Hz, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 21.07$ (d, $J = 7.7$ Hz, CH_3), 23.97 [d, $J = 5.4$ Hz, $OCH(\underline{C}H_3)_2$], 23.98 [d, $J = 5.4$ Hz, $OCH(\underline{C}H_3)_2$], 24.01 [d, $J = 3.8$ Hz, 2C, $OCH(\underline{C}H_3)_2$], 33.99 (d, $J = 141.5$ Hz, CH_2P), 41.04 (CH_2Cl), 68.66 (OCH), 70.47 [d, $J = 5.4$ Hz, $O\underline{C}H(CH_3)_2$], 70.54 [d, $J = 6.0$ Hz, $O\underline{C}H(CH_3)_2$], 166.39 (CO); anal. calcd. (%) for $C_{11}H_{22}ClO_5P$: C 43.94, H 7.37; found: C 43.72, H 7.11.

(±)-Diisopropyl 2-Chloroacetoxy-3-methybutylphosphonate [(±)-10b]

This chloroacetate was prepared from hydroxyphosphonate (±)-**3b** (6.05 mmol) by General Procedure C. Flash chromatography (hexane/ethyl acetate, 1:2, $R_f = 0.50$) gave (±)-**10b** as a colorless oil; yield: 1.89 g (95%). IR (Si): $\tilde{\nu} = 2978$, 1762, 1252, 1178, 987 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.89$ [d, $J = 6.8$ Hz, 6H, $(C\underline{H}_3)_2CH$], 1.27 [d, $J = 6.3$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.277 [d, $J = 5.8$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.28 [d, $J = 6.1$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.29 [d, $J = 5.8$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.97 (m, 2H, CH_2P), 4.03 (AB system, $J = 14.6$ Hz, 2H, CH_2Cl), 4.66 [m, 2H, $OC\underline{H}(CH_3)_2$], 5.13 (ddt, $J = 4.6$, 8.8, 10.9 Hz, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 16.88$ [$CH(\underline{C}H_3)_2$], 18.11 [$CH(\underline{C}H_3)_2$], 23.93 [d, $J = 5.4$ Hz, $OCH(C\underline{H}_3)_2$], 23.97 [d, $J = 6.2$ Hz, $OCH(C\underline{H}_3)_2$], 24.00 [d, $J = 5.4$ Hz, 2C, $OCH(C\underline{H}_3)_2$], 29.21 (d, $J = 143.8$ Hz, CH_2P), 32.29 [d, $J = 12.2$ Hz, $O\underline{C}H(CH_3)_2$], 41.08 (s, CH_2Cl), 70.33 [d, $J = 6.1$ Hz, $O\underline{C}H(CH_3)_2$], 70.48 [d, $J = 6.1$ Hz, $O\underline{C}H(CH_3)_2$], 74.79 (d, $J = 4.6$ Hz, CHO), 166.5 (CO); anal. calcd. (%) for $C_{13}H_{26}ClO_5P$: C 47.49, H 7.97; found: C 47.61, H 7.75.

(±)-Diisopropyl 2-Chloroacetoxyheptylphosphonate [(±)-10c]

This chloroacetate was prepared from hydroxyphosphonate (±)-**3c** (5 mmol) by General Procedure C. Flash chromatography (hexane/ethyl acetate, 1:2, $R_f = 0.60$) gave (±)-**10c** as a colorless oil; yield: 1.47 g (83%). IR (Si): $\tilde{\nu} = 2979$, 2959, 1761, 1246, 1178, 986 cm^{-1}; ^1H NMR(400.1 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.7$ Hz, 3H, CH_3), 1.27 (m, 6H, CH_2), 1.28 [d, $J = 5.8$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.289 [d, $J = 6.3$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.29 [d, $J = 6.3$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.30 [d, $J = 5.8$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.67 (m, 2H, CH_2), 2.02 (AB part of ABMX system, $J_{AB} = 15.4$ Hz, $J_{AP} = 18.4$ Hz, $J_{AH} = 7.3$ Hz, $J_{BP} = 19.2$ Hz, $J_{BH} = 6.1$ Hz, 2H, CH_2P), 4.02 (AB system, $J_{AB} = 14.9$ Hz, 2H, CH_2Cl), 4.67 [m, 2H, $OC\underline{H}(CH_3)_2$] 5.21 (m, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.91$ (CH_3), 22.42 (CH_2), 23.97 [d, $J = 5.4$ Hz, $OCH(\underline{C}H_3)_2$], 23.98 [d, $J = 2.3$ Hz, $OCH(\underline{C}H_3)_2$], 24.00 [d, $J = 6.9$ Hz, $OCH(\underline{C}H_3)_2$], 24.04 [d, $J = 6.0$ Hz, $OCH(\underline{C}H_3)_2$], 24.55 (CH_2), 31.33 (CH_2), 32.25 (d, $J = 142.3$ Hz, CH_2P), 34.95 (d, $J = 8.4$ Hz, C-3), 41.08 (CH_2Cl), 70.41 [d, $J = 6.9$ Hz, $O\underline{C}H(CH_3)_2$], 70.52 [d, $J = 6.9$ Hz, $O\underline{C}H(CH_3)_2$], 71.51 (d, $J = 2.3$ Hz, CHO), 166.58 (CO); anal. calcd. (%) for $C_{15}H_{30}ClO_5P$: C 50.49, H 8.47; found: C 50.42, H 8.22.

(±)-Diethyl 2-Chloroacetoxy-2-(2-thienyl)ethylphosphonate [(±)-10d]

This chloroacetate was prepared from hydroxyphosphonate (±)-**3d** (5 mmol) by General Procedure C. Flash chromatography (hexane/ethyl acetate, 1:4, $R_f = 0.40$) gave (±)-**10d** as a colorless oil; yield: 1.57 g (92%). IR (Si): $\tilde{\nu} = 2984$, 1762, 1440, 1393, 1260, 1163, 1100, 1024, 970 cm^{-1}; ^1H NMR(400.1 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 6.8$ Hz, 3H, $OCH_2C\underline{H}_3$), 1.23 (t, $J = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$), 2.54 (AB part of ABMX system, $J_{AB} = 15.6$ Hz, $J_{AP} = 17.6$ Hz, $J_{AH} = 8.6$ Hz, $J_{BP} = 19.2$ Hz, $J_{BH} = 5.5$ Hz, 2H, CH_2P), 4.04 (AB system, J_{AB}=14.9 Hz, 2H, CH_2Cl), 4.05 (m, 4H, $OC\underline{H}_2CH_3$), 6.44 (dt, $J = 5.5$, 8.6 Hz, 1H, $C\underline{H}O$), 6.94 (dd, $J = 3.5$, 5.1 Hz, 1H, H_{arom}), 7.12 (dd, $J = 1.2$, 5.1 Hz, 1H, H_{arom}), 7.29 (dd, $J = 1.2$, 3.5 Hz, 1H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 16.25$ (d, $J = 4.6$ Hz, $OCH_2\underline{C}H_3$), 16.31 (d, $J = 6.1$ Hz, $OCH_2\underline{C}H_3$), 33.33 (d, $J = 142.3$ Hz, CH_2P), 40.85 (d, $J = 22.9$ Hz, CH_2Cl), 62.23 (d, $J = 6.9$ Hz, $O\underline{C}H_2CH_3$), 62.39 (d, $J = 6.9$ Hz, $O\underline{C}H_2CH_3$), 67.90 (d, $J = 1.5$ Hz, OCH), 123.39 (HC_{arom}), 124.70 (HC_{arom}), 126.57 (HC_{arom}), 141.35 (d, $J = 19.1$ Hz, $C_{arom.}$), 165.98 (CO); anal. calcd. (%) for $C_{12}H_{18}ClO_5PS$: C 42.29, H 5.32; found: C 42.27, H 5.18.

(±)-Diisopropyl 2-Chloroacetoxy-2-(2-thienyl)ethylphosphonate [(±)-10e]

This chloroacetate was prepared from hydroxyphosphonate (±)-**3e** (4.99 mmol) by General Procedure C. Flash chromatography (hexane/ethyl acetate, 1:2, $R_f = 0.50$) gave (±)-**10e** as a colorless oil; yield: 1.67 g (91%). IR (Si): $\tilde{\nu} = 2980$, 1763, 1244, 1164, 986 cm^{-1}; ^1H NMR(400.1 MHz, $CDCl_3$): $\delta = 1.23$ [d, $J = 6.1$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.24 [d, $J = 5.8$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.25 [d, $J = 6.1$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 1.27 [d, $J = 6.1$ Hz, 3H, $OCH(C\underline{H}_3)_2$], 2.45 (AB part of ABMX system, $J_{AB} = 15.4$ Hz, $J_{AP} = 17.2$ Hz, $J_{AH} = 8.6$ Hz, $J_{BP} = 19.2$ Hz, $J_{BH} = 5.4$ Hz, 2H, CH_2P), 4.03 (AB system, $J_{AB} = 15.2$ Hz, 2H, CH_2Cl), 4.64 [m, 2H, $OC\underline{H}(CH_3)_2$], 6.43 (dt, $J = 5.4$, 8.6 Hz, 1H, OCH), 6.93 (dd, $J = 3.5$, 5.1 Hz, 1H, H_{arom}), 7.09 (dd, $J = 1.0$, 3.5 Hz, 1H, H_{arom}), 7.27 (dd, $J = 1.0$, 5.1 Hz, 1H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.85$ [d, $J = 4.6$ Hz, $OCH(\underline{C}H_3)_2$], 23.89 [d, $J = 3.1$ Hz, 2C, $OCH(\underline{C}H_3)_2$], 23.99 [d, $J = 3.8$ Hz, $OCH(\underline{C}H_3)_2$], 34.62 (d, $J = 143.0$ Hz, CH_2P), 40.09 (CH_2Cl), 68.13 (d, $J = 2.3$ Hz, OCH), 70.65 [d, $J = 6.9$ Hz, $O\underline{C}H(CH_3)_2$], 70.76 [d, $J = 6.9$ Hz, $O\underline{C}H(CH_3)_2$], 126.15 (HC_{arom}), 126.66 (HC_{arom}), 126.77 (HC_{arom}), 141.68 (d, $J = 13.1$ Hz, C_{arom}), 165.92 (CO); anal. calcd. (%) for $C_{14}H_{22}ClO_5PS$ 45.06, H 5.77.

(±)-Diisopropyl 2-Chloroacetoxy-2-phenylethylphosphonate [(±)-10f]

This chloroacetate was prepared from hydroxyphosphonate (±)-**3f** (1.92 mmol) by General Procedure C. Flash chromatography (hexane/ethyl acetate, 1:2, $R_f = 0.23$) gave (±)-**10f** as a colorless liquid; yield: 0.60 g (86%). IR (Si): $\tilde{\nu} = 2980, 1764, 1252, 1170, 989\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.20$ [d, $J = 6.1$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 1.23 [d, $J = 5.8$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 1.25 [d, $J = 6.1$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 1.28 [d, $J = 6.3$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 2.36 (AB part of ABMX system, $J_{AB} = 15.2$ Hz, $J_{AP} = 19.4$ Hz, $J_{AH} = 8.3$ Hz, $J_{BP} = 19.5$ Hz, $J_{BH} = 5.3$ Hz, 2H, CH_2P), 4.05 (AB system, $J_{AB} = 14.9$ Hz, 2H, CH_2Cl), 4.64 [m, 2H, OC$\underline{H}$(CH$_3$)$_2$], 6.15 (dt, $J = 5.3$, 8.3 Hz, 1H, CHO), 7.33 (m, 5H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.89$ [d, $J = 3.8$ Hz, 2C, OCH(C$\underline{H}_3$)$_2$], 23.92 [d, $J = 3.8$ Hz, OCH(C$\underline{H}_3$)$_2$], 24.02 [d, $J = 3.1$ Hz, OCH(C$\underline{H}_3$)$_2$], 34.48 (d, $J = 142.3$ Hz, CH_2P), 40.90 (CH_2Cl), 70.56 [d, $J = 6.1$ Hz, OC$\underline{H}$(CH$_3$)$_2$], 70.69 [d, $J = 6.9$ Hz, OC$\underline{H}$(CH$_3$)$_2$], 72.92 (d, $J = 2.3$ Hz, CHO), 126.68 (2C, HC_{arom}), 128.65 (2C, HC_{arom}), 128.71 (HC_{arom}), 139.10 (d, $J = 10.7$ Hz, C_{arom}), 165.98 (CO); anal. calcd. (%) for $C_{16}H_{24}ClO_5P$: C 52.97, H 6.66; found: C 52.73, H 6.49.

(*R*)-(−)-Diethyl 2-Hydroxypropylphosphonate [(*R*)-12]

A solution of (*R*)-(−)-diethyl 2-benzyloxyethylphosphonate [(*R*)-**11**] (6.5 g, 22.7 mmol), prepared in analogy[21] to the deuterated compound from (*R*)-isobutyl lactate except that $LiAlD_4$ was replaced by $LiAlH_4$, in dry ethanol (75 mL) was hydrogenated in a Parr apparatus for 3 h at 3.4 bar using palladium on charcoal (0.2 g, 10%). The catalyst was removed and the filtrate was concentrated under reduced pressure. The residue was bulb-to-bulb distilled (90–92 °C/0. 3 Torr) to afford β-hydroxyphosphonate (*R*)-**12** as a colorless liquid; yield: 4.35 g (98%), $[\alpha]_D^{20}$: −7.0 (*c* 1.625, methanol), $[\alpha]_{578}^{20}$: −7.3 (*c* 1.625, methanol), $[\alpha]_D^{20}$: −11.02 (*c* 1.625, acetone), lit.[11] $[\alpha]_{578}^{20}$: +7.3 (*c* 2.0, methanol); ee >98% [by ^1H NMR of (*R*)-Mosher ester]. The spectroscopic data are identical with those of the racemate.[21]

(*S*)-(−)- and (*R*)-(+)-Diisopropyl 2-Azido-3-metylbutylphosphonates [(*S*)- and (*R*)-15b]

Diisopropyl azodicarboxylate (0.222 g, 0.216 mL, 1.10 mmol) was added to a stirred solution of β-hydroxyphosphonate (*R*)-**8b** {0.185 g, 0.733 mmol, $[\alpha]_D^{20}$: −14.8 (*c* 1.15, acetone), ee 98%} and triphenylphosphane (0.289 g, 1.1 mmol) in a mixture of dry toluene (15 mL) and dry CH_2Cl_2 (3 mL) at 0 °C, followed immediately by HN_3 in toluene (0.73 mL, 1.5 M, 1.1 mmol). The solution was stirred for 15 min at 0 °C and 4 h at 50 °C. Evaporation of the solvent under reduced pressure and column chromatography (hexane/diethyl ether, 1:2, then diethyl ether for azide; $R_f = 0.32$ for hexane/diethyl ether, 1:2) gave azide (*S*)-**15b** as an oil (azide **15b**/olefin **16b** 87:13, by ^1H NMR); yield: 0.133 g (66%), $[\alpha]_D^{20}$: −0.5 (*c* 1.19, acetone).

Similarly, β-hydroxyphosphonate (*S*)-**8b** {0.213 g, 0.844 mmol, $[\alpha]_D^{20}$: +9.9 (*c* 1.0, acetone), ee 65%} was transformed into azide (*R*)-**15b** as an oil (azide **15b**/olefin **16b** 82:18, by ^1H NMR); yield: 0.191 g (82%), $[\alpha]_D^{20}$: +2.6 (*c* 1.25, acetone).

The spectroscopic data of (*S*)- and (*R*)-**15b** are identical. IR (Si): $\tilde{\nu} = 211\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.90$ [d, $J = 6.8$ Hz, 3H, (C$\underline{H}_3$)$_2$CH$_2$], 0.95 [d, $J = 6.8$ Hz, 3H, (C$\underline{H}_3$)$_2$CH], 1.31 [d, $J = 6.3$ Hz, 12H, OCH(C$\underline{H}_3$)$_2$], 1.86 (m, 2H, CH_2P), 3.53 (m, 1H, N_3CH), 4.71 [m, 2H, OC$\underline{H}$(CH$_3$)$_2$]; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 17.04$ (CH_3), 19.22 (CH_3), 23.94 [d, $J = 4.0$ Hz, OCH(C$\underline{H}_3$)$_2$], 23.98 [d, $J = 3.5$ Hz, OCH(C$\underline{H}_3$)$_2$], 24.03 [d, $J = 2.3$ Hz, OCH(C$\underline{H}_3$)$_2$], 24.07 [d, $J = 3.3$ Hz, OCH(C$\underline{H}_3$)$_2$], 30.10 (d, $J = 143.8$ Hz, CH_2P), 33.75 [d, $J = 11.2$ Hz, (CH$_3$)$_2$C$\underline{H}$], 63.71 (d, $J = 5.4$ Hz, CHN_3), 70.48 [d, $J = 6.9$ Hz, OC$\underline{H}$(CH$_3$)$_2$], 70.49 [d, $J = 6.9$ Hz, OC$\underline{H}$(CH$_3$)$_2$].

16b: ^1H NMR (400.1 MHz, $CDCl_3$, from the mixture with azide): $\delta = 1.02$ [d, $J = 6.8$ Hz, 6H, (C$\underline{H}_3$)$_2$CH], 1.26 [d, $J = 6.3$ Hz, 6H, OCH(C$\underline{H}_3$)$_2$], 1.30 [d, $J = 6.6$ Hz, 6H, OCH(C$\underline{H}_3$)$_2$], 2.4 [m, 1H, (CH$_3$)$_2$C$\underline{H}$], 4.62 [m, 2H, OC$\underline{H}$(CH$_3$)$_2$], 5.56 (ddd, $J = 1.5$, 17.2, 20.5 Hz, 1H, CH=C$\underline{H}$P), 9 (ddd, $J = 6.1$, 17.2, 22.2 Hz, 1 H, C$\underline{H}$=CHP).

(*S*)-(+)- and (*R*)-(−)-Diisopropyl 2-Azido-2-phenylethylphosphonate [(*S*)- and (*R*)-15f]

To a stirred solution of β-hydroxyphosphonate (*R*)-**8f** {0.572 g, 2.00 mmol, $[\alpha]_D^{20}$: −22.9 (*c* 2.0, acetone), ee 50%} and triphenylphosphane (0.79 g, 3.0 mmol) in a mixture of dry toluene (16 mL) and dry THF (4 mL) at 0 °C was added diisopropyl azodicarboxylate (0.59 mL, 3.0 mmol) and HN_3 in toluene (1.98 mL, 1.5 M). The solution was stirred for 15 min at 0 °C and allowed to room temperature over 5 h. Evaporation of the solvent under reduced pressure and column chromatography (hexane/diethyl ether, 1:2, then diethyl ether for azide; $R_f = 0.49$ for hexane/diethyl ether, 1:3) afforded azide (*S*)-**15f** as an oil; yield: 0.561 g (90%), $[\alpha]_D^{20}$: +34.87 (*c* 2.05, acetone).

Similarly, α-hydroxyphosphonate (*S*)-**8b** {0.548 g, 1.92 mmol, $[\alpha]_D^{20}$: +37.45 (*c* 0.55, acetone), ee 95%} was transformed into azide (*R*)-**15f**; yield: 0.439 g (73%); $[\alpha]_D^{20}$: −68.78 (*c* 1.275, acetone).

The spectroscopic data of (*S*)- and (*R*)-**15f** are identical. IR (Si): $\tilde{\nu} = 2980, 2103, 1249, 987\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.18$ [d, $J = 6.1$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 1.24 [d, $J = 6.1$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 1.26 [d, $J = 5.8$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 1.27 [d, $J = 5.8$ Hz, 3H, OCH(C$\underline{H}_3$)$_2$], 2.22 (AB part of ABMX system, $J_{AB} = 15.4$ Hz, $J_{AP} = 17.7$ Hz, $J_{AH} = 8.3$ Hz, $J_{BP} = 18.2$ Hz, $J_{BH} = 6.1$ Hz, 2H, CH_2P), 4.59 [m, 1H, OC$\underline{H}$(CH$_3$)$_2$], 4.68 [m, 1H, OC$\underline{H}$(CH$_3$)$_2$], 4.81 (dt, $J = 6.1$, 8.3 Hz, 1H, CHN_3), 7.35 (m, 5H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 23.81$ [d, $J = 4.6$ Hz, OCH(C$\underline{H}_3$)$_2$], 23.85 [d, $J = 3.8$ Hz, OCH(C$\underline{H}_3$)$_2$], 23.99 [d, $J = 4.6$ Hz, OCH(C$\underline{H}_3$)$_2$], 24.03 [d, $J = 3.8$ Hz, OCH(C$\underline{H}_3$)$_2$], 34.49 (d, $J = 142.3$ Hz, CH_2P), 61.22 (d, $J = 2.3$ Hz, N_3CH), 70.46 [d, $J = 6.9$ Hz, OC$\underline{H}$(CH$_3$)$_2$], 70.63 [d, $J = 6.9$ Hz, OC$\underline{H}$(CH$_3$)$_2$], 126.85 (2C, HC_{arom}), 128.59 (HC_{arom}), 128.86 (2C, HC_{arom}), 139.28 (d, $J = 10.7$ Hz, C_{arom}); ^{31}P NMR (161.98 MHz, $CDCl_3$): $\delta = 24.99$; anal. calcd. (%) for $C_{14}H_{22}N_3O_5P$: C 54.01, H 7.12, N 13.50; found: C 53.96, H 6.95, N 13.24.

(*S*)-(−)- and (*R*)-(+)-2-Amino-3-methylbutylphosphonic Acids [(*S*)- and (*R*)-17b]

Azide (*R*)-**15b** (0.191 g, 0.688 mmol, azide/olefin, 82:18) was transformed by General Procedure H into β-aminophosphonic

acid (*S*)-**17b** as a crystalline solid using 0.1 M CH_3CO_2H as eluent for column with Dowex 1X8, AcO^-; yield: 86 mg (75%).

Similarly, azide (*S*)-**15b** (0.109 g, 0.392 mmol, azide/olefin 83:17) was transformed into β-aminophosphonic acid (*R*)-**17b** as a crystalline solid; yield: 38 mg (58%).

The spectroscopic data (^1H, ^{13}C, ^{31}P NMR) of (*R*)- and (S)-**17b** are identical. ^1H NMR (400.1 MHz, D_2O): δ = 0.93 [d, *J* = 6.8 Hz, 3H, $(C\underline{H}_3)_2CH$], 0.94 [d, *J* = 6.8 Hz, 3H, $(C\underline{H}_3)_2CH$], 1.65 (dt, *J* = 11.1, 15.4 Hz, 1H, CH_2P), 1.97 [m, 2H, CH_2P and $(CH_3)_2C\underline{H}$], 3.25 (ddt, *J* = 3.0, 5.8, 11.0 Hz, 1H, $C\underline{H}CH_2P$); ^{13}C NMR (100.6 MHz, D_2O): δ = 17.37 [$(\underline{C}H_3)_2CH$], 17.49 [$(\underline{C}H_3)_2CH$], 28.02 (d, *J* = 130.0 Hz, CH_2P), 31.39 [d, *J* = 13.0 Hz, $(CH_3)_2\underline{C}H$], 54.41 (d, *J* = 5.4 Hz, NCH); ^{31}P NMR (161.98 MHz, D_2O): δ = 21.24.

(*S*)-(+)- and (*R*)-(-)-2-Amino-2-phenylethylphosphonic Acids [(*S*)- and (*R*)-17f]

Azide (*R*)-**15f** (0.173 g, 0.556 mmol) was transformed by General Procedure H into β-aminophosphonic acid (*R*)-**17f** as a crystalline solid using 5% HCO_2H as eluent for column with Dowex 1X8, AcO^-; yield: 88 mg (79%); TLC: R_f = 0.46; PC: R_f = 0.85.

Similarly, azide (*S*)-**15f** (0.156 g, 0.50 mmol) was transformed into β-aminophosphonic acid (*S*)-**17f** as a crystalline solid; yield: 93 mg (93%)

The spectroscopic data (^1H, ^{13}C, ^{31}P NMR) of (*R*)- and (*S*)-**17f** are identical. ^1H NMR (400.1 MHz, D_2O): δ = 2.42 (dd, *J* = 7.3, 18.4 Hz, 2H, CH_2P), 4.61 (dt, *J* = 7.3, 9.1 Hz, 1H, $NH_2C\underline{H}$), 7.43 (m, 5H, $H_{arom.}$); ^{13}C NMR (100.6 MHz, D_2O): δ = 32.72 (d, *J* = 130.8 Hz, CH_2P), 52.49 (d, *J* = 2.5 Hz, NH_2CH), 127.44 (2C, HC_{arom}), 129.64 (2C, HC_{arom}), 129.81 (HC_{arom}),147.17 (d, *J* = 14.5 Hz, C_{arom}); ^{31}P NMR (161.98 MHz, D_2O): δ = 21.08; anal. calcd. (%) for $C_8H_{12}NO_3P$: C 47.77, H 6.01, N 6.96; found: C 46.24, H 5.65, N 6.12.

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