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Enzymes in Organic Chemistry VI [1]. Enantioselective Hydrolysis of 1-Chloroacetoxycycloalkylmethylphosphonates with Lipase AP 6 from *Aspergillus niger* and Chemoenzymatic Synthesis of Chiral, Nonracemic 1-Aminocyclohexylmethylphosphonic Acids

Frank Wuggenig and **Friedrich Hammerschmidt***

Institut für Organische Chemie, Universität Wien, A-1090 Wien, Austria

Summary. Racemic α-chloroacetoxyphosphonates derived from cycloalkanecarbaldehydes and three branched aldehydes were prepared and tested for kinetic resolution by lipase AP 6 which hydrolyses preferentially the (*S*) esters. The enantiomeric excess and the reaction rate are significantly influenced by the size of the cycloalkyl group. The optical antipodes of α-hydroxycyclohexylmethylphosphonates (**3d**; *ee* 90% and $\geq$99%, respectively) were transformed into the corresponding α-aminophosphonic acids **6**.

Keywords. α-Hydroxyphosphonates; α-Chloroacetoxyphosphonates; Enzymatic resolution; Lipase; α-Aminophosphonic acids.

Enzyme in der organischen Chemie, 6. Mitt. [1]**. Enantioselektive Hydrolyse von 1-Chloracetoxycycloalkylmethylphosphonaten mit Lipase AP 6 aus *Aspergillus niger* und chemoenzymatische Synthese chiraler nichtracemischer 1-Aminocyclohexylmethylphosphonsäuren**

Zusammenfassung. Racemische α-Chloroacetoxyphosphonate, die sich von Cycloalkancarbaldehyden und drei verzweigten Aldehyden ableiten, wurden hergestellt und für die kinetische Racematspaltung mit der Lipase AP 6, die bevorzugt die (*S*)-Ester hydrolysiert, verwendet. Der Enantiomerenüberschuß und die Reaktionsgeschwindigkeit werden signifikant von der Ringgröße des Cycloalkylrestes beeinflußt. Die optischen Antipoden des α-Hydroxycyclohexylmethylphosphonates (**3d**; *ee* 90% bzw. $\geq$ 99%) wurden in die entsprechenden α-Aminophosphonsäuren **6** übergeführt.

* Corresponding author

Introduction

Chiral, nonracemic α-hydroxyphosphonates are valuable starting materials for other α-substituted phosphonates and phosphonic acids, especially α-aminophosphonic acids. They can be prepared by a number of methods, the more prominent ones being resolution [2], enantioselective addition of dialkyl phosphites to aldehydes [3], $TiCl_4$ catalyzed enantioselective opening of homochiral 1,3-dioxane acetals by triethyl phosphite [4], diastereoselective addition of homochiral phosphorus acid derivatives to aldehydes [5], enantioselective reduction of α-oxophosphonates [6], phosphate-phosphonate rearrangement [7], and lipase-catalyzed [1] kinetic resolution of α-acyloxyphosphonates. In preceeding papers we have developed protocols for the easy preparation [8] of racemic α-hydroxyphosphonates, their acetylation [8] or chloroacetylation [9], and their lipase catalyzed hydrolysis [8] in a stirred biphasic phosphate buffer at *pH* 7.0 using an autotitrator. Furthermore, the enantiomeric excesses and the absolute configurations of the α-hydroxyphosphonates were determined using ^{31}P NMR spectroscopy of corresponding *Mosher* esters [10]. Two enzymes, lipases AP 6 (from *Aspergillus niger*) and FAP 15 (From *Rhizopus oryzae*) have shown good to very good enantioselectivity with a variety of substrates derived from straight chain aliphatic [8], aromatic, and heteroaromatic [9] aldehydes. Lipase AP 6 has the broader substrate specificity. In general, chloroacetates were hydrolyzed more easily than acetates, and the *ee* was highest for diisopropyl phosphonates.

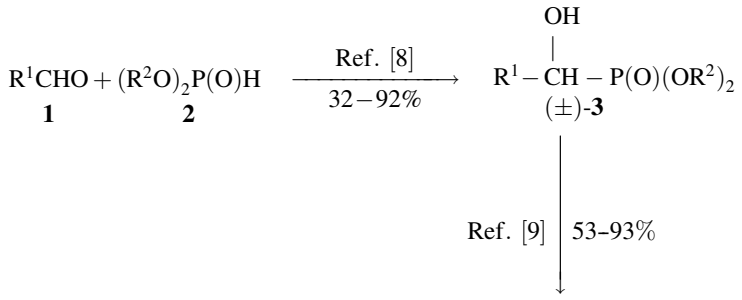
Results and Discussion

Lipase catalyzed kinetic resolution of α-acyloxyphosphonates

This paper focuses on the hydrolysis of α-chloroacetoxyphosphonates derived from cycloalkanecarbaldehydes with a ring size ranging from cyclopropyl to cyclooctyl. We intended to study the influence of the alicyclic ring on the reaction rate and the enantioselectivity as compared to planar five and six membered aromatic and heteroaromatic systems. Thus aldehydes **1a–f** were transformed into racemic α-hydroxyphosphonates (±)-**3a–g** by addition of diethyl- (**2b**) or preferentially diisopropyl phosphite (**2a**) under catalysis of a substoichiometric amount of the phosphazene base P_1-*t*-Bu (*tert*-butylamino-*tris*-(dimethylamino)-phosphorane) (*Abramov* reaction, Scheme 1) [8].

The aldehydes were of commericial origin or were prepared by *Swern* oxidation and used without further purification. The yields of α-hydroxyphosphonates were as high as 92%. The low yield (32%) for (±)-**3g** is attributed to the low purity of the crude cyclooctanecarbaldehyde prepared from cyclooctanone [11]. The α-hydroxyphosphonates (±)-**3a–g** were chloroacetylated [9] using chloroacetic anhydride/pyridine to give chloroacetoxyphosphonates (±)-**4** (Scheme 1). To see whether a dichloroacetate is more reactive or enantioselective than a monochloroacetate, dichloroacetate (±)-**4b** was prepared as well. It was obtained in 53% yield by esterification of α-hydroxyphosphonate (±)-**3a** with the imidazolide generated from N,N′-carbonyldiimidazole and dichloroacetic acid.

The enzymatic hydrolyses were carried out on a 1 mmol scale employing an appropriate amount of lipase AP 6 or FAP 15 (entries 2, 3, and 5) in a well



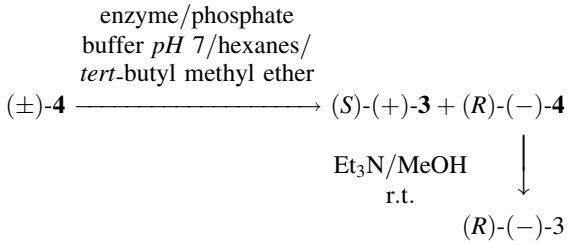
1	R^1	**2**	R^2	$R^1-CH(OCOR^3)-P(O)(OR^2)_2$ (±)-**4**
a	*c*-C_3H_5	**a**	*i*-Pr	
b	*c*-C_4H_7	**b**	Et	
c	*c*-C_5H_9			
d	*c*-C_6H_{11}			
e	*c*-C_7H_{13}			
f	*c*-C_8H_{15}			
g	*c*-$C_6H_{11}CH_2CH_2$			
h	$(CH_3)_2CH$			
i	$(CH_3)_2CHCH_2$			
j	$(CH_3)_3C$			

3	R^1	R^2	**4**	R^1	R^2	R^3
a	*c*-C_3H_5	*i*-Pr	**a**	*c*-C_3H_5	*i*-Pr	CH_2Cl
b	*c*-C_4H_7	*i*-Pr	**b**	*c*-C_3H_5	*i*-Pr	$CHCl_2$
c	*c*-C_5H_9	*i*-Pr	**c**	*c*-C_4H_7	*i*-Pr	CH_2Cl
d	*c*-C_6H_{11}	*i*-Pr	**d**	*c*-C_5H_9	*i*-Pr	CH_2Cl
e	*c*-C_7H_{13}	*i*-Pr	**e**	*c*-C_6H_{11}	*i*-Pr	CH_2Cl
f	*c*-C_7H_{13}	Et	**f**	*c*-C_7H_{13}	*i*-Pr	CH_2Cl
g	*c*-C_8H_{15}	Et	**g**	*c*-C_7H_{13}	Et	CH_2Cl
h	*c*-$C_6H_{11}CH_2CH_2$	Et	**h**	*c*-C_8H_{15}	Et	CH_2Cl
i	$(CH_3)_2CH$	*i*-Pr	**i**	*c*-$C_6H_{11}CH_2CH_2$	Et	CH_2Cl
j	$(CH_3)_2CHCH_2$	*i*-Pr	**j**	$(CH_3)_2CH$	*i*-Pr	CH_2Cl
k	$(CH_3)_3C$	*i*-Pr	**k**	$(CH_3)_2CHCH_2$	*i*-Pr	CH_2Cl
			l	$(CH_3)_3C$	*i*-Pr	CH_2Cl

Scheme 1

stirred biphasic system at room temperature as reported previously (Scheme 2, Table 1) [8].

The biphasic system consisted of 17 ml of a 50 m*M* sterile phosphate buffer (*pH* 7.0) and a mixture of *tert*-butyl methyl ether and hexanes (2 ml of each). The *pH* was kept constant by an autotitrator, and the reaction was stopped at a conversion of about 45% based on the consumption of 0.5 *N* NaOH by a addition of 2 *N* HCl (*pH* 4.0). Extractive workup and separation by flash chromatography furnished α-hydroxyphosphonate (+)-**3** and α-acyloxyphosphonate (−)-**4** which was hydrolyzed chemically [8, 9] (Et_3N/MeOH) to give (−)-**3**. The data of the individual runs are compiled in Table 1. The chiral, nonracemic α-hydroxyphosphonates **3** were derivatized with (*S*)-(+)-*MTPA*-Cl, and the ^1H and ^{31}P NMR



Scheme 2

spectra were recorded to determine both enantiomeric excess and absolute configuration of the underlying α-hydroxyphosphonate **3** [10]. The phosphorus resonances of the *Mosher* esters derived from (*S*)-**3** resonate at lower field than those derived from (*R*)-**3** throughout, and the chemical shift differences vary from 0.39 to 0.65 ppm except for α-hydroxyphosphonate **3k** having a branched alkyl group (see later) and displaying a shift difference of 0.11 ppm which is in accordance with literature data (Table 2). The same relation is observed in the ^{1}H NMR spectra for the methoxy group of *MTPA* except for **3a**, but the shift differences are too small (+0.10 to −0.01 ppm) to be used for a secure assignment of the absolute configuration. The reversal of the resonances for **3a** is probably caused by the deshielding effect of the cyclopropyl group.

Lipases AP 6 and FAP 15 hydrolyze in all cases tested preferentially the (*S*) esters of (±)-**4** (Table 1). The enzyme FAP 15 accepts only the cyclopropyl derivative (±)-**4a** as substrate, but not the cyclobutyl derivative (±)-**4c**. The reaction rate is fairly low compared to AP 6, and the *ee* is just 50% (entries 2 and 1). Surprisingly, the corresponding dichloroacetate (±)-**4b** is not hydrolyzed more rapidly than chloroacetate (±)-**4a** (entry 3), and the *ee* is even lower (38%). Other cyclic substrates were not investigated for kinetic resolution using lipase FAP 15. Reaction rates of cyclic chloroacetates and the *ee* of (*S*) configurated α-hydroxyphosphonates **4** formed are dramatically influenced by the ring size. The reaction rate decreases from the cyclopropyl derivative (±)-**4a** to the cyclobutyl and cyclopentyl derivatives (±)-**4c** and (±)-**4d**, then increases by going to the cyclohexyl derivative (±)-**4e**, and finally drops again for the cycloheptyl derivative (±)-**4f** (entries 1, 4, 6, 7, 8). The *ee* is 71% for (±)-**4a** and 75% for (±)-**4c**. It increases to 86% for (±)-**4d** and (±)-**4e** and then drops to 75% for (±)-**4f**. When the isopropyl groups of (±)-**4f** are replaced by ethyl groups, the reaction rate increases by a factor of ten, but the *ee* (54%) is reduced (entries 8 and 9). The cyclooctylmethylphosphonate (±)-**4h** is still a substrate for lipase AP 6, but the enantioselectivity of hydrolysis (17% *ee*) is too low to be of preparative value. Addition of two extra methylene groups as spacers between the cyclohexyl and the chloroacetoxy substituted carbon atoms of (±)-**4e** and replacement of the isopropyl by ethyl groups has little influence on reaction rate and *ee* (entries 7 and 11). The acitve site of AP 6 accommodates best the α-chloroacetoxyphosphonates with a cylcopentyl and cyclohexyl ring, the latter even when fitted with a short spacer.

The transformation of these cyclic substrates which can be viewed as α-acyloxyphosphonates with a branching at the β-carbon led us to reinvestigate the enzyme catalyzed hydrolysis of acyloxyphosphonates with a branched alkyl group.

Table 1. Enzymatic hydrolysis of (±)−**4**

Entry	Sub-strate	Enzyme, mg	Temp. (°C)	Time (h); Convsn[a] (%)	Produced alcohol				Recovered ester	Alcohol from recovered ester			
					Yield (%)	*ee*[b] (%)	Conf	$[\alpha]_D^c(c)$	$[\alpha]_D^c(c)$	Yield[d] (%)	*ee*[b] (%)	Conf	$[\alpha]_D^c(c)$
1	**4a**	AP 6, 7	22	4.0; 45/48	41	71 (71)	(*S*)	+0.28 (2.1)	−0.40 (1.5)	39	58 (59)	(*R*)	−0.6 (0.7)[e]
2	**4a**	FAP 15, 146	24	27.1; 45	39	47 (50)	(*S*)	+0.22 (1.8)	−0.32 (1.6)	36	47 (47)	(*R*)	−0.4 (2.5)[e]
3	**4b**	FAP 15, 147	22	30.8; 45/45	36	35 (38)	(*S*)	+0.20 (1.5)	−1.0 (5.8)				
4	**4c**	AP 6, 26	21	9.5; 45/47	33	74 (75)	(*S*)	+15.9 (1.2)	−12.3 (1.5)	45	65 (65)	(*R*)	−13.9 (1.3)
5	**4c**	FAP 15, 149	20	17.0; 0	not worked up								
6	**4d**	AP 6, 28	20	24.9; 45/48	41	85 (86)	(*S*)	+12.6 (4.4)	−13.2 (1.0)	43	78 (78)	(*R*)	−11.4 (3.5)
7	**4e**	AP 6, 27	22	14.4; 46/46	37	84 (86)	(*S*)	+8.4 (0.9)	−7.4 (1.0)				
8	**4f**	AP 6, 110	24	20.0; 45/47	39	73 (75)	(*S*)	+5.3 (4.1)	−5.1 (1.4)	30	62 (63)	(*R*)	−3.9 (2.3)
9	**4g**	AP 6, 53	22	4.0; 45/47	43	55 (54)	(*S*)	+3.7 (1.3)	−3.0 (1.5)	39	46 (47)	(*R*)	−2.4 (1.1)
10	**4h**	AP 6, 61	22	24.1; 44/41	31	17 (17)	(*S*)	+1.1 (1.4)	−0.35 (1.7)	42	11 (12)	(*R*)	−0.54 (1.4)
11	**4i**	AP 6, 47	22	4.3; 45/45	42	78 (82)	(*S*)	+14.3 (1.1)	−12.5 (1.5)	47	67 (68)	(*R*)	−10.8 (1.1)
12	**4j**	AP 6, 106	22	5.8; 45/47	28	61 (64)	(*S*)	+6.7 (1.5)	−15.5 (1.6)	35	56 (55)	(*R*)	−5.9 (1.3)
13	**4k**	AP 6, 58	24	19.5; 45/43	28	33 (35)	(*S*)	+8.6 (1.5)	−9.8 (1.9)	41	27 (24)	(*R*)	−6.1 (1.1)
14	**4l**	AP 6, 188	23	36.8; 0	not worked up								

[a] Convsn = conversion determined from 0.5 *N* NaOH consumed/conversion determined by ^{1}H NMR; [b]*ee* as determined by ^{1}H NMR spectroscopy (by ^{31}P NMR spectroscopy); [c]in 2 ml acetone solution at 20°C, concentration rounded to the nearest tenth; [d]yield of ester after enzymatic hydrolysis multiplied by yield of chemical hydrolysis; [e]optical rotation measured at 365 nm

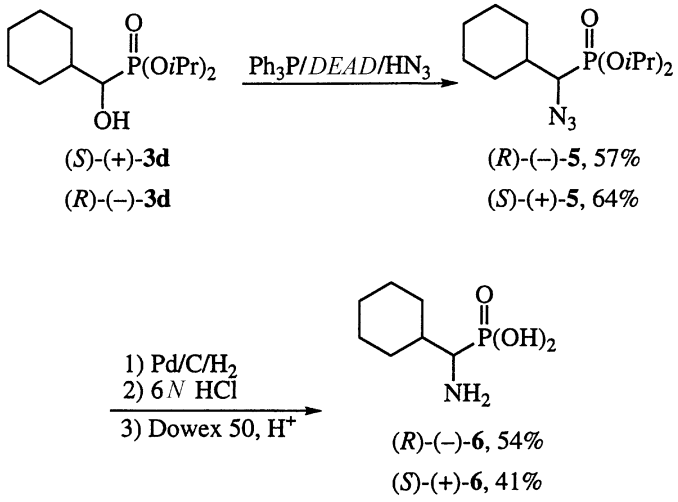
Table 2. Assignment of configuration at C-1 of diastereomeric *Mosher* esters prepared from α-hydroxyphosphonates **3** on the basis of ^{1}H (for methoxy group of *MTPA*) and ^{31}P NMR chemical shifts

Mosher ester of	Chemical shifts δ (ppm) (S) (^{1}H/^{31}P)	(R) (^{1}H/^{31}P) at C-1 of **3**	$\Delta\delta$ (^{1}H/^{31}P)
3a	3.53/16.23	3.54/15.58	−0.01/0.65
3b	3.61/16.93	3.57/16.39	0.04/0.54
3c	3.62/17.39	3.54/17.00	0.08/0.39
3d	3.62/17.49	3.55/17.04	0.07/0.45
3e	3.63/17.67	3.55/17.15	0.08/0.52
3f	3.61/19.67	3.54/19.16	0.07/0.51
3g	3.59/19.76	3.52/19.27	0.07/0.49
3h	3.61/19.93	3.55/19.43	0.06/0.50
3i	3.62/17.39	3.55/16.97	0.07/0.42
3j	3.61/18.17	3.54/17.69	0.07/0.48
3k	3.63/17.01	3.53/16.90	0.10/0.11

Diisopropyl 1-acetoxyphosphonates derived from isobutyraldehyde and 3-methylbutyraldehyde are not hydrolyzed by lipase AP 6 as reported recently [8]. Therefore, the α-chloroacetoxyphosphonates (±)-**4j**, **4k**, and **41** derived from these two aldehydes and pivalaldehyde, were prepared according to Scheme 1 and tested as substrates for lipase AP 6 (Table 1, entries 12, 13 and 14). The first two were hydrolyzed and the enantiomeric excesses were 64% and 35%, respectively. The reaction rate of (±)-**4j** is much slower than that of (±)-**4a**, although both are structurally very similar. A cyclopropyl ring has been replaced by an isopropyl group. The chloroacetate (±)-**4l**, derived from pivalaldehyde, is not a substrate of lipase AP 6. The corresponding diethyl phosphonate is one, but the *ee* is merely 15% [8]. The results reported add further to the broad substrate specificity of lipase AP 6.

Chemoenzymatic synthesis of (R)- and (S)-1-aminocyclohexylmethylphosphonic acid

To demonstrate its preparative utility, the antipodes of 1-aminocyclohexylmethylphosphonic acid (**6**) were prepared from α-hydroxyphosphonates **3d** (Scheme 3). We are interested in this compound as a structural analogue of 2-phenyl-1-aminoethylphosphonic acid, a phenyl alanine ammonia lyase inhibitor [12] with a reduced ring being directly attached to the α-carbon of the phosphonic acid. Protected (*R*)-1-aminophosphonic acid **6** has recently been synthesized for incorporation into a hapten [13]. To get adequate amounts of the required α-hydroxyphosphonates (*R*)- and (*S*)-**3d**, 10 mmol of chloroacetoxyphosphonate (±)-**4e** were hydrolyzed in a biphasic system (50 ml of phosphate buffer *pH* 7.0, 10 ml each of hexanes and *tert*-butyl methyl ether, 363 mg AP 6, 6.5 h). The reaction was stopped at a conversion of 30% as determined by consumption of 0.5 *N* NaOH and ^{1}H NMR spectroscopy to get a high *ee* for α-hydroxyphosphonate (*S*)-**3d**. Workup and separation of ester and alcohol afforded α-hydroxyphosphonate (*S*)-**3d** (24%;



Scheme 3

$[\alpha]_D^{20} = +8.3$ ($c = 1.0$); *ee* 90%) and chloroacetate (*R*)-**4e** (63%; $[\alpha]_D^{20} = -4.2$ ($c = 1.3$)) which was subjected to a second hydrolysis (50 ml buffer, 10 ml each of hexanes and *tert*-butyl methyl ether, 281 mg AP 6, 94 h, conversion 48% by consumption of 0.5 *N* NaOH, 51% by ^{1}H NMR spectroscopy). The isolated α-hydroxyphosphonate (*S*)-**3d** had a low enantiomeric excess (35%; $[\alpha]_D^{20} = +1.6$ ($c = 3.4$)). The chloroacetate (*R*)-**4e** (42%; $[\alpha]_D^{20} = -11.2$ ($c = 1.5$)) was hydrolyzed using MeOH/NEt_3 to yield homochiral α-hydroxyphosphonate (*R*)-**3d** (97%; $[\alpha]_D^{20} = -9.9$ ($c = 1.4$); *ee* $\geq$99%). These two samples of antipodes were transformed into the corresponding free aminophosphonic acids **6** (Scheme 3). The hydroxyl group was replaced under *Mitsunobu* conditions [14, 15] to produce azides **5** which were reduced catalytically on Pd/C. The products were then deblocked by refluxing in 6 *N* hydrochloric acid and purified by ion exchange chromatography on Dowex 50, H^+ to give the desired α-aminophosphonic acids **6**. Assuming that inversion of configuration upon azide formation is complete and all intermediates on the way to the end products being configurationally stable, the products should have *ee*s of 90% and $\geq$ 99%, respectively. We intend to have them tested as phenyl alanine ammonia lyase inhibitors.

In summary, lipase AP 6 is a useful enzyme for the enantioselective hydrolysis of α-chloroacetoxyphosphonates derived from cycloalkanecarbaldehydes with a ring size ranging from cyclopropane to cycloheptane. The enantiomers of 1-hydroxycyclohexylmethylphosphonate (**3d**) prepared on a preparative scale with high optical purity are transformed by chemical means to the corresponding α-aminophosphonic acids **6**.

Experimental

All starting materials and enzymes were obtained from 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 tetramethylsilane as internal standard, on a Bruker AM 400 WB NMR 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 and coupling constants (J) in Hz. IR spectra were run on a Perkin Elmer 1600 FT-IR spectrometer; liquid samples were measured as films between NaCl plates, solids as nujol mulls. Optical rotations were measured at 20°C on a Perkin Elmer 241 polarimeter in a 1 dm cell. TLC was carried out on 0.25 mm thick Merck plates (silica gel 60 F_{254}). Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualized by dipping the plate into a solution of 24 g of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ and 1 g of $Ce(SO_4)_2 \cdot 4H_2O$ in 500 ml of 10% H_2SO_4 in water, followed by heating with a hot gun. A Metrohm 702 SM Titrino instrument was used as an autotitrator. (*S*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (JPS Chimie; $[\alpha]_D^{20} = +136.5$ ($c = 5.2$, CCl_4), *ee* $> 99.5\%$) was used for derivatization of α-hydroxyphosphonates. Abbreviations used: MC = methylene chloride; EA = ethyl acetate.

Aldehydes **1a**, **1d**, **1h**, **1i**, and **1j** were used as supplied. Aldehydes **1b**, **1c**, **1e**, and **1g** were obtained by *Swern* oxidation [16] of the corresponding alcohols; **1f** was prepared in low yield and purity from cyclooctanone [11].

Dialkyl 1-hydroxymethylphosphonates (±)-**3** were prepared from phosphite (10 mmol) and aldehyde (11 mmol of commercially available ones or crude aldehydes obtained by *Swern* oxidation of 15 mmol of alcohol) as reported in a preceeding paper [8]. Yields refer to product purified by flash chromatography. Solids were crystallized from hexanes and oils were bulb-to-bulb distilled for analysis. The R_f values given at the individual compounds refer to MC:EA = 5:3 (1:1 for compound **3a**). α-Hydroxyphosphonate (±)-**3g** was prepared from 7 mmol of crude **1f**. α-Hydroxyphosphonates (±)-**3i** and **3j** are known compounds [8].

Dialkyl 1-chloroacetoxyphosphonates (±)-**4** were obtained by a known procedure [9]. All crude products were purified by flash chromatography and were bulb-to-bulb distilled (except **4h**). R_f values given at the individual compounds refer to MC:EA = 5:3. Esters (±)-**4** were hydrolyzed enzymatically using 1 mmol of substrate, 17 ml of phosphate buffer, 2 ml of hexanes, 2 ml of *tert*-butyl methyl ether, and lipase AP 6 or FAP 15 (Table 1) [8].

Chloroacetates (−)-**4** and dichloroacetoxyphosphonate (−)-**4b** recovered from enzymatic resolution were hydrolyzed within about 16 h using Et_3N/MeOH [8, 9].

Diisopropyl 1-hydroxy-cyclopropylmethylphosphonate ((±)-**3a**)

72% yield; oil; $R_f = 0.16$; b.p.: 80–90°C/0.05 torr; IR: $\nu = 3300$, 1386, 1215, 988 cm^{-1}; ^{1}H NMR: $\delta = 0.42$ (m, 2H, CH_2), 0.60 (m, 2H, CH_2), 1.14 (m, 1H, CH), 1.31 (d, $J = 7.4$, 3H, Me), 1.32 (d, $J = 6.4$, 3H, Me), 1.33 (d, $J = 5.9$, 6H, Me) 3.10 (1H, dt, $J = 5.7$, 10.8, 1H, PCH), 3.44 (t, $J = 5.7$, 1H, OH), 4.62 (m, 2H, CHO); ^{13}C NMR: $\delta = 3.12$ (d, $J = 1.8$), 3.35 (d, $J = 12.8$), 12.23 (d, $J = 2.7$), 23.97 (d, $J = 4.9$), 24.15 and 24.19 (2d, $J = 3.8$), 71.02 (d, $J = 7.5$), 71.17 (d, $J = 7.2$), 71.02 (d, $J = 164.3$); $C_{10}H_{21}O_4P$ (236.25); calc.: C 50.84, H 8.96; found: C 50.74, H 9.21.

Diisopropyl 1-hydroxy-cyclobutylmethylphosphonate ((±)-**3b**)

84% yield; oil; $R_f = 0.15$; b.p.: 95–110°C/0.1 torr; IR: $\nu = 3301$, 1385, 1222, 987 cm^{-1}; ^{1}H NMR: $\delta = 1.29$ (d, $J = 5.4$, 3H, Me), 1.30 (d, $J = 5.9$, 6H, Me), 1.31 (d, $J = 5.9$, 3H, Me), 1.70−2.10 (m, 6H, CH_2), 2.69 (sept, $J = 7.9$ 1H, CH), 3.30 (t, $J = 5.8$, 1H, OH), 3.68 (dt, $J = 5.8$, 6.9, 1H, PCH), 4.71 (dsept, $J = 6.4$, 12.3, 2H, CHO); ^{13}C NMR: $\delta = 18.37$, 23.98 (d, $J = 5.5$), 24.11 and 24.14 (2d, $J = 2.8$), 24.75 (d, $J = 5.5$), 24.85, 36.49, 70.76 and 70.92 (2d, $J = 7.4$), 72.26 (d, $J = 157.9$); $C_{11}H_{23}O_4P$ (250.28); calc.: C 52.79, H 9.26; found: C 52.93, H 9.51.

Diisopropyl 1-hydroxy-cyclopentylmethylphosphonate ((±)-**3c**)

88% yield; oil; $R_f = 0.22$; b.p.: 110–120°C/0.5 torr; IR: $\nu = 3301$, 1385, 1221, 987 cm^{-1}; ^1H NMR: $\delta = 1.30$ and 1.31 (2d, $J = 6.4$, 6H each, Me), 1.35–1.65 (m, 6H, CH_2), 1.74 (m, 1H, CH_2), 1.85 (m, 1H, CH_2) 2.19 (sept, $J = 6.9$, 1H, CH), 3.24 (t, $J = 5.4$, 1H, OH), 3.62 (dt, $J = 5.4$, 6.9, 1H, PCH), 4.72 (m, 2H, CHO); ^{13}C NMR: $\delta =$ 23.99 (2 overlapping d, $J = 4.7$), 24.14 and 24.15 (2d, $J = 3.6$), 25.23, 25.43, 28.83 (d, $J = 10.0$), 29.38 (d, $J = 6.3$), 41.44, 70.88 (d, $J = 7.4$), 70.92 (d, $J = 7.1$), 71.67 (d, $J = 158.3$); $C_{12}H_{25}O_4P$ (264.31); calc.: C 54.53, H 9.53; found: C 54.65, H: 9.70.

Diisopropyl 1-hydroxy-cyclohexylmethylphosphonate ((±)-**3d**)

83% yield; $R_f = 0.27$; m.p.: 78–79°C; IR: $\nu = 3222$, 1261, 1202, 994 cm^{-1}; ^1H NMR: $\delta = 1.05$–1.33 (m, 5H, CH_2) 1.33 (d, $J = 5.9$, 6H, Me), 1.34 (d, $J = 6.4$, 6H, Me), 1.65 (br d, $J = 11.8$, 1H, CH_2), 1.76 (m, 4H, CH_2), (br d, 1H, $J = 12.3$, CH), 2.35 (br s, 1H, OH) 3.56 (t, $J = 6.2$, 1H, PCH), 4.75 (m, 2H, CHO); ^{13}C NMR: $\delta =$ 23.97 (2 overlapping d, $J = 4.8$), 24.12 (d, $J = 3.3$), 24.15 (d, $J = 3.0$), 25.95, 26.17, 26.19, 27.95 (d, $J = 7.6$), 29.91 (d, $J = 8.5$), 39.76, 70.91 (d, $J = 7.3$), 70.92 (d, $J =$ 7.5), 72.85 (d, $J = 156.6$); $C_{13}H_{27}O_4P$ (278.33); calcd.: C 56.10, H 9.78; found: C 56.09, H 9.72.

Diisopropyl 1-hydroxy-cycloheptylmethylphosphonate ((±)-**3e**)

86% yield; $R_f = 0.23$; m.p.: 38–40°C; IR: $\nu = 3226$, 1196, 986 cm^{-1}; ^1H NMR: $\delta = 1.31$ and 1.32 (2d, $J = 6.4$, 6H each, Me), 1.36–1.60 (m, 8H, CH_2), 1.69 (m, 2H, CH_2), 1.79 (m, 1H), 1.93 (m, 2H), 2.76 (t, $J = 6.9$, 1H, OH), 3.63 (dt, $J = 5.4$, 6.9, 1H, PCH), 4.73 (m, 2H, CHO); ^{13}C NMR: $\delta = 23.94$ (d, $J = 3.5$), 23.98 (d, $J = 4.0$), 24.11 (d, $J = 3.8$), 24.15 (d, $J = 3.7$), 26.60, 26.81, 28.10, 28.53, 28.57 (d, $J = 7.5$), 31.81 (d, $J = 9.8$), 41.31, 70.87 (2 overlapping d, $J = 7.6$), 73.39 (d, $J = 155.8$); $C_{14}H_{29}O_4P$ (292.36) calcd.: C 57.52, H 10.00; found: C 57.81, H 10.11.

Diethyl 1-hydroxy-cycloheptylmethylphosphonate ((±)-**3f**)

38% yield; oil; $R_f = 0.15$; b.p.: 130–140°C/0.02 torr; IR: $\nu = 3301$, 1392, 1216, 966 cm^{-1}; ^1H NMR: $\delta = 1.32$ and 1.33 (2t, $J = 6.9$, 3H each, Me), 1.35–1.65 (m, 8H, CH_2), 1.69 (m, 2H, CH_2), 1.79 (m, 1H), 1.93 (m, 2H), 2.76 (t, $J = 6.9$, 1H, OH), 3.63 (dt, $J = 5.4$, 6.9, 1H, PCH), 4.15 (m, 4H, CH_2O); ^{13}C NMR: $\delta =$ 16.47 (2 overlapping d, $J = 5.5$), 26.55, 26.79, 28.08, 28.48, 28.56 (d, $J = 5.9$), 31.73 (d, $J = 9.8$), 41.33, 62.27 and 62.36 (2d, $J = 7.3$), 73.09 (d, $J = 155.0$); $C_{12}H_{25}O_4P$ (264.30), calc.: C 54.53, H: 9.53; found: C 54.51, H 9.66.

Diethyl 1-hydroxy-cyclooctylmethylphosphonate ((±)-**3g**)

32% yield; oil (not distilled); $R_f = 0.22$; IR: $\nu = 3301$, 1392, 1220, 965 cm^{-1}; ^1H NMR: $\delta = 1.32$ and 1.33 (2t, $J = 6.9$, 3H each, Me), 1.40–1.80 (m, 13H, CH_2), 1.90 (m, 1H), 2.01 (m, 1H), 2.82 (t, $J = 6.4$, 1H, OH), 3.70 (q, $J = 6.4$, 1H, PCH), 4.15 (m, 4H, CH_2O); ^{13}C NMR: $\delta = 16.48$ (d, $J = 5.5$), 25.25, 26.06, 26.43, 26.59, 26.88, 27.06 (d, $J = 6.2$), 30.61, (d, $J = 9.8$), 39.03 (d, $J = 2.2$), 62.27 and 62.34 (2d, $J = 7.6$), 73.37 (d, $J = 155.0$); $C_{13}H_{27}O_4P$ (278.33); calc.: C 56.10, H 9.78; found: C 56.26, H 10.04.

Diethyl 1-hydroxy-3-cyclohexylpropylphosphonate ((±)-**3h**)

92% yield; oil (not distilled); $R_f = 0.14$; IR: $\nu = 3301$, 1392, 1230, 966 cm^{-1}; ^1H NMR: $\delta = 0.88$ (m, 2H, CH_2), 1.06–1.29 (m, 5H, CH_2), 1.32 and 1.33 (2t, $J = 6.9$, 3H each, Me), 1.52 (m, 1H), 1.58–1.73

(m, 6H, CH_2), 1.77 (m, 1H), 3.34 (dd, $J = 4.4$, 6.4, 1H, OH), 3.79 (m, 1H, PCH), 4.15 (m, 4H, CH_2O); ^{13}C NMR: $\delta = 16.49$ (d, $J = 5.1$), 26.29, 26.32, 26.61, 28.76, 33.06, 33.35, 33.34 (d, $J = 12.9$), 37.44, 62.44 (d, $J = 7.1$), 62.53, (d, $J = 7.3$), 68.21 (d, $J = 159.7$) $C_{13}H_{27}O_4P$ (278.33) calc.: C 56.10, H 9.78; found: C 56.32, H 9.78.

Diisopropyl 1-hydroxy-2,2-dimethylpropylphosphonate ((±)-**3k**)

89% yield; $R_f = 0.35$; m.p.: 73–74°C; IR: $\nu = 3359$, 1228, 1012 cm^{-1}; ^1H NMR: $\delta = 1.07$ (s, 9H, *t*-Bu), 1.32 (d, $J = 6.4$, 9H, Me), 1.33 (d, $J = 6.4$, 3H, Me), 2.61 (t, $J = 6.9$, 1H, OH), 3.46 (dd, $J = 6.9$, 7.9, 1H, PCH), 4.75 (m, 2H, CHO); ^{13}C NMR: $\delta = 23.94$ (d, $J = 4.9$), 23.99 (d, $J = 5.0$), 24.14 (d, $J = 2.7$), 24.23 (d, $J = 2.3$), 26.70 (d, $J = 6.4$), 34.58 (d, $J = 2.5$), 70.89 (d, $J = 7.4$), 70.95 (d, $J = 7.3$), 76.64 (d, $J = 153.9$); $C_{11}H_{25}O_4P$ (252.29) calc.: C 52.37, H 9.99; found: C 52.66, H 9.76.

Diisopropyl 1-chloroacetoxy-cyclopropylmethylphosphonate ((±)-**4a**)

74% yield; oil; $R_f = 0.53$; b.p.: 120–130°C/0.1 torr; IR: $\nu = 1765$, 1260, 995 cm^{-1}; ^1H NMR: $\delta = 0.46$ (m, 1H, CH_2), 0.59 (m, 2H, CH_2), 0.75 (m, 1H, CH_2), 1.26 (m, 1H, CH), 1.31 and 1.32 (2d, $J = 6.4$, 3H each, Me), 1.34 (d, $J = 6.4$, 6H, Me), 4.13 (AB system, $J = 14.8$, CH_2Cl), 4.56 (t, $J = 10.1$, 1H, PCH), 4.77 (m, 2H, CHO); ^{13}C NMR: $\delta = 4.20$, 4.41 (d, $J = 12.9$), 10.79 (d, $J = 2.1$), 23.86 and 23.98 (2d, $J = 5.2$), 24.07 (d, $J = 3.6$), 24.19 (d, $J = 3.2$), 40.76, 71.59 (d, $J = 7.2$), 71.69 (d, $J = 6.7$), 75.12 (d, $J = 174.6$), 166.56 (d, $J = 6.7$); $C_{12}H_{22}ClO_5P$ (312.73); calc.: C 46.09, H 7.09; found: C 46.08, H 7.12.

Diisopropyl 1-dichloroacetoxy-cyclopropylmethylphosphonate ((±)-**4b**)

Dichloroacetic acid (1.75 g, 1.12 ml, 13.6 mmol) was added dropwise to a suspension of N,N′-carbonyldiimidazole (1.62 g, 13.6 mmol) in dry MC (30 ml). Stirring was continued for 20 min at room temperature, and a solution of α-hydroxyphosphonate (±)-**3a** (1.60 g, 6.8 mmol) in dry MC (15 ml) was added. After stirring for 3 h the mixture was diluted with H_2O (20 ml), and the aqueous phase was extracted with MC (3 × 20 ml). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (MC:EA = 5:3) and bulb to bulb distillation under reduced pressure.

53% yield; oil; $R_f = 0.59$; b.p.: 115–125°C/0.1 torr; IR: $\nu = 1767$, 1262, 995 cm^{-1}; ^1H NMR: $\delta = 0.47$ (m, 1H, CH_2), 0.57 (m, 1H, CH_2), 0.64 (m, 1H, CH_2), 0.78 (m, 1H, CH_2), 1.28 (m, 1H, CH), 1.32 and 1.35 (2d, $J = 6.4$, 3H each, Me), 1.33 and 1.34 (2d, $J = 6.4$, 3H each), 4.55 (t, $J = 9.8$, 1H, PCH), 4.78 (m, 2H, CHO), 6.00 (s, $CHCl_2$); ^{13}C NMR: $\delta = 4.12$, 4.20, 10.59 (d, $J = 1.9$), 23.84 (d, $J = 3.9$), 24.03 (d, $J = 4.7$), 24.07 (d, $J = 3.3$), 24.22 (d, $J = 3.2$), 64.12, 71.85 (d, $J = 7.3$), 71.96 (d, $J = 6.6$), 76.48 (d, $J = 173.9$), 166.56 (d, $J = 6.7$); $C_{12}H_{21}Cl_2O_5P$ (347.18); calc.: C 41.51, H 6.10; found: C 41.37, H 6.16.

Diisopropyl 1-chloroacetoxy-cyclobutylmethylphosphonate ((±)-**4c**)

93% yield; oil; $R_f = 0.57$; b.p.: 115–130°C/0.1 torr; IR: $\nu = 1768$, 1250, 993 cm^{-1}; ^1H NMR: $\delta = 1.29$ (d, $J = 5.9$, 3H, Me), 1.28, 1.30 and 1.31 (3d, $J = 6.4$, 3H each, Me), 1.70–2.10 (m, 6H, CH_2), 2.85 (m, 1H, CH), 4.12 (AB system, $J = 15.0$, CH_2Cl), 4.70 (m, 2H, CHO), 5.21 (dd, $J = 7.9$, 8.9, 1H, PCH); ^{13}C NMR: $\delta = 18.28$, 23.82 and 24.16 (2d, $J = 5.1$), 23.98 (d, $J = 4.8$), 24.03 (d, $J = 3.7$), 25.00, 25.10 (d, $J = 3.1$), 34.92, 40.63, 71.36, (d, $J = 7.3$), 71.52 (d, $J = 6.7$), 73.04 (d, $J = 166.8$), 166.65 (d, $J = 5.3$); $C_{13}H_{24}ClO_5P$ (326.76); calc.: C 47.78, H 7.40; found: C 47.83, H 7.47.

Diisopropyl 1-chloroacetoxy-cyclopropylmethylphosphonate ((±)-**4d**)

81% yield; oil; $R_f = 0.62$; b.p.: 125–140°C/0.02 torr; IR: $\nu = 1767$, 1253, 990 cm^{-1}; ^1H NMR: $\delta = 1.29$ (d, $J = 6.4$, 3H, Me), 1.31 (d, $J = 4.9$, 3H, Me), 1.33 (d, $J = 5.9$, 6H, Me), 1.34–1.90 (m, 8H, CH_2), 2.38 (sept, $J = 8.0$, 1H, CH), 4.10 (AB system, $J = 15.0$, CH_2Cl), 4.73 (m, 2H, CHO), 5.17 (t, $J = 8.0$, 1H, PCH); ^{13}C NMR: $\delta = 23.79$, and 23.97 (2d, $J = 5.9$), 24.03 (d, $J = 4.0$), 24.16 (d, $J = 3.2$), 24.80, 25.23, 29.18 (d, $J = 9.8$), 29.35 (d, $J = 5.8$), 40.01, 40.65, 71.37 (d, $J = 7.4$), 71.52 (d, $J = 6.8$), 73.60 (d, $J = 168.0$), 166.65 (d, $J = 3.5$); $C_{14}H_{26}ClO_5P$ (340.79); calc.: C 49.34, H: 7.69; found: C 49.61, H 7.80.

Diisopropyl 1-chloroacetoxy-cyclohexylmethylphosphonate ((±)-**4e**)

83% yield; oil; $R_f = 0.68$; b.p.: 160–165°C/0.05 torr; IR: $\nu = 1768$, 1248, 993 cm^{-1}; ^1H NMR: $\delta = 1.00$–1.25 (m, 5H, CH_2), 1.29 (d, $J = 5.9$, 3H, Me), 1.31 (d, $J = 5.9$, 3H, Me), 1.33 (d, $J = 5.9$, 6H, Me), 1.64 (br d, $J = 12.3$, 1H, CH_2), 1.74 (m, 2H, CH_2), 1.89 (m, 3H), 4.12 (AB system, $J = 15.0$, CH_2CI), 4.73 (m, 2H, CHO), 5.09 (dd, $J = 6.7$, 9.6, 1H, PCH); ^{13}C NMR: $\delta = 23.80$ (d, $J = 5.2$), 23.99 (d, $J = 4.7$), 24.03 (d, $J = 3.9$), 24.19 (d, $J = 3.5$), 25.73, 25.86, 25.93, 28.26 (d, $J = 7.7$), 29.84 (d, $J = 7.2$), 38.52, 40.64, 71.41 (d, $J = 7.4$), 71.53 (d, $J = 6.8$), 74.40 (d, $J = 167.3$), 166.54 (d, $J = 5.2$); $C_{15}H_{28}ClO_5P$ (354.81); calc.: C 50.78, H 7.95; found: C 50.48, H: 8.08.

Diisopropyl 1-chloroacetoxy-cycloheptylmethylphosphonate ((±)-**4f**)

87% yield; oil; $R_f = 0.67$; b.p.: 150–165°C/0.05 torr; IR: $\nu = 1767$, 1252, 989 cm^{-1}; ^1H NMR: $\delta =$ 1.28 and 1.30 (2d, $J = 5.9$, 3H each, Me), 1.32 (d, $J = 6.4$, 6H, Me), 1.33–1.60 (m, 8H, CH_2), 1.65 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 2.08 (m, 1H, CH), 4.10 (AB system, $J = 15.0$, CH_2Cl), 4.72 (m, 2H, CHO), 5.13 (dd, $J = 5.9$, 9.8, 1H, PCH); ^{13}C NMR: $\delta =$ 23.80 and 23.97 (2d, $J = 5.2$), 24.03 and 24.18 (2d, $J = 3.6$), 26.22, 26.43, 28.13, 28.22, 29.23 (d, $J = 6.1$), 31.49 (d, $J = 8.5$), 40.02 (d, $J = 1.0$), 40.69, 71.34 (d, $J = 7.5$), 71.49 (d, $J = 6.8$), 74.98 (d, $J = 166.7$), 166.59 (d, $J = 5.1$); $C_{16}H_{30}ClO_5P$ (368.84); calc.: C 52.10, H 8.20; found: C 52.25, H 8.25.

Diethyl 1-chloroacetoxy-cycloheptylmethylphosphonate ((±)-**4g**)

84% yield; oil; $R_f = 0.58$; b.p.: 120–130°C/0.01 torr; IR: $\nu = 1766$, 1252, 969 cm^{-1}; ^1H NMR: $\delta = 1.29$ and 1.30 (2d, $J = 6.9$, 3H each, Me), 1.34–1.60 (m, 8H, CH_2), 1.65 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 2.10 (m, 1H, CH), 4.10 (AB system, CH_2Cl) overlapping with 4.11 (m, 4H, CH_2O), 5.17 (dd, $J = 6.2$, 9.1, 1H, PCH); ^{13}C NMR: $\delta = 16.29$ and 16.40 (2d, $J = 5.7$), 26.13, 26.36, 28.08, 28.17, 29.21 (d, $J = 6.2$), 31.33 (d, $J = 8.4$), 39.87 (d, $J = 1.0$), 40.57, 62.59 (d, $J = 6.3$), 62.62 (d, $J = 7.2$), 74.29 (d, $J = 164.0$), 166.55 (d, $J = 3.6$); $C_{14}H_{26}ClO_5P$ (340.79); calcd.: C 49.34, H 7.69; found: C 49.59, H 7.87.

Diethyl 1-chloroacetoxy-cyclooctylmethylphosphonate ((±)-**4h**)

66% yield; $R_f = 0.56$; oil (not distilled); IR: $\nu = 1766$, 1252, 970 cm^{-1}; ^1H NMR: $\delta = 1.30$ and 1.32 (2t, $J = 6.9$, 3H each, Me), 1.38–1.90 (m, 14H, CH_2), 2.19 (m, 1H, CH), 4.11 (AB system, CH_2Cl) overlapping with 4.13 (m, 4H, CH_2O), 5.16 (dd, $J = 6.4$, 8.9, 1H, PCH); ^{13}C NMR: $\delta = 16.34$ (d, $J = 6.0$), 16.44 (d, $J = 5.7$), 25.14, 25.44, 26.39, 26.45, 26.74, 27.54 (d, $J = 6.9$), 29.87 (d, $J = 8.4$), 37.83 (d, $J = 1.1$), 40.62, 62.62 (d, $J = 7.3$), 62.64 (d, $J = 6.1$), 74.60 (d, $J = 164.4$), 166.61 (d, $J = 4.0$); $C_{15}H_{28}ClO_5P$ (354.81); calc.: C 50.78, H 7.95; found: C 50.48, H 7.97.

Diethyl 1-chloroacetoxy-3-cyclohexylpropylphosphonate ((±)-**4i**)

88% yield; oil; $R_f = 0.59$; b.p.: 140–150°C/0.01 torr; IR: $\nu = 1767$, 1256, 970 cm^{-1}; ^1H NMR: $\delta = 0.86$ (m, 2H, CH_2), 1.05–1.28 (m, 6H, CH_2), 1.31 and 1.32 (2t, $J = 7.2$, 3H each, Me), 1.65 (m, 5H, CH_2), 1.80 (m, 1H, CH_2), 1.91 (m, 1H, CH_2), 4.10 (AB system, CH_2Cl) overlapping with 4.14 (m, 4H, CH_2O), 5.24 (ddd, $J = 3.9$, 8.1, 10.1, 1H, PCH); ^{13}C NMR: $\delta = 16.35$ (d, $J = 5.8$), 16.35 (d, $J = 5.5$), 26.17, 26.20, 26.48, 26.69, 32.96, 33.16, 33.11 (d, $J = 9.8$), 37.19, 40.57, 62.82 (d, $J = 7.5$), 62.83 (d, $J = 5.8$), 70.20 (d, $J = 167.1$), 166.54 (d, $J = 4.8$); $C_{15}H_{28}ClO_5P$ (354.81); calcd.: C 50.78, H 7.95; found: C 51.00, H 7.68.

Diisopropyl 1-chloroacetoxy-2-methylpropylphosphonate ((±)-**4j**)

86% yield; oil; $R_f = 0.55$; b.p.: 90–115°C/0.1 torr; IR: $\nu = 1769$, 1257, 1000 cm^{-1}; ^1H NMR: $\delta = 1.02$ and 1.04 (2d, $J = 6.9$, 3H each, Me), 1.29, 1.31 and 1.33 (3d, $J = 6.4$, 3H each, Me_2CHO), 1.32 (d, $J = 5.4$, 3H, Me_2CHO), 2.24 (doct, $J = 6.9$, 8.9, 1H, PCHC*H*), 4.11 (AB system, $J = 14.8$, CH_2CI), 4.73 (m, 2H, CHO), 5.06 (dd, $J = 6.9$, 9.4, 1H, PCH); ^{13}C NMR: $\delta = 18.26$ (d, $J = 7.7$), 19.76 (d, $J = 8.2$), 23.80 (d, $J = 5.0$), 23.99 (d, $J = 4.8$), 24.03 (d, $J = 3.6$), 24.19 (d, $J = 3.3$), 29.25, 40.62, 71.39 (d, $J = 7.3$), 71.54 (d, $J = 6.8$), 74.98 (d, $J = 167.8$), 166.56 (d, $J = 5.3$); $C_{12}H_{24}ClO_5P$ (314.75); calc.: C 45.79, H 7.69; found: C 45.88, H 7.50.

Diisopropyl 1-chloroacetoxy-2-methylbutylphosphonate ((±)-**4k**)

97% yield; oil; $R_f = 0.52$; b.p.: 100–120°C/0.05 torr; IR: $\nu = 1766$, 1261, 990 cm^{-1}; ^1H NMR: $\delta = 0.90$ and 0.93 (2d, $J = 6.4$, 3H each, CH_3), 1.30 (d, $J = 5.9$, 3H, Me_2CHO), 1.31 (d, $J = 5.4$, 3H, Me_2CHO), 1.33 (d, $J = 6.4$, 6H, Me_2CHO), 1.62 (m, 2H), 1.81 (m, 1H), 4.11 (AB system, $J = 15.2$, CH_2Cl), 4.73 (m, 2H, CHO), 5.34 (ddd, $J = 2.3$, 9.0, 11.2, 1H, PCH); ^{13}C NMR: $\delta = 21.19$, 23.15, 23.82 (d, $J = 5.1$), 23.95 (d, $J = 5.3$), 24.01 (d, $J = 3.9$), 24.15 (d, $J = 3.3$), 24.44 (d, $J = 12.8$), 38.02, 40.64, 68.82 (d, $J = 169.9$), 71.49 (d, $J = 7.1$), 71.70 (d, $J = 6.8$), 166.43 (d, $J = 4.6$); $C_{13}H_{26}ClO_5P$ (328.77); calc.: C 47.49, H 7.97; found: C 47.70, H 8.10.

Diisopropyl 1-chloroacetoxy-2,2-dimethylpropylphosphonate ((±)-**4l**)

88% yield; oil; $R_f = 0.59$; b.p.: 100–120°C/0.01 torr; IR: $\nu = 1770$, 1251, 995 cm^{-1}; ^1H NMR: $\delta = 1.06$ (s, 9H, *t*-Bu), 1.26 and 1.28 (2d, $J = 5.9$, 3H each, Me), 1.29 and 1.30 (2d, $J = 6.4$, 3H each, Me), 4.10 (AB system, $J = 14.8$, CH_2Cl), 4.70 (m, 2H, CHO), 5.03 (d, $J = 10.8$, 1H, PCH); ^{13}C NMR: $\delta = 23.75$ (d, $J = 5.3$), 24.02 (d, $J = 4.7$), 24.06 (d, $J = 3.5$), 24.23 (d, $J = 3.4$), 26.82 (d, $J = 6.1$), 34.67 (d, $J = 2.3$), 40.66, 71.36 (d, $J = 7.9$), 71.44 (d, $J = 7.3$), 77.51 (d, $J = 164.8$), 166.42 (d, $J = 4.6$); $C_{13}H_{26}ClO_5P$ (328.77); calcd.: C 47.49, H 7.97; found: C 47.50, H 7.93.

(R)-(−)- and (S)-(+)-Diisopropyl 1-azido-cyclohexylmethylphosphonate
*((R)-(−)- and (S)-(+)-***5**)

Diethyl azodicarboxylate (463 mg, 2.66 mmol) was added dropwise to a stirred solution of Ph_3P (698 mg, 2.66 mmol) in dry MC (6 ml) at −5°C. The pale orange solution was then cooled to −10°C, and a solution of HN_3 in toluene (3.6 ml, 0.77 *M*) was added dropwise. After stirring for 5 min at 0°C, a solution of α-hydroxyphosphonate (*S*)-(+)-**3** (618 mg, 2.22 mmol, $[\alpha]_D^{20} = +8.3$ ($c = 1.0$, acetone), 90% *ee*) in dry MC (4 ml) was added. The mixture was stirred for 30 min at 0°C and then for 20 h at room temperature. The precipitate formed was removed, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography ($R_f = 0.50$, MC:EA

= 10:1) to afford azide (*R*)- (−)- (**5**) (384 mg (57%), $[\alpha]_D^{20} = -46.6$ ($c = 1.0$, acetone)) as an oil. (*R*)-(−)-**3** (645 mg, 2.32 mmol, $[\alpha]_D^{20} = -9.9$ ($c = 1.4$, acetone)) was transformed by a modified procedure [15] into (*S*)-(+)-5 (425 mg (60%), $[\alpha]_D^{20} = +50.2$ ($c = 1.4$, acetone)). The spectroscopic data of (*R*)- (−)- and (*S*)-(+)-**5** are identical.

IR: $\nu = 2980, 2931, 2854, 2102, 1452, 1386, 1257, 1105, 987\,cm^{-1}$; ^1H NMR: $\delta = 1.07$–1.32 (m, 5H, CH_2), 1.34 (d, $J = 5.9$, 3H, Me), 1.35 (3 overlapping d, $J = 6.4$, 9H, Me), 1.65 (m, 1H, CH_2), 1.78 (m, 4H, CH_2), 1.97 (br d, $J = 12.8$, 1H, CH_2), 3.23 (dd, $J = 5.7$, 13.0, 1H, CHP), 4.78 (m, 2H, OCH); ^{13}C NMR: $\delta = 23.94$ (d, $J = 4.7$), 23.98 (d, $J = 4.9$), 24.14 (d, $J = 3.7$), 24.20 (d, $J = 3.5$), 25.90 ($2 \times CH_2$), 26.11, 28.84 (d, $J = 6.6$), 31.14 (d, $J = 9.2$), 38.63, 64.14 (d, $J = 155.5$), 71.40 (d, $J = 7.1$), 71.56 (d, $J = 7.6$); $C_{13}H_{26}N_3O_3P$ (303.34); calc.: C 51.47, H 8.64, N 13.85; found: C 51.68, H 8.36, N 14.11.

(R)-(−)- and (S)-(+)-1-Amino-cyclohexylmethylphosphonic acid ((*R*)-(−)- and (*S*)-(+)-**6**)

Azide (*R*)-(−)-**5** (354 mg, 1.17 mmol) was hydrogenated in ethanol (60 ml, 1 ml of conc. HCl) on Pd/C (10%, 120 mg) in a *Parr* apparatus (3.4 bar, 6.5 h, 20°C). The catalyst was removed, and the solvent was evaporated *in vacuo*. The residue was refluxed in 6 *N* HCl (50 ml) for 13 h and then concentrated. The crude product was purified by ion exchange chromatography on Dowex 50, H^+ using water as eluent. Ninhydrine positive fractions were pooled, concentrated *in vacuo*, and finally lyophilized to give 1-aminophosphonic acid (*R*)-(−)-**6** (121 mg, 54%), m.p.: 280–282°C, $[\alpha]_D^{20} = -6.3$ ($c = 1.0$, 0.5 N NaOH). Similarly, (*S*)-(+)-**5** (250 mg, 0.82 mmol) was transformed into (*S*)-(+)-**6** (121 mg, 41%), m.p.: 277–279°C, $[\alpha]_D^{20} = +6.5$ ($c = 0.6$, 0.5 *N* NaOH). The spectoscopic data of (*R*)-(−)-and (*S*)-(+)-6 are identical.

IR (Nujol): $\nu = 1626, 1524, 1142, 1052, 921\,cm^{-1}$; ^1H NMR: (D_2O/NaOD): $\delta = 0.83$–1.28 (m, 5H, CH_2), 1.58 (m, 5H, CH_2), 1.81 (br d, $J = 12.3$, 1H, CH_2), 2.29 (dd, $J = 3.9$, 12.3, 1H, PCH); ^{13}C NMR: (D_2O/NaOD): $\delta = 26.93$, 27.01, 27.35, 26.97 (2 overlapping d, $J = 7.9$), 39.81, 56.34 (d, $J = 137.4$); $C_7H_{16}NO_3P$ (193.18); calc.: C 43.52, H: 8.35, N: 7.25; found: C 43.12, H 8.21, N 6.75.

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