

Enantioselective reduction of ketophosphonates using adducts of chiral natural acids with sodium borohydride

E.V. Gryshkun, V. Nesterov, and O. I. Kolodyazhnyi*

Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Science of Ukraine, ul. Murmanskaya 1, Kiev 02094, Ukraine
E-mail: olegkol321@rambler.ru

Dedicated to Prof. Pawel Kafarski to honor the achievements within his career

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Abstract

A method for asymmetric reduction of α - and β -ketophosphonates using chiral complexes prepared from sodium borohydride and natural aminoacids or tartaric acids was developed. Reduction of α - or β -ketophosphonates by these reagents led to formation of chiral (*S*)- or (*R*)-hydroxyphosphonates. Reduction of chiral di-(1*R*,2*S*,5*R*)-menthylketophosphonates by the chiral complexes NaBH₄/(*R,R*)-proline or NaBH₄/(*R,R*)-tartaric acid due to the double matched asymmetric induction resulted in increased stereoselectivity of the reaction and led to the formation of hydroxyphosphonates up to 90% *ee* or higher. Dimethyl 2-hydroxy-3-chloropropylphosphonate was utilized as a chiron for the preparation of a number of biologically active compounds in multigram quantity.

Keywords: Asymmetric synthesis, asymmetric reduction, hydroxyphosphonates, ketophosphonates, L-prolin, tartaric acid

Introduction

Hydroxyphosphonic acids are an important class of compounds occurring in nature.¹ Many of these compounds have attracted considerable attention in recent years for their role in biologically relevant processes.¹⁻³ They possess antibacterial, antiviral, antibiotic, pesticidal, anticancer, and enzyme inhibitor properties.^{1,2} In our previous publications we have reported methods for the preparation of optically active α - and β -hydroxyphosphonic acids, including efficient methods for the enantioselective reduction of ketophosphonates.²⁻⁴ The previously employed methods provide access to many α -hydroxyphosphonates, but the use of chiral auxiliaries and/or catalysts is required to improve the stereoselectivity of these methods. A

possible method for the stereoselective introduction of the hydroxyl group is a stereoselective reduction of prochiral keto compounds.

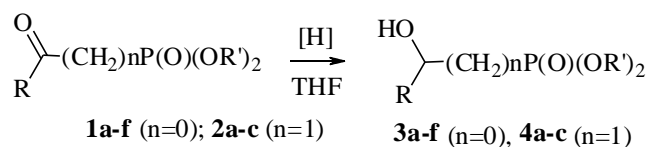
The asymmetric reduction of ketophosphonates has been studied earlier. It included reduction with borane or catecholborane in the presence of chiral oxazaborolydine catalysts,⁶ reduction with chiral chlorodiisopinacampheylboranes⁷ and enantioselective hydrogenation in the presence of chiral BINAP-ruthenium(II) catalyst⁸ (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl). However all these methods require application of expensive reagents and specific reaction conditions which often are too complicated to be reproduced.

The asymmetric reduction can occur under the control of chiral auxiliaries, which are included in the ketophosphonate, under the control of asymmetric catalysts, or chiral reagents. The reduction of diethyl α -ketophosphonates⁹ with borane in the presence of chiral β -butyloxazaborolidines as a catalyst yielded (*S*)- or (*R*)-diethyl 1-hydroxyalkylphosphonates in good yields and moderate enantiomeric excesses (53–83% ee).¹⁰ Acylphosphonic and bis-acylphosphonic acid sodium salts were directly reduced by sodium borohydride to the corresponding hydroxyphosphonates and dihydroxy-alkanebisphosphonates.¹¹ The reduction of [(*N*-*p*-toluenesulfonyl) amino]- β -ketophosphonates¹² with different borohydrides gave [(*N*-*p*-toluenesulfonyl)amino]- β -hydroxyphosphonates in good chemical yields and moderate diastereoselectivity. Only the zinc borohydride reduction of ketophosphonates resulted in the formation of hydroxy-aminophosphonates with good diastereoselectivity.¹³

For these reasons, in continuation of our studies on application of available natural compounds as the reagents in asymmetric synthesis,¹⁴⁻¹⁶ we attempted to find simple procedures for the reduction of the ketophosphonates with chiral reagents prepared on the basis of sodium borohydride and the chiral natural acids such as tartaric acid or aminoacid proline.

Results and Discussion

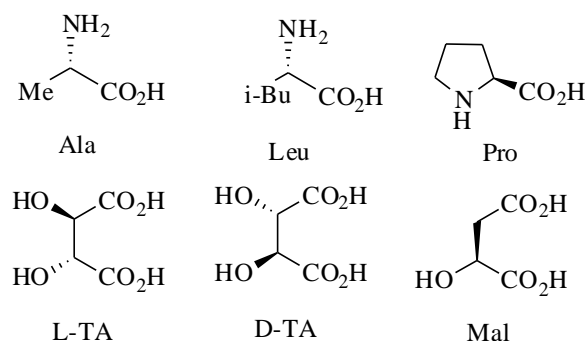
The reduction of ketophosphonates **1,2** with sodium borohydride proceeds with low stereoselectivity (~30–35% *de*).¹⁷ Therefore we have tried to increase the stereoselectivity *via* the complexation of sodium borohydride with chiral natural acids (Scheme 1).¹⁵



R = Ph, R' = Mnt, n = 0 (**1,3 a**); R = C₆H₄F-4, R' = Mnt, n = 0 (**1,3 b**); R = C₆H₄OMe-2 (2-An), R' = Mnt, n = 0 (**1,3 c**); R = *i*-Pr, R' = Mnt, n = 0 (**1,3 d**); R = Pyperonyl, R' = Mnt, n = 0 (**1,3 e**); R = Ph, R' = Et, n = 0 (**1,3 f**); R = CH₂Cl, R' = Et, n = 1 (**2,4 a**); R = CH₂Cl, R' = Mnt, n = 1 (**2,4 b**), R = Ph, R' = Et, n = 1 (**2,4 c**);

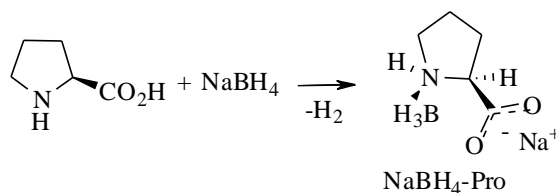
Scheme 1

In this article we have tested natural amino acids: L-alanine (Ala), L-leucine (Leu), L-proline (Pro), and hydroxycarbonic acids: L-(+)-tartaric acid (L-TA), D-(-)-tartaric acid (D-TA), (S)-malic acid (Mal) as chiral auxiliaries in the reaction of ketophosphonates with sodium borohydride (Scheme 2).



Scheme 2

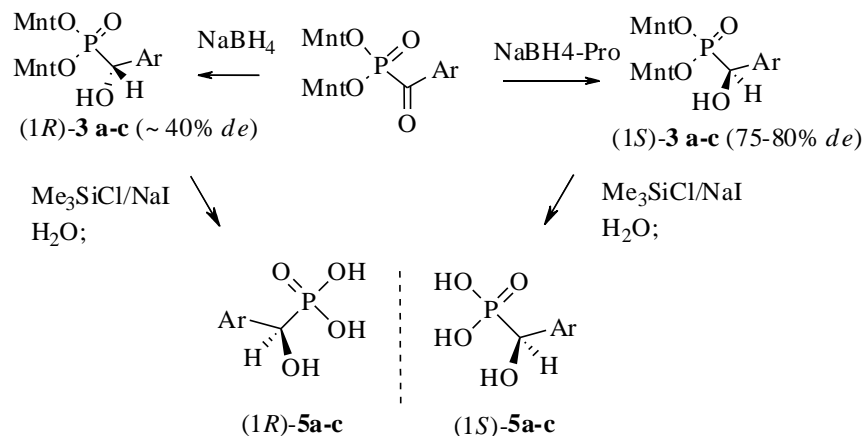
The best results in improving of stereoselectivity of ketophosphonate reduction were attained with chiral complex of sodium borohydride with natural amino acid - L-proline (NaBH₄-Pro) (Scheme 3). At the same time P-alanine and L-leucine showed moderate stereoselectivity (See Table 1). For the preparation of this reducing reagent, an equimolar amount of L-proline was added to sodium borohydride suspended in THF, and the mixture was stirred at room temperature for several hours.¹⁸



Scheme 3

The ketophosphonates **3a-c** were then added to NaBH₄-Pro, resulting in the formation of (S)-hydroxyphosphonate with a stereoselectivity in the range from 52% to 79% *de* purity (Method a). Compounds (S)-**3a-c** were crystallized from hexane and isolated in approximately 100% optical purity (Scheme 4) The chiral menthyl groups of **3a-c** were cleaved off under mild conditions by a modified procedure of Morita et al.¹⁹ The reaction of the dimethyl α -hydroxyphosphonates **3a-c** with trimethylsilyl chloride and NaI in acetonitrile led to bis(trimethylsilyl)- α -hydroxyphosphonates, which were finally hydrolyzed in a mixture of water/ethanol to afford the optically active α -hydroxyphosphonic acids **5a-c**. The treatment of α -hydroxyphosphonates **3a-c** with hydrochloric acid in water/dioxane solution also gave the

corresponding free optically active phosphonic acids **5a–c** in good yields. Owing to the steric hindrance of the esters **1a–c**, it was necessary to use longer reaction times and higher temperatures ketophosphonates with sodium borohydride (Scheme 4).



Scheme 4

Compounds **3** and **5** were identified by ^1H , ^{13}C , and ^{31}P NMR spectroscopy and liquid chromatography. Dimethyl α -hydroxyphosphonates are easily crystallizable compounds, which are obtained in a stereochemically pure state.

^{31}P NMR spectra of compounds **3a–c** show signals for the two diastereomers, with δ_{P} values in the area of 21.0–21.5 ppm. The downfield signal belongs to the (*R*)-diastereomer and the upfield signal to the (*S*)-diastereomer of α -hydroxyphosphonates **3**. ^1H NMR spectra of compounds **3a–c** revealed that the signals belong to the protons of the menthyl group, aromatic protons of appropriate multiplicity and intensity, a broad signal due to the OH group at $\delta_{\text{H}} = 3.7$ ppm, and a CH doublet at $\delta_{\text{H}} = 4.9$ ppm. ^1H and ^{13}C NMR spectra of compounds **3a–c** indicate that the molecules are asymmetric, because the signals of the two menthyl groups bonded to phosphorus are magnetically nonequivalent. The configuration of (*R*)-(+)- α -hydroxybenzylphosphonic acid **5a** was confirmed by comparing its optical rotation with literature data.²⁰

The reduction of dimethyl ketophosphonates with NaBH_4 led preferably to the formation of (*R*)- α -hydroxyphosphonates, whereas the reduction with $\text{NaBH}_4\text{-Pro}$ furnishes (*S*)-hydroxyphosphonates.

The preferential formation of (*R*)-diastereomers observed in the reduction of α -ketophosphonates **1** with NaBH_4 in ethanol can be anticipated to some extent by examining their molecular models. The molecular structures of α -ketophosphonate **1a** and α -hydroxyphosphonate **3b** indicate the high asymmetry of the molecules owing to a propeller-like arrangement of the menthyl groups around the phosphorus atom. Thus, one can make the reasonable assumption that the attack of the reducing agent on the carbonyl group will take place preferentially from the side leading to the (*R*)-configuration rather than from the opposite side, which is shielded by the

menthyl group (Figure 1, left). This corresponds to an approach to the more exposed face of the α -ketophosphonate. The selectivity of the reduction with NaBH₄-Pro depends upon the geometry of the complex formed by coordination of the carbonyl oxygen to the boron atom and of the carboxylic sodium to the oxygen of the P-O group. The reaction cycle inside the favored intermediate complex is shown in Fig. 1, right. It is evident that in this case the attack of the chiral reducing agent on the carbonyl group will take place preferentially from the side leading to the (*S*)- configuration rather than the opposite *Re* side. In summary, the described asymmetric reduction of dimethyl α -ketophosphonates provides an easy route to both stereoisomers of optically active α -hydroxyphosphonic acids in good yield and in enantiomeric excess.

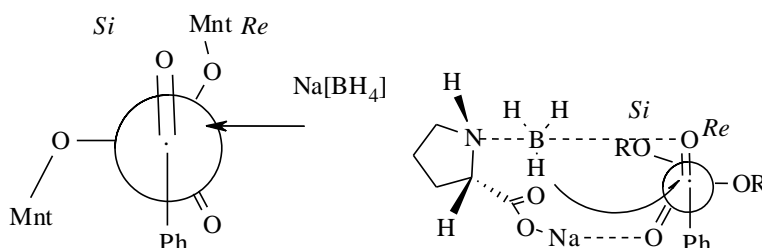
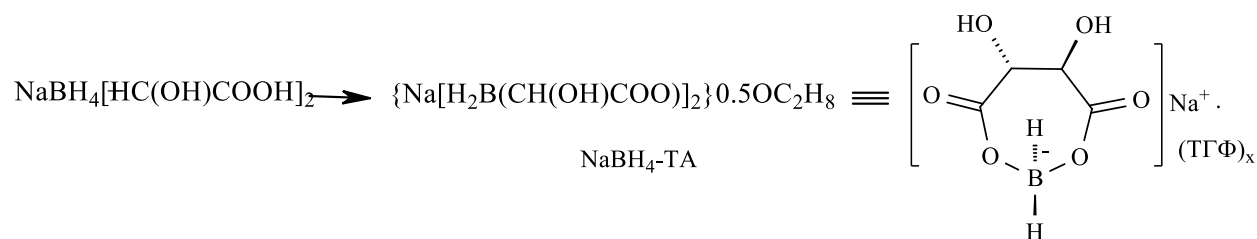


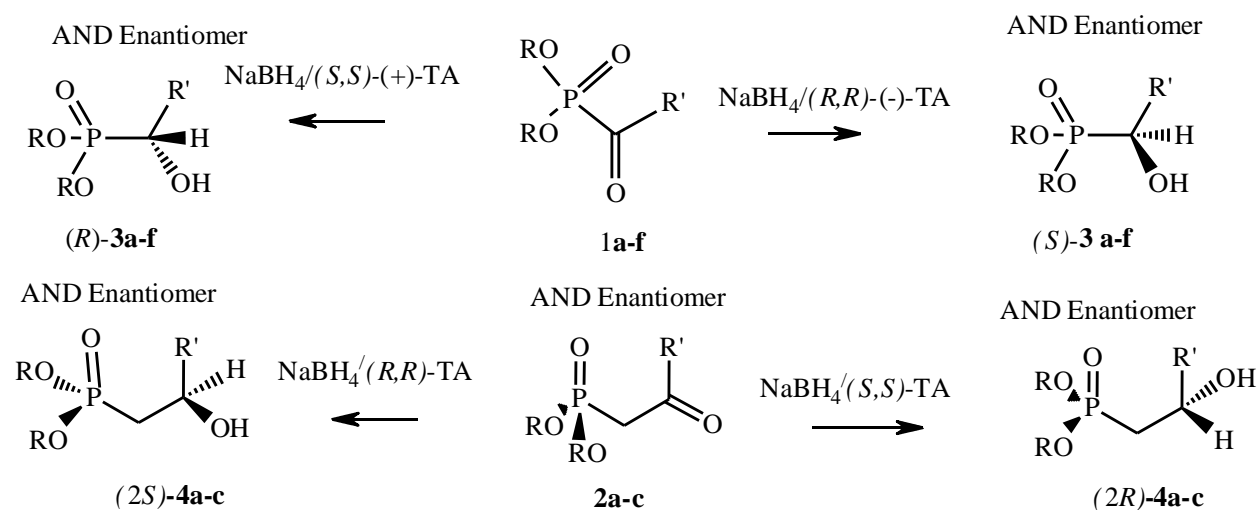
Figure 1. Facial attack on the α -phenylketophosphonate carbonyl group by NaBH₄ (left) and NaBH₄-Pro (right).

We succeeded in the further improvement of the stereoselectivity of ketophosphonate hydroboration when used chiral complex of sodium borohydride with natural (*R,R*)-(+)-tartaric acids.^{21,22} This reducing reagent was prepared by mixing sodium borohydride with tartaric acids in 1:1 ratio in THF followed by refluxing the mixture. After removing the solvent the adduct could be isolated as a colorless fine crystalline substance with high melting point (>250°C). The compound is very hygroscopic and reacts with water. It contains coordinatively bonded THF (0.5 equiv.) as confirmed by ¹H NMR spectrum which contains a multiplet at 1.7 ppm (CH₂C), a multiplet at 3.7 ppm (CH₂O) and a multiplet at 4.5 ppm (CHOH). Detailed study of structure is restricted due to its low solubility in ordinary organic solvents. Note that compounds obtained by treatment of sodium borohydride with achiral carboxylic acids (acetic or trifluoroacetic) to which structure of Na[BH(OAc)₃] or Na[BH₂(OAc)₂] (depending on the initial reagent ratio) is assigned are well known and are used as reducing reagents in organic synthesis (Scheme 5).²³



Scheme 5

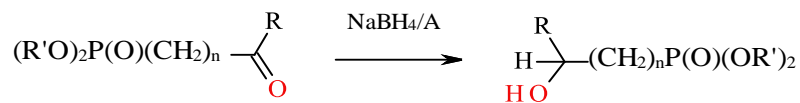
Reduction of ketophosphonates **3,4** with the reagent was performed at cooling to -30°C in THF (Method b). Reduction of diethyl α -ketophosphonates with the NaBH_4 - (R,R) -TA chiral reagent yielded diethyl $(1S)$ - α -hydroxybenzylphosphonates with optical purity 60%, while reduction of dimethyl ketophosphonates led to formation of $(1S)$ - α -hydroxybenzylphosphonates **3** with diastereomeric purity up to 80-93% *de* (Table 1 and Scheme 6).



TA - Tartaric Acid;

Scheme 6

The higher stereoselectivity of reduction in the case of dimethyl arylketophosphonates we explain by the effect of double asymmetric induction,²⁴ because here the asymmetric inductions due to menthyl groups supplementes that of tartaric acid. At the same time, reduction of dimethyl ketophosphonates with the sodium borohydride (S,S) - tartaric acid reagent resulted in lower stereoselectivity. For example, reduction of dimethyl 1-oxobenzylphosphonate yielded corresponding hydroxyphosphonate with 45% *de*. It is obviously that asymmetric inductions due to $(1R,2S,5R)$ -menthyl groups and (R,R) -tartaric acids are compatible and therefore are summated and increase the total stereoselectivity. On the other hand, asymmetric inductions of $(1R,2S,5R)$ -menthyl groups and (S,S) -tartaric acid act in opposite directions and diminish resulting stereoselectivity. The reduction of chiral di $(1R,2S,5R)$ -dimethyl ketophosphonate **2b** with the chiral complex (R,R) -TA/ NaBH_4 proceeded under control of double stereoselectivity to yield the (S) - β -hydroxyphosphonate **4b** with 96% *de* that was considerably higher than the single stereoselectivity when the achiral diethyl 2-keto-3-chloropropylphosphonate **2a** was reduced with (R,R) -TA/ NaBH_4 with 80% *ee* (Table 2).

Table 1. Asymmetric reduction of ketophosphonates to hydroxyphosphonates

Entry	Comp-d	R	R'	n	Yield (%)	Auxiliary (A)	Config of 3,4	ee (%)
1	3a	Ph	Mnt	0	90	L-Pro	<i>S</i>	52.6
2	3b	2-F-C ₆ H ₄	Mnt	0	90	L-Pro	<i>S</i>	79.2
3	3c	2-An	Mnt	0	90	L-Pro	<i>S</i>	60.6
4	3f	Ph	Et	0	85	L-Leu	-	21
5	3a	Ph	Mnt	0	95	L-TA	<i>R</i>	92.4
6	3a	Ph	Mnt	0	98	D-TA	<i>S</i>	46
7	3b	2-F-C ₆ H ₄	Mnt	0	97	L-TA	<i>S</i>	80.5
8	3c	2-An	Mnt	0	96	L-TA	<i>S</i>	74
9	3d	i-Pr	Mnt	0	97.6	L-TA	<i>S</i>	68
10	3e	Pyperonyl	Mnt	0	97	L-TA	<i>S</i>	96
11	3f	Ph	Et	0	95	L-TA	<i>S</i>	60
12	3f	Ph	Et	0	94	D-TA	<i>R</i>	60
13	4a	CH ₂ Cl	Et	1	86	L-TA	<i>S</i>	80
14	4a	CH ₂ Cl	Et	1	82	D-TA	<i>R</i>	80
15	4a	CH ₂ Cl	Et	1	70	Mal	-	25
16	4b	CH ₂ Cl	Mnt	1	94	L-TA	<i>S</i>	96
17	4b	CH ₂ Cl	Mnt	1	80	D-TA	<i>R</i>	82
18	4c	Ph	Et	1	95	D-TA	<i>S</i>	44

Table 2. Stereoselectivity of reduction of ketophosphonates

Entry	Ketophos- phonate	R	R'	Config TA	ee or de of 3	Config of 3	Type of Stereoselectivity
1	1f	Et	Ph	NaBH ₄	0	-	-
2	1f	Et	Ph	<i>R,R</i> -TA	82	<i>S</i>	Single
3	1f	Et	Ph	<i>S,S</i> -TA	78	<i>R</i>	Single
4	1a	Mnt	Ph	NaBH ₄	30	<i>R</i>	Single
5	1a	Mnt	Ph	<i>R,R</i> -TA	92.5	<i>S</i>	Matched double
6	1a	Mnt	Ph	<i>S,S</i> -TA	46	<i>R</i>	Unmatched double

Insofar as reduction of ketophosphonates with the complex NaBH₄/(*R,R*)-tartaric acid affords (*S*)-hydroxyphosphonates, it is very probable that P=O group is involved to the transition state leading to formation of hydroxyphosphonates as it shown in Figure 2, and promotes stereofacial attack of carbonyl group by hydride ion from the *Si* side.

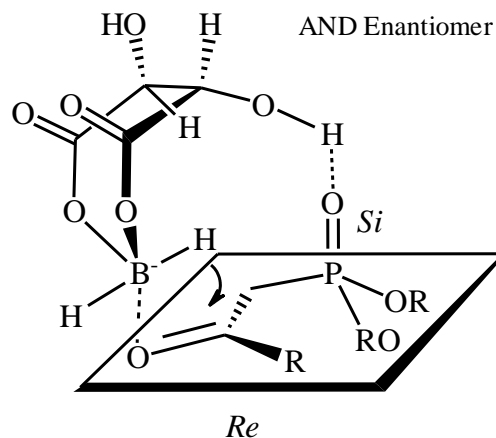


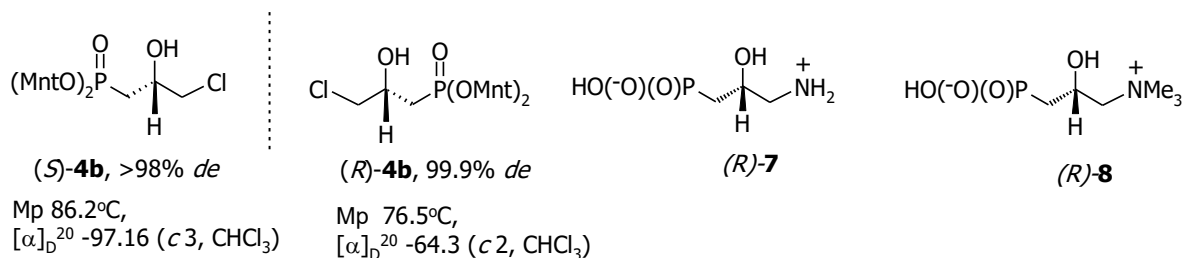
Figure 2. MOPAC-8 stereochemical modeling of reduction of ketophosphonate with $\text{NaBH}_4/(\text{R,R})$ -tartaric acid reagent.

Diethyl α - and β -hydroxyphosphonates were purified by column chromatography. Dimethyl α - and β -hydroxyphosphonates were obtained enantiomerically pure after crystallization from acetonitrile (Table 2).

Several methods were used for elucidation optical purity of the synthesized compounds. The diastereoisomeric ratio of hydroxyphosphonate dimethyl esters was registered by $^{31}\text{P}\{-^1\text{H}\}$ NMR spectroscopy directly. In the case of homochiral diethyl hydroxyphosphonates the optical purity was determined after derivatization with di-(1*R*,2*S*,5*R*)-menthyl chlorophosphite resulted in formation of diastereomers of the derivatives with a significant difference in chemical shifts δ_{P} in ^{31}P NMR spectra, which provided accurate integration of signals and correct measuring of their diastereomeric ratio.²¹

For determination of optical purity of diethyl hydroxyphosphonates we found convenient to use natural cinchonidine as a chiral solvating reagent. In this case the signals of the hydroxyphosphonate (*R*)- and (*S*)-enantiomers in $^{31}\text{P}\{-^1\text{H}\}$ NMR spectra were separated up to zero line and could be easily measured by integration.^{32,33} The absolute configuration of dimethyl hydroxyphosphonates was determined by the method of chemical extrapolation. The dimethyl esters were hydrolysed to free hydroxyphosphonic acids whose configuration was determined earlier.²⁵⁻³² For example, the hydrolysis of dimethyl 2-hydroxy-3-chloropropylphosphonate **4b** with conc. hydrochloric acid in dioxane afforded the enantiopure (*S*)-2-Hydroxy-3-chloropropylphosphonic acid (*S*)-**6b** with high yield.

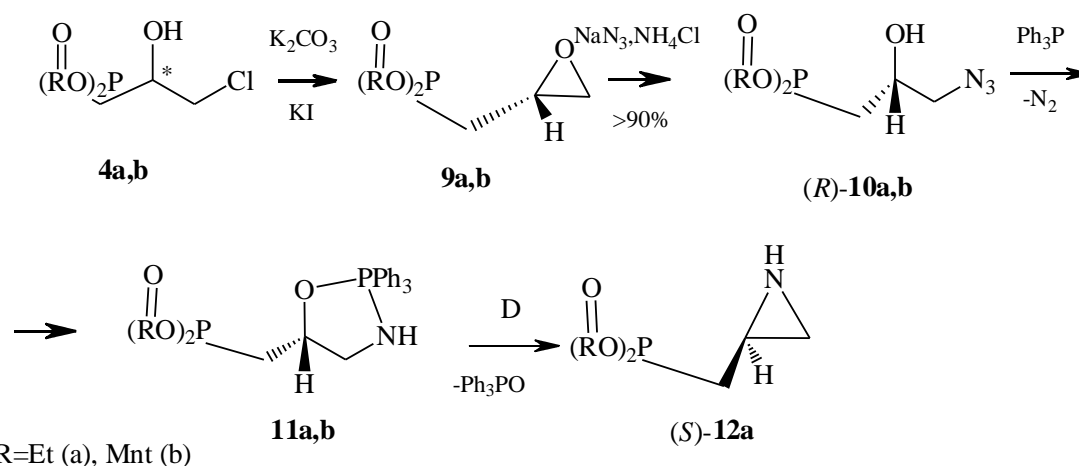
Stereoisomers of dimethyl 2-hydroxy-3-chloropropylphosphonate **4b** and 2-hydroxy-3-chloropropylphosphonic acid **6b** of high optical purity represent useful chiral synthetic building blocks (chirons) for the synthesis of enantiomerically pure β -hydroxyphosphonates. By means of these chirons we have earlier obtained biologically important β -hydroxyphosphonic acids, chiral compounds, γ -amino- β -hydroxypropylphosphonic acid (phosphono-GABOB, **7**) and phosphono-carnitine **8** in the multigram scale (Scheme 7).^{14-16,22}



Scheme 7

The treatment of (S) -**4a,b** with K₂CO₃ in acetonitrile–DMF in the presence of potassium iodide led quantitatively to the formation of epoxide (R) -**9a** with 99% *de*. The reaction of epoxide **9a** with sodium azide in the presence of ammonium chloride in methanol afforded the (R) -2-hydroxy-3-azidopropylphosphonate **10a** in very high yield (Scheme 8). The epoxides **9a,b** were converted consequently into azides **10a,b** and aziridine **12**.

The diethyl $(2R)$ -2,3-epoxypropylphosphonate (R) -**9a,b** reacted readily with sodium azide in the presence of ammonium chloride in methanol to afford dialkyl $(2R)$ -2-hydroxy-3-azidopropylphosphonates **10a,b**. The reaction of azidophosphonates **10a,b** with triphenylphosphine at room temperature led at first to the formation of intermediate products **11a,b**, bearing pentacoordinated phosphorus, which were registered by ³¹P NMR spectra. Thus, the ³¹P NMR spectrum of the product **11a** reveals two signals: δ_P -55.1 (pentacoordinated phosphorus) and +26.9 ppm (tetraordinated phosphorus) of equal intensity according to the structure of this compound. Then, upon heating, **11a** converts into triphenylphosphine oxide (δ_P 30.2 ppm) and aziridinophosphonate **12a** (δ_P 29 ppm), which were isolated in good yields. The diethyl $(2S)$ -aziridine-2-yl-propylphosphonate (S) -**12a** was purified by distillation under vacuum and isolated in pure state as colorless liquid



Scheme 8

The dimethyl aziridine-2-yl-propylphosphonate **12 b** was also prepared, however this product contained ~20% of by-products, which we were not able to separate by column chromatography to obtain this compound in pure state. We are continuing this work with aim to prepare pure **12 b**.

The enantiomeric purity of diethyl β -hydroxy- γ -chloropropylphosphonates **4a** was analyzed using cinchonidine as a chiral solvated reagent,³³ and dimethylchlorophosphite as a chiral derivatizing reagent.²¹ The ¹H NMR spectra of β -hydroxyphosphonates are of special interest. They disclose signals of diastereotopic protons in PCH₂ and CH₂X groups as doublet doublets due to spin-spin coupling with phosphorus atom, proton of CHOH group (vicinal constant ³J_{HH}), and due to mutual coupling ²J_{HH}. The NMR spectra allows to perform conformational analysis of the obtained compounds. 2-Hydroxy-3-chloropropylphosphonate **4a** probably exist mainly as *trans*-conformers at the C₁-C₂ bond, as follows from the values of vicinal constants ³J_{HP} = 18 Hz and geminal constants ³J_{HH} and ³J_{HH} equal to 15-18 Hz and 6.3-8.0 Hz, respectively. In the molecules of β -hydroxyphosphonates probably there is an intramolecular hydrogen bond between hydrogen atom of CH-OH group and P=O group, in consistence with the downfield shift of the signal of hydroxyl proton to 4.7-5 ppm. Stability of the *trans*-conformers probably is higher due to formation six-membered ring with conformation approaching chair form. In the phosphocarnitine molecule this intramolecular hydrogen bond is probably especially strong, as follows from even greater downfield shift of the signal of OH proton, to 5-5.1 ppm, because in this case it involves negatively charged oxygen atom in P=O-group.

Conclusions

In summary, a series of optically active γ -amino- β -hydroxyphosphonic acids can be synthesized starting from the dialkyl (*S*)- or (*R*)-2-hydroxy-3-chloropropylphosphonates. These compounds give access to (*R*)- or (*S*)-phosphono-carnitines, phosphono-GABOB, and 2-hydroxy-3-aminophosphonates. The described asymmetric reduction of dialkyl α - and β -ketophosphonates provides an easy route to both stereoisomers of optically active α - and β -hydroxyphosphonic acids in good yield and in enantiomeric excess. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-2-hydroxy-3-chloropropylphosphonate *via* the formation of the epoxide and reaction with sodium azide was converted into the (*S*)-2-hydroxy-3-azidopropylphosphonate

Experimental Section

General. Melting points are uncorrected. NMR spectra were registered on a Varian VXR-300 instrument at 300 (¹H) and 126.16 (³¹P) MHz with internal TMS (¹H) and external 85% H₃PO₄ in D₂O (³¹P). Optical rotation angles were measured on a Polax-2L polarimeter (Japan) and on a Perkin-Elmer Model 241 spectropolarimeter Column chromatography was performed with

Merck 60 silica gel. All experiments were performed in inert atmosphere (Ar). For the reaction anhydrous solvents were used: THF was freshly distilled over sodium in the presence of benzophenone, methylene chloride was distilled over P₄O₁₀. The Fluka tartaric acids, sodium borohydride and menthol were used. Tartaric acids and sodium borohydride priority to use were kept for 2 h in a vacuum at 30 °C.

Reduction of ketophosphonates (1a–c) with NaBH₄-Pro by Method a

To a suspension of sodium borohydride (0.045 g, 1.19 mmol) in 8 mL of THF, L-proline (0.137 g, 1.19 mmol) was added. The mixture was stirred at room temperature for 6 to 12 h. Ketophosphonate **1a** (0.368 g, 0.795 mmol) was then added, and the mixture was stirred for further 24 h at room temperature. The solvent was evaporated and 10 mL of water/ethyl acetate (1:1) mixture was added to the residue. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The extract was washed with 1N HCl, then with sodium carbonate solution, again with water, and finally dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the crystalline solid.

Reduction of ketophosphonates (1a–f, 2a–c) with NaBH₄-TA by Method b

To a suspension of sodium borohydride (0.36 g, 10 mmol) in 35 ml of THF was added (*R,R*)-(+)-tartaric acid (1.5 g, 10 mmol), then the reaction mixture was refluxed for 4 h. After that a solution of ketophosphonate (2.5 mmol) in 10 ml of the THF was added at –30°C and the reaction mixture was stirred at this temperature for 24 h. Then to the reaction mixture was added 15 ml of ethyl acetate and 35 ml of 1 N hydrochloric acid dropwise. The organic layer was separated, the aqueous phase was saturated with NaCl and extracted two times with ethyl acetate. The organic extracts were washed with a saturated solution of Na₂CO₃ and dried with Na₂SO₄. The solvent was removed under vacuum, the residue was crystallized from acetonitrile.

Di(1*R*,2*S*,5*R*)-menthyl (*S*)-hydroxy(phenyl)methylphosphonate (*S*)-(3a). (Method b) Yield: 80 %, colorless crystals, mp. 112–113°C. $[\alpha]_D^{20}$ –87.6 (c 1.3, CHCl₃). ¹H NMR (C₆D₆): δ_H 1.01 (3 H, d, ³J_{HH}=6.9, CH₃), 1.04 (3H, d, ³J_{HH}=6.9, CH₃), 1.08 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 1.18 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 1.20 (3H, d, ³J_{HH} 6.9 Hz, CH₃), 1.21 (3H, d, ³J_{HH}=6.9 Hz, CH₃), 1.40–2.6 (14H, m, CH₃ and CH), 2.00 [1H, m, CH(CH₃)₂], 2.4 [1H, m, CH(CH₃)₂], 4.49 (2H, m, OCH), 5.2 (1H, d, J_{HP}=10.5 Hz, CHP), 5.10 (1H, br, OH), 7.48 (3H, m, ArH), 7.8 (2H, m, ArH). dC (100.6 MHz, CDCl₃) 127.98 (d, J= 2.5 Hz), 127.8 (d, J= 2.5 Hz), 127.4 (d, J= 9.6 Hz), 71.8 (d, J= 160 Hz), 48.4 (d, J= 14 Hz), 48.3 (d, J= 13.2 Hz), 45.66, 42.53, 34.01, 31.5, 25.33, 22.7, 21.98, 21.13, 21.03, 15.73, 15.61; ³¹P NMR (CDCl₃), δ: 22.3. Mass-spectrum (70 eV): m/z 464 (M⁺). Anal. Calcd for C₂₇H₄₅O₄P: C, 69.80; H, 9.76; P, 6.67. Found C, 69.53; H, 9.80; P, 6.38.

Di(1*R*,2*S*,5*R*)-menthyl (*R*)-hydroxy(phenyl)methylphosphonate (*R*)-(3a). (Method a) Yield: 50%; colorless crystals; mp 139 °C; $[\alpha]_D^{20}$ –70 (c 1, toluene). ¹H NMR (CDCl₃): δ_H 0.7 – 1.0 (m, CH₃); 1.1 – 1.23 (m, CH₂+CH); 3.7 (br, OH); 4.2 (dt, OCH, J_{HH}=2.3 Hz, J_{HH}=4.1); 4.92 (d, CHP, J_{HP}=11 Hz); 7.2 – 7.3 (m, C₆H₅); 7.3 – 7.5 (m, C₆H₅). ¹³C NMR (CDCl₃): δ_C 127.99 (d, J= 2.5 Hz); 127.8 (d, J_{CP}=2.5 Hz); 127.3 (d, J_{CP}=9.6 Hz, C₆H₅); 71.6 (d, J_{CP}=60 Hz, PC); 48.6 (d,

$^a J_{CP}=14$ Hz, CHO); 48.5 (d, $J_{CP}=13.2$ Hz, CHO^b); 45.66, s; 42.53, s; 34, s; 31.5, s; 25.31, s; 22.7, s; 21.97, s; 21.13, s; 21.03, s; 15.74, 15.60 (diastereotopic menthyl groups). ^{31}P NMR (CDCl_3), $\delta_P=23.71$. (**Method b**) Yield 95%, mp 139°C, $[\alpha]_D^{20} -70$ (c 1.07, CHCl_3). ^1H NMR (CDCl_3): δ_H 0.7–1.0 (18H, m CH_3), 1.1–1.23 (18H, m CH_2+CH), 3.7 (1H, br, OH), 4.2 (2H, dt, OCH, $J_{HH}=2.3$ Hz, $J_{HH}=4.1$ Hz), 4.92 (1H, d, $J_{HP}=11$ Hz, CHP), 7.2–7.3 (3H, m, C_6H_5), 7.3–7.5 (2H, m C_6H_5). ^{13}C NMR (CDCl_3): δ_C 127.99 (d, $J=2.5$ Hz), 127.8 (d, $J_{CP}=2.5$), 127.3 (d, C_6H_5 , $J_{CP}=9.6$ Hz), 71.6 (d, PC, $J_{CP}=160$ Hz), 48.6 (d, $J_{CP}=14$ Hz, CHO^a), 48.5 (d, $J_{CP}=13.2$ Hz, CHO^b), 45.66, s; 42.53, s; 34, s; 31.5, s; 25.31, s; 22.7, s; 21.97, s; 21.13, s; 21.03, s; 15.74, 15.60. Mass-spectrum (70 eV): m/z 464 (M^+).

Di(1*R*,2*S*,5*R*)-menthyl (S)-hydroxy(2-fluorophenyl)methylphosphonate (S)-(3b). (Method a)

Yield: 97%; colorless crystals; mp 137.5–138.5°C. $[\alpha]_D^{20} -83.7$ (c 1.3, CHCl_3). ^1H NMR (C_6D_6): δ_H 0.71 (3H, d, $^3J_{HH}=6.9$, CH_3); 0.76 (3H, d, $^3J_{HH}=6.9$, CH_3); 0.86 (3H, d, $^3J_{HH}=6.9$ Hz, CH_3); 0.91 (d, $^3J_{HH}=6.9$ Hz, CH_3); 1.00–2.25 (m, CH_3 and CH); 1.74 [m, $\text{CH}(\text{CH}_3)_2$]; 2.0 [m, $\text{CH}(\text{CH}_3)_2$]; 4.04 (1H, d, $J_{HH}=22.5$ Hz, CHP); 4.2 (1H, m, OCH), 5.18 (1H, br, OH); 6.9 (2H, t, $J_{HH}=8.2$ Hz, C_6H_4); 7.45 (2H, m, C_6H_4). ^{31}P NMR (CDCl_3), $\delta_P=19.8$. (**Method b**). Yield 97%, mp 137.5–138.5°C, $[\alpha]_D^{20} -83.7$ (c 1.3, CHCl_3). ^1H NMR (C_6D_6): δ_H 0.71 (3H, d, $^3J_{HH}=6.9$ Hz, CH_3), 0.76 d (6H, CH_3 , $^3J_{HH}=6.9$ Hz), 0.86 d (6H, CH_3 , $^3J_{HH}=6.9$ Hz), 0.91 d (3H, CH_3 , $^3J_{HH}=6.9$ Hz), 1.00–2.25 m (14H, CH_3 and CH), 1.74 m [1H, $\text{CH}(\text{CH}_3)_2$], 2.0 m [1H, $\text{CH}(\text{CH}_3)_2$], 4.04 d (1H, CHP, $J_{HH}=22.5$), 4.2 m (2H, OCH), 5.18 br (1H, OH), 6.9 t (3H, $J_{HH}=8.2$ Hz, C_6H_4), 7.45 m (2H, C_6H_4). δ_C (100.6 MHz, CDCl_3) 164.2, 164.1, 161.6, 161.5, 130.7, 130.4, 130.3, 130.2, 125.8, 116.4, 116.1, 114.2, 114.4, 72.4, 70.8, 49.3, 49.16, 49.0, 48.3, 45.7, 42.5, 34.0, 31.5, 25.3, 22.7, 22.0, 21.1, 21.0, 15.7, 15.6; ^{31}P NMR (CDCl_3): δ_P 19.8. Anal. Calcd for $\text{C}_{27}\text{H}_{44}\text{FO}_4\text{P}$: C 67.20; H 9.19; P, 6.42. Found: C 67.00; H 9.20; P, 6.38.

Di(1*R*,2*S*,5*R*)-menthyl (S)-hydroxy-(2-methoxyphenyl)methylphosphonate (S)-(3c). (Method a)

Prepared similarly to compound **3a**. Yield: 74%; colorless crystals; mp 116–117°C. $[\alpha]_D^{20} -75.2$ (c 0.66, CHCl_3). ^1H NMR (C_6D_6): δ_H 0.60 (d, CH_3 , $^3J_{HH}=6.9$ Hz); 0.52 (d, CH_3 , 3H, $J_{HH}=6.9$ Hz); 0.73 (d, CH_3 , $^3J_{HH}=6.9$); 0.79 (m, 2 CH_3); 0.84 (d, CH_3 , $^3J_{HH}=6.9$ Hz); 0.92–1.54 (m, CH_2 and CH); 2.14 [m, $\text{CH}(\text{CH}_3)_2$]; 2.40 [m, $\text{CH}(\text{CH}_3)_2$]; 3.59 (s, OCH_3); 4.17 (m, OCH); 4.03 (m, OCH); 4.54 (br, OH); 5.24 d (1H, CHP, $J_{HH}=13.2$ Hz); 6.59 d (1H, ArH, $J_{HH}=8.1$ Hz); 6.80 (t, 1H, ArH, $J_{HH}=7.9$ Hz); 7.04 (t, 1H, ArH, $J_{HH}=7.9$ Hz); 7.60 (d, ArH, $J_{HH}=7.5$ Hz). ^{31}P NMR (CDCl_3), $\delta_P=21.13$. (**Method b**) Yield 74%, mp 116–117°C, $[\alpha]_D^{20} -75.2$ (c 0.66, CHCl_3). ^1H NMR (C_6D_6): δ_H 0.60 d (3H, $^3J_{HH}=6.9$ Hz, CH_3), 0.52 (3H, d, $^3J_{HH}=6.9$ Hz, CH_3), 0.73 (3H, d, $^3J_{HH}=6.9$ Hz, CH_3), 0.79 (6H, m, CH_3), 0.84 (3H, d, $^3J_{HH}=6.9$ Hz, CH_3), 0.92–1.54 (14H, m, CH_2 and CH), 2.14 [1H, m, $\text{CH}(\text{CH}_3)_2$], 2.40 [1H, m, $\text{CH}(\text{CH}_3)_2$], 3.59 (3H, OCH_3), 4.17 (1H, m, OCH), 4.03 (1H, m, OCH), 4.54 (1H, br, OH), 5.24 (1H, d, $J_{HH}=13.2$ Hz, CHP), 6.59 (1H, d, $J_{HH}=8.1$ Hz, ArH), 6.80 (1H, t, $J_{HH}=7.9$ Hz, ArH), 7.04 (1H, t, $J_{HH}=7.9$ Hz, ArH), 7.60 (1H, d, $J_{HH}=7.5$ Hz, ArH). ^{13}C NMR (CDCl_3), δ_C 157.10 (d, $J=6.5$ Hz), 129.00 (d, $J=2.8$ Hz), 128.8 (d, $J_{CP}=2.8$ Hz), 125.3 (d, $J_{CP}=5.5$ Hz), 120.6 (d, $J_{CP}=2.0$ Hz), 110.5 128.8 (d, $J_{CP}=2.0$ Hz, C_6H_5), 66.6 (d, PC, $J_{CP}=161$ Hz), 55 (s, CH_3O), 48.8 (d, CHO^a, $J_{CP}=35$ Hz), 48.5 (d, CHO^b, $J_{CP}=34$ Hz), 43.8, s; 34.09, s; 33.9, s; 31.5, s; 25.24, s; 22.7, s; 21.97, s; 21.87, s; 21.21, s; 21.05; 15.72,

15.62. ^{31}P NMR (CDCl_3), δ_{P} 20.98. Anal. Calcd for $\text{C}_{28}\text{H}_{47}\text{O}_5\text{P}$: C, 67.99; H, 9.58; P, 6.26. Found: C, 68.16; H, 9.50; P, 6.27.

Di(1*R*,2*S*,5*R*)-menthyl (S)-hydroxy(isopropyl)methylphosphonate (3d). (Method b) Yield: 97.6%, colorless crystals, mp 71°C (MeCN), $[\alpha]_{\text{D}}^{20}$ -82.8 (*c* 2.2, CHCl_3). ^1H NMR (C_6D_6): δ_{H} 0.73–0.84 (18H, m, CH_3), 0.87–2.3 (18H, m, CH_2 and CH), 0.95 (3H, d, $J_{\text{HH}} = 6.3$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.97 (3H, d, $\text{CH}(\text{CH}_3)_2$ $J_{\text{HH}} = 6.3$ Hz), 1.94 [1H, m, $\text{CH}(\text{CH}_3)_2$], 3.33 (1H, m, CHOH), 4.09 (2H, m, OCH). ^{31}P NMR (CDCl_3), δ_{P} 24.04. Anal. Calcd for $\text{C}_{24}\text{H}_{47}\text{O}_4\text{P}$: C, 66.94; H, 11.0; P, 7.19. Found: C, 66.90; H, 10.93; P, 7.18.

Di(1*R*,2*S*,5*R*)-menthyl (S)-hydroxy(piperonyl)methylphosphonate (3e). (Method b) Yield 70%, colorless crystals, mp 96°C (MeCN), $[\alpha]_{\text{D}}^{20}$ -74 (*c* 1, CHCl_3). ^1H NMR (C_6D_6): δ_{H} 0.62 (3H, d, $J_{\text{HH}} = 6.9$ Hz, CH_3), 0.66 (3H, d, $J_{\text{HH}} = 6.9$ Hz, CH_3), 0.67 (3H, d, $J_{\text{HH}} = 6.9$ Hz, CH_3), 0.76 (3H, d, $J_{\text{HH}} = 6.9$ Hz, CH_3), 0.77 (3H, d, $J_{\text{HH}} = 6.9$ Hz, CH_3), 0.81 (3H, d, $J_{\text{HH}} = 6.9$ Hz, CH_3), 0.9–2.27 (16H, m, CH_2 and CH), 1.48 [1H, m, $\text{CH}(\text{CH}_3)_2$], 1.94 [1H, m, $\text{CH}(\text{CH}_3)_2$], 4.09 (2H, m, OCH), 4.7 (1H, d, $J_{\text{HP}} = 10.5$, CHP), 5.38 (1H, br, OH), 5.65 (2H, s, CH_2O_2), 6.57 (1H, d, $J_{\text{HH}} = 7.9$ Hz, C_6H_3), 6.85 (1H, d, $J_{\text{HH}} = 7.9$ Hz, C_6H_3), 6.98 (1H, s, C_6H_3). ^{31}P NMR (CDCl_3), δ_{P} 19.8. Anal. Calcd for $\text{C}_{28}\text{H}_{45}\text{O}_6\text{P}$: C, 66.12; H, 8.92; P, 6.09%. Found: C, 66.17; H, 8.83; P, 6.14.

Diethyl (S)-hydroxy(phenyl)methylphosphonate (S)-(3f). (Method b) Yield: 95 %, colorless solid, mp 74–76°C. $[\alpha]_{\text{D}}^{20}$ -15.4 (*c* 2.6, CHCl_3). ^1H NMR (C_6D_6): δ_{H} 1.21 (3H, t, $^3J_{\text{HH}} = 7.1$, CH_3), 1.26 (3H, t, $^3J_{\text{HH}} = 7.1$, CH_3), 3.8 (1H, br, OH), 3.90–4.13 (4H, m, CH_2), 5.01 (1H, d, $J_{\text{PH}} = 10.9$ Hz, CH), 7.3–7.38 (3 H, m, ArH), 7.49 (2H, d, ArH). ^{31}P NMR (CDCl_3), δ_{P} 22.00 that corresponds to 29

Diethyl-(*R*)-hydroxy(phenyl)methylphosphonate (*R*)-(3f). (Method b) Yield 94%, mp 74–76°C. $[\alpha]_{\text{D}}^{20}$ +28.3 (*c* 2.1, CHCl_3), that corresponds to 31 .

Diethyl (S)-(-)-2-hydroxy-3-chloropropylphosphonate (S)-(4a). (Method b) Yield: 85%. $[\alpha]_{\text{D}}^{20}$ -12.42 (*c* 3.22, CHCl_3). ^1H NMR (C_6D_6): δ_{H} 1.18 (6H t, $^3J_{\text{HH}} = 7.2$ Hz, CH_3CH_2), 1.79 ddd (1H, $^2J_{\text{HP}} = 17.1$ Hz, $^2J_{\text{HH}} = 15.3$ Hz, $^3J_{\text{HH}} = 9.4$ Hz, PC^{aH}), 2.02 (1H, ddd, $^2J_{\text{HP}} = 18.9$ Hz, $^2J_{\text{HH}} = 15.3$ Hz, $^3J_{\text{HH}} = 3.4$ Hz, PC^{bH}), 3.26 (1H, dd, $^2J_{\text{HH}} = 10.8$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, C^{aHCl}), 3.44 (1H, ddd, $^2J_{\text{HH}} = 10.8$ Hz, $^3J_{\text{HH}} = 4.4$ Hz, $^4J_{\text{PH}} = 3.4$ Hz, C^{bHCl}), 3.96 (5H, m $\text{CH}_2\text{O} + \text{CHOH}$), 4.62 (1H, m OH). ^{31}P NMR (CDCl_3), δ_{P} 29.4. Anal. Calcd for $\text{C}_7\text{H}_{16}\text{ClO}_4\text{P}$: C, 36.46; H, 6.99; P, 13.43. Found: C, 36.2; H, 6.4; P, 13.50.

Diethyl (*R*)-(+)-2-hydroxy-3-chloropropylphosphonate (*R*)-(4a). (Method b) Yield: 85%. $[\alpha]_{\text{D}}^{20}$ +12.4 (*c* 3.2, CHCl_3). ^1H NMR (C_6D_6): δ_{H} 1.18 (6H, t, $^3J_{\text{HH}} = 7.2$ Hz, CH_3CH_2), 1.79 (1H, ddd, $^2J_{\text{HP}} = 17.1$ Hz, $^2J_{\text{HH}} = 15.3$ Hz, $^3J_{\text{HH}} = 9.4$ Hz, PC^{aH}), 2.02 (1H, ddd, $^2J_{\text{HP}} = 18.9$ Hz, $^2J_{\text{HH}} = 15.3$ Hz, $^3J_{\text{HH}} = 3.4$ Hz, PC^{bH}), 3.26 (1H, dd, $^2J_{\text{HH}} = 10.8$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, C^{aHCl}), 3.44 (1H, ddd, $^2J_{\text{HH}} = 10.8$ Hz, $^3J_{\text{HH}} = 4.4$ Hz, $^4J_{\text{PH}} = 3.4$ Hz, C^{bHCl}), 3.96 (5H, m, $\text{CH}_2\text{O} + \text{CHOH}$), 4.62 (1H, m, OH). ^{31}P NMR (CDCl_3), δ_{P} 29.4. Anal. Calcd for $\text{C}_7\text{H}_{16}\text{ClO}_4\text{P}$: C, 36.46; H, 6.99; P, 13.43. Found: C, 36.27; H, 6.54; P, 13.51.

Di(1*R*,2*S*,5*R*)-menthyl (S)-(-)-2-hydroxy-3-chloropropylphosphonate (S)-(4b). (Method b) Yield 95%, colorless solid. Mp 86.2 °C. $[\alpha]_{\text{D}}^{20}$ -97.16 (*c* 3, CHCl_3). ^1H NMR (C_6D_6): δ_{H} 0.71 (3H, d, $^3J_{\text{HH}} = 6.9$ Hz, CH_3), 0.76 (3H, d, $^3J_{\text{HH}} = 6.9$ Hz, CH_3), 0.81–0.84 (12H, m, CH_3), 0.88–

2.18 (17H, m, CH₂+CH), 1.53 [1H, m, CH(CH₃)₂], 1.73 (1H, m, CH^aP), 1.97 (1H, m, CH^bP), 1.96 [1H, m, CH(CH₃)₂], 3.29 (1H, dd, ²J_{HH} = 10.8 Hz, ³J_{HH} = 6.7 Hz, CH^aCl), 3.43 (1H, ddd, ²J_{HH} = 10.8 Hz, ³J_{HH} = 4.7 Hz, ⁴J_{PH} = 2.8 Hz, CH^bCl), 3.9–4.10 (2H, m, OCH), 4.15 (1H, m, CHOH), 4.44 (1H, br, OH). δ_C (100.6 MHz, CDCl₃) 78.37 (d, *J* = 7.5 Hz), 78.34 (d, *J* = 7.5 Hz), 67.29 (d, *J* = 3.6 Hz), 49.36 (d, *J* = 18.2 Hz), 49.08 (d, *J* = 6.5 Hz), 49.07 (d, *J* = 6.5 Hz), 44.13, 43.62, 34.49, 34.49, 32.61 (d, *J* = 141.2 Hz), 32.01, 31.98, 26.12, 26.00, 23.41, 23.40, 22.25, 22.24, 21.41, 21.34, 16.36, 16.13. ³¹P NMR (CDCl₃), δ_P 28.81. Anal. Calcd for C₂₃H₄₄ClO₄P: C, 61.25; H, 9.83; P, 6.87. Found: C, 61.28; H, 9.86; P, 6.88.

Di(1*R*,2*S*,5*R*)-menthyl (*R*)-(-)-2-hydroxy-3-chloropropylphosphonate (*R*)-(4b). (Method b) Colorless solid, mp 76.5 °C. [α]_D²⁰ -64.3 (*c* 2, CHCl₃). ¹H NMR (C₆D₆): δ_H 0.72 (3H, d, ³J_{HH} = 6.9 Hz, CH₃), 0.73 (3H, d, ³J_{HH} = 6.9 Hz, CH₃), 0.81–0.84 (12H, m, CH₃), 0.88–2.18 (17H, m, CH₂+CH), 1.53 [1H, m, CH(CH₃)₂], 1.71 (1H, ddd, ²J_{HP} = 15.7 Hz, ²J_{HH} = 15.5, ³J_{HH} = 9.1 Hz, CH^aP), 1.97 (1H, m CH^bP), 1.96 [1H, m, CH(CH₃)₂], 3.29 (1H, dd, ²J_{HH} = 10.8 Hz, ³J_{HH} = 7.4, CH^aCl), 3.43 (1H, ddd, ²J_{HH} = 10.8 Hz, ³J_{HH} = 4.4 Hz, ⁴J_{PH} = 3.4 Hz, CH^bCl), 3.9–4.05 (2H, m, OCH), 3.95 (1H, m, CHOH), 4.25 (1H, br, OH). δ_C (100.6 MHz, CDCl₃) 78.36 (d, *J* = 7.5 Hz), 78.33 (d, *J* = 7.5 Hz), 67.29 (d, *J* = 3.6 Hz), 49.36 (d, *J* = 18.2 Hz), 49.08 (d, *J* = 6.5 Hz), 49.07 (d, *J* = 6.5 Hz), 44.13, 43.62, 34.49, 34.49, 32.64 (d, *J* = 141.2 Hz), 32.01, 31.98, 26.12, 26.00, 23.43, 23.40, 22.25, 22.24, 21.41, 21.34, 16.37, 16.13. ³¹P NMR (CDCl₃): δ_P 28.7. Anal. Calcd for C₂₃H₄₄ClO₄P: C, 61.25; H, 9.83; P 6.87. Found: C, 61.28; H, 9.86; P, 6.88.

Diethyl (*R*)-2-hydroxy-2-phenylethylphosphonate (*R*)-(4c). (Method b) Yield 95%, yellow oil; [α]_D²⁰ -25 (*c* 2.38, CHCl₃). ¹H NMR (C₆D₆): δ_H 1.10 (3H, t, ³J_{HH} = 6.9 Hz, CH₃), 1.11 (3H, t, ³J_{HH} = 6.9 Hz, CH₃), 1.90–2.12 (2 H, m, CH₂), 3.77–3.99 (4H, m, 2CH₂), 4.75 (1H, br, OH), 4.96–5.06 (1H, m, CHOH), 7.05 (1H, t, C₆H₅, *J*_{HH} = 7.2 Hz), 7.14 (2H, t, *J*_{HH} = 7.2 Hz, C₆H₅), 7.28 (2H, d, *J*_{HH} = 7.2 Hz, C₆H₅). ³¹P NMR (CDCl₃): δ_P 29.6. Anal. Calcd for C₁₂H₁₉O₄P: C, 55.81; H, 7.42; P, 11.99. Found: C, 55.86; H, 7.47; P, 11.90.³²

(*S*)-1-Phenyl(1-hydroxyl)methylphosphonic acid (*S*)-(5a). To a solution of hydroxyphosphonate **3a** (1.15 g, 2.5 mmol) in 50 ml of dioxane was placed in a flask, and 25 ml of 6 N. hydrochloric acid was added. The reaction mixture was left for 3 days at 80 °C. The course of reaction was monitored by ³¹P NMR spectroscopy. When the reaction was completed, the solvent was evaporated, the residue was dissolved in ethanol and the excess of cyclohexylamine (~1.5 ml) was added, the dicyclohexylammonium salt was filtered off. Yield: 50%, colorless solid, mp 226 °C. [α]_D²⁰ -14.0 (*c* 1, MeOH-water 1:1) corresponds to the (*S*)-configuration of **5a**.^{15,25}

(*R*)-1-Phenyl-1-hydroxymethylphosphonic acid (*R*)-(5a)

(Method a). A solution of hydroxymethylphosphonate **3a** (1 g, 2 mmol) in 50 mL of dioxane was placed in a flask and 25 mL of 6N hydrochloric acid was added. The reaction mixture was then left for 3 days at 80 °C. The hydrolysis was monitored by ³¹P NMR spectroscopy. When the reaction was complete, the solvent was evaporated under reduced pressure, the residue was

dissolved in ethanol, followed by the excess addition of cyclohexylamine (~1.5 ml). The precipitate of the dicyclohexylammonium salt was collected by filtration.

(Method b). In a round-bottomed flask, NaI (4 equiv.) and trimethylchlorosilane (4 equiv.) were added to a solution of α -hydroxyphosphonates **3a–c** (1 equiv.) in CH₃CN (10 mL), and the resulting mixture was refluxed for 12 h. The sodium chloride that was precipitated was filtered off. After removal of the solvent under reduced pressure, a solution of ethanol (3 mL) and H₂O (2.5 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. The organic layer was separated and the water phase was evaporated in vacuo. Yield: 50%; mp 226 °C. $[\alpha]_D^{20} +14.0$ (c=1, 50% aqueous MeOH) corresponding to the (*R*)-configuration of acid (**R**)-**5a**. The hydroxyphosphonic acid was dissolved in ethanol, and excess cyclohexylamine was added to obtain a solid precipitate, which was purified by crystallization.

(*R*)-2 α -Cyclohexylammonium salt: mp >200 °C. $[\alpha]_D^{20} +24.0$ (c=1, CHCl₃).²⁵

(*R*)-1-(*o*-Methoxy)phenyl-1-hydroxymethylphosphonic Acid (*R*)-(5b) The preparation was as described for compound **3a**. The product was purified by crystallization from hexane and acetonitrile, colorless solid. (*R*)-(5b)-(Cyclohexylammonium salt). Yield: 50%. mp >200 °C. $[\alpha]_D^{20} +30.0$ (c=1, CHCl₃). ³¹P NMR (CDCl₃), $\delta_P = 17.0$

(*S*)-2-Hydroxy-3-chloropropylphosphonic acid (*S*)-(6b). (a) To a solution of dimethyl hydroxyphosphonate **4b** (4.5 g, 10 mmol) in 250 ml of dioxane was added 100 ml of conc. hydrochloric acid. The reaction mixture was left for 3 days at 85 °C. Then the solvent was removed under reduced pressure, to the residue was added 50 ml of water and the mixture was washed with toluene (3 x 25 ml). The water was removed in vacuo, the residue was dissolved in ethanol and treated with activated charcoal. The solvent was evaporated under reduced pressure to give **6b** as a colorless oil. Yield: 1.56 g (~90 %). Spectroscopically pure product was used without further purification.

(b) A solution of hydroxyphosphonate **4b** (2.3 g, 10 mmol) in 50 ml of CH₂Cl₂ was treated with 10.5 ml (80 mmol) of trimethylbromosilane and was left overnight. The solvent was evaporated, the residue was dissolved in 25 ml of 60% aqueous ethanol. Then the solvent was removed under reduced pressure, to the residue was added 100 ml of water and the mixture was washed with toluene (3 x 25 ml). The solvent was evaporated under reduced pressure to give **6b** as a colorless oil. Yield: 1.7 g (~98%) spectroscopically pure oil, which was used without further purification. ¹H NMR (CD₃OD): δ_H 1.6–1.9 (2H, m, PCH₂), 3.2–3.4 (2H, m, CH₂Cl), 4.8 (1H, m, CHO). ³¹P NMR (CDCl₃): δ_P 25.5.²⁹

Di(1*R*,2*S*,5*R*)-menthyl (2*R*)-(oxirane-2-yl)methylphosphonate (9b). To a stirred solution of di(1*R*,2*S*,5*R*)-menthyl (2*S*)-3-chloro-2-hydroxypropylphosphonate **4b** (4.5 g, 10 mmol) in a 10:3.5 mixture of acetonitrile–DMF (100 ml) were added K₂CO₃ (3.0 g) and KI (0.3 g). The mixture was refluxed for 8 h. Then the mixture was filtered off and the filtrate was evaporated under reduced pressure to give **9b** (4.05 g, 98%) as a colorless oil. $[\alpha]_D^{20} -62.4$ (c 7.0, CHCl₃). ¹H NMR (C₆D₆): δ_H 0.8 (3H, d, ³J_{HH} = 7 Hz), 0.88 (3H d, ³J_{HH} = 7 Hz), 0.89 (3H, d, ³J_{HH} = 7 Hz),

0.90 (3H, d, $^3J_{\text{HH}}=7$ Hz), 0.91 (3H, d, $^3J_{\text{HH}}=7$ Hz), 0.8–1.65 (16H, m, CH_2C), 2.15–2.05 (5H, m, $\text{PCH}_2+\text{CH}_2+\text{CH}$), 2.4 (1H, dd, $^2J_{\text{HH}}=5.1$ Hz, $^3J_{\text{HH}}=2.1$ Hz, $\text{CH}^{\text{a}}\text{O}$), 3.0 (1H, dd, $^2J_{\text{HH}}=5.1$ Hz, $^3J_{\text{HH}}=4$ Hz, $\text{CH}^{\text{b}}\text{O}$), 3.0 (1H, m, CHO), 4.24 (2H, m, CHOP). ^{31}P NMR (CDCl_3), δ_{P} 25.3. Anal. Calcd for $\text{C}_{23}\text{H}_{43}\text{O}_4\text{P}$: C, 66.64; H, 10.45; P, 7.47. Found: C, 66.34; H, 10.27; P, 7.11.

Di(1*R*,2*S*,5*R*)-menthyl (2*R*)-3-azido-2-hydroxypropylphosphonate (10b). To a solution of 2,3-epoxypropylphosphonate **9b** (0.5 g, 1.2 mmol) in 7 ml of methanol was added the sodium azide (0.188 g, 2.89 mmol) and ammonium chloride (0.115 g, 2.15 mmol). The mixture was refluxed for 4 h. Then the solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate and the solution was washed with water. The organic layer was separated, dried with Na_2SO_4 and concentrated to give **10b** as a colorless oil. Yield: 96 %. $[\alpha]_{\text{D}}^{20} -74.2$ (c 2.5, CHCl_3). ^1H NMR (C_6D_6), δ_{H} 0.79, (3H, d, $^3J_{\text{HH}}=7$ Hz, CH_3), 0.81 (3H, d, $^3J_{\text{HH}}=7$ Hz, CH_3), 0.91 (3H, d, $^3J_{\text{HH}}=7$ Hz, CH_3), 0.92 (3H, d, $^3J_{\text{HH}}=7$ Hz, CH_3), 0.93 (3H, d, $^3J_{\text{HH}}=7$ Hz, CH_3), 0.94 (3H, d, $^3J_{\text{HH}}=7$ Hz, CH_3), 1.0–2.0 (16H, m, CH_2C), 1.8 (2H, m, PCH), 3.15 (2H, m, CH_2N), 4.05 (2H, m, CHO), 4.14 (2H, m, $\text{CHOH}+\text{OH}$). ^{31}P NMR (CDCl_3), δ_{P} 27.4. IR: ν_{max} 2120 cm^{-1} (N_3). Anal. Calcd for $\text{C}_{23}\text{H}_{44}\text{N}_3\text{O}_4\text{P}$: C, 60.37; H, 9.69; N, 9.18. Found C, 60.28; H, 9.57; N, 8.84

Diethyl (2*R*)-2-hydroxy 3-azidopropylphosphonate (10a). Compound **10a** was prepared analogously to **10b**. Yield: 90%, yellow oil; ν_{max} (liquid film) 3681, 2984, 2105, 1225, 1099, 967 cm^{-1} ; ^1H NMR (C_6D_6): δ_{H} 1.23 (6H, t, $^3J_{\text{HH}}=7.0$ Hz, CH_3), 1.87 (2H, m, CH_2P), 3.24 (2H, m, CH_2N_3), 3.6 (1H, br, OH), 4.03 (5H, m, OCH_2 and CHOH). ^{31}P NMR (CDCl_3), δ_{P} 29.5. IR: ν_{max} 1225 (P=O), 2105 (N_3), 3336 (OH). Anal. Calcd for $\text{C}_7\text{H}_{16}\text{N}_3\text{O}_4\text{P}$: C, 35.45; H, 6.80; P, 13.06%. Found C, 35.30; H, 6.71; P, 12.99

Diethyl (2*S*)-aziridine-2-yl-propylphosphonate (12a). To a solution of diethyl-(2*S*)-2-hydroxy-3-azidopropylphosphonate **10a** (1.487 g, 6.27 mmol) in 45 ml of toluene was added triphenylphosphine (1.65 g, 6.29 mmol). The reaction mixture was stirred at room temperature for 1-2 hr and was refluxed for 1 h. The solvent was removed under reduced pressure and diethyl ether was added to the residue. The precipitate was filtered off, the filtrate was evaporated and the residue was distilled under vacuum to afford **12a** as a colorless liquid. Yield: 60%, bp 92–93 °C (0.07 mm Hg). ^1H NMR (C_6D_6): δ_{H} 1.166 (3H, t, $J_{\text{HH}}=7.0$, CH_3), 1.171 (3H, t, $J_{\text{HH}}=7.0$ Hz, CH_3), 1.13–1.18 (1H, m, CH_2N), 1.43–1.52 (1H, m, CH_2P), 1.55 (1H, d, $J_{\text{HH}}=5.4$ Hz, CH_2N), 1.6–1.73 (1H, m, CH_2P), 1.93 (1H, m, CHN), 3.82–4.01 (4H, m, CH_2). ^{13}C NMR (CDCl_3), δ_{C} 61.98, 61.91, 31.46 (d, $J=142.7$ Hz), 25.65, 24.58, 16.83, 16.76 ^{31}P NMR (CDCl_3), δ_{P} 29.0. Anal. Calcd for $\text{C}_7\text{H}_{16}\text{NO}_3\text{P}$: C, 43.52; H, 8.35; N, 7.25; P, 16.03. Found C, 43.48; H, 8.29; N, 7.23; P, 16.00.

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