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Enantioselective Reduction of Ketophosphonates Using Chiral Acid Adducts with Sodium Borohydride

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Abstract — A method for asymmetric reduction of α- and β-ketophosphonates using a chiral complex prepared from sodium borohydride and *D*- or *L*-tartaric acid is developed. Reduction of α- or β-ketophosphonates by these reagents led to formation of corresponding (*S*)- or (*R*)-hydroxyphosphonates. Reduction of chiral di(1*R*,2*S*,5*R*)-menthylketophosphonates by the chiral complex $NaBH_4$/(*R*,*R*)-tartaric acid due to the dual compliant asymmetric induction resulted in increased stereoselectivity of the reaction and led to formation of the hydroxyphosphonates with *ee* 90% or higher. On the other hand, reduction of di(1*R*,2*S*,5*R*)-methylketophosphonates by the chiral complex $NaBH_4$/(*S*,*S*)-tartaric acid proceeded as non-compliant dual asymmetric induction and resulted in decreased reaction stereoselectivity leading to formation of hydroxyphosphonates with ~45–60% *ee*. The developed methodology was applied to the synthesis of (*R*)-phosphocarnitine in multigram amounts.

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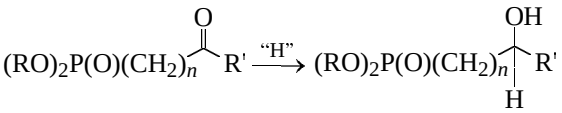
Hydroxyphosphinic acids comprise an important class of compounds whose representatives are widely distributed in the nature [1–3]. Some of these compounds possess interesting physiological properties being antibacterial, antiviral and anticancer preparations, antibiotics, ferment inhibitors, aminoacid mimetics and pesticides [2].

Some of compounds are used in clinics for treating different diseases. Although existing methods allow ease preparation of racemic hydroxyphosphonates, synthesis of chiral compounds of this class remains a complicated synthetic challenge and commonly requires specific approach in a particular case. Note that most of the earlier developed procedures require application of hardly available reagents and catalysts [4, 5].

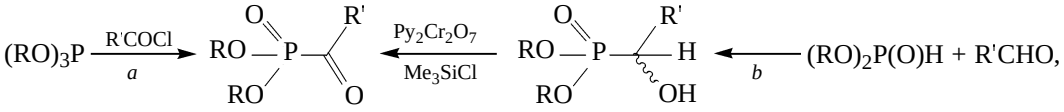
In this communication we describe asymmetric synthesis of the optically active α- and β-hydroxyphosphonates **II** and acids by reduction of related ketophosphonates **I**. The asymmetric reduction of ketophosphonates has been studied earlier. It included reduction with borane or catecholborane in the presence of chiral oxazaborolydine catalysts [6], reduction with chiral chlorodiisopynacampheylboranes [7] and enantioselective hydrogenation in the presence of chiral BINAP–ruthenium(II) catalyst [8] (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. By this reasons, in continuation of our studies on application of available natural compounds as the reagents in asymmetric synthesis [9, 10], 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 acids such as tartaric acid or proline.



I **II**

n = 0, 1.

The initial α-ketophosphonates **I** were prepared by two procedures: one-step reaction of trialkyl phosphites with aroyl chlorides (method *a*) and by two-step procedure (method *b*), which comprise preparation of racemic α-hydroxyphosphonates by reaction of dialkyl phosphites with aldehydes followed by their conversion in high yield (90–100%) without isolation and purification to ketophosphonates **II** at the treatment using pyridinium bichromate–trimethylchlorosilane oxidizing system. The ketophosphonates prepared by the method *a* were purified by column chromatography and isolated with satisfactory yields (60–80%). For example, reaction of 4-fluorobenzoyl chloride with trimenthyl phosphite in toluene proceeded smoothly at room temperature resulting in formation of α-ketophosphonate **II** in 70% yield.

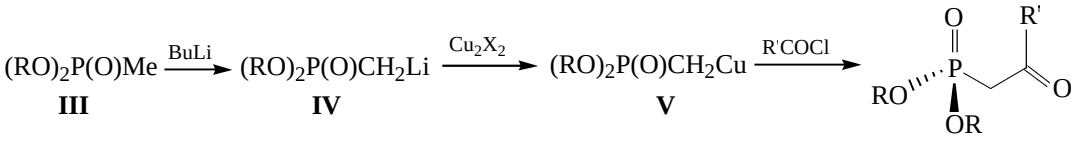


Ia–**If** **IIa**–**IIf**

R = Et, R' = Ph (**a**); R = (1*R*,2*S*,5*R*)-Mnt, R' = Ph (**b**), C_6H_4F-2 (**c**), C_6H_4OMe-2 (**d**), piperonyl (**e**), *i*-Pr (**f**).

Chemical purity and yield of the ketophosphonates prepared by the method *b* is considerably higher than *a*, achieving 90% and more. Therefore the ketophosphonates prepared by this procedure were used in further transformations without purification.

The β-ketophosphonates were synthesized from dialkyl methylphosphonates **III** by reaction in THF with butyllithium to form carbanion **IV** followed by the reaction with carboxylic acid chlorides or methyl esters. Diminishing in the effect of the permetallation reaction on the final result was achieved by addition of cuprous bromide to the reaction mixture for conversion of the lithium derivative **IV** into cuprous derivative **V**.



III **IV** **V** **VI**

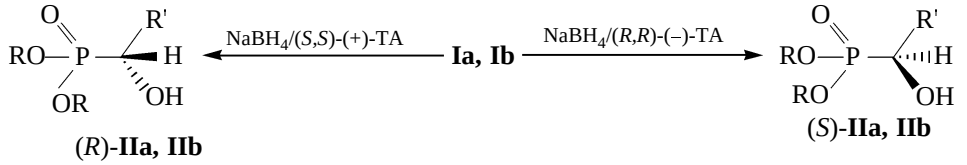
X = Br, I; R = Et, R' = Ph (**a**), CH_2Cl (**b**).

Reduction of the dimenthyl ketophosphonates with sodium borohydride in ethanol led to (*R*)-α-hydroxyphosphonates in a low stereoselectivity (30–35% *de*) and yield [11]. In THF reduction of dimenthyl ketophosphonate proceeded with higher yield but stereoselectivity remained low. The (*S*)-hydroxyphosphonates obtained could be purified by crystallization from acetonitrile and isolated stereochemically pure.

We succeeded in improvement of the stereoselectivity of ketophosphonate hydroborination when used chiral complex of sodium borohydride with natural (*R*,*R*)-(+)-tartaric acids [12,13]. This reducing reagent was prepared by mixing sodium borohydride with tartaric acids in 1 : 1 ration in THF followed by refluxing the mixture. After removing the solvent the target compound 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 equv.) as confirmed by ^{1}H NMR spectrum which contains a multiplet at 1.7 ppm (CH_2C), a multiplet at 3.7 ppm (CH_2O) 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 $Na[BH_2(OAc)_2]$ (depenting on the initial reagent ratio) is assigned are well known and are used as reducing reagents in organic synthesis [14].

$$NaBH_4 + (HOOCC^*HOH)_2 \longrightarrow \{Na[B(OOCC^*HOH)_2]\} \cdot 0.5OC_4H_8.$$

Reduction of ketophosphonates with that reagent was performed at cooling to –30°C in THF (method *a*). Reduction of diethyl α-ketophosphonates with the sodium borohydride–(*R*,*R*)-tartaric acid chiral reagent yielded diethyl (1*S*)-α-hydroxybenzylphosphonates with optical purity ~60%, while reduction of dimethyl ketophosphonates led to formation of (1*S*)-α-hydroxybenzylphosphonates **I** with diastereomeric purity up to 80–93%. The higher stereoselectivity of reduction in the case of dimenthyl arylketophosphonates we explain by the effect of dual asymmetric induction [15], because here the asymmetric inductions due to menthyl groups supplementes that of tartaric acid. At the same time, reduction of dimenthyl ketophosphonates with the sodium borohydride–(*S*,*S*)-tartaric acid reagent resulted in lower stereoselectivity. For example, reduction of dimenthyl 1-oxobenzylphosphonate yielded corresponding hydroxyphosphonate with 45% *de* only. It is obviously that asymmetric inductions due to (1*R*,2*S*,5*R*)-menthyl groups and (*R*,*R*)-tartaric acids are compatible and therefore are



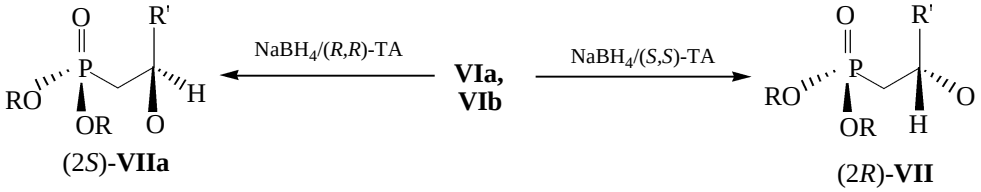
Here and hereinafter: TA is tartaric acid.

Table 1. Stereoselectivity of reduction of ketophosphonates **Ia** and **Ib**

R	Tartaric acid configuration	*ee*	Compound **II** configuration	Type of stereoselectivity
Et	*R*,*R*	63	*S*	Singular
Et	*S*,*S*	62	*R*	"
Mnt	*R*,*R*	92.5	*S*	Dual, compliant
Mnt	*S*,*S*	46	*R*	Dual, opposite

summated and increase the total stereoselectivity. On the other hand, asymmetric inductions of (1*R*,2*S*,5*R*)-menthyl groups and (*S*,*S*)-tartaric acid act in opposite directions and diminish resulting stereoselectivity (Table 1).

Stereochemistry of reduction of α- and β-ketophosphonates with sodium borohydrid–tartaric acid reagent depends on the absolute configuration of tartaric acid. With the reagent prepared from (*R*)-tartaric acid the reaction results in formation of (*S*-α-hydroxyphosphonates, while the reagent from (*S*)-tartaric acid gives (*R*)-α-hydroxyphosphonates. Reduction of α-ketophosphonates **VI** with the sodium borohydride–(*R*)-tartaric acid reagent also led to α-hydroxyphosphonates (*S*)-**VII**, while with the sodium borohydride–(*S*)-tartaric acid reagent to α-hydroxyphosphonates (*R*)-**VII**.



Insofar as reduction of ketophosphonates with the complex $NaBH_4$/(*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 Fig. 1, and promotes stereofacial attack of carbonyl group by hydride ion from the *Si* side.

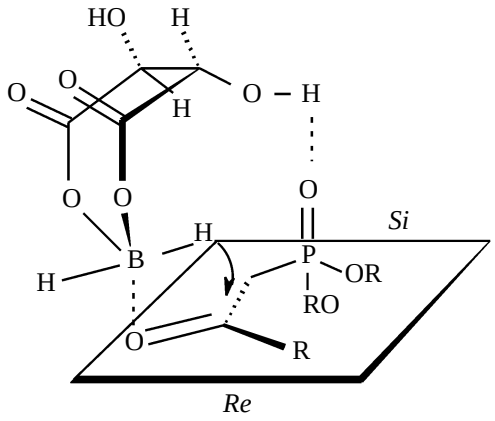


Fig. 1. MOPAC-8 stereochemical modeling of reduction of ketophosphonate with $NaBH_4$/(*R*,*R*)-tartaric acid reagent.

High stereoselectivity was revealed also by the sodium borohydride complex with (*L*)-proline (method *b*). For its preparation, to sodium borohydride suspended in THF was added equimolar amount of (*L*)-proline and the mixture was stirred at room temperature for several hours. Then to the such generated chiral complex a ketophosphonate was added, and this resulted in formation of an (*S*)-hydroxyphosphonate. Compounds **IIa**, **IIb**, and also **VIIb** were isolated with stereoselectivity 60–70%.

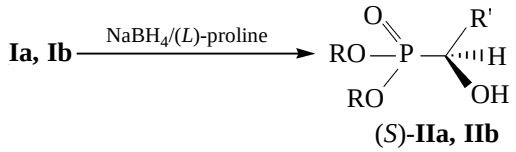


Table 2. Asymmetric reduction of ketophosphonates by sodium borohydride–tartaric acids complex to hydroxyphosphonates

Comp. no.	*n*	Yield, %	Tartaric acid configuration	$[\alpha]_D^{20}$, deg	*c*	Configuration [a]	*ee* (*R*:*S*)
IIa	0	95	*R*,*R*	–15.4	2.6	*S*	2:8 [b]
IIa	0	94	*S*,*S*	+28.3	2.1	*R*	8:2 [c]
IIb	0	95	*R*,*R*	–87.6	1.3	*S*	3.8:96.2
IIb	0	98	*S*,*S*	–70.0	1.0	*R*	73:27
IIc	0	97	*R*,*R*	–83.7	1.3	*S*	9.8:90.1
IId	0	96	*R*,*R*	–75.2	1.0	*S*	13:87
IIe	0	97	*R*,*R*	–74.0	1.0	*S*	98:2
IIf	0	97.6	*R*,*R*	–82.8	2.2	*S*	84:16
VIIa	1	95	*R*,*R*	–25.0	2.4	*R*	28:72 [c]
VIIb	1	82	*R*,*R*	–12.4	3.2	*S*	9:1 [c]

[a] Configuration of the predominating enantiomer was found from comparison of the measured values with published data. [b] Determined by means of ^{31}P NMR spectra after derivatization with dimenthyl chlorophosphite. [c] Determined by means of ^{31}P NMR spectra with quinine as chiral solvating reagent.

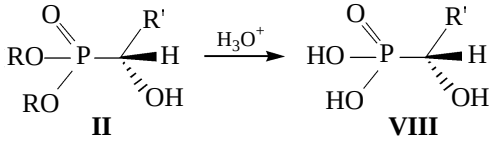
Diethyl α-hydroxyphosphonates were purified by column chromatography. Dimenthyl α-hydroxyphosphonates were obtained enantiomericaly pure after crystallization from acetonitrile (Table 2).

Several methods were used for elucidation optical purity of the synthesized compounds. The diastereoisomeric ratio of hydroxyphosphonate dimenthyl esters was registered by ^{31}P–{^{1}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 (**I**) 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 [12].

$$(MntO)_2PCl + \mathbf{II} \xrightarrow{Et_3N} (MntO)_2P{-}O{-}CH(R)P(O)(OEt)_2$$

For determination of optical purity of diethyl hydroxyphosphonates we found convenient to use natural quinine as a chiral solvating reagent. In this case the signals of the hydroxyphosphonate (*R*)- and (*S*)-enantiomers in ^{31}P–{^{1}H} NMR spectra were separated up to zero line and could be easily measured by integration.

The absolute configuration of dimenthyl hydroxyphosphonates was determined by the method of chemical extrapolation. The dimenthyl esters were hydrolysed to free hydroxyphosphonic acids whose configuration was determined earlier [16–23].

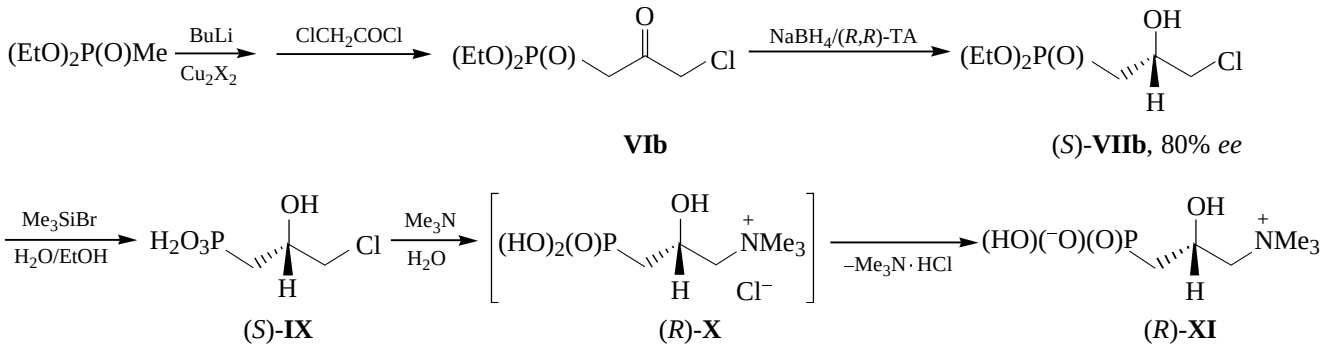


II **VIII**

The developed procedure for reduction of the ketophosphonates we applied to the synthesis of phosphocarnitine **XI**.

(*R*)-Carnitine possess important biological properties and is used in pharmacology as an important component for β-oxidation of fatty acids: it performs transport of the fatty acids in mytohondrial membrane. A great attention was paid to the modificated carnitines, in part, the phosphocarnitine, synthesized earlier by means of chemoenzymatic methods. Unfortunately, information on the properties of the prepared representatives of the phosphocarnitine are contradictory and inconsistent with one another. Mikolajczyk and coworkers described (*S*)-phosphocarnitine as an oil with optical rotation angle $[\alpha]_D^{20}$ –24° (*c* 2.3, MeOH–H_2O) [18]. Wroblewski described the same compound as a solid fine crystalline substance, mp 270°C and $[\alpha]_D^{20}$ –17.4° (*c* 1.15, H_2O) [21], and Yuan and Wang as a substance with $[\alpha]_D^{20}$ –15° (*c* 2.1, H_2O) [25]. This discrepancy arises probably due to small amounts (milligrams) of the phosphocarnitine synthesized. Therefore we performed first synthesis of (*R*)-phosphocarnitine by ordinary chemical procedure through asymmetric reduction of corresponding diethyl 2-ketophosphonate [17].

We also developed a multigram procedure for the synthesis (*R*)-phosphocarnitine by means of enantioselective hydroborination of diethyl 2-keto-3-chloropropylphosphonate **VI**.



X = Br, I.

In the first step, diethyl 3-chloro-2-oxopropylphosphonate (**VIb**) was prepared from available diethyl methylphosphonate. Then by enantioselective reduction of β-ketophosphonate **VI** we prepared optically active diethyl 3-chloro-2-hydroxypropylphosphonate (**VI**), the precursor of phosphocarnitine (**XI**). Enantiomeric purity of compound **VIIb**, 80% *ee*, was measured by means of ^{31}P NMR spectroscopy with dimenthyl chlorophosphite as a derivatizating reagent and quinine as a chiral solvating reagent. The ^{31}P NMR spectrum of **VIIb** with quinine contains two signals, δ_P 29.4 and 29.11 ppm, in the ratio 90 : 10 (reduction by the method *a*) or 19.7 : 80.3 (method *b*) The values of optical purity in parallel measurements coincided. Then **VIIb** was dealkylated with trimethylbromosilane followed by treating by aqueous alcohol to free phosphonic acid **IX** and then treated by water solution of trimethylamine. The chloride **VII** thus was converted into trimethylammonium salt **X** which in the reaction course was dehydrochlorinated to form trimethylammonium chloride and phosphocarnitine as betain **XI**. The product was isolated from the reaction mixture by column chromatography on silica gel. Pure (*R*)-phosphocarnitine was obtained in high yield with good optical purity. Structure of compound **XI** was confirmed by elemental analysis and NMR spectroscopy. The (*R*)-phosphocarnitine (**XI**) synthesized by us is a crystalline compound decomposed at heating above 250°C.

The ^{1}H NMR spectra of β-hydroxyphosphonates are of special interest. They disclose signals of diastereotopic protons in PCH_2 and CH_2X groups as doublet doublets due to spin-spin coupling with phosphorus atom, proton of CHOH group (vicinal constan $^3J_{HH}$), and due to mutual coupling $^2J_{HH}$. The NMR spectra allows to perform conformational analysis of the obtained compounds. Phosphocarnitine and 2-hydroxy-3-chloropropylphosphonate probably exist mainly as *trans* conformers at the C^1–C^2 bond (Fig. 2a), as follows from the values of vicinal constants $^3J_{HP}$ ~18 Hz and geminal constants $^3J_{H^{1a}H^2}$ and $^3J_{H^{1b}H^2}$ 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 (Fig. 3). In the phosphocarnitine molecule

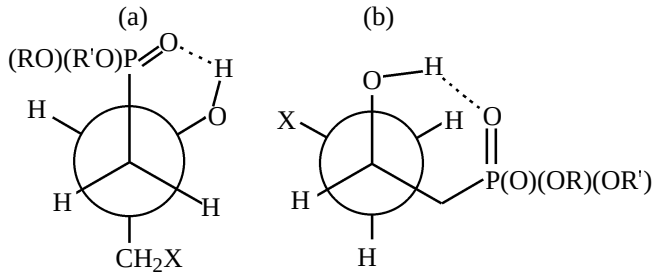


Fig. 2. Conformational analysis of β-hydroxyphosphonates: (a) Newman projection at C^α–C^β bond, (b) Newman projection at C^β–C^γ bond. X= Cl, Me_3N^+.

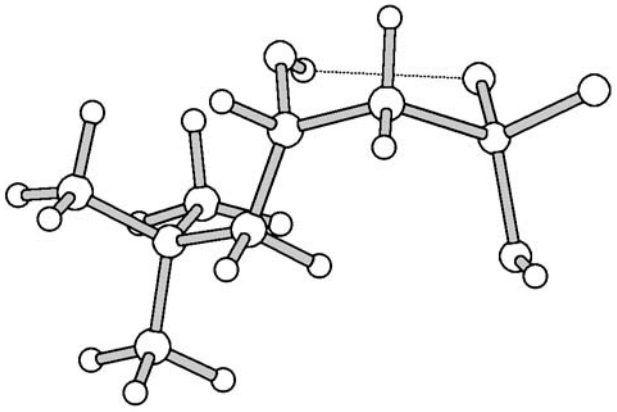


Fig. 3. MM^+ conformation with the energy minimum of phosphocarnitine.

Table 3. Conformations of β-hydroxyphosphonates **VII, XI**

Comp. no.	Experimentf (by NMR spectra)				Calculation (MM^+)	
	$^3J_{HH}$, Hz	$HC^1–C^2H$ angle	$^3J_{HH}$, Hz	$HC^2–C^3H$ angle	$HC^1–C^2H$ angle	$HC^2–C^3H$ angle
VII	3.6	47.50	6.9	28.38	69.69	–54.39
	9	171.25	6.3	146.33	176.21	78.56
XI	6.6	25.88	1.2	65.34	72.59	–50.81
	6.9	150.38	9.5	~180	–176.08	176.08

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.

The bond $C^2–C^3$ in phosphocarnitine and 2-hydroxy-3-chloropropylphosphonate molecules, is probably in *staggered cisoid* conformation as follows from small values of vicinal constants: $J_{H^{2a}H^3}$ 6.9 Hz and $J_{H^{2b}H^3}$ 6.3 Hz

Modeling the molecule by MM^+ calculation allow to reveal values of dihedral angles in energetically most preferable conformations of the molecules of hydroxyphosphonates **VIIb** and **XI** (Fig. 3) [26]. The theoretically calculated values well correspond to the experimental values of the dihedral angles obtained from the data of NMR spectra by calculation with the Karplus equation [27], confirming our conclusions (Table 3).

EXPERIMENTAL

Melting points are not corrected. NMR spectra were registered on a Varian VXR-300 instrument at 300 (^1H) and 126.16 (^{31}P) MHz with internal TMS (^1H) and external 85% H_3PO_4 in D_2O (^{31}P). Optical rotation angles were measured on a Polax-2L polarimeter (Japan).

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 P_4O_{10}. The Fluka tartaric acids, sodium borohydride and menthol were used. Tartaric acids and sodium borohydride priory to use were kept for 2 h in a vacuum at 30°C.

Di(1*R*,2*S*,5*R*)-(–)-menthyl benzoylphosphonate (Ib). To pyridinium bichromate (1.68 g, 4.47 mmol) in 30 ml of methylene chloride with stirring was added trimethylchlorosilane (0.6 g, 5.5 mmol) at 0°C, and then racemic dimenthyl α-hydroxyphosphonate prepared from 1.75 mol of dimenthyl phosphite and 1.75 mol of benzaldehyde. The reaction mixture was stirred at room temperature to the reaction completing (2–4 h), filtered through silica gel and washed with small amount of ethyl acetate. After evaporation a colorless liquid obtained was purified by column chromatography. Yield 95%, R_f 0.3 (hexane–ethyl acetate, 4:1). $[\alpha]_D^{20}$ –62° (*c* 1.5, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.7–1.0 m (CH_3); 1.1–2.2 m (CH_2 + CH); 4.15 d.t (OCH, J_{HH} 2.3, J_{HH} 4.1); 7.35 m (C_6H_5); ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: –2.3. Found, %: P 6.61. $C_{27}H_{43}O_4P$. Calculated, %: P 6.70.

Di(1*R*,2*S*,5*R*)-(–)-menthyl 2-fluorobenzoyl phosphonate (Ic). Prepared similarly to compound **Ia**. R_f 0.74 (hexane : ethyl acetate = 5 : 1). Yield 90%. $[\alpha]_D^{20}$ –72° (*c* 1, toluene). ^1H NMR spectrum NMR ($CDCl_3$), δ, ppm, (*J*, Hz): 0.6–0.9 m (CH_3); 0.8–2.0 m (CH_2 + CH); 4.0 d.t. (OCH, J_{HH} 2.3, J_{HH} 4.1); 7.4 m (C_6H_4). ^{31}P NMR spectrum ($CDCl_3$): δ_P, ppm: –3.1. Found, %: P 6.44 $C_{27}H_{42}FO_4P$. Calculated, %: P 6.38.

Di(1*R*,2*S*,5*R*)-(–)-menthyl 2-methoxybenzoyl phosphonate (Id). Prepared similarly to compound **Ib**. Yield 96%, The product was purified by column chromatography. R_f 0.33 (hexane–ethyl acetate, 4:1). ^1H NMR spectrum NMR ($CDCl_3$), δ, ppm (*J*, Hz): 0.7–1.0 m (CH_3); 1.1–2.2 m (CH_2 + CH); 3.9 s (OCH_3); 4.15 d.t (OCH, J_{HH} 2.3, J_{HH} 4.1); 6.6–6.8 m (C_6H_4); 7.0–7.2 m (C_6H_4). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: –3.5. Found, %: P 6.25. $C_{28}H_{45}O_5P$. Calculated, %: P 6.39.

Di(1*R*,2*S*,5*R*)-(–)-menthyl piperonoylphosphonate (Ie). Prepared similarly to compound **Ib**. Yield 82%, R_f 0.51 (eluent hexane–ethyl acetate, 4:1). $[\alpha]_D^{20}$ –63.8° (*c* 5.48, $CHCl_3$). ^1H NMR spectrum (CDCl3), δ, ppm, (*J*, Hz): 0.7–1.0 m (CH_3); 1.1–2.2 m (CH_2 + CH); 4.15 d.t (2H, J_{HH} 2.3, J_{HH} 4.1, OCH); 5.8 s (2H, OCH_2O); 6.75 d (1H, *J* 10); 7.23 s (1H); 7.66 s (1H); 8.25 d (1H, C_6H_4, *J* 10). ^{31}P NMR

spectrum ($CDCl_3$), δ_P, ppm: –1.8. Found, %: P 6.14. $C_{28}H_{45}O_6P$. Calculated, %: P 6.09.

Di(1*R*,2*S*,5*R*)-(–)-menthyl 2-methylpropionylphosphonate (If). Prepared similarly to compound **Ia**. Yield 86%, R_f 0.73 (eluent hexane–ethyl acetate, 10:1). $[\alpha]_D^{20}$ –90.4° (*c* 0.75, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.7–1.0 m (CH_3); 1.1–2.2 m (CH_2 + CH); 3.15 m (1H, $CHCH_3$); 4.2 d.t (OCH, J_{HH} 2.3, J_{HH} 4.1). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm): –3.4. Found, %: P 7.04. $C_{25}H_{47}O_4P$. Calculated, %: P 7.00.

Diethyl (*S*)-hydroxy(phenyl)methylphosphonate (IIa). To sodium borohydride (7.16 mmol) in 25 ml of THF *L*-(+)-tartaric acid (7.16 mmol) was added and the reaction mixture was refluxed for 4 h. The mixture was cooled to –30°C, ketophosphonate (1.79 mol) in 8 ml THF was added to it while stirring and the mixture was left overnight for 24 h at –30°C. Then 15 ml of ethyl acetate was added and 25 ml of 1 N hydrochloric acid was added dropwise. Organic layer vas separated and aqueous layer was extracted twice with ethyl acetate. Combined organic extracts were washed with saturated solution of sodium carbonate and dried over Na2SO4. Solvent was removed in a vacuum and residue was recrystallized from acetonitrile. Yield 95%, mp 74–76°C, $[\alpha]_D^{20}$ –15.4° (*c* 2.6, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.21 t (3H, CH_3, J_{HH} 7.1); 1.26 t (3H, CH_3, J_{HH} 7.1); 3.8 br (1H, OH); 3.90–4.13 m (4H, $2CH_2$); 5.01 d (1H, CH, J_{PH} 10.9); 7.3–7.38 m (3H, ArH); 7.49 d (2H, ArH). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 22.00 (correspondence with [19, 20]).

Diethyl (*R*)-hydroxy(phenyl)methylphosphonate (IIa). Prepared similarly from sodium borohydride, (*S*,*S*-(–)-tartaric acid and ketophosphonate *Ia* in THF. Yield 94%, mp 74–76°C, $[\alpha]_D^{20}$ +28.32° (*c* 2.1, $CHCl_3$), corresponding to the data for the compound described earlier [22].

Di[(1*R*,2*S*,5*R*)-(–)-Menthyl] (*S*)-1-phenyl-1-hydroxymethylphosphonate (IIb). *a*. To sodium borohydride (4 mmol) in 15 ml of THF *L*-(+)-tartaric acid (4 mmol) was added and the reaction mixture was refluxed for 4 h. The mixture was cooled to –30°C, ketophosphonate (0.99 mol) in 5 ml of THF was added and the mixture was left for 24 h at –30°C. Then to the mixture 8 ml of ethyl acetate was added and 20 ml of 1 N hydrochloric acid was added dropwise. Organic layer was separated and aqueous layer was extracted with ethyl acetate. Solvent was removed in a vacuum and residue was recrystallized from acetonitrile, mp 112–113. Yield 80%.

b. 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 6–12 h. Then to the mixture ketophosphonate (0.368 g, 0.795 mmol) was added and stir was continued for 24 h. Then solvent was evaporated and 10 ml of water–ethyl acetate (1:1) mixture was added to the residue. Organic layer was separated and aqueous layer was extracted with ethyl acetate. The extract was washed with 1 N HCl, then with sodium carbonate solution, again with water, and died over anhydrous sodium sulfate. Solvent was evaporated. Yield 0.367 g (70%), mp 112–113, $[\alpha]_D^{20}$ –87.6° (*c* 1.3, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.01 d (3H, CH_3, J_{HH} 6.9); 1.04 d (3H, CH_3, J_{HH} 6.9); 1.08 d (3H, CH_3, J_{HH} 6.9); 1.18 d (3H, CH_3, J_{HH} 6.9); 1.20 d (3H, CH_3, J_{HH} 6.9); 1.21 d (3H, CH_3, J_{HH} 6.9); 1.40–2.6 m (14H, C*H*$_3$ and CH); 2.00 m [1H, $CH(CH_3)_2$]; 2.4 m [1H, $CH(CH_3)_2$]; 4.49 m (2H, OCH); 5.2 d (1H, CHP, J_{HH} 10.5); 5.10 br (1H, OH); 7.48 m (3H, Ar*H*); 7.8 m (2H, Ar*H*). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 22.3. Found, %: P 6.38. $C_{27}H_{45}O_4P$. Calculated, %: P 6.67.

Di[(1*R*,2*S*,5*R*)-(–)-menth-2-yl] (*S*)-hydroxy-(2-fluorophenyl)methylphosphonate (IIc). Prepared similarly to compound **IIa**. Yield 97%, mp 137.5–138.5°C, $[\alpha]_D^{20}$ –83.7° (*c* 1.3, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm(*J*, Hz): 0.71 d (3H, CH_3, J_{HH} 6.9); 0.76 d (6H, CH_3, J_{HH} 6.9); 0.86 d (6H, CH_3, J_{HH} 6.9); 0.91 d (3H, CH_3, J_{HH} 6.9); 1.00–2.25 m (14H, C*H*$_3$ and CH); 1.74 m [1H, $CH(CH_3)_2$]; 2.0 m [1H, $CH(CH_3)_2$]; 4.04 d (1H, C*H*P, J_{HH} 22.5); 4.2 m (2H, OCH); 5.18 br (1H, OH); 6.9 t (3H, J_{HH} 8.2, Ar*H*); 7.45 m (2H, Ar*H*). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 19.8. Found, %: P 6.38. $C_{27}H_{44}FO_4$ P. Calculated, %: P 6.42.

Di[(1*R*,2*S*,5*R*)-(–)-menth-2-yl] (*S*)-hydroxy-(2-methoxyphenyl)methylphosphonate (IId). Prepared similarly to compound **IIa**. Yield 74%, mp 116–117°C, $[\alpha]_D^{20}$ –75.2° (*c* 0.66, $CHCl_3$). ^1H NMR spectrum (C_6D_6), δ, ppm: (*J*, Hz): 0.60 d (3H, CH_3, J_{HH} 6.9); 0.52 d (3H, CH_3, J_{HH} 6.9); 0.73 d (3H, CH_3, J_{HH} 6.9); 0.79 m (6H, $2CH_3$); 0.84 d (3H, CH_3, J_{HH} 6.9); 0.92–1.54 m (14H, CH_2 and CH); 2.14 m (1H, C*H*·$(CH_3)_2$); 2.40 m (1H, $CH(CH_3)_2$); 3.59 (3H, OCH_3); 4.17 m (1H, OCH); 4.03 m (1H, OCH); 4.54 br (1H, OH); 5.24 d (1H, C*H*P, J_{HH} 13.2); 6.59 d (1H, ArH, J_{HH} 8.1); 6.80 t (1H, Ar*H*, J_{HH} 7.9); 7.04 t (1H, Ar*H*, J_{HH} 7.9); 7.60 d (1H, Ar*H*, J_{HH} 7.5). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 20.98. Found, %: P 6.27. $C_{28}H_{47}O_5P$. Calculated, %: P 6.26.

(–)-[(1*R*,2*S*,5*R*)-Menth-2-yl]-(*R*)-hydroxy (2-methoxyphenyl)methylphosphonate (*R*)-(IId). Prepared similarly to compound *R*-**IIa**. The product

was purified by recrystallization from hexane or acetonitrile. Yield 50%, mp 138°C, $[\alpha]_D^{20}$ –56.4° (*c* 1, toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.7–1.0 m (CH_3); 1.1–1.23 m (CH_2 + CH); 3.4 br (OH); 3.55 s (OCH_3); 4.0 d.t (OCH, J_{HH} 2.3, J_{HH} 4.1); 5.17 d (CHP, J_{HP} 11); 6.6–6.8 m (C_6H_4); 7.0–7.2 m (C_6H_4). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 21.49. Found, %: P 6.27. $C_{28}H_{47}O_5P$. Calculated, %: P 6.26.

Di[(1*R*,2*S*,5*R*)-(–)-menth-2-yl] (*S*)-hydroxy-(piperonyl)methylphosphonate (IIe). Prepared similarly to compound **IIa**. Yield 70%, mp 96°C, $[\alpha]_D^{20}$ –74° (*c* 1, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.09 m (2H, OCH), 4.7 d (1H, CHP, J_{HH} 10.5); 5.38 ¼ (1H, OH); 5.65 s (2H, CH_2O_2); 6.57 d (1H, Ar*H*, J_{HH} 7.9); 6.85 d (1H, Ar*H*, J_{HH} 7.9); 6.98 s (1 H, Ar*H*). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 19.8. Found, %: P 6.26 $C_{30}H_{49}O_6P$; Calculated, %: P: 5.77.

Di[(1*R*,2*S*,5*R*)-(–)-menth-2-yl] (*S*)-hydroxy(isopropyl)methylphosphonate (IIf). Prepared similarly to compound **IIa** and purified by crystallization from acetonitrile. Yield 97.6%, mp 71°C, $[\alpha]_D^{20}$ –82.8° (*c* 2.2, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.31 br (1H, OH); 4 t (0.3H, CHP, J_{HH} 5.7); 3.43 t (0.7H, CHP, J_{HH} 5.7); 4.09 m (2H, OCH); ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 24.04; 24.27. Found, %: P 7.18. $C_{24}H_{47}O_4P$. Calculated, %: P 7.19.

(–)-(*S*)-Phenyl(hydroxymethyl)phosphonic acid (VIII). *a*. To a solution of hydroxymethylphosphonate **II** (1 g) in 50 ml of dioxane was added 25 ml of 6 N hydrochloric acid was added. The reaction mixture was left for 3 days at 80°C. The process of hydrolysis was monitored by ^{31}P NMR spectroscopy. After completing the solvent was evaporated, the residue was dissolved in ethanol and cyclohexylamine excess (~1.5 ml) was added. The dicyclohexylammonium salt precipitate was filtered off.

b. Sodium iodide (1 equiv.), trimethylchlorosilane (1 equiv.) and a solution of α-hydroxyphosphonate **IIa**–**IIc** (1 equiv.) in acetonitrile (10 ml) were mixed. The reaction mixture was refluxed for 12 h. The precipitate formed was filtered off, solvent was evaporated in a vacuum and a mixture of methylene chloride (3 ml) and water (2.5 ml) was added. The mixture was stirred at room temperature for 2 h and then volatile products were removed in a vacuum. The residual hydroxyphosphonic acid was dissolved in ethanol and cyclohexylamine excess was added. Dropped solid was filtered off and recrystallized. The compound obtained is (–)-(*S*)-**VIIIb**: yield 50%, mp 226°C, $[\alpha]_D^{20}$ +14.0 (*c* 1, MeOH–water 1 : 1) which corresponds to (*S*)-configuration of the acid **VIII**. The (–)-(*S*)-hydroxy(phenyl)methylphosphonic acid dicyclohexylammonium salt has been described [16].

Diethyl (*S*)-2-hydroxy-2-phenylethylphosphonate (VIIa). Yield 95%, $[\alpha]_D^{20}$ –25° (*c* 2.38, $CHCl_3$). ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 1.10 t (3H, CH_3, J_{HH} 6.9); 1.11 t (3H, CH_3, J_{HH} 6.9); 1.90–2.12 m (2H, CH_2); 3.77–3.99 m (4H, $2CH_2$); 4.75 br (1H, OH); 4.96–5.06 m (1H, C*H*OH); 7.05 t (1H, Ar*H*, J_{HH} 7.2); 7.14 t (2H, Ar*H*, J_{HH} 7.2); 7.28 d (2H, Ar*H*, J_{HH} 7.2). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 29.6, which corresponds to the earlier described compound [22, 23].

Diethyl 2-oxo-3-chloropropylphosphonate (VIb). To a solution of butyllithium (1.7 N, 0.077 mol) at stirring and cooling to –78°C was added consecutively 50 ml of THF and a solution of 0.07 mol of diethyl methylphosphonate in 25 ml of THF. After 20 min stirring 0.077 mol of Cu_2Br_2 was added to the mixture and stir was continued for 1.5 h at –60 to –40°C. Then 0.073 mol of chloroacetyl chloride in 30 ml of ether was added, stir was continued for 1.5 h at –40 to –30°C and the mixture was left overnight at the same temperature. Then 65 ml of water was added, precipitate was separated and aqueous layer was twice extracted with chloroform 40 ml portions. The extract was washed with solution of sodium carbonate and dried over Na_2SO_4. Solvent was evaporated and residue was distilled in a vacuum. Yield 60%, colorless oil, bp 97—99°C (0.04 mm Hg). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 18.8, which corresponds to the compound described earlier [20].

Diethyl (*S*)-(–)-2-hydroxy-3-chloropropylphosphonate (VIIb). *a*. To 0.463 g of sodium borohydride in 30 ml of THF with stirring was added 1.839 g of (*R*,*R*-(+)-tartaric acids. The mixture was refluxed for 4 h. Then at –30°C to the mixture was added a solution of 0.7 g of diethyl 2-oxo-3-chloropropylphosphonate in 7 ml of THF and after stirring for 24 h 18 ml of ethyl acetate and 20 ml of 1 N HCl was added. Organic layer was separated and aqueous layer was extracted with ethyl acetate (3 portions 10 ml). Combined extracts were dried over anhydrous sodium sulfate. After evaporation 0.65 g (92%) of colorless oil was obtained.

b. To sodium borohydride (1.19 mmol) suspended in 8 ml of THF (*L*)-proline (1.19 mmol) was added. The mixture was stirred at room temperature for 12 h and then ketophosphonate (0.795 mmol) was added with stirring. Stir was continued for 24 h, solvent was evaporated and 10 ml of water–ethyl acetate mixture (1 : 1) was added to the residue. Organic layer was separated and water layer was extracted with ethyl acetate. The extract was washed with 1 N HCl, then

with solution of sodium carbonate and again with water. After evaporation colorless oil was obtained, yield 85%, $[\alpha]_D^{20}$ –12.42° (*c* 3.22, $CHCl_3$). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.35 t (6H, $^3J_{HH}$ 7.2, CH_3CH_2); 1.9 d.d.d (1H, 2JHP 18.6, $^3J_{HH}$ 3.6, $^2J_{HH}$ 15.3, PC^aH); 2.12, d.d.d (1H, $^2J_{HP}$ 17.4, $^3J_{HH}$ 9, $^2J_{HH}$ 15.3, PC^bH); 3.35, d.d (1H, $^3J_{HP}$ 11.2, $^2J_{HH}$ 6.9, $^4J_{HH}$ 1, C^aHCl); 3.53, d.d.d (1H, $^3J_{HP}$ 10, $^2J_{HH}$ 6.3, $^4J_{HH}$ 3.3, C^bHCl); 4.05, m (5H, CH_2O + *CH*OH); 4.7 m (1H, OH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 29.4. Found, %: P 13.50. $C_7H_{16}ClO_4P$. Clculated, %: P 13.43.

(*S*)-2-Hydroxy-3-chloropropylphosphonic acid (IX). A solution of 0.433 g (1.87 mmol) of hydroxyphosphonate **VIIb** in methylene chloride was treated by 2 ml of trimethylbromosilane and left overnight. The mixture was then evaporated and 4.5 ml of 60% aqueous ethanol was added to the residue. Yield ~98%, oil. The product was spectroscopically pure and therefore was used for further reaction without additional purification. ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.6–1.9 m (2H, PCH_2); 3.2–3.4 m (2H, CH_2Cl); 4.8 m (1H, CHO); 4.9 br (OH). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 25.5.

(*R*)-(+)-2-Hydroxy-3-(*N*,*N*,*N*-trimethylammonium)propylphosphonic acids [(*R*)-(+)-Phosphocarnitine] (XI). To the acid *S*-**IX** (1.88 mmol) 16 ml of 29% aqueous trimethylamine was added and the mixture was left for 48 h at 400C. After evaporation an oil was obtainet in residue which was purified by column chromatography with silica gel, eluent methanol–water. Colorless crystalline compound was obtained. Yield 80%, mp above 2500C (decomp.), $[\alpha]_D^{20}$ +17.85° (*c* 1.26, H_2O). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.80 d.d.d (1H, $^3J_{HH}$ 6.6, $^2J_{HH}$ 14.7, $^2J_{HP}$ 18, PC^aH); 1.89 d.d.d (1H, $^3J_{HH}$ 6.9, $^2J_{HH}$ 14.8, $^2J_{HP}$ 17.7, PC^bH); 3.2 s (9H, CH_3N); 3.4 d.d ($^2J_{HH}$ 13.8, $^3J_{HH}$ 9.8, CH^aN); 3.6 d.d ($^2J_{HH}$ 13.8, $^3J_{HH}$ 1.2, CH^bN); 4.5 m (1H, CHOH); 4.9–5.0 br (1H, OH). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 18.7. Found, %: P 15.62. $C_5H_{16}NO_4P$. C^alculated, %: P 15.63.

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