ISSN 1070-3632, Russian Journal of General Chemistry, 2008, Vol. 78, No. 11, pp. 2043–2051. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.O. Kolodyazhnaya, V.P. Kukhar, O.I. Kolodyazhnyi, 2008, published in Zhurnal Obshchei Khimii, 2008, Vol. 78, No. 11, pp. 1808–1817.

Organic Catalysis of Phospha-Aldol Condensation

A. O. Kolodyazhnaya, V. P. Kukhar, and O. I. Kolodyazhnyi

Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev, 02094 Ukraine
e-mail:oikol123@rambler.ru

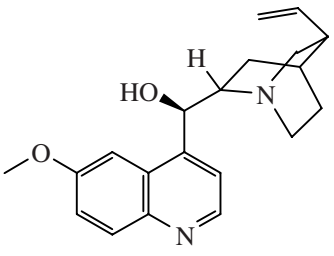
Received February 18, 2008

Abstract—Phospha-aldol reaction of dialkylphosphites with carbonyl compounds is catalyzed by cinchonine alkaloids and thier modified derivatives to give optically active hydroxyphosphonates. The use of diastereomeric pairs of alkaloids allowed obtaining both optical antipodes of hydroxyphosphonates. Cinchonine alkaloids show the highest enantioselectivity as organic catalysts. It was found that ordinary crystallization of some enantiomerically enriched hydroxyphosphonates leads to isolation of the enantiomerically pure stereoisomers. Hydroxyphosphonic acids were obtained by hydrolysis of phosphonates. Fluoroalkylphosphonates were obtained by reaction with diethylaminotrifluorosulfurane (DAST).

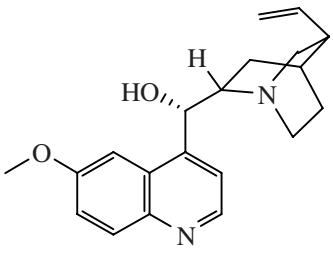
DOI: 10.1134/S1070363208110091

In the recent years the asymmetric catalysis of organic reactions with chiral natural compounds free of metal atoms, known as organic catalysts, was rapidly developing [1–3]. Organic catalysts like metal complex catalysts are low molecular weight compounds. At the same time they resemble enzymes being substances modeling action of the latter. Asymmetric organic catalysis offers doubtless advantages over the metal complex catalysis since organic catalysts are generally stable in the presence of the air oxygen and moisture in contrast to metal complexes. They are also cheaper and more available. Alkaloids [3], amino acids [5], and other natural compounds [4–10] are used as asymmetric organic catalysts. The most effective organic catalysts were obtained on the base of quinine [10] and L-proline derivatives [4, 8] that were successfully used as catalysts of aldol reaction [6, 8], Michael [7] and Henry [9] reactions, etc.

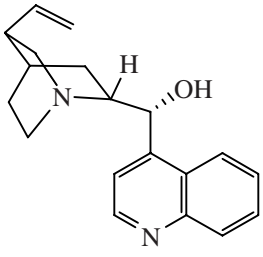
In this work we investigated catalytic action of some cinchonine alkaloids and also already reported by us [11] application of L-proline derivatives in the phospha-aldol reaction (Abramov reaction).



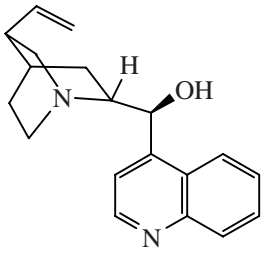
QN



QND



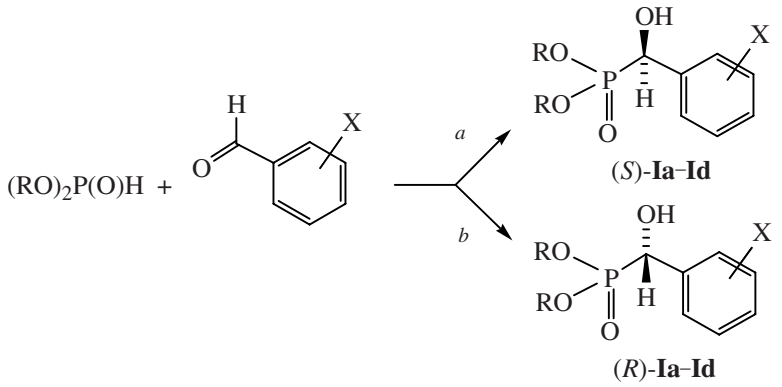
CN



CND

Cinchonine alkaloids such as quinine (QN), quinidine (QND), cinchonine (CN) and cinchonidine (CND) catalyze addition reaction of dialkylphosphites with aromatic aldehydes. This reaction was carried out in toluene or in the absence of solvent, in the presence of 20 mol% of alkaloid. The reaction progress was monitored by TLC and ^{31}P NMR spectroscopy. The ratio of diastereomers was determined using ^{31}P NMR by measuring the integral intensity of the signals of different diastereomers. Reaction proceeds slowly, however with high yields of chiral hydroxyphosphonates, (*S*)- or (*R*)-(**I**). It is best to use the

concentrated (~30–50%) solutions of initial substances in toluene since in the more dilute solutions reaction proceeds very slowly or does not proceeds at all. From 1 to 3 days are needed for the reaction completing at 20°C.



R = (1*R*,2*S*,5*R*)-Mwnthyl-(1*R*,2*S*,5*R*)-Mnt; X = 2-NO_2 (**a**); R = (1*R*,2*S*,5*R*)-Mnt; X = 2-MeO (**b**); R = Me, X = 2-MeO (**c**), R = Me, X = 2-NO_2 (**d**); *a* = QN, CN, *b* = QND, CND.

Asymmetric induction in the reaction of chiral dimenthylphosphite with achiral aldehydes was much higher at the catalysis with such chiral bases as quinine, quinidine, cinchonine and cinchonidine, in comparison with the reaction catalyzed by achiral amines (triethylamine or DBU). Thus, the reaction of dimenthylphosphite with 2-nitrobenzaldehyde in the presence of cinchonidine gives rise to hydroxylphosphonate (*R*)-**Ia** with diastereomeric enrichment of 75%, whereas in the case of catalysis with DBU the same hydroxyphosphonate was obtained only with 40% *de*. Unlike reaction catalyzed with quinine, reaction of dimenthylphosphate with 2-nitrobenzaldehyde in the presence of DBU proceeded fast and with self-heating, therefore the reaction mixture should be cooled. Stereoselectivity of reaction catalyzed with quinine and cinchonine was significantly higher than in the case of reaction catalyzed with quinidine and cinchonidine. This fact is due to the the effect of double concerted versus non-concerted asymmetric induction [12]. Stereochemical direction of reaction changed depending on the nature and stereoselectivity of the chiral catalyst. For example, according to the NMR data reaction of dimenthylphosphite with 2-nitrobenzaldehyde or 2-anisaldehyde in the presence of quinine yielded predominantly (*S*)-hydroxyphosphonate, while in the presence of quinidine (*R*)-hydroxyphosphonate formed. Analogously, reaction with cinchonine produced (*S*)-hydroxyphosphonate, and with cinchonidine, (*R*)-hydroxyphosphonate.

Crystallization of the mixture of dimenthylhydroxyphosphonates diastereomers **Ia**, **Ib** gives optically pure (*S*)- or (*R*)-hydroxyphosphonates with good yields. Stereochemical purity of these compounds was monitored by ^{1}H and ^{13}C NMR spectroscopy and also by ^{31}P NMR spectra in some chiral solvating media. Noteworthy the extremely high optical rotation angles of hydroxyphosphonate with ortho-nitrophenyl group **Ia** ($[\alpha]_D$ = 300–400 deg) not observed in any known hydroxyphosphonate [13].

Achiral dimethylphosphite reacted with aromatic aldehydes in the presence of chiral catalysts with low stereoselectivity which did not exceed 30% *ee*. Reaction in the presence of cinchonine or quinine gave excess of (*R*)-hydroxyphosphonate as well as in case of dimenthylphosphite, whereas reaction catalyzed with cinchonidine or quinidine led to formation of a product enriched by (*S*)-hydroxyphosphonate. It was established that crystallization of the enantiomerically enriched hydroxyphosphonates from appropriate solvents resulted in their separation, allowing isolation of enantiomerically pure compounds. For example, a single crystallization of dimethylhydroxy-(2-nitrophenyl)methylphosphonate (ratio of enantiomers 6:4) from diethyl ether gave optically pure product. We also succeeded in purifying hydroxyphosphonate **Ib** by the usual crystallization. Enantiomeric composition of hydroxyphosphonates was determined by derivatization with dimenthylchlorophosphite or using chiral solvating reagents, in the presence of which signals separation of various enantiomers occurred in the ^{31}P NMR spectra.

The crystallization of dimethylhydroxy-(2-nitrophenyl)methylphosphonate from two-phase solvent

system ethyl acetate–hexane led to formation of the regularly shaped prismatic crystals. The two-phase solvent system was prepared in such a manner that phosphonate was dissolved in the bottom layer of ethyl acetate and the top layer constited of pure hexane. Crystallization of pure dimethyl (*S*)-hydroxy-(2-nitrophenyl)methylphosphonate gave asymmetric left-centered rhombic crystals under these conditions, and crystallization of dimethyl (*R*)-hydroxy-(2-nitrophenyl)methylphosphonate gave asymmetric right-centered rhombic crystals.

The crystallization of enantiomerically enriched phosphonate from the above solvent system gave both left- and right-centered asymmetric rhombuses. In the ^{1}H and ^{13}C NMR spectra of some enantiomerically enriched hydroxyphosphonates, specifically of compound **Ia**, an interesting effect was revealed. In the NMR spectra of these compounds signals of PCH–, methoxy groups, and aromatic protons were doubled, with integral intensity of these signals corresponding to the ratio of enantiomers (Fig. 1).

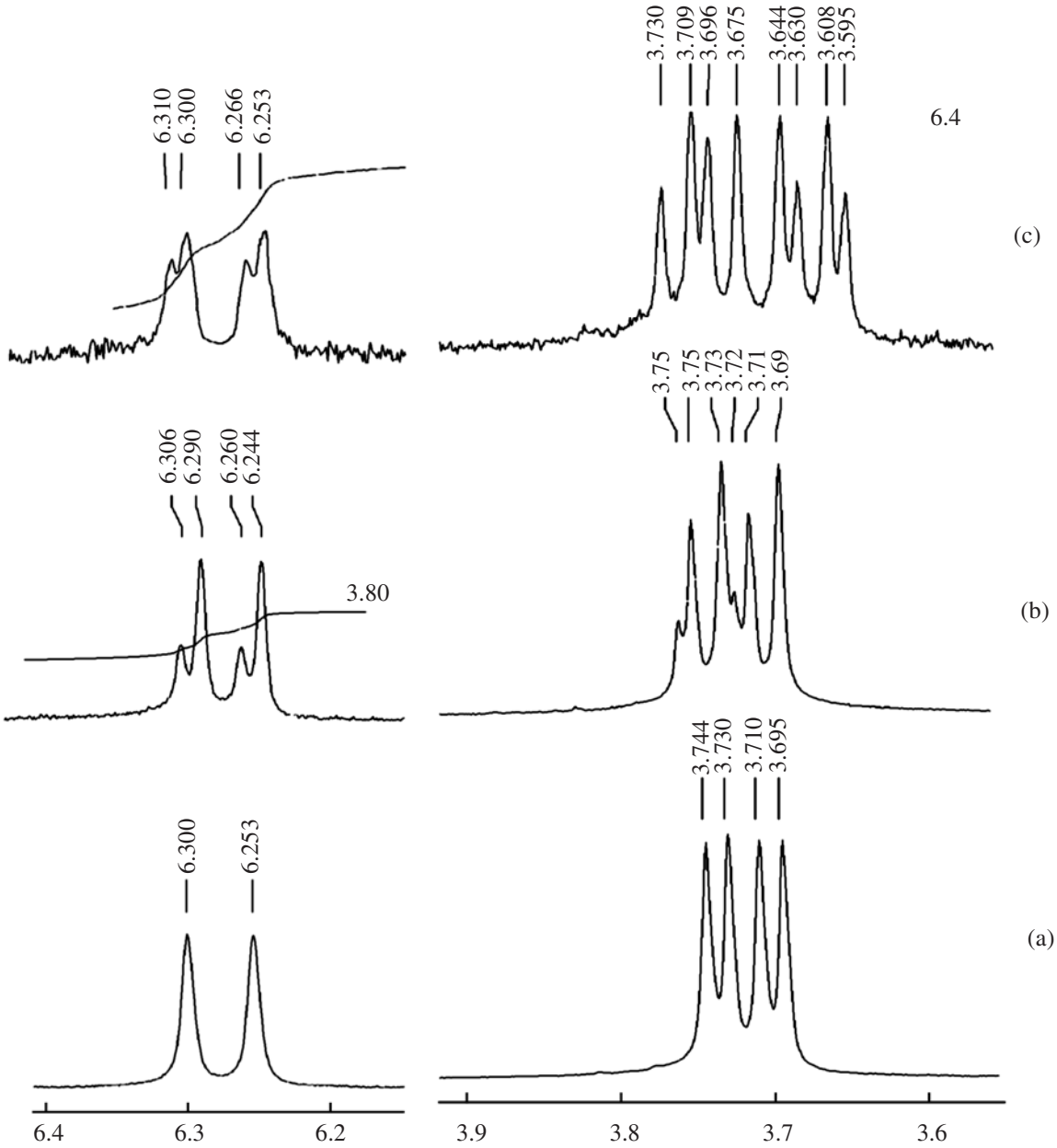


Fig. 1. The ^{1}H NMR spectra of dimethylhydroxy-(2-nitrophenyl)methylphosphonate (**Ia**) at the different ratios of enantiomers R/S: (a) ~ 0:100, (b) 1:3, and (c) 4:6.

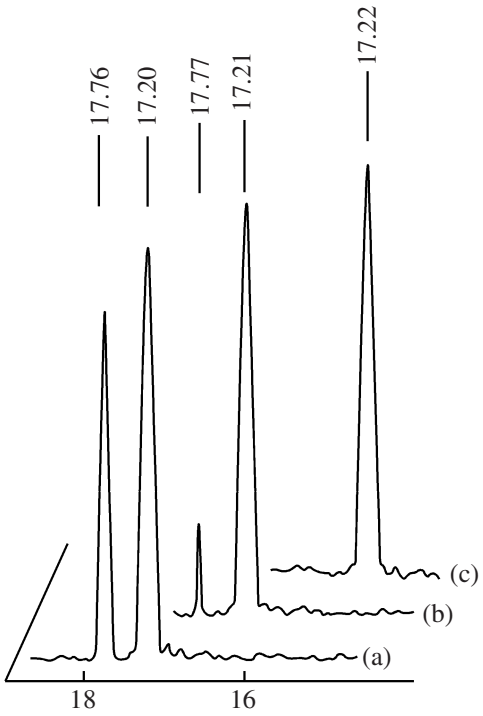


Fig. 2. The ^{31}P spectra of dimethylhydroxy-(2-nitrophenyl)-methylphosphonate (**Ia**) in the presence of cinchonidine as a chiral solvating reagent at different ratios of R/S-enantiomers: (a) 4:6, (b) 9:1, and (c) ~100:0.

In the case of the enantiomerically pure compounds and racemates (ratio of enantiomers 50:50) this effect was not observed and also signals were not separated. This effect also was not observed and signals were not separated when the excess of one of enantiomers was less than 10%. Thus, in ^{1}H NMR spectrum of the enantiomerically pure dimethylhydroxyarylphosphonate were found a sharply defined doublet of PCH-proton and two doublets of diastereotropic signals of CH_3O-groups, which in the enantiomerically enriched mixtures were doubled forming a double doublet (PCH) and two double doublets (CH_3O) respectively. Similarly, signals of methoxy groups, the α-carbon atom and carbon atoms of aromatic rings were split in keeping with the ratio of enantiomers in the ^{13}C NMR spectra of the corresponding enantiomerically enriched hydroxyphosphonates. The observed effect can be explained by autosolvation and autoassociation of chiral hydroxyphosphonate, therefore the latter acted as a chiral solvating reagent causing resolution of signals in the NMR spectra. Respectively, in both ^{1}H and ^{31}P NMR spectra of racemic hydroxyphosphonates resolution of enantiomeric signals occurred in the presence of others chiral solvating reagents, for example, quinine [14] (Fig. 2).

X-ray diffraction analysis showed clear alternation of (*S*)- and (*R*)-stereoisomers in the crystal lattice of racemic hydroxyphosphonate with ortho-nitrobenzene rings located above the phosphorus atom. These rings are capable of inducing strong deshielding effect, if, as might be assumed, similar arrangement of molecules is retained to some extent in solution (Fig. 3).

Absolute configuration of compounds was confirmed using the classical approach developed by Mosher and based on the analysis of ^{1}H and ^{31}P NMR spectra of diastereomeric derivatives obtained by derivatization of phosphonates at OH group with (*S*)-methylamygdalic acid chloride [15, 16]. The various orientation of the mandelates phenyl ring leads to selective shielding or deshielding of $P(O)(OR)_2$-groups, as a result of which in the O-acylated

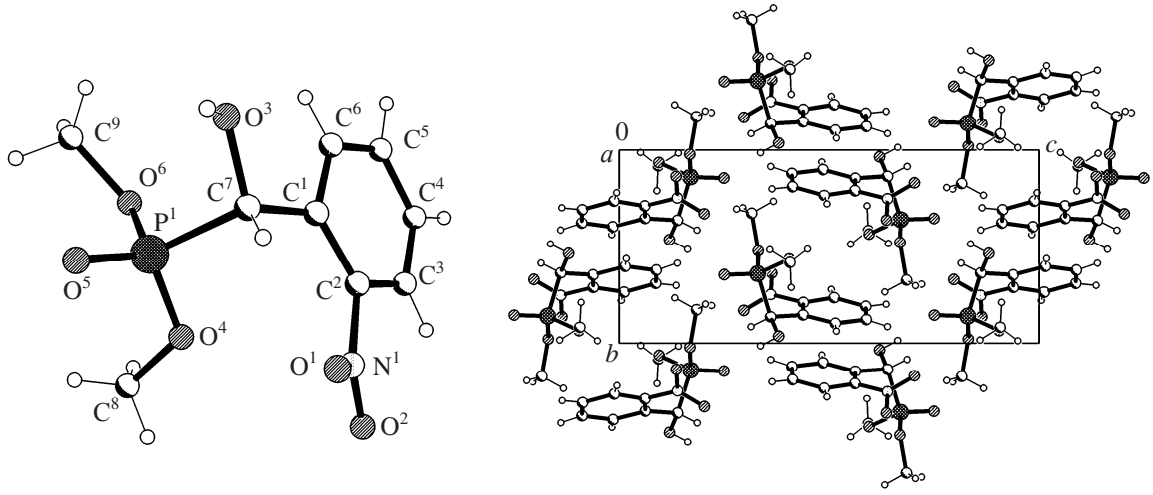
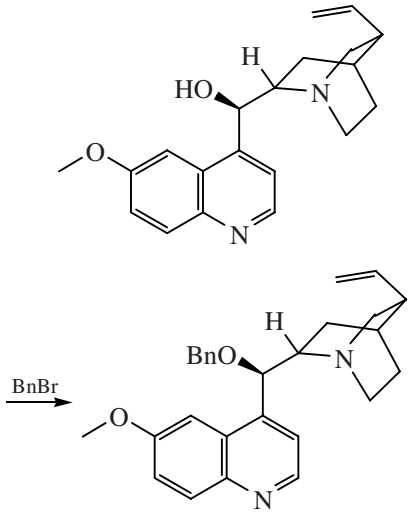


Fig. 3. X-ray diffraction analysis of dimethylhydroxy-(2-nitrophenyl)methylphosphonate (**Ia**).

compounds the signals of (*S*)-diastereomers appear downfield from the signals of (*R*)-diastereomers.

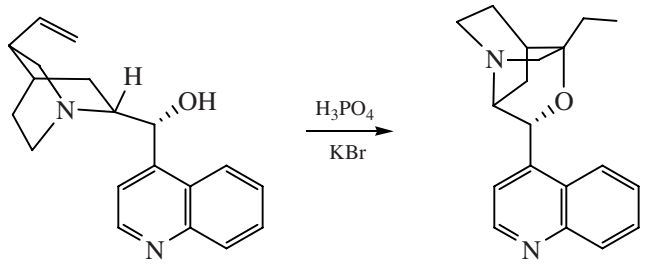
Modification of quinine with benzylation at the hydroxy group by known method [17–19] gave a more effective organic catalyst **II** providing the higher reaction stereoselectivity.



II

Oxazatwistane **III** was found to be the most effective organic catalyst as compared with parent cinchonidine. It was obtained by the intramolecular cyclization of cinchonidine in the presence of phosphoric acid and potassium bromide. Some representatives of oxazatwistanes were described earlier and used as organic catalysts of the Baylis–Hillman reaction [20, 21]. We obtained a new representative of oxazatwistanes **III**.

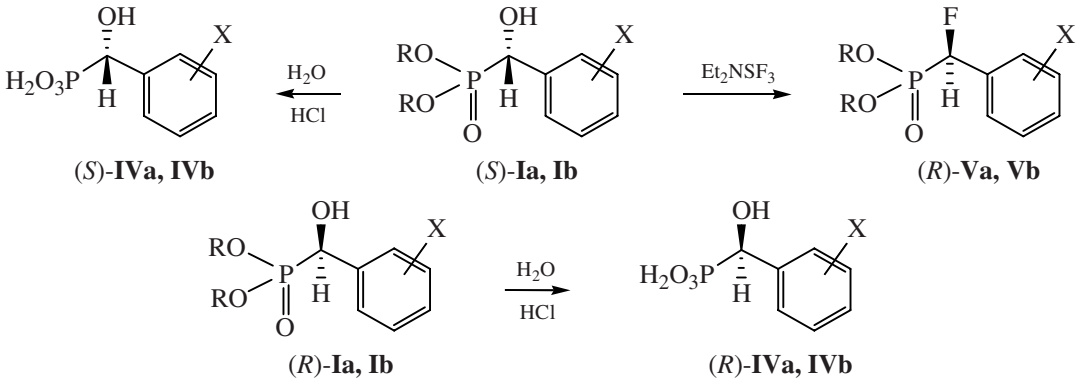
Reaction of dimethylphosphite with 2-nitrobenzaldehyde in the presence of oxazatwistane **III** afforded the enantiomerically enriched hydroxyphosphonate with higher content of (*S*)-enantiomer (>50% *ee*), which was isolated in pure form after recrystallization from ether.



III

Esters of substituted hydroxybenzylphosphonic acids were hydrolyzed with hydrochloric acid in water-dioxane solution to form the corresponding hydroxyphosphonic acids **IV**. Note a very high value of optical rotation angle of 2-nitrophenyl(hydroxy)methylphosphonic acid ($[\alpha]_D^{20}$ = 500 deg).

Hydroxyphosphonates readily reacted with diethylaminotrifluorosulfurane (DAST) at room temperature affording fluorophosphonates **V** with high yields and stereospecificity. Fluorophosphonates were purified by crystallization from hexane.



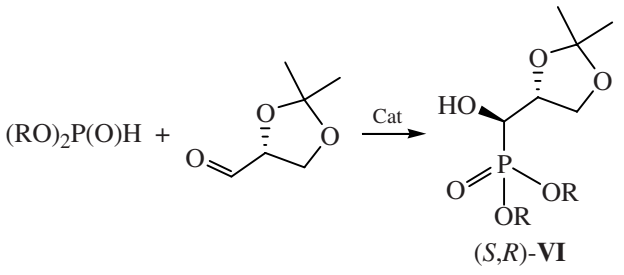
(*S*)-**IVa, IVb** (*S*)-**Ia, Ib** (*R*)-**Va, Vb**

(*R*)-**Ia, Ib** (*R*)-**IVa, IVb**

R = Mnt, X = OMe (**a**); R = Mnt, X = H (**b**).

Addition of glyceraldehyde acetonide to dimethyl- and dimenthylphosphite in the presence of cinchonine alkaloids proceeded slowly, apparently because of poor basicity of alkaloids. As a result glyceraldehyde had an opportunity to polymerize substantially with formation of the difficultly separated mixture of compounds containing a product of addition with low yield. Therefore the more basic L-prolinole was used

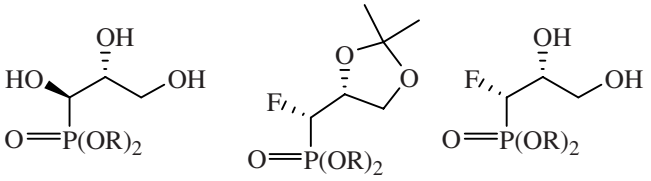
as catalyst, in the presence of which reaction proceeded rapidly and stereoselectively giving the addition product with good yield.



(*S*,*R*)-**VI**

R = (1*R*,2*S*,5*R*)Menthyl, Cat = L-prolynole.

The synthesized hydroxyphosphonate **VI** was hydrolyzed to form 1,2,3-trihydroxyphosphonate **VIIa**. Then hydroxyphosphonate **VI** was transformed into fluorophosphonate **VIII**, which in turn was converted into 1-fluoro-2,3-dihydroxypropylphosphonate **IX** after removal of acetonide. Reaction of hydroxylphosphonate **VI** with DAST readily proceeded at room temperature to give fluorophosphonate **VIIIa** in high yield. Fluorophosphonate **VIIIa** was purified by crystallization from hexane or by flash-chromatography.



(*S*,*R*)-**VIIa, VIIb** (*R*,*R*)-**VIIIa** (*R*,*R*)-**IXa**

R = Mnt (**a**), H (**b**).

Absolute configuration of hydroxyphosphonate (*S,R*) **VI** we determined earlier by X-ray diffraction analysis [22]. Removal of acetonide protection in compound **VI** does not involve the asymmetric centers, therefore absolute configuration of compounds **VIIa, VIIb** should be the same (*S,R*). As known from published data [13, 23], replacing hydroxy group with the fluorine atom at the tetrahedral carbon atom occurs with inversion of configuration. Hence absolute configuration of compounds **VIII**, **IX** should be (*R,R*).

1,2,3-Trihydroxypropylphosphonic acid and 2,3-dihydroxy-1-fluoropropylphosphonic acid are interesting synthetic blocks for obtaining of C–P analogs of glycerylphosphates [24].

EXPERIMENTAL

The ^{31}P and ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (126.16 and 300 MHz respectively). Chemical shifts are given against external reference 85% H_3PO_4 (^{31}P) and internal reference TMS (^{1}H). The optical rotation angles were measured on a Polax-2L polarimeter (Japan). The melting points are not corrected. Silica gel Merck 60 was used for column chromatography. Reactions were carried out in inert atmosphere (Ar). Reagents (Merck, Fluka) were used without special purification. Solvents were distilled over Na (THF, in the presence of benzophenone) and P_4O_{10} (CH_2Cl_2).

Di[(1*S*,2*R*,5*R*)-menthyl)] (*S*)-hydroxy(2-nitrophenyl)methylphosphonate (*S*)-Ia. To a mixture of 0.01 mol of dimenthylphosphite and 0.01 mol of 2-nitrobenzaldehyde in 5 ml of THF was added 0.002 mol of quinine or cinchonine as a catalyst. The mixture was kept for 48 h. In the NMR spectrum of the reaction mixture we observed signals of two diastereomers at δ_P 20.3 and 19.9 ppm in the ratio as above mentioned. The optically pure (*S*)-diastereomer was isolated by crystallization from acetonitrile. The other diastereomer was isolated by crystallization from hexane. Yield 35%, mp 150–159°C (MeCN), $[\alpha]_D^{20}$ 396 (0.6, $CHCl_3$). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.61 d (3 H, CH_3, J_{HH} 6.9 Hz), 0.066 d (3H, CH_3, J_{HH} 6.9 Hz), 0.71 d (3H, CH_3, J_{HH} 6.9 Hz), 0.83 d (3H, CH_3,J_{HH} 6.9 Hz), 0.86 d (3H, CH_3, J_{HH} 6.9 Hz), 0.87 d (3H, CH_3, J_{HH} 6.9 Hz), 1.00–1.6 m (14H, C*H*$_3$ and CH), 1.90 m [1H, $CH(CH_3)_2$], 2.15 m [1H, $CH(CH_3)_2$], 4.2 m (2H, OCH), 6.1 d (1H, CHP, J_{HH} 16.5 Hz), 4.2 s (1H, OH), 7.4 m (1H, Ar<u>H</u>), 7.6 m (1H, Ar<u>H</u>), 7.9 m (2H, Ar<u>H</u>). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 19.4. Found, %: N 2.75; P 6.38. $C_{27}H_{44}NO_6P$. Calculated, %: N 2.75; P 6.08.

Di(*1S,2R,5R*-menthyl) (*R*)-hydroxy(2-nitrophenyl)methylphosphonate (*R*)-Ia was obtained analogously using quinidine as a catalyst. $[\alpha]_D^{20}$ +300° (*c* 0.6, $CHCl_3$). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.61 d (3H, CH_3, J_{HH} 6.9 Hz), 0.066 d (3H, CH_3, J_{HH} 6.9 Hz), 0.71 d (3H, CH_3, J_{HH} 6.9 Hz), 0.83 d (3H, CH_3, J_{HH} 6.9 Hz), 0.86 d (3H, CH_3, J_{HH} 6.9), 0.87 d (3H, CH_3, J_{HH} 6.9 Hz), 1.00–1.6 m (14H, C*H*$_3$ and CH), 1.90 m [1H, $CH(CH_3)_2$], 2.15 m [1H, $CH(CH_3)_2$], 4.2 m (2H, OCH), 6.1 d (1H, CHP, J_{HH} 16.5 Hz), 4.2 s (1H, OH), 7.4 m (1H, Ar*H*), 7.6 m (1H, Ar*H*), 7.9 m (2H, Ar*H*). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 21.37. Found, %: N 2.75; P 6.38. $C_{27}H_{44}NO_6P$. Calculated, %: N 2.75; P 6.08.

Di[(1*R*,2*S*,5*R*)-(–)-menthyl] (*S*)-hydroxy-(2-metoxyphenyl)methylphosphonate (*S*)-Ib was obtained analogously to compound **Ia**. Yield 74%, mp 116–117°C, $[\alpha]_D^{20}$ –75.2 (*c* 0.66, $CHCl_3$). ^1H NMR spectrum, C_6D_6, δ, ppm: 0.60 d (3H, CH_3, J_{HH} 6.9 Hz), 0.52 d (3H, CH_3, J_{HH} 6.9 Hz), 0.73 d (3H, CH_3, J_{HH} 6.9 Hz), 0.79 m (6H, $2CH_3$), 0.84 d (3H, CH_3, J_{HH} 6.9 Hz), 0.92–1.54 m (14H, C*H*$_2$ and CH), 2.14 m [1H, C*H*$(CH_3)_2$], 2.40 m [1H, C*H*$(CH_3)_2$], 3.59 (3H, OCH_3), 4.17 m (1H, OCH), 4.03 m (1H, OCH), 4.54 s (1H, OH), 5.24 d (1H, C*H*P, 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 (1H, ArH, J_{HH} 7.5 Hz). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 20.98 [25].

Di[(1*R*,2*S*,5*R*)-(–)-menthyl]-(*R*)-hydroxy-(2-methoxyphenyl)methylphosphonate (*R*)-Ib was obtained analogously to compound (*R*)-**Ia** and purified by crystallization from hexane or acetonotrile. Yield 50%, mp 138°C, $[\alpha]_D^{20}$ –56.4° (*c* 1, toluene). ^1H NMR spectrum, C_6D_6, δ, ppm: 0.7–1.0 m (CH_3), 1.1–1.23 m (CH_2+CH), 3.4 s (OH), 3.55 s (OCH_3), 4.0 d. t (OCH, J_{HH} 2.3 Hz, J_{HH} 4.1 Hz), 5.17 d (CHP, J_{HP} 11 Hz), 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 [25].

Dimethyl (*S*)-hydroxy-(2-nitrophenyl)methylphosphonate (*S*)-Id. To a cooled to 0°C mixture of 1.1 g of (0.01 mol) of dimethylphosphite and 1.5 g (0.01 mol) of 2-nitrobenzaldehyde in 2 ml of toluene was added 0.002 mol of cinchonine. The mixture was kept for 48 h. Then solvent was removed. In the ^{31}P NMR spectrum of the reaction mixture signals of two diastereomers at δ_P 23.0 and 23.09 were recorded in the presence of cinchonidine as the chiral solvating reagent. The optically pure (*S*)-diastereomer was isolated by crystallization from diethyl ether. Yield 25%. Crystallization from chloroform–hexane mixture gives a racemic product. Yield 60%, mp 109–110°C (ether), $[\alpha]_D^{20}$ –495 (*c* 1, MeOH) [10]. ^1H NMR spectrum, $CDCl_3$, δ, ppm: 3.7 d (OCH_3, J_{HH} 10.5 Hz), 3.74 (OCH_3, J_{HH} 10.5 Hz), 5.64 s (OH), 6.28 d (PCH, J_{HP} 14.4 Hz), 7.99 t (H–Ar, *J* 7.5 Hz). ^{13}C NMR spectrum, $CDCl_3$, δ_C, ppm: 147.85 d *J* 7 [C6(Ar)], 133.35 d *J* 3, 132.95, 129.25 d, *J* 5, 126.8 d, *J* 3 [C^2(Ar)–C^5(Ar)], 124.7 d, *J* 3 [C^1(Ar)], 65.88 d *J* 161 (P–C), 54.9 d *J* 7 (CH_3^aO), 54.05 d *J* 7 (CH_3^bO). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 23.0. Found, %: C 41.45; H 4.71. $C_9H_{12}NO_6P$. Calculated, %: C 41.39; H 4.63.

Dimethyl (*R*)-hydroxy(2-nitrophenyl)methylphosphonate (*R*)-Id was obtained analogously using cinchonidine as a catalyst. The optically pure (*R*)-diastereomer was isolated by crystallization from diethyl ether with the yield of 20%. Crystallization from chloroform–hexane mixture gives a racemic product. Yield 60%, mp 109–110°C (ether), $[\alpha]_D^{20}$ +498 (*c* 1, MeOH) [10]. ^1H NMR spectrum, $CDCl_3$, δ, ppm: 3.7 d (OCH_3, *J* 10.5 Hz), 3.74 d (OCH_3, *J* 10.5 Hz), 5.64 s (OH), 6.28 d (PCH, J_{HP} 14.4), 7.99 t (*J* 7.5); 7.67 t, (*J* 7.5); 7.44 t (*J* 7.5, H–Ar). ^{13}C NMR spectrum, $CDCl_3$, δ_C, ppm: 147.85 d {[C^6(Ar), *J* 7 Hz}, 133.35 d (*J* 3 Hz), 132.95, 129.25 d (*J* 5 Hz), 126.8 d {*J* 3Hz, [C^2(Ar)–C^5(Ar)]}, 124.7 d {*J* 3 Hz, [C^1(Ar)]}, 65.88 d (*J* 161 Hz, P–C), 54.9 d (*J* 7 Hz, CH_3^aO), 54.05 d (*J* 7 Hz, CH_3^bO). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 23.0. Found, %: P 11.93. $C_9H_{12}NO_6P$. Calculated, %: P 11.86.

3-Ethyl-5-qunolin-4-yl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]-decane (III). To 10 ml of phosphoric acid was added 1 g of cinchonidine and 3.5 g of potassium bromide. The mixture was heated at 100°C for 48 h. Then it was cooled and washed with aqueous alkali till pH 7. To the mixture of aqueous ammonia was added to pH 8. The product was extracted with chloroform. The solvent was removed under a vacuum, and the residue was purified by column chromatography on silica gel (R_f 0.54, Silufol, MeOH:$CHCl_3$ 1:3). Color-less crystal product. Yield 50%, mp 250–255°C. ^1H NMR spectrum, $CDCl_3$, δ, ppm: 1.02 t (*J* 7.5 Hz, 3H), 1.24 d. d (*J* 13.6 Hz, 1H), 1.40–1.8 m (4H), 2.21–2.19 m (1H), 2.7 d (*J* 15 Hz, 1H), 2.9–3.3 m (1H), 3.0 d. d (*J* 9.0 Hz, 4 Hz, 1H), 3.4 d (*J* 4.0 Hz, 1H), 3.6 d (*J* 13.8 Hz, 1H), 6,05 s (1H), 7.5 t (*J* 7.5 Hz, 1H), 7.73 t (*J* 4 Hz, 1H), 7.75 d (*J* 4.5 Hz, 1H), 7.97 d (*J* 8.5 Hz, 1 H), 8.1 d (*J* 8.5 Hz, 1 H), 7.99 br.s (1H), 8.6 d (*J* 4.0 Hz, 1H). Found, %: C 77.54; H 7.51; N 9.50. $C_{19}H_{22}N_2O$. Calculated, %: C 77.52; H 7.53; N 9.52.

(*S*)-[Hydroxy(2-nitrophenyl)methyl]phosphonic acid (*S*)-IV. A solution of 1 g of hydroxymethylphosphonate **II** in 50 ml of dioxane was placed into a flask, and 25 ml of 6 N hydrochloric acid was added. The reaction mixture was allowed to stand for 3 days at 80°C. The hydrolysis progress was followed by ^{31}P NMR spectroscopy. After the reaction completion the solvent was removed. Yield 85%, $[\alpha]_D^{20}$ –490 (*c* 1, MeOH) [10]. ^1H NMR spectrum, CD_3OD, δ, ppm: 5 d (PCH), 7.5–8.0 m (C_6H_4). ^{31}P NMR spectrum, CH_3OH, δ_P, ppm: 15. Found, %: N 6.21; P 13.17. $C_7H_8NO_6P$. Calculated, %: N 6.01; P 13.29.

(*R*)-[Hydroxy(2-nitrophenyl)methyl]phosphonic acid (*R*)-IV. Yellowish oil. Yield 85%, $[\alpha]_D^{20}$ +490 (*c* 1, MeOH). ^1H NMR spectrum, CD_3OD, δ, ppm: 5 d

(PCH), 7.5–8.0 m (C_6H_4). ^{31}P NMR spectrum, CH_3OH, δ_P, ppm: 17. Found, %: N 6.21; P 13.17. $C_7H_8NO_6P$. Calculated, %: N 6.01; P 13.29.

Di-(1*R*,2*S*,5*R*)-menthyl (*S*)-[flouro(2-anisyl)methyl]-phosphonate (*S*)-Va. To a solution of 0.01 mol of di-(1*R*,2*S*,5*R*)-menthyl[hydroxy(2-anisyl)methyl]phosphonate in chloroform was added 0.015 mol of DAST, and the mixture was kept for 2 h at room temperature. Then the solvent was distilled off. The residue was recrystallyzed from hexane. Yield 60% after crystallization, mp 90–93°C, $[\alpha]_D^{20}$ –70 (*c* 1, $CHCl_3$). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.71 d (3 H, CH_3, J_{HH} 6.9 Hz), 0.72 d (3H, CH_3, J_{HH} 6.9 Hz), 0.74 d (3H, CH_3, J_{HH} 6.9 Hz), 0.80 d (3H, CH_3, J_{HH} 6.9 Hz), 0.81 d (3H, CH_3, J_{HH} 6.9 Hz), 0.83 d (3H, CH_3, J_{HH} 6.9 Hz), 1.40–2.6 m (14H, C*H*$_3$ and CH), 2.00 m [1H, $CH(CH_3)_2$], 2.4 m [1H, $CH(CH_3)_2$], 3.75 s (OCH_3), 4.1 m (2H, CHO), 5.35 d. d (1H, CHP, J_{HP} 8.5 Hz, J_{HF} 45 Hz), 6.9 m, 7.4 m (5H, Ar*H*). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 15,5 d. d (J_{PF} 130 Hz, J_{HP} 8.5 Hz). ^{19}F NMR spectrum, δ_F, ppm: 198.7 d.d ($^2J_{PF}$ 89, $^2J_{HP}$ 45 Hz). Found, %: C 67.72; H 9.34. $C_{28}H_{46}FO_4P$. Calculated, %; C 67.72; H 9.34.

Di[(1*R*,2*S*,5*R*)-menthyl] fluoro(phenyl)methyl-phosphonate (*S*)-Va was obtained similarly and purified column chromatography. Yield 80%. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.54 d (3 H, CH_3, J_{HH} 6.9 Hz), 0.57 d (3H, CH_3, J_{HH} 6.9 Hz), 0.7 d (3H, CH_3, J_{HH} 6.9 Hz), 0.73 d (3H, CH_3, J_{HH} 6.9 Hz), 0.83 d (3H, CH_3, J_{HH} 6.9 Hz), 0.85 d (3H, CH_3, J_{HH} 6.9 Hz), 1.40–2.6 m (14H, C*H*$_3$ and CH), 2.00 m [1H, $CH(CH_3)_2$], 2.4 m [1H, $CH(CH_3)_2$], 4.16 m (2H, OCH), 5.4 d.d (1H, *J* 7.5 Hz, *J* 45.6 Hz), 7.1–7.4 m (5H, Ar*H*). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 14,5 d. d (J_{PF} 87 Hz, J_{HP} 8.5 Hz). ^{19}F NMR spectrum, δ_F, ppm: 198.7 d.d ($^2J_{PF}$ 86 Hz, $^2J_{HP}$ 45 Hz). Found, %: F 4.17; P 6.69. $C_{27}H_{44}FO_3P$. Calculated, %: F 4.07; P 6.64.

Di[(1*R*,2*S*,5*R*)-menthyl] (*S*,*R*)-2,3-O-isopropylidene-1,2,3-trihydroxypropylphosphonate (VI). To a mixture of 0.01 mol of dimenthylphosphite and 0.012 mol of glyceraldehyde acetonide in 5 ml of THF cooled to 0°C was added 0.0005 mol of catalyst. In the NMR spectrum of the reaction mixture we observed signals of two diastereomers at δ_P 20.9 and 19.98 ppm in the ratio as above mentioned. Solvents were distilled off, the residue was purified by column chromatography and crystallized. The optically pure (*S,R*)-diastereomer was isolated by two successive crystallizations from acetonitrile. Yield 50%, mp 90°C (prisms), $[\alpha]_D^{20}$ –65 (*c* 2, $CHCl_3$). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.76 d (*J* 7.0 Hz, 6H, C*H*$_3$-Mnt), 0.87 d (*J* 6.6 Hz, 12H, (C*H*$_3$)$_2$CH-Mnt), 1.1–2.2 m (CH_2 + CH-Mnt), 1.33 s, 1.40 s (6H, (C*H*$_3$)$_2$C), 1.62 d (*J* 11.1 Hz, CH-Mnt, 2H), 2.1-2.27 m (CH-Mnt, 2H), 2.65 s (*J* 12 Hz, 1H,OH), 4.05 d. t (*J* 6.6 Hz, *J* 10.5 Hz, $OCHCH_2$+PCH), 4.23 d.t, *J* 7 Hz (*J* ABX-system, J_{AB} 6 Hz, CH_2), 4.39 m 2H, CH_2). ^{31}P NMR spectrum, $CDCl_3$, δ_P, ppm: 20.9.

(*R,R*)-Diastereomer containing small impurity of (*S,R*)-diastereomer was isolated by column chromatography (hexane–ethyl acetate 4:1). Yield 5–15% (depending on a catalyst nature). ^{1}H NMR spectrum, $CDCl_3$, δ_P, ppm: 20.0 in agreement with that of **VI** we had reported ealier [22].

Di[(1*R*,2*S*,5*R*)-menthyl] (*S,R*)-1,2,3-trihydroxypropylphosphonate (VIIa). To a solution of 0.005 mol of compound **I** in 5 ml of dioxane was added 2–3 ml of concentrated hydrochloric acid. The mixture was kept for a night. The solution was evaporated under a vacuum and the residue was recrystallized from hexane. Yield 90%, mp 108–109°C (needles), $[\alpha]_D^{20}$ –60 (*c* 2, $CHCl_3$). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.782 d, (*J* 6.9 Hz, 3H, (C*H*$_3$)$_2$C), 0.778 d (*J* 6.6 Hz, 3H, (C*H*$_3$)$_2$C), 0.887 d (*J* 6.0 Hz, 6H, C*H*$_3$-Mnt), 0.895 d (*J* 6.6 Hz, 6H, C*H*$_3$-Mnt), 1.0–1.5 m (CH_2 + CH-Mnt), 1.626 m (2H, *H*-Mnt), 1.662 m (2H, *H*-Mnt), 2.131 (2H, H-Mnt), 2.234 m (2H,H-Mnt), 2.74 s (3H, OH), 3.831 m (3H, POCH, 2H), 3.899 m (PCH, 1H), 4.234 m (2H, CH_2). ^{31}P NMR spectrum, $CDCl_3$, δ, ppm: 22.51 [22,26].

(*S,R*)-1,2,3-Trihydroxypropylphosphonic acid (VIIb). 0.005 mol of **VI** was dissolved in 40% hydrochloric acid in dioxane and was kept at 80°C for 48 h. Then the solution was evaporated under a vacuum. The residue was dissolved in 4 ml of alcohol and 0.01 mol of cyclohexylamine was added. Cyclohexylammonium salt was filtered off.

Yield 65%, mp >200°C (decomp.). ^{1}H NMR spectrum, CD_3OD + $CDCl_3$, δ, ppm: 0.9–1.2 m (2H, CH_2), 1.6 m (4H, CH_2), 1.75 m (4H, CH_2), 2.7 m (2H, CH_2), 3.1 s (4H, OH), 3.4–3.6 m (2H, NH + CH). ^{31}P NMR spectrum, CD_3OD, δ_P, ppm: 18.1. Found, %: P 11.03. $C_9H_{22}NO_6P$. Calculated, %: P 11.42.

Di[(1*R*,2*S*,5*R*)-menthyl] (*S,R*)-[(2,2-dimethyl-1,3-dioxolan-4-yl)-fluoromethylphosphonate (VIIIa) was obtained analogously to compound (*S*)-**Va**. Product was purified by column chromatography. Yield 60%. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.78 d (3H, CH_3, J_{HH} 6.9 Hz), 0.80 d (3H, CH_3, J_{HH} 6.9 Hz), 0.96 d

(3H, CH_3, J_{HH} 6.9 Hz), 0.88 d (3H, CH_3, J_{HH} 6.9 Hz), 0.90 d (3H, CH_3, J_{HH} 6.9 Hz), 1.40–2.6 m (14H, CH_3 and CH), 2.00 m [1H, CH$(CH_3)_2$], 2.4 m [1H, CH $(CH_3)_2$], 2.98, 3.08 (CH_3), 4.16 m (2H, OCH), 3.85 d. d (1H, *J* 13.2 Hz, *J* 78 Hz, PCH), 3.44 m (CH_2O), 4.24 m (2H, CHO). ^{19}F NMR spectrum, δ, ppm: 196.2 d ($^2J_{PF}$ 50). Found, %: F 3.78; P 6.39. $C_{26}H_{48}FO_5$. Calculated, %: F 3.87; P 6.31.

Di[(1*R*,2*S*,5*R*)-menthyl] (*R*,*R*)-1-fluoro-2,3-dihydrooxypropylphosphonate (IXa) was obtained analogously to compound (*S*)-**VIIa**. The product was purified by column chromatography. Yield 65%. ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 0.77 d (*J* 6.9 Hz, 3H, $(CH_3)_2$C), 0.78 d [*J* 6.6 Hz, 3H, $(CH_3)_2$C], 0.89 d (*J* 6.6 Hz, 6H, CH_3-Mnt), 0.89 d (*J* 6.6 Hz, 6H, CH_3-Mnt), 1.0–1.5 m (CH_2 + CH-Mnt), 1.67 m (2H, *H*-Mnt), 1.66 m (2H, *H*-Mnt), 2.13 m (2H, H-Mnt), 2.23 m (2H,H-Mnt), 2.9 s (3H, OH), 3.8 m (2H, POCH), 3.9–4 m (PCH + OCH, 2H), 4.23 m (2H, CH_2). ^{31}P NMR spectrum, $CDCl_3$, δ, ppm: 17.8. Found, %: P 6.89. $C_{22}H_{44}FO_5P$. Calculated, %: P 6.87.

ACKNOWLEDGMENTS

This research was carried out at a financial support of the National Academy of Sciences of Ukraine.

REFERENCES

1. France, S., Guerin, D. J., Miller, S. J., and Lectka, Th., *Chem. Rev*., 2003, vol. 103, no. 8, p. 2985.
2. Hoffmann, H.M.R. and Frackenpohl, J., *Eur. J. Org. Chem*., 2004, p. 4293.
3. Horikawa, M., Busch-Petersen, J., and Corey, E.J., *Tetrahedron Lett*., 1999, vol. 40, no. 20, p. 3843.
4. List, B., *Tetrahedron*, 2002, vol. 58, no. 28, p. 5573.
5. Jarvo, E.R and Miller, S.J., *Tetrahedron*, 2002, vol. 58, no. 13, p. 2481.
6. List, B., *Synlett*, 2001, no. 11, p. 1675.
7. Dalko, P.I. and Moisan, L., *Angew. Chem., Int. Ed*., 2004, vol. 43, no. 39, p. 5138.
8. List, B., Lerner, R.A., and Barbas, C.F., *J. Am. Chem. Soc.*, 2000, vol. 122, no. 10, p. 2395.
9. Bernardi, L., Fini, F., Herrera, R.P., Ricci, A., and Sgarzani, V., *Tetrahedron*, 2006, vol. 62, no. 2, p. 375.
10. Smaardijk, Ab.A., Noorda, S., van Bolhuis, F., and Wynberg, H., *Tetrahedron Lett*., 1985, vol. 26, no. 4, p. 493.
11. Kolodiazhnaya, A.O., Kukhar, V.P., and Kolodiazhnyi, O.I., Abstract of Papers, *XVII Intern. Conf. on Phosph. Chem. (ICPC-17)*, Xiamen, 2007, p. 110.
12. Kolodiazhnyi, O.I., *Tetrahedron*, 2003, vol. 59, no. 32, p. 5923.
13. Kolodiazhnyi, O.I., *Tetrahedron: Asymmetry*, 2005, vol. 16, no. 20, p. 3295.
14. Kolodiazhnaya, A.O., Kukhar, V.P., and Kolodiazhnyi, O.I., *Zh. Obshch. Khim*., 2006, vol. 74, no. 8, p. 1398.
15. Dale, J.A. and Mosher, H.S., *J. Am. Chem. Soc*., 1973, vol. 95, no. 2, p. 512.
16. Kozlowski, J.K., Rath, N.P., and Spilling, C.D., *Tetrahedron*, 1995, vol. 51, no. 23, p. 6385.
17. Li, H., Wang, Y., Tang, L., and Deng, L., *J. Am. Chem. Soc*., 2004, vol. 126, no. 32, p. 9906.
18. Liu, X., Li, H., and Deng, L., *Org. Lett*., 2005, vol. 7, no. 1, p. 167.
19. Marcelli, T., van der Haas, R.N.S., van Maarseveen, J.H., and Hiemstra, H., *Synlett*, 2005, no. 18, p. 2817.
20. Braje, W., Frackenpohl, J., Langer P., and Hoffmann, H.M.R., *Tetrahedron*, 1998, vol. 54, no. 14, p. 3495.
21. Iwabuchi, Y., Nakatani, M., Yokoyama, N., and Hatakeyama, S., *J. Am. Chem. Soc*., 1999, vol. 121, no. 43, p. 10219.
22. Kolodiazhnaya, A.O., Kukhar, V.P., Chernega, A.N., and Kolodiazhnyi, O.I., *Tetrahedron Asymmetry*, 2004, vol. 15, no. 13, p. 1961.
23. Smyth, M.S., Ford, Jr.H., and Burke, Jr.T.R., *Tetrahedron Lett*., 1992, vol. 33, no. 29, p. 4137.
24. Nieschalk, J., Batsanov, A., Hagan, D., and Howard, J. A.K., *Tetrahedron*, 1996, vol. 32, no. 1, p. 165.
25. Nesterov, V. and Kolodyazhnyi, O.I., *Zh. Obshch. Khim.*, 2006, vol. 76, no. 7, p. 1068.
26. Kolodiazhnaya, A.O., Kukhar, V.P., and Kolodiazhnyi, O.I., *Zh. Obshch. Khim*., 2004, vol. 74, no. 6, p. 965.