Nonracemic menthyl phosphorylacetates

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Phosphorylacetic acid esters containing the menthoxy fragment at the phosphorus atom or at the carbonyl group were synthesized. The configurations of the enantiomerically pure compounds, *viz.*, methyl (ethoxy)(menthyloxy)phosphorylacetate and menthyl [(2-chloroethoxy)(4-dimethylaminophenyl)phosphoryl]acetate, were established by X-ray diffraction and NMR spectroscopy.

Key words: phosphorylacetic acids, menthol, stereoisomerism, diastereomers, configuration, X-ray diffraction analysis, NMR spectroscopy.

Since phosphorylcarboxylic acid derivatives are analogs of biogenic compounds, they can exhibit high biological activity.[1,2] For example, the study of the structure—biological activity relationship in a series of phosphorylacetic acids revealed promising representatives having unique effects on the central nervous system.[3] For example, [(2-chloroethoxy)(4-dimethylaminophenyl)phosphoryl]acethydrazide (CAPAH) not only exhibits antidepressant activity but also improves memory and trainee's ability.[4] The molecule of this compound contains the asymmetric phosphorus atom. According to X-ray diffraction data, the CAPAH racemate crystallizes as a racemic compound containing equal amounts of (*R*) and (*S*) enantiomers in the unit cell.[5] Since individual enantiomers usually differ substantially in biological activity, the synthesis of phosphorylacetic acid derivatives in the enantiomerically pure form is an important problem. One of approaches to the solution of this problem is based on the synthesis of derivatives containing a chiral fragment with the authentic absolute configuration followed by the separation of individual diastereomers and the determination of the absolute configuration of the chiral center in question relative to the reference center. This problem can easily be solved by X-ray diffraction if high-quality single crystals are available. Evidently, modern methods of multidimensional NMR spectroscopy providing information on the mutual arrangement of fragments in a molecule can be used for the determination of the relative configuration of liquid or dissolved compounds.

With the aim of preparing enantiopure biologically active organophosphorus compounds and determining their configurations, we synthesized phosphorylacetic acid esters containing the (1*R*,2*S*,5*R*)-menthol fragment at the phosphorus atom or the carbonyl group. Some of the isolated enantiomerically pure diastereomers were studied by different two-dimensional NMR methods. The indirect results for menthyl [(2-chloroethoxy)(4-dimethylaminophenyl)phosphoryl]acetate were compared with the direct X-ray diffraction data.

Results and Discussion

The reaction of diethyl menthyl phosphite (**1**) or di-*O*,*O*-menthyl phenylphosphonite (**2**) with menthyl chloroacetate (Scheme 1) proceeds under more drastic conditions than the reaction with methyl chloroacetate, requires the presence of catalytic amounts of zinc chloride, and is accompanied by elimination of chloroethane, while the menthoxy substituent remains intact. The presence of the latter in products **3—5** was confirmed by mass spectrometry and ^{1}H NMR spectroscopy. The CI mass spectra of compounds **3** and **5** contain peaks of the protonated molecular ions $[MH]^+$, whose weights correspond to the calculated values.

The reactions of 2-chloroethoxy esters of phosphorus(III) acids with menthyl chloroacetate afforded target products **9—11** (Scheme 2). However, this reaction, like the reaction with ethyl chloroacetate studied earlier,[6] is

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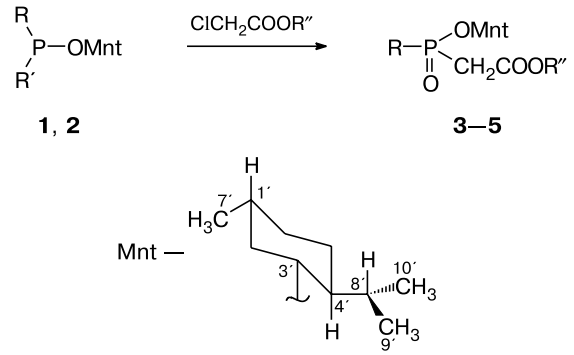
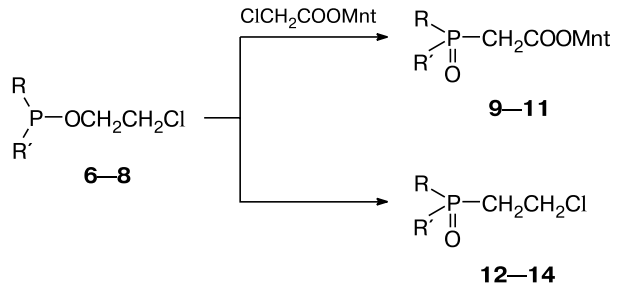
Scheme 1



R = R′ = OEt (**1**); R = Ph, R′ = OMnt (**2**)
R = OEt, R″ = Me (**3**); R = Ph, R″ = Me (**4**); R = OEt, R″ = Mnt (**5**)

complicated by isomerization giving rise to compounds **12—14** as by-products.

Scheme 2



R = R′ = Ph (**6**, **9**, **12**); R = Ph, R′ = Et (**7**, **10**, **13**);
R = 4-$Me_2NC_6H_4$, R′ = OCH_2CH_2Cl (**8**, **11**, **14**)

Due to the presence of the enantiomerically pure menthol fragment in molecules **3—5**, **10**, and **11**, the reactions produce mixtures of two diastereomers, which differ in the configuration of the chiral center at the phosphorus atom. The ratios of diastereomers were determined based on the integral intensities of the signals for the phosphorus atoms in the ^{31}P NMR spectra (see the Experimental section).*

The presence of the menthyl fragment provides an additional possibility to identify diastereomers. Earlier,[7] studies of menthyl phosphinates have demonstrated that a doublet belonging to one of the Me groups, $C(9')H_3$, of the isopropyl substituent in the menthyl fragment (see Scheme 1) is characterized by an upfield shift in the ^1H NMR spectra. If the phosphorus atom is chiral, the chemical shifts of these signals for two diastereomers are substantially different and can be used for the determination of their ratio. For example, the ^1H NMR spectrum of $Ph_2P(O)OMnt$ shows only the signal of the methyl groups of the isopropyl fragment at δ 0.57, whereas the spectrum of Ph(Me)P(O)OMnt has two signals at δ 0.34 and 0.89 corresponding to these groups.[7]

The chemical shifts of the protons of the $C(9')H_3$ group in the resulting compounds are given in the Experimental section. These protons in the spectra of derivatives **1** and **9** containing the achiral phosphorus atom are characterized by the only high-field doublet. The shift δ for the $C(9')H_3$ group remains virtually unchanged regardless of whether the menthyl substituent is present at the phosphorus atom or in the ester fragment. Derivatives containing the chiral phosphorus center are characterized by two signals of the $C(9')H_3$ group. In the spectra of *P*-aryl-substituted compounds **4** and **10**, one of the signals is substantially shifted upfield (the considerable shielding effect of diamagnetic anisotropy of the aryl ring[7]).

This effect is consistent with our estimates of the shielding of the protons of all Me groups in the menthyl fragment of ester **4** by the aryl substituent for both (R_P and S_P) diastereomers (the geometry was optimized by the MM2 method, the semiclassical model of ring currents,[8] the Shields program). According to the calculations, a considerable (up to 0.6 ppm) shielding effect should be observed for the protons of the $C(9')H_3$ group in the S_P isomer (for the $C(10')H_3$ group, this effect ≤0.2 ppm; for C(8′)H, ≤0.5 ppm). By contrast, an insignificant effect of the aromatic moiety (at most 0.1 ppm) should be observed only for the protons of the $C(7')H_3$ group in the R_P isomer.

An analysis of the NMR spectroscopic data for the reaction mixtures (see Schemes 1 and 2 and the Experimental section) demonstrated that the reactions are stereoselective and produce predominantly one of diastereomers. Apparently, higher stereoselectivity of these reactions is favored by the steric and electronic effects of the aryl substituent.[9] Samples substantially enriched in one of diastereomers were obtained by column chromatography and fractional crystallization. In the case of esters **3b** and **11b**, we succeeded in isolating individual diastereomers, and the assignment of their configurations was made by NMR spectroscopy and X-ray diffraction.

Since the individual diastereomer of methyl (ethoxy)(menthyloxy)phosphorylacetate (**3b**) was obtained as low-melting crystals (see the Experimental section), the determination of its structure by X-ray diffraction presented difficulties. The information on its constitution (the chemical structure and the binding of fragments) was obtained by 1D and 2D NMR experiments (DEPT, 2D COSY, 2D HSQC, 2D HMBC, and 1D DPFGNOE).[10,11]

The ^1H NMR spectrum of isomer **3b** shows a group of multiplets at δ 0.7—4.4. The spin systems belonging to

* Hereinafter, the diastereomers are denoted by the letters **a** and **b**, the letter **a** is ascribed to the stereoisomer characterized by smaller δ in the ^{31}P NMR spectrum. The letters **a** and **b** are not directly related to the configuration of the phosphorus atom.

the protons of two functional groups (the ethoxy and menthoxy fragments) were unambiguously distinguished in the 2D COSY spectrum. Taking into account the 2D HSQC spectroscopic data, the signals of the proton-containing carbon atoms of these fragments were reliably identified. The structures of the fragments and their binding to the phosphorus atom were conclusively determined based on $^1H—^{13}C$ HMBC and $^1H—^{31}P$ HSQC correlations. In the 2D HMBC ($^1H—^{13}C$) spectrum, there are correlations between the $C(2)H_2$ protons (δ 2.95) and the C(4) atom (δ 52.34), between the $C(4)H_3$ protons (δ 3.72) and the C(2) atom (δ 35.25), and between the $C(2)H_2$ (δ 2.95) and $C(4)H_3$ (δ 3.72) protons and the C(3) atom (δ 166.32) (Fig. 1). The 2D HSQC ($^1H—^{31}P$) spectrum shows cross-peaks between the $C(2)H_2$ (δ 2.95) and $C(4)H_3$ (δ 3.72) protons and the P(1) atom (δ 18.72) (Fig. 2). The combined analysis of the spectroscopic results allowed the establishment of the structure of the $P—CH_2—CO—OCH_3$ fragment up to the phosphorus atom inclusive (Fig. 3).

The cross-peaks between the $C(5)H_2$ (δ 4.17) and $C(6)H_3$ (δ 1.33) protons and the P(1) atom (δ 18.72) observed in the 2D HSQC ($^1H—^{31}P$) spectrum (see Fig. 2) confirm the presence of the bond between the ethoxy fragment and the phosphorus atom (see Fig. 3). In addition, this spectrum shows cross-peaks between the proton of the oxymenthyl substituent C(3′)H (δ 4.27) and the P(1) atom (δ 18.72) (see Fig. 2). The presence of this cross-peak is indicative of the presence of a covalent bond between the menthoxy fragment of this isomer and the phosphorus atom (see Fig. 3). Therefore, the combined use of different homo- ($^1H—^1H$) and heterocorrelation ($^1H—^{13}C$ and $^1H—^{31}P$) experiments made it possible to successively determine the constitution of compound **3b** (along with that of diastereomer **3a**).

Unlike enantiomers, diastereomers differ in scalar characteristics, including intramolecular internuclear distances. This means that the absolute configuration of the phosphorus atom in crystalline stereoisomer **3b** can be determined based on the correlations due to NOE directly dependent on internuclear distances,[11] if the absolute configuration of the starting menthyl fragment and the conformation of the chain between the chiral phosphorus atom and the menthoxy fragment are known.

According to the published data,[7,12] the nearly synperiplanar orientation of the P=O bond with respect to the C(3′)—H bond is dominant for the analogous chain in menthyl phosphinates and other related compounds. The analysis of the possible conformers with respect to the (P)O—C(3′) bond in ester **3b** by the MM2 method[13] showed that the synperiplanar conformers are dominant in this case as well (Fig. 4).

The 1D DPFGNOE spectra of stereoisomer **3b** show intense NOEs between $C(4)H_3$ (δ 3.72) and C(8′)H (δ 2.08), $C(9′)H_3$ (δ 0.79) and between $C(2)H_2$ (δ 2.95) and C(8′)H (δ 2.08), $C(9′)H_3$ (δ 0.79). This is indicative of the spatial proximity of the isopropyl group of the menthyl fragment and the $P—CH_2—CO_2Me$ fragment (see

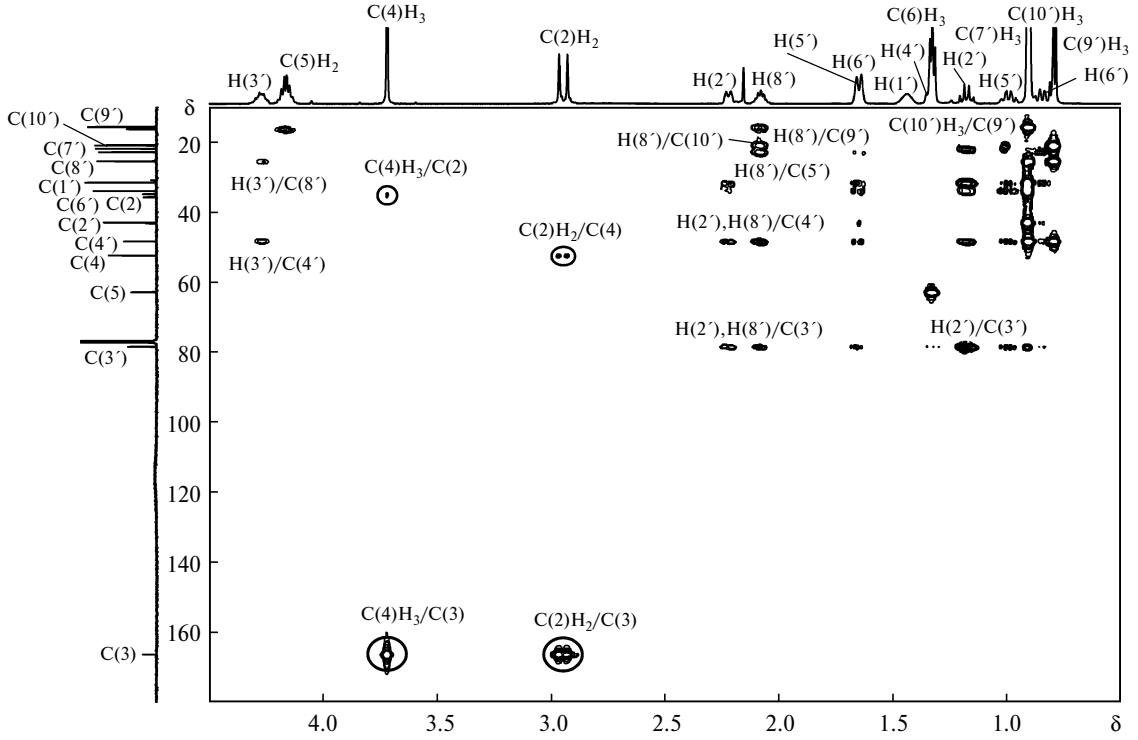


Fig. 1. 2D HMBC ($^1H—^{13}C$) spectrum of stereoisomer **3b** in $CDCl_3$ (T = 303 K).

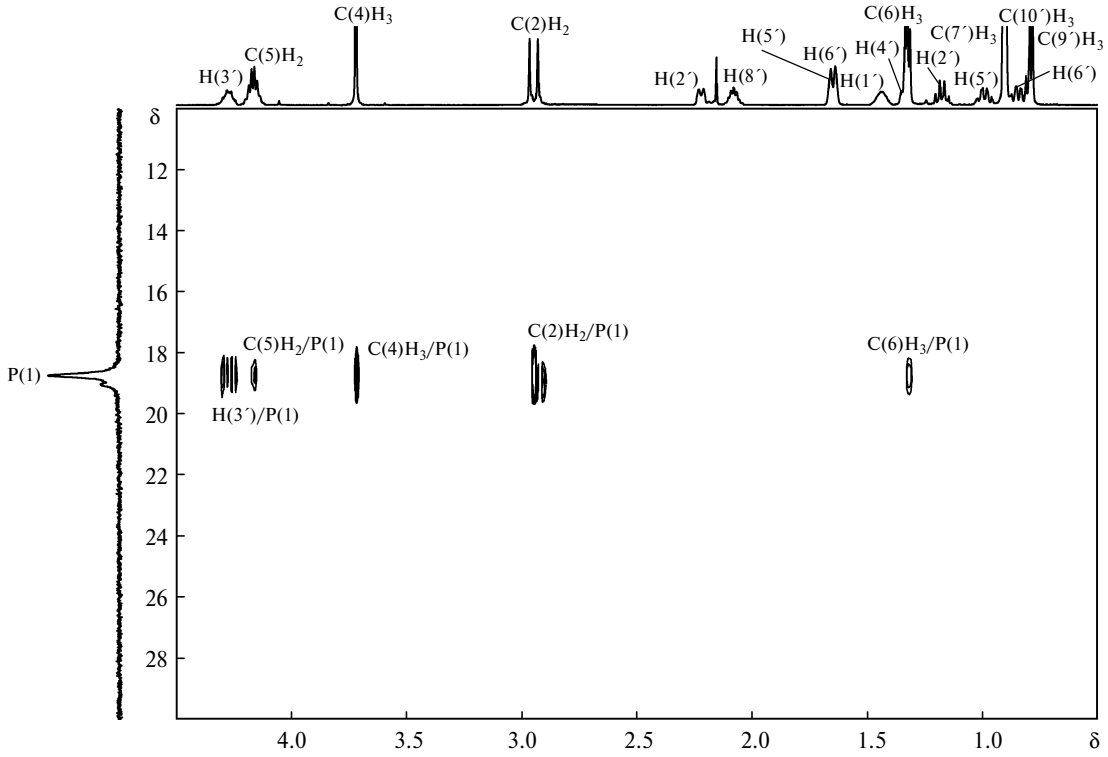


Fig. 2. 2D HSQC (^{1}H—^{31}P) spectrum of stereoisomer **3b** in $CDCl_3$ (T = 303 K).

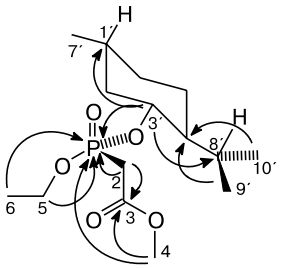


Fig. 3. Principal ^{1}H—^{13}C HMBC correlations (from protons to carbon atoms) and ^{1}H—^{31}P HSQC correlations (from protons to the phosphorus atom) for compound **3b**.

Fig. 4). In another diastereomer (in which the OEt and CH_2CO_2Me substituents change places), such spatial proximity is hardly probable. Therefore, the experimental Overhauser effects suggest that the phosphorus atom in the diastereomer under study has an *S* configuration shown in Fig. 4.

The major diastereomer of menthyl [(2-chloroethoxy)(4-dimethylaminophenyl)phosphoryl]acetate (**11b**), whose percentage in the crude reaction mixture is higher than 80%, can easily be isolated in the crystalline state (see the Experimental section). The single-crystal X-ray diffraction study of compound **11b** demonstrated that this compound crystallizes in the chiral space group $P2_1$ (Z = 2), *i.e.*, there is one molecule per asymmetric unit cell (Fig. 5).

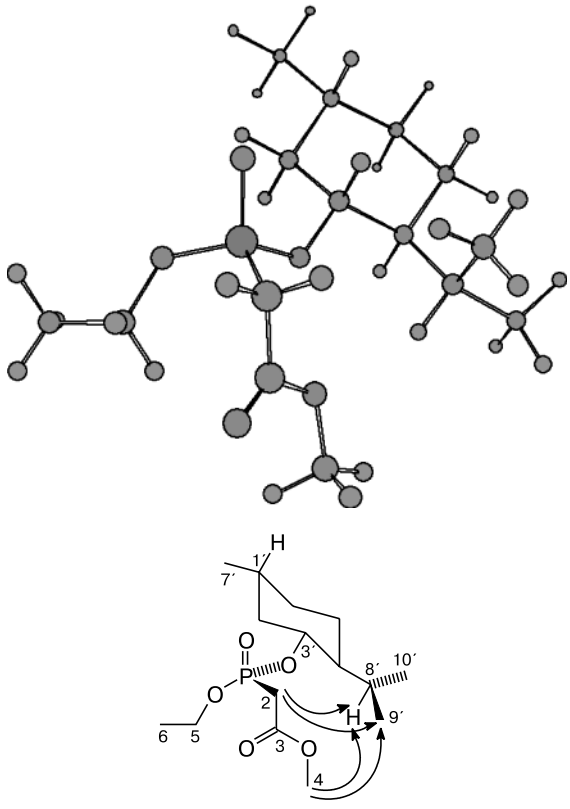


Fig. 4. Calculated major conformation of diastereomer **3b** and the observed principal NOEs.

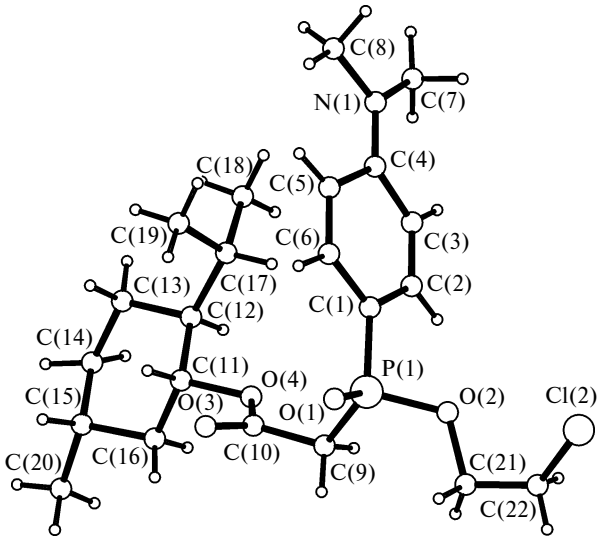


Fig. 5. Geometry of the menthyl [(2-chloroethoxy)(4-dimethylaminophenyl)phosphoryl]acetate molecule (**11b**).

The bond lengths at the P(1) atom are typical of such bonds (P(1)=O(1), 1.486(6) Å; P(1)—O(2), 1.615(6) Å). Classical hydrogen bonds in this structure are absent, and the main supramolecular motif, *viz.*, the zigzag chains along the crystallographic axis 0*y*, is stabilized by the C(9)—H(92)...O(1′) (–*x*, –1/2 + *y*, –*z*) (C—H, 0.96 Å; H...O, 2.48 Å; C...O, 3.408(9) Å; C—H...O, 165°) and C(22)—H(222)...O(3′) (C—H, 0.91 Å; H...O, 2.51 Å; C...O, 3.168(16) Å; C—H...O, 129°) hydrogen bonds.

Since the configuration of the chiral carbon atoms of the menthyl fragment is known in advance (C(11*R*), C(12*S*), C(15*R*)), the configuration of the P(1) atom was identified as *S*. Figure 5 shows that diastereomer **11b** is characterized by the spatial proximity of the isopropyl group of the menthyl fragment and the aryl substituent at the phosphorus atom.

The data on the structure of **11b** in solution obtained by NMR spectroscopy are consistent with the X-ray diffraction data. The chemical structure of compound **11b** was established according to the scheme analogous to that used for the structure of **3**. Hence, we analyzed only the observed Overhauser effects for this compound (Fig. 6). In this case, the determination of the configuration of the phosphorus atom based only on NOEs is complicated by the presence of the potentially conformationally flexible P—CH_2—C(O)—O—C(3′) chain between the menthyl fragment and the phosphorus atom. However, the fact that the NOEs are observed between the isopropyl substituent and the atoms of the aromatic ring provides evidence for the similarity of the conformations of this diastereomer in the crystal and solution. To the contrary, when assuming the conformational restrictions reasonable for this chain (the *s-cis* conformation of the ester group and the sinclinal orientation along the P—CH_2 bond), the expected NOEs

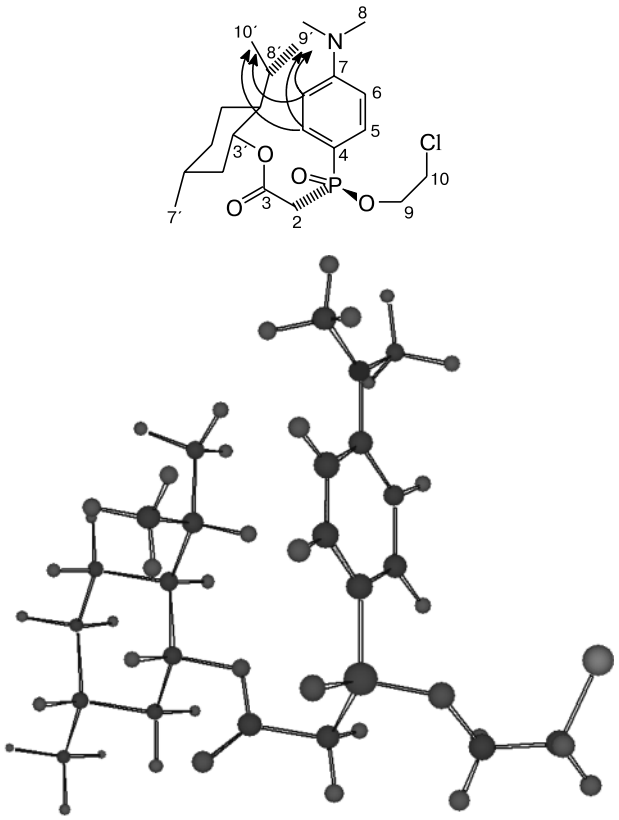


Fig. 6. Principal NOEs and their correlation with the structure of diastereomer **11b**.

are consistent with those observed for the S_P diastereomer of ester **11**.

In summary, the results of a series of 2D NMR experiments allowed us to unambiguously determine the constitutions of compounds **3b** and **11b** in solution. The configurations of the compounds under study were initially assumed based on the quantitative consideration of the anisotropic magnetic shielding due to the presence of the aromatic fragments of the molecules. The absolute configuration of the phosphorus atom in both compounds was more reliably established based on the detailed consideration of the experimental nuclear Overhauser effects. The validity of the established conformations of the molecular fragments in compound **11b** was confirmed by comparing the data from NMR spectroscopy for solutions with the single-crystal X-ray data.

Experimental

The ^{1}H, ^{13}C, and ^{31}P ^{1}H NMR spectra were recorded on a Bruker AVANCE-600 instrument (600.00 MHz for ^{1}H, 150.864 MHz for ^{13}C, and 242.88 MHz for ^{31}P) in $CDCl_3$ at 30 °C. The chemical shifts of the protons are given relative to Me_4Si; the chemical shifts of the phosphorus atoms, relative to 85% phosphoric acid.

The electron ionization mass spectra were obtained on a Finnigan MAT-212 mass spectrometer (the electron current was 0.1 mA, the ionizing voltage was 60 V, the ion source temperature was 120 °C, direct inlet system, the temperature of the direct inlet probe was 60 °C). If the compounds under study did not give molecular ion peaks, the chemical ionization mass spectra were measured (pentane as the reagent gas). The compositions were determined by superposing the peaks of the reference compound with the peak of the molecular or protonated ion at the instrumental resolution of 7000. The optical rotation was measured on a Perkin—Elmer 341A polarimeter equipped with a sodium lamp (λ = 589 nm).

The physicochemical studies were performed in the Departments of NMR, X-ray Diffraction Methods, and Chromatographic Methods of Analysis of the Multiple-Access Center, the Spectroanalytical Center (SC SAC) for Physicochemical Investigations of Structure, Properties, and Composition of Substances and Materials, and the Federal Center for Collective Use of Physicochemical Investigations of Substances and Materials (FCCU PI) (State Contracts of the Ministry of Education and Science of the Russian Federation, Nos 02.451.11.7036 and 02.451.11.7019).

Menthyl diethyl phosphite (1). Pyridine (8.7 g, 0.11 mol) was added to a solution of *l*-menthol (15.6 g, 0.1 mol) in anhydrous benzene (150 mL) under argon with cooling to 0 °C. Then diethyl chlorophosphite (15.65 g, 0.1 mol) was added dropwise. The reaction mixture was stirred at −5—0 °C for 2 h. The precipitate of pyridine hydrochloride was filtered off, benzene was removed in vacuum, and the residue was distilled. Compound **1** was obtained in a yield of 17.2 g (62%), b.p. 126—128 °C (0.01 Torr), $[\alpha]_D^{20}$ −58.9 (*c* 0.54, $CHCl_3$). Found (%): C, 60.55; H, 10.50; P, 10.27. $C_{14}H_{29}O_3P$. Calculated (%): C, 60.87; H, 10.51; P, 10.69. ^{31}P NMR, δ: 138.65. ^{1}H NMR, δ: 3.82 (m, 4 H, $CH_3C\underline{H}_2OP$); 1.21 (t, 6 H, $C\underline{H}_3CH_2OP$, $^3J_{H,H}$ = 7.0 Hz); 0.87 and 0.83 (both d, 6 H, 2 Me_{Mnt}, *J* = 7.0 Hz); 0.78 (d, 3 H, C(9′)H_3, $^3J_{H,H}$ = 7.0 Hz).

Di-*O*,*O*-menthyl phenylphosphonite (2) was synthesized analogously to compound **1** from phenyldichlorophosphine (8.95 g, 0.05 mol), a solution pyridine (8.7 g, 0.11 mol) in anhydrous diethyl ether (100 mL), and a solution of *l*-menthol (15.6 g, 0.1 mol) in anhydrous diethyl ether (75 mL). Product **2** was isolated by silica gel column chromatography (chloroform as the eluent) in a yield of 10.1 g (47%) as a transparent oil, $[\alpha]_D^{20}$ −61.2 (*c* 0.62, $CHCl_3$). Found (%): C, 74.44; H, 10.28; P, 7.13. $C_{26}H_{43}O_2P$. Calculated (%): C, 74.64; H, 10.28; P, 10.41. ^{31}P NMR, δ: 159.27.

Methyl (ethoxy)(menthyloxy)phosphorylacetates 3a,b were synthesized by heating compound **1** (6.5 g, 0.02 mol) in a 5-fold excess of methyl chloroacetate (12.3 g, 0.11 mol) at 100 °C for 4 h. Then the excess methyl chloroacetate was removed under vacuum (10 Torr) at 100 °C. The reaction mixture (^{31}P NMR, δ: 17.94, 18.75 (the ratio of diastereomers was 2 : 3)) was purified by silica gel column chromatography. Elution with chloroform afforded diastereomer **3b** in a yield of 0.6 g (10%), m.p. 40 °C. ^{1}H NMR, δ: 4.27 (m, 1 H, H(3′)); 4.17 (m, 2 H, CH_2O); 3.72 (s, 3 H, OMe); 2.95 (d, 2 H, PCH_2, $^2J_{H,P}$ = 21.6 Hz); 2.22 (m, 1 H, H(2′)); 2.08 (m, 1 H, H(8′)); 1.65 (m, 2 H, H(5′), H(6′)); 1.44 (br.s, 1 H, H(1′)); 1.33 (m, 4 H, H(4′), Me); 1.18 (m, 1 H, H(2′)); 0.99 (m, 1 H, H(5′)); 0.91 (m, 6 H, C(7′)H_3, C(10′)H_3); 0.85 (m, 1 H, H(6′)); 0.79 (d, 3 H, C(9′)H_3, $^3J_{H,H}$ = 7.0 Hz). ^{13}C NMR, δ: 166.32 (d, C(3), $^2J_{P,C}$ = 6.6 Hz); 78.48 (d, C(3′), $^2J_{P,C}$ = 7.6 Hz); 62.85 (d, CH_2O, $^2J_{P,C}$ = 6.1 Hz); 52.34 (OMe); 48.39 (d, C(4′), $^3J_{P,C}$ = 6.6 Hz); 42.94 (C(2′)); 35.25 (d, PCH_2, $^1J_{P,C}$ = 135.3 Hz); 33.98 (C(6′)); 31.52 (C(1′)); 25.46 (C(8′)); 22.83 (C(5′)); 21.87 (C(7′)H_3); 20.83 (C(10′)H_3); 16.28 (d, Me, $^3J_{P,C}$ = 6.6 Hz); 15.61 (C(9′)H_3). ^{31}P NMR, δ: 18.72. Further elution with ethyl acetate gave a mixture of diastereomers **3a,b** in a yield of 2.9 g (46%) as a transparent oil. Found (%): C, 56.44; H, 9.10; P, 9.87. $C_{15}H_{29}O_5P$. Calculated (%): C, 56.25; H, 9.06; P, 9.68. MS, *m/z*: 321.18 $[M + H]^+$. ^{31}P NMR, δ: 17.94, 18.75 (1 : 3 ratio). ^{1}H NMR, δ: 4.03 (m, 2 H, $CH_3C\underline{H}_2OP$); 3.64 (s, 3 H, MeO); 2.95 (dd, 2 H, CH_2P, $^2J_{H,P}$ = 21.8 Hz); 1.28 (t, 3 H, $C\underline{H}_3CH_2OP$, $^3J_{H,H}$ = 7.0 Hz); 0.92 and 0.90 (both d, 6 H, 2 Me_{Mnt}, *J* = 7.0 Hz); 0.80 and 0.79 (both d, 1 : 3 ratio, 3 H, Me_{Mnt}, $^3J_{H,H}$ = 7.0 Hz).

Methyl (menthyloxy)(phenyl)phosphorylacetates 4a,b were synthesized by heating compound **2** (4.18 g, 0.01 mol) in a 10-fold excess of methyl chloroacetate (12.3 g, 0.11 mol) at 100 °C for 4 h. Then the excess methyl chloroacetate was removed under vacuum (10 Torr) at 100 °C. The reaction mixture (^{31}P NMR, δ: 32.90, 33.96 sh) was purified by silica gel column chromatography. Elution with chloroform afforded diastereomer **4b** in a yield of 1.4 g (40%). Found (%): C, 64.57; H, 8.14; P, 8.52. $C_{19}H_{29}O_4P$. Calculated (%): C, 64.73; H, 8.23; P, 8.80. MS, *m/z*: 352. ^{31}P NMR, δ: 33.96. ^{1}H NMR, δ: 7.48—7.82 (m, 5 H, Ph); 4.21 (m, 1 H, OCH_{Mnt}); 4.08 (s, 3 H, MeO); 3.61 (d, 2 H, CH_2P, $^2J_{H,P}$ = 18.2 Hz); 0.97 and 0.83 (both m, 6 H, 2 Me_{Mnt}); 0.45 (d, 3 H, Me_{Mnt}, $^3J_{H,H}$ = 7.0 Hz). Further elution with a 1 : 1 chloroform—ethyl acetate mixture gave a mixture of diastereomers **4a,b** in a yield of 0.7 g (20%) as an oil. ^{31}P NMR, δ: 32.90, 33.96 (3 : 5 ratio).

Menthyl (ethoxy)(menthyloxy)phosphorylacetates 5a,b were synthesized by refluxing compound **1** (5.52 g, 0.02 mol) with menthyl chloroacetate (6.95 g, 0.03 mol) in toluene (20 mL) in the presence of catalytic amounts of $ZnCl_2$ for 4 h. Volatile products were removed under vacuum (10 Torr) at 100 °C. The reaction mixture (^{31}P NMR, δ: 18.99, 19.21 (3 : 2 ratio)) was purified by silica gel column chromatography (chloroform as the eluent). A mixture of diastereomers **5a,b** was obtained in a yield of 5.7 g (64%) as a transparent oil. Found (%): C, 64.52; H, 10.12; P, 6.43. $C_{24}H_{45}O_5P$. Calculated (%): C, 64.86; H, 10.13; P, 6.76. MS, *m/z*: 445.3 $[M + H]^+$. ^{31}P NMR, δ: 18.81, 19.15 (1 : 1 ratio). ^{1}H NMR, δ: 4.63 and 4.21 (both m, 2 H, 2 OCH_{Mnt}); 4.08 (m, 2 H, $CH_3C\underline{H}_2OP$); 3.03 (d, 2 H, CH_2P, $^2J_{H,P}$ = 21.3 Hz); 1.28 (m, 3 H, $C\underline{H}_3CH_2OP$); 0.67, 0.72, and 0.74 (all d, 2 : 4 : 1 ratio, 3 H, Me_{Mnt}, $^3J_{H,H}$ = 7.0 Hz).

Menthyl diphenylphosphorylacetate (9). Ethylene oxide (4.05 g, 0.072 mol) was added to a solution of a mixture of diphenylchlorophosphine (5.3 g, 0.24 mol) and menthyl chloroacetate (8.9 g, 0.04 mol) in anhydrous benzene (20 mL) under dry nitrogen with cooling to −5—0 °C. The reaction mixture was kept at 5 °C for 15 min. Then the temperature was slowly raised to ~20 °C. The excess ethylene oxide was purged with dry nitrogen under atmospheric pressure for 0.5 h and then under vacuum (10 Torr) for 15 min. Then the temperature of the reaction mixture was slowly raised to 125 °C for 1 h, benzene being simultaneously distilled off. The reaction was completed after evacuation at 100—110 °C (10 Torr). An oil was obtained in an amount of 13.4 g (^{31}P NMR, δ: 35.80 (6.5%), 25.85 (93.5%)). The reaction mixture was purified by silica gel column chroma-

tography (chloroform as the eluent). After extraction with hexane, the eluted fraction crystallized out. Compound **9** was obtained in a yield of 3.76 g (71%), m.p. 63—65 °C. Found (%): P, 7.53. $C_{24}H_{31}O_3P$. Calculated (%): P, 7.79. ^{31}P NMR, δ: 25.96. ^{1}H NMR, δ: 7.71 and 7.44 (both m, 10 H, 2 Ph); 3.45 (d, 2 H, CH_2P, $^2J_{H,P}$ = 18.5 Hz); 4.52 (td, 1 H, OCH_{Mnt}, $^3J_{H,H}$ = 11 Hz, $^3J_{H,H}$ = 4.4 Hz); 0.77 and 0.74 (both m, 6 H, 2 Me_{Mnt}); 0.55 (d, 3 H, Me_{Mnt}, $^3J_{H,H}$ = 7.0 Hz). Further elution with a 3 : 1 chloroform—ethanol mixture afforded (2-chloroethyl)diphenylphosphine oxide (**12**) as a by-product of isomerization in a yield of 0.41 g (6.5%), m.p. 125—126 °C. Found (%): Cl, 12.78; P, 12.55. $C_{14}H_{14}ClOP$. Calculated (%): Cl, 13.42; P, 11.72. ^{31}P NMR, δ: 35.56.

Menthyl (ethyl)(phenyl)phosphorylacetates 10a,b. Ethylene oxide (1.6 g, 0.036 mol) was added to a solution of a mixture of phenylethylchlorophosphine (4.7 g, 0.017 mol) and menthyl chloroacetate (6.1 g, 0.026 mol) in anhydrous benzene (20 mL) under dry nitrogen with cooling to –5—0 °C. Then the synthesis was performed analogously to compound **9**. An oil was obtained in a amount of 8.45 g. ^{31}P NMR, δ: 39.30 (23%), 36.74 (60%), 36.40 (17%). The reaction mixture was purified by silica gel column chromatography. Elution with a 9 : 1 chloroform—ethanol mixture afforded a mixture of diastereomers **10a,b** in a yield of 3.56 g (60%). Found (%): P, 8.61. $C_{20}H_{31}O_3P$. Calculated (%): P, 8.85. ^{31}P NMR, δ: 36.40 (26%), 36.70 (74%). ^{1}H NMR, δ: 7.64 (m), 7.54 (t), 7.33 (m), 7.26 (t) (5 H, Ph, $^3J_{H,P}$ = 12.1 Hz, $^3J_{H,H}$ = 8.8 Hz); 4.40 (m, 1 H, OCH_{Mnt}); 2.98 and 2.95 (both d, 2 H, CH_2P, $^2J_{H,P}$ = 18.0 Hz); 2.02 and 1.90 (both q, 2 H, $PC\underline{H}_2CH_3$, $J_{H,H}$ = 7.0 Hz, $^2J_{H,P}$ = 14 Hz); 0.97 and 0.94 (both t, 3 H, $PCH_2C\underline{H}_3$, $J_{H,H}$ = 7.0 Hz); 0.65 and 0.58 (both m, 6 H, 2 Me_{Mnt}); 0.40 and 0.47 (both d, 1 : 3 ratio, 3 H, Me_{Mnt}, $J_{H,H}$ = 7.0 Hz). Further elution with a 1 : 1 chloroform—ethanol mixture gave (2-chloroethyl)(ethyl)(phenyl)phosphine oxide (**13**) in a yield of 0.6 g (17%). Found (%): Cl, 15.83; P, 13.97. $C_{10}H_{14}ClOP$. Calculated (%): Cl, 16.40; P, 14.32. ^{31}P NMR, δ: 39.03.

Menthyl [(2-chloroethoxy)(4-dimethylaminophenyl)phosphoryl]acetates 11a,b. A solution of menthyl chloroacetate (8.65 g, 0.037 mol) in anhydrous benzene (20 mL) was added to a solution of (4-dimethylaminophenyl)dichlorophosphine (6.8 g, 0.03 mol) in anhydrous benzene (20 mL). Then ethylene oxide (5.25 g, 0.12 mol) was added with stirring and cooling to 0—5 °C under dry nitrogen for 1 h at such a rate as to maintain the temperature of the reaction mixture no higher than 10 °C. Then the synthesis was performed analogously to compound **9**. The reaction mixture was obtained in a yield of 9.2 g (^{31}P NMR, δ: 36.68, 37.28 (1 : 16 ratio)), and diastereomer **11b** was isolated in a yield of 2.1 g (39%), m.p. 123—124 °C, $[\alpha]_D^{20}$ –34.7 (*c* 1.0, MeOH). Found (%): C, 57.62; H, 8.34; Cl, 8.20; N, 3.28; P, 6.81. $C_{22}H_{35}ClNO_4P$. Calculated (%): C, 57.52; H, 7.89; Cl, 8.00; N, 3.16; P, 6.99. MS, *m/z*: 443.3 $[M]^+$. ^{31}P NMR, δ: 37.28. ^{1}H NMR, δ: 7.68 (dd, 2 H, H(3), H(5), $^3J_{H,P}$ = 12.1 Hz, $^3J_{H,H}$ = 8.8 Hz); 6.90 (d, 2 H, H(2), H(6), $^3J_{H,H}$ = 7.7 Hz); 4.61 (td, 1 H, H(3′), $^3J_{H,H}$ = 11 Hz, $^3J_{H,H}$ = 4.4 Hz); 4.24 and 4.08 (both m, 2 H, $POCH_2$, $^3J_{H,P}$ = 12 Hz); 3.66 (m, 2 H, CH_2Cl); 3.12 (d, 2 H, PCH_2, $^3J_{H,P}$ = 18.3 Hz); 3.04 (s, 6 H, Me_2N); 1.80 (m, 2 H, H(2′), H(8′)); 1.62 (m, 2 H, H(5′), H(6′)); 1.39 (br.s, 1 H, H(1′)); 1.30 (tt, 1 H, H(4′), $^3J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 2.9 Hz); 0.97 (m, 1 H, H(5′)); 0.83 (m, 8 H, H(2′), H(6′), C(7′)H_3, C(10′)H_3); 0.68 (d, 3 H, C(9′)H_3, $^3J_{H,H}$ = 7.0 Hz). ^{13}C NMR, δ: 165.37 (d, C(3), $^2J_{P,C}$ = 4.8 Hz); 152.01 (br.s, C(7)); 133.50 (C(5), $^2J_{P,C}$ = 12.0 Hz); 116.49 (d, C(4), $J_{P,C}$ = 150.2 Hz); 112.84 (d, C(6), $^3J_{P,C}$ = 13.8 Hz); 64.11 (d, $POCH_2$, $^2J_{P,C}$ = 5.4 Hz); 42.64 (d, CH_2Cl, $^3J_{P,C}$ = 6.6 Hz); 40.90 (s, Me_2N); 38.94 (d, PCH_2, $J_{P,C}$ = 90.7 Hz); 75.54 (C(3′)); 46.65 (C(4′)); 40.49 (C(2′)); 34.07 (C(6′)); 31.28 (C(1′)); 25.74 (C(8′)); 23.09 (C(5′)); 21.87 (C(7′)H_3); 20.83 (C(10′)H_3); 16.01 (C(9′)H_3).

2-Chloroethyl (2-chloroethyl)(4-dimethylaminophenyl)phosphinate (14). Ethylene oxide (2 g, 0.048 mol) was added to a solution of (4-dimethylaminophenyl)dichlorophosphine (2.7 g, 0.012 mol) in anhydrous benzene (4 mL) under dry argon at 0 °C. The reaction mixture was kept at 0 °C for 0.5 h, warmed to ~20 °C, and stirred for 1 h. The excess ethylene oxide was removed by purging with dry nitrogen under atmospheric pressure followed by storage under vacuum using a water-jet pump. Then the reaction mixture was slowly warmed to 80—100 °C for 1 h, benzene being simultaneously distilled off. Silica gel column chromatography of the residue (chloroform—ethyl acetate, 1 : 1, as the eluent) afforded a viscous oil. Found (%): C, 44.93; H, 6.08; Cl, 22.40; N, 4.28; P, 9.27. $C_{12}H_{18}Cl_2NO_2P$. Calculated (%): C, 45.00; H, 5.62; Cl, 22.18; N, 4.37; P, 9.69. ^{31}P NMR, δ: 41.87. ^{1}H NMR, δ: 7.37 (dd, 2 H, *o*-H_{Ph}, $^3J_{H,P}$ = 12.1 Hz, $^3J_{H,H}$ = 8.8 Hz); 6.51 (d, 2 H, *m*-H_{Ph}, $^3J_{H,H}$ = 7.7 Hz); 3.98 and 3.76 (both m, 2 H, $POCH_2$, $^3J_{H,P}$ = 12.0 Hz); 3.44—3.46 (m, 4 H, CH_2Cl); 2.87 (s, 6 H, Me_2N); 2.25 and 2.15 (both m, 2 H, CH_2P, $^3J_{H,P}$ = 5 Hz).

X-ray diffraction study of compound 11b. Crystallographic data for compound **11b** at 20 °C: crystals of $C_{22}H_{35}ClNP$ are monoclinic, space group $P2_1$, a = 14.260(7) Å, b = 6.035(4) Å, c = 14.32(1) Å, β = 98.54(5)°, V = 1219(1) Å^3, Z = 2, M = 426.95, d_{calc} = 1.163 g cm^{-3}, $F(000)$ = 458. The intensities of 4257 reflections were measured on an Enraf Nonius CAD-4 diffractometer at 20 °C (λ(Cu-Kα), ω/2θ-scanning technique, θ_{max} < 78.4°), of which 2264 reflections were with $I > 3\sigma$. The intensities of three check reflections showed no decrease in the course of X-ray data collection. No absorption correction was applied, because no strong reflections with χ ≥ 80° were found for measuring ψ-scan curves required for the empirical absorption correction (μ(Cu) = 21.86 cm^{-1}). The structure was solved by direct methods using the SIR program[14] and refined first isotropically and then anisotropically. The hydrogen atoms were located in difference electron density maps. Their contributions to the structure amplitudes were taken into account in the final step of the refinement with fixed positional and isotropic thermal parameters. All calculations were carried out using the MOLEN program package[15,16] on an AlphaStation 200 computer. To establish the absolute structure and, consequently, the absolute configuration of the molecule, the direct and inverted structures were refined. The R factors were as follows: R = 0.068, R_w = 0.069 and R = 0.070, R_w = 0.071 for the direct and inverted structures, respectively. According to the Hamilton test,[17] the direct structure corresponds to the absolute structure with the probability of 95%. The final R factors were as follows: R = 0.068, R_w = 0.070 based on 1439 independent reflections with $F^2 \geq 3\sigma$.

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