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Synthesis of α-Trifluoromethyl-α-hydroxycarboxylate Dervatives and Their Phosphorus-Containing Analogs with the Use of Fluorinated Diazo Compounds

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Abstract—Approach was developed underlain by the use of fluorinated diazocompounds to the synthesis of derivatives of α-trifluoromethyl-α-hydroxycarboxylic acids and their phosphorus-containing analogs, α-trifluoromethyl-α-hydroxyphosphonic acids. Methyl 2-diazo-3,3,3-trifluoropropionate and diethyl 1-diazo-2,2,2-trifluoroethylphosphonate under the action of catalytic quantities of dirhodium tetraacetate $Rh_2(OAc)_4$ easily inserted into the O–H bond leading to the formation of the corresponding products in high yields.

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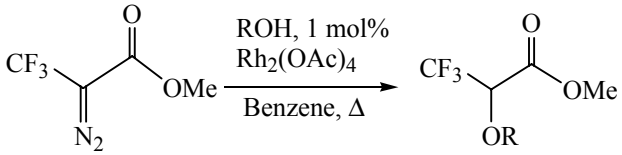
The introduction of fluorine or fluoroalkyl moieties into molecules of biologically active compounds is an important process in the development of new efficient drugs [1–4]. A special attention is attracted by the synthesis of trifluoromethyl-containing derivatives due to the unique properties of the trifluoromethyl group (hydrophobic character, high electronegativity, steric bulk) positively affecting the transport characteristics of the potential drugs. Besides the presence of a fluorine atom provides a possibility of monitoring the chemical surrounding of the fluorine-containing groups, of the conformational analysis, and of the study of metabolic processes by ^{19}F NMR spectroscopy. These unique features facilitated the fast development of the chemistry of biologically active organofluorine compounds, in particular, fluorinated α-hydroxy acids and their derivatives.

The phosphonic group (PO_3^{2-}) is the common structural fragment for a wide range of biologically active compounds and pharmaceuticals. Phosphonic acids and their derivatives are important analogs of the corresponding carboxylic acids. Their synthesis and biological activity is in the center of the interest of organic and pharmaceutical chemistry [5]. Many compounds of this class are haptenes in the enzyme-catalyzed formation of antibodies, they also exhibit activity as inhibitors of various proteolytic enzymes, wide range of physiological activity, in particular, antibacterial and antitumor ones [6].

It was shown previously that the simultaneous introduction of the trifluoromethyl and carboxylate or dialkylphosphonate groups was easily performed with the help of the corresponding trifluoromethylated carbenes, like $CF_3\ddot{C}O_2R$ [7] or $CF_3\ddot{C}P(O)(OR)_2$ [8]. The carbenes were formed from the appropriate diazo compounds under the action of catalytic quantities of derivatives of transition metals.

Isolated instances were published concerning the application of methyl-2-diazo-3,3,3-trifluoropropionate (**I**) to the insertion into the O–H bond by examples of amino acids [9] and phenol [10]. We considerably extended the applicability of this reaction bringing into this process various classes of hydroxyl-containing substrates, like carboxylic acids, aliphatic alcohols, phenols, and substituted amino acids. The chemical process was carried out with the catalysis by $Rh_2(OAc)_4$ (2–3 mol%). This catalyst is widely used in the chemistry of diazo compounds for it makes it possible to perform the reactions under mild conditions providing a high yield of

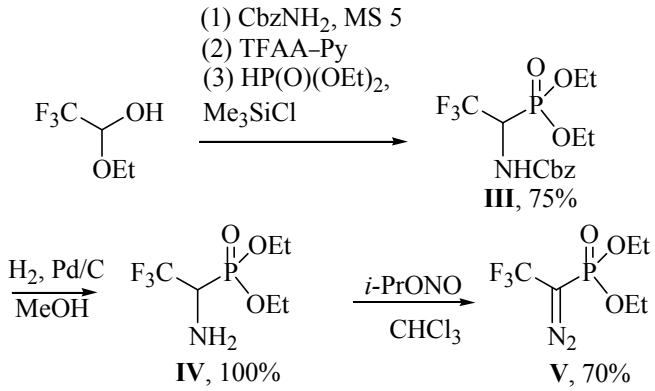
Scheme 1.



I **IIa–IId**

R = Bz (**a**), Ph (**b**), Bn (**c**), PhtNCH(*s*-Bu)C(O) (**d**).

Scheme 2.



Products of insertion into O–H bond of diazo compounds **I** and **V**

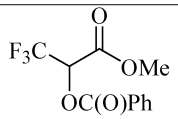
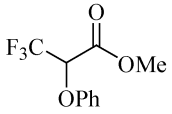
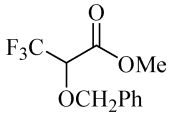
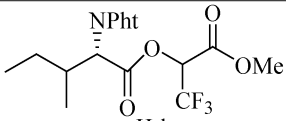
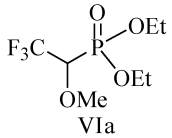
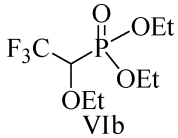
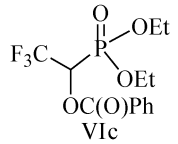
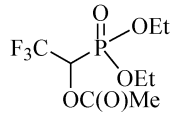
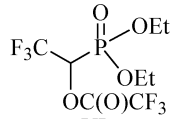
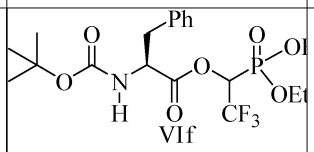
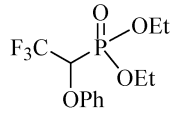
Run no.	Diazo compd.	ROH	Reaction product	Yield, %
1	I	PhC(O)OH	 IIa	74
2	**I**	PhOH	 IIb	79
3	**I**	$PhCH_2OH$	 IIc	85
4	**I**	Pht-i-Leu-OH	 IId	58
5	**V**	MeOH	 VIa	88

Table (Contd.)

Run no.	Diazo compd.	ROH	Reaction product	Yield, %
6	**V**	EtOH	 VIb	93
7	**V**	PhC(O)OH	 VIc	57
8	**V**	MeC(O)OH	 VId	57
9	**V**	$CF_3C(O)OH$	 VIe	86
10	**V**	BocPheOH	 VIf	69
11	**V**	PhOH	 VIg	82

the final products. In all studied cases we isolated insertion products **IIa–IId** in high yields (see Scheme 1, Table, runs nos. *1–4*).

We formerly prepared a phosphorus analog of compound **I**, diethyl 1-diazo-2,2,2-trifluorophosphonate (**V**), the first representative of fluorinated α-diazophosphonates [8]. We report here on the complete procedure of its synthesis. The method includes four simple stages: (1) The condensation of commercially available trifluoroacetic aldehyde ethylhemiacetal with benzyl carbamate; (2) diethyl phosphite addition to formed *in situ* fluoral N-benzyloxycarbonylimine in the presence of trimethylchlorosilane; (3) removal of Cbz-protection from diethyl aminophosphonate **III** in conditions of catalytic hydrogenation; (4) diazotization of α-aminophosphonate (**IV**) with isopropyl nitrite (Scheme 2).

In developing the key diazotization stage we tested the classic procedures like the treatment of compound **IV** with sodium nitrite in various mineral acids (hydrochloric, sulfuric) or in acetic acid. However in all studied events the yield of the target diazo compound did not exceed 25%. The best result was obtained by treating aminophosphonate **IV** with isopropyl nitrite. In this case we isolated trifluoromethyldiazophosphonate **V** in the analytically pure state in 70% yield. The product turned out to be stable light-yellow liquid boiling at 47–50°C (1 mm Hg). The developed synthesis of the new diazo compound was successfully scaled to 50 g.

In the course of further research we found that diazo compound **V** readily reacted with alcohols and carboxylic acids. The reaction completed within 5–10 h at boiling in benzene in the presence of catalytic quantities (1–3 mol%) of $Rh_2(OAc)_4$ giving the corresponding products of insertion into the O–H bond **VI** in good yields (see Scheme 3, Table, runs nos. *5–11*). The character of R substituent insignificantly affects the process.

The product of insertion in O–H bond of the trifluoroacetic acid **VIe** (see Table, run no. *9*) proved to be hydrolytically unstable; during the purification by column chromatography it lost the trifluoroacyl group and converted into the corresponding 2-hydroxy-3,3,3-trifluoroethylphosphonate.

Hence we developed a simple preparative method for the synthesis of derivatives of α-CF_3-substituted hydroxycarboxylates and hydroxyphosphonates by the reaction of α-CF_3-substituted diazocarboxylate **I** and diazophosphonate **V** under the catalysis with $Rh_2(OAc)_4$. A wide range of OH-containing substrates was brought into the reaction: alcohols, phenols, carboxylic acids, and substituted amino acids, and the corresponding insertion products were obtained in good yields.

EXPERIMENTAL

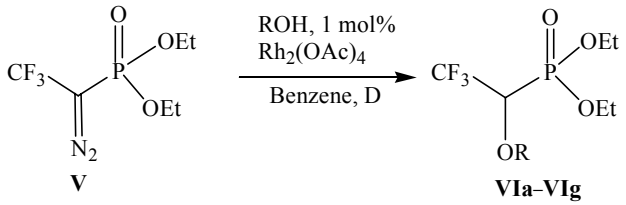
NMR spectra were registered on spectrometers Bruker AV-300 and AV-400 at operating frequencies 300 and 400 (^{1}H), 75 and 100 (^{13}C), 288 and 376 MHz (^{19}F) (internal reference $CFCl_3$); 121.5 and 162 MHz (^{31}P) (external reference H_3PO_4). All solvents used in the reactions were dried with appropriate drying agents. The reaction progress was monitored by TLC on plates with silica gel Merck 60 F_{254}. Spots were visualized by UV irradiation or by treating with cerium molibdate in 5% H_2SO_4 solution. The column chromatography was carried out on silica gel Merck 60 (230–400 mesh ASTM).

Synthesis of Diethyl 1-diazo-2,2,2-trifluoroethylphosphonate

1-(Benzyloxycarbonylamino)-2,2,2-trifluoroethanol [11]. To a solution of 20 g (132 mmol) of benzyl carbamate, 21 g (146 mmol) of trifluoroacetaldehyde ethylhemiacetal, and 6.6 g (61 mmol) of triethylamine in 200 ml of anhydrous CH_2Cl_2 was added 100 g of molecular sieves 5 A, and the reaction mixture was left standing at room temperature for 14 days. Then 100 ml of ethyl acetate was added, the molecular sieves were filtered off and thoroughly washed with ethyl acetate. The organic solutions were combined, the solvent was evaporated, the residue was recrystallized from CH_2Cl_2. Yield 29 g (88%), colorless crystals. ^{1}H NMR spectrum (CD_3CN), δ, ppm: 5.1 s (2H), 5.45–5.55 m (1H), 5.88–5.93 m (1H), 7.3 m (5H). ^{19}F NMR spectrum CD_3CN), δ, ppm: –4.5. The spectral data are in agreement with those formerly published [11].

Diethyl {1-[(benzyloxycarbonyl)amino]-2,2,2-trifluoroethyl}phosphonate (III) [12]. To a solution of 26 g(105 mmol)of the above prepared hemiaminal in 200 ml of anhydrous pyridine at –20°C was added 24.1 g (114 mmol) of trifluoroacetic anhydride. While maintaining the temperature of the reaction mixture at –20°C a solution was added of 28.8 g (209 mmol) of diethyl phosphite in 200 ml of CH_2Cl_2, and then was added dropwise 45.3 g (417 mmol) of trimethylchlorosilane. The mixture was gradually warmed to room temperature and left overnight at this temperature. The solution obtained was washed with 10% HCl for pyridine removal, then with saturated solution of $NaHCO_3$, and dried with $MgSO_4$. The solvent was evaporated, the residue was recrystallized from the mixture petroleum ether–ethyl acetate, 9:1 v/v. Yield 32.4 g (84%), colorless crystals, mp 53.5–56°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm:

Scheme 3.



V **VIa–VIg**

R = Me (**a**), Et (**b**), Bz (**c**), Ac (**d**), $CF_3C(O)$ (**e**), BocNHCH(Bn)C(O) (**f**), Ph (**g**).

1.25–1.45 m (6H), 4.1–4.3 m (4H), 4.7–4.9 m (1H), 5.2 d (2H, ^2J 12.1 Hz), 6.12 d (1H, ^2J 2 Hz), 7.4 m (5H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 8.2 t (J_{FP} 7.6 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 13.2 q (J_{FP} 6 Hz). The spectral data are in agreement with those formerly published [11].

Diethyl (1-amino-2,2,2-trifluoroethyl)phosphonate (IV). To a solution of 31 g (83 mmol) of benzyloxycarbonyl-substituted aminophosphonate **III** in methanol was added 2 g 10% Pd/C, and a weak flow of hydrogen was bubbled through the solution at room temperature. After the disappearance of the initial compound (TLC monitoring) (~12 h) the mixture was filtered, and the solvent was distilled off. The obtained oily substance was pure according to NMR data, and was used in the next study without additional purification. Yield 19.6 g (100%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.37 t (6H, ^2J 7.1 Hz), 2.76 br.s (2H), 3.61 m (1H), 4.18–4.31 m (4H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 6.2 t (J_{FP} 7.8 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 16.5 q (J_{FP} 7.4 Hz).

Diethyl (1-diazo-2,2,2-trifluoroethyl)phosphonate (V). To a solution of 19.6 g (83 mmol) of aminophosphonate **IV** in 300 ml of anhydrous chloroform was added dropwise 9.5 g (106 mmol) of isopropyl nitrite at vigorous stirring within 30 min. After adding about a half of the isopropyl nitrite the reaction mixture self-heated to boiling. After the end of addition the stirring was continued for another 30 min, and the temperature decreased to ambient. The solvent was evaporated on a rotary evaporator, the reaction product was distilled in a vacuum. Yield 13.6 g (70%). Yellow liquid, bp 47–50°C (1 mm Hg). IR spectrum (KBr), ν, cm^{-1}: 2160, 1150. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 t (6H, ^2J 7.1 Hz), 4.15–4.30 m (4H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.9, 63.6, 118.6 m, 124.1 d.q (J_{CF} 271.0, J_{CP} 12.1 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 23.0. ^{31}P ($CDCl_3$), δ, ppm: 9.23.

Insertion into O–H bond catalyzed with $Rh_2(OAc)_4$. General procedure. To a solution of 1.0 mmol of diazo compound **I** or **V** in 3 ml of anhydrous benzene was added 1.0–1.5 mmol of hydroxyl-containing compound and 1 mol% of dirhodium tetraacetate. The mixture was boiled for 3–5 h (TLC monitoring), thereafter the solvent was distilled off on a rotary evaporator. The residue was subjected to chromatography on silica gel (eluent ethyl acetate–petroleum ether, 1 : 5 v/v).

Methyl 2-benzoyloxy-3,3,3-trifluoropropanoate (IIa). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.91 s (3H), 5.74 q (1H, ^2J 6.7 Hz), 7.51 t (2H, ^2J 8.0 Hz), 7.67 t (1H, ^2J 8.0 Hz), 8.14 d (2H, ^2J 8.0 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 4.8 s. Found, %: C 50.45; H 3.50. $C_{11}H_9F_3O_4$. Calculated, %: C 50.39; H 3.46.

Methyl 2-phenoxy-3,3,3-trifluoropropanoate (IIb). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.90 s (3H), 5.03 q (1H, ^2J 6.8 Hz), 6.97 d (2H, ^2J 8.0 Hz), 7.12 t (1H, ^2J 6.0 Hz), 7.35 d.t (2H, $^2J_1$ 8.0, $^2J_2$ 6.0 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 3.7 s. Found, %: C 59.42; H 3.82. $C_{10}H_9F_3O_3$. Calculated, %: C 59.29; H 3.87.

Methyl 2-benzyloxy-3,3,3-trifluoropropanoate (IIc). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.85 s (3H), 4.35 q (1H, ^2J 6.7 Hz), 4.72 d (1H, ^2J 12.0 Hz), 4.85 d (1H, ^2J 12.0 Hz), 7.40 s (5H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 3.8 s. Found, %: C 53.25; H 4.50. $C_{11}H_{11}F_3O_3$. Calculated, %: C 53.23; H 4.47.

1-(Methoxycarbonyl)-2,2,2-trifluoroethyl-*N*-phthaloyl-L-isoleucinate (IId) was obtained as a mixture of diastereomers which was separated by column chromatography.

Diastereomer A. Oily substance, $[\alpha]_D^{25}$ –13.4° (*c* 1.37, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.89 t (3H, CH_3, ^2J 7.2 Hz), 1.09 m (1H, CH_2), 1.15 d (3H, CH_3, ^2J 7.9 Hz), 1.59 m (1H, CH_2), 2.58 m (1H, CH), 3.85 s (3H, OCH_3), 4.85 d (1H, CHN, ^2J 8.1 Hz), 5.41 q (1H, $CHCF_3$, ^2J 6.9 Hz), 7.76 m ($2H_{arom}$), 7.88 m ($2H_{arom}$). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 4.78. Mass spectrum: *m*/*z* 401 $[M]^+$.

Diastereomer B. Oily substance, $[\alpha]_D^{25}$ –3.5° (*c* 0.86, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 t (3H, CH_3, ^2J 7.4 Hz), 1.07 m (1H, CH_2), 1.14 d (3H, CH_3, ^2J 6.8 Hz), 1.60 m (1H, CH_2), 2.62 m (1H, CH), 3.75 s (3H, OCH_3), 4.83 d (1H, CHN, ^2J 8.7 Hz), 5.56 q (1H, $CHCF_3$, ^2J 7.2 Hz), 7.77 m ($2H_{arom}$), 7.90 m ($2H_{arom}$). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 4.88. Found, %: C 52.32; H 4.89; N 3.69. $C_{17}H_{18}F_3NO_6$. Calculated, %: C 52.44; H 4.62; N 3.60.

Diethyl (1-methoxy-2,2,2-trifluoroethyl)phosphonate (VIa). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 t (6H, ^2J 7.0 Hz), 3.65 s (3H), 3.78–3.9 m (1H), 4.2–4.3 m (4H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 6.7 t (J_{FP} 8.5 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 11.8 q (J_{FP} 8.9 Hz). Found, %: C 33.75; H 5.75. $C_7H_{14}F_3O_4P$. Calculated, %: C 33.61; H 5.64.

Diethyl (2,2,2-trifluoro-1-ethoxyethyl)phosphonate (VIb). Oily substance. ^{1}H NMR spectrum

($CDCl_3$), δ, ppm: 1.28 t (^2J 7.1 Hz), 1.38 t (6H, ^2J 7.1 Hz), 3.83 q (2H, ^2J 7.1 Hz), 3.86–4.0 m (1H), 4.17–4.3 m (4H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 6.55 t (J_{FP} 8.5 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 12.0 q (J_{FP} 8.9 Hz). Found, %: C 36.50; H 6.15. $C_8H_{16}F_3O_4P$. Calculated, %: C 36.37; H 6.10.

Diethyl (2,2,2-trifluoro-1-benzoyloxyethyl)-phosphonate (VIc). Oily substance. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.35 d.t (6H, $^2J_1$ 1.8, $^2J_2$ 7.1 Hz), 4.15–4.31 m (4H), 5.88–6.0 m (1H), 7.48–7.58 m (2H), 7.63–7.73 m (1H), 8.12–8.19 m (2H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 6.6 t (J_{FP} 7.4 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 9.7 q (J_{FP} 7.4 Hz). Found, %: C 46.07; H 4.81. $C_{13}H_{16}F_3O_5P$. Calculated, %: C 45.89; H 4.74.

Diethyl (2,2,2-trifluoro-1-acetoxyethyl)phosphonate (VId). Oily substance. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 d.t (6H, $^2J_1$ 2.7, $^2J_2$ 7.1 Hz), 2.23 s (3H), 4.20–4.32 m (4H), 5.65–5.8 m (1H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 7.2. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 9.8 q (J_{FP} 7.4 Hz). Found, %: C 34.62; H 5.11. $C_8H_{14}F_3O_5P$. Calculated, %: C 34.54; H 5.07.

Diethyl [2,2,2-trifluoro-1-(trifluoroacetyloxy)-ethyl]phosphonate (VIe). Yield 86% as shown by ^1H NMR spectrum. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 t (6H, ^2J 7.1 Hz), 4.25–4.45 m (4H), 5.75–5.85 m (1H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 7.3 t (J_{FP} 7.1 Hz), 3.25 C (3H). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 6.6.

2,2,2-Trifluoro-1-(diethoxyphosphoryl)ethyl-*N*-(*tert*-butoxycarbonyl)-L-phenylalaninate (VIf). Oily substance. Diastereomers mixture in the ratio 1:1. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.35–1.45 m (6H), 1.45 s (9H), 3.1 d.d.d (1H, $^2J_1$ 4.1, $^2J_2$ 6.4, $^2J_3$ 14.0 Hz), 3.28 d.t (1H, $^2J_1$ 5.5, $^2J_2$ 14.0 Hz), 4.20–4.37 m (4H), 4.78 m (1H), 4.98 m (1H), 5.68–5.83 m (1H), 7.20–7.30 m (2H), 7.30–7.41 m (3H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 7.63 t (J_{FP} 7.3 Hz), 7.84 t (J_{FP} 7.3 Hz), 1:1. ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 8.7 q (J_{FP} 7.4 Hz), 9.3 q (J_{FP} 7.4 Hz). Found, %: C 49.51; H 6.21; N 2.75. $C_{20}H_{29}F_3NO_7P$. Calculated, %: C 49.70; H 6.00; N 2.90.

Diethyl (1-phenoxy-2,2,2-trifluoroethyl)phosphonate (VIg). Oily substance. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 t (6H, ^2J 7.1 Hz), 4.2–4.4 m (4H), 4.88–5.0 m (1H), 7.05–7.15 m (3H), 7.4–7.5 m (2H). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 7.10 t (J_{FP} 8.2 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 10.6 q (J_{FP} 8.9 Hz). Found, %: C 46.27; H 5.21. $C_{12}H_{16}F_3O_4P$. Calculated, %: C 46.16; H 5.17.

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