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Synthesis of Ethyl 4,5-Bis(diethoxyphosphorylmethyl)-3-furoate

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Abstract—Preparative procedure for 4,5-bis(diethoxyphosphorylmethyl)-3-furoate from 4-chloromethyl-3-furoate is developed. It includes substitution of chlorine with iodine, phosphorylation by means of the Arbuzov reaction, chloromethylation of 4-(diethoxyphosphorylmethyl)-3-furoate in the position 5 of the furan ring, substitution of chlorine with iodine in the obtained chloromethyl derivative, and repeated phosphorylation with triethyl phosphite. It was found that ethyl 4-(diethoxyphosphorylmethyl)-5(chloromethyl)-3-furoate reacts with sodium diethyl phosphite by two pathways. Besides usual nucleophilic substitution leading to phosphonate, transfer of the reaction center in the position 2 of the furan ring takes place. The ambident diethylphosphite anion in this case reacts at the oxygen to give tertiary phosphite. The latter is oxidized with the air oxygen to form ethyl 2-(diethoxyphosphoryloxy)-4-(diethoxyphosphorylmethyl)-5-methyl-3-furoate. Unlike that analogous iodomethyl phosphonate is phosphorylated selectively under the conditions of the Arbuzov reaction.

Keywords: furoic acids, bis(phosphonates), chloromethylation, Finkelstein reaction, phosphorus nucleophiles

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Two neighboring dialkoxyphosphorylmethyl groups form the chelate unit which is capable of binding fairly bulky particles due to coordination with the P=O fragments. Recently we have developed the approaches to the preparation of 2-functionalyzed 3,4- and 4,5-bis(diethoxyphosphorylmethyl)furans and investtigated some of their transformations [1, 2]. Unlike that 3-functionalyzed bis(phosphonates) of the furan series are unknown up to now. At the same time 3-functionalyzed furans are widespread among the native products and play an important role in the life of plants and animals [3–6]. Therefore the synthesis of their analogs having phosphorus-containing chelate center seems promising for the search of new biologically active compounds.

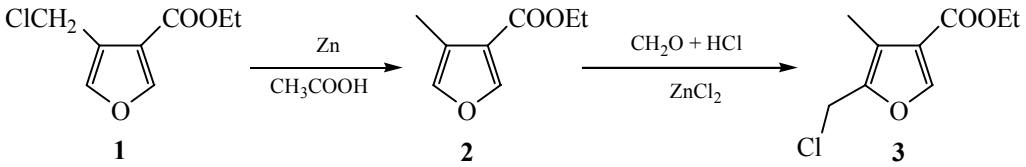
In the furan series building of definitely substituted compounds begins usually by preparing furylcarboxylates as the most available and stable compounds. In our case we have chosen the recently synthesized ethyl 4-chloromethyl-3-furoate **1** as the starting substance [7]. One more chloromethyl group can not be directly introduced in this substance. Therefore the first stage of the synthesis was the reduction of chloromethyl to methyl group under the action of zinc in 90% acetic acid analogously to [8]. 4-Methyl-3-furoate **2** was obtained in 62% yield as a colorless liquid of bp 111°C (15 mmHg). Details of the protocol and spectral characteristics are given in Experimental.

Ester **2** was subjected to chloromethylation. The reaction was carried out in dichloroethane at 25–30°C and the molar ratio of the furan, paraformaldehyde, and zinc chloride of 1 : 15 : 0.25. The substituent entered exclusively the position 5 of the furan ring. The target product **3** was prepared in 49% yield as an oil of bp 127–128°C (2 mmHg). In the ^{1}H NMR spectrum of this substance the signal of the furan ring proton H^5 at 7.18 ppm disappeared. Signal of chloromethyl group protons was observed at 4.59 ppm, and the signal of the corresponding carbon atom was located at 35.52 ppm (Scheme 1).

Chloromethylfuran **3** was phosphorylated by sodium diethyl phosphite in benzene at 80°C under the conditions of the Michaelis–Becker reaction. It was found that the substitution of chlorine proceeds much slower than even in furfuryl chloride. After refluxing for 10 h the conversion of chloride **3** was only 58%, and the yield of phosphonate **4**, 43%.

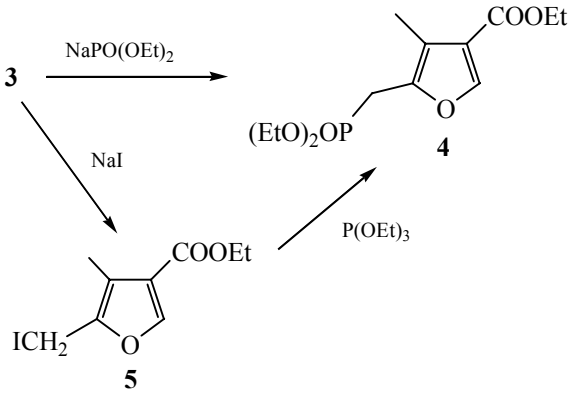
Finding a low activity of substrate under the conditions of the Michaelis–Becker reaction we decided to

Scheme 1.



use the Arbuzov reaction. For activation of the substrate **3** it was necessary to convert it to iodide **5**.

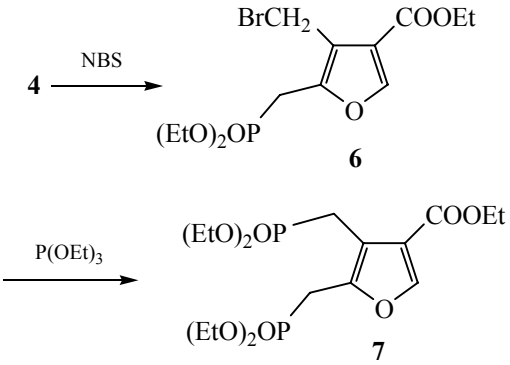
The halogen exchange was carried out at room temperature using the concentrated solution of sodium iodide dihydrate in acetone. Iodide **5** was isolated in 77% yield as colorless crystals of mp 51°C. Under the action of light these crystals liberate iodine and acquire grayish brown color in the course of 10–15 min. The dilute chloroform solutions of iodide **5** occurred to be especially light sensitive. Because of that we failed to obtain NMR spectra of this substance.



The synthesized compound **5** was as fast as possible brought in the reaction with triethyl phosphite. The liberation of ethyl iodide began at 130°C, and in the temperature range 130–175°C it completed in 10 min. The phosphonate **4** formed was isolated by vacuum distillation in 71% yield. The signal of phosphorus atom in the ^{31}P NMR spectrum of this compound was found at 22.84 ppm. Doublet of the methylene group protons in the ^{1}H NMR spectrum was observed at 3.16 ppm (J_{PH} = 20.4 Hz), and the doublet of the corresponding carbon atom appeared at 25.11 ppm ($^{1}J_{PC}$ = 143.5 Hz).

The bromination of phosphonate **4** was carried out with NBS in the presence of AIBN. It occurred unexpectedly that in the course of the reaction many side products are formed, but the formation of bromide **6** was traced spectroscopically. Signal of its phosphorus atom was observed at 21.26 ppm, the doublet of bromomethyl group protons was observed at 4.65 ppm (J_{PH} = 1.2 Hz), and the signal of the corresponding carbon atom at 25.11 ppm. Detailed spectral characteristics are listed in the Experimental.

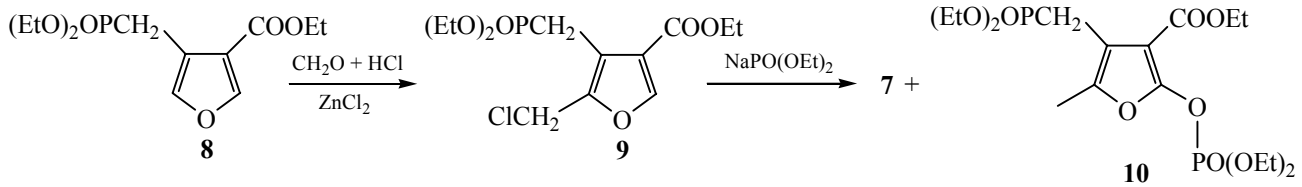
Treating of the obtained mixture with an excess of triethyl phosphite and heating the resulting mixture in the temperature range 130–175°C followed by removing the products of bp below 60°C (1mmHg) permitted to prepare comparatively pure diphosphonate **7** as a viscous syrup. Signals of phosphorus nuclei in the ^{31}P NMR spectrum appeared as doublets at 23.02 (P^5) and 26.54 ppm (P^4) with the coupling constant 18.1 Hz. Doublets of the methylene group protons were observed at 3.38 ppm (C^4H_2, J_{PH} = 20.8 Hz) and 3.41 ppm (C^5H_2, J_{PH} = 20.8 Hz). Signals of the corresponding carbon atoms were present at 20.55 ppm (C^4, $^{1}J_{PC}$ = 140.3 Hz) and 25.24 ppm (C^5, $^{1}J_{PC}$ = 141.7 Hz).



The established ambiguity of bromination of the phosphonate **4** forced us to try another path starting from the previously synthesized phosphonate **8** [7].

The first stage of this protocol was chloromethylation of compound **8** in dichloroethane at room temperature. Molar ratio of phosphonate, paraformaldehyde, and zinc chloride was 1 : 1.5 : 0.25. The reaction was carried out under the conditions of saturation of the reaction mixture with hydrogen chloride. The introduction of chloromethyl group occurred selectively in the position 5 of the furan ring. Diethoxyphosphoryl group proved to be surprisingly inert to the action of hydrogen chloride. It permitted to prepare chloromethyl derivative **9** in 79% yield as a light brown oil. Its structure was confirmed by the

Scheme 2.



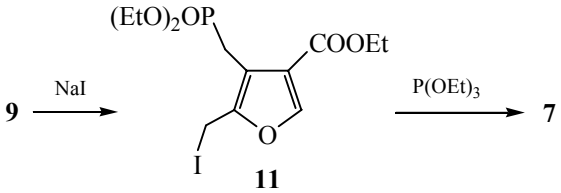
presence of the doublet of the chloromethyl group protons at 4.68 ppm (J_{PH} = 1.6 Hz) and of the signal of the corresponding carbon atom at 35.45 ppm in the ^{1}H and the ^{13}C NMR spectra respectively.

Chloromethylphosphonate **9** was involved in the reaction with sodium diethyl phosphite in benzene at 80°C. The phosphorylation proceeded for 19 h and lead to the formation of the diphosphonate **7** and the compound **10** having the phosphonate and the phosphate groups. Molar ratio of the compounds **7** and **10** was 2 : 1. In the ^{1}H NMR spectrum of compound **10** the doublet at 2.35 ppm (J_{PH} = 4.0 Hz) was present. Signal of corresponding carbon atom was found at 12.23 ppm. These data unambiguously proved that one of the positions in the furan ring was substituted with the methyl group. The signal of the phosphonate phosphorus nuclei in this compound was observed at 25.78 ppm. The methylene group protons gave a doublet at 3.21 ppm (J_{PH} = 21.2 Hz), and a doublet of the corresponding carbon atom was present at 21.75 ppm ($^1J_{PC}$ = 142.6 Hz). These data proved that the position 4 of the furan ring was occupied with diethoxyphosphorylmethyl group. The proton signal characteristic of H^2 in the furan ring was absent. Signal of the phosphate phosphorus was observed at 2.74 ppm. Its intensity was equal to the intensity of the phosphonate phosphorus signal. The obtained data permit to characterize compound **10** as 2-(diethoxyphosphoryloxy)-4-(diethoxyphosphorylmethyl)-5-methyl-3-furoate.

We observed recently the formation of phosphates in the Michaelis–Becker reaction for (1-chloroethyl)furans [9]. In these substances chlorine is easily eliminated as an anion, and in the carbocation formed the transition of the reaction center from the side chain into the conjugated position of the heteroring takes place. In (1-chloroethyl)furans polarization of C–Cl bond proceeds due to the donation of electronic density by the methyl group of the side chain. In the case found now, the role of electron-donating group is played by phosphorus-containing substituent in the adjacent position of the furan ring. Chlorine atom may be coordinated with phosphorus as well as with the phosphoryl group oxygen. In any case the transfer of electron density should occur through space (Scheme 2).

Ambiguity of phosphorylation of the chloride **9** under the Michaelis–Becker reaction conditions suggested to us to apply the Finkelstein reaction to convert it to iodide. Halogen exchange similarly to the above-mentioned case was carried out with sodium iodide dihydrate in acetone at room temperature in the absence of light. After keeping the reaction mixture for a night iodide **11** was isolated in 77% yield as a yellow syrup. The structure of the compound obtained was proved by the presence of a doublet of iodomethyl group protons at 4.50 ppm (J_{PH} = 1.6 Hz) and the signal of the corresponding carbon atom at –7.18 ppm. Unlike iodide **5** phosphonate **11** was slightly sensitive to the action of light. It may be probably connected with the presence of phosphorus-containing fragment in the structure of the molecule. Compound **11** is the first example of iodomethyl derivatives in the series of furylmethanephosphonates.

The introduction of the second diethoxyphosphoryl group was carried out by Arbuzov reaction. The mixture of iodide **11** and of excess triethyl phosphite was heated with stirring in the temperature range 90–170°C. Under these conditions the distillation off of ethyl iodide and some amount of triethyl phosphite took place. Total reaction time was 10 min. After distillation of triethyl phosphite and diethyl ethanephosphonate in a vacuum diphosphonate **7** was obtained in 98% yield.



Hence, new approach to the synthesis of 4,5-bis(diethoxyphosphorylmethyl)-3-furoates is developed. It makes this compound available for the use in the

organic synthesis with the purpose of obtaining phosphopylated analogs of native bioregulators. In this work chloromethylation of esters of the phosphonocarboxylic acids and the use of Finkelstein reaction for obtaining of iodomethyl derivatives of this class of substances is carried out for the first time. The latter occurred to be sufficiently stable though the light-sensitive compounds. They are of interest for further use in organic synthesis.

EXPERIMENTAL

Melting points were measured on the Boëtius apparatus. ^{1}H, ^{13}C, and ^{31}P NMR spectra were taken on a Bruker DPX-400 spectrometer [400.13 MHz (^{1}H), 161.97 MHz (^{31}P), and 100.16 MHz (^{13}C), respectively] in $CDCl_3$.

Ethyl 4-methylfuran-3-carboxylate (2). To a solution of 14.7 g of ethyl 4-chloromethylfuran-3-carboxylate **1** in the mixture of 43 mL of glacial acetic acid and 5 mL of water 15.3 g of zinc powder was added under the intense stirring. The obtained reaction mixture was heated to 45°C and then vigorous reaction accompanied with foaming took place. The temperature of the reaction mixture rose to 110°C. After the completion of heat evolution the reaction mixture was stirred for 15 h at 100°C and then poured in 150 mL of water. The target product was extracted with chloroform (4 × 20 mL), the extract was washed with water and dried over calcium chloride. Distillation in a vacuum gave 7.4 g (62%) of compound **2** as the fraction of bp 111°C (15 mmHg). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, CH_3-ethyl, J_{HH} = 7.2 Hz), 2.17 s (3H, CH_3-furan), 4.27 q (2H, CH_2O-ethyl, J_{HH} = 7.2 Hz), 7.18 s (1H, H^5-furan), 7.93 s (1H, H^2-furan). ^{13}C NMR spectrum δ_C, ppm: 9.01 (CH_3-furan), 14.22 (CH_3-ethyl), 60.00 (CH_2O), 118.90 (C^4-furan), 120.53 (C^3-furan), 140.91 (C^5-furan), 148.62 (C^2-furan), 163.74 (C=O).

Ethyl 4-methyl-5-(chloromethyl)furan-3-carboxylate (3). To a solution of 7.4 g of the ester **2** in 80 mL of dichloroethane 2.2 g of paraformaldehyde and 1.6 g of finely pulverized zinc chloride was added. Through the mixture obtained hydrogen chloride was passed under the intense stirring. The temperature of the reaction mixture was maintained in the range 25–30°C. After the completion of heat evolution the reaction mixture was stirred for 1.5 h at room temperature, washed with water (2 × 30 mL), dried over calcium chloride, and distilled in a vacuum. Yield of compound **3** 4.8 g (49%), bp 127–126°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3-ethyl, J_{HH} = 7.0 Hz), 2.25 s (3H, CH_3-furan), 4.30 q (2H, CH_2O-ethyl, J_{HH} = 7.2 Hz), 4.59 s (2H, CH_2Cl), 7.96 s (1H, H^2-furan). ^{13}C NMR spectrum, δ_C, ppm: 9.14 (CH_3-furan), 14.23 (CH_3-ethyl), 35.52 (CH_2Cl), 60.23 (CH_2O), 119.79, 119.96 (C^{3,4}-furan), 147.63 (C^5-furan), 148.22 (C^2-furan), 163.30 (C=O).

Ethyl 4-methyl-5-(iodomethyl)furan-3-carboxylate (5). (The target compound decomposes under the action of light. All operations were carried out with protection from light). A mixture of 1.7 g of chloride **3** and a solution of 1.7 g of sodium iodide dihydrate in 10 mL of acetone was left overnight at room temperature. On the next day the reaction mixture was poured in 40 mL of water, the product was extracted with chloroform (3 × 15 mL), the extract was washed successively with sodium sulfite solution and with water, and dried over calcium chloride. After removing the solvent 1.9 g (77%) of compound **5** was obtained. Colorless crystals, mp 51°C.

Ethyl 4-methyl-5-(diethoxyphosphorylmethyl)-furan-3-carboxylate (4). *a.* To a solution of sodium diethyl phosphite prepared from 0.6 g of sodium and 4.5 mL of diethyl hydrogen phosphite in 40 mL of benzene the solution of 4.8 g of chloride **3** in 5 mL of benzene was added in one portion. The mixture obtained was stirred for 10 h at 80°C. After that the reaction mixture was washed with water (2 × 10 mL) and dried over sodium sulfate. Distillation in a vacuum gave 2.0 g of chloride **3** of bp 110°C (1 mmHg) and 1.8 g of phosphonate **4** of bp 170–173°C (1 mmHg). Conversion of compound **3** 58%, yield of phosphonate **4** 43%. ^{1}H NMR spectrum, δ, ppm: 1.27 t (6H, CH_3-phosphohate, J_{HH} = 7.2 Hz), 1.31 t (3H, CH_3-ethyl, J_{HH} = 6.8 Hz), 2.15 d (3H, CH_3-furan, J_{PH} = 4.0 Hz), 3.16 d (2H, CH_2P, J_{PH} = 20.4 Hz), 4.05 d.q (4H, CH_2O-phosphonate, J_{HH} = 7.2 Hz, J_{PH} = 14.0 Hz), 4.25 q (2H, CH_2O-ethyl, J_{HH} = 6.8 Hz), 7.88 d (1H, H^2-furan, J_{PH} = 2.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 9.11 (CH_3-furan), 14.26 (CH_3-ethyl), 16.35 d (CH_3-phosphonate, $^{3}J_{PC}$ = 5.8 Hz), 25.01 d (CH_2P, $^{1}J_{PC}$ = 143.5 Hz), 60.03 (CH_2O-ester), 62.29 d (CH_2O-phosphonate, $^{2}J_{PC}$ = 6.4 Hz), 117.54 d (C^4-furan, $^{3}J_{PC}$ = 8.9 Hz), 119.64 d (C^3-furan, $^{4}J_{PC}$ = 3.0 Hz), 143.36 d (C^5-furan, $^{2}J_{PC}$ = 12.9 Hz), 147.14 d (C^2-furan, $^{3}J_{PC}$ = 2.7 Hz), 163.58 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 22.84.

b. The mixture of 1.9 g of iodide **5** and 2 mL of triethyl phosphite was heated with stirring. At 130°C

the distillation of ethyl iodide began which completed at 175°C. Total reaction time was 10 min. Distillation in a vacuum gave 1.4 g (71%) of phosphonate **4** of bp 171°C (1 mmHg). Spectral characteristics of this preparation were identical to the above-described.

Bromination of phosphonate 4 with *N*-bromosuccinimide. To the solution of 1.8 g of phosphonate **4** in 30 mL of carbon tetrachloride 1.2 g of NBS and 0.1 g of AIBN were added. The mixture obtained was refluxed under the intense stirring for about 2 h until the disappearance of the NBS crystals and was left overnight. On the next day succinimide was filtered off, the solvent was removed on the rotary evaporator, and the residue was kept in a vacuum (1 mmHg) for 1 h at room temperature. Light brown syrup, 2.0 g, was obtained. Its main component was **ethyl 4-(bromomethyl)-5-(diethoxyphosphorylmethyl)-3-furoate 6.** ^{1}H NMR spectrum, δ, ppm: 1.22–1.35 m (CH_3-phosphonate, CH_3-ethyl), 3.27 d (2H, CH_2P, J_{PH} = 20.8 Hz), 4.03–4.11 m (CH_2O-phosphonate), 4.25–4.30 m (CH_2O-ethyl), 4.65 d (2H, CH_2Br, J_{PH} = 1.2 Hz), 7.99 s (1H, H^2-furan). ^{13}C NMR spectrum, δ_C, ppm: 14.18 (CH_3-ethyl), 14.26 (CH_3-ethyl), 16.32 d (CH_3-phosphonate, $^3J_{PC}$ = 5.2 Hz), 25.11 (CH_2Br), 25.51 d (CH_2P, $^1J_{PC}$ = 143.0 Hz), 60.04 (CH_2O-ester), 62.71 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.0 Hz), 119.25 d (C^4-furan, $^3J_{PC}$ = 8.7 Hz), 120.00 d (C^3-furan, $^4J_{PC}$ = 3.9 Hz), 146.71 d (C^5-furan, $^2J_{PC}$ = 12.7 Hz), 147.66 d (C^2-furan, $^3J_{PC}$ = 1.5 Hz), 162.49 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 21.26.

Ethyl 4-(diethoxyphosphorylmethyl)-5-(chloromethyl)furan-3-carboxylate (9). To the solution of 2.6 g of ethyl 4-(diethoxyphosphorylmethyl)furan-3-carboxylate **8** in 30 mL of dichloroethane 0.4 g of paraformaldehyde and 0.3 g of finely pulverized zinc chloride were added under the intense stirring. Hydrogen chloride was passed through this mixture at room temperature under the intense stirring for 3 h. Then the mixture formed was stirred at room temperature for additional 3 h, washed with water (2 × 20 mL) and dried with sodium sulfate for a night. After removing the solvent the residue was kept in a vacuum (1 mmHg) for 1.5 h at room temperature. Yield 2.4 g (79%), light brown oil. ^{1}H NMR spectrum, δ, ppm: 1.22 t (6H, CH_3-phosphonate, J_{HH} = 7.0 Hz), 1.31 t (3H, CH_3-ethyl, J_{HH} = 7.2 Hz), 3.38 d (2H, CH_2P, J_{PH} = 21.6 Hz), 4.02 d.q (4H, CH_2O-phosphonate, J_{HH} = 7.0 Hz, J_{PH} = 14.8 Hz), 4.26 q (2H, CH_2O-ethyl, J_{HH} = 7.2 Hz), 4.68 d (2H, CH_2Cl, J_{PH} = 1.6 Hz), 7.93 s (1H, H^2-furan). ^{13}C NMR spectrum, δ_C, ppm: 14.22 (CH_3-ethyl), 16.27 d (CH_3-phosphonate, $^3J_{PC}$ = 6.0 Hz), 21.07 d (CH_2P, $^1J_{PC}$ = 141.0 Hz), 35.45 (CH_2Cl), 60.38 (CH_2O-ester), 62.20 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.5 Hz), 114.28 d (C^4-furan, $^2J_{PC}$ = 11.0 Hz), 119.02 d (C^3-furan, $^3J_{PC}$ = 2.9 Hz), 148.18 (C^2-furan), 149.69 d (C^5-furan, $^3J_{PC}$ = 8.7 Hz), 162.75 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 25.25.

Ethyl 4-(diethoxyphosphorylmethyl)-5-(iodomethyl)furan-3-carboxylate (11). To the solution of 6.8 g of sodium iodide dihydrate in a smal amount of acetone the solution of 8.9 g of chloride **9** in acetone was added. Total amount of acetone was 33 mL. The reaction mixture was kept at room temperature in the dark for a night. On the next day it was poured in 120 mL of water. The oil formed was extracted with chloroform (3 × 30 mL), washed with sodium sulfite solution until discoloration, then with water, and dried over sodium sulfate in the darkness. After removing of solvent the residue was kept in a vacuum (1 mmHg) for 1.5 h at room temperature. Yield 8.7 g (77%), yellow syrup. ^{1}H NMR spectrum, δ, ppm: 1.22 t (6H, CH_3-phosphonate, J_{HH} = 7.0 Hz), 1.29 t (3H, CH_3-ethyl, J_{HH} = 7.2 Hz), 3.30 d (2H, CH_2P, J_{PH} = 20.8 Hz), 4.02 d.q (4H, CH_2O-phosphonate, J_{HH} = 7.0 Hz, J_{PH} = 14.4 Hz), 4.25 q (2H, CH_2O-ethyl, J_{HH} = 7.2 Hz), 4.50 d (2H, CH_2I, J_{PH} = 1.6 Hz), 7.94 s (1H, H^2-furan). ^{13}C NMR spectrum, δ_C, ppm: –7.18 (CH_2I), 14.24 (CH_3-ethyl), 16.33 d (CH_3-phosphonate, $^3J_{PC}$ = 6.0 Hz), 21.74 d (CH_2P, $^1J_{PC}$ = 144.1 Hz), 60.37 (CH_2O-ester), 62.21 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.6 Hz), 112.77 d (C^4-furan, $^2J_{PC}$ = 10.8 Hz), 119.53 d (C^3-furan, $^3J_{PC}$ = 3.1 Hz), 147.56 (C^2-furan), 150.84 d (C^5-furan, $^3J_{PC}$ = 8.6 Hz), 162.71 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 24.29.

Reaction of ethyl 4-(diethoxyphosphorylmethyl)-5-(chloromethyl)furan-3-carboxylate (9) with sodium diethyl phosphite. To the solution of sodium diethyl phosphite prepared from 0.2 g of sodium and 1.6 mL of diethyl hydrogen phosphite in 30 mL of benzene the solution of 2.4 g of chloride **9** in 3 mL of benzene was added in one portion. The mixture formed was refluxed with stirring for 19 h at 80°C, washed with water (2 × 10 mL), and dried over sodium sulfate. After removing the solvent the residue was kept in a vacuum (1 mmHg) for 1 h at room temperature. The mixture of diphosphonate **7** and compound **10**, 2.0 g, was obtained. Molar ratio of components was 2 : 1. ^{1}H NMR spectrum, δ, ppm: common signals: 1.21–1.38 m (CH_3-ethyl), 4.00–4.10 m (CH_2O–P), 4.24–4.36 m (CH_2O–C); diphosphonate **7:** 3.41 d.d (P^4CH_2, J_{PH} =

20.4, 2.6 Hz), 3.45 d.d (P^5CH_2, J_{PH} = 21.2, 2.0 Hz), 7.90 br.s (H^2-furan); phosphate **10**: 2.35 d (CH_3-furan, J_{PH} = 4.0 Hz), 3.21 d (2H, CH_2P, J_{PH} = 21.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: common signals: 16.33 br.s (CH_3-phosphonate, CH_3-phosphate), 61.97 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.3 Hz), 62.32 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.5 Hz), 119.09 (C^3-furan); diphosphonate **7**: 14.25 (CH_3-ethyl), 20.60 d (P^4CH_2, $^1J_{PC}$ = 140.7 Hz), 25.30 d (P^5CH_2, $^1J_{PC}$ = 142.5 Hz), 60.22 (CH_2O-ester), 112.50 t (C^4-furan, $^2J_{PC}$ = $^3J_{PC}$ = 9.5 Hz), 145.97 d.d (C^5-furan, $^2J_{PC}$ = 12.0 Hz, $^3J_{PC}$ = 9.1 Hz), 147.23 d (C^2-furan, $^3J_{PC}$ = 2.0 Hz), 163.71 (C=O); phosphate **10**: 12.23 (CH_3-furan), 13.96 (CH_3-ethyl), 21.75 (P^4CH_2, $^1J_{PC}$ = 142.6 Hz), 61.11 (CH_2O-ester), 63.08 d (CH_2O-phosphate, $^2J_{PC}$ = 5.3 Hz), 111.94 d (C^4-furan, $^2J_{PC}$ = 9.5 Hz), 148.38 (C^2-furan), 155.54 (C^5-furan), 162.53 (C=O). ^{31}P NMR spectrum, δ_P, ppm: diphosphonate **7**: 26.60 d (P^4), 23.08 d (P^5), $^5J_{P4P5}$ = 18.2 Hz; phosphate **10**: 25.78 (P^4), 2.74 (P^2).

Ethyl 4,5-bis-(diethoxyphosphorylmethyl)furan-3-carboxylate (7). *a.* The preparation obtained by bromination of phosphonate **4** with NBS, 4.0 g, was mixed with 4 mL of triethyl phosphite, and the mixture obtained was gradually heated with stirring to 175°C. At 130°C distillation of ethyl bromide began which completed at 170°C. Total reaction time was 10 min. The fraction boiling in the range 30–55°C (1 mmHg) was distilled off, and the residue was kept at this residual pressure and the bath temperature 60–65°C for 30 min. Main component of the preparation obtained (3.8 g) was diphosphonate **7**. ^1H NMR spectrum, δ, ppm: 1.18–1.34 m (CH_3-ethyl), 3.38 br.d (P^4CH_2, J_{PH} = 20.8 Hz), 3.41 br.d (P^5CH_2, J_{PH} = 20.8 Hz), 3.98–4.06 m (CH_2O–P), 4.19-4.32 m (CH_2O–C), 7.86 br.s (H^2-furan). ^{13}C NMR spectrum, δ_C, ppm: 14.11 (CH_3-ethyl), 16.37 br.s (CH_3-phosphonate), 20.54 d (P^4CH_2, $^1J_{PC}$ = 140.3 Hz), 25.24 d (P^5CH_2, $^1J_{PC}$ = 141.7 Hz), 60.22 (CH_2O-ester), 62.01 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.6 Hz), 62.34 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.5 Hz), 112.44 t (C^4-furan, $^2J_{PC}$ = $^3J_{PC}$ = 9.6 Hz), 119.04 (C^3-furan), 145.91 d.d (C^5-furan, $^2J_{PC}$ = 11.8 Hz, $^3J_{PC}$ = 9.9 Hz), 147.21 d (C^2-furan, $^3J_{PC}$ = 2.2 Hz), 163.05 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 26.54 d (P^4), 23.02 d (P^5), $^5J_{P4P5}$ = 18.1 Hz.

b. The mixture of 8.7 g of iodide **11** and 6 mL of triethyl phosphite was gradually heated under the intense stirring. Distillation of ethyl iodide began at 90°C and completed at 165°C. The reaction mixture formed was heated to 170°C and then cooled. Total reaction time was 10 min. Triethyl phosphite and diethyl ethanephosphonate were distilled in a vacuum (1 mmHg) in the temperature range 30–65°C. The residue was diphosphonate **7**. Yield 7.8 g (98%), light yellow syrup. ^1H NMR spectrum, δ, ppm: 1.13–1.33 m (9H, CH_3-ethyl), 3.40 d.d (2H, P^4CH_2, J_{PH} = 20.4, 2.4 Hz), 3.44 d.d (2H, P^5CH_2, J_{PH} = 21.2, 2.0 Hz), 3.95–4.09 m (4H, CH_2O–P), 4.26 q (2H, CH_2O–C, J_{HH} = 7.2 Hz), 7.88 d (1H, H^2-furan, J_{PH} = 2.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.23 (CH_3-ethyl), 16.82 d (CH_3-phosphonate, $^3J_{PC}$ = 3.1 Hz), 20.58 d (P^4CH_2, $^1J_{PC}$ = 140.3 Hz), 25.29 d (P^5CH_2, $^1J_{PC}$ = 142.2 Hz), 60.19 (CH_2O-ester), 61.96 d (CH_2O-phosphonate, $^2J_{PC}$ = 6.1 Hz), 62.29 d (CH_2O-phosphonate, $^2J_{PC}$ = 5.9 Hz), 112.48 t (C^4-furan, $^2J_{PC}$ = $^3J_{PC}$ = 9.5 Hz), 119.07 br.s (C^3-furan), 145.95 t (C^5-furan, $^2J_{PC}$ = $^3J_{PC}$ = 10.1 Hz), 147.19 br.s (C^2-furan, 163.07 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 26.56 d (P^4), 23.04 d (P^5), $^5J_{P4P5}$ = 18.0 Hz.

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