Heteroatom Chemistry
Volume 9, Number 7, 1998

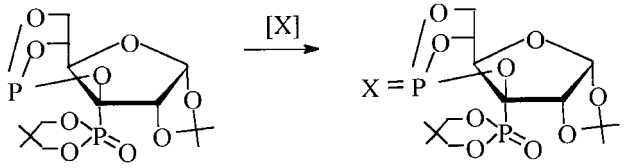
Study of Chemical Properties of Glucose 3,5,6-Bicyclophosphitophosphates

Edward E. Nifantiev, Mikhail P. Koroteev, Natal'a A. Zhukova, Larisa K. Vasyanina, Adam I. Stash, and Vitalii K. Bel'skii

Moscow Pedagogical State University, per. Nesvizhskii, Moscow, 119021, Russia

Received 26 March 1998; revised 16 June 1998

ABSTRACT: *A study has been made of oxidation, sulfurization, and other reactions of 3-*C*-phosphoryl-1,2-*O*-isopropylidene-α-*D*-glucofuranose 3,5,6-bicyclophosphites. Methods for the synthesis of new types of α-*D*-glucofuranose diphosphorus derivatives were proposed on the basis of these transformations.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9: 631–636, 1998



1 **2,3**

2 [X] = O2/hν **3** [X] = S_8

SCHEME 1

Previously, we developed a stereospecific method for the synthesis of 3-*C*-phosphoryl-1,2-*O*-isopropylidene-α-*D*-glucofuranoses from the corresponding ketosaccharides and silyl phosphites. On this basis, 3-*C*-dialkylphosphoryl-1,2-*O*-isopropylidene-α-*D*-glucofuranose 3,5,6-bicyclophosphites such as **1** were obtained [1,2]. In this article, we report special chemical characteristics of these bicyclophosphites in transformations involving a phosphobicyclic fragment.

It has been reported that only ozone successfully oxidizes phospholane-phosphinane bicyclophosphites of saccharides into bicyclophosphites [3]. We have now performed an oxidation of 3-*C*-neopentylenephosphoryl-1,2-*O*-isopropylidene-α-*D*-glucofuranose 3,5,6-bicyclophosphite (**1**) by oxygen under ultraviolet irradiation (Scheme 1).

The reaction was conducted in a methylene chloride solution contained in a quartz vessel at room temperature. The process was monitored by the use of TLC and ^{31}P-NMR spectroscopy. The signal at δ = 115 corresponding to the bicyclophosphite moiety disappeared within 2 hours, and a new signal close to δ = 10 arose, characteristic of 1,2-alkylideneglucofuranose 3,5,6-bicyclophosphates [4]. The δ ^{31}P from the phosphonate fragment remained essentially constant, confirming the structure of 3-*C*-neopentylenephosphoryl-1,2-*O*-isopropylidene-α-*D*-glucofuranose 3,5,6-bicyclophosphate (**2**). The yield of this new phosphate-phosphonate was 90–95%, but we failed to purify it because of its high lability. Therefore, **2** was used without additional purification.

The reaction of bicyclophosphitophosphonate **1** with sulfur proceeded under severe conditions in chlorobenzene at 140–150°C in a sealed ampoule (Scheme 1). The reaction was monitored by the use of ^{31}P-NMR spectroscopy. Within 26 hours, the signal of the tricoordinated phosphorus atom at δ = 115

Correspondence to: Edward E. Nifant'ev.
Dedicated to Prof. Robert R. Holmes on the occasion of his seventieth birthday.
© 1998 John Wiley & Sons, Inc. CCC 1042-7163/98/070631-06

had disappeared, and only two singlets at $\delta = 69$ and 3 were observed. The bicyclothionophosphate **3** was purified by column chromatography. Its structure was supported by ^{1}H- and ^{31}P-NMR spectroscopy and X-ray diffraction analysis (Figure 1, Tables 1 and 2). From the X-ray diffraction data, it follows that the dioxaphosphinane ring of the bicyclothionophosphate unit has a chair conformation; atoms P1, O3, C4, and C5 lie in one plane with a deviation of 0.03 Å; atoms O5 and C3 deviate from this plane by $+0.88$ and -0.28 Å, respectively. The phospholane ring of this fragment adopts an envelope conformation with the atom O5 deviating by 0.65 Å (the best coplanarity consisting of 0.02 Å for the C5C6O6P1 plane). The neopentylene moiety also has a chair conformation with the C12 and P2 atoms deviating by $+0.71$ and -0.22 Å, respectively. Atom O7 is equatorial. The carbohydrate furanose ring has an envelope conformation with the C2 atom deviating by 0.34 Å. The comparison between the X-ray data for the bicyclothionophosphate-phosphonate **3** and glucose 3,5,6-bicyclothionophosphate, obtained previously [5], reveals that both molecules have similar structures. The sole significant difference is observed for the P1O3C3 angle: Its value in **3** is 5.6°, larger than that in the bicyclothionophosphate. This is most likely related to the presence of a phosphonate fragment at the C3 atom in the molecule of **3**.

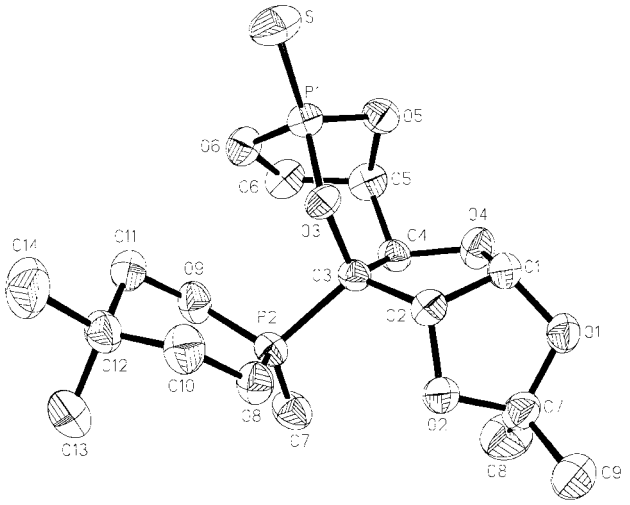


FIGURE 1

TABLE 1 Principal Lengths of Bonds [Å] and Angles [°] in the Molecule of **3**

S–P1	1.880(*2*)	*SP1O6*	*116.1*(*2*)
O6–P1	1.578(4)	SP1O5	119.6(2)
O3–P1	1.597(3)	SP1O3	112.6(1)
O5–P1	1.599(4)	P1O6C6	109.6(3)
O3–C3	1.460(5)	P1O3C3	122.4(3)
		P1O5C5	102.5(3)
		O6P1O5	98.0(2)
		O6P1O3	105.6(2)
		O3P1O5	102.9(2)

When bicyclophosphitophosphonate **1** reacts with hydrogen peroxide, the bicyclophosphite group undergoes fragmentation into a 3,6-cyclophosphate group. This process apparently proceeds via the formation of an intermediate bicyclophosphate **2**, because the reaction of the latter with water also gives the analogous 3-*C*-neopentylenephosphoryl-1,2-*O*-isopropylidene-*α*-*D*-glucofuranose 3,6-cyclophosphate (**4**) (Scheme 2).

When a dioxane solution of cyclophosphate **4** was treated with amines (e.g., *tert*-butylamine or cyclohexylamine), crystalline ammonium salts (**5** and **6**) were formed, the structures of which were supported by ^{1}H-, ^{13}C-, and ^{31}P-NMR spectroscopy data (Tables 2 and 3). Thus, the ^{31}P-NMR spectrum of ammonium salt **5** displayed doublets at $\delta = 6.3$ and -6.5 and $J_{PP} = 39.7$ Hz. It should be noted that no splitting of phosphorus signals was observed in the spectra of the initial compounds, which points to a geometrical difference between these vicinal diphosphorus systems. In the ^{13}C-NMR spectrum, $J_{C5\text{-}P}$ disappeared, which suggested the rupture of the O5–P bond in the reaction. In contradistinction to glucose 3,6-cyclophosphate, studied previously [3], no splitting of the C4 signal was observed. This phenomenon is indubitably associated with the different steric organization of the cyclophosphate fragment in the salt **5**.

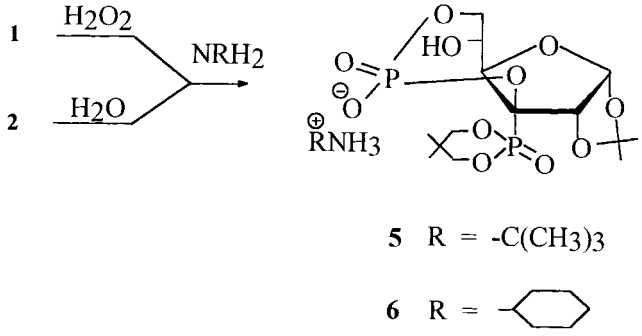
A different behavior of the bicyclophosphite function in **1** was observed for homolytic transformations, which formally follow the Arbuzov rearrangement. The reaction of bicyclophosphitophosphonate **1** with halogens or haloamines involves the rupture of the C6–O6 bond in the most strained phospholane ring, with the transformation of the 3,5,6-bicyclophosphite system into a 3,5-cyclophosphate (Scheme 3).

Thus, reactions with halogens gave 6-desoxy-6-halo-3-*C*-neopentylenephosphoryl-1-2-*O*-isopropylidene-*α*-*D*-glucofuranose 3,5-halocyclophosphates (**7**, **8**). Because of their instability, acid halides **7** and **8** were not isolated, and they were converted by reactions with amines and alcohols into readily identifiable derivatives. The reaction between **7** and piperidine afforded a mixture of *cis*- and *trans*-isomers in a 1:1 ratio (the similar chromatographic mobility of the isomers not permitting their separation by column chromatography); **8** gave only the *cis*-isomer under similar conditions, with preservation of the

TABLE 2 ^{1}H and ^{31}P NMR Chemical Shifts δ and Coupling Constants J (in Hz) of Compounds **3, 5, 9,** and **10.**

	P	*H1*	*H2*	*H4*	*H5*	*H6*	*H6′*	*H-protected groups*	*H-cyclic*	*He*	*Ha*	*other H*
3	69.8							1.36	0.97			
	3.2	6.18	4.82	5.14	5.04	4.46	4.15	1.60	1.42	4.10	4.42	
5								1.27				NH_2 8.51
	6.3							1.44	0.83			OH 5.41
	−5.5	6.20	4.96	5.06	4.37	4.10	3.47		1.28	3.96	4.77	$(CH_3)C$ 1.41
9	3.07							1.28	0.94			cyclohexyl 1.51,
	−5.94	6.15	4.93	4.83	4.27	4.41	4.13	1.51	1.35	4.03	4.90	3.11
10	3.66							1.25	0.97			cyclohexyl 1.54,
	−5.64	5.96	4.72	4.89	4.11	4.31	4.00	1.39	1.33	3.86	4.80	1.63, 3.12

	J PP	*J 1,2*	*J 4,5*	*J 5,6*	*J 5,6′*	*J 4,P1*	*J 4,P2*	*J 5,P*	*J 6,P*	*J 6′,P*	*J 6,6′*	*other J*
3		3.4	3.4	3.8	1.3	3.8	7.3	6.0	9.8	2.6	8.5	HaHe 10.2 HeP 11.1
5	39.7	3.9	<1	2.4	9.8		4.9		4.0	18.6	9.8	HaHe 10.3 HaP <1 HeP 17.5
9		3.8	2.6	3.8	9.8			19.6			10.7	HH 6.1; HP 9.8 (cyclohexyl) HaHe 10.5 HaP 3.0 HeP 14.9
10		3.9	1.7	4.9	9.8	3.9	4.4	13.7			10.3	HH 6.1; HP 9.8 (cyclohexyl) HaHe 7.3 HeP 12.7



5 R = -C(CH3)3

6 R =

SCHEME 2

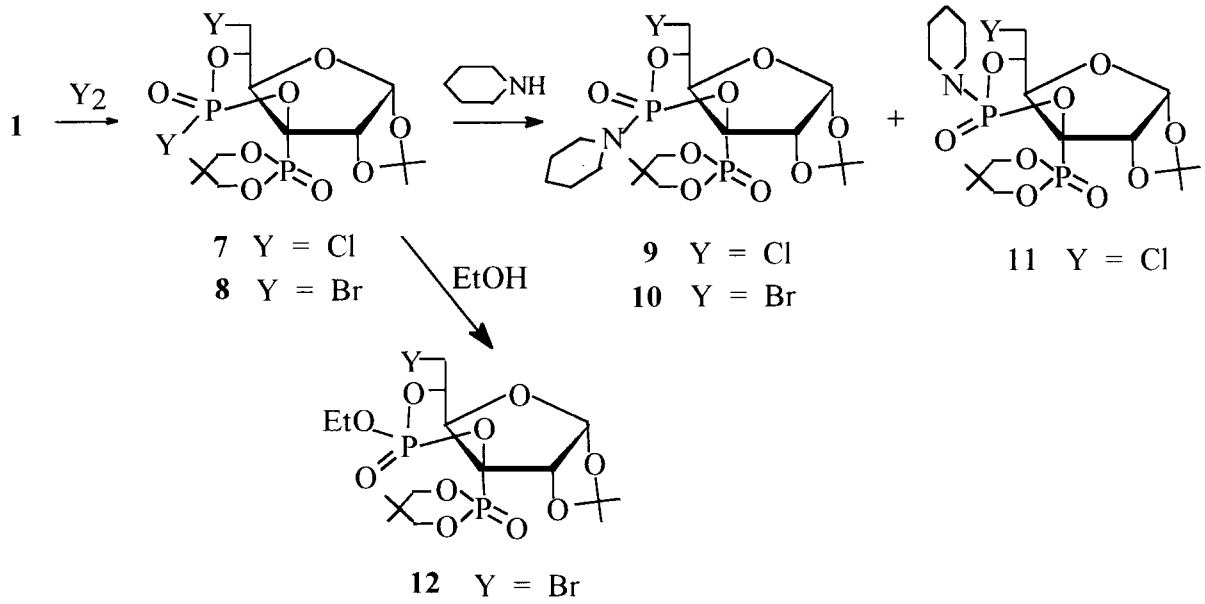
TABLE 3 ^{13}C NMR Data of Compounds 5 and 12: δ ^{13}C (J_{PC} in Hz)

	C1	*C2*	*C3*	*C4*	*C5*	*C6*
5	105.79	89.04	80.47	85.86	69.17	62.19
	(9.9)	(10.09)	(12.17, 13.15)	(0)	(0)	(5.76)
12	104.88	88.44	76.51	79.49	81.08	30.42
	(9.96)	(6.64)	(12.18, 35.42)	(7.30)	(8.05)	(10.10)

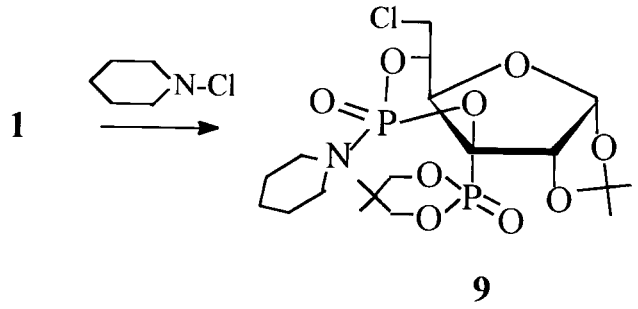
configuration that the cyclophosphate unit had in the initial acid bromide. The reaction between the acid bromide and ethanol, by contrast, was accompanied by the reversal of configuration to give the *trans*-ester (**12**). In contradistinction to acid halides of glucose studied previously [6,7], compounds **7** and **8** reacted with amines and alcohols in other ways.

The reaction between bicyclophosphitophosphonate **1** and *N*-chloropiperidine resulted in the formation of *cis*-6-desoxy-6-chloro-3-*C*-neopentylenephosphoryl-1,2-*O*-isopropylidene-*α*-*D*-glucofuranose 3,5-piperididocyclophosphate (**9**) (Scheme 4).

The structures of the amides and the ester were supported by ^{1}H-, ^{13}C-, and ^{31}P-NMR spectroscopy (Tables 2 and 3). The assignments of conformations for amides **9–11** and ester **12** were based on ^{31}P-NMR spectroscopic data. The spectrum of the initial acid halide had two *singlet* signals, at $\delta = 2$ (phosphonate unit) and -10 (halophosphate unit). The spectra of **9** and **10** also exhibited two singlets at $\delta = 3.7$ and -5.6 (**9**) and at 3.1 and -5.9 (**10**). The ^{31}P-NMR spectra of **11** and **12** were quite different. They displayed *doublets* at $\delta = 6.5$ and -3 with $^{3}J_{PP} = 20.32$ Hz (**11**) and at $\delta = 2.1$ and -12.8 with $^{3}J_{PP} = 5.81$



SCHEME 3



SCHEME 4

Hz (**12**). The appearance of these coupling constants suggests that the configurations of **11** and **12** differ from those of the initial halocyclophosphates (**7** and **8**) and amidocyclophosphates (**9** and **10**); that is, they are *trans*-compounds.

Thus, a conclusion can be drawn that the chemical properties of glucose bicyclophosphitophosphonates are similar to those of the glucose bicyclophosphites studied previously [3–7]. The presence of the second phosphorus atom in the molecule changes the configurations of the products of the reactions with amides and alcohols.

EXPERIMENTAL

All syntheses were performed under a dry nitrogen atmosphere. Column chromatography was effected on L 100/160 silica gel; TLC, on UV 254 Silufol plates using (a) benzene–dioxane 3:1 and (b) benzene–dioxane 1:1 as eluants. ^{1}H-NMR spectra were recorded on a Bruker WM-250 instrument; ^{31}P-NMR spectra were recorded on a Bruker WP-80 at 32.4 MHz (85% H_3PO_4 having been used as an external standard); ^{13}C-NMR spectra were recorded on a Bruker AC-200P at 50.3 MHz. The X-ray diffraction analysis was performed on a Syntex P1 instrument, Mo-K_α radiation. Prismatic colorless crystal of 3 ($C_{14}H_{22}O_9P_2S$, M = 513.24), size 0.50 × 0.50 × 0.20 mm, orthorhombic, space group $P2_12_12_1$, a = 7.8030 (10), b = 10.9250 (10), c = 26.522 (3) Å. V = 2260.9 (4) Å^3. Z = 4 (1.508 Mg/m^3). μ = 0.564 mm^{-1}, F(000) = 1064. $\theta/2\theta$ data collection, θ range 2.42–25.05° in $0 \le h \le 9$, $0 \le k \le 13$, $0 \le l \le 30$; independent reflections: 2223 (R_{int} = 0.0429); max./min. transmission, 0.8956/0.7657. Refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 2223/0/359, GoF on F^2 = 1.030, final R indices [l > 2θ(l)]: $k1$ = 0.0429, $wk2$ = 0.1038, largest difference peak/hole: 0.476/−0.344 c Å^{-3}.

*3-C-Neopentylenephosphoryl-1,2-*O*-isopropylidene-α-*D*-glucofuranose 3,5,6-Bicyclophosphate* (**2**). Synthesis was effected in a quartz vessel. Oxygen was passed through a solution of 100 mg (0.25 mmol) of bicyclophosphitophosphonate **1** in 5 mL of methylene chloride for 2 hours under ultraviolet irradiation. The yield of **2** was quantitative. R_f 0.52 (*b*).

*3-*C*-Neopentylenephosphoryl-1,2-*O*-isopropylidene-α-*D*-glucofuranose 3,5,6-Bicyclothionophosphate* (**3**). Sulfur (10 mg, 0.3 mmol) was added to a solution of 100 mg (0.25 mmol) of bicyclophos-

phitophosphonate **1** in 4 mL of chlorobenzene. The reaction mixture was heated in a sealed ampoule at 140–150°C for 26.5 hours. Next, the solvent was removed in vacuo, and the residue was chromatographed on a column fitted with silica gel with solvent system *a* as eluent. Yield was 80 mg (74%); mp 220–221°C; R_f 0.5 (a). Anal. calcd for $C_{14}H_{22}O_9P_2S$: C, 39.25; H, 5.14; P, 14.49; S, 7.48. Found: C, 39.38; H, 5.20; P, 14.41; S, 7.40.

N-*Alkylammonium Salts of 3,6-Cyclophosphate-3*-C-*neopentylenephosphoryl-1,2*-O-*isopropylidene-α*-D-*glucofuranose* (**5** *and* **6**): General Procedure. Five drops of 40% hydrogen peroxide were added to a solution of 100 mg (0.25 mmol) of bicyclophosphitophosphonate **1** in 6 mL of dioxane. After 1 hour, 0.25 mmol of the corresponding *N*-alkylamine was added to the dioxane solution. The precipitate that had formed was filtered off and washed with dioxane.

N-Tert-butylammonium Salt (**5**). Yield, 105 mg (82.7%); mp 218°C. Anal. calcd for $C_{18}H_{35}NO_{11}P_2$: C, 42.94; H, 6.96; P, 12.33. Found: C, 42.72; H, 7.12; P, 12.38.

N-Tert-cyclohexylammonium Salt (**6**). Yield, 105 mg (80.0%); mp 180°C. Anal. calcd for $C_{20}H_{31}NO_{11}P_2$: C, 45.89; H, 5.93; P, 11.85. Found: C, 45.80; H, 6.02; P, 11.70.

Cis(*trans*)*-6-desoxy-6-chloro-3-C-neopentylenephosphoryl-1,2-O-isopropylidene-α-D-glucofuranose 3,5-Piperididocyclophosphate* (**9, 11**). A solution of 35 mg (0.5 mmol) of chlorine in 2 mL of methylene chloride was added to a solution of 200 mg (0.5 mmol) of bicyclophosphitophosphonate **1** in 2 mL of methylene chloride under cooling (0–5°C) and stirring. The reaction mixture was heated to room temperature and stirred for 30 minutes. Then the reaction mixture was cooled to 0–5°C again, and 0.12 mL (1 mmol) of piperidine in 1 mL of methylene chloride was added dropwise. When the reaction had terminated, the solvent was evaporated in vacuo. The residue was dissolved in a small amount of eluent *b* and chromatographed on a column with silica gel. Yield (total), 200 mg (77.6%); R_f 0.25 (*a*).

Cis-6-desoxy-6-chloro-3-C-neopentylenephosphoryl-1,2-O-isopropylidene-α-D-glucofuranose 3,5-Piperididocyclophosphate (**9**). A solution of 30 mg (0.25 mmol) of *N*-chloropiperidine in 0.5 mL of methylene chloride was added to a solution of 100 mg (0.00025 mol) of bicyclophosphitophosphonate **1** in 3 mL of methylene chloride under cooling (0–5°C) and stirring. When the reaction had terminated, the solvent was evaporated in vacuo. The residue was dissolved in a small amount of eluent *b* and chromatographed on a column with silica gel. Yield 77 mg (60%); mp 110°C; R_f 0.3 (*a*). Anal. calcd for $C_{19}H_{32}ClNO_9P_2$: C, 44.23; H, 6.21; P, 12.03. Found: C, 44.50; H, 6.48; P, 11.85.

Cis-6-desoxy-6-bromo-3-C-neopentylenephosphoryl-1,2-O-isopropylidene-α-D-glucofuranose 3,5-Piperididocyclophosphate (**10**). A solution of 0.015 mL (0.25 mmol) of bromine in 0.5 mL of methylene chloride was added to a solution of 100 mg (0.25 mmol) of bicyclophosphitophosphonate **1** in 1 mL of methylene chloride under cooling (0–5°C) and stirring. The reaction mixture was heated to room temperature and stirred for 30 minutes. Then the reaction mixture was cooled to 0–5°C again, and 0.06 mL (0.5 mmol) of piperidine in 0.5 mL of methylene chloride was added dropwise. When the reaction had terminated, the solvent was evaporated in vacuo. The residue was dissolved in a small amount of eluent *a* and chromatographed on a column with silica gel. Yield, 42 mg (30%); mp 130°C; R_f 0.2 (*a*). Anal. calcd for $C_{19}H_{32}BrNO_9P_2$: C, 40.71; H, 5.71; P, 11.07. Found: C, 40.63; H, 5.86; P, 10.87.

Trans-6-desoxy-6-bromo-3-C-neopentylenephosphoryl-1,2-O-isopropylidene-α-D-glucofuranose 3,5-Ethylcyclophosphate (**12**). A solution of 0.015 mL (0.25 mmol) of bromine in 0.5 mL of methylene chloride was added to a solution of 100 mg (0.25 mmol) of bicyclophosphitophosphonate **1** in 3 mL of methylene chloride under cooling (0–5°C) and stirring. The reaction mixture was heated to room temperature and stirred for 30 minutes. Then the reaction mixture was cooled to 0–5°C again, and a solution of 0.023 mL (0.4 mmol) of ethanol and 0.04 mL of triethylamine in 1 mL of methylene chloride was added dropwise. The reaction mixture was kept at room temperature for 24 hours. When the reaction had terminated, the solvent was evaporated in vacuo. The residue was dissolved in a small amount of dioxane, filtered to remove triethylamine hydrochloride, concentrated, and chromatographed on a column with silica gel and eluent *a*. Yield, 78 mg (60%); syrup; R_f 0.42 (*a*). Anal. calcd for $C_{16}H_{27}BrNO_{10}P_2$: C, 36.85; H, 5.18; P, 11.90. Found: C, 36.90; H, 5.32; P, 11.76.

REFERENCES

[1] E. E. Nifantiev, M. P. Koroteev, N. A. Zhukova, A. R. Bekker, V. K. Bel'skii, L. K. Vasyanina, *Zh. Org. Khim., 32,* 1996, 1837.

[2] E. E. Nifantiev, M. P. Koroteev, N. A. Zhukova, V. K. Bel'skii, *Carbohydr. Lett.,* 1997, 229.

[3] E. E. Nifantiev, M. P. Koroteev, N. M. Pugashova, A. A. Borisenko, N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1986, 1917.
[4] M. P. Koroteev, E. E. Nifantiev, *Zh. Obshch. Khim., 63,* 1993, 481.
[5] M. P. Koroteev, N. M. Pugashova, A. R. Bekker, N. G. Magomedova, V. K. Bel'skii, A. M. Il'inets, E. E. Nifantiev, *Zh. Obshch. Khim., 60,* 1990, 2312.
[6] S. B. Kherbtova, M. P. Koroteev, N. M. Pugashova, A. R. Bekker, V. K. Bel'skii, A. I. Stash, A. A. Nazarov, A. R. Ignatenko, E. E. Nifantiev, *Zh. Obshch. Khim., 66,* 1996, 752.
[7] M. P. Koroteev, S. B. Kherbtova, A. R. Bekker, N. M. Pugashova, V. K. Bel'skii, A. Yu. Zotov, E. E. Nifantiev, *Zh. Obshch. Khim., 66,* 1996, 1615.