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Bis(2-chloroethyl) Ethenylphosphonate in the Diels–Alder Reaction

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Abstract — The diene synthesis reactions of bis(2-chloroethyl) ethenylphosphonate with 3-methyl-3-thiolene 1,1-dioxide that generates isoprene under the reaction conditions, as well as with 2,3-dimethylbuta-1,3-diene, cyclohexa-1,3-diene, cyclopentadiene, furan, and anthracene are studied. A series of cycloalkenyl- and heterylphosphonates derived from cyclohexene, bicyclooctene, norbornene, oxanorbornene, and 9,10-dihydro-9,10-ethanoanthracene are synthesized.

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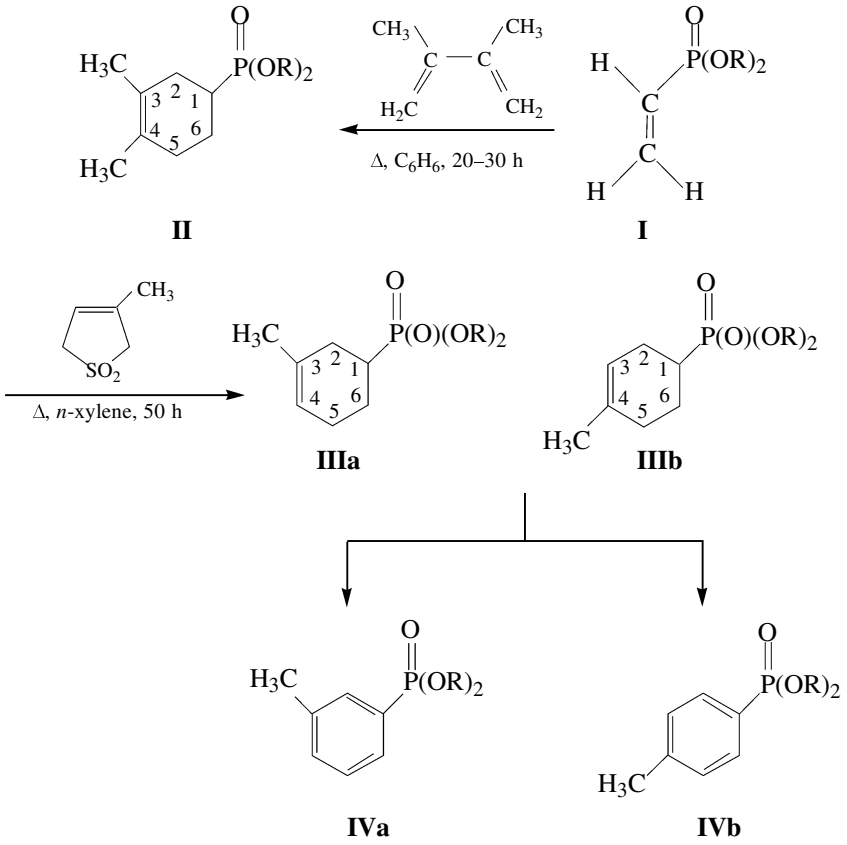
Vinylphosphonates are convenient starting reagents for the synthesis of a wide variety of organophosphorus compounds. They are used to prepare, in particular, nitroethenylphosphonates and their derivatives [1, 2] and phosphorylated carbo- [3–5] and heterocyclic compounds [6–8]. Cycloalkylphosphonates are interesting due to their broad-spectrum practical application. Representative of these compounds are used as insecticides [9], plasticizers [10], and intermediates in the synthesis of bioactive substances, including precursors of cyclic phosphonic acids [11–13].

One of convenient synthetic approaches to phosphorylated cyclic systems is a [π4 + π2] cycloaddition reaction in which vinylphosphonate derivatives act as dieno- or dipolarophiles. The synthesis of five-membered heterylphosphonates (pyrazolines, triazolines) by 1,3-dipolar cycloaddition of diazo compounds [6–8], phenyl azide, and other 1,3-dipoles to vinylphosphonates [14]. However, there have been few publications on diene condensations involving these dienophiles, and they are represented mostly by patents dating back to 1950–60s [5, 9, 10] and several articles in the periodic literature, describing the reactions of bis(2-chloroethyl) and diethyl ethenylphosphonates with butadiene and its methylated analogs (isoprene, piperylene and 2,3-dimethylbuta-1,3-diene) and of diethyl ethenylphosphonate with cyclopentadiene [3, 4]. It was noted that vinylphosphonates enter the Diels–Alder reaction under rigid conditions only: many-hour heating at high temperatures in an ampule or autoclave (150–200°C, 5–25 h) [3–5].

Our study of the reactions of bis(2-chloroethyl) ethenylphosphonate (**I**) with 3-methyl-3-thiolene 1,1-dioxide (isoprene precursor), furan, anthracene, an cyclopenta- and cyclohexadienes showed that this dienophile is capable of entering diene condensation reactions under much milder conditions than those described in [3–5]. Thus, vinylphosphonate **I**, in contrast to known data (autoclave, 150°C, 7–10 h, yield 36% [3, 4]) reacts with 2,3-dimethylbuta-1,3-diene even under reflux in benzene (20 h), affording (3,4-dimethylcyclohex-3-en-1-yl)phosphonate **II** in 64% yield; increase in the reaction duration to 30 h decreases the product yield to 30%, due, probably, to reversibility of the diene synthesis (Table 1).

Condensation of vinylphosphonate **I** with isoprene generated in situ from 3-methyl-3-thiolene 1,1-dioxide requires more rigid conditions (20 h, reflux in *p*-xylene) because of the increased desulfonylation temperature of the latter. Being an unsymmetrical diene, isoprene gave a mixture of regioisomeric [3- and (4-methylcyclohex-3-en-1-yl)phosphonates] **IIIa** and **IIIb**. According to the ^{1}H and ^{31}P NMR spectral data, the *meta/para* ratio **IIIa/IIIb** was 1 : 2 (total yield 55%). Along with cyclohexenes **IIIa** and **IIIb**, we detected in the reaction mixture regioisomeric *p*- and *m*-tolylphosphonates **IVa** and **IVb** (15%) whose formation can be attributed to intramolecular dehydrogenation of the initially forming cyclohexenes. Note that in the reaction of vinylphosphonate with isoprene in an autoclave (190°C, 15 h), Daniewski and Griffin [4] obtained regioisomeric cyclohexenes only. The aromatization of the latter to the corresponding isomeric arylphosphonates the referees observed upon additional heating of the cyclohexenes in nitrobenzene (150°C, 24–72 h) in the presence of a palladium catalyst.



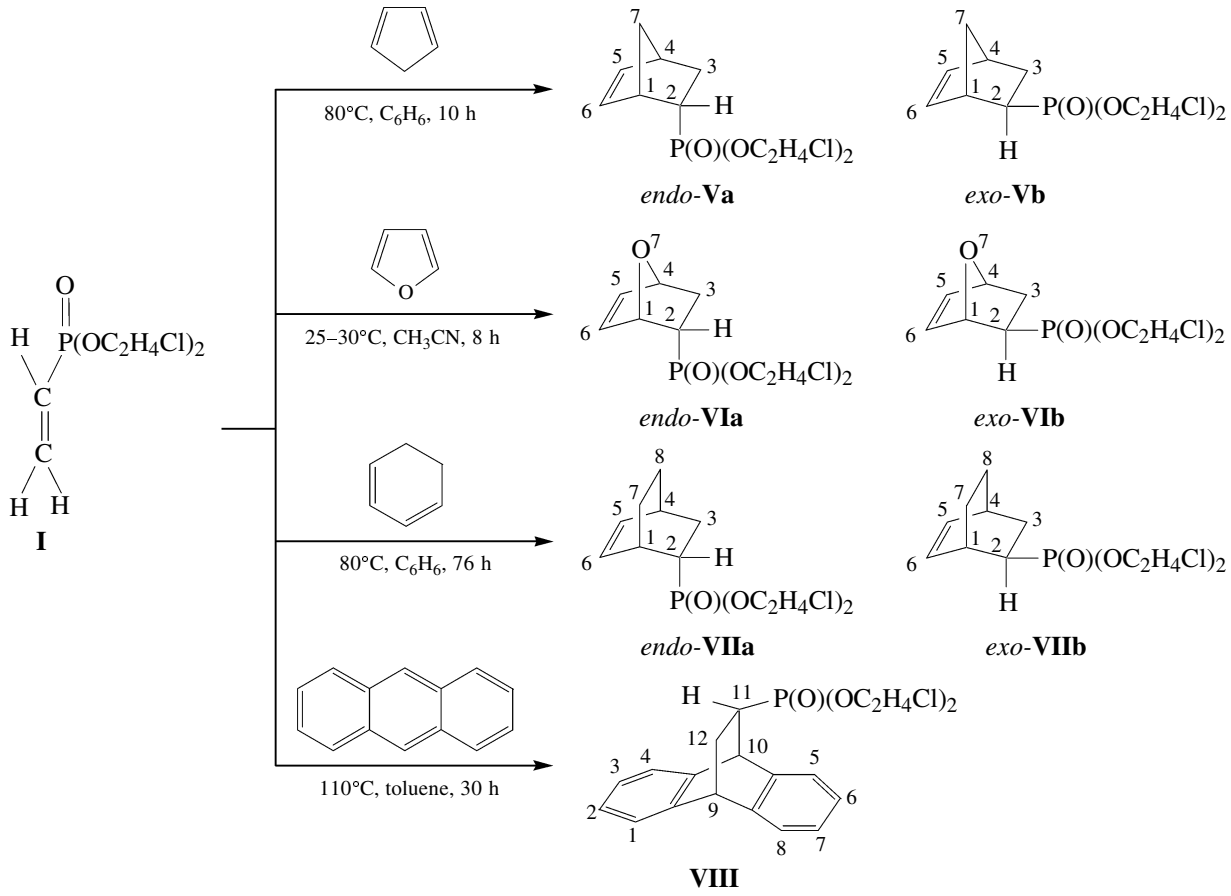
R = C_2H_4 (**I, II, IIIa, IIIb, IVa, IVb**).

The formation of two regioisomeric cyclohexenes **IIIa** and **IIIb** and arenes **IVa** and **IVb** is evidenced by the dubling of methyl proton signals and phosphorus signals in the ^1H and ^{31}P NMR spectra, respectively (Table 2). Cyclohexenes **IIIa** and **IIIb**, too, characteristically give double sets of methine H^1 and

Table 1. Yields, R_f values, and elemental analyses of phosphorylated carbo- and heterocycles **II–VIII**

Comp. no.	Yield, % (a : b)	R_f	Found, %			Formula	Calculated, %		
			C	H	P		C	H	P
II	64	0.38	45.59 45.53	6.60 6.57	10.43 10.46	$C_{12}H_{21}Cl_2O_3P$	45.71	6.67	9.84
IIIa, IIIb	55 (1 : 2)[a]	0.67 0.84	43.93 43.89	6.45 6.49	10.21 10.16	$C_{11}H_{19}Cl_2O_3P$	43.85	6.31	10.29
IVa, IVb	15 (1 : 2)[a]	0.32 0.39	44.23 44.29	5.25 5.28	10.51 10.55	$C_{11}H_{15}Cl_2O_3P$	44.40	5.05	10.44
Va, Vb	62 (1 : 1)	0.62 0.57	44.59 44.63	5.48 5.50	10.20 10.22	$C_{11}H_{17}Cl_2O_3P$	44.15	5.69	10.37
VIa, VIb	43 (1 : 1)	0.21 0.25	39.25 39.26	4.37 4.32	10.04 10.07	$C_{10}H_{15}Cl_2O_4P$	39.87	4.98	10.30
VIIa, VIIb	45 (3 : 1)	0.47 0.52	45.82 45.85	6.40 6.41	9.57 9.63	$C_{12}H_{19}Cl_2O_3P$	46.00	6.07	9.90
VIII	48	0.38	58.50 58.48	5.53 5.50	7.80 7.82	$C_{20}H_{21}Cl_2O_3P$	58.39	5.11	7.54

[a] For compounds **IIIa, IIIb, IVa**, and **IVb**, *meta/para* ratio (a : b) is given, and for other compounds, *endo/exo* ratio.



olefin $H^{3(4)}$ proton signals. The spectral parameters of compounds **IIIa, IIIb, IVa**, and **IVb** are consistent with those reported for their structural analogs [4].

Cyclopentadiene, being a more reactive diene, reacted with vinylphosphonate **I** in benzene under reflux (10 h) (published data [10]: 180°C, 16 h, autoclave) to form a mixture of diastereomeric *endo*- and *exo*-[bicyclo[2.2.1]hept-5-en-1-yl]phosphonates **Va** and **Vb** in a 1:1 ratio (^{1}H and ^{31}P NMR data) in a total yield of 62% (Table 1).

The reaction of dienophile **I** with furan proceeded at 25–30°C in acetonitrile (8 h) and provided [7-oxabicyclo[2.2.1]hept-5-en-1-yl]phosphonates **VIa** and **VIb** in a 1:1 ratio (yield 43%).

The diene condensation of vinylphosphonate **I** with cyclohexa-1,3-diene was accomplished by refluxing the reagent mixture in benzene for 76 h; the corresponding *endo*- and *exo*-[bicyclo[2.2.2]oct-5-en-1-yl]-phosphonates **VIIa** and **VIIb** were obtained in a 3:1 ratio with a total yield of 45% (Table 1).

The ^{1}H and ^{31}P NMR spectra of the products showed double sets of proton signals of the bicyclic

Table 2. IR and ^{1}H and ^{31}P NMR spectra of cyclohexenyl- and arylphosphonates **II, IIIa, IIIb, IVa**, and **IVb**

Comp. no.	^{1}H NMR spectra, δ, ppm ($CDCl_3$)								IR spectra, ν, cm^{-1}	
	CH_3	H^1	H^2	H^5, H^6	H^3 (H^4)	CH_2Cl	OCH_2	^{31}P	P=O	POC
II	1.60 s	2.20 m	1.70–2.0 m		–	3.65 m	4.12 m	34.5	1240	1033 1086
IIIa	1.65 s	2.70 m	1.80–2.39 m		(4.96 m)	3.68 m	4.23 m	33.0	1245	1030
IIIb	1.60 s	3.32 m	1.80–2.39 m		5.65 m			33.7		1080
IVa	2.0 s	–	6.40–6.80 m			3.70 m	4.30 m	30.0	1235	1030
IVb	1.95 s	–						29.2		1075

Table 3. IR and ^{1}H and ^{31}P NMR spectra of norbornenes **Va** and **Vb** and bicyclooctenes **VIIa** and **VIIb**

Comp. no.	^{1}H NMR spectra, δ, ppm ($CDCl_3$)										IR spectra, ν, cm^{-1}	
	H^1	H^2	H^3	H^4	H^5	H^6	H^7 (H^8)	CH_2Cl	OCH_2	^{31}P	P=O	POC
Va	2.47	3.00	2.15–2.25 m		5.65	5.78		3.71	4.25	34.0		
	$J_{1,2}$ 12.5,		$J_{2,3}$ 8.5,		$J_{1,6}$ 2.0,		1.65–				1236	1025
	J_{PH^2} 17.0		$J_{4,5}$ 1.7		$J_{5,6}$ 7.0		1.85 m					1080
Vb	2.58	2.93	2.15–2.25 m		5.53	5.73		3.73	4.27	35.0		
	$J_{1,2}$ 13.0		$J_{2,3}$ 6.5,		$J_{1,6}$ 2.0,							
			$J_{4,5}$ 1.7		$J_{5,6}$ 6.5							
VIa	4.98	3.60	2.95	4.75	6.25	6.45	–	3.72	4.28	33.0		
	$J_{1,2}$ 6.0,		$J_{2,3}$ 4.5,		$J_{1,6}$ 2.0,						1238	1032
	J_{PH^1} 16.0		$J_{4,5}$ 1.5		$J_{5,6}$ 7.0							1082
	J_{PH^2} 16.0				J_{PH^2} 4.0							
VIb	5.06	3.50	2.95	4.82	6.18	6.30	–	3.72	4.28	34.3		
					$J_{5,6}$ 8.0							
VIIa	2.30	2.55	2.0	2.0	5.05	5.63		3.68	4.37	33.0		
	$J_{1,6}$ 2.0		$J_{4,5}$ 1.5		$J_{5,6}$ 7.0		1.2–				1240	1030
VIIb	2.20	2.47	2.0	2.0	4.86	5.45	1.3 m	3.68	4.37	35.0		1086
	$J_{1,2}$ 13.0,		$J_{2,3}$ 6.0									
	J_{PH^1} 12.0,											
	J_{PH^2} 16.0											

carcass and phosphonate group and of phosphorus signals (Table 3). The signals to the *endo* and *exo* isomers were assigned on the basis of the ring methine H^2 and olefin $H^{5,6}$ proton signals located differently in the spectra of these isomers. As the analytical criterion for the assignment to the *endo*- or *exo*-series we used the chemical shifts of the methine protons on C^2, as accepted in the literature [15] for structurally related compounds. The difference in the chemical shifts of these isomers is due to the magnetically anisotropic double bond with respect to which the methine protons differ in spacial orientation. As follows from the data in Table 3, the signal of the *exo*-arranged H^2 proton in the *endo* isomer is commonly shifted downfield, while that in the *exo* isomer is typically shifted upfield (*endo* orientation of C^2–H) [15].

Anthracene, owing to its aromaticity, reacted with vinylphosphonate **I** under more rigid conditions: 30 h under reflux in toluene in the presence of $AlCl_3$. The process was completed by the formation of (9,10-dihydro-9,10-ethanoanthracen-11-yl)phosphonate (**VIII**) in 48% yield (Table 1).

The structure of compound **VIII** was established by a comparison of its ^{1}H and ^{31}P NMR spectra with those of similar compounds described in the literature [16]; in the spectrum of compound **VIII**, the aromatic protons appear as several multiplets in the range 7.1–8.1 ppm, the base protons $H^{9,10}$ resonate in the regions of 4.00 and 4.65 ppm, respectively, and the signals of the bridgehead protons $H^{11,12}$ appear at 3.50 and 3.30 ppm.

It is noteworthy that in each experiment 20 to 30% of unreacted vinylphosphonate **I** was isolated from the reaction mixture. This fact was also noted earlier [4] and is probably explained by a retrodiene process typical in rigid reaction conditions.

EXPERIMENTAL

The IR spectra were registered on an Infra-LYuM FT-2 spectrometer in chloroform (*c* 0.1–0.001 M). The ^{1}H and ^{31}P NMR spectra were registered on a Bruker AC-200 (200 MHz) instrument in deuterochloroform; the chemical shifts were measured in δ against external HMDS with an accuracy 0.5 Hz; the ^{31}P NMR spectra were measured against external 85% phosphoric acid. Separation and purification of the compounds was performed by means of preparative column chromatography on silica gel Chemapol (100/200 μm). The individuality of the compounds was checked and the reaction progress was monitored by TLC on Silufol UV-254 plates in hexane–acetone (3 : 2), developer iodine vapor. The compositions of the mixtures were determined by means of ^{1}H and ^{31}P NMR spectroscopy after column chromatography.

Commercial vinylphosphonate **I** was used in all reactions.

Bis(2-chloroethyl) (3,4-dimethylcyclohex-3-en-1-yl)phosphonate (II). To a solution of 1.5 g of bis(2-chloroethyl) ethenylphosphonate (**I**) in 5 ml of anhydrous benzene, 0.1 g of hydroquinone and 1.53 ml of 2,3-dimethylbuta-1,3-diene were added. The reaction mixture was refluxed for 20 h. The solvent was removed on a rotary evaporator, and the residue was subjected to chromatography on silica gel to obtain 1.7 g of a mixture of starting alkene **I** and cyclohexenylphosphonate **II** (eluent chloroform) in a 1 : 4 ratio. Repeated chromatography of the mixture gave 1.29 g (64%) of cyclohexene **II** (eluent chloroform) as a dark brown oil, R_f 0.38, n_D 1.5041 (published data [5]: n_D 1.5051, yield 36%).

Bis(2-chloroethyl) [3(4)-methylcyclohex-3-en-1-yl]phosphonate (IIIa, IIIb) and bis(2-chloroethyl) [3(4)-methylphenyl]phosphonates (IVa, IVb). To a solution of 0.56 g of bis(2-chloroethyl) ethenylphosphonate (**I**) in 5 ml of anhydrous p-xylene, 0.1 g of hydroquinone and 0.63 g of 3-methyl-3-thiolene 1,1-dioxide were added; the reaction mixture was refluxed with stirring for 20 h. The solvent was then removed on a rotary evaporator, and the residue was subjected to chromatography on silica gel to obtain 0.17 g (30%) of starting vinylphosphonate **I** (eluent benzene), 0.40 g (55%) of cyclohexenylphosphonates **IIIa** and **IIIb** (eluent chloroform) as a brown oil, R_f 0.67 and 0.84, and 0.11 g (15%) of arylphosphonates **IVa** and **IVb** (eluent ether) as a brown oil with R_f 0.32 and 0.39.

Bis(2-chloroethyl) [bicyclo[2.2.1]hept-5-en-2-yl]-phosphonates (Va, Vb). To a solution of 1.5 g of bis-(2-chloroethyl) ethenylphosphonate (**I**) in 5 ml of anhydrous benzene, 0.1 g of hydroquinone and 0.86 g of cyclopentadiene were added. The reaction mixture was refluxed for 10 h. The solvent was removed on a rotary evaporator, and the residual oil was subjected to chromatography on silica gel to obtain 1.65 g of a mixture of vinylphosphonate **I** and isomeric nonbornenes **Va** and **Vb** (eluent benzene) (**I**:**Va**,**Vb** ratio 1 : 5). Repeated chromatography of the mixture of compounds **I** and **Va**, **Vb** gave 1.18 g (62%) of a mixture of diastereomers **Va** and Vb (eluent chloroform) as an oil, R_f 0.62 and 0.57.

Bis(2-chloroethyl) [7-oxabicyclo[2.2.1]hept-5-en-2-yl]phosphonates (VIa, VIb). To a solution of 0.5 g of vinylphosphonate **I** in 5 ml of acetonitrile, 0.28 g of furan was added. The reaction mixture was heated for 10 h at 30–35°C, the solvent was removed, and the residue was subjected to chromatography on alumina. From the fraction washed out with carbon tetrachloride, 0.5 g of a mixture of starting vinylphosphonate **I** and oxanonbornenes **VIa** and **VIb** was isolated. Repeated chromatography of the mixture of compounds **I**, **VIa**, and **VIb** gave 0.27 g (43%) of a mixture of isomers **VIa** and **VIb** (eluent benzene), R_f 0.21 and 0.25.

Bis(2-chloroethyl) [bicyclo[2.2.2]oct-5-en-2-yl]-phosphonate (VIIa, VIIb). To a solution of 1.8 g of vinylphosphonate **I** in 5 ml of absolute *p*-xylene, 0.1 g of hydroquinone and 1.23 g of 1,3-cyclohexadiene were added. The reaction mixture was refluxed for 76 h. The solvent was removed on a rotary evaporator, and the residue was subjected to chromatography on silica gel. From the fraction washed out with carbon tetrachloride, 1.5 g of a mixture of starting vinylphosphonate **I** and bicyclooctenes **VIIa** and **VIIb** was isolated. Repeated chromatography of the mixture of compounds **I, VIIa**, and **VIIb** gave 1.09 g (45%) of a mixture of isomers **VIIa** and **VIIb** (eluent carbon tetrachloride) as an oil, R_f 0.47 and 0.52.

Bis(2-chloroethyl) (9,10-dihydro-9,10-ethanoanthracen-11-yl)phosphonate (VIII). To a solution of 0.5 g of vinylphosphonate **I** in 5 ml of anhydrous toluene, 0.1 g of hydroquinone and 0.37 g of anthracene were added. The reaction mixture was refluxed for 30 h. The solvent was removed on a rotary evaporator, and the residue was subjected to chromatography on silica gel to isolate 0.70 g of a mixture of starting vinylphosphonate **I** and ethanoanthracene **VIII** (eluent chloroform) in a 1 : 5 ratio. Repeated chromatography of the mixture of compounds **I** and **VIII** gave 0.41 g (48%) of compound **VIII** as a dark brown oil, R_f 0.38. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.65 (1H, H^{10}, $J_{10,11}$ 4.0, $J_{PH^{10}}$ 12.0 Hz), 3.50 (1H, H^{11}, $J_{10,11}$ 4.0, $J_{PH^{11}}$ 18.0, $J_{11,12}$ 4.0 Hz), 3.30 (2H, H^{12}, $J_{11,12}$ 4.0, $J_{9,12}$ 5.1, $J_{PH^{12}}$ 16.0 Hz), 4.00 (1H, H^9, $J_{9,12}$ 5.1 Hz), 7.1–8.1 m (8H, H^{1-4}, H^{5-8}), 4.28 (4H, OCH_2), 3.70 (4H, CH_2C^1). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 35.0. IR spectrum ($CHCl_3$), ν, cm^{-1}: 1248 (P=O), 1028, 1081 (P–O–C).

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