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Dedicated to the 110th anniversary of M.I. Kabachnik's birth

New Possibilities of the Kabachnik–Fields and Pudovik Reactions in the Phthalocyanine-Catalyzed Syntheses of α-Aminophosphonic and α-Aminophosphinic Acid Derivatives

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Abstract—The results of systematic studies demonstrated wide possibilities of the three-component Kabachnik–Fields and two-component Pudovik reactions catalyzed by metal phthalocyanines in the synthesis of structurally diverse α-aminophosphonates. Extension of this catalytic method to the synthesis α-aminophosphinates gave rise to a series of α-amino- and α-hydrazinophosphinates based on biogenic amino acids. A number of α-hydrazinophosphonates showed a good antioxidant activity.

Keywords: α-aminophosphonic acids, α-aminophosphinates, α-hydrazinophosphonates, α-hydrazinophosphinates, biogenic amino acids

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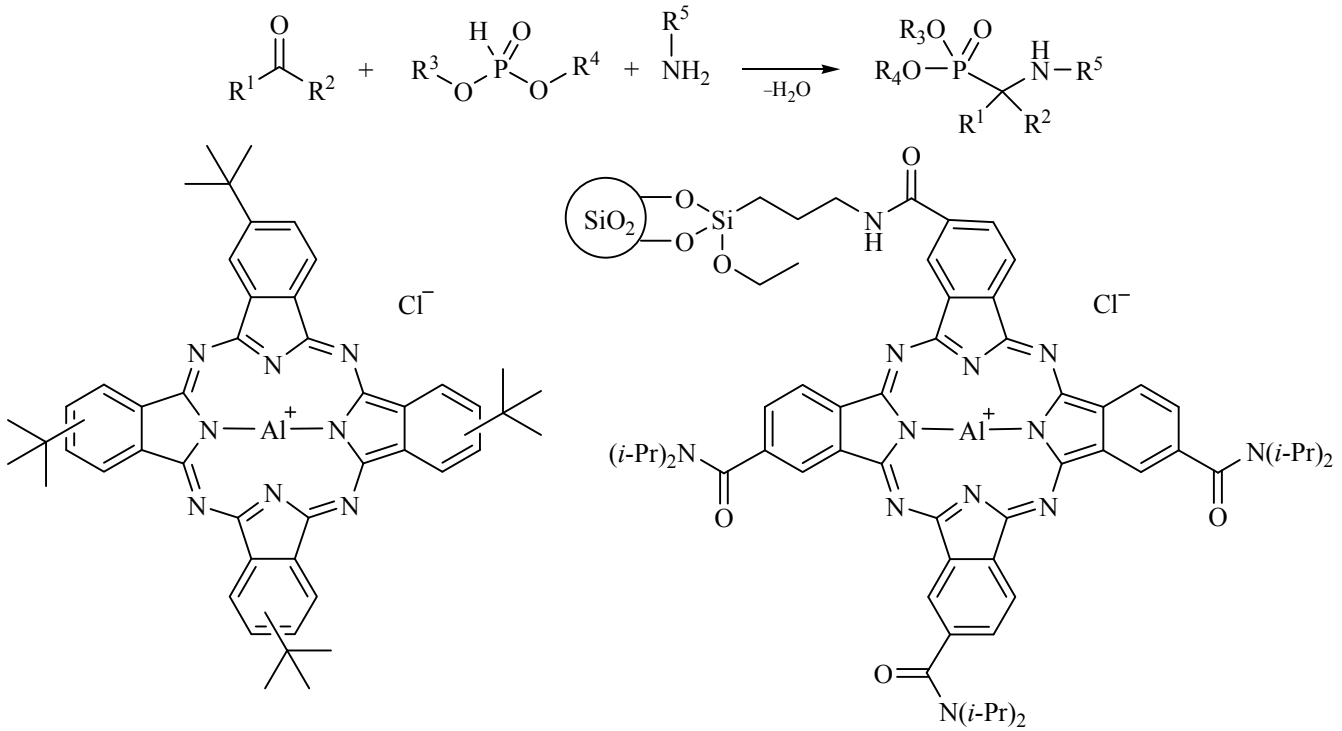
α-Aminophosphonic acids and -phosphonates constitute an important class of compounds exhibiting a broad spectrum of biological activity. Molecules of α-aminophosphonic acids and -phosphonates contain a stable carbon–phosphorus bond which is resistant to hydrolysis, thermal dissociation, and photolysis. There are both natural and anthropogenic α-aminophosphonic acids and -phosphonates. In this respect, α-aminophosphonic acids are interesting as bioisosteric analogs of α-amino acids [1]. Most frequently, α-aminophosphonic acids display inhibitory effect toward those enzymes or receptors to which natural amino acids usually bind, i.e., they act as receptor antagonists [2–5] and enzyme inhibitors [6, 7].

The inhibitory effect of α-aminophosphonic acids determines their physiological activity. Aminophosphonic acids and their derivatives exhibit antiphytoviral [8], anticancer, antibiotic [9], antifungal [14], herbicidal [10], and fungicidal activities [11–15]. It was also found that aminophosphonic acid derivatives are components of natural hypertensive tripeptides [16] and that they can act as catalytic antibody haptenes [17, 18]. Ethylenediamine phosphonates of the piperidine series show growth-stimulating activity, as well as complexing properties [19]. Thus, aminophosphonic acids and their derivatives undoubtedly attract interest from the viewpoints of medicinal chemistry and chemistry of pesticides [20].

On the other hand, α-aminophosphonic acids are key monomers of phosphopeptides that are subjects of growing interest as stable tetrahedral transition state analogs and hence models of activated complex in the hydrolysis of natural peptides [21–23]. α-Aminophosphonic acids themselves, as well as their mono- and diesters and some other derivatives, are used in peptide synthesis.

Extensive and comprehensive studies of various modifications of α-aminophosphonic acids have become possible as a result of the discovery of the three-component Kabachnik–Fields reaction 65 years ago. This reaction provided a convenient approach to phosphorus-containing amino acid analogs; it was

Scheme 1.



developed simultaneously by M.I. Kabachnik (in collaboration with T.Ya. Medved') [24] and E. Fields [25] and was named after them. The Kabachnik–Fields reaction remains very important until present (Scheme 1). This reaction has initiated the creation of the chemistry of organophosphorus analogs which possess many advantages in comparison with carboxy counterparts.

During the past 30 years, there have been performed many studies on the synthesis of α-aminophosphonates and their biological activity. Several review have been published on the synthesis [26–30] and asymmetric synthesis of α-aminophosphonates [31, 32]. A vast number of aldehydes and their functional derivatives were used as carbonyl component in the aminophosphorylation reactions [21–24]. However, except for a few publications [31, 32, 34], there are almost no data on the participation of ketones in these processes.

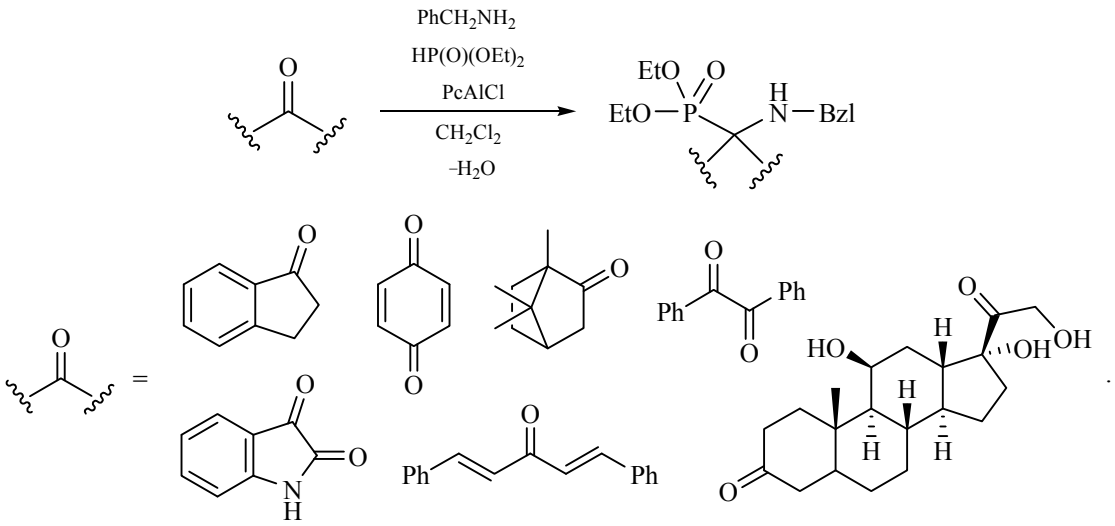
In the first part of this article we will make a survey of our studies on the synthesis of α-aminophosphonates via new catalytic versions of the Kabachnik–Fields [27] and Pudovik reactions [35], which were developed by us and considerably extended the scope of these unique processes. We used phthalocyanine metal complexes as catalysts and compared the catalytic activities of mono- and dinuclear phthalocyanine complexes.

The catalytic procedure was modified by immobilizing phthalocyanines on a silicon support. On the basis of solid-phase phthalocyanine catalysts thus obtained we have developed a procedure for the synthesis of aminophosphonates under heterogeneous conditions and found that aminophosphonates with almost any desired structure can be prepared in this way [36, 37].

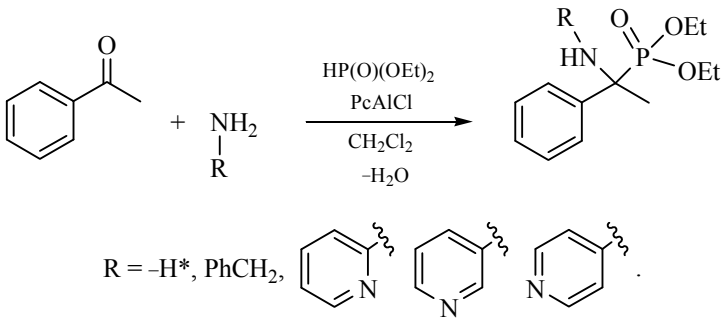
Among the examined complexes, the unique one, (tetra-*tert*-butylphthalocyaninato)aluminum chloride (*t*-PcAlCl), turned out to be the most active in both heterogeneous and homogeneous versions. It ensured preparation of α-aminophosphonates from almost any carbonyl compound such aromatic, carbocyclic, heterocyclic, and steroidal ketones, α-diketones, α,β-unsaturated aldehydes and ketones, and quinones (Scheme 2) [38].

The developed procedure makes it possible to obtain aminophosphonates from ammonia, fatty–aromatic amines, and aminopyridines (Scheme 3) [39, 40]. Such pharmacophoric amines as natural amino acids, their esters, dipeptides, and tripeptides were successfully used as amino components (Scheme 4) [41–43]. A general method for the synthesis of phosphonopeptides from natural and unnatural amino acids has been proposed on the basis of the developed catalytic

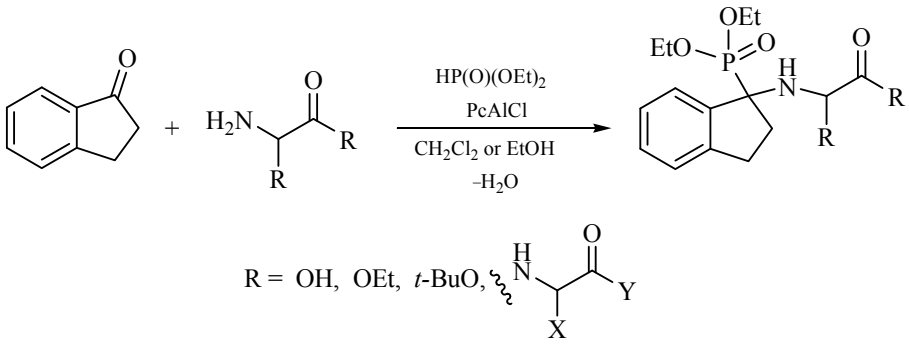
Scheme 2.



Scheme 3.



Scheme 4.



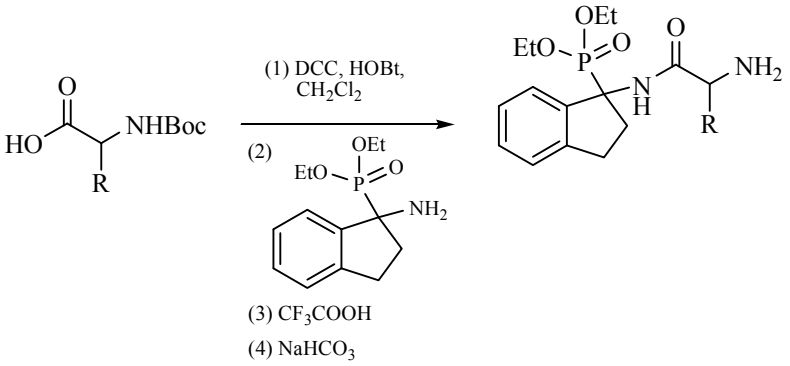
procedure for the synthesis of aminophosphonic acids (Scheme 5) [44].

The catalysis by *t*-PcAlCl was extended to the two-component reaction known as the Pudovik reaction, which is the final stage of the three-component Kabachnik–Fields reaction. Some examples of hydrophosphorylation of azines and hydrazones [45–47] have been reported previously, but there has been proposed no general approach to the synthesis of hydrazinophosphonates.

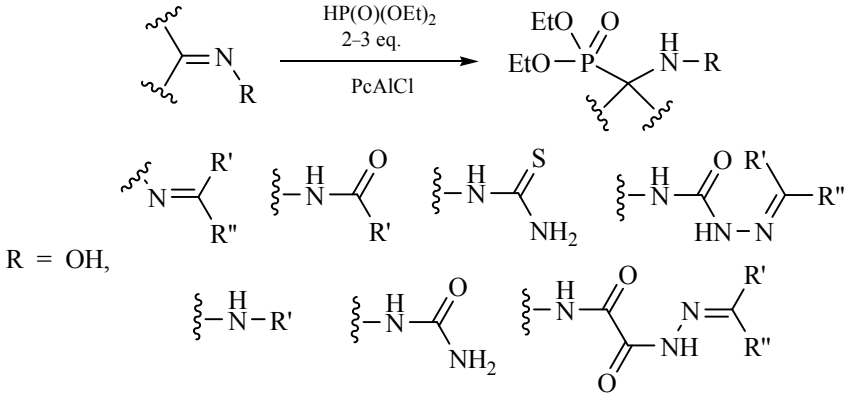
We have synthesized a series of previously inaccessible hydrazinophosphonates based on aldazines, ketazines, hydrazones, alkyl- and acylhydrazones, semicarbazones, thiosemicarbazones, carbohydrazones, and oxalylhydrazones (Scheme 6).

It has been shown that the reactivity of hydrazones strongly depends on the substituent on the nitrogen atom. Benzoylhydrazones turned out to be most universal reagents in the catalytic hydrophosphoryla-

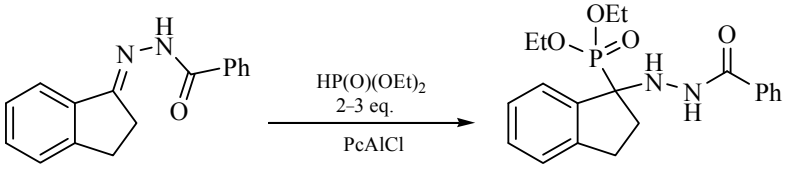
Scheme 5.



Scheme 6.



Scheme 7.

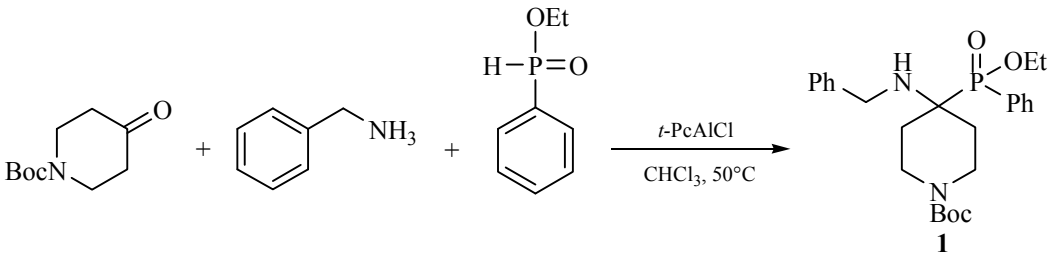


tion. With the use of benzoylhydrazones it was possible to obtain hydrazinophosphonates from a wide series of carbonyl compounds, including aromatic aldehydes and ketones, which opened wide prospects for synthetic design of this class of compounds (Scheme 7) [48–50].

Hydrazones derived from natural and unnatural amino acid hydrazides, such as glutathione hydrazide and pyridinecarbohydrazides, ensured good yields in the phthalocyanine-catalyzed hydrophosphorylation reactions [51].

In continuation of our studies on the synthetic potential of three-component Kabachnik–Fields and two-component Pudovik reactions catalyzed by phthalocyanines, we focused on variation of the phosphorus-containing component. Various modifications of this approach have been successfully applied to the synthesis of α-aminophosphinates from aldehydes. However, there are almost no published data on analogous reactions with ketones, though such reactions are of particular interest for medicinal chemistry. The use of ketones in the Kabachnik–Fields reaction should open the way to α-aminophosphinates containing a quaternary carbon atom in the α-position, which are interesting subjects for study. Analogous α-substituted synthetic amino acids showed a higher biological stability than the corresponding monoalkyl derivatives [52]; they found application as enzyme inhibitors [53], as well as models for studying mechanisms of binding to biological targets [54]. Although aminophosphonic acids show a high affinity for enzymes, their use in medicine is often restricted due to their low bioavailability. They readily undergo

Scheme 8.



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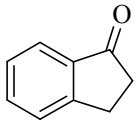
deprotonation under physiological conditions and therefore poorly penetrate through cell membranes [55]. An important line in the design of biologically active compounds is modification of phosphonic acids and their analogs with the goal of obtaining derivatives demonstrating best farmacokinetic properties.

In view of the aforesaid, a reasonable extension of this work was study of the scope of the developed catalytic method as applied to the synthesis of α-aminophosphinates with the use of ethyl phenylphosphinate as a phosphorus component.

The necessity and expedience of using *t*-PcAlCl to catalyze the given process was demonstrated in the three-component reaction of *N*-Boc-piperidin-4-one with benzylamine and ethyl phenylphosphinate. For this purpose, two parallel runs were performed, in the presence of *t*-PcAlCl and without it. The use of *t*-PcAlCl considerably accelerated the formation of α-aminophosphinates and favored almost quantitative conversion. The reaction in the absence of a catalyst afforded 45% of the target product in 24 h (the conversion of the carbonyl component being complete), whereas in the presence of *t*-PcAlCl the yield was 98% (Scheme 8). Using *N*-Boc-piperidin-4-one as an example, we have shown that the three-component catalytic addition of ethyl phenylphosphinate is applicable to the synthesis of α-aminophosphinates not only from aldehydes but also from ketones. The involvement of ketones in the given reaction is a separate problem, and the use of ketones containing pharmacophoric fragments (such as cyclopropyl methyl ketone, indan-1-one, and *N*-Boc-piperidin-4-one) could give rise to bioisosteric analogs of natural glutamate and GABA receptor ligands.

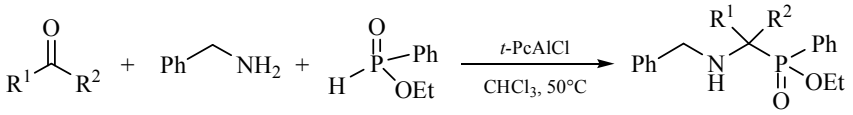
When the three-component catalytic reaction was carried out in chloroform at moderate temperature, α-aminophosphinates **1**–**5** were obtained in good preparative yields (Scheme 9, Table 1). Benzylamine

Table 1. Synthesis of α-aminophosphinates

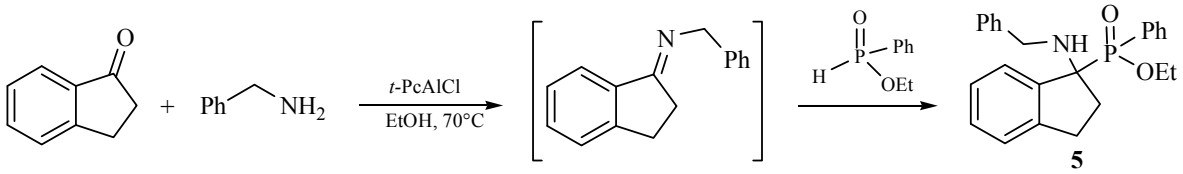
Comp. no.	$R^1C(O)R^2$		Reaction time, h	Yield,[a] %	Diastereoisomer reatio
	R^1	R^2			
1	$–(CH_2)_2–NBoc–(CH_2)_2–$		24	98 (78)	
2	$–(CH_2)_5–$		36	98 (63)	
3		CH_3	36	70 (54)	48:52
			60	88 (60)	47:53
4	C_6H_5	H	36	80 (55)	48:52
5			60	15	32:68
			36	73 (31)[b]	37:63

[a] According to the ^{31}P NMR data; the isolated yield is given in parentheses.
[b] Yield in the pseudo-two-component reaction.

Scheme 9.



Scheme 10.



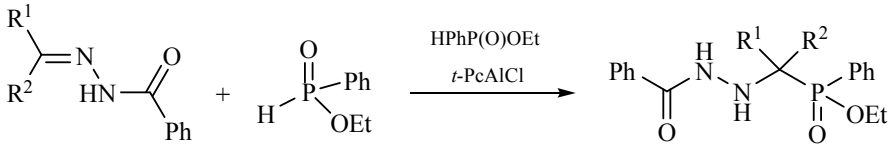
was selected as amine component taking into account high reactivity of the primary amino group therein and the ease of removal of benzyl group by hydrogenolysis, which could lead to unsubstituted aminophosphinates. The isolation of α-aminophosphinates **1**–**5** by column chromatography involved partial loss of the target product (from 10 to 40%; Table 1). However, these losses were significantly lower than those reported in [56] for the hydrophosphinylation of aldimines (80%).

A good isolated yield of α-benzylaminophosphinate **5** was achieved when ethyl phenylphosphinate was added to the reaction mixture in 3–4 h after mixing the other reactants (Scheme 10). This is a pseudo-three-component reaction where the phosphorus component is added to the Schiff base generated *in situ*. The catalyst was added to the reaction mixture in the first stage since phthalocyanine complexes have been shown previously to favor formation of Schiff bases. The yields of α-benzylaminophosphinata **5** in the three-component reaction and in the reaction with successive addition of the reactants are collected in Table 1.

Only two examples of two-component hydrophosphinylation have been reported, namely the reactions with benzaldehyde and propanal hydrazones [57]. We tried *N*-benzoylhydrazones for the synthesis of hydrazinophosphinic acids by the proposed catalytic method (Scheme 11). It was found that the best yields of hydrazinophosphinates **6**–**10** were achieved using ethyl phenylphosphinate simultaneously as reagent and solvent (Table 2). The yields of α-hydrazinophosphinates **6**–**10** ranged from 70 to 90%. The relatively low yield of phosphinate **10** is likely to be related to its conformational rigidity.

Endogenous amino acids can also be used as amine component in the catalytic hydrophosphinylation (Scheme 12). The reactions with amino acid esters considerably extend the range of structural variations

Scheme 11.



Scheme 12.

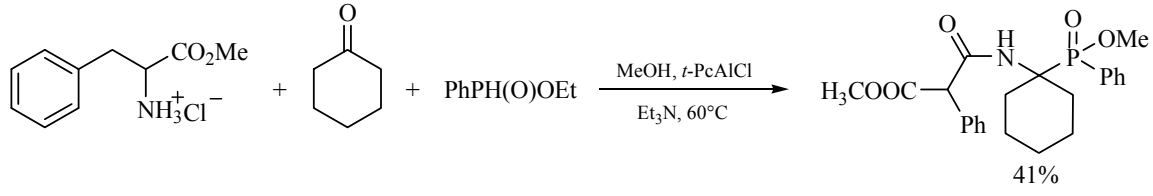
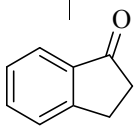


Table 2. Synthesis of α-hydrazinophosphinates from *N*-benzoylhydrazones

Comp. no.	R^1 / R^2		Ratio hydrazone–PhPH(O)OEt	Reaction time, h	Yield,[a] %	Diastereoisomer ratio
	R^1	R^2				
6	C_6H_5	H	1:2.2	60	85 (70)	46:54
7	$-(CH_2)_5-$		1:1.7	48	97 (90)	
8	$-(CH_2)_2-NBoc-(CH_2)_2-$		1:2.2	60	80 (75)	
9		CH_3	1:1.8	60	93 (83)	49:51
10			1:1.8	60	47 (40)	41:59

[a] According to the ^{31}P NMR data; the isolated yield is given in parentheses.

of aminophosphinates. The formation of compound **11** is accompanied by transesterification of the phosphorus component with methanol used as solvent.

The *t*-PcAlCl catalysis made it possible to react for the first time hydrazones derived from natural amino acid hydrazides with ethyl phenylphosphinate (Scheme 13). *N*-Boc-protected L-amino acids, isoleucine **12** and phenylalanine **13**, reacted with excess ethyl phenylphosphinate as solvent under homogeneous catalysis conditions at 60°C to give previously unknown hydrazinophosphinates **14** and **15** in 67 and 62% yield, respectively, as mixtures of two (**14**) or four diastereoisomers (**15**).

The structure of compounds **1**–**12** and **14**–**15** was confirmed by elemental analyses and IR, ^1H, ^{13}C, and ^{31}P NMR, and high-resolution mass spectra.

Thus, the synthesis of α-amino- and α-hydrazinophosphinates based on ketones and amino acids or their derivatives can be efficiently catalyzed by metal phthalocyanines.

Taking into account that the vast series of amino- and hydrazinophosphonates synthesized by us contain compounds with various pharmacophoric fragments, a part of them were screened biological activity; in particular, α-hydrazinophosphonates AP1–AP5 were tested for antioxidant activity. In keeping with recent data, oxidative stress is the key factor in the pathogenesis of various diseases, primarily of acute and chronic cerebral circulation disorders, neurodegenerative pathologies and encephalopathies of different origins, heart ischemia, atherosclerosis, diabetic angiopathies, autoimmune and oncological diseases,

Scheme 13.

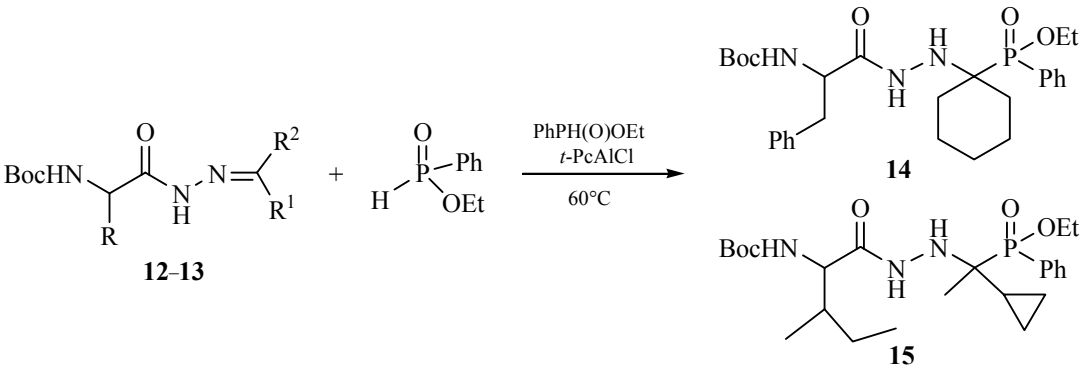


Table 3. Radical-scavenging (ABTS-assay) and iron-reducing (FRAP assay) activities of α-hydrazinophosphonates

Compound no.	TEAC[a]	IC_{50} ($ABTS^{+\cdot}$), μM	FRAP[b]
AP1	0.9±0.07	19.1±2.2	0.94±0.08
AP2	1.35±0.13	14.1±1.1	0.88±0.08
AP3	0.75±0.07	27.2±1.1	0.71±0.06
AP4	0.89±0.06	22.2±1.4	0.81±0.09
AP5	1.5±0.13	12.4±0.9	0.73±0.07
Trolox	1.0	20.1±1.2 (n = 8)	1.0
Ascorbic acid	0.98±0.09	21.4±2.25 (n = 7)	1.03±0.04

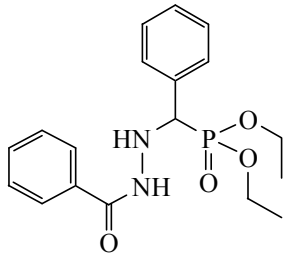
[a] TEAC (Trolox equivalent antioxidant capacity) is the antioxidant activity expressed in trolox equivalents as the ratio of the slopes of the dependences of the $ABTS^{+\cdot}$ concentration upon the concentration of the tested compound and Trolox.

[b] The FRAP value is given in relative units defined as the ratio of the slopes of the concentration dependences for the tested compound (α_A) and Trolox (α_T): FRAP = α_A/α_T.

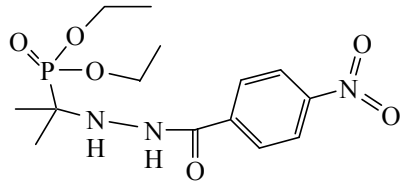
etc. [58–60]. Oxidative stress is characterized by sharp enhancement of oxidative processes in organism and insufficient efficiency of the endogenous antioxidant system. This indicates the necessity of using exogenous antioxidants capable of binding free radicals and suggests prospects of the design of new compounds possessing antioxidant properties [61–63].

The antioxidant activity of the synthesized α-hydrazinophosphonates was evaluated by two methods, by the ability to bind radical species (ABTS assay) and by the ability to reduce iron [FRAP (Ferric reducing antioxidant power) assay]. The ABTS assay is based on generation of stable colored (dark green) $ABTS^{+\cdot}$ radical cation by incubation of ABTS [2,2′-azobis(3-ethyl-2,3-dihydro-1,3-benzothiazole-6-sulfonic acid)] with potassium peroxodisulfate. The subsequent reaction of $ABTS^{+\cdot}$ with an antioxidant leads to reduction of the absorbance at λ 734 nm [64]. The FRAP assay is based on the reduction of the iron(III) complex with 2,4,6-(tripyridin-2-yl)-1,3,5-triazine $[Fe^{3+}–(TPTZ)_2]^{3+}$ in the presence of an antioxidant to the corresponding iron(II) complex $[Fe^{2+}–(TPTZ)_2]^{2+}$ which is characterized by intense blue color (λ_{max} 595 nm) [65, 66]. The reducing ability of a compound is an important parameter characterizing its potential antioxidant activity [67, 68]. The results are presented in Table 3.

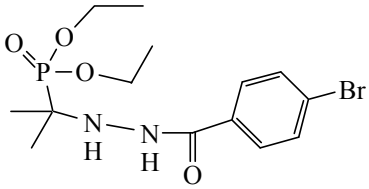
The data in Table 3 show that the examined hydrazinophosphonates exhibit a high $ABTS^{+\cdot}$-binding activity, which is comparable or even higher than the activity of the standard antioxidant Trolox and known antioxidant ascorbic acid. The highest radical-scavenging activity was observed for compounds containing a nitro group in the *para* position (AP2 and AP5); their bromo-substituted analog (AP3) displayed a lower activity. The nature of substituent on the carbon atom attached to phosphorus (P–C) has no significant effect on the antiradical activity (cf. AP1 and AP4, AP2 and AP5).



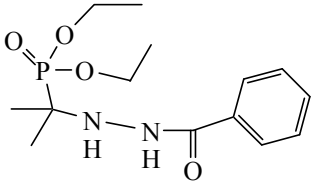
AP1



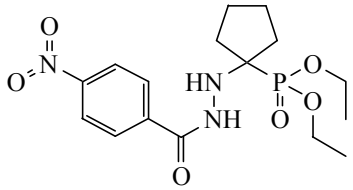
AP2



AP3



AP4



AP5

All tested α-hydrazinophosphonates also showed high iron-reducing power (FRAP assay) approaching the activity of Trolox. Compound AP1 with a phenyl substituent on the phosphonate carbon atom exhibited the maximum activity. Insignificant reduction of the activity was observed for *para*-bromo-substituted derivative AP3, as in the ABTS assay.

Taking into account that the FRAP assay is a non-radical method (its mechanism is based exclusively on electron transfer [69], in contrast to the ABTS assay where radical quenching may follow both hydrogen transfer and electron transfer mechanisms), concurrent use of both methods is helpful for the estimation of the mechanism of proper antioxidant activity of compounds [70]. The high antiradical and and iron-reducing activities of the examined compounds suggest that the antioxidant effect of α-aminophosphonates is based on electron transfer.

Thus, α-hydrazinophosphonates are quite promising compounds from the viewpoint of their antioxidant properties.

EXPERIMENTAL

The ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on Bruker DPX-300 (300.1, 121.5, and 75.4 MHz, respectively) and Agilent 400 MR spectrometers (400, 161, and 100 MHz, respectively) from solutions in CD_2Cl_2, $CDCl_3$, CD_3CN, and CD_3OD using the residual proton signal of the solvent as reference. The IR spectra were measured on a Thermo Scientific Nicolet IR 200 spectrometer with Fourier transform, equipped with an ATR accessory (ZnSe). The elemental analyses were obtained on a Vario-II CHN analyzer. The high-resolution mass spectra (electrospray ionization) were recorded on a Bruker micrOTOF II instrument (positive and negative ion detection, capillary voltage 4500 and 3200 V, respectively). The progress of reactions and chromatographic separation was monitored by thin-layer chromatography on Merck TLC Silica gel 60 F_{254} plates; Macherey-Nagel Kieselgel 60 (0.04–0.063 mm, 230–400 mesh) was used for column chromatography.

The catalyst, tetra-*tert*-butylphthalocyaninato)aluminum chloride (*t*-PcAlCl) was synthesized according to the procedure described in [43]. Ethyl phenylphosphinate was prepared as reported in [71]. Phenylalanine methyl ester hydrochloride was commercial product (Aldrich).

***N-tert*-Butoxycarbonyl-L-phenylalanine hydrazide** was synthesized according to [72]. Yield 2.5 g (61%), mp 122–125°C.

***N-tert*-Butoxycarbonyl-L-isoleucine hydrazide** was synthesized according to [73]. Yield 1.3 g (50%), mp 119–121°C.

Hydrazones derived from phenylalanine and isoleucine hydrazides were synthesized according to the general procedure described in [74].

***tert*-Butyl [1-benzyl-2-oxoethyl-2-(2-cyclohexylidenehydrazinyl)]carbamate (12).** Yield 85%, white crystals, mp. 124–125°C [75].

***tert*-Butyl [1-{[2-(1-cyclopropylethylidene)hydrazinyl]carbonyl}-2-methylbutyl)carbamate (13).** Yield 64% (mixture of two diastereoisomers), white crystals, mp 118–120°C. IR spectrum, ν, cm^{-1}: 1660, 1680 (C=O), 3250–3330 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.67–0.83 m, 0.83–0.92 m, and 0.93–0.97 m [10H, **(**$CH_2)_{2cycl}$, $CH_2C\mathbf{H}_3$, $CHC\mathbf{H}_3$)]; 1.01–1.19 m and 1.51–1.61 m (2H, $C\mathbf{H}_2CH_3$), 1.40 s and 1.42 s [9H, $(CH_3)_3C$], 1.52–1.61 m [1H, CH_{cycl}]; 1.63 s, 1.76 s, 1.83 and s (3H, $C{=}CCH_3$); 1.72–1.88 m and 1.87–2.05 m (1H, $C\mathbf{H}CH_3$), 4.96–5.07 m [1H, NHC**H**C(O)], 5.23–5.29 m [1H, NHC(O)O]; 8.70 s, 9.10 s, and 9.48 s [1H, C(O)NHN]. ^{13}C NMR spectrum ($SDCl_3$), δ_C, ppm: 5.11, 5.16, 5.39, 5.60, 6.58 [CH_{2cycl}]; 9.87, 10.55, 10.98, 11.60, 12.10, 13.92, 15.58, 15.77, 15.91 ($CH_2\mathbf{C}H_3$, $CH\mathbf{C}H_3$, $C\mathbf{C}H_3$); 17.76, 18.16, 19.86, 20.08 ($CH_{cycl.}$); 23.61, 23.81, 24.74 ($\mathbf{C}H_2CH_3$); 28.24 and 28.29 [$(\mathbf{C}H_3)_3C$]; 36.07, 37.52, 37.69 ($\mathbf{C}HCH_3$); 55.17, 55.46, 58.24 [NH**C**HC(O)]; 79.15 and 80.00 [$(CH_3)_3\mathbf{C}$]; 153.75, 155.76, 156.12 [NHC(O)O]; 165.34, 166.71, 167.66 ($CH_3\mathbf{C}{=}N$), 173.84 [NH**C**(O)CH_2]. Found, %: C 61.65; H 9.27; N 13.54. $C_{16}H_{29}N_3O_3$. Calculated, %: C 61.71; H 9.39; N 13.49.

Synthesis of α-aminophosphinates *(general procedure).* A mixture of 2 mL of chloroform, 1 mmol of carbonyl compound, 1 mmol of benzylamine, 1 mmol of ethyl phenylphosphinate, 0.05 mmol of *t*-PcAlCl, and 4-Å molecular sieves was stirred at 50°C for 24–60 h. The precipitate (molecular sieves) was filtered off and washed with chloroform–methanol (5 : 1), the filtrate was evaporated, the residue was dissolved in a minimum volume of chloroform, and the product was isolated by silica gel column chromatography.

***tert*-Butyl 4-(benzylamino)-4-[ethoxy(phenyl)phosphoryl]piperidine-1-carboxylate (1).** Reaction time 24 h; eluent $CHCl_3$–MeOH (100 : 1). Yield 63%, white

crystals, mp 110–112°C. IR spectrum, ν, cm^{-1}: 1040 (P–O–C), 1210 (P=O), 1685 (C=O), 3310 (NH). ^1H NMR spectrum (CD_3CN), δ, ppm: 1.32 t (3H, $OCH_2C\mathbf{H}_3$, J_{HH} = 6.9 Hz), 1.38 s [9H, $(CH_3)_3C$], 1.61–1.90 m (4H, cycl.), 3.11 br.s (2H, cycl.), 3.85–3.94 m (2H, cycl.), 3.85–3.94 m (1H, $OC\mathbf{H}_2CH_3$), 4.04–4.13 m (1H, $OC\mathbf{H}_2CH_3$), 3.97 d.d (1H, $C\mathbf{H}_2NH$, $^2J_{HH}$ = 12.7, $^4J_{HP}$ = 2.5 Hz,), 4.03 d.d (1H, $C\mathbf{H}_2NH$, $^2J_{HH}$ = 12.7, $^4J_{HP}$ = 2.9 Hz), 7.20–7.27 m (1H, H_{arom}), 7.27–7.34 m (2H, H_{arom}), 7.34–7.41 m (2H, H_{arom}), 7.49–7.57 m (2H, H_{arom}), 7.58–7.64 m (1H, H_{arom}), 7.74–7.83 m (2H, H_{arom}). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 17.29 d ($^3J_{CP}$ = 5.7 Hz, $OCH_2\mathbf{C}H_3$), 28.84 [$(\mathbf{C}H_3)_3C$], 29.50 (cycl.), 30.33 (cycl.), 39.53 (cycl.), 48.08 ($NHCH_2$), 56.68 d ($^1J_{CP}$ = 103.8 Hz, PCH), 61.93 d ($^2J_{CP}$ = 8.0 Hz, $O\mathbf{C}H_2CH_3$), 80.02 [$(CH_3)_3\mathbf{C}$], 128.05, 129.39, 129.52, 130.18 d ($^1J_{CP}$ = 108.7 Hz), 129.75, 129.86, 133.61 d ($^4J_{CP}$ = 2.7 Hz), 134.20 d ($^3J_{CP}$ = 9.2 Hz), 142.58, 155.77. ^{31}P NMR spectrum (CD_3CN): δ_P 43.73 ppm. Found, %: C 65.74; H 7.70; N 6.30. $C_{25}H_{35}N_2O_4P$. Calculated, %: C 65.48; H 7.69; N 6.11.

Ethyl [(benzylamino)cyclohexyl]phenylphosphinate (2). Reaction time 36 h; eluent $CHCl_3$–MeOH (100 : 1). Yield 63%, white crystals, mp 111–113°C. IR spectrum, ν, cm^{-1}: 1030 (P–O–C), 1220 (P=O), 3310 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.37 t (J_{HH} = 7.07 Hz, 3H, $OCH_2C\mathbf{H}_3$); 1.42–1.55 m, 1.60–1.74 m, 1.76–1.84 m, and 1.85–1.93 (10H, cycl.); 3.87–3.97 m and 4.12–4.24 m (2H, $OC\mathbf{H}_2CH_3$), 3.99 d.d (1H, $C\mathbf{H}_2NH$, $^2J_{HH}$ = 13.0, $^4J_{HP}$ = 2.9 Hz), 4.06 d.d (1H, $C\mathbf{H}_2NH$, $^2J_{HH}$ = 12.6, $^4J_{HP}$ = 3.3 Hz), 7.20–7.26 m (1H, H_{arom}), 7.28–7.35 m (2H, H_{arom}), 7.35–7.42 m (2H, H_{arom}), 7.43–7.51 m (2H, H_{arom}), 7.51–7.58 m (1H, H_{arom}), 7.77–7.84 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.72 d ($^3J_{CP}$ = 6.1 Hz, $OCH_2\mathbf{C}H_3$), 19.97 d ($^3J_{CP}$ = 9.9 Hz), 25.53 d ($^4J_{CP}$ = 1.5 Hz), 28.71 d ($^2J_{CP}$ = 3.8 Hz), 29.06 d ($^2J_{CP}$ = 4.6 Hz), 46.98 ($NHCH_2$), 56.85 d (PCH, $^1J_{CP}$ = 102.2 Hz), 60.65 d ($^2J_{CP}$ = 7.6 Hz, $O\mathbf{C}H_2CH_3$), 126.75, 128.11, 128.23 d ($^3J_{CP}$ = 3.1 Hz), 128.32, 129.14 d ($^1J_{CP}$ = 106.8 Hz), 131.99 d ($^4J_{CP}$ = 2.3 Hz), 133.02 d ($^2J_{CP}$ = 8.4 Hz), 141.46. ^{31}P NMR spectrum ($CDCl_3$): δ_P 46.64 ppm. Found, %: C 70.74; H 8.06; N 3.74. $C_{21}H_{28}NO_2P$. Calculated, %: C 70.57; H 7.90; N 3.92.

Ethyl [1-(benzylamino)-1-cyclopropylethyl]phenylphosphinate (3). Reaction time 60 h; eluent $CHCl_3$–MeOH (100 : 1). Yield 60% (mixture of two diastereoisomers), pale yellow oil. IR spectrum, ν, cm^{-1}: 1040 (C–O–P), 1220 (P=O), 3430–3470 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.32–0.39 m (4H, CH_2, cycl.), 0.92–1.07 m (1H, CH, cycl.), 1.04 d (3H, CCH_3, $^3J_{HP}$ = 15.4 Hz), 1.12 d (3H, CCH_3, $^3J_{HP}$ = 15.1 Hz), 1.33 t (3H, $OCH_2C\mathbf{H}_3$, J_{HH} = 7.0 Hz), 1.34 t (3H, $OCH_2C\mathbf{H}_3$, J_{HH} = 7.1 Hz), 3.92–4.01 and 4.14–4.21 m (2H, $OC\mathbf{H}_2CH_3$), 3.92–4.01 m (2H, $C\mathbf{H}_2NH$), 7.17–7.32 m (5H, H_{arom}), 7.42–7.54 m (3H, H_{arom}), 7.69–7.91 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 0.51 d (CH_2, $^3J_{CP}$ = 9.2 Hz), 0.80 d (CH_2, $^3J_{CP}$ = 9.2 Hz), 0.98 d (CH_2, $^3J_{CP}$ = 3.1 Hz), 1.31 d (CH_2, $^3J_{CP}$ = 3.1 Hz), 14.62 d ($C\mathbf{C}H_3$, $^2J_{CP}$ = 4.6 Hz), 15.19 d (CCH_3, $^2J_{CP}$ = 4.6 Hz), 15.49 d (CH, $^2J_{CP}$ = 3.1 Hz), 15.59 d (CH, $^2J_{CP}$ = 6.9 Hz), 16.69 d ($OCH_2\mathbf{C}H_3$, $^2J_{CP}$ = 6.1 Hz), 46.84 d and 46.90 d ($NHCH_2$, $^3J_{CP}$ = 3.1 Hz), 56.06 d (PCH, $^1J_{CP}$ = 107.58 Hz), 56.23 d (PCH, $^1J_{CP}$ = 109.9 Hz), 60.94 d ($O\mathbf{C}H_2CH_3$, $^3J_{CP}$ = 7.6 Hz), 126.67, 126.71, 128.00 d and 128.05 d ($^3J_{CP}$ = 11.4 Hz), 128.03, 128.04, 128.18, 128.22, 129.54 d and 129.66 d ($^1J_{CP}$ = 113.7 Hz), 131.96 d ($^4J_{CP}$ = 3.1 Hz), 133.26 d ($^2J_{CP}$ = 9.2 Hz), 133.34 d ($^2J_{CP}$ = 8.4 Hz), 141.48, 141.50. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 45.71, 45.62. Mass spectrum: *m*/*z* 366.1586 [*M* + Na] (calculated for $C_{20}H_{26}NNaO_2P$: 366.1593).

Ethyl [(benzylamino)(phenyl)methyl]phenylphosphinate (4). Reaction time 36 h; eluent $CHCl_3$–MeOH (100 : 1). Yield 55% (mixture of two diastereoisomers), light oil. IR spectrum, ν, cm^{-1}: 1050 (C–O–P), 1225 (P=O), 3290 (NH). ^1H NMR spectrum (CD_3CN), δ, ppm: 1.08 t and 1.27 t (3H, $OCH_2C\mathbf{H}_3$, J_{HH} = 7.0 Hz), 2.59 br.s (1H, NH), 3.39 d and 3.48 d (1H, $C\mathbf{H}_2NH$, $^2J_{HH}$ = 13.6 Hz), 3.72 d and 3.77 d (1H, $C\mathbf{H}_2NH$, $^2J_{HH}$ = 13.0 Hz), 3.67–3.83 m, and 3.88–3.99 m (2H, $OC\mathbf{H}_2CH_3$), 4.08 d and 4.10 d (1H, PCH, $^2J_{HP}$ = 16.4, 16.2 Hz); 7.00–7.03 m, 7.16–7.40 m, and 7.48–7.71 m (15H, H_{arom}). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 16.78 d and 16.97 d ($OCH_2\mathbf{C}H_3$, $^3J_{CP}$ = 5.9 Hz), 51.51 d and 51.87 d ($\mathbf{C}H_2NHCHP$, $^3J_{CP}$ = 16.1, 14.8 Hz), 62.36 d (PCH, $^1J_{CP}$ = 110.6 Hz), 63.18 d (PCH, $^1J_{CP}$ = 107.7 Hz), 62.02 d and 62.35 d ($O\mathbf{C}H_2CH_3$, $^2J_{CP}$ = 6.8 Hz), 127.89, 127.99, 128.58 d and 128.72 d ($^4J_{CP}$ = 3.0 Hz), 129.06 d and 129.17 d ($^3J_{CP}$ = 8.05, 8.9 Hz), 129.08, 129.28, 129.14, 129.33, 129.25, 129.32, 129.92 d ($^3J_{CP}$ = 5.5 Hz), 130.07 d ($^3J_{CP}$ = 5.1 Hz), 130.79 d and 131.26 d ($^1J_{CP}$ = 125.0, 125.4 Hz), 133.21 d and 133.29 d ($^4J_{CP}$ = 2.5 Hz), 133.29 d and 133.41 d ($^2J_{CP}$ = 8.9 Hz), 136.98, 140.70, 140.80. ^{31}P NMR spectrum (CD_3CN), δ_P, ppm: 39.70, 38.04. Found, %: C 71.95; H 6.44; N 3.65. $C_{22}H_{24}NO_2P$. Calculated, %: C 72.31; N 6.62; N 3.83.

Ethyl [1-(benzylamino)-2,3-dihydro-1*H*-inden-1-yl]phenylphosphinate (5). Reaction time 60 h; eluent

$CHCl_3$–MeOH (75 : 1). Yield 60% (mixture of two diastereoisomers), dark brown oil. IR spectrum, ν, cm^{-1}: 1045 (C–O–P), 1220 (P=O), 3250–3330 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t and 1.29 t (3H, OCH_2CH_3, J_{HH} = 7.1, 7.0 Hz), 2.29–2.56 m [2H, $(CH_2)_2$, cycl.], 2.60–2.73 m [1H, $(CH_2)_2$, cycl.], 2.78–2.96 m [1H, $(CH_2)_2$, cycl.], 3.50 d and 3.55 d (1H, CH_2NH, $^2J_{HH}$ = 13.1, 12.9 Hz), 3.74 d and 3.77 d (1H, CH_2NH, $^2J_{HH}$ = 13.1, 12.9 Hz), 3.96–4.06 m and 4.08–4.29 m (2H, OCH_2CH_3), 7.12–7.17 m (2H, H_{arom}), 7.23–7.25 m (2H, H_{arom}), 7.29–7.34 m (4H, H_{arom}), 7.35–7.39 m (2H, H_{arom}), 7.51–7.55 m (2H, H_{arom}), 7.58–7.62 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.35 d and 16.53 d (OCH_2CH_3, $^2J_{CP}$ = 6.6, 5.1 Hz), 30.55 (CH_2, cycl.), 30.92 d and 30.13 d [$(CH_2)_2$, cycl., $^2J_{CP}$ = 4.0, 5.8 Hz], 61.38 d and 61.60 d (OCH_2CH_3, $^2J_{CP}$ = 7.3 Hz), 71.08 d and 71.25 d (PCH, $^1J_{CP}$ = 113.4, 111.2 Hz), 124.56, 124.69, 125.62, 125.97, 125.74, 126.08, 126.67, 126.77, 127.67 d and 127.71 d ($^2J_{CP}$ = 11.7 Hz), 127.99, 128.08, 128.22, 130.01 d ($^1J_{CP}$ = 162.9 Hz), 130.11 d ($^1J_{CP}$ = 167.6 Hz), 131.98, 132.07, 133.28 d and 133.48 d ($^3J_{CP}$ = 8.8 Hz), 139.65, 139.69, 140.76, 140.83, 145.19 d ($^2J_{CP}$ = 6.6 Hz), 145.37 d ($^2J_{CP}$ = 5.9 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 41.13, 43.06. Mass spectrum: *m*/*z* 414.1585 $[M + Na]^+$ (calculated for $C_{24}H_{26}NNaO_2P$: 414.5193).

Synthesis of α-hydrazinophosphinates *(general procedure)*. A mixture of 1 mmol of the corresponding hydrazone, 1.2–3 mmol of ethyl phenylphosphinate, and 0.05 mmol of *t*-PcAlCl was stirred at 80°C for 60 h. The mixture was dissolved in a minimum volume of chloroform and subjected to column chromatography on silica gel.

Ethyl [(2-benzoylhydrazinyl)(phenyl)methyl]-phenylphosphinate (6). Ratio hydrazone–PhPH(O)OEt 1 : 2.2; eluent $CHCl_3$–MeOH (100 : 1). Yield 70% (mixture of two diastereoisomers). IR spectrum, ν, cm^{-1}: 1035 (C–O–P), 1210 (P=O), 3220–3290 (NH–NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t and 1.32 t (3H, OCH_2CH_3, J_{HH} = 7.1 Hz), 3.94–4.10 m and 4.12–4.26 m (2H, OCH_2CH_3), 4.75 d and 4.78 d (1H, PCH, $^2J_{HP}$ = 17.2, 15.5 Hz), 5.62 br.s (1H, CHNH), 7.10–7.77 m (15H, H_{arom}), 8.28 s and 8.73 s [1H, NHC(O)]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.41 (OCH_2CH_3, $^3J_{CP}$ = 6.1 Hz), 61.57 d and 61.81 d (OCH_2CH_3, $^2J_{CP}$ = 6.9), 65.52 d and 65.60 d (PCH, $^1J_{CP}$ = 109.1 Hz), 127.20 d and 127.22 d ($^1J_{CP}$ = 122.8 Hz), 126.81, 126.87, 127.91, 128.03, 128.11, 128.16 d and 128.22 d ($^3J_{CP}$ = 3.0, 3.8 Hz), 128.41, 128.47, 128.58 d ($^3J_{CP}$ = 5.3 Hz), 129.04 d ($^3J_{CP}$ = 4.6 Hz), 131.62, 131.66, 132.49 d ($^4J_{CP}$ = 4.6 Hz), 129.49 d ($^4J_{CP}$ = 3.0 Hz), 132.48 d ($^2J_{CP}$ = 9.9 Hz), 132.85 d ($^2J_{CP}$ = 9.2 Hz), 133.37 d ($^2J_{CP}$ = 6.1 Hz), 133.58 d ($^2J_{CP}$ = 5.3 Hz), 166.14, 166.65 (C=O). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 36.47, 39.19. Found, %: C 66.84; H 6.15; N 6.68. $C_{22}H_{23}N_2O_3P$. Calculated, %: C 67.00; H 5.88; N 7.10.

Ethyl [1-(2-benzoylhydrazinyl)cyclohexyl]phenylphosphinate (7). Ratio hydrazone–PhPH(O)OEt 1 : 1.7; eluent $CHCl_3$–MeOH (100 : 1). Yield 90%, white crystals, mp 105–106°C. IR spectrum, ν, cm^{-1}: 1030 (P–O–C), 1225 (P=O); 3220, 3320 (NH–NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.07–1.14 m (1H, cycl.), 1.43–1.60 m and 1.63–1.74 m (8H, cycl.), 2.00–2.10 m (1H, cycl.), 1.39 t (3H, OCH_2CH_3), 3.98–4.11 m and 4.18–4.29 m (2H, OCH_2CH_3), 5.33 br.s (1H, CHNH), 7.40–7.52 m (5H, H_{arom}), 7.59 d.d (1H, H_{arom}, J_{HH} = 6.8 Hz), 7.75–7.89 m (4H, H_{arom}), 9.33 s [1H, NHC(O)]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.58 d (OCH_2CH_3, $^3J_{CP}$ = 6.1 Hz), 19.67 d (cycl., J_{CP} = 8.2 Hz), 19.77 d (cycl., J_{CP} = 7.4 Hz), 25.07 d (cycl., J_{CP} = 1.3 Hz), 26.17 d (cycl., J_{CP} = 1.3 Hz), 27.57 d (cycl., J_{CP} = 2.6 Hz), 59.42 d (PC, $^1J_{CP}$ = 117.9 Hz), 61.65 d (OCH_2CH_3, $^2J_{CP}$ = 7.4 Hz), 126.72, 127.28 d ($^1J_{CP}$ = 119.2 Hz), 128.40 d ($^2J_{CP}$ = 11.7 Hz), 128.57, 131.43, 132.61 d ($^4J_{CP}$ = 3.0 Hz), 132.71, 133.14 d ($^3J_{CP}$ = 9.1 Hz), 164.02 (C=O). ^{31}P NMR spectrum ($CDCl_3$): δ_P 46.41 ppm. Found, %: C 65.21; H 6.76; N 7.02. $C_{21}H_{27}N_2O_3P$. Calculated, %: C 65.27; H 7.04; N 7.25.

***tert*-Butyl 4-[ethoxy(phenyl)phosphoryl]-4-[2-benzoylhydrazinyl]piperidine-1-carboxylate (8).** Ratio hydrazone–PhPH(O)OEt 1 : 2.2; eluent $CHCl_3$–MeOH (100 : 1). Yield 75% (mixture of two diastereoisomers), white crystals, mp 105–106°C. IR spectrum, ν, cm^{-1}: 1030 (C–O–P), 1255 (P=O), 1690 (C=O), 3220–3290 (NH–NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.26–1.51 m [12H, OCH_2CH_3, $(CH_3)_3C$], 1.51–2.05 m (4H, cycl.), 3.26 br.s (2H, cycl.), 3.83 br.s (2H, cycl.), 3.97–4.12 m and 4.15–4.30 m (1H each, OCH_2CH_3), 4.84 br.s (1H, CHNH), 7.37–7.57 m (5H, H_{arom}), 7.57–7.67 m (1H, H_{arom}), 7.71–7.88 m (4H, H_{arom}), 9.30 s [1H, NHC(O)]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.53 d (OCH_2CH_3, $^3J_{CP}$ = 5.7 Hz), 26.28 (cycl.), 27.41 (cycl.), 36.98 (cycl.), 38.87 (cycl.), 28.29 [$(CH_3)_3C$], 57.87 d (PCH, $^1J_{CP}$ = 114.1 Hz), 61.89 d (OCH_2CH_3, $^2J_{CP}$ = 7.6 Hz), 79.51 [$(CH_3)_3C$], 126.83, 127.81 d ($^1J_{CP}$ = 137.6 Hz), 128.61, 128.74 d ($^3J_{CP}$ = 11.8 Hz), 131.67, 132.57, 132.97, 133.05 d ($^4J_{CP}$ = 2.3 Hz), 154.60 [OC(O)N], 165.15 [(C(O)Ph]. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 45.16, 44.75. Found, %: C 62.26; H

7.38; N 8.39. $C_{26}H_{36}N_3O_5P$. Calculated, %: C 62.26; H 7.23; N 8.38.

Ethyl [1-(2-benzoylhydrazinyl)-1-cyclopropylethyl]-phenylphosphinate (9). Ratio hydrazone–PhPH(O)OEt 1:1.8; eluent $CHCl_3$–MeOH (100:1). Yield 83% (mixture of two diastereoisomers). IR spectrum, ν, cm^{-1}: 1040 (P–O–C), 1220 (P=O), 1650 (C=O); 3280, 3440–3460 (NH–NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.26–0.59 m [4H, $(CH_2)_2$, cycl.], 0.86 d and 1.06 d (3H, CCH_3, $^3J_{HP}$ = 16.0, 14.1 Hz), 1.19–1.34 m (1H, CH, cycl.), 1.38 t and 1.40 t (3H, $OCH_2C\mathbf{H}_3$, J_{HH} = 7.0, 6.9 Hz), 4.01–4.35 m (2H, $OC\mathbf{H}_2CH_3$), 7.39–7.54 m (5H, H_{arom}), 7.58 m (1H, H_{arom}), 7.77–7.85 m (2H, H_{arom}), 7.85–7.93 m (2H, H_{arom}), 8.85 s and 9.12 s [1H, NH**N**H**H**C(O)]. ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: –0.46 d and 0.09 d (CH_2, cycl., $^3J_{CP}$ = 9.2 Hz), 2.15 s and 2.62 s (CH_2, cycl.), 12.20 d and 13.17 d ($C\mathbf{C}H_3$, $^2J_{CP}$ = 3.1 Hz), 12.52 d and 13.86 d (CH, cycl., $^2J_{CP}$ = 6.1, 4.6 Hz), 16.60 d and 16.65 d ($OCH_2\mathbf{C}H_3$, $^3J_{CP}$ = 5.3, 6.1 Hz), 60.18 d and 60.46 d (PCH, $^1J_{CP}$ = 119.8, 116.7 Hz), 61.56 d and 61.85 d ($O\mathbf{C}H_2CH_3$, $^2J_{CP}$ = 7.63 Hz); 126.74, 126.78, 128.51 d and 128.08 d ($^1J_{CP}$ = 128.02, 120.6 Hz), 128.29 d ($^3J_{CP}$ = 12.21 Hz), 128.60, 128.63, 131.48, 131.54, 132.54 d ($^4J_{CP}$ = 2.3 Hz), 132.67, 132.69, 133.06 d and 133.18 d ($^2J_{CP}$ = 9.2 Hz), 164.87 and 165.09 [C(O)NHNH]. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 45.30, 46.14. Found, %: C 64.40; H 6.96; N 7.77. $C_{20}H_{25}N_2O_3P$. Calculated, %: C 64.50; H 6.77; N 7.52.

Ethyl [1-(2-benzoylhydrazinyl)-2,3-dihydro-1*H*-inden-1-yl]phenylphosphinate (10). Reactant ratio 1:1.8; eluent $CHCl_3$–MeOH (75:1). Yield 40% (mixture of two diastereoisomers). IR spectrum, ν, cm^{-1}: 1040 (C–O–P), 1220 (P=O), 1680 (C=O), 3200–3250 (NH–NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.33–1.44 m (3H, $OCH_2C\mathbf{H}_3$); 2.05–2.35 m (2H), 2.60–2.68 m, 2.74–2.84 m, and 2.89–2.99 m [2H, $(CH_2)_2$, cycl.]; 3.95–4.14 m and 4.16–4.30 m (2H, $OC\mathbf{H}_2CH_3$), 5.79 br.s and 5.89 br.s [1H, N**H**NHC(O)], 7.05–7.24 m (4H, H_{arom}), 7.30–7.63 m (8H, H_{arom}), 7.76–7.84 m (2H, H_{arom}), 8.94 br.s and 9.02 br.s [1H, NHN**H**C(O)]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.51 d ($OCH_2\mathbf{C}H_3$, $^3J_{CP}$ = 6.1 Hz), 30.08 d and 33.00 d (CH_2, cycl., $^3J_{CP}$ = 4.3 Hz), 62.22 d ($O\mathbf{C}H_2CH_3$, $^2J_{CP}$ = 7.8 Hz), 80.20 d (CP, $^1J_{CP}$ = 122.3), 125.91 d ($^3J_{CP}$ = 3.5 Hz), 126.80, 127.56, 128.12 d ($^3J_{CP}$ = 12.4 Hz), 128.59, 128.71 d ($^1J_{CP}$ = 116.3 Hz), 129.10 d ($^4J_{CP}$ = 3.4 Hz), 131.56, 132.68 d ($^4J_{CP}$ = 2.7 Hz), 132.86 d ($^2J_{CP}$ = 9.5 Hz), 133.59, 135.19, 137.13, 138.27, 165.19 (C=O). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 40.69, 44.35. Mass spectrum: *m*/*z*: 447.1483 $[M + Na]^+$ (calculated for $C_{24}H_{25}N_2NaO_3P$: 443.1495).

Methyl 2-({1-[methoxy(phenyl)phosphoryl]cyclohexyl}amino)-3-phenylpropanoate (11). A mixture of 2 mL of methanol, 1 mmol of phenylalanine methyl ester hydrochloride, 1 mmol of cyclohexanone, 1 mmol of ethyl phenylphosphinate, 1 mmol of triethylamine, 0.05 mmol of *t*-PcAlCl, and 4-Å molecular sieves was stirred at 60°C for 36 h. The precipitate (molecular sieves) was filtered off and washed with methanol–chloroform (5:1). The filtrate was evaporated, and the residue was dissolved in a minimum volume of chloroform and subjected to column chromatography on silica gel using $CHCl_3$–MeOH (75:1) as eluent. Yield 40%. IR spectrum, ν, cm^{-1}: 1035 (P–O–C), 1220 (P=O), 1745 (C=O), 3370 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87–1.02 m (1H, cycl.), 1.11–11.30 m (2H, cycl.), 1.40–1.58 m (3H, cycl.), 1.61–1.69 m (1H, cycl.), 1.73–1.92 m (3H, cycl.), 2.91 d and 2.93 d (1H, $C\mathbf{H}_2CH$, $^2J_{HH}$ = 13.0 Hz), 2.98 d and 3.00 d (1H, $C\mathbf{H}_2CH$, $^2J_{HH}$ = 13.0 Hz), 3.62 d (3H, $POCH_3$, $^3J_{HP}$ = 8.0 Hz), 3.63 s (3H, OCH_3), 4.04–4.24 m [1H, C(O)C**H**NH], 7.11–7.36 m (5H, H_{arom}), 7.45–7.49 m (2H, H_{arom}), 7.53–7.56 m (1H, H_{arom}), 7.75–7.79 m (2H, H_{arom}). ^{13}C NMR spec-trum ($CDCl_3$), δ_C, ppm: 19.23 d (cycl., $^3J_{CP}$ = 11.1 Hz), 19.77 d (cycl., $^3J_{CP}$ = 10.4 Hz), 25.39 (cycl.), 30.80 d (cycl., $^2J_{CP}$ = 4.3 Hz), 32.05 d (cycl., $^2J_{CP}$ = 2.6 Hz), 42.45 ($\mathbf{C}H_2Ph$), 51.80 d ($POCH_3$, $^2J_{CP}$ = 7.8 Hz), 51.35 (OCH_3), 57.08 [C(O)**C**HNH], 58.75 d (PC, cycl., $^1J_{CP}$ = 125.7 Hz), 126.48, 128.10, 128.29 d ($^2J_{CP}$ = 11.3 Hz), 129.66, 132.02 d ($^4J_{CP}$ = 2.6 Hz), 132.40 d ($^3J_{CP}$ = 9.5 Hz), 137.67, 175.85 (C=O). ^{31}P NMR spectrum ($CDCl_3$): δ_P 47.38 ppm. Mass spectrum: *m*/*z* 438.1806 $[M + Na]^+$ (calculated for $C_{23}H_{30}NNaO_4P$ 438.1805).

Ethyl-[1-(2{2-[*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazinyl)cyclohexyl]phenylphosphinate (14) was synthesized from hydrazide **12** according to the general procedure; eluent $CHCl_3$–MeOH (100:1). Yield 67% (mixture of two diastereoisomers), colorless crystals, mp 165–167°C. IR spectrum, ν, cm^{-1}: 1030 (P–O–C), 1190 (P=O); 1650, 1710 (C=O), 3240 (NH); 3400, 3460 (NH–NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.97–1.13 m (1H, cycl.), 1.14–1.79 m (9H, cycl.), 1.20–1.34 m (3H, $OCH_2C\mathbf{H}_3$), 1.41 s and 1.42 s [9H, $(CH_3)_3C$], 2.95–3.14 m (2H, $PhC\mathbf{H}_2$), 3.83–3.94 m and 4.03–4.12 m (2H, $OC\mathbf{H}_2CH_3$), 4.26–4.39 m [1H, NHC**H**C(O)], 5.00 br.s (1H, NHN**H**C), 7.15–7.36 m (5H, H_{arom}), 7.37–7.48 m (2H, H_{arom}), 7.48–7.70 m (3H, H_{arom}), 8.39 br.s

and 8.45 br.s [1H, C(O)N**H**NH]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.47 d and 16.53 d ($OCH_2\mathbf{C}H_3$, $^3J_{CP}$ = 5.9 Hz), 19.65 d (cycl., $^3J_{CP}$ = 8.8 Hz), 19.69 d (cycl., $^3J_{CP}$ = 8.1 Hz), 25.02 (cycl.), 26.34 (cycl.), 26.59 (cycl.), 28.25 [($\mathbf{C}H_3)_3C$], 38.37 (Ph$\mathbf{C}H_2$), 54.91 [NH**C**HC(O)], 58.72 d and 58.82 d (PCH, $^1J_{CP}$ = 117.1 Hz), 61.45 d and 61.50 d ($O\mathbf{C}H_2CH_3$, $^2J_{CP}$ = 5.0, 5.1 Hz), 126.84, 128.24 d ($^3J_{CP}$ = 11.7 Hz), 128.64, 128.64 d ($^1J_{CP}$ = 155.2 Hz), 128.87 d ($^1J_{CP}$ = 163.9 Hz), 129.28, 132.46, 133.18 d ($^2J_{CP}$ = 8.8 Hz), 136.51, 155.17 [OC(O)N], 167.72 [C(O)NH]. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 46.26, 46.38. Mass spectrum: *m*/*z* 552.2594 [M + Na]$^+$ (calculated for $C_{28}H_{40}N_3NaO_5P$: 552.2598).

Ethyl [1-(2-{2-[(*tert*-butoxycarbonyl)amino]-3-methylpentanoyl}hydrazinyl)-1-cyclopropylethyl]-phenylphosphinate (15) was synthesized from hydrazide **13** according to the general procedure for the synthesis of hydrazinophosphinates; eluent $CHCl_3$–MeOH (100:1). Yield 62% (mixture of four diastereoisomers), colorless crystals, mp 118–120°C. IR spectrum, ν, cm^{-1}: 1040 (P–O–C), 1180 (P=O); 1670, 1720 (C=O); 3300, 3450 (NH, NH–NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.18–0.43 m [4H, $(CH_2)_2$, cycl.], 0.78–0.96 m (9H, CCH_3, $CH_2C\mathbf{H}_3$, $CHC\mathbf{H}_3$), 1.04–1.16 m (1H, CH, cycl.), 1.33 t and 1.34 t (3H, $OCH_2C\mathbf{H}_3$, J_{HH} = 7.0, 7.6 Hz), 1.40 s and 1.41 s [9H, $(CH_3)_3C$], 1.79–1.91 m (1H, C**H**CH_3), 3.91–4.06 m [1H, NHC**H**C(O)], 3.91–4.06 m and 4.09–4.22 m (2H, O$\mathbf{C}H_2CH_3$); 5.07 s, 5.09 s, 5.12 s, and 5.14 s (1H, NHN**H**C); 7.40–7.48 m (2H, H_{arom}), 7.50–7.54 m (1H, H_{arom}), 7.72–7.85 m (2H, H_{arom}); 8.20 br.s, 8.43 br.s, and 8.47 br.s [1H, C(O)N**H**NH]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: –0.50 d, –0.33 d, and –0.10 d [$(CH_2)_2$, cycl., $^3J_{CP}$ = 9.5 Hz], –0.09 d [$(CH_2)_2$, cycl., $^3J_{CP}$ = 11.3 Hz], 2.10 [$(CH_2)_2$, cycl.], 2.06 [$(CH_2)_2$, cycl.], 1.95 [$(CH_2)_2$, cycl.], 1.87 [$(CH_2)_2$, cycl.], 11.29 ($CH_2\mathbf{C}H_3$), 11.30 ($CH_2\mathbf{C}H_3$), 11.34 ($CH_2\mathbf{C}H_3$), 11.37 ($CH_2\mathbf{C}H_3$), 12.05 ($CH\mathbf{C}H_3$), 12.09 ($CH\mathbf{C}H_3$), 12.16 ($CH\mathbf{C}H_3$), 12.19 ($CH\mathbf{C}H_3$), 12.99 d ($C\mathbf{C}H_3$, $^2J_{CP}$ = 2.6 Hz), 13.19 d ($C\mathbf{C}H_3$, $^2J_{CP}$ = 3.5 Hz), 13.47 d and 13.71 d ($C\mathbf{C}H_3$, $^2J_{CP}$ = 4.3 Hz), 15.41 d and 15.52 d (CH, cycl., $^2J_{CP}$ = 4.3, 3.5 Hz), 16.47 d and 16.50 d ($OCH_2\mathbf{C}H_3$, $^3J_{CP}$ = 6.1 Hz), 24.52 ($\mathbf{C}H_2CH_3$), 24.55 ($\mathbf{C}H_2CH_3$), 24.57 ($\mathbf{C}H_2CH_3$), 24.59 ($\mathbf{C}H_2CH_3$), 28.20 [($\mathbf{C}H_3)_3C$], 37.00 ($\mathbf{C}HCH_3$), 37.11 ($\mathbf{C}HCH_3$), 37.14 ($\mathbf{C}HCH_3$), 37.18 ($\mathbf{C}HCH_3$), 58.09 [NH**C**HC(O)], 58.12 [NH**C**HC(O)], 58.15 [NH**C**HC(O)], 58.19 [NH**C**HC(O)], 59.64 d (NHCP, $^1J_{CP}$ = 117.1 Hz), 59.67 d (NHCP, $^1J_{CP}$ = 117.9 Hz), 59.88 d and 59.92 d (NHCP, $^1J_{CP}$ = 117.1 Hz), 61.33 d ($O\mathbf{C}H_2CH_3$, $^2J_{CP}$ = 7.8 Hz), 61.43 d ($O\mathbf{C}H_2CH_3$, $^2J_{CP}$ = 6.9 Hz), 61.50 d and 61.56 d ($O\mathbf{C}H_2CH_3$, $^2J_{CP}$ = 6.1 Hz), 79.56 [$(CH_3)_3\mathbf{C}$], 79.59 [$(CH_3)_3\mathbf{C}$], 79.65 [$(CH_3)_3\mathbf{C}$], 79.68 [$(CH_3)_3\mathbf{C}$], 128.13 d ($^1J_{CP}$ = 114.5 Hz), 128.17 d ($^1J_{CP}$ = 118.8 Hz), 128.36 d ($^1J_{CP}$ = 120.5 Hz), 128.41 d ($^1J_{CP}$ = 119.7 Hz); 128.08 d, 128.10 d, and 128.11 d ($^3J_{CP}$ = 12.1 Hz); 132.31 d ($^4J_{CP}$ = 2.6 Hz), 132.34 d ($^4J_{CP}$ = 3.0 Hz), 133.06 d ($^2J_{CP}$ = 7.8 Hz), 133.11 d ($^2J_{CP}$ = 9.5 Hz), 155.49 [NHC(O)O], 155.52 [NHC(O)O], 155.55 [NHC(O)O], 155.61 [NHC(O)O], 169.17 [NH**C**(O)CH_2], 169.21 [NH**C**(O)CH_2], 169.36 [NH**C**(O)CH_2], 169.38 [NH**C**(O)CH_2]. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 45.54, 45.43, 44.82, 44.48. Mass spectrum: *m*/*z* 504.2602 [M + Na]$^+$ (calculated for $C_{24}H_{40}N_3NaO_5P$ 504.2598).

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CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

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