Synthesis of α-hydrazino phosphonates from L-amino acid- and L-glutathione-derived hydrazones

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[Tetra(*tert*-butyl)phthalocyanine]aluminum chloride catalyzed hydrophosphorylation of cyclic ketone hydrazones, which were derived from hydrazides of L-amino acids and glutathione, resulted in polyfunctional α-hydrazino phosphonates.

Key words: L-amino acid hydrazides, L-glutathione dihydrazide, hydrazones, α-hydrazino phosphonates, [tetra(*tert*-butyl)phthalocyanine]aluminum chloride, diethyl phosphite, the Pudovik reaction.

Structural analogs of α-amino phosphonates serving as amino acid mimetics and possessing different biological activity,[1,2] α-hydrazino phosphonates, are still poorly studied compounds in terms of their synthesis and biological activity, while α-hydrazino phosphonates of amino acids and peptides are not described in the literature.

Previously, we have developed the approach toward α-amino phosphonates based on three-component Kabachnik—Fields reaction[3] in the presence of [tetra(*tert*-butyl)phthalocyanine]aluminum chloride (^{t}PcAlCl) as a catalyst. This method makes it possible to synthesize α-amino phosphonates on the base of L-amino acids and peptides.[4] Later, catalysis with ^{t}PcAlCl was successfully applied for the synthesis of α-hydrazino phosphonates of azines and hydrazones.[5—7] The method involved addition of diethyl phosphite at the C=N bond of the corresponding hydrazones.

In continuation of this research, in the present work, hydrazones derived from enantiomerically pure L-amino acid hydrazides, L-glutathione dihydrazide, and carbocyclic ketones were used as the amine component.

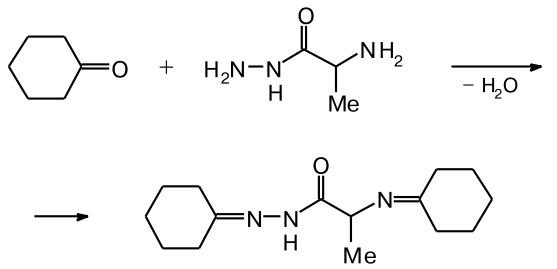
Starting hydrazones **1—5** were synthesized by the reaction of hydrazides of amino acids (in some cases *N*-protected) with the corresponding cyclic ketones in the yields of 85—98% (Scheme 1).

Dihydrazone **6** derived from glutathione dihydrazide and *N*-Boc-piperidone was prepared in 95% yield (Scheme 2).

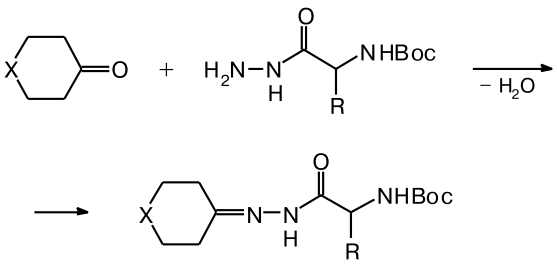
The hydrazones synthesized were involved in the catalytic phosphorylation. It was shown that diethyl phosphite adds to both C=N bonds of hydrazono imine **1** to give diphosphonate **7** in 55% yield within 20 h (Scheme 3).

Chemoselective phosphorylation was achieved with *N*-protected hydrazones **2—5**, which gave the corresponding α-hydrazino phosphonates **8—11** in 68—75% yields (Scheme 4).

Scheme 1



1



2—5 (85—98%)

Compound	R	X	Compound	R	X
2	Me	CH_2	**4**	CH_2Ph	CH_2
3	Me	NBoc	**5**	CH_2Ph	NBoc

Taking α-hydrazino phosphonate **9** as an example, both Boc-protecting groups and ethoxy groups at phosphorus atom were removed by the action of trimethylsilyl bromide (TMSBr) followed by quenching with propylene

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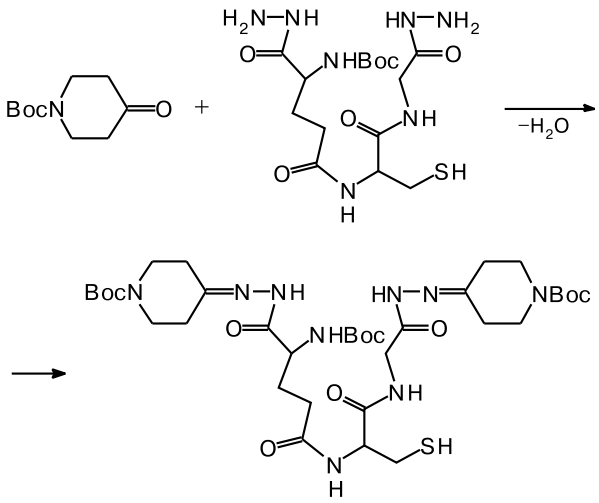
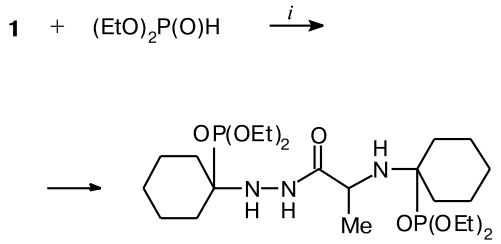
Scheme 2



6 (95%)

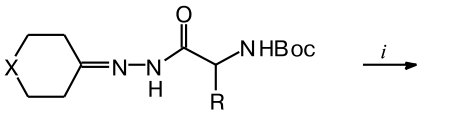
Scheme 3



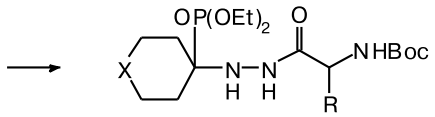
7 (55%)

i. ^{t}PcAlCl, 80 °C, 20 h.

Scheme 4



2—5



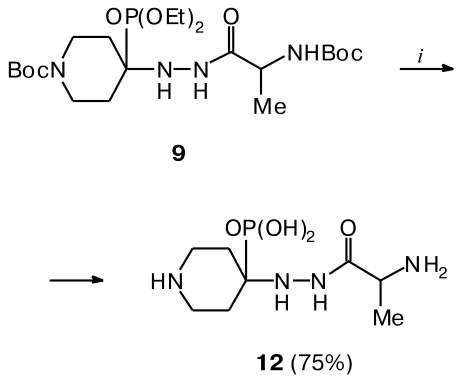
8—11 (68—75%)

i. $(EtO)_2P(O)H$, ^{t}PcAlCl, 80 °C, 8—10 h.

Compound	R	X	Compound	R	X
2, **8**	Me	CH_2	**4**, **10**	CH_2Ph	CH_2
3, **9**	Me	NBoc	**5**, **11**	CH_2Ph	NBoc

oxide in methanol. The reaction afforded α-hydrazino phosphonic acid **12**, which may be regarded as a conformationally fixed bioisosteric analog of the natural ligand to $GABA_C$-receptor, γ-aminobutyric acid, and several known synthetic ligands[8] as well (Scheme 5).

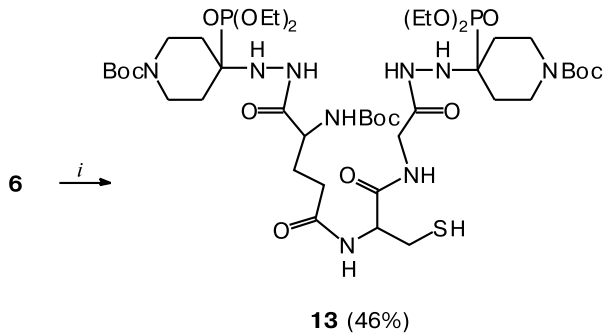
Scheme 5



i. 1) TMSBr; 2)  , MeOH.

To date, it is known that several synthetic peptides (*e.g.*, heptapeptide "Semax",[9] which is used in clinical practice, and tripeptide "RER"[10—12]) can improve brain cognitive function. Natural tripeptide glutathione is involved in redox processes in the living organisms. Recently, application of glutathione as a component for neuroprotective and antisclerotic pharmaceuticals was documented.[13] One of the way to design the promising "twin-drugs" is the combination of the peptide moiety and phosphonate group in one molecule. With this aim, we involved hydrazone **6** prepared from L-glutathione hydrazide and *N*-Boc-piperidone in hydrophosphorylation. The reaction was carried for 20 h and the corresponding diphosphorylation product **13** was obtained in 46% yield (Scheme 6).

Scheme 6



i. $(EtO)_2P(O)H$, ^{t}PcAlCl, 80 °C, 20 h.

Structures of hydrazones **1—6**, α-hydrazino phosphonates **7—11**, **13**, and phosphonic acid **12** were established

by IR spectroscopy, NMR ^{1}H, ^{13}C, and ^{31}P spectroscopy and confirmed by elemental analysis and high resolution mass spectrometry.

The IR spectra of α-hydrazino phosphonates **7**—**11** and **13** contained absorption bands at 1230—1260 cm^{-1} corresponding to the P=O group and at 3230—3290 cm^{-1} attributed to the NH group. The ^{31}P NMR of the compounds synthesized exhibited signals for the phosphorus atoms in the range of δ 25—30. In the ^{31}P NMR spectra of diphosphonates **7** and **13**, the signals for two phosphorus atoms were observed at δ 27.73, 30.46 and 25.66, 25.74, respectively. In case of α-hydrazino phosphonates **8**—**11**, the ^{31}P NMR spectra exhibited two signals for the phosphorus atom in the range of δ 26.41—29.28 with relative intensities 1 : 20, which can probably be explained by the existence of rotamers.[6] This issue is confirmed by the fact that with an increase in temperature, the signals for the phosphorus atom of phosphonate **9** are broadened and approached each other; however, no coalescence of the signals was achieved. Thus, the NMR ^{31}P (DMSO-d_6) of phosphonate **9** at 22 °C exhibited signals for the phosphorus atoms at δ 26.41 and 26.83; at 70 °C these signals were observed at δ 26.41 and 26.68, while at 120 °C these signals became closer and appeared at δ 26.41 and 26.56. The NMR ^{1}H and ^{13}C spectroscopy data confirmed also the structures of α-hydrazino phosphonates **7**—**11** and **13**.

In summary, in the present work, hitherto unknown α-hydrazino phosphonates derived from hydrazides of natural L-amino acid and natural tripeptide L-glutathione were synthesized, opening broad prospects for the design of compounds of pharmacological value.

Experimental

NMR ^{1}H (400.13 MHz), ^{13}C (100.61 MHz), and ^{31}P (161.98 MHz) were run on a «Bruker Avance 400» instrument in $CDCl_3$ and D_2O relative to Me_4Si (^{1}H and ^{13}C, internal standard) and 85% aqueous H_3PO_4 (^{31}P, external standard). IR spectra were recorded on a UR-20 spectrophotometer in CCl_4. Elemental analysis was carried out on a Vario-II CHN analyzer. Mass spectra were recorded on a Finnigan Mat Incos 50 quadrupole mass spectrometer (EI, 70 eV, direct inlet). High resolution mass spectra were run on a micrOTOF II instrument (Bruker Daltonics) in the positive ion mode (electrospray ionization (ESI)), scanning mass range was 50—3000 Da, capillary cap voltage was 4.5 kV). The sample was injected *via* syringe pump, MeCN was used as a solvent, flow rate was 3 μL min^{-1}, chamber temperature was 180 °C, carrier gas was nitrogen (4.0 L min^{-1}). Specific rotation was measured on a EPO-1 AVNIEKIPRODMASh polarimeter at 23 °C in MeOH or H_2O at concentrations *c* 1 g (100 mL)$^{-1}$. Diethyl phosphite (Aldrich) was used as purchased. [Tetra(*tert*-butyl)phthalocyanine]aluminum chloride was synthesized by the known procedure.[14] The course of the reaction and purity of compounds were monitored by TLC on ALUGRAM SIL G/UV$_{254}$ plates. Column chromatography was performed on silica gel (MN Kieselgel 60, 0.04—0.063 mm).

L-Alanine hydrazide (L-AlaNHNH$_2$). To a solution of L-alanine methyl ester (0.516 g, 5 mmol, prepared from the corresponding hydrochloride by treatment with aqueous NaOH) in MeOH (5 mL), hydrazine hydrate (1.25 mL, 25 mmol) was added and the reaction mixture was stirred for 18 h. The solvent was removed *in vacuo*, purification of the residue by column chromatography (silica gel, elution with MeOH—$CHCl_3$, 1 : 1) afforded L-AlaNHNH$_2$ (0.438 g, 85%) as transparent oil, $[\alpha]_D^{23}$ +14.0 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.27 (d, 3 H, Me, $^3J_{H,H}$ = 6.6 Hz); 3.41, 3.42 (both q, 1 H, CH, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 7.1 Hz); 4.33 (br.s, 5 H, NHNH$_2$, NH$_2$). ^{13}C NMR ($CDCl_3$), δ: 27.53 (s, Me); 49.20 (s, CH); 176.04 (s, C=O). IR, ν/cm^{-1}: 1670 (C=O); 3300 (NH). Found (%): C, 34.86; H, 8.61; N, 40.54. $C_3H_9N_3O$. Calculated (%): C, 34.94; H, 8.80; N, 40.75.

Synthesis of hydrazides of *N*-Boc-protected L-amino acids (general procedure). To a solution of *N*-Boc-protected amino acid methyl ester (5 mmol) in MeOH (10 mL), hydrazine hydrate (2.45 ml, 50 mmol) was added and the reaction mixture was stirred for 18 h. Removal of the solvent *in vacuo* afforded the corresponding hydrazide of *N*-Boc-protected amino acid as colorless crystals.

***N-tert*-Butoxycarbonyl-L-alanine hydrazide (Boc-L-AlaNHNH$_2$).** Yield 0.97 g (60 %), $[\alpha]_D^{23}$ −28.0 (MeOH); m.p. 95—96 °C (*cf.* Ref. 15: $[\alpha]_D^{20}$ −25.4 (*c* 1, MeOH), m.p. 96—97 °C).

***N-tert*-Butoxycarbonyl-L-phenylalanine hydrazide (Boc-L-PheNHNH$_2$).** Yield 1.23 g (68%), $[\alpha]_D^{23}$ +9.8 (MeOH); m.p. 121—123 °C (*cf.* Ref. 16: $[\alpha]_D^{20}$ +9.7 (*c* 1, MeOH), m.p. 120—122 °C).

***N-tert*-Butoxycarbonyl-L-glutathione dihydrazide** was synthesized according to the general procedure using two-fold excess of hydrazine hydrate per 1 mol of *N-tert*-butoxycarbonyl-L-glutathione dimethyl ester. Yield 1.48 g (64%), m.p. 170—171 °C; $[\alpha]_D^{23}$ −230.5 (H_2O). ^{1}H NMR (D_2O), δ: 1.33 (s, 9 H, Bu^t); 1.80—188, 1.90—2.02 (both m, 1 H each, CHC$\underline{H}_2$CH$_2$); 2.34—2.36 (m, 2 H, CHCH$_2$C$\underline{H}_2$); 2.85—2.91, 3.15—3.19 (both m, 1 H each, C$\underline{H}_2$SH); 3.82 (AB system, H$_A$, 1 H, CH$_2$, Gly, $^2J_{H,H}$ = 16.7 Hz); 3.86 (AB system, H$_B$, 1 H, CH$_2$, Gly, $^2J_{H,H}$ = = 16.7 Hz); 3.86—3.92 (m, 1 H, C$\underline{H}$CH$_2$CH$_2$); 4.60—4.64 (m, 1 H, C$\underline{H}$CH$_2$SH). ^{13}C NMR (D_2O), δ: 26.95 (s, $\underline{C}$H$_2$SH); 27.62 (Me, Bu^t); 31.34 (s, CH$\underline{C}$H$_2$CH$_2$); 38.25 (s, CHCH$_2\underline{C}$H$_2$); 41.39 (s, NH$\underline{C}$H$_2$); 52.60 (s, $\underline{C}$HCH$_2$CH$_2$); 52.92 (s, $\underline{C}$HCH$_2$SH); 81.51 (s, C, Bu^t); 157.15 (s, C=O, C(O)OBu^t); 169.97, 172.74; 173.06; 175.12 (C=O, C(O)NH). IR, ν/cm^{-1}: 1640—1690 (C=O, Boc, C(O)NH); 2290—3340 (NH, NH$_2$). Found (%): C, 41.29; H, 6.50; N, 22.38. $C_{15}H_{29}N_7O_6S$. Calculated (%): C, 41.37; H, 6.71; N, 22.51.

Synthesis of hydrazones 1, 2, and 4 derived from L-amino acid hydrazides (general procedure). A mixture of cyclohexanone (9 mmol) and the corresponding hydrazide (3 mmol) was refluxed for 1—3 h, the reaction mixture was cooled to room temperature, the precipitate that formed was filtered off, washed with diethyl ether and dried *in vacuo*.

(*S*)-*N*′-Cyclohexylidene-2-(cyclohexylideneamino)propanehydrazide (1). Yield 85%, m.p. 103—105 °C; $[\alpha]_D^{23}$ +36.4 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.11—1.22 (m, 1 H, CH$_2$, cycl.); 1.36 (d, 3 H, Me, $^3J_{H,H}$ = 7.1 Hz); 1.40—1.52 (m, 3 H, CH$_2$, cycl.); 1.54—1.69 (m, 9 H, CH$_2$, cycl.); 1.75—1.87 (m, 3 H, CH$_2$, cycl.); 1.92—1.99 (m, 1 H, CH$_2$, cycl.); 2.11—2.18 (m, 1 H, CH$_2$, cycl.); 2.22—2.33 (m, 1 H, CH$_2$, cycl.); 2.37—2.50 (m, 2 H, CH$_2$, cycl., NH); 3.50 (q, 1 H, CH, $^3J_{H,H}$ = 6.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 17.91 (s, Me); 22.31, 22.83, 24.88, 25.61, 26.71,

27.65, 30.74, 31.61, 35.87, 37.51 (all s, CH_2, cycl.); 53.07 (s, CH); 168.98 (s, C=N), 173.63 (s, C=NNH); 178.25 (s, C=O). IR (CCl_4), ν/cm^{-1}: 1630 (C=N); 1680 (C=O); 3270 (NH). Found (%): C, 68.37; H, 9.83; N, 15.89. $C_{15}H_{25}N_3O$. Calculated (%): C, 68.40; H, 9.57; N, 15.95.

***tert*-Butyl *N*-[(*S*)-1-methyl-2-oxo-2-(2-cyclohexylidenehydrazino)ethyl]carbamate (2).** Yield 85%, m.p. 110—112 °C; $[\alpha]_D^{23}$ +21.4 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.34, 1.37 (both d, 3 H, Me, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 7.0 Hz); 1.41, 1.42 (both s, 9 H, Bu^t); 1.57—1.69 (m, 6 H, CH_2, cycl.); 2.24—2.37 (m, 4 H, CH_2, cycl.); 4.22—4.29, 5.02—5.10 (both m, 1 H, CH); 5.29, 5.39 (br.s, d, 1 H, NHBoc, $^3J_{H,H}$ = 8.1 Hz); 9.11, 9.70 (both br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 17.91, 18.72 (Me, CHMe); 25.56, 25.88, 25.95, 26.11, 26.91, 27.03 (CH_2, cycl.); 28.28, 28.35 (Me, Bu^t); 35.50 (CH_2, cycl.); 47.13, 48.78 (CH); 79.30, 80.36 (C, Bu^t); 155.16, 156.24 (C=N); 156.84, 161.55 (C=O, Boc); 169.22, 175.41 (C=O, C(O)NH). IR, ν/cm^{-1}: 1645 (C=N), 1660—1690 (C=O, C(O)NH, C=N); 1720 (C=O, Boc), 3230 (NH). Found (%): C, 59.46; H, 8.90; N, 14.89. $C_{14}H_{25}N_3O_3$. Calculated (%): C, 59.34; H, 8.89; N, 14.83.

***tert*-Butyl *N*-[(*S*)-1-benzyl-2-oxo-2-(2-cyclohexylidenehydrazino)ethyl]carbamate (4).** Yield 85%, m.p. 124—125 °C; $[\alpha]_D^{23}$ + 25.0 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.37 (s, 9 H, Bu^t); 1.50—1.68 (m, 6 H, CH_2, cycl.); 1.97—2.04 (m, 1 H, CH_2, cycl.); 2.20—2.38 (m, 3 H, CH_2, cycl.); 2.88—3.16 (m, 2 H, CH_2Ph); 4.44—4.48, 5.35—5.41 (both m, 1 H, CH); 5.28, 5.46 (d, $^3J_{H,H}$ = 8.3 Hz, br.s, 1 H, NHBoc); 7.20—7.27 (m, 5 H, CH, Ph); 9.31, 9.51 (both br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 25.47, 25.55, 25.90, 26.18, 26.74, 26.84, 26.96 (CH_2, cycl.); 28.25, 28.31 (Me, Bu^t); 35.44, 35.55 (CH_2, cycl.); 38.36, 38.58 (CH_2Ph); 52.25, 54.95 (CH); 79.36, 80.25 (C, Bu^t); 126.54, 126.75 (CH, Ph); 128.16, 128.58, 129.41, 129.57 (CH, Ph); 136.94 (C, Ph); 155.19, 155.96 (C=N); 157.29, 162.16 (C(O)NH); 167.97, 173.99 (C=O, Boc). IR, ν/cm^{-1}: 1660—1880 (C=O, C(O)NH, C=N); 1710 (C=O, Boc); 3260 (NH). Found (%): C, 66.70; H, 7.99; N, 11.58. $C_{20}H_{29}N_3O_3$. Calculated (%): C, 66.83; H, 8.13; N, 11.69.

(*S*)-1-*tert*-Butoxycarbonyl-4-({2-[(*tert*-butoxycarbonyl)amino]propanoyl}hydrazino)piperidine (3). A mixture of *N*-Boc-piperidone (0.398 g, 2 mmo) and Boc-L-AlaNHNH$_2$ (0.406 g, 2 mmol) was heated at 100 °C for 1.5 h. A reaction mixture was cooled to room temperature, the precipitate that formed was filtered off, washed with diethyl ether, and dried *in vacuo*. Yield 97%, m.p. 138—140 °C; $[\alpha]_D^{23}$ +47.0 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.23, 1.27 (both d, 3 H, CHMe, $^3J_{H,H}$ = 7.0 Hz); 1.31, 1.32 (both s, 9 H, Bu^t); 1.34, 1.35 (both s, 9 H, Bu^t); 2.30—2.41 (m, 4 H, CH_2, cycl.); 3.37—3.52 (m, 4 H, CH_2, cycl.); 4.11—4.18, 4.92—4.96 (both m, 1 H, CH); 5.23 (br.d, 1 H, NHBoc, $^3J_{H,H}$ = 8.4 Hz); 9.18, 9.78 (both br.s, 1 H, NHC(O)). ^{13}C NMR ($CDCl_3$) δ: 17.07, 18.59 (Me, CHMe); 25.56, 27.36 (CH_2, cycl.); 28.36 (Me, Bu^t); 33.79, 33.91, 41.10, 43.67 (CH_2, cycl.); 47.09, 48.87 (CH); 79.45, 80.09, 80.14, 80.50 (C, Bu^t, NBoc, NHBoc); 152.12, 154.55 (C=N); 155.18, 156.37 (C=O, NHBoc); 157.02 (C=O, NBoc); 169.22, 175.41 (C=O, C(O)NH). IR, ν/cm^{-1}: 1650—1690 (C=O, C(O)NH, C=N), 1710 (C=O, Boc); 3300 (NH). Found (%): C, 56.20; H, 8.53; N, 14.35. $C_{18}H_{32}N_4O_5$. Calculated (%): C, 56.23; H, 8.39; N, 14.57.

(*S*)-1-*tert*-Butoxycarbonyl-4-(2-{2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazino)piperidine (5). A mixture of *N*-Boc-piperidone (0.398 g, 2 mmo) and Boc-L-PheNHNH$_2$ (0.558 g, 2 mmol) was heated at 30 °C for 1.5 h. The reaction mixture was cooled to room temperature, the precipitate that formed was filtered off, washed with diethyl ether, and dried *in vacuo*. Yield 98%, m.p. 163—165 °C; $[\alpha]_D^{23}$ +40.0 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.31, 132 (both s, 9 H, Bu^t); 1.39, 1.41 (both s, 9 H, Bu^t); 1.98—2.42 (m, 4 H, CH_2, cycl.); 2.85—3.06 (m, 2 H, CH_2Ph); 3.29—3.52 (m, 4 H, CH_2, cycl.); 4.35—4.40, 5.28—5.33 (both m, 1 H, CH); 5.17, 5.37 (both br.d, 1 H, NH, $^3J_{H,H}$ = 9.4 Hz, $^3J_{H,H}$ = 7.0 Hz); 7.10—7.22 (m, 5 H, Ph); 9.25 (br.s, 1 H, NHC(O)). ^{13}C NMR ($CDCl_3$), δ: 26.46, 27.02 (CH_2, cycl.); 28.28 (Me, Bu^t), 28.40 (Me, Bu^t); 33.74, 33.88 (CH_2, cycl.); 38.19, 38.71 (CH_2Ph); 41.13 (CH_2, cycl.); 43.60 (CH_2, cycl.); 52.20, 55.01 (CH); 79.58, 80.13, 80.43 (C, Bu^t, NBoc, NHBoc); 126.61, 126.84, 128.18, 128.61, 129.42, 129.57 (CH, Ph); 136.85 (C, Ph); 152.45, 154.55 (C=N); 155.19, 156.06 (C=O, NHBoc); 157.68 (C=O, NBoc); 168.10, 173.98 (C=O, C(O)NH). IR, ν/cm^{-1}: 1650—1710 (C=O, Boc, C=O, C(O)NH, C=N), 3300 (NH). Found (%): C, 62.65; H, 7.98; N, 12.20. $C_{24}H_{36}N_4O_5$. Calculated (%): C, 62.59; H, 7.88; N, 12.16.

(2*S*,7*R*)-1,11-Bis[2-(1-*tert*-butoxycarbonylpiperidin-4-ylidene)hydrazino]-2-*tert*-butoxycarbonylamino-7-sulfanylmethyl-6,9-diazaundecane-1,5,8,11-tetraone (6). A mixture of *N*-Boc-piperidone (0.796 g, 4 mmol) and *N*-*tert*-butoxycarbonyl-L-glutathione dihydrazide (0.870 g, 2 mmol) in DMF (2 mL) was heated at 70 °C for 3 h. The solvent was removed *in vacuo*, the precipitate that formed was washed with diethyl ether and dried *in vacuo*. Yield 95%, m.p. 142—144 °C; $[\alpha]_D^{23}$ −14.7 (MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.35, 1.39, 1.40 (all s, 9 H each, Bu^t); 1.82—1.95, 1.99—2.12 (both m, 1 H each, CHCH_2CH$_2$); 2.29—2.48 (m, 10 H, CHCH$_2$CH_2, CH_2, cycl.); 2.98—3.06 (br.m, 2 H, CH_2SH); 3.15 (s, 2 H, NHCH_2C(O)); 3.42—3.56 (m, 8 H, CH_2, cycl.); 4.08—4.16 (m, 1 H, CHCH$_2$CH$_2$); 4.71—5.02 (m, 1 H, CHCH$_2$SH). ^{13}C NMR ($CDCl_3$), δ: 26.58, 27.25 (CH_2, cycl.); 27.68 (CH_2SH); 28.20 (Me, Bu^t); 31.78, 33.36, 43.57 (CH_2, cycl.); 33.70 (CHCH_2CH$_2$); 41.20 (CHCH$_2$CH_2); 41.98 (NHCH$_2$); 52.32 (CHCH$_2$CH$_2$); 52.76 (CHCH$_2$SH); 80.32 (C, Bu^t); 154.70, 156.26 (C=O, C(O)OBu^t); 159.46, 166.16 (C=N); 169.20, 170.82, 171.38, 173.15 (C=O, C(O)NH). IR, ν/cm^{-1}: 1650—1720 (C=O, Boc, C(O)NH, C=N); 2250—3320 (NH, NH_2). Found (%): C, 52.76; H, 7.27; N, 15.55, S, 3.90. $C_{35}H_{59}N_9O_{10}S$. Calculated (%): C, 52.68; H, 7.45; N, 15.80; S, 4.02.

Synthesis of α-hydrazino phosphonates derived from hydrazides of L-amino acids and L-glutathione 7—11 and 13 (general procedure). Diethyl phosphite (5 mmol) and ^{t}PcAlCl (0.05 mmol) were added to hydrazone (1 mmol) and the reaction mixture was stirred under argon at 80 °C until completion of the reaction (TLC monitoring). The volatiles were removed *in vacuo*, the residue was dissolved in small amount of CH_2Cl_2—MeOH (70 : 1) and subjected to column chromatography (silica gel, column height 15 cm, diameter 1.5—2.0 cm).

Diethyl (*S*)-{1-[2-(2-{[1-(diethoxyphosphoryl)cyclohexyl]amino}propanoyl)hydrazino]cyclohexyl}phosphonate (7) was synthesized from hydrazone **1**, reaction time was 20 h. Yield 55%; $[\alpha]_D^{23}$ −16.9 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.12—1.21 (m, 2 H, CH_2, cycl.); 1.26—1.31 (m, 12 H, 4 Me, POEt); 1.34 (d, 3 H, Me, $^3J_{H,H}$ = 7.1 Hz); 1.40—1.94 (m, 18 H, CH_2, cycl.); 2.39 (br.s, 1 H, NH); 3.69 (q, 1 H, CH, $^3J_{H,H}$ = 6.6 Hz); 4.03—4.18 (m, 8 H, 4 OCH_2); 5.20 (br.d, 1 H, NHNHC(O), $^3J_{H,H}$ = = 23.0 Hz); 9.21 (br.s, 1 H, NHNHC(O)). ^{13}C NMR ($CDCl_3$), δ: 16.42—16.55 (m, Me, POEt); 19.51 (d, Me, $^4J_{C,P}$ = 11.7 Hz); 19.78 (d, $^3J_{C,P}$ = 10.3 Hz); 19.89 (d, $^3J_{C,P}$ = 10.9 Hz); 20.24 (d, $^3J_{C,P}$ = 11.7 Hz); 21.49, 25.07, 25.44, 26.42, 27.37, 28.26,

32.27 (CH_2, cycl.); 51.50 (s, CH); 56.07 (d, C, $^1J_{C,P}$ = 142.0 Hz); 58.51 (d, C, $^1J_{C,P}$ = 164.6 Hz); 61.69, 61.95, 62.12, 63.38 (all d, OCH_2, $^2J_{C,P}$ = 7.3 Hz, $^2J_{C,P}$ = 8.1 Hz, $^2J_{C,P}$ = 7.4 Hz, $^2J_{C,P}$ = = 8.0 Hz); 172.64 (s, C=O). ^{31}P NMR ($CDCl_3$), δ: 27.73, 30.46. IR, ν/cm^{-1}: 1030, 1070 (P—O—C); 1230 (P=O); 1660 (C=O); 3330 (NH). Found (%): C, 51.26; H, 8.47; N, 7.56. $C_{23}H_{47}N_3O_7P_2$. Calculated (%): C, 51.20; H, 8.78; N, 7.79.

Diethyl (*S*)-[1-(2-{2-[(*tert*-butoxycarbonyl)amino]propanoyl}hydrazino)cyclohexyl]phosphonate (8) was synthesized from hydrazone **2**, the reaction time was 8 h. Yield 75%, m.p. 79—81 °C; $[\alpha]_D^{23}$ –22.5 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.27, 1.28 (both t, 6 H, 2 Me, POEt, $^3J_{H,H}$ = 7.1 Hz); 1.29 (d, 3 H, Me, $^3J_{H,H}$ = = 7.1 Hz); 1.37 (s, 9 H, Me, Bu^t); 1.41—1.64 (m, 8 H, CH_2, cycl.); 1.73—1.79 (m, 2 H, CH_2, cycl.); 4.05—4.14 (m, 5 H, 2 OCH_2, CH); 4.88 (br.s, 1 H, N<u>H</u>NHC(O)); 5.07 (d, 1 H, N<u>H</u>Boc, $^3J_{H,H}$ = 6.9 Hz); 8.34 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR ($CDCl_3$), δ: 16.51 (d, Me, POEt, $^3J_{C,P}$ = 4.0 Hz); 18.64 (s, Me); 19.76 (d, $^3J_{C,P}$ = 10.4 Hz); 19.86 (d, $^3J_{C,P}$ = = 10.5 Hz); 25.13, 27.28, 27.70 (CH_2, cycl.); 28.27 (s, Me, Bu^t); 49.23 (s, CH); 58.61 (d, C, $^1J_{C,P}$ = 160.7 Hz); 62.70, 62.86 (both d, OCH_2, $^2J_{C,P}$ = 7.2 Hz, $^2J_{C,P}$ = 8.0 Hz); 79.81 (s, C, Bu^t); 155.18 (s, C=O, Boc); 169.69 (s, C(O)NH). ^{31}P NMR ($CDCl_3$), δ: 28.23, 29.28. IR, ν/cm^{-1}: 1030, 1070 (P—O—C); 1240 (P=O); 1670 (C=O, C(O)NH); 1720 (C=O, Boc), 3280 (NH). Found (%): C, 51.22; H, 8.50; N, 9.81. $C_{18}H_{36}N_3O_6P$. Calculated (%): C, 51.30; H, 8.61; N, 9.97.

(*S*)-1-*tert*-Butoxycarbonyl-4-(2-{2-[*tert*-butoxycarbonyl)amino]propanoyl}hydrazino)-4-(diethyxyphosphoryl)piperidine (9) was synthesized from hydrazone **3**, the reaction time was 8 h. Yield 70%; $[\alpha]_D^{23}$ –25.9 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.32, 1.33 (both t, 6 H, 2 Me, POEt, $^3J_{H,H}$ = 7.1 Hz); 1.34 (d, 3 H, Me, $^3J_{H,H}$ = 6.8 Hz); 1.42 (s, 9 H, Me, Bu^t); 1.43 (s, 9 H, Bu^t); 1.70—1.88 (m, 4 H, CH_2, cycl.); 3.18—3.24 (m, 2 H, CH_2, cycl.); 3.78—3.38 (m, 2 H, CH_2, cycl.); 4.06—4.09 (br.m, 2 H, CH, N<u>H</u>NHC(O)); 4.11—4.20 (m, 4 H, 2 OCH_2); 5.06 (d, 1 H, NHBoc, $^3J_{H,H}$ = 7.1 Hz); 8.40 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR ($CDCl_3$), δ: 16.53 (d, Me, POEt, $^3J_{C,P}$ = 5.1 Hz); 18.43 (s, Me); 27.09, 27.49 (CH_2, cycl.); 28.25 (s, Me, Bu^t); 28.39 (s, Me, Bu^t); 37.96 (CH_2, cycl.); 49.35 (s, CH); 56.97 (d, C, $^1J_{C,P}$ = 158.8 Hz); 62.94, 63.03 (both d, OCH_2, $^2J_{C,P}$ = = 9.6 Hz, $^2J_{C,P}$ = 8.7 Hz); 79.52 (s, C, Bu^t); 79.96 (s, C, Bu^t); 154.63, 155.28 (C=O, NBoc, NHBoc); 170.87 (s, C(O)NH). ^{31}P NMR ($CDCl_3$), δ: 26.41, 27.07. IR, ν/cm^{-1}: 1030, 1050 (P—O—C); 1250 (P=O); 1660 (C=O, C(O)NH, C=N); 1660—1710 (C=O, C(O)OBu^t), 3280 (NH). Found (%): C, 50.60; H, 8.41; N, 10.88. $C_{22}H_{43}N_4O_8P$. Calculated (%): C, 50.56; H, 8.29; N, 10.72.

Diethyl (*S*)-[1-(2-{2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazino)cyclohexyl]phosphonate (10) was synthesized from hydrazone **4**, the reaction time was 10 h. Yield 72%; $[\alpha]_D^{23}$ –20.3 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.08—1.19 (m, 1 H, CH_2, cycl.); 1.26, 1.27 (both t, 6 H, 2 Me, POEt, $^3J_{H,H}$ = 7.1 Hz); 1.37 (s, 9 H, Me, Bu^t); 1.41—1.61 (m, 8 H, CH_2, cycl.); 1.70—1.75 (m, 1 H, CH_2, cycl.); 3.00—3.03 (m, 2 H, CH_2Ph); 3.99—4.10 (m, 5 H, 2 OCH_2, N<u>H</u>NHC(O)); 4.31 (br.m, 1 H, CH); 5.04 (d, 1 H, NHBoc, $^3J_{H,H}$ = 7.1 Hz); 7.16—7.19 (m, 3 H, Ph); 7.23—7.26 (m, 2 H, Ph); 8.20 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR ($CDCl_3$), δ: 16.48 (d, Me, POEt, $^3J_{C,P}$ = 5.1 Hz); 19.79 (d, CH_2, cycl., $^3J_{C,P}$ = 10.2 Hz); 25.08 (s, CH_2, cycl.); 27.21 (d, CH_2, cycl., $^2J_{C,P}$ = 16.8 Hz); 28.21 (s, Me, Bu^t); 38.30 (s, CH_2Ph); 54.84 (s, CH); 58.25 (d, C, $^1J_{C,P}$ = 160.3 Hz); 62.65, 62.83 (both d, OCH_2, $^2J_{C,P}$ = 7.3 Hz); 79.97 (s, C, Bu^t); 126.82, 128.58, 129.26, 136.48 (C, Ph); 155.14 (s, C=O, Boc); 167.87 (s, C(O)NH). ^{31}P NMR ($CDCl_3$), δ: 28.15, 28.84. IR, ν/cm^{-1}: 1040, 1060 (P—O—C); 1235 (P=O); 1645 (C=N), 1670 (C=O, C(O)NH); 1710 (C=O, Boc), 3270 (NH). Found (%): C, 57.63; H, 8.08; N, 8.29. $C_{24}H_{40}N_3O_6P$. Calculated (%): C, 57.93; H, 8.10; N, 8.45.

(*S*)-1-*tert*-Butoxycarbonyl-4-(2-{2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazino)-4-(diethoxyphosphoryl)-piperidine (11) was synthesized from hydrazone **5**, the reaction time was 10 h. Yield 68%; $[\alpha]_D^{23}$ –13.2 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.29, 1.30 (both t, 6 H, 2 Me, POEt, $^3J_{H,H}$ = 7.1 Hz); 1.41, 1.45 (both s, 18 H, Me, Bu^t); 1.57—1.68 (m, 2 H, CH_2, cycl.); 1.71—1.80 (m, 1 H, CH_2, cycl.); 2.98—3.30 (m, 4 H, C<u>H</u>$_2$Ph, CH_2, cycl.); 3.69—3.80 (m, 2 H, CH_2, cycl., NHBoc); 4.03—4.14 (m, 4 H, 2 OCH_2, CH); 4.26—4.31 (br.m, 1 H, CH); 5.01 (d, 1 H, N<u>H</u>NHC(O), $^3J_{H,H}$ = 7.3 Hz); 7.19—7.24 (m, 3 H, Ph); 7.28—7.32 (m, 2 H, Ph); 8.15 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR ($CDCl_3$), δ: 16.51 (d, Me, POEt, $^3J_{C,P}$ = 5.1 Hz); 26.79, 27.30 (CH_2, cycl.); 28.24 (s, Me, Bu^t); 28.31 (s, Me, Bu^t); 37.89, 37.90 (CH_2, cycl.); 38.28 (s, <u>C</u>H$_2$Ph); 55.03 (s, CH); 56.60 (d, C, $^1J_{C,P}$ = 158.8 Hz); 62.89, 63.01 (both d, OCH_2, $^2J_{C,P}$ = 6.6 Hz, $^2J_{C,P}$ = 7.3 Hz); 79.54 (C, Bu^t), 80.18 (C, Bu^t); 126.98, 128.71, 129.26, 136.36 (C, Ph); 154.62, 155.20 (C=O, NBoc, NHBoc); 169.04 (s, C(O)NH). ^{31}P NMR ($CDCl_3$), δ: 26.41, 26.58. IR, ν/cm^{-1}: 1030, 1050 (P—O—C); 1250 (P=O); 1650—1710 (C=O, C(O)NH, Boc), 3300 (NH). Found (%): C, 56.10; H, 8.13; N, 9.27. $C_{28}H_{47}N_4O_8P$. Calculated (%): C, 56.17; H, 7.91; N, 9.36.

(2*S*,7*R*)-1,11-Bis[2-(1-*tert*-butoxycarbonyl-4-diethoxyphosphorylpiperidin-4-yl)hydrazino]-2-*tert*-butoxycarbonylamino-7-sulfanylmethyl-6,9-diazaundecane-1,5,8,11-tetraone (13) was synthesized from hydrazone **6**, the reaction time was 20 h. Yield 46%; $[\alpha]_D^{23}$ –31.8 (MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.25—1.29 (m, 12 H, 2 Me, POEt); 1.35, 1.36, 1.37 (all s, 9 H each, Me, Bu^t); 1.60—1.88 (m, 8 H, CH_2, cycl.); 1.92—2.07 (m, 2 H, $CHC<u>H</u>_2CH_2$); 2.22—2.44 (m, 2 H, $CHCH_2C<u>H</u>_2$); 3.04—3.27, 3.64—3.85 (both m, 4 H each, CH_2, cycl.); 3.93—3.98 (br.m, 2 H, $NHC<u>H</u>_2C(O)$); 4.05—4.10 (m, 4 H, 2 OCH_2); 4.61—4.89 (m, 2 H, C<u>H</u>CH_2CH_2, C<u>H</u>CH_2SH). ^{13}C NMR ($CDCl_3$), δ: 16.50 (s, Me, POEt); 27.34 (br.m, CH_2, cycl.); 28.39 (s, Me, Bu^t); 29.62 (s, CH_2SH); 31.73 (s, $CH<u>C</u>H_2CH_2$); 37.99, 38.37 (CH_2, cycl.); 41.08 (s, $CHCH_2<u>C</u>H_2$); 42.35 (s, $NHCH_2$); 52.22 (s, <u>C</u>HCH_2CH_2); 52.46 (s, <u>C</u>HCH_2SH); 56.72 (d, C, $^1J_{C,P}$ = = 154.2 Hz); 56.97 (d, C, $^1J_{C,P}$ = 156.2 Hz); 62.98 (s, OCH_2); 79.46, 79.75, 79.86 (all s, C, Bu^t); 154.66, 155.36 (both s, C=O, C(O)OBu^t); 167.09, 170.17, 171.23, 173.06 (all s, C=O, C(O)NH). ^{31}P NMR ($CDCl_3$), δ: 25.66, 25.74. IR, ν/cm^{-1}: 1040, 1060 (P—O—C); 1250 (P=O); 1650—1720 (C=O, Boc, C(O)NH); 2250—3330 (NH). Found (%): C, 48.34; H, 7.64; N, 11.60. $C_{43}H_{81}N_9O_{16}P_2S$. Calculated (%): C, 46.08; H, 7.60; N, 11.74.

(*S*)-{4-[2-(2-Aminopropanoyl)hydrazino]piperidin-4-yl}phosphonic acid (12). To a solution of α-hydrazino phosphonate **9** (404 mg, 0.8 mmol) in anhydrous MeCN (2 mL), trimethylsilyl bromide (5 mL, 5 mol, freshly distilled) was added. The reaction mixture was stirred at room temperature for 24 h, the volatiles were removed *in vacuo*. To the residue, MeOH (3 mL) was added and the mixture was stirred for 2 h, then propylene oxide (0.5 mL) was added. The precipitate that formed was filtered off and washed with MeOH (3×2 mL) to give compound **12** (160 mg, 75%), m.p. 265—268 °C; $[\alpha]_D^{23}$ –22.5 (H_2O). ^{1}H NMR (D_2O),

δ: 1.45 (d, 3 H, Me, $^3J_{H,H}$ = 7.1 Hz); 1.78—1.88, 1.99—2.05, 3.16—3.20, 3.30—3.40 (all m, 2 H each, CH_2, cycl.); 4.03 (q, 1 H, CH, $^3J_{H,H}$ = 7.0). ^{13}C NMR (D_2O), δ: 16.36 (s, Me); 24.95 (d, CH_2, $^2J_{C,P}$ = 28.5 Hz); 38.57 (d, CH_2, $^3J_{C,P}$ = 9.5 Hz); 49.17 (s, CH); 53.97 (d, C, $^1J_{C,P}$ = 144.1 Hz); 170.16 (s, C=O). ^{31}P NMR (D_2O), δ: 19.83, 20.32. IR, ν/cm^{-1}: 1220 (P=O); 1710 (C=O); 3270 (NH). MS (EI), *m/z*: 266 $[M]^+$, 201 $[M - P(O)(OH)_2]^+$, 82 $[Ppy - H]^+$, 65 $[P(O)(OH)_2]^+$. MS (ESI): $[M + H]^+$, found 267.1217, calculated 267.1217, $C_8H_{19}N_4O_4P$.

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