Synthesis of a "memory tripeptide" (Arg—Glu—Arg, RER) and the Kabachnik—Fields reaction with di- and tripeptides as a method for the synthesis of phosphorus-containing peptide analogs

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Methods for the synthesis of potential "twin-drugs" containing fragments of the glutamate receptor antagonist and cognitive function enhancing oligopeptides were developed. The "memory tripeptide" Arg—Glu—Arg (RER) containing the tripeptide sequence of a protein $APP_{328-330}$, a β-amyloid precursor, was synthesized. A method for the synthesis of α-aminophosphonates with oligopeptides as the amine component of the one-pot three-component Kabachnik—Fields reaction was developed. A method for the synthesis of phosphonopeptides by the introduction of α-aminophosphonates into the peptide chain was proposed.

Key words: arginyl—glutamyl—arginine, phosphonopeptides, phosphorus-containing peptides, peptide synthesis, α-aminophosphonates, the Kabachnik—Fields reaction, [tetra(*tert*-butyl)phthalocyanine]aluminum chloride.

A topical problem of organic synthesis is the design of substances with specified properties, in particular, new-generation drugs for the treatment of neurodegenerative disorders. One of the promising directions for solving this problem is the development of bioisosteric analogs of the known biologically active substances[1] or the synthesis of "twin-drugs" on the basis of the so-called "fragment-based design." [2] This area of various classes of physiologically active substances comprise oligopeptides capable of improving cognitive functions and influencing the central nervous system. Let us concentrate our attention on two examples.

An actively studied class of endogenous peptide regulators is represented by peptides similar to adrenocorticotropic and melatocyte stimulating hormones, which are known by the general name of melanocortins. At present, synthetic heptapeptide Semax (Met—Glu—His—Phe——Pro—Gly—Pro), being a structural analog of adrenocorticotropic hormone devoid of hormonal activity ($ACTH_{4-10}$),[3] is the single widely used nootropic drug used in clinical practice.[4]

In addition, it is known that the protein APP, *viz.*, the β-amyloid precursor (playing, probably, the key role in the genesis of Alzheimer´s disease), performs important functions in normal brain tissues and, particularly, plays a specific role in the formation of long-term memory.[5,6] When studying the mechanism of its action, a specific pentapeptide sequence $APP_{328-332}$, namely, Arg—Glu—Arg——Met—Ser (RERMS), was identified as an active domain responsible for the above-mentioned functions. Moreover, analogous synthetic pentapeptides RERMS and SMRER also eliminate memory deficiency. It is most interesting that even palindromic tripeptide Arg—Glu—Arg (RER) containing the tripeptide sequence $APP_{328-330}$ protects from memory loss induced by β-amyloid.[6,7] It was shown[8,9] that both the family of pentapeptide derivatives corresponding to the amino acid sequence $APP_{328-332}$ and the family of tripeptide derivatives corresponding to the amino acid sequence $APP_{328-330}$ can be used as enhancers of cognitive functions for the treatment of Alzheimer´s disease. Interestingly, the "memory tripeptide" RER (Arg—Glu—Arg) retains activity upon both inversion of the configuration of one of the arginine residues and partial acylation.[6—8] Note that analogous tri- and pentapeptides are potential inhibitors of urokinase receptors[10] and angiotensin-I-converting enzymes[11] and possess antithrombotic[9] activity.

We have previously[12] developed a convenient method for the synthesis of the antagonist for the first subtype of glutamate receptors of 1-aminoindane-1,5-dicarboxylic acid (AIDA). In continuation of these studies, we decided to create hybrid molecules containing both the fragments

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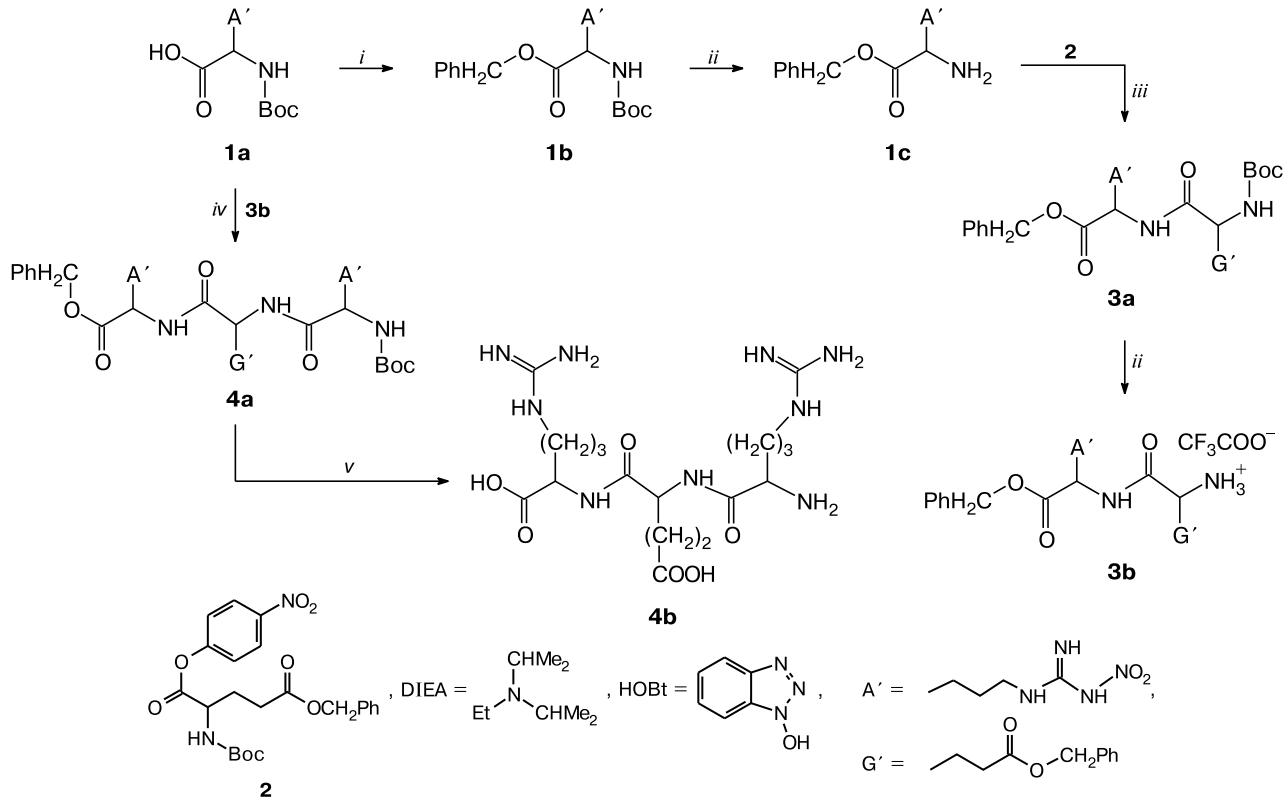
of AIDA and its bioisosteres, aminophosphonates,[13,14] and the oligopeptide chain mimicking this "memory tripeptide" RER (Arg—Glu—Arg). At the same time, the development of a method for the synthesis of phosphorus analogs of peptides, *i.e.*, phosphonopeptides based on α-aminophosphonates, is an independent problem.

A possible approach to the synthesis of α-aminophosphonates is based on the involvement of amino acids and their esters as the amine component into a new catalytic process developed by us.[14—16] In the present work, we extended the synthetic potential of the described method and applied it to di- and tripeptides.

Although tripeptide Arg—Glu—Arg is commercially available (Cambridge Research Biochemicals Ltd; MWG-Biotech Ltd, UK), we synthesized it using the peptide synthesis method[17—19] adapted for laboratory practice according to Scheme 1 from the derivatives of ω-nitro-L-arginine (**1a—c**) and α-*p*-nitrophenyl γ-benzyl *N*-Boc-L-glutamate (**2**). Benzyl *N*-Boc-ω-nitro-L-argininate (**1b**) was prepared from commercially available *N*-Boc-ω-nitro-L-arginine (**1a**) in 95% yield. The subsequent *N*-Boc-deprotection in compound **1b** affords benzyl ω-nitro-L-argininate (**1c**) in nearly quantitative yield. The protecting groups of the starting amino acids were selected in such a way that they could be removed in one step by catalytic hydrogenolysis. Then the coupling of *N*-Boc-protected *p*-nitrophenyl γ-benzyl glutamate (**2**) with C-protected nitroarginine (**1c**) gave dipeptide glutamylarginine (**3a**) (93% yield). The *N*-Boc-deprotection afforded the salt of dipeptide **3b** with trifluoroacetic acid. In the next step, *N*-Boc-protected nitroarginine (**1a**) was introduced into the reaction with dipeptide **3b** in the presence of dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HOBt). As a result, protected tripeptide **4a** was obtained in 60% yield. The target "memory tripeptide" **4b** was obtained as a salt upon treatment of compound **4a** with trifluoroacetic acid followed by hydrogenolysis on palladium.

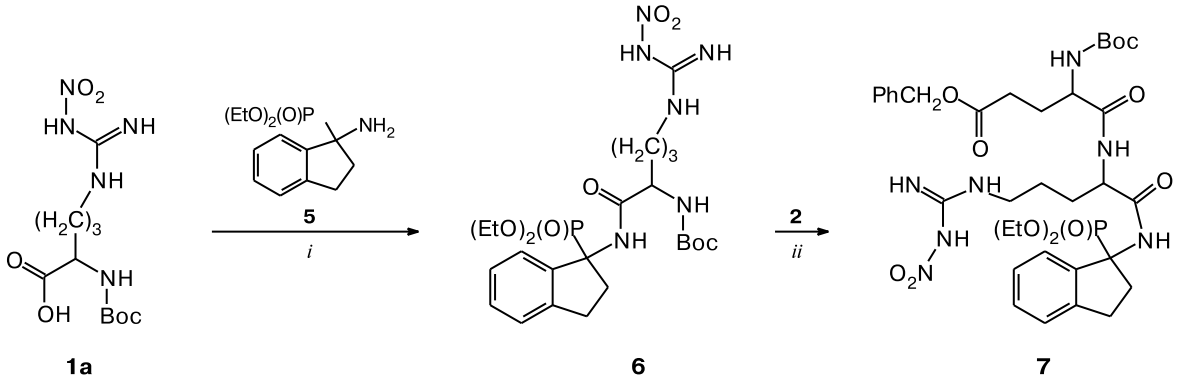
The introduction of α-aminophosphonate as a C-terminus of the peptide fragment allows one to synthesize phosphonopeptides, whose physiological activity is sometimes several orders of magnitude higher than that of peptides.[20,21] The synthesis of a phosphonopeptide was exemplified by coupling of arginine, glutamic acid, and α-aminophosphonate **5** (Scheme 2). In the first step, *N*-Boc-protected arginine (**1a**), pre-activated with DCC, reacted with α-aminophosphonate **5** to give phosphonodipeptide

Scheme 1



Reagents and conditions: *i*. $PhCH_2Cl$, DIEA, NaI, DMF; *ii*. TFA, 2 h; *iii*. DMF, DIEA, HOBt; *iv*. DCC, CH_2Cl_2, HOBt, 0 °C, 2 h; *v*. 1) TFA, 2 h; 2) $HCOONH_4$, Pd/C, AcOH—MeOH, 48 h.

Scheme 2



Reagents and conditions: 1) *i.* DCC, HOBt, CH_2Cl_2, 0 °C, 2 h; 2) **5**; *ii.* 1) TFA, 2 h; 2) DMF, DIEA, HOBt, **2**

6 in 60% yield. In the second step, phosphonotripeptide **7** was obtained in 90% yield upon coupling of phosphonodipeptide **6** with Boc-protected α-(*p*-nitrophenyl) γ-benzyl glutamate (**2**).

Model dipeptides were primarily used for the evaluation of a possibility of using peptides as an amine component in the catalytic version of the Kabachnik—Fields reaction developed by us earlier.[16] We found that glycylleucine methyl ester (**8a**) reacts with benzaldehyde and diethyl phosphite using [tetra(*tert*-butyl)phthalocyanine]-aluminum chloride (^{t}PcAlCl) as the catalyst to give the corresponding α-aminophosphonate **9a**. The reaction was carried out in methanol at ambient temperature in the presence of molecular sieves 4 Å, but the yield of dipeptide **9a** was only 15% because of the side formation of compounds **10** and **11** (Scheme 3).

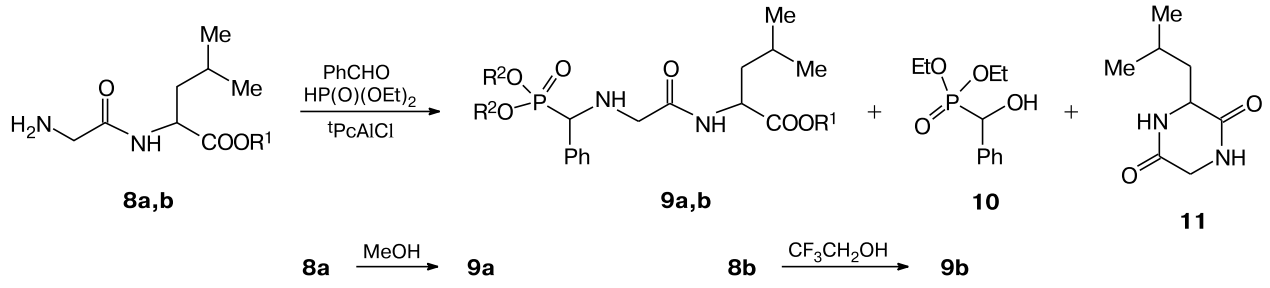
We found that the reaction of non-esterified dipeptide **8b** with benzaldehyde catalyzed by phthalocyanines affords the corresponding α-aminophosphonate **9b**. Since dipeptide **8b** is almost insoluble in methanol, the reaction was carried out in boiling 2,2,2-trifluoroethanol. Since the dipeptide in this medium is a zwitterion, an equimolar amount of triethylamine was added to the reaction mixture to liberate the amino group. In this case, aminophosphonate **9b** was obtained in 75% yield. The transesterification of the phosphonate group seems to occur as a side process.

Analogously we carried out the reactions with glycylglycine (**12**) and glutathione (**13**). α-Aminophosphonates **14** and **15** were synthesized in 70 and 40% yields, respectively (Scheme 4).

It is most likely that partial transesterification of the phosphonate group occurs in trifluoroethanol, which is detected in the ^{31}P NMR spectra (additional signals appeared at δ 20—24).

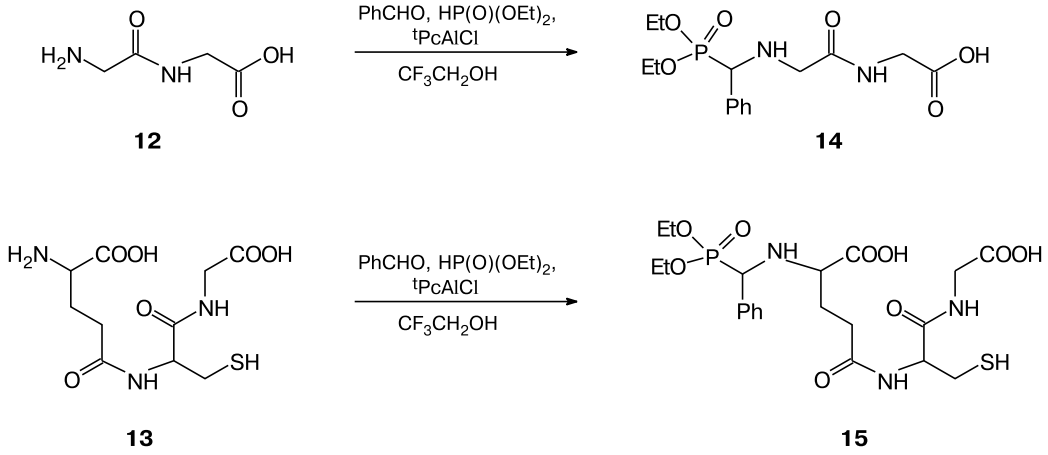
We introduced dipeptide **3b** into the Kabachnik—Fields reaction. Indan-1-one, *viz.*, the structural fragment of the ligand of the AIDA glutamate receptors,[22] was used as the carbonyl component (Scheme 5). Due to the high solubility of protected dipeptide **3b** in organic solvents, the reaction occurs readily in dichloromethane at 30 °C to form aminophosphonate **16** in 60% yield.

Scheme 3



8: R^1 = Me (**a**), H (**b**)
9: R^1 = Me, R^2 = Et (**a**); R^1 = H, R^2 = Et (**b**)

Scheme 4



The next step to the synthesis of "memory tripeptide" analogs was the introduction of tripeptide **4a** as the amine component into the catalytic Kabachnik—Fields reaction (Scheme 6). Indan-1-one and 5-benzyloxycarbonylindan-1-one as the carbonyl components and diethyl phosphite as the P—H component were used in the reaction. The Boc group was removed from protected arginylglutamylarginine **4a** by treatment with trifluoroacetic acid and the resulting salt was introduced into the Kabachnik—Fields reaction in the presence of ^{t}PcAlCl and an equimolar amount of diisopropylethylamine. As a result, aminophosphonates **17** and **18** were obtained in 60% yields. The final step of the synthesis of the phosphorus-containing "memory tripeptide" analog, namely, removal of protecting groups, for compound **17** was carried out by catalytic hydrogenolysis in the presence of Pd/C in aqueous acetic acid at ambient temperature. The target aminophosphonate **19** was obtained in 95% yield.

The approach developed opens a way to the synthesis of phosphonopeptides.

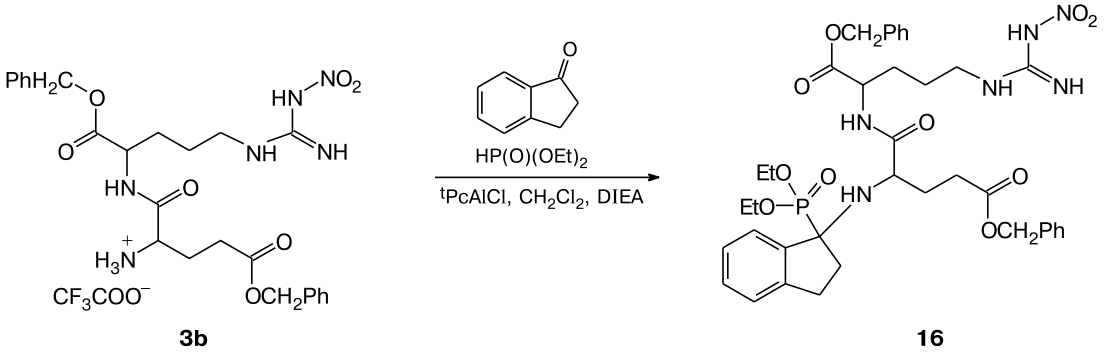
All oligopeptides synthesized and their phosphorus analogs were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, IR spectroscopy, and mass spectrometry.

The IR spectra of compounds **6**, **7**, **9**, and **14—19** contain absorption bands at 1250—1260 cm^{-1} corresponding to the P=O group, at 1600—1640 cm^{-1} corresponding to the C=N group of the guanidine fragments and the NO_2 group (for compounds **7** and **16—19**), and at 1680—1690 and 1720—1740 cm^{-1} characteristic of C=O of the amide and carboxylic acid groups . The broad bands corresponding to the OH and NH groups are observed at 3250—3500 cm^{-1}.

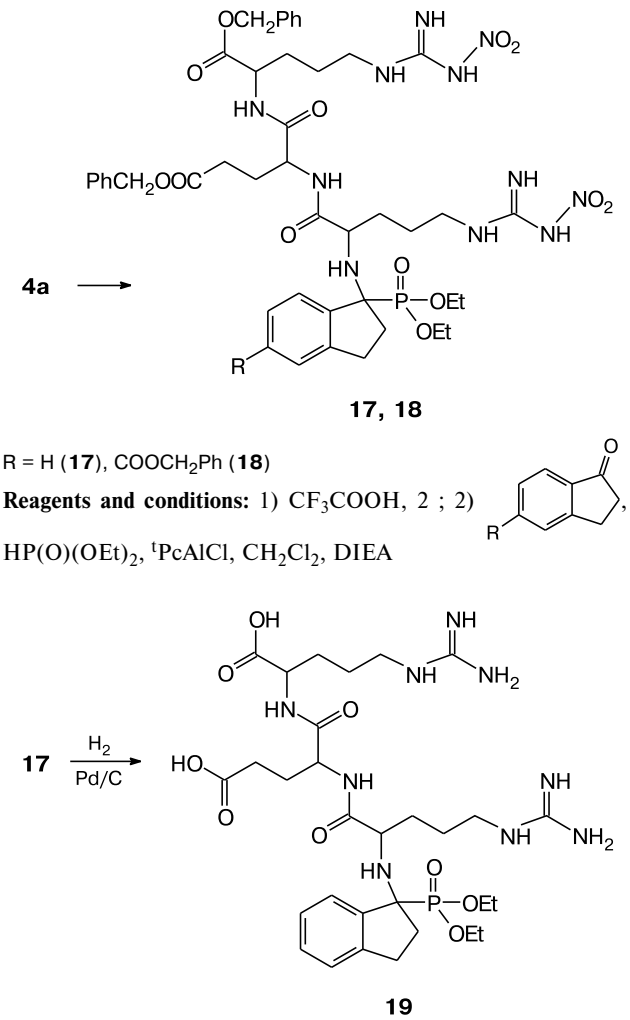
Since in this process we used peptides based on optically active L-amino acids, aminophosphonates **6**, **7**, **9**, and **15—19** are mixtures of diastereomers that differ in configurations of the carbon atom bound to the phosphorus atom. Therefore, the ^{31}P, ^{1}H, and ^{13}C NMR spectra exhibit doubling or broadening of the majority of signals. The ^{31}P NMR spectra of compounds **6**, **7**, **9**, and **14—19** contain signals at δ 20—31 corresponding to the dialkylaminophosphonate groups.

The ^{1}H NMR spectra of all synthesized aminophosphonates **6**, **7**, **9**, and **14—19** exhibit signals for nonequivalent phosphonate ethoxy groups: triplets of the methyl

Scheme 5



Scheme 6



groups at δ 1.0—1.4 and multiplets of the methylene protons at δ 3.6—4.6. The signals for the proton at the α-carbon atom of the aminophosphonate unit (compounds **9**, **14**, and **15**) are observed at δ 3.3—5.0 as two doublets of the diastereomeric pair with the spin-spin coupling constant $^2J_{H,P}$ = 10.6—14.6 Hz. In compounds **9** and **14**, the signals for the diastereotopic methylene protons appear as two doublets at δ 3.0—3.7 (J_{AB} = 17.0—18.8 Hz). No protons of the hydroxy and amino groups are manifested due to deuterioexchange. The signals corresponding to the α-protons of the amino acid fragments appear at δ 3.5—4.7.

The ^{13}C NMR spectra of the phosphorus analogs of peptides **6**, **7**, **9**, and **15—19** contain doubled signals of diastereomeric mixtures. The signal for the α-carbon atom at the phosphorus atom appears at δ 53—69 with $^1J_{P,C}$ = = 149—165 Hz. The chemical shifts of the diastereotopic ethoxy groups at the phosphorus atom lie at δ 15.5—20 (CH_3) and δ 62—65 (OCH_2). The signals of the chiral carbon atoms of the peptide fragment appear at δ 51—56. The chemical shifts of the carbon atoms of the guanidine groups lie at δ 159—160 (δ 155.6 for the unprotected group of compound **19**). The signals of the carboxylic and amide carbon atoms are present at δ 169—179. Other signals in the ^{1}H and ^{13}C NMR spectra of the α-phosphorus peptide analogs correspond to the structure of the carbon skeleton of the starting carbonyl compound and peptides.

Experimental

The ^{1}H (400 MHz), ^{13}C (100.61 MHz), and ^{31}P (161.98 MHz) NMR spectra were recorded for solutions in $CDCl_3$, CD_3OD, D_2O, and CD_3COOD on a Bruker Avance 400 instrument relative to Me_4Si as an internal standard (^{1}H, ^{13}C). Chemical shifts were measured in the δ scale. IR spectra were obtained on a UR-20 instrument in CCl_4. Elemental analysis was carried out on a Vario-II CHN analyzer. Mass spectra (MALDI—TOF) were measured on an Autoflex II instrument (Bruker Daltonics) using dihydroxybenzoic acid (DHB) as a matrix.

N^{α}-Boc-N^{ω}-nitro-L-arginine (**1a**) and α-*p*-nitrophenyl γ-benzyl *N*-Boc-glutamate (**2**) (Reanal) were used without additional purification. [Tetra(*tert*-butyl)phthalocyanine]aluminum chloride was synthesized according to the known[23] procedure.

The reactions were monitored, and chromatographic separation was carried out, using TLC on plates Merck TLC Silica gel 60 F_{254} and on columns with silica gel Merck 60 (70—230 mesh ASTM).

Benzyl N^{α}-Boc-N^{ω}-nitro-L-argininate (1b).[17] A mixture of N^{α}-Boc-N^{ω}-nitro-L-arginine (**1a**) (9.6 g, 30 mmol), diisopropylethylamine (DIEA) (7 mL, 40 mmol), benzyl chloride (5.6 mL, 48 mmol), and NaI (0.35 g) in DMF (20 mL) was stirred for 7 h at 80 °C. The reaction mixture was cooled and poured into ice water (150 mL). The reaction product was extracted with ethyl acetate (100 mL). The extract was consecutively washed with a 1 *M* solution of $NaHCO_3$ and brine and dried with sodium sulfate. The solution was concentrated *in vacuo*. A yellow oily substance was obtained in a yield of 11.72 g (95%), R_f 0.65 ($CHCl_3$: CF_3CH_2OH, 10 : 1). ^{1}H NMR, δ: 1.42 (s, 9 H, Bu^t); 1.68 (br.m, 2 H, $CHCH_2\underline{CH_2}CH_2$, Arg); 1.87 (br.m, 2 H, $CH\underline{CH_2}CH_2CH_2$, Arg); 3.27, 3.44 (both br.m, 2 H, $CHCH_2CH_2\underline{CH_2}$, Arg); 4.35 (m, 1 H, CH, Arg); 5.16 (m, 2 H, CH_2Ph); 7.34 (m, 5 H, arom.).

Benzyl N^{ω}-nitro-L-argininate trifluoroacetate (1c).[17] Benzyl *N*-Boc-N^{ω}-nitro-L-argininate (**1b**) (8.2 g, 20 mmol) was dissolved in trifluoroacetic acid (60 mL). The solution was stirred for ~2 h until the starting compound disappeared from the reaction mixture (TLC monitoring). Trifluoroacetic acid was evaporated *in vacuo*. A yellow oily substance was obtained in a yield of 8.45 g (99%), R_f 0.05 ($CHCl_3$—CF_3CH_2OH, 10 : 1). ^{1}H NMR, δ: 1.64, 1.74, 1.97 (all br.m, 4 H, $CH\underline{CH_2}\underline{CH_2}CH_2$, Arg); 3.22, 3.24 (both t, 2 H, $CHCH_2CH_2\underline{CH_2}$, Arg, $^2J_{H,H}$ = 5.8 Hz); 4.18 (t, 1 H, CH, Arg, $^2J_{H,H}$ = 5.8 Hz); 5.26 (m, 2 H, CH_2Ph); 7.41 (m, 5 H, arom.).

Benzyl N^{α}-Boc-(γ-benzyl α-L-glutamyl)-N^{ω}-nitro-L-argininate (3a).[19] A solution of compound **2** (3 g, 6.54 mmol) and *N*-hydroxybenzotriazole (HOBt) (0.88 g, 6.54 mmol) in DMF (11 mL) was added to a solution of $HArg(NO_2)OBzl \cdot CF_3COOH$ (**1c**) (2.77 g, 6.54 mmol) and DIEA (2.3 mL, 13.2 mmol) in DMF

(15 mL) cooled to 4 °C. The mixture was stirred with cooling for 2 h and kept for 12 h at 4 °C. Then the reaction mixture was poured into water and extracted with ethyl acetate (250 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (3×60 mL), brine (2×60 mL), a 10% solution of citric acid (2×60 mL), and again with brine (2×60 mL) and dried with Na_2SO_4. The solution was concentrated *in vacuo*, the residue was dissolved in a minimum amount of dichloromethane, and chromatographed on a column with silica gel in dichloromethane—methanol (50 : 1) solvent mixture as the eluent. A solid yellow glassy substance was isolated in a yield of 3.82 g (93%), R_f 0.35 ($CHCl_3$—CF_3CH_2OH, 10 : 1). ^{1}H NMR, δ: 1.38 (s, 9 H, Bu^t); 1.60 (br.m, 2 H, $CHCH_2\underline{CH_2}CH_2$, Arg); 1.73, 1.87 (both br.m, 2 H, $CH\underline{CH_2}CH_2CH_2$, Arg); 1.97, 2.14 (both m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.49 (m, 2 H, $CHCH_2\underline{CH_2}$, Glu); 3.19, 3.41 (both br.m, 2 H, $CHCH_2CH_2\underline{CH_2}$, Arg); 4.33 (m, 1 H, CH, Arg); 4.63 (m, 1 H, CH, Glu); 5.10 (m, 4 H, CH_2Ph); 7.33 (m, 10 H, arom.). ^{13}C NMR, δ: 24.25 (C(4), Arg); 27.33 (C(3), Glu); 28.05 (CH_3, Bu^t); 29.30 (C(4), Glu); 30.15 (C(3), Arg); 40.34 (C(5), Arg); 51.16 (C(2), Glu); 53.64 (C(2), Arg); 66.39, 67.27 ($\underline{C}H_2Ph$); 80.08 (C, Bu^t); 128.01, 128.11, 128.20, 128.40, 128.47, 134.86, 135.49 (C arom.); 155.81 (C=O, Boc); 159.09 (C=NH, Arg); 171.23 (NHC=O, Arg); 172.92 (C(O)OBzl, Arg, Glu).

Benzyl (γ-benzyl α-L-glutamyl)-N^{ω}-nitro-L-argininate trifluoroacetate (3b).[19] Boc-Glu(OBzl)Arg(NO_2)OBzl (**3a**) (1.9 g, 3 mmol) was dissolved in 20 mL of trifluoroacetic acid. The solution was stirred for ~2 h until the starting compound disappeared from the reaction mixture (TLC). Trifluoroacetic acid was evaporated *in vacuo*. A yellow oily substance was obtained in a yield of 1.93 g (99%), R_f 0.07 ($CHCl_3$—CF_3CH_2OH, 10 : 1). ^{1}H NMR, δ: 1.62 (br.m, 2 H, $CHCH_2\underline{CH_2}CH_2$, Arg); 1.71, 1.93 (both br.m, 2 H, $CH\underline{CH_2}CH_2CH_2$, Arg); 2.15 (br.m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.58 (m, 2 H, $CHCH_2\underline{CH_2}$, Glu); 3.13, 3.21 (both br.m, 2 H, $CHCH_2CH_2\underline{CH_2}$, Arg); 4.41 (m, 1 H, CH, Arg); 4.60 (m, 1 H, CH, Glu); 5.07 (m, 4 H, CH_2Ph); 7.33 (m, 10 H, arom.).

Benzyl N^{α}-Boc-N^{ω}-nitro-L-arginyl-(γ-benzyl α-L-glutamyl)-N^{ω}-nitro-L-argininate (4a). A solution of N^{α}-Boc-N^{ω}-nitro-L-arginine (**1a**) (0.96 g, 3 mmol) and HOBt (0.54 g, 4 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C, and DCC (0.62 g, 3 mmol) was gradually added with stirring at a temperature not higher than 5 °C. The mixture was stirred with cooling for 2 h and kept for 12 h at 4 °C. After this, a solution of compound **3b** (1.93 g, 3 mmol) and DIEA (1.05 mL, 6 mmol) in CH_2Cl_2 (15 mL) was added dropwise with cooling to the mixture. The mixture was stirred with cooling for 4 h and left for 12 h at 4 °C. Then the mixture was poured into water and extracted with ethyl acetate (100 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (2×40 mL), brine (1×40 mL), a 10% solution of citric acid (2×40 mL), and again with brine (1×40 mL) and dried with Na_2SO_4. A white crystalline substance was isolated by column chromatography on silica gel (dichloromethane—methanol (20 : 1) as the eluent) in a yield of 1.5 g (60%). Found (%): C, 52.28; H, 6.16; N, 18.55. $C_{36}H_{51}N_{11}O_{12}$. Calculated (%): C, 52.10; H, 6.19; N, 18.57. ^{1}H NMR, δ: 1.39 (s, 9 H, Bu^t); 1.61 (br.m, 4 H, $CHCH_2\underline{CH_2}CH_2$, 2 Arg); 1.74, 1.90 (both br.m, 4 H, $CH\underline{CH_2}CH_2CH_2$, 2 Arg); 1.97, 2.10 (both m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.46 (m, 2 H, $CHCH_2\underline{CH_2}$, Glu); 3.14, 3.62 (both br.m, 4 H, $CHCH_2CH_2\underline{CH_2}$, 2 Arg); 4.18, 4.48 (both m, 2 H, CH, 2 Arg); 4.58 (m, 1 H, CH, Glu); 5.12 (m, 4 H, 2 CH_2Ph); 7.32 (m, 10 H, arom.). ^{13}C NMR, δ: 24.08, 24.41 (C(4), 2 Arg); 26.63 (C(3), Glu); 28.14 (CH_3, Bu^t); 29.15 (C(4), Glu); 30.11 (C(3), 2 Arg); 40.63 (C(5), 2 Arg); 51.51 (C(2), Glu); 52.97, 53.48 (C(2), 2 Arg); 66.79, 67.65 ($\underline{C}H_2Ph$); 80.78 (C, Bu^t); 128.18, 128.38, 128.52, 128.59, 128.66, 134.89, 135.49 (C arom.); 155.36 (C=O, Boc); 159.07, 159.16 (C=NH, 2 Arg); 171.36, 172.08 (NHC=O, 2 Arg); 173.17, 173.39 (C(O)OBzl, Arg, Glu). MS (MALDI—TOF), *m/z*: 829 $[M]^+$.

L-Arginyl-α-L-glutamyl-L-arginine tetraacetate (4b). Compound **4a** (415 mg, 0.5 mmol) was dissolved in a mixture of trifluoroacetic acid (8 mL) and dichloromethane (8 mL). The resulting solution was stirred for ~3 h until the starting compound disappeared from the reaction mixture (TLC). Trifluoroacetic acid was evaporated *in vacuo*, and the residue was dried to a constant weight. The obtained glassy substance was dissolved in a mixture of acetic acid (5 mL) and methanol (5 mL), and ammonium formate (300 mg) was added; 5% Pd/C (600 mg) was added in 200-mg portions every 8 h. The mixture was stirred for 48 h (TLC). After the reaction was over, the catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue (oily substance) was dissolved in 50% AcOH, the solvent was evaporated, and the residue was triturated with acetonitrile. A light orange amorphous substance was obtained in a yield of 330 mg (90%). ^{1}H NMR, δ: 1.58—1.93 (m, 8 H, $CH\underline{CH_2}CH_2CH_2$, 2 Arg); 1.98—2.20 (m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.29—2.41 (m, 2 H, $CHCH_2\underline{CH_2}$, Glu); 3.21—3.38 (m, 4 H, $CHCH_2CH_2\underline{CH_2}$, 2 Arg); 4.11 (t, 1 H, CH, Arg, J = 6.23 Hz); 4.18 (dd, 1 H, CH, Arg, J = 5.61 Hz, J = 7.47 Hz); 4.39 (dd, 1 H, CH, Glu, J = 4.98 Hz, J = 9.34 Hz). ^{13}C NMR, δ: 26.26, 27.22 (C(4), 2 Arg); 30.38, 30.81, 31.47 (C(3), 2 Arg, C(3), Glu); 36.22 (C(4), Glu); 40.18, 40.46 (C(5), 2 Arg); 55.43, 56.84, 57.64 (C(2), Glu, C(2), 2 Arg); 159.52, (br.s, C=NH, 2 Arg); 172.42, 175.28, (NHC=O, Arg, Glu); 180.88, 184.06 (COOH, Arg, Glu, AcOH). MS (MALDI—TOF), *m/z*: 459 $[M]^+$.

Diethyl (1-amino-2,3-dihydro-1*H*-inden-1-yl)phosphonate (5).[24] Ammonium carbonate (0.58 g, 6 mmol), molecular sieves 4 Å (1.5 g), and Pc^{t}AlCl (0.16 g, 0.2 mmol) were added to a solution of 2,3-dihydro-1*H*-inden-1-one (0.8 g, 6 mmol) in anhydrous ethanol (9 mL). The reaction mixture was heated to 60 °C and stirred for 3—4 h, and then diethyl phosphite (0.93 mL, 7.2 mmol) was added. The reaction mixture was refluxed with stirring for 24 h. The molecular sieves were filtered off and washed with methanol (3×2 mL), and the filtrate was concentrated *in vacuo*. Column chromatography in CH_2Cl_2—MeOH (10 : 1) as the eluent afforded an orange oily substance in a yield of 0.57 g (35%), R_f 0.22 ($CHCl_3$—MeOH, 20 : 1). ^{1}H NMR, δ: 1.15, 1.30 (both t, 6 H, 2 CH_3, J = 7.07 Hz); 2.24, 2.80 (both m, 2 H, CH_2 cycl.); 3.02 (m, 2 H, cycl.); 3.10 (br.m, NH_2); 3.91, 4.09 (both m, 4 H, OCH_2); 7.24, 7.62 (both m, 4 H, arom.). ^{31}P NMR, δ: 23.18. IR, ν/cm^{-1}: 1235 (P=O); 3290, 3375, 3470 (NH_2).

N^{α}-Boc-*N*-[1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl]-N^{ω}-nitro-L-argininamide (6). A solution of N^{α}-Boc-N^{ω}-nitro-L-arginine (**1a**) (0.32 g, 1 mmol) and *N*-hydroxybenzotriazole (0.32 g, 1.2 mmol) in DMF (5 mL) was cooled to 0 °C. Then DCC (0.21 g, 1 mmol) was gradually added with cooling at such a rate that the temperature of the solution did not exceed 5 °C. The mixture was stirred with cooling for 1 h, and a solution of diethyl (1-amino-2,3-dihydro-1*H*-inden-1-yl)phosphonate (**5**) (0.27 g, 1 mmol) and diisopropylethylamine (0.36 mL, 2 mmol) in DMF (4 mL) was added dropwise. The mixture was stirred

with cooling for 2 h and kept for 12 h at 4 °C, then poured into water, and extracted with ethyl acetate (60 mL). The organic phase was worked up as described for the synthesis of **4a**. An orange glassy solid substance was obtained in a yield of 0.35 g (60%). ^{1}H NMR, δ: 1.17, 1.34 (both t, 6 H, 2 CH_3, J = 7.07 Hz); 1.41 (s, 9 H, Bu^t); 1.70 (br.m, 2 H, $CHCH_2\underline{CH_2}CH_2$, Arg); 1.92 (br.m, 2 H, $CH\underline{CH_2}CH_2CH_2$, Arg); 2.48—2.73 (m, 2 H, CH_2 cycl.); 3.05—3.33 (m, 4 H, CH_2 cycl., $CHCH_2CH_2\underline{CH_2}$, Arg); 4.29—4.40 (m, 4 H, 2 OCH_2); 4.67 (m, 1 H, CH, Arg); 7.28 (m, 4 H, arom.). ^{31}P NMR: δ 23.32.

N^{α}-[*N*-Boc-(γ-Benzyl) α-L-glutamyl]-*N*-[1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl]-N^{ω}-nitro-L-argininamide (7). N^{α}-Boc-*N*-[1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl]-N^{ω}-nitro-L-argininamide (**6**) (0.34 g, 0.6 mmol) was dissolved in trifluoroacetic acid (15 mL). The solution was stirred for 16 h. Trifluoroacetic acid was evaporated *in vacuo*. The amine (0.39 g) was obtained as a salt. This salt and DIEA (0.21 mL, 1.2 mmol) were dissolved in DMF (5 mL). The solution was cooled to 4 °C, and a solution of compound **2** (0.28 g, 0.6 mmol) and HOBt ((0.11 g, 0.8 mmol) in DMF (5 mL) was added. The mixture was stirred with cooling for 3 h and kept for 12 h at ambient temperature. Then the reaction mixture was poured into water and extracted with ethyl acetate (50 mL). Work-up as described above and column chromatography ($CHCl_3$—MeOH, 20 : 1) afforded an orange glassy solid substance in a yield of 0.43 g (90%). ^{1}H NMR, δ: 1.23, 1.37 (both t, 6 H, 2 CH_3, J = 7.07 Hz); 1.40 (s, 9 H, Bu^t); 1.65 (br.m, 2 H, $CHCH_2\underline{CH_2}CH_2$, Arg); 1.85—1.99 (m, 2 H, $CH\underline{CH_2}CH_2CH_2$, Arg); 2.12—2.21 (m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.34 (m, 2 H, $CHCH_2\underline{CH_2}$, Glu); 2.48—2.53 (m, 2 H, CH_2 cycl.); 3.23, 3,42 (both m, 2 H, CH_2 cycl.); 3.61 (br.m, 2 H, $CHCH_2CH_2\underline{CH_2}$, Arg); 4.09 (m, H, CH, Glu); 4.29, 4.42—4.48 (both m, 4 H, 2 OCH_2); 4.64—4.69 (m, 1 H, CH, Arg); 5.09 (m, 2 H, CH_2Ph); 7.32 (m, 9 H, arom.). ^{31}P NMR, δ: 22.42. ^{13}C NMR, δ: 19.86 (CH_3, POEt); 24.70, 24.81 (C(4), Arg); 27.55 (C(3), Glu); 27.83 (C(3)H_2, cycl.); 28.00 (C(4), Glu); 28.27 (CH_3, Bu^t); 30.28, 30.34 (C(3), Arg); 33.82 ($^2CH_2$, cycl.); 40.22, 40.29 (C(5), Arg); 51.24, 51.34 (C(2), Arg); 53.53 (C(2), Glu); 64.58 (d, C(1), cycl., $^1J_{C,P}$ =154.4 Hz); 60.39, 61.06 (OCH_2); 66.5 ($\underline{C}H_2Ph$); 80.24 (C, Bu^t); 125.7, 126.60, 126.95, 127.23, 128.13, 128.30, 128.57, 135.69, 138.36, 142.00 (C arom.); 158.55 (C=NH, Arg); 172.01, 173.09, 173.22, 176.16, 176.21 (NHC=O, Glu, Arg, $\underline{C}$(O)OBzl, Glu). MS (MALDI—TOF), *m/z*: 789 $[M]^+$, 652 $[M - P(O)(OEt)_2]^+$.

Methyl *N*-{(diethoxyphosphoryl)(phenyl)methyl}glycyl-L-leucinate (9a). A solution of methyl glycyl-L-leucinate hydrochloride (**8a**) (0.75 g, 3.2 mmol) in 1 *M* NaOH (20 mL) was extracted with ethyl acetate (3×29 mL). The extract was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Benzaldehyde (0.2 mL, 2 mmol), molecular sieves 4 Å, and ^{t}PcAlCl (0.08 g, 0.1 mmol) were added to a solution of the obtained methyl glycyl-L-leucinate (0.3 g, 1.5 mmol) in methanol (3 mL). The reaction mixture was stirred for 3 h, and an additional portion of the dipeptide ester (0.3 g, 1.5 mmol) was added. The reaction mixture was stirred for 3 h more, and diethyl phosphite (0.39 mL, 3 mmol) was added. After 72 h (TLC), molecular sieves were filtered off and washed with methanol (3×2 mL). The filtrate was concentrated *in vacuo*. After column chromatography (CH_2Cl_2—MeOH, 20 : 1), an orange oily substance was obtained in a yield of 0.13 g (15%), R_f 0.50 ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR, δ: 0.85, 0.88 (both d, 6 H, 2 CH_3 (Leu), J = 6.0 Hz); 1.01, 1.21 (both t, 6 H, 2 CH_3 (Et), J = 7.07 Hz); 1.49—1.60 (m, 3 H, CH_2, $\underline{CH}(CH_3)_2$); 3.04 (H_A), 3.23 (H_B) (AB system, 2 H, Gly, $^2J_{H,H}$ = 17.1 Hz); 3.39 (d, α-CH, $J_{H,P}$=10.6 Hz); 3.64, 3.66 (both s, 3 H, OMe); 3.77—4.07 (m, 4 H, 2 OCH_2); 4.50—4.55 (m, 1 H, CH (Leu)); 7.19—7.27, 7.40—7.51 (both m, 5 H, arom.). ^{31}P NMR, δ: 21.65, 21.77. IR, ν/cm^{-1}: 990, 1180 (P—O—Alk); 1250 (P=O); 1680 (C=O, amide); 1740 (C=O); 3270 (NH).

Diethyl [hydroxy(phenyl)methyl]phosphonate (10) was isolated in a yield of 0.17 g (35%), R_f 0.49 ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR, δ: 1.22, 1.27 (both t, 6 H, 2 CH_3, J = 7.07 Hz); 4.06, 4.15 (both m, 4 H, 2 OCH_2); 4.39 (br.s, 1 H, OH); 5.03 (d, 1 H, CH, $^2J_{H,P}$ = 11 Hz); 7.37—7.50 (m, 5 H, arom.). ^{31}P NMR, δ: 21.58. IR, ν/cm^{-1}: 1240 (P=O); 3280 (OH). Found (%): C, 54.29; H, 7.00. $C_{11}H_{17}O_4P$. Calculated (%): C, 54.09; H, 6.97.

3-Isobutylpiperazine-2,5-dione (11) was also isolated from the reaction mixture in a yield of 0.45 g (81%), R_f 0.05 ($CHCl_3$—MeOH, 10 : 1). IR, ν/cm^{-1}: 1675, 1690 (C=O), 3250 (NH). M.p. 255 °C.

***N*-{(Diethoxyphosphoryl)phenyl)methyl}glycyl-L-leucine (9b).** Glycyl-L-leucine (**8b**) (0.42 g, 2.2 mmol), molecular sieves 4 Å (500 g), Pc^tAlCl (0.08 g, 0.1 mmol), and triethylamine (0.3 mL, 2.2 mmol) were added to a solution of benzaldehyde (0.2 mL, 2 mmol) in 2,2,2-trifluoroethanol (4 mL). The reaction mixture was heated to 60 °C and stirred for 3 h, and diethyl phosphite (0.39 mL, 3 mmol) was added. The reaction mixture was refluxed with stirring for 120 h. Molecular sieves were filtered off and washed with methanol (3×2 mL), and the filtrate was concentrated *in vacuo*. After column chromatography ($CHCl_3$—MeOH, 10 : 1), an orange oily substance was obtained in a yield of 0.63 g (75%), R_f 0.31 ($CHCl_3$: MeOH, 10 : 1). Found (%): C, 55.15; H, 7.74; N, 6.60. $C_{19}H_{31}N_2O_6P$. Calculated (%): C, 55.06; H, 7.54; N, 6.76. ^{1}H NMR, δ: 0.94, 0.99 (both d, 6 H, 2 CH_3 (Leu), J = 6.0 Hz); 1.07—1.13, 1.27—1.36 (both t, 6 H, 2 CH_3 (Et), J = 7.07 Hz); 1.57—1.81 (m, 3 H, CH_2, $\underline{CH}(CH_3)_2$); 3.13 (H_A), 3.40 (H_B) (AB system, 2 H, Gly, $^2J_{H,H}$ = 17.0 Hz); 3.30 (d, α-CH, $^2J_{H,P}$ = 11.3 Hz); 3.64—3.78, 3.87—3.97, 4.06—4.30 (three m, 4 H, 2 OCH_2); 4.50—4.55 (m, 1 H, $\underline{CH}$(COOH)); 7.34—7.43 (m, 5 H, arom.). ^{31}P NMR: δ 23.13, 23.41. ^{13}C NMR, δ: 16.23—16.43 (CH_3, Et); 21.83, 22,88, 24.85, 29.69 (Leu); 40.61, 40.96 (Leu); 50.80, 50.90 (CH_2, Gly); 59.83 (d, α-C, $^1J_{C,P}$ = = 158.1 Hz); 63.54, 64.07 (both d, 2 OCH_2); 128.19—128.91 (C arom.); 174.84, 175.02 (C=O, Gly, Leu). IR, ν/cm^{-1}: 980, 1190 (P—O—Alk); 1250 (P=O); 1690 (C=O, amide); 1745 (C=O, acidic); 3280 (NH).

***N*-{(Diethoxyphosphoryl)(phenyl)methyl}glycylglycine (14).** Glycylglycine (**12**) (0.29 g, 2.2 mmol), molecular sieves 4 Å (500 g), ^{t}PcAlCl (0.08 g, 0.1 mmol), and triethylamine (0.3 mL, 2.2 mmol) were added to a solution of benzaldehyde (0.2 mL, 2 mmol) in 2,2,2-trifluoroethanol (6 mL). The reaction mixture was heated to 60 °C and stirred for 3 h, and diethyl phosphite (0.39 mL, 3 mmol) was added. The reaction mixture was refluxed with stirring for 120 h. Molecular sieves were filtered off and washed with methanol (3×2 mL), and the filtrate was concentrated *in vacuo*. After column chromatography ($CHCl_3$—MeOH, 10 : 1), an orange oily substance was obtained in a yield of 0.51 g (70%), R_f 0.27 ($CHCl_3$: MeOH, 10 : 1). Found (%): C, 50.05; H, 6.37; N, 7.90. $C_{15}H_{23}N_2O_6P$. Calculated (%): C, 50.28; H, 6.47; N, 7.82. ^{1}H NMR, δ: 1.27 (t, 6 H, 2 CH_3 (Et), J = 7.07 Hz); 3.46 (H_A), 3.70 (H_B) (AB system, 2 H, Gly, $^2J_{H,H}$ = 18.8 Hz); 3.43—3.60, 3.66—3.89, 4.00—4.09 (all m, 4 H, 2 OCH_2); 4.19 (m, 2 H, $\underline{CH_2}$(COOH)); 4.79 (d, α-CH, $^2J_{H,P}$=14.6 Hz); 7.34—7.43 (m, 5 H, atom.). ^{31}P NMR, δ: 21.61. IR, ν/cm^{-1}: 980,

1190 (P—O—Alk); 1250 (P=O); 1690 (C=O, amide); 1745 (C=O, acidic); 3280 (NH).

***N*-[(Diethoxyphosphoryl)phenyl)methyl]-L-γ-glutamyl-L-cysteinylglycine (15).** Glutathione (**13**) (0.68 g, 2.2 mmol), molecular sieves 4 Å (500 mg), ^{t}PcAlCl (0.08 g, 0.1 mmol), and triethylamine (0.46 mL, 3.3 mmol) were added to a solution of benzaldehyde (0.2 mL, 2 mmol) in 2,2,2-trifluoroethanol (4 mL). The reaction mixture was heated to 60 °C and stirred for 3 h, and diethyl phosphite (0.39 mL, 3 mmol) was added. The mixture was refluxed with stirring for 120 h. Molecular sieves were filtered off and washed with methanol (3×2 mL), and the filtrate was concentrated *in vacuo*. After column chromatography ($CHCl_3$—MeOH, 15 : 1), an orange oily substance was obtained in a yield of 0.46 g (40%), R_f 0.37 ($CHCl_3$: MeOH, 10 : 1). Found (%): C, 47.65; H, 6.27; N, 7.74. $C_{21}H_{32}N_3O_9PS$. Calculated (%): C, 47.27; H, 6.05; N, 7.88. ^{1}H NMR, δ: 1.20, 1.25 (both t, 6 H, 2 CH_3 (Et), J = 7.07 Hz); 1.81—2.04, 2.23—2.50 (both m, 4 H, CH_2CH_2, Glu); 3.45—3.87 (m, 3 H, $^3CH_2$, Cys, ^{2}CH, Glu); 3.93—4.25 (m, 6 H, 2 OCH_2, CH_2, Gly); 4.31—4.37 (m, H, ^{2}CH, Cys); 5.01 (d, α-CH, $^2J_{HP}$ = 11.1 Hz); 7.28—7.39, 7.49 (m, 5 H, arom.). ^{31}P NMR, δ: 21.54.

Benzyl *N*-(1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl)-(γ-benzyl)-α-L-glutamyl-N^{ω}-nitro-L-argininate (16). 2,3-Dihydro-1*H*-inden-1-one (0.4 g, 3 mmol), molecular sieves 4 Å (500 mg), Pc^{t}AlCl (0.08 g, 0.1 mmol), and diisopropylethylamine (0.35 mL, 2 mmol) were added to a solution of dipeptide **3b** (1.3 g, 2 mmol) in dichloromethane (7 mL). The reaction mixture was stirred for 3 h at 30 °C, diethyl phosphite (0.39 mL, 3 mmol) was added, and the mixture was stirred for 1 day at 30 °C. Then more diethyl phosphite (2 mmol) was added. The duration of the reaction was 72 h (TLC). Molecular sieves were filtered off and washed with methanol (3×2 mL), and the filtrate was concentrated *in vacuo*. After column chromatography ($CHCl_3$—MeOH, 20 : 1), an orange oily substance was obtained in a yield of 1.09 g (60%). ^{1}H NMR, δ: 1.30 (t, 6 H, 2 CH_3, J = 7.07 Hz); 1.57 (br.m, 2 H, $CHCH_2\underline{CH_2}CH_2$, Arg); 1.67, 1.83 (both br.m, 2 H, $CH\underline{CH_2}CH_2CH_2$, Arg); 1.86, 2.01 (both m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.37—2.66 (m, 4 H, $CHCH_2\underline{CH_2}$, Glu, CH_2 cycl.); 3.24 (m, 2 H, CH_2 cycl.); 3.41 (br.m, 2 H, $CHCH_2CH_2\underline{CH_2}$, Arg); 3.58 (m, 1 H, CH, Arg); 4.06—4.14 (m, 4 H, 2 OCH_2); 4.56 (m, 1 H, CH, Glu); 5.13 (m, 4 H, CH_2Ph); 7.32 (m, 14 H, arom.). ^{31}P NMR, δ: 30.35. ^{13}C NMR, δ: 16.56 (CH_3); 24.39 (C(4), Arg); 29.63 (C(3), Glu); 30.23 (C(4), Glu); 30.76 (C(3), Arg); 31.41 (C(3)H_2, cycl.); 33.18 (C(2)H_2, cycl.); 40.32 (C(5), Arg); 50.71 (C(2), Glu); 53.18 (d, C(1), cycl., $^1J_{C,P}$ = 149.3 Hz); 56.12 (C(2), Arg); 62.40, 62.62 (both d, OCH_2, $^2J_{C,P}$ = 7.3 Hz); 66.54, 67.45 ($\underline{C}H_2$Ph); 125.6, 126.71, 127.05, 127.33, 128.24, 128.51, 128.55, 128.66, 135.00, 135.74, 138.46, 142.10 (C arom.); 159.45 (C=NH, Arg); 171.54 (NHC=O, Glu); 173.11, 176.18 ($\underline{C}$(O)OBzl, Arg, Glu). IR, ν/cm^{-1}: 970, 1190 (P—O—Alk); 1250 br (N=O, NO_2, P=O); 1600, 1630 br (N=O, NO_2, C=N, amide); 1730 (C=O); 3300 (NH). MS (MALDI—TOF), m/z: 780 $[M]^+$, 643 $[M - P(O)(OEt)_2]^+$.

Benzyl [N^{α}-(1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl)-N^{ω}-nitro-L-arginyl]-(γ-benzyl) α-L-glutamyl-N^{ω}-nitro-L-argininate (17). Tripeptide **4a** (0.83 g, 1 mmol) was dissolved in a mixture of trifluoroacetic acid (15 mL) and dichloromethane (15 mL). The solution was stirred for ~4 h until the starting compound disappeared from the reaction mixture (TLC). The solvents were evaporated *in vacuo* to a constant weight. The obtained glassy substance was dissolved in dichloromethane (8 mL), and 2,3-dihydro-1*H*-inden-1-one (0.4 g, 3 mmol), molecular sieves 4 Å (500 mg), ^{t}PcAlCl (0.08 g, 0.1 mmol), and DIEA (0.35 mL, 2 mmol) were added. The reaction mixture was stirred for 3 h at 30 °C, diethyl phosphite (0.2 mL, 1.5 mmol) was added, and the mixture was stirred for 1 day at 30 °C. Then more diethyl phosphite (0.2 mL, 1.5 mmol) was added. The reaction was monitored by TLC, this lasted for 120 h. The molecular sieves were filtered off and washed with methanol (3×2 mL), and the filtrate was concentrated *in vacuo*. After column chromatography ($CHCl_3$—MeOH, 20 : 1), an orange oily substance was obtained in a yield of 0.59 g (60%). ^{1}H NMR, δ: 1.18—1.35 (m, 6 H, 2 CH_3); 1.58 (br.m, 4 H, $CHCH_2\underline{CH_2}CH_2$, 2 Arg); 1.73, 1.91 (both br.m, 4 H, $CH\underline{CH_2}CH_2CH_2$, 2 Arg); 1.98, 2.10 (both m, 2 H, $CHCH_2CH_2$, Glu); 2.30—2.60 (m, 4 H, $CHCH_2\underline{CH_2}$, Glu, C(2)H_2, cycl.); 2.87—3.06 (m, 2 H, $^3CH_2$, cycl.); 3.12—3.33 (br.m, 4 H, $CHCH_2CH_2\underline{CH_2}$, 2 Arg); 3.57, 3.81 (both m, H, CH, Arg); 4.01, 4.62 (both m, 6 H, CH, Arg, CH, Glu, 2 OCH_2); 5.09 (m, 4 H, 2 CH_2Ph); 7.18—7.76 (m, 14 H, arom.). ^{31}P NMR, δ: 25.17, 25.62. ^{13}C NMR, δ: 15.97—16.21 (Me, POEt); 24.37, 24.48 (C(4), 2 Arg); 26.58 (C(3), Glu); 28.83 (C(4), Glu); 30.08 (C(3), 2 Arg); 32.01 ($^3CH_2$, cycl.); 33.28 ($^2CH_2$, cycl.); 40.67 (C(5), 2 Arg); 51.86, 52.53 (C(2), Glu); 52.96, 54.49, 55.50, 55.84 (C(2), 2 Arg); 63.21, 64.04 (OCH_2); 66.81, 67.62 ($\underline{C}H_2$Ph); 68.06, 68.40 (both d, C(1), $^1J_{C,P}$ = 158.8 Hz, $^1J_{C,P}$ = 159.5 Hz); 125.14, 126.48, 126.69, 128.19, 128.38, 128.63, 129.12, 134.93, 135.46, 139.33, 144.81 (C arom.); 159.17 (br.s, C=NH, 2 Arg); 171.40, 173.24 (NHC=O, Arg, Glu); 173.50, 176.34 ($\underline{C}$(O)OBzl, Arg, Glu). IR, ν/cm^{-1}: 970, 1190 (P—O—Alk); 1250 (br, N=O, NO_2, P=O); 1600, 1630 (br, N=O, NO_2, C=N, amide); 1730 (C=O); 3300 (NH). MS (MALDI—TOF), m/z: 981 $[M]^+$, 844 $[M - P(O)(OEt)_2]^+$.

Benzyl [N^{α}-(5-benzyloxycarbonyl-1-(diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl)-N^{ω}-nitro-L-arginyl]-(γ-benzyl) α-L-glutamyl-N^{ω}-nitro-L-argininate (18) was synthesized using benzyl-1-oxo-2,3-dihydro-1*H*-indene-5-carboxylate as the carbonyl component using the method of synthesis of α-aminophosphonate **17**. An orange oily substance was obtained in a yield of 0.68 g (60%). ^{1}H NMR, δ: 1.09—1.35 (m, 6 H, 2 CH_3); 1.46—1.82 (br.m, 8 H, $CH\underline{CH_2}CH_2CH_2$); 1.86—2.12 (m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.34—2.57 (m, 4 H, $CHCH_2CH_2$, Glu, C(2)H_2, cycl.); 2.87—3.00 (m, 2 H, C(3)H_2, cycl.); 3.10—3.37 (br.m, 4 H, $CHCH_2CH_2\underline{CH_2}$, 2 Arg); 3.56, 3.73 (both m, 1 H, CH, Arg); 4.00—4.65 (m, 6 H, CH, Arg, CH, Glu, 2 OCH_2); 5.09—5.17 (m, 6 H, 2 CH_2Ph); 7.10—7.78 (m, 19 H, arom.). ^{31}P NMR, δ: 27.66, 27.77. ^{13}C NMR, δ: 15.96—16.20 (Me, POEt); 24.26, 24.49 (C(4), 2 Arg); 26.62 (C(3), Glu); 28.79 (C(4), Glu); 29.66 (C(3)H_2, cycl.); 30.06 (C(3), 2 Arg); 32.03 (C(2)H_2, cycl.); 40.67 (C(5), 2 Arg); 51.66, 51.77 (C(2), Glu); 52.95, 54.49, 55.50, 55.85 (C(2), 2 Arg); 63.20, 64.00 (OCH_2); 66.52, 66.81, 67.62 ($\underline{C}H_2$Ph); 68.70, 69.10 (both d, C(1), $^1J_{C,P}$ = 157.4 Hz, $^1J_{C,P}$ = 158.5 Hz); 124.23, 125.64, 128.18, 128.37, 128.63, 129.07, 129.73, 134.91, 135.47, 136.41, 144.57, 150.17 (C arom.); 159.18, (br.s, C=NH, 2 Arg); 171.41, 171.84 (NHC=O, Arg, Glu); 173.22, 173.49, 176.32 ($\underline{C}$(O)OBzl, Arg, Glu). IR, ν/cm^{-1}: 970, 1190 (P—O—Alk); 1250 (br, N=O, NO_2, P=O); 1600, 1630 (br, N=O, NO_2, C=N, amide); 1730 (C=O); 3300 (NH). MS (MALDI—TOF), m/z: 1115 $[M]^+$, 978 $[M - P(O)(OEt)_2]^+$.

{N^{α}-[1-(Diethoxyphosphoryl)-2,3-dihydro-1*H*-inden-1-yl]-L-arginyl}-α-L-glutamyl-L-arginine (19). A flow of hydrogen was passed through a solution of α-aminophosphonate **17** (0.2 g) in a mixture of acetic acid (8 mL) and water (2 mL) (300 mL h^{-1})

with stirring, the Pd/C catalyst being added portionwise (50 mg a day, 10 mg with an interval of 1.5 h). The process was monitored by TLC. When the reaction was over, the catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The obtained oily substance was dissolved in 50% acetic acid, the solvent was evaporated, and the residue was triturated with acetonitrile until a powder-like light brown amorphous substance was obtained. The yield was 0.14 g (95%). ^{1}H NMR, δ: 1.05—1.17 (m, 6 H, 2 CH_3); 1.30—1.70 (br.m, 8 H, $CH\underline{CH_2CH_2}CH_2$, 2 Arg); 1.78—2.10 (br.m, 2 H, $CH\underline{CH_2}CH_2$, Glu); 2.18—2.56 (m, 4 H, $CHCH_2\underline{CH_2}$, Glu, C(2)H_2, cycl.); 2.72—3.26 (br.m, 6 H, C(3)H_2, cycl., $CHCH_2CH_2\underline{CH_2}$, 2 Arg); 3.77, 3.85 (both m, 2 H, CH, Arg, CH, Glu); 3.88—4.06 (m, 4 H, 2 OCH_2); 4.23 (m, 1 H, CH, Arg); 7.06—7.55 (m, 4 H, arom.). ^{31}P NMR, δ: 27.04, 27.10. ^{13}C NMR, δ: 15.62 (Me, POEt); 24.33, 24.43 (C(4), 2 Arg); 26.70, 26.89 (C(4), Glu); 27.94, 28.39 (C(3), 2 Arg); 29.54, 29.94 (C(3)H_2, cycl.); 31.24, 31.41 (C(2)H_2, cycl.); 31.73, 31.89 (C(3), Glu); 40.31, 40.57 (C(5), 2 Arg); 52.47, 52.55 (C(2), Glu); 53.24, 53.58, 54.32, 54.54 (C(2), 2 Arg); 64.33, 64.73 (both d, OCH_2, $^2J_{C,P}$ = 8.43 Hz); 66.73, 68.64 (both d, C(1), $^1J_{C,P}$ = = 164.4 Hz, $^1J_{C,P}$ = 161.8 Hz); 125.27, 127.06, 128.92, 129.58, 138.14, 143.13 (C arom.); 155.61 (br.s, C=NH, 2 Arg); 169.41, 172.20, 172.28 (NHC=O, Arg, Glu); 176.81, 177.19, 178.50, 178.96 (COOH, Arg, Glu). IR, ν/cm^{-1}: 970, 1190 (P—O—Alk); 1250 (P=O); 1600, 1630 (C=N, amide); 1735 (C=O); 3000—3500 (NH, OH). MS (MALDI—TOF), *m/z*: 711 $[M]^+$, 574 $[M - P(O)(OEt)_2]^+$.

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