Electronic supplementary information

NEW PHOSPHORUS-CONTAINING AMINO ACIDS AND THEIR ANALOGS AS PROMISING BIOACTIVE SUBSTANCES

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Experimental section

General remarks

The ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$, C_6D_6, or D_2O at 400, 100, and 162 MHz, respectively. The chemical shifts are reported in ppm relative to TMS (^{1}H, ^{13}C) or 85% H_3PO_4 in D_2O (^{31}P). The NMR spectra of compounds **1–12** contain characteristic signals of $PC(1)H_2NC(2)H_2$ moieties, as well as the fragments of amino acid derivatives, the parameters of which are given below. Some of the compounds obtained contain amide units NC(O) and are mixtures of two conformers that differ by the NMR signals, which is typical for the stereochemistry of *N*-substituted amides of carboxylic acids. The ratio of the conformers was determined by a complex superposition of the spatial and electronic properties of the substituents at the amide fragments. Thus, compounds **1e**, **4d**, **9a**, **9b**, **9d**, **10c**, **10d** consist of only one conformer. For some compounds, the proton signals of both conformers are multiplets that overlap in the ^{1}H NMR spectra.

The melting points were determined in open capillaries and are uncorrected. The elemental analyses data were obtained on a PerkinElmer Series II CHNS/O 2400 Analyser. Analysis of compounds **1a**–**e**, which are easily oxidized or hydrolyzed, was carried out for their stable derivatives **2a**–**e**, and the structures of phosphonites **1a**–**e** were also confirmed by NMR spectroscopy. All reactions were carried out under a dry argon atmosphere in anhydrous solvents.

Compounds **1b**, **3b**, **3c**, 3**d**, **4b**, **4c**, **4d**, **5**, **11**, **12** were synthesized and described by us earlier [1–5], but were not characterized by the complete set of spectral data.

Syntheses

General procedure for the synthesis of phosphonites 1. A solution of *N*-chloromethyl-*N*-ethoxycarbonylamino acid alkyl ester (65 mmol) in dichloromethane (35 mL) was added

dropwise to a stirred solution of bis(trimethylsiloxy)phosphine (90 mmol) in CH_2Cl_2 (30 mL) at 10 °C. The reaction mixture was stirred at room temperature for 1 h. Then triethylamine (70 mmol) was added, and the resulting mixture was stirred for another 2 h. The solvent was removed under vacuum, and the residue obtained was treated with pentane (150 mL) and filtered. The filtrate was evaporated to dryness, and the resulting residue was distilled to give phosphonites **1**.

***N*-Ethoxycarbonyl-*N*-(methoxycarbonylmethyl)aminomethylphosphonous acid bis(trimethylsilyl) ester (1a).** Yield: 57%. Bp: 108 °C (0.5 Torr). First isomer (60%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.08 (s, 18 H, 2 Me_3Si), 1.04 (t, 3 H, CH_3, $^3J_{HH}$ = 7.2), 3.49 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 9.8), 3.58 (s, 3 H, CH_3O), 3.94 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.2), 4.21 (s, 2 H, C(2)H_2). ^{13}C{^{1}H} NMR ($CDCl_3$, δ, ppm, J/Hz): 1.24 (s, 2 Me_3Si), 14.14 (s, Me), 50.58 (s, C(2)), 51.74 (s, MeO), 58.72 (d, C(1), $^1J_{PC}$ = 26.4), 61.84 (s, CH_2O), 156.47 (s, NC=O), 169.89 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, δ, ppm): 148.34 (s). Second isomer (40%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0. 11 (s, 18 H, 2 Me_3Si), 1.04 (t, 3 H, CH_3, $^3J_{HH}$ = 7.2), 3.42 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 10.0), 3.54 (s, 3 H, CH_3O), 3.94 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.2), 4.16 (s, 2 H, C(2)H_2). ^{13}C{^{1}H} NMR ($CDCl_3$, δ, ppm, J/Hz): 1.29 (s, 2 Me_3Si), 14.14 (s, Me), 50.52 (s, C(2)), 51.62 (s, MeO), 58.34 (d, C(1), $^1J_{CP}$ = 26.1), 61.72 (s, CH_2O), 156.26 (s, NC=O), 169.42 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, δ, ppm): 149.34 (s).

***N*-Ethoxycarbonyl-*N*-(ethoxycarbonylmethyl)aminomethylphosphonous acid bis(trimethylsilyl) ester (1b).** Yield: 76%. Bp: 130 °C (2 Torr). First isomer (70%). ^{1}H NMR (C_6D_6, δ, ppm, J/Hz): 0.20 (s, 18H, 2 Me_3Si), 1.08–1.15 (m, 6H, 2 CH_3), 3.47 (d, 2H, C(1)H_2, $^2J_{HP}$ = 9.6), 3.76–3.91 (m, 4H, 2 CH_2O), 4.15 (s, 2H, C(2)H_2). ^{13}C{^{1}H} NMR (C_6D_6, δ, ppm, J/Hz): 1.33 (s, 2 Me_3Si), 14.52 (s, 2 Me), 50.58 (s, C(2)), 58.66 (d, C(1), $^1J_{CP}$ = 26.1), 62.03 (s, 2 CH_2O), 156.51 (s, NC=O), 169.31 (s, C=O). ^{31}P{^{1}H} NMR (C_6D_6, δ, ppm): 149.40 (s). Second isomer (30%). ^{1}H NMR (C_6D_6, δ, ppm, J/Hz): 0.20 (s, 18 H, 2 Me_3Si), 1.08–1.15 (m, 6H, 2 CH_3), 3.38 (d, 2H, C(1)H_2, $^2J_{HP}$ = 10.1), 3.76–3.91 (m, 4H, 2 CH_2O), 4.05 (s, 2H, C(2)H_2). ^{13}C{^{1}H} NMR (C_6D_6, δ, ppm, J/Hz): 1.33 (s, 2 Me_3Si), 14.52 (s, 2 Me), 50.52 (s, C(2)), 58.28 (d, C(1), $^1J_{CP}$ = 25.7), 62.03 (s, 2 CH_2O), 156.15 (s, NC=O), 169.31 (s, C=O). ^{31}P{^{1}H} NMR (C_6D_6, δ, ppm): 148.47 (s).

***N*-Ethoxycarbonyl-*N*-(2-methoxycarbonylethyl)aminomethylphosphonous acid bis(trimethylsilyl) ester (1c).** Yield: 73%. Bp: 118 °C (1 Torr). First isomer (60%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.09 (s, 18 H, 2 Me_3Si), 1.07 (t, 3 H, CH_3, $^3J_{HH}$ = 7.2), 3.34–3.40 (m, 4 H, C(1)H_2, C(2)H_2), 3.52 (s, 3 H, CH_3O), 3.94 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.2). ^{13}C{^{1}H} NMR ($CDCl_3$, δ, ppm, J/Hz): 1.25 (s, 2 Me_3Si), 14.62 (s, Me), 31.16 (s, $CH_2C(O)$), 50.54 (s, C(2)), 52.03 (s, MeO), 58.62 (d, C(1), $^1J_{CP}$ = 26.0), 61.78 (s, CH_2O), 156.59 (s, NC=O), 170.23 (s,

C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 149.36 (s). Second isomer (40%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.09 (s, 18 H, 2 Me_3Si), 1.07 (t, 3 H, CH_3, $^{3}J_{HH}$ = 7.2), 3.34–3.40 (m, 4 H, C(1)H_2, C(2)H_2), 3.48 (s, 3 H, CH_3O), 3.94 (q, 2 H, CH_2O, $^{3}J_{HH}$ = 7.2). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 1.25 (s, 2 Me_3Si), 14.62 (s, Me), 31.16 (s, $CH_2C(O)$), 50.47 (s, C(2)), 52.03 (s, MeO), 58.51 (d, C(1), $^{1}J_{CP}$ = 26.2), 61.78 (s, CH_2O), 156.46 (s, NC=O), 170.12 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 150.18 (s).

***N*-Ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)aminomethylphosphonous acid bis(trimethylsilyl) ester (1d).** Yield: 78%. Bp: 121 °C (1 Torr). First isomer (60%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.05 (s, 18 H, 2 Me_3Si), 0.95–1.06 (m, 6 H, 2 CH_3), 2.45–2.54 (m, 2 H, $CH_2C(O)$), 3.38–3.44 (m, 4 H, C(1)H_2, C(2)H_2), 3.81–4.18 (m, 4 H, 2 CH_2O). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 1.22 (s, 2 Me_3Si), 14.07 (s, Me), 14.68 (s, Me), 31.21 (s, $CH_2C(O)$), 50.58 (s, C(2)), 58.66 (d, C(1), $^{1}J_{CP}$ = 25.9), 60.74 (s, CH_2O), 61.82 (s, CH_2O), 156.26 (s, NC=O), 171.09 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 149.25 (s). Second isomer (40%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.05 (s, 18 H, 2 Me_3Si), 0.95–1.06 (m, 6 H, 2 CH_3), 2.45–2.54 (m, 2 H, $CH_2C(O)$), 3.38–3.44 (m, 4 H, C(1)H_2, C(2)H_2), 3.81–4.18 (m, 4 H, 2 CH_2O). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 1.22 (s, 2 Me_3Si), 14.07 (s, Me), 14.68 (s, Me), 31.13 (s, $CH_2C(O)$), 50.50 (s, C(2)), 58.26 (d, C(1), $^{1}J_{CP}$ = 25.7), 60.70 (s, CH_2O), 61.64 (s, CH_2O), 156.18 (s, NC=O), 169.98 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 150.12 (s).

***N*-Ethoxycarbonyl-*N*-(3-methoxycarbonylpropyl)aminomethylphosphonous acid bis(trimethylsilyl) ester (1e).** Yield: 77%. Bp: 124 °C (1 Torr). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.12 (s, 18 H, 2 Me_3Si), 0.97 (t, 3 H, CH_3, $^{3}J_{HH}$ = 7.2), 1.62–1.78 (m, 2 H, CH_2), 2.42–2.51 (m, 2 H, $CH_2C(O)$), 3.38 (s, 3 H, CH_3O), 3.43–3.57 (m, 4 H, C(1)H_2, C(2)H_2), 3.96 (q, 2 H, CH_2O, $^{3}J_{HH}$ = 7.2). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 0.98 (s, 2 Me_3Si), 14.72 (s, Me), 23.10 (s, CH_2), 31.04 (s, $CH_2C(O)$), 50.46 (s, C(2)), 51.19 (s, MeO), 56.95 (d, C(1), $^{1}J_{CP}$ = 26.4), 55.10 (s, MeO), 61.49 (s, CH_2O), 156.13 (s, NC=O), 172.83 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 149.78 (s).

General procedure for the synthesis of sodium salts of amino acids and their analogs 2, 9. A solution of phosphonite **1** (40 mmol) or phosphonates **4** (20 mmol**)** in diethyl ether (30 mL) was added to a stirred solution of sodium methylate (40 mmol) in methanol (70 mL) at 10 °C. The reaction mixture was heated to reflux, and the solvent was distilled off. The residue obtained was kept under vacuum (1 Torr) for 1 h to give compounds **2**, **9** as white crystals.

***N*-Ethoxycarbonyl-*N*-(methoxycarbonylmethyl)aminomethylphosphonous acid sodium salt (2a).** Yield: 97%. Mp: 151 °C (dec.). Anal. Calcd for $C_7H_{13}NNaO_6P$: C, 32.19; H, 5.02. Found: C, 32.03; H, 4.96%. ^{1}H NMR (D_2O, δ, ppm, J/Hz): 1.07 (t, 3 H, CH_3, $^{3}J_{HH}$ = 7.0), 3.42 (d, 2 H, C(1)H_2, $^{2}J_{HP}$ = 9.2), 3.55 (s, 3 H, CH_3O), 3.96 (q, 2 H, CH_2O, $^{3}J_{HH}$ = 7.0), 4.23 (s, 2

H, C(2)H_2), 6.84 (d, 1 H, PH, $^1J_{HP}$ = 518.4). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.16 (s, Me), 50.64 (s, C(2)), 51.78 (s, MeO), 52.87 (d, C(1), $^1J_{CP}$ = 89.5), 61.96 (s, CH_2O), 156.58 (s, NC=O), 169.98 (s, C=O). ^{31}P NMR (D_2O, δ, ppm, J/Hz): 22.74 (d, 1 P, PH, $^1J_{PH}$ = 518.4). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 22.74 (s).

***N*-Ethoxycarbonyl-*N*-(ethoxycarbonylmethyl)aminomethylphosphonous acid sodium salt (2b).** Yield: 96%. Mp: 166 °C (dec.). Anal. Calcd for $C_8H_{15}NNaO_6P$: C, 34.92; H, 5.49. Found: C, 34.78; H, 5.40%. ^1H NMR (D_2O, δ, ppm, J/Hz): 1.04–1.15 (m, 6 H, 2 CH_3), 3.50 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 8.3), 3.75–3.91 (m, 4 H, 2 CH_2O), 4.24 (s, 2 H, C(2)H_2), 6.87 (d, PH, 1 H, $^1J_{HP}$ = 516.3). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.20 (s, 2 Me), 50.54 (s, C(2)), 53.59 (d, C(1), $^1J_{CP}$ = 88.9), 62.15 (s, 2 CH_2O), 156.60 (s, NC=O), 169.68 (s, C=O). ^{31}P NMR (D_2O, δ, ppm, J/Hz): 21.98 (d, 1 P, PH, $^1J_{PH}$ = 516.3). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 21.98 (s).

***N*-Ethoxycarbonyl-*N*-(2-methoxycarbonylethyl)aminomethylphosphonous acid sodium salt (2c).** Yield: 95%. Mp: 142 °C (dec.). Anal. Calcd for $C_8H_{15}NNaO_6P$: C, 34.92; H, 5.49. Found: C, 34.72; H, 5.43%. ^1H NMR (D_2O, δ, ppm, J/Hz): 1.05 (t, 3 H, CH_3, $^3J_{HH}$ = 7.1), 3.38–3.45 (m, 6 H, C(1)H_2, C(2)H_2), $CH_2C(O)$), 3.59 (s, 3 H, CH_3O), 4.01 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.1), 6.88 (d, 1 H, PH, $^1J_{HP}$ = 522.1). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.76 (s, Me), 31.88 (s, $CH_2C(O)$), 50.89 (s, C(2)), 52.23 (s, MeO), 53.04 (d, C(1), $^1J_{CP}$ = 90.1), 61.82 (s, CH_2O), 156.65 (s, NC=O), 170.46 (s, C=O). ^{31}P NMR (D_2O, δ, ppm, J/Hz): 22.94 (d, 1 P, PH, $^1J_{PH}$ = 522.1). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 22.94 (s).

***N*-Ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)aminomethylphosphonous acid sodium salt (2d).** Yield: 96%. Mp: 164 °C (dec.). Anal. Calcd for $C_9H_{17}NNaO_6P$: C, 37.38; H, 5.93. Found: C, 37.29; H, 5.88%. ^1H NMR (D_2O, δ, ppm, J/Hz): 1.04–1.13 (m, 6 H, 2 CH_3), 2.47–2.53 (m, 2 H, $CH_2C(O)$), 3.45–3.53 (m, 4 H, C(1)H_2, C(2)H_2), 3.83–4.15 (m, 4 H, 2 CH_2O), 6.85 (d, 1 H, PH, $^1J_{HP}$ = 519.0). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.11 (s, Me), 14.74 (s, Me), 31.26 (s, $CH_2C(O)$), 50.62 (s, C(2)), 52.94 (d, C(1), $^1J_{CP}$ = 89.8), 60.79 (s, CH_2O), 61.86 (s, CH_2O), 156.48 (s, NC=O), 171.12 (s, C=O). ^{31}P NMR (D_2O, δ, ppm, J/Hz): 22.28 (d, 1 P, PH, $^1J_{PH}$ = 519.0). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 22.28 (s).

***N*-Ethoxycarbonyl-*N*-(3-methoxycarbonylpropyl)aminomethylphosphonous acid sodium salt (2e).** Yield: 95%. Mp: 168 °C (dec.). Anal. Calcd for $C_9H_{17}NNaO_6P$: C, 37.38; H, 5.93. Found: C, 37.26; H, 5.86%. ^1H NMR (D_2O, δ, ppm, J/Hz): 1.04 (t, 3 H, CH_3, $^3J_{HH}$ = 7.2), 1.67–1.81 (m, 2 H, CH_2), 2.45–2.54 (m, 2 H, $CH_2C(O)$), 3.42 (s, 3 H, CH_3O), 3.49–3.63 (m, 4 H, C(1)H_2, C(2)H_2), 4.02 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.2), 6.82 (d, 1 H, PH, $^1J_{HP}$ = 520.1). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.78 (s, Me), 23.14 (s, CH_2), 31.13 (s, $CH_2C(O)$), 50.57 (s, C(2)), 51.22 (s, MeO), 52.68 (d, C(1), $^1J_{CP}$ = 90.2), 55.06 (s, MeO), 61.64 (s, CH_2O), 156.28 (s, NC=O), 172.95

(s, C=O). ^{31}P NMR (D_2O, δ, ppm, J/Hz): 22.44 (d, 1 P, PH, $^1J_{PH}$ = 520.1). ^{31}P{^{1}H} NMR (D_2O, δ, ppm): 22.44 (s).

General procedure for the synthesis of phosphonates 3–5 and phosphinates 6–8. A solution of *N*-chloromethylamide (35 mmol) in dichloromethane (40 mL) was added dropwise to a stirred solution of tri-coordinate phosphorus acid ester (40 mmol) in CH_2Cl_2 (35 mL) at 10 °C. The reaction mixture was stirred at room temperature for 1 h and then heated to reflux. The solvent was distilled off, and the residue obtained was distilled to give compounds **3**–**8**.

***N*-Ethoxycarbonyl-*N*-(methoxycarbonylmethyl)aminomethylphosphonic acid diethyl ester (3a).** Yield: 87%. Bp: 165 °C (3 Torr). Anal. Calcd for $C_{11}H_{22}NO_7P$: C, 42.44; H, 7.12. Found: C, 42.26 H, 7.08%. First isomer (60%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.98–1.12 (m, 9 H, 3 CH_3), 3.48 (s, 3 H, CH_3O), 3.58 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 11.4), 3.84–3.92 (m, 6 H, 3 CH_2O), 4.30 (s, 2 H, C(2)H_2). ^{13}C{^{1}H} NMR ($CDCl_3$, δ, ppm, J/Hz): 13.95 (s, Me), 15.82 (d, Me, $^3J_{CP}$ = 6.1), 15.88 (d, Me, $^3J_{CP}$ = 6.1), 42.15 (d, C(1), $^1J_{CP}$ = 159.1), 48.08 (s, C(2)), 51.48 (s, MeO), 61.76 (s, Me), 61.89 (d, 2 Me, $^2J_{CP}$ = 6.3), 155.36 (s, NC=O), 169.22 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, δ, ppm): 19.60 (s). Second isomer (40%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.98–1.12 (m, 9 H, 3 CH_3), 3.48 (s, 3 H, CH_3O), 3.55 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 11.4), 3.84–3.92 (m, 6 H, 3 CH_2O), 4.34 (s, 2 H, C(2)H_2). ^{13}C{^{1}H} NMR ($CDCl_3$, δ, ppm, J/Hz): 13.95 (s, Me), 15.82 (d, Me, $^3J_{CP}$ = 6.1), 15.88 (d, Me, $^3J_{CP}$ = 6.1), 42.32 (d, C(1), $^1J_{CP}$ = 158.5), 47.97 (s, C(2)), 51.48 (s, MeO), 61.76 (s, Me), 61.89 (d, 2 Me, $^2J_{CP}$ = 6.3), 155.36 (s, NC=O), 169.22 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, δ, ppm): 19.22 (s).

***N*-Ethoxycarbonyl-*N*-(ethoxycarbonylmethyl)aminomethylphosphonic acid diethyl ester (3b).** Yield: 85%. Bp: 153 °C (2 Torr). Anal. Calcd for $C_{12}H_{24}NO_7P$: C, 44.30; H, 7.44. Found: C, 44.40 H, 7.41%. First isomer (60%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.90 (t, 6 H, 2 CH_3, $^3J_{HH}$ = 7.2), 1.02 (t, 6 H, 2 CH_3, $^3J_{HH}$ = 6.8), 3.28–4.04 (m, 10 H, C(1)H_2, 4 CH_2O), 4.28 (s, 2 H, C(2)H_2). ^{13}C{^{1}H} NMR ($CDCl_3$, δ, ppm, J/Hz): 14.07 (s, 2 Me), 14.47 (s, Me), 16.40 (s, Me), 43.23 (d, C(1), $^1J_{CP}$ = 158.4), 49.06 (s, C(2)), 60.90 (s, CH_2O), 62.02 (s, CH_2O), 62.12 (d, 2 CH_2O, $^2J_{CP}$ = 7.3), 156.20 (d, NC=O, $^3J_{CP}$ = 4.6), 169.35 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, δ, ppm): 19.39 (s). Second isomer (40%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.90 (t, 6 H, 2 CH_3, $^3J_{HH}$ = 7.2), 1.02 (t, 6 H, 2 CH_3, $^3J_{HH}$ = 6.8), 3.28–4.04 (m, 10 H, C(1)H_2, 4 CH_2O), 4.41 (s, 2 H, C(2)H_2). ^{13}C{^{1}H} NMR ($CDCl_3$, δ, ppm, J/Hz): 14.02 (s, 2 Me), 14.47 (s, Me), 16.35 (s, Me), 43.28 (d, C(1), $^1J_{CP}$ = 158.1), 48.98 (s, C(2)), 60.90 (s, CH_2O), 62.02 (s, CH_2O), 62.12 (d, 2 CH_2O, $^2J_{CP}$ = 7.3), 156.49 (d, NC=O, $^3J_{CP}$ = 3.1), 169.37 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, δ, ppm): 19.25 (s).

***N*-Ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)aminomethylphosphonic acid diethyl ester (3c).** Yield: 90%. Bp: 185 °C (3 Torr). Anal. Calcd for $C_{13}H_{26}NO_7P$: C, 46.01; H, 7.72.

Found: C, 45.86; H, 7.64%. First isomer (60%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.84–1.04 (m, 12 H, 4 CH_3), 2.18–2.29 (m, 2 H, $CH_2C(O)$), 3.16–3.28 (m, 2 H, C(2)H_2), 3.34–3.43 (m, 2 H, C(1)H_2), 3.66–3.82 (m, 8 H, 4 CH_2O). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 13.27 (s, 2 Me), 13.72 (s, Me), 15.51 (s, Me), 32.47 (s, $CH_2C(O)$), 42.11 (d, C(1), $^{1}J_{CP}$ = 158.5), 42.90 (s, C(2)), 59.54 (s, CH_2O), 59.54 (s, CH_2O), 60.99 (s, CH_2O), 61.27 (s, 2 CH_2O), 155.01 (s, NC=O), 170.57 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 20.12 (s). Second isomer (40%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.84–1.04 (m, 12 H, 4 CH_3), 2.18–2.29 (m, 2 H, $CH_2C(O)$), 3.16–3.28 (m, 2 H, C(2)H_2), 3.34–3.43 (m, 2 H, C(1)H_2), 3.66–3.82 (m, 8 H, 4 CH_2O). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 13.27 (s, 2 Me), 13.72 (s, Me), 15.51 (s, Me), 31.81 (s, $CH_2C(O)$), 42.50 (d, C(1), $^{1}J_{CP}$ = 155.9), 43.48 (s, C(2)), 59.54 (s, CH_2O), 60.84 (s, CH_2O), 61.27 (s, 2 CH_2O), 154.49 (s, NC=O), 170.85 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 19.71 (s).

***N*-Ethoxycarbonyl-*N*-(3-methoxycarbonylpropyl)aminomethylphosphonic acid diethyl ester (3d).** Yield: 92%. Bp: 175 °C (2 Torr). Anal. Calcd for $C_{13}H_{26}NO_7P$: C, 46.01; H, 7.72. Found: C, 45.81; H, 7.68%. First isomer (70%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.98–1.02 (m, 9 H, 3 CH_3), 1.57–1.61 (m, 2 H, CH_2), 2.02–2.54 (m, 2 H, $CH_2C(O)$), 3.37 (s, 3 H, CH_3O), 3.45–3.70 (m, 4 H, C(1)H_2, C(2)H_2), 3.86–4.04 (m, 6 H, 3 CH_2O). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 14.60 (s, Me), 16.43 (d, Me, $^{3}J_{CP}$ = 5.4), 23.24 (s, CH_2), 31.00 (s, $CH_2C(O)$), 42.59 (d, C(1), $^{1}J_{CP}$ = 156.0), 46.92 (s, C(2)), 51.11 (s, MeO), 61.59 (s, CH_2O), 61.90 (d, 2 CH_2O, $^{2}J_{CP}$ = 6.1), 156.11 (s, NC=O), 172.96 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 20.27 (s). Second isomer (30%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.98–1.02 (m, 9 H, 3 CH_3), 1.57–1.61 (m, 2 H, CH_2), 2.02–2.54 (m, 2 H, $CH_2C(O)$), 3.37 (s, 3 H, CH_3O), 3.45–3.70 (m, 4 H, C(1)H_2, C(2)H_2), 3.86–4.04 (m, 6 H, 3 CH_2O). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 14.60 (s, Me), 16.43 (d, Me, $^{3}J_{CP}$ = 5.4), 22.91 (s, CH_2), 31.00 (s, $CH_2C(O)$), 42.59 (d, C(1), $^{1}J_{CP}$ = 156.0), 47.30 (s, C(2)), 51.11 (s, MeO), 61.59 (s, CH_2O), 61.90 (d, 2 CH_2O, $^{2}J_{CP}$ = 6.1), 155.72 (s, NC=O), 172.96 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 19.94 (s).

***N*-Ethoxycarbonyl-*N*-(methoxycarbonylmethyl)aminomethylphosphonic acid bis(trimethylsilyl) ester (4a).** Yield: 82%. Bp: 168 °C (2 Torr). Anal. Calcd for $C_{13}H_{30}NO_7PSi_2$: C, 39.08; H, 7.57. Found: C, 38.89; H, 7.52%. First isomer (65%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.10 (s, 18 H, 2 Me_3Si), 1.09 (t, 3 H, CH_3, $^{3}J_{HH}$ = 7.2), 3.61 (s, 3 H, CH_3O), 3.83 (d, 2 H, C(1)H_2, $^{2}J_{HP}$ = 10.0), 3.98 (q, 2 H, CH_2O, $^{3}J_{HH}$ = 7.2), 4.33 (s, 2 H, C(2)H_2). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 0.82 (s, 2 Me_3Si), 14.14 (s, Me), 45.37 (d, C(1), $^{1}J_{CP}$ = 167.0), 48.60 (s, C(2)), 51.52 (s, MeO), 61.99 (s, CH_2O), 156.06 (s, NC=O), 169.84 (s, C=O). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm): 1.32 (s). Second isomer (35%). ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.10 (s, 18 H, 2 Me_3Si), 1.09 (t, 3 H, CH_3, $^{3}J_{HH}$ = 7.2), 3.61 (s, 3 H, CH_3O), 3.77 (d, 2 H, C(1)H_2, $^{2}J_{HP}$ = 10.0), 3.98 (q, 2 H, CH_2O, $^{3}J_{HH}$ = 7.2), 4.46 (s, 2 H, C(2)H_2). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz):

0.82 (s, 2 Me_3Si), 14.14 (s, Me), 45.08 (d, C(1), $^1J_{CP}$ = 165.7), 48.40 (s, C(2)), 51.47 (s, MeO), 62.13 (s, CH_2O), 156.10 (s, NC=O), 169.88 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 1.51 (s).

***N*-Ethoxycarbonyl-*N*-(ethoxycarbonylmethyl)aminomethylphosphonic acid bis(trimethylsilyl) ester (4b).** Yield: 81%. Bp: 132 °C (0.5 Torr). Anal. Calcd for $C_{14}H_{32}NO_7PSi_2$: C, 40.66; H, 7.80. Found: C, 40.53; H, 7.68%. First isomer (60%). ^1H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.18 (s, 18 H, 2 Me_3Si), 0.84–0.99 (m, 6 H, 2 CH_3), 3.85 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 10.0), 3.90–4.02 (m, 4 H, 2 CH_2O), 4.34 (s, 2 H, C(2)H_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, *J*/Hz): 1.16 (s, 2 Me_3Si), 14.20 (s, Me), 14.63 (s, 2 Me), 45.46 (d, C(1), $^1J_{CP}$ = 167.0), 48.77 (s, C(2)), 60.62 (s, CH_2O), 61.08 (s, CH_2O), 156.15 (d, NC=O, $^3J_{CP}$ = 4.5), 169.40 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 1.36 (s). Second isomer (40%). ^1H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.15 (s, 18 H, 2 Me_3Si), 0.84–0.99 (m, 6 H, 2 CH_3), 3.79 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 10.0), 3.90–4.02 (m, 4 H, 2 CH_2O), 4.48 (s, 2 H, C(2)H_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, *J*/Hz): 1.16 (s, 2 Me_3Si), 14.05 (s, Me), 14.63 (s, 2 Me), 45.13 (d, C(1), $^1J_{CP}$ = 166.6), 48.53 (s, C(2)), 60.62 (s, CH_2O), 62.12 (s, CH_2O), 156.11 (d, NC=O, $^3J_{CP}$ = 3.1), 169.44 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 1.56 (s).

***N*-Ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)aminomethylphosphonic acid bis(trimethylsilyl) ester (4c).** Yield: 85%. Bp: 171 °C (2 Torr). Anal. Calcd for $C_{15}H_{34}NO_7PSi_2$: C, 42.14; H, 8.01. Found: C, 41.94; H, 7.92%. First isomer (70%). ^1H NMR ($CDCl_3$, δ, ppm, *J*/Hz): –0.01 (s, 18 H, 2 Me_3Si), 0.90–1.02 (m, 6 H, 2 CH_3), 2.32–2.38 (m, 2 H, $CH_2C(O)$), 3.34–3.42 (m, 4 H, C(1)H_2, C(2)H_2), 3.76–4.02 (m, 4 H, 2 CH_2O). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.29 (s, 2 Me_3Si), 13.56 (s, 2 Me), 32.63 (s, $CH_2C(O)$), 42.94 (s, C(2)), 44.49 (d, C(1), $^1J_{CP}$ = 165.6), 61.08 (s, CH_2O), 155.16 (s, NC=O), 170.78 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 1.47 (s). Second isomer (30%). ^1H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.01 (s, 18 H, 2 Me_3Si), 0.90–1.02 (m, 6 H, 2 CH_3), 2.32–2.38 (m, 2 H, $CH_2C(O)$), 3.34–3.42 (m, 4 H, C(1)H_2, C(2)H_2), 3.76–4.02 (m, 4 H, 2 CH_2O). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.29 (s, 2 Me_3Si), 14.08 (s, 2 Me), 31.94 (s, $CH_2C(O)$), 43.44 (s, C(2)), 44.49 (d, C(1), $^1J_{CP}$ = 165.6), 59.79 (s, CH_2O), 154.80 (s, NC=O), 171.05 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 1.54 (s).

***N*-Ethoxycarbonyl-*N*-(3-methoxycarbonylpropyl)aminomethylphosphonic acid bis(trimethylsilyl) ester (4d).** Yield: 82%. Bp: 155 °C (1 Torr). Anal. Calcd for $C_{15}H_{34}NO_7PSi_2$: C, 42.14; H, 8.01. Found: C, 41.88; H, 7.96%. ^1H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.20 (s, 18 H, 2 Me_3Si), 1.00 (t, 3 H, CH_3, $^3J_{HH}$ = 7.2), 1.65–1.80 (m, 2 H, CH_2), 1.95–2.12 (m, 2 H, $CH_2C(O)$), 3.35 (s, 3 H, CH_3O), 3.38–3.65 (m, 4 H, C(1)H_2, C(2)H_2), 3.97 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.94 (s, 2 Me_3Si), 14.74 (s, Me), 23.14 (s, CH_2), 31.02 (s, $CH_2C(O)$), 44.67 (d, C(1), $^1J_{CP}$ = 160.4), 46.61 (s, C(2)), 51.09 (s, MeO), 61.47 (s, CH_2O), 155.97 (s, NC=O), 172.75 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 2.14 (s).

***N*-Ethoxycarbonyl-*N*-(ethoxycarbonylmethyl)aminomethylphosphonic acid diisopropyl ester (5).** Yield: 74%. Bp: 141 °C (1 Torr). Anal. Calcd for $C_{14}H_{28}NO_7P$: C, 47.59; H, 7.99. Found: C, 47.73; H, 8.02%. First isomer (60%). ^{1}H NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 0.89–1.04 (m, 6 H, 2 CH_3), 1.08–1.21 (m, 12 H, 4 CH_3), 3.78–4.03 (m, 6 H, C(1)H_2, 2 CH_2O), 4.34 (s, 2 H, C(2)H_2), 4.56–4.73 (m, 2 H, 2 CH). ^{13}C{^{1}H} NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 14.53 (s, 2 Me), 23.87 (d, 4 Me, $^3J_{CP}$ = 4.8), 43.52 (d, C(1), $^1J_{CP}$ = 160.7), 48.32 (s, C(2)), 60.87 (s, CH_2O), 62.94 (d, CH_2O, $^2J_{CP}$ = 4.5), 70.78 (s, 2 CHO), 155.61 (d, NC=O, $^3J_{CP}$ = 5.4), 168.79 (s, C=O). ^{31}P{^{1}H} ($CDCl_3$, *δ*, ppm): 17.71 (s). Second isomer (40%). ^{1}H NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 0.89–1.04 (m, 6 H, 2 CH_3), 1.08–1.21 (m, 12 H, 4 CH_3), 3.78–4.03 (m, 6 H, C(1)H_2, 2 CH_2O), 4.48 (s, 2 H, C(2)H_2), 4.56–4.73 (m, 2 H, 2 CH). ^{13}C{^{1}H} NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 14.03 (s, 2 Me), 23.74 (d, 4 Me, $^3J_{CP}$ = 5.7), 43.52 (d, C(1), $^1J_{CP}$ = 160.7), 48.21 (s, C(2)), 60.87 (s, CH_2O), 62.94 (d, CH_2O, $^2J_{CP}$ = 4.5), 70.78 (s, 2 CHO), 155.52 (d, NC=O, $^3J_{CP}$ = 3.4), 168.79 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, *δ*, ppm): 17.47 (s).

Methyl[*N*-ethoxycarbonyl-*N*-(methoxycarbonylmethyl)aminomethyl]phosphinic acid isopropyl ester (6). Yield: 87%. Bp: 157 °C (2 Torr). Anal. Calcd for $C_{11}H_{22}NO_6P$: C, 44.74; H, 7.51. Found: C, 44.59; H, 7.45%. First isomer (65%). ^{1}H NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 0.92 (t, 3 H, CH_3, $^3J_{HH}$ = 7.0), 1.07 (d, 6 H, 2 CH_3, $^3J_{HP}$ = 6.4), 1.35 (d, 3 H, PCH_3, $^2J_{HP}$ = 14.0), 3.36 (s, 3 H, CH_3O), 3.49–3.72 (m, 2 H, C(1)H_2), 3.82–4.04 (m, 2 H, CH_2O), 4.23 (s, 2 H, C(2)H_2), 4.46–4.52 (m, 1 H, CHO). ^{13}C{^{1}H} NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 13.59 (d, PMe, $^1J_{CP}$ = 90.2), 14.49 (s, Me), 24.24 (s, 2 Me), 47.61 (d, C(1), $^1J_{CP}$ = 106.1), 49.41 (s, C(2)), 51.60 (s, MeO), 62.16 (s, CH_2O), 69.46 (d, CHO, $^2J_{CP}$ = 5.4), 156.27 (s, NC=O), 169.94 (s, C=O). ^{31}P{^{1}H} ($CDCl_3$, *δ*, ppm): 44.82 (s). Second isomer (35%). ^{1}H NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 0.92 (t, 3 H, CH_3, $^3J_{HH}$ = 7.0), 1.05 (d, 6 H, 2 CH_3, $^3J_{HP}$ = 6.0), 1.26 (d, 3 H, PCH_3, $^2J_{HP}$ = 14.0), 3.33 (s, 3 H, CH_3O), 3.49–3.72 (m, 2 H, C(1)H_2), 3.82–4.04 (m, 2 H, CH_2O), 4.33 (s, 2 H, C(2)H_2), 4.46–4.52 (m, 1 H, CHO). ^{13}C{^{1}H} NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 13.39 (d, PMe, $^1J_{CP}$ = 90.0), 14.49 (s, Me), 24.24 (s, 2 Me), 47.48 (d, C(1), $^1J_{CP}$ = 105.0), 49.41 (s, C(2)), 51.55 (s, MeO), 62.16 (s, CH_2O), 69.46 (d, CHO, $^2J_{CP}$ = 5.4), 156.76 (s, NC=O), 169.87 (s, C=O). ^{31}P{^{1}H} NMR ($CDCl_3$, *δ*, ppm): 44.23 (s).

Methyl[*N*-ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)aminomethyl]phosphinic acid isopropyl ester (7). Yield: 87%. Bp: 177 °C (1.5 Torr). Anal. Calcd for $C_{13}H_{26}NO_6P$: C, 48.29; H, 8.11. Found: C, 48.07; H, 8.06%. First isomer (70%). ^{1}H NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 0.67–0.68 (m, 6 H, 2 CH_3), 0.75–0.78 (m, 6 H, 2 CH_3), 0.91 (d, 3 H, CH_3P, $^2J_{HP}$ = 14.0), 2.04–2.12 (m, 2 H, $CH_2C(O)$), 3.01–3.28 (m, 4 H, C(1)H_2, C(2)H_2), 3.52–3.64 (m, 4 H, 2 CH_2O), 4.10–4.22 (m, 1 H, CHO). ^{13}C{^{1}H} NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 13.01 (s, Me), 13.46 (s, Me), 13.24 (d, MeP, $^1J_{CP}$ = 88.7), 23.15 (s, 2 Me), 32.14 (s, $CH_2C(O)$), 43.11 (s, C(2)), 46.26 (d, C(1), $^1J_{CP}$ =

104.7), 59.16 (s, CH_2O), 60.67 (s, CH_2O), 68.26 (s, CHO), 154.80 (s, NC=O), 170.16 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 45.58 (s). Second isomer (30%). ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.67–0.68 (m, 6 H, 2 CH_3), 0.75–0.78 (m, 6 H, 2 CH_3), 0.91 (d, 3 H, CH_3P, $^2J_{HP}$ = 14.0), 2.04–2.12 (m, 2 H, $CH_2C(O)$), 3.01–3.28 (m, 4 H, C(1)H_2, C(2)H_2), 3.52–3.64 (m, 4 H, 2 CH_2O), 4.10–4.22 (m, 1 H, CHO). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 13.01 (s, Me), 13.46 (s, Me), 13.24 (d, MeP, $^1J_{CP}$ = 88.7), 23.15 (s, 2 Me), 31.45 (s, $CH_2C(O)$), 43.57 (s, C(2)), 46.26 (d, C(1), $^1J_{CP}$ = 104.7), 59.16 (s, CH_2O), 60.54 (s, CH_2O), 68.26 (s, CHO), 153.98 (s, NC=O), 170.37 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 44.93 (s).

Methyl[*N*-ethoxycarbonyl-*N*-(3-methoxycarbonylpropyl)aminomethyl]phosphinic acid isopropyl ester (8). Yield: 84%. Bp: 150 °C (1 Torr). Anal. Calcd for $C_{13}H_{26}NO_6P$: C, 48.29; H, 8.11. Found: C, 48.12; H, 8.03%. First isomer (70%). ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.97 (t, 3 H, CH_3, $^2J_{HH}$ = 7.2), 1.08 (d, 6 H, 2 CH_3, $^2J_{HH}$ = 6.0), 1.28 (d, 3 H, CH_3P, $^2J_{HP}$ = 14.2), 1.62–1.76 (m, 2 H, CH_2), 1.93–2.08 (m, 2 H, $CH_2C(O)$), 3.37 (s, 3 H, CH_3O), 3.43–3.66 (m, 4 H, C(1)H_2, C(2)H_2), 3.94 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.2), 4.50–4.62 (m, 1 H, CHO). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 14.62 (s, Me), 14.95 (d, MeP, $^1J_{CP}$ = 89.8), 24.33 (d, 2 Me, $^3J_{CP}$ = 3.1), 31.00 (s, $CH_2C(O)$), 46.83 (d, C(1), $^1J_{CP}$ = 103.5), 47.34 (s, C(2)), 51.12 (s, MeO), 61.58 (s, CH_2O), 68.92 (d, CHO, $^2J_{CP}$ = 6.2), 156.24 (s, NC=O), 172.93 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 44.09 (s). Second isomer (30%). ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.97 (t, 3 H, CH_3, $^2J_{HH}$ = 7.2), 1.11 (d, 6 H, 2 CH_3, $^2J_{HH}$ = 6.0), 1.18 (d, 3 H, CH_3P, $^2J_{HP}$ = 14.2), 1.62–1.76 (m, 2 H, CH_2), 1.93–2.08 (m, 2 H, $CH_2C(O)$), 3.37 (s, 3 H, CH_3O), 3.43–3.66 (m, 4 H, C(1)H_2, C(2)H_2), 3.94 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.2), 4.50–4.62 (m, 1 H, CHO). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 14.62 (s, Me), 14.95 (d, MeP, $^1J_{CP}$ = 89.8), 24.33 (d, 2 Me, $^3J_{CP}$ = 3.1), 31.00 (s, $CH_2C(O)$), 46.83 (d, C(1), $^1J_{CP}$ = 103.5), 47.34 (s, C(2)), 51.12 (s, MeO), 61.58 (s, CH_2O), 68.92 (d, CHO, $^2J_{CP}$ = 6.2), 155.54 (s, NC=O), 172.93 (s, C=O). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 43.56 (s).

***N*-Ethoxycarbonyl-*N*-(methoxycarbonylmethyl)aminomethylphosphonic acid disodium salt (9a).** Yield: 95%. Mp: 204 °C (dec.). Anal. Calcd for $C_7H_{12}NNa_2O_7P$: C, 28.11; H, 4.04. Found: C, 27.96; H, 3.98%. ^1H NMR (D_2O, δ, ppm, J/Hz): 1.02 (t, 3 H, CH_3, $^3J_{HH}$ = 7.0), 3.60 (s, 3 H, CH_3O), 3.86 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 10.0), 4.03 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.0), 4.35 (s, 2 H, C(2)H_2). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.08 (s, Me), 44.91 (d, C(1), $^1J_{CP}$ = 152.4), 48.84 (s, C(2)), 51.55 (s, MeO), 62.12 (s, CH_2O), 63.38 (s, CH_2O), 156.86 (s, NC=O), 170.16 (s, C=O). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 16.89 (s).

***N*-Ethoxycarbonyl-*N*-(ethoxycarbonylmethyl)aminomethylphosphonic acid disodium salt (9b).** Yield: 95%. Mp: 197 °C (dec.). Anal. Calcd for $C_8H_{14}NNa_2O_7P$: C, 30.68; H, 4.51. Found: C, 30.42; H, 4.47%. ^1H NMR (D_2O, δ, ppm, J/Hz): 0.95–1.06 (m, 6 H, 2 CH_3), 3.74 (d, 2

H, C(1)H_2, $^2J_{HP}$ = 10.2), 3.92–4.04 (m, 4 H, 2 CH_2O), 4.36 (s, 2 H, C(2)H_2). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.22 (s, Me), 14.66 (s, 2 Me), 45.01 (d, C(1), $^1J_{CP}$ = 151.8), 48.89 (s, C(2)), 60.66 (s, CH_2O), 61.12 (s, CH_2O), 156.22 (s, NC=O), 167.31 (s, C=O). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 17.04 (s).

***N*-Ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)aminomethylphosphonic acid disodium salt (9c).** Yield: 96%. Mp: 192 °C (dec.). Amal. Calcd for $C_9H_{16}NNa_2O_7P$: C, 33.04; H, 4.93. Found: C, 32.86; H, 4.89%. ^1H NMR (D_2O, δ, ppm, J/Hz): 1.05–1.15 (m, 6 H, 2 CH_3), 2.34–2.39 (m, 2 H, $CH_2C(O)$), 3.37–3.44 (m, 4 H, C(1)H_2, C(2)H_2), 3.82–4.07 (m, 4 H, 2 CH_2O). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 13.72 (s, Me), 32.09 (s, $CH_2C(O)$), 42.53 (s, C(2)), 44.91 (d, C(1), $^1J_{CP}$ = 151.4), 61.10 (s, CH_2O), 155.29 (s, NC=O), 170.95 (s, C=O). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 17.09 (s).

***N*-Ethoxycarbonyl-*N*-(3-methoxycarbonylpropyl)aminomethylphosphonic acid disodium salt (9d).** Yield: 95%. Mp: 193 °C (dec.). Anal. Calcd for $C_9H_{16}NNa_2O_7P$: C, 33.04; H, 4.93. Found: C, 32.83; H, 4.85%. ^1H NMR (D_2O, δ, ppm, J/Hz): 1.08 (t, 3 H, CH_3, $^3J_{HH}$ = 7.0), 1.60–1.77 (m, 2 H, CH_2), 1.98–2.10 (m, 2 H, $CH_2C(O)$), 3.89 (s, 3 H, CH_3O), 3.42–3.69 (m, 4 H, C(1)H_2, C(2)H_2), 4.01 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.0). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.78 (s, Me), 23.19 (s, CH_2), 31.12 (s, $CH_2C(O)$), 44.49 (d, C(1), $^1J_{CP}$ = 152.2), 46.92 (s, C(2)), 51.12 (s, MeO), 61.58 (s, CH_2O), 156.13 (s, NC=O), 172.97 (s, C=O). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 17.34 (s).

General procedure for the synthesis of functionalized acids 10. A solution of phosphonate **4** or phosphinate **15**–**24** (40 mmol) in diethyl ether (30 mL) was added upon stirring to methanol (50 mL) at 10 °C. The reaction mixture was heated to reflux, the solvent was distilled off, and the residue obtained was kept under vacuum (1 Torr) for 1 h to give acids **10** as viscous oils or crystals.

***N*-Ethoxycarbonyl-*N*-(methoxycarbonylmethyl)aminomethylphosphonic acid (10a).** Yield: 95%. Viscous oil. Anal. Calcd for $C_7H_{14}NO_7P$: C, 32.95; H, 5.53. Found: C, 32.78; H, 5.48%. <u>First isomer</u> (65%). ^1H NMR (D_2O, δ, ppm, J/Hz): 1.12 (t, 3 H, CH_3, $^3J_{HH}$ = 7.1), 3.94 (s, 3 H, CH_3O), 3.94 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 10.1), 4.07 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.1), 4.35 (s, 2 H, C(2)H_2). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.16 (s, Me), 45.39 (d, C(1), $^1J_{CP}$ = 152.3), 48.68 (s, C(2)), 51.57 (s, MeO), 62.04 (s, CH_2O), 156.69 (s, NC=O), 171.24 (s, C=O). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 16.32 (s). <u>Second isomer</u> (35%). ^1H NMR (D_2O, δ, ppm, J/Hz): 1.12 (t, 3 H, CH_3, $^3J_{HH}$ = 7.1), 3.63 (s, 3 H, CH_3O), 3.86 (d, 2 H, C(1)H_2, $^2J_{HP}$ = 10.1), 4.07 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.1), 4.48 (s, 2 H, C(2)H_2). $^{13}C\{^1H\}$ NMR (D_2O, δ, ppm, J/Hz): 14.14 (s, Me), 45.39 (d, C(1), $^1J_{CP}$ = 152.3), 48.40 (s, C(2)), 51.67 (s, MeO), 62.04 (s, CH_2O), 156.95 (s, NC=O), 171.18 (s, C=O). $^{31}P\{^1H\}$ NMR (D_2O, δ, ppm): 17.21 (s).

***N*-Ethoxycarbonyl-*N*-(ethoxycarbonylmethyl)aminomethylphosphonic acid (10b).** Yield: 97%. Viscous oil. Anal. Calcd for $C_8H_{16}NO_7P$: C, 35.69; H, 5.99. Found: C, 35.49; H, 5.94%. First isomer (55%). ^{1}H NMR (D_2O, *δ*, ppm, *J*/Hz): 1.15–1.28 (m, 6 H, 2 CH_3), 3.75–3.81 (m, 2 H, C(1)H_2), 4.03–4.22 (m, 6 H, 2 CH_2O, C(2)H_2). ^{13}C{^{1}H} NMR (D_2O, *δ*, ppm, *J*/Hz): 13.49 (s, Me), 13.89 (s, Me), 44.62 (d, C(1), $^1J_{CP}$ = 151.6), 49.72 (s, C(2)), 62.49 (s, CH_2O), 63.23 (s, CH_2O), 157.58 (s, NC=O), 171.46 (s, C=O). ^{31}P{^{1}H} NMR (D_2O, *δ*, ppm): 16.79 (s). Second isomer (45%). ^{1}H NMR (D_2O, *δ*, ppm, *J*/Hz): 1.15–1.28 (m, 6 H, 2 CH_3), 3.75–3.81 (m, 2 H, C(1)H_2), 4.03–4.22 (m, 6 H, 2 CH_2O, C(2)H_2). ^{13}C{^{1}H} NMR (D_2O, *δ*, ppm, *J*/Hz): 13.49 (s, Me), 13.89 (s, Me), 44.62 (d, C(1), $^1J_{CP}$ = 151.6), 49.72 (s, C(2)), 62.49 (s, CH_2O), 63.23 (s, CH_2O), 157.39 (s, NC=O), 171.24 (s, C=O). ^{31}P{^{1}H} NMR (D_2O, *δ*, ppm): 17.14 (s).

***N*-Ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)aminomethylphosphonic acid (10c).** Yield: 96%. Viscous oil. Anal. Calcd for $C_9H_{18}NO_7P$: C, 38.17; H, 6.41. Found: C, 37.98; H, 6.38%. ^{1}H NMR (D_2O, *δ*, ppm, *J*/Hz): 1.07–1.15 (m, 6 H, 2 CH_3), 2.27–2.43 (m, 2 H, $CH_2C(O)$), 3.48–3.59 (m, 4 H, C(1)H_2, C(2)H_2), 3.85–4.04 (m, 4 H, 2 CH_2O). ^{3}C{^{1}H} NMR (D_2O, *δ*, ppm, *J*/Hz): 13.76 (s, 2 Me), 32.68 (s, $CH_2C(O)$), 42.98 (s, C(2)), 46.15 (d, C(1), $^1J_{CP}$ = 152.8), 61.12 (s, CH_2O), 155.43 (s, NC=O), 172.18 (s, C=O). ^{31}P{^{1}H} NMR (D_2O, *δ*, ppm): 17.92 (s).

***N*-Ethoxycarbonyl-*N*-(3-methoxycarbonylpropyl)aminomethylphosphonic acid (10d).** Yield: 97%. Viscous oil. Anal. Calcd for $C_9H_{18}NO_7P$: C, 38.17; H, 6.41. Found: C, 37.95; H, 6.37%. ^{1}H NMR (D_2O, *δ*, ppm, *J*/Hz): 1.08 (t, 3 H, CH_3, $^3J_{HH}$ = 7.0), 1.69–1.82 (m, 2 H, CH_2), 1.98–2.14 (m, 2 H, $CH_2C(O)$), 3.40 (s, 3 H, CH_3O), 3.43–3.76 (m, 4 H, C(1)H_2, C(2)H_2), 4.04 (q, 2 H, CH_2O, $^3J_{HH}$ = 7.0). ^{13}C{^{1}H} NMR (D_2O, *δ*, ppm, *J*/Hz): 14.78 (s, Me), 23.23 (s, CH_2), 31.11 (s, $CH_2C(O)$), 44.04 (d, C(1), $^1J_{CP}$ = 152.4), 47.97 (s, C(2)), 51.15 (s, MeO), 61.64 (s, CH_2O), 155.92 (s, NC=O), 172.85 (s, C=O). ^{31}P{^{1}H} NMR (D_2O, *δ*, ppm): 17.72 (s).

Synthesis of methyl esters of *N*-(spirophosphoranylmethyl)sarcosine 11 or proline 12. A mixture of spirophosphorane **D** (100 mmol) and bis[*N*-methyl-*N*-(methoxycarbonylmethyl)amino]methane or *N*-ethoxymethylproline methyl ester (110 mmol) was heated at 100 °C for 2 h. The resulting mixture was distilled under vacuum to give phosphoranes **11**, **12**.

5-[*N*-Methyl-*N*-(methoxycarbonylmethyl)aminomethyl]-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (11). Yield: 83%. Bp: 130 °C (1.5 Torr). Anal. Calcd for $C_9H_{18}NO_6P$: C, 40.45; H, 6.79. Found: C, 40.31; H, 6.58%. ^{1}H NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 2.43 (s, 3 H, CH_3N), 3.28 (d, 2 H, PCH_2N, $^3J_{HP}$ = 7.5), 3.41 (d, 2 H, $NCH_2C(O)$, $^4J_{HP}$ = 2.2). 3.46 (s, 3 H, CH_3O), 3.91–3.98 (m, 8H, 2 OCH_2CH_2O). ^{13}C{^{1}H} NMR ($CDCl_3$, *δ*, ppm, *J*/Hz): 43.51 (d, MeN, $^3J_{CP}$ = 8.6), 51.15 (s, MeO), 57.89 (d, PCH_2N, $^1J_{CP}$ = 180.8), 58.29 (d, $NCH_2C(O)$, $^3J_{CP}$ =

7.5), 61.08 (d, OCH_2CH_2O, $^3J_{CP}$ = 2.8), 171.36 (d, C=O, $^4J_{CP}$ = 2.6). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): –9.63 (s).

5-(2-Methoxycarbonylpyrrolidin-1-ylmethyl)-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (12). Yield: 74%. Bp: 168 °C (21.5 Torr). Anal. Calcd for $C_{11}H_{20}NO_6P$: C, 45.05; H, 6.87. Found: C, 44.91; H, 6.72%. ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 1.36–1.52 (m, 2H, CH_2). 1.71–2.57 (m, 2H, CH_2). 3.40 (ABX m, 2 H, PCH_2N, $^2J_{HP}$ = 7.5, $^2J_{HP}$ = 15.5, $^2J_{HH}$ = 15.8), 3.30–3.44 (m, 3H, CH_2N, CHN), 3.49 (s, 3 H, CH_3O), 3.89–4.02 (m, 8H, 2 OCH_2CH_2O). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm, J/Hz): 17.78 (s, CH_2), 22.24 (s, CH_2), 51.23 (s, MeO), 54.40 (d, PCH_2N, $^1J_{CP}$ = 179.2), 54.46 (d, CH_2N, $^3J_{CP}$ = 2.9), 61.04 (d, OCH_2CH_2O, $^3J_{CP}$ = 2.6), 65.13 (d, CHN, $^3J_{CP}$ = 10.4), 174.31 (d, C=O, $^4J_{CP}$ = 2.9). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): –9.37 (s).

References

1. A. A. Prishchenko, M. V. Livantsov, D. N. Kustrya, E. V. Grigoriev, *Zh. Obshch. Khim.*, **1995**, *65*, 1211–1213.
2. A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, *Russ. J. Gen. Chem.*, **2006**, *76*, 1960–1962. DOI: 10.1134/S1070363206120243
3. A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, V. S. Petrosyan, *Heteroat. Chem.*, **2010**, *21*, 361–367. DOI: 10.1002/hc.20620
4. A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, V. S. Petrosyan, *Heteroat. Chem.*, **2010**, *21*, 515–520. DOI: 10.1002/hc.20642
5. A. A. Prishchenko, R. S. Alekseyev, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, V. I. Terenin, V. S. Petrosyan, *Heteroat. Chem.*, **2017**, *28*, e21353. DOI: 10.1002/hc.21353