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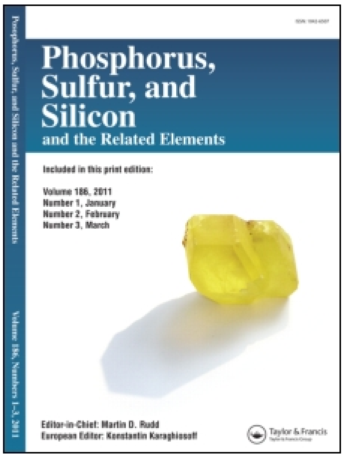

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A Convenient Synthesis of ω-[(Arylphosphonomethyl)Amino] Alkylphosphonic and Carboxylic Acids via in Situ-Generated Arylideneaminoalkyl- Phosphonic or Carboxylic Acids

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A CONVENIENT SYNTHESIS OF ω-[(ARYLPHOSPHONOMETHYL)AMINO] ALKYLPHOSPHONIC AND CARBOXYLIC ACIDS VIA IN SITU–GENERATED ARYLIDENEAMINOALKYL-PHOSPHONIC OR CARBOXYLIC ACIDS

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Department of Organic and Applied Chemistry, University of Łódź, Łódź, Poland

ω-[(Arylphosphonomethyl)amino]alkylphosphonic and carboxylic acids are prepared in an easy work-up procedure, by addition of diethyl phosphite to in situ–generated arylideneaminoalkylphosphonic or carboxylic acids followed by hydrolysis with hydrochloric acid

Keywords Aminodiphosphonic acids; aminophosphonocarboxylic acids; arylideneaminoalkanoic acids; arylideneaminophosphonic acids; nucleophilic addition

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INTRODUCTION

The chemistry of organophosphorus compounds is a rapidly developing area because of their importance in biochemical, medicinal, and synthetic applications.[1,2] Aminophosphonic acid derivatives bearing two or more phosphonic or carboxylic groups constitute a class of compounds that exhibit very useful properties and utilities. For instance, they have been used to prepare new materials with microporous or open frame structures with further potential applications in ion-exchange, catalysis, and sensors.[3,4] Furthermore some aminoalkyldiphosphonic acid derivatives have gained importance in medicinal chemistry, e.g., for treatment of bone diseases.[5,6]

Aminodiphosphonic acid derivatives are most often prepared by a Mannich-type reaction,[7] by reaction of chloroalkylphosphonic acids with amines,[8] by replacement of the carboxy group on phosphonic group,[9] or by addition of a phosphorylating agent to an aldimine generated from aldehyde and the appropriate aminophosphonic ester.[10,11] Herein we provide a new synthetic approach to the above mentioned class of compounds.

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RESULTS AND DISCUSSION

Previously we have established an efficient route to N-benzyl functionalized amino alkylphosphonic acids via in situ–generated arylideneaminoalkylphosphonic acids.[12] Now, we have used these reactive arylideneaminoalkylphosphonic acids in the synthesis of aminophosphonic acids bearing two phosphonic functions. As shown in Scheme 1, the reaction required three steps. First, we generated the imine from aminoalkylphosphonic acid (1 eq) and aromatic aldehyde (1 eq) in methanol as a solvent and in the presence of triethylamine (3 eq). This stage required 1–2 h. Then diethyl phosphite was added, and the mixture was stirred for a period of 12–72 h. The hydrolysis with concentrated hydrochloric acid of the residue obtained after evaporation of the solvent resulted in the formation of aminodiphosphonic acids (Table I, entries a, b, c, e, f, and g). However, when furfural was used as the starting aldehyde instead of hydrochloric acid, we used in situ–generated iodotrimethylsilane[13,14] in acetonitrile, followed by methanolysis of intermediate trimethylsilyl ester (Table I, entry d).

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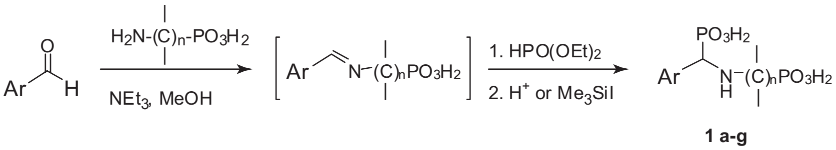
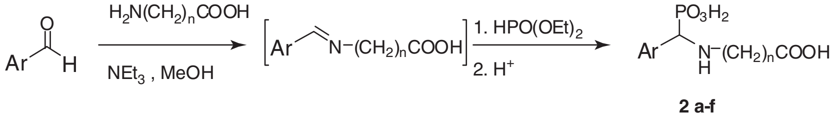


Scheme 1

Encouraged by the results obtained with aminoalkylphosphonic acids, we turned our attention to carboxylic amino acids as starting materials to the synthesis of phosphonocarboxylic amino acids. In the literature, we found the addition reactions of dialkyl phosphite to imines generated only from aromatic amino acids to form aminophosphonic esters bearing carboxylic function connected to aromatic ring.[15–17] As shown in Scheme 2, we used nonaromatic amino acids and aromatic aldehydes. The reaction was performed under similar conditions as for aminoalkylphosphonic acids. The results are summarized in Table II.



Scheme 2

The final aminodiphosphonic acids and aminophosphonocarboxylic acids are stable compounds and can be stored at room temperature for months without decomposition. Their structure was confirmed by NMR and elemental analyses.

In summary, the protocol described here provides a new and simple access to both aminodiphosphonic acids and aminophosphonocarboxylic acids with different chain lengths between the amino and phosphonic or carboxylic groups from easy available amino acids and aromatic or heteroaromatic aldehydes. The reaction is general, gives moderate to good yields, and avoids chromatographic purification.

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Table I Synthesis of ω-[(arylphosphonomethyl)amino]alkylphosphonic acids **1a–g**

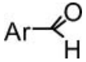
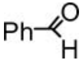
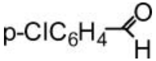
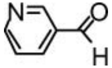
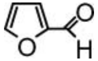
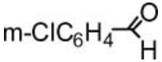
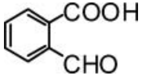
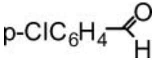
Entry		$-(\overset{\vert}{\underset{\vert}{C}})_n-$	Imine formation conditions	Addition conditions	Hydrolysis conditions	Product	Isolated yield (%)	Mp (°C)
a		$-CH_2-$	rt, 1 h	rt, 12 h	Conc. HCl (aq), reflux 7 h	**1a**	71	270–274
b		$-CH_2-$	rt, 1 h	rt, 48 h	Conc. HCl (aq), reflux 12 h	**1b**	54	301–304
c		$-CH_2-$	rt, 1 h	rt, 72 h	Conc. HCl (aq), reflux 7 h	**1c**	43	252–255
d		$-CH_2-$	rt, 1 h	rt, 12 h	Me_2SiI/MeCN, 24 h, next MeOH/H_2O	**1d**	60	183–185
e		$-(CH_2)_2-$	rt, 2h	rt, 48 h	Conc. HCl (aq), reflux 12 h	**1e**	32	254–257
f		$-(CH_2)_2C(OH)(PO_3H_2)$-	rt, 1 h	50°C, 2 h	Conc. HCl (aq), reflux 2 h	**1f**	29	236–239
g		$-(CH_2)_3C(OH)(PO_3H_2)$-	rt, 1 h	50°C, 2 h	Conc. HCl (aq), reflux 2 h	**1g**	51	241–243

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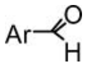
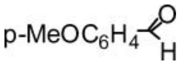
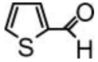
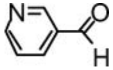
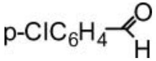
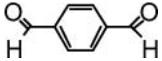
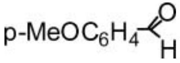
Table II Synthesis of ω-[(arylphosphonomethyl)amino]alkanoic acids **2a–f**

Entry		$-(CH_2)_n-$	Imine formation conditions	Addition conditions	Hydrolysis conditions	Product	Isolated yield (%)	Mp (°C)
a		$-CH_2-$	rt, 1 h	rt, 12 h	Conc. HCl aq, reflux 2 h	**2a**	60	230–234
b		$-CH_2-$	rt, 1 h	rt, 12 h	Conc. HCl aq, reflux 7 h	**2b**	39	223–226
c		$-CH_2-$	rt, 4 h	rt, 72 h	Conc. HCl aq, reflux 6 h	**2c**	30	238–239
d		$-(CH_2)_2-$	rt, 1 h	rt, 48 h	Conc. HCl aq, reflux 2 h	**2d**	77	246–247
e		$-(CH_2)_2-$	rt, 1h	rt, 12 h	Conc. HCl aq, reflux 2 h	**2e**	68	>300 (decomp)
f		$-(CH_2)_3$	rt, 1 h	rt, 12 h	Conc. HCl aq, reflux 2 h	**2f**	64	189–193

EXPERIMENTAL

Melting points were uncorrected. NMR spectra were obtained on a Bruker DPX 250, Varian Gemini 200, and Tesla BS 687 spectrometers operating at 250, 200, and 80 MHz, respectively, for ^{1}H (TMS); 63, 50, and 20 MHz for ^{13}C; 101 and 80 MHz for ^{31}P (H_3PO_4). The elemental analysis was performed by the Laboratory of Microanalysis of the Centre of Molecular and Macromolecular Studies, Polish Academy of Science in Łódź.

General Procedure for the Synthesis of ω-[(Arylphosphonomethyl) amino]alkylphosphonic Acids 1a–g

To a suspension of primary aminophosphonic acid (10 mmol) in MeOH (100 mL), NEt_3 (3.00 g, 30 mmol, Table I, entries a, b, c, d, and e; 6.00 g, 60 mmol, entries f and g) was added, and the mixture was stirred at rt for 20 min. Next, aromatic aldehyde (10 mmol) was added, and stirring was continued (temperature and time given in Table I). To the clear solution thus obtained, diethyl phosphite (1.38 g, 10 mmol) was added, and stirring was continued (temperature and time given in Table I). Then the solvent was evaporated, and the residue was worked up in different ways:

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{[(Phenyl)(phosphono)methyl]amino}methylphosphonic Acid (1a)

The residue was dissolved in conc. HCl (aq) solution (50 mL) and refluxed for 7 h. The mixture was cooled and left in a refrigerator for 12 h. The product precipitated as colorless crystals that required additional purification by crystallization from water. ^{1}H NMR (D_2O/NaOD, 250 MHz): δ 2.91 (d, $^2J_{HP}$ = 12.3 Hz, 2H, CH_2), 4.36 (d, $^2J_{HP}$ = 15.3 Hz, 1H, CH), 7.31–7.43 (m, 5H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 42.0 (dd, $^1J_{CP}$ = 133.0 Hz, $^3J_{CP}$ = 5.4 Hz, CH_2), 60.9 (dd, $^1J_{CP}$ = 131.0 Hz, $^3J_{CP}$ = 5.7 Hz CH), 127.2 (5 CH_{arom}), 129.7 (Cq_{arom}). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 8.91, 9.26. Anal. Calcd for $C_8H_{13}NO_6P_2$: C, 34.18; H, 4.66; N, 4.98%. Found: C, 34.05; H, 4.31; N, 4.92%.

{[(4-Chlorophenyl)(phosphono)methyl]amino}methylphosphonic Acid (1b). The residue was treated with water solution of KOH (1 mol/L, 15 mL) and evaporated to remove traces of NEt_3. Then conc. HCl (aq) solution (50 mL) was added and refluxed for 12 h. After evaporation of hydrochloric acid, the residue was crystallized from water to give the colorless crystals of product. ^{1}H NMR (D_2O/NaOD, 250 MHz): δ 3.01 (d, $^2J_{HP}$ = 12.8 Hz, 2H, CH_2), 4.47 (d, $^2J_{HP}$ = 15.8 Hz, 1H, CH), 7.37 (s, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 20 MHz): δ 45.7 (dd, $^1J_{CP}$ = 131.8 Hz, $^3J_{CP}$ = 5.5 Hz, CH_2), 64.0 (dd, $^1J_{CP}$ = 129.4 Hz, $^3J_{CP}$ = 5.5 Hz CH), 130.7 (2 CH_{arom}), 132.3 (d, $^3J_{CP}$ = 4.9 Hz, 2 CH_{arom}), 132.7 (Cq_{arom}), 135.8 (d, $^2J_{CP}$ = 1.8 Hz, Cq_{arom}). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 8.73, 8.95. Anal. Calcd for $C_8H_{12}ClNO_6P_2$: C, 30.45; H, 3.83%. Found: C, 30.46; H, 3.81%.

{[(Phosphono)(pyridin-3-yl)methyl]amino}methylphosphonic Acid Hydrochloride (1c). The residue was dissolved in MeOH (25 mL), and Et_2O (25 mL) was added. The solution was left in a refrigerator for 12 h, filtered, the filtrate was evaporated, and the residue was refluxed with conc. HCl (aq) solution (50 mL) for 7 h. After evaporation of hydrochloric acid, the residue was evaporated with water (5 × 50 mL). Then the residue was dissolved in MeOH (180 mL) and left in a refrigerator for 12 h. The precipitate was filtered off, treated with water (5 mL), and left at rt for 24 h. The pure product was collected as a white solid. ^{1}H NMR (D_2O, 80 MHz): δ 3.33 (d, $^2J_{HP}$ = 12.5

Hz, 2H, CH_2), 5.02 (d, $^2J_{HP}$ = 16.0 Hz, 1H, CH), 8.16–9.06 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O, 50 MHz): δ 47.7 (dd, $^1J_{CP}$ = 127.0 Hz, $^3J_{CP}$ = 4.9 Hz, CH_2), 64.1 (dd, $^1J_{CP}$ = 121.7 Hz, $^3J_{CP}$ = 5.9 Hz CH), 127.0 (CH_{arom}), 132.7(d, $^2J_{CP}$ = 3,4 Hz, Cq_{arom}), 140.3 (d, $^3J_{CP}$ = 3.9 Hz, CH_{arom}), 150.8 (CH_{arom}), 151.4 (d, $^3J_{CP}$ = 5,2 Hz, CH_{arom}). ^{31}P NMR (D_2O, 80 MHz): δ 6.40, 6.51. Anal. Calcd for $C_7H_{13}ClN_2O_6P_2 \cdot H_2O$: C, 23.71; H, 4.83%. Found: C, 24.11; H, 4.86%.

{[(Furan-2-yl)(phosphono)methyl]amino}methylphosphonic Acid (1d). The residue was dissolved in MeOH (5 mL), and toluene (50 mL) was added. Then the solvent was evaporated, and the residue was co-evaporated with toluene (50 mL). The residue was dissolved in MeCN (70 mL), and NaI (10.50 g, 70 mmol) was added. The mixture was stirred and cooled to 0–5°C and under nitrogen, and chlorotrimethylsilane (7.60 g, 70 mmol) was added over a period of 5 min. Stirring was continued for 24 h at rt. The mixture was filtered, then the filtrate was treated with MeOH (20 mL) and evaporated. The residue was dissolved in water and extracted with CH_2Cl_2 (3 × 50 mL). The water phase was evaporated, and the residue was dissolved in cold (–20°C) conc. HCl (aq) solution (22 mL) and left at this temperature for 1 h. The precipitate of NaCl was filtrated off, and hydrochloric acid was evaporated under reduced pressure (0.5 mm Hg). The residue was washed with acetone (5 mL) then dissolved in water (50 mL). Activated carbon was added, and the mixture was stirred at rt for 1 h. The mixture was filtered, and the filtrate was evaporated to give the product as a white solid. ^1H NMR (D_2O, 80 MHz): δ 3.26 (d, $^2J_{HP}$ = 12.8 Hz, 2H, CH_2), 4.88 (d, $^2J_{HP}$ = 17.1 Hz, 1H, CH), 6.57–7.71 (m, 3H, CH_{arom}). ^{13}C NMR (D_2O, 50 MHz): δ 44.7 (dd, $^1J_{CP}$ = 138.7 Hz, $^3J_{CP}$ = 5.0 Hz, CH_2), 56.9 (dd, $^1J_{CP}$ = 139.1 Hz, $^3J_{CP}$ = 5.8 Hz CH), 113.7 (CH_{arom}), 116.5 (d, $^3J_{CP}$ = 5.1 Hz, CH_{arom}), 145.6 (d, $^3J_{CP}$ = 5.0 Hz, Cq_{arom}), 147.6 (CH_{arom}). ^{31}P NMR (D_2O, 80 MHz): δ 5.87, 8.66. Anal. Calcd for $C_6H_{11}NO_7P_2$: C, 26.58; H, 4.09%. Found: C, 26.45; H, 3.96%.

2-{[(3-Chlorophenyl)(phosphono)methyl]amino}ethylphosphonic Acid (1e). The residue was treated in the same way as in the case of **1b**. After evaporation of hydrochloric acid, the residue was crystallized from water/acetone (1:5) to give the product as colorless crystals. ^1H NMR (D_2O/NaOD, 250 MHz): δ 1.69–1.93 (m, 2H, CH_2), 3.02–3.16 (m, 2H, CH_2), 4.23 (d, $^2J_{HP}$ = 15.8 Hz, 1H, CH), 7.28–7.46 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 20 MHz): δ 26.9 (d, $^1J_{CP}$ = 125.1 Hz, C-1), 45.9 (dd, $^2J_{CP}$ = 6.1 Hz, $^3J_{CP}$ = 2.5 Hz, C-2), 63.2(d, $^1J_{CP}$ = 125.1 Hz, 122.7, CH), 128.9 (d, J_{CP} = 4.3 Hz, CH_{arom}), 130.1 (d, J_{CP} = 1.8 Hz, CH_{arom}), 130.4 (d, J_{CP} = 4.9 Hz, CH_{arom}), 132.0 (d, J_{CP} = 1.2 Hz, CH_{arom}), 135.5 (d, J_{CP} = 1.8 Hz, Cq_{arom}), 137.4 (d, J_{CP} = 4.3 Hz, Cq_{arom}). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 8.91, 19.09. Anal. Calcd for $C_9H_{14}ClNO_6P_2 \cdot H_2O$: C, 31.10; H, 4.64%. Found: C, 30.55; H, 4.42%.

2-[(3-Hydroxy-3,3-bisphosphonopropylamino)phosphonomethyl]benzoic Acid (1f). The residue was treated with water solution of NaOH (1 mol/L, 60 mL) and evaporated. The residue was dissolved in conc. HCl (aq) solution (50 mL) and refluxed for 2 h. After evaporation of hydrochloric acid, the residue was crystallized from water/acetone (1:2) to give the product as colorless crystals. ^1H NMR (D_2O/NaOD, 250 MHz): δ 2.13–2.43 (m, 2H, CH_2), 3.85–4.17 (m, 2H, CH_2), 4.90 (d, $^2J_{HP}$ = 17.0 Hz, 1H, CH), 7.33–7.71 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 29.5 (CH_2) 36.2 (CH_2), 58.7 (d, $^1J_{CP}$ = 139.0 Hz, CH), 70.6 (t, $^1J_{CP}$ = 140.3 Hz, $C[PO_3H_2]_2$), 121.0 (CH_{arom}), 122.2 (CH_{arom}), 126.4 (CH_{arom}), 128.9 (Cq_{arom}), 130.3 (CH_{arom}), 139.9 (Cq_{arom}), 169.2 (COOH). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 11.70 (s, 1P), 18.66 (s, 2P). Anal. Calcd for $C_{11}H_{18}NO_{12}P_3$: C, 29.41; H, 4.04%. Found: C, 29.28; H, 4.01%.

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4-{[(4-Chlorophenyl)(phosphono)methyl]amino}-1-hydroxy-1-phosphonobutylphosphonic Acid (1g). The residue was treated in the same way as in the case of **1f**, but the product was contaminated with starting aminoacid (38% based on ^{1}H NMR). This contaminated product was once again treated in the same way as the starting amino acid using NEt_3 (4.68 g, 46 mmol) in MeOH (100 mL), aldehyde (7 mmol), diethyl phosphite (0.97 g, 7 mmol), NaOH/H_2O (1mol/L, 23 mL), and conc. HCl (aq) (50 mL). After crystallization from water/acetone (1:2), the pure product was collected as colorless crystals. ^{1}H NMR (D_2O/NaOD, 250 MHz): δ 1.92–2.09 (m, 4H, 2CH_2), 3.02–3.12 (m, 2H, CH_2), 4.43 (d, $^2J_{HP}$ = 15.8 Hz, 1H, CH), 7.62 (s, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 19.1 (CH_2) 28.9 (CH_2), 46.0 (CH_2), 58.3 (d, $^1J_{CP}$ = 139.0 Hz, CH), 71.7 (t, $^1J_{CP}$ = 140.3 Hz, C-1), 127.4 (CH_{arom}), 128.1 (Cq_{arom}), 128.7 (CH_{arom}), 132.8 (Cq_{arom}). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 9.06 (s, 1P), 17.98 (s, 2P). Anal. Calcd for $C_{11}H_{19}ClNO_{10}P_3$ $3H_2O$: C, 26.02; H, 4.96%. Found: C, 25.65; H, 4.62%.

General Procedure for the Synthesis of ω-[(Arylphosphonomethyl) amino]alkanoic Acids 2a–f

To a suspension of primary aminoalkanoic acid (10 mmol, Table II, entries a, b, c, d, and f; 20 mmol entry e) in MeOH (100 mL), NEt_3 (2.25 g, 22 mmol, entries a, b, c, d, and f; 4.50 g, 44 mmol, entry e) was added, and the mixture was stirred at rt for 20 min. Next, the aromatic aldehyde (10 mmol) was added, and stirring was continued (temperature and time given in Table I). To the clear solution thus obtained, diethyl phosphite (1.38 g, 10 mmol, entries a, b, c, d, and f; 2.76 g, 20 mmol, entry e) was added, and stirring continued at rt (time given in Table II). Then the solvent was evaporated, and the residue was worked up in different ways:

{[(4-Methoxyphenyl)(phosphono)methyl]amino}acetic Acid (2a). The residue was treated with water solution of NaOH (1 mol/L, 60 mL) and evaporated. The residue was dissolved in conc. HCl (aq) solution (50 mL) and refluxed for 2 h. After evaporation of hydrochloric acid, the residue was crystallized from water (with activated carbon) to give the product as colorless crystals. ^{1}H NMR (D_2O/NaOD, 250 MHz): δ 3.37 (AB, J_{AB} = 16.5 Hz, 1H, CH_2), 3.48 (AB, J_{AB} = 16.5 Hz, 1H, CH_2), 3.75 (s, 3H, CH_3), 4.34 (d, $^2J_{HP}$ = 15.8 Hz, 1H, CH), 6.93–7.38 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 45.9 (d, $^3J_{CP}$ = 5.8 Hz, CH_2), 53.7 (CH_3) 58.1 (d, $^1J_{CP}$ = 138.3 Hz, CH), 112.9 (CH_{arom}), 121.0 (Cq_{arom}), 128.9 (CH_{arom}), 154.7 (Cq_{arom}), 169.0 (COOH). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 9.81. Anal. Calcd for $C_{10}H_{14}NO_6P$: C, 43.65; H, 5.13%. Found: C, 43.46; H, 5.15%.

{[(Phosphono)(thiophen-2-yl)methyl]amino}acetic Acid (2b). The residue was treated in the same way as in the case of **2a**. After evaporation of hydrochloric acid, the residue was dissolved in water (50 mL), activated carbon (0.1 g) was added, and the mixture stirred at rt for 1 h. The mixture was filtered, the filtrate evaporated, and the residue crystallized from water/acetone (1:1) to give the product as colorless crystals. ^{1}H NMR (D_2O/NaOD, 80 MHz): δ 3.58 (s, 2H, CH_2), 4.69 (d, $^2J_{HP}$ = 15.1 Hz, 1H, CH), 7.12–7.64 (m, 3H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 44.5 (d, $^3J_{CP}$ = 4.9 Hz, CH_2), 53.3 (d, $^1J_{CP}$ = 140.1 Hz, CH), 125.9 (CH_{arom}), 127.2 (CH_{arom}), 128.9 (Cq_{arom}), 129.6 (CH_{arom}), 167.7 (COOH). ^{31}P NMR (D_2O/NaOD, 80 MHz): δ 7.28. Anal. Calcd for $C_7H_{10}NO_5PS$: C, 33.47; H, 4.01%. Found: C, 34.08; H, 3.96%.

{[(Phosphono)(pyridin-3-yl)methyl]amino}acetic Acid (2c). The residue was dissolved in MeOH (25 mL), and Et_2O (25 mL) was added. The solution was left in

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a refrigerator for 12 h, filtered, the filtrate evaporated, and the residue was refluxed with conc. HCl (aq) solution (50 mL) for 6 h. After evaporation of hydrochloric acid, the residue was evaporated with water (3 × 50 mL). The residue was treated with MeOH/EtOH (1:1, 20 mL), and the precipitate was filtered off. The solid was dissolved in MeOH/H_2O (1:1, 40 mL), propylene oxide was added, and the mixture was left in the refrigerator for 12 h. The product crystallized as colorless crystals. ^1H NMR (D_2O/NaOD, 80 MHz): δ 3.60 (s, 2H, CH_2), 4.44 (d, $^2J_{HP} = 15.3$ Hz, 1H, CH), 7.52–8.64 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 50 MHz): δ 50.9 (d, $^3J_{CP} = 5.5$ Hz, CH_2), 60.8 (d, $^1J_{CP} = 128.1$ Hz, CH), 128.0 (CH_{arom}), 132.8 (d, $^2J_{CP} = 4.0$ Hz, Cq_{arom}), 143.1 (d, $^3J_{CP} = 4.0$ Hz, Cq_{arom}), 149.0 (CH_{arom}), 149.2 (CH_{arom}), 173.6 (COOH). ^{31}P NMR (D_2O/NaOD, 80 MHz): δ 13.68. Anal. Calcd for $C_8H_{11}N_2O_5P$: C, 39.04; H, 4.50%. Found: C, 39.01; H, 4.55%.

3-{[(4-Chlorophenyl)(phosphono)methyl]amino}propionic Acid (2d). The residue was dissolved in conc. HCl (aq) solution (50 mL) and refluxed for 2 h. After evaporation of hydrochloric acid, the residue was crystallized from water and washed with MeOH to give the colourless crystals of product. ^1H NMR (D_2O/NaOD, 80 MHz): δ 2.37–2.96 (m, 4H, $2CH_2$), 3.93 (d, $^2J_{HP} = 16.7$ Hz, 1H, CH), 7.48 (s, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 35.2 (C-2), 42.7 (d, $^3J_{CP} = 13.4$ Hz, C-3), 61.2 (d, $^1J_{CP} = 134.0$ Hz, CH), 125.9 (2 CH_{arom}), 128.1 (2 CH_{arom}), 129.0 (Cq_{arom}), 137.4 (Cq_{arom}), 179.6 (C-1). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 15.92. Anal. Calcd for $C_{10}H_{13}ClNO_5P$: C, 40.90; H, 4.46%. Found: C, 41.07; H, 4.46%.

3-[({4-[(2-Carboxyethylamino)(phosphono)methyl]phenyl}phosphonomethyl)amino]propionic Acid (2e). The residue was treated with water solution of NaOH (1 mol/L, 65 mL) and evaporated. The residue was dissolved in conc. HCl (aq) solution (50 mL) and refluxed for 2 h. After evaporation of hydrochloric acid, the residue was crystallized from water to give the product as colorless crystals. ^1H NMR (D_2O/NaOD, 250 MHz): δ 2.17 (t, $^3J_{HH} = 7.0$ Hz, 4H, $2CH_2$), 2.49 (t, $^3J_{HH} = 7.0$ Hz, 4H, $2CH_2$), 3.53 (d, $^2J_{HP} = 17.0$ Hz, 2H, 2CH), 7.17 (s, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 35.3 ($2CH_2$), 42.9 (d, $^3J_{CP} = 13.4$ Hz, $2CH_2$), 61.5 (d, $^1J_{CP} = 134.0$ Hz, 2CH), 126.2 ($4CH_{arom}$), 136.7 ($2Cq_{arom}$), 179.7 (2COOH). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 16.59. Anal. Calcd for $C_{14}H_{22}N_2O_{10}P_2 \cdot H_2O$: C, 36.69; H, 5.28%. Found: C, 36.70; H, 4.78%.

4-{[(4-Methoxyphenyl)(phosphono)methyl]amino}butyric Acid (2f). The residue was treated in the same way as in the case of **2a**. The product was obtained as colorless crystals. ^1H NMR (D_2O/NaOD, 250 MHz): δ 1.15–1.26 (m, 2H, CH_2), 1.65 (t, $^3J_{HH} = 7.5$ Hz, 2H, CH_2), 1.89 (t, $^3J_{HH} = 6.6$ Hz, 2H, CH_2), 3.20 (d, $^2J_{HP} = 17.5$ Hz, 1H, CH), 3.30 (s, CH_3) 6.49–6.92 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ 23.5 (C-3), 33.3 (C-2), 45.5 (d, $^3J_{CP} = 13.1$ Hz, C-4), 53.7 (CH_3), 60.7 (d, $^1J_{CP} = 135.2$ Hz, CH), 111.5 (CH_{arom}), 127.9 (CH_{arom}), 131.4 (Cq_{arom}), 181.1 (C-1). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ 16.70. Anal. Calcd for $C_{12}H_{18}NO_6P \cdot 2H_2O$: C, 42.48; H, 6.54%. Found: C, 42.28; H, 6.31%.

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