Studies on Organophosphorus Compounds; LXIII. A New and Facile Synthetic Route to Protected Phosphonodipeptides: A Backbone for the Formation of Oligophosphonopeptides

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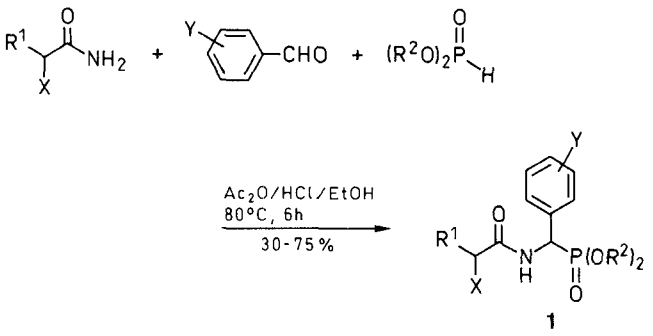
A modified three-component condensation of 2-haloalkanamides, benzaldehydes and dialkyl phosphites leading to α-(2-haloacylamino)-substituted dialkyl benzylphosphonates **1** is described. Compounds **1** upon reaction with phthalimide and potassium carbonate under phase transfer catalysis conditions afford protected phosphonodipeptides, which can be used as important intermediates for the synthesis of oligophosphonopeptides.

Since the discovery of biologically active aminophosphonic acids and phosphonopeptides,[1] a great deal of effort has been devoted to the convenient synthesis of various derivatives of aminophopshonic acids including phosphonopeptides.[2-10] As a result of our systematic studies, the most attractive and facile method for the preparation of aminophosphonic acid derivatives is based on a three-component condensation reaction involving an aldehyde, a phosphite and a compound with an amide group.[11,12] Although this is a multistep synthesis, it can be performed as a one-pot operation affording in high yield and good purity the expected products. Unfortunately, we found out that acetamide or trifluoroacetamide gave only very low yield of the condensation product.

In this paper we wish to report a new modification of this three-component condensation leading to derivatives of aminophosphonic acid based on the addition of ethanolic hydrogen chloride or *p*-toluenesulfonic acid in acetic anhydride as the condensing agent. Thus, α-(2-haloacylamino)-substituted benzylphosphonates **1** are prepared by direct condensation of 2-halogenated amides, substituted benzaldehydes and dialkyl phosphites in the presence of acetic anhydride containing ethanolic hydrogen chloride. This condensation reaction goes smoothly and gives **1** in satisfactory yield.



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Compound **1** is a precursor of phosphonodipeptides, since it can be successfully reacted with a corresponding amino compound by a modified Gabriel procedure,[13] where the halogen atom in **1** is directly amidated by phthalimide in the presence of potassium carbonate using tetraethylammonium bromide as the phase transfer catalyst. Also, if more than 0.5 molar equivalent of potassium carbonate was employed, in addition to the normal product **2**, a ring rupture product **3** was also isolated.

Stoichiometry of potassium carbonate was found to have a significant influence on the product ratio of **2** and **3**. However, **3** can be converted easily to **2** in high yield either by heating at an elevated temperature or by treatment with thionyl chloride and 4-methylmorpholine. It is also interesting to note that, as observed by us, from a derivative of **1** (R^1 = Et, R^2 = Et, X = Br, Y = 3,4-OCH_2O), a pair of diastereoisomers resulted from two asymmetric centers of the molecule and were easily separated by fractional crystallization.

Compound **2** is a protected phosphonodipeptide – a key intermediate or backbone for the formation of phosphonooligopeptides by elongation either from the N- or from the P-terminal. Upon hydrazinolysis, **2** is transformed into the corresponding phosphonodipeptide **4** with a free amino group which is capable of coupling to another amino acid molecule on the terminal N forming phenylanalylglycyl-substituted phenylalanine-P **5**. On the other hand, treatment of **2** with hydrogen bromide in acetic acid provided **6** which is then converted, via partial *O*-alkylation, to *N*-protected phosphonodipeptide **7**.

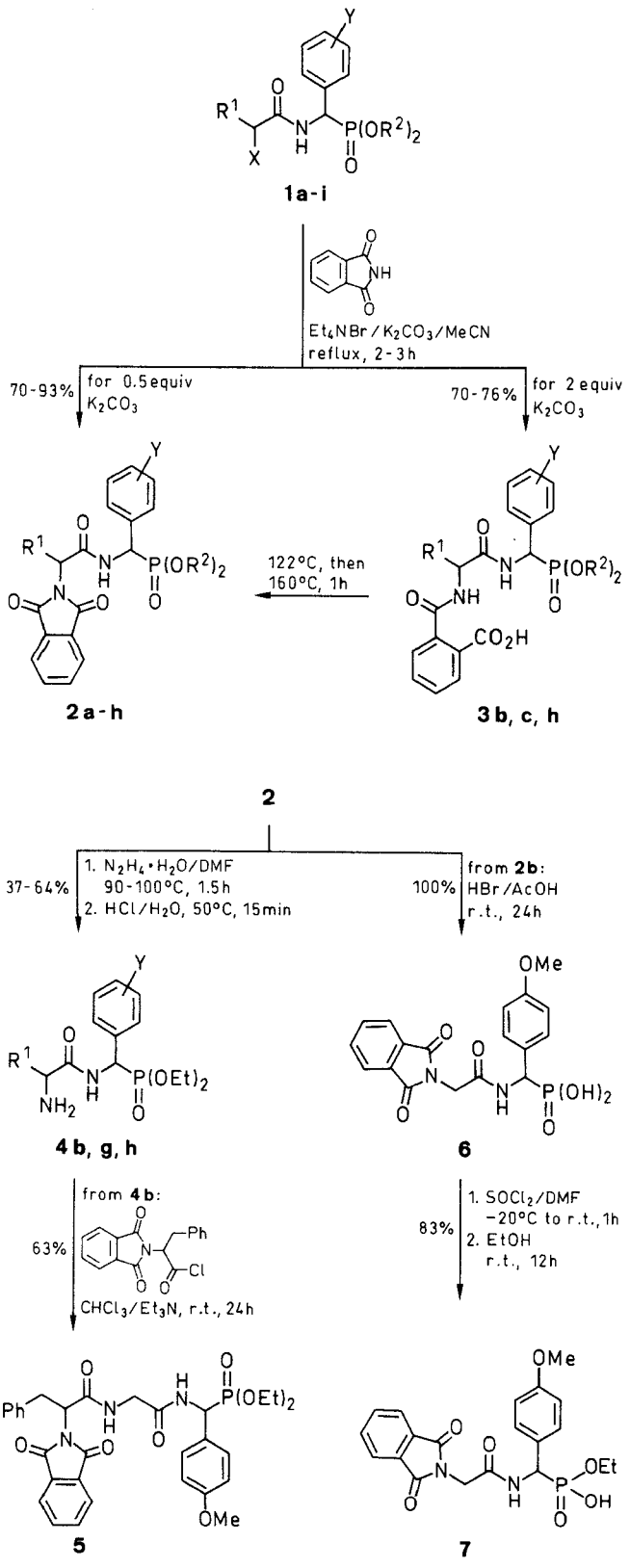

Table 1. Compounds **1** Prepared

Product	R^1	R^2	X	Y	Yield (%)	mp (°C)	Molecular Formula[a]
1a	H	Et	Cl	H	36	124–125	$C_{13}H_{19}ClNO_4P$ (319.7)
1b	H	Et	Cl	4-MeO	75	106–108	$C_{14}H_{21}ClNO_5P$ (349.7)
1c	H	Et	Cl	3,4-OCH_2O	74	122–124	$C_{14}H_{19}ClNO_6P$ (363.5)
1d	H	Bu	Cl	4-Me	65	oil	$C_{18}H_{29}ClNO_5P$ (405.9)
1e	Me	Et	Br	H	30	130–132	$C_{14}H_{21}BrNO_4P$ (378.2)
1f	Me	Et	Br	4-MeO	31	138–140	$C_{15}H_{23}BrNO_5P$ (408.2)
1g	Me	Et	Br	3,4-OCH_2O	43	170–172	$C_{15}H_{21}BrNO_6P$ (422.2)
1h	Et	Et	Br	4-MeO	40	158–160	$C_{16}H_{25}BrNO_5P$ (422.2)
1i	Et	Et	Br	3,4-OCH_2O	41	[b]	$C_{16}H_{23}BrNO_6P$ (436.2)

[a] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.3, N ± 0.3, except **1a** C – 0.54.

[b] Two pairs of diastereoisomers were isolated by fractional crystallization from EtOAc/petroleum ether: One of which has mp 200–202 °C.

$C_{16}H_{23}BrNO_6P$ (436.3) calc. C 44.04 H 5.32 N 3.21
found 43.94 5.25 3.06

IR (KBr disk): ν = 3400, 3200 (N–H), 1685 (C=O), 1240 (P=O), 1030 (POC).

^{1}H NMR (90 MHz, DMSO-d_6): δ = 0.70–1.30 (m, 9H, $3CH_3$), 1.70–2.10 (m, 2H, CH_2CBr), 3.61–4.20 (m, 4H, $2CH_2O$), 4.52 (t, J = 7.2, 1H, CHBr), 5.30 (dt, 1H, J = 5, 21, CHP), 6.00 (s, 2H, OCH_2O), 6.88 (s, $2H_{arom}$), 7.00 (s, $1H_{arom}$), 9.16 (d, 1H, J = 9, NH).

^{31}P NMR (DMSO-d_6): δ = 20.94.

MS (EI, 70 eV): m/z (%) = 436 (M^+, 38.87), 298 (M–HPO_3Et_2, 42.55), 150 (100).

The other one has mp 174–175 °C.

$C_{16}H_{23}BrNO_6P$ (436.3) calc. C 44.04 H 5.32 N 3.21
found 44.04 4.79 3.29

IR (KBr disk): ν = 3200 (N–H), 1670 (C=O), 1230 (P=O), 1020 (POC).

^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.88–1.41 (m, 9H, $3CH_3$), 1.88–2.20 (m, 2H, CH_2CBr), 3.74–4.42 (m, 5H, $2CH_2O$, CHBr), 5.40 (dd, 1H, CHP), 5.96 (s, 2H, OCH_2O), 6.70–7.00 (m, $3H_{arom}$), 8.10–8.40 (m, 1H, NH).

^{31}P NMR (DMSO-d_6): δ = 20.87.

MS (EI, 70 eV): m/z (%) = 437 (M + 1), 18.78), 298 (100), 150 (9.56).

Table 2. Spectroscopic Data of Compounds **1**

Compound	IR (cm^{-1}) ν N–H, C=O, P=O, POC	^1H NMR (solvent), δ, J (Hz)
1a	3200, 1680, 1190, 1010	1.00 (t, 3H, J = 6; CH_3CH_2), 1.25 (t, 3H, J = 6, CH_3CH_2), 3.95 (S, 2H, $ClCH_2$), 3.60–4.20 (m, 4H, $2CH_2O$), 5.20–5.70 (dd, 1H, J = 10, 22, CHP), 7.35 (S, 5H_{arom}), 8.30 (b, 1H, NH); ($CDCl_3$)
1b	3210, 1680, 1240, 1020	0.75–1.05 (m, 6H), 3.40 (S, 2H), 3.35–4.00 (m, 4H, $2CH_2O$), 5.15 (d, 1H, J = 20), 6.60 (d, 2H, J = 9), 7.10 (d, 2H, J = 9); (CD_3OD)
1c	3270, 1690, 1220, 1020	1.10 (t, 3H, J = 7), 1.30 (t, 3H, J = 7), 3.90 (s, 2H), 3.50–4.40 (m, 4H), 5.40 (dd, 1H, J = 9, 21), 5.90 (S, 2H), 6.60–7.00 (m, 4H), 8.40 (br, 1H); ($CDCl_3$)
1d	3200, 1685, 1240, 1020	0.75 (s, 6H), 1.25 (6S, 8H), 3.55–4.25 (m, 9H), 5.40 (dd, 1H, J = 9, 21), 6.65 (d, J = 9, 2H), 7.30 (d, J = 9, 2H), 9.05 (d, J = 9, 1H); (CCl_4)
1e	3200, 1680, 1240, 1010	1.10 (t, 3H, J = 7), 1.34 (t, J = 7, 3H), 1.77 (d, 3H, J = 8), 3.25–4.85 (m, 5H), 5.50 (dd, 1H, J = 9, 21), 7.30 (S, 5H), 8.70 (m, 1H); ($CDCl_3$)
1f	3200, 1680, 1215, 1015	1.08 (t, 3H, J = 7), 1.31 (t, 3H, J = 7), 1.60 (d, 3H, J = 6), 3.68 (S, 3H), 3.50–4.55 (m, 5H), 5.40 (dd, 1H, J = 9, 21), 6.70 (d, 2H), 7.40 (d, 2H, J = 8), 8.70–9.20 (br, 1H); (CCl_4)
1g	3200, 1685, 1240, 1020	1.05–1.50 (m, 6H), 1.78 (d, 3H, J = 7), 3.70–4.80 (m, 5H), 5.40 (dd, J = 10, 21, 1H), 5.95 (S, 2H), 6.68–7.25 (m, 3H), 8.00–8.60 (br, 1H); ($CDCl_3$)
1h	3200, 1680, 1210, 1015	0.90–1.40 (m, 9H, $3CH_3$), 2.00 (t, 2H, J = 6), 3.80 (S, 3H, OCH_3), 3.90–4.60 (m, 5H, $2CH_2O$ + CHBr), 5.46 (dd, 1H, J = 11, 21, CHP), 6.85 (d, 2H_{arom}), 7.45 (d, 2H_{arom}, J = 9), 8.30–9.00 (m, 1H, NH); (CCl_4)

Table 3. Compounds **2** Prepared

Product	R^1	R^2	Y	Yield (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C)
2a	H	Et	H	93	174–176 ($MeCN/H_2O$)	195–196[17]
2b	H	Et	4-MeO	92	263–264 ($MeCN/H_2O$)	$C_{22}H_{25}N_2O_7P$ (460.4)
2c	H	Et	3,4-OCH_2O	87	241–242 ($MeCN/H_2O$)	$C_{22}H_{23}N_2O_8P$ (474.4)
2d	Me	Et	4-MeO	74	204–206 (MeCN)	$C_{23}H_{27}N_2O_7P$ (474.5)
2e	Me	Et	3,4-OCH_2O	86	192–193 ($EtOH/H_2O$)	$C_{23}H_{25}N_2O_8P$ (488.4)
2f	Et	Et	4-MeO	86	204–205 (EtOH)	$C_{24}H_{29}N_2O_7P$ (488.5)
2g	H	Bu	4-MeO	75	152–154 ($MeCN/H_2O$)	$C_{26}H_{33}N_2O_7P$ (516.5)
2h	Et	Et	3,4-OCH_2O	70	228–230 (DMF/H_2O)	$C_{24}H_{27}N_2O_8P$ (502.5)

[a] Satisfactory microanalyses: C ±0.39, H ±0.29, N ±0.31.

Formation of a phosphonotripeptide with a P–N bond can be achieved from **7** in the usual manner. The interest in such peptides is growing due to the fact that they are excellent mimetics of the tetrahedral transition state of enzymatic peptide hydrolysis and, consequently, are potent inhibitors of proteases.[14–16]

Melting points are not corrected. IR spectra were obtained on a Shimadzu 440 spectrophotometer. ^1H and ^{31}P NMR spectra were taken from a Varian EM-360A (60 MHz) or FX-90Q (90 MHz) or XL-200 (200 MHz) spectrometers with internal TMS (^1H) or external 85% H_3PO_4 (^{31}P) as standard, and coupling constants J in Hz. The starting material and solvents used were purified by standard procedures prior to use.

α-(2-Haloacylamino)-Substituted Dialkyl Benzylphosphonates 1; General Procedure:

To a stirred solution of 2-chloro- or 2-bromoalkanamide (0.1 mol) and substituted benzaldehyde (0.11 mol) in Ac_2O (60 mL) was added 30% HCl in EtOH (10 mL). Stirring was continued until the reaction subsided. Dialkyl phosphite (0.1 mol) was then introduced into the mixture in one portion. After heating at 80 °C for 6 h, the resultant solution was concentrated to a minimum volume on a rotatory evaporator. The residue was dissolved in EtOAc (60 mL), washed with sat. aq $NaHSO_3$ (2 × 30 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the product thus obtained was a viscous oil which was solidified on standing and can be purified by recrystallization from EtOAc/hexane. In one case, the oily product, **1k**, was purified by column chromatography on silica gel (Tables 1, 2).

α-(2-Phthalimidoacylamino)-Substituted Dialkyl Benzylphosphonates (2); General Procedure:

To a stirred solution of **1** (2.0 mmol) and phthalimide (2.2 mmole) in dried MeCN (10 mL) was added finely powdered K_2CO_3 (1.0 mmol) and Et_4NBr (11 mg, 0.05 mmol) or 18-crown-6 (13 mg, 0.05 mmol). The mixture was then refluxed at 80 °C for 2–3 h. After removal of the volatile components under reduced pressure, the white solid obtained was stirred with H_2O (10 mL) for 30 min. The solid product was collected and recrystallized from the appropriate solvent as described (Tables 3, 4).

α-[2-(2-Carboxybenzoylamino)acylamino]-Substituted Dialkyl Benzylphosphonates 3; General Procedure:

The synthetic procedure was similar to that described for **2** except that a large excess (4.0 mmol) of K_2CO_3 was employed. The solvent was removed and the residue stirred with H_2O for 1 h and the insoluble substances removed by filtration. The filtrate was acidified with 6 N HCl to pH 2–3 and extracted with EtOAc (4 × 10 mL). The extract was, after being dried (Na_2SO_4), stripped to dryness under reduced pressure. The oily product obtained was solidified when triturated with Et_2O and a trace amount of acetone. Recrystallization from $CHCl_3$/petroleum ether gave a colorless crystalline powder.

3b (R^1 = H, R^2 = Et, Y = 4-MeO): yield: 76%; mp 122–123 °C.

$C_{22}H_{27}N_2O_8P$ (478.5)	calc.	C 55.22	H 5.70	N 5.86
	found	54.79	5.63	5.76

IR (KBr): ν = 3600–3010 (OH, NH), 1700 (CO_2), 1680 (CON), 1670 (CON), 1240 (PO), 1020 cm^{-1} (POC).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.08 (t, 3H, J = 7, CH_3), 1.35 (t, 3H, J = 7, CH_3), 3.58–3.94 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 4.14–4.27 (m, 2H, OCH_2), 4.32–4.34 (d, 2H, J = 5.6, CH_2N), 5.42–5.58 (dd, 1H, J = 9.8, 21.5, CHP), 6.37–6.43 (t, 1H, J = 5.8, NH), 6.83–6.87 (d, 2H_{arom}, J = 8.8), 7.32–7.37 (dd, 2H_{arom}, J = 2.0, 8.8), 7.47–7.57 (m, 3H_{arom}), 8.02–8.06 (dd, 1H_{arom}, J = 1.8, 6.6), 8.71–8.75 (m, 1H, NH).

MS (FAB): m/z = 479 (M + 1).

Table 4. Spectroscopic Data of Compounds **2**

Compound	IR (KBr disk) (cm^{-1}) ν N–H, C=O, CON, P=O, POC	^1H NMR (solvent), δ, J (Hz)
2a	3220, 1715, 1660, 1245, 1030	0.70–1.40 (q, 6H), 3.50–4.10 (m, 4H, $2CH_2O$), 4.25 (s, 2H, NCH_2), 5.30 (bd, 1H, J = 20, CHP), 7.30 (S, 5H), 7.80 (s, 4H), 9.10–9.50 (br, 1H, NH); (DMSO-d_6)
2b	3150, 1710, 1680, 1240, 1020	0.80–1.20 (q, 6H), 3.60 (s, 3H), 3.50–4.05 (m, 4H), 4.20 (S, 2H), 4.90–5.50 (dd, J = 9, 22, 1H), 6.70–6.90 (d, J = 9, 2H), 7.22–7.38 (d, J = 9, 2H), 7.80 (S, 4H), 9.00–9.40 (b, 1H); (DMSO-d_6)
2c	3180, 1710, 1685, 1240, 1020	0.90–1.25 (m, 6H), 3.70–4.20 (m, 4H), 4.25 (s, 2H), 5.25 (dd, 1H, J = 6, 21), 5.95 (s, 2H), 6.85 (s, 2H), 7.00 (s, 1H), 7.80 (s, 4H), 9.20 (d, 1H, J = 8); (DMSO-d_6)
2d	3200, 1705, 1680, 1220, 1020	1.00–1.30 (m, 6H), 1.60 (t, 3H, J = 7), 3.70 (S, 3H), 3.60–4.20 (m, 4H), 4.70–4.90 (q, 1H), 5.30 (dd, J = 9, 21.6, 1H), 6.90 (dd, J = 4, 9, 2H), 7.30 (d, J = 9, 2H), 7.80 (s, 4H), 9.00 (t, 1H, J = 9); (DMSO-d_6)
2e	3200, 1710, 1680, 1210, 1015	1.12 (t, 3H, J = 7.2), 1.20–1.40 (m, 3H), 1.68–1.80 (dd, 3H, J = 3.6, 7.2), 3.64–4.28 (m, 4H), 4.96 (q, 1H, J = 7.2, 14.4), 5.36 (dd, 1H, J = 9, 22), 5.92 (s, 2H), 6.67–6.92 (m, 3H), 7.28–7.56 (m, 1H), 7.62–7.88 (m, 4H); ($CDCl_3$)
2f	3200, 1705, 1680, 1210, 1025	0.86–0.96 (m, 3H), 1.06–1.15 (m, 3H), 1.26–1.33 (t, 3H, J = 7), 2.20–2.50 (m, 2H), 3.78 (S, 3H), 3.77–4.13 (m, 4H), 4.77–4.81 (m, 1H), 5.20–5.30 (m, 1H, CHP), 6.83–6.87 (d, 2H, J = 8.8), 7.33–7.37 (d, 2H, J = 8.4), 7.60 (br, 1H), 7.71–7.75 (m, 2H), 7.83–7.88 (m, 2H); ($CDCl_3$)
2g	3250, 1735, 1700, 1240, 1035	0.50–2.20 (m, 14H, $2CH_3CH_2CH_2$), 3.85 (s, 3H, OCH_3), 4.5 (s, 2H), 3.40–4.30 (m, 4H, $2CH_2O$), 5.55 (dd, J = 9, 21, 1H), 6.95 (d, J = 8, 2H), 7.45 (d, J = 8, 2H), 7.45 (t, $2H_{arom}$), 7.85 (S, $4H_{arom}$), 8.40–8.70 (b, 1H, NH); ($CDCl_3$)
2h	3250, 1720, 1660, 1240, 1030	0.65–1.00 (m, 9H), 1.00–2.30 (m, 2H), 3.70–4.49 (m, 4H), 4.50–4.90 (m, 1H), 5.45 (dd, 1H, J = 9, 20), 5.90 (s, 2H), 6.10–6.50 (d, 1H, J = 8), 6.80–7.60 (m, 6H), 7.70–8.10 (m, 1H), 8.20–8.60 (m, 1H); ($CDCl_3$)

Conversion of **3b** *to* **2b**: In a test tube, **3b** (0.24 g, 0.5 mmol) was heated gently to melt (122 °C) then solidified (around 160 °C) and kept at this temperature for 1 h. The spectroscopic data including IR and ^1H NMR are identical with that of **2b**.

3c (R^1 = H, R^2 = Et, Y = 3,4-OCH_2O): yield: 75%; mp 179–180 °C.

$C_{22}H_{25}N_2O_9P$ (492.5) calc. C 53.65 H 5.13 N 5.69; found 53.80 5.04 5.59

IR (KBr): ν = 3300, 3230 (O–H, N–H), 1710 (C=O), cm^{-1} 1690 (C=O), 1660 (HNC=O), 1650 (HNC=O), 1252 (P=O), 1040 (POC).

^1H NMR (90 MHz, $CDCl_3$): δ = 1.15 (t, 3H, J = 7, CH_3), 1.35 (t, 3H, J = 7, CH_3), 3.5–4.4 (m, 6H, $2CH_2O + CH_2N$), 5.45 (dd, 1H, J = 10, 21.6, CHP), 5.9 (b, 2H, OCH_2O), 6.46 (t, 1H, NH, J = 5.4), 6.68–6.96 (m, $3H_{arom}$), 7.40–7.60 (m, $3H_{arom}$), 7.92–8.12 (m, $1H_{arom}$), 8.69 (dd, 1H, J = 5.04, 9.7, NHCP).

MS (FAB): m/z = 493 (M + 1), 355 [M–OP(OEt)$_2$], 150 (base).

3h (R^1 = Et, R^2 = Et, Y = 3,4-OCH_2O): yield: 70% mp 170–171.5 °C.

$C_{24}H_{29}N_2O_9P$ (520.5) calc. C 55.38 H 5.63 N 5.38; found 55.21 5.44 5.32

IR (KBr): ν = 3400, 3250 (O–H, N–H), 1720 (C=O), 1660 (HNC=O), 1240 (P=O), 1030 cm^{-1} (POC).

^1H NMR (60 MHz, $CDCl_3$): δ = 0.65–1.00 (m, 9H, $3CH_3$), 1.00–2.30 (m, 2H, CH_2), 3.70–4.40 (m, 4H, $2CH_2O$), 4.50–4.90 (m, 1H, CHN), 5.45 (dd, 1H, J = 9, 20, CHP), 5.90 (S, 2H, CH_2O_2), 6.10–6.50 (d, 1H, J = 8, NH), 6.80–7.60 (m, $6H_{arom}$), 7.70–8.10 (m, $1H_{arom}$), 8.20–8.60 (m, 1H, NH).

α-(2-Aminoacylamino)-Substituted Dialkyl Benzoylphosphonates 4; General Procedure:

A mixture of **2** (4.4 mmole) in DMF (2.5 mL) was heated to 80 °C and followed by addition of hydrazine hydrate (0.33 g, 6.6 mmol). The mixture was stirred at 90–100 °C for 1.5 h. After it cooled down to r.t., cold H_2O (20 mL) was added and then acidified with 6 N HCl to pH 2–3. The acidic mixture was heated at 50 °C for 15 min to ensure completion of reaction. The mixture was then filtered, the pH value of the filtrate adjusted to 9–10 by adding sat. aq K_2CO_3 solution, extracted with CH_2Cl_2 (4 × 40 mL) and dried (Na_2SO_4). Upon removal of solvent, **4** was usually obtained as oily product which gave crystalline oxalate with a sharp mp.

4b (R^1 = H, R^2 = Et, Y = 4-MeO, Oxalate): yield: 50%, mp 162–163 °C (EtOH/Et_2O): IR (KBr): ν = 3400, 3200 (N–), 1690 (C=O), 1240 (P=O), 1020 cm^{-1} (POC).

^1H NMR (90 MHz, D_2O): δ = 0.90–1.20 (m, 6H, $2CH_3$), 3.64 (s, 3H, OCH_3), 3.50–4.50 (m, 6H, $2CH_2O + CH_2N$), 5.32 (d, 1H, J = 21, CHP), 6.80 (d, J = 9, $2H_{arom}$), 7.20 (d, J = 9, $2H_{arom}$).

4g (R^1 = H, R^2 = Bu, Y = 4-MeO, oxalate): yield: 37%, mp 109–111 °C.

$C_{20}H_{33}N_2O_9P$ (476.5) calc. C 50.41 H 6.99 N 5.88; found 50.21 6.90 5.95

IR (KBr): ν = 3400, 3200 (N–H), 1690 (C=O), 1240 (P=O), 1020 cm^{-1} (POC).

^1H NMR (60 MHz, D_2O): δ = 0.60–0.90 (m, 6H, $2CH_3$), 0.90–1.70 (m, 8H, $2CH_2CH_2$), 3.50–4.10 (m, 9H, $2CH_2O + CH_3O + CH_2N$), 5.30 (d, 1H, J = 21, CHP), 6.90 (d, J = 9, 2H), 7.30 (d, J = 9, 2H).

4h (R^1 = Et, R^2 = Et, Y = 3,4-OCH_2O, oxalate): yield: 64% mp 114–116 °C (EtOH/Et_2O).

$C_{18}H_{27}N_2O_{10}P$ (462.4) calc. C 46.75 H 5.90 N 6.06; found 46.47 5.75 5.93

IR (KBr): ν = 3400, 3200 (N–H), 1680 (C=O), 1240 (P=O), 1030 cm^{-1} (POC).

^1H NMR (60 MHz, D_2O): δ = 0.70–1.39 (m, 9H, $3CH_3$), 1.70–2.10 (m, 2H, CH_2), 3.80–4.30 (m, 4H, $2CH_2O$), 5.45 (d, 1H, J = 21, CHP), 5.90 (s, 2H, OCH_2O), 6.90 (s, $3H_{arom}$).

Diethyl 4-Methoxy-α-(*N*-phthaloyl-L-phenylalanylglycylamino)benzylphosphonate (5):

A solution of *N*-phthalolyl-L-phenylalanyl chloride (0.15 g, 0.5 mmol) in $CHCl_3$ (5 mL) was added dropwise to a stirred solution of **4b** (0.21 g, 0.5 mmol) and Et_3N (0.3 mL, 2.1 mmol) in $CHCl_3$ (3 mL). The mixture was stirred at r.t. for 4 h and kept overnight. After removal of the solvent on a rotary evaporator, a viscous oil was obtained. EtOAc (10 mL) was added and the resultant suspension

was stirred for 0.5 h. The precipitated $Et_3N \cdot HCl$ was filtered off. The filtrate was washed successively with dilute aq HCl (2 × 10 mL), H_2O (10 mL), sat. aq K_2CO_3 (2 × 10 mL), H_2O (10 mL) and sat. aq NaCl solution (10 mL) and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the product was obtained as colorless solid, 0.19 g, yield 63%. The product was purified by column chromatography on silica gel using EtOAc/petroleum ether (20:1) as eluent, mp 144–146°C.

$C_{31}H_{34}N_3O_8P$	calc.	C 61.28	H 5.65	N 6.92
(607.6)	found	61.03	5.56	6.88

IR (KBr): ν = 3350, 3250 (2N–H, 1780, 1720 (C=), 1670 (HNC=O), 1240 (P=O), 1020 cm^{-1} (POC).

^1H NMR (60 MHz, $CDCl_3$): δ = 0.90–1.34 (m, 6H, $2CH_3$), 3.46 (3.46 (d, 2H, CH_2Ph), 3.70 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2CO), 3.60–4.30 (m, 4H, $2CH_2O$), 5.00 (t, 1H, J = 7.2, CHBn), 5.35 (dd, 1H, J = 10, 21, CHP), 6.75 (d, J = 8, $2H_{arom}$), 7.00 (s, $5H_{arom}$), 7.25 (d, J = 8, $2H_{arom}$), 7.2 (m, 1H, NH), 7.6 (s, 4H, Pht), 8.4 (br, 1H, NH).

4-Methoxy-α-(*N*-phthaloylglycylamino)benzylphosphonic Acid (6):
Compound **2b** (0.95 g, 2 mmol) was treated with 41% HBr/AcOH (10 mL) at r.t. for 24 h. The resulting clear solution was concentrated to a minimum volume on a rotatory evaporator with a bath temperature below 80°C. The residue was treated with EtOH and the precipitated colorless solid was collected by filtration, washed thoroughly with EtOH and dried, 0.82 g, yield 100%. The product such obtained was pure enough as indicated by ^1H NMR spectra and it could be used in the following procedure without further purification.

IR (KBr): ν = 3400, 3200 (N–H, O–H), 1775, 1720 (C=O), 1660 (HNC=O), 1250 (P=O), 1025 cm^{-1} (POC).

^1H NMR (60 MHz, TFA): δ = 3.51 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2), 5.10–5.80 (m, 1H, CHP), 6.74 (d, J = 9, $2H_{arom}$), 7.17 (d, J = $2H_{arom}$), 7.62 (s, 4H, Pht), 8.00–8.40 (m, 1H, NH).

Ethyl Hydrogen 4-Methoxy-α-(*N*-phthaloylglycylaminobenzylphosphonate (7):
To a cooled solution of **2b** (0.105 g, 0.25 mmol) in DMF (2 mL) was slowly added a solution of $SOCl_2$ in DMF (4%, 0.7 mL) at –20°C. The solution was stirred at this temperature for 0.5 h and then at r.t. for another 0.5 h, after that, anhydr. EtOH (0.5 mL) was added. After being stirred at r.t. for 12 h, the solution was concentrated on a rotatory evaporator. Sat. aq $NaHCO_3$ solution (3 mL) and H_2O (3 mL) were added spontaneously. The undissolvable material was filtered off and the filtrate was extracted with EtOAc (2 × 5 mL) and acidified with conc. HCl (Congo Red). The resulting white precipitate was collected and dried, **7** (0.09 g) was obtained as a colorless solid, yield: 83%; mp 224–225°C.

$C_{20}H_{21}N_2O_7P$	calc.	C 55.55	H 4.90	N 6.48
(432.4)	found	55.19	4.85	6.46

IR (KBr): ν = 3700–2300 (O–H, N–H), 1780, 1730 (C=O), 1665 (HNC=O), 1250 (P=O), 1030 cm^{-1} (POC).

^1H NMR (60 MHz, DMSO-d_6): δ = 0.80–1.20 (t, 3H, J = 7.2, CH_3), 3.65 (s, 3H, OCH_3), 3.60–4.05 (m, 2H, CH_2O), 4.20 (s, 2H, CH_2N), 5.10 (dd, 1H, J = 9, 21, CHP), 6.80 (d, J = 9, $2H_{arom}$). 7.30 (d, J = 9, $2H_{arom}$), 7.80 (s, 4H, Pht), 9.10 (dd, 1H, J = 3, 10, NH).

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(1) Kafarski, P.; Lejczak, B.; Mastalerz, P. *Phosphonopeptide – Synthesis and Biological Activity. Beitr. Wirkstofforsch;* 1985; Vol. 25, and references cited therein.
(2) Kukhar, V.P.; Solodenko, V.A. *Russ. Chem. Rev.* **1987**, *6*, 859.
(3) Soloka, M. *Liebigs Ann. Chem.* **1990**, 331 and references cited therein.
(4) Yuan, C.Y.; Qi, Y.M. *Synthesis* **1986**, 821.
(5) Hanissioan, S.; Bennani, Y.L. *Tetrahedron Lett.* **1990**, *31*, 6465.
(6) Shatzmiller, S.; Dolitzky, B.-Z.; Meirovich, R.; Neidleion, R.; Weik, C. *Liebigs Ann. Chem.* **1991**, 161.
(7) Yamauchi, K. *Yuki Gosei Kagaku Kyokaishi* **1988**, *46*, 654; *Chem. Abstr.* **1988**, *110*, 58016.
(8) Kafarski, P.; Lejczak, B. *Tetrahedron* **1989**, *45*, 7387.
(9) Solodenko, V.; Kasheva, T.; Kukhar, V. *Synth. Commun.* **1991**, *21*, 1631.
(10) Cheng, L.; Goodwin, C.A. *Tetrahedron Lett.* **1991**, *32*, 7333.
(11) Yuan, C.Y.; Wang, G.H.; Chen, S.J. *Synthesis* **1990**, 522.
(12) Yuan, C.Y.; Chen, S.J.; Wang, G.H. *Synthesis* **1991**, 490.
(13) Landini, D.; Penso, M. *J. Org. Chem.* **1991**, *56*, 420.
(14) Hanson, J.E.; Kaplan, A.P.; Bartlett, P.A. *Biochemistry* **1989**, *28*, 6294 and references cited therein.
(15) Giannousis, P.P.; Bartlett, P.A. *J. Med. Chem.* **1987**, *30*, 1603. Giannousis, P.P.; Bartlett, P.A. *Ibid.* **1989**, *32*, 1866.
(16) Bartlett, P.A.; Hanson, J.E.; Giannousis, P.P. *J. Org. Chem.* **1990**, *55*, 6268.
(17) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2528.