A Facile Conversion of Aminoalkanephosphonic Acids into Their Diethyl Esters. The Use of Unblocked Aminoalkanephosphonic Acids in Phosphono Peptide Synthesis

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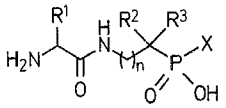
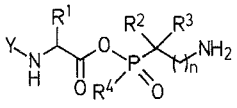
A simple and efficient, two-step procedure for the preparation of diethyl aminoalkylphosphonates from aminoalkylphosphonic acids is reported. The obtained esters are useful as substrates in phosphono peptide synthesis.

A great many efforts have been made in recent years to synthesize phosphono peptides and investigate their biological activities.[1] Among these peptides those containing *P*-terminal aminoalkanephosphonic acids (peptides **1**) have received much more attention than other categories of phosphono peptides, since they are useful as carriers of aminoalkanephosphonic acids through bacterial cell wall[1-4] or into plant tissues.[1,5,6]



1 (X = OH, alkyl)



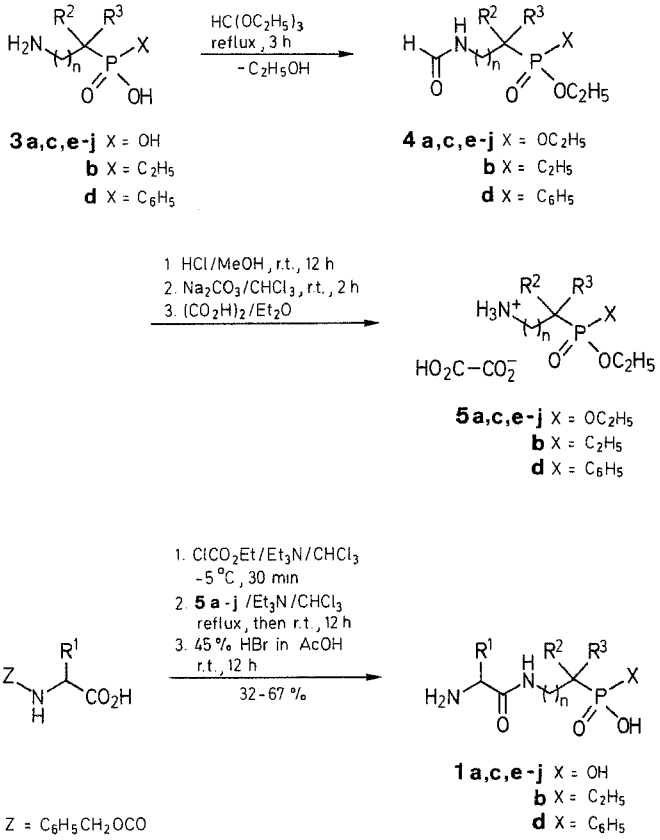
2 (Y = *N*-protecting group)

The peptides **1** have been prepared by condensation of N-blocked amino acids with aminoalkanephosphonic acids, as well as their dialkyl or diphenyl esters.[1] Free aminoalkanephosphonic acids, although readily available, are particularly unsuitable as substrates for the synthesis of phosphono peptides, because the yield in the acylation of these acids in aqueous media is usually low. This is probably caused by the competitive formation of mixed anhydride **2** between aminoalkanephosphonic acid and acylating agent, followed by its fast hydrolysis.[7,8]

Much more satisfactory results were achieved using dialkyl[9] or diphenyl[10] esters of aminoalkanephosphonic acids. Although quite a few syntheses of aminoalkanephosphonic acids proceed via their esters, the separation of these intermediates is rarely described in the literature. Thus, the esters commonly used in phosphono peptide synthesis are obtained by a limited number of specific synthetic methods, which results in a restriction in the variety of possible structures of these peptides.

On the other hand, a direct method for the esterification of aminoalkanephosphonic acids is lacking. All the methods described for complete esterification of the phosphonic group are successful only when carried out using *N*-protected aminophosphonic acid[1] and are generaly unsuitable for the esterification of *N*-unprotected compounds, because of undesirable reactions of the esterifying agent, with the amino function of the aminoalkanephosphonic acid. Thus, preparation of esters from free acids requires multistep procedure involving blocking of amino group (difficult to achieve in good yield), esterification of the *N*-blocked derivative, and removal of *N*-masking substituent.

We now report a simple and efficient, two-step procedure for converting of aminophosphonic acids **3** into their diethyl esters. Our approach involves the use of triethyl orthoformate for the esterification of the phosphonic group (as described earlier for *N*-protected aminoalkanephosphonates[11-13] (with simultaneous formylation of the amino group. As a result diethyl (*N*-formylamino)alkane-phosphonates **4** (Table 1) are obtained in good yield (with the exception for phosphonic analogues of glycine **3a** and alanine **3c**). Standard removal of the formyl group with hydrogen chloride in methanol solution[14] gives diethyl aminoalkanephosphonates, which are isolated as oxalates **5**[15] (the free esters are unstable) (Table 2). By variation of the orthoformate used, this method also affords other dialkyl aminoalkanephosphonates.



3–5	n	R^2	R^3	Peptide	Amino Acid	Amino Phosphonate
a	0	H	H	**1a**	Gly	**3a**
b	0	H	H	**1b**	Gly	**3b**
c	0	H	CH_3	**1c**	L-Pro	**3c**
d	0	H	CH_3	**1d**	L-Ala	**3d**
e	0	H	$(CH_3)_2CH$	**1e**	L-Ala	**3e**
f	0	CH_3	CH_3CH_2	**1f**	L-Leu	**3f**
g	0	CH_3	$(CH_3)_2CH$	**1g**	L-Phe	**3f**
h	0	*c*-C_3H_5	*c*-C_3H_5	**1h**	L-Pro	**3g**
i	0	$-(CH_2)_4-$		**1i**	L-Ala	**3i**
j	1	H	C_6H_5	**1j**	L-Pro	**3j**

The oxalates **5** were further used for the preparation of phosphono peptides **1** (Table 3). They were coupled with *N*-benzyloxycarbonyl-L-amino acids by the standard mixed carboxylic-carbonic anhydride procedure,[4,9] followed by removal of masking groups with hydrogen bromide in glacial acetic acid solution.

Table 1. Diethyl (*N*-Formylamino)alkylphosphonates **4**

Product	Yield (%)	Molecular Formula[a]	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	36[b]	$C_6H_{14}NO_4P$ (195.2)	3260 (NH), 1685 (CO), 1530 (NH), 1230 (PO), 1050, 1025 (POC)	1.43 (t, 6H, J_{HH} = 7.5, $2CH_3$); 3.55–3.85 (m, 2H, NCH_2); 4.17 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OCH_2$); 8.05–8.25 (m, 1H, NH); 8.25 (s, 1H, CHO)
4b	100	$C_6H_{14}NO_3P$ (179.2)	3250 (NH), 1675 (CO), 1540 (NH), 1190 (PO), 1040 (POC)	1.16 (tt, 3H, J_{HH} = 7.5, J_{PH} 16.5, PCH_2CH_3); 1.33 (t, 3H, J_{HH} = 7.5, $POCH_2CH_3$); 1.79 (qq, 2H, J_{HH} = 7.5, J_{PH} = 16.0, PCH_2); 3.45–3.85 (m, 2H, NCH_2); 4.12 (qq, 2H, $J_{HH} = J_{PH}$ = 7.5, $POCH_2$); 8.26 (s, 1H, CHO); 8.4–8.7 (m, 1H, NH)
4c	55[c]	$C_7H_{16}NO_4P$ (209.2)	3250 (NH), 1680 (CO), 1530 (NH), 1230 (PO), 1050, 1025 (POC)	1.33, 1.35 (t, 3H each, J_{HH} = 7.5, OCH_2CH_3); 1.35 (dd, 3H, $J_{HH} = J_{PH}$ = 7.5, $CHCH_3$); 4.15, 4.18 (qq, 2H each, $J_{HH} = J_{PH}$ = 7.5, OCH_2); 4.2–4.8 (m, 1H, CHP); 8.16 (d, 1H, J_{HH} = 9.5, NH); 8.22 (s, 1H, CHO)
4d	93	$C_{10}H_{16}NO_3P$ (229.2)	3250 (NH), 1670 (CO), 1520 (NH), 1190 (PO), 1010 (POC)	0.95–1.5 (m, 2H, $2CH_3$); 3.75–4.95 (m, 3H, OCH_2, CHP); 7.3–8.1 (m, 5H, C_6H_5); 8.27 (s, 1H, CHO); 8.34 (d, J_{HH} = 11.5, 1H, NH)
4e	77	$C_9H_{20}NO_4P$ (237.2)	3255 (NH), 1675 (CO), 1515 (NH), 1225 (PO), 1045, 1010 (POC)	1.00, 1.04 (d, 3H each, J_{HH} = 7.0, $CHCH_3$); 1.28, 1.33 (t, 3H each, J_{HH} = 7.5, OCH_2CH_3); 1.9–2.45 (m, 1H, $CHCHCH_3$); 4.11, 4.15 (qq, 2H each, $J_{HH} = J_{PH}$ = 7.5, OCH_2); 4.21 (dddd, 1H, J_{HH} = 7.0, J_{HH} = 10.5, J_{PH} = 19.0, CHP); 8.13 (d, 1H, J_{HH} = 10.5, NH); 8.33 (s, 1H, CHO)
4f	100	$C_9H_{20}NO_4P$ (237.2)	3240 (NH), 1690 (CO), 1530 (NH), 1250 (PO), 1040 (POC)	0.96 (t, 3H, J_{HH} = 7.0, $PCCH_2CH_3$); 1.33 (t, 6H, J_{HH} = 7.5, $2OCH_2CH_3$); 1.4–2.05 (m, 5H, CCH_2, CCH_3); 4.18 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OCH_2$); 8.15–8.4 (m, 2H, CHO, NH)
4g	93	$C_{10}H_{22}NO_4P$ (251.3)	3225 (NH), 1685 (CO), 1525 (NH), 1225 (PO), 1050, 1015 (POC)	0.98, 1.06 (d, 3H each, J_{HH} = 7.0, $CHCH_3$); 1.32 (t, 6H, J_{HH} = 7.5, $2OCH_2CH_3$); 1.48 (dd, 3H, J_{HH} = 14.0, J_{PH} = 16.0, $PCCH_3$); 8.17 (s, 1H, NH); 8.32 (d, 1H, J_{HH} = 14.0, 1H, CHO)
4h	80[d]	$C_{12}H_{22}NO_4P$ (275.3)	3255 (NH), 1695 (CO), 1240 (CO), 1020 (POC)	1.36 (t, 6H, J_{HH} = 7.5, $2CH_3$); 1.25–2.53 (m, 10H, cyclopropyl); 4.1–4.5 (m, 4H, $2OCH_2$); 8.17 (s, 1H, NH); 8.48 (d, J_{HH} = 12.0, 1H, CHO)
4i	99	$C_{10}H_{20}NO_4P$ (229.1)	3240 (NH), 1690 (CO), 1525 (NH), 1220 (PO), 1045, 1010 (POC)	1.35 (t, 6H, J_{HH} = 7.5, $2OCH_2CH_3$); 1.6–2.3 (m, 8H, $-(CH_2)_4-$); 4.18 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OCH_2$); 8.13 (s, 1H, NH); 8.33 (d, J_{HH} = 10.0, 1H, CHO)

[a] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.3, P ±0.3.
[b] Substrate, aminomethanephosphonic acid was recovered in 64% yield.
[c] Substrate, 1-aminoethanephosphonic acid, was recovered in 45% yield.
[d] Substrate, amino(dicyclopropyl)methylphosphonic acid, was recovered in 10% yield.

Table 2. Oxalates of Diethyl Aminoalkylphosphonates **5**

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR (D_2O, $HMDSO_{ext}$) δ, J (Hz)
5a	62	121–122	$C_7H_{16}NO_7P$ (257.2)	3600–2200, 3405 (NH_3^+), 1710, 1595 (CO), 1210 (PO), 1005 (POC)	1.65 (t, 6H, J_{HH} = 7.5, $2OCH_2CH_3$); 3.80 (d, 2H, J_{PH} = 14.0, CH_2P); 4.34 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OCH_2$)
5b	68	104–106	$C_7H_{16}NO_6P \cdot 0.5C_4H_{10}O$ (278.2)	3600–2200, 3480 (NH_3^+), 1710, 1650 (CO), 1175 (PO), 1020 (POC)	1.50 (tt, 3H, J_{HH} = 7.5, J_{PH} = 19.0, PCH_2CH_3); 1.67 (t, 3H, J_{HH} = 7.5, OCH_2CH_3); 2.38 (qq, 2H, J_{HH} = 7.5, J_{PH} = 15.0, PCH_2CH_3); 3.82 (d, 2H, J_{PH} = 9.0, NCH_2P); 4.32 (qq, 2H, $J_{HH} = J_{PH}$ = 7.5, OCH_2)
5c	72	101–103	114–117[15]	3600–2200, 3400 (NH_3^+), 1715, 1600 (CO), 1205 (PO), 1030, 100 (POC)	1.67 (t, 6H, J_{HH} = 7.5, $2CH_2CH_3$); 1.85 (dd, 3H, J_{HH} = 7.5, J_{PH} = 18.0, $CHCH_3$); 2.12 (qq, 1H, J_{HH} = 7.5, J_{PH} = 14.0, PCH); 4.58 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OCH_2$)
5d	86	136–138	$C_{11}H_{18}NO_6P$ (291.2)	3600–2200, 3450 (NH_3^+), 1710, 1610 (CO), 1210, 1200 (PO), 1020 (POC)	1.61, 1.64 (t, 1.5H each, J_{HH} = 7.5, $0.5CH_2CH_3$); 1.76 (dd, 3H, J_{HH} = 7.5, J_{PH} = 16.0, $CHCH_3$); 2.0–2.6 (m, 5H, $2OCH_2$, CHP); 7.75–8.25 (m, 5H, C_6H_5)
5e	71	118–119	121–123[15]	3600–2200, 3420 (NH_3^+), 1705, 1610 (CO), 1215 (PO), 1040, 1005 (POC)	1.43, 1.45 (d, 3H each, J_{HH} = 7.5, $CHCH_3$); 1.68 (t, 6H, J_{HH} = 7.5, $2OCH_2CH_3$); 2.62 (oct-oct, 1H, J_{HH} = 7.5, J_{PH} = 13.0, PCHCH); 3.92 (dd, 1H, J_{HH} = 7.5, J_{PH} = 15.0, CHP); 4.58, 4.59 (qq, 2H each, $J_{HH} = J_{PH}$ = 7.5, OCH_2)
5f	78	68–69	$C_{10}H_{22}NO_7P$ (299.3)	3600–2200, 3440 (NH_3^+), 1710, 1600 (CO), 1215, 1205 (PO), 1040, 1005 (POC)	1.38 (t, 3H, J_{HH} = 7.5, CCH_2CH_3); 1.69 (t, 6H, J_{HH} = 7.5, $2OCH_2CH_3$); 1.87 (d, 3H, J_{PH} = 15.5, CCH_3); 2.24 (tt, 2H, J_{HH} = 7.5, J_{PH} = 14.5, CCH_2CH_3); 4.60 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OCH_2$)
5g	72	124–125	$C_{11}H_{24}NO_7P$ (313.3)	3600–2200, 3440 (NH_3^+), 1695, 1620 (CO), 1220, 1200 (PO), 1045, 1005 (POC)	1.42, 1.44 (d, 3H each, J_{HH} = 7.5, $CHCH_3$); 1.69 (t, 6H, J_{HH} = 7.5, $2OCH_2CH_3$); 1.82 (d, 3H, J_{PH} = 16.0, CCH_3); 2.63 (hep-hep, 1H, J_{HH} = 7.5, J_{PH} = 15.0, CCH); 4.62 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OCH_2$)
5h	82	semisolid	$C_{13}H_{24}NO_7P$ (337.3)	semisolid	1.67, 1.71 (t, 3H, each, J_{HH} = 7.5, $2OCH_2CH_3$); 1.3–2.7 (m, 10H, cyclopropyl); 4.35–4.8 (m, 4H, $2OCH_2$)

Table 2. (continued)

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν(cm^{-1})	^{1}H-NMR (D_2O, $HMDSO_{ext}$) δ, J(Hz)
5i	71	82–83	$C_{11}H_{22}NO_7P$ (311.3)	3600–2200, 3420 (NH_3^+), 1745, 1685 (CO), 1190 (PO), 1045, 1010 (POC)	1.69 (t, 6H, J_{HH} = 7.5, $2OCH_2C\underline{H}_3$); 1.9–2.5 (m, 8H, cyclopentyl); 4.60 (qq, 4H, $J_{HH} = J_{PH}$ = 7.5, $2OC\underline{H}_2$)
5j	50[b]	131–132	$C_{14}H_{22}NO_7P$ (347.3)	3600–2200, 3445 (NH_3^+), 1730, 1640 (CO), 1205 (PO), 1040, 1010 (POC)	1.48, 1.59 (t, 3H each, J_{HH} = 7.5, $OCH_2C\underline{H}_3$); 3.7–4.65 (m, 7H, $3CH_2C\underline{H}P$); 7.77 (br s, 5H, C_6H_5)

[a] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.3, P ±0.3.
[b] Without isolation and characterization of **4j**.

Table 3. Phosphono Dipeptides **1**.

Product	Yield (%)	mp (dec) (°C)	$[\alpha]_{578}^{20}$ (c = 1, H_2O)	Molecular Formula[a], or Lit. mp and [α]	IR (KBr) ν(cm^{-1})	^{1}H-NMR ($D_2O + D_2SO_4$, $HMDSO_{ext}$) δ, J(Hz)
1a	65	221–223	–	205 °C[17]	3600–2000, 3230 (NH), 1680 (CO), 1570 (NH), 1130, 1065 (PO_3H^-)	4.20 (d, 2H, J_{PH} = 12.5, CH_2P); 4.33 (s, 2H, CH_2CO)
1b	32	242–244	–	$C_5H_{13}N_2O_3P$ (180.2)	3600–3200, 3275 (NH), 1655 (CO), 1545 (NH), 1130, 1020 (PO_2^-)	1.04 (tt, 3H, J_{HH} = 6.5, J_{PH} = 17.5, CH_3); 1.56 (qq, 2H, J_{HH} = 6.5, J_{PH} = 13.0, $PC\underline{H}_2 = CH_3$); 3.43 (d, 2H, J_{PH} = 9.5, NCH_2P); 3.86 (s, 2H, NCH_2CO)
1c[c]	48	278–281	−40	$C_7H_{15}N_2O_4P \cdot H_2O$ (240.2)	3700–2000, 3280 (NH), 1640 (CO), 1550 (NH), 1145, 1045 (PO_3H^-)	1.35 (dd, 3H, J_{HH} = 7.5, J_{PH} = 16.0, CH_3); 1.95–2.6 (m, 4H, $CHC\underline{H}_2C\underline{H}_2$); 3.48 (t, 2H, J_{HH} = 7.0, CH_2N); 3.7–4.6 (m, 2H, 2CH)
1d[c]	55	197–200	+ 4	$C_{11}H_{17}N_2O_3P \cdot 1.5H_2O$ (283.3)	3700–2200, 3400 (NH), 1660 (CO), 1510 (NH), 1140 (PO_2^-)	1.45 (dd, 3H, J_{HH} = 7.0, J_{PH} = 19.0, $PCHC\underline{H}_3$); 1.73 (d, 3H, J_{HH} = 7.5, $C\underline{H}_3CHCO$); 4.05–4.3 (m, 2H, 2CH); 7.2–8.0 (m, 5H, C_6H_5)
1e[c]	67	264–268	+10	262–264 °C[10] $[\alpha]_{578}^{20} = +12°$ (c 1, H_2O)	3600–2000, 3280 (NH), 1660 (CO), 1545 (NH), 1160, 1050 (PO_3H^-)	1.10 (d, 6H, J_{HH} = 7.5, $2CHC\underline{H}_3$); 1.67, 1.71 (d, 1.5H each, J_{HH} = 7.5, $CHC\underline{H}_3CO$); 2.10–2.35 (m, 1H, $C\underline{H}CH_3$); 4.1–4.6 (m, 2H, 2CHN)
1f[c]	32	229–231	+36	$C_{10}H_{23}N_2O_4P \cdot 2H_2O$ (302.3)	3600–2000, 3220 (NH), 1680 (CO), 1530 (NH), 1135, 1070 (PO_3H^-)	1.32 (t, 3H, J_{HH} = 7.0, $PCH_2C\underline{H}_3$); 1.36 (d, 6H, J_{HH} = 7.0, $2CHC\underline{H}_3$); 1.89, 1.91 (d, 1.5H each, J_{PH} = 17.0, $PCCH_3$); 1.9–2.4 (m, 4H, $C\underline{H}_2CHCH_3$, $PCC\underline{H}_2CH_3$); 2.25–2.9 (m, 1H, $C\underline{H}CH_3$); 4.2–4.8 (m, 1H, NCHCO)
1g[c]	41	198–202	+28	$C_{13}H_{20}N_2O_4P \cdot 2H_2O$ (335.3)	3700–2000, 3400 (NH), 1680 (CO), 1530 (NH), 1155, 1045 (PO_3H^-)	1.08 (t, 3H, J_{HH} = 7.5, $PCCH_2C\underline{H}_3$); 1.71, 1.78 (d, 1.5H each, J_{PH} = 15.5, $PCCH_3$); 1.8–2.3 (m, 2H, CH_2CP); 3.55 (br d, 2H, J_{HH} = 7.0, $C\underline{H}_2C_6H_5$); 4.62 (t, 1H, J_{HH} = 7.0, CH); 7.71 (s, 5H, C_6H_6)
1h[c]	33	192–194	− 9	$C_{10}H_{21}N_2O_4P \cdot 4H_2O$ (336.4)	3700–2200, 3220 (NH), 1675 (CO), 1550 (NH), 1145, 1115 (PO_3H^-)	1.26 (br d, 6H, J_{HH} = 7.0, $2CH=CH_3$); 1.4–2.0 (m, 4H, J_{PH} = 17.0, $PCCH_3$, $C\underline{H}CH_3$); 2.4–3.1 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$); 3.75 (br t, 2H, J_{HH} = 7.0, NCH_2); 4.72 (br, 1H, J_{HH} = 7.0, NCHCO)
1i	51	257–258	+ 3	$C_8H_{17}N_2O_4P$ (236.2)	3700–2200, 3400 (NH), 1665 (CO), 1560 (NH), 1130, 1060 (PO_3H^-)	1.84 (d, 3H, J_{HH} = 7.5, CH_3); 1.8–2.8 (m, 8H, cyclopentyl); 4.37 (q, 1H, J_{HH} = 7.5, CH)
1j	42	191–193	− 4.5[b]	$C_{13}H_{19}N_2O_4P \cdot H_2O$ (316.3)	3700–2000, 3400 (NH), 1670 (CO), 1550 (NH), 1140, 1030 (PO_3H^-)	3.4–4.85 (m, 10H, $4CH_2$, 2CH); 7.75 (s, 5H, C_6H_5)

[a] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.3, P ±0.3.
[b] (c = 0.67, 0.33 M HCl).
[c] Mixture of diastereomers.

Melting points were determined on a Köffler hot plate and are uncorrected. Optical rotations were measured using a Carl Zeiss Polamat polarimeter. IR spectra were recorded with a Perkin-Elmer 621 spectrophotometer and NMR spectra were obtained with Tesla BS 497 spectrometer at 100 MHz. Aminoalkanephosphonic acids were gifts from Dr. M. Soroka and Dr. R. Tyka, or were prepared according to a standard procedure.[16]

Amino(dicyclopropyl)methanephosphonic Acid (3i):
Following the literature procedure[16] dicyclopropyl ketone is converted into **3i**; yield: 55%; mp 138–141 °C (dec.).

$C_7H_{14}NO_3P$ (178.0)	calc.	N 7.86	P 17.40	C 47.23	H 7.93
	found	7.77	17.50	47.01	8.08

IR (KBr): ν = 3800–2000; 1175, 1045 cm^{-1} (PO_3H^-).
^{1}H-NMR (D_2O, $HMDSO_{ext}$): δ = 0.75–2.15 (m).

Diethyl (*N*-Formylamino)alkanephosphonates 4; General Procedure:
A suspension of aminoalkanephosphonic acid (0.02 mol) in ethyl orthoformate (70 mL) is refluxed carefully in an apparatus for simple distillation for 3 h with removal of the EtOH formed. The unreacted phosphonic acid as well as traces of other impurities, are filtered, and

the filtrate evaporated in vacuo to give oily compounds **4** of satisfactory purity (Table 1).

Prolonged reaction time or increased amounts of orthoformate do not improve the yield.

Oxalates of Diethyl Aminoalkylphosphonates (5); General Procedure:
Diethyl (*N*-formylamino)alkylphosphonate (**4**; 0.02 mol) is dissolved in a saturated solution HCl in MeOH (70 mL) and allowed to stand for ca. 12 h at room temperature. The reaction mixture is evaporated *in vacuo*, and the oily residue suspended in $CHCl_3$ (100 mL). To the stirred suspension, anhydrous Na_2CO_3 (25 g, 0.24 mol) is added in portions. The resulting mixture is stirred for an additional 2 h, solid material is filtered and solvent evaporated *in vacuo*. The resultant oil is dissolved in Et_2O (30 mL) and this solution is slowly poured into a vigorously stirred solution of anhydrous oxalic acid (1.8 g, 0.02 mol) in Et_2O (70 mL). This mixture is allowed to stand overnight in a refrigerator, and the product **5** is collected by filtration (Table 2).

Phosphono Dipeptides (1); General Procedure:
N-Benzyloxycarbonyl-L-amino acid (0.01 mol) is dissolved in dry $CHCl_3$ (30 mL) containing Et_3N (1.5 mL) and cooled to −5 °C. Ethyl chloroformate (1.0 mL, 0.011 mol) is added, and the mixture kept at −5 °C for 30 min. A solution of the oxalate **5** (0.01 mol) in dry $CHCl_3$ (30 mL) containing Et_3N (3.0 mL) is added. The mixture is slowly heated to boiling, cooled to room temperature and allowed to stand ca. 12 h. The resulting solution is then washed successively with water (30 mL), 5% aq. HCl (2 × 20 mL), water (30 mL), sat. aq. $NaHCO_3$ (2 × 30 mL), water (30 mL) and brine (30 mL) and dried (Na_2SO_4) (5 g). Solvent is evaporated under reduced pressure. The resulting oil is dissolved in a 45% solution of HBr in glacial AcOH (20 mL) and left ca. 12 h. The volatile components are then removed *in vacuo*, and the residue dissolved in water (40 mL). This solution is extracted with Et_2O (2 × 30 mL) to remove benzyl bromide and decolorized with charcoal. The water is removed under reduced pressure, the residue dissolved in EtOH (30 mL) and phosphono peptide **1** precipitated by addition of pyridine (unitl pH reached 5–6) (Table 3).

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