A One-Pot Conversion of α-Aminoalkylphosphonous Acids into Monomethyl α-Aminoalkylphosphonates

Katja Štrancar, Stanislav Gobec*

University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia
Fax +386(1)4258031; E-mail: gobecs@ffa.uni-lj.si

Received 4 November 2003; revised 8 December 2003

Abstract: An excellent method for a one-pot conversion of N-protected α-aminoalkylphosphonous acids into the corresponding monomethyl phosphonates, using thionyl chloride in methanol, has been devised. N-Protected monomethyl α-aminoalkylphosphonates are valuable intermediates in the preparation of phosphapeptides.

Key words: α-aminoalkylphosphonous acids, α-aminoalkylphosphonate monomethyl esters, thionyl chloride, oxidation, selective esterification

Replacement of peptide bonds by phosphonamidate, phosphonate or phosphinate moieties results in peptide analogues (phosphapeptides) which closely resemble the high-energy tetrahedral transition state of enzyme-catalyzed amide bond hydrolysis or formation.[1] These stable transition-state analogues form an important class of enzyme, particularly protease, inhibitors.[2] Complex phosphapeptides play an important role in the development of catalytic antibodies with protease-like activity and specificity.[3]

The three phosphorus peptide bond replacements have both similarities and differences in the ways in which they are assembled. The synthesis of phosphonates and phosphonamidates commonly begins with N-protected α-aminoalkylphosphonate monoesters**.** These are usually first converted into the phosphonochloridates, using chlorinating reagents like thionyl or oxalyl chloride,[4] and then coupled with the appropriate alcohol or amine component, respectively. For the preparation of phosphonate peptide analogues, N-protected α-aminoalkylphosphonate monoesters can be also activated by BOP-Cl,[5] BOP,[6] PyBOP[6] and TPP/DIAD in a modified Mitsunobu reaction[7], and then coupled to the appropriate alcohol. Syntheses of phosphonamidates from the same precursors (N-protected α-amino phosphonate monoesters), activated by DPPA,[8] DCC[9] and BOP,[10] have also been reported, but data on the usefulness of these methods are contradictory. An alternative synthesis of the phosphonates and phosphonamidates involves the in situ conversion of N-protected *H*-phosphinate esters into phosphonochloridates, using carbon tetrachloride and triethylamine.[11]

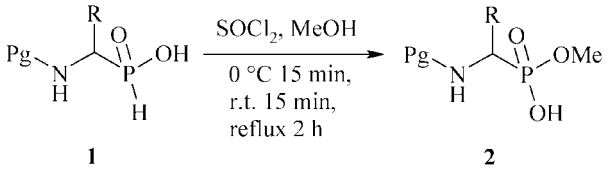
Phosphonic acid monoesters are thus very important synthons for preparing phosphapeptides. They can be prepared by one of three methods: via direct monoesterification of phosphonic acids with alcohols in the presence of condensing reagents (such as DCC,[12] DCC/TEA,[13] CCl_3CN,[14] $SOCl_2$/DMF,[15] BroP[16] or TpyClU[16]), via hydrolytic (LiOH, NaOH)[17] or nonhydrolytic (NaN_3,[18] LiN_3,[18] Me_3SiBr,[7a,17b,19] *t*-$BuNH_2$,[20] DABCO,[21] NaI,[22] PhSH[23]) selective ester cleavage of symmetrical or unsymmetrical phosphonate diesters, or via hydrolysis of the corresponding phosphonochloridates,[24a] prepared by the direct action of PCl_5[24a] or $(COCl)_2$[24b] on a phosphonate diester, or by treatment of a phosphonyl dichloride with one equivalent of the appropriate alcohol.[25] In addition, monomethyl esters of alkylphosphonic acids can be successfully converted into other monoesters, since methyl esters are easily removed.[7a,17b]

In 1986 Karanewsky described an alternative synthesis of phosphonic monoesters from phosphonous acid.[26] It is a two step procedure in which phosphonate monoesters are prepared by DCC/DMAP-mediated esterification of phosphonous acid, followed by oxidation of the resulting phosphinate ester in a second reaction step. However, the transformation involves two separate synthetic steps. Fastrez et al. have achieved a one-pot conversion of α-aminoalkyl phosphonous acids into monoethyl α-aminoalkylphosphonates using iodine/ethanol.[27] However, there is no indication on the applicability of this reaction for the synthesis of N-protected monomethyl α-aminoalkylphosphonates. The latter are much more common and convenient synthons for preparing phosphonate-,[4,17b,22b,28] phosphonamidate-[4,29] and even phosphinate-peptides,[30] as well as building blocks for assembling combinatorial libraries[31] than the ethyl counterparts, since the deprotection of a methyl ester appears to be more facile than that of an ethyl ester.[4,8a]

To the best of our knowledge, a one-pot transformation of phosphonous acid into phosphonate monomethyl ester has not yet been described. We report here a new, short, one-pot synthesis of N-protected monomethyl α-aminoalkylphosphonates **2** from N-protected α-aminoalkylphosphonous acids **1** (Scheme 1). We succeeded in achieving this single step transformation during the course of our investigations aimed at developing new phosphapeptides with potential biological activity.[8b,32] The starting compounds **1** were readily synthesized by N-protection of α-aminoalkylphosphonous acids,[33–35] which were obtained by the method developed by Baylis et al.[34]

SYNTHESIS 2004, No. 3, pp 0359–0362
Advanced online publication: 26.01.2004
DOI: 10.1055/s-2004-815922; Art ID: P09003SS

This method, which involves Strecker-type condensation of amines with aldehydes and anhydrous hypophosphorous acid, has been recently improved using microwave irradiation under solvent free conditions.[36] α-Aminoalkylphosphonous acids can also be prepared by alkylation of the N-protected aminomethylphosphonous acid at the $C_α$-position.[37]



1 2

Scheme 1

We have now found that racemic N-protected α-aminoalkylphosphonus acids **1a**–**h** are rapidly transformed into the corresponding monomethyl phosphonates **2a**–**h**, using thionyl chloride in methanol (Scheme 1, Table 1). In order to show the generality of the reaction we have prepared several monomethyl phosphonate analogues of α-amino acids, N-protected with the two most commonly used protecting groups, benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc) (Table 1). The overall yields of the reactions are high, especially if we take into consideration the fact that two reactions, oxidation and selective esterification occur in a single step.

Table 1 Monomethyl α-Aminoalkylphosphonates **2a**–**h** Prepared (Scheme 1)

Product	R	Pg	Yield[a,b] (%)	mp (°C)
2a	CH_3	Cbz	65	105–108[c]
2b	$CH(CH_3)_2$	Cbz	69	93–95[d]
2c	$CH_2CH(CH_3)_2$	Cbz	77	114–115[e]
2d	$CH(CH_3)CH_2CH_3$	Cbz	79	84–87
2e	CH_3	Fmoc	71	158–160[f]
2f	$CH(CH_3)_2$	Fmoc	84	135–137[f]
2g	$CH_2CH(CH_3)_2$	Fmoc	75	136–138
2h	$CH(CH_3)CH_2CH_3$	Fmoc	86	147–149

[a] Yields of isolated, pure products.
[b] The structures of all compounds were confirmed by ^{1}H NMR, ^{31}P NMR, IR and mass spectra. For new compounds satisfactory elemental analyses were obtained.
[c] Lit.[29b] mp 108 °C.
[d] Lit.[14b] mp 93–96 °C.
[e] Lit.[28b] mp 118–119 °C.
[f] Melting points not given in the literature.[38]

To summarize, we have presented here an expeditious one-pot conversion of N-protected α-aminoalkylphosphonous acids into the corresponding monomethyl phosphonates. The reaction is fast, the procedure is simple and it leads to versatile N-protected monomethyl α-aminoalkylphosphonates, which are valuable intermediates for preparing phosphapeptides. Speed and simplicity make this method attractive and potentially useful in the field of preparative and medicinal chemistry.

All reagents and solvents were of commercial grade and used as such. Melting points were determined using a Reichert hot stage microscope and are uncorrected. Elemental C, H, N analyses were performed at the Faculty of Chemistry and Chemical Engineering, University of Ljubljana, on a Perkin-Elmer elemental analyzer 240 C. IR spectra were measured by a Perkin-Elmer FTIR 1600 instrument on KBr pelleted samples. Mass spectra were obtained by a Micromass AutospecQ mass spectrometer using FAB ionization. NMR spectra were obtained on a Bruker Avance DPX 300 instrument. ^{1}H NMR spectra were done at 300.13 MHz with tetramethylsilane as an internal standard and ^{31}P NMR spectra were done at 121 MHz using H_3PO_4 as an external standard.

1-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-3-methylbutylphosphinic Acid [1g; Pg = Fmoc, R = $CH_2CH(CH_3)_2$]

Compound **1g** was prepared from 1-amino-3-methylbutylphosphinic acid according to the literature procedure of Yiotakis.[35b] Yield: 97%; mp 158–160 °C; R_f 0.59 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3284, 2958, 1724, 1547, 1451, 1267, 1098, 985, 140, 530 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 0.83 (d, 3 H, *J* = 6.4 Hz, CH_3), 0.90 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.30–1.44 [m, 1 H, C*H*(CH_3)$_2$], 1.45–1.72 (m, 2 H, CH_2CH), 3.56–3.71 (m, 1 H, PCH), 4.18–4.39 (m, 3 H, CHCH_2O), 6.725 (d, 1 H, *J* = 518 Hz, PH), 7.28–7.93 (m, 8 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 29.79.

MS (FAB): *m*/*z* = 374 (M + H)$^+$, 396 (M + Na)$^+$.

Anal. Calcd for $C_{20}H_{24}NO_4P·0.25H_2O$: C, 63.57; H, 6.53; N, 3.71. Found: C, 63.61; H, 6.21; N, 3.40.

1-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-2-methylbutylphosphinic Acid [1h; Pg = Fmoc, R = $CH(CH_3)CH_2CH_3$]

Compound **1h** was prepared from 1-amino-2-methylbutylphosphinic acid according to the literature procedure of Yiotakis.[35b] Yield: 95%; mp 128–130 °C; R_f 0.66 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3290, 2966, 1689, 1534, 1450, 1294, 974, 740 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 0.84 [2 t, *J* = 7.345, 7.345 Hz, 3 H, CH(CH_3)CH_2CH_3], 0.97 [2 d, *J* = 6.78, 6.78 Hz, 3 H, CH(CH_3)CH_2CH_3], 1.12–1.95 [m, 3 H, C*H*(CH_3)CH_2CH_3], 3.43–3.78 (m, 1 H, PCH), 4.18–4.38 (m, 3 H, CHCH_2O), 6.79 (2 d, 1 H, $^1J_{PH}$ = 509.8, 506.7 Hz, PH), 7.27–7.94 (m, 8 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 30.03 (1 P), 29.10 (1 P).

MS (FAB): *m*/*z* = 374 (M + H)$^+$, 396 (M + Na)$^+$.

Anal. Calcd for $C_{20}H_{24}NO_4P$: C, 64.33; H, 6.48; N, 3.75. Found: C, 64.53; H, 6.65; N, 3.60.

N-Protected Monomethyl α-Aminoalkylphosphonates 2a–h from N-Protected α-Aminoalkylphosphonous Acid 1a–h; General Procedure

N-Protected α-aminoalkylphosphonous acid **1a**–**h** (3 mmol) was dissolved in anhyd MeOH (25 mL), cooled to 0 °C, and $SOCl_2$ (0.714 g, 6 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C for 15 min, then allowed to warm to r.t. and stirred for an additional 15 min. Afterwards the mixture was refluxed for 2 h and concentrated in vacuo. The residue was triturated with CH_2Cl_2 (50 mL), filtered and the filtrate was concentrated in vacuo. The concentrated filtrate was suspended in H_2O (50 mL) (the

pH of the solution was 1–2), triturated, cooled to 0 °C and aq 2 M NaOH added dropwise with constant stirring until pH of the solution became 9–10. The alkaline solution was washed with EtOAc (3 × 30 mL), cooled to 0 °C and acidified to pH 1 by dropwise addition of conc. HCl while stirring. The product **2a**–**h** was precipitated as a white solid, which was filtered and washed with Et_2O (3 × 10 mL). All products thus obtained were identified by comparison of their NMR, IR, MS data and melting points with the values reported in the literature.[14b,28b] For all new compounds (**2d**, **2g**, **2h**) satisfactory elemental analyses were also obtained.

Methyl Hydrogen 1-{[(Benzyloxy)carbonyl]amino}ethylphosphonate (2a)
Mp 105–108 °C (Lit.[29b] mp 108 °C); R_f 0.42 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3291, 1693, 1544, 1455, 1305, 1056, 817, 694 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.37 (2 d, 3 H, *J* = 7.54, 7.15 Hz, CH_3), 3.73 (d, 3 H, *J* = 10.93 Hz, $POCH_3$), 4.05–4.30 (m, 1 H, PCH), 5.13 (s, 2 H, ArCH_2), 7.30–7.40 (m, 5 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 29.46.

MS (FAB): *m*/*z* = 274 $(M + H)^+$.

Methyl Hydrogen 1-{[(Benzyloxy)carbonyl]amino}-2-methylpropylphosphonate (2b)
Mp 93–95 °C (Lit.[14b] mp 93–96 °C); R_f 0.51 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3329, 2969, 2284, 1716, 1682, 1531, 1456, 1390, 1294, 1254, 1170, 1049, 1002, 911 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.995 (d, 3 H, *J* = 6.78 Hz, CH_3), 1.03 (d, 3 H, *J* = 6.78 Hz, CH_3), 2.14–2.30 [m, 1 H, C*H*$(CH_3)_2$], 3.71 (d, 3 H, *J* = 10.93 Hz, $POCH_3$), 3.99–4.15 (m, 1 H, PCH), 5.15 (s, 2 H, ArCH_2), 7.30–7.40 (m, 5 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 24.00.

MS (FAB): *m*/*z* = 302 $(M + H)^+$, 324 $(M + Na)^+$.

Methyl Hydrogen 1-{[(Benzyloxy)carbonyl]amino}-3-methylbutylphosphonate (2c)
Mp 114–115 °C; R_f 0.46 (H_2O–MeOH–MeCN, 1:1:3).

IR (KBr): 3284, 2956, 1688, 1544, 1450, 1309, 1269, 1184, 1037, 790, 696, 568 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.825 (d, 3 H, *J* = 6.4 Hz, CH_3), 0.88 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.31–1.46 [m, 1 H, C*H*$(CH_3)_2$], 1.49–1.70 [m, 2 H, CH_2CH$(CH_3)_2$], 3.55 (d, 3 H, *J* = 10.55 Hz, $POCH_3$), 3.75–3.93 (m, 1 H, PCH), 5.05 (s, 2 H, ArCH_2), 7.28–7.38 (m, 5 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 25.43.

MS (FAB): *m*/*z* = 316 $(M + H)^+$, 338 $(M + Na)^+$.

Methyl Hydrogen 1-{[(Benzyloxy)carbonyl]amino}-2-methylbutylphosphonate (2d)
Mp 84–87 °C; R_f 0.43 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3299, 2963, 1719, 1541, 1457, 1244, 1168, 1059, 990, 742, 568 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.83 [2 t, *J* = 7.335, 6.785 Hz, 3 H, CH(CH_3)CH_2CH_3], 0.945 [2 d, *J* = 6.78, 6.78 Hz, 3 H, CH(CH_3)CH_2CH_3], 1.06–1.88 [m, 3 H, C*H*(CH_3)CH_2CH_3], 3.535 (2 d, 3 H, *J* = 10.565, 10.535 Hz, $POCH_3$), 3.64–3.99 (m, 1 H, PCH), 5.06 (s, 2 H, ArCH_2), 7.28–7.40 (m, 5 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 24.69 (1 P), 24.54 (0.5 P).

MS (FAB): *m*/*z* = 316 $(M + H)^+$, 338 $(M + Na)^+$.

Anal. Calcd for $C_{14}H_{22}NO_5P$: C, 53.33; H, 7.03; N, 4.44. Found: C, 52.97; H, 7.17; N, 4.50.

Methyl Hydrogen 1-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}ethylphosphonate (2e)
Mp 158–160 °C (Lit.[38] mp not reported); R_f 0.42 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3284, 3065, 1690, 1542.5, 1450, 1305, 1048, 739 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.24 (2 d, 3 H, *J* = 7.16, 7.16 Hz, CH_3), 3.55 (d, 3 H, *J* = 10.55 Hz, $POCH_3$), 3.75–3.92 (m, 1 H, PCH), 4.17–4.35 (m, 3 H, C*H*CH_2O), 7.27–7.94 (m, 8 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 25.02.

MS (FAB): *m*/*z* = 362 $(M + H)^+$.

Methyl Hydrogen 1-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-2-methylpropylphosphonate (2f)
Mp 135–137 °C (Lit.[38] mp not reported); R_f 0.47 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3290, 2960, 1689, 1543, 1450, 1214, 1045, 990, 741 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.96 (t, 6 H, *J* = 6.78 Hz, CH_3), 1.98–2.15 [m, 1 H, C*H*$(CH_3)_2$], 3.55 (d, 3 H, *J* = 10.55 Hz, $POCH_3$), 3.62–3.78 (m, 1 H, PCH), 4.16–4.33 (m, 3 H, C*H*CH_2O), 7.27–7.93 (m, 8 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 24.54.

MS (FAB): *m*/*z* = 390 $(M + H)^+$, 412 $(M + Na)^+$.

Methyl Hydrogen 1-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-3-methylbutylphosphonate (2g)
Mp 136–139 °C; R_f 0.63 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3300, 3066, 2955, 1710, 1536, 1450, 1265, 1044, 988, 739, 563 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.82 (d, 3 H, *J* = 6.4 Hz, CH_3), 0.90 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.34–1.51 [m, 1 H, C*H*$(CH_3)_2$], 1.53–1.75 (m, 2 H, CH_2CH), 3.57 (d, 3 H, *J* = 10.55 Hz, $POCH_3$), 3.75–3.95 (m, 1 H, PCH), 4.16–4.35 (m, 3 H, C*H*CH_2O), 7.27–7.92 (m, 8 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 25.55.

MS (FAB): *m*/*z* = 404 $(M + H)^+$, 426 $(M + Na)^+$.

Anal. Calcd for $C_{21}H_{26}NO_5P·0.5\ H_2O$: C, 61.16; H, 6.60; N, 3.40. Found: C, 61.09; H, 6.71; N, 3.67.

Methyl Hydrogen 1-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-2-methylbutylphosphonate (2h)
Mp 147–149 °C; R_f 0.59 ($CHCl_3$–MeOH–AcOH, 7:2:1).

IR (KBr): 3313, 2962, 1711, 1530, 1450, 1247, 1048, 740, 566 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.84 [q, *J* = 7.79 Hz, 3 H, CH(CH_3)CH_2CH_3], 0.99 [t, *J* = 6.97 Hz, 3 H, CH(CH_3)CH_2CH_3], 1.10–1.94 [m, 3 H, C*H*(CH_3)CH_2CH_3], 3.56 (2 d, 3 H, *J* = 10.55, 10.55 Hz, $POCH_3$), 3.66–4.03 (m, 1 H, PCH), 4.15–4.33 (m, 3 H, C*H*CH_2O), 7.27–7.92 (m, 8 H_{arom}).

^{31}P NMR (DMSO-d_6): δ = 24.95 (1 P), 24.82 (0.9 P).

MS (FAB): *m*/*z* = 404 $(M + H)^+$, 426 $(M + Na)^+$.

Anal. Calcd for $C_{21}H_{26}NO_5P·0.75H_2O$: C, 60.50; H, 6.65; N, 3.36. Found: C, 60.77; H, 6.58; N, 3.61.

Acknowledgment

The Ministry of Education, Science and Sport of the Republic of Slovenia financially supported this work. The authors thank Professor Dr. Roger Pain, Professor Dr. Danijel Kikelj and Dr. Renata Jakše for critical reading of the manuscript.

References

(1) (a) Hanson, J. E.; Kaplan, A. P.; Bartlett, P. A. *Biochemistry* **1989**, *28*, 6294. (b) Grobelny, D.; Goli, U. B.; Galardy, R. E. *Biochemistry* **1989**, *28*, 4948.

(2) (a) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengeler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B. III *J. Am. Chem. Soc.* **1997**, *119*, 8177. (b) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359; and references cited therein.

(3) (a) Lerner, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659. (b) Hirschmann, R.; Smith, A. B. III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234. (c) Smithrud, D. B.; Benkovic, P. A.; Benkovic, S. J.; Taylor, C. M.; Yager, K. M.; Witherington, J.; Philips, B. W.; Sprengeler, P. A.; Smith, A. B. III; Hirschmann, R. *J. Am. Chem. Soc.* **1997**, *119*, 278. (d) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281.

(4) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7616.

(5) Morgan, B. P.; Scholtz, J. M.; Ballinger, M. D.; Zipkin, I. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 297.

(6) Campagne, J.-M.; Coste, J.; Jouin, P. *J. Org. Chem.* **1995**, *60*, 5214.

(7) (a) Campbell, D. A. *J. Org. Chem.* **1992**, *57*, 6331. (b) Campbell, D. A.; Bermak, J. C. *J. Org. Chem.* **1994**, *59*, 658.

(8) (a) Yamauchi, K.; Ohtsuki, S.; Kinoshita, M. *J. Org. Chem.* **1984**, *49*, 1158. (b) Gobec, S.; Urleb, U. *Molecules* **2002**, *7*, 394.

(9) (a) Natchev, I. A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3705. (b) Natchev, I. A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4491. (c) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2528.

(10) Chen, S.; Lin, C.-H.; Kwon, D. S.; Walsh, C. T.; Coward, J. K. *J. Med. Chem.* **1997**, *40*, 3842.

(11) (a) Atherton, F. R.; Oppenshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, 660. (b) Sampson, N. A.; Bartlett, P. A. *J. Org. Chem.* **1988**, *53*, 4500.

(12) Burger, A.; Anderson, J. *J. Am. Chem. Soc.* **1957**, *79*, 3575.

(13) Gilmore, W. F.; McBride, H. A. *J. Pharm. Sci.* **1974**, *63*, 965.

(14) (a) Wasielewski, C.; Hoffmann, M.; Witkowska, E. J. *Rocz. Chem.* **1975**, *49*, 1795; *Chem. Abstr.* **1976**, *84*, 90218. (b) Wasielewski, C.; Hoffmann, M.; Witkowska, E.; Rachon, J. *Rocz. Chem.* **1976**, *50*, 1613; *Chem. Abstr.* **1977**, *86*, 89948.

(15) Hoffmann, M. *Synthesis* **1986**, 557.

(16) Galéotti, N.; Coste, J.; Bedos, P.; Jouin, P. *Tetrahedron Lett.* **1996**, *37*, 3997.

(17) (a) Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654. (b) Bartlett, P. A.; Hanson, J. E.; Giannousis, P. P. *J. Org. Chem.* **1990**, *55*, 6268.

(18) Holý, A. *Synthesis* **1998**, 381.

(19) Salomon, C. J.; Breuer, E. *Tetrahedron Lett.* **1995**, *36*, 6759.

(20) (a) Gray, M. D. M.; Smith, D. J. H. *Tetrahedron Lett.* **1980**, *21*, 859. (b) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7625.

(21) (a) Saady, M.; Lebeau, L.; Mioskowski, C. *J. Org. Chem.* **1995**, *60*, 2946. (b) Hoffman, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *134/135*, 109.

(22) (a) Hoffmann, M. *J. Prakt. Chem.* **1988**, *330*, 820. (b) Brachwitz, H.; Ölke, M.; Bergmann, J.; Langen, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1739 SS>. (c) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591.

(23) (a) Daub, G. W.; Van Tamelen, E. E. *J. Am. Chem. Soc.* **1977**, *99*, 3526. (b) Norbeck, D. W.; Kramer, J. B.; Lartey, P. A. *J. Org. Chem.* **1987**, *52*, 2174. (c) Campbell, D. A.; Bermauk, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 6039.

(24) (a) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2531. (b) Ikeda, K.; Achiwa, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 225.

(25) Green, M.; Hudson, R. F. *J. Chem. Soc.* **1958**, 3129.

(26) Karanewsky, D. S.; Badia, M. C. *Tetrahedron Lett.* **1986**, *27*, 1751.

(27) Fastrez, J.; Jespers, L.; Lison, D.; Renard, M.; Sonveaux, E. *Tetrahedron Lett.* **1989**, *30*, 6861.

(28) (a) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622. (b) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603.

(29) (a) Yang, K.-W.; Brandt, J. J.; Chatwood, L. L.; Crowder, M. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1085. (b) Quang-Vo, Y.; Gravey, A. M.; Simonneau, R.; Quang-Vo, L.; Lacoste, A. M.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 6167. (c) Musiol, H.-D.; Grams, F.; Rudolph-Böhner, S.; Moroder, L. *J. Org. Chem.* **1994**, *59*, 6144. (d) Camp, N. P.; Perrey, D. A.; Kinchington, D.; Hawkins, P. C. D.; Gani, D. *Bioorg. Med. Chem.* **1995**, *3*, 297. (e) Camp, N. P.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1047. (f) Chen, S.; Lin, C.-H.; Kwon, D. S.; Walsh, C. T.; Coward, J. K. *J. Med. Chem.* **1997**, *40*, 3842.

(30) Bartlett, P. A.; Kezer, W. B. *J. Am. Chem. Soc.* **1984**, *106*, 4282.

(31) Campbell, D. A.; Bernak, J. C.; Burkoth, T. S.; Patel, D. V. *J. Am. Chem. Soc.* **1995**, *117*, 5381.

(32) Gobec, S.; Štrancar, K.; Urleb, U. *Tetrahedron Lett.* **2002**, *43*, 167.

(33) α-Aminoalkylphosphonous acids were N-protected by Cbz and Fmoc protecting group using standard methods.[34,35] The structures of new N-protected α-aminoalkylphosphonous acids **1g** [Pg = Fmoc, R = $CH_2CH(CH_3)_2$] and **1h** [Pg = Fmoc, R = $CH(CH_3)CH_2CH_3$] were confirmed by ^1H NMR, ^{31}P NMR, IR, mass spectra, and elemental analysis.

(34) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845.

(35) (a) Dumy, P.; Escale, R.; Girard, J. P.; Parello, J.; Vidal, J. P. *Synthesis* **1992**, 1226. (b) Georgiadis, D.; Matziari, M.; Yiotakis, A. *Tetrahedron* **2001**, *57*, 3471.

(36) Kaboudin, B.; As-habei, N. *Tetrahedron Lett.* **2003**, *44*, 4243.

(37) McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319.

(38) Dumy, P.; Escale, R.; Girard, J. P.; Parello, J.; Vidal, J. P. In *Peptides 1990, Proc. Eur. Pept. Symp.*; Giralt, E.; Andreu, D., Eds.; ESCOM Sci. Publ.: Leiden, **1991**, 440.