Pergamon

Tetrahedron 57 (2001) 1619–1625

TETRAHEDRON

O-Ethyl 1-azidoalkylphosphonic acids—versatile reagents for the synthesis of protected phosphonamidate peptides

Dorota Sikora, Tomasz Nonas and Tadeusz Gajda*

Institute of Organic Chemistry, Technical University (Politechnika), Żeromskiego St. 116, 90-924 Lodz, Poland

Received 29 September 2000; revised 10 November 2000; accepted 30 November 2000

Abstract—A new methodology for the synthesis of protected phosphonamidate peptides from *O*-ethyl 1-azidoalkylphosphonic acids and amino acids esters was developed. The method is general and the corresponding *N*-Boc protected phosphonopeptides as well as their azido analogs have been obtained in good yields. An efficient preparation of *O*-ethyl 1-azidoalkylphosphonic acids is also presented. © 2001 Elsevier Science Ltd. All rights reserved.

Among peptidomimetics, considerable attention is paid to the phosphonopeptides[1] obtained by the incorporation of an aminoalkylphosphonic unit into the peptide framework. Substitution of an amide bond for phosphonamidate bond in the peptides leads to the phosphonopeptides in which a tetrahedral phosphorus atom is a stable analog of the tetrahedral transition states for many enzyme-catalyzed reactions.[1b]

The syntheses of phosphonopeptides have been recently reviewed.[1a] Most often phosphonamidate peptides are prepared by coupling monoalkyl or monoaryl *N*-protected aminoalkylphosphonochloridates with an appropriate amino acid ester or suitably protected peptide.[1a] Phosphonochloridates in turn have been usually obtained by reaction of phosphonic monoesters with thionyl or oxalyl chloride,[2–12] although cleavage of a single ester linkage in N-protected phosphonate diesters by means of phosphorus pentachloride[11,13–15] or oxidative chlorination of phosphinate esters with carbon tetrachloride, using the Atherton–Todd procedure were also reported.[12,16]

On the other hand the utility of azides as masking groups for amines has been demonstrated in many fields of organic synthesis.[17,18] The application of the azido acid derivatives as convenient reagents in peptide synthesis is also well documented.[19–29]

1. Results and discussion

In connection with our interest in the chemistry of bifunctional organic compounds containing both phosphorus and azide moieties we have recently become involved in the application of diethyl 1-azidoalkylphosphonates[30] in the synthesis of diethyl 1-(isothiocyano)alkylphosphonates[31] and phosphonopeptides with an N-terminal amino acid.[32]

In this context, we wish to report a new methodology for the preparation of phosphonamidate peptides. To the best of our knowledge there are no reports[33] on the application of *O*-ethyl 1-azidoalkylphosphonic acids as key reagents in the synthesis of the above-mentioned phosphonopeptides. The azido group is easily converted into an amine, thus azidophosphonates can be considered to be azide-masked equivalents of aminophosphonates or their N-protected derivatives.

1.1. *O*-Ethyl 1-azidoalkylphosphonic acids 2

The preparation of phosphonic monoesters from the corresponding symmetrical diesters usually involves either an alkaline hydrolysis[2,9b,13a,34–37] of such diesters or their selective dealkylation under non-hydrolytic conditions by means of sodium iodide,[38] lithium bromide[39] and azide,[40] *tert*-butylamine[8,41] or tertiary amines.[42]

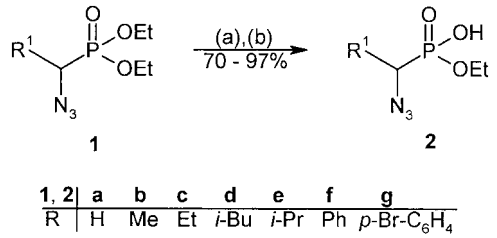
So far, *O*-alkyl 1-azidoalkylphosphonic acids have not been systematically studied and a survey of the literature on this subject reveals few publications.[43–45] Initially a method for selective dealkylation of diethyl 1-azidoalkylphosphonates **1** was developed. The starting diethyl 1-azidoalkylphosphonates[30] **1** are readily available from diethyl 1-hydroxyalkylphosphonates[46] and hydrazoic acid by the Mitsunobu reaction.[18]

Thus, treatment of diethyl 1-azidoalkylphosphonate **1** with lithium bromide[39b] at 105–110°C, in 2-pentanone as a solvent gave the corresponding lithium salt of **2**. This in turn was simply converted into a free acid **2** by the action

Keywords: phosphonopeptides; phosphonamidates; diethyl 1-azidoalkylphosphonates; amino acids; *O*-ethyl 1-azidoalkylphosphonic acids.

* Corresponding author. Tel.: +48-42-631-3146; fax: +48-42-636-5530; e-mail: tmgajda@ck-sg.p.lodz.pl

PII: S0040-4020(00)01143-1



Scheme 1. *Reagents and conditions*: (a) LiBr/2-pentanone, 105–110°C, 2 h; (b) HCl aq./CH_2Cl_2.

of aqueous hydrogen chloride prior to which the removal of traces of unreacted substrate with diethyl ether takes place (Scheme 1). The monodealkylation described here is general and *O*-ethyl 1-azidoalkylphosphonic acids **2** were isolated in high yields (70–97%) and with good analytical purity. The results are summarized in Table 1.

Additionally, some *O*-ethyl 1-azidoalkylphosphonic acids **2** were also prepared under hydrolytic conditions by heating diethyl 1-azidoalkylphosphonates **1** and aqueous potassium hydroxide in ethanol. However, besides lower yields, the above-mentioned procedure is limited to azidophosphonates **1** with alkyl substituents at C-1 only (Table 1, footnote b and c, respectively). For the phenyl analog **1f** the decomposition of azide takes place under the reaction conditions (Table 1, footnote d).

1.2. Phosphonamidate peptides 6

Having achieved an efficient synthesis of *O*-ethyl 1-azidoalkylphosphonic acids **2**, we proceeded with the synthesis of phosphonamidate peptides **6** via the phosphonochloridate[1a] approach.

For this purpose *O*-ethyl 1-azidoalkylphosphonic acid **2** was quantitatively converted by means of oxalyl chloride[7,8] into *O*-ethyl 1-azidoalkylphosphonochloridate **3** (^{31}P NMR: δ_P=32.3 ppm for **3a**) within two hours at room temperature. Crude **3**, after the removal of the excess of chlorinating agent, was immediately coupled with an amino acid methyl ester hydrochloride **4** to afford the corresponding azide-masked phosphonopeptide **5**. The above-mentioned reaction was performed in methylene chloride at room temperature in the presence of triethylamine as a base (Scheme 2). All azido derivatives **5** thus formed were isolated in good yields (50–70%) after flash chromatography as an inseparable mixture of isomers. Their structure was unequivocally confirmed by ^{31}P and ^{1}H NMR spectroscopy (Table 2).

Table 1. *O*-Ethyl 1-azidoalkylphosphonic acids **2a–g** prepared

Entry	Compound	R^1	Reaction conditions (time h, temp °C)	Yield (%)[a]
1	**2a**	H	2, 105–110	97[b]
2	**2b**	Me	2, 105–110	90[c]
3	**2c**	Et	2, 105–110	73
4	**2d**	*i*-Bu	2, 105–110	82
5	**2e**	*i*-Pr	2, 105–110	77
6	**2f**	Ph	2, 105–110	78[d]
7	**2g**	*p*-BrC_6H_4	2, 105–110	70

[a] Yields of pure **2** based on **1**.
[b] Heating of **1a** and aqueous KOH for 2 h in ethanol gave **2a** in 78% yield.
[c] Heating of **1b** and aqueous KOH for 2 h in ethanol gave **2b** in 83% yield.
[d] Decomposition of the azide **1f** occurred on heating with aqueous KOH in ethanol.

Unmasking of the azide-masked amino group of an azidophosphonate often involves a catalytic reduction of the azide moiety.[47] Hence the azido derivative **5** was hydrogenated at room temperature over 10% Pd/C under 3.06 atm pressure in the presence of di-*tert*-butyl dicarbonate to give an analytically pure phosphonamidate peptide **6** in good yield (62–83%) after flash chromatography. Our attempt to resolve the diastereomeric mixture was unsuccessful. The results are summarized in Table 2.

2. Conclusions

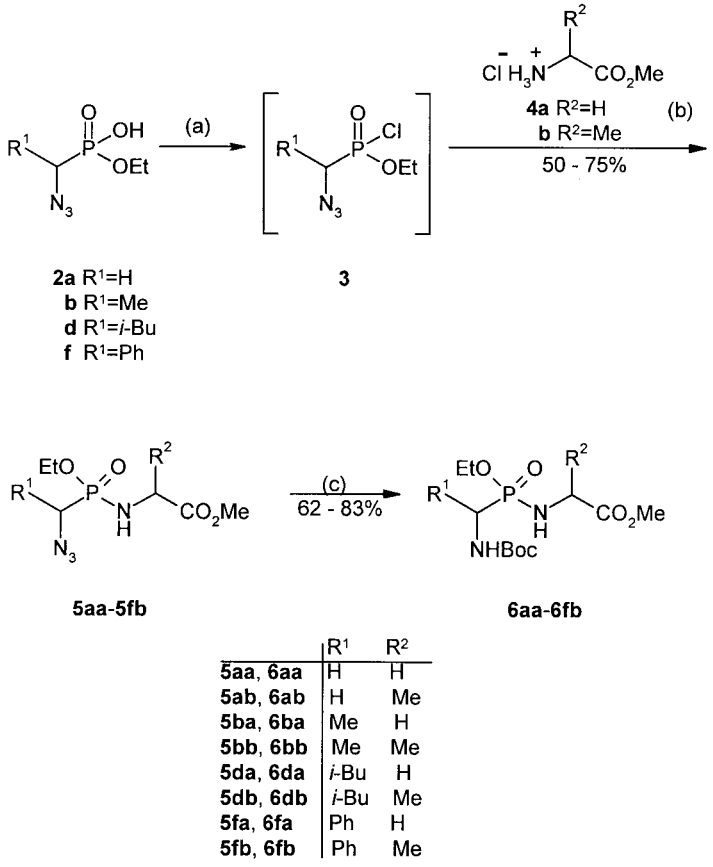
A new methodology ('azide approach') for the synthesis of phosphonamidate peptides as well as their azido analogs was developed. The method is general and novel phosphonopeptides were formed in good yields. Readily available *O*-ethyl 1-azidoalkylphosphonic acids were used in this protocol as stable azide-masked equivalents of N-protected 1-aminoalkylphosphonate derivatives. The advantage of such an approach lies in the fact that no N-protection of the phosphonic component is needed before the coupling reaction. To improve the value of the above-mentioned methodology an efficient synthesis of *O*-ethyl 1-azidoalkylphosphonic acids was also developed.

3. Experimental

NMR spectra were recorded on a Bruker AVANCE DPX 250 instrument at 250.13 MHz for ^{1}H and at 62.9 MHz for ^{13}C and 101.3 MHz for ^{13}P NMR, respectively, in $CDCl_3$ solution, using tetramethylsilane as internal and 85% H_3PO_4 as external standard. Positive chemical shifts are downfield from external 85% H_3PO_4 for ^{31}P NMR spectra. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. FAB/MS were recorded on a APO Electron (Ukraine) model MI 12001E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). IR spectra were measured on a Specord M80 (Zeiss) instrument and are reported in wavenumbers (cm^{-1}). Flash chromatography was performed with glass column packed with Baker silica gel (30–60 μm). Eluents: AcOEt (A); AcOEt/MeOH 30/1 (B); CH_2Cl_2/MeOH 95/5 (C); CH_2Cl_2/MeOH 90/10 (D); Acetone (E). Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and used without further purification. The diethyl 1-azidoalkylphosphonates **1** were prepared according to the literature procedure.[30]

3.1. *O*-Ethyl 1-azidoalkylphosphonic acids (2a–g)—general procedure

LiBr (0.0072 mol, 0.63 g) was added in one portion to a solution of diethyl 1-azidoalkylphosphonate (**1**) (0.006 mol) in 2-pentanone (3 mL). The mixture was heated at 105–110°C for 2 h. Then the solvent was evaporated



Scheme 2. *Reagents and conditions*: (a) $(COCl)_2$/DMF(cat.)/CH_2Cl_2, 0°C to room temperature, 2 h; (b) Et_3N/CH_2Cl_2, 0°C to room temperature, 24 h; (c) H_2/10% Pd–C/Boc_2O/AcOEt, 3.06 atm, room temperature, 4 h.

under reduced pressure, and the solid residue was washed with diethyl ether (3×5 mL). The crude lithium salt of **2** was suspended in CH_2Cl_2 (10 mL) and 20% HCl aq. was added to the suspension until pH~1 was reached. Solid NaCl (2.0 g) was added to the two-phase mixture, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×5 mL). The combined extracts were dried over anhydrous Na_2SO_4, the solvent evaporated under reduced pressure and the rest of the volatile material was removed at 30°C/0.1 Torr to give analytically pure *O*-ethyl 1-azidoalkylphosphonate **2** as a colorless or yellow oil (Table 1).

3.1.1. *O*-Ethyl azidomethylphosphonic acid (2a).[43] Yield: 97%, colorless oil; ^{1}H NMR: δ=1.39 (t, J=7.25 Hz, 3H, CH_3), 3.50 (d, J=12.26 Hz, 2H, CH_2N_3), 4.20 (qu,

Table 2. Azidophosphonamidates **5** and phosphonopeptides **6** prepared

Entry	Compound	R^1	R^2	Reaction conditions (time h, temp °C)	Yield (%)[a]	d.r.[b]
1	**5aa**	H	H	24, room temperature	70	–
2	**5ab**	H	Me	24, room temperature	50	52:48
3	**5ba**	Me	H	24, room temperature	57	52:48
4	**5bb**	Me	Me	24, room temperature	58	26:26:48
5	**5da**	*i*-Bu	H	24, room temperature	75	50:50
6	**5db**	*i*-Bu	Me	24, room temperature	73	74:26
7	**5fa**	Ph	H	24, room temperature	75	50:50
8	**5fb**	Ph	Me	24, room temperature	70	50:25:25
9	**6aa**	H	H	4, room temperature	68	–
10	**6ab**	H	Me	4, room temperature	62	55:45
11	**6ba**	Me	H	4, room temperature	74	52:48
12	**6bb**	Me	Me	4, room temperature	83	28:26:29:17
13	**6da**	*i*-Bu	H	4, room temperature	78	43:57
14	**6db**	*i*-Bu	Me	4, room temperature	76	22:27:29:22
15	**6fa**	Ph	H	4, room temperature	70	50:50
16	**6fb**	Ph	Me	4, room temperature	63	25:50:25

[a] Yields of pure azide **5** based on **1**, or phosphonopeptide **6** based on **5**.
[b] Diastereomer ratio based on ^{31}P NMR spectra of the crude reaction mixture. In some cases the signals overlap.

J=7.25 Hz, 2H, CH_2O), 11.68 (bs, 1H, OH); ^{31}P NMR: δ=22.03; ^{13}C NMR: δ=16.28 (d, $^3J_{PC}$=5.90 Hz, CH_3), 45.30 (d, $^1J_{PC}$=158.68 Hz, CH_2N_3), 63.06 (d, $^2J_{PC}$=6.81 Hz, CH_2O); IR (film) ν=2992, 2096, 1248, 1168, 1040; FAB/MS *m/z* (%): 166(100); Anal. Calcd for $C_3H_8N_3O_3P$ (165.09): C: 21.83; H: 4.88; N: 25.45. Found: C: 21.70; H: 4.79; N: 25.32.

3.1.2. *O*-Ethyl 1-azidoethylphosphonic acid (2b). Yield: 90%, colorless oil; ^1H NMR: δ=1.38 (t, J=7.25 Hz, 3H, CH_3), 1.49 (dd, J=7.21,17.26 Hz, 3H, CH_3), 3.58 (dq, J=7.25, 14.51 Hz, 1H, CHN_3), 4.22 (qu, J=7.25 Hz, 2H, CH_2O), 11.45 (bs, 1H, OH); ^{31}P NMR: δ=25.15; ^{13}C NMR: δ=13.69 (d, $^2J_{PC}$=1.51 Hz, CH_3), 16.36 (d, $^3J_{PC}$=5.98 Hz, CH_3), 52.12 (d, $^1J_{PC}$=161.14 Hz, CHN_3), 62.92 (d, $^2J_{PC}$=7.30 Hz, CH_2O); IR (film): ν=2984, 2120, 1208, 1128, 1036; FAB/MS *m/z* (%): 180(84); Anal. Calcd for $C_4H_{10}N_3O_3P$ (179.11): C: 26.82; H: 5.63; N: 23.46. Found: C: 26.70; H: 5.54; N: 23.29.

3.1.3. *O*-Ethyl 1-azidopropylphosphonic acid (2c). Yield: 73%, colorless oil; ^1H NMR: δ=1.11 (t, J=7.25 Hz, 3H, CH_3), 1.38 (t, J=7.00 Hz, 3H, CH_3), 1.69–2.00 (m, 2H, CH_2), 3.28–3.43 (m, 1H, CHN_3), 4.16–4.28 (m, 2H, CH_2O), 9.30 (bs, 1H, OH); ^{31}P NMR: δ=25.22; ^{13}C NMR: δ=11.22 (d, $^2J_{PC}$=14.08 Hz, CH_3), 16.26 (d, $^3J_{PC}$=5.82 Hz, CH_3), 21.85 (s, CH_3), 58.89 (d, $^1J_{PC}$=158.56 Hz, CHN_3), 62.80 (d, $^2J_{PC}$=7.29 Hz, CH_2O); IR (film): ν=2976, 2104, 1230,1196, 1040; FAB/MS *m/z* (%): 194(73); Anal. Calcd for $C_5H_{12}N_3O_3P$ (193.14): C: 31.09; H: 6.26; N: 21.76. Found: C: 31.01; H: 6.20; N: 21.65.

3.1.4. *O*-Ethyl 1-azido-3-methylbutylphosphonic acid (2d).[44] Yield: 82%, pale yellow oil; ^1H NMR: δ=0.94, 0.99 (2d, J=6.75 Hz, 6H, $2CH_3$), 1.39 (t, J=7.00 Hz, 3H, CH_3), 1.53–1.96 (m, 3H, CH_2, CH), 3.40–3.58 (m, 1H, CHN_3), 4.13–4.37 (m, 2H, CH_2O), 10.11 (bs, 1H, OH); ^{31}P NMR: δ=25.83; ^{13}C NMR: δ=16.32 (d, $^3J_{PC}$=5.74 Hz, CH_3), 20.78 (s, CH_3), 23.06 (s, CH_3), 24.91 (d, $^3J_{PC}$=13.74 Hz, CH), 36.55 (s, CH_2), 55.25 (d, $^1J_{PC}$=158.77 Hz, *C*HN_3), 62.85 (d, $^2J_{PC}$=7.32 Hz, CH_2O); IR (film): ν=2960, 2104, 1216, 1084, 1048; FAB/MS *m/z* (%): 222(66); Anal. Calcd for $C_7H_{16}N_3O_3P$ (221.19): C: 38.01; H: 7.29; N: 19.00. Found: C: 37.93; H: 7.20; N: 18.91.

3.1.5. *O*-Ethyl 1-azido-2-methylpropylphosphonic acid (2e). Yield: 77%, colorless oil; ^1H NMR: δ=1.07, 1.11 (2d, J=6.75 Hz, 6H, $2CH_3$), 1.37 (t, J=7.25 Hz, 3H, CH_3), 2.09–2.27 (m, 1H, CH), 3.37 (dd, J=13.00, 5.25 Hz, 1H, CHN_3), 4.20 (qu J=7.25 Hz, 2H, CH_2O), 10.26 (bs, 1H, OH); ^{31}P NMR: δ=24.36; ^{13}C NMR: δ=16.32 (d, $^3J_{PC}$=6.06 Hz, CH_3), 18.38 (d, $^3J_{PC}$=6.43 Hz, CH_3), 20.93 (d, $^3J_{PC}$=10.59 Hz, CH_3), 29.09 (bs, CH), 62.33 (d, $^2J_{PC}$=7.28 Hz, CH_2O), 64.07 (d, $^1J_{PC}$=156.63, CHN_3); IR (film): ν=2968, 2104, 1248, 1128, 1040; FAB/MS *m/z* (%): 208(39); Anal. Calcd for $C_6H_{14}N_3O_3P$ (207.17): C: 34.78; H: 6.81; N: 20.28. Found: C: 34.69; H: 6.72; N: 20.14.

3.1.6. *O*-Ethyl azidophenylmethylphosphonic acid (2f). Yield: 78%, yellow oil; ^1H NMR: δ=1.24 (t, J=7.05 Hz, 3H, CH_3), 3.91–4.06 (2m, 2H, CH_2O), 4.63 (d, J=17.00 Hz, 1H, CHN_3), 6.47 (bs, 1H, OH), 7.31–7.40 (m, $5H_{arom}$); ^{31}P NMR: δ=21.11; ^{13}C NMR: δ=16.50 (d, $^3J_{PC}$=5.91 Hz, CH_3), 61.75 (d, $^1J_{PC}$=160.15 Hz, CHN_3), 63.86 (d, $^2J_{PC}$=7.30 Hz, CH_2O), 128.58–132.67 (C_{arom}); IR (film); ν=2984, 2104, 1240, 1112, 1040; FAB/MS *m/z* (%): 242(52); Anal. Calcd for $C_9H_{12}N_3O_3P$ (241.19): C: 44.82; H: 5.02; N: 17.42. Found: C: 44.71; H: 4.90; N: 17.33.

3.1.7. *O*-Ethyl azido(4-bromophenyl)methylphosphonic acid (2g). Yield: 70%, yellow oil; ^1H NMR: δ=1.27 (t, J=7.00 Hz, 3H, CH_3), 3.91–4.08 (m, 2H, CH_2O), 4.64 (d, J=16.76 Hz, 1H, CHN_3), 7.20–7.55 (m, 4H, AA′XX′ of *p*-BrC_6H_4), 9.18 (bs, 1H, OH); ^{31}P NMR: δ=20.55; ^{13}C NMR: δ=16.16 (d, $^3J_{PC}$=5.89 Hz, CH_3), 60.67 (d, $^1J_{PC}$=160.05 Hz, CHN_3), 63.56 (d, $^2J_{PC}$=7.38 Hz, CH_2O), 122.78–131.65 (C_{arom}); IR (film): ν=2984, 2104, 1248, 1164, 1016, 788; FAB/MS *m/z* (%): 320/322(1); Anal. Calcd for $C_9H_{11}N_3O_3PBr$ (320.08): C: 33.77; H: 3.46; N: 13.13. Found: C: 33.63; H: 3.35; N: 12.99.

3.2. *N*-[Ethoxy(1-azidoalkyl)phosphinyl] amino acids methyl esters (5aa–5fd)—general procedure

Oxalyl chloride (0.005 mol, 0.635 g, 0.44 mL) was added via syringe to a cooled to 0°C solution of *O*-ethyl 1-azidoalkylphosphonic acid **2** (0.0025 mol) and DMF (50 μL) in dry CH_2Cl_2 (8 mL). The mixture was stirred for 30 min at 0°C, and 1.5 h at room temperature. Then the volatile material was carefully evaporated under reduced pressure. The crude phosphonochloridate **3** was dissolved in dry CH_2Cl_2 (5 mL) and the solution was added dropwise to the mixture of amino acid methyl ester hydrochloride **4** (0.003 mol) and Et_3N (0.02 mol, 2.02 g) in CH_2Cl_2 (15 mL), cooled to 0°C. The resulting mixture was stirred for 24 h at room temperature. The solvent and an excess of Et_3N were then evaporated, $CHCl_3$ (50 mL) was added to the semi-solid residue, and the mixture was successively washed with water (5 mL), 1 M NaOH aq. (2×5 mL), water (2×5 mL), 5% HCl aq. (2×5 mL), 5% $NaHCO_3$ aq. (2×5 mL) and water (2×5 mL). Organic layer was dried over anhydrous $MgSO_4$, solvent removed under reduced pressure and the crude azide subjected to flash chromatography to give analytically pure *N*-[ethoxy(1-azidoalkyl)-phosphinyl] amino acid methyl ester **5** as a yellow oil (Table 2).

3.2.1. Methyl *N*-[ethoxy(azidomethyl)phosphinyl] glycinate (5aa). Yield: 70%, pale yellow oil; R_f=0.25 (A); ^1H NMR: δ=1.37 (t, J=7.25 Hz, 3H, CH_3), 3.24–3.35 (m, 1H, NH), 3.50 (four lines, 1H, J=15.0, 11.76 Hz, part A of the ABX system, CH_2P), 3.58 (four lines, 1H, J=15.00, 11.76 Hz, part B of the ABX system, CH_2P), 3.76 (s, 3H, CH_3O), 3.85 (dd, J=7.00, 11.00 Hz, NCH_2), 4.06–4.30 (m, 2H, CH_2O); ^{31}P NMR: δ=24.35; IR (film) ν=3456, 2960, 2096, 1752, 1256, 1112, 1036; FAB/MS *m/z* (%): 237 (100); Anal. Calcd for $C_6H_{13}N_4O_4P$ (236.17): C: 30.51; H: 5.55; N: 23.72. Found: C: 30.31; H: 5.51; N: 23.52.

3.2.2. Methyl *N*-[ethoxy(azidomethyl)phosphinyl]-L-alanate (5ab). Yield: 50%; pale yellow oil; R_f=0.34 (B); (the mixture of diastereomers); ^1H NMR: δ=1.36, 1.37 (2t, J=7.25 Hz, 3H, CH_3), 1.43, 1.46 (2d, J=6.75 Hz, 3H, CH_3), 3.25–3.60 (m, 3H, CH_2P, NH), 3.75, 3.76 (2s, 3H, CH_3O),

4.05–4.26 (m, 3H, CH_2O, NCH); ^{31}P NMR: δ=22.76, 23.59 (52:48); IR (film) ν=3184, 2984, 2096, 1748, 1252, 1152, 1036; FAB/MS *m/z* (%): 251 (100); Anal. Calcd for $C_7H_{15}N_4O_4P$ (250.20): C: 33.60; H: 6.04; N: 22.39. Found: C: 33.40; H: 5.92; N: 22.23.

3.2.3. Methyl *N*-[ethoxy(1-azidoethyl)phosphinyl] glycinate (5ba). Yield: 57%; yellow oil; R_f=0.50 (B); (the mixture of diastereomers); ^1H NMR: δ=1.37 (bt, *J*=7.00 Hz, 3H, CH_3), 1.45, 1.52 (2dd, *J*=7.25, 16.25 Hz, 3H, CH_3), 3.18–3.26 (m, 1H, NH), 3.51–3.76 (m, 1H, CHP), 3.78, 3.81 (2s, 3H, CH_3O), 3.82–3.91 (m, 2H, NCH_2), 4.10–4.30 (m, 2H, CH_2O); ^{31}P NMR: δ=27.19, 27.52 (52:48); IR (film) ν=3190, 2985, 2100, 1750, 1250, 1140, 1038; FAB/MS *m/z* (%): 251 (100); Anal. Calcd for $C_7H_{15}N_4O_4P$ (250.19): C: 33.60; H: 6.04; N: 22.39. Found: C: 33.52; H: 5.99; N: 22.21.

3.2.4. Methyl *N*-[ethoxy(1-azidoethyl)phosphinyl]-L-alanate (5bb). Yield: 58%; yellow oil; R_f=0.41 (B); (the mixture of diastereomers); ^1H NMR: δ=1.23, 1.24 (2t, *J*=7.25 Hz, 3H, CH_3), 1.30–1.54 (m, 6H, CH_3, CH_3CP), 3.18–3.30 (m, 1H, NH), 3.37–3.65 (m, 1H, CHP), 3.72, 3.73, 3.74 (3s, 3H, CH_3), 4.03–4.20 (m, 3H, CH_2O, CH); ^{31}P NMR: δ=25.71, 26.51, 26.69 (26:26:48); IR (film) ν=3256, 2992, 2120, 1744, 1204, 1152, 1024; FAB/MS *m/z* (%): 265 (100); Anal. Calcd for $C_8H_{17}N_4O_4P$ (264.22): C: 36.37; H: 6.49; N: 21.20. Found: C: 36.17; H: 6.38; N: 21.07.

3.2.5. Methyl *N*-[ethoxy(1-azido-3-methylbutyl)phosphinyl] glycinate (5da). Yield: 75%, yellow oil; R_f=0.45 (B); (the mixture of diastereomers); ^1H NMR: δ=0.94, 0.95, 0.98, 1.00 (4d, *J*=6.50 Hz, 6H, $2CH_3$), 1.36, 1.37 (2t, *J*=7.00 Hz, 3H, CH_3), 1.57–1.60 (m, 1H, CH), 1.60–1.98 (m, 2H, CH_2), 3.20–3.35 (m, 1H, NH), 3.38–3.63 (m, 1H, CHN_3), 3.76, 3.77 (2s, 3H, CH_3O), 3.80–3.96 (m, 2H, NCH_2), 4.06–4.30 (m, 2H, OCH_2); ^{31}P NMR: δ=27.35, 27.48 (50:50); IR (film): ν=3208, 2960, 2112, 1756, 1440, 1216, 1152, 1036; FAB/MS *m/z* (%): 293(100); Anal. Calcd for $C_{10}H_{21}N_4O_4P$ (292.27): C: 41.09; H: 7.24; N: 19.17. Found: C: 40.94; H: 7.12; N: 19.03.

3.2.6. Methyl *N*-[ethoxy(1-azido-3-methylbutyl)phosphinyl]-L-alanate (5db). Yield: 73%, yellow oil; R_f=0.42 (C); (the mixture of diastereomers); ^1H NMR: δ=0.93, 0.94, 0.98, 1.00 (4d, *J*=6.50 Hz, 6H, $2CH_3$), 1.35, 1.37 (2t, *J*=7.00 Hz, 3H, CH_3), 1.41–1.47 (m, 3H, CH_3), 1.53–1.90 (m, 3H, CH_2, CH), 3.10–3.60 (m, 2H, NCH, NH), 3.75, 3.76 (2s, 3H, CH_3O), 4.00–4.25 (m, 3H, OCH_2, N_3CH); ^{31}P NMR: δ=25.86, 26.67 (74:26); IR (film): ν=3200, 2960, 2112, 1748, 1448, 1220, 1156, 1036; FAB/MS *m/z* (%): 307(89); Anal. Calcd for $C_{11}H_{23}N_4O_4P$ (306.30); C: 43.13; H: 7.57; N: 18.29. Found: C: 43.00; H: 7.48; N: 18.11.

3.2.7. Methyl *N*-[ethoxy(azidophenylmethyl)phosphinyl] glycinate (5fa). Yield: 75%, yellow oil; R_f=0.55 (D); (the mixture of diastereomers); ^1H NMR: δ=1.31, 1.34 (2t, *J*=7.00 Hz, 3H, CH_3), 3.07–3.18 (m, 1H, NH), 3.53–3.70 (m, 2H, NCH_2), 3.73 (s, 3H, CH_3O), 4.01–4.28 (m, 2H, OCH_2), 4.77, 4.82 (2d, *J*=15.76 Hz, 1H, CHN_3), 7.35–7.47 (m, $5H_{arom}$); ^{31}P NMR: δ=23.01, 23.26 (50:50); IR (film): ν=3328, 2984, 2104, 1752, 1496, 1216, 1148; 1036, 700; FAB/MS *m/z* (%): 313(78); Anal. Calcd for $C_{12}H_{17}N_4O_4P$ (312.26); C: 46.16; H: 5.49; N: 17.94. Found: C: 46.03; H: 5.38; N: 17.81.

3.2.8. Methyl *N*-[ethoxy(azidophenylmethyl)phosphinyl]-L-alanate (5fb). Yield: 70%, yellow oil; R_f=0.49 (B); (the mixture of diastereomers); ^1H NMR: δ=1.14–1.39 (m, 6H, $2CH_3$), 3.02–3.40 (m, 1H, NH), 3.70, 3.71, 3.72 (3s, 3H, CH_3O), 3.75–4.23 (m, 3H, OCH_2, NCH), 4.70, 4.73, 4.79, 4.80 (4d, *J*=16.00 Hz, 1H, N_3CH), 7.33–7.44 (m, $5H_{arom}$); ^{31}P NMR: δ=22.06, 22.34, 22.78 (50:25:25); IR (film): ν=3216, 3080, 2104, 1744, 1456, 1224, 1152, 1032, 700; FAB/MS *m/z* (%): 327(76); Anal. Calcd for $C_{13}H_{19}N_4O_4P$ (326.29); C: 47.85; H: 5.87; N: 17.17. Found: C: 47.68; H: 5.79; N: 17.12.

3.3. *N*-[Ethoxy(1-*N*-*t*-butoxycarbonylaminoalkyl)phosphinyl] amino acids methyl esters 6aa–6fb—general procedure

A solution of *N*-[ethoxy(1-azidoalkyl)phosphinyl] amino acid methyl ester **5** (0.001 mol) in ethyl acetate (30 mL) was hydrogenated at room temperature for 4 h over 10% Pd/C (70 mg) under a pressure of 3.06 atm in the presence of di-*tert*-butyl dicarbonate (0.0012 mol, 0.262 g). The catalyst was removed by filtration through Celite, and the filtrate was successively washed with 1 M $KHSO_4$ (2×5 mL), water (5 mL), 5% $NaHCO_3$ aq. (2×5 mL) and water (5 mL). The organic layer was dried over anhydrous $MgSO_4$, the solvent removed under reduced pressure and the crude phosphonopeptide was subjected to flash chromatography to give analytically pure *N*-[ethoxy(1-*N*-*t*-butoxycarbonylaminoalkyl)phosphinyl] amino acid methyl ester **6** as a yellow oil or colorless crystals (Table 2).

3.3.1. Methyl *N*-[ethoxy(*N*-*t*-butoxycarbonylaminomethyl)phosphinyl] glycinate(6aa). Yield: 68%; colorless prisms, mp 77–79°C; R_f=0.21 (C); ^1H NMR: δ=1.32 (t, *J*=7.00 Hz, 3H, CH_3), 1.44 (s, 9H, $3CH_3$), 3.15 (bs, 1H, NH), 3.35–3.70 (m, 2H, CH_2P), 3.74 (s, 3H, CH_3O), 3.74–3.84 (m, 2H, NCH_2), 4.04–4.21 (m, 2H, CH_2O), 5.16 (bs, 1H, NHBoc); ^{31}P NMR: δ=27.75; IR (film) ν=3304, 2974, 1752, 1712, 1528, 1368, 1204, 1152, 1040; FAB/MS *m/z* (%): 311 (25); Anal. Calcd for $C_{11}H_{23}N_2O_6P$ (310.29): C:42.58; H: 7.47; N: 9.03. Found: C: 42.42; H: 7.31; N: 8.89.

3.3.2. Methyl *N*-[ethoxy(*N*-*t*-butoxycarbonylaminomethyl)phosphinyl]-L-alanate (6ab). Yield: 62%; yellow oil; R_f=0.57 (E); (the mixture of diastereomers), ^1H NMR: δ=1.26, 1.31 (2t, *J*=7.25 Hz, 3H, CH_3), 1.39, 1.42 (2d, *J*=7.00 Hz, 3H, CH_3), 1.44, 1.45 (2s, 9H, $3CH_3$), 3.25–3.69 (m, 3H, CH_2P, NH), 3.74 (s, 3H, CH_3O), 4.02–4.16 (m, 3H, CH_2O, CH), 4.96, 5.08 (2bs, 1H, NHBoc); ^{31}P NMR: δ=26.55, 27.20 (55:45); IR (film) ν=3344, 2984, 1812, 1752, 1712, 1512, 1368, 1256, 1212, 1120, 1068; FAB/MS *m/z* (%): 325 (17); Anal. Calcd for $C_{12}H_{25}N_2O_6P$ (324.32): C: 44.44; H: 7.77; N: 8.64. Found: C: 44.25; H: 7.61; N: 8.52.

3.3.3. Methyl *N*-[ethoxy(1-*N*-*t*-butoxycarbonylaminoethyl)phosphinyl] glycinate (6ba). Yield: 74%; colorless needles, mp 86–88°C (dec); R_f=0.38 (B); (the mixture of diastereomers); ^1H NMR: δ=1.31, 1.32 (2t, *J*=7.00 Hz, 3H,

CH_3), 1.36 (dd, J=7.25, 16.75 Hz, 3H, CH_3), 1.43, 1.45 (2s, 9H, $3CH_3$), 3.10–3.24 (m, 1H, NH), 3.74, 3.75 (2s, 3H, CH_3O), 3.76–3.85 (m, 2H, NCH_2), 3.98–4.21 (m, 3H, CH_2O, CHP), 4.76, 5.00 (2bd, J=8.75 Hz, 1H, NHBoc); ^{31}P NMR: δ=30.04, 30.88 (52:48); IR (film) ν=3330, 1750, 1715, 1521, 1261, 1214, 1162, 1043; FAB/MS *m/z* (%): 325 (47); Anal. Calcd for $C_{12}H_{25}N_2O_6P$ (324.32): C: 44.44; H: 7.77; N: 8.64. Found: C: 44.31; H: 7.63; N: 8.49.

3.3.4. Methyl *N*-[ethoxy(1-*N*-*t*-butoxycarbonylaminoethyl)phosphinyl]-L-alanate (6bb). Yield: 83%; colorless solid, mp 94–96°C (dec); R_f=0.41 (B); (the mixture of diastereomers); ^{1}H NMR: δ=1.28–1.45 (m, 18H, $6CH_3$), 3.13–3.27 (m, 1H, NH), 3.74, 3.75 (2s, 3H, CH_3O), 3.90–4.20 (m, 4H, CH_2O, NCH, CHP), 4.60–4.75, 4.80–4.95 (2m, 1H, NHBoc); ^{31}P NMR: δ=28.85, 29.39, 30.01, 30.27 (28:26:29:17); IR (film) ν=3368, 3200, 2960, 1736, 1728, 1708, 1696, 1688, 1516, 1300, 1276, 1160, 1048; FAB/MS *m/z* (%): 339 (37); Anal. Calcd for $C_{13}H_{27}N_2O_6P$ (338.34): C: 46.15; H: 8.04; N: 8.28. Found: C: 45.95; H: 7.84; N: 8.18.

3.3.5. Methyl *N*-[ethoxy(1-*N*-*t*-butoxycarbonylamino-3-methylbutyl)phosphinyl] glycinate (6da). Yield: 78%, colorless solid, mp 105–108°C; R_f=0.42 (B); (the mixture of diastereomers); ^{1}H NMR: δ=0.90–0.96 (m, 6H, $2CH_3$), 1.31 (t, J=7.00 Hz, 3H, CH_3), 1.42, 1.44 (2s, 9H, $3CH_3$), 1.50–1.75 (m, 3H, CH_2, CH), 3.05–3.20 (m, 1H, NH), 3.74, 3.75 (2s, 3H, OCH_3), 3.77–3.89 (m, 2H, NCH_2), 4.02–4.23 (m, 3H, OCH_2, NCH), 4.61, 4.81 (2d, J=10.00 Hz, 1H, NHBoc); ^{31}P NMR: δ=30.06, 30.90 (43:57); IR (film): ν=3336, 3296, 2960, 1696, 1732, 1212, 1168, 1040; FAB/MS *m/z* (%): 367(41); Anal. Calcd for $C_{15}H_{31}N_2O_6P$ (366.39); C: 49.17; H: 8.53; N: 7.64. Found: C: 48.99; H: 8.40; N: 7.51.

3.3.6. Methyl *N*-[ethoxy(1-*N*-*t*-butoxycarbonylamino-3-methylbutyl)phosphinyl]-L-alanate (6db). Yield: 76%, colorless solid, mp 91–93°C; R_f=0.44 (B); (the mixture of diastereomers); ^{1}H NMR: δ=0.90–0.96 (m, 6H, $2CH_3$), 1.26, 1.30, 1.31, 1.39 (4t, J=7.00 Hz, 3H, CH_3), 1.41–1.50 (m, 12H, $(CH_3)_3C$, CH_3), 1.55–1.80 (m, 3H, CH_2, CH), 3.20–3.36 (m, 1H, NH), 3.73, 3.74 (2s, 3H, OCH_3), 3.89–4.20 (m, 4H, OCH_2, *i*-BuCH, NCH), 4.58, 4.62, 4.80, 4.93 (4d, J=9.75 Hz, 1H, NHBoc); ^{31}P NMR: δ=28.85, 29.51, 30.15, 30.48 (22:27:29:22); IR (film): ν=3232, 2960, 1744, 1692, 1208, 1156, 1048; FAB/MS *m/z* (%): 381(38); Anal. Calcd for $C_{16}H_{33}N_2O_6P$ (380.42); C: 50.52; H: 8.74; N: 7.36. Found: C: 50.42; H: 8.67; N: 7.25.

3.3.7. Methyl *N*-[ethoxy(*N*-*t*-butoxycarbonylaminophenylmethyl)phosphinyl] glycinate (6fa). Yield: 70%, colorless solid, mp 103–105°C; R_f=0.49 (B); (the mixture of diastereomers); ^{1}H NMR: δ=1.16, 1.30 (2t, J=7.00 Hz, 3H, CH_3), 1.42 (bs, 9H, $3CH_3$), 2.90–2.97, 3.20–3.27 (2m, 1H, NH), 3.48–3.70 (m, 2H, NCH_2), 3.71, 3.75 (2s, 3H, OCH_3), 3.94–4.16 (m, 2H, OCH_2), 4.98–5.10 (m, 1H, PhCH), 5.58–5.61, 5.62–5.67 (2m, 1H, NHBoc), 7.30–7.41 (m, $5H_{arom}$); ^{31}P NMR: δ=26.27, 26.43 (50:50); IR (film): ν=3381, 2956, 1810, 1717, 1690, 1457, 1208, 1153, 1042, 788; FAB/MS *m/z* (%): 387(18); Anal. Calcd for $C_{17}H_{27}N_2O_6P$ (386.38); C: 52.84; H: 7.04; N: 7.25. Found: C: 52.73; H: 6.97; N: 7.13.

3.3.8. Methyl *N*-[ethoxy(*N*-*t*-butoxycarbonylaminophenylmethyl)phosphinyl]-L-alanate (6fb). Yield: 63%, colorless needles, mp 102–104°C; R_f=0.68 (B); (the mixture of diastereomers); ^{1}H NMR:δ=1.04–1.20 (m, 3H, CH_3), 1.26–1.33 (m, 3H, CH_3), 1.41 (bs, 9H, $3CH_3$), 2.95–3.35 (m, 1H, NH), 3.67, 3.68, 3.72, 3.74 (4s, 3H, OCH_3), 3.82–3.96 (m, 1H, NCH), 4.01–4.17 (m, 2H, OCH_2), 4.92–5.03 (m, 1H, PhCH), 5.54–5.80 (m, 1H, NHBoc), 7.30–7.40 (m, $5H_{arom}$); ^{31}P NMR: δ=25.48, 25.80, 25.90 (25:50:25); IR (film): ν=3328, 3088, 1748, 1684, 1496, 1208, 1160, 1044, 788; FAB/MS *m/z* (%): 401(12); Anal. Calcd for $C_{18}H_{29}N_2O_6P$ (400.41); C: 53.99; H: 7.30; N: 7.00. Found: C: 53.81; H: 7.22; N: 6.89.

Acknowledgements

The financial support of this work by the Polish State Committee for Scientific Research under grant number 3 T09A 103 14 is gratefully acknowledged.

References

1. Kafarski, P.; Lejczak, B.; Aminophosphonic and Aminophosphinic Acids Chemistry and Biological Activity. In *Synthesis of phosphono- and phosphinopeptides*; Kukhar, V. P.; Hudson, H. R.; Eds.; John Wiley: Chichester, 2000; pp. 173–205. (b) Kafarski, P.; Lejczak, B. *The biological activity of phosphono- and phosphinopeptides*; ibid; pp. 407–443
2. Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654–657.
3. Vo-Quang, Y.; Gravey, A. M.; Simmonneau, S.; Vo-Quang, L.; Lacoste, A. M.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 6167–6170.
4. Camp, N.; Hawkins, P. C. D.; Hitchock, P. B. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1047–1052.
5. (a) Dumy, P.; Escale, R.; Girrard, J. P.; Parello, J.; Vidal, J. P. *Synthesis* **1992**, 1226–1228. (b) Maffre-Lafon, D.; Dumy, P.; Escale, R.; Vidal, J. P.; Girard, J. P.; Alattia, T. *Lett. Pept. Sci.* **1994**, *1*, 51–55.
6. Bateson, J. H.; Gasson, B. C.; Khushi, T.; Neale, J. E.; Payne, D. J.; Tolson, D. A.; Walker, G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1667–1672.
7. Musiol, H-J.; Grams, F.; Rudolph-Böhner, S.; Moroder, L. *J. Org. Chem.* **1994**, *59*, 6144–6146.
8. (a) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7616–7624. (b) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7625–7634.
9. (a) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengler, P. A.; Philips, B. W.; Moore, W.; Smith III, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6370–6371. (b) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengler, P. A.; Philips, B. W.; Moore, W.; Smith III, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8177–8190.
10. Kakinuma, H.; Shimazaki, K.; Takahashi, N.; Takahashi, H.; Niihata, S.; Aoki, Y.; Hamada, K.; Matsuhita, H.; Nishi, Y. *Tetrahedron* **1999**, *55*, 2559–2572.
11. Elliott, R. L.; Marks, N.; Berg, M. J.; Portoghese, P. S. *J. Med. Chem.* **1985**, *28*, 1208–1216.
12. Mucha, A.; Kafarski, P.; Plenat, F.; Cristau, H.-J. *Tetrahedron* **1994**, *50*, 12743–12754.

13. (a) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn* **1972**, *45*, 2528–2530. (b) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn* **1972**, *45*, 2531–2534. (c) Yamauchi, K.; Mitsuda, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn* **1975**, *48*, 3285–3286.
14. Hariharan, M.; Chaberek, S.; Martell, A. M. *Synth. Commun.* **1973**, *3*, 375–379.
15. McLeod, D. A.; Brinkworth, R. I.; Ashley, J. A.; Janda, K. D.; Wirsching, P. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 653–658.
16. (a) Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, 660–663. (b) Sampson, N. C.; Bartlett, R. A. *J. Org. Chem.* **1988**, *53*, 4500–4503.
17. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 351–368.
18. Hughes, D. L. In *Organic Reactions*, Wiley: New York, 1992; 42, pp 335–656. Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127–164.
19. Freudenberg, H.; Eichel, H. *Chem. Ber.* **1932**, *65*, 1183–1191.
20. Bertho, A.; Maier, J. *Liebigs Ann. Chem.* **1932**, *498*, 50–61.
21. Ojima, I.; Yoda, N.; Yatabe, M.; Tanaka, T.; Kogure, T. *Tetrahedron* **1984**, *40*, 1255–1268.
22. (a) Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173–5176. (b) Zaloom, J.; Calandra, M.; Roberts, D. C. *J. Org. Chem.* **1985**, *50*, 2601–2603.
23. (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063–1072. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030. (c) Evans, D. A.; Watson, P. S. *Tetrahedron Lett.* **1996**, *37*, 3251–3254.
24. Stone, M. J.; Dyk, M. S.; van Booth, P. M.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1629–1635.
25. Hoffman, R. V.; Kim, H.-O. *Tetrahedron* **1992**, *48*, 3007–3020.
26. Effenberger, F.; Kühlwein, F.; Hopf, M.; Stelzer, U. *Liebigs Ann. Chem.* **1993**, 1303–1312.
27. (a) Pearson, A. J.; Park, J. G. *J. Org. Chem.* **1992**, *57*, 1744–1752. (b) Pearson, A. J.; Shin, H. G. *J. Org. Chem.* **1994**, *59*, 2314–2323. (c) Pearson, A. J.; Chelliah, M. V.; Bignan, G. C. *Synthesis* **1997**, 536–540. (d) Pearson, A. J.; Chelliah, M. V. *J. Org. Chem.* **1998**, *63*, 3087–3098.
28. Rao, A. V. R.; Reddy, K. L.; Rao, A. S.; Vittal, T. V. S. K.; Reddy, M. M.; Pathi, P. L. *Tetrahedron Lett.* **1996**, *37*, 3023–3026.
29. Meldal, M.; Juliano, M. A.; Jansson, A. M. *Tetrahedron Lett.* **1997**, *38*, 2531–2534.
30. Gajda, T.; Matusiak, M. *Synthesis* **1992**, 367–368.
31. Sikora, D.; Gajda, T. *Phosphorus Sulfur and Silicon* **2000**, *157*, 201–210.
32. Sikora, D.; Gajda, T. *Tetrahedron* **2000**, *56*, 3755–3761.
33. Gajda, T.; Sikora, D.; Nonas, T. *Phosphorus Sulfur Silicon* **1999**, *144–146*, 581–584 (Preliminary communication: Proceedings of the XIVth International Conference on Phosphorus Chemistry).
34. (a) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603–1609. (b) Bartlett, P. A.; Hanson, J. E.; Giannousis, P. P. *J. Org. Chem.* **1990**, *55*, 6268–6274.
35. Yuan, C.; Wang, G.; Yuan, S. *Synthesis* **1990**, 522–524.
36. Szewczyk, J.; Lejczak, B.; Kafarski, P. *Synthesis* **1982**, 409–412.
37. Kelley, J. L.; McLean, E. W.; Crouch, R. C.; Averett, D. R.; Tuttle, J. V. J. *J. Med. Chem.* **1995**, *38*, 1005–1014.
38. (a) Hoffmann, M. *J. Prakt. Chem.* **1988**, *330*, 820–824. (b) Jacques, J.; Leclercq, M.; Brienne, M.-J. *Tetrahedron* **1981**, *37*, 1727–1733.
39. Wasielewski, C.; Sobczak, A.; Szewczyk, J. *Roczn. Chem.* **1976**, *50*, 1795 (*Chem. Abstr.* **1977**, *86*, 121739g). Krawczyk, H. *Synth. Commun.* **1997**, *27*, 3151–3161.
40. Holý, A. *Synthesis* **1998**, 381–385.
41. Gray, D. M.; Smith, D. J. H. *Tetrahedron Lett.* **1980**, *21*, 859–860.
42. (a) Saady, M.; Lebeau, L.; Mioskowski, C. *J. Org. Chem.* **1995**, *60*, 2946–2947. (b) Hoffmann, M. *Phosphorus Sulfur Silicon* **1998**, *134/135*, 109–118.
43. Commonwealth Sci. and Ind. Res. Orig. and ICI of Australia and New Zealand. British Patent 1087066, **1967**; *Chem. Abstr.* **1968**, *68*, 95956g.
44. Yokomatsu, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1992**, *3*, 377–378.
45. Berte-Verrando, S.; Nief, F.; Patois, C.; Savignac, P. *Phosphorus Sulfur and Silicon* **1995**, *103*, 91–100.
46. Engel, R. *Organic Reactions*, Vol. 36; Wiley: New York, 1988 (176–248).
47. For recent examples see: (a) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930–7933. (b) Hammerschmidt, F.; Wuggenning, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1709–1721.