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A New Synthesis of Protected Phosphonodipeptides with an N-Terminal Amino Acid

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Abstract—A new simple protocol for the direct synthesis of phosphonodipeptides from *N*-protected amino acids, diethyl 1-azidoalkylphosphonates and tertiary alkyl phosphine (Bu_3P, Me_3P) was developed. The method is general and the coupling occurred with good yield (42–97%). Depending on the phosphine used and/or mechanism operating during the condensation, the reaction can be accomplished at room temperature, or on heating in toluene.

Phosphonate analogs of α-amino acids and their derivatives[1] have received considerable attention in bioorganic and medicinal chemistry due to their unique biological activities.[2] In turn, the peptide mimetics—phosphonopeptides can be obtained by different methods[3] but generally, the reactions employed in the formation of the peptide bond between 1-aminoalkylphosphonates and amino acids are similar to those used in standard peptide chemistry. Thus, the diester of the 1-aminoalkylphosphonate is directly coupled with the *N*-protected amino acid mostly by means of dicyclohexylcarbodiimide as condensation agent, or the carboxylic moiety is activated by formation of mixed anhydrides prior to condensation.[4]

An alternative synthesis of carboxamides from carboxylic acids could also be realized in a one-pot reaction of a carboxylic acid, azide and tertiary alkyl or aryl phosphine under non-acidic conditions, by taking advantage of the Staudinger reaction (formation of phosphine imines from azides and tertiary phosphines).[5] In this way, several carboxamides and small peptides were successfully obtained.[6–13] Also carboxylic mixed anhydrides were successfully applied as substrates in the synthesis of small peptides from azidoesters and trialkylphosphines.[14,15] The above mentioned reactions were proved to proceed without the epimerisation at the stereogenic center of the α-amino acid.[8,15]

Since azides[16] are excellent and often used precursors of the amino group, the above presented synthetic approach enables the synthesis of *N*-protected amines without the necessity of azide reduction prior to coupling.

Results and Discussion

In connection with our interest in the chemistry of bifunctional organic compounds containing both phosphorus and nitrogen moieties we have recently become engaged in the application of diethyl 1-azidoalkylphosphonates[17] **1** in the synthesis of diethyl 1-(isothiocyano)alkylphosphonates[18] and derivatives of 1-[1-(diethoxyphosphoryl)alkyl]-1*H*-1,2,3-triazoles.[19]

Herein, we wish to report a new application of the above-mentioned reagent **1** in the synthesis of phosphonopeptides **6** with N-terminal amino acids (Scheme 1). To the best of our knowledge there are no reports[20] on the application of Staudinger reaction based methodology for the preparation of phosphonopeptides.

Starting diethyl 1-azidoalkylphosphonates[17] **1** are easily available from diethyl 1-hydroxyalkylphosphonates[21] and hydrazoic acid by the Mitsunobu reaction.[22] The above-mentioned azides **1** are stable, distillable liquids and can be stored for unlimited periods of time in a refrigerator without any signs of decomposition. Several *N*-benzyloxycarbonyl and *N*-*t*-butyloxycarbonyl amino acids **4** as well as *N*-*t*-butyloxycarbonyl-*N*-methyl valine were used as acid components.

Thus, according to Scheme 1, diethyl 1-azidoalkylphosphonate **1** was converted by the Staudinger reaction[5] with appropriate phosphine **2** into the respective iminophosphorane **3**. This in turn, by reaction with an *N*-protected amino acid **4**, was transformed via the intermediate salt **5** into the

Keywords: phosphonopeptides; diethyl 1-azidoalkylphosphonates; amino acids; phosphines; phosphine imines; Staudinger reaction.

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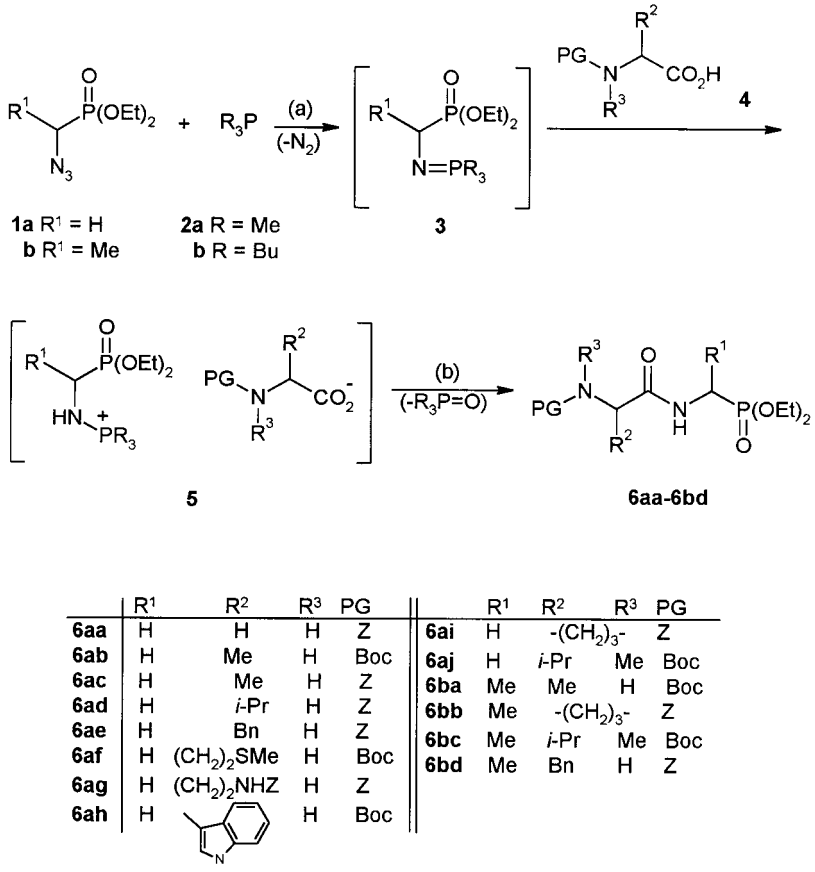


	R1	R2	R3	PG		R1	R2	R3	PG
6aa	H	H	H	Z	**6ai**	H	-(CH2)3-		Z
6ab	H	Me	H	Boc	**6aj**	H	*i*-Pr	Me	Boc
6ac	H	Me	H	Z	**6ba**	Me	Me	H	Boc
6ad	H	*i*-Pr	H	Z	**6bb**	Me	-(CH2)3-		Z
6ae	H	Bn	H	Z	**6bc**	Me	*i*-Pr	Me	Boc
6af	H	$(CH_2)_2SMe$	H	Boc	**6bd**	Me	Bn	H	Z
6ag	H	$(CH_2)_2NHZ$	H	Z					
6ah	H		H	Boc					

Scheme 1. Reagents and conditions: (a) Toluene, room temperature, 1.5 h; (b) Toluene, 80–85°C or reflux, 3–12 h or room temperature, 24 h–3 days.

Table 1. Phosphonopeptides **6aa–6bd** prepared via the iminophosphorane route

Entry	Compound	R_3P	R^1	PG-Aa-OH	Reaction conditions (time, temp °C)	Yield (%)[a]	$[\alpha]_D$ (*c*) (MeOH)
1	**6aa**	Bu_3P	H	*Z*-Gly-OH	12h, 80–85	58	–
2	**6ab**			Boc-(L)-Ala-OH	3 h, 80–85	63	−22.69 (1.04)
3	**6ac**			*Z*-(L)-Ala-OH	8 h, 80–85	92	−23.28 (0.76)
4	**6ad**			*Z*-(L)-Val-OH	12 h, 80–85	76	−22.40 (0.54)
5	**6ae**			*Z*-(L)-Phe-OH	12 h, 80–85[b]	67[c,d]	−11.11[e] (0.62)
6	**6af**			Boc-(D)-Met-OH	4 h, 80–85	97	+23.18 (0.91)
7	**6ag**			*Z,Z*-(L)-Lys-OH	4 h, 80–85	68	−14.33 (1.05)
8	**6ah**			Boc-(L)-Trp-OH	4 h, 80–85	73	−7.30 (0.78)
9	**6ai**			*Z*-(L)-Pro-OH	12 h, 80–85	93	−57.13 (0.74)
10	**6aj**			Boc-(D)-N(Me)-Val-OH	5 h, reflux	63	+65.06 (0.77)
11	**6ac**	Me_3P	H	*Z*-(L)-Ala-OH	24 h, room temperature	63	−22.12 (2.26)
12	**6ae**			*Z*-(L)-Phe-OH	24 h, room temperature	62	−10.50 (3.34)
13	**6ai**			*Z*-(L)-Pro-OH	48 h, room temperature	59	−56.46 (1.81)
14	**6ba**	Bu_3P	Me	*Z*-(L)-Ala-OH	8 h, 80–85	42[f,g]	−14.88[h] (0.77)
15	**6bb**			*Z*-(L)-Pro-OH	10 h, reflux	63	−55.71 (0.14)
16	**6bc**			Boc-(D,L)-N(Me)-Val-OH	5 h, reflux	62	–
17	**6ba**	Me_3P	Me	*Z*-(L)-Ala-OH	3 days, room temperature	65	−9.42[h] (1.21)
18	**6bb**			*Z*-(L)-Pro-OH	3 days, room temperature	70	−43.26 (1.04)
19	**6bd**			*Z*-(L)-Phe-OH	3 days, room temperature	67	−2.19 (0.73)

[a] Yields of pure phosphonopeptides **6**, based on **1**.
[b] No peptide formation was observed after 24 h at room temperature.
[c] Also independently synthesized from *Z*-Phe-OH and diethyl aminomethylphosphonate[25] via mixed anhydride method[24] with *i*-BuOCOCl; yield: 47%, mp 100–102°C, $[\alpha]_D$=−10.94 (*c* 0.8, MeOH).
[d] For the reaction with Ph_3P instead of Bu_3P about 65% of conversion was achieved after 12 h in boiling toluene.
[e] Lit.[26]: $[\alpha]_D$=−9.8 (EtOH).
[f] Also independently synthesized from *Z*-Phe-OH and diethyl 1-aminoethylphosphonate[25] via mixed anhydride method[24] with *i*-BuOCOCl; yield: 55%, oil, $[\alpha]_D$=−15.18 (*c* 0.9, MeOH).
[g] For the reaction with Ph_3P instead of Bu_3P about 40% of conversion was achieved after 24 h in boiling toluene.
[h] Lit.[27]: $[\alpha]_D$=−9.8 (MeOH).

corresponding phosphonodipeptide **6**. The above-mentioned reaction was performed in toluene at room temperature or on heating, depending on the reactivity of the iminophosphorane **3** used. The results are summarized in Table 1. All phosphonodipeptides **6** thus formed were isolated in good overall yields (42–93%) and their structures were unequivocally confirmed by ^{31}P and ^{1}H NMR spectroscopy.

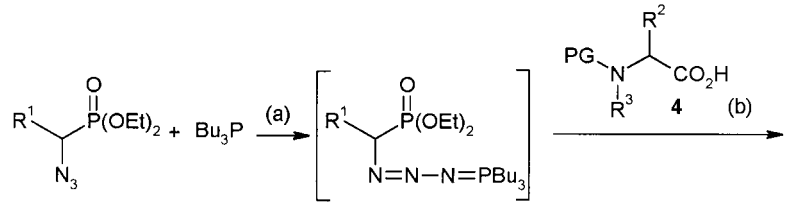
The coupling of **1** with **4** by means of tributylphosphine **2b** needs heating of the reaction mixture in toluene at 80–85°C or in reflux. The condensation of amino acids **4** by means of Bu_3P **2b** with the more hindered diethyl 1-azidoethylphosphonate **1b** requires heating of the reaction mixture in boiling toluene for completion (Table 1, entry 15 and 16). At the temperature 80–85°C the desired phosphonodipeptide **6ba** was also formed but with a lower yield (Table 1, entry 14). Triphenylphosphine is less reactive than Bu_3P (see footnote d and g to Table 1).

The replacement Bu_3P **2b** with Me_3P[23] **2a** enables the coupling at room temperature (Table 1, entry 11–13 and 17–19), however prolonged time is necessary for completing the reaction. The application of Me_3P eliminates the need for chromatography as the way of isolating the final product **6** since the by-product, trimethylphosphine oxide, can be simply washed away with water. The scope of the above mentioned synthesis can be easily broadened to the derivatives of *N*-methyl amino acids (Table 1, entry 10 and 16).

To compare the methodology proposed here with the existing methods[4] compounds **6ae** and **6ba** were additionally synthesized via the mixed anhydride method.[24] Thus, the mixed anhydride from *N*-(benzyloxycarbonyl)-(L)-phenylalanine and isobutyl chloroformate was coupled with diethyl azidomethyl- and 1-azidoethylphosphonate[25] to give the expected peptides **6ae** and **6ba** with 47 and 55% yield, respectively, (see footnote c and f to Table 1). The products resulting from these two methods were in all cases shown to be identical by their optical rotation values and ^{31}P and ^{1}H NMR spectroscopy.

The progress of the reactions shown in Scheme 1 can be easily monitored by ^{31}P NMR spectroscopy. Thus, after mixing the diethyl 1-azidoethylphosphonate[17] **1b** (δ_P=22.8 ppm) with Bu_3P **2b** (δ_P=−30.0 ppm) and the evolution of N_2 at room temperature, the signals of substrates disappeared and the new set of absorption of iminophosphorane **3** was observed at δ_P=28.05d and 30.55d ppm respectively with J=30.38 Hz. The signals of **3** vanished, after the addition of *N*-(benzyloxycarbonyl)-(L)-alanine and two new doublets of the salt **5** appeared at δ_P=24.68d and 58.16d ppm, respectively (J=8.1 Hz). Heating of the reaction mixture caused slow transformation of **5** into the final product **6ba** (δ_P=25.83 and 25.94 ppm) and tributylphosphine oxide (δ_P=49.2 ppm). Unfortunately no additional pentacovalent phosphorus intermediate was observed in ^{31}P NMR spectroscopy.[7,8,11,28]

On the other hand Inazu et al.[12,13] have suggested that the formation of the amide bond from glycosyl azide and N-protected amino acids by means of trialkylphosphine has occurred via the intermediate triazaphosphadiene[5b,c,15] instead of iminophosphorane at −78°C. Following this and other observations[15,28] we found that if the reaction between diethyl 1-azidoalkylphosphonates **1**, *N*-protected amino acids **4**, and tributylphosphine **2b** has been accomplished in toluene at −15°C to room temperature, the appropriate phosphonodipeptide **6** was formed in moderate yield, as depicted in Scheme 2. The results are summarized in Table 2.



	R^1	R^2	R^3	PG
6ae	H	Bn	H	Z
6af	H	$(CH_2)_2SMe$	H	Boc
6ba	Me	Me	H	Z

Scheme 2. Reagents and conditions: (a) Toluene, −15°C, 30 min; (b) Toluene, −15°C to room temperature, 24 h.

Table 2. Phosphonopeptides (**6ae**–**6ca**) obtained via the triazaphosphadiene approach

Entry	Compound	R^1	PG-Aa-OH	Reaction conditions (time, temp °C)	Yield (%)[a]	$[\alpha]_D$ (*c*) (MeOH)
1	**6ae**	H	*Z*-(L)-Phe-OH	24 h, room temperature	55	−10.14 (0.54)
2	**6af**	H	Boc-(D)-Met-OH	24 h, room temperature	52	+22.08 (1.0)
3	**6ba**	Me	*Z*-(L)-Ala-OH	24 h, room temperature	46	−15.83 (1.0)

[a] Yields of pure phosphonopeptides **6**, based on **1**.

It should be stressed that in this case, unlike the reactions described in Scheme 1, the formation of the amide bond with the participation of Bu_3P **2b** occurs at room temperature. According to the literature,[12,13] we assume that the generation of **6** would proceed via the intermediate triazaphosphadiene **7** as a result of the concerted evolution of nitrogen, intramolecular amide formation, and elimination of tributylphosphine oxide from **8** (Scheme 2).

Conclusions

In summary the protocol described here provides a new and simple access to phosphonodipeptides with N-terminal amino acids from readily accessible starting materials. The method is general and the coupling occurred with good yield. Several differentially *N*-protected amino acids were used without the necessity of activation of the carboxyl group. The reaction can be also extended to *N*-methyl derivatives of amino acids. Generally coupling is not very sensitive to steric hindrance on the α-substituent of the amino acid moiety, and the presence of an alkyl group on the α-carbon of the azidophosphonate has insignificant influence on the yields of condensation. Depending on the phosphine used and/or mechanism operating during the condensation, reaction can be conducted at room temperature or at elevated temperature. Additionally the application of the trimethylphosphine allows elimination of chromatography as a method of isolation of final products.

Experimental

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^1H and 101.3 MHz for ^{13}P NMR, respectively, in $CDCl_3$ solution, using tetramethylsilane as internal and 85% H_3PO_4 as ext. standard, respectively. Positive chemical shifts are downfield from ext. 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) Modell 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}). Optical rotations were measured in 1 dm cell on a Horiba polarimeter. Flash chromatography was performed with glass column packed with Baker silica gel (30–60 μm). Eluents: CH_2Cl_2/MeOH 90/10 (A); Acetone/MeOH 30/1 (B); AcOEt/MeOH 30/1 (C); AcOEt/MeOH 15/1 (D); Acetone/hexanes 10/1 (E); CH_2Cl_2/MeOH 95/5 (F); Acetone (G). 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,[17] (**1**) were prepared according to the literature procedure.

Preparation of phosphonopeptides (6aa–6bd) via the iminophosphorane route—general procedure

Reaction with tributylphosphine. Bu_3P (**2b**) (0.0021 mol, 0.425 g) was added in one portion to a cooled (ice-water bath) solution of the diethyl 1-azidoalkylphosphonate (**1**) (0.002 mol) in anhydrous toluene (5 mL). Vigorous evolution of the nitrogen took place. The water bath was removed and the solution was stirred for 1.5 h at room temperature. Then the *N*-protected amino acid (**4**) (0.0021 mol) was added in one portion. The solution was heated at 80–85°C or under reflux for the time given (see Table 1 for details). The resulting mixture was evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (25 mL), washed successively with H_2O (5 mL), 5%HCl aq. (5 mL), H_2O (5 mL), 5% $NaHCO_3$ aq. (2×5 mL), and H_2O (5 mL). Organic layer was dried over anhydrous Na_2SO_4, and the residue was subjected to flash chromatography to give pure phosphonodipeptide (**6**) (Table 1) as a yellow oil or colorless solid.

Reaction with trimethylphosphine. Me_3P (**2a**) (0.004 mol, 1 M solution in toluene) was slowly added via syringe to a cooled (ice-water bath) solution of the diethyl 1-azidoalkylphosphonate (**1**) (0.003 mol) in anhydrous toluene (5 mL). The vigorous evolution of the nitrogen took place. The water bath was removed and the solution was stirred for 1 h at room temperature. Then the *N*-protected amino acid (**4**) (0.0036 mol) was added in one portion, and the solution was stirred at room temperature for the time given (see Table 1 for details). The excess of Me_3P was removed under reduced pressure. The residue was diluted with toluene (100 mL), washed successively with H_2O (2 mL), 5% HCl aq. (2 mL), H_2O (2 mL), 5% $NaHCO_3$ aq. (2×2 mL), H_2O (2 mL), and dried over anhydrous Na_2SO_4. Toluene was evaporated and the rest of volatile material was removed at 40°C/0.04 Torr to give pure phosphonodipeptides (**6**) (Table 1).

Preparation of phosphonopeptides (6ae–6ca) via the triazaphosphadiene route—general procedure

Bu_3P (**2b**) (0.0022 mol, 0.445 g) was slowly added (10 min) to a cooled to −15°C solution of the diethyl 1-azidoalkylphosphonate (**1**) (0.002 mol), and the *N*-protected amino acid (**4**) (0.0022 mol) in anhydrous toluene (5 mL). The resulting solution was kept for 15 min at this temperature and the mixture was stirred for 24 h at room temperature (see Table 2 for details). The solution was diluted with CH_2Cl_2 (25 mL), washed successively with H_2O (5 mL),

5% HCl aq. (5 mL), H_2O (5 mL), 5% $NaHCO_3$ aq. (2×5 mL), and H_2O (5 mL). Organic layer was dried over anhydrous Na_2SO_4, and the residue was subjected to flash chromatography to give pure phosphonodipeptides (**6ae**–**6ba**) (Table 2).

Diethyl (*N*-benzyloxycarbonyl-glycyl)aminomethylphosphonate[29] (6aa). Yield: 58%, colorless oil; R_f=0.50 (A); ^{1}H NMR: δ=1.31 (t, J=7.25 Hz, 6H, $2CH_3$), 3.70 (dd, J=5.75, 12.0 Hz, 2H, CH_2), 3.92 (d, J=5.25 Hz, 2H, CH_2), 4.11 (qu, J=7.25 Hz, 4H, $2CH_2$), 5.12 (s, 2H, CH_2), 5.69 (bs, 1H, NH), 6.88 (bs, 1H, NH), 7.28–7.36 (m, $5H_{arom}$); ^{31}P NMR: δ=22.85; IR (film): ν=3264, 1720, 1700, 1600, 1532, 1456, 1392, 1248, 1160, 1024, 976, 740, 700; FAB/MS *m*/*z* (%): 359 (59); Anal. Calcd for $C_{15}H_{23}N_2O_6P$ (358.33): C; 50.28; H: 6.47; N: 7.82. Found: C; 50.09; H: 6.31; N: 7.70.

Diethyl (*N*-*t*-butyloxycarbonyl-L-alanyl)aminomethylphosphonate[30] (6ab). Yield: 63%, colorless oil; R_f=0.58 (B); ^{1}H NMR: δ=1.33 (t, J=7.0 Hz, 6H, $2CH_3$), 1.37 (d, J=5.25 Hz, 3H, CH_3), 1.45 (s, 9H, $3CH_3$), 3.71 (dd, J=6.25, 12.25 Hz, CH_2), 4.14 (q, J=7.0 Hz, 4H, 2 CH_2), 4.16–4.23 (m, 1H, CH), 4.98 (d, J=6.75 Hz, 1H, NH), 6.62 (bs, 1H, NH); ^{31}P NMR: δ=22.99; IR (neat): ν=3296, 2984, 1712, 1696, 1528, 1448, 1368, 1248, 1192, 1024, 976; FAB/MS *m*/*z* (%): 339 (72); Anal. Calcd for $C_{13}H_{27}N_2O_6P$ (338.34): C; 46.15; H: 8.04; N: 8.28. Found: C; 46.02; H: 7.90; N: 8.01.

Diethyl (*N*-benzyloxycarbonyl-L-alanyl)aminomethylphosphonate[31] (6ac). Yield: 92%, colorless needles, mp 69–70°C, (lit.[31] mp 72–74°C); R_f=0.27 (C); ^{1}H NMR: δ=1.31 (t, J=7.0 Hz, 6H, $2CH_3$), 1.39 (d, J=7.25 Hz, 3H, CH_3), 3.69 (dd, J=5.75, 12.0 Hz, CH_2), 4.05–4.17 (m, 4H, $2CH_2$), 4.30 (bqu, J=7.25 Hz, 1H, CH), 5.08 (part A of the AB system, J=12.0 Hz, 1H, CH), 5.12 (part B of the AB system, J=12.0 Hz, 1H, CH), 5.51 (bd, J=8.25 Hz, 1H, NH), 6.82 (bs, 1H, NH), 7.31–7.37 (m, $5H_{arom}$); ^{31}P NMR: δ=22.89; IR (film): ν=3264, 3064, 2984, 1720, 1700, 1672, 1528, 1452, 1252, 1160, 1024, 976, 776, 696; FAB/MS *m*/*z* (%): 373 (54); Anal. Calcd for $C_{16}H_{25}N_2O_6P$ (372.35): C; 51.61; H: 6.77; N: 7.52. Found: C; 51.50; H: 6.66; N: 7.33.

Diethyl (*N*-benzyloxycarbonyl-L-valyl)aminomethylphosphonate (6ad). Yield: 76%, colorless needles, mp 96–98°C; R_f=0.37 (C); ^{1}H NMR: δ=0.92 (d, J=7.0 Hz, 3H, CH_3), 0.97 (d, J=7.0 Hz, 3H, CH_3), 1.30 (t, J=7.0 Hz, 6H, $2CH_3$), 2.03–2.25 (m, 1H, CH), 3.60–3.84 (m, 2H, CH_2), 4.05–4.21 (m, 5H, $2CH_2$, CH), 5.10 (bs, 2H, CH_2), 5.52 (bd, J=8.75 Hz, 1H, NH), 6.78 (bs, 1H, NH), 7.33–7.40 (m, $5H_{arom}$); ^{31}P NMR: δ=22.85; IR (film): ν=3280, 2960, 1720, 1700, 1536, 1388, 1232, 1144, 1024, 968, 744, 700; FAB/MS *m*/*z* (%): 401 (55); Anal. Calcd for $C_{18}H_{29}N_2O_6P$ (400.41): C; 53.99; H: 7.30; N: 7.00. Found: C; 53.90; H: 7.21; N: 6.89.

Diethyl (*N*-benzyloxycarbonyl-L-phenylalanyl)aminomethylphosphonate[26] (6ae). Yield: 67%, pale yellow needles, mp 100–102°C; (lit.[26] mp 102–104°C); R_f=0.38 (C); ^{1}H NMR: δ=1.27, 1.28 (2t, J=7.1 Hz, 6H, $2CH_3$), 2.99–3.15 (m, 2H, CH_2), 3.56 (ddd, J=5.6, 12.1, 15.8 Hz, 1H, CH), 3.70 (ddd, J=6.3, 12.5, 15.8 Hz, 1H, CH), 4.00–4.14 (m, 4H, $2CH_2$), 4.48 (bq, J=7.0 Hz, 1H, CH), 5.04 (part A of the AB system, J=12.25 Hz, 1H, CH), 5.07 (part B of the AB system, J=12.25 Hz, 1H, CH), 5.44 (bd, J=8.0 Hz, 1H, NH), 6.47–6.53 (m, 1H, NH), 7.15–7.40 (m, $10H_{arom}$); ^{31}P NMR: δ=22.58; IR (film): ν=3264, 3064, 2984, 1720, 1698, 1668, 1536, 1456, 1252, 1028, 760, 704; FAB/MS *m*/*z* (%): 449 (55); Anal. Calcd for $C_{22}H_{29}N_2O_6P$ (448.45): C; 58.92; H: 6.52; N: 6.25. Found: C; 58.89; H: 6.44; N: 6.14.

Diethyl (*N*-*t*-butyloxycarbonyl-D-methionyl)aminomethylphosphonate (6af). Yield: 97%, colorless needles, mp 79–81°C; R_f=0.30 (C); ^{1}H NMR: δ=1.33, 1.34 (2t, J=7.0 Hz, 6H, $2CH_3$), 1.45 (s, 9H, $3CH_3$), 1.82–2.20 (m, 2H, CH_2), 2.11 (s, 3H, CH_3), 2.55–2.62 (m, 2H, CH_2), 3.63–3.85 (m, 2H, CH_2), 4.07–4.20 (m, 4H, $2CH_2$), 4.25–4.35 (m, 1H, CH), 5.16–5.22 (m, 1H, NH) 6.60 (bs, 1H, NH); ^{31}P NMR: δ=22.76; IR (film): ν=3272, 3080, 2976, 1712, 1660, 1556, 1528, 1392, 1248, 1204, 1168, 1024, 784; FAB/MS *m*/*z* (%): 399 (18); Anal. Calcd for $C_{15}H_{31}N_2O_6PS$ (398.46): C; 45.21; H: 7.84; N: 7.03. Found: C; 45.10; H: 7.71; N: 6.90.

Diethyl [*N*,*N*-bis(benzyloxycarbonyl)-L-lysyl]aminomethylphosphonate (6ag). Yield: 68%, colorless flakes, mp 110–112°C; R_f=0.68 (E); ^{1}H NMR: δ=1.28, 1.29 (2t, J=7.1 Hz, 6H, $2CH_3$), 1.33–1.45 (m, 2H, CH_2), 1.45–1.56 (m, 2H, CH_2), 1.61–1.74 (m, 2H, CH_2), 1.75–1.91 (m, 2H, CH_2), 3.16–3.25 (m, 2H, CH_2), 3.60–3.80 (m, 2H, CH_2), 4.03–4.15 (m, 4H, $2CH_2$), 4.15–4.25 (m, 1H, CH), 4.96–5.07 (m, 1H, NH), 5.05–5.15 (m, 4H, $2CH_2$), 5.55–5.61 (m, 1H, NH), 6.69 (bs, 1H, NH), 7.30–7.40 (m, $10H_{arom}$); ^{31}P NMR: δ=22.32; IR (CCl_4): ν=3304, 3072, 2920, 1716, 1652, 1456, 1280, 1244, 1196, 1104, 1056, 1044, 1024, 944, 760, 704; FAB/MS *m*/*z* (%): 564 (24); Anal. Calcd for $C_{27}H_{38}N_3O_8P$ (563.58): C; 57.54; H: 6.79; N: 7.45. Found: C; 57.41; H: 6.62; N: 7.33.

Diethyl (*N*-*t*-butyloxycarbonyl-L-tryptyl)aminomethylphosphonate (6ah). Yield: 73%, colorless solid, mp 80–85°C; R_f=0.38 (C); ^{1}H NMR: δ=1.26 (t, J=7.25 Hz, 6H, $2CH_3$), 1.41 (s, 9H, $3CH_3$), 3.15–3.34 (m, 2H, CH_2), 3.58 (dd, J=6.0, 12.0 Hz, 2H, CH_2), 3.95–4.20 (m, 4H, $2CH_2$), 4.40–4.50 (m, 1H, NH), 5.02–5.12 (m, 1H, NH), 6.15–6.22 (m, 1H, NH), 7.06–7.23 (m, $2H_{arom}$), 7.36 (bd, J=7.75 Hz, $1H_{arom}$), 7.64 (bd, J=7.75 Hz, $1H_{arom}$), 8.19 (bs, $1H_{arom}$); ^{31}P NMR: δ=22.76; IR (CCl_4): ν=3320, 3064, 2984, 1768, 1676, 1496, 1392, 1248, 1168, 1024, 996; FAB/MS *m*/*z* (%): 454 (5); Anal. Calcd for $C_{21}H_{32}N_3O_6P$ (453.47): C; 55.62; H: 7.11; N: 9.27. Found: C; 55.51; H: 7.00; N: 9.16.

Diethyl (*N*-benzyloxycarbonyl-L-prolyl)aminomethylphosphonate (6ai). Yield: 93%, colorless oil; R_f=0.41 (F); ^{1}H NMR: δ=1.31 (bt, J=7.0 Hz, 6H, $2CH_3$), 1.74–2.05 (m, 4H, $2CH_2$), 3.40–3.62 (m, 2H, CH_2), 3.70 (dd, J=6.0, 12.0 Hz, 2H, CH_2), 4.05–4.18 (m, 4H, $2CH_2$), 4.35–4.43 (m, 1H, CH), 5.14 (part A of the AB system, J=13.25 Hz, 1H, CH), 5.17 (part B of the AB system, J=13.25 Hz, 1H, CH), 6.25–6.40 (m, 1H, NH), 7.15–7.45 (m, $5H_{arom}$); ^{31}P NMR: δ=23.10; IR (film): ν=3272, 3064, 2984, 1708, 1680, 1536, 1416, 1356, 1216, 1192, 1168, 1120, 1028, 976, 768, 696; FAB/MS *m*/*z* (%): 399 (72); Anal. Calcd for $C_{18}H_{27}N_2O_6P$ (398.39): C; 54.27; H: 6.83; N: 7.03. Found: C; 54.11; H: 6.71; N: 6.96.

Diethyl (*N*-*t*-butyloxycarbonyl-*N*-methyl-D-valyl)aminomethylphosphonate (6aj). Yield: 63%, colorless oil; R_f=0.55 (C); ^{1}H NMR: δ=0.87, 0.94 (2d, J=6.50 Hz, 6H, $2CH_3$), 1.32 (t, J=7.25 Hz, 6H, $2CH_3$), 1.48 (s, 9H, $3CH_3$), 2.21–2.36 (m, 1H, CH), 2.80 (s, 3H, CH_3), 3.69 (dd, J=5.75, 11.50 Hz, 2H, CH_2), 4.13 (bqu, J=7.25 Hz, 4H, $2CH_2$), 6.46 (bs, 1H, NH); ^{31}P NMR: δ=23.05; IR (film): ν=3264, 2976, 1680, 1552, 1480, 1444, 1392, 1368, 1336, 1252, 1156, 1028; 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: 8.64; N: 7.27.

Diethyl 1-(*N*-benzyloxycarbonyl-L-alanyl)aminoethylphosphonate[27] (6ba). Yield: 42%, colorless oil; R_f=0.48 (C); (the 1:1 mixture of diastereomers); ^{1}H NMR: δ=1.25–1.35 (m, 9H, $3CH_3$), 1.38, 1.39 (2d, J=7.00 Hz, 3H, CH_3), 4.00–4.20 (m, 4H, $2CH_2$), 4.21–4.33 (m, 1H, CH), 4.37–4.60 (m, 1H, CH), 5.11 (s, 2H, CH_2), 5.29–5.32 (m, 1H, NH), 6.28–6.32, 6.45–6.52 (2m, 1H, NH), 7.33–7.40 (m, $5H_{arom}$); ^{31}P NMR: δ=25.83, 25.94 (1:1); IR (film): ν=3272, 3064, 2984, 1720, 1696, 1680, 1532, 1448, 1244, 1024, 972, 748, 696; FAB/MS *m*/*z* (%): 387 (26); Anal. Calcd for $C_{17}H_{27}N_2O_6P$ (386.38): C; 52.54; H: 7.04; N: 7.25. Found: C; 52.38; H: 6.90; N: 7.03.

Diethyl 1-(*N*-benzyloxycarbonyl-L-prolyl)aminoethylphosphonate[24] (6bb). Yield: 63%, pale yellow oil; R_f=0.56 (G); (the mixture of diastereomers); ^{1}H NMR: δ=1.12–1.31 (m, 9H, $3CH_3$), 1.85–2.25 (m, 4H, $2CH_2$), 3.40–3.60 (m, 2H, CH_2), 4.05–4.20 (m, 4H, $2CH_2$), 4.25–4.52 (m, 2H, $2CH_2$), 5.05–5.25 (m, 2H, CH_2), 6.10–6.20, 6.75–6.90 (m, 1H, NH), 7.20–7.30 (m, $5H_{arom}$); ^{31}P NMR: δ=25.99 (bs); IR (CCl_4): ν=3264, 2984, 1708, 1690, 1416, 1236, 1120, 1028, 968, 788; FAB/MS *m*/*z* (%): 413 (19); Anal. Calcd for $C_{19}H_{29}N_2O_6P$ (412.42): C; 55.33; H: 7.09; N: 6.79. Found: C; 55.23; H: 7.00; N: 6.62.

Diethyl 1-(*N*-*t*-butyloxycarbonyl-*N*-methyl-D,L-alanyl)-aminoethylphosphonate (6bc). Yield: 62%, colorless prisms, mp 113–115°C; R_f=0.53 (C); (the mixture of diastereomers); ^{1}H NMR: δ=0.79, 0.82, 0.87 (3d, J=6.5 Hz, 6H, $2CH_3$), 1.23, 1.24 (2t, J=7.0 Hz, 6H, $2CH_3$), 1.30 (dd, J=16.75, 7.5 Hz, 3H, CH_3), 1.41 (bs, 9H, $3CH_3$), 3.95–4.13 (m, 5H, $2CH_2$, CH), 4.30–4.51 (m, 1H, CH), 6.29–6.34 (m, 1H, NH); ^{31}P NMR: δ=25.98 (bs); IR (CCl_4) ν=3248, 2976, 1700, 1672, 1540, 1444, 1392, 1368, 1240, 1156, 1028, 968; FAB/MS *m*/*z* (%): 395 (68); Anal. Calcd for $C_{17}H_{35}N_2O_6P$ (394.44): C; 51.76; H: 8.94; N: 7.10. Found: C; 51.66; H: 8.83; N: 6.97.

Diethyl 1-(*N*-benzyloxycarbonyl-L-phenylalanyl)aminoethylphosphonate[30,31] (6bd). Yield: 67%, pale yellow oil; R_f=0.46 (C); (the 1:1.1 mixture of diastereomers); ^{1}H NMR: δ=1.15 (dd, J=7.25, 16.78 Hz, 3H, CH_3), 1.21–1.36 (m, 6H, $2CH_3$), 2.95–3.15 (m, 2H, CH_2), 3.90–4.15 (m, 4H, $2CH_2$), 4.30–4.55 (m, 2H, 2CH), 4.98–5.15 (m, 2H, CH_2), 5.40, 5.56 (2bd, J=8.25 Hz, 1H, NH), 6.34, 6.60 (2bd, J=8.25 Hz, 1H, NH), 7.15–7.40 (m, $10H_{arom}$); ^{31}P NMR: δ=25.53, 25.66 (1:1.1); IR (film) ν=3264, 3064, 2984, 1724, 1696, 1660, 1536, 1452, 1392, 1248, 1160, 1052, 972, 748, 700; FAB/MS *m*/*z* (%): 463 (32); Anal. Calcd for $C_{23}H_{31}N_2O_6P$ (462.48): C; 59.73; H: 6.76; N: 6.06. Found: C; 59.60; H: 6.63; N: 5.91.

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