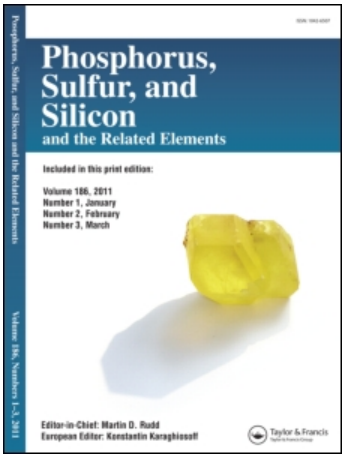

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SYNTHESIS OF PHOSPHONOPEPTIDES CONTAINING 1-AMINOALKYLPHOSPHONIC ACID

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SYNTHESIS OF PHOSPHONOPEPTIDES CONTAINING 1-AMINOALKYLPHOSPHONIC ACID

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Four phosphonodipeptides containing 1-aminoalkylphosphonate were synthesized by applying four different coupling methods. One of them was then converted into monoacid, ethyl hydrogen 1-(N-acetyl-prolyl)amino-2-phenylethyl phosphonate. Three phosphonodipeptides containing ethyl 1-amino-2-phenylethylphosphonamidate were also prepared by converting phosphono monoacid into phosphonochloridate and reacting it with amino acid ester. Benzyl ethoxyphosphonyl-glycyl-glycine ethyl ester also was synthesized from ethyl glycylglycinate and ethyl benzylphosphonochloridate derived from direct chlorination of diethyl benzylphosphonate with phosphorus oxychloride.

Keywords: 1-Aminoalkylphosphonic acid; Phosphonamidate peptide; 1 -Aminophosphonate peptide

The concept of transition state analogues is a successful one for the design of potent enzyme inhibitors[1,2]. Transition state analogue inhibitors seek to make advantage of the binding interactions between an enzyme and the substrate by incorporating key structural elements of the unstable transition state form of the substrate in the stable structure of the inhibitor. The phosphorus analogues of peptides are one of the important stable structure of the inhibitor[2,3,4].

Replacement of the carboxy group in amino acids by the phosphono group leads to phosphorus analogues of amino acids possessing inhibitory or substrate activity against certain enzymes, such as carboxypetidase A[3], angiotensin-converting enzyme[4], zinc peptidase thermolysin[2] and so on[5].

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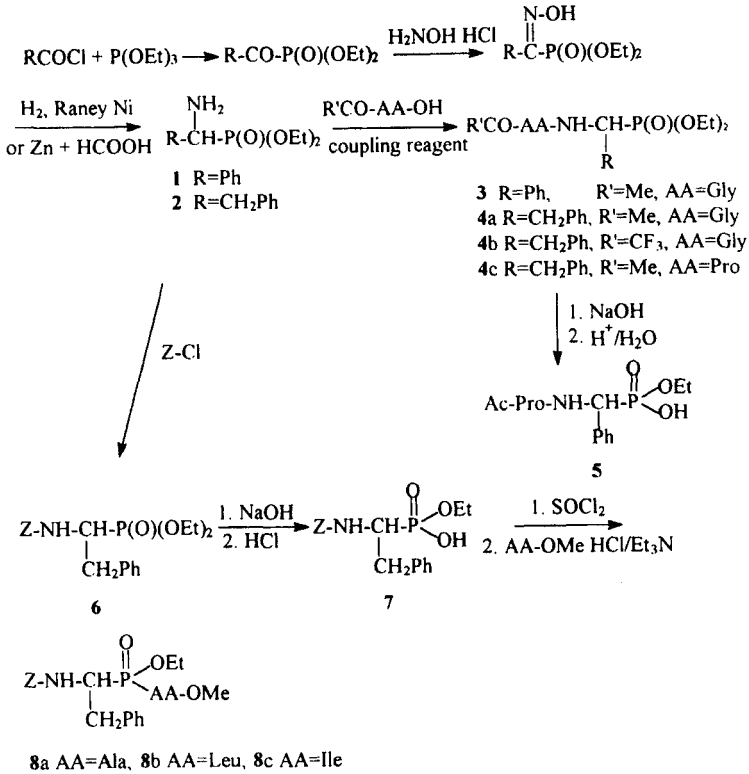
According to a literature method[6,7], benzoyl chloride reacted with diethyl phosphite to give triethyl benzoylphosphonate. It was converted into diethyl 1-amino-1-phenylmethylphosphonate **1** by reacting it with hydroxyamine hydrochloride and reducing the oxime with hydrogen using Raney nickel as a catalyst[7,8]. The reaction of diethyl 1-amino- 1-phenylmethylphosphonate and acetylglycine produced diethyl N-acetylglycylamino-1 -phenylmethylphosphonate **3** with the mixed carbonic anhydride method using ethyl chloroformate[9].

Diethyl 1-amino-2-phenylethylphosphonate **2** was synthesized by using the above method. However, reduction with dilute hydrochloride-washed zinc powder and formic acid[10] is a better method than the hydrogenation using Raney nickel as a catalyst. Diethyl 1-amino-2-phenylethylphosphonate reacted with acetylglycine to yield 1-(N-acetylglycyl)amino-2-phenylethylphosphonate diethyl ester **4a** in yields 61%, 75%, and 78% with the mixed carbonic anhydride method, DPPA (diphenylphosphoryl azide)[11]or DEPBT [3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3)-one][12] as coupling reagents, respectively. Another two phosphodipeptides, diethyl 1-(N-trifluoro-acetylglycyl)amino-2-phenylethylphosphonate **4b** and diethyl 1-(N-acetylprolyl)amino-2-phenylethyl-phosphonate **4c** also were synthesized by DPPA[11] and DCC[13] as coupling reagents, respectively. Diethyl 1-(N-acetylprolyl)amino-2-phenylethylphosphonate then was selectively hydrolyzed to obtain the monoacid[5], ethyl hydrogen 1-(N-acetylprolyl)amino-2-phenylethylphosphonate **5.**

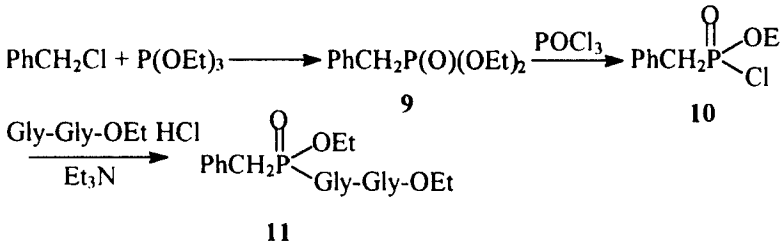
The phosphonamidate peptide is a kind of a stable mimic of the transition state analogues of the enzyme inhibitor. Recently we have synthesized some phosphonamidate peptides containing ethyl 1-amino-2-phenylethylphosphonamidate. At first, diethyl 1-benzyloxycarbonylamino-2-phenylethylphosphonate **6** was prepared from diethyl 1-amino-2-phenylethylphosphonate **2** and benzyl chloroformate for protecting the amino group. And then it was converted into monoacid, ethyl hydrogen 1-benzyloxycarbonylamino-2-phenylethylphosphonate **7** by the selective base hydrolysis with two mol/L aqueous sodiun hydroxide[5]. The monoacid **7** was then converted to phosphonochloridate by applying the standard thionyl chloride procedure[5]. This was then caused to react with amino acid methyl ester hydrochlorides in the presence of triethylamine to yield ethyl N-(1-benzyloxycarbonylamino-2-phenylethylphosphono)amino acid methyl ester **8,** phosphonamidate peptide.



SCHEME 1

An alkylphosphonate, diethyl benzylphosphonate **9** also was synthesized by the reaction of diethyl phosphite with benzyl chloride[14]. It was then converted directly into ethyl benzylphosphonochloridate **10** with phosphorus oxychloride[15] and caused to react with ethyl glycylglycinate hydrochloride in the presence of triethylamine to give (1-phenylmethyl)ethoxyphosphonyl-glycyl-glycine ethyl ester **11.**

All products were characteristized by IR, ^{1}HNMR, ^{31}PNMR MS spectrometries and elemental analysis. In most cases in the ^{1}HNMR, the two CH_3CH_2 groups in the ethoxy groups of compounds **3** and **4** were magnetically nonequivalent. Every CH_3 group was split into a triplet and every CH_2 group was split into quartet but with different chemical shift.



SCHEME 2

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and uncorrected. Elemental analyses were carried out on a Perkin-Elmer 240C analyzer. The ^{1}HNMR spectra were recorded on a Varian mercury 200 or Brucker ARX400 spectrometers with TMS as an internal standard in $CDCl_3$. ^{31}PNMR spectra were obtained on a Varian mercury 200 at 81 MHz and the chemical shifts values are referenced to 85% H_3PO_4 with negative shifts upfield. The IR spectra were taken on a Nicolet 5MX-S spectrometer in KBr. Mass spectra were obtained on a VG ZAB-HS mass spectrometer.

Synthesis of phosphonopeptides containing diethyl 1-amino-alkylphosphonate 3 and 4 Synthesis of diethyl 1-(N-acctyl-glycyl)amino-1-phenylmethyl phosphonate 3

Method A, mixed carbonic anhydride method

0.42 g (3.6 mmol) Of N-acetyl-glycine was dissolved in 10 mL of THF and the solution was cooled to −5 to −10°C. 0.39 g (3.6 mmol) Of ethyl chloroformate was added to the stirred solution. After 15 mins, 0.37 g (3.6 mmol) of triethylamine was added dropwise and the reaction mixture was stirred for 30 mins. A solution of 1.0 g (3.6 mmol) diethyl 1-amino-1-phenyl-methylphosphate hydrochloride and 0.37 g (3.6 mmol) triethylamine in 10 mL of DMF was added dropwise at −5 to −10°C. After removing the cooling bath, the reaction mixture was stirred overnight. After vaporization of the solvent, the residue was dissolved in ethyl ace-

tate, washed with saturated aqueous Na_2CO_3, 1 mol/L citric acid, saturated aqueous NaCl and dried over anhydrous sodium sulfate. A yellow oily residue was obtained after removal of the solvent. It was recrystallized from a mixture of ethyl acetate and petroleum ether to give a white powder 0.86 g with a yield of 70%, mp 158–160°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.11(t, CH_3, 3H, J = 7 Hz), 1.33 (t, CH_3, 3H, J = 7 Hz). 2.01 (s, MeCO, 3H), 3.71–3.73 & 3.92–3.94 (m & m, CH_2, 2H), 3.94–4.01 (q, CH_2O, 2H, J = 7 Hz), 4.12–4.17 (q, CH_2O, 2H, J = 7 Hz), 5.50 (2 × d, CH, 1H, J = 21 Hz), 6.40 (s, NH, 1H), 7.31–7.46 (m, ArH, 5H), 7.97 (br, NH, 1H). ^{31}P NMR ($CDCl_3$) δ (ppm): 23.91. IR (KBr) υ (cm^{-1}) 3450, 3090, 1665, 1660, 1258, 1016, 700. MS/FAB m/z: 343 (M^++H). Anal. Calcd for $C_{15}H_{23}N_2O_5P$ (342.33): C, 52.63; H, 6.77: N. 8.18. Found: C, 52.48; H, 6.88; N, 7.99.

Synthesis of diethyl 1-(N-acetyl-glycyl)amino-2-phenylethyl phosphonate 4a

Method A, mixed carbonic anhydride method

Colorless crystal, yield 61%, mp 130–131°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.27–1.39 (2 × t, $2CH_3$, 6H), 1.98 (s, MeCO, 3H), 2.85–2.89 & 3.20–3.26 (m & m, CH_2, 2H), 3.79–3.81 (dd, CH_2Ph, 2H). 4.09–4.19 (2 × q, $2CH_2O$, 4H), 4.68–4.72 (m, CH, 1H), 6.28 (br, NH. 1H), 6.88 (d, NH, 1H, J = 9.8 Hz), 7.20–7.29 (m, ArH, 5H). ^{31}P NMR ($CDCl_3$) δ (ppm): 23.89, IR (KBr) υ (cm^{-1}) 3452, 3091, 1675, 1660, 1260, 1018, 700. MS/FAB m/z 357 (M^++H), 256 (M^+-$AcNHCH_2CO$). Anal. Calcd for $C_{16}H_{25}N_2O_5P$ (356.36): C, 53.93; H, 7.07; N, 7.86. Found: C, 53.60; H, 7.01; N, 7.67.

Method B, DEPBT as a coupling reagent

To a solution of 0.63 g (2.45 mmol) of diethyl 1-amino-2-phenylethyl phosphonate **2** and 0.316 g (2.69 mmol) of N-acetyl-glycine and 0.804 g (2.69 mmol) of DEPBT in 10 mL of DMF was added 0.272 g (2.69 mmol) of triethylamine and the mixture stirred at room temperature for 8 hrs. To the reaction mixture was added 30 mL of saturated aqueous NaCl, then extracted with three 30 mL portions of ethyl acetate. The combined organic layers were washed with 1 mol/L HCl, 5% aqueous Na_2CO_3, saturated aqueous NaCl and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized from a mixture of ethyl acetate and petroleum ether to give colorless crystals 0.68 g, yield 78%.

Method C, DPPA as a coupling reagent

To a solution of 0.388 g (1.5 mmol) of diethyl 1-amino-2-phenylethyl phosphonate **2,** 0.194 g (1.6 mmol) of N-acetyl-glycine, 0.44 g (1.6 mmol) of DPPA in 10 mL of DMF was added 0.162 g (1.6 mmol) of triethylamine and the mixture stirred at room temperature for 10 hrs, To the reaction mixture was added 30 mL of saturated aqueous NaCl, then extracted with three 30 mL portions of ethyl acetate. The combined organic layer, were washed with 1 mol/L HCl, 5% aqueous Na_2CO_3, saturated aqueous NaCl and dried over anhydrous sodium sulfate. After removal of solvent, the residue was recrystallized in a mixture of ethyl acetate and petroleum ether to give colorless crystals 0.40 g, yield 75%.

Synthesis of diethyl 1-(N-trifluoroacetyl-glycyl)amino-2-phenylethyl phosphonate 4b

Method C, DPPA as a coupling reagent

Colorless crystal, yield 80%, mp 122–124°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (t, CH_3, 3H, J = 7Hz), 1.37 (t, CH_3, 3H, J = 7 Hz), 2.82–2.93 & 3.00–3.25 (m & m, CH_2, 2H), 3.92 (ddd, CH_2Ph, 2H, J = 5, 17 Hz, $J_{P\text{-}H}$ = 72.3 Hz), 4.04–4.23 (m, CH_2O, 4H), 4.66–4.76 (m, CH, 1H), 7.20–7.30 (m, ArH. 5H), 7.38 (s, NH, 1H), 7.74 (d, NH, 1H, J = 9.6Hz). ^{31}P NMR ($CDCl_3$) δ (ppm): 23.87. IR (KBr) υ (cm^{-1}) 3449, 3090, 1665, 1659, 1258, 1020, 700. MS/FAB m/z: 411 (M^++H). Anal. Calcd for $C_{16}H_{22}F_3N_2O_5P$ (410.33): C, 46.83: H, 5.40; N, 6.83, Found: C, 46.67; H, 5.68; N, 7.09.

Synthesis of diethyl 1-(N-acetyl-L-prolyl)amino-2-phenylethyl phosphonate 4c

Method D, DCC as a coupling reagent

Colorless powder, yield 49%, mp 122–124°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.26–1.38 (2 × t, $2CH_3$, 6H), 1.54–2.17 (m, CH_2CH_2, 4H), 2.03 (s, MeCO, 3H). 2.85–3.26 (m, CH_2N & CH_2Ph, 4H), 3.98–4.17 (2 × q, $2CH_2O$, 4H), 4.61–4.70 (m, 2CH, 2H), 6.26 (br, NH, 1H), 6.87 (d, NH, 1H), 7.15–7.31 (m, ArH, 5H), ^{31}P NMR ($CDCl_3$) δ (ppm): 23.95. IR (KBr) υ (cm^{-1}) 3500, 3440, 3320, 3000, 1670, 1640, 1230, 1030. 700. MS/FAB m/z: 397

(M^++H). Anal. Calcd for $C_{19}H_{29}N_2O_5P$ (396.42): C, 57.57; H, 7.37; N, 7.07. Found: C, 57.48; H, 7.48; N, 7.26.

Synthesis of ethyl hydrogen 1-(N-acetyl-L-prolyl)amino-2-phenylethyl phosphonate 5

A solution of 1.5 g (3.79 mmol) of diethyl 1-(N-acetyl-prolyl)amino-2-phenylethyl phosphonate and 6 mL of 2 mol/L NaOH (11.7 mmol) in 8 mL of ethanol was stirred at room temperature for 2 days. The mixture was washed twice with diethyl ether, acidified with 6 mol/L HCl, and extracted with four 40 mL portions of dichloromethane. The combined dichloromethane layer was dried and evaporated, and the residue was crystallized from a mixture of chloroform and diethyl ether to give a colorless solid product 1.20 g, yield 86%, mp 140–142°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.23–1.40 (2 × t, CH_3, 3H), 1.56–2.18(m. CH_2CH_2, 4H), 2.08 (s, MeCO, 3H), 3.10–3.60 (m, CH_2N & CH_2Ph, 4H), 4.02–4.25 (m, 2CH, 2H), 3.98–4.23 (2 × q, CH_2O, 2H), 7.10–7.35 (m, ArH, 5H). ^{31}P NMR ($CDCl_3$) δ (ppm): 24.52. IR (KBr) υ (cm^{-1}) 3420, 3280, 3000, 1660, 1630, 1210, 1140, 700. MS/FAB m/z: 369 (M^++H). Anal. Calcd for $C_{17}H_{25}N_2O_5P$ (368.37): C, 55.43; H,6.84; N, 7.60. Found: C, 55.47; H, 6.88; N, 7.49.

Synthesis of phosphonopeptides containing phosphonamidate bond 8

Synthesis of N-[(1-benzyloxycarbonylamino-2-phenylethyl) ethoxyphosphonyl]-L-lecine methyl ester 8a

0.50 g (1.37 mmol) Of monoacid **7** was dissolved in 15 mL of anhydrous ethanol-free chloroform and then treated with 0.12 mL (1.64 mmol) of thionyl chloride at 25°C for 4 hrs under nitrogen. After evaporation of the volatile materials, the last traces of SO_2 and HCl were swept out of the residue by dilution with 10 mL of chloroform and reevaporization three times, the residue was dissolved with 0.30 g (1.64 mmol) of leucine methyl ester hydrochloride in 10 mL of dried ethanol-free chloroform, the solution was cooled to 0°C, and 0.57 mL (4.1 mmol) of triethylamine was added after 10 mins. After stirring at 25°C for 18 hrs, the solution was concentrated, the residue was dissolved in 20 mL of ethyl acetate and triethylamine hydrochloride was removed by filtration, After washing with brine,

drying over anhydrous sodium sulfate, and evaporating under reduced pressure on a rotary evaporator, the material was purified by silica gel chromatography with ethyl acetate as eluent to give a colorless solid product (diastereomeric mixture) 0.32 g, yield 47%, mp 107–110 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85–0.97 [2 × d, $(CH_3)_2$-, 6H], 1.20–1.33 (2 × t, CH_3, 3H), 1.40–1.70 (m, $CHCH_2$, 3H), 3.17–3.38 (m. CH_2Ph, 2H), 3.70 & 3.71 (2 × s, OCH_3, 3H). 3.95–4.20 (m, CH_2O & 2CH, 4H), 4.97 & 5.01 (2 × s, OCH_2Ph, 2H), 5.19 (br, NH, 1H), 7.15–7.41 (m, ArH, 10H), ^{31}P NMR ($CDCl_3$) δ (ppm): 27.39, 28.36. IR (KBr) υ (cm^{-1}) 3300, 3080, 3048, 2975, 1700, 1600, 1540, 1225, 1060, 1039, 700. MS/FAB m/z: 491(M^++H), 346(M^++H-LeuOMe). Anal. Calcd for $C_{25}H_{35}N_2O_6P$ (490.54): C, 61.21; H, 7.19; N, 5.71. Found: C, 61.16; H, 7.18; N, 5.43.

Synthesis of N-[(1-benzyloxycarbonylamino-2-phenylethyl) ethoxyphosphonyl]-L-isoleucine methyl ester 8b

Colorless solid product (diastereomeric mixture), yield 64%, mp 84–87 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.78–0.99 (m, $2CH_3$ in Ile, 3H), 1.11–1.37 (2 × t, CH_3, 3H), 1.39–1.82 (m, $CHCH_2$, 3H). 3.03–3.39 (m, CH_2Ph, 2H), 3.68 (s, OCH_3, 3H), 3.84–4.18 (m, CH_2O & CH, 3H), 4.18–4.42 (m, CH, 1H), 4.97 & 5.00 (2 × s, OCH_2Ph, 2H), 5.30 (br. NH, 1H), 5.49 (br, NH, 1H) 7.10–7.50 (m, ArH, 10H), ^{31}P NMR ($CDCl_3$) δ (ppm): 27.36, 28.33. IR (KBr) υ (cm^{-1}) 3300, 3080, 3050, 2970, 1690, 1600, 1540, 1224, 1072, 1030, 700. MS/FAB m/z: 491 (M^++H), 357 (M^++H-Z), 346 (M^++H-IleOMe). Anal. Calcd for $C_{25}H_{35}N_2O_6P$ (490.54): C, 61.21; H, 7.19; N, 5.71. Found: C, 61.62; H, 7.31; N, 5.53.

Synthesis of N-[(1-benzyloxycarbonylamino-2-phenylethyl) ethoxyphosphonyl]-L-alanine methyl ester 8c

Colorless solid product (diastereomeric mixture), yield 64%, mp 83–86 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.20–1.30 (2 × t, CH_3, 3H), 1.30–1.40 (2 × d, CH_3, 3H), 3.10–3.39 (m, CH_2Ph, 2H), 3.70 & 3.71 (2 × s, OCH_3, 3H), 3.98–4.18 (m, CH_2O & CH, 3H), 4.18–4.38 (m, CH, 1H), 4.97 & 4.99 (2 × S, OCH_2Ph, 2H), 5.37 (br, NH, 1H), 5.50 (br, NH, 1H), 7.15–7.41 (m, ArH, 10H), ^{31}P NMR ($CDCl_3$) δ (ppm): 27.44, 28.21. IR (KBr) υ (cm^{-1}) 3300, 3080, 3051, 2970, 1710, 1600, 1540, 1220, 1070, 1030, 700. MS/FAB m/z: 449 (M^++H). Anal. Calcd for $C_{22}H_{29}N_2O_6P$ (448.46): C, 58.92; H, 6.52; N, 6.25. Found: C, 59.03; H, 6.48; N, 6.49.

Synthesis of (1-phenylmethyl)ethoxyphosphonyl-glycyl-glycine ethyl ester 11

Synthesis of diethyl benzylphosphonate 9

Diethyl benzylphosphonate was synthesized according to literature method[14] bp 152–153°C/2 mmHg.

Synthesis of ethyl benzylphosphonochloridate 10

A mixture of 2.3 g (10 mmol) of diethyl benzylphosphonate **9** and 1.7 g (11 mmol) of freshly purified phosphorus oxychloride was heated under nitrogen atmosphere with magnetic stirring. The bath temperature must be carefully keeped at 60°C for 4 hrs. After excess of phosphorus oxychloride and ethoxyphosphorus dichloride had been removed under reduced pressure, 0.5 g of product was obtained at 80°C/0.5 mmHg, yield 20%. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.34 (t, CH_3, 3H, J = 7Hz), 3.50 & 3.56 (s & s, CH_2, 2H), 4.19–4.29 (m, CH_2O, 2H), 7.30–7.39 (m, ArH, 5H). MS m/z: 218 (M^+), 190 (M^+-CH_2 = CH_2), 91 ($PhCH_2^+$).

Synthesis of (1-phenylmethyl)ethoxyphosphonyl-glycyl-glycine ethyl ester 11

A solution of 0.4 g (1.8 mmol) of ethyl benzylphosphonochloridate **10** in 10 mL of dichloromethane was added dropwise into a solution of 0.4 g (2 mmol) of ethyl glycylglycinate hydrochloride and 0.35 mL (2.5 mmol) of triethylamine in 10 mL of dichloromethane. The mixture was stirred at room temperature for 10 hrs. After washing with 5% aqueous Na_2CO_3, water, 1 mol/L HCl, water, drying over anhydrous sodium sulfate, and evaporating under reduced pressure on a rotary evaporator, the residue was recrystallized with ethyl acetate to give a colorless product (diastereomeric mixture) 0.15 g, yield 24%, mp 83.5-86 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.26 (t, $2CH_3$, 6H, J = 7.2Hz). 3.13 & 3.18 (s & s, CH_2, 2H), 3.52 (d, CH_2, 2H, J= 9.9 Hz), 3.50–3.56 (br, NH, 1H), 3.92 (dd, CH_2, 2H, J = 5.9, 6.1 Hz), 3.98–4.08 (2 × q, CH_2O, 2H, J = 7.2Hz), 4.14–4.19 (q, CH_2O, 2H, J = 7.2Hz), 6.95–7.08 (br, NH, 1H), 7.22–7.29 (m, ArH, 5H), ^{31}P NMR ($CDCl_3$) δ (ppm): 31.03. IR (KBr) υ (cm^{-1}) 3008, 2945, 1700, 1600, 1540, 1225, 1060, 1039, 840, 700. MS/FAB m/z: 343 (M^++H), 240 (M^+-$NHCH_2CO_2Et$), 212 (M^+-$CONHCH_2CO_2Et$), 184, 91. Anal. Calcd

for $C_{15}H_{23}N_2O_5P$ (342.33): C, 52.63; H, 6.77; N, 8.18. Found: C, 52.37; H, 7.01; N, 8.43.

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