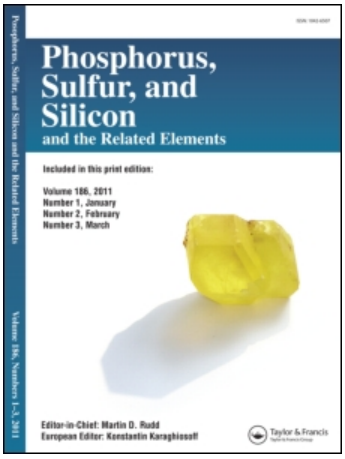

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 65, A FACILE SYNTHETIC ROUTE TO PHOSPHONOPEPTIDES

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 65, A FACILE SYNTHETIC ROUTE TO PHOSPHONOPEPTIDES

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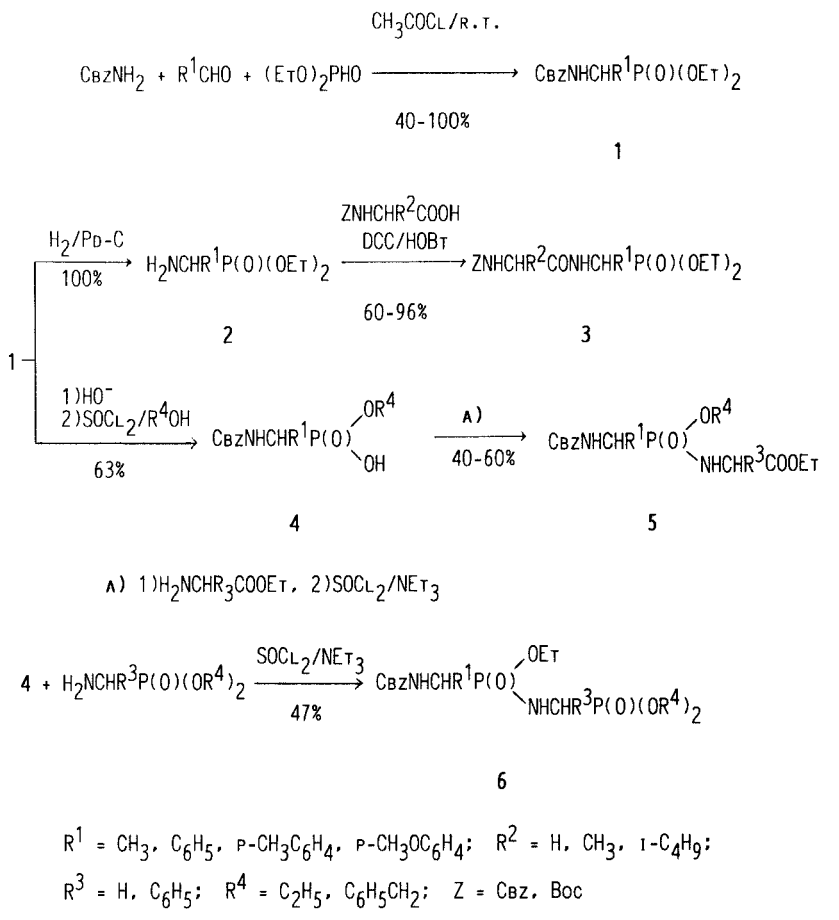
A direct procedure for the preparation of phosphonopeptides, containing either a N- or C-terminal phosphonic acid residue, is described. This method is based on a three component condensation reaction leading to diethyl 1-(N-carbobenzyloxylamino)-alkylphosphonate which is then coupled either with N-protected aminocarboxylic acid or aminocarboxylic ester or even with another molecule of aminophosphonic ester to form a phosphonopeptide with a N- or P-terminal peptide bond respectively.

Key words: Phosphonopeptide; aminophosphonic acid; tricomponent condensation reaction.

The attractive biological activities of phosphonopeptides[1–3] arouse the interest of synthetic phosphorus chemists in the exploration of new and convenient method for the preparation of this important class of compounds for structure-activity studies. As a building block, the aminophosphonic acid is the key intermediate in the synthesis of phosphonopeptides. Among numerous methods published in the literature for the synthesis of aminophosphonic acids, the three component condensation involving aldehyde, amide and trivalent phosphorus described by Mastalerz[4–6] is of great interest due to the easy availability of the starting material, mild reaction condition as well as the satisfactory yield and purity of the products. As a result of our systematic studies on this type of condensation reaction, a substantial improvement has been achieved and the scope of application of this reaction was thus expanded.[7–13] These results serve as the basis for the direct and convenient synthesis of phosphonopeptides. The classic and traditional methods for the formation of these peptides is a time consuming and tedious operation which involve multistep procedures including protection and deprotection of one of the functional groups of the amino phosphonic acid in addition to various coupling processes. Furthermore, as a dibasic acid, the phosphonic acid function is quite difficult to protect by direct esterification while O-alkylation of the carboxylic acid residue is easily achieved. It is fully understandable that development of a new direct and convenient method for the synthesis of phosphonopeptides is extremely important.

RESULTS AND DISCUSSIONS

In this paper, we wish to report a facile procedure for the preparation of phosphonopeptides. The method is based on a tricomponent condensation involving benzyl carbamate, aldehyde and diethyl phosphite, affording 1-(N-benzylcarbox-



SCHEME I

ylamino)-alkylphosphonates **1**, which upon catalytic hydrogenation using palladium on carbon as catalyst can be converted to 1-amino-substituted benzyl phosphonates **2** in almost quantitively yield. The latter was directly coupled, without isolation, with a protected aminocarboxylic acid using dicyclohexylcarbodimide(DCC) and N-hydroxybenzotriazole (HOBT) as condensation agent. This method gave phosphonopeptides **3**, containing a C-terminal aminophosphonic acid in moderate to excellent yield. On the other hand, the phosphonate group can be partially dealkylated providing the corresponding monoeseter **4** which can be condensed with ethyl amino carboxylate producing the phosphonopeptide **5** in satisfactory yield. Compound **4** can also be coupled with another molecule of aminophosphonate in the presence of thionyl chloride and triethylamine to form the phosphonopeptides **6** in which two molecules of aminophosphonic acid are bonded through a phosphonoamide linkage. Both, **5** and **6** are of particular interest since such compounds can be considered as excellent mimetics of the tetrahedral transition state of enzymetic peptide hydrolysis and consequently are potential inhibitors of proteases.[14]

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 400 spectrophotometer. ^1H and ^{31}P spectra were taken from a Varian EM-360A (60 MHz) or FX-90Q (90 MHz) spectrophotometer. Chemical shifts are in parts per million downfield from internal TMS (^1H) and external 85% H_3PO_4(^{31}P). The starting materials and solvent used were purified by standard procedure prior to use.

Synthesis of Phosphonopeptides of Type **3**, *General Procedure:* To a mixture of benzylcarbamate (0.75 g, 5 mmol), diethylphosphite (0.67 g, 5 mmol) and acetyl chloride (5 mL) was added aldehyde (6 mmol) in slight excess at 0°C. The reaction mixture was then stirred at ambient temperature for 6 h and the volatile components were removed under reduced pressure. The resulting solid residue was recrystallized from EtOH/H_2O; in case of an oily residue, it was purified by dissolving in CH_2Cl_2 (15 mL) and then washing successively with water (10 mL), sat. $NaHSO_3$ solution (2 × 15 mL), dil. $NaHCO_3$ solution (3 × 15 mL) and water (2 × 15 mL). Upon evaporation of the solvents, compounds **1** are usually obtained as crystalline solids, which can be used directly for the formation of phosphonopeptides. Thus, a mixture of **1** (2 mmol), 10% Pd on carbon (0.2 g) and methanol (10 mL) was hydrogenated at r.t. (15–25°C) under atmospheric pressure until the absorbtion of hydrogen ceased. The catalyst was filtered off and washed with methanol. The filtrate and methanolic washings were dried with $MgSO_4$ and evaporated to dryness. The resulting oily residue was dissolved inh anhydrous CH_2Cl_2 (5 mL) followed by addition of N-protected amino acid (2 mmol), HOBT (0.28 g, 2 mmol) and a solution of DCC (0.42 g, 2 mmol) in dried CH_2Cl_2 (5 mL) at 0°C. The reaction mixture was then allowed to warm to r.t. for 12. h. After that, ethyl acetate (20 mL) was slowly added with stirring and the precipitated dicyclohexylurea was filtered off. The filtrate was successively washed with 1N HCl (2 × 10 mL) water (10 mL), saturated solution of $NaHCO_3$ (2 × 10 mL) and water (3 × 10 mL), and then dried over Na_2SO_4 and evaporated under reduced pressure. Most of the reaction product **3** was obtained as a colorless solid after recrystallization from EtOAc/petroleum ether. The yield, mp and molecular formula are summarized in Table I.

3a. Calculated for $C_{16}H_{25}N_2O_2P$ (372.1) P 8.32; Found P 8.51. IR(KCl) ν = 1720, 1680, 1220, 1020 cm^{-1}. ^{1}HNMR(CCl_4) δ = 1.30 (m, 9H, $2CH_3CH_2$, CH_3CH), 3.80–4.80 (m, 7H, $2CH_2CH_3$, CH—P, CH_2CO), 5.10 (s, 2H, $PhCH_2$), 5.80–6.30 (br, 1H, CONH), 7.40 (s, 5H, H_{aryl}) ppm.

TABLE I
Compounds **3** Prepared

	Z	R^1	R	Yield (%)	mp (°C)	Lit. mp. or Molecular Formula
3a	Cbz	CH_3	H	81	oil	$C_{16}H_{25}N_2O_2P$(372.1)
3b	Cbz	C_6H_5	H	77	87-89	88-89[15]
3c	Cbz	p-$CH_3C_6H_4$	H	83	140-142	$C_{22}H_{29}N_2O_6P$(448.2)
3d	Cbz	p-$CH_3OC_6H_4$	H	91	129-131	$C_{22}H_{29}N_2O_7P$(464.2)
3e	Cbz	CH_3	CH_3	86	glassy gum[15]	
3f	BOC	C_6H_5	H	71	82-84	$C_{18}H_{29}N_2O_6P$(400.1)
3g	BOC	p-$CH_3C_6H_5$	H	85	125-127	$C_{19}H_{31}N_2O_6P$(414.2)
3h	BOC	p-$CH_3OC_6H_4$	H	76	121-123	$C_{19}H_{31}N_2O_7P$(430.2)
3i	BOC	CH_3	CH_3	78	glassy gum	$C_{14}H_{29}O_6N_2P$(352.1)
3j	BOC	CH_3	i-Bu	62	glassy gum	$C_{17}H_{35}N_2O_6P$(394.1)
3k	BOC	C_6H_5	i-Bu	52	49-52	$C_{22}H_{37}N_2O_6P$(456.2)
3l	BOC	p-$CH_3C_6H_4$	i-Bu	57	126-128	$C_{23}H_{39}N_2O_6P$(470.2)
3m	BOC	p-$CH_3OC_6H_4$	i-Bu	67	112-113	$C_{23}H_{39}N_2O_7P$(486.2)

3b. IR(KCl) ν = 1720, 1671, 1219, 1022 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 1.18 (m, 6H, $2CH_2CH_3$), 4.03 (m, 6H, $2CH_2CH_3$, NCH_2), 5.06 (s, 2H, $PhCH_2$), 5.65 (m, 1H, CH—P), 5.80–6.00 (CONH), 7.40 (s, 10H, H_{aryl}), 9.00–9.45 (br, 1H, CONH) ppm.

3c. Calculated for $C_{22}H_{29}N_2O_6P$ (448.2) C 58.83, H 6.47, N 6.24, P 6.89; Found C 58.74, H 6.14, N 6.56, P 6.73. IR(KCl) ν = 1717, 1687, 1228, 1075 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 1.15 (m, 6H, $2CH_2CH_3$), 2.30 (s, 3H, $ArCH_3$), 3.65–4.30 (m, 6H, $2CH_2CH_3$, NCH_2), 5.00 (s, 2H, $PhCH_2$), 5.75–6.00 (br, 1H, CONH), 7.00–7.50 (m, 9H, H_{aryl}), 9.00–9.30 (br, 1H, CONH) ppm. ^{31}P($CDCl_3$/TMS) δ = 21.46 ppm.

3d. Calculated for $C_{22}H_{29}N_2O_7P$ (464.2) C 56.80, H 6.24, N 6.02; Found C 57.02, H, 6.21, N, 6.40. IR(KCl) ν = 1726, 1675, 1220, 1121 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 0.95–1.05 (dt, 6H, J = 7 Hz, $2CH_2CH_3$), 3.75 (s, 3H, $ArOCH_3$), 3.70–4.20 (m, 6H, $2CH_2CH_2$, NCH_2), 5.03 (s, 2H, $PhCH_2$), 5.10–5.40 (m, 1H, CH—P), 5.65–5.95 (br, 1H, CONH), 6.72–7.05 (m, 9H, H_{aryl}), 8.08–8.30 (br, 1H, CONH) ppm. ^{31}P($CDCl_3$/TMS) δ = 21.31 ppm.

3e. IR(neat): ν = 1730, 1675, 1235, 1040 cm^{-1}. 1HNMR(CCl_4/TMS) δ = 1.10–1.45 (m, 12H, $2CH_2CH_3$, $2CHCH_3$), 3.80–4.60 (m, 6H, CHCONHCH, $2OCH_2$), 5.10 (s, 2H, CH_2Ph), 7.20 (s, 5H, H_{aryl}) ppm. ^{31}P($CDCl_3$, 90 Hz) δ = 25.13, 25.47 ppm.

3f. Calculated for $C_{18}H_{29}N_2O_6P$ (400.1) P 7.70; Found P 7.92. IR(KCl) ν = 1706, 1675, 1224, 1022 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 0.90–1.50 (m, 15H, $C(CH_3)_3$, $2CH_2CH_3$), 3.60–4.25 (m, 6H, $2CH_2CH_3$, NCH_2), 5.20–5.70 (m, 2H, CONH, CH—P), 7.05–7.55 (m, 5H, H_{aryl}), 8.70–9.20 (br. 1H, CONH) ppm.

3g. Calculated for $C_{19}H_{31}O_6N_2P$ (414.16) C 54.96, H 7.48, N 6.75; Found C 55.27, H 7.47, N, 6.74, IR(KCl) ν = 1718, 1675, 1220, 1096 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 1.10–1.65 (m, 15H, $C(CH_3)_3$, $2CH_2CH_3$), 2.40 (s, 3H, $ArCH_3$), 3.80 (d, 2H, NCH_2), 4.10 (m, 4H, $2CH_2CH_3$), 5.20–5.75 (m, 2H, CH—P, CONH), 7.00–7.55 (m, 4H, H_{aryl}), 8.85–9.05 (br, 1H, CONH) ppm.

3h. Calculated for $C_{19}H_{31}N_2O_7P$ (430.2) C 53.93, H 7.21, N 6.50; Found C 53.28, H 7.36, N 6.77. IR(KCl) ν = 1710, 1680, 1240, 1040 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 1.00–1.50 (m, 15H, $C(CH_3)_3$, CH_2CH_3), 3.75 (s, 3H, $ArOCH_3$), 3.70–4.20 (m, 6H, $2CH_2CH_3$, NCH_2), 5.15–5.75 (m, 2H, CONH, CH—P), 6.65–7.45 (m, 4H, H_{aryl}), 8.15–8.45 (br, 1H, CONH) ppm. ^{31}P($CDCl_3$/85% H_3PO_4) δ = 21.41 ppm.

3i. Calculated for $C_{17}H_{35}N_2O_6P$ (352.1) P 8.80; Found P 9.03. IR(neat) ν = 1710, 1675, 1240, 1030 cm^{-1}. ^{1}HNMR δ = 0.92–1.89 m, 21H, $C(CH_3)_3$, $2CH_2CH_3$, $2CHCH_3$), 3.8–4.8 (m, 6H, $2OCH_2$, CHCONHCH) ppm. ^{31}P NMR δ = 12.56, 12.16 ppm.

3j.Calculated for $C_{17}H_{35}N_2O_6P$ (394.1) P 7.8; Found P 8.03. IR ν = 1710, 1675, 1240, 1030. ^{1}HNMR(CCl_4/TMS) δ = 0.50–1.50 (m, 27H, C(CH3)3, $2CH_2CH_3$, $CHCH_3$, $CH_2CH(CH_3)_2$), 3.25–4.76 (m, 6H, $2CH_2CH_3$, CHCONHCH) ppm.

3k. Calculated for $C_{22}H_{37}N_2O_6P$ (456.2) P 6.79; Fohnd P 7.21. IR(KCl) ν = 1705, 1660, 1230, 1020 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 0.60–1.55 (m, 24H, $C(CH_3)_3$, $2CH_2CH_3$, $CHCH_3$, $CH_2CH(CH_3)_2$), 3.70–4.50 (m, 5H, $2CH_2CH_3$, HNCH), 5.30–5.90 (m, 2H, CH—P, CONH) ppm. ^{31}P ($CDCl_3$/85% H_3PO_4) δ = 21.42, 20.80 ppm. MS: 457 (M^+ + 1, 6.62%), 319 (9.08%), 228 (28.42%), 158 (8.56%), 130 (29.32%), 106 (100%), 86 (65.09%), 57 (85.20%).

3l. Calculated for $C_{23}H_{39}N_2O_6P$ (470.2) C 58.63, H 8.29, N 5.95; Found C 58.96, H 8.57, N 5.71. IR(KCl) ν = 1714, 1670, 1242, 1099 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 0.75–1.50 (m, 24H, $C(CH_3)_3$, $2CH_2CH_3$, $CH_2CH(CH_2)_2$), 2.35 (s, 3H, $ArCH_3$), 3.85–4.40 (m, 5H, $2CH_2CH_3$, CH—P), 6.85–7.45 (m, 4H, H_{aryl}) ppm.

3m. Calculated for $C_{23}H_{39}N_2O_7P$ (486.2) C 56.70, H 8.02, N 5.75; Found C 56.97, H 8.43, N 5.47. IR(KCl) ν = 1715, 1670, 1246, 1029 cm^{-1}. ^{1}HNMR(CCl_4/TMS) δ = 0.90–1.70 (m, 24H, $C(CH_3)_3$, $2CH_2CH_3$, $CH_2CH(CH_2)_3$, 3.75 (s, 3H, $ArOCH_3$), 4.10 (m, 5H, $2CH_2CH_3$, NCH), 5.10–5.70 (m, 2H, CH—P, CONH), 6.70–7.40 (m, 4H, H_{aryl}) ppm. ^{31}P($CDCl_3$/85% H_3PO_4, 90 Hz) δ = 21.22, 21.62 ppm.

Synthesis of Phosphonopeptides of type **5**, *General Procedure:* To a suspension of **4** (1.5 mmol), prepared according to our previously described method,[13] in CH_2Cl_2 (5 mL) was added $SOCl_2$ (0.1 mL) at r.t. followed by vigorous stirring for 4 h. After removal of volatile components, the residue was redissolved in CH_2Cl_2 (5 mL) followed by addition of ethyl amino carboxylate (1.5 mmol) and Et_3N (0.4 mL) at 0°C. Then the mixture was stirred at r.t. for 12 h and the reaction mixture was diluted with 20 mL of $CHCl_3$. The organic solution was washed successively with water (2 × 10 mL), saturated $NaHCO_3$ solution and water (2 × 10 mL). Upon being dried ($MgSO_4$) and evaported under reduced pressure. The residue after crystallization from EtOAc/petroleum ether afforded phosphonopeptides

of type **5** as colorless solids. The yield, mp, and ^{31}P NMR data of compounds **5** are collected in Table II.

5a. Calculated for $C_{27}H_{31}N_2O_6P$ (510.5) P 6.45; Found P 6.07. IR(KCl) ν = 3319 (NH), 1737 1690 (C=O), 1216 (P=O), 1039, 1028 (P—O—C) cm^{-1}. ^{1}HNMR($CDCl_3$/TMS): δ = 0.95–1.45 (m, 3H, CH_3), 2.75 (m, 2H, OCH_2CH_2), 3.20–3.50 (m, 2H, NCH_2), 4.05 (m, 4H, $POCH_2$, $COCH_2$), 5.05 (s, 2H, $PhCH_2O$), 4.80–5.30 (m, 1H, CH—P), 6.20 (br, 1H, PNH), 7.30 (m, 10H, H_{aryl}) ppm.

5b. Calculated for $C_{22}H_{29}N_2O_6P$ (448.4) P 6.91; Found P 7.06. IR: (KCl) ν = 3321 (NH), 1740, 1688 (C=O), 1252, 1210 (P=O), 1038 (P—O—C) cm^{-1}. ^{1}HNMR($CDCl_3$/TMS) δ = 1.40 (m, 6H, $2CH_3$), 2.50 (s, 3H, $ArCH_3$), 3.50–3.95 (m, 6H, $2OCH_2$,NCH_2), 4.30 (m, 2H, $POCH_2$), 5.20 (s, 2H, $PhCH_2$), 4.95–5.50 (m, 1H, CH—P), 6.40 (br, 1H, PONH), 7.20–7.50 (m, 9H, H_{aryl}) ppm.

5c. Calculated for $C_{21}H_{26}N_2O_6PCl$ (468.6) C 53.87, H 5.54, N 5.97; Found C 53.46, H 5.71, N 6.08. IR(KCl) ν = 3314 (N—H), 1736, 1687 (C=O), 1213 (P=O), 1044 (P—O—C) cm^{-1}. ^{1}HNMR($CDCl_3$/TMS) δ = 1.20 (m, 6H, $2CH_2CH_3$), 3.45–4.10 (m, 6H, P—OCH_2, $COCH_2$, NCH_2), 4.90–5.50 (m, 1H, CH—P), 5.12 (s, 2H, $PhCH_2O$), 6.90–7.70 (m, 9H, H_{aryl}) ppm.

5d. Calculated for $C_{22}H_{29}N_2O_7P$ (464.4) C 56.77, H 6.28, N 6.02; Found C 56.82, H 6.02, N 6.21. IR(KCl) ν = 3300 (NH), 1744, 1705 (C=O), 1247, 1216 (P=O), 1140, 1111 (P—O—C) cm^{-1}. ^{1}HNMR($CDCl_3$/TMS) δ = 1.27 (t, 6H, $2CH_2CH_3$), 3.05–4.35 (m, 6H, $2OCH_2CH_3$, NCH_2), 3.80 (s, 3H, $ArOCH_3$), 5.10 (s, 3H, $PhCH_2$), 4.75–5.35 (m, 1H, CH—P), 6.15 (br, 1H, PONH), 6.85–7.65 (m, 9H, H_{aryl}) ppm. MS: 464 (M^+, 4.8%), 373 (2.76%), 270 (100%), 162 (16.54%).

5e. Calculated for $C_{27}H_{31}N_2O_7P$ (526.5) C 61.59, H 5.88, N 5.31, P 5.88; Found C 61.13, H 5.43, N 5.22, P. 5.97. IR(KCl) ν = 3390 (NH), 1743, 1706 (C=O), 1247, 1214 (P=O), 1033 (P—O—C) cm^{-1}. ^{1}HNMR($CDCl_3$/TMS) δ = 0.85–1.30 (m, 6H, $2CH_3$), 3.10–3.80 (m, 7H, $ArOCH_3$, $2OCH_3$), 4.80–5.10 (d, $2PhCH_2$), 6.20 (br, 1H, PONH), 6.70–7.30 (m, 14H, H_{aryl}) ppm.

Synthesis of Phosphonopeptides of type **6**: The preparation was performed as described for phosphonopeptides of type **5** except that ethyl aminocarboxylate was replaced by diethyl aminophosphonate. The yield, mp and ^{31}P NMR data are given in Table II.

TABLE II

Compounds **5** and **6** prepared

	R^1	R^2	R^3	R^4	Yield(%)	M.P.(°C)	^{31}PNMR(ppm)
5a	C_6H_5	$C_2H_4C_6H_5$	H	C_2H_5	37	127-129	
5b	p-$CH_3C_6H_4$	C_2H_5	H	C_2H_5	64	106-108	27.29;26.90
5c	p-ClC_6H_4	C_2H_5	H	C_2H_5	51	114-116	
5d	p-$CH_3OC_6H_4$	C_2H_5	H	C_2H_5	62.3	148-150	
5e	p-$CH_3OC_6H_4$	C_2H_5	H	$C_6H_5CH_2$	41	110-112	25.77;25.45
6	p-$CH_3OC_6H_4$	C_2H_5	C_6H_5	C_2H_5	47	202-204	24.48;23.73 23.14;22.39

6. Calculated for $C_{19}H_{38}N_2O_8P_2$ (604.72) C 57.53, H 6.33, N 10.22, P 4.63; Found C 57.70, H 5.94, N 10.42, P 4.47. IR(KCl) ν = 3402 (NH), 1706 (C=O), 1244 (P=O), 1031 (P—O—C) cm^{-1}. ^{1}HNMR(DMSO/TMS): δ = 0.95–1.40 (m, 6H, $2CH_3$), 3.35–4.20 (m, 8H, $2OCH_2$, NCH_2, PNCHP), 3.75 (s, 3H, $ArOCH_3$), 4.70–5.10 (m, 1H, CH—P), 5.08 (s, 2H, $PhCH_2O$), 6.85–7.40 (m, 14H, H_{aryl}) ppm. MS: 604 (M^+, 6.38%), 335 (9.95%), 270 (43.78%), 226 (43.84%), 91 (100%).

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REFERENCES

1. P. Kafarski, B. Lezczak and P. Mastalerz, Phosphonopeptide—Synthesis and Biological Activity, Bertr. Wirkstofforsch, Vo. 25, 1985 and references cited therein.
2. V. P. Kukhav and V. A. Soplodenko, *Russ. Chem. Rev.*, **6,** 859 (1987).
3. M. Soloka, *Liebigs Ann. Chem.*, 331 (1990) and references cited therein.
4. J. Oleksyszyn and R. Tyka, *Tetrahedron Lett.*, 2823 (1977).
5. J. Oleksyszyn, *J. Prakt. Chem. Band,* **329,** Heft 1, 19 (1987).
6. P. Mastalerz, *Synthesis,* 985 (1979).
7. C. Y. Yuan, Y. M. Qi and C. L. Xing, *Acta. Chemica Sinica,* **43,** 243 (1985).
8. C. Y. Yuan and Y. M. Qi, *Acta Chemica Sinica,* **44,** 280 (1986).
9. C. Y. Yuan and Y. M. Qi, *Synthesis,* 821 (1986).
10. C. Y. Yuan and Y. M. Qi, *Synthesis,* 472 (1988).
11. C. Y. Yuan and G. H. Wang, *Synthesis,* 256 (1990).
12. C. Y. Yuan, G. H. Wang and S. J. Chen, *Synthesis,* 522 (1990).
13. C. Y. Yuan, S. J. Chen and G. H. Wang, *Synthesis,* 490 (1991).
14. P. A. Bartlett, J. E. Hanson and P. P. Giannousis, *J. Org. Chem.*, **55,** 6268 (1990).
15. W. F. Gilmore and M. A. McBride, *J. Pharm. Sci.*, **63,** 965 (1974); *ibid* **63,** 1087 (1974).