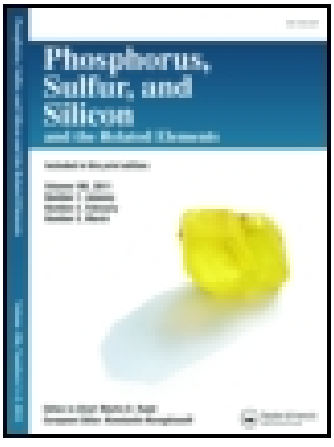

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SYNTHESIS OF BIHETEROCYCLIC α-AMINOPHOSPHONIC ACID DERIVATIVES

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SYNTHESIS OF BIHETEROCYCLIC α-AMINOPHOSPHONIC ACID DERIVATIVES

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We report here the synthesis of biheterocyclic α-aminophosphonic acid derivatives by 1,3 dipolar cycloaddition of acetylenic compounds, prepared in the laboratory, on α-azido α-amino phosphonic esters **1**[1a].

Keywords: α-aminophosphonic acid; biheterocycle; 1,2,3-triazole; tetrazole

INTRODUCTION

α-aminophosphonic acids, analogues of α-amino acids display diverse and useful biological properties[2–4]: these compounds are found to be substrates and inhibitors of enzymes, as well as plant growth regulators and herbicides. They also display antibacterial properties and neuronal activities[3–4].

In this paper we describe new heterocyclic analogues of α-amino acids able to present an interesting biological activity due to the presence of heterocyclic cores as in the case of tetrazolic glycine[5] and proline[6] derivatives This approach consists of preparing, firstly, tetrazolic dipolarophiles by nucleophilic substitution of propargyl bromide by 5-aryl substituted tetrazoles.

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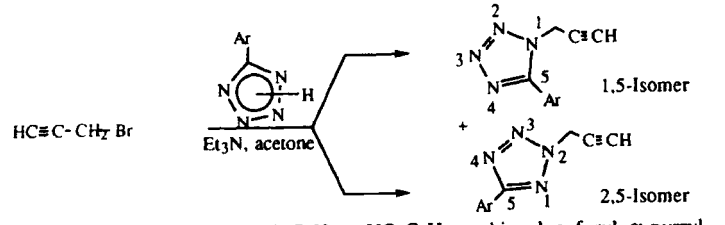
RESULTS

Tetrazole derivatives were obtained as described in the literature[7], the yields (35 to 75%) being improved in our team[1c,7]. There is literature[8] report which illustrates the existence of the two tetrazole tautomeric forms (scheme 1).

SCHEME 1

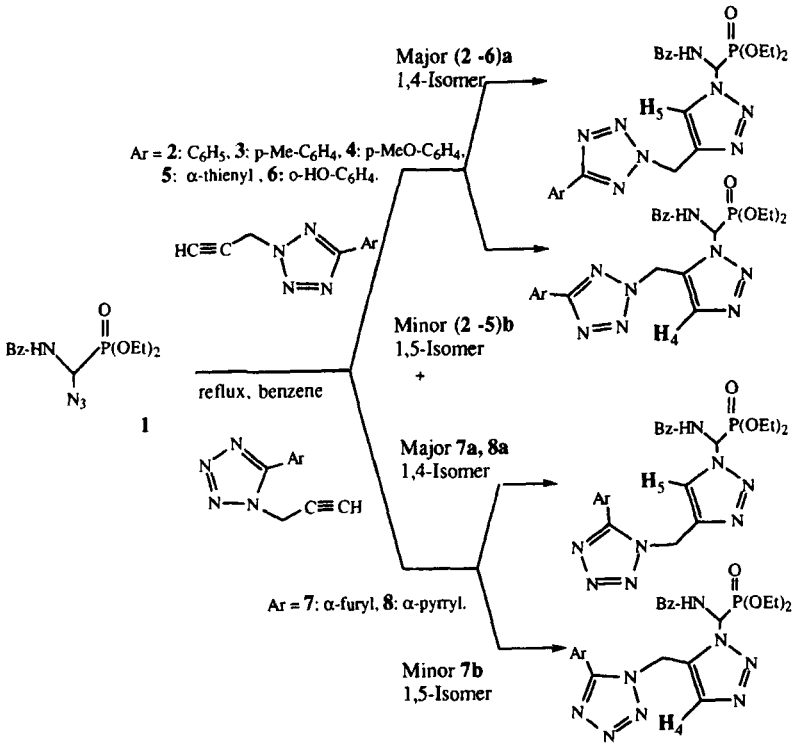
Treatment of 5-aryl substituted tetrazoles with propargyl bromide in the presence of triethylamine in acetone at room temperature during 4 h afforded the two regioisomers (2,5-disubstituted / 1,5-disubstituted) in good yields (70–85%) in a ratio of approximately 80/20, separable by column chromatography, whose structures were determined unambiguously by X-Ray diffraction analysis (scheme 2)[9].



Ar = C_6H_5, p-Me-C_6H_4, p-MeO-C_6H_4, o-HO-C_6H_4, α-thienyl, α-furyl, α-pyrryl.

SCHEME 2

The 2,5 and 1,5-disubstituted tetrazoles thus prepared were submitted to cycloaddition reaction with azide **1** (scheme 3). The azide 1 was obtained by reaction[1a] of sodium azide on the α-bromo-α-amino phosphonic ester. Results are summarised in table I.



SCHEME 3

TABLE I Synthesis of biheterocyclic α-amino phosphonic acid derivatives (2-8) a,b

Product	*Ar*	*m.p. (°C)*	*Time (h)*	*Yield (%)*	*Ratio of isomers 1,5/1,4*
2b	C_6H_5	127–129	48	80	20
2a		139–141			80
3b	p-Me-C_6H_4	145–147	48	75	47
3a		116–118			53
4b	p-MeO-C_6H_4	110–112	48	73	40
4a		98–100			60
5b	α-thienyl	101–103	48	69	25
5a		122–124			75
6a	o-HO-C_6H_4	186–188	48	75	>98
7b	α-furyl	151–153	48	72	10
7a		139–140			90
8a	α-pyrryl	170–172	48	79	>98

If we consider now the triazole ring after cycloaddition reaction, two regioisomers (1,4-isomer and 1,5-isomer) were formed in good yields and separated.The regioselectivity was excellent, only the 1,4-isomer was obtained in two cases: from **6a** (Ar = o-HO-C_6H_4) and **8a** (Ar = α-pyrryl).

The structures of the two regioisomers **(2-8) a,b** were assigned on the basis of literature data[1d,8,10–12] concerning the chemical shifts of triazolic protons[1d,10,11] and the chemical shifts of the carbons of the triazole ring in positions 4 and 5. The studies carried out[1d,10,11] have shown that the triazolic proton signal for the 1,5-isomer lies downfield from the corresponding signal for the 1,4-isomer but in ^{13}C NMR[8,12] the carbon signal (HC_4) for the 1,5-isomer lies upfield from the corresponding carbon signal (HC_5) for the 1,4-isomer. (Table II)

TABLE II The chemical shifts of triazolic protons and carbons in ^1H NMR and ^{13}C NMR for 1,4 and 1,5-isomers

Ar	*Isomer 1,5*	*Isomer 1,4*	*^1H NMR*		*^{13}C NMR*	
			δH_4 ppm	*δH_5 ppm*	*δC_4H ppm*	*δC_5H ppm*
C_6H_5	**2b**	-	7.76	-	135.04	- 58
	-	**2a**	-	8.28	-	124.58
p-Me-C_6H	**3b**	-	7.75	-	135.06	-
	-	**3a**	-	8.35	-	124.63
p-MeO-C_6H_4	**4b**	-	7.75	-	135.00	-
	-	**4 a**	-	8.3 1	-	124.57
α-thienyl	**5b**	-	7.75	-	135.03	-
	-	**5a**	-	8.30	-	124.65
o-HO-C_6H_4		**6**	-	8.52	-	125.30
α-furyl	**7b**	-	7.57	-	134.56	-
	-	**7 a**	-	8.30	-	124.5 1
α-pyrryl	-	**8**	-	8.39	-	124.21

By this strategy we have obtained different biheterocyclic α-aminophosphonic acid derivatives in good yields.

EXPERIMENTAL

Melting points were obtained on a electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on VARIAN EM – 360 (60 MHz) and BRUCKER (250 MHz) instruments, TMS as internal standard. ^{13}C NMR spectra were obtained on BRUCKER (200 MHz) instrument. Microanalyses were performed by the ENCT (Toulouse). Mass spectra were measured on a JEOL-JMS-DX 300 FAB instrument and Desorption in chiemical ionisation with NH_3 D/CI instrument. 5-substituted tetrazoles have been prepared using Alami's method[1c].

Cycloaddition reaction: General procedure

The azide **1** and the dipolarophile were magnetically stirred in a minimum volume of benzene at reflux (see table II for the reaction conditions). After evaporation of the solvent, the residue was chromatographied over silica gel or by preparative liquid chromatography (HPLC). The solid compounds are recrystallized from ether/dichloromethane and/or from acetone.

Minor isomer **2b:** Rf = 0.24 (ether).

^{1}H NMR ($CDCl_3$) δ: 1.08 (t, 3H, J = 7Hz), 1.31 (t, 3H, J = 7Hz), 3.75–4.35 (m, 2x2H), 5.93 (s, 2H), 7.09 (dd, 1H, J_1 = 10Hz, J_2 = 15,5Hz), 7.35–7.4 (m, 6H), 7.52 (dd, NH, J_1= 10Hz, J_3 = 4Hz), 7.76 (s,lH), 7.79–7.88 (m, 2H), 8.07–8.14 (m, 2H).

^{13}C NMR ($CDCl_3$) δ: 16.32 (2x$\underline{C}H_3CH_2O$), 48.03 (-$\underline{C}H_2$-), 64.09 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 180.2Hz), 64.45 (2x$\underline{C}H_2O$), 126.9, 127.1, 127.6, 128.8, 128.93, 130.52, 132.35,132.72 (2x$\underline{C}_6H_5$), 135.04 ($\underline{C}H_4$=C), 141.88 (CH_4=$\underline{C}$), 165.63 (C_6H_5-$\underline{C}N_4$), 166.8 (C=O). $C_{22}H_{25}N_8O_4P$ (496): M.S [D.C.I/NH_3 $(M+H)^+$ = 497 and $(M+NH_4)^+$ = 514].

Major isomer **2a:** m.p. = 139–141°C Rf = 0.16 (ether).

^{1}H NMR ($CDCl_3$) δ: 1.06 (t, 3H, J = 7Hz), 1.29 (t, 3H, J = 7Hz), 3.75–4.35 (m, 2x2H), 5.98 (s, 2H), 7.08 (dd, 1H, J_1 = 10Hz, J_2 = 16Hz), 7.26–7.5 (m, 6H), 7.64–7.69 (m, 2H), 8.04–8.09 (m, 2H), 7.28 (s, 1H), 8.6 (dd, NH, J_1 = 10Hz, J_3 = 4Hz).

^{13}C NMR ($CDCl_3$) δ: 16.2 (2xCH_3CH_2O), 48.3 (-$\underline{C}H_2$-), 60.4 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 182Hz), 64.76 (2x$\underline{C}H_2O$), 124.58 ($\underline{C}H_5$=C), 126.9, 127.2, 127.89,

128.6, 128.87, 130.41, 132.23,132.7 (2x$\underline{C}_6H_5$), 140.55 (CH_5=$\underline{C}$), 165.46 (C_6H_5-$\underline{C}N_4$), 167.5 (C=O). Anal. calcd. for $C_{22}H_{25}N_8O_4P$: C, 53.22, H,5.04, N,22.58.

Found.C, 52.93, H,4.96, N,22.50.

Minor isomer **3b:** Rf = 0.3 (ether).

^{1}H NMR ($CDCl_3$) δ: 1.06 (t, 3H, J = 7Hz), 1.31 (t, 3H, J = 7Hz), 2.38 (s, 3H), 3.7–4.31 (m, 2x2H), 5.91 (s, 2H), 7.1 (dd, 1H, J_1= 10Hz, J_2 = 15,5Hz), 7.2–7.6 (m, 5H), 7.75 (s, 1H), 7.8–8.03 (m, 5H).

^{13}C NMR ($CDCl_3$) δ: 16.4 (2x$\underline{C}H_3CH_2O$), 21.52 ($\underline{C}H_3$), 47.96 (-$\underline{C}H_2$-), 64.05 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 180.4Hz), 64.47 (2x$\underline{C}H_2O$), 124.29, 126.81, 127.35, 127.64, 128.8, 129.63, 132.72, 140.73 ($\underline{C}_6H_5$ and p-Me-$\underline{C}_6H_4$), 135.06 ($\underline{C}H_4$=C), 141.95 (CH_4=$\underline{C}$), 165.7 (Me-C_6H_4-$\underline{C}N_4$), 166.8 (C=O).

Anal. calcd. for $C_{23}H_{27}N_8O_4P$: C, 54.12, H,5.3, N,21.96.

Found.C, 53.87, H,5.36, N,21.93.

Major isomer **3a:** Rf = 0.22 (ether).

^{1}H NMR ($CDCl_3$) δ: 1.02 (t, 3H, J = 7Hz), 1.26 (t, 3H, J = 7Hz), 2.35 (s, 3H), 3.64–4.28 (m, 2x2H), 5.97 (s, 2H), 7.15 (dd, 1H, J_1= 10Hz, J_2 = 16,7Hz), 7.16–7.56 (m, 5H), 7.84–7.96 (m, 4H), 8.35 (s, 1H), 8.95 (dd, NH, J_1 = 10Hz, J_3 = 4Hz).

^{13}C NMR ($CDCl_3$) δ: 16.26 (2x$\underline{C}H_3CH_2O$), 21.5 ($\underline{C}H_3$), 48.22 (-$\underline{C}H_2$-), 60.4 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 182.78Hz), 64.8 (2x$\underline{C}H_2O$), 124.63 ($\underline{C}H_5$=C), 124.38, 126.78, 128, 128.5, 129.56, 132.3, 132.6 140.56 ($\underline{C}_6H_5$ and p-Me-$\underline{C}_6H_4$), 140.6 (CH_5=$\underline{C}$), 165.5 (Me-C_6H_5-$\underline{C}N_4$), 167.6 (C=O).

$C_{23}H_{27}N_8O_4P$ (510): M.S [D.C.I/NH_3 $(M+H)^+$ = 511 and $(M+NH_4)^+$= 528].

Minor isomer **4b:** Rf = 0.33 (AcOEt/DCM 3/7).

^{1}H NMR ($CDCl_3$) δ: 1.07 (t, 3H, J = 7Hz), 1.31 (t, 3H, J = 7Hz), 3.84 (s, 3H), 3.7–4.31 (m, 2x2H), 5.9 (s, 2H), 7.09 (dd, 1H, J_1= 10Hz, J_2 = 15,5Hz), 7.3–7.87 (m, 5H+NH), 7.56 (AA'BB'System, 4H, $J_{AB} = J_{A'B'}$ = 9Hz), 7.75 (s,1H).

^{13}C NMR ($CDCl_3$) δ: 16.31 (2x$\underline{C}H_3CH_2O$), 48.33 (-$\underline{C}H_2$-), 55.4 ($\underline{C}H_3O$), 64.05 (d, -$\underline{C}$H, $^1J_{C\text{-}P}$ = 180.2 Hz), 64.45 (2x$\underline{C}H_2O$), 114.33, 119.68, 127.61, 128.41, 128.68, 130.43, 132.35, 132.72, 161.43 ($\underline{C}_6H_5$ and p-MeO-$\underline{C}_6H_4$), 135 ($\underline{C}H_4$=C), 141.99 (CH_4=$\underline{C}$), 165.5 (MeO-C_6H_4-$\underline{C}N_4$), 166.8 (C=O).

Anal. calcd. for $C_{23}H_{27}N_8O_5P$: C, 52.47, H,5.13, N,21.29.
Found.C, 52.53, H,5.10, N,21.57.

Major isomer **4a:** Rf = 0.2 (AcOEt/DCM 3/7).

^{1}H NMR ($CDCl_3$) δ: 1.04 (t, 3H, J = 7Hz), 1.27 (t, 3H, J = 7Hz), 3.82 (s, 3H), 3.80–4.30 (m, 2x2H), 5.96 (s, 2H), 7.1 (dd, 1H, J_1= 10Hz, J_2 = 15,5Hz), 7.24–7.95 (m, 5H), 7.45 (AA'BB'System, 4H, J_{AB}=$J_{A'B'}$ = 9Hz), 8.31 (s, 1H), 8.8 (dd, NH, J_1= 10Hz, J_3 = 4Hz)

^{13}C NMR ($CDCl_3$) δ: 16.35 (2x$\underline{C}H_3CH_2O$), 48.10 (-$\underline{C}H_2$-), 55.38 ($\underline{C}H_3O$), 60.4 (d, -$\underline{C}$H, $^1J_{C\text{-}P}$ = 182.5Hz), 64.81 (2x$\underline{C}H_2O$), 124.57 ($\underline{C}H_5$=C), 114.27, 119.78, 127.74, 127.94, 128.38, 128.57, 128.72, 132.23, 132.66, 161.32 ($\underline{C}_6H_5$and p-MeO-$\underline{C}_6H_4$), 140.63 (CH_5=$\underline{C}$), 165.3 (Me-C_6H_5-$\underline{C}N_4$), 167.5 (C=O).

$C_{23}H_{27}N_8O_5P$ (526): M.S [D.C.I/NH_3 $(M+H)^+$= 527 and $(M+NH_4)^+$= 544].

Minor isomer **5b:** Rf = 0.36 (AcOEt/Et_2O 1/2).

^{1}H NMR ($CDCl_3$) δ: 1.08 (t, 3H, J = 7Hz), 1.32 (t, 3H, J = 7Hz), 3.72–4.35 (m, 2x2H), 5.9 (s, 2H), 7.1 (dd, 1H, J_1 = 10Hz, J_2 = 15,5Hz), 7.11–7.13 (m, 1H), 7.39–7.9 (m, 8H), 7.75 (s,lH).

^{13}C NMR ($CDCl_3$) δ: 16.31 (2x$\underline{C}H_3CH_2O$), 48.01 (-$\underline{C}H_2$-), 64.12 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$= 180.16 Hz), 64.47 (2x$\underline{C}H_2O$), 127.63, 127.98, 128.1, 128.18, 128.8, 132.34, 132.7 ($\underline{C}_6H_5$ and $\underline{C}_4H_3S$), 135.03 ($\underline{C}H_4$=C), 141.7 (CH_4=$\underline{C}$), 161.9 (α-Thienyl-$\underline{C}N_4$), 166.8 (C=O). Anal. calcd. for $C_{20}H_{23}N_8O_4PS$: C, 47.81, H,4.58, N,22.31.
Found.C, 47.41, H,4.55, N,22.16.

Major isomer **5a:** Rf = 0.28 (AcOEt/Et_2O 1/2).

^{1}H NMR ($CDCl_3$) δ: 1.06 (t, 3H, J = 7Hz), 1.28 (t, 3H, J = 7Hz), 3.74–4.32 (m, 2x2H), 5.96 (s, 2H), 7.07–7.1 (m, 1H), 7.14 (dd, 1H, J_1= 10Hz, J_2 = 15,5Hz), 7.26–7.94 (m, 6H), 7.7–7.73 (m, 1H), 7.3 (s,lH), 8.77 (dd, NH, J_1 = 10Hz, J_3 = 4Hz).

^{13}C NMR ($CDCl_3$) δ: 16.2 (2x$\underline{C}H_3CH_2O$), 48.27 (-$\underline{C}H_2$-), 60.45 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 182.43 Hz), 64.78 (2x$\underline{C}H_2O$), 124.65 ($\underline{C}H_5$=C), 127.42, 127.94, 128, 128.55, 128.82, 132, 132.26, 132.64 ($\underline{C}_6H_5$and $\underline{C}_4H_3S$), 140.36 (CH_5=$\underline{C}$), 161.5 (α-Thienyl-$\underline{C}N_4$), 167.5 (C=O).

Anal. calcd. for $C_{20}H_{23}N_8O_4PS$: C, 47.81, H,4.58, N,22.31.
Found.C, 47.72, H,4.59, N,21.85.

Major isomer **6a:** Rf = 0.2 (AcOEt/DCM 2/3).

^{1}H NMR ($CDCl_3$+DMSO d_6) δ: 1.06 (t, 3H, J = 7Hz), 1.24 (t, 3H, J = 7Hz), 3.73–4.27 (m, 2x2H), 6.04 (s, 2H), 6.8–8 (m, 9H), 7.2 (dd, 1H, J_1 = 10Hz, J_2 = 15.5Hz), 8.52 (s, lH), 9.68 (dd, NH, J_1 = 10Hz, J_3 = 4Hz), 11.5 (s, 1H).

^{13}C NMR ($CDCl_3$+DMSO d_6) δ: 16.8 (2x$\underline{C}H_3CH_2O$), 49.13 (-$\underline{C}H_2$-), 62.96 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 180.1Hz), 64.7 (2x$\underline{C}H_2O$), 125.3 ($\underline{C}H_5$=C), 112.15, 118, 120.5, 126.4, 128.6, 128.8, 132.7, 132.9, 133.1, 156.64 ($\underline{C}_6H_5$ and o-HO-$\underline{C}_6H_4$), 140.67 (CH_5=$\underline{C}$), 165.1 (o-HO-C_6H_4-$\underline{C}N_4$), 168 (C=O).

Anal. calcd. for $C_{22}H_{25}N_8O_5P$: C, 51.56, H,4.88, N,21.87.

Found.C, 51.40, H,4.71, N,21.55.

Minor isomer **7b:** Rf = 0.67 (ether).

^{1}H NMR ($CDCl_3$) δ: 1.01 (t, 3H, J = 7Hz), 1.29 (t, 3H, J = 7Hz), 3.63–4.28 (m, 2x2H), 5.92 (s, 2H), 6.54–6.56 (m, 1H), 7.1 (dd, 1H, J_1= 10Hz, J_2 = 16Hz), 7.25–7.27 (m, 1H), 7.3–7.84 (m, 5H), 7.62–7.64 (m, 1H), 7.57 (s, lH), 8.1 (dd, NH, J_1 = 10Hz, J_3= 4Hz).

^{13}C NMR ($CDCl_3$) δ : 16.2 (2x$\underline{C}H_3CH_2O$), 43.71 (-$\underline{C}H_2$-), 64.04 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 180.52 Hz), 64.4 (2x$\underline{C}H_2O$), 112.56, 115.44, 139.1, 145.5 ($\underline{C}_4H_3O$), 127.50, 128.56, 132.23, 132.7 ($\underline{C}_6H_5$), 134.56 ($\underline{C}H_4$=C), 142.51 (CH_4=$\underline{C}$), 145.91 (α-Furyl-$\underline{C}N_4$), 167 (C=O). $C_{20}H_{23}N_8O_5P$ (486): M.S [D.C.I/NH_3 $(M+H)^+$ = 487 and $(M+NH_4)^+$ = 504].

Major isomer **7a:** Rf = 0.48 (ether).

^{1}H NMR ($CDCl_3$) δ: 1.02 (t, 3H, J = 7Hz), 1.25 (t, 3H, J = 7Hz), 3.58–4.32 (m, 2x2H), 5.97 (s, 2H),6.54–6.57 (m, 1H), 7.12 (dd, 1H, J_1= 10Hz, J_2 = 16Hz), 7.18–7.9 (m, 7H), 8.3 (s, lH), 9 (dd, NH, J_1 = 10Hz, J_3 = 4Hz).

^{13}C NMR ($CDCl_3$) δ: 16.3 (2x$\underline{C}H_3CH_2O$), 43.8 (-$\underline{C}H_2$-), 60.42 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 182.43 Hz), 64.7 (2x$\underline{C}H_2O$), 124.51 ($\underline{C}H_5$=C), 112.4, 115.36, 139.18, 145.8 ($\underline{C}_4H_3O$), 128, 128.47, 132.3, 132.6 ($\underline{C}_6H_5$ and $\underline{C}_4H_3S$), 141.2 (CH_5=$\underline{C}$), 146.4 (α-Furyl-$\underline{C}N_4$), 167 (C=O).

Anal. calcd. for $C_{20}H_{23}N_8O_5P$: C, 49.38, H,4.73, N,23.04.

Found.C, 48.98, H,4.66, N,22.71.

Major isomer **8a:** Rf = 0.17 (AcOEt/DCM 1/1).

^{1}H NMR ($CDCl_3$+DMSO d_6) δ: 1.03 (t, 3H, J = 7Hz), 1.21 (t, 3H, J = 7Hz), 3.65–4.27 (m, 2x2H), 5.85 (s, 2H), 6.19–6.28 (m, 1H), 6.86–6.87 (m, 1H), 6.97–6.98 (m, 1H), 7.14 (dd, 1H, J_1 = 10Hz, J_2 = 16Hz),

7.3–7.8 (m, 5H), 8.39 (s, lH), 9.75 (dd, NH, J_1 = 10Hz, J_3 = 4Hz), 11.88 (m, NHpyrryl).

^{13}C NMR ($CDCl_3$+DMSO d_6) δ: 16.49 (2x$\underline{C}H_3CH_2O$), 43.42 (-$\underline{C}H_2$-), 60.67 (d, -$\underline{C}$H-, $^1J_{C\text{-}P}$ = 182.43 Hz), 64.22 (2x$\underline{C}H_2O$), 110.38, 112.53, 114.32, 123.4 ($\underline{C}_4H_4N$), 124.21 ($\underline{C}H_5$=C), 128.35, 128.52, 132.5, 132.84 ($\underline{C}_6H_5$), 141.56 (CH_5=$\underline{C}$), 148.53 (α-Pyrryl-$\underline{C}N_4$), 167.3 (C=O).

Anal. calcd. for $C_{20}H_{24}N_9O_4P$: C, 49.48, H,4.95, N,25.98.

Found.C, 49.14, H,4.83, N,25.95.

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