

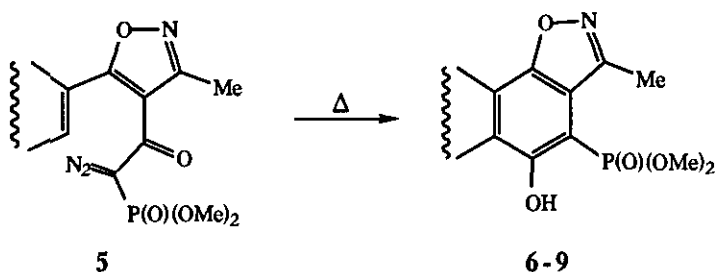
**A THERMAL WOLFF REARRANGEMENT-BENZANNULATION ROUTE TO NAPHTH[2,1-*d*]ISOXAZOLES, [1]BENZOFURO-[6,7-*d*]- or [5,4-*d*]ISOXAZOLES AND 1,2-BENZISOXAZOLES**

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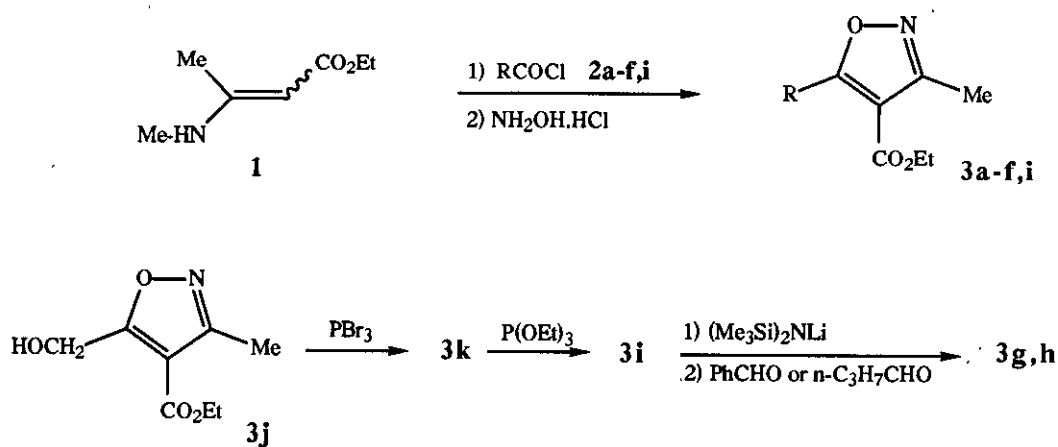
**Abstract** - The title compounds substituted in position 4 by a dimethylphosphono group and in position 5 by a hydroxy group were prepared by the thermal decomposition of dimethyl 2-(5-aryl-(or furyl or alkenyl)-3-methylisoxazol-4-yl)-2-oxo-1-diazoethylphosphonates through a tandem Wolff rearrangement-benzannulation sequence.

The  $6\pi$  electrocyclic ring closure of dienyl ketenes is a useful procedure which leads to the formation of a variety of highly substituted aromatic, heteroaromatic and quinoïd compounds.<sup>1</sup> The dienyl ketenes are generally obtained by thermolysis of cyclobutenones bearing an alkenyl or aryl substituent at the 4-position, these cyclobutenones being either starting materials<sup>2,3</sup> or non isolated intermediates.<sup>4,5</sup> Recently the photochemical or thermal decomposition of  $\alpha$ -diazo-2-vinylacetophenone leading to  $\beta$ -naphthol has been explained by the formation of an intermediate *o*-vinylphenyl ketene resulting from a Wolff rearrangement and subsequent cyclization.<sup>6</sup> We have also reported, in a recent note,<sup>7</sup> that the thermal decomposition of some  $\alpha$ -diazo- $\beta$ -keto- $\gamma,\delta$ -alkenylphosphonates substituted in the  $\delta$  position by an aryl or an alkenyl group led to the formation of various phenolic compounds, these products being formed by the  $6\pi$  electrocyclization of a dienyl ketene resulting from a thermal Wolff rearrangement. In the aim of exploring the synthetic possibilities of this sequence and in connection with our interest directed toward the chemistry of isoxazoles,<sup>8</sup> we have incorporated the  $\gamma,\delta$ -double bond as a part of an isoxazole ring and we report here that the thermal decomposition of the corresponding dimethyl 2-(5-aryl-(or furyl or alkenyl)-3-methylisoxazol-4-yl)-2-oxo-1-diazoethylphosphonates (5) allow the synthesis of a variety of new 4-dimethylphosphono-5-hydroxy-fused isoxazoles (6)-(9).



The requisite precursors needed for the synthesis of the  $\alpha$ -diazo- $\beta$ -ketophosphonates (**5a-h**) are the ethyl 3-methyl-4-isoxazolecarboxylates (**3a-h**) (Scheme 2). The isoxazoles (**3a-f**) (R = aryl or furyl) were prepared (Scheme 1) by reaction of ethyl 3-methylamino-2-butenate (**1**) with the acid chlorides (**2a-f**) followed by treatment of the non isolated intermediate ethyl 2-acyl-3-methylamino-2-butenates by hydroxylamine; <sup>8a,9,10</sup> pure compounds (**3a-f**) were obtained, in yields ranging from 47 to 69%, by chromatography on silica gel of crude mixtures containing about 5% of the isomeric ethyl 5-methyl-4-isoxazolecarboxylates. The isoxazoles (**3g,h**) (R = alkenyl) were prepared (Scheme 1) by condensation under basic conditions of ethyl 5-diethylphosphonomethyl-3-methyl-4-isoxazolecarboxylate (**3i**) (*vide infra*) with benzaldehyde or n-butyraldehyde (yields 82 and 86%). The E-geometry of the carbon-carbon double bond in **3h** was established by the coupling constant of 16.2 Hz between the two ethylenic protons in the <sup>1</sup>H-nmr spectrum; by analogy with **3h**, the styryl moiety in **3g** must have the same E-geometry.

Scheme 1



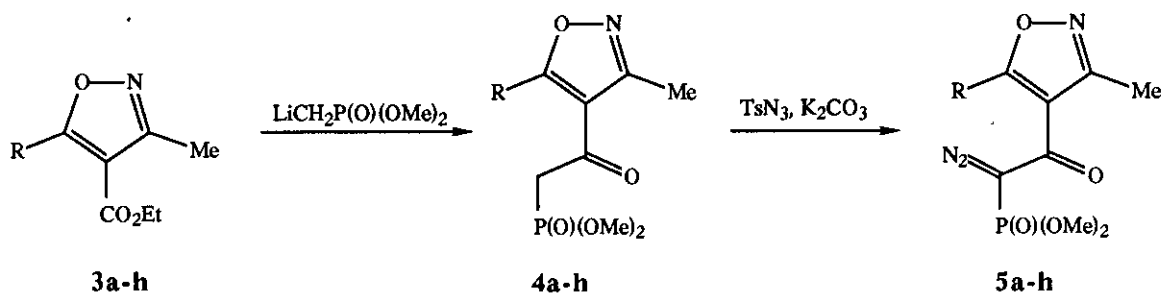
2, 3, 4 & 5	R	2, 3, 4 & 5	R
a	C <sub>6</sub> H <sub>5</sub> -	g	(E) C <sub>6</sub> H <sub>5</sub> -CH=CH-
b	4-MeO-C <sub>6</sub> H <sub>4</sub> -	h	(E) n-Pr-CH=CH-
c	4-Cl-C <sub>6</sub> H <sub>4</sub> -	i	(EtO) <sub>2</sub> (O)P-CH <sub>2</sub> -
d	3,5-diMeO-C <sub>6</sub> H <sub>3</sub> -	j	HO-CH <sub>2</sub> -
e	2-furyl	k	Br-CH <sub>2</sub> -
f	3-furyl		

Two paths were tested for the preparation of the phosphonate (**3i**). Path 1: following the method described above for the synthesis of **3a-f** with the enamine (**1**) and diethylphosphonoacetyl chloride (**2i**),<sup>11</sup> compound (**3i**) was obtained, after chromatographic purification, with a yield of 23% from **1**. Path 2: the ethyl 5-hydroxymethyl-3-methyl-4-isoxazolecarboxylate (**3j**), prepared from the enamine (**1**) with a yield of 58%<sup>8a</sup> was transformed into the corresponding bromide (**3k**) which was reacted with triethyl phosphite to give compound (**3i**) with a yield of 40% from **1**. Path 2 appears to be more attractive with a better yield and since products (**3j**), (**3k**) and (**3i**) can be distilled and thus obtained on a large scale. The synthesis of the isomeric

ethyl 3-diethylphosphonomethyl-5-methyl-4-isoxazolecarboxylate by a different method has been recently published.<sup>12</sup>

Reaction of the isoxazoles (3a-h) with the anion of dimethyl methylphosphonate (Scheme 2) gave the  $\beta$ -ketophosphonates (4a-h) which were easily transformed into the corresponding  $\alpha$ -diazo- $\beta$ -ketophosphonates (5a-h) by diazo-transfer with tosyl azide and potassium carbonate in acetonitrile, the yields of the sequence (3)→(5) ranging from 52 to 84%.

Scheme 2

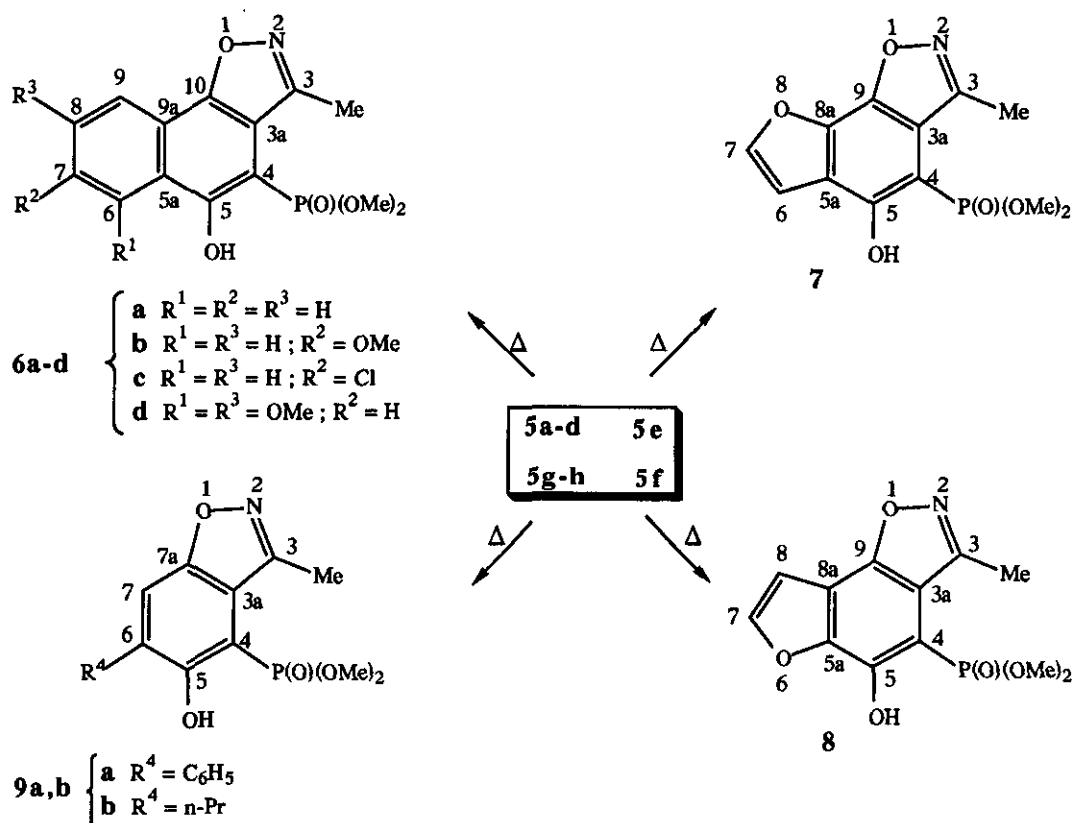


When benzene solutions of compounds (5a-h) were heated in a high-pressure autoclave according to the conditions indicated in Table 1, the fused isoxazoles (6)-(9) (Scheme 3) were formed with fair yields. The structures of compounds (6)-(9) are consistent with the ir, <sup>1</sup>H- and <sup>13</sup>C-nmr spectra and microanalysis. The presence of a phenolic proton is shown by the ir ( $\nu_{\text{OH}}$  3400-2500  $\text{cm}^{-1}$ ) and <sup>1</sup>H-nmr spectra ( $\delta_{\text{OH}}$  11.33 to 12.04 ppm). The ring closure is evidenced by the chemical shifts and <sup>13</sup>C<sub>CP</sub> values of the carbons [C-3a,C-4,C-5,C-5a,C-9a,C-10] for (6a-d), [C-3a,C-4,C-5,C-5a,C-8a,C-9] for (7-8) and [C-3a,C-4,C-5,C-6,C-7,C-7a] for (9a-b) in the <sup>13</sup>C-nmr spectra as indicated in Table 2. In the isoxazole rings the chemical shifts of carbons bonded to oxygen [C-10 or C-9 or C-7a] are very close to those of carbons bonded to nitrogen [C-3]; this can be explained by the shielding effect produced by the para relationship of the 5-hydroxy group on carbons [C-10 or C-9 or C-7a]. The values of <sup>3</sup>J<sub>CP</sub> for carbons [C-10 or C-9 or C-7a] (14.5-16.9 Hz) on one hand, and for carbons [C-3] (1.5-2.2 Hz) on the other hand, are very different; this is related to the respective trans or cis positions of carbon and phosphorus atoms with respect to the C3a-C4 bond. The correct attribution of resonances to carbons [C-10 or C-9 or C-7a] and [C-3] was further confirmed by examination of the coupled spectrum of (6a): C-3 appears at 155.10 ppm as a quadruplet of doublets with <sup>2</sup>J<sub>CH</sub> = 6.9 Hz and <sup>3</sup>J<sub>CP</sub> = 1.5 Hz whereas C-10 appears at 156.80 ppm as a doublet of doublets with <sup>3</sup>J<sub>CP</sub> = 14.6 Hz and <sup>3</sup>J<sub>C-H</sub> = 4.0 Hz.

Table 1 : Decomposition of the  $\alpha$ -diazo- $\beta$ -ketophosphonates (5a-h)

$\alpha$ -diazo- $\beta$ -ketophosphonate	5a	5b	5c	5d	5e	5f	5g	5h
Temp [°C]	160	160	160	160	160	160	130	130
Time [h]	7	7	7	7	3	3	3	3
Yield [%] (Product)	66 (6a)	60 (6b)	43 (6c)	73 (6d)	80 (7)	72 (8)	65 (9a)	73 (9b)

## Scheme 3



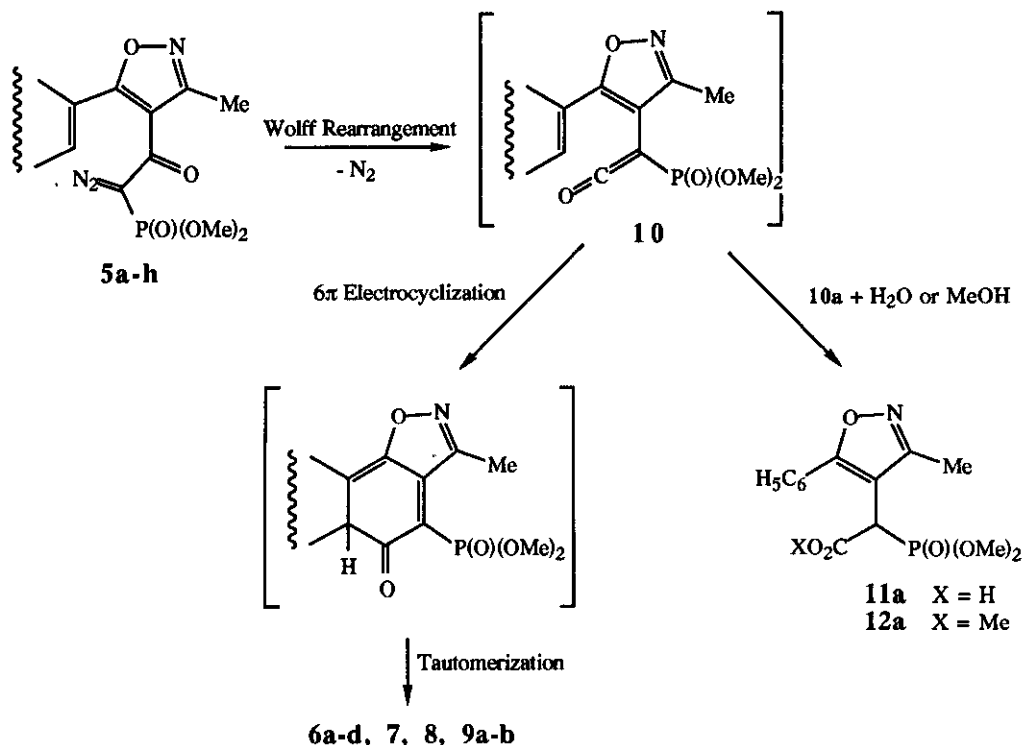
The formation of compounds (6)-(9) results from a thermal Wolff rearrangement giving rise to the ketenes (10) followed by  $6\pi$  electrocyclicization and tautomerization (Scheme 4). It appears that the electrocyclicization is slower than the Wolff rearrangement on the basis of the following experiments: *a*) When a toluene solution of the  $\alpha$ -diazo- $\beta$ -ketophosphonate (5a) was heated to reflux, the reaction being monitored by tlc, a long spot of small  $R_f$  appeared progressively whereas 5a disappeared. The spot of small  $R_f$  is due, presumably, to the acid (11a) formed by hydrolysis of the ketene (10a) on the chromatographic plate. The decomposition of 5a was completed after approximately 2 h, but only a minute amount of 6a was formed. If anhydrous methanol was added after 2 h, the ester (12a) could be isolated with a 75% yield. *b*) If the toluene solution of 5a was heated to reflux for 30 h, compound (6a) was isolated as the sole product, but with a yield of only 27%. These results indicate that, although the ketene (10a) is formed quite rapidly and is rather stable, the temperature of refluxing toluene is too low to allow the electrocyclicization to proceed readily. Thus degradation of the ketene leading to tars competes with ring closure and lowers the yield of 6a. Consequently the thermal decomposition of the  $\alpha$ -diazo- $\beta$ -ketophosphonates (5) was conducted in an autoclave, at 130-160°C, permitting the electrocyclicization to occur at a sufficient rate. As shown in Table 1 the conditions for the preparation of the fused isoxazoles are more severe going from 9 to 7-8 and then to 6. The  $6\pi$  electrocyclicization of 10 requires the temporary disruption of aromaticity of the isoxazole ring, and of the furyl [for 7-8] or aryl [for 6] rings. Thus the reaction conditions are roughly correlated with the resonance energies of the alkenyl, furyl and aryl groups.

**Table 2 :**  $^{13}\text{C}$ -Nmr data ( $\text{CDCl}_3$ ) of fused isoxazoles (6)-(9) [ $\delta$  (ppm) and  $^n\text{J}_{\text{CP}}$  (Hz)]

<b>6a*</b>	C-3 155.10 $^3\text{J} = 1.5$	C-3a 113.31 $^2\text{J} = 7.3$	C-4 88.88 $^1\text{J} = 186.7$	C-5 160.98 $^2\text{J} = 7.0$	C-5a 126.07 $^3\text{J} = 14.1$	C-6 125.19 $^4\text{J} = 1.4$	C-7 128.38 $^5\text{J} = 1.0$	C-8 130.59	C-9 121.67	C-9a 122.55 $^4\text{J} = 2.3$	C-10 156.80 $^3\text{J} = 14.6$	3-Me 11.74	P(O)(OMe) <sub>2</sub> 52.90 $^2\text{J} = 4.7$	-
<b>6b</b>	C-3 154.87 $^3\text{J} = 1.5$	C-3a 111.52 $^2\text{J} = 7.2$	C-4 89.37 $^1\text{J} = 186.2$	C-5 159.83 $^2\text{J} = 6.9$	C-5a 127.62 $^3\text{J} = 14.4$	C-6 104.48 $^4\text{J} = 1.6$	C-7 159.77	C-8 123.20	C-9 121.79	C-9a 117.08 $^4\text{J} = 2.3$	C-10 156.88 $^3\text{J} = 14.9$	3-Me 11.67	P(O)(OMe) <sub>2</sub> 52.90 $^2\text{J} = 4.7$	7-MeO 55.56
<b>6c</b>	C-3 155.07 $^3\text{J} = 1.7$	C-3a 113.62 $^2\text{J} = 7.0$	C-4 90.40 $^1\text{J} = 186.7$	C-5 159.65 $^2\text{J} = 7.2$	C-5a 126.81 $^3\text{J} = 14.5$	C-6 124.6 $^4\text{J} = 1.6$	C-7 134.61 $^5\text{J} = 1.9$	C-8 131.04	C-9 123.09	C-9a 120.48 $^4\text{J} = 2.3$	C-10 156.12 $^3\text{J} = 14.5$	3-Me 11.66	P(O)(OMe) <sub>2</sub> 53.03 $^2\text{J} = 4.9$	-
<b>6d</b>	C-3 155.13 $^3\text{J} = 1.7$	C-3a 114.48 $^2\text{J} = 7.2$	C-4 87.10 $^1\text{J} = 190.2$	C-5 162.31 $^2\text{J} = 8.5$	C-5a 111.37 $^3\text{J} = 14.2$	C-6 160.26 $^4\text{J} = 1.4$	C-7 94.02	C-8 161.98	C-9 101.00	C-9a 126.06 $^4\text{J} = 2.2$	C-10 156.03 $^3\text{J} = 15.3$	3-Me 11.98	P(O)(OMe) <sub>2</sub> 52.75 $^2\text{J} = 4.7$	6,8-diMeO 55.77 56.43
<b>7</b>	C-3 154.91 $^3\text{J} = 2.1$	C-3a 118.12 $^2\text{J} = 8.5$	C-4 89.16 $^1\text{J} = 187.2$	C-5 157.88 $^2\text{J} = 8.1$	C-5a 120.83 $^3\text{J} = 16.2$	C-6 106.31 $^4\text{J} = 2.0$	C-7 145.97	-	-	C-8a 141.84 $^4\text{J} = 2.8$	C-9 146.12 $^3\text{J} = 15.0$	3-Me 11.66	P(O)(OMe) <sub>2</sub> 52.99 $^2\text{J} = 4.9$	-
<b>8</b>	C-3 154.86 $^3\text{J} = 1.9$	C-3a 114.41 $^2\text{J} = 7.4$	C-4 90.41 $^1\text{J} = 187.2$	C-5 149.91 $^2\text{J} = 8.1$	C-5a 145.65 $^3\text{J} = 21.3$	-	C-7 148.01	C-8 104.76	-	C-8a 117.35 $^4\text{J} = 2.2$	C-9 152.61 $^3\text{J} = 16.9$	3-Me 11.72	P(O)(OMe) <sub>2</sub> 53.06 $^2\text{J} = 4.8$	-
<b>9a</b>	C-3 154.34 $^3\text{J} = 2.1$	C-3a 119.24 $^2\text{J} = 6.9$	C-4 96.35 $^1\text{J} = 184.1$	C-5 159.31 $^2\text{J} = 7.6$	C-6 134.96 $^3\text{J} = 13.0$	-	-	-	-	C-7 117.58 $^4\text{J} = 2.9$	C-7a 158.32 $^3\text{J} = 15.6$	3-Me 11.75	P(O)(OMe) <sub>2</sub> 53.04 $^2\text{J} = 4.9$	6-C <sub>6</sub> H <sub>5</sub> 136.84 ( $^4\text{J} = 2.1$ ) 129.57 128.24 128.20
<b>9b</b>	C-3 155.22 $^3\text{J} = 2.2$	C-3a 117.83 $^2\text{J} = 7.0$	C-4 94.96 $^1\text{J} = 184.2$	C-5 160.35 $^2\text{J} = 7.0$	C-6 136.35 $^3\text{J} = 12.3$	-	-	-	-	C-7 116.43 $^4\text{J} = 2.8$	C-7a 158.43 $^3\text{J} = 15.4$	3-Me 11.70	P(O)(OMe) <sub>2</sub> 52.92 $^2\text{J} = 4.9$	6-n-C <sub>3</sub> H <sub>7</sub> 33.11 ( $^4\text{J} = 1.7$ ) 22.10 13.95

\* Coupled spectrum of **6a** C-3 : qd,  $^2\text{J}_{\text{CH}} = 6.9$  Hz,  $^3\text{J}_{\text{CP}} = 1.5$  Hz ; C-3a : dq,  $^2\text{J}_{\text{CP}} = 7.3$  Hz,  $^3\text{J}_{\text{CH}} = 2.6$  Hz ; C-4 : dd,  $^1\text{J}_{\text{CP}} = 186.7$  Hz,  $^3\text{J}_{\text{CH}} = 3.3$  Hz ; C-5 : app pent,  $^2\text{J}_{\text{CP}} = 7.0$  Hz,  $^2\text{J}_{\text{CH}} = 3.4$  Hz,  $^3\text{J}_{\text{CH}} = 3.4$  Hz ; C-10 : dd,  $^3\text{J}_{\text{CP}} = 14.6$  Hz,  $^3\text{J}_{\text{CH}} = 4.0$  Hz.

Scheme 4



## EXPERIMENTAL

All melting points were determined on a Kofler block apparatus. The ir spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer. The nmr spectra were obtained with a Bruker AC 200 spectrometer. The chemical shifts reported are in parts per million from internal TMS. Microanalyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69300 Vernaison, France. THF was distilled prior use from sodium benzophenone ketyl. Benzene and toluene were dried over sodium. Column chromatography was performed using Merck Silica gel 60 (70-230 mesh). The acid chlorides (2a-e) were purchased from Aldrich Chemical Co. The acid chloride (2f) was prepared by heating the corresponding acid with thionyl chloride at 50°C for 6 h followed by distillation (bp 45-50°C/12 Torr ; Yield : 78 %).

### Ethyl 3-methyl-4-isoxazolecarboxylates (3a-f)

To a stirred solution of ethyl 3-methylamino-2-butenate (1)<sup>9</sup> (3.58 g, 25 mmol) and pyridine (2 ml, 25 mmol) in anhydrous ethyl ether (50 ml), cooled in a water-ice bath, was added dropwise a solution of acyl chloride (2a-f) (30 mmol) in anhydrous ethyl ether (20 ml). The resulting mixture was stirred for 48 h at room temperature. The ethereal solution was washed three times with 20 ml of water and dried over anhydrous sodium sulfate. After evaporation of the solvent the crude residue was dissolved in acetic acid (50 ml). Hydroxylamine hydrochloride (1.74 g, 25 mmol) was added and the mixture was refluxed for 0.5 h. Acetic acid was evaporated *in vacuo* and ethyl ether (80 ml) was added. The solution was washed with saturated sodium bicarbonate solution (3 x 20 ml), brine (2 x 20 ml) and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with tetrachloromethane-ether 4/1 for 3a, dichloromethane for 3b, ether-pentane 3/7 for 3c,f, ether-pentane 1/1 for 3d, ether-pentane 3/2 for 3e.

3a Yield 60%. mp 56°C.<sup>10</sup>

**3b** Yield 59%. mp 65°C. Ir (CHCl<sub>3</sub>) 1710, 1610. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.91 (m, 2H), 6.97 (m, 2H), 4.32 (q, 2H, J = 7.1 Hz), 3.87 (s, 3H), 2.49 (s, 3H), 1.37 (t, 3H, J = 7.1 Hz). Anal. Calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>4</sub> : C 64.36, H 5.79, N 5.36 : Found C 64.65, H 6.02, N 5.31.

**3c** Yield 69%. mp 62°C. Ir (CHCl<sub>3</sub>) 1710, 1605, 1585. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.88 (m, 2H), 7.44 (m, 2H), 4.31 (q, 2H, J = 7.2 Hz), 2.50 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz). Anal. Calcd for C<sub>13</sub>H<sub>12</sub>NO<sub>3</sub>Cl : C 58.77, H 4.55, N 5.27, Cl 13.34 : Found C 58.74, H 4.60, N 5.37, Cl 13.33.

**3d** Yield 51%. mp 74°C. Ir (CHCl<sub>3</sub>) 1710, 1600, 1585. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.09 (d, 2H, J = 2.3 Hz), 6.59 (t, 1H, J = 2.3 Hz), 4.30 (q, 2H, J = 7.1 Hz), 3.81 (s, 6H), 2.49 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz). Anal. Calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>5</sub> : C 61.85, H 5.88, N 4.81 : Found C 61.88, H 5.96, N 4.83.

**3e** Yield 65%. mp 66°C. Ir (CHCl<sub>3</sub>) 3160, 1710, 1610, 1565. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) : δ 7.72 (d, 1H, J = 3.6 Hz), 7.66 (d, 1H, J = 1.6 Hz), 6.61 (d, 1H, J = 3.6 Hz, J = 1.6 Hz), 4.38 (q, 2H, J = 7.1 Hz), 2.49 (s, 3H), 1.41 (t, 3H, J = 7.1 Hz). Anal. Calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>4</sub> : C 59.73, H 5.01, N 6.33 : Found C 60.47, H 5.30, N 6.36.

**3f** Yield 47%. mp 28-29°C. Ir (CHCl<sub>3</sub>) 3160, 1715, 1610, 1570. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) : δ 8.61 (br s, 1H), 7.51 (t, 1H, J = 1.7 Hz), 7.02 (d, 1H, J = 1.7 Hz), 4.36 (q, 2H, J = 7.1 Hz), 2.48 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz). Anal. Calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>4</sub> : C 59.73, H 5.01, N 6.33 : Found C 59.44, H 5.01, N 6.23.

**Ethyl 5-diethylphosphonomethyl-3-methyl-4-isoxazolecarboxylate (3i) from ethyl 3-methylamino-2-butenate (1).**

To a stirred solution of ethyl 3-methylamino-2-butenate (1) (7g, 49 mmol) and pyridine (3.92 ml, 49 mmol) in anhydrous ethyl ether (100 ml), cooled in a water-ice bath, was added dropwise a solution of crude diethylphosphonoacetyl chloride (2i) prepared according to the procedure of Cooke and Biciunas<sup>11</sup> (10.5 g, 49 mmol) in anhydrous ethyl ether (35 ml). The resulting mixture was stirred for 1.5 h at room temperature. The ethereal solution was filtered and then evaporated. The crude residue was dissolved in acetic acid (100 ml), hydroxylamine hydrochloride (3.4 g, 49 mmol) was added and the mixture was refluxed for 30 mn. Acetic acid was evaporated *in vacuo*. The residual oil was concentrated twice again after addition of 80 ml of dry benzene. The residue was purified by chromatography on silica gel eluting with ethyl acetate to afford 4.8 g of 3i.

**3i** Yield 23%. oil. Ir (CHCl<sub>3</sub>) 1720, 1610, 1260, 1140, 1090, 1025, 975. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 4.34 (q, 2H, J = 7.1 Hz), 4.15 (app pent, 4H), 3.78 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.3 Hz), 2.45 (s, 3H), 1.38 (t, 3H, J = 7.0 Hz), 1.32 (t, 6H, J = 7.0 Hz). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 169.31 (d, <sup>2</sup>J<sub>CP</sub> = 11.5 Hz), 161.86, 159.92, 110.07 (d, <sup>3</sup>J<sub>CP</sub> = 6.6 Hz), 62.80 (d, <sup>3</sup>J<sub>CP</sub> = 6.4 Hz), 60.89, 26.25 (d, <sup>1</sup>J<sub>CP</sub> = 137.8 Hz), 16.31 (d, <sup>3</sup>J<sub>CP</sub> = 6.2 Hz), 14.22, 11.84. Anal. Calcd for C<sub>12</sub>H<sub>20</sub>NO<sub>6</sub>P : C 47.21, H 6.60, N 4.59, P 10.15 : Found C 46.52, H 6.81, N 4.55, P 10.15.

**Ethyl 5-bromomethyl-3-methyl-4-isoxazolecarboxylate (3k).**

A mixture of ethyl 5-hydroxymethyl-3-methyl-4-isoxazolecarboxylate (3j)<sup>8a</sup> (12.4 g, 67 mmol), phosphorous tribromide (2.8 ml, 28 mmol) and anhydrous toluene (270 ml) was refluxed for 1 h. The solvent was evaporated *in vacuo* and the residue was purified by distillation under reduced pressure.

**3k** Yield 81%. bp 100-102°C/1Torr. Ir (CHCl<sub>3</sub>) 1720, 1610, 1220, 1140, 1090, 1050, 1020. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 4.74 (s, 2H), 4.38 (q, 2H, J = 7.1 Hz), 2.47 (s, 3H), 1.41 (t, 3H, J = 7.1 Hz). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 171.66, 161.22, 160.21, 109.62, 61.17, 17.66, 14.13, 11.70. Anal. Calcd for C<sub>8</sub>H<sub>10</sub>NO<sub>3</sub>Br : C 38.73, H 4.06, N 5.65, Br 32.21 : Found C 38.65, H 4.06, N 5.62, Br 32.16.

**Ethyl 5-diethylphosphonomethyl-3-methyl-4-isoxazolecarboxylate (3i) from ethyl 5-bromo-methyl-3-methyl-4-isoxazolecarboxylate (3k).**

To triethylphosphite (16 ml, 92.4 mmol) heated at 130 °C was added dropwise ethyl 5-bromomethyl-3-methyl-4-isoxazolecarboxylate (**3k**) (21 g, 84 mmol). After heating for 1 h at 130 °C, the residue was purified by distillation under reduced pressure (bp 155-160 °C/0.5 Torr) to afford 22.3 g (yield 87%) of compound (**3i**).

#### Ethyl 3-methyl-5-(2-(E)-alkenyl)-4-isoxazolecarboxylates (**3g,h**).

To a stirred solution of ethyl 5-diethylphosphonomethyl-3-methyl-4-isoxazolecarboxylate (**3i**) (3.06 g, 10 mmol) in anhydrous THF (100 ml) cooled at -70 °C, under nitrogen, was added dropwise a 1M solution of lithium bis(trimethylsilyl)amide in THF (11 ml). The mixture was kept for 1 h at -60 °C. A solution of aldehyde (benzaldehyde : 1.04 g, 9.8 mmol, or n-butanal : 0.76 g, 10.5 mmol) in anhydrous THF (10 ml) was then added. The cooling bath was removed and the mixture was allowed to react for 4 h. Water (20 ml) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 30 ml). The organic extracts were washed with brine (2 x 20 ml) and dried over sodium sulfate. After evaporation of the solvent *in vacuo*, the residue was purified either by recrystallization from cyclohexane to afford 1.76 g of **3g** or by chromatography on silica gel eluting with pentane-ether 9/1 to afford 1.88 g of **3h**.

**3g** Yield 82%. mp 100 °C. <sup>13</sup>Ir (CHCl<sub>3</sub>) 1710, 1630, 1580, 970. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.61-7.56 (m, 4H), 7.46-7.37 (m, 3H), 4.37 (q, 2H, J = 7.1 Hz), 2.47 (s, 3H), 1.42 (t, 3H, J = 7.1 Hz). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 170.82, 162.20, 160.14, 138.30, 135.26, 129.81, 128.90, 127.70, 112.81, 107.89, 60.70, 14.26, 11.93. Anal. Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub> : C 70.02, H 5.88, N 5.44 : Found C 70.26, H 6.21, N 5.47.

**3h** Yield 86%. oil. Ir (CHCl<sub>3</sub>) 1720, 1650, 1575, 980. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 6.94 (d, A part of an ABX<sub>2</sub> system, 1H, J<sub>AB</sub> = 16.2 Hz), 6.90-6.75 (m, B part of an ABX<sub>2</sub> system, 1H, J<sub>AB</sub> = 16.2 Hz, J<sub>BX</sub> = 6.0 Hz), 4.33 (q, 2H, J = 7.1 Hz), 2.43 (s, 3H), 2.29 (app q, 2H, J ~ 7.1 Hz), 1.55 (sext, 2H, J = 7.3 Hz), 1.38 (t, 3H, J = 7.1 Hz), 0.97 (t, 3H, J = 7.3 Hz). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 171.00, 162.40, 160.07, 143.23, 115.96, 106.65, 60.62, 35.41, 21.66, 14.27, 13.70, 11.95. Anal. Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub> : C 64.55, H 7.67, N 6.27 : Found C 64.44, H 7.72, N 6.34.

#### 4-(2-Dimethylphosphono-1-oxoethyl)-3-methylisoxazoles (**4a-h**).

To a stirred solution of dimethyl phosphonate (2.48 g, 20 mmol) in anhydrous THF (40 ml) cooled at -80 °C, under nitrogen, was added dropwise a 1.6 M solution of butyllithium in hexane (12.5 ml, 20 mmol). The mixture was kept for 45 mn at -80 °C. A solution of isoxazole (**3a-h**) (10 mmol) in THF (10 ml) was then added. The cooling bath was removed and the mixture was allowed to react for 3 h. The mixture was cooled with a water-ice bath and a 1M hydrochloric acid aqueous solution (10 ml) was added. The aqueous phase was extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with brine (2 x 20 ml) and dried over sodium sulfate. After evaporation of the solvent *in vacuo*, the residue was purified either by recrystallization from ethyl acetate-pentane 4/1 for **4g** or by chromatography on silica gel eluting with ethyl acetate for **4a-d,f,h** and ethyl acetate-methanol 9/1 for **4e**.

**4a** Yield 92%. oil. Ir (neat) 1670, 1605, 1260, 1055, 1025. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.68-7.49 (m, 5H), 3.69 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.3 Hz), 3.23 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.2 Hz), 2.48 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 187.40 (d, <sup>2</sup>J<sub>CP</sub> = 7.3 Hz), 172.44, 160.06, 131.75, 129.16, 126.91, 116.98 (d, <sup>3</sup>J<sub>CP</sub> = 3.5 Hz), 52.97 (d, <sup>2</sup>J<sub>CP</sub> = 6.4 Hz), 40.20 (d, <sup>1</sup>J<sub>CP</sub> = 130.6 Hz), 11.63 ; only 3 resonances are observed for the aromatic carbons. Anal. Calcd for C<sub>14</sub>H<sub>16</sub>NO<sub>5</sub>P : C 54.37, H 5.21, N 4.53, P 10.02 : Found : C 54.12, H 5.28, N 4.42, P 10.04.

**4b** Yield 91%. oil. Ir (neat) 1665, 1605, 1260, 1055, 1025. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.60 and 7.04 (AA'XX' system, 4H, J<sub>AX</sub> = 8.6 Hz, J<sub>AX'</sub> = 0.3 Hz, J<sub>AA'</sub> = J<sub>XX'</sub> = 2.4 Hz), 3.89 (s, 3H), 3.71 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.2 Hz), 3.27 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.2 Hz), 2.46 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 187.50 (d, <sup>2</sup>J<sub>CP</sub> = 7.3 Hz), 172.51, 162.33, 160.02, 130.81, 118.96, 116.21 (d, <sup>3</sup>J<sub>CP</sub> = 3.6 Hz), 114.63, 55.52, 52.99 (d, <sup>2</sup>J<sub>CP</sub> = 6.4 Hz), 40.05 (d, <sup>1</sup>J<sub>CP</sub> = 130.8 Hz), 11.69. Anal. Calcd for C<sub>15</sub>H<sub>18</sub>NO<sub>6</sub>P : C 53.10, H 5.35, N 4.13, P 9.13 : Found C 53.13, H 5.30, N 4.07, P 9.07.



**4c** Yield 91%. mp 63°C. Ir (CHCl<sub>3</sub>) 1670, 1600, 1240, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.64 (m, 2H), 7.53 (m, 2H), 3.72 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.3 Hz), 3.25 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.2 Hz), 2.49 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 187.19 (d, <sup>2</sup>J<sub>CP</sub> = 7.1 Hz), 171.17, 159.96, 138.16, 130.46, 129.48, 125.29, 117.18 (d, <sup>3</sup>J<sub>CP</sub> = 3.2 Hz), 53.06 (d, <sup>2</sup>J<sub>CP</sub> = 6.4 Hz), 40.47 (d, <sup>1</sup>J<sub>CP</sub> = 130.7 Hz), 11.72. Anal. Calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>5</sub>PCl : C 48.92, H 4.40, N 4.08, P 9.01, Cl 10.31 : Found C 48.80, H 4.46, N 4.15, P 8.27, Cl 10.44.

**4d** Yield 82%. oil. Ir (neat) 1670, 1570, 1255, 1060, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 6.75 (d, 2H, J = 2.1 Hz), 6.65 (t, 1H, J = 2.1 Hz), 3.85 (s, 6H), 3.71 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.2 Hz), 3.29 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.1 Hz), 2.46 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 187.51 (d, <sup>2</sup>J<sub>CP</sub> = 7.1 Hz), 172.28, 161.20, 160.12, 128.39, 117.05 (d, <sup>3</sup>J<sub>CP</sub> = 3.5 Hz), 107.13, 103.77, 55.66, 53.00 (d, <sup>2</sup>J<sub>CP</sub> = 6.4 Hz), 40.14 (d, <sup>1</sup>J<sub>CP</sub> = 130.6 Hz), 11.60. Anal. Calcd for C<sub>16</sub>H<sub>20</sub>NO<sub>7</sub>P : C 52.04, H 5.46, N 3.79, P 8.39 : Found C 51.56, H 5.70, N 3.68, P 8.31.

**4e** Yield 90%. oil. Ir (neat) 3120, 1670, 1250, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.71 (dd, 1H, J = 1.8 Hz, J = 0.7 Hz), 7.36 (dd, 1H, J = 3.7 Hz, J = 0.7 Hz), 6.65 (dd, 1H, J = 3.7 Hz, J = 1.8 Hz), 3.74 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.3 Hz), 3.65 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.3 Hz), 2.48 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 186.69 (d, <sup>2</sup>J<sub>CP</sub> = 7.3 Hz), 161.47, 159.81, 146.11, 141.79, 115.34, 112.67, 53.03 (d, <sup>2</sup>J<sub>CP</sub> = 6.5 Hz), 41.17 (d, <sup>1</sup>J<sub>CP</sub> = 131.3 Hz), 11.76. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>NO<sub>6</sub>P : C 48.17, H 4.72, N 4.68, P 10.35 : Found C 47.91, H 4.69, N 4.53, P 10.27.

**4f** Yield 93%. oil. Ir (neat) 3120, 1670, 1560, 1250, 1040. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 8.62 (s, 1H), 7.56 (m, 1H), 6.94 (m, 1H), 3.79 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.3 Hz), 3.49 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.2 Hz), 2.58 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 186.09 (d, <sup>2</sup>J<sub>CP</sub> = 6.9 Hz), 167.42, 158.52, 146.41, 143.87, 116.21, 113.75, 109.50, 53.17 (d, <sup>2</sup>J<sub>CP</sub> = 6.4 Hz), 40.26 (d, <sup>1</sup>J<sub>CP</sub> = 132.3 Hz), 12.61. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>NO<sub>6</sub>P : C 48.17, H 4.72, N 4.68 P 10.35 : Found C 48.07, H 4.83, N 4.49, P 10.17.

**4g** Yield 73%. mp 116°C. Ir (CHCl<sub>3</sub>) 1665, 1630, 1540, 1260, 1035. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.66-7.56 (m, 4H), 7.44-7.39 (m, 3H), 3.83 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.2 Hz), 3.49 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.2 Hz), 2.56 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 185.94 (d, <sup>2</sup>J<sub>CP</sub> = 7.0 Hz), 171.16, 158.80, 140.52, 135.00, 130.23, 128.98, 127.96, 115.79 (d, <sup>3</sup>J<sub>CP</sub> = 3.8 Hz), 112.72, 53.21 (d, <sup>2</sup>J<sub>CP</sub> = 6.6 Hz), 40.68 (d, <sup>1</sup>J<sub>CP</sub> = 132.0 Hz), 12.54. Anal. Calcd for C<sub>16</sub>H<sub>18</sub>NO<sub>5</sub>P : C 57.32, H 5.41, N 4.18, P 9.24 : Found C 57.35, H 5.49, N 4.18, P 8.93.

**4h** Yield 93%. mp 116°C. Ir (CHCl<sub>3</sub>) 1675, 1650, 1555, 1260, 1040. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 6.93-6.88 (m, 2H), 3.83 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.3 Hz), 3.45 (d, 2H, <sup>2</sup>J<sub>HP</sub> = 22.1 Hz), 2.50 (s, 3H), 2.37-2.27 (m, 2H), 1.57 (sext, 2H, J = 7.3 Hz), 0.98 (t, 3H, J = 7.3 Hz). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 186.00 (d, <sup>2</sup>J<sub>CP</sub> = 7.1 Hz), 171.00, 158.84, 145.68, 115.85, 114.84 (d, <sup>3</sup>J<sub>CP</sub> = 3.9 Hz), 53.17 (d, <sup>2</sup>J<sub>CP</sub> = 6.5 Hz), 40.58 (d, <sup>1</sup>J<sub>CP</sub> = 132.6 Hz), 35.52, 21.61, 13.69, 12.47. Anal. Calcd for C<sub>13</sub>H<sub>20</sub>NO<sub>5</sub>P : C 51.83, H 6.69, N 4.65, P 10.28 : Found C 52.27, H 6.47, N 4.62, P 10.41.

#### 4-(2-Diazo-2-dimethylphosphono-1-oxoethyl)-3-methylisoxazoles (5a-h)

To a mixture of β-ketophosphonates (**4a-h**) (6 mmol) and potassium carbonate (1 g, 7.2 mmol) in acetonitrile (20 ml) cooled in a water-ice bath, under nitrogen, was added dropwise with stirring a solution of tosyl azide<sup>14</sup> (1.42 g, 7.2 mmol) in acetonitrile (5 ml). The cooling bath was removed and the mixture was stirred at room temperature. The disappearance of compounds (**4**) was monitored by tlc. After ~ 1 h potassium carbonate was filtered off and acetonitrile was evaporated *in vacuo*. Anhydrous ethyl ether (50 ml) was added and the ethereal solution was filtered on celite; ethyl ether was evaporated *in vacuo* and the residue was purified by chromatography on silica gel eluting with ethyl acetate for **5a-d,f-h** or ethyl acetate-pentane 65/35 for **5e**.

**5a** Yield 87%. mp 65°C. Ir (CHCl<sub>3</sub>) 2120, 1630, 1270, 1040. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.74-7.68 (m, 2H), 7.57-7.48 (m, 3H), 3.72 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.9 Hz), 2.39 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 180.82 (d, <sup>2</sup>J<sub>CP</sub> = 9.5 Hz), 167.88, 159.28, 131.58, 129.42, 127.11, 126.71, 113.59 (d, <sup>3</sup>J<sub>CP</sub> = 3.9 Hz), 66.20 (d, <sup>1</sup>J<sub>CP</sub> = 221.0 Hz), 54.00 (d, <sup>2</sup>J<sub>CP</sub> = 6.1 Hz), 10.47. Anal. Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>3</sub>O<sub>5</sub>P : C 50.16, H 4.21, N 12.53, P 9.24 : Found C 49.89, H 4.24, N 12.69, P 8.84.

**5b** Yield 82%. mp 96°C. Ir (CHCl<sub>3</sub>) 2110, 1630, 1605, 1260, 1040, 1025. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.65 and 7.02 (AA'XX' system, 4H, J<sub>AX</sub> = 8.6 Hz, J<sub>AX'</sub> = 0.3 Hz, J<sub>AA'</sub> = J<sub>XX'</sub> = 2.5 Hz), 3.98 (s, 3H), 3.78 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.91 Hz), 2.37 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 180.82 (d, <sup>2</sup>J<sub>CP</sub> = 9.1 Hz), 168.11, 162.21, 159.30, 128.78, 119.05, 114.88, 112.53 (d, <sup>3</sup>J<sub>CP</sub> = 4.6 Hz), 65.80 (d, <sup>1</sup>J<sub>CP</sub> = 221.0 Hz), 55.50, 54.09 (d, <sup>2</sup>J<sub>CP</sub> = 6.1 Hz), 10.51. Anal. Calcd for C<sub>15</sub>H<sub>16</sub>N<sub>3</sub>O<sub>6</sub>P : C 49.32, H 4.41, N 11.50, P 8.48 : Found C 49.43, H 4.59, N 11.28, P 8.36.

**5c** Yield 91%. mp 96°C. Ir (CHCl<sub>3</sub>) 2120, 1635, 1265, 1050, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.81 and 7.50 (AA'XX' system, 4H, J<sub>AX</sub> ~ 8.0 Hz, J<sub>AX'</sub> ~ 0.5 Hz, J<sub>AA'</sub> = J<sub>XX'</sub> ~ 2.8 Hz), 3.73 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.9 Hz), 2.38 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 180.66 (d, <sup>2</sup>J<sub>CP</sub> = 9.9 Hz), 166.57, 159.19, 137.80, 129.73, 128.35, 125.09, 113.84 (d, <sup>3</sup>J<sub>CP</sub> = 3.4 Hz), 66.44 (d, <sup>1</sup>J<sub>CP</sub> = 221.4 Hz), 54.05 (d, <sup>2</sup>J<sub>CP</sub> = 6.1 Hz), 10.41. Anal. Calcd for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>PCl : C 45.48, H 3.40, N 11.37, P 8.38, Cl 9.59 : Found C 45.49, H 3.59, N 11.22, P 8.43, Cl 9.53.

**5d** Yield 80%. mp 108°C. Ir (CHCl<sub>3</sub>) 2125, 1635, 1600, 1580, 1275. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 6.82 (d, 2H, J = 2.2 Hz), 6.61 (t, 1H, J = 2.2 Hz), 3.83 (s, 6H), 3.79 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 12.0 Hz), 2.38 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 180.59 (d, <sup>2</sup>J<sub>CP</sub> = 9.0 Hz), 167.80, 161.46, 159.42, 128.07, 113.66 (d, <sup>3</sup>J<sub>CP</sub> = 4.8 Hz), 105.05, 103.52, 66.09 (d, <sup>1</sup>J<sub>CP</sub> = 220.5 Hz), 55.60, 54.12 (d, <sup>2</sup>J<sub>CP</sub> = 6.1 Hz), 10.50. Anal. Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>3</sub>O<sub>7</sub>P : C 48.61, H 4.59, N 10.63, P 7.84 : Found C 48.67, H 4.81, N 10.50, P 7.88.

**5e** Yield 66%. mp 120°C. Ir (CHCl<sub>3</sub>) 2120, 1635, 1275, 1055, 1035, 1055, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.65 (d, 1H, J = 1.7 Hz), 7.10 (d, 1H, J = 3.5 Hz), 6.63 (dd, 1H, J = 3.5 Hz, J = 1.7 Hz), 3.82 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 12.0 Hz), 2.37 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 179.66 (d, <sup>2</sup>J<sub>CP</sub> = 9.2 Hz), 159.14, 158.34, 145.73, 141.86, 113.90, 112.68, 112.16 (d, <sup>3</sup>J<sub>CP</sub> = 4.5 Hz), 66.07 (d, <sup>1</sup>J<sub>CP</sub> = 219.4 Hz), 54.03 (d, <sup>2</sup>J<sub>CP</sub> = 6.0 Hz), 10.28. Anal. Calcd for C<sub>12</sub>H<sub>12</sub>N<sub>3</sub>O<sub>6</sub>P : C 44.32, H 3.72, N 12.92, P 9.52 : Found C 44.47, H 3.76, N 12.79, P 9.01.

**5f** Yield 75%. mp 122°C. Ir (CHCl<sub>3</sub>) 2110, 1630, 1270, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 8.04 (s, 1H), 7.58 (m, 1H), 6.78 (m, 1H), 3.84 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.9 Hz), 2.39 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 180.07 (d, <sup>2</sup>J<sub>CP</sub> = 9.2 Hz), 162.69, 158.46, 144.73, 143.21, 113.44, 113.36, 108.12, 65.86 (d, <sup>1</sup>J<sub>CP</sub> = 220.6 Hz), 54.22 (d, <sup>2</sup>J<sub>CP</sub> = 6.1 Hz), 10.46. Anal. Calcd for C<sub>12</sub>H<sub>12</sub>N<sub>3</sub>O<sub>6</sub>P : C 44.32, H 3.72, N 12.92, P 9.52 : Found C 44.47, H 3.77, N 13.15, P 9.58.

**5g** Yield 71%. oil. Ir (neat) 2120, 1630, 1260, 1050, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 7.59-7.50 (m, 3H), 7.47-7.31 (m, 3H), 6.97 (d, 1H, J = 16.4 Hz), 3.86 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.9 Hz), 2.38 (s, 3H). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>) δ 180.17 (d, <sup>2</sup>J<sub>CP</sub> = 9.4 Hz), 167.36, 159.22, 139.20, 135.34, 130.74, 129.63, 128.20, 115.00 (d, <sup>3</sup>J<sub>CP</sub> = 4.1 Hz), 111.58, 66.05 (d, <sup>1</sup>J<sub>CP</sub> = 221.2 Hz), 54.80 (d, <sup>2</sup>J<sub>CP</sub> = 6.2 Hz), 11.10. Anal. Calcd for C<sub>16</sub>H<sub>16</sub>N<sub>3</sub>O<sub>5</sub>P : C 53.19, H 4.46, N 11.63, P 8.57 : Found C 52.99, H 4.43, N 11.74, P 7.83.

**5h** Yield 76%. oil. Ir (neat) 2120, 1635, 1270, 1030.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  6.89-6.73 (m, 1H), 6.39-6.26 (m, 1H), 3.87 (d, 6H,  $^3\text{J}_{\text{HP}} = 11.9$  Hz), 2.34 (s, 3H), 2.34-2.23 (m, 2H), 1.54 (sext, 2H,  $J = 7.3$  Hz), 0.98 (t, 3H,  $J = 7.3$  Hz).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  179.58 (d,  $^2\text{J}_{\text{CP}} = 8.6$  Hz), 166.71, 158.71, 143.84, 114.28, 113.14 (d,  $^3\text{J}_{\text{CP}} = 5.3$  Hz), 65.18 (d,  $^1\text{J}_{\text{CP}} = 219.4$  Hz), 54.26 (d,  $^2\text{J}_{\text{CP}} = 6.2$  Hz), 35.39, 21.72, 13.67, 10.52. Anal. Calcd for  $\text{C}_{13}\text{H}_{18}\text{N}_3\text{O}_5\text{P}$ : C 47.71, H 5.54, N 12.84, P 9.46 : Found C 47.96, H 5.54, N 12.57, P 9.19.

**4-Dimethylphosphono-5-hydroxynaphth[2,1-*d*]isoxazoles (6a-d), 4-Dimethylphosphono-5-hydroxy[1]benzofuro[6,7-*d*]isoxazole (7), 4-Dimethylphosphono-5-hydroxy[1]benzofuro[5,4-*d*]isoxazole (8) and 4-Dimethylphosphono-5-hydroxy-1,2-benzisoxazoles (9a,b).**

To the  $\alpha$ -diazo- $\beta$ -ketophosphonates (5a-h) (2.5 mmol) was added anhydrous benzene (30 ml) and benzene was evaporated *in vacuo*. This operation was repeated once again. Compounds (5a-h) were then dissolved in anhydrous benzene (100 ml) and the solution was introduced in a high-pressure autoclave and heated under the conditions described in Table 1. Benzene was evaporated *in vacuo* and the residue was purified by chromatography on silica gel eluting with ethyl acetate for 6b,6d, ethyl ether for 6c,9a,9b, ethyl ether-pentane 65/35 for 6a or ethyl ether-pentane 4/1 for 7,8. For  $^{13}\text{C-nmr}$  data of compounds (6-9), see Table 2.

**6a** Yield 67%. mp 78°C. Ir ( $\text{CHCl}_3$ ) 3400-2500, 1635, 1575, 1170, 1030.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  12.03 (d, 1H,  $^4\text{J}_{\text{HP}} = 1.1$  Hz), 8.35 (dd, 1H,  $J = 8.2$  Hz,  $J = 1.2$  Hz), 8.32 (dd, 1H,  $J = 7.6$  Hz,  $J = 1.1$  Hz), 7.81 (br td, 1H,  $J = 7.1$  Hz,  $J = 1.3$  Hz), 7.68 (br td, 1H,  $J = 7.1$  Hz,  $J = 1.3$  Hz), 3.83 (d, 6H,  $^3\text{J}_{\text{HP}} = 11.7$  Hz), 2.64 (s, 3H). Anal. Calcd for  $\text{C}_{14}\text{H}_{14}\text{NO}_5\text{P}$ : C 54.73, H 4.59, N 4.56, P 10.08 : Found C 54.68, H 4.49, N 4.68, P 10.08.

**6b** Yield 60%. mp 162°C. Ir ( $\text{CHCl}_3$ ) 3400-2500, 1630, 1600, 1575, 1175, 1025.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  12.02 (d, 1H,  $^4\text{J}_{\text{HP}} = 1.2$  Hz), 8.23 (d, 1H,  $J = 8.9$  Hz), 7.79 (d, 1H,  $J = 2.5$  Hz), 7.42 (dd, 1H,  $J = 8.9$  Hz,  $J = 2.5$  Hz), 3.99 (s, 3H), 3.82 (d, 6H,  $^3\text{J}_{\text{HP}} = 11.8$  Hz), 2.62 (s, 3H). Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{NO}_6\text{P}$ : C 53.42, H 4.78, N 4.15, P 9.18 : Found C 54.04, H 5.03, N 3.79, P 9.19.

**6c** Yield 43%. mp 145°C. Ir ( $\text{CHCl}_3$ ) 3400-2500, 1570, 1175, 1030.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  12.04 (s, 1H), 8.47 (d, 1H,  $J = 2.1$  Hz), 8.26 (d, 1H,  $J = 8.7$  Hz), 7.75 (dd, 1H,  $J = 8.7$  Hz,  $J = 2.1$  Hz), 3.83 (d, 6H,  $^3\text{J}_{\text{HP}} = 11.7$  Hz), 2.64 (s, 3H). Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{NO}_5\text{PCl}$ : C 49.21, H 3.83, N 4.10, P 9.06, Cl 10.38 : Found C 49.16, H 3.84, N 4.07, P 9.07, Cl 10.73.

**6d** Yield 73%. mp 134°C. Ir ( $\text{CHCl}_3$ ) 3400-2500, 1630, 1600, 1585, 1175, 1050, 1030.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  12.17 (s, 1H), 7.15 (d, 1H,  $J = 2.2$  Hz), 6.63 (d, 1H,  $J = 2.2$  Hz), 4.01 (s, 3H), 3.98 (s, 3H), 3.83 (d, 6H,  $^3\text{J}_{\text{HP}} = 11.7$  Hz), 2.63 (s, 3H). Anal. Calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_7\text{P}$ : C 52.32, H 4.94, N 3.81, P 8.43 : Found C 51.63, H 4.96, N 3.53, P 8.19.

**7** Yield 80%. mp 140°C. Ir ( $\text{CHCl}_3$ ) 3400-2500, 1605, 1175, 1050, 1030.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  11.74 (d, 1H,  $^4\text{J}_{\text{HP}} = 1.2$  Hz), 7.78 (d, 1H,  $J = 2.1$  Hz), 7.11 (d, 1H,  $J = 2.1$  Hz), 3.82 (d, 6H,  $^2\text{J}_{\text{HP}} = 11.7$  Hz), 2.64 (s, 3H). Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{NO}_6\text{P}$ : C 48.50, H 4.07, N 4.71, P 10.42 : Found C 48.65, H 4.13, N 4.71, P 9.98.

**8** Yield 72%. mp 138°C. Ir ( $\text{CHCl}_3$ ) 3400-2500, 1630, 1600, 1175, 1050, 1030.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  11.72 (s, 1H), 7.90 (dd, 1H,  $J = 1.9$  Hz,  $J = 0.6$  Hz), 7.14 (d, 1H,  $J = 1.9$  Hz), 3.85 (d, 6H,  $^2\text{J}_{\text{HP}} = 11.8$  Hz), 2.64 (s, 3H). Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{NO}_6\text{P}$ : C 48.50, H 4.07, N 4.71, P 10.42 : Found C 48.50, H 4.22, N 4.79, P 10.24.

**9a** Yield 65%. mp 140°C. Ir (CHCl<sub>3</sub>) 3400-2500, 1600, 1175, 1050, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 11.53 (s, 1H), 7.70 (s, 1H), 7.63-7.50 (m, 2H), 7.50-7.38 (m, 3H), 3.83 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.7 Hz), 2.63 (s, 3H). Anal. Calcd for C<sub>16</sub>H<sub>16</sub>NO<sub>5</sub>P : C 57.66, H 4.84, N 4.20, P 9.29 : Found C 57.99, H 4.82, N 4.25, P 9.16.

**9b** Yield 73%. oil. Ir (CHCl<sub>3</sub>) 3400-2500, 1600, 1175, 1050, 1020. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 11.33 (s, 1H), 7.54 (s, 1H), 3.82 (d, 6H, <sup>3</sup>J<sub>HP</sub> = 11.4 Hz), 2.73 (t, 2H, J = 7.3 Hz), 2.58 (s, 3H), 1.71 (sext, 2H, J = 7.4 Hz), 1.00 (t, 3H, J = 7.3 Hz). Anal. Calcd for C<sub>13</sub>H<sub>18</sub>NO<sub>5</sub>P : C 52.18, H 6.06, N 4.68, P 10.35 : Found C 52.49, H 6.13, N 4.64, P 10.34.

#### 4-[(Dimethylphosphono)(methoxycarbonyl)methyl]isoxazole (12a)

To the α-diazo-β-ketophosphonate (5a) (100 mg, 0.3 mmol) was added anhydrous benzene (30 ml) and benzene was evaporated *in vacuo*. This operation was repeated once again. Anhydrous toluene (5 ml) was then added and the solution was heated to reflux under nitrogen ; the disappearance of compound (5a) was monitored by tlc. After ~ 2 h anhydrous methanol (1 ml) was added and the solution was refluxed for 5 mn. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel eluting with ethyl acetate.

**12a** Yield 75%. oil. Ir (CHCl<sub>3</sub>) 1735, 1260, 1030. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 8.49-8.32 (m, 2H), 7.67-7.49 (m, 3H), 4.47 (d, 1H, <sup>2</sup>J<sub>HP</sub> = 26.8 Hz), 3.83 (d, 3H, <sup>3</sup>J<sub>HP</sub> = 11.1 Hz), 3.74 (s, 3H), 3.69 (d, 3H, <sup>3</sup>J<sub>HP</sub> = 11.0 Hz), 2.47 (s, 3H).

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