AN EFFICIENT SYNTHESIS OF 3-PHOSPHORYLATED 4(1*H*)-PYRIDONES AND 4-CHLOROPYRIDINES FROM β-ENAMINOPHOSPHONATES

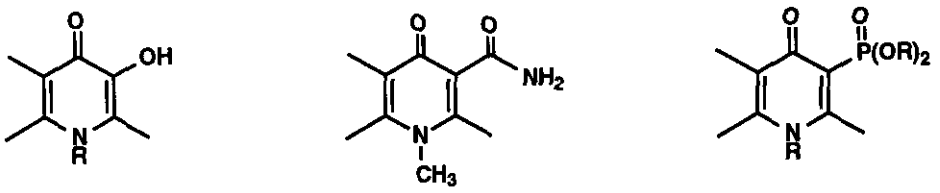
Francisco Palacios*, Ana Mª Ochoa de Retana, and Julen Oyarzabal

Departamento de Química Orgánica, Facultad de Farmacia, Universidad del País Vasco,
Apartado 450, 01080 Vitoria, Spain

Abstract- An easy and efficient synthesis of 4(1*H*)-pyridones (**1**) substituted with a phosphate group in the 3-position is described. The key step is an addition of β-enaminophosphonates (**2**) to acylketene (**3**) generated either from diketene (**4**) or from the "diketene-acetone adduct", 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**5**). Subsequent treatment of 4(1*H*)-pyridones with phosphorus oxychloride in the presence of dimethylformamide afforded the substituted 4-chloropyridine (**6**).

Pyridone ring systems represent an important class of compounds[1] and have attracted an attention in recent years for their biological activities.[2] 4(1*H*)-Pyridones constitute the backbone not only of mimosine (**I**) (R= $CH_2CH(NH_2)COOH$), a rare amino acid derived from *Mimosa* and *Leucaena* plants[3a,b] that inhibits the replication of animal cells *"in vitro"*,[3c,d] but also of modified nucleoside isolated from human urine,[4] while pyridone (**II**) is the major metabolite of nicotinamide and nicotinic acid in rats,[5a] useful as a biological marker to assess the amino acid intake[5b] and useful for the biotransformation of tryptophan to niacin[5c] (Scheme 1). Likewise, 4(1*H*)-pyridones have been used as antiinflammatory[6a] and antibacterial agents,[6b] as neuromuscular membrane-permeant antagonists,[6c] as enzymatic inhibitors[6d] and for prevention of leucaena toxicosis in cattle.[6e] Furthermore, 4(1*H*)-pyridones are key intermediates in the synthesis of oxidopyridinium ylides,[7a] nucleosides[7b,c] as well as of semi-synthetic antibiotics with excellent antibacterial activity such as MT 0703[7d] and KP 736 cephalosporins[7e] and carbapenems,[7f,g] while 1,2-dimethyl-3-hydroxy-4(1*H*)-pyridone (**I**) (R= CH_3) forms stable chelators with metals[8a,b] and may find application for the removal of metals from the body in the chelation therapy of aluminium intoxication[8c,d] and as radiopharmaceuticals.[8e] Likewise, pyridones are iron chelators suitable for oral administration[9a] and have been used for both urinary and biliary iron excretion,[9b] for the treatment of anemias,[9c] and for the inhibition of tyrosinase.[9d] In these types of 4(1*H*)-pyridones the presence of an hydroxy or a carbonyl group in the position 3 (see compounds (**I**) and (**II**), Scheme 1) seems to play a key role in the biological activity of these compounds.

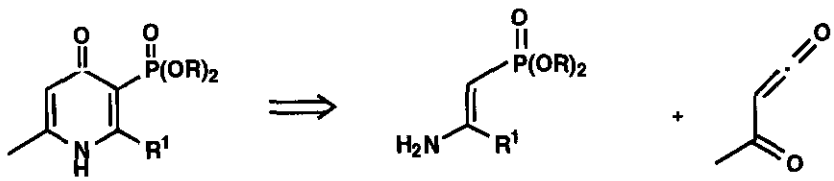
Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday



I II 1

Scheme 1

With this in mind, we are interested in the design of new 4(1*H*)-pyridone derivatives substituted with a phosphonate group in the 3 position of the heterocyclic system. This substitutent could regulate important biological functions and could increase the biological activity of these type of compounds, in a similar way to that reported for other pharmaceuticals.[10] Classical approaches[1a] to 4(1*H*)-pyridones involving heterocyclic precursors[11] as well as heterocyclization reactions from pentadiyones,[12a] 1,3,5,-triketones,[12b] 1,4-dien-3-ones[12c,d] azirines,[13a] imines[13b,c] and enamines,[6a,13d-e] have been reported. However, to the best of our knowledge, the synthesis of phosphorus substituted 4(1*H*)-pyridones has not been reported. In connection with our interest in the synthesis of five-[14] and six-membered[15] phosphorylated nitrogen heterocycles we have used β-functionalized enamines derived from phosphazenes, phosphonium salts, phosphine oxides and phosphonates as synthetic intermediates in the synthesis of acyclic derivatives such as oximes,[16a] allylamines,[16b] hydrazones,[16c] azadienes, [16d] aminodienes,[16e] and β-amino functionalizaed compounds[16f,g] as well as phosphorus containing heterocycles.[17] In this context, it is noteworthy that, retrosynthetically, 4(1*H*)-pyridones (**1**) substituted by a phosphonate group in 3-position could be envisaged by reaction of primary enamines (**2**) with acylketene (**3**) (Scheme 2).

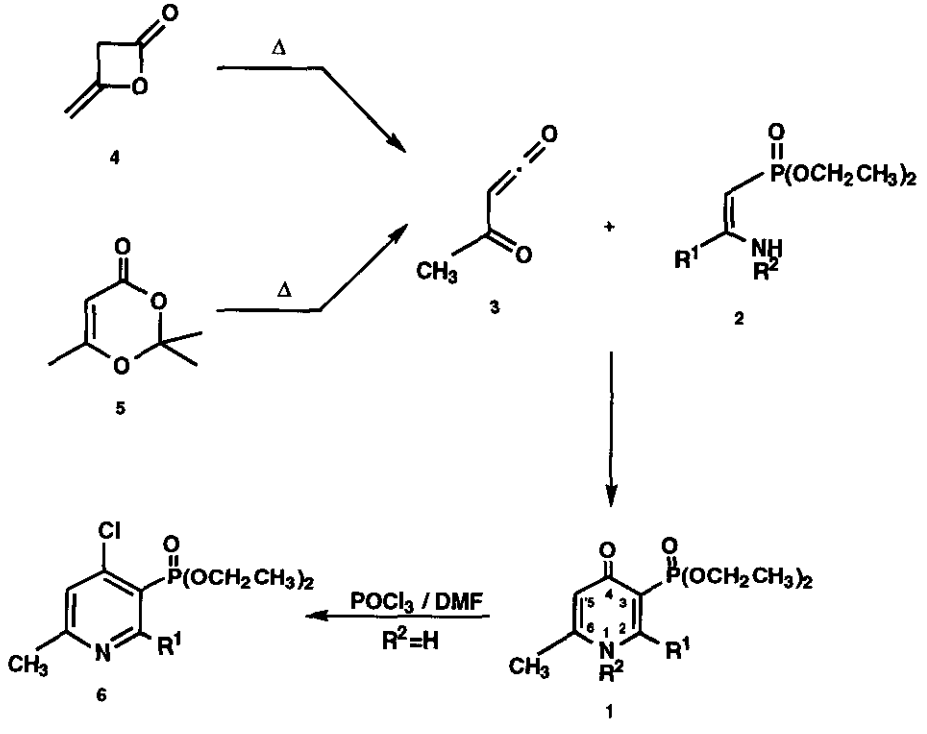


1 2 3

Scheme 2

Primary enamines are, however, not stable unless conjugated with an electron-withdrawing group on the β-carbon.[18] In previous papers we have reported a preparation of primary β-enamines derived from phosphazenes[19] and from phosphonates[15b] and we have used them in the synthesis of cyclic[15b,17,20] and acyclic[16g,19] compounds. Continuing with our interest in the synthesis of new phosphorus substituted heterocycles and with the reactivity of functionalized enamines, we report here an easy and high yielding synthesis of 3-phosphonylpyridones (**1**) from primary β-enaminophosphonates (**2**) and acylketenes generated either from diketene (**4**) or from thermolysis of the commercially available and inexpensive 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**5**).[21,22]

When primary β-enaminophosphonates (R^2=H) (**2**) were allowed to react with an equimolecular amount of diketene (**4**) in toluene at 110°C (7 d) or heating above 100°C in the absence of solvent (12 h), 4(1*H*)-pyridones (**1**) were obtained (see Table 1) in a regioselective fashion (Scheme 3). Compounds (**1**) were characterized on the basis of their spectroscopic data. Thus, in the ^{1}H-NMR spectrum of compound (**1a**), heterocyclic proton (H-5) of pyridone resonates at δ_H= 6.90 ppm as a well resolved doublet with the long-range coupling constant $^4J_{PH}$= 3.9 Hz, while the the ^{13}C-NMR spectrum of this compound (**1a**) showed absorptions at δ_C= 176.5 ($^2J_{PC}$= 5.5 Hz) ppm assignable to the carbonyl group, as well as doublets at 159.0 ($^2J_{PC}$= 12.8 Hz), 115.8 ($^1J_{PC}$= 164.2 Hz) and 114.3 ($^3J_{PC}$= 9.0 Hz) for C-2, C-3 and C-5, respectively.



Scheme 3

In order to enhance the scope and the synthetic use of this reaction, the synthesis of pyridone (**1**) derivatives substituted with phosphonic ester groups using synthetic analogues of diketene (**4**) was explored. We chose 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**5**), the "diketene-acetone adduct", a commercialy available and inexpensive reagent. [21,22] Thermolysis of dioxin-4-one (**5**) above 100°C yields acetylketene and this powerful acetoacetylating agent reacts (12 h) with primary enamines (R^2=H) (**2**) affording pyridones (**1**) in excellent yields (see Table 1).

Table 1. 4(1*H*)-Pyridones (**1**) and 4-Chloropyridine (**6**).

Compound	R^1	R^2	Yield (%)			mp (°C)
1a	*p*-CH_3-C_6H_4	H	88[a]	91[b]	90[c]	267-268
1b		H		87[b]	92[c]	265-266
1c		H	71[a]	84[b]		248-249
1d		H		88[b]		240-241
1e		H		86[b]		242-243
1f					94[c]	180-181
1g		*p*-Cl-C_6H_4			81[c]	210-211
6		-		72[d]		153-154

[a]Yield of isolated products (**1**) based on **2** in toluene at 110°C from diketene (**4**). [b]Yield of isolated products based on **2** without solvent from diketene (**4**). [c]Yield of isolated products based on **2** from dioxin-4-one (**5**). [d]Yield of isolated product (**6**) based on **1**.

These results prompted us to extend this reaction and to explore whether secondary enamines with acetylketenes showed a similar reaction pattern leading to new *N*-substituted pyridones (**1**) (R^2= aryl) with phosphonic ester groups. Thus, the reaction of enamines (**2**) (R^2=aryl) with "diketene-acetone-adduct" (**5**) at 110°C (12 h) yielded *N*-substituted pyridones (**1f,g**) (see Table 1). Spectral data are in agreement with the structure (**1**) and are consistent with previously reported data for compounds (**1a-e**). Therefore, this methodology can be used not only for the preparation of *N*-unsubstituted pyridones (**1a-e**) but also can be applied to the synthesis of *N*-substituted heterocyles (**1f-g**).

On the other hand, 4(1*H*)-pyridones (**1**) are useful intermediates for the preparation of 4-chloropyridines. Treatment of compound (**1b**) with phosphorus oxychloride in dimethylformamide (DMF) and dichlormethane at rt led to the formation of 4-chloropyridine (**6**) (Scheme 3) in excellent yield. Spectroscopic data were in agreement with the assigned structure. MS of **6** showed the molecular ion peak (*m/z*, 339, 40%) as well as M+2 (*m/z*, 341, 14%). To the best of our knowledge, this route

describes the first synthesis of phosphorylated 4-chloropyridines. In this context, it is noteworthy that 4-chloropyridines are key intermediates for the preparation of biologically active compounds such as the benzodiazepine receptor ligand S-8510,[23a] antibiotics, [23b] and complexes with antitumor[23c] or mutagenic activity. [23d]

Table 2. Selected spectral data for the compounds.

Compound	^{31}P-NMR (CD_3OD)[a] δ (ppm)	^{1}H-NMR (CD_3OD)[a] δ (ppm)	^{13}C-NMR (CD_3OD)[a] δ (ppm)	IR[b] ν (cm^{-1})	MS[c] (m/z)
1a	8.4	0.86 (t, 6H, $^{3}J_{HH}$=6.9 Hz, CH_3), 2.28 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.41 (m, 4H, OCH_2), 6.91 (d, 1H, $^{4}J_{PH}$=3.9 Hz, CH), 7.3 (m, 4H, arom)	16.5 (d, $^{3}J_{PC}$=8.0 Hz, CH_3), 19.1 (CH_3), 21.5 (CH_3), 62.1 (d, $^{2}J_{PC}$=6.0 Hz, OCH_2), 114.3 (d, $^{3}J_{PC}$=9.0 Hz, C-5), 115.8 (d, $^{1}J_{PC}$=164.2 Hz, C-3), 129.7-130.4 (C-arom), 142.2 (C-ipso arom), 155.4 (C-6), 159.0 (d, $^{2}J_{PC}$=12.8 Hz, C-2), 176.2 (d, $^{2}J_{PC}$=5.5 Hz, C=O)	3076(NH) 1651(C=O) 1205 (P=O)	335 (M^+, 30%)
1b	8.5	0.80 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 2.38 (s, 3H, CH_3), 3.34 (m, 4H, OCH_2), 6.87 (d, 1H, $^{4}J_{PH}$=3.8 Hz, CH), 7.32-7.43 (m, 5H, arom)	16.5 (d, $^{3}J_{PC}$=7.6 Hz, CH_3), 19.2 (CH_3), 62.1 (d, $^{2}J_{PC}$=5.5 Hz, OCH_2), 114.3 (d, $^{3}J_{PC}$=8.6 Hz, C-5), 115.8 (d, $^{1}J_{PC}$=166.2 Hz, C-3), 129.1-130.5 (C-arom), 134.4 (C-ipso arom), 155.6 (C-6), 158.8 (d, $^{2}J_{PC}$=12.6 Hz, C-2), 176.1 (d, $^{2}J_{PC}$=5.5 Hz, C=O)	3092 (NH) 1648 (C=O) 1211 (P=O)	321 (M^+, 35%)
1c	8.2	0.90 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.45 (s, 3H, CH_3), 3.58 (m, 4H, OCH_2), 6.54-7.86 (m, 3H, arom), 6.80 (d, 1H, $^{4}J_{PH}$=3.4 Hz, CH)	16.4 (d, $^{3}J_{PC}$=7.1 Hz, CH_3), 19.4 (CH_3), 62.5 (d, $^{2}J_{PC}$=5.6 Hz, OCH_2), 112.0 (d, $^{1}J_{PC}$=159.6 Hz, C-3), 114.1 (d, $^{3}J_{PC}$=8.1 Hz, C-5), 114.2-147.7 (C-arom), 145.1 (C-ipso arom), 146.5 (d, $^{2}J_{PC}$=10.6 Hz, C-2), 156.0 (C-6), 176.5 (d, $^{2}J_{PC}$=4.6 Hz, C=O)	3151 (NH) 1647 (C=O) 1206 (P=O)	311 (M^+, 100%)
1d	8.2	0.88 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.41 (s, 3H, CH_3), 3.48 (m, 4H, OCH_2), 6.88 (d, 1H, $^{4}J_{PH}$=3.5 Hz, CH), 7.0-7.6 (m, 3H, arom)	16.6 (d, $^{3}J_{PC}$=7.6 Hz, CH_3), 19.2 (CH_3), 62.3 (d, $^{2}J_{PC}$=5.9 Hz, OCH_2), 114.7 (d, $^{3}J_{PC}$=8.6 Hz, C-5), 116.8 (d, $^{1}J_{PC}$=163.2 Hz, C-3), 128.2-133.9 (C-arom), 132.7 (C-ipso arom), 152.3 (d, $^{2}J_{PC}$=11.6 Hz, C-2), 156.1 (C-6), 176.1 (d, $^{2}J_{PC}$=5.1 Hz, C=O)	3129 (NH) 1645 (C=O) 1229 (P=O)	327 (M^+, 100%)
1e	7.9	0.84 (t, 6H, $^{3}J_{HH}$=6.9 Hz, CH_3), 2.48 (s, 3H, CH_3), 3.47 (m, 4H, OCH_2), 7.00 (d, 1H, $^{4}J_{PH}$=3.8 Hz, CH), 7.5-8.6 (m, 5H, arom)	16.4 (d, $^{3}J_{PC}$=7.6 Hz, CH_3), 19.5 (CH_3), 62.2 (d, $^{2}J_{PC}$=5.5 Hz, OCH_2), 114.9 (d, $^{3}J_{PC}$=8.1 Hz, C-5), 115.7 (d, $^{1}J_{PC}$=161.6 Hz, C-3), 126.8-150.2 (C-arom), 151.9 (C-ipso arom), 156.0 (d, $^{2}J_{PC}$=12.6 Hz, C-2), 156.5 (C-6), 176.0 (d, $^{2}J_{PC}$=6.0 Hz, C=O)	3084 (NH) 1642 (C=O) 1217 (P=O)	322 (M^+, 42%)

Table 2. (continuation)

Compound	^{31}P-NMR ($CDCl_3$)[a] δ (ppm)	^{1}H-NMR ($CDCl_3$)[a] δ (ppm)	^{13}C-NMR ($CDCl_3$)[a] δ (ppm)	IR[b] υ (cm^{-1})	MS[c] (m/z)
1f	15.4	1.09 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 1.91 (s, 3H, CH_3), 3.89 (m, 2H, OCH_2), 4.06 (m, 2H, OCH_2), 6.41 (d, 1H, $^{4}J_{PH}$=5.9 Hz, CH), 6.93-7.21 (m, 10H, arom)	16.1 (d, $^{3}J_{PC}$=6.5 Hz, CH_3), 21.8 (CH_3), 61.8 (d, $^{2}J_{PC}$=6.0 Hz, OCH_2), 117.4 (d, $^{1}J_{PC}$=194.9 Hz, C-3), 119.2 (d, $^{3}J_{PC}$=9.0 Hz, C-5), 127.0-129.2 (C-arom), 134.5 (C-ipso arom), 139.3 (C-ipso arom), 148.7 (C-6), 157.5 (d, $^{2}J_{PC}$=18.1 Hz, C-2), 178.2 (d, $^{2}J_{PC}$=4.0 Hz, C=O)	3051 (NH) 1635 (C=O) 1246 (P=O)	397 (M^+, 5%)
1g	15.0	1.44 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.27 (s, 3H, CH_3), 4.24 (m, 2H, OCH_2), 4.38 (m, 2H, OCH_2), 6.76 (d, 1H, $^{4}J_{PH}$=6.3 Hz, CH), 7.23-7.89 (m, 9H, arom)	16.1 (d, $^{3}J_{PC}$=6.0 Hz, CH_3), 21.9 (CH_3), 61.9 (d, $^{2}J_{PC}$=6.0 Hz, OCH_2), 117.7 (d, $^{1}J_{PC}$=195.9 Hz, C-3), 119.3 (d, $^{3}J_{PC}$=9.1 Hz, C-5), 127.3-130.5 (C-arom), 134.2 (C-ipso arom), 134.8 (C-ipso arom), 137.8 (C-ipso arom), 148.5 (C-6), 157.4 (d, $^{2}J_{PC}$=18.6 Hz, C-2), 178.1 (d, $^{2}J_{PC}$=4.0 Hz, C=O)	3068 (NH) 1642 (C=O) 1238 (P=O)	431 (M^+, 15%)
6	12.9	1.10 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.59 (s, 3H, CH_3), 3.80 (m, 2H, OCH_2), 3.96 (m, 2H, OCH_2), 7.27 (d, 1H, $^{4}J_{PH}$=3.3 Hz, CH), 7.41-7.59 (m, 5H, arom)	15.9 (d, $^{3}J_{PC}$=7.0 Hz, CH_3), 24.3 (CH_3), 62.2 (d, $^{2}J_{PC}$=6.0 Hz, OCH_2), 119.5 (d, $^{1}J_{PC}$=195.9 Hz, C-3), 123.5 (d, $^{3}J_{PC}$=7.5 Hz, C-5), 127.7-128.9 (C-arom), 141.8 (C-ipso arom), 148.8 (d, $^{2}J_{PC}$=3.0 Hz, C-4), 161.0 (C-6), 164.5 (d, $^{2}J_{PC}$=9.6 Hz, C-2)	1255 (P=O)	339 (M^+, 40%)

[a] Obtained on a Varian VXR 300 Spectrometer. [b] Recorded in a Nicolet FTIR Magna 550. [c] Obtained on a Hewlett Packard 5890 Spectrometer.

In conclusion, the synthesis described here provides an efficient and easy access to 4(1*H*)-pyridones (**1**) and 4-chloropyridine (**6**) substituted with a phosphonate group in 3-position, making use of readily available starting materials. 4-(1*H*)-Pyridones and 4-chloropyridines are useful compounds in medicinal chemistry since these products display a broad range of biological activities and have been widely used as pharmaceuticals.[3-9,23]

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REFERENCES AND NOTES

1. For excellent reviews see: a) G. Jones, "Comprehensive Heterocyclic Chemistry," Vol. 2, ed. by A. R. Katrizky, C. W. Rees, A.J. Boulton and A. McKillop, Pergamon, Oxford, 1984, p. 395. b). D. Lednicer and L. A. Mitscher "The

Organic Chemistry of Drug Synthesis," Vols. 1-3, ed by Willey, New York, 1977, 1980, 1984; c) D. Lednicer, L. A. Mitscher, and G. I. Georg "The Organic Chemistry of Drug Synthesis," Vol. 4, ed. by Willey, New York, 1990.

2. a) J. Matulic-Adamic and L. Beigelman, *Tetrahedron Lett.*, 1997, **38**, 1669; b) Q. Li, D. T. Chu, A. Claiborne, C. S. Cooper, C. M. Lee, K. Raye, K. B. Berst, P. Donner, W. Wang, L. Hasvold, A. Fung, Z. Ma, M. Tufano, R. Flamm, L. L. Shen, J. Baranowski, A. Nilius, J. Alder, J. Meulbroek, K. Marsh, D. Crowell, Y. Hui, L. Seif, L. M. Melcher, R. Henry, S. Spanton, R. Faghih, L. L. Klein, S. K. Tanaka, and J. J. Plattner, *J. Med. Chem.*, 1996, **39**, 3070; c). J. Alder, J. Clement, J. Meulbroek, N. Shipkowitz, M. Mitten, and K. Jarvis, *Antimicrob. Agents. Chemother.*, 1995, **39**, 971; d) G. M. Eliopoulos, C. B. Wennersten, G. Cole, D. Chu, D. Pizzuti, and R. C. Moellering, *Antimicrob. Agents. Chemother.*, 1995, **39**, 850; e) R. Bergmann and R. Gericke, *J. Med. Chem.*, 1990, **33**, 492; f) C. Im, E. E. Knauss, R. P. Thuynsma, and T. M. Allen, *Drug Des. Deliv.*, 1990, **5**, 238; g) W. C. Groutas, M. A. Stanga, M. J. Brubaker, T. L. Huang, M. K. Moi, and R. T. Carrol, *J. Med. Chem.*, 1985, **28**, 1106; h) R. E. Dolle and K. C. Nicolau, *J. Am. Chem. Soc.*, 1985, **107**, 1691; i). A. Attia and M. Michael, *Pharmazie*, 1982, **37**, 551.

3. a) T. A. Hughes and P. R. Cook, *Experim. Cell. Res.*, 1996, **222**, 275; b) K. Lalitha, C. M. Vargheere, and N. Balasubramanian, *Anal. Biochem.*, 1993, **213**, 57; c) Y. Dai, B. Gold, J. K. Vishwanatha, and S. L. Rhode, *Virology*, 1994, **205**, 210; d) M. Soedarjo and D. Borthakur, *Plant and Soil*, 1996, **186**, 87.

4. G. B. Cheda, H. B. Patryzc, H. A. Tworek, and S. P. Dutta, *Nucleosides and Nucleotides*, 1995, **14**, 1519.

5. a) K. Shibata and H. Matsuo, *Am. J. Clin. Nutr.*, 1989, **50**, 114; b) K. Shibata and H. Matsuo, *J. Nutr.*, 1989, **119**, 896; c) K. Shibata, H. Shimada, and H. Tayuchi, *Biosci. Biotechnol. Biochem.*, 1996, **60**, 1204.

6. a) J. B. Pierce, Z. V. Ariyan, and G. S. Ovenden, *J. Med. Chem.*, 1982, **25**, 131; b) J. M. Domagala, L. D. Hanna, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. P. Sanchez, and M. Solomm, *J. Med. Chem.*, 1986, **29**, 394; c) R. D. Crosland, *Pharmacol. Toxicol.*, 1995, **77**, 231; d) R. Azoni, J. Schneider, N. X. Dong, H. Dabire, M. Safar, and J. L. Cuche, *Life Sci.*, 1997, **60**, 357; e) A. C. Hammond, M. J. Allison, M. J. Williams, G. M. Prine, and D. B. Bates, *Am. J. Vet. Res.*, 1989, **50**, 2176.

7. a) A. Rumbo, A. Mouriño, L. Castedo, and J. L. Mascareñas, *J. Org. Chem.*, 1996, **61**, 6114; b) G. Lui, F. W. Brunger, A. M. Barrios, and S. C. Miller, *Nucleosides and Nucleotides*, 1995, **14**, 1901; c) J. Matulic, C. Gonzalez, N. Usman, and L. Beigelman, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 373; d) H. Ogino, K. Iwamatsu, K. Katano, S. Nakabayashi, T. Yoshida, S. Shibahara, T. Tsuruoka, S. Inouye, and J. Kendo, *J. Antibiot.*, 1990, **43**, 189; e) Y. Tatsumi, T. Maejimo, and S. Mitsuhashi, *Antimicrob. Agents Chemother.*, 1995, **39**, 613; f) M. Sunagawa, A. Sasaki, H. Yamoga, H. Shinagawa, M. Fukasawa, and Y. Sumita, *J. Antibiot.*, 1994, **47**, 1354; g) M. Sendai, M. Nakao, and Y. Ishibashi, Jpn. Kukai Tokkyo Koho JP 07,179,474, (1995) (*Chem. Abstr.*, 1995, **123**, 285638g).

8. a) J. Burgess, B. Decastro, C. Oliveira, M. Rangel, and W. Schlindwein, *Polyhedron*, 1997, **16**, 789; b) A. H. Jammal, P. L. Howell, M. A. Turner, N. Li, and D. M. Templeton, *J. Med. Chem.*, 1994, **37**, 461; c) D. D. Allen, C. Orvig, and R. A. Yukel, *Toxicol.*, 1994, **92**, 193; d) A. E. Martell, R. D. Hancock, R. M. Smith, and R. J. Mutekaitis, *Coord. Chem. Rev.*, 1996, **149**, 311; e) D. S. Edwards, S. Liu, D. M. Lyster, M. J. Poisier, C. Vo, G. A. Webb, Z. Zhang, and C. Orvig, *Nucl. Med. Biol.*, 1993, **20**, 857.

9. a) S. Ghosh, W. H. Ujala, W. B. Gleason, and D. J. Grant, *J. Pharm. Sci.*, 1995, **84**, 1392; b) J.J. Mulenda, M. M. Jones, D. S. Johnston, E. M. Walker, and D. J. Cannon, *J. Med. Chem.*, 1994, **37**, 4363; c) S. Ghosh, D. A. Adsmond, and D. J. N. Grant, *J. Pharm. Sci.*, 1995, **84**, 568; d) R. C. Hider and K. Lerch, *Biochem. J.*, 1989, **257**, 289.

10. A. D. F. Toy and E. N. Walsh, "Phosphorus Chemistry in Everyday Living". American Chemical Society, Washington D. C., 1987. R. Engel, "Handbook of Organophosphorus Chemistry". M. Dekker Inc., New York, 1992.

11. a) W. C. Patt and M. A. Massa, *Tetrahedron Lett.*, 1997, **38**, 1297; b) R. Gericke, J. Harting, Y. Lues, and C. Schittenhelm, *J. Med. Chem.*, 1990, **34**, 3074; c) J. M. Domagala, *J. Org. Chem.*, 1984, **49**, 127; d) R. Neier and P. Guerry, *Synthesis*, 1984, 485; e) A. E. Wieck, U.K. Patent G.B. 2,013,190, (1979) (*Chem. Abstr.*, 1979, **91**, 211273h).

12. a) J. Chauvelier, *Bull. Soc. Chim. Fr.*, 1954, 734; b) Carbide and Carbon Corp. *U.S. Patent* 2,185,243 (1940) (*Chem. Abstr.*, 1940, **34**, 2863); c) G. Errera, *Chem. Ber.*, 1898, **31**, 1682; d) H. M. Feid-Allah, *Pharmazie*, 1981, **36**, 672.

13. a) A. Hassner and A. Kascheres, *J. Org. Chem* ., 1972, **37**, 2328; b) J. Barluenga, F. J. Gonzales, R. Perez, and S. Fustero, *J. Org. Chem* ., 1991, **56**, 6751; c) J. Barluenga, F. Lopez, F. Palacios, and V. Gotor, *Synth. Commun*., 1983, **13**, 411; d) R. F. Abdilla, T. L. Emmick, and H. M. Taylor, *Synth. Commun*., 1977, **7**, 305; e) E. Ziegler, Y. Herbst, and T. Kappe, *Monatsh. Chem.*, 1969, **100**, 132.

14. For recent contributions see: a) F. Palacios, J. Pagalday, V. Piquet, F. Dahan, A. Baceiredo, and G. Bertrand, *J. Org. Chem.*, 1997, **61**, 292; b) F. Palacios, D. Aparicio, and J. M. de los Santos, *Tetrahedron*, 1996, **52**, 4123; c) F. Palacios, J. Pagalday, and A. Ochoa de Retana, *Heterocycles*, 1995, **40**, 543.

15. a) F. Palacios, D. Aparicio, and J. García, *Tetrahedron*, 1997, **53**, 2931; b) F. Palacios, J. García, A. Ochoa de Retana, and J. Oyarzabal, *Heterocycles*, 1995, **41**, 1915.

16. a) F. Palacios, D. Aparicio, and J. M. de los Santos, *Tetrahedron Lett*., 1996, **37**, 1289; b) F. Palacios, D. Aparicio, and J. García, *Synlett*, 1994, 260; c) F. Palacios, D. Aparicio, and J. M. de los Santos, *Tetrahedron*, 1994, **50**, 12727; d) J. Barluenga, I. Merino, and F. Palacios, *Tetrahedron Lett*., 1990, **31**, 6713; e) J. Barluenga, I. Merino, and F. Palacios, *Tetrahedron Lett*., 1989, **30**, 5493; f) F. Palacios, D. Aparicio, and J. García, *Tetrahedron*, 1996, **52**, 9609; g) F. López, E. Pelaez, F. Palacios, J. Barluenga, S. García, B. Tejerina, and A. García, *J. Org. Chem.*, 1994, **59**, 1984.

17. a) J. Barluenga, F. López, and F. Palacios, *J. Organomet. Chem.*, 1990, **382**, 61. b) J. Barluenga, F. López, and F. Palacios, *J. Chem. Soc., Chem. Commun.*, 1988, 1596. c) J. Barluenga, F. López, and F. Palacios, *Tetrahedron Lett*., 1987, **28**, 2875.

18. G. Erker, M. Riedel, S. Koeb, T. Jödicke, and Würthwein, *J. Org. Chem.*, 1995, **60**, 5284.

19. J. Barluenga, F. Lopez, F. Palacios, F. H. Cano, and M.C. Foces, *J. Chem. Soc., Perkin Trans. I*, 1988, 2329.

20. F. Palacios, A. Ochoa de Retana, and J. Oyarzabal, *Tetrahedron Lett.*, 1996, **37**, 4577.

21. a) J. A. Hyatt, P. L. Feldman, and R. J. Clemens, *J. Org. Chem.*, 1984, **49**, 5105. b) R. J. Clemens and J. S. Witzeman, J. Am. Chem. Soc., 1989, **111**, 2186.

22. For recent synthetic applications of this reagent see for example: a) A. D'Annibale, A. Pesce, S. Resta, and C. Trogolo, *Tetrahedron Lett.*, 1996, **37**, 7429. b) S.W.E. Eisenberg, C. Chen, J. Wu, C. Lebrilla, and M.J. Kurth, *Tetrahedron Lett.*, 1996, **37**, 7683.

23. a) M. Adachi, T. Sasatani, N. Chomei, and S. Takada, *Tetrahedron Lett.*, 1996, **37**, 8871; b) J. Pernak, L. Michalak, J. Krysinski, and Z. Kuncewicz, *Archiv. Pharm.*, 1995, **328**, 531; c) L. S. Hollis, A.R. Amundsen, and E. W. Stern, *J. Med. Chem.*, 1989, **32**, 128; d) H. I. Ogawa, S. Y. Liu, K. Sakata, Y. Niyitani, S. Tsuruta, and Y. Kato, *Mutat. Res.*, 1988, **204**, 117.

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