Pergamon

Tetrahedron 54 (1998) 3807–3816

TETRAHEDRON

Synthesis of *(Z)* and *(E)* α - Alkenyl Phosphonic Acid Derivatives of Purines and Pyrimidines[1]

H. B. Lazrek*[a], A. Rochdi[a], H. Khaider[a], J.-L. Barascut[b], J.-L. Imbach[b], J. Balzarini[c], M. Witvrouw [c], C. Pannecouque[c] and E. De Clercq[c].

[a] Laboratoire de Chimie Bio-Organique, Faculté des Sciences Semlalia, Marrackeh; Maroc;
[b] Laboratoire de Chimie Bio-Organique, Université des Sciences et Techniques MontpellierII, France;
[c] Rega institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium.

Received 25 June 1997; accepted 6 February 1998

Abstract: *(Z)* and *(E)*-2-(purin-9-yl/ pyrimidin-1-yl)ethylen-1-ylphosphonic acid **10-18** were synthetized by Michael addition of heterocyclic base with the diethylethynylphosphonate and deprotection of the acyclic nucleoside phosphonate with bromotrimethylsilane.

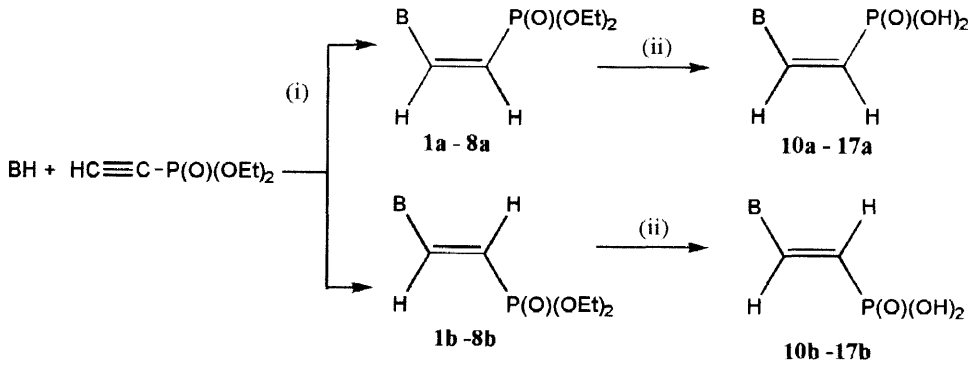
Most of the nucleoside analogues showing antiviral activity need to be phosphorylated to the corresponding triphosphates before exerting their biological effects. In an effort to circumvent the first highly selective phosphorylation step, considerable research effort has been directed towards the synthesis of nucleoside analogues containing a phosphonomethoxy group as a stabilized phosphate mimic.[2-14] Actually, many analogues of acyclic nucleoside phosphonic acids have been synthetised,[9-19] but very few have an α,β-unsaturated phosphonic acid moiety as the phosphate mimic.[20,21] Some *trans*-alkenylphosphonic acid nucleoside analogues are endowed with anti-retrovirus and anti-herpesvirus activity.[21] Therefore, acyclic nucleotide analogues containing the alkenylphosphonyl group as the phosphate mimic may be considered as potentially effective antiviral agents.

In view of these observations, we initiated the synthesis of a nouvel serie of ethenylphosphonic acid analogues of nucleosides. In these phosphonate derivatives the phosphorus atom is attached to the heterocyclic base via an enamine (N-C=C-P) bond, thus forming a linkage which is not susceptible to hydrolysis by esterases.[22,23] The formation of such nitrogen-carbon bonds is obtained from a conjugate addition of multifunctional nitrogenous nucleophiles to carbon-carbon triple bonds (Michael reaction).[24] These reactions usually involve a basic catalysis and several methods using anionic activation have been applied.[25]

In this paper, we present the results obtained when Michael donors, namely the pyrimidines [U, T, C, 5-FU, 5-BrU, 5-($HOCH_2$)U, 5-IU] and purines (A, N-AcG) are reacted with a phosphonate Michael acceptor[26] using basic catalysis.

Corresponding author Fax : 212-4-43-67-69. E-mail : fssm.chim@cybernet.net.ma

0040-4020/98/$19.00
PII: S0040-4020(98)00107-0



(i) : [tBuOK, CH_3CN or DMF, 18-crown-6] or [K_2CO_3, DMF]

(ii) : a) $(H3C)_3SiBr$, DMF; b) H_2O

- Phosphonates derivatives **1-8** :

BH	Adenine	N-Acguanine	Uracil	Thymine	Cytosine	5-Fluorouracil	5-Bromouracil	5-Hydroxymethyluracil
Z	1a	2a	3a	4a	5a	6a	-	8a
E	1b	2b	3b	4b	5b	6b	7b	8b

- Phosphonic acid derivatives **10-17** :

BH	Adenine	N-Acguanine	Uracil	Thymine	Cytosine	5-Fluorouracil	5-Bromouracil	5-Hydroxymethyluracil
Z	10a	11a	12a	13a	14a	15a	-	17a
E	10b	11b	12b	13b	14b	15b	16b	17b

Scheme 1

Phase Transfer Catalysis (PTC) is one of the most efficient and widespread technique for anionic activation. We have recently reported[27-30] that Solid-Liquid Phase Transfer Catalysis (SLPTC), using potassium tert-butoxide as base, 18-crown-6 as catalyst, CH_3CN or DMF as solvent, was an efficient method for the preparation of acyclonucleoside analogues. So, the alkylation of purines or pyrimidines bases with the methyl propiolate ($H-C\equiv C-CO_2Me$) was accomplished by application of Solid-Liquid Phase Transfer Catalysis to Michael type addition and gave a very interesting result.[31] However, the use of these conditions for preparation of ethylenylphosphonate derivatives **1-5** led to two isomers (*Z* and *E*) in moderate overall yield in approximate $Z/E > 1$ ratio (Table 1). These results suggest that the reaction can undergo a retro-Michael addition reaction.[25] During the synthesis of diethylethylenylphosphonates **1-5**, side products (N1/N3 or N1/N4 bis alkylated) were noticed for thymine and cytosine.

To overcome these inconveniences, the reaction was carried out with potassium carbonate as base and DMF as solvent. This process gave the two isomers (*Z* and *E*) in good overall yield (Table 2). All isomers synthetized were separated by chromatography on silica gel. Iodinaton of uracil derivatives **3a** and **3b** has beeen effected using iodine monochloride in dichloromethan to provide the 5-iodouracil derivatives **9a** and **9b** in good yield.

The position of alkylation (N-1, N-9) parallels that reported for related pyrimidine and purines Michael-type additions to several Michael acceptors[32-36].

Table1: Yield and (*Z*/*E*) ratio of compounds **1** to **5** obtained with SLCTP conditions

N°	Heterocyclic base	Ratio *Z*/*E*	Yield (%)
1	Adenine	8/2	35
2	*N*-Acetylguanine	6/4	35
3	Uracil	5/5	36
4	Thymine	6/4	32
5	Cytosine	6/4	41

Table 2: Yield and (*Z/E*) ratio of compounds 1 to 9 obtained with K_2CO_3 /DMF

N°	Heterocyclic base	Ratio (*Z/E*)	Yield (%)
1	Adenine	8/2	70
2	*N*-Acetylguanine	8/2	67
3	Uracil	2/8	76
4	Thymine	2/8	81
5	Cytosine	2/8	72
6	5-Fluorouracil	2/8	66
7	5-Bromouracil	E only	83
8	5-Hydroxymethyluracil	2/8	64
9a	5-Iodouracil	Z	92
9b	5-Iodouracil	E	92

From the results described in Table 1 and 2, we conclude that the overall yield increase and the isomer ratio (*Z/E*) depended upon the reaction conditions. The *E* isomer becomes major for pyrimidine analogues when K_2CO_3/DMF conditions were used, however the *Z/E* ratio for purines analogues remains unchanged. Confirmation of the isomeric structure of these products was based on ^{1}H-N.M.R. spectra. The large coupling constante of *trans* proton-phosphorus versus *cis* proton-phosphorus provides a simple determination of structure. Indeed, the *Z*-isomer was characterised by the ^{3}J[P, B-CH=CP] coupling constants amounting to 41-43 Hz, but in *E*-isomer this coupling constants decreased to 17 Hz. It would be expected that the significant diamagnetic anisotropy of the phosphonate group would lead to a greater deshielding of the vinyl "H-2" in the *E* isomers than in *Z* isomers (Table 3).

Table 3 : Shift (ppm) of H_2 in compounds 1-9.

N°	1		2		3		4		5		6		7		8		9	
form	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*
δ(H_2) (ppm)	7.74	7.90	8.03	8.27	7.31	7.71	7.33	7.72	7.45	7.88	7.33	7.68	-	7.65	7.34	7.74	7.43	7.61

The deprotection of acetyl group of **2a** and **2b** was achieved using MeOH /HCl.[21] Treatment of *(Z)* or *(E)* diethylphosphonate acyclonucleosides **1a, b** to **9a, b** in anhydrous DMF with TMS-bromide (Scheme 1) was followed by evaporation to dryness, and the remaining residue was dissolved in H_2O. Further addition of acetone gave a quantitative yield of crystalline acids **10a, b** to **18a, b** (see experimental). The structure of these compounds was established by 250 MHz proton NMR and characterized by the usual physical methods. We have ascertained that the acid isomer forms (*Z* and *E*) do not interconvert under the conditions of their formation.

Biological activity:

These compounds were evaluated for their activities against human immunodeficiency virus type 1 (HIV-1 (III_B) and HIV-2 (ROD) in human T-lymphocyte (CEM) cells, and against herpes simplex virus type 1 (HSV-1)(strain KOS), thymidine kinase-deficient (TK^-) HSV-1 (strain B2006), herpes simplex virus

type 2 (HSV-2) (strain G), vaccinia virus and vesicular stomatitis virus[37,38] in human embryonic skin-muscle (ESM) fibroblasts according to previously established procedure. Virus-induced cytopathocity was used as antiviral parameter to estimate the antiviral potential of the test compounds. No antiviral activity was observed at concentrations up to 100-200µg/ml (data not shown). Most of the compounds showed no toxicity for the host cells at the concentration up to 200 µg/ml. Two compounds, namely **15a** and **18b** proved to be toxic to CEM cells, at a 50% cytotoxic concentration (CC50) of 13 and 76 µg/ml, respectively.

EXPERIMENTAL

^{1}H-NMR spectra were recorded in a Bruker AC 250 and AM 300 spectrometer in DMSO-d6. Chemical shifts (δ) are quoted in parts per million relative to tetramethylsilane set at 0.0 ppm as internal reference. The signals are described as: s, singlet; d, doublet; t, triplet; dd, double doublet; m, multiplet.

UV spectra were recorded with CARY 219 spectrophotometer in MeOH for esters derivatices and in Water for acids derivativses. (Precoated) (EK-F_{254}) silica gel plates were used for TLC. Column chromatography was performed on Merck silica gel (230-400 mesh)

Mass spectra were performed on a JEOL JMS DX 300. Elemental analyses were carried out by the "service de microanalyses du CNRS, division de Vernaison France."

1- (Z) and (E)-DIETHYL-2-(PURIN-9-YL/PYRIMIDIN-1-YL)ETHYLEN-1-YL PHOSPHONATES ***1 - 9*** *:*

General procedure

Method A:

A mixture of heterocyclic base (7.40 mmol), potassium tert-butoxide (720 mg, 6.43 mmol) and 18-crown-6 (326 mg, 1.23 mmol) in acetonitrile (150 ml) was stirred at room temperature for 15 min. Diethyl ethynylphosphonate (1.44 g, 8.89 mmol) was then added and the solution was kept for 2-40 hours at room temperature. The solid was filtered off and the filtrate was evaporated. The residue was chromatographed on a silica gel column with the eluent system: CH_2Cl_2/MeOH.

Method B:

A mixture of heterocylic base (7.40 mmol), K_2CO_3 (511 mg, 3.7 mmol) in DMF (100 ml) was stirred at room temperature for 15 min. Diethyl ethynylphosphonate (1.44 g, 8.89 mmol) was then added and the solution was kept for 4-24 hours at room temperature. Work-up of the mixture was the same as described in method A.

(Z)-diethyl-2-(adenyl-9-yl)ethylen-1-ylphosphonate **1a** *and (E)-diethyl-2-(adenyl-9-yl)ethylen-1-ylphosphonate* **1b :**

1a : Yield = 56%; mp: 178-180 °C [CH_2Cl_2/Ether]; R_f : 0.58 (CH_2Cl_2/MeOH : 80/20); ^{1}H-NMR δ : 8.90 (s, 1H, H-8'); 8.23 (s, 1H, H-2'); 7.74 (dd,1H, H-2, $J_{2,1}$=11.92Hz, $J_{2,P}$=42.28Hz); 7.55 (Brs, 2H, NH_2); 5.80 (dd., 1H, H-1, $J_{1,2}$=11.92Hz, $J_{1,P}$=8.70Hz); 4.04 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=8.02Hz , $J_{CH_2\text{-}CH_3}$=7.06Hz) ; 1.20 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.06Hz); UV : λ_{max}=245 nm (ε=10800), 282 nm (ε=2600); M.S. (FAB>0): 298 $[MH]^+$. Anal. calcd. for $C_{11}H_{16}N_5O_3P$, 1/8 H_2O : C, 44.11; H, 5.47; N, 23.38. Found : C, 44.12; H, 5.60; N, 23.20.

1b : Yield = 14%; mp: 175-177 °C [CH_2Cl_2/Ether]; R_f : 0.54 (CH_2Cl_2/MeOH : 80/20); ^{1}H-NMR δ : 8.61 (s, 1H, H-8'); 8.27 (s, 1H, H-2'); 7.53 (Brs, 2H, NH_2); 7.90 (dd, 1H, H-2, $J_{2,1}$=15.62Hz, $J_{2,P}$=17.46Hz); 6.91 (dd., 1H, H-1, $J_{1,2}$=15.62Hz, $J_{1,P}$=12.93Hz); 4.05 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=8.25Hz, $J_{CH_2\text{-}CH_3}$=7.05Hz); 1.28 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.05Hz); UV : λ_{max}=239 nm (ε=13000),

285 nm (ε=1900); M.S. (FAB>0): 298 $[MH]^+$. Anal. calcd. for $C_{11}H_{16}N_5O_3P$: C, 44.45; H, 5.43; N, 23.56. **Found**: C, 44.51; H, 5.54; N, 23.42.

(Z)-diethyl-2-(2-N-acetylguanin-9-yl)ethylen-1-ylphosphonate **2a** *and (E)-diethyl-2-(2-N-acetylguanin-9-yl) ethylen-1-ylphosphonate* **2b :**

2a : Yield = 54%; mp: 222-224 °C [CH_2Cl_2/Ether]; R_f : 0.37 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 11.78 (Brs, 1H, NH-Ac); 11.14 (Brs, 1H, NH-3); 9.16 (s, 1H, H-8'); 8.03 (d.d,1H, H-2, $J_{2,1}$=11.90Hz, $J_{2,P}$=42.03Hz); 5.77 (dd., 1H, H-1, $J_{1,2}$=11.90Hz, $J_{1,p}$=8.74Hz); 4.08 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=8.39Hz, $J_{CH_2\text{-}CH_3}$=7.07Hz); 2.21 (s, 3H, CH_3); 1.22 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.07Hz); UV : λ_{max}=301nm (ε=13000); M.S. (FAB>0): 356 $[MH]^+$. Anal. calcd. for $C_{13}H_{18}N_5O_5P$: C, 43.95; H, 5.11; N, 19.71. Found: C,43.74; H, 5.27 ; N, 19.57.

2b : Yield = 13%; mp: 200-204 °C (CH_2Cl_2/Ether]; R_f : 0.33 (CH_2Cl_2/MeOH : 90/10); 1H-NMR δ: 12.09 (Brs, 1H, NH-Ac); 11.65 (Brs, 1H, NH-3); 9.72 (s, 1H, H-8'); 8.27 (dd,1H, H-2, $J_{2,1}$=15.79Hz, $J_{2,P}$=17.41Hz); 7.13 (dd., 1H, H-1, $J_{1,2}$=15.79Hz, $J_{1,p}$=11.49Hz); 4.10 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=8.65Hz , $J_{CH_2\text{-}CH_3}$=7.08Hz); 2.29 (s, 3H, CH_3); 1.26 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.08Hz); UV: λ_{max}=302 nm (ε=16800); M.S. (FAB>0): 356 $[MH]^+$. Anal. calcd. for $C_{13}H_{18}N_5O_5P$: C, 43.95; H, 5.11; N, 19.71. **Found**: C, 43.84; H, 5.22; N, 19.63.

(Z)-diethyl-2-(uracil-1-yl)ethylen-1-ylphosphonate **3a** *and (E)-diethyl-2-(uracil-1-yl)ethylen-1-ylphosphonate* **3b :**

3a : Yield = 15%; mp: 102-103°C [CH_2Cl_2 / Ether]; R_f : 0.40 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 11.66 (Brs, 1H, NH-3); 7.84 (d, 1H, H-6' , $J_{6'\text{-}5'}$=8.06Hz); 7.31 (dd,1H, H-2, $J_{2,1}$=11.18Hz, $J_{2,P}$=42.74 Hz); 5.77 (d, 1H, H-5', $J_{5',6'}$=8.06Hz); 5.76 (dd., 1H, H-1, $J_{1,2}$=11.18Hz, $J_{1,p}$=9.24Hz); 4.01 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=8.16Hz, $J_{CH_2\text{-}CH_3}$=7.05Hz); 1.22 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.05Hz). UV: λ_{max}=273 nm (ε=14400); M.S. (FAB>0): 275 $[MH]^+$; Anal. calcd. for $C_{10}H_{15}N_2O_5P$, 1/10 H_2O : C, 43.52; H, 5.55; N, 10.15; Found: C, 43.49; H, 5.60 ; N, 10.36.

3b : Yield = 61%; mp: 120-122 °C [CH_2Cl_2/Ether]; R_f : 0.36 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 11.72 (Brs, 1H, NH-3); 8.14 (d, 1H, H-6', $J_{6'\text{-}5'}$=8.27Hz); 7.71 (dd, 1H, H-2, $J_{2,1}$=15.97Hz, $J_{2,P}$=18.29Hz); 6.13 (dd., 1H, H-1, $J_{1,2}$=15.97Hz, $J_{1,p}$=10.60Hz); 5.83 (d, 1H, $H_{5'}$, $J_{5',6'}$= 8.27Hz); 4.00 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=8.13Hz , $J_{CH_2\text{-}CH_3}$=7.06Hz); 1.24 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.06Hz); UV: λ_{max}=278nm (ε=20100); M.S. (FAB>0): 275 $[MH]^+$; Anal. calcd. for $C_{10}H_{15}N_2O_5P$, 1/4 H_2O: C, 43.09; H, 5.61; N, 10.05. Found: C, 43.13; H, 5.53; N, 9 .98.

(Z)-diethyl-2-(thymin-1-yl)ethylen-1-ylphosphonate **4a** *and (E)-diethyl-2-(thymin-1-yl)ethylen-1-ylphosphonate* **4b :**

4a : Yield = 16%; mp: 99-101 °C [CH_2Cl_2/Ether]; R_f :0.48 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 11.70 (Brs, 1H, NH-3); 7.83 (s, 1H, H-6'); 7.33 (dd, 1H, H-2, $J_{2,1}$=11.34Hz, $J_{2,P}$= 42.18Hz); 5.67 (dd., 1H, H-1, $J_{1,2}$=11.34Hz, $J_{1,p}$=9.08Hz); 4.00 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=7.51Hz , $J_{CH_2\text{-}CH_3}$=7.05Hz); 1.79 (s, 3H, CH_3), 1.22 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.05Hz); UV : λ_{max}=279nm (ε=14200); M.S. (FAB>0): 289 $[MH]^+$; Anal. calcd. for $C_{11}H_{17}N_2O_5P$, 1/3 H_2O : C, 44.90; H, 6.05; N, 9.52. Found: C, 44.86; H, 5.97; N, 9.41 .

4b : Yield = 65%; mp: 155 - 157 °C [CH_2Cl_2/Ether]; R_f : 0.45 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ: 11.73 (Brs, 1H, NH-3); 8.06 (s, 1H, H-6'); 7.72 (dd, 1H, H-2, $J_{2,1}$=15.94Hz, $J_{2,P}$=18.26Hz); 6.05 (dd., 1H, H-1, $J_{1,2}$=15.94Hz, $J_{1,p}$=10.67Hz); 3.99 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=8.04Hz, $J_{CH_2\text{-}CH_3}$=7.03Hz); 1.84 (s, 3H, CH_3); 1.24 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.03Hz); UV : λ_{max}=278 nm (ε=15000); M.S. (FAB>0): 289 $[MH]^+$. Anal. calcd. for $C_{11}H_{17}N_2O_5P$: C, 45.84; H, 5.94 ; N, 9.72. Found: C, 45.60; H, 5.86; N, 9.80.

(Z)-diethyl-2-(cytosyl-1-yl)ethylen-1-ylphosphonate **5a** *and (E)-diethyl-2-(cytosyl-1-yl)ethylen-1-ylphosphonate* **5b :**

5a : Yield = 14%; mp: 177-179 °C [CH_2Cl_2/Ether]; R_f : 0.44 (CH_2Cl_2/MeOH : 80/20); ^{1}H-NMR δ : 7.86 (d, 1H, H-6' , $J_{6'-5'}$=7.48Hz); 7.59 (Brs, 2H, 4-NH_2); 7.45 (dd,1H, H-2, $J_{2,1}$ 11.39Hz, $J_{2,P}$ 43.03Hz); 5.82 (d, 1H, H-5', $J_{5',6'}$=7.48Hz); 5.53 (dd., 1H, H-1, $J_{1,2}$=11.39Hz, $J_{1,P}$=9.75Hz); 3.97 (qd, 4H, 2OCH_2, J_{CH_2-P}= 8.29Hz , $J_{CH_2-CH_3}$=7.05Hz); 1.20 (t, 6H, 2CH_3, $J_{CH_2-CH_3}$=7.05Hz); UV: λ_{max}=287 nm (ε=16000); M.S. (FAB +0): 274 $[MH]^+$. Anal. calcd. for $C_{10}H_{16}N_3O_4P$, H_2O : C, 41.24; H, 6.23; N, 14.43; Found: C, 40.98; H, 6.59; N, 14.21.

5b : Yield = 58%; mp: 216-218 °C [CH_2Cl_2/Ether]; R_f : 0.39 (CH_2Cl_2/MeOH : 80/20); ^{1}H-NMR δ : 8.05 (d, 1H, H-6' , $J_{6'-5'}$=7.69Hz); 7.88 (dd, 1H, H-2, $J_{2,1}$=16.13Hz, $J_{2,P}$=18.23Hz); 7.73 (Brs, 2H, 4-NH_2); 5.96 (dd., 1H, H-1, $J_{1,2}$=16.13Hz, $J_{1,P}$=11.53Hz); 5.89 (d, 1H, H-5', $J_{5',6'}$=7.69Hz); 3.99 (qd, 4H, 2OCH_2, J_{CH_2P} 8.10Hz , $J_{CH_2-CH_3}$=7.06Hz); 1.24 (t, 6H, 2CH_3, $J_{CH_2-CH_3}$= 7.06 Hz); UV : λ_{max}=296nm (ε=10200); M.S. (FAB +0): 274 $[MH]^+$. Anal. calcd. for $C_{10}H_{16}N_3O_4P$, 1/2 H_2O : C, 42.56; H, 6.07; N, 14.89. Found: C, 42.56; H, 5.99; N, 14.88.

(Z)-diethyl-2-(5-fluorouracil-1-yl)ethylen-1-ylphosphonate **6a** *and (E)-diethyl-2-(5-fluorouracil-1-yl) ethylen-1-ylphosphonate* **6b :**

6a : Yield = 13%; mp: 143-145°C [CH_2Cl_2/Ether]; R_f : 0.52 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR (DMSO-d6)δ : 12.24 (Brs 1H, NH-3); 8.43 (d, 1H, H-6', $J_{6'-F}$=7.13Hz); 7.33 (dd, 1H, H-2, $J_{2,1}$ 11.39Hz, $J_{2,P}$=42.10Hz); 5.72 (dd., 1H, H-1, $J_{1,2}$=11.39Hz, $J_{1,P}$=8.09Hz); 3.98 (qd, 4H, 2OCH_2, J_{CH_2-P}=7.98Hz, $J_{CH_2-CH_3}$=7.04Hz); 1.23 (t, 6H, 2CH_3, $J_{CH_2-CH_3}$=7.04Hz); UV (MeOH) : λ_{max}=281 nm (ε=14300);M.S. (FAB +0): 293 $[MH]^+$. Anal. calcd. for $C_{10}H_{14}FN_2O_5P$: C, 41.10; H, 4.83; N, 9.59. Found: C, 41.20; H, 4.80; N, 9.63.

6b : Yield = 53%; mp: 186-188 °C [CH_2Cl_2/Ether]; R_f : 0.49 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 12.25 (Brs, 1H, NH-3); 8.54 (d, 1H, H-6', $J_{6'-F}$=7.18Hz); 7.68 (dd, 1H, H-2, $J_{2,1}$=15.94Hz, $J_{2,P}$=16.10Hz); 6.09 (dd., 1H, H-1, $J_{1,2}$=15.94Hz, $J_{1,P}$=10.16Hz); 3.99 (qd, 4H, 2OCH_2, J_{CH_2-P} 8.08Hz , $J_{CH2-CH3}$=7.04Hz); 1.24 (t, 6H, 2CH_3, $J_{CH_2-CH_3}$=7.04Hz); UV: λ_{max}=280 nm (ε=16900); M.S. (FAB +0): 293 $[MH]^+$. Anal. calcd. for $C_{10}H_{14}FN_2O_5P$ C, 41.10; H, 4.83; N, 9.59. Found: C, 41.10; H, 4.89; N, 9 .58.

(E)-diethyl-2-(5-bromouracil-1-yl)ethylen-1-ylphosphonate **7b :**

Yield : 83%; mp: 137-139°C [CH_2Cl_2/Ether]; R_f : 0.54 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 12.13 (Brs, 1H, NH-3); 8.57 (s, 1H, H-6'); 7.65 (dd, 1H, H-2, $J_{2,1}$=15.93Hz, $J_{2,P}$=16.29Hz); 6.13 (dd., 1H, H-1, $J_{1,2}$=15.93Hz, $J_{1,P}$=10.41Hz); 4.02 (qd, 4H, 2OCH_2, J_{CH_2-P}=7.91Hz , $J_{CH_2-CH_3}$=7.04Hz); 1.23 (t, 6H, 2CH_3, $J_{CH_2-CH_3}$=7.04Hz); UV : λ_{max}=294 nm (ε=9800); M.S. (FAB +0): 354 $[MH]^+$. Anal. calcd. for $C_{10}H_{14}BrN_2O_5P$, 1/10 H_2O : C, 33.84; H, 4.03; N, 7.89. Found: C, 33.81; H, 4.12; N, 7.65.

(Z)-diethyl-2-(5-hydroxymethyluracil-1-yl)ethylen-1-ylphosphonate **8a** *and (E)-diethyl-2-(5-hydroxymethyluracil-1-yl) ethylen-1-ylphosphonate* **8b :**

8a : Yield = 13%; mp: 133-135°C [CH_2Cl_2/Ether]; R_f : 0.36 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 11.70 (Brs, 1H, NH-3); 7.81 (s, 1H, H-6'); 7.34 (dd,1H, H-2, $J_{2,1}$=11.20Hz, $J_{2,P}$=41.97Hz); 5.72 (dd., 1H, H-1, $J_{1,2}$=11.20Hz, $J_{1,P}$=9.44Hz); 5.13 (t, 1H, OH, J_{OH-CH_2}=4.99Hz); 4.24 (d, 2H, CH_2, J_{CH_2-OH}=4.99Hz); 4.04 (qd, 4H, 2OCH_2, J_{CH_2-P}=7.48Hz, $J_{CH_2-CH_3}$=7.05Hz); 1.22 (t, 6H, 2CH_3, $J_{CH_2-CH_3}$ 7.05Hz); UV : λ_{max}=276 nm (ε=20800); M.S. (FAB +0): 305 $[MH]^+$. Anal. calcd. for $C_{11}H_{17}N_2O_6P$: C, 43.43; H, 5.63; N, 9.21. Found: C, 43.51; H, 5.69; N, 9.39.

8b : Yield = 51%; mp: 154-157 °C [CH_2Cl_2/Ether]; R_f : 0.32 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 11.77 (Brs 1H, NH-3); 7.99 (s, 1H, H-6'); 7.74 (dd,1H, H-2, $J_{2,1}$=15.96Hz, $J_{2,P}$=18.23Hz); 6.10 (dd., 1H, H-1, $J_{1,2}$=15.96Hz, $J_{1,P}$=10.49Hz); 5.04 (t, 1H, OH, J_{OH-CH_2}=5.03Hz) ; 4.19 (d, 2H , CH_2, J_{CH_2-OH}=5.03Hz); 4.03 (qd, 4H, 2OCH_2, J_{CH_2-P}=7.86Hz , $J_{CH_2-CH_3}$=7.05Hz); 1.24 (t, 6H, 2CH3, J_{CH_2-}

CH_3=7.05Hz); UV : λ_{max}=283 nm (ε=22800); M.S.(FAB>0): 305 $[MH]^+$. Anal. calcd. for $C_{11}H_{17}N_2O_6P$: C, 43.43; H, 5.63; N, 9.21. Found: C, 43.31; H, 5.64; N, 9.09.

(Z)-diethyl-2-(5-iodouracil-1-yl)ethylen-1-ylphosphonate **9a** *and (E)-diethyl-2-(5-iodouracil-1-yl) ethylen-1-ylphosphonate* **9b :**

A solution of **3a** (or **3b**) (200 mg, 0.73mmol) and ICl (0.95 mmol) in CH_2Cl_2 (100 ml) was refluxed for 2 hours. The reaction mixture was then diluted with 10 ml of dichloromethane and discoloured with $NaHSO_3$ (2% in water). The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtred and concentrated, the residue was chromatographed on silica gel column with the ethyl acetate /hexane (30/70) to give **9a** (or **9b**).

9a : Yield = 92%; mp: 168-170°C [CH_2Cl_2/Ether]; R_f : 0.59 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 12.01 (Brs, 1H, NH-3); 8.48 (d, 1H, H-6'); 7.43 (dd, 1H, H-2, $J_{2,1}$=11.23Hz, $J_{2,P}$=42.25Hz); 6.18 (dd., 1H, H-1, $J_{1,2}$=11.23Hz, $J_{1,P}$=9.21Hz); 4.01 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=7.99Hz , $J_{CH_2\text{-}CH_3}$=7.05Hz); 1.23 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.05Hz); UV : λ_{max}=301 nm (ε=11650); M.S. (FAB>0): 401 $[MH]^+$. Anal. calcd. for $C_{10}H_{14}IN_2O_5P$: C, 30.02; H, 3.53; N, 7.00 . Found: C, 30.05; H, 3.61; N, 6.83.

9b : Yield = 92%; mp: 220-222 °C (CH_2Cl_2/Ether]; R_f : 0.56 (CH_2Cl_2/MeOH : 90/10); ^{1}H-NMR δ : 12.05 (Brs, 1H, NH-3); 8.59 (d, 1H, H-6'); 7.61 (dd, 1H, H-2, $J_{2,1}$=15.92Hz, $J_{2,P}$=16.03Hz); 6.29 (dd., 1H, H-1, $J_{1,2}$=15.92Hz, $J_{1,P}$=10.34Hz); 4.03 (qd, 4H, $2OCH_2$, $J_{CH_2\text{-}P}$=7.45Hz , $J_{CH_2\text{-}CH_3}$=7.05Hz); 1.24 (t, 6H, $2CH_3$, $J_{CH_2\text{-}CH_3}$=7.05Hz); UV : λ_{max}=303 nm (ε=12750); M.S. (FAB>0): 401 $[MH]^+$. Anal. calcd. for $C_{10}H_{14}IN_2O_5P$: C, 30.02; H, 3.53; N, 7.00. Found: C, 29.84; H, 3.57; N, 6.74.

II- (Z) and (E)-2-(PURIN-9-YL /PYRIMIDIN-1-YL)ETHYLEN-1-YL PHOSPHONIC ACID **10-18**:

General procedure

The *Z* (or *E*) diethyl ester (0.67 mmol) was dissolved in DMF (15 ml) and treated with bromotrimethylsilane (0.7 ml , 5.39 mmol). The reaction mixture was heated at 70 °C overnight and was concentrated under vaccum. The residue was then treated with 10 ml of water and free acid was precipitated by addition of acetone.

(Z)-2-(adenin-9-yl)ethylen-1-ylphosphonic acid **10a**

Yield : 70 %; mp:198-200 °C [H_2O] (decompose); R_f: 0.58 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 9.09 (s, 1H, H-8'); 8.22 (s, 1H, H-2'); 7.51 (Brs, 2H, 6-NH_2); 7.49 (dd, 1H, H-2, $J_{2,1}$=11.92Hz, $J_{2,P}$=27.12Hz); 5.79 (dd., 1H, H-1, $J_{1,2}$=11.92Hz, $J_{1,P}$=7.29Hz); UV : λ_{max}=251 nm (ε=13100); M.S. (FAB<0): 242 $[MH]^-$. Anal. calcd. for $C_7H_8N_5O_3P$, H_2O : C, 32.44; H, 3.89; N, 27.02. Found: C, 32.27; H, 3.93; N, 26.85.

(E)-2-(adenin-9-yl)ethylen-1-ylphosphonic acid **10b :**

Yield : 68 %; mp > 250 °C [H_2O] (decompose); R_f : 0.29 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 8.63 (s, 1H, H-8'); 8.25 (s, 1H, H-2'); 7.55 (Brs, 2H, 6-NH_2); 7.73 (dd, 1H, H-2, $J_{2,1}$=$J_{2,P}$= 16.05Hz); 6.89 (dd., 1H, H-1, $J_{1,2}$=16.05Hz, $J_{1,P}$=11.54Hz); UV: λ_{max}=257 nm (ε=12600); M.S. (FAB<0): 242 $[MH]^-$. Anal. calcd. for $C_7N_8N_5O_3P$: C, 34.87; H, 3.34; N, 29.04. Found: C, 34.97; H, 3.48; N, 28.89.

(Z)-2-(2-N-acetylguanin-1-yl)ethylen-1-ylphosphonic acid **11a :**

Yield : 89%; mp>250 °C [H_2O] (decompose); R_f : 0.41 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 9.01 (s, 1H, H-8'); 7.84 (dd,1H, H-2, $J_{2,1}$=11.49Hz, $J_{2,P}$=27.52Hz); 5.62 (dd., 1H, H-1, $J_{1,2}$= 11.49Hz, $J_{1,P}$=7.81Hz); 2.21 (s, 3H, CH_3); UV: λ_{max}=298 nm (ε=19800); M.S. (FAB<0) : 298 $[MH]^-$. Anal. calcd. for $C_9H_{10}N_5O_5P$,1/4 H_2O : C, 35.60; H, 3.48; N, 23.06. Found: C, 35.52; H, 3.58; N, 23.21.

(E)-2-(2-N-acetylguanin-1-yl) ethylen-1-ylphosphonic acid **11b :**

Yield : 83 %; mp>250 °C [H_2O] (decompose); R_f : 0.37 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 9.54 (s, 1H, H-8'); 8.10 (dd, 1H, H-2, $J_{2,1}$=15.86Hz, $J_{2,P}$= 16.09Hz); 6.86 (dd., 1H, H-1, $J_{1,2}$=15.86Hz, $J_{1,P}$=9.37Hz); 2.09(s, 3H, CH_3); UV : λ_{max}=303 nm (ε=21100); M.S. (FAB<0): 298

$[MH]^-$. Anal. calcd. for $C_9H_{10}N_5O_5P$,2/3 H_2O : C, 34.73; H, 3.67; N, 22.50. Found: C, 34.91; H, 3.49; N, 22.43.

(Z)-2-(uracil-1-yl)ethylen-1-ylphosphonic acid **12a :**

Yield : 78 %; mp: 205-207°C [H_2O/Acetone] (decompose); R_f: 0.43 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 11.58 (Brs, 1H, NH-3); 7.79 (d, 1H, H-6', $J_{6'-5'}$=7.59Hz); 7.27 (dd, 1H, H-2, $J_{2,1}$ 11.42Hz, $J_{2,P}$=27.24Hz); 5.69 (dd., 1H, H-1, $J_{1,2}$=11.42Hz, $J_{1,P}$=7.69Hz); 5.73 (d, 1H, H-5', $J_{5',6'}$=7.59 Hz); UV : λ_{max}=274 nm (ε=14250); M.S. (FAB<0): 217 $[MH]^-$. Anal. calcd. for $C_6H_7N_2O_5P$: C, 33.04; H, 3.23; N, 12.84. Found: C, 33.21; H, 3.42; N, 12.62.

(E)-2-(uracil-1-yl) ethylen-1-ylphosphonic acid **12b :**

Yield : 81 %; mp: 228-230 °C [H_2O/Acetone] (decompose); R_f : 0.39 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 11.66 (Brs, 1H, NH-3); 8.12(d, 1H, H-6', $J_{6'-5'}$=7.67Hz); 7.60 (dd, 1H, H-2, $J_{2,1}$=15.92Hz, $J_{2,P}$=15.77Hz); 6.06 (dd., 1H, H-1, $J_{1,2}$=15.92Hz, $J_{1,P}$=9.34Hz); 5.77 (d, 1H, H-5', $J_{5',6'}$=7.67Hz); UV: λ_{max}=278 nm (ε=20100); M.S. (FAB<0): 217 $[MH]^-$. Anal. calcd. for $C_6H_7N_2O_5P$. 1/7 H_2O: C, 32.66; H, 3.33; N, 12.69. Found: C, 32.61; H, 3.49; N, 12.48.

(Z)-2-(Thymin-1-yl)ethylen-1-ylphosphonic acid **13a :**

Yield : 75 %; mp: 224-226°C [H_2O/Acetone] (decompose); R_f: 0.47 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 11.63 (Brs, 1H, NH-3); 7.81 (s, 1H, H-6'); 7.21 (dd, 1H, H-2, $J_{2,1}$ 11.31Hz, $J_{2,P}$ 27.10Hz); 5.64 (dd., 1H, H-1, $J_{1,2}$=11.31Hz, $J_{1,P}$=7.83Hz); UV: λ_{max}=281 nm (ε=17100); M.S. (FAB<0): 231 $[MH]^-$. Anal. calcd. for $C_7H_9N_2O_5P$, 1/2 H_2O : C, 34.87; H, 4.18; N, 11.62. Found: C, 34.92; H, 4.31; N, 11.43.

(E)-2-(Thymin-1-yl)ethylen-1-ylphosphonic acid **13b :**

Yield : 73 %; mp: 210-212°C [H_2O/Acetone] (decompose); R_f: 0.42 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 11.65 (Brs, 1H, NH-3); 8.04 (s, 1H, H-6'); 7.60 (dd,1H, H-2, $J_{2,1}$=15.94Hz, $J_{2,P}$= 17.62Hz); 6.02 (dd., 1H, H-1, $J_{1,2}$=15.94Hz, $J_{1,P}$=9.43Hz); UV: λ_{max}=285 nm (ε=16050); M.S. (FAB<0): 231 $[MH]^-$. Anal. calcd. for $C_7H_9N_2O_5P$: C, 36.22; H, 3.91; N, 12.07. Found: C, 36.08; H, 3.99; N, 12.28.

(Z)-2-(cytosin-1-yl)ethylen-1-ylphosphonic acid **14a :**

Yield : 88 %; mp >250°C [H_2O] (decompose); R_f :0.27 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 7.90 (d, 1H, H-6' , $J_{6'-5'}$=7.19Hz); 7.57 (Brs, 2H, 4-NH_2); 7.55 (dd,1H, H-2, $J_{2,1}$=11.88Hz, $J_{2,P}$ 27.39Hz); 5.80 (dd., 1H, H-1, $J_{1,2}$=11.88Hz, $J_{1,P}$=7.82Hz); 5.54 (d, 1H, H-5, $J_{5',6'}$=7.19Hz); UV : λ_{max}=282 nm (ε=15650); M.S. (FAB>0): 218 $[MH]^+$. Anal. calcd. for $C_6H_8N_3O_4P$, 1/3 H_2O : C, 32.30; H, 3.91; N, 18.83. Found: C, 32.19; H:,3.96; N, 18.54.

(E)-2-(cytosin-1-yl)ethylen-1-ylphosphonic acid **14b :**

Yield : 79 %; mp >250°C [H_2O] (decompose); R_f : 0.39 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR : 8.02 (d, 1H, H-6' , $J_{6'-5'}$=7.22Hz); 7.76 (dd, 1H, H-2, $J_{2,1}$=16.08Hz, $J_{2,P}$=16.25Hz); 7.63 (Brs, 2H, 4-NH_2); 5.89 (dd., 1H, H-1, $J_{1,2}$=16.08Hz, $J_{1,P}$=10.21Hz); 5.85 (d, 1H, H-5', $J_{5',6'}$=7.22Hz); UV : λ_{max}=289nm (ε=13200); M.S. (FAB>0): 218 $[MH]^+$. Anal. calcd. for $C_6H_8N_3O_4P$, 3/4 H_2O : C, 31.25; H, 4.15; N, 18.22. Found: C, 31.27; H, 4.26; N, 18.09.

(Z)-2-(5-fluorouracil-1-yl)ethylen-1-ylphosphonic acid **15a :**

Yield : 79 %; mp: 198-201°C [H_2O/Acetone] (decompose); R_f : 0.50 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 7.96 (d, 1H, H-6' , $J_{6'-F}$ 6.45Hz); 7.29 (dd, 1H, H-2, $J_{2,1}$=11.09Hz, $J_{2,P}$= 27.18Hz); 5.52 (dd., 1H, H-1, $J_{1,2}$=11.09Hz, $J_{1,P}$=7.36Hz); UV: λ_{max}=282 nm (ε=16800); M.S. (FAB<0): 235 $[MH]^-$. Anal. calcd. for $C_6H_6FN_2O_5P$: C, 30.52; H, 2.56; N, 11.87. Found: C, 30.73; H, 2.39; N, 12.10.

(E)-2-(5-fluorouracil-1-yl)ethylen-1-ylphosphonic acid **15b :**

Yield : 82 %; mp:241-243 [H_2O/Acetone] (decompose); R_f : 0.47 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 8.04(d, 1H, H-6', $J_{6'-F}$: 6.40Hz); 7.41 (dd, 1H, H-2, $J_{2,1}$=$J_{2,P}$=15.79Hz); 5.81 (dd., 1H, H-1, $J_{1,2}$=15.79Hz, $J_{1,P}$=9.07Hz); UV: λ_{max}=286 nm (ε=16000); M.S. (FAB<0): 235 [MH]$^-$. Anal. calcd. for $C_6H_6FN_2O_5P$, 1/5 H_2O : C, 30.07; H, 2.69; N, 11.69. Found: C, 30.10; H, 2.85; N, 11.91.

(E)-2-(5-bromouracil-1-yl) ethylen-1-ylphosphonic acid **16b :**

Yield : 86 %; mp: 238-240 °C [H_2O/Acetone] (decompose), R_f : 0.52 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 8.41 (s, 1H, H-6'); 7.59 (dd,1H, H-2, $J_{2,1}$=15.93Hz, $J_{2,P}$= 16.85Hz); 6.32 (dd., 1H, H-1, $J_{1,2}$=15.93Hz, $J_{1,P}$=9.36Hz); UV : λ_{max}=295 nm (ε=13400); M.S. (FAB<0): 296 [MH]$^-$. Anal. calcd. for $C_6H_6BrN_2O_5P$, 2/5 H_2O : C, 23.69; H, 2.25; N, 9.21. Found: C, 23.38; H, 2.38; N, 9.29.

(Z)-2-(5-hydroxymethyluracil-1-yl)ethylen-1-ylphosphonic acid **17a :**

Yield : 78 %; mp: 232-235 °C [H_2O/Acetone] (decompose); R_f : 0.36 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR δ : 7.65 (s, 1H, H-6'); 7.24 (dd,1H, H-2, $J_{2,1}$=10.99Hz, $J_{2,P}$=27.05Hz); 5.58 (dd., 1H, H-1, $J_{1,2}$ 10.99Hz, $J_{1,P}$=7.42Hz); 4.51 (s, 2H , CH_2); UV : λ_{max}=277 nm (ε=17300); M.S. (FAB<0): 247 [MH]$^-$. Anal. calcd. for $C_7H_9N_2O_6P$, H_2O : C, 31.59; H, 4.17; N, 10.53. Found: C, 31.73; H, 3.92; N, 10.67.

(E)-2-(5-hydroxymethyluracil-1-yl) ethylen-1-ylphosphonic acid **17b :**

Yield : 80 %; mp: 250 °C [H_2O/Acetone] (decompose); R_f : 0.31 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR (D_2O) δ : 7.84 (s, 1H, H-6'); 7.50 (dd,1H, H-2, $J_{2,1}$=$J_{2,P}$=15.84Hz); 5.89 (dd., 1H, H-1, $J_{1,2}$=15.84Hz, $J_{1,P}$=9.26Hz); 4.67 (s, 2H, CH_2); UV : λ_{max}=280 nm (ε=15800); M.S. (FAB<0): 247 [MH]$^-$. Anal. calcd. for $C_7H_9N_2O_6P$, 3/5H_2O : C, 32.47; H, 3.97; N, 10.82. Found: C, 32.22; H, 3.89; N, 10.89.

(Z)-2-(5-iodouracil-1-yl)ethylen-1-ylphosphonic acid **18a :**

Yield : 83 %; mp: 189-191°C [H_2O/Acetone] (decompose); R_f : 0.57 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR (D_2O) δ: 8.22 (d, 1H, H-6'); 7.19 (dd,1H, H-2, $J_{2,1}$=11.48Hz, $J_{2,P}$=27.51Hz); 5.73 (dd., 1H, H-1, $J_{1,2}$=11.48Hz, $J_{1,P}$=7.64Hz); UV: λ_{max}=282 nm (ε=13900); M.S. (FAB<0): 343 [MH]$^-$. Anal. calcd. for $C_6H_6IN_2O_5P$, 1/7 H2O : C, 20.79; H, 1.83; N, 8.08. Found: C, 20.88; H, 1.78; N, 7.91.

(E)-2-(5-Iodouracil-1-yl) ethylen-1-ylphosphonic acid **18b :**

Yield : 77 %; mp: 215-217 °C [H_2O/Acetone] (decompose); R_f: 0.53 (Isopropanol/NH_4OH/H_2O : 3/1/1); ^{1}H-NMR (D_2O) δ : 8.59 (s, 1H, H-6'); 7.59 (dd,1H, H-2, $J_{2,1}$=15.87Hz, $J_{2,P}$ 16.35Hz); 6.10 (dd., 1H, H-1, $J_{1,2}$=15.87Hz, $J_{1,P}$=9.25Hz); UV: λ_{max}=287 nm (ε=12700); M.S. (FAB<0): 343 [MH]$^-$. Anal. calcd. for $C_6H_6IN_2O_5P$: C, 20.95; H, 1.76; N, 8.14. Found: C, 21.06; H, 1.64; N, 8.29.

Acknowledgments:

This work was supported in part by the Biomedical Research Programme of the European Commission. We thank the CNRS, the ANRS (France), the CNR (Maroc) and the DFG (Germany) for supporting this work. We thank Mrs. A. Absillis, Mrs. F. De Meyer and Mrs. A. Van Lierde for excellent technical assistance.

REFERENCES

1. This paper is dedicated to Professor W. Pfleiderer on the occasion of his 70th birthday.
2. McGuigan, C.; Shaaka, H.; Mahmood, N.; Hay, A. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 1203-1206.
3. Périgaud, C.; Girardet, J.-L. ; Gosselin, G.; Imbach, J.-L. In: *Advances in Antiviral Drug Design*, 1996, *vol. 2*, De Clercq, E., ed. JAI Press Inc., Greenwich, CT, 147-172.

4. Harnden, M.R.; Jarvest, R.L. *Bioorg. Med. Chem. Lett.*, **1992**, *2*, 1559-1560.
5. Naesens, L.; Balzarini, J.; De Clercq, E. *Drug, Metab. Dispos.*, **1992**, *20*, 747-752.
6. Balzarini, J.; Holý, A.; Jindrich, J.; Naesens, L.; Snoeck, R.; Schols, D.; De Clercq, E. *Antimicrob. Agents Chemother.*, **1993**, *37*, 332-338.
7. Dvorakova, H.; Masojidkova, M.; Holý, A.; Balzarini, J.; Andrei, G.; Snoeck, R.; De Clercq, E. *J. Med. Chem.*, **1996**, *39*, 3263-3268.
8. Chamberlain, S.D.; Biron, K.K.; Dornsife, R.E.; Averett, D.R.; Beauchamp, L.; Koszalka, G.W. *J. Med. Chem.*, **1994**, *37*, 1371-1377.
9. Kim, C.U.; Luh, B.Y.; Misco, P.F.; Bronson, J.J.; Hitchcock, M.J.M.; Ghazzouli, I.; Martin, J.C. *J. Med. Chem.* **1990**, *33*, 1207-1213.
10. Kim, C.U.; Misco, P.F.; Martin, J.C. *Heterocycles*, **1990**, *31*, 1571-1574.
11. Parkin, A. *J. Chem. Soc. Perkin Trans. I*, **1991**, 2983-2990.
12. Harnden, M.R., Jennings, L.J. *Antiviral Chem. Chemother.*, **1993**, *4*, 215-227.
13. Balzarini, J.; De Clercq, E. *Antiviral Chemotherapy*, ed Jeffries, D.J. and De Clercq, E. **1995**, *2*, 41-63.
14. Labataille, P.; Pélicano, H.; Maury, G.; Imbach, J.-L.; Gosselin, G. *Bioorg. Med. Chem. Lett.*, **1995**, *3*, 2315-2320.
15. Racha, S.; Vargeese, C.; Vemishetti, P.; EL-Subbagh, H.I.; Abushanab, E.; Panzica, R.P. *J. Med. Chem.*, **1996**, *39*, 1130-1135.
16. Yu, K.-L.; Bronson, J.J.; Yang, H.; Patick, A.; Alam, M.; Brankovan, V.; Datema, R.; Hitchcock, M.J.M.; Martin, J.C. *J. Med. Chem.* **1992**, *35*, 2958-2969.
17. Harnden, M.R.; Jarvest, R.L.; Parrat, M.J. *J.Chem. Soc. Perkin Trans I*, **1992**, 2259-2263.
18. Secrist III, J.A.;. Riggs, R.M; Comber, R.N.; Montgomery, J.A. *Nucleosides & Nucleotides*, **1992**, *11*, 947-956.
19. Vellemin, D.; Starzyk, F.I. *Synthetic. Commun.*, **1993**, *23*, 1053-1059.
20. Megati, S.; Phadtare, S.; Zemlicka, J. *J. Org. Chem.*, **1992**, *57*, 2320-2327.
21. Harnden, M.R.; Parkin, A.;.Parratt, M.J.; Perkins, R.M. *J. Med. Chem.*, **1993**, *36*, 1343-1355.
22. Balzarini, J.; De Clercq, E. *J. Biol. Chem.*, **1991**, *266*, 8686-8689.
23. Sisky, M. S.; Bass, R. G. *J. Heterocyclic Chem.*, **1984**, *21*, 759-768.
24. Winterfeldt, E.; Preuss, H. *Chem. Ber.* , **1966**, *99*, 450-458.
25. Bram, G.; Sansoulet, J.. Galons, H.; Miocque, M; *Synthetic Commun.*, **1988**, *18*, 367-380.
26. Lazrek, H.B.; khaider, H.; Rochdi,A.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides & Nucleotides*, **1994**, *13*, 811-817.
27. Lazrek, H.B.; Taourirte, M.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides & Nucleotides*, **1991**, *10*, 1285-1293.
28. Taha, M. L.; Lazrek, H.B. *Bull. Soc. Chim. Belg.* **1995**, *104*, 591-594.
29. Lazrek, H.B.; Taourirte, M.; Barascut, J.-L.; Imbach, J.-L. *Bull. Soc. Chim. Belg.* **1996**, *105*, 391-395.
30. Lazrek, H.B.; Taourirte, M.; Barascut, J.-L.; Imbach, J.-L. *Bull. Soc. Chim. Belg.* **1997**, *106*, 19-24.
31. Lazrek, H.B.; Cissoko, S., I.; Barascut, J.-L.; Imbach, J.-L. *in preparation.*
32. Scheiner, P.; Geer, A.; Bucknor, A.M.; Gadler,H.; Price, R.W. *Nucleosides & Nucleotides*, **1989**, *8*, 1441-1451.
33. Scheiner, P.; Geer, A.; Bucknor, A.M.; Imbach, J.L.; Schinazi, R.F., *J. Med. Chem.*, **1989**, *32*, 73-76.
34. Baker, B.R.; Tanna, P. M. *J. Org. Chem.* **1965**, *30*, 2857-2858.
35. Lira, E. P.; Huffman, C. W. *J. Org. Chem.* **1966**, *31*, 2188-2191
36. Geen, G.R.; Kincey, P. M. *Tetrahedron Lett.*, **1992**, *33*, 4609-4612.
37. Witvrouw, M.; Schols, D.; Andrei, G.; Snoeck, R.; Ikeda, S.; Pauwels, R.; Van Schepdael, A.; Arnout, J.; Claes, P.; Desmyter, J.; De Clercq, E. *Antiviral Chem. Chemother.*, **1992**, *3*, 351-360.