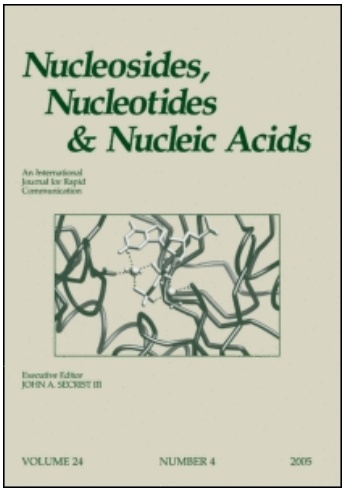

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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[a] Laboratoire de Chimie Bio-Organique, Université de NICE-SOPHIA ANTIPOLIS, Faculté des Sciences, NICE Cédex 2, FRANCE [b] the WELLCOME Research Laboratories, The WELLCOME Foundation Ltd, Beckenham, Kent, ENGLAND

To cite this Article Forestier, M. A. , Ayi, A. I. , Condom, R. , Boyode, B. P. , Colin, J. N. , Selway, J. , Challand, R. and Guedj, R.(1993) 'Synthesis of Some New Nucleoside Analogues as Potential Antiviral Agents', Nucleosides, Nucleotides and Nucleic Acids, 12: 9, 915 — 924
To link to this Article: DOI: 10.1080/07328319308018562
URL: http://dx.doi.org/10.1080/07328319308018562

NUCLEOSIDES & NUCLEOTIDES, 12(9), 915-924 (1993)

SYNTHESIS OF SOME NEW NUCLEOSIDE ANALOGUES AS POTENTIAL ANTIVIRAL AGENTS.

M. A. Forestier[1], A. I. Ayi [1], R. Condom[1], B. P. Boyode[1], J. N. Colin[2], J. Selway[2], R. Challand[2] and R. Guedj[1]*.

[1] Université de NICE-SOPHIA ANTIPOLIS, Faculté des Sciences, Laboratoire de Chimie Bio-Organique
B.P. N° 71, F-06 108 NICE Cédex 2-FRANCE.
[2] The WELLCOME Foundation Ltd, the WELLCOME Research Laboratories, Langley Court, South Eden Park Road, Beckenham, Kent BR3 3BS, ENGLAND.

Abstract : A novel series of pyrimidine nucleoside analogues was synthesized. 2,3-Dideoxy-2,3-anhydro-β-D-lyxofuranose was opened by sodium azide to give the corresponding azido compound, which was reduced by lithium aluminium hydride to lead to 2,3-dideoxy-2,3-epimino-β-D-ribofuranose. Pyrimidine bases were glycosylated with this synthon to give potential antiviral molecules : 1-(2,3-dideoxy-2,3-epimino-β-D-ribofuranosyl)pyrimidines.

INTRODUCTION

Since the discovery of Human Immunodeficiency Virus (HIV) as the etiologic agent of Acquired Immunodeficiency Syndrome (AIDS), several steps of its replication cycle have been chosen as targets[1]. Among these, reverse transcription by the enzyme Reverse Transcriptase (RT) has been the most studied[2]. It actually consists of three steps : transcription of the single-stranded viral RNA to RNA.DNA hybrid, degradation of the RNA component of the RNA.DNA hybrid and duplication of the remaining single-stranded DNA chain to double-stranded DNA. Many compounds of different chemical families targeting RT show some activity *in vitro* and *in vivo*[3]. Among them, 2',3'-dideoxynucleosides take a very important place[4,5] because they prove that a chemical modification in the sugar moiety or base can in some circumstances convert a normal

substrate for nucleic acid synthesis into a potent inhibitor of the infectivity and replication of HIV.

Generally the various dideoxynucleosides are not equivalent in either activity or toxicity profiles *in vitro* or *in vivo*. This large variety of nucleoside analogues, including 2',3'-dideoxynucleosides (3'-azido-2',3'-dideoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxy-2',3'-didehydrothymidine (d4T), 1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)cytosine (3TC)...), have been found to inhibit HIV replication through an action targeted at the HIV-associated reverse transcriptase[6]. Clinical experience with these compounds and sometimes their association with AZT has shown :

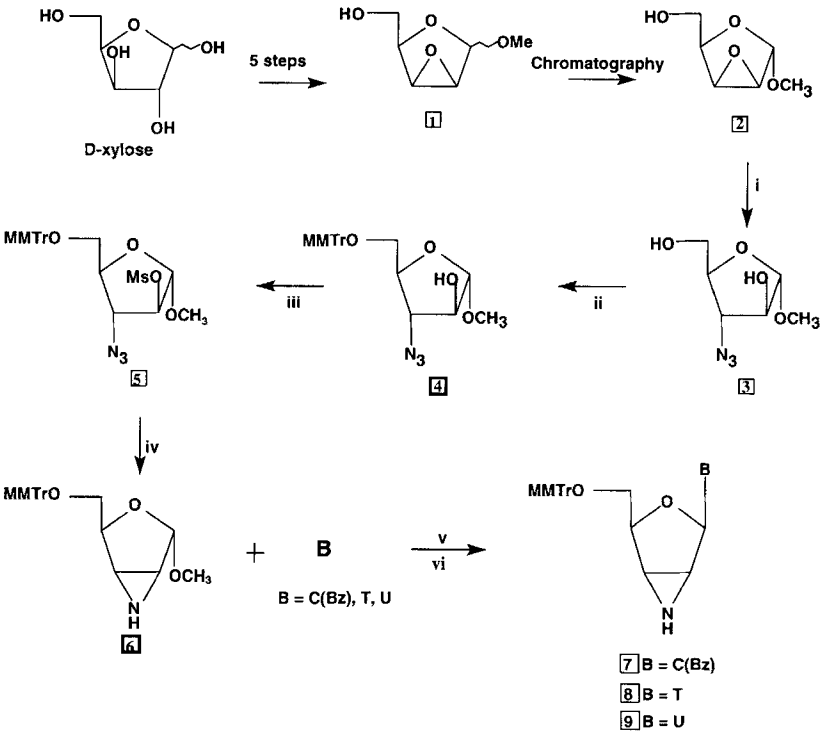
- relative failure of AZT or ddI in long term monotherapies (toxicity, therapeutic resistance) [7,11]
- the emergence of resistant viral strains [12]
- toxicity decreasing by reducing respective doses of the used nucleosides [13]
- search for a synergy to increase antiviral activity and to decrease nucleoside-insensitive HIV variants (clinical trials AZT+ddC, AZT+ddI) [14,15].

These observations show that 2',3'-dideoxynucleosides are a promising family but *in vivo*, the compounds now used have a limited activity. Moreover the knowledge in terms of structure-activity relationships has not really emerged. Nevertheless we think we have to get new nucleoside analogues with, for example, new functions in 2',3' positions that would be more selective. In this perspective, we describe the synthesis of new 2',3' -dideoxynucleoside analogues bearing an aziridine ring in position 2 ',3' .

In the literature, few publications reported the preparation of such related compounds : synthesis of the 9-(2,3-dideoxy-2,3-epimino-β-D-ribofuranosyl)adenine[16] and preparation of the 1-(5-O-*para*-monomethoxytrityl-2,3-dideoxy-2,3-epimino-β-D-ribofuranosyl)uracil[17] are described. These synthetic methods to obtain the 2',3'-epimino nucleoside derivatives involved, after many laborious transformations, the following principal reaction steps : ring-opening of the 2',3'-anhydronucleoside with azide salts and reduction of the obtained azido alcohol with hydrazine in the presence of Raney Nickel[16], or ring opening of the 2',3' anhydronucleoside by $PhSe^-$ ion and treatment with potassium *tert*-butoxide, after protection of the hydroxyl group. This intermediate is then oxidized with *meta*-chloroperbenzoic acid and allowed to react with aqueous ammonia [17].

New and less fastidious synthetic approaches should therefore be developed to prepare this important class of potential antiviral nucleoside derivatives.

There are many methods to obtain aziridines[18], and coupling these compounds with an appropriate base will be a convenient route to obtain the title nucleosides. We report here a facile synthesis of 1-(5-O-*para*-monomethoxytrityl-2,3-dideoxy-2,3-epimino-β-D-ribofuranosyl)thymine, uracil and benzoyl cytosine.



Scheme 1 : Reaction conditions : (i) NaN_3, NH_4Cl, EtOH, H_2O (ii) MMTrCl, Py (iii) MsCl, Py (iv)$LiAlH_4$, Et_2O. (v) B = T, U : HMDS, TMSCl, 124°C; B = C(Bz) : HMDS, $(NH_4)_2SO_4$, 124°C (vi) [6], CF_3SO_3Si-tBuMe$_2$, CH_3CN.

RESULTS AND DISCUSSION

The best route to the title compounds seemed to be to prepare the aziridine [6] and in a second step to condense it with an appropriate protected base.

Synthesis of methyl-5-O-*para*-monomethoxytrityl-2,3-dideoxy-2,3-epimino-β-D-ribofuranose [6] :

The starting methyl-2,3-dideoxy-2,3-anhydro-β-D-lyxofuranose [1] was obtained from D-xylose as previously described by Baker et al.[19], as a mixture of α– and β-isomers from which the α- isomer [2], isolated by silica gel column chromatography, represented 55% of the mixture. During glycosylation reactions, 2'-benzoyl or -acetyl groupments form a benzyloxonium (or an acyloxonium) ion to lead exclusively to the ß nucleoside[20]. As we have not such a groupment, we found it judicious to condense the base on a sugar with a 1'-

substituant of α conformation, to favour the formation of the ß nucleoside. For this reason, we chose to go on with the sugar functionnalization on the α anomer only of [1].

Ring opening by sodium azide of [2] in the presence of ammonium sulfate[21] provided compound [3] in good yield. It was treated without further purification with *para*-monomethoxytrityl chloride (MMTr-Cl) in anhydrous pyridine to give [4]. This compound reacted with methanesulfonyl chloride (MsCl) in dry pyridine to lead to compound [5]. The azido furanoside [5] was allowed to react with lithium aluminium hydride in anhydrous diethyl ether at room temperature[22], and 2,3-dideoxy-2,3-epimino-5-O-*para*-monomethoxytrityl-1-O-methyl-α-D-ribofuranose [6] was isolated with 50% yield after purification by chromatography on a silica gel column . This novel aziridine was characterized by N.M.R., I.R., M.S. and elementary analysis. It could be easily prepared on a large scale in a pure form (Scheme1).

Synthesis of 1-(2,3-dideoxy-2,3-epimino-β-D-ribofuranosyl)pyrimidine derivatives [7]-[9] :

The next step consisted of coupling compound [6] with silylated bases. For this step, the literature reports the following methods :

- after isolation of the silylated base, sugar is added in the presence of a Lewis acid catalyst [23] : $SnCl_4$, $BF_3.Et_2O$, trimethylsilyl trifluoromethanesulfonate...
- or a one-pot reaction that consists of the heating under reflux, for 20 minutes to 5 hours, a mixture of sugar, base, silylating agents and catalyst [24].

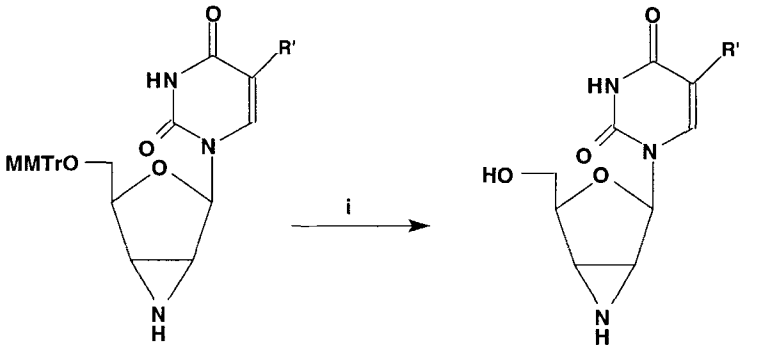
Several attempts to get the desired molecules following these methods failed. Finally we succeded following a different procedure. Using the well-known HMDS-TMSCl or $(NH_4)_2SO_4$ silylating agent[25], the chosen base was silylated, then after complete dissolution, the glycosylation reactants were added without isolation of the silylated base.

In this manner, we obtained the desired compounds [7], [8] and [9] with 20% yield after purification by chromatography on a silica gel column.

Deprotection in 5' position of compounds [8] (and its α anomer) and [9] was achieved as previously described[26](scheme 2) in a quantitative yield.

U.V. spectrum confirmed glycosylation on N-1, and according to the literature [27,28], ^1H N.M.R. data permitted the determination of the anomeric conformation of each nucleoside analogue (very low value for $J_{1',2'}$).

Total deprotection of [7] and its purification is under investigation.



[8] : R' = CH_3 , Thymine
[9] : R' = H, Uracil

[10] : R' = CH_3 , Thymine
[11] : R' = H, Uracil

Scheme 2 : (i) CF_3COOH, CH_2Cl_2

EXPERIMENTAL PART

Instruments : ^1H NMR spectra were recorded in $CDCl_3$ or CD_3OD solutions using Bruker spectrometers, models AC 200 E (200 MHz) , WP-90 (84.67 Mhz) and/or WP-80 (80 MHz). Signal positions are given in ppm, with tetramethylsilane as internal standard. Infrared (IR) spectra were measured in solution ($CHCl_3$) using a Bruker FT- IFS spectrometer. Microanalyses were performed by Le Service de Microanalyse du C.N.R.S., Vernaison, France. U. V. spectra were recorded in methanol, on a Varian spectrometer, 634 series. Mass spectra were obtained from a Ribermag R10-10B spectrometer. Silica gel chromatography was performed on grade 60 70-230 mesh ASTM silica gel (Merck) and TLC on silica gel 60 F-254 glass plates (Merck). The solvents employed were freshly distilled before use.

[1] was prepared following Baker's method [19]. The crude product (α and β isomers), obtained in 55% yield starting from D-xylose, was purified by column chromatography on silica gel. The α-isomer [2] was obtained in 30% yield from D-xylose.

Methyl-3-deoxy-3-azido-α-D-arabinofuranose [3] :

5.6 g of [2] (38.3 mmoles, 1 eq.) were dissolved in a solution of 196 ml of ethanol and 46 ml of distilled water, then 8.5 g of sodium azide (0.13 mole, 3.4 eq.) and 7.8 g of ammonium chloride (0.12 mole, 3.2 eq.) were added. The solution was heated under reflux for three days, then the mixture was evaporated to dryness. The solid residue was taken into dichloromethane and stirred overnight. The solution was filtered and evaporated under reduced pressure. [3] was obtained with 75% yield as an oil.

^{1}H N.M.R. : δ : 3.43 (3, s, CH_3O); 3.6-3.8 (3, m, $H_{5,5'}$, H_3); 4.06 (2, m, H_4, H_2); 4.93 (1, s, H_1).

I.R. : 2100 cm^{-1} (ν[N_3]).

Methyl-3-deoxy-3-azido-5-O-*para*-monomethoxytrityl-α-D-arabinofuranose [4] :

1.9 g of [3] (10 mmoles, 1 eq.) were dissolved in 16 ml of dry pyridine. A solution of 3.6 g of *para*-monomethoxytrityl chloride (11.7 mmoles, 1.17 eq.) in 12 ml of dry pyridine was added all at once. This mixture was stirred at room temperature for 17 hours, then water was added and pyridine was evaporated under reduced pressure. The residue was taken into dichloromethane and washed three times with water. The organic layer was dried over sodium sulfate, filtered, evaporated under reduced pressure. The residue was dissolved in toluene and removed under reduced pressure. After complete evaporation, [4] was recovered with quantitative yield as a syrup.

^{1}H N.M.R. : δ : 3.29 (1, large s, OH); 3.45 (3, s, CH_3O); 3.78 (3, s, CH_3O-MMTr) ; 3.91-4.5 (5, m, H_2, H_3, H_4, $H_{5,5'}$); 5.28 (1, s, H_1); 6.95-7.4 (14, m, H arom.).

Methyl-3-deoxy-3-azido-5-O-*para*-monomethoxytrityl-2-mesyloxy-α-D-arabinofuranose [5] :

4.5 g of [4] (9.76 mmoles, 1 eq.) were dissolved in 5.5 ml of dry pyridine. This solution was cooled with an ice bath. Methanesulfonyl chloride (1.2 ml, 15.5 mmoles, 1.6 eq.) were added dropwise and the mixture was stirred for 15 mn. The ice bath was then removed and the mixture was stirred at room temperature for 17 hours. After addition of cold water, the mixture was extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was dissolved in toluene. After evaporation, [5] was recovered with 92 % yield as a syrup.

^{1}H N.M.R. : δ : 3.0 (3, s, CH_3SO_2); 3.38 (3, s, CH_3O); 3.77 (3, s, CH_3O-MMTr); 4.02-4.6 (4, m, H_2, H_4, $H_{5,5'}$); 4.90 (1, large s, H_3); 5.11 (1, s, H_1); 6.8-7.5 (14, m, H arom.)

Methyl-2,3-dideoxy-2,3-epimino-5-O-*para*-monomethoxytrityl-α-D-ribo--furanose [6] :

5.7 g of [5] (10.5 mmoles, 1 eq.) dissolved in a minimum amount of dry ether was added dropwise to a suspension of $LiAlH_4$ (1 g, 2.5 eq.) in 18 ml of dry ether, cooled with an ice bath. The mixture was stirred for 12 hours and the temperature was allowed to reach progressively 20°C. Water was then carefully added. The mixture was diluted with ether, stirred for two hours then filtered. The solid residue was washed with ether. The filtrate was evaporated under reduced pressure and the crude product was purified by chromatography

on a silica gel column (dichloromethane progressively enriched with methanol). Compound [6] was recovered after chromatography with 50% yield as a pale yellow solid.

^{1}H N.M.R.: δ : 0.95 (1, large s, NH); 2.57 (1, d, H_3); 2.81 (1, d, H_2); 3.2 (2, t, $H_{5,5'}$); 3.51 (3, s, CH_3O); 3.79 (3, s, CH_3O-MMTr); 4.24 (1, t, H_4); 5.34 (1, s, H_1); 6.8-7.6 (14, m, H arom).

IR : 3500 cm^{-1}(N-H), 1607cm^{-1}(secondary amine). M.S. : m/z = 418 (M^+).

Elemental analysis : calculated (%) : C : 73.37, H : 6.91; found : C : 73.48, H : 6.62.

1-[(2,3-Dideoxy-2,3-epimino-5-O-*para*-monomethoxytrityl)-β-D-ribofuranosyl]pyrimidine [7]-[9] :

Cytosine was first benzoylated as previously described[29].

1.1 eq of the chosen pyrimidine base was suspended under nitrogen in a mixture of 13.4 eq of 1,1,1,3,3,3-hexamethyldisilazane (HMDS). Then 2.25 eq of trimethylsilyl chloride (TMSCl) for thymine and uracil or a catalytic amount of ammonium sulfate for benzoylcytosine were added. The mixture was heated to 124°C until the base was completely dissolved (one night for thymine, 1h30 for uracil and 2h for N-6 benzoylcytosine). The solution was allowed to cool to room temperature. Then, without further isolation, 1 eq of [6] dissolved into a minimum amount of dry acetonitrile was added dropwise. At the end of the addition, 1.3 eq of *tert*-butyldimethylsilyl trifluoromethanesulfonate were added and the mixture was heated at 80°C. At the end of the reaction, the mixture was evaporated to dryness under reduced pressure.The residue was taken into dichloromethane and quenched with sodium hydrogencarbonate 1M. The aqueous phase was extracted with dichloromethane.The organic layers were washed with distilled water. After being dried on sodium sulfate, it was filtered and evaporated to dryness under reduced pressure. The crude product was purified by chromatography on a silica gel column, which permited to get 20% of pure nucleoside (for thymine, 72% of the β anomer and 28 % of the α-anomer were separated, and for uracil and cytosine, β anomers were only recovered).

[7] : ^{1}H N.M.R. : δ : 2.29 (1, d, $H_{3'}$, $J_{2',3'}$ = 4.9 Hz); 3.1 (3, m, $H_{2'}$ et $H_{5,5'}$); 3,8 (3, s, CH_3O-MMTr); 4. 69 (1, large t, $H_{4'}$, $J_{4',5'} = J_{4',5''}$ = 4.5 Hz); 5.80 (1, d, H_5, $J_{5,6}$ = 7.3 Hz); 6.07 (1, little d, $H_{1'}$, $J_{1',2'}$ = 1 Hz); 6.74-7.50 (19, m, H arom.); 7.93 (1, d, H_6 $J_{5,6}$ = 7.3 Hz). M. S. : m/z = 105 (Bz), ; m/z = 107 (cytosine); m/z = 112 (ose); m/z = 273 (monomethoxytrityl).

[8] : ^{1}H N. M . R. : [8]α : δ : 1.95 (3, s, CH_3-thymine); 2.34 (1, d, $H_{3'}$, $J_{2',3'}$ = 5 Hz); 3.00 (1, dd, $H_{2'}$, $J_{1'\alpha,2'}$ = 2.2 Hz, $J_{2',3'}$ = 5 Hz); 3.17 (2, t, $H_{5',5''}$, $J_{4',5'} = J_{4',5''}$ = 5 Hz); 3.8 (3, s, CH_3O-MMTr); 4.79 (1, t, $H_{4'}$, $J_{4',5'}$, = $J_{4',5''}$ = 5 Hz); 6.1 (1, d, $H_{1'}$, $J_{1',2'}$ = 2.2 Hz); 6.8-7.7 (14, m, H arom.); 7.82 (1, s, H_6); 9.4 (1, broad s, NH-thymine).

M. S. : m/z = 511 (M^+). [8]β : δ : 1.98 (3, s, CH_3-thymine); 2.95 (1, dd, $H_{3'}$, $J_{2',3'}$ = 4.9 Hz, $J_{3',4'}$ = 1.9 Hz); 3.25 (3, m, $H_{2'}$ and $H_{5',5''}$); 3.8 (3, s, CH_3O-MMTr); 4.4 (1, t, $H_{4'}$,

$J_{4',5'} = J_{4',5''} = 4.2$ Hz); 6.32 (1, little d, $J_{1',2'} = 1.7$ Hz); 6.8-7.6 (14, m, H arom.); 7.8 (1, s, H_6); 9.3 (1, broad s, NH-thymine).M. S. : m/z = 511 (M^+).

[9] : ^{1}H N.M.R. : δ : 2.90 (1, d, $H_{3'}$, $J_{3',4'} = 4.5$ Hz); 3.23 (3, m, $H_{5,5'}$ and H2'); 4.33 (1, t, $H_{4'}$, $J_{4',5'} = J_{4',5'} = 5.6$ Hz); 5.68 (1, d, H_5, $J_{5,6} = 9.8$ Hz); 6.32 (1, d, $J_{1',2'} = 1.4$ Hz); 6.8-7.6 (14, m, H arom.); 7.88 (1, d, H_6, $J_{5,6} = 9.8$ Hz). M. S. : m/z = 497 (M^+).

1-[(2,3-Dideoxy-2,3-epimino)-α- and -β-D-ribofuranosyl]thymine [10] :

1 eq of [8] (or its α anomer) was placed in a solution of trifluoroacetic acid 3% in freshly distilled dichloromethane, 30 ml per millimole. The solution was stirred at room temperature for half an hour. The reaction mixture was washed several times with distilled water, then the combined aqueous layers were extracted with ether. The aqueous layer was lyophilized and [10] (or its α anomer) was recovered as a white powder, in a quantitative yield.

[10] :^{1}H N.M.R.. : δ : 1.95 (3, s, CH_3-thymine); 3.6-4.0 (4, m; $H_{5',5''}$,$H_{2'}$,$H_{3'}$); 4.5 (1, t, $H_{4'}$,$J_{4',5'} = J_{4',5''}$=3.5 Hz); 6.25 (1, little d, $H_{1'}\alpha$, $J_{1',2'} = 1.9$ Hz); 6.3 (1, s, $H_{1'}\beta$); 7.65 (1, s; H_6-thymine). M. S. : m/z =239 (M^+). U.V. : λ max = 264 nm (ε = 4717).

1-[(2,3-Dideoxy-2,3-epimino)-β-D-ribofuranosyl]uracil [11]:

The uracil analogue was deprotected as described above for [8]. [11] was recovered after lyophilization with a quantitative yield.

[11] : 1H N.M.R. : d : 3.67 (1, d, $H_{3'}$, $J_{2',3'} = 5.01$ Hz); 3.80 (1, d, $H_{5'}$, $J_{5',5''} = 12.4$ Hz); 3.87 (1, d, $H_{5''}$, $J_{5',5''}$ =12.4 Hz) (syst. ABX); 3.96 (1, dd, $H_{2'}$, $J_{2',3'} = 5.05$ Hz);4.51 (1, t, $H_{4'}$, $J_{4',5'} = J_{4',5''} = 3.46$ Hz); 5.73 (1, d, H_5, $J_{5,6} = 8.13$ Hz); 6.27 (1, little d, $H_{1'}$, $J_{1',2'} = 1.45$ Hz); 7.83 (1, d, H_6, $J_{6,5} = 8.15$ Hz). M. S. : m/z = 226 (M+H); U. V. : λmax = 260 nm, ε = 2993.

Acknowledgement : The authors gratefully acknowledge the following sources for their financial support : The WELLCOME Research Laboratories of Beckenham (England) and PACA Region (Provence Alpes Côte d'Azur). We also greatly thank J. L. Imbach and G. Gosselin (Laboratoire de Chimie Bio-organique Montpellier, France) who helped us in developing our program on potential anti-HIV nucleoside analogues.

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Received 5/26/93
Accepted 7/14/93