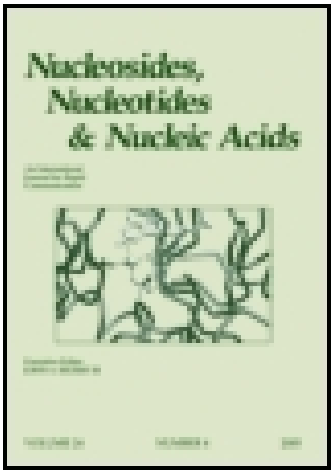

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Synthesis of Three New Carbocyclic Analogues of 3′-Deoxy Purine Ribonucleosides

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SYNTHESIS OF THREE NEW CARBOCYCLIC ANALOGUES OF 3'-DEOXY PURINE RIBONUCLEOSIDES.

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Abstract: The 1-hydroxymethyl-3-cyclopentene (**4**) was converted, after epoxidation, to two new exocyclic amino carbocyclic nucleosides (**1**, **2**), and a new cyclopentane nucleoside analogue (**3**), with potential biological activities. The regioselectivity of the epoxidation (**4**), which is the key step, is governed by steric control using aryl and silyl hydroxyl protecting groups.

Introduction ;

For about ten years, several carbocyclic analogues of nucleosides have been synthesized and seem to be an important group of anti-viral and anti-tumour agents[1-7]. The isostere replacement of oxygen of the furanose ring by a methylene group is of great interest since the cyclopentane analogues have a greater stability towards the enzymes hydrolase and phosphorylase, which cleave the glycosidic linkage of the nucleosides. In particular, neplanocin and (±)-5'-norasteromycin[9-12] derivatives of aristeromycin which were first synthesized in racemic form by Shealy and Clayton[8] in 1966, show activity against human cytomegalovirus (HCMV). The first carbocyclic nucleoside of biological interest was the carbocyclic analogue of 2'-deoxyguanosine[13] (2'-CDG), active against Herpes Simplex Virus types 1 and 2 (HSV-1, HSV-2). The 2'-deoxy-carbocyclic uridines, C-bromovinyldeoxyuridine[14-16] (C-BVDU) and C-2'-ara-fluoro-guanosine[17-19], are also good anti HSV-1 and HSV-2 agents. C-BVDU, which is more stable to

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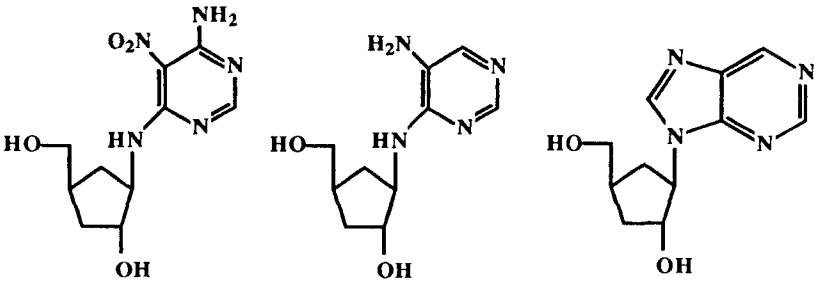


(±)-1 (±)-2 (±)-3

Scheme 1

degradation in vivo than BVDU, also displays anti varicella zoster virus (VZV) activity. More recently, Carbovir[20-21] (C-2',3'-dideoxy-2',3'-didehydroguanosine), displays potent activity against HIV, comparable to that of AZT; other anti-HIV carbocyclic nucleosides are synthetic carbocyclic oxetanocin[22-23] and a 5'-hydroxymethyl derivative of Carbovir[24].

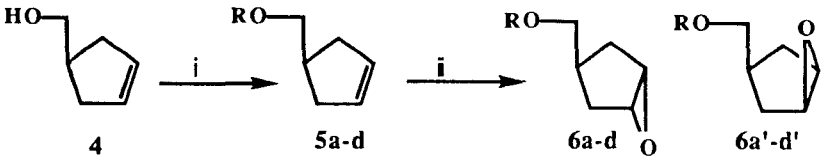
As part of continuing search for new carbocyclic nucleosides with anti-viral properties, we describe here the total synthesis of two new exocyclic amino carbocyclic nucleosides **1** and **2**, which are analogs of biologically active nucleosides[25-28], and a new carbocyclic analogue **3**, (Scheme 1).

The synthesis of some C-3'-deoxyribopurine has been described by Shealy *et al*[13,29]. Neverthless, the lacking of regioselectivity of their method and the use of such reactions as oxidative cleavage and Hofmann reaction, produced a mixture of C-2'- and C-3'-deoxyribonucleosides in low yield. We describe here a rapid and original method for a regioselective obtention of C-3'-deoxyribonucleosides and their derivatives.

Results and discussion :

Generally, the synthesis of such compounds occurs first by the formation of a functionalized cyclopentylamine, and then by the coupling of a pyrimidine or purine precursor on the amino group[13,30,31]. The main problem in those syntheses is the formation of a cyclopentylamine with the different substituents having the required configurations. We obtained the cyclopentylamine by opening an epoxide ring via a trans addition with an azide ion followed by a catalytic hydrogenation.

The epoxidation, which is the key step, is governed by electronic and steric interactions; in the literature, 1-hydroxymethyl-3-cyclopentene[32] **4** led to a ratio of 1.1:1



Reagents and conditions : a: R = Bz; b: R = Fmoc; c: R = $(Ph)_3Si$; d: R = TBDMS
i, RCl, pyridine, O°C; ii, mCPBA, CH_2Cl_2, gentle reflux

Scheme 2

anti:syn epoxides[33]. In fact, only the anti isomer is used in the course of synthetic studies on carbocyclic analogues. The rigidity and the almost planeity of cyclopentenes and the steric hindrance of the syn side by a free rotation of the hydroxyl protecting groups favors the majority formation of the anti isomer. Wolff and Halazy[34] have used this approach to obtain derivatives of phophodiester-epoxides.

We protected[35] the hydroxymethyl group by means of bulky groups with low electronic effects. After the epoxidation of the alkene **5a-d** with MCPBA in an aprotic solvent with gentle reflux, we obtained the corresponding epoxides in a mixture of anti-epoxides **6a-d** and syn **6a'-d'** (Scheme 2).

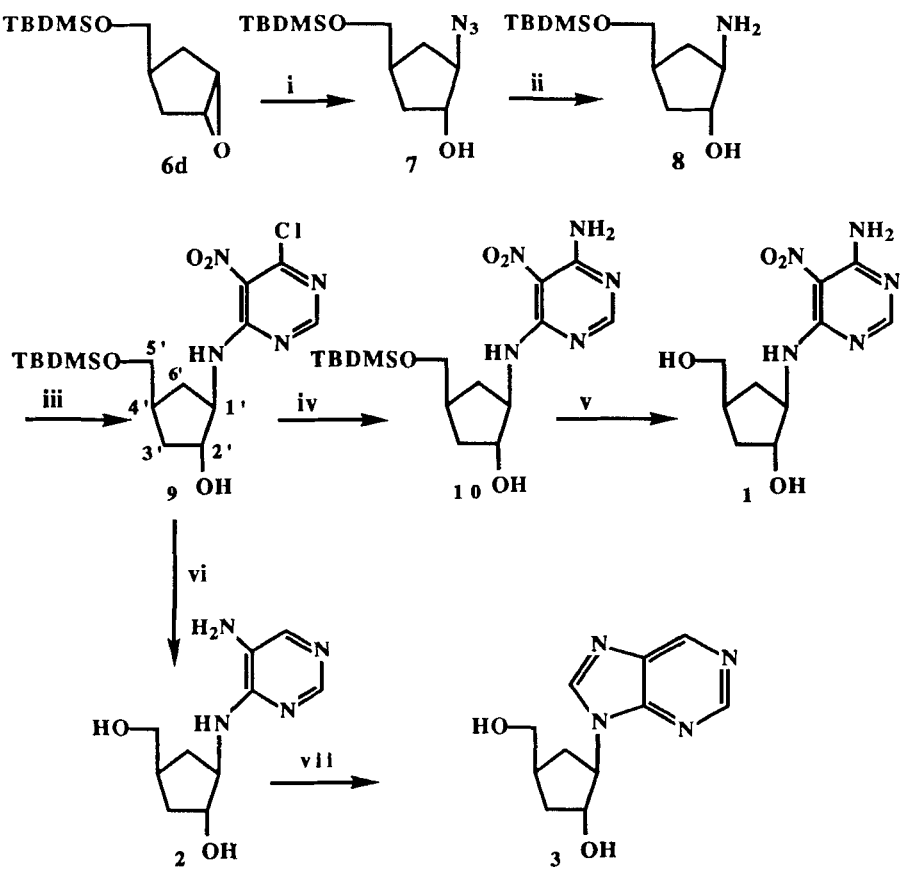
The ratio of anti:syn epoxides was determined by ^1H NMR spectra. The constants and the chemical shifts were found to vary considerably from the syn or anti isomers; this is a characteristic of the quadrupolary effect of the O atom of the epoxide on the CH_2OR. Table I represents these variations :

Table I

R	Anti		Syn		ratio
	δ ppm	J Hz	δ ppm	J Hz	anti:syn
H	3.80	m	3.29	m	1.1:1
Bz	4.26	5.3	4.16	8.1	2.3:1
FMOC	4.16	5.3	4.08	7.2	3:1
Ph_3Si	3.81	4.6	3.65	8.1	4:1
TBDMS	3.52	4.6	3.35	8.5	8.2:1

* From R = Bz to R = FMOC, we observed an increase of the anti isomer; it is due to the increase of steric hindrance.

* From R = aryl to R = silyl, we observed a global increase of the anti epimer due to the absence of hydrogen bond between the peracid and R-protecting group.



Reagents and conditions : i) NaN_3, H_2O, EtOH, NH_4Cl, gentle reflux; ii) H_2 Pd/C 10%, MeOH; iii) 4.6-dichloro-5-nitropyrimidine, Et_2O, Et_3N, O°C then room temperature; iv) NH_3, MeOH, room temperature; v) NH_4F, MeOH, 60°C; vi) H_2 Pd/C 5%, MeOH; vii) $(EtO)_3CH$, H^+, DMF.

Scheme 3

The greatest selectivity for the anti-isomer is shown by the tertbutyldimethylsilyl analogue **6d**; ratio of anti:syn epoxide **8.2:1**. It is worth noting that the triphenylsilyl group did not provide the best ratio of anti epoxide; the electronic repulsion between the Π-orbitals of phenyl and alkene could explain this observation, in accordance with Coe *et al*[36].

The sequence of reactions leading to **1**, **2** and **3** was as follows (Scheme 3) : The opening of the epoxide ring of **6d** by NaN3 yielded **7** (43%); after catalytic

hydrogenation, the aminoalcohol **8** was obtained quantitatively. The reaction of **8** with 4,6-dichloro-5-nitropyrimidine gave **9** (51%) which reacted with a solution of NH_3/MeOH to yield 72% of **10**. The deprotection of **10** was performed by addition of a solution of NH_4F in MeOH[37]. The use of other reagents of desilylation such as TBAF/THF produced a lot of byproducts. The carbocycle **1**, (±)-1'-(β)-[4-(6-amino-5-nitro)-pyrimidine]-amino-2'-(α)-hydroxy-4'-hydroxymethylcyclopentane, was then obtained[38,39]. The NMR studies of compounds **10** and **1** have shown, in accordance with Kubo *et al*[40], hydrogen bonds between the 4-NH and NO_2, and 6-NH_2 and NO_2. This result was obtained by a NMR study as a function of temperature, or by addition of D_2O to the NMR sample. In view of the antiviral activity of **1**, it seems important to note that this exocyclic aminopyrimidine moiety can be assimilated into a planar tricycle.

The catalytic hydrogenation over Pd/C 5% of **9** afforded **2** quantitatively. It is worth noting the interest of this step : the hydrogenolysis of the chlorine atom occured, releasing HCl which cleaved the O-silyl protected group and reduced the nitro- group to an amino group. The resulting diamine **2**, (±)-1'-(β)-[4-(2H,6H-5-amino)-pyrimidine]-amino-2'-(α)-hydroxy-4'-hydroxymethylcyclopentane, obtained in four steps with 30% yield from **6d**, was cyclised to provide to the new carbocyclic nucleoside **3**.

The structure of **10**, **1**, **2** and **3** was determined by $^1H/^1H$ 2D and $^1H/^{13}C$ 2D NMR spectra.

Compounds **1**, **2** and **3** were evaluated for activity against viruses HCMV, VZV, HSV-1, HSV-2, FLU, HIV *in vitro*, using different cell lines and found to be inactive except for compound **1**, which has anti-HCMV activity ($\mathbf{IC_{50}}$ = **44** μM, $\mathbf{CCID_{50}}$ **>500** μM). The activity of the compounds against FLU, HSV-1, HSV-2, VZV, FLU, and HCMV was determined in plaque reduction assays[41], and HIV-1 following a colorimetric assay[42]. African green Monkey (Vero) cells were used for HVS; Madin Darby Canine Kidney (MDCK) cells were used for FLU; Human embryo lung (MRC5) cells were used for HCMV and VZV; and human T4 cell line infected with HTLV-1 (MT4) were used for HIV.

Experimental section :

General Chemical Procedure : Solvents and chemicals were reagent grade and were used without further purification. ^1H and ^{13}C NMR spectra were measured, in $CDCl_3$, on a Bruker 200 NMR spectrometer; all values are reported in parts per million (δ) from $(CH_3)_4Si$ unless otherwise stated; I.R. spectra were recorded on a Perkin-Elmer spectrophotometer with KBr pellets. Analytical thin-layer chromatography (TLC) was

carried out with Merck silica gel 60 F-254 glass backed plates. All chromatographic purifications were carried out on Merck silica gel 60. High-performance liquid chromatography (HPLC) was performed on a Merck gradient liquid chromatography with an UV wavelength detector set at 254 nM. Reactions were routinely monitored by TLC, ^1H NMR and the purity was measured on a Merck HPLC using a C-18 reverse phase column (CH_3CN:H_2O 70:30). Elemental analyses were performed by CNRS, Vernaison, and are within ±0.4% of the theoretical values.

3-(Benzoyloxy)methylcyclopentene (5a) :

A solution of (**4**)[32] (10 g, 102 mmoles) in CH_2Cl_2 (50 ml) was cooled at 0°C. 4-Methylmorpholine (NMM) (15.45 g, 153 mmoles), freshly distilled from KOH, and benzoyl chloride (14.34 g, 102 mmoles) were then added under nitrogen flux and stirred at room temperature. The reaction was monitored by TLC. The mixture was worked up in the usual way, the residue obtained purified by distillation under reduced pressure to give 14.47 g (88%) of (**5a**) as a colorless liquid. *Bp: 80-85°C / 0.01mm/Hg. Rf 0.73 (n-Hex-AcOEt, 7:3, v/v).* ^1H *NMR* δ *($CDCl_3$) 8.15 (Dd, 2H, J = 8.2, 1.57 Hz, $H_{o,o'}$), 7.51 (t, 1H, J = 7.3 Hz, H_p), 7.43 (t, 2H, J = 7.0 Hz, $H_{m,m'}$), 5.70 (s, 2H, 1-H, 5-H), 4.24 (d, 2H, ^3J = 7.0 Hz, OCH_2), 2.70 (m, 1H, 3 -H), 2.60-2.25 (m, 4H, 2-H, 4-H).* ^{13}C *NMR* δ *($CDCl_3$) 166.7 (C(O)), 132.8 (C_1, C_5), 130.5, 129.5, 129.6, 128.4 (C Bz), 68.6 (OCH_2), 36.1 (C_3), 35.8 (C_2, C_4). IR* ν *(cm^{-1}) 3057, 2937, 2851, 1720, 1600, 1451, 1273. MS : (M+) 202, 125, 81. Anal. Calcd. For $C_{13}H_{14}O_2$: C 77.20; H 6.98. Found : C 77.09; H 6.83.*

3-(9-Fluorenylmethoxycarbonyloxy)methylcyclopentene (5b) :

A solution of (**4**) (10 g, 102 mmoles) in CH_2Cl_2 (10 ml) was cooled at 0°C; 9-fluorenylmethyl chloroformate (FMOC-Cl) (2.90 g, 11.22 mmoles) and freshly distilled NMM (1.08 g, 10.71 mmoles) were added. The solution was stirred and the reaction monitored by TLC. After the usual workup, a liquid chromatography (n-Hexane-AcOEt, 7:3, v/v) yielded (63%, 2.08 g) of (**5b**). Rf 0.37 (n-Hex-AcOEt, 9:1, v/v). ^1H *NMR* δ *($CDCl_3$) 7.80-7.30 (m, 8H, $H_{arom.}$), 5.69 (s, 2H, 1-H, 5-H), 4.40 (d, 2H, J = 7.0 Hz, CH_2Fmoc), 4.21 (t, 1H, J = 7.0 Hz, CH_{Fmoc}), 4.12-4.09 (d, 2H, ^3J = 7.1 Hz, OCH_2), 2.70-2.10 (m, 5H, 3-H, 2-H, 4-H).* ^{13}C *NMR* δ *($CDCl_3$) 155.3 (OC(O)O), 143.5, 141.4 (C-quaternary), 129.4 (C_1, C_5), 127.9, 127.2, 125.2, 120.1 (C_{arom}), 71.8, 69.8 (OCH_2, CH_2Fmoc), 46.8 (CH_{Fmoc}), 36.0 (C_3), 35.7 (C_2, C_4). IR* ν *(cm^{-1}) 3083, 2945, 1751, 1605, 1450, 1130, 750. MS : (M+) 336. Anal. Calcd. For $C_{21}H_{20}O_3$: C 78.73; H 6.29. Found : C 78.54; H 6.11.*

3-(Triphenylsilyloxy)methylcyclopentene (5c) :

A solution of (**4**) (0.5 g, 5.1 mmoles) and triphenylsilyl chloride (1.65 g, 5.6 mmoles) in anhydrous pyridine (30 ml) was stirred at 0°C and the reaction monitored by TLC. After usual workup, the residue was chromatographed (n-Hexane) to give 1.31 g (71%) of (**5c**). *Rf 0.92 (CH_2Cl_2). ^1H NMR δ ($CDCl_3$) 7.74-7.63 (Dd, 6H, J = 7.1, 1.7 Hz, $H_{m,m'}$), 7.47-7.42 (m, 9H, Ho,o', Hp), 5.67 (s, 2H, 1-H, 5-H), 3.76-3.73 (d, 2H, ^3J = 6.79 Hz, OCH_2), 1.30-2.20 (m, 5H, 2-H, 4-H, 3-H). ^{13}C NMR δ ($CDCl_3$) 135.5, 130.0, 127.8 (H_o, H_m, H_p), 129.6 (C_1, C_5), 67.7 (OCH_2), 39.3 (C_3), 35.6 (C_2, C_4). IR ν (cm^{-1})* 3053, 1653, 1285, 1117, 1435. *MS : (M+) 356. Anal. Calcd. For $C_{24}H_{24}OSi$: C 80.85; H 6.78. Found : C 80.97; H 6.53.*

3-(*tert*- Butyldimethylsilyloxy)methylcyclopentene (5d) :

A solution of (**4**) (2 g, 20.4 mmoles) and *tert*-butyldimethylsilyl chloride (4.6 g, 30.6 mmoles) in anhydrous pyridine (20 ml) was stirred at 0°C and the reaction monitored by TLC. After usual workup, the residue was chromatographed (n-Hexane) to give 3.67 g (84%) of (**5d**). *Rf* 0.85 (CH_2Cl_2). *^1H NMR δ ($CDCl_3$) 5.63 (s, 2H, 1-H, 5-H), 3.51-3.45 (d, ^3J = 5.7 Hz, OCH_2), 2.50-2.05 (m, 5H, 2-H, 4-H, 3-H), 0.90 (s, 9H, tBu), 0.04 (s, 6H, $(CH_3)_2Si$). ^{13}C NMR δ ($CDCl_3$) 129.4 (C_1, C_5), 64.8. (OCH_2), 39.2 (C_3), 35.3 (C_2, C_4), 25.6(tBu), -5.3 ($(CH_3)_2Si$). IR ν (cm^{-1}) 3049, 1612, 1472-1464. MS : (M+) 212. Anal. Calcd. For $C_{12}H_{24}OSi$: C 67.86; H 11.39. Found : C 67.92; H 11.24.*

Typical procedure for the epoxidation :

Anhydrous MCPBA (1.20 moles), previously dissolved in CH_2Cl_2 were added to a solution of (**5a-d**) (1mole) in CH_2Cl_2. The reaction was stirred with gentle reflux and monitored by TLC; then the mixture was cooled and filtered. The organic solution was washed with $Na_2S_2O_3$ 10%, $NaHCO_3$ 10% and NaCl solution, dried over Na_2SO_4, and evaporated to dryness without heating, under reduced pressure. The residue was purified by liquid chromatography (CH_2Cl_2 ---> CH_2Cl_2-AcOEt, 98:2, v/v). The reactions proceed in 61-69% yield and all epoxides have been characterized by ^{1}H-NMR, ^{13}C-NMR, IR, MS, elemental analysis.

3-(Benzoyloxy)methyl-1,5-epoxicyclopentane (6a:anti and 6a':syn):

data for 6a : Rf 0.69 (CH_2Cl_2-AcOEt, 98:2, v/v). ^1H NMR δ ($CDCl_3$) 8.05 (Dd, 2H, J = 8.2, 1.6 Hz, $H_{o,o'}$), 7.58 (m, 3H, $H_{m,m'}$, H_p), 4.26 (d, 2H, ^3J = 5.3 Hz, OCH_2),

3.51 (s, 2H, 1-H, 5-H), 2.31-1.49 (m, 5H, 3-H, 2-H, 4-H). ^{13}C NMR δ ($CDCl_3$) 166.5 (C(O)), 133.1, 130.3, 129.6, 128.5 (C Bz), 66.9 (OCH_2), 56.8 (C_1, C_5), 32.4 (C_3), 30.5 (C_2, C_4). IR ν (cm^{-1}) 3032, 2953, 1718, 1603, 1450, 1115, 837. MS : (M^+) 220. Anal. Calcd for $C_{13}H_{14}O_3$: C 71.54; H 6.47. Found : C 71.22; H 6.49.

data for 6a' : Rf 0.73 (CH_2Cl_2-AcOEt, 98:2, v/v). ^1H NMR δ ($CDCl_3$) 8.05 (Dd, 2H, J = 8.2, 1.6 Hz, $H_{o,o'}$), 7.58 (m, 3H, $H_{m,m'}$, H_p), 4.16 (d, 2H, ^3J = 8.1 Hz, OCH_2), 3.51 (s, 2H, 1-H, 5-H), 2.31-1.49 (m, 5H, 3-H, 2-H, 4-H).

3-(9-Fluorenylmethoxycarbonyloxy)methyl-1,5-epoxicyclopentane (6b:anti and 6b':syn) :

data for 6b : Rf 0.57 (CH_2Cl_2-AcOEt, 99:1, v/v). ^1H NMR δ ($CDCl_3$) 7.74-7.27 (m, 8H, $H_{arom.}$), 4.44-4.40 (d, 2H, J = 6.5 Hz, CH_2 Fmoc), 4.31-4.27 (t, 1H, J = 6.4 Hz, CH_{Fmoc}), 4.16 (d, 2H, ^3J = 5.3 Hz, OCH_2), 3.52 (s, 2H, 1-H, 5-H), 2.16-1.48 (m, 5H, 3-H, 2-H, 4-H). ^{13}C NMR δ ($CDCl_3$) 155.3 (OC(O)O), 143.4, 141.3 (C-quaternary), 127.9, 127.2, 125.1, 120.1 (C_{arom}), 70.1, 69.8 (OCH_2, CH_2Fmoc), 56.7 (C_1, C_5), 46.8 (CH_{Fmoc}), 32.3 (C_3), 30.8 (C_2, C_4). IR ν (cm^{-1}) 3083, 3038, 2955, 1749, 1605, 1450, 1398, 837, 737. MS: (M^+) 354. Anal. Calcd for $C_{21}H_{20}O_4$: C 74.98; H 5.99. Found : C 74.73; H 5.88.

data for 6b' : Rf 0.61 (CH_2Cl_2-AcOEt, 99:1, v/v). ^1H NMR δ ($CDCl_3$) 7.74-7.27 (m, 8H, $H_{arom.}$), 4.44-4.40 (d, 2H, J = 6.5 Hz, CH_2 Fmoc), 4.31-4.27 (t, 1H, J = 6.4 Hz, CH_{Fmoc}), 4.08 (d, 2H, ^3J = 7.2 Hz, OCH_2), 3.52 (s, 2H, 1-H, 5-H), 2.16-1.48 (m, 5H, 3-H, 2-H, 4-H).

3-(Triphenylsilyloxy)methyl-1,5-epoxicyclopentane (6c:anti and 6c':syn) :

data for 6c : Rf 0.74 (CH_2Cl_2-AcOEt, 99:1, v/v). ^1H NMR δ ($CDCl_3$) 7.74-7.66 (Dd, 6H, J = 7.7, 1.3 Hz, $H_{m,m'}$), 7.51-7.40 (m, 9H, $H_{o,o'}$, H_p), 3.81 (d, 2H, ^3J = 4.6 Hz, OCH_2), 3.52 (s, 2H, 1-H, 5-H), 2.23-1.52 (m, 5H, 3-H, 2-H, 4-H). ^{13}C NMR δ ($CDCl_3$) 135.5, 130.1, 127.9 (C-H_o, C-H_m, C-H_p), 65.7 (OCH_2), 57.2 (C_1, C_5), 35.3 (C_3), 30.7 (C_2, C_4). IR ν (cm^{-1}) 3071, 3053, 1429, 1285, 1117, 1084, 739. MS : (M^+) 372. Anal. Calcd. for $C_{24}H_{24}O_2Si$: C 77.20; H 6.74. Found : C 77.37; H 6.49.

data for 6c' : Rf 0.77 (CH_2Cl_2-AcOEt, 99:1, v/v). ^1H NMR δ ($CDCl_3$) 7.74-7.66 (Dd, 6H, J = 7.7, 1.3 Hz, $H_{m,m'}$), 7.51-7.40 (m, 9H, $H_{o,o'}$, H_p), 3.65 (d, 2H, ^3J = 8.1 Hz, OCH_2), 3.52 (s, 2H, 1-H, 5-H), 2.23-1.52 (m, 5H, 3-H, 2-H, 4-H).

3-(*tert*-Butyldimethylsilyloxy)methyl-1,5-epoxicyclopentane (6d:anti and 6d':syn) :

data for 6d : Rf 0.76 (CH2Cl2-AcOEt, 99:1, v/v). ^1H NMR δ (CDCl3) 3.52 (d, 2H, ^3J = 4.6 Hz, OCH2), 3.44 (s, 1H, 1-H, 5-H), 2.11-1.94 (m, 3H, 3-H, 2-Hβ, 4-Hβ), 1.52-1.41 (m, 2H, 2-Hα, 4-Hα), 0.87 (s, 9H, tBu), 0.01 (s, 6H, (CH3)2Si.). ^{13}C NMR δ (CDCl3) 64.6 (OCH2), 57.2 (C1, C5), 35.2 (C3), 30.5 (C2, C4), 25.8 (tBu), -5.4 ((Me)2Si)). IR ν (cm^{-1}) 3028, 2955-2958, 1472, 1258, 1090, 837. MS : (M$^+$) 228. Anal. Calcd. For $C_{12}H_{24}O_2Si$: C 63.10; H 10.59. Found : C 62.84; H 10.70.

data for 6d' : Rf 0.82 (CH2Cl2-AcOEt, 99:1, v/v). ^1H NMR δ (CDCl3) 3.35 (d, 2H, ^3J = 8.5 Hz, OCH2), 3.44 (s, 1H, 1-H, 5-H), 2.11-1.94 (m, 3H, 3-H, 2-Hβ, 4-Hβ), 1.52-1.41 (m, 2H, 2-Hα, 4-Hα), 0.87 (s, 9H, tBu), 0.01 (s, 6H, (CH3)2Si.).

(±)-2-(β)-Azido-1-(α)-hydroxy-4-β-(tertbutyldimethylsilyloxy)methylcyclopentane (7) :

A solution of (**6d**) (1.02 g, 4.5 mmoles) and NaN_3 (0.59 g, 9.0 mmoles) was stirred in H_2O (7 ml) and EtOH (30 ml) with gentle reflux for 48h. The residue was then allowed to cool to room temperature and concentrated under reduced pressure. H_2O (10 ml) was added and extracted with CH_2Cl_2 (4 x 20 ml). The aqueous phase was saturated with NaCl and stirred for 24h with CH_2Cl_2 (30 ml). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The yellow oil obtained was chromatographed (CH_2Cl_2-AcOEt, 98:2, v/v) to give 514 mg (43%) of (**7**). *Rf 0.65 (CH_2Cl_2-AcOEt, 99:1, v/v). ^1H NMR δ (CDCl3) 4.08-3.73 (q, 1H, J = 6.5 Hz, 1-H), 3.73-3.62 (q, 1H, J = 7.0 Hz, 2-H), 3.51-3.48 (d, 2H, J = 5.7 Hz, OCH2), 2.41-2.31 (q l, 1H, 4-H), 2.23-2.05 (m, 2H, 3-Hα, OH), 1.9-1.6 (m, 2H, 5-Hβ, 3-Hβ), 1.5-1.42 (m, 1H, 5-Hα). ^{13}C NMR δ (CDCl3) 76.9 (C1), 68.4 (C2), 66.5 (OCH2), 36 (C4), 34 (C5), 31 (C3), 25.8 (tBu), -5.4 ((Me)2Si). IR ν (cm^{-1}) 3354, 2955, 2930, 2104, 1472, 1464, 1259, 1090, 837. MS : (M$^+$) 271, 243, 225, 94, 75, 67. Anal. Calcd. For $C_{12}H_{25}N_3O_2Si$: C 53.10; H 9.28; N 15.48. Found : C 53.54; H 9.32; N 14.96.*

(±)-2-(β)-Amino-1-(α)-hydroxy-4-β-(tertbutyldimethylsilyloxy)methylcyclopentane (8) :

To a solution of (**7**) (0.5 g, 1.84 mmoles) in anhydrous MeOH (20 ml), Pd/C 10% (0.062 g) was added under N_2. The suspension was stirred at room temperature under H_2 for 5h, filtered over celite and the filtrate concentrated under reduced pressure to give 440 mg (96%) of (**8**). *Rf 0.12 (CH_2Cl_2-AcOEt, 7:3, v/v). ^1H NMR δ (CDCl3) 3.7-3.5 (m,*

1-H, 2-H, OH), 3.45-3.42 (d, 2H, ^3J = 5.55 Hz, OCH_2), 3 (br s, NH_2), 2.3-1.9 (m, 2H, 5-H), 1.8-1.5 (m, 2H, 3-H), 1.2 (m, 1H, 4-H), 0.85 (s, 9H, tBu), 0.006 (s, 6H, $(Me)_2Si$). ^{13}C NMR δ ($CDCl_3$) 78.6 (C_1), 66.7 (OCH_2), 59 (C_2), 36 (C_4), 35 (C_5), 34.4 (C_3), 25.9 (tBu), -5 ($(Me)_2Si$). IR ν (cm^{-1}) 3341, 2928, 2858, 1472, 1387, 1258, 1094, 837. MS : (M^+) 245. Anal. calcd. For $C_{12}H_{27}NO_2Si$: C 58.72; H 11.09; N 5.71. Found : C 58.46; H 10.87; N 5.62.

(±)-1'-(β)-[4-(6-Chloro-5-nitro)pyrimidine]-amino-2'-(α)-hydroxy-4'-O-tertbutyldimethylsilyl-4'-hydroxymethylcyclopentane (**9**) :

The intermediate (**8**) (200 mg, 0.816 mmole), dissolved in 5 ml of anhydrous ether, was added to a suspension of 4,6-dichloro-5-nitropyrimidine (160.5 mg, 0.827 mmole) in anhydrous ether (5 ml) at O°C, the mixture cooled and stirred for 3h. Anhydrous NEt_3 (0.115 ml, 0.82 mmole) was added, the solution allowed to warm to room temperature, stirred for 8h and the reaction monitored by TLC. After filtration over celite, the filtrate was dried under reduced pressure without heating. The residue was chromatographed (n-Hexane-AcOEt, 7:3, v/v) to give 165 mg of (**9**) (51%) as a yellow oil. *Rf 0.63 (n-Hex-AcOEt, 7:3, v/v). ^1H NMR δ ($CDCl_3$) 8.4 (s, 1H, 2-H), 7.6 (d broad, NH), 4.3-4.2 (m, 1H, 1'-H), 4.15-4.0 (m, 1H, 2'-H), 3.8 (OH), 3.64-3.49 (2Dd, 2H, J = 9.81 Hz - 5.19 Hz,5'-H), 2.4 (m, 2H, 4'-H, 6'-Hβ), 1.8 (m, 2H, 3'-H), 1.5 (m, 1H, 6'-Hα), 0.9 (s, 9H, tBu), 0.05 (s, 6H, $(Me)_2Si$). ^{13}C NMR δ ($CDCl_3$) 157.9 (C_2), 78.16 ($C_{1'}$), 65.7 ($C_{5'}$), 62.4 ($C_{2'}$), 37.9 ($C_{4'}$), 35.5 ($C_{3'}$), 34.1 ($C_{6'}$), 25.9(tBu), -5.3 ($(Me)_2Si$). IR ν (cm^{-1}) 3396, 3055, 2957, 1590, 1428, 1266, 739. MS : (M^+) 404, 402, 344, 230. Anal. Calcd. For $C_{16}H_{27}ClN_4O_4Si$: C 47.69; H 6.75; N 13.90. Found : C 47.83; H 6.51; N 13.75.*

(±)-1'-(β)-[4-(6-Amino-5-nitro)pyrimidine]-amino-2'-(α)-hydroxy-4'-O-tertbutyldimethylsilyl-4'-hydroxymethylcyclopentane (**10**) :

A solution of (**9**) (333 mg, 0.827 mmole) and NH_3/MeOH 1.1 M (1.65 mmoles) in anhydrous methanol was stirred under N_2 at room temperature for 18h. The solution was then concentrated under reduced pressure and the residue subjected to liquid chromatography (CH_2Cl_2-MeOH, 8:2, v/v) to give 239 mg of (**10**), (76%) as a yellow powder. *Rf 0.25 (n-Hex-AcOEt, 5:5, v/v). ^1H NMR δ ($CDCl_3$) 9.22 (d, NH), 8.62 (broad, NH_2), 8.03 (s, 1H, 2-H), 4.23 (m, 1H, 1'-H), 4.15 (m, 1H, 2'-H), 3.56 (2Dd, 2H, J = 9.75 Hz - 5.23 Hz, 5'-H), 2.44 (m, 2H, 4'-H, 6'-Hβ), 1.85 (m, 2H, 3'-H), 1.51 (m, 1H, 6'-Hα), 0.90 (s, 9H, tBu), 0.06 (s, 6H, $(Me)_2Si$). ^{13}C NMR δ ($CDCl_3$) 159.3*

(C_2), 78.6 ($C_{1'}$), 66.0 ($C_{5'}$), 62.7 ($C_{2'}$), 38.16 ($C_{4'}$), 35.7 ($C_{3'}$), 34.5 ($C_{6'}$), 25.9 (tBu), -5.3 ($(Me)_2Si$). IR ν (cm^{-1}) 3437, 3125, 2958, 1653, 1602, 1517, 1257, 1098, 836. MS : (M+) 383, 326. Anal. Calcd. For $C_{15}H_{29}N_5O_4Si$: C 48.50; H 7.87; N 18.85. Found : C 48.11; H 7.57; N 18.63.

(±)-1'-(β)-[4-(6-Amino-5-nitro)pyrimidine]-amino-2'-(α)-hydroxy-4'-hydroxymethylcyclopentane (**1**):

A suspension of (**10**) (50 mg, 0.13 mmole) and NH_4F (50 mg, 1.35 mmoles) in anhydrous methanol was stirred at room temperature and the reaction monitored by TLC. Silica gel (0.5 g) was added, the mixture concentrated under reduced pressure, and the dry powder added to a silica column (1 x 3 cm, packed in AcOEt). The column was eluted successively with AcOEt (50 ml) and MeOH/AcOEt 1:9 and appropriately pooled fractions were combined and evaporated. The colorless residue was dried to give 26 mg (78%) of (**1**). *Rf 0.14 (CH_2Cl_2-AcOEt, 2:8, v/v). ^1H NMR δ (DMSO-D_6) 9.26 (d, 1H, NH), 8.58 (s, 2H, NH_2), 7.97 (s, 1H, 2-H), 4.92 (d, 1H, 2'-OH), 4.75 (t, 1H, 3'-OH), 4.42 (q, 1H, J = 4.5 Hz, 1'-H), 3.95 (q, 1H, J = 4.5 Hz, 2'-H), 3.41 (d, 2H, J = 8.1 Hz, 5'-H), 2.24 (m, 2H, 4'-H, 6'-Hβ), 1.67 (m, 2H, 3'-H), 1.32 (m, 1H, 6'-Hα). ^{13}C NMR δ (DMSO-D_6) 160.9 (C_2), 177.2 ($C_{1'}$), 65.8 ($C_{5'}$), 60.8 ($C_{2'}$), 38.2 ($C_{4'}$), 36.2 ($C_{3'}$), 34.1 ($C_{6'}$). IR ν (cm^{-1}) 3436, 3289, 3129, 2954, 1660, 1609, 1517, 1234, 1037, 793. MS (M^+) 270, 252, 234, 165, 157. Anal. Calcd. For $C_{10}H_{15}N_5O_4$: C 44.61; H 5.62; N 26.01. Found : C 44.58; H 5.57; N 25.96*

(±)-1'-(β)-[4-(2H,6H-5-Amino)pyrimidine]-amino-2'-(α)-hydroxy-4'-hydroxymethylcyclopentane (**2**):

Pd/C 5% (0.060 g) was added to a solution of (**9**) (0.15 g, 0.37 mmoles) in anhydrous MeOH (50 ml), under N_2. The suspension was stirred at room temperature under H_2 for 8h, filtered over celite and the filtrate concentated under reduced pressure. The yellow oil obtained was chromatographed (CH_2Cl_2-MeOH, 7:3, v/v) to give 79 mg (94%) of (**2**). *Rf 0.52 (CH_2Cl_2-MeOH, 7:3, v/v). ^1H NMR δ (CD_3OD) 8.01 (s, 1H, 2-H), 7.47 (s, 1H, 6-H), 4.13 (q, 1H, J = 7.3 Hz, 1'-H), 3.98 (q, 1H, J = 6.7 Hz, 2'-H), 3.42 (d, 2H, J = 5.6 Hz, 5'-H), 2.28 (m, 2H, 4'-H, 6'-Hβ), 1.73 (m, 2H, 3'-H), 1.32 (m, 1H, 6'-Hα). ^{13}C NMR δ (CD_3OD) 154.7 (C_2), 147.7 (C_4), 133.3 (C_6), 129.5 (C_5), 78.4 ($C_{1'}$), 66.8 ($C_{5'}$), 61.4 ($C_{2'}$), 38.8 ($C_{4'}$), 36.2 ($C_{3'}$), 34.6 ($C_{6'}$). IR ν (cm^{-1}) 3261, 2953, 2899, 1607, 1480, 1350, 1038. MS (M^+) 225 (M+1), 216, 37, 110, 102. Anal. Calcd. For $C_{10}H_{16}N_4O_2$: C 53.56; H 7.19; N 24.98. Found : C 53.32; H 7.24 N 24.67.*

(±)-9-[4'-(β)-(Hydroxymethyl)-2'-(α)-hydroxy-cyclopentyl]-purine (3) :

A solution of (2) (100 mg, 0.45 mmoles), triethylorthoformate (3 ml, 15.6 mmoles) and 12N HCl (0.10 ml) in DMF (1 ml) was stirred at O°C for 1h then at room temperature for 12h. After evaporation, 0.5N HCl (30ml) was added to the residue, the mixture stirred for 2h at room temperature, neutralized with 1N NaOH, and concentrated in vacuo to dryness. The residue obtained was purified by liquid chromatography on silica gel (CH_2Cl_2-MeOH, 8:2, v/v), and 88 mg (85%) of (3) isolated. *Rf 0.35 (CH_2Cl_2-MeOH, 8:2, v/v). ^1H NMR δ (CD_3OD) 9.11 (s, 1H, 8-H), 8.89 (s, 1H, 2-H), 8.68 (s, 1H, 6-H), 4.65 (m, 2H, 1'-H, 2'-H), 3.52 (d, 2H, J = 6.6 Hz, 5'-H), 2.22 (m, 2H, 4'-H, 6'-Hβ), 1.91 (m, 2H, 6'-Hα, 3'-Hβ), 1.63 (m, 1H, 3'-Hα). ^{13}C NMR δ (CD_3OD) 152.1 (C_8), 151.7 (C_2), 148.2 (C_6), 146.5 (C_4), 134.6 (C_5), 74.0 ($C_{1'}$), 65.5 ($C_{5'}$), 63.3 ($C_{2'}$), 36.4 ($C_{4'}$), 35.0 ($C_{3'}$), 32.6 ($C_{6'}$). IR ν (cm^{-1}) 3403, 2967, 1646, 1617, 1412, 1044. MS (M^+) 234. Anal. Calcd. For $C_{11}H_{14}N_4O_2$: C 56.40; H 6.02; N 23.92. Found : C 55.97; H 5.83; N 23.65.*

REFERENCES

1 Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.*, **1990**, 168, 912

2 Borthwick, A.; Biggadike, K.; Holman, S.; Mo, C. *Tetrahedron Lett.*, **1990**, 31, 767

3 Kim, S.; Fuller, R.; Marquez, V. *Nucleosides & Nucleotides*, **1990**, 9, 663

4 Legraverend, M.; Huel, C.; Zerial, A.; Lemaitre, M.; Bisagni, E. *Nucleosides & Nucleotides*, **1990**, 9, 639

5 Borthwick, A.; Evans, D.; Kirk, B.; Biggadike, K.; Exall, A.; Youds, S.; Roberts, S.; Knight, D.; Coates, J. *J. Med. Chem.*, **1990**, 33, 179

6 for a review on carbocyclic nucleosides : Marquez, V.; Lim, M. *Med. Res. Rev.*, **1986**, 6, 1

7 for a review on synthesis of chiral carbocyclic nucleosides : Borthwick, A.; Biggadike, K. *Tetrahedron*, **1992**, 48, 571

8 Shealy, Y.; Clayton, J. *J. Am. Chem. Soc.*, **1966**, 88, 3885

9 Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otami, M. *J. Antibiot.*, **1968**, 21, 255

10 Kishi, T.; Moroi, M.; Kusaka, T.; Nishikawa, M.; Kamiya, K.; Mizuro, K. *J. Chem. Soc., Chem. Commun.*, **1967**, 857

11 Kishi, T.; Moroi, M.; Kusaka, T.; Nishikawa, M.; Kamiya, K.; Mizuro, K. *Chem. Pharm. Bull.*, **1972**, 20, 940

12 Lim, M.; Marquez, V. *Tetrahedron Lett.*, **1983**, 24, 5559
13 Shealy, Y.; O'Dell, C.; Shannon, W.; Arnett, G. *J. Med. Chem.*, **1984**, 27, 1416
14 De Clercq, E.; Balzarini, J.; Bernaerts, R.; Herdewijn, P.; Verbruggen, A. *Biochem. Biophys. Res. Commun.*, **1985**, 126, 397
15 Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, H. *J. Med. Chem.*, **1985**, 28, 550
16 Ravenscroft, P.; Newton, R.; Scopes, D.; Williamson, C. *Tetrahedron Lett.*, **1986**, 27, 747
17 Borthwick, A.; Butt, S.; Biggadike, K.; Exall, A.; Roberts, S.; Youds, P.; Kirk, B.; Booth, B.; Cameron, J.; Cox, S.; Marr, C.; Shill, M. *J. Chem. Soc., Chem. Commun.*, **1988**, 656
18 Borthwick, A.; Kirk, B.; Biggadike, K.; Exall, A.; Butt, S.; Roberts, S.; Knight, D.; Coates, J.; Ryan, D. *J. Med. Chem.*, **1991**, 34, 907
19 Blackburn, G.; Kent, D. *J. Chem. Soc., Perkin Trans I*, **1986**, 913
20 Vince, R.; Hua, M. *J. Med. Chem.*, **1990**, 33, 17
21 Vince, R.; Daluge, S. *J. Med. Chem.*, **1977**, 20, 612
22 Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.; Takuhashi, K. *J. Antibiot.*, **1989**, 42, 1854
23 Norbeck, D.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J.; Erickson, J.; Clement, J.; Swanson R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.*, **1990**, 33, 1281
24 Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsurno, T. *J. Med. Chem.*, **1992**, 35, 1882
25 Palmer C.; Parry, K.; Roberts, S. *Tetrahedron Lett.*, **1990**, 31, 279
26 Moss, R.; Petrie C.; Meyer, R.; DeeNord, L.; Wilis, R.; Smith, R.; Larson S.; Kini, G.; Robins, R. *J. Med. Chem.*, **1988**, 31, 786
27 Ramasamy, K.; Ugarkar, B.; McKernam, P.; Robins, R.; Revankar, G. *J. Med. Chem.*, **1986**, 29, 2231
28 Petrie, C.; Revankar, G.; Dalley, N.; George, R.; NcKernam, P.; Hamill, R.; Robins, R. *J. Med. Chem.*, **1986**, 29, 268
29 Shealy, Y.; O'Dell, C. *Tetrahedron Lett.*, **1969**, 27, 2231
30 Shaw, G.; Warrener, R. *J. Chem. Soc.*, **1958**, 157
31 Shealy, Y.; O'Dell, C. *J. Heterocycl. Chem.*, **1976**, 13, 1041
32 a) Hutchison, A.; Grim, M.; Chen, J. *J. Heterocycl. Chem.*, **1989**, 26, 451 b) Depres, J-P.; Greene, A. *J. Org. Chem.*, **1984**, 49, 928
33 a) Spurlock, L.; Fayter, R. *J. Am. Chem. Soc.*, **1972**, 94, 2707 b) Feeya, D. *J. Org. Chem.*, **1981**, 46, 3512

34 Wolff-Kugel D.; Halazy, S. *Nucleosides & Nucleotides*, **1993**, 12, 279

35 Agrofoglio, L.; Condom, R.; Guedj, R. *Tetrahedron Lett.*, **1992**, 33, 5503

36 Coe, D.; Myers, P.; Parry, D.; Roberts, S.; Storer, R. *J. Chem. Soc., Chem. Commun.*, **1990**, 151

37 Zhang, W.; Robins, M. *Tetrahedron Lett.*, **1992**, 3, 1177

38 Agrofoglio, L.; Condom, R.; Guedj, R.; Challand, R.; Selway, J. *Tetrahedron Lett.*, **1993**, 34, 6271

39 carbocyclic analogues 1,2 and 3, and their precursors 9 and 10 will be identified using the same numbering system used to describe their furanose isosteres with the carbon replacing the furan ring oxygen being designated as C-6'. Therefore, substituents on the cyclopentane ring are designated 1'-β, 2'-α and 4'-β.

40 Kubo, I.; Kim, M.; Wood, W.; Naoki, H. *Tetrahedron Lett.*, **1986**, 27, 4277

41 Collins, P.; Bauer, D.*Annals N. Y. Acad. Sci.*, **1977**, 284, 49

42 Pauwells, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. of Virol. Methods*, **1988**, 20, 309

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