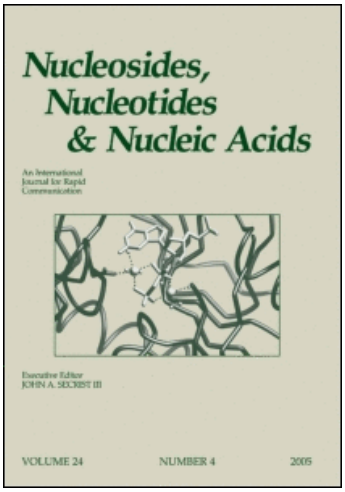

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Synthesis of N-1β-D-Arabinofuranosyl and N-1-2'-Deoxy-β-D-*erythro*-pentofuranosyl Thieno [3,2-*d*] Pyrimidine Nucleosides

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SYNTHESIS OF N-1-β-D-ARABINOFURANOSYL AND N-1-2'-DEOXY-β-D-*ERYTHRO*-PENTOFURANOSYL THIENO[3,2-*d*] PYRIMIDINE NUCLEOSIDES.

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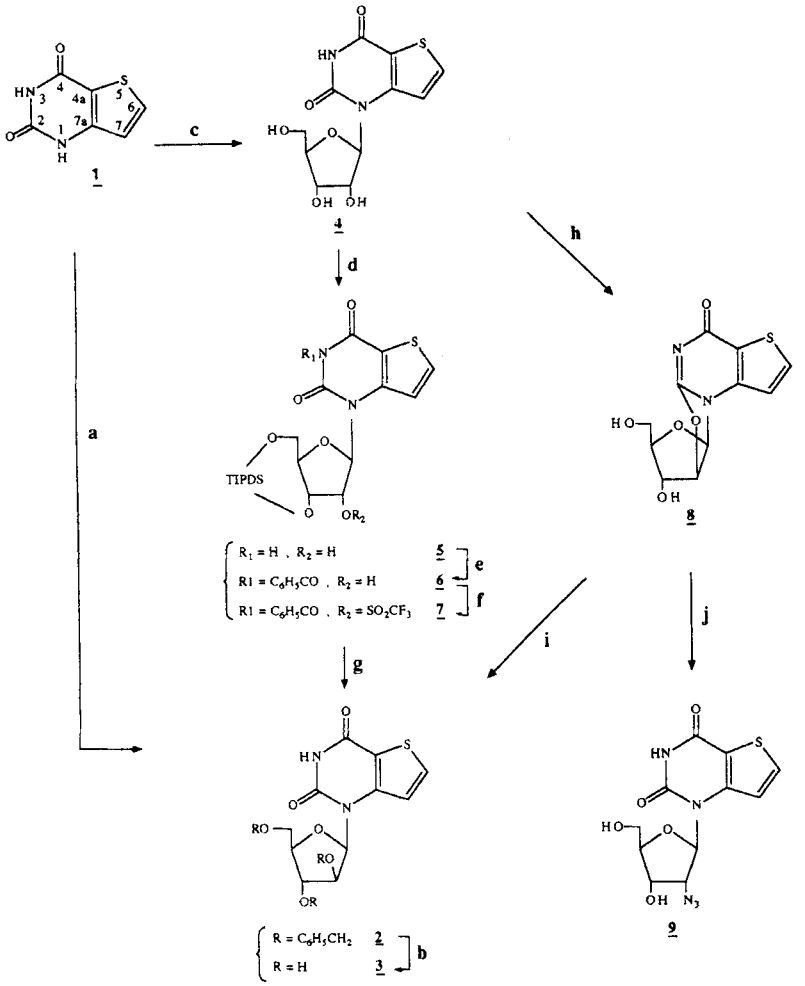
Abstract: Synthetic methods for 1-(β–D-arabinofuranosyl) and 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-diones from the corresponding 1-(β-D-ribofuranosyl) nucleoside have been developed in this report. These compounds were tested against HIV-1 in CEM cl 13 cell cultures, but none of them exhibited significant inhibitory activity against this virus.

1-(β-D-arabinofuranosyl)uracil [1,2] and 1-(β-D-arabinofuranosyl)-5-iodo uracil [3] are known to exhibit significant antiviral activity against herpes simplex virus. It seems thus worthwhile to develop the synthesis of bicyclic nucleosides with an arabinofuranosyl moiety residing in the pyrimidine ring, since research for active drugs against HIV for new therapies in the treatment of acquired immunodeficiency syndrome (AIDS) has concentrated in recent years on nucleosides analogues. It was also of great interest to introduce another substituent into the 2'-arabino position in place of the hydroxyl group since cytotoxicity of these compounds is not only dependent upon the aglycon, but also may vary with the sugar moiety.

The discovery of antiviral activity of 5(E)-1-(2-bromovinyl)-2'-deoxyuridine (BVDU) against HSV-1 [4] led us to initiate as part of our discovery program for AIDS the synthesis of 2'-deoxynucleoside analogues in hope to obtain a novel class of potential antiviral agents. The stereoselectivity of glycosylation was nevertheless poor yielding to an anomeric mixture, and we also reported an efficient and improved synthetic method using preformed ribonucleoside as the starting material which appear more attractive.

CHEMISTRY

The synthetic route we used for the preparation of 1-(β-D-arabinofuranosyl)thieno[3,2-*d*] pyrimidine-2,4-dione 3 is outlined in Scheme I. The heterocycle thieno[3,2-*d*]pyrimidine-2,4-dione 1 [5] was converted into its (bis)trimethylsilyl derivative with use of hexamethyldisilazane (HMDS)



(**a**) 2,3,5-tri-*O*-benzyl-1-*O*-p-nitrobenzoyl-D-arabinofuranose, $CF_3SO_3Si(CH_3)_3$ in CH_3CN for 2 (12%) ; (**b**) $Pd(OH)_2$ in EtOH/cyclohexene Δ for 3 (60%) ; (**c**) 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose, $SnCl_4$ in 1,2-dichloroethane and MeOH/NH_3 for 4 (67%) ; (**d**) TIPDS, imidazole in DMF for 5 (92%) ; (**e**) C_6H_5COCl, n-Bu_4 N^+Br^- in aqueous K_2CO_3/CH_2Cl_2 for 6 (32%) ; (**f**) CF_3SO_2Cl, TEA, DMAP in pyridine for 7 (6%) (**g**) 7 to 3 : 2N NaOH/CH_2Cl_2 and TBAF in THF (13%) ; (**h**) $(C_6H_5O)_2CO$, $NaHCO_3$ in DMF Δ for 8 (81%) ; (**i**) 2N NaOH for 3 (56%) ; (**j**) NaN_3, $C_6H_5CO_2H$ in DMF Δ for 9 (15%).

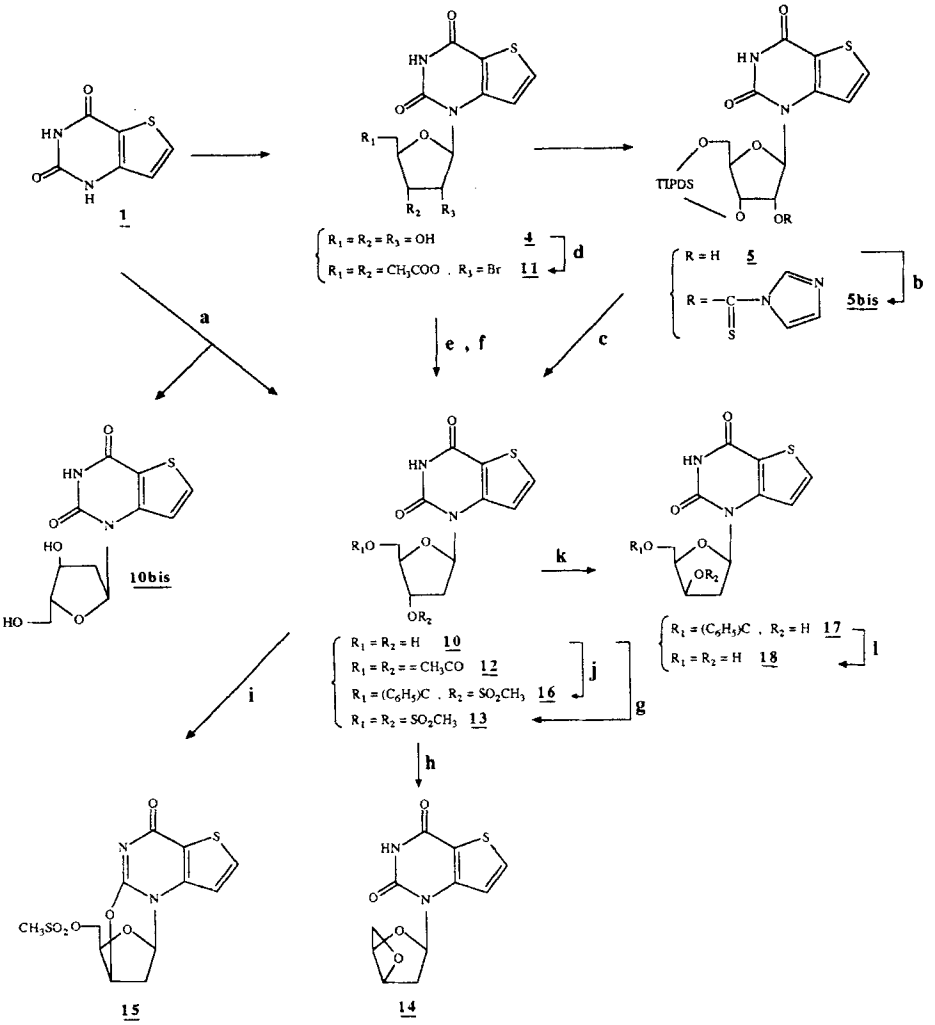
SCHEME I

and heating at reflux temperature [6]. With use of the Lewis acid catalyzed silyl procedure reported by NIEDBALLA and VORBRÜGGEN [7], the silyl derivative was condensed with 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose in the presence of trimethylsilyl trifluoromethanesulfonate in acetonitrile to furnish the blocked nucleoside 2.

Debenzylation of 2 with palladium hydroxide in cyclohexene at reflux afforded the free nucleoside 3 in 7% overall yield [8]. The reduction required prolonged reaction time to effect the debenzylation but the thiophen ring was therefore not reduced under these smooth conditions. The ^{1}H NMR spectrum of 3 exhibited a doublet (J=4.9Hz) for H-1' at 6.27 ppm which showed that the 2'-hydroxy group was oriented to *cis* to the glycosidic linkage. Moreover, the ^{13}C NMR spectral pattern of 3 was quite similar to that of 1-(β-D-arabino-furanosyl)uridine (*ara*-U) [9], relatively to the sugar moiety.

Due to the poor yield obtained following this procedure, it seemed worthwhile to develop a synthetic method starting from readily accessible ribonucleoside 4 [10]. Compoud 4 was converted to the 3',5'-tetraisopropyl-disiloxanyl (TIPDS) derivative 5 by a standard method in 92% yield as an oil. In order to avoid the formation of the O^2-2'-cyclonucleoside during the intermolecular nucleophilic substitution at the 2'-position having a leaving group, a chemoselective protection of the N^3-imide function of the pyrimidine moiety has been developed by use of benzoyl chloride in the presence of triethylamine as a base which gave the N^3-alkylated product 6. Reaction of 6 with trifluoromethanesulfonyl chloride in pyridine gave the 2'-*O*-trifluoromesylate 7 which was furthermore treated with a sodium hydroxide solution (2N). Deblocking of the sugar silyl groups was subsequently carried out in tetrahydrofuran with tetra-*n*-butylammonium fluoride (TBAF) to provide the arabinonucleoside 3 showing the same physical properties as the authentic sample. However, the overall yield of 3 was still so modest (13%) that we initiated an alternative route using as starting material compound 4 which can be converted into the O^2-2'-cyclonucleoside 8 (80%) by treatment of 4 with diphenyl carbonate and sodium bicarbonate in DMF [10]. The anhydro bridge of 8 was cleaved using a 1N sodium hydroxide solution to afford the expected arabinonucleoside 3 in an overall 45% yield from 4. Nucleophilic opening of the anhydro nucleosidic linkage of 8 with sodium azide in the presence of benzoic acid in *N,N*-dimethylformamide afforded the expected 2'-α-azido derivative 9 in 15% after silica gel chromatography, which showed an azide streching at 2100 cm^{-1} in its infrared spectrum. The ^{1}H NMR spectrum of this nucleoside exhibited a doublet (J=6.8 Hz) for H-1' at 6.18 ppm while the H-1' of ribonucleoside 4 appeared at 6.09 ppm (J=6.8 Hz). Although this implied that an azide group was introduced into the 2'-α-position. Further support was given by examination of the ^{13}C NMR spectra of 9 which exhibited a strong upfield chemical shift for carbon C-2' ($\Delta\delta$ = 8.3 ppm) when compared to 4 [11].

The bis(trimethylsilyl) derivative 1 was then condensed with 2-deoxy-3,5-di-*O*-p-toluoyl-D-erythropentosyl chloride in chloroform under triflate catalysis at room temperature to yield an anomeric mixture α / β (35% / 65%). These anomers had very similar *Rf* values and a chromatographic separation was very tedious [7] (Scheme II). Removal of the protecting groups with methanolic ammonia at 20 °C was also carried out without purification and led to free anomeric nucleosides α / β we assigned the structures 10 (65% anomer β) and 10bis (35% anomer α) on the basis of spectrometric data ^{1}H and ^{13}C NMR.



(a) 2-deoxy-3,5-di-*O*-p-toluoyl-D-erythropentosyl chloride, $CF_3SO_3Si(CH_3)_3$ in $CHCl_3$ and NH_3-MeOH for anomeric mixture of 10 (65%) and 10bis (35%) ; **(b-c)** TCDI in CH_3CN Δ for 5bis ; $(nBu)_3SnH$, AIBN in toluene and n-$Bu_4N^+F^-$ in THF for 10 (44%) ; **(d)** CH_3COBr in CH_3CN Δ for 11 (94%) ; **(e)** 11 to 12 : $(nBu)_3SnH$, AIBN in toluene Δ (43%) ; **(f)** 11 to 10 : $(nBu)_3SnCl$, $NaBH_4$ in EtOH (4%) ; **(g)** CH_3SO_2Cl in pyridine for 13 (53%) **(h)** 13 to 14 : 1N NaOH Δ (27%) ; **(i)** 13 to 15 : DBU in CH_2Cl_2 Δ (30%) ; **(j)** $(C_5H_5)_3CCl$ in pyridine Δ and CH_3SO_2Cl in pyridine for 16 (18%) ; **(k)** 0.5N NaOH in EtOH Δ (45%) for 17 ; **(l)** CH_3CO_2H/H_2O (43%) for 18.

SCHEME II

In order to circumvent the difficulty of a chromatographic separation, we undertook the regiospecific 2'-deoxygenation of preformed ribonucleoside 4. As shown in Scheme II, the ribonucleoside 4 was also subjected to the four-stage procedure developed by Barton and co-workers [12] without isolation of intermediates. This conversion required protection of 4 as its 3',5'-*O*-TIPDS derivative 5, thiocarbonylimidazolidation of its 2'-hydroxyl group to give 5bis, reductive deoxygenation with tri-*n*-butyltin hydride in the presence of a catalytic amount of azobis isobutyronitrile (AIBN) in toluene at 60°C under nitrogen. After deprotection of the 3',5'-*O*-TIPDS-2'-deoxynucleoside with tetra-*n*-butylammonium fluoride in tetrahydrofuran at room temperature, the 2'-deoxynucleoside 10 was isolated in 40% overall yield. The ^{1}H NMR analysis of 10 showed clearly the protons at the 2'-position at 2.42 ppm and its ^{13}C NMR spectrum the carbon C-2' at 37.2 ppm.

Generation of 2'-deoxynucleoside from halogenated precursor seemed also to be an attractive process because of the easy accessibility to the 3',5'-di-*O*-acetyl-2'-bromo-2'-deoxynucleoside 11 [13] from ribonucleoside 4. Reductive dehalogenation of 11 with tri-*n*-butyltin hydride and AIBN in refluxing toluene followed by deacetylation with methanolic ammonia afforded the 2'-deoxynucleoside 10 in an overall yield of 21%. A similar reaction of 11 with tri-*n*-butyltin chloride and sodium borohydride in absolute ethanol afforded readily the expected 2'-deoxynucleoside 10 in a low yield of 4%. Compound 11 was also converted to 10 by catalytic hydrogenation in the presence of palladium barium sulfate and subsequent deacetylation in only 4% yield. Afterwards this 2'-deoxynucleoside 10 was subjected to chemical transformations. Compound 10 treated with an excess of methanesulfonyl chloride in pyridine provided the bismesylate 13 in 53% yield. Treatment of 13 with an aqueous NaOH 1N solution afforded the oxetane 14 in 27% yield whereas when reaction of 13 was run with DBU in dichloromethane, the O^2-3'-cyclonucleoside 15 was isolated in 30% yield. However, the anhydro linkage of this compound was found too stable to undergo nucleophilic opening. The next approach we undertook was to tritylate 10 selectively at C-5' and mesylate at C-3' to give 16 which has been achieved without purification. The 3'-sulfonate group of 16 has been readily displaced with sodium hydroxide to give 17 which has been detritylated with acetic acid to the 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione 18.

ANTIVIRAL ASSAYS on CEM cl 13 CELLS

Compounds 3, 10, 11 and 14 were evaluated for their protective activity against the cytopathic effect (CPE) induced by the human HIV-1 (LAV-Bru strain, 100-200 $CCID_{50}$) in CEM cl 13 cell cultures (5.10^4 cells/ml) in the concentration range of 0.01-30 µg/ml. They were all found devoid of cytotoxicity as mock-infected cultures were carried out in parallel. At non toxic concentration, these compounds were found inactive against the replication of HIV-1 after evaluation of cell viability by MTT method [14].

EXPERIMENTAL SECTION

Melting points (mp) were determined with a KOFLER apparatus and were uncorrected. Infrared (IR) spectra were obtained on a PHILIPS SP-3 Pye Unicam spectrophotometer with samples in KBr disk. Ultraviolet (UV) spectra were recorded on a SECONAM S-1000G spectrometer. Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a JEOL FX 200 or a JEOL EX-90 spectrometer, and chemical shifts were expressed in δ ppm relative to tetramethylsilane (TMS) as an internal standard. Thin layer chromatography (TLC) was performed on silica gel 60F-254 plates purchased from E. MERCK and Co. (spots were detected by ultraviolet examination) and column chromatography was performed on silica gel 60 (230 - 400 mesh, ASTM, Merck).

Thieno[3,2-*d*]pyrimidine-2,4-dione (1) [5] A solution of potassium cyanate (16.2 g, 200 mmol) in H_2O (35 ml) was added dropwise to a mixture of methyl 3-amino-2-thiophencarboxylate (15.7 g, 100 mmol) in aqueous acetic acid (250 ml, 50%). The reaction mixture was stirred for 5 hr at room temperature. The precipitate which has formed was collected by filtration and then dissolved in 2N NaOH solution (250 ml). The solution was then acidified at 0 °C with acetic acid and filtered to give 13.4 g (80%) of 1 ; mp > 260°C; IR (KBr) cm^{-1} : 3480-3380 (NH), 1670 (CO), 1570, 1540, 1450, 780; ^1H NMR (DMSO-d_6) : δ 6.90 (d, 1H, H-7, *J* =5.4 Hz), 8.05 (d, 1H, H-6, *J* =5.4 Hz), 11.20 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 111.0 (C-4a), 117.0 (C-7), 135.8 (C-6), 146.3 (C-7a), 151.4 (C-2), 158.9 (C-4).

General procedure for the silylation of thieno[3,2-*d*]pyrimidine-2,4-dione 1 (1.68 g, 10 mmol) was silylated with hexamethyldisilazane (HMDS, 40 ml) in the presence of a catalytic amount of ammonium sulfate by heating the solution at reflux temperature for 5 hr with exclusion of moisture. The excess HMDS was removed by vacuum distillation to give the silylated intermediate.

1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (2) 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose (5.57 g, 10 mmol) and trimethylsilyl trifluoromethanesulfonate (2 ml) were added successively to a solution of the above silylated base in acetonitrile (40 ml) under nitrogen atmosphere. The solution was stirred at room temperature for 24 hr and then partitioned between CH_2Cl_2 (40 ml) and aqueous $NaHCO_3$ solution (40 ml). The organic layer was separated, washed successively with aqueous $NaHCO_3$ solution (40 ml) and with brine (3X60 ml), dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The residue was coevaporated several times with CH_3OH. The residue could be crystallized only very slowly from methanol giving 700 mg (12%) of 2 (white crystalline solid) mp : 190 °C, IR (KBr) cm^{-1} : 3280 (NH), 1755-1695 (CO), 1550, 1440, 1070, 700; ^1H NMR (DMSO-d_6) : δ 3.56 (m, 2H, CH_2-5'), 4.46 (s, 2H, benzyl CH_2), 4.09-4.61-4.93 (m, 3H, osidic H), 6.15 (d, 1H, H-1', *J* =4.9Hz), 7.29 (m, 15H, phenyl protons), 8.05 (d, 1H, H-6, *J* =5.4 Hz); Anal. Calcd. For $C_{32}H_{30}N_2O_6S_2$ (570.6) : C, 67.35 ; H, 5.30 ; N, 4.91 ; S, 5.62. Found : C, 67.14 ; H, 5.49 ; N, 4.87 ; S, 5.59.

1-(β-D-arabinofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (3) *Method 1:* palladium hydroxide (5 g) was added to a solution of 2 (3.48 g, 6.10 mmol) in a mixture of ethanol (150 ml) and cyclohexene (30 ml) under a nitrogen atmosphere. The reaction mixture was heated under reflux for 14 hr, cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* and the residue was crystallized from a mixture of diethyl oxide-petroleum ether (20 ml-20 ml) to give 1.1 g (60%) of 3 (white crystalline solid). *Method 2:* A solution of 7 (400 mg, 0.51 mmol) in sodium hydroxide (2N, 20 ml) and dichloromethane (20 ml) was stirred vigorously for 18 hr at room temperature and evaporated *in vacuo*. The residual oil dissolved in dry tetrahydrofuran (10 ml) was treated with tetrabutylammonium fluoride (TBAF) in THF (1M, 0.8 ml). The reaction mixture was stirred at room temperature for 1 hr and concentrated *in vacuo*. The residue was triturated with diethyl oxide (30 ml) to afford 20 mg (13%) of 3. *Method 3:* An aqueous solution of 8 (1 g, 3.54 mmol) in sodium hydroxide 2N (20 ml) was stirred vigorously for 14 hr at room temperature. The solution was then neutralized with hydrochloric acid 1N and concentrated *in vacuo*. The residue was treated with pyridine and the resulting mineral salts were eliminated by filtration. The filtrate was evaporated *in vacuo* and the residual syrup was crystallized from diethyl oxide to afford 600 mg (56%) of 3. mp : 112 °C; $[\alpha]_D^{20}$ = + 25 ° (DMF) ; IR (KBr) cm^{-1} : 3240-3100 (OH), 1650 (CO), 1440, 1380, 1020, 980; ^1H NMR (DMSO-d_6) : δ 3.63 (m, 2H, CH_2-5'), 3.69-3.98-4.10 (osidic H), 5.40 (1H, OH), 6.27 (d, 1H, H-1', *J* =4.9Hz), 7.62 (d, 1H, H-7, *J* =5.4 Hz), 7.89 (d, 1H, H-6, *J*=5.4Hz), 8.58 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 60.0 (C-5'), 76.2 (C-3'), 76.7 (C-2'), 83.1 (C-4'), 85.9 (C-1'), 113.1 (C-4a), 122.2 (C-7), 132.4 (C-6), 146.1 (C-7a), 150.8 (C-2), 157.8 (C-4); UV $_{\lambda max}$ (log ε) : 297 (3.82) (pH 1, HCl), 296 (3.76) (pH 7, H_2O), 299 (3.67) (pH 14, NaOH); Anal. Calcd. For $C_{11}H_{12}N_2O_6S$ (300.3) : C, 44.00 ; H, 4.03 ; N, 9.33 ; S, 10.68. Found : C, 43.71 ; H, 4.29 ; N, 9.40 ; S, 10.40.

1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (4) [10] 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (5.06 g; 0.01 mol) and stannic chloride (4 ml) were added successively to a solution of the above silylated base 1 in 1,2-dichoroethane (40 ml). The solution was stirred at room temperature for 18 hr. Pyridine (3 ml) was then added to complex the excess of stannic chloride. The reaction mixture was stirred for 1 hr, and the precipitate which had formed was collected by filtration. The precipitate was washed with $CHCl_3$ (2X80 ml), and the combined filtrates were then washed successively with aqueous $NaHCO_3$ solution (100 ml) and H_2O (2X100 ml). The organic layer was dried over $MgSO_4$, the drying agent was removed by filtration, and the organic layer evaporated *in vacuo* to give 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione. A solution of this blocked nucleoside (6 g; 9.79 mmol) in methanolic ammonia (200 ml) was stirred at room temperature for 3 days. The solvent was removed *in vacuo* and the residue was co-evaporated several times with methanol to give a yellow oil which was crystallized from methanol after 3 days (67%). mp : 250 °C; $[\alpha]_D^{20}$ = - 6 ° (DMF) ; ^1H NMR (DMSO-d_6) : δ 3.64 (m, 2H, CH_2-5'), 3.83 (m, 1H, H-4'), 4.10 (m, 1H, H-2'), 4.31 (m, 1H, H-3'), 5.07 (1H, OH), 5.13 (1H, OH), 5.28 (1H, OH), 6.09 (d, 1H, H-1', *J* = 6.8 Hz), 7.69 (d, 1H, H-7, *J* =5.4 Hz), 8.09 (d, 1H, H-6, *J*=5.4Hz), 11.63 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 60.9 (C-5'), 68.7 (C-3'), 69.6 (C-2'), 84.0 (C-4'), 88.4 (C-1'), 114.0 (C-4a), 119.4 (C-7), 134.9 (C-6), 144.5 (C-7a), 151.1 (C-2), 157.7 (C-4) ; Anal. Calcd. For $C_{11}H_{12}N_2O_6S$ (300.3) : C, 44.00 ; H, 4.03 ; N, 9.33 ; S, 10.68. Found : C, 43.72 ; H, 4.13 ; N, 9.54 ; S, 10.40.

1-(3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (5) Imidazole (1.36 g, 19.96 mmol) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.77 ml, 5.55 mmol) were added successively to a solution of 4 (1.5 g, 4.99 mmol) in anhydrous *N,N*-dimethylformamide (20 ml) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 hr and partitioned between H_2O (100 ml) and $CHCl_3$ (100 ml). The organic layer was separated, washed with aqueous $NaHCO_3$ solution (2X100 ml) and then with H_2O (4X100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 5 as a syrup (2.5 g, 92%, TLC CH_2Cl_2:CH_3OH 98:2 *Rf*=0.29) IR (KBr) cm^{-1} : 3600-3440 (OH), 1710-1660 (CO), 1490, 1390, 1110, 1050; ^1H NMR (DMSO-d_6) : δ 1.05 (s, 24H, CH_3), 3.97 (m, 2H, CH_2-5'), 4.54 (m, 1H, H-4'), 4.68 (m, 1H, H-3'), 5.17 (m, 1H, H-2'), 5.81 (1H, H-1'), 6.15 (1H, OH), 7.37 (d, 1H, H-7, *J* =5.4 Hz), 8.12 (d, 1H, H-6, *J*=5.4Hz), 11.62 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 17.0 (CH_3), 61.4 (C-5'), 70.2 (C-3'), 71.4 (C-2'), 80.9 (C-4'), 92.6 (C-1'), 113.5 (C-4a), 117.6 (C-7), 135.4 (C-6), 145.5 (C-7a), 150.3 (C-2), 157.5 (C-4); Anal. Calcd. For $C_{23}H_{38}N_2O_7SSi_2$ (542.8) : C, 50.89 ; H, 7.06 ; N, 5.16 ; S, 5.91 ; Si, 10.35. Found : C, 50.78 ; H, 6.89 ; N, 5.07 ; S, 5.81 ; Si, 10.22.

3-*N*-benzoyl-1-(3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (6) *Method 1*: Benzoyl chloride (0.3 ml, 2.03 mmol) and triethylamine (0.5 ml, 3.59 mmol) were added successively to a solution of 5 (1 g, 1.84 mmol) in dry CH_2Cl_2 (20 ml) at 0°C. The reaction mixture was then stirred at room temperature for 4 hr and concentrated *in vacuo*. The residue (1.8 g) was dissolved in $CHCl_3$ (100 ml) and the organic layer was washed with aqueous $NaHCO_3$ solution (100 ml) then with H_2O (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil (1.5 g) was purified by column chromatography on silica gel using as eluent a gradient of 0 to 90% CH_3OH in CH_2Cl_2 to yield 200 mg (17%) of 6 (white solid, TLC CH_2Cl_2:CH_3OH 95:5 *Rf*=0.42). *Method 2*: Tetrabutylammonium bromide (75 mg, 0.23 mmol) and an aqueous solution of K_2CO_3 (2N, 200 ml) were added successively to a solution of 5 (2.9 g, 5.35 mmol) in CH_2Cl_2 (100 ml). Benzoyl chloride (0.8 ml, 6.95 mmol) was then added to the reaction mixture at 10°C and stirred vigorously at room temperature for 24 hr. The organic layer was then separated, washed with H_2O (2X100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residual oil was dissolved in 1,2-dichloroethane (50 ml) and the resulting solution was refluxed for 90 min. The organic layer was evaporated *in vacuo* and the resulting oil was purified by column chromatography on silica gel using as eluent a gradient of 0 to 90% CH_3OH in CH_2Cl_2 to yield 700 mg (32%) of 6. mp : decomposed at 250 °C; IR (KBr) cm^{-1} : 3540-3420 (OH), 1750-1700-

1670 (CO), 1470, 1250, 1090, 1040; ^{1}H NMR (DMSO-d_6) : δ 1.00 (s, 24H, CH_3), 3.85–3.95–4.54 (osidic H), 5.25 (1H,OH), 5.90 (1H, H-1'), .7.50-7.60-7.77 (5H, benzoyl H), 8.04 (d, 1H, H-7, J =5.4 Hz), 825 (d, 1H, H-6, J=5.4Hz); ^{13}C NMR (DMSO-d_6) : δ 16.9 (CH_3), 61.0 (C-5'), 69.7 (C-3'), 71.2 (C-2'), 81.4 (C-4'), 92.8 (C-1'), 113.0 (C-4a), 118.2 (C-7), 128.5-129.3-130.3-131.1-137.1 (benzoyl C), 135.3 (C-6), 145.4 (C-7a), 149.0 (C-2), 156.4 (C-4), 168.7 (benzoyl CO); Anal. Calcd. For $C_{30}H_{42}N_2O_8SSi_2$ (646.9) : C, 55.70 H, 6.54 ; N, 4.33 ; S, 4.96 ; Si, 8.68. Found : C, 55.62 ; H, 6.38 ; N, 4.31 ; S, 4.86 ; Si, 8.64.

3-*N*-benzoyl-1-(3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-2-*O*-trifluoromethanesulfonyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (7) Triethylamine (0.24 ml, 1.70 mmol) and 4-dimethylaminopyridine (DMAP, 190 mg) were added successively to a solution of 6 (1 g, 1.55 mmol) in dry pyridine (20 ml) at 0°C. Trifluoromethanesulfonyl chloride (0.33 ml, 1.70 mmol) was added dropwise to the reaction mixture which was stirred at room temperature for 44 hr then heated at 50°C for 4 hr. The solvent was removed *in vacuo* and the resulting oil was triturated with diethyl oxide (80 ml) to give 800 mg of 1 which was collected by filtration. The filtrate was concentrated *in vacuo* and the residual syrup (1.1 g) was purified over a silica gel column using as eluent a gradient of 0 to 100% CH_2Cl_2 in hexane to yield 70 mg (6%) of 7 (white solid, TLC CH_2Cl_2:CH_3OH 85:15 Rf=0.94) mp : 90 °C; IR (KBr) cm^{-1} : 1640 (CO), 1280-1030 (R-SO_2-O-R), 1560, 1255, 1215, 1150; ^{1}H NMR (DMSO-d_6) : δ 0.79–1.01 (m, 24H, CH_3), 4.01–5.04–6.03 (osidic H), 6.17 (1H, H-1'), .7.56 and 8.06 (m, 5H, benzoyl H),7.65 (d, 1H, H-7, J =5.1 Hz), 813 (d, 1H, H-6, J=5.1Hz); ^{13}C NMR (DMSO-d_6) : δ 12.0-17.0 (CH_3), 61.5 (C-5'), 70.1 (C-3'), 74.6 (C-2'), 81.4 (C-4'), 89.8 (C-1'), 97.0 (CF_3, $J_{C\text{-}F}$=184.6Hz), 113.4 (C-4a), 117.8 (C-7), 128.4-129.2-133.3 (benzoyl C), 135.6 (C-6), 146.1 (C-7a), 150.4 (C-2), 157.7 (C-4), 164.7 (benzoyl CO); Anal. Calcd. For $C_{31}F_3H_{41}N_2O_{10}S_2Si_2$ (779.0) : C, 47.80 ; H, 5.30 ; N, 3.60 ; S, 8.23; Si, 7.21. Found : C, 47.72 ; H, 5.22 ; N, 3.47 ; S, 8.17 ; Si, 7.17.

2,2'-anhydro-1-(β-D-arabinofuranosyl)thieno[3,2-*d*]pyrimidin-4-one (8) [10] Diphenyl carbonate (0.46; 2.15 mmol) and $NaHCO_3$ (10 mg) were added successively to a solution of 3 (500 mg; 1.67 mmol) in DMF (10 ml). The reaction mixture was heated under reflux for 1 h, then cooled to room temperature. After removal the solvent *in vacuo*, the resulting oil was triturated in diethyl oxide to give crystals which were purified by column chromatography using as eluent a gradient of 0 to 60 % CH_3OH in CH_2Cl_2 to afford 5 (white solid- 81 %- TLC, CH_2Cl_2:CH_3OH 85:15, Rf = 0.33); mp : 236 °C; $[\alpha]_D^{20}$ = - 172 ° (DMF) ; IR (KBr) cm^{-1} : 3280-3380 (OH), 1620-1600 (CO), 1520, 1495, 1075, 1000, 780; ^{1}H NMR (DMSO-d_6) : δ 3.25 (m, 2H, CH_2-5'), 4.12 (m, 1H, H-4'), 4.45 (m, 1H, H-3'), 4.93 (1H, OH-5'), 5.30 (d, 1H, H-2', J =5.9 Hz), 5.94 (1H, OH-3'), 6.69 (d, 1H, H-1', J= 5.9Hz), 7.37 (d, 1H, H-7, J =5.4 Hz), 8.15 (d, 1H, H-6, J=5.4Hz); ^{13}C NMR (DMSO-d_6) : δ 60.7 (C-5'), 74.6 (C-3'), 88.9 (C-2'), 89.3 (C-4'), 89.4 (C-1'), 116.2 (C-4a), 118.8 (C-7), 134.8 (C-6), 140.7 (C-7a), 159.8 (C-4), 165.2 (C-2); Anal. Cald. For $C_{11}H_{10}N_2O_5S$ (282.3) : C, 46.81 ; H, 3.57 ; N, 9.92 ; S, 11.86. Found : C, 46.63 ; H, 3.37 ; N, 9.74 ; S, 11.62.

1-(2-azido-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (9) Sodium azide (210 mg, 3.19 mmol) and benzoic acid (20 mg) were added respectively to a solution of 8 (600 mg, 2.12 mmol) in dry *N*,*N*-dimethylformamide (20 ml) under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 hr, heated under reflux for 4 hr and concentrated *in vacuo*. The resulting oil was purified over a silica gel column using as eluent a gradient of 0 to 80% CH_3OH in CH_2Cl_2 to yield 100 mg (15%) of 9 recrystallized from diethyl oxide - Hexane (white solid, TLC CH_2Cl_2:CH_3OH 8:2 Rf=0.48). mp : decomposed at 100 °C; IR (KBr) cm^{-1} : 3440-3200 (OH), 2100 (N_3), 1710-1670 (CO), 1580, 1420, 1090,

760; ^{1}H NMR (DMSO-d_6) : δ 3.65 (CH_2OH), 3.86–4.27–4.44 (osidic H), 5.16-5.97 (2H, OH), 6.18 (d, 1H, H-1', *J* =6.8Hz), 7.65 (d, 1H, H-7, *J* =5.4 Hz), 8.11 (d, 1H, H-6, *J*=5.4Hz), 11.59 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 60.3 (C-5'), 61.3 (CN_3), 69.8 (C-3'), 85.0 (C-4'), 86.1 (C-1'), 115.3 (C-4a), 118.9 (C-7), 135.2 (C-6), 143.9 (C-7a), 150.7 (C-2), 157.5 (C-4); Anal. Calcd. For $C_{11}H_{11}N_5O_5S$ (325.3): C, 40.62 ; H, 3.41; N, 21.53 ; S, 9.86. Found : C, 40.44 ; H, 3.29 ; N, 21.37 ; S, 9.79.

Anomeric mixture of β and α 1-(2-deoxy-D-erythropentosyl)thieno[3,2-*d*]pyrimidine-2,4-diones (10) and (10bis) 2-deoxy-3,5-di-*O*-p-toluoyl-D-erythropentosyl chloride (4.3 g; 11 mmol) and trimethylsilyl trifluoromethanesulfonate (3 ml) were added successively to a solution of the above silylated base 1 in chloroform (70 ml). The solution was stirred at room temperature for 3 hr and then partitioned between $CHCl_3$ (70 ml) and aqueous $NaHCO_3$ solution (100 ml). The organic layer was separated, washed successively with brine (100 ml) and with H_2O (100 ml), dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give an oil which crystallized from methanol after 24 hr (yellow solid). This resulting crude anomeric mixture (1.18 g, 2.27 mmol) was without purification dissolved in methanolic ammonia (120 ml). The reaction mixture was strirred at room temperature for 24 hr and concentrated to drynes *in vacuo*. A solution of the residual oil in methanol (10 ml) was applied to preparative TLC and developed with $CHCl_3$ - methanol (95:5) as eluent. Elution of the major product was constituted of β / α anomeric mixture (10: 65% / 10bis : 35%) (500 mg).

1-(2-deoxy-β-D-erythropentosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (10) *Method 1:* *N,N'*-thiocarbonyldiimidazole (770 mg, 3.81 mmol) was added to a solution of 5 (1 g, 1.84 mmol) in anhydrous acetonitrile (65 ml). The reaction mixture was refluxed for 3 hr and then cooled to room temperature. The solvent was removed *in vacuo* and the residue (1.4 g) was dissolved in dry toluene (180 ml). The resulting solution heated at 60 °C under nitrogen atmosphere was treated dropwise with a mixture of tri-*n*-butyltin hydride (1.74 ml, 6.49 mmol) and a catalytic amount of α,α'-azoisobutyronitrile (AIBN, 700 mg, 4.25 mmol) in dry toluene (3.5 ml). The mixture was refluxed for an additional 1 hr then the solvent was evaporated *in vacuo*. The residue was dissolved in acetonitrile (10 ml) and the resulting solution was washed with hexane (100 ml). The acetonitrile layer was separated and concentrated *in vacuo*. The residual oil (800 mg) was treated with a solution of tetrabutylammonium fluoride in tetrahydrofuran (1M, 1.8 ml). The reaction mixture was stirred at room temperature for 1 hr and concentrated *in vacuo*. The residue was washed with diethyl oxide to afford 100 mg (44%) of 10 (white solid). *Method 2:* A solution of 12 (400 mg, 1.05 mmol) in methanolic ammonia (80 ml) was stirred at room temperature for 5 days and concentrated *in vacuo* to give a crude product which was triturated with diethyl oxide (80 ml). The resulting crystals were collected by filtration to give 150 mg (50%) of 10. *Method 3:* A solution of 11 (1.5g, 3.35 mmol) in ethanol (40 ml) was heated at 65°C and treated with tri-*n*-butyltin chloride (0.3 ml, 1.03 mmol) and sodium borohydride (200 mg, 5.18 mmol). The reaction mixture was stirred at 65°C for 20 min and added with oxalic acid (30 mg) to decompose the excess of sodium borohydride. The stirring was maintained at 65 °C for an additional 1 hr and the mixture was concentrated to 20 ml. The mineral salts were eliminated by filtration and the filtrate concentrated *in vacuo*. The resulting oil was triturated in $CHCl_3$ (70 ml) and the residual mineral salts were eliminated by filtration again. The filtrate was evaporated *in vacuo* and the crude product was purified over a silica gel column using as eluent a gradient of 0 to 70% CH_3OH in CH_2Cl_2 to yield 40 mg (4%) of 10 (TLC, CH_2Cl_2:CH_3OH 9:1, *Rf*=0.20) mp : 218 °C; $[\alpha]_D^{20}$ = + 16 ° (DMF) ; IR (KBr) cm^{-1} : 3500-3420 (OH), 3180 (NH), 1675 (CO), 1490, 1420, 1090, 1040; ^{1}H NMR (DMSO-d_6) : δ 2.42 (m, 2H, CH_2-2'), 3.65 (m, 2H, CH_2-5'), 3.73 (m, 1H, H-4'), 4.36 (m, 1H, H-3'), 5.00-5.24 (OH), 6.52 (1H, H-1'), 7.67 (1H, H-7), 8.06 (1H, H-6), 11.52 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 37.2 (C-2', $J_{C2'-H2'}$ =131.9Hz), 60.6 (C-5', $J_{C5'-H5'}$=140.7Hz), 69.4 (C-3', $J_{C3'-H3'}$=149.5Hz), 83.7 (C-4', $J_{C4'-H4'}$=164.1Hz), 86.7 (C-1',

$J_{C1'-H1'}$=146.5Hz), 114.0 (C-4a), 119.4 (C-7, J_{C7-H7}=178.8Hz), 134.7 (C-6, J_{C6-H6}=190.5Hz), 144.2 (C-7a), 150.7 (C-2), 157.7 (C-4); Anal. Calcd. For $C_{11}H_{12}N_2O_5S$ (284.3) : C, 46.47 ; H, 4.25; N, 9.85 ; S, 11.28. Found : C, 46.62 ; H, 4.14 ; N, 9.72 ; S, 10.98.

1-(2-bromo-2-deoxy-3,5-di-*O*-acetyl-β-D-*erythro*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (11) [13] Acetyl bromide (1.45 ml, 19.42 mmol) was added dropwise to a boiling suspension of 1 (1 g, 3.33 mmol) in anhydrous acetonitrile (20 ml). The reaction mixture was stirred at 80°C for 3 min and allowed to room temperature. The solvent was removed *in vacuo* and the residue diluted with CH_2Cl_2 (100 ml). The organic layer was washed twice with H_2O (2X100 ml), dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.4 g (94%) of 11 which was crystallized from diethyl oxide (TLC, CH_2Cl_2:CH_3OH 85:15, Rf = 0.74). mp : 220 °C, IR (KBr) cm^{-1} : 3240 (NH), 1740-1690 (CO), 1260, 1230, 1220, 1070; ^1H NMR (DMSO-d_6) : δ 2.10 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 4.34 (m, CH_2-5'), 5.24 (t, 1H, H-4', *J* =6.8 Hz), 5.36-5.75 (m, H-2' and H-3'), 6.47 (d, 1H, H-1', *J* =6.8 Hz), 7.49 (d, 1H, H-7, *J* =5.4 Hz), 8.21 (d, 1H, H-6, *J*=5.4Hz), 11.79 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 20.4 (CH_3), 47.1 (C-2'), 62.5 (CH_2-5'), 70.2 (C-3'), 79.0 (C-4'), 89.8 (C-1'), 114.2 (C-4a), 117.9 (C-7), 135.8 (C-6), 143.9 (C-7a), 150.5 (C-2), 157.5 (C-4), 169.3-169.9 (2 CO); MS m/z=446-448 (relative abondance 1:1).

1-(2-deoxy-3,5-di-*O*-acetyl-β-D-*erythro*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (12) *Method 1:* A mixture of 11 (1.56 g, 3.35 mmol) in CH_3OH (15 ml), H_2O (15 ml) and sodium acetate (800 mg, 9.50 mmol) was treated with hydrogen at atmospheric pressure in the presence of palladium on barium sulfate (340 mg) for 4 hr at room temperature. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting oil (1.1 g) was dissolved in $CHCl_3$ (100 ml). The organic layer was washed with H_2O (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil (300 mg) was purified over a silica gel column using as eluent a gradient of 0 to 85% CH_3OH in CH_2Cl_2 to yield 100 mg (8%) of 12 (beige crystalline solid,TLC CH_2Cl_2:CH_3OH 9:1 *Rf*=0.18). *Method 2:* A solution of 11 (1.1 g, 2.46 mmol) in hot toluene (200 ml) under a nitrogen atmosphere was treated dropwise with a mixture of tri-*n*-butyltin hydride (2 ml, 7.44 mmol) and a catalytic amount of α,α'-azoisobutyronitrile (AIBN, 800 mg, 4.87 mmol) in dry toluene (4ml). The mixture was then stirred at room temperature for 14 hr then the solvent was evaporated *in vacuo*. The residue was dissolved with acetonitrile (100 ml) and the resulting solution was washed with hexane (100 ml). The acetonitrile layer was separated and concentrated *in vacuo*. The crude product was triturated with diethyl oxide (50 ml) to afford 400 mg (43%) of 12. mp : 146 °C; IR (KBr) cm^{-1} : 1750-1700 (CO), 1490, 1430, 1375, 1230; ^1H NMR (DMSO-d_6) : δ 2.07 (s, 6H, CH_3), 2.78 (m, 2H, CH_2-2'), 4.16 (m, 2H, CH_2-5'), 4.31-5.31 (H-3' and H-4'), 6.47 (m, 1H, H-1'), 7.44 (d, 1H, H-7, *J* = 5.4Hz), 8.16 (1H, H-6, *J*=5.4Hz), 11.62 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 20.4-20.6 (CH_3), 34.2 (C-2'), 63.2 (C-5'), 72.9 (C-3'), 80.5 (C-4'), 84.4 (C-1'), 112.9 (C-4a), 118.1 (C-7), 135.1 (C-6), 144.4 (C-7a), 150.4 (C-2), 157.7 (C-4), 169.9 (CO); Anal. Calcd. For $C_{16}H_{16}N_2O_7S$ (380.4): C, 50.52 ; H, 4.24; N, 7.36 ; S, 8.43. Found : C, 50.34 ; H, 4.17 ; N, 7.27 ; 8.27.

1-(2-deoxy-3,5-di-*O*-methanesulfonyl-β-D-*erythro*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (13) Methanesulfonyl chloride (1 ml, 12.92 mmol) was added to a solution of 10 (1 g, 3.52 mmol) in anhydrous pyridine (15 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 7 hr, then for an additional 18 hr at 5°C and poured into ice (10 g). The aqueous phase was extracted with toluene (80 ml). The organic layer was separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 800 mg (53%) of 13 (white solid). mp : 88 °C; IR (KBr) cm^{-1} : 1730-1670 (CO), 1335-1175 (SO_2), 1490, 1310, 970, 770; ^1H NMR (DMSO-d_6) : δ 2.94 (m, 2H, CH_2-2'), 3.22 (s, 1H, -SO_2CH_3), 3.31 (s, 1H, O_2CH_3), 4.34 (m, 2H, CH_2-5'), 4.43-4.50 (m, 2H, H-3' and H-4'), 6.52 (1H, H-1'), 7.38 (d, 1H, H-7, *J* =5.4Hz), 8.14 (d, 1H,

H-6, *J*=5.4Hz); Anal. Calcd. For $C_{13}H_{16}N_2O_9S_3$ (440.4) : C, 35.45 ; H, 3.66; N, 6.36 ; S, 21.84. Found : C, 35.24 ; H, 3.54 ; N, 6.24 ; S, 21.71.

1-(2-deoxy-3,5-oxide-β-D-*erythro*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (14) A solution of 13 (800 mg, 2.12 mmol) in sodium hydroxide (1N, 10 ml) was refluxed for 45 min. The reaction mixture was then cooled to room temperature and neutralized with hydrochloric acid 1N. The resulting precipitate was collected by filtration, washed with H_2O and dried. This crude solid was purified over a silica gel column using as eluent a gradient of 0 to 75% CH_3OH in CH_2Cl_2. Evaporation of the appropriate fractions and crystallization of the residue from acetone gave 150 mg (27%) of 14 (white solid, TLC CH_2Cl_2:CH_3OH 85:15 *Rf*=0.73). mp : 191 °C ; ^1H NMR (DMSO-d_6) : δ 3.22 (m, 2H, CH_2-2'), 4.19 (m, 2H, CH_2-5'), 4.71 and 4.80 (m, 2H, H-3' and H-4'), 6.65 (1H, H-1'), 7.94 (d, 1H, H-7, *J* =5.4Hz), 8.21 (1H, H-6, *J*=5.4Hz); ^{13}C NMR (DMSO-d_6) : δ 35.4 (C-2'), 72.1 (C-5'), 77.3 (C-3'), 85.4 (C-4'), 87.0 (C-1'), 114.6 (C-4a), 118.6 (C-7), 136.1 (C-6), 143.6 (C-7a), 150.9 (C-2), 157.6 (C-4); Anal. Calcd. For $C_{11}H_9N_2O_4S$ (265.3) : C, 49.62 ; H, 3.78;N, 10.52 ; S, 12.04. Found : C, 49.52 ; H, 3.71 ; N, 10.44 ; S, 11.94.

2,3'-anhydro-1-(2-deoxy-5-*O*-methanesulfonyl-β-D-*threo*-pentofuranosyl)thieno[3,2-*d*]pyrimidin-4-one (15) A solution of 13 (1.5 g, 3.41 mmol) in dry CH_2Cl_2 (40 ml) was added to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.6 ml). The reaction mixture was stirred at room temperature for 1 hr then heated under reflux for 15 min and evaporated to dryness *in vacuo*. The resulting crude solid was purified over a silica gel column using as eluent a gradient of 0 to 75% CH_3OH in CH_2Cl_2. Evaporation of the appropriate fractions and crystallization of the residue from $CHCl_3$ - petroleum ether gave 350 mg (30%) of 15 (white solid, TLC CH_2Cl_2:CH_3OH 8:2 *Rf*=0.48) mp : decomposed at 100 °C; IR (KBr) cm^{-1} : 1620 (CO), 1350-1170 (SO_2), 1580, 1485, 1080, 950 ^1H NMR (DMSO-d_6) : δ 2.74 (m, 2H, CH_2-2'), 3.17 (s, 3H, -SO_2CH_3), 4.56 (m, 2H, CH_2-5'), 4.31 and 5.45 (m, 2H, H-3' and H-4'), 6.59 (m, 1H, H-1'), 7.66 (d, 1H, H-7, *J* =5.4Hz), 8.14 (d, 1H, H-6, *J*=5.4Hz); ^{13}C NMR (DMSO-d_6) : δ 32.4 (C-2'), 36.5 (CH_3), 67.8 (C-5'), 77.4 (C-3'), 82.0 (C-4'), 84.6 (C-1'), 119.4 (C-4a), 116.2 (C-7), 134.2 (C-6), 143.4 (C-7a), 153.5 (C-4), 164.4 (C-2); Anal. Calcd. For $C_{12}H_{12}N_2O_6S_2$ (344.3) : C, 41.86 ; H, 3.51; N, 8.14 ; S, 18.52. Found : C, 41.72 ; H, 3.25 ; N, 7.94 ; S, 18.45.

1-(2-deoxy-3-methanesulfonyl-5-*O*-triphenylmethyl-β-D-*erythro*-pentofuranosyl)thieno [3,2-*d*]pyrimidine-2,4-dione (16) Triphenylmethyl chloride (6.5 g, 24.57 mmol) was added portionwise to a solution of 10 (4.2 g, 14.77 mmol) in dry pyridine (50 ml). The reaction mixture was refluxed for 2 hr and cooled to room temperature before poured into ice (50 g). The aqueous phase was extracted twice with $CHCl_3$ (2X100 ml). The combined organic layers were dried over $CaCl_2$, filtered and concentrated *in vacuo*. A solution of the resulting oil in dry pyridine (50 ml) was cooled at 0°C and added dropwise with methanesulfonyl chloride (3 ml, 38.76 mmol) and the stirring continued for 2 hr at 0°C. The reaction mixture was poured into ice (50 g). The aqueous phase was extracted twice with $CHCl_3$ (2X100 ml) and the combined organic layers were dried over $CaCl_2$, filtered then concentrated *in vacuo*. The crude product was purified over a silica gel column using as eluent a mixture of hexane and ethyl acetate (7:3). Evaporation of the appropriate fractions and crystallization of the residue from ethanol gave 1.5 g (18%) of 16 (white solid, TLC hexane:ethyl acetate 7:3 *Rf*=0.53) mp : 118 °C; IR (KBr) cm^{-1} : 3180 (NH), 1720-1670 (CO), 1360-1180 (SO_2), 1490, 1360, 1180, 710; ^1H NMR (DMSO-d_6) : δ 2.83 (m, 2H, CH_2-2'), 3.23 (s, 3H, SO_2CH_3), 4.22 (m, 2H, CH_2-5'), 4.63-5.30 (m, 2H, H-3' and H-4'), 6.54 (1H, H-1'), 7.32 (m, 15H, trityl H), 7.69 (d, 1H, H-7, *J* = 5.4Hz), 8.18 (1H, H-6, *J*=5.4Hz), 11.69 (1H, NH); Anal. Calcd. For $C_{31}H_{28}N_2O_7S_2$ (604.7) : C, 61.51 ; H,4.67; N, 4.63 ; S, 10.60. Found : C, 61.42 ; H, 4.48; N, 4.42 ; S, 10.32.

1-(2-deoxy-5-*O*-triphenylmethyl-β-D-*threo*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (17) A solution of 16 (1.5 g, 2.61 mmol) in ethanol (50 ml) and sodium hydroxide (0.5 N, 10 ml) was refluxed for 24 hr and concentrated *in vacuo*. The residual syrup was added with H_2O (20 ml) and the precipitate which appeared was collected by filtration. The resulting solid was purified over a silica gel column using as eluent a mixture of ethyl acetate and hexane (7:3) to yield 0.6 g (45%) of 17 (white solid, TLC ethyl acetate:hexane 7:3 *Rf*=0.39) mp : 150 °C; IR (KBr) cm^{-1} : 3200 (NH), 1720-1660 (CO), 1550, 1490, 1450, 710; ^1H NMR (DMSO-d_6) : δ 2.61 (m, 2H, CH_2-2'), 4.01 (m, 2H, CH_2-5'), 4.33-5.40 (m, 2H, H-3' and H-4'), 6.42 (1H, H-1'), 7.25-7.35 (m, 15H, trityl H), 7.82 (d, 1H, H-7, *J* = 5.4Hz), 8.05 (1H, H-6, *J*=5.4Hz), 11.66 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 37.4 (C-2'), 62.6 (C-5'), 69.7 (C-3'), 80.7 (C-4'), 82.6 (C-1'), 114.2 (C-4a), 119.6 (C-7), 126.8-127.7-128.2 (trityl C), 134.4 (C-6), 143.8 (C-7a), 150.9 (C-2), 157.7 (C-4); Anal. Calcd. For $C_{30}H_{24}N_2O_4S$ (508.6) : C, 70.85 ; H, 4.76; N, 5.51 ; S, 6.30. Found : C, 70.67 ; H, 4.54 ; N, 5.37 ; S, 6.11.

1-(2-deoxy-β-D-*threo*-pentofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (18) A solution of 17 (500 mg, 0.98 mmol) in a mixture of acetic acid (40 ml) and H_2O(10 ml) was stirred at room temperature for 18 hr and concentrated *in vacuo*. The residue was purified over a silica gel column using as eluent a gradient of 0 to 70% CH_3OH in CH_2Cl_2 to yield 120 mg (43%) of 18 as a syrup (TLC, CH_2Cl_2:CH_3OH 85:15, *Rf*=0.31) IR (KBr) cm^{-1} : 3500-3380 (OH), 1680 (CO), 1550, 1490, 1470, 1100; ^1H NMR (DMSO-d_6) : δ 2.54 (m, 2H, CH_2-2'), 3.67 (m, 2H, CH_2-5'), 4.37 (m, 2H, H-3' and H-4'), 6.31 (1H, H-1'), 7.93 (d, 1H, H-7, *J* =5.4Hz), 8.03 (1H, H-6, *J*=5.4Hz); ^{13}C NMR (DMSO-d_6) : δ 38.2 (C-2'), 59.0 (C-5'), 69.3 (C-3'), 79.0 (C-4'), 82.5 (C-1'), 114.5 (C-4a), 119.6 (C-7), 133.0 (C-6), 144.0 (C-7a), 152.2 (C-2), 159.2 (C-4); Anal. Calcd. For $C_{11}H_{12}N_2O_5S$ (284.3) : C, 46.47 ; H, 4.25; N, 9.85 ; S, 11.28. Found : C, 46.21 ; H, 4.04 ; N, 9.67 ; S, 11.02.

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