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Synthesis and Structure Determination of the First 1'-*C* -Cyano-β-D-Nucleosides

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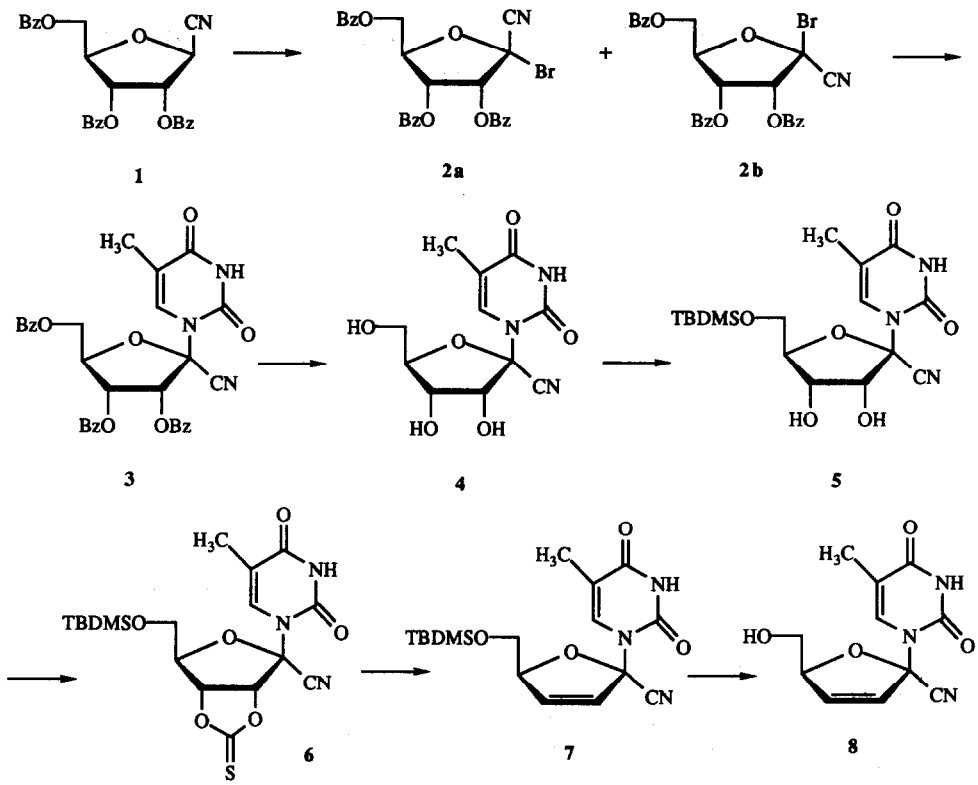
Abstract : The 1'-cyano -2',3' -D-unsaturated nucleoside 8 was synthesised according to the following steps. Photobromination of the ribofuranosyl cyanide 1 using N-bromosuccinimide (NBS) as a radical source gave the two isomers of the new C-1 gem disubstituted sugar 2. Its condensation with silylated thymine afforded the blocked nucleoside 3, the stereochemistry and molecular shape of which were deduced from NMR studies and molecular simulation. After deprotection of 3 into 4, thiocarbonylation of the silylated derivative 5, followed by olefination of 6, led to 7 which was deblocked to the 1'-cyano substituted d4T 8.

As a part of a program on the synthetic approaches to ketofuranosyl nucleosides as potent antiviral agents,[1] we have recently investigated the study of new 1'-cyano analogues. The cyano group is a substituent of particular interest since it has low steric bulk and a great electron withdrawing character. Therefore, it has much less ability to stabilize the α carbenium ion formed during the hydrolysis of a nucleoside, in comparison with that of other substituents such as the hydroxymethyl group at C-1' of the antibiotic ketonucleoside "psicofuranine".[2,3,4] This structural effect on the solvolyse rate of the glycosyl-base bond is very important when considering the potent antiretroviral activity of such a nucleoside. We also reasoned that ketose nucleosides are unique among all naturally occuring nucleosides because their activity does not depend on conversion to the corresponding nucleotides.[5] It may induce some specificity against HIV reverse transcriptase. Since completing this work, one communication describing the synthesis of 4'-cyanothymidine, an inhibitor of HIV, has been reported.[6] Moreover, a prepatent[7] describing the preparation and the anti-tumour or anti-viral activity of cyclopentenyl carbocyclic nucleosides, disubstituted in 1' with halogeno, cyano, purinyl and pyrimidinyl groups, prompted us to report our results concerning the synthesis and structural elucidation of the blocked 1(1-cyano-β-D-ribofuranosyl) thymine **3**. After its deprotection into **4**, deoxygenation of its cyclic thiocarbonate led to the 2',3'-unsaturated derivative **8**, the 1'-cyano analogue of 1(2,3-dideoxy-β-D-*glycero* -pent-2-enofuranosyl) thymine (d4T), which was found to be inactive against human immunodeficiency virus type I.



RESULTS AND DISCUSSION

Synthesis. The new 1'-cyano derivative **4** of 1(β-D-ribofuranosyl) thymine was synthesized according to the following steps.

First, the starting nitrile **1** was prepared according to the very convenient procedure of K. Utimoto[8] by reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose with trimethylsilyl cyanide and anhydrous stannous chloride.

This nitrile was submitted to photobromination carried out with an excess of *N*-bromosuccinimide as radical source in hot carbon tetrachloride over a 250 W. tungsten lamp. The two epimers **2a** and **2b** of the cyano sugar **2**, monobrominated at C-1, were obtained in a 3 : 7 ratio and separated for structural analysis by column chromatography.[9]

The condensation of the **2a** and **2b** mixture with 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine[10] in nitromethane and in the presence of mercuric cyanide afforded the β-nucleoside **3** which was converted to the free nucleoside **4** by ammonolysis. It is noteworthy that all other attempts of coupling methods for the preparation of **3** failed in our hands.

5'-*O*-(tert-butyldimethylsilyl) protected nucleoside **5** was reacted with phenoxy (thiocarbonyl) chloride in the presence of dibutyltin oxide to give 2',3'-*O*-thionocarbonate **6**.[11] Treatment of **5** with *N*, *N'*

-thiocarbonyldiimidazole afforded only a very low yield of **6**. When **6** was heated with triethyl phosphite, compound **7** was formed which was deprotected with tetrabutylammonium fluoride in tetrahydrofuran to **8**, the 1'-cyano substituted d4T.

Structural elucidation. The two epimers of **2** were distinguished through the examination of their heteronuclear chemical shift correlation spectrum and the $^3J_{CN,H-2}$ value. Their stereochemical assignment was difficult because of the lack of the C-1 proton. Nevertheless, it was deduced from the n.m.r. data summarized in Table I, which paralleled the observations of I. Farkas et al. for a series of 1-bromo-D-glycosyl cyanides[12] and those of R. J. Ferrier who studied similar 4-bromo-D-ribofuranosyl derivatives.[13] In the epimer **2b**, in which the ester function at C-2 and the bromo atom at C-1 are *trans* -related, the H-2 proton is shifted ca. O.5 ppm to lower field if compared to the δ-value observed in the starting nitrile **1**. This effect was not observed in the epimer **2a**. Additional support for this assignment was provided by the three-bond spin-spin coupling constant $^3J_{CN,H-2}$. The zero value, reported for **2b**, was consistent with a vicinal coupling constant of a *trans* -relationship between the C-2 proton and the 1-cyano substituent. Moreover $[\alpha]_D$ values, respectively equal to +71.7° (*c* 1.535) for **2a** and - 59.4° (*c* 1.085) for **2b**, are in agreement with the attributed structures and the Hudson rule.[14]

Table I. N.M.R. Parameters of compounds **1**, **2a** and **2b**

	^{1}H Chemical shifts (δ; $CDCl_3$)					Observed coupling constants (Hz)			
Compound	H-2	H-3	H-4	H-5a	H-5b	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$
1	5.89	6.05	4.72	4.72	4.60	5.3	5.3	4.7	4.7
2a	5.82	5.88	4.93	4.80	4.80	6.4	2.7	2.6	2.6
2b	6.38	6.22	5.00	4.83	4.62	4.6	6.6	3.5	4.7

	^{13}C Chemical shifts (δ; $CDCl_3$)						Observed coupling constants (Hz)
Compound	C-1	C-2	C-3	C-4	C-5	CN	$^3J_{CN,H-2}$
1	69.3	74.4	71.8	80.7	63.1	115.9	3.7
2a	80.4	74.7	69.4	85.2	62.5	114.1	2.9
2b	77.4	79.8	70.0	83.9	62.4	113.0	0.0

The δ-values of the different carbon atoms in **3** were assigned by a ^{13}C-^{1}H shift-correlated 2-D NMR experiment. The β-configuration of **3** and the *anti* -conformation of its aglycone around the glycosidic bond were deduced from a 2D NOESY experiment. Indeed, it is well known that the nuclear overhauser effect is a good way to collect information about the geometry of molecules. But the use of the NOE difference technique is not very secured in our case, because for **3** the usable information comes from the H-6 proton which appears in the aromatic region. On the one hand the irradiation of H-6 involves the one of the aromatic protons and therefore uncontrolled NOE effects; on the other hand, the integration of NOE effects on H-6 from H-2',3' or

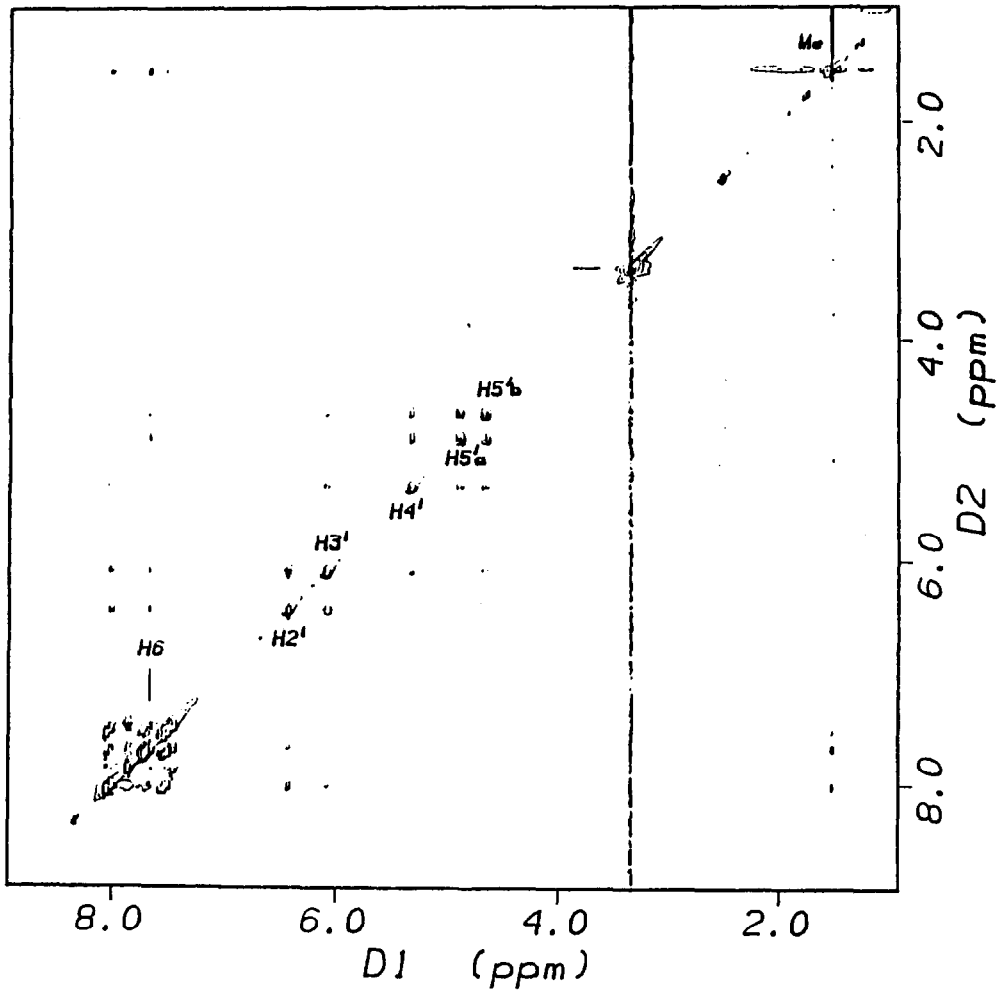
5' is hazardous.Therefore, it was decided to use a 2D NOESY experiment [15] to get qualitative and quantitative information. Figure 1 represents the plot of the 8.5-1.0 p.p.m portion of the 2D NOESY spectrum of **3**. The cross peaks arising between the thymine H-6- and the H-2', H-3', H-5'a, H-5'b protons are of particular interest because it are those which could be expected for a β -configuration and an *anti* -conformation of the compound **3**. All other spacial geometries were considered and none of them could generate this set of cross peaks.

An attempt to quantify distances were made with a NOE buildup experiment as used in protein studies.[16] In this technique, a series of phase sensitive NOESY 2D matrices is collected with an increasing mixing time τ_m. The cross peaks intensity Ic for a 2 spins system is given by : $Ic = k[\exp(-\lambda_2.\tau_m)-\exp(-\lambda_1.\tau_m)]$ where $\lambda_2 = R_1 + \rho - \sigma$, $\lambda_1 = R_1 + \rho + \sigma$, ρ is the dipolar relaxation rate, σ the cross relaxation rate, and R_1 the rate of other relaxation pathways. The initial slope of the curves $Ic = F(\tau_m)$ gives σ. If we assume a fast isotropic motion of the molecule, then σ is proportional to τ_c / r^6, and starting from the distance between the geminal H-5' protons, it is possible to calculate other distances.Figure 2 represents the NOE buildup curves for some couples of protons adjusted on experimental points. We assumed that $R_1=0$ and $\rho= 2\sigma$. Only 2 parameters were adjusted: k and σ. The distances, obtained by this method, between the H-6- and the H-2', H-3', H-5'a, H-5'b protons are respectively 3.1, 3.3, 2.6 A. Because of the flexibility of the molecule and the diffusion effects on the NOE buidup, these values must be used with caution. However it is noteworthy that they are very near. For the α anomer it is not possible to observe simultaneously the NOE crosspeaks H-6/H-2' and H-6/H-3' with H-6/H-5'a or 5'b.These results are consequently in favour of the β configuration and the *anti* conformation of **3**.This stereochemistry was confirmed by the conformational studies done on the deblocked nucleoside **4** by ^{1}H-NMR spectroscopy and molecular mechanics calculations[17]. Moreover, the cyano-nucleoside **3** was reduced into D-psicofuranosylthymine[18], identical with the β-*anti* -isomer of this ketonucleoside, previously synthesised according to another procedure[17].

NMR spectral data for **6**, **7** and **8** were fully consistent with structure. The deshielding of H-2' and H-3' in **6**, in comparison with **5**, is in accordance with a cyclic thionocarbonyl product. The presence of the 2',3'-double bond in **7** and **8** was clearly shown by the occurance of low-field doublets of doublets assigned to the 2'- and 3'- protons.

Biological evaluation. Compounds **4** and **8** were tested *in vitro* in CEM- c 113 cells against Human Immunodeficiency virus type I (HIV-1).[19] The screened compounds were devoid of anti-HIV activity. Although the introduction of a cyano-group at the 1'-position in d4T increased the stability of the glycosidic bond (the half-life of depyrimidination for **4** and **8** is superior to 4 days at various pH and different temperatures), it led to a loss of activity, keeping however the same cytotoxicity. A similar observation was done by S. Broder et al. who found 1(3-cyano-2,3-dideoxy-β -D-*erythro* -pentofuranosyl) thymine to be inactive vs HIV.[20] They rationalized this loss of activity by two hypotheses which can also be suggested in our case : either the phosphorylation step is necessary and does not occur, or the modification introduced in the nucleoside analogue is not compatible with the structure-activity relationship needed for reverse transcriptase inhibition. More work on the conformation of these nucleosides would be necessary to understand their inactivity.

Figure 1. NOESY matrix of **3**, obtained with the standard NOESYPH. AU BRUKER experiment. The acquisition parameters are AQ = 0.3 s, SW = 3401 Hz, SI = 2048, NS = 16, DS = 2, TE = 303 °C, SF =300.13 MHz, NE = 512, D_1 = 2s. The dimension of final real matrix 1k.1k. The time domain data were multiplicated by a $\cos^2$ fonction before FT in the 2 dimensions



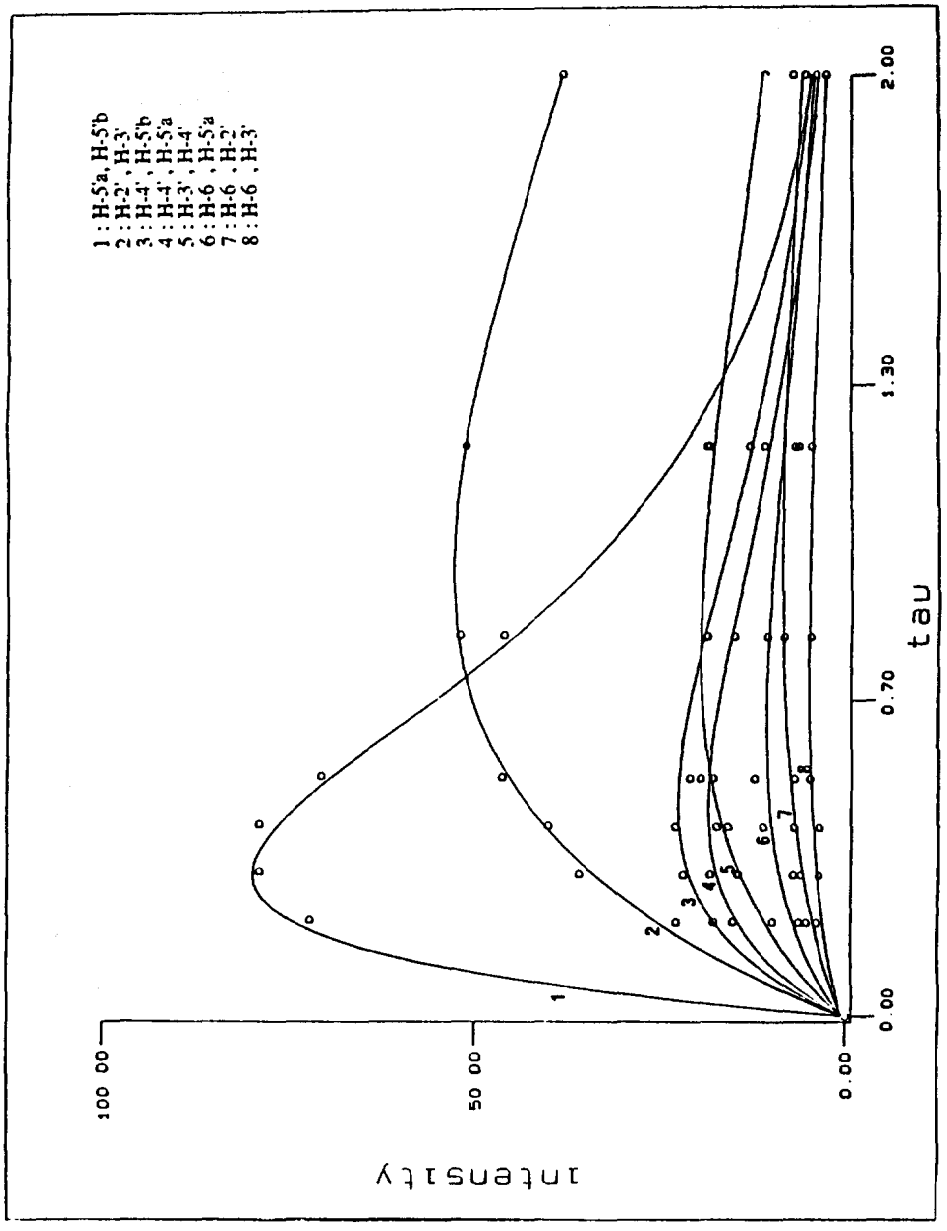


Figure 2. NOE buildup curves for the τ_m series 0.2, 0.3, 0.4, 0.5, 0.8, 1.2, 2s

EXPERIMENTAL SECTION.

General Procedures. Solvents were dried by distillation from the appropriate drying agent. Acetonitrile, N,N-dimethylformamide and tetrahydrofuran were distilled from calcium hydride. Nitromethane was dried over magnesium sulphate for 48 hr and distilled from phosphorus pentoxide after filtration. Melting points were determined on an electrothermal IA 9100 melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Kieselgel 60F-254 plates (E.Merk). Column chromatography was carried out on Kieselgel 60 (250-400 mesh, E. Merck), and shortwave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. Ultraviolet absorption spectra were recorded on a Shimadzu UV-160 A spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded at 300.13 and 75.5 MHz on a BRUKER AM 300 spectrometer. Values are given in part per million (ppm) downfield from the internal standard tetramethylsilane in the following format : chemical shift (multiplicity, integration, coupling constant in hertz). Fast atom bombardment and high-resolution mass spectra were collected on a ZAB V.G. mass spectrometer (8 kV acceleration voltage, 35 keV Ce^{+} ion bombardment). Elemental analyses were performed at the Service Central de Microanalyse of CNRS at Lyon, France : results are within $^{+}$ 0.4% of theoretical values unless noted otherwise. Optical rotations were measured in 1-dm cells of 1mL capacity with a Perkin-Elmer Model 241 polarimeter. Concentrations are reported in grams per deciliter.

2, 3, 5-tri -*O* -benzoyl-1-bromo-D-ribofuranosyl cyanide (2). The cyanide **1** (3.92 g, 8.3 mmol) and *N*-bromosuccinimide (3.6 g, 20 mmol), in a flat-bottomed erlenmeyer flask equipped with a condenser, were heated under reflux in dry carbon tetrachloride (200 mL) for 35 min over a 250 W tungsten lamp, the flask and the lamp being maintained at a constant distance equal to 4 cm. The insoluble materials were removed from the cooled mixture by filtration and the filtrate was diluted with chloroform and washed successively with aqueous sodium thiosulphate, aqueous sodium hydrogen carbonate and water. The organic phase was dried over magnesium sulphate and evaporated. The crude product containing two main components was fractionated by silica gel column chromatography (system benzene/ether 97.5:2.5) to give **2a** (1.24 g, 27%) and **2b** (2.84 g, 62%) as foams. Anal. Calcd for $C_{27}H_{20}BrNO_7$: C, 58.92; H, 3.66; Br, 14.52; N, 2.55. Found: C, 58.78; H, 3.86; Br, 14.56; N, 2.45.

2a : *Rf* 0.29 (benzene / ether 97.5:2.5); *Rf* 0.49 (hexane / ether 1:1); $[\alpha]^{25}_{D}$ +71.7° (c 1.535, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.1-7.3 (m, 15 H, H arom.), 5.88 (dd, 1H, $J_{3,4}$ = 2.7 Hz, H-3), 5.82 (d, 1H, $J_{2,3}$ = 6.4 Hz, H-2), 4.93 (dt, 1H, $J_{4,5a} = J_{4,5b}$ = 2.6 Hz, H-4), 4.80 (m, 2H, H-5a and 5b); ^{13}C NMR ($CDCl_3$) δ 165.7, 165.2, 163.9 (CO), 114.1 (CN), 85.2 (C-4), 80.4 (C-1), 74.7 (C-2), 69.4 (C-3), 62.5 (C-5), $^{3}J_{CN,H-2}$ = 2.9 Hz.

2b : *Rf* 0.41 (benzene / ether 97.5 : 2.5); $[\alpha]^{25}_{D}$ -59.4 ° (c 1.085, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.1-7.3 (m, 15H, H arom.), 6.38 (d, 1H, $J_{2,3}$ = 4.6 Hz, H-2), 6.22 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3), 5.00 (m, 1H, H-4), 4.83 (dd, 1H, $J_{5a,5b}$ = 12.6 Hz, $J_{4,5a}$ = 3.5 Hz, H-5a), 4.62 (dd, 1H, $J_{4,5b}$ = 4.7 Hz, H-5b); ^{13}C NMR ($CDCl_3$) δ 165.8, 164.9, 163.9 (CO), 113.0 (CN), 83.9 (C-4), 79.8 (C-2), 77.4 (C-1), 70.0 (C-3), 62.4 (C-5), $^{3}J_{CN,H-2}$ = 0.0 Hz.

1(1-cyano-2,3,5-tri-*O*-benzoyl-β -D-ribofuranosyl)thymine (3) A solution of **2** (2.5 g, 4.5 mmol) in anhydrous nitromethane (75 mL) was heated for 30 min at 110 °C under a dry nitrogen atmosphere in the presence of molecular sieves (4A, 1.8 g). To this solution, cooled to 20 °C, were added 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine (1.84 g, 6.8 mmol) and mercuric cyanide (1.6 g, 6.35 mmol). The mixture

was stirred 3 days at room temperature, with another addition of pyrimidine (0.92 g) and mercury salt (0.80 g) after 24 hr. The suspension was filtered. After evaporation of the filtrate, the residue was dissolved in chloroform which was subsequently washed with a 50% potassium iodide in half-saturated sodium chloride and a saturated sodium chloride solution. Finally the organic layer was dried over magnesium sulphate. The volatile compounds were evaporated and the white residue was purified by silica gel column chromatography with 1:5 hexane/ether as eluent to afford **3** as a foam (1.5 g, 56%) : *Rf* 0.45 (hexane/ether 1:5); mp 110-111 °C; $[\alpha]^{25}_D$ -163° (c 0.145 , $CHCl_3$); UV (95% EtOH): λmax 270 nm (ε 46800), 203 (70600) ; ^1H NMR ($CDCl_3$) δ 8.81 (s, 1H, NH), 8.1-7.3 (m, 15H, H arom.), 7.50 (s, 1H, H-6), 6.36 (d, 1H, $J_{2',3'}$ = 5.5 Hz, H-2'), 5.93 (dd, 1H, $J_{3',4'}$ = 5.8 Hz, H-3'), 5.06 (m, 1H, $J_{4',5'a}$ = 1.8 Hz, $J_{4',5'b}$ = 3.2 Hz, H-4'), 4.98 (dd, 1H, $J_{5'a,5'b}$ = 12.8 Hz,H-5'a), 4.55 (dd, 1H, H-5'b), 1.70 (s, 3H, CH_3-5); ^{13}C NMR ($CDCl_3$) δ 165.7, 165.1, 164.2 (CO benzoyl), 162.8 (C-4),149.0 (C-2), 132.6 (C-6), 131.7-127.5 (18C arom.), 112.9 (CN), 112.1 (C-5), 89.6 (C-1'), 83.06 (C-4'), 76.04 (C-2'), 70.3 (C-3'), 61.93 (C-5'), 12.5 (CH_3-5); MS (FAB, 3-nitrobenzyl alcohol matrix) *m/z* (rel intensity) 596 (MH^+, 15), 470 (M^+ - base, 18), 105 ($C_6H_5CO^+$, 39); HRMS (MH^+) calcd for $C_{32}H_{25}N_3O_9$ 596.1669, found 596.1682.

1(1-cyano-β-D-ribofuranosyl)thymine (4) A suspension of the blocked nucleoside **3** (1.4 g, 2.4 mmol) in a mixture of methanol (16 mL) and concentrated ammonium hydroxide (25 mL) was stirred at room temperature for 12 hr. The homogeneous solution was concentrated under vacuum and the residue was taken up in water. The insoluble material was filtered and the aqueous filtrate was evaporated to dryness *in vacuo*. The crude product was purified by column chromatography on silica gel. Elution with a chloroform/15% methanol mixture gave **4** (0.46 g, 68%) as a solid :*Rf* 0.18 ($CHCl_3$/15% MeOH); mp 100-101 °C;$[\alpha]^{25}_D$ -38.5°(c 0.058, MeOH); UV (95% EtOH): λ max 263.2 nm (ε 10584); ^1H NMR (Me_2SO-d_6) δ 11.66 (s, 1H, NH), 8.0 (s, 1H, H-6), 6.75 (d, 1H, $J_{2',OH}$ = 5.7 Hz, OH-2'), 5.32 (t, 1H, $J_{5',OH}$ = 5 Hz, OH-5'), 5.21 (d, 1H, $J_{3',OH}$ = 7.5 Hz, OH-3'), 4.35 (dd, 1H, $J_{2',3'}$ = 4.2 Hz, H-2'), 4.12 (m, 1H, H-4'), 3.9 (m, 2H, H-3' and H-5'a), 3.58 (m, 1H, H-5'b), 1.76 (s, 3H, CH_3-5); ^{13}C NMR (Me_2SO-d_6) δ 163.6 (C-4), 149.7 (C-2), 133.6 (C-6), 115.1 (CN), 108.9 (C-5), 90.6 (C-1'), 84.6 (C-4'), 75.8 (C-2'), 66.5 (C-3'), 57.8 (C-5'), 12.25 (CH_3-5); MS (FAB, glycerol matrix) *m/z* (rel intensity) 284 (MH^+, 100), 127 (base + $2H^+$, 87); HRMS (MH^+) calcd for $C_{11}H_{13}N_3O_6$ 284.0883, found 284.0938.

1(5-*O*-*tert*-butyldimethylsilyl-1-cyano-β-D-ribofuranosyl)thymine (5).To a solution of **4** (0.40 g, 1.4 mmol) and imidazole (0.27 g, 3.97 mmol) in anhydrous DMF (0.5 mL), was added *tert* -butyldimethylsilyl chloride (0.24 g, 1.6 mmol) in one portion. The resulting solution was stirred for 12 hr at room temperature and diluted in water. The product was extracted with ethyl acetate. The organic phase was back-extracted with water and dried on magnesium sulphate. The solvent was evaporated and the product was purified by column chromatography with $CHCl_3$/15% MeOH as eluent to give pure **5** as a foam (0.46 g, 83%) : *Rf* 0.35 ($CHCl_3$/15% MeOH); $[\alpha]^{25}D$ -43° (c 0.266, $CHCl_3$); UV(95% EtOH): λmax 262.8 nm (ε 11900), 208.6 (11100); ^1H NMR (Me_2SO-d_6) δ 11.67 (s, 1H, NH), 7.63 (s, 1H, H-6), 6.73 (d, 1H, $J_{OH,2'}$ = 5.0 Hz, OH-2'), 5.23 (d, 1H, $J_{OH,3'}$ = 7.1 Hz, OH-3'), 4.44 (dd, 1H, $J_{2',3'}$ = 4.8 Hz, H-2'), 4.2 (m, 1H, H-4'), 4.06 (m, 1H, H-5'a), 3.9 (m, 1H, $J_{3',4'}$ = 8.8 Hz, H-3'), 3.75 (m, 1H, H-5'b), 1.77 (s, 3H, CH_3-5), 0.87 [s, 9H, $(CH_3)_3$-C-Si], 0.02 and 0.01 [2s, 2x3H, $(CH_3)_2$Si]; ^{13}C NMR (Me_2SO-d_6) δ 163.5 (C-4), 149.7 (C-2), 132.9 (C-6), 115.1 (CN), 109.1 (C-5), 90.8 (C-1'), 84.5 (C-4'), 75.8 (C-2'), 66.9 (C-3'), 60.3 (C-5'), 25.7 [(CH_3)3-C-Si], 18.1 (C-Si), 12.7 (CH_3-5), -5.6 and -5.7 [$(CH_3)_2$Si]; MS (FAB, thioglycerol

matrix) *m/z* (rel intensity) 398 (MH^+, 29), 127 (base + $2H^+$, 100); HRMS (MH^+) calcd for $C_{17}H_{27}N_3O_6Si$ 398.1747, found 398.1763.

1(5-*O*-*tert*-butyldimethylsilyl-1-cyano-2,3-*O*-thiocarbonyl-β-D-ribofuranosyl)thymine (6). Method A : To a suspension of the nucleoside **5** (325 mg, 0.825 mmol) in CH_3CN (25 mL), were added dibutyltin oxide (275 mg, 1.1 mmol) and phenoxy(thiocarbonyl) chloride (171 µL, 1.24 mmol). The mixture was stirred for 12 hr at room temperature and then filtered through florisil. The solvent was evapored to dryness. The residual product was purified by silica gel chromatography column ($CHCl_3$/20% CH_3COCH_3), giving 250 mg of pure **6** (69%) as an oil.

Method B : By using *N, N'* -thiocarbonyldiimidazole, the protected nucleoside **5** (205 mg, 0.52 mmol) was dissolved under an argon atmosphere into anhydrous THF (2.5 mL) and thiocarbonyldiimidazole (115 mg, 0.645 mmol) was added. The yellow mixture was stirred at room temperature for 72 hr. The solution was evapored and the crude product was purified by silica gel chromatography to give **6** (27 mg, 12% yield) : *Rf* 0.46 ($CHCl_3$ / 20% CH_3COCH_3) , *Rf* 0.3 (hexane / ethyl acetate 1/1); $[\alpha]^{25}_D$ -77.9°(c 0.085, $CHCl_3$); ^1H NMR (Me_2SO- *d6*) δ 11.91 (s, 1H, NH), 7.67 (s, 1H, H-6), 5.7 (m, 2H, H-2' and H-3'), 5.30 (m, 1H, H-4'), 4.03 (m, 2H, $J_{5'a,5'b}$ = 12.05 Hz, H-5'a and H-5'b), 1.81 (s, 3H, CH_3-5), 0.75 [s, 9H, $(CH_3)_3$-C-Si], 0.02 and 0.01 [2s, 2x3H, $(CH_3)_2$-Si]; ^{13}C NMR (Me_2SO-*d6*). δ 189.6 (C=S), 163.5 (C-4), 150.2 (C-2), 133.1 (C-6), 112.8 (CN), 110.5 (C-5), 92.1 (C-1'), 90.6, 89.6, 87.7 (C-2'; C-3'; C-4'), 62.2 (C-5'), 25.6 [($\underline{C}H_3)_3$-C-Si], 17.8 (C-Si), 12.4 (CH_3-5), -5.8 and -5.9 [$(CH_3)_2$-Si]; MS (FAB, thioglycerol matrix) *m/z* (rel. intensity) 440 (MH^+, 100), 413 (MH^+ - HCN, 15), 289 (MH^+ - base - CN, 13); HRMS (MH^+) calcd for $C_{18}H_{25}N_3O_6SSi$ 440.1312, found 440.1339.

1(5-*O*-*tert*-butyldimethylsilyl-1-cyano-2,3-dideoxy-β-*D*-*glycero*-pent-2-enofuranosyl) thymine (7). Under an argon atmosphere, **6** (210 mg, 0.48 mmol) was heated at 150 °C in triethyl phosphite (1 mL, 6 mmol) for 1 hr. The solvent was removed *in vacuo* and the resultant solid was purified by column chromatography on silica gel with $CHCl_3$ / 20% CH_3COCH_3 as eluent. 77 mg of **7** were isolated as a foam in 44% yield: *Rf* 0.56 (hexane/ethyl acetate 1:1), *Rf* 0.52 ($CHCl_3$ / 20% CH_3COCH_3); $[\alpha]^{25}_D$ -73° (c 0.39, $CHCl_3$); UV (95% EtOH): λmax 261 nm (ε 3596), 210 nm (3624); ^1H NMR ($CDCl_3$) δ 8.68 (s, 1H, NH), 7.51 (s, 1H, H-6), 6.59 (dd, 1H, $J_{2',3'}$ = 5.9 Hz, $J_{3',4'}$= 2.3 Hz, H-3'), 6.29 (dd, 1H, $J_{2',4'}$ = 1.4 Hz, H-2'), 5.30 (m, 1H, $J_{4',5'a}$ = $J_{4',5'b}$ = 3.1 Hz, H-4'), 3.94 (dd, 1H, $J_{5'a,5'b}$ = 11.8 Hz, H-5'a), 3.77 (dd, 1H, H-5'b), 1.92 (s, 3H, CH_3-5), 0.81 [s, 9H, ($\underline{C}H_3)_3$-C-Si], 0.02 and 0.01[2s, 2x3H, $(CH_3)_2$-Si]; ^{13}C NMR ($CDCl_3$) δ 163.5 (C-4), 149.3 (C-2), 134.6 (C-6), 133.7 (C-3'), 126.6 (C-2'), 114.7 (CN), 110.6 (C-5), 91.5 (C-1'), 90.6 (C-4'), 63.0 (C-5'), 25.6 [($\underline{C}H_3)_3$-C-Si], 18.2 (C-Si), 12.9 (CH_3-5), -5.5 [$(CH_3)_2$Si]; MS (FAB, 3-nitrobenzyl alcohol matrix) *m/z* (rel intensity) 364 (MH^+, 50), 337 (MH^+ - HCN, 22), 213 (MH^+ - base - CN, 12), 127 (base + $2H^+$, 95); HRMS (MH^+) calcd for $C_{17}H_{25}N_3O_4Si$ 364.1693, found 364.1

1(1-cyano-2,3-dideoxy-β-*D*-*glycero*-pent-2-enofuranosyl)thymine (8). The blocked nucleoside **7** (120 mg, 0.332 mmol) was treated with tetrabutylammonium fluoride (1.1M THF solution, 3.32 mL, 3.66 mmol) at room temperature for 15 min.The solvent was evaporated and the residue was chromatographed on a silica gel column($CHCl_3$ / 15% CH_3OH as eluent) to afford **8** as an oil: (40 mg, 48%): *Rf* 0.6 (chloroform/15%methanol);$[\alpha]^{25}D$ -0.08° (c 0.24,CH_3OH); UV (EtOH 95%) λmax 260.4 nm (ε 19303), 211.4 (17582); ^1H NMR (Me_2SO-*d6*) δ 11.62 (s, 1H, NH), 7.50 (s, 1H, H-6), 6.68 (dd , 1H, $J_{2',3'}$ = 5.9 Hz, $J_{3',4'}$ = 1.5 Hz, H-3'), 6.40 (dd, 1H, $J_{2',4'}$ = 2.1 Hz, H-2'), 5.20 (m, 1H, H-4'), 4.97 (t,

1H, OH-5'), 3.61 (m, 1H, $J_{4',5'a} = J_{4',5'b} = 2.82$ Hz, H-5'a), 3.49 (m, 1H, $J_{5'a,5'b} = 12.4$ Hz, H-5'b), 1.76 (s, 3H, CH_3-5); MS (FAB^-, thioglycerol matrix) *m/z* (rel intensity) 248 (MH^-, 73); HRMS $(M-H)^-$ calcd for ($C_{11}H_{11}N_3O_4$) 248.0671, found 248.0689.

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