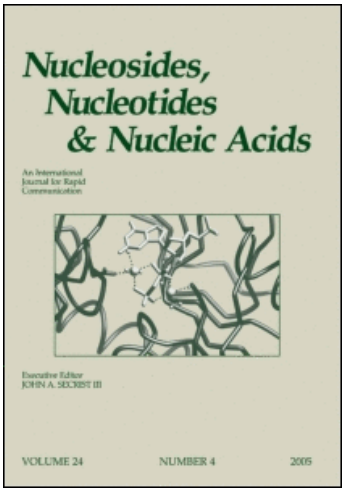

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4'-AZA-3',5'-DIHOMOTHYMIDINE AND DERIVATIVES

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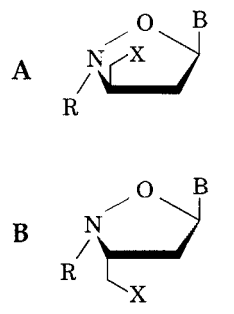
Abstract : A series of 3'-branched 4'-azanucleoside analogues have been prepared. These compounds comprise three asymmetric atoms, two carbons and one nitrogen. They constitute nucleoside analogues imparted with a "flickering configuration", the nitrogen inversion replacing a D-L epimerization of their natural congeners. The 1',3'-*cis* and 1',3'-*trans* isomers have been separated and their configuration established by ^{1}H NMR and the X-ray diffraction structure of one crystalline example. The configurations of the frozen invertomers were assessed by low temperature ^{1}H NMR experiments assisted by molecular mechanics simulations. None of these compounds exhibited any significant *in vitro* antiviral activity.

INTRODUCTION

Given the current interest[1] in the antiviral activity exhibited by nucleoside analogues of the "wrong" configuration (either L or α or even eventually both), we prepared 4'-aza nucleoside analogues. In these compounds, the asymmetric carbon atom responsible for the D or L configuration of classical nucleosides is replaced with a nitrogen atom. This substitutes an easy nitrogen inversion to an almost impossible D-L epimerization. At room temperature, such compounds can adopt conformations that would represent either a D or a L configuration in the case of their carbon analogues. They can supposedly adjust their configuration to the steric requirements of a macromolecular partner. Our first examples of such compounds[2] were analogues of 2',3'-dideoxynucleosides, for which, in the rule, the anomeric carbon was the only asymmetric carbon. In such a case, for a given configuration at that chiral center, two invertomers were present simulating a β-D:α-L or a α-D:β-L pair. We describe here examples of 4'-aza 3'-branched nucleosides. These compounds possess three asymmetric atoms, two carbons and

one nitrogen, thus allowing for eight isomers. All these compounds have been obtained as racemic mixtures. For their naming, we use an approach as close as possible to that of carbohydrate nomenclature, assigning the α configuration to compounds bearing the anomeric substituent on the same face of the ring as the 3(')-substituent. The configuration of the asymmetric nitrogen atom is described, when necessary relatively to C-3 (or C-3') as *r*-3(')*,t*-4(') or *r*-3(')*,c*-4('). In these conditions, all configurational assignments are relative, thus valid in both D and L series. For example the compound **A** belongs to the *r*-3'*,t*-4'-α series whereas **B** corresponds to a *r*-3'*,c*-4'-β configuration.

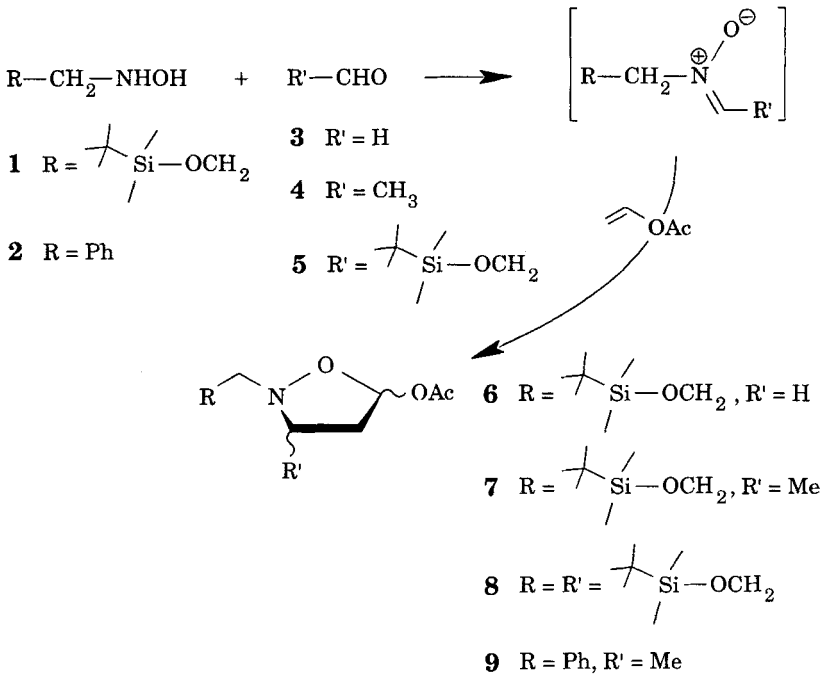


RESULTS AND DISCUSSION

Upon reaction of one of the *N*-monosubstituted hydroxylamines **1** and **2** with one of the aldehydes **3-5**, the corresponding nitrone was formed but not isolated and immediately treated (one-pot reaction) with vinyl acetate (Scheme 1).

The 1,3-dipolar cycloaddition reaction was regiospecific and the only compounds formed were the 4-aza sugar analogues **6-9**, as established by their ^{1}H NMR chemical shifts (TABLES 1 and 2) in particular their $\delta_{H\text{-}1}$ values in the range 6.22-6.31 ppm. These compounds were obtained as racemic modifications, in 83% yield in the case of **6**, consisting in a pair of enantiomers, and in yields ranging from 50 to 58% for compounds **7** and **9**, obtained as two isolated α and β diastereoisomers each as a racemic.

Compounds **6-8** were then desilylated using tetrabutylammonium fluoride and acetylated. The unbranched diacetyl derivative **10** was obtained from **6** in 68% yield (Scheme 2). Each anomer of **11** was prepared from the corresponding anomeric modification of **7** in 68% yield for **α-11** and 56% yield for **β-11**. In the same conditions, an α/β mixture of **8** gave the corresponding unresolved mixture (37%) of **α-12** and **β-12**. Nucleosidation of **10** afforded **13** (52%). Concerning branched-chain acetylated sugar analogues, **11**, **12**, and **9** afforded the corresponding blocked 4'-azanucleosides **14**, **15**, and **16** respectively, always as anomeric mixtures regardless of the anomeric purity of the starting material. Thus, **α-14** (45%) and **β-14** (22%) were obtained either from **α-11** or **β-11**, whereas a 7:4 unresolvable mixture (73%) of **α-15** and **β-15** was obtained from an anomeric mixture of **12**. Pure **α-16** (63%) and **β-16** (21%) were prepared either from **α-9** or **β-9**. Deacetylation of **13**, **14**, and **15** afforded in excellent yields **17**, **18**, and **19**



Scheme 1

TABLE 1. Selected ^{1}H NMR Data (200 MHz, $CDCl_3$) of Unbranched Isoxazolidine Sugar and Nucleoside Analogues.[a]

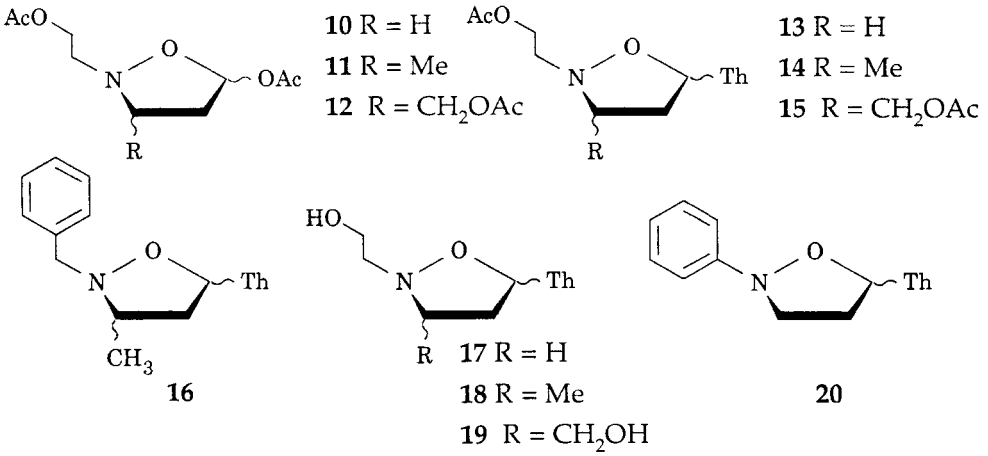
		Compounds								
		6	**10**		**13**		**17**		**20**
	temp °C	+60	+60	-40	+60	-20	+60	-40	+30
Chemical shifts	H-1	6.22	6.32		6.17	6.17	6.12	6.19	6.42
	H-2α	2.56	2.59		2.90	2.92	2.84	2.92	3.00
	H-2β	2.35	2.39		2.38	2.35	2.35	2.38	2.50
	H-3α	2.90	2.91	2.91	2.76	2.67	2.75	2.67	3.28
	H-3β	3.28	3.22		3.44	3.45	3.40	3.45	3.89
Coupling constants	$J_{1,2\alpha}$	6.0	6.0		7.5	7.0	7.0	7.0	7.5
	$J_{1,2\beta}$	2.0	2.0		3.8	3.8	4.0	3.5	3.0
	$J_{2\alpha,2\beta}$								
	$J_{2\alpha,3\alpha}$	8.0	6.0	7.5	8.0	8.0	8.0	7.0	7.5
	$J_{2\alpha,3\beta}$	6.0	8.0		3.0	2.0	3.0	2.5	4.0
	$J_{2\beta,3\alpha}$	7.0	7.0	10.0	8.0	10.0	8.0	9.5	7.3
	$J_{2\beta,3\beta}$	7.5	6.5		8.0	8.0	8.0	7.5	7.3
	$J_{3\alpha,3\beta}$	x							

[a] Protons of the isoxazolidine rings are referred as α or β depending on the face of the ring on which they are situated.

TABLE 2. Selected ^{1}H-NMR Data (200 MHz, $CDCl_3$) of 3-Substituted 1-O-Acetyl-4-Azafuranoses.[a]

Cmpd	t/°C	δ_{H-1}	$\delta_{H-2\alpha}$	$\delta_{H-2\beta}$	δ_{H-3}	$J_{1,2\alpha}$	$J_{1,2\beta}$	$J_{2\alpha,2\beta}$	$J_{2\alpha,3}$	$J_{2\beta,3}$
α-7[b]	+25	6.26	2.74	2.02	2.82	6.0	3.0	-12.0	7.5	8.5
α-8[b]	+25	6.31	2.69	2.17	3.10	6.3	2.0	-13.7	8.5	6.5
α-9[b]	+25	6.29	2.76	2.04	2.91	6.5	2.7	-13.0	7.5	8.0
α-11[b]	+60	6.24	~2.75	~2.10	~2.75	6.0	3.0	-13.0	~7.5	10.0
α-12[b]	+25	6.36	2.78	2.19	3.22	6.0	1.2	-13.5	8.5	6.3
β-7	+60	6.29	2.20	2.42	3.30	5.0	1.2	-13.0	8.5	6.5
	-40	6.27	2.21	2.45	3.27	4.5	1.0	-12.5	10.5	5.5
β-8	+60	6.33	2.36	2.45	3.39	5.0	1.8	-13.5	7.5	6.8
β-9	+60	6.22	2.27	2.48	3.32	5.0	1.0	-13.0	9.0	6.5
	-40	6.28	2.28	2.48	3.33	4.5	~0.	-13.0	10.0	6.0
β-11	+60	6.28	2.20	2.39	3.15	5.0	1.0	-13.0	9.0	6.0
β-12	+60	6.37	2.36	2.52	3.59	5.5	1.5	-13.5	7.8	7.2

[a] See footnote [a] in Table 1. [b] Spectra unsensitive to temperature changes for α anomers.



Scheme 2

respectively. Compound **20** was obtained in 44% yield from a one-pot reaction between 1-vinylthymine, *N*-phenylhydroxylamine and paraformaldehyde.

In most cases where two anomers existed (two asymmetric carbon atoms), they were isolated. In the few instances where the isolation was impossible, ^{1}H NMR data for each anomer were at least obtained (TABLES 1-3).

Compounds bearing two asymmetric carbon atoms were divided into two groups on the basis of their chromatographic behavior : a faster-moving (less polar) and a slower-moving (more polar). Each group appeared as structurally homogeneous. Compounds from the faster-moving group exhibited well-resolved ^{1}H NMR spectra at room temperature and when lowering the temperature, it was impossible to reveal the presence of two frozen invertomers. An opposite situation prevealed for members of the slower-moving group and some thermodynamic and kinetic data relative to their nitrogen inversion ($\Delta G^{\neq}$ values estimated from a line shape analysis of variable temperature 1H NMR data) are collected in TABLE 4.

On the basis of ^{1}H NMR data (TABLES 2 and 3) and of the X-ray diffraction structure (see below) of the faster-moving anomer of **18**, for each anomeric pair, the α configuration was assigned to the more lipophilic anomer. When comparing the time-averaged ^{1}H NMR data of compounds of the α and β series, some trends can be noted. The sum of the $J_{2,3}$ values amounts to 15-17.5 Hz for the α anomers and 11.5-15.5 for the β anomers. Furthermore, the H-3$^{(')}$ proton is always more shielded for the α than for the β anomer. Low temperature NMR spectra of β anomers allow their configuration to be unambiguously assessed in each case where a frozen conformer exhibits either a small or a very large vicinal coupling constant making possible a configurational assignment (α or β position) of the corresponding proton. For example, the configuration of **β-9** is established from the fact that the major invertomer exhibits a null coupling between H-1 and one of the H-2 proton whereas the second H-2 proton is strongly coupled (10 Hz) with H-3.

To estimate whether it could be possible to assess the configuration of these molecules from calculated lipophilic properties, some computations were performed. Compounds **9**, **16**, and **18** were selected as representative examples of the series, the four isomers of each were build and for each of the twelve structures, 1200 conformers were generated using a Monte Carlo search (MacroModel 4.5 software)[3] and minimized. The geometry optimization was performed without solvent contribution using the MM2 force field[4] including the parameters we have developed for *N*-hydroxyamino compounds.[5] For each structure, the six most

TABLE 3. Selected ^{1}H-NMR Data (200 MHz, $CDCl_3$) of 3'-Branched 4'-Aza-2'-3'-Dideoxynucleosides.[a]

Cmpd	t/°C	$\delta_{H\text{-}1'}$	$\delta_{H\text{-}2'\alpha}$	$\delta_{H\text{-}2'\beta}$	$\delta_{H\text{-}3'}$	$J_{1,2\alpha}$	$J_{1',2'\beta}$	$J_{2'\alpha,2'\beta}$	$J_{2'\alpha,3'}$	$J_{2'\beta,3'}$
α-14[b]	+25	6.10	3.08	1.99	2.86	7.5	4.5	-13.5	7.0	10.0
α-15[b]	+25	6.12[c]	~3.12[c]	2.18[c]	~3.12[c]	7.0[c]	3.5[c]	-12.5[c]	8.0[c]	8.0[c]
α-16[b]	+60	5.94[c]	3.11[c]	1.99[c]	2.94[c]	7.5[c]	4.0[c]	-13.5[c]	7.0[c]	8.9[c]
α-18[b,d]	+25	6.18	3.07	1.99	2.93	7.5	5.0	-12.5	7.5	10.0
α-19[b]	+25	6.54	2.98	2.07	3.10	7.0	4.0	-12.5	8.0	8.0
β-14[b]	+55	6.18	2.54	2.46	3.40	7.0	5.0	-13.5	5.0	6.5
	-40	6.24	2.66	~2.49	3.70	~6		-13.0	~1	
		6.24	2.49	~2.49	~2.98					
β-15	+25	6.12	2.72	2.50	3.60	7.2	4.5	-13.5	5.0	7.3
β-16	+55	6.08[c]	2.58[c]	2.46[c]	3.47[c]	7.5[c]	4.0[c]	-13.5[c]	5.0[c]	7.0[c]
	-30	5.98[b]	2.67[c]	2.52[c]	3.78[c]	7.0[c]	4.0[c]	-14.0[c]	0.5[c]	7.0[c]
		6.17	~2.50	2.21	3.05	7.5	2.5	-13.5	10.0	7.0
β-18	+60	6.18	2.51	2.42	3.33	6.5	5.0	-13.5	6.5	6.5
β-19	+25	6.12	2.59	2.47	3.37	7.5	5.0	-13.0	7.5	8.0

[a] See footnote [a] in Table 1. [b] Spectra of α anomers exhibit a null or very low sensitivity to temperature changes. [c] PANIC simulation. [d] In pyridine-d_5.

TABLE 4. Selected Thermodynamic and Kinetic Data for the Nitrogen Inversion of 4-Azafuranose Derivatives.

Cmpd	6	β-7	10	β-11	13	17[c]	β-18	β-19[c]
$\Delta G^{\neq}$[a](t)[b]	14.8(0)	14.7(0)	14.4(20)	~13.8(0)	~15.0(10)	~13.8(10)	13.9(15)	12.4(-20)
K(t)[b]	~3(-40)	15(-40)	2.5(-40)	~20(-40)	~30(-40)	~30(-40)	1.2(-40)	5.0(-60)

[a] In kcal/mol. [b] In °C. [c] In methanol-d_4.

stable conformers were retained amounting to 74-100% of the conformational equilibrium. The Boltzmann-averaged log *P* and lipophilicities following Fauchere's equation[6] using either the Ghose-Crippen's[7] or the Broto-Moreau-Vandycke's[8] tables were computed using the MAD software[9] and collected in TABLE 5. The log *P* values based on a connectivity description of the molecules only indicate a global lipophilicity for each of the compounds computed.

From the Fauchere's values, it appears that the α-β dichotomy is negligible in regard of the *cis* or *trans* relationship between the anomeric and pyramidal nitrogen substituents. In other terms, the fact that the α anomers are more lipophilic than their β congeners depends on a change in the relative stability of their invertomers induced by the configuration of their asymmetric carbon atoms.

The best index of the configuration of the asymmetric nitrogen atom is the shielding effect of the nitrogen lone pair upon an antiperiplanar vicinal hydrogen atom.[10,11] This indicates a *r*-3$^{(')}$,*t*-4$^{(')}$ configuration for the unique invertomer in the α series whereas the preponderant invertomer of the β series adopts a *r*-3$^{(')}$,*c*-4$^{(')}$ configuration. The configuration of **α-18** was confirmed by an X-ray diffraction study (FIG. 1).

The isoxazolidine ring adopts an envelope conformation $^{4'}E$ with a minimum value of the asymmetry parameters[12] associated to a quasi ideal C_s symmetry with the σ plane passing through the N(4') atom [$\Delta C_s = 0.008(1)$]. The molecular packing is fixed by a network of hydrogen bond interactions involving both potential donors of the molecule (FIG. 2). The 6'-hydroxy group was disordered and only the preponderant form (72%) is represented in FIG. 1 and 2.

The Monte Carlo study (see above) predicted for **α-18**, the *r*-3',*t*-4' configuration to be more stable by 14 kcal/mol than its invertomer *r*-3',*c*-4'. Moreover, the more stable conformer adopted a $^{4'}E$ conformation as found in the crystalline state. For **β-18**, the molecular mechanics simulation predicted as the most favorable form, the *r*-3',*c*-4' invertomer in the $^{4'}E$ conformation.

Representative examples of these novel 4'-azanucleoside analogues were submitted to biological testing using previously described procedures.[2] Results collected in TABLE 6 show that no significant biological activity was found against *E. coli*, *B. subtilis* or HIV. On the other hand, the cytotoxicity of these molecules is very low. The only border-line activity found, was a partial inhibition, or a provoked delay in the cytopathogenic effect of the oncovirus SV_{40} exhibited by **α-** and **β-14**, **(α+β)-18**, and **20**.

TABLE 5. Computed Lipophilic Properties of Representative Examples of Isoxazolidine Derivatives (Lipophil. Stands for Fauchère's Lipophilicity).

Cmpd	Config.	1,4 relationship	log *P*-1[a]	Lipophil.-1[a]	log *P*-2[b]	Lipophil.-2[b]
9	*r*-3,*t*-4-α	*trans*	2.70	6.12	3.99	3.21
	r-3,*c*-4-α	*cis*	2.70	8.09	3.99	3.73
	r-3,*t*-4-β	*cis*	2.70	7.80	3.99	3.13
	r-3,*c*-4-β	*trans*	2.70	6.64	3.99	3.19
16	*r*-3,*t*-4-α	*trans*	4.13	5.98	3.12	8.81
	r-3,*c*-4-α	*cis*	4.13	6.74	3.12	9.88
	r-3,*t*-4-β	*cis*	4.13	6.51	3.12	9.57
	r-3,*c*-4-β	*trans*	4.13	6.12	3.12	8.97
18	*r*-3,*t*-4-α	*trans*	1.75	5.72	0.48	6.71
	r-3,*c*-4-α	*cis*	1.75	4.35	0.48	5.74
	r-3,*t*-4-β	*cis*	1.75	4.51	0.48	5.74
	r-3,*c*-4-β	*trans*	1.75	6.01	0.48	6.77

[a] Calculated using the Ghose-Crippen's table. [b] Calculated using the Broto-Moreau-Vandycke's table.

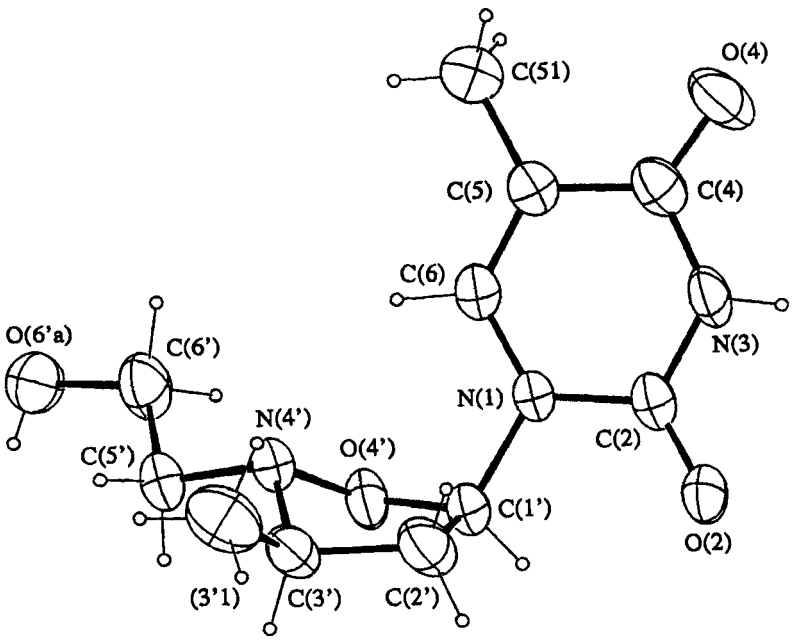


Figure 1. Molecular structure of compound **α-18** with the atomic numbering. Ellipsoids are represented for a 40% probability.

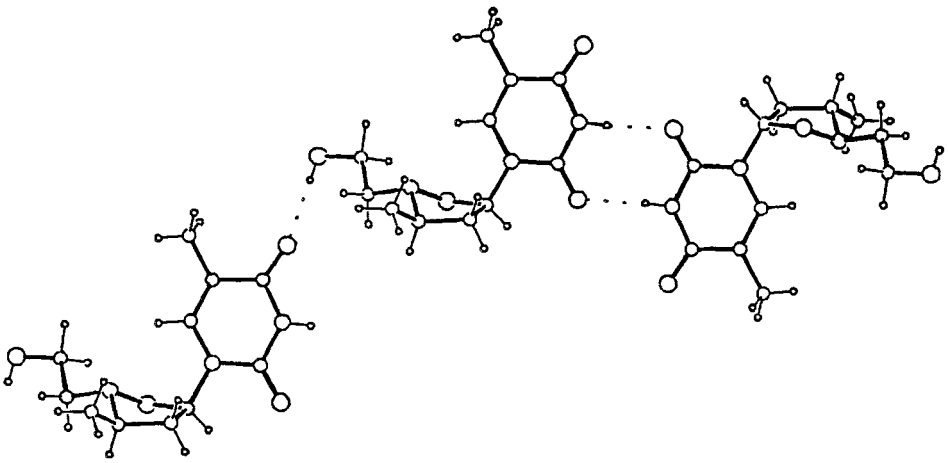


Figure 2. Partial view of the molecular packing of **α-18** showing the hydrogen bond interactions.

TABLE 6. Some Biological Properties of 4'-Azanucleosides.

Cmpd	MIC[a] *E.coli*	MIC[a] *B.subtilis*	Cytotoxic concentration[a]	MIC[a] SV_{40}	IC_{50}[a] HIV-1
13	>705	>705	>705	>705	>200
α-14	>337	>337	>674	337(PI)[b]	
β-14	>337	>337	>674	337(PI)[b]	
17	>830	>830	>830	>830	
α-18	>392	>392	>979	392[c]	>200
(α+β)-19	369	369	>369	>369	>200
20	>366	>366	>782	183[d]	

[a] μM concentrations. [b] Partial inhibition. [c] Cytopathogenic effect delayed by 6 h. [d] Cytopathogenic effect delayed by 24 h.

EXPERIMENTAL

General Methods.[13]

Crystallography

Single crystals were grown at room temperature from acetone/hexane solutions. The diffracted intensities were measured at room temperature on a Stoe STADI4 diffractometer with monochromated Mokα radiation (λ = 0.71069 Å). Corrections for Lorentz-polarization were applied but not for absorption. The structure was solved by direct methods (MULTAN 87)[14] and refined by full-matrix least-squares with XTAL program.[15] Atomic scattering factors and anomalous dispersion terms were taken from ref.[16] The hydroxyl group is disordered and two atomic sites (O(6'a) and O(6'b) have been observed and refined with anisotropic displacement parameters and occupancy factors of 0.722 and 0.278 respectively. All coordinates of the H atoms were observed and refined except for H(C(6')) which are calculated with respect to the disorder on O(6'a). The hydrogen atom of the minor moiety of the disordered hydroxyl (O(6'b)) has not been observed. A summary of crystal data, intensity measurement and structure refinement is given in TABLE 7. Final positional parameters and geometrical parameters are reported in TABLES 8 and 9 respectively.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Center, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, England.

***N*-(2-*tert*-Butyldimethylsilyloxyethyl)hydroxylamine (1).** - A mixture of 2-(*tert*-butyldimethylsilyloxy)ethanal[17] **5** (15.7 g, 90 mmol), *N*-hydroxyammonium chloride (18.7 g, 270 mmol) and pyridine (22 mL, 270 mmol) was stirred for 16 h. The reaction mixture was partitioned between ether (2x50 mL) and water (50 mL). The organic phase was dried ($MgSO_4$), concentrated and the residue distillated to afford a 1:1 E/Z mixture of 2-(*tert*-butyldimethylsilyloxy)-1-*N*-hydroxyiminoethane (12.7 g, 74%): syrup, bp 76-78 °C/1.3.10^{-1} mmHg; λ_{max}^{EtOH} 208 nm (ε 1185); ν_{max}^{film} 3317, 2931, 1473, 1256, 1114, and 836 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ 9.30 and 8.90 (*bs*, 2 H, 2xOH), 7.46 (*t*, 1 H, *J* = 5 Hz, CH, *E*), 6.87 (*t*, 1 H, *J* = 3.5 Hz, CH, Z), 4.54 (*d*, 2 H, *J* = 3.5 Hz, CH_2, Z), 4.28 (*d*, 2 H, *J* = 5 Hz, CH_2, *E*), 0.93 and 0.91 (2 *s*, 2x9 H, 6Me, *E* and *Z*), 0.10 and 0.09 (2 *s*, 2x6 H, 4 Me, *E* and *Z*). EIMS: *m/z* (%) 57 (14), 75 (100), 84 (12), 114 (18), 132 (48), 149 (16), 174 (12), and 189 (<1, M^{+}).

Anal. Calcd for $C_8H_{19}NO_2Si$ (189.33): C, 50.75; H, 10.12; N, 7.40. Found: C, 50.83; H, 10.04; N, 7.44.

To a solution of this oxime (1.89 g, 10 mmol) in methanol (100 mL), sodium cyanoborohydride (6.9 g, 110 mmol) was added at 25 °C and the pH of the reaction

TABLE 7. Summary of Crystal Data, Intensity Measurement and Structure Refinement for **α-18**.

Formula	$C_{11}H_{17}N_3O_4$	μ(MoKα) mm^{-1}	0.096
Mol. wt.	255.3	$((\sin\theta)/\lambda)_{max}$ ($Å^{-1}$)	0.58
Crystal system	Triclinic	Temperature (K)	293
Space Group	$P\bar{1}$	No. measured reflc.	2139
a (Å)	7.712(1)	No. observed reflc.	1458
b (Å)	9.122(2)	Criterion for observed	$\|Fo\| > 4\sigma(Fo)$
c (Å)	9.666(2)	Refinement (on F)	Full-matrix
α (°)	69.37(1)	No. parameters	217
β (°)	87.20(2)	Weighting scheme	$\omega = 1/\sigma^2(Fo)$
γ (°)	87.82(1)	Max. and average Δ/σ	0.002 , 0.027
V ($Å^3$)	635.5(2)	Max. and min. Δρ ($e.Å^{-3}$)	0.23 , -0.31
Z	2	S	3.24
F(000)	272	R , ωR	0.047 , 0.042
Dc $gr.cm^{-3}$	1.33		

mixture was kept at 4 by dropwise addition of 3 M HCl. After completion of the reaction (no spontaneous pH change, 45 min), the reaction mixture was concentrated, the residue was diluted with water and the pH of the aqueous solution brought to 10 (6 M KOH). The aqueous solution was extracted with dichloromethane (3x50 mL) and the organic phase, dried ($MgSO_4$), concentrated, was submitted to a distillation which afforded **1** (1.15 g, 60%): syrup, bp 64-65 °C/ $2.5.10^{-2}$ mmHg; λ_{max}^{EtOH} 203 nm (ε 404), and 230 (ε 115); ν_{max}^{film} 3280, 2858, 1472, 1256, 1104, and 836 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ 6.15 (*s*, 2 H, NH and OH), 3.70 (*t*, 2 H, *J* = 6 Hz, CH_2-O-), 2.92 (*t*, 2 H, *J* = 6 Hz, CH_2-N-), 0.83 (*s*, 9 H, 3 Me), and 0.00 (*s*, 6 H, 2 Me). EIMS: *m/z* (%) 46 (17), 60 (12), 73 (41), 75 (100), 89 (32), 105 (33), 116 (18), 134 (12), 149 (2), 176 (3), and 192 (13, M^{+}).

Anal. Calcd for $C_8H_{21}NO_2Si$ (191.35): C, 50.22; H, 11.06; N, 7.32. Found: C, 50.00; H, 10.99; N, 7.45.

***(1RS)*-1-*O*-Acetyl-4-aza-6-*O*-(dimethyl-*tert*-butylsilyl)-2,3,5-trideoxyhexo-1,4-furanose (6)**. - A mixture of hydroxylamine **1** (0.9 g, 4.7 mmol) and paraformaldehyde (0.17 g, 5.7 mmol) in dichloromethane (10 mL) was stirred for 4 h at 40 °C. After distillation of dichloromethane, vinyl acetate (10 mL, 100 mmol)

TABLE 8. Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å^2) with e.s.d.'s in Parenthesis for **α-18**. U_{eq} is the Average of Eigenvalues of *U*.

	x/a	y/b	z/c	U_{eq}	PP (if ≠1)
C(1')	0.1111(4)	0.4502(3)	0.1719(3)	0.051(1)	
C(2')	-0.0184(4)	0.5587(4)	0.2125(4)	0.065(1)	
C(3')	0.0490(4)	0.7217(3)	0.1285(3)	0.052(1)	
C(3'1)	0.0164(5)	0.8395(5)	0.2041(5)	0.077(2)	
N(4')	0.2357(3)	0.6863(2)	0.1163(2)	0.0430(8)	
O(4')	0.2328(2)	0.5463(2)	0.0720(2)	0.0485(7)	
C(5')	0.3289(4)	0.8015(3)	-0.0068(3)	0.052(1)	
C(6')	0.5197(4)	0.7622(3)	-0.0049(4)	0.066(1)	
O(6'a)	0.6273(4)	0.8743(4)	-0.1058(4)	0.077(2)	0.722(6)
O(6'b)	0.587(1)	0.769(1)	0.117(1)	0.096(5)	0.278(6)
N(1)	0.2016(3)	0.3393(2)	0.3017(2)	0.0451(9)	
C(2)	0.1207(4)	0.2017(3)	0.3769(3)	0.047(1)	
O(2)	-0.0204(3)	0.1708(2)	0.3419(2)	0.0606(8)	
N(3)	0.2090(3)	0.1042(3)	0.4942(3)	0.052(1)	
C(4)	0.3661(4)	0.1289(3)	0.5433(3)	0.052(1)	
O(4)	0.4273(3)	0.0311(3)	0.6526(2)	0.077(1)	
C(5)	0.4451(3)	0.2753(3)	0.4571(3)	0.047(1)	
C(51)	0.6172(5)	0.3100(4)	0.4994(4)	0.069(2)	
C(6)	0.3604(4)	0.3717(3)	0.3423(3)	0.049(1)	

was added and the reaction mixture stirred at 70 °C for 2 h. The excess of vinyl acetate was distilled and the residue dissolved in dichloromethane (20 mL). The organic phase was washed (H_2O, 2x10 mL), dried ($MgSO_4$), concentrated, and the residue submitted to a flash column chromatography (1:2 ethyl acetate/hexane) to give **6** (1.25 g, 83%): syrup, R_F 0.3 (1:2 ethyl acetate/hexane); λ_{max}^{EtOH} 204 nm (ε 7082); ν_{max}^{film} 1748 (C=O), 1102, and 936 cm^{-1}. ^{1}H NMR ($CDCl_3$, 60 °C): δ 3.84 (*t*, 2 H, $J_{5,6}$ = 6 Hz, CH_2-O), 3.03 (*m*, 2 H, CH_2-N), 2.05 (*s*, 3 H, Ac), 0.92 (*s*, 9 H, Me_3CSi), and 0.10 (*s*, 6 H, Me_2Si). EIMS: *m/z* (%) 75 (69), 89 (75), 102 (100), 117 (67), 146 (39), 172 (15), and 289 (0.6, $M^{\cdot+}$).

TABLE 9. Selected Bond Lengths (Å), Bond Angles and Torsional Angles (°) for **α-18.**

C(1')-C(2')	1.514(5)	C(6')-O(6'a)	1.403(4)
C(1')-O(4')	1.399(3)	N(1)-C(2)	1.366(3)
C(1')-N(1)	1.490(3)	N(1)-C(6)	1.378(4)
C(2')-C(3')	1.518(4)	C(2)-N(3)	1.364(3)
C(3')-N(4')	1.472(4)	N(3)-C(4)	1.377(4)
N(4')-O(4')	1.485(3)	C(4)-C(5)	1.441(3)
N(4')-C(5')	1.459(3)	C(5)-C(6)	1.331(4)
C(5')-C(6')	1.501(4)		
C(2')-C(1')-O(4')	106.3(2)	C(3')-N(4')-C(5')	114.5(2)
C(2')-C(1')-N(1)	113.3(3)	O(4')-N(4')-C(5')	103.9(2)
O(4')-C(1')-N(1)	109.6(2)	C(1')-O(4')-N(4')	103.6(2)
C(1')-C(2')-C(3')	104.4(2)	N(4')-C(5')-C(6')	110.9(2)
C(2')-C(3')-N(4')	100.6(2)	C(5')-C(6')-O(6'a)	116.6(2)
C(3')-N(4')-O(4')	101.4(2)		
O(4')-C(1')-C(2')-C(3')	-1.7(3)	C(2')-C(1')-N(1)-C(2)	87.0(3)
C(1')-C(2')-C(3')-N(4')	-27.0(3)	C(2')-C(3')-N(4')-C(5')	156.1(3)
C(2')-C(3')-N(4')-O(4')	44.9(3)	C(3')-N(4')-C(5')-C(6')	176.2(3)
C(3')-N(4')-O(4')-C(1')	-47.9(2)	N(4')-C(5')-C(6')-O(6'a)	-172.0(3)
C(2')-C(1')-O(4')-N(4')	29.9(3)		
Hydrogen bonds			
O(6'a)....O(4) x , y+1 , z-1 = 2.777(4)		O(6'a)-H(6'a)....O(4) = 167(4)°	
N(3)·····O(2) -x , -y , 1-z = 2.858(3)		N(3)-H(3)····O(2) = 175(3)°	

Anal. Calcd for $C_{13}H_{27}NO_4Si$ (289.45): C, 53.95; H, 9.40; N, 4.84. Found: C, 53.93; H, 9.28; N, 4.97.

1-*O*-Acetyl-4-aza-2,3,5-trideoxy-6-*O*-(dimethyl-*tert*-butylsilyl)-3-*C*-methyl-α-DL-*glycero*-hexo-1,4-furanose (α-7). - A solution of hydroxylamine **1** (1 g, 5.2 mmol) in ethanal (10 mL, 177 mmol) was stirred at 25 °C for 1 h. The excess of ethanal was then distilled and vinyl acetate (10 mL, 108 mmol) added. The reaction mixture was stirred at 70 °C for 24 h, concentrated, and submitted to a flash chromatography (2:3 ether/hexane) to give **α-7** (0.46 g, 29%), and **β-7** (0.46 g, 29%), syrup: R_F 0.43 (2:3 ether/hexane); λ_{max}^{EtOH} 204 nm (ε 3283); ν_{max}^{film} 1742 (C=O), 1095, and 827 cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 3.85 (*m*, 2 H, $J_{6a,6b}$ = 10.5 Hz, $J_{6a,5}$ = 7 Hz, $J_{6b,5}$ = 7.5 Hz and 5.5 Hz, 2H-C_6), 3.04 (*m*, 1 H, Hb-C_5), 2.77 (*m*, 1 H, $J_{5a,5b}$ = 13 Hz, Ha-C_5), 2.06 (*s*, 3 H, OAc), 1.22 (*d*, 3 H, $J_{3,CH3}$ = 6 Hz, MeC_3), 0.91 (*s*, 9 H, Me_3CSi), 0.10 (*s*, 6 H, Me_2Si). EIMS: *m/z* (%) 59 (39), 73 (92), 116 (98), 144 (48), 158 (80), 168 (72), 186 (100), 228 (35), and 303 (17, $M^{\cdot+}$).

Anal. Calcd for $C_{14}H_{29}NO_4Si$ (303.48): C, 55.41; H, 9.63; N, 4.62. Found: C, 55.35; H, 9.70; N, 4.72.

1-*O*-Acetyl-4-aza-2,3,5-trideoxy-6-*O*-(dimethyl-*tert*-butylsilyl)-3-*C*-methyl-β-DL-*glycero*-hexo-1,4-furanose (β-7). - Obtained as described for **α-7**, syrup: R_F 0.35 (2:3 ether/hexane); λ_{max}^{EtOH} 204 nm (ε 3035); ν_{max}^{film} 1751 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 3.88 and 3.82 (2 *dt*, 2 H, $J_{6a,6b}$ = 10 Hz, $J_{5,6}$ = 6.5 Hz, 2H-C_6), 3.07 (*t*, 2 H, $J_{5,6}$ = 6.5 Hz, 2H-C_5), 2.05 (*s*, 3 H, OAc), 1.21 (*d*, 3 H, $J_{3,CH3}$ = 6.5 Hz, MeC_3), 0.93 (*s*, 9 H, Me_3CSi), and 0.10 (*s*, 6 H, Me_2Si). EIMS: *m/z* (%) 56 (41), 73 (68), 89 (25), 116 (100), 158 (74), 186 (22), 228 (12), 303 (8, $M^{\cdot+}$).

Anal. Calcd for $C_{14}H_{29}NO_4Si$ (303.48): C, 55.41; H, 9.63; N, 4.62. Found: C, 55.62; H, 9.73; N, 4.73.

1-*O*-Acetyl-4-aza-2,3,5-trideoxy-6-*O*-(dimethyl-*tert*-butylsilyl)-3-*C*-(dimethyl-*tert*-butylsilylmethyl)-α and β-DL-*glycero*-hexo-1,4-furanose (α-8) and (β-8). - A mixture of hydroxylamine **1** (1.47 g, 7.68 mmol), aldehyde **5** (1.29 g, 7.4 mmol), and vinyl acetate (30 mL, 324 mmol) was stirred for 0.5 h at 25 °C and 16 h at 70 °C. The excess of vinyl acetate was removed by distillation and the residue, submitted to a flash column chromatography (1:4 ether/hexane) gave **α-8** (1.3 g, 40%), and **β-8** (0.32 g, 10%).

Properties of **α-8**: syrup, R_F 0.33 (1:4 ether/hexane); λ_{max}^{EtOH} 204 nm (ε 5057); ν_{max}^{film} 1752 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 3.84 (~ *t*, 2 H, 2xH-C_6), 3.77 and 3.71 (2 *dd*, 2x1 H, $J_{3'a,3'b}$ = 10 Hz, $J_{3'a,3}$ = 6 Hz, $J_{3'b,3}$ = 6.8 Hz, 2xH-$C_{3'}$), 3.22 (*dt*, 1 H, $J_{1,5b}$ = 0.5 Hz, $J_{5b,6}$ = 6 Hz, Hb-C_5), 2.94 (*dt*, 1 H, $J_{5a,5b}$ = 12.5 Hz, $J_{5a,6}$ = 6 Hz, Ha-C_5), 2.09 (*s*, 3 H, OAc), 0.91 and 0.89 (2 *s*, 2x9 H, 2xMe_3CSi), 0.09 and 0.08 (2x*s*, 2x6 H, 2xMe_2Si).

Properties of **β-8**: syrup, R_F 0.24 (1:4 ether/hexane); λ_{max}^{EtOH} 204 nm (ε 6099); ν_{max}^{film} 1753 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 3.84 (~ *t*, 2 H, 2H-C_6), 3.73 (*dd*, 1 H, $J_{3'b,3}$ = 6.2 Hz, Hb-$C_{3'}$), 3.58 (*dd*, 1 H, $J_{3'a,3'b}$ = 10 Hz, $J_{3'a,3}$ = 6.7 Hz, Ha-$C_{3'}$), 3.21 (*dt*, 1 H, $J_{5b,6}$ = 6 Hz, Hb-C_5), 3.11 (*bdt*, 1 H, $J_{5a,6}$ = 7 Hz, $J_{5a,5b}$ = 12 Hz, $J_{5a,1}$ = 0.5 Hz, Ha-C_5), 2.06 (*s*, 3 H, OAc), 0.92 (*s*, 18 H, 2xMe_3CSi), 0.10 (*s*, 12 H, 2xMe_2Si).

EIMS: *m/z* (%) 59 (21), 73 (100), 89 (61), 115 (16), 172 (12), 228 (24), 288 (22), 374 (5), and 433 (1, $M^{\cdot+}$).

Anal. Calcd for $C_{20}H_{43}NO_5Si_2$ (433.74): C, 55.38; H, 9.99; N, 3.23. Found: C, 55.25; H, 9.91; N, 3.45.

1-*O*-Acetyl-4-aza-2,3,5-trideoxy-3-*C*-methyl-5-*C*-phenyl-α-DL-*glycero*-pento-1,4-furanose (α-9). - Substituting hydroxylamine **2** (2 g, 16.2 mmol) to hydroxylamine **1** in the procedure describing the preparation of **7**, gave **α-9** (1 g, 26%) and **β-9** (0.99 g, 26%), mp 56.3-56.4 °C; R_F 0.37 (2:3 ether/hexane); λ_{max}^{EtOH} 207

nm (ε 8322); ν_{max}^{KBr} 1737 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 7.32 (*m*, 5 H, Ar), 4.08 and 3.93 (2 *d*, 2xH, J_{AB} = 14 Hz, NCH_2Ph), 2.06 (*s*, 3 H, OAc), and 1.20 (*d*, 3 H, $J_{3,Me}$ = 6.5 Hz, MeC_3). EIMS: m/z (%) 65 (15), 91 (100), 106 (12), 123 (20), 134 (10), 139 (9), and 235 (7, $M^{\cdot+}$).

Anal. Calcd for $C_{13}H_{17}NO_3$ (235.29): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.37; H, 7.19; N, 6.06.

1-*O*-Acetyl-4-aza-2,3,5-trideoxy-3-*C*-methyl-5-*C*-phenyl-β-DL-*glycero*-pento-1,4-furanose (β-9). - Prepared as described for **α-9**: syrup, R_F 0.30 (2:3 ether/hexane); λ_{max}^{EtOH} 207 nm (ε 9573); ν_{max}^{film} 1749 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 7.35 (*m*, 5 H, Ar), 4.18 and 4.09 (2 *d*, 2xH, J_{AB} = 14 Hz, NCH_2Ph), 2.08 (*s*, 3 H, OAc), and 1.18 (*d*, 3 H, $J_{3,Me}$ = 6.5 Hz, MeC_3). EIMS: *m/z* (%) 65 (11), 91 (100), 106 (8), 123 (14), 150 (9), 193 (10), and 235 (11, $M^{\cdot+}$).

Anal. Calcd for $C_{13}H_{17}NO_3$ (235.29): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.27; H, 7.37; N, 6.05.

***(1RS)*-1,6-Di-*O*-acetyl-4-aza-2,3,5-trideoxy-hexo-1,4-furanose (10).** - To a solution of **6** (1.06 g, 3.66 mmol) in tetrahydrofurane (15 mL), tetrabutylammonium fluoride (1 equivalent) was added and the mixture stirred at 20 °C until complete de-*O*-silylation (0.5-2 h, TLC). After concentration, the residue was passed through a short silice gel column (1:15 $MeOH/CH_2Cl_2$, concentrated, and dissolved in a mixture of pyridine (4 mL) and acetic anhydride (1 mL). After 3 h stirring at 20 °C, the excess of reagents was removed by codistillation with toluene and the residue submitted to a flash column chromatography (4:1 ether/hexane) followed by a vacuum distillation to afford **10** (0.54 g, 68%) as a syrup: bp 108 °C/6.10^{-2} mmHg; R_F 0.2 (1:35 $MeOH/CH_2Cl_2$); λ_{max}^{EtOH} 202 nm (ε 597); ν_{max}^{film} 1739 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 4.28 (*t*, 2 H, 2xH-C_6), 3.12 (*t*, 2 H, $J_{5,6}$ = 6 Hz, 2xH-C_5), and 2.08 (*s*, 6 H, 2xOAc). EIMS: *m/z* (%) 59 (18), 72 (17), 87 (15), 102 (100), 115 (32), 144 (19), 157 (11), 175 (13), and 217 (10, $M^{\cdot+}$).

Anal. Calcd for $C_8H_{15}NO_5$ (217.22): C, 49.76; H, 6.96; N, 6.45. Found: C, 49.55; H, 7.01; N, 6.44.

1,6-Di-*O*-acetyl-4-aza-2,3,5-trideoxy-3-*C*-methyl-α-DL-*glycero*-hexo-1,4-furanose (α-11). - The procedure described for the preparation of **10**, applied to **α-7** (0.35 g, 1.15 mmol) afforded **α-11** (0.18 g, 68%): bp 110 °C/2.10^{-1} mmHg; R_F 0.3 (4:1 ether/hexane); λ_{max}^{EtOH} 204 nm (ε 2256); ν_{max}^{film} 1741 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 4.36 and 4.26 (2 *ddd*, 2x1 H, $J_{6a,6b}$ = 12 Hz, 2xH-C_6), 3.19 (*ddd*, 1 H, $J_{5b,6a}$ = 7 Hz, $J_{5b,6b}$ = 5.5 Hz, Hb-C_5), 2.86 (*dt*, 1 H, $J_{5a,5b}$ = 13 Hz, $J_{5a,6a}$ = $J_{5a,6b}$ = 5.5 Hz, Ha-C_5), 2.10 and 2.08 (2 *s*, 2x3 H, 2xOAc), and 1.22 (*d*, 3 H, $J_{3,Me}$ = 5.5 Hz, Me-C_3).

EIMS: *m/z* (%) 56 (43), 59 (29), 71 (35), 86 (40), 87 (100), 128 (47), 130 (69), 154 (30), 158 (45), 172 (49), and 231 (14, $M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{17}NO_5$ (231.25): C, 51.94; H, 7.41; N, 6.06. Found: C, 51.68; H, 7.40; N, 6.03.

1,6-Di-*O*-acetyl-4-aza-2,3,5-trideoxy-3-*C*-methyl-β-DL-*glycero*-hexo-1,4-furanose (β-11). - The procedure described for the preparation of **10**, applied to **β-7** (0.4 g, 1.33 mmol) afforded **β-11** (0.18 g, 56%): bp 108 °C/2.10^{-1} mmHg; λ_{max}^{EtOH} 204 nm (ε 1986); ν_{max}^{film} 1741 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 60 °C): δ 4.38 and 4.29 (2 *dt*, 2x1 H, $J_{6a,6b}$ = 11.5 Hz, 2xH-C_6), 3.05 (*t*, 2 H, $J_{5,6}$ = 5.75 Hz, 2xH-C_5), 2.09 (*s*, 6 H, 2xOAc), 1.20 (*d*, 3 H, $J_{3,Me}$ = 6 Hz, MeC_3). EIMS: *m/z* (%) 56 (31), 59 (26), 71 (36), 86 (25), 87 (56), 116 (100), 158 (24), 171 (10), and 231 (6, $M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{17}NO_5$ (231.25): C, 51.94; H, 7.41; N, 6.06. Found: C, 51.69; H, 7.36; N, 6.00.

3-*C*-Acetoxymethyl-1,6-di-*O*-acetyl-4-aza-2,3,5-trideoxy-α (and β)-DL *glycero*-hexo-1,4-furanoses (α-12) and (β-12). - The procedure described for the preparation of **10**, except for the final vacuum distillation, was applied to a 4:1 mixture of **α-8** and **β-8** (2.6 g, 6 mmol) to afford a 6:1 mixture of **α-12** and **β-12** (0.63 g, 37%): syrup, R_F 0.27 (9:1 ether/hexane); λ_{max}^{EtOH} 207 nm (ε 9168); ν_{max}^{film} 1731 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 55 °C): δ 4.19 (*dd*, 1 H, $J_{3,3'a}$ = 7 Hz, $J_{3'a,3'b}$ = 11.5 Hz, Ha-$C_{3'}$, **α-12**), 3.22 (*m*, 1 H, Hb-C_5), 3.08 (*dt*, 1 H, $J_{5a,6}$ = 5.5 Hz, $J_{5a,5b}$ = 13.5 Hz, Ha-C_5, **α-12**), 2.10 and 2.08 (2 *s*, 12 H, 4xOAc, **α-12** and **β-12**). EIMS: *m/z* (%) 56 (11), 59 (14), 69 (56), 87 (100), 102 (5), 114 (10), 156 (5), 174 (29), 216 (11), and 289 (1, $M^{\cdot+}$).

Anal. Calcd for $C_{12}H_{19}NO_7$ (289.29): C, 49.82; H, 6.62; N, 4.84. Found: C, 49.80; H, 6.62; N, 4.74.

Nucleosidation reactions. A mixture of thymine (1.2 equiv.), ammonium sulfate (15 mg, 0.113 mmol) and hexamethyldisilazane (10 mL) was kept at 130 °C under nitrogen for 15 h. After concentration of the reaction mixture, a solution of one of the acetoxyisoxazolidines **9-12** (1 equiv.) in dichloromethane (10 mL) and trimethylsilyl triflate (1 equiv,) were added. After 3 h stirring at 25 °C, the reaction mixture was partitioned between cold dichloromethane (20 mL) and saturated aqueous sodium bicarbonate (10 mL). The organic phase, washed (water, 5 mL), dried ($MgSO_4$) was submitted to a flash column chromatography (1:1 ethyl acetate/ether) to afford nucleoside analogues **13-16**.

1-[(1*RS*)-6-*O*-Acetyl-4-aza-2,3,5-trideoxy-hexo-1,4-furanosyl]thymine (13). The nucleosidation reaction, performed on **10** (0.46 g, 2.11 mmol) afforded **13** (0.31 g, 52%): mp 140-141 °C; R_F 0.35 (1:1 ethyl acetate/ether); λ_{max}^{EtOH} 208 nm (ε 7476) and 268 (ε 7161); ν_{max}^{KBr} 1730, 1698, and 1666 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$,

60 °C): δ 7.69 (*q*, 1H, H-C_6), 4.34 (*ddd*, 1 H, Hb-$C_{6'}$), 4.27 (*dt*, 1 H, $J_{6'a,6'b}$ = 11.5 Hz, Ha-$C_{6'}$), 3.19 (*ddd*, 1 H, $J_{5'b,6'a}$ = 5 Hz, $J_{5'b,6'b}$ = 7 Hz, Hb-$C_{5'}$), 3.09 (*dt*, 1 H, $J_{5'a,5'b}$ = 14 Hz, $J_{5'a,6'a}$ = $J_{5'a,6'b}$ = 5 Hz, Ha-$C_{5'}$), 2.03 (*s*, 3 H, OAc), and 1.89 (*d*, 3 H, $J_{6,Me}$ = 1 Hz, Me (thym.)). EIMS: *m/z* (%) 55 (28), 72 (16), 87 (27), 122 (100), 165 (88), 210 (12), 283 (10, $M^{\cdot+}$).

Anal. Calcd for $C_{12}H_{17}N_3O_5$ (283.29): C, 50.88; H, 6.05; N, 14.83. Found: C, 50.84; H, 6.03; N, 14.82.

1-[6-*O*-Acetyl-4-aza-2,3,5-trideoxy-3-*C*-methyl-α-DL-*glycero*-hexo-1,4-furanosyl]thymine (α-14). The nucleosidation reaction performed on either **α-11** or **β-11** (0.2 g, 0.86 mmol) afforded **α-14** (0.12 g, 45%) and **β-14** (0.06 g, 22%) which were recrystallized in ether: mp 122-123 °C; R_F 0.42 (1:1 ethyl acetate/ether); λ_{max}^{EtOH} 208 nm (ε 15757) and 268 (ε 13974); ν_{max}^{KBr} 1744, 1711, 1650 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 55 °C): δ 8.32 (*bs*, 1 H, NH), 7.69 (*q*, 1 H, H-C_6), 4.43 (*ddd*, 1 H, Hb-$C_{6'}$), 4.33 (*dt*, 1 H, $J_{6'a,6'b}$ = 11.5 Hz, Ha-$C_{6'}$), 3.27 (*ddd*, 1 H, $J_{5'b,6'a}$ = 5.5 Hz, $J_{5'b,6'b}$ = 8 Hz, Hb-$C_{5'}$), 2.80 (*dt*, 1 H, $J_{5'a,6'}$ = 4.5 Hz, $J_{5'a,5'b}$ = 14 Hz, Ha-$C_{5'}$), 2.09 (*s*, 3 H, OAc), 2.00 (*d*, 3 H, $J_{6,Me}$ = 1 Hz, Me(thym.), and 1.22 (*d*, 3 H, $J_{3',Me}$ = 6 Hz, Me-$C_{3'}$). EIMS: *m/z* (%) 56 (37), 87 (43), 136 (72), 179 (100), 224 (10), and 297 (3, $M^{\cdot+}$).

Anal. Calcd for $C_{13}H_{19}N_3O_5$ (297.31): C, 52.52; H, 6.44; N, 14.13. Found: C, 52.48; H, 6.43; N, 14.21.

1-[6-*O*-Acetyl-4-aza-2,3,5-trideoxy-3-*C*-methyl-β-DL-*glycero*-hexo-1,4-furanosyl]thymine (β-14). Obtained as described for the preparation of **α-14**: mp 134-135 °C; R_F 0.34 (1:1 ethyl acetate/ether); λ_{max}^{EtOH} 209 nm (ε 10500) and 266 (9300); ν_{max}^{KBr} 1739, 1708, 1661 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 55 °C): δ 8.00 (*bs*, NH), 7.48 (*s*, 1 H, H-C_6), 4.40 (*dt*, 1 H, Hb-$C_{6'}$), 4.30 (*dt*, 1 H, $J_{6'a,6'b}$ = 11.5 Hz, Ha-$C_{6'}$), 3.18 (*dt*, 1 H, $J_{5'b,6'a}$ = $J_{5'b,6'b}$ = 5.5 Hz, Hb-$C_{5'}$), 3.02 (*dt*, 1 H, $J_{5'a,5'b}$ = 13.5 Hz, $J_{5'a,6'a}$ = $J_{5'a,6'b}$ = 6 Hz, Ha-$C_{5'}$), 2.09 (*s*, 3 H, OAc), 1.99 (*s*, 3 H, Me(thym.)), and 1.18 (*d*, 3 H, $J_{3',Me}$ = 6 Hz, Me-$C_{3'}$). EIMS: *m/z* (%) 56 (36), 60 (22), 70 (15), 87 (58), 103 (14), 109 (13), 136 (70), 146 (10), 172 (25), 179 (100), and 297 (2, $M^{\cdot+}$).

Anal. Calcd for $C_{13}H_{19}N_3O_5$ (297.31): C, 52.52; H, 6.44; N, 14.13. Found: C, 52.27; H, 6.32; N, 13.98.

1-[6-*O*-Acetoxy-3-*C*-acetoxymethyl-2,3,5-trideoxy-α (and β)-DL-*glycero*-hexo-1,4-furanosyl]thymine (α-15) and (β-15). The nucleosidation reaction performed on an anomeric mixture of **12** (0.3 g, 1 mmol) afforded a 7:4 mixture of **α-15** and **β-15** (0.27 g, 73%) as a solid: mp 124-126 °C; R_F 0.31 (1:20 MeOH/CH_2Cl_2); λ_{max}^{EtOH} 207 nm (ε 13944) and 267 (9558); ν_{max}^{KBr} 1741, 1710, and 1651 (C=O) cm^{-1}. EIMS: *m/z* (%) 55 (19), 69 (27), 84 (12), 87 (100), 109 (5), 127 (58), 156 (14), 195 (11), 230 (9), 237 (4), and 355 (2, $M^{\cdot+}$).

^{1}H NMR ($CDCl_3$, 25 °C) of **α-15**: δ 8.16 (*bs*, 1 H, NH), 7.70 (*q*, 1 H, H-C_6), 4.42 (*ddd*, 1 H, $J_{5'a,6'b}$ = 4 Hz, $J_{5'b,6'b}$ = 8.5 Hz, $J_{6'a,6'b}$ = 11.5 Hz, Hb-$C_{6'}$), 4.32 (*dd*, 1 H, $J_{3',3''b}$ = 3.5 Hz, Hb-$C_{3''}$), 4.30 (*m*, 1 H, Ha-$C_{6'}$), 4.06 (*dd*, 1 H, $J_{3',3''a}$ = 5 Hz, $J_{3''a,3''b}$ = 11.5 Hz, Ha-$C_{3''}$), 3.41 (*ddd*, 1 H, $J_{5'b,6'a}$ = 5 Hz, $J_{5'b,6'b}$ = 8 Hz, Hb-$C_{5'}$), 3.00 (*dt*, 1 H, $J_{5'a,5'b}$ = 14 Hz, $J_{5'a,6'}$ = 4 Hz, Ha-$C_{5'}$), 2.10 and 2.08 (2 *s*, 2x3 H, 2xOAc), and 1.97 (*d*, 3 H, $J_{6,Me}$ = 1 Hz, Me (thym.)).

^{1}H NMR ($CDCl_3$, 25 °C) of **β-15**: δ 8.50 (*bs*, 1 H, NH), 7.43 (*s*, 1 H, H-C_6), 4.35 (*m*, 2 H, 2xH-$C_{6'}$), 4.21 (*d*, 2 H, $J_{3',3''}$ = 5.2 Hz, 2xH-$C_{3''}$), 3.30 (*dt*, 1 H, $J_{5'b,6'}$ = 5.5 Hz, Hb-$C_{5'}$), 3.19 (*dt*, 1 H, $J_{5'a,5'b}$ = 14 Hz, $J_{5'a,6'}$ = 5.5 Hz, Ha-$C_{5'}$), 2.12 (*s*, 6 H, 2xOAc), and 1.98 (*s*, 3 H, Me (thym.).

Anal. Calcd for $C_{15}H_{21}N_3O_7$ (355.35): C, 50.70; H, 5.96; N, 11.82. Found: C, 50.53; H, 6.03; N, 11.74.

1[4-Aza-2,3,5-trideoxy-3-*C*-methyl-5-*C*-phenyl-α-DL-*glycero*-pento-1,4-furanosyl]thymine (α-16). The nucleosidation reaction performed either on **α-9** or **β-9** (0.2 g, 0.85 mmol) afforded **α-16** (0.165 g, 63%) and **β-16** (0.055 g, 21%) which were recrystallized in acetone/hexane: mp 183-184 °C; R_F 0.47 (1:15 MeOH/CH_2Cl_2; λ_{max}^{EtOH} 208 nm (ε 14500) and 268 (7800); ν_{max}^{KBr} 1712 and 1664 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 60 °C): δ 8.92 (*bs*, 1 H, NH), 7.40 (*m*, 5 H, Ar), 7.35 (*bs*, 1 H, H-C_6), 4.18 and 3.22 (2 *d*, 2x1 H, J_{AB} = 14 Hz, NCH_2Ph), 1.79 (*d*, 3 H, $J_{6,Me}$ = 1 Hz, Me (thym.)), and 1.27 (*d*, 3 H, $J_{3',Me}$ = 6 Hz, Me-$C_{3'}$). EIMS: *m/z* (%) 55 (15), 65 (15), 77 (5), 91 (100), 106 (7), 136 (14), 176 (10), 179 (21), and 301 (0.5, $M^{\cdot+}$).

Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301.35): C, 63.77; H, 6.36; N, 13.94. Found: C, 63.65; H, 6.37; N, 13.78.

1[4-Aza-2,3,5-trideoxy-3-*C*-methyl-5-*C*-phenyl-β-DL-*glycero*-pento-1,4-furanosyl]thymine (β-16). Obtained as described under **α-16**: mp 175.7-177.2 °C; R_F 0.37 (1:15 MeOH/CH_2Cl_2); λ_{max}^{EtOH} 208 nm (ε 13300) and 266 (7100); ν_{max}^{KBr} 1703 and 1667 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 55 °C): δ 8.07 (*bs*, 1 H, NH), 7.38 (*m*, 5 H, Ar), 7.20 (*bs*, 1 H, H-C_6), 4.10 and 3.96 (2 *d*, 2x1 H, J_{AB} = 14 Hz, NCH_2Ph), 1.81 (*s*, 1 H, Me (thym.)), and 1.23 (*d*, 3 H, $J_{3',Me}$ = 6 Hz, Me-$C_{3'}$). EIMS: m/z (%) 55 (21), 65 (19), 79 (5), 91 (100), 106 (11), 134 (11), 136 (21), 147 (7), 176 (19), 179 (21), 217 (2), and 301 (0.7, $M^{\cdot+}$).

Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301.35): C, 63.77; H, 6.36; N, 13.94. Found: C, 63.65; H, 6.38; N, 13.82.

De-*O*-acetylation of compounds 13-15. A solution of one of the compounds **13-15** in methanol (10 mL) was saturated with gazeous ammoniac stirred at 25 °C for 24 h, then concentrated and the residue submitted to a flash column

chromatography [1:15 methanol/ether (**13-14**) or 1:5 methanol/ether (**15**)], then recrystallized.

1-[(*1RS*)-4-Aza-2,3,5-trideoxy-hexo-1,4-furanosyl]thymine (17). The de-*O*-acetylation reaction applied to **13** (130 mg, 0.46 mmol) afforded, after recrystallization (MeOH), **17** (95 mg, 86%): mp130-131 °C; R_F 0.26 (1:15 MeOH/CH_2Cl_2); λ_{max}^{EtOH} 208 nm (ε 9650); ν_{max}^{KBr} 3416 (OH), and 1700 (broad, C=O) cm^{-1}. ^1H NMR (CD_3OD, 60 °C): δ 7.75 (*q*, 1 H, H-C_6 (thym.)), 3.86 (*m*, 2 H, $J_{6'a,6'b}$ = 11 Hz, 2xH-$C_{6'}$), 3.01 (~*t*, 2 H, $J_{5',6'}$ = 6 Hz, 2xH-$C_{5'}$), and 1.88 (*d*, 3 H, $J_{6,Me}$ = 1.5 Hz, Me (thym.). EIMS: *m/z* (%) 55 (57), 80 (15), 122 (100), 165 (91), 210 (25), and 241 (13, $M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{15}N_3O_4$ (241.25): C, 49.79; H, 6.27; N, 17.42. Found: C, 49.77; H, 6.26; N, 17.36.

1-(4-Aza-2,3,5-trideoxy-3-*C*-methyl-α-DL-*glycero*-hexo-1,4-furanosyl)thymine (α-18). The de-*O*-acetylation reaction performed on **α-14** (155 mg, 0.52 mmol) afforded, after recrystallization (acetone/hexane) **α-18** (110 mg, 83%): mp 145-146 °C; R_F 0.36 (1:15 MeOH/ether); λ_{max}^{EtOH} 208 nm (ε 4471) and 268 (3663); ν_{max}^{KBr} 3478 (OH), and 1677 (broad, C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ 8.75 (*bs*, 1 H, NH), 7.68 (*q*, 1 H, H-C_6), 3.88 (*m*, 2 H, $J_{6'a,6'b}$ = 12 Hz, H_2-$C_{6'}$), 3.19 (*ddd*, 1 H, $J_{5'b,6'a}$ = 4.5 Hz, $J_{5'b,6'b}$ = 8 Hz, Hb-$C_{5'}$), 2.82 (*ddd*, 1 H, $J_{5'a,5'b}$ = 13.5 Hz, $J_{5'a,6'a}$ = 5 Hz, $J_{5'a,6'b}$ = 3.2 Hz, Hb-$C_{5'}$), 2.19 (*t*, 1 H, $J_{OH,6'}$ = 5.7 Hz, OH), 1.99 (*d*, 3 H, $J_{6,Me}$ = 1.2 Hz, Me (thym.)), and 1.22 (*d*, 3 H, $J_{3',Me}$ = 6 Hz, Me-$C_{3'}$). EIMS: *m/z* (%) 55 (100), 71 (19), 94 (10), 104 (26), 136 (67), 153 (7), 179 (82), 224 (18), and 255 (5, $M^{\cdot+}$).

Anal. Calcd for $C_{11}H_{17}N_3O_4$ (255.28): C, 51.76; H, 6.71; N, 16.46. Found: C, 51.66; H, 6.67; N, 16.46.

1-(4-Aza-2,3,5-trideoxy-3-*C*-methyl-β-DL-*glycero*-hexo-1,4-furanosyl)thymine (β-18). The de-*O*-acetylation reaction performed on **β-14** (50 mg, 0.17 mmol) afforded, after recrystallization (acetone/hexane), **β-18** (33 mg, 76%): mp 144-145 °C; R_F 0.22 (1:15 MeOH/ether); λ_{max}^{EtOH} 208 nm (ε 6728) and 266 (5671); ν_{max}^{KBr} 3477 (OH), 1691 and 1658 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 60 °C): δ 8.32 (*bs*, 1 H, NH), 7.39 (*bs*, 1 H, H-C_6), 3.85 (*bq*, 2 H, 2xH-$C_{6'}$), 3.12 (*dt*, 1 H, $J_{5'b,6'}$ = 5.5 Hz, Hb-$C_{5'}$), 2.94 (*dt*, 1 H, $J_{5'a,5'b}$ = 13.5 Hz, $J_{5'a,6'}$ = 5.2 Hz, Ha-$C_{5'}$), 2.12 (*t*, 1 H, $J_{OH,6'}$ = 5.5 Hz, OH), 1.94 (*d*, 3 H, $J_{6,Me}$ = 1 Hz, Me (thym.)), and 1.20 (*d*, 3 H, $J_{3',Me}$ = 6 Hz, Me-$C_{3'}$). EIMS: *m/z* (%) 56 (65), 60 (77), 70 (22), 72 (12), 80 (20), 104 (41), 109 (15), 126 (8), 130 (35), 136 (79), 179 (100), 224 (22), and 255 (5, $M^{\cdot+}$).

Anal. Calcd for $C_{11}H_{17}N_3O_4$ (255.28): C, 51.76; H, 6.71; N, 16.46. Found: C, 51.47; H, 6.73; N, 16.17.

1-[4-Aza-2,3,5-trideoxy-3-*C*-hydroxymethyl-α (and β)-DL-*glycero*-hexo-1,4-furanosyl]thymine (α-19 and β-19). The de-*O*-acetylation reaction performed on **(α + β)-15** (288 mg, 0.81 mmol) afforded **α-19** (120 mg, 55%) and **β-19** (55 mg, 24%).

Properties of **α-19**: mp 147.5-148.5 °C (from acetone/hexane); R_F 0.38 (1:5 MeOH/ether); λ_{max}^{EtOH} 206 nm (ε 6239) and 268 (4560); ν_{max}^{KBr} 3410 (OH), 1715 and 1657 (C=O) cm^{-1}. ^1H NMR (CD_3OD, 25 °C): δ 7.99 (*q*, 1 H, H-C_6), 3.87 (*ddd*, 1 H, $J_{6'a,6'b}$ = 11 Hz, Hb-$C_{6'}$), 3.72 (*dd*, 1H, $J_{3',3''b}$ = 3 Hz, Hb-$C_{3''}$), 3.70 (*m*, 1 H, Ha-$C_{6'}$), 3.61 (*dd*, 1 H, $J_{3',3''a}$ = 4 Hz, $J_{3''a,3''b}$ = 12 Hz, Ha-$C_{3''}$), 3.29 (*ddd*, 1 H, $J_{5'b,6'a}$ = 5.3 Hz, $J_{5'b,6'b}$ = 9 Hz, Hb-$C_{5'}$); 2.82 (*dt*, 1 H, $J_{5'a,5'b}$ = 13.5 Hz, $J_{5'a,6'}$ = 3.7 Hz, Ha-$C_{5'}$), and 1.89 (*d*, 3 H, $J_{6,Me}$ = 1 Hz, Me (thym.)).

Properties of **β-19**: mp 147-148 °C (from acetone/hexane); R_F 0.23 (1:5 MeOH/ether); λ_{max}^{EtOH} 208 nm (ε 4069) and 266 (2831); ν_{max}^{KBr} 3446 (OH), 1710 and 1678 (C=O) cm^{-1}. ^1H NMR (CD_3OD, 25 °C): δ 7.62 (*q*, 1 H, H-C_6), 3.73 (*m*, 2 H, $J_{6'a,6'b}$ = 11.5 Hz, 2xH-$C_{6'}$), 3.68 (*d*, 2 H, 2xH-$C_{3''}$), 3.26 (*ddd*, 1 H, $J_{5'b,6'a}$ = 5 Hz, $J_{5'b,6'b}$ = 7 Hz, Hb-$C_{5'}$), 3.05 (*dt*, 1 H, $J_{5'a,5'b}$ = 13 Hz, $J_{5'a,6'a}$ =5.2 Hz, $J_{5'a,6'b}$ = 5.2 Hz, Ha-$C_{5'}$), and 1.90 (*d*, 3 H, $J_{6,Me}$ = 1,2 Hz, Me (thym.)).

EIMS: *m/z* (%) 55 (97), 69 (30), 84 (28), 126 (100), 145 (11), 240 (13), and 271 (3, M^{+}).

Anal. Calcd for $C_{11}H_{17}N_3O_5$ (271.28): C, 48.70; H, 6.32; N, 15.49. Found: C, 48.70; H, 6.32; N, 15.37.

1-[(*1RS*)-4-Aza-2,3-dideoxy-4-phenyl-tetro-1,4-furanosyl]thymine (20). A mixture of 1-vinylthymine[18] (190 mg, 1.25 mmol), *N*-phenylhydroxylamine (236 mg, 2.16 mmol), paraformaldehyde (72 mg, 2.4 mmol) and ethanol (5 mL) was stirred at 70 °C for 24 h. The reaction mixture was then concentrated and the residue submitted to a flash column chromatography (5:1 ethyl acetate/ hexane) and recrystallized (ethyl acetate/hexane) to give **20** (150 mg, 44%): mp 165.2-166 °C; R_F 0.27 (5:1 ethyl acetate/hexane); λ_{max}^{EtOH} 205 nm (ε 13665), 245 (6913), and 264 (7389); ν_{max}^{KBr} 1775 (broad C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ 8.49 (*bs*, 1 H, NH), 7.57 (*q*, 1 H, H-C_6), 7.35 and 7.10 (2 *m*, 5 H, Ph), and 1.93 (*d*, 3 H, $J_{6,Me}$ = 1.5 Hz, Me (thym.)). EIMS: *m/z* (%) 55 (41), 65 (18), 77 (55), 93 (42), 106 (100), 126 (60), 147 (42), 165 (23), and 273 (12, M^{+}).

Anal. Calcd for $C_{14}H_{15}N_3O_3$ (273.29): C, 61.53; H, 5.53; N, 15.38. Found: C, 61.36; H, 5.49; N, 15.29.

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