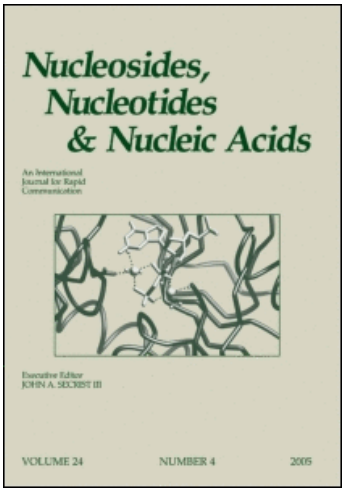

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ANTI-HIV DERIVATIVES OF 1-(2,3-DIDEOXY-3-*N*-HYDROXYAMINO-β-D-*THREO*-PENTOFURANOSYL)THYMINE

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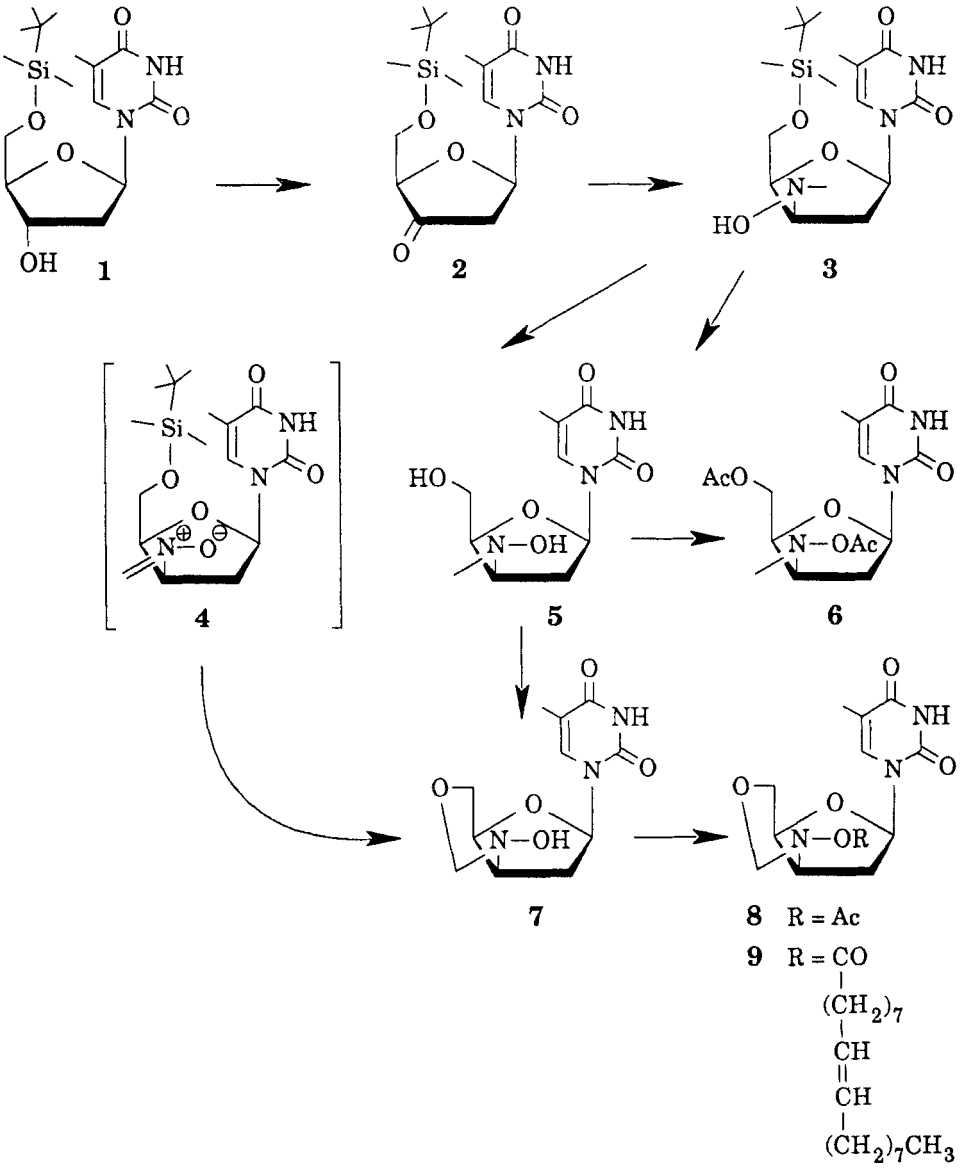
Abstract: Representative examples of the title compounds including bicyclic analogs (**7-9**) in which a perhydro-1,3-oxazine is *ortho*-fused to the furanose ring, have been prepared in good to excellent yields. Compounds **5** and **7** showed marked activity against HIV-1 and HIV-2 replication in CEM cells (50% inhibitory concentration: 0.80-4.3μg/mL). Their di-*O*-acetylated (**6**) and mono-*O*-acetylated (**8**) derivatives were considerably less effective. To the best of our knowledge, these β-D-*threo* anti-HIV nucleoside analogs constitute the first examples of anti-HIV active nucleosides bearing this configuration.

Typically, nucleoside analogs exhibiting anti-HIV activity belong either to the β-D-*glycero* series (no substituent on either position 2' and 3', e.g. ddI) or to the β-D-*erythro* family (one substituent on the α face, e.g. AZT).[1] To the best of our knowledge, these β-D-*threo* anti-HIV nucleoside analogs we report here, some of which have been the object of a preliminary communication,[2] constitute the first examples of active nucleosides bearing this configuration.

Compound **1**[3] was obtained following one of the Ogilvies's procedures[3] but with an improved yield (Scheme 1). Its oxidation (pyridinium dichromate) to **2** proceeded easily in 74% yield. The ketothymidine derivative **2** is not very stable, easily β-eliminating thymine, but the corresponding *N*-methylnitrone was found to be even less stable. When formed by reacting **2** with methylhydroxylamine, it was not isolated but directly reduced (sodium cyanoborohydride) to **3**. The reaction was



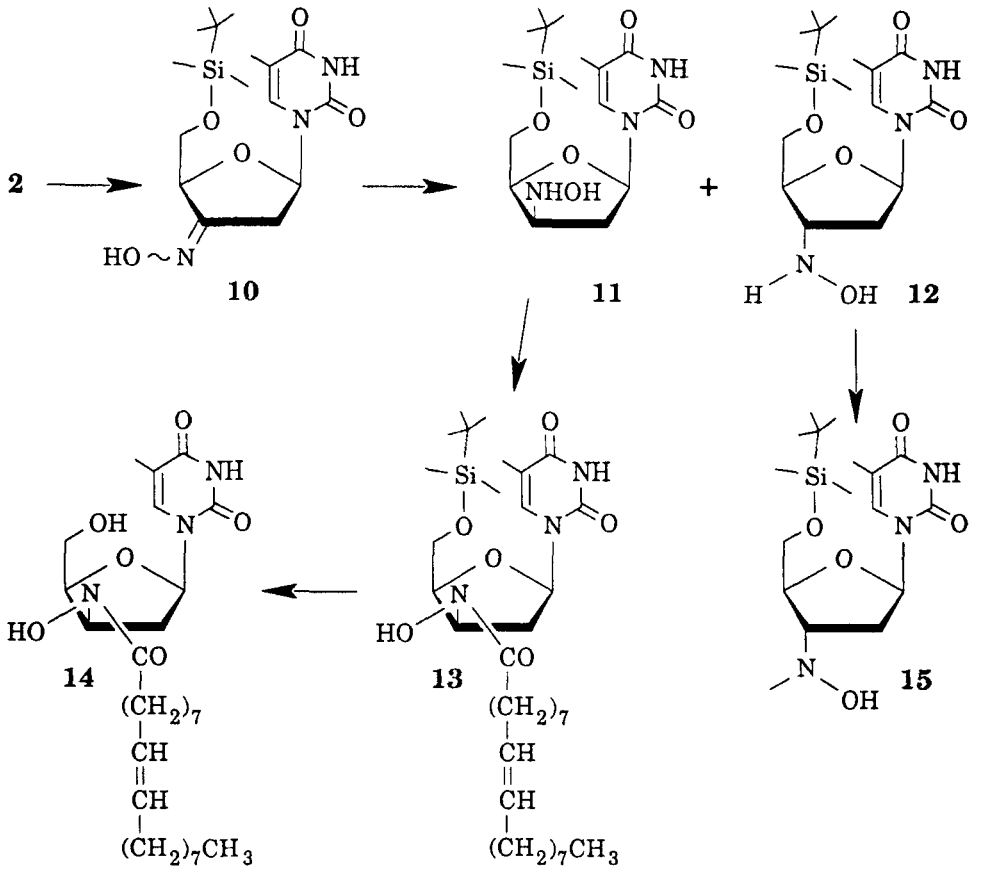
Scheme 1

stereospecific, proceeding from the α face, and **3** was the only compound isolated (86%). The β-D-*threo* configuration of **3** was most safely assigned from the structure of **7** (*vide infra*). Upon oxidation by a variety of oxidizing agents (lead dioxide, periodates or quinones), the most satisfactory being 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), **3** led to the "methylenic nitrone" **4**, structure of which was established by spectroscopy (^{1}H-NMR: 6.40 and 6.59, 2 *d*, *J* = 7.0 Hz; CH_2=N; MS 384 ($M^{\cdot+}$), 368 ($M^{\cdot+}$ - O). Upon de-*O*-silylation, **4** underwent intramolecular nucleophilic cyclization to **7** which was more easily obtained from **3** by successive de-*O*-silylation to **5**, then oxidation and spontaneous cyclization. Compound **5** was di-*O*-acetylated to **6**, whereas **7** could be monoacylated to **8** and **9**.

Oxime **10** was prepared in 80% yield from **2** and obtained as a 2:1 *E*/*Z* mixture. Sodium cyanoborohydride reduction of **10** was only stereoselective leading to a 4:1 resolvable mixture of **11** and **12** (Scheme 2). Upon treatment with oleoyl chloride, **11** reacted regiospecifically to give only the *N*-acylated compound **13** which was de-*O*-silylated to **14**. The β-D-*erythro* isomer **12** was *N*-methylated by reductive alkylation to **15**, the 3'-epimer of **3**.

^{1}H-NMR data concerning the ring protons of compounds bearing a sp^3 C-3' carbon atom are presented in TABLES 1 and 2. The diastereotopic protons borne by C-2' have been assigned as belonging to the α (2'α) or β (2'β) face, tentatively in the case of some D-*threo* nucleosides. It is clear from TABLE 2 that members of the three distinct structural families exhibit specific spectroscopic features. The monocyclic β-D-*erythro* compounds (**1**, **12** and **15**) are unambiguously characterized by having both small $J_{2'\alpha,3'}$ and $J_{3',4'}$ values (2-3.5 Hz, conformation close to $^0T_1$). For the monocyclic β-D-*threo* nucleosides (**3-6**, **11**, **13**, and **14**) all $J_{1',2'}$, $J_{2',3'}$ and $J_{3',4'}$ have intermediate values comprised between 5 and 9 Hz, except for $J_{2'\alpha,3'}$ of **4** (3.0 Hz) owing to the electron withdrawing effect of the 3'-substituent. This is not too far from the ^{2}E conformation. The bicyclonucleosides (**7-9**) exhibit a characteristic null value of $J_{2'\beta,3'}$.

The perhydrooxazine ring of the bicyclonucleosides **7-9** adopts a conformation intermediate between a $^{O5'}C_{3'}$ chair and a $^{O,N}F$ flattened[4] chair as shown by the two small $J_{4',5'}$ couplings and a small ^4J W coupling between $H_{pro\text{-}R}$-(N-CH_2O) and $H_{pro\text{-}S}$-5' and not the alternative $^{3'}C_{O5'}$ form. This conformation is the same as that previously established[5] for uridine



Scheme 2

bicyclonucleosides of the same type. This conformation of the perhydrooxazine ring is also confirmed by that of the furanose part which is tightly dependent upon that of the six-membered ring, the only possible flexibility for a given conformation of the perhydrooxazine ring being limited to the 1' position. For **7**, bearing a free *N*-hydroxy group, the conformation of the furanose ring is close to $^{3'}E$. Upon acylation to **8** or **9**, the base moves a little away from N-3' and the furanose adopts a conformation closer to $E_{4'}$. As compounds **7** and **8** represent relatively rigid anti-HIV nucleosides, potentially useful for receptor mapping, their NMR time-averaged structural features were established as precisely as possible. The *(S)* configuration

TABLE 1. Furanose Ring Protons Chemical Shifts for the β-D-*threo* and β-D-*erythro* Nucleosides (200 MHz ^{1}H-NMR, $CDCl_3$, 20 °C, δ values).

Cmpd	H-1'	Hα-2'	Hβ-2'	H-3'	H-4'	Ha-5'	Hb-5'
1	6.40	2.38	2.10	4.48	4.05	3.87	3.90
3	6.11	2.41	2.09	3.50	4.10	4.10	3.90
4	6.22	2.69	2.80	4.70	3.9-4.1	3.9-4.1	3.9-4.1
5[a]	6.00	2.12	1.99	3.33	3.99	~3.70	~3.70
6	6.17	2.10	2.61	3.75	4.30	4.38	4.21
6[a]	6.08	2.15	2.40	3.78	~4.20	~4.90	~4.10
7	6.08	2.42	2.85	3.23	4.15	4.30	3.78
8	6.41	2.56	2.18	3.47	4.08	4.28	3.78
9	6.42	2.54	2.15	3.45	4.07	4.28	3.75
11	6.12	2.02	2.61	3.88	4.0-4.2	4.0-4.2	4.0-4.2
12	6.40	2.40	2.05	3.80	4.20	3.98	3.80
13	6.12	2.18	2.72	5.44	3.98	3.86	4.12
14[b]	5.45	2.20	2.58	5.12	4.03	3.62	3.62
15[c]	6.21	2.66	1.93	3.40	4.23	3.80	4.00

[a] DMSO-d_6. [b] DMSO-d_6, 100 °C. [c] 55 °C.

(equatorial position) of the most stable invertomer was deduced from the small absolute value of the geminal coupling of the neighbouring methylene group (7 Hz). It has long been known[6] that the presence of a lone pair of electrons syn- or antiperiplanar to a C-H bond of a vicinal methylene impart a small positive increment to the $^2J_{CH2}$ value. The comparison with $^2J_{5'a,5'b}$ (13 Hz, one antiperiplanar lone pair on oxygen) established the presence of an extra antiperiplanar lone pair on the 3'-nitrogen atom. Concerning the conformation around the nucleosidic bond of **8**, a $^3J_{C6\text{-}N1\text{-}C1'\text{-}H1'}$ value of *ca* 5.2 Hz was measured, corresponding to a torsional angle of *ca* 150°, whereas NOE experiments indicated a population transfer between H-6 and Hβ-2' and none between H-6 and H-1', thus establishing an *anti* conformation. To test the reliability of the MM2 parameters concerning the N(sp^3)-O(sp^3) bond we obtained from *ab initio* computations,[7] we submitted **7** to a Monte Carlo

TABLE 2. Furanose Ring Interproton Couplings for the β-D-*threo* and β-D-*erythro* Nucleosides (200 MHz ^{1}H-NMR, $CDCl_3$, 20 °C, *J* in Hz).

Cmpd	$J_{1',2'\alpha}$	$J_{1',2'\beta}$	$J_{2'\alpha,3'}$	$J_{2'\beta,3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$
1	6.0	8.5	2.0	6.0	2.5	2.5	2.5
3	6.5	8.0	7.5	8.0	6.5		6.0
4	6.5	7.5	3.0	8.0	5.5		
5[a]	6.5	8.0	7.5	9.0	6.5	5.0	5.0
6	7.5	6.0	6.0	7.5	6.0	2.0	7.0
6[a]	7.8	7.0	8.5	7.5	~5.5	2.0	?
7	7.2	0.0	4.5	0.0	3.5	0.0	2.0
8	8.7	3.0	5.3	0.0	4.0	0.5	2.2
9	9.0	3.0	5.5	0.0	3.5	0.5	2.0
11	5.5	7.0	5.5	7.0	5.0	?	?
12	6.5	8.0	2.0	8.0	~2.5	2.5	2.5
13	7.5	7.5	5.0	9.0	6.5	0.5	3.5
14[b]	7.0	7.0	5.5	9.0	7.0	5.0	5.0
15[c]	7.5	7.5	3.0	8.0	3.5	3.0	3.0

[a] DMSO-d_6. [b] DMSO-d_6 100 °C. [c] 55 °C.

search using the MacroModel 3.5 software,[8] the MM2 force field[9] and the Still's continuum solvation model[10] with the chloroform parameters. Both invertomers of **7** were submitted to the computation, 4000 conformations generated and each of them minimized. The search was deemed exhaustive as all stable conformers were found several times (typically 5 to 50 times). The most stable conformer found (A, FIG. 1) was very close to the time-averaged experimental (NMR) structure, in particular *anti* conformation of the nucleosidic bond (C6-N1-C1'-H1' torsional angle of 151.5°) and an equatorial hydroxy group on the nitrogen atom of the perhydrooxazine ring. Its computed population amounts to *ca* 70% of the conformational mixture and its furanose ring interproton torsional angles (TABLE 3) are in good agreement with the experimental NMR couplings of the acylated derivatives **8** and **9**. The only significant difference between conformers A and B, which

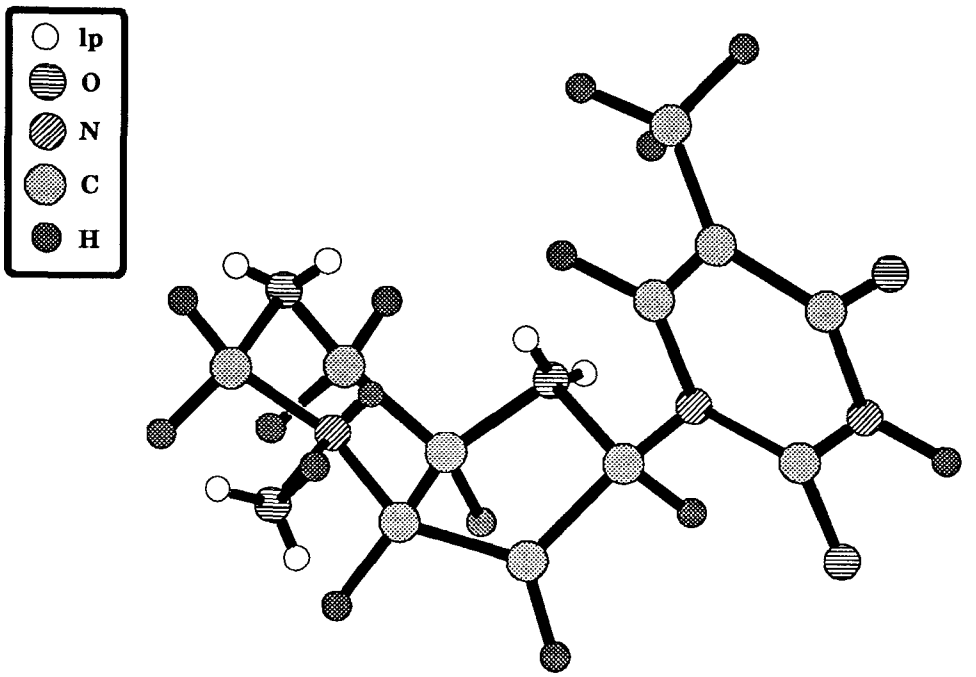


FIG. 1. The most stable conformer of **7** as found by a Monte Carlo search. The lone pairs on sp^3 hetero atoms were explicitly computed and drawn.

TABLE 3. Selected Geometric Features of the More Stable Conformers of **7** (**A-E**) as Obtained from a MonteCarlo Search.

Conf.	Pop. %	Interproton Torsional Angles						
		1',2'α	1',2'β	2'α,3'	2'β,3'	3',4'	4',5'a	4',5'b
A	69.95	4.9	125.2	26.2	-93.4	-46.0	-69.0	50.0
B	15.5	12.0	131.0	18.8	-100.0	-41.6	-72.8	46.6
C	5.3	15.9	167.5	-44.8	-167.9	36.4	-162.9	-43.0
D	1.5	49.9	170.8	-32.1	-154.9	7.5	-72.0	48.0
E	1.1	31.5	154.4	-45.5	-167.3	178.6	56.0	177.8

together represent 85% of the conformational mixture, consists in the configuration of the inverting nitrogen atom of the perhydrooxazine ring (*S* for A, *R* for B).

Upon spontaneous oxidation in the air, diglyme solutions of nucleoside hydroxylamines and hydroxamic acids led to the corresponding free radicals, representative EPR data of which are collected in TABLE 4. The aminoxyl radicals from the 3'-deoxy-3'-(*N*-hydroxy-*N*-methylamino) nucleosides **3**, **5**, and **15** exhibited large hyperfine couplings with nitrogen and the methyl protons, a small β-coupling with the 3' proton and very small long-range γ-couplings (three in the case of **3** and **5**, one in the case of **15**). The $a^{\beta}_{H3'}$ coupling is indicative of the conformational equilibrium around the C-3'-N bond.[11] The silylation of **3** to **5** does not affect the conformational equilibrium in which the conformer having its H-C3' bond in the aminoxyl plane is preponderant. The 3' epimer of **3**, **15**, seems to be slightly conformationally freer, the population of conformers corresponding to larger a_H values being superior, at least at 140 °C. In all cases, however, the conformation in which the aminoxy plane eclipses the H-C3' bond ($a_H \sim 0$ G) is preferred over the two alternate eclipsed ones ($a_H \sim 20$ G). For the bicyclonucleoside **7**, the larger a_H coupling corresponds to H-3'. This has been established by replacing both hydrogen atoms of the neighbouring methylene group with methyl groups.[12] The measured a_H values indicate that the aminoxyl radical adopts the same flattened chair conformation as its diamagnetic precursor. For the free radical corresponding to the hydroxamic acid **13**, the distribution by resonance of the spin density over the carbonyl group divides by *ca* 2 the hyperfine coupling constants.

Compounds **5**, **6**, **7** and **8** were evaluated for their inhibitory effects on HIV-1- and HIV-2-induced cytopathicity in MT-4 cells and HIV1- and HIV-2-induced syncytium (giant cell) formation in CEM cells, and MSV-induced transformation of C3H/3T3 cells *in vitro* (TABLE 5). Compounds **5** and **7** proved markedly inhibitory to HIV-1 and HIV-2 replication in MT-4 cells (EC_{50}: 0.80-0.86 μg/mL and 3.83-4.30 μg/mL, respectively). Their anti-HIV activity in CEM cells was 5-fold lower than in MT-4 cells. The acetyl derivatives **6** and **8** proved less inhibitory to HIV-1 and HIV-2 than their parent compounds **5** and **7**, irrespective of the cell line used for evaluation. In fact, compound **5** proved at least 100-fold more effective an anti-HIV agent

TABLE 4. EPR Data (diglyme, a in G) of Aminoxyl Radicals from Some Modified Nucleosides.

Cmpd	t (°C)	g	a_N	$a_{H(CH3)}$	$a_{H(CH2)}$	$a_{H(CH)}$	long-range a_H
3	115	2.0060	14.9	12.6		3.3	3x0.8
5	80	2.0060	14.6	12.9		3.6	2x1.0
							0.8
7	70	2.0060	15.1		15.8	20.0	
					4.8		
13	85	2.0066	7.6			2.45	
15	140	2.0060	15.2	12.3		4.9	0.8

TABLE 5. Anti-HIV and anti-MSV Activity and Cytotoxic Properties of 1-(2,3-dideoxy-3-*N*-hydroxyamino-β-D-*threo*-pentofuranosyl)thymine derivatives.

Cmpd	EC_{50}[a] (μg/mL)					CC_{50}[b] (μg/mL)
	MT-4		CEM		C3H/3T3	MT-4
	HIV-1	HIV-2	HIV-1	HIV-2	MSV	
7	3.8 ± 0.66	4.3 ± 0.42	20 ± 0.0	25 ± 7.1	> 100	158 ± 29
8	15 ± 1.4	19 ± 1.8	> 50	> 50	337 ± 13	207 ± 19
5	0.86 ± 0.03	0.80 ± 0.14	3.7 ± 2.9	5.3 ± 2.9	⩾ 500	181 ± 40
6	89 ± 19	75 ± 16	> 250	> 250	> 500	> 250
AZT	10^{-3}±10^{-4}	10^{-3}±10^{-4}	10^{-3} ±10^{-4}	10^{-3}±2x10^{-4}	10^{-2}±4x10^{-3}	1.5±5x10^{-3}
DDI	1.2±0.08	-	1.80±0.74	2.52±1.11	48	> 200

[a] 50% Effective concentration or concentration required to protect MT-4 or CEM cells against the cytopathicity of HIV or to inhibit MSV-induced C3H/3T3 cell transformation by 50%. [b]Cytotoxic concentration, or concentration required to reduce MT-4 cell viability by 50%.

than compound **6**. The difference in antiviral potency between compounds **7** and **8** was only 5-fold.

None of the compounds proved markedly inhibitory to MSV-induced C3H/3T3 cell transformation. The different antiviral activities of compounds **5-8** in different cell lines (i.e. MT-4, CEM, C3H/3T3 point to the differences in the metabolism of the compounds, i.e. the rate/extent of their intracellular conversion to the active metabolite(s) (presumably the 5'-triphosphates). Further investigations are required to clarify this issue.

EXPERIMENTAL

General Methods.[13]

5'-*O*-(*tert*-Butyldimethylsilyl)thymidine (1). - A mixture of thymidine (6 g, 24.8 mmol), pyridine (100 mL) and TBDMSCl (4 g, 26.5 mmol) was stirred for 14 h at 25 °C, then the pyridine removed by vacuum distillation. The residue was dissolved in ethyl acetate (300 mL) and the organic phase washed (H_2O 3x20 mL), dried (Na_2SO_4) and concentrated to dryness. Recrystallization (EtOAc) of the white solid obtained, gave **1** (2 g, 87%): mp 196.9-197.5 °C; $[\alpha]_D^{24}$ +4.2° (*c* 1.07, CCl_3); R_F 0.46 (9:1 CH_2Cl_2/MeOH); λ_{max}^{EtOH} 209 nm (ε 9953) and 267 (9848); ν_{max}^{KBr} 3530 (NH), 3490 (OH), 3040, 2940, 2900, 2840 (CH), 1680, and 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): see TABLES 1 and 2, δ 9.23 (*bs*, 1 H, NH), 7.55 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 2.95 (*d*, 1 H, $J_{3',OH}$ = 4 Hz, OH), 1.92 (*d*, 3 H, Me-5), 0.92 (*s*, 9 H, Me_3C), and 0.02 (*ss*, 6 H, 2xSiMe). MS: *m/z* (%) 73 (100), 89 (90), 105 (74), 173 (52), 155 (47), 126 (28, thymine), 59 (22, $Me_3C^{\cdot+}$), 281 (8), 299 (7, $M^{\cdot+}$ - $Me_3C^{\cdot}$), and 323 (0.5).

Anal. Calcd for $C_{16}H_{28}N_2O_5Si$ (356.50): C, 53.91; H, 7.92; N, 7.86. Found: C, 53.84; H, 7.86; N, 7.88.

5'-*O*-(*tert*-Butyldimethylsilyl)-3'-ketothymidine (2). - A slurry of powdered 3Å molecular sieves (5 g) and pyridinium dichromate (5 g, 13.3 mmol) in dichloromethane (50 mL) was stirred for 15 min at 20 °C. A solution of **1** (3 g, 8.42 mmol) in dichloromethane (10 mL) was then added in one portion and the reaction monitored by TLC. After *ca* 2 h stirring, the reaction mixture was filtered, the collected solids washed with dichloromethane (30 mL) and the combined filtrates concentrated to a brown syrup which was dissolved in ethyl acetate (100 mL), filtered over a bed of

powered 3 Å molecular sieves, then concentrated and dissolved in the minimum amount of ethyl acetate from which **2** (2.2 g, 74%) was precipitated with petroleum ether as a light tan powder sufficiently pure for the further syntheses. The analytical sample was obtained by repeating purification procedure using ether instead of ethyl acetate. The compound decomposes even on the TLC plate to give 2-(*tert*-butyldimethylsilyloxymethyl)-2,3-dihydrofuran-3-one. Properties of **2**: mp 114.9-115.8 °C; $[\alpha]_D^{27}$ +87.4° (*c* 0.91, $CHCl_3$); R_F 0.38 (19:1 CH_2Cl_2/MeOH); λ_{max}^{EtOH} 209 nm (ε 8730) and 267 (26752); ν_{max}^{KBr} 3190 (NH), 2955, 2929 (CH), 1772, 1708, and 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.88 (*bs*, 1 H, NH), 7.63 (*q*, 1 H, $J_{Me,6}$ = 1.2 Hz, H-6), 6.50 (*dd*, 1 H, $J_{1',2'a}$ = 6.5 Hz, $J_{1',2'b}$ = 8.2 Hz, H-1'), 4.15 (*bt* (unresolved *dd*), 1 H, H-4'), 4.02 (*dd*, 2 H, Ha,b-5'), 3.00 (*dd*, 1 H, $J_{2'a,2'b}$ = 18 Hz, Ha-2'), 2.40 (*dd*, 1 H, Hb-2'), 1.95 (*d*, 1 H, Me), 1.40 (*s*, 9 H, Me_3C), 0.12 and 0.08 (2 *s*, 2x3 H, 2xSiMe). MS: *m/z* (%) 75 (100), 171 (28), 197 (22), 96 (18), 259 (13), 55 (12), 126 (12, thymine), 297 (7, $M^{\cdot+}$ - $Me_3C^{\cdot}$), 313 (4), and 337 (2).

Anal. Calcd for $C_{16}H_{26}N_2O_5Si$ (354.48): C, 54.21; H, 7.39; N, 7.90. Found: C, 54.18; H, 7.38; N, 7.98.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-3-(*N*-hydroxy-*N*-methylamino-β-D-*threo*-pentofuranosyl]thymine (3). - To a solution of *N*-methylhydroxylamine hydrochloride (1.5 g, 18 mmol) in MeOH (30 mL) was added at 0 °C under N_2, pyridine (1.45 mL, 18 mmol), then immediately crude **2** (2.15 g, 6 mmol) in MeOH (5 mL). The color of the solution changed from light-brown to greenish in 15-20 min. The reaction was monitored by TLC. When all the starting material was consumed, $NaBH_3CN$ (1.5 g, 85%, 20 mmol) was added in one portion. After 2 h stirring at 20 °C, the reaction mixture, concentrated, was partitioned between ethyl acetate (200 mL) and water (10 mL). The organic phase, dried (Na_2SO_4), concentrated, was submitted to a column chromatography (40:1, CH_2Cl_2/MeOH) to give **3** (2 g, 86%), mp 150-152 °C; $[\alpha]_D^{23}$ +55.2° (*c* 0.46, EtOH); R_F 0.33 (19:1, CH_2Cl_2/MeOH); λ_{max}^{EtOH} 207 nm (ε 10735), and 269 (61135); ν_{max}^{KBr} 3490 (NH,OH), 2960, 2920 (CH), 1700 and 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): see TABLES 1 and 2, δ 9.46 (*bs*, 1 H, NH), 7.57 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 7.09 (*bs*, 1 H, N-OH), 2.61 (*s*, 3 H, NMe), 1.91 (d, 3 H, Me-5), 0.92 (*s*, 9 H, Me_3C), 0.12 and 0.10 (2 *s*, 2x3 H, 2xSiMe). ^{13}C-NMR ($CDCl_3$): δ 164 (C-4), 150.6 (C-2), 135.8 (C-6), 110.9 (C-5), 83.5 (C-1'), 80.8 (C-4'), 68.6 (C-3'), 61.8 (C-5'), 46 (NMe), 32.2 (C-

2'), 25.8 (Me_3C), 18.3 (Me_3C), and 12.6 (**Me**-C-5), -5.5 (Si**Me**). MS: *m/z* (%) 70 (100), 89 (95), 160 (53), 110 (42), 126 (21, thymine), 213 (18), 253 (12), 328 (5, $M^{\cdot+}$ - $Me_3C^{\cdot}$), 370 (3, $M^{\cdot+}$ - Me), and 385 (1, $M^{\cdot+}$).

Anal. Calcd for $C_{17}H_{31}N_3O_5Si$ (385.54): C, 52.96; H, 8.10; N, 10.90. Found: C, 53.14; H, 8.22; N, 10.76.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-3-(*N*-methylenamino)-β-D-*threo*-pentofuranosyl]thymine *N*-oxide (4). - To a solution of **3** (100 mg, 0.26 mmol) in dichloromethane (10 mL), a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 60 mg, 0.26 mmol) in dichloromethane (2 mL) was added and the reaction monitored by TLC. After 10 min, the reaction mixture was concentrated and the residue submitted to a flash column chromatography (9:1, CH_2Cl_2/MeOH) to give **4** (57 mg, 57%) as a white foam which could not be obtained in analytically pure form: R_F 0.15 (9:1, CH_2Cl_2/MeOH); ν_{max}^{KBr} 2956, 2930, 2856 (C-H), 1708, 1691 (C=O), and 1568 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): see TABLES 1 and 2, δ 8,78 (*bs*, 1 H, NH), 8.18 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 6.40 and 6.59 (2 *d*, 2x1 H, *AB*, J_{AB} = 7 Hz, NCH_2), 1.96 (*d*, 3 H, Me-5), 0.9 (*s*, 9 H, Me_3C), 0.08 (*s*, 6 H, Me_2Si). MS: *m/z* (%) 73 (100), 89 (93), 81 (87), 55 (45), 155 (23), 165 (23), 145 (20), 126 (15.8, thymine), 326 (11.5, $M^{\cdot+}$ - $Me_3C^{\cdot}$), 258 (7, $M^{\cdot+}$ - thymine), 384 (1.3, $M^{\cdot+}$), 368 (0.3, $M^{\cdot+}$ - Me).

1-[2,3-Dideoxy-3-(*N*-hydroxy-*N*-methylamino)-β-D-*threo*-pentofuranosyl]thymine (5). - A mixture of **3** (1 g) and 85% acetic acid (30 mL) was stirred 14 h at 20 °C, then the reaction mixture was concentrated and the last traces of acetic acid removed by codistillation with toluene. Submitted to column chromatography (9:1, CH_2Cl_2/MeOH), the residue yielded **5** (0.60 g, 86%), mp 171-173 °C; $[\alpha]_D^{26}$ +43.41° (*c* 0.44, MeOH); R_F 0.4 (9:1 CH_2Cl_2/MeOH); λ_{max}^{EtOH} 204 nm (ε 3984), and 264 (3999); ν_{max}^{KBr} 3387, 3280 (NH,OH), 2950, 2930 (CH), 1713, 1669 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): see TABLES 1 and 2, δ 11.25 (*bs*, 1 H, NH), 8.05 (*bs*, 1 H, N-OH), 7.88 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 4.63 (*t*, 1 H, $J_{5',OH}$ = 4 Hz, OH), 2.47 (*s*, 3 H, NMe), and 1.75 (*d*, 3 H, Me-5). ^{13}C-NMR (DMSO-d_6): δ 163.8 (C-H), 150.5 (C-2), 136.4 (C-6), 108.9 (C-5), 83.2 (C-1'), 81.6 (C-4'), 67.9 (C-3'), 61.1 (C-5'), 47.7 (NMe), 33.0 (C-2'), and 12.4 (Me). MS: *m/z* (%) 69 (100), 84 (72), 99 (63), 55 (32), 127 (20, thymine), 146 (10, $M^{\cdot+}$ - thymine), 210 (5), 272 (1.3, $M^{\cdot+}$ + 1), 194 (0.7), 256 (0.4, $M^{\cdot+}$ - Me).

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, 6.33; N, 15.47.

1-[5-*O*-Acetyl-3-(*N*-acetoxy-*N*-methylamino)-2,3-dideoxy-β-D-*threo*-pentofuranosyl]thymine (6). - **5** (0.5 g, 1.85 mmol) was acetylated overnight at room temp in pyridine (10 mL) with acetic anhydride (3mL). The reaction mixture, purified by column chromatography (19:1, CH_2Cl_2/MeOH) gave **6** (0.59 g, 90%), mp 196.7-197.3 °C; $[\alpha]_D^{23}$ +129.9° (*c* 1.04, $CHCl_3$); R_F =0.31 (19:1, CH_2Cl_2/MeOH); λ_{max}^{EtOH} 207 nm (ε 37809) and 266 (29423); ν_{max}^{KBr} 3200 (NH), 1760, 1737, 1701, and 1678 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): see TABLES 1 and 2, δ 9.18 (*bs*, 1 H, NH), 7.62 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 2.77 (*bs*, 3 H, $J_{3',NMe}$ ~ 0.5 Hz, NMe), 2.08 and 2.12 (2 *s*, 2x3 H, 2xCO**Me**), and 1.95 (*d*, 3 H, Me-5). ^{13}C-NMR ($CDCl_3$): δ 170.5, 168.3 (**CO**Me), 163.7 (C-2), 150.4 (C-4), 135.2 (C-6), 111.1 (C-5), 84.2 (C-1'), 79.0 (C-4'), 66.9 (C-3'), 63.4 (C-5'), 45.7 (**NMe**), 34.7 (C-2'), 20.9, 19.6 (CO**Me**), and 12.5 (Me). MS: *m/z* (%) 81 (100), 127 (22, thymine), 55 (13), 110 (7.9), 187 (5.6), 210 (2.4), 313 (0.7, $M^{\cdot+}$ - Ac), 253 (0.4), 230 (0.2, $M^{\cdot+}$ - thymine), and 356 (0.18, $M^{\cdot+}$ + 1).

Anal. Calcd for $C_{15}H_{21}N_3O_7$ (355.35): C, 50.70; H, 5.96; N, 11.82. Found: C, 50.40; H, 6.01; N, 11.76.

1-[2,3-Dideoxy-3-(*N*-hydroxyamino)-3-*N*,5-*O*-methano-β-D-*threo*-pentofuranosyl]thymine (7). - To a solution of **5** (0.6 g, 2.21 mmol) in 3:1 CH_2Cl_2/THF (40 mL) a solution of DDQ (0.55 g, 2.42 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After completion of the reaction (TLC) the reaction mixture was concentrated and after two purifications by column chromatography (19:1, CH_2Cl_2/MeOH) gave **7** (0.38 g, 63 %) which could also be obtained in good yield by acid hydrolysis of **4** (following the procedure described for the preparation of **5**), mp 197.6-198.5 °C; $[\alpha]_D^{23}$ +168° (*c* 0.45, $CHCl_3$); R_F 0.32 (19:1, CH_2Cl_2/MeOH); λ_{max}^{EtOH} 206 nm (ε 8982), and 266 (8482); ν_{max}^{KBr} 3488 (NH), 3392 (OH), 1636, and 1661 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 9.96 (*bs*, 1 H, NH), 8.03 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 7.75 (*bs*, 1 H, N-OH), 6.08 (*d*, 1 H, $J_{1',2'pro\text{-}R}$ = 7.2 Hz, $J_{1',2'pro\text{-}S}$ = 0 Hz, H-1'), 4.62 and 3.85 (2 *d*, 2x1 H, J_{AB} = 7.5 Hz, NCH_2), 4.30 (*d*, 1 H, $J_{5'pro\text{-}R,5'pro\text{-}S}$ = 13 Hz, $J_{5'pro\text{-}S,4'}$ = 0 Hz, H-5'pro-*S*), 4.15 (*dd*, 1 H, $J_{3',4'}$ = 3.5 Hz, $J_{5'pro\text{-}R,4'}$ = 2.0 Hz, H-4'), 3.78 (*dd*, 1 H, H-5'pro-*R*), 3.23 (*dd*, 1 H, $J_{2'pro\text{-}R,3'}$ = 4.5 Hz, $J_{2'pro\text{-}S,3'}$ = 0 Hz, H-3'), 2.85 (*d*, 1 H, $J_{2'pro\text{-}R,2'pro\text{-}S}$ = 14.5 Hz, H-2'pro-*S*), 2.42 (*ddd*, 1 H, H-2'pro-*R*), and 1.85 (*d*, 3 H, Me-5). MS: *m/z* (%) 81 (100), 127 (64, thymine), 68 (38), 143 ($M^{\cdot+}$ - thymine), 99 (18), 196 (1.2), 252 (0.6, $M^{\cdot+}$ - OH), and 269 (0.5, $M^{\cdot+}$).

Anal. Calcd for $C_{11}H_{15}N_3O_5$ (269.26): C, 49.07; H, 5.62; N, 15.61. Found: C, 48.86; H, 5.62; N, 15.32.

1-[3-(*N*-Acetoxyamino)-2,3-dideoxy-3-*N*,5-*O*-methano-β-D-*threo*-pentofuranosyl]thymine (8). - Acetylation of **7** (0.15 g, 0.56 mmol) in pyridine with Ac_2O as described for **6**, gave **8** (0.16 g, 92 %), mp 172.3-173.8 °C; $[\alpha]_D^{23}$ -79.4° (*c* 0.63, $CHCl_3$); R_F 0.46 (19:1 CH_2Cl_2/MeOH); λ_{max}^{EtOH} 206 nm (ε 10608), and 265 (9339); ν_{max}^{KBr} 3490 (NH), 3040, 2980 (CH), 1760, 1709, and 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.42 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 8.34 (*bs*, 1 H, NH), 6.41 (*dd*, 1 H, $J_{1',2'pro-R}$ = 8.7 Hz, $J_{1',2'pro-S}$ = 3 Hz, H-1'), 4.76 and 3.99 (2 *d*, 2x1 H, J_{AB} = 7 Hz, NCH_2), 4.28 (*d*, 1 H, $J_{4',5'pro-S}$ = 0.5 Hz, $J_{5'pro-R,5'pro-S}$ = 13 Hz, H-5'pro-*S*), 4.08 (*dd*, 1 H, $J_{3',4'}$ = 4 Hz, $J_{4',5'pro-R}$ = 2.2 Hz, H-4'), 3.78 (*dd*, 1 H, H-5'pro-*R*), 3.47 (*dd*, 1 H, $J_{2'pro-R,3'}$ = 5.3 Hz, H-3'), 2.56 (*ddd*, 1 H, H-2'pro-*R*), 2.18 (*dd*, 1 H, $J_{2'pro-R,2'pro-S}$ = 15 Hz, $J_{2'pro-S,3'}$ = 0 Hz, H-2'pro-*S*), 2.05 (*s*, 3 H, OCOMe), and 2.00 (*d*, 3 H, Me-5). ^{13}C-NMR ($CDCl_3$): δ 168.4 (**C**OMe), 163.9 (C-4), 150.9 (C-2), 138.4 (C-6), 111.1 (C-5), 83.6 (O**C**H_2N), 83.5 (C-1'), 77.8 (C-4'), 66.6 (C-5'), 63.1 (C-3'), 37.0 (C-2'), 19.0 (CO**C**Me), and 12.1 (Me). MS: *m/z* (%) 81 (100), 127 (71, thymine), 55 (35), 68 (30), 269 (15, $M^{\cdot+}$ - Ac), 143 (11), 252 (2.8, $M^{\cdot+}$ - OAc), and 311 (2.2, $M^{\cdot+}$).

Anal. Calcd for $C_{13}H_{17}N_3O_6$ (311.30): C, 50.16; H, 5.50; N, 13.50. Found: C, 49.93; H, 5.36; N, 13.21.

1-[2,3-Dideoxy-3-*N*,5-*O*-methano-3-(*N*-oleoyloxyamino)-β-D-*threo*-pentofuranosyl]thymine (9). - To a solution of **7** (100 mg, 0.37 mmol) in pyridine (10 mL) oleoyl chloride (0.13 mL, 0.40 mmol) was added and the mixture stirred overnight at room temp. After usual work-up, a purification by column chromatography was performed. After washing out the excess oleic acid from the column with Et_2O, elution with 1:1 Et_2O/EtOAc mixture afforded **9** (170 mg, 86%): mp 80.5-83.6 °C; $[\alpha]_D^{28}$ -94.8° (*c* 0.96, $CHCl_3$); R_F 0.65 (19:1, CH_2Cl_2/MeOH); λ_{max}^{EtOH} 206 nm (ε 890) and 265 (809); ν_{max}^{KBr} 3160 (NH), 3030, 2980, 2900, 2820 (CH), 1730, 1690, and 1670 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.48 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 8.32 (*bs*, 1 H, NH), 6.42 (*dd*, 1 H, H-1'), 5.35 (*m*, 2 H, HC=CH), 4.75 and 3.96 (2 *d*, 2x1 H, J_{AB} = 7 Hz, NCH_2), 4.28 (*d*, 1 H, $J_{4',5'pro-S}$ = 0.5 Hz, $J_{5'pro-R,5'pro-S}$ = 13 Hz, H-5'pro-*S*), 4.07 (*dd*, 1 H, $J_{4',5'pro-R}$ = 2 Hz, H-4'), 3.75 (*dd*, 1 H, H-5'pro-*R*), 3.45 (*dd*, 1 H, $J_{2'pro-R,3'}$ = 5.5 Hz, $J_{2'pro-S,3'}$ = 0 Hz, $J_{3',4'}$ = 3.5 Hz, H-3'), 2.54 (*ddd*, 1 H, $J_{1',2'pro-R}$ = 9.0 Hz, H-2'pro-*R*), 2.28 (*t*, 2 H, COCH_2), 2.15 (*dd*, 1 H, $J_{2'pro-R,2'pro-S}$ = 15 Hz, $J_{1',2'pro-S}$ =

3.0 Hz, H-2'pro-*S*), 2.00 (*m*, 7 H, Me-5 + $2CH_2$), and 1.8-0.8 (m, 25 H, oleic chain). MS: *m/z* (%) 55 (100), 126 (95, thymine), 81 (93), 69 (55), 97 (30), 269 (13, $M^{\cdot+}$ - oleoyl), 251 (11, $M^{\cdot+}$ - oleoyl), 531 (1), and 534 (0.45, $M^{\cdot+}$).

Anal. Calcd for $C_{29}H_{47}N_3O_6$ (533.71): C, 65.26; H, 8.88; N, 7.87. Found: C, 65.15; H, 8.86; N, 7.88.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-3-*N*-hydroxyimino)-β-D-*glycero*-pentofuranosyl]thymine (10). - To a solution of **2** (1 g, 2.84 mmol) in MeOH (20 mL), pyridine (3 mL) was added then hydroxylamine hydrochloride (1 g, 14.4 mmol). The reaction mixture was stirred at room temp for 1 h (TLC). After evaporation, the residue was extracted with EtOAc (100 mL), washed with H_2O (10 mL) and brine (10 mL), and the organic phase dried ($MgSO_4$), filtered, and evaporated to dryness. Flash column chromatography (EtOAc) gave **10** (0.85 g, 82%) as a mixture of isomers (2:1 *E*/*Z*), mp 172.7-173.7 °C; $[\alpha]_D^{25}$ +58.2° (*c* 1.07, $CHCl_3$); R_F 0.60, 0.47 (EtOAc); λ_{max}^{EtOH} 204 nm (ε 21800) and 265 (13548); ν_{max}^{KBr} 3380-3140 (NH,OH), 1730-1660 (C=O), and 1470 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 9.50 (*bs*, 1 H, NH), 9.00 (N-OH *E*), 8.75 (N-OH *Z*), 7.78 H-6 *Z*), 7.65 (H-6 *E*), 6.35 (H-1'), 4.95 (H-4' *Z*), 4.63 (H-4' *E*), 4.20 (Ha,b-5' *Z*), 4.05 (Ha,b-5' *E*), 3.48 (*dd*, Ha-2' *E*), 3.12 (*dd*, Ha-2' *Z*), 2.65 (*dd*, Hb-2' *Z*), 2.53 (*dd*, Hb-2' *E*), 1.95 (Me-5), 0.90 (Me_3C), and 0.12 (Me_2Si). MS: *m/z* (%) 186 (100), 75 (82), 89 (38), 117 (30, Me_3C - $SiMe_2^{\cdot}$), 59 (18, $Me^{\cdot}$), 126 (17, thymine), 294 (0.55), 312 (0.45, $M^{\cdot+}$ - $Me_3C^{\cdot}$), 369 (0.15, $M^{\cdot+}$), 281 (0.12), and 339 (0.1).

Anal. Calcd for $C_{16}H_{27}N_3O_5Si$ (369.50): C, 52.01; H, 7.37; N, 11.37. Found: C, 52.29; H, 7.45; N, 11.09.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-3-*N*-hydroxyamino)-β-D-*threo*-pentofuranosyl]thymine (11). - To a solution of **10** (0.5 g, 1.36 mmol) in acetic acid at room temp, $NaBH_3CN$ (0.91 g, 14.5 mmol) was added. After completion of the reaction (30 min, TLC), the reaction mixture was concentrated, the solvent coevaporated 3-5 times with toluene and the residue dissolved in EtOAc (100 mL), washed (2x10 mL aqueous saturated $NaHCO_3$, then 10 mL brine), dried (Na_2SO_4), concentrated then submitted to flash column chromatography (30:1 to 20:1 Et_2O/MeOH) to give a 4:1 mixture of **11** and **12** (0.36 g, 71.6%) which was resolved by column chromatography (30:1, CH_2Cl_2/MeOH). Properties of **11**: mp 69.5-70.1 °C; $[\alpha]_D^{18}$ +21.4° (*c* 0.9, $CHCl_3$); R_F 0.22 (19:1 CH_2Cl_2/MeOH); λ_{max}^{EtOH} 208 nm (ε

8798) and 267 (8528); ν_{max}^{KBr} 3380, 3260 (NH,OH), 2930, 2910, 2820 (CH), 1690, and 1670 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): see TABLES 1 and 2, δ 9.74 (*bs*, 1 H, NH), 7.70 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 6.55 (*bs*, 1 H, NHOH), 5.0-6.0 (*bs*, 1 H, NHOH), 1.90 (*d*, 3 H, Me-5), 0.95 (*s*, 9 H, Me_3C), and 0.13 (*s*, 6 H, Me_2Si). MS: *m/z* (%) 75 (100), 89 (57), 186 (47), 146 (42), 117 (30, $Me_3CSiMe_2^{\cdot}$), 127 (25, thymine), 56 (22), 314 (3, $M^{\cdot+}$ - $Me_3C^{\cdot}$), and 371 (2, $M^{\cdot+}$).

Anal. Calcd for $C_{16}H_{29}N_3O_5Si$ (371.51): C, 51.73; H, 7.87; N, 11.31. Found: C, 51.80; H, 7.98; N, 11.29.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-3-(*N*-hydroxyamino)-β-D-*erythro*-pentofuranosyl]thymine (12). - Prepared as described for **11**: mp 177.8-178.6 °C; $[\alpha]_D^{26}$ -14.4° (*c* 0.9, $CHCl_3$); R_F 0.15 (19:1, CH_2Cl_2/MeOH); λ_{max}^{EtOH} 204 nm (ε 14590) and 269 (31136); ν_{max}^{KBr} 3240, 3160 (NH,OH), 2920, 2900, 2810 (CH), 1680, and 1650 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): see TABLES 1 and 2, δ 10.20 (*bs*, 1 H, NH), 7.62 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 6.90 (*bs*, 1 H, NHOH), 5.30 (*bs*, 1 H, NHOH), 1.93 (*d*, 3 H, Me-5), 0.94 (*s*, 9 H, Me_3C), and 0.15 (*s*, 6 H, Me_2Si). MS: *m/z* (%) 75 (100), 89 (58), 146 (52), 126 (27, thymine), 56 (22), 170 (17), 281 (13), 298 (10), 213 (7), 314 (2, $M^{\cdot+}$ - $Me_3C^{\cdot}$), and 371 (1.5, $M^{\cdot+}$).

Anal. Calcd for $C_{16}H_{29}N_3O_5Si$ (371.51): C, 51.73; H, 7.87, N, 11.31. Found: C, 51.68; H, 7.55; N, 11.46.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-3-(*N*-hydroxy-*N*-oleoylamino)-β-D-*threo*-pentofuranosyl]thymine (13). -To a solution of **11** (100 mg, 0.27 mmol) in pyridine (5 mL), oleoyl chloride (0.1 mL, 0.31 mmol) was added, and the reaction mixture stirred overnight at room temp. Column chromatography of the product (12:8:1 ether/cyclohexane/MeOH) gave **13** as a syrup (115 mg, 67%), $[\alpha]_D^{20}$ +6.1° (*c* 1, $CHCl_3$); R_F 0.12 (12:8:1, ether/cyclohexane/MeOH); λ_{max}^{EtOH} 208 nm (ε 17197) and 266 (10684); ν_{max}^{KBr} 3306, 3290 (NH,OH), 2952, 2930, 2855 (CH), 1700, and 1657 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): see TABLES 1 and 2, δ 8.72 (*bs*, 1 H, NH), 8.56 (*bs*, 1 H, NOH), 7.62 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 5.30-5.55 (*m*, 3 H, CH=CH, H-3'), 1.95 (*d*, 3 H, Me-5), 2.50, 2.05, 1.8-1.1 (*m*, oleic acid chain), 0.95 (*s*, 9 H, Me_3C), 0.9 (*t*, 3 H, Me-oleic acid chain), and 0.18 (*s*, 6 H, Me_2Si). MS: *m/z* (%) 81 (100), 55 (72), 155 (50), 126 (32, thymine), 436 (35), 562 (20, $M^{\cdot+}$ - $Me_3C^{\cdot}$ - Me), 578 (6, $M^{\cdot+}$ - $Me_3C^{\cdot}$), 509 (3, $M^{\cdot+}$ - thymine), 620 (2, $M^{\cdot+}$ - Me), and 636 (0.5, $M^{\cdot+}$).

Anal. Calcd for $C_{34}H_{61}N_3O_6Si$ (635.97): C, 64.21; H, 9.67; N, 6.61. Found: C, 63.93; H, 9.59; N, 6.70.

1-[2,3-Dideoxy-3-(*N*-hydroxy-*N*-oleoylamino)-β-D-*threo*-pentofuranosyl]thymine (14). - Desilylation of **13** (0.4 g, 0.63 mmol) in 80% acetic acid (as described for **5**) gave, after column chromatography (19:1, CH_2Cl_2/MeOH) **14** (0.23 g, 70%) as a syrup, $[\alpha]_D^{19}$ +24.8° (*c* 0.3, $CHCl_3$); λ_{max}^{EtOH} 207 nm (ε 10463) and 265 (9906); ν_{max}^{KBr} 3400-3150 (NH,OH), 2990, 2952, 2930, 2850 (CH), 1680, 1660, and 1632 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): see TABLES 1 and 2, δ 10.75 (*bs*, 1 H, NH), 9.22 (*bs*, 1 H, N-OH), 7.65 (*q*, 1 H, H-6), 5.35 (*m*, 1 H, HC=CH), 4.60 (*t*, 1 H, $J_{5',OH}$ = 5.5 Hz, 5'-OH), 2.40 (*t*, 2 H, CH_2CO), 2.00 (*m*, 4 H, 2xCH_2CH=), 1.82 (*d*, 3 H, Me-5), 1.7-1.1 (*m*, oleic chain), 0.88 (*t*, 3 H, Me-oleoyl). MS: *m/z* (%) 55 (100), 69 (54), 111 (42), 83 (29), 97 (19), 127 (16, thymine), 264 (1.9, oleic acid chain), 394 (0.53, $M^{\cdot+}$ - thymine), 376 (0.51), 506 (0.14, $M^{\cdot+}$ - Me), and 522 (0.05, $M^{\cdot+}$).

Anal. Calcd for $C_{28}H_{47}N_3O_6.1/2H_2O$ (403.01): C, 63.36; H, 9.12; N, 7.92. Found: C, 63.38; H, 9.01; N, 7.80.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-3-(*N*-hydroxy-*N*-methylamino)-β-D-*erythro*-pentofuranosyl]thymine (15). - To a solution of **12** (0.13 g, 0.35 mmol) in MeOH (20 mL) formaldehyde (0.1 mL, 1.33 mmol 40% aq. solution) was added. After consumption of **12** (15 min, TLC), sodium cyanoborohydride (0.3 g, 4.8 mmol) was added in one portion and the mixture stirred for 30 min. The reaction mixture was treated as described for the preparation of **3** and submitted to column chromatography (19:1, CH_2Cl_2/MeOH) to give **15** (0.1 g, 74%), mp 73.5-74.5 °C; $[\alpha]_D^{26}$ -21.2° (*c* 0.35, $CHCl_3$); R_F 0.16 (19:1, CH_2Cl_2/MeOH); λ_{max}^{EtOH} 207 nm (ε 12607) and 268 (18910); ν_{max}^{KBr} 3390 (NH), 3240 (OH), 2940, 2900, 2830 (CH), 1680, and 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 55 °C): see TABLES 1 and 2, δ 10.62 (*bs*, 1 H, NH), 7.62 (*q*, 1 H, $J_{6,Me}$ = 1.2 Hz, H-6), 5.60 (*bs*, 1 H, N-OH), 2.70 (*s*, 3 H, NMe), 2.66 (*m*, 1 H, Hα-2'), 1.93 (*m*, 4 H, Hβ-2', Me-5), 0.95 (*s*, 9 H, Me_3C), and 0.15 (*s*, 6 H, Me_2Si). MS: *m/z* (%) 89 (100), 73 (94), 59 (40), 145 (29), 45 (14, N(OH)Me), 126 (10, thymine), 243 (3.9), 281 (3.9), 259 (2.6, $M^{\cdot+}$ - thymine), 310 (1.2), 328 (0.7, $M^{\cdot+}$ - $Me_3C^{\cdot}$), and 385 (0.2, $M^{\cdot+}$).

Anal. Calcd for $C_{17}H_{31}N_3O_5Si$ (385.54): C, 52.96; H, 8.10; N, 10.90. Found: C, 52.67; H, 8.20; N, 10.91.

Activity of the test compounds against replication of HIV-1 and HIV-2 in CEM and MT4 cells. CEM and MT-4 cells were suspensed at 250,000 cell/mL of culture medium and infected with HIV-1(III_B) or HIV-2(ROD).

Then, 100 μL of the infected cell suspensions were added to 200-μL microtiter plate wells containing 100 μL of an appropriate dilution of the test compounds. After 4-5 days of incubation at 37 °C, the cell cultures were examined for microscopically visible syncytia (CEM) of cell lysis (MT-4), upon staining of the cell culture with trypan blue. The EC_{50} was determined as the compound concentration required to inhibit syncytium formation (CEM) or reduce cell viability (MT-4) by 50%.

Activity of the test compounds against Moloney murine sarcoma virus (MSV)-induced C3H/3T3 cell transformation. C3H/3R3 cells were seeded in 48-well microtitet plates and grown to confluency. Then, the cell cultures were infected with 75 foci-forming units of MSV and the test compounds were added at the appropriate dilutions in a total volume of 1 mL per well. At day 6 post infection, MSV-induced cell transformation was recorded under the microscope. The EC_{50} was determined as the compound concentration required to inhibit MSV-induced cell transformation by 50%.

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