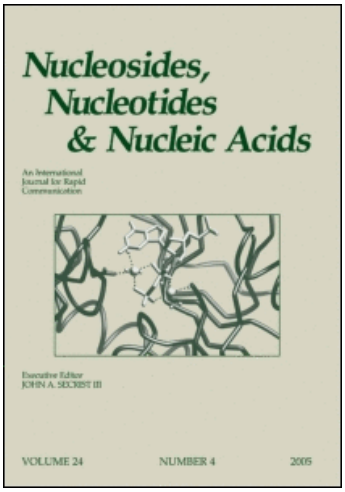

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Systematic Synthesis and Antiviral Evaluation of α-L-Arabinofuranosyl and 2'-Deoxy-α-L-*Erythro*-Pento-Furanosyl Nucleosides of the Five Naturally Occurring Nucleic Acid Bases

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SYSTEMATIC SYNTHESIS AND ANTIVIRAL EVALUATION OF α-L-ARABINOFURANOSYL AND 2'-DEOXY-α-L-*ERYTHRO*-PENTOFURANOSYL NUCLEOSIDES OF THE FIVE NATURALLY OCCURRING NUCLEIC ACID BASES.

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- Dedicated to the memory of Professor Tohru UEDA -

ABSTRACT.

The α-L-arabinofuranosyl and 2'-deoxy-α-L-*erythro*-pentofuranosyl analogues of the naturally occurring nucleosides have been synthesized and their antiviral properties examined. The α-L-arabinofuranosyl nucleosides were prepared by glycosylation of purine and pyrimidine aglycons with a suitably peracyl-α-L-arabinose, followed by removal of the protecting groups. Their 2'-deoxy derivatives were obtained by sequential selective 2'-O-deacylation and

deoxygenation. All the prepared compounds were tested for their activity against a variety of RNA and DNA viruses, but they did not show significant antiviral activity.

During the last decades there has been considerable interest in the synthesis and in the biological evaluation of sugar-modified nucleoside analogues, mainly as potential antiviral and antitumor agents.[1,2] Recently, we initiated a comprehensive program in order to define structure-activity relationships. Thus, in earlier papers we have discussed the α,β-D-xylofuranosyl[3] and α,β-D-lyxofuranosyl[4] nucleosides, and it was found that four of these compounds, namely 9-β-D-xylofuranosyl-adenine and -guanine as well as 1-β-D-xylofuranosylcytosine and 9-α-D-lyxofuranosyladenine, showed marked biological activity.[3-6] Moreover, recent interest in the field of modified oligonucleotides as antisense regulators of gene expression[7,8] led us to consider the potential relevance of unnatural sugar configurations. Initially, we investigated oligodeoxynucleotides consisting of α-D-anomeric 2'-deoxy-*erythro*-pentofuranonucleoside units and showed that these compounds possess desirable biological properties.[9] Now we are in the process of extending these studies, to α-D-oligoribofuranonucleotides[10] and α-L-oligopentofuranonucleotides. For the latter compounds, we need as starting synthons the α-L-arabinofuranonucleosides and 2'-deoxy-α-L-*erythro*-pentofuranonucleosides of the naturally occurring nucleic acid bases. A thorough literature survey revealed that, while numerous studies have been concentrated on β-L-ribofuranonucleosides and on their 2'-deoxy derivatives,[11-20] little attention has been given to the synthesis and biological evaluation of α-L-pentofuranosyl nucleosides. For instance, to the best of our knowledge, only one report concerning the synthesis of

α-L-arabinofuranosylpyrimidines[21] and another mentioning the obtention of 2'-deoxy-α-L-guanosine and adenosine[22] have been published.

In view of the general paucity of both chemical and biological information of α-L-nucleosides, we have undertaken a systematic study of all α-L-arabinofuranosyl analogues of the naturally occurring nucleosides as well as of their 2'-deoxy derivatives.

CHEMISTRY.

Synthesis of α-L-Arabinofuranosyl Nucleosides (Scheme I).

Direct condensation of a suitably protected L-arabinofuranose and the purine or pyrimidine bases was employed to prepare these α-L (trans-1',2') nucleosides. In accord with Baker's rule,[23] a 2-O-acyl-L-arabinofuranose was required for preferential or exclusive formation of the α anomers in the arabinose series. As starting sugar we used syrupy 1,2-di-O-acetyl-3,5-di-O-benzoyl-L-arabinofuranose (1), hitherto unknown and specially prepared from L-arabinose for our present purpose.[24] Glycosylations were effected by various procedures which, except for the guanine series, did not require prior protection of the heterocyclic bases. Thus, the method of Saneyoshi et al.[25,26] was successful with adenine, while the nucleosides of thymine, uracil and cytosine were obtained by Vorbruggen procedures.[27-29] From adenine, thymine and cytosine, only the expected α-L-9-N (2) and α-L-1-N (4,6) protected nucleosides were obtained whereas glycosylation of uracil resulted in a separable mixture containing the α-L-1-N (5) isomer along with the undesirable α-L-3-N isomer. In the guanine series, application of the procedure of Wright and Dudycz[30,31] to

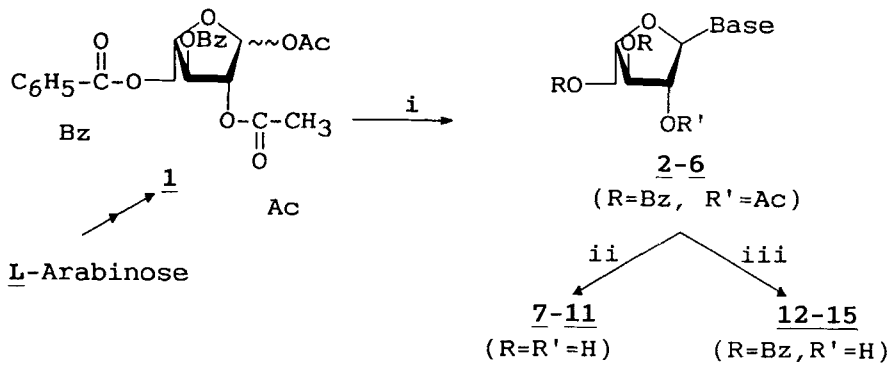
N^2-palmitoylguanine[32] afforded an unseparable mixture of the two α-L-9-N (3) and α-L-7-N isomers. Treatment of this mixture with hydrazine hydrate resulted in their 2'-O-deacetylated derivatives which could be easily isolated separately by silica gel column chromatography.

Removal of the acyl protecting groups from 2, 4-6 and 13 with methanolic ammonia afforded the desired α-L-arabinofuranosyl nucleosides 7-11.

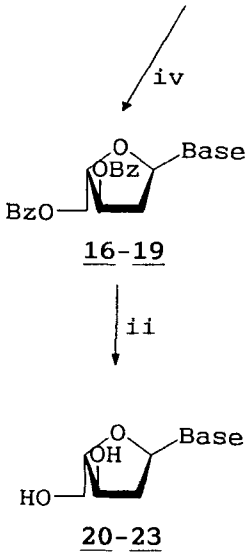
Synthesis of 2'-Deoxy-α-L-*erythro*-pentofuranosyl Nucleosides (Scheme I).

A priori, at least four general methods can be envisaged for the preparation of these 2'-deoxy derivatives of the α-L-ribo- and arabinofuranosyl nucleosides: (**a**) glycosylation with a suitably protected 2'-deoxy-L-*erythro*-pentofuranose; (**b**) nucleophilic oxirane ring opening of the 2,3-anhydro-α-L-ribofuranonucleosides with benzylthiolate followed by desulfurization,[33] with bromide ion followed by hydrogenolysis with tributyltin hydride,[34] or by lithium aluminium hydride reduction,[35] as previously described in other series; (**c**) deoxygenative [1,2]-hydride shift rearrangement on 2'-O-sulfonyl-α-L-lyxofuranosyl nucleosides as has already been applied to β-D-ribofuranosyl nucleosides;[36-41] (**d**) Barton-type deoxygenative hydrogenolysis[42] of 2'-thionocarbonate ester derivatives of suitably protected α-L-ribo- or arabinofuranosyl nucleosides. We discarded the first two possibilities owing to their lack of stereospecificity and regioselectivity. Using 2'-O-sulfonic esters of α-L-lyxofuranosyl nucleosides was also excluded owing to the expected difficulties in preparing these starting compounds. Thus, we turned to the last method, which has been already successfully applied in the selective 2'-deoxygenation of β-D-pentofuranosyl nucleosides.[43-45]

Selective 2'-O-deacylation of 2'-O-acetyl-3',5'-di-O-benzoyl-α-L-arabinofuranosyl nucleosides 2-5 was effected by the Ishido procedure with hydrazine hydrate in a buffe-



Compound	Base
2, 7, 12, 16, 20	adenine-9-yl
3, 13, 17	N^2-palmitoyl-guanine-9-yl
8, 21	guanine-9-yl
4, 9, 14, 18, 22	thymine-1-yl
5, 10, 15, 19, 23	uracil-1-yl
6, 11,	cytosine-1-yl

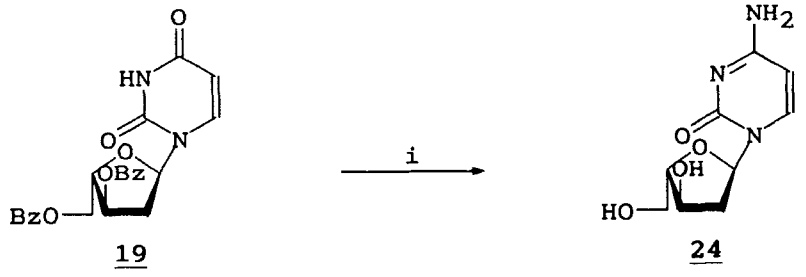


Reaction conditions : **i)** Adenine, $SnCl_4/CH_3CN$ for 2; N^2-palmitoylguanine, BSA, TMSTF/CH_3CN for 3; thymine or uracil, HMDS, TMSCl, $SnCl_4/CH_3CN$ for 4 or 5; silylated cytosine, TMSTF/$ClCH_2CH_2Cl$ for 6. **ii)** NH_3/CH_3OH. **iii)** $NH_2NH_2 \cdot H_2O/CH_3COOH$-$C_5H_5N$. **iv)** DMAP, C_6H_5OCSCl/CH_3CN, then Bu_3SnH, AIBN/toluene.

- Scheme I -

red acetic acid-pyridine mixture[46] to give the 3',5'-di-O-benzoyl derivatives **12**-**15**. Direct treatment of these compounds with phenyl chlorothionocarbonate and 4-(dimethylamino)pyridine (DMAP) in methylene chloride or acetonitrile gave the corresponding 2'-O-(phenoxythiocarbonyl) derivatives which were treated with tributyltin hydride and α,α'-azobisisobutyronitrile (AIBN, a free-radical initiator) in toluene to afford, after purification by column chromatography, the protected 2'-deoxygenated products **16**-**19**. Removal of their acyl protecting groups with methanolic ammonia afforded four of the desired 2'-deoxy-α-L-*erythro*-pentofuranosyl nucleosides **20**-**23**.

In the cytosine series, owing to possible N^4 thionoacylation and subsequent side reactions as observed previously with cytidine,[44] we did not apply a nucleoside 2'-deoxygenation method but, instead we used a procedure of site-specific modification of uracil to cytosine derivatives. Thus, 1-(2-deoxy-3,5-di-O-benzoyl-α-L-*erythro*-pentofuranosyl)uracil (**19**) was treated with *o*-chlorophenyl phosphorodichloridate and 1,2,4-triazole according to a procedure similar to the one described by Sung[47] to give the 4-triazolylpyrimidinone intermediate. By subsequent treatment with an ammonium hydroxide-dioxane mixture followed by saturated methanolic ammonia, we obtained the last desired compound **24** (Scheme II).



19 **24**

- **Scheme II** - *Reaction conditions :* i) *o*-$Cl_6H_4OPOCl_2$, 1,2,4-triazole/C_5H_5N, then NH_4OH/dioxane, then NH_3/CH_3OH.

- **Table I** - Antiviral Activity of α-L-Arabinofuranosyl and 2'-Deoxy-α-L-*Erythro*-Pentofuranosyl Nucleosides Against Three Viruses in Two Different Cell Systems.

Compound	minimum cytotoxic concentration (CC_{50})[a] (mM)	50% Inhibitory Dose (ID_{50}),[b] (mM)			
		Human diploid (MRC-5) cells	Human heteroploid (KB) cells		
	MRC-5 cells	KB cells	Human cytomegalovirus (AD 169)	Coxsackie virus B3	Polio virus-1 (Mahoney)
7	> 1	> 1	1	> 1	> 1
8	> 1	> 1	> 1	> 1	> 1
9	> 1	> 1	> 1	> 1	> 1
10	> 1	> 1	> 1	> 1	> 1
11	> 1	> 1	> 1	> 1	> 1
20	> 1	> 1	1	> 1	> 1
21	> 1	> 1	1	> 1	> 1
22	> 1	> 1	> 1	> 1	> 1
23	> 0.1	> 0.1	> 0.1	> 0.1	> 0.1
24	>0.01	>0.01	>0.01	>0.01	>0.01
Vidarabine	> 1	> 1	0.05	> 1	> 1
Acyclovir	> 1	> 1	0.1	> 1	> 1
Ribavirin	> 1	> 1	1	0.01	0.01

[a] Require to cause a microscopically detectable alteration of normal cell morphology, when incubated with cells for the same duration as required to measure antiviral activity. [b] Require to reduce virus-induced cytopathogenecity by 50%. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures. The multiplicity of infection (MOI) was invariably 100 × $CCID_{50}$, that is 100 times the virus dose needed to infect 50% of the cells.

- **Table II** - Antiviral Activity of α-L-Arabinofuranosyl and 2'-Deoxy-α-L-*Erythro*-Pentofuranosyl Nucleosides Against Different Viruses in a Vero B Cell System.

Compound	CC_{50}[a] (mM)	50% Inhibitory Dose (ID_{50}),[b] (mM) African green monkey kidney (Vero B) cells				
	Vero B cells	Herpes simplex virus-1 (F)	Herpes simplex virus-II (G)	Vaccinia virus (Copenhagen)	Parainfluenza virus-III	Respiratory syncytial virus (A2)
7	> 1	1	1	1	> 1	> 1
8	> 1	> 1	> 1	> 1	> 1	> 1
9	> 1	> 1	> 1	> 1	> 1	> 1
10	> 1	> 1	> 1	> 1	> 1	> 1
11	> 1	> 1	> 1	> 1	> 1	> 1
20	> 1	1	1	> 1	> 1	> 1
21	> 1	1	1	> 1	> 1	> 1
22	> 1	> 1	> 1	> 1	> 1	> 1
23	> 0.1	> 0.1	> 0.1	> 0.1	> 0.1	> 0.1
24	> 0.01	> 0.01	> 0.01	> 0.01	> 0.01	> 0.01
Vidarabine	> 1	0.001	0.005	0.001	> 1	> 1
Acyclovir	> 1	0.001	0.001	0.5	> 1	> 1
Ribavirin	> 1	1	1	0.05	0.05	0.01

[a,b] : See Table I.

- Table III - Inhibitory Effect of α-L-Arabinofuranosyl and 2'-Deoxy-α-L-*Erythro*-Pentofuranosyl Nucleosides on HIV-induced Cytopathogenicity in MT-4 and CEM Cells.

Compound	MT-4 cells		CEM cells	
	ED_{50}[a]	CD_{50}[b]	ED_{50}[a]	CD_{50}[b]
7	> 0.1	$1>CD_{50}>0.1$	> 1	> 1
8	> 0.1	0.1	> 0.1	> 0.1
9	> 1	> 1	> 1	> 1
10	> 1	> 1	0.5	> 1
11	> 1	> 1	> 1	> 1
20	> 1	> 1	> 1	> 1
21	> 0.1	0.05	> 0.1	$1>CD_{50}>0.5$
22	> 1	> 1	> 1	> 1
23	> 0.1	> 0.1	ND[c]	ND[c]
24	> 0.01	$0.01>CD_{50}>0.001$	ND[c]	ND[c]
zidovudine	$9\ 10^{-7}$	$1>CD_{50}>0.1$	10^{-7}	1
2',3'-dideoxycytidine	$2.5\ 10^{-4}$	0.3	10^{-5}	$6\ 10^{-3}$

[a] Fifty percent effective dose or dose required to protect HIV-infected cells by 50%, ED_{50} in mM.

[b] Fifty percent cytotoxic dose or dose required to reduce the viability of mock-infected cells by 50%, CD_{50} in mM.

[c] Not determined.

Structural assignments for the reported α-L-arabinofuranonucleosides 7-11 and their 2'-deoxy derivatives 20-24 are based on elemental analysis and on their physical properties.

BIOLOGICAL EVALUATION.

All the prepared α-L-pentofuranosyl nucleosides 7-11 and 20-24 were tested for their *in vitro* inhibitory effects on the replication of a number of DNA viruses [*i.e.* human cytomegalovirus (AD 169), herpes simplex virus type 1 (F) and type 2 (G), vaccinia virus] and RNA viruses (parainfluenza virus type III, respiratory syncytial virus, Coxsackie virus B3 and polio virus-1) in three cell systems (MRC-5, Vero and KB cells) [Tables I and II; for comparative purposes, the data of the well-known antiviral compounds vidarabine, acyclovir and ribavirin are also included]. With few exceptions, none of the α-L-nucleosides showed a marked antiviral effect at doses up to 1 mM. At this concentration, compounds 7,20 and 21 were active against human cytomegalovirus and herpes viruses, while 7 was also active against vaccinia virus. Furthermore, none of the compounds produced any detectable alteration of host cell morphology at the highest concentration tested (1 mM).

When evaluated in two anti-human immunodeficiency virus assays, none of the α-L-nucleosides showed a marked antiviral effect at a concentration less than 10-fold lower than the minimal concentration causing a detectable alteration of MT-4 and CEM host cell viability (Table III).

CONCLUSION.

According to the present results, it is obvious that the α-L-configuration of nucleoside analogues results in a lack of inhibition of virus multiplication. Several hypothesis can be proposed to explain the inactivity of these

nucleoside analogues. For instance, they are not able to enter into cells or they cannot serve as substrates for the intracellular enzymes catalyzing triphosphorylation. Another possibility is that although they may enter the cells and be triphosphorylated, their triphosphate forms are not inhibitors of polymerases. Further research is needed to test these hypotheses. Whatever is the source of their inactivity, studies on these α-L-nucleosides as monomeric units of unnatural oligonucleotides designed as potential artificial antisense inhibitors of gene expression are now in progress in our Laboratory and a preliminary report on the synthesis, biophysical properties and stability against nucleases of an oligo(α-L-dT)$_8$ has recently been published.[48]

EXPERIMENTAL SECTION.

Chemical Synthesis. General Procedures.

Evaporation of solvents was done with a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. Ultraviolet spectra (UV) were recorded on an Uvikon 810 (KONTRON) spectrophotometer; numbers in parentheses are extinction coefficients. Proton nuclear magnetic resonances were determined at ambient temperatures in Me_2SO-d_6 with a Bruker WM 360 WB spectrometer. Chemical shifts are expressed in parts per million, Me_2SO-d_5 being set at 2.49 ppm as a reference; deuterium exchange and decoupling experiments were performed to confirm proton assignments. Fast-atom bombardment mass spectra (FAB-MS) were recorded in the positive- or negative-ion mode on a JEOL DX 300 mass spectrometer, with a JMA-DA 5000 mass data system; xenon was used for the atom gun at 3 keV with a total discharge current of 20 mA and the matrix was glycerol (G), a mixture of glycerol and thioglycerol (50:50, v/v) (G-T) or *meta*-

nitrobenzyl alcohol (NBA). Optical rotations were measured in a 1-cm cell on a Perkin-Elmer Model 241 spectropolarimeter in the indicated solvents. Elemental analyses were determined by the Service de Microanalyse du CNRS, Division de Vernaison, France.Thin-layer chromatography (TLC) was performed on precoated aluminium sheets of silica gel 60 F_{254} (Merck, n° 5554), visualization of products being accomplished by UV absorbance followed by charring with 10% ethanolic sulfuric acid and heating. Column chromatography was performed with silica gel 60 (Merck, n° 9385) under atmospheric pressure.

9-(2-O-Acetyl-3,5-di-O-benzoyl-α-L-arabinofuranosyl)adenine (2).

Adenine (2.38 g, 17.61 mmol, 1.12 eq) was suspended in a solution of 1,2-di-O-acetyl-3,5-di-O-benzoyl-L-arabinofuranose (1)[24] (6.95 g, 15.71 mmol, 1.0 eq) in anhydrous acetonitrile (500 mL). Stannic chloride (3.7 mL, 31.62 mmol, 2.01 eq) in anhydrous acetonitrile (50 mL) was added and the mixture was stirred at room temperature for 18 h with exclusion of moisture. The reaction mixture was concentrated and sodium hydrogen carbonate (9.2 g) and water (32 mL) were carefully added with stirring. When the evolution of carbon dioxide had ceased, the mixture was evaporated to dryness. The residue was then triturated with boiling $CHCl_3$ and filtered through a sintered funnel. This operation was repeated three times. The combined filtrates were washed with water, dried over sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column using as eluent a stepwise gradient of methanol (0-5%) in methylene chloride led, after evaporation of the pooled appropriate fractions, to the isolation of pure 2 (5.4 g, 66% yield) as a foam: mp 91-95°C; UV (EtOH) λ_{max} 231 nm (ϵ, 34,800), 259 nm (ϵ, 18,600), λ_{min} 249 nm (ϵ, 16,800); (0.1N HCl) λ_{max} 234 nm (ϵ_1), 257 nm (ϵ_2; ϵ_2/ϵ_1= 0.53), λ_{min} 252 nm; (0.1N NaOH) λ_{max} 229 nm (ϵ_1), 259 nm (ϵ_2; ϵ_2/ϵ_1= 0.68), λ_{min} 245 nm; ^1H NMR δ 8.38 and 8.17 (2s, 1H each,

H-2 and H-8), 8.1-7.5 (m, 10H, 2 C_6H_5CO), 7.33 (s, 2H, NH_2), 6.42 (d, 1H, H-1'; $J_{1',2'}$= 3.5 Hz), 6.37 (t, 1H, H-2'), 4.74 (dd, 1H; H-3', $J_{2',3'}$= 3.9 Hz; $J_{3',4'}$= 5.4 Hz), 5.1 (m, 1H, H-4'), 4.6 (m, 2H, H-5',5"), 2.04 (s, 3H, CH_3CO); mass spectrum (matrix, G-T), FAB > 0: 518 $(M+H)^+$, 136 $(BH_2)^+$; $[\alpha]_D^{20}$ - 35.3° (c 0.99, Me_2SO). Anal. Calcd. for $C_{26}H_{23}N_5O_7 \cdot$ 1/6 CH_2Cl_2: C, 59.11; H, 4.39, N, 13.17. Found: C, 59.41; H, 4.45; N, 12.91.

1-(2-O-Acetyl-3,5-di-O-benzoyl-α-L-arabinofuranosyl)thymine (4) and uracil (5).

To a mixture of thymine (1.0 g, 7.93 mmol) or uracil (0.89 g, 7.93 mmol) and the protected sugar 1 (3.52 g, 7.93 mmol, 1.0 eq) in anhydrous acetonitrile (120 mL) were added consecutively hexamethyldisilazane (HMDS, 1.30 mL, 6.35 mmol, 0.8 eq), trimethylchlorosilane (TMSCl, 0.81 mL, 6.38 mmol, 0.8 eq) and $SnCl_4$ (1.11 mL, 9.52 mmol, 1.2 eq). For thymine, the resulting clear solution was refluxed for 1.5 h; for uracil, it was stirred at room temperature for 60 h. The reaction mixtures were concentrated to a small volume, diluted with methylene chloride (240 mL), then washed with the same volume of saturated aqueous sodium hydrogen carbonate and finally with water. The organic layers were dried over sodium sulfate, filtered through celite, and evaporated. The resulting crude materials were purified by silica gel column chromatography using as eluent a stepwise gradient of methanol (0-2%) in methylene chloride to give pure 4 (2.58 g, 64% yield) in the case of thymine, and pure 5 (2.71 g, 69% yield) as well as its N-3 isomer (0.43 g, 11% yield) in the case of uracil.

4: mp 73-75°C (lyophilized from dioxane); UV (EtOH) λ_{max} 265 nm (ε, 10,600), λ_{min} 241 nm (ε, 8,700); (0.1N HCl) λ_{max} 232 nm (ϵ_1), 266 nm (ϵ_2; ϵ_2/ϵ_1= 0.45), λ_{min} 255 nm; (0.1N NaOH) λ_{max} 222 nm (ϵ_1), 268 nm (ϵ_2; ϵ_2/ϵ_1=0.33), λ_{min} 250 nm; ^1H NMR δ 11.4 (s, 1H, NH-3), 8.0-7.5 (m, 11H, H-6 and 2 C_6H_5CO), 6.08 (d, 1H, H-1'; $J_{1',2'}$= 4.0 Hz), 5.76 (t, 1H, H-2'; $J_{2',3'}$= 4.0 Hz), 5.66 (t, 1H, H-3'; $J_{3',4'}$= 4.0 Hz), 5.0 (m, 1H, H-4'), 4.6 (m, 2H, H-5',5"), 2.05 (s,

3H, CH_3CO), 1.77 (d, 3H, CH_3-5; J_{6,CH_3}= 0.8 Hz); mass spectrum (matrix, G-T), FAB > 0: 509 $(M+H)^+$; $[\alpha]_D^{20}$ -9.3° (c 0.97, Me_2SO). Anal. Calcd. for $C_{26}H_{24}N_2O_9 \cdot 1/4\ C_4H_8O_2$: C, 61.12; H, 4.94; N, 5.28. Found: C, 60.96; H, 4.90; N, 5.05.

5: mp 90-93°C (lyophilized from dioxane); UV (EtOH) λ_{max} 259 nm (ϵ, 13,500), 231 nm (ϵ, 27,000), λ_{min} 249 nm (ϵ, 11,200); (0.1N HCl) λ_{max} 234 nm (ϵ_1), 262 (ϵ_2; ϵ_2/ϵ_1= 0.41), λ_{min} 255 nm; (0.1N NaOH) λ_{max} 222 nm (ϵ_1), 263 nm (ϵ_2; ϵ_2/ϵ_1= 0.32), λ_{min} 249 nm; ^1H NMR δ 11.50 (s, 1H, NH-3), 8.0-7.5 [m, 11H, H-6 and 2 C_6H_5CO; 7.88 (d, H-6; $J_{5,6}$= 8.0 Hz)], 6.07 (d, 1H, H-1'; $J_{1',2'}$= 3.9 Hz), 5.82 (t, 1H, H-2'; $J_{2',3'}$= 3.9 Hz), 5.7 (m, 2H, H-3' and H-5), 5.0 (m, 1H, H-4'), 4.6 (m, 2H, H-5',5"), 2.07 (s, 3H, CH_3CO); mass spectrum (matrix, G-T), FAB > 0: 495 $(M+H)^+$; $[\alpha]_D^{20}$ +5.0° (c 1.00, Me_2SO). Anal. Calc. for ($C_{25}H_{22}N_2O_9$): C, 60.72; H, 4.49; N, 5.67. Found: C, 60.85; H, 4.47; N, 5.59.

1-(2-O-Acetyl-3,5-di-O-benzoyl-α-L-arabinofuranosyl)cytosine (6).

A suspension of cytosine (1.60 g, 14.36 mmol, 1.14 eq) and ammonium sulfate (0.15 g, 1.14 mmol) in a mixture of HMDS (48 mL, 234.46 mmol) and pyridine (17.4 mL) was heated under reflux for 45 min. After cooling, the excess of HMDS and pyridine was removed *in vacuo* and by codistillation with anhydrous xylene. The resulting silylated cytosine was dissolved in anhydrous 1,2-dichloroethane (48 mL), then a solution of sugar 1 (5.55 g, 12.54 mmol, 1.0 eq) in 1,2-dichloroethane (117 mL) and a solution of trimethylsilyl triflate (TMSTF, 2.73 mL, 14.12 mmol, 1.13 eq) in the same solvent were added successively. The reaction mixture was heated under reflux for 16 h, cooled to room temperature, and then poured into ice-cold saturated aqueous hydrogen carbonate. The organic phase was separated, twice washed with water, dried over sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column using as eluent a stepwise gradient of methanol (0-12%) in methy-

lene chloride led to the isolation of pure 6 (3.45 g, 56% yield): mp 113-117°C (foam); UV (EtOH) λ_{max} 272 nm (ε, 9,900), 231 nm (ε, 3,400), λ_{min} 257 nm (ε, 8,700); (0.1N HCl) λ_{max} 231 nm (ϵ_1), 277 nm (ϵ_2; ϵ_2/ϵ_1= 0.53), λ_{min} 255 nm; (0.1N NaOH) λ_{max} 271 nm, λ_{min} 254 nm; ^{1}H NMR δ 8.1-7.4 (m, 10H, 2 C_6H_5CO), 7.76 (d, 1H, H-6; $J_{5,6}$= 7.4 Hz), 7.3 (br s, 2H, NH_2), 5.94 (d, 1H, H-1'; $J_{1',2'}$= 3.2 Hz), 5.78 (t, 1H, H-2'; $J_{2',3'}$= 3.2 Hz), 5.73 (d, 1H, H-5), 5.59 (dd, 1H, H-3'; $J_{3',4'}$= 4.5 Hz), 5.0 (m, 1H, H-4'), 4.5 (m, 2H, H-5',5"), 2.06 (s, 3H, CH_3CO); mass spectrum (matrix G-T), FAB > 0: 494 $(M+H)^+$; $[\alpha]_D^{20}$ +16.1° (c 0.95, Me_2SO). Anal. Calcd. for $C_{25}H_{23}N_3O_8$: C, 60.85; H, 4.70; N, 8.52. Found: C, 60.59; H, 4.77; N, 8.37.

N^2- Palmitoyl-9-(3,5-di-O-benzoyl-α-L-arabinofuranosyl)guanine (13).

A suspension of N^2-palmitoylguanine[32] (2.34 g, 6.0 mmol, 1.3 eq) in anhydrous acetonitrile (30 mL) was treated with bis(trimethylsilyl)acetamide (BSA) (5.9 mL, 23.87 mmol, 5.1 eq) during 15 min under reflux. To the resulting solution was added the sugar 1 (2.08 g, 4.70 mmol, 1.0 eq) in acetonitrile (20 mL), followed by addition of TMSTF (1.36 mL, 7.04 mmol, 1.5 eq). The solution was heated under reflux for 6 h. After cooling to room temperature, the reaction mixture was evaporated to dryness and to the residue were added $CHCl_3$ and saturated aqueous hydrogen carbonate. The organic phase was separated, washed with water and dried over sodium sulfate. The residue obtained by evaporation of the organic solution was dissolved in an acetic acid-pyridine mixture (1:4, v/v, 52 mL) and treated with hydrazine hydrate (0.88 mL, 18.14 mmol, 3.86 eq) with stirring at room temperature for 7 h. Reaction was quenched by acetone (30 mL) with stirring at room temperature. After 4 h, the mixture was partially evaporated *in vacuo* and extracted from water (100 mL) into chloroform (2×150 mL). Combined organic phases were washed several times with water, dried over sodium sulfate, filtered and evaporated to dryness. Chromatography of the residue on a silica gel

column using as eluent a stepwise gradient of methanol (0-6%) in methylene chloride led to the isolation of the N-7 isomer (0.55 g, 16% yield) and of pure 13 (1.85 g, 54% yield): mp 133-135°C (foam); UV (EtOH) λ_{max} 280 nm (ϵ, 6,600), 274 nm (ϵ, 6,400), 260 nm (ϵ, 8,000), 254 nm (ϵ, 8,100), 230 nm (ϵ, 13,800), λ_{min} 270 nm (ϵ, 6,300), 247 nm (ϵ, 7,500); (0.1N HCl) λ_{max} 231 nm (ϵ_1), 274 nm (ϵ_2; ϵ_2/ϵ_1= 0.63), λ_{min} 258 nm; (0.1N NaOH) λ_{max} 270 nm, λ_{min} 254 nm; ^{1}H NMR δ 12.15 and 11.67 (2s, 1H each, 2NH), 8.34 (s, 1H, H-8), 8.0-7.5 (m, 10H, 2 C_6H_5CO), 6.4 (sl, 1H, OH-2'), 6.07 (d, 1H, H-1'; $J_{1',2'}$= 3.8 Hz), 5.53 (t, 1H, H-3'; $J_{2',3'}$= $J_{3',4'}$= 4.3 Hz), 5.1 (m, 1H, H-2'), 5.0 (m, 1H, H-4'), 4.6 (m, 2H, H-5',5"), 2.45 (t, 2H, CH_2), 1.6 and 1.2 (2m, 2 and 24 H, 13 CH_2), 0.84 (t, 3H, CH_3); mass spectrum (matrix G-T), FAB > 0: 730 $(M+H)^+$, 390 $(BH_2)^+$; $[\alpha]_D^{20}$ 0° (c 0.95, Me_2SO). Anal. Calcd. for $C_{40}H_{51}N_5O_8 \cdot 1/6\ CH_2Cl_2$: C, 64.84; H, 6.96; N, 9.41. Found: C, 64.91; H, 6.99; N, 9.53.

General Procedure for the Preparation of selectively 2'-O-deacetylated 3',5'-di-O-benzoyl-α-L-Arabinofuranosyl Nucleosides 12, 14 and 15.

To a solution of 3.8 mmol of 2 (1.97 g), 4 (1.93 g) or 5 (1.88 g) in an acetic acid-pyridine mixture (1:4, v/v, 34 mL) was added hydrazine hydrate (0.59 mL, 11.4 mmol, 3.0 eq). The solutions were stirred for 7 h (2) or 24 h (4 and 5) at ambient temperature and acetone (20 mL) was added. Stirring was continued for 2 h, the solutions were evaporated, and the residues were partitioned between water (80 mL) and methylene chloride (2×100 mL). The combined organic phases were washed with saturated aqueous hydrogen carbonate and water, then dried over sodium sulfate, filtered, evaporated and coevaporated with toluene. The resulting foams were chromatographed on a silica gel column using as eluent a stepwise gradient of methanol (0-4%) in methylene chloride. Evaporation of appropriate fractions gave 1.30 g (72% yield) of 12, 1.19 g (67% yield) of 14 and 1.14 g (66% yield) of 15.

9-(3,5-di-O-Benzoyl-α-L-arabinofuranosyl)adenine (12).

Mp 203-205°C (foam); UV (EtOH) λ_{max} 260 nm (ε, 17,700), 231 nm (ε, 32,800), λ_{min} 248 nm (ε, 14,800), 221 nm (ε, 26,000); (0.1N HCl) λ_{max} 234 nm (ϵ_1), 258 nm (ϵ_2; ϵ_2/ϵ_1= 0.53), λ_{min} 254 nm; (0.1N NaOH) λ_{max} 225 nm (ϵ_1), 259 nm (ϵ_2; ϵ_2/ϵ_1= 0.76), λ_{min} 243 nm; ^{1}H NMR δ 8.47 and 8.19 (2s, 1H each, H-2 and H-8), 8.1-7.5 (m, 10H, 2 C_6H_5CO), 7.37 (s, 2H, NH_2), 6.4 (br s, 1H, OH-2'), 6.18 (d, 1H, H-1'; $J_{1',2'}$= 4.2 Hz), 5.55 (t, 1H, H-3'; $J_{2',3'}$= $J_{3',4'}$= 4.8 Hz), 5.3 (m, 1H, H-2'), 4.96 (dd, 1H, H-4'), 4.59 (d, 2H, H-5',5"; J = 4.7 Hz); mass spectrum (matrix G-T), FAB > 0: 476 $(M+H)^+$, 136 $(BH_2)^+$; $[\alpha]_D^{20}$ -19.4° (c 1.08, Me_2SO). Anal. Cald. for ($C_{24}H_{21}N_5O_6$): C, 60.63; H, 4.45; N, 14.73. Found: C, 60.89; H, 4.37; N, 14.55.

1-(3,5-di-O-Benzoyl-α-L-arabinofuranosyl)thymine (14).

Mp 80-82°C (lyophilized from dioxane); UV (EtOH) λ_{max} 266 nm (ε, 10,000), λ_{min} 249 nm (ε, 7,300); (0.1N HCl) λ_{max} 232 nm (ϵ_1), 270 nm (ϵ_2; ϵ_2/ϵ_1= 0.36), λ_{min} 256 nm; (0.1N NaOH) λ_{max} 222 nm (ϵ_1), 268 nm (ϵ_2; ϵ_2/ϵ_1= 0.32), λ_{min} 255 nm; ^{1}H NMR δ 11.3 (s, 1H, NH-3), 8.1-7.5 (m, 11H, H-6 and 2 C_6H_5CO), 6.29 (d, 1H, OH-2'; J = 4.5 Hz), 5.94 (d, 1H, H-1'; $J_{1',2'}$= 3.4 Hz), 5.4 (t, 1H, H-3'; $J_{2',3'}$= 3.5 Hz), 4.99 (d, 1H, H-4', $J_{3',4'}$= 3.8 Hz), 4.56 (m, 3H, H-2',5' and 5"), 1.77 (s, 3H, CH_3-5); mass spectrum (matrix, G), FAB > 0: 467 $(M+H)^+$, 127 $(BH_2)^+$; $[\alpha]_D^{20}$ +4.2° (c 0.97, Me_2SO).

1-(3,5-di-O-Benzoyl-α-L-arabinofuranosyl)uracil (15).

Mp 116-123°C (lyophilized from dioxane); UV (EtOH) λ_{max} 262 nm (ε, 11,000), 231 nm (ε, 26,500), λ_{min} 251 (ε, 9,200); (0.1N HCl) λ_{max} 233 nm (ϵ_1), 263 nm (ϵ_2; ϵ_2/ϵ_1= 0.37), λ_{min} 256 nm; (0.1N NaOH) λ_{max} 221 nm (ϵ_1), 263 nm (ϵ_2; ϵ_2/ϵ_1= 0.35), λ_{min} 250 nm; ^{1}H NMR δ 11.34 (s, 1H, NH-3), 8.0-7.5 [m, 11H, H-6 and 2 C_6H_5CO; 7.87 (d, H-6; $J_{5,6}$= 8.1 Hz)], 6.3 (br s, 1H, OH-2'), 5.90 (d, 1H, H-1'; $J_{1',2'}$= 4.5 Hz), 5.60 (d, 1H, H-5), 5.39 (t, 1H, H-3'; $J_{2',3'}$=

$J_{3',4'}$ = 3.6 Hz), 4.92 (dd, 1H, H-4'), 4.6 (m, 1H, H-2'), 4.54 (d, 2H, H-5',5"; J = 5.4 Hz); mass spectra (matrix, G-T), FAB>0: 453 $(M+H)^+$, 113 $(BH_2)^+$; FAB < 0: 451 $(M+H)^-$, 111 $(B)^-$; $[\alpha]_D^{20}$ +14.3° (c 0.98, Me_2SO). Anal. Calcd. for $C_{23}H_{20}N_2O_8 \cdot 2/3\ C_4H_8O_2$: C, 60.30; H, 4.99; N, 5.48. Found: C, 60.02; H, 4.93; N, 5.96.

General Procedure for the Preparation of 2'-Deoxy-3',5'-di-O-benzoyl-α-L-*erythro*-pentofuranosyl Nucleosides 16-19.

To a solution of 2.0 mmol of 12 (0.95 g), 13 (1.46 g), 14 (0.93 g) or 15 (0.91 g) in anhydrous methylene chloride (22 mL, for 12, 14, 15) or acetonitrile (30 mL, for 13) were added phenyl chlorothionocarbonate (0.55 mL, 4.0 mmol, 2.0 eq) and 4-(dimethylamino)pyridine (DMAP, 0.98 g, 8.0 mmol, 4.0 eq). The solutions were stirred for 5 h at ambient temperature and, then, diluted with methylene chloride. Water was added and the organic phases were successively washed with ice-cold 1N aqueous hydrochloric acid, water, saturated aqueous hydrogen carbonate and water, then dried over sodium sulfate, filtered, and evaporated to dryness. The resulting foams were dissolved in dry toluene, evaporated *in vacuo*, and this process was repeated three times. The residues were dissolved in dry toluene (50 mL) and treated with tributyltin hydride (1.45 mL, 5.4 mmol, 2.7 eq) and α,α'-azobisisobutyronitrile (AIBN, 99 mg, 0.6 mmol, 0.3 eq) at 80°C for 4 h. The solutions were evaporated to leave crude 16-19 which were precipitated from hexane. Purifications were accomplished by silica gel column chromatography using as eluent a stepwise gradient of methanol (0-4%) in methylene chloride. Pooling and evaporation of the appropriate fractions as indicated by TLC gave pure 16 (0.73 g, 79% yield), 17 (0.77 g, 54% yield), 18 (0.58 g, 64% yield) and 19 (0.70 g, 80% yield).

9-(2-Deoxy-3,5-di-O-benzoyl-α-L-*erythro*-pentofuranosyl)adenine (16).

Mp 170-176°C (foam); UV (EtOH) λ_{max} 260 nm (ε, 12,200), 231 nm (ε, 22,400), λ_{min} 249 nm (ε, 10,200);

(0.1N HCl) λ_{max} 234 nm (ϵ_1), 257 nm (ϵ_2; ϵ_2/ϵ_1= 0.54), λ_{min} 253 nm; (0.1N NaOH) λ_{max} 225 nm (ϵ_1), 258 nm (ϵ_2; ϵ_2/ϵ_1= 0.85), λ_{min} 242 nm; ^{1}H NMR δ 8.38 and 8.12 (2s, 1H each, H-2 and H-8), 8.1-7.5 (m, 10H, 2 C_6H_5CO), 7.30 (s, 2H, NH_2), 6.6 (br s, 1H, H-1'), 5.7 (m, 1H, H-3'), 5.0 (m, 1H, H-4'), 4.55 (d, 2H, H-5',5"; J = 4.6 Hz), 3.1 (m, 2H, H-2',2"); mass spectrum (matrix, G-T), FAB>0: 460 $(M+H)^+$, 136 $(BH_2)^+$; $[\alpha]_D^{20}$ -21.1° (c 0.95, Me_2SO). Anal. Calcd. for $C_{24}H_{21}N_5O_5 \cdot 1/3\ H_2O$: C, 61.93; H, 4.69; N, 15.05. Found: C, 62.01; H, 4.45; N, 15.05.

N^2-Palmitoyl-9-(2-deoxy-3,5-di-O-benzoyl-α-L-*erythro*-pentofuranosyl)guanine (17).

UV (EtOH) λ_{max} 281 nm (ε, 8,800), 275 nm (ε, 8,900), 260 nm (ε, 12,000), 255 nm (ε, 12,000), 232 nm (ε, 18,700), λ_{min} 271 nm (ε, 8,800), 249 nm (ε, 10,000); ^{1}H NMR δ 12.08 and 11.69 (2s, 1H each, 2NH), 8.27 (s, 1H, H-8), 8.1-7.5 (m, 10H, 2 C_6H_5CO), 6.45 (d, 1H, H-1'; $J_{1',2'}$= 4.7 Hz), 5.70 (d, 1H, H-3'; $J_{2',3'}$= 5.2 Hz), 5.0 (br s, 1H, H-4'), 4.55 (s, 2H, H-5',5"), 3.0 (m, 2H, H-2',2"), 2.44 (t, 2H, CH_2), 1.6 and 1.2 (2m, 2 and 24H, 13 CH_2), 0.85 (t, 3H, CH_3); mass spectrum (matrix, NBA), FAB>0: 714 $(M+H)^+$, 390 $(BH_2)^+$.

1-(2-Deoxy-3,5-di-O-benzoyl-α-L-*erythro*-pentofuranosyl)thymine (18).

Mp 183-185°C (crystallized from ethyl acetate); UV (EtOH) λ_{max} 267 nm (ε, 12,400), λ_{min} 249 nm (ε, 8,900); (0.1N HCl) λ_{max} 232 nm (ϵ_1), 271 nm (ϵ_2; ϵ_2/ϵ_1= 0.42), λ_{min} 255 nm; (0.1N NaOH) λ_{max} 221 nm (ϵ_1), 266 nm (ϵ_2; ϵ_2/ϵ_1= 0.32), λ_{min} 250 nm; ^{1}H NMR δ 11.3 (s, 1H, NH-3), 8.1-7.5 (m, 11H, H-6 and 2C_6H_5CO), 6.23 (dd, 1H, H-1'; $J_{1',2'}$= 2.0 Hz, $J_{1',2"}$= 7.0 Hz), 5.58 (d, 1H, H-3'; $J_{2",3'}$= 6.4 Hz), 5.09 (t, 1H, H-4'; J = 5.1 Hz), 4.46 (d, 2H, H-5',5"; J = 5.1 Hz), 2.9 (m, 1H, H-2"), 2.41 (dd, 1H, H-2'; $J_{2',2"} \simeq$ 15.1 Hz), 1.73 (s, 3H, CH_3-5); mass spectrum (matrix, G-T), FAB > 0: 451 $(M+H)^+$, 127 $(BH_2)^+$; FAB < 0: 449 $(M-H)^-$, 125 $(B)^-$; $[\alpha]_D^{20}$ +16.3° (c 0.98, Me_2SO). Anal.

Calcd. for $C_{24}H_{22}N_2O_7 \cdot 1/4\ H_2O$: C, 63.36; H, 4.99; N, 6.16. Found: C, 63.40; H, 4.84; N, 6.08.

1-(2-Deoxy-3,5-di-O-benzoyl-α-L-*erythro*-pentofuranosyl)uracil (19).

Mp 157-158°C (crystallized from methanol); UV (EtOH) λ_{max} 264 nm (ϵ, 13,000), 231 nm (ϵ, 28,800), λ_{min} 249 nm (ϵ, 10,600); (0.1N HCl) λ_{max} 233 nm (ϵ_1), 264 nm (ϵ_2; ϵ_2/ϵ_1= 0.40), λ_{min} 254 nm; (0.1N NaOH) λ_{max} 222 nm (ϵ_1), 262 nm (ϵ_2; ϵ_2/ϵ_1= 0.35), λ_{min} 249 nm; ^{1}H NMR δ 11.3 (br s, 1H, NH-3), 8.1-7.5 [m, 11H, H-6 and 2 C_6H_5CO; 7.83 (d, 1H, H-6; $J_{5,6}$= 8.1 Hz)], 6.19 (dd, 1H, H-1'; $J_{1',2'}$= 1.8 Hz, $J_{1',2''}$= 6.7 Hz), 5.57 [m, 2H, H-3' and H-5; after D_2O exchange: 5.59 (d, 1H, H-5) and 5.55 (d, 1H, H-3'; $J_{2'',3'}$= 6.4 Hz)], 5.03 (t, 1H, H-4'), 4.47 (d, 2H, H-5',5"; J = 4.9 Hz), 2.9 (m, 1H, H-2"), 2.49 (m, 1H, H-2' partially obscured by Me_2SO-d_5); mass spectra (matrix, G-T) FAB>0: 437 $(M+H)^+$, 113 $(BH_2)^+$; FAB < 0: 435 $(M-H)^-$, 111 $(B)^-$; $[\alpha]_D^{20}$ +42.7° (c 0.96, Me_2SO). Anal. Calcd. for $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42. Found: 63.30; H, 4.64; N, 6.28.

General Procedures for the Preparation of Unprotected α-L-Arabinofuranosyl Nucleosides 7-11 and 2'-Deoxy-α-L-*erythro*-pentofuranosyl Nucleosides 20-23.

The protected nucleosides **2**, **4-6**, **13**, and **16-19** were dissolved with stirring in methanolic ammonia (previously saturated at -10°C and tightly stoppered) (*ca.* 25 mL/mmol). When TLC indicated that the reactions were complete, the solutions were evaporated to dryness, and to the residues water was added. The aqueous phases were washed twice with ethyl ether and then evaporated to dryness to afford the deblocked nucleosides, which were further purified by either chromatography or direct crystallization. The results of these unblockings and the physical properties of unprotected nucleosides are presented below:

9-α-L-Arabinofuranosyladenine (7): 60% yield [after preparative TLC (eluent: 25% methanol in methylene chloride) and

then crystallization from methanol], mp 216°C; UV (H_2O) λ_{max} 259 nm (ε, 14,400), λ_{min} 226 nm (ε, 2,400); (0.1N HCl) λ_{max} 256 nm, λ_{min} 230 nm; (0.1N NaOH) λ_{max} 257 nm, λ_{min} 228 nm; ^{1}H NMR δ 8.32 and 8.15 (2s, 1H each, H-2 and H-8), 7.28 (s, 2H, NH_2), 5.83 (d, 1H, H-1'; $J_{1',2'}$= 4.9 z), 5.76 (d, 1H, OH-2'; J = 5.3 Hz), 5.63 (d, 1H, OH-3'; J = 5.0 Hz), 4.87 (t, 1H, OH-5'; J = 5.5 Hz), 4.7 (m, 1H, H-2'), 4.15 (m, 1H, H-4'), 4.0 (m, 1H, H-3'), 3.6-3.4 (m, 2H, H-5',5"); mass spectrum (matrix, G-T), FAB>0: 268 $(M+H)^+$; $[\alpha]_D^{20}$ -90.5° (c 0.93, Me_2SO). Anal. Calcd. for $C_{10}H_{13}N_5O_4$• 1/6 CH_4O: C, 44.80; H, 5.05; N, 25.69. Found: C, 44.88; H, 4.82; N, 25.47.

9-α-L-Arabinofuranosylguanine (8): 53% yield [after silanized silica gel (RP2, Merck n°7719) column chromatography (eluent: H_2O), and then crystallization from H_2O]; mp 229-239°C, decomposition; UV (H_2O) λ_{max} 252 nm (ε, 12,600), 270 nm (sh, ε, 8,900), λ_{min} 223 nm (ε, 2,800); (0.1N HCl) λ_{max} 255 nm, 275 nm (sh), λ_{min} 227 nm; (0.1N NaOH) λ_{max} 258 nm (sh), 264 nm, λ_{min} 233 nm; ^{1}H NMR δ 10.65 (s, 1H, NH-1), 7.92 (s, 1H, H-8), 6.47 (s, 2H, NH_2), 5.75 (d, 1H, OH-2'; J = 5.3 Hz), 5.66 (d, 1H, H-1'; $J_{1',2'}$= 5.1 Hz), 5.54 (d, 1H, OH-3'; J = 4.8 Hz), 4.89 (t, 1H, OH-5'; J = 5.4 Hz), 4.48 (dd, 1H, H-2'; $J_{2',3'}$= 5.2 Hz), 4.1 (m, 1H, H-4'), 4.0 (m, 1H, H-3'), 3.6-3.4 (m, 2H, H-5',5"); mass spectrum (matrix, G-T), FAB>0: 284 $(M+H)^+$, 152 $(BH_2)^+$; $[\alpha]_D^{20}$ -71.5° (c 1.02, Me_2SO). Anal. Calcd. for $C_{10}H_{13}N_5O_5$•H_2O: C, 39.87; H, 5.02; N, 23.25. Found: C, 39.75; H, 5.20; N, 22.44.

1-α-L-Arabinofuranosylthymine (9)[21]: 61% yield [after silica gel 60 column chromatography (eluent: stepwise gradient of methanol (0-20%) in methylene chloride), and then lyophilization from a dioxane-water mixture]; mp 70-73°C; UV (EtOH) λ_{max} 266 nm (ε, 9,500), λ_{min} 234 nm (ε, 2,200); (0.1N HCl) λ_{max} 266 nm, λ_{min} 235 nm; (0.1N NaOH) λ_{max} 267 nm, λ_{min} 247 nm; ^{1}H NMR δ 11.2 (br s, 1H, NH-3), 7.57 (d, 1H, H-6; J_{6,CH_3}= 1.1 Hz), 5.71 (d, 1H, H-1'; $J_{1',2'}$= 5.0 Hz), 5.61 and 5.40 (2d, 2×1H, OH-2' and 3'; J = 5.3 and

4.3 Hz, respectively), 4.86 (t, 1H, OH-5'; J = 3.5 Hz), 4.1 (m, 2H, H-2' and 4'), 3.9 (m, 1H, H-3'), 3.6-3.3 (m, 2H, H-5' and 5"), 1.78 (d, 3H, CH_3-5); mass spectrum (matrix, G), FAB>0: 259 $(M+H)^+$, 127 $(BH_2)^+$; $[\alpha]_D^{20}$ -52.6° (c 0.94, Me_2SO). Anal. Calcd. for $C_{10}H_{14}N_2O_6 \cdot 1/3\ H_2O$, 1/4 $C_4H_8O_2$: C, 46.15; H, 5.87; N, 9.79. Found: C, 46.34; H, 5.91; N, 9.61.

1-α-L-Arabinofuranosyluracil (10)[21]: 87% yield [after silica gel 60 column chromatography (eluent: stepwise gradient of methanol (0-20%) in methylene chloride), and then lyophilization from a dioxane-water mixture]; hygroscopic compound; UV (EtOH) λ_{max} 262 nm (ε, 9,000), λ_{min} 230 nm (ε, 1,800); (0.1N HCl) λ_{max} 261 nm, λ_{min} 230 nm; (0.1N NaOH) λ_{max} 262 nm, λ_{min} 243 nm; ^1H NMR δ 11.2 (br s, 1H, NH-3), 7.68 (d, 1H, H-6, $J_{5,6}$= 8.1 Hz), 5.70 (d, 1H, H-1'; $J_{1',2'}$= 4.1 Hz), 5.66 (d, 1H, OH-2'; J = 5.1 Hz), 5.60 (d, 1H, H-5), 5.41 (d, 1H, OH-3'; J = 3.8 Hz), 4.90 (t, 1H, OH-5'; J = 5.3 Hz), 4.1 (m, 2H, H-2' and 4'), 3.92 (dd, 1H, H-3'; $J_{2',3'}$= $J_{3',4'}$= 3.8 Hz), 3.6-3.4 (m, 2H, H-5',5"); mass spectra (matrix, G-T), FAB>0: 245 $(M+H)^+$, 113 $(BH_2)^+$, FAB < 0: 243 $(M-H)^-$, 111(B)$^-$; $[\alpha]_D^{20}$ -35.4° (c 0.96, Me_2SO). Anal. Calcd. for $C_9H_{12}N_2O_6 \cdot 1/3\ H_2O$, 1/4 $C_4H_8O_2$: C, 44.11; H, 5.43; N, 10.29. Found: C, 44.21; H, 5.52; N, 10.34.

1-α-L-Arabinofuranosylcytosine (11)[21]: 50% yield (after direct crystallization from ethanol); mp 180°C; UV (EtOH) λ_{max} 271 nm (ε, 9,200), λ_{min} 249 nm (ε, 6,300); (0.1N HCl) λ_{max} 280 nm, λ_{min} 240 nm; (0.1N NaOH) λ_{max} 271 nm, λ_{min} 250 nm; ^1H NMR δ 7.59 (d, 1H, H-6; $J_{5,6}$= 7.4 Hz), 7.2-7.0 (br s, 2H, NH_2), 5.7 [m, 2H, H-5 and H-1'; 5.74 (d, 1H, H-5) and 5.67 (d, 1H, H-1'; $J_{1',2'}$= 3.3 Hz) after D_2O exchange], 5.59 (d, 1H, OH-2'; J = 5.1 Hz), 5.32 (d, 1H, OH-3'; J = 4.0 Hz), 4.93 (t, 1H, OH-5'; J = 5.5 Hz), 4.1 (m, 1H, H-4'), 4.0 (m, 1H, H-2'), 3.9 (m, 1H, H-3'), 3.6-3.4 (m, 2H, H-5',5"); mass spectrum (matrix, G-T), FAB>0: 244 $(M+H)^+$, 112 $(BH_2)^+$; $[\alpha]_D^{20}$ -29.5° (c 0.95, Me_2SO). Anal. Calcd for $C_9H_{13}N_3O_5 \cdot 1/3\ H_2O$: C, 43.37; H, 5.53; N, 16.86. Found: C, 43.77; H, 5.56; N, 16.57.

9-(2-Deoxy-α-L-*erythro*-pentofuranosyl)adenine (20)[22]: 76% yield [after silanized silica gel (RP2, Merck n° 7719) column chromatography (eluent: linear gradient of methanol (0-10%) in water), and then crystallization from methanol]; mp 213-215 °C; λ_{max} 260 nm (ε, 16,800), λ_{min} 227 nm (ε, 2,800); (0.1N HCl) λ_{max} 257 nm, λ_{min} 229 nm; (0.1N NaOH) λ_{max} 256 nm, λ_{min} 226 nm; ^{1}H NMR δ 8.37 and 8.13 (2s, 1H each, H-2 and H-8), 6.32 (dd, 1H, H-1', $J_{1',2'}$= 3.0 Hz and $J_{1',2"}$= 7.9 Hz), 5.76 (d, 1H, OH-3'; J = 4.4 Hz), 4.84 (t, 1H, OH-5'; J = 5.6 Hz), 4.3 (m, 1H, H-3'), 4.1 (m, 1H, H-4'), 3.4 (m, 2H, H-5',5"), 2.7 (m, 1H, H-2"), 2.3 (ddd, 1H, H-2'; $J_{2',3'}$= 2.8 Hz, $J_{2',2"}$= 14.2 Hz); mass spectrum (matrix, G-T), FAB>0: 252 $(M+H)^+$, 136 $(BH_2)^+$; $[\alpha]_D^{20}$ -85.7° (c 0.97, Me_2SO). Anal. Calcd. for $C_{10}H_{13}N_5O_3$:C, 47.80; H, 5.21; N, 27.88; O, 19.11. Found: C, 48.04; H, 5.30; N, 27.64; O, 18.66.

9-(2-Deoxy-α-L-*erythro*-pentofuranosyl)guanine (21)[22]: 81% yield [after silinazed silica gel (RP 2, Merck n° 7719) column chromatography (eluent: water), and then lyophilization from a dioxane-water mixture); mp 265°C, decomposition; UV (H_2O) 252 nm (ε, 12,400), 271 nm (sh, ε, 8,700), λ_{min} 223 nm (ε, 2,800); (0.1N HCl) λ_{max} 254 nm, λ_{min} 275 nm (sh); (0.1N NaOH) λ_{max} 256 nm (sh), 264 nm, λ_{min} 233 nm; ^{1}H NMR δ 10.62 (s, 1H, NH-1), 7.95 (s, 1H, H-8), 6.45 (s, 2H, NH_2), 6.08 (dd, 1H, H-1'; $J_{1',2'}$= 2.9 Hz and $J_{1',2"}$= 7.9 Hz), 5.45 (d, 1H, OH-3'; J = 3.8 Hz), 4.81 (t, 1H, OH-5'; J = 5.5 Hz), 4.3 (m, 1H, H-3'), 4.05 (dd, 1H, H-4'; $J_{3',4'}$= 7.5 Hz and $J_{4',5'}$= 4.5 Hz), 3.4 (m, 2H, H-5',5"), 2.7 (m, 1H, H-2"), 2.18 (dt, 1H, H-2'; $J_{2',2"}$= 14.1 Hz); mass spectrum (matrix, G-T), FAB>0: 268 $(M+H)^+$, 152 $(BH_2)^+$; $[\alpha]_D^{20}$ -94.8° (c 0.96, Me_2SO). Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot$ 4/5 H_2O: C, 42.64; H, 5.22; N, 24.87. Found: C, 42.94; H, 5.26; N, 24.58.

1-(2-Deoxy-α-L-*erythro*-pentofuranosyl)thymine (22): 82% yield [after silica gel 60 column chromatography (eluent:

stepwise gradient of methanol (0-20%) in methylene chloride), and then crystallization from methanol]; mp 189-192 °C; UV (EtOH) λ_{max} 266 nm (ϵ, 11,100), λ_{min} 234 (ϵ, 3,000); (0.1N HCl) λ_{max} 267 nm, λ_{min} 235 nm; (0.1N NaOH) λ_{max} 266 nm, λ_{min} 245 nm; ^{1}H NMR δ 11.2 (s, 1H, NH-3), 7.74 (d, 1H, H-6; J_{6,CH_3}= 1.1 Hz), 6.10 (dd, 1H, H-1'; $J_{1',2'}$= 3.1 Hz and $J_{1',2"}$= 7.7 Hz), 5.29 (br s, 1H, OH-3'), 4.79 (br s, 1H, OH-5'), 4.2 (br s, 1H, H-3'), 4.1 (m, 1H, H-4'), 3.38 (pt, 2H, H-5',5"; J = 4.5 Hz), 2.5 (m, 1H, H-2"), 1.9 (m, 1H, H-2'), 1.77 (d, 3H, CH_3-5); mass spectrum (matrix, G), FAB>0: 243 $(M+H)^+$, 127 $(BH_2)^+$; $[\alpha]_D^{20}$ -47.5° (c 0.96, Me_2SO). Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.84; H, 5.67; N, 11.49.

1-(2-Deoxy-α-L-*erythro*-pentofuranosyl)uracil (23): 73% yield [after silica gel 60 column chromatography (eluent: stepwise gradient of methanol (0-20%) in methylene chloride), and then lyophilization from dioxane]; hygroscopic compound; UV (EtOH) λ_{max} 263 (ϵ, 9,000), λ_{min} 231 nm (ϵ, 1,500); (0.1N HCl) λ_{max} 262 nm, λ_{min} 231 nm; (0.1N NaOH) λ_{max} 260 nm, λ_{min} 242 nm; ^{1}H NMR δ 11.2 (br s, 1H, NH-3), 7.85 (d, 1H, H-6; $J_{5,6}$= 8.1 Hz), 6.09 (dd, 1H, H-1'; $J_{1',2'}$= 2.4 Hz and $J_{1',2"}$= 7.6 Hz), 5.61 (d, 1H, H-5), 5.29 (d, 1H, OH-3'; J = 3.0 Hz), 4.80 (t, 1H, OH-5'; J = 5.6 Hz), 4.2 (br s, 1H, H-3'), 4.13 (br t, 1H, H-4'), 3.37 (t, 2H, H-5',5"; J = 5.0 Hz), 2.6 (m, 1H, H-2"), 1.9 (br s, 1H, H-2'); mass spectrum (matrix, G-T), FAB>0: 229 $(M+H)^+$, 113 $(BH_2)^+$; $[\alpha]_D^{20}$ +7.0° (c 1.15, Me_2SO). Anal. Calcd. for $C_9H_{12}N_2O_5 \cdot 1/4\ C_4H_8O_2$: C, 47.99; H, 5.63; N, 11.20. Found: C, 47.89; H, 5.82; N, 11.24.

1-(2-Deoxy-α-L-*erythro*-pentofuranosyl)cytosine (24).

Compound **19** (0.30 g, 0.69 mmol) was dissolved in dry pyridine (4 mL) and 1,2,4-triazole (0.15 g, 2.1 mmol, 3.1 eq) was added. The reaction mixture was stirred in a cold-water bath, and *o*-chlorophenyl phosphorodichloridate (0.17 mL, 1.0 mmol, 1.5 eq) was added dropwise. The reaction mixture was stirred at room temperature for 72 h

and then evaporated *in vacuo*. The residue was dissolved in methylene chloride (10 mL) and successively washed with water (2×10 mL), saturated aqueous hydrogen carbonate (2×10 mL), and water (2×10 mL) again. The organic phase was clarified with charcoal and dried over sodium sulfate. Evaporation of the filtrate gave the 4-triazolylpyrimidinone intermediate which was immediately dissolved in a dioxane-ammonium hydroxide (d, 0.91) mixture (3:1, v/v; 20 mL) and stirred at room temperature for 4.5 h. The solution was evaporated to dryness, coevaporated with methanol, and the residue was dissolved in saturated methanolic ammonia (20 mL). The solution was stirred at room temperature for 24 h, then evaporated to dryness, and the residue was partitioned between methylene chloride (10 mL) and water (10 mL). The aqueous phase was evaporated, and the residue chromatographed on a silica gel column using as eluent a stepwise gradient of methanol (0-25%) in methylene chloride. The appropriate fractions were pooled, evaporated to dryness, dissolved in water and passed through a Sep-Pak C_{18} cartridge (Millipore, Waters Associates), to give after lyophilization from water pure **24** (63 mg, 40% yield); mp 116-123 °C; UV (EtOH) λ_{max} 273 nm (ϵ, 8,000), λ_{min} 251 nm (ϵ, 5,500); (0.1N HCl) λ_{max} 279 nm, λ_{min} 240 nm; (0.1N NaOH) λ_{max} 269 nm, λ_{min} 248 nm; ^{1}H NMR δ 7.73 (d, 1H, H-6; $J_{5,6}$= 7.4 Hz), 7.0 (br s, 2H, NH_2), 6.03 (dd, 1H, H-1'; $J_{1',2'}$= 2.8 Hz and $J_{1',2''}$= 7.4 Hz), 5.68 (d, 1H, H-5), 5.2 (br s, 1H, OH-3'), 4.8 (br s, 1H, OH-5'), 4.2 (br s, 1H, H-3'), 4.1 (m, 1H, H-4'), 3.37 (m, 2H, H-5',5"), 2.5 (m, 1H, H-2"), 1.8 (m, 1H, H-2'); mass spectra (matrix, G-T), FAB>0: 228 $(M+H)^+$, 112 $(BH_2)^+$; FAB<0: 226 $(M-H)^-$, 110 $(B)^-$; $[\alpha]_D^{20}$ +6.6° (c 0.91, Me_2SO). Anal. Calcd. for $C_9H_{13}N_3O_4 \cdot 2/3\ H_2O$: C, 45.18; H, 6.04; N, 17.57. Found: C, 45.07; H, 5.70; N, 16.12.

BIOLOGICAL METHODS.

Broad Antiviral Assays on Cell culture.

The antiviral assay was performed by a method adapted from that described by De Clercq et al.[49,50] The following

viruses were used: Herpes virus type 1 (HSV 1), strain F (ATCC VR-733); Herpes virus type 2 (HSV-2), strain G (ATCC VR-734); Human Cytomegalovirus (HCMV), strain AD169 (ATCC VR-538); Vaccinia virus, strain Copenhague; Poliovirus type I, strain Mahoney (ATCC VR-59); Coxsackie virus B3 (ATCC VR-30); Respiratory syncytial virus (RSV), strain A2 and Paramyxovirus type III (these two later viruses were provided by Pr. P. Halonen, Turku, Finland). HSV-1, HSV-2, Vaccinia virus, RSV and Paramyxovirus type III were propagated on Vero cells, HCMV was grown on human embryonic fibroblasts (cell line MRC5) and the two enteroviruses, Poliovirus type I and Coxsackie virus B3 on KB cells. All assays were carried out on confluent cells in 96-wells microtiters plates. The cells were grown in Eagle's minimum essential medium (MEM) supplemented with 5% fetal bovine serum. They were infected with 100 $CCID_{50}$ of virus for 1 hour at 37°C and immediately thereafter exposed to various concentrations of the test compounds (from 1 mM to 1 μM). The viral cytopathic effect (CPE) was recorded daily. Antiviral activity was expressed as ID_{50} (50% inhibitory dose), that is the concentration of compound required to reduce the viral cytopathic effect by 50% when it had reached completion in the control virus infected cell cultures.

Anti-Human Immunodeficiency Virus (HIV) Assays.

Cells and virus. CEM and MT4 cells were grown in RPMI 1640 medium containing 10% heat inactivated fetal bovine serum (FBS), 2 mM L-glutamine and 50 μg/mL gentamicin. HIV-1 (strain HTLV-IIIB)[51] was obtained from the culture supernatant of a chronically HIV infected H9 cell line and titrated in MT4-cells to determine the minimum dose required to cause the death of 90% of the cells. The isolate HIV-1 BRU[52] was propagated by *de novo* infection of CEM cells. From the third day after infection the medium was collected daily and titrated on CEM cells by numeration of syncytia. Virus stocks were stored aliquoted at -80°C.

Cytotoxicity assay on MT4 cells. Multiplication of HIV-1 in MT4 cells was measured by the reduction in viability of the cells resulting from the infection. Exponentially growing cells were infected with the minimum dose of HIV-1 (HTVL-IIIB) required to cause 90% cell death after 5 days. After adsorption of the virus for 30 min, unbound particles were removed, infected cells were resuspended in RPMI + 20% FBS ($4\ 10^5$ cells/mL) and distributed in 96 well microtiter plates (0.1 mL/well). The compounds to be tested for antiviral activity were dissolved in dimethyl sulfoxyde at the concentration 10^{-2} M, before being serialy diluted in RPMI; 100 μL of each dilutions was added to 4 wells of infected cells. The cells were then incubated for 5 days at 37°C in air -5% CO_2. In parallel, a series of mock-infected cells were treated with the same compounds. The viability of the cells was measured by a colorimetric reaction based on their capacity to reduce 3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide (MTT) in formazan, a property due to mitochondrial dehydrogenases according to the described procedure.[53] Fifty percent effective dose (ED_{50}) was defined as the concentration of compound required to achieve protection of infected cells by 50%.[54] Fifty percent cytotoxic dose (CD_{50}) was defined as the concentration of compound that reduced the viability of uninfected cells by 50%.

Syncytium reduction assay on CEM Cells. Multiplication of HIV-1 BRU in CEM cells was measured by the number of syncytia produced after 4 days of infection. CEM were infected with 100 to 200 syncytia forming units of HIV per $4\ 10^5$ cells. After 30 min adsorption, the residual free virus was eliminated; infected cells were resuspended in RPMI, 10% FBS. They were distributed in 24-well plates (0.9 mL containing $4\ 10^5$ cells/well) and 0.1 mL of different dilutions of the antiviral drugs were added to the cells. After 4 days at 37°C, the syncytia were numerated under light microscopy. Fifty percent effective dose (ED_{50}) was defined as the concentration of drug that reduced the

number of syncytia by 50%. Inhibition of virus multiplication was confirmed by comparing the reverse transcriptase activity associated to the virus particles released in the culture medium after 4 days of infection in the presence or in the absence of the drug. Fifty percent cytotoxic dose (CD_{50}) was determined by the MTT dye reduction assay as described for MT4 cells.

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