Synthesis and Antiviral Activity Acyclic Nucleosides with a 3(S),5-Dihydroxypentyl or 4(R)-Methoxy-3(S),5-dihydroxypentyl Side Chain

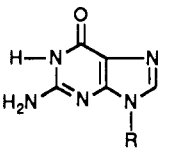
Frank Vandendriessche,† Robert Snoeck,‡ Gerard Janssen,† Jos Hoogmartens,† Arthur Van Aerschot,† Erik De Clercq,‡ and Piet Herdewijn*,†

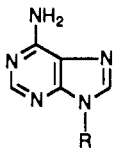
Laboratory of Pharmaceutical Chemistry, Instituut voor Farmaceutische Wetenschappen, and Laboratory of Chemotherapy, Faculteit Geneeskunde, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium. *Received June 24, 1991*

Optically pure acyclic nucleoside analogues with a 3(S),5-dihydroxypentyl or 4(R)-methoxy-3(S),5-dihydroxypentyl side chain were synthesized starting from 2-deoxy-D-ribose. The acyclic nucleosides were obtained by alkylation of the bases with the mesylates **16** and **17**. Of these series of novel nucleoside analogues only 9-[3(S),5-dihydroxypent-1-yl]guanine (**6d**) showed marked antiviral activity. It inhibited the cytopathogenicity of herpes simplex virus type 1 (HSV-1) at a concentration of 0.4–0.6 μg/mL, which thus points to a greater antiviral activity than recently reported for the mixture of the R and S enantiomers (12.5 μg/mL). In contrast with **6d**, its 4(R)-methoxy derivative **7d** did not show antiviral activity, which implies that the 4'-methoxy group is unable to mimic the 1',4'-oxygen bridge of the normal furanose ring.

Introduction

The discovery of acyclovir (ACV) (**1a**)[1] as a potent antiviral compound which inhibits the replication of herpes simplex virus has prompted the synthesis of various other acyclic nucleoside analogues.[2] This research resulted in the discovery of several new molecules with antiviral activity: for example, 9-[(1,3-dihydroxy-2-propoxy)-methyl]guanine (DHPG) (**1b**),[3] (S)-9-(2,3-dihydroxypropyl)adenine (**5**),[4] (S)-9-[(2,3-dihydroxy-1-propoxy)-methyl]guanine (**3**),[5] and (R)-9-(3,4-dihydroxybutyl)-guanine (DHBG) (**1c**).[6] From this series, DHPG is used for the treatment of cytomegalovirus (CMV) infections in immunocompromised patients. Recently, the synthesis of some 9-alkoxypurines was reported. 9-(3-Hydroxypropoxy)guanine (**2a**),[7] 9-[3-hydroxy-2-(hydroxymethyl)propoxy]guanine (**2b**),[7] (S)-9-(2,3-dihydroxypropoxy)guanine (**2c**),[8] and (S)-9-(1,4-dihydroxybut-2-oxy)guanine (**4**)[8] have potent and selective activity against herpes viruses. Compounds **1c**, **2c**, **3**, **4**, and **5** are molecules with a chiral





1a: R = $CH_2OCH_2CH_2OH$ (ACV)
b: R = $CH_2OCH(CH_2OH)_2$ (DHPG)
c: R = $CH_2CH_2CH(OH)CH_2OH$ [(R)-DHBG]
2a: R = $OCH_2CH_2CH_2OH$
b: R = $OCH_2CH(CH_2OH)_2$
c: R = $OCH_2CH(OH)CH_2OH$ (S-isomer)
3: R = $CH_2OCH_2CH(OH)CH_2OH$ [(S)-iNDG]
4: R = $OCH(CH_2OH)CH_2CH_2OH$ (S-isomer)

5: R = $CH_2CH(OH)CH_2OH$ [(S)-DHPA]

center. Their respective enantiomers differ in activity, which points to the importance of synthesizing optically pure compounds for antiviral evaluation. It should also be mentioned that the antiviral activity found for a racemic mixture is not necessarily half of the activity of the more active enantiomer.

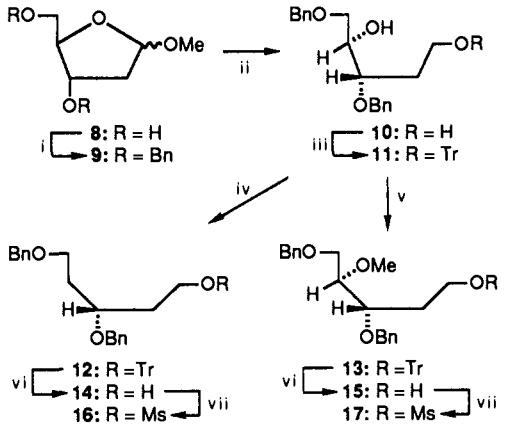
We synthesized the acyclic nucleoside series **6** and **7**, both lacking the normal glycosidic part. However, these compounds have a primary and a secondary hydroxyl group which can mimic the 5'- and 3'-hydroxyl groups of natural nucleosides. The side chain of compounds **6** and **7** can be considered as analogous to the front part of the deoxyribofuranosyl moiety of normal deoxynucleosides. Compounds **6a–d** have a 3(S),5-dihydroxypent-1-yl side chain. With the introduction of a 4(R)-methoxy group in **7a–d** we aimed at mimicking the ring oxygen of natural

† Instituut voor Farmaceutische Wetenschappen.
‡ Faculteit Geneeskunde.

(1) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. 9-(2-Hydroxyethoxymethyl)guanine Activity Against Viruses of the Herpes Group. *Nature* **1978**, *272*, 583–585.
(2) Chu, C. K.; Cutler, S. J. Chemistry and Antiviral Activities of Acyclonucleosides. *J. Heterocycl. Chem.* **1986**, *23*, 289–319.
(3) (a) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. 9-[(1,3-Dihydroxy-2-propoxy)methyl]-guanine: A New Potent and Selective Antiherpes Agent. *J. Med. Chem.* **1983**, *26*, 759–761. (b) Smith, K. O.; Galloway, K. S.; Kennell, W. L.; Ogilvie, K. K.; Radatus, B. K. A New Nucleoside Analog, 9-[[2-Hydroxy-1-(Hydroxymethyl)Ethoxy]-Methyl]Guanine, Highly Active In Vitro Against Herpes Simplex Virus Types 1 and 2. *Antimicrob. Agents Chemother.* **1982**, *22*, 55–61. (c) Field, A. K.; Davies, M. E.; DeWitt, C.; Perry, H. C.; Liou, R.; Germershausen, J.; Karkas, J. D.; Ashton, W. T.; Johnston, D. B. R.; Tolman, R. L. 9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine: A Selective Inhibitor of Herpes Group Virus Replication. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 4139–4143.
(4) De Clercq, E.; Descamps, J.; De Somer, P.; Holý, A. (S)-9-(2,3-Dihydroxypropyl)adenine: An Aliphatic Nucleoside Analog with Broad-Spectrum Antiviral Activity. *Science* **1978**, *200*, 563–565.
(5) Ashton, W. T.; Canning, L. F.; Reynolds, G. F.; Tolman, R. L.; Karkas, J. D.; Liou, R.; Davies, M-E. M.; DeWitt, C. M.; Perry, H. C.; Field, A. K. Synthesis and Antiherpetic Activity of (S)-,(R)-, and (±)-9-[(2,3-Dihydroxy-1-propoxy)methyl]-guanine, Linear Isomers of 2'-Nor-2'-deoxyguanosine. *J. Med. Chem.* **1985**, *28*, 926–933.
(6) Larsson, A.; Öberg, B.; Alenius, S.; Hagberg, C.-E.; Johansson, N.-G.; Lindborg, B.; Stening, G. 9-(3,4-Dihydroxybutyl)-guanine, a New Inhibitor of Herpesvirus Multiplciation. *Antimicrob. Agents Chemother.* **1983**, *23*, 644–670.
(7) Harnden, M. R.; Wyatt, P. G.; Boyd, M. R.; Sutton, D. Synthesis and Antiviral Activity of 9-Alkoxypurines. 1. 9-(3-Hydroxypropoxy)- and 9-[3-Hydroxy-2-(hydroxymethyl)propoxy]purines. *J. Med. Chem.* **1990**, *33*, 187–196.
(8) Bailey, S.; Harnden, M. R.; Jarvest, R. L.; Parkin, A.; Boyd, M. R. Synthesis and Antiviral Activity of 9-Alkoxypurines. 2. 9-(2,3-Dihydroxypropoxy)-, (3,4-Dihydroxybutoxy)-, and 9-(1,4-Dihydroxybut-2-oxy)purines. *J. Med. Chem.* **1991**, *34*, 57–65.

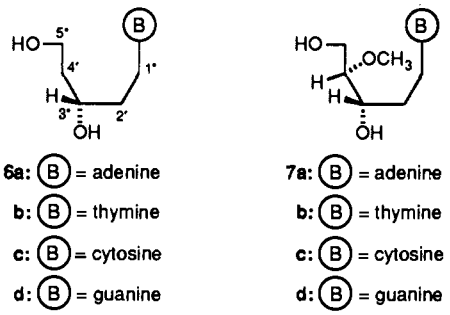
0022-2623/92/1835-1458$03.00/0

Scheme I[a]



[a] (i) NaH, BnBr, DMF; (ii) HOAc, H_2O; $NaBH_4$, EtOH; (iii) TrCl, Et_3N, CH_2Cl_2; (iv) NaH, imidazole, CS_2, MeI, THF; Bu_3SnH, AIBN, toluene; (v) NaH, MeI, THF; (vi) p-$CH_3C_6H_4SO_3H$, CH_2Cl_2, MeOH; (vii) MsCl, Et_3N, CH_2Cl_2.

nucleosides. It should be recognized, however, that the steric bulk of the methoxy group may hinder any potential interactions.



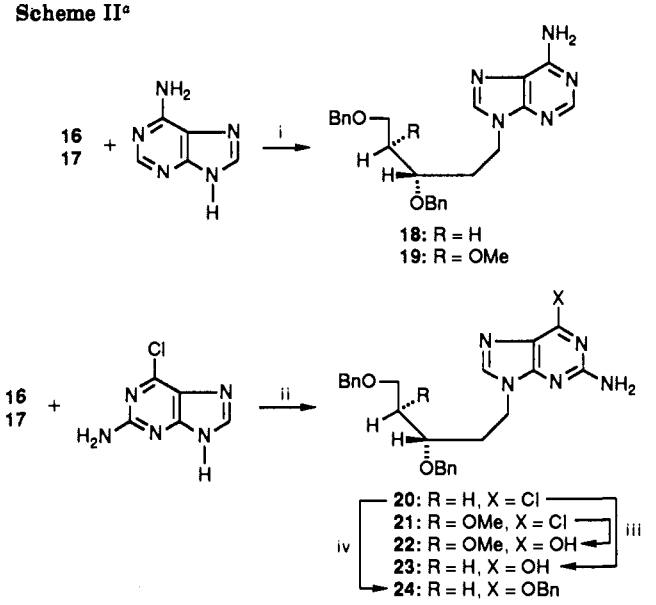
During the course of this work, the synthesis of **6a–d** was described as a racemic mixture.[9] Only the guanine analogue **6d** showed moderate activity against herpes simplex virus type 1 (HSV-1): 50% inhibition of the cytopathic effect was induced at 12.5 μg/mL and complete suppression at 50 μg/mL. The other analogues were reported to be inactive against HSV-1, CMV, and human immunodeficiency virus type 1 (HIV-1).[9] Compound **6a** was previously shown to be inactive against HSV-1, vaccinia virus, and vesicular stomatitis virus (VSV).[4,10]

Our synthetic strategy started from 2-deoxy-D-ribose which led to compounds in which the stereochemistry of the optically active carbons is the same as in the natural occurring nucleosides, i.e. C3′(*S*) and C4′(*R*).

Chemistry

3,5-Di-*O*-benzyl-2-deoxy-D-ribitol (**10**) was obtained from 1-*O*-methyl-2-deoxy-D-ribofuranose (**8**)[11] by reaction with

Scheme II[a]



[a] (i) NaH, DMF; (ii) K_2CO_3, DMF; (iii) Me_3N, DBU, $HOCH_2CH_2CN$; (iv) BnOH, NaH, DMF.

sodium hydride/benzyl bromide[12] followed by deprotection of the O-glycosidic function with 80% aq acetic acid[12] and reduction of the aldehyde function with $NaBH_4$ (Scheme I). The thus formed primary hydroxyl function of **10** was protected with a trityl group to give **11** in about 28% yield from 2-deoxy-D-ribose. This compound was used as starting material for the synthesis of both series **6a–d** and **7a–d**.

For the syntheses of **6a–d**, the secondary hydroxyl group of **11** was removed by converting it to the *S*-methylxanthate (NaH, CS_2, MeI) followed by a Barton-type reduction[13] (Bu_3SnH, AIBN) to give compound **12**. In the absence of AIBN, the yield of **12** is somewhat reduced because of the formation of the starting material **11** (indicated by TLC) as a side component.[14] The yield of **12** could also be improved by working under dilute conditions.[14] Alkylation of **11** with methyl iodide in the presence of NaH[15] gave **13**, which served as the starting material for the synthesis of **7a–d**.

Detritylation of **12** and **13** with *p*-toluenesulfonic acid in CH_2Cl_2/MeOH (80/20) afforded good yields of **14** and **15**, respectively. In contrast, detritylation with 80% aqueous acetic acid at reflux temperature or 98% formic acid at room temperature gave several unidentified side products, which points to the lability of the compounds in acidic aqueous medium. Finally, the primary hydroxyl group was mesylated[16] yielding **16** and **17**.

The intermediate **17** seemed to be unstable. During purification on silica gel several degradation products were formed which are described below. Therefore, the mesylated compounds **16** and **17** were used as such, without

(9) Legraverend, M.; Boumchita, H.; Zerial, A.; Huel, C.; Lemaitre, M.; Bisagni, E. Synthesis of New (±)-3,5-Dihydroxypentyl Nucleoside Analogues from 1-Amino-5-(benzyloxy)pentan-3-ol and Their Antiviral Evaluation. *J. Med. Chem.* **1990**, *33*, 2476–2480.

(10) De Clercq, E.; Holý, A. Antiviral Activity of Aliphatic Nucleoside Analogues: Structure–Function Relationship. *J. Med. Chem.* **1979**, *22*, 510–513.

(11) Hoffer, M. α-Thymidin. *Chem. Ber.* **1960**, *93*, 2777–2781.

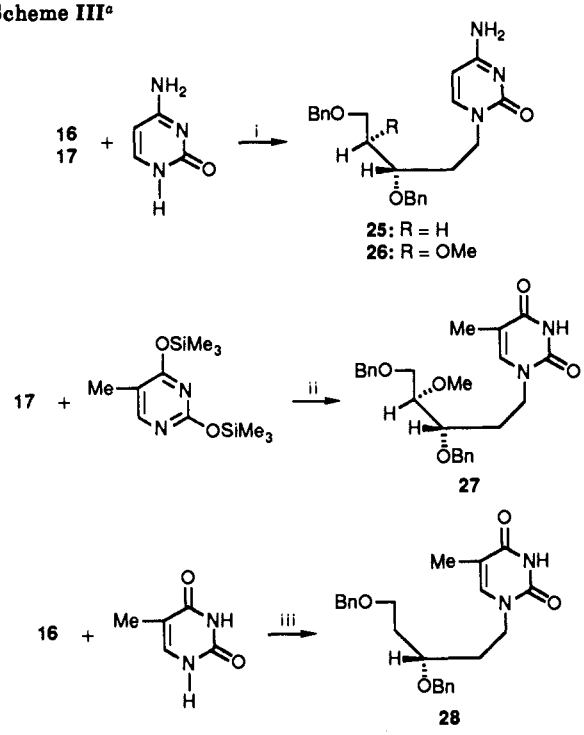
(12) Wierenga, W.; Skulnick, H. I. Stereochemical Control as a Function of Protecting-group Participation in 2-Deoxy-D-*erythro*-pentofuranosylnucleosides. *Carbohydr. Res.* **1981**, *90*, 41–52.

(13) Barton, D. H. R.; McCombie, S. W. A New Method for the Deoxygenation of Secondary Alcohols. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.

(14) Robins, M. J.; Wilson, J. S.; Hansske, F. Nucleic Acid Related Compounds. 42. A General Procedure for the Efficient Deoxygenation of Secondary Alcohols. Regiospecific and Stereoselective Conversion of Ribonucleosides to 2′-Deoxynucleosides. *J. Am. Chem. Soc.* **1983**, *105*, 4059–4065.

(15) Brimacombe, J. S. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York & London, 1972; Vol. VI, pp 376–378.

Scheme III[a]



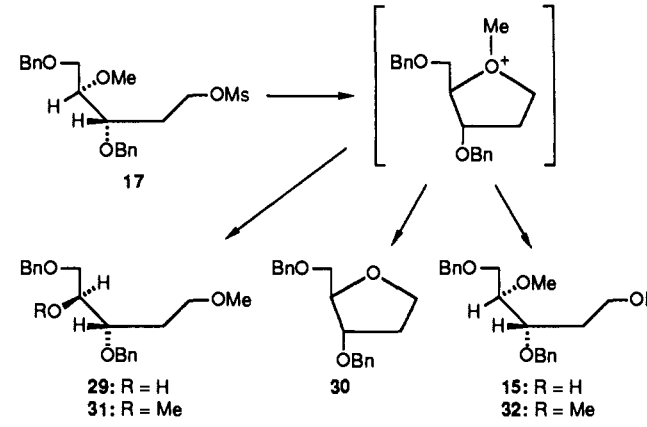
[a] (i) $CsCO_3$, DMF; (ii) MeCN; (iii) K_2CO_3, NaI, DMF.

intermediate purification, as alkylating agents for the different purine and pyrimidine bases. The conditions of alkylation we used are those described in literature to give the best results for similar reactions.

The adenosine analogues **18** and **19** were obtained by reaction of **16** and **17**, respectively, with the sodium salt of adenine (Scheme II).[17]

Reaction of **16** and **17** with 2-amino-6-chloropurine in the presence of K_2CO_3 afforded the compounds **20** and **21** together with their N^7-isomers. The site of alkylation was deduced from their UV maxima;[18] the ^{13}C-NMR data were also in agreement with literature data.[19] Attempts to convert the 2-amino-6-chloropurine base to a guanine base moiety with acid (2 N HCl, reflux)[18] or with base (2.5 N NaOH in H_2O/dioxane (50:50), reflux)[20] met with little success. Although we succeeded in obtaining **22** and **23**, several side products were detected and reproducibility was low. Compound **22** could be obtained more efficiently by reaction of **21** with trimethylamine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), and 3-hydroxypropionitrile in CH_2Cl_2.[21] The feasibility of this method was confirmed

Scheme IV



by the easy and clean conversion of **20** into **23**. The NMR and UV data agreed with those normally found for guanosine analogues.[22]

The conversion to the guanosine analogue was also achieved via the *O*-benzyl derivative **24**. Therefore the 6-chloro function was converted to a 6-*O*-benzyl function by reaction with benzyl alcohol/NaH in DMF. This compound (**24**) is then hydrogenated to give the fully debenzylated guanine derivative **6d**.

The cytosine analogues **25** and **26** were obtained by reacting **16** and **17** with cytosine in DMF in the presence of $CsCO_3$[23] (Scheme III). As mentioned by Bronson et al.,[23] the O-alkylated analogues were formed as side products. Both isomers of compound **25** were isolated and characterized by NMR and UV. The less polar compound appeared to be the O-alkylated isomer, the more polar was the N^1-isomer. Assignment of the alkylation site was based on the NMR and UV data, which were in agreement with those found in literature.[23]

For the synthesis of the thymidine analogues we first tried the method described by Robins et al.[24] Thus, thymidine was silylated with hexamethyldisilazane (HMDS) in the presence of a catalytic amount of $(NH_4)_2SO_4$ followed by addition of the mesylate **17**. The major product isolated was characterized as the N^1-alkylated thymine **27**. However, the yield was rather low (ca. 30%). Therefore, we tried to alkylate thymine via the sodium salt.[18] The mesylate **16** was reacted with thymine in the presence of K_2CO_3/NaI in DMF to give the N^1-alkylated thymine **28** as major product. The isolated yield was slightly better (about 45%) than for the synthesis of **27**.

The benzyl protecting groups of **18**/**19** and **22**–**28** were finally removed by transfer hydrogenation ($Pd(OH)_2$/C, cyclohexene, EtOH)[22] to give the fully deprotected acyclic nucleoside analogues **6a**–**d** and **7a**–**d**.

As mentioned before, the mesylated compound **17** is not very stable. When this compound is stirred in the presence

(16) Crossland, R. K.; Servis, K. L. A Facile Synthesis of Methanesulfonate Esters. *J. Org. Chem.* **1970**, *35*, 3195–3196.
(17) Holý, A. Synthesis of 3-Amino- and 3-Azidoanalogs of 9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA). *Collect. Czech. Chem. Commun.* **1989**, *54*, 446–454.
(18) Ashton, W. T.; Canning Meurer, L.; Cantone, C. L.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wagner, A. F.; Walton, E.; Tolman, R. L. Synthesis and Antiherpetic Activity of (±)-9-[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]guanine and Related Compounds. *J. Med. Chem.* **1988**, *31*, 2304–2315.
(19) Haines, D. R.; Tseng, C. K. H.; Marquez, V. E. Synthesis and Biological Activity of Unsaturated Carboacyclic Purine Nucleoside Analogues. *J. Med. Chem.* **1987**, *30*, 943–947.
(20) Seela, F.; Muth, H.-P. Synthesis of 4-Substituted 2-Aminopyrrolo[2,3-d]pyrimidine 2′,3′-Dideoxyribonucleosides. *Liebigs Ann. Chem.* **1990**, 227–232.
(21) Ashwell, M.; Bleasdale, C.; Golding, B. T.; O'Neill, I. K. An Improved Route to Guanines Substituted at N-9. *J. Chem. Soc., Chem. Commun.* **1990**, 955–956.
(22) Tippie, M. A.; Martin, J. C.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. Antiherpes Simplex Virus Activity of 9-[4-Hydroxy-3-(hydroxymethyl)-1-butyl]guanine. *Nucleosides Nucleotides* **1984**, *3*, 525–535.
(23) Bronson, J. J.; Ghazzouli, I.; Hitchcock, M. J. M.; Webb, R. R.; Martin, J. C. Synthesis and Antiviral Activity of the Nucleotide Analogue (*S*)-1-[3-Hydroxy-2-(phosphonylmethoxy)-propyl]cytosine. *J. Med. Chem.* **1989**, *32*, 1457–1463.
(24) Robins, M. J.; Hatfield, P. W. Nucleic Acid Related Compounds. 37. Convenient and High-yield Syntheses of N-[(2-Hydroxyethoxy)methyl] Heterocycles as "Acyclic Nucleoside" Analogues. *Can. J. Chem.* **1982**, *60*, 547–553.

Table I. Inhibitory Effects of Compound 6d, (S)-DHPA, and ACV on Virus-Induced Cytopathogenicity in E_6SM Cells

		MIC[b] (μg/mL)									
		HSV-1			TK⁻ HSV-1		HSV-2				
compound	MCC[a] (μg/mL)	KOS	F	McIntyre	B2006	VMW 1837	G	196	Lyons	VV	VSV
6d	>400	0.4	0.4	0.6	>400	>400	4	20	5	>400	>400
(S)-DHPA	>400	300	70	70	300	>400	300	300	250	70	70
ACV	>400	0.07	0.04	0.02	70	10	0.04	0.015	0.02	>400	>400

[a] Minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology. [b] Minimum inhibitory concentration, required to reduce virus-induced cytopathogenicity by 50%.

of silica gel, four major compounds could be isolated: the starting material **17**, the demesylated compound **15**, and two other compounds which were identified as **29** and **30** (^1H NMR, ^{13}C NMR, and CIMS). The formation of **15**, **29**, and **30** can be explained by a neighboring group participation reaction as depicted in Scheme IV. As a result of the attack of the oxygen atom of the methoxy group on the C-1 carbon atom, an intermediate onium salt is formed which undergoes nucleophilic attack at the methyl group or at the primary (C-1) or secondary (C-4) positions. Attack at C-1 gives compound **15** whereas attack at the secondary C-4 atom yields compound **29**. Although it has not been established here, this ring-opening should occur with inversion of configuration. The third compound **30** results from nucleophilic attack on the methyl group. This solvolysis is analogous to the solvolysis of *p*-bromobenzenesulfonates described by Allred and Winstein.[25]

The absence of compounds which result from a migration of the benzyl group is in agreement with the results of Allred and Winstein that the five-membered ring is being closed 14 times faster than the six-membered ring.[26] It should also be mentioned that these studies were done in absence of MeOH. In the presence of MeOH, other compounds like **31** and **32** are formed resulting from attack of MeOH instead of H_2O. Compound **17** is not stable at room temperature, and the described interconversion also took place in the absence of silica although at a much lower rate.

Biological Activity

Compounds **6a–d** and **7a–d** were evaluated for their inhibitory effect on the cytopathogenicity of herpes simplex virus type 1 (HSV-1, strains KOS, F, and McIntyre), thymidine kinase deficient (TK⁻) HSV-1 (strains B2006 and VMW 1837), herpes simplex virus type 2 (HSV-2, strains G, Lyons and 196), vaccinia virus (VV), and vesicular stomatitis virus (VSV) in E_6SM cell cultures.[27,28] Only 9-[3(*S*),5-dihydroxypent-1-yl]guanine (**6d**) showed activity. It effected a 50% reduction of the virus-induced cytopathogenicity of HSV-1 and HSV-2 at a concentration of 0.4–0.6 μg/mL and 4–20 μg/mL, respectively (Table I). It was not active against TK⁻ HSV-1, VV, or VSV.

No antiviral activity was noted with any of the eight acyclic nucleoside analogues when evaluated for their inhibitory effect on the cytopathogenicity of parainfluenza virus type 3, reovirus type 1, Sindbis virus, Coxsackie virus type B4, Semliki forest virus in Vero cells, poliovirus type 1 in HeLa cells, varicella-zoster virus (VZV, strains Oka and YS), TK⁻ VZV (strains 07-1 and YSR), and cytomegalovirus (CMV, strains AD169 and Davis) in human embryonic lung (HEL) cells. None of the compounds (**6a–d** and **7a–d**) showed cytotoxicity at the highest concentration tested (400 μg/mL) in any of the cell cultures used (E_6SM, Vero, HeLa, HEL).

Discussion and Conclusion

A prerequisite for acyclic nucleoside analogues to inhibit the viral DNA polymerase of herpes simplex virus, and consequently its replication, is the phosphorylation of the compounds to their triphosphate form.[29] This can be done by cellular as well as by viral kinases. When the compound has a higher affinity for viral kinases and is phosphorylated to a lesser extent by cellular kinases, a first level of selectivity is achieved. This was demonstrated with ACV and other acyclic nucleosides, which are phosphorylated to their monophosphate by viral thymidine kinase to a much higher degree than by cellular kinases. The monophosphate is then further converted to the triphosphate which inhibits the viral DNA polymerase or can be incorporated into DNA and eventually acts as chain terminator.[29] A second level of selectivity is achieved when the triphosphate has a greater affinity for the viral DNA polymerase than for the cellular DNA polymerases. The effectiveness of an acyclic nucleoside analogue to serve as either substrate for the phosphorylating enzymes or inhibitor for the DNA polymerases is likely to be dependent on the ability of the acyclic side chain to mimic the glycosyl moiety of the natural substrates.[18]

In comparison with the natural nucleosides, the acyclic nucleoside analogues **6a–d** only lack the ring oxygen. The distance between the base moiety and the primary alcoholic function, which might mimic the 5′-OH function, and the distance between the primary alcohol and the secondary alcohol are the same as in natural nucleosides. Of the four acyclic nucleoside analogues **6a–d**, only the guanine analogue **6d** showed antiviral activity. This is in agreement with previous observations that the heterocyclic moiety of acyclic nucleoside analogues possessing antiviral activity (ACV, DHPG, DHBG)[2] mostly consists of guanine.

(25) Allred, E. L.; Winstein, S. The Role of Neighbouring Groups in Replacement Reactions. XXVII. 5-Methoxyl Participation in Some Solvolysis Reactions. *J. Am. Chem. Soc.* **1967**, *89*, 3991–3997.

(26) Allred, E. L.; Winstein, S. 6-Methoxyl Participation and Ion Pairs in Some Solvolysis Reactions. *J. Am. Chem. Soc.* **1967**, *89*, 4012–4017.

(27) De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. Comparative Efficacy of Antiherpes Drugs Against Different Strains of Herpes Simplex Virus. *J. Infect. Dis.* **1980**, *141*, 563–574.

(28) De Clercq, E.; Holý, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. A Novel Selective Broad-spectrum anti-DNA Virus Agent. *Nature* **1986**, *323*, 464–467.

(29) Öberg, B.; Johansson, N.-G. The Relative Merits and Drawbacks of New Nucleoside Analogues with Clinical Potential. *J. Antimicrob. Chemother.* **1984**, *14* (Suppl. A), 5–26.

Compound **6d** is not active against TK^- virus strains, which indicates that phosphorylation by the virus-specified thymidine kinase is necessary for antiviral activity.

Comparison with the data of Legraverend et al.[9] who synthesized a mixture of the *R*- and *S*-enantiomer of **6d** is difficult because of differences in the cell systems and virus strains used. However, the difference in antiviral activity between their **6d** racemate, which inhibited the cytopathic effect of HSV-1 by 50% at 12.5 μg/mL, and our **6d** *S*-enantiomer, which shows an MIC of 0.2–0.4 μg/mL against HSV-1, is rather striking. This points to the importance of synthesizing optically pure compounds for biological evaluation. A preference for one of the enantiomeric forms is common in biological systems. In terms of antiviral activity, this preference was first shown for (*S*)-DHPA which proved to have broad-spectrum antiviral activity whereas its *R*-enantiomer was virtually inactive.[4]

The acyclic nucleoside analogues **7a–d** were synthesized in attempts to mimic even more closely the natural nucleoside by installing an oxygen at the 4′-position. However, compounds **7a–d** were devoid of antiviral activity, which is most likely due to steric hindrance by the methoxy group.

Experimental Section

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Philips PU 8700 UV/vis spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard for the ^1H NMR spectra and DMSO-d_6 (39.6 ppm) or $CDCl_3$ (76.9 ppm) for the ^{13}C NMR spectra (s = singlet, d = doublet, dd = double doublet, t = triplet, br s = broad signal, m = multiplet). Chemical ionization mass spectra (CIMS) were obtained using a Kratos Concept 1H mass spectrometer. Precoated Macherey-Nagel Alugram Sil G/UV_{254} plates were used for TLC, and the spots were examined with UV light and sulfuric acid–anisaldehyde spray. Column chromatography was performed on Janssen Chimica silica gel (0.060–0.200 mm). Preparative TLC was done on glass plates coated with Macherey-Nagel silica gel P/UV_{254}. Anhydrous solvents were obtained as follows: methanol was refluxed on magnesium methoxide (I_2, Mg, MeOH) overnight and then distilled; water was removed from DMF by distillation with benzene followed by distillation in vacuo; dichloromethane was stored on calcium hydride, refluxed, and distilled; tetrahydrofuran and acetonitrile were refluxed overnight on lithium aluminum hydride and distilled; toluene was refluxed overnight on sodium and distilled. Elemental analyses were obtained from Dr. W. Rozdzinski, Institut für Organische Chemie, Biochemie und Isotopenforschung, D-7000 Stuttgart 80, Germany.

1-*O*-Methyl-2-deoxy-D-ribose (8). A solution of 15.70 g (117.0 mmol) of 2-deoxy-D-ribose in 280 mL of anhydrous MeOH containing 8 mmol (3.15 mL of 10 wt/v% HCl in MeOH) of hydrochloric acid was kept for 10 min at room temperature. After addition of 15 g of $MgCO_3$ (pH = 6), the suspension was filtered, and the filtrate was concentrated in vacuo and coevaporated three times with toluene. This gave 19.28 g of a yellow oil which was used in the next step without further purification.

1-*O*-Methyl-3,5-di-*O*-benzyl-2-deoxy-D-ribose (9). A solution of 19.28 g of crude 1-*O*-methyl-2-deoxy-D-ribose in 40 mL of anhydrous DMF was added dropwise to a cooled (0 °C) suspension of 10.3 g of NaH (60% dispersion, 257 mmol) in anhydrous DMF (200 mL) over a period of 45 min. The reaction mixture was heated at 50 °C for 1 h and cooled to room temperature. After dropwise addition of 31 mL (257 mmol) of benzyl bromide, the reaction mixture was stirred for 18 h, neutralized with 3 N HCl, and evaporated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (200 mL), washed with saturated $NaHCO_3$ solution (100 mL) and H_2O (2 × 100 mL), dried, and evaporated. The crude mixture was purified by column chromatography (EtOAc–hexane, 15:85) affording 27.40 g as an oil (83.5 mmol, 71% yield) of a mixture of the α and β anomers of 1-*O*-methyl-3,5-di-*O*-benzyl-2-deoxy-D-ribose. ^1H NMR and ^{13}C NMR were taken from two fractions containing only one of both isomers. α anomer: ^1H NMR ($CDCl_3$) δ 7.27 (s, 10 H, Ar), 5.04 (dd, J = 5.1 Hz and J' = 1.7 Hz, 1 H, H-1′), 4.51 (s, 4 H, CH_2Ar), 4.40–4.12 (m, 1 H, H-4′), 4.21–3.81 (m, 1 H, H-3′), 3.60–3.45 (d, J = 4.1 Hz, 2 H, H-5′), 3.38 (s, 3 H, Me), 2.28–1.83 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 138.0 (Ar), 128.0, 127.5, and 127.3 (Ar), 104.9 (C1′), 84.9 and 78.5 (C3′ and C4′), 73.2, 71.3, and 70.1 (C5′ and CH_2Ar), 54.8 (Me), 38.6 (C2′). β anomer: ^1H NMR ($CDCl_3$) δ 7.42–7.18 (m, 10 H, Ar), 5.08 (t, J = 3.7 Hz, 1 H, H-1′), 4.56 (d, 1.7 Hz, 2 H, CH_2Ar), 4.48 (d, 1.7 Hz, 2 H, CH_2Ar), 4.40–3.98 (m, 2 H, H-3′ and H-4′), 3.52 (d, J = 6.2 Hz, 2 H, H-5′), 3.29 (s, 3 H, Me), 2.27–2.03 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 138.1 (Ar), 128.1 and 127.4 (Ar), 105.3 (C1′), 82.7 and 79.9 (C3′ and C4′), 73.1, 71.8, and 71.4 (C5′ and CH_2Ar), 54.7 (Me), 39.2 (C2′).

3,5-Di-*O*-benzyl-2-deoxy-D-ribitol (10). A solution of 10 g (30.5 mmol) of 1-*O*-methyl-3,5-di-*O*-benzyl-2-deoxy-D-ribose in 100 mL of 80% aqueous acetic acid was heated at 100 °C for 30 min. The solution was evaporated and coevaporated with toluene (3 times), and the resulting oil was used in the next step without further purification.

A mixture of crude 3,5-di-*O*-benzyl-2-deoxy-D-ribose (obtained in the previous reaction) and 1.20 g (32.7 mmol) of sodium borohydride in 200 mL of ethanol was stirred at 0 °C for 30 min. After addition of 20 mL of acetone and further stirring for 30 min at room temperature, the reaction mixture was concentrated, diluted with CH_2Cl_2 (100 mL), washed successively with 0.1 M HCl (1 × 50 mL), saturated $NaHCO_3$ solution (1 × 50 mL), and H_2O (2 × 50 mL), dried, and evaporated. The resulting oil was purified by column chromatography (CH_2Cl_2–MeOH, 99:1) affording 5.8 g (18.3 mmol, 60% yield) of 3,5-di-*O*-benzyl-2-deoxy-D-ribitol as an almost colorless oil: ^1H NMR ($CDCl_3$) δ 7.42–7.23 (m, 10 H, Ar), 4.54 (s, 2 H, CH_2Ar), 4.52 (s, 2 H, CH_2Ar), 4.07–3.43 (m, 6 H, H-4′, H-3′, H-1′, and H-5′), 3.12–2.72 (br s, 2 H, exch, OH), 2.00–1.68 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 137.7 (Ar), 128.3, 127.9, and 127.6 (Ar), 77.8 (C3′), 73.2, 72.0, 71.5, and 71.0 (C4′, C5′, and CH_2Ar), 59.2 (C1′), 32.5 (C2′); CIMS (NH_3): 317 (MH^+), 334 (MNH_4^+).

1-*O*-Trityl-3,5-di-*O*-benzyl-2-deoxy-D-ribitol (11). A solution of 12.5 g (39.6 mmol) of 3,5-di-*O*-benzyl-2-deoxy-D-ribitol, 12.1 g (43.5 mmol) of trityl chloride, and 8.3 mL (59.3 mmol) of triethylamine in 250 mL of anhydrous CH_2Cl_2 was stirred for 18 h at room temperature. The reaction mixture was washed with saturated $NaHCO_3$ solution (1 × 100 mL) and with H_2O (2 × 100 mL), dried, and evaporated. The residual yellow oil was purified by column chromatography (CH_2Cl_2), affording 14.8 g (26.5 mmol, 67% yield) of 1-*O*-trityl-3,5-di-*O*-benzyl-2-deoxy-D-ribitol as a yellow viscous oil: ^1H NMR ($CDCl_3$) δ 7.33–6.80 (m, 25 H, Ar), 4.50 (s, 2 H, CH_2Ar), 4.40 (d, J = 2.4 Hz, 2 H, CH_2Ar), 3.97–3.45 (m, 4 H, H-4′, H-3′, and H-5′), 3.45–3.18 (m, 2 H, H-1′), 2.82–2.48 (br s, 1 H, exch, OH), 2.07–1.69 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 144.2 (Ar), 138.3 (Ar), 128.5, 128.3, 128.1, 127.8, 127.6, and 126.7 (Ar), 86.6 (Ph_3C), 77.0 (C3′), 73.3, 72.3, 72.0, and 70.9 (CH_2Ar, C4′, and C5′), 60.1 (C1′), 30.9 (C2′); CIMS (NH_3): 576 (MNH_4^+).

1-*O*-Trityl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol (12). A mixture of 14.8 g (26.5 mmol) of 1-*O*-trityl-3,5-di-*O*-benzyl-2-deoxy-D-ribitol, 100 mg (1.5 mmol) of imidazole, and 2.12 g of NaH (60% dispersion, 53 mmol) in 150 mL of anhydrous THF was stirred at 0 °C (ice bath) for 30 min and then at room temperature for another 30 min. After addition of 13 mL (212 mmol) of CS_2 and stirring for 1 h at room temperature, 5 mL (80.3 mmol) of MeI was added, and the mixture was kept at room temperature for 3 h. Five milliliters of H_2O was added, and the mixture was concentrated, diluted with CH_2Cl_2 (200 mL), washed successively with saturated $NaHCO_3$ solution (1 × 100 mL) and H_2O (2 × 100 mL), dried, and evaporated.

The resulting yellow oil was dissolved in 75 mL of anhydrous toluene. Nitrogen was bubbled through the solution for 20 min which was then added dropwise under N_2 to a refluxing solution of 15.5 mL (57.7 mmol) of tri-*n*-butyltin hydride and 800 mg (4.8 mmol) of 2,2′-azobis(isobutyronitrile) in 200 mL of anhydrous toluene. After refluxing for 18 h, the mixture was evaporated, dissolved in CH_2Cl_2 (200 mL), washed with saturated $NaHCO_3$ solution (100 mL) and H_2O (2 × 100 mL), dried, and evaporated. The crude material was purified by column chromatography (hexane–EtOAc, 95:5) to give 7.8 g (14.5 mmol, 54% yield) of 1-*O*-trityl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol as an almost colorless oil: ^1H NMR ($CDCl_3$) δ 7.58–7.02 (m, 25 H, Ar), 4.46

(d, J = 1.8 Hz, 2 H, CH_2Ar), 4.39 (d, J = 1.8 Hz, 2 H, CH_2Ar), 3.84 (t, J = 5.8 Hz, 1 H, H-3′), 3.56 (t, J = 6.3 Hz, 2 H, H-5′), 3.28 (t, J = 6.4 Hz, 2 H, H-1′), 1.84 (m, 4 H, H-2′ and H-4′); ^{13}C NMR ($CDCl_3$) δ 144.2 (Ar), 138.7 and 138.5 (Ar), 128.6, 128.2, 128.1, 127.6, 127.2, and 126.7 (Ar), 86.5 (Ph_3C), 73.7, 72.8, and 71.3 (CH_2Ar and C_3′), 66.9 (C5′), 60.3 (C1′), 35.1 and 34.4 (C4′ and C2′); CIMS (NH_3): 560 (MNH_4^+).

1-*O*-Trityl-4-*O*-methyl-3,5-di-*O*-benzyl-2-deoxy-D-ribitol (13). A mixture of 7.4 g (13.3 mmol) of 1-*O*-trityl-3,5-di-*O*-benzyl-2-deoxy-D-ribitol and 1.06 g of NaH (60% dispersion, 26.5 mmol) in 130 mL of anhydrous THF was stirred for 1 h at 0 °C (ice bath). After addition of 2.5 mL (39.8 mmol) of MeI and stirring for 2 h at room temperature, H_2O (5 mL) was added and the mixture was evaporated. The residue was dissolved in 150 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ solution (1 × 50 mL) and H_2O (2 × 50 mL), dried, and concentrated in vacuo. The resulting oil (8 g, 13.9 mmol, 100% yield) was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 7.60–6.90 (m, 25 H, Ar), 4.53 (s, 2 H, CH_2Ar), 4.42 (d, J = 1.7 Hz, 2 H, CH_2Ar), 3.97–3.69 (m, 2 H, H-4′ and H-3′), 3.60 (d, J = 4.4 Hz, 2 H, H-5′), 3.43 (s, 3 H, Me), 3.24 (m, 2 H, H-1′), 2.03–1.56 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 144.2 (Ar), 138.2 (Ar), 128.6, 128.2, 128.0, 127.5, 127.2, and 126.7 (Ar), 86.4 (Ph_3C), 82.4 (C4′), 76.1 (C3′), 73.2 and 72.4 (CH_2Ar), 69.6 (C5′), 60.2 (C1′), 58.4 (Me), 31.5 (C2′); CIMS (NH_3): 590 (MNH_4^+).

3,5-Di-*O*-benzyl-2,4-dideoxy-D-ribitol (14). A solution of 7.85 g (14.5 mmol) of 1-*O*-trityl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol in 150 mL of CH_2Cl_2–MeOH (8:2) containing 2% of *p*-TsOH was stirred for 30 min at room temperature. After addition of 150 mL of saturated $NaHCO_3$ solution, the organic layer was separated, washed with H_2O (2 × 50 mL), dried, and evaporated. The crude material was purified by column chromatography (CH_2Cl_2–MeOH, 99:1) to give 3.31 g (11.0 mmol, 76% yield) of 3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol as an almost colorless oil: ^1H NMR ($CDCl_3$) δ 7.28 (s, 10 H, Ar), 4.49 (d, J = 1.7 Hz, 2 H, CH_2Ar), 4.45 (d, J = 1.7 Hz, 2 H, CH_2Ar), 3.91–3.44 (m, 5 H, H-3′, H-1′, and H-5′), 2.51 (s, 1 H, exch, OH), 2.06–1.60 (m, 4 H, H-2′ and H-4′); ^{13}C NMR ($CDCl_3$) δ 138.2 (Ar), 128.1, 127.6, and 127.4 (Ar), 75.2 (C3′), 72.8 and 71.1 (CH_2Ar), 66.5 (C5′), 59.9 (C1′), 36.3 and 34.0 (C2′ and C4′); CIMS (NH_3): 301 (MH^+), 318 (MNH_4^+).

3,5-Di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol (15). The same procedure as for the synthesis of 14 was used for the preparation of 15. An amount of 7.7 g (13.4 mmol) of 1-*O*-trityl-3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol yielded 3.65 g (11.1 mmol, 82% yield) of 3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.30 (s, 10 H, Ar), 4.56 (d, J = 1.8 Hz, 2 H, CH_2Ar), 4.53 (s, 2 H, CH_2Ar), 3.80–3.53 (m, 6 H, H-1′, H-4′, H-3′, and H-5′), 3.47 (s, 3 H, Me), 1.96–1.67 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 138.0 (Ar), 128.1, 127.7, and 127.4 (Ar), 81.7 (C4′), 77.6 (C3′), 73.2 and 72.7 (CH_2Ar), 69.2 (C5′), 59.7 (C1′), 58.4 (Me), 32.9 (C2′); CIMS (NH_3): 331 (MH^+), 348 (MNH_4^+).

1-*O*-Mesyl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol (16). A solution of 1.83 g (6.1 mmol) of 3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol, 1.3 mL (9.3 mmol) of triethylamine, and 520 μL (6.7 mmol) of methanesulfonyl chloride in 60 mL of anhydrous CH_2Cl_2 was stirred for 1 h at 0 °C. After addition of 20 mL of H_2O and stirring for 30 min, the organic layer was separated, washed with saturated $NaHCO_3$ solution (20 mL) and H_2O (2 × 20 mL), dried, and evaporated. The resulting oil (2.71 g, 7.1 mmol, 100% yield) was used without further purification in the next reaction: ^1H NMR ($CDCl_3$) δ 7.30 (s, 10 H, Ar), 4.49 (s, 2 H, CH_2Ar), 4.46 (s, 2 H, CH_2Ar), 4.30 (t, J = 6.4 Hz, 2 H, H-1′), 3.77 (t, J = 5.9 Hz, 1 H, H-3′), 3.57 (t, J = 6.3 Hz, 2 H, H-5′), 2.86 (s, 3 H, Ms), 2.13–1.74 (m, 4 H, H-2′ and H-4′); ^{13}C NMR ($CDCl_3$) δ 138.2 (Ar), 128.1, 127.6, and 127.4 (Ar), 72.8, 72.6, and 71.2 (CH_2Ar and C3′), 66.8 and 66.2 (C1′ and C5′), 37.0 (Ms), 34.1 and 33.9 (C2′ and C4′); CIMS (NH_3): 379 (MH^+), 396 (MNH_4^+).

1-*O*-Mesyl-3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol (17). The same procedure as described for 16 was used for the synthesis of 17. Reaction of 830 mg (2.5 mmol) of 3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol yielded 1 g of crude mesylate as an oil which was used in the next reaction without purification: ^1H NMR ($CDCl_3$) δ 7.31 (s, 10 H, Ar), 4.54 (s, 4 H, CH_2Ar), 4.33 (t, J = 6.6 Hz, 2 H, H-1′), 3.92–3.44 (m, 7 H, H-4′, H-3′, H-5′, and Me), 2.88 (s, 3 H, Ms), 2.16–1.83 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 137.9 (Ar), 128.2, 127.8, and 127.5 (Ar), 81.3 (C4′), 75.0 (C3′), 73.3 and 72.3 (CH_2Ar), 68.8 (C5′), 67.1 (C1′), 58.5 (Me), 37.1 (Ms), 30.3 (C2′); CIMS (NH_3): 409 (MH^+), 426 (MNH_4^+).

9-(3,5-Di-*O*-benzyl-2,4-dideoxy-D-ribityl)adenine (18). A mixture of 580 mg (4.3 mmol) of adenine and 160 mg of sodium hydride (60% dispersion, 4.0 mmol) in 40 mL of dry DMF was stirred at 90 °C for 1 h. After addition of a solution of 1.08 g (2.9 mmol) of crude 1-*O*-mesyl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol in 20 mL of dry DMF and further stirring at 90 °C for 17 h, the reaction mixture was cooled and evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), and the organic phase was washed with saturated $NaHCO_3$ solution (25 mL) and H_2O (2 × 10 mL), dried, and evaporated. The crude material was purified by column chromatography ($CHCl_3$–MeOH, 97:3), affording on evaporation 720 mg (1.7 mmol, 59% yield) of 9-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)adenine as a powder: UV (MeOH) λ_{max} = 261 nm; ^1H NMR ($CDCl_3$) δ 8.35 (s, 1 H, H-2), 7.48 (s, 1 H, H-8), 7.37–7.21 (m, 10 H, Ar), 6.7 (br s, 2 H, exch, NH_2), 4.54–4.36 (m, 4 H, CH_2Ar), 4.24 (t, J = 6.8 Hz, 2 H, H-1′), 3.77–3.41 (m, 3 H, H-3′ and H-5′), 2.34–1.76 (m, 4 H, H-4′ and H-2′); ^{13}C NMR ($CDCl_3$) δ 155.7 (C6), 152.6 (C2), 149.8 (C4), 140.1 (C8), 138.0 (Ar), 128.1, 127.6, and 127.3 (Ar), 119.5 (C5), 73.2, 72.8, and 70.8 (C3′ and CH_2Ar), 66.2 (C5′), 40.3 (C1′), 34.2 and 33.6 (C2′ and C4′); CIMS (NH_3): 418 (MH^+).

9-(3,5-Di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)adenine (19). The same procedure as described for 18 was used for the synthesis of 19. An amount of 1.16 g (2.8 mmol) of crude 1-*O*-mesyl-3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol yielded 610 mg (1.4 mmol, 50% yield) of 9-(3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)adenine, which solidified on standing: UV (MeOH) λ_{max} = 262 nm; ^1H NMR ($CDCl_3$) δ 8.33 (s, 1 H, H-2), 7.59–6.97 (m, 11 H, H-8 and Ar), 6.2 (br s, exch, 2 H, NH_2), 4.80–4.37 (m, 4 H, CH_2Ar), 4.25 (t, 2 H, H-1′), 3.70–3.00 (m, 7 H, H-4′, H-3′, H-5′, and Me), 2.38–1.93 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 155.4 (C6), 152.6 (C2), 149.9 (C4), 140.4 (C8), 138.0 (Ar), 128.3, 127.9, and 127.5 (Ar), 119.3 (C5), 81.1 (C4′), 75.7 (C3′), 73.2 and 71.8 (CH_2Ar), 68.8 (C5′), 58.5 (Me), 40.6 (C1′), 30.4 (C2′); CIMS (NH_3): 448 (MH^+).

9-(3,5-Di-*O*-benzyl-2,4-dideoxy-D-ribityl)-2-amino-6-chloropurine (20). A mixture of 1.05 g (2.8 mmol) of crude 1-*O*-mesyl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol, 565 mg (3.5 mmol) of 2-amino-6-chloropurine, and 500 mg (3.6 mmol) of dry K_2CO_3 in 50 mL of dry DMF was stirred at 90 °C for 16 h. The reaction mixture was cooled and evaporated, and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ solution (30 mL) and H_2O (2 × 30 mL), dried, and evaporated. Purification of the crude material by column chromatography (CH_2Cl_2–MeOH, 99:1) afforded 630 mg (1.4 mmol, 50% yield) of 9-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)-2-amino-6-chloropurine as a solid: UV (MeOH) λ_{max} = 311 nm; ^1H NMR ($CDCl_3$) δ 7.47 (s, 1 H, H-8), 7.31 and 7.28 (2 × s, 10 H, Ar), 5.3 (br s, 2 H, exch, NH_2), 4.60–4.28 (m, 4 H, CH_2Ar), 4.13 (t, J = 7.2 Hz, 2 H, H-1′), 3.98–3.27 (m, 3 H, H-3′ and H-5′), 2.37–1.63 (m, 4 H, H-2′ and H-4′); ^{13}C NMR ($CDCl_3$) δ 158.9 (C2), 153.7 (C4), 151.0 (C6), 142.2 (C8), 138.0 (Ar), 128.3, 128.2, 127.7, and 127.5 (Ar), 125.2 (C5), 73.4, 72.9, and 70.9 (C3′ and CH_2Ar), 66.3 (C5′), 40.3 (C1′), 34.0 and 33.7 (C2′ and C4′); CIMS (NH_3): 452 (MH^+).

9-(3,5-Di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)-2-amino-6-chloropurine (21). The same procedure as used for the synthesis of 20 was used to synthesize 21. One gram (2.4 mmol) of 1-*O*-mesyl-3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol afforded 535 mg (1.1 mmol, 46% yield) of the title compound as a solid: UV (MeOH) λ_{max} = 312 nm; ^1H NMR ($CDCl_3$) δ 7.43 (s, 1 H, H-8), 7.32 and 7.29 (2 × s, 10 H, Ar), 5.4 (br s, 2 H, exch, NH_2), 4.67–4.30 (m, 4 H, CH_2Ar), 4.21 (t, J = 6.9 Hz, 2 H, H-1′), 3.68–3.32 (m, 7 H, H-3′, H-4′, H-5′, and Me), 2.31–1.88 (m, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 158.9 (C2), 153.7 (C4), 150.9 (C6), 142.3 (C8), 137.9 and 137.7 (Ar), 128.3, 128.2, 127.8, and 127.4 (Ar), 125.2 (C5), 80.9 (C4′), 75.8 (C3′), 73.3 and 71.8 (CH_2Ar), 68.7 (C5′), 58.4 (Me), 40.5 (C1′) and 30.1 (C2′); CIMS (NH_3): 482 (MH^+).

9-(3,5-Di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)guanine (22). To a solution of 880 mg (1.8 mmol) of 9-(3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)-2-amino-6-chloropurine and 623 μL (9.1 mmol) of 3-hydroxypropionitrile in 50 mL of CH_2Cl_2 at 0 °C (ice bath) was added 4 mL of trimethylamine and 408

μL (2.7 mmol) of DBU. The mixture was stirred at 4 °C for 17 h and at room temperature for another 23 h and evaporated. The residue was dissolved in EtOAc (50 mL), and the organic layer was washed successively with 0.1 M HCl solution (30 mL), saturated $NaHCO_3$ solution (30 mL), and H_2O (30 mL), dried, and evaporated. The crude material was purified by column chromatography (CH_2Cl_2–MeOH, 95:5) affording 475 mg (1.0 mmol, 56% yield) of 9-(3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)guanine as a solid: UV (MeOH) λ_{max} = 256 nm; ^1H NMR (DMSO-d_6) δ 10.5 (br s, 1 H, exch, NH), 7.58 (s, 1 H, H-8), 7.32 and 7.30 (2 × s, 10 H, Ar), 6.4 (br s, 2 H, exch, NH_2), 4.52 (d, *J* = 2.6 Hz, 2 H, CH_2Ar), 4.45 (s, 2 H, CH_2Ar), 4.03 (t, *J* = 7.1 Hz, 2 H, H-1′), 3.52 (s, 4 H, H-3′, H-4′, and H-5′), 3.36 (s, 3 H, Me), 2.18–1.78 (m, 2 H, H-2′); ^{13}C NMR (DMSO-d_6) δ 156.7 (C6), 153.4 (C2), 151.1 (C4), 138.5, 138.3 (Ar), 137.2 (C8), 128.1, 127.8, and 127.4 (Ar), 116.7 (C5), 80.6 (C4′), 76.2 (C3′), 72.3 and 71.2 (CH_2Ar), 69.1 (C5′), 58.0 (Me), 39.9 (C1′), 30.4 (C2′).

9-(3,5-Di-*O*-benzyl-2,4-dideoxy-D-ribityl)guanine (23). The same procedure was used as for the synthesis of compound **22**. An amount of 400 mg (0.9 mmol) of 9-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)-2-amino-6-chloropurine afforded 420 mg of crude 9-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)guanine as a solid. The product was used without further purification in the next reaction: UV (MeOH) λ_{max} = 256 nm; ^1H NMR (DMSO-d_6) δ 10.5 (br s, 1 H, exch, NH), 7.59 (s, 1 H, H-8), 7.30 and 7.28 (2 × s, 10 H, Ar), 6.4 (br s, 2 H, exch, NH_2), 4.45 and 4.41 (2 × s, 4 H, CH_2Ar), 4.03 (t, *J* = 6.9 Hz, 2 H, H-1′), 3.76–3.40 (m, 3 H, H-3′ and H-5′), 2.19–1.64 (m, 4 H, H-2′ and H-4′); ^{13}C NMR (DMSO-d_6) δ 156.9 (C6), 153.4 (C2), 151.3 (C4), 138.8 and 138.5 (Ar), 137.5 (C8), 128.2, 127.8, 127.5, and 127.4 (Ar), 116.8 (C5), 73.6 (C3′), 72.1 and 70.2 (CH_2Ar), 66.3 (C5′), 34.0 and 33.5 (C2′ and C4′), C1′ hidden by DMSO multiplet.

6-*O*-Benzyl-9-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)guanine (24). A mixture of 70 mg (0.6 mmol) of benzyl alcohol and 27 mg of NaH (60% dispersion, 0.7 mmol) in 20 mL of dry dioxane was heated for 1 h at 50 °C after which 200 mg (0.4 mmol) of 9-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)-2-amino-6-chloropurine in 5 mL of dry dioxane was added. After heating at 100 °C for 22 h, the reaction mixture was cooled and evaporated. The residue was dissolved in 50 mL of CH_2Cl_2, and the organic layer was successively washed with saturated $NaHCO_3$ solution (30 mL) and with H_2O (30 mL), dried, and evaporated. Column chromatography (CH_2Cl_2–MeOH, 99:1) afforded 102 mg (0.2 mmol, 50% yield) of 6-*O*-benzyl-9-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)guanine as a white solid: UV (MeOH) λ_{max} = 251 nm and 284 nm; ^1H NMR ($CDCl_3$) δ 7.59–7.09 (m, 16 H, H-8 and Ar), 5.53 (s, 2 H, CH_2Ar), 5.2 (br s, 2 H, exch, NH_2), 4.65–4.27 (m, 4 H, CH_2Ar), 4.09 (t, *J* = 6.7 Hz, 2 H, H-1′), 3.52 (m, 3 H, H-3′ and H-5′), 2.26–1.68 (m, 4 H, H-2′ and H-4′); ^{13}C NMR ($CDCl_3$) δ 160.8 (C6), 159.0 (C2), 153.8 (C4), 139.2 and 138.1 (Ar), 136.3 (C8), 128.1, 127.8, 127.6, and 127.4 (Ar), 115.2 (C5), 73.4, 72.8, 70.8, and 67.7 (C3′ and CH_2Ar), 66.2 (C5′), 40.0 (C1′), 34.2 and 33.6 (C2′ and C4′); CIMS (NH_3): 524 (MH^+).

1-(3,5-Di-*O*-benzyl-2,4-dideoxy-D-ribityl)cytosine (25). A mixture of 1.28 g (3.4 mmol) of crude 1-*O*-mesyl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol, 451 mg (4.1 mmol) of cytosine, and 2.2 g (6.8 mmol) of $CsCO_3$ in 50 mL of dry DMF was stirred at 90 °C for 18 h. The reaction mixture was cooled and evaporated. The residue was dissolved in 50 mL of EtOAc, washed with saturated $NaHCO_3$ solution (30 mL) and H_2O (2 × 20 mL), dried, and evaporated. The crude material was purified by column chromatography (CH_2Cl_2–MeOH, 97:3) giving 41 mg (1.0 mmol, 29% yield) of the O^2-isomer, and 690 mg (1.8 mmol, 52% yield) of the desired 1-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)cytosine as a slightly yellow powder. N^1-isomer: UV (MeOH) λ_{max} = 276 nm; ^1H NMR (DMSO-d_6) δ 7.45 (d, *J* = 7.2 Hz, 1 H, H-6), 7.30 (s, 10 H, Ar), 7.0 (br s, 2 H, exch, NH_2), 5.63 (d, *J* = 7.2 Hz, 1 H, H-5), 4.56–4.34 (m, 4 H, CH_2Ar), 3.83–3.27 (m, 5 H, H-1′, H-3′, and H-5′), 2.00–1.65 (m, 4 H, H-2′ and H-4′); ^{13}C NMR (DMSO-d_6) δ 166.1 (C4), 155.9 (C2), 146.1 (C6), 139.0 (Ar), 128.4, 127.9, 127.6, and 127.5 (Ar), 93.5 (C5), 73.7, 72.2, and 70.0 (C3′ and CH_2Ar), 66.5 (C5′), 45.8 (C1′), 33.8 and 33.2 (C2′ and C4′); CIMS (NH_3): 394 (MH^+). O^2-isomer: UV (MeOH) λ_{max} = 273 nm; ^1H NMR (DMSO-d_6) δ 7.88 (d, *J* = 5.9 Hz, 1 H, H-6), 7.30 (s, 10 H, Ar), 6.8 (br s, 2 H, exch, NH_2), 6.12 (d, *J* = 5.7 Hz, 1 H, H-5), 4.46 (s, 2 H, CH_2Ar), 4.44 (s, 2 H, CH_2Ar), 4.30 (t, *J* = 7.0 Hz, 2 H, H-1′), 3.86–3.66 (m, 1 H, H-3′), 3.53 (t, *J* = 6.3 Hz, 2 H, H-5′), 2.11–1.60 (m, 4 H, H-2′ and H-4′); ^{13}C NMR (DMSO-d_6) δ 165.5 (C4), 164.8 (C2), 156.1 (C6), 138.9 and 138.6 (Ar), 128.1, 127.4, and 127.2 (Ar), 99.3 (C5), 73.3, 72.0, and 70.3 (C3′ and CH_2Ar), 66.3 (C5′), 62.6 (C1′), 34.1 and 33.2 (C2′ and C4′); CIMS (NH_3): 394 (MH^+).

1-(3,5-Di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)cytosine (26). For the synthesis of compound **26** we used the same procedure as for **25**. Reaction of 640 mg (1.6 mmol) of crude 1-*O*-mesyl-3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol with cytosine afforded 239 mg (0.6 mmol, 38% yield) of 1-(3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)cytosine, which solidified on standing: UV (MeOH) λ_{max} = 276 nm; ^1H NMR (DMSO-d_6) δ 7.45–7.25 (m, 11 H, H-6 and Ar), 7.0 (br s, 2 H, exch, NH_2), 5.61 (d, *J* = 6.0 Hz, 1 H, H-5), 4.53–4.47 (m, 4 H, CH_2Ar), 3.92–3.15 (m, 9 H, H-1′, H-4′, H-3′, H-5′, and Me), 2.10–1.64 (m, 2 H, H-2′); ^{13}C NMR (DMSO-d_6) δ 165.8 (C4), 155.7 (C2), 145.8 (C6), 138.6 and 138.4 (Ar), 128.2, 127.8, and 127.4 (Ar), 93.2 (C5), 80.8 (C4′), 76.4 (C3′), 72.4 and 70.1 (CH_2Ar), 69.3 (C5′), 58.0 (Me), 46.0 (C1′), 29.6 (C2′); CIMS (NH_3): 424 (MH^+).

1-(3,5-Di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)thymine (27). A mixture of 380 mg (3.0 mmol) of thymine and a few milligrams of $(NH_4)_2SO_4$ in 10 mL of hexamethyldisilazane was refluxed for 18 h. The mixture was cooled, evaporated, three times coevaporated with xylene, and dissolved in 50 mL of dry CH_3CN. After addition of a solution of 740 mg (1.8 mmol) of crude 1-*O*-mesyl-3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribitol in 20 mL of dry CH_3CN, the mixture was refluxed for 18 h, cooled, and evaporated. The residue was dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ solution (30 mL) and H_2O (2 × 30 mL), dried, and evaporated. Purification by column chromatography (CH_2Cl_2–MeOH, 98:2) afforded 542 mg (0.6 mmol, 30% yield) of 1-(3,5-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-ribityl)thymine as a colorless oil: UV (MeOH) λ_{max} = 273 nm; ^1H NMR ($CDCl_3$) δ 10.2 (br s, 1 H, exch, NH), 7.31 (s, 10 H, Ar), 6.77 (s, 1 H, H-6), 4.77–4.35 (m, 4 H, CH_2Ar), 3.87–3.40 (m, 9 H, H-1′, H-3′, H-4′, H-5′, and Me), 2.11–1.67 (m, 5 H, H-2′ and MeTh); ^{13}C NMR ($CDCl_3$) δ 164.1 (C4), 150.7 (C2), 140.6 (C6), 138.0 (Ar), 128.3, 127.7, and 127.5 (Ar), 110.2 (C5), 81.2 (C4′), 76.2 (C3′), 73.4 and 71.8 (CH_2Ar), 68.9 (C5′), 58.5 (Me), 45.6 (C1′), 29.5 (C2′), 12.0 (MeTh); CIMS (NH_3): 439 (MH^+), 456 (MNH_4^+).

1-(3,5-Di-*O*-benzyl-2,4-dideoxy-D-ribityl)thymine (28). A mixture of 1.26 g (3.3 mmol) of crude 1-*O*-mesyl-3,5-di-*O*-benzyl-2,4-dideoxy-D-ribitol, 462 mg (3.7 mmol) of thymine, 1.1 g (8.0 mmol) of dried K_2CO_3, and 600 mg (4.0 mmol) of NaI in 50 mL of dry DMF was stirred at 90 °C for 16 h. The reaction mixture was cooled and evaporated, and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ solution (25 mL) and H_2O (2 × 20 mL), dried, and evaporated. The crude material was then purified by column chromatography (CH_2Cl_2–MeOH, 99:1), affording 640 mg (1.6 mmol, 47% yield) of 1-(3,5-di-*O*-benzyl-2,4-dideoxy-D-ribityl)-thymine as an oil: UV (MeOH) λ_{max} = 271 nm; ^1H NMR (DMSO-d_6) δ 11.2 (br s, 1 H, exch, NH), 7.41 (s, 1 H, H-6), 7.30 (s, 10 H, Ar), 4.44 (s, 4 H, CH_2Ar), 3.85–3.40 (m, 5 H, H-1′, H-5′, and H-3′), 2.02–1.60 (m, 7 H, H-2′, H-4′, and MeTh); ^{13}C NMR (DMSO-d_6) δ 164.1 (C4), 150.7 (C2), 142.2 (C6), 138.7 and 138.5 (Ar), 128.1, 127.5, 127.4, and 127.2 (Ar), 108.4 (C5), 73.5, 71.9 and 69.8 (C3′ and CH_2Ar), 66.2 (C5′), 44.2 (C1′), 33.4 and 32.7 (C2′ and C4′), 11.8 (MeTh).

Deprotection of Benzylated Acyclic Nucleosides. The benzylated product (1 mmol) was dissolved in a mixture of 10 mL of cyclohexene and 30 mL of EtOH, and nitrogen was bubbled through the mixture for 20 min. An equal amount in weight of $Pd(OH)_2/C$ (20%) was added, and after refluxing for 18 h, the reaction mixture was filtered and evaporated. The crude material was purified by preparative TLC and crystallized. Yields refer to the amount of product isolated after chromatography.

9-(2,4-Dideoxy-D-ribityl)adenine (6a): starting material 18, 1.6 mmol; yield 200 mg (0.8 mmol, 50%); mp (EtOH) 178 °C; UV (MeOH) λ_{max} = 261 (ε = 14 000); ^1H NMR (DMSO-d_6) δ 8.15 (s, 2 H, H-2 and H-8), 7.2 (br s, 2 H, exch, NH_2), 4.25 (t, *J* = 7.0 Hz, 2 H, H-1′), 4.09–3.28 (m, 5 H, H-3′, H-5′, 3′-OH, and 5′-OH), 2.29–1.69 and 1.69–1.36 (2 × m, 4 H, H-2′, and H-4′); ^{13}C NMR (DMSO-d_6) δ: 155.9 (C6), 152.2 (C2), 149.5 (C4), 140.9 (C8), 118.8 (C5), 64.7 (C3′), 57.8 (C5′), 40.5 and 40.2 (C1′ and C4′), 37.2 (C2′).

Anal. ($C_{10}H_{15}N_5O_2 \cdot {}^1/_4H_2O$) C, H, N.

9-(4-*O*-Methyl-2-deoxy-D-ribityl)adenine (7a): starting material **19**, 1.1 mmol; yield 231 mg (0.9 mmol, 80%); mp (EtOH) 139 °C; UV (MeOH) λ_{max} = 262 nm (ϵ = 15100); ^{1}H NMR (DMSO-d_6) δ 8.16 and 8.12 (2 × s, 2 H, H-2 and H-8), 7.19 (s, 2 H, exch, NH_2), 4.94 (d, J = 5.7 Hz, 1 H, exch, 3′-OH), 4.46 (t, J = 6.8 Hz, 1 H, exch, 5′-OH), 4.25 (t, J = 6.7 Hz, 2 H, H-1′), 3.72–3.16 (m, 6 H, H-3′, H-5′, and Me), 3.04 (m, 1 H, H-4′), 2.29–1.50 (m, 2 H, H-2′). ^{13}C NMR (DMSO-d_6) δ 155.9 (C6), 152.3 (C2), 149.6 (C4), 141.0 (C8), 118.9 (C5), 85.2 (C4′), 67.1 (C3′), 60.0 (C5′), 57.8 (Me), 40.5 (C1′), 32.9 (C2′). Anal. ($C_{11}H_{17}N_5O_3 \cdot 1.5H_2O$) C, H, N.

1-(2,4-Dideoxy-D-ribityl)thymine (6b): starting material **28**, 1.6 mmol; yield 220 mg (1.0 mmol, 62%) as a colorless oil; UV (MeOH) λ_{max} = 272 nm; ^{1}H NMR (DMSO-d_6) δ 11.1 (br s, 1 H, exch, NH), 7.48 (s, 1 H, H-6), 4.68–4.45 (br s, 1 H, exch, 3′-OH), 4.45–4.21 (br s, 1 H, exch, 5′-OH), 3.99–3.30 (m, 5 H, H-1′, H-5′, H-3′), 1.76 (s, 3 H, MeTh), 1.69–1.37 (m, 4 H, H-2′ and H-4′); ^{13}C NMR (DMSO-d_6) δ 164.3 (C-4), 150.8 (C2), 141.6 (C6), 108.3 (C5), 65.0 (C3′), 57.9 (C5′), 44.9 (C1′), 40.3 (C4′), 36.3 (C2′), 11.9 (MeTh); FAB HRMS m/z 229.1189 for (MH^+) (calcd for $C_{10}H_{17}N_2O_4$, 229.1188).

1-(4-*O*-Methyl-2-deoxy-D-ribityl)thymine (7b): starting material **27**, 0.46 mmol; yield 80 mg (0.3 mmol, 65%); mp (acetone) 127 °C; UV (MeOH) λ_{max} = 272 nm (ϵ = 8950); ^{1}H NMR (DMSO-d_6) δ 11.1 (br s, 1 H, exch, NH), 7.45 (s, 1 H, H-6), 4.76 (d, J = 5.9 Hz, 1 H, exch, 3′-OH), 4.47 (t, J = 5.6 Hz, 1 H, exch, 5′-OH), 3.98–3.28 (m, 8 H, H-1′, H-5′, H-3′, and Me), 3.02 (t, J = 4.7 Hz, 1 H, H-4′), 1.90–1.24 (m, 5 H, H-2′ and MeTh); ^{13}C NMR (DMSO-d_6) δ 164.4 (C4), 150.9 (C2), 141.8 (C6), 108.4 (C5), 85.2 (C4′), 67.4 (C3′), 60.1 (C5′), 57.8 (Me), 45.2 (C1′), 31.9 (C2′), 12.0 (MeTh). Anal. ($C_{11}H_{18}N_2O_5$) C, H, N.

1-(2,4-Dideoxy-D-ribityl)cytosine (6c): starting material **25**, 1.2 mmol; yield 123 mg (0.6 mmol, 50%); mp (EtOH–Et_2O) 134 °C; UV (MeOH) λ_{max} = 278 nm (ϵ = 8900); ^{1}H NMR (DMSO-d_6) δ 7.54 (d, J = 7.0 Hz, 1 H, H-6), 7.0 (br s, 2 H, exch, NH_2), 5.66 (d, J = 7.0 Hz, 1 H, H-5), 3.9 (br s, 2 H, exch, 3′-OH and 5′-OH), 3.71 (t, J = 6.7 Hz, 2 H, H-1′), 3.49 (m, 3 H, H-3′ and H-5′), 1.83–1.28 (m, 4 H, H-2′ and H-4′); ^{13}C NMR (DMSO-d_6) δ 165.9 (C4), 156.2 (C2), 146.1 (C6), 93.2 (C5), 64.7 (C3′), 58.0 (C5′), 46.0 (C1′), 40.2 (C4′), 36.8 (C2′). Anal. ($C_9H_{15}N_3O_3 \cdot 1.5H_2O$) C, H, N.

1-(4-*O*-Methyl-2-deoxy-D-ribityl)cytosine (7c): starting material **26**, 0.7 mmol; yield 114 mg (0.47 mmol, 67%); mp (CH_3CN) 141 °C; UV (MeOH) λ_{max} = 279 nm (ϵ = 8000); ^{1}H NMR (DMSO-d_6) δ 7.53 (d, J = 7.0 Hz, 1 H, H-6), 7.0 (br s, exch, NH_2), 5.65 (d, J = 7.0 Hz, 1 H, H-5), 3.87–3.10 (m, 10 H, 3′-OH, 5′-OH, H-3′, H-5′, H-1′, and Me), 2.99 (m, 1 H, H-4′), 2.16–1.43 (m, 2 H, H-2′); ^{13}C NMR (DMSO-d_6) δ 166.0 (C4), 156.2 (C2), 146.2 (C6), 93.4 (C5), 85.3 (C4′), 67.1 (C3′), 60.4 (C5′), 57.8 (Me), 46.2 (C1′), 32.3 (C2′). Anal. ($C_{10}H_{17}N_3O_4 \cdot {}^1/_4H_2O$) C, H, N.

9-(2,4-Dideoxy-D-ribityl)guanine (6d): starting material **23**, 1.0 mmol; yield 90 mg (0.36 mmol, 36%); mp (EtOH–H_2O) 237 °C; UV (MeOH) λ_{max} = 255 (ϵ = 14850) and 270 (sh) (ϵ = 10600); ^{1}H NMR (DMSO-d_6) δ 7.65 (s, 1 H, H-8), 6.8 (br s, 2 H, exch, NH_2), 4.02 (t, J = 6.8 Hz, 2 H, H-1′), 3.79–3.06 (m, 5 H, H-3′, H-5′, 3′-OH and 5′-OH), 1.95–1.66 and 1.66–1.34 (2 × m, 4 H, H-2′ and H-4′); ^{13}C NMR (DMSO-d_6) δ 157.2 (C6), 153.9 (C2), 151.2 (C4), 137.3 (C8), 116.6 (C5), 64.7 (C3′), 57.9 (C5′), 40.2 and 39.9 (C1′ and C4′), 37.4 (C2′). Anal. ($C_{10}H_{15}N_5O_3 \cdot H_2O$) C, H, N.

9-(4-*O*-Methyl-2-deoxy-D-ribityl)guanine (7d): starting material **22**, 1.5 mmol; yield 210 mg (0.74 mmol, 49%); mp (H_2O) 280 °C; UV_{max} (MeOH) λ = 255 (ϵ = 15150) and 270 (sh) (ϵ = 10800); ^{1}H NMR (DMSO-d_6) δ 10.5 (br s, 1 H, exch, NH), 7.64 (s, 1 H, H-8), 6.4 (br s, 2 H, exch, NH_2), 4.87 (d, J = 6.2 Hz, 1 H, exch, 3′-OH), 4.43 (t, J = 5.5 Hz, 1 H, exch, 5′-OH), 4.02 (m, 2 H, H-1′), 3.60–3.44 (m, 3 H, H-3′ and H-5′), 3.31 (s, 3 H, Me), 3.02 (m, 1 H, H-4′), 2.31–1.38 (m, 2 H, H-2′); ^{13}C NMR (DMSO-d_6) δ 156.8 (C6), 153.4 (C2), 151.1 (C4), 137.4 (C8), 116.6 (C5), 85.2 (C4′), 67.0 (C3′), 60.0 (C5′), 57.7 (Me), 32.9 (C2′), C1′ hidden by DMSO multiplet. Anal. ($C_{11}H_{17}N_5O_4 \cdot {}^3/_4H_2O$) C, H, N.

Antiviral Assay Procedures. The acyclic nucleoside analogues **6a–d** and **7a–d** were evaluated for their antiviral in vitro activity according to well established procedures.[27,28] The origin of the viruses has been described previously.[27,28]

Acknowledgment. Frank Vandendriessche is a Research Assistant, Robert Snoeck is a Senior Research Assistant, and Arthur Van Aerschot is a Research Associate of the National Fund for Scientific Research of Belgium. This work has been supported by grants from the Belgian FGWO (Fonds voor Geneeskundig Wetenschappelijk Onderzoek, projects 3.0040.83, 3.0026.91, 3.0001.90). We are indebted to Prof. E. Esmans of the R.U.C.A. for the HRMS of compound **6b**. We thank Guy Schepers, Anita Van Lierde, Frieda De Meyer, and Anita Camps for technical assistance, and Dominique Brabants and Anne Vansteenwegen for editorial help.