A clear, chunky prism of dimensions 0.20 × 0.40 × 0.30 mm was used for intensity measurement on a Syntex P1 diffractometer controlled by a Harris computer. Cu Kα radiation and a graphite monochromator were used for intensity measurement. The step scan technique was used with a scan speed of 2°/min, a scan width of 3.4°, and a $2\theta_{max}$ of 138°. Ten reflections periodically monitored showed no loss of intensity during the data collection. Of the 2753 unique reflections measured, 2584 had intensities greater than 3σ; standard deviations in the intensities were approximated by the equation

$$\sigma^2(I) = \sigma^2(I)_{\text{countingstatistics}} + (0.020I)^2$$

where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Unit cell parameters were determined accurately by least-squares fit of Cu $K\alpha_1$ 2θ values (λ(Cu kα_1) = 1.5402) for 25 high 2θ reflections.[23] Lorentz and polarization corrections appropriate for a monochromator with 50% perfect character were applied without absorption correction. A partial trial solution, 30 atoms, was obtained by direct methods, using RANTAN81.[24] The remaining atoms were found by successive Fourier syntheses. Hydrogen atom positions were found in difference maps very close to positions generated by using planar or tetrahedral geometry, so generated positions were used. The structure was refined by least squares with coordinates including hydrogens and anisotropic temperature factors for nonhydrogen atoms included in the refinement. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle and Turner,[25] except for hydrogen, which was from Stewart et al.[26] In the final refinement cycle, all shifts were $<0.84\sigma$. The final R was 0.041, and the standard deviation of fit was 2.79. A final difference map showed no peaks >0.2 e Å^{-3}. The CRYM system of computer programs was used.[27]

Biology

Inhibition of Human Plasma Renin. Peptides VII–X were assayed for plasma renin inhibitory activity as follows: Lyophiized human plasma with 0.1% EDTA was obtained commercially (New England Nuclear). The angiotensin I generation step utilized 250 μL of plasma, 2.5 μL of phenylmethanesulfonyl fluoride, 25 μL of maleate buffer (pH 6.0), and 10 μL of an appropriate concentration of inhibitor in a 1% Tween 80 in water vehicle. Incubation was for 90 min at 37 °C. Radioimmunoassay for angiotensin I was carried out with a commercial kit (Clinical Assays). Plasma renin activity values for inhibitor tubes were compared to those for control tubes to estimate percent inhibition. The inhibition results were expressed as IC_{50} values, which were obtained by plotting three to four inhibitor concentrations on semilog graph paper and estimating the concentration producing 50% inhibition.

Acknowledgment. We are grateful to Margaret R. Schuette for technical assistance.

Supplementary Material Available: Tables of fractional coordinates, bond lengths, bond angles, torsion angles, close intermolecular contacts, and thermal parameters (6 pages). Ordering information is given on any current masthead page.

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Systematic Synthesis and Biological Evaluation of α- and β-D-Lyxofuranosyl Nucleosides of the Five Naturally Occurring Nucleic Acid Bases

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The α- and β-D-lyxofuranosyl analogues of the naturally occurring nucleosides have been synthesized and their antiviral properties examined. The α anomers were prepared by glycosylation of purine and pyrimidine aglycons with tetra-*O*-acetyl-α-D-lyxofuranose, followed by removal of the blocking groups. The β anomers were obtained by sequential oxidation and reduction of 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-xylofuranosyl nucleosides. The lyxofuranosyl nucleosides were tested for their activity against a variety of RNA and DNA viruses and for inhibition of cell growth. One compound, 9-α-D-lyxofuranosyladenine, showed activity against herpes simplex virus types 1 and 2 both in vitro and in vivo.

During the last decades there has been considerable interest in the synthesis and biological evaluation of sugar-modified nucleoside analogues.[1] In order to define structure–activity relationships, we initiated a comprehensive program to systematically study anomeric D-pentofuranosyl nucleosides.[2,3] Thus, in an earlier paper we have discussed the α- and β-D-xylofuranosyl nucleosides, and it was found that three of these compounds, 9-β-D-xylofuranosyladenine and -guanine as well as 1-β-D-xylofuranosylcytosine, showed marked biological activity.[4] These findings prompted us to investigate in the current study the α- and β-D-lyxofuranosyl nucleosides of the five naturally occurring nucleic acid bases. A thorough literature survey revealed that little attention has been given to the synthesis and biological evaluation of this class of analogues.[5] For the β (cis-1′,2′) anomers this can be

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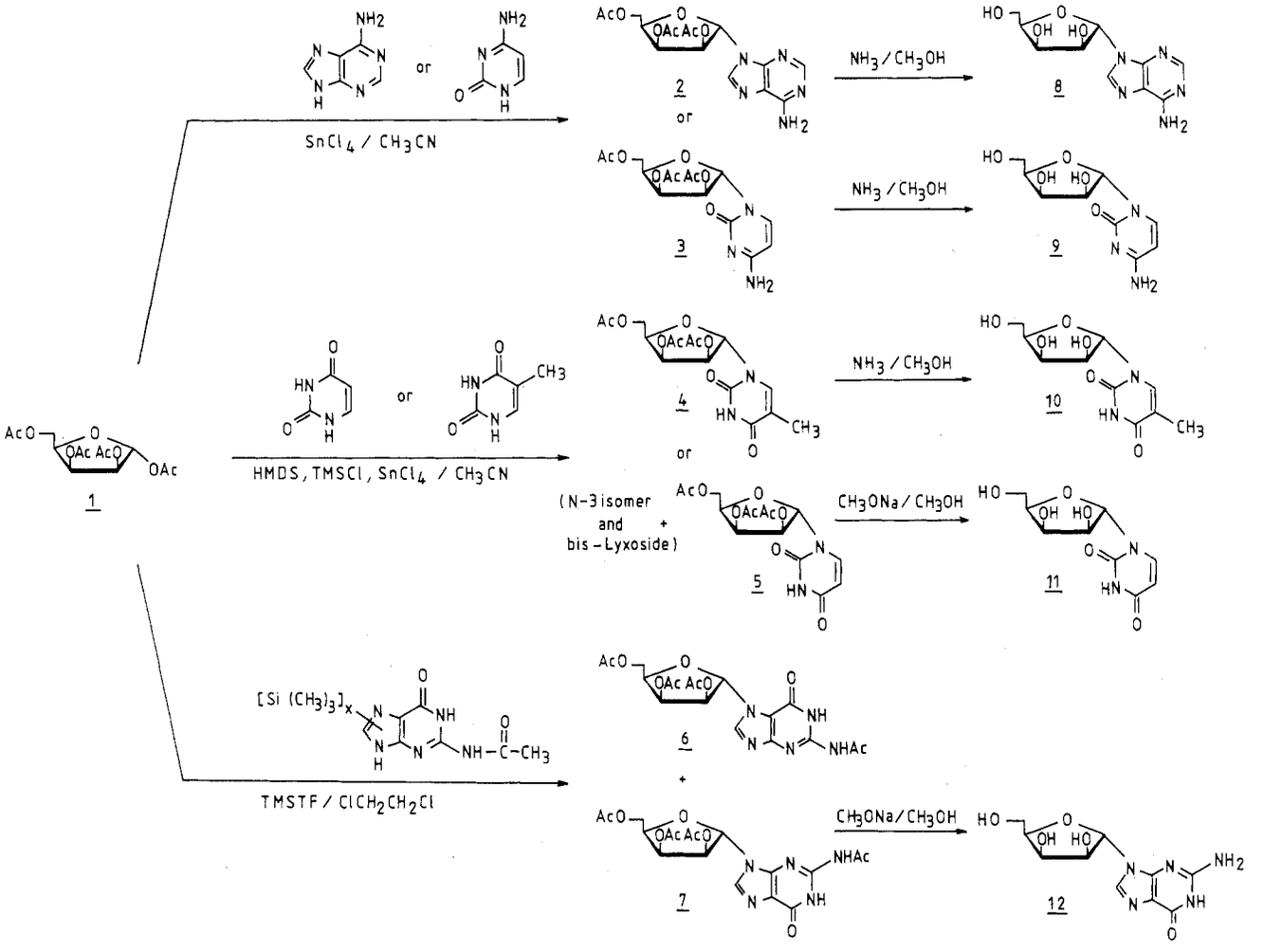
Scheme I



attributed to the difficulty in their synthesis, and for the α (trans-1′,2′) anomers to the generally accepted notion that α-nucleosides are inactive. The latter concept, however, may require reconsideration since several α-nucleosides are now known to exhibit significant antimetabolic properties.[6] Of particular interest in this regard is the presently reported in vitro and in vivo antiherpetic activity of 9-α-D-lyxofuranosyladenine (α-lyxoA) (**8**).

Chemistry

Synthesis of α-D-Lyxofuranosyl Nucleosides (Scheme I). In accord with Baker's rule,[7] direct condensation of a suitably protected 2′-*O*-acyl-D-lyxofuranose and purine or pyrimidine bases was employed to prepare the α (trans-1′,2′) nucleosides. As starting sugar we used syrupy tetra-*O*-acetyl-α-D-lyxofuranose (**1**), prepared and purified as previously described.[8] Except for the guanine series, glycosylations were effected under conditions similar to those used for the synthesis of protected β-D-xylofuranosyl nucleosides in our earlier paper.[4] For the guanine we found it more amenable to start from silylated N^2-acetylguanine and to use the procedure of Vorbruggen et al. with trimethylsilyl triflate (TMSTF) as catalyst.[9]

From adenine, cytosine, and thymine, only the α-9-N (**2**) and α-1-N (**3, 4**) protected nucleosides were obtained. On the other hand, glycosylation of uracil and N^2-acetylguanine resulted in separable mixtures containing α-1-N **5** and α-9-N **7**, respectively, along with other undesirable isomers. All protected α-D-lyxofuranosyl nucleosides **2–5** and **7** were isolated in moderate to satisfactory yields after purification by silica gel column chromatography. Removal of the acetyl blocking groups with methanolic ammonia or methanolic sodium methoxide then afforded the desired α-D-lyxofuranosyl nucleosides **8–12**. The results of these condensations and the physical properties of these α-D-nucleosides are presented in Table I.

Synthesis of β-D-Lyxofuranosyl Nucleosides. A priori, three methods can be envisaged for the preparation of the β (cis-1′,2′) anomers: (a) glycosylation with a suitably protected D-lyxofuranose having in its 2-O-position a nonparticipating group; (b) construction of the heterocyclic moiety from a D-lyxose derivative possessing a 2-oxazoline ring fused in the cis-1′,2′ configuration; (c) epimerization of the 2′- or 3′-position, respectively, of a β-D-xylo- or arabinofuranosyl nucleoside derivative. We discarded the first possibility owing to its lack of regioselectivity and stereospecificity. Building the heterocyclic moiety was also excluded owing to the failure of D-lyxose to cyclize to a pentofuranooxazoline.[16,17] This sugar prefers

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Table I. Preparation and Physical Properties of α-D-Lyxofuranosyl Nucleosides

no.[a]	yield,[b] %	mp, °C	λ_{max}, nm ($\epsilon \times 10^{-3}$) [solvent]	mass spectra, $M^{+\cdot}$	^{1}H NMR spectral data: solvent	^{1}H NMR spectral data: characteristic peaks	formula[c]
2	*d*	white foam	ND[f]	383	$CDCl_3$	2.0, 2.03, and 2.16 (3 s, 3 × 3 H, 3 CH_3CO), 4.1–4.6 (m, 2 H, H-5′,5″), 4.9–5.4 (m, 1 H, H-4′ or 3′), 5.7–6.4 (m, 3 H, H-1′,2′ and 3′ or 4′), 6.8 (br s, 2 H, NH_2), 7.92 and 8.23 (2 s, 2 × 1 H, H-2 and H-8)	ND[f]
3	31, a	white foam	271 and 231, [0.01 N NaOH], 276 and 212 [0.1 N HCl]	369	$CDCl_3$	2.03 (s, 6 H, 2 CH_3CO), 2.10 (s, 3 H, CH_3CO), 4.1–4.4 (m, 2 H, H-5′,5″), 4.8–5.1 (m, 1 H, H-4′ or 3′), 5.6–6.1 (m, 4 H, H-1′,2′ and 3′ or 4′ + H-5), 6.1–8.0 (br s, 2 H, NH_2), 7.33 (d, 1 H, H-6, $J_{5,6}$ = 7.5 Hz)	$C_{15}H_{19}N_3O_8 \cdot {}^1/_6CHCl_3$
4	60, b	white foam	264 [0.1 N HCl]	384	$CDCl_3$	1.93 (s, 3 H, CH_3), 2.06 (s, 6 H, 2 CH_3CO), 2.16 (s, 3 H, CH_3CO), 4.0–4.5 (m, 2 H, H-5′,5″), 4.7–5.0 (m, 1 H, H-3′ or 4′), 5.6–6.1 (m, 3 H, H-1′,2′ and 3′ or 4′), 7.12 (s, 1 H, H-6), 9.9 (br s, 1 H, NH)	$C_{16}H_{20}O_9N_2$
5	49, c	white foam	257 [EtOH]	370	$CDCl_3$	2.03 (s, 6 H, 2 CH_3CO), 2.13 (s, 3 H, CH_3CO), 4.1–4.4 (m, 2 H, H-5′,5″), 4.6–5.0 (m, 1 H, H-3′ or 4′), 5.6–5.9 (m, 4 H, H-1′,2′ and 3′ or 4′ + H-5), 7.13 (d, 1 H, H-6, $J_{5,6}$ = 7.0 Hz), 9.25 (s, 1 H, NH)	ND[f]
6	14, d	white foam	263, 283 (sh) [EtOH]	451	$CDCl_3$	2.06 (s, 6 H, 2 CH_3CO), 2.18 (s, 3 H, CH_3CO), 2.37 (s, 3 H, $NCOCH_3$), 4.0–4.3 (m, 2 H, H-5′,5″), 5.1–6.2 (m, 4 H, H-1′,2′,3′ and 4′), 7.95 (s, 1 H, H-8), 12.4 (br s, 1 H, NH)	$C_{18}H_{21}N_5O_9 \cdot {}^1/_7CHCl_3$
7	33, d	white foam	257, 282 [EtOH]	451	$CDCl_3$	2.00 (s, 6 H, 2 CH_3CO), 2.10 (s, 3 H, CH_3CO), 2.33 (s, 3 H, $NCOCH_3$), 4.0–4.3 (m, 2 H, H-5′,5″), 4.8–5.0 (m, 1 H, H-3′ or 4′), 5.4–6.2 (m, 3 H, H-1′,2′ and 3′ or 4′), 7.77 (s, 1 H, H-8), 12.3 (br s, 1 H, NH)	$C_{18}H_{21}N_5O_9 \cdot {}^1/_3CHCl_3$
8	72[e]	243–244 (H_2O)	258 (15.6) [H_2O]	267	$(CD_3)_2SO$	3.5–3.9 (m, 2 H, H-5′,5″), 4.1–4.3, 4.4–4.6, and 4.8–5.2 (3 m, 3 × 1 H, H-2′,3′ and 4′), 4.76 (t, 1 H, OH-5′, $J_{H,OH-5'}$ = 5.4 Hz), 5.18 (d, 1 H, OH-2′ or 3′, $J_{H,OH}$ = 4.2 Hz), 5.53 (d, 1 H, OH-2′ or 3′, $J_{H,OH}$ = 6.9 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 6.9 Hz), 7.27 (s, 2 H, NH_2), 8.20 and 8.40 (2 s, 2 × 1 H, H-2 and H-8)	$C_{10}H_{13}N_5O_4$
9	68, e	198–200 (EtOH)	271 (8.0), 231 (sh, 7.4) [0.001 N NaOH], 280 (12.4) [0.1 N HCl]	226 (M − NH_3)	$(CD_3)_2SO$	3.4–3.7 (m, 2 H, H-5′,5″), 4.0–4.2 (m, 1 H, H-3′ or 4′), 4.2–4.5 (m, 2 H, H-2′ and 3′ or 4′), 4.6 (t, 1 H, OH-5′), 4.93 (d, 1 H, OH-2′ or 3′, $J_{H,OH}$ = 3.8 Hz), 5.25 (d, 1 H, OH-2′ or 3′, $J_{H,OH}$ = 5.3 Hz), 5.7–5.9 (2 d, 2 × 1 H, H-1′ and H-5, $J_{1',2'}$ = 7.0 Hz), 7.17 (s, 2 H, NH_2), 7.63 (d, 1 H, H-6, $J_{5,6}$ = 7.1 Hz)	$C_9H_{12}N_2O_5$
10	66, f	201–202 (EtOH, 100)	268 (9.2) [H_2O]	258	$(CD_3)_2SO$	1.82 (s, 3 H, CH_3), 3.4–3.7 (m, 2 H, H-5′,5″), 4.0–4.2 (m, 1 H, H-3′ or 4′), 4.2–4.5 (m, 2 H, H-2′ and 3′ or 4′), 4.6, 4.9, and 5.3 (3 m, 3 × 1 H, OH-2′,3′ and 5′), 5.80 (d, 1 H, H-1′, $J_{1',2'}$ = 7.2 Hz), 7.59 (s, 1 H, H-6), 11.2 (br s, 1 H, NH-3)	$C_{10}H_{14}N_2O_6$

Table I (Continued)

no.[a]	yield,[b] %	mp, °C	λ_{max}, nm ($\epsilon \times 10^{-3}$) [solvent]	mass spectra, $M^{+\cdot}$	^{1}H NMR spectral data: solvent	^{1}H NMR spectral data: characteristic peaks	formula[c]
11	64	204–205 (EtOH/MeOH, 3:1, v/v)	261 (13.3) [H_2O], 261 [0.01 N NaOH]	244	$(CD_3)_2SO$	3.4–3.7 (m, 2 H, H-5′,5″), 4.0–4.1 (m, 1 H, H-3′ or 4′), 4.2–4.4 (m, 2 H, H-2′ and 3′ or 4′), 4.66 (t, 1 H, OH-5′, $J_{H,OH-5'}$ = 5.5 Hz), 5.08 and 5.40 (2 d, 2 × 1 H, OH-2′ and 3′, $J_{H,OH}$ = 4.1 and 6.6 Hz), 5.66 (d, 1 H, H-5, $J_{5,6}$ = 8.1 Hz), 5.79 (d, 1 H, H-1′, $J_{1',2'}$ = 7.4 Hz), 7.76 (d, 1 H, H-6), 11.3 (br s, 1 H, NH-3)	$C_9H_{12}N_2O_6$
12	61	246 dec (H_2O)	257 (15.4), 276 (sh, 11.0) [0.1 N HCl], 253 (16.6), 274 (sh, 11.9) [H_2O], 264 (br, 12.6) [0.1 N NaOH]	*g*	$(CD_3)_2SO$	3.5–3.8 (m, 2 H, H-5′,5″), 4.1–4.2, 4.3–4.5, and 4.7–4.9 (3 m, 3 × 1 H, H-2′,3′ and 4′), 4.6–4.7, 4.9–5.2, and 5.3–5.5 (3 m, 3 × 1 H, OH-2′,3′ and 5′), 5.72 (d, 1 H, H-1′, $J_{1',2'}$ = 7.4 Hz), 6.5 (br s, 2 H, NH_2), 7.95 (s, 1 H, H-8), 10.2–11.0 (br s, 1 H, NH-1)	$C_{10}H_{13}N_5O_5 \cdot H_2O$

[a] References of previously described compounds: 8,[10] 10,[11-13] 11.[11,12,14,15] [b] See Experimental Section. Yields are based on directly crystallized pure samples or are calculated after silica gel column chromatography with the following eluents: a, $CHCl_3$/MeOH (92:8, v/v); b, CH_2Cl_2/MeOH (98:2, v/v); c, $CHCl_3$; d, stepwise gradient of MeOH in $CHCl_3$ from 0% to 2%; e, $CHCl_3$/MeOH (6:4, v/v); f, CH_2Cl_2/MeOH (82:18, v/v). [c] Chemical formulas are given for compounds that were analyzed for all the elements except oxygen; all analytical results were within ±0.4% of the theoretical values. [d] Yield almost quantitative; this compound was used directly without further purification for the preparation of 8. [e] From adenine. [f] Not determined. [g] Spectrum virtually useless owing to pyrolysis.

the pyranoid structure.[18,19] Thus, we turned to the third possibility, using β-D-xylofuranosyl nucleosides with free 2′-hydroxyl groups and suitably protected 3′,5′-hydroxyls.

Two distinct approaches were considered for the realization of the desired 2′ inversion of configuration. In principle, a 2′-*O*-sulfonic ester of the β-D-xylofuranosyl nucleoside can be displaced by a suitable nucleophile, via an S_N2 mechanism. This approach, although often used in transforming the sugar moiety of nucleosides,[20-31] seemed inadequate for our purpose due to the several possible side reactions: sulfonylation of the heterocyclic functions of bases and intramolecular attack of a 3′ neighboring group or the 2-carbonyl of the pyrimidine bases.[20] The second approach consists of a 2′ selective oxidation of a β-D-xylofuranosyl nucleoside, followed by reduction of the intermediate 2′-keto derivative with sodium borohydride. Although a similar approach has been successfully used in the synthesis of β-D-arabinofuranosyl nucleosides from 3′,5′-O-tritylated,[20,32] -acylated,[33,34] or -silylated[35,36] β-D-ribofuranosyl nucleosides, there have been few reports in other nucleosidic series.[20,37-39] For our purpose this method seemed particularly suitable, since it does not require special protection of exocyclic functions of the aglycon, and the reduction would be expected to occur stereospecifically, giving the β-D-lyxo isomers, due to the large steric hindrance on the β face of the xylose ring. Among the mild and selective oxidizing agents described in the literature,[40] we chose the Pfitzner–Moffatt reagent (Me_2SO/DCC).

Since we have recently obtained β-D-arabinofuranosyl nucleosides from 3,5-di-*O*-benzoyl-β-D-xylofuranosyl nu-

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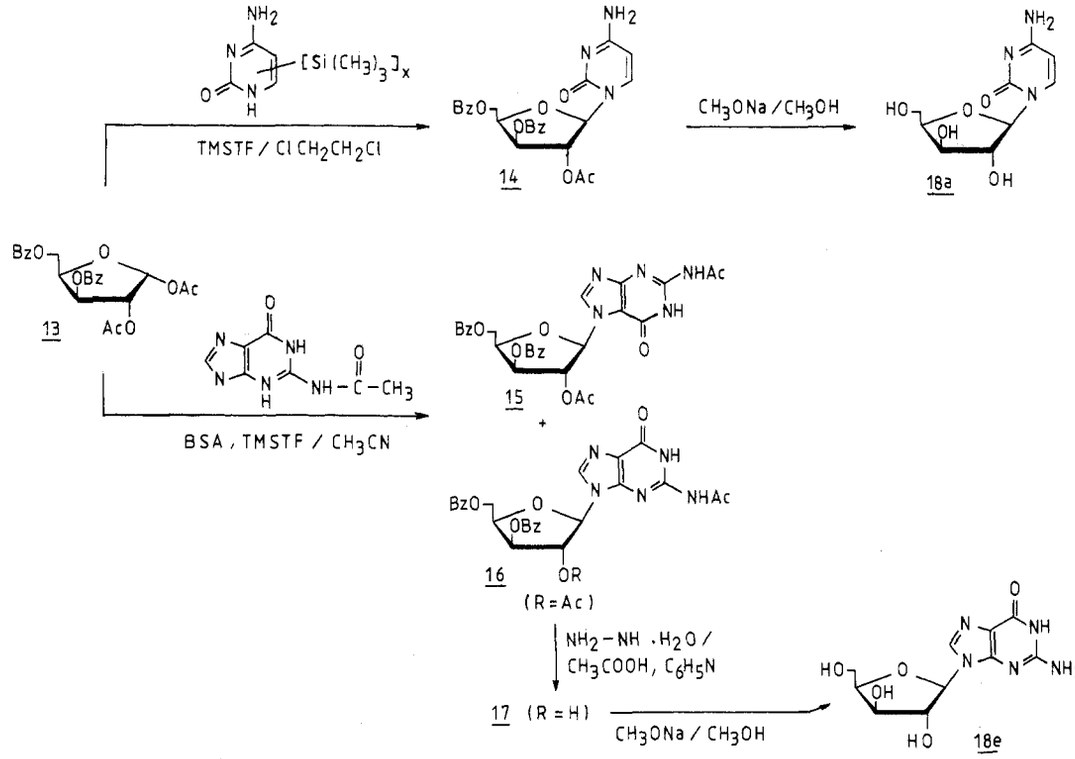
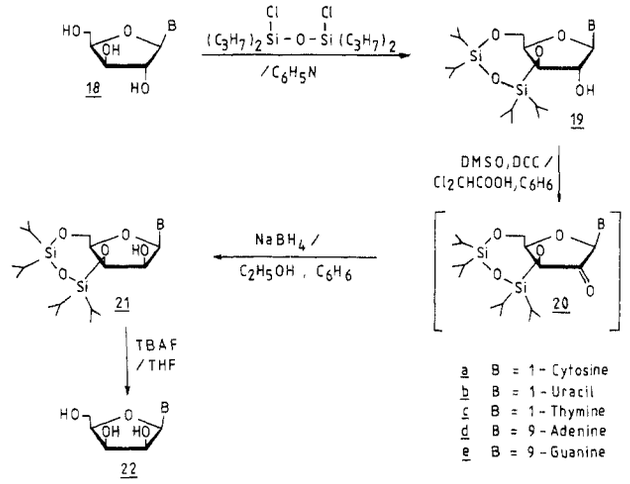
Scheme II



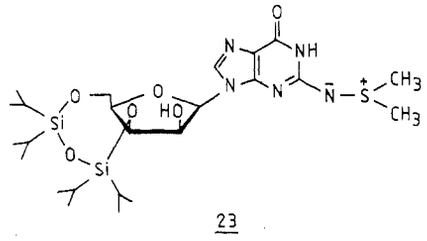
cleosides by an oxidation, reduction, deacylation procedure,[41] it was first necessary to evaluate other more suitable 3′,5′-protecting groups. The 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TPDS) group of Markiewicz[42] was considered the best choice in view of its high 3′,5′ selectivity and stability in xylose series. We previously had synthesized the starting unprotected β-D-xylofuranosyl nucleosides **18**.[4] Although the yields were satisfactory for adenine, thymine, and uracil, they were low for cytosine and guanine. To improve these yields, a literature survey was undertaken in order to find better glycosylation conditions. Application of the procedure of Vorbruggen et al.[9] in the cytosine series and that of Wright and Dudycz[43,44] in the guanine series effectively improved the yields. The new syntheses of 1-β-D-xylofuranosylcytosine (**18a**) and 9-β-D-xylofuranosylguanine (**18e**) are presented in Scheme II.

Treatment of β-D-xylofuranosyl nucleosides **18** with TPDSCl results in the 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) derivatives **19** in moderate to high yields. Oxidation of these compounds was effected by using the Me_2SO/DCC method with dichloroacetic acid as the proton source.[45] Examination of the crude reaction mixtures by TLC showed essentially a single new spot, which gave a positive carbonyl test upon spraying with *o*-dianisidine reagent.[46] Purification at this stage was not attempted owing to the known instability of the furan-2′-ulosides on silica gel. The crude reaction mixtures were therefore dissolved in ethanol for **20d,e** or in benzene/ethanol (1:1, v/v) for **20a–c** and directly treated with sodium borohydride at 0 °C (Scheme III).

Scheme III



In all series, only the expected protected β-D-lyxofuranosyl nucleosides **21a–e** were isolated after silica gel column chromatography. However, in the guanine series, examination of the reduction mixture by TLC showed that in addition to the desired product **21e** another compound (**23**) was present. This compound, which converted to **21e**



on standing in ethanol, was isolated by preparative TLC and characterized as a sulfilimine derivative from its UV, ^1H NMR, and mass spectra. Formation of **23** as a side product was not surprising since it is known that mildly

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basic aromatic amines react with Me_2SO and DCC to form corresponding *N*-aryl-*S*,*S*-dimethylsulfilimines.[47]

Desilylation of **21a–e** was achieved with tetra-*n*-butylammonium fluoride in THF and gave the desired β-D-lyxofuranosyl nucleosides **22a–e** in satisfactory yields after chromatographic purification. Structural assignments for the reported compounds are based on elemental analysis and their physical properties. Unless otherwise noted, our data were in accord with literature values for previously described compounds. Furthermore, on analytical TLC and HPLC, compounds **22a–d** migrated as did authentic samples of β-lyxoC, -U, -T, and -A, respectively. The synthesis and physical properties of **19**, **21**, and **22** are presented in Table II.

Biological Evaluation

All of the prepared α- and β-D-lyxofuranosyl nucleosides **8–12** and **22a–e** were evaluated in vitro against various viruses in four cell systems (Table III). From these studies it is apparent that, with the exception of β-lyxoC (**22a**), none of the test compounds caused a microscopically detectable alteration of host-cell morphology at a concentration of 400 μg/mL. Six compounds, namely **12** and **22a–e**, exhibited some activity against some viruses (vaccinia, Coxsackie, Rhinovirus-9); but the most promising compound was α-lyxoA (**8**), which exhibited a distinct antiviral activity against two DNA viruses (HSV-2, vaccinia), one (+)RNA virus (Coxsackie), and one (−)RNA virus (parainfluenza-3).

In additional experiments aimed at assessing the inhibitory effects of the compounds on virus growth, it was ascertained that α-lyxoA (**8**) was virtually inactive against herpes simplex virus-1 (KOS) in primary rabbit kidney cells, but inhibited the replication of herpes simplex virus-2 (strain 196) in the same cells. When assayed at 400 μg/mL, compound **8** reduced the 24-h HSV-2 virus yield from 5.3 to 3.8 log PFU/mL (Table IV).

Acute toxicity of compound **8** (α-lyxoA) was determined in mice. The LD_{50} (50% lethal dose) upon intraperitoneal administration was >2 g/kg, while acyclovir, evaluated for acute toxicity in parallel with α-lyxoA, gave an LD_{50} of 1.25 g/kg. Thus, α-lyxoA appeared to be remarkably nontoxic in vivo.

Compound **8** (α-lyxoA) offered partial protection in hairless (hr/hr) mice against several parameters (lesions, paralysis, and death) of a cutaneous HSV-1 or HSV-2 infection (Table V) when applied topically in Me_2SO at 5%. This dosage regimen appeared optimal for acyclovir to confer complete protection against HSV-1 infection (Table V).

The protective activity offered by α-lyxoA in the cutaneous HSV-1 and HSV-2 infection models was similar to that of vidarabine (Table V), which is rather remarkable in view of the lesser activity of **8** against HSV-1 and HSV-2 in vitro. More work will be required to establish both the basis of the antiviral activity and the chemoterapeutic potency of α-lyxoA (**8**). Due to the lack of toxicity, compound **8** may be used at higher doses than those employed thus far (Table V), and additional studies have been planned to evaluate the efficacy of **8** at doses up to 40% topically in the cutaneous HSV-1 and HSV-2 infection models.

Experimental Section

Chemical Synthesis. General procedures and instrumentation used were described in ref 4. Proton nuclear magnetic resonance of **21e**, **22**, and **23** was determined at ambient temperature with a Bruker WP 200 SY spectrometer.

9-(2′,3′,5′-Tri-*O*-acetyl-α-D-lyxofuranosyl)adenine (2) and 1-(2′,3′,5′-Tri-*O*-acetyl-α-D-lyxofuranosyl)cytosine (3). Aglycon (adenine or cytosine) was suspended in a solution of tetra-*O*-acetyl-α-D-lyxofuranose[8] (**1**) (1 equiv) in anhydrous acetonitrile (30 mL/mmol of aglycon). Stannic chloride (2 equiv) in anhydrous acetonitrile (6 mL/equiv) was added, and the mixture was stirred at room temperature for 23 h for adenine or refluxed for 1.5 h for cytosine with exclusion of moisture. Subsequent workup was similar to that described in ref 4 (method A).

1-(2′,3′,5′-Tri-*O*-acetyl-α-D-lyxofuranosyl)thymine (4) and 1-(2′,3′,5′-Tri-*O*-acetyl-α-D-lyxofuranosyl)uracil (5). To a mixture of the aglycon (thymine or uracil) and the protected starting sugar **1** (1 equiv) in anhydrous acetonitrile (15 mL/mmol of aglycon) were added consecutively hexamethyldisilazane (HMDS, 0.8 equiv), trimethylchlorosilane (TMSCl, 0.8 equiv), and $SnCl_4$ (1.2 equiv). For thymine, the resulting clear solution was refluxed for 25 min; for uracil it was stirred at room temperature for 22 h. Subsequent workup was similar to that described in ref 4 (method B). In the case of uracil, chromatography of the residue on a silica gel column led to the isolation of the desired N-1 derivative **5** as well as two other compounds, which were identified from their ^1H NMR and UV spectra as the N-3 isomer (14%) and the *N*-1,*N*-3-bis-lyxoside (11%).

***N*^{2}-Acetyl-9-(2′,3′,5′-tri-*O*-acetyl-α-D-lyxofuranosyl)guanine (7) and Its 7-α Isomer (6).** A suspension of *N*^{2}-acetylguanine[54] (2.37 g, 12.27 mmol) in HMDS (40 mL) was heated under reflux. After 2 h the base did not dissolve, and pyridine (15 mL) was added to accelerate the silylation. The reflux was continued for an additional 1 h. After cooling, the excess of HMDS and pyridine was removed in vacuo and by codistillation with anhydrous xylene. Silylated *N*^{2}-acetylguanine was dissolved in anhydrous 1,2-dichloroethane (40 mL). A solution of sugar **1** (3.4 g, 10.69 mmol) in 1,2-dichloroethane (100 mL) and a solution of trimethylsilyl triflate (TMSTF) (2.34 mL, 12.89 mmol) in the same solvent (16 mL) were added. The reaction mixture was heated under reflux for 1 h and then cooled to room temperature. After dilution with 1,2-dichloroethane, the solution was poured into ice-cold saturated aqueous $NaHCO_3$. The organic phase was separated, twice washed with water, dried over sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column led, after evaporation of the appropriate fractions, to the isolation of pure **6** and **7**.

1-(2′-*O*-Acetyl-3′,5′-di-*O*-benzoyl-β-D-xylofuranosyl)cytosine (14). This compound was prepared from cytosine (4.5 g, 40.5 mmol) as described above for the synthesis of **6** and **7** with the following modifications: a trace of ammonium sulfate was added as catalyst with pyridine during silylation and the starting sugar was the di-*O*-acetyl-1,2-di-*O*-benzoyl-3,5-α-D-xylofuranose[55] (**13**). After standard workup, the resulting residue was chromatographed on a silica gel column in a stepwise gradient of methanol in chloroform (0%, 0.5%, and 1%) to afford 15 g (75%) of **14**. This compound was crystallized from MeOH: mp 220–221 °C; UV (EtOH) λ_{max} 273 nm (ε 8.1), 230 (25.6), λ_{min} 257 nm (ε 6.9); ^1H NMR (Me_2SO-d_6) δ 2.15 (s, 3 H, CH_3CO), 4.6–5.0 (m, 3 H, H-4′,5′,5″), 5.5 (m, 1 H, H-2′ or 3′), 5.7 (m, 1 H, H-2′ or 3′), 5.97 (d, 1 H, H-5, $J_{5,6}$ = 7.5 Hz), 6.00 (s, 1 H, H-1′), 7.3–8.5 (m, 13 H, 2 C_6H_5CO + NH_2 + H-6). Anal. ($C_{25}H_{23}N_3O_8$) C, H, N.

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Table II. Preparation and Physical Properties of 3′,5′-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-xylo- and -lyxofuranosyl Nucleosides and of Unprotected β-D-Lyxofuranosyl Nucleosides

no.[a]	yield,[b] %	mp, °C	λ_{max}, nm ($\epsilon \times 10^{-3}$) [solvent]	mass spectra, $M^{+\cdot}$	^{1}H NMR spectral data: solvent	^{1}H NMR spectral data: characteristic peaks	formula[c]
19a	80, A, a	252–255 (ethyl acetate/hexane)	274 (8.9) [EtOH]	485	$CDCl_3$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 3.8–4.6 (m, 5 H, H-2′,3′,4′,5′,5″), 5.67 (d, 1 H, H-5, $J_{5,6}$ = 7.5 Hz), 5.77 (s, 1 H, H-1′), 7.63 (d, 1 H, H-6)	$C_{21}H_{39}N_3O_6Si_2 \cdot {}^1/_2H_2O$
19b	35, A, b	lyophilized	263 (10.8) [EtOH]	443 (M − *i*-Pr)	$CDCl_3$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 3.9–4.6 (m, 5 H, H-2′,3′,4′,5′,5″), 5.69 (d, 1 H, H-5, $J_{5,6}$ = 8.0 Hz), 5.79 (s, 1 H, H-1′), 7.64 (d, 1 H, H-6), 11.8 (br s, 1 H, NH-3)	$C_{21}H_{38}N_2O_7Si_2$
19c	56, A, b	lyophilized	268 (8.1) [EtOH]	500	$CDCl_3$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 1.87 (s, 3 H, CH_3), 3.9–4.7 (m, 5 H, H-2′,3′,4′,5′,5″), 5.79 (s, 1 H, H-1′), 7.44 (s, 1 H, H-6), 11.8 (br s, 1 H, NH-3)	$C_{22}H_{40}N_2O_7Si_2$
19d	89, A, c	120–128 (ethyl acetate)	258 (14.4) [EtOH]	509	$CDCl_3$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 3.9–4.6 (m, 5 H, H-2′,3′,4′,5′,5″), 6.14 (s, 1 H, H-1′), 6.5 (br s, 2 H, NH_2), 8.10 and 8.24 (2 s, 2 × 1 H, H-2 and H-8)	$C_{22}H_{39}N_5O_5Si_2$
19e	68, A, d	262–266 (EtOH)	253 (14.5), 276 (sh, 8.9) [EtOH]	525	$(CD_3)_2SO$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 3.8–4.4 (m, 5 H, H-2′,3′,4′,5′,5″), 5.75 (s, 1 H, H-1′), 6.12 (d, 1 H, OH-2′), 6.5 (br s, 2 H, NH_2), 7.67 (s, 1 H, H-8), 10.7 (s, 1 H, NH-1)	$C_{22}H_{39}N_5O_6Si_2 \cdot {}^1/_2H_2O$
21a	48, A, a	141–143, lyophilized	272 (6.0) [EtOH]	485	$CDCl_3$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 3.8–4.8 (m, 5 H, H-2′,3′,4′,5′,5″), 5.48 (d, 1 H, H-5, $J_{5,6}$ = 7.5 Hz) 6.33 (d, 1 H, H-1′, $J_{1',2'}$ = 6.8 Hz), 7.77 (d, 1 H, H-6)	$C_{21}H_{39}N_3O_6Si_2 \cdot {}^1/_3CHCl_3$
21b	55, A, b	lyophilized	260 (12.3) [EtOH]	443 (M − *i*-Pr)	$CDCl_3$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 2.5–3.5 (br s, 1 H, OH-2′), 3.97 (s, 2 H, H-5′,5″), 4.3–4.7 (m, 3 H, H-2′,3′,4′), 5.60 (d, 1 H, H-5, $J_{5,6}$ = 8.0 Hz), 6.17 (d, 1 H, H-1′, $J_{1',2'}$ = 6.8 Hz), 7.60 (d, 1 H, H-6), 9.7 (br s, 1 H, NH-3)	$C_{21}H_{38}N_2O_7Si_2$
21c	49, A, b	lyophilized	266 (9.6) [EtOH]	500	$CDCl_3$	1.0–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 1.87 (d, 3 H, CH_3, $J_{CH_3,H\text{-}6}$ = 1.2 Hz), 2.7 (br s, 1 H, OH-2′), 4.0 (m, 2 H, H-5′,5″), 4.3–4.7 (m, 3 H, H-2′,3′,4′), 6.15 (d, 1 H, H-1′, $J_{1',2'}$ = 6.3 Hz), 7.33 (d, 1 H, H-6), 9.3 (br s, 1 H, NH-3)	$C_{22}H_{40}N_2O_7Si_2$
21d	28, A, c	lyophilized	258 (13.4) [EtOH]	509	$CDCl_3$	1.0–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 2.5–3.8 (br s, 1 H, OH-2′), 3.9–4.9 (m, 5 H, H-2′,3′,4′,5′,5″), 6.1 (br s, 2 H, NH_2), 6.32 (d, 1 H, H-1′, $J_{1',2'}$ = 6.8 Hz), 8.13 and 8.23 (2 s, 2 × 1 H, H-2 and H-8)	$C_{22}H_{39}N_5O_5Si_2$
21e	26, A, d	210 start of dec (EtOH)	253 (18.0), 270 (sh, 11.4) [EtOH]	525	$(CD_3)_2SO$	0.9–1.1 (m, 28 H, 4 × $(CH_3)_2CH$), 3.8 (m, 2 H, H-5′,5″), 4.0 (m, 1 H, H-4′), 4.3 (m, 1 H, H-3′), 4.7 (m, 1 H, H-2′), 5.58 (d, 1 H, OH-2′, $J_{OH,H\text{-}2'}$ = 6.4 Hz), 5.96 (d, 1 H, H-1′, $J_{1',2'}$ = 7.7 Hz), 6.39 (s, 2 H, NH_2), 7.89 (s, 1 H, H-8), 10.55 (s, 1 H, NH-1)	$C_{22}H_{39}N_5O_6Si_2 \cdot H_2O$
22a	66, B, e	188[d] start of dec, 192–193 effervesced (EtOH)	273 (9.1) [H_2O]	226 (M − NH_3)	$(CD_3)_2SO$	3.6–4.0 (m, 3 H, H-4′,5′,5″), 4.10 (t, 1 H, H-2′ or 3′), 4.40 (t, 1 H, H-2′ or 3′), 4.8, 5.4, and 5.5 (3 br s, 3 × 1 H, OH-2′,3′ and 5′), 6.04 (d, 1 H, H-1′, $J_{1',2'}$ = 7.0 Hz), 6.09 (d, 1 H, H-5), 8.07 (d, 1 H, H-6, $J_{5,6}$ = 7.5 Hz), 8.4 (br s, 1 H, D_2O exchangeable)	$C_9H_{13}N_3O_5 \cdot HCl$
22b	62, A, d	182–183 (EtOH)	263 (10.2) [H_2O]	244	$(CD_3)_2SO$	3.5–4.2 (m, 4 H, H-3′,4′,5′,5″), 4.3 (m, 1 H, H-2′), 4.7 (t, 1 H, OH-5′), 5.17 and 5.37 (2 d, 2 × 1 H, OH-2′ and 3′), 5.53 (d, 1 H, H-5, $J_{5,6}$ = 8.3 Hz), 6.03 (d, 1 H, H-1′, $J_{1',2'}$ = 6.8 Hz), 7.57 (d, 1 H, H-6), 11.2 (br s, 1 H, NH-3)	$C_9H_{12}N_2O_6$

Table II (Continued)

no.[a]	yield,[b] %	mp, °C	λ_{max}, nm ($\epsilon \times 10^{-3}$) [solvent]	mass spectra, $M^{+\cdot}$	^{1}H NMR spectral data: solvent	^{1}H NMR spectral data: characteristic peaks	formula[c]
22c	77, A, d	203–205 (EtOH)	268 (11.6) [H_2O]	258	$(CD_3)_2SO$	1.73 (d, 3 H, CH_3, $J_{CH_3,H\text{-}6}$ = 1.2 Hz), 3.6–4.2 (m, 4 H, H-3′,4′,5′,5″), 4.3 (m, 1 H, H-2′), 4.73 (t, 1 H, OH-5′), 5.15 and 5.35 (2 d, 2 × 1 H, OH-2′ and 3′), 5.99 (d, 1 H, H-1′, $J_{1',2'}$ = 6.8 Hz), 7.72 (d, 1 H, H-6), 11.2 (br s, 1 H, NH-3)	$C_{10}H_{14}N_2O_6$
22d	69, B, f	lyophilized	258 (16.4) [H_2O]	267	D_2O[e]	3.9–4.1 (m, 2 H, H-5′,5″), 4.2–4.6 (m, 2 H, H-3′,4′), 4.7–4.9 (m, 1 H, H-2′), 6.30 (d, 1 H, H-1′, $J_{1',2'}$ = 6.9 Hz), 8.10 and 8.30 (2 s, 2 × 1 H, H-2 and H-8)	$C_{10}H_{13}N_5O_4 \cdot {}^2/_3H_2O$
22e[f]	45, C[g]	240 start of dec (H_2O)	256 (13.7), 278 (sh, 9.4) [0.1 N HCl], 252 (15.2), 274 (sh, 10.4) [H_2O], 262 (br, 12.8) [0.1 N KOH]	*h*	$(CD_3)_2SO$	3.55–3.60 (m, 1 H, H-5′), 3.69–3.75 (m, 1 H, H-5″, $J_{5',5''}$ = 10.7 Hz), 3.89–3.93 (m, 1 H, H-4′), 4.12–4.15 (m, 1 H, H-3′, $J_{3',4'}$ = 4.9 Hz), 4.42–4.46 (m, 1 H, H-2′, $J_{2',3'}$ = 4.9 Hz), 4.74 (t, 1 H, OH-5′, $J_{H,OH\text{-}5'}$ = 5.3 Hz), 5.36 (d, 1 H, OH-2′, $J_{H,OH\text{-}2'}$ = 6.3 Hz), 5.40 (d, 1 H, OH-3′, $J_{H,OH\text{-}3'}$ = 4.2 Hz), 5.94 (d, 1 H, H-1′, $J_{1',2'}$ = 6.9 Hz), 6.40 (s, 2 H, NH_2) 7.94 (s, 1 H, H-8), 9.0 (br s, 1 H, NH-1)	$C_{10}H_{13}N_5O_5 \cdot {}^1/_2H_2O$

[a] References of previously described compounds: **22a**,[48,49] **22b**,[11,12,50,51] **22c**,[11,12,52] **22d**.[53] [b] See Experimental Section. Yeilds are calculated after purification by column chromatography with silica gel (A) or Dowex 1-X2 (OH^-) ion-exchange resin (B) or by HPLC (C), with the following eluents: a, stepwise gradient of MeOH in $CHCl_3$ from 0% to 3%; b, stepwise gradient of MeOH in CH_2Cl_2 from 0% to 1%; c, stepwise gradient of MeOH in CH_2Cl_2 from 0% to 4%; d, stepwise gradient of MeOH in CH_2Cl_2 from 0% to 15%; e, H_2O; f, linear gradient of MeOH in H_2O from 0% to 40%. [c] Chemical formulas are given for compounds that were analyzed for all the elements except oxygen; all analytical results were within ±0.4% of the theoretical values. [d] Crystallized after transformation in its hydrochloride salt form. [e] Shifts from 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$ sodium salt. [f] $[\alpha]^{20}_D$ −57.4° (*c* 1.08, Me_2SO). [g] Apparatus and conditions for HPLC were the same as we had previously described for the purification of 9-α-D-xylofuranosylguanine.[4] [h] Spectrum virtually useless owing to pyrolysis.

N^2-Acetyl-7-(2′-*O*-acetyl-3′,5′-di-*O*-benzoyl-β-D-xylofuranosyl)guanine (15) and N^2-Acetyl-9-(3′,5′-di-*O*-benzoyl-β-D-xylofuranosyl)guanine (17). A suspension of N^2-acetylguanine[54] (5 g, 25.9 mmol) in anhydrous acetonitrile (110 mL) was treated with bis(trimethylsilyl)acetamide (BSA) (25.3 mL, 103.5 mmol) during 15 min under reflux. To the resulting solution was added starting sugar **13**[55] (9.55 g, 21.6 mmol) in acetonitrile (110 mL), followed by addition of TMSTF (5.9 mL, 32.4 mmol). 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 $CHCl_3$ (750 mL) and H_2O (370 mL). The cloudy biphasic mixture was filtered by using Whatman phase separator. The organic phase was separated, washed four times with water, dried over sodium sulfate, and evaporated to dryness. Chromatography of the residue on a silica gel column using a stepwise gradient of MeOH in $CHCl_3$ (from 0% to 2%) led to the isolation of two combined fractions.

The first combined fractions contained pure N-7 isomer **15** (1.2 g, 9%), which was crystallized from ethyl acetate: mp 223–226 °C; UV (EtOH) λ_{max} 266 nm (ε 19.8), 224 (35.8), λ_{min} 250 nm (ε 18.2); ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3 H, 2′-O-$COCH_3$), 2.35 (s, 3 H, N^2-$COCH_3$), 4.6–5.0 (m, 3 H, H-4′,5′,5″), 5.65 (m, 1 H, H-2′ or 3′), 5.75 (m, 1 H, H-2′ or 3′), 6.55 (d, 1 H, H-1′, $J_{1',2'}$ = 2.2 Hz), 7.2–8.1 (m, 10 H, 2 C_6H_5CO), 8.28 (s, 1 H, H-8), 11.2 (br s, 1 H, N^2-H or NH-1), 11.8–12.8 (br s, 1 H, N^2-H or NH-1). Anal. ($C_{28}H_{25}N_5O_9$) C, H, N.

The second combined fractions (9.9 g) contained N-9 isomer **16** contaminated by some impurities, chief among which was the N-7 isomer **15**. A solution of these fractions in an acetic acid/pyridine mixture (1:4, v/v, 195 mL) was treated with hydrazine hydrate[55] (2.58 mL) with stirring at room temperature for 4 h. Reaction was quenched by acetone (46 mL) with stirring at room temperature. After 2 h, the mixture was partially evaporated in vacuo and extracted from water (200 mL) into chloroform (2 × 300 mL). Combined organic phases were washed several times with water, dried over sodium sulfate, and evaporated to dryness. Chromatography of the residue on a silica gel column using a stepwise gradient of MeOH in $CHCl_3$ (from 0% to 3%) led to the isolation of pure **17** (6.8 g, 59%) as a powder after trituration with petroleum ether: mp 144–146 °C; UV (EtOH) λ_{max} 279 nm (ε 13.0), 256 (16.8), 232 (28.1), λ_{min} 271 nm (ε 12.9), 249 (16.3); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3 H, N^2-$COCH_3$), 4.4–5.3 (m, 4 H, H-4′,5′,5″ and 2′ or 3′), 5.7 (m, 1 H, H-2′ or 3′), 5.90 (d, 1 H, H-1′, $J_{1',2'}$ = 3.0 Hz), 7.1–8.0 (m, 11 H, 2 C_6H_5CO + H-8), 10.5 (br s, 1 H, N^2-H or NH-1), 12.1 (br s, 1 H, N^2-H or NH-1). Anal. ($C_{26}H_{23}N_5O_8 \cdot {}^1/_2H_2O$) C, H, N.

General Procedures for the Preparation of Unprotected α-D-Lyxofuranosyl Nucleosides 8–12 and β-D-Xylofuranosyl Nucleosides 18a and 18e. With Methanolic Sodium Methoxide. Workup was similar to that described in ref 4 (method D), except for the nucleosides of N^2-acetylguanine, which were refluxed for 0.5 h in a freshly prepared methanol solution of 0.3 N sodium methoxide.

With Methanolic Ammonia. The protected nucleosides were dissolved with stirring in methanolic ammonia (previously saturated at −10 °C and tightly stoppered) (ca. 25 mL/mmol). When TLC indicated that the reaction was complete (ca. 4 h), the solution was evaporated to dryness to afford the deblocked nucleosides, which could be further purified by either column chromatography or direct crystallization.

General Procedure for the Preparation of 3′,5′-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-xylofuranosyl Nucleosides 19a–e. To a stirred suspension of dried β-D-xylofuranosyl nucleosides **18a–e**[4] (11.2 mmol) in pyridine (36 mL) for **18a–d** or in a mixture of dioxane (160 mL) and pyridine (12 mL) for **18e** was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (3.86 mL, 12.32 mmol, 1.1 equiv). When TLC showed the reaction to be complete (ca. 4 h), the solution was evaporated and the residue was partitioned between $CHCl_3$ and saturated NaCl/H_2O. The aqueous phase was extracted twice with $CHCl_3$, and the organic extracts were dried over sodium sulfate and evaporated. The residue was evaporated with several portions of toluene and then chromatographed on a silica gel column to afford, after crystallization or lyophilization, pure **19a–e**.

General Procedure for the Preparation of 3′,5′-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-lyxofuranosyl Nucleosides 21a–e. To a stirred solution of **19** (4.0 mmol) and *N,N′*-dicyclohexylcarbodiimide (DCC, 12.0 mmol) in a mixture of anhydrous benzene (29 mL) and dimethyl sulfoxide (29 mL) was added dichloroacetic acid (0.16 mL, 2.02 mmol). The solution turned the characteristic orange color, and a precipitate of dicyclohexylurea (DCU) began to form. After the mixture was

Table III. Antiviral Activity of D-Lyxofuranosyl Nucleosides against Different Viruses in Different Cell Systems

	minimum cytotoxic concn,[a] μg/mL				minimum inhibitory concentration,[b] μg/mL													
					primary rabbit kidney cells				HeLa cells			African green monkey kidney (Vero B) cells					human diploid (WI-38) cells	
compd	PRK cells	HeLa cells	Vero B cells	WI-38 cells	herpes simplex virus-1 (KOS)	herpes simplex virus-2 (G)	vaccinia virus	vesicular stomatitis virus	polio virus-1	Coxsackie B4		para-influenza virus-3	Reo virus-1	Sindbis virus	Semliki forest virus		rhino-virus 1A	rhino-virus 9
α-lyxoA (8)	>400	>400	>400	>400	>400	100	70	>400	>400	>400	>400	70	70	>400	>400	>400	>200	>200
α-lyxoC (9)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400
α-lyxoT (10)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>200	>400	>400	>400	>400
α-lyxoU (11)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>200	>400	>400	>400	>400
α-lyxoG (12)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	200
β-lyxoC (22a)	≥200	>200	>200	200	>200	>200	70	>200	>200	>200	>200	>200	>100	>200	>100	>200	>200	>200
β-lyxoU (22b)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>100	>400	>400	>400	>400	>400	100
β-lyxoT (22c)	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	150
β-lyxoA (22d)	>400	>400	>400	>400	>400	>400	200	>400	>400	>400	>400	100	>200	>200	>400	>400	>400	>400
β-lyxoG (22e)	>400	>400	>400	>400	>400	400	100	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400	>400
tubercidin	1	≥1	≥0.4	≥4	>0.4	>0.4	0.2	0.07	0.07	0.07	0.2	0.2	>0.1	>0.1	0.2	>0.4	0.02	≥4
(*S*)-DHPA	>400	>400	≥400	≥400	>400	>400	40	20	70	>400	>400	150	20	150	>400	300	>400	≥400
ribavirin	≥400	≥200	>400	>400	>400	>400	20	150	20	70	70	10	70	70	70	>400	150	>400
carbocyclic 3-deaza-adeno-sine	≥400	≥400	≥400	>400	>400	150	0.7	0.2	0.7	>400	>400	0.04	0.7	1	70	>200	>400	>400

[a] Required 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] Required to reduce virus-induced cytopathogenicity 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 cell.

Table IV. Virus Yield Reduction of HSV-1 (KOS) and HSV-2 (196) after 24 and 48 h in Primary Rabbit Kidney Cell Cultures by α-lyxoA (8), β-araA, and Acyclovir

	virus yield,[a] $\log_{10}$ PFU/mL					virus yield,[a] $\log_{10}$ PFU/mL			
	24 h		48 h			24 h		48 h	
compd	HSV-1	HSV-2	HSV-1	HSV-2	compd	HSV-1	HSV-2	HSV-1	HSV-2
α-lyxoA (8) (400 μg/mL)	6.2	3.8	6.6	5.1	acyclovir (4 μg/mL)	2.0	<2.0	3.3	3.8
α-lyxoA (8) (100 μg/mL)	6.8	5.1	6.7	5.3	acyclovir (1 μg/mL)	3.6	3.1	5.3	5.3
α-lyxoA (8) (40 μg/mL)	6.8	5.4	7.0	5.5	acyclovir (0.4 μg/mL)	4.1	4.1	5.0	5.0
β-araA (40 μg/mL)	3.0	<1.6	5.5	4.3	acyclovir (0.1 μg/mL)	5.2	4.8	5.6	5.6
β-araA (10 μg/mL)	5.7	4.7	6.8	5.2	acyclovir (0.04 μg/mL)	5.6	5.8	5.9	5.7
β-araA (4 μg/mL)	6.7	5.0	6.8	5.7	control herpes simplex virus	6.5	5.3	6.9	5.8

[a] As determined by plaque formation in Vero cells, and expressed in plaque forming units (PFU).

Table V. Effect of Topically Applied α-lyxoA (8) on the Development of Cutaneous HSV-1 (KOS) and HSV-2 (196) Infection in Hairless (hr/hr) Mice

		HSV-1			HSV-2		
		no. of mice with given characteristics			no. of mice with given characteristics		
compd	characteristics of mice[a]	from day 0 to day 3	from day 12 to day 20	survival rate at 20th day	from day 0 to day 3	from day 12 to day 20	survival rate at 20th day
α-lyxoA (8)	N	10	4	4/10	10	3	3/10
	P						
	D		6			7	
β-araA	N	10	3	4/10	10	3	3/10
	P		1				
	D		6			7	
acyclovir	N	10	10	10/10	10	5	5/10
	P						
	D					5	
placebo (Me_2SO)	N	10		0/10	10		0/10
	P						
	D		10			10	

[a] N: normal, without lesion. P: with skin lesions plus paralysis. D: dead. The compounds were applied topically four times a day for 5 days, starting immediately after virus infection; they were formulated at 5% in Me_2SO.

stirred for 2 days in the case of **19d** and overnight in the other cases, it was diluted with ethyl acetate, and a solution of oxalic acid (1.51 g, 12.0 mmol) in methanol (3.2 mL) was carefully added. After 1 h at ambient temperature, the resulting mixture was filtered and the insoluble DCU was washed with ethyl acetate. The combined filtrate and wash were successively extracted with aqueous saturated sodium chloride, aqueous 3% sodium hydrogen carbonate, and water and then dried over sodium sulfate. The residue obtained by evaporation of the organic solution was dissolved in ethanol (60 mL) for **20d–e** or in a mixture of benzene (30 mL) and ethanol (30 mL) for **20a–c**. The resulting solution was stirred magnetically and kept below 5 °C in an ice bath while sodium borohydride (0.23 g, 6.04 mmol) was added in portions. The solution was stirred for 1 h after addition was complete, then diluted with ethyl acetate, and filtered. The filtrate was extracted with aqueous saturated sodium chloride and water and then dried over sodium sulfate. The solvent was evaporated to dryness, and the residue was either allowed to stand for 2 weeks in ethanol and then chromatographed (guanine series) or directly chromatographed (other series) on a silica gel column to afford, after crystallization or lyophilization, pure **21a–e**.

2-(*S*,*S*-Dimethylsulfilimino)-6-hydroxy-9-[3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-lyxofuranosyl]purine (23). An aliquot of the reduction mixture from **20e** was subjected to preparative TLC (acetone/$CHCl_3$/H_2O, 50:19:1, v/v, silica gel) to give a more mobile zone of **21e** and a less mobile zone of **23**: mp 201–202 °C after recrystallization from EtOH; UV (EtOH) λ_{max} 321 and 272 nm ($\epsilon_{272}/\epsilon_{321}$ = 3.42), λ_{min} 310 and 243 nm ($\epsilon_{243}/\epsilon_{310}$ = 2.90); ^1H NMR (Me_2SO-d_6) δ 0.9–1.1 (m, 28 H, 4 $(CH_3)_2CH$), 2.78 (s, 6 H, 2 SCH_3), 3.7–3.9 (m, 2 H, H-5′,5″), 4.0 (m, 1 H, H-4′), 4.35 (t, 1 H, H-3′), 4.8 (m, 1 H, H-2′), 5.63 (d, 1 H, OH-2′, $J_{H,OH-2'}$ = 5.7 Hz), 6.03 (d, 1 H, H-1′, $J_{1',2'}$ = 7.5 Hz), 7.86 (s, 1 H, H-8), 10.73 (s, 1 H, NH-1); mass spectrum, *m/z* 585 ($M^{+\cdot}$), 563 (M − CH_3), 542 (M − C_3H_7), then superimposable on the spectrum of **21e**.

General Procedure for the Preparation of Unprotected β-D-Lyxofuranosyl Nucleosides 22a–e. Compound **21** (0.5 mmol) was dissolved in dry tetrahydrofuran (THF, 9 mL), and a 1 M solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (1 mL) was added. The solution was stirred for 1 h at ambient temperature, then poured into chloroform, and extracted with water. The aqueous layers were combined, evaporated to dryness, and coevaporated three times with absolute ethanol. The resulting crude material was purified by column chromatography to afford, after crystallization or lyophilization, pure **22a–e**.

Biological Methods. Assays on Cell Culture. The origin of the viruses and the techniques used for measuring inhibition of virus-induced cytopathogenicity and virus replication (yield) have been described previously.[56,57]

Assays on Animals. The procedure for evaluation of the acute toxicity for mice has also been described previously.[4]

For evaluation of topical treatment of cutaneous HSV-1 or HSV-2 infection in hairless (hr/hr) mice, mice (25–30 days old and weighing 15–20 g) were inoculated intracutaneously in the lumbosacral area with HSV-1 (KOS) at $10^{4.7}$ PFU/0.05 mL per mouse or with HSV-2 (strain 196) at $10^{3.7}$ PFU/0.05 mL per mouse. Immediately after virus infection, the mice were treated topically with the compound at 5% in Me_2SO, four times a day for 5 days. Development of herpetic skin lesions, paralysis of the hind legs, and mortality of mice were observed during 20 days.

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