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Synthesis and Antiviral Activity of Novel Isonucleoside Analogs

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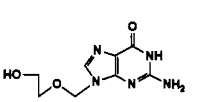
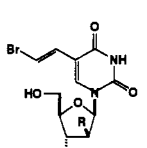
A series of branched-chain sugar isonucleosides was synthesized and evaluated for antiviral activity against herpesviruses. The preparation of homochiral [3*S*-(3α,4β,5α)]-2-amino-1,9-dihydro-9-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-6*H*-purin-6-one (**7**, BMS-181,164) and related compounds was stereospecifically achieved starting from 1,2-isopropylidene-D-xylofuranose (**10**). An efficient two-step reduction of the anomeric center of bis-acetate **18** involved formation of the chloride intermediate **19**, followed by diisobutylaluminum hydride reduction. Tosylation of the resulting alcohol **20** provided the key intermediate **21**, which was coupled with a variety of nucleobase anions. Several members of this new class of compounds possess activity against herpes simplex virus types 1 and 2 (HSV-1 and -2), varicella-zoster virus (VZV), and human cytomegalovirus (HCMV). Compound **7** exhibits potent and selective activity against thymidine kinase encoding herpesviruses, in particular, HSV-1 and HSV-2. Evaluation of compound **7** for inhibition of WI-38 cell growth indicated an ID_{50} of >700 μM. Although the antiherpetic activity in vitro of **7** is less than that of acyclovir (**1**), compound **7** displays superior efficacy in mouse model infections. The (bromovinyl)uridine analog **8** (BMS-181,165) also exhibits selective activity against HSV-1 and VZV, with no cytostatic effect on WI-38 cell growth at >800 μM. Compound **8** is active against simian varicella virus and is efficacious in the corresponding monkey model.

Introduction

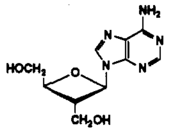
In the search for effective, selective, and nontoxic antiviral agents, a variety of strategies have been devised to design nucleoside analogs that interfere with viral replication without affecting cellular processes. These strategies have encompassed several formal modifications of the naturally occurring nucleosides; specifically, alteration of the carbohydrate moiety (acyclovir, **1**),[1] the nucleobase moeity (BVDU, [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine], **2**),[2] or both (BVaraU, [1-β-D-arabinofuranosyl-(*E*)-5-(2-bromovinyl)uracil], **3**).[3] Several classes of nucleoside analogs containing significantly altered carbohydrate portions have recently been reported as potent antiviral agents, including the four-membered ring containing compounds **4** (oxetanocin-A),[4] **5** (SQ-32,829),[5] and **6** ((±)-BHCG).[6,7] We believe that considerable room remains for the design and identification of nucleoside-analog antivirals containing other types of surrogate "sugar templates". Optimally, these templates should allow a spatial orientation of the hydroxy and nucleobase pharmacophores which mimics that found in natural nucleosides. An analog with an altered sugar template could be selectively recognized by the less discriminating viral enzymes, such as thymidine kinase, without affecting host cellular processes. Our search for novel templates has led to the discovery of a new class of branched-chain isonucleosides with potent activity against a variety of herpesviruses.[8] The preparation and biological activities of compounds **7** (BMS-181,164), **8** (BMS-181,165), and related isonucleosides are described in this paper.



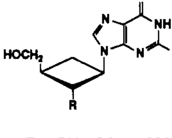
1 Acyclovir



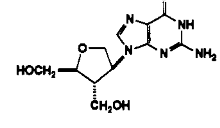
2 R = H : BVDU
3 R = OH : BVaraU



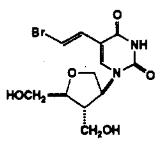
4 Oxetanocin-A



5 R = OH ; SQ-32,829
6 R = CH2OH ; (±) BHCG

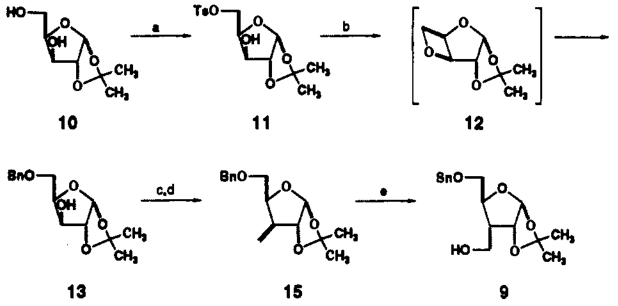


7 BMS-181,164



8 BMS-181,165

Scheme I[a]



[a] (a) TsCl, pyridine; (b) Na^0, BnOH; (c) CrO_3/pyridine, CH_2Cl_2; (d) $(Ph)_3PCH_2$, THF, rt to 50 °C; (e) (1) BH_3/THF, (2) NaOH, 30% H_2O_2.

Chemistry

We chose D-xylofuranose as the starting point for the efficient and stereospecific synthesis of homochiral **7** and related compounds. Using modified literature procedures,[9] the known alcohol **9**[10] was prepared from commercially available 1,2-isopropylidene-D-xylofuranose (**10**) (Scheme I). Reaction of the primary alcohol **10** with TsCl gave **11**, which was treated with the sodium salt of benzyl alcohol at 100 °C to afford **13** through the intermediate oxetane **12**. Oxidation of **13** with Collins' reagent followed by Wittig olefination of the crude ketone **14** gave the exo olefin **15**. Hydroboration of olefin **15** with BH_3/THF afforded alcohol **9**, which had melting point, $[\alpha]_D$, and ^1H NMR data consistent with that reported previously.[10]

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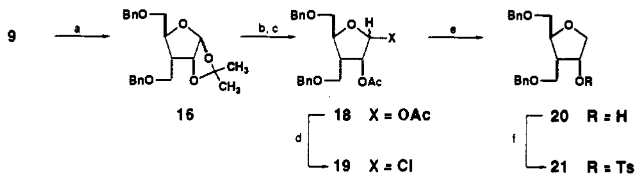
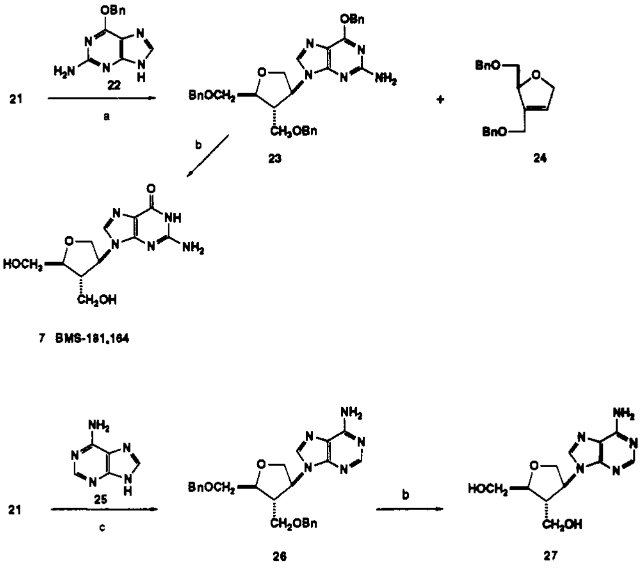
Scheme II[a]



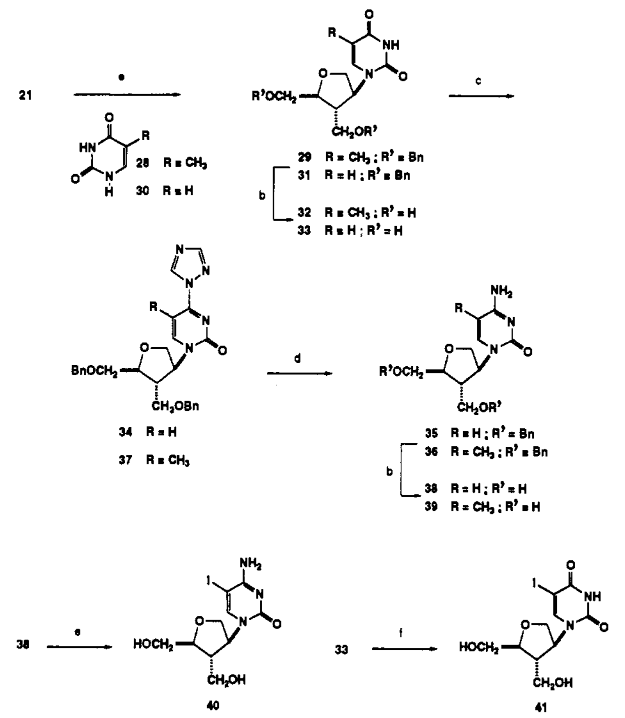
[a] (a) NaH, DMSO, then BnBr; (b) AcOH, H_2O; (c) Ac_2O, pyridine; (d) HCl, toluene; (e) Dibal, toluene, THF; (f) TsCl, pyridine.

Scheme III[a]



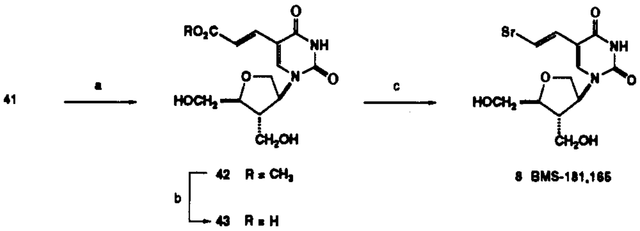
[a] (a) K_2CO_3, 18-crown-6, DMF, 90 °C; (b) Na^0, THF/NH_3, then 0.5 N HCl; (c) K_2CO_3, 18-crown-6, DMF, 67–90 °C.

Scheme IV[a]



[a] (a) Thymine, K_2CO_3, 18-crown-6, DMF, 90 °C; or uracil, K_2CO_3, 18-crown-6, DMSO, 90 °C; (b) $Pd(OH)_2/C$, 95% EtOH, cyclohexene, 90 °C; (c) *p*-chlorophenyl phosphorodichloridate, 1,2,4-triazole, pyridine; (d) NH_4OH, dioxane; (e) I_2, HIO_3, aqueous AcOH, CCl_4, 50 °C; (f) I_2, HNO_3, dioxane, reflux.

Scheme V[a]



[a] (a) $Pd(OAc)_2$, Ph_3P, Et_3N, methyl acrylate, DMF, 75 °C; (b) aqueous KOH, then HCl; (c) NBS, $KHCO_3$, DMF.

Protection of the primary hydroxyl group of **9** required forcing conditions (Scheme II). Treatment of **9** with sodium dimsylate, followed by benzyl bromide, gave **16** in 87% yield. Removal of the acetonide group with aqueous acetic acid, followed by acetylation of the crude lactol-alcohol **17**, gave diacetate **18** as a mixture of α- and β-anomers. Conversion of the anomeric acetates to the corresponding anomeric chlorides **19** with HCl in toluene and subsequent DIBAL reduction gave **20** in 79% overall yield. Alternatively, DIBAL reduction of the anomeric bromides prepared by treatment of **18** with TMSBr[11] also provided **20**, but in a lower overall yield. The key intermediate **21** was prepared in 85% yield by treatment of alcohol **20** with TsCl at low temperature.

Tosylate **21** was coupled with 2-amino-6-(benzyloxy)-purine (**22**) in the presence of K_2CO_3/DMF to give **23** in 27% yield (Scheme III). A major byproduct was olefin **24**, produced in ca. 30% yield by elimination of the tosylate group. Birch reduction of **23** provided the desired guanine-containing nucleoside analog **7**. Likewise, the adenosine analog **27** was prepared by coupling tosylate **21** with adenine in the presence of K_2CO_3 and 18-crown-6 in DMF, followed by Birch reduction of the coupled product **26** (Scheme III).

The pyrimidine analogs were also synthesized from tosylate **21** (Scheme IV). Reaction of **21** with thymine and K_2CO_3 in DMSO provided a 28% yield of **29**. Similar conditions were utilized to couple **21** with uracil to give **31** in 24% yield. In both coupling reactions, formation of olefin **24** was a major byproduct. Both **29** and **31** were deprotected under transfer hydrogenolysis conditions using $Pd(OH)_2$ to give **32** and **33**, respectively. The cytidine analog could not be prepared efficiently by direct coupling of **21** with cytosine. Reacting **31** with *p*-chlorophenyl phosphorodichloridate and 1,2,4-triazole, followed by aminolysis of the triazoyl intermediate **34**, gave the protected cytosine **35** in 62% yield.[12] In an analogous sequence, the 5-methylcytosine intermediate **36** was prepared from **29**. Both **35** and **36** were deprotected by transfer hydrogenolysis to give **38** and **39**, respectively. Iodination at C-5 of **38** by reaction with I_2 and HIO_3 afforded the 5-iodocytidine analog **40**.[13] The uracil **33** was iodinated by reaction with I_2 and HNO_3 in refluxing dioxane to give **41**.[14]

Compound **41** was further elaborated under standard conditions to provide the (*E*)-5-(2-bromovinyl)uridine analog **8** (Scheme V).[15] Palladium-mediated coupling of methyl acrylate with iodouracil **41** in DMF gave the methyl ester **42**.[16] Hydrolysis of ester **42** with KOH, followed by treatment of acid **43** with *N*-bromosuccinimide, gave **8**.[17]

Biological Results and Discussion

The results of virus plaque-reduction assays for the guanine-containing analog **7**, the (bromovinyl)uridine analog **8**, and other base analogs are summarized in Table I. These compounds display antiviral activities against

Table I. Antiviral Efficacy and Cell Growth Inhibition of Isonucleoside Analogs in Cell Culture

	ID_{50} (μM)[a]					
virus (strain)	**7**	**8**	**27**	**38**	**32**	acyclovir (**1**)
HSV-1 (Schooler)	7–18	1–3	4–8	20–40	2–4	0.4–0.9*
HSV-1 (KOS)	4–7*	1–3*	2–4*	ND[b]	4–8	0.4–2*
HSV-1 (BVaraU^R)[c]	90–180	>290	4–8	ND	>400	>440*
HSV-2 (186)	1–4*	>290	4–8	20–40	200–400	0.4–0.9*
HSV-2 (2′NDG^R)[c]	90–180	ND	4	ND	ND	>440*
VZV (Ellen)	20–40	0.03–0.1*	2–4	0.2–0.4*	10–20	1–4*
HCMV (AD169)	>360*	>290	2–4*	40–100*	>400	20–40*
vaccinia (CL)	>360	>290	10–20	40–400	ND	>440*
cell growth inhibition						
WI-38	>700	>800	40–90	130–160	ND	≥800*

[a] ID_{50} values show the range of single assays, unless designated otherwise (*). [b] Not determined. [c] Thymidine kinase deficient strains isolated as BVaraU and ganciclovir (2′NDG) resistant mutants of HSV-1 (KOS) and HSV-2 (186), respectively.

Table II. Efficacy of Compound 8 and Acyclovir (1) against different Strains of VZV in Cell Culture

	ID_{50} (μM)[a]	
VZV strain	**8**	acyclovir (**1**)
Ellen	0.03–0.1	1–4
9021	0.3–0.5	0.5–2
ppIIa	0.1–0.3	1–4
Oka	0.5–3	1–4
Ito	0.03–0.06*	0.4–2
Kanno–Kohmura[b]	>300*	40–100
SVV Strain		
G815	5–30	40–100

[a] ID_{50} values show the range of repeat assays, unless designated otherwise (*). [b] Thymidine kinase deficient strain.[21]

Table III. Antiherpes Activities of Compounds 33 and 39–41

	ID_{50} (μM)[a]			
virus (strain)	**33**	**39**	**40**	**41**
HSV-1 (Schooler)	>410	390	70–140	70–140
HSV-2 (186)	>410	390	>270	>270*
VZV (Ellen)	40–100	40–200*	5–14*	30–70
HCMV (AD169)	>410	>390	>270	>270

[a] ID_{50} values show the range of single assays, unless designated otherwise (*).

Table IV. Efficacy of 7 (BMS-181,164) against a Herpes Simplex Virus Type 1 Infection in Mice

compd (mg/kg/day)	survivors (alive/total)	PD_{50} (mg/kg/day)	mean day of death for total dead ± SD
7 (BMS-181,164)			
200	9/10	84	
150	7/10		12.3 ± 1.1[a]
100	6/10		14.7 ± 4.3[a]
50	0/10		10.1 ± 2.2[a]
25	2/10		9.1 ± 1.4[a]
12.5	0/10		9.6 ± 1.8[a]
acyclovir			
200	2/10		14.0 ± 1.6[a]
150	2/10		11.8 ± 2.1[a]
100	2/10	>200	9.3 ± 1.8[a]
50	1/10		9.0 ± 1.2[a]
25	3/10		7.8 ± 0.7
12.5	0/10		8.3 ± 1.2
placebo	1/10		7.5 ± 0.9

[a] $P < 0.05$. Sample is significantly different from placebo. Statistical analysis was computed only for groups with 2 or more deaths.

several herpesviruses. Compound **7** displays potent and selective activity against thymidine kinase (TK) encoding herpesviruses, in particular, HSV-1 and HSV-2. The decrease in activity against TK-deficient strains of both HSV-1 and -2 indicates that the antiviral activity of **7** against HSV is highly dependent on phosphorylation by viral TK. The selectivity of **7** is also apparent by its inactivity against vaccinia virus (VV) and HCMV and its lack of inhibition of WI-38 cell proliferation at the highest concentrations tested (>700 μM).

Changing the nucleobase has a marked effect on the potency and spectrum of activity of the other members of the class. Unlike compound **7**, the adenosine analog **27** is not dependent on herpes thymidine kinase for activity and is equally active against HSV-1, HSV-2, VZV, HCMV, and VV. The inhibition of WI-38 cell growth at relatively low concentrations by **27** might be a reflection of this indiscriminate activity. The cytidine analog **38** exhibits potent and selective activity against VZV; however, cell growth inhibition was also observed.

The thymidine and (bromovinyl)uridine analogs **32** and **8**, respectively, possess selective activity against HSV-1 and VZV. All strains of VZV tested are very sensitive to compound **8** (Table II). In addition, compound **8** inhibits the replication of simian varicella virus (SVV), but at higher concentrations. The lack of activity of **8** and **32** against TK-deficient strains of VZV and HSV-1, respectively, indicates an important role for viral TK. The uridine, 5-iodouridine, 5-methylcytidine, and 5-iodocytidine analogs (**33**, **41**, **39**, and **40**, respectively) display only moderate antiherpetic activity (Table III).

In cell culture protection studies, compound **7** is approximately 5–10-fold less potent than acyclovir against HSV-1 and HSV-2. However, when administered subcutaneously, compound **7** is efficacious against lethal HSV-1 and HSV-2 systemic infections with PD_{50} values of 84 and 52 mg/kg/day, respectively, while acyclovir displays PD_{50} values of >200 mg/kg/day in both these models (Tables IV and V). No overt toxicity is observed in mice at the highest doses tested (200 mg/kg of **7** for 5 days). Compound **8** administered orally twice daily at 2 mg/kg for 10 days starting 24 h after intratracheal simian varicella virus infection prevented vesicular rash development and suppressed viremia.[18]

In conclusion, a promising class of nucleoside analogs using a novel sugar surrogate has been discovered. This sugar surrogate was designed to serve as a "template" to hold the hydroxyl and nucleobase pharmacophores in spatial positions approximating those found in the natural nucleosides. As was the case with the cyclobutyl analogs **5**[5] and **6**,[6,7] this concept of template design has proven successful. In particular, compounds **7** and **8** display promising activity against thymidine kinase encoding herpesviruses. The potency and selectivity of compounds **7** and **8** in cell culture, and their efficacy in animal models, indicate that these compounds warrant further evaluation as agents for the treatment of herpesviral infections.

Table V. Efficacy of 7 (BMS-181,164) against a Herpes Simplex Virus Type 2 Infection in Mice

compound (mg/kg/day)	survivors (alive/total)	PD_{50} (mg/kg/day)	mean day of death for total dead ± SD
7 (BMS-181,164)			
200	9/10	52	
150	9/10		
100	6/10		12.2 ± 1.2
50	2/10		10.9 ± 1.1
25	6/10		12.5 ± 3.3
12.5	0/10		10.3 ± 1.5
acyclovir			
200	5/10		13.0 ± 2.1
150	4/10		13.0 ± 1.7[a]
100	2/10	>200	13.5 ± 2.6[a]
50	1/10		11.7 ± 3.2
25	0/10		11.6 ± 2.4
12.5	0/10		10.0 ± 1.3
placebo	0/10		10.7 ± 2.2

[a] $P < 0.05$. Sample is significantly different from placebo. Statistical analysis was computed only for groups with 2 or more deaths.

Experimental Section

Chemistry. Nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were obtained with a JEOL GX-270 or GSX-400 spectrometer with tetramethylsilane (TMS) as internal reference, unless otherwise specified. Chemical shifts are expressed in δ units (parts per million). Mass spectra (CI or FAB) were obtained on a Finnigan TSQ or VG-ZAB-2F mass spectrometer. High-resolution mass spectra (FAB, M + H) were obtained on a JEOL-HX or -SX mass spectrometer. Ultraviolet spectra were recorded on a Shimadzu UV-260. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter spectrometer. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Diaion CHP20P is a reverse-phase resin for chromatography and was obtained from Mitsubishi Chemical Industries Limited. Flash chromatography was performed on silica gel (Merck silica gel 60, 230–400 mesh), unless otherwise specified. TLCs were run on Merck silica gel 60 F254 plates, and purities of samples, when measured by densitometry at 254 nm, were determined on Shimadzu CS-930 or CS-9000 TLC scanners. Micellar electrokinetic capillary chromatography[19] (MECC) was performed on an Applied Biosystems Model 270Å capillary electrophoresis system. A fused silica capillary column (72 cm × 50-mm i.d.) was used with a pH 9, 20 mM borate/phosphate buffer containing 200 mM SDS, a voltage of 20 kV, a temperature of 30 °C, and a detection wavelength of 200 nm.

Antiviral Assays. Viruses, Cells, Media. Viruses, cells, and assays have been described in detail previously.[6b,20] In brief, herpes simplex virus type 1 (HSV-1), strain Schooler, and HSV-2, strains 186 and Curtis, were prepared as extracts from infected Vero cell cultures. Human cytomegalovirus (HCMV) strain AD169, varicella-zoster virus (VZV) strains Ellen, Ito, Kanno-Kohmura,[21] Oka, ppIIa, and 9021 were prepared as suspensions of infected WI-38 cells. HSV-1 ($BVaraU^R$) and HSV-2 (186, $2'NDG^R$) are thymidine kinase deficient (TK^-) viruses and were isolated as BVaraU or ganciclovir (2′NDG) resistant mutants of HSV-1 (KOS) and HSV-2 (186), respectively.[20] VZV strain Ito is a BUdR-resistant, acyclovir-sensitive, TK-altered clinical isolate, and VZV strain Kanno-Kohmura is a TK-mutant of Kanno, provided by Dr. S. Shigeta, Fukushima Medical Center, Fukushima, Japan. VZV strain ppIIa is a clinical isolate provided by Dr. J. Ostrove, NIH. VZV strain 9021 is a recent clinical isolate provided by Dr. L. Fenkel, Robert Wood Johnson Viral Diagnostic Laboratory. VZV strains Ellen (VR-58) and Oka (VR-795) were obtained from ATCC. Simian varicella virus (SVV) strain G815 was obtained from Dr. K. Soike, Tulane University Regional Primate Research Center, and was prepared from infected Vero cell cultures.[22] WI-38 (CCL75) and Vero (CCL81) cells were obtained from ATCC and were grown in Eagles minimum essential medium with Earle's salts (EMEM) supplemented with 2 mM L-glutamine, 100 units/mL penicillin, 100 μg/mL streptomycin, and 10% FBS (Gibco Laboratories, Grand Island, NY).

Plaque Reduction Assay. HSV-1, HSV-2, HCMV, and VZV were assayed on WI-38 cell monolayers. SVV was assayed on Vero cell monolayers. Viruses were adsorbed to cell culture monolayers in 6-well culture plates (Costar, Cambridge, MA) for 1–2 h prior to addition of maintenance medium containing duplicate dilutions of the test compound (EMEM plus supplements, 1% carboxymethyl cellulose, 2.5% FBS ± drug). Inhibition of plaque development for all viruses was evaluated on monolayers stained after 4–6 days of incubation at 37 °C. ID_{50} values were determined from the drug concentration which conferred 50% plaque reduction compared to virus controls. All titrations were done in duplicate.

Cell Growth Inhibition Studies. WI-38 cells were plated at 1.2×10^5 cells per well in 12-well Costar plates containing 2 mL of growth medium. Following overnight incubation at 37 °C, the cultures were refed with fresh growth medium containing serial dilutions of drug (or no drug), and incubation was continued at 37 °C for an additional 3 days. Quadruplicate cultures for each concentration of drug evaluated were harvested by trypsinization and counted daily for viable cells by staining with trypan blue. Untreated control cell cultures increased approximately 3–5-fold.

In Vivo Antiviral Assays. Female Swiss-Webster mice weighing 20–23 g, obtained from Taconic Farms, Germantown, NY, were employed for all studies. Mice were infected intraperitoneally with 10^3 PFU of HSV-1 strain Schooler or 10^5 PFU of HSV-2 strain Curtis contained in 0.5 mL of 0.3% BSA-PBS. The HSV-1 and HSV-2 strains were prepared as freeze–thawed extracts from infected Vero cells suspended in maintenance medium. Compound 7 was prepared for animal studies in phosphate buffered (0.05 M) saline adjusted to pH 11. Acyclovir (Zovirax, Burroughs Wellcome Co.) was prepared as per the package insert and diluted in PBS buffer. Both compounds were administered subcutaneously twice a day in 0.5 mL of PBS beginning at 1-h postinfection and continued twice daily for 5 days.

Animal survival was determined for 21 days at which time the remaining animals were sacrificed. Mean day of death (MDD) was calculated to determine extended survival time for treated groups of animals. The protective dose 50% (PD_{50}) based on survival was calculated by probit analysis (Finney, D. *Probit Analysis*; Cambridge University Press: New York, 1971). Comparisons were made for statistical analysis between treatment groups and placebo-treated infected controls. Student's *t*-test was used to analyze MDD (extended survival).

1,2-*O*-(1-Methylethylidene)-α-D-xylofuranose 5-(4-Methylbenzenesulfonate) (11). A solution of **10** (200 g, 1.05 mol) in pyridine (1.05 L) was cooled to 0 °C, and a $CHCl_3$ (420 mL) solution of TsCl (200 g, 1.05 mol) was added. The reaction mixture was stirred overnight at room temperature, H_2O (4 mL) was added, and the mixture was stirred for 30 min. After the volatiles were evaporated in vacuo, the residue was partitioned between H_2O (1.5 L) and $CHCl_3$ (750 mL), and the aqueous layer was back-extracted with $CHCl_3$ (1 L). The combined organic layers were washed with H_2O (3 × 1 L) and brine (1 L), dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was triturated with Et_2O and filtered to afford **11** (317 g, 88% yield) as a colorless solid: mp 134–136 °C; ^1H NMR (DMSO-d_6) δ 1.21 (s, 3 H), 1.33 (s, 3 H), 2.42 (s, 3 H), 4.02 (m, 2 H), 4.13 (m, 1 H), 4.24 (dd, J = 3 Hz, 10.5 Hz, 1 H), 4.37 (d, J = 3.5 Hz, 1 H), 5.41 (d, J = 7.5 Hz, 1 H), 5.81 (d, J = 4.5 Hz, 1 H), 7.49 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 21.0, 26.0, 26.5, 69.3, 73.6, 77.7, 84.7, 104.6, 110.7, 127.6, 132.2, 145.0. Anal. ($C_{15}H_{20}O_7S$) C, H, S.

1,2-*O*-(1-Methylethylidene)-5-*O*-(phenylmethyl)-α-D-xylofuranose (13). Sodium metal (29.5 g, 1.28 mol) was dissolved in benzyl alcohol (800 mL) at 100 °C, and solid **11** (72.4 g, 0.21 mol) was added. The reaction mixture was heated at 100 °C for 15 h, cooled to room temperature, and treated with H_2O (50 mL) and glacial AcOH (64.3 g, 1.07 mol). The mixture was partitioned between Et_2O and H_2O, and the organic layer washed twice with H_2O and dried over Na_2SO_4. After the volatiles were evaporated in vacuo, the remaining benzyl alcohol was removed at 130 °C (0.1 mmHg) to leave a thick, oily residue. The residue was crystallized from Et_2O/hexanes to give **13** (48 g, 81% yield) as a colorless solid: mp 60–62 °C; ^1H NMR (DMSO-d_6) δ 1.23 (s, 3 H), 1.37 (s, 3 H), 3.52 (dd, *J* = 7, 10.5 Hz, 1 H), 3.68 (dd, *J* = 4, 10.5 Hz, 1 H), 3.98 (m, 1 H), 4.14 (m, 1 H), 4.38 (d, *J* = 3.5 Hz, 1 H), 4.50 (s, 2 H), 5.22 (d, *J* = 4.5 Hz, 1 H), 5.82 (d, *J* = 4 Hz, 1 H), 7.33 (m, 5 H). Anal. ($C_{15}H_{20}O_5$) C, H.

3-Deoxy-3-methylene-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-α-D-xylofuranose (15). To a rapidly stirred solution of pyridine (110 mL, 1.36 mol) in CH_2Cl_2 (1 L) at 0 °C under argon was added CrO_3 (86 g, 0.86 mol). After the mixture was stirred for 30 min at room temperature, Celite (220 g) was added, and the reaction mixture placed in a cold water bath (~18 °C). With rapid stirring, a CH_2Cl_2 (100 mL) solution of **13** (30 g, 0.108 mol) was added rapidly in one portion. After 2 h the reaction mixture was filtered through Celite, washing the filter pad well with Et_2O. The combined filtrates were evaporated in vacuo, the resulting residue was triturated with Et_2O, and the slurry was filtered through Celite. The filtrate was evaporated in vacuo, and the residue was azeotroped twice with toluene and finally triturated again with Et_2O. Filtration through Celite and concentration in vacuo gave crude ketone 14 (30.1 g, >100% crude yield) as an oil, which was used in the subsequent reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.45 (s, 3 H), 3.72 (m, 2 H), 4.33 (m, 1 H), 4.44 (m, 1 H), 4.50 (m, 2 H), 6.11 (m, 1 H), 7.28 (m, 5 H).

To a THF (1.1 L) suspension of methyltriphenylphosphonium bromide (134 g, 0.376 mol) at −70 °C under argon was added *n*-BuLi (210 mL, 0.357 mol, 1.7 M in hexanes), and the mixture was warmed to room temperature, resulting in an orange-yellow, nearly homogeneous solution. The reaction was cooled to −70 °C, and a THF (200 mL) solution of 14 (33.5 g, ca. 0.122 mol) was added. After being stirred at room temperature for 1 h, the reaction mixture was warmed to 55 °C for 2 h. The resulting slurry was quenched at 0 °C with saturated NH_4Cl (600 mL) and the aqueous layer extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo, and the oily residue was triturated with 10% EtOAc in hexane and filtered. The filtrate was concentrated in vacuo to provide an oil (40 g), which was then purified by flash chromatography (Mallinkrodt SilicAR, 100–200-mesh silica gel, type 60A special), eluting with EtOAc/hexanes (5%, then 10% EtOAc) to give **15** (26 g, 80% yield) as a colorless oil: homogeneous (UV detection) by TLC [R_f 0.41, heptane/EtOAc (4:1)]; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.50 (s, 3 H), 3.55 (dd, *J* = 5.2, 10.5 Hz, 1 H), 3.66 (dd, *J* = 3.5, 10.5 Hz, 1 H), 4.57 (s, 2 H), 4.87 (m, 1 H), 4.89 (d, *J* = 4.1 Hz, 1 H), 5.18 (m, 1 H), 5.41 (m, 1 H), 5.86 (d, *J* = 4.1 Hz, 1 H), 7.24–7.33 (m, 5 H).

3-Deoxy-3-(hydroxymethyl)-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-α-D-ribofuranose (9). To neat **15** (16.1 g, 0.058 mol) was added BH_3·THF (125 mL, 1 M solution) with rapid stirring. After 1 h at room temperature, the reaction mixture was cooled to 0 °C, and THF/H_2O (60 mL, 1:1), NaOH (180 mL, 2 M), and then 30% H_2O_2 (90 mL) were added carefully. After the mixture was stirred an additional 65 min at room temperature, the volatiles were evaporated in vacuo and the resulting residue was partitioned between brine and EtOAc. The aqueous layer was extracted two more times with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. After combining this residue with one derived from 0.012 mol of **15**, the mixture was purified by flash column chromatography. The column was eluted with a stepwise gradient of hexanes/EtOAc (4:1–3:2) to give **9** (16.4 g, 79% yield) as a colorless solid: homogeneous (UV detection) by TLC [R_f 0.25, hexanes/EtOAc (1:1)]; mp 67–70 °C [lit.[10] mp 69–70 °C]; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.51 (s, 3 H), 2.17 (m, 1 H), 2.70 (m, 1 H), 3.65 (m, 2 H), 3.83 (m, 2 H), 4.21 (m, 1 H), 4.59 (m, 2 H), 4.75 (dd, *J* = 3.5, 4.2 Hz, 1 H), 5.81 (d, *J* = 3.5 Hz, 1 H), 7.28–7.35 (m, 5 H); $[\alpha]_D$ +36° [*c* 1.88, $CHCl_3$] (lit.[10] $[\alpha]_D$ +37° [*c* 2, $CHCl_3$]); HRMS calcd for $C_{16}H_{23}O_5$ 295.1545, found 295.1554.

3-Deoxy-1,2-*O*-(1-methylethylidene)-3-[(phenylmethoxy)methyl]-5-*O*-(phenylmethyl)-α-D-ribofuranose (16). To a DMSO (150 mL) solution of **9** (34.3 g, 116.6 mmol) at ~18 °C under argon was added dropwise DMSO sodium salt (65.2 mL of a 2 M solution in DMSO, 130.4 mmol, generated at 75 °C with NaH). The mixture was heated to 40 °C for 1 h, cooled to ~18 °C, and then treated with benzyl bromide (13.9 mL, 116.6 mmol). After 50 min at room temperature, the reaction was quenched with saturated NH_4Cl and the aqueous layer extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and the volatiles evaporated in vacuo. The residue (48 g) was purified by flash chromatography, eluting with a gradient of hexanes/EtOAc (9:1, 4:1, and then 7:3) to give **16** (33 g, 74% yield) as a colorless oil: homogeneous (UV detection) by TLC [R_f 0.63, hexanes/EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 2.36 (m, 1 H), 3.53 (m, 2 H), 3.78 (m, 2 H), 4.05 (m, 1 H), 4.50 (m, 2 H), 4.56 (s, 2 H), 4.71 (dd, *J* = 3.5, 4.2 Hz, 1 H), 5.84 (d, *J* = 3.5 Hz, 1 H), 7.25–7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.7, 45.4, 66.6, 70.4, 73.2, 73.5, 79.9, 81.0, 105.0, 111.7, 127.5, 127.7, 128.3, 138.2 [4 aromatic peaks doubled]; MS (CI) *m/e* 385 (M + H); HRMS calcd for $C_{23}H_{29}O_5$ 385.2015, found 385.1996.

3-Deoxy-3-[(phenylmethoxy)methyl]-5-*O*-(phenylmethyl)-D-ribofuranose Diacetate (18). A solution of **16** (16.2 g, 0.042 mol) in acetic acid/H_2O (3:1 ratio, 450 mL) was heated at 80 °C for 5 h. The reaction solution was then evaporated in vacuo, and the resulting oil was azeotroped twice with toluene. The yellow oily-solid residue containing lactol–alcohol 17 was used in the subsequent reaction without purification.

Acetic anhydride (50 mL) was added to a pyridine (330 mL) solution of the above residue, and the reaction mixture was stirred for 7.5 h under argon. The volatiles were removed in vacuo, and the resulting residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give **18** (16.5 g, 92% yield for the two steps) as a colorless oil: homogeneous (UV detection) by TLC [R_f 0.25, hexanes/EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3 H), 1.99 (s, 3 H), 2.78 (m, 1 H), 3.50–3.71 (m, 4 H), 4.20 (m, 1 H), 4.47 (m, 2 H), 4.56 (s, 2 H), 5.30 (d, *J* = 3.7 Hz, 1 H), 6.06 (s, 1 H), 7.25–7.37 (m, 10 H).

1,3-Dideoxy-3-[(phenylmethoxy)methyl]-5-*O*-(phenylmethyl)-D-ribofuranose (20). A toluene (200 mL) solution of 18 (7.85 g, 18.3 mmol) was cooled to 0 °C and treated with a stream of dry HCl gas until saturated. The solution was allowed to stand at 0 °C for 20 min and then evaporated in vacuo without heat. The resulting oily residue was azeotroped with toluene to give crude **19**, which was used in the subsequent reaction without further purification.

A toluene (180 mL) solution of crude **19** (ca. 18.3 mmol) at 0 °C was cannulated over 15 min into a mixture of DIBAL (180 mL, 1.0 M solution in toluene) and THF (180 mL, added to prevent cleavage of the furan ring[23]) at 0 °C under N_2. After stirring for 30 min at 0 °C, the mixture was quenched by dropwise addition of dry MeOH (22 mL), followed in 10 min by H_2O (32 mL). The mixture was diluted to 1 L with Et_2O, stirred at room temperature for 1.5 h, and then filtered through Celite, washing the filter pad with Et_2O and EtOAc. The combined filtrates were evaporated in vacuo to an oily residue, which was dissolved in isopropyl ether (10 mL) and diluted with hexane until cloudy. The resulting mixture was kept at −30 °C overnight, and the resulting crystals were filtered, washed with hexane, and dried in vacuo to give **20** (4.79 g, 80% yield for the two steps) as a colorless crystalline solid: mp 57–59 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (m, 1 H), 3.40–3.90 (m, 7 H), 4.24 (m, 1 H), 4.46 (m, 2 H), 4.48 (s, 2 H), 4.87 (d, *J* = 4.7 Hz, 1 H), 7.25–7.36 (m, 10 H); MS (CI) *m/e* 329 (M + H). Anal. ($C_{20}H_{24}O_4$) C, H.

1,3-Dideoxy-3-[(phenylmethoxy)methyl]-5-*O*-(phenylmethyl)-D-ribofuranose 2-(4-Methylbenzenesulfonate) (21). TsCl (4.38 g, 23.0 mmol) was added to a pyridine (28.7 mL) solution of **20** (4.71 g, 14.3 mmol) at 0 °C. After 1 h at 0 °C, the reaction was stirred at 5 °C for 26 h. Starting material was observed at this point, and a second portion of TsCl (0.078 g, 0.41 mmol) was added. After a total of 70 h at 5 °C, the volatiles were removed in vacuo to give an orange residue, which was partitioned between saturated $NaHCO_3$ and EtOAc. The combined organic layers were evaporated in vacuo, and the residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give **21** (6.18 g, 89% yield) as a colorless solid: mp 57–59 °C; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3 H), 2.57 (m, 1 H), 3.44–3.70 (m, 4 H), 3.93 (m, 2 H), 3.98 (m, 1 H), 4.37 (m, 2 H), 4.52 (m, 2 H), 5.16 (m, 1 H), 7.25–7.36 (m, 12 H), 7.70–7.76 (m, 2 H); MS (CI) *m/e* 483 (M + H). Anal. ($C_{27}H_{30}O_6S$) C, H, S.

[3*S*-(3α,4β,5α)]-6-(Phenylmethoxy)-9-[tetrahydro-4,5-bis-[(phenylmethoxy)methyl]-3-furanyl]-9*H*-purin-2-amine (23). A mixture of **21** (0.56 g, 1.15 mmol), 2-amino-6-(benzyloxy)purine (**22**) (0.55 g, 2.3 mmol), 18-crown-6 (0.3 g, 1.15 mmol), and K_2CO_3

(0.3 g, 2.18 mmol) in DMF (9 mL) was heated under argon at 90 °C. After 11 h, the reaction was cooled, and the volatiles were removed by Kugelrohr distillation (40 °C, 0.25 mmHg). The resulting orange oily-solid residue was preabsorbed on silica gel (Baker reagent, 60–230 mesh) and purified by flash chromatography, eluting with CH_2Cl_2, then a gradient of i-PrOH/CH_2Cl_2 (1, 2, 3, 4, and then 8% i-PrOH) to give **23** (0.17 g, 27% yield) as a colorless powder: homogeneous (UV detection) by TLC [R_f 0.41, 5% MeOH:CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 2.68 (m, 1 H), 3.54–3.78 (m, 4 H), 4.02–4.16 (m, 3 H), 4.49 (s, 2 H), 4.60 (m, 2 H), 4.78 (br s, 1 H), 5.00 (m, 1 H), 5.60 (s, 2 H), 7.25–7.55 (m, 15 H), 7.88 (s, 1 H); MS (CI) *m/e* 552 (M + H).

[3*S*-(3α,4β,5α)]-2-Amino-1,9-dihydro-9-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-6*H*-purin-6-one (7). To a THF (3 mL)/NH_3 (20 mL) suspension of **23** (0.17 g, 0.31 mmol) at −78 °C was added Na metal (0.50 g, 22 mmol). The reaction mixture was stirred at −78 °C for 5 min, allowed to come to reflux for 20 min, and then quenched with solid NH_4Cl, and the volatiles were evaporated with a stream of N_2. The resulting white solid was brought to pH 8 with 0.5 N HCl, and the volatiles were evaporated in vacuo. The residue was purified on CHP-20P resin, eluting first with H_2O and then a gradient of H_2O to CH_3CN/H_2O (1:1). Fractions containing pure compound were concentrated, and the residue was lyophilized to give **7** (0.074 g, 85% yield) as a colorless solid: 96.9% pure by TLC [UV densitometry, R_f 0.13, $CHCl_3$–MeOH–NH_4OH (6:3:1)]; mp 195–205 °C dec. Analytically pure material was obtained by triturating with hot H_2O, cooling to 0 °C, and collecting the colorless solid: 98.8% pure by MECC (k' = 0.83); mp 264–270 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.50 (m, 1 H), 3.45–3.95 (m, 7 H), 4.78 (m, 1 H, shifts to 5.0 with TFA-*d*), 4.86 (m, 1 H, exchanges with TFA-*d*), 4.93 (m, 1 H, exchanges with TFA-*d*), 6.42 (br s, 2 H, exchanges with TFA-*d*), 7.84 (s, 1 H), 10.45 (br s, 1 H, exchanges with TFA-*d*); ^{13}C (DMSO-d_6) δ 49.0, 56.4, 60.3, 61.9, 71.7, 82.4, 116.3 (C-5), 135.4 (C-8), 150.9 (C-4), 153.4 (C-2), 156.7 (C-6); UV (H_2O, pH 7.2, phosphate buffer) λ_{max} 253.2 (ε 11 723), sh 270 nm (ε 8544); $[\alpha]_D$ −45.8° [*c* 0.48, DMSO]; MS (FAB) *m/e* 282 (M + H). Anal. ($C_{11}H_{15}N_5O_4 \cdot 0.5H_2O$) C, H, N.

[3*S*-(3α,4β,5α)]-9-[Tetrahydro-4,5-bis[(phenylmethoxy)-methyl]-3-furanyl]-9*H*-purin-6-amine (26). A mixture of **21** (0.335 g, 0.695 mmol), adenine (**25**) (0.28 g, 2.08 mmol), 18-crown-6 (0.18 g, 0.68 mmol), and K_2CO_3 (0.37 g, 2.67 mmol) in DMF (6 mL) was heated under argon at 67 °C for 24 h and then for a further 9 h at 90 °C. After the mixture was cooled to room temperature, the volatiles were removed by Kugelrohr distillation (40 °C, 0.25 mmHg). The orange oily-solid residue was purified by flash chromatography, eluting with CH_2Cl_2 and then a gradient of i-PrOH/CH_2Cl_2 (2, then 8% i-PrOH) to give **26** (0.10 g, 33% yield) as a colorless powder: homogeneous (UV detection) by TLC [R_f 0.45, 10% MeOH–CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 2.74 (m, 1 H), 3.59–3.71 (m, 3 H), 3.82 (m, 1 H), 4.07 (m, 1 H), 4.10–4.17 (m, 2 H), 4.50 (m, 2 H), 4.62 (m, 2 H), 5.17 (m, 1 H), 5.93 (br s, 2 H), 7.25–7.37 (m, 10 H), 8.16 (s, 1 H), 8.33 (s, 1 H); MS (CI) *m/e* 446 (M + H).

[3*S*-(3α,4β,5α)]-9-[Tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-9*H*-purin-6-amine (27). Sodium metal (0.2 g, 8.7 mmol) was added to a THF (4 mL)/NH_3 (25 mL) suspension of **26** (0.10 g, 0.225 mmol) at −78 °C, and the resulting blue solution was stirred at −78 °C for 10 min and then allowed to come to reflux. After 25 min, the reaction was quenched with solid NH_4Cl, and the volatiles were evaporated with a stream of N_2. The resulting colorless solid was dissolved in H_2O and brought to pH 8 with 0.5 N HCl, and the volatiles were evaporated in vacuo. The residue was purified on CHP-20P resin, eluting first with H_2O and then a gradient of H_2O to CH_3CN/H_2O (1:1), to give **27** (0.042 g, 70% yield) as a hygroscopic, colorless solid after lyophilization, contaminated with 5.8% of [3*S*-(3α,4β,5α)]-9-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-9*H*-purine, resulting from overreduction of the adenine moiety: 93% pure by TLC [UV densitometry, R_f 0.53, $CHCl_3$–MeOH–NH_4OH (6:3:1)]; mp 185–195 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.55 (m, 1 H), 3.53–3.78 (m, 5 H), 3.92–4.00 (m, 2 H), 4.88 (t, *J* = 5.3 Hz, 1 H, exchanges with D_2O), 4.94 (t, *J* = 5.3 Hz, 1 H, exchanges with D_2O), 4.99 (m, 1 H), 7.16 (br s, 2 H, exchanges with D_2O), 8.12 (s, 1 H), 8.25 (s, 1 H), [8.74 (s, 1 H), 8.93 (s, 1 H), 9.14 (s, 1 H), purine H's from the overreduced contaminate]; ^{13}C NMR (DMSO-d_6) δ 49.1, 57.0, 60.4, 62.0, 71.3, 82.4, 118.6 (C-5), 139.1 (C-8), 149.2 (C-4), 152.2 (C-2), 155.9 (C-6); UV (H_2O) λ_{max} 261.2 (ε 19 040), (pH 1) 259.5 nm (ε 18 145); MS (FAB) *m/e* 266 (M + H); HRMS calcd for $C_{11}H_{16}N_5O_3$ 266.1253, found 266.1255.

[3*S*-(3α,4β,5α)]-5-Methyl-1-[tetrahydro-4,5-bis[(phenylmethoxy)methyl]-3-furanyl]-2,4(1*H*,3*H*)-pyrimidinedione (29). A mixture of **21** (1.2 g, 2.45 mmol), K_2CO_3 (1.35 g, 9.8 mmol), 18-crown-6 (0.65, 2.45 mmol), and thymine (**28**) (0.62 g, 4.90 mmol) in dry DMSO (14 mL) was heated to 90 °C under argon for 6.5 h and then kept at room temperature for 48 h. The reaction was centrifuged, and the supernatant was concentrated by Kugelrohr distillation (40 °C, 0.25 mmHg). A CH_2Cl_2 slurry of the resulting residue was purified by flash chromatography, eluting with EtOAc/hexanes (7:3, then 1:1) and finally 100% EtOAc to give **29** (0.22 g, 28% yield) as a colorless oil: homogeneous (UV detection) by TLC [R_f 0.55, EtOAc]; ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3 H), 2.55 (m, 1 H), 3.62 (d, *J* = 5.3 Hz, 2 H), 3.65 (m, 1 H), 3.85–4.00 (m, 4 H), 4.52 (s, 2 H), 4.56 (m, 1 H), 4.61 (d, *J* = 11.7 Hz, 1 H), 7.30–7.40 (m, 10 H), 7.51 (s, 1 H), 8.05 (br s, 1 H); MS (FAB) *m/e* 437 (M + H).

[3*S*-(3α,4β,5α)]-5-Methyl-1-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-2,4(1*H*,3*H*)pyrimidinedione (32). A mixture of **29** (0.22 g, 0.50 mmol), cyclohexene (6 mL), and $Pd(OH)_2$ (0.2 g, 20% on carbon) in 95% EtOH (20 mL) was refluxed at 90 °C. After 4 h, the reaction mixture was filtered through Celite and the filter pad washed with MeOH/H_2O (1:1). The filtrate was concentrated to a colorless oil in vacuo and the residue purified on CHP-20P resin, eluting with H_2O and then a gradient of H_2O to CH_3CN/H_2O (1:1), to give **32** (0.07 g, 54% yield) as a colorless solid after lyophilization: homogeneous (UV detection) by TLC [R_f 0.30, $CHCl_3$–MeOH–NH_4OH (6:3:1)]; mp 93–96 °C; $[\alpha]_D$ +40.8° [*c* 0.21, AcOH]; UV (H_2O, pH 7.2, phosphate buffer) λ_{max} 272.2 (ε 10 500), (1 N NaOH) 271.0 nm (ε 7770); ^{1}H NMR (DMSO-d_6) δ 1.75 (s, 3 H), 2.23 (m, 1 H), 3.60–3.90 (m, 7 H), 4.84 (m, 1 H), 4.93 (m, 2 H, OH exchanges with D_2O), 7.64 (s, 1 H), 11.17 (s, 1 H, NH exchanges with D_2O); ^{13}C NMR (DMSO-d_6) δ 12.3 (CH_3), 48.8, 57.9, 60.6, 61.6, 71.2, 82.8, 109.6 (C-5), 138.3 (C-6), 151.1 (C-2), 164.0 (C-4); MS (FAB) *m/e* 257 (M + H); HRMS calcd for $C_{11}H_{17}N_2O_5$ 257.1138, found 257.1146. Anal. ($C_{11}H_{16}N_2O_5 \cdot 0.5H_2O$) C, H, N.

[3*S*-(3α,4β,5α)]-1-[Tetrahydro-4,5-bis[(phenylmethoxy)-methyl]-3-furanyl]-2,4(1*H*,3*H*)-pyrimidinedione (31). A mixture of **21** (0.94 g, 1.95 mmol), K_2CO_3 (1.08 g, 7.80 mmol), uracil (**30**) (0.44 g, 3.90 mmol), and 18-crown-6 (0.52 g, 1.95 mmol) in dry DMSO (11 mL) was heated to 90 °C for 7.5 h. After the mixture was cooled to room temperature, the volatiles were removed in vacuo. The resulting residue was purified by flash chromatography, eluting with EtOAc/hexanes (3:7, then 1:1) and finally EtOAc (100%) to give **31** (0.23 g, 28% yield) as a colorless oil: homogeneous (UV detection) by TLC [R_f 0.31, hexanes–EtOAc (1:2)]; ^{1}H NMR ($CDCl_3$) δ 2.50–2.60 (m, 1 H), 3.61 (d, *J* = 5.6 Hz, 2 H), 3.65 (dd, *J* = 3.4, 10.7 Hz, 1 H), 3.88 (dd, *J* = 2.1, 10.7 Hz, 1 H), 3.91–3.96 (m, 3 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 5.12–5.15 (m, 1 H), 5.80 (d, *J* = 8.1 Hz, 1 H), 7.25–7.35 (m, 10 H), 7.73 (d, *J* = 8.1 Hz, 1 H), 7.90 (br s, 1 H).

[3*S*-(3α,4β,5α)]-1-[Tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-2,4(1*H*,3*H*)-pyrimidinedione (33). A mixture of **31** (0.22 g, 0.52 mmol), $Pd(OH)_2$ (0.2 g, 20% on carbon), and cyclohexene (6 mL) in 95% EtOH (20 mL) was refluxed for 6 h at 90 °C. After being cooled to room temperature, the mixture was filtered through Celite, the filter cake was washed with MeOH/H_2O (1:1), and the combined filtrates were concentrated in vacuo to a colorless oil. The residue was purified on CHP-20P resin, eluting first with H_2O and then a gradient of H_2O to CH_3CN/H_2O (1:1), to give **33** (0.075 g, 60% yield) as a colorless solid after lyophilization: mp 129–130 °C; $[\alpha]_D$ +67.4° [*c* 1.1, AcOH]; UV (H_2O, pH 7.2, phosphate buffer) λ_{max} 268.2 (ε 7290), (1 N NaOH) 266.0 nm (ε 5458); ^{1}H NMR (JEOL GX 400 MHz, DMSO-d_6) δ 2.20–2.26 (m, 1 H), 3.48–3.60 (m, 3 H), 3.62–3.72 (m, 2 H), 3.77 (m, 1 H), 3.85 (m, 1 H), 4.80–4.95 (m, 3 H), 5.58 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 11.15 (br s, 1 H); MS (CI) *m/e* 243 (M + H). Anal. ($C_{10}H_{14}N_2O_5$) C, H, N.

[3*S*-(3α,4β,5α)]-4-Amino-1-[tetrahydro-4,5-bis[(phenylmethoxy)methyl]-3-furanyl]-2(1*H*)-pyrimidinone (35). A pyridine (5.6 mL) solution of **31** (0.726 g, 1.72 mmol) under argon was treated with *p*-chlorophenyl phosphorodichloridate (1.14 g, 4.64 mmol), followed by 1,2,4-triazole (0.653 g, 9.46 mmol). After being stirred at room temperature for 96 h, the resulting dark solution was concentrated in vacuo to a brown residue. The residue was partitioned between CH_2Cl_2 and H_2O, and the organic layer was extracted three times with H_2O and once with saturated $NaHCO_3$ and then concentrated in vacuo. The crude **34** was used without further purification in the subsequent reaction.

A slurry of **34** in dioxane (12 mL) and NH_4OH (12 mL, 29% solution) was stirred at room temperature for 24 h and then concentrated in vacuo. The dark residue was partitioned between CH_2Cl_2 and 5% NaOH, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was preabsorbed on silica gel (Baker, 60-200 mesh) and purified by flash chromatography, eluting with EtOAc and then a gradient of MeOH/EtOAc (2, 4, 6, 8, and then 10% MeOH), to give **35** (0.446 g, 62% yield from **31**) as a yellow solid: homogeneous (UV detection) by TLC [R_f 0.56, EtOAc–i-PrOH (1:3)]; ^1H NMR ($CDCl_3$) δ 2.45–2.55 (m, 1 H), 3.58–3.75 (m, 3 H), 3.87 (dd, J = 2.3, 10.6 Hz, 1 H), 3.90–4.05 (m, 3 H), 4.45–4.55 (m, 3 H), 4.59 (d, J = 11.7 Hz, 1 H), 5.25 (dt, J = 3.5, 4.1 Hz, 1 H), 5.34 (d, J = 7.0 Hz, 1 H), 5.50 (br s, 2 H), 7.10–7.40 (m, 10 H), 7.81 (d, J = 7.0 Hz, 1 H); MS (CI) *m/e* 422 (M + H).

[3*S*-(3α,4β,5α)]-4-Amino-1-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-2(1*H*)pyrimidinone (38). A mixture of **35** (0.11 g, 0.26 mmol), cyclohexene (6 mL), and $Pd(OH)_2$ (0.05 g, 20% on carbon) in 95% EtOH (20 mL) was refluxed at 90 °C. After 48 h, a second portion of $Pd(OH)_2$ (0.015 g, 20% on carbon) was added, and the mixture was refluxed an additional 24 h. The reaction was cooled to room temperature and filtered through Celite, washing the filter pad with $MeOH/H_2O$ (1:1). The filtrate was concentrated in vacuo to give a yellow oily residue. The residue was purified on CHP-20P resin, eluting with H_2O to give **38** (0.048 g, 75% yield) as an off-white solid: 99.7% pure by HPLC analysis [Chromega C-22 column, 4.6 by 150 mm, UV detection (λ = 286.5 nm), isocratic 0.25% MeOH in 0.001 M K_2HPO_4 over 25 min]; UV (H_2O, pH 7.2, phosphate buffer) λ_{max} 274.6 (ε 10 800), (1 N HCl) 284.8 nm (ε 25 000); ^1H NMR (DMSO-d_6) δ 2.05–2.19 (m, 1 H), 3.45–3.70 (m, 5 H), 3.75–3.85 (m, 2 H), 4.75–4.85 (m, 2 H, exchanges with D_2O), 4.91 (dt, J = 4.1, 5.3 Hz, 1 H), 5.70 (d, J = 7.0 Hz, 1 H), 7.05 (br s, 2 H, exchanges with D_2O), 7.69 (d, J = 7.0 Hz, 1 H); MS (FAB) *m/e* 242 (M + H); HRMS calcd for $C_{10}H_{16}N_3O_4$ 242.1140, found 242.1142.

[3*S*-(3α,4β,5α)]-4-Amino-5-methyl-1-[tetrahydro-4,5-bis[(phenylmethoxy)methyl]-3-furanyl]-2(1*H*)-pyrimidinone (36). A solution of **29** (410 mg, 0.94 mmol) in dry pyridine (3 mL) at ~18 °C under argon was treated with *p*-chlorophenyl phosphodichloridate (623 mg, 2.54 mmol) and dry 1,2,4-triazole (357 mg, 5.17 mmol). The reaction mixture was stirred for 96 h at room temperature, and the volatiles were removed in vacuo. The reddish-brown glasslike residue was dissolved in CH_2Cl_2 (8 mL), and the organic layer was washed twice with H_2O (10 mL) and once with 5% $NaHCO_3$ (12 mL) and then dried over Na_2SO_4. The organic layer was concentrated in vacuo to give crude **37** (498 mg, >100% crude yield), which was used without further purification in the subsequent reaction.

A dioxane (10 mL) solution of **37** (489 mg, <0.94 mmol) and concentrated NH_4OH (29% solution, 10 mL) was stirred at room temperature for 24 h. The volatiles were removed in vacuo, and the oily residue was partitioned between CH_2Cl_2 (25 mL) and 5% NaOH. The organic layer was concentrated in vacuo, and the residue was preabsorbed on silica gel (Baker reagent, 60–230 mesh) and purified by flash chromatography, eluting first with EtOAc and then with a gradient of MeOH/EtOAc (2, 4, 6, and finally 8% MeOH), to give a yellow oil. This residue was redissolved in CH_2Cl_2 and evaporated in vacuo to give **36** (276 mg, 68% yield for the two steps) as a yellow solid: ^1H NMR ($CDCl_3$) δ 1.59 (s, 3 H), 2.49–2.55 (m, 1 H), 3.62–3.76 (m, 3 H), 3.88 (dd, J = 2.3, 10.5 Hz, 1 H), 3.92–3.99 (m, 3 H), 4.45–4.50 (m, 2 H), 4.55–4.62 (m, 2 H), 5.26 (dt, J = 4.1, 4.1 Hz, 1 H), 7.26–7.35 (m, 10 H), 7.55 (s, 1 H).

[3*S*-(3α,4β,5α)]-4-Amino-5-methyl-1-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-2(1*H*)-pyrimidinone (39). A mixture of **36** (273 mg, 0.63 mmol), cyclohexene (20 mL), and $Pd(OH)_2$ (136 mg, 20% on carbon) in 95% EtOH (40 mL) was refluxed at 90 °C for 26 h under argon. The hot reaction mixture was filtered through Celite, the filter pad was washed well with a mixture of $MeOH/H_2O$ (1:1), and the filtrate was concentrated in vacuo. The residue was purified on CHP-20P resin, eluting first with H_2O and then with 5% CH_3CN/H_2O, to give **39** (127 mg, 79% yield) as a colorless solid: 99% pure by TLC [UV densitometry, R_f 0.52, *n*-BuOH–H_2O–HOAc–CH_3CN (3:1:1:1)]; mp 208–212 °C dec; $[\alpha]_D$ +51.9° [*c* 0.42, AcOH]; UV (H_2O, pH 7.2, phosphate buffer) λ_{max} 282 (ε 7350), 213 (ε 10 690), (0.1 N HCl, pH 1.5) 292 (ε 10 612), 213 nm (ε 10 140); ^1H NMR (JEOL, GX-400 MHz, DMSO-d_6) δ 1.90 (s, 3 H), 2.25 (m, 1 H), 3.55 (m, 3 H), 3.65–3.85 (m, 3 H), 3.88 (dd, J = 2.6, 9.9 Hz, 1 H), 4.85 (br s, 1 H, exchanges with D_2O), 4.94 (m, 2 H, 1 H exchanges with D_2O), 7.84 (s, 1 H), 8.01 (br s, 2 H, exchanges with D_2O); ^{13}C (DMSO-d_6) δ 12.6, 48.9, 58.9, 60.5, 61.4, 71.1, 82.6, 101.5 (C-5), 142.4 (C-6), 158.1 (C-2), 161.3 (C-4); HRMS calcd for $C_{11}H_{18}N_3O_4$ 256.1297, found 256.1305.

[3*S*-(3α,4β,5α)]-4-Amino-5-iodo-1-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-2(1*H*)-pyrimidinone (40). To a solution of **38** (96.5 mg, 0.40 mmol) in H_2O (160 μL), AcOH (320 μL), and CCl_4 (80 μL) was added HIO_3 (36 mg, 0.20 mmol) and I_2 (60 mg, 0.24 mmol). The resulting mixture was heated at 50 °C for 2 h and then concentrated in vacuo to yield a dark residue. Excess I_2 was removed by coevaporation with MeOH. The crude residue was dissolved in H_2O (3 mL), and the pH was adjusted to 7 with 1 N NaOH. The resulting aqueous mixture was purified on CHP-20P resin, eluting with H_2O (150 mL) and then 5% CH_3CN/H_2O (300 mL), to give **40** (55 mg, 38% yield) as a colorless solid: 99% pure by TLC [UV densitometry, R_f 0.57, *n*-BuOH–H_2O–HOAc–CH_3CN (3:1:1:1)]; mp 212–216 °C dec; $[\alpha]_D$ –4.0° [*c* 0.32, AcOH]; UV (H_2O, pH 7.2, phosphate buffer) λ_{max} 298 (ε 6150), 222 (ε 14 590), (0.1 N HCl, pH 1.5) 312 (ε 9100), 223 nm (ε 13 360); ^1H NMR (DMSO-d_6) δ 2.24 (m, 1 H), 3.51 (m, 3 H), 3.60–3.72 (m, 2 H), 3.75 (dd, J = 5.9, 10.0 Hz, 1 H), 3.83 (dd, J = 2.5, 10.0 Hz, 1 H), 4.80 (t, J = 5.2 Hz, 1 H), 4.87 (m, 1 H), 4.92 (t, J = 5.2 Hz, 1 H), 6.50 (br s, 1 H), 7.65 (br s, 1 H), 8.16 (s, 1 H); ^{13}C (DMSO-d_6) δ 49.1, 56.0, 59.2, 60.9, 61.4, 71.5, 82.6, 148.9 (C-6), 154.5 (C-2), 163.4 (C-4); HRMS calcd for $C_{10}H_{15}N_3O_4I$ 368.0108, found 368.0101. Anal. ($C_{10}H_{14}IN_3O_4{\cdot}H_2O$) C, H, N.

[3*S*-(3α,4β,5α)]-5-Iodo-1-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-2,4(1*H*,3*H*)-pyrimidinedione (41). A mixture of **33** (0.075 g, 0.31 mmol), I_2 (0.09 g, 0.36 mmol), and HNO_3 (2.4 mL, 0.8 N) in dioxane (6 mL) was refluxed for 5 h at 130 °C. The solution was cooled to 90 °C and sodium thiosulfate (0.040 g, 0.25 mmol) was added. The volatiles were then removed in vacuo to give a yellow residue, which was purified on CHP-20P resin, eluting with H_2O, followed by a gradient of H_2O to H_2O/CH_3CN (1:1), to give **41** (0.094 g, 83% yield) as a colorless solid: 99% pure by TLC [UV densitometry, R_f 0.24, $CHCl_3$–MeOH–NH_4OH (6:3:1)]; UV (H_2O, pH 7.2, phosphate buffer) λ_{max} 292 (ε 7472), (1 N NaOH) 284 nm (ε 5682); ^1H NMR (DMSO-d_6) δ 2.31 (m, 1 H), 3.40–3.90 (m, 7 H), 4.84–5.20 (m, 3 H, 2 H's exchange with D_2O), 8.26 (s, 1 H), 11.56 (br s, 1 H, exchanges with D_2O); ^{13}C (DMSO-d_6) δ 48.4, 58.5 (C-5), 60.5, 61.1, 68.9, 71.3, 82.4, 146.8 (C-6), 150.6 (C-2), 160.5 (C-4); MS (CI) *m/e* 369 (M + H). Anal. ($C_{18}H_{13}IN_2O_5{\cdot}0.5H_2O$) C, H, N.

[3*S*-(3α(*E*),4β,5α)]-3-[1,2,3,4-Tetrahydro-2,4-dioxo-1-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-5-pyrimidinyl]-2-propenoic Acid (43). A solution of **41** (85.8 g, 0.233 mol) in DMF (1 L) was partially concentrated in vacuo, and the resulting solution (~160 mL of DMF) was degassed in vacuo at 25 °C with argon. A mixture of $Pd(OAc)_2$ (3.0 g, 0.013 mol) and Ph_3P (6.95 g, 0.026 mol) in DMF (500 mL) was degassed in vacuo with argon. To this dark solution was added Et_3N (45 mL, 0.32 mol), and the mixture was heated at 75 °C under argon for 10 min, resulting in a red-black solution. The DMF solution of **41** was added rapidly, followed by methyl acrylate (38 mL, 0.422 mol), and the resulting mixture was heated at 75 °C for 10 h, cooled, and evaporated in vacuo to a thick oil. The residue was preabsorbed onto silica gel and purified by flash chromatography, eluting with CH_2Cl_2 and then EtOH–CH_2Cl_2 (5, 10, and then 20% EtOH), to give two portions of **42**, one from earlier fractions contaminated with a slightly less polar material and a larger one from later fractions essentially homogeneous by TLC. The smaller portion was triturated with CH_2Cl_2, isopropyl ether, and then hexanes, and the solid was dried in vacuo to give **42** (12.0 g), homogeneous by TLC and ^1H NMR. The larger portion was slurried in EtOH, diluted with hexanes, filtered, washed with hexanes, and dried in vacuo to give **42** (30.4 g; total 42.4 g, 56% yield) as a colorless solid: homogeneous (UV detection) by TLC [R_f 0.53, $CHCl_3$–MeOH (4:1)]; ^{1}H NMR (JEOL-FX-270, CD_3OD) δ 2.45 (m, 1 H), 3.60–4.20 (m, 10 H), 5.09 (m, 1 H), 6.90 (d, $J = 13.7$ Hz, 1 H), 7.40 (d, $J = 13.7$ Hz, 1 H), 8.29 (s, 1 H); MS (FAB) *m/e* 327 (M + H).

A solution of **42** (0.316 g, 0.822 mmol) in aqueous KOH (4.84 mL, 2 M solution) was stirred at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C and slowly brought to pH 2 by using 6 N HCl, and the white precipitate was collected by filtration and washed with H_2O (4 mL). Concentration of the filtrate to 2 mL gave a white precipitate, which was collected by filtration and washed with H_2O. The combined precipitates were dried in vacuo over P_2O_5 to give **43** (0.147 g, 57% yield) as a colorless solid: homogeneous (UV detection) by TLC [R_f 0.67, *n*-BuOH–H_2O–HOAc–CH_3CN (3:1:1:1)]; mp 230–235 °C; ^{1}H NMR (DMSO-d_6) δ 2.36 (m, 1 H), 3.50–3.80 (m, 6 H), 3.95 (m, 1 H), 4.85 (t, $J = 5.3$ Hz, 1 H), 4.97 (m, 1 H), 5.08 (t, $J = 5.8$ Hz, 1 H), 6.75 (d, $J = 15.3$ Hz, 1 H), 7.30 (d, $J = 15.3$ Hz, 1 H), 8.30 (s, 1 H), 11.55 (s, 1 H), 12.10 (br s, 1 H). Anal. ($C_{16}H_{16}N_2O_7 \cdot 2H_2O$) C, H, N.

[3*S*-(3α(E),4β,5α)]-5-(2-Bromoethenyl)-1-[tetrahydro-4,5-bis(hydroxymethyl)-3-furanyl]-2,4(1*H*,3*H*)-pyrimidinedione (8). To a mixture of **43** (143 mg, 0.46 mmol, dried by coevaporation with DMF) and $KHCO_3$ (141 mg, 1.41 mmol) in DMF (2 mL) at room temperature was added a DMF (1 mL) solution of *N*-bromosuccinimide (84 mg, 0.47 mmol). After 2.5 h, the mixture was filtered and concentrated in vacuo. The resulting residue was concentrated twice from H_2O (5 mL), slurried in H_2O, and purified by CHP-20P resin chromatography. The column was eluted with H_2O and then a continuous gradient of 15% to 40% CH_3CN/H_2O to give **8** (89 mg, 55% yield) as a colorless solid: 98.8% pure by MECC ($k' = 2.23$); mp 142–143 °C; $[\alpha]_D$ −62.9° [*c* 0.17, DMSO]; ^{1}H NMR (DMSO-d_6) δ 2.31 (m, 1 H), 3.40–4.00 (m, 7 H), 4.83 (m, 1 H), 4.94 (m, 1 H), 5.03 (m, 1 H), 6.84 (d, $J = 13.6$ Hz, 1 H), 7.22 (d, $J = 13.6$ Hz, 1 H), 8.03 (s, 1 H), 11.46 (br s, 1 H); MS (FAB) *m/z* 347, 349(M + H). Anal. ($C_{12}H_{15}N_2O_5Br \cdot 0.25\ H_2O$) C, H, N.

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