Design, Synthesis, and Antiviral Activity of α-Nucleosides: D- and L-Isomers of Lyxofuranosyl- and (5-Deoxylyxofuranosyl)benzimidazoles

Michael T. Migawa, Jean-Luc Girardet, John A. Walker II,† George W. Koszalka,‡ Stanley D. Chamberlain,‡ John C. Drach, and Leroy B. Townsend*

Department of Chemistry, College of Literature, Science and Arts, Department of Medicinal Chemistry, College of Pharmacy, and Department of Biologic and Materials Sciences, School of Dentistry, University of Michigan, Ann Arbor, Michigan 48109-1065, and Department of Chemistry, Glaxo Wellcome Company, Research Triangle Park, North Carolina 27709

Received August 13, 1997

Several 2-substituted α-D- and α-L-lyxofuranosyl and 5-deoxylyxofuranosyl derivatives of 5,6-dichloro-2-(isopropylamino)-1-(β-L-ribofuranosyl)benzimidazole (1263W94) and 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) were synthesized and evaluated for activity against two herpesviruses (HSV-1 and HCMV) and for their cytotoxicity against HFF and KB cells. Condensation of 1,2,3,5-tetra-*O*-acetyl-L-lyxofuranose (**2a**) with 2,5,6-trichlorobenzimidazole (**1**) yielded the α-nucleoside **3a**. The 2-bromo derivative and 2-methylamino derivative were prepared by treatment of **3a** with HBr followed by deprotection or from methylamine, respectively. Compound **3a** was deprotected and the resultant nucleoside used to prepare the 2-cyclopropylamino and 2-isopropylamino derivatives. The 2-alkylthio nucleosides were prepared by condensing **2a** with 5,6-dichlorobenzimidazole-2-thione followed by deprotection. Alkylation of this adduct gave the 2-methylthio and 2-benzylthio derivatives. Condensation of 5-deoxy-1,2,3-tri-*O*-acetyl-L-lyxofuranosyl, prepared from L-lyxose, with **1** or 2-bromo-5,6-dichlorobenzimidazole (**15**), followed by deprotection, gave the 2-chloro or 2-bromo-5′-deoxylyxofuranosyl derivative, respectively. The cyclopropylamino derivative was prepared from the 2-chloro derivative. All D-isomers were prepared in an analogous fashion from D-lyxose. Either compounds were inactive against HSV-1 or weak activity was poorly separated from cytotoxicity. In contrast, the 2-halogen derivatives in both the α-lyxose and 5-deoxy-α-lyxose series were active against the Towne strain of HCMV. The 5-deoxy α-L analogues were the most active, IC_{50}'s = 0.2−0.4 μM, plaque assay; IC_{90}'s = 0.2−2 μM, yield reduction assay. All of the 2-isopropylamino or 2-cyclopropylamino derivatives were less active (IC_{50}'s = 60−100 μM, plaque assay; IC_{90}'s = 17−100 μM, yield reduction assay) and were not cytotoxic. The methylamino, thio, and methylthio derivatives were neither active nor cytotoxic. The benzylthio derivatives were weakly active, but this activity was poorly separated from cytotoxicity. The α-lyxose L-isomers were more active in a plaque assay against the AD169 strain of HCMV compared to the Towne strain, thereby providing additional evidence of antiviral specificity.

Introduction

Human cytomegalovirus (HCMV), a human herpesvirus, is an important opportunistic pathogen among immunosuppressed individuals and neonates.[1−3] Currently, only three drugs have been approved by the United States Food and Drug Administration for the treatment of HCMV infections: ganciclovir,[4] foscarnet,[5] and cidofovir.[6] All of these drugs have poor oral bioavailability, and their use can lead to serious adverse effects such as granulocytopenia (ganciclovir) and renal dysfunction (foscarnet and cidofovir). Additionally, emergence of drug resistance[7] is a continuing problem thereby amplifying the need for more potent and selective compounds.

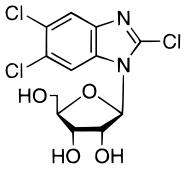
As part of our search for new antiviral drugs, we have been interested in halogenated benzimidazole nucleoside analogues. The first reported synthesis and antiviral evaluation of this class of compounds indicated that 5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (DRB) was an active antiviral compound.[8] Unfortunately, DRB was found to affect multiple cellular processes; therefore, activity was poorly separated from cytotoxicity.[9] Subsequently, we reported studies involving the synthesis of many DRB analogues modified on the heterocyclic ring.[10] More recently, we have found that certain 2-substituted 5,6-dichlorobenzimidazole ribonucleosides were very active against HCMV.[11−14] For example, 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB; Chart 1) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB) were found to be potent inhibitors of HCMV, and this activity was well-separated from cytotoxicity.[11] Additionally, several 2-alkylthio and 2-benzylthio analogues were prepared but were considerably less active against HCMV than TCRB.[15]

In addition to modifications of the heterocyclic moiety, several sugar-ring-modified analogues have been synthesized and evaluated for their antiviral properties.[16−18] Although acyclic analogues of TCRB were inactive,[16] replacement of the 5′-hydroxyl group with a number of

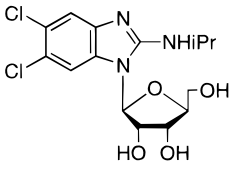
† Present address: ProtoGene Laboratories, Inc., 1454 Page Mill Rd., Palo Alto, CA 94304.
‡ Glaxo Wellcome Co.

S0022-2623(97)00545-1 CCC: $15.00
Published on Web 03/15/1998

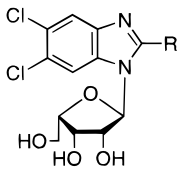
Chart 1. Structures of a *β*-D-Ribofuranosyl Nucleoside (TCRB), a *β*-L-Ribofuranosyl Nucleoside (1263W94), α-L-Lyxofuranosyl Nucleosides (**a** Series), and α-D-Lyxofuranosyl Nucleosides (**b** Series)



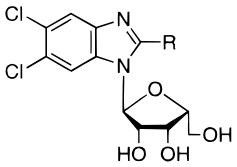
TCRB



1263W94



α-L-Lyxoses (**a** series)



α-D-Lyxoses (**b** series)

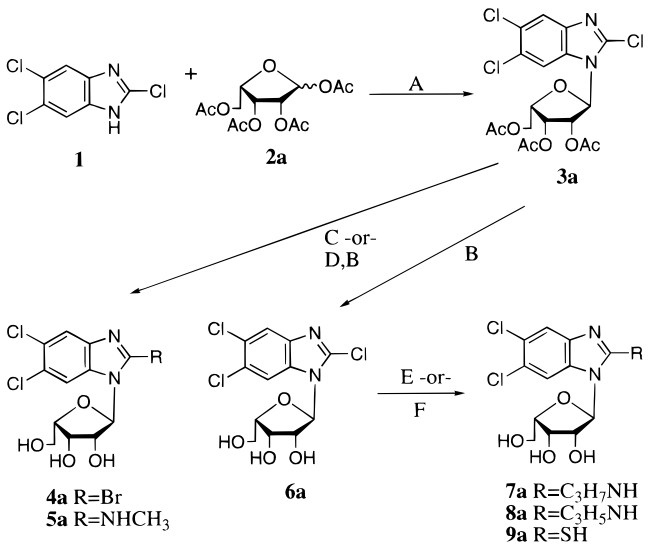
different substituents was well-tolerated.[17] Interestingly, 2,5,6-trichloro-1-(5-deoxy-*β*-D-ribofuranosyl)benzimidazole (5′-dTCRB) was more active than TCRB,[18] demonstrating that the 5′-hydroxyl group is not required for activity against HCMV. In addition to these D-carbohydrate derivatives, several carbocyclic[19] and L-carbohydrate derivatives[20] have been synthesized and evaluated. From among these, the L-nucleoside 5,6-dichloro-2-(isopropylamino)-1-(*β*-L-ribofuranosyl)benzimidazole (1263W94; Chart 1) was chosen for clinical trials due to its potent and selective in vitro activity and its superior pharmacokinetic properties.[20]

In light of these results, and to better understand the structure−activity relationship involving the 5-position of the carbohydrate moiety, we synthesized a variety of 2-substituted 5,6-dichloro-1-(lyxofuranosyl)benzimidazoles. As Chart 1 illustrates, the α-L-lyxose derivatives (**a** series) and α-D-lyxose derivatives (**b** series) can be viewed as 4′-epimers of TCRB and 1263W94, respectively. Moreover, we explored the effect of removing the 5′-OH; therefore, several 2-substituted 1-(5-deoxy-α-L-lyxofuranosyl)-5,6-dichlorobenzimidazoles and 2-substituted 1-(5-deoxy-α-D-lyxofuranosyl)-5,6-dichlorobenzimidazoles were prepared, and their biological activity was determined.

Results and Discussion

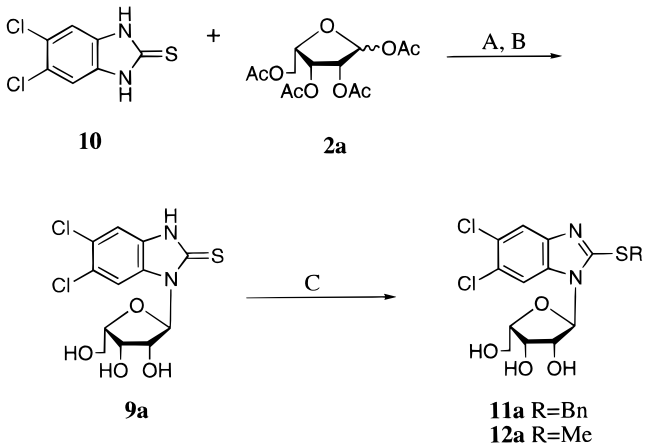
Chemistry. It has been shown that 2,3,5-tri-*O*-acetylglycofuranosyl nucleosides can be prepared by a modified Vorbrüggen procedure from 1,2,3,5-tetra-*O*-acetylglycosides.[21] The anomeric configuration is predominantly trans with respect to the 1′-heterocyclic moiety and 2′-OAc group, in most cases.[22] Thus, we prepared 1,2,3,5-tetra-*O*-acetyl-L-lyxofuranose (**2a**) and 1,2,3-tri-*O*-acetyl-5-deoxy-L-lyxofuranose (**14a**) for use as the glycosyl donors in analogous condensations. However, due to the high cost of L-lyxose, all synthetic procedures were first developed using the enantiomeric, and substantially less-expensive, D-lyxose. Our discussion will concentrate on the development and optimization of procedures using the D-sugars, while Schemes 1−4 and the Experimental Section will detail the application of these procedures to the synthesis of the L-lyxosides. Physical and biological data will be presented for all compounds synthesized (i.e., both D- and L-lyxosides). Therefore, starting with commercially available D-lyxose, tetra-*O*-acetyl-D-lyxofuranose (**2b**) can be prepared in three steps from a procedure developed by Guthrie and Smith.[23] After carrying out this synthesis as reported,[38] we obtained a 3:1 mixture of the furanose and pyranose isomers, respectively, as determined by ^{1}H NMR. In an effort to further optimize conditions in favor of the furanose isomer, both Dowex-50 acidic ion-exchange resin and acetyl chloride were substituted for sulfuric acid in the first step of this procedure. Substituting these new conditions into the three-step procedure[23,38] resulted in a furanose:pyranose ratio of 1.5:1 (Dowex) and 5:1 (acetyl chloride) as

Scheme 1[a,b]



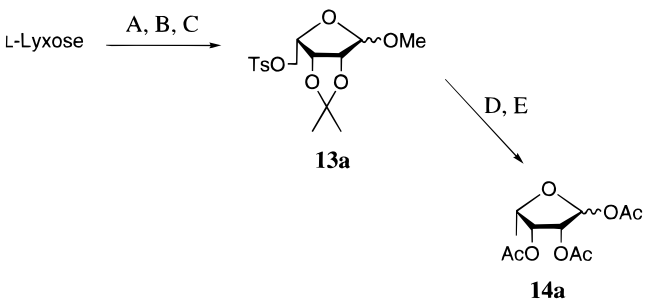
[a] (A) (1) BSA/CH_3CN, (2) **2a**, TMSOTf; (B) MeOH/EtOH/H_2O (1:1:1), Na_2CO_3; (C) $MeNH_2$, EtOH; (D) HBr (g), CH_2Cl_2; (E) isopropylamine or cyclopropylamine in EtOH, 70 °C; (F) thiourea, EtOH, reflux. [b] For clarity, only the L-lyxose derivatives (**a** series) are shown, although the chemical pathways followed for the enantiomeric D-lyxose derivatives (**b** series) are identical.

Scheme 2[a,b]



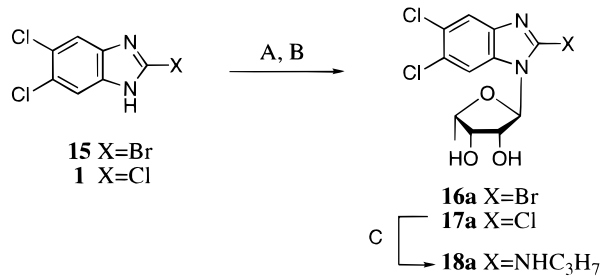
[a] (A) (1) BSA/CH_3CN, (2) **2a**, TMSOTf; (B) 95% EtOH/H_2O, Na_2CO_3; (C) (1) H_2O/CH_3CN (5:3), NH_4OH, (2) BnBr or MeI. [b] For clarity, only the L-lyxose derivatives (**a** series) are shown, although the chemical pathways followed for the enantiomeric D-lyxose derivatives (**b** series) are identical.

Scheme 3[a,b]



[a] (A) H_2SO_4, MeOH; (B) $CuSO_4$, acetone; (C) TsCl, pyridine; (D) $LiAlH_4$, Et_2O, toluene, reflux; (E) AcOH, Ac_2O, H_2SO_4. [b] For clarity, only the L-lyxose derivatives (**a** series) are shown, although the chemical pathways followed for the enantiomeric D-lyxose derivatives (**b** series) are identical.

Scheme 4[a,b]



[a] (A) (1) BSA/CH_3CN, (2) **14a**, TMSOTf; (B) 90% EtOH/H_2O, Na_2CO_3; (C) isopropylamine, EtOH, 60 °C. [b] For clarity, only the L-lyxose derivatives (**a** series) are shown, although the chemical pathways followed for the enantiomeric D-lyxose derivatives (**b** series) are identical.

determined by ^{1}H NMR. Since the pyranose isomer was formed in each case, the sulfuric acid or acetyl chloride conditions proved sufficient for our purpose, and after silica gel chromatography, **2b**[38] could be obtained in about a 50% overall yield as a mixture of anomers.

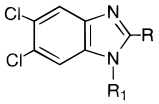
In a fashion analogous to the preparation of 2,5,6-trichloro-(1-β-D-ribofuranosyl)benzimidazole[11] (TCRB), 2,5,6-trichlorobenzimidazole[24] (TCB) was silylated with bis(trimethylsilyl)acetamide[25] (BSA) in dry acetonitrile and then glycosylated with **2b** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to give 1-(2,3,5-tri-*O*-acetyl-α-D-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (**3b**). Hydrolysis of **3b** under basic conditions then yielded 1-(α-D-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (**6b**). Both 1-(2,3,5-tri-*O*-acetyl-α-L-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (**3a**) and 1-(α-L-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (**6a**) were prepared from **2a** in a similar fashion (Scheme 1).

The 2-chloro substituent[26] of 1-substituted 2,5,6-trichlorobenzimidazoles can be conveniently displaced by a variety of nucleophiles. Following this approach, **3b** was treated with anhydrous hydrogen bromide in dichloromethane[44] and subsequently deprotonated under basic conditions to give 2-bromo-5,6-dichloro-1-(α-D-lyxofuranosyl)benzimidazole (**4b**). Additionally, the methylamino derivative **5b** could be prepared in one step by treatment of **3b** with 33% methylamine/ethanol in a sealed vial. Preparation of the isopropylamino and cyclopropylamino derivatives, **7b** and **8b**, respectively, was more conveniently accomplished by treating the deprotected nucleoside **6b** directly with the appropriate primary amine in ethanol. The enantiomers **4a**−**8a** were prepared in a similar fashion (Scheme 1). The 2-thio derivative **9a** was prepared by heating **6a** in an ethanol/thiourea mixture at reflux temperature for 19 h. Alternatively, commercially available 5,6-dichlorobenzimidazole-2-thione (**10**) was silylated with BSA in dry acetonitrile and then glycosylated with **2b** in the presence of TMSOTf to give, after deprotection, **9b**. Compound **2a** was glycosylated under identical conditions to give a compound which was subsequently shown to be identical with **9a**. This unequivocally establishes the site of glycosylation as having occurred at N-1 and not at the 2-thio moiety. Finally, treatment of **9b** with ammonium hydroxide in acetonitrile/water, followed by alkylation with benzyl bromide or methyl iodide, gave 2-(benzylthio)-5,6-dichloro-1-(α-D-lyxofuranosyl)benzimidazole (**11b**) and 5,6-dichloro-1-(α-D-lyxofuranosyl)-2-(methylthio)benzimidazole (**12b**), respectively. The enantiomers, **11a** and **12a**, were prepared in a similar fashion (Scheme 2).

Several reports of the synthesis of 5-deoxy-D- and -L-lyxose have been described in the literature.[27−29] However, none of these methods employ lyxose as the starting material, and we opted to develop a more direct route to our desired compound, **14b**, than has been reported. Implementing the first step of the Guthrie and Smith procedure, as mentioned previously, yields a mixture of 1-*O*-methyl-D-lyxofuranose and 1-*O*-methyl-D-lyxopyranose. This mixture was treated with cupric sulfate in acetone to give a mixture of 2,3-*O*-isopropylidene-1-*O*-methyl-D-lyxofuranose and 3,5-*O*-isopropylidene-1-*O*-methyl-D-lyxofuranose, along with some of the pyranose isomer which was removed by silica gel chromatography. The primary hydroxyl group of 2,3-*O*-isopropylidene-1-*O*-methyl-D-lyxofuranose was then selectively tosylated, and 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-tosyl-α-D-lyxofuranose (**13b**)[27] was obtained in a 49% yield after silica gel chromatography. Reduction of **13b** was then carried out with LAH in diethyl ether and toluene at reflux. At this point, several attempts at concomitant deprotection/acetylation were unsuccessful, presumably due to the difficulty of ring closure of the acyclic *lyxo* configuration,[30] and only linear acetylated products were obtained. Similar difficulties have been reported for certain ribofurano[31−34] and xylofurano[34−36] derivatives, and a very precise concentration of the acid catalyst was required to obtain favorable amounts of the cyclic product **14b**. After determining the optimum conditions, **14b** was obtained in a 47% yield from **13b** as a mixture of anomers. Compounds **13a** and **14a** were prepared in a similar manner in a 57% and 53% yield, respectively (Scheme 3).

Finally, compound **1** and 2-bromo-5,6-dichlorobenzimidazole (**15**)[14] were condensed, individually, with **14b** by the modified Vorbrüggen procedure[21,25] as previously described. After deprotection under basic conditions, 1-(5-deoxy-α-D-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (**17b**) and 2-bromo-1-(5-deoxy-α-D-lyxofuranosyl)-5,6-dichlorobenzimidazole (**16b**) were obtained, respectively. The isopropylamino derivative **18b** was prepared by treating **17b** with isopropylamine in ethanol at 60 °C in a sealed flask. The enantiomers, **16a**−**18a**, were prepared by analogous routes (Scheme 4). The anomeric configuration was assigned according to Baker's rules[22]

Table 1. Antiviral Activity and Cytotoxicity of 2-Substituted 5,6-Dichloro-α-L-lyxosyl Benzimidazoles



				IC_{50} or IC_{90} (μM)				
				antiviral activity				
				HCMV[a]		HSV-1[b]	cytotoxicity[c]	
no.	R	R_1	isomer	plaque	yield	ELISA	visual[d]	growth
4a	Br	lyxose	L	2.8[d]	0.8[d]	>100[e]	>100	>100
4b	Br	lyxose	D	6	65[d]	50	>100	>100
5a	$NHCH_3$	lyxose	L	>100		>100	>100	>100
5b	$NHCH_3$	lyxose	D	>100	>100	>100	>100	>100
6a	Cl	lyxose	L	18	3.4	>100	190	>100
6b	Cl	lyxose	D	18	>100[d]	90	>100	>100
7a	NHC_3H_7	lyxose	L	>100	19	>100	>100	>100
7b	NHC_3H_7	lyxose	D	60	17	>100	>100	>100
8a	NHC_3H_5	lyxose	L	>100	35[d]	>100	>100	>100
8b	NHC_3H_5	lyxose	D	>100[d]	70	>100	>100	>100
9a	SH	lyxose	L	>100	>100	>100	>100	>100
9b	SH	lyxose	D	>100	>100	>100	>100	>100
11a	SBn	lyxose	L	32	17	60	32	40
11b	SBn	lyxose	D	32	15	55	32	60
12a	SCH_3	lyxose	L	>100		>100	>100	>100
12b	SCH_3	lyxose	D	>100	>100	>100	>100	>100
16a	Br	5′-D-lyxose	L	0.4	2.0	>100	32	60
16b	Br	5′-D-lyxose	D	32	12	50	100	>100
17a	Cl	5′-D-lyxose	L	0.2	0.2	20	32	60
17b	Cl	5′-D-lyxose	D	32	8.0	60	45	75
18a	NHC_3H_7	5′-D-lyxose	L	32	2.8	>100	100	65
18b	NHC_3H_7	5′-D-lyxose	D	10	2.0		>100	
foscarnet[f]				39 ± 26			>100	
ganciclovir (DHPG)[g]				7.4 ± 6.5	1.6 ± 1.2	3.5 ± 2.1	>100	>100

[a] Plaque and yield reduction assays were performed in duplicate as described in the text. Results from plaque assays are reported as IC_{50}'s, those for yield reduction experiments as IC_{90}'s. [b] The plaque assay was used to determine the activity of DHPG against HSV-1; all other compounds were assayed by ELISA in quadruplicate wells. [c] Visual cytotoxicity was scored on HFF cells at time of HCMV plaque enumeration. Results of duplicate experiments are presented. Inhibition of KB cell growth was determined as described in the text in quadruplicate assays. Results are presented as IC_{50}'s. [d] Average derived from two to four experiments. [e] >100 indicates IC_{50} or IC_{90} greater than the noted (highest) concentration tested. [f] Average ± standard deviation from 15 experiments. [g] Average ± standard deviation from 108, 33, and 3 experiments, respectively.

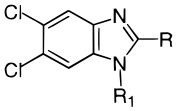
and confirmed by NOE difference experiments.[37] For example, after compound **9a** was fully assigned by COSY NMR, the signal of 7.62 ppm (H-7) was irradiated resulting in a 6.6% increase in the signal corresponding to H-2′ and a 3.4% increase in the signal corresponding to H-4′. Irradiation at 7.40 (H-4) or 6.46 (H-1′) results in no observable NOE enhancement. Likewise, after assigning the deoxy series by homonuclear decoupling experiments, the signal at 8.39 (H-7) was irradiated (compound **17a**) and a 5.8% increase was observed at the multiplet corresponding to H-2′ and H-4′. These data confirmed the anomeric assignments for both series of compounds.

Biology. All compounds in this series were evaluated for activity against HCMV and herpes simplex virus type 1 (HSV-1) as well as for cytotoxicity in two cell lines. As we have found previously with the β-D-ribofuranosylbenzimidazole nucleosides[11−15] and with the acyclic benzimidazoles,[16] all of the α-lyxofuranosyl and 5′-deoxy-α-lyxofuranosyl nucleosides either were inactive against HSV-1 or demonstrated weak activity which was poorly separated from cytotoxicity (Table 1). Thus, there was no evidence for inhibition of a specific HSV-1 target.

In contrast, certain α-lyxofuranosyl- and (5′-deoxy-α-lyxofuranosyl)benzimidazoles were very active against HCMV. In both series, the 2-halogen substituted compounds were more active than the 2-amino- or 2-thio-substituted derivatives. In the α-lyxofuranosyl series, the 2-methylamino analogues (**5a**,**b**) were completely inactive but the 2-isopropylamino and 2-cyclopropylamino analogues (**7a**,**b**, **8a**,**b**) were modestly active against HCMV and were not cytotoxic. The activity was more apparent in yield assays compared to plaque assays; consequently the compounds were investigated against another strain of HCMV—see below and Table 2. The 2-thio and 2-thiomethyl compounds (**9a**,**b**, **12a**,**b**) were inactive, and the 2-thiobenzyl compounds (**11a**,**b)** were weakly active against HCMV. The latter activity, however, was poorly separated from cytotoxicity. We have observed the same weak activity/cytotoxicity with all other 2-(thiobenzyl)-5,6-dichlorobenzimidazoles synthesized to date.[11−15]

Unlike the 2-amino or 2-thio derivatives, the 2-chloro and 2-bromo analogues in both the α-lyxofuranosyl series and the 5′-deoxy-α-lyxofuranosyl series were active against HCMV. The α-lyxosides (**4a**,**b**, **6a**,**b**) were less active and less cytotoxic than the 5′-deoxy-α-lyxosides (**16a**,**b**, **17a**,**b**). More cytotoxicity was observed with the 5′-deoxy-α-lyxofuranosyl compounds. Several of these compounds were more active than the original lead compound, the β-nucleoside TCRB; likewise they were more active than ganciclovir or foscarnet (Tables 1 and 2). In both series, the L-isomers were more active than the D-isomers. This difference was most pronounced in the HCMV yield assay in which little activity was observed for the D-isomers in the lyxose series (**4b**, **6b**) but some activity was found for the D-isomers in the 5′-deoxy series (**16b**, **17b**). Because the yield assay measures the amount of infectious virus produced in a culture, results from this assay are most representative of in vivo viral replication. Consequently

Table 2. Activity of Benzimidazole Nucleosides against Two Strains of HCMV



compd	R	R_1	isomer	IC_{50} or IC_{90} (μM), HCMV strain: Towne[a] plaque	Towne[a] yield	AD169 plaque
TCRB[b]	Cl	β-ribose	D	2.9	1.4	1.8
4a	Br	α-lyxose	L	2.8	0.8	0.8
4b	Br	α-lyxose	D	6	65[c]	4.2
6a	Cl	α-lyxose	L	18	3.4	2.6
6b	Cl	α-lyxose	D	18	>100[c]	9
7a	NHC_3H_7	α-lyxose	L	>100[d]	19	11
7b	NHC_3H_7	α-lyxose	D	60	17	32
8a	NHC_3H_5	α-lyxose	L	>100	35	160[c]
8b	NHC_3H_5	α-lyxose	D	>100[c]	70	>100
11a	SBn	α-lyxose	L	32	17	32
11b	SBn	α-lyxose	D	32	15	32

[a] Plaque and yield reduction assays were performed in duplicate as described in the text. Data for Towne strain are also presented in Table 1. Results from plaque assays are reported as IC_{50}'s, those for yield reduction experiments as IC_{90}'s. [b] 2,5,6-Trichloro-1-(β-D-ribofuransoyl)benzimidazole, data published previously as compound **9** in ref 11. [c] Average derived from two or three experiments. [d] >100 indicates IC_{50} or IC_{90} greater than the noted (highest) concentration tested.

we interpret these data to mean that the L- but not the D-isomers are very active against HCMV.

Although the potency was lower, the difference in activity between plaque and yield assays also was observed with the 2-isopropylamino and 2-cyclopropylamino analogues in the lyxose series (**7a**,**b**, **8a**,**b**). With these compounds, little or no activity was found in the plaque assay but activity was observed in the yield assay. To determine if this difference was related to the HCMV strain used in the plaque assay, several compounds were tested using the AD169 strain of HCMV. We had previously observed that the β-D-ribonucleoside, TCRB, was slightly more active against HCMV strain AD169 than against the Towne strain (Table 2). This strain-related difference appeared to hold with the α-lyxofuranosyl nucleosides, particularly with the 2-halogen-substituted L-analogues. Data in Table 2 show that **4a** and **6a** were more active in the plaque assay with AD169 than with Towne, whereas this was less apparent with **4b** and **6b**. A similar but less-pronounced relationship held with the amine analogues (**7a**,**b**, **8a**,**b**). The relationship did not hold for the 2-thiobenzyl analogues (**11a**,**b**) which were more cytotoxic or with the 2-methylamine (**5a**,**b**), 2-thio, and 2-thiomethyl (**9a**,**b**, **12a**,**b**) analogues which were inactive in all assays (data not presented). Regardless of the strain difference, the foregoing results firmly establish that 2-halo α-lyxofuranosyl- and (5′-deoxy-α-lyxofuranosyl)benzimidazoles are inhibitors of HCMV replication at noncytotoxic concentrations.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Silica gel, SilicAR 40−63 μm 230−400 mesh (Mallinckrodt), was used for chromatography. Thin-layer chromatography (TLC) was performed on prescored SilicAR 7GF plates (Analtech, Newark, DE). TLC plates were developed in the following solvent systems: system 1 (2% MeOH/$CHCl_3$, v/v), system 2 (10% MeOH/$CHCl_3$, v/v), system 3 (35% EtOAc/hexanes, v/v), system 4 (25% EtOAc/hexanes, v/v), system 5 (5% MeOH/$CHCl_3$, v/v), system 6 (15% MeOH/$CHCl_3$, v/v), system 7 (20% EtOAc/hexanes, v/v), and system 8 (50% EtOAc/hexanes, v/v). Compounds were visualized by illuminating with UV light (254 nm) or by treatment with 10% methanolic sulfuric acid followed by charring on a hot plate. Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature not exceeding 45 °C, unless specified otherwise. ^{1}H NMR spectra were recorded on either a Bruker 200-, 300-, 360-, or 500-MHz instrument. The chemical shifts are expressed in parts per million relative to the standard chemical shift of the solvent, DMSO-d_6 (δ = 2.50). All ^{1}H NMR assignments reported were made by homonuclear decoupling experiments, except compound **9a**, which was assigned by a COSY experiment. Microanalytical results were performed by the University of Michigan, Department of Chemistry, and are within ±0.4% of the theoretical values, unless otherwise specified. Unless otherwise noted, all materials were obtained from commercial suppliers.

1-(2,3,5-Tri-*O*-acetyl-α-L-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (3a). A 500-mL round-bottom flask equipped with a Claisen adapter and stirrer was evacuated and backflushed with argon. 2,5,6-Trichlorobenzimidazole[24] (**1**; 1.74 g, 7.85 mmol) was then suspended in dry CH_3CN (100 mL), and bis(trimethylsilyl)acetamide (1.94 mL, 8.84 mmol) was added dropwise via a syringe, at which time the heterocycle went into solution. A solution of 1,2,3,5-tetra-*O*-acetyl-L-lyxofuranose[23,38] (**2a**; 3.25 g, 10.2 mmol) dissolved in CH_3CN (50 mL) was added to the stirred solution, and this was followed immediately by TMSOTf (1.8 mL, 9.3 mmol). After 20 h the solvent was evaporated under reduced pressure to afford a yellow residue. This residue was dissolved in ethyl acetate (100 mL) and washed successively with water, $NaHCO_3$ (saturated), and then brine (1 × 75 mL each). The organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to yield a yellow oil. This oil was subjected to column chromatography (3 × 25 cm, solvent system 3), and the appropriate fractions were combined to yield 2.59 g (67%) of **3a** as a yellow glass. This glass was used without further purification in subsequent reactions. R_f = 0.53 (solvent system 3). ^{1}H NMR (DMSO-d_6): δ 8.19 (s, 1 H), 8.00 (s, 1 H), 6.28 (d, 1 H, J = 7.9 Hz), 5.97 (m, 1 H), 5.74 (m, 1 H), 5.17 (m, 1 H), 4.26 (m, 2 H), 2.19 (s, 3 H), 2.03 (s, 3 H), 1.96 (s, 3 H). HRMS: calcd for CHN, M^+, 478.0101; found, 478.0098 (M^+).

1-(2,3,5-Tri-*O*-acetyl-α-D-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (3b). The procedure is the same as that described for **3a**, except that **2b** was used instead of **2a**. The TLC (cospots in solvent system 3) and proton spectrum were identical with that obtained for **3a**. Yield: 3.40 g (88%) as a yellow glass. HRMS: calcd for CHN, M^+, 478.0101; found, 478.0085 (M^+).

2-Bromo-5,6-dichloro-1-(α-L-lyxofuranosyl)benzimidazole (4a). A 3-neck round-bottom flask was charged with **3a** (460 mg, 0.96 mmol) and dichloromethane (50 mL). Anhydrous hydrogen bromide was slowly bubbled into the solution for 40 min while the mixture was stirred at room temperature. The gas was then turned off for 90 min; then the gas was turned back on, and a white precipitate formed. The hydrogen bromide was turned off again after 135 min,

and the mixture was allowed to stir for an additional 3 h. At this time $NaHCO_3$ (saturated) was added slowly until the evolution of gas ceased. The clear solution was washed with $NaHCO_3$ (saturated, 50 mL) and brine (50 mL) and dried over magnesium sulfate. The solvent was evaporated and coevaporated with diethyl ether under reduced pressure to yield a yellow glass. $R_f = 0.53$ (solvent system 3). ^{1}H NMR (DMSO-d_6): δ 8.18 (s, 1 H), 8.01 (s, 1 H), 6.25 (d, 1 H, $J = 7.8$ Hz), 5.97 (m, 1 H), 5.74 (m, 1 H), 5.17 (m, 1 H), 4.26 (m, 2 H), 2.19 (s, 3 H), 2.03 (s, 3 H), 1.97 (s, 3 H).

The yellow glass was then dissolved in a stirred (1:1:1) solution of ethanol, MeOH, and water (50 mL). The solution was charged with sodium carbonate (380 mg, 3.6 mmol). After 100 min, glacial acetic acid (0.5 mL) was added and the alcohol was evaporated under reduced pressure. An additional 25 mL of cold water was added, and the mixture was filtered. The resulting solid was recrystallized from methanol/water and dried at 78 °C under reduced pressure for 2 days to give 194 mg (64%) of **4a** as white crystals. $R_f = 0.06$ (solvent system 5), $R_f = 0.30$ (solvent system 2). Mp: 178−179 °C. ^{1}H NMR (DMSO-d_6): δ 8.00 (s, 1 H), 7.91 (s, 1 H), 5.96 (d, 1 H, $J = 8.1$ Hz), 5.58 (d, 1 H, $J = 6.6$ Hz, D_2O exchangeable), 5.29 (d, 1 H, $J = 4.3$ Hz, D_2O exchangeable), 4.71 (m, 2 H), 4.59 (m, 1 H), 4.19 (m, 1 H), 3.65 (m, 2 H). HRMS: calcd for $C_{12}H_{11}O_4N_2Cl_2Br$, 395.9279 (M^+); found, 395.9273 (M^+). Anal. ($C_{12}H_{11}O_4N_2Cl_2Br$) C, H, N.

2-Bromo-5,6-dichloro-1-(α-D-lyxofuranosyl)benzimidazole (4b). The procedure is the same as that described for **4a**, except that **3b** was used instead of **3a**. The TLC (cospots in solvent system 2) and proton spectrum were identical with that obtained for **4a**. Yield: 255 mg (84%, two steps) as white crystals. Mp: 178−179 °C. HRMS: calcd for $C_{12}H_{11}O_4N_2Cl_2Br$, M^+, 395.9279; found, 395.9261 (M^+). Anal. ($C_{12}H_{11}O_4N_2Cl_2Br$) C, H, N.

5,6-Dichloro-1-(α-L-lyxofuranosyl)-2-(methylamino)benzimidazole (5a). A 250-mL pressure bottle was charged with **3a** (480 mg, 1.0 mmol) and a 33% solution of methylamine in absolute ethanol (25 mL). The vessel was sealed, and the reaction mixture was stirred at room temperature for 16 h. The solvent was then evaporated and coevaporated with hexanes and diethyl ether under reduced pressure. The remaining solid was recrystallized twice from a methanol and water mixture and dried at 78 °C under reduced pressure to yield 259 mg (72%) of **5a** as a white solid. $R_f = 0.09$ (solvent system 1). Mp: 131−132 °C. ^{1}H NMR (DMSO-d_6): δ 7.40 (s, 1 H), 7.36 (s, 1 H), 6.81 (m, 1 H, D_2O exchangeable), 5.73 (d, 1 H, $J = 8.1$ Hz), 5.27 (d, 1 H, $J = 4.4$ Hz, D_2O exchangeable), 5.24 (d, 1 H, $J = 4.3$ Hz, D_2O exchangeable), 4.66 (t, 1 H, $J = 5.6$ Hz, D_2O exchangeable), 4.57 (m, 1 H), 4.44 (m, 1 H), 4.16 (m, 1 H), 3.63 (m, 2 H), 2.88 (d, 3 H, $J = 4.40$ Hz). Anal. ($C_{13}H_{15}O_4N_3Cl_2$) C, H, N.

5,6-Dichloro-1-(α-D-lyxofuranosyl)-2-(methylamino)benzimidazole (5b). The procedure is the same as that described for **5a**, except that **3b** was used instead of **3a**. The TLC (cospots in solvent system 1) and proton spectrum were identical with that obtained for **5a**. Yield: 223 mg (62%) as a white solid. Mp: 126−128 °C. Anal. ($C_{13}H_{15}O_4N_3Cl_2$) C, H, N.

1-(α-L-Lyxofuranosyl)-2,5,6-trichlorobenzimidazole (6a). A 200-mL round-bottom flask was charged with **3a** (464 mg, 1.0 mmol) which was then dissolved in 75 mL of an equimolar mixture (v/v) of ethanol and water. Anhydrous sodium carbonate (370 mg, 3.5 mmol) was added to the stirred solution, and then the reaction mixture was allowed to stir at room temperature for an additional 3 h. Acetic acid (4 mL) was added, and the solvent was evaporated under reduced pressure. The resultant solid was dissolved in ethyl acetate, and the solution was washed successively with water, $NaHCO_3$ (saturated), and brine (1 × 50 mL each). The organic layers were collected and dried over sodium sulfate. The solvent was evaporated under reduced pressure to yield, upon vacuum-drying, 200 mg (57%) of **6a** as a white foam. $R_f = 0.30$ (solvent system 2). Mp: 159−161 °C. ^{1}H NMR (DMSO-d_6): δ 7.98 (s, 1 H), 7.92 (s, 1 H), 5.97 (d, 1 H, $J = 9.3$ Hz), 5.49 (d, 1 H, $J = 6.8$ Hz, D_2O exchangeable), 5.30 (d, 1 H, $J = 4.2$ Hz, D_2O exchangeable), 4.71 (m, 2 H), 4.58 (m, 1 H), 4.2 (m, 1 H), 3.6 (m, 2 H). HRMS: calcd for $C_{12}H_{11}O_4N_2Cl_3$, M^+, 351.9784; found, 351.9782 (M^+). Anal. ($C_{12}H_{11}O_4N_2Cl_3$) C, H, N.

1-(α-D-Lyxofuranosyl)-2,5,6-trichlorobenzimidazole (6b). The procedure is the same as that described for **6a**, except **3b** (632 mg, 1.07 mmol) was used instead of **3a**. The TLC (cospots in solvent system 2) and proton spectrum were identical with that obtained for **6a**. Yield: 175 mg (76%) as a white foam. Mp: 175−176 °C. HRMS: calcd for $C_{12}H_{11}O_4N_2Cl_3$, M^+, 351.9784; found, 351.9773 (M^+). Anal. ($C_{12}H_{11}O_4N_2Cl_3 \cdot H_2O$) C, H; N: calcd, 7.07; found, 7.54.

5,6-Dichloro-2-(isopropylamino)-1-(α-L-lyxofuranosyl)benzimidazole (7a). 1-(α-L-Lyxofuranosyl)-2,5,6-trichlorobenzimidazole (**6a**; 300 mg, 0.85 mmol) was dissolved in ethanol (5 mL), and isopropylamine (10 mL) was then added. The flask was sealed, and the reaction mixture stirred at 70 °C for 2 days. The mixture was then evaporated under reduced pressure and subjected to silica gel chromatography (3 × 25 cm), eluting with solvent system 5. After the solvent was evaporated under reduced pressure, the resultant solid was stirred in 10 mL of benzene for 12 h and then collected by filtration. The solid was dried under reduced pressure at 78 °C for 2 days to give 202 mg (63%) of analytically pure **7a**. Mp: 198−201 °C. ^{1}H NMR (DMSO-d_6): δ 7.40 (s, 1 H), 7.32 (s, 1 H), 6.57 (bs, 1 H, D_2O exchangeable), 5.79 (m, 1 H), 5.28 (m, 1 H, D_2O exchangeable), 5.21 (m, 1 H, D_2O exchangeable), 4.67 (bs, 1 H, D_2O exchangeable), 4.54 (m, 1 H), 4.42 (m, 1 H), 4.17 (m, 1 H), 4.03 (m, 1 H), 3.68 and 3.59 (m, 2 H), 1.21 (bs, 6 H). Anal. ($C_{15}H_{19}O_4N_3Cl_2$) C, H, N.

5,6-Dichloro-2-(isopropylamino)-1-(α-D-lyxofuranosyl)benzimidazole (7b). The procedure is the same as that described for **7a**, except that **6b** (274 mg, 0.77 mmol) was used instead of **6a**. The TLC (cospots in solvent system 1) and proton spectrum were identical with that obtained for **7a**. Yield: 205 mg (64%) as a white solid. Mp: 201−202 °C. Anal. ($C_{15}H_{19}O_4N_3Cl_2$) C, H, N.

2-(Cyclopropylamino)-5,6-dichloro-1-(α-L-lyxofuranosyl)benzimidazole (8a). The procedure is the same as that described for **7a**, except that cyclopropylamine was used instead of isopropylamine and **6a** (300 mg, 0.80 mmol) was used. Yield: 299 mg (65%) as a white solid. Mp: 184−186 °C. ^{1}H NMR (DMSO-d_6): δ 7.47 (s, 1 H), 7.36 (s, 1 H), 7.05 (bs, 1 H, D_2O exchangeable), 5.72 (m, 1 H), 5.24 (m, 1 H, D_2O exchangeable), 5.17 (m, 1 H, D_2O exchangeable), 4.65 (bs, 2 H, D_2O exchangeable), 4.53 (m, 1 H), 4.42 (m, 1 H), 4.15 (m, 1 H), 3.66 and 3.57 (m, 2 H), 2.75 (m, 1 H), 0.86 (m, 2 H), 0.57 (m, 1 H), 0.50 (m, 1H). Anal. ($C_{15}H_{17}O_4N_3Cl_2$) C, H, N.

2-(Cyclopropylamino)-5,6-dichloro-1-(α-D-lyxofuranosyl)benzimidazole (8b). The procedure is the same as that described for **7a**, except that cyclopropylamine was used instead of isopropylamine and **6b** (248 mg, 0.66 mmol) was used instead of **6a**. The TLC (cospots in solvent system 1) and proton spectrum were identical with that obtained for **8a**. Yield: 247 mg (67%) as a white solid. Mp: 183−185 °C. Anal. ($C_{15}H_{17}O_4N_3Cl_2$) C, H, N.

5,6-Dichloro-1-(α-L-lyxofuranosyl)benzimidazole-2-thione (9a). Method A: A 500-mL round-bottom flask equipped with a Claisen adapter and a stirrer was evacuated and backflushed with argon. Dry 5,6-dichlorobenzimidazole-2-thione[15] (**10**; 1.53 g, 7.0 mmol) was then suspended in CH_3CN (80 mL). Bis(trimethylsilyl)acetamide (1.95 mL, 7.9 mmol) was added dropwise via a syringe, and the mixture was heated until the heterocycle went into solution (30−40 °C). Compound **2a**[23,38] (2.5 g, 7.9 mmol) dissolved in CH_3CN (40 mL) was added to the stirred solution followed immediately by TMSOTf (1.5 mL, 7.9 mmol). After 24 h, the solvent was evaporated under reduced pressure and the remaining residue was subjected to silica gel chromatography (3 × 25 cm), eluting first with solvent system 4 and then solvent system 3. Both **10** (40 mg) and the protected nucleoside (2.84 g, 87% based on consumed heterocycle) were obtained as separate compounds. $R_f = 0.45$ (compound **10**, solvent system 3). ^{1}H NMR (DMSO-d_6): δ 13.33 (bs, 1 H), 7.93 (s, 1 H), 7.41 (s, 1 H), 6.75 (d, 1 H, $J =$

8.3 Hz), 6.13 (m, 1 H), 5.74 (m, 1 H), 5.13 (m, 1 H), 4.23 (m, 2 H), 2.19 (s, 3 H), 2.03 (s, 3 H), 1.94 (s, 3 H).

A 200-mL round-bottom flask was charged with the protected nucleoside (2.75 g, 5.66 mmol) and dissolved in 92% ethanol/water (50 mL, v/v). Sodium carbonate (4.0 g, 37 mmol) was added to this stirred solution, and the reaction mixture was allowed to stir at room temperature for 24 h. Acetic acid (2 mL) was added, and then the ethanol was evaporated under reduced pressure. The resulting mixture was taken up in an additional 275 mL of cold water and extracted with EtOAc (15 × 50 mL). The solvent was then evaporated under reduced pressure. The resulting solid was recrystallized from methanol and dried under reduced pressure at 78 °C for 2 days to give 1.48 g (74%) of **9a** as white crystals. $R_f = 0.27$ (solvent system 2). Mp: 235−236 °C. ^{1}H NMR (DMSO-d_6): δ 13.15 (bs, 1 H, D_2O exchangeable, NH), 7.62 (s, 1 H, H7), 7.40 (s, 1 H, H4), 6.46 (d, 1 H, $J = 8.2$ Hz, H1′), 5.31 (d, 1 H, $J = 6.7$ Hz, D_2O exchangeable, 2′-OH), 5.15 (d, 1 H, $J = 3.8$ Hz, D_2O exchangeable, 3′-OH), 4.81 (m, 1 H, H2′), 4.67 (m, 1 H, H4′), 4.50 (m, 1 H, H4′), 4.18 (m, 1 H, H3′), 3.61 (m, 2 H, H5′a and H5′b). Anal. ($C_{12}H_{12}N_2O_4Cl_2S$) C, H, N.

Method B: A 10-mL round-bottom flask was charged with **6a** (42 mg, 0.12 mmol), thiourea (36 mg, 0.48 mmol), and absolute ethanol (2 mL). The reaction mixture was heated at reflux temperature for 19 h, the solvent was evaporated under reduced pressure, and then the resultant residue was triturated with 5 mL of water. After standing for 3 h, the solid was collected by filtration and dried under reduced pressure at 60 °C for 48 h to yield 30 mg (71%) of a white solid. The TLC (cospots in solvent system 2) and proton spectrum were identical with that obtained for **9a** (method A). Mp: 234−236 °C.

5,6-Dichloro-1-(α-D-lyxofuranosyl)benzimidazole-2-thione (9b). The procedure is the same as that described for **9a** (method A), except that **2b**[23,38] was used instead of **2a**. The TLC (cospots in solvent system 2) and proton spectrum were identical with that obtained for **9a** (methods A and B). The yield on the first step was 91% (based on consumed heterocycle), and the yield on the second step was quantitative (2.0 g). An analytical sample was prepared by recrystallization from methanol and drying as for **9a**. Mp: 234−236 °C. Anal. ($C_{12}H_{12}N_2O_4Cl_2S$) C, H, N.

2-(Benzylthio)-5,6-dichloro-1-(α-D-lyxofuranosyl)-benzimidazole (11a). A 100-mL round-bottom flask was charged with **9a** (351 mg, 1.0 mmol), H_2O (25 mL), and CH_3CN (15 mL). To the suspension was added 12 drops of concentrated ammonium hydroxide to effect a solution. Benzyl bromide (0.12 mL, 1.0 mmol) was then added, and the mixture stirred at room temperature for 16 h. The excess acetonitrile was then evaporated under reduced pressure, and the aqueous layer was extracted with EtOAc (2 × 40 mL). The organic extracts were combined and dried ($MgSO_4$), and the solvent was evaporated to yield 410 mg (93%) of a white solid. This was subsequently recrystallized from methanol/water and dried under reduced pressure at 78 °C for 2 days to yield 361 mg (82%) of **11a** as white crystals. Mp: 210−212 °C. ^{1}H NMR (DMSO-d_6): δ 7.89 (s, 1 H), 7.78 (s, 1 H), 7.37 (m, 5 H), 5.80 (d, 1 H, $J = 7.9$ Hz), 5.51 (d, 1 H, $J = 7.3$ Hz, D_2O exchangeable), 5.26 (d, 1 H, $J = 4.2$ Hz, D_2O exchangeable), 4.67 (t, 1 H, $J = 5.7$ Hz, D_2O exchangeable), 4.62 (m, 3 H), 4.50 (m, 1 H), 4.15 (m, 1 H), 3.60 (m, 2 H). Anal. ($C_{19}H_{18}N_2O_4Cl_2S$) C, H, N.

2-(Benzylthio)-5,6-dichloro-1-(α-D-lyxofuranosyl)-benzimidazole (11b). The procedure is the same as that described for **11a**, except that **9b** was used instead of **9a**. The TLC (cospots in solvent system 1) and proton spectrum were identical with that obtained for **11a**. Yield: 207 mg (47%) as white crystals. Mp: 196−198 °C. Anal. ($C_{19}H_{18}N_2O_4Cl_2S$) C, H, N.

5,6-Dichloro-1-(α-L-lyxofuranosyl)-2-(methylthio)-benzimidazole (12a). The procedure is the same as that described for **11a**, except that methyl iodide (0.06 mL, 1.0 mmol) was used instead of benzyl bromide. Yield: 305 mg (84%) of **12a** as white crystals. Mp: 210−212 °C. ^{1}H NMR (DMSO-d_6): δ 7.86 (s, 1 H), 7.77 (s, 1 H), 5.80 (d, 1 H, $J = 8.1$ Hz), 5.52 (d, 1 H, $J = 7.1$ Hz, D_2O exchangeable), 5.28 (d, 1 H, $J = 3.6$ Hz, D_2O exchangeable), 4.70 (t, 1 H, $J = 5.6$ Hz, D_2O exchangeable), 4.63 (m, 1 H), 4.52 (m, 1 H), 4.17 (m, 1 H), 3.63 (m, 2 H), 2.72 (t, 3 H). Anal. ($C_{13}H_{14}N_2O_4Cl_2S$) C, H, N.

5,6-Dichloro-1-(α-D-lyxofuranosyl)-2-(methylthio)-benzimidazole (12b). The procedure is the same as that described for **11b**, except that methyl iodide (0.06 mL, 1.0 mmol) was used instead of benzyl bromide. The TLC (cospots in solvent system 1) and proton spectrum were identical with that obtained for **12a**. Yield: 142 mg (39%) as white crystals. Mp: 204−206 °C. Anal. ($C_{13}H_{14}N_2O_4Cl_2S$) C, H, N.

1-*O*-Methyl-2,3-*O*-isopropylidene-5-*O*-tosyl-L-lyxofuranose (13a). To a solution of L-lyxose (12 g, 80 mmol) in methanol (192 mL) was added sulfuric acid (97%, 0.96 mL), and the mixture was stirred for 24 h at room temperature. Pyridine (50 mL) was then added, and the reaction mixture was evaporated under reduced pressure and coevaporated with toluene (5 × 10 mL) and acetone (5 × 10 mL). TLC (solvent system 6) of the crude material showed one major product ($R_f = 0.38$) and one minor product ($R_f = 0.27$) with both of them different from the starting material ($R_f = 0.08$). This mixture was suspended in acetone (240 mL), and then cupric sulfate (12.1 g, 76 mmol) and sulfuric acid (1.2 mL) were added. The reaction mixture was stirred at room temperature for 20 h and filtered, and the filtrate was made basic by the rapid addition of ammonium hydroxide (8 mL) and then filtered again. The pale-yellow filtrate was evaporated under reduced pressure and then coevaporated with ethanol (3 × 10 mL) and toluene (3 × 10 mL). The residue was dissolved in a minimal amount of dichloromethane and subjected to silica gel chromatography (5 × 15 cm, gradient of methanol (0−2%) in dichloromethane) to give a mixture of the 2,3-di-*O*-isopropylidine-protected sugar and the 3,5-di-*O*-isopropylidine-protected sugar as an oil, slightly contaminated by the pyranose isomer. A solution of tosyl chloride (12.0 g, 63 mmol) in 30 mL of chloroform was added to a solution of this mixture (12.2 g, 60 mmol) in pyridine (180 mL), at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was allowed to stir at room temperature for 24 h. The mixture was then poured onto ice water (200 mL) and diluted with dichloromethane (200 mL). The two layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined and washed successively with aqueous sodium bicarbonate (20 mL) and water (20 mL). After drying over sodium sulfate and filtering, the solvent was evaporated under reduced pressure. The resultant residue was dissolved with the minimal amount of dichloromethane, subjected to silica gel chromatography (5 × 15 cm, gradient of methanol (0−2%) in dichloromethane), and then recrystallized from toluene to give 16.3 g (57% from L-lyxose) of **13a**. $R_f = 0.55$ (solvent system 8). Mp: 76−78 °C (lit.[28] mp 76−77 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.81 and 7.49 (2 d, 4 H, phenyl, $J = 8.2$ Hz), 4.84 (s, 1 H, H-1), 4.7 (m, 1 H, H-3), 4.49 (d, 1 H, $J = 5.8$ Hz, H-2), 4.3−4.2 (m, 1 H, H-5a), 4.1−4.0 (m, 2 H, H-5b, H-4), 3.18 (s, 3 H, OCH_3), 2.43 (s, 3 H, H_3C-phenyl), 1.25 and 1.19 (2 s, 6 H, $(CH_3)_2$).

1-*O*-Methyl-2,3-*O*-isopropylidene-5-*O*-tosyl-D-lyxofuranose (13b). The procedure is the same as that described for **13a**, except D-lyxose was used instead of L-lyxose. The TLC (cospots in solvent system 8) and proton spectrum were identical with that obtained for **13a**. Lit.[28] ^{1}H NMR ($CDCl_3$, 60 MHz): δ 7.70 and 7.21 (2 d, 4 H, phenyl, $J = 9$ Hz), 4.52 (m, 2 H, H-2, H-3), 4.17 (m, 3 H, H-4, H-5a, H5-b), 3.22 (s, 3 H, OCH_3), 2.40 (s, 3 H, H_3C-phenyl), 1.30 and 1.22 (2 s, 6 H, $(CH_3)_2$). Yield: 14.0 g (49%) as a solid. Mp: 75−77 °C (lit.[28] mp 81−81.5 °C).

1,2,3-Tri-*O*-acetyl-5-deoxy-L-lyxofuranose (14a). A solution of **13a** (5.0 g, 14 mmol) in diethyl ether (84 mL) and toluene (14 mL) was added to a 1 M solution of $LiAlH_4$ in diethyl ether (46 mL) at reflux. After 22 h at reflux temperature, the reaction mixture was allowed to cool to room temperature, and then ethyl acetate (10 mL) followed by water

(2 mL) was added slowly to destroy the excess hydride. The white precipitate was collected by filtration, first by suction filtration (water aspirator) and then by gravity. The filtrate was concentrated under reduced pressure until an oil (2.06 g) was obtained. A solution of this oil (480 mg, 2.55 mmol) in acetic acid (12 mL) and acetic anhydride (1.2 mL) was stirred at 0 °C. Sulfuric acid (0.66 mL) was then added over a 30-min period. The icy mixture was allowed to reach room temperature and, after 20 h of stirring, was poured onto ice water (50 mL) and diluted with ethyl acetate (100 mL). The ethyl acetate was separated, the aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were washed successively with aqueous sodium bicarbonate (10 mL) and water (10 mL). The organic layer was dried over sodium sulfate, filtered, evaporated under reduced pressure, and dried under reduced pressure at 30 °C for 2 days to afford **14a** (450 mg, 53% from **13a**) as an oil. ^{1}H NMR (DMSO-d_6): δ 6.27 (d, 0.55 H, J = 4.6 Hz, H-1 α or β), 5.92 (s, 0.45 H, H-1 α or β), 5.2−5.0 (m, 2 H, H-2, H-3 α and β), 4.5−4.4 (m, 1 H, H-4 α and β), 2.11, 2.09, 2.09, 2.06, 2.05, and 2.04 (6 s, 9 H, acetyls), 1.16 (d, 1.6 H, H-5,5′,5″ α or β, J = 6.5 Hz), 1.10 (d, 1.4 H, H-5,5′,5″ α or β, J = 6.4 Hz). Anal. ($C_{11}H_{16}O_7$) C, H.

1,2,3-Tri-*O*-acetyl-5-deoxy-D-lyxofuranose (14b). The procedure is the same as that described for **14a**, except that **13b** was used instead of **13a**. The proton spectrum was identical with that obtained for **14a**. Yield: 1.3 g (47%) as an oil. Anal. ($C_{11}H_{16}O_7$) H; C: calcd, 50.77; found, 50.18.

2-Bromo-1-(5-deoxy-α-L-lyxofuranosyl)-5,6-dichlorobenzimidazole (16a). The procedure is the same as that described for **17a**, except 2-bromo-5,6-dichlorobenzimidazole (**15**)[11] was used instead of **1**. Yield: 410 mg (57%) as a solid. R_f = 0.41 (solvent system 2). Mp: 125−127 °C. ^{1}H NMR (DMSO-d_6): δ 8.42 and 7.96 (2 s, 2 H, H-4, H-7), 5.95 (d, 1 H, OH-2′, J = 5.0 Hz), 5.7 (m, 2 H, H-1′, OH-3′), 4.3−4.2 (m, 2 H, H-2′, H-4′), 3.9 (m, 1 H, H-3′), 1.29 (d, 3 H, H-5′,5″,5‴, J = 6.3 Hz). Anal. ($C_{12}H_{11}O_3N_2Cl_2Br$) C, H, N.

2-Bromo-1-(5-deoxy-α-D-lyxofuranosyl)-5,6-dichlorobenzimidazole (16b). The procedure is the same as that described for **16a**, except **14b** was used instead of **14a**. The TLC (cospots in solvent system 2) and proton spectrum were identical with that obtained for **16a**. Yield: 170 mg (51%) as a solid. Mp: 124−126 °C. Anal. ($C_{12}H_{11}O_3N_2Cl_2$) C, H, N.

1-(5-Deoxy-α-L-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (17a). BSA (1.4 mL, 5.8 mmol) was added to a suspension of **1**[24] (850 mg, 3.8 mmol) in acetonitrile (65 mL) at 40 °C, and the reaction mixture was allowed to stir for 15 min. Compound **14a** (1.0 g, 3.8 mmol) in acetonitrile (11 mL) and TMSOTf (0.89 mL, 4.6 mmol) were then added to the clear solution, and the mixture was allowed to stir at room temperature. After 16 h, the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (75 mL), washed with aqueous sodium bicarbonate (10 mL) and water (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in a minimal amount of dichloromethane and subjected to silica gel chromatography (2.5 × 15 cm, gradient of methanol (0−1.6%) in dichloromethane). The appropriate fractions were combined and concentrated under reduced pressure until a foam was obtained. Sodium carbonate (825 mg, 7.8 mmol) was added to a stirred solution of this foam in ethanol (39 mL), and the reaction mixture was then stirred for 16 h. The mixture was then evaporated under reduced pressure, and the resultant residue was dissolved in a 4:1 mixture of ethyl acetate and dichloromethane (75 mL, v/v). The organic layer was washed with water (10 mL), dried over sodium sulfate, filtered, and evaporated under reduced pressure to yield a solid. This solid was then recrystallized from 2% methanol/dichloromethane to give 380 mg (56% based on consumed heterocycle) of compound **17a**. R_f = 0.41 (solvent system 2). Mp: 120−122 °C. ^{1}H NMR (DMSO-d_6): δ 8.39 and 7.96 (2 s, 2 H), 5.95 (d, 1 H, D_2O exchangeable, J = 4.9 Hz), 5.7 (m, 2 H, collapses to a multiplet of 1 H upon D_2O addition), 4.3−4.2 (m, 2 H), 3.9 (m, 1 H), 1.30 (d, 3 H, J = 6.3 Hz). Anal. ($C_{12}H_{11}O_3N_2Cl_3$) C, H, N.

1-(5-Deoxy-α-D-lyxofuranosyl)-2,5,6-trichlorobenzimidazole (17b). The procedure is the same as that described for **17a**, except **14b** was used instead of **14b**. The TLC (cospots in solvent system 2) and proton spectrum were identical with that obtained for **17a**. Yield: 480 mg (64%) as a solid. Mp: 118−120 °C. Anal. ($C_{12}H_{11}O_3N_2Cl_3$) C, H, N.

1-(5-Deoxy-α-L-lyxofuranosyl)-5,6-dichloro-2-(isopropylamino)benzimidazole (18a). Compound **17a** (280 mg, 0.83 mmol) was dissolved in ethanol (6.5 mL), and isopropylamine (6.5 mL) was added. The flask was sealed, and the reaction mixture stirred at 60 °C for 2 days. The mixture was decanted, and the solvent was evaporated to dryness under reduced pressure. The residue was dissolved in a 4:1 mixture of ethyl acetate and dichloromethane (50 mL, v/v) and washed with water (10 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure. The resultant solid was recrystallized from dichloromethane to give 190 mg (62%) of **18a**. All attempts to obtain **18a** as a solid free of dichloromethane by extended drying time and elevated drying temperatures, or by recrystallizing in another solvent, were unsuccessful. R_f = 0.38 (solvent system 2). Mp: 209−211 °C. ^{1}H NMR (DMSO-d_6): δ 7.67 and 7.36 (2 s, 2 H, H-4, H-7), 7.01 (d, 1 H, NH, J = 7.3 Hz), 6.11 (d, 1 H, OH-3′, J = 3.6 Hz), 5.87 (d, 1 H, OH-2′, J = 4.2 Hz), 5.63 (d, 1 H, H-1′, J = 3.1 Hz), 4.21 (t, 1 H, H-2′, J = 3.6 Hz), 4.1 (m, 1 H, H-4′), 4.0 (m, 1 H, C*H*$(CH_3)_2$), 3.87 (t, 1 H, H-3′, J = 3.3 Hz), 1.24 (d, 3 H, H-5′,5″,5‴, J = 6.3 Hz), 1.20 (d, 6 H, CH(C*H*$_3)_2$, J = 6.5 Hz). Anal. ($C_{15}H_{19}O_3N_3Cl_2 \cdot {}^1/_{12}CH_2Cl_2$)[45] C, H, N.

1-(5-Deoxy-α-D-lyxofuranosyl)-5,6-dichloro-2-(isopropylamino)benzimidazole (18b). The procedure is the same as that described for **18a**, except **17b** was used instead of **17a**. All attempts to obtain **18b** as a solid free of dichloromethane by extended drying time and elevated drying temperatures, or by recrystallizing in another solvent, were unsuccessful. The TLC (cospots in solvent system 2) and proton spectrum were identical with that obtained for **18a**. Yield: 240 mg (79%) as a solid. Mp: 208−210 °C. Anal. ($C_{15}H_{19}O_3N_3Cl_2 \cdot {}^1/_{12}CH_2Cl_2$)[45] C, H, N.

Biological Evaluation. 1. Cell Culture Procedures. The routine growth and passage of KB, BSC-1, and HFF cells was performed in monolayer cultures using minimal essential medium (MEM) with either Hanks salts (MEM(H)) or Earle salts (MEM(E)) supplemented with 10% calf serum or 10% fetal bovine serum (HFF cells). The sodium bicarbonate concentration was varied to meet the buffering capacity required. Cells were passaged at 1:2 to 1:10 dilutions according to conventional procedures by using 0.05% trypsin plus 0.02% EDTA in a HEPES-buffered salt solution.[39]

2. Virological Procedures. The Towne strain, plaque-purified isolate P_o, of HCMV was kindly provided by Dr. Mark Stinski, University of Iowa; the AD169 strain was from Dr. William M. Shannon, Southern Research Institute. The KOS strain of HSV-1 was used in most experiments and was provided by Dr. Sandra K. Weller, University of Connecticut. Stock HCMV was prepared by infecting HFF cells at a multiplicity of infection (moi) of <0.01 plaque-forming units (pfu)/cell as detailed previously.[40] High-titer HSV-1 stocks were prepared by infecting KB cells at an moi of <0.1, also as detailed previously.[40] Virus titers were determined using monolayer cultures of HFF cells for HCMV and monolayer cultures of BSC-1 cells for HSV-1 as described earlier.[41] Briefly, HFF or BSC-1 cells were planted as described above in 96-well cluster dishes and incubated overnight at 37 °C. The next day cultures were inoculated with HCMV or HSV-1 and serially diluted 1:3 across the remaining 11 columns of the 96-well plate. After virus adsorption the inoculum was replaced with fresh medium, and cultures were incubated for 7 days for HCMV and for 2 or 3 days for HSV-1. Plaques were enumerated under 20-fold magnification in wells having the dilution which gave 5−20 plaques/well. Virus titers were calculated according to the following formula: titer (pfu/mL) = number of plaques × 5 × 3^n, where n represents the nth

dilution of the virus used to infect the well in which plaques were enumerated.

3. HCMV Plaque Reduction Assay. HFF cells in 24-well cluster dishes were infected with approximately 100 pfu of HCMV/cm^2 of cell sheet using the procedures detailed above. Following virus adsorption, compounds dissolved in growth medium were added to duplicate wells in four to eight selected concentrations. After incubation at 37 °C for 7 days, cell sheets were fixed and stained with crystal violet and microscopic plaques enumerated as described above. Drug effects were calculated as a percentage of reduction in number of plaques in the presence of each drug concentration compared to the number observed in the absence of drug.

4. HCMV Yield Assay. HFF cells were planted as described above in 96-well cluster dishes and incubated overnight, the medium was removed, and the cultures were inoculated with HCMV at an moi of 0.5−1 pfu/cell, as reported elsewhere.[41] After virus adsorption, inoculum was replaced with 0.2 mL of fresh medium containing test compounds. The first row of 12 wells was left undisturbed and served as virus controls. Each well in the second row received an additional 0.1 mL of medium with test compound at 3 times the desired final concentration. The contents of the 12 wells were mixed by repeated pipetting and then serially diluted 1:3 along the remaining wells. In this manner, six compounds could be tested in duplicate on a single plate with concentrations from 100 to 0.14 μM. Plates were incubated at 37 °C for 7 days, subjected to one cycle of freezing and thawing; aliquots from each of the eight wells of a given column were transferred to the first column of a fresh 96-well monolayer culture of HFF cells. Contents were mixed and serially diluted 1:3 across the remaining 11 columns of the secondary plate. Each column of the original primary plate was diluted across a separate plate in this manner. Cultures were incubated, plaques were enumerated, and titers were calculated as described above.

5. HSV-1 ELISA. An ELISA was employed[42] to detect HSV-1; 96-well cluster dishes were planted with 10 000 BSC-1 cells/well in 200 μL/well of MEM(E) plus 10% calf serum. After overnight incubation at 37 °C, selected drug concentrations in quadruplicate and HSV-1 at a concentration of 100 pfu/well were added. Following a 3-day incubation at 37 °C, medium was removed, plates were blocked and rinsed, and horseradish peroxidase conjugated rabbit anti-HSV-1 antibody was added. Following removal of the antibody-containing solution, plates were rinsed and then developed by adding 150 μL/well of a solution of tetramethylbenzidine as substrate. The reaction was stopped with H_2SO_4, and absorbance was read at 450 and 570 nm. Drug effects were calculated as a percentage of the reduction in absorbance in the presence of each drug concentration compared to absorbance obtained with virus in the absence of drug.

6. Cytotoxicity Assays. Two different assays were used for routine cytotoxicity testing: (i) Cytotoxicity produced in stationary HFF cells was determined by microscopic inspection of cells not affected by the virus used in plaque assays.[40] (ii) The effect of compounds during two population doublings of KB cells was determined by crystal violet staining and spectrophotometric quantitation of dye eluted from stained cells as described earlier.[43] Briefly, 96-well cluster dishes were planted with KB cells at 3000−5000 cells/well. After overnight incubation at 37 °C, test compound was added in quadruplicate at six to eight concentrations. Plates were incubated at 37 °C for 48 h in a CO_2 incubator, rinsed, fixed with 95% ethanol, and stained with 0.1% crystal violet. Acidified ethanol was added, and plates were read at 570 nm in a spectrophotometer designed to read 96-well ELISA assay plates.

7. Data Analysis. Dose−response relationships were constructed by linearly regressing the percent inhibition of parameters derived in the preceding sections against log drug concentrations. Fifty percent inhibitory concentrations (IC_{50}'s) or IC_{90}'s were calculated from the regression lines. Samples containing positive controls (acyclovir for HSV-1, ganciclovir for HCMV, and 2-acetylpyridine thiosemicarbazone for cytotoxicity) were used in all assays.

Acknowledgment. We thank Julie M. Breitenbach, Carolyn Oh, and Roger G. Ptak for expert performance of antiviral and cytotoxicity assays, Jack M. Hinkley for the synthesis of TCB and BDCB, and Ms. Marina Savic for preparation of the manuscript. These studies were supported by research Grant UOI-AI31718 from the National Institute of Allergy and Infectious Diseases and Research Agreement DRDA-942921 with Glaxo Wellcome Co.

References

(1) Alford, C. A.; Britt, W. J. Cytomegalovirus. In *The Human Herpesviruses*. Roizman, B., Whitley, R. J., Lopez, C., Eds.; Raven Press: New York, 1993; pp 227−255.

(2) Alford, C. A.; Stagno, S.; Pass, R. F.; Brit, W. J. Congenital and Perinatal Cytomegalovirus Infections in Bone Marrow Transplants. *Rev. Infect. Dis.* **1990**, *12*, s793−s804.

(3) Gallant, J. E.; Moore, R. D.; Richman, D. D.; Keruly, J.; Chaisson, R. E. Incidence and Natural History of Cytomegalovirus Disease in Patients with Advanced Immunodeficiency Virus Disease Treated with Zidovudine. *J. Infect. Dis.* **1992**, *166*, 1223−1227.

(4) Crumpacker, C. S. Ganciclovir. *N. Engl. J. Med.* **1996**, *335*, 721−729.

(5) Chrisp, P.; Clissold, S. P. Foscarnet. A Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Use in Immunocompromised Patients with Cytomegalovirus Retinitis. *Drugs* **1991**, *41*, 104−129.

(6) (a) Hitchcock, M. J.; Jaffe, H. S.; Martin, J. C.; Stagg, R. J. Cidofovir, a new agent with potent anti-herpesvirus activity. *Antiviral Chem. Chemother.* **1996**, *7*, 115−127. (b) Lalezari, J. P.; Drew, W. L.; Glutzer, E.; James, C.; Miner, D.; Flaherty, J.; Fisher, P. E.; Cundy, K.; Hannigan, J.; Martin, J. C.; Jaffe, H. S. (S)-1-[3-Hydroxy-2-(phosphonylmethoxy)propyl]cytosine (Cidofovir): Results of a Phase I/II Study of a Novel Antiviral Nucleotide Analogue. *J. Infect. Dis.* **1995**, *171*, 788−796.

(7) Field, A. K.; Biron, K. K. "The End of Innocence" Revisited: Resistance of Herpesviruses to Antiviral Drugs. *Clin. Microbiol. Rev.* **1994**, *7*, 1−13.

(8) Tamm, I.; Folkers, K.; Shunk, C. H.; Horsfall, F. L., Jr. Inhibition of Influenza Virus Multiplication by N.-Glycosides of Benzimidazoles. *J. Exp. Med.* **1954**, *99*, 227−250.

(9) (a) Bucknall, R. A. The Effects of Substituted Benzimidazoles on the Growth of Viruses and the Nucleic Acid Metabolism of Host Cells. *J. Gen. Virol.* **1967**, *1*, 89−99. (b) Tamm, I.; Sehgal, P. B. Halobenzimidazole Ribosides and RNA Synthesis of Cells and Viruses. *Adv. Virus Res.* **1978**, *22*, 187−258.

(10) Townsend, L. B.; Revankar, G. R. Benzimidazole Nucleosides, Nucleotides, and Related Derivatives. *Chem. Rev.* **1970**, *70*, 389−438.

(11) Townsend, L. B.; Devivar, R. V.; Turk, S. T.; Nassiri, M. R.; Drach, J. C. Design, Synthesis, and Antiviral Activity of Certain 2,5,6-Trihalo-1-(β-D-ribofuranosyl)benzimidazoles. *J. Med. Chem.* **1995**, *38*, 4098−4105.

(12) Zou, R.; Ayres, K. R.; Drach, J. C.; Townsend, L. B. Synthesis and Antiviral Activity of Certain Disubstituted Benzimidazole Ribonucleotides. *J. Med. Chem.* **1996**, *39*, 3477−3482.

(13) Zou, R.; Drach, J. C.; Townsend, L. B. Design, Synthesis, and Antiviral Evaluation of 2-Chloro-5,6-dihalo-1-β-D-ribofuranosylbenzimidazoles as Potential Agents for Human Cytomegalovirus Infections. *J. Med. Chem.* **1997**, *40*, 811−818.

(14) Zou, R.; Drach, J. C.; Townsend, L. B. Design, Synthesis, and Antiviral Evaluation of 2-Substituted 4,5-Dichloro- and 4,6-Dichloro-1-β-D-ribofuranosylbenzimidazoles as Potential Agents for Human Cytomegalovirus Infections. *J. Med. Chem.* **1997**, *40*, 802−810.

(15) Devivar, R. V.; Kawashima, E.; Revankar, G. R.; Breitenbach, J. M.; Kreske, E. D.; Drach, J. C.; Townsend, L. B. Benzimidazole Ribonucleosides: Design, Synthesis, and Antiviral Activity of Certain 2-(Alkylthio)- and 2-(Benzylthio)-5,6-dichloro-1-β-D-ribofuranosyl)benzimidazoles. *J. Med. Chem.* **1994**, *37*, 2942−2948.

(16) Saluja, S.; Zou, R.; Drach, J. C.; Townsend, L. B. Structure−Activity Relationship among 2-Substituted 5,6-Dichloro-, 4,6-Dichloro-, and 4,5-Dichloro-1-[(2-hydroxyethoxy)methyl]- and -1-[(1,3-dihydroxy-2-propoxy)methyl]benzimidazoles. *J. Med. Chem.* **1996**, *39*, 881−891.

(17) Gudmundsson, K. S.; Drach, J. C.; Wotring, L. L.; Townsend, L. B. Synthesis and Antiviral Activity of Certain 5′-Modified Analogues of 2,5,6-Trichloro-1-(β-D-ribofuranosyl)benzimidazole. *J. Med. Chem.* **1997**, *40*, 785−793.

(18) Drach, J. C.; Bush, P. M.; Ptak, R. G.; Devivar, R. V.; Townsend, L. B.; Davis, M. G.; Underwood, M. R.; Biron, K. K. Halogenated Benzimidazole 5′-Deoxyribonucleosides Are Potent and Selective Inhibitors of Human Cytomegalovirus Replication. Presented at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 1995.

(19) Townsend, L. B.; Drach, J. C.; Good, S. S.; DaLuge, S. M.; Martin, M. C. Therapeutic Nucleosides. U.S. Patent 5, 534, 535, 1996.
(20) Koszalka, G. W.; Chamberlain, S. D.; Harvey, R. J.; Frick, L. W.; Good, S. S.; Davis, M. L.; Smith, A.; Drach, J. C.; Townsend, L. B.; Biron, K. K. Benzimidazoles for the treatment of human cytomegalovirus infection. *Antiviral Res.* **1996**, *30*, A43.
(21) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. Nucleoside Synthesis with Trimethylsilyl Triflate and Perchlorate as Catalysts. *Chem. Ber.* **1981**, *114*, 1234−1255.
(22) Baker, B. R.; Joseph, J. P.; Schaub, R. E.; Williams, J. H. Puromycin Synthetic Studies. V. 6-Dimethylamino-9-(2′-acetylamino-β-D-glucopyranosyl)purine. *J. Org. Chem.* **1954**, *19*, 1786−1792.
(23) Guthrie, R. D.; Smith, S. C. An Improved Preparation of 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose. *Chem. Ind.* **1968**, 547−548.
(24) Kawashima, E.; Gupta, P. K.; Devivar, R. V.; Townsend, L. B. 2,5,6-Trichlorobenzimidazole. In *Nucleic Acid Chemistry, Part 4*; Townsend, L. B., Tipson, R. S., Eds.; John Wiley and Sons: New York, 1991; pp 24−26.
(25) Vorbrüggen, H.; Hofle, G. On the Mechanism of Nucleoside Synthesis. *Chem. Ber.* **1981**, *114*, 1256−1268.
(26) Harrison, D.; Ralph, J. T. Nucleophilic Substitution Reaction of 2-Chlorobenzimidazoles. Part 1. Formation of Benzimidazolin-2-ones and 2-Alkoxybenzimidazoles. *J. Chem. Soc.* **1965**, 236−239.
(27) Hulyalkar, R. K.; Perry, M. B. The Preparation of L-Lyxuronic acid, L-Lyxose, and 5-Deoxy-L-lyxose. *Can. J. Chem.* **1965**, *43*, 3241−3246.
(28) Lerner, L. M. Enantiomeric Forms of 9-(5-Deoxy-β-erythro-pent-4-enofuranosyl)adenine and a New Preparation of 5-Deoxy-D-lyxose. *Carbohydr. Res.* **1977**, *53*, 177−185.
(29) Snyder, J. R.; Serianni, A. S. Synthesis and NMR-Spectral Analysis of Unenriched and [1-^{13}C]-Enriched 5-Deoxypentoses and 5-*O*-Methylpentoses. *Carbohydr. Res.* **1987**, *163*, 169−188.
(30) Snyder, J. S.; Serianni, A. S. Furanose Ring Anomerization: A Kinetic Study of 5-Deoxypentoses and 5-*O*-Methylpentoses. *Carbohydr. Res.* **1988**, *184*, 13−25.
(31) Thomas, H. J.; Tiwari, K. N.; Clayton, S. J.; Secrist, J. A., III; Montgomery, J. A. Synthesis and Biological Activity of Purine 2′-Deoxy-2′-fluoro-ribonucleosides. *Nucleosides Nucleotides* **1994**, *13*, 309−323.
(32) Gold, A.; Sangaiah, R. 1,3,5-Tri-*O*-acetyl-2-deoxy-α,β-D-*erythro*-pentofuranose from 2-Deoxy-D-*erythro*-pentose. *Nucleosides Nucleotides* **1990**, *9*, 907−912.
(33) Cimpoia, A. R.; Hunter, P. J.; Evans, C. A.; Jin, H.; Breining, T.; Mansour, T. S. On the Conversion of Arabino- and Ribofuranosyl Methyl Glycosides to Their 1-*O*-Acetyl Derivatives. *J. Carbohydr. Chem.* **1994**, *13*, 1115−1119.
(34) Bischofberger, K.; Hall, R. H. Acetolysis: The Formation of Acyclic Byproducts. *Carbohydr. Res.* **1975**, *42*, 175−179.
(35) Magnani, A.; Mikuriya, Y. 9-α-D-Xylofuranosyladenine. Acetolysis of 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-xylofuranose. *Carbohydr. Res.* **1973**, *28*, 158−164.
(36) Gosselin, G.; Puech, F.; Genu-Dellac, C.; Imbach, J.-L. 1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-fluoro-D-xylofuranose. A Versatile Precursor for the Synthesis of 3-Deoxy-3-fluoro-β-D-xylofuranosyl Nucleosides as Potential Antiviral Agents. *Carbohydr. Res.* **1993**, *42*, 175−179.
(37) Rosemeyer, H.; Toth, G.; Seela, F. Assignment of Anomeric Configuration of D-Ribo-Arabino-2′-Deoxyribo-, and 2′,3′-Dideoxyribonucleotides by NOE Difference Spectroscopy. *Nucleosides Nucleotides* **1989**, *8*, 587−597.
(38) Kam, B. L.; Barascut, J.-L.; Imbach, J.-L. A General Method of Synthesis and Isolation, and an NMR-Spectroscopic Study, of Tetra-*O*-acetyl-D-aldopentofuranoses. *Carbohydr. Res.* **1979**, *69*, 135−142.
(39) Shipman, C., Jr.; Smith, S. H.; Carlson, R. H.; Drach, J. C. Antiviral Activity of Arabinofuranosyladenine and Arabinofuranosylhypoxanthine in Herpes Simplex Virus-Infected KB Cells. I. Selective Inhibition of Viral DNA Synthesis in Synchronized Suspension Cultures. *Antimicrob. Agents Chemother.* **1976**, *9*, 120−127.
(40) Turk, S. R.; Shipman, C., Jr.; Nassiri, M. R.; Genzingler, G.; Krawczyk, S. H.; Townsend, L. B.; Drach, J. C. Pyrrolo[2,3-*d*]-pyrimidine Nucleosides as Inhibitors of Human Cytomegalovirus. *Antimicrob. Agents Chemother.* **1987**, *31*, 544−550.
(41) Prichard, M. N.; Turk, S. R.; Coleman, L. A.; Engelhardt, S. L.; Shipman, C., Jr.; Drach, J. C. A Microtiter Virus Yield Reduction Assay for the Evaluation of Antiviral Compounds Against Human Cytomegalovirus and Herpes Simplex Virus. *J. Virol. Methods* **1990**, *28*, 101−106.
(42) Prichard, M. N.; Shipman, C., Jr. A Three-Dimensional Model to Analyze Drug-Drug Interactions. *Antiviral Res.* **1990**, *14*, 181−206.
(43) Prichard, M. N.; Prichard, L. E.; Baguley, W. A.; Nassiri, M. R.; Shipman, C., Jr. Three-Dimensional Analysis of the Synergistic Cytotoxicity of Ganciclovir and Zidovudine. *Antiviral Res.* **1991**, *35*, 1060−1065.
(44) Unpublished data from our laboratory.
(45) Integration of the dichloromethane singlet and the anomeric proton of **18a**,**b** (^{1}H NMR) confirmed that 1 mol of dichloromethane was present for every 12 mol of **18**.

JM970545C