Synthesis and Antiviral Activity of Certain 5′-Modified Analogs of 2,5,6-Trichloro-1-(β-D-ribofuranosyl)benzimidazole

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A series of 5′-modified 2,5,6-trichlorobenzimidazole ribonucleosides has been synthesized and tested for activity against two human herpesviruses and for cytotoxicity. The 5′-methoxy, 5′-ethoxy, and 5′-butoxy analogs of 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) were prepared by coupling the appropriate 5-*O*-alkyl-1,2,3-tri-*O*-acetyl-β-D-ribose derivatives with 2,5,6-trichlorobenzimidazole followed by removal of the protecting groups. The 5′-deoxy-5′-fluoro, -5′-chloro, -5′-bromo, -5′-iodo, -5′-azido, and -5′-thiomethyl derivatives were synthesized in a similar fashion. All of these 5′-modified derivatives had significant activity against HCMV in plaque and yield reduction assays (IC_{50}'s = 0.5−14.2 μM) but had little activity (IC_{50}'s > 100 μM) against HSV-1. This pattern is similar to the antiviral activity profile observed for TCRB. The 5′-halogenated derivatives were more active than the other 5′-modified derivatives with antiviral activity well separated from cytotoxicity. In general, cytotoxicity of all the 5′-modified derivatives was greater in human foreskin fibroblasts (HFF cells) than in L1210 or KB tumor cells. These results indicate that the viral target tolerates significant modifications of TCRB at the 5′-position without adversely affecting activity against HCMV, whereas the 5′-modifications increased cytotoxicity in human diploid cells.

Introduction

Human cytomegalovirus (HCMV) is one of eight human herpesviruses. It is estimated that by adulthood, more than one-half of all Americans will have been infected with HCMV.[1] HCMV infections in immunocompetent individuals are usually asymptomatic. However, in immunocompromised patients, HCMV infections are often life-threatening. Transplant recipients[2] and individuals with acquired immune deficiency syndrome (AIDS)[3] are particularly vulnerable to these infections. HCMV is also a leading cause of birth defects as a consequence of fetal infection *in utero*.[4] Currently, there are three FDA-approved drugs available for the treatment of HCMV infections: ganciclovir (**1**),[5] foscarnet (**2**),[6] and cidofovir (**3**).[7] Unfortunately, all three drugs can produce significant side effects and have limited oral bioavailability. Moreover virus strains resistant to each of these drugs are emerging.[8] Consequently, there is a need for a more potent and selective antiviral drug to treat HCMV infections.

As part of our search for new anticancer[9] and antiviral drugs,[10,11] a number of benzimidazole nucleosides have been synthesized. Certain compounds, including 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB, **4**) (Figure 1), show potent activity against HCMV with low cellular toxicity at concentrations which inhibit viral growth.[10] Biological evaluation of TCRB has established that its antiviral activity does not involve inhibition of DNA, RNA, or protein synthesis.[12] It appears to act by a unique mechanism, which involves inhibition of viral DNA processing and virus assembly,[13] but the exact viral target is unknown.

Structure−activity relationship studies involving derivatives of **4**, modified in either the heterocycle or carbohydrate moiety, have been undertaken in our laboratory.[9−11,14] We now describe studies on the effect that 5′-modifications of **4** have on antiviral activity and selectivity.

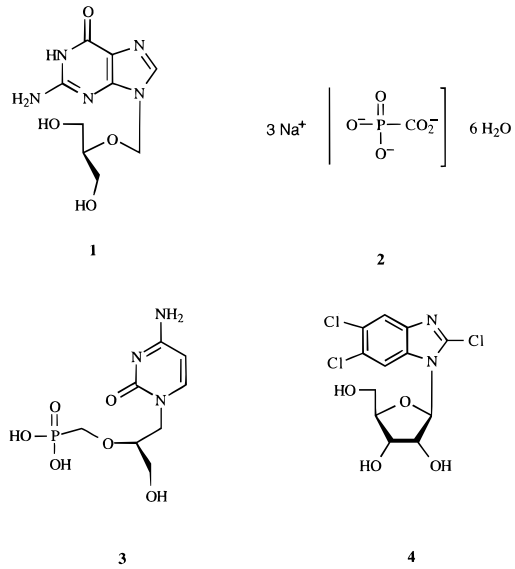

Figure 1. Structures of ganciclovir (**1**), foscarnet (**2**), cidofovir (**3**), and TCRB (**4**).

Results and Discussion

Chemistry. Preparation of the desired 5′-*O*-alkylated nucleosides via 5′-tosylation or 5′-mesylation of a suitably protected derivative of **4**, followed by nucleophilic displacement, can not be used due to the lability of the chlorine at C-2 of the benzimidazole moiety. Thus, we initiated research into an alternative route for their preparation. Methyl 5-*O*-alkyl-2,3-*O*-isopropylidene-D-ribofuranoside derivatives **5a**−**c** were synthesized as described in the literature.[15] Compounds

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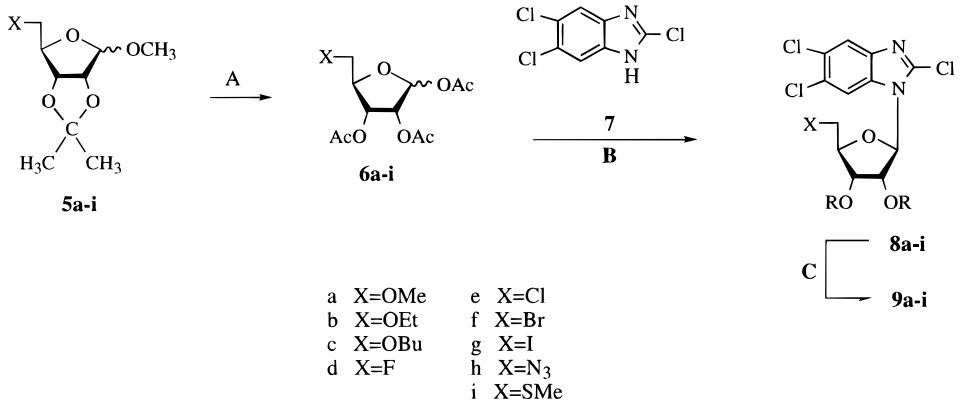
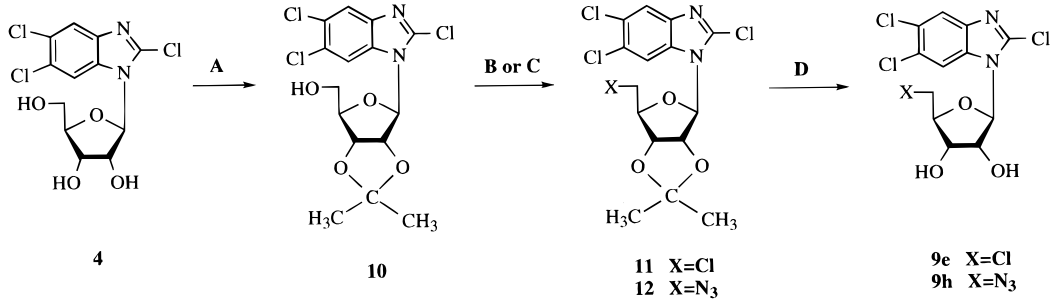
Scheme 1[a]



[a] (A) (1) 0.04 N HCl, reflux, (2) Ac_2O, pyridine; (B) (1) bis(trimethylsilyl)acetamide (BSA), CH_3CN, (2) **6a**−**i**, trimethylsilyl trifluoromethanesulfonate (TMSOTf), CH_3CN; (C) Na_2CO_3, aq EtOH.

Scheme 2[a]



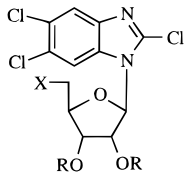
[a] (A) Acetone, 2,2-dimethoxypropane, Dowex 50 H^+; (B) PPh_3, CCl_4, CH_3CN; (C) diethyl azodicarboxylate, PPh_3, diphenyl phosphorazidate, THF; (D) 2 N HCl, THF.

5a−**c** were subsequently converted to the 1,2,3-tri-*O*-acetyl-5-*O*-alkyl-D-ribofuranose derivatives **6a**−**c** by removing the isopropylidene and methoxy groups in dilute hydrochloric acid followed by acetylation with acetic anhydride in pyridine. The carbohydrate derivatives **6a**−**c** were isolated in good yields as anomeric mixtures which contained 5−10% of the α-anomer as determined by ^{1}H-NMR. Compounds **6a**−**c** were coupled with 2,5,6-trichlorobenzimidazole (**7**) using modified Vorbruggen conditions[16] to give exclusively 2,5,6-trichloro-1-(2,3-di-*O*-acetyl-5-*O*-alkyl-*β*-D-ribofuranosyl)benzimidazoles **8a**−**c** in high yields. The protected nucleosides **8a**−**c** were treated with sodium carbonate in aqueous ethanol to give the desired 2,5,6-trichloro-1-(5-*O*-alkyl-*β*-D-ribofuranosyl)benzimidazoles **9a**−**c** (Scheme 1).

We envisioned two different routes for the synthesis of the 2,5,6-trichloro-1-(5-deoxy-5-halogeno-*β*-D-ribofuranosyl)benzimidazoles **9d**−**g**. The first route involved protection of the 2′- and 3′-OH groups of TCRB (**4**) followed by a replacement of the 5′-OH group with an appropriate halogen. In the second route, an appropriate 1,2,3-tri-*O*-acetyl-5-deoxy-5-halogeno-*β*-D-ribofuranose was synthesized and subsequently coupled to the heterocycle **7** under Vorbruggen conditions. Following the first route, the 2,5,6-trichloro-1-(5-chloro-5-deoxy-*β*-D-ribofuranosyl)benzimidazole (**9e**) was synthesized in three steps from **4**. Isopropylidene protection of **4** gave 2,5,6-trichloro-1-(2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)-benzimidazole (**10**). Chlorination of **10** using carbon tetrachloride and triphenylphosphine yielded **11**, which upon acidic deprotection gave **9e** (Scheme 2). Following the second route, derivative **9e** was synthesized in four steps from methyl 5-chloro-5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranoside (**5e**).[17] Compound **5e** was converted into 1,2,3-tri-*O*-acetyl-5-chloro-5-deoxy-*β*-D-ribofuranose (**6e**), and coupled to the heterocycle **7** to give 2,5,6-trichloro-1-(2,3-di-*O*-acetyl-5-chloro-5-deoxy-*β*-D-ribofuranose)benzimidazole (**8e**), which upon deprotection gave **9e**. Thus, the second approach used methodology similar to the one used for the 5′-*O*-alkyl-TCRB derivatives **9a**−**c**. We elected to synthesize the other 5′-halogeno derivatives (**9d**,**f**,**g**) using the second approach. In this highly convergent approach, **7** is coupled to the halogenated carbohydrate precursors **6d**−**g** at the end of the synthesis, and by using this approach, there is no risk of undesired halogen exchange at the C-2 position of the benzimidazole moiety. We synthesized methyl 5-deoxy-5-fluoro-2,3-*O*-isopropylidene-D-ribofuranoside (**5d**),[18] methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranoside (**5f**),[19] and methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-D-ribofuranoside (**5g**)[20] as described in the literature. These compounds were deprotected and acetylated to give 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-*β*-D-ribofuranose (**6d**),[18] 1,2,3-tri-*O*-acetyl-5-bromo-5-deoxy-*β*-D-ribofuranose (**6f**), and 1,2,3-tri-*O*-acetyl-5-deoxy-5-iodo-*β*-D-ribofuranose (**6g**)[21] which were coupled with **7** and deprotected as described above to give **9d**,**f**,**g** in high yields.

Finally, we synthesized 2,5,6-trichloro-1-(5-deoxy-5-(methylthio)-*β*-D-ribofuranosyl)benzimidazole (**9i**) and 2,5,6-trichloro-1-(5-azido-5-deoxy-*β*-D-ribofuranosyl)benzimidazole (**9h**). Compound **9h** was synthesized by two different routes. 1,2,3-Tri-*O*-acetyl-5-azido-5-deoxy-*β*-D-ribofuranose (**6h**)[22] was coupled with **7** to give 2,5,6-trichloro-1-(2,3-di-*O*-acetyl-5-azido-5-deoxy-*β*-D-ribofuranosyl)benzimidazole (**8h**). Subsequent deprotection of **8h** gave **9h**. Compound **9h** was also synthesized from **4** via the isopropylidene-protected derivative **10** using

Table 1. Antiviral Activity and Cytotoxicity of 5′-Modified Trichlorobenzimidazole Ribonucleosides



			50% or 90% inhibitory concentration (μM)				
			antiviral activity				
	substituent		HCMV[a]		HSV-1[b]	cytotoxicity[c]	
compd no.	R	X	plaque[d]	yield	ELISA	visual[d]	growth
8a	Ac	OMe	2.8		>100[e]	26	80
8b	Ac	OEt	4.3		>100	33	60
8c	Ac	OBu	21		>100	66	>100
8d	Ac	F	0.6	0.19	>100	32	100
8e	Ac	Cl	1.4	0.31	>100	32	90
8f	Ac	Br	2.7		>100	32	60
8g	Ac	I	2.7		>100	32	60
8h	Ac	N_3	1.5		>100	32	70
8i	Ac	SMe	4.8		>100	32	>100
9a	H	OMe	3.0	2.0	>100	32	90
9b	H	OEt	4.6		>100	26	80
9c	H	OBu	14.2		>100	32	60
9d	H	F	0.5	0.22	>100	32	>100
9e	H	Cl	1.0	0.52[d]	>100	32	90
9f	H	Br	1.5	0.50	>100	32	90
9g	H	I	3.2		>100	32	
9h	H	N_3	1.5	0.60	>100	32	70
9i	H	SMe	4.5		>100	32	>100
11	$C(CH_3)_2$[f]	Cl	14		>100	32	100
12	$C(CH_3)_2$[f]	N_3	11			32	
4 (TCRB)[g]	H	OH	2.8 ± 0.8	1.3 ± 0.8	102	238	210
1 (ganciclovir)[h]	na[i]	na	7.4 ± 6.5	1.6 ± 1.2	3.5 ± 2.1	>100	>100

[a] Plaque and yield reduction assays were performed using the Towne strain of HCMV 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] All compounds were assayed by ELISA in quadruplicate wells. [c] Visual cytotoxicity was scored on HFF cells at the time of plaque enumeration. Inhibition of KB cell growth was determined as described in the text in quadruplicate assays. Results are presented as IC_{50}'s. [d] Averaged results from duplicate or triplicate experiments. [e] >100 μM indicates IC_{50} not reached at the noted (highest) concentration tested. [f] Compounds **10** and **11** are 2,3-*O*-isopropylidene derivatives. [g] Reported as compound **9** in ref 11; averages ± SD from 5 and 15 experiments. [h] Averages ± SD derived from 108, 33, and 3 experiments, respectively, in which ganciclovir was used as a positive control. [i] na: not applicable.

Mitsunobo conditions. The reaction of **10** with triphenylphosphine, diethyl azodicarboxylate, and diphenyl phosphorazidate[23,24] gave 2,5,6-trichloro-1-(5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)benzimidazole (**12**) which was then deprotected under acidic conditions to give **9h**. To prepare **9i**, 1,2,3-tri-*O*-acetyl-5-deoxy-5-(methylthio)ribofuranose (**6i**) was prepared as described by Montgomery et al.[25] and then coupled with **7** to give, after deprotection, **9i** as the only anomer.

Condensation of the 2′,3′-*O*-acetylated carbohydrate derivatives **6a**−**i** with **7** under Vorbruggen conditions was employed to obtain the benzimidazole nucleosides **8a**−**i**. In accord with Baker's rule,[26] due to 2′-*O*-acetyl participation during the condensation, the desired β-anomers (*trans* 1′-H and 2′-H) were obtained as the only isolated products. Compounds **9e**,**h** were synthesized from **4** (through the isopropylidene derivative **10**) as well as with a Vorbruggen coupling reaction. The fact that both routes gave the same final products as determined by ^{1}H-NMR shows that compounds **9e**,**h** both have the β-configuration. Comparison of chemical shifts and coupling constants then substantiates the assignment of **9a**−**d**,**f**,**g**,**i** as the β-anomers.

Biology. This series of compounds was evaluated for activity against HCMV and HSV-1 as well as for cytotoxicity (Table 1). The 5′-*O*-alkyl benzimidazole nucleosides **8a**−**c** and **9a**−**c** showed good activity against HCMV. Several of these compounds had activity similar to the lead compound TCRB (**4**) and thus were more active than ganciclovir or foscarnet in plaque reduction assays. The activity decreased with an increase in the size of the alkyl group, from methyl (**9a**) to butyl (**9c**).

The 5′-halogenated derivatives **8d**−**g** and **9d**−**g** were somewhat more active against HCMV than TCRB (**4**) in plaque reduction assays. Compound **9g** was also tested against the AD169 strain of HCMV. Activity in a plaque reduction assay (IC_{50} = 2.9 μM) was nearly identical with that obtained with the Towne strain (IC_{50} = 3.2 μM, Table 1). Results from the yield reduction assays established more firmly that the 5′-halogenated analogs were more active than TCRB (**4**) and ganciclovir. Like TCRB none of the 5′-modified analogs were active against HSV-1. Antiviral activity was nearly the same for the di-*O*-acetates **8a**−**i** compared to the ribosides **9a**−**i**. We speculate this was due to deacetylation of **8a**−**i** by serum esterases in the cell culture medium. There were only small differences in activity against HCMV among the different 5′-halogenated derivatives, indicating that neither the electronegativity nor the size of the 5′-substituent had a major effect on the activity of these benzimidazole nucleosides. Substitution of the 5′-hydroxyl with azide (**9h**) or thiomethyl (**9i**) did not markedly affect activity since both compounds had activity against HCMV comparable to TCRB (**4**).

Compounds **8a**−**i** and **9a**−**i** were more cytotoxic than TCRB in HFF cells, but in every case cytotoxicity was

Table 2. Antiproliferative Activity of Several 5′-Modified Trichlorobenzimidazole Ribonucleosides against L1210 Murine Leukemia Cells *in Vitro*

compd no.	initial screen conctn (μM)	initial screen (% of control)[a]	IC_{50} (μM)[b]
8a	1	95	*c*
8b	10	83	>10[d]
8c	10	92	*c*
8d	10	122	*c*
8e	10	96	*c*
8f	100	94	*c*
8h	10	110	*c*
9a	100	4	60
9b	100	9	59
9c	100	64	>100
9d	100	81	>100
9e	100	73	>100
9f	100	54	100
9h	100	29	80
9i	100	73	>100
4 (TCRB)	100	76	>100

[a] The effect of each compound at the initial screen concentration on the growth rate or L1210 cells. [b] IC_{50} is the concentration required to decrease the cell density in the treated cultures to one-half of the control. [c] No significant growth inhibition observed at the initial screen concentration, which was the highest concentration tested. [d] The highest concentration tested.

separated from antiviral activity. Because the compounds appeared to be somewhat more cytotoxic by visual inspection of normal cells (diploid HFF cells) than in cancer cells (KB and L1210 cells; see Tables 1 and 2), the effect of the most active compound (**9d**) on the growth of HFF and KB cells was determined. Figure 2 shows that compound **9d** did not affect the growth of either HFF or KB cells at concentrations up to 30 μM. A 100 μM concentration inhibited the growth of both cell lines; consistent with the screening results in Tables 1 and 2, growth of HFF cells was inhibited to a greater extent.

Together these results firmly establish that compound **9d** has highly selective activity against HCMV. The data further indicate that the HCMV receptor for TCRB tolerates significant modification in bulk and electronegativity at the 5′-position without adversely affecting antiviral activity. The results also are consistent with our initial reports that the 5′-deoxy analog of TCRB is more active than TCRB itself.[27]

Experimental Section

General Chemical Procedures. Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 360 or 300 MHz with a Bruker WP 360 SY or 300 SY instrument. The chemical shift values are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. IR spectra were obtained on a Nicolet 5DXB FT-IR spectrophotometer. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, University of Michigan. Flash column chromatography was performed using silica gel 60, 230−400 mesh (ICN), and the technique described by Still et al.[28] Thin layer chromatography (TLC) was performed on prescored silica gel GHLF plates (Analtech, Newark, DE). Compounds were visualized by illumination under UV light (254 nm) or by spraying with 20% methanolic sulfuric acid followed by charring on a hot plate. Evaporations were carried out under reduced pressure (water aspirator) with water bath temperatures below 40 °C unless otherwise specified. All solvents were dried prior to use as described by the handbook *Purification of Laboratory Chemicals*[29] and stored over 4 Å sieves, under argon. Materials obtained from commercial suppliers were used without purification.

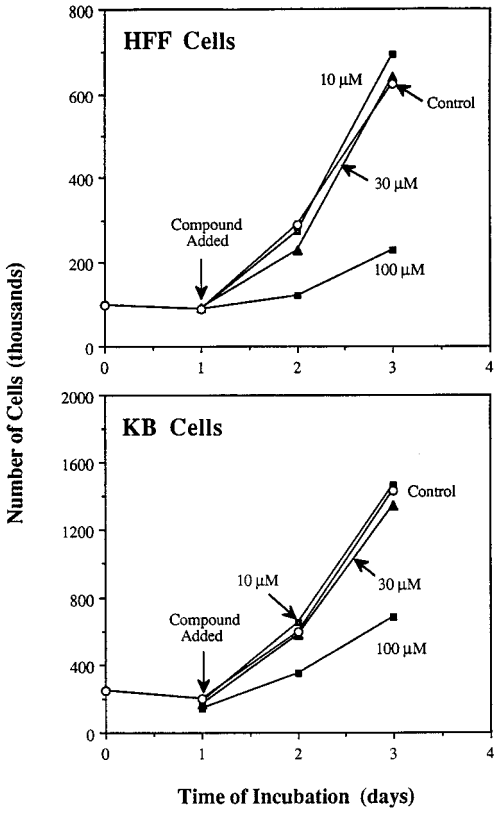


Figure 2. Effect of compound **9d** on the proliferation of human foreskin fibroblasts (HFF cells) and KB cells. Cultures of cells were planted and incubated for 24 h; medium was removed and replaced with medium containing no drug or compound **9d** at the indicated concentrations. Duplicate cultures were harvested at the times shown, and the number of cells was determined.

General Procedure for the Synthesis of 6a−i. To the methyl 2,3-*O*-isopropylideneriboside derivatives **5a−i** (0.02 mol) was added 0.04 N HCl (50 mL), and the emulsion that formed upon stirring was heated at reflux for 2 h. This mixture was cooled to room temperature. Amberlyst ion exchange resin, 47-OH^- form, was added to the mixture until a pH of 7 was reached. The resin was removed by filtration and washed with water (300 mL). The resulting aqueous solution was concentrated to a syrup under reduced pressure. This syrup was dissolved in dry pyridine (50 mL), and acetic anhydride (12.3 mL, 0.12 mol) was added. The reaction mixture was stirred for 24 h at ambient temperature. Then the reaction mixture was poured into ice-cold saturated aqueous bicarbonate (200 mL) and the acetylated sugar extracted into $CHCl_3$ (3 × 100 mL). The organic phase was washed with water (2 × 100 mL), dried over magnesium sulfate, and filtered, and the solvent was removed *in vacuo* to give **6a−i** as syrups which were purified as described for each compound below.

1,2,3-Tri-*O*-acetyl-5-*O*-methyl-D-ribofuranose (6a). Methyl 2,3-*O*-isopropylidene-5-*O*-methyl-D-ribofuranoside (**5a**; 2.15 g, 0.01 mol) gave, after deprotection, acetylation, and workup as described above, a brown oil which was purified by flash chromatography (EtOAc/hexane, 1:1, 5 cm × 20 cm). Elution yielded initially the pure β-anomer of **6a** which was followed by a mixture of the α- and β-anomers (as determined by ^{1}H-NMR, where the signal from the 1-H for the β-anomer was upfield (6.00 ppm) from the signal from the 1-H for the α-anomer (6.28 ppm)). Fractions containing the pure β-anomer were pooled and evaporated to dryness to give 1.4 g (48%) of β-**6a** as a transparent syrup. Subsequent fractions were combined and concentrated to dryness to give 1.2 g (40%) of a 1:3 mixture of α- and β-anomers of **6a** as a syrup. β-**6a**: R_f 0.71 (EtOAc/hexane, 1:2); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.00 (s, 1H, 1-H), 5.21 (m, 2H, 2-H, 3-H), 4.22 (m, 1H, 4-H), 3.50

(m, 2H, 5-H), 3.28 (s, 3H, CH_3), 2.00−2.11 (m, 9H, acetyls). Anal. ($C_{12}H_{18}O_8$) C, H.

1,2,3-Tri-*O*-acetyl-5-*O*-ethyl-D-ribofuranose (6b). Methyl 5-*O*-ethyl-2,3-*O*-isopropylidene-D-ribofuranoside (**5b**; 2.3 g, 0.01 mol) gave, after deprotection, acetylation, and workup as described in the general procedure, a dark brown syrup. This syrup was chromatographed on a silica gel column (EtOAc/hexane, 1:2, 5 cm × 20 cm). Elution yielded initially the pure β-anomer of **6b** which was followed by a mixture of α- and β-anomers (as determined by ^{1}H-NMR, where the signal from the 1-H for the β-anomer was upfield (6.00 ppm) from the signal from the 1-H for the α-anomer (6.27 ppm)). Fractions containing the pure β-anomer were pooled and evaporated to dryness to give 1.3 g (44%) of the β-anomer of **6b** as a transparent syrup. Subsequent fractions were combined and concentrated to dryness to give 1.4 g (43%) of a 1:3 mixture of α- and β-anomers as a syrup. A small amount of the β-anomer was crystallized out of MeOH for analytical purposes. β-**6b**: mp 58−60 °C; R_f 0.50 (EtOAc/hexane, 1:2), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.00 (s, 1H, 1-H), 5.23 (m, 2H, 2-H, 3-H), 4.20 (m, 1H, 4-H), 3.42−3.55 (m, 2H, 5-H, OCH_2), 2.00−2.11 (m, 9H, acetyls), 1.09 (t, 3H, CH_3). Anal. ($C_{13}H_{20}O_8$) C, H.

1,2,3-Tri-*O*-acetyl-5-*O*-butyl-D-ribofuranose (6c). Methyl 5-*O*-butyl-2,3-*O*-isopropylidene-D-ribofuranoside (**5c**; 5.4 g, 0.02 mol) gave, after deprotection, acetylation, and workup as described in the general procedure, a yellow syrup. This syrup was purified by flash chromatography (EtOAc/hexane, 1:2, 5 cm × 20 cm). Elution yielded initially the pure β-anomer of **5c**, which was followed by a mixture of the α- and β-anomers (as determined by ^{1}H-NMR, where the signal from the 1-H for the β-anomer was upfield (6.00 ppm) from the signal from the 1-H for the α-anomer (6.28 ppm)). Fractions containing the pure β-anomer were pooled and evaporated to dryness to give 1.0 g (14%) of β-**6c** as a transparent syrup. Subsequent fractions were combined and concentrated to dryness to give 4.2 g (64%) of a 1:9 mixture of the α- and β-anomers as a white syrup. β-**6c**: R_f 0.31 (EtOAc/hexane, 1:2); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.00 (s, 1H, 1-H), 5.26−5.18 (m, 2H, 2-H, 3-H), 4.21 (m, 1H, 4-H), 3.52−3.39 (m, 2H, 5-H, OCH_2), 1.98−2.11 (m, 9H, acetyls), 1.45 (m, 2H, CH_2), 1.31 (m, 2H, CH_2), 0.87 (t, 3H, CH_3). Anal. ($C_{15}H_{24}O_8$) C, H.

1,2,3-Tri-*O*-acetyl-5-chloro-5-deoxy-β-D-ribofuranose (6e). Methyl 5-chloro-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranoside (**5e**; 3.0 g, 0.018 mol) gave, after deprotection, acetylation, workup, and crystallization of the reaction mixture from MeOH, 2.7 g (50%) yield of the pure β anomer of **6e** as a white crystalline solid: mp 81−82 °C; R_f 0.65 (EtOAc/hexane, 1:2); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.02 (s, 1H, 1-H), 5.24−5.31 (m, 2H, 2-H, 3-H), 4.38 (m, 1H, 4-H), 3.89 (dd, 1H, 5-H), 3.78 (dd, 1H, 5-H), 2.10 (s, 3H, acetyl), 2.07 (s, 3H, acetyl), 2.04 (s, 3H, acetyl). Anal. ($C_{11}H_{15}ClO_7$) C, H.

1,2,3-Tri-*O*-acetyl-5-bromo-5-deoxy-β-D-ribofuranose (6f). Methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranoside (**5f**; 4 g, 0.01 mol) gave, after deprotection, acetylation, workup, and crystallization of the reaction mixture from MeOH, 1.5 g (44%) of the pure β-anomer of **5f** as a white crystalline solid: mp 96−97 °C; R_f 0.70 (EtOAc/hexane, 1:2); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 6.03 (s, 1H, 1-H), 5.26 (m, 2H, 2-H, 3-H), 4.37 (m, 1H, 4-H), 3.75 (dd, 1H, 5-H), 3.66 (dd, 1H, 5-H), 2.04−2.10 (m, 9H, acetyls). Anal. ($C_{11}H_{15}BrO_7$) C, H.

General Procedure for the Synthesis of the Diacetylated Benzimidazole Ribose Derivatives 8a−i. Compound **7** (1 equiv) was placed in a flame-dried flask under an argon atmosphere. Dry CH_3CN and BSA (2 equiv) were added, and the reaction mixture was stirred at room temperature for 30 min. The appropriate carbohydrate (**6a−i**, 1 equiv) dissolved in dry CH_3CN was added to the reaction mixture via a canula. Finally TMSOTf (1.2 equiv) was added, and the reaction mixture was stirred at room temperature for 15 min. Saturated $NaHCO_3$ was added to quench the reaction and the resulting mixture extracted with EtOAc. The combined organic fractions were washed with saturated NaCl solution, decolorized with charcoal, dried over magnesium sulfate, filtered, and evaporated to dryness. The syrup or solid obtained was purified as described for each individual compound below.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-*O*-methyl-β-D-ribofuranosyl)benzimidazole (8a). Compound **6a** (0.75 g, 3.4 mmol) was coupled to **7** (0.8 g, 3.6 mmol) under Vorbruggen conditions to give after workup a solid which was purified by flash chromatography (EtOAc/hexane, 1:1, 2 cm × 15 cm). The fractions that contained a UV active product, which charred upon H_2SO_4 spraying, were pooled and evaporated to dryness to afford, after recrystallization from MeOH, 0.92 g (60%) of **8a** as a white crystalline solid: mp 150−151 °C; R_f 0.51 (EtOAc/hexane, 1:1), R_f 0.67 (EtOAc/hexane, 5:1); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H, C_7-H), 8.00 (s, 1H, C_4-H), 6.19 (d, 1H, 1′-H, $J_{1',2'} = 7.0$ Hz), 5.45 (m, 2H, 2′-H, 3′-H), 4.44 (m, 1H, 4′-H), 3.75 (m, 2H, 5′-H), 3.52 (s, 3H, OCH_3), 2.16 (s, 3H, acetyl), 1.98 (s, 3H, acetyl). Anal. ($C_{17}H_{17}Cl_3N_2O_6$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-*O*-ethyl-β-D-ribofuranosyl)benzimidazole (8b). Compound **6b** (1.2 g, 3.9 mmol) was coupled with **7** (0.87 g, 3.9 mmol) under Vorbruggen conditions to give after workup as described above a solid. This solid was purified by flash chromatography (EtOAc/hexane, 1:1, 4 cm × 15 cm). The fractions that contained a UV active product, which charred upon H_2SO_4 spraying, were pooled and evaporated to dryness to afford, after recrystallization from MeOH, 2 g (78%) of **8b** as a white crystalline solid: mp 125−126 °C; R_f 0.42 (EtOAc/hexane, 1:1), R_f (EtOAc/hexane, 5:1); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.27 (s, 1H, C_7-H), 7.99 (s, 1H, C_4-H), 6.19 (d, 1H, 1′-H, $J_{1',2'} = 6.7$ Hz), 5.45 (m, 2H, 2′-H, 3′-H), 4.44 (m, 1H, 4′-H), 3.55−3.84 (m, 2H, 5′-H, OCH_2CH_3), 2.16 (s, 3H, acetyl), 1.99 (s, 3H, acetyl), 1.28 (t, 1H, OCH_2CH_3). Anal. ($C_{18}H_{19}Cl_3N_2O_6$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-*O*-butyl-β-D-ribofuranosyl)benzimidazole (8c). Compound **6c** (2 g, 6.0 mmol) was coupled with **7** (1.2 g, 5.4 mmol) under Vorbruggen conditions to give after workup as described above a viscous syrup. This syrup was purified by flash chromatography (EtOAc/hexane, 1:1, 4 cm × 15 cm). The fractions that contained a UV active product, which charred upon H_2SO_4 spraying, were pooled and evaporated to dryness to afford, after recrystallization from MeOH, 1.5 g (55%) of **8c** as a white crystalline solid: mp 143−144 °C; R_f 0.47 (EtOAc/hexane, 1:1), R_f 0.69 (EtOAc/hexane, 5:1); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 1H, C_7-H), 7.97 (s, 1H, C_4-H), 6.19 (d, 1H, 1′-H, $J_{1',2'} = 7.0$ Hz), 5.44 (m, 2H, 2′-H, 3′-H), 4.43 (m, 1H, 4′-H), 3.49−3.83 (m, 2H, 5′-H, OCH_2R), 2.15 (s, 3H, acetyl), 1.98 (s, 3H, acetyl), 1.65 (m, 2H, $OCH_2CH_2CH_2$R), 1.40 (m, 2H, OCH_2-CH_2CH_2R), 0.89 (t, 3H, -CH_3). Anal. ($C_{20}H_{23}Cl_3N_2O_6$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)benzimidazole (8d). Compound **6d** (0.9 g, 3.2 mmol) was coupled to **7** (0.8 g, 3.6 mmol) under Vorbruggen conditions. The reaction mixture was worked up as described in the general procedure and gave, after crystallization from MeOH, 1.2 g (87%) of **8d** as a white crystalline solid: mp 128−129 °C; R_f 0.70 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.04 (d, 1H, C_7-H, $J_{C7,F} = 1.9$ Hz, long range coupling to F), 8.02 (s, 1H, C_4-H), 6.28 (d, 1H, 1′-H, $J_{1',2'} = 6.6$ Hz), 5.46−5.55 (m, 2H, 2′-H, 3′-H), 4.87 (dm, 2H, 5′-H, $J_{5,F} = 47$ Hz, $J_{4',5'} = 3.6$ Hz), 4.53 (m, 1H, 4′-H, $J_{4',F} = 29$ Hz, $J_{4',5'} = 3.6$ Hz), 2.15 (s, 3H, acetyl), 2.01 (s, 3H, acetyl). Anal. ($C_{16}H_{14}$-$Cl_3FN_2O_5$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-chloro-5-deoxy-β-D-ribofuranosyl)benzimidazole (8e). Compound **6e** (1.0 g, 3.4 mmol) was coupled to **7** (0.7 g, 3.1 mmol) under Vorbruggen conditions to give after workup a solid which was purified by flash chromatography (EtOAc/hexane, 1:2, 4 cm × 15 cm). The fractions that contained a UV active product, which charred upon H_2SO_4 spraying, were pooled and evaporated to dryness to afford, after recrystallization from EtOAc/hexane, 1.5 g (55%) of **8e** as a white crystalline solid: mp 160−161 °C; R_f 0.26 (EtOAc/hexane, 1:2), R_f 0.67 (EtOAc/hexane, 5:1); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H, C_7-H), 8.01 (s, 1H, C_4-H), 6.28 (d, 1H, 1′-H, $J_{1',2'} = 7.1$ Hz), 5.59 (t, 1H, 2′-H), 5.46 (q, 1H, 3′-H), 4.50 (q, 1H, 4′-H), 4.15 (m, 2H, 5′-H), 2.14 (s, 3H, acetyl), 2.02 (s, 3H, acetyl). Anal. ($C_{16}H_{14}Cl_4N_2O_5$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-bromo-5-deoxy-β-D-ribofuranosyl)benzimidazole (8f). Compound **6f** (0.5 g, 1.5

mmol) was coupled to **7** (0.33 g, 1.5 mmol) under Vorbruggen conditions to give, after recrystallization from MeOH, 0.7 g (95%) of **8f** as a white crystalline solid: mp 150−152 °C; R_f 0.67 (EtOAc/hexane, 5:1); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.25 (s, 1H, C_7-H), 8.02 (s, 1H, C_4-H), 6.28 (d, 1H, 1′-H, $J_{1',2'} = 7.1$ Hz), 5.63 (t, 1H, 2′-H), 5.43 (q, 1H, 3′-H), 4.48 (q, 1H, 4′-H), 3.94−4.08 (m, 2H, 5′-H), 2.14 (s, 3H, acetyl), 2.01 (s, 3H, acetyl). Anal. ($C_{16}H_{14}BrCl_3N_2O_5$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-deoxy-5-iodo-β-D-ribofuranosyl)benzimidazole (8g). Compound **6g** (1.5 g, 5.2 mmol) was coupled to **7** (1.0 g, 4.7 mmol) under Vorbruggen conditions to give, after recrystallization from MeOH, 1.8 g (70%) of **8g** as a white crystalline solid: mp 170−171 °C; R_f 0.31 (EtOAc/hexane, 1:2); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 1H, C_7-H), 8.01 (s, 1H, C_4-H), 6.26 (d, 1H, 1′-H, $J_{1',2'} = 7.1$ Hz), 5.69 (t, 1H, 2′-H), 5.38 (q, 1H, 3′-H), 4.31 (m, 1H, 4′-H, 5′-H), 3.80 (m, 1H, 5′-H), 2.14 (s, 3H, acetyl), 2.01 (s, 3H, acetyl). Anal. ($C_{16}H_{14}Cl_3IN_2O_5$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-azido-5-deoxy-β-D-ribofuranosyl)benzimidazole (8h). Compound **6h** (1.3 g, 4.3 mmol) was coupled to **7** (0.9 g, 3.9 mmol) under Vorbruggen conditions to give after workup a solid. This solid was purified by flash chromatography (EtOAc/hexane, 1:1, 4 cm × 15 cm). The fractions that contained a UV active product, which charred upon H_2SO_4 spraying, were pooled and evaporated to dryness to afford, after recrystallization from MeOH, 1.4 g (75%) of **8h** as a white crystalline solid: mp 149−150 °C; R_f 0.35 (EtOAc/hexane, 1:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.23 (s, 1H, C_7-H), 8.02 (s, 1H, C_4-H), 6.26 (d, 1H, 1′-H, $J_{1',2'} = 7.0$ Hz), 5.61 (t, 1H, 2′-H), 5.41 (q, 1H, 3′-H), 4.38 (m, 1H, 4′-H), 3.91 (m, 2H, 5′-H), 2.13 (s, 3H, acetyl), 2.02 (s, 3H, acetyl). Anal. ($C_{16}H_{14}Cl_3N_5O_5$) C, H, N.

2,5,6-Trichloro-1-(2,3-di-*O*-acetyl-5-deoxy-5-(thiomethyl)-β-D-ribofuranosyl)benzimidazole (8i). Compound **6i** (2.3 g, 7.4 mmol) was coupled with **7** (1.5 g, 7.4 mmol) under Vorbruggen conditions to give after workup a solid. This solid was purified by flash chromatography (EtOAc/hexane, 1:1, 4 cm × 15 cm). The fractions that contained a UV active product, which charred upon H_2SO_4 spraying, were pooled and evaporated to dryness to afford, after recrystallization from MeOH, 2.1 g (65%) of **8i** as a white crystalline solid: mp 108−110 °C; R_f 0.40 (EtOAc/hexane, 1:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.21 (s, 1H, C_7-H), 8.00 (s, 1H, C_4-H), 6.21 (d, 1H, 1′-H, $J_{1',2'} = 6.8$ Hz), 5.64 (t, 1H, 2′-H), 5.43 (q, 1H, 3′-H), 4.37 (m, 1H, 4′-H), 3.01−3.10 (m, 2H, 5′-H), 2.13 (s, 3H, SCH_3), 2.11 (s, 3H, acetyl), 2.01 (s, 3H, acetyl). Anal. ($C_{17}H_{17}Cl_3N_2O_5S$) C, H, N.

General Procedure for the Deprotection of Derivatives 8a−i. The appropriate acetylated nucleoside (1 equiv) was dissolved in EtOH/H_2O (2:1), and Na_2CO_3 (2 equiv) was added to this solution. The reaction mixture was stirred for 4 h and then neutralized to pH 7 with glacial acetic acid. The EtOH was removed under reduced pressure, and the solid that had formed was collected by filtration. This solid was recrystallized to give the pure deprotected nucleosides **9a−i**.

2,5,6-Trichloro-1-(5-*O*-methyl-β-D-ribofuranosyl)benzimidazole (9a). Compound **8a** (0.3 g, 6.6 mmol) was deprotected as described above and recrystallized twice from MeOH to give 0.2 g (80%) of **9a** as white crystals: mp 104−105 °C; R_f 0.43 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.33 (s, 1H, C_7-H), 7.97 (s, 1H, C_4-H), 5.89 (d, 1H, 1′-H, $J_{1',2'} =$ 7.8 Hz), 5.54 (d, 1H, 2′-OH), 5.38 (d, 1H, 3′-OH), 4.37 (m, 1H, 2′-H), 4.11 (m, 2H, 3′-H, 4′-H), 3.65 (m, 2H, 5′-H), 3.47 (s, 3H, OCH_3); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.24, 141.04, 132.26, 125.87, 125.80, 120.23, 114.71, 89.22, 84.70, 72.04, 71.68, 70.05, 58.61. Anal. ($C_{13}H_{13}Cl_3N_2O_4$) C, H, N.

2,5,6-Trichloro-1-(5-*O*-ethyl-β-D-ribofuranosyl)benzimidazole (9b). Compound **8b** (0.3 g, 6.4 mmol) was deprotected as described above and recrystallized twice from MeOH to give 0.19 g (78%) of **9b** as white crystals: mp 88−90 °C; R_f 0.47 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.25 (s, 1H, C_7-H), 7.98 (s, 1H, C_4-H), 5.89 (d, 1H, 1′-H, $J_{1',2'} = 7.8$ Hz), 5.54 (d, 1H, 2′-OH), 5.38 (d, 1H, 3′-OH), 4.36 (m, 1H, 2′-H), 4.12 (m, 2H, 3′-H, 4′-H), 3.56−3.73 (m, 2H, 5′-H, OCH_2CH_3), 1.26 (s, 3H, OCH_2CH_3); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.29, 141.09, 132.27, 125.88 (2C), 120.31, 114.44, 89.12, 84.75, 71.79, 69.99, 69.66, 66.20, 14.99. Anal. ($C_{14}H_{15}Cl_3N_2O_4$) C, H, N.

2,5,6-Trichloro-1-(5-*O*-butyl-β-D-ribofuranosyl)benzimidazole (9c). Compound **8c** (0.4 g, 8.1 mmol) was deprotected as described above and recrystallized twice from MeOH to give 0.23 g (80%) of **9c** as white crystals: mp 70−72 °C; R_f 0.51 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.23 (s, 1H, C_7-H), 7.98 (s, 1H, C_4-H), 5.89 (d, 1H, 1′-H, $J_{1',2'} = 7.9$ Hz), 5.54 (d, 1H, 2′-OH), 5.38 (d, 1H, 3′-OH), 4.36 (q, 1H, 2′-H), 4.11 (m, 2H, 3′-H, 4′-H), 3.62−3.74 (m, 2H, 5′-H, OCH_2CH_2-), 1.64 (m, 2H, OCH_2CH_2-), 1.36 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.90 (t, 3H, $OCH_2CH_2CH_2CH_3$); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.29, 141.09, 132.26, 125.88 (2C), 120.31, 114.39, 89.10, 84.81, 71.80, 70.59, 70.01, 69.95, 31.10, 18.83, 13.78. Anal. ($C_{16}H_{19}Cl_3N_2O_4$) C, H, N.

2,5,6-Trichloro-1-(5-deoxy-5-fluoro-β-D-ribofuranosyl)benzimidazole (9d). Compound **8d** (0.3 g, 7.1 mmol) was deprotected as described above and recrystallized twice from MeOH to give 0.21 g (81%) of **9d** as white crystals: mp 132−133 °C; R_f 0.46 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.01 (s, 1H, C_4-H), 7.92 (d, 1H, C_7-H, $J = 3.1$ Hz, long range coupled to F), 5.94 (d, 1H, 1′-H, $J_{1',2'} = 7.5$ Hz), 5.67 (d, 1H, 2′-OH), 5.53 (d, 1H, 3′-OH), 4.67−4.89 (2 octuplets, 2H, 5′-H, $J_{5',F} = 47.1$ Hz) 4.38 (m, 1H, 2′-H), 4.13−4.23 (m, 2H, 3′-H, 4′-H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.27, 141.06, 132.32, 126.12, 125.12, 120.45, 113.65 ($J = 7.3$ Hz, long range coupling with F), 89.33 (1′-C), 83.74 (4′-C, $J = 18.0$ Hz), 83.18 (5′-C, $J = 167.5$ Hz), 71.55 (2′-C), 68.90 (3′-C, $J = 4.9$ Hz); HRMS m/z calcd for $C_{12}H_{10}Cl_3FN_2O_3$ 353.9741, found 353.9746. Anal. ($C_{12}H_{10}Cl_3FN_2O_3$) C, H, N.

2,5,6-Trichloro-1-(5-chloro-5-deoxy-β-D-ribofuranosyl)benzimidazole (9e). Compound **8e** (0.2 g, 4.4 mmol) was deprotected as described above and recrystallized twice from MeOH to give 0.12 g (75%) of **9e** as white crystals: mp 160−161 °C; R_f 0.53 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.06 (s, 1H, C_7-H), 8.00 (s, 1H, C_4-H), 5.91 (d, 1H, 1′-H, $J_{1',2'} = 7.5$ Hz), 5.66 (d, 1H, 2′-OH), 5.52 (d, 1H, 3′-OH), 4.49 (q, 1H, 2′-H), 4.18−3.98 (m, 4H, 3′-H, 4′-H, 5′-H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.24, 140.97, 132.31, 126.18, 125.99, 120.37, 113.85, 89.15, 83.99, 71.09, 69.95, 44.77. Anal. ($C_{12}H_{10}Cl_4N_2O_3$) C, H, N.

2,5,6-Trichloro-1-(5-bromo-5-deoxy-β-D-ribofuranosyl)benzimidazole (9f). Compound **8f** (0.2 g, 4.0 mmol) was deprotected as described above and recrystallized twice from MeOH to give 0.14 g (82%) of **9f** as white crystals:mp 159−160 °C; R_f 0.50 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.09 (s, 1H, C_7-H), 8.01 (s, 1H, C_4-H), 5.91 (d, 1H, 1′-H, $J_{1',2'} = 7.2$ Hz), 5.66 (m, 1H, 2′-OH), 5.54 (m, 1H, 3′-OH), 4.53 (m, 1H, 2′-H), 4.09−4.16 (m, 2H, 3′-H, 4′-H), 3.96 (dd, 1H, 5′-H), 3.86 (dd, 1H, 5′-H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.27, 140.96, 132.31, 126.21, 126.01, 120.35, 113.92, 89.19, 83.72, 70.97, 70.91, 33.77. Anal. ($C_{12}H_{10}BrCl_3N_2O_3$) C, H, N.

2,5,6-Trichloro-1-(5-deoxy-5-iodo-β-D-ribofuranosyl)benzimidazole (9g). Compound **8g** (0.2 g, 3.6 mmol) was deprotected as described above and recrystallized twice from MeOH to give 0.12 g (70%) of **9g** as white crystals: mp 120−121 °C; R_f 0.40 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.07 (s, 1H, C_7-H), 8.01 (s, 1H, C_4-H), 5.90 (d, 1H, 1′-H, $J_{1',2'} = 7.5$ Hz), 5.64 (d, 1H, 2′-OH), 5.51 (d, 1H, 3′-OH), 4.59 (m, 1H, 2′-OH), 4.02 (m, 2H, 3′-H, 4′-H), 3.76 (m, 1H, 5′-H), 3.57 (m, 1H, 5′-H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.27, 140.94, 132.28, 126.29, 126.07, 120.33, 114.00, 89.39, 84.03, 72.23, 70.89, 7.41. Anal. ($C_{12}H_{10}Cl_3IN_2O_{31}\cdot{}^1/_{10}$hexane) C, H, N.

2,5,6-Trichloro-1-(5-azido-5-deoxy-β-D-ribofuranosyl)benzimidazole (9h). Compound **8h** (0.3 g, 6.5 mmol) was deprotected and recrystallized twice from MeOH to give 0.18 g (72%) of **9h** as white crystals: mp 150−151 °C; R_f 0.42 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.11 (s, 1H, C_7-H), 8.01 (s, 1H, C_4-H), 5.90 (d, 1H, 1′-H, $J_{1',2'} = 7.2$ Hz), 5.64 (d, 1H, 2′-OH), 5.45 (d, 1H, 3′-OH), 4.49 (q, 1H, 2′-H), 4.06 (m, 2H, 3′-H, 4′-H), 3.82 (m, 2H, 5′-H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.20, 140.96, 132.36, 126.12, 125.96, 120.38, 113.91, 89.38, 83.28, 71.17, 69.75, 51.63; IR (cm^{-1}) 2096 (azide);

HRMS calcd for $C_{12}H_{10}Cl_3N_5O_3$ 376.9849, found 376.9821. Anal. ($C_{12}H_{10}Cl_3N_5O_3$) C, H, N.

2,5,6-Trichloro-1-(5-deoxy-5-(thiomethyl)-β-D-ribofuranosyl)benzimidazole (9i). Compound **8i** (0.3 g, 6.4 mmol) was deprotected as described before and recrystallized twice from MeOH to give 0.19 g (77%) of **9i** as white crystals: mp 111−112 °C; R_f 0.63 (EtOAc/hexane, 5:1); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.05 (s, 1H, C_7-H), 8.00 (s, 1H, C_4-H), 5.88 (d, 1H, 1′-H, $J_{1',2'} = 7.3$ Hz), 5.60 (m, 1H, 2′-OH), 5.41 (m, 1H, 3′-OH), 4.51 (m, 1H, 2′-H), 4.07 (m, 2H, 3′-H, 4′-H), 3.0 (dd, 1H, 5′-H), 2.90 (dd, 1H, 5′-H), 2.12 (s, 3H, CH_3S); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 142.12, 140.96, 132.34, 126.12, 125.92, 120.32, 113.84, 89.42, 84.16, 71.36, 71.15, 35.69, 15.82. Anal. ($C_{13}H_{13}Cl_3N_2O_3S$) C, H, N.

2,5,6-Trichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)benzimidazole (10). Compound **4** (2.5 g, 7 mmol) was suspended in dry acetone (30 mL). Dowex 50 (H^+) resin (0.5 g) and 2,2-dimethoxypropane (5 mL) were added, and the reaction mixture was stirred under an argon atmosphere at room temperature for 2 h. The resin was removed by filtration and washed with acetone. The filtrate was evaporated under reduced pressure to give an oil which was crystallized from EtOH to give 2 g (73%) of **10** as a white crystalline solid: mp 142−143 °C; R_f 0.60 (EtOAc/hexane, 1:1); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 1H, C_7-H), 7.98 (s, 1H, C_4-H), 6.08 (d, 1H, 1′-H, $J_{1',2'} = 4.2$ Hz), 5.40 (t, 1H, 5′-OH), 5.07 (m, 1H, 2′-H), 5.01 (m, 1H, 3′-H), 4.18 (m, 1H, 4′-H), 3.74 (m, 2H, 5′-H), 1.58 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). Anal. ($C_{15}H_{15}Cl_3N_2O_4$) C, H, N.

2,5,6-Trichloro-1-(5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)benzimidazole (12). Compound **10** (350 mg, 8.9 mmol) was dissolved in dry THF, and triphenylphosphine (0.7 g, 29.4 mmol) was added to the reaction mixture. Diethyl azodicarboxylate (0.4 mL, 29.4 mmol) was added. The reaction mixture was stirred for 30 min, then diphenyl phosphorazidate (0.6 mL, 29.4 mmol) was added, and the resulting mixture was stirred at ambient temperature for 24 h under argon. The organic solvent was removed under reduced pressure and the remaining solid purified by flash chromatography (EtOAc/hexane, 1:2, 2 cm × 15 cm). The fractions that contained a UV active product, which charred upon H_2SO_4 spraying, were pooled, and the solvent was removed under reduced pressure. These fractions were shown by ^{1}H-NMR to be contaminated with an aromatic impurity. They were thus rechromatographed using chloroform as eluent ($CHCl_3$, 2 cm × 15 cm). Fractions containing the product were combined, evaporated to dryness, and recrystallized from MeOH to give 248 mg (71%) of product **12** as white crystals: mp 70−72 °C; R_f 0.21 (EtOAc/hexane, 1:2); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H, C_7-H), 8.00 (s, 1H, C_4-H), 6.15 (d, 1H, 1′-H, $J_{1',2'} = 4.4$ Hz), 5.24 (q, 1H, 2′-H), 5.00 (q, 1H, 3′-H), 4.25 (m, 1H, 4′-H), 3.85 (m, 2H, 5′-H), 1.58 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 141.33, 140.87, 132.43, 126.54, 126.23, 120.34, 115.30, 113.57, 89.99, 82.11, 81.85, 79.91, 51.19, 26.89, 25.26; IR (cm^{-1}) 2106 (azide); MS (DCI with NH_3) m/z 418 (M + H). Anal. ($C_{15}H_{14}Cl_3N_5O_3 \cdot {}^1/_2$MeOH) C, H, N.

2,5,6-Trichloro-1-(5-azido-5-deoxy-β-D-ribofuranosyl)-benzimidazole (9h). Compound **12** (95 mg, 0.27 mmol) was dissolved in THF (10 mL), and 2 N HCl (10 mL) was added to the solution. This reaction mixture was stirred for 6 h. Water (50 mL) was added to the reaction mixture, and the mixture was extracted with EtOAc (3 × 30 mL). The organic extract was washed successively with $NaHCO_3$ and with saturated NaCl solution, dried over sodium sulfate, decolorized with charcoal, filtered through Celite, and concentrated under reduced pressure to give a solid. This solid was purified by flash chromatography (EtOAc, 2 cm × 15 cm). The fractions containing a UV active product, which charred upon H_2SO_4 spraying, were pooled, concentrated to dryness, and crystallized from EtOAc/hexane to give 60 mg (70%) of white crystals which were identical by TLC and ^{1}H-NMR with **9h** previously prepared from **8h**.

2,5,6-Trichloro-1-(5-chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)benzimidazole (11). Compound **10** (200 mg, 0.51 mmol) was dissolved in dry CH_3CN, and triphenylphosphine (263 mg) was added to the solution. CCl_4 (0.1 mL, 1 mmol) was then added to the reaction mixture and the mixture stirred at ambient temperature for 12 h under an argon atmosphere. The organic solvent was removed under reduced pressure and the remaining solid purified by flash chromatography (EtOAc/hexane, 1:2, 2 cm × 15 cm). Fractions, containing a UV active product which charred upon H_2SO_4 spraying, were combined, evaporated to dryness, and recrystallized from MeOH/H_2O to give 100 mg (48%) of **11** as white crystals: mp 121−124 °C; R_f 0.60 (EtOAc/hexane, 1:2); ^{1}H-NMR (360 MHz, DMSO-d_6) δ 8.09 (s, 1H, C_7-H), 8.00 (s, 1H, C_4-H), 6.17 (d, 1H, 1′-H, $J_{1',2'} = 4.6$ Hz), 5.23 (q, 1H, 2′-H), 5.02 (q, 1H, 3′-H), 4.35 (q, 1H, 4′-H), 4.01−4.08 (m, 2H, 5′-H), 1.58 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 141.33, 140.73, 132.29, 126.46, 126.17, 120.37, 115.44, 113.64, 89.68, 82.36, 81.63, 80.12, 43.98, 26.86, 25.23. Anal. ($C_{15}H_{14}Cl_4N_2O_3$) C, H, N.

2,5,6-Trichloro-1-(5-chloro-5-deoxy-β-D-ribofuranosyl)-benzimidazole (9e). Compound **11** (50 mg, 0.1 mmol) was deprotected and purified as described for **12** to give 20 mg (54%) of white crystals identical by TLC and ^{1}H-NMR with **9e** previously prepared from **8e**.

Biological Evaluation. 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.[30]

Virological Procedures. The Towne strain, plaque-purified isolate P_o, of HCMV was kindly provided by Dr. Mark Stinski, University of Iowa. 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.[31] High-titer HSV-1 stocks were prepared by infecting KB cells at an MOI of <0.1 also as detailed previously.[31] 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.[32] 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, 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.

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 the number of plaques in the presence of each drug concentration compared to the number observed in the absence of drug.

HCMV Yield Assay. HFF cells were planted as described above in 96-well cluster dishes and incubated overnight, medium was removed, and the cultures were inoculated with HCMV at a MOI of 0.5−1 PFU/cell as reported elsewhere.[32] 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 and 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.

HSV-1 ELISA. An ELISA was employed[33] to detect HSV-1. Ninety-six-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 horse radish 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.

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,[31] and (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.[34] 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.

The cytotoxicity of compound **9d** was explored in more detail. Replicate cultures of HFF and KB cells were planted at 100 000 and 250 000 cells/well, respectively, in 6-well cluster plates and incubated for 24 h. Medium was removed and replaced with medium containing 0, 10, 30, or 100 μM compound **9d**. Duplicate cultures were harvested 24 and 48 h later, and the number of cells was determined in a Coulter counter.

***In Vitro* Antiproliferative Activity.** Antiproliferative activity was evaluated by measuring the effect of the compounds on the growth of L1210 mouse leukemic cells. Cells were maintained in exponential growth in static suspension cultures at 37 °C with 5% CO_2, 95% air using RPMI 1640 medium supplemented with 10% heat-inactivated (56 °C, 30 min) horse serum. For evaluation of antiproliferative activity, cells were plated in 96-well plates (2000 cells/well), compounds were added to the wells the following day, and after 3 days of incubation with the compounds, the cell density was assayed using the MTS tetrazolium reduction assay.[35] In control experiments the cells were found to remain in exponential growth throughout the duration of this protocol (control population doubling time, 12 h), and the optical density of the formazan product was proportional to the number of cells. Optical density was used as the measurement of cell growth and is expressed as percent of control. Values of 2% or less indicate no increase in cell number after addition of the compounds. For compounds that inhibited cell proliferation by less than 50% in the initial screen (i.e., optical density > 50% of control), the value reported is the average of two evaluations at 100 μM (or the highest concentration permitted by the solubility of the compound as indicated in Table 2). For compounds that caused more than 50% inhibition (i.e., optical density < 50% of control) in the initial screen, two concentration−response experiments were performed. In these cases, the values for growth at the screen concentration are the average values from three independent experiments, and the IC_{50} values are the average values from two independent experiments.

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.

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