Synthesis and Antiviral Evaluation of Polyhalogenated Imidazole Nucleosides: Dimensional Analogues of 2,5,6-Trichloro-1-(β-D-ribofuranosyl)benzimidazole

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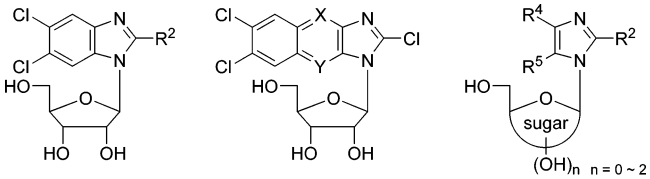
A series of polyhalogenated imidazole nucleosides were designed and synthesized as ring-contracted analogues of 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) and its 2-bromo analogue (BDCRB) in an effort to explore the spatial limitation of the active pocket(s) in the target protein(s). 2,4,5-Trichloro-, 2-bromo-4,5-dichloro-, and 2,4,5-tribromoimidazole nucleosides were prepared by a condensation of the preformed heterocycles with the appropriate sugar precursors. The ribofuranosyl and xylofuranosyl analogues were prepared by a direct glycosylation using the Vorbruggen's silylation method and provided exclusively the β-anomers. The arabinofuranosyl analogues were prepared by the sodium salt method to give both the α- and β-anomers. The absolute configurations were established by ^{1}H NMR spectroscopy. Alkylation of the polyhalogenated imidazoles with the appropriate bromomethyl ethers gave the acyclic acyclovir and ganciclovir analogues. In general, the parent polyhalogenated imidazoles showed some activity against human cytomegalovirus (HCMV) ($IC_{50} \sim 35$ μM). However, with the exception of two tribromo analogues (**7c**, **13c-**β), most of their nucleoside derivatives were inactive against both HCMV and herpes simplex virus type-1 (HSV-1) and were not cytotoxic. The results suggest that the ring-contracted nucleoside analogues of TCRB and BDCRB interacted weakly or not at all with viral and cellular targets.

Introduction

Human cytomegalovirus (HCMV) is a significant pathogen for immunocompromised individuals such as bone marrow and organ transplant as well as AIDS patients.[1,2] Current FDA approved drugs including ganciclovir,[3] valganciclovir (a prodrug of ganciclovir),[4] foscarnet,[5] cidofovir,[6] and the antisense oligonucleotide fomivirsen[7] have been used clinically for the treatment of HCMV patients. Although they are effective, several disadvantages exist. These drugs have poor oral bioavailability (except the prodrug valganciclovir) and produce certain toxicities.[8,9] Drug-resistant strains of the virus have been identified,[10] and the mechanism of action for the first four drugs is similar in that they target viral DNA synthesis. These deficiencies have limited the clinical uses of these drugs and provide a strong rationale for the development of new drugs effective against HCMV infections.

2,5,6-Trichloro-1-(β-D-ribofuranosyl)benzimidazole (**1a**, TCRB) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)-benzimidazole (**1b**, BDCRB) were previously synthesized in our laboratory and both compounds are active against HCMV at noncytotoxic concentrations.[11] TCRB and BDCRB possess a unique mechanism of action that involves inhibition of viral DNA processing, but not viral DNA synthesis.[12] In an effort to investigate the mechanism of action and interaction with their putative protein target(s), as well as optimizing their antiviral activities vs cytotoxicities, intensive structure−activity relationship (SAR) studies have been conducted in our research group.[13] In an effort to explore the spatial requirements of the binding site(s) of the putative target protein(s) to the heterocyclic aglycons, we have synthesized and evaluated a series of polyhalogenated tricyclic nucleosides (**2a**−**c**). These compounds were designed as dimensional extended analogues[14−17] of the polyhalogenated benzimidazole nucleosides (TCRB and BDCRB) to probe the possible binding sites.These studies revealed that the extended analogues retained some antiviral activity but also were somewhat cytotoxic. To continue our SAR studies involving dimensional analogues, a series of polyhalogenated imidazole nucleosides have been designed as ring-contracted analogues of TCRB and BDCRB. 2,4,5-Trichloro-, 2-bromo-4,5-dichloro-, and 2,4,5-tribromoimidazoles (**3a**−**c**)[18] were selected as the polyhalogenated imidazole precursors for this study. We now report the synthesis and the antiviral



1a R^2 = Cl **TCRB**
1b R^2 = Br, **BDCRB**
1c R^2 = H, **DRB**

2a X = Y =CH
2b X = CH, Y = N
2c X = N, Y = CH

$R^2 = R^4 = R^5$ = Cl
R^2 = Br, $R^4 = R^5$ = Cl
$R^2 = R^4 = R^5$ = Br

Figure 1. Benzimidazole nucleosides (**1b**−**c**), tricyclic nucleosides (**2a**−**c**), and imidazole nucleosides synthesized and evaluated as potential antiviral agents.

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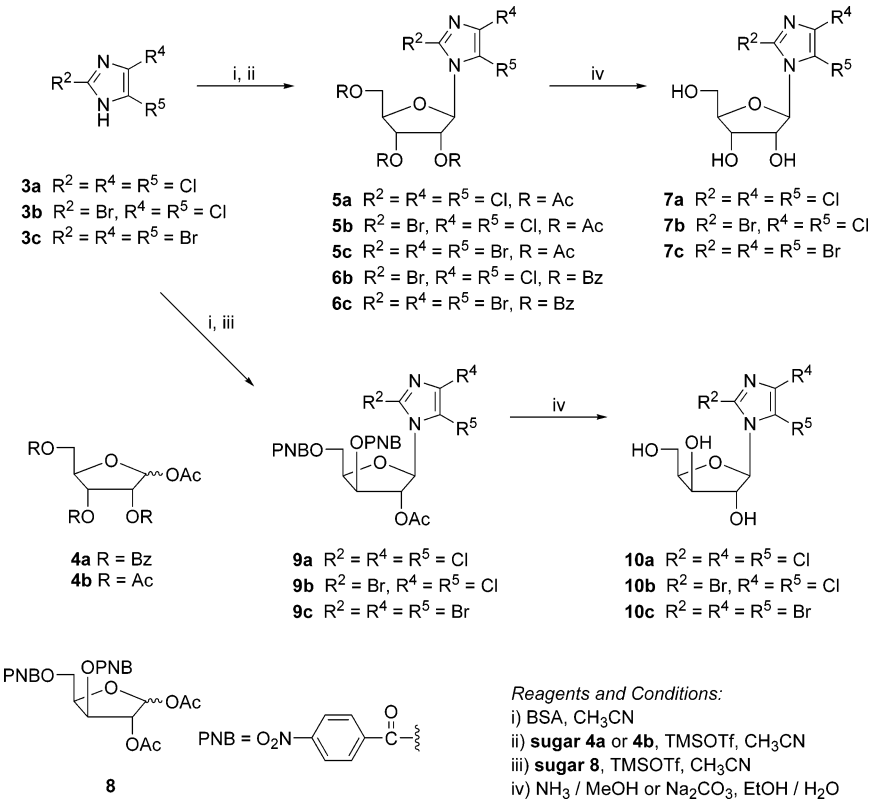
Scheme 1



evaluation of a series of polyhalogenated imidazole nucleosides with different moieties at the N-1 position.

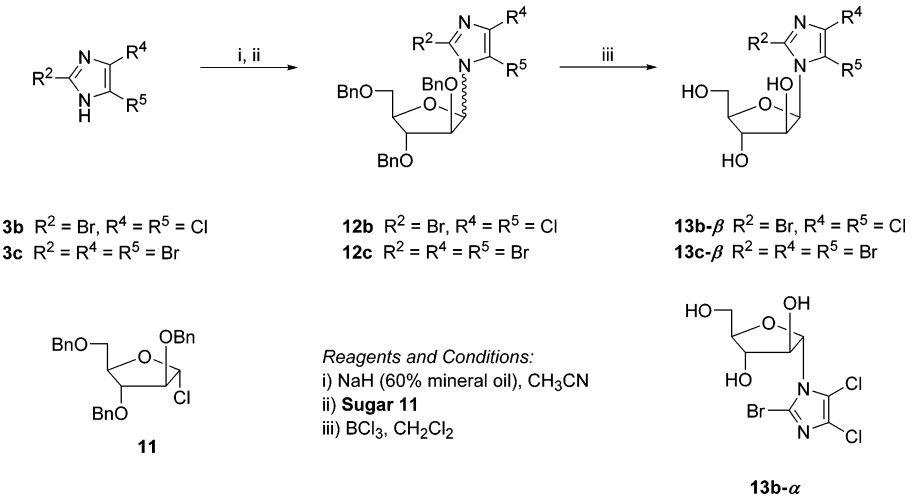
Results and Discussion

Chemistry. The most straightforward approach for the synthesis of these polyhalogenated imidazole nucleosides appeared to be a direct glycosylation or alkylation of the preformed heterocycles with the appropriate protected sugars. The polyhalogenated imidazole precursors, 2,4,5-trichloro-, 2-bromo-4,5-dichloro-, and 2,4,5-tribromoimidazoles (**3a**−**c**), were prepared from commercially available imidazole by the literature procedures.[18] Compounds **3a**−**c** were coupled with 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose (**4b**) or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (**4a**) under modified Vorbruggen's conditions.[19,20] This gave exclusively the *β*-anomers of the sugar-protected ribonucleoside analogues **5a**−**c** and **6b**−**c** in good yields. Similarly, glycosylation of compounds **3a**−**c** with 1,2-di-*O*-acetyl-3,5-di-*O*-(4-nitrobenzoyl)-1-*β*-D-xylofuranose[21] (**8**) under Vobruggen's conditions afforded the protected xylosyl nucleoside analogues **9a**−**c**. Deprotection of the nucleosides **5a**−**c**, **6b**−**c**, and **9a**−**c** with methanolic ammonia or aqueous sodium carbonate gave the desired ribosyl and xylosyl analogues (**7a**−**c**, **10a**−**c**) (Scheme 1).

Preparation of the *β*-D-arabinofuranosyl derivatives **13b**−**c** was accomplished by a condensation of the halogenated imidazoles (**3b**−**c**) with the appropriate sugar derivatives by the sodium salt method.[22] The sodium salts of **3b**−**c** were obtained in situ by adding sodium hydride into the acetonitrile solution of the imidazoles **3b**−**c**, and these sodium salts were then condensed with freshly prepared 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride[23,24] (**11**). These glycosylation reactions gave a mixture of α- and *β*-anomeric diastereoisomers, which were separated by flash column chromatography. 2-Bromo-4,5-dichloro-1-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)imidazole (**12b**) was obtained in about a 1:1 ratio of the α- and *β*-isomers (**12b-**α: 35%; **12b-***β*: 35%) as determined by subsequent NMR studies. However, the *β*-isomer of 2,4,5-tribromo-1-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)imidazole was found to be predominant (**12c-**α: 5%; **12c-***β*: 81%). Removal of the benzyl groups was accomplished with boron trichloride at −78 °C in methylene chloride instead of the usual hydrogenation methods to avoid a removal of halogen substituents on the heterocycles.[25] Debenzylation of **12b**−**c** afforded the corresponding products **13b**−**c** (Scheme 2).

The anomeric configuration of the arabinonucleosides **13b**−**c** was established by ^{1}H, proton-decoupling, and 1-D NOE differential NMR spectroscopy data. A doublet at *δ* 6.06 (*J* = 6.3 Hz) was assigned as the anomeric hydrogen (1′-H) of **13b-***β*. Since the 4′-H and 5′-H protons of **13b-***β* appear as a multiplet at *δ* 3.71−3.63, it is difficult to identify individual chemical shifts and study the NOE between 1′-H and 4′-H. A proton-decoupling experiment with irradiation at *δ* 6.06 only affected the chemical shift at *δ* 4.18, which was then assigned as 2′-H. Subsequent decoupling experiments with irradiation at *δ* 4.18 and 5.69 (2′-OH) confirmed the previous assignment and the peak at *δ* 3.96 was then assigned as 3′-H. The 1-D NOE irradiation of **13b-***β* at the 1′-H (*δ* 6.06) shows a significant NOE enhancement at the 2′-H but not the 3′-H. Therefore, on the basis of the above studies, the absolute configuration at the anomeric position of **13b-***β* was assigned as *β*. The α-anomer (**13b-**α) exhibits a peak for the anomeric proton at *δ* 5.65 (*J* = 7.5 Hz). The proton-decoupling and D_2O exchange experiments suggested the following

Scheme 2



3b R^2 = Br, R^4 = R^5 = Cl
3c R^2 = R^4 = R^5 = Br

12b R^2 = Br, R^4 = R^5 = Cl
12c R^2 = R^4 = R^5 = Br

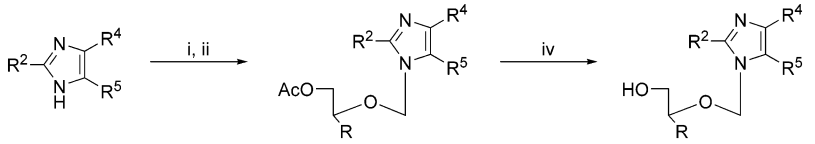
13b-β R^2 = Br, R^4 = R^5 = Cl
13c-β R^2 = R^4 = R^5 = Br

11

Reagents and Conditions:
i) NaH (60% mineral oil), CH_3CN
ii) **Sugar 11**
iii) BCl_3, CH_2Cl_2

13b-α

Scheme 3



3a R^2 = R^4 = R^5 = Cl
3b R^2 = Br, R^4 = R^5 = Cl
3c R^2 = R^4 = R^5 = Br

15a R^2 = R^4 = R^5 = Cl, R = CH_2OAc
15b R^2 = Br, R^4 = R^5 = Cl, R = CH_2OAc
15c R^2 = R^4 = R^5 = Br, R = CH_2OAc
18a R^2 = R^4 = R^5 = Cl, R = H
18b R^2 = Br, R^4 = R^5 = Cl, R = H
18c R^2 = R^4 = R^5 = Br, R = H

16a R^2 = R^4 = R^5 = Cl, R = CH_2OH
16b R^2 = Br, R^4 = R^5 = Cl, R = CH_2OH
16c R^2 = R^4 = R^5 = Br, R = CH_2OH
19a R^2 = R^4 = R^5 = Cl, R = H
19b R^2 = Br, R^4 = R^5 = Cl, R = H
19c R^2 = R^4 = R^5 = Br, R = H

Reagents and Conditions:
i) NaH (60% mineral oil), CH_3CN
ii) $(AcOCH_2)_2CHOCH_2Br$ (**14**) or $AcOCH_2CH_2OCH_2Br$ (**17**)
iv) NH_3 / MeOH or Na_2CO_3, EtOH / H_2O

assignments: 2′-H at δ 4.51, 2′-OH at δ 5.85, 3′-OH at δ 5.66, 3′-H at δ 4.07, and 4′-H at δ 4.02. The 1-D NOE study of **13b-**α revealed that on irradiation of the 1′-H only NOE enhancement of the 3′-H was observed, which supports the assignment of the α-configuration to this compound. The anomeric coupling constant of **13b-**β is 6.3 Hz, while **13b-**α is 7.5 Hz. A similar trend ($J_\beta < J_\alpha$) was also observed for compounds **12b,c**. Furthermore, the chemical shifts of the β-anomeric protons are about 0.4 ppm more downfield than the chemical shifts of the α-anomeric protons. This result is consistent with our previous observation that the peaks assigned to the anomeric protons of the H1′−H2′-cis nucleosides (i.e. β-arabinonucleosides) appear at lower field than the peaks for the anomeric protons of the corresponding H1′−H2′-trans nucleosides (i.e. α-arabinonucleosides).[26] The absolute configuration of **13c-**β was determined in the same manner and was confirmed to be the β-anomer.

Preparation of the acyclic analogues was accomplished by using the sodium salt method.[22] The sodium salt of **3a**−**c** obtained in situ was condensed with (1,3-diacetoxy-2-propoxy)methyl bromide[27] (**14**) and (2-acetoxyethoxy)methyl bromide[28] (**17**), prepared by the literature procedures, to furnish the protected acyclic analogues **15a**−**c** and **18a**−**c**. Deprotection of **15a**−**c** and **18a**−**c** using either methanolic ammonia or aqueous sodium carbonate afforded the desired acyclic nucleosides **16a**−**c** and **19a**−**c** (Scheme 3).

The 4,5-dihalogenated imidazole nucleosides can be viewed as ring-contracted analogues of DRB[29,30] (**1c**). The synthesis of 4,5-dihalogenated imidazole nucleosides[31−33] was approached by two different routes: (1) debromination at the 2-position of a previously prepared imidazole nucleoside and (2) the direct glycosidation of certain 4,5-dihalogenated imidazoles. 2-Bromo-4,5-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**6b**) was treated with triphenylphosphine in a mixture of toluene and methanol and the mixture was heated at reflux temperature for 24 h. This reaction afforded the debrominated product **21b**, which was identical to the product obtained from the direct glycosidation of 4,5-dichloroimidazole[18] (**20b**) by Vorbruggen's method. However, a selective debromination of 2,4,5-tribromo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**6c**) under the above conditions was unsuccessful.

Although a model reaction had demonstrated that 1-methyl-2,4,5-tribromoimidazole could be selectively debrominated under the same conditions to give 1-methyl-4,5-dibromoimidazole, the tribromoimidazole nucleoside **6c** remained resistant toward a selective debromination at the 2-position when it was treated under the same conditions. Therefore, 4,5-dibromoimidazole (**20c**), prepared from **3c** via the same debromination conditions,[34] was coupled with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**4b**) to give the protected nucleoside **21c**.[31,32] Deprotection of the peracylated nucleosides

Scheme 4

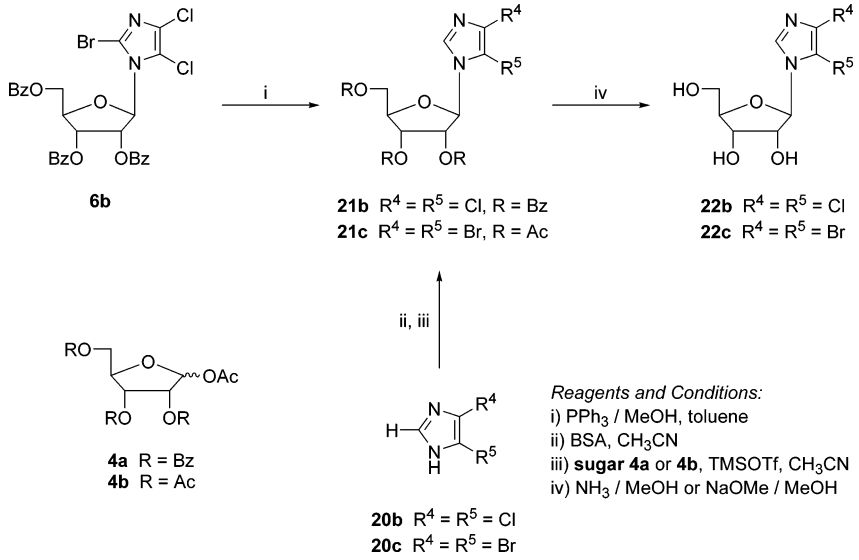
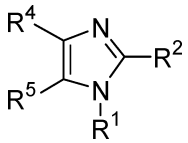


Table 1. Antiviral Activity and Cytotoxicity of Polyhalogenated Imidazole Nucleoside Analogues



compd no.	substituent R^1	substituent R^2	R^4	R^5	50% inhibitory concentration (μM): antiviral activity HCMV[a] plaque	antiviral activity HSV-1[b] ELISA	cytotoxicity[c] visual	cytotoxicity[c] growth
3a	H	Cl	Cl	Cl	30		75	
3b	H	Br	Cl	Cl	41		>100[d]	
3c	H	Br	Br	Br	37		75	
7a	ribose	Cl	Cl	Cl	>100	>100	>100	>100
7b	ribose	Br	Cl	Cl	>100	>100	>100	>100
7c	ribose	Br	Br	Br	30	60	100	65
10a	xylose	Cl	Cl	Cl	>100	50	>100	>100
10b	xylose	Br	Cl	Cl	>100	>100	>100	>100
10c	xylose	Br	Br	Br	>100[e]	>100[e]	>100[e]	>100[e]
13b-*β*	arabinose	Br	Cl	Cl	>100	>100	>100	>100
13c-*β*	arabinose	Br	Br	Br	32	>100	>100	90
16a	DHPM[f]	Cl	Cl	Cl	>100	30	>100	25[e]
16b	DHPM	Br	Cl	Cl	>100	>100	>100	>100
16c	DHPM	Br	Br	Br	>100	>100	>100	>100
19a	HEM[f]	Cl	Cl	Cl	>100	35	45	25
19b	HEM	Br	Cl	Cl	>100	>100	>100	>100
19c	HEM	Br	Br	Br	>100	>100	>100	>100
22b	ribose	H	Cl	Cl	>100	>100	>100	>100
22c	ribose	H	Br	Br	>100	>100	>100	>100
1a (TCRB)[g]					2.9	102	238	>100
1b (BDCRB)[g]					0.7	130	118	>100
1c (DRB)[g]					42	30	24	36
2a[h]					2.0	26	3.2	19
2b[h]					18	90	18	8
2c[h]					2	70	21	11
GCV[g]					7.4	3.5	>100	>100

[a] Plaque reduction assays were performed in duplicate as described in the text. [b] 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 presented. Inhibition of KB cell growth was determined as described in the text in triplicate assays. [d] >100 indicates IC_{50} greater than the noted (highest) concentration tested. [e] Average derived from two experiments. [f] Abbreviations used: DHPM, (1,3-dihydroxy-2-propoxy)methyl; HEM, (2-hydroxyethoxy)methyl. [g] Data presented previously in ref 11. [h] Data presented previously in ref 17.

21b−**c** with methanolic ammonia gave the desired 4,5-dihalogenated imidazole ribonucleosides **22b**−**c** (Scheme 4) as ring-contracted analogues of DRB.

Biological Evaluations. All new perhalogenated imidazole nucleosides were screened for antiviral activities against HCMV and herpes simplex virus type-1 (HSV-1) and for cytotoxicity. The results (Table 1) show that only the parent perhalogenated imidazoles **3a**−**c** were slightly active against the HCMV, but only **3b** was free of cytotoxicity. Overall, the perhalogenated imida-

zole nucleoside derivatives showed little significant cytotoxicity and were mostly inactive against both HCMV and HSV-1. Interestingly, the 1-ribosyl and 1-arabinosyl 2,4,5-tribromoimidazoles (**7c**, **13c**) had some activity against HCMV at noncytotoxic concentrations but both were less active than the polyhalogenated benzimidazoles **1a**−**b**[11] and the tricyclic analogues **2a**−**c**.[17] This result implies that only **7c** and **13c** can fit into a putative benzimidazole binding site. Since the bromine atom is considerably bigger than the chlorine atom, the bispherical bromo atoms may substitute for the *o*-dichlorobenzene ring in TCRB (**1a**) or BDCRB (**1b**) in space and contributed certain binding affinity to the binding pocket to retain the activity. Furthermore, the 4,5-dibromoimidazole nucleoside **22c** showed no activity against either virus, which revealed that the removal of the 2-bromo group from **7c** eliminated the antiviral activity. This trend is consistent with our previous observation that DRB[30] (**1c**) is less active than TCRB (**1a**) and BDCRB (**1b**). The acyclic nucleoside analogues **16a**−**c** and **19a**−**c** were nearly inactive and noncytotoxic. This result also parallels our early conclusion for acyclic nucleoside analogues of polyhalogenated benzimidazoles.[35] In general, low activity and no cytotoxicity suggested that the ring-contracted analogues lost their binding affinity for the HCMV target and did not affect cellular enzymes. Therefore, the ring extension linearly along the C2 axis of the imidazole ring is critical for activity against HCMV.

Experimental Section

General Chemical Procedures. Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 300, 360, or 500 MHz with Bruker DPX300, WP360SY, or DRX500 instruments. The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift of tetramethylsilane (TMS). The coupling constant values are expressed in hertz (Hz). Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ, or by the Analytical Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, MI. Mass spectrometry was performed by the Analytical Laboratory, Department of Chemistry, University of Michigan. Thin-layer chromatography (TLC) was performed on silica gel GHLF-254 plates (Merck Reagents). Compounds on thin-layer chromatography were visualized by illumination under UV light (254 nm) or dipped into 10% methanolic sulfuric acid followed by charring on a hot plate. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). E. Merck silica gel (230−400 mesh) was used for flash column chromatography, and this technique has been described by Still et al (*J. Org. Chem.* **1978**, *43*, 2923−2925). The reported yields have not been optimized. Sodium hydride of 60% oil dispersion (Aldrich) was used for all the sodium salt glycosylation reactions unless specified otherwise. A 1 M solution of boron trichloride in dichloromethane (Aldrich) was used for the debenzylation process. Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

2,4,5-Trichloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (5a). To a solution of 2,4,5-trichloroimidazole[18] (**3a**, 0.4 g, 2.3 mmol) in CH_3CN (100 mL) was added *N,O*-bis-(trimethylsilyl)acetamide (BSA) (0.86 mL, 0.702 g, 3.45 mmol, 1.5 equiv) and the reaction mixture was stirred at room temperature for 20 min. This solution was treated with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**4b**, 0.89 g, 2.7 mmol, 1.2 equiv) and trimethylsilyl triflate (TMSOTf) (0.54 mL, 0.613 g, 2.76 mmol, 1.2 equiv) and stirred at 60 °C for an additional 2 h. The reaction mixture was cooled to room temperature and CH_3CN was removed under reduced pressure to dryness. The residue was dissolved in EtOAc (150 mL). The organic layer was successively washed with a saturated solution of $NaHCO_3$ (2 × 50 mL), NaCl (2 × 50 mL), and H_2O (50 mL) and then dried over anhydrous Na_2SO_4 and evaporated to dryness. The resulting oil was purified by column chromatography (Hex/EtOAc = 7:3) to give **5a** (0.69 g, 1.61 mmol, oil, 70%): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.82 (d, 1 H, J = 5.8 Hz, 1′-H), 5.64 (t, 1 H, J = 6.2 Hz), 5.35 (t, 1 H, J = 6.2 Hz), 4.43−4.45 (m, 1 H), 4.24−4.16 (m, 2 H, 5′-H), 2.08 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3).

2-Bromo-4,5-dichloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (5b). Compound **5b** (oil, 0.43 g, 0.91 mmol, 51%) was prepared from 2-bromo-4,5-dichloroimidazole[18] (**3b**, 0.40 g, 1.8 mmol) using BSA (0.67 mL, 0.549 g, 2.7 mmol, 1.5 equiv), CH_3CN (40 mL), and then **4b** (0.707 g, 2.2 mmol, 1.2 equiv) and TMSOTf (0.42 mL, 0.48 g, 2.16 mmol, 1.2 equiv) by the method described for **5a** and purified by column chromatography (Hex/EtOAc = 85:15−8:2): ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.93 (d, 1 H, J = 5.4 Hz, 1′-H), 5.57 (dd, 1 H, J = 5.4 & 7.3 Hz), 5.32 (t, 1 H, J = 6.9 Hz), 4.42−4.36 (m, 2 H), 4.24−4.20 (m, 1 H), 2.09 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3). Anal. ($C_{14}H_{15}BrCl_2N_2O_7$) C, H, N.

2,4,5-Tribromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (5c). Compound **5c** (oil, 2.34 g, 4.18 mmol, 64%) was prepared from 2,4,5-tribromoimidazole[18] (**3c**, 2.0 g, 6.56 mmol) using BSA (2.41 mL, 1.98 g, 9.71 mmol, 1.48 equiv), CH_3CN (100 mL), and then **4b** (2.7 g, 8.48 mmol, 1.3 equiv) and TMSOTf (1.27 mL, 1.46 g, 6.56 mmol, 1 equiv) by the method described for **5a** and purified by column chromatography (Hex/EtOAc = 8:2): ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.94 (d, 1 H, J = 5.4 Hz, 1′-H), 5.57 (dd, 1 H, J = 5.5 & 7.3 Hz), 5.33 (t, 1 H, J = 6.8 Hz), 4.42−4.36 (m, 2 H), 4.22 (dd, 1 H, J = 6.5 & 13.2 Hz), 2.10 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3). Anal. ($C_{14}H_{15}Br_3N_2O_7$) C, H, N.

2-Bromo-4,5-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (6b). Compound **6b** (foam, 1.41 g, 2.14 mmol, 92%) was prepared from 2-bromo-4,5-dichloroimidazole[18] (**3b**, 0.50 g, 2.32 mmol) using BSA (0.69 mL, 0.566 g, 2.78 mmol, 1.2 equiv), CH_3CN (20 mL), and then 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4a**, 1.40 g, 2.78 mmol, 1.2 equiv) and TMSOTf (0.49 mL, 0.567 g, 2.55 mmol, 1.1 equiv) by the method described for **5a** and purified by column chromatography ($CHCl_3$/MeOH = 99.5:0.5, R_f = 0.36): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−8.12 (m, 15 H, Ph), 6.22 (d, 1 H, J = 5.7 Hz), 6.08 (dd, 1 H, J = 5.5 & 6.8 Hz), 5.94 (dd, 1 H, J = 5.7 & 6.8 Hz), 4.90−4.97 (m, 1 H), 4.67−4.73 (m, 2 H, 5′-H). Anal. ($C_{29}H_{21}BrCl_2N_2O_7$) C, H, N.

2,4,5-Tribromo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazole (6c). Compound **6c** (foam, 0.736 g, 0.98 mmol, 60%) was prepared from 2,4,5-tribromoimidazole[18] (**3c**, 0.50 g, 1.64 mmol) using BSA (0.53 mL, 0.434 g, 2.13 mmol, 1.3 equiv), CH_3CN (20 mL), and then **4a** (0.99 g, 1.97 mmol, 1.2 equiv) and TMSOTf (0.38 mL, 0.437 g, 1.97 mmol, 1.2 equiv) by the method described for **5a** and purified by column chromatography [Hex/CH_2Cl_2 = 3:7, R_f = 0.36 (Hex/$CHCl_3$ = 3:7)]: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11−7.38 (m, 15 H, Ph), 6.30−6.26 (m, 2 H), 6.20 (dd, 1 H, J = 5.3 & 6.6 Hz), 4.87−4.82 (m, 1 H), 4.76 (dd, 1 H, J = 3.6 & 12.2 Hz, 5′−H), 4.61 (dd, 1 H, J = 4.5 & 12.2 Hz, 5′−H); MS (FAB) *m/z* 154 (100), 201 (22), 307 (25), 445 (40), 747 (5) (M^+). Anal. ($C_{29}H_{21}Br_3N_2O_7$) C, H, N.

2,4,5-Trichloro-1-(β-D-ribofuranosyl)imidazole (7a). A mixture of **5a** (1.14 g, 2.6 mmol), Na_2CO_3 (1.7 g, 16.0 mmol), and 10% aqueous EtOH (100 mL) was stirred at room temperature for 12 h. The excess ethanol was evaporated under reduced pressure to dryness. The mixture was diluted with H_2O (100 mL), extracted with EtOAc (250 mL), washed with H_2O (50 mL), and dried (anhydrous Na_2SO_4), and the solvent was removed under reduced pressure. The resulting mixture was purified by column chromatography ($CHCl_3$/MeOH = 9:1) to give **7a** (0.32 g, 42%). The product (**7a**) was

recrystallized from Hex/EtOAc (0.198 g, 26%): mp 110−112 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.64 (d, 1 H, J = 6.7 Hz, 1′-H), 5.63 (d, 1 H, J = 6.2 Hz, 2′-OH), 5.30 (d, 1 H, J = 5.2 Hz, 3′-OH), 4.90 (t, 1 H, J = 5.7 Hz, 5′-OH), 4.51 (dd, 1 H, J = 6.2 & 12.5 Hz), 4.02 (dt, 1 H, J = 3.6 & 5.4 Hz), 3.84 (dt, 1 H, J = 3.6 & 5.5 Hz), 3.59 (dd, 1 H, J = 5.5 & 11.7 Hz, 5′-H), 3.52 (dd, 1 H, J = 5.8 & 11.7 Hz, 5′-H). Anal. ($C_8H_9Cl_3N_2O_4$) C, H, N.

2-Bromo-4,5-dichloro-1-(β-D-ribofuranosyl)imidazole (7b). A mixture of **5b** (0.39 g, 0.82 mmol) and methanolic ammonia (40 mL) was stirred at room temperature for 12 h. The excess MeOH and NH_3 were removed under reduced pressure. The resulting residue was purified by column chromatography ($CHCl_3$/MeOH = 95:5) followed by crystallization from Hex/EtOAc to give **7b** (0.17 g, 60%): mp 135−138 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.64 (d, 1 H, J = 6.7 Hz, 1′-H), 5.61 (d, 1 H, J = 6.1 Hz, OH), 5.28 (d, 1 H, J = 5.1 Hz, OH), 4.89 (t, 1 H, J = 5.6 Hz, 5′-OH), 4.51 (dd, 1 H, J = 6.2 & 12.4 Hz), 4.01 (dd, 1 H, J = 4.8 & 9.8 Hz), 3.82 (dd, 1 H, J = 5.6 & 9.3 Hz), 3.62−3.49 (m, 2 H, 5′-H). Anal. ($C_8H_9BrCl_2N_2O_4$) C, H, N.

2,4,5-Tribromo-1-(β-D-ribofuranosyl)imidazole (7c). Method A. Compound **7c** (0.293 g, 0.67 mmol, 61%) was obtained from the deprotection of **5c** (0.62 g, 1.10 mmol) with Na_2CO_3 (0.35 g, 3.30 mmol, 3 equiv) in EtOH/H_2O [50 mL, 9:1 (v/v)] as described for **7a** and then purified by column chromatography ($CHCl_3$/MeOH = 9:1): mp 162−165 °C (dec) (Hex/EtOAc).

Method B. Compound **7c** (1.54 g, 3.53 mmol, 76%) was obtained from the deprotection of **6c** (3.48 g, 4.64 mmol) with 28% NH_4OH/MeOH/acetone [100 mL, 2:2:1 (v/v/v)] as described for **7b**, and then purified by column chromatography [$CHCl_3$/MeOH = 95:5, R_f = 0.3 ($CHCl_3$/MeOH = 9:1)]. An analytical sample of **7c** was obtained by recrystallization from CH_3CN: mp 165−167 °C (CH_3CN).

Compound **7c**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.71 (d, 1 H, J = 4.7 Hz, 1′-H), 5.53 (d, 1 H, J = 5.9 Hz, OH), 5.26 (d, 1 H, J = 5.3 Hz, OH), 4.78 (t, 1 H, J = 5.6 Hz, OH), 4.52 (dd, 1 H, J = 5.0 & 10.2 Hz), 4.11 (dd, 1 H, J = 4.8 & 9.5 Hz), 3.89 (dd, 1 H, J = 4.9 & 9.7 Hz), 3.37−3.50 (m, 2 H, 5′-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 129.9, 120.0, 101.0, 92.4, 86.8, 74.0, 71.3, 62.7; MS (CI, CH_4) *m/z* 133 (100), 226 (30), 306 (45), 408 (15), 435 (5) (M^+ + 1); HRMS calcd for $C_8H_{10}Br_3N_2O_4$ (M + 1) 434.8191, found 434.8176. Anal. ($C_8H_9Br_3N_2O_4$) C, H, N.

2,4,5-Trichloro-1-[2-*O*-acetyl-3,5-di-*O*-(4-nitrobenzoyl)-1-β-D-xylofuranosyl]imidazole (9a). Compound **9a** (oil, 1.46 g, 2.27 mmol, 61%) was prepared from 2,4,5-trichloroimidazole[18] (**3a**, 0.634 g, 3.70 mmol) using BSA (1.19 mL, 0.978 g, 4.81 mmol, 1.3 equiv), CH_3CN (40 mL), and then 1,2-di-*O*-acetyl-3,5-di-*O*-(4-nitrobenzoyl)-1-β-D-xylofuranose[21] (**8**, 1.97 g, 3.70 mmol, 1.0 equiv) and TMSOTf (1.07 mL, 1.23 g, 5.55 mmol, 1.5 equiv) by the method described for **5a** and purified by column chromatography [Hex/EtOAc = 7:3−5:5, R_f = 0.37 (Hex/EtOAc = 65:35)]: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37 (d, 2 H, J = 8.8 Hz, Ph), 8.30 (d, 2 H, J = 8.8 Hz, Ph), 8.22 (d, 2 H, J = 8.9 Hz, Ph), 8.19 (d, 2 H, J = 8.9 Hz, Ph), 5.91 (d, 1 H, J = 5.6 Hz, 1′-H), 5.88 (dd, 1 H, J = 3.4 & 6.3 Hz), 5.81 (dd, 1 H, J = 1.9 & 5.6 Hz), 4.83−4.72 (m, 3 H), 2.21 (s, 3 H, CH_3); ^{13}C & DEPT135 NMR ($CDCl_3$, 125 MHz) δ 169.8, 164.5, 163.9, 151.6, 151.3, 134.8, 134.0, 131.3 (2 × CH), 130.1, 127.8, 124.4 (CH), 124.1 (CH), 113.9, 89.3 (CH), 79.8 (CH), 77.8 (CH), 77.4 (CH), 62.5 (CH_2), 20.8 (CH_3).

2-Bromo-4,5-dichloro-1-[2-*O*-acetyl-3,5-di-*O*-(4-nitrobenzoyl)-1-β-D-xylofuranosyl]imidazole (9b). Compound **9b** (oil, 4.81 g, 6.99 mmol, 89%) was prepared from 2-bromo-4,5-dichloroimidazole[18] (**3b**, 1.70 g, 7.89 mmol) using BSA (2.55 mL, 2.09 g, 10.25 mmol, 1.3 equiv), CH_3CN (100 mL), and then **8** (5.45 g, 10.25 mmol, 1.3 equiv) and TMSOTf (2.44 mL, 2.81 g, 12.62 mmol, 1.6 equiv) by the method described for **5a** and purified by column chromatography [Hex/EtOAc = 7:3−5:5, R_f = 0.23 (Hex/EtOAc = 7:3)]: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37 (d, 2 H, J = 8.8 Hz, Ph), 8.31 (d, 2 H, J = 8.8 Hz, Ph), 8.22 (d, 2 H, J = 8.7 Hz, Ph), 8.19 (d, 2 H, J = 8.7 Hz, Ph), 5.95 (d, 1 H, J = 5.8 Hz, 1′-H), 5.89 (dd, 1 H, J = 1.8 & 5.0 Hz), 5.82 (dd, 1 H, J = 2.0 & 5.8 Hz), 4.84−4.73 (m, 3 H), 2.07 (s, 3 H, CH_3); ^{13}C & DEPT135 NMR ($CDCl_3$, 125 MHz) δ 169.8, 164.5, 164.0, 151.6, 151.3, 134.8, 134.1, 131.3 (2 × CH), 129.4, 124.4 (CH), 124.1 (CH), 117.3, 114.5, 90.3 (CH), 79.8 (CH), 77.6 (CH), 77.3 (CH), 62.5 (CH_2), 20.8 (CH_3).

2,4,5-Tribromo-1-[2-*O*-acetyl-3,5-di-*O*-(4-nitrobenzoyl)-1-β-D-xylofuranosyl]imidazole (9c). Compound **9c** (foam, 2.44 g, 3.14 mmol, 53%) was prepared from 2,4,5-tribromoimidazole[18] (**3c**, 2.00 g, 6.55 mmol, 1.1 equiv) using BSA (1.92 mL, 1.58 g, 7.75 mmol, 1.3 equiv), CH_3CN (60 mL), and then **8** (3.17 g, 5.96 mmol) and TMSOTf (1.61 mL, 1.86 g, 8.34 mmol, 1.4 equiv) by the method described for **5a** and purified by column chromatography [Hex/EtOAc = 6:4−5:5, R_f = 0.40 (Hex/EtOAc = 6:4)]. An analytical sample was obtained by recrystallization from Hex/EtOAc: mp 111−114 °C (dec) (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (d, 2 H, J = 8.9 Hz, Ph), 8.30 (d, 2 H, J = 8.9 Hz, Ph), 8.23 (d, 2 H, J = 8.9 Hz, Ph), 8.19 (d, 2 H, J = 8.9 Hz, Ph), 6.01 (d, 1 H, J = 6.1 Hz, 1′-H), 5.90 (dd, 1 H, J = 2.3 & 5.5 Hz, 3′-H), 5.86 (dd, 1 H, J = 2.3 & 6.1 Hz, 2′-H), 4.86−4.82 (m, 1 H, 4′-H), 4.81−4.77 (m, 2 H, 5′-H), 2.20 (s, 3 H, CH_3); ^{13}C & DEPT135 NMR ($CDCl_3$, 125 MHz) δ 169.8, 164.5, 164.0, 151.5, 151.3, 134.8, 134.1, 131.3 (2 × CH), 124.4 (CH), 124.1 (CH), 120.4, 119.0, 104.1, 90.4 (CH), 79.9 (CH), 77.8 (CH), 77.2 (CH), 62.5 (CH_2), 20.8 (CH_3). Anal. ($C_{24}H_{17}Br_3N_4O_{11}\cdot{}^1/_2$EtOAc) C, H, N.

2,4,5-Trichloro-1-(β-D-xylofuranosyl)imidazole (10a). Compound **10a** (0.488 g, 1.61 mmol, 71%) was obtained from the deprotection of **9a** (1.45 g, 2.27 mmol) with methanolic ammonia (23 mL) as described for **7b** and then purified by column chromatography [$CHCl_3$/MeOH = 95:5−93:7, R_f = 0.33 ($CHCl_3$/MeOH = 9:1)]. An analytical sample of **10a** was obtained by recrystallization from EtOAc/MeOH: mp 187−190 °C (dec) (EtOAc/MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 5.87 (d, 1 H, J = 5.4 Hz, OH), 5.53 (d, 1 H, J = 6.4 Hz, 1′-H), 5.39 (d, 1 H, J = 4.7 Hz, OH), 4.56 (t, 1 H, J = 5.7 Hz, OH), 4.45 (dd, 1 H, J = 5.4 & 10.7 Hz), 4.17 (dd, 1 H, J = 4.6 & 10.7 Hz), 4.11 (dt, 1 H, J = 4.3 & 6.7 Hz), 3.73−3.68 (m, 1 H, 5′-H), 3.66−3.61 (m, 1 H, 5′-H); ^{13}C & DEPT135 NMR (DMSO-d_6, 500 MHz) δ 130.5, 125.8, 114.5, 91.3 (CH), 82.4 (CH), 79.6 (CH), 76.1 (CH), 60.9 (CH_2). Anal. ($C_8H_9Cl_3N_2O_4$) C, H, N.

2-Bromo-4,5-dichloro-1-(β-d-xylofuranosyl)imidazole (10b). Compound **10b** (0.49 g, 1.41 mmol, 63%) was obtained from the deprotection of **9b** (1.53 g, 2.22 mmol) with methanolic ammonia (30 mL) as described for **7b**, and then purified by column chromatography ($CHCl_3$/MeOH = 95:5−93:7, R_f = 0.20 ($CHCl_3$/MeOH = 93:7)). An analytical sample of **10b** was obtained by recrystallization from MeOH. mp 185−187 °C (dec) (MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 5.86 (d, 1 H, J = 5.6 Hz, OH), 5.53 (d, 1 H, J = 6.7 Hz, 1′-H), 5.39 (d, 1 H, J = 4.8 Hz, OH), 4.55 (t, 1 H, J = 5.6 Hz, 5′-OH), 4.48 (dd, 1 H, J = 5.6 Hz, 11.0 Hz), 4.18 (dt, 1 H, J = 4.7 & 6.4 Hz), 4.11 (dt, 1 H, J = 4.1 & 6.9 Hz), 3.73−3.68 (m, 1 H, 5′-H), 3.66−3.62 (m, 1 H, 5′-H); ^{13}C & DEPT135 NMR (DMSO-d_6, 75 MHz) δ 127.3, 119.0, 114.8, 92.1 (CH), 82.2 (CH), 79.5 (CH), 76.2 (CH), 61.0 (CH_2). Anal. ($C_8H_9BrCl_2N_2O_4$) C, H, N.

2,4,5-Tribromo-1-(β-D-xylofuranosyl)imidazole (10c). Compound **10c** (0.794 g, 1.82 mmol, 58%) was obtained from the deprotection of **9c** (2.44 g, 3.14 mmol) with methanolic ammonia (31 mL) as described for **7b** and then purified by column chromatography [$CHCl_3$/MeOH = 93:7−9:1, R_f = 0.19 ($CHCl_3$/MeOH = 9:1)]. An analytical sample of **10c** was obtained by recrystallization from MeOH: mp 186−188 °C (dec) (MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 5.84 (d, 1 H, J = 5.6 Hz, OH), 5.55 (d, 1 H, J = 7.0 Hz, 1′-H), 5.41 (d, 1 H, J = 4.7 Hz, OH), 4.56−4.52 (m, 2 H, OH & CH), 4.20 (dd, 1 H, J = 4.7 & 11.2 Hz), 4.12 (dt, 1 H, J = 4.5 & 6.8 Hz), 3.74−3.69 (m, 2 H, 5′-H); ^{13}C & DEPT135 NMR (DMSO-d_6, 125 MHz) δ 120.5, 119.1, 105.5, 92.1 (CH), 82.0 (CH), 79.6 (CH), 76.2 (CH), 61.1 (CH_2); MS (EI, 70 eV) *m/z* 302 (37), 304 (100), 306 (97), 308 (35), 434 (5) (M^+), 436 (25) (M + 2), 438 (24) (M + 4), 440 (4) (M + 6); HRMS calcd for $C_8H_9Br_3N_2O_4$ (M^+): 433.8112, found 433.8114. Anal. ($C_8H_9Br_3N_2O_4$) C, H, N.

2-Bromo-4,5-dichloro-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)imidazole (12b-α) and 2-Bromo-4,5-dichloro-

1-(2,3,5-tri-*O*-benzyl-*β*-D-arabinofuranosyl)imidazole (12b-*β*). NaH (0.39 g, 13.2 mmol, 80% oil dispersion) was added to a stirred suspension of 2-bromo-4,5-dichloroimidazole[18] (**3b**, 2.4 g, 11.1 mmol) in dry CH_3CN (120 mL) under a nitrogen atmosphere. The solution was stirred until hydrogen evolution has ceased and a clear solution was obtained (30 min). A solution of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride[24] [**11**, prepared from 5.9 g (10.3 mmol) of 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenoyl)-D-arabinose] in CH_3CN (20 mL) was then added dropwise. The reaction mixture was stirred for an additional 16 h. The resulting mixture was concentrated under reduced pressure to dryness. The residue was dissolved in EtOAc (200 mL). The organic layer was washed with H_2O (100 mL) and dried over anhydrous Na_2SO_4. The resulting syrup was purified by flash column chromatography (Hex/EtOAc = 9:1) to give the following products: 1.58 g (2.56 mol) of **12b-**α, 2.14 g of a mixture of **12b-**α and **12b-***β*, and 1.46 g (2.36 mmol) of **12b-***β*. The mixture was rechromatographed (Hex/EtOAc = 9:1) to give 0.82 g (1.33 mmol) of **12b-**α and 0.98 g (1.58 mmol) of **12b-***β*.

12b-α: foam, 2.40 g (3.90 mmol), 35% from **3b**; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 7.37−7.11 (m, 15 H, 3 × Ph), 5.88 (d, 1 H, *J* = 6.7 Hz, 1′-H), 4.70 (t, 1 H, *J* = 6.4 Hz, CH), 4.62−4.42 (m, 7 H, 3 × CH_2 and 1 × CH), 4.32 (t, 1 H, *J* = 6.4 Hz, CH), 3.65 (dd, 1 H, *J* = 2.9 & 11.0 Hz, 5′-H), 3.60 (dd, 1 H, *J* = 4.3 & 11.0 Hz, 5′-H).

12b-*β*: foam, 2.44 g (3.94 mmol), 35% from **3b**; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 7.39−6.84 (m, 15 H, 3 × Ph), 6.36 (d, 1 H, *J* = 6.4 Hz, 1′-H), 4.62−3.74 (m, 11 H, 3 × CH_2, 2′-H, 3′-H, 2 × 5′-H).

2,4,5-Tribromo-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)imidazole (12c-α) and 2,4,5-Tribromo-1-(2,3,5-tri-*O*-benzyl-*β*-D-arabinofuranosyl)imidazole (12c-*β*). Compound **12c-**α and **12c-***β* were prepared from 2,4,5-tribromoimidazole[18] (**3c**, 2.4 g, 7.9 mmol) using NaH (60% in mineral oil, 0.426 g, 10.7 mmol, 1.35 equiv), CH_3CN (120 mL), then **11** (prepared from 5.5 g (9.8 mmol) of 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenoyl)-D-arabinose)[24] as described for **12b-**α and **12b-***β*, and purified by flash column chromatography (Hex/EtOAc = 9:1) to give the following products: 0.30 g (0.42 mmol) of **12c-**α, 0.37 g (0.52 mmol) of a mixture of **12c-**α and **12c-***β* (analyzed by ^{1}H NMR showing 1:1 ratio), and 4.45 g (6.29 mmol) of **12c-***β*.

12c-α: foam, 0.30 g (0.42 mmol), 5% from **3c**; ^{1}H NMR (DMSO-d_6, 360 MHz) δ7.35−7.08 (m, 15 H, 3 × Ph), 5.92 (d, 1 H, *J* = 7.1 Hz, 1′-H), 4.73 (t, 1 H, *J* = 6.7 Hz), 4.65−4.43 (m, 7 H, 3 × CH_2, and CH), 4.34 (t, 1 H, *J* = 6.7 Hz), 3.65 (dd, 1 H, *J* = 3.0 & 11.1 Hz, 5′-H), 3.62 (dd, 1 H, *J* = 4.4 & 11.0 Hz, 5′-H). **12c-*β***: foam, 4.45 g (6.29 mmol), 81% from **3c**; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 7.35−7.00 (m, 15 H, 3 × Ph), 6.36 (d, 1 H, *J* = 6.3 Hz, 1′-H), 4.61−3.98 (m, 9 H, 3 × CH_2, 2′-H, 3′-H and 4′-H), 3.84 (dd, 1 H, *J* = 7.0 & 10.8 Hz, 5′-H), 3.75 (dd, 1 H, *J* = 3.5 & 10.8 Hz, 5′-H).

2-Bromo-4,5-dichloro-1-(*β*-D-arabinofuranosyl)imidazole (13b-*β*). To a solution of **12b-***β* (1.49 g, 2.4 mmol) in dry CH_2Cl_2 (75 mL) at −78 °C under a nitrogen atmosphere was added dropwise 1 M BCl_3 in CH_2Cl_2 (25 mL) while the bath temperature was maintained at −78 °C. The reaction mixture was stirred for an additional 2 h. The resulting mixture was brought to 0 °C and stirred for an additional 2 h and kept in a 0 °C freezer for 16 h. MeOH (20 mL) was added at −78 °C and the reaction mixture was brought to room temperature, neutralized (pH = 7) with 28% NH_4OH, and then concentrated to yield an oil. The resulting oil was diluted with H_2O (100 mL), extracted with EtOAc (200 mL), washed with H_2O (100 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The resulting oil was purified by column chromatography ($CHCl_3$/MeOH = 8:2) to give **13b-***β* (0.47 g, 1.35 mmol, 56%). An analytical sample was recrystallized from MeOH: mp 190−192 °C (dec) (MeOH); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 6.06 (d, 1 H, *J* = 6.3 Hz, 1′-H), 5.69 (d, 1 H, exchanges with D_2O, *J* = 5.2 Hz, 2′-OH), 5.54 (m, 1 H, exchanges with D_2O, OH), 4.85 (bs, 1 H, exchanges with D_2O, OH), 4.18 (dd, 1 H, *J* = 5.2 & 11.2 Hz, 2′-H), 3.96 (m, 1 H, 3′-H), 3.71−3.63 (m, 3 H, 4′-H, and 2 × 5′-H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 125.5, 117.0, 115.0, 88.1, 83.2, 76.3, 75.8, 61.2. Anal. ($C_8H_9BrCl_2N_2O_4$) C, H, N.

The α-isomer, 2-bromo-4,5-dichloro-1-(α-D-arabinofuranosyl)imidazole (13b-α), was obtained by debenzylation of **12b-**α (1.54 g, 2.5 mmol) with 1 M BCl_3 in CH_2Cl_2 (20 mL) in dry CH_2Cl_2 (70 mL) by the method described for **13b-***β* to give **13b-**α (0.7 g, 2.01 mmol, 80%). An analytical sample was recrystallized from EtOH: mp 186−189 °C (dec) (EtOH); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.85 (d, 1 H, exchanges with D_2O, *J* = 5.7 Hz, 2′-OH), 5.66 (d, 1 H, exchanges with D_2O, *J* = 5.6 Hz, 3′-OH), 5.65 (d, 1 H, *J* = 7.5 Hz, 1′-H), 4.90 (dd, 1 H, exchanges with D_2O, *J* = 5.0 & 6.4 Hz, 5′-OH), 4.51 (dd, 1 H, *J* = 7.8 & 13.5 Hz, 2′-H), 4.06−4.01 (m, 2 H, 3′-H & 4′-H), 3.61 (dd, 1 H, *J* = 4.3 & 11.9 Hz, 5′-H), 3.46 (ddd, 1 H, *J* = 3.4, 6.5, 12.2 Hz, 5′-H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 126.3, 117.6, 113.4, 91.2, 84.0, 77.7, 73.0, 60.3. Anal. ($C_8H_9BrCl_2N_2O_4$) C, H, N.

2,4,5-Tribromo-1-(*β*-D-arabinofuranosyl)imidazole (13c-*β*). Compound **13c-***β* (0.70 g, 1.60 mmol, 64%) was obtained by debenzylation of **12c-***β* (1.77 g, 2.5 mmol) with 1 M BCl_3 in CH_2Cl_2 (25 mL) in dry CH_2Cl_2 (60 mL) by the method described for **13b-***β*. An analytical sample was recrystallized from EtOAc: mp 173−175 °C (dec) (EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 6.06 (d, 1 H, *J* = 6.2 Hz, 1′-H), 5.63 (d, 1 H, exchanges with D_2O, *J* = 6.0 Hz, 2′-OH), 5.53 (bs, 1 H, exchanges with D_2O, OH), 4.84 (bs, 1 H, exchanges with D_2O, OH), 4.14 (dd, 1 H, *J* = 4.9 & 10.8 Hz, 2′-H), 4.08−4.03 (m, 1 H, 3′-H), 3.71−3.67 (m, 3 H, 4′-H and 2 × 5′-H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 118.8, 117.1, 105.3, 88.5, 83.4, 76.4, 76.2, 61.3. Anal. ($C_8H_9Br_3N_2O_4$) C, H, N.

2,4,5-Trichloro-1-[(1,3-diacetoxy-2-propoxy)methyl]imidazole (15a). NaH (60% in mineral oil, 0.12 g, 3.0 mmol) was added to a stirred solution of 2,4,5-trichloroimidazole[18] (**3a**, 0.35 g, 2.0 mmol) in dry CH_3CN (30 mL) under a N_2 atmosphere. The solution was stirred until hydrogen evolution has ceased and a clear solution was obtained (20 min). (1,3-Diacetoxy-2-propoxy)methyl bromide[27] (**14**, 0.65 g, 2.4 mmol) in CH_3CN (10 mL) was then added dropwise. The reaction mixture was stirred for an additional 3 h at room temperature. The resulting mixture was concentrated under reduced pressure to dryness, diluted with H_2O (50 mL), extracted with EtOAc (150 mL), washed with H_2O (100 mL), and dried (anhydrous Na_2SO_4(s)), and the solvent was removed under reduced pressure to yield an oil. The resulting oil was purified by flash column chromatography (Hex/EtOAc = 65:35) to give **15a** (oil, 0.57 g, 78%): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.35 (s, 2 H, 1′-H), 4.24−3.87 (m, 5 H, 2 × CH_2 & CH), 1.83 (s, 6 H, 2 × CH_3).

2-Bromo-4,5-dichloro-1-[(1,3-diacetoxy-2-propoxy)methyl]imidazole (15b). Compound **15b** (oil, 1.0 g, 2.49 mmol, 54%) was prepared from 2-bromo-4,5-dichloroimidazole[18] (**3b**, 1.0 g, 4.6 mmol) using NaH (60% in mineral oil, 0.22 g, 5.5 mmol, 1.2 equiv), CH_3CN (125 mL), and then **14** (1.49 g, 5.5 mmol, 1.2 equiv) by the method described for **15a** and purified by column chromatography (Hex/EtOAc = 85:15). An analytical sample of **15b** was obtained by recrystallization from Hex/EtOAc: mp 76−78 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.42 (s, 2 H, 1′-H), 4.12 (dd, 2 H, *J* = 2.9 & 11.7 Hz, CH_2), 4.01 (dd, 2 H, *J* = 6.7 & 11.7 Hz, CH_2), 3.95−3.93 (m, 1 H, CH), 1.96 (s, 6 H, 2 × CH_3). Anal. ($C_{11}H_{13}BrCl_2N_2O_5$) C, H, N.

2,4,5-Tribromo-1-[(1,3-diacetoxy-2-propoxy)methyl]imidazole (15c). Compound **15c** (oil, 0.541 g, 1.10 mmol, 85%) was prepared from 2,4,5-tribromoimidazole[18] (**3c**, 0.4 g, 1.3 mmol) using NaH (60% in mineral oil, 0.61 g, 1.5 mmol, 1.15 equiv), CH_3CN (40 mL), and then **14** (0.422 g, 1.5 mmol, 1.15 equiv) by the method described for **15a** and purified by column chromatography (Hex/EtOAc = 95:5−8:2). An analytical sample of **15c** was obtained by recrystallization from Hex/EtOAc: mp 76−77 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.43 (s, 2 H, 1′-H), 4.12 (dd, 2 H, *J* = 3.3 & 11.7 Hz, CH_2), 4.01 (dd, 2 H, *J* = 6.8 & 11.7 Hz, CH_2), 3.96−3.92 (m, 1 H, CH), 1.96 (s, 6 H, 2 × CH_3). Anal. ($C_{11}H_{13}Br_3N_2O_5$) C, H, N.

2,4,5-Trichloro-1-[(1,3-dihydroxy-2-propoxy)methyl]-imidazole (16a). Compound **16a** (0.34 g, 1.24 mmol, 93%) was obtained from the deprotection of **15a** (0.480 g, 1.34 mmol) with methanolic ammonia (25 mL) as described for **7b** and then purified by column chromatography ($CHCl_3$/MeOH = 93:7): mp 79−80 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.36 (s, 2 H, 1′-H), 4.72 (t, 2 H, J = 7.1 Hz, 2 × OH), 3.55−3.14 (m, 5 H, 2 × CH_2 & CH). Anal. ($C_7H_9Cl_3N_2O_3$) C, H, N.

2-Bromo-4,5-dichloro-1-[(1,3-dihydroxy-2-propoxy)-methyl]imidazole (16b). Compound **16b** (0.219 g, 0.69 mmol, 92%) was obtained from the deprotection of **15b** (0.30 g, 0.74 mmol) with methanolic ammonia (15 mL) as described for **7b** and recrystallized from Hex/EtOAc: mp 119−121 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.43 (s, 2 H, 1′-H), 4.70 (t, 2 H, J = 5.4 Hz, 2 × OH), 3.57−3.51 (m, 1 H, CH), 3.46−3.40 (m, 2 H, CH_2), 3.34−3.27 (m, 2 H, CH_2). Anal. ($C_7H_9BrCl_2N_2O_3$) C, H, N.

2,4,5-Tribromo-1-[(1,3-dihydroxy-2-propoxy)methyl]-imidazole (16c). Compound **16c** (0.167 g, 0.41 mmol, 97%) was obtained from the deprotection of **15c** (0.20 g, 0.42 mmol) with methanolic ammonia (30 mL) as described for **7b** and recrystallized from Hex/EtOAc (97%): mp 113−115 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.44 (s, 2 H, 1′-H), 4.66 (bs, 2 H, 2 × OH), 3.58 −3.52 (m, 1 H, CH), 3.44 (dd, 2 H, J = 4.7 & 11.4 Hz, CH_2), 3.31 (dd, 2 H, J = 6.1 & 11.4 Hz, CH_2). Anal. ($C_7H_9Br_3N_2O_3$) C, H, N.

2,4,5-Trichloro-1-[(2-acetoxyethoxy)methyl]imidazole (18a). Compound **18a** (oil, 0.41 g, 1.43 mmol, 84%) was prepared from 2,4,5-trichloroimidazole[18] (**3a**, 0.30 g, 1.7 mmol) using NaH (60% in mineral oil, 0.104 g, 2.6 mmol, 1.5 equiv), CH_3CN (25 mL), and then (2-acetoxyethoxy)methylbromide[28] (**17**, 0.336 g, 1.7 mmol, 1.0 equiv) by the method described for **15a** and purified by column chromatography (Hex/EtOAc = 8:2): ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.37 (s, 2 H, 1′-H), 4.07 (t, 2 H, J = 4.5 Hz, CH_2), 3.70 (t, 2 H, J = 4.5 Hz, CH_2), 1.95 (s, 3 H, CH_3).

2-Bromo-4,5-dichloro-1-[(2-acetoxyethoxy)methyl]imidazole (18b). Compound **18b** (0.626 g, 1.90 mmol, 82%) was prepared from 2-bromo-4,5-dichloroimidazole[18] (**3b**, 0.50 g, 2.3 mmol) using NaH (60% in mineral oil, 0.12 g, 3.0 mmol, 1.3 equiv), CH_3CN (10 mL), and then **17** (0.57 g, 3.0 mmol, 1.3 equiv) by the method described for **15a** and purified by column chromatography (Hex/EtOAc = 8:2): mp 68−71 °C (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.38 (s, 2 H, 1′-H), 4.23 (t, 2 H, J = 4.6 Hz, CH_2), 3.76 (t, 2 H, J = 4.6 Hz, CH_2), 2.08 (s, 3 H, CH_3). Anal. ($C_8H_9BrCl_2N_2O_3$) C, H, N.

2,4,5-Tribromo-1-[(2-acetoxyethoxy)methyl]imidazole (18c). Compound **18c** (0.411 g, 0.98 mmol, 61%) was prepared from 2,4,5-tribromoimidazole[18] (**3b**, 0.50 g, 1.6 mmol) using NaH (60% in mineral oil, 0.088 g, 2.2 mmol, 1.38 equiv), CH_3CN (40 mL), and then **17** (0.40 g, 2.1 mmol, 1.3 equiv) by the method described for **15a** and purified by column chromatography (Hex/EtOAc = 8:2, oil, 59%): ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.37 (s, 2 H, 1′-H), 4.09 (t, 2 H, J = 4.5 Hz, CH_2), 3.69 (t, 2 H, J = 4.5 Hz, CH_2), 1.98 (s, 3 H, CH_3).

2,4,5-Trichloro-1-[(2-hydroxyethoxy)methyl]imidazole (19a). Compound **19a** (0.26 g, 1.07 mmol, 83%) was obtained from the deprotection of **18a** (0.37 g, 1.29 mmol) with Na_2CO_3 (0.137 g, 1.29 mmol, 1 equiv) in EtOH/H_2O [30 mL, 9:1 (v/v)] as described for **7a** and then purified by column chromatography ($CHCl_3$/MeOH = 97:3): mp 57−58 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.37 (s, 2 H, 1′-H), 4.73 (t, 1 H, J = 5.2 Hz, OH), 3.53−3.46 (m, 4 H, 2 × CH_2). Anal. ($C_6H_7Cl_3N_2O_2$) C, H, N.

2-Bromo-4,5-dichloro-1-[(2-hydroxyethoxy)methyl]imidazole (19b). Compound **19b** (0.372 g, 1.28 mmol, 68%) was obtained from the deprotection of **18b** (0.623 g, 1.88 mmol) with Na_2CO_3 (0.416 g, 3.92 mmol, 2.1 equiv) in EtOH/H_2O [50 mL, 9:1 (v/v)] as described for **7a** and purified by column chromatography (Hex/EtOAc = 1:1): mp 89−91 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.35 (s, 2 H, 1′-H), 4.74 (bs, 1 H, OH), 3.51−3.44 (m, 4 H, 2 × CH_2). Anal. ($C_6H_7BrCl_2N_2O_2$) C, H, N.

2,4,5-Tribromo-1-[(2-hydroxyethoxy)methyl]imidazole (19c). Compound **19c** (0.21 g, 0.55 mmol, 75%) was obtained from the deprotection of **18c** (0.31 g, 0.73 mmol) with Na_2CO_3 (0.67 g, 0.63 mmol, 0.86 equiv) in MeOH/EtOH/H_2O (5 mL:5 mL:1 mL) as described for **7a** and purified by column chromatography ($CHCl_3$/MeOH = 9:1). An analytical sample of **19c** was obtained by recrystallization from Hex/EtOAc: mp 97 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.37 (s, 2 H, 1′-H), 4.75 (t, 1 H, J = 5.3 Hz, OH), 3.52−3.41 (m, 4 H, 2 × CH_2). Anal. ($C_6H_7Br_3N_2O_2$) C, H, N.

4,5-Dichloro-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-imidazole (21b). Method A. A mixture of **6b** (1.32 g, 2.0 mmol) and triphenylphosphine (1.05 g, 4 mmol, 2 equiv) was suspended in a mixture of toluene (15 mL) and methanol (5 mL). The reaction mixture was heated at reflux for 24 h. The solvents were evaporated under vacuum. To the resulting mixture ethyl acetate (30 mL) was added and the precipitate was collected by filtration (identified as methyl triphenylphosphinium bromide). The solution was concentrated and the resulting oil was purified by column chromatography (Hex/EtOAc = 75:25) to give **21b** [oil, 0.83 g, 1.43 mmol, 71%, R_f = 0.38 (Hex/EtOAc = 7:3)].

Method B. To a solution of 4,5-dichloroimidazole[18] (**20b**, 0.55 g, 4 mmol) in dry CH_3CN (40 mL) was added BSA (1.19 mL, 0.976 g, 4.8 mmol, 1.2 equiv) and the reaction mixture was stirred at 35 °C for 20 min. To this solution was added **4a** (1.77 g, 3.51 mmol) and TMSOTf (1.01 mL, 1.16 g, 5.2 mmol, 1.3 equiv) and the reaction was stirred at 65 °C for 90 min. The reaction mixture was cooled to room temperature and the acetonitrile was removed under reduced pressure. To the residue was added EtOAc (80 mL), and the organic layer was successively washed with solutions of saturated $NaHCO_3$ (40 mL), H_2O (40 mL), and saturated NaCl (40 mL) and then dried over anhydrous $MgSO_4$ and evaporated to dryness. The resulting oil was chromatographed on a silica gel flash column (Hex/EtOAc = 6:4) to give **21b** [foam, 1.76 g, 3.03 mmol, 86% from sugar **4a**, R_f = 0.70 (Hex/EtOAc = 5:5)]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12−7.96 (m, 6 H, Ph), 7.69 (1 H, s, 2-H), 7.65−7.29 (m, 9 H, Ph), 6.13 (d, 1 H, J = 5.1 Hz), 5.96−5.93 (m, 2 H), 4.88 (dd, 1 H, J = 2.9 & 12.4 Hz), 4.81 (dd, 1 H, J = 3.4 & 6.6 Hz), 4.71 (dd, 1 H, J = 3.6 & 12.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 165.6, 165.2, 134.4, 134.3, 134.1, 133.1, 130.3, 130.2, 130.1, 129.44, 129.24, 129.04, 129.02, 128.87, 128.54, 128.07, 113.2, 87.6, 81.3, 74.8, 71.4, 63.8; MS (FAB) *m/z* 105 (100), 445 (64), 581 (1.53) (M + 1); HRMS calcd for $C_{29}H_{23}Cl_2N_2O_7$ (M + 1) 581.0882, found 581.0904. Anal. ($C_{29}H_{22}Cl_2N_2O_7$) C, H, N.

4,5-Dibromo-1-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-imidazole[31,32] (21c). To a solution of 4,5-dibromoimidazole[34] (**20c**, 0.45 g, 2.0 mmol) in dry CH_3CN (30 mL) was added BSA (0.60 mL, 0.488 g, 2.4 mmol, 1.2 equiv) and the reaction mixture was stirred at 35 °C for 20 min. To this solution was added **4b** (0.76 g, 2.4 mmol, 1.2 equiv) and TMSOTf (0.46 mL, 0.533 g, 2.4 mmol, 1.2 equiv) and the mixture stirred at 65 °C for 90 min. The reaction mixture was cooled to room temperature and the acetonitrile was removed under reduced pressure. To the residue was added EtOAc (40 mL), and the organic layer was successively washed with solutions of saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and saturated NaCl (20 mL) and then dried over anhydrous $MgSO_4$ and evaporated to dryness. The resulting oil was purified by column chromatography (Hex/EtOAc = 5:5) to give **21c** (oil, 0.91 g, 1.89 mmol, 95%, R_f = 0.29): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (s, 1 H, 2-H), 5.81 (d, 1 H, J = 5.1 Hz, 1′-H), 5.50 (t, 1 H, J = 5.2 Hz), 5.36 (t, 1 H, J = 5.2 Hz), 4.41−4.38 (m, 1 H), 4.33−4.32 (m, 2 H), 2.10 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.9, 169.4, 135.8, 118.8, 103.0, 88.6, 74.1, 70.2, 62.9, 50.6, 21.1, 20.9, 20.8; MS (CI, CH_4) *m/z* 259 (100), 405 (16), 483 (9.62) (M + 1), 485 (18.29) (M + 3), 487 (9.50) (M + 5); HRMS calcd for $C_{14}H_{17}Br_2N_2O_7$ (M + 1) 482.9402, found 482.9405.

4,5-Dichloro-1-(*β*-D-ribofuranosyl)imidazole (22b). A mixture of **21b** (0.87 g, 1.50 mmol) and 28% NH_4OH/MeOH/acetone [30 mL, 2:2:1 (v/v/v)] was stirred at room temperature for 12 h. The solvents and NH_3 were removed under reduced pressure. The resulting oil was chromatographed on a silica

gel flash column (EtOAc/MeOH = 98:2) to give the crude product. The product was recrystallized from Hex/EtOAc to give **22b** [0.359 g, 1.33 mol, 89%, R_f = 0.33 (EtOAc/MeOH = 95:5)]: mp 103−104 °C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.14 (s, 1 H, 2-H), 5.63 (d, 1 H, J = 6.0 Hz, OH), 5.52 (d, 1 H, J = 5.4 Hz, 1′-H), 5.28 (d, 1 H, J = 5.2 Hz, OH), 5.08 (t, 1 H, J = 5.3 Hz, OH), 4.32 (dd, 1 H, J = 5.3 & 10.6 Hz), 4.06 (dd, 1 H, J = 4.8 & 9.2 Hz), 3.92 (dd, 1 H, J = 3.8 & 7.7 Hz), 3.63−3.51 (m, 2 H, 5′-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 135.3, 125.8, 112.9, 89.7, 86.4, 75.1, 70.6, 61.6; MS (CI, CH_4) *m/z* 137 (71), 139 (49), 141 (10), 269 (100) (M + 1), 270 (14) (M + 2), 271 (64) (M + 3), 273 (14) (M + 5); HRMS calcd for $C_8H_{11}Cl_2N_2O_4$ (M + 1) 269.0096, found 269.0084. Anal. ($C_8H_{10}Cl_2N_2O_4$) C, H, N.

4,5-Dibromo-1-(β-D-ribofuranosyl)imidazole (22c). A mixture of **21c** (0.91 g, 1.89 mmol) and MeONa (0.41 g, 7.55 mmol, 4 equiv) in MeOH (40 mL) was stirred at room temperature for 1 h. The methanol was evaporated under reduced pressure. H_2O (20 mL) was added to the residue and then extracted with EtOAc (40 mL), washed with H_2O (50 mL), and dried (anhydrous Na_2SO_4), and the solvent was removed under reduced pressure. The resulting mixture was purified by column chromatography (EtOAc/MeOH = 99:1) to give the crude product [oil, 0.295 g, 0.824 mmol, 44%, R_f = 0.27 (EtOAc/MeOH = 97:3)]. The oil was crystallized from a mixture of $CHCl_3$/EtOAc to give **22c** (0.143 g, 0.40 mmol, 21%): mp 105−107 °C ($CHCl_3$/EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.21 (s, 2-H), 5.59 (d, 1 H, J = 6.1 Hz, OH), 5.51 (d, 1 H, J = 5.3 Hz, 1′-H), 5.26 (d, 1 H, J = 5.1 Hz, OH), 5.07 (t, 1 H, J = 5.3 Hz, OH), 4.3 (t, 1 H, J = 5.0 Hz), 4.05 (t, 1 H, J = 4.3 Hz), 3.91 (dd, 1 H, J = 3.7 & 7.6 Hz), 3.61 (dd, 1 H, J = 3.7 & 12.0 Hz, 5′-H), 3.52 (dd, 1 H, J = 3.6 & 12.0 Hz, 5′-H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 137.1, 116.5, 103.4, 89.9, 85.5, 74.4, 69.8, 60.7; MS (CI, CH_4) *m/z* 225 (51), 227 (100), 229 (49), 357 (6) (M + 1), 359 (11) (M + 3), 361 (6) (M + 5); HRMS calcd for $C_8H_{11}Br_2N_2O_4$ (M + 1) 356.9086, found 356.9088. Anal. ($C_8H_{10}Br_2N_2O_4$) C, H, N.

Biological Evaluation. Cell Culture Procedures. The routine growth and passage of KB, BSC-1, and HFF cells were 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.[36]

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) per cell as detailed previously.[37] High titer HSV-1 stocks were prepared by infecting KB cells at an moi of <0.1 also as detailed previously.[37] 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.[38] 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 2 or 3 days for HSV-1. Plaques were enumerated under 20-fold magnification in wells having the dilution that gave 5−20 plaques per 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 per cm^2 cell sheet using the procedures detailed above. Following virus adsorption, the compounds, prepared as 10 mg/mL stock solutions in DMSO, were diluted with growth medium and were added to duplicate wells in four to eight selected concentrations. After incubation at 37 °C for 7−10 days, cell sheets were fixed and stained with crystal violet, and microscopic plaques were 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.

HSV-1 ELISA. An ELISA was employed[39] to detect HSV-1. Ninety-six-well cluster dishes were planted with 10000 BSC-1 cells per well in 200 μL per 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 per 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.[37] (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.[40] Briefly, 96-well cluster dishes were planted with KB cells at 3000−5000 cells per 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.

Data Analysis. Dose−response relationships were used to quantitate drug effects by linear regression of the percent inhibition of parameters derived in the preceding assays against log drug concentrations. Fifty percent inhibitory concentrations (IC_{50}'s) were calculated from the linear portions of the regression lines. Samples containing positive controls (acyclovir for HSV-1, GCV for HCMV, and 2-acetylpyridine thiosemicarbazone for cytotoxicity) were used in all assays.

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References

(1) Wingard, J. R.; Piantadosi, S.; Burns, W. H.; Zahurak, M. L.; Santos, G. W.; Saral, R. Cytomegalovirus Infections in Bone-Marrow Transplant Recipients Given Intensive Cytoreductive Therapy. *Rev. Infect. Dis.* **1990**, *12*, S793−S804.
(2) Rubin, R. H. Impact of Cytomegalovirus-infection on Organ Transplant Recipients. *Rev. Infect. Dis.* **1990**, *12*, S754−S766.
(3) Crumpacker, C. S. Drug Therapy—Ganciclovir. *New Engl. J. Med.* **1996**, *335*, 721−729.
(4) Reusser, P. Oral Valganciclovir: A New Option for Treatment of Cytomegalovirus Infection and Disease in Immunocompromised Hosts. *Expert Opin. Inv. Drug.* **2001**, *10*, 1745−1753.
(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) Hitchcock, M. J. M.; Jaffe, H. S.; Martin, J. C.; Stagg, R. J. Cidofovir, a New Agent with Potent anti-Herpesvirus Activity. *Antivir. Chem. Chemother.* **1996**, *7*, 115−127.
(7) Marwick, C. First "Antisense" Drug Will Treat CMV Retinitis. *J. Am. Med. Assoc.* **1998**, *280*, 871−871.

(8) Polis, M. A.; Spooner, K. M.; Baird, B. F.; Manischewitz, J. F.; Jaffe, H. S.; Fisher, P. E.; Falloon, J.; Davey, R. T.; Kovacs, J. A.; Walker, R. E.; Whitcup, S. M.; Nussenblatt, R. B.; Lane, H. C.; Masur, H. Anticytomegaloviral Activity and Safety of Cidofovir in Patients with Human-immunodeficiency-virus Infection and Cytomegalovirus Virurria. *Antimicrob. Agents Chemother.* **1995**, *39*, 882−886.

(9) Jacobson, M. A. Current Management of Cytomegalovirus Disease in Patients with AIDS. *AIDS Res. Hum. Retrovir.* **1994**, *10*, 917−923.

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

(11) Townsend, L. B.; Devivar, R. V.; Turk, S. R.; 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) Underwood, M. R.; Harvey, R. J.; Stanat, S. C.; Hemphill, M. L.; Miller, T.; Drach, J. C.; Townsend, L. B.; Biron, K. K. Inhibition of Human Cytomegalovirus DNA Maturation by a Benzimidazole Ribonucleoside is Mediated through the UL89 Gene Product. *J. Virol.* **1998**, *72*, 717−725.

(13) Townsend, L. B.; Gudmundsson, K. S.; Daluge, S. M.; Chen, J. J.; Zhu, Z. J.; Koszalka, G. W.; Boyd, L.; Chamberlain, S. D.; Freeman, G. A.; Biron, K. K.; Drach, J. C. Studies Designed to Increase the Stability and Antiviral Activity (HCMV) of the Active Benzimidazole Nucleoside, TCRB. *Nucleosides Nucleotides* **1999**, *18*, 509−519.

(14) Zhu, Z. J.; Drach, J. C.; Townsend, L. B. Synthesis of 2,6,7-Trichloro-1-(β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole: A Linear Dimensional Analogue of the Antiviral Agent. TCRB. *J. Org. Chem.* **1998**, *63*, 977−983.

(15) Zhu, Z. J.; Saluja, S.; Drach, J. C.; Townsend, L. B. Synthesis of Imidazo[4,5-*b*]quinoxaline Ribonucleosides as Linear Dimensional Analogues of Antiviral Polyhalogenated Benzimidazole Ribonucleosides. *J. Chin. Chem. Soc.* **1998**, *45*, 465−474.

(16) Zhu, Z. J.; Lippa, B.; Townsend, L. B. Synthesis and Regioselective Ribosylation of 6,7-Dichloroimidazo[4,5-*b*]quinolin-2-one. *J. Org. Chem.* **1999**, *64*, 4159−4168.

(17) Zhu, Z. J.; Lippa, B.; Drach, J. C.; Townsend, L. B. Design, Synthesis, and Biological Evaluation of Tricyclic Nucleosides (Dimensional Probes) as Analogues of Certain Antiviral Polyhalogenated Benzimidazole Ribonucleosides. *J. Med. Chem.* **2000**, *43*, 2430−2437.

(18) Lutz, A. W.; De Lorenzo, S. A. Novel Halogenated Imidazoles. Chloroimidazoles. *J. Heterocycl. Chem.* **1967**, *4*, 399−402.

(19) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. Nucleoside Syntheses 22. Nucleoside Synthesis with Trimethylsilyl Triflate and Perchlorate as Catalysts. *Chem. Ber.* **1981**, *114*, 1234−1255.

(20) Vorbruggen, H.; Bennua, B. Nucleoside Syntheses 25. A New Simplified Nucleoside Synthesis. *Chem. Ber.* **1981**, *114*, 1279−1286.

(21) Poopeiko, N. E.; Kvasyuk, E. I.; Mikhailopulo, I. A.; Lidaks, M. J. Modified Nucleosides 27. Stereospecific Synthesis of β-D-Xylofuranosides of Adenine and Guanine. *Synthesis* **1985**, 605−609.

(22) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. Synthesis of 2′-Deoxytubercidin, 2′-Deoxyadenosine, and Related 2′-Deoxynucleosides via a Novel Direct Stereospecific Sodium-salt Glycosylation Procedure. *J. Am. Chem. Soc.* **1984**, *106*, 6379−6382.

(23) Barker, R.; Fletcher, H. G. 2,3,5-Tri-*O*-benzyl-D-ribosyl and -L-Arabinosyl Bromides. *J. Org. Chem.* **1961**, *26*, 4605−4609.

(24) Glaudemans, C. P. J.; Fletcher, H. G. Syntheses with Partially Benzylated Sugars 3. A Simple Pathway to a cis-Nucleoside, 9-β-D-Arabinofuranosyladenine (Spongoadenosine). *J. Org. Chem.* **1963**, *28*, 3004−3006.

(25) Ogilvie, K. K.; Nguyenba, N.; Hamilton, R. G. Antiviral and Ring-open Nucleoside Analogs 6. A Trihydroxy Acyclonucleoside Series. *Can. J. Chem.* **1984**, *62*, 1622−1627.

(26) Townsend, L. B. Chapter 7. Nuclear Magnetic Resonance Spectroscopy in the Study of Nucleic Acid Components and Certain Related Derivatives. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Wiley: New York, 1973; Vol. 2, p 267−398.

(27) Beauchamp, L. M.; Serling, B. L.; Kelsey, J. E.; Biron, K. K.; Collins, P.; Selway, J.; Lin, J. C.; Schaeffer, H. J. Effect of Acyclic Pyrimidines Related to 9-[(1,3-Dihydroxy-2-propoxy)methyl]-guanine on Herpesviruses. *J. Med. Chem.* **1988**, *31*, 144−149.

(28) Robins, M. J.; Hatfield, P. W. Nucleic Acid Related Compounds 37. Convenient and High-yield Syntheses of N-[(2-Hydroxyethoxy)methyl] Heterocycles as Acyclic Nucleoside Analogs. *Can. J. Chem.* **1982**, *60*, 547−553.

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

(30) 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*, 2942−2949.

(31) Seley, K. L.; Zhang, L.; Hagos, A.; Quirk, S. "Fleximers". Design and Synthesis of a New Class of Novel Shape-modified Nucleosides. *J. Org. Chem.* **2002**, *67*, 3365−3373.

(32) Seley, K. L.; Zhang, L.; Hagos, A. "Fleximers". Design and Synthesis of Two Novel Split Nucleosides. *Org. Lett.* **2001**, *3*, 3209−3210.

(33) Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. Radical Rearrangement of 2-O−(Diphenylphosphoryl)glycosyl Bromides. A New Synthesis for 2-Deoxy Disaccharides and 2-Deoxy Ribonucleosides. *J. Org. Chem.* **1993**, *58*, 1083−1089.

(34) Maatschappij, N. V. *Chem. Abstr.* **1965**, *63*, 16369c.

(35) Saluja, S.; Zou, R. M.; Drach, J. C.; Townsend, L. B. Structure−activity Relationships 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.

(36) Shipman, C., Jr.; Smith, S. H.; Carlson, R. H.; Drach, J. C. Antiviral Activity of Arabinosyladenine and Arabinosylhypoxanthine in Herpes-simplex Virus-infected KB Cells—Selective-inhibition of Viral Deoxyribonucleic-acid Synthesis in Synchronized Suspension Cultures. *Antimicrob. Agents Chemother.* **1976**, *9*, 120−127.

(37) Turk, S. R.; Shipman, C., Jr.; Nassiri, R.; Genzlinger, 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.

(38) 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.

(39) Prichard, M. N.; Shipman, C., Jr. A 3-Dimensional Model To Analyze Drug−drug Interactions. *Antiviral Res.* **1990**, *14*, 181−206.

(40) Prichard, M. N.; Prichard, L. E.; Baguley, W. A.; Nassiri, M. R.; Shipman, C., Jr. 3-Dimensional Analysis of the Synergistic Cytotoxicity of Ganciclovir and Zidovudine. *Antimicrob. Agents Chemother.* **1991**, *35*, 1060−1065.

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