Synthesis and Antiviral Activity of Novel Erythrofuranosyl Imidazo[1,2-*a*]pyridine C-Nucleosides Constructed via Palladium Coupling of Iodoimidazo[1,2-*a*]pyridines and Dihydrofuran

Kristjan S. Gudmundsson,[†] John D. Williams, John C. Drach, and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy; Department of Chemistry, College of Literature, Sciences and the Arts; and Department of Biologic and Materials Sciences, School of Dentistry; The University of Michigan, Ann Arbor, Michigan 48019-1065

2,5,6-Trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) and certain analogues have shown significant activity against human cytomegalovirus. The metabolic instability of the glycosidic linkage in TCRB prompted us to synthesize the structurally similar imidazo[1,2-*a*]pyridine erythrofuranosyl C-nucleosides. As an approach to the synthesis of polychlorinated imidazo-[1,2-*a*]pyridine C-3-erythrofuranosides, a palladium-based methodology for coupling 2,3-dihydro-furan with chlorinated 3-iodoimidazo[1,2-*a*]pyridines was developed and optimized to give 80−90% yields of 2,6-dichloro- and 2,6,7-trichloro-3-(2,3-dideoxy-2,3-didehydro-D/L-erythrofuranosyl)-imidazo[1,2-*a*]pyridine. Dihydroxylation of these didehydro derivatives with osmium tetroxide or with AD-mix α gave a mixture of erythrofuranosyl C-nucleosides that were separated by standard and then chiral chromatography. When screened for anti-HCMV and HSV-1 activity, the α-D anomer of 2,6,7-trichloro-3-(erythrofuranosyl)imidazo[1,2-*a*]pyridine proved to be the most active member of the series, while the β-anomers all proved to be inactive.

Introduction

The C-nucleosides differ from the more commonly occurring N-nucleosides by virtue of a hydrolytically resistant carbon−carbon bond linking the carbohydrate moiety and heterocycle instead of the labile aminal linkage (carbon−nitrogen bond). The C-nucleosides of several different heterocycles, such as purines, pyrimidines, and pyridines, have been reported.[1] Several C-nucleosides, both naturally occurring and synthetic, have significant antibacterial, antiviral, and antitumor activities.[2] Some of these biological activities have been postulated to depend on the resistance of the carbon−carbon linkage to hydrolytic or enzymatic cleavage.[3]

The nucleoside 2,5,6-trichloro-1-(β-D-ribofuranosyl)-benzimidazole (TCRB, **1**)[4−7] shows potent and very selective activity against human cytomegalovirus with low cellular toxicity at concentrations inhibiting viral growth.[6−8] However, pharmacokinetic studies in rats and monkeys revealed that TCRB disappears rapidly from the bloodstream following either intravenous or oral dosage.[9] The disappearance of TCRB was correlated with a concomitant increase in blood concentration of its heterocyclic base, 2,5,6-trichlorobenzimidazole (**2**). This indicated that the glycosidic bond (aminal linkage) is unstable in vivo. The metabolic instability of the glycosidic bond in this benzimidazole nucleoside prompted us to consider the synthesis of the structurally related imidazo[1,2 -*a*]pyridine C-nucleosides (**3** and **4**), which should be more stable than their N-nucleoside counterparts.
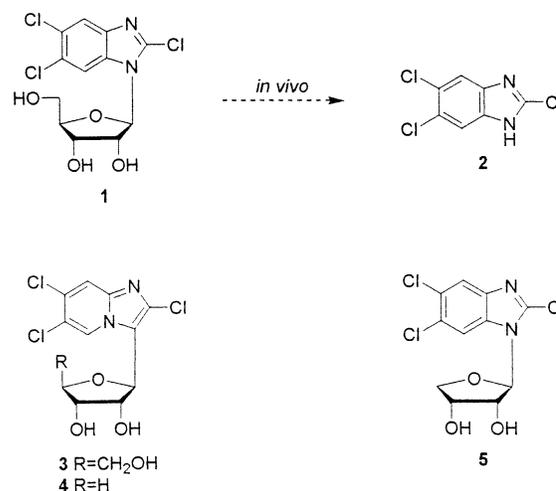
Figure 1. Benzimidazole and imidazo[1,2-*a*]pyridine nucleosides.

We have previously described the synthesis of 2,6,7-trichloro-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**3**) via an enantioselective construction of the ribose moiety and a synthesis of the regioisomeric 2,6,7-trichloro-5-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine by condensing a lithiated imidazo[1,2-*a*]pyridine with a suitably protected ribonolactone derivative.[10,11] As the erythroside 2,5,6-trichloro-1-(β-D-erythrofuranosyl)benzimidazole (**5**) had greater antiviral activity (10-fold) than the corresponding riboside **1**,[12] we became interested in the synthesis of the novel C-3 erythrofuranosyl imidazo[1,2-*a*]pyridine C-nucleoside **4**. The most direct route to the desired C-nucleoside appeared to be a palladium coupling of an iodinated imidazo[1,2-*a*]pyridine with 2,3-dihydrofuran. The synthetic utility of the palladium coupling reaction[13−15] for the formation of C-glycosides

* To whom correspondence should be addressed: University of Michigan, College of Pharmacy, 428 Church St., Ann Arbor, MI 48109-1065, phone: (734) 764−7547; fax: (734) 763−5633; e-mail: ltownsen@umich.edu.
† Present address: GlaxoSmithKline, Five Moore Dr., PO Box 13398, Research Triangle Park, NC 27709.

Scheme 1
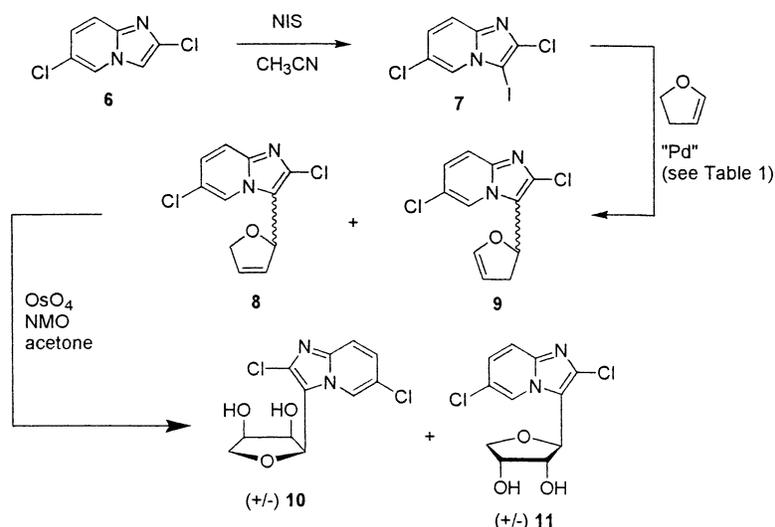
Table 1. Coupling of 3-Iodoimidazo[1,2-*a*]pyridine **7a** and 2,3-dihydrofuran

entry[a]	base (2 mol equiv)	ligand (0.2 mol equiv)	solvent	Ag$_2$CO$_3$ (2 mol equiv)	temp (°C)	% yields[b] 8	9
1[c]	Et$_3$N	Ph$_3$P	CH$_3$CN	−	25	10	11
2[c]	Et$_3$N	Ph$_3$P	DMF	−	25	20	10
3	Et$_3$N	Ph$_3$As	CH$_3$CN	−	25	20	25
4	Et$_3$N	Ph$_3$As	CH$_3$CN	−	60	15	30
5	Bu$_3$N	(*o*-tol)$_3$P	DMF	−	25	30	15
6	Et$_3$N	Ph$_3$As	DMF	−	25	55	35
7	Bu$_3$N	Ph$_3$As	DMF	−	25	55	35
8[d]	Et$_3$N	Ph$_3$As	DMF	+	60	60	25
9[d]	Et$_3$N	Ph$_3$As	DMF	+	45	81	0

[a] A typical procedure is outlined in the Experimental Section. [b] Isolated yields. [c] Increasing reaction temperature decreased the reaction time but did not improve the yield. [d] Other silver species, such as AgNO$_3$, did not improve the yield.

and C-nucleosides is impressive.[16−19] Among the C-nucleosides that have been synthesized via palladium coupling are various pyrazolo[4,3-*d*]pyrimidine,[20] pyrazine,[21] and pyrimidine[22,23] C-nucleosides. To date palladium coupling has not been used for the synthesis of imidazo[1,2-*a*]pyridine C-nucleosides. We now describe the synthesis of novel erythrofuranosyl imidazo[1,2-*a*]-pyridine C-nucleosides via palladium coupling and dihydroxylation, and the preliminary antiviral activities of these compounds.

Results and Discussion

Chemistry. As an initial approach, we chose to study the coupling of 2,3-dihydrofuran with 2,6-dichloro-3-iodoimidazo[1,2-*a*]pyridine (**7**). 2,6-Dichloroimidazo[1,2-*a*]pyridine (**6**)[24] was iodinated using *N*-iodosuccinimide in CH$_3$CN to give 2,6-dichloro-3-iodoimidazo[1,2-*a*]-pyridine (**7**) (Scheme 1). Iodination occurred only at the C3 position as shown by the splitting pattern of the heterocyclic protons, where the signal from the 5-H at 8.44 ppm is a doublet of doublets as a result of coupling to both 7-H and 8-H. Compound **7** was coupled to 2,3-dihydrofuran using palladium acetate under various conditions (see Table 1) to give racemic mixtures of 2,6-dichloro-3-(2,3-dideoxy-2,3-didehydro-*β*-D/L-erythro-furanosyl)imidazo[1,2-*a*]pyridine (**8**) and 2,6-dichloro-3-(2,3-dideoxy-3,4-didehydro-*β*-D/L-erythrofuranosyl)-

imidazo[1,2-*a*]pyridine (**9**). Initial yields from the palladium catalyzed coupling reaction were low, but have been optimized by changing several reaction conditions as outlined in Table 1.

The ratio of base (Et$_3$N or Bu$_3$N):Pd(OAc)$_2$:ligand (Ph$_3$P or Ph$_3$As or tri-(*o*-tolyl)phosphine) was kept constant for all entries. The selected ratio was based on results from Daves,[20] Heck,[13,25] and Czerneski.[26] Variations in the use of ligands were based on the fact that triphenylarsine[27] and tri-(o-tolyl)phosphine[28] have been reported to accelerate the rate of coupling over those rates obtained by using triphenylphosphine. Subsequent experiments showed that the amount of Pd(OAc)$_2$ may be varied between 0.05 and 0.3 equiv and that the ratio of Pd(OAc)$_2$ to Ph$_3$As (as long as the equivalent ratio of Ph$_3$As/Pd(OAc)$_2$ is greater than 2) did not adversely affect yields. Replacing the Pd(OAc)$_2$ with other palladium species (Pd(Ph$_3$P)$_4$ or other Pd° species) did not improve the yield. DMF proved to be a superior solvent to CH$_3$CN, CH$_3$NO$_2$, or toluene, presumably due to improved solubilization of salts formed during the reaction. Once conditions that gave an excellent combined yield of **8** and **9** were realized, reaction conditions were adjusted so that **8** could be obtained selectively as shown in entries 8 and 9. This was accomplished by adding silver salts to the reactions, as silver salts are known to prevent double bond migration in palladium reactions.[23,29−31] The addition of silver salts, however, slowed the coupling reaction to such an extent that it was not complete even after several days at room temperature. This effect was offset by increasing the reaction temperature. If the coupling reactions were run in the presence of a silver salt at 60 °C or a higher temperature, the formation of significant quantities of **9** was still observed. However, by lowering the temperature to 45 °C, **8** was formed exclusively and in good yield.

Finally, dihydroxylation of **8** using catalytic OsO$_4$ in the presence of *N*-methylmorpholine *N*-oxide (NMO)[32] gave a 1:2 mixture of the erythrofuranosyl C-nucleosides 2,6-dichloro-3-(*α*-D/L-erythrofuranosyl)imidazo[1,2-*a*]-pyridine (**10**) and its *β* anomer **11**, which were separated by column chromatography. Compounds **10** and **11** were assigned as being hydroxylated from the *β*- and *α*-face,

Scheme 2
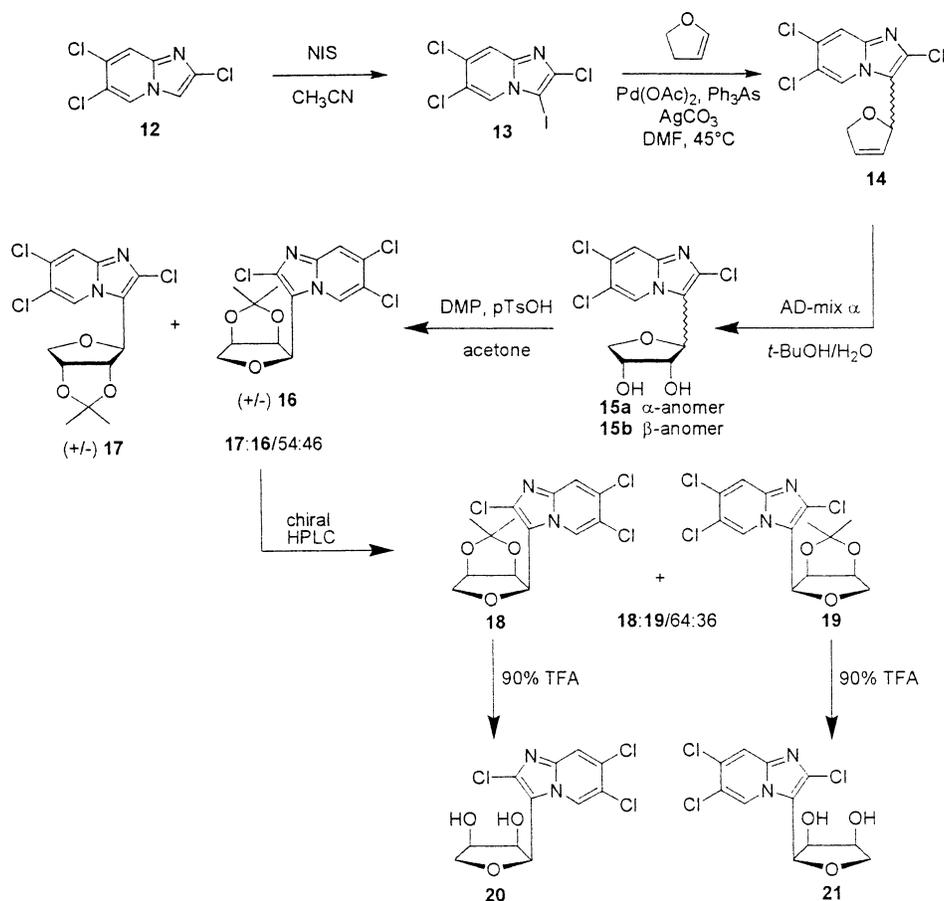
respectively, based on the shift of their anomeric protons.[33,34] The signal from the 1′-H in **10** appeared at 5.26 ppm while the 1′-H signal from **11** appeared at 5.03 ppm. Further support for this stereochemical assignment was obtained by NOE studies on **11** which showed positive NOE between the 2′-H on the erythrose moiety and the C_5-H on the imidazo[1,2-a]pyridine moiety. A similar NOE was not observed for derivative **10**. 2′,3′-Dideoxy-2′,3′-didehydro ribose nucleoside derivatives have been hydroxylated selectively from the α-face because the β-face is sterically hindered.[35] However, it was not surprising that the erythrose analogue gave a significant amount of **10** resulting from hydroxylation on the β-face, since the lack of a 4′-substituent significantly reduces steric hindrance to the β-face.

2,6,7-Trichloro-3-(β-D/L-erythrofuranosyl)imidazo[1,2-a]pyridines (**15b**) and its α-anomer (**15a**) were prepared using a similar palladium coupling and hydroxylation method. Thus, 2,6,7-trichloroimidazo[1,2-a]pyridine (**12**)[24] was iodinated to give 3-iodo-2,6,7-trichloroimidazo[1,2-a]pyridine (**13**) (Scheme 2). Compound **13** was coupled to 2,3-dihydrofuran in the presence of silver salts to give only the 2′,3′-dideoxy-2′,3′-didehydro erythroside **14** and not any of the isomeric 2′,3′-dideoxy-3′,4′-didehydro analogue. Compound **14** was dihydroxylated using AD-mix α to give a mixture of α and β anomers of 2,6,7-trichloro-3-(D/L-erythrofuranosyl)imidazo[1,2-a]pyridine (**15**). The use of AD-mix instead of osmium tetroxide/NMO was based upon the expectation that the desired enantiomer could be synthesized in excess, and later separated. Both AD-mix α and AD-mix β were utilized, but the biological activity of the compounds synthesized

with AD-mix α was greater. This was presumably because the proportion of the active component (i.e., **20**) was higher in the reactions using AD-mix α than in the reactions using AD-mix β. Therefore, AD-mix α was then chosen for all subsequent syntheses. Compound **15** was separated into two components, **15a** and **15b**; compound **15a** was ultimately assigned as a mixture of α-anomers. This assignment was based upon an X-ray crystal structure of the derivative **18**. Compound **15b** was consequently assigned as a mixture of β-anomers because of the previous assignment of its anomer **15a**. Antiviral evaluation of **15a** and **15b** revealed that the most active mixture was actually the mixture of α-anomers, **15a**.

It was further hypothesized that only one of the enantiomers of **15a** could be responsible for the activity of the mixture. To determine the activity of the different enantiomers of **15a**, we needed to effect a chiral resolution of the two enantiomers. To facilitate the separation of the anomers as well as later chiral chromatography, the acetonide of the mixture **15** was synthesized using 2,2-dimethoxypropane and acetone catalyzed by p-toluenesulfonic acid. The acetonide-protected 2,6,7-trichloro-3-(α-D/L-erythrofuranosyl)imidazo[1,2-a]pyridine (**16**) was then easily separated from its β anomer **17** (the ratio of **16**:**17** was 46:54) and then separated into the enantiomerically purified compounds **18** and **19** using chiral chromatography (the ratio of **18**:**19** was 64:36). Hydrolysis of the acetonides **18** and **19** using 90% aqueous TFA provided the erythrosides 2,6,7-trichloro-3-(α-D-erythrofuranosyl)imidazo[1,2-a]pyridine (**20**) and 2,6,7-trichloro-3-(α-L-erythrofuranosyl)imidazo[1,2-a]-
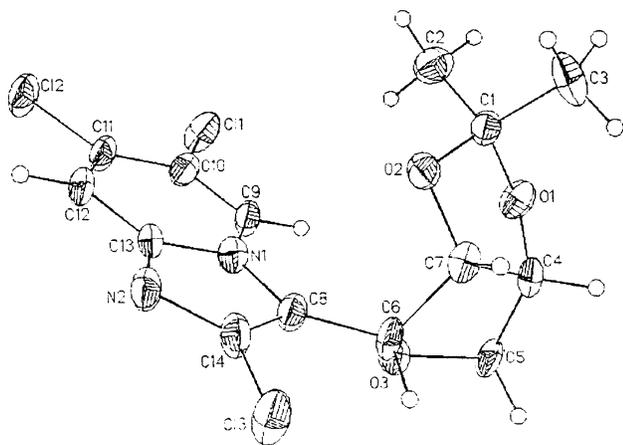
Figure 2. ORTEP diagram of intermediate **18**.

Table 2. Antiviral Activity and Cytotoxicity of Imidazo[1,2-*a*]pyridine C-Nucleosides

| no. | enan-tiomer | anomer | X | 50% inhibitory concentration (μM) | | | |
| | | | | antiviral activity | | cytotoxicity[c] | |
				HCMV[a] plaque	HSV-1[b] ELISA	visual	growth
11	D/L	α	H	>100[d]	>100	>100	>100
10	D/L	β	Cl	>100	>100	>100	>100
15a	D/L	α	Cl	8 ± 1	24 ± 33	>100	>100
15b	D/L	β	Cl	>100	>100	>100	>100
20	D	α	Cl	2.9 ± 1.6	14 ± 15	100	68 ± 4
21	L	α	Cl	>100	>100	>100	>100
TCRB[e]				2.9	102	238	210
DHPG[f]				7.4 ± 6.5	3.5 ± 2.1	>100	>100

[a] Plaque reduction assays were performed in duplicate as described in the text. Results are presented as means of 2−5 experiments ± standard deviations. [b] Compounds were assayed by ELISA in quadruplicate wells. [c] Visual cytotoxicity was scored on HFF cells at time of HCMV plaque enumeration. Inhibition of KB cell growth was determined as described in the text in quadruplicate assays. [d] >100 indicates IC$_{50}$ greater than the noted (highest) concentration tested. [e] Data for TCRB published previously as compound 9 in ref 6. [f] Average ± standard deviation from 108, 33, and 3 experiments, respectively.

pyridine (**21**), respectively. The absolute configuration as well as the anomeric configuration of these compounds were determined through X-ray crystallography of the acetonide-protected intermediate **18** (Figure 2).

Biological Evaluation. The new C-nucleosides were evaluated for activity against two selected herpes viruses and for cytotoxicity. The racemic 2,6-dichloro-3-(β-D/L-erythrofuranosyl)imidazo[1,2-*a*]pyridine (**10**) and 2,6-dichloro-3-(α-D/L-erythrofuranosyl)imidazo[1,2-*a*]-pyridine (**11**) were both inactive against HCMV and HSV-1 and not cytotoxic in uninfected cells (Table 2). In contrast, the enantiomeric mixture of 2,6,7-trichloro-3-(α-D/L-erythrofuranosyl)imidazo[1,2-*a*]pyridine (**15a**) was active against both HCMV and HSV-1. Surprisingly, the α-anomers (**15a**) were more active than the β-anomers (**15b**). These results are in direct contrast to the activity of TCRB[6] and its erythrofuranosyl

congener[12] against HCMV where the β-anomers are active, and the α-anomers are completely inactive.

Evaluation of the enantiomerically purified 2,6,7-trichloro-3-(α-D-erythrofuranosyl)imidazo[1,2-*a*]pyridine (**20**) and the L-enantiomer (**21**) revealed that all of the activity against the two herpes viruses resided in **20** whereas the L-enantiomer **21** was completely devoid of antiviral activity and was also noncytotoxic. Further details regarding the antiviral activity and mechanism of action of 2,6,7-trichloro-3-(α-D-erythrofuranosyl)-imidazo[1,2-*a*]pyridine (**20**) will be published elsewhere.

Experimental Section

General Procedures. Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 360 or 300 MHz. Flash column chromatography was performed using silica gel 60 230−400 mesh. Thin-layer chromatography (TLC) was performed on prescored Silica gel GHLF. 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 with a water bath at or below 40 °C. All solvents were dried prior to use as described by the handbook Purification of Laboratory Chemicals[36] and stored over 4 Å sieves, under argon. Materials obtained from commercial suppliers were used without purification.

2,6-Dichloro-3-iodoimidazo[1,2-*a*]pyridine (7). To a suspension of 2,6-dichloroimidazo[1,2-*a*]pyridine (**6**, 4.0 g, 0.02 mol) in dry CH$_3$CN (50 mL) was added *N*-iodosuccinimide (5.3 g, 0.024 mol) and the mixture stirred at room temperature for 1 h. The reaction mixture was heated at reflux for 10 min and then cooled to room temperature. Chloroform (200 mL) was added to the reaction mixture and the organic phase washed successively with 10% NaOH (100 mL), sodium thiosulfate (100 mL), and water (2 × 100 mL) and then dried over magnesium sulfate, filtered, and concentrated to dryness under reduced pressure. The resulting solid was suspended in MeOH and filtered to give 5.0 g (80%) of **7** as a white crystalline solid: mp 234−235 °C; R_f 0.43 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, DMSO-d_6):δ 8.44 (dd, 1H, J = 0.8 Hz, J = 2.0 Hz), 7.63 (dd, 1H, J = 0.8 Hz, J = 9.5 Hz), 7.45 (dd, 1H, J_7 = 9.5 Hz, J = 2.0 Hz).^{13}C NMR (90 MHz, DMSO-d_6):δ 144.39, 141.02, 127.45, 125.17, 121.33, 117.39, 66.49. Anal. Calcd for C$_7$H$_3$-Cl$_2$IN$_2$: C, H, N.

2,6-Dichloro-3-(2,3-dideoxy-2,3-didehydro-β-D/L-erythrofuranosyl)imidazo[1,2-*a*]pyridine (8) and 2,6-Dichloro-(2,3-dideoxy-3,4-didehydro-β-D/L-erythrofuranosyl)-imidazo[1,2-*a*]pyridine (9). Procedure A: Pd(OAc)$_2$ (85 mg, 0.38 mmol) and Ph$_3$As (0.24 g, 0.77 mmol) were placed in a flame-dried flask under argon. Dry DMF (7 mL) was added and the solution stirred at room temperature for 1 h. 2,6-Dichloro-3-iodoimidazo[1,2-*a*]pyridine (**7**, 0.5 g, 1.6 mmol) was then added to the reaction mixture, followed by the addition of Et$_3$N (1 mL, 6.4 mmol) and 2,3-dihydrofuran (0.6 mL, 8 mmol). The reaction mixture was stirred under argon overnight, EtOAc (30 mL) was added, and the resulting slurry was filtered through SiO$_2$ (30 g). The silica pad was washed with EtOAc (100 mL), and the organic phase was concentrated to dryness. The resulting solid was purified by flash column chromatography (EtOAc/hexane 1:5, 15 cm × 2 cm). The fractions containing each product (as determined by UV absorbance) were pooled, concentrated to dryness under reduced pressure, and recrystallized from a H$_2$O/MeOH mixture to give 219 mg (55%) of **8** as a white crystalline solid and 140 mg (35%) of **9** as a white crystalline solid.

Procedure B: Same as procedure A except that 2 equiv of Ag$_2$CO$_3$ were added to the reaction mixture at the same time as the heterocycle **7**. Following the addition of Et$_3$N and dihydrofuran, the reaction mixture was heated at 45 °C for 48 h. The reaction mixture was worked up as described for procedure A to give an 80% yield of **8** after recrystallization. **8**: mp 95−96 °C; R_f 0.21 (EtOAc/hexane 1:5); ^{1}H NMR (300

MHz, CDCl$_3$):δ 7.99 (dd, 1H, J = 0.8 Hz, J = 1.5 Hz), 7.46 (dd, 1H, J = 0.8 Hz, J = 9.5 Hz), 7.19 (dd, 1H, J = 1.5 Hz, J = 9.5 Hz), 6.29 (m, 2H), 5.92 (m, 1H), 4.90 (m, 2H). ^{1}H NMR (360 MHz, DMSO-d_6):δ 8.34 (d, 1H, J = 1.9 Hz), 7.65 (d, 1H, J = 9.5 Hz), 7.46 (dd, 1H, J = 1.9 Hz, J = 9.5 Hz), 6.40 (m, 1H), 6.28 (m, 1H), 6.07 (m, 1H), 4.86 (m, 1H), 4.70 (m, 1H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 141.41; 134.06; 130.00; 126.82; 125.14; 122.61; 120.32; 117.78; 117.71; 77.27; 75.34. HRMS m/z calcd for C$_{11}$H$_8$Cl$_2$N$_2$O 254.0013, found 254.0002. Anal. Calcd for C$_{11}$H$_8$Cl$_2$N$_2$O: C, H, N. **9**: mp 109−110 °C; R_f 0.29 (EtOAc/hexane 1:5); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.21 (d, 1H, J = 1.9 Hz), 7.65 (d, 1H, J = 9.6 Hz), 7.45 (dd, 1H, J = 9.6 Hz, J = 1.9 Hz), 6.68 (d, 1H), 6.01 (dd, 1H, J = 9.4 Hz, J = 11.8 Hz), 5.26 (m, 1H), 2.95 (m, 2H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 145.334; 141.338; 128.597; 126.648; 122.738; 120.388; 118.536; 117.425; 99.951; 71.876; 31.750. HRMS m/z calcd for C$_{11}$H$_8$Cl$_2$N$_2$O 254.0013, found 254.0002. Anal. Calcd for C$_{11}$H$_8$Cl$_2$N$_2$O: C, H, N.

2,6-Dichloro-3-(β-D/L-erythrofuranosyl)imidazo[1,2-a]-pyridine (10) and 2,6-Dichloro-3-(α-D/L-erythrofurano-syl)imidazo[1,2-a]pyridine (11). Compound **8** (260 mg, 1 mmol) was added to a solution of acetone (8 mL) and water (3 mL) containing *N*-methylmorpholine *N*-oxide (158 mg, 1.4 mmol) and osmium tetroxide (2.5 mg, 0.01 mmol). The mixture was stirred at room temperature for 12 h. Sodium sulfite (1 g) was added and the mixture stirred for an additional 1 h and then partitioned between EtOAc (50 mL) and water (50 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic extracts were subsequently washed with 2 N NaOH (20 mL), dried over magnesium sulfate, filtered, and evaporated to dryness under reduced pressure to give a yellowish residue. This residue was purified by flash chromatography (EtOAc/hexane 2:1, 15 cm × 2 cm) to give in order of elution **10** (R_f 0.43 EtOAc/hexane 2:1) and **11** (R_f 0.38 EtOAc/hexane 2:1). Appropriate fractions were combined, solvent removed under reduced pressure and each solid recrystallized from aqueous methanol to give 66 mg (23%) of **11** and 135 mg (47%) of **10**. **11**: mp 183 °C; R_f 0.43 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.83 (d, 1H, J = 2.0 Hz), 7.58 (d, 1H, J = 9.6 Hz), 7.40 (dd, 1H, J = 9.6 Hz, J = 2.0 Hz), 5.40 (d, 1H, J = 4.2 Hz, D$_2$O exchangeable), 5.26 (m, 2H, simplifies to d, 1H, J = 4.3 Hz upon D$_2$O wash), 4.40 (t, 1H, J = 5.3 Hz), 4.26 (m, 1H), 3.82 (q, 1H), 3.89 (q, 1H); ^{13}C NMR (90 MHz, DMSO-d_6): δ 141.44, 134.85, 126.60, 123.36, 120.22, 117.37, 117.11, 73.65, 73.44, 72.32, 70.28; UV λ_{max} (ethanol) 291 (4162), 233 (19596); (pH 11) 289 (4458), 233 (26566); (pH 1) 288 (6416), 226 (26295); HRMS m/z calcd for C$_{11}$H$_{10}$Cl$_2$N$_2$O$_3$ 288.0068, found 288.0079. Anal. Calcd for C$_{11}$H$_{10}$Cl$_2$N$_2$O$_3$: C, H, N. **10**: mp 180−181 °C; R_f 0.38 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.49 (d, 1H, J = 2.0 Hz), 7.64 (d, 1H, J = 9.6 Hz), 7.45 (dd, 1H, J = 9.6 Hz, J = 2.0 Hz), 5.19 (d, 1H, J = 6.3 Hz, D$_2$O exchangeable), 5.11 (broad s, 1H, D$_2$O exchangeable), 5.03 (d, 1H, J = 9.03 Hz), 4.43 (m, 1H), 4.32 (m, 1H), 4.20 (m, 1H), 3.75 (m, 1H); ^{13}C NMR (90 MHz, DMSO-d_6): δ 141.79, 134.14, 126.50, 125.85, 118.77, 116.68, 116.56, 75.74, 73.83, 71.10, 70.96; UV λ_{max} (ethanol) 291 (3740), 234 (25960); (pH 11) 288 (4339), 233 (27841); (pH 1) 287 (7748), 227 (28099); HRMS m/z calcd for C$_{11}$H$_{10}$Cl$_2$N$_2$O$_3$ 288.0068, found 288.0065. Anal. Calcd for C$_{11}$H$_{10}$Cl$_2$N$_2$O$_3$: C, H, N.

3-Iodo-2,6,7-trichloroimidazo[1,2-a]pyridine (13). Following the preparation of **7**, compound **12** (1.7 g, 7.7 mmol) was treated with NIS to give 2.2 g (82%) of **13** as a white crystalline solid: mp 215−216 °C; R_f 0.54 (EtOAc/hexane 1:2); ₁H NMR (360 MHz, DMSO-d_6): δ 8.62 (s, 1H), 7.69 (s, 1H); ^{1}H NMR (360 MHz, CDCl$_3$) δ 8.20 (d, 1H, J = 0.5 Hz), 7.69 (d, 1H, J = 0.5 Hz);^{13}C NMR (90 MHz, DMSO-d_6): δ 144.08, 141.85, 130.14, 126.64, 119.98, 116.49, 66.67; HRMS m/z calcd for C$_7$H$_2$Cl$_3$IN$_2$ 345.8329, found 345.8332. Anal. Calcd for C$_7$H$_2$-Cl$_3$IN$_2$: C, H, N.

2,6,7-Trichloro-3-(2,3-dideoxy-2,3-didehydro-β-D/L-eryth-rofuranosyl)imidazo[1,2-a]pyridine (14). Following the preparation of **8**, compound **13** (200 mg, 0.58 mmol) was treated according to procedure B, described above, and **14** was

obtained (163 mg, 98%) as a white crystalline solid. **14**: mp 134−135 °C; R_f 0.21 (EtOAc/hexane 1:10); ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.10 (d, 1H, J = 0.6 Hz), 7.66 (d, 1H, 0.6 Hz), 6.32 (m, 1H), 6.27 (m, 1H), 5.94 (m, 1H), 4.9 (m, 2H); ^{13}C NMR (90 MHz, CDC$_{13}$): δ 142.59, 136.52, 131.46, 130.31, 125.78, 123.76, 120.58, 117.2, 116.99, 78.53, 75.86. Anal. Calcd for C$_{11}$H$_7$-Cl$_3$N$_2$O·^{1}/$_4$H$_2$O: C, H, N.

2,6,7-Trichloro-3-(β-D/L-erythrofuranosyl)imidazo[1,2-a]pyridine (15b) and 2,6,7-Trichloro-3-(α-D/L-erythro-furanosyl)imidazo[1,2-a]pyridine (15a). Compound **14** (1.18 g, 4.1 mmol) was added in one portion to a solution of water (30 mL) and *tert*-butyl alcohol (30 mL) and stirred until mostly dissolved. The solution was cooled in an ice bath while AD-mix α (9.27 g) and methanesulfonamide (0.40 g, 4.2 mmol) were added with vigorous stirring. The resulting two-phase suspension was stirred vigorously at 4 °C for 36 h. The reaction was quenched by adding sodium bisulfite until the yellow color of the suspension disappeared. The reaction was then diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over magnesium sulfate, filtered, and evaporated to dryness under reduced pressure to give 1.28 g of **15a** and **15b** as a cream-colored powder (97%). Analytical samples of **15a** and **15b** were prepared by purifying a portion of the crude material by flash chromatography (EtOAc/hexane 2:1). **15b**: mp 190−192 °C; R_f 0.11 (4% MeOH in CHCl$_3$); R_f 0.41 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6):δ 8.69 (s, 1H), 8.06 (s, 1H), 5.18 (d, 1H, J = 6.8 Hz, D$_2$O exchangeable), 5.11 (d, 1H, J = 3.8 Hz, D$_2$O exchangeable), 5.04 (d, 1H, J = 8.9 Hz, 1′-H), 4.42 (m, 1H), 4.33 (dd, 1H, J = 9.5 Hz, J = 4.3 Hz), 4.2 (m, 1H), 3.75 (dd, 1H, J = 9.5 Hz, J = 1.6 Hz); ^{13}C NMR (90 MHz, DMSO-d_6): δ 141.48, 135.42, 129.47, 124.79, 118.99, 117.40, 116.58, 73.73, 73.40, 72.64, 70.26; UV λ_{max} (ethanol) 325 (3103), 296 (3000), 287 (3008), 237 (19676); (pH 11) 320 (1000), 295 (2697), 243 (22889); (pH 1) 297 (3553), 237 (18940). HRMS m/z calcd for C$_{11}$H$_{10}$Cl$_3$N$_2$O$_3$ 321.9679, found 321.9683. **15a**: mp 224 °C (dec); R_f 0.18 (4% MeOH in CHCl$_3$); R_f 0.45 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6):δ 9.03 (s, 1H), 8.00 (s, 1H), 5.40 (d, 1H, J = 4.5 Hz, D$_2$O exchangeable), 5.31 (d, 1H, J = 5.5 Hz, D$_2$O exchangeable), 5.24 (d, 1H, J = 4.8 Hz, 1′-H), 4.39 (m, 1H), 4.28 (m, 1H), 3.84 (m, 2H); ^{13}C NMR (90 MHz, DMSO-d_6): δ 141.82, 134.87, 129.39, 127.08, 117.59, 116.74, 115.93, 75.49, 73.79, 71.07, 71.02; UV λ_{max} (ethanol) 320 (1040), 296 (1080), 285 (1012), 235 (14600); (pH 11) 320 (3700), 296 (4100), 243 (29600); (pH 1) 297 (5500), 236 (24691); HRMS m/z calcd for C$_{11}$H$_{10}$Cl$_3$N$_2$O$_3$ 321.9679, found 321.9694.

2,6,7-Trichloro-3-(2,3-O-isopropylidene-β-D/L-erythro-furanosyl)imidazo[1,2-a]pyridine (17) and 2,6,7-Trichloro-3-(2,3-O-isopropylidene-α-D/L-erythrofuranosyl)imidazo-[1,2-a]pyridine (16). The crude compound **15** (1.08 g, 3.3 mmol) and *p*-toluenesulfonic acid hydrate (20 mg, 0.1 mmol) were suspended in a mixture of 10 mL of dry acetone and 10 mL of 2,2-dimethoxypropane and stirred at room temperature until completely dissolved. The solvent was removed under reduced pressure, and the resulting viscous residue was dissolved in EtOAc (100 mL). The organic phase was washed with 5% aqueous Na$_2$CO$_3$ then brine, dried over magnesium sulfate, filtered, and evaporated to dryness under reduced pressure to give a clear oil which solidified upon standing. This solid was purified by flash chromatography (hexane/EtOAc 3:1, 45 cm × 5 cm) to give, in order of elution, **17** (R_f = 0.33, 3:1 hexane:EtOAc) and **16** (R_f = 0.20, 3:1 hexane:EtOAc). Appropriate fractions were combined, and the solvent was removed under reduced pressure to give 0.60 g of **17** and 0.51 g of **16** (92% combined yield) as a cream-colored powder. **17**: mp 178−181 °C; R_f 0.33 (hexane:EtOAc 3:1); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.87 (s, 1H), 7.60 (s, 1H), 4.98 (s, 1H), 4.93 (s, 1H), 4.87 (s, 1H), 4.31 (d, 1H, J = 10 Hz), 3.70 (d, 1H, J = 10 Hz), 1.53 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 142.93, 135.80, 131.42, 127.23, 119.23, 116.31, 113.80, 112.55, 82.48, 80.64, 73.07, 25.89, 23.63. HRMS m/z calcd for C$_{14}$H$_{13}$-Cl$_3$N$_2$O$_3$ 361.9992, found 361.9979. Anal. Calcd for C$_{14}$H$_{13}$-Cl$_3$N$_2$O$_3$: C, H, N. **16**: mp 174−175°C; R_f 0.20 (hexane:EtOAc

3:1); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.36 (s, 1H), 7.67 (s, 1H), 5.59 (dd, 1H, $J = 6$ Hz, $J = 2$ Hz), 5.33 (s, 1H), 5.06 (t, 1H, $J = 5$ Hz), 4.03 (d, 1H, $J = 9$ Hz), 3.74 (dd, 1H, $J = 4$ Hz, $J = 11$ Hz), 1.60 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 142.47, 135.43, 132.23, 123.46, 121.42, 116.59, 115.66, 113.50, 81.95, 81.26, 73.04, 26.77, 25.12. HRMS m/z calcd for C$_{14}$H$_{13}$-Cl$_3$N$_2$O$_3$ 361.9992, found 361.9984. Anal. Calcd for C$_{14}$H$_{13}$-Cl$_3$N$_2$O$_3$: C, H, N.

2,6,7-Trichloro-3-(2,3-*O*-isopropylidene-α-D-erythrofuranosyl)imidazo[1,2-*a*]pyridine (18) and 2,6,7-Trichloro-3-(2,3-*O*-isopropylidene-α-L-erythrofuranosyl)imidazo-[1,2-*a*]pyridine (19). Compound **16** (1.00 g, 2.8 mmol) was submitted to Chiral Technologies, Inc. of Exton, PA for chiral resolution. The sample was subjected to chiral HPLC (CHIRAL-PAK AD, 50 cm × 5 cm, 89.95:10:0.05 acetonitrile:2-propanol:diethylamine) to give, in order of elution, compound **18** (3.65 min, 1.0 mL/min., 21 kg/cm^2) in 99% ee and compound **19** (5.22 min, 1.0 mL/min., 21 kg/cm^2) in 98% ee. Appropriate fractions were combined, and the solvent removed under reduced pressure to give 0.61 g (61%) of **18** as a white powder and 0.34 g (34%) of **19** as a white powder. **18**: mp 174−175 °C; R_f 0.20 (hexane:EtOAc 3:1); spectroscopic data matches that for compound **16**. **19**: mp 174−175 °C; R_f 0.20 (hexane:EtOAc 3:1); spectroscopic data matches that for compound **16**.

2,6,7-Trichloro-3-(α-D-erythrofuranosyl)imidazo[1,2-*a*]-pyridine (20). Compound **18** (209 mg, 0.57 mmol) was suspended in 10 mL of 90% TFA/water and stirred at room temperature for 10 min. The solvent was then removed under vacuum, and the resulting residue was suspended in 30 mL of 5% sodium carbonate. The aqueous suspension was extracted with EtOAc (2 × 25 mL). The organic extract was then washed with brine (25 mL), dried over magnesium sulfate, and evaporated to yield a pale yellow powder. This residue was purified by flash chromatography (4:1 EtOAc:hexane, 35 cm × 4 cm). The fractions containing the product were pooled and concentrated to dryness under reduced pressure to give 76 mg of **20** (41%) as a white powder: mp 212−215 °C; R_f 0.45 (EtOAc/hexane 2:1); spectroscopic data matches that found for compound **15a**, except: Anal. Calcd for C$_{11}$H$_9$Cl$_3$N$_2$O$_3$·$^1/_5$EtOAc: C, H, N.

2,6,7-Trichloro-3-(α-L-erythrofuranosyl)imidazo[1,2-a]-pyridine (21). Following the preparation of compound **20**, compound **19** (112 mg, 0.31 mmol) was treated with 90% TFA/water to yield 52 mg (53%) of **21** as a white powder: mp 213-216 °C; R_f 0.45 (EtOAc/hexane 2:1); spectroscopic data matches that found for compound **15a**.

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.[37]

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.[38] High titer HSV-1 stocks were prepared by infecting KB cells at an moi of <0.1 also as detailed previously.[38] 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.[39] 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 eleven 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 to 20 plaques per well. Virus titers were calculated according to the following formula: Titer (pfu/mL) = number of plaques x 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, 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, stained with crystal violet and microscopic plaques enumerated as described above. Drug effects were calculated as a percentage of reduction in number of plaques in the presence of each drug concentration compared to the number observed in the absence of drug.

HSV-1 ELISA. An ELISA was employed[40] 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$_2$SO$_4$ 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.[38] (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.[41] 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 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 linearly regressing 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, ganciclovir for HCMV, and 2-acetylpyridine thiosemicarbazone for cytotoxicity) were used in all assays.

References

(1) Watanabe, K. A. The Chemistry of C-Nucleosides. *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1994; Vol. 3, pp 421−535.

(2) Hacksell, U.; Daves, G. D., Jr. The Chemistry and Biochemistry of C-Nucleosides and C-Arylglycosides. *Progress in Medicinal Chemistry*; Elsevier: Amsterdam, 1985; Chapter 1, pp 1−65.

(3) Daves, G. D., Jr. The Occurrence of Natural Stable Analogues: Implications for the Design of Therapeutic Agents. *Acta Pharm. Suec.* **1987**, *24*, 275−288.

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

(5) Revankar, G. R.; Townsend, L. B. The Synthesis of 2-Chloro-1-(β-D-ribofuranosyl)benzimidazole and Certain Related Derivatives. *J. Heterocycl. Chem* **1968**, *5*, 477−483.

(6) 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.

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

(8) 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 Nucleoside is Mediated Through the UL89 Gene Product. *J. Virol.* **1998**, *72*, 717−725.

(9) Good, S. S.; Owens, B. S.; Townsend, L. B.; Drach, J. C. The Disposition in Rats and Monkeys of 2-Bromo-1-(β-D-ribofuranosyl)benzimidazole (BDCRB) and its 2,5,6-Trichloro Congener (TCRB). *Antiviral Res.* **1994**, *23(S)*, 103.

(10) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. The Condensation of 2,6-Dichloroimidazo[1,2-a]pyridine with Ribonolactone Gives a Novel Imidazo[1,2-a]pyridine C-Nucleoside with an Unexpected Site of Ribosylation. *Tetrahedron Lett.* **1996**, *37*, 2365−2368.

(11) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. Synthesis of Imidazo[1,2-a]pyridine C-Nucleosides with an Unexpected Site of Ribosylation. *J. Org. Chem.* **1997**, *62*, 3453−3459.

(12) Gudmundsson, K. S.; Tidwell, J.; Lippa, N.; Koszalka, G. W.; van Draanen, N.; Ptak, R. G.; Drach, J. C.; Townsend, L. B. Synthesis and Antiviral Evaluation of Halogenated β-D- and L-Erythrofuranosylbenzimidazoles. *J. Med. Chem.* **2000**, *43*, 2464−2472.

(13) Heck, R. F. Coupling of Aryl Halides with Alkenes. *Palladium Reagents in Organic Synthesis*; Heck, R. F., Ed.; Academic Press: New York, 1985; pp 276−287.

(14) Heck, R. F.; Nolley, J. P., Jr. Paladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides. *J. Org. Chem.* **1972**, *37*, 2320−2322.

(15) Sonogashira, K.; Tohda, Y.; Hagirara, N. A Convenient Synthesis of Acetylenes: catalytic Substitutions of Acetylenic Hydrogen with Bromoalkanes, Iodoarenes, and Bromopyridines. *Tetrahedron Lett.* **1975**, 4467−4470.

(16) Daves, G. D., Jr. C-Glycoside Synthesis by Palladium-Mediated Glycal-Aglycon Coupling Reactions. *Acc. Chem. Res.* **1990**, *23*, 201−206.

(17) Daves, G. D., Jr. Glycals in Palladium-Mediated C-Glycosyl Bond Formation. *Carbohydrates: Synthetic Methods and Applications in Medicinal Chemistry*; VCH Publishers: New York, 1992; pp 49−65.

(18) Jaramillo, C.; Knapp, S. Synthesis of Aryl C-Glycosides. *Synthesis* **1994**, 1−20.

(19) Postema, M. H. D. Recent Developments in the Synthesis of C-Glycosides. *Tetrahedron* **1992**, *48*, 8545−8599.

(20) Zhang, H.-C.; Daves, G. D., Jr. Synthesis of 2′-Deoxypseudouridine, 2′-Deoxyformycin B, and 2′, 3′-Dideoxyformycin B by Palladium-Mediated Glycal-Aglycon Coupling. *J. Org. Chem.* **1992**, *57*, 4690−4696.

(21) Chen, J. J.; Walker, J. A., II; Liu, W.; Wise, D. S.; Townsend, L. B. An Efficient and Stereospecific Synthesis of Novel Pyrazine C-Nucleosides. *Tetrahedron Lett.* **1995**, *36*, 8363−8366.

(22) Cheng, J. C.-Y.; Hacksell, U.; Daves, G. D., Jr. Facile Synthesis of 2′-Deoxy-3′-Keto- and 2′-Deoxypseudouridine Derivatives and Analogues. Palladium(II)-Mediated Coupling Reactions of Furanoid Glycals. *J. Org. Chem.* **1986**, *51*, 3093−3098.

(23) Zhang, H.-C.; Daves, G. D., Jr. Enantio- and Diastereoisomers of 2,4-Dimethoxy-5-(2,3-dideoxy-5-O-tritylribofuranosyl)pyrimidine. 2′,3′-Dideoxy Pyrimidine C−Nucleosides by Palladium-Mediated Glycal-Aglycon Coupling. *J. Org. Chem.* **1993**, *58*, 2557−2560.

(24) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. An Improved Synthesis of 2-Chlorinated Imidazo[1,2-a]pyridines and the Application of this Procedure for the Synthesis of Several Polychlorinated Imidazo[1,2-a]pyridines. *Synth. Commun.* **1997**, *27*, 1763−1776.

(25) Heck, R. F. New Applications of Palladium in Organic Syntheses. *Pure Appl. Chem.* **1978**, *50*, 691−701.

(26) Benhaddou, R.; Czerneski, S.; Ville, G.; Zegar, A. A Kinetic Investigation of Some Electronic and Ligand Effects in the Heck Reaction with Allylic Alcohols. *Organometallics* **1988**, *7*, 2435−2439.

(27) Farina, V.; Krishnan, B. Large Rate Accelerations in the Stille Reaction with Tri-2-furylphosphine and Triphenylarsine as Palladium Ligands: Mechanistic and Synthetic Implications. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(28) Zebovitz, T. C.; Heck, R. F. Palladium-Catalyzed Arylation of Unsaturated Acetals and Ketals. *J. Org. Chem.* **1977**, *42*, 3907−3909.

(29) Karabelas, K.; Westerlund, C.; Hallberg, A. The Effect of Added Silver Nitrate on the Palladium-Catalyzed Arylation of Allyltrimethylsilanes. *J. Org. Chem.* **1985**, *50*, 3896−3900.

(30) Larock, R. C.; Gong, W. H. Palladium-Catalyzed Synthesis of *trans*-2,5-Diaryltetrahydrofurans, Potent Platelet Activating Factor Antagonists. *J. Org. Chem.* **1990**, *55*, 407−408.

(31) Larock, R. C.; Gong, W. H.; Baker, B. E. Improved Procedure for the Palladium-Catalyzed Intermolecular Arylation of Cyclic Alkenes. *Tetrahedron Lett.* **1989**, *30*, 2603−2606.

(32) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. Catalytic Osmium Tetroxide Oxidation of Olefins: *cis*-1,2-Cyclohexanediol. *Organic Syntheses*; Noland, W., Ed.; John Wiley and Sons: New York, 1988; Collective Vol. 6; pp 342−348.

(33) Chu, C. K.; El-Kabbani, F. M.; Thompson, B. B. Determination of the Anomeric Configuration of C-Nucleosides by ^{1}H and ^{13}C NMR Spectroscopy. *Nucleosides Nucleotides* **1984**, *3*, 1−31.

(34) Townsend, L. B. Nuclear Magnetic Respnance Spectroscopy in the Study of Nucleic Acid Components and Certain Related Derivatives. *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Wiley-Interscience: New York, 1973; Vol. 2; pp 267−398.

(35) Skaric, V.; Matulic-Adamic, J. Synthesis of 5-Methyluridine and Its 5′-Mercapto-, 2-Amino-, and 4′,5′-Unsaturated Analogues. *Helv. Chim. Acta* **1980**, *63*, 2179−2186.

(36) Perrin, D. D.; Armarengo, W. L. F. *Purification of Laboratory Chemicals,* 3rd ed.; Pergamon Press: New York, 1988.

(37) Shipman, C., Jr.; Smith, S. H.; Carlson, R. H.; Drach, J. C. Antiviral Activity of Arabinofuranosyladenine and Arabinofuranosylhypoxanthine in Herpes Simplex Virus-Infected KB Cells. Selective Inhibition of Viral DNA Synthesis in Synchronized Suspension Cultures. *Antimicrob. Agents Chemother.* **1976**, *9*, 120−127.

(38) 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.

(39) Prichard, M. N.; Turk, S. R.; Coleman, L. A.; Engelhardt, S. L.; Shipman, C., Jr., Drach, J. C. A Mictotiter Virus Yield Reduction Assay for the Evaluation of Antiviral Compounds Against Human Cytomegalovirus and Herpes Simplex Virus. *J. Virol. Methods* **1990**, *28*, 101−106.

(40) Prichard, M. N.; Shipman, C., Jr. A Three-Dimensional Model to Analyze Drug-Drug Interactions. *Antiviral Res.* **1990**, *14*, 181−206.

(41) Prichard, M. N.; Prichard, L. E.; Baguley, W. A.; Nassiri, M. R.; Shipman, C., Jr. Three-Dimensional Analysis of the Synergistic Cytotoxicity of Ganciclovir and Zidovudine. *Antiviral Res.* **1991**, *35*, 1060−1065.