Design, Synthesis, and Antiviral Activity of Certain 3-Substituted 2,5,6-Trichloroindole Nucleosides

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A series of trichlorinated indole nucleosides has been synthesized and tested for activity against human cytomegalovirus (HCMV) and herpes simplex virus type-1 (HSV-1) and for cytotoxicity. Modifications of the previously reported 2,5,6-trichloro-1-(β-D-ribofuranosyl)indole at the 3-position of the heterocycle were designed in part to test our hypothesis that hydrogen bonding is required at that position for antiviral activity. Analogues were synthesized using electrophilic addition at the 3-position or by synthesis of modified indole heterocycles followed by glycosylation and modification of the sugar. Among the modifications at the 3-position, only those analogues with hydrogen-bond-accepting character were active against HCMV (e.g., 3-formyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole, FTCRI, IC_{50} = 0.23 μM). Conversely, analogues with non-hydrogen-bonding substituents at the 3-position (e.g., 3-methyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole) were much less active (IC_{50} = 32 μM) than those with the requisite hydrogen-bonding capacity. The 5′-*O*-acyl analogue of FTCRI was obtained as an intermediate and also found to be a potent inhibitor of HCMV (IC_{50} < 0.1 μM). The synthesis of some additional 5′-*O*-acylated analogues did not provide a compound with increased antiviral activity. None of the indole nucleosides had significant activity against HSV-1, and none were cytotoxic to uninfected cells in their antiviral dose range. Results obtained from the antiviral evaluations have validated our hypothesis that hydrogen bonding at the 3-position is required for antiviral activity in this series of chlorinated indole nucleosides.

Introduction

Human cytomegalovirus (HCMV) is an opportunistic pathogen that is endemic in both industrialized and developing nations.[1] It is estimated that 50% of the American public is seropositive for HCMV.[2] Although HCMV poses little risk to healthy individuals, a variety of immunocompromised populations are susceptible to HCMV-related pathologies. AIDS patients, for example, are susceptible to retinitis and gastritis, transplant recipients are susceptible to organ rejection, and neonates are at risk for a host of birth defects and developmental disorders.[1,3]

There are currently five FDA-approved drugs used for the treatment of HCMV infections, namely, ganciclovir,[4] valganciclovir,[5] cidofovir,[6] foscarnet,[7] and fomivirsen.[8] All of these compounds suffer limitations, however, including poor oral bioavailability and toxicity. Furthermore, all of the licensed compounds (with the exception of fomivirsen) act upon the viral DNA polymerase, making the emergence of new drug-resistant viral strains likely.

The search for new compounds with fewer or less severe limitations has led our laboratory to synthesize a wide range of nucleoside analogues, including 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (**1**, TCRB).[9] Although TCRB demonstrated excellent antiviral activity and selectivity in vitro, it was degraded (via glycosidic bond cleavage) too rapidly in vivo to be of interest as a clinical candidate.[10] Further investigations have led to the syntheses of numerous TCRB analogues with stabilized glycosidic bonds. Included among these compounds is 2,5,6-trichloro-1-(β-D-ribofuranosyl)indole[11] (TCRI, **3**). TCRI should be more stable to glycosidic bond cleavage because protonation of the heterocyclic base is a likely mechanism involved in enzymatic degradation, and the indole heterocycle is much more difficult to protonate than benzimidazole owing to the basic nitrogen at the benzimidazole 3-position (see Figure 1). Although TCRI itself is inactive against HCMV, it was hypothesized that the installation of a hydrogen-bonding substituent at the 3-position of the indole ring would act as a surrogate for the 3-nitrogen in TCRB, thus restoring antiviral activity. We now describe the synthesis of a series of chlorinated indole nucleosides with exocyclic groups at the 3-position of the heterocycle and the effect that these groups exert on their antiviral activity and cytotoxicity.

Results and Discussion

Chemistry. For our initial studies in this area, we elected to investigate the procedures and methods that would add certain exocyclic groups directly to TCRI at the 3-position. Because the 3-position of indole is quite electrophilic, many possibilities were attractive, among them the Vilsmeier−Haack formylation, Friedel−Crafts

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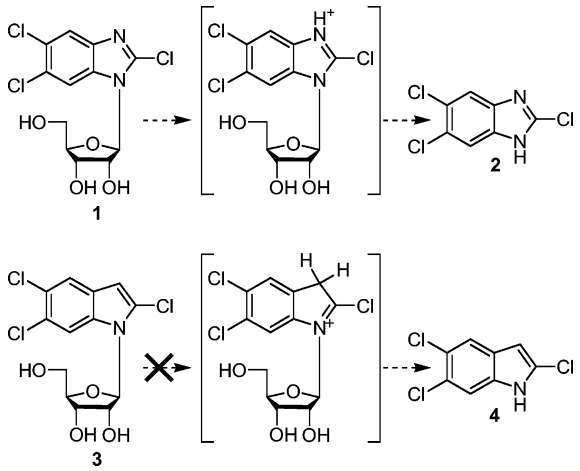


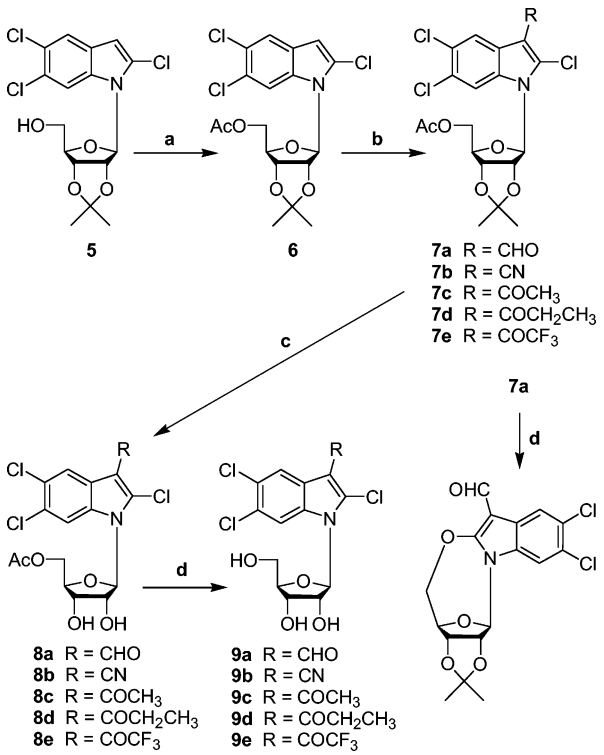
Figure 1. Proposed in vivo degradation of TCRB and resistance of indole nucleosides to glycosidic cleavage.

acylations, and electrophilic cyanation with chlorosulfonyl isocyanate.[12] The known intermediate 2,5,6-trichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)indole[11] (**5**), produced by a modification of the previous procedure, was protected as the 5′-*O*-acetate ester to provide **6**. Formylation and cyanation of **6** proceeded in moderate yield to provide the expected compounds **7a** and **7b**. A reaction of **6** under Friedel−Crafts conditions with aluminum chloride and either acetyl or propionyl chloride provided low yields of **7c** and **7d**. The attempted trifluoroacetylation using trifluoroacetic anhydride and aluminum chloride was unsuccessful, but the procedure of Kiselyov,[13] using a mixture of trifluoroacetic anhydride and BF_3/SMe_2, did provide the desired trifluoroacetyl derivative **7e** in yields comparable to the previous Lewis acid-catalyzed acylations.

All of the analogues thus produced were deprotected in a two-part procedure. The acetonide was first hydrolyzed using 90% aqueous trifluoroacetic acid to provide the 5′-*O*-acetylated intermediates **8a**−**e**. The acetate esters were then hydrolyzed using methanolic sodium methoxide to provide the fully deprotected nucleosides **9a**−**e**. The order in which the protecting groups are removed is very important. If the fully protected nucleoside analogue **7a** is treated first with sodium methoxide, an anhydro nucleoside is produced as the only product (see Scheme 1).

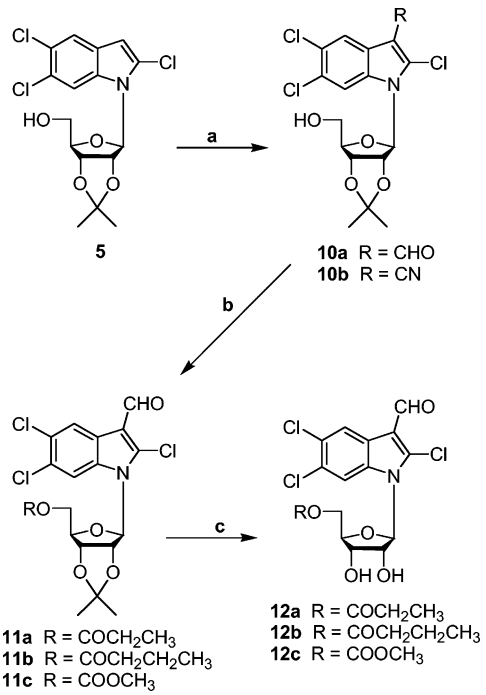
Our initial antiviral screening indicated that the 5′-*O*-acetylated indole nucleoside analogue **8a** was particularly potent against HCMV. To further explore this interesting activity, we decided to synthesize a number of **8a** analogues with other acyl protecting groups at the 5′-position. To minimize the number of synthetic transformations necessary for the completion of this series, the 5′-unprotected nucleoside **10a** was required. However, because this intermediate could not be synthesized by a partial deprotection of **7a** (because of anhydro nucleoside formation, vide supra), another strategy was needed to provide **10a** (Scheme 2). Therefore, we used the easily hydrolyzed trifluoroacetate ester as a "temporary protecting group". The precursor **5** was trifluoroacetylated with trifluoroacetic anhydride, and the crude material was subjected to either formylation or cyanation reactions under the previous conditions. Aqueous workup was sufficient in this case to cleave the trifluoroacetate ester and provide **10a** and **10b** in

Scheme 1[a]



[a] Reagents and conditions: (a) Ac_2O, 100 °C, 4 h; (b) $POCl_3$, DMF, 70 °C, 16 h or CSI, CH_2Cl_2, 20 °C, 16 h, then DMF, 20 °C, 1 h or RCOCl, $AlCl_3$, 20 °C, 1 h or TFAA, BF_3/SMe_2, 20 °C, 90 min; (c) 90% TFA, 20 °C, 2 min; (d) NaOMe, MeOH, 20 °C, 15−90 min.

Scheme 2[a]

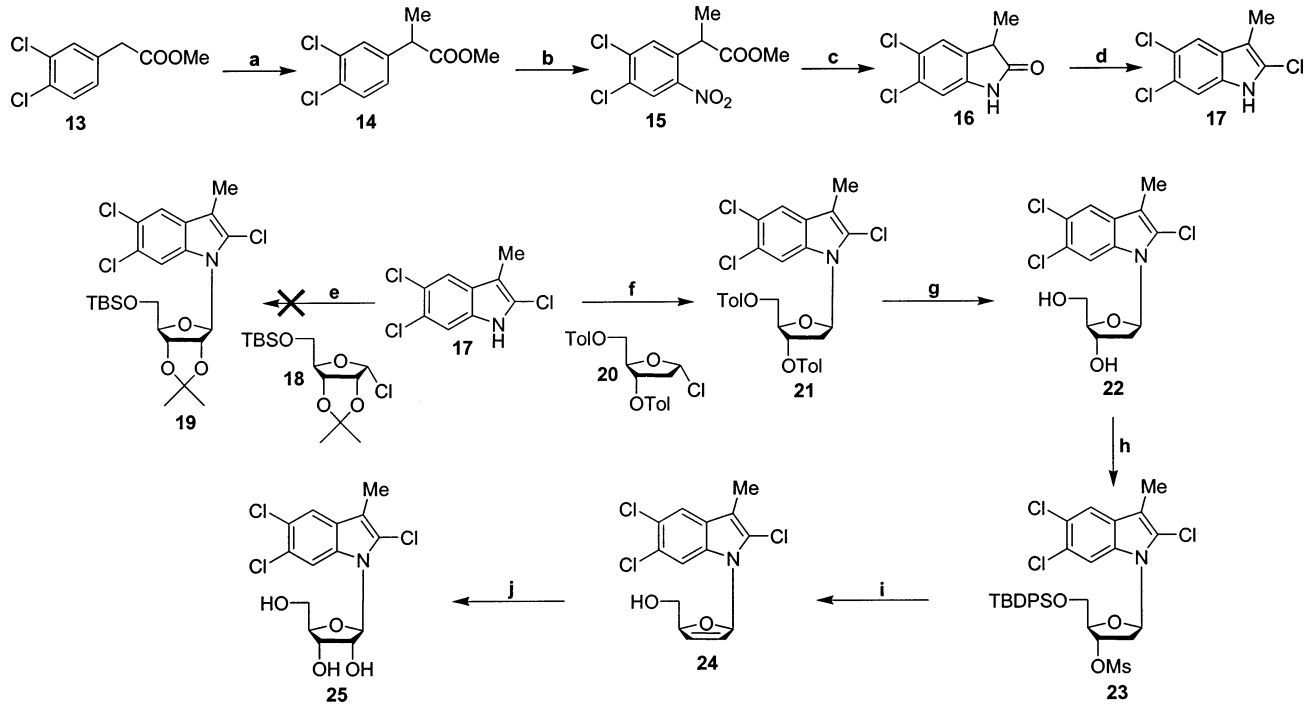


[a] Reagents and conditions: (a) TFAA, CH_2Cl_2, 20 °C, 90 min, then $POCl_3$, DMF, 70 °C, 16 h or CSI, CH_2Cl_2, 20 °C, 16 h, then DMF, 20 °C, 1 h, aqueous workup; (b) $(RCO)_2O$, DMAP, pyridine, 120 °C, 12 min; (c) 90% TFA, 20 °C, 2 min.

reasonable yield without the formation of any anhydro nucleoside.

We then carried out the desired acylations with either propionic or butyric anhydride and DMAP in pyridine

Scheme 3[a]



[a] Reagents and conditions: (a) $NaNH_2$, NH_3(l), −78 °C, 30 min, then MeI, −78 °C, 30 min; (b) HNO_3, H_2SO_4, 5 °C, 35 min; (c) H_2, PtO_2, Na_2SO_4, 20 °C, 4 h, then AcOH, 20 °C, 2 h; (d) $POCl_3$, CH_3CN, 100 °C, 1 h, then imidazole, 100 °C, 16 h; (e) NaH, THF, 0 °C, 10 min, then **18**, THF/toluene, 60 °C, 16 h; (f) NaH, THF, 0 °C, 10 min, then **20**, THF/toluene, 20 °C, 3 h; (g) NaOMe, MeOH, 20 °C, 2 h; (h) TBDPSCl, pyridine, 20°C, 24 h, then MsCl, pyridine, 20 °C, 4 h; (i) *t*-BuOK, DMSO/H_2O 20 °C, 10 min; (j) OsO_4, NMO, acetone/H_2O, 20 °C, 18 h.

with heating to provide **11a** and **11b** in low yield (less harsh conditions did not produce the desired acylated compounds). Treatment of **10a** with methyl chloroformate and pyridine provided the carbonate **11c** in good yield. The 5′-*O*-acylated nucleosides **11a**−**c** were then treated with 90% aqueous trifluoroacetic acid to yield the target compounds **12a**−**c**.

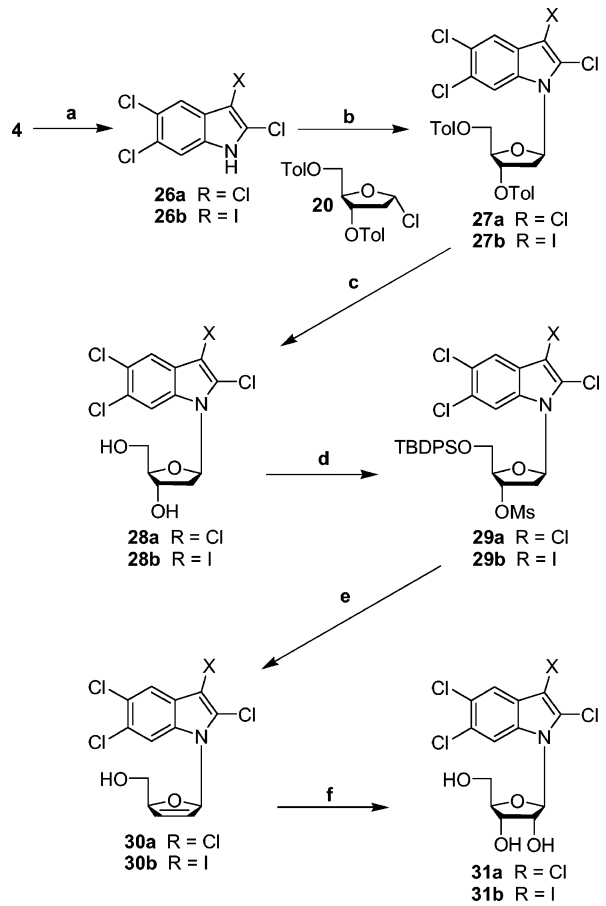
Our antiviral screening assays indicated that the addition of a hydrogen-bonding substituent at the 3-position did indeed impart good antiviral activity to this series of compounds. With these promising initial biological results, a more extensive exploration of the structure−activity relationship (SAR) in this series was undertaken.

These studies were initiated in an effort to determine what other factors might be involved in the binding of this class of compounds to their target. Synthesis of the 3-methyl derivative would be useful to determine whether the hydrogen-bonding effects are actually required for activity or whether steric and van der Waals contacts are sufficient. No efficient method for the electrophilic introduction of simple alkyl groups was available, so it was necessary to synthesize the requisite chlorinated 3-methylindole heterocycle and couple that heterocycle with an appropriate glycosyl donor. Ethyl 3,4-dichlorophenylacetate (**13**) was deprotonated with a mixture of sodium amide in liquid ammonia and then methylated with methyl iodide.[14] By optimization of the amount of sodium amide and methyl iodide used, little of the dialkylated product was obtained. The resulting dichlorophenylpropionate ester **14** was then nitrated with HNO_3/H_2SO_4. Reduction of the nitro group followed by an acid-catalyzed ring closure provided the oxindole **16**. Compound **16** was then chlorinated with phosphorus oxychloride and imidazole to yield 3-methyl-2,5,6-trichloroindole (**17**).

Unfortunately, the sodium salt method used to synthesize TCRI[11] did not work in the case of the 3-methyl derivative. Because the synthesis of **19** using the α-chlorosugar **18**[15] and the indole **17** was unsuccessful, the desired riboside was synthesized via the manipulation of a 2′-deoxyribofuranoside. Thus, 3-methyl-2,5,6-trichloroindole (**17**) was deprotonated with sodium hydride and reacted with the α-chlorosugar 3,5-di-*O*-(*p*-toluoyl)-2-deoxy-α-D-ribofuranosyl chloride[16] (**20**), which produced the nucleoside **21** in good yield (Scheme 3). The protected nucleoside **21** was deprotected with sodium methoxide in methanol and converted to the 3′-*O*-mesylate after the 5′-position had been protected with the bulky TBDPS protecting group. Base-promoted elimination of the mesylate and concomitant removal of the silyl protecting group resulted in the formation of the 2,3-dideoxy-2,3-didehydro nucleoside **24**, which was dihydroxylated with osmium tetroxide. Dihydroxylation occurred exclusively on the α-face of the sugar because of steric hindrance of the β-face and provided 3-methyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (**25**) in good yield.

The 3-chloro and 3-iodo derivatives of the indole nucleosides were also desirable targets because they would provide non-hydrogen bonding, electron-withdrawing substituents at the 3-position. Furthermore, the 3-iodo derivative could be used in palladium-catalyzed coupling reactions to further explore the structural requirements of the 3-position. Direct electrophilic halogenation of the protected indole nucleoside **6** using several different procedures was unsuccessful (data not presented), so a strategy similar to that used

Scheme 4[a]



[a] Reagents and conditions: (a) NCS or NIS, CH_3CN, 20 °C, 1 h; (b) NaH, THF, 0 °C, 10 min, then **20**, THF/toluene, 20 °C, 3 h; (c) NaOMe, MeOH, 20 °C, 2 h; (d) TBDPSCl, pyridine, 20°C, 24 h, then MsCl, pyridine, 20 °C, 4 h; (e) *t*-BuOK, DMSO/H_2O, 20 °C, 10 min; (f) OsO_4, NMO, acetone/H_2O, 20 °C, 18 h.

in the synthesis of the 3-methyl analogue **25** was initiated. The 3-halogenated heterocycles 2,3,5,6-tetrachloroindole (**26a**) and 3-iodo-2,5,6-trichloroindole (**26b**) were prepared easily by a reaction of 2,5,6-trichloroindole[11] (**4**) with *N*-chlorosuccinimide and *N*-iodosuccinimide, respectively (Scheme 4). The heterocycles were deprotonated with sodium hydride and glycosylated with the α-chlorosugar **20**. Deprotection of the 2′-deoxyribofuranosyl nucleoside intermediates **27a** and **27b** followed by 5′-*O*-silylation and 3′-*O*-mesylation led to the intermediates **29a** and **29b**. Base-promoted elimination followed by dihydroxylation with osmium tetroxide yielded the expected ribofuranosides **31a** and **31b**.

Having synthesized the ribofuranosyl derivative of 3-iodo-2,5,6-trichloroindole, our attention turned to the palladium-catalyzed coupling of the iodinated nucleoside with other heterocyclic components. Either Suzuki-[17] or Stille-type[18] couplings could be used for this purpose, but the former was selected largely because of the toxicity of tin derivatives required for Stille couplings. 2-Furylboronic acid and 3-thiopheneboronic acid were selected as coupling partners because of their availability, relatively small size, and potential hydrogen-bonding ability.

The ribofuranosides **35a** and **35b** were synthesized from 3-iodo-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (**31b**). Compound **31b** was first protected with 2,2-dimethoxypropane and chloromethyl methyl ether to avoid the side reaction of boronic ester formation during the Suzuki coupling. The resulting 2′,3′-*O*-isopropylidene-5′-*O*-methoxymethyl intermediate **33** was then subjected to the coupling conditions as described by Huff[19] (Scheme 5). The protected 3-aryl nucleoside analogues **34a** and **34b** were synthesized in good yield and then deprotected in wet methanolic HCl to produce the desired analogues **35a** and **35b**.

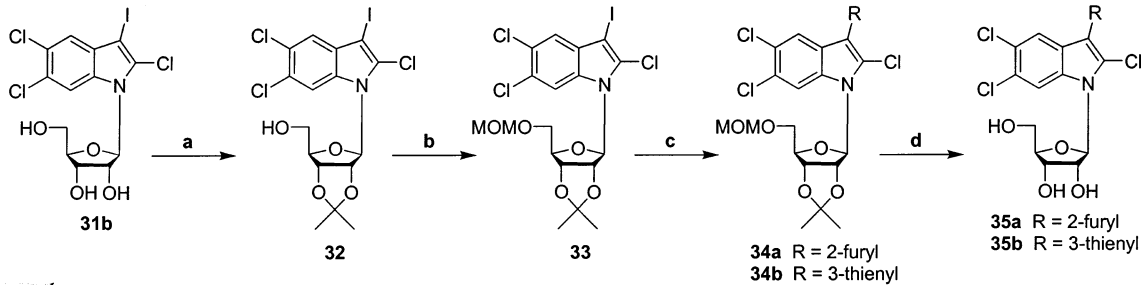
Another desirable synthetic target was the homoaldehyde **38**. This extended aldehyde can be compared to the 3-acetyl derivative **7c**. Both of these compounds have very similar steric bulk and hydrogen-bonding capacity, but the homoaldehyde has more conformational flexibility. This compound was synthesized from the protected 3-formylindole nucleoside **7a** (Scheme 6). Wittig olefination of the aldehyde using the phosphorus ylide derived from (methoxymethyl)triphenylphosphonium chloride provided the vinyl ether **36** as a mixture of cis and trans isomers. The aldehyde was unmasked and the sugar was deprotected by treatment with wet methanolic HCl, but the aldehyde was immediately converted in situ to the dimethyl acetal **37**, which was not rigorously characterized. The acetal was then hydrolyzed with 90% aqueous trifluoroacetic acid to provide the desired nucleoside **38**.

It has been established that 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB) is more active against HCMV than TCRB.[9] The structural similarity of the benzimidazole nucleosides compared to the indole nucleosides synthesized in the present investigation prompted us to initiate some studies on the synthesis of the 2-bromo analogues of selected indole nucleosides. The carboxaldehyde **9a** and its 5′-*O*-acetyl analogue **8a** were very active and selective inhibitors, and we therefore chose the 2-bromo analogues of these compounds (**42** and **43**, respectively) as synthetic targets.

In a methodology analogous to the synthesis of **8a** and **9a**, 2-bromo-5,6-dichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)indole[11] (**39**) was acetylated at the 5′-position with acetic anhydride in pyridine. The protected nucleoside was then subjected to Vilsmeier−Haack formylation conditions using a mixture of phosphorus oxybromide and DMF (use of phosphorus oxychloride led to halogen exchange at the 2-position; data not presented). Deprotection of the 3-formyl intermediate **41** with 90% aqueous trifluoroacetic acid provided the desired nucleoside **42**. Further reaction of **42** with methanolic sodium methoxide provided the fully deprotected nucleoside **43** (Scheme 7).

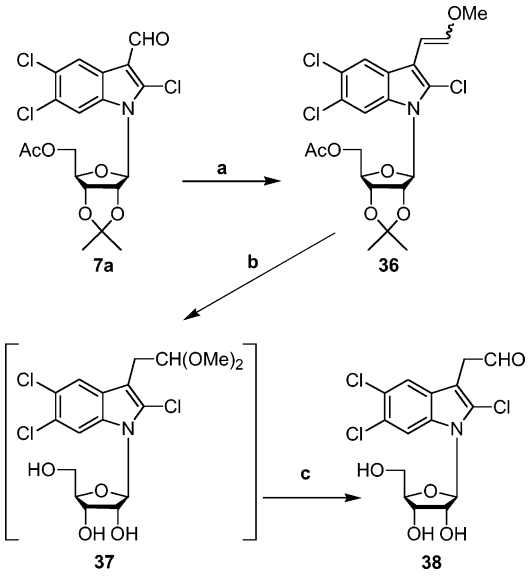
Biological Evaluation. The compounds synthesized above were tested for activity against HCMV and HSV-1 and for cytotoxicity. Although none of the compounds demonstrated potent and selective inhibition of HSV-1 replication, our initial exploration into substituents at the 3-position provided several active and selective compounds against HCMV replication. The 3-formyl analogue **9a** was the most potent against HCMV with an IC_{50} of 0.23 μM, whereas the 3-acetyl analogue **9c** was somewhat less cytotoxic and therefore more selective. Further increasing the length of the acyl chain at the 3-position (i.e., 3-propionyl analogue **9d**) resulted

Scheme 5[a]



[a] Reagents and conditions: (a) DMP, *p*-TsOH, acetone, 20 °C, 15 min; (b) MOMCl, DIPEA, CH_2Cl_2, 20 °C 16 h; (c) Ar−$B(OH)_2$, $Pd(OAc)_2$, $(o\text{-tol})_3P$, Na_2CO_3, DMF/*n*-PrOH/H_2O, 120 °C, 5−15 min; (d) HCl, MeOH/H_2O, 60 °C, 45 min.

Scheme 6[a]



[a] Reagents and conditions: (a) Ph_3P=CHOMe, THF, 0 °C, 1 h; (b) HCl, MeOH/H_2O, 60 °C, 1 h; (c) 90% TFA, 20 °C, 2 min.

in a decrease in the activity of the compound. The 3-nitrile **9b** was slightly less active and slightly more toxic than **9a** or **9c**. The 3-trifluoroacetyl analogue **9e** was also substantially less active than the aforementioned acyl analogues (Table 1).

The 3-methyl, 3-chloro, and 3-iodo analogues **25**, **31a**, and **31b**, respectively, were all substantially less active, but no less cytotoxic, than the analogues with hydrogen-bonding capacity. This suggests that steric and van der Waals forces between the nucleosides and their enzymatic target are not sufficient for potent antiviral activity and that electron-withdrawing substituents are also not sufficient in the absence of hydrogen-bond acceptors. Interestingly, the nucleosides do not require hydrogen bonding for cytotoxicity, thereby suggesting the specific inhibition of a viral target. The presence of van der Waals interactions is necessary for cytotoxicity, however, because TCRI (which lacks a substituent at the 3-position) is not cytotoxic.

Although the 2-furyl and 2-thienyl analogues **35a** and **35b** could be involved in hydrogen bonding, they were much less potent than the 3-acyl analogues above. Perhaps these substituents are too bulky or the additional aryl system contributed to unfavorable interactions in the putative viral target. Additionally, the homoaldehyde **38** was also much less active than either **9a** or **9c**. Because the homoaldehyde has bulk similar to that of the very potent **9c**, we hypothesize that the additional degrees of rotational freedom afforded by the methylene bridge resulted in an entropic binding penalty and was therefore less potent.

The 5′-*O*-acetyl analogues **8b**−**d**, synthesized en route to the initial series of analogues, had activities comparable to those of their 5′-unprotected congeners (Table 2). One difference was noted for the 3-formyl analogue **8a**, which was more potent than the fully deprotected **9a** in initial plaque-reduction assays without being substantially more cytotoxic. This prompted us to synthesize some other acylated derivatives (**12a**−**c**). However, the other 5′-*O*-acyl groups and the 5′-carbonate were less active against HCMV than **8a**, and no additional modifications were pursued.

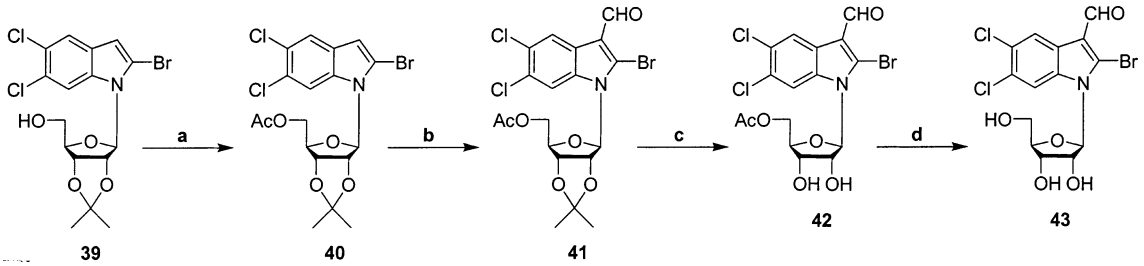
The 2-bromo homologues of **8a** and **9a** (**42** and **43**, respectively) also were potent and selective inhibitors of HCMV replication. The antiviral activity of the FTCRI analogue **43** was comparable to FTCRI (**9a**), and the activity of **42** was less than its 2-chloro congener **8a**. These results are in direct contrast to the relationship of TCRB and its 2-bromo homologue BDCRB, where the latter is more active and selective than the 2-chloro homologue.[9]

The results of our HCMV screening assays (Tables 1 and 2) are in good agreement with our initial hypothesis that hydrogen-bond acceptors are required for the potent activity of this series of indole nucleosides against HCMV. Furthermore, this suggests that the difference in activity between TCRB and TCRI can be explained in terms of hydrogen bonding and not by changes in the electronic character of the heterocycle.

Experimental Section

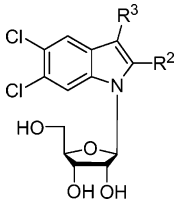
General Procedures. All solvents were dried prior to use according to known procedures. All reagents were obtained from commercial sources or were synthesized from literature procedures and were used without further purification unless otherwise noted. Air-sensitive reactions were performed under slight positive pressure of argon. Room temperature is assumed to be between 20 and 25 °C. Evaporation of solvents was accomplished under reduced pressure (water aspirator, 12 mmHg), at less than 40 °C, unless otherwise noted. Chromatography solvent systems are expressed in v/v ratios or as % vol. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Thin-layer chromatography was performed on silica gel GHLF plates from Analtech (Newark, DE). Chromatograms were visualized under UV light at 254 nm. Spectra for all compounds are presented in the Supporting Information. ^1H NMR spectra were obtained at 500 MHz on a Bruker DRX500 spectrometer. ^{13}C NMR spectra were obtained at 125 MHz on a Bruker DRX500 spectrometer. ^{19}F NMR spectra were obtained at 300 MHz on a Bruker

Scheme 7[a]



[a] Reagents and conditions: (a) Ac_2O, pyridine, 20 °C, 4 h; (b) $POBr_3$, DMF, 70 °C, 16 h; (c) 90% TFA, 20 °C, 2 min; (d) NaOMe, MeOH, 20 °C, 15−90 min.

Table 1. Antiviral Activity and Cytotoxicity of 3-Substituted Indole Nucleosides



			50% inhibitory concentration (μM)			
			antiviral		cytotoxicity	
compd	R^2	R^3	HCMV plaque[a]	HSV-1 ELISA[b]	HFF visual[c]	KB growth[c]
9a	−Cl	−CHO	0.23	40	45	45
9b	−Cl	−CN	0.55	15	32	65
9c	−Cl	$-COCH_3$	0.31	20	>100[d]	50
9d	−Cl	$-COCH_2CH_3$	2.5	20	>100	100
9e	−Cl	$-COCF_3$	6.2	15	32	20
25	−Cl	$-CH_3$	32	70	32	>100
31a	−Cl	−Cl	38	45	32	80
31b	−Cl	−I	12	20	32	65
35a	−Cl	−(2-furyl)	42	50	32	80
35b	−Cl	−(3-thienyl)	31	45	>100	60
38	−Cl	$-CH_2CHO$	4.0	>100	>100	70
43	−Br	−CHO	0.32	20	32	50
TCRB[e]			2.9	102	238	210
BDCRB[e]			0.70	130	118	>100
GCV[f]			7.4	3.5	>100	>100

[a] Plaque reduction assays were performed in duplicate wells as described in the text. [b] Compounds were assayed by ELISA in quadruplicate wells. [c] Visual cytotoxicity was scored on HFF cells at the time of HCMV plaque enumeration in duplicate wells; inhibition of KB cell growth was determined in triplicate wells as described in the text. [d] >100 indicates an IC_{50} greater than the highest concentration tested. [e] Data for TCRB and BDCRB (2,5,6-trichloro- and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole, respectively) were published previously as compounds **9** and **11**, respectively, in ref 9. [f] Averages from 108, 33, and 3 experiments, respectively, using ganciclovir (GCV).

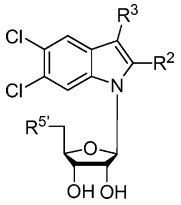
DPX300 spectrometer. Chemical shift values for ^1H were determined relative to an internal tetramethylsilane standard (0.00 ppm). Chemical shift values for ^{13}C were determined relative to the solvent used (39.52 ppm for DMSO-d_6 and 77.23 ppm for $CDCl_3$). Chemical shift values for ^{19}F were determined relative to an external TFA standard (−76.50 ppm). Mass spectrometry and elemental analysis for selected compounds (listed in Supporting Information) were performed at the University of Michigan, Department of Chemistry mass spectrometry facility and elemental analysis facility, respectively.

2,5,6-Trichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)indole (5). (**5** was prepared on a large scale by a modification of the procedure of Chen.[11]) 2,3-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranose[15] (18.27 g, 60.0 mmol) was dissolved in dry toluene (120 mL) to which was added dry carbon tetrachloride (25 mL, 40 g, 260 mmol). The solution was cooled to −20 °C in an ice/salt bath, and hexamethylphosphorus triamide (13.0 mL, 11.5 g, 72 mmol) was added dropwise over 20 min. Once the addition was complete, the resulting cloudy suspension was stirred at −20 °C for an additional 30 min, and then the suspension was poured into cold brine (500 mL). The organic layer was separated, and the aqueous layer was extracted with an additional portion of cold toluene (200 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the filtrate was diluted to 400 mL total volume to yield a solution of crude α-chlorosugar **18** in toluene, which was used immediately without further purification.

2,5,6-Trichloroindole[11] (11.03 g, 50.0 mmol) was dissolved in dry THF (200 mL) and cooled to 5 °C on an ice bath. To the cooled solution was added sodium hydride (60% in mineral oil, 2.5 g, 63 mmol) in small portions. The resulting suspension was stirred at <10 °C for 10 min until gas evolution had ceased. The resulting suspension was filtered, and the solids were rinsed with dry THF (50 mL). The filtrate was diluted to 400 mL total volume with dry THF, then combined with the crude solution of **18**. The combined solution was heated on a 70 °C oil bath for 16 h, then cooled to room temperature and evaporated to yield a red oil. The oil was dissolved in EtOAc (500 mL), washed with water (200 mL) and brine (200 mL), then dried over $MgSO_4$, filtered, and evaporated to yield a red oil. The oil was dissolved in $CHCl_3$ (15 mL) and subjected to column chromatography (100 mm × 1000 mm) on silica gel with 5:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 14.41 g (57%) of a clear oil, which solidified upon standing.

The above solid (14.41 g, 28.4 mmol) was dissolved in dry DMF (125 mL) to which was added cesium fluoride (8.65 g,

Table 2. Antiviral Activity and Cytotoxicity of Sugar-Modified Indole Nucleosides



				50% inhibitory concentration (μM)			
				antiviral		cytotoxicity	
compd	R^2	R^3	$R^{5'}$	HCMV plaque[a]	HSV-1 ELISA[b]	HFF visual[c]	KB growth[c]
8a	−Cl	−CHO	$-OCOCH_3$	<0.1[d]	20	32	35
8b	−Cl	−CN	$-OCOCH_3$	2.5	50	32	70
8c	−Cl	$-COCH_3$	$-OCOCH_3$	0.30	20	32	40
8d	−Cl	$-COCH_2CH_3$	$-OCOCH_3$	3.2	15	>100[e]	100
12a	−Cl	−CHO	$-OCOCH_2CH_3$	0.22	10	32	50
12b	−Cl	−CHO	$-OCOCH_2CH_2CH_3$	0.25	9.0	32	40
12c	−Cl	−CHO	$-OCOOCH_3$	0.20	15	32	50
42	−Br	−CHO	$-OCOCH_3$	0.32	15	32	40
TCRB[f]				2.9	102	238	210
BDCRB[f]				0.70	130	118	>100
GCV[g]				7.4	3.5	>100	>100

[a] Plaque reduction assays were performed in duplicate wells as described in Experimental Section. [b] Compounds were assayed by ELISA in quadruplicate wells. [c] Visual cytotoxicity was scored on HFF cells at the time of HCMV plaque enumeration in duplicate wells; inhibition of KB cell growth was determined in triplicate wells as described in Experimental Section. [d] <0.1 indicates an IC_{50} less than the lowest concentration tested. [e] >100 indicates an IC_{50} greater than the highest concentration tested. [f] Data for TCRB and BDCRB (2,5,6-trichloro- and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole, respectively) were published previously as compounds **9** and **11**, respectively, in ref 9. [g] Averages from 108, 33, and 3 experiments, respectively, using ganciclovir (GCV).

57 mmol). The suspension was stirred vigorously at room temperature for 2 h, and then the solvent was removed under vacuum (0.5 mmHg, 40 °C). The residual oil was suspended in brine (300 mL) and extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The oil was dissolved in $CHCl_3$ (10 mL) and subjected to column chromatography (100 mm × 1000 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 10.27 g (92%) of **5**[11] as a clear syrup. R_f = 0.5 (2:1 hexane/EtOAc). ^{1}H NMR and ^{13}C NMR results match literature precedent.[11]

2,5,6-Trichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-*β*-D-ribofuranosyl)indole (6). Compound **5**[11] (544 mg, 1.4 mmol) was dissolved in acetic anhydride (20 mL) and heated to 100 °C for 4 h. The solution was then cooled to room temperature and evaporated to dryness. The viscous residue was suspended in 5% aqueous Na_2CO_3 (30 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The oil was dissolved in $CHCl_3$ (2 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 3:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 503 mg (84%) of **6** as a clear oil. R_f = 0.3 (5:1 hexane/EtOAc).

3-Formyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-*β*-D-ribofuranosyl)indole (7a). Compound **6** (1.00 g, 2.3 mmol) was dissolved in dry DMF (40 mL) to which was added phosphorus oxychloride (1.1 mL, 1.8 g, 11.8 mmol). The resulting solution was stirred at room temperature for 10 min, then heated on a 60 °C oil bath for 16 h. The resulting orange solution was evaporated under high vacuum (0.5 mmHg, 40 °C), and the residual oil was poured into 10% aqueous $NaHCO_3$ (200 mL). The aqueous suspension was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The oil was dissolved in $CHCl_3$ (2 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 1:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 0.55 g (52%) of **7a** as a pale-yellow solid: mp 148−149 °C; R_f = 0.3 (2:1 hexane/EtOAc).

3-Cyano-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-*β*-D-ribofuranosyl)indole (7b). Compound **6** (3.50 g, 8.1 mmol) was dissolved in dry CH_2Cl_2 (100 mL) to which was added chlorosulfonyl isocyanate (1.05 mL, 1.71 g, 12.1 mmol). The resulting solution was stirred at room temperature for 16 h, then dry DMF (5.0 mL) was added and the solution stirred for an additional 1 h. Water (50 mL) was added, and the biphasic mixture was stirred vigorously for 15 min and then poured into 10% $NaHCO_3$ (200 mL). The aqueous suspension was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The oil was dissolved in $CHCl_3$ (4 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 1:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 2.01 g (54%) of **7b** as a pale-yellow solid: mp 154−155 °C; R_f = 0.5 (2:1 hexane/EtOAc).

3-Acetyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-*β*-D-ribofuranosyl)indole (7c). Compound **6** (341 mg, 0.78 mmol) was dissolved in dry CH_2Cl_2 (10 mL) to which were added acetyl chloride (84 μL, 93 mg, 1.2 mmol) and anhydrous aluminum(III) chloride (160 mg, 1.2 mmol). The resulting solution was stirred at room temperature for 1 h and then poured into 10% aqueous $NaHCO_3$ (100 mL). The aqueous suspension was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a yellow-orange oil. The oil was dissolved in $CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 129 mg (34%) of **7c** as a white solid: mp 129−130 °C; R_f = 0.4 (2:1 hexane/EtOAc).

3-Propionyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-*β*-D-ribofuranosyl)indole (7d). Compound **6** (435 mg, 1.0 mmol) was treated with propionyl chloride (130 μL, 138 mg, 1.5 mmol) and anhydrous aluminum(III) chloride (200 mg, 1.5 mmol) as per **7c** above to yield 200 mg (41%) of **7d** as a pale-yellow solid. A portion was recrystallized from boiling $CHCl_3$/hexane: mp 141−142 °C; R_f = 0.5 (2:1 hexane/EtOAc).

3-Trifluoroacetyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-*β*-D-ribofuranosyl)indole (7e). A solution of trifluoroacetic anhydride (0.35 mL, 0.52 g, 2.5 mmol) in dry CH_2Cl_2 was cooled to −78 °C, and boron trifluoride methyl sulfide complex (0.21 mL, 0.26 g, 2.0 mmol) was added dropwise. The resulting mixture was stirred for 20 min, with

slow warming to room temperature, and then compound **6** (0.43 g, 0.99 mmol) was added in one portion. The mixture was stirred at room temperature for 90 min and then poured into 5% aqueous Na_2CO_3 (25 mL). The aqueous suspension was extracted with $CHCl_3$ (2 × 25 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a pale-yellow oil. The oil was dissolved in $CHCl_3$ (2 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 1:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 0.18 g (35%) of **7e** as a colorless foam. R_f = 0.4 (2:1 hexane/EtOAc).

3-Formyl-2,5,6-trichloro-1-(5-*O*-acetyl-β-D-ribofuranosyl)indole (8a). Compound **7a** (540 mg, 1.2 mmol) was dissolved in 90% aqueous TFA (10 mL) and stirred at room temperature for 5 min. The solvent was then removed under vacuum, and the residue was dissolved in EtOAc (100 mL). The organic solution was washed with 10% aqueous $NaHCO_3$ (50 mL), then dried over $MgSO_4$, filtered, and evaporated to yield a white powder, which was recrystallized from EtOAc/hexane to yield 420 mg (86%) of **8a** as a white solid: mp 154−155 °C; R_f = 0.5 (10% MeOH/$CHCl_3$). Anal. ($C_{16}H_{14}Cl_3NO_6 \cdot {}^1/_4EtOAc$) C, H, N.

3-Cyano-2,5,6-trichloro-1-(5-*O*-acetyl-β-D-ribofuranosyl)indole (8b). Compound **7b** (2.45 g, 5.3 mmol) was treated with 90% aqueous TFA (25 mL) as per **8a** above, and the resulting solid recrystallized from boiling hexane/$CHCl_3$ to yield 1.85 g (83%) of **8b** as a white solid: mp 103−104 °C; R_f = 0.6 (10% MeOH/$CHCl_3$). Anal. ($C_{16}H_{13}Cl_3N_2O_5$) C, H, N.

3-Acetyl-2,5,6-trichloro-1-(5-*O*-acetyl-β-D-ribofuranosyl)indole (8c). Compound **7c** (375 mg, 0.79 mmol) was treated with 90% aqueous TFA (10 mL) as per **8a** above, and the resulting solid recrystallized from $CHCl_3$/hexane to yield 318 mg (93%) of **8c** as a white solid: mp 178−179 °C; R_f = 0.5 (10% MeOH/$CHCl_3$). Anal. ($C_{17}H_{16}Cl_3NO_6$) C, H, N.

3-Propionyl-2,5,6-trichloro-1-(5-*O*-acetyl-β-D-ribofuranosyl)indole (8d). Compound **7d** (178 mg, 0.36 mmol) was treated with 90% aqueous TFA (10 mL) as per **8a** above, and the resulting solid recrystallized from warm MeOH to yield 152 mg (93%) of **8d** as a white solid: mp 168−169 °C; R_f = 0.6 (10% MeOH/$CHCl_3$). Anal. ($C_{18}H_{18}Cl_3NO_6$) C, H, N.

3-Trifluoroacetyl-2,5,6-trichloro-1-(5-*O*-acetyl-β-D-ribofuranosyl)indole (8e). Compound **7e** (130 mg, 0.24 mmol) was treated with 90% aqueous trifluoroacetic acid (10 mL) as per **8a** above and evaporated to yield a pale-yellow oil. The oil was dissolved in a minimum of $CHCl_3$ and added dropwise to rapidly stirred hexane (25 mL). The solids were triturated for 15 min, then filtered and rinsed with hexane (5 mL) to yield 98 mg (82%) of **8e** as a pale-yellow powder: mp 71−74 °C; R_f = 0.4 (10% MeOH/$CHCl_3$).

3-Formyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (9a). Compound **8a** (148 mg, 0.35 mmol) was dissolved in dry MeOH (20 mL) to which was added sodium methoxide (21 mg, 0.39 mmol). The solution was stirred at room temperature for 30 min, and the solvent was then removed under vacuum. The residue was suspended in brine (50 mL), and the suspension was extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a white solid. The solid was dissolved in MeOH (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 20% MeOH/$CHCl_3$. Fractions containing product were pooled and evaporated, then recrystallized from boiling EtOAc/hexane to yield 55 mg (41%) of **9a** as a white powder: mp 216−218 °C; R_f = 0.3 (10% MeOH/$CHCl_3$). Anal. ($C_{14}H_{12}Cl_3NO_5 \cdot {}^1/_2H_2O$) C, H, N.

3-Cyano-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (9b). Compound **8b** (1.95 g, 4.6 mmol) was treated with sodium methoxide (300 mg, 5.6 mmol) as per **9a** above, and the resulting solid recrystallized from boiling EtOAc/hexane to yield 1.45 g (83%) of **9b** as a white solid: mp 237−238 °C; R_f = 0.3 (10% MeOH/$CHCl_3$). Anal. ($C_{14}H_{11}Cl_3N_2O_4$) C, H, N.

3-Acetyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (9c). Compound **8c** (232 mg, 0.53 mmol) was treated with sodium methoxide (35 mg, 0.65 mmol) as per **9a** above, and the resulting solid recrystallized from boiling EtOAc/hexane to yield 170 mg (81%) of **9c** as a white solid: mp 249−250 °C; R_f = 0.4 (10% MeOH/$CHCl_3$). Anal. ($C_{15}H_{14}Cl_3NO_5$) C, H, N.

3-Propionyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (9d). Compound **8d** (90 mg, 0.21 mmol) was treated with sodium methoxide (14 mg, 0.26 mmol) as per **9a** above, and the resulting solid recrystallized from boiling EtOAc to yield 60 mg (67%) of **9d** as a white solid: mp 239−240 °C; R_f = 0.3 (10% MeOH/$CHCl_3$). Anal. ($C_{16}H_{16}Cl_3NO_5$) C, H, N.

3-Trifluoroacetyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (9e). Compound **8e** (94 mg, 0.19 mmol) was treated with sodium methoxide (12 mg, 0.22 mmol) as per **9a** above, and the resulting solid recrystallized from MeOH/H_2O to yield 48 mg (56%) of **9e** as a pale-yellow powder: mp 179−180 °C; R_f = 0.3 (10% MeOH/$CHCl_3$). Anal. ($C_{15}H_{11}Cl_3F_3NO_5$) C, H, N.

3-Formyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)indole (10a). Compound **5**[11] (4.70 g, 12.0 mmol) was dissolved in dry CH_2Cl_2 (50 mL) to which was added trifluoroacetic anhydride (8.0 mL, 12 g, 57 mmol). The solution was stirred at room temperature for 1 h, the solvent was removed under vacuum, and the residue was dried under high vacuum (0.5 mmHg, 30 °C) for 1 h. The residue was then dissolved in dry DMF (100 mL), and phosphorus oxychloride (6.0 mL, 9.9 g, 64 mmol) was added in one portion. The resulting orange solution was heated on a 60 °C oil bath for 16 h and cooled to room temperature, and the solvent was removed under high vacuum (0.5 mmHg, 40 °C). The residual oil was poured into 10% aqueous $NaHCO_3$ (300 mL, foaming!), and the aqueous suspension was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a dark-orange oil. The oil was dissolved in $CHCl_3$ (3 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 1:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield a clear oil, which was crystallized from CH_2Cl_2/hexane to yield 3.18 g (63%) of **10a** as a white solid: mp 183−184 °C; R_f = 0.4 (1:1 hexane/EtOAc).

3-Cyano-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)indole (10b). Compound **5**[11] (744 mg, 1.9 mmol) was dissolved in dry CH_2Cl_2 (20 mL) to which was added trifluoroacetic anhydride (3.0 mL, 4.5 g, 21 mmol). The solution was stirred at room temperature for 1 h. The solvent was then removed under vacuum, and the residue was dried under high vacuum (0.5 mmHg, 30 °C) for 1 h. The residue was dissolved in dry CH_2Cl_2 (20 mL), and chlorosulfonyl isocyanate (0.25 mL, 0.41 g, 2.9 mmol) was added in one portion. The resulting solution was stirred at room temperature for 1 h, dry DMF (1.0 mL) was added, and the solution was stirred for an additional 16 h. Water (5 mL) was added, and the biphasic suspension was stirred vigorously for 15 min, then poured into 10% aqueous $NaHCO_3$ (50 mL), and the aqueous suspension was extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a pale-yellow oil. The oil was dissolved in $CHCl_3$ (3 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 1:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield a white solid, which was recrystallized from EtOAc/hexane to yield 296 mg (37%) of **10b** as a white solid: mp 191−192 °C; R_f = 0.6 (1:1 hexane/EtOAc).

3-Formyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-propionyl-β-D-ribofuranosyl)indole (11a). Compound **10a** (315 mg, 0.75 mmol) was dissolved in propionic anhydride (6 mL) to which was added dry pyridine (1.5 mL) and 4-(dimethylamino)pyridine (90 mg, 0.75 mmol). The resulting solution was heated on a 120 °C oil bath for 12 min and cooled to room temperature, and the solvent was removed under vacuum (0.5 mmHg, 50 °C). The residual oil was dissolved in EtOAc (75 mL), washed with 0.25 M aqueous HCl (50 mL), 10% aqueous $NaHCO_3$ (50 mL), and brine (50 mL), then dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The oil was dissolved in $CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and

evaporated to yield 175 mg (49%) of **11a** as a pale-yellow solid: mp 153−154 °C; R_f = 0.4 (2:1 hexane/EtOAc).

3-Formyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-butyryl-β-D-ribofuranosyl)indole (11b). Compound **10a** (250 mg, 0.59 mmol) was treated with butyric anhydride (8 mL) and 4-(dimethylamino)pyridine (75 mg, 0.61 mmol) as per **11a** above to yield 75 mg (26%) of **11b** as a pale-yellow solid: mp 165−166 °C; R_f = 0.4 (2:1 hexane/EtOAc).

3-Formyl-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-methoxycarbonyl-β-D-ribofuranosyl)indole (11c). Compound **10a** (167 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (10 mL) and dry pyridine (0.5 mL). A solution of methyl chloroformate (0.5 mL) in CH_2Cl_2 (10 mL) was added dropwise over 30 min. The resulting solution was stirred at room temperature for 12 h. The solvent was then removed under vacuum, and the residual oil was dissolved in EtOAc (75 mL). The organic solution was washed with 0.25 M aqueous HCl (50 mL), 10% aqueous $NaHCO_3$ (50 mL), and brine (50 mL), then dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The oil was dissolved in $CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield a pale-yellow solid, which was recrystallized from $CHCl_3$/hexane to yield 171 mg (90%) of **11c** as a pale-yellow solid: mp 120−121 °C; R_f = 0.4 (2:1 hexane/EtOAc).

3-Formyl-2,5,6-trichloro-1-(5-*O*-propionyl-β-D-ribofuranosyl)indole (12a). Compound **11a** (169 mg, 0.35 mmol) was treated with 90% aqueous TFA (10 mL) as per **8a** above, and the resulting solid recrystallized from boiling EtOAc/hexane to yield 112 mg (72%) of **12a** as a pale-yellow solid: mp 139−140 °C; R_f = 0.6 (10% MeOH/$CHCl_3$). Anal. ($C_{17}H_{16}Cl_3NO_6$) C, H, N.

3-Formyl-2,5,6-trichloro-1-(5-*O*-butyryl-β-D-ribofuranosyl)indole (12b). Compound **11b** (164 mg, 0.33 mmol) was treated with 90% aqueous TFA (10 mL) as per **8a** above, and the resulting solid recrystallized from boiling EtOAc/hexane to yield 111 mg (74%) of **12b** as a pale-yellow solid: mp 128−129 °C; R_f = 0.6 (10% MeOH/$CHCl_3$). Anal. ($C_{18}H_{18}Cl_3NO_6$) C, H, N.

3-Formyl-2,5,6-trichloro-1-(5-*O*-methoxycarbonyl-β-D-ribofuranosyl)indole (12c). Compound **11c** (191 mg, 0.40 mmol) was treated with 90% aqueous TFA (10 mL) as per **8a** above, and the resulting solid recrystallized from MeOH/H_2O to yield 126 mg (72%) of **12c** as a pale-yellow solid: mp 148−149 °C; R_f = 0.5 (10% MeOH/$CHCl_3$). Anal. ($C_{16}H_{14}Cl_3NO_7$) C, H, N.

Methyl 2-(3,4-Dichlorophenyl)propionate (14). Sodium amide (3.50 g, 88 mmol) was suspended in liquid ammonia (250 mL) maintained at −78 °C. To this rapidly stirred suspension was slowly added a solution of methyl (3,4-dichlorophenyl)acetate[20] (**13**, 10.96 g, 50.0 mmol) in dry THF (45 mL). The resulting orange suspension was stirred at −78 °C for 30 min, then methyl iodide (30 g, 210 mmol) was added in one portion. The reaction mixture was stirred at −78 °C for 30 min, then quenched with ammonium chloride (20 g), diluted with EtOAc (200 mL), and allowed to warm to room temperature over 16 h. The remaining organic suspension was diluted with H_2O (200 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (200 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to yield an orange oil. The crude oil was distilled on a Kugelrohr (100 °C, 0.5 mmHg) to provide 10.41 g (89%) of **14** as a clear oil: R_f = 0.3 (9:1 hexane/EtOAc).

Methyl 2-(3,4-Dichloro-6-nitrophenyl)propionate (15). Compound **14** (8.25 g, 35.4 mmol) was dissolved in concentrated sulfuric acid (20 mL) and cooled to >5 °C on an ice/water bath. Concentrated aqueous nitric acid (2.7 mL, 43 mmol) was added dropwise over 15 min, and the resulting orange solution was stirred at 0 °C for 20 min. The orange solution was then poured into ice/water (250 mL) and extracted with cold Et_2O (2 × 250 mL). The combined organic extracts were washed with water (1 × 250 mL), 10% aqueous $NaHCO_3$ (1 × 250 mL), and brine (1 × 100 mL), then dried over $MgSO_4$, filtered, and evaporated to yield 9.63 g (98%) of **15** as a pale-yellow oil, which crystallized upon standing 4−5 days: mp 102−105 °C; R_f = 0.4 (9:1 hexane/EtOAc).

3-Methyl-5,6-dichlorooxindole (16). Compound **15** (9.63 g, 34.7 mmol) was dissolved in toluene (100 mL), to which was added sodium sulfate (50 g) and platinum(IV) oxide (100 mg). This suspension was shaken under 20−30 psi of hydrogen at room temperature for 4 h. The resulting gray suspension was diluted with EtOAc (25 mL) and filtered. The solids were rinsed with 80% toluene/EtOAc (125 mL) and discarded, and the filtrate was evaporated to yield a yellow oil. The oil was dissolved in glacial AcOH (50 mL) and stirred at room temperature for 2 h. The solvent was then removed under vacuum to yield a damp, orange solid. This solid was recrystallized from boiling hexane to yield 3.72 g (50%) of **16** as a white solid: mp 202−203 °C; R_f = 0.5 (1:1 hexane/EtOAc).

3-Methyl-2,5,6-trichloroindole (17). Compound **16** (3.67 g, 17.0 mmol) was suspended in dry CH_3CN (100 mL) and heated on a 100 °C oil bath until completely dissolved. Phosphorus oxychloride (3.2 mL, 5.3 g, 34 mmol) was added in one portion, and the resulting solution was gently refluxed for 1 h. A solution of imidazole (2.90 g, 42 mmol) in dry CH_3CN (25 mL) was slowly added, and the resulting cloudy solution was gently refluxed with vigorous stirring for 16 h. The reaction mixture was then cooled to room temperature and diluted with EtOAc (100 mL). The suspension thus obtained was filtered, and the solids were rinsed with EtOAc (100 mL) and discarded. The filtrate was evaporated to provide an orange solid, which was dissolved in a minimum of EtOAc and adsorbed onto 20 mL of silica gel. The adsorbed material was placed on a pad of silica gel (50 mm × 75 mm) and eluted with 4:1 hexane/EtOAc until no more product was obtained. The eluent was evaporated to yield a white solid, which was recrystallized from EtOAc/hexane to yield 1.54 g (39%) of **17** as a white solid: mp 155−156 °C; R_f = 0.7 (3:1 hexane/EtOAc).

3-Methyl-2,5,6-trichloro-1-[3,5-di-*O*-(*p*-toluoyl)-2-deoxy-β-D-ribofuranosyl]indole (21). Compound **17** (1.15 g, 4.9 mmol) was dissolved in dry THF (25 mL) to which was added 60% sodium hydride in mineral oil (0.25 g, 6.3 mmol). The suspension was stirred at room temperature for 15 min until gas evolution had ceased, then filtered into a suspension of 3,5-di-*O*-(*p*-toluoyl)-2-deoxy-α-D-ribofuranosyl chloride[16] (**20**, 1.91 g, 4.9 mmol) in toluene (25 mL). The resulting solution was stirred at room temperature for 3 h, then evaporated to dryness. The residue was suspended in brine (90 mL) and water (10 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield an orange syrup. The crude material was dissolved in $CHCl_3$ (4 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 3:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 2.42 g (84%) of **21** as a colorless foam. An analytical sample was prepared by recrystallization from MeOH/$CHCl_3$: mp 137−139 °C; R_f = 0.5 (3:1 hexane/EtOAc).

3-Methyl-2,5,6-trichloro-1-(2-deoxy-β-D-ribofuranosyl)-indole (22). Compound **21** (1.15 g, 1.96 mmol) was suspended in dry MeOH (75 mL) to which was added sodium methoxide (0.43 g, 8.0 mmol). The suspension was stirred at room temperature until the solution cleared (2 h). The solvent was then removed under vacuum, and the residue was suspended in brine (100 mL) and water (10 mL). The aqueous mixture was extracted with EtOAc (2 × 100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a clear oil. The residue was dissolved in EtOAc (2 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 1:2 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield a clear oil, which was coevaporated with $CHCl_3$ (4 × 10 mL) to yield 0.39 g (57%) of **22** as a white powder: mp 66−68 °C; R_f = 0.4 (1:2 hexane/EtOAc).

3-Methyl-2,5,6-trichloro-1-(2-deoxy-3-*O*-methanesulfonyl-5-*O*-*tert*-butyldiphenylsilyl-β-D-ribofuranosyl)indole (23). Compound **22** (0.44 g, 1.3 mmol) was dissolved in

dry pyridine (20 mL) to which was added *tert*-butyldiphenylsilyl chloride (0.41 g, 1.5 mmol). The solution was stirred at room temperature for 16 h, then methanesulfonyl chloride (5.0 mL, 7.4 g, 64 mmol) was added, and the reaction mixture was stirred at room temperature for an additional 4 h. Methanol (10 mL) was added, and the solution was stirred at room temperature for 30 min. The solvent was then removed under vacuum, and the residue was dissolved in EtOAc (100 mL). The organic suspension was washed with water (100 mL) and brine (100 mL), then dried over $MgSO_4$, filtered, and evaporated to yield a pale-yellow oil. The oil was dissolved in $CHCl_3$ (2 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with $CHCl_3$. Fractions containing product were pooled and evaporated to yield 0.53 g (63%) of **23** as a clear viscous residue. $R_f = 0.6$ ($CHCl_3$).

3-Methyl-2,5,6-trichloro-1-(2,3-dideoxy-2,3-didehydro-β-D-ribofuranosyl)indole (24). Compound **23** (515 mg, 0.77 mmol) was dissolved in dry DMSO (10 mL) to which was added water (100 μL) and potassium *tert*-butoxide (0.45 g, 4.0 mmol). The resulting dark solution was swirled at room temperature for 10 min and then poured into cold water (150 mL). The aqueous mixture was extracted with EtOAc (3 × 100 mL), and the organic extracts were washed successively with brine (150 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield an orange oil. The oil was dissolved in $CHCl_3$ and subjected to column chromatography (50 mm × 450 mm) on silica gel with 1:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 240 mg (93%) of **24** as a clear oil: $R_f = 0.6$ (1:1 hexane/EtOAc).

3-Methyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (25). Compound **24** (212 mg, 0.64 mmol) was dissolved in acetone (8 mL) and water (1 mL) to which were added *N*-methylmorpholine *N*-oxide (0.20 g, 1.7 mmol) and 2.5% osmium tetroxide solution in *t*-BuOH (0.65 mL, 0.065 mmol). The resulting solution was stirred at room temperature for 2 h, and then additional *N*-methylmorpholine *N*-oxide (0.20 g, 1.7 mmol) was added. The solution was then stirred at room temperature for an additional 16 h. The solvent volume was reduced to approximately 2 mL, and the solution was poured into 5% aqueous sodium thiosulfate (30 mL). The resulting mixture was extracted with EtOAc (2 × 30 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield an orange oil. The oil was dissolved in 50% MeOH/$CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 10% MeOH/$CHCl_3$. Fractions containing product were pooled and evaporated to yield 144 mg (62%) of **25** as a white powder: mp 190−191 °C; $R_f = 0.4$ (10% MeOH/$CHCl_3$). Anal. ($C_{14}H_{14}Cl_3NO_4 \cdot {}^1/_2H_2O$) C, H, N.

2,3,5,6-Tetrachloroindole (26a). 2,5,6-Trichloroindole[11] (**4**, 0.55 g, 2.5 mmol) was dissolved in dry CH_3CN (20 mL) to which was added *N*-chlorosuccinimide (0.58 g, 4.3 mmol). The resulting solution was stirred at room temperature for 1 h, the solvent was removed under vacuum, and the residue was suspended in 10% aqueous sodium thiosulfate (100 mL). The organic suspension was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a pale-yellow solid. The solid was dissolved in EtOAc (2 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 5:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 0.45 g (70%) of **26a** as a white solid: mp 162−163 °C; $R_f = 0.5$ (hexane/EtOAc 5:1).

3-Iodo-2,5,6-trichloroindole (26b). 2,5,6-Trichloroindole[11] (**4**, 2.21 g, 10.0 mmol) was dissolved in 30 mL of dry CH_3CN to which was added *N*-iodosuccinimide (2.70 g, 12.0 mmol). The orange solution was stirred at room temperature for 30 min, then the solvent was removed under vacuum. To the residual dark-red solid was added 25 mL of 10% sodium thiosulfate and 25 mL of 10% Na_2CO_3. The aqueous suspension was extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a red solid. The solid was subjected to column chromatography (50 mm × 450 mm) on silica gel with 5:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to dryness. The resulting pink solid was recrystallized from EtOAc/hexane to yield 3.02 g (87%) of **26b** as a pink solid: mp 153−154 °C; $R_f = 0.5$ (hexane/EtOAc 5:1).

2,3,5,6-Tetrachloro-1-[3,5-di-*O*-(*p*-toluoyl)-2-deoxy-β-D-ribofuranosyl]indole (27a). Compound **26a** (1.14 g, 4.5 mmol) was treated with 60% sodium hydride in mineral oil (0.40 g, 10 mmol) and 3,5-di-*O*-(*p*-toluoyl)-2-deoxy-α-D-ribofuranosyl chloride[16] (**20**, 1.82 g, 4.7 mmol) as per **21** above to yield 2.27 g (83%) of **27a** as a pale-yellow solid: mp 123−124 °C; $R_f = 0.6$ (3:1 hexane/EtOAc).

3-Iodo-2,5,6-trichloro-1-[3,5-di-*O*-(*p*-toluoyl)-2-deoxy-β-D-ribofuranosyl]indole (27b). Compound **26b** (4.87 g, 14.1 mmol) was treated with 60% sodium hydride in mineral oil (0.80 g, 20 mmol) and compound **20**[16] (5.49 g, 14.1 mmol) in toluene (50 mL) as per **21** above, and the resulting solid recrystallized from $CHCl_3$/MeOH to yield 7.26 g (74%) of **27b** as a pale-yellow powder: mp 115−117 °C; $R_f = 0.6$ (3:1 hexane/EtOAc).

2,3,5,6-Tetrachloro-1-(2-deoxy-β-D-ribofuranosyl)indole (28a). Compound **27a** (2.24 g, 3.7 mmol) was suspended in absolute MeOH (250 mL) to which was added potassium carbonate (1.53 g, 11 mmol). The suspension was stirred vigorously at room temperature for 2 h, after which time the solution clarified. The solvent was then removed under vacuum, and the residue was suspended in 40 mL of brine and extracted with EtOAc (2 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a pale-yellow oil. The oil was adsorbed onto silica gel (50 mL) and then placed onto a silica gel column (50 × 100 mL). The column was eluted with 3:1 hexane/EtOAc until no more methyl *p*-toluoylate was eluted. Then the column was further eluted with 1:3 hexane/EtOAc until the product was completely eluted from column. The solvent was then removed under vacuum to yield a clear residue, which was recrystallized from $CHCl_3$/hexane to yield 0.93 g (68%) of **28a** as a pale-yellow powder: mp 132−133 °C; $R_f = 0.4$ (10% MeOH/$CHCl_3$).

3-Iodo-2,5,6-trichloro-1-(2-deoxy-β-D-ribofuranosyl)indole (28b). Compound **27b** (1.75 g, 2.5 mmol) was treated with sodium methoxide (0.41 g, 7.6 mmol) as per **22** above, and the resulting solid recrystallized from $CHCl_3$/hexane to yield 0.91 g (78%) of **28b** as a white solid: mp >100 °C (dec); $R_f = 0.3$ (10% MeOH/$CHCl_3$).

2,3,5,6-Tetrachloro-1-(2-deoxy-3-*O*-methanesulfonyl-5-*O*-*tert*-butyldiphenylsilyl-β-D-ribofuranosyl)indole (29a). Compound **28a** (0.90 g, 2.4 mmol) was treated with *tert*-butyldiphenylsilyl chloride (0.87 g, 3.2 mmol) and methanesulfonyl chloride (1.0 mL, 1.48 g, 13 mmol) as per **23** above to yield 1.45 g (87%) of **29a** as a colorless foam. $R_f = 0.5$ (3:1 hexane/EtOAc).

3-Iodo-2,5,6-trichloro-1-(2-deoxy-3-*O*-methanesulfonyl-5-*O*-*tert*-butyldiphenylsilyl-β-D-ribofuranosyl)indole (29b). Compound **28b** (1.92 g, 4.1 mmol) was treated with *tert*-butyldiphenylsilyl chloride (1.50 g, 5.5 mmol) and methanesulfonyl chloride (2.0 mL, 3.0 g, 25 mmol) as per **23** above to yield 2.75 g (85%) of **29b** as a colorless foam: mp 64−70 °C; $R_f = 0.4$ (3:1 hexane/EtOAc).

2,3,5,6-Tetrachloro-1-(2,3-dideoxy-2,3-didehydro-β-D-ribofuranosyl)indole (30a). Compound **29a** (1.27 g, 1.8 mmol) was treated with potassium *tert*-butoxide (1.05 g, 9.4 mmol) as per **24** above to yield 0.30 g (46%) of **30a** as a red oil. $R_f =$ 0.5 (1:1 hexane/EtOAc).

3-Iodo-2,5,6-trichloro-1-(2,3-dideoxy-2,3-didehydro-β-D-ribofuranosyl)indole (30b). Compound **29b** (2.69 g, 3.5 mmol) was treated with potassium *tert*-butoxide (1.95 g, 17.4 mmol) as per **24** above to yield 0.86 g (56%) of **30b** as a slightly red oil. $R_f = 0.5$ (1:1 hexane/EtOAc).

2,3,5,6-Tetrachloro-1-(β-D-ribofuranosyl)indole (31a). Compound **30a** (0.30 g, 0.85 mmol) was treated with *N*-methylmorpholine *N*-oxide (0.50 g, 4.2 mmol) and 2.5% osmium tetroxide solution in *tert*-BuOH (1.0 mL, 0.10 mmol) as per **25** above, and the solid recrystallized from 50% MeOH/$CHCl_3$ and hexane to yield 0.60 g (48%) of **31a** as a white

powder: mp 197−198 °C; R_f = 0.3 (10% MeOH/$CHCl_3$). Anal. ($C_{13}H_{11}Cl_4NO_4$) C, H, N.

3-Iodo-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (31b). Compound **30b** (0.77 g, 1.7 mmol) was treated with *N*-methylmorpholine *N*-oxide (1.02 g, 8.6 mmol) and 2.5% osmium tetroxide solution in *tert*-BuOH (1.7 mL, 0.17 mmol) as per **25** above, and the solid recrystallized from 50% MeOH/$CHCl_3$ and hexane to yield 0.60 g (72%) of **31b** as a white solid: mp 201−202 °C; R_f = 0.3 (10% MeOH/$CHCl_3$). Anal. ($C_{13}H_{11}Cl_3INO_4$) C, H, N.

3-Iodo-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)indole (32). Compound **31b** (2.22 g, 4.6 mmol) was dissolved in dry acetone (50 mL) to which were added 2,2-dimethoxypropane (10 mL) and *p*-toluenesulfonic acid hydrate (20 mg). The solution was stirred at room temperature for 15 min. The solvent was then removed under vacuum, and the residue was suspended in 10% $NaHCO_3$ (100 mL). The aqueous suspension was extracted with EtOAc (2 × 75 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a pale-yellow oil. The oil was diluted with absolute MeOH (50 mL) and glacial acetic acid (2 mL). The resulting suspension was stirred at room temperature for 1 h, at which time the solids had completely dissolved. The solvent was then removed under vacuum, and the residue was suspended in 10% $NaHCO_3$ (100 mL). The aqueous suspension was extracted with EtOAc (2 × 75 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a clear oil. The oil was dissolved in $CHCl_3$ (3 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield a white solid, which was recrystallized from $CHCl_3$/hexane to yield 2.17 g (90%) of **32** as a white solid: mp 78−80 °C; R_f = 0.5 (2:1 hexane/EtOAc).

3-Iodo-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-methoxymethyl-β-D-ribofuranosyl)indole (33). Compound **32** (1.00 g, 1.9 mmol) was dissolved in dry CH_2Cl_2 (50 mL) to which were added diisopropylethylamine (4 mL, 23 mmol) and chloromethyl methyl ether (0.75 mL, 0.80 g, 9.9 mmol). The solution was stirred at room temperature for 16 h. The solvent was then removed under vacuum, and the residue was suspended in 10% $NaHCO_3$ (75 mL). The aqueous suspension was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield an orange oil. The oil was dissolved in $CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 3:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield a clear oil, which was recrystallized from warm hexane to yield 0.76 (70%) of **33** as a white solid: mp 120−121 °C; R_f = 0.6 (3:1 hexane/EtOAc).

3-(2-Furyl)-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-methoxymethyl-β-D-ribofuranosyl)indole (34a). Compound **33** (250 mg, 0.44 mmol) and 2-furanboronic acid (60 mg, 0.53 mmol) were suspended in 1-propanol (4 mL) and dry DMF (1.0 mL). The suspension was stirred at room temperature for 10 min, then palladium(II) acetate (20 mg, 0.09 mmol) and tri-*o*-tolylphosphine (84 mg, 0.28 mmol) were added, followed by 2.0 M aqueous Na_2CO_3 (400 μL, 0.80 mmol) and H_2O (1.0 mL). The resulting suspension was heated on a 120 °C oil bath for 15 min. The resulting dark solution was cooled and poured into EtOAc (50 mL). The organic solution was washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to yield an orange solid. The solid was dissolved in $CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 5:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 185 mg (83%) of **34a** as an orange oil. R_f = 0.3 (5:1 hexane/EtOAc).

3-(3-Thienyl)-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-methoxymethyl-β-D-ribofuranosyl)indole (34b). Compound **33** (250 mg, 0.44 mmol) was treated with 3-thiopheneboronic acid (69 mg, 0.54 mmol), palladium(II) acetate (20 mg, 0.09 mmol), tri-*o*-tolylphosphine (84 mg, 0.28 mmol), and 2.0 M aqueous Na_2CO_3 (400 μL, 0.80 mmol) as per **34a** above to yield 175 mg (76%) of **34b** as an orange oil. R_f = 0.4 (5:1 hexane/acetone).

3-(2-Furyl)-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (35a). Compound **34a** (105 mg, 0.21 mmol) was dissolved in absolute MeOH (10 mL) to which was added concentrated aqueous HCl (2 mL). The resulting suspension was heated on a 60 °C oil bath for 45 min, cooled to room temperature, and evaporated until no more MeOH remained. The remaining aqueous suspension was diluted with brine (25 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with 10% $NaHCO_3$ (25 mL), dried over $MgSO_4$, filtered, and evaporated to yield a dark oil. The oil was dissolved in 10% MeOH/$CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 10% MeOH/$CHCl_3$. Fractions containing product were pooled and evaporated to yield 63 mg (65%) of **35a** as a pale-gray powder: mp 139−140 °C; R_f = 0.3 (10% MeOH/$CHCl_3$). Anal. ($C_{17}H_{14}Cl_3NO_5$) C, H, N.

3-(3-Thienyl)-2,5,6-trichloro-1-(β-D-ribofuranosyl)indole (35b). Compound **34b** (175 mg, 0.34 mmol) was treated with absolute MeOH (10 mL) and aqueous HCl (2 mL) as per **35a** above, and the resulting solid recrystallized from MeOH/H_2O to yield 110 mg (75%) of **35b** as a tan solid: mp 152−153 °C; R_f = 0.4 (10% MeOH/$CHCl_3$). Anal. ($C_{17}H_{14}Cl_3NO_4S$) C, H, N.

3-[1-(2-Methoxy)vinyl]-2,5,6-trichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-β-D-ribofuranosyl)indole (36). Methoxymethyltriphenylphosphonium chloride (0.70 g, 2.0 mmol) was suspended in dry THF (25 mL), and the suspension was cooled to 0 °C. A solution of *n*-butyllithium (1.6 M) in hexane (1.0 mL, 1.6 mmol) was added dropwise over 15 min, resulting in an orange suspension to which was added a solution of compound **7a** (441 mg, 0.95 mmol) in dry THF (10 mL). The resulting yellow suspension was stirred at 0 °C for 1 h, then poured into brine (50 mL) and H_2O (10 mL). The aqueous suspension was extracted with EtOAc (2 × 50 mL), and the combined extracts were dried over $MgSO_4$, filtered, and evaporated to yield a yellow-orange oil. The oil was dissolved in $CHCl_3$ (3 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield a clear oil. The oil was coevaporated twice with MeOH to yield 185 mg (40%) of **36** as a white solid, which was an inseparable 7:3 mixture of trans/cis isomers. A portion was recrystallized from warm MeOH to provide an analytical sample: mp 135−136 °C; R_f = 0.4 (3:1 hexane/EtOAc).

3-Formylmethyl-2,5,6-trichloro-1-(β-D-ribofuranosyl)-indole (38). Compound **36** (185 mg, 0.38 mmol) was dissolved in absolute MeOH (10 mL) to which was added concentrated aqueous HCl (2 mL). The resulting suspension was heated on a 60 °C oil bath for 1 h, then cooled to room temperature and evaporated until no more MeOH remained. The remaining aqueous suspension was diluted with brine (25 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with 10% $NaHCO_3$ (25 mL), dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The oil was dissolved in 90% aqueous TFA (10 mL), and the solution was stirred at room temperature for 2 min. The solvent was evaporated until approximately 1 mL remained, and the remainder was poured into 10% aqueous $NaHCO_3$ (50 mL). The aqueous suspension was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to yield a white powder. The solid was dissolved in MeOH (1 mL) and subjected to column chromatography (40 mm × 350 mm) on C18 reverse-phase silica gel with 75% MeOH/H_2O. Fractions containing product were pooled and evaporated to yield 93 mg (62%) of **38** as a tan powder: mp 119−121 °C; R_f = 0.2 (10% MeOH/$CHCl_3$). Anal. ($C_{15}H_{14}Cl_3NO_5$) C, H, N.

2-Bromo-5,6-dichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-β-D-ribofuranosyl)indole (40). 2-Bromo-5,6-dichloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)indole[11] (**39**, 1.35 g, 3.1 mmol) was dissolved in dry pyridine (12 mL) to which was added acetic anhydride (4 mL). The resulting solution was

stirred at room temperature for 4 h, and the solvent was then removed under high vacuum (0.5 mmHg, 40 °C). The residual oil was dissolved in EtOAc (100 mL), washed successively with 0.25 M aqueous HCl (100 mL), 10% $NaHCO_3$ (100 mL), brine (25 mL), then dried over $MgSO_4$, filtered, and evaporated to afford a clear oil. The oil was dissolved in $CHCl_3$ (3 mL) and subjected to column chromatography (50 mm × 450 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 1.41 g (95%) of **40** as a colorless foam: mp 49−54 °C; R_f = 0.6 (2:1 hexane/EtOAc).

3-Formyl-2-bromo-5,6-dichloro-1-(2,3-*O*-isopropylidene-5-*O*-acetyl-β-D-ribofuranosyl)indole (41). Compound **40** (0.47 g, 0.98 mmol) was dissolved in dry DMF (15 mL) to which was added phosphorus oxybromide (2.2 g, 7.6 mmol). The resulting suspension was stirred vigorously for 10 min at room temperature and then heated on a 70 °C oil bath for 16 h. The resulting solution was cooled to room temperature and evaporated under high vacuum (0.5 mmHg, 40 °C) to yield an orange oil. The oil was poured into cold 10% $NaHCO_3$ (150 mL), and the resulting aqueous suspension was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to yield an orange oil. The oil was dissolved in $CHCl_3$ (1 mL) and subjected to column chromatography (40 mm × 350 mm) on silica gel with 2:1 hexane/EtOAc. Fractions containing product were pooled and evaporated to yield 278 mg (56%) of **41** as a white solid: mp 178−179 °C; R_f = 0.3 (2:1 hexane/EtOAc).

3-Formyl-2-bromo-5,6-dichloro-1-(5-*O*-acetyl-β-D-ribofuranosyl)indole (42). Compound **41** (257 mg, 0.51 mmol) was treated with 90% aqueous trifluoroacetic acid (10 mL) as per **8a** above, and the resulting solid recrystallized from EtOAc and hexane to yield 220 mg (93%) of **42** as a white solid: mp 159−160 °C; R_f = 0.5 (10% MeOH/$CHCl_3$). Anal. ($C_{16}H_{14}BrCl_2NO_6 \cdot {}^1/_4$ hexane) C, H, N.

3-Formyl-2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)indole (43). Compound **42** (101 mg, 0.22 mmol) was treated with sodium methoxide (25 mg, 0.46 mmol) as per **9a** above, then dissolved in MeOH (1 mL) and subjected to column chromatography (40 mm × 350 mm) on C18 reverse-phase silica gel with 75% MeOH/H_2O. Fractions containing product were pooled and evaporated to yield a white solid, which was recrystallized from MeOH/H_2O to yield 43 mg (47%) of **43** as a pale-tan powder: mp 210−211 °C; R_f = 0.2 (10% MeOH/$CHCl_3$). Anal. ($C_{14}H_{12}BrCl_2NO_5$) 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.[21]

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.[22] High titer HSV-1 stocks were prepared by infecting KB cells at a moi of <0.1 also as detailed previously.[22] 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.[23] 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[24] to detect HSV-1. Ninety-six-well cluster dishes were planted with 10 000 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 and HSV-1 at 100 pfu/well were added in quadruplicate wells. Following a 3-day incubation at 37 °C, the 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 2.0 N H_2SO_4 (50 μL) after 15 min, 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 uninfected cells.[22] (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.[25] 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 $\log_{10}$ drug concentrations. Fifty percent inhibitory concentrations (IC_{50} values) 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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Supporting Information Available: ^1H NMR, ^{13}C NMR, and ^{19}F NMR for all new compounds and HRMS and elemental analysis results for all target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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