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Convergent Synthesis of Polyhalogenated Quinoline *C*-Nucleosides as Potential Antiviral Agents

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2,5,6-Trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB) are benzimidazole nucleosides that exhibit strong and selective anti-HCMV activity. We proposed to synthesize 2-halo-6,7-dichloro-4-(β-D-ribofuranosyl)quinolines as 6 + 6 bicyclic analogues of TCRB. The synthesis used Wittig reactions in two key steps. The first Wittig reaction coupled a fully functionalized benzene with a ribofuranose derivative to provide (*Z*)-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-1,2-dideoxy-3,4-*O*-isopropylidene-D-allo-1-enitol (**5**) as the basic skeleton for the target compounds. The following electrophile-mediated intramolecular cyclization of the *cis*-alkene (**5**) was found to afford (1*S*,2*S*)-2,5-anhydro-1-bromo-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (**8**) as the major product. This α-stereoselectivity was contrary to the literature precedence. A double-bond isomerization was established to be the cause of the unexpected stereochemistry. The bromo group of **8** was displaced by a hydroxyl group. Oxidation of the hydroxy group and the reduction of a phenylnitro group provided (2*S*)-1-(2-amino-4,5-dichlorophenyl)-2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-allose (**11**), which was subjected to the second Wittig reaction with a phosphacumulene to construct 4-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-ribofuranosyl]-6,7-dichloroquinolin-2-one (**13**). Halogenation followed by deprotection of **13** and led to the synthesis of 4-(α-D-ribofuranosyl)-2,6,7-trichloroquinoline (**17**) as the major product. The 2-aminophenone α-nucleoside (**11**) was successfully anomerized to the β-anomer (**19**), which led to the synthesis of the targeted 2-chloro- and 2-bromo-6,7-dichloro-4-(β-D-ribofuranosyl)quinolines (**18** and **21**, respectively).

Introduction

A series of 2-substituted benzimidazole nucleosides have been synthesized in our laboratory and displayed strong antiviral activities.[1] The lead compounds, including 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)-benzimidazole (BDCRB) (Figure 1), have shown potent activity against HCMV with low cellular toxicity at concentrations inhibiting viral growth (TCRB: $IC_{50} = 2.8$ μM, $CC_{50} = 238$ μM, BDCRB: $IC_{50} = 0.7$ μM, $CC_{50} = 118$ μM in a plaque assay in human foreskin fibroblasts). TCRB is very selective against HCMV. It was found that TCRB displays only weak antiviral activity against HSV-1, HSV-2, VZV, and even murine cytomegalovirus. TCRB was also found to be inactive against a selection of RNA viruses including the A and B strains of influenza, respiratory syncytia, measles virus, and HIV-1. Moreover, TCRB was found to be active against three distinct clinical isolates of HCMV that had become resistant to ganciclovir. Overall, TCRB and BDCRB were determined

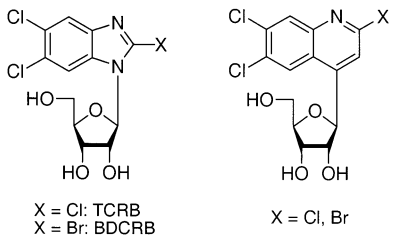

FIGURE 1.

to be promising anti-HCMV agents with high potency, high selectivity, and low cytotoxicity.[2] However, subsequent studies in rats and monkeys revealed the instability of the glycosidic bond in vivo.[3]

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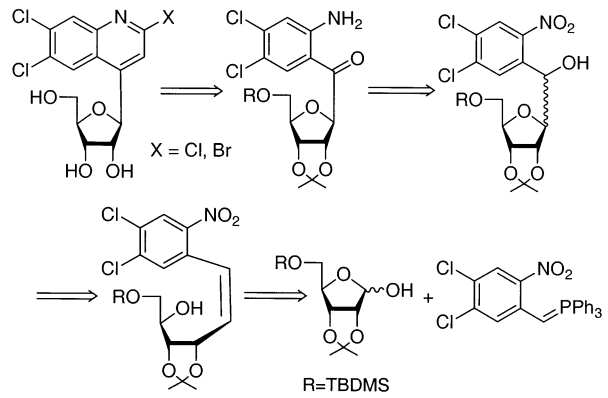
This prompted a broadened synthetic effort to prepare analogues with increased glycosidic bond stability. The efforts produced several other promising compounds[4] including 1263W94 (maribavir).[5] 1263W94 is an L-ribosyl benzimidazole that is a potent and selective inhibitor of HCMV replication.[5] Its mechanism of action, however, is different from TCRB and BDCRB and involves the inhibition of viral DNA synthesis.[5] A mutation in the HCMV UL97 protein kinase produced resistance implying UL97 is the target for this compound.[5] Development of 1263W94 has progressed to phase I/II clinical trials for the treatment of HCMV infections.[5]

Another approach to analogues with increased glycosidic bond stability involves indole and imidazo[1,2-*a*]-pyridine bicyclic heterocycles structurally related to the benzimidazoles. Several polyhalogenated indole *N*-nucleosides and imidazo[1,2-*a*]pyridine *C*-nucleosides have been prepared as TCRB analogues.[4] Some of these nucleosides have also displayed some interesting antiviral activities. Indole and imidazo[1,2-*a*]pyridine are 6 + 5 bicyclic ring systems, which may bear the same exocyclic substitution pattern as that of TCRB. Several 6 + 6 bicyclic ring systems, such as a quinoline, have the potential for a substitution pattern similar to that of TCRB. Therefore, we initiated a study designed to synthesize some quinoline *C*-nucleosides (Figure 1) as part of our substantial SAR studies on TCRB. The 2-chloro- and 2-bromo-6,7-dichloro-4-(β-D-ribofuranosyl)-quinolines should be sufficient to evaluate the potential antiviral activity of this type of nucleoside as analogues of TCRB.

Quinoline *C*-nucleosides have been reported in the literature.[6,7] However, most of these compounds were nucleosides with a ribofuranosyl group substituted at the 2-position of a simple quinoline.[6] The only reported 4-(β-D-ribofuranosyl)quinoline was prepared via a unique enaminone glycoside procedure.[7] However, this procedure was not suitable for the synthesis of our target compounds. To prepare the polyhalogenated quinoline *C*-nucleosides regioselectively, we elected to use a homo-*C*-nucleoside approach (Scheme 1). In this approach, a ribofuranose derivative could be coupled with a fully functionalized benzene through a Wittig reaction to give a key alkene intermediate.[8,9] Then an electrophile-mediated intramolecular cyclization (EMIC) reaction [10,11]

SCHEME 1



could be used to install a functional group at the benzylic position of the resulting homo-*C*-nucleoside. This homo-*C*-nucleoside could then be elaborated to a 2-aminophenone nucleoside intermediate. From this intermediate, several methods are available for the construction of a quinoline ring.[12−14]

Results and Discussion

4,5-Dichloro-2-nitrotoluene (**1**)[15] under radical conditions was brominated to yield 4,5-dichloro-2-nitrobenzyl bromide (**2**) (Scheme 2). (4,5-Dichloro-2-nitrobenzyl)-triphenylphosphonium bromide (**3**) was then obtained by simply stirring compound **2** with triphenylphosphine at room temperature for 4 days. The Wittig reaction has been widely used in *C*-nucleoside syntheses.[16] In most reports, the alkene products were not isolated; instead, the alkenes were cyclized to afford homo-*C*-nucleosides under basic conditions as a result of an intramolecular Michael addition.[9,17−19] If compound **3** was directly coupled with a ribofuranose derivative in the presence of triethylamine as a base, the desired alkene products, i.e., (*Z*)-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-1,2-dideoxy-3,4-*O*-isopropylidene-D-allo-1-enitol (**5**) and (*E*)-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-1,2-dideoxy-3,4-*O*-isopropylidene-D-allo-1-enitol (**6**), were formed. However, compounds **5** and **6** underwent an intramolecular Michael addition under the basic conditions, and undesired (2*S*)-2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (**7**) and its α-anomer were obtained in a substantial amount along with **5** and **6**. To prevent this base-induced cyclization, compound **3** was first converted to (4,5-dichloro-2-nitrobenzyl)triphen-

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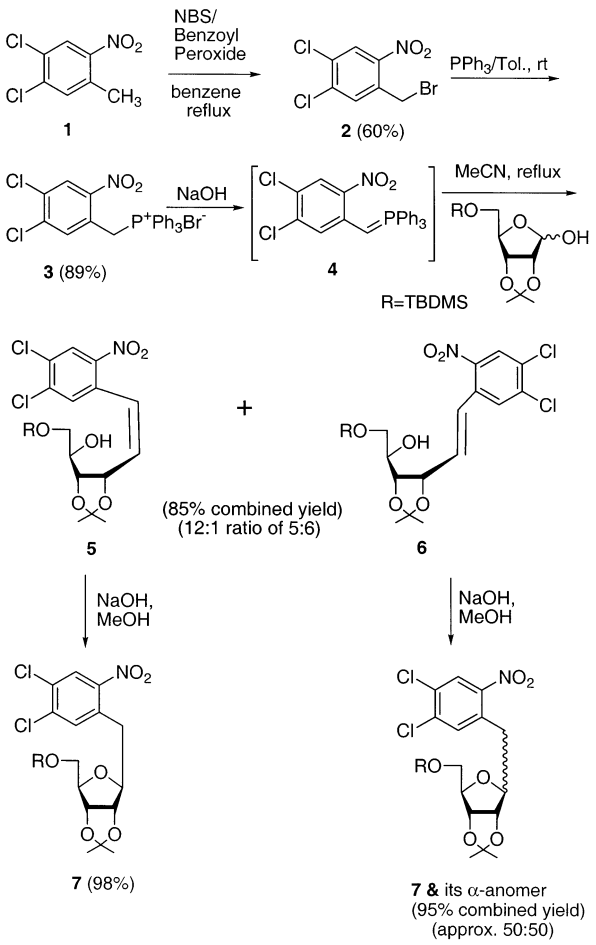
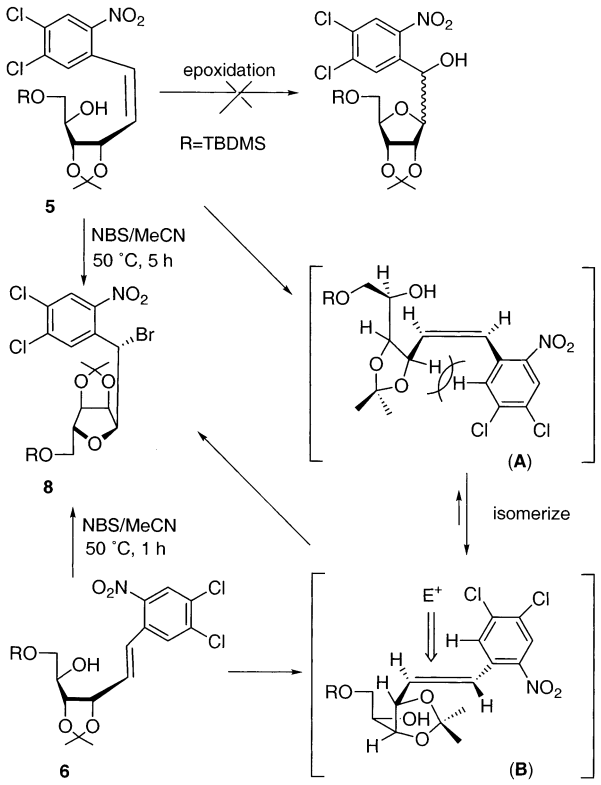
SCHEME 2



SCHEME 3



ylphosphorane (**4**) with sodium hydroxide. The deep purple ylide **4** was then used directly in the Wittig reaction without any base and provided the *cis*-alkene **5** and *trans*-alkene **6** in a combined 85% yield and a 12:1 ratio, respectively. The configuration of the alkenes was based on the coupling constants for the alkene protons, i.e., 11.7 Hz for the cis isomer **5** and 15.2 Hz for the trans isomer **6**. Compound **7** was obtained as the major product when the *cis*-alkene (**5**) was treated with NaOH in MeOH. If the *trans*-alkene (**6**) was treated with NaOH in MeOH, compound **7** and its α-anomer were obtained as a mixture in almost equal amounts. Compound **7** was most likely the *β*-anomer because the chemical shift for the H-1′ of **7** was upfield from the peak observed for the H-1′ of the other anomer.

To prepare a 2-aminophenone intermediate, we proposed to oxidize the alkene **5** to an epoxide. An intramolecular cyclization would then give a homo-*C*-nucleoside with a benzylic hydroxyl group. Oxidation of this benzylic hydroxy group and a reduction of the nitro group should provide the desired 2-aminophenone intermediate. However, the *π*-electron-deficient nitrophenyl alkene **5** resisted a number of strong epoxidation conditions (Scheme 3). For example, it did not give any significant amount of an epoxide even under strong *m*-CPBA conditions[20] or trifluoroperacetic acid (TFPAA).

To circumvent the epoxidation step, an electrophile-mediated intramolecular cyclization (EMIC) reaction was applied. The EMIC reaction has been used previously in the synthesis of *C*-ribofuranosides.[11,21−23] The stereoselectivity of this intramolecular cyclization of ribose-derived alkenes was systematically studied by Freeman and co-workers.[10] They found that a *cis*-alkene predominantly yielded a *β*-homonucleoside, while a *trans*-alkene predominantly gave an α-anomer. Since the *cis*-alkene **5** was the major Wittig product in our case, the EMIC reaction should fulfill our requirement of a *β*-homonucleoside. Thus, the *cis*-alkene **5** was subjected to an EMIC reaction using NBS as the electrophile. The reaction was conducted in acetonitrile at 50 °C and was completed in 5 h (Scheme 3). This reaction furnished one major product, (1*S*,2*S*)-2,5-anhydro-1-bromo-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (**8**), along with several inseparable impurities. According to Freeman's results,[10] we expected to obtain a cyclized *β*-anomer as the major product. However, the Δ*δ* of the isopropylidene of compound **8** was quite small, only equal to 0.06 ppm, while a *β*-anomer normally has Δ*δ* > 0.15 ppm according to the Imbach rules and Freeman's experimental results.[10] When the *trans*-alkene **6** was subjected to the same reaction conditions as those described for **5**, compound **6** was converted to compound **8** in 1 h without any of the impurities that were observed in the EMIC reaction of the *cis*-alkene **5**. This experimental result and the Δ*δ* value of compound **8** suggested that compound **8** was an

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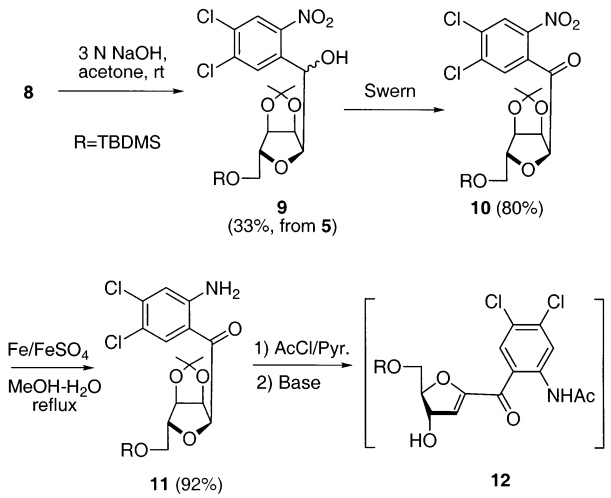
α-homonucleoside. The stereochemical outcome of this EMIC reaction was quite surprising, since Freeman's results were supported by others.[21,22] The close resemblance of our alkenes and Freeman's substrates suggested that Freeman's reactive conformer models were still applicable. The alkenes may exist in two low energy reactive conformers **A** and **B**. In conformer **B**, the lone pair of the oxygen is delocalized into the π-bond. Thus, this conformer is more abundant than conformer **A** in the *trans*-alkene due to a low energy level and gave the α-nucleoside as the major product in an EMIC reaction. In the *cis*-alkene, the substituent attached to the double bond interferes sterically with the methyl groups of the isopropylidene group. Thus, conformer **A** should be more abundant than conformer **B** and result in the β-anomer as the major product. However, in our case, the nitrophenyl substituent of alkene **5** was much bulkier than the simple methyl group in Freeman's substrate. Thus, the predicted conformer **A** of the *cis*-alkene may not exist due to the strong steric hindrance. It was possible that the *cis*-alkene **5** isomerized first to the *trans*-alkene **6**. This isomerization could be catalyzed by the bromonium ion in the EMIC reaction and provided the conformer **B** of the *trans*-alkene. This conformer would not have the steric interactions that were associated with the *cis*-alkene (**A** conformer). The *trans*-alkene would then proceed to give the α-homo-*C*-nucleoside **8**. This hypothesis was supported by the following facts: (1) both alkenes **5** and **6** afforded the same product; (2) there was a dramatic difference between the reaction rates of **5** and **6**. If our hypothesis is correct, the *trans*-alkene should be detected in the EMIC reaction of the *cis*-alkene due to the proposed isomerization. Thus, a small-scale EMIC reaction of **5** was conducted in deuterated acetonitrile and followed closely by ^{1}H NMR. Indeed, the characteristic peaks for the *trans*-alkene **6** appeared in the ^{1}H NMR spectra taken during the reaction process. The amount of this isomerization product was consistently low, since it underwent an EMIC reaction much faster than **5**. Thus, this ^{1}H NMR study further supported our isomerization hypothesis.

We also tried other conditions to test the EMIC reactions of alkene **5**. Solvents other than acetonitrile, e.g., DMF, carbon tetrachloride, and THF, resulted in either the decomposition of starting material or no reaction. Electrophiles other than NBS, e.g., bromine, iodine, and mercury acetate, resulted in either the decomposition of starting material or no reaction. Although compound **8** possessed the wrong anomeric configuration, its benzylic bromide would be transformed to a phenone attached to a ribofuranosyl moiety. The anomeric proton of this phenone α-nucleoside could allow some anomerization in subsequent reactions. Therefore, we used compound **8** as the starting material for the subsequent reactions in our proposed retrosynthetic route.

The retrosynthetic design required an oxidation of compound **8** directly to a phenone nucleoside. However, the secondary benzyl bromide seemed to resist a number of oxidizing conditions, including heated DMSO, bis(tetrabutylammonium) dichromate,[24] and 4-(dimethylamino)pyridine *N*-oxide.[25] We then attempted to displace

SCHEME 4



the benzyl bromide with an acetate, a soft oxygen nucleophile, and convert the acetate product to a phenone. However, compound **8** also resisted the acetate displacement under a number of conditions, including KOAc/18-crown-6, AgOAc, and $Hg(OAc)_2$.[26] Therefore, we elected to displace the bromide of **8** with a hydroxyl group to give 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (**9**) under strong basic conditions (Scheme 4). A number of solvents were used, e.g., acetone, THF, MeOH, MeCN, and 2-propanol. Acetone gave the best results, but the yield over two steps (EMIC and displacement) was only 30−40%. The low yield was probably due to a possible elimination on the ribofuranosyl moiety and/or a nucleophilic substitution of the dichloronitrobenzene moiety. Compound **9** consisted of two equal diastereomers because the nucleophilic substitution of a secondary halide is not stereospecific. A Swern oxidation of compound **9** afforded the 2-nitrophenone (2*S*)-2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allose (**10**) in a good yield. The nitro group of compound **10** was then reduced to give (2*S*)-1-(2-amino-4,5-dichlorophenyl)-2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-allose (**11**).

Simple quinolin-2-ones have been constructed from 2-aminophenones or 2-acetylaminophenones via an intramolecular aldol condensation.[12,13,27] Following the procedure of Hino et al.,[13] compound **11** was first protected with an acetyl group and then treated with NaOMe in EtOH. The starting material was consumed in less than 5 min on the basis of TLC. However, the major product isolated from the reaction was not a quinolin-2-one nucleoside. The ^{1}H NMR spectrum of this compound showed a D_2O exchangeable doublet in the midfield (indicating a secondary hydroxy), a total of five sugar protons, and no isopropylidene group protons. On the basis of these data, the compound was tentatively assigned as a 4,5-dihydrofuran **12** (Scheme 4). It was likely that a deprotonation at the anomeric position

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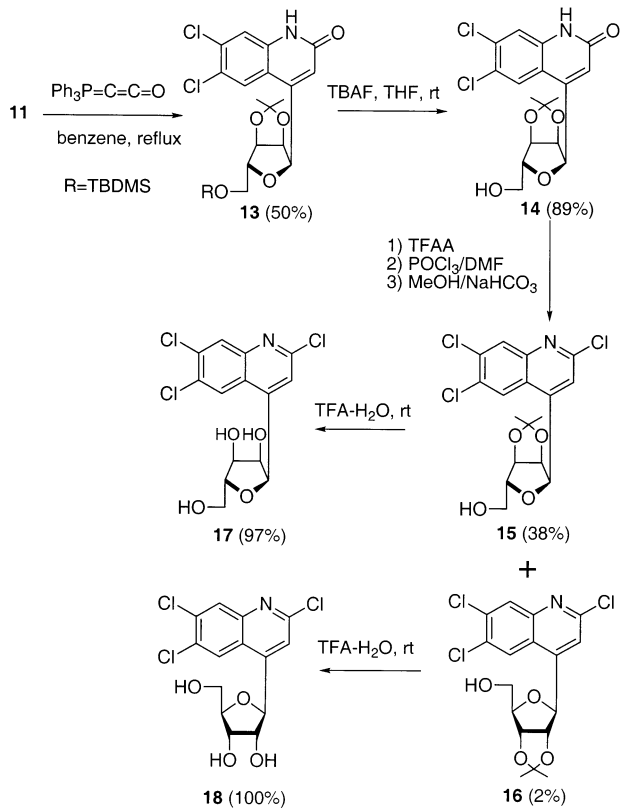
SCHEME 5



induced a fragmentation and this reaction resulted in a loss of the isopropylidene group. Compound **12** was found to be highly susceptible for further elimination to a furan derivative. Mass spectroscopy did not show the expected peaks for the proposed structure of compound **12**. However, a major peak corresponding to a $[M - H_2O]^+$ for a furan analogue was observed.

Another possible route to construct a quinolin-2-one was to apply a Wittig reaction. An ylide, such as methoxycarbonylmethylene(triphenyl)phosphorane (MCMTP), could couple with the ketone functionality of **11** to provide a two-carbon unit extension. A subsequent amide formation, under acid-catalyzed conditions, could provide the desired quinolin-2-one nucleoside. However, several trials at elevated temperatures did not yield any of the desired product. It was likely that MCMTP was not a strong enough ylide to attack a sterically hindered ketone, since this ylide was deactivated by the electron-withdrawing carboxylate group. Keteneylidene(triphenyl)phosphorane, derived from MCMTP,[28] has been used in the preparation of a simple quinolin-2-one from an 2-aminophenylcarboxylate.[14] We found that when compound **11** was treated with this ketene ylide in benzene at reflux temperature, a 50% yield of the desired quinolin-2-one nucleoside, 4-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-ribofuranosyl]-6,7-dichloroquinolin-2-one (**13**) (Scheme 5), was obtained. It would appear that the amino group attacked the ketene first to afford an amide ylide, and then the resulting ylide underwent an intramolecular Wittig reaction to furnish the quinolin-2-one. Compound **13** was then treated with tetrabutylammonium fluoride (TBAF) to afford 6,7-dichloro-4-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)quinolin-2-one (**14**). The values of the isopropylidene groups of **13** and **14** were both smaller than 0.15 ppm, which indicated that both nucleosides were the α-anomers. Compound **14** was treated with trifluoroacetic anhydride (TFAA) to protect the 5′-hydroxy group in situ, and the protected nucleoside was chlorinated with $POCl_3$/DMF. The crude chlorinated product was stirred in MeOH overnight to remove the labile trifluoroacetyl protecting group and resulted in the formation of 4-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)-2,6,7-trichloroquinoline (**15**), along with a small amount (2%) of the *β*-anomer **16**. The *β*-anomer (**16**) was most likely obtained from the minor *β*-anomers of **8**−**14**. Treatment of compounds **15** and **16** with aqueous TFA furnished the desired target compounds 4-(α-D-ribofuranosyl)-2,6,7-trichloroquinoline and 4-(*β*-D-ribofuranosyl)-2,6,7-trichloroquinoline (**17** and **18**), respectively.

The anomeric configurations of the quinoline *C*-nucleosides were based on their ^{1}H NMR spectral data. For example, the $\Delta\delta$ is equal to 0.00 ppm for the α-anomer **15** and 0.36 ppm for the *β*-anomer **16**. Anomeric assignments based on these observations agreed with the Imbach rules.[29] The H-1′s of **15** and **17** are also at lower field than those of **16** and **18**, respectively. This chemical shift difference is consistent with the general observations for *β*- and α-nucleosides. A nuclear Overhauser enhancement (NOE) study involving the irradiation of H-1′ of **16** gave 4.2% of NOE at H-4′. This enhancement was only possible with a *β*-nucleoside.

The α-homo-*C*-nucleoside **11** should anomerize easily due to the acidic anomeric proton. However, treatment of **11** with strong bases, e.g., NaOH, K_2CO_3, *i*-$PrNH_2$, or DBU at room temperature, only afforded the elimination product **12**. Treatment of **11** with weak bases, such as $NaHCO_3$, pyridine, or Et_3N, did not effect any conversion at temperatures up to 60 °C. The treatment of **11** with LDA only gave unidentified decomposed products. After a number of trials, we discovered that a small amount of the *β*-anomer **19** could be obtained with excess (>20 equiv) DMAP in benzene at reflux temperature. It was quite surprising that the R_f value between **11** and **19** was greater than 0.3 on TLC (30% EtOAc/Hex). This dramatic difference afforded a facile chromatographic separation of the two anomers after the anomerization. However, the combined recovery of both anomers under the DMAP conditions was only 50%. Thus, we reinvestigated other weak bases, i.e., pyridine and Et_3N. Pyridine did provide almost a 100% recovery; however, the conversion was only 15% at reflux temperature after 2 days. Pure Et_3N gave mostly the elimination product **12** at reflux temperature, while a 25% conversion and a 96% combined recovery can be achieved in a 20% Et_3N solution in benzene at reflux temperature for 36 h (Scheme 6). The elimination product **12** started to accumulate if the reaction was kept longer and resulted in a lower combined recovery.

Treatment of **19** with the ketene ylide afforded 4-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl]-6,7-dichloroquinolin-2-one (**20**) in a 52% yield. Conversion of **20** to the target compounds was simplified

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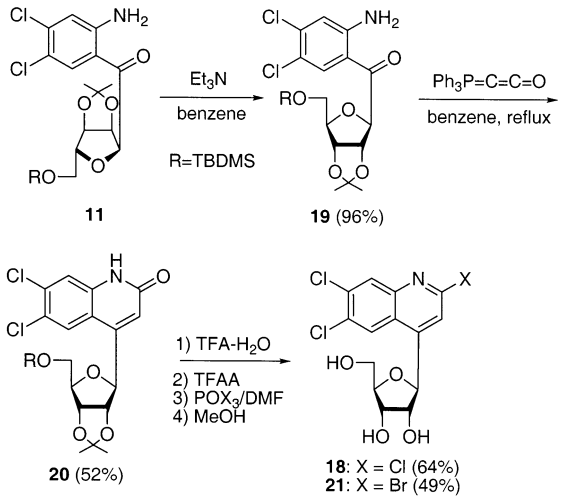
(29) Chu, C. K.; El-Kabbani, F. M.; Thompson. *Nucleosides Nucleotides* **1984**, *3*, 1−31.

SCHEME 6



to a four-step procedure without isolation of any of the intermediates. Both the TBDMS and the isopropylidene groups of **20** were first removed under strong acidic conditions. The resulting nucleoside was then protected with the trifluoroacetyl groups. The protected nucleoside was subjected to halogenation reactions, and this was followed by a removal of the trifluoroacetyl groups to afford the target compounds **18** and **21** in 64% and 49% yields, respectively.

In conclusion, we have developed a multistep synthesis of the targeted 2-halo-6,7-dichloro-4-(β-D-ribofuranosyl)-quinolines. In the process, we discovered that an electrophile-mediated intramolecular cyclization of an alkene intermediate afforded an nucleoside with an α-configuration, which was contrary to the literature precedence. We established that a double-bond isomerization was the cause of the unexpected stereochemistry. A key Wittig reaction was used to construct a quinolin-2-one nucleoside with a ketene ylide from a 2-aminophenone nucleoside, which was susceptible for elimination by conventional construction methods under basic conditions.

Biological Results

Compounds **18** and **21** were evaluated for antiviral activity against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1) as well as for cytotoxicity to uninfected cells using techniques we have described previously.[1] Neither compound was active against HSV-1 but both had modest activity against HCMV. Compounds **18** and **21** were active in a plaque reduction assay ($IC_{50} = 30\ \mu M$) and in a yield reduction assay (IC_{90}'s = 31 and 37 μM, respectively). However, **18** produced cytotoxicity in stationary human foreskin fibroblasts ($IC_{50} = 32\ \mu M$) and in growing KB cells ($IC_{50} = 70\ \mu M$) suggesting the apparent antiviral activity could be a manifestation of cytotoxicity. In contrast, compound **21** did not produce significant cytotoxicity at the highest concentration tested (100 μM) indicating this compound selectively inhibited HCMV replication.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used as provided. Acetonitrile (calcium hydride), dichloromethane (phosphorus pentoxide), toluene (phosphorus pentoxide), dimethylformamide (calcium oxide), and tetrahydrofuran (sodium/benzophenone) were distilled from the indicated drying agent and stored under a positive pressure of argon prior to use (if not used immediately). The phrases "evaporated in vacuo" and "concentrated" were meant to imply the use of a rotary evaporator with a bath temperature not exceeding 40 °C using a water aspirator. Thin-layer chromatography (TLC) was carried out on Analtech 60F-254 silica gel plates, and detection of components on TLC was made by UV light absorption at 254 nm, 365 nm, staining with iodine vapor, or heating to a char following treatment with 10% sulfuric acid in methanol. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v %). Flash column chromatography refers to the chromatography technique described by Still (*J. Org. Chem*. **1978**, *43*, 2923−2925). (*X*% EtOAc/Hex, *Y* cm × *Z* cm): the solvent system that was used in the column, the diameter of the column size, and the height of silica gel. Mallinckrodt SilicAR 230−400 mesh (40−63 μm) was used for chromatography. Melting points were determined and are uncorrected. The ^{1}H (300, 360, or 500 MHz) and ^{13}C (67.5, 90, or 125 MHz) NMR spectra were recorded with the chemical shift values being expressed in ppm (parts per million) relative to tetramethylsilane as an internal standard or the standard chemical shift of the solvents for ^{1}H NMR, and relative to the standard chemical shift of the solvent for ^{13}C NMR. The coupling constant values are expressed in Hz. Mass spectroscopy and elemental analyses were performed by the University of Michigan Chemistry Department.

4,5-Dichloro-2-nitrobenzyl Bromide (2). 4,5-Dichloro-2-nitrotoluene[15] **1** (20.2 g, 98.1 mmol), NBS (20.9 g, 117 mmol), and benzoyl peroxide (1.19 g, 4.9 mmol) were suspended in 120 mL of benzene. The mixture was heated at reflux temperature for 14 h. The resulting orange suspension was cooled to room temperature, and water (50 mL) was added, followed by sodium bisulfite (4 g). The resulting mixture was stirred at room temperature for 2 h to destroy any of the remaining benzoyl peroxide. The mixture was then extracted with toluene (3 × 100 mL). The combined toluene extracts were washed with 200 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by flash column chromatography (from hexane to 3% EtOAc/Hex, then to 5% EtOAc/Hex, 5 cm × 20 cm) to give 19.7 g (60%) of **2** as a yellow solid. Mp: 57−58 °C. R_f (10% EtOAc/Hex) = 0.45. ^{1}H NMR ($CDCl_3$): δ 4.78 (s, 2H), 7.70 (s, 1H), 8.20 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 27.6, 127.8, 133.0, 134.1, 134.2, 138.9, 146.2. Anal. Calcd for $C_7H_4BrCl_2NO_2$: C, 29.51; H, 1.42; N, 4.92. Found: C, 29.65; H, 1.59; N, 4.94.

(4,5-Dichloro-2-nitrobenzyl)triphenylphosphonium Bromide (3). To a solution of compound **2** (18.2 g, 64.0 mmol) in 200 mL of toluene was added dropwise a solution of triphenylphosphine (16.8 g, 64.0 mmol) in 100 mL of toluene over a period of 30 min at room temperature. The resulting pale-yellow mixture was stirred at room temperature for 4 days to give a milky suspension. The precipitate was separated by filtration and dried in vacuo to give 31.0 g (89%) of **3** as a pale-yellow powder. Mp: 250 °C (dec started from 180 °C). ^{1}H NMR ($CDCl_3$): δ 6.18 (d, 2H, J = 15.1), 7.6−7.8 (m, 15H), 8.01 (s, 1H), 8.23 (d, 1H, J = 2.7). ^{13}C NMR ($CDCl_3$): δ 116.6, 117.3, 124.5, 127.3, 130.7, 130.8, 134.4, 135.7, 135.8, 136.5, 136.6, 139.9, 146.8. Anal. Calcd for $C_{25}H_{19}BrCl_2NO_2P\cdot 0.9$toluene (amount of toluene was verified by ^{1}H NMR): C, 59.70; H, 4.05; N, 2.22. Found: C, 59.71; H, 4.31; N, 2.25.

(4,5-Dichloro-2-nitrobenzyl)triphenylphosphorane (4). Compound **3** (29.7 g, 54.2 mmol) was partitioned in 150 mL of water and 150 mL of CH_2Cl_2, and NaOH (31 mL, 3.5 N, 108 mmol) was added dropwise at room temperature. The mixture was stirred vigorously for 1 h and extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 extracts were washed with 300 mL of brine, dried over $MgSO_4$, and concentrated to dryness

to give 25.3 g (99%) of **4** as a deep-purple foam. This compound was used in the next reaction directly without further purification.

(*Z*)-6-*O*-(*tert*-Butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-1,2-dideoxy-3,4-*O*-isopropylidene-D-allo-1-enitol (5) and (*E*)-6-*O*-(*tert*-Butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-1,2-dideoxy-3,4-*O*-isopropylidene-D-allo-1-enitol (6). Compound **4** (25.3 g, 54.2 mmol) and 5-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribose[11] (6.20 g, 20.4 mmol) were dissolved in 300 mL of CH_3CN to provide a deep-purple solution. The solution was heated at reflux temperature for 16 h and then concentrated to dryness. The residue was subjected to a short column (50% EtOAc/Hex, 4 cm × 5 cm) to remove most of the triphenylphosphine oxide. Fractions containing the alkene products were combined and concentrated to dryness. The residue was subjected to flash column chromatography (from 5% EtOAc/Hex to 10% EtOAc/Hex, then to 15% EtOAc/Hex, 4 cm × 15 cm) to give 8.53 g (85%) of a mixture of **5** and **6** as a yellow oil in a 12:1 ratio (based on ^{1}H NMR, peaks used for integration are underlined below). Pure samples of each compound were obtained by using preparative TLC.

5. R_f (10% EtOAc/Hex) = 0.40. ^{1}H NMR (DMSO-d_6): δ 0.04 (s, 6H), 0.87 (s, 9H), 1.21 (s, 3H), 1.36 (s, 3H), 3.57 (m, 1H), 3.61 (dd, 1H, J = 10.5, 5.0), 3.72 (dd, 1H, J = 10.5, 2.1), 4.05 (dd, 1H, J = 9.2, 6.0), 4.65 (dd, 1H, J = 10.0, 5.9), 5.03 (d, 1H, J = 5.1, D_2O exchangeable), 5.99 (dd, 1H, J = 11.6, 10.2), 6.78 (d, 1H, J = 11.7), 8.00 (s, 1H), *8.40* (s, 1H). ^{13}C NMR (DMSO-d_6): δ −5.3, −5.2, 18.2, 25.4, 25.9, 28.1, 65.6, 69.2, 73.2, 76.8, 108.3, 126.0, 126.5, 131.0, 131.1, 131.2, 133.2, 136.2, 146.4. Anal. Calcd for $C_{21}H_{31}Cl_2NO_6Si$: C, 51.22; H, 6.34; N, 2.84. Found: C, 51.25; H, 6.32; N, 2.96.

6. R_f (10% EtOAc/Hex) = 0.35. ^{1}H NMR (DMSO-d_6): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.30 (s, 3H), 1.42 (s, 3H), 3.48 (m, 1H), 3.57 (m, 1H), 3.70 (m, 1H), 4.12 (m, 1H), 4.82 (pseudo t, 1H), 4.98 (d, 1H, J = 6.1, D_2O exchangeable), 6.65 (dd, 1H, J = 15.7, 6.4), 6.84 (d, 1H, J = 15.7), 8.10 (s, 1H), *8.30* (s, 1H). ^{13}C NMR (DMSO-d_6): δ −5.3, −5.2, 18.2, 25.3, 25.9, 27.5, 65.6, 69.6, 77.1, 77.3, 108.3, 122.6, 126.2, 129.7, 130.4, 131.6, 135.1, 136.2, 146.2. Anal. Calcd for $C_{21}H_{31}Cl_2NO_6Si\cdot{}^1/_2H_2O$: C, 50.29; H, 6.43; N, 2.79. Found: C, 50.47; H, 6.16; N, 2.73.

(2*S*)-2,5-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (7). Method 1. To a solution of compound **5** (140 mg, 0.28 mmol) in 2 mL of MeOH was added aqueous NaOH (0.1 mL, 3.5 N, 0.35 mmol) at room temperature. The mixture was stirred at 50 °C for 2 h. The resulting yellow solution was diluted with 5 mL of water and extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with 10 mL of brine, dried over $MgSO_4$ and concentrated to dryness. The residue was subjected to flash column chromatography (20% EtOAc/Hex, 2 cm × 10 cm) to give 127 mg (98%) of **7** as a yellow oil.

Method 2. The procedure is the same as that described in method 1, except that **6** (40 mg, 0.16 mmol) was used instead of **5**. This reaction provided a mixture of compound **7** and its α-anomer as an oil in a combined 95% yield and 1:1 ratio.

From Method 1. R_f (10% EtOAc/Hex) = 0.45. ^{1}H NMR (DMSO-d_6): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.25 (s, 3H), 1.41 (s, 3H), 3.19 (m, 1H), 3.28 (m, 1H), 3.60 (m, 2H), 3.88 (m, 1H), 4.04 (m, 1H), 4.46 (m, 1H), 4.54 (m, 1H), 7.84 (s, 1H), 8.27 (s, 1H). ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.35 (s, 3H), 1.53 (s, 3H), 3.08 (m, 1H), 3.34 (m, 1H), 3.72 (m, 2H), 4.07 (m, 1H), 4.15 (m, 1H), 4.39 (m, 1H), 4.68 (m, 1H), 7.60 (s, 1H), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$): δ −5.2, −5.1, 18.6, 25.8, 26.2, 27.7, 36.4, 63.8, 82.1, 83.9, 85.0, 85.1, 114.2, 126.7, 131.8, 133.7, 134.6, 137.6, 148.0. HRMS for $C_{21}H_{31}Cl_2NO_6Si$ [M + H]$^+$: calcd 492.1376, found 492.1375.

(1*S*,2*S*)-2,5-Anhydro-1-bromo-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (8). Method 1. To a solution of compound **5** (2.28 g, 4.63 mmol) in 50 mL of CH_3CN was added NBS (0.91 g, 5.11 mmol). The mixture was heated at 50 °C for 5 h. The resulting yellow solution was cooled and quenched with 20 mL of saturated $NaHCO_3$. The mixture was concentrated to remove most of the organic solvents and then extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were washed with 100 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was subjected to flash column chromatography (5% EtOAc/Hex, 4 cm × 10 cm) to give 2.30 g (87%) of **8** as a yellow oil (contained a small amount of inseparable impurities).

Method 2. The procedure is the same as that described in method 1, except that **6** (100 mg, 0.40 mmol) was used instead of **5**. This reaction provided compound **8** (without any of the impurities that were observed in method 1) as a yellow oil in a 95% yield.

From Method 2. R_f (10% EtOAc/Hex) = 0.50. ^{1}H NMR (DMSO-d_6): δ −0.01 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.30 (s, 3H), 1.36 (s, 3H), 3.57 (m, 2H), 3.92 (m, 1H), 4.71 (dd, 1H, J = 9.7, 3.8), 4.75 (d, 1H, J = 6.0), 4.86 (dd, 1H, J = 5.8, 3.8), 5.55 (d, 1H, J = 9.7), 8.00 (s, 1H), 8.33 (s, 1H). HRMS for $C_{21}H_{30}BrCl_2NO_6Si$ [M + H]$^+$: calcd 570.0681, found 570.0480.

(1*R*,2*R*)-2,5-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (9R) (1*S*,2*R*)-2,5-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allitol (9S). To a solution of compound **8** (4.00 g, 7.01 mmol) in 100 mL of acetone−water (9:1) was added aqueous NaOH (4.0 mL, 3.5 N, 14 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting yellow solution was diluted with 20 mL of H_2O. The mixture was concentrated to remove most of the organic solvents and then extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with 100 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was subjected to flash column chromatography (20% EtOAc/Hex, 4 cm × 15 cm) to give 1.17 g (33%) of a mixture of **9R** and **9S** as a yellow oil (1:1). R_f (20% EtOAc/Hex) = 0.30. ^{1}H NMR (DMSO-d_6): δ −0.17 (s, 3H), −0.16 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.73 (s, 9H), 0.84 (s, 9H), 1.06 (s, 3H), 1.24 (s, 3H), 1.29 (s, 3H), 1.43 (s, 3H), 3.40 (m, 2H), 3.62 (m, 2H), 3.72 (m, 2H), 3.96 (m, 1H), 4.11 (m, 1H), 4.19 (m, 1H), 4.55 (d, 1H, J = 6.1), 4.61 (d, 1H, J = 6.0), 4.74 (m, 1H), 5.25 (m, 1H), 5.57 (m, 1H), 6.06 (d, 1H, J = 5.2, D_2O exchangeable), 6.17 (d, 1H, J = 5.2, D_2O exchangeable), 7.86 (s, 1H), 7.89 (s, 1H), 8.15 (s, 1H), 8.19 (s, 1H). ^{13}C NMR (DMSO-d_6): δ −5.8, −5.7, −5.6, −5.5, 17.7, 24.5, 25.1, 25.4, 25.6, 25.7, 25.8, 26.4, 63.0, 63.7, 63.8, 66.3, 80.4, 80.5, 82.4, 82.5, 84.0, 84.3, 84.6, 85.8, 111.4, 111.6, 125.9, 126.1, 129.7, 130.2, 130.8, 131.2, 135.5, 135.7, 136.7, 139.2, 147.6, 147.9. HRMS for $C_{21}H_{31}Cl_2NO_7Si$ [M + NH_4]$^+$: calcd 525.1590, found 525.1566.

(2*S*)-2,5-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-(4,5-dichloro-2-nitrophenyl)-3,4-*O*-isopropylidene-D-allose (10). To a solution of DMSO (1.16 mL, 16.4 mmol) in 60 mL of CH_2Cl_2 at −78 °C was added dropwise oxalyl chloride (0.72 mL, 8.2 mmol). The mixture was stirred at −78 °C for 15 min, and then a solution of a mixture of compounds **9R** and **9S** (1.39 g, 2.73 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The resulting mixture was stirred at −78 °C for 40 min, and then Et_3N (3.42 mL, 24.6 mmol) was added. The reaction was warmed to room temperature and stirred for 40 min. After being quenched with 30 mL of saturated NH_4Cl, the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were washed with 100 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was subjected to flash column chromatography (10% EtOAc/Hex, 3 cm × 15 cm) to give 1.10 g (80%) of **10** as a yellow solid. Mp: 100−111 °C. R_f (20% EtOAc/Hex) = 0.60. ^{1}H NMR (DMSO-d_6): δ 0.03 (s, 6H), 0.85 (s, 9H), 1.22 (s, 3H), 1.24 (s, 3H), 3.57 (m, 2H), 3.90 (m, 1H), 4.68 (d, 1H, J = 5.9), 4.94 (d, 1H, J = 4.3), 5.05 (pseudo t, 1H), 7.61 (s, 1H), 8.49 (s, 1H). ^{13}C NMR (DMSO-

d_6): δ −5.8, −5.6, 17.8, 23.9, 25.4, 25.7, 63.6, 81.6, 82.7, 85.2, 85.8, 112.0, 125.6, 129.9, 133.8, 134.5, 137.8, 145.4, 198.0. Anal. Calcd for $C_{21}H_{29}Cl_2NO_7Si$: C, 49.80; H, 5.77; N, 2.77. Found: C, 49.65; H, 5.80; N, 2.85.

(2*S*)-1-(2-Amino-4,5-dichlorophenyl)-2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-allose (11). To a solution of compound **10** (1.10 g, 2.17 mmol) in 120 mL of MeOH−H_2O (9:1) were added Fe (1.2 mg, 21.7 mmol) and $FeSO_4$ (0.60 g, 2.17 mmol). The mixture was heated at reflux temperature for 7 h. The resulting suspension was filtered through Celite. The Celite and the solid residue were washed with hot MeOH. The combined MeOH solutions were concentrated to dryness. The resulting yellow foam was subjected to flash column chromatography (from 20% EtOAc/Hex to 40% EtOAc/Hex, then to 50% EtOAc/Hex, 3 cm × 10 cm) to give 0.95 g (92%) of **11** as a yellow foam. Mp: 63−66 °C. R_f (30% EtOAc/Hex) = 0.35. ^{1}H NMR (DMSO-d_6): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.18 (s, 3H), 1.23 (s, 3H), 3.68 (m, 2H), 4.15 (m, 1H), 4.73 (d, 1H, J = 6.1), 5.13 (pseudo t, 1H), 5.37 (d, 1H, J = 4.8), 7.03 (s, 1H), 7.36 (broad s, 2H, D_2O exchangeable), 7.95 (s, 1H). ^{13}C NMR (DMSO-d_6): δ −5.5, −5.4, 17.9, 24.7, 25.8, 63.2, 82.4, 82.5, 83.5, 84.0, 112.3, 115.2, 115.3, 117.8, 131.7, 136.4, 150.6, 193.6. Anal. Calcd for $C_{21}H_{31}Cl_2NO_5Si$: C, 52.94; H, 6.56; N, 2.94. Found: C, 52.74; H, 6.43; N, 2.74.

1-(2-Acetylamino-4,5-dichlorophenyl)-2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-2,3-didehydro-D-allose (12). To a solution of compound **11** (40 mg, 0.084 mmol) in 0.5 mL of pyridine at 0 °C was added dropwise AcCl (30 μL, 0.42 mmol). The resulting suspension was warmed to room temperature and stirred for 10 min. The resulting mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 extracts were washed with 10 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was subjected to a short column (40% EtOAc/Hex, 1 cm × 4 cm) to give 42 mg of the acetyl intermediate as a yellow oil. This intermediate was used in the following reaction directly without further purification. (HRMS of the acetyl intermediate $C_{23}H_{33}Cl_2NO_6Si$ $[M + H]^+$ calcd 518.1532, found 518.1547). To a solution of this intermediate (20 mg) in 1.5 mL of EtOH at room temperature was added NaOMe (3 mg). The resulting yellow solution was stirred for 30 min. The mixture was then diluted with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with 10 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was subjected to preparative TLC (40% EtOAc/Hex, 1 plate) to give 10 mg of compound **12** as a yellow oil. R_f (40% EtOAc/Hex) = 0.30. ^{1}H NMR (DMSO-d_6): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.84 (s, 9H), 2.00 (s, 3H), 3.70 (m, 2H), 4.31 (m, 1H), 4.78 (m, 1H), 5.51 (d, 1H, D_2O exchangeable, J = 6.0), 5.77 (d, 1H, J = 3.0), 7.74 (s, 1H), 7.89 (s, 1H), 10.2 (broad s, 1H, D_2O exchangeable). This compound was found to be very unstable. Decomposition was observed immediately after purification based on TLC and NMR. Thus, we were only able to obtain an accurate ^{1}H NMR spectrum, which indicated the proposed structure. Mass spectroscopy did not show the expected peaks for the proposed 4,5-dihydrofuran **12**. However, a major peak was $[M - H_2O]^+$, which indicated that the expected decomposition product was a furan.

4-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-ribofuranosyl]-6,7-dichloroquinolin-2-one (13). Compound **11** (300 mg, 0.630 mmol) and keteneylidene(triphenyl)-phosphorane[28] (0.90 g, 3.0 mmol) were suspended in 30 mL of benzene. The mixture was heated at reflux temperature for 14 h. The resulting dark orange solution was directly subjected to flash column chromatography (from 30% EtOAc/Hex to 60% EtOAc/Hex, then to 80% EtOAc/Hex, 3 cm × 10 cm) to give 158 mg (50%) of **13** as a yellow solid. Mp: 213−215 °C (EtOAc/Hex). R_f (40% EtOAc/Hex) = 0.30. ^{1}H NMR (DMSO-d_6): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.17 (s, 3H), 1.20 (s, 3H), 3.76 (m, 2H), 4.21 (pseudo t, 1H), 4.82 (d, 1H, J = 6.0), 5.14 (pseudo t, 1H), 5.42 (d, 1H, J = 4.0), 6.57 (s, 1H), 7.52 (s, 1H), 7.94 (s, 1H), 11.9 (broad s, 1H, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ −5.5, −5.4, 17.9, 24.7, 25.8, 25.9, 62.6, 78.7, 81.4, 82.8, 83.5, 111.9, 116.9, 117.3, 120.2, 123.9, 125.3, 132.6, 138.3, 145.7, 161.1. HRMS for $C_{23}H_{31}Cl_2NO_5Si$ $[M + H]^+$: calcd 500.1427, found 500.1447. Anal. Calcd for $C_{23}H_{31}Cl_2NO_5Si$: C, 55.20; H, 6.24; N, 2.80. Found: C, 54.91; H, 6.22; N, 2.70.

6,7-Dichloro-4-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)-quinolin-2-one (14). To a solution of compound **13** (160 mg, 0.32 mmol) in 10 mL of THF was added dropwise TBAF (0.38 mL, 0.38 mmol, 1.0 M solution in THF) at room temperature. The mixture was stirred for 1 h and then concentrated to dryness. The residue was subjected to flash column chromatography (from 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2, 2 cm × 10 cm) to give 110 mg (89%) of **14** as a yellow solid. Mp: 234−236 °C. R_f (60% EtOAc/Hex) = 0.15. ^{1}H NMR (DMSO-d_6): δ 1.16 (s, 3H), 1.19 (s, 3H), 3.53 (t, 2H, J = 5.7), 4.16 (t, 1H, J = 6.0), 4.81 (d, 1H, J = 5.9), 4.97 (t, 1H, D_2O exchangeable, J = 5.5), 5.16 (pseudo t, 1H), 5.40 (d, 1H, J = 3.9), 6.58 (s, 1H), 7.52 (s, 1H), 8.06 (s, 1H), 11.9 (broad s, 1H, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 24.7, 25.8, 60.3, 78.3, 81.4, 82.7, 83.7, 111.7, 116.8, 117.4, 120.2, 123.9, 125.7, 132.5, 138.2, 146.1, 161.2. Anal. Calcd for $C_{17}H_{17}Cl_2NO_5 \cdot {}_4^1H_2O$: C, 52.26; H, 4.51; N, 3.58. Found: C, 52.02; H, 4.48; N, 3.50.

4-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)-2,6,7-trichloroquinoline (15) and 4-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-2,6,7-trichloroquinoline (16). To a solution of compound **14** (107 mg, 0.277 mmol) in 6 mL of CH_2Cl_2 was added TFAA (78 μL, 0.54 mmol). The mixture was stirred at room temperature for 1 h and then concentrated to dryness. The residue was kept in vacuo for 1 h and then dissolved in 0.5 mL of DMF. In a separate flask, $POCl_3$ (0.20 mL, 2.2 mmol) was added to DMF (2 mL) at approximately 10 °C. After the $POCl_3$/DMF solution was stirred at room temperature for 5 min, the trifluoroacetyl compound in DMF was added at room temperature. The resulting yellow solution was stirred at 60 °C for 3 h. The mixture was cooled to room temperature and diluted with 5 mL of EtOAc and 3 mL of cold water. The resulting mixture was stirred at room temperature for 30 min and then extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with 10 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was dissolved in 20 mL of MeOH and stirred for 24 h. The solvents were removed in vacuo. The residue was subjected to preparative TLC (40% EtOAc/Hex, 2 plates) to give 43 mg (41%) of **15** as a white solid and 2 mg (2%) of **16** as a white solid.

15. Mp: 187−188 °C. R_f (40% EtOAc/Hex) = 0.30. ^{1}H NMR (DMSO-d_6): δ 1.13 (s, 6H), 3.59 (t, 2H, J = 5.8), 4.26 (t, 1H, J = 5.9), 4.87 (d, 1H, J = 5.9), 5.01 (t, 1H, D_2O exchangeable, J = 5.4), 5.25 (pseudo t, 1H), 5.76 (d, 1H, J = 4.3), 7.57 (s, 1H), 8.30 (s, 1H), 8.51 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 24.4, 25.6, 60.4, 78.6, 81.7, 82.9, 84.0, 111.7, 120.8, 123.7, 125.7, 129.7, 130.3, 133.6, 145.9, 148.0, 151.3. Anal. Calcd for $C_{17}H_{16}Cl_3NO_4$: C, 50.46; H, 3.99; N, 3.46; Found: C, 50.22; H, 3.99; N, 3.36.

16. R_f (40% EtOAc/Hex) = 0.35. ^{1}H NMR (DMSO-d_6): δ 1.30 (s, 3H), 1.66 (s, 3H), 3.65 (m, 2H), 4.21 (m, 1H), 4.57 (m, 1H), 4.77 (m, 1H), 5.10 (t, 1H, D_2O exchangeable, J = 5.5), 5.52 (d, 1H, J = 5.4), 7.76 (s, 1H), 8.32 (s, 1H), 8.39 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 25.4, 27.2, 61.2, 81.6, 81.8, 84.6, 85.0, 113.9, 119.3, 123.6, 126.1, 129.6, 130.0, 133.6, 146.1, 149.9, 151.7. HRMS for $C_{17}H_{16}Cl_3NO_4$ $[M + H]^+$: calcd 404.0223, found 404.0205.

4-(α-D-Ribofuranosyl)-2,6,7-trichloroquinoline (17). Compound **15** (32 mg, 0.08 mmol) was dissolved in 1 mL of TFA/H_2O (9:1). The mixture was stirred at room temperature for 30 min and then concentrated to dryness. The residue was subjected to preparative TLC (10% MeOH/CH_2Cl_2, 2 plates) to give 28 mg (97%) of compound **17** as a white solid. Mp: 245−246 °C. R_f (10% MeOH/CH_2Cl_2) = 0.50. ^{1}H NMR (DMSO-d_6): δ 3.50 (m, 1H), 3.72 (m, 1H), 3.95 (m, 1H), 4.17 (m, 1H), 4.40 (m, 1H),4.80 (m, 2H, D_2O exchangeable), 4.96 (d, 1H, D_2O

exchangeable, $J = 7.3$), 5.72 (d, 1H, $J = 3.3$), 7.56 (s, 1H), 8.29 (s, 1H), 8.51 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 61.4, 72.4, 73.0, 78.5, 82.3, 121.1, 124.3, 125.7, 129.5, 130.0, 133.3, 145.9, 150.3, 151.4. Anal. Calcd for $C_{14}H_{12}Cl_3NO_4$: C, 46.12; H, 3.32; N, 3.84. Found: C, 46.16; H, 3.72; N, 3.49.

4-(β-D-Ribofuranosyl)-2,6,7-trichloroquinoline (18). Method 1. Compound **16** (2 mg, 0.005 mmol) was dissolved in 0.2 mL of TFA/H_2O (9:1). The mixture was stirred at room temperature for 30 min and then concentrated to dryness. The residue was subjected to preparative TLC (10% MeOH/CH_2Cl_2, 1 plate) to give 2 mg (100%) of compound **18** as a white solid. This solid has the same ^{1}H NMR spectrum as that obtained from method 2.

Method 2. Compound **20** (150 mg, 0.30 mmol) was dissolved in 1.0 mL of TFA/H_2O (9:1). The mixture was stirred at room temperature for 1 h and then concentrated to dryness and kept in vacuo for 1 h to give a yellow solid. This solid was then suspended in 7 mL of CH_2Cl_2, and TFAA (0.33 mL, 2.4 mmol) was added. The mixture was stirred at room temperature for 2 h, concentrated to dryness, and kept in vacuo for 1 h to give a yellow solid. This solid was dissolved in 4 mL of DMF, and $POCl_3$ (0.22 mL, 2.4 mmol) was added at 0 °C. The resulting yellow solution was stirred at 60 °C for 3 h. The mixture was cooled to room temperature and diluted with 10 mL of EtOAc and 10 mL of cold water, followed by $NaHCO_3$ (0.5 g). The resulting mixture was stirred at room temperature for 15 min and then extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with 15 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was dissolved in 5 mL of MeOH and stirred for 24 h. The solvents were evaporated in vacuo. The residue was subjected to flash column chromatography (10% MeOH/CH_2Cl_2, 1 cm × 10 cm) to give a crude product, which was crystallized from MeOH/EtOAc to give 42 mg of **18** as a pale yellow solid. The filtrate was subjected to preparative TLC (10% MeOH/CH_2Cl_2, 2 plates) to give an additional 28 mg (total 64%) of **18**. Mp: 195−196 °C. R_f (10% MeOH/CH_2Cl_2) = 0.50. ^{1}H NMR (DMSO-d_6): δ 3.61 (m, 1H), 3.72 (m, 1H), 3.84 (m, 1H), 3.94 (m, 2H), 5.01 (t, 1H, D_2O exchangeable, $J = 5.5$), 5.12 (d, 1H, D_2O exchangeable, $J = 5.1$), 5.34 (d, 1H, $J = 5.7$), 5.56 (d, 1H, D_2O exchangeable, $J = 6.3$), 7.86 (s, 1H), 8.29 (s, 1H), 8.52 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 60.9, 70.8, 77.3, 79.7, 84.8, 119.6, 124.1, 126.3, 129.4, 129.9, 133.5, 146.1, 151.4, 151.8. HRMS for $C_{14}H_{12}Cl_3NO_4$ $[M]^+$: calcd 362.9832, found 362.9834. Anal. Calcd for $C_{14}H_{12}Cl_3NO_4 \cdot {}^1/_2H_2O$: C, 45.00; H, 3.51; N, 3.75. Found: C, 45.20; H, 3.35; N, 3.75.

(2*R*)-1-(2-Amino-4,5-dichlorophenyl)-2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-allose (19). A solution of **11** (866 mg, 1.82 mmol) in 2 mL of Et_3N and 8 mL of benzene was kept at reflux temperature for 36 h, and the yellow solution was then concentrated to dryness. The resulting yellow foam was subjected to flash column chromatography (from 15% EtOAc/Hex to 30% EtOAc/Hex, then to 40% EtOAc/Hex, 2 cm × 10 cm) to give 200 mg (23%, 96% based on recovered starting material) of **19** as a yellow foam and 660 mg (76%, 99% combined recovery) of **11** as a yellow foam. R_f (30% EtOAc/Hex) = 0.65. ^{1}H NMR (DMSO-d_6): δ −0.07 (s, 6H), 0.77 (s, 9H), 1.30 (s, 3H), 1.50 (s, 3H), 3.50 (m, 2H), 4.14 (m, 1H), 4.59 (m, 1H), 5.04 (m, 1H), 5.19 (d, 1H, $J = 3.6$), 7.03 (s, 1H), 7.41 (broad s, 2H, D_2O exchangeable), 8.03 (s, 1H). ^{13}C NMR (DMSO-d_6): δ −5.6, −5.5, 18.0, 25.3, 25.7, 27.0, 63.3, 81.5, 81.8, 85.5, 86.1, 112.6, 114.5, 115.0, 117.7, 133.6, 136.8, 151.2, 196.5. HRMS for $C_{21}H_{31}Cl_2NO_5Si$ $[M + H]^+$ calcd 476.1427, found 476.1411.

4-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]-6,7-dichloroquinolin-2-one (20). Compound **19** (220 mg, 0.462 mmol) and keteneylidene(triphenyl)-phosphorane (0.42 g, 1.4 mmol) were suspended in 8 mL of benzene. The mixture was heated at reflux temperature for 8 h. The resulting dark orange solution was directly subjected to flash column chromatography (from 30% EtOAc/Hex to 60% EtOAc/Hex, then to 80% EtOAc/Hex, 1 cm × 10 cm) to give 120 mg (52%) of **20** as a yellow solid. R_f (40% EtOAc/Hex) = 0.40. ^{1}H NMR (DMSO-d_6): δ 0.04 (s, 6H), 0.80 (s, 9H), 1.30 (s, 3H), 1.62 (s, 3H), 3.76 (m, 2H), 4.21 (m, 1H), 4.50 (pseudo t, 1H), 4.68 (m, 1H), 5.23 (d, 1H, $J = 5.5$), 6.67 (s, 1H), 7.50 (s, 1H), 7.94 (s, 1H), 11.9 (broad s, 1H, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ −5.6, −5.5, 17.9, 25.4, 25.7, 27.3, 63.2, 81.7, 81.9, 84.1, 84.7, 113.6, 116.8, 117.0, 118.6, 123.6, 126.2, 132.6, 138.6, 148.2, 161.2. HRMS for $C_{23}H_{31}Cl_2NO_5Si$ $[M + H]^+$: calcd 500.1427, found 500.1411.

2-Bromo-6,7-dichloro-4-(β-D-ribofuranosyl)quinoline (21). Compound **20** (167 mg, 0.334 mmol) was dissolved in 1.0 mL of TFA/H_2O (9:1). The mixture was stirred at room temperature for 1 h, concentrated to dryness, and kept in vacuo for 1 h to give a yellow solid. This solid was then suspended in 7 mL of CH_2Cl_2, and TFAA (0.37 mL, 2.6 mmol) was added. The mixture was stirred at room temperature for 2 h. It was then concentrated to dryness and kept in vacuo for 1 h to give a yellow solid. The solid was dissolved in 4 mL of DMF, and $POBr_3$ (0.76 g, 2.6 mmol) was added at 0 °C. The resulting yellow solution was stirred at 60 °C for 3 h. The mixture was cooled to room temperature and diluted with 10 mL of EtOAc and 10 mL of cold water, followed by $NaHCO_3$ (0.5 g). The resulting mixture was stirred at room temperature for 15 min and then extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with 15 mL of brine, dried over $MgSO_4$, and concentrated to dryness. The residue was dissolved in 5 mL of MeOH and stirred for 24 h. The solvents were evaporated in vacuo. The residue was subjected to flash column chromatography (10% MeOH/CH_2Cl_2, 1 cm × 10 cm) to give a crude product, which was crystallized from MeOH/EtOAc to give 38 mg of **21** as a pale-yellow solid. The filtrate was subjected to preparative TLC (10% MeOH/CH_2Cl_2, 2 plates) to give an additional 28 mg (total 49%) of **21**. Mp: 171−172 °C. R_f (10% MeOH/CH_2Cl_2) = 0.50. ^{1}H NMR (DMSO-d_6): δ 3.61 (m, 1H), 3.71 (m, 1H), 3.82 (m, 1H), 3.96 (m, 2H), 5.02 (t, 1H, D_2O exchangeable, $J = 5.5$), 5.12 (d, 1H, D_2O exchangeable, $J = 4.1$), 5.29 (d, 1H, $J = 5.5$), 5.56 (d, 1H, D_2O exchangeable, $J = 6.3$), 7.94 (s, 1H), 8.26 (s, 1H), 8.48 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 60.9, 70.8, 77.3, 79.6, 84.7, 123.0, 124.3, 126.4, 129.5, 130.0, 133.5, 143.6, 146.6, 150.6. Anal. Calcd for $C_{14}H_{12}BrCl_2NO_4$: C, 41.11; H, 2.96; N, 3.42. Found: C, 41.00; H, 3.08; N, 3.34.

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