Synthesis and Regioselective Ribosylation of 6,7-Dichloroimidazo[4,5-*b*]quinolin-2-one

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The polyhalogenated benzimidazole nucleosides 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) and the 2-bromo analogue (BDCRB) were synthesized in our laboratory and established as potent and selective antiviral agents against human cytomegalovirus (HCMV) with a novel mode of action. In an effort to study the behavior of the key substructure of these analogues in a dimensionally stretched-out manner and probe the spatial limitation of the target enzyme(s), a series of N1- and N3-ribonucleosides of imidazo[4,5-*b*]quinolines were designed as linear dimensional analogues. The nucleosides 6,7-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one and 6,7-dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one were selected and prepared as the key intermediates in this study. During this study, a novel photoassisted annulation was developed for the synthesis of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one, which overcame several problems that were encountered with the literature annulation method. Regioselective ribosylations of this heterocycle were developed and gave both the N1 and the N3 isomers in high yield.

Introduction

Human cytomegalovirus[1] (HCMV) is a significant pathogen for immunocomprised individuals[2] such as bone marrow[3]and organ transplant[4] patients and individuals with AIDS.[5] Recently, a series of polyhalogenated benzimidazole ribonucleosides (**1**) were found to have potent and selective activity against human cytomegalovirus (HCMV).[6] The lead compounds, 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (**1a**) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (**1b**), were more active and less toxic than the clinically used agents ganciclovir and foscarnet in cell culture studies.

Furthermore, both TCRB and BDCRB were found to act by a unique mechanism that does not involve inhibition of DNA synthesis but does involve inhibition of DNA processing.[7] To further study the behavior of some key substructures of these benzimidazole ribonucleosides in a dimensionally stretched-out manner and probe the spatial limitation of the binding site of the incompletely characterized targeted enzyme(s), a series of 6,7-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolines (**2**) and 6,7-dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolines (**3**), with different substituents at the 2-positions, were designed as dimensional analogues[8] of **1** (Figure 1).

A convergent approach for the generation of target compounds would involve functional group transformations at the 2-position of certain stable nucleoside intermediates, e.g., protected 6,7-dichloro-1-(β-D-ribofuranosyl)-imidazo[4,5-*b*]quinolin-2-one (**4**) and 6,7-dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5**) (Scheme 1). A facile method for the preparation of both **4** and **5** would be a regioselective ribosylation of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**). Although imidazo[4,5-*b*]-quinolines have been known since the 1930s, nucleosides of imidazo[4,5-*b*]quinolines have not been reported in the literature. We would now like to report[9] a novel annulation method for the synthesis of a derivative of imidazo-

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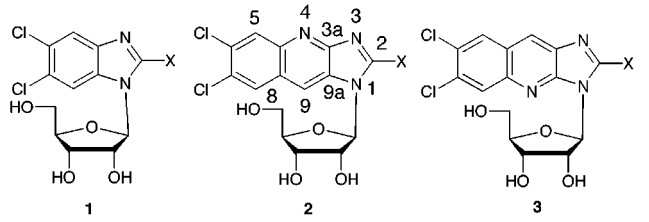


Figure 1.

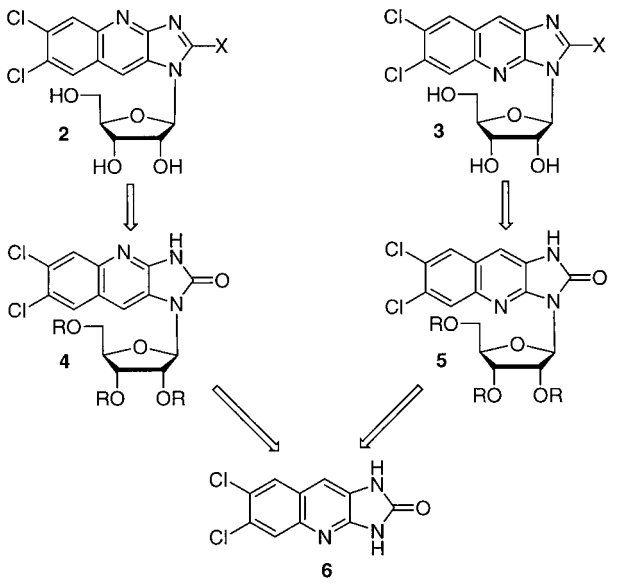
[4,5-*b*]quinolin-2-one and the subsequent study involving regioselective ribosylation of this heterocycle.

Results and Discussion

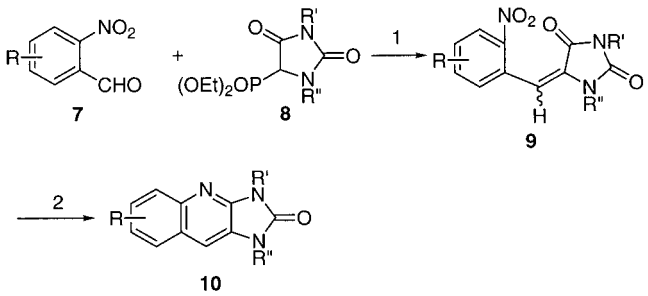
Synthesis of the Heterocycle. Several methods have been reported for the preparation of imidazo[4,5-*b*]-quinolin-2-ones.[10] The need for convergent and efficient methods for the synthesis of imidazo[4,5-*b*]quinolin-2-ones has become increasingly important since the discovery that certain derivatives of imidazo[4,5-*b*]quinolin-2-one are potent inhibitors of blood platelet low cAMP phosphodiesterase and induced aggregation and exhibit antithrombotic activity in animal models.[10c] Except for one example,[10b] approaches for the synthesis of this parent structure have all involved a closure of the central ring as the final synthetic transformation either from 5-[(2-nitrophenyl)methyl]-2,4-imidazolidinediones[10c,d] or from 5-[(2-nitrophenyl)methylene]-2,4-imidazolidinediones[10a,d] (**9**). In an improved method recently reported by Meanwell and co-workers,[10c,d] a Horner−Wadsworth−Emmons type of olefin-forming reaction was used as the key step in the preparation of imidazo[4,5-*b*]quinolin-2-ones (**10**) (Scheme 2). By this method, **10** can be generated rapidly and reliably in excellent yields under mild conditions.

To use the approach reported by Meanwell and co-workers,[10d] 4,5-dichloro-2-nitrobenzaldehyde[11] (**14**) was prepared from 4,5-dichloro-2-nitroaniline (**11**) through 4,5-dichloro-2-nitrobenzonitrile (**12**) in an overall 50% yield (Scheme 3). The preparation of **12** from **11** was improved from the reported[12] 20% yield to 94% yield through the corresponding diazonium tetrafluoroborate salt by a nonaqueous diazotization.[13] The condensation between 4,5-dichloro-2-nitrobenzaldehyde (**14**) and di-

Scheme 1

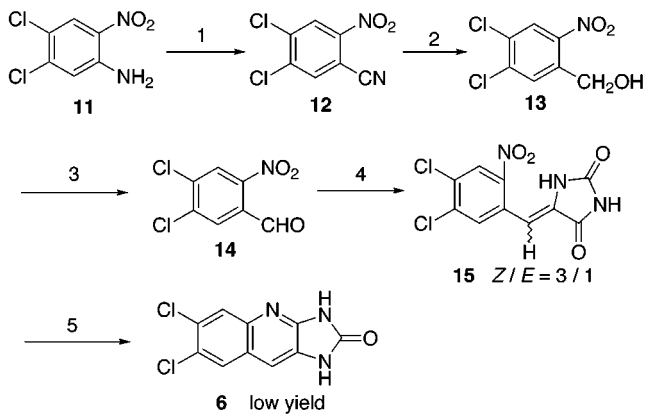


Scheme 2[a]



[a] Key: (1) base; (2) (a) Pd/C, H_2, (b) TsOH, MeOH, (c) I_2, MeOH, reflux.

Scheme 3[a]



[a] Key: (1) (a) *t*-BuONO, BF_3·OEt_2, (b) NaCN, CuCN, 94% overall; (2) (a) BH_3·THF, (b) $NaNO_2$, AcOH, H_2O, (c) NaOH, H_2O, 66%; (3) PCC, CH_2Cl_2, 80%; (4) diethyl 2,4-dioxoimidazolidine-5-phosphonate, Et_3N, CH_3CN, quantitative; (5) (a) Pd/C, H_2, (b) TsOH, MeOH, (c) I_2, MeOH, reflux.

ethyl 2,4-dioxoimidazolidine-5-phosphonate,[10d] in the presence of triethylamine in acetonitrile, gave 5-[(4,5-dichloro-2-nitrophenyl)methylene]imidazolidine-2,4-dione (**15**) as a mixture of *Z*/*E* isomers (3/1) in a quantitative yield. The pure *Z* isomer ((*Z*)-**15**) was isolated by a collection of the precipitate directly from the reaction mixture in a 63% yield. The pure *E* isomer ((*E*)-**15**) was obtained in 14% yield by a recrystallization of the remaining *Z*/*E* mixture from 1,4-dioxane. The regio-

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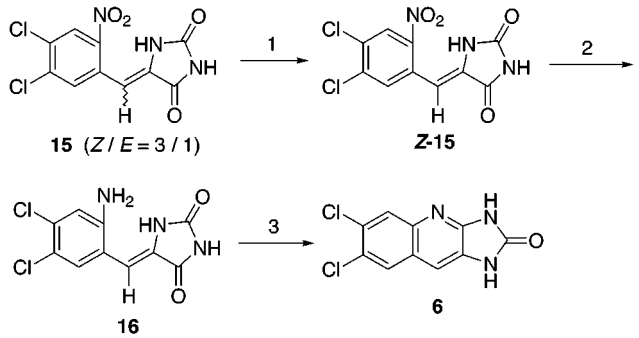
Scheme 4[a]



[a] Key: (1) (a) NaOH, MeOH, (b) 10% HCl, quantitative; (2) Fe, $FeSO_4$, MeOH, H_2O, reflux, 99%; (3) *hν*, AcOH, rt, 90%.

chemical assignment was based on a previous study[14] that demonstrated that, in general, in the ^{1}NMR spectrum, the olefinic proton of the *Z* isomer is downfield from the olefinic proton of the *E* isomer.

When **15** (mixture of *E* and *Z*) was subjected to the literature annulation method involving hydrogenation catalyzed by 10% Pd/C in DMF followed by an acid-catalyzed ring closure and an oxidative aromatization, **6** was obtained in very low yield. A ^{1}H NMR spectrum of the crude products revealed that severe dechlorination had occurred.

We then decided to proceed with the reduction of the nitro group and the double bond in two separate steps. The nitro group of (*Z*)-**15** was selectively reduced by an iron reduction to give (*Z*)-5-[(2-amino-4,5-dichlorophenyl)-methylene]imidazolidine-2,4-dione (**16**) in 99% yield. On the other hand, when *E*-**15** was subjected to the same iron reduction conditions, compound **6** was obtained instead of the reduced form of *E*-**15**. However, this rather insoluble solid (**6**) was very difficult to separate from the solid mixture of Fe and FeO_n. This makes a direct reduction of the nitro group of the *Z*/*E* mixture of **15** less productive due to the loss of **6** during the workup. Other methods for a selective reduction of the nitro group of the *Z*/*E* mixture of **15** were studied, including hydrogenation catalyzed by palladium on carbon or Raney nickel, reduction by stannous chloride, etc. However, none of these reduction conditions gave a clean reaction. It was reported by Meanwell and co-workers that a *Z*/*E* mixture of (*Z*)-**15** and (*E*)-**15** could be isomerized completely to the *Z* isomer under alkaline conditions.[10d]

A selective iron reduction of the nitro group then gave **16** in 99% yield for the two steps (Scheme 4). Reduction of the double bond of **16** was then attempted using various hydrogenation conditions. It was found that palladium on carbon or Raney nickel would not reduce the double bond without effecting a dehalogenation, and no apparent reaction was observed when chlorotris-(triphenylphosphine)rhodium(I)[15] was used as the catalyst under normal hydrogenation conditions.

To rotate the 2,4-dioxoimidazolidine moeity of (*Z*)-**15** to the appropriate juxtaposition for ring closure without reducing the double bond, double-bond photoisomerization[16] was considered. We surmised that if **16** could ring close to give **6** during the double-bond photoisomerization, it would provide an additional driving force to push the photoequilibrium in the direction of the *E* isomer. Indeed, when **16**, in acetic acid, was irradiated by a medium-pressure mercury lamp at room temperature, a 40% yield of **6** was isolated. It was assumed that the short wavelength portion of the medium-pressure mercury lamp could be implicated in the low yield and the side products. A UV spectrum of **16** revealed peaks at 230, 315, and 374 nm. The UV peak centered at 374 nm slopes down to 440 nm. We decided to monitor the peak at 374 nm for our study on the double-bond isomerization. When a cupric sulfate/ammonium hydroxide solution was selected as the filter solution,[16b] to filter off light with wavelengths shorter than 405 nm, **6** was obtained in a 90% yield after 60 h irradiation in acetic acid at 25 °C. The assumption that the peak at 374 nm could be attributed to the double bond isomerization was also confirmed by using potassium chromate/ammonium hydroxide solution[16b] as the UV light filter solution. This solution can filter off light with wavelengths shorter than 450 nm, and under this condition no product was formed.

Thus, a novel photoassisted annulation reaction was developed for the synthesis of imidazo[4,5-*b*]quinolin-2-ones that avoids a reduction of the double bond by stringent hydrogenation conditions and should tolerate a variety of functional groups. By this method, 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**) was synthesized from **15** in an overall 89% yield.

Selective Ribosylation. Although glycosylation of imidazo[4,5-*b*]quinolin-2-ones or the imidazo[4,5-*b*]quinolines, per se, was unknown, the ribosylation of a structurally related ring system, imidazo[4,5-*b*]pyridine, was well documented.[17] The glycosylation of imidazo[4,5-*b*]-pyridine and its derivatives has been studied by using different methods, including the mercury salt method, the acid-catalyzed fusion method, the direct condensation method, and the silyl−Hilbert−Johnson method. In most of these studies, the N-3 isomers were found to be the major product. In a study on the ribosylation of imidazo-[4,5-*b*]pyridine by Itoh and co-workers,[18] the N-4 ribonucleoside could also be obtained as the major product under the kinetic conditions dictated by the silyl−Hilbert−Johnson method.

The ribosylation of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**) was first studied by a direct acid-catalyzed condensation. When **6** was treated with 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-*β*-D-ribofuranose (TBAR), catalyzed by stannic chloride in acetonitrile at 50 °C for 4 h, 6,7-dichloro-3-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo-[4,5-*b*]quinolin-2-one (**5a**) was obtained in a 89% yield (Scheme 5). This regioselectivity is in agreement with that reported[17,18] for imidazo[4,5-*b*]pyridine.

The ribosylation of **6** was then studied by using the silyl−Hilbert−Johnson method.[19] Silylation of the het-

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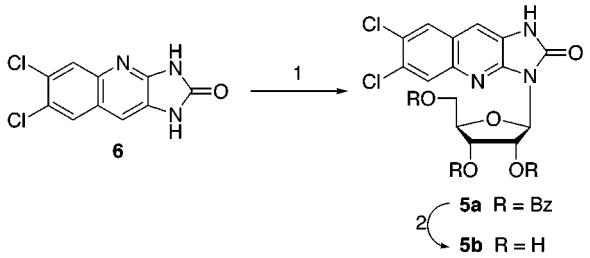
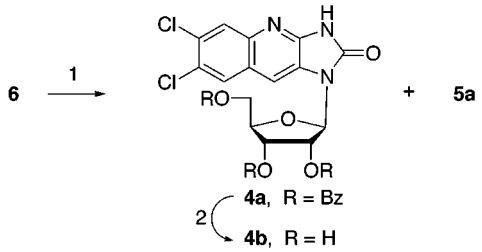
Scheme 5[a]



[a] Key: (1) TBAR, $SnCl_4$, CH_3CN, 50 °C, 89%; (2) NH_3, MeOH, 94%.

Scheme 6[a]



[a] Key: (1) see Table 1; (2) NH_3, MeOH, 97%.

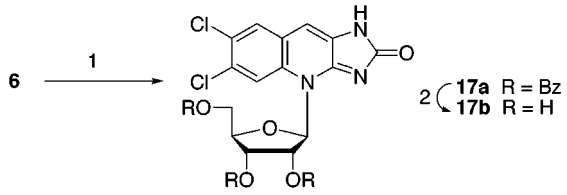
Table 1. Ribosylation of Silylated 6 with TBAR

entry	Lewis acid[a]	$ClCH_2CH_2Cl$/ CH_3CN	*T* (°C)	time (h)	**4a**/**5a**[b]	yield[c] (%)
1	$SnCl_4$	3/4	70	1	2.1/1	65
2	$SnCl_4$	3/1	70	1	1.8/1	75
3	$SnCl_4$	3/1	rt	6	1.5/1	61
4	$SnCl_4$	0/1	rt	6	2.0/1	60
5	TMSOTf	3/4	70	1	20/1[d]	85
6	TMSOTf	3/1	70	1	5.2/1	86
7	TMSOTf	3/4	50	5	17/1	68
8	TMSOTf	0/1	70	1	4.2/1	76

[a] Two equivalents of a Lewis acid were used in all cases. [b] Ratios determined from HPLC analysis. [c] Combined yield of **4a** and **5a** isolated from flash chromatography. [d] Ratio from isolated products.

erocycle was conducted by using *N*,*O*-bis(trimethylsilyl)-acetamide (BSA).[20] It was found that silylated **6** was insoluble in acetonitrile but soluble in 1,2-dichloroethane. However, in 1,2-dichloroethane hardly any ribosylation was detected when silylated **6** was treated with TBAR in the presence of a Lewis acid. Thus, the ribosylation reaction was carried out by first silylating **6** in 1,2-dichloroethane followed by diluting the reaction with a certain amount of acetonitrile before the addition of TBAR and a Lewis acid. In this way, a homogeneous solution was maintained throughout the reaction and produced a smooth ribosylation. When silylated **6** was condensed with TBAR in the presence of stannic chloride in 1,2-dichloroethane/acetonitrile (3/4) at 70 °C, a mixture of the N3- and N1-ribonucleoside was obtained (Scheme 6, Table 1, entry 1). Surprisingly, the N1 isomer, 6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo-[4,5-*b*]quinolin-2-one (**4a**), was found to be the major product. This is different from the ribosylation of imidazo-[4,5-*b*]pyridine[18] using the silyl−Hilbert−Johnson method.

Scheme 7[a]



[a] Key: (1) (a) BSA, CH_3CN, rt, (b) TBAR, TMSOTf, 50 °C, 29%; (2) NaOMe, MeOH, 48%.

A systematic study was then initiated to study the effect of temperature, solvent system, and Lewis acid on the distribution of the sites of ribosylation (Scheme 6, Table 1).

In general, when the ribosylations were conducted under Vorbruggen conditions[21] using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the Lewis acid instead of stannic chloride, a dramatic increase in the formation of **4a** was observed. A highly regioselective ribosylation was achieved to give a 20/1 ratio of **4a**/**5a** in a combined 85% yield (Table 1, entry 5) when the reaction was catalyzed by TMSOTf in $ClCH_2CH_2Cl/CH_3CN$ (3/4) at 70 °C for 1 h. When the polarity of the solvent system was decreased ($ClCH_2CH_2Cl/CH_3CN$, 3/1), a decrease of regioselectivity was observed (Table 1, entry 6). However, when acetonitrile was used as the only solvent, a mixture of **4a** and **5a** in a ratio of 4.2/1 was obtained in a combined 76% yield (Table 1, entry 8). This low regioselectivity is presumably due to the incomplete silylation in acetonitrile. It was found that a high temperature was also required for the ribosylation when TMSOTf was used as the Lewis acid. It is apparent that the type of Lewis acid, solvent, and temperature are all important for the regioselective formation of the N1-riboside **4a**.

Mechanism for the Regioselective Formation of 4a. When the silyl−Hilbert−Johnson ribosylation was conducted at low temperature (Table 1, entries 3, 4, and 7), the ribosylation proceeded at a lower rate and the generation of N4-riboside (**17a**) was observed first, very shortly after the addition of the Lewis acids. However, both **4a** and **5a** began to appear shortly after the formation of **17a**. With a continuation of the reactions, the amount of **4a** and **5a** continued to increase while the amount of **17a** was maintained at a relatively constant level until gradually disappearing toward the end of the reactions. By quenching the ribosylations a short time after the addition of the Lewis acids, a small amount of **17a** was isolated (Scheme 7). When treated with BSA and TMSOTf at 70 °C in $ClCH_2CH_2Cl/CH_3CN$ (3/4), **17a** was converted to **4a** and **5a** in a ratio of 15/1 in a combined 83% yield. And when **17a** was treated with BSA and stannic chloride under the same conditions, **4a** and **5a** were obtained in a ratio of 4.7/1 in a combined 86% yield (Scheme 8). This would suggest that **17a** is a kinetic product under the silyl−Hilbert−Johnson conditions. Furthermore, the high regioselective transformation of **17a** to **4a** in the presence of TMSOTf and the observed initial formation of **17a** during the ribosylation implied the possible key role of **17a** in the regioselective generation of **4a**.

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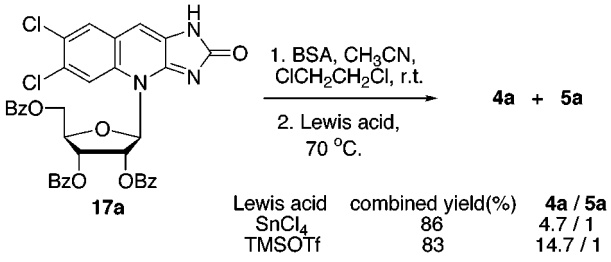
(21) (a) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. Nucleoside Synthesis XII. Nucleoside Synthesis with Trimethylsilyl Triflate and Perchlorate as Catalysts. *Chem. Ber.* **1981** *114*, 1234−1255. (b) Vorbruggen, H.; Bennua, B. Nucleoside Synthesis XXV. A New Simplified Nucleoside Synthesis. *Chem. Ber.* **1981**, *114*, 1279−1286.

Scheme 8



Lewis acid	combined yield(%)	4a / 5a
$SnCl_4$	86	4.7 / 1
TMSOTf	83	14.7 / 1

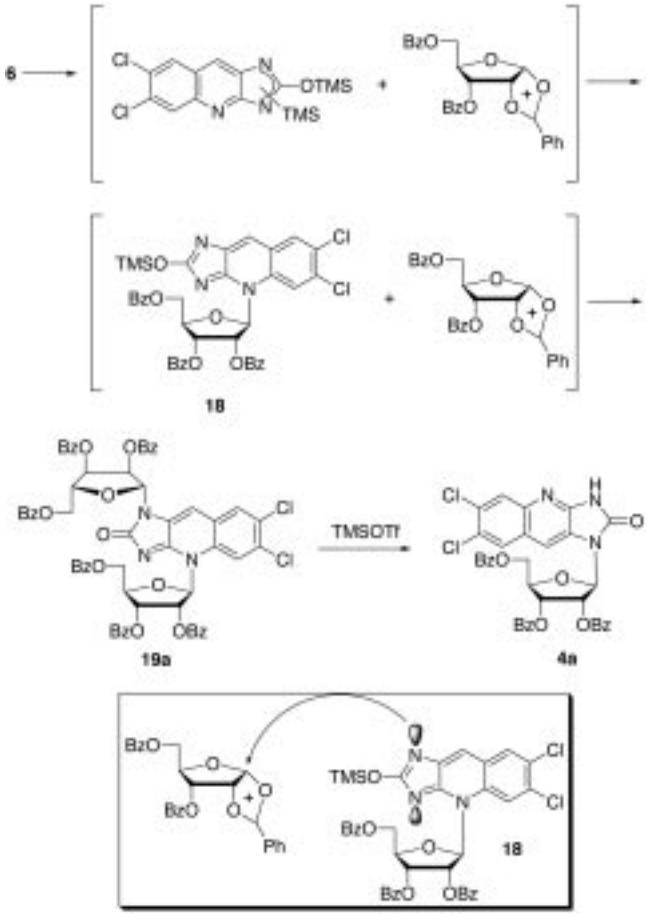
Transglycosylation among regioisomers of nucleosides and the reversibility of glycosylation have been reported in many systems.[22] The overall yield of a particular isomer under thermodynamic conditions is believed to depend on the relative stability of the isomer. Among the regioisomers of imidazo[4,5-*b*]pyridine ribonucleoside, the N3 isomer was considered[17,18] as the most stable isomer since it was found to be the major product both under the thermodynamic ribosylation conditions and through the transglycosylation of the corresponding N4-isomer. By analogy, compound **5a** (N3-isomer) would be more stable than **4a** (N1-isomer). However, no reaction was observed when either **4a** or **5a** was treated with BSA (2 equiv) and TMSOTf (2 equiv) in acetonitrile/1,2-dichloroethane (1/1) at 75 °C for 12 h. Also, no reaction was observed when **4a** was treated with stannic chloride in acetonitrile at 50 °C for 24 h. This suggested that both **4a** and **5a** are stable products under the applied ribosylation conditions and stability is, most likely, not the determining factor in the regioselective formation of **4a**.

On the basis of the implicit role of **17a** in the formation of **4a**, we proposed that this unexpected high regioselective formation of **4a** could undergo the following mechanism (Scheme 9). First, ribosylation of silylated **6** occurred at the N4 position (to give **18**), and this was followed by a second ribosylation. The second ribosylation preferably took place at the N1 position due to the block of the N3 position by the first ribosyl moiety and gave the corresponding 1,4-diribosylated nucleoside (**19a**). The rather labile ribosyl moiety at the N4 position of **19a** was then removed in the presence of the Lewis acid to give the N1 ribonucleoside **4a**.

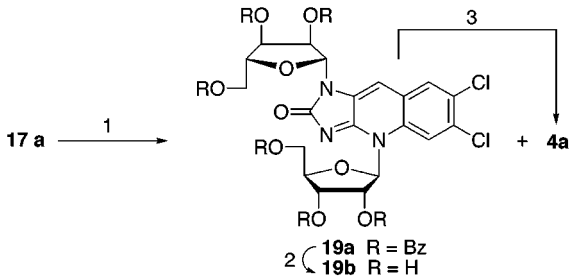
After a reexamination of this ribosylation, we indeed isolated a small quantity of 1,4-diribosylated nucleoside **19a** (details of the structure assignment is discussed in the next section). When **19a** was treated with TMSOTf at room temperature, it was completely converted to **4a** in less than 5 min. To further prove the mechanism, **17a** was silylated by BSA followed by the addition of TBAR and TMSOTf at room temperature (Scheme 10). Monitoring the reaction by TLC indicated that **19a** was formed first, before the generation of **4a**. After 3 h at room temperature, **19a** (27%) was obtained with **4a** (5%) and a recovery of **17a** (50%). When the reaction time was extended to 3.5 h, **19a** and **4a** were obtained in a 42% and 26% yield, respectively, with the recovery of **17a** (18%). This clearly indicated that the selective formation of **4a** from **17a** was achieved through the generation of the diribonucleoside **19a**.

(22) (a) See refs 18, 20, and 21b. (b) Garner, P.; Ramakanth, S. A. Regiocontrolled Synthesis of N^7- and N^9-Guanine Nucleoside. *J. Org. Chem.* **1988**, *53*, 1294−1298. (c) Wood, S. G.; Dalley, N. K.; George, R. D.; Robins, R. K.; Revankar, G. R. Synthesis and Structural Studies of Certain Novel Imidazo[1,2-*b*]pyrazole Nucleosides. *J. Org. Chem.* **1984**, *49*, 3534−3540.

Scheme 9



Scheme 10[a]



[a] Key: (1) (a) BSA, CH_3CN, rt, (b) TBAR, TMSOTf; (2) NaOMe, MeOH, 66%; (3) TMSOTf, CH_3CN, rt, 90%.

Regiochemical Assignment. To make the regiochemical assignment of compounds **4a**, **5a**, and **17a**, they were first deprotected by using either methanolic ammonia or sodium methoxide in methanol to give the corresponding ribonucleosides 6,7-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**4b**), 6,7-dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5b**), and 6,7-dichloro-4-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**17b**), respectively. The UV spectra of compounds **4b**, **5b**, **17b**, and 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**) were obtained in methanol, pH 11 buffer, and pH 1 buffer. The UV spectra of compound **4b** and **5b** were found to be quite similar to that of **6**. However, the UV spectrum of **17b** was significantly different from that of **6**. This indicated that compound **17b** was the N4-ribosylated nucleoside since substitution on N4 would significantly alter the aromaticity of the ring. However, no distinguishible difference was observed between com-

Table 2. Chemical Shifts and $^{13}C-^{1}H$ Coupling Constants for the Aromatic Carbons of 4b and 5b

	δ (ppm) (J (Hz))									
compd	C2	C3a	C4a	C6	C8	C5	C7	C8a	C9a	C9
4b	154.01, d ($J_{H1'-C2}$ = 2.44)	146.68, d (J_{H9-C3a} = 6.11)	141.72, m	129.17, dd (J_{H8-C6} = 8.55, J_{H5-C6} = 3.66)	128.26, dd (J_{H8-C8} = 168.45, J_{H9-C8} = 4.85)	127.92, d (J_{H5-C5} = 170)	126.21, dd (J_{H8-C7} = 3.66, J_{H5-C7} = 8.54)	124.88, d (J_{H5-C8a} = 6.1)	124.13, d ($J_{H1'-C9a}$ = 4.88)	111.73, dd (J_{H9-C9} = 172.12, J_{H8-C9} = 4.89)
5b	153.77, d ($J_{H1'-C2}$ = 3.66)	146.31, dd (J_{H9-C3a} = 7.33, $J_{H1'-C3a}$ = 4.89)	140.86, m	129.16, dd (J_{H8-C6} = 9.76, J_{H5-C6} = 4.88)	128.29, dd (J_{H8-C8} = 168.5, J_{H9-C8} = 4.89)	127.62, d (J_{H5-C5} = 169.7)	126.70, dd (J_{H8-C7} = 3.66, J_{H5-C7} = 8.54)	125.33, d (J_{H5-C8a} = 6.1)	124.53, s	110.41, dd (J_{H8-C9} = 6.24, J_{H9-C9} = 169.7)

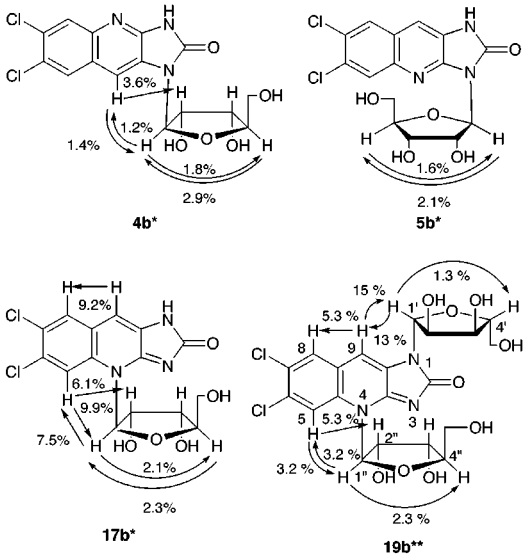


Figure 2. NOE difference experiments. *In DMSO-d_6 at room temperature. **In CD_3OD, at room temperature.

pound **4b** and **5b** in acidic, basic, and neutral media. This excluded the possibility of using UV for the regiochemical assignment of compound **4b** and **5b**. The carbon-13 spectra showed the same trend as the UV spectra. The ^{13}C spectra of **4b** and **5b** showed similar patterns and were quite different from that of **17b** in the aromatic region.

Besides support from the UV spectrum, further proof of the regiochemistry of **17b** came from the NOE difference experiments (Figure 2). First, for the three aromatic protons of **17b**, the peak at 8.63 ppm does not have any NOE with the other two aromatic protons, while the peak at 8.22 ppm showed NOE enhancements with a peak at 7.40 ppm. This indicated that the peak at 8.63 ppm is H5 and the peaks at 8.22 and 7.40 ppm are either H8 or H9. When H5 was irradiated, a 6.1% enhancement of H2′ and a 9.9% enhancement of H1′ were observed while irradiation of H1′ gave a 7.5% enhancement of H5. This provided further proof that the ribosyl moiety of **17b** was residing at N4. For compound **5b**, no NOE enhancement was observed between any aromatic protons and any protons on the ribosyl moiety. For compound **4b**, when the aromatic proton at 8.21 ppm was irradiated, a 3.6% enhancement of H2′ and a 1.4% enhancement of H1′ were observed while irradiation of H1′ gave a 1.2% enhancement of the peak at 8.21 ppm. NOE enhancement was also observed between aromatic protons at 8.21 and 8.15 ppm while no NOE enhancement was observed for the aromatic proton at 8.06 ppm with the other aromatic protons. This indicated that the proton at 8.06 ppm is H5 and the protons at 8.21 and 8.15 ppm are either H8 or H9. This provides evidence that the site of ribosylation of **4b** could be at N1.

To unequivocally determine the position of ribosylation for compound **4b** and **5b**, a study of three-bond $^{13}C-^{1}H$ spin−spin long-range coupling between the proton at the anomeric position of the nucleoside and the α carbons of the heterocycle next to the glycosylation site[23] was conducted. To make this determination, the entire aro-

(23) Cline, B.; Fagerness, P. E.; Panzica, R. P.; Townsend, L. B. The use of Carbon-13 Magnetic Resonance Chemical Shifts and Long-range $^{13}C-^{1}H$ Constants for Assigning the Site of Glycosylation of Nitrogen Heterocycles. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1586−1591.

matic region of the ^{13}C NMR spectra of both **4b** and **5b** were first unequivocally assigned by using the long-range $^{1}H-^{13}C$ selective decoupling method.[24] The carbon-13 assignments[25] and the $^{13}C-^{1}H$ coupling constants for the aromatic carbons of **4b** and **5b** are listed in Table 2.

When the anomeric proton of **4b** was irradiated, carbons C2 and C9a were decoupled, which confirmed that the ribosyl moiety of **4b** was attached to the N1 position. On the other hand, when the anomeric proton of **5b** was irradiated, carbon C2 and C3a were decoupled, which indicated that the ribosyl moiety of **5b** was attached at the N3 position.

The protected diribosylated nucleoside **19a** was deprotected by the use of sodium methoxide in methanol to give 6,7-dichloro-1-(β-D-ribofuranosyl)-4-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**19b**). The NOE enhancements between H9 and H1′ together with the NOE enhancements between H5 and H1″ or H2″ indicated that the two ribosyl moieties are located at the N1 and N4 positions (Figure 2). The NOE enhancements between H1′ and H4′, and H1″ and H4″ confirmed that both anomeric bonds of the two ribosyl moieties have the β-configuration.

Conclusions

A novel photoassisted annulation method was developed for the preparation of 6,7-dichloroimidazo[4,5-*b*]-quinolin-2-one (**6**), which is expected to accommodate a variety of functional groups. Regioselective ribosylation methods were developed to give both the N1 and the N3 ribonucleosides of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one in high yield. This represented the first synthesis of a ribonucleoside of imidazo[4,5-*b*]quinolines. A study of the mechanism for the regioselective formation of **4a** under Vorbruggen conditions revealed, for the first time, that steric requirements of a sequential ribosylation, instead of relative stability, determine the site of final ribosylation. The possible application of this ribosylation mechanism to other heterocyclic ring systems is now under investigation. The synthesis of the target dimensional analogues (**2** and **3**) from **4a** and **5a** together with an evaluation of their biological activities will be reported in a separate paper.

Experimental Section

General Procedures. Melting points were taken on a melting point apparatus and are uncorrected. The silica gel used for chromatography was silica gel 60 230−400 mesh. Thin layer chromatography (TLC) was performed on prescored SilicAR 7GF plates. Compounds were visualized by illumination under UV light (254 nm). Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 40 °C, unless specified otherwise. UV spectra were performed on a UV/vis spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined at 360 MHz. The chemical shift values are expressed in δ values (parts per million) relative to the standard chemical shift of TMS or the solvent used. Elemental analyses were performed by a commercial laboratory. Photoreaction experiments were carried out in a 1000 mL photochemical reaction assembly with 450 W medium-pressure mercury lamp (cat. no. 7825-34).

4,5-Dichloro-2-nitrobenzonitrile (12). Boron trifluoride etherate (9.2 mL, 75 mmol) was placed into a 1000 mL three-neck flask equipped with a thermometer and two dropping funnels under an argon atmosphere. The solution was cooled to −10 °C by a dry ice−acetone bath. A solution of 4,5-dichloro-2-nitroaniline (**11**, 10.35 g, 50 mmol, Aldrich) in a mixture of dry THF (80 mL) and dry dichloromethane (160 mL) was added dropwise to the reaction solution at a rate that the temperature was maintained below −5 °C to give a yellow suspension. After the temperature was returned to −10 °C, *tert*-butyl nitrite (8 mL, 60 mmol) in dry dichloromethane (60 mL) was added at a rate sufficient to maintain the temperature around −10 °C. After the addition, the solution became clear and remained clear for about 5 min before a large amount of a yellow precipitate appeared. The suspension was stirred under −10 °C for an additional 20 min and then in an ice bath for 40 min followed by the addition of hexane (200 mL). The solid was collected by filtration, washed with ether, and dried under vacuum at room temperature to give (4,5-dichloro-2-nitrophenyl)diazonium tetrafluoroborate (13.8 g, 90 %) as a slightly yellow solid. Without further purification, the salt was used for the following reaction.

The diazonium tetrafluoroborate salt (25.5 g, 83.3 mmol) was added in portions over a period of 15 min to a solution of cuprous cyanide (20 g, 222 mmol) and sodium cyanide (28 g, 570 mmol) in water (200 mL) in a 500 mL three-neck flask equipped with a mechanical stirrer in an ice bath. During the addition, a small amount of ice was added frequently for efficient cooling. The suspension was stirred continuously in an ice bath for an additional 2 h and then at room temperature overnight. The brown suspension was extracted with ether (1000 mL), and the ether solution was washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether solution was concentrated to about 60 mL and then allowed to stand in a refrigerator (5 °C) for 1 h. The solid was collected by filtration and dried under vacuum at room temperature to give 4,5-dichloro-2-nitrobenzonitrile (**12**, 15.14 g, 84%) as a brown solid. The filtrate was further purified by silica gel flash chromatography (2 × 6 cm) with elution by 5% ethyl acetate in hexane. The appropriate fractions, as identified by TLC, were collected, the solvent was evaporated, and the solid was dried under vacuum at room temperature to give an additional 1.7 g of **12** (10%) as a yellow solid. The total yield was 94%: mp 125−127 °C (lit.[12] mp 129−130 °C); ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 146.6, 140.0, 139.0, 136.3, 127.5, 113.1, 107.2.

4,5-Dichloro-2-nitrobenzenemethanol (13). Borane·THF complex in THF (1 M, 137 mL, 137 mmol) was added dropwise through a dropping funnel to a solution of 4,5-dichloro-2-nitrobenzonitrile (**12**, 14.9 g, 68.5 mmol) in dry THF (90 mL) in a 1000 mL three-neck flask under an argon atmosphere. The solution was stirred at room temperature overnight to give a clear dark solution. Hydrogen chloride (10 %, 171 mL) was added cautiously to the reaction solution. After the addition, the solution was heated at reflux for 30 min to afford a clear orange solution. The THF was removed under reduced pressure to give a yellow suspension. The suspension was extracted by diethyl ether (2 × 200 mL), and the ether layer, containing byproducts (TLC, R_f = 0.7−0.8, 40% AcOEt in hexane), was discarded. The aqueous suspension was neutralized by the addition of concentrated ammonium hydroxide and then extracted with ether (2 × 200 mL). The ether layer was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The ether was evaporated, and the solid was dried under vacuum at room temperature overnight to give 4,5-dichloro-2-nitrobenzylamine (12.6 g, 83.6 %) as a yellow solid that was immediately used for the next step since exposure to air for a period of time will produce side products.: ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.65 (s, 1H), 4.14 (s, 2H), 1.66 (bs, 2H).

Sodium nitrite (5.93 g, 86.0 mmol) in water (22.5 mL) was added dropwise into the solution of 4,5-dichloro-2-nitrobenzylamine (12.6 g, 57.3 mmol) in acetic acid (43 mL) and water

(24) (a) Kalinowski, H.-O.; Gerger, S.; Braun, S. *Carbon-13 Spectroscopy*; John Wiley & Sons Inc.: New York, 1986; pp 57−59. (b) Bock, K.; Pederson, C. Assignment of Long-range Carbon-proton Couplings Through Selective Proton Decoupling. *J. Magn. Reson.* **1977**, *5*, 227−230.

(25) See the Supporting Information for details.

(28.8 mL) in an ice bath with vigorous stirring. After the complete addition, the suspension was continuously stirred in an ice bath for 10 min and then at room temperature for 15 min. The suspension was extracted with dichloromethane (3 × 100 mL). The combined dichloromethane extracts were dried over anhydrous sodium sulfate and evaporated to dryness (first by an aspirator and then by an oil pump) at room temperature. The solid was redissolved in methanol (64 mL), and 1 N sodium hydroxide (64 mL) was added over a period of 20 min with vigorous stirring. After the addition, the solution was continuously stirred for an additional 10 min at room temperature and then extracted with dichloromethane (3 × 100 mL). The combined dichloromethane extracts were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The solid was subjected to silica gel flash chromatography (5 × 15 cm) with elution by 5% ethyl acetate in hexane and then 20% AcOEt in hexane to give 4,5-dichloro-2-nitrobenzenemethanol (**13**, 9.9 g, 79%) as a yellow solid. A small amount of the sample was recrystallized from ethyl acetate and hexane for analysis: ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.95 (s, 1H), 5.02 (s, 2H), 2.39 (bs, 1H). Anal. Calcd for $C_7H_5Cl_2NO_3$: C, 37.84; H, 2.25; N, 6.31. Found: C, 38.02; H, 2.22; N, 6.17.

4,5-Dichloro-2-nitrobenzaldehyde (14). A solution of 4,5-dichloro-2-nitrobenzenemethanol (**13**, 11.41 g, 51.6 mmol) in HPLC-grade dichloromethane (260 mL) was added, with stirring, to a mixture of pyridinium chlorochromate (22.7 g, 105.3 mmol) in HPLC-grade dichloromethane (90 mL). The mixture was stirred vigorously for 5 h at room temperature and diluted with dichloromethane (1000 mL). The organic layer was decanted, and the tarry residue was washed with dichloromethane (200 mL). The combined organic solution was concentrated and filtered through a silica gel column (6 × 6 cm). The silica gel paste was washed with dichloromethane until all of the product was washed out as detected by TLC. The solvent was evaporated to give 4,5-dichloro-2-nitrobenzaldehyde[11] (**14**, 9.02 g, 80%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 8.27 (s, 1H), 8.05 (s, 1H).

(*Z*)-5-[(4,5-Dichloro-2-nitrophenyl)methylene]imidazolidine-2,4-dione ((*Z*)-15) and (*E*)-5-[(4,5-Dichloro-2-nitrophenyl)methylene]imidazolidine-2,4-dione ((*E*)-15). Dry triethylamine (3.49 mL, 25.1 mmol) was added to a suspension of diethyl 2,4-dioxoimidazolidine-5-phosphonate[10d] (5.91 g, 25.1 mmol) in dry acetonitrile (40 mL) and stirred for 10 min to give a clear solution. A suspension of 4,5-dichloro-2-nitrobenzaldehyde (**14**, 5.0 g, 22.8 mmol) in dry acetonitrile (30 mL) was added in one portion. The solution immediately became dark brown. After the solution was stirred at room temperature for several minutes, a large amount of precipitate appeared. The suspension was continuously stirred at room temperature for an additional 1 h. The solid was collected by filtration and washed with acetonitrile until the solid became almost colorless. The solid was added to water (40 mL) and stirred at room temperature for 30 min. The solid was collected by filtration, washed with water, and dried under vacuum at 78 °C to give (*Z*)-5-[(4,5-dichloro-2-nitrophenyl)methylene]-imidazolidine-2,4-dione ((*Z*)-**15**, 4.36 g, 63%): ^{1}H NMR (DMSO-d_6) δ 11.30 (bs, 2H), 8.41 (s, 1H), 7.94 (s, 1H), 6.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 164.2, 155.0, 146.1, 136.5, 132.1, 132.0, 130.6, 128.1, 126.1, 99.6. Anal. Calcd for $C_{10}H_5Cl_2N_3O_4$: C, 39.74; H, 1.66; N, 13.91, Found: C, 39.80; H, 1.53; N, 13.99. The filtrate was concentrated to about 5 mL under reduced pressure, and water (30 mL) was added to give a slightly yellow suspension. The solid was collected by filtration, dried under vacuum, and recrystallized from 10 mL of 1,4-dioxane to give (*E*)-5-[(4,5-dichloro-2-nitrophenyl)methylene]imidazolidine-2,4-dione ((*E*)-**15**, 1.04 g, 14%) as slightly yellow needles: ^{1}H NMR (DMSO-d_6) δ 10.84 (bs, 1 H), 10.57 (bs, 1 H), 8.37 (s, 1 H), 8.18 (s, 1H), 6.42 (s, 1 H); ^{13}C NMR(DMSO-d_6) δ 162.9, 153.5, 146.1, 135.1, 133.7, 132.0, 130.5, 128.4, 125.5, 105.2. Anal. Calcd for $C_{10}H_5Cl_2N_3O_4$: C, 39.74; H, 1.66; N, 13.91. Found: C, 39.97; H, 1.48; N, 13.70. The mother liquor was evaporated to dryness and gave an additional quantity of the (*Z*)-**15** and (*E*)-**15** (1.5 g, 23%) mixture.

Conversion of a mixture of (*Z*)-/(*E*)-5-[(4,5-dichloro-2-nitrophenyl)methylene]imidazolidine-2,4-dione ((*Z*)-/(*E*)-15) to (*Z*)-15. A sodium hydroxide solution (50%) was added dropwise to a yellow suspension of (*Z*)- and (*E*)-5-[(4,5-dichloro-2-nitrophenyl)methylene]imidazolidine-2,4-dione ((*Z*)-/(*E*)-**15**, 3/1, 5.54 g) in methanol (280 mL) at room temperature until a clear red solution was generated. The solution was stirred at room temperature for an additional 10 min. The reaction solution was then neutralized by the dropwise addition of hydrochloric acid (6 N) to give a yellow suspension. The methanol was removed under reduced pressure, and water (500 mL) was added to the residue. The suspension was stirred at room temperature for 3 h and allowed to stand at 5 °C for 2 h. The solid was collected by filtration and dried under vacuum to give (*Z*)-5-[(4,5-dichloro-2-nitrophenyl)methylene]-imidazolidine-2,4-dione ((*Z*)-**15**, 5.5 g, quantitative) as a yellow solid. The purity of (*Z*)-**15** was verified by ^{1}H NMR.

(*Z*)-5-[(2-Amino-4,5-dichlorophenyl)methylene]imidazolidine-2,4-dione (16). (*Z*)-5-[(4,5-Dichloro-2-nitrophenyl)-methylene]imidazolidine-2,4-dione ((*Z*)-**15**, 4.07 g), iron powder (12 g), and ferric sulfate (1.2 g) were heated in a mixture of water (200 mL) and methanol (100 mL) at reflux temperature for 2 h with mechanical stirring. The methanol was removed under reduced pressure, and water (200 mL) was added. The suspension was extracted with ethyl acetate (3 × 500 mL). The combined ethyl acetate extracts were washed with a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The solvent was evaporated to give (*Z*)-5-[(2-amino-4,5-dichlorophenyl)methylene]imidazolidine-2,4-dione (**16**, 3.63 g, 99%) as a yellow solid. A small amount of sample was recrystallized from ethanol for analysis: mp dec above 250 °C; ^{1}H NMR (DMSO-d_6) δ 11.20 (s, 1 H), 10.60 (s, 1 H), 7.37 (s, 1 H), 6.88 (s, 1 H), 6.30 (s, 1H), 5.81 (bs, 2 H); ^{13}C NMR (DMSO-d_6) δ 165.1, 155.5, 147.5, 131.0, 130.0, 128.9, 117.5, 117.0, 115.7, 102.7; UV [λ_{max}, nm (ϵ)] (MeOH) 374.0 (2040), 342.4 (610), 306.4 (5450), 217.0, (16400). Anal. Calcd for $C_{10}H_7Cl_2N_3O_2 \cdot 0.5EtOH$: C, 44.75; H, 3.38; N, 14.24. Found: C, 44.72; H, 3.46; N, 14.10.

6,7-Dichloroimidazo[4,5-*b*]quinolin-2-one (6). (*Z*)-5-[(2-Amino-4,5-dichlorophenyl)methylene]imidazolidine-2,4-dione (**16**, 4.8 g, 9.4 mmol) was dissolved in acetic acid (1000 mL) and transferred into a photochemical reaction assembly containing a 1000 mL photochemical reaction flask, a borosilicate photochemical immersion well, a Pyrex sleeve, and a 450 W medium-pressure mercury-vapor lamp. A cupric sulfate/ammonium hydroxide solution (40 g cupric sulfate pentahydrate and 68 mL concentrated ammonia hydroxide per liter of water) was pumped through the photochemical immersion well, which can filter light with wavelengths shorter than 405 nm. The filter solution was also circulated through a condenser cooled by ice−water. In this way, the temperature of the reaction was maintained at approximately 25 °C throughout the reaction. The solution was irradiated by a medium-pressure mercury lamp, with stirring, for 60 h to give a slightly yellow suspension. The solid was collected by filtration, washed with a small amount of acetic acid, and dried under vacuum. The solid was then stirred in water (90 mL) and neutralized by the addition of sodium bicarbonate. The neutralized solid was collected by filtration, washed with water, and dried under vacuum (0.01 mmHg/78 °C) to give 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**, 4.01 g, 90%) as a white solid: mp 262−264 °C; ^{1}H NMR (DMSO-d_6) δ 11.72 (bs, 1H, D_2O exchangeable), 11.28 (bs, 1H), 8.32 (s, 1H), 8.00 (s, 1H), 7.64 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 155.5, 148.4, 141.9, 128.6, 128.2, 127.9, 126.1, 126.0, 125.5, 109.1; UV [λ_{max}, nm (ϵ)] (MeOH) 342.0 (23 500), 334.0 (13 100), 326.6 (14 800), 228.2 (51 300); (pH 1) 351.4 (15 400), 340.6 (19 700), 251.4 (21 100), 223.8 (37 700); (pH 11) 351.0 (20 800), 336.0 (17 600), 247.0 (59 600); MS *m*/*z* 253 (M^+). Anal. Calcd for $C_{10}H_5Cl_2N_3O$: C, 47.24; H, 1.97; N, 16.53. Found: C, 47.00; H, 2.05; N, 16.39.

6,7-Dichloro-3-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-imidazo[4,5-*b*]quinolin-2-one (5a). Stannic chloride (0.7 mL, 5.9 mmol) was added in one portion to a mixture of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**, 0.5 g, 1.97 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (TBAR) (2.98

g, 5.9 mmol) in dry acetonitrile (60 mL). The suspension was stirred at 50 °C for 4 h to give a clear brown solution. The solution was diluted with ethyl acetate (300 mL), washed with a saturated sodium bicarbonate solution (4 × 100 mL) and a saturated sodium chloride solution (50 mL), and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel flash chromatography (3 × 20 cm) and eluted by 1% methanol in chloroform. After evaporation of the solvent, the solid was recrystallized from 2-propanol to give 6,7-dichloro-3-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5a**, 1.05 g, 77%). The mother liquor was subjected again to silica gel flash chromatography (3 × 30 cm) and eluted by 1% methanol in chloroform. The solid obtained from the chromatography purification was recrystallized from 2-propanol to give an additional 0.157 g of **5a** (12%). The total combined yield was 89%: mp 236−239 °C; ^{1}H NMR ($CDCl_3$) δ 9.86 (bs, 1H), 8.06−7.06 (m, 18H), 6.73 (dd, J = 2.93, 6.01 Hz, 1H), 6.59 (q, J = 6.6 Hz, 1H), 6.43 (d, J = 2.9 Hz, 1H), 4.84 (dd, 1H), 4.78−4.69 (m, 2H). Anal. Calcd for $C_{36}H_{25}Cl_2N_3O_8$: C, 61.89; H, 3.58; N, 6.02. Found: C, 61.65; H, 3.77; N, 5.80.

6,7-Dichloro-3-(*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (5b). 6,7-Dichloro-3-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5a**, 0.415 g) was stirred in a saturated methanolic ammonia solution (100 mL) at room temperature for 3 days. The solution was evaporated, and the solid was triturated with hot hexane (3 × 10 mL). The hexane was decanted, and the solid was recrystallized twice from ethanol to give 6,7-dichloro-3-(*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5b**, 0.133 g, 61%) as a white solid. The mother liquor was subjected to silica gel flash chromatography (2 × 10 cm) and eluted by 5% methanol in chloroform to give an additional 0.072 g of **5b** (33%) as a white solid. The total combined yield was 94%: mp 272−274 °C; ^{1}H NMR (DMSO-d_6) δ 8.30 (s, 1H), 8.02 (s, 1H), 7.79 (s, 1H), 5.86 (d, J = 6.23 Hz, 1H), 5.07 (bs, 3H), 5.04 (t, J = 5.74 Hz, 1H), 4.25 (dd, J = 3.2, 5.2 Hz, 1H), 3.94 (q, 1H), 3.72 (dd, J = 4.4, 11.8 Hz, 1H), 3.55 (dd, J = 4.9, 11.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 153.8, 146.3, 140.9, 129.2, 128.3, 127.6, 126.7, 125.3, 124.5, 110.4, 85.8, 85.5, 80.0, 69.8, 62.4; UV [λ_{max}, nm (ϵ)] (MeOH) 343.0 (21 500), 335.4 (12 200), 327.8 (13 700), 251.0 (35 100, shoulder), 229.8 (47 000); (pH 1) 341.4 (22 000), 334.0 (14 200), 326.2 (15 500), 272.4 (45 500), 253.4 (55 000), 227.0 (81 800), 206.2 (116 000); (pH 11) 350.6 (21 400), 256.2 (50 100), 238.0 (46 000, shoulder). Anal. Calcd for $C_{15}H_{13}Cl_2N_3O_5$: C, 46.63; H, 3.37; N, 10.88. Found: C, 46.71; H, 3.58; N, 10.50.

6,7-Dichloro-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (4a). *N*,*O*-Bis(trimethylsilyl)acetamide (BSA, 0.85 mL, 3.6 mmol) was added to a suspension of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**, 0.85 g, 3.34 mmol) in dry 1,2-dichloroethane (60 mL). After the solution was stirred at room temperature for 5 min, dry acetonitrile (20 mL) and an additional quantity of BSA (0.85 mL, 3.6 mmol) were added. The mixture was stirred at room temperature for 60 min to give a clear solution. The solution was then diluted with dry acetonitrile (60 mL) followed by the addition of TBAR (2.02 g, 4.0 mmol) and TMSOTf (1.6 mL, 6.7 mmol). The solution was stirred at 70 °C for 1 h and then at room temperature for 2 h. The reaction solution was concentrated to 50 mL and diluted with ethyl acetate (400 mL). The solution was washed with a saturated sodium bicarbonate solution (3 × 100 mL) and a saturated sodium chloride solution (100 mL) and then dried over anhydrous sodium sulfate. The ethyl acetate was removed by evaporation, and the residue was redissolved in chloroform (100 mL). The chloroform solution was filtered through a short silica gel column (5 × 8 cm) and eluted by 0.5% methanol in chloroform. The solvent was removed by evaporation, and the solid was recrystallized from a mixture of chloroform and methanol (20 mL/5 mL) to give 6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo-[4,5-*b*]quinolin-2-one (**4a**, 1.3 g, 56%) as a white solid. The mother liquor was then concentrated to give additional **4a** (0.46 g, 19%) as a white solid. The second mother liquor was then subjected to silica gel flash chromatography (3 × 15 cm) and eluted by 1% methanol in chloroform to give an additional quantity of **4a** (0.13 g, 6%). The total yield of **4a** (1.89 g) was 81%: mp 248−250 °C; ^{1}H NMR (DMSO-d_6) δ 12.32 (bs, 1H), 8.08−8.40 (m, 15H), 8.05 (s, 1H,), 8.01 (s, 1H), 7.66 (s, 1H), 6.37 (d, J = 5.49 Hz, 1H), 6.25 (t, J = 6.0 Hz, 1H), 6.11 (t, J = 6.0 Hz, 1H), 4.88−4.69 (m, 3H). Anal. Calcd for $C_{36}H_{25}Cl_2N_3O_8$: C, 61.89; H, 3.58; N, 6.02; Found: C, 61.94; H, 3.74; N, 5.94. Compound **5a** (0.11 g, 4%) was also obtained from flash chromatography of the mother liquor.

6,7-Dichloro-1-(*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (4b). 6,7-Dichloro-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**4a**, 3.11 g, 4.5 mmol) was stirred in a saturated methanolic ammonia solution (300 mL) at room temperature for 24 h. The solution was evaporated, and the solid was triturated with hot hexane (3 × 100 mL). The hexane was decanted, and the solid was dried under vacuum (0.01 mmHg/78 °C) for 24 h to give 6,7-dichloro-1-(*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**4b**, 1.66 g, 97%) as a white solid. A small sample was recrystallized from methanol for analysis: mp dec above 290 °C; ^{1}H NMR (DMSO-d_6) δ 12.17 (bs, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 5.75 (d, J = 7.25 Hz, 1H), 5.35 (d, J = 5.88 Hz, 1H), 5.20 (t, J = 4.70 Hz, 1H), 5.16 (d, J = 4.42 Hz, 1H), 4.57 (q, J = 6.18 Hz, 1H), 4.13 (m, 1H), 3.91 (d, 1H), 3.68 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 154.2, 146.9, 141.9, 129.4, 128.5, 128.1, 126.4, 125.1, 124.3, 111.9, 85.9, 85.3, 70.3, 69.7, 61.8; UV [λ_{max}, nm (ϵ)] (MeOH) 342.0 (23 300), 334.0 (13 100), 327.0 (14 700), 231.0 (50 700); (pH 1) 350.8 (10 100, shoulder), 341.2 (24 000), 334.0 (17 400), 326.6 (17 100), 272.6 (50 500), 255.0 (60 800), 224.8 (94 200), 206.8 (133 000); (pH 11) 351.6 (20 400), 337.0 (17 000), 247.8 (55 000). Anal. Calcd for $C_{15}H_{13}Cl_2N_3O_5 \cdot H_2O$: C, 44.55; H, 3.71; N, 10.40. Found: C, 44.50; H, 3.80; N, 10.18.

6,7-Dichloro-4-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (17a). BSA (0.07 mL, 0.29 mmol) was added to a suspension of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**, 67 mg, 0.26 mmol) in dry acetonitrile (7 mL) and stirred for 5 min at room temperature. An additional quantity of BSA (0.07 mL, 0.29 mmol) was added, and the suspension became clear. This was followed by a reprecipitation in a few minutes. The reaction mixture was stirred at room temperature for an additional 30 min followed by the addition of TBAR (0.157 g, 0.31 mmol) and TMSOTf (0.06 mL, 0.31 mmol). After the addition, the reaction flask was moved immediately to a 50 °C oil bath. After the mixture was stirred for 5 min, additional TMSOTf (0.06 mL, 0.31 mmol) was added, and the reaction was stirred for an additional 10 min to give a clear solution. The reaction solution was then diluted with ethyl acetate (20 mL), washed with a saturated solution of sodium bicarbonate (3 × 20 mL) and a saturated sodium chloride solution (20 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated, and the solid was subjected to silica gel chromatography (2 × 30 cm) and eluted by 2% methanol in chloroform. The corresponding fraction was collected, and the solvent was evaporated to give a solid that was recrystallized from methanol/ethyl acetate to give 6,7-dichloro-4-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**17a**, 68 mg, 29%) as a white solid: mp 158−162 °C; ^{1}H NMR (DMSO-d_6) δ 11.22 (bs, 1H), 8.55 (s, 1H), 8.25 (s, 1H), 8.0−7.44 (m, 16H), 7.15 (bs, 1H), 6.68 (m, 1H), 6.46 (t, J = 7.5 Hz, 1H), 4.85 (m, 1H), 4.78 (m, 1H), 4.66 (m, 1H). Anal. Calcd for $C_{36}H_{25}Cl_2N_3O_8$: C, 61.89; H, 3.58; N, 6.02. Found: C, 61.62; H, 3.70; N, 5.87.

6,7-Dichloro-4-(*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (17b). Sodium methoxide (38 mg, 0.7 mmol) was added to a suspension of 6,7-dichloro-4-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**17a**, 100 mg, 0.14 mmol) in methanol (10 mL) and stirred at room temperature for 30 min. Ammonium chloride (75 mg, 1.4 mmol) was added, and the reaction mixture was continuously stirred for a couple of minutes. The reaction mixture was diluted with ethyl acetate, washed with water (2 × 40 mL), a saturated sodium bicarbonate solution (40 mL), and a saturated sodium chloride solution (20 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated, and the solid was triturated with hexane (3 × 10 mL). The hexane was decanted, and the solid was dried under 0.01 mmHg/78 °C for 24 h. The

solid was then recrystallized from methanol to give 6,7-dichloro-4-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**17b**, 30 mg, 48%) as a white solid: mp dec above 200 °C; ^{1}H NMR (DMSO-d_6) δ 11.087 (bs, 1H), 8.63 (s, 1H), 8.22 (s, 1H), 7.40 (s, 1H), 6.73 (d, J = 7.3 Hz, 1H), 5.54 (t, 1H), 5.36 (d, J = 6.6 Hz, 1H), 5.3 (d, J = 5.2 Hz, 1H), 4.76 (q, J = 6.6, 1H), 4.23 (m, 1H), 4.08 (m, 1H), 3.69 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 165.2, 160.1, 132.5, 131.6, 129.5, 129.0, 126.3, 123.8, 119.3, 106.6, 91.6, 86.8, 70.2, 69.5, 61.1; UV [λ_{max}, nm (ϵ)]: (MeOH) 363.8 (16 200), 346.4 (16 600), 331.4 (10 700), 241.0 (23 800, shoulder), 227.2 (27 900); (pH 1) 351.0 (12 900), 340.8 (15 700), 253.0 (25 900), 223.8 (45 200); (pH 11) 362.8 (16 800), 346.4 (17 300), 238.5 (23 000), 209.0 (33 500). Anal. Calcd for $C_{15}H_{13}Cl_2N_3O_5 \cdot 1.5H_2O$: C, 43.58; H, 3.87; N, 10.16. Found: C, 43.89; H, 3.70; N, 9.86.

General Procedure for the Transglycosylation of 17a. BSA (2 equiv) was added to a solution of 6,7-dichloro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**17a**) in 1,2-dichloroethane and acetonitrile (3/4), and the reaction solution was stirred at room temperature for 1 h. The Lewis acid (2 equiv) was added, and the reaction solution was stirred at 70 °C for 1 h. The reaction solution was diluted with ethyl acetate, and the organic solution was washed with a saturated sodium bicarbonate solution and a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was subjected to silica gel chromatography with elution by chloroform. The fractions containing nucleoside components were collected and combined. The solvent was evaporated, and the ratio of **4a** and **5a** was determined by HPLC.

When **17a** was treated with BSA and, subsequently, TMSOTf, **4a** and **5a** (14.7/1, 83% combined yield) were obtained.

When **17a** was treated with BSA and, subsequently, stannic chloride, **4a** and **5a** (4.7/1, 86% combined yield) were obtained.

6,7-Dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]-quinolin-2-one (19a). BSA (0.036 mL, 0.14 mmol) was added to a suspension of 6,7-dichloro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**17a**, 50 mg, 0.072 mmol) in dry acetonitrile under an argon atmosphere and stirred at room temperature for 1 h to give a clear colorless solution. TBAR (55 mg, 0.11 mmol) was added followed by the addition of TMSOTf (0.017 mL, 0.088 mmol). After being stirred at room temperature for 3 h, the reaction solution was diluted with dichloromethane (30 mL), washed sequentially with saturated sodium bicarbonate (3 × 20 mL) and saturated sodium chloride (20 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel chromatography (2 × 11 cm) with elution by chloroform. The appropriate fractions were collected, and the solvent was evaporated to give 6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**19a**, 22 mg, 27%) and **4a** (6 mg, 5%) with a recovery of **17a** (25 mg, 50%). In a separate experiment, when the reaction was stopped after 3.5 h, **19a** (35 mg, 42%), **4a** (13 mg, 26%), and **17a** (9 mg, 18%) were isolated using the same workup procedure. A small amount of **19a** was recrystallized from methanol/chloroform for analysis: mp 128−132 °C; ^{1}H NMR ($CDCl_3$) δ 8.30−7.36 (m, 31H), 7.2 (s, 1H), 7.02 (d, J = 4.7 Hz, 1H), 6.57 (m, 1H), 6.46 (s, 1H), 6.43 (dd, 1H), 6.29 (t, J = 6.9 Hz, 1H), 6.1 (m, 2H), 4.91 (m, 2H), 4.76 (m, 4H). Anal. Calcd for $C_{62}H_{45}Cl_2N_3O_{15} \cdot 2MeOH$: C, 63.68; H, 4.39; N, 3.48. Found: C, 63.76; H, 4.52; N, 3.34.

6,7-Dichloro-1-(β-D-ribofuranosyl)-4-(β-D-ribofuranosyl)-imidazo-[4,5-*b*]quinolin-2-one (19b). 6,7-Dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**19a**, 90 mg, 0.079 mmol) and sodium methoxide (90 mg, 1.7 mmol) in methanol (10 mL) were stirred at room temperature for 15 min. Ammonium chloride (99 mg, 1.8 mmol) was added, and the reaction solution was stirred for an additional 3 min. The reaction solution was directly absorbed on a small amount of silica gel and subjected to silica gel chromatography (2.5 × 4 cm) with elution by 14% of methanol in chloroform. The appropriate fractions were collected, and the solvents were evaporated to give 6,7-dichloro-1-(β-D-ribofuranosyl)-4-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**19b**, 27 mg, 66%) as a white solid. A small amount of sample was recrystallized from methanol and water for analysis: mp dec >250 °C; ^{1}H NMR (DMSO-d_6) δ 8.76 (s, 1H), 8.15 (s, 1H), 7.92 (s, 1H), 6.80 (d, J = 7.4 Hz, 1H, H1′), 5.69 (d, J = 7.2 Hz, 1H, H1″), 5.48 (t, 1H, D_2O exchangeable), 5.41 (d, 1H, D_2O exchangeable), 5.32 (m, 2H, D_2O exchangeable), 5.14 (m, 2H, D_2O exchangeable), 4.72 (q, 1H, H2′), 4.51 (q, 1H, H2″), 4.25 (m, 1H, H3′), 4.1 (m, 1H, H3″), 4.05 (q, 1H, H4′), 3.88 (q, 1H, H4″), 3.69 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 163.1, 159.7, 131.2, 130.3, 130.1, 129.1, 126.5, 123.3, 119.6, 109.5, 91.4, 86.6, 86.0, 84.9, 70.3, 70.0, 69.9, 69.2, 61.7, 60.7; MS FAB m/z 518 ($[M + H]^+$, 7.4; HRMS calcd for $C_{20}H_{22}Cl_2N_3O_9$ 518.0733, found 518.0724.

Conversion of Compound 19a to 4a. TMSOTf (0.005 mL, 0.025 mmol) was added to a solution of **19a** (17 mg, 0.015 mmol) in dry acetonitrile/1,4-dichloroethane (0.8 mL/0.6 mL), and the solution was stirred at room temperature for 5 min. TLC indicated a complete disappearance of **19a**. The product was purified by the normal method (see the synthesis of **4a**) to give **4a** (9.4 mg, 90%).

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Supporting Information Available: The carbon-13 assignments of compounds **4b** and **5b** in the aromatic region by using the selective long-range $^{13}C-^1H$ decoupling method. This material is available free of charge via the Internet at http://pubs.acs.org.

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