Synthesis of Imidazo[1,2-*a*]pyridine C-Nucleosides with an Unexpected Site of Ribosylation

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Several new polychlorinated imidazo[1,2-*a*]pyridine C-nucleosides have been prepared. Lithiated imidazo[1,2-*a*]pyridines were condensed with protected ribonolactones, trapped as 1′-acetoxy derivatives, and these 1′-acetoxy derivatives were reductively deacetoxylated and deprotected to give C-nucleosides. Long-range proton−carbon decoupling experiments were used to determine the actual site of ribosylation and established that the ribose moiety was unexpectedly attached to the C5 position of the imidazo[1,2-*a*]pyridines. This method has provided C-nucleosides, such as 2,6-dichloro-5-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine and 2,6,7-trichloro-5-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine and the corresponding α-products.

Introduction

C-Nucleosides differ from the more commonly occurring N-nucleosides by having their carbohydrate moiety and heterocycle linked via a hydrolytically resistant carbon−carbon bond instead of the more reactive aminal linkage. Several C-nucleosides, both naturally occurring and synthetic, have significant antibacterial, antiviral, and antitumor activities.[1] Some of these biological activities have been postulated to depend on the resistance of the carbon−carbon linkage to hydrolytic or enzymatic cleavage.[2] C-Nucleosides of several different heterocycles, such as purines, pyrimidines, and pyridines, have been reported.[3] Since several halogenated benzimidazole nucleosides[4] have demonstrated significant antiviral activity against human cytomegalovirus, we became interested in the synthesis of halogenated imidazo[1,2-*a*]pyridine C-nucleosides that would be structurally related to the active benzimidazole nucleosides. This prompted us to explore the possibility of attaching a ribose moiety to chlorinated imidazo[1,2-*a*]-pyridines. A highly convergent approach to obtaining ribosylated imidazo[1,2-*a*]pyridine C-nucleosides would be to condense lithiated imidazo[1,2-*a*]pyridines with protected ribonolactones.

Several C-glycosides and C-nucleosides[1] have been synthesized by the addition of an organometallic reagent to a lactone to form a hemiacetal, which could subsequently be reduced to the corresponding cyclic ether. C-Glycosides, such as papulacadin and medermycin,[2] have been synthesized using this approach. The condensation of lithiated heterocycles with protected ribonolactones, followed by a reductive removal of the 1′-OH, has been used to synthesize 2,4-dichloro-3-(β-D-ribofuranosyl)pyridine,[3] 3-(β-D-ribofuranosyl)benzamide,[4] and 2-(β-D-ribofuranosyl)thiazole.[5] The literature further describes the synthesis of 3-(1-hydroxycyclohexyl)imidazo[1,2-*a*]pyridine (**3**)[6] and 2,6-dichloroimidazo[1,2-*a*]pyridine-3-sulfinic acid (**5**)[7] from the corresponding heterocycles via lithiation and condensation with cyclohexanone (**2**) or sulfur dioxide, respectively, as shown in Figure 1.

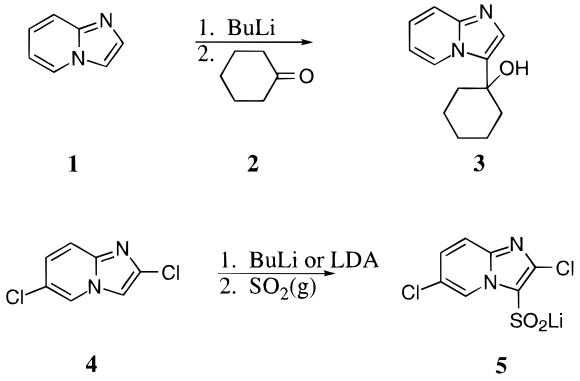

Figure 1. Reported lithiation reactions of imidazo[1,2-*a*]pyridines.

On the basis of these results, we opted to investigate the condensation of lithiated imidazo[1,2-*a*]pyridines with ribonolactones for the synthesis of imidazo[1,2-*a*]pyridine C-nucleosides, with the ribosyl moiety at C3.

Results and Discussion

Ribosylation of 2,6-Dichloroimidazo[1,2-*a*]pyridine (4). To optimize reaction conditions for the condensation, we investigated the lithiation of **4**, followed by condensation with protected ribonolactones. The initial investigation of this coupling reaction revealed that the choice of lithiation reagent, protecting groups for the lactone, reaction times, and temperature were important for obtaining good yields. Thus, when lithiated tetramethylpiperidine (LTMP) was used, higher yields (80%) were obtained than when lithiated diisopropylamine (LDA) or phenyllithium (yields 70% and 50%, respectively) were used. 5-*O*-(*tert*-Butyldimethylsilyl)-

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

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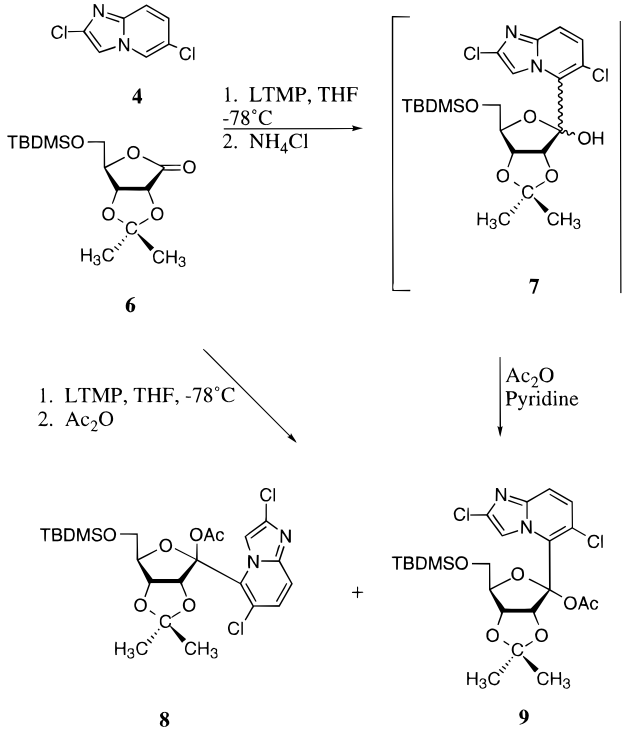
(6) Paudler, W. H.; Shin, H. G. *J. Org. Chem.* **1968**, *33*, 1638−1639.

(7) Ishida, Y.; Ohta, K.; Nakahama, T.; Yoshikawa, H. European Patent 0 238 070 A2, 1987.

S0022-3263(96)01934-2 CCC: $14.00

Scheme 1



2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**6**)[8] was coupled with lithiated **4** to give a high yield of a C-nucleoside which we assumed initially to be the 3-ribosylated C-nucleoside. However, this nucleoside was subsequently determined to be the 5-ribosylated C-nucleoside **7** on the basis of NMR studies. The 2,3,5-tri-*O*-benzyl-D-ribono-1,4-lactone[9] under the same reaction conditions gave mixtures of inseparable products. Thus, treatment of **4** with LTMP in THF at −78 °C, followed by the addition of **6** to the reaction mixture at −78 °C and quenching with an ammonium chloride buffer after 20−30 min, gave the highest yields of crude hemiacetal intermediate **7** (Scheme 1). Longer reaction times and higher reaction temperatures gave lower yields.

Several attempts to dehydroxylate crude **7** with triethylsilane in the presence of $BF_3{\cdot}OEt_2$ or TMSOTf gave decomposition products and unreacted starting material. Similar combinations of silane and Lewis acids are known to reduce ketols.[3−5] Unsuccessful dehydroxylation of **7**, along with the fact that **7** was not stable enough to purify to homogeneity, prompted us to isolate the hemiacetal as the more stable acetyl derivative. The hemiacetal **7** could be acetylated either *in situ*, by quenching the reaction mixture with Ac_2O, or by quenching the reaction with an ammonium chloride buffer, isolation, and partial purification of the hemiacetal **7**, followed by treatment with Ac_2O in pyridine.

When the reaction between lactone **6** and the lithiated **4** was quenched *in situ* with acetic anhydride, the major product isolated was 2,6-dichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-1-acetoxy-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**9**, 65%) whereas the *β*-anomer **8** was the minor product (10%). When the reaction was quenched with NH_4OH, followed by isolation of the hemiacetal **7** and treatment of **7** with Ac_2O in pyridine, only the *β*-anomer **8** was isolated in a 72% overall yield. The assignment of **9** as the α-anomer and **8** as the *β*-anomer was based on ^{1}H NMR where the 2′-H in **8** is shifted downfield by 0.76 ppm (from 4.7 ppm in **9** to 5.46 ppm in **8**) due to deshielding effects of the 1′-OAc group which is on the same side of the furan ring as the 2′-H in **8**.[10]

While unsuccessful reductive dehydroxylation of **7** was experienced at the early stages of this work, we were able to remove the acetoxy group from **9** (or **8**) with high efficiency (Scheme 2). The substrate:silane:Lewis acid ratio was found to be crucial for a successful reductive deacetoxylation with a 1:10:2.5 ratio being the preferred combination. Considering that the bridgehead nitrogen in the imidazo[1,2-*a*]pyridine heterocycle is basic, the requirement for at least 2 equiv of the Lewis acid is understandable. A greater excess of the Lewis acid (5 equiv) increased the formation of anhydro[11] and decomposition products (entry 3 in Table 1). Reactions did not proceed at lower temperatures (−20 to 0 °C), irrespective of which Lewis acid was used for catalysis. Whether toluene or CH_2Cl_2 was used as solvents (entries 1 and 2 in Table 1) did not significantly affect the yields. The improved yields when TMSOTf was used as a Lewis acid, instead of $BF_3{\cdot}OEt_2$, for the deacetoxylation of **9** (or **8**), may be due to a shorter reaction time. The fact that only the *β*-anomer, 2,6-dichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**10**), was isolated from these reductive deacetoxylation reactions in the presence of a solvent is consistent with a reaction mechanism where the hydride delivery occurs cis to the adjacent oxygen (2′-O) of the presumed oxonium ion intermediate. Such a reaction mechanism has been proposed in the literature.[12] When the deacetoxylation was conducted in Et_3SiH (in the absence of solvent), a 1:1 mixture of the anomers **10** and **11** was obtained. The high concentration of Et_3SiH used in this instance evidently results in a random delivery of hydride from either side of the oxonium ion intermediate.

Deprotection of **10** in a mixture of 2 N HCl and THF at room temperature gave a good yield[13] of 2,6-dichloro-5-(*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**12**). 2,6-Dichloro-5-(2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)-imidazo[1,2-*a*]pyridine (**13**) was obtained by the treatment of **10** with TBAF in THF. The α-anomer **11** was more resistant to acidic deprotection, but was deprotected by treatment of **11** with 4 N HCl in THF at room temperature to give the α-anomer **14** (Scheme 3).

The anomeric assignment of **12** and **14** was based partially upon the well-known[13−15] upfield shift of the 1′-H signal for the *β*-anomer **12** compared to the 1′-H signal for the α-anomer **14**. The criteria for the determination of configuration of 2,3-*O*-isopropylidene deriva-

(8) Cheng, J. C.-Y.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778−2780.

(9) (a) Timpe, W.; Dax, K.; Wolf, N.; Weidmann, H. *Carbohydr. Res.* **1975**, *39*, 53−60. (b) Baker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605−4609.

(10) Similar α to *β* ratios upon acetylation in situ or after isolation of the 1′-OH intermediate **7** have been described in the literature for the reaction of ribonolactones with lithiated thiazoles. See ref 5.

(11) 1,5-Anhydro-2,3-*O*-isopropylidene-1-*C*-(2,6-dichloroimidazo[1,2-*a*]pyridine-5-yl)-*β*-D-ribofuranose was identified by ^{1}H NMR and mass spectrum as being one of the side products.

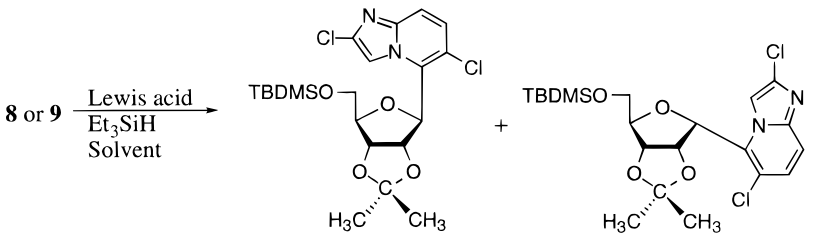
(12) Calzada, E.; Clarke, C. A.; Roussin-Bouchard, C.; Wightman, R. H. *J. Chem. Soc., Perkin Trans.* **1995**, 517−518.

(13) Other deprotection methods such as formic acid in methanol or trifluoroacetic acid in chloroform gave lower yields.

(14) Tam, S. Y.-K.; Klein, R. S.; de las Heras, F. G.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4854−4862.

(15) Sokolova, T. N.; Yartseva, I. V.; Preobrazhenskaya, M. N. *Carbohydr. Res.* **1981**, *93*, 19−34.

Scheme 2



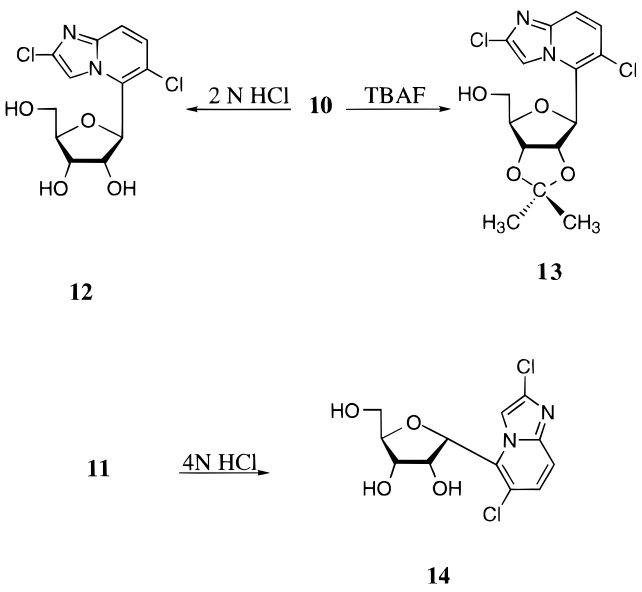
10 **11**

Table 1. Conditions for Reductive Deacetoxylation of 1′-Acetoxy Compound 9 (or 8)[a]

entry[b]	solvent	Lewis acid (equiv)	reaction time (h)	yields (%)[c] 10	11
1	toluene	$BF_3{\cdot}OEt_2$ (2.5)	4	45	<3
2	CH_2Cl_2	$BF_3{\cdot}OEt_2$ (2.5)	4	50	<3
3	CH_2Cl_2	$BF_3{\cdot}OEt_2$ (5.0)	3	15	<3
4	CH_2Cl_2	TMSOTf (2.5)	0.5	78	<3
5	none	$BF_3{\cdot}OEt_2$ (2.5)	4	34	34

[a] Same results were obtained whether **8** or **9** or a mixture of the two was used as starting material. This is consistent with a mechanism where hydride delivery occurs to a oxonium ion. [b] Excess Et_3SiH (20 equiv) was used for all entries; a smaller excess of Et_3SiH resulted in lower yields. [c] Isolated yields.

Scheme 3



12 **13** **14**

tives of nucleosides ($\Delta\delta(CH_3) > 0.15$ ppm for the β-anomer and $\Delta\delta(CH_3) < 0.15$ ppm for the α-anomer) should be limited to ribofuranoses with no 5′-substituent. However, although the C-nucleosides do not always meet the above criteria, for pairs of anomeric C-nucleosides, the $\Delta\delta(CH_3)$ for the α-anomer has been generally observed to be smaller than the $\Delta\delta(CH_3)$ for the β-anomer.[14−16] Examination of the ^{1}H-NMR spectra of the 2,3-*O*-isopropylidene derivative **10** showed that the $\Delta\delta(CH_3)$ was 0.30 ppm, while the $\Delta\delta(CH_3)$ for **11** was 0.01 ppm. Desilylation of **10** gave **13**, which had a $\Delta\delta(CH_3)$ of 0.27 ppm and provided further proof for the anomeric assignment. The coupling constant for the β-anomer **12** is $J_{1',2'} = 9.0$ Hz while it is 3.2 Hz for the α-anomer **14**. This larger $J_{1',2'}$ for the β-anomer has also been observed for indole C-nucleoside, benzimidazoles,[17] and imidazo[1,2-*a*]pyrazine C-nucleosides.[18] Finally, NOE experiments showed a positive NOE between the 1′-H and the 4′-H for compound **12** while no NOE was observed for the α-derivative **14**.

The site of ribosylation for this series of compounds was determined by NMR studies. The heterocyclic part of the proton spectrum of **8**−**14** did not show the expected splitting pattern for a 2,6-dichloroimidazo[1,2-*a*]pyridine with a ribose moiety at C3. Signals assigned to protons at C7 and C8 were doublets, but did not show any coupling with the third heterocyclic proton. The spectral data, analysis, and mass spectrum showed that neither chlorine had been replaced. Therefore the observed splitting pattern indicated that coupling had most likely occurred at C5 rather than at C3. This regioisomeric assignment was confirmed by studies of fully coupled and partially decoupled carbon spectra of **12**. The heterocyclic portion of the carbon spectra of **12** was fully assigned on the basis of fully coupled and partially decoupled spectral data, as well as on chemical shift trends. Selective carbon−proton decoupling experiments outlined in Figure 2 showed that irradiation of the heterocyclic proton singlet at 8.80 ppm led to a decoupling of the carbon signal at 134.73 ppm, assigned as C2, from a doublet to a singlet. This shows that the irradiated proton singlet at 8.80 ppm must be the signal from a proton at C3 since a proton at C5 could not be coupled to the C2 carbon.

More evidence for this assignment was obtained by irradiating the 1′-H resonance at 5.43 ppm and observing a simplification of the signal at 121.07 ppm, assigned as C6, from two triplets to two doublet. Also, irradiation of the 2′-H resonance at 4.38 ppm caused a simplification of the carbon signal at 131.35 ppm, assigned as C5.

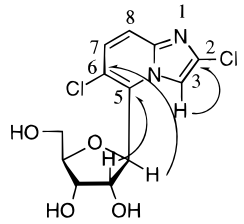
On the basis of previously cited literature,[6,7] the fact that ribosylation had occurred at the C5 position of the imidazo[1,2-*a*]pyridine was entirely unexpected. This prompted experiments where **4** was lithiated and the lithio derivative was added to excess D_2O (Figure 3). These D_2O quenching experiments showed that proton−deuterium exchange occurred only at the C5 position to give 5-deuterio-2,6-dichloroimidazo[1,2-*a*]pyridine (**15**), even when 1.3 equiv of LTMP (LDA or PhLi) was used for deprotonation. Thus, formation of the C5-ribosylated product was a result of selective lithiation at the C5 position, not lithiation at either C3 and C5, followed by a selective condensation of the C5 lithio species with the ribonolactone.

Ribosylation of Other Imidazo[1,2-*a*]pyridines. 2,6,7-Trichloro-5-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyri-

(16) MacCoss, M.; Robins, M. J.; Rayner, B.; Imbach, J.-L. *Carbohydr. Res.* **1977**, *59*, 575−579.

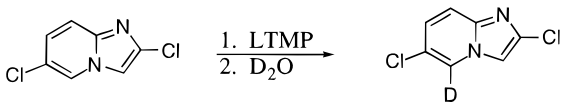
(17) Southon, I. W.; Pfleiderer, W. *Chem. Ber.* **1978**, *111*, 996−1005.

(18) MacCoss, M.; Meurer, L. C.; Hoogsteen, K.; Springer, J. P.; Koo, G.; Peterson, L. B.; Tolman, R. L.; Emini, E. *J. Heterocycl. Chem.* **1993**, *30*, 1213−1220.



12

Figure 2. Two- and three-bond proton−carbon decoupling experiments to show that the imidazo[1,2-*a*]pyridine C-nucleoside **12** is C5 ribosylated.



4 **15**

Figure 3. Proton−deuterium experiments to show that lithiation occurs at C5 for **12**.

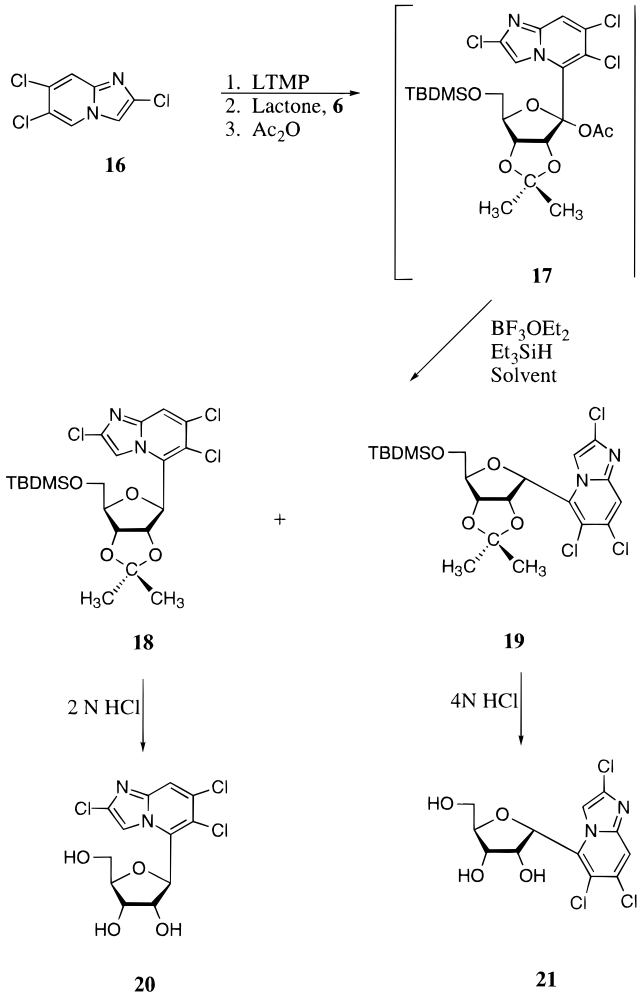
dine (**20**) and the α-anomer **21** were synthesized from 2,6,7-trichloroimidazo[1,2-*a*]pyridine (**16**)[19] using methodology similar to that described above with the exception that deacetoxylation of 2,6,7-trichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-1-acetoxy-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**17**) was accomplished using $BF_3{\cdot}OEt_2$ as a Lewis acid (Scheme 4). Deacetoxylation using TMSOTf as the Lewis acid gave only low yields (20−25%) of the desired C-nucleosides 2,6,7-trichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**18**) and the α-anomer **19**. However, a large quantity of an unidentified unstable side product was also present and appeared to be a dimer on the basis of an ^{1}H-NMR spectrum of the crude product. Acidic deprotection of **18** and **19** gave **20** and **21**, respectively. Anomeric and regioisomeric assignments of **20** and **21** were based on evidence similar to that used for the assignment of **12** and **14**.

Imidazo[1,2-*a*]pyridine heterocycle derivatives have been previously reported to be readily reduced to 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine derivatives.[20,21] However, we were able to remove the chlorines of **10** and **18** without reducing the heterocyclic system by using H_2 at atmospheric pressure and 5% Pd on charcoal as a catalyst. The compound 5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**22**) was deprotected under acidic conditions to give 5-(*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**23**). Reductive dechlorination of **10** gave the same product (**22**) as the reductive dechlorination of **18**, which provided additional proof for the anomeric and regioisomeric assignment of **18** (and **20**).

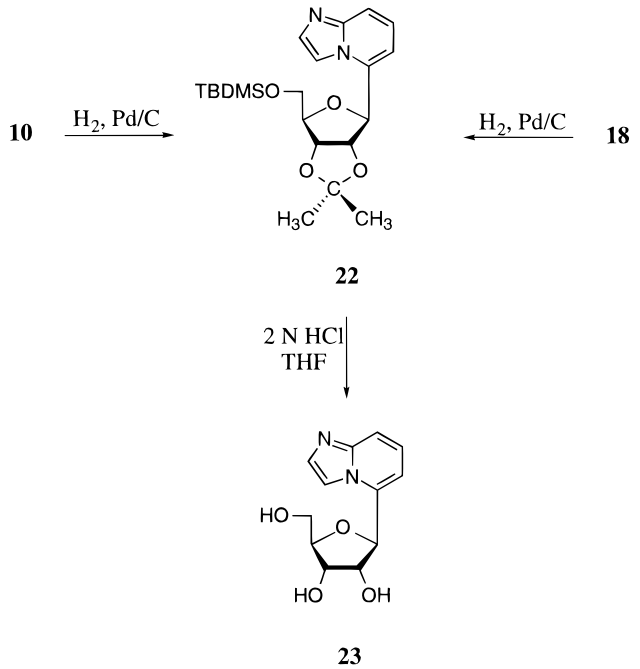
Conclusion

The condensation of lithiated **4** or **16** with **6** which occurred at the C5 position, but not at the C3 position, was unexpected since the C3 position of imidazo[1,2-*a*]pyridines is generally viewed as more reactive toward electrophilic substitution and more easily deprotonated than the C5 position.[22] We are only aware of a single previous literature example where treatment of an imid-

Scheme 4



Scheme 5



(19) (a) Ohta, K; Ishida, Y.; Yoshikawa, H. European Patent 0 383 319 A2, 1990. (b) Ohta, K.; Minami, K.; Yoshikawa, H; Ishida, Y. *Biosci. Biotech. Biochem.* **1993**, *57*, 1844−1848.

(20) Katsura, Y.; Nishino, S.; Inoue, Y.; Tomoi, M.; Takasugi, H. *Chem. Pharm. Bull.* **1992**, *40*, 371−380.

(21) Katsura, Y.; Nishino, S.; Takasugi, H. *Chem. Pharm. Bull.* **1991**, *39*, 2937−2943.

azo[1,2-*a*]pyridine with a proton at the C3 position gave a product where the reaction occurred at the C5 position. Thus, Hand and Paudler[23] obtained 5,5′-biimidazo[1,2-*a*]pyridine in a low yield by treating imidazo[1,2-*a*]pyridine with KNH_2 at room temperature. By quenching lithiated **4** with D_2O we have shown that the C5 proton is exchanged exclusively, even when up to 30% excess LiTMP was used for the lithiation.

This investigation indicates that the chlorination pattern on the imidazo[1,2-*a*]pyridines affects the relative reactivity of the C3 versus the C5 position toward lithiation. The results indicate that the chlorine at the C6 position directs lithiation and subsequent ribosylation toward the C5 position.

Antiviral evaluation revealed that the reported imidazo[1,2-*a*]pyridine C-nucleoside analogs did not have significant activity against human cytomegalovirus (IC_{50} > 100 μM in a plaque reduction assay)[24] or HSV-1 (IC_{50} > 100 μM in an ELISA assay).[25] These derivatives were neither cytotoxic against diploid human fibroblasts (HFF cells) nor against carcinoma cells (L1210 and KB cells).

Experimental Section

General Chemical Procedures. Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 360 or 300 MHz. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, University of Michigan. Flash column chromatography was performed using silica gel 60, 230−400 mesh.[26] Thin layer chromatography (TLC) was performed on prescored silica gel GHLF plates. Compounds were visualized by illumination under UV light (254 nm) or by being sprayed with 20% methanolic sulfuric acid followed by being charred on a hot plate. Evaporations were carried out under reduced pressure (water aspirator) with water bath temperatures below 40 °C unless otherwise specified.

2,6-Dichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-1-acetoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (8). To a solution of TMP (0.47 mL, 2.8 mmol) in THF (15 mL) at 0 °C was added *n*-BuLi (1.6 mL, 2.6 mmol, 1.6 M solution in hexanes). This solution was stirred for 30 min at 0 °C and then cooled to −78 °C, and a solution of **4** (0.4 g, 2.14 mmol) in THF (5 mL) was added dropwise over a period of 5 min. The resulting dark brown solution was stirred at −78 °C for 20 min. A solution of the lactone **6** (0.85 g, 2.8 mmol) in THF (5 mL) was added dropwise over a period of 7 min, and the resulting black reaction mixture was stirred for 30 min at −78 °C. The reaction mixture was poured into an NH_4Cl buffer (100 mL). This aqueous solution was extracted with diethyl ether (3 × 70 mL), and the combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give **7** as a dark oil. This oil was purified by flash chromatography (EtOAc/hexane 1:5, 15 cm × 4 cm) to give 830 mg (80%) of **7** as a syrup. Compound **7** (1.3 g, 2.7 mmol) was dissolved in dry pyridine (15 mL), and acetic anhydride (2.5 mL, 27 mmol) was added to this solution. The reaction mixture was stirred under an argon atmosphere for 12 h and then poured into an ice−water mixture (120 mL). This aqueous phase was subsequently extracted with EtOAc (3 × 80 mL), and the combined organic extracts were dried over magnesium sulfate and evaporated to dryness to give a white solid. This solid was purified by flash chromatography (EtOAc/hexane 1:5, 15 cm × 4 cm) to give, after recrystallization from EtOH, 1.4 g (98%) of **8** as a white solid: mp 165−166 °C; R_f 0.45 (EtOAc/hexane 1:5); ^{1}H NMR (300 MHz, DMSO-d_6), δ 8.61 (s, 1H), 7.59 (d, 1H, J = 9.5 Hz), 7.37 (d, 1H, J = 9 Hz), 5.46 (d, 1H, J = 5.6 Hz), 4.94 (d, 1H, J = 5.6 Hz), 4.70 (t, 1H, J = 7.1 Hz), 3.73 (d, 2H, J = 7.1 Hz), 2.02 (s, 3H), 1.22 (s, 3H), 0.84−0.91 (m, 12 H), 0.12 (two s, 6H). Anal. Calcd for $C_{23}H_{32}Cl_2N_2O_6Si$: C, 51.98; H, 6.07; N, 5.27. Found: C, 52.30; H, 5.98; N, 5.34.

2,6-Dichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-1-acetoxy-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (9). To a solution of TMP (1.0 mL, 5.6 mmol) in THF (15 mL) at 0 °C was added *n*-BuLi (3.2 mL, 5.2 mmol, 1.6 M solution in hexanes). This solution was stirred for 20 min at 0 °C and then cooled to −78 °C. A solution of **4** (0.8 g, 4.28 mmol) in THF (10 mL) was then added dropwise to the above solution over a period of 5 min. The resulting dark brown solution was stirred at −78 °C for 20 min. A solution of the lactone **6** (1.7 g, 5.6 mmol) in THF (10 mL) was then added dropwise over a period of 10 min, and the resulting black reaction mixture was stirred for 30 min at −78 °C. Acetic anhydride (2 mL, 20 mmol) was added dropwise to the reaction mixture, and the mixture was stirred at −78 °C for an additional 30 min. The reaction mixture was then poured into an NH_4Cl buffer (150 mL). This mixture was extracted with EtOAc (3 × 100 mL), and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure to give a yellowish oil which was purified by flash chromatography (toluene/EtOAc 20:1, 15 cm × 5 cm), to give 1.5 g (65%) of **9** as a clear syrup and 0.23 g (10%) of **8** as a white solid. **9**: R_f 0.14 (toluene/EtOAc 20:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.57 (d, 1H, J = 9.4 Hz), 7.35 (d, 1H, J = 9.4 Hz), 4.95 (d, 1H, 3′-H, J = 5.5 Hz), 4.69−4.72 (m, 2H), 3.87 (dd, 1H, J = 2.2 Hz and J = 11.5 Hz), 3.74 (dd, 1H, J = 2.2 Hz and J = 11.5 Hz), 2.04 (s, 3H), 1.65 (s, 3H), 1.37 (s, 3H), 0.59(s, 9 H), −0.18 (s, 3H), −0.30 (s, 3H). Anal. Calcd for $C_{23}H_{32}Cl_2N_2O_6Si$: C, 51.98; H, 6.07; N, 5.27. Found: C, 52.31; H, 6.08; N, 5.35.

2,6-Dichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (10) and 2,6-Dichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (11). Method A. Compound **9** (1.05 g, 2 mmol) was placed in a flask, activated 4 Å molecular sieves (600 mg) and dry CH_2Cl_2 (5 mL) were added, and this mixture was cooled to 0 °C in an ice bath under an argon atmosphere. To this mixture were added consecutively Et_3SiH (3.2 mL, 20 mmol) and TMSOTf (0.96 mL, 5 mmol). The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 30 min. Triethylamine (2 mL) was then added to neutralize the reaction mixture. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and filtered through Celite. The organic phase was then extracted with water (2 × 50 mL) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/hexane 1:5, 15 cm × 5 cm) to give 730 mg (78%) of **10** as a white foam.

Method B. Compound **9** (1.27 g, 2.4 mmol) was placed in a flask under argon, and Et_3SiH (7.5 mL, 48 mmol) was added. The solution was cooled to 0 °C in an ice bath, and $BF_3{\cdot}OEt_2$ (0.74 mL, 6.0 mmol) was added. The reaction was stirred under an argon atmosphere at room temperature for 4 h. Saturated $NaHCO_3$ (40 mL) was added to neutralize the reaction mixture, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was dried over magnesium sulfate, filtered, and concentrated. The resulting residue was purified by flash chromatography (EtOAc/hexane 1:5, 15 cm × 2 cm) to give 400 mg (35%) of **10** and 385 mg (34%) of **11** both as white foams. **10**: R_f 0.26 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.46 (d, 1H, J = 7.8 Hz), 7.22 (d, 1H, J = 7.8 Hz), 5.66 (d, 1H, J = 6.3 Hz), 4.98 (m, 2H), 4.27 (m, 1H), 4.08 (dd, 1H, J = 1.8 Hz, J = 11.7 Hz), 3.99 (dd, 1H, J = 1.8 Hz, J = 11.7 Hz), 1.67 (s, 3H, acetyl), 1.37 (s,

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3H, acetyl), 0.99 (s, 9H), 0.21 (s, 3H), 0.22 (s, 3H). Anal. Calcd for $C_{21}H_{30}Cl_2N_2O_4Si$: C, 53.27; H, 6.38; N, 5.92. Found: C, 53.48; H, 6.29; N, 6.27. **11**: R_f 0.2 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.44 (d, 1H, J = 9.4 Hz), 7.18 (d, 1H, J = 9.4 Hz), 6.06 (d, 1H, J = 4.7 Hz), 5.11 (dd, 1H), 4.99 (d, 1H), 4.56 (t, 1H), 4.08 (dd, 1H), 3.98 (dd, 1H), 1.31 (s, 3H, acetyl), 1.30 (s, 3H, acetyl), 0.97 (s, 9H), 0.13 (s, 6H). Anal. Calcd for $C_{21}H_{30}Cl_2N_2O_4Si$: C, 53.27; H, 6.38; N, 5.92. Found: C, 53.03; H, 6.42; N, 5.77.

2,6-Dichloro-5-(2,3-di-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (13). Compound **10** (240 mg, 0.5 mmol) was dissolved in THF (5 mL) and treated with a solution of TBAF in THF (0.5 mL, 1.0 mmol, 2 N in THF). The reaction mixture was stirred for 1 h, water (50 mL) was added to the reaction mixture, and the mixture was extracted with EtOAc (3 × 70 mL). The combined organic extracts were dried over magnesium sulfate and filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (EtOAc/hexane 2:1, 15 cm × 2 cm) to give, after recrystallization from MeOH, 160 mg (89%) of **13** as a white crystalline solid: mp 250 °C dec; R_f 0.65 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.64 (d, 1H, J = 9.5 Hz), 7.45 (d, 1H, J = 9.5 Hz), 5.52 (m, 2H, simplifies on D_2O exchange to give d, 1H, J = 5.6 Hz), 5.00 (m, 2H), 4.20 (m, 1H), 3.76 (m, 2H), 1.56 (s, 3H, acetyl), 1.29 (s, 3H, acetyl). Anal. Calcd for $C_{15}H_{16}Cl_2N_2O_4$: C, 50.16; H, 4.49; N, 7.80. Found: C, 49.96; H, 4.54; N, 7.49.

2,6-Dichloro-5-(*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (12). Compound **10** (730 mg, 1.5 mmol) was dissolved in THF (30 mL), and to this solution was added 2 N HCl (30 mL). This reaction mixture was stirred at room temperature for 8 h. Solid Na_2CO_3 was then added in portions to the mixture until it became basic to litmus (pH 8). The resulting mixture was extracted with EtOAc (3 × 80 mL), and the organic phase was dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 2:1, 15 cm × 5 cm) to give, after recrystallization from MeOH, 470 mg (98%) of **12** as a white crystalline solid: mp 232−233 °C; R_f 0.36 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.80 (s, 1H), 7.60 (d, 1H, J = 9.5 Hz), 7.44 (d, 1H, J = 9.5 Hz), 5.43 (m, 2H, simplifies on D_2O exchange to d, 1H, J = 9.0 Hz), 5.21 (d, 1H, D_2O exchangeable), 5.14 (d, 1H, D_2O exchangeable), 4.38 (m, 1H), 4.16 (m, 1H), 3.97 (m, 1H), 3.71 (m, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 142.53, 134.73, 131.35, 127.19, 121.07, 116.87, 111.12, 87.41, 77.97, 70.32, 69.80, 60.66; UV λ_{max} (ethanol) 294 (5573), 233 (22 020); (pH 11) 276 (13 800), 232 (37 342); (pH 1) 294 (8400), 226 (24 800); HRMS m/z calcd for $C_{12}H_{12}Cl_2N_2O_4$ 318.0174, found 318.0169. Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_4$: C, 45.16; H, 3.79; N, 8.78. Found: C, 45.06; H, 3.87; N, 8.39.

2,6-Dichloro-5-(α-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (14). Compound **11** (350 mg, 0.7 mmol) was dissolved in THF (20 mL), and to this solution was added 4 N HCl (20 mL). This reaction mixture was stirred at room temperature for 24 h. Solid Na_2CO_3 was then added in portions to the mixture until it became basic to litmus (pH 8). The resulting mixture was extracted with EtOAc (3 × 80 mL), and the organic phase dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 2:1, 15 cm × 5 cm) to give, after recrystallization from MeOH, 212 mg (90%) of **14** as a white crystalline solid: mp 245−246 °C; R_f 0.30 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.56 (d, 1H, J = 9.5 Hz), 7.39 (d, 1H, J = 9.5 Hz), 5.65 (d, 1H, J = 3.2 Hz), 5.39 (d, 1H, D_2O exchangeable), 5.16 (d, 1H, D_2O exchangeable), 4.87 (t, 1H, D_2O exchangeable), 4.31 (m, 1H), 4.25 (m, 1H), 4.11 (m, 1H), 3.74 (m, 1H), 3.55 (m, 1H); ^{13}C NMR (DMSO-d_6, 90.556 MHz) δ 142.74, 133.55, 132.40, 126.76, 118.75, 116.15, 111.64, 82.59, 79.49, 74.00, 71.40, 61.24; UV λ_{max} (ethanol) 294 (5573), 233 (22 020); (pH 11) 276 (13 800), 232 (37 342); (pH 1) 294 (8400), 226 (24 800). Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_4$: C, 45.16; H, 3.79; N, 8.78. Found: C, 44.95; H, 3.93; N, 8.65.

2,6,7-Trichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (18) and 2,6,7-Trichloro-5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (19). To a solution of TMP (1.0 mL, 5.9 mmol) in THF (15 mL) at 0 °C was added *n*-BuLi (3.4 mL, 5.4 mmol, 1.6 M solution in hexanes). This solution was stirred for 30 min at 0 °C and then cooled to −78 °C, and a solution of **16** (1.0 g, 4.51 mmol) in THF (10 mL) was added dropwise over a period of 5 min. The resulting dark brown solution was stirred at −78 °C for 20 min. A solution of the lactone **6** (1.4 g, 4.5 mmol) in THF (10 mL) was then added dropwise over a period of 10 min, and the resulting black reaction mixture was stirred for 30 min at −78 °C. Acetic anhydride (4 mL, 40 mmol) was added dropwise to the reaction mixture, and the mixture was stirred at −78 °C for an additional 1 h. The reaction mixture was poured into an NH_4Cl buffer (150 mL) and extracted with EtOAc (3 × 100 mL). The organic phase was dried over magnesium sulfate. The EtOAc was removed under reduced pressure to give a yellowish oil which was purified by flash chromatography (EtOAc/hexane 1:5, 15 cm × 4 cm) to give 2.1 g (83%) of **17** as a syrup. **17**: R_f 0.47 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, $CDCl_3$) 8.49 (s, 1H), 7.65 (s, 1H), 4.91 (d, 1H, J = 5.5 Hz), 4.68 (m, 2H), 3.95 (d, 1H, J = 11.4 Hz), 3.70 (d, 1H, J = 11.4 Hz), 2.09 (s, 3H), 1.71 (s, 3H, acetyl), 1.40 (s, 3H, acetyl), 0.62 (s, 9 H), −0.13 (s, 3H), −0.29 (s, 3H). Compound **17** (770 mg, 1.4 mmol) was placed in a flask under argon and dissolved in CH_2Cl_2 (20 mL), and to this solution were added consecutively Et_3SiH (4.5 mL, 28 mmol) and $BF_3{\cdot}OEt_2$ (0.43 mL, 3.5 mmol). The reaction was stirred under an argon atmosphere at room temperature for 4 h. Saturated $NaHCO_3$ (40 mL) was then added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The resulting residue was purified by flash chromatography (EtOAc/hexane 1:5, 15 cm × 2 cm) to give 410 mg (58%) of **18** as a white solid.

When the reaction was conducted according to procedure B, as described for **10**, 200 mg (29%) of **18** as a white solid and 170 mg (25%) of **19** as a white foam were obtained.

18: mp 142−143 °C; R_f 0.46 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.67 (s, 1H), 5.74 (d, 1H, J = 6.6 Hz), 4.97 (m, 2H), 4.27 (m, 1H), 4.07 (dm, 1H), 3.98 (dm, 1H), 1.67 (s, 3H, acetyl), 1.37 (s, 3H, acetyl), 0.99 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H); HRMS m/z calcd for $C_{21}H_{29}Cl_3N_2O_4Si$ 506.0962, found 506.0964. Anal. Calcd for $C_{21}H_{29}Cl_3N_2O_4Si$: C, 49.66; H, 5.76; N, 5.52; Found: C, 49.55; H, 5.73; N, 5.63. **19**: R_f 0.42 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.63 (s, 1H), 6.11 (d, 1H, J = 4.7 Hz), 5.14 (t, 1H), 4.99 (d, 1H), 4.57 (m, 1H), 3.90 (m, 2H), 1.29 (s, 3H, acetyl), 1.28 (s, 3H, acetyl), 0.97 (s, 9H), 0.13 (s, 6H). Anal. Calcd for $C_{21}H_{29}Cl_3N_2O_4Si{\cdot}{}^1/_2H_2O$: C, 48.79; H, 5.85; N, 5.42. Found: C, 49.09; H, 5.63; N, 5.08.

2,6,7-Trichloro-5-(*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (20). Compound **18** (150 mg, 0.3 mmol) was dissolved in THF (5 mL) and treated with 2 N HCl (5 mL) as described for the deprotection of **10**. After purification by flash chromatography (EtOAc/hexane 2:1, 15 cm × 2 cm) and recrystallization from MeOH, 100 mg (99%) of **20** was obtained as a white crystalline solid: mp 270−271 °C; R_f 0.34 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.07 (s, 1H), 5.55 (d, 1H, J = 8.9 Hz), 5.46 (t, 1H, J = 4.5 Hz, D_2O exchangeable), 5.26 (d, 1H, J = 6.7 Hz, D_2O exchangeable), 5.18 (d, 1H, J = 4.5 Hz, D_2O exchangeable), 4.36 (m, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.73 (m, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 141.73, 135.50, 133.23, 129.77, 119.70, 116.32, 111.23, 87.63, 78.83, 70.36, 70.27, 60.56; UV λ_{max} (ethanol) 300 (4464), 245 (25724), 238 (25 280), 227 (25 944); (pH 11) 298 (3957), 243 (20 214), 237 (82 044); (pH 1) 297 (7154), 236 (22 472); HRMS m/z calcd for $C_{12}H_{12}Cl_2N_2O_4$ 351.9784, found 351.9801. Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_4$: C, 40.76; H, 3.14; N, 7.92. Found: C, 40.43; H, 3.21; N, 7.65.

2,6,7-Trichloro-5-(α-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (21). Compound **19** (130 mg, 0.2 mmol) was dissolved in THF (5 mL) and treated with 4 N HCl (10 mL) as described for the deprotection of **11**. After purification by flash chromatography (EtOAc/hexane 2:1, 15 cm × 2 cm) and recrystallization from aqueous MeOH, 80 mg (88%) of **21** was obtained as a white crystalline solid: mp 267−268 °C; R_f 0.34 (EtOAc/

hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.13 (s, 1H), 8.01 (s, 1H), 5.73 (d, 1H, J = 3.4 Hz), 5.42 (d, 1H, D_2O exchangeable), 5.16 (d, 1H, D_2O exchangeable), 4.88 (t, 1H, D_2O exchangeable), 4.37 (m, 1H), 4.24 (m, 1H), 4.13 (m, 1H), 3.75 (m, 1H), 3.55 (m, 1H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 142.05, 134.45, 129.33, 117.23, 115.43, 111.5, 82.77, 80.45, 73.71, 71.23, 61.20; UV λ_{max} (ethanol) 300 (4450), 245 (23 212), 238 (23 044), 228 (22 756); (pH 11) 298 (4655), 243 (23 696), 237 (23 277); (pH 1) 298 (7169), 236 (23 277); HRMS m/z calcd for $C_{12}H_{12}Cl_2N_2O_4$ 351.9784, found 351.9772. Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_4 \cdot {}^1/_2H_2O$: C, 39.75; H, 3.34; N, 7.73. Found: C, 39.79; H, 3.35; N, 7.42.

5-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (22). Compound **10** (250 mg, 0.47 mmol) was dissolved in EtOH (25 mL). To this solution were added Et_3N (2 mL) and 5% Pd/C (150 mg). The resulting mixture was stirred under an H_2 atmosphere at 1 atm for 3 h. The reaction mixture was filtered through Celite and the filtrate evaporated to dryness under reduced pressure. The resulting syrup was purified by flash chromatography (EtOAc/hexane 1:2, SiO_2) to give 110 mg (58%) of **22** as a syrup: R_f 0.19 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.88 (d, 1H, J = 1.2 Hz), 7.65 (d, 1H, J = 1.2 Hz), 7.58 (d, 1H, J = 9.0 Hz), 7.16 (q, 1H, J = 6.9 Hz, J = 9.0 Hz), 7.00 (d, 1H, J = 6.9 Hz), 5.09 (d, 1H, J = 4.8 Hz), 4.82 (m, 1H), 4.67 (m, 1H), 4.32 (m, 1H), 3.92 (dd, 1H, J = 3.2 Hz, J = 11.3 Hz), 3.84 (dd, 1H, J = 3.2 Hz, J = 11.3 Hz), 1.66 (s, 3H, methyl), 1.36 (s, 3H, methyl), 0.85 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.14, 135.93, 134.08, 124.08, 117.04, 114.86, 111.05, 109.54,85.32, 83.67, 83.51, 81.77, 63.27, 27.71, 25.98, 25.60, 18.42, −5.25, −5.41. Anal. Calcd for $C_{21}H_{32}N_2O_4Si$: C, 62.34; H, 7.97; N, 6.92. Found: C, 62.36; H, 8.22; N, 6.84.

5-(β-D-Ribofuranosyl)imidazo[1,2-*a*]pyridine (23). Compound **22** (250 mg, 0.6 mmol) was dissolved in THF (5 mL). To this solution was added 2 N HCl (5 mL), and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was neutralized by the addition of IRA-47 (OH^-). The resin was removed by filtration, and the filtrate was evaporated to dryness. The resulting solid was purified by flash chromatography (EtOAc/hexane 2:1, 15 cm × 2 cm) to give, after recrystallization from EtOH, 80 mg (54%) of **23** as a white solid: mp 145−146 °C; R_f 0.3 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.06 (d, 1H, J = 1.0 Hz), 7.64 (d, 1H, J = 1.0 Hz), 7.54 (d, 1H, J = 8.9 Hz), 7.27 (q, 1H, J = 8.9 Hz, J = 6.9 Hz), 7.10 (d, 1H, J = 6.9 Hz), 5.45 (d, 1H, J = 5.8 Hz, D_2O exchangeable), 5.11 (d, 1H, J = 2.5 Hz, D_2O exchangeable), 5.02 (t, 1H, D_2O exchangeable), 4.97 (d, 1H, J = 5.6 Hz), 4.08 (m, 1H), 3.96 (m, 2H), 3.70 (dd, 1H, J = 12.0 Hz), 3.61 (dd, 1H, J = 12.0 Hz); ^{13}C NMR (90 MHz, DMSO-d_6) δ 145.11, 137.06, 133.29, 124.15, 115.98, 111.25, 109.67, 84.50, 80.64, 73.10, 70.65, 61.02; UV λ_{max} (ethanol) 301 (4250), 280 (4742), 225 (11 671); (pH 11) 279 (4188), 225 (13 524); (pH 1) 281 (8604), 214 (18 375); HRMS m/z calcd for $C_{12}H_{14}N_2O_4$ 250.0954, found 250.0957. Anal. Calcd for $C_{12}H_{14}N_2O_4 \cdot {}^1/_2H_2O$: C, 55.59; H, 5.83; N, 10.80. Found: C, 55.91; H, 5.97; N, 10.40.

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