Synthesis of the First C3 Ribosylated Imidazo[1,2-*a*]pyridine C-Nucleoside by Enantioselective Construction of the Ribose Moiety

Kristjan S. Gudmundsson, John C. Drach, and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy; Department of Chemistry, College of Literature, Sciences and the Arts; and Department of Biologic and Materials Sciences, School of Dentistry; The University of Michigan, Ann Arbor, Michigan 49019-1065

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The metabolic instability of the glycosidic linkage in 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole prompted us to synthesize the structurally related C-nucleoside 2,6,7-trichloro-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine. Synthesis of this first C3-ribofuranosylimidazo[1,2-*a*]pyridine was accomplished by developing a modification of existing iodocyclization methodology for obtaining a 1′,4′-syn furanosyl precursor, without an extensive protection scheme. This 1′,4′-syn precursor was elaborated into the desired ribofuranosyl C-nucleoside. X-ray crystallography was used to unambiguously determine structure and absolute stereochemistry of this C-nucleoside.

Introduction

2,5,6-Trichloro-1-(β-D-ribofuranosyl)benzimidazole (**1**),[1] shows potent activity against human cytomegalovirus[2] with low cellular toxicity at concentrations inhibiting viral growth. However, pharmacokinetic studies of **1** in rats and monkeys[3] revealed that **1** disappears rapidly from the bloodstream following either intravenous or oral dosage. The disappearance of **1** was correlated with an increased blood concentration of 2,5,6-trichlorobenzimidazole (**2**) and would suggest that the glycosidic bond in **1** (aminal linkage) is unstable in vivo. This instability of the glycosidic bond prompted us to initiate studies on the synthesis of a C-nucleoside analogue of **1**, since a C-glycosidic bond would be more stable in vivo.[4] On the basis of computer (molecular) modeling studies involving the structural correlation of the exocyclic groups, we elected to synthesize 2,6,7-trichloro-3-(β-D-ribofuranosyl)-imidazo[1,2-*a*]pyridine (**3**) due to the very close structural resemblance of **3** to **1**. In addition, several C-nucleosides, both naturally occurring and synthetic, have exhibited significant antibacterial, antiviral, and antitumor activities.[5] Some of these biological activities have been postulated to depend on the resistance of the C−C linkage to hydrolytic or enzymatic cleavage.[4]

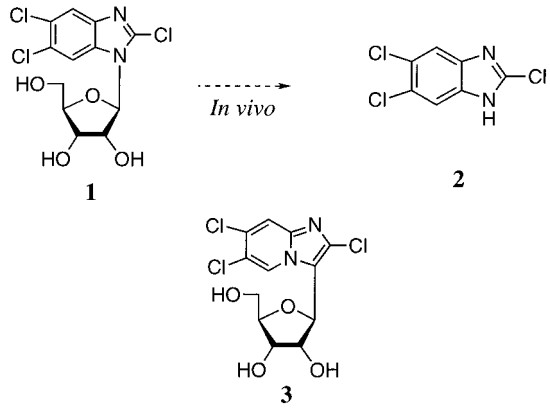

Figure 1. TCRB (**1**) is metabolically unstable in vivo and is cleaved at the glycosidic bond to give the aglycon **2**. The imidazo[1,2-*a*]pyridine C-nucleoside **3** has a C-glycosidic bond that should be more stable in vivo.

Results and Discussion

This synthesis presented a significant challenge since we had previously explored several unsuccessful routes toward the synthesis of **3**. Our initial attempts involved the reaction of lithiated imidazo[1,2-*a*]pyridines with ribonolactone derivatives which unexpectedly led to ribosylation at the C-5 position.[6] Other approaches toward obtaining the C 3 ribosylated C-nucleoside **3** by

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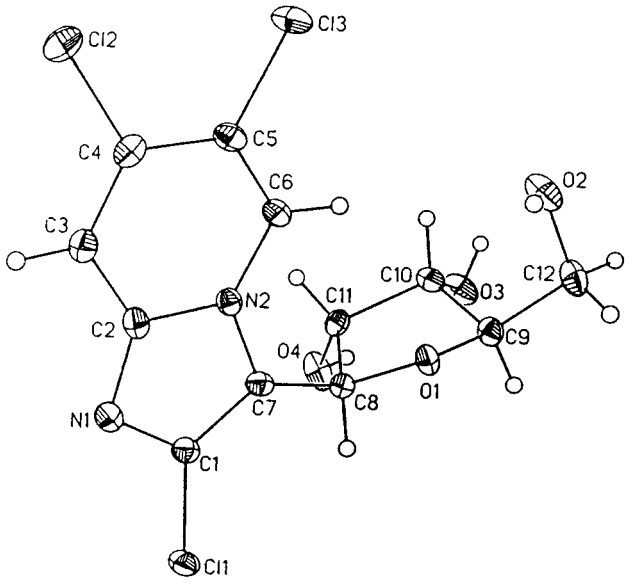
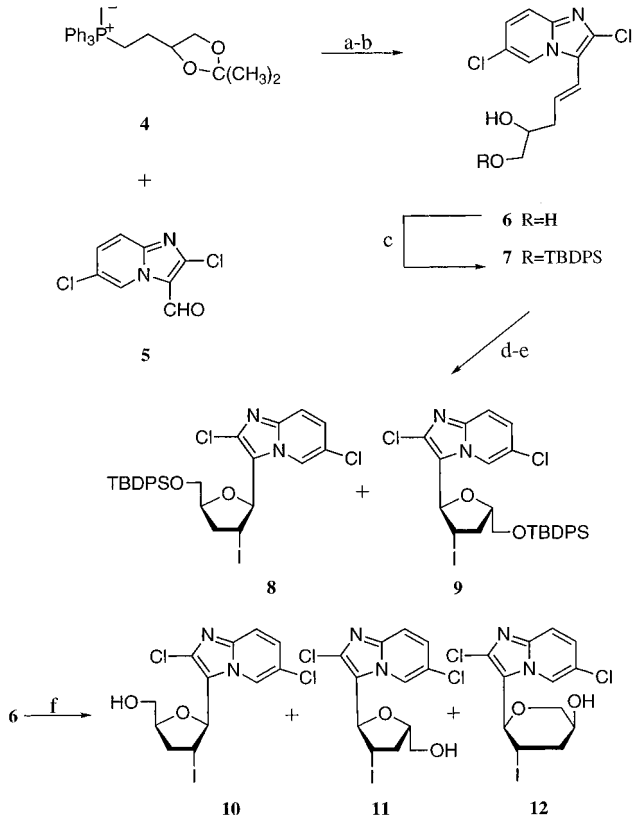


Figure 2. ORTEP diagram of **3**.

a palladium coupling[7] of 3-iodoimidazo[1,2-*a*]pyridines with ribofuranoid glycals, Lewis acid catalyzed ribosylations of imidazo[1,2-*a*]pyridines and attempts to construct the imidazo[1,2-*a*]pyridine heterocycle onto functionalized ribose derivatives were also unsuccessful. However, the construction of a ribose ring via an intramolecular iodocyclization process has recently been employed to prepare a limited number of C-nucleosides containing phenyl or furan aglycons.[8] This led us to investigate a similar approach for the synthesis of **3**. We now report an enantioselective synthesis of **3** by constructing the ribose moiety onto a heterocyclic moiety. This approach involved a iodocyclization of an unprotected diol intermediate to form 1′,4′-syn substituted furanose derivatives.

Since 2,6-dichloro-3-formylimidazo[1,2-*a*]pyridine (**5**)[9] was easier to synthesize than 3-formyl-2,6,7-trichloroimidazo[1,2-*a*]pyridine,[9] we elected to conduct our initial studies on 5 and racemic 3,4-*O*-isopropylidene-3,4-hydroxybut-1-yl triphenyl phosphonium iodide (**4**).[10] Wittig olefination of 4 in THF at 0 °C gave, after deprotection with pyridinium *p*-toluenesulfonate in aqueous methanol, 2,6-dichloro-3-(1,2-dihydroxy-pent-4(*E*)-en-5-yl)imidazo-[1,2-*a*]pyridine (**6**) as the only isomer. Treatment of **6** with TBDPSCl in a pyridine-CH_2Cl_2 mixture in the presence of a catalytic amount of DMAP gave 2,6-dichloro-3-(1-*O*-(*tert*-butyldiphenylsilyl)-1,2-dihydroxypent-4(*E*)-en-5-yl)imidazo[1,2-*a*]pyridine (**7**). Compound **7** was

Scheme 1[a]



[a] Reagents and conditions: (a) n-BuLi (1.1 equiv), THF, 0 °C, 10 min; 5 (1 equiv) in THF, 0 °C, 1 h, 75%; (b) PPTS in MeOH−H_2O, 25 °C, 95%; (c) TBDPSCl (1.2 equiv), DMAP (0.2 equiv), pyridine−CH_2Cl_2, 25 °C, 87%; (d) TESOTf (1.3 equiv), 2,6-lutidine (1.3 equiv), CH_2Cl_2, 0 °C; (e) the TES-derivative added to a solution of I_2 (5−10 equiv) and K_2CO_3 (2 equiv), 25 °C, yield 20% of 8:9 in 1:2 ratio (addition of t-BuOH and Et_3N to the reaction mixture as described in ref 8 did not improve yield or syn selectivity); (f) see Table 1.

treated with TESOTf and 2,6-lutidine in CH_2Cl_2, and this diprotected derivative was subjected to the conditions of iodocyclization as described in the literature.[8] However, these conditions provided **8** and **9** in a combined yield less than 20% with the desired 1′,4′-syn derivative **8** being present in a lower yield than the 1′,4′-anti derivative **9**.[11] Repeated attempts to iodocyclize derivatives of **6** with other primary and secondary protecting groups (reported to direct iodocyclization of other diprotected pent-4-ene-1,2-diols to give 1′,4′-syn derivatives in higher yield than the corresponding 1′,4′-anti derivatives[8]) failed to improve the yield or selectivity for formation of the desired 1′,4′-syn derivative **8**.

However, we subsequently found that iodocyclization of the unprotected diol **6** proceeded in better yield and selectivity. In all cases, using **6** as substrate, a third product was isolated and characterized by ^{1}H NMR, mass spectral, and analytical data as being the pyranose product **12**. As shown in Table 1, product ratios were highly dependent on reaction conditions, e.g. iodocyclization of the diol **6** in the presence of base (entries 1−3) gave consistently the anti product **11** in a 2−3-fold excess over the syn product **10**. The highest yield of the syn

(7) For synthesis of the related imidazo[1,2-a]pyridine erythrofuranosyl C-nucleosides see: Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *Tetrahedron Lett.* **1996**, *37*, 6275−6278.

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(11) Assignment of **8** as the syn derivative and **9** as the anti derivative was based on NOE experiments, where an NOE (2.2%) was observed between the 1′ and the 4′−H for **8**. Such an NOE was not observed for compound **9**.

Table 1. Selected Conditions for the Iodocyclization of Unprotected Diol 6

entry	solvent	method[a] (temp)	product ratio **10**:**11**:**12**	combined yield (%)
1	CH_2Cl_2	A (25 °C)	25:71:14	82
2	THF	A (25 °C)	30:54:16	94
3	CH_3CN	A (25 °C)	24:51:25	88
4	CH_2Cl_2	B (25 °C)	25:71:4	75
5	THF	B (25 °C)	57:18:25	91
6	CH_3CN	B (25 °C)	51:21:28	80

[a] Method A: The diol **6** was dissolved in the specified solvent and added to a solution of 5−10 equiv of I_2 and 2 equiv of K_2CO_3. Whether **6** was added to the I_2 and K_2CO_3 solution or the I_2 added to a solution of **6** and K_2CO_3 did not affect the yield of the lactonization. Method B: Same as method A except K_2CO_3 was not initially added to the I_2 solution. Two equivalents of K_2CO_3 were added in two portions, 30 min and 60 min after the addition of substrate to the I_2 solution.

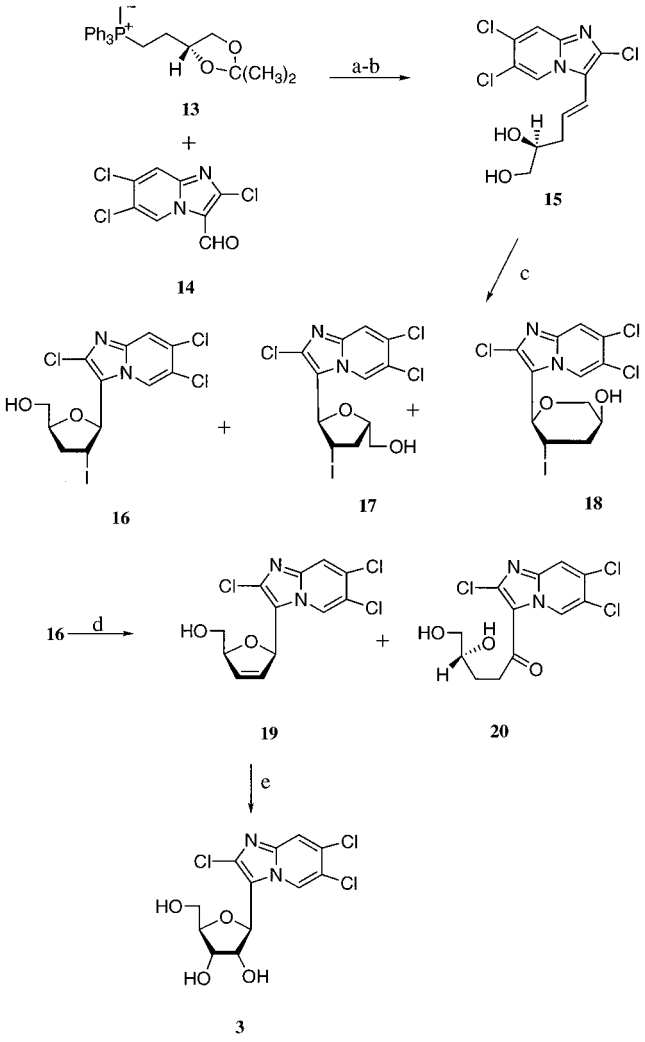
product **10**, using method A, was obtained by iodoetherification of **6** in THF at rt. Using other solvents or lower temperatures gave lower yields of **10** and a higher yield of the anti product **11**. The pyranose side product **12** was obtained in yields ranging from 14 to 25% with the highest yields of **12** being obtained in CH_3CN at rt.

Certain iodolactonization and iodocyclization reactions[12] have been reported to give different product ratios when conducted in the absence of base (K_2CO_3). In the presence of base, those reactions are irreversible and are considered kinetic, whereas in the absence of base these reactions become reversible and are considered more thermodynamic in nature. These reports prompted us to attempt the iodine catalyzed cyclization of 6 in the absence of K_2CO_3. We found that the cyclization did not proceed to completion in the absence of base, but by adding K_2CO_3 portionally, at 30 and 60 min after the addition of iodine to a solution of **6**, the reaction went to completion and the ratio of products **10**, **11**, and **12** was different from the ratio obtained by adding iodine to a solution of **6** containing K_2CO_3. These conditions (method B) gave **10** in a 3-fold excess over **11** when the cyclization was carried out in a polar solvent. Formation of **12** could not be avoided, as all attempts to protect the primary hydroxyl group resulted in the formation of **11** in a greater yield than **10** under the iodocyclization conditions.

Having developed an efficient synthesis for the preparation of the 1′,4′-syn derivative **10** as the major iodocyclization product, we applied this methodology to the enantioselective preparation of the desired 2,6,7-trichloro-3-(*β*-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**3**) from 3,4-(S)-O-isopropylidene-3,4-dihydroxybut-1-yl triphenylphosphonium iodide (**13**)[10] and 3-formyl-2,6,7-trichloroimidazo[1,2-*a*]pyridine (**14**).[9]

Wittig olefination of **14** gave, after deprotection, the diol 2,6,7-trichloro-3-(1,2(*S*)-dihydroxypent-4(*E*)en-5-yl)-imidazo[1,2-*a*]pyridine (**15**) in a 63% yield. This diol **15** was treated with iodine in THF and the subsequent addition of K_2CO_3 (method B) to give three isomeric compounds, separable by flash chromatography. Two of these were identified as the 1′,4′-syn product 2,6,7-trichloro-3-(2,3-dideoxy-2-iodo-*β*-D-ribofuranosyl)imidazo-[1,2-*a*]pyridine (**16**) and the 1′,4′-anti product 2,6,7-trichloro-3-(2,3-dideoxy-2-iodo-α-D-lyxofuranosyl)imidazo[1,2-*a*]pyridine (**17**) by a comparison of their spectral data with the analogous 2,6-dichloroimidazo[1,2-*a*]pyridine derivatives. The spectral data for the third compound was compared with **12** and assumed to be 2,6,7-trichloro-3-(2,3-dideoxy-2-iodo-α-D-lyxopyranosyl)imidazo[1,2-*a*]pyridine (**18**). The structure and absolute stereochemistry of **18** was unequivocally determined by X-ray crystallography.[13]

Scheme 2[a]



[a] Reagents and conditions: (a) n-BuLi (1.1 equiv), THF, 0 °C, 10 min; 14 (1 equiv) in THF, 0 °C, 1 h, 70%; (b) PPTS in MeOH−H_2O, 25 °C, 90%; (c) **15** treated as described for method B in Table 1, 16 (45%), 17 (16%), 18 (21%); (d) DBU (5 equiv), DMF, 90 °C, followed by aqueous workup, 19 (62%), 20 (15%); (e) OsO_4, NMO (1.5 equiv), acetone−H_2O 4:1, 25 °C, 95%.

Treatment of **16** with DBU in DMF at 80 °C for 24 h gave after aqueous workup the dideoxy-didehydro derivative **19** in 67% yield and a side product in 15% yield. Structural assignment of the side product was based on the fact that ^{13}C-spectra showed it contained a carbonyl functionality. The ^1H NMR showed that the resonance for the C5-H on the imidazo[1,2-*a*]pyridine heterocycle was shifted downfield from 9.5 to 10.0 ppm. This downfield shift of 0.5 ppm is characteristic for imidazo-[1,2-*a*]pyridine containing a carbonyl group attached to

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(13) An ORTEP diagram and other crystallographic data are included in the Supporting Information.

the C3 position.[14] This led us to assign structure **20** to the byproduct. Attempts to improve the yield of **19**, by using lower reaction temperatures or other bases to affect the elimination (such as sodium methoxide), failed.

Finally, dihydroxylation of **18** was accomplished using osmium tetraoxide in the presence of morpholine *N*-oxide in an acetone−water mixture to give, as the only product, the desired 2,6,7-trichloro-3-(β-D-ribofuranosyl)imidazo-[1,2-*a*]pyridine (**3**). The structure and absolute stereochemistry of the new C-nucleoside **3** was unequivocally determined by X-ray crystallography.[15]

We have successfully synthesized the first C3-ribofuranosylimidazo[1,2-*a*]pyridine C-nucleoside (**3**). This was accomplished by developing a modification of existing iodocyclization methodology for obtaining a 1′,4′-syn furanosyl precursor, without an extensive protection scheme.

Antiviral evaluation revealed that the reported imidazo[1,2-*a*]pyridine C-nucleosides did not have significant activity against human cytomegalovirus (IC_{50} > 100 μM in a plaque reduction assay)[16] or HSV-1 (IC_{50} > 100 μM in an ELISA assay).[17] These derivatives were not cytotoxic.

Further investigation on the application of this methodology for the synthesis of C-nucleosides is in progress in our laboratories.

Experimental Section

General Procedures. Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 360 or 300 MHz. Flash column chromatography was performed using silica gel 60 230−400 mesh (ICN). Thin-layer chromatography (TLC) was performed on prescored Silica gel GHLF. Compounds were visualized by illumination under UV light (254 nm) or by spraying with 20% methanolic sulfuric acid followed by charring on a hot plate. Evaporations were carried out under reduced pressure with water bath at below 40 °C. All solvents were dried prior to use as described by the handbook *Purification of Laboratory Chemicals*[18] and stored over 4 Å sieves, under argon. Materials obtained from commercial suppliers were used without purification.

2,6-Dichloro-3-(1,2-dihydroxypent-4(*E*)-en-5-yl)imidazo-[1,2-*a*]pyridine (6). The phosphonium iodide **4** (1.32 g, 2.55 mmol) was suspended in dry THF (10 mL). The suspension was cooled to 0 °C (ice−water bath) under an argon atmosphere and n-BuLi (1.8 mL of 1.6 M solution in hexanes, 2.81 mmol) was added dropwise to this suspension. The reddish solution that formed was stirred at 0 °C for 10 min, and then a solution of the formyl compound **5** (0.55 g, 2.55 mmol) in THF (10 mL) was added. The reaction mixture was stirred at 0 °C for 1 h and then poured into a saturated solution of $NaHCO_3$ (100 mL). The resulting mixture was extracted with EtOAc (3 × 70 mL) and the organic phase dried ($MgSO_4$), filtered, and concentrated. The solid residue was purified by flash chromatography (Et_2O/hexane 4:1, 15 cm × 4 cm). Fractions containing the product were combined and concentrated to dryness to give, after recrystallization from EtOH, 625 mg (75%) of a white crystalline solid. This solid was dissolved in a 1:1 mixture of H_2O and MeOH (50 mL). To this solution was added pyridinium *p*-toluenesulfonate (0.7 g, 3.6 mmol) and the reaction mixture heated at 60 °C for 12 h. Methanol was removed under reduced pressure, and the resulting aqueous mixture was extracted with EtOAc (3 × 80 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (EtOAc/hexane 2:1, 15 cm × 5 cm). Fractions containing the product were combined and evaporated to dryness to give, after recrystallization from EtOH, 0.52 g (95%) of **6** as a white solid: mp 67−70 °C; R_f 0.12 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.85 (d, 1H, J = 1.8 Hz), 7.60 (d, 1H, J = 9.5 Hz), 7.39 (dd, J = 1.8 Hz, J = 9.5 Hz), 6.77 (d, 1H, J = 16.2 Hz), 6.60 (dt, 1H, J = 16.2 Hz, J = 7.1 Hz, J = 7.1 Hz), 4.71 (d, 1H, D_2O exchangeable, J = 5.0 Hz), 4.61 (t, 1H, D_2O exchangeable, J = 5.7 Hz), 3.59 (m, 1H), 3.35 (m, 3H), 2.30 (m, 1H). Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_2 \cdot {}^1/_2$EtOH: C, 50.34; H, 4.87; N, 9.03. Found: C, 50.22; H, 5.22; N, 8.76.

2,6-Dichloro-3-(1-O-(*tert*-butyldiphenylsilyl)-1,2-dihydroxypent-4(*E*)-en-5-yl)imidazo[1,2-*a*]pyridine (7). Compound **6** (140 mg, 0.49 mmol) was suspended in CH_2Cl_2 (5 mL), and to this suspension were added sequentially pyridine (0.5 mL, 6.2 mmol), DMAP (10 mg, 0.08 mmol), and TBDPSCl (0.16 mL, 0.6 mmol). The resulting reaction mixture was stirred for 12 h at ambient temperature. Water was added and the mixture extracted with EtOAc (3 × 40 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (EtOAc/hexane 1:2, 15 cm × 2 cm). Fractions containing the product were combined and evaporated to dryness to give, after recrystallization from EtOH, 225 mg (87%) of **7** as a white crystalline solid: mp 155−156 °C; R_f 0.46 (EtOAc/hexane 1:2); H NMR (360 MHz, $CDCl_3$) δ 8.10 (d, 1H, J = 2.0 Hz), 7.7 (m, 4H), 7.49 (d, 1H), 7.40 (m, 6H), 7.19 (dd, 1H, J = 9.5 Hz, J = 2.0 Hz), 6.46 (m, 2H), 3.94 (m, 1H), 3.77 (dd, 1H), 3.65 (dd, 1H), 2.52 (t, 2H), 1.70 (broad s, 1H, D_2O exchangeable), 1.10 (s, 9H); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.80 (d, 1H), 7.62 (m, 5H), 7.38 (m, 7H), 6.78 (d, 1H, J = 16.2 Hz), 6.57 (dt, 1H, J = 16.2 Hz, J = 7.4 Hz, J = 7.4 Hz), 4.9 (d, 1H, D_2O exchangeable, J = 5.1 Hz), 3.79 (m, 1H), 3.62 (m, 1H), 3.56 (m, 1H), 2.59 (m, 1H), 2.47 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 140.2, 135.1, 133.1, 132.4, 131.1, 129.8, 127.8, 126.2, 122.6, 120.6, 118.1, 117.2, 115.3, 70.3, 67.5, 38.1, 26.7, 18.8. Anal. Calcd for $C_{28}H_{30}Cl_2N_2O_2Si$: C, 63.99; H, 5.75; N, 5.33. Found: C, 63.78; H, 5.92; N, 5.26.

2,6-Dichloro-3-(2,3-dideoxy-2-iodo-5-O-(*tert*-butyldiphenylsilyl)-β-D/L-ribofuranosyl)imidazo[1,2-*a*]pyridine (8) and 2,6-Dichloro-3-(2,3-dideoxy-2-iodo-5-O-(*tert*-butyldiphenylsilyl)-α-D/L-lyxofuranosyl)imidazo[1,2-*a*]-pyridine (9). A solution of **7** (178 mg, 0.34 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C, and 2,6-lutidine (51 μL, 0.44 mmol) and TESOTf (95 μL, 0.42 mmol) were then added. This reaction mixture was stirred at 0 °C for 30 min and then concentrated in vacuo to a syrup. The residue was purified by flash chromatography (EtOAc/hexane 1:10, 15 cm × 2 cm), fractions containing the product were pooled and concentrated to dryness to give the TES-intermediate[19] as a syrup. The TES-intermediate was dissolved in dry CH_3CN (7 mL) containing Et_3N (30 μL, 0.17 mmol) and added dropwise to a solution of iodine (860 mg, 3.4 mmol), K_2CO_3 (94 mg, 0.68 mmol), and t-BuOH (130 μL, 1.3 mmol) in CH_3CN (6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at rt for an additional 1 h. The reaction mixture was subsequently poured into EtOAc (100 mL) and extracted with saturated aqueous $Na_2S_2O_3$ (50 mL × 2), dried ($MgSO_4$), filtered, and concentrated to a solid. This solid contained two

(14) ^{1}H NMR information reported in ref 9 shows similar shift differences for the C5-H proton of 2,6-dichloroimidazo[1,2-a]pyridine and 2,6-dichloro-3-formylimidazo[1,2-a]pyridine and also for the C5-H proton of 2,6,7-trichloroimidazo[1,2-a]pyridine and 2,6-trichloro-3-formylimidazo[1,2-a]pyridine.

(15) The crystal was grown in methanol and the X-ray obtained from the X-ray laboratory of The Department of Chemistry at The University of Michigan. Crystal data for **3**: white crystals, orthorhombic, $P2(1)2(1)2(1)$; a = 6.8890(10) A, b = 13.349(2) A, c = 17.1340(10) A.; V = 1575.9(3) Å^3; Z = 4; D_{calc} =1.626. Of 6939 reflections collected, 3093 were unique; R = 0.0239 and Rw = 0.0620.

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compounds that were separated by flash chromatography (EtOAc/hexane 1:5, 15 cm × 2 cm). Fractions containing the individual products were pooled and concentrated to dryness to give 32 mg (13%) of 8 and 10 mg (4%) of **9** as white solids. **8**: mp 130−132 °C; R_f 0.35 (EtOAc/hexane 1:5); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.36 (d, 1H, J = 2.0 Hz), 7.66 (m, 4H), 7.50 (d, 1H, J = 9.5 Hz), 7.4 (m, 6H), 7.21 (dd, 1H, J = 2.0 Hz, J = 9.5 Hz), 5.43 (d, 1H, J = 9.2 Hz), 4.58 (q, 1H), 4.35 (m, 1H), 3.97 (dd, 1H, J = 11.4 Hz, J = 3.5 Hz), 3.76 (dd, 1H, J = 11.4 Hz, J = 4.0 Hz), 2.80 (m, 1H), 2.54 (m, 1H), 1.14 (s, 9H). Anal. Calcd for $C_{28}H_{29}Cl_2IN_2O_2Si$: C, 51.62; H, 4.49; N, 4.30. Found: C, 51.73; H, 4.67; N, 4.14. **9**: mp 80−82 °C; R_f 0.32 (EtOAc/hexane 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 1H, J = 2.0 Hz), 7.7 (m, 4H), 7.52 (d, 1H, J = 9.5 Hz), 7.40 (m, 6H), 7.26 (dd, 1H, J = 9.5 Hz, J = 2.0 Hz), 5.59 (d, 1H, 10.4 Hz), 4.56 (m, 1H), 4.39 (m, 1H), 3.92 (dd, 1H, J = 11.2 Hz, J = 3.3 Hz), 3.71 (dd, 1H, J = 11.2 Hz, J = 3.2 Hz), 2.8 (m, 2H), 1.14 (s, 9H). Anal. Calcd for $C_{28}H_{29}Cl_2IN_2O_2Si\cdot H_2O$: C, 50.23; H, 4.79; N, 4.18. Found: C, 50.01; H, 4.65; N, 4.14.

2,6-Dichloro-3-(2,3-dideoxy-2-iodo-β-D/L-ribofuranosyl)-imidazo[1,2-*a*]pyridine (10), 2,6-dichloro-3-(2,3-dideoxy-2-iodo-α-D/L-lyxofuranosyl)imidazo[1,2-*a*]pyridine (11) and 2,6-dichloro-3-(2,3-dideoxy-2-iodo-α-D-lyxopyranosyl)imidazo[1,2-*a*]pyridine (12). A solution of **6** (570 mg, 2 mmol) in dry THF (20 mL) was added to a solution of iodine (2.5 g, 9.85 mmol) in THF (10 mL). The reaction mixture was stirred for 30 min at rt, and then K_2CO_3 (285 mg, 2.1 mmol) was added, followed by the addition of another portion of K_2CO_3 (285 mg, 2.1 mmol) after an additional 60 min. Once all the starting material had reacted as observed by TLC, the reaction mixture was poured into EtOAc (100 mL) and extracted with saturated aqueous $Na_2S_2O_3$ (50 mL × 2). The organic phase was dried over $MgSO_4$, filtered, and concentrated to an oil. The resulting oil contained three products that were separated by flash chromatography (EtOAc/hexane 1:2, 15 cm × 5 cm). Fractions containing the individual products were pooled and volatiles removed in vacuo, and each component was crystallized from aqueous EtOH to give 430 mg (52%) of **10**, 130 mg (16%) of **11**, and 185 mg (23%) mg of **12**, all as white solids. **10**: mp 190−191 °C; R_f 0.55 (EtOAc/hexane 1:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.18 (d, 1H), 7.65 (d, 1H, J = 9.6 Hz), 7.46 (dd, 1H, J = 9.6 Hz, J = 1.9 Hz), 5.39 (d, 1H, J = 10.1 Hz), 5.34 (t, 1H, D_2O exchangeable, J = 4.8 Hz), 4.57 (q, 1H), 4.30 (m, 1H), 3.68 (m, 1H), 3.54 (m, 1H), 2.70 (m, 1H), 2.53 (m, 1H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 142, 135.8, 127.2, 125.1, 120.4, 117.3, 114.1, 80.3, 79.2, 62.5, 39.1, 19.1. Anal. Calcd for $C_{12}H_{11}Cl_2IN_2O_2$: C, 34.89; H, 2.68; N, 6.78. Found: C, 35.09; H, 2.85; N,6.73. **11**: mp 158−160 °C; R_f 0.40 (EtOAc/hexane 1:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.59 (d, 1H), 7.66 (d, 1H, J = 9.6 Hz), 7.47 (dd, 1H), 5.38 (d, 1H, J = 10.6 Hz), 4.98 (t, 1H, D_2O exchangeable, J = 5.6 Hz), 4.77 (m, 1H), 4.34 (m, 1H), 3.57 (m, 1H), 3.47 (m, 1H), 2.77 (m, 1H), 2.32 (m, 1H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 141.9, 135.7, 127.2, 124, 120.4, 117.4, 114.3, 80, 79.1, 63.1, 39.6, 19.7. Anal. Calcd for $C_{12}H_{11}Cl_2IN_2O_2$: C, 34.89; H, 2.68; N, 6.78. Found: C, 34.81; H, 2.71; N, 6.80. **12**: mp 205 °C; R_f 0.45 (EtOAc/hexane 1:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.85 (d, 1H, J = 1.9 Hz), 7.67 (d, 1H, J = 9.6 Hz), 7.47 (dd, 1H, J = 9.6 Hz, J = 1.9 Hz), 5.34 (m, 1H, D_2O exchangeable), 5.1−5.2 (m, 2H), 3.91 (m, 2H), 3.71 (m, 1H), 2.55 (m, 2H). Anal. Calcd for $C_{12}H_{11}Cl_2IN_2O_2$: C, 34.89; H, 2.68; N, 6.78. Found: C, 34.89; H, 2.53; N, 6.64.

2,6,7-Trichloro-3-(1,2(*S*)-dihydroxy-pent-4(*E*)-en-5-yl)-imidazo[1,2-*a*]pyridine (15). A suspension of **13** (7.18 g, 0.014 mol) in dry THF (30 mL) was cooled to 0 °C under an argon atmosphere. To this suspension was added dropwise n-BuLi (9.9 mL of 1.6 M solution in hexanes, 0.016 mol). The reddish solution obtained was stirred at 0 °C for 10 min, and then a solution of **14** (3.3 g, 0.013 mol) in THF (30 mL) was added. The reaction mixture was stirred at 0 °C for 1 h and then poured into a saturated aqueous solution of $NaHCO_3$ (200 mL) and extracted with EtOAc (3 × 150 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to a solid. This solid was purified by flash chromatography (Et_2O/hexane 4:1, 15 cm × 5 cm). Fractions containing the product were combined and evaporated to dryness to give, after recrystallization from EtOH, 3.34 g (70%) of a white crystalline solid. To a solution of this solid (0.7 g, 1.9 mmol) in a 1:1 mixture of H_2O and MeOH (40 mL) was added pyridinium *p*-toluenesulfonate (0.7 g, 2.8 mmol) and the reaction mixture heated to 60 °C for 24 h. The methanol was removed under reduced pressure, and the resulting aqueous mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated, and the resulting solid was purified by flash chromatography (EtOAc/hexane 2:1, 15 cm × 2 cm). Fractions containing the product were combined and evaporated to dryness, and the solid was recrystallized from EtOH to give 0.56 g (90%) of **15** as a white solid: mp 161−163 °C; R_f 0.25 (EtOAc/hexane 2:1); ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.00 (s, 1H), 6.79 (d, 1H, J = 16.2 Hz), 6.62 (dt, 1H, J = 16.2 Hz, J = 7.1 Hz), 4.71 (d, 1H, D_2O exchangeable), 4.61 (t, 1H, D_2O exchangeable), 3.61 (m, 1H), 3.33 (m, 2H), 2.5 (m, 1H), 2.3 (m, 1H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 140.1, 132.8, 132.2, 128.9, 124.2, 119.1, 118.2, 116.3, 114.8, 71, 65.5, 38.1. Anal. Calcd for $C_{12}H_{11}Cl_3N_2O_2$: C, 44.82; H, 3.45; N, 8.71. Found: C, 45.13; H, 3.81; N, 8.58.

2,6,7-Trichloro-3-(2,3-dideoxy-2-iodo-β-D-ribofuranosyl)-imidazo[1,2-*a*]pyridine (16), 2,6,7-Trichloro-3-(2,3-dideoxy-2-iodo-α-D-lyxofuranosyl)imidazo[1,2-*a*]pyridine (17), and 2,6,7-Trichloro-3-(2,3-dideoxy-2-iodo-α-D-lyxopyranosyl)-imidazo[1,2-*a*]pyridine (18). A solution of **15** (340 mg, 1.1 mmol) in dry THF (10 mL) was added to a stirred solution of iodine (1.3 g, 5.3 mmol) in THF (10 mL). After 30 min K_2CO_3 (150 mg, 1.1 mmol) was added, followed by the addition of a second portion of K_2CO_3 (150 mg, 1.1 mmol) after 60 min. Once all the starting material had reacted, as determined by TLC, the reaction mixture was poured into EtOAc (100 mL) and extracted with saturated aqueous $Na_2S_2O_3$ (50 mL × 2), dried over $MgSO_4$, filtered, and concentrated to a solid. This solid contained three compounds that were separated by flash chromatography (EtOAc/hexane 1:2, 15 cm × 5 cm). Fractions containing each component were pooled, and solvent was removed in vacuo to give, after recrystallization from aqueous EtOH, 193 mg (45%) of **16**, 70 mg (16%) of **17**, and 120 mg (27%) of **18** as white solids. **16**: mp 206−207 °C; R_f 0.27 (EtOAc/hexane 1:2); ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.08 (s, 1H), 5.42 (t, 1H, D_2O exchangeable), 5.39 (d, 1H, J = 10.0 Hz), 4.56 (q, 1H), 4.31 (m, 1H), 3.69 (m, 1H), 3.56 (m, 1H), 2.70 (m, 1H), 2.55 (m, 1H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 142.2, 136.4, 130.2, 126.6, 119.1, 116.5, 114.3, 80.3, 79.3, 62.4, 39.1, 19.3. Anal. Calcd for $C_{12}H_{10}Cl_3IN_2O_2$: C, 32.21; H, 2.25; N, 6.26. Found: C, 32.13; H, 2.35; N, 5.86. **17**: mp 167−168 °C; R_f 0.14 (EtOAc/hexane 1:2); ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.11 (s, 1H), 5.38 (d, 1H, J = 9.5 Hz), 4.97 (t, 1H, D_2O exchangeable), 4.75 (q, 1H), 4.36 (m, 1H), 3.56 (m, 1H), 3.47 (m, 1H), 2.76 (m, 1H), 2.33 (m, 1H); 13C NMR (90 MHz, DMSO-d_6) δ 142, 136.3, 130.2, 125.4, 119.2, 116.7, 114.53, 80, 79, 63.1, 39.5, 19.8. Anal. Calcd for $C_{12}H_{10}Cl_3IN_2O_2$: C, 32.21; H, 2.25; N, 6.26. Found: C, 32.40; H, 2.32; N,6.10. **18**: mp 199−200 °C; R_f 0.17 (EtOAc/hexane 1:2); ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.09 (s, 1H), 5.34 (m, 1H, D_2O exchangeable), 5.18 (d, 1H, J = 11.3 Hz), 5.10 (m, 1H), 3.92 (m, 2H), 3.71 (m, 1H), 3.56 (m, 2H);13C NMR (90 MHz, DMSO-d_6) δ 141.4, 135.2, 129.9, 125.2, 119.2, 118.5, 116.7, 74.2, 71.9, 65.9, 43.1, 24; HRMS *m*/*z* calcd for $C_{12}H_{11}Cl_2IN_2O_2$ 445.8853, found 445.8842. Anal. Calcd for $C_{12}H_{10}Cl_3IN_2O_2$: C, 32.21; H, 2.25; N, 6.26. Found: C, 32.02; H, 2.29; N,5.99. Structure and absolute stereochemistry of **18** was determined by X-ray crystallography.

2,6,7-Trichloro-3-(2,3-dideoxy-2,3-didehydro-β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (19) and 2,6,7-Trichloro-3-(4(*S*),5-dihydroxy-1-oxopentane)imidazo[1,2-*a*]pyridine (20). To a solution of **16** (400 mg, 0.89 mmol) in dry DMF (10 mL) was added DBU (0.67 mL, 4.4 mmol), and the resulting solution was stirred at 90 °C for 16 h. The reaction mixture was partitioned between water (50 mL) and CH_2Cl_2 (100 mL), and the phases were separated. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, and the resulting solid was purified by flash chromatog-

raphy (EtOAc/hexane 1:5, 15 cm × 2 cm). Fractions containing a faster migrating minor product were pooled and concentrated in vacuo to give, after recrystallization from aqueous CH_3CN, 48 mg (15%) of **20** as a white powder. Fractions containing the slower migrating major product were subsequently combined and concentrated in vacuo to give, after recrystallization from aqueous CH_3CN, 170 mg (62%) of **19** as white powder: 19: mp 147−148 °C; R_f 0.40 (EtOAc/hexane 1:2); ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.42 (d, 1H, J = 0.4 Hz), 8.05 (d, 1H, J = 0.4 Hz), 6.34 (m, 1H), 6.15 (m, 1H), 6.10 (m, 1H), 5.20 (t, 1H), 4.85 (m, 1H), 3.70 (m, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 141.8, 135.3, 132.8, 130, 127.2, 126.1, 118.6, 117.3, 116.3, 87, 76.9, 62.5. Anal. Calcd for $C_{12}H_9Cl_3N_2O_2$: C, 45.10; H, 2.84; N, 8.76. Found: C, 45.20; H, 2.89; N, 8.63. **20**: mp 165−166 °C; R_f 0.20 (EtOAc/hexane 1:2); ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.30 (s, 1H), 4.57 (d, 1H), 4.54 (t, 1H), 3.5 (m, 1H), 3.3 (m, 2H), 3.14 (m, 2H), 1.90 (m, 1H), 1.60 (m, 1H); 1H NMR (360 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.79 (s, 1H), 3.84 (m, 1H), 3.74 (m, 1H), 3.52 (m, 1H), 3.32 (t, 2H), 2.59 (d, 1H), 1.98 (m, 3H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 190.3, 143.7, 142.1, 134, 127.5, 121.5, 119, 116.8, 70.3, 65.8, 37.5, 27.7; HRMS m/z calcd for $C_{12}H_{11}Cl_3N_2O_3$ 335.9834, found 335.9823. Anal. Calcd for $C_{12}H_{11}Cl_3N_2O_3 \cdot {}^1/_4H_2O$: C, 42.13; H, 3.39; N, 8.20. Found: C, 41.89; H, 3.14; N, 8.05.

2,6,7-Trichloro-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (3). Compound **19** (70 mg, 0.22 mmol) was dissolved in a 4:1 mixture of acetone and water (5 mL), and then *N*-methylmorpholine *N*-oxide (40 mg, 0.33 mmol) and osmium tetraoxide (150 μL of 2.5% OsO_4 in *tert*-butyl alcohol) were added. After stirring at rt for 16 h, Na_2HSO_3 (20 mL, concentrated aqueous solution) was added and the solution stirred for 1 h and then extracted with EtOAc (40 mL x 3). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a solid which was purified by flash chromatography (EtOAc/hexane 2:1, 10 cm × 2 cm). Fractions containing product were combined, concentrated to a solid, and crystallized from CH_3CN to give 73 mg (95%) of **3** as a white solid: mp 239−240 °C; R_f 0.30 (EtOAc/hexane 2:1); $[\alpha]^{20}_D$ = −232.7° (MeOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.06 (s, 1H), 5.41 (t, 1H, D_2O exchangeable), 5.13 (d, 1H, D_2O exchangeable), 5.10 (d, 1H, D_2O exchangeable), 5.02 (d, 1H, J = 9.1 Hz, 1′-H), 4.30 (m, 1H), 4.10 (m, 1H), 3.95 (m, 1H), 3.6−3.7 (m, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 141.8, 136, 129.6, 126.3, 118.9, 116.9, 116.5, 86.4, 74.6, 71.3, 71, 61.40; UV λ_{max} (MeOH) 325 (1555), 245 (11652), 238 (9935), 229 (8194); (pH 11) 295 (8226), 243 (61612), 335 (58064), 230 (48710); (pH 1) 294 (12290), 236 (59225); HRMS m/z calcd for $C_{12}H_{11}Cl_3N_2O_4$ 351.9783, found 351.9771. Anal. Calcd for $C_{12}H_{11}Cl_3N_2O_4$: C, 40.73; H, 3.14; N, 7.92. Found: C, 40.76; H, 3.07; N, 7.89. Structure and absolute stereochemistry of **3** was determined by X-ray crystallography.

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Supporting Information Available: An ORTEP diagram of **18** and crystallographic data for **18** and **3** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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