Synthesis of 2,6-disubstituted pyridin-3-yl C-2′-deoxyribonucleosides through chemoselective transformations of bromo-chloropyridine C-nucleosides†

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2-Bromo-6-chloro- and 6-bromo-2-chloropyridin-3-yl deoxyribonucleosides were prepared by the Heck coupling of bromo-chloro-iodopyridines with TBS-protected deoxyribose glycal. Some of their Pd-catalyzed cross-coupling reactions proceeded chemoselectively at the position of the bromine, whereas nucleophilic substitutions were unselective and gave mixtures of products. The mono-substituted intermediates were used for another coupling or nucleophilic substitution giving rise to a small library of title 2,6-disubstituted pyridine C-deoxyribonucleosides. The title nucleosides did not exert antiviral or cytostatic effects.

Introduction

C-Nucleosides are important analogues of natural nucleosides useful for many applications in medicinal chemistry and chemical biology.1 Diverse aryl and hetaryl-C-2′-deoxyribonucleosides were extensively studied as candidates for novel base-pairs in the quest for extension of the genetic alphabet and some of their artificial base-pairs were efficiently replicated by DNA polymerases with high fidelity.2 Moreover, some pyridine C-nucleosides have been used as probes for studying the mechanism of polymerases.3 Most of the current approaches to the synthesis of C-nucleosides suffer from moderate efficiency and/or stereoselectivity.1 Our group has developed a modular approach4 based on the synthesis of halogenated (het)aryl C-nucleoside intermediates and their functionalization by Pd-catalyzed cross-couplings, aminations, carboxylations or hydroxylations. Very recently, the same approach was used even for the functionalization of C-nucleoside triphosphate derivatives.5 Apart from the variation of one substituent, the synthesis of a 2D library of 2,4-disubstituted pyrimidin-5-yl C-2′-deoxyribonucleosides has been developed6 through two consecutive regioselective cross-coupling reactions of the corresponding 2,4-dichloropyrimidine C-nucleoside intermediate. Here we report on the synthesis of a series of 2,6-disubstituted pyridine C-nucleosides.

Results and discussion

In our previous synthesis of 2,4-disubstituted pyrimidine C-nucleosides,6 we have advantageously used the different reactivities of the two chlorines in 2,4-dichloropyrimidine for regioselective reactions. However, in the analogous 2,6-dichloropyridine C-nucleosides, the reactivity of the chlorines is comparable and thus no selectivity would be expected. Therefore our strategy for the target 2,6-disubstituted pyridin-3-yl C-2′-deoxyribonucleosides was based on chemoselective transformations7,8 of either 2-bromo-6-chloro- or 6-bromo-2-chloropyridin-3-yl C-deoxyribonucleoside intermediates.

The synthesis of both bromo-chloropyridine C-nucleoside intermediates started from 3′-O-TBS-protected glycal 1 which can be easily prepared in three steps from thymidine.9 The Heck coupling of 6-bromo-2-chloro-3-iodopyridine with glycal 1 in the presence of Pd(OAc)2, tris(pentafluorophenyl)phosphine and silver carbonate was performed in freshly distilled chloroform at 70 °C (Scheme 1). After 10 hours all starting material was consumed and, because partial desilylation was observed by TLC, the crude reaction mixture was directly treated with Et3N·3HF in THF to give fully deprotected ketone 2 in 52% yield (for two steps) as a pure β-anomer. The subsequent stereoselective reduction of 2 by NaBH(OAc)3 proceeded smoothly giving rise to the desired C-2′-deoxyribonucleoside intermediate 3 in very good 85% yield. The crystal
structure of 6-bromo-2-chloropyridine C-nucleoside 3 was determined by X-ray diffraction, which independently confirmed its β-configuration (Fig. 1). Re-protection of 3 by treatment with TBSCl gave the silylated C-nucleoside 4 in 78% yield. An analogous Heck coupling of 1 with 2-bromo-6-chloro-3-iodopyridine under the same conditions as above gave regioisomeric ketone 5 in 59% yield (for two steps) (Scheme 1).

Subsequent reduction by NaBH(OAc)₃ afforded C-2′-deoxyribonucleoside 6 in 87% yield, which was again silylated to give the desired protected nucleoside intermediate 7 in excellent 92% yield.

Having the free (3 and 6) as well as the protected (4 and 7) key bromo-chloropyridine C-nucleoside intermediates, we investigated the chemoselectivity of cross-coupling reactions and nucleophilic substitutions. The bromine atom should be more reactive than chlorine but, on the other hand, steric and other factors can also play a role.

The cross-coupling of protected 6-bromo-2-chloropyridine C-nucleoside 4 with 1.1 equiv. of Me₃Al in the presence of Pd(PPh₃)₄ proceeded chemoselectively to give 2-chloro-6-methylpyridine C-nucleoside 8a as the only product in excellent 87% yield (Scheme 2). When the same reaction was performed with 4 equiv. of Me₂Al and prolonged reaction time, the product of dissubstitution 9a was isolated in 80% yield. Deprotection of 8a and 9a with Et₃N·3HF afforded free C-nucleosides 8b (89%) and 9b (88%). The structure of free 2-chloro-6-methylpyridine C-nucleoside 8b was also confirmed by X-ray analysis (Fig. 1). In contrast, cross-coupling of the isomeric 2-bromo-6-chloropyridine intermediate 7 with 1.1 equivalents of Me₂Al was completely nonselective and only an unseparable mixture of the starting compound and both products of mono-substitution was obtained.

Mono-methylated 2-chloropyridine nucleoside 8a was used for a series of follow-up transformations (Scheme 2). The Sonogashira cross-coupling with trimethylsilyletylene catalyzed by Pd(PPh₃)₄Cl₂ followed by ammonolysis afforded C-2′-deoxyribonucleoside 6 in 87% yield, which was again silylated to give the desired protected nucleoside intermediate 7 in excellent 92% yield.

The Suzuki-Miyaura cross-coupling of 2-bromo-6-chloropyridine C-nucleoside 7 with 0.9 equivalent of phenylboronic acid in the presence of Ph(PPh₃)₄ at 60 °C proceeded chemoselectively at position 2 by displacement of the bromine to afford
6-chloro-2-phenylpyridine C-nucleoside 13a in 63% yield (Scheme 3). When we used 3 equiv. of phenylboronic acid and increased the temperature to 100 °C, 2,6-diphenylpyridine C-nucleoside 14a was obtained as a product of double substitution in excellent 95% yield. An analogous reaction of regioisomeric 6-bromo-2-chloropyridine C-nucleoside 4 with 1 equiv. of phenyl boronic acid afforded an unseparable mixture of the starting compound with the product of substitution of the bromine atom at position 6. Silylated nucleosides 13a and 14a were deprotected using Et₃N·3HF to obtain free C-nucleosides 13b (91%) and 14b (81%).

Mono-substituted 6-chloro-2-phenylpyridine C-nucleoside 13a was then used for subsequent cross-coupling reactions. Hartwig–Buchwald amination with LiN(SiMe₃)₂ gave 6-amino-2-phenylpyridine C-nucleoside 15a in excellent 91% yield. Cross-coupling with trimethylaluminum afforded 6-methyl-2-phenylpyridine C-nucleoside 16a in excellent 91% yield. Deprotection of silylated intermediates gave free C-nucleosides 15b (67%) and 16b (83%).

In order to introduce amino or methoxy groups, we have studied the reactivity of intermediates 3 and 6 in nucleophilic substitutions. Our previous studies showed good regioselectivity of nucleophilic aminations of 2,4-dichloropyrimidine C-nucleoside. Therefore, we tested reactions of 3 or 6 with methanolic ammonia or copper(i)-catalyzed reaction with liquid ammonia in an autoclave using temperatures up to 120 °C but in all cases only the starting material was recovered and we did not observe any reaction. Surprisingly, attempted Buchwald–Hartwig aminations of protected intermediates 4 or 7 did not work either. Nucleophilic substitution of 6 with NaOMe proceeded only at elevated temperature (80 °C) to give an unseparable mixture of the starting compound and both mono-substituted derivatives. The same reaction at higher temperature (120 °C) led to complex mixtures. It seems that the mono-substituted intermediates (containing an electron-donating substituent) are deactivated for another nucleophilic substitution.

Next we studied nucleophilic substitutions with sodium methanethiolate (Scheme 4). The reaction of silylated intermediate 4 with 10 equivalents of NaSMe in DMF at 80 °C led to double substitution with simultaneous deprotection (due to basic conditions) affording 2,6-bis(methylsulfanyl)pyridine C-nucleoside 17 in good 79% yield. The reaction of 4 with 1.2 equivalents of sodium methanethiolate at rt in DMF gave a mixture of both mono-substituted derivatives 18a and 19a in the ratio ca. 1 : 1. Luckily, we were able to separate them using the flash purification system with a very slow gradient of hexanes to 1% EtOAc in hexanes to obtain 2-chloro-6-(methylsulfanyl)pyridine C-nucleoside 18a (48%) and 6-bromo-2-(methylsulfanyl)pyridine C-nucleoside 19a (43%). Pd-catalyzed
methylation of compounds 18a or 19a with trimethylaluminum gave two regioisomeric methyl-(methylsulfanyl)pyridine C-nucleosides 20a (49%) and 21a (58%). All silylated compounds were deprotected to a free C-nucleosides 18b–21b.

Attempted Sonogashira chemoselective cross-couplings of 4 with (trimethylsilyl)acetylene (TMSA) (Scheme 5) were very difficult to perform since the desired 2-chloro-6-(TMS-ethynyl)pyridine C-nucleoside was unseparable from starting intermediate 4. Finally, we found out that Sonogashira cross-coupling with 1 equiv. of trimethylsilylacetylene catalyzed by Pd(PPh3)2Cl2 followed by direct amonolysis gave us a separable mixture of starting compound 4 (37%) and desired product 22a in acceptable 53% yield. When we performed the same reaction with the excess of trimethylsilylacetylene (10 equiv.) and increased the temperature to 70 °C, 12 h.

Scheme 4 Reagents and conditions: (i) MeSnNa 10 equiv., DMF, 80 °C, 12 h; (ii) MeSnNa 1.2 equiv., DMF, rt, 12 h; (iii) Et3N·3HF, THF, rt, 14 h; (iv) Me3Al, Pd(PPh3)4, 90 °C, 12 h.

Unfortunately, only deprotection was observed despite having tried many different conditions.

The Stille cross-coupling reaction was used for the synthesis of bipyridine and terpyridine C-nucleosides (Scheme 6). The reaction of 4 with tributyl[2-pyridyl]stannane catalyzed by PdCl2(PPh3)2 gave only compound 24a, as a product of chemoselective replacement of the bromine atom, in very good 82% yield even when we used 2 equiv. of stannane. The palladium catalyst is probably strongly coordinated to the bipyridine scaffold and any second reaction is prevented. In contrast, the Stille cross-coupling catalyzed by Pd(PPh3)4 cleanly afforded terpyridine C-nucleoside 25a, as a product of double substitution, in excellent 92% yield. Deprotection gave bi- and terpyridine C-nucleosides 24b and 25b which could be used in metalla-base pairs.14

Finally, we attempted to introduce a vinyl group by Fürstner’s Fe-catalyzed cross-coupling reaction15 with vinylmagnesium bromide (Scheme 7). Unfortunately the cross-coupling did not proceed and, instead, the magnesiation of the bromopyridine occurred which, after hydrolytic work-up, gave chloropyridine 26a, as a product of debromination, in moderate 47% yield. Also this compound was deprotected to free nucleoside 26b.

All the title free nucleosides were subjected to biological activity screening. The cytotoxic activity in vitro was studied on
the following cell cultures: (i) human promyelocytic leukemia HL60 cells (ATCC CCL 240); (ii) human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2); (iii) human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119), and (iv) hepatocellular carcinoma cells HepG2 (ATCC HB 8065). Cell viability was determined following a 3-day incubation using a metabolic 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) based method.\textsuperscript{16} The antiviral activity was tested against HCV genotype 1A, 1B and 2A replicons.\textsuperscript{17} None of the nucleosides showed any significant cytotoxicity or antiviral activity in these assays at concentrations up to 10 μM.

Conclusions

Systematic study of the chemoselectivity of cross-coupling reactions and nucleophilic substitutions of regioisomeric 2-bromo-6-chloro- and 6-bromo-2-chloropyridin-3-yl deoxyribo-nucleosides 7 and 4 was performed. The cross-couplings generally proceeded with good chemoselectivity at the position of the bromine but the choice of the starting compound depended on the separability of the mono-substituted products from the starting compound. On the other hand, nucleophilic substitution with NaSMe was unselective giving a separable mixture of both mono-substituted products, whereas the reactions with ammonia or NaOMe did not proceed or led to complex mixtures (at elevated temperature). The mono-substituted halo-pyridine C-nucleoside intermediates were used for another coupling or S\textsubscript{N} to give a small library of 2,6-disubstituted pyridin-3-yl C-deoxyribonucleosides. None of the title nucleosides exerted any antiviral or cytostatic activity in concentrations up to 10 μM. Some of the disubstituted pyridine nucleosides will be converted to triphosphates and further tested for polymerase incorporation in the quest for the extension of the genetic alphabet.\textsuperscript{2}

Experimental

All cross-coupling reactions were carried out in evacuated flame-dried glassware with magnetic stirring under an argon atmosphere. THF, toluene, and hexanes were dried and distilled from sodium–benzophenone. Other reagents were purchased from commercial suppliers and used as received. NMR
spectra were recorded on a 400 MHz spectrometer (1H at 400 MHz, 13C at 100.6 MHz), a 500 MHz spectrometer (1H at 500 and 13C MHz at 125.8), and/or a 600 MHz spectrometer (1H at 600 MHz, 13C at 151 MHz). The samples were measured in CDCl₃ using TMS as an internal standard or in DMSO-d₆ referenced to the residual solvent signal (1H NMR δ 2.50 ppm, 13C NMR 39.7 ppm). Chemical shifts are given in ppm (δ scale) and coupling constants (J) in hertz. Complete assignment of all NMR signals was performed using a combination of 2D-NMR (H,H-COSY, H,C-HSQC, and H,C-HMBC) experiments and configurations were established by two-dimensional ROESY spectra. High performance flash chromatography (HFPC) purifications were performed with Biotage SP1 apparatus on KP-Sil and KP-C18-HS columns. Cytostatic and anti-HCV activity screening was performed according to literature procedures.

**General procedure for the deprotection of the TBDMS group**

Et₃N·3HF (320 µL, 1.95 mmol) was added to a solution of silylated C-nucleoside (0.44 mmol) in THF (2 mL), and the mixture was stirred at room temperature for 14 h. After the reaction was completed (TLC in hexanes–EtOAc 10:1), solvents were removed under reduced pressure, and the crude product was chromatographed on silica gel (20 g) eluted with a gradient of chloroform to 15% MeOH in chloroform to give free C-nucleosides.

1H-(6-Bromo-2-chloropyridin-3-yl)-1,2-dideoxy-3,5-di-O-(tet-butyl-dimethylsilyl)-o-ribofuranose (4). Imidazole (1.27 g, 18.6 mmol) and then TBDMSCI (4.49 mg, 29.8 mmol) were added to a flame-dried flask containing a solution of the nucleoside 3 (2.3 g, 7.45 mmol) in dry DMF (50 mL) at 0 °C under argon and the solution was allowed to warm to room temperature and was stirred for 14 h. The reaction mixture was then poured into a saturated solution of NaCl (100 mL) and extracted with EtOAc (3 × 30 mL). Collected organic fractions were washed with a saturated NaCl solution, dried over MgSO₄, and the solvents were evaporated under vacuum. The crude product was chromatographed on silica gel in a gradient of hexanes to 5% EtOAc in hexanes to give the desired nucleoside 4 (3.1 g, 78%) as a colorless oil. HRMS (ESI) for C₂₂H₂₄BrCl₃NO₅S₂ [M + H] calculated, 536.1413; found, 536.1413. 1H NMR (500 MHz, CDCl₃): 3093, 3060, 2956, 2897, 1575, 1545, 1472, 1463, 1424, 1407, 1390, 1362, 1257, 1223, 1098, 1030, 1006, 939, 838, 671.
1-{(3-Bromo-6-chloropyridin-3-yl)-2,3-trideoxy-3-oxo-α-ribofuranose (5).} Freshly distilled CHCl₃ (18 mL) was added to an argon-purged, flame-dried flask containing Pd(OAc)₂ (562 mg, 2.34 mmol) and P(Ph₃)₃ (2.49 g, 4.69 mmol), and the mixture was stirred at room temperature for 30 min. This solution was then added via a syringe to a mixture of 2-{(3-bromo-6-chloro-3-iodopyridine (4.48 g, 14.06 mmol), glycal (1.27 g, 11.72 mmol) and Ag₂CO₃ (4.83 g, 17.58 mmol) in CHCl₃ (18 mL), and the reaction mixture was stirred at 70 °C for 10 h. The reaction mixture was then cooled and filtered on a pad of Celite and eluted with CHCl₃. Solvents were then removed in vacuum, and the crude product was dissolved in THF (100 mL), Et₃N-3HF (3 mL; 18.5 mmol) was added and the solution was stirred at rt for 15 min. The solvents were removed under vacuum, and the crude product was chromatographed on silica gel eluting with a gradient of chloroform to 1% MeOH in chloroform to give 5 (2.12 g, 59% for two steps) as a yellow foam. HRMS (ESI) for C₁₈H₁₄BrClN₂O₄Si [M + H] calculated, 536.1413; found, 536.1412. ¹H NMR (500 MHz, CDCl₃) 0.85, 0.89 and 0.10 (4 × s, 4 × 3H, CH₃Si); 0.90 and 0.91 (2 × s, 2 × 9H, (CH₃)₃C); 1.68 (dd, 1H, J₆,₅ = 12.6 Hz, J₅,₄ = 9.4 Hz, J₄,₃ = 5.6 Hz, H-2'α); 2.45 (dd, 1H, J₆,₅ = 12.6 Hz, J₅,₄ = 5.9 Hz, J₄,₃ = 2.6 Hz, H-2'β); 3.72 (dd, 1H, J₆,₅ = 10.9 Hz, J₄,₃ = 4.5 Hz, H-2'α); 5.37 (dd, 1H, J₆,₅ = 9.0 Hz, J₄,₃ = 3.3 Hz, H-2'β); 3.97 (dd, 1H, J₆,₅ = 3.3 Hz, J₅,₄ = 2.6 Hz, H-3'); 4.38 (bddd, 1H, J₆,₅ = 5.6 Hz, J₅,₄ = 2.7 Hz, J₄,₃ = 0.6 Hz, H-3'); 5.31 (ddq, 1H, J₆,₅ = 9.4 Hz, J₄,₃ = 5.9 Hz, J₅,₄ = 9.4 Hz, J₄,₃ = 0.6 Hz, H-1'); 7.26 (dd, 1H, J₆,₅ = 8.1 Hz, J₄,₃ = 0.6 Hz, H-5'); 7.95 (dd, 1H, J₆,₅ = 8.1 Hz, J₄,₃ = 0.7 Hz, H-4'). ¹³C NMR (125.7 MHz, CDCl₃): −5.50, −5.42, −4.76 and −4.62 (4 × CH₃Si); 17.98 and 18.28 [(CH₃)₃C]; 25.74 and 25.87 [(CH₃)₃C]; 42.47 (CH₂-2'); 63.21 (CH₂-5'); 73.65 (CH-3'); 77.50 (CH-1'); 88.00 (CH-4'); 123.41 (CH-5'); 138.08 (CH-4'); 139.00 and 139.07 (C-2',3); 148.66 (C-6). IR spectrum (CCL₃): 3093, 3059, 2956, 2897, 1577, 1545, 1472, 1463, 1406, 1390, 1362, 1278, 1258, 1097, 939, 891, 838.

1-{(2-Chloro-6-methylpyridin-3-yl)-1,2-dideoxy-3,5-di-O-α-(t-butyldimethylsilyl)-α-ribofuranose (8a).} Me₃Al (1.5 mL, 1.5 mmol, 1.1 equiv, 1 M in heptane) was added to a flame-dried flask containing 4 (729 mg, 1.36 mmol) and Pd(PPh₃)₄ (161 mg, 0.14 mmol, 10 mol%) under argon. The solution was stirred at 70 °C for 3 h, quenched by pouring into saturated NaHPO₄ (50 mL), and extracted with EtOAc (3 × 50 mL). The crude product was chromatographed on silica gel eluting with a gradient of hexanes to 5% EtOAc in hexanes to give 8a (555 mg, 87%) as a colorless oil. HRMS (ESI) for C₂₃H₂₄ClNO₃SiCl₂ [M + H] calculated, 472.2465; found, 472.2465. ¹H NMR (500 MHz, CDCl₃) 0.83, 0.85, 0.87, and 0.93 (4 × s, 4 × 3H, CH₃Si); 0.90 and 0.91 (2 × s, 2 × 9H, (CH₃)₃C); 1.70 (dd, 1H, J₆,₅ = 12.7 Hz, J₅,₄ = 9.5 Hz, J₄,₃ = 5.6 Hz, H-2'α); 2.40 (dd, 1H, J₆,₅ = 12.7 Hz, J₅,₄ = 5.8 Hz, J₄,₃ = 2.5 Hz, H-2'β); 2.51 (s, 3H, CH₃); 3.69 (dd, 1H, J₆,₅ = 10.8 Hz, J₄,₃ = 4.9 Hz, H-2'α); 3.77 (dd, 1H, J₆,₅ = 10.8 Hz, J₄,₃ = 3.5 Hz, H-2'β); 3.96 (dd, 1H, J₆,₅ = 4.9 Hz, J₄,₃ = 3.5 Hz, H-3'); 4.38 (bddd, 1H, J₆,₅ = 5.6 Hz, J₅,₄ = 2.6 Hz, J₄,₃ = 0.7 Hz, H-3'); 5.37 (bddd, 1H, J₆,₅ = 9.5 Hz, J₄,₃ = 0.8 Hz, H-4'). ¹³C NMR (125.7 MHz, CDCl₃): −5.48, −5.42, −4.76 and −4.62 (CH₃Si); 17.98 and 18.29 [(CH₃)₃C]; 23.71 (CH₃); 25.76 and 25.88 [(CH₃)₃C]; 42.42 (CH₂-2'); 63.33 (CH₂-5'); 73.73 (CH-3'); 76.14 (CH-1'); 87.74 (CH-4'); 122.18
56.10 (CH-4); 157.50 (C-6). IR spectrum (125.7 MHz, CD2OD): 21.20 (CH2); 23.30 (CH6); 43.24 (CH2); 63.84 (CH2); 74.32 (CH2); 77.38 (CH2); 89.01 (CH2); 122.59 (CH3); 134.68 (C-3); 155.88 (C-4); 150.9 (C-5); 157.15 (C-6). IR spectrum (KBr): 3307, 1598, 1583, 1476, 1453, 1318, 1281, 1142, 1058, 1031, 976, 961.

1β-(2-Chloro-6-methylpyridin-3-yl)-1,2-dideoxy-α-ribofuranose (10b). Compound 10b was prepared from 10a (97 mg, 0.11 mmol) by the general procedure to yield 10b (32 mg, 63%) as a yellow foam. HRMS (ESI) for C12H13NO5Si: [M + Na] calculated, 256.0944; found, 256.0944. 1H NMR (500 MHz, DMSO-d6): 3.85 (tdd, 1H, J = 8.1 Hz, H-5); 5.93 (dd, 1H, J = 11.2 Hz, H-4); 4.37 (ddt, 1H, J = 5.2 Hz, H-5, H-4); 3.72 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.72 (dd, 1H, J = 10.9 Hz, H-4); 4.03 (dd, 1H, J = 11.2 Hz, H-4); 3.94 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.55 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.48 (dd, 1H, J = 11.2 Hz, H-4); 3.42 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.41 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.37 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.32 (dd, 1H, J = 11.2 Hz, H-4); 3.27 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.18 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.14 (dd, 1H, J = 11.2 Hz, H-4); 3.10 (dd, 1H, J = 10.9 Hz, H-5, H-4); 3.04 (dd, 1H, J = 11.2 Hz, H-4); 3.00 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.97 (dd, 1H, J = 11.2 Hz, H-4); 2.94 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.89 (dd, 1H, J = 11.2 Hz, H-4); 2.85 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.80 (dd, 1H, J = 11.2 Hz, H-4); 2.75 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.70 (dd, 1H, J = 11.2 Hz, H-4); 2.65 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.60 (dd, 1H, J = 11.2 Hz, H-4); 2.55 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.50 (dd, 1H, J = 11.2 Hz, H-4); 2.45 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.40 (dd, 1H, J = 11.2 Hz, H-4); 2.35 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.30 (dd, 1H, J = 11.2 Hz, H-4); 2.25 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.20 (dd, 1H, J = 11.2 Hz, H-4); 2.15 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.10 (dd, 1H, J = 11.2 Hz, H-4); 2.05 (dd, 1H, J = 10.9 Hz, H-5, H-4); 2.00 (dd, 1H, J = 11.2 Hz, H-4); 1.95 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.90 (dd, 1H, J = 11.2 Hz, H-4); 1.85 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.80 (dd, 1H, J = 11.2 Hz, H-4); 1.75 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.70 (dd, 1H, J = 11.2 Hz, H-4); 1.65 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.60 (dd, 1H, J = 11.2 Hz, H-4); 1.55 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.50 (dd, 1H, J = 11.2 Hz, H-4); 1.45 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.40 (dd, 1H, J = 11.2 Hz, H-4); 1.35 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.30 (dd, 1H, J = 11.2 Hz, H-4); 1.25 (dd, 1H, J = 10.9 Hz, H-5, H-4); 1.20 (dd, 1H, J = 11.2 Hz, H-4); 0.90 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.85 (dd, 1H, J = 11.2 Hz, H-4); 0.80 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.75 (dd, 1H, J = 11.2 Hz, H-4); 0.70 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.65 (dd, 1H, J = 11.2 Hz, H-4); 0.60 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.55 (dd, 1H, J = 11.2 Hz, H-4); 0.50 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.45 (dd, 1H, J = 11.2 Hz, H-4); 0.40 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.35 (dd, 1H, J = 11.2 Hz, H-4); 0.30 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.25 (dd, 1H, J = 11.2 Hz, H-4); 0.20 (dd, 1H, J = 10.9 Hz, H-5, H-4); 0.15 (dd, 1H, J = 11.2 Hz, H-4); 0.10 (dd, 1H, J = 10.9 Hz, H-5, H-4).
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1f-(2-Amino-6-methylpyridin-3-yl)-1,2-dideoxy-3,5-di-O-(t-butyl-dimethylsilyl)-α-ribofuranose (11a). LiN(SiMe3)2 (1.6 mL, 1.6 mmol, 3 equiv. 1.0 M solution in THF) was added to a flame-dried and argon-purged flask containing 8a (255 mg, 0.54 mmol), Ph2SiH2 (297 mg, 1.1 mmol), Pd2(dba)2 (28 mg, 0.027 mmol, 5 mol%), and (biphenyl-2-yl)dicyclohexylphosphine (38 mg, 0.11 mmol, 20 mol%), and the mixture was stirred at 50 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with Et2O (30 mL) and washed with 2 M HCl (10 mL) and 1 M NaOH (15 mL). The crude product was chromatographed on silica gel eluting with a gradient of hexanes to 17% EtOAc in hexanes to give 11a (167 mg, 68%) as a colorless oil. HRMS (ESI) for C21H24Na2O2Si2: [M + Na]+ calculated, 353.1407; found, 353.1408.

1H NMR (500 MHz, CDCl3) 0.07, 0.079, 0.081 and 0.089 (4 × s, 4 × 3H, CH3Si); 0.82 and 0.92 (2 × s, 2 × 9H, ((CH3)3C)); 1.81 (ddd, 1H, J = 12.8 Hz, Jα,β = 5.6 Hz, Jα,γ = 1.6 Hz, H-2α); 2.35 (s, 3H, CH3); 2.38 (ddd, 1H, J = 12.8 Hz, Jα,β = 10.8 Hz, Jα,γ = 6.5 Hz, H-2β); 3.77 (dd, 1H, J = 11.1 Hz, Jα,α = 2.4 Hz, H-5α); 3.83 (dd, 1H, J = 11.1 Hz, Jα,α = 3.0 Hz, H-5β); 3.90 (bd, 1H, Jα,β = 10.8 Hz, Jα,γ = 5.6 Hz, H-1); 5.31 (bs, 2H, NH2); 6.42 (bd, 1H, Jα,γ = 7.4 Hz, H-5); 7.19 (d, 1H, Jα,γ = 7.4 Hz, H-4). 13C NMR (125.7 MHz, CDCl3): −5.57, −5.51, −4.72 and −4.58 (CH3Si); 18.02 and 18.43 ((CH3)3C); 23.73 (CH3); 25.80 and 25.88 ((CH3)3C); 39.94 (CH2-2); 62.93 (CH3-5); 73.55 (CH3-3); 80.27 (CH-1′); 88.23 (CH-4′); 112.1 (CH-5); 114.81 (C-3); 137.04 (CH-4′); 155.94 (C-6); 156.38 (C-2). IR spectrum (CCl4): 3488, 3372, 3062, 2956, 2930, 2896, 2585, 1609, 1595, 1582, 1472, 1463, 1445, 1408, 1390, 1374, 1362, 1258, 1097, 1006, 938, 837.

1f-(2-Amino-6-methylpyridin-3-yl)-1,2-dideoxy-3,5-di-O-(t-butyl-dimethylsilyl)-α-ribofuranose (11b). Compound 11b was prepared from 11a (97 mg, 0.11 mmol) by the general procedure to yield 11b (85 mg, 82%) as a yellow solid. HRMS (ESI) for C14H14Na2O2Si: [M + H]+ calculated, 255.1234; found, 255.1234. 1H NMR (500 MHz, DMSO-d6): 1.88 (ddd, 1H, J = 12.7 Hz, Jα,β = 5.6 Hz, Jα,γ = 1.8 Hz, H-2α); 2.03 (ddd, 1H, J = 12.7 Hz, Jα,β = 10.5 Hz, Jα,γ = 6.3 Hz, H-2β); 2.21 (s, 3H, CH3); 3.50 (ddd, 1H, J = 11.5 Hz, Jα,α = 5.4 Hz, Jα,γ = 3.9 Hz, H-5α); 3.54 (ddd, 1H, J = 11.5 Hz, Jα,α = 4.9 Hz, Jα,β = 3.6 Hz, H-5β); 3.73 (dd, 1H, Jα,α = 5.6 Hz, Jα,β = 3.8 Hz, H-3); 4.20 (m, 1H, H-3′); 5.49 (dd, 1H, Jα,γ = 10.5 Hz, Jα,β = 5.6 Hz, H-1); 5.91 (t, 1H, Jα,γ = 5.2 Hz, H-5′); 5.02 (d, 1H, Jα,α = 4.1 Hz, OH-3′); 5.76 (bs, 2H, NH2); 6.34 (bddd, 1H, Jα,γ = 7.4 Hz, Jα,α = 0.6 Hz, H-5); 7.26 (bd, 1H, Jα,α = 7.4 Hz, H-4). 13C NMR (125.7 MHz, DMSO-d6): 23.68 (CH3); 39.76 (CH2-2); 61.72 (CH2-5); 72.13 (CH3-3); 78.13 (CH-1′); 87.82 (CH-4′); 111.08 (CH-115.60 (C-3); 135.83 (CH-4′); 150.00 (C-6); 156.60 (C-2). IR spectrum (KBr): 3393, 3317, 3200, 3139, 3086, 2951, 2919, 2773, 1626, 1595, 1587, 1444, 1379, 1347, 1328, 1281, 1185, 1100, 1081, 1042, 977, 938, 831.

1f-(2-Methoxy-6-methylpyridin-3-yl)-1,2-dideoxy-3,5-di-O-(t-butyldimethylsilyl)-α-ribofuranose (12). MeONa (605 mg, 11 mmol) was added to a solution of the nucleoside 8b (53 mg, 0.22 mmol) in methanol (10 mL) and the mixture was stirred for 10 days at 120 °C. Then the solvents were evaporated under vacuum. The crude product was chromatographed on silica gel in a gradient of chloroform to 6% MeOH in chloroform to give 12 (40 mg, 77%) as a white solid. HRMS (ESI) for C17H17NO3: [M + Na]+ calculated, 262.1050; found, 262.1050. 1H NMR (500 MHz, CD3OD): 1.77 (ddd, 1H, J = 13.1 Hz, Jα,β = 10.2 Hz, Jα,γ = 6.0 Hz, H-2α); 2.31 (ddd, 1H, J = 13.1 Hz, Jα,β = 5.6 Hz, Jα,γ = 1.9 Hz, H-2β); 2.40 (s, 3H, CH3); 3.64 (dd, 1H, J = 11.6 Hz, Jα,α = 5.1 Hz, H-5′); 3.66 (dd, 1H, J = 11.6 Hz, Jα,β = 5.2 Hz, H-5′); 3.91 (s, 3H, CH3); 3.92 (td, 1H, Jα,α = 5.2 Hz, Jα,γ = 2.7 Hz, H-4′); 4.27 (ddd, 1H, Jα,β = 6.0 Hz, Jα,γ = 2.7 Hz, H-4′); 0.67 (dm, 1H, J = 7.4 Hz, H-5′); 7.71 (dd, 1H, Jα,γ = 7.4 Hz, H-1′); 8.26 (s, 1H, CH2O). 13C NMR (125.7 MHz, CD3OD): 36.79 (CH2-2); 42.93 (CH2-4); 53.54 (CH2O-2); 64.01 (CH2-5); 74.32 (CH3-3); 76.08 (CH-1′); 88.69 (CH4-4′); 118.38 (CH-5); 129.92 (C-3); 136.38 (CH-4′); 155.78 (C-6); 161.26 (C-2). IR spectrum (KBr): 3386, 3079, 2988, 2951, 2923, 2853, 1603, 1588, 1461, 1444, 1383, 1327, 1246, 1192, 1116, 1089, 1082, 1049, 1031, 966, 942, 821.

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1β-(6-Chloro-2-phenylpyridin-3-yl)-1,2-dideoxy-α-ribofuranose (13b). Compound 13b was prepared from 13a (160 mg, 0.30 mmol) by the general procedure to yield 13b (84 mg, 91%) as a white solid. HRMS (ESI) for C_{22}H_{21}NO_{3}: [M + H] calculated, 348.1594; found, 348.1593. 1H NMR (500 MHz, CD3OD): 2.06 (dd, 1H, J_{gem} = 3.2 Hz, J_{2x,y} = 5.8 Hz, H_{2x,y}); 2.00 (H-2, 6H); 1.84-1.67 (m, 2H, H-3, H-2); 1.29 (CH3Si); 0.82 and 0.93 (2 × s, 2 × 9H, ((CH3)3C)); 1.91 (dd, 1H, J_{gem} = 12.7 Hz, J_{2x,y} = 10.2 Hz, J_{2x,y}′ = 5.4 Hz, H-2′); 2.03 (H-2, 6H); 1.86 and 1.91 (2 × s, 2 × 9H, ((CH3)3C)); 0.93 (dd, 1H, J_{gem} = 12.5 Hz, J_{2x,y} = 5.3 Hz, J_{2x,y}′ = 1.9 Hz, H-2′); 3.8 (H-4). 13C NMR (125.7 MHz, CD3OD): 2.06 (dd, 1H, J_{gem} = 3.2 Hz, J_{2x,y} = 5.8 Hz, H_{2x,y}); 129.57 (C-6); 128.59 (C-2, m, CH2-2); 128.03 (C-3); 127.59 (C-1); 126.92 (C-3′); 126.74 (C-2′); 117.19 (C-1′); 114.23 (CH3Si); 113.82 (C-4); 110.06 (C-4′); 68.42 (CH-3); 41.35 (CH-2); 32.34 (CH2-2); 23.82; 22.95; 15.23 (CH3). IR spectrum (KBr): 3412, 3084, 3061, 3031, 1574, 1534, 1505, 1497, 1461, 1408, 1388, 1361, 1257, 1087, 1027, 1006, 939, 838.

1β-(2,6-Diphenylpyridin-3-yl)-1,2-dideoxy-α-ribofuranose (14b). Compound 14b was prepared from 14a (205 mg, 0.36 mmol) by the general procedure to yield 14b (100 mg, 81%) as a white solid. HRMS (ESI) for C_{22}H_{21}NO_{3}: [M + H] calculated, 348.1594; found, 348.1593. 1H NMR (500 MHz, CD3OD): 2.06 (dd, 1H, J_{gem} = 13.2 Hz, J_{2x,y} = 10.1 Hz, J_{2x,y}′ = 5.9 Hz, H-2′); 2.00 (H-2, 6H); 1.84-1.67 (m, 2H, H-3, H-2); 1.29 (CH3Si); 0.82 and 0.93 (2 × s, 2 × 9H, ((CH3)3C)); 1.91 (dd, 1H, J_{gem} = 13.2 Hz, J_{2x,y} = 5.8 Hz, J_{2x,y}′ = 2.0 Hz, H-2′); 3.70 (m, 1H, H-5′); 3.72 (m, 1H, H-5′); 3.85 (btd, 1H, J_{3′,4′} = 10.7 Hz, J_{4′,5′} = 10.7 Hz, J_{4′,5′} = 1.9 Hz, H-4). 13C NMR (125.7 MHz, CD3OD): 2.06 (dd, 1H, J_{gem} = 3.2 Hz, J_{2x,y} = 5.8 Hz, H_{2x,y}); 129.57 (C-6); 128.59 (C-2, m, CH2-2); 128.03 (C-3); 127.59 (C-1); 126.92 (C-3′); 126.74 (C-2′); 117.19 (C-1′); 114.23 (CH3Si); 113.82 (C-4); 110.06 (C-4′); 68.42 (CH-3); 41.35 (CH-2); 32.34 (CH2-2); 23.82; 22.95; 15.23 (CH3). IR spectrum (KBr): 3412, 3084, 3061, 3031, 1574, 1534, 1497, 1461, 1408, 1388, 1361, 1257, 1087, 1027, 1006, 939, 838.
1f-(6-Methyl-2-phenylpyridin-3-yl)-1,2-dideoxy-o-ribofuranose (16b). Compound 16b was prepared from 16a (144 mg, 0.28 mmol) by the general procedure to yield 16b (68 mg, 85%) as a white solid. HRMS (ESI) for C36H52NO5SSi2 [M + H] calculated, 586.4138; found, 586.4138. 1H NMR (500 MHz, CD3OD): 1.93 (ddd, 1H, Jgem = 13.2 Hz, J2a,1 = 10.2 Hz, J2b,1 = 5.9 Hz, H-2a); 1.99 (ddd, 1H, Jgem = 13.2 Hz, J2b,1 = 5.8 Hz, J2b,2 = 1.9 Hz, H-2b); 2.54 (s, 3H, CH3-6); 3.64-3.71 (m, 2H, H-5'); 3.80 (ddd, 1H, J2a,5b = 5.0 Hz, J2b,5b = 4.5 Hz, J2b,4 = 2.7 Hz, H-4'); 4.27 (ddd, 1H, J2a,5b = 6.0 Hz, J2b,5b = 2.7 Hz, J2b,4 = 2.7 Hz, H-4'); 5.10 (ddd, 1H, J2b,1 = 10.2 Hz, J2b,2 = 5.8 Hz, H-1'); 7.32 (bd, 1H, Jgem = 8.1 Hz, H-5); 7.42 (m, 2H, H-2, H-3, H-4); 7.43-7.51 (m, 3H, H-m-p-Ph); 8.09 (d, 1H, Jgem = 8.1 Hz, H-4'). 13C NMR (125.7 MHz, CD3OD): 23.38 (CH3-6); 44.85 (CH2-5); 63.82 (CH3-5'); 74.36 (CH3-6'); 77.47 (CH1-4); 89.02 (CH2-4); 124.14 (CH5-4); 129.40 (CH-m-Ph); 129.52 (CH-p-Ph); 130.11 (CH-Ph); 134.25 (C-3); 137.65 (H-4); 140.70 (C-Ph); 158.02 (C-6); 158.29 (C-2). IR spectrum (KBr): 1595, 1573, 1496, 1476, 1447, 1380, 1311, 1146, 1086, 1040, 961.

1f-(2,6-Bis(methylsulfanyl)pyridin-3-yl)-1,2-dideoxy-o-ribofuranose (17). MeSnA (59 mg, 0.84 mmol) was added to a solution of the nuclease 4 (45 mg, 0.084 mmol) in DMF (2 mL) and the mixture was stirred for 12 h at 80 °C. Then the solvents were evaporated under vacuum. The crude product was chromatographed on silica gel in a gradient of chloroform to 7% MeOH in chloroform to give 17 (19 mg, 79%) as a pale yellow solid. HRMS (ESI) for C32H43NO3S3Si [M + Na] calculated, 310.0542; found, 310.0542. 1H NMR (500 MHz, CDCl3): 1.75 (ddd, 1H, Jgem = 13.1 Hz, J2a,1 = 10.1 Hz, J2a,3 = 6.0 Hz, H-2a); 2.36 (ddd, 1H, Jgem = 13.1 Hz, J2b,1 = 5.6 Hz, J2b,2 = 2.0 Hz, H-2b); 2.57 (s, 3H, CH3-S); 2.59 (s, 3H, CH3-S'); 3.67-3.70 (m, 7H, H-5') 3.92 (bd, 1H, J2a,4 = 4.9 Hz, J2b,4 = 2.8 Hz, H-4'); 4.30 (ddd, 1H, J2b,1 = 6.1 Hz, J2b,2 = 2.8 Hz, J2b,3 = 0.7 Hz, H-3'); 5.27 (ddq, 1H, J2a,1 = 10.1 Hz, J2b,2 = 5.6 Hz, J2a,1 = J1b,1 = 0.7 Hz, H-1'); 6.93 (bd, 1H, Jgem = 8.1 Hz, J2b,1 = 0.8 Hz, H-5); 7.65 (dd, 1H, Jgem = 8.1 Hz, J1b,1 = 0.8 Hz, H-4'). 13C NMR (125.7 MHz, CDCl3): 11.46 and 11.56 (CH3-S, S'); 41.24 (CH2-S); 62.13 (CH2-S'); 72.62 (CH-S); 75.06 (CH-S'); 87.16 (CH-4'); 115.88 (CH5-3); 130.16 (C-3); 132.32 (CH-4'); 155.15 (C-2); 157.48 (C-6). IR spectrum (KBr): 3411, 2989, 2924, 1565, 1430, 1418, 1335, 1308, 1217, 1049, 962, 840, 778.

1f-(2-Chloro-6-(methylsulfanyl)pyridin-3-yl)-1,2-dideoxy-o-ribofuranose (18a). MeSnA (48 mg, 0.69 mmol, 1.2 equiv.) was added to a solution of the nuclease 4 (310 mg, 0.58 mmol) in DMF (5 mL) and the mixture was stirred for 12 h at rt. Then the solvents were evaporated under vacuum. The crude product was purified using high performance flash chromatography with a gradient of hexanes to 1% EtOAc in hexanes to give products 18a (141 mg, 48%) as a white solid and 19a (136 mg, 43%) as a white solid. Compound 18a: HRMS (ESI) for C32H43ClNO3S3Si [M + H] calculated, 504.2185; found, 504.2183. 1H NMR (500 MHz, CDCl3): 0.88, 0.84 and 0.09 (4 x s, 4 x 3H, CH3-Si); 0.90 and 0.91 (2 x s, 2 x 9H, [(CH3)2C]); 1.70 (ddd, 1H, Jgem = 12.7 Hz, J2b,1 = 9.5 Hz, J2a,4 = 5.6 Hz, H-2a); 2.37 (ddd, 1H, Jgem = 12.7 Hz, J2b,1 = 5.9 Hz, J2b,3 = 2.5 Hz, H-2b); 2.56 (s, 3H, CH3-S); 3.69;
5.7 Hz, 5.7 Hz, J = 5.6 Hz, H-3); 4.8 Hz, J = 4.8 Hz, 2.7 Hz, H-4); 4.31 (ddd, 1H, J = 4.8 Hz, J = 5.0 Hz, H-5); 3.70 (ddd, 1H, J = 11.8 Hz, J = 5.6 Hz, H-6); 2.42 (dd, 1H, J = 5.6 Hz, H-2); 1.98 (s, 3H, CH3-Si); 1.76 (s, 3H, CH2-3); 0.99 (s, 3H, CH2-4); 0.91 (s, 3H, CH3-5). HRMS (ESI) for C12H17NO3S: [M + H] calculated, 295.08; found, 295.07. 1H NMR (500 MHz, CDCl3): 1.91 (t, 3H, CH3); 1.88 (ddd, 1H, J = 6.0 Hz, 8.0 Hz, 2.8 Hz, H-4); 1.62 (ddd, 1H, J = 9.0 Hz, 9.0 Hz, 2.8 Hz, H-3); 1.59 (t, 3H, CH3); 1.47 (ddd, 1H, J = 11.8 Hz, 5.6 Hz, H-1); 1.38 (m, 2H, CH2-5); 1.2 (m, 2H, CH2-6); 0.9 (t, 3H, CH3). IR spectrum (KBr): 3333, 3284, 1048, 1585, 1576, 1435, 1217, 1219, 957, 832.

1-[6-Bromo-2-(methylsulfonyl)pyridin-3-yl]-1,2-dideoxy-3,5-di-O-(t-butyldimethylsilyl)-O-ribofuranose (19b). Compound 19b was prepared from 18a (141 mg, 0.28 mmol) by the general procedure to yield 18b (66 mg, 86%) as a white solid. HRMS (ESI) for C12H12Br2NO3SSi: [M + Na] calculated, 295.08; found, 295.07. 1H NMR (500 MHz, CDCl3): 7.77 (dd, 1H, J = 13.1 Hz, H-2); 7.42 (m, 1H, J = 8.0 Hz, H-3); 7.17 (m, 1H, J = 8.0 Hz, H-4); 4.31 (ddd, 1H, J = 8.0 Hz, 9.0 Hz, 3.8 Hz, H-5); 3.70 (ddd, 1H, J = 11.8 Hz, 5.6 Hz, H-6); 2.42 (dd, 1H, J = 5.6 Hz, H-2); 1.98 (s, 3H, CH3-Si); 1.76 (s, 3H, CH2-3); 0.99 (s, 3H, CH2-4); 0.91 (s, 3H, CH3-5). HRMS (ESI) for C12H17NO3S: [M + Na] calculated, 295.08; found, 295.07. 1H NMR (500 MHz, CDCl3): 7.77 (dd, 1H, J = 13.1 Hz, H-2); 7.42 (m, 1H, J = 8.0 Hz, H-3); 7.17 (m, 1H, J = 8.0 Hz, H-4); 4.31 (ddd, 1H, J = 8.0 Hz, 9.0 Hz, 3.8 Hz, H-5); 3.70 (ddd, 1H, J = 11.8 Hz, 5.6 Hz, H-6); 2.42 (dd, 1H, J = 5.6 Hz, H-2); 1.98 (s, 3H, CH3-Si); 1.76 (s, 3H, CH2-3); 0.99 (s, 3H, CH2-4); 0.91 (s, 3H, CH3-5). IR spectrum (KBr): 3333, 3284, 1048, 1585, 1576, 1435, 1217, 1219, 957, 832.
lated, 484.2731; found, 484.2732. 1H NMR (500 MHz, CDCl3) of starting material (65 mg, 37%) was also isolated during chromatography. HRMS (ESI) for C82H64ClNO6Si2 [M + H] calculated, 2828.4308; found, 2828.4307.

10.4 Hz, J1′,2′b = 5.5 Hz, J1′,3′ = J1′,4 = 0.6 Hz, H-1′); 7.22 (dt, 1H, J4,3′ = 8.4 Hz, J4,5′ = 0.6 Hz, H-5); 7.96 (bd, 1H, J4,3′ = 8.4 Hz, H-4). 13C NMR (125.7 MHz, CD2OD): 13.15 (CH3–5′); 23.99 (CH–6); 43.01 (CH2–2′); 63.84 (CH–5′); 74.31 (CH–3′); 76.92 (CH–1′); 88.80 (CH–4′); 119.77 (CH–5′); 133.88 (C–3); 134.17 (CH–4); 156.15 (C–2); 158.08 (C–6). IR spectrum (KBr): 3395, 3060, 2926, 1584, 1471, 1432, 1374, 1172, 1069, 1049, 963, 946, 911, 827, 722.

1β-(2-Chloro-6-ethylpyridin-3-yl)-1,2-dideoxy-3,5-di-O-(6-butyldimethylsilyl)-β-rifoburanose (22a). DMF (2 mL) and TMSA (35 μL, 0.25 mmol, 0.8 equiv.) was added through a septum to an argon-purged vial containing 4 (170 mg, 0.32 mmol), Pd(PPh3)4Cl2 (22 mg, 0.032 mmol), Cul (1 mg, 0.005 mmol) and Et3N (89 μL, 0.64 mmol). The resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was then cooled and filtered on a pad of Celite and eluted with CHCl3. Solvents were then removed under vacuum, the crude product was dissolved in methanolic ammonia (28%, 10 mL) and the solution was stirred at rt for 1 h. The solvents were removed under vacuum, and the crude product was chromatographed on silica gel eluting with a gradient of hexanes to 3% EtOAc in hexanes to give 22a (81 mg, 53% for two steps) as a colorless oil. A portion of starting material 4 (65 mg, 37%) was also isolated during chromatography. HRMS (ESI) for C32H36ClNO3Si2 [M + H] calculated, 482.2308; found, 482.2307. 1H NMR (500 MHz, CDCl3): 0.08, 0.086 and 0.093 (4 × 8, 4 × 3H, CD3Si); 0.89 and 0.91 (2 × 2, 2 × 9H, [(CH3)3C]); 1.69 (ddd, 1H, Jgem = 12.6 Hz, J2′a,1′ = 9.4 Hz, J2′a,1′ = 5.7 Hz, H-2′a); 2.35 (dd, 1H, Jgem = 12.6 Hz, J2′a,1′ = 5.8 Hz, J2′a,1′ = 2.5 Hz, H-2′b); 2.48 (s, 3H, CH3–6); 2.58 (3H, s, CH–S2); 3.67 (dd, 1H, Jgem = 10.8 Hz, J5′b,4′b = 5.2 Hz, H-5′a); 3.78 (dd, 1H, Jgem = 10.8 Hz, J5′b,4′b = 3.7 Hz, H-5′b); 3.93 (ddd, 1H, J5′b,4′b = 5.2 Hz, J5′b,4′b = 3.7 Hz, J5′b,4′b = 2.7 Hz, H-4′); 4.38 (ddd, 1H, J5′b,4′b = 5.7 Hz, J5′b,4′b = 2.6 Hz, J5′b,4′b = 0.6 Hz, H-3′); 5.33 (bdds, 1H, J1′,2′b = 9.4 Hz, J1′,2′b = 5.8 Hz, H-1′); 6.82 (bds, 1H, J1′,2′b = 7.7 Hz, H-5′); 7.66 (dd, 1H, J4,3′ = 7.7 Hz, J4,3′ = 0.8 Hz, H-4). 13C NMR (125.7 MHz, CDCl3): –5.46, –5.39, –4.75 and –4.59 (CH3Si); 12.94 (CH3–S2)–18.01 and 18.32 [(CH3)3C]; 24.09 (CH3–6)–25.80 and 25.91 (CH3Si); 42.06 (CH2–2′)–63.39 (CH–5′)–73.86 (CH–3′)–75.41 (CH–1′)–87.41 (CH–4′)–118.46 (CH–5′)–132.52 (CH–4′)–132.99 (C–3)–154.61 (C–2)–154.42 (C–6). IR spectrum (CCl4): 2830, 2956, 2897, 1585, 1573, 1472, 1463, 1407, 1390, 1374, 1361, 1258, 1210, 1097, 1077, 1031, 971, 963, 939, 838.

1β-(2-Methyl-2-(methylsulfonyl)pyridin-3-yl)-1,2-dideoxy-3,5-di-O-(6-butyldimethylsilyl)-β-rifoburanose (21b). Compound 21b was prepared from 21a (108 mg, 0.22 mmol) by the general procedure to yield 21b (46 mg, 81%) as a white solid. HRMS (ESI) for C18H14NO5S [M + Na] calculated, 278.0821; found, 278.0822. 1H NMR (500 MHz, CD2OD): 1.73 (ddd, 1H, Jgem = 13.1 Hz, J2′a,1′ = 10.1 Hz, J2′a,1′ = 6.1 Hz, H-2′a); 2.39 (ddd, 1H, Jgem = 13.1 Hz, J2′a,1′ = 5.7 Hz, J2′a,1′ = 2.0 Hz, H-2′b); 2.47 (s, 3H, CH3–6); 2.55 (s, 3H, CH–S2); 3.66–3.72 (m, 2H, H–5′); 3.93 (td, 1H, J1′,2′b = 5.0 Hz, J1′,2′b = 2.8 Hz, H–4′); 4.30 (ddd, 1H, J1′,2′b = 6.1 Hz, J1′,2′b = 2.8 Hz, J1′,2′b = 0.7 Hz, H–3′); 5.31 (bdds, 1H, J1′,2′b = 10.1 Hz, J1′,2′b = 5.7 Hz, H–3′); 6.94 (dt, 1H, J4,3′ = 7.8 Hz, J4,3′ = 0.6 Hz, H–5); 7.73 (dd, 1H, J4,3′ = 7.8 Hz, J4,3′ = 0.8 Hz, H–4). 13C NMR (125.7 MHz, CD2OD): 13.15 (CH3–5′–5′); 23.99 (CH–6); 43.01 (CH–2); 63.84 (CH–5′–5′); 74.31 (CH–3′–3′); 76.92 (CH–1′–1′); 88.80 (CH–4′–4′); 119.77 (CH–5′–5′); 133.88 (C–3); 134.17 (CH–4); 156.15 (C–2); 158.08 (C–6). IR spectrum (KBr): 3395, 3060, 2926, 1584, 1471, 1432, 1374, 1172, 1069, 1049, 963, 946, 911, 827, 722.
and TMSA (360 μL, 2.6 mmol) were added through a septum to an argon-purged vial containing 4 (138 mg, 0.26 mmol), Pd(PPh₃)₄Cl₂ (18 mg, 0.026 mmol), Cul (1 mg, 0.005 mmol) and Et₃N (725 μL, 5.2 mmol). The resulting mixture was stirred at 90 °C for 12 h. The reaction mixture was then cooled and filtered on a pad of Celite and eluted with CHCl₃. The solvents were removed under vacuum, and the crude product was chromatographed on silica gel eluting with a gradient of hexanes to 1% EtOAc in hexanes to give 23a (150 mg, 95%) as a colorless oil. HRMS (ESI) for C₂₅H₄₆NO₃Si₄ [M + Na] calculated, 616.3488; found, 616.3490. ¹H NMR (500 MHz, CDCl₃): 0.083, 0.085 and 0.089 (3 × s, 2 × 3H, CH₃Si); 0.24 and 0.26 (2 × s, 2 × 9H, (CH₃)₃Si); 0.90 and 0.91 (s, 2 × 9H, (CH₃)₃Si); 1.74 (ddd, 1H, J₂,2′a = 12.7 Hz, J₂,2′b = 9.4 Hz, J₂,2′a = 5.7 Hz, H-2′a); 2.41 (ddd, 1H, J₁,2′a = 12.7 Hz, J₁,2′b = 6.0 Hz, J₁,2′b′ = 2.3 Hz, H-2′b); 3.72 (dd, 1H, J₁,2′a = 10.8 Hz, J₁,2′a = 4.6 Hz, H-5′a); 3.77 (dd, 1H, J₁,2′b = 10.8 Hz, J₁,2′b = 3.4 Hz, H-5′b); 3.98 (ddd, 1H, J₁,2′a = 4.6 Hz, J₁,2′a = 3.4 Hz, H-5′a = 2.5 Hz, H-4′); 4.39 (ddt, 1H, J₁,2′a = 5.7 Hz, J₁,2′b = 2.4 Hz, J₁,2′b′ = 0.7 Hz, H-3′); 5.54 (ddt, 1H, J₁,2′a = 9.6 Hz, J₁,2′b = 6.0 Hz, J₁,2′b′ = 1.5 Hz, H-1′); 7.36 (dd, 1H, J₁a,5a = 8.1 Hz, J₁a,5a = 0.7 Hz, H-5); 7.92 (dd, 1H, J₁a,5a = 8.1 Hz, J₁a,5a = 0.8 Hz, H-4); 1.¹C NMR (125.7 MHz, CDCl₃): −5.51, −5.41, −4.74 and −4.56 (CH₃Si); −0.32 and −0.30 (CH₃Si); 18.37 and 18.32 ((CH₃)₃Si); 25.88 and 25.90 ((CH₃)₃Si); 43.17 (CH₂); 63.49 (CH₂); 74.07 (CH₃); 76.82 (CH); 88.06 (CH); 94.68 and 100.17 (2 × C(==Si)); 100.91 (C(==Si-C); 103.29 (C(==Si-C); 126.94 (CH₅); 133.37 (CH₄); 140.32 (C-2); 141.47 (C-3); 141.73 (C-6). IR spectrum (KBr): 3087, 2928, 2929, 2911, 2916, 2915, 1752, 1743, 1463, 1444, 1408, 1390, 1362, 1258, 1252, 1232, 1097, 1031, 939, 846.

1f-2,6-Bis(ethylamino)pyridin-3-yl)-1,2-dideoxy-3,5-di-O-(butyl- dimethylsilyl)-o-ribofuranose (23b). Methanolic ammonia (25%, 10 mL) was added to a flask containing nucleoside 23a (287 mg, 0.47 mmol) and the mixture was stirred for 30 min at room temperature. Then the solvents were evaporated under vacuum and the crude product was chromatographed on silica gel in a gradient of hexanes to 6% EtOAc in hexanes to give 23b (167 mg, 76%) as a colorless oil. HRMS (ESI) for C₂₅H₄₆NO₃Si₄ [M + Na] calculated, 535.2574; found, 535.2574. ¹H NMR (500 MHz, CDCl₃): 0.098, 0.100, 0.107 and 0.109 (4 × s, 4 × 3H, CH₃Si); 0.91 and 0.92 (2 × s, 2 × 9H, (CH₃)₃Si); 1.77 (ddd, 1H, J₁,2′a = 12.7 Hz, J₁,2′a = 9.6 Hz, J₁,2′a = 5.6 Hz, H-2′a); 2.46 (ddd, 1H, J₁,2′a = 12.7 Hz, J₁,2′a = 5.9 Hz, J₁,2′a = 2.4 Hz, H-2′b); 3.74 (dd, 1H, J₁,2′a = 10.9 Hz, J₁,2′a = 4.8 Hz, H-5′a); 3.81 (dd, 1H, J₁,2′a = 10.9 Hz, J₁,2′a = 3.5 Hz, H-5′b); 4.00 (ddd, 1H, J₁,2′a = 4.8 Hz, J₁,2′a = 3.5 Hz, J₁,2′a = 2.6 Hz, H-4′); 4.42 (ddd, 1H, J₁,2′a = 5.7 Hz, J₁,2′a = 2.5 Hz, J₁,2′a = 0.7 Hz, H-3′); 5.45 (ddq, 1H, J₁,2′a = 9.6 Hz, J₁,2′a = 5.9 Hz, J₁,2′a = 0.7 Hz, J₁,2′a = 0.7 Hz, H-1′); 7.33 (dd, 1H, J₁a,5a = 7.5 Hz, J₁a,5a = 4.8 Hz, J₁a,5a = 1.2 Hz, H-5′a); 7.82 (td, 1H, J₁a,5a = 7.8 Hz, J₁a,5a = 1.8 Hz, H-4′); 8.14 (dd, 1H, J₁a,5a = 8.0 Hz, J₁a,5a = 0.8 Hz, H-4′); 8.35 (bd, 1H, J₁a,5a = 8.0 Hz, H-5); 8.40 (dt, 1H, J₁a,5a = 8.0 Hz, J₁a,5a = 1.0 Hz, H-3′); 8.67 (ddd, 1H, J₁a,5a = 4.8 Hz, J₁a,5a = 1.8 Hz, J₁a,5a = 0.9 Hz, H-6′). ¹C NMR (125.7 MHz, CDCl₃): −5.47, −5.37, −4.75 and −4.62 (CH₃Si); 18.00 and 18.31 ((CH₂)₃Si); 25.77 and 25.90 ((CH₂)₃Si); 42.47 (CH₂); 63.30 (CH₂); 73.67 (CH₃); 78.67 (CH₄); 119.89 (CH₅); 121.43 (CH₃-py); 124.06 (CH₅-py); 136.73 (CH₄); 137.21 (CH₄-py); 137.65 (C-2); 147.92 (C-2); 148.96 (C-6-py); 154.50 (C-2-py); 154.79 (C-6). IR
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**1f-[2-Chloro-6-(pyridyl)pyridin-3-yl]-1,2-dideoxy-o-ribofuranose (24b).** Compound 24b was prepared from 24a (207 mg, 0.39 mmol) by the general procedure to yield 24b (102 mg, 86%) as a white solid. HRMS (ESI) for C13H10Cl2N4O8Si; [M + H] calculated, 307.0844; found, 307.0844. 1H NMR (500 MHz, CDCl3): 1.84 (ddd, 1H, J_gem = 13.1 Hz, Jα,β = 10.1 Hz, Jα,γ = 6.0 Hz, H-2'a); 2.54 (ddd, 1H, J_gem = 13.1 Hz, Jβ,γ = 5.7 Hz, Jβ,γ = 2.0 Hz, H-2'b); 3.72 (dd, 1H, J_gem = 11.8 Hz, Jα,β = 7.2 Hz, H-3'a); 3.75 (ddd, 1H, JGem = 11.8 Hz, Jβ,γ = 4.5 Hz, H-5's); 4.01 (td, 1H, Jα,β = 4.8 Hz, Jα,γ = 2.7 Hz, H-4'); 4.36 (ddd, 1H, JGem = 6.0 Hz, Jα,β = 2.7 Hz, Jα,γ = 2.0 Hz, Jα,δ = 0.7 Hz, H-3'); 5.44 (ddq, 1H, Jα,β = 10.1 Hz, Jα,γ = 5.7 Hz, Jα,δ = 1.8 Hz, Jα,γ = 0.7 Hz, H-1'); 7.46 (ddd, 1H, Jα,β = 7.6 Hz, Jα,γ = 4.9 Hz, Jα,δ = 1.2 Hz, H-5-py); 7.96 (ddd, 1H, Jα,β = 8.0 Hz, Jα,γ = 7.6 Hz, Jα,δ = 1.8 Hz, H-4-py); 8.25 (ddd, 1H, Jα,β = 8.0 Hz, Jα,γ = 0.8 Hz, H-4'); 8.30 (bd, 1H, Jα,β = 8.0 Hz, H-5-py); 8.35 (dt, 1H, Jα,β = 8.0 Hz, Jα,δ = 1.1 Hz, H-3-py); 8.65 (ddd, 1H, Jα,β = 4.9 Hz, Jα,γ = 1.8 Hz, Jα,δ = 0.9 Hz, H-6-py); 3.74 (ddq, 1H, Jα,β = 11.8 Hz, Jα,γ = 7.2 Hz, H-5-py); 13C NMR (125.7 MHz, CDCl3), 43.20 (CH-2'); 63.76 (CH-5'); 74.19 (CH-3'); 77.64 (CH-1'); 89.22 (CH-4'); 121.14 (CH-5'); 122.68 (CH-3-py); 125.72 (CH-5-py); 138.33 (CH-4'); 138.80 (C-3); 139.05 (C-4-py); 149.22 (C-2'); 150.14 (CH-6-py); 155.57 (C-2-py); 156.02 (C-6). IR spectrum (KBr): 3420, 3336, 3096, 3066, 1587, 1573, 1547, 1478, 1434, 1256, 1173, 1149, 993, 1063, 1047, 993.

**1f-[2,6-Bis-(2-pyridyl)pyridin-3-yl]-1,2-dIDEOXY-o-ribofuranose (25b).** Compound 25b was prepared from 25a (209 mg, 0.36 mmol) by the general procedure to yield 25b (110 mg, 87%) as a white solid. HRMS (ESI) for C25H24N4O8Si; [M + H] calculated, 350.1499; found, 350.1498. 1H NMR (500 MHz, CDCl3): 1.94 (ddd, 1H, J_gem = 13.3 Hz, Jα,β = 10.1 Hz, Jα,γ = 6.2 Hz, H-2'a); 2.35 (ddd, 1H, J_gem = 13.3 Hz, Jβ,γ = 5.7 Hz, Jβ,γ = 2.0 Hz, H-2'b); 3.72 (dd, 1H, J_gem = 11.7 Hz, Jα,β = 5.0 Hz, H-5'a); 3.74 (dd, 1H, J_gem = 11.7 Hz, Jα,γ = 4.5 Hz, H-5'b); 3.89 (bd, 1H, Jα,β = 4.8 Hz, Jα,γ = 2.9 Hz, H-4'); 4.30 (ddd, 1H, Jα,β = 6.2 Hz, Jα,γ = 2.9 Hz, Jα,δ = 2.0 Hz, H-4'); 0.6 Hz, H-3'; 5.62 (dd, 1H, Jα,β = 10.1 Hz, Jα,γ = 5.7 Hz, H-1'); 7.44 (ddd, 1H, Jγ,δ = 7.5 Hz, Jα,β = 4.9 Hz, Jα,γ = 1.2 Hz, H-5-py-6); 7.48 (m, 1H, H-5-py-2); 7.93 (ddd, 1H, Jα,β = 8.0 Hz, Jα,δ = 7.5 Hz, Jα,γ = 1.8 Hz, H-4-py); 7.98-8.01 (m, 2H, H-3-py-4); 8.38 (bd, 1H, Jα,δ = 8.3 Hz, H-5); 8.40 (bd, 1H, Jα,β = 8.3 Hz, H-4); 8.46 (dt, 1H, Jα,δ = 8.0 Hz, Jα,γ = 1.1 Hz, H-3-py-4); 8.65 (ddd, 1H, Jα,β = 4.9 Hz, Jα,γ = 1.8 Hz, Jα,δ = 0.9 Hz, H-6-py); 8.68 (dt, 1H, Jα,δ = 4.9 Hz, Jα,β = 1.4 Hz, H-6-py-2). 13C NMR (125.7 MHz, CDCl3): 45.16 (CH-2'); 63.87 (CH-5'); 74.36 (CH-3'); 77.73 (CH-1'); 89.01 (CH-4'); 121.89 (CH-5); 122.68 (CH-3-py-6); 124.62 (CH-5-py-2); 125.31 (CH-3-py-6); 125.85 (CH-3-py-3); 136.72 (CH-4); 138.47 (CH-4-py-2); 138.73 (CH-4-py-6); 138.91 (C-3); 149.38 (CH-6-py-2); 150.11 (CH-6-py-6); 155.26 (C-6); 155.51 (C-2); 157.08 (C-2-py-6); 159.27 (C-2-py-2). IR spectrum (KBr): 3415, 3088, 3062, 2929, 1590, 1575, 1565, 1577, 1473, 1445, 1434, 1425, 1353, 1254, 1201, 1174, 1150, 1095, 1071, 1050, 1021, 942, 855.

**1f-(2-Chloropyridin-3-yl)-1,2-dIDEOXY-o-ribofuranose (26a).** Vinylmagnesium chloride (1 M solution in THF, 1 mL, 1.0 mmol) was added dropwise to a flame-dried flask containing a solution of the nucleoside 4 (100 mg, 0.19 mmol) and Fe(acac)3 (13 mg, 0.038 mmol) in dry THF (3.0 mL) under Ar. The reaction mixture was then stirred at rt for 12 h. Then the mixture was poured onto a mixture of ice (100 mL) and NH4Cl (1 g), and extracted with chloroform (3 × 100 mL). Evaporation of the organic phase followed by column chromatography on silica gel eluting with a gradient of hexanes to 4% EtOAc in hexanes afforded the nucleoside 26a (40 mg, 47%) as a colorless oil. HRMS (ESI) for C22H14ClNO6Si2; [M + Na] calculated, 480.2128; found, 480.2126. 1H NMR (500 MHz, CDCl3): 0.086, 0.088, 0.090 and 0.10 (4 × s, 4 × CH3, CH3Si); 0.89 and 0.92 (2 × s, 2 × 9H, ((CH3)3C); 1.73 (ddd, 1H, JGem = 12.6 Hz, Jα,β = 9.5 Hz, Jα,γ = 5.5 Hz, H-2'a); 2.44 (ddd, 1H, JGem = 12.6 Hz, Jα,β = 5.9 Hz, Jα,γ = 2.5 Hz, H-2'b); 3.71 (dd, 1H, JGem = 10.9 Hz, Jα,δ = 4.9 Hz, Jα,γ = 1.8 Hz, H-6-py).
4.8 Hz, H-5'a); 3.78 (dd, 1H, J_{gem} = 10.9 Hz, J_{5b,4'} = 3.5 Hz, H-5'b); 3.99 (ddd, 1H, J_{1',2'a} = 4.8 Hz, J_{5b,3'} = 3.5 Hz, H-2'); 4.39 (dt, 1H, J_{1,2'a} = 5.5 Hz, J_{1',2'b} = 2.6 Hz, H-3'); 5.40 (dd, 1H, J_{1,2'a} = 9.5 Hz, J_{1',2'b} = 5.9 Hz, H-1'); 7.23 (dd, 1H, J_{3'a} = 7.7 Hz, J_{5'a} = 4.6 Hz, H-5'); 8.03 (dd, 1H, J_{1a} = 7.6 Hz, J_{5a} = 1.3 Hz, H-4'); 8.28 (bd, 1H, J_{6a} = 4.6 Hz, H-6).

13C NMR (125.7 MHz, CD3OD): 

- 77.4° and 291 parameters. The absolute configuration of the stereogenic centers was confirmed by refinement of the Flack parameter (resulting value −0.008 (12)). The structure was deposited into the Cambridge Structural Database under number CCDC 927314.

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