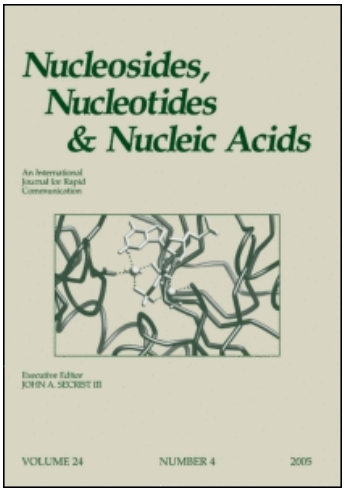


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# Novel 2'-Deoxy Pyrazine *C*-Nucleosides Synthesized VIA Palladium-Catalyzed Cross-Couplings

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# NOVEL 2'-DEOXY PYRAZINE *C*-NUCLEOSIDES SYNTHESIZED VIA PALLADIUM-CATALYZED CROSS-COUPLINGS

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**ABSTRACT:** The palladium-catalyzed cross-couplings of 2-chloro-3,5-diamino-6-iodopyrazine (**1a**) and methyl 3-amino-6-iodopyrazine-2-carboxylate (**1b**) with 1,4-anhydro-3,5-*O*-bis[(*tert*-butyl)dimethylsilyl]-2-deoxy-D-*erythro*-pent-1-enitol (**2**) followed by desilylation and stereospecific reduction of the 2'-deoxy-3'-keto adduct leads to the formation of 2-chloro-6-(2-deoxy-ß-D-ribofuranosyl)-3,5-diaminopyrazine (**4a**) and methyl 3-amino-6-(2-deoxy-ß-D-ribofuranosyl)pyrazine-2-carboxylate (**4b**) in 58% yield and 21% yield, respectively. These are the first syntheses of the heretofore unknown 2'-deoxy pyrazine *C*-nucleosides and demonstrate the utility of a convergent approach for the synthesis of pyrazine *C*-nucleosides.

## INTRODUCTION

Nucleosides possess a broad spectrum of biological functions ranging from their primary roles as building blocks in the genetic code to other functions such as biosynthetic intermediates, energy donors, metabolic regulators, and cofactors in enzymatic processes. Because of this, nucleosides and their synthetic analogs have generated considerable scientific interest in their chemistry and biology.[1] Although *N*-nucleosides are the most abundant and therefore the most studied group, there is also a group of naturally occurring nucleosides in which the glycosidic bond is formed via a C1'-C linkage.[2] Of the vast array of pyrimidine-like nucleosides which have been prepared, the synthesis of pyrazine (1,4-

diazine) *C*-nucleosides has only recently been reported. Benner's group has reported the step-wise construction of the pyrazine *C*-nucleoside isosteres of 5-methylcytidine and 5-methylisocytidine in order to expand the "genetic alphabet."[3] These syntheses involved multistep elaborations of a protected C1'-substituted ribose that resulted in a low overall yield of the specific targets. Our research group has also been interested in the synthesis of pyrazine *C*-nucleosides and we have developed two convergent approaches to pyrazine *C*-ribosides[4a] and 2'-deoxy pyrazine *C*-nucleosides.[4b]

Daves' group has explored the palladium-mediated cross-couplings of iodoheterocycles with various glycals to form C1'-C bonds. Their studies have led to very efficient synthetic routes that give good yields of 2'-deoxy-*C*-furanosides such as the 2'-deoxy analogs of the naturally occurring nucleosides pseudouridine and formycin B.[5] Other groups have also used this method to prepare unnatural heterocyclic *C*-nucleoside derivatives.[6] Pertinent to our work is the fact that iodopyrazines have been shown to react under Heck reaction conditions. Chapdelaine and coworkers synthesized several acetylenic pyrazines from 2-chloro-3,5-diamino-6-iodopyrazine[7] and Quéguiner and coworkers have used some iodopyrazines in palladium-catalyzed cross-couplings.[8,9] We would now like to report on the palladium-catalyzed cross-couplings of iodopyrazines with a furanoid glycal to yield substituted (2-deoxy-β-D-ribofuranosyl)pyrazines.



## RESULTS AND DISCUSSION

For our initial studies into the synthesis of 2'-deoxy pyrazine *C*-nucleosides, we chose to use iodopyrazines and furanoid glycals that were reported in the literature and could be easily prepared in multigram quantities. Furanoid glycals are often synthesized from 1-halogenoses using a low-temperature lithium/liquid ammonia-promoted reductive fragmentation.[10] However, we have developed an alternate route to these glycals from protected 2-deoxy-1-*O*-methylsulfonyl-D-ribofuranoses via a base-promoted β-elimination.[11] For the aglycon of the target compounds, we were interested in using

iodopyrazines that contained additional functional groups which were amenable to further chemical transformations. A survey of the literature revealed two ideal candidates in 2-chloro-3,5-diamino-6-iodopyrazine (**1a**)[7] and methyl 3-amino-6-iodopyrazine-2-carboxylate (**1b**).[12] The literature preparation of **1a** was sufficient for our needs, but the low-yielding (24%) mercuration/iododemercuration of methyl 3-aminopyrazine-2-carboxylate[13] to give **1b** needed some improvement. It is known that pyrazines are deactivated towards electrophilic reactions at the carbons,[14] but the addition of electron-donating groups (e.g., amino) enhances the ring's susceptibility to this type of reaction. Also, the use of an iodine/silver (I) system can generate very electrophilic iodonium species.[15] This prompted us to treat methyl 3-aminopyrazine-2-carboxylate[13] with an *in situ* generated solution of iodine (I) trifluoroacetate in methanol which furnished >50 grams of **1b** in a 49% yield, a vast improvement over the literature method.[12]



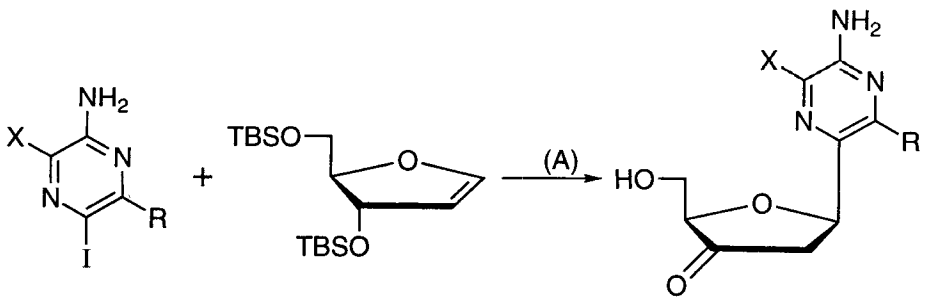
We then initiated studies designed to provide optimal conditions for the cross-coupling reaction. Most iodoheterocycles are reported to behave rather well under Heck conditions. Although it has been noted that exocyclic amino groups can interfere with the reaction,[16] we encountered no problems using **1a** and **1b** as the free amines (*vide infra*). Also, though ribofuranoid glycals with bulky substituents at the 3-position and a free 5-hydroxy have generally been used to optimize the β-selectivity of the cross-coupling reaction, it is not necessary to have a free 5-hydroxy in order to achieve this selectivity.[17] We have found that the presence of *tert*-butyldimethylsilyl groups on both the 3- and 5-hydroxy (e.g., glycal **2**)[11] leads to only trace amounts of α-products[4b] and yields of cross-coupled products are not diminished.[18]

Compounds **1a** and **2** were allowed to react in the presence of palladium (II) acetate (10 mol%), triphenylarsine (40 mol%), and triethylamine in acetonitrile for 48 hours. We found that the initially formed 3'-silyl enol ether adduct was unstable under our slightly basic conditions and prolonged reaction times led to the formation of a 3'-keto adduct. It was not necessary to purify this compound, but rather the mixture could be treated with an excess of tetrabutylammonium fluoride (TBAF) to effect full desilylation. The product was

isolated and purified by silica gel chromatography to give a 69% yield of 2-chloro-3,5-diamino-6-(β-D-*glycero*-pentofuran-3-ulos-1-yl)pyrazine (**3a**). As stated previously, we encountered no difficulties due to the presence of the exocyclic amines of **1a**. However, in the case where **1b** serves as the aglycon, the reaction was not as straightforward. This pyrazine is sparingly soluble in acetonitrile and dimethylformamide was used as the solvent for the cross-coupling reaction. Also, we found that reactions involving **1b** were extremely moisture sensitive, thus necessitating the use of some specialty glassware and the meticulous drying of all reagents prior to use. In contrast, reactions involving **1a** could be conducted in acetonitrile that had not been subjected to any special drying and yields of the product were not greatly diminished.

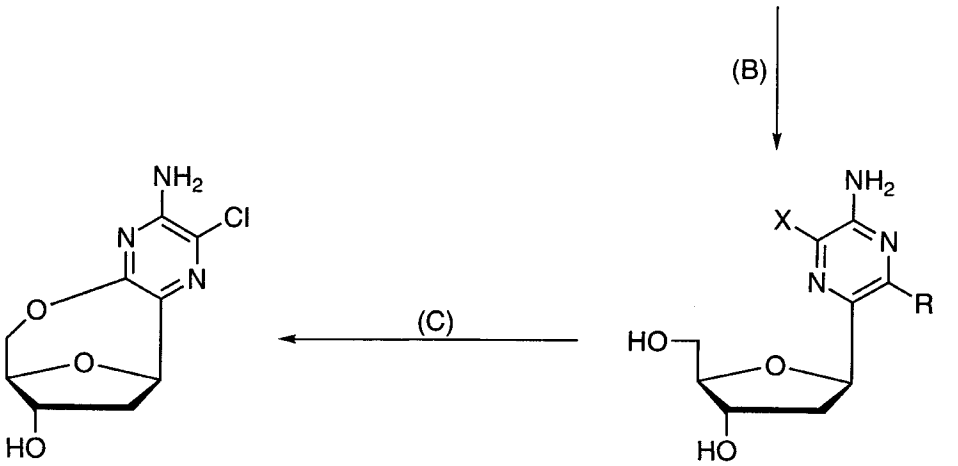


Similar to the above reaction, **1b** and **2** were allowed to react in the presence of palladium (II) acetate (20 mol%), triphenylarsine (40 mol%), and triethylamine in dimethylformamide. This reaction was more sluggish, requiring 170 hours for all of **1b** to be consumed. Treatment of the reaction mixture with TBAF furnished **3b**, but in a 25% yield overall. A variety of perturbations to the cross-coupling reaction were explored, such as variations in catalyst, bases, and complexing agents, but with no significant improvement being observed. The use of "preformed" palladium (0) species such as tetrakis(triphenylphosphine)palladium (0) or bis(dibenzylideneacetone)palladium (0) resulted in no reaction. Also, the use of other palladium (II) species such as palladium (II) chloride resulted in no cross-coupling. If triphenylarsine was replaced in the reaction by triphenylphosphine, the reaction time increased from 24 hours to 48 hours while a decrease to 15% in yield was observed. If tri(*o*-tolulyl)phosphine[19] was used as the ligand, then no cross-coupling occurred. No reaction was observed when bases other than tertiary amines were employed, such as sodium acetate,[20] tetrabutylammonium chloride/triethylamine,[21] or silver carbonate.[22] Although we were limited in our choice of solvent due to the insolubility of **1b**, deoxygenation of the dry dimethylformamide did not increase the yield nor did the addition of water or the use of a 1:1 water/ethanol system.[23]



**1a** X = Cl; R = $NH_2$ **2** **3a** (69% from **1a**)

**1b** X = $CO_2Me$; R = H **3b** (25% from **1b**)



**5** (50%) **4a** (84%)

**4b** (85%)

(A) i) $Pd(OAc)_2$, $Ph_3As$, $Et_3N$, $CH_3CN$ or DMF. ii) $Bu_4NF$, THF.
(B) $NaBH(OAc)_3$, $CH_3CN$, 0 °C.
(C) $(CH_3)_2CHCH_2ONO$, $CHCl_3$, AcOH.

The 2'-deoxy-3'-keto nucleosides **3a** and **3b** were then treated with sodium (triacetoxy)borohydride which resulted in a stereospecific reduction[24] to give 2-chloro-6-(2-deoxy-β-D-ribofuranosyl)-3,5-diaminopyrazine (**4a**) and methyl 3-amino-6-(2-deoxy-β-D-ribofuranosyl)pyrazine-2-carboxylate (**4b**) in 84% and 85% yields, respectively. The $^1$H NMR spectra of **4a** and **4b** showed the anomeric signals as clear double doublets and the $\Delta\delta$ 2',2" of both compounds is less than 0.5 ppm. These spectral features are indicative of 2'-deoxy-β-D-*C*-ribosides.[25,26] Furthermore, **4a** was analyzed by NOE difference spectroscopy. Selective irradiation of the H1' signal resulted in an enhancement of the H4' signal by 2.5% and irradiation of the H4' signal gave a 4% enhancement of H1', which supports the assignment of the β-configuration.[27] We confirmed this assignment unequivocally by chemical means. Treatment of **4a** with isoamyl nitrite resulted in a diazotization of the 5-amino group and subsequent ring closure to give 3-amino-5,5'-anhydro-2-chloro-6-(2-deoxy-β-D-ribofuranosyl)pyrazine (**5**) in a 50% yield.

Thus, we have prepared some heretofore unknown 2'-deoxy pyrazine *C*-nucleosides via palladium-catalyzed cross-couplings of iodopyrazines with a furanoid glycal. The presence of exocyclic amines on the pyrazine does not prevent the reaction from occurring and substituents on the 5-hydroxy of the glycal do not alter the β-selectivity of this process. We are continuing to pursue studies on the use of convergent routes for the synthesis of various pyrazine *C*-nucleosides.



## EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used as provided. Acetonitrile (calcium hydride) and dimethylformamide (calcium oxide) were distilled from the indicated drying agent, and stored over activated 4 Å molecular sieves under a positive pressure of argon prior to use (if not used immediately). Triethylamine was stored over potassium hydroxide pellets under a positive pressure of argon prior to use. Methyl 3-aminopyrazine-2-carboxylate was synthesized via the method

of Chen *et al.*[13] 2-Chloro-3,5-diamino-6-iodopyrazine (**1a**) was synthesized via the method of Chapdelaine *et al.*[7] 1,4-Anhydro-3,5-*O*-bis[(*tert*-butyl)dimethylsilyl]-2-deoxy-D-*erythro*-pent-1-enitol (**2**) was synthesized via the method of Walker *et al.*[11] The phrase "evaporated *in vacuo*" is meant to imply the use of a rotary evaporator with a bath temperature not exceeding 40 °C using a water aspirator. Thin-layer chromatography (TLC) was carried out on Analtech 60F-254 silica gel plates, and detection of components on TLC was made by UV light absorption at 254 nm, 365 nm, staining with iodine vapor, or heating to a char following treatment with 10% sulfuric acid in methanol. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). Mallinckrodt SilicAR® 230-400 mesh (40-63 microns) was used for chromatography, which was carried out utilizing Ace Glass Michel-Miller columns. A Rainin Rabbit HPX pump was used for solvent delivery. UV light-active product-containing fractions were detected on an Isco V$^4$ UV detector and collected by an Isco Foxy fraction collector. Flow rates, sample loading, and fraction size were determined using the guidelines outlined by Still and coworkers.[28] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The $^1$H (300, 360, or 500 MHz) and $^{13}$C (90 or 125 MHz) NMR spectra were recorded on Bruker instruments. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard for $^1$H NMR, and relative to the standard chemical shift of the solvent for $^{13}$C NMR. Mass spectroscopy was performed by the University of Michigan Chemistry Department. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ or by the University of Michigan Chemistry Department. The presence of solvent as indicated by analysis was always confirmed by $^1$H NMR spectroscopy.

**Methyl 3-Amino-6-iodopyrazine-2-carboxylate (1b).** A flame-dried, evacuated, 3-neck, 5 L round-bottom flask equipped with an addition funnel was charged with a solution of iodine (101.2 g, 0.4 mol) in 2 L of methanol under argon. A solution of silver(I) trifluoroacetate (111.2 g, 0.5 mol) in 1 L of methanol was slowly added over a period of 90 minutes. The resulting suspension was stirred for an additional 15 minutes,

then methyl 3-aminopyrazine-2-carboxylate[13] (61.2 g, 0.4 mol) was added in one portion. After this mixture had been stirred for 8 hours at room temperature, triethylamine (69.7 mL, 0.5 mol) was added, and stirring was continued for an additional 30 minutes. The mixture was filtered through Celite, the filter cake was washed with MeOH (3 X 200 mL) then placed in a soxhlet extractor and continuously extracted with acetone (3 X 1L) for a total of 96 hours. The reaction filtrate and acetone extracts were combined and concentrated *in vacuo* to yield a bright yellow solid. This solid was heated and stirred for 30 minutes in boiling MeOH (1L). On cooling to room temperature, the product was collected by filtration and dried on the filter at room temperature to yield 54.8g (49%) of **1b** as a light yellow solid. An analytical sample was obtained by recrystallization from acetic acid: Mp 204-206 °C (lit. 200-202 °C).[12] $R_f$ = 0.52 (30% ethyl acetate/hexane). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.48 (s, 1), 7.49 (bs, 2, $D_2O$ exchangeable), 3.84 (s, 3). $^{13}$C NMR (90 MHz, DMSO-$d_6$) δ 166.4, 155.9, 155.7, 125.7, 98.6, 53.2. UV $\lambda_{max}$ (e x $10^4$): [ethanol] 261 (0.484), 367 (0.214). HRMS calcd for $C_6H_6IN_3O_2$: 278.9507. Found 278.9505. Anal. Calcd for $C_6H_6IN_3O_2 \cdot {}^1/_4$ AcOH: C, 26.55; H, 2.40; N, 14.29. Found: C, 26.33; H, 2.20; N, 14.56.

**2-Chloro-3,5-diamino-6-(β-D-*glycero*-pentofuran-3-ulos-1-yl)pyrazine (3a).** A flame-dried, evacuated 1000 mL round-bottom flask was charged with palladium acetate (336 mg, 1.6 mmol) and triphenylarsine (1.44 g, 4.8 mmol) under argon. Dry acetonitrile (100 mL) was added and the pale yellow suspension stirred at room temperature for 30 minutes. To this suspension was added a solution containing **1a**[7] (4.33 g, 16.0 mmol), **2**[11] (5.70 g, 16.5 mmol), and triethylamine (4.8 mL, 32 mmol) in 300 mL of dry acetonitrile via a cannula. The resultant black solution was stirred at 50 °C for 48 hours. The mixture was cooled to room temperature and tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 36 mL, 36 mmol) was added and stirring was continued at room temperature for an additional 2 hours. After TLC analysis had indicated that desilylation was complete, 15 mL of methanol was added to quench the reaction. The solvent was evaporated *in vacuo* to give a dark oil which was subjected to column

chromatography ($SiO_2$, 50 x 250 mm, 8% methanol/chloroform, *Rf* = 0.25) to give a yellow solid. This impure product was resubjected to column chromatography ($SiO_2$, 40 x 150 mm, 8% methanol/chloroform, *Rf* = 0.25) to give 2.86 g (69%) of **3a** as a yellow solid: Mp 151.0-152.5 °C. $^1H$ NMR (360 MHz, DMSO-$d_6$) δ 6.26 (bs, 2, $D_2O$ exchangeable), 6.16 (bs, 2, $D_2O$ exchangeable), 5.24 (pt, 1, *J* = 4.6 Hz, $D_2O$ exchangeable), 5.15 (dd, 1, *J* = 6.0 Hz, 10.0 Hz), 3.95 (t, 1, *J* = 2.5 Hz), 3.63 (m, 2), 2.77 (dd, 1, *J* = 10.0 Hz, 18.0 Hz), 2.54 (dd, 1, *J* = 6.0 Hz, 18.0 Hz). $^{13}C$ NMR (90 MHz, DMSO-$d_6$) δ 214.5, 151.9, 150.4, 122.3, 116.0, 82.0, 76.3, 60.0, 39.1. Anal. Calcd for $C_9H_{11}ClN_4O_3$: C, 41.79; H, 4.28; N, 21.66. Found: C, 42.29; H, 4.32; N, 21.38.

**Methyl 3-Amino-6-(β-D-*glycero*-pentofuran-3-ulos-1-yl)pyrazine-2-carboxylate (3b).** A flame-dried, evacuated 50 mL Schlenk reaction vessel was charged with palladium acetate (45 mg, 0.2 mmol) and triphenylarsine (245 mg, 0.8 mmol) under argon. Dry dimethylformamide (5 mL) was added and the pale yellow suspension stirred at room temperature for 45 minutes. The vessel was cooled in an ice bath and **1b** (279 mg, 1.0 mmol) was added along with an additional 2.5 mL of dry dimethylformamide. After 60 minutes, **2**[11] (775 mg, 2.25 mmol) in 2.5 mL of dry dimethylformamide and triethylamine (556 μL, 4.0 mmol) were added via separate syringes. Stirring was continued concominant with a slow warming to room temperature (approx. 2 hours). The vessel was placed in an oil bath at 50 °C for 170 hours. The mixture was then cooled to room temperature and filtered through Celite with ethyl acetate washes. After solvent evaporation, the brown oil was dissolved in 2 mL of tetrahydrofuran. To this solution was added tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 3.0 mL, 3.0 mmol) and stirring was continued at room temperature for an additional 3 hours. After TLC analysis had indicated that desilylation was complete, 1 mL of methanol was added to quench the reaction. The solvent was evaporated *in vacuo* to give a dark oil which was subjected to column chromatography ($SiO_2$, 50 x 100 mm, 10% methanol/chloroform, *Rf* = 0.58) to give a yellow glass. This impure product was

resubjected to column chromatography ($SiO_2$, 50 x 100 mm, 8% methanol/chloroform, *Rf* = 0.46) to give 66 mg (25%) of **3b** as a clear glass that was sufficiently pure for the next reaction: $^1H$ NMR (500 MHz, DMSO-$d_6$) δ 8.59 (s, 1), 7.43 (bs, 2, $D_2O$ exchangeable), 5.24 (dd, 1, *J* = 6.3 Hz, 10.1 Hz), 4.50 (pt, 1, *J* = 5.5 Hz, $D_2O$ exchangeable), 4.02 (m, 1), 3.87 (s, 3), 3.65 (m, 2), 2.82 (dd, 1, *J* = 6.4 Hz, 17.8 Hz), 2.67 (dd, 1, *J* = 10.1 Hz, 17.8 Hz). HRMS calcd for $C_{11}H_{13}N_3O_5$: 267.0855. Found 267.0842.

**2-Chloro-6-(2-deoxy-β-D-ribofuranosyl)-3,5-diaminopyrazine (4a).** A 100 mL round-bottom flask was charged with **3a** (259 mg, 1.0 mmol) and this was dissolved in 60 mL of acetonitrile. The solution was cooled to 0 °C and to this was added, in one portion, sodium triacetoxyborohydride (640 mg, 3.0 mmol) with stirring continuing at 0 °C for 5.5 hours. Methanol (5 mL) was added and the solution was warmed to room temperature. The solvent was evaporated *in vacuo* and the compound was subjected to column chromatography ($SiO_2$, 30 x 150 mm, 8% methanol/chloroform, *Rf* = 0.35). The solvent was evaporated to give 219 mg (84%) of **4a** as a yellow solid. An analytical sample was obtained by recrystallization from acetonitrile: Mp 125.0-127.0 °C. $^1H$ NMR (360 MHz, DMSO-$d_6$) δ 6.08 (bs, 2, $D_2O$ exchangeable), 6.02 (bs, 2, $D_2O$ exchangeable), 5.00 (d, 1, *J* = 4.0 Hz, $D_2O$ exchangeable), 4.96 (pt, 1, *J* = 5.1 Hz, $D_2O$ exchangeable), 4.90 (dd, 1, *J* = 5.7 Hz, 10.4 Hz), 4.19 (m, 1), 3.73 (m, 1), 3.48 (m, 2), 2.23 (ddd, 1, *J* = 6.0 Hz, 10.3 Hz, 12.8 Hz), 1.75 (dd, 1, *J* = 5.4 Hz, 12.7 Hz). $^{13}C$ NMR (90 MHz, DMSO-$d_6$) δ 151.7, 149.7, 124.2, 115.7, 87.7, 79.0, 71.9, 61.6, 38.1. Anal. Calcd for $C_9H_{13}ClN_4O_3$: C, 41.47; H, 5.03; N, 21.49. Found: C, 41.49; H, 4.99; N, 21.16.

**Methyl 3-Amino-6-(2-deoxy-β-D-ribofuranosyl)pyrazine-2-carboxylate (4b).** A 10 mL round-bottom flask was charged with **3b** (44 mg, 0.16 mmol) and this was dissolved in 2 mL of acetonitrile. The solution was cooled to 0 °C and to this was added, in one portion, sodium triacetoxyborohydride (106 mg, 0.5 mmol) with stirring continuing at 0 °C for 30 minutes. Methanol (2 mL) was added along with a

minimal amount of silica gel. The solvent was evaporated *in vacuo* and the compound (absorbed on silica gel) was subjected to column chromatography ($SiO_2$, 50 x 100 mm, 10% methanol/chloroform, *Rf* = 0.33). The solvent was evaporated to give 37 mg (85%) of **4b** as a clear glass. An attempt to solidify this glass by trituration with ethyl acetate was unsuccessful: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.42 (s, 1), 7.32 (bs, 2, $D_2O$ exchangeable), 5.06 (d, 1, *J* = 3.8 Hz, $D_2O$ exchangeable), 5.00 (dd, 1, *J* = 6.8 Hz, 7.4 Hz), 4.75 (pt, 1, *J* = 5.6 Hz, $D_2O$ exchangeable), 4.21 (m, 1), 3.85 (s, 3), 3.80 (m, 1), 3.47 (pt, 2, *J* = 5.1 Hz, 5.4 Hz), 2.07-2.03 (m, 2). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 167.3, 156.1, 147.2, 144.9, 121.9, 88.2, 79.2, 73.0, 63.2, 53.0, 42.2. Anal. Calcd for $C_{11}H_{15}N_2O_5 \cdot {}^1/_2$ EtOAc: C, 48.85; H, 6.23; N, 13.67. Found: C, 48.89; H, 6.18; N, 13.36.

**3-Amino-5,5'-anhydro-2-chloro-6-(2-deoxy-β-D-ribofuranosyl)-pyrazine (5).** A flame-dried, evacuated 10 mL round-bottom flask equipped with a Claisen adapter and a reflux condenser was charged with **4a** (28 mg, 0.1 mmol) under argon and this was suspended in a mixture of chloroform (3 mL) and acetic acid (1 mL). To this mixture was added isoamyl nitrite (36 μL, 0.26 mmol) via a syringe beneath the surface of the mixture. The reaction was stirred at room temperature for 30 minutes and then heated at reflux for 15 minutes. At this time, the reaction was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography ($SiO_2$, 10 x 150 mm, 10% methanol/chloroform, *Rf* = 0.59) to yield, after solvent evaporation, 13 mg (50%) of **5** as a yellow oil: $^1$H NMR (360 MHz, DMSO-$d_6$) δ 6.74 (bs, 2, $D_2O$ exchangeable), 5.10 (d, 1, $D_2O$ exchangeable), 5.03 (dd, 1, *J* = 2.5 Hz, 8.6 Hz), 4.47 (m, 1), 4.33 (dd, 1, *J* = 2.3 Hz, 12.8 Hz), 4.13 (m, 1), 3.78 (d, 1, *J* = 13.0 Hz), 2.05 (m,2). $^{13}$C NMR (90 MHz, DMSO-$d_6$) δ 157.3, 149.7, 135.7, 122.8, 85.3, 80.0, 74.1, 71.9, 41.7. HRMS Calcd for $C_9H_{10}ClN_3O_3$: 243.0411. Found: 243.0418.

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