A Convenient Route for the Synthesis of 3-Deazaspongossine

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The first chemical synthesis of the 3-deazaspongossine nucleoside is described, starting from commercially available 4-amino-2,6-dichloropyridine. The key step is the introduction of required functional groups at the 2 and 6 positions of the 4-amino-3-nitropyridine without any conflict in the synthesis of nucleobase. Regioselective nucleophilic substitution with allyl alkoxide at the 2 position of 4-amino-2,6-dimethoxypyridine, followed by sequential deallylation and chlorination

led to the desired 2-chloro derivative. Ring closure of the 3,4-diaminopyridine and stereoselective glycosylation of the imidazo[4,5-c]pyridine with tetraacetate-protected ribofuranose gave only the *N*⁹- β -isomer. A final nucleophilic displacement of the 6-chloride by hydrazine followed by reduction with Raney Nickel gave the desired 3-deazaspongossine.

Introduction

There is much evidence in the scientific literature that modification of the nucleobase and/or the sugar moiety of naturally occurring purine nucleosides can result in analogues that show interesting biological effects.^[1–5] The nitrogen atoms in purine nucleosides are of particular interest, as they are important for binding to enzymes.^[6,7] 3-Deazapurine nucleosides deserve extra attention, because N³ of purine nucleosides is considered to be involved in stabilizing the *syn* conformation by intramolecular hydrogen bonding (5'-OH–N³H).^[8] A literature survey revealed that several 3-deazapurine^[9,10] nucleosides and nucleotides have been synthesized, and that these compounds have been found to have antibacterial,^[11] antiviral,^[12,13] immunosuppressive,^[14] anti-inflammatory,^[15] and anticancer activities.^[16] Thus, we aimed to synthesize the 3-deaza analogue of spongossine nucleoside **1** (Figure 1).

2-Alkoxyadenosine is a purine nucleoside comprising a 2-alkoxyadenine unit attached to a ribose moiety by a β -*N*⁹-glycosidic bond. 2-Alkoxyadenosines are well known for their biological activities, for example, as potent and selective agonists of the coronary artery A2 adenosine receptor,^[17] and as antibacterial adenosine LigA inhibitors.^[18,19] One such compound, 2-methoxyadenosine (**1**, Figure 1), commonly known as spongossine,^[20,21] which was isolated from the Caribbean sponge *Cryptotethia crypta*, has been shown to have antiviral activity^[22] and antiplatelet properties.^[23] It is also used in the treatment of B-cell proliferative diseases^[24] and in the treatment of pain.^[25] Spongossine was not only the first methoxy purine to be found in nature, but also one of the first *O*-methyl compounds to be isolated from animal tissues.^[26]

3-Deazaspongossine (**2**) could be a synthon for the synthesis of 3-deazaisoguanosine (**3b**), which could be considered to be a new nonstandard nucleoside.^[27,28] Despite the remarkable properties of spongossine as described above, to date, no strategy for the synthesis of its 3-deaza analogues has been reported. Only its 8-aza analogue has been synthesized by Kobe et al.^[29,30] As part of our continuing research in nucleoside chemistry,^[31,32] in this paper, we report the first preparation of the hitherto unknown 3-deazaspongossine nucleoside **2**.

In our retrosynthetic planning, we proposed three synthetic routes (Scheme 1). In proposed route A, 3-deazaspongossine (**2**) could be obtained from nucleoside **7** by ammonolysis of the chloride at the 2 position, followed by nucleophilic substitution of second chloride. Nucleoside **7** could be synthesized by coupling 2,6-dichloroimidazo[4,5-*c*]pyridine (**6**) with tetraacetate-protected ribofuranose in the presence of a Lewis acid. Compound **6** could be obtained from 4-amino-2,6-dichloro-3-nitropyridine (**5**) by reduction of the nitro group followed by ring closure. In pro-

Figure 1. Structures of spongossine, 3-deazaspongossine, and 3-deazaisoguanosine.

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posed route B, compound **2** could be prepared from nucleoside **13** by displacement of the methoxy group at the 4 position using an ammonia source. Nucleoside **13** could be synthesized by performing a glycosylation between intermediate **12** and tetraacetate-protected ribofuranose in the presence of a Lewis acid. Imidazo[4,5-*c*]pyridine **12** could be synthesized from 4-amino-2,6-dimethoxy-3-nitropyridine (**10**) by reduction of the nitro group followed by ring closure. In route C, compound **2** could be prepared from nucleoside **19** by nucleophilic substitution of the 2-chloride by an ammonia source. Nucleoside **19** could be synthesized by coupling of 4-chloro-6-methoxyimidazo[4,5-*c*]pyridine (**18**) with tetraacetate-protected ribofuranose in the presence of a Lewis acid. Imidazopyridine **18** could be synthesized from 4-amino-2-chloro-6-methoxy-3-nitropyridine **17** by reduction of the nitro group followed by ring closure, as shown in Scheme 1.

Scheme 1. Retrosynthetic analysis of 3-deazaspongine (**2**).

Results and Discussion

The required 2,6-dichloro-3-nitropyridin-4-amine (**5**) was prepared from commercially available 4-amino-2,6-dichloropyridine (**4**) as reported by Cosstick et al. (Scheme 2).^[33] Reduction of the nitro group of compound **5**^[34,35] gave 3,4-diaminopyridine, which was used without purification in the ring closure reaction. Thus, the crude material was heated at reflux in triethyl orthoformate and then in formic acid to give 4,6-dichloro-imidazo[4,5-*c*]pyridine (**6**) in 72% yield over three steps. Coupling of nucleobase **6** with tetraacetate-protected ribofuranose **9** in the presence of *p*-toluenesulfonic acid gave nucleoside **7** in good yield, as reported by Montgomery et al.^[36] Treatment of derivative **7** with ammonia (30% aq.) at 200 °C for 5 d resulted in regioselective displacement of the 2-chloride and concomitant deacetylation to give compound **8** (80% yield). The spectral and analytical data of **8** were found to be consistent with those reported.^[36] Unfortunately, all our

attempts to displace the second chloride of imidazo[4,5-*c*]pyridine **8** using sodium methoxide or palladium-catalyzed cross-coupling reactions^[37] failed.

Scheme 2. Reagents and conditions: (a) ref.^[33]; (b) (i) Fe, HCl, EtOH; (ii) triethyl orthoformate, reflux; (iii) formic acid, reflux, 72%; (c) **9**, *p*-toluenesulfonic acid, 160 °C, 10 min, 76%; (d) NH₃ (30% aq.), 200 °C, 5 d, 80%.

As our attempts to displace the second chloride in intermediate **8** were unsuccessful, we decided to perform a nucleophilic substitution at an earlier stage, with a more reactive starting material such as **5**. Treatment of pyridine **5** with a solution of sodium methoxide in methanol at 60 °C for 12 h led to the desired disubstituted derivative (i.e., **10**) in 90% yield (Scheme 3). Reduction of the nitro group was performed by treatment with sodium dithionite at room temperature for 15 min to give 3,4-diamino derivative **11** in 75% yield. Subsequent ring closure with triethyl orthoformate and formic acid gave 4,6-dimethoxy-imidazo[4,5-*c*]pyridine (**12**) in 85% yield. Glycosylation of **12** with tetraacetate-protected ribofuranose **9** using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and TMSOTf (trimethylsilyl trifluoromethanesulfonate) gave a mixture of *N*⁹ (**13a**) and *N*⁷ (**13b**) nucleoside isomers in a 7:3 ratio in 82% yield. The structure of the *N*⁹ and *N*⁷ isomers was confirmed by HMBC spectral analysis. When we attempted to displace the methoxy group by an NH₂ group, we only observed

Scheme 3. Reagents and conditions: (a) NaOMe, MeOH, 12 h, 60 °C, 90%; (b) (i) Na₂S₂O₄, EtOH/H₂O (1:1), room temp., 15 min, 75%; (c) (i) triethyl orthoformate, reflux, 5 h; (ii) formic acid, reflux, 5 h, 85%; (d) **9**, TMSOTf, DBU, CH₃CN, 0 °C to 65 °C, 12 h; (e) NH₂NH₂, EtOH, 100 °C, 12 h, 95%.

cleavage of the protective groups to give derivative **14**. A number of attempts were made using ammonia (methanolic or aqueous solutions) in a sealed tube, ammonia/CuI,^[38] or hydrazine (85%), but none of these methods led to the desired 3-deazaspongine.

As an alternative synthetic route, the regioselective addition of allyl alcohol was achieved by treating **10** with a solution of sodium allyl alkoxide (5 M in allyl alcohol) at 60 °C for 1.5 h to give monosubstituted derivative **15** in 82% yield (Scheme 4). Deallylation of **15** was accomplished by treatment with palladium(0) and 1,3-dimethylbarbituric acid at room temperature in anhydrous dichloromethane to give hydroxy derivative **16** in 98% yield.^[39] Compound **16** was heated at reflux in POCl₃ for 2.5 h to give chlorinated intermediate **17** in 78% yield. The synthesis of imidazo[4,5-*c*]pyridine **18** was performed in three sequential steps. First, the nitro group was reduced by treatment with sodium dithionite at room temperature for 15 min, then ring closure was achieved by refluxing successively in triethyl orthoformate and formic acid. Stereoselective glycosylation was carried out using DBU and TMSOTf to give the *N*⁹-β-isomer only. An attempted one-pot nucleophilic displacement and removal of the acetate groups by treatment with ammonia solution at 160 °C led to the decomposition of nucleoside **19**. We thus envisioned that the deprotection and nucleophilic substitution could be achieved by treatment with hydrazine. In fact, when nucleoside **19** was treated with an aqueous solution of hydrazine (80%) at 100 °C for 2 h, followed by an additional step with Raney Nickel at 100 °C for 1.5 h, 3-deazaspongine (**2**) was formed. The structure of *N*⁹ isomer **2** was confirmed by HMBC analysis (correlation between C-4 and 1'-H).

Scheme 4. Reagents and conditions: (a) sodium allylate, allyl alcohol, 60 °C, 1.5 h, 82%; (b) Pd(PPh₃)₄, 1,3-dimethylbarbituric acid, CH₂Cl₂, room temp., 2.5 h, 98%; (c) POCl₃, reflux, 2.5 h, 78%; (d) (i) Na₂S₂O₄, EtOH/H₂O (1:1), room temp., 15 min. (ii) triethyl orthoformate, reflux, 5 h; (iii) formic acid, reflux, 5 h, 68%; (e) **9**, TMSOTf, DBU, CH₃CN, 65 °C, 12 h, 74%; (f) (i) 80% NH₂NH₂, EtOH, 100 °C, 2 h; (ii) Raney Ni (50% aq.), EtOH, 100 °C, 1.5 h, 65%.

Conclusions

In conclusion, we have developed an efficient route for the synthesis of 3-deazaspongine (**2**) starting from 2,6-dichloro-4-amino-pyridine (**4**). The key steps were the selective introduction/removal of allyl alkoxide group, and the

chlorination leading to **17**. Stereoselective glycosylation of imidazo[4,5-*c*]pyridine **18** with tetraacetate-protected ribofuranose **9** yielded only the *N*⁹-β-isomer **19** in good yield. A final nucleophilic displacement with hydrazine and reduction with Raney Nickel led to 3-deazaspongine (**2**). This approach is general, as it is useful for the synthesis of a series of 2-alkoxyadenosine derivatives.

Experimental Section

General Remarks: ¹H and ¹³C NMR spectra were recorded with 300 MHz (¹H, 300 MHz; ¹³C, 75 MHz), 500 MHz (¹H, 500 MHz; ¹³C, 125 MHz), or 600 MHz (¹H, 600 MHz; ¹³C, 150 MHz) spectrometers. 2D NMR spectra (H,H-COSY, HSQC, and HMBC) were used for the assignment of all the intermediate and final compounds. Mass spectra were acquired with a quadrupole orthogonal acceleration time-of-flight mass spectrometer. Melting points were obtained with a melting point apparatus using open capillary tubes. Column chromatographic separations were carried out on silica gel (100–200 mesh or 230–400 mesh) by gradient elution with combinations of two/three solvents. Solvents for reactions were distilled before use: THF and toluene from Na/benzophenone; CH₂Cl₂ and CH₃CN from CaH₂; Et₃N and pyridine from KOH.

4,6-Dichloro-1*H*-imidazo[4,5-*c*]pyridine (6**):** Iron powder (1.3 g, 24.04 mmol), H₂O (4.3 mL, 240 mmol), and HCl (concentrated; 1 mL, 28.85 mmol) were added to 4-amino-2,6-dichloro-3-nitropyridine (**5**; 1 g, 4.81 mmol) in ethanol (23 mL). The mixture was heated at reflux for 16 h. The mixture was cooled to room temperature, then it was neutralized with sodium hydrogen carbonate (saturated aq.). The mixture was filtered, and the filter residue was washed with ethyl acetate. The filtrate was concentrated. The residue was dissolved in ethyl acetate and washed with water (10 mL). The organic layer was dried (MgSO₄) and evaporated. The solid residue was used in the next step without further purification.

A mixture of 3,4-diaminopyridine (500 mg, 22.81 mmol) and triethyl orthoformate (6.5 mL, 39.32 mmol) was heated at reflux at 145 °C for 5 h. The solution was then evaporated to dryness using a rotary evaporator. The residue was dissolved in formic acid (99%; 6.3 mL), and the solution was heated at reflux at 110 °C for 5 h. When the reaction was complete, the excess formic acid was removed with the rotary evaporator. The residue was purified by column chromatography (dichloromethane/methanol, 97:3) to give **6** (390 mg, 72%) as a yellow solid. *R*_f = 0.65 (dichloromethane/methanol, 9:1). m.p. 252–254 °C. ¹H NMR (300 MHz, [D₆]DMSO): δ = 8.54 (s, 1 H, 2-H), 7.75 (s, 1 H, 7-H) ppm. ¹³C NMR (75 MHz, [D₆]DMSO): δ = 146.3 (C-2), 143.4, 139.6, 137.6, 135.5 (C-6, C-4, C-3a, C-7a), 108.3 (C-7) ppm. HRMS (ESI⁺): calcd. for C₆H₃Cl₂N₃ [M + H]⁺ 187.9776; found 187.9771.

4,6-Dichloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3-deazapurine (7**):** Reaction of nucleobase **6** with tetraacetate-protected ribofuranose **9** in the presence of *p*-toluenesulfonic acid gave nucleoside **7**, as reported by Montgomery et al.^[36] Spectral and analytical data were in agreement with previous reports. *R*_f = 0.3 (*n*-hexane/ethyl acetate, 1:1). m.p. 240–242 °C. ¹H NMR (500 MHz, [D₆]DMSO): δ = 8.79 (s, 1 H, 8-H), 8.03 (s, 1 H, 3-H), 6.40 (d, *J* = 5.70 Hz, 1 H, 1'-H), 5.62 (t, *J* = 5.70 Hz, 1 H, 2'-H), 5.41–5.45 (m, 1 H, 3'-H), 4.31–4.50 (m, 3 H, 4'-H, 5a'-H, 5b'-H), 2.13 (s, 3 H, CH₃), 2.09 (s, 3 H, CH₃), 2.04 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, [D₆]DMSO): δ = 170.1, 169.5, 169.4 (3 C=O), 146.0 (C-6), 141.8, 140.8, 139.6, 137.3 (C-2, C-4, C-8, C-5), 107.3 (C-3), 86.8 (C-1'), 79.9 (C-4'), 72.2 (C-2'), 69.4 (C-3'), 62.9 (C-5'), 20.6, 20.4, 20.2 (3

CH₃) ppm. HRMS (ESI⁺): calcd. for C₁₇H₁₇Cl₂N₃O₇ [M + H]⁺ 446.0503; found 446.0504.

2,6-Dichloro-9-(β-D-ribofuranosyl)-3-deazapurine (8): A solution of **13a** (300 mg, 672 μmol) in ammonia (30% aq.) was heated at 200 °C for 5 d. The reaction mixture was concentrated, and the residue was purified by column chromatography (dichloromethane/methanol, 9:1) to give **14** (180 mg, 93%) as a solid. *R*_f = 0.5 (dichloromethane/methanol, 9:1). m.p. 224–226 °C. ¹H NMR (600 MHz, CD₃OD): δ = 8.33 (s, 1 H, 8-H), 7.07 (s, 1 H, 3-H), 5.82 (d, *J* = 5.80 Hz, 1 H, 1'-H), 4.38 (t, *J* = 5.80 Hz, 1 H, 2'-H), 4.25 (dd, *J* = 3.60, 5.80 Hz, 1 H, 3'-H), 4.11 (dt, *J* = 3.60, 6.0 Hz, 1 H, 4'-H), 3.84 (dd, *J* = 6.0, 12.0 Hz, 1 H, 5a'-H), 3.77 (dd, *J* = 3.60, 12.0 Hz, 1 H, 5b'-H) ppm. ¹³C NMR (125 MHz, CD₃OD): δ = 152.5 (C-6), 143.2 (C-2), 142.1 (C-8), 141.1 (C-4), 126.8 (C-5), 97.8 (C-3), 91.0 (C-1'), 87.3 (C-4'), 76.1 (C-2'), 71.7 (C-3'), 62.5 (C-5') ppm. HRMS (ESI⁺): calcd. for C₁₁H₁₃Cl₂N₄O₄ [M + H]⁺ 301.0698; found 301.0693.

2,6-Dimethoxy-3-nitropyridin-4-amine (10): Sodium methoxide (5 M in MeOH; 2.8 mL) was added to a solution of **5** (500 mg, 2.4 mmol) in methanol (14 mL), and the mixture was heated at 60 °C for 12 h. The mixture was concentrated, then the residue was dissolved in ethyl acetate and washed with water (5 mL). The solution was dried (MgSO₄) and concentrated, and the residue was purified by column chromatography (*n*-hexane/ethyl acetate, 9:1) to give **12** (430 mg, 90%) as a yellow solid. *R*_f = 0.25 (*n*-hexane/ethyl acetate, 8:2). m.p. 136–138 °C. ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.35 (br. s, 2 H, NH₂), 5.78 (s, 1 H, 5-H), 3.89 (s, 3 H, OCH₃), 3.81 (s, 3 H, OCH₃) ppm. ¹³C NMR (125 MHz, [D₆]DMSO): δ = 162.8 (C-6), 158.6 (C-2), 153.9 (C-4), 115.8 (C-3), 86.2 (C-5), 54.0, 53.7, (2 OCH₃) ppm. HRMS (ESI⁺): calcd. for C₇H₉N₃O₄ [M + H]⁺ 200.0665; found 200.0670.

2,6-Dimethoxypyridine-3,4-diamine (11): A solution of sodium dithionite (1.2 g, 7.53 mmol) in water (12.5 mL) was added to a solution of **10** (500 mg, 2.51 mmol) in ethanol (12.5 mL), and the mixture was stirred at room temperature for 15 min. The ethanol was evaporated at 20 °C. The residue was dissolved in ethyl acetate and washed with water (6 mL). The organic layer was dried (MgSO₄), and concentrated. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1) to give **11** (320 mg, 75%) as a yellow solid. *R*_f = 0.3 (*n*-hexane/ethyl acetate, 1:1). m.p. 70–72 °C. ¹H NMR (300 MHz, [D₆]DMSO): δ = 5.64 (s, 1 H, 5-H), 5.35 (br. s, 2 H, NH₂), 3.51 (br. s, 2 H, NH₂), 3.79 (s, 3 H, OCH₃), 3.67 (s, 3 H, OCH₃) ppm. ¹³C NMR (75 MHz, [D₆]DMSO): δ = 154.7, 150.0 (C-6, C-2), 146.0 (C-4), 109.0 (C-3), 86.9 (C-5), 52.5, 52.4 (2 OCH₃) ppm. HRMS (ESI⁺): calcd. for C₇H₁₁N₃O₂ [M + H]⁺ 170.0923; found 170.0927.

4,6-Dimethoxy-1*H*-imidazo[4,5-*c*]pyridine (12): A mixture of 3,4-diaminopyridine **11** (600 mg, 3.55 mmol) and triethyl orthoformate (8.2 mL, 49.65 mmol) was heated at reflux for 5 h at 145 °C. The solution was evaporated to dryness using a rotary evaporator. The residue was dissolved in formic acid (99%; 27 mL), and the solution was heated at reflux at 110 °C for 5 h. When the reaction was complete, the excess formic acid was removed using the rotary evaporator, and the residue was purified by column chromatography (dichloromethane/methanol, 97:3) to give **12** (540 mg, 85%) as a yellow solid. *R*_f = 0.6 (dichloromethane/methanol, 9:1). m.p. 232–234 °C. ¹H NMR (300 MHz, [D₆]DMSO): δ = 8.06 (s, 1 H, 2-H), 6.43 (s, 1 H, 7-H), 3.99 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃) ppm. ¹³C NMR (75 MHz, [D₆]DMSO): δ = 157.7 (s, C-4, C-6), 152.1 (C-7a), 141.6 (C-2), 121.9 (C-3a), 83.7 (C-7), 52.5, 52.4 (2 OCH₃) ppm. HRMS (ESI⁺): calcd. for C₈H₉N₃O₂ [M + H]⁺ 180.0767; found 180.0777.

4,6-Dimethoxy-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3-deazapurine (13a) and 4,6-Dimethoxy-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3-deazapurine (13b): TMSOTf (1.22 mL, 6.70 mmol) was added to a stirred solution of compound **12** (600 mg, 3.35 mmol), sugar **9** (1.1 g, 3.68 mmol), and DBU (0.56 mL, 3.68 mmol) in CH₃CN (15 mL) at 0 °C. The mixture was stirred at 60 °C for 12 h, then it was poured into NaHCO₃ (aq. solution). The mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried (MgSO₄), and filtered, and the solvents were evaporated. The residue was purified by silica gel column chromatography (dichloromethane/methanol, 98:2) to give compound **13a** (740 mg, 50%) as a pale yellow foam. *R*_f = 0.3 (*n*-hexane/ethyl acetate, 1:1). ¹H NMR (500 MHz, CDCl₃): δ = 7.89 (s, 1 H, 8-H), 6.48 (s, 1 H, 3-H), 5.94 (d, *J* = 5.70 Hz, 1 H, 1'-H), 5.52 (t, *J* = 5.70 Hz, 1 H, 2'-H), 5.40 (dd, *J* = 4.20, 5.70 Hz, 1 H, 3'-H), 4.11–4.46 (m, 3 H, 4'-H, 5a'-H, 5b'-H), 4.11 (s, 3 H, OCH₃), 3.94 (s, 3 H, OCH₃), 2.21 (s, 3 H, CH₃), 2.15 (s, 3 H, CH₃), 2.08 (s, 3 H, CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 170.5, 169.7, 169.3 (3 C=O), 159.3 (C-6), 154.1 (C-2), 142.1 (C-4), 139.3 (C-8), 124.2 (C-5), 87.2 (C-1'), 82.6 (C-3), 80.4 (C-4'), 72.9 (C-2'), 70.2 (C-3'), 62.9 (C-5'), 54.3, 53.7 (2 OCH₃), 20.9, 20.6, 20.4 (3 CH₃) ppm. HRMS (ESI⁺): calcd. for C₁₉H₂₃N₃O₉ [M + H]⁺ 438.1506; found 438.1506.

Further elution (dichloromethane/MeOH, 97:3) gave **13b** (310 mg, 32%) as a pale yellow foam. *R*_f = 0.31 (*n*-hexane/ethyl acetate, 1:1). ¹H NMR (600 MHz, CDCl₃): δ = 8.04 (s, 1 H, 8-H), 6.17 (s, 1 H, 3-H), 5.53 (d, *J* = 5.80 Hz, 1 H, 1'-H), 5.52 (t, *J* = 5.80 Hz, 1 H, 2'-H), 5.40 (t, *J* = 5.80 Hz, 1 H, 3'-H), 4.16–4.26 (m, 3 H, 4'-H, 5a'-H, 5b'-H), 3.89 (s, 3 H, OCH₃), 3.73 (s, 3 H, OCH₃), 1.97 (s, 3 H, CH₃), 1.96 (s, 3 H, CH₃), 1.92 (s, 3 H, CH₃) ppm. ¹³C NMR (150 MHz, CDCl₃): δ = 169.9, 169.1, 168.7 (3 C=O), 158.2 (C-6), 154.6 (C-2), 148.1 (C-4), 143.1 (C-8), 112.7 (C-5), 89.5 (C-3), 88.5 (C-1'), 78.8 (C-4'), 74.0 (C-2'), 68.7 (C-3'), 62.1 (C-5'), 53.9, 53.2 (2 OCH₃), 20.3, 20.0, 20.0 (3 CH₃) ppm. HRMS (ESI⁺): calcd. for C₁₉H₂₃N₃O₉ [M + H]⁺ 438.1506; found 438.1505.

2,6-Dimethoxy-9-(β-D-ribofuranosyl)-3-deazapurine (14): Hydrazine (80%; 7 mL) was added to a solution of **13a** (200 mg, 457 μmol) in ethanol (1 mL), and the mixture was heated at 100 °C for 12 h. The reaction mixture was concentrated, and the residue was purified by column chromatography (dichloromethane/methanol, 9:1) to give **14** (136 mg, 95%) as a solid. *R*_f = 0.5 (dichloromethane/methanol, 9:1). ¹H NMR (500 MHz, CD₃OD): δ = 8.26 (s, 1 H, 8-H), 6.74 (s, 1 H, 3-H), 5.77 (d, *J* = 6.20 Hz, 1 H, 1'-H), 5.51 (s, 1 H, OH), 5.25 (s, 1 H, OH), 5.16 (s, 1 H, OH), 4.32 (br. s, 1 H, 2'-H), 4.11 (br. s, 1 H, 3'-H), 3.96–3.80 (m, 4 H, OCH₃, 4'-H), 3.85 (s, 3 H, OCH₃), 3.50–3.68 (m, 2 H, 5a'-H, 5b'-H) ppm. ¹³C NMR (125 MHz, CD₃OD): δ = 158.0 (C-6), 153.0 (C-2), 142.7 (C-4), 141.5 (C-8), 123.5 (C-5), 88.8 (C-1'), 85.7 (C-3), 83.0 (C-4'), 73.6 (C-2'), 70.1 (C-3'), 61.2 (C-5'), 53.9, 53.0 (2 OCH₃) ppm. HRMS (ESI⁺): calcd. for C₁₃H₁₇N₃O₆ [M + H]⁺ 312.1190; found 312.1194.

2-(Allyloxy)-6-methoxy-3-nitropyridin-4-amine (15): Sodium allyl alkoxide (5 M in allyl alcohol; 5 mL, 25.1 mmol) was added to a solution of **10** (1.0 g, 5.2 mmol) in allyl alcohol (25 mL), and the mixture was heated at 60 °C for 1.5 h. The mixture was concentrated, the residue was dissolved in ethyl acetate and washed with water (10 mL). The organic layer was dried (MgSO₄) and concentrated. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 9:1) to give **15** (805 mg, 82%) as a yellow solid. *R*_f = 0.3 (*n*-hexane/ethyl acetate, 8:2). m.p. 68–70 °C. ¹H NMR (500 MHz, CDCl₃): δ = 6.29 (br. s, 2 H, NH₂), 5.95–6.01 (m, 1 H, CH=C), 5.63 (s, 1 H, 5-H), 5.43 (dd, *J* = 1.52, 17.2 Hz, 1 H, CH₂=C), 5.22 (dd, *J* = 1.52, 10.30 Hz, 1 H, CH₂=C), 4.85–4.93 (m, 2 H, CH₂), 3.83 (s, 3 H, OCH₃) ppm. ¹³C NMR (125 MHz,

CDCl_3): δ = 162.6 (C-6), 157.9 (C-4), 152.8 (C-2), 131.4 (CH=C), 116.8 (s, C=CH, C-3), 86.3 (C-5), 66.8 (CH_2), 53.0 (OCH_3) ppm. HRMS (ESI⁺): calcd. for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4$ [$\text{M} + \text{H}$]⁺ 226.0822; found 226.0818.

4-Amino-6-methoxy-3-nitropyridin-2-ol (16): Compound **15** (800 mg, 3.55 mmol) was dissolved in dry dichloromethane (25 mL), and tetrakis(triphenylphosphine)palladium(0) (40 mg, 35 μmol) and 1,3-dimethylbarbituric acid (832 mg, 5.33 mmol) were added simultaneously. The reaction mixture was stirred at room temp for 2.5 h. The resulting precipitate was obtained by filtration, and it was washed with cold dichloromethane to give **16** (540 mg, 98%) as a yellow solid. R_f = 0.21 (ethyl acetate). m.p. 241–243 °C. ¹H NMR (600 MHz, [D_6]DMSO): δ = 11.40 (s, 1 H, OH), 8.24 (br. s, 2 H, NH_2), 5.34 (s, 1 H, 5-H), 3.79 (s, 3 H, OCH_3) ppm. ¹³C NMR (150 MHz, [D_6]DMSO): δ = 158.6, 157.1, 156.6 (C-4, C-2, C-6), 115.6 (C-3), 75.4 (C-5), 56.2 (OCH_3) ppm. HRMS (ESI⁺): calcd. for $\text{C}_6\text{H}_7\text{N}_3\text{O}_4$ [$\text{M} + \text{H}$]⁺ 186.0509; found 186.0507.

2-Chloro-6-methoxy-3-nitropyridin-4-amine (17): A solution of **16** (400 mg, 2.16 mmol) in POCl_3 (2.5 mL) was heated at 95 °C for 4 h. Then the reaction mixture was allowed to cool down to room temperature, and the POCl_3 was evaporated. The residue was dissolved in ethyl acetate, and this solution was washed with NaHCO_3 (saturated aq.; 2×5 mL). The organic phase was dried with MgSO_4 and concentrated. The oily residue was purified by silica gel column chromatography (dichloromethane) to give **17** (290 mg, 78%) as a yellow solid. R_f = 0.35 (*n*-hexane/ethyl acetate, 7:3). m.p. 140–142 °C. ¹H NMR (500 MHz, [D_6]DMSO): δ = 6.11 (s, 1 H, 5-H), 3.81 (s, 3 H, OCH_3) ppm. ¹³C NMR (125 MHz, [D_6]DMSO): δ = 162.5, 151.7, 141.8 (C-4, C-2, C-6), 127.8 (C-3), 92.1 (C-5), 54.3 (OCH_3) ppm. HRMS (ESI⁺): calcd. for $\text{C}_6\text{H}_6\text{ClN}_3\text{O}_3$ [$\text{M} + \text{H}$]⁺ 204.0170; found 204.0172.

4-Chloro-6-methoxy-1*H*-imidazo[4,5-*c*]pyridine (18): A solution of sodium dithionite in water (10 mL) was added to a solution of **17** (400 mg, 1.96 mmol) in ethanol (10 mL), and the mixture was stirred at room temperature for 15 min. The mixture was concentrated, the residue was dissolved in ethyl acetate and washed with water (5 mL). The organic layer was dried with MgSO_4 and concentrated. The crude oily 3,4-diaminopyridine was used in the next step without further purification. A mixture of crude 3,4-diaminopyridine (300 mg, 1.73 mmol) and triethyl orthoformate (4 mL, 24.19 mmol) was heated at reflux at 145 °C for 5 h. The solution was evaporated to dryness using a rotary evaporator. The residue was dissolved in formic acid (99%; 4 mL) and the solution was heated at reflux at 110 °C for 5 h. When the reaction was complete, the excess formic acid was removed using a rotary evaporator. The residue was purified by column chromatography to give **18** (216 mg, 68%) as a yellow solid. R_f = 0.15 (*n*-hexane/ethyl acetate, 4:6). m.p. 233–235 °C. ¹H NMR (300 MHz, [D_6]DMSO): δ = 8.31 (s, 1 H, 2-H), 6.87 (s, 1 H, 7-H), 3.86 (OCH_3) ppm. ¹³C NMR (75 MHz, [D_6]DMSO): δ = 158.3 (C-6), 145.1 (C-2), 143.8, 135.6, 132.2 (C-7a, C-3a, C-4, assigned by HMBC), 90.5 (C-7), 54.3 (OCH_3) ppm. HRMS (ESI⁺): calcd. for $\text{C}_7\text{H}_6\text{ClN}_3\text{O}$ [$\text{M} + \text{H}$]⁺ 184.0272; found 184.0278.

6-Chloro-2-methoxy-9-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-3-deazapurine (19): TMSOTf (0.89 mL, 4.99 mmol) was added to a stirred solution of compound **17** (450 mg, 2.45 mmol), sugar **9** (858 mg, 2.70 mmol), and DBU (0.41 mL, 2.70 mmol) in CH_3CN (12 mL) at 0 °C. The mixture was stirred at 60 °C for 12 h, then it was poured into NaHCO_3 (aq. solution). The mixture was extracted with ethyl acetate ($3 \times$). The combined organic extracts were washed with brine, dried (MgSO_4), and filtered, and the solvents were evaporated. The residue was purified by silica gel col-

umn chromatography (*n*-hexane/ethyl acetate, 6:4) to give compound **19** (783 mg, 74%) as a thick yellow liquid. R_f = 0.27 (*n*-hexane/ethyl acetate, 1:1). ¹H NMR (600 MHz, CDCl_3): δ = 8.05 (s, 1 H, 8-H), 6.89 (s, 1 H, 3-H), 5.96 (d, J = 5.80 Hz, 1 H, 1'-H), 5.50 (d, J = 5.80 Hz, 1 H, 2'-H), 5.40 (dd, J = 3.93, 5.80 Hz, 1 H, 3'-H), 4.31–4.49 (m, 3 H, 4'-H, 5a'-H, 5b'-H), 3.98 (s, 3 H, OCH_3), 2.23 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3) ppm. ¹³C NMR (150 MHz, CDCl_3): δ = 170.4, 169.7, 169.4 (3 C=O), 159.7 (C-2), 142.3 (C-8), 141.6 (C-6), 139.0 (C-4), 134.4 (C-5), 90.1 (C-3), 87.4 (C-1'), 80.6 (C-4'), 72.7 (C-2'), 70.0 (C-3'), 62.8 (C-5'), 54.8 (OCH_3), 20.9, 20.6, 20.4 (3 CH_3) ppm. HRMS (ESI⁺): calcd. for $\text{C}_{18}\text{H}_{20}\text{ClN}_3\text{O}_8$ [$\text{M} + \text{H}$]⁺ 442.1011; found 442.1012.

6-Amino-2-methoxy-9-(β -D-ribofuranosyl)-3-deazapurine (2): Hydrazine (80%; 10 mL) was added to a solution of **19** (340 mg, 769 μmol) in ethanol (1 mL), and the mixture was heated at 100 °C for 2 h. The reaction mixture was concentrated, Raney Ni (50%; 10 mL) was added, and the mixture was heated at 100 °C for 2 h. The reaction mixture was filtered through Celite, the filtrate was concentrated, and the residue was purified by column chromatography (dichloromethane/methanol, 9:1) to give **2** (149 mg, 65%) as a thick liquid. R_f = 0.25 (ethyl acetate/methanol, 6:1). ¹H NMR (500 MHz, CD_3OD): δ = 8.19 (s, 1 H, 8-H), 6.38 (s, 1 H, 3-H), 5.80 (d, J = 5.80 Hz, 1 H, 1'-H), 4.44 (dd, J = 4.11, 5.80 Hz, 1 H, 2'-H), 4.26 (dd, J = 4.11, 5.80 Hz, 1 H, 3'-H), 4.11 (d, J = 4.11 Hz, 1 H, 4'-H), 3.70–3.90 (m, 5 H, OCH_3 , 5a'-H, 5b'-H) ppm. ¹³C NMR (125 MHz, CD_3OD): δ = 161.9 (C-2), 150.8 (C-6), 142.7 (C-4), 140.8 (C-8), 123.3 (C-5), 90.8 (C-1'), 87.0 (C-4'), 78.9 (C-3), 75.6 (C-2'), 71.7 (C-3'), 62.6 (C-5'), 55.0 (OCH_3) ppm. HRMS (ESI⁺): calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_5$ [$\text{M} + \text{H}$]⁺ 297.1193; found 297.1194.

Supporting Information (see footnote on the first page of this article): ¹H and ¹³C NMR spectra.

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