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The Synthesis of 4-Deazaformycin A

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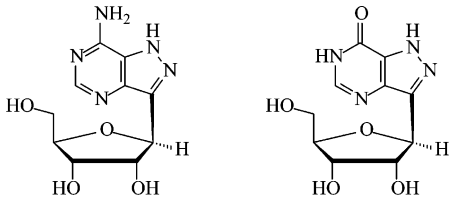
Abstract: The preparation of 4-deazaformycin A has been achieved. The synthesis features the condensation of a suitably substituted, lithiated 4-picoline with 2,3,5-*tri*-*O*-benzyl-D-ribonolactone, dehydration of the resulting hemiacetal, and ionic hydrogenation, followed by manipulation of the protecting groups and subsequent ring closure with the formation of 7-amino-3-(*β*-D-ribofuranosyl)pyrazolo[3,4-*c*]pyridine.

The biochemical and pharmacological significance of natural nucleosides and their modified synthetic analogues have attracted wide interest for many years. A number of nucleoside derivatives have been approved for the clinical treatment of viral and cancer diseases,[1] while several structurally related agents are under active investigation by research groups throughout the world. As a consequence, there is a need for the development of synthetic approaches that allow access to these novel potentially bioactive nucleoside derivatives with modified bases or sugars. C-Nucleosides represent a unique class of compounds, in which the carbohydrate moiety and the aglycon are linked via a hydrolytically and enzymatically stable carbon−carbon bond.[2]The potential applications of C-nucleosides in nucleic acid chemistry have recently attracted wide interest.[3]In fact, a number of C-nucleosides are important antibiotics, which possess interesting chemotherapeutic properties.[4] Some of the most interesting C-nucleoside antibiotics are the purine-like C-nucleosides formycin A (**1**)[5] and formycin B (**2**)[6] (Figure 1), which closely mimic the isosteric naturally occurring N-nucleosides adenosine and inosine and substitute for them in many enzymatic reactions.[7]



1 Formycin A **2** Formycin B

FIGURE 1. Structure of the formycins.

As a continuation of our ongoing efforts toward the design and synthesis of C-nucleoside antibiotics and structurally related analogues[8] we present here details on the preparation of 7-amino-3-(*β*-D-ribofuranosyl)pyrazolo[3,4-*c*]pyridine. This nucleoside can be viewed as a single modification of formycin A (4-deaza) and thus provides a very useful probe for chemical and biological studies on the importance of the 4-nitrogen of formycin A.

For the synthesis of the target compound (Scheme 1), we used as starting material the Boc-protected aminopyridine **3**,[9] which is suitable in terms of its stability to anionic reaction conditions.[10] The lithiation of **3** was accomplished by using 3.7 equiv of *n*-butyllithium in dry THF at −78 °C. The resulting 4-methylene anion attacks the carbonyl of the easily accessible 2,3,5-*tri*-*O*-benzyl-D-ribonolactone (**4**)[11] to provide a 8:1 α-D/*β*-D[12] anomeric mixture of the hemiacetals **5**, as estimated by ^{1}H NMR. The major isomer was isolated pure by column chromatography on silica gel and characterized on the basis of 1-D and 2-D NMR data. We observed strong correlation peaks between one of the 5′-protons and one proton of the 4-methylene group. The observed stereochemistry at the anomeric center is in agreement with the expectation that steric effects would direct the attack of the nucleophile **3** to the less hindered *β*-face of the sugar lactone

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(12) It should be pointed out that for hemiacetals **5** the prefix α refers to the position of the glycosidic OH group relative to the configuration at the reference C-atom (C-4′ in **5**; i.e., the methylpyridinyl moiety is in the *β*-position). For C-glycosides (no glycosidic OH present), the prefix α-D refers to the alkyl (or aryl) position relative to the reference C-atom.

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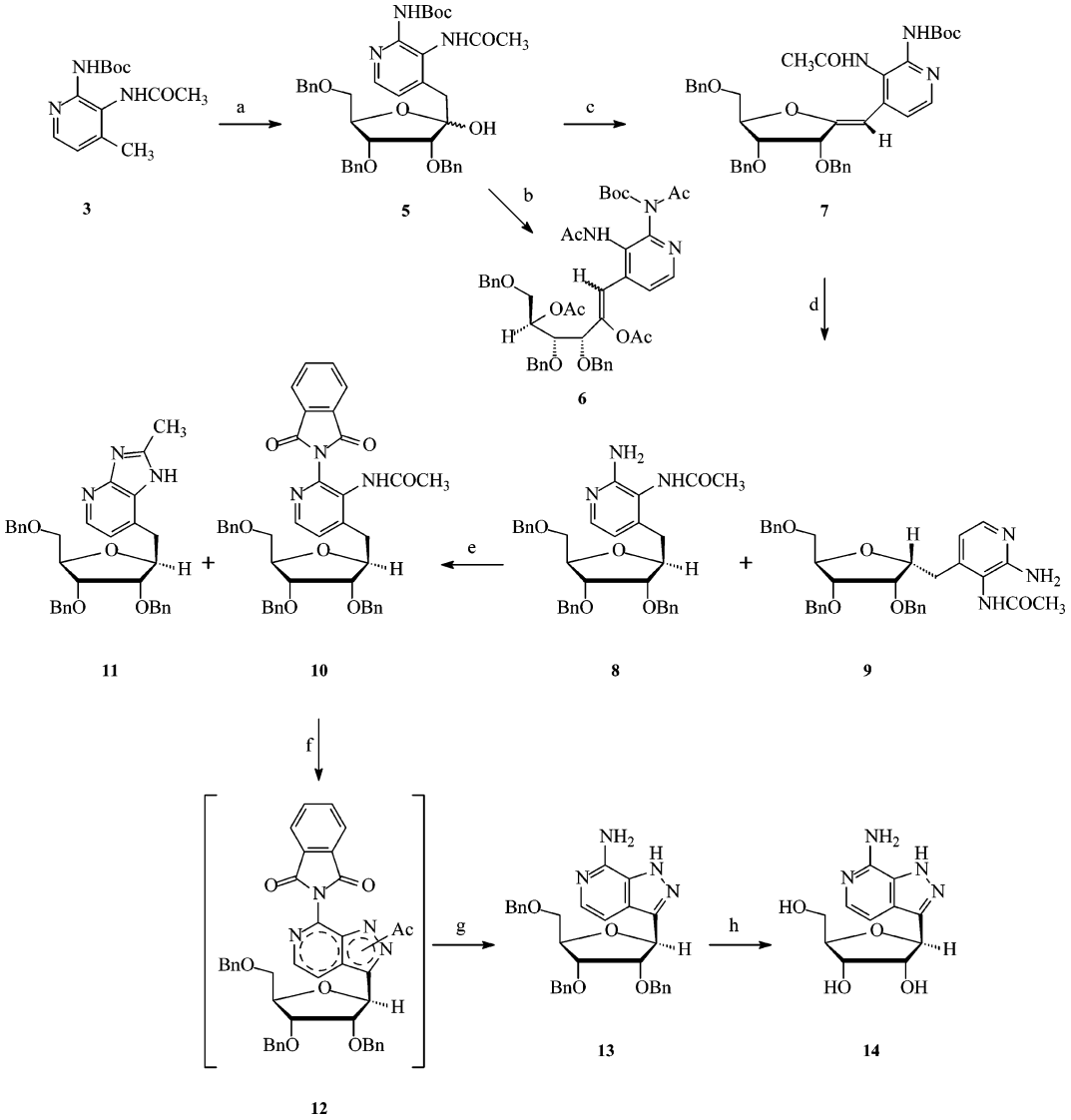
SCHEME 1[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C, (ii) 2,3,5-*tri*-*O*-benzyl-D-ribonolactone (**4**), THF, −78 °C up to room temperature; (b) Ac_2O, Et_3N, CH_2Cl_2, rt; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C; (d) CF_3CO_2H, Et_3SiH, CH_2Cl_2, rt; (e) phthalic anhydride, toluene, 50 °C; (f) AcOK, Ac_2O, isoamyl nitrite, C_6H_6, reflux; (g) CH_3ONa/ CH_3OH, rt; (h) BCl_3, CH_2Cl_2, −78 °C.

4.[13] To isolate and characterize the β-anomer as well we have acetylated the hemiacetal **5** after treatment with acetic anhydride in triethylamine. This reaction did not provide the hemiacetal acetates but resulted in the open-chain enol ester **6**.

Reaction of the hemiacetal **5** with boron trifluoride diethyl etherate in dichloromethane solution gave excellent yield of the olefin **7**, with exclusive *Z*-stereoselectivity. The stereochemistry was unambiguously determined on the basis of NOE spectral data, where we observed a strong correlation peak between the olefinic proton and the 2′-H. Compound **7** was submitted to catalytic hydrogenation over Pd/C to afford a complex mixture of products. We subsequently found that the application of ionic hydrogenation to **7**, using triethylsilane as a hydride ion donor and trifluoroacetic acid as the proton donor,[14] furnished, after chromatographic separation, *N*-[2-amino-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)methylpyridin-3-yl]acetamide (**8**) as the major product (48%) and the α-anomer **9** as the minor product (12%). The configuration at C-1′ was assigned on the basis of NOE experiments and for compound **8** we observed a clear cross-peak between the 1′ and 4′ hydrogens. The concomitant deprotection of the 2-amino group of **7** is in favor of the reaction sequence, since according to our previous observations the direct cyclization of the *N*-Boc protected derivative would result in the formation of the corresponding 7-(ribofuranosylmethyl)imidazolo[4,5-*b*]pyridin-2-one.[9] This annulation occurs through an intermolecular nucleophilic attack of the acetamide nitrogen to the carbamate carbonyl, followed by ring closure and elimination of *tert*-butyl alcohol. Therefore, we have converted

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the aminopyridine **8** to the corresponding *N*-phthaloyl derivative **10**, by treatment of **8** with phthalic anhydride in THF at 50 °C. This protecting group is stable under the conditions of the cyclization reaction that follows and at the same time the formation of the above mentioned imidazolo[4,5-*b*]pyridinone is avoided. Our first attempt to prepare the *N*-phthaloyl derivative involved heating a solution of **8** in THF at reflux temperature, in the presence of phthalic anhydride. However, we isolated **10** together with a significant amount (35%) of the 7-substituted 2-methylimidazolo[4,5-*b*]pyridine **11**. This compound (**11**) was obviously obtained through an intermolecular nucleophilic attack of the 2-amino group to the 3-acetamide carbonyl of **8**. We subsequently found that the formation of this byproduct (**11**) is minimal (less than 5%) if the reaction is conducted at lower temperature (50 °C).

Compound **10** was then heated at reflux in benzene (90 °C) with isoamyl nitrite, in the presence of acetic anhydride.[15] This furnished a mixture of the 1- and 2-acetylpyrazolo[3,4-*c*]pyridines **12** through a rearrangement of the intermediate *N*-nitroso compound.

Both the *N*-phthaloyl and acetyl groups were easily cleaved upon treatment of **12** with methanolic ammonia. This provided the tri-*O*-benzyl derivative **13** which was then converted to the target compound 7-amino-3-(β-D-ribofuranosyl)pyrazolo[3,4-*c*]pyridine (**14**) by a reaction of **13** with boron trichloride in a dichloromethane solution.

In conclusion, we have developed an efficient method to prepare 4-deazaformycin A, through the attachment of a protected ribonolactone to a suitably substituted picoline, followed by an elaboration of the pyrazolo[3,4-*c*]pyridine ring system, with the appropriate exocyclic functional groups.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use, while dichloromethane was freshly distilled from calcium hydride. Melting points are uncorrected. ^{1}H NMR spectra and 2-D spectra (^{1}H−^{1}H COSY, NOESY, HMQC, and HMBC) were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 50 MHz in deuterated solvents and were referenced to TMS (δ scale). Flash column chromatography was accomplished with silica gel 60 (0.040−0.063 mm). Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) silica gel F-254 plates. Elemental analyses were performed at the Microanalytical Sections of the National Hellenic Research Foundation and are within ±0.4% of the theoretical values.

***tert*-Butyl-*N*-[3-acetamido-4-(2,3,5-tri-*O*-benzyl-1-hydroxy-α,β-D-ribofuranosyl)methylpyridin-2-yl] Carbamate (5).** To a solution of picoline **3**[9] (1 g, 3.77 mmol) in dry THF (100 mL) at −78 °C was added under argon *n*-BuLi (9.4 mL, 15.04 mmol, 1.6 M solution in hexanes). The resulting light-yellow solution was stirred at −78 °C for 15 min and the temperature then raised to 5 °C for 20 min. The orange solution was cooled to −78 °C and a solution of the D-ribonolactone **4**[11] (1.81 g, 4.33 mmol) in dry THF (10 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 15 min and then at room temperature for an additional 5 h. A saturated ammonium chloride solution was then added to the reaction mixture to quench the excess *n*-BuLi. The solvent was vacuum evaporatedand water was added to the residue and then extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried (Na_2SO_4) and concentrated to dryness to give an oil that was purified by flash chromatography (silica gel 40 × 3 cm), using a mixture of CH_2Cl_2/AcOEt 7/3 as the eluent. This resulted in 700 mg (27%) of pure (α)-**5** as a colorless syrup and 500 mg (19%) of a 7/3 mixture of (α)- and (β)-**5**, as determined by ^{1}H NMR. Data for **5**, α-anomer: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H, *t*-Bu), 2.04 (s, 3H, CH_3), 2.92 (d, 1H, 4-CH_2, J = 14.08 Hz), 3.14 (d, 1H, 4-CH_2, J = 14.08 Hz), 3.19 (dd, 1H, H-5′, $J_{5',4'}$ = 5.09 Hz, $J_{5',5'}$ = 10.17 Hz), 3.33 (dd, 1H, H-5′, $J_{5',4'}$ = 3.52 Hz, $J_{5',5'}$ = 10.17 Hz), 3.63 (d, 1H, H-2′, $J_{2',3'}$ = 5.08 Hz), 3.83 (m, 1H, H-3′), 4.32−4.62 (m, 7H, H-4′, 6 × benzylic methylene H), 4.71 (br s, 1H, OH, D_2O exchangeable), 6.59 (d, 1H, H-5, $J_{5,6}$ = 5.08 Hz), 7.23−7.38 (m, 15H, 3 × C_6H_5), 7.78 (br s, 1H, NHBoc, D_2O exchangeable), 8.19 (d, 1H, H-6, $J_{6,5}$ = 5.08 Hz), 9.06 (br s, 1H, −NHAc, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ 23.2, 28.2, 39.2, 69.8, 72.4, 73.3, 73.4, 76.2, 77.6, 80.3, 80.5, 104.7, 122.7, 124.7, 127.9, 128.1, 128.3, 128.4, 128.5, 136.5, 136.7, 137.3, 141.4, 146.0, 147.0, 152.3, 169.8. Anal. Calcd for $C_{39}H_{45}N_3O_8$: C, 68.50; H, 6.63; N, 6.15. Found: C, 68.23; H, 6.51; N, 6.06.

(1*R*,2*S*,3*S*)-4-Acetoxy-5-[[3-acetamido-2-(*N*-acetyl-*N*-*tert*-butoxycarbonyl)amino]pyridin-4-yl]-2,3-bis-benzyloxy-1-benzyloxymethylpent-4-enyl Acetate (6). To a solution of **5** (46 mg, 0.067 mmol) in dry CH_2Cl_2 (2 mL) was added Ac_2O (0.06 mL) and triethylamine (0.06 mL) and the reaction was stirred at room temperature overnight. The solvents were vacuum evaporated and the residue was purified by flash chromatography (silica gel 12 × 1 cm), using a mixture of cyclohexane/AcOEt 7/3 as the eluent, to give pure **6**, as an oil (44 mg, 80%). ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H, *t*-Bu), 1.97 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.53(s, 3H, CH_3), 3.62 (dd, 1H, H-1a, $J_{1a,1}$ = 3.91 Hz, $J_{1a,1a}$ = 10.95 Hz), 3.68 (dd, 1H, H-1a, $J_{1a,1}$ = 5.86 Hz, $J_{1a,1a}$ = 10.95 Hz), 3.93 (m, 1H, H-2), 4.11 (d, 1H, H-3, $J_{3,4}$ = 5.47 Hz), 4.40−4.49 (m, 3H, 3 × benzylic methylene H), 4.61 (br s, 2H, 2 × benzylic methylene H), 4.69 (d, 1H, 1 × benzylic methylene H, J = 11.74 Hz), 5.38 (m, 1H, H-1), 6.24 (s, 1H, H-5), 7.19−7.33 (m, 15H, 3 × C_6H_5), 7.57 (d, 1H, H-5′, $J_{5',6'}$ = 5.09 Hz), 8.51 (d, 1H, H-6′, $J_{6',5'}$ = 5.09 Hz). ^{13}C NMR ($CDCl_3$) δ 21.0, 21.1, 25.7, 26.0, 27.5, 68.3, 71.7, 71.8, 73.0, 73.8, 78.5, 78.6, 84.4, 112.6, 123.1, 127.6, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 131.5, 137.0, 137.6, 137.9, 143.5, 148.7, 150.5, 151.1, 151.9, 167.8, 170.0, 172.6, 172.9. Anal. Calcd for $C_{45}H_{51}N_3O_{11}$: C, 66.73; H, 6.35; N, 5.19. Found: C, 66.50; H, 6.51; N, 5.24.

(*Z*)-*tert*-Butyl-*N*-[3-acetamido-4-(2,3,5-tri-*O*-benzyl-D-ribofuranosylidenemethyl)pyridin-2-yl] Carbamate (7). Boron trifluoride diethyl etherate (0.45 mL, 3.6 mmol) was added dropwise under argon at −20 °C to a solution of **5** (α/β) (0.82 g, 1.2 mmol) in dry CH_2Cl_2 (20 mL). The resulting solution was stirred at −20 °C for 6 h and then neutralized (pH 7) with a saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried (Na_2SO_4) and then concentrated to dryness. The residue was purified by flash chromatography (silica gel, 18 × 1 cm), using a mixture of CH_2Cl_2/AcOEt 7/3 as the eluent to give 0.80 g (99%) of compound **7**. Mp 155−156 °C (AcOEt−*n*-hexane). ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H, *t*-Bu), 2.12 (s, 3H, CH_3), 3.59 (dd, 1H, H-5′, $J_{5',4'}$ = 4.40 Hz, $J_{5',5'}$ = 11.24 Hz), 3.77 (dd, 1H, H-5′, $J_{5',4'}$ = 2.69 Hz, $J_{5',5'}$ = 11.24 Hz), 4.03 (dd, 1H, H-3′, $J_{3',2'}$ = 4.89 Hz, $J_{3',4'}$ = 6.60 Hz), 4.36 (d, 1H, H-2′, $J_{2',3'}$ = 4.89 Hz), 4.48−4.79 (m, 7H, H-4′, 6 × benzylic methylene H), 5.48 (s, 1H, C=CH), 7.12 (br s, 1H, NHAc, D_2O exchangeable), 7.22−7.41 (m, 15H, 3 × C_6H_5), 7.83 (d, 1H, H-5, $J_{5,6}$ = 5.38 Hz), 8.16 (d, 1H, H-6, $J_{6,5}$ = 5.38 Hz), 8.47 (br s, 1H, NHBoc, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ 23.5, 28.3, 68.8, 70.3, 72.2, 73.5, 76.0, 76.6, 81.7, 84.1, 96.5, 120.8, 121.7, 127.7, 127.9, 128.0, 128.2, 128.6, 137.4, 137.6, 137.9, 143.0, 146.1, 146.7, 154.3, 158.4, 168.8. Anal. Calcd for $C_{39}H_{43}N_3O_7$: C, 70.36; H, 6.51; N, 6.31. Found: C, 70.02; H, 6.65; N, 6.07.

***N*-[2-Amino-4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-methylpyridin-3-yl]acetamide (8).** Trifluoracetic acid (1.16 mL, 15 mmol) and Et_3SiH (1.20 mL, 7.5 mmol) were added under argon at 0 °C to a solution of **7** (500 mg, 0.75 mmol) in dry CH_2Cl_2 (10 mL). The resulting solution was stirred overnight at room temperature and then neutralized with a saturated $NaHCO_3$

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solution. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 18 × 1 cm), using a mixture of CH_2Cl_2/MeOH 98/2 as the eluent to give **8** (217 mg, 51%), together with the corresponding α-anomer **9** (80 mg, 19%). Data for **8**: ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H, CH_3), 2.62 (dd, 1H, 4-CH_2, J = 13.89, 6.58 Hz), 2.96 (dd, 1H, 4-CH_2, J = 13.89, 2.93 Hz), 3.19 (dd, 1H, H-5′, $J_{5',4'}$ = 5.12 Hz, $J_{5',5'}$ = 10.24 Hz), 3.38 (dd, 1H, H-5′, $J_{5',4'}$ = 3.65 Hz, $J_{5',5'}$ = 10.24 Hz), 3.49 (dd, 1H, H-2′, $J_{2',1'}$ = 7.67 Hz, $J_{2',3'}$ = 5.11 Hz), 3.64 (dd, 1H, H-3′, $J_{3',2'}$ = 5.11 Hz, $J_{3',4'}$ = 2.93 Hz), 4.14 (m, 1H, H-4′), 4.25 (m, 1H, H-1′), 4.34−4.64 (m, 6H, 6 × benzylic methylene H), 4.75 (br s, 2H, NH_2, D_2O exchangeable), 6.27 (d, 1H, H-5, $J_{5,6}$ = 5.12 Hz), 7.18−7.38 (m, 15H, 3 × C_6H_5), 7.81 (d, 1H, H-6, $J_{6,5}$ = 5.12 Hz), 8.82 (br s, 1H, NHAc, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ 23.2, 34.2, 70.1, 71.9, 72.3, 73.4, 76.2, 78.8, 81.5, 81.7, 116.7, 119.3, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 137.3, 141.9, 145.4, 154.9, 168.9. Anal. Calcd for $C_{34}H_{37}N_3O_5$: C, 71.94; H, 6.57; N, 7.40. Found: C, 71.76; H, 6.45; N, 7.67. Data for the α-anomer (**9**): ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, CH_3), 2.52 (d, 1H, 4-CH_2, J = 13.54 Hz), 2.89 (d, 1H, 4-CH_2, J = 13.54 Hz), 3.71 (m, 3H, H-4′, 2 × H-5′), 4.02 (m, 1H, H-2′), 4.24 (m, 1H, H-3′), 4.50−4.69 (m, 6H, H-1′, 5 × benzylic methylene H), 4.85−4.92 (m, 3H, 1 × benzylic methylene H, NH_2, D_2O exchangeable), 6.31 (d, 1H, H-5, $J_{5,6}$ = 5.12 Hz), 7.24−7.38 (m, 15H, 3 × C_6H_5), 7.77 (d, 1H, H-6, $J_{6,5}$ = 5.12 Hz), 9.82 (br s, 1H, NHAc, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ 23.1, 39.0, 70.0, 71.4, 73.5, 73.6, 74.1, 79.3, 80.2, 82.7, 117.6, 120.2, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 137.5, 137.9, 138.0, 141.7, 144.6, 154.7, 169.0. Anal. Calcd for $C_{34}H_{37}N_3O_5$: C, 71.94; H, 6.57; N, 7.40. Found: C, 72.08; H, 6.51; N, 7.15.

***N*-[4-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)methyl-2-phthalimidopyridin-3-yl]acetamide (10).** Phthalic anhydride (157 mg, 1.06 mmol) was added to a solution of **8** (600 mg, 1.06 mmol) in dry toluene (60 mL) and the reaction mixture was heated at 50 °C, under argon, overnight. The suspension was filtered, the solvent was vacuum evaporated, and the residue was purified by flash chromatography (silica gel, 23 × 2 cm), using a mixture of CH_2Cl_2/AcOEt 8/2 as the eluent to give pure **10** (642 mg, 87%) and **11** (30 mg, 5%). Data for **10**: Oil. ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H, CH_3CO), 2.77 (dd, 1H, 4-CH_2, J = 13.90, 5.48 Hz), 3.12 (dd, 1H, 4-CH_2, J = 13.90, 3.29 Hz), 3.43 (dd, 1H, H-5′, $J_{5',5'}$ = 10.35 Hz, $J_{5',4'}$ = 4.26 Hz), 3.51 (m, 2H, H-5′, H-2′), 3.79 (dd, 1H, H-3′, J = 2.56, 5.12 Hz), 4.25 (m, 1H, H-4′), 4.34 (m, 2H, H-1′, 1 × benzylic methylene H), 4.43 (br s, 2H, 2 × benzylic methylene H), 4.50−4.68 (m, 3H, 3 × benzylic methylene H), 6.81 (d, 1H, H-5, $J_{5,6}$ = 4.76 Hz), 7.21−7.38 (m, 15H, 3 × C_6H_5), 7.78 (m, 2H, H-4″, H5″), 7.92 (m, 2H, H-3″, H-6″), 8.29 (d, 1H, H-6, $J_{6,5}$ = 4.76 Hz), 8.42 (br s, 1H, NHAc, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ 22.9, 34.0, 70.2, 72.0, 72.3, 73.2, 76.4, 78.5, 80.3, 82.2, 123.7, 124.0, 126.6, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 128.7, 128.8, 131.5, 132.0, 132.4, 134.3, 134.4, 137.4, 137.5, 137.9, 143.1, 145.2, 146.9, 166.1, 166.2, 168.0. Anal. Calcd for $C_{42}H_{39}N_3O_7$: C, 72.29; H, 5.63; N, 6.02. Found: C, 72.53; H, 5.52; N, 5.95. Data for 2-methyl-7-[(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)methyl]imidazolo[4,5-*b*]pyridine (**11**): Oil. ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H, CH_3), 3.21 (dd, 1H, 4-CH_2, J = 14.19, 7.83 Hz), 3.31 (dd, 1H, 4-CH_2, J = 14.19, 4.41 Hz), 3.48 (dd, 1H, H-5′, $J_{5',5'}$ = 10.76 Hz, $J_{5',4'}$ = 4.89 Hz), 3.55 (dd, 1H, H-5′, $J_{5',5'}$ = 10.76 Hz, $J_{5',4'}$ = 4.40 Hz), 3.78 (m, 1H, H-2′), 3.89 (m, 1H, H-3′), 4.25 (m, 1H, H-4′), 4.34−4.55 (m, 7H, H-1′, 6 × benzylic methylene H), 7.04 (d, 1H, H-6, $J_{6,5}$ = 4.89 Hz), 7.14−7.33 (m, 15H, 3 × C_6H_5), 8.19 (d, 1H, H-5, $J_{5,6}$ = 4.89 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4, 35.1, 70.1, 71.8, 71.9, 73.4, 77.1, 80.1, 80.8, 81.1, 118.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 129.2, 130.7, 130.8, 137.6, 137.7, 137.9, 141.8, 153.1. Anal. Calcd for $C_{34}H_{35}N_3O_4$: C, 74.29; H, 6.42; N, 7.64. Found: C, 73.97; H, 6.31; N, 7.78.

7-Amino-3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazolo-[3,4-*c*]pyridine (13). To a suspension of **10** (237 mg, 0.34 mmol) in dry benzene (50 mL) were added under argon AcOK (33 mg, 0.34 mmol) and Ac_2O (0.1 mL, 1.02 mmol). This reaction mixture was heated at 80° C and isoamyl nitrite (0.07 mL, 0.51 mmol) was then added dropwise. The resulting mixture was heated at reflux for 6 h. The insoluble material was filtered off and washed with hot toluene (10 mL), and the combined filtrates were evaporated to dryness to afford a yellowish solid (215 mg), corresponding to a mixture of the acetamides **12**. A saturated methanolic ammonia solution (50 mL) was added to the above mixture and the resulting solution was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was purified by flash chromatorgaphy (silica gel, 25 × 1 cm), using a mixture of CH_2Cl_2/MeOH 95/5 as the eluent, to give pure **13** (153 mg, 84%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 3.63 (dd, 1H, H-5′, $J_{5',5'}$ = 10.27 Hz, $J_{5',4'}$ = 3.43 Hz), 3.79 (dd, 1H, H-5′, $J_{5',5'}$ = 10.27 Hz, $J_{5',4'}$ = 2.94 Hz), 4.17 (m, 1H, H-3′), 4.33 (m, 1H, H-2′), 4.40 (m, 1H, H-4′), 4.48−4.66 (m, 6H, 6 × benzylic methylene H), 5.50 (d, 1H, H-1′, $J_{1',2'}$ = 5.38 Hz), 6.90 (d, H-4, $J_{4,5}$ = 5.86 Hz), 7.16−7.35 (m, 15H, 3 × C_6H_5), 7.47 (d, 1H, H-5, $J_{5,4}$ = 5.86 Hz). ^{13}C NMR ($CDCl_3$) δ 69.4, 72.6, 72.6, 73.7, 77.3, 77.8, 81.1, 81.2, 104.8, 122.8, 128.1, 128.6, 128.7, 132.9, 136.2, 137.4, 137.6, 137.8, 140.0, 148.3. Anal. Calcd for $C_{32}H_{32}N_4O_4$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.81; H, 6.12; N, 10.09.

7-Amino-3-(β-D-ribofuranosyl)pyrazolo[3,4-*c*]pyridine (14). A solution of BCl_3 (1 M in hexane, 2.46 mL) was added dropwise under argon to a solution of **13** (110 mg, 0.205 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then a cold solution of CH_2Cl_2/MeOH (1/1.8 mL) was added. The solvents were evaporated and the residue was purified by flash chromatography (silica gel, 4.5 × 1.2 cm), using a mixture of CH_2Cl_2/MeOH 8/2 as the eluent to give pure **14** (44 mg, 81%) as an oil. ^{1}H NMR (CD_3OD) δ 3.77 (dd, 1H, H-5′, $J_{5',5'}$ = 12.36 Hz, $J_{5',4'}$ = 4.30 Hz), 3.86 (dd, 1H, H-5′, $J_{5',5'}$ = 12.36 Hz, $J_{5',4'}$ = 3.23 Hz), 4.08 (m, 1H, H-4′), 4.17 (m, 2H, H-2′, H-3′), 5.16 (d, 1H, H-1′, $J_{1',2'}$ = 6.45 Hz), 7.21 (d, H-4, $J_{4,5}$ = 6.72 Hz), 7.29 (d, 1H, H-5, $J_{5,4}$ = 6.72 Hz). ^{13}C NMR (CD_3OD) δ 62.9, 72.7, 76.9, 78.2, 87.6, 106.3, 121.5, 123.9, 136.4, 138.8, 151.4. Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.72; H, 5.22; N, 20.88.

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