A NOVEL SYNTHESIS OF *C*-NUCLEOSIDES HAVING PYRROLO[1,2-*f*]PTERIDINE, 6- AND 8-DEAZAPYRROLO[1,2-*f*]-PTERIDINE RING SYSTEMS FROM 6-HYDROXY-6-(2,3,5-TRI-*O*-BENZOYL-β-D-RIBOFURANOSYL)- 2*H*-PYRAN-3(6*H*)-ONE

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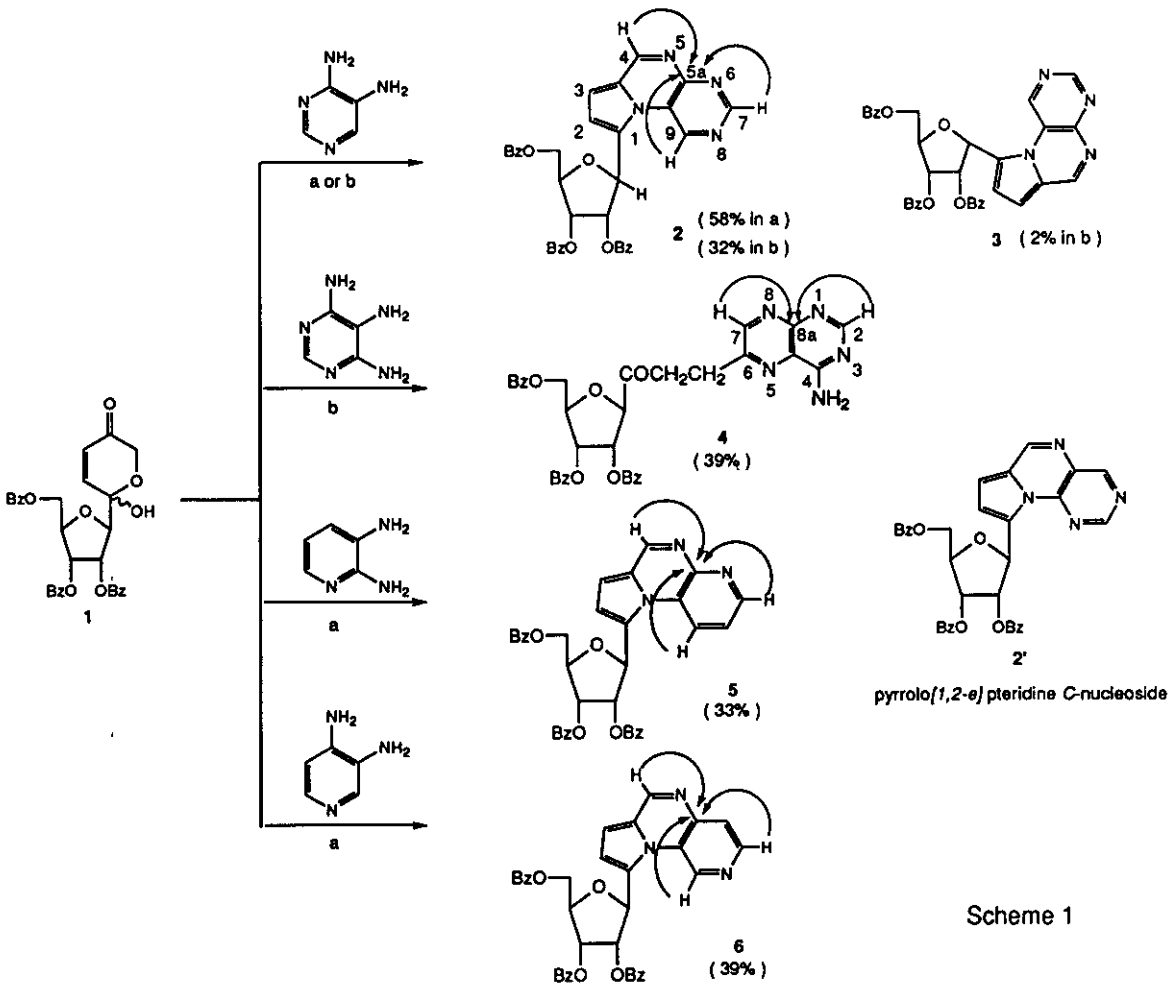
Abstract ——— A versatile intermediate pyranulose glycoside (**1**) for *C*-nucleoside synthesis was treated with 4,5-diaminopyrimidine in AcOH to give 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-*f*]pteridine (**2**) in 58% yield. However, treatment of **1** with 4,5,6-triaminopyrimidine in TFA afforded the 4-aminopteridine (**4**) without formation of the pyrrolo[1,2-*f*]pteridine. Similar reaction of 2,3- and 3,4-diaminopyridines with **1** in AcOH led to formation of 8- and 6-deazapyrrolo[1,2-*f*]pteridines (**5** and **6**), respectively. Removal of the sugar protecting groups in **2**, **5**, and **6** with sodium carbonate gave the deprotected *C*-nucleosides (**7**, **8** and **9**).

During our efforts to develop a general synthetic method for *C*-nucleosides, we have prepared an extremely useful intermediate, *viz*, 6-hydroxy-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2*H*-pyran-3(6*H*)-one (**1**), from which some ring transformations with a variety of amines have been reported.[1] We now describe the preparation of *C*-nucleosides having tricyclic systems, pyrrolo[1,2-*f*]pteridine, pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (8-deazapyrrolo[1,2-*f*]-pteridine), pyrido[3,4-*e*]pyrrolo[1,2-*a*]pyrazine (6-deazapyrrolo[1,2-*f*]pteridine), through the cyclocondensation of **1** with 1,2-diaminoheterocycles (pyrimidines and pyridines). The structure of pyrrolo[1,2-*f*]pteridine is somewhat similar to that of 5,10-methylenetetrahydrofolic acid, which participates in one carbon transfer reaction *in vivo*. The tricyclic *C*-nucleosides may show interesting and / or improved biologocal effects. Two previous syntheses of pyrrolo[1,2-*f*]pteridine derivatives have been reported by different routes,[2,3] and here we also report a facile

one-pot synthesis of this ring system, as a part of our program of synthesis of *C*-nucleoside.

The starting pyranulose glycoside (**1**) used in this work was prepared from the furan glycoside by the procedure previously reported.[1a] The cyclocondensation of the pyranulose glycoside (**1**) with 4,5-diaminopyrimidine in acetic acid at room temperature for 3 days gave 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-*f*]pteridine (**2**) as a major reaction product in 58% yield without any formation of the isomeric pyrrolo[1,2-*e*]pteridine isomer (**2'**). Structural determination of **2** was made by MS and NMR experiments. The ^{1}H NMR spectrum of **2** showed two doublets at δ 7.04 (J = 3.1 Hz) and δ 7.33 (J = 3.1 Hz) characteristic of the pyrrole moiety. The C-5a (δ_C 152.6) shows correlation with H-4 (δ_H 9.11), H-7 (δ_H 9.31), and H-9 (δ_H 9.75) in the ^{1}H-^{13}C long-range COSY spectrum of **2**. These data indicate the ring system of pyrrolo[1,2-*f*]pteridine in **2**.



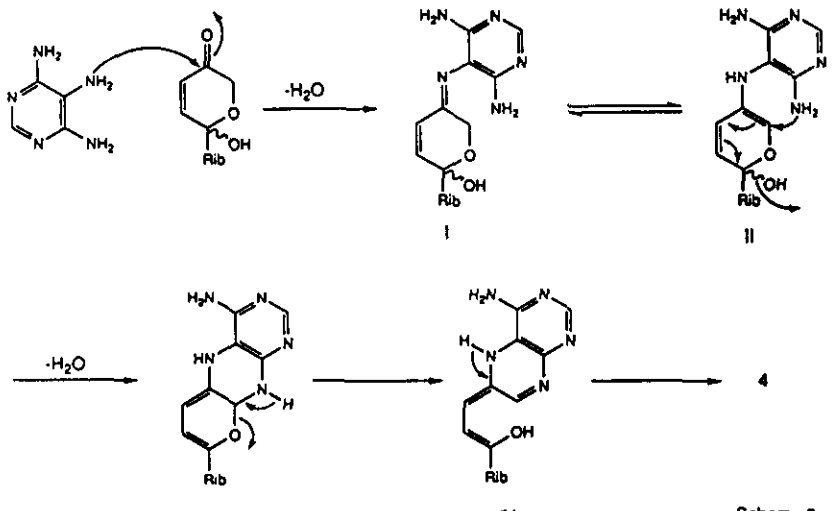
Scheme 1

Solvent : (a), acetic acid ; (b), TFA.
The ^{1}H-^{13}C long range COSY experiments of compounds (**2**, **4**, **5**, and **6**).

In trifluoroacetic acid (TFA), 2 was obtained in 32% yield as the main product and its α isomer (3) was obtained in 2 % yield. The stereochemistry of the C-1' position in compounds (**2** and **3**) was confirmed by NOE experiments. Irragiation of the H-1' (δ 6.24) in **3** gave a 10.1% enhancement of the signal at δ 6.35 assignable to the H-2'. This enhancement was not observed for **2**.

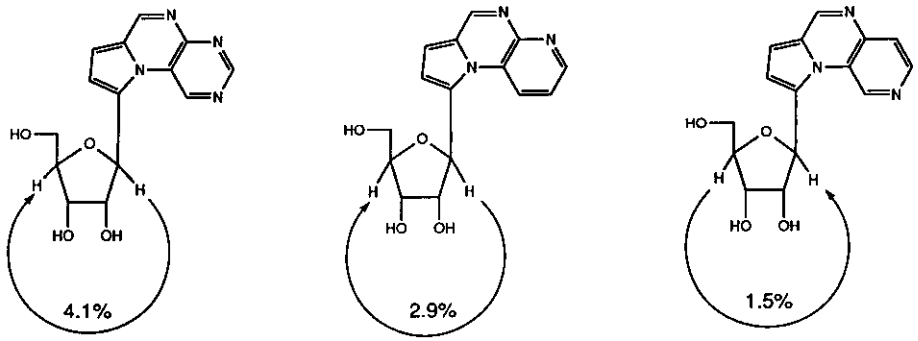
Next, the cyclocondensation of the pyranulose glycoside (**1**) with 4,5,6-triaminopyrimidine in TFA at room temperature gave 4-amino-6-[3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-oxopropyl]pteridine (**4**) in 39% yield without formation of the corresponding tricyclic compound. The position of the ribofuranosyl group in **4** was confirmed by a ^{1}H-^{13}C long-range COSY experiment. The C-8a (δ_C 162.7) shows correlation with H-2 (δ_H 8.91) and H-7 (δ_H 8.69). This data indicated that the ribofuranosyl moiety is linked at the 6 position. A plausible explanation for the formation of **4** involves nucleophilic attack by the more basic 5-amino group of 4,5,6-triaminopyrimidine on the carbonyl carbon of the pyranone moiety of **1** with subsequent formation of a Schiff's base (**I**), which then isomerizes to give ***II***. *Dehydration of II would lead to tricyclic compound (III), which is then opened to give the* unstable ring-opened intermediate (**IV**). **IV** is converted to **4** by a proton shift (Scheme 2). We think that the *formation of* **2** proceeds by the same mechanism as that for the formation of pyrroloquinoxaline described in a previous paper.[1a]

The pyranulose glycoside (**1**) reacted with 2,3-diaminopyridine in acetic acid at room temperature for 3 days, gave 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**5**) in 33% yield. The ^{1}H NMR spectrum of **5** clearly showed two doublets at δ 6.90 (J = 4.1 Hz) and δ 7.05 (J = 4.1 Hz) characteristic of the pyrrole moiety. When the similar reaction of **1** with 3,4-diaminopyridine was performed, corresponding tricyclic compound (**6**), 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[4,3-*e*]pyrrolo[1,2-*a*]pyrazine, was obtained in 39% yield.



Scheme 2

Structural determination of **5** and **6** was made by MS and ^{1}H-^{13}C long-range COSY experiments (Scheme 1). Roba and his collaborators[4] have synthesized pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine ring system by intramolecular cyclization of 3-(1-pyrrolyl)-2-pycolinyl azide. The ring structure of **6**, pyrido[4,3-*e*]pyrrolo[1,2-*a*]pyrazine, comes into new entry of a novel heterocyclic system. The removel of the sugar protecting groups in compounds (**2**, **5**, and **6**) was readily accomplished with aqueous sodium carbonate to afford the compounds (**7**, **8**, and **9**). The stereochemistry of the C-1' position in compounds (**7**, **8**, and **9**) was confirmed as to be β by NOE experiments (Figure 1). Thus, the NOE indicates that the β-ribofuranoside configuration have been preserved during the reaction sequence.



7 **8** **9**

Figure 1. NOE expenments of compounds (**7**, **8**, and **9**).

ACKNOWLEDGEMENT

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EXPERIMENTAL

MS spectra were taken on a Hitachi M-80 instrument by direct insertion at 70 eV; fast-atom bombardment MS spectra (FABMS) were run on a JMS-HX 110 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JNM-A-400 or an A-600 (JEOL) spectrometer, with tetramethylsilane as an internal standard. Optical rotations were measured with a Jasco DIP-370 polarimeter (10-cm cell) at 25 °C. Analytical TLC was performed on glass plates coated with a 0.5-mm layer of Silica Gel GF_{254} (E. Merck). The compounds were detected by UV light (254 nm).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-*f*]pteridine (2): To a solution of 1 (103.2 mg, 0.185 mmol) in acetic acid (5 mL) was added 4,5-diaminopyrimidine (24.1 mg, 0.221 mmol) and the mixture was stirred at rt for 3 days. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and then extracted with $CHCl_3$ (3X10 mL). The extracts were combined, washed with water, dried over $MgSO_4$, and evaporated to dryness. The residual syrup was purified by PTLC with $CHCl_3$-MeOH (49:1) as eluent. This afforded 65.9 mg (58%) of **2** as a pale yellow foam; ^{1}H NMR ($CDCl_3$) δ 4.56 (dd, 1 H, J = 3.5, 12.3 Hz, H-5'a), 4.77 (dd, 1 H, J = 3.5, 12.3 Hz, H-5'b), 4.94 (m, 1 H, H-4'), 5.79 (d, 1 H, J = 6.6 Hz, H-1'), 6.03 (dd, 1 H, J = 3.7, 4.6 Hz, H-3'), 6.43 (dd, 1 H, J = 4.6, 6.6 Hz, H-2'), 7.04 (d, 1 H, J = 3.1 Hz, H-2), 7.33 (d, 1 H, J = 3.1 Hz, H-3), 7.26-8.02 (m, 15 H, Ph), 9.11 (s, 1H, H-4), 9.31 (s, 1 H, H-7), 9.75 (s, 1 H, H-9); ^{13}C NMR ($CDCl_3$) δ 63.6 (C-5'), 72 6 (C-3'), 73.0 (C-2'), 74.4 (C-1'), 81.0 (C-4'), 110.6 (C-2), 115.3 (C-3), 123.0-133.7 (C-1, 3a, 9a, Ph),147.8 (C-9), 152.6 (C-5a), 153.6 (C-7), 155.1 (C-4), 165.1, 165.5, 165.8 (C=O). HRFABMS Found: MH$^+$ 615.1855 Calcd for $C_{35}H_{27}N_4O_7$; MH 615.1880 Nitrobenzyl alcohol (NBA) as matrix.

1-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)pyrrolo[1,2-*f*]pteridine (3): In the same manner (reaction solvent was used TFA) as described above for **2**, 5.5 mg (2%) of **3** was obtained as a foam from 218.4 mg (0.391 mmol) of **1** and 4,5-diaminopyrimidine together with 76.8 mg (32%) of **2**. **Compound 3:** ^{1}H NMR ($CDCl_3$) δ 4 76 (dd, 1 H, J = 4.4, 12.1 Hz, H-5'a), 4.84 (dd, 1 H, J = 3.7, 12.1 Hz, H-5'b), 4.93 (m, 1 H, H-4'), 6.07 (dd, 1 H, J = 5.4 Hz, H-3'), 6.24 (d, 1 H, J = 5.4 Hz, H-1'), 6.35 (dd, 1 H, J = 5.4 Hz, H-2'), 7.08 (d, 1 H, J = 4.4 Hz, H-2), 7.26-8.12 (m, 16 H, H-3, Ph), 9.11 (s, 1H, H-4), 9 23 (s, 1 H, H-7), 9.72 (s, 1 H, H-9); ^{13}C NMR ($CDCl_3$) δ 64.0 (C-5'), 72 9 (C-3'), 73.1 (C-2'), 75.4 (C-1'), 79.3 (C-4'), 110.6 (C-2), 117 7 (C-3), 123.3-133.7 (C-1, 3a, 9a, Ph),147.3 (C-9), 152.9 (C-5a), 153.3 (C-7), 155.0 (C-4), 164.8, 165.3, 166.2 (C=O).

4-Amino-6-[3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-oxopropyl]pteridine (4): In the same manner (TFA as the solvent) as described above for **2**, 170.9mg (39%) of **4** was obtained as a yellow foam from 373.7mg (0.669 mmol) of **1** and 4,5,6-triaminopyrimidine: ^{1}H NMR ($CDCl_3$) δ 3.12-3.45 (m, 4 H, CH_2CH_2), 4.61 (dd, 1 H, J = 4.2, 12.3 Hz, H-5'a), 4.76 (m, 1 H, H-4'), 4.83 (d, 1 H, J = 5 1 Hz, H-1'), 4.90 (dd, 1 H, J = 3.1, 12.3 Hz, H-5'b), 5.69 (dd, 1 H, J = 5.4 Hz, H-3'), 5 85 (dd, 1 H, J = 5.4 Hz, H-2'), 7 27-8.04 (m, 15 H, Ph), 8.69 (s, 1 H, H-7), 8.91 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 28.2. 35.7 (CH_2CH_2), 63.5 (C-5'), 72.3 (C-3'), 72.7 (C-2'), 80.5 (C-1'), 85.4 (C-4'), 123 0-133.7 (C-4a, Ph), 152.2 (C-7), 152 4 (C-4), 154.4 (C-6), 158.1 (C-2), 162.7 (C-8a), 165.3, 165.5, 166.1, 205 5 (C=O). HRFABMS Found: MH$^+$ 648.2119 Calcd for $C_{36}H_{30}N_5O_8$; MH 648.2094. NBA as matrix.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (5): This compound was prepared from **1** and 2,3-diaminopyridine as described above for **2**: colorless oil, 33%; ^{1}H NMR ($CDCl_3$): δ 4.60 (dd, 1 H, J = 2.9, 12.1 Hz, H-5'a), 4.79 (dd, 1 H, J = 2.9, 12.1 Hz, H-5'b), 4.91 (m, 1 H, H-4'), 5 83

(d, 1 H, J= 7.0 Hz, H-1'), 6.02 (dd, 1 H, J= 3.7, 5.5 Hz, H-3'), 6.39 (dd, 1 H, J= 5.5, 7.0 Hz, H-2'), 6.90 (d, 1 H, J= 4.1 Hz, H-2), 7.05 (d, 1 H, J= 4.1 Hz, H-3), 7.28-8.00 (m, 16 H, H-8, Ph), 8.78 (d, 1 H, J= 4.4 Hz, H-7), 8.85 (d, 1 H, J = 8.1 Hz, H-9), 8.97 (s, 1 H, H-4); ^{13}C NMR ($CDCl_3$): δ 63.6 (C-5'), 72.6 (C-3'), 73.3 (C-2'), 74.9 (C-1'), 80.7 (C-4'), 108.0 (C-2), 114.8 (C-3), 122.4 (C-8), 125.6 (C-9), 125.1, 128.4-133.7 (C-1, 3a, 9a, Ph), 146.8 (C-7), 148.2 (C-5a), 149.1 (C-4), 165.2, 165.5, 165.9 (C=O); HRFABMS Found: MH$^+$ 614.1927 Calcd for $C_{36}H_{28}N_3O_7$; MH 614.1935. NBA as matrix.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[3,4-*e*]pyrrolo[1,2-*a*]pyrazine (6): This compound was prepared from **1** and 3,4-diaminopyridine as described above for **2**: colorless oil, 39%; ^{1}H NMR ($CDCl_3$): δ 4.60 (dd, 1 H, J= 3.5, 12.2 Hz, H-5'a), 4.75 (dd, 1 H, J= 3.5, 12.2 Hz, H-5'b), 4.94 (m, 1 H, H-4'), 5.93 (d, 1 H, J= 7.8 Hz, H-1'), 6.02 (dd, 1 H, J= 3.4, 5.6 Hz, H-3'), 6.40 (dd, 1 H, J= 5.6, 7.8 Hz, H-2'), 6.97 (d, 1 H, J= 4.2 Hz, H-2), 7.05 (d, 1 H, J= 4.2 Hz, H-3), 7.30-8.06 (m, 15 H, Ph), 7.84 (d, 1 H, J= 5.4 Hz, H-6), 8.69 (d, 1 H, J= 5.4 Hz, H-7), 8.89 (s, 1 H, H-4), 9.87 (s, 1 H, H-9); ^{13}C NMR ($CDCl_3$): δ 63.9 (C-5'), 72.7 (C-3'), 73.2 (C-2'), 74.6 (C-1'), 80.9 (C-4'), 109.4 (C-2), 114.5 (C-3), 122.8 (C-6), 125.7-133.6 (C-1, 3a, 9a, Ph), 140.2 (C-9), 141.8 (C-5a), 145.7 (C-7), 150.1 (C-4), 165.2, 165.5, 167.0 (C=O). HRFABMS Found: MH$^+$ 614.1924 Calcd for $C_{36}H_{28}N_3O_7$; MH 614.1935. NBA as matrix.

General Procedure for the Deprotection. Sufficient amount of methanolic sodium carbonate (0.5 mL, 0.4 mmol) was added to the protected *C*-nucleoside (0.04 mmol) in MeOH (2 mL). The mixture was kept at room temperature for 5 h, and evaporated under reduced pressure. The residue was purified by PTLC to afford the corresponding deprotected free *C*-nucleoside.

1-(β-D-Ribofuranosyl)pyrrolo[1,2-*f*]pteridine (7): colorless solid, mp 247 ℃ (decomp) (from methanol); 41%; $[\alpha]_D$ -37.0° (c 0.4, Me_2SO); ^{1}H NMR [$(CD_3)_2SO$]: δ 3.49 (m, 2 H, H-5'), 4.05 (m, 2 H, H-3', 4'), 4.12, 4.86, 5.34 (each br, 3 H, OH exchanges with D_2O), 4.44 (dd, 1 H, J = 4.8, 7.1 Hz, H-2'), 5.28 (d, 1 H, J= 7.1Hz, H-1'), 7.26 (d, 1 H, J= 4.2 Hz, H-2), 7.33 (d, 1 H, J= 4.2 Hz, H-3), 9.20, 9.28 (each s, 2 H, H-4, 7), 9.75 (s, 1 H, H-9); ^{13}C NMR $(CD_3)_2SO$): δ 61.6 (C-5'), 71.2 (C-3'), 73.8 (C-2'), 75.6 (C-1'), 85.4 (C-4'), 111.1 (C-2), 115.6 (C-3), 122.9, 128.1, 134.4 (C-1, 3a, 9a), 148.1 (C-9), 152.3 (C-5a), 153.9 (C-7), 154.5 (C-4). HRFABMS Found: M-H 301.0937 Calcd for $C_{14}H_{13}N_4O_4$; M-H 301.0966. Triethanolamine as matrix.

1-(β-D-Ribofuranosyl)pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (8): colorless solid, mp 239 ℃ (decomp) (from methanol); 36%; $[\alpha]_D$ -96.5° (c 0.4, Me_2SO); ^{1}H NMR [$(CD_3)_2SO$]: δ 3.50 (m, 2 H, H-5'), 4.05 (m, 2 H, H-3', -4'), 4.43 (m, 1 H, H-2'), 4.84, 5.21 (each br, 3H, OH exchanged with D_2O), 5.19 (d, 1 H, J= 7.3 Hz, H-1'), 7.13 (d, 1 H, J= 4.2 Hz, H-2), 7.17 (d, 1 H, J = 4.2 Hz, H-3), 7.66 (dd, 1 H, J= 4.5, 8.4 Hz, H-8), 8.70 (dd, 1 H, J = 1.5, 4.5 Hz, H-7), 8.82 (dd, 1 H, J = 1.5, 8.4 Hz, H-9), 9.09 (s, 1 H, H-4); ^{13}C NMR [$(CD_3)_2SO$]: δ 61.6

(C-5'), 71.1 (C-3'), 73.7 (C-2'), 75.4 (C-1'), 85.3 (C-4'), 108.1 (C-2), 115.0 (C-3), 122.5 (C-8), 126.0 (C-9), 124.5, 127.4, 132.5 (C-1, 3a, 9a), 146.3 (C-7), 147.7 (C-5a), 149.1 (C-4). HRFABMS Found: MH^+ 302.1141 Calcd for $C_{15}H_{16}N_3O_4$; MH302.1186. NBA as matrix.

1-(β-D-Ribofuranosyl)pyrido[3,4-*e*]pyrrolo[1,2-*a*]pyrazine (9): colorless solid, mp 271 ℃ (decomp) (from methanol); 22%; $[\alpha]_D$ -32.1° (*c* 0.3, Me_2SO); ^1H NMR [$(CD_3)_2SO$]: δ 3.50 (m, 2 H, H-5'), 4.06 (m, 2 H, H-3', 4'), 4.45, 5.26 (each br, 3 H, OH exchanged with D_2O), 4.83 (dd, 1 H, J = 5.5 Hz, H-2'), 5.21 (d, 1 H, J = 5 5 Hz, H-1'), 7.19 (d, 1 H, J = 4.8 Hz, H-2), 7.22 (d, 1 H, J = 4.8 Hz, H-3), 7.82 (d, 1 H, J = 5.1 Hz, H-6), 8.64 (d, 1 H, J = 5.1 Hz, H-7), 9.07 (s, 1 H, H-4), 9.66 (s, 1 H, H-9); ^{13}C NMR [$(CD_3)_2SO$]: δ 61.6 (C-5'), 71.1 (C-3'), 73.7 (C-2'), 75 6 (C-1'), 85.3 (C-4'), 109.6 (C-2), 114.6 (C-3), 122.2 (C-6), 125.2, 128.1, 132.2 (C-1, 3a, 9a), 140.2 (C-9), 141.3 (C-5a), 145 4 (C-7), 150.3 (C-4). HRFABMS Found: M-H 300.0894 Calcd for $C_{15}H_{14}N_3O_4$; M-H 300.0994. Triethanolamine as matrix.

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