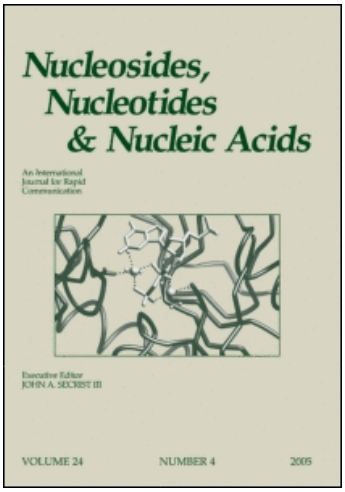

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Synthesis of 4-Formyl-4-imidazolin-2-one Nucleosides, Isomers of Uridine and 2′-Deoxyuridine†

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ABSTRACT

The syntheses of the ribo- and deoxyribonucleoside derivatives of 4-formyl-4-imidazolin-2-one, isosteric isomers of uridine and 2′-deoxyuridine, respectively, were carried out by ring contraction of the corresponding 5-bromouracil nucleosides, followed by conversion of the carboxyl side-chain of the products to the respective carboxaldehyde derivatives.

Key Words: Uridine; 2′-Deoxyuridine; Nucleosides.

INTRODUCTION

Nucleosides that contain 5-membered heterocycles are of considerable interest, due to their diverse biological activities. Figure 1 illustrates the structures of some representative nucleosides in this class. The antibiotics bredinin (**1**) and pyrazofurin (**2**) are examples of naturally occurring ribonucleosides, which have immunosuppressant, antimicrobial, and antitumor activities.[1–3] They are structurally related to 5-amino-imidazole-4-carboxamide riboside (AICAR, **3**), which, in its 5′-monophosphorylated

†In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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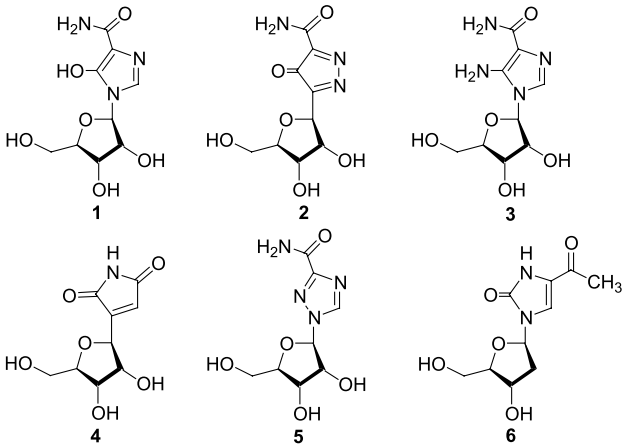


Figure 1. Examples of 5-membered heterocyclic nucleosides. **1**: Bredinine; **2**: pyrazofurin; **3**: AICAR; **4**: showdomycin; **5**: ribavirin; **6**: imidine.

form, is a key intermediate in de novo purine biosynthesis. The antibiotic showdomycin (**4**) owes its cytotoxicity to the chemically reactive maleimide moiety that may alkylate sulfhydryl goups of important biological macromolecules.[3] Pyrazofurin and showdomycin are examples of naturally occurring C-nucleosides.[4] Ribavirin (**5**) is a broad spectrum antiviral agent developed by Robins and his coworkers in the early seventies.[5,6] A number of 4-substituted imidazole nucleoside analogues related to ribavirin were also reported.[7]

Imidine (**6**) is a 5-membered ring isomer of thymidine, the triphosphate of which was shown to be a potent inhibitor of HIV reverse transcriptase, competing with thymidine triphosphate for incorporation into DNA, and causing premature termination of DNA synthesis and enhanced miscoding.[8,9] In the imidine molecule, the exocyclic carbonyl group in the substituent replaces the carbonyl at the 4-position of the pyrimidine ring, and compensates for absence of the latter in the ring-contracted

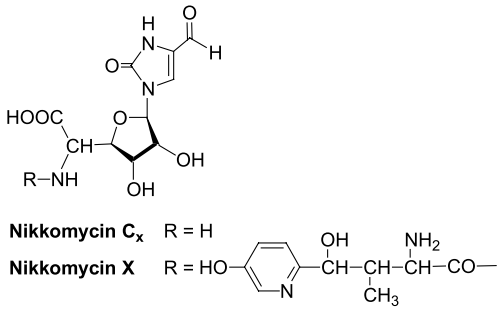


Figure 2. Structures of nikkomycin antibiotics C_x and X. In nikkomycin I, the COOH-group of nikkomycin X is in an amide linkage with glutamic acid.

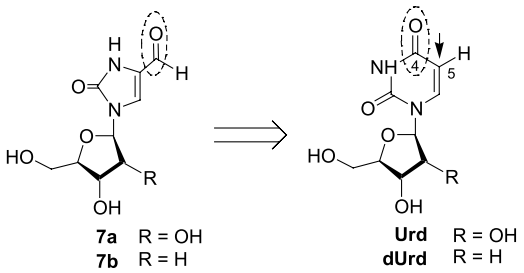


Figure 3. Transformation of the uracil base to 4-formyl-4-imidazolin-2-one. Retrosynthetic scheme showing the shift of the endocyclic C═O to the exocyclic position during ring contraction. Urd: uridine; dUrd: 2′-deoxyuridine.

imidazolinone. The synthesis of the related unsubstituted imidazolone ribonucleoside was reported earlier.[10]

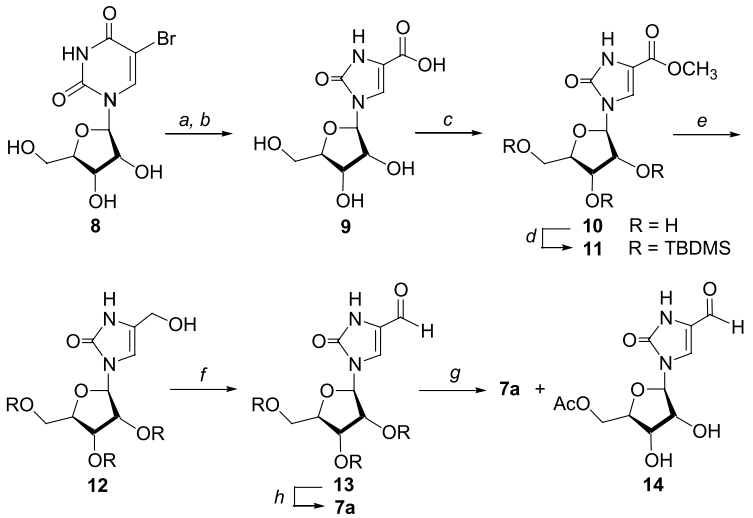
4-Formyl-4-imidazolin-2-one is the aglycon of the antifungal nucleoside antibiotics nikkomycin C_x, X and I (see Figure 2), which are potent chitin synthase inhibitors, due to their structural analogy to UDP-*N*-acetylglucosamine, the natural substrate of this enzyme.[11–13] In these antibiotics 4-formyl-4-imidazolin-2-one mimics the uracil moiety of UDP-*N*-acetylglucosamine, which, combined with our previous results with imidine the analogous thymidine isomer,[8,9] suggested that other 4-formyl-4-imidazolin-2-one nucleosides may have potentially interesting biological activities. Thus, the synthesis of compounds **7a** and **7b**, the 4-formyl-4-imidazolin-2-one analogues of uridine and 2′-deoxyuridine (see Figure 3), as potential antimetabolites of their natural counterparts, was undertaken.

It is interesting to note that in the biosynthesis of nikkomycins, the 5′-phosphate of **7a** was proposed as an intermediate, which is formed from 4-formyl-4-imidazolin-2-one and PRPP via pyrophosphoryl transfer catalyzed by the *nikR* gene product.[14] Indeed, **7a** was recently isolated as the hydrolysis product of this putative intermediate that accumulated in *nikO* mutants blocked in the utilization of this intermediate.[15] Thus, in spite of being an artifact of mutation, **7a** should be regarded as a natural product, and the present work as the first report on its synthesis.

In our synthetic approach to the target compounds, the transfer of the 4-carbonyl group of the pyrimidine ring of uridine and deoxyuridine from the endocyclic to the exocyclic position (see Figure 3) was accomplished by ring-contraction of the corresponding 5-bromouracil derivatives according to the method of Otter et al.[16,17]

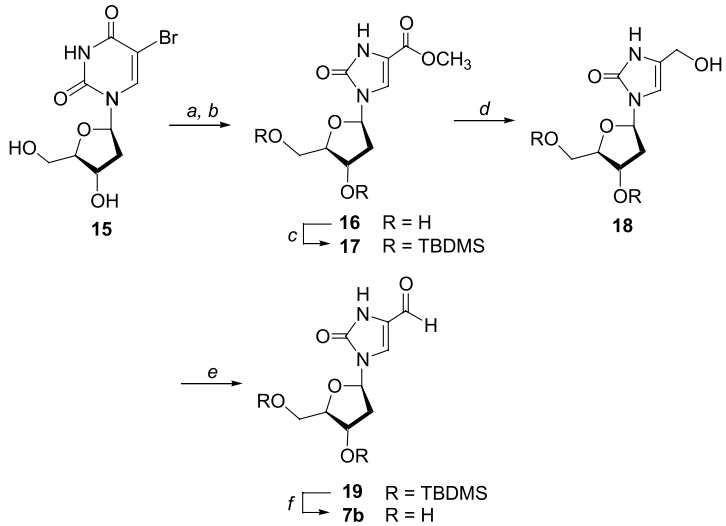
RESULTS AND DISCUSSION

The synthesis of **7a** is outlined in Scheme 1. Ring contraction of the acetonide of commercial 5-bromouridine (**8**) was achieved by refluxing in 0.1 N NaOH under N_2 for 3.5 h to yield the carboxylic acid intermediate (**9**) as described,[16,17] followed by methylation of the carboxylic acid product, using diazomethane. The resulting ester (**10**) was silylated using *t*-butyldimethylsilyl chloride (TBDMSCl),[18] followed by



Scheme 1. Outline of the synthesis of **7a**. *a*, iPr(OMe)$_2$, TsOH, DMF; *b*, 0.1 N NaOH, Δ; *c*, CH_2N_2; *d*, TBDMSCl, imidazole, DMF, RT; *e*, $LiAlH_4$, THF; *f*, MnO_2, CH_2Cl_2, RT; *g*, 80% AcOH, Δ; *h*, 60% aq. CF_3COOH, RT.

reduction with $LiAlH_4$ in THF[19] to yield the alcohol (**12**). An alternate route to **10** was previously published by Tanaka et al.[20] via its triacetate; the total synthesis of the latter was reported earlier by Srivastava et al.[21] Oxidation of **12** using MnO_2[22] yielded the corresponding aldehyde (**13**), which was heated in 80% acetic acid at 80–90°C for 30 h to yield **7a** (43.5%), together with the 5′-acetylated derivative **14**



Scheme 2. Outline of the synthesis of **7b**. *a*, 0.16 M $NaHCO_3$, Δ; *b*, CH_2N_2; *c*, TBDMSCl, imidazole, DMF, RT; *d*, $LiAlH_4$, THF; *e*, MnO_2, CH_2Cl_2, RT; *f*, Dowex 50W X8, H^+, aq. MeOH, RT.

(23.7%), as a biproduct. Alternatively, deprotection of **13** could be achieved more satisfactorily by stirring in 60% aqueous CF_3COOH at RT for 20 h to yield **7a** in 68.2% yield after silica gel chromatography.

An analogous procedure was used for the synthesis of **7b**, as outlined in Scheme 2. Commercial 5-bromo-2′-deoxyuridine (**15**) was refluxed in aqueous $NaHCO_3$ solution for 20 h, and the resultant ring-contracted free carboxylic acid was methylated without isolation by treatment with CH_2N_2 to yield ester **16**. After silylation, the protected ester **17** was reduced with $LiAlH_4$ to alcohol **18**, which was oxidized to aldehyde **19**, using MnO_2. Deprotection of **19** was affected by stirring with acidic ion-exchange resin in aqueous MeOH to yield **7b** in 76% yield.

The success of the ring contraction reaction in the synthesis of the 4-formyl-4-imidazolone deoxyribonucleoside **7b** provides an alternate route for the synthesis of imidine (**6**), the corresponding 4-acetyl derivative, which was previously prepared via coupling of the heterocyclic base with the protected sugar.[8] Hydrolysis of the ester intermediate **17** synthesized in this work, would yield the corresponding sugar-protected carboxylic acid that can be transformed to the desired methyl ketone in one step using MeLi.[8] Removal of the silyl protecting groups to yield **6** can be easily accomplished, as illustrated by the conversion of **19** to **7b**.

The availability of the methods described in this paper for the synthesis of **7a** and **7b**, opens the door for the synthesis of new nikkomycin analogues for the studies of structure–activity relationships, and for the development of potential antifungal agents. In addition, **7a** and **7b** may serve as building blocks for analogues of a variety of uridine- and deoxyuridine-containing metabolites and other biologically active natural products.

EXPERIMENTAL

All chemicals and reagents were the highest purity available. 5-Bromouridine and 5-bromo-2′-deoxyuridine were obtained from Aldrich and Sigma, respectively. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer. Mass spectra (ESI) were obtained on a Thermo Finnigan LCQ Advantage mass spectrometer. TLC was performed on Analtech GHFL Uniplate and spots were determined under UV light. Elemental analyses were carried out by Atlantic Microlab, Norcross, Georgia.

Methyl 1-(β-D-ribofuranosyl)imidazolin-2-one-4-carboxylate (10). 5-Bromouridine (**8**) was first converted to the 2′,3′-isopropylidene derivative **9**[17] in DMF, using dimethoxypropane (40 eq) and a catalytic amount of *p*-tolenesulfonic acid (0.04 eq). The acetonide **9** (4.1 g, 11.3 mmol) was refluxed in 570 mL 0.1 N NaOH under N_2 for 3.5 h. The reaction mixture was acidified with ion exchange resin (50W-X8, H^+) and evaporated under reduced pressure (35–45°C), which resulted in complete deprotection of the sugar. To a MeOH solution of the residue, CH_2N_2 in ether was added portionwise at 0–5°C until no starting material remained (by TLC). The resulting product was absorbed on silicagel, dried and was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 25:1) to yield **10** (0.95 g, 30.4%). A sample for elemental analysis was recrystallized from MeOH. Mp 183–186°C, lit. mp 187–189°C.[20] ^{1}H-NMR (DMSO–d_6) δ 3.51 (m, 2H, H-5′), 3.74 (s, 3H, $OCOCH_3$),

3.78 (m, H-3′), 3.98 (m, 1H, H-2′), 4.16 (m, 1H, H-4′), 4.96 (m, 1H, OH-5′), 5.01 (d, J = 4.15 Hz, 1H, OH), 5.25 (d, J = 5.37 Hz, 1H, OH), 5.41 (m, 1H, H-1′), 7.59 (s, 1H, H-5), 10.90 (s, 1H, NH). Anal. calcd for $C_{10}H_{14}N_2O_7$: C, 43.80; H, 5.15; N, 10.22. Found: C, 43.94; H, 5.12; N, 10.11.

Methyl 1-(2,3,5-tri-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)imidazolin-2-one-4-carboxylate (11). To a solution of **10** (1.14 g, 4.18 mmol) and imidazole (1.88 g, 27.6 mmol) in dry DMF (8.5 mL), *t*-butyldimethylsilyl chloride (2.08 g, 13.8 mmol) was added. The reaction mixture was stirred at room temperature overnight, followed by removal of the solvent and excess reagent under reduced pressure. The residue was dissolved in $CHCl_3$, washed twice with water and dried over Na_2SO_4, followed by chromatography on silica gel (CH_2Cl_2/MeOH = 100:1) to yield 2.5 g (96.9%) of **11** as a white foam. ^{1}H-NMR ($CDCl_3$) δ 0.075 (m, 18H, $Si(CH_3)_2$), 0.90 (m, 27H, $C(CH_3)_3$), 3.71–3.73 (m, 2H, H-5′), 3.82 (s, 3H, $COOCH_3$), 4.02 (m, 1H, H-3′), 4.14 (m, 1H, H-2′), 4.22 (m, 1H, H-4′), 5.66 (m, 1H, H-1′), 7.4 (s, 1H, H-5), 7.75 (s, 1H, NH). Anal. calcd for $C_{28}H_{56}N_2O_7Si_3$: C, 54.50; H, 9.15; N, 4.54. Found: C, 54.61; H, 9.29; N, 4.43.

1-(2,3,5-Tri-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)-4-hydroxymethyl-4-imidazolin-2-one (12). To a suspension of $LiAlH_4$ (152 mg, 4 mmol) in THF, a solution of compound **11** (617 mg, 1.05 mmol) in THF was added dropwise at 0–4°C, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was added portionwise to a mixture of MeOH/H_2O at 0–4°C with vigorous stirring, which was continued for 15 min at room temperature. Filtration, followed by silica gel chromatography (CH_2Cl_2/MeOH = 150:1) yielded 417 mg (70.8%) of **12**, as a white foam. ^{1}H-NMR ($CDCl_3$) δ 0.05 (m, 18H, $Si(CH_3)_2$), 0.90 (m, 27H, $C(CH_3)_3$), 1.66 (br, 1H, OH), 3.71 (q, J = 2.44 and 11.28 Hz, 1H, H-5′), 3.98 (m, 1H, H-3′), 4.17 (m, 2H, H-2′ and H-4′), 4.37 (s, 2H, CH_2OH), 5.63 (d, J = 5.38 Hz, 1H, H-1′), 6.46 (s, 1H, H-5), 9.03 (s, 1H, NH). Anal. calcd for $C_{27}H_{56}N_2O_6Si_3$: C, 55.05; H, 9.58; N, 4.76. Found: C, 54.94; H, 9.60; N, 4.74.

1-(2,3,5-Tri-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)imidazolin-2-one-4-carboxaldehyde (13). To a solution of **12** (59 mg, 0.1 mmol) in CH_2Cl_2, MnO_2 (20 mg) was added. After 18 h stirring at room temperature, the reaction mixture was filtered and evaporated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 200:1) to yield 33 mg (56.2%) of **13** as a white foam. ^{1}H-NMR ($CDCl_3$) δ 0.16 (m, 18H, $Si(CH_3)_2$), 0.97 (m, 27H, $C(CH_3)_3$), 3.77 (q, J = 1.8 and 11.6 Hz, 1H, H-5′), 4.00 (q, J = 2.74 and 11.6 Hz, 1H, H-5′), 4.06 (m, 1H, H-3′), 4.16 (m, 1H, H-2′), 4.22 (m, 1H, H-4′), 5.64 (d, J = 3.97 Hz, 1H, H-1′), 7.66 (s, 1H, H-5), 7.97 (br, 1H, NH), 9.26 (s, 1H, CHO). Anal. calcd for $C_{27}H_{54}N_2O_6Si_3$: C, 55.24; H, 9.27; N, 4.77. Found: C, 55.69; H, 9.14; N, 4.65.

1-(β-D-ribofuranosyl)-4-imidazolin-2-one carboxaldehyde (7a). Compound **13** (78 mg, 0.13 mmol) was dissolved in 3 mL of 80% aqueous acetic acid and the solution was heated at 80–90°C for 30 h. The solvent was removed under reduced pressure and twice coevaporated with water. The residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 5:1) to yield 12.4 mg (43.5%) of target compound **7a** and 9 mg (23.7%) of compound **14**, as a biproduct.

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Compound **7a**: mp 140–141°C. ^{1}H-NMR (DMSO–d_6) δ 3.54 (m, 2H, 5′-H), 3.83 (m, 1H, 3′-H), 4.00 (m, 1H, 2′-H), 4.16 (m, 1H, 4′-H), 4.98 (m, 1H, 5′-OH), 5.12 (d, J = 4.95 Hz, 1H, OH), 5.38 (d, J = 6.04 Hz, 1H, OH), 5.43 (d, J = 5.8 Hz, 1H, 1′-H), 7.9 (s, 1H, 5-H), 9.23 (s, 1H, CHO), 11.11 (br, 1H, NH). ^{13}C-NMR (D_2O) δ 61.2 (C-5′), 70.1 (C-3′), 73.6 (C-2′), 84.7 (C-4′), 86.9 (C-1′), 124.3 (C-5), 125.7 (C-4), 153.7 (C-2), 180.4 (CHO). MS *m/e* 245 (MH^+). Anal. calcd for $C_9H_{12}N_2O_6 \cdot$ 0.4 MeOH: C, 43.93; H, 5.30; N, 10.90. Found: C, 43.92; H, 5.10; N, 10.88.

Compound **14**: ^{1}H-NMR (DMSO–d_6) δ 2.05 (s, 3H, $OCOCH_3$), 4.01 (m, 1H, H-2′), 4.11 (m, 1H, H-3′), 4.22 (m, 2H, H-5′), 5.32 (m, 1H, OH), 5.47 (d, J = 3.42 Hz, 1H, H-1′), 5.52 (m, 1H, OH), 7.86 (s, 1H, H-5), 9.24 (s, 1H, CHO), 11.14 (s, 1H, NH). Anal. calcd for $C_{11}H_{14}N_2O_7$: C, 46.14; H, 4.93; N, 9.79. Found: C, 46.54; H, 5.16: N, 9.79.

Methyl 1-(2-deoxy-β-D-ribofuranosyl)imidazolin-2-one 4-carboxylate (16). 5-Bromo-2′-deoxyuridine (**15**) was dissolved in 0.16 M $NaHCO_3$ and the solution was refluxed for 20 h under argon. The reaction mixture was acidified by passing through a column of ion exchange resin (50W-X8, H^+) and concentrated under reduced pressure. After addition of MeOH to the residue, CH_2N_2 in ether was added in portions at 4°C until all the carboxylic acid was consumed (by TLC). After evaporation of the solvent, the product was purified by chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) and crystallized from MeOH/ether to obtain **16** in 61.5% yield as a white powder. Mp 157–160°C. ^{1}H-NMR (DMSO–d_6) δ 2.00 (m, 1H, H-2′), 2.26 (m, 1H, H-2′), 3.47 (m, 2H, H-5′), 3.73 (m, 4H, $COOCH_3$ + H-3′), 4.23 (m, 1H, H-4′), 4.91 (m, 1H, OH-5′), 5.20 (m, 1H, OH-3′), 5.84 (m, 1H, H-1′), 7.56 (s, 1H, H-5), 10.93 (s, 1H, NH). Anal. calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.51; H, 5.48; N, 10.77.

Methyl 1-(2-deoxy-3,5-di-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)imidazolin-2-one 4-carboxylate (17). To a solution of **16** (3.78 g, 15 mmol) and imidazole (4.5 g, 66 mmol) in 30 mL of anhydrous DMF was added TBDMSCl (4.97 g, 33 mmol) and the reaction mixture was stirred for 24 h at room temperature. The residue was dissolved in 30 mL $CHCl_3$ and washed with water 3 times. The product obtained was subjected to silica gel chromatography (CH_2Cl_2/MeOH = 100:1) to yield 7.2 g (95%) of **17** as a foam. ^{1}H-NMR ($CDCl_3$) δ 0.10 (m, 12H, $Si(CH_3)_2$), 0.93 (m, 18H, $C(CH_3)_3$), 2.12–2.30 (m, 2H, H-2′), 3.77 (m, 2H, H-5′), 3.82 (s, 1H, $COOCH_3$), 3.91 (m, 1H, H-3′), 4.54 (m, 1H, H-4′), 6.09 (t, J = 6.59 Hz, 1H, H-1′), 7.33 (s, 1H, H-5), 8.46 (br, 1H, NH). Anal. calcd for $C_{22}H_{42}N_2O_6Si_2 \cdot H_2O$: C, 52.34; H, 8.79; N; 5.55. Found: C, 52.67; H, 8.53; N, 5.56.

1-(2-Deoxy-3,5-di-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)-4-hydroxymethylimidazolin-2-one (18). To a suspension of $LiAlH_4$ (152 mg, 4 mmol) in 10 mL of THF, a solution of **17** (504 mg, 1 mmol) in 8 mL of THF was added dropwise with vigorous stirring at 0–4°C for 1h, then 1 h at room temperature, followed by filtration on celite and subsequent washing of the cake with $CHCl_3$/MeOH (7:3). After concentration of the combined filtrate and washings, the product was purified on a silica gel column ($CHCl_3$/MeOH = 15:1) to yield 308 mg (67.1%) of **18** as a foam. ^{1}H-NMR (DMSO–d_6) δ 0.075 (m, 12H, $Si(CH_3)_2$), 2.20 (m, 1H, H-2′), 2.26 (m, 1H,

H-2′), 3.57 (m, 2H, H-5′), 3.67 (m, 1H, H-3′), 4.07 (m, 2H, CH_2OH), 4.35 (m, 1H, H-4′), 4.95 (m, 1H, OH), 5.79 (m, 1H, H-1′), 6.39 (s, 1H, H-5), 10.06 (s, 1H, NH). Anal. calcd for $C_{21}H_{42}N_2O_5Si_2$: C, 54.98; H, 9.23; N, 6.11. Found: C, 54.70; H, 9.16; N, 6.12.

1-(2-Deoxy-3,5-di-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)imidazolin-2-one-4-carboxaldehyde (19). MnO_2 (800 mg) was added to a solution of **18** (458.8 mg, 1 mmol) in 60 mL of CH_2Cl_2 and stirred for 20 h at room temperature. The reaction mixture was filtered through a celite pad and evaporated to dryness. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH = 100:1) to yield 382 mg (80.5%) of **19** as a foam. An analytical sample was prepared by preparative TLC on silica gel (CH_2Cl_2/MeOH = 30:1). ^{1}H-NMR (DMSO–d_6) δ 0.074 (m, 12H, $Si(CH_3)_2$), 0.87 (m, 18H, $C(CH_3)_3$), 2.23 (m, 1H, H-2′), 2.40 (m, 1H, H-2′), 3.64 (m, 2H, H-5′), 3.75 (m, 1H, H-3′), 4.43 (m, 1H, H-4′), 5.85 (m, 1H, H-1′), 7.81 (s, 1H, H-5), 9.21 (s, 1H, CHO), 11.11 (s, 1H, NH). Anal. calcd for $C_{21}H_{40}N_2O_5Si_2 \cdot 0.25\ H_2O$: C, 54.68; H, 8.85; N, 6.08. Found: C, 54.94; H, 9.02; N, 6.04.

1-(2-Deoxy-β-D-ribofuranosyl)imidazolin-2-one-4-carboxaldehyde (7b). A solution of **19** (372 mg, 0.83 mmol) in a mixture of MeOH and H_2O (17:3) was stirred with 8–10 g wet ion exchange resin (50W-X8, H^+) for 20 h at room temperature. The reaction mixture was filtered and the resin was washed with MeOH. The combined filtrate and washings were evaporated to dryness, and the residue was recrystallized from MeOH to yield 127 mg (76%) of **7b** as white crystals. Mp 179–182°C. ^{1}H-NMR (DMSO–d_6) δ 2.08 (m, 1H, H-2′), 2.25 (m, 1H, H-2′), 3.49 (m, 2H, H-5′), 3.76 (m, 1H, H-3′), 4.26 (m, 1H, H-4′), 4.91 (m, 1H, OH-5′), 5.24 (m, 1H, OH-3′), 5.86 (m, 1H, H-1′), 7.87 (s, 1H, H-5), 9.21 (s, 1H, CHO), (s, 1H, NH). ^{13}C-NMR (D_2O) δ 38.4 (C-2′), 61.5 (C-5′), 70.9 (C-3′), 83.2 (C-1′), 86.8 (C-4′), 124.0 (C-5), 125.8 (C-4), 153.5 (C-2), 180.3 (CHO). MS *m/e* 229 (MH^+). Anal. calcd for $C_9H_{12}N_2O_5$: C, 47.36; H, 5.30, 12.28. Found: C, 47.24, H, 5.24; 12.17.

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