Nucleosides and Nucleotides. 143. Synthesis of 5-Amino-4-imidazolecarboxamide (AICA) Deoxyribosides from Deoxyinosines and Their Conversion into 3-Deazapurine Derivatives[1)]

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An efficient and large scale chemical synthesis of 5-aminoimidazole-4-carboxamide (AICA) 2′-deoxyriboside (5a) and its 3′-deoxyriboside 5b is described. Treatment of 3′,5′-di-*O*-acetyl-N^1-triphenylmethyl-2′-deoxyinosine (3a) with 5 N NaOH in EtOH, followed by anhydrous trifluoroacetic acid gave 5a in 59% yield from 2′-deoxyinosine (1a). AICA 3′-deoxyriboside (5b) was also obtained in a similar manner as for 5a in 73% yield from 3′-deoxyinosine (1b). Conversion of these AICA derivatives (5a, b) into 3-deazapurine derivatives (9a, b, 15a, b, 20a, b) is also described.

Key words nucleoside; 5-aminoimidazole-4-carboxamide (AICA) deoxyriboside; deoxyinosine; 3-deazapurine deoxynucleoside

5-Aminoimidazole-4-carboxamide (AICA) riboside (AICAR) 5′-monophosphate is a key intermediate in the *de novo* biosynthesis of purine nucleotides, and has been converted into inosine 5′-monophosphate by enzymatic formylation of the amino group at the 5-position followed by ring closure.[2)] Nucleoside analogues that inhibit *de novo* purine biosynthesis have shown anticancer and antiviral activities.[3)] Therefore, there has been interest in the synthesis and evaluation of analogues of AICAR.[4)] The nucleoside has also been recognized as an important intermediate to synthesize purine[5)] and imidazodiazepine[6)] nucleosides. Furthermore, it is quite recently reported that AICAR itself has inhibitory activities toward both adenosine deaminase and *S*-adenosyl-L-homocystaine hydrolase,[7)] and is currently undergoing Phase III clinical trials to assess the cardioprotective properties of the drug in patients undergoing coronary artery bypass surgery.[8)]

In our laboratory, we have been investigating the design and synthesis of enzyme inhibitors of *de novo* purine biosynthesis pathway and thus far reported the synthesis of 5-alkynylimidazole nucleosides,[9)] imidazoazepine nucleosides,[10)] and 3-deazapurine nucleosides,[11)] which show significant anticancer and/or antiviral activities, with modification of the base moiety of AICAR. The methods would be applicable to AICA deoxyribosides (AICAdRs) and would be expected to develop new potent anticancer and antiviral nucleosides, since it is known that deoxynucleoside derivatives as well as ribonucleosides show significant biological activities. However, it is necessary to deoxygenate the sugar hydroxyl group of AICAR in the modification of AICAR. We have already reported radical deoxygenation of the 2′-thiocarbonyl derivatives,[12)] however it does not appear to be suitable for large scale synthesis of the deoxynucleoside.

Alkaline treatment of N-1 substituted purine nucleosides causes a ring-opening reaction at C-2 position in the pyrimidine of the purine ring to give AICA derivatives.[13)] Shaw has reported the synthesis of AICAR from inosine by using benzyl,[14)] *p*-toluenesulfonyl,[15)] and methoxymethyl[16)] groups as N-1 substituents. Montgomery *et al.*[17)] have improved approaches to the synthesis of AICAR and applied them to the synthesis of deoxy and arabinofuranosyl derivatives of AICA. However, little has been reported on the efficient synthesis of AICA 2′-deoxyriboside (AICA-2′dR, **5a**). In the meantime, Pochet *et al.*[18)] and Betbeder *et al.*[19)] have reported the chemical and enzymatic synthesis of **5a**, respectively, but they are not yet satisfactory in overall yield and the scale of operations. Therefore, it seems worthwhile to develop an efficient large scale synthetic route for AICAdRs **5a, b**, especially AICA-2′dR (**5a**).

In this paper, we describe the synthesis of **5a** and **5b** from 2′-deoxy and 3′-deoxyinosine (**1a, b**), respectively, by using a triphenylmethyl (trityl) group as a N-1 substituent. The conversion into 3-deazapurine derivatives is also described.

Results and Discussion

We first attempted the synthesis of **5a** from N^1-methoxymethylinosine derivatives as reported by Shaw[16)] and Taniyama *et al.*,[20)] since the N-1 substituent could be removed simultaneously with the ring opening by alkaline treatment to give AICA nucleoside. However, treatment of N^1-methoxymethyl-3′,5′-di-*O*-acetyl-2′-deoxyinosine[21)] with ethanolic aqueous alkali gave 2′-deoxyinosine (**1a**) along with **5a**.[22)] The formation of 2′-deoxyinsone (**1a**) was a serious problem for the synthesis of **5a** because of the difficulty of separation of them. In the course our many efforts, we found the trityl group was a choice of the N-1 substituent to afford AICAdRs from deoxyinosines. The synthetic route of AICAdRs is illustrated in Chart 1. Treatment of 3′,5′-di-*O*-acetyl-2′-deoxyinosine (**2a**) with trityl chloride and K_2CO_3 in the presence of 18-crown-6-ether in dimethylformamide (DMF) at 40 °C gave exclusively N^1-tritylinosine derivative **3a** without formation of the O^6-tritylated derivative. When 5 N NaOH solution was added to an EtOH solution of **3a** under reflux, **1a** was obtained in fairly large quantities along with 5-aminoimidazole-4-*N*-tritylcarboxamide derivative **4a**, though they could be separated easily by partitioning

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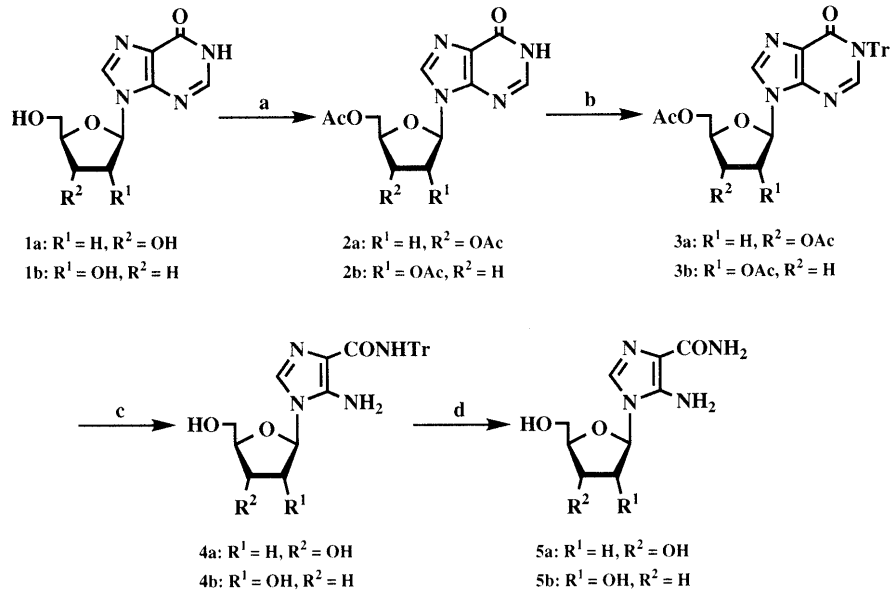


a. Ac_2O in pyridine. b. trityl chloride, K_2CO_3, 18-crown-6-ether in DMF, 40 °C. c. 5 N NaOH in EtOH, 100 °C. d. anhydrous TFA in CH_2Cl_2.

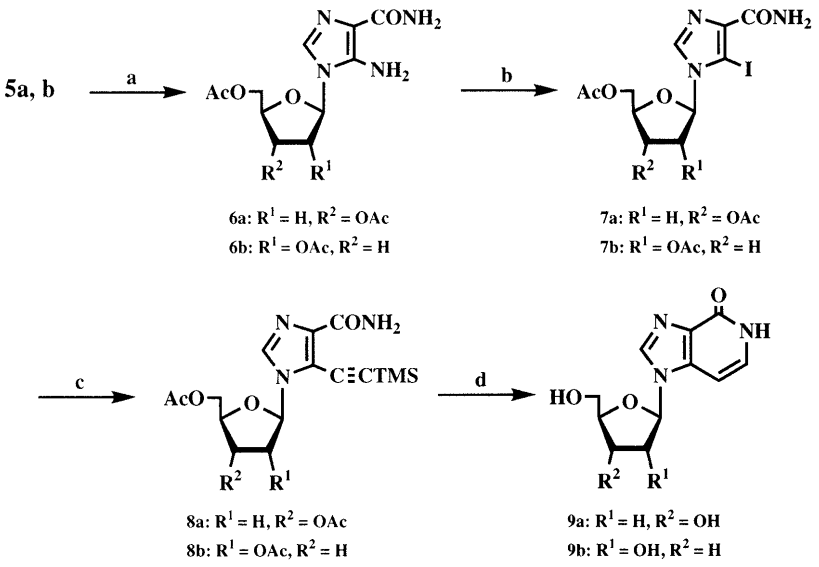
Chart 1

between $CHCl_3$ and water. It was proved that the trityl group at the N-1 position was relatively unstable and liberated from the N-1 position even in hot EtOH solution though it was stable on drying. However, the formation of undesired **1a** was avoided almost completely to give **4a** exclusively when the ring opening of the pyrimidine moiety of **3a** was done under operating conditions as followings: a mixture of 5 N NaOH and EtOH was heated under reflux and this was poured into a round-bottom flask containing **3a** quickly. Removal of the remaining trityl group in **4a** was done by treatment with anhydrous trifluoroacetic acid (TFA) in CH_2Cl_2 to give desired **5a** in good yield without any cleavage of glycosidic bond after neutralization with aqueous NaOH, followed by a desalting operation with activated charcoal. For practical large scale synthesis of **5a**, it is not necessary to make any purification except for partitioning and isolation of intermediates **3a** and **4a**, and **5a** was obtained in 59% yield from **1a** on a 20 g scale (see Experimental). This method is superior to the methods previously reported in the overall yield, scale of operations, and handling. In a similar manner as described for **5a**, AICA-3′dR (**5b**) was also synthesized from 3′-deoxyinosine (**1b**) in 73% yield without isolation of **3b** and **4b**.

We further examined the synthesis of 3-deazapurine deoxynucleosides from AICAdRs. Biological activities for some 3-deazapurine deoxynucleosides have been reported as well as those of ribonucleosides.[23] Furthermore, 2′-deoxy analogues of 3-deazapurine nucleoside were used as valuable probes for the study of protein–nucleic acid interactions.[24] Therefore, it seems worthwhile to convert AICAdRs into 3-deazapurine deoxynucleosides. We have already reported an easy chemical synthesis of 3-deazapurine nucleosides from AICAR[11] and the conversion was achieved according to the method reported. After acetylation of hydroxyl groups of **5a**, **6a** was diazotized with isoamyl nitrite in diiodomethane at 100 °C to give 5-iodo derivative **7a** in 41% yield. Introduction of a trimethylsilylethynyl group at the 5-position was done by treatment of **7a** with trimethyl[(tributylstannyl)ethynyl]-silane[25] in the presence of bis(benzonitrile)palladium dichloride in a sealed glass tube to give **8a** in 69% yield. Treatment of **8a** with aqueous dimethylamine, followed by 50% aqueous acetic acid–EtOH (1 : 1) gave 3-deaza-2′-deoxyinosine (**9a**) in 75% yield after crystallization. In a quite similar manner, 3-deaza-3′-deoxyinosine (**9b**) was also prepared from **5b** in 33% overall yield (Chart 2).

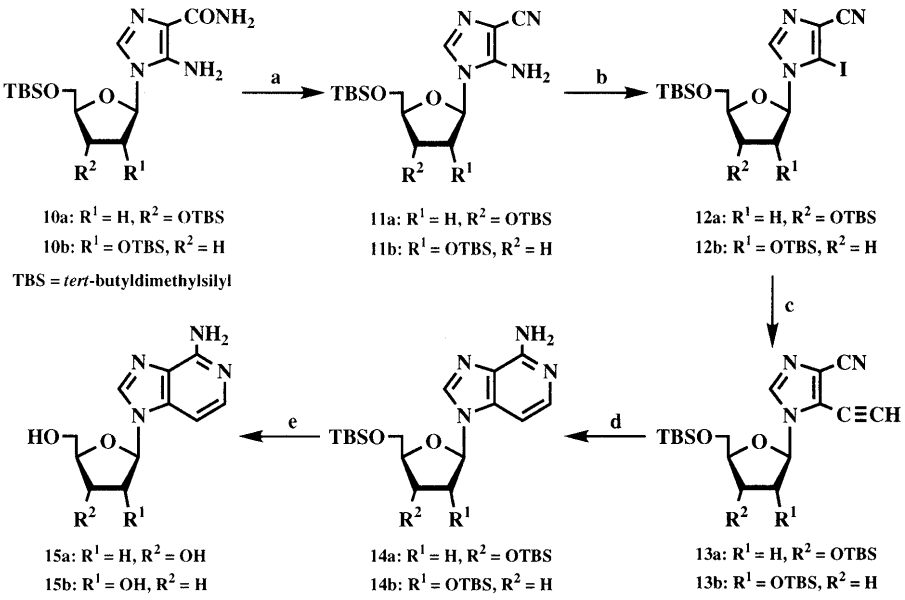
The synthesis of 3-deaza-deoxyadenosines **15a** and **15b** was achieved according to the route illustrated in Chart 3. The substrates of palladium-catalyzed cross-coupling reaction, **12a** and **12b**, were obtained by silylation of **5a** and **5b**, dehydration of **10a** and **10b**, followed by iodination of **11a** and **11b**, respectively. Since the palladium-catalyzed cross-coupling reaction of **12a** with trimethyl[(tributyl-stannyl)ethynyl]silane gave a mixture of 5-trimethylsilyl-ethynyl and 5-ethynyl derivatives **13a**, of which the trimethylsilyl group was liberated during the reaction, the reaction mixture was subsequently treated with methanolic ammonia at room temperature to give 5-ethynyl derivative **13a** in 79% yield. The 3′-deoxy derivative **13b** was also prepared in the same manner. Conversion of **13a** and **13b** into 3-deaza-deoxyadenosine derivatives **14a** and **14b** was done by treatment with methanolic ammonia at 120 °C in a sealed tube, which were then deprotected with tetra-butylammonium fluoride (TBAF) to give 3-deaza-2′-deoxyadenosine (**15a**)[26] and 3′-deoxyadenosine (**15b**), respectively.

For the synthesis of 3-deaza-deoxyguanosines **20a** and **20b**, we first prepared silylated 5-iodo derivatives **16a** and **16b**. After conversion of **16a, b** into 5-trimethylsilylethynyl derivatives **17a** and **17b**, they were treated with aqueous dimethylamine, followed by hydroxylamine hydrochloride to give 5-hydroxyiminoethyl derivatives **18a** and **18b** in 89% and 77% yields, respectively. In our previous



a. Ac_2O, Et_3N, DMAP in MeCN. b. isoamyl nitrite in CH_2I_2, 100 °C.
c. $TMSC{\equiv}CSnBu_3$, $(PhCN)_2PdCl_2$ in MeCN, 100 °C. d. aqueous Me_2NH in EtOH, 80 °C, then 50% aqueous AcOH in EtOH.

Chart 2

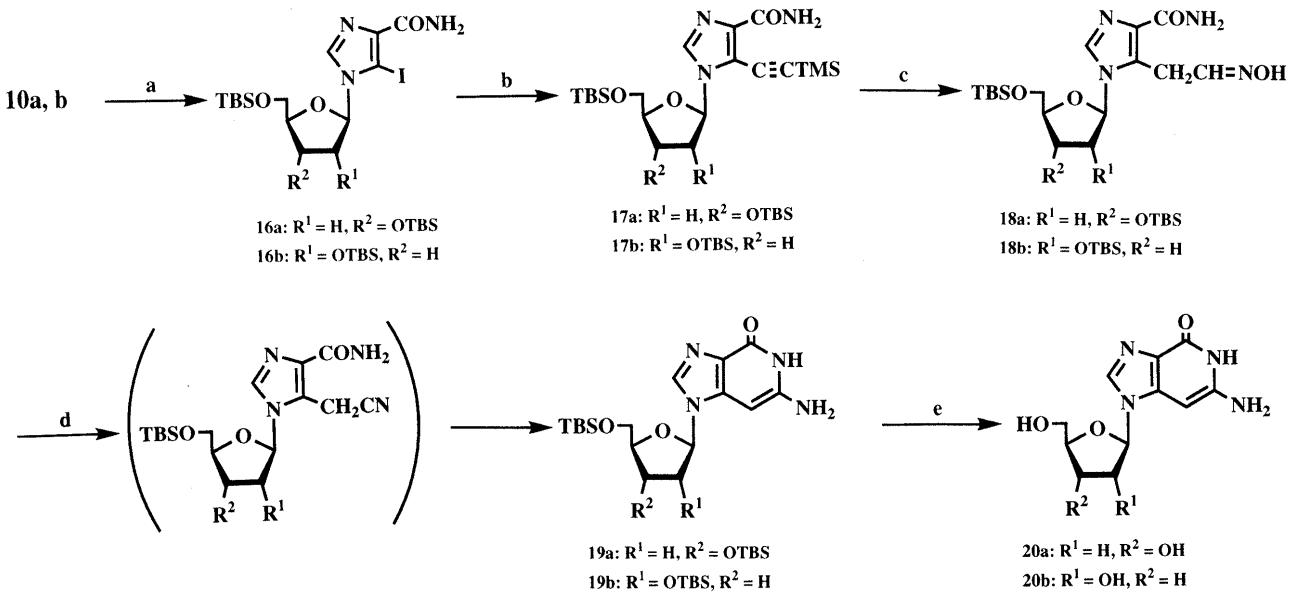


a. *p*-toluenesulfonyl chloride in pyridine. b. isoamyl nitrite in CH_2I_2, 100 °C.
c. $TMSC{\equiv}CSnBu_3$, $(PhCN)_2PdCl_2$ in MeCN, 100 °C, then NH_3/MeOH.
d. NH_3/MeOH, 120 °C. e. 1 M TBAF in THF.

Chart 3

paper,[11] we used phenyl isocyanate as a dehydrating agent to convert 3-deazaguanosine derivative *via* 5-cyanomethyl derivative, however 3-deaza-2′-deoxyguanosine derivative **19a** was obtained in less than 20% yield in the case of using phenyl isocyanate. After several attempts, we found 1-(trifluoroacetyl)imidazole[27] to be suitable for the dehydration. Treatment of **18a** with 1-(trifluoroacetyl)-imidazole in tetrahydrofuran (THF) under reflux conditions gave the cyanomethyl derivative easily, which was subsequently heated in a mixture of 5% aqueous Na_2CO_3 in EtOH to furnish **19a** in 75% yield. Compound **19a** was then deprotected to the free nucleoside, 3-deaza-2′-deoxyguanosine (**20a**).[23a] 3-Deaza-3′-deoxyguanosine (**20b**) was also synthesized in the same manner (Chart 4).

In conclusion, we developed efficient and large scale chemical synthesis of AICAdRs from deoxyinosines by using a trityl group as the N-1 substituent. Additionally, we converted AICAdRs into 3-deaza-deoxyinosines, -adenosines, and -guanosines, and thereby we established a synthetic route for 3-deazapurine deoxynucleosides from deoxyinosines. Further applications using AICAdRs will be reported in due course.



a. isoamyl nitrite in CH_2I_2, 100 °C. b. $TMSC{\equiv}CSnBu_3$, $(PhCN)_2PdCl_2$ in MeCN, 100 °C. c. aqueous Me_2NH in EtOH, 80 °C, then $NH_2OH{\cdot}HCl$ AcOH. d. 1-(trifluoroacetyl)imidazole in THF, then 5% aqueous Na_2CO_3-EtOH, 100 °C. e. 1 M TBAF in THF

Chart 4

Experimental

General Methods Physical data were measured as follows: Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL GX-270 or Bruker AMX-500 instruments in $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6 as the solvent with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV spectra were recorded with a Shimadzu UV-260 spectrophotometer. Mass spectra were recorded on a JEOL JMS DX-303 or JEOL JMS HX-110 spectrometer. TLC was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70—230 mesh).

Practical Synthesis of 5-Amino-1-(2-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (5a) from 2′-Deoxyinosine (1a) Acetic anhydride (22.4 ml, 0.237 mol) was added to a suspension of 2′-deoxyinosine (**1a**, 20.0 g, 79.3 mmol) in dry pyridine (200 ml). The reaction mixture was stirred for 24 h at room temperature and EtOH (10 ml) was added to the mixture to decompose an excess of acetic anhydride. The mixture was concentrated *in vacuo* and the residue was coevaporated several times with toluene. The resulting white solid was collected and washed with ice-cold EtOH to give **2a** (dried over P_2O_5 *in vacuo* at 40 °C overnight). Compound **2a** was dissolved in dry DMF (300 ml), and potassium carbonate (16.3 g, 0.118 mol, dried over P_2O_5 *in vacuo* at 60 °C overnight) and 18-crown-6-ether (2.08 g, 7.87 mmol) were added to the solution. The mixture was heated at 40 °C and trityl chloride (11.0 g, 39.5 mmol) was added to the mixture three times every 12 h. The reaction mixture was stirred for 36 h more at 40 °C. The reaction was quenched by addition of EtOH and the reaction mixture was filtered through a Celite pad and washed with EtOH. The combined filtrate and washings were concentrated *in vacuo* and the residue was dissolved in AcOEt, which was washed with H_2O, followed by brine. The separated organic layer was dried (Na_2SO_4) and concentrated to dryness *in vacuo* to give a crude **3a**. A mixture of EtOH (450 ml) and 5 N NaOH (91 ml) was heated under reflux and this was quickly poured into a round-bottom flask containing **3a**. The whole was heated for 50 min under reflux. The reaction mixture was cooled in an ice bath and neutralized with 5 N HCl. The solution was concentrated *in vacuo* and the residue was partitionated between $CHCl_3$ and H_2O. The organic layer was washed further with brine and dried (Na_2SO_4). The solution was concentrated to dryness *in vacuo* to give a crude **4a**. Compound **4a** was dissolved in dry CH_2Cl_2 (400 ml) and anhydrous TFA (70 ml) was added to the solution. The whole was stirred for 3 h at room temperature. The reaction mixture was cooled in an ice bath and neutralized with 5 N NaOH. The mixture was partitionated between CH_2Cl_2 and H_2O and the organic layer was extracted with H_2O three times. The aqueous layers were combined and activated charcoal was added to the solution until the optical density at 266 nm went below 1% (about 120 g). This suspension was packed into a glass column, which was washed with H_2O (5 l), then eluted with a mixture of 28% NH_4OH and EtOH (3 : 7). The UV absorbing fractions were collected and concentrated to dryness *in vacuo* to give **5a** (11.33 g, 59% from **1a**, crystallized from MeOH). mp 177—178 °C (lit.[17a] mp 174—176 °C). $\lambda_{max}^{H_2O}$ 267 nm (ε 11700); $\lambda_{max}^{0.5\,N\,HCl}$ 268 nm (ε 10200); $\lambda_{max}^{0.5\,N\,NaOH}$ 267 nm (ε 12000). ^{1}H-NMR (DMSO-d_6) δ: 7.32 (s, 1H, H-2), 6.75 and 6.62 (each br s, each 1H, $CONH_2$), 5.92 (m, 3H, H-1′, NH_2), 5.25 (d, 1H, 3′-OH, $J_{OH,3'}$ = 3.8 Hz), 5.09 (t, 1H, 5′-OH, J = 5.0 Hz), 4.32 (m, 1H, H-3′), 3.80 (m, 1H, H-4′), 3.53 (m, 2H, H-5′a, b), 2.41 (ddd, 1H, H-2′a, J = 6.3, 7.7, 13.2 Hz), 2.14 (ddd, 1H, H-2′b, J = 2.7, 6.0, 13.2 Hz).

Practical Synthesis of 5-Amino-1-(3-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (5b) from 3′-Deoxyinosine (1b) In the same manner as described for **5a**, 3′-deoxyinosine (**1b**, 20.0 g, 79.3 mmol) was acetylated and tritylated, followed by the ring-opening reaction. The reaction mixture was cooled in an ice bath and neutralized with 5 N HCl. The solution was concentrated *in vacuo* and H_2O (300 ml) was added to the residue. An insoluble material was collected and washed with ice-cold EtOH to give **4b**. Compound **4b** was suspended in dry CH_2Cl_2 (400 ml) and anhydrous TFA (70 ml) was added to the suspension. The whole was stirred for 5.5 h at room temperature. The reaction mixture was partitionated between CH_2Cl_2 and H_2O (100 ml × 2) and the aqueous layers were concentrated *in vacuo*. The residue was coevaporated with EtOH several times and then dissolved in H_2O (800 ml). The solution was neutralized with 1 N NaOH and desalted by activated charcoal treatment as described above to give **5b** (13.96 g, 73% from **1b**, crystallized from aqueous MeOH). mp 214—216 °C. EI-MS *m/z*: 242 (M^+). UV $\lambda_{max}^{H_2O}$ 267 nm (ε 12000); $\lambda_{max}^{0.5\,N\,HCl}$ 268 nm (ε 9900); $\lambda_{max}^{0.5\,N\,NaOH}$ 267 nm (ε 12900). ^{1}H-NMR (DMSO-d_6) δ: 7.33 (s, 1H, H-2), 6.70 (m, 2H, $CONH_2$), 5.83 (br s, 2H, NH_2), 5.53 (d, 1H, 2′-OH, $J_{OH,2'}$ = 4.0 Hz), 5.42 (d, 1H, H-1′, $J_{1',2'}$ = 2.2 Hz), 5.08 (t, 1H, 5′-OH, J = 5.1 Hz), 4.32 (m, 1H, H-2′), 4.26 (m, 1H, H-4′), 3.64 and 3.50 (each m, each 1H, H-5′a, b), 2.12 and 1.84 (each m, each 1H, H-3′a, b). *Anal.* Calcd for $C_9H_{14}N_4O_4$: C, 44.63; H, 5.83; N, 23.13. Found: C, 44.80; H, 5.99; N, 22.99.

5-Amino-1-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (6a) Triethylamine (9.2 ml, 66 mmol) was added to a

suspension of **5a** (4.0 g, 16.5 mmol) in dry MeCN (90 ml) containing Ac_2O (3.5 ml, 66 mmol) and dimethylaminopyridine (DMAP) (10 mg). The reaction mixture was stirred for 2 h at room temperature and MeOH (5 ml) was added to the mixture to decompose an excess of Ac_2O. The mixture was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$, which was washed with saturated aqueous $NaHCO_3$, followed by brine. The separated organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on a silica gel column (7.7 × 15 cm), eluted with 12% EtOH in $CHCl_3$, to give **6a** (5.23 g, 97% as a white foam). EI-MS *m/z*: 326 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.05 (s, 1H, H-2), 6.54 (br s, 1H, CONH), 5.86 (dd, 1H, H-1′, $J_{1',2'a}$ = 5.5, $J_{1',2'b}$ = 8.8 Hz), 5.30 (m, 4H, H-3′, CONH, NH_2), 4.41 (dd, 1H, H-5′a, $J_{5'a,4'}$ = 3.8, $J_{5'a,b}$ = 12.6 Hz), 4.27 (m, 2H, H-4′, 5′b), 2.85 (ddd, 1H, H-2′b, $J_{2'b,1'}$ = 8.8, $J_{2'b,a}$ = 14.3, $J_{2'b,3'}$ = 6.6 Hz), 2.38 (ddd, 1H, H-2′a, $J_{2'a,1'}$ = 5.5, $J_{2'a,b}$ = 14.3, $J_{2'a,3'}$ = 5.5 Hz), 2.12 and 2.08 (each s, each 3H, Ac). HR-MS (M^+): Calcd for $C_{13}H_{18}N_4O_6$: 326.1226. Found: 326.1208.

5-Amino-1-(3-deoxy-2,5-di-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (6b) Compound **5b** (2.37 g, 11.3 mmol) was acetylated as described for the synthesis of **6a** to give **6b** (3.58 g, 97%, crystallized from EtOH as white crystals). mp 170—171 °C. EI-MS *m/z*: 326 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.27 (s, 1H, H-2), 6.65 (br s, 1H, CONH), 5.67 (br s, 2H, NH_2), 5.62 (s, 1H, H-1′), 5.27 (br s, 1H, CONH), 5.24 (m, 1H, H-2′), 4.64 (m, 1H, H-4′), 4.42 (dd, 1H, H-5′a, $J_{5'a,4'}$ = 2.8, $J_{5'a,b}$ = 12.6 Hz), 4.37 (dd, 1H, H-5′b, $J_{5'b,4'}$ = 4.0, $J_{5'b,a}$ = 12.6 Hz), 2.24 (ddd, 1H, H-3′a, J = 5.1, 10.8, $J_{3'a,b}$ = 14.1 Hz), 2.17 (m, 1H, H-3′b), 2.18 and 2.14 (each s, each 3H, Ac). *Anal.* Calcd for $C_{13}H_{18}N_4O_6$: C, 47.85; H, 5.56; N, 17.17. Found: C, 47.88; H, 5.62; N, 17.02.

5-Iodo-1-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (7a) A solution of isoamyl nitrite (5.6 ml, 41.7 mmol) in diiodomethane (50 ml) was heated at 100 °C. A CH_2Cl_2 solution (10 ml) of **6a** (2.71 g, 8.3 mmol) was added to the solution over 10 min and the whole was stirred for 20 min at 100 °C. After cooling to room temperature, the reaction mixture was purified on a silica gel column (4.6 × 20 cm), eluted with 0—8% EtOH in $CHCl_3$, to give **7a** (1.5 g, 41% as an orange solid) which was crystallized from EtOH as orange crystals. mp 143—145 °C. EI-MS *m/z*: 437 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.93 (s, 1H, H-2), 7.01 (br s, 1H, CONH), 6.12 (dd, 1H, H-1′, $J_{1',2'a}$ = 5.5, $J_{1',2'b}$ = 7.7 Hz), 5.39 (br s, 1H, CONH), 5.31 (br d, 1H, H-3′), 4.36 (m, 3H, H-4′, 5′a, b), 2.68 and 2.41 (each m, each 1H, H-2′a, b), 2.15 and 2.10 (each s, each 3H, Ac). *Anal.* Calcd for $C_{13}H_{16}IN_3O_6$: C, 35.71; H, 3.69; N, 9.61. Found: C, 35.42; H, 3.68; N, 9.56.

5-Iodol-1-(3-deoxy-2,5-di-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (7b) Compound **6b** (1.2 g, 3.68 mmol) was converted as above to give **7b** (804 mg, 50% as an orange foam). EI-MS *m/z*: 437 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.98 (s, 1H, H-2), 7.01 (br s, 1H, CONH), 5.91 (s, 1H, H-1′), 5.42 (m, 2H, CONH, H-2′), 4.63 (m, 1H, H-4′), 4.43 (dd, 1H, H-5′a, $J_{5'a,4'}$ = 2.9, $J_{5'a,b}$ = 12.5 Hz), 4.34 (dd, 1H, H-5′b, $J_{5'b,4}$ = 4.4, $J_{5'b,a}$ = 12.5 Hz), 2.26—2.11 (m, 8H, H-3′a, b, Ac × 2). HR-MS (M^+): Calcd for $C_{13}H_{16}IN_3O_6$: 437.0086. Found: 437.0058.

5-Trimethylsilylethynyl-1-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (8a) A mixture of **7a** (1.56 g, 3.57 mmol), bis(benzonitrile)palladium dichloride (68 mg, 5 mol%), and trimethyl-[(tributylstannyl)ethnyl]silane (2.07 g, 5.35 mmol) in dry MeCN (10 ml) in a sealed glass tube was heated at 100 °C for 14 h. The reaction mixture was filtered through a Celite pad and washed with EtOH. The combined filtrate and washings were concentrated *in vacuo* and the residue was purified on a silica gel column (3.6 × 15 cm), eluted with hexane/AcOEt (1 : 2), to give **8a** (1.0 g, 69% as a brown foam). EI-MS *m/z*: 407 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.67 (s, 1H, H-2), 6.86 (br s, 1H, CONH), 6.16 (dd, 1H, H-1′, $J_{1',2'a}$ = 5.1, $J_{1',2'b}$ = 7.1 Hz), 5.39 (br s, 1H, CONH), 5.30 (m, 1H, H-3′), 4.34 (m, 3H, H-4′, 5′a, b), 2.65 (ddd, 1H, H-2′a, $J_{2'a,1'}$ = 8.8, $J_{2'a,b}$ = 14.1, $J_{2'a,3'}$ = 2.4 Hz), 2.44 (dt, 1H, H-2′b, $J_{2'b,1'}$ = $J_{2'b,3'}$ = 7.1, $J_{2'a,b}$ = 14.1 Hz), 2.12 and 2.09 (each s, each 3H, acetyl), 0.30 (s, 9H, TMS). HR-MS (M^+): Calcd for $C_{18}H_{25}N_3O_6Si$: 407.1512. Found: 407.1487.

5-Trimethylsilylethynyl-1-(3-deoxy-2,5-di-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (8b) Compound **7b** (1.63 g, 3.73 mmol) was converted as above to give **8b** (1.2 g, 79% as a brown foam). EI-MS *m/z*: 407 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.75 (s, 1H, H-2), 6.86 (br s, 1H, CONH), 5.96 (s, 1H, H-1′), 5.44 (m, 2H, CONH, H-2′), 4.62 (m, 1H, H-4′), 4.38 (m, 2H, H-5′a, b), 2.27—2.05 (m, 8H, H-3′a, b, Ac × 2), 0.27 (s, 9H, TMS). HR-MS (M^+): Calcd for $C_{18}H_{25}N_3O_6Si$: 407.1512. Found: 407.1493.

1-(2-Deoxy-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (9a) Aqueous dimethylamine (50%, 5 ml) was added to a solution of **8a** (540 mg, 1.33 mmol) in EtOH (10 ml) and the mixture was heated at 80 °C for 5 h in a sealed tube. After the starting material was completely consumed, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in a mixture of EtOH (10 ml)–50% aqueous AcOH (10 ml), and the mixture was stirred for 12 h at room temperature. The solvent was removed *in vacuo* and then coevaporated several times with EtOH. The resulting solid was crystallized from aqueous EtOH to give **9a** (250 mg, 75% as pale brown crystals). mp 170—171 °C. FAB-MS *m/z*: 252 (MH^+). UV $\lambda_{max}^{H_2O}$ 258 nm (ε 10400); $\lambda_{max}^{0.5\,N\,HCl}$ 269 nm (ε 9100); $\lambda_{max}^{0.5\,N\,NaOH}$ 265 nm (ε 10300). ^{1}H-NMR (DMSO-d_6) δ: 11.19 (br s, 1H, NH), 8.24 (s, 1H, H-2), 7.15 (br d, 1H, H-6), 6.68 (d, 1H, H-7, J = 7.3 Hz), 6.22 (dd, 1H, H-1′, $J_{1',2'a}$ = 6.4, $J_{1',2'b}$ = 6.8 Hz), 5.33 (d, 1H, 3′-OH, $J_{OH,3'}$ = 3.9 Hz), 4.96 (dd, 1H, 5′-OH, $J_{OH,5'a}$ = 4.6, $J_{OH,5'b}$ = 5.4 Hz), 4.36 (m, 1H, H-3′), 3.85 (m, 1H, H-4′), 3.54 (m, 2H, H-5′a, b), 2.48 and 2.30 (each m, each 1H, H-2′a, b). *Anal.* Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.73. Found: C, 52.60; H, 5.24; N, 16.67.

1-(3-Deoxy-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (9b) Compound **8b** (234 mg, 0.57 mmol) was converted as above to give **9b** (125 mg, 87% as pale brown crystals). mp 194—196 °C. FAB-MS *m/z*: 252 (MH^+). UV $\lambda_{max}^{H_2O}$ 258 nm (ε 11100); $\lambda_{max}^{0.5\,N\,HCl}$ 269 nm (ε 10300); $\lambda_{max}^{0.5\,N\,NaOH}$ 265 nm (ε 11400). ^{1}H-NMR (DMSO-d_6) δ: 11.20 (br s, 1H, NH), 8.27 (s, 1H, H-2), 7.17 (m, 1H, H-6), 6.66 (d, 1H, H-7, J = 6.6 Hz), 5.73 (s, 1H, H-1′), 5.72 (d, 1H, 2′-OH, $J_{OH,2'}$ = 6.6 Hz), 5.04 (dd, 1H, 5′-OH, $J_{OH,5'a}$ = 5.0, $J_{OH,5'b}$ = 5.5 Hz), 4.34 (m, 2H, H-2′, 4′), 3.67 and 3.52 (each m, each 1H, H-5′a, b), 2.14 and 1.87 (each m, each 1H, H-3′a, b). *Anal.* Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.73. Found C, 52.96; H, 5.25; N, 16.62.

5-Amino-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (10a) A mixture of **5a** (3.82 g, 15.8 mmol), *tert*-butyldimethylsilyl chloride (8.34 g, 55.3 mmol), and imidazole (7.53 g, 111 mmol) in dry DMF (80 ml) was stirred for 14 h at room temperature, and then the reaction was quenched by addition of EtOH (10 ml). The mixture was concentrated *in vacuo* and the residue was dissolved in AcOEt. The solution was washed with H_2O, followed by brine. The separated organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on a silica gel column (4.6 × 10 cm), eluted with 4% EtOH in $CHCl_3$, to give **10a** (7.27 g, 98% as a yellow foam). EI-MS *m/z*: 470 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 6.97 (s, 1H, H-2), 6.46 (br s, 1H, CONH), 5.88 (dd, 1H, H-1′, $J_{1',2'a}$ = 5.8, $J_{1',2'b}$ = 8.4 Hz), 5.56 (br s, 2H, NH_2), 5.05 (br s, 1H, CONH), 4.53 (ddd, 1H, H-3′, $J_{3',2'a}$ = 2.8, $J_{3',2'b}$ = 6.3, $J_{3',4'}$ = 5.1 Hz), 3.94 (ddd, 1H, H-4′, $J_{4',3'}$ = 5.1, $J_{4',5'a}$ = 2.2, $J_{4',5'b}$ = 2.8 Hz), 3.85 (dd, 1H, H-5′b, $J_{5'b,4'}$ = 3.8, $J_{5'b,a}$ = 11.4 Hz), 3.77 (dd, 1H, H-5′a, $J_{5'a,4'}$ = 2.2, $J_{5'a,b}$ = 11.4 Hz), 2.62 (ddd, 1H, H-2′b, $J_{2'b,1'}$ = 8.4, $J_{2'b,a}$ = 13.1, $J_{2'b,3'}$ = 6.3 Hz), 2.13 (ddd, 1H, H-2′a, $J_{2'a,1'}$ = 5.8, $J_{2'a,b}$ = 13.1, $J_{2'a,3'}$ = 2.8 Hz), 0.92 and 0.84 (each s, each 9H, *tert*-butyl), 0.12, 0.11, −0.04, and −0.08 (each s, each 3H, Me). *Anal.* Calcd for $C_{21}H_{42}N_4O_4Si_2$: C, 53.58; H, 8.99; N, 11.90. Found: C, 53.49; H, 8.92; N, 11.98.

5-Amino-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (10b) Compound **5b** (2.64 g, 10.9 mmol) was silylated as described for the synthesis of **10a** to give **10b** (3.9 g, 79% as a yellow foam). EI-MS *m/z*: 470 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.08 (s, 1H, H-2), 6.51 (br s, 1H, CONH), 5.64 (br s, 2H, NH_2), 5.30 (d, 1H, H-1′, $J_{1',2'}$ = 5.3 Hz), 5.01 (br s, 1H, CONH), 4.65 and 4.39 (each m, each 1H, H-2′, 4′), 3.96 (dd, 1H, H-5′a, $J_{5'a,4'}$ = 2.2, $J_{5'a,b}$ = 11.5 Hz), 3.63 (dd, 1H, H-5′b, $J_{5'b,4'}$ = 2.2, $J_{5'b,a}$ = 11.5 Hz), 2.35 (ddd, 1H, H-3′a, J = 5.7, 7.7, $J_{3'a,b}$ = 14.6 Hz), 2.01 (ddd, 1H, H-3′b, J = 6.3, 8.3, $J_{3'b,a}$ = 14.6 Hz), 0.92 and 0.84 (each s, each 9H, *tert*-Bu), 0.12, 0.11, −0.03, and −0.08 (each s, each 3H, Me). HR-MS (M^+): Calcd for $C_{21}H_{42}N_4O_4Si_2$: 470.2744. Found: 470.2766.

5-Amino-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (11a) *p*-Toluenesulfonyl chloride (3.28 g, 17.2 mmol) was added to a solution of **10a** (5.68 g, 12.1 mmol) in dry pyridine (80 ml) and the whole was stirred for 24 h at room temperature. The reaction was quenched by addition of EtOH (10 ml) and the mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt, which was washed with H_2O, followed by brine. The separated organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on a silica gel column (4.6 × 20 cm), eluted with 2% EtOH in $CHCl_3$, to give **11a** (5.3 g, 97% as a yellow foam). EI-MS *m/z*: 452 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.03 (s, 1H, H-2), 5.88 (dd, 1H, H-1′, $J_{1',2'a}$ = 5.8, $J_{1',2'b}$ = 8.4 Hz), 4.80 (br s, 2H, NH_2), 4.51 (br d, 1H, H-3′), 3.96 (m, 1H, H-4′), 3.88 (dd, 1H, H-5′a, $J_{5'a,4'}$ = 2.5, $J_{5'a,b}$ = 11.4 Hz), 3.78 (dd, 1H,

H-5′b, $J_{5'b,4'}=1.5$, $J_{5'b,a}=11.4$ Hz), 2.55 (m, 1H, H-2′a), 2.14 (ddd, 1H, H-2′b, $J_{2'b,1'}=5.7$, $J_{2'b,a}=13.0$, $J_{2'b,3'}=2.0$ Hz), 0.92 and 0.90 (each s, each 9H, *tert*-Bu), 0.11, 0.10, 0.09, and 0.07 (each s, each 3H, Me). HR-MS (M^+): Calcd for $C_{21}H_{40}N_4O_3Si_2$: 452.2639. Found: 452.2635.

5-Amino-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (11b) Compound **10b** (1.33 g, 2.83 mmol) was converted as above to give **11b** (1.23 g, 96% as a yellow foam). EI-MS *m/z*: 452 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.03 (s, 1H, H-2), 5.28 (d, 1H, H-1′, $J_{1'2'}=6.5$ Hz), 4.84 (br s, 2H, NH_2), 4.59 and 4.39 (m, 2H, H-2′, 4′), 3.97 (dd, 1H, H-5′a, $J_{5'a,4'}=2.0$, $J_{5'a,b}=11.5$ Hz), 3.63 (dd, 1H, H-5′b, $J_{5'b,4'}=1.8$, $J_{5'b,a}=11.5$ Hz), 2.34 (m, 1H, H-3′a), 2.03 (ddd, 1H, H-3′b, $J=6.7$, 8.6, $J_{3'a,b}=12.8$ Hz), 0.95 and 0.92 (each s, each 9H, *tert*-Bu), 0.12, 0.11, 0.10, and 0.08 (each s, each 3H, Me).

5-Iodo-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (12a) In the same manner as described for **7a**, **11a** (5.3 g, 11.7 mmol) was treated with isoamyl nitrite in diiodomethane giving **12a** (3.65 g, 55%, crystallized from hexane). mp 120—122 °C. EI-MS *m/z*: 563 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H, H-2), 5.96 (t, 1H, H-1′, $J_{1'2'a}=J_{1'2'b}=6.1$ Hz), 4.52 (dt, 1H, H-3′, $J_{3'2'a}=4.1$, $J_{3'2'b}=J_{3'4'}=5.6$ Hz), 4.00 (m, 1H, H-4′), 3.86 (dd, 1H, H-5′a, $J_{5'a,4'}=3.2$, $J_{5'a,b}=11.5$ Hz), 3.78 (dd, 1H, H-5′b, $J_{5'b,4'}=2.5$, $J_{5'b,a}=11.5$ Hz), 2.44 (ddd,1H, H-2′a, $J_{2'a,1'}=6.1$, $J_{2'a,b}=13.1$, $J_{2'a,3'}=4.4$ Hz), 2.21 (m, 1H, H-2′b), 0.92 and 0.89 (each s, each 9H, *tert*-Bu), 0.10 and 0.08 (each s, each 6H, Me × 2). *Anal.* Calcd for $C_{21}H_{38}IN_3O_3Si_2$: C, 44.75; H, 6.80; N, 7.46. Found: C, 44.83; H, 6.86; N, 7.53.

5-Iodo-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (12b) In the same manner as described for **7a**, **11b** (1.2 g, 2.65 mmol) was treated with isoamyl nitrite in diiodomethane giving **12b** (700 mg, 47%, crystallized from hexane). mp 138—140 °C. EI-MS *m/z*: 563 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.36 (s, 1H, H-2), 5.60 (d, 1H, H-1′, $J_{1',2'}=1.0$ Hz), 4.52 and 4.35 (each m, each 1H, H-2′, 4′), 4.13 (dd, 1H, H-5′a, $J_{5'a,4'}=2.0$, $J_{5a',b}=11.8$ Hz), 3.78 (dd, 1H, H-5′b, $J_{5'b,4'}=2.0$, $J_{5'b,a}=11.8$ Hz), 2.26 (m, 1H, H-3′a), 1.83 (ddd, 1H, H-3′b, $J=2.5$, 5.6, 13.1 Hz), 0.95 and 0.91 (each s, each 9H, *tert*-Bu), 0.14, 0.13, 0.12, and 0.08 (each s, each 3H, Me). *Anal.* Calcd for $C_{21}H_{38}IN_3O_3Si_2$: C, 44.75; H, 6.80; N, 7.46. Found: C, 44.73; H, 6.70; N, 7.30.

5-Ethynyl-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (13a) In the same manner as described for **8a**, **12a** (2.2 g, 3.9 mmol) was treated with trimethyl[(tributhylstannyl)ethnyl]silane in the presence of bis(benzonitrile)palladium dichloride, followed by NH_3/MeOH (saturated at 0 °C) giving **13a** (1.41 g, 79% as a brown foam). EI-MS *m/z*: 461 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.96 (s, 1H, H-2), 6.11 (t, 1H, H-1′, $J_{1'2'a}=J_{1'2'b}=6.0$ Hz), 4.52 (m, 1H, H-3′), 3.98 (m, 1H, H-4′), 3.93 (dd, 1H, H-5′a, $J_{5'a,4'}=3.3$, $J_{5'a,b}=10.2$ Hz), 3.83 (s, 1H, acetylene proton), 3.76 (dd, 1H, H-5′b, $J_{5'b,4'}=2.2$, $J_{5'b,a}=10.2$ Hz), 2.44 and 2.18 (each m, each 1H, H-2′a, b), 0.91 and 0.90 (each s, each 9H, *tert*-Bu), 0.10 and 0.09 (each s, each 6H, Me × 2). HR-MS ($M^+ - tert$-butyl): Calcd for $C_{19}H_{30}N_3O_3Si_2$: 404.1826. Found: 404.1805.

5-Ethynyl-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (13b) In the same manner as described for **8a**, **12b** (550 mg, 0.98 mmol) was treated with trimethyl[(tributylstannyl)ethnyl]silane in the presence of bis(benzonitrile)palladium dichloride, followed by NH_3/MeOH (saturated at 0 °C) giving **13b** (410 mg, 91%, crystallized from hexane). mp 99—100 °C. EI-MS *m/z*: 461 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.23 (s, 1H, H-2), 5.74 (s, 1H, H-1′), 4.54 and 4.38 (each m, each 1H, H-2′, 4′), 4.15 (dd, 1H, H-5′a, $J_{5'a,4'}=2.2$, $J_{5'a,b}=11.5$ Hz), 3.81 (s, 1H, acetylene proton), 3.74 (dd, 1H, H-5′b, $J_{5'b,4'}=2.2$, $J_{5'b,a}=11.5$ Hz), 2.24 and 1.82 (each m, each 1H, H-3′a, b), 0.94 and 0.90 (each s, each 9H, *tert*-Bu), 0.14, 0.13, 0.10, and 0.07 (each s, each 3H, Me). *Anal.* Calcd for $C_{23}H_{39}N_3O_3Si_2$: C, 59.83; H, 8.51; N, 9.01. Found: C, 59.83; H, 8.53; N, 9.12.

4-Amino-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (14a) Methanolic ammonia (saturated at 0 °C, 30 ml) was added to a solution of **13a** (2.47 g, 5.36 mmol) in MeOH (10 ml) and the mixture was heated at 120 °C for 12 h in a sealed tube. The reaction mixture was concentrated *in vacuo* and the residue was purified on a silica gel column (4.6 × 15 cm), eluted with hexane/AcOEt (1 : 4), to give **14a** (1.78 g, 70%, crystallized from hexane). mp 156—158 °C. EI-MS *m/z*: 478 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.03 (s, 1H, H-2), 7.85 (d, 1H, H-6, $J=5.5$ Hz), 6.87 (d, 1H, H-7, $J=5.5$ Hz), 6.19 (dd, 1H, H-1′, $J_{1'2'a}=6.0$, $J_{1'2'b}=7.7$ Hz), 5.15 (br s, 2H, NH_2), 4.58 (m, 1H, H-3′), 4.02 (m, 1H, H-4′), 3.81 (m, 2H, H-5′a, b), 2.44 (ddd, 1H, H-2′b, $J_{2'b,1'}=7.7$, $J_{2'b,a}=13.2$, $J_{2'b,3'}=2.2$ Hz), 2.34 (ddd, 1H, H-2′a, $J_{2'a,1'}=6.0$, $J_{2'a,b}=13.2$, $J_{2'a,3'}=3.3$ Hz), 0.92 (s, 18H, *tert*-Bu × 2), 0.11 and 0.10 (each s, each 6H, Me × 2). *Anal.* Calcd for $C_{23}H_{42}N_4O_3Si_2$: C, 57.70; H, 8.84; N, 11.70. Found: C, 57.72; H, 8.77; N, 11.68.

4-Amino-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole[4,5-*c*]pyridine (14b) Compound **13b** (700 mg, 1.52 mmol) was converted as above to give **14b** (410 mg, 56%, crystallized from hexane). mp 83—85 °C. EI-MS *m/z*: 478 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.18 (s, 1H, H-2), 7.86 (d, 1H, H-6, $J=6.0$ Hz), 6.83 (d, 1H, H-7, $J=6.0$ Hz), 5.71 (d, 1H, H-1′, $J_{1',2'}=3.3$ Hz), 5.15 (br s, 2H, NH_2), 4.51 (m, 2H, H-2′, 4′), 4.07 (dd, 1H, H-5′a, $J_{5'a,4'}=2.2$, $J_{5'a,b}=11.5$ Hz), 3.74 (dd, 1H, H-5′b, $J_{5'b,4'}=2.2$, $J_{5'b,a}=11.5$ Hz), 2.31 (ddd, 1H, H-3′a, $J_{3'a,2'}=1.7$, $J_{3'a,b}=12.6$, $J_{3'a,4'}=6.0$ Hz), 1.96 (ddd, 1H, H-3′b, $J_{3'b,2'}=6.6$, $J_{3'b,a}=12.6$, $J_{3'b,4'}=4.4$ Hz), 0.96 and 0.86 (each s, each 9H, *tert*-Bu), 0.15, 0.14, −0.03, and −0.06 (each s, each 3H, Me). *Anal.* Calcd for $C_{23}H_{42}N_4O_3Si_2$: C, 57.70; H, 8.84; N, 11.70. Found: C, 57.59; H, 8.89; N, 11.76.

4-Amino-1-(2-deoxy-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (15a) A THF solution of TBAF (1 M, 1.0 ml, 1.0 mmol) was added to a solution of **14a** (200 mg, 0.42 mmol) in THF (10 ml) at 0 °C and the mixture was stirred for 2 h at room temperature. The mixture was concentrated *in vacuo* and the residue was purified on a silica gel column (2.4 × 15 cm), eluted with 15% MeOH in $CHCl_3$, to give **15a** (95 mg, 91%, crystallized from acetone–EtOH). mp 208—210 °C (lit.[26] mp 209—211 °C). EI-MS *m/z*: 250 (M^+). UV $\lambda_{max}^{H_2O}$ 263 nm (ε 10200); $\lambda_{max}^{0.5\,N\,HCl}$ 262 nm (ε 10200); $\lambda_{max}^{0.5\,N\,NaOH}$ 266 nm (ε 11100). ^{1}H-NMR (DMSO-d_6) δ: 8.29 (s, 1H, H-2), 7.65 (d, 1H, H-6, $J=5.5$ Hz), 6.68 (d, 1H, H-7, $J=5.5$ Hz), 6.29 (br s, 2H, NH_2), 6.24 (dd, 1H, H-1′, $J_{1',2'a}=6.2$, $J_{1',2'b}=7.3$ Hz), 5.32 (d, 1H, 3′-OH, $J_{OH,3'}=4.4$ Hz), 4.95 (t, 1H, 5′-OH, $J_{OH,5'a}=J_{OH,5'b}=5.5$ Hz), 4.34 (m, 1H, H-3′), 3.83 (m, 1H, H-4′), 3.53 (m, 2H, H-5′a, b), 2.52 and 2.30 (each m, each 1H, H-2′a, b).

4-Amino-1-(3-deoxy-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (15b) Compound **14b** (350 mg, 0.73 mmol) was desilylated as described for the synthesis of **15a** to give **15b** (130 mg, 71%, crystallized from MeOH). mp 220—222 °C. EI-MS *m/z*: 250 (M^+). UV $\lambda_{max}^{H_2O}$ 263 nm (ε 10100); $\lambda_{max}^{0.5\,N\,HCl}$ 263 nm (ε 10200); $\lambda_{max}^{0.5\,N\,NaOH}$ 266 nm (ε 11100). ^{1}H-NMR (DMSO-d_6) δ: 8.31 (s, 1H, H-2), 7.67 (d, 1H, H-6, $J=6.0$ Hz), 6.86 (d, 1H, H-7, $J=6.0$ Hz), 6.14 (br s, 2H, NH_2), 5.74 (d, 1H, H-1′, $J_{1',2'}=2.8$ Hz), 5.69 (d, 1H, 3′-OH, $J_{OH,3'}=3.8$ Hz), 5.03 (t, 1H, 5′-OH, $J_{OH,5'a}=J_{OH,5'b}=5.5$ Hz), 4.38 (m, 2H, H-2′, 4′), 3.66 (ddd, 1H, H-5′a, $J_{5'a,4'}=3.3$, $J_{5'a,b}=12.1$, $J_{5'a,OH}=5.5$ Hz), 3.53 (ddd, 1H, H-5′b, $J_{5'b,4'}=3.8$, $J_{5'b,a}=12.1$, $J_{5'b,OH}=5.5$ Hz), 2.15 and 1.87 (each m, each 1H, H-3′a, b). *Anal.* Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found C, 52.68; H, 5.74; N, 22.34.

5-Iodo-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (16a) In the same manner as described for **7a**, **10a** (1.2 g, 2.55 mmol) was treated with isoamyl nitrite in diiodomethane giving **16a** (920 mg, 62% as an orange foam, which was crystallized from hexane). mp 125—126 °C. EI-MS *m/z*: 524 ($M^+ - tert$-butyl). ^{1}H-NMR ($CDCl_3$) δ: 8.07 (s, 1H, H-2), 7.03 (br s, 1H, CONH), 6.08 (t, 1H, H-1′, $J_{1',2'a}=J_{1',2'b}$ 6.2 Hz), 5.40 (br s, 1H, CONH), 4.51 (m, 1H, H-3′), 3.99 (m, 1H, H-4′), 3.86 (dd, 1H, H-5′a, $J_{5'a,4'}=3.3$, $J_{5'a,b}=11.4$ Hz), 3.78 (dd, 1H, H-5′b, $J_{5'b,4'}=2.6$, $J_{5'b,a}=11.4$ Hz), 2.45 (ddd, 1H, H-2′a, $J_{2'a,1'}=6.2$, $J_{2'a,b}=13.2$, $J_{2'a,3'}=2.6$ Hz), 2.19 (m, 1H, H-2′b), 0.92 and 0.91 (each s, each 9H, *tert*-Bu), 0.10 and 0.08 (each s, each 6H, Me × 2). *Anal.* Calcd for $C_{21}H_{40}IN_3O_4Si_2$: C, 43.37; H, 6.93; N, 7.22. Found: C, 43.22; H, 6.86; N, 7.04.

5-Iodo-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (16b) In the same manner as described for **7a**, **10b** (1.88 g, 4.0 mmol) was treated with isoamyl nitrite in diiodomethane giving **16b** (1.39 g, 60%, crystallized from hexane). mp 123—124 °C. EI-MS *m/z*: 524 ($M^+ - tert$-Bu). ^{1}H-NMR ($CDCl_3$) δ: 8.34 (s, 1H, H-2), 7.12 (br s, 1H, CONH), 5.75 (s, 1H, H-1′), 5.33 (br s, 1H, CONH), 4.51 and 4.38 (each m, each 1H, H-2′, 4′), 4.14 (dd, 1H, H-5′a, $J_{5'a,4'}=2.2$, $J_{5'a,b}=11.7$ Hz), 3.75 (dd, 1H, H-5′b, $J_{5'b,4'}=2.4$, $J_{5'b,a}=11.7$ Hz), 2.23 (m, 1H, H-3′a), 1.80 (ddd, 1H, H-3′b, $J=2.2$, 5.5, 13.1 Hz), 0.95 and 0.91 (each s, each 9H, *tert*-Bu), 0.14 and 0.13 (each s, each 6H, Me × 2). *Anal.* Calcd for $C_{21}H_{40}IN_3O_4Si_2$: C, 43.37; H, 6.93; N, 7.22. Found: C, 43.20; H, 6.83; N, 7.04.

5-Trimethylsilylethynyl-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (17a) In the same manner as described for **8a**, **16a** (1.17 g, 2.01 mmol) was treated with trimethyl-[(tributylstannyl)ethnyl]silane in the presence of bis(benzonitrile)-palladium dichloride giving **17a** (822 mg, 74% as a yellow foam). EI-MS *m/z*: 551 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.81 (s, 1H, H-2), 6.87 (br s, 1H,

CONH), 6.17 (dd, 1H, H-1′, $J_{1',2'a}=6.0$, $J_{1',2'b}=6.6$ Hz), 5.31 (br s, 1H, CONH), 4.48 (m, 1H, H-3′), 4.00 (q, 1H, H-4′, $J=3.3$ Hz), 3.80 (m, 2H, H-5′a, b), 2.41 and 2.20 (each m, each 1H, H-2′a, b), 2.19 (m, 1H, H-2′b), 0.91 and 0.90 (each s, each 9H, *tert*-Bu), 0.28 (s, 9H, TMS), 0.10 and 0.09 (each s, each 6H, Me × 2). HR-MS ($M^+ - tert$-butyl): Calcd for $C_{22}H_{40}N_3O_4Si_3$: 494.2326. Found: 494.2298.

5-Trimethylsilylethynyl-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (17b) In the same manner as described for **8a**, **16b** (1.16 g, 2.0 mmol) was treated with trimethyl-[(tributhylstannyl)ethynyl]silane in the presence of bis(benzonitrile)-palladium dichloride giving **17b** (833 mg, 76% as a brown foam). EI-MS *m/z*: 494 ($M^+ - tert$-Bu). ^{1}H-NMR ($CDCl_3$) δ: 8.03 (s, 1H, H-2), 6.97 (br s, 1H, CONH), 5.80 (d, 1H, H-1′, $J_{1',2'}=1.6$ Hz), 5.41 (br s, 1H, CONH), 4.49 and 4.34 (each m, each 1H, H-2′, 4′), 4.08 (dd, 1H, H-5′a, $J_{5'a,4'}=1.8$, $J_{5'a,b}=11.7$ Hz), 3.74 (dd, 1H, H-5′b, $J_{5'b,4'}=2.4$, $J_{5'b,a}=11.7$ Hz), 2.28 (ddd, 1H, H-3′a, $J=5.0$, 9.3, 13.1 Hz), 1.85 (ddd, 1H, H-3′b, $J=2.6$, 5.7, 13.1 Hz), 0.94 and 0.89 (each s, each 9H, *tert*-Bu), 0.28 (s, 9H, TMS), 0.13, 0.12, 0.08, and 0.05 (each s, each 3H, Me).

5-(2-Hydroxyiminoethyl)-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (18a) Aqueous dimethylamine (50%, 5 ml) was added to a solution of **17a** (500 mg, 0.91 mmol) in EtOH (10 ml) and the mixture was heated at 50 °C for 4 h in a sealed tube. The reaction mixture was transferred to a round-bottom flask, and hydroxylamine hydrochloride (150 mg, 2.15 mmol) and acetic acid (4 ml) were added to the solution at 0 °C. The whole was stirred for 2 h at room temperature and the reaction was quenched by addition of acetone (10 ml). The mixture was concentrated *in vacuo* and the residue was dissolved in AcOEt. The solution was washed successively with H_2O, saturated aqueous $NaHCO_3$ and brine. The separated organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on a silica gel column (2.6 × 10 cm), eluted with hexane/AcOEt (1 : 2), to give **18a** (412 mg, 89% as a yellow foam). EI-MS *m/z*: 512 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.34 (br s, 0.56H, NOH of isomer A), 8.53 (br s, 0.44H, NOH of isomer B), 7.78 (s, 0.56H, H-2 of A), 7.76 (s, 0.44H, H-2 of B), 7.51 (t, 0.44H, $CH_2\underline{CH}$ of B, $J=40$ Hz), 7.15 (br s, 1H, CONH), 6.84 (t, 0.56H, $CH_2\underline{CH}$ of A, $J=5.5$ Hz), 6.07 (m, 0.56H, H-1′, of A), 5.99 (m, 0.44H, H-1′ of B), 5.61 (br s, 1H, CONH), 4.52 (m, 1H, H-3′), 4.34—3.91 (m, 3H, H-4′, $C\underline{H}_2CH$), 3.77 (m, 2H, H-5′a, b), 2.39—2.17 (m, 2H, H-2′a, b), 0.91, 0.90, 0.89, and 0.88 (each s, 18H, *tert*-Bu × 2), 0.10, 0.09, and 0.08 (each s, 12H, Me × 4). *Anal.* Calcd for $C_{23}H_{44}N_4O_5Si_2$: C, 53.87; H, 8.65; N, 10.93. Found: C, 53.81; H, 8.76; N, 10.63.

5-(2-Hydroxyiminoethyl)-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazole-4-carboxamide (18b) Compound **17b** (810 mg, 1.47 mmol) was converted as above to give **18b** (582 mg, 77% as a white foam). EI-MS *m/z*: 512 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.67 (br s, 0.6H, NOH of isomer A), 7.96 (br s, 0.4H, NOH of isomer B), 7.89 (s, 0.6H, H-2 of A), 7.87 (s, 0.4H, H-2 of B), 7.52 (dd, 0.4H, $CH_2C\underline{H}$ of B, $J=5.0$, 5.9 Hz), 7.12 (br s, 1H, CONH), 6.86 (dd, 0.6H, $CH_2C\underline{H}$ of A, $J=5.0$, 5.6 Hz), 5.66 (d, 0.6H, H-1′ of A, $J=2.6$ Hz), 5.61 (d, 0.4H, H-1′ of B, $J=3.0$ Hz), 5.50 (br s, 1H, CONH), 4.46—3.66 (m, 6H, H-3′, 4′, 5′a, b, $C\underline{H}_2CH$), 2.27 (m, 1H, H-2′a), 1.93 (m, 1H, H-2′b), 0.94, 0.93, and 0.86 (each s, 18H, *tert*-Bu × 2), 0.11, 0.01 (each s, 12H, Me × 4). *Anal.* Calcd for $C_{23}H_{44}N_4O_5Si_2$: C, 53.87; H, 8.65; N, 10.93. Found: C, 53.91; H, 8.66; N, 10.88.

6-Amino-1-(2-deoxy-3,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (19a) 1-(Trifluoroacetyl)imidazole (0.24 ml, 2.14 mmol) was added to a solution of **18a** (909 mg, 1.78 mmol) in dry THF (40 ml) and the mixture was heated under reflux for 3.5 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in a mixture of EtOH (20 ml)–5% aqueous Na_2CO_3 (15 ml). The mixture was heated under reflux for 45 min. The mixture was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$, which was washed with H_2O, followed by brine. The separated organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on a silica gel column (3.6 × 12 cm), eluted with 8% EtOH in $CHCl_3$, to give **19a** (655 mg, 75%, crystallized from hexane–EtOH). mp 203—208 °C (dec.). EI-MS *m/z*: 494 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 12.40 (br s, 1H, NH), 7.83 (s, 1H, H-2), 5.94 (t, 1H, H-1′, $J_{1',2'a}=J_{1',2'b}=6.5$ Hz), 5.51 (s, 1H, H-7), 4.99 (m, 2H, NH_2), 4.52 (m, 1H, H-3′), 3.96 (m, 1H, H-4′), 3.75 (m, 2H, H-5′a, b), 2.34 (m, 2H, H-2′a, b), 0.92 and 0.90 (each s, each 9H, *tert*-Bu), 0.11 (s, 6H, Me × 2), 0.07 and 0.06 (each s, each 3H, Me). *Anal.* Calcd for $C_{23}H_{42}N_4O_4Si_2 \cdot 1/3H_2O$: C, 53.87; H, 8.65; N, 10.93. Found: C, 53.81; H, 8.76; N, 10.63.

6-Amino-1-(3-deoxy-2,5-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (19b) Compound **18b** (700 mg, 1.37 mmol) was converted as above to give **19b** (448 mg, 66% as a pale blue foam). EI-MS *m/z*: 494 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 12.57 (br s, 1H, NH), 7.93 (s, 1H, H-2), 5.94 (t, 1H, H-1′, $J_{1',2'a}=J_{1',2'b}=6.5$ Hz), 5.51 (s, 1H, H-7), 4.99 (m, 2H, NH_2), 4.52 (m, 1H, H-3′), 3.96 (m, 1H, H-4′), 3.75 (m, 2H, H-5′a, b), 2.34 (m, 2H, H-2′a, b), 0.92 and 0.90 (each s, each 9H, *tert*-Bu), 0.11 (s, 6H, Me × 2), 0.07 and 0.06 (each s, each 3H, Me). *Anal.* Calcd for $C_{23}H_{42}N_4O_4Si_2 \cdot 1/3H_2O$: C, 53.87; H, 8.65; N, 10.93. Found: C, 53.81; H, 8.76; N, 10.63.

6-Amino-1-(2-deoxy-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (20a) In the same manner as described for **15a**, **19a** (655 mg, 1.32 mmol) was treated with TBAF in THF. The solvent was removed *in vacuo* and the residue was dissolved in H_2O. The solution was washed with $CHCl_3$ and activated charcol was added to the aqueous solution until the optical density at 271 nm went below 1%. This suspension was packed into a glass column, which was washed with H_2O, then eluted with 28% NH_4OH/EtOH (0 : 100—30 : 70). The UV absorbing fractions were collected and concentrated to dryness *in vacuo* to give **20a** (320 mg, 91%, crystallized from EtOH–H_2O). mp 203 °C (dec.) (lit.[23a] mp 230—231 °C). ^{1}H-NMR (DMSO-d_6) δ: 10.31 (br s, 1H, NH), 7.87 (s, 1H, H-2), 5.94 (m, 1H, H-1′), 5.58 (br s, 2H, NH_2), 5.43 (s, 1H, H-7), 5.32 (d, 1H, 3′-OH, $J_{OH,3'}=4.3$ Hz), 4.91 (t, 1H, 5′-OH, $J=5.3$ Hz), 4.31 (m, 1H, H-3′), 3.81 (m, 1H, H-4′), 3.50 (m, 2H, H-5′a, b), 2.45 and 2.22 (each m, each 1H, H-2′a, b).

6-Amino-1-(3-deoxy-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridin-4(5*H*)-one (20b) In the same manner as described for **15a**, **19b** (310 mg, 0.63 mmol) was treated with TBAF in THF. The solvent was removed *in vacuo* and the residue was dissolved in H_2O. The solution was washed with $CHCl_3$ and the aqueous layer was concentrated *in vacuo*. The residue was coevaporated with EtOH twice and EtOH was added to the residue. The resulting precipitate was collected and washed with ice-cold EtOH to give **20b** (138 mg, 82%, crystallized from aqueous MeOH). mp 232—234 °C (dec.). FAB-MS *m/z*: 267 ($M^+ + 1$). ^{1}H-NMR (DMSO-d_6) δ: 10.26 (br s, 1H, NH), 7.89 (s, 1H, H-2), 5.64 (d, 1H, 2′-OH, $J_{2'\text{-OH},2'}=4.0$ Hz), 5.57 (br s, 2H, NH_2), 5.47 (d, 1H, H-1′, $J_{1',2'}=2.1$ Hz), 5.43 (s, 1H, H-7), 4.96 (t, 1H, 5′-OH, $J=5.4$ Hz), 4.31 (m, 2H, H-2′, 4′), 3.65 (ddd, 1H, H-5′a, $J_{5'a,4'}=3.6$, $J_{5'a,5'\text{-OH}}=5.4$, $J_{5'a,b}=11.9$ Hz), 3.52 (ddd, 1H, H-5′b, $J_{5'b,4'}=4.4$, $J_{5'b,5'\text{-OH}}=5.4$, $J_{5'b,a}=11.9$ Hz), 2.10 (ddd, 1H, H-3′a, $J=6.0$, 9.2, $J_{3'a,b}=13.1$ Hz), 1.87 (ddd, 1H, H-3′b, $J=2.7$, 6.1, $J_{3'b,a}=13.1$ Hz). *Anal.* Calcd for $C_{11}H_{14}N_4O_4 \cdot 2/3$MeOH: C, 48.72; H, 5.84; N, 19.48. Found: C, 48.32; H, 5.60; N, 19.50.

References and Notes

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22) When N^1-methoxymethyl-3′,5′-di-*O*-acetyl-2′-deoxyinosine was treated with 5 N NaOH in EtOH under reflux condition, AICA-2′dR (**5a**) was obtained along with unseparable 2′-deoxyinosine (**1a**). The yield of **5a** and **1a** were estimated to be 69 and 28% yields, respectively, integration of ^{1}H-NMR spectrum.
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