Synthesis of 5-(Alkylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamides, Key Intermediates for the Synthesis of 3-Alkyl-9-β-D-ribofuranosylpurine Derivatives

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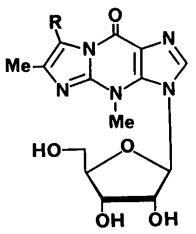
An alternative synthesis of 2′,3′,5′-tri-*O*-benzoyl-*N*,*N*,3-trimethyladenosine iodide (9a) was attained by the reaction of *N*,*N*,3-trimethyladenine (11a) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10) in the presence of $SnCl_4$ followed by treatment with NaI. Although 3-benzyl-*N*,*N*-dimethyladenine (11c) did not react with 10 under similar conditions, the ribosylation of 3-ethyl-*N*,*N*-dimethyladenine (11b) followed by alkaline hydrolysis led to the first synthesis of 5-(ethylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (15b). A more general procedure for the synthesis of 5-(alkylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamides (15) was developed *via* a series of reactions: alkylation of *N*′-benzyloxy-5-formamido-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (12) with alkyl halides in the presence of K_2CO_3, catalytic hydrogenolysis, and alkaline hydrolysis. By means of this method, 5-(benzylamino)- (15c) and 5-(isopropylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (15d) were synthesized for the first time.

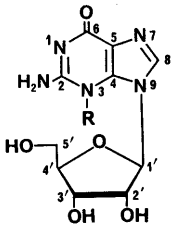
Keywords imidazole-4-carboxamide; imidazole nucleoside; ribosylation; formamido *N*-alkylation; *N*-alkoxyamidine hydrogenolysis; imidazolecarboxamidine; carboxamidine hydrolysis; (alkylamino)imidazole

Remarkable lability to acidic hydrolysis at the *N*-glycosidic bond is a characteristic of the tricyclic compounds **1**,[1] the putative structures for the fluorescent nucleosides isolated from unfractionated transfer ribonucleic acids (tRNAs) of extremely thermophilic archaebacteria[2] and yeast phenylalanine tRNAs.[3] The structures **1** are unique in that they contain the 3-methyl-9-β-D-ribofuranosylpurine moiety. In order to establish the relationship between the structure and the rate of hydrolysis at the glycosidic bond, we have synthesized 3-methyladenosine (**3**),[4] 3-methylguanosine (**2a**),[1b,e,5] 3-methylinosine (**4**),[6] 3-methylxanthosine (**5**),[7] and 3-methylisoguanosine (**6**),[8] as typical examples of 3-methyl-9-β-D-ribofuranosylpurines, and found that all these nucleosides undergo unusually fast cleavage at the glycosidic bond under acidic conditions. One plausible explanation for the high sensitivity is that this is a case of steric assistance of the methyl group situated at the *peri* position.[1d] Taking this as a working hypothesis, we attempted to obtain higher 3-alkyl homologues of these nucleosides, none of which had been synthesized. Since **2a**, **4**, **5**, and **6** have been synthesized from 5-(methylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (**15a**), the title compounds **15** should be good intermediates for the syntheses of our targets. This paper presents a detailed account of a general synthesis of **15**.[9]



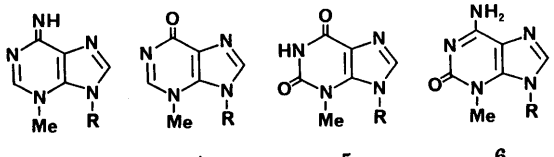
1

a: R = H
b: R = Me
c: R = CH_2CH_2–C(H, CO_2Me)–$NHCO_2Me$



2

a: R = Me
b: R = Et
c: R = $PhCH_2$
d: R = Me_2CH

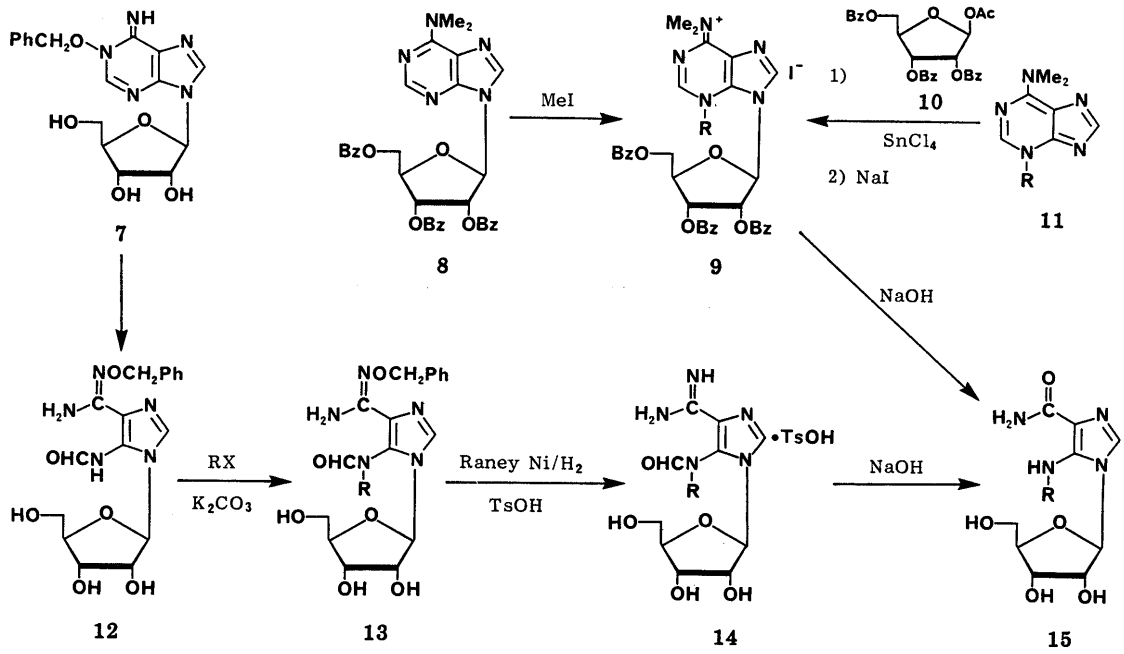


3 **4** **5** **6**

R = β-D-ribofuranosyl

Compound **15a** and its 2′,3′-*O*-isopropylidene derivative have been synthesized by reductive methylation of appropriate imidazole nucleosides.[1a,10] Alternatively, we have obtained **15a** by methylation of 2′,3′,5′-tri-*O*-benzoyl-*N*,*N*-dimethyladenosine (**8**) followed by alkaline hydrolysis.[6a,11] In the present study, however, ethylation of **8** with EtI or benzylation with $PhCH_2Br$ did not afford the corresponding quaternary salt [**9b** or **9c** (Br^- for I^-)]. We have shown that alkylation of either *N*,*N*,9- (type **8**, alkyl for the tri-*O*-benzoylribofuranosyl group) or *N*,*N*,3-trialkyladenines (type **11**) gives *N*,*N*,3,9-tetraalkyladeninium salts (type **9**, alkyl for the tri-*O*-benzoylribofuranosyl group) and that the latter reaction proceeds faster than the former.[12] This knowledge encouraged us to try the condensation of *N*,*N*,3-trimethyladenine (**11a**)[13] with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**10**).[14] Treatment of **11a** with **10** in $(CH_2Cl)_2$ at room temperature in the presence of $SnCl_4$[15] followed by anion exchange afforded the desired **9a**[11] in 35% yield. Similar treatment of 3-ethyl-*N*,*N*-dimethyladenine (**11b**)[13] followed by alkaline hydrolysis[11] gave **15b** in 12% overall yield.[16] The structure **15b** was assignable by comparison of the ultraviolet (UV) and the nuclear magnetic resonance (NMR) spectra with those of **15a**. 3-Benzyl-*N*,*N*-dimethyladenine (**11c**),[13] however, hardly reacted with **10**.

The third access to **15** was achieved by utilization of *N*′-benzyloxy-5-formamido-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (**12**),[17] the stable intermediate of the Dimroth rearrangement of 1-benzyloxyadenosine (**7**). We have already established the synthesis of 1-alkyl-5-(alkylamino)-1*H*-imidazole-4-carboxamides (type **15**, alkyl for the ribofuranosyl group) by alkaline hydrolysis of 1-alkyl-5-(*N*-alkylformamido)-1*H*-imidazole-4-carboxamidines (type **14**, alkyl for the ribofuranosyl group), which are obtainable by alkylation of *N*′-alkoxy-1-alkyl-5-form-



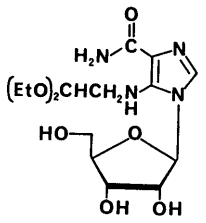
7 8 9 10 11 12 13 14 15

a: R=Me b: R=Et c: R=$PhCH_2$ d: R=Me_2CH

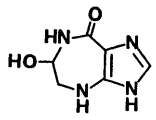
Chart 1

amido-1*H*-imidazole-4-carboxamidines (type **12**, alkyl for the ribofuranosyl group) followed by catalytic hydrogenolysis.[18] We have also reported the synthesis of **14a** by methylation of **12** with MeI in the presence of K_2CO_3 followed by catalytic hydrogenolysis using Raney Ni in the presence of 1 molar equivalent of TsOH.[4] Thus, hydrolysis of **14a** should lead to a new synthesis of **15a**. In fact, when heated in 1 N aqueous NaOH under reflux, **14a** gave **15a** in 46% overall yield based on **12**. Compound **12** was similarly treated with EtI in $HCONMe_2$ in the presence of anhydrous K_2CO_3 at room temperature, furnishing **13b** in 79% yield. Removal of the *N'*-benzyloxy group from **13b** and successive hydrolysis of the resulting **14b** were conducted in a manner similar to that described above for the preparation of **15a** to afford **15b** in 62% yield. The reactions of **12** with $PhCH_2Br$ and with Me_2CHI under similar conditions gave the corresponding *N*-alkylformamido derivatives **13c, d** in 66% and 26% yields, respectively. The use of 18-crown-6 in the latter reaction improved the yield of **13d** to 61%. Compounds **13c, d** were also transformed into **15c, d** through **14c, d** in 50% and 53% yields, respectively.

In the present study, we also improved the procedure for the preparation of the key intermediate **12**, which had been obtained in 79% yield by hydrolysis of 1-benzyloxyadenosine perchlorate (**7**·$HClO_4$) in 0.5 M $NaHCO_3$–Na_2CO_3 buffer of pH 9.5 at 39—41 °C for 4 h.[17a] The reaction mixture had been concentrated under reduced pressure at the initial stage of work-up. Since this process is accompanied with a pH shift to the higher region owing to partial decomposition of the buffer component $NaHCO_3$ to Na_2CO_3, it promotes the ring closure of **12** to *N*-benzyloxyadenosine,[17a] causing a severe reduction in yield in the case of a large-scale preparation. When a solution of **7**·$HClO_4$ in plain water was adjusted to pH 9.5 with aqueous NaOH and kept at 40 °C for 4 h, we found that the pH changed to a much lesser extent throughout the reaction than we had expected. Such a small change in pH may be interpreted as a beneficial consequence of the buffering action of the $HClO_4$–**7** and **12**–NaOH system, since **7** (basic pK_a 7.90[19]) and **12** (acidic pK_a 9.93[19]) have their pK_a's near 9.5. Accordingly, the reaction mixture can be easily maintained at pH 9.5, without resort to the carbonate buffer, by occasional supply of a small amount of aqueous NaOH. This procedure improved the yield of **12** to 95%.



15e



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In conclusion, among the above three synthetic routes to **15**, the third route **12**→**13**→**14**→**15** has proved to be the most general. Since we have already accomplished the synthesis of **2b**—**d** from **15b**—**d**,[1d,20] syntheses of 4-alkyl homologues of **1a**—**c** should be attainable according to our own synthetic routes to **1a**—**c** from **2a**.[1b,d,e,h,j] The present synthesis of **15b**—**d** should also permit the syntheses of 3-alkyl homologues of **4**—**6**. Quite recently, syntheses of azepinomycin (**16**), an antitumor antibiotic from *Streptomyces* species, have been reported by Issiki *et al.*[21] and Fujii *et al.*[22] The latter group utilized the third of the methods for the synthesis of the key intermediate **15e**.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Spectra reported herein were recorded on a Hitachi 320 UV spectrophotometer using solutions in 95% aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13), and a JEOL

JNM-FX-100 NMR spectrometer at 25 °C using Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-181 polarimeter. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dq = doublet-of-quartets, m = multiplet, s = singlet, sh = shoulder, t = triplet.

2′,3′,5′-Tri-*O*-benzoyl-*N*,*N*,3-trimethyladenosine Iodide (9a) Anhydrous $SnCl_4$ (0.15 ml, 1.3 mmol) was added to a solution of **11a**[13] (177 mg, 1.0 mmol) and **10**[14] (504 mg, 1.0 mmol) in $(CH_2Cl)_2$ (5 ml). The mixture was stirred at room temperature for 4 h. The resulting clear solution was washed successively with H_2O (2 × 10 ml), saturated aqueous $NaHCO_3$ (2 × 10 ml), and H_2O (3 × 20 ml), dried over Na_2SO_4, and concentrated *in vacuo* to leave a colorless foam. This was dissolved in EtOH (4.5 ml) and a solution of NaI (300 mg, 2 mmol) in EtOH (0.7 ml) was added. The resulting precipitate was collected by filtration, washed successively with H_2O (0.5 ml) and EtOH (0.5 ml), and dried to give **9a** (264 mg, 35%), mp 186—189 °C (dec.). Recrystallization from MeOH gave colorless prisms, mp 189—190 °C (dec.). This sample was identical [by mixture melting point test and comparison of the infrared (IR) spectrum] with an authentic specimen.[11]

***N′*-Benzyloxy-5-formamido-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (12)** A suspension of 1-benzyloxyadenosine perchlorate monohydrate ($7 \cdot HClO_4 \cdot H_2O$)[23] (35.98 g, 74.2 mmol) in H_2O (1400 ml) was adjusted to pH 9.5 with 10% aqueous NaOH at 40 °C. The mixture was stirred at that temperature for 4 h, being kept at pH 9.5 by occasional addition of 10% aqueous NaOH. The resulting solution was chilled, neutralized with 10% aqueous HCl, and concentrated *in vacuo* to a small volume. The precipitate that separated was collected by filtration, washed with cold H_2O (60 ml), and dried to give **12** (27.26 g, 95%), mp 156—160 °C (dec.) [lit.[17a] mp 158—160 °C (dec.)], identical [by mixture melting point test and comparison of the IR spectrum] with an authentic sample.[17a]

***N′*-Benzyloxy-5-(*N*-ethylformamido)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (13b)** A mixture of **12** (783 mg, 2.0 mmol), anhydrous K_2CO_3 (415 mg, 3.0 mmol), and $HCONMe_2$ (12 ml) was stirred at room temperature for 1 h. Ethyl iodide (940 mg, 6 mmol) in $HCONMe_2$ (1 ml) was added and stirring was continued for a further 24 h. The mixture was concentrated *in vacuo* and the residue was dissolved in H_2O (10 ml). Saturated aqueous NaCl (10 ml) was added to the solution and the resulting precipitate was filtered off, washed with a little H_2O, and dried to give a colorless solid (665 mg, 79%), mp 146—148 °C. Recrystallization from AcOEt afforded an analytical sample as colorless prisms, mp 147—148 °C, $[\alpha]_D^{20}$ −44.6° (*c* = 0.999, MeOH); UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 6500); $\lambda_{max}^{H_2O}$ (pH 1) 246 (sh) (8400); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (6100); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (6000); ^{1}H-NMR [$(CD_3)_2SO$] δ:[24] 0.87 (3H, t, *J* = 7 Hz, Me), 3.54 [4H, m, MeC$\underline{H}_2$, C(5′)-H_2], 3.89 [1H, m, C(4′)-H], 4.05 [1H, m, C(3′)-H], 4.32 [1H, m, C(2′)-H], 4.85 with a shoulder at 4.89 (2H, s, PhC$\underline{H}_2$), 5.02 (1H, t, *J* = 5 Hz, 5′-OH), 5.21 (1H, d, *J* = 5 Hz, 3′-OH), 5.24 [1H, d, *J* = 6 Hz, C(1′)-H], 5.47 (1H, d, *J* = 6 Hz, 2′-OH), 5.78 with a small peak at 5.70 (2H, br, NH_2), 7.33 (5H, m, Ph), 7.94 with a small peak at 8.22 (1H, s, CHO),[25] 8.09 with two small peaks at 8.03 and 8.06 [1H, s, C(2)-H].[25] *Anal.* Calcd for $C_{19}H_{25}N_5O_6$: C, 54.41; H, 6.01; N, 16.70. Found: C, 54.12; H, 5.96; N, 16.70.

***N′*-Benzyloxy-5-(*N*-benzylformamido)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (13c)** A mixture of **12** (587 mg, 1.5 mmol), anhydrous K_2CO_3 (311 mg, 2.2 mmol), and $HCONMe_2$ (9 ml) was stirred at room temperature for 1 h, and then $PhCH_2Br$ (260 mg, 1.5 mmol) in $HCONMe_2$ (1 ml) was added. After stirring had been continued for 30 h, the reaction mixture was concentrated *in vacuo*. The residue was mixed with H_2O (1 ml) and saturated aqueous NaCl (4 ml). The mixture was extracted with AcOEt (2 × 10 ml). The combined extracts were washed with saturated aqueous NaCl (2 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified on a silica gel (20 g) column [$CHCl_3$–EtOH (6 : 1, v/v)] to give **13c** (480 mg, 66%) as a colorless foam, UV $\lambda_{max}^{95\%\ EtOH}$ 250 nm (sh) (ε 6800); $\lambda_{max}^{H_2O}$ (pH 1) 246 (sh) (7900); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (6000); $\lambda_{max}^{H_2O}$ (pH 13) 250 (sh) (6000); ^{1}H-NMR [$(CD_3)_2SO$] δ:[24] 3.53 [2H, m, C(5′)-H_2], 3.78 [1H, m, C(4′)-H], 3.85—4.25 [2H, m, C(3′)-H and C(2′)-H], 4.40—4.75 (2H, m, NC$\underline{H}_2$Ph), 4.88 (2H, s, OC$\underline{H}_2$Ph), 4.90—5.20 [3H, m, C(1′)-H, 3′-OH, and 5′-OH], 5.35 (1H, br, 2′-OH), 5.66 (2H, br, NH_2), 7.15 (5H, m, $NCH_2\underline{Ph}$), 7.34 (5H, m, $OCH_2\underline{Ph}$), 8.12 with two small peaks at 8.32 and 8.42 (1H, s, CHO),[25] 7.97 with a small peak at 8.00 [1H, s, C(2)-H].[25]

***N′*-Benzyloxy-5-(*N*-isopropylformamido)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (13d)** A mixture of **12** (5.48 g, 14 mmol), anhydrous K_2CO_3 (1.93 g, 14 mmol), and $HCONMe_2$ (70 ml) was stirred at room temperature for 1 h, then 18-crown-6 (2.04 g, 7.7 mmol) was added. Stirring was continued for a further 0.5 h and then Me_2CHI (2.62 g, 15.4 mmol) was added. The whole was stirred at 30 °C for 48 h and concentrated *in vacuo*. The residue was mixed with ice-water (50 ml) and saturated aqueous NaCl (50 ml). The mixture was extracted with $CHCl_3$ (3 × 60 ml) and the combined organic layers were dried over $MgSO_4$ and then concentrated *in vacuo* to leave a brown oil. The residue was washed with Et_2O (3 × 20 ml) and purified on a silica gel (200 g) column [$CHCl_3$–MeOH (5 : 1, v/v)] to give **13d** (3.70 g, 61%) as a yellowish foam, UV $\lambda_{max}^{95\%\ EtOH}$ 256 nm (sh) (ε 6000); $\lambda_{max}^{H_2O}$ (pH 1) 246 (sh) (7300); $\lambda_{max}^{H_2O}$ (pH 7) 250 (sh) (5600); $\lambda_{max}^{H_2O}$ (pH 13) 247 (sh) (5800); ^{1}H-NMR [$(CD_3)_2SO$] δ:[24] 0.87 and 0.93 (a total of 3H, d each, *J* = 6.5 Hz, Me), 1.11 and 1.16 (a total of 3H, d each, *J* = 6.5 Hz, Me), 3.54 [2H, m, C(5′)-H_2], 3.88 [1H, m, C(4′)-H], 3.94—4.54 [3H, m, C(3′)-H, C(2′)-H, and $Me_2C\underline{H}$], 4.85 with a shoulder at 4.89 (2H, s, PhC$\underline{H}_2$), 5.04 (1H, t, *J* = 6 Hz, 5′-OH), 5.18 (1H, d, *J* = 4 Hz, 3′-OH), 5.27 and 5.30 [a total of 1H, d each, *J* = 6.5 Hz, C(1′)-H], 5.45 and 5.47 (a total of 1H, d each, *J* = 6.5 Hz, 2′-OH), 5.78 with a shoulder at 5.64 (2H, br, NH_2), 7.32 (5H, m, Ph), 7.88 and 7.90 with a small peak at 8.37 (a total of 1H, s each, CHO),[25] 8.10 with a small peak at 8.07 [1H, s, C(2)-H].[25]

5-(Methylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (15a) Compound **14a** was prepared from **13a** (405 mg, 1 mmol) according to the reported procedure[4b] and dissolved in 1 N aqueous NaOH (10 ml). The solution was refluxed for 30 min and applied to a column of Dowex 50W-X8 (H^+) (10 ml). The column was washed with H_2O (50 ml). The product was eluted with 5% aqueous NH_3 and the eluate (550 ml) was concentrated *in vacuo*. The residue was washed with EtOH (3 ml) to give a chromatographically pure sample of **15a** (146 mg, 54%), mp 168—170 °C. Recrystallization from EtOH afforded almost colorless prisms, mp 179—181 °C (lit.[11] mp 182—184 °C). This sample was identical (by comparison of the IR spectrum and paper chromatographic behavior) with an authentic specimen.[11]

5-(Ethylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (15b) i) From **11b**: The reaction of **11b**[13] (382 mg, 2.0 mmol) and **10**[14] was carried out in a manner similar to that described above for the ribosylation of **11a** to give a crude product as a colorless foam. This was dissolved in EtOH (5 ml) and a solution of NaI (600 mg, 4 mmol) in EtOH (1.6 ml) was added. The resulting mixture was concentrated *in vacuo* and the residue was washed with H_2O (3 × 20 ml) and dried to give a colorless solid (812 mg), mp 102—129 °C (dec.). A part (500 mg) of this sample was refluxed in a mixture of 2 N aqueous NaOH (6 ml) and EtOH (3 ml) for 2 h, concentrated *in vacuo* to half the initial volume, and then cooled. Ion exchange resin [Bio-Rad AG 50W-X8 (H^+)] (5 ml) and EtOH (3 ml) was added to the solution. The resulting mixture was put on a column packed with more resin (3 ml). Then, the column was washed successively with H_2O–EtOH (2 : 1, v/v) (40 ml) and H_2O (20 ml). The column was eluted with cold 5% aqueous NH_3 (6 ml) and then with concentrated aqueous NH_3 (60 ml). The combined ammoniac eluates were concentrated *in vacuo* to leave a caramel (150 mg). This was purified on a silica gel (5 g) column [$CHCl_3$–MeOH (5 : 1, v/v)] to give **15b** (43 mg, 12%)[16] as a colorless glass. Identity of this sample with that described below was confirmed by ^{1}H-NMR spectroscopy.

ii) From **13b**: A solution of **13b** (4.20 g, 1.0 mmol) and *p*-toluenesulfonic acid monohydrate (1.90 g, 1.0 mmol) in H_2O (250 ml) was hydrogenated over Raney Ni (7 ml) at room temperature and atmospheric pressure for 2 h. The catalyst was filtered off and washed with H_2O (90 ml). The combined filtrate and washings were concentrated *in vacuo* to give **14b** as an oily residue. This was dissolved in 1 N aqueous NaOH (100 ml) and the solution was refluxed for 10 min and then put on a column of Dowex 50W-X8 (H^+) (100 ml). The column was washed with H_2O (500 ml) then eluted successively with 5% aqueous NH_3 (350 ml) and concentrated aqueous NH_3 (1200 ml). The combined ammoniac eluates were concentrated *in vacuo* and the residue was purified on a silica gel (96 g) column [$CHCl_3$–MeOH (5 : 1, v/v)] to give **15b** (1.79 g, 62%) as a colorless glass, UV $\lambda_{max}^{95\%\ EtOH}$ 266 nm (ε 9200); $\lambda_{max}^{H_2O}$ (pH 1) 257 (6500); $\lambda_{max}^{H_2O}$ (pH 7) 263 (7500); $\lambda_{max}^{H_2O}$ (pH 13) 265 (7500); ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.08 (3H, t, *J* = 7 Hz, $Me\underline{C}H_2$), 3.15 (2H, dq, *J* = 7 Hz each, MeC$\underline{H}_2$), 3.56 [2H, br, C(5′)-H_2], 3.88 [1H, m, C(4′)-H], 4.05 [1H, m, C(3′)-H], 4.31 [1H, m, C(2′)-H], 5.03 (1H, t, *J* = 5 Hz, 5′-OH), 5.18 (1H, d, *J* = 5 Hz, 3′-OH), 5.44 [d, *J* = 6 Hz, overlapped with signals due to 2′-OH and NH, C(1′)-H], 6.89 and 7.03 (1H each, br, NH_2), 7.60 [1H, s, C(2)-H].

5-(Benzylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (15c) A solution of **13c** (3.31 g, 6.87 mmol) and *p*-toluenesulfonic acid monohydrate (1.31 g, 6.89 mmol) in a mixture of H_2O (140 ml) and EtOH (40 ml) was hydrogenated over Raney Ni (5 ml) at room temperature and atmospheric pressure for 6 h. The mixture was worked up in a manner

similar to that described above for the hydrogenolysis of **13b**. The product **14c** was hydrolyzed by refluxing in 1 N aqueous NaOH (80 ml) for 30 min. The resulting solution was neutralized with concentrated hydrochloric acid, concentrated *in vacuo* to *ca.* 60 ml, and extracted with AcOEt (10 × 100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to leave **15c** (1.19 g, 50% yield) as a colorless solid, mp 149—150 °C. Recrystallization from EtOH gave an analytical sample as colorless needles, mp 153—154 °C; $[\alpha]_D^{20}$ −47.7° (c = 1.00, MeOH); UV $\lambda_{max}^{95\%\,EtOH}$ 266 nm (ε 9200); $\lambda_{max}^{H_2O}$ (pH 1) 258 (7500); $\lambda_{max}^{H_2O}$ (pH 7) 265 (8000); $\lambda_{max}^{H_2O}$ (pH 13) 268 (8000); ^{1}H-NMR [$(CD_3)_2SO$] δ: 3.58 [2H, br, C(5′)-H_2], 3.90 [1H, m, C(4′)-H], 4.06 [1H, m, C(3′)-H], 4.31 [1H, m, C(2′)-H], 4.36 (2H, br, PhCH_2), 5.06, 5.17, and 5.45 (1H each, br, 5′-, 3′-, and 2′-OH), 5.54 [1H, d, J = 6 Hz, C(1′)-H], 6.12 (1H, br, NH), 6.88 and 7.02 (1H each, br, NH_2), 7.31 (5H, m, Ph), 7.60 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 55.19; H, 5.67; N, 16.20.

5-(Isopropylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (15d) Compound **13d** (1.73 g, 3.99 mmol) was hydrogenated over Raney Ni and worked up in a manner similar to that described above for **15b**. The crude **15d** thus obtained was crystallized by treating it with EtOH (3 ml) to give colorless pillars (573 mg), mp 162—164 °C. An additional crop (67 mg; the total yield was 53%) was obtained from the mother liquor by silica gel (10 g) column chromatography [$CHCl_3$–MeOH (5 : 1, v/v)]. Recrystallization from EtOH gave an analytical sample as colorless pillars, mp 163—165 °C; $[\alpha]_D^{21}$ −50.6° (c = 0.497, MeOH); UV $\lambda_{max}^{95\%\,EtOH}$ 266 nm (ε 9300); $\lambda_{max}^{H_2O}$ (pH 1) 257 (6800); $\lambda_{max}^{H_2O}$ (pH 7) 264 (8700); $\lambda_{max}^{H_2O}$ (pH 13) 265 (8800); ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.06 and 1.08 (3H each, d, J = 6 Hz, Me_2), 3.44 (1H, m, Me_2CH), 3.55 (2H, m, CH_2), 3.86 [1H, m, C(4′)-H], 4.04 [1H, m, C(3′)-H], 4.30 [1H, m, C(2′)-H], 4.98 (1H, t, J = 5 Hz, 5′-OH), 5.17 (1H, d, J = 5 Hz, 3′-OH), 5.39 [1H, d, J = 6 Hz, overlapped with signals due to 2′-OH and NH, C(1′)-H], 6.86 and 7.02 (1H each, br, NH_2), 7.62 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{12}H_{20}N_4O_5$: C, 47.99; H, 6.71; N, 18.66. Found: C, 47.82; H, 6.99; N, 18.61.

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24) The observed complexity of the signals is probably due to *cis–trans* isomerism of the *N*-substituted formamido group (ref. 18*c* and references cited therein) and diastereoisomerism produced by a combination of atropisomerism caused by restricted rotation about the imidazole-to-nitrogen bond and chirality of the ribofuranosyl group (refs. 4*b* and 7*b* and references cited therein).

25) Selective deuteration at the 2-position (treatment with boiling D_2O for 4 h)[18c] permitted the assignment.