

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-carboxamide (**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.

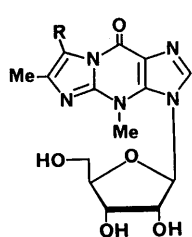
Keywords imidazole-4-carboxamide; imidazole nucleoside; ribosylation; formamido *N*-alkylation; *N*-alkoxyamidine hydrogenolysis; imidazolecarboxamidine; carboxamidine hydrolysis; (alkylamino)imidazole

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 archaebacteria²⁾ 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⁾

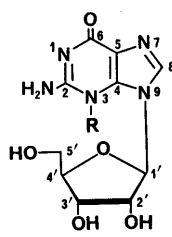
Compound **15a** and its 2',3'-*O*-isopropylidene derivative have been synthesized by reductive methylation of appropriate imidazole nucleosides.^{1a, 10)} Alternatively, we have obtained **15a** by methylation of 2',3',5'-tri-*O*-benzoyl-*N,N*-dimethyladenosine (**8**) followed by alkaline hydrolysis.^{6a, 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 $(\text{CH}_2\text{Cl})_2$ 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 hydrolysis¹¹⁾ 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-



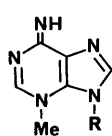
1

- a: R = H
b: R = Me
c: R = $\text{CH}_2\text{CH}_2-\text{C}(\text{H})(\text{CO}_2\text{Me})(\text{NHCO}_2\text{Me})$

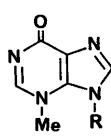


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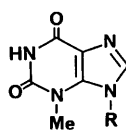
- a: R = Me
b: R = Et
c: R = PhCH_2
d: R = Me_2CH



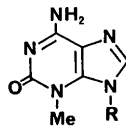
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4

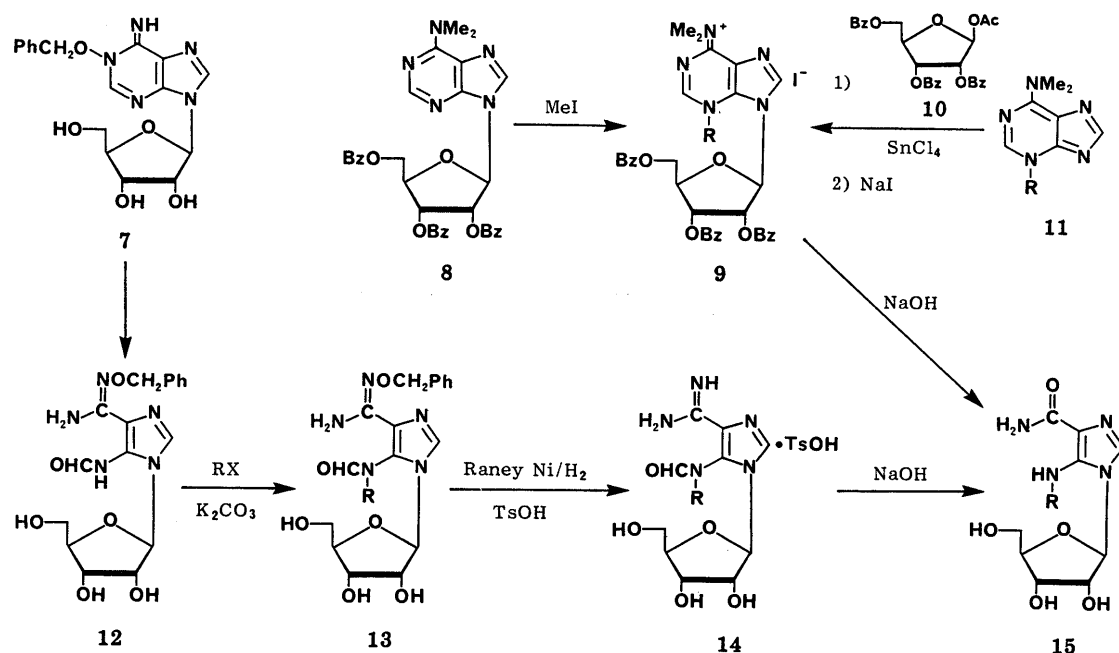


5



6

R = β -D-ribofuranosyl

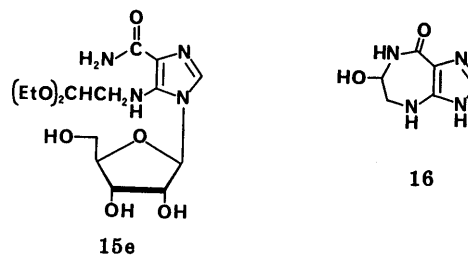


a: R = Me b: R = Et c: R = PhCH₂ d: R = Me₂CH

Chart 1

amido-1*H*-imidazole-4-carboxamides (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 K₂CO₃ 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 HCONMe₂ in the presence of anhydrous K₂CO₃ 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 PhCH₂Br and with Me₂CHI 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-benzoyloxyadenosine perchlorate (7·HClO₄) in 0.5 *M* NaHCO₃–Na₂CO₃ 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 NaHCO₃ to Na₂CO₃, 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·HClO₄ 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 HClO₄–7 and 12–NaOH system, since 7 (basic p*K*_a 7.90¹⁹⁾) and 12 (acidic p*K*_a 9.93¹⁹⁾) have their p*K*_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%.

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 Me₄Si 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 SnCl₄ (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 (CH₂Cl)₂ (5 ml). The mixture was stirred at room temperature for 4 h. The resulting clear solution was washed successively with H₂O (2 × 10 ml), saturated aqueous NaHCO₃ (2 × 10 ml), and H₂O (3 × 20 ml), dried over Na₂SO₄, 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 H₂O (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'-Benzoyloxy-5-formamido-1-β-D-ribofuranosyl-1H-imidazole-4-carboxamide (12) A suspension of 1-benzoyloxyadenosine perchlorate monohydrate (7·HClO₄·H₂O)²³⁾ (35.98 g, 74.2 mmol) in H₂O (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 H₂O (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'-Benzoyloxy-5-(N-ethylformamido)-1-β-D-ribofuranosyl-1H-imidazole-4-carboxamide (13b) A mixture of **12** (783 mg, 2.0 mmol), anhydrous K₂CO₃ (415 mg, 3.0 mmol), and HCONMe₂ (12 ml) was stirred at room temperature for 1 h. Ethyl iodide (940 mg, 6 mmol) in HCONMe₂ (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 H₂O (10 ml). Saturated aqueous NaCl (10 ml) was added to the solution and the resulting precipitate was filtered off, washed with a little H₂O, 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, [α]_D²⁰ –44.6° (c=0.999, MeOH); UV λ_{max}^{95% EtOH} 250 nm (sh) (ε 6500); λ_{max}^{H₂O} (pH 1) 246 (sh) (8400); λ_{max}^{H₂O} (pH 7) 250 (sh) (6100); λ_{max}^{H₂O} (pH 13) 250 (sh) (6000); ¹H-NMR [(CD₃)₂SO] δ: 0.87 (3H, t, J=7 Hz, Me), 3.54 [4H, m, MeCH₂, C(5')-H₂], 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, PhCH₂), 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, NH₂), 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 C₁₉H₂₅N₅O₆: C, 54.41; H, 6.01; N, 16.70. Found: C, 54.12; H, 5.96; N, 16.70.

N'-Benzoyloxy-5-(N-benzylformamido)-1-β-D-ribofuranosyl-1H-imidazole-4-carboxamide (13c) A mixture of **12** (587 mg, 1.5 mmol), anhydrous K₂CO₃ (311 mg, 2.2 mmol), and HCONMe₂ (9 ml) was stirred at room temperature for 1 h, and then PhCH₂Br (260 mg, 1.5 mmol) in HCONMe₂ (1 ml) was added. After stirring had been continued for 30 h, the reaction mixture was concentrated *in vacuo*. The residue was mixed with H₂O (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 MgSO₄, and concentrated *in vacuo*. The residue was purified on a silica gel (20 g) column [CHCl₃–EtOH (6:1, v/v)] to give **13c** (480 mg, 66%) as a colorless foam, UV λ_{max}^{95% EtOH} 250 nm (sh) (ε 6800); λ_{max}^{H₂O} (pH 1) 246 (sh) (7900); λ_{max}^{H₂O} (pH 7) 250 (sh) (6000); λ_{max}^{H₂O} (pH 13) 250 (sh) (6000); ¹H-NMR [(CD₃)₂SO] δ: 2.43 [2H, m, C(5')-H₂], 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, NCH₂Ph), 4.88 (2H, s, OCH₂Ph), 4.90–5.20 [3H, m, C(1')-H, 3'-OH, and 5'-OH], 5.35 (1H, br, 2'-OH), 5.66 (2H, br, NH₂), 7.15 (5H, m, NCH₂Ph), 7.34 (5H, m, OCH₂Ph), 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'-Benzoyloxy-5-(N-isopropylformamido)-1-β-D-ribofuranosyl-1H-imidazole-4-carboxamide (13d) A mixture of **12** (5.48 g, 14 mmol), anhydrous K₂CO₃ (1.93 g, 14 mmol), and HCONMe₂ (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 Me₂CHI (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 CHCl₃ (3 × 60 ml) and the combined organic layers were dried over MgSO₄ and then concentrated *in vacuo* to leave a brown oil. The residue was washed with Et₂O (3 × 20 ml) and purified on a silica gel (200 g) column [CHCl₃–MeOH (5:1, v/v)] to give **13d** (3.70 g, 61%) as a yellowish foam, UV λ_{max}^{95% EtOH} 256 nm (sh) (ε 6000); λ_{max}^{H₂O} (pH 1) 246 (sh) (7300); λ_{max}^{H₂O} (pH 7) 250 (sh) (5600); λ_{max}^{H₂O} (pH 13) 247 (sh) (5800); ¹H-NMR [(CD₃)₂SO] δ: 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')-H₂], 3.88 [1H, m, C(4')-H], 3.94–4.54 [3H, m, C(3')-H, C(2')-H, and Me₂CH], 4.85 with a shoulder at 4.89 (2H, s, PhCH₂), 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, NH₂), 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-1H-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 H₂O (50 ml). The product was eluted with 5% aqueous NH₃ 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-1H-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 H₂O (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 H₂O–EtOH (2:1, v/v) (40 ml) and H₂O (20 ml). The column was eluted with cold 5% aqueous NH₃ (6 ml) and then with concentrated aqueous NH₃ (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 [CHCl₃–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 ¹H-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 H₂O (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 H₂O (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 H₂O (500 ml) then eluted successively with 5% aqueous NH₃ (350 ml) and concentrated aqueous NH₃ (1200 ml). The combined ammoniac eluates were concentrated *in vacuo* and the residue was purified on a silica gel (96 g) column [CHCl₃–MeOH (5:1, v/v)] to give **15b** (1.79 g, 62%) as a colorless glass, UV λ_{max}^{95% EtOH} 266 nm (ε 9200); λ_{max}^{H₂O} (pH 1) 257 (6500); λ_{max}^{H₂O} (pH 7) 263 (7500); λ_{max}^{H₂O} (pH 13) 265 (7500); ¹H-NMR [(CD₃)₂SO] δ: 1.08 (3H, t, J=7 Hz, MeCH₂), 3.15 (2H, dq, J=7 Hz each, MeCH₂), 3.56 [2H, br, C(5')-H₂], 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, NH₂), 7.60 [1H, s, C(2)-H].

5-(Benzylamino)-1-β-D-ribofuranosyl-1H-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 H₂O (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 MgSO₄ 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 $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 266 nm (ϵ 9200); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 258 (7500); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 265 (8000); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 268 (8000); ¹H-NMR [(CD₃)₂SO] δ : 3.58 [2H, br, C(5')-H₂], 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, PhCH₂], 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, NH₂), 7.31 (5H, m, Ph), 7.60 [1H, s, C(2)-H]. Anal. Calcd for C₁₆H₂₀N₄O₅: 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-1H-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 [CHCl₃–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 $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 266 nm (ϵ 9300); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 257 (6800); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 264 (8700); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 265 (8800); ¹H-NMR [(CD₃)₂SO] δ : 1.06 and 1.08 (3H each, d, *J* = 6 Hz, Me₂), 3.44 (1H, m, Me₂CH), 3.55 (2H, m, CH₂), 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, NH₂), 7.62 [1H, s, C(2)-H]. Anal. Calcd for C₁₂H₂₀N₄O₅: 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. 18c 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. 4b and 7b and references cited therein).
- 25) Selective deuteration at the 2-position (treatment with boiling D₂O for 4 h)^{18c)} permitted the assignment.