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Purines. LXIII.[1] Syntheses of Azepinomycin, an Antitumor Antibiotic from *Streptomyces* Species, and Its 3-β-D-Ribofuranoside and Their 8-Imino Analogues

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Three variants of a synthetic route to the antitumor antibiotic azepinomycin (3) from 1-substituted *N′*-alkoxy-5-formamidoimidazole-4-carboxamidine (type 10) are described. The synthesis started with the monocycles 10a—c and proceeded through the intermediates 11a—c, 12a—c, 13a—c, 14a—c, and 4a, b and 3-β-D-ribofuranosylazepinomycin (4c). The benzyl version (series a), including the permutation 14a→15→3, was found to produce the antibiotic (3) most efficiently. The starting materials 10a—c were readily prepared from the 9-substituted adenines 7a—c *via* the *N*-oxides 8a—c and the 1-alkoxy derivatives 9a—c. The 8-imino analogues (17 and 18) of 3 and 4c were also synthesized from 12a and 12c, respectively.

Keywords azepinomycin synthesis; ribofuranosylazepinomycin; 1-alkoxyadenine; adenine ring opening; amide *N*-alkylation; hydrogenolysis *N*-alkoxy

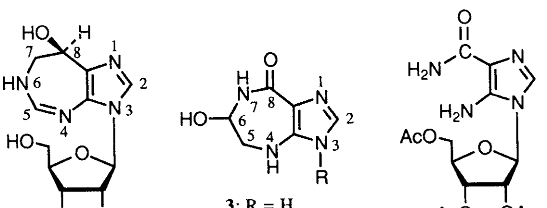
Imidazodiazepines form a small but chemically, biochemically, and pharmacologically interesting group of fused heterocyclic ring systems.[2] They may be regarded as purine analogues ring-expanded in the pyrimidine moiety with or without oxygen functions. The best known among them are probably the antibiotics coformycin (**1**)[3] and pentostatin (**2**),[4] which are nucleosides bearing the imidazo[4,5-*d*][1,3]diazepine ring system.[5] In 1983, Umezawa *et al.*[6] disclosed the isolation of azepinomycin (**3**), a novel imidazodiazepine regarded as a ring-expanded hypoxanthine, from the culture filtrate of *Streptomyces* sp. MF718-03. The substance was found to be a strong inhibitor of guanine deaminase and to have antileukemic activity against murine L5178Y cells *in vitro*.[6] Its chemical structure (**3**) was established by X-ray crystallographic analysis[6] and by two chemical syntheses of **3**,[7] which started from 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**5**) and proceeded through 3-β-D-ribofuranosylazepinomycin (**4c**).

We designed an alternative synthesis of **3**, which was feasible in three variants, on the basis of our favorite "fission and reclosure" technology[8] for modification of the adenine ring (**6**); the nucleoside **4c** and the 8-imino analogues (**17** and **18**) of **3** and **4c** were also selected as targets for synthesis. Our approach features the use of 1-substituted *N′*-alkoxy-5-formamidoimidazole-4-carboxamidines (type **10**), the ring-opened intermediates[8a,b,9] in the Dimroth rearrangement of 9-substituted 1-alkoxyadenines (type **9**), as the starting materials. A brief account of a part of the results reported here has been published in a preliminary form.[10]

The first version of our new synthetic route to azepinomycin (**3**) started with the benzyl analogue **10a**,[11] which was prepared from adenine (**6**) through 9-benzyladenine (**7a**),[12] the *N*-oxide **8a**,[13] and the 1-ethoxy derivative **9a**[13] according to previously reported procedures (Chart 1). To obtain the key intermediate **14a** from **10a**, we took advantage of the methodology employed by us[8a,11,14—16] for the syntheses of 3,9-disubstituted purines and 1-substituted 5-aminoimidazole-4-carboxamidines and -4-carboxamides. Thus, alkylation of **10a** with 1,1-diethoxy-2-iodoethane[17] ($HCONMe_2$, K_2CO_3/18-crown-6, 30 °C, 21 h) gave the *N*-(2,2-diethoxyethyl)formamido derivative **11a** in 93% yield. When this *N*-alkylation was effected in the absence of 18-crown-6 at 30 °C for 120 h, the yield of **11a** was lowered to 68%. On treatment with boiling 1 N aqueous NaOH for 3 h, **11a** afforded the deformylated product **12a** in 94% yield. Deethoxylation of **12a** by catalytic hydrogenolysis [Raney Ni/H_2, H_2O/HCl (1 molar eq), 1 atm, room temp., 6 h] and subsequent hydrolysis (boiling 1 N aqueous NaOH, 4 h) of the resulting amidine **13a** furnished the carboxamide **14a** in 45% overall yield (from **12a**).

The carboxamide **14a** was then debenzylated (10% Pd–C/H_2, MeOH, 1 atm, 50 °C, 5 h) to yield the N(1)-unsubstituted imidazole **15**, and deacetalization and cyclization of **15** were conducted in 1 N aqueous HCl (room temp., 5 h), producing the target compound **3** in 70% overall yield (from **14a**). The UV [H_2O (pH 1 or 7)], IR (KBr), and ^{1}H-NMR (D_2O or D_2O+DCl) spectra of the synthetic **3** matched those of natural azepinomycin. In an alternative partial sequence of reactions, **14a** was first cyclized in 1 N aqueous HCl at room temperature for 30 min, and the resulting bicyclic compound **4a** (obtained in 92% yield) was then debenzylated (10% Pd–C/H_2, MeOH, 1 atm, 50 °C, 10 h) to provide the desired compound **3** in 46% yield. The overall yield of **3** from **10a** *via* the permutation **14a**→**15**→**3** was 28%.

In a second version of the above new synthesis, we



1: Z = OH
2: Z = H

3: R = H
4c: R = β-D-ribofuranosyl

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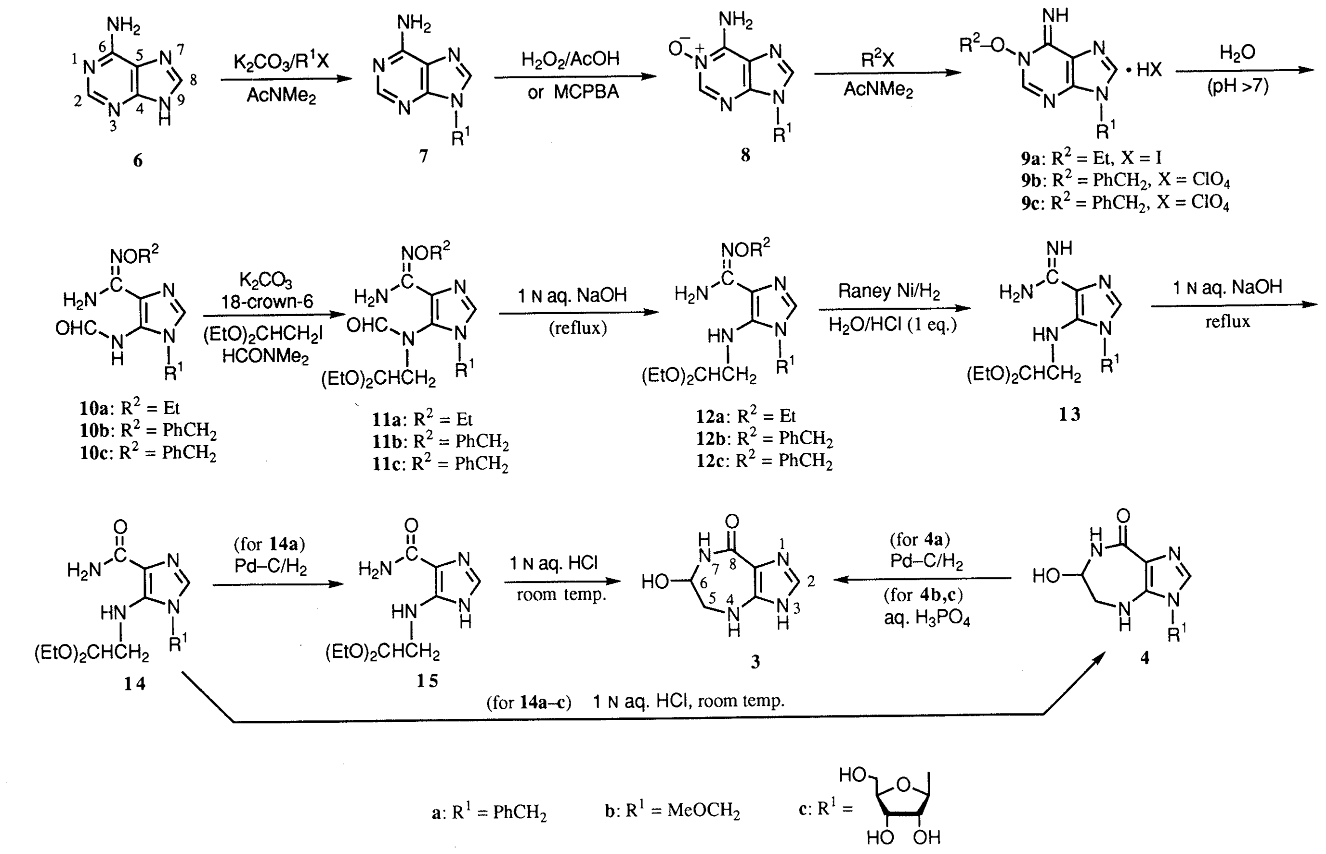

Chart 1

employed the methoxymethyl analogues (series **b**) instead of the benzyl analogues (series **a**), as shown in Chart 1. Treatment of adenine (**6**) with chloromethyl methyl ether in the presence of anhydrous K_2CO_3 ($AcNMe_2$, room temp., 1.5 h), an application of the previously reported[12] general N(9)-alkylation procedure for **6**, gave 9-(methoxymethyl)adenine (**7b**) in 39% yield. Oxidation of **7b** with *m*-chloroperoxybenzoic acid (MCPBA) was then effected in MeOH at room temperature for 6 h, affording the N(1)-oxide **8b** in 77% yield. Benzylation of **8b** with $PhCH_2Br$ ($AcNMe_2$, room temp., 16 h) furnished, after treatment of the primary product (**9b**: X = Br in place of ClO_4) with $NaClO_4$ in H_2O, the 1-benzyloxy derivative **9b** in 97% yield. Ring opening of **9b** in H_2O at pH 9.2 and 40 °C for 5 h provided the monocycle **10b** in 90% yield. The steps beyond **10b** were parallel to those described above for the **a**-series: **10b**→**11b** (30 °C, 27 h; 74% yield)→**12b**·HCl (95%)→**13b**→**14b** [57% (from **12b**·HCl)]→**4b** (room temp., 1 h; 97%). Finally, removal of the methoxymethyl group from **4b** was achieved in boiling 5% aqueous H_3PO_4 for 10 h, giving the target **3** in 20% yield. The overall yield of **3** from **10b** was 8%.

For the third version of the present synthesis of **3**, we followed the sequence of reactions constituting the **c**-series in Chart 1. The starting point for this version was *N'*-benzyloxy-5-formamido-1-*β*-D-ribofuranosylimidazole-4-carboxamidine (**10c**),[9c,16] which was prepared from adenosine (**7c**) through the *N*-oxide **8c**[8b] and the 1-benzyloxy derivative **9c**[13] according to our previous procedures. The subsequent steps were essentially the same as those in the above **b**-series, affording the following results: **10c**→**11c** (room temp., 93 h)→**12c** [room temp., 2 h; 40% yield (from **10c**)]→**13c**→**14c** [reflux, 30 min; 63% (from **12c**)]→**4c** (room temp., 1 h; 94%). The nucleoside **4c**, isolated as a foam and presumed to be a diastereomeric mixture due to the newly formed asymmetric center at C(6), was identical with a sample synthesized by Isshiki *et al.*[7] On treatment with 5% aqueous H_3PO_4 at 95 °C[7] for 10 h, **4c** furnished the aglycone **3** in 48% yield. The overall yield of **3** from **10c** was 11%.

Compounds structurally analogous to azepinomycin (**3**) and its 3-riboside (**4c**) include the 8-imino analogues **17** and **18**, which may be regarded as ring-expanded adenine and adenosine analogues, respectively, and therefore might have inhibitory activity against adenosine deaminase. This led us to select them as the next targets for synthesis (Chart 2). Thus, crude **13a**·HCl, obtained from **12a** by deethoxylation (*vide supra*), was subjected to catalytic hydrogenolysis (10% Pd–C/H_2, H_2O, 1 atm, 50 °C, 15 h) to give the debenzylated product **16**. Treatment of crude **16** with 1 N aqueous HCl at room temperature for 3 h furnished the desired compound **17**[18] in 53% overall yield (from **12a**). On the other hand, catalytic hydrogenolysis of **12c** [10% Pd–C/H_2, H_2O/HCl (1 molar eq), 1 atm, 50 °C, 6 h] yielded the carboxamidine **13c**·HCl. Deacetalization and cyclization of crude **13c**·HCl were then effected in 1 N aqueous HCl at room temperature for 4 h, affording the desired nucleoside **18**[18] in 58% overall yield (from **12c**). Characterization of **17** and **18** as the 8-imino analogues of **3** and **4c**, respectively was readily

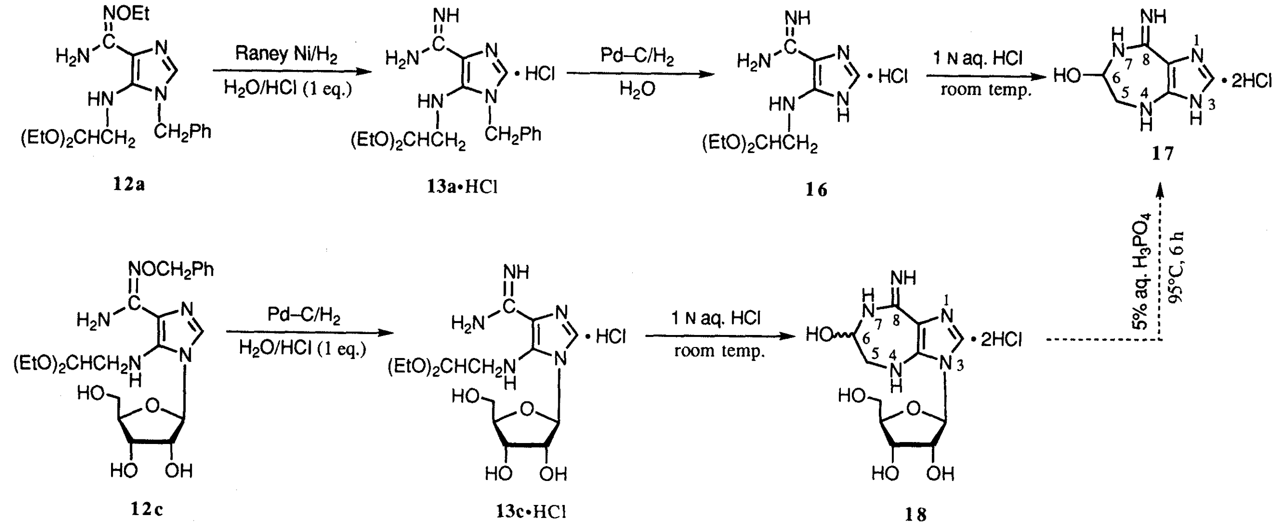

Chart 2

achieved by elemental analyses and measurements of their ^{1}H-NMR spectra, in which the coupling patterns of the C(5)-H_2 and C(6)-H protons were similar to those of **3** and **4a**—**c**. Glycosidic hydrolysis of **18** in 5% aqueous H_3PO_4 at 95 °C for 6 h gave a complex mixture of products, from which we were unable to obtain the desired aglycone (**17**).

In conclusion, the present results have established three versions of a novel synthetic route to azepinomycin (**3**), which are applicable to the synthesis of the 8-imino analogue **17**. They also demonstrate the synthetic utility of our "fission and reclosure" technology[8] for modification of the adenine ring (**6**). The synthesis using the benzyl analogues (series **a** in Chart 1) appears to be superior to the other two (series **b** and **c**) with regard to simplicity in operation and the overall yield of **3** (28% from **10a** through **14a** and **15**). This benzyl version also appears to be much more efficient than the previous synthesis[7] of **3** from **5** (5—6% overall yield), subject to the availability of the starting monocycle **10a**, a synthetic equivalent for **5**, in sufficient quantity.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. TLC was conducted on Merck silica gel 60 F_{254} plates (0.25-mm thickness), and spots were detected by means of UV absorbance measurement (at 254 nm). Flash chromatography[19] was carried out by using Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on a Hitachi, 320 UV spectrophotometer [on solutions in 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13)], a JASCO A-202 IR spectrophotometer, a Hitachi M-80 mass spectrometer, or a JEOL JNM-FX-100 NMR spectrometer at 25 °C. Unless otherwise noted, chemical shifts are reported in ppm downfield from internal Me_4Si. Optical rotations were measured with a JASCO DIP-181 polarimeter using a 1-dm sample tube. For the measurements of pH values, a Toa HM-18ET pH meter equipped with a Toa type GST-155C glass electrode was employed. Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

9-(Methoxymethyl)adenine (7b) A stirred mixture of adenine (**6**) (5.41 g, 40.0 mmol) and anhydrous K_2CO_3 (8.29 g, 60.0 mmol) in $AcNMe_2$ (160 ml) was heated at 110 °C for 2 h. The mixture was cooled to room temperature, and chloromethyl methyl ether (4.83 g, 60.0 mmol) was added dropwise over a period of 1 h. The resulting mixture was stirred at room temperature for a further 30 min. The reaction mixture was concentrated *in vacuo* to leave a yellowish orange solid, which was extracted with boiling AcOEt. The AcOEt extract (*ca.* 250 ml) was concentrated *in vacuo*, and the residue was dissolved in boiling EtOH (60 ml) to give an orange solution. On the other hand, the insoluble solid that was left after the above extraction with AcOEt was then extracted with boiling EtOH (80 ml), and this ethanolic extract and the above ethanolic orange solution were combined, decolorized with charcoal in the usual manner, and concentrated *in vacuo*. The residual solid was recrystallized twice from EtOH (*ca.* 90 ml), giving **7b** (2.77 g, 39%) as colorless needles, mp 201—202 °C. Further recrystallization from EtOH afforded an analytical sample as colorless needles, mp 202—203 °C; MS *m/z*: 179 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 260 nm (ε 14100); $\lambda_{max}^{H_2O}$ (pH 1) 257 (14400); $\lambda_{max}^{H_2O}$ (pH 7) 260 (14600); $\lambda_{max}^{H_2O}$ (pH 13) 260 (14500); ^{1}H-NMR (Me_2SO-d_6) δ: 3.27 (3H, s, OMe), 5.48 [2H, s, N(9)-CH_2O], 7.26 (2H, br, NH_2), 8.16 [1H, s, C(2)-H],[20] 8.26 [1H, s, C(8)-H].[20] *Anal.* Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.92; H, 5.00; N, 39.06.

In a separate run on a 30-g scale, it was possible to omit the process of extraction with AcOEt in the work-up procedure, but the yield of **7b** was lowered to 27%.

9-(Methoxymethyl)adenine 1-Oxide (8b) Compound **7b** (4.41 g, 24.6 mmol) was dissolved in hot MeOH (140 ml), and the solution was cooled to room temperature with stirring. *m*-Chloroperoxybenzoic acid (of 80% purity) (7.94 g, 36.8 mmol) was added to the resulting suspension, and stirring was continued at room temperature for 6 h, during which time the suspension turned into a clear solution and then started to deposit colorless crystals. The crystals that deposited were collected by filtration, washed successively with MeOH and boiling AcOEt (50 ml), and dried to give **8b** (3.71 g, 77%), mp 263.5 °C (dec.). Recrystallization from MeOH provided an analytical sample as colorless minute prisms, mp 264—265 °C (dec.); MS *m/z*: 195 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 235 nm (ε 33600), 263 (6900); $\lambda_{max}^{H_2O}$ (pH 1) 258 (12700); $\lambda_{max}^{H_2O}$ (pH 7) 232 (41100), 262 (8700); $\lambda_{max}^{H_2O}$ (pH 13) 231 (23900), 268 (9100); ^{1}H-NMR (Me_2SO-d_6) δ: 3.28 (3H, s, OMe), 5.50 [2H, s, N(9)-CH_2O], 8.0—8.4 (2H, br, NH_2), 8.44 [1H, s, C(8)-H],[20] 8.64 [1H, s, C(2)-H].[20] *Anal.* Calcd for $C_7H_9N_5O_2$: C, 43.08; H, 4.65; N, 35.88. Found: C, 43.01; H, 4.66; N, 36.00.

1-Benzyloxy-9-(methoxymethyl)adenine Perchlorate (9b) A mixture of **8b** (1.50 g, 7.69 mmol) and $PhCH_2Br$ (6.58 g, 38.5 mmol) in $AcNMe_2$ (12 ml) was stirred at room temperature for 16 h. The reaction mixture was diluted with ether (20 ml), and the insoluble solid was filtered off, washed with ether, and then dissolved in warm H_2O (25 ml). The aqueous solution was mixed with a solution of $NaClO_4 \cdot H_2O$ (1.19 g, 8.47 mmol) in H_2O (2 ml) and cooled in an ice bath. The colorless precipitate that resulted was filtered off, washed with H_2O (3 ml), and dried to give **9b** (2.87 g, 97%), mp 167—168 °C. Recrystallization from EtOH yielded an analytical sample as colorless needles, mp 171.5—172.5 °C; UV

$\lambda_{max}^{95\%\ aq.\ EtOH}$ 258 nm (ε 12600); $\lambda_{max}^{H_2O}$ (pH 1) 259 (12900); $\lambda_{max}^{H_2O}$ (pH 7) 259 (12800); $\lambda_{max}^{H_2O}$ (pH 13) 256 (12900), 265 (sh) (10800); ^{1}H-NMR (Me_2SO-d_6) δ: 3.30 (3H, s, OMe), 5.42 [2H, s, N(1)-OC$\underline{H}_2$Ph], 5.59 [2H, s, N(9)-CH_2O], 7.3—7.8 (5H, m, OCH$_2\underline{Ph}$), 8.70 [1H, s, C(8)-H],[20] 8.93 [1H, s, C(2)-H],[20] 10.1 (2H, br, NH's). *Anal.* Calcd for $C_{14}H_{15}N_5O_2 \cdot HClO_4$: C, 43.59; H, 4.18; N, 18.15. Found: C, 43.52; H, 4.22; N, 17.87.

***N′*-Benzyloxy-5-formamido-1-(methoxymethyl)-1*H*-imidazole-4-carboxamidine (10b)** A stirred suspension of **9b** (2.92 g, 7.57 mmol) in H_2O (150 ml) was warmed to 40 °C, and the pH of the mixture was brought to 9.2 by addition of 10% aqueous NaOH. The resulting solution was stirred at 40 °C for 5 h, neutralized with 10% aqueous HCl, and then concentrated *in vacuo* to a volume of *ca.* 10 ml. The colorless solid that deposited was filtered off, washed with H_2O, and dried to give **10b** (2.07 g, 90%), mp 114—115 °C. Recrystallization from benzene furnished an analytical sample as a colorless microcrystalline solid, mp 114.5—115.5 °C; MS *m/z*: 303 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 230 nm (sh) (ε 17200), 264 (sh) (8000); $\lambda_{max}^{H_2O}$ (pH 1) 253 (7400); $\lambda_{max}^{H_2O}$ (pH 7) 263 (sh) (5500); $\lambda_{max}^{H_2O}$ (pH 13) 254 (12100); IR ν_{max}^{Nujol} cm^{-1}: 3500 and 3370 (NH_2, CONH), 1710 (ArNHCHO), 1650 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 3.18 (3H, s, OMe), 4.88 and 4.94 (1H each, s, OC$\underline{H}_2$Ph), 5.15 and 5.21 [1H each, s, N(1)-CH_2O], 5.75 and 5.76 (2H, dull s each, NH_2), 7.34 (5H, m, OCH$_2\underline{Ph}$), 7.81 and 7.84 [0.5H each, s, C(2)-H], 8.05 (*ca.* 0.5H, d, *J* = 11 Hz, *trans*-$\underline{H}$CONH), 8.20 (*ca.* 0.5H, s, *cis*-$\underline{H}$CONH), 9.44 (*ca.* 0.5 Hz, d, *J* = 11 Hz, *trans*-HCONH̲), 9.70 (*ca.* 0.5H, s, *cis*-HCON$\underline{H}$).[21] *Anal.* Calcd for $C_{14}H_{17}N_5O_3$: C, 55.44; H, 5.65; N, 23.09. Found: C, 55.41; H, 5.70; N, 22.91.

1-Benzyl-5-[*N*-(2,2-diethoxyethyl)formamido]-*N′*-ethoxy-1*H*-imidazole-4-carboxamidine (11a) A mixture of **10a**[11] (1.00 g, 3.48 mmol) and anhydrous K_2CO_3 (730 mg, 5.28 mmol) in $HCONMe_2$ (20 ml) was stirred at room temperature for 1 h. After addition of 18-crown-6 (1.39 g, 5.26 mmol), stirring was continued for a further 30 min, and then a solution of 1,1-diethoxy-2-iodoethane[17] (of 96% purity) (2.65 g, 10.4 mmol) in $HCONMe_2$ (3 ml) was added. The resulting mixture was stirred at 30 °C for 21 h and then concentrated *in vacuo*. The residue was extracted with boiling AcOEt (2 × 40 ml), and the AcOEt extracts were concentrated *in vacuo* to leave a brown oil. Purification of the oil by means of flash chromatography[19] [silica gel, AcOEt–hexane (3 : 1, v/v)] gave **11a** (1.31 g, 93%) as a yellow oil, MS *m/z*: 403 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3430 (NH_2), 1690 (NCHO), 1640 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 0.8—1.3 (9H, m, three OCH$_2\underline{Me}$'s), 3.0—3.7 [6H, m, NC$\underline{H}_2$CH(OC$\underline{H}_2$Me)$_2$], 3.84 (2H, q, *J* = 7 Hz, NOC$\underline{H}_2$Me), 4.65 (1H, t, *J* = 5 Hz, NCH$_2$C$\underline{H}$), 5.19 [2H, m, N(1)-C$\underline{H}_2$Ph], 5.64 (2H, s, NH_2), 7.0—7.4 [5H, m, N(1)-CH$_2\underline{Ph}$], 7.48 (0.28H) and 7.56 (0.72H) [s each, C(2)-H],[21] 7.87 (0.72H) and 8.29 (0.28H) (s each, NCHO).[21]

In a separate run, **10a**[11] (1.00 g, 3.48 mmol), anhydrous K_2CO_3 (728 mg, 5.27 mmol), and 1,1-diethoxy-2-iodoethane[17] (of 96% purity) (2.87 g, 11.3 mmol) were allowed to react in $HCONMe_2$ (20 ml) at 30 °C for 120 h in the absence of 18-crown-6. The reaction mixture was worked up in a manner similar to that described above, giving **11a** in 68% yield.

***N′*-Benzyloxy-5-[*N*-(2,2-diethoxyethyl)formamido]-1-(methoxymethyl)-1*H*-imidazole-4-carboxamidine (11b)** Compound **10b** (1.07 g, 3.53 mmol), anhydrous K_2CO_3 (731 mg, 5.29 mmol), 18-crown-6 (1.40 g, 5.30 mmol), and 1,1-diethoxy-2-iodoethane[17] (of 96% purity) (2.69 g, 10.6 mmol) were mixed in $HCONMe_2$ (15 ml) in a manner similar to that described above for **11a**. The resulting mixture was stirred at 30 °C for 27 h, and the reaction mixture was worked up as described above for **11a**, yielding **11b** (1.10 g, 74%) as a yellow solid, mp 72.5—73.5 °C. Recrystallization from hexane–benzene (10 : 1, v/v) gave an analytical sample as colorless needles, mp 73.5—74 °C; MS *m/z*: 419 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 255 nm (sh) (ε 6200); $\lambda_{max}^{H_2O}$ (pH 1) 252 (7900); $\lambda_{max}^{H_2O}$ (pH 7) 253 (sh) (5800); $\lambda_{max}^{H_2O}$ (pH 13) 253 (sh) (5700); IR ν_{max}^{Nujol} cm^{-1}: 3520, 3400 (NH_2), 1690 (NCHO), 1650 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 0.98 (6H, t, *J* = 7 Hz, OCH$_2\underline{Me}$'s), 3.21 (3H, s, OMe), 3.0—3.7 [6H, m, NC$\underline{H}_2$CH(OC$\underline{H}_2$Me)$_2$], 4.48 (1H, t, *J* = 5 Hz, NCH$_2$C$\underline{H}$), 4.88 (*ca.* 1.7H, s) and 4.92 (*ca.* 0.3H, dull s) (OC$\underline{H}_2$Ph), 5.07 (*ca.* 0.3H) and 5.23 (*ca.* 1.7H) [s each, N(1)-CH_2O], 5.79 (2H, dull s, NH_2), 7.0—7.4 (5H, m, OCH$_2\underline{Ph}$), 7.86 (*ca.* 0.15H) and 7.92 (*ca.* 0.85H) [s each, C(2)-H], 7.98 (*ca.* 0.85H) and 8.13 (*ca.* 0.15H) (s each, NCHO).[21] *Anal.* Calcd for $C_{20}H_{29}N_5O_5$: C, 57.27; N, 6.97; N, 16.70. Found: C, 57.36; H, 7.05; N, 16.62.

***N′*-Benzyloxy-5-[*N*-(2,2-diethoxyethyl)formamido]-1-*β*-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (11c)** Compound **10c**[9c,16] (3.72 g, 9.50 mmol), anhydrous K_2CO_3 (1.97 g, 14.3 mmol), 18-crown-6 (3.77 g, 14.3 mmol), and 1,1-diethoxy-2-iodoethane[17] (of 96% purity) (23.2 g, 91.3 mmol) were mixed in $HCONMe_2$ (50 ml) in a manner similar to that described above for **11a**. The resulting mixture was stirred at 16—19 °C for 93 h and then concentrated *in vacuo*. The residue was combined with an ice-cooled mixture of H_2O (35 ml) and saturated aqueous NaCl (35 ml) and extracted with $CHCl_3$ (4 × 30 ml). The $CHCl_3$ extracts were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a brown oil. Repeated purifications of the oil by flash chromatography[19] [silica gel, $CHCl_3$; $CHCl_3$–MeOH (6 : 1, v/v); benzene–MeOH–H_2O (170 : 29 : 1, v/v)] afforded a slightly impure oily sample (937 mg, *ca.* 19%) and a pure oily sample (1.82 g, 38%) of **11c**, $[\alpha]_D^{20}$ −26.6° (*c* = 1.00, MeOH); MS *m/z*: 507 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 and 3400 (OH, NH_2), 1690 (NCHO), 1640 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 1.04 (6H, t, *J* = 7 Hz, OCH$_2\underline{Me}$'s), 3.17 (2H, m, NC$\underline{H}_2$CH), 3.60 [6H, m, CH(OC$\underline{H}_2$Me)$_2$ and C(5′)-H's], 3.87 [1H, m, C(4′)-H], 4.07 [1H, m, C(3′)-H], 4.43 [2H, m, C(2′)-H and NCH$_2$C$\underline{H}$], 4.87 (2H, s, OC$\underline{H}_2$Ph), 5.09—5.19 [2H, m, C(5′)-OH and C(3′)-OH], 5.37 [1H, m, C(1′)-H], 5.42 [1H, m, C(2′)-OH], 5.77 (2H, s, NH_2), 7.32 (5H, m, OCH$_2\underline{Ph}$), 8.01 [1H, m, C(2)-H], 8.06 (1H, m, NCHO).[21–23]

Both samples of **11c** were separately used in the deformylation step (*vide infra*).

1-Benzyl-5-(2,2-diethoxyethylamino)-*N′*-ethoxy-1*H*-imidazole-4-carboxamidine (12a) A stirred mixture of **11a** (710 mg, 1.76 mmol) and 1 N aqueous NaOH (8.8 ml) was heated under reflux for 3 h. After cooling, the reaction mixture was neutralized with 1 N aqueous HCl and extracted with AcOEt (2 × 10 ml). The AcOEt extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, leaving **12a** (618 mg, 94%) as a slightly brownish solid, mp 66—72 °C. Recrystallization from hexane yielded an analytical sample as slightly brownish plates, mp 74.5—75.5 °C; MS *m/z*: 375 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 224 nm (sh) (ε 11900), 257 (9700); $\lambda_{max}^{H_2O}$ (pH 1) 285 (sh) (5500); $\lambda_{max}^{H_2O}$ (pH 7) 224 (sh) (10700), 252 (8200); $\lambda_{max}^{H_2O}$ (pH 13) 224 (sh) (10400), 252 (8100); IR ν_{max}^{Nujol} cm^{-1}: 3540, 3350 (NH, NH_2), 1640 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 1.1—1.3 [9H, m, NOCH$_2\underline{Me}$ and CH(OCH$_2\underline{Me}$)$_2$], 2.7—2.9 (2H, m, NHC$\underline{H}_2$CH), 3.2—3.7 [4H, m, CH(OC$\underline{H}_2$Me)$_2$], 3.89 (2H, q, *J* = 7 Hz, NOC$\underline{H}_2$Me), 4.43 (1H, t, *J* = 5.5 Hz, NHCH$_2$C$\underline{H}$), 5.0—5.3 [3H, m, N(1)-C$\underline{H}_2$Ph and C(5)-NH], 5.52 (2H, dull s, NH_2), 7.40 [s, C(2)-H], 7.1—7.5 [m, N(1)-CH$_2\underline{Ph}$]. *Anal.* Calcd for $C_{19}H_{29}N_5O_3$: C, 60.78; H, 7.78; N, 18.65. Found: C, 60.89; H, 7.98; N, 18.67.

***N′*-Benzyloxy-5-(2,2-diethoxyethylamino)-1-(methoxymethyl)-1*H*-imidazole-4-carboxamidine Hydrochloride (12b·HCl)** A stirred mixture of **11b** (8.81 g, 21.0 mmol) and 1 N aqueous NaOH (105 ml) was heated under reflux for 3 h. The reaction mixture was worked up in a manner similar to that described above for **12a**, giving crude **12b** (8.13 g) as a colorless oil. The oil was dissolved in EtOH (5 ml), and 10% ethanolic HCl (*ca.* 28 ml) was added. The colorless crystals that deposited were filtered off, washed with ether, and dried to give a first crop (2.81 g) of **12b**·HCl. Dilution of the ethanolic filtrate with ether furnished a second crop (5.70 g). The total yield of **12b**·HCl was 8.51 g (95%). Recrystallization of the crude **12b**·HCl from EtOH yielded an analytical sample as colorless plates, mp 117.5—118 °C; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 227 nm (ε 13200), 257 (9600); $\lambda_{max}^{H_2O}$ (pH 1) 263 (sh) (6600); $\lambda_{max}^{H_2O}$ (pH 7) 226 (13300), 249 (sh) (9000); $\lambda_{max}^{H_2O}$ (pH 13) 226 (12900), 249 (sh) (8900); ^{1}H-NMR (Me_2SO-d_6) δ: 1.07 [6H, t, *J* = 7 Hz, CH(OCH$_2\underline{Me}$)$_2$], 3.16 (2H, m, NHC$\underline{H}_2$CH), 3.29 (3H, s, OMe), 3.3—3.6 [4H, m, CH(OC$\underline{H}_2$Me)$_2$], 4.46 (1H, t, *J* = 5 Hz, NHCH$_2$C$\underline{H}$), 3.7—5.8 (br, NH's), 5.01 (2H, s, OC$\underline{H}_2$Ph), 5.34 [2H, s, N(1)-CH_2O], 7.2—7.5 (5H, m, OCH$_2\underline{Ph}$), 8.40 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{19}H_{29}N_5O_4 \cdot HCl$: C, 53.33; H, 7.07; N, 16.37. Found: C, 53.24; H, 7.21; N, 16.30.

***N′*-Benzyloxy-5-(2,2-diethoxyethylamino)-1-*β*-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine (12c)** A solution of the slightly impure sample (937 mg) of **11c** (*vide supra*) in 1 N aqueous NaOH (9.2 ml) was stirred at room temperature for 2 h. The reaction mixture was cooled in an ice bath, neutralized with 1 N aqueous HCl, and extracted with AcOEt (4 × 10 ml). The AcOEt extracts were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a pale brown syrup. Purification of the syrup by flash chromatography[19] [silica gel, benzene–MeOH–H_2O (170 : 29 : 1, v/v)] furnished **12c** (339 mg) as a colorless syrup, $[\alpha]_D^{22}$ −20.6° (*c* = 1.00, MeOH); MS *m/z*: 479 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510 and 3400 (OH, NH, and NH_2), 1630 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 1.11 (6H, t, *J* = 7 Hz, OCH$_2\underline{Me}$'s), 3.04 (2H, m, NHC$\underline{H}_2$CH), 3.3—3.7 [6H, m, CH(OC$\underline{H}_2$Me)$_2$ and C(5′)-H's], 3.84 [1H, m, C(4′)-H], 4.03 [1H, m, C(3′)-H], 4.30 [1H, m, C(2′)-H], 4.48

(1H, t, $J=5$ Hz, $NHCH_2C\underline{H}$), 4.92 (2H, s, $OC\underline{H}_2Ph$), 4.95 (1H, t, $J=5$ Hz, $N\underline{H}CH_2CH$), 5.11 [1H, d, $J=4.5$ Hz, C(3′)-OH], 5.19 [1H, t, $J=8$ Hz, C(5′)-OH], 5.37 [1H, d, $J=6$ Hz, C(2′)-OH], 5.41 [1H, d, $J=6$ Hz, C(1′)-H], 5.65 (2H, dull s, NH_2), 7.36 (5H, m, $OCH_2\underline{Ph}$), 7.62 [1H, s, C(2)-H].[23)]

The pure sample (1.82 g) of **11c** (*vide supra*) was similarly deformylated to give **12c** (1.49 g) as a colorless syrup. The total yield of **12c** was 1.83 g (40% overall yield from **10c**).

1-Benzyl-5-(2,2-diethoxyethylamino)-1*H*-imidazole-4-carboxamide (14a) A solution of **12a** (4.85 g, 12.9 mmol) in a mixture of H_2O (120 ml) and 1 N aqueous HCl (12.9 ml) was hydrogenated over Raney Ni W-2 catalyst[24)] (9.5 ml) at atmospheric pressure and room temperature for 6 h. The catalyst was removed by filtration and washed with H_2O (500 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave 1-benzyl-5-(2,2-diethoxyethylamino)-1*H*-imidazole-4-carboxamidine hydrochloride (**13a**·HCl) as a pinkish oil. The oil was then treated with boiling 1 N aqueous NaOH (65 ml) for 4 h with stirring. After cooling, the reaction mixture was neutralized with 1 N aqueous HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a brown solid. Purification of the solid by flash chromatography[19)] [silica gel, CH_2Cl_2–MeOH (10 : 1, v/v)], followed by recrystallization from benzene–hexane (3 : 1, v/v), yielded **14a** (1.94 g, 45%) as a colorless solid, mp 125.5—127 °C. Further recrystallization from the same solvent system gave an analytical sample of **14a** as colorless prisms, mp 128—128.5 °C; MS *m/z*: 332 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 268 nm (ε 10100); $\lambda_{max}^{H_2O}$ (pH 1) 252 (6500); $\lambda_{max}^{H_2O}$ (pH 7) 269 (9100); $\lambda_{max}^{H_2O}$ (pH 13) 269 (9000); IR ν_{max}^{Nujol} cm^{-1}: 3450, 3350 (NH and $CONH_2$), 1650 ($CONH_2$); ^{1}H-NMR (Me_2SO-d_6) δ: 1.04 (6H, t, $J=7$ Hz, $OCH_2\underline{Me}$'s), 3.02 (2H, m, $NHC\underline{H}_2CH$), 3.2—3.7 (4H, m, $OC\underline{H}_2Me$'s), 4.39 (1H, t, $J=5.5$ Hz, $NCH_2C\underline{H}$), 5.18 [2H, s, N(1)-$C\underline{H}_2Ph$], 5.80 (1H, t, $J=7$ Hz, $N\underline{H}CH_2CH$), 6.88 (2H, dull s, $CONH_2$), 7.33 [s, C(2)-H], 7.0—7.5 [m, N(1)-$CH_2\underline{Ph}$]. *Anal.* Calcd for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.86. Found: C, 61.40; H, 7.42; N, 16.71.

5-(2,2-Diethoxyethylamino)-1-(methoxymethyl)-1*H*-imidazole-4-carboxamide (14b) A solution of **12b**·HCl (1.98 g, 4.63 mmol) in H_2O (35 ml) was hydrogenated over Raney Ni W-2 catalyst[24)] (4 ml) at atmospheric pressure and room temperature for 3 h. The reaction mixture was worked up in a manner similar to that described above for **14a**, leaving crude 5-(2,2-diethoxyethylamino)-1-(methoxymethyl)-1*H*-imidazole-4-carboxamidine hydrochloride (**13b**·HCl) as a reddish oil. The oil was treated with boiling 1 N aqueous NaOH (24 ml) for 1.5 h with stirring. The alkaline reaction mixture was neutralized with 1 N aqueous HCl and cooled in an ice bath. The brownish solid that deposited was collected by filtration and dissolved in boiling H_2O (40 ml). The aqueous solution was cooled, after treatment with charcoal in the usual manner, in a refrigerator, and the colorless minute crystals that deposited were filtered off and dried to give **14b** (757 mg, 57%), mp 158—159 °C. Further recrystallization from H_2O afforded an analytical sample of **14b** as colorless plates, mp 158.5—159.5 °C; MS *m/z*: 286 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 271 nm (ε 9900); $\lambda_{max}^{H_2O}$ (pH 1) 254 (7700); $\lambda_{max}^{H_2O}$ (pH 7) 271 (9300); $\lambda_{max}^{H_2O}$ (pH 13) 271 (9200); IR ν_{max}^{Nujol} cm^{-1}: 3390, 3290, and 3220 (NH, $CONH_2$), 1610 ($CONH_2$); ^{1}H-NMR (Me_2SO-d_6) δ: 1.10 (6H, t, $J=7$ Hz, $OCH_2\underline{Me}$'s), 3.26 (s, OMe), 3.1—3.8 (m, $NHC\underline{H}_2CH$ and $OC\underline{H}_2Me$'s), 4.53 (1H, t, $J=5.5$ Hz, $NHCH_2C\underline{H}$), 5.23 [2H, s, N(1)-$C\underline{H}_2O$], 6.15 (1H, br, $N\underline{H}CH_2CH$), 6.87 (2H, br, $CONH_2$), 7.38 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{12}H_{22}N_4O_4$: C, 50.34; H, 7.74; N, 19.57. Found: C, 50.24; H, 7.99; N, 19.50.

5-(2,2-Diethoxyethylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (14c) Hydrogenolysis of **12c** (329 mg, 0.686 mmol) for 8 h was effected in a manner similar to that described above for **14a**. The crude 5-(2,2-diethoxyethylamino)-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamidine hydrochloride (**13c**·HCl) thus obtained was then treated with boiling 1 N aqueous NaOH (3.1 ml) for 30 min, and the reaction mixture was concentrated *in vacuo* after addition of 1 N aqueous HCl (2.5 ml). The residual solid was dried and then extracted with boiling EtOH (10 ml). The ethanolic extracts were concentrated *in vacuo* to leave a foam. Purification of the foam by flash chromatography[19)] [silica gel, CH_2Cl_2–MeOH (5 : 1, v/v)] gave **14c** (162 mg, 63% from **12c**) as a brownish foam, $[\alpha]_D^{22}$ −44.6° ($c=1.00$, MeOH); MS *m/z*: 374 (M^+); ^{1}H-NMR (Me_2SO-d_6) δ: 1.11 (6H, t, $J=7$ Hz, $OCH_2\underline{Me}$'s), 3.23 (2H, m, $NHC\underline{H}_2CH$), 3.4—3.7 [6H, m, $OC\underline{H}_2Me$'s and C(5′)-H's], 3.87 [1H, m, C(4′)-H], 4.03 [1H, m, C(3′)-H], 4.34 [1H, m, C(2′)-H], 4.53 (1H, t, $J=6$ Hz, $NHCH_2C\underline{H}$), 5.00 [1H, t, $J=5$ Hz, C(5′)-OH], 5.16 [1H, d, $J=5$ Hz, C(3′)-OH], 5.45 [1H, d, $J=6$ Hz, C(2′)-OH], 5.47 [1H, d, $J=6$ Hz, C(1′)-H], 5.79 (1H, t, $J=7$ Hz, $N\underline{H}CH_2CH$), 6.92 (2H, br, $CONH_2$), 7.57 [1H, s, C(2)-H].[23)]

5(4)-(2,2-Diethoxyethylamino)imidazole-4(5)-carboxamide (15) A solution of **14a** (707 mg, 2.13 mmol) in MeOH (30 ml) was hydrogenated over 10% Pd–C (1.06 g) at atmospheric pressure and 50 °C for 5 h. The catalyst was removed by filtration and washed with MeOH (300 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave crude **15** (568 mg) as a colorless oil, MS *m/z*: 242 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 238 nm (ε 5100), 279 (11600); $\lambda_{max}^{H_2O}$ (pH 1) 244 (8600), 279 (10500); $\lambda_{max}^{H_2O}$ (pH 7) 235 (4500), 279 (11500); $\lambda_{max}^{H_2O}$ (pH 13) 231 (sh) (3400), 287 (11700); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 and 3450 (NH, $CONH_2$), 1650 ($CONH_2$), 1610 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, t, $J=7$ Hz, $OCH_2\underline{Me}$'s), 3.31 (2H, m, $NHC\underline{H}_2CH$), 3.4—4.1 (4H, m, $OC\underline{H}_2Me$'s), 4.55 (1H, t, $J=5$ Hz, $NHCH_2C\underline{H}$), 5.0—6.6 (2H, br, $CONH_2$), 7.03 [1H, s, C(2)-H]. This sample was so unstable (turning purple on standing) that it was used directly in the next cyclization step without purification.

3-Benzyl-4,5,6,7-tetrahydro-6-hydroxyimidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one (3-Benzylazepinomycin) (4a) A mixture of **14a** (500 mg, 1.50 mmol) and 1 N aqueous HCl (7.5 ml) was stirred at room temperature for 30 min. The reaction mixture was cooled in an ice bath and neutralized by addition of 1 N aqueous NaOH (7.5 ml). The colorless crystals that resulted were collected by filtration, washed with cold H_2O (2 ml), and dried to give **4a** (358 mg, 92%), mp 181—196 °C (dec.). Recrystallization from MeOH yielded an analytical sample as colorless minute crystals, mp 185—200 °C (dec.); MS *m/z*: 258 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 276 nm (ε 8600); $\lambda_{max}^{H_2O}$ (pH 1) 251 (sh) (5400), 280 (10000); $\lambda_{max}^{H_2O}$ (pH 7) 280 (10200); $\lambda_{max}^{H_2O}$ (pH 13) 282 (9400); IR ν_{max}^{Nujol} cm^{-1}: 3300 and 3220 (OH, NH), 1640 (lactam CO); ^{1}H-NMR (Me_2SO-d_6) δ: 2.90 [1H, dd, $J=5$ and 13.5 Hz, C(5)-H], 3.4—3.6 [1H, m, C(5)-H], 4.74 [1H, m, C(6)-H], 4.91 (1H, d, $J=7.5$ Hz) and 5.23 (1H, d, $J=7.5$ Hz) [N(3)-$C\underline{H}_2Ph$], 5.64 [1H, m, N(7)-H or C(6)-OH], 6.45 [1H, m, N(4)-H], 7.1—7.5 [6H, m, C(2)-H and N(3)-$CH_2\underline{Ph}$], 7.63 [1H, m, C(6)-OH or N(7)-H]. *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.55; H, 5.40; N, 21.69.

4,5,6,7-Tetrahydro-6-hydroxy-3-(methoxymethyl)imidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one [3-(Methoxymethyl)azepinomycin] (4b) A solution of **14b** (1.30 g, 4.54 mmol) in 1 N aqueous HCl (22.8 ml) was stirred at room temperature for 1 h. The reaction mixture was passed through a column of Amberlite IRA-402 (HCO_3^-) (54 ml), and the column was eluted with H_2O (300 ml). The eluates were combined and concentrated *in vacuo* to leave a colorless solid, which was dried over P_2O_5 at 3 mmHg and 50 °C for 10 h to give **4b**·1/3H_2O (960 mg, 97%), mp 157—163 °C (dec.). Recrystallization from 95% (v/v) aqueous EtOH and drying over P_2O_5 at 4 mmHg and 75 °C for 6 h furnished an analytical sample of **4b**·1/3H_2O as colorless minute prisms, mp 165—167 °C (dec.); MS *m/z*: 212 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 244 nm (sh) (ε 5300), 276 (9000); $\lambda_{max}^{H_2O}$ (pH 1) 255 (sh) (6300), 278 (9800); $\lambda_{max}^{H_2O}$ (pH 7) 242 (sh) (4200), 281 (9700); $\lambda_{max}^{H_2O}$ (pH 13) 282 (8700); IR ν_{max}^{Nujol} cm^{-1}: 3300 and 3230 (OH, NH), 1640 (lactam CO); ^{1}H-NMR (Me_2SO-d_6) δ: 2.92 [1H, dd, $J=5$ and 13 Hz, C(5)-H], 3.22 (3H, s, OMe), 3.25—3.8 [m, C(5)-H], 4.74 [1H, m, C(6)-H], 5.06 and 5.17 [1H each, d, $J=11$ Hz, N(3)-CH_2O], 5.60 [1H, d, $J=5$ Hz, N(7)-H or C(6)-OH], 6.35 [1H, m, N(4)-H], 7.33 [1H, s, C(2)-H], 7.58 [1H, d, $J=6$ Hz, C(6)-OH or N(7)-H]. *Anal.* Calcd for $C_8H_{12}N_4O_3$·1/3H_2O: C, 44.03; H, 5.85; N, 25.68. Found: C, 44.12; H, 5.60; N, 25.54.

4,5,6,7-Tetrahydro-6-hydroxy-3-β-D-ribofuranosylimidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one (3-β-D-Ribofuranosylazepinomycin) (4c) A mixture of **14c** (32.2 mg, 0.0860 mmol) and 1 N aqueous HCl (0.43 ml) was stirred at room temperature for 1 h. The reaction mixture was passed through a column of Amberlite IRA-402 (HCO_3^-) (1 ml), and the column was eluted with H_2O (7 ml). The eluates were combined and concentrated *in vacuo* to leave a slightly yellowish foam, which was dried to give a diastereomeric mixture of **4c** (24.4 mg, 94%), $[\alpha]_D^{22}$ −70° ($c=1.00$, H_2O); UV $\lambda_{max}^{H_2O}$ (pH 1) 251 nm (sh) (ε 6300), 278 (10400); $\lambda_{max}^{H_2O}$ (pH 7) 242 (4400), 282 (10600); $\lambda_{max}^{H_2O}$ (pH 13) 282 (9600); IR ν_{max}^{Nujol} cm^{-1}: 3270 (br, OH and NH), 1620 (lactam CO); ^{1}H-NMR (D_2O) δ (relative to external Me_4Si): 3.16 [1H, d, $J=14$ Hz, C(5)-H], 3.74 [1H, dd, $J=5.5$ and 14 Hz, C(5)-H], 3.7—3.9 [2H, m, C(5′)-H's], 4.25 [1H, m, C(4′)-H], 4.56 [1H, m, C(3′)-H], 4.66 [1H, m, C(2′)-H], 5.12 [1H, d, $J=5.5$ Hz, C(6)-H], 5.63 [1H, m, C(1′)-H], 7.54 [1H, s, C(2)-H].[23)]

This sample was identical (by comparison of the UV, IR, and ^{1}H-NMR spectra and TLC mobility) with a sample synthesized by Isshiki *et al.*[7)]

4,5,6,7-Tetrahydro-6-hydroxyimidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one (Azepinomycin) (3) i) From **14a** through **15**: A mixture of the crude **15**

(*vide supra*) (568 mg) and 1 N aqueous HCl (10.7 ml) was stirred at room temperature for 5 h. The reaction mixture was cooled in an ice bath and neutralized with 1 N aqueous NaOH. The colorless solid that deposited was filtered off, washed with a little H_2O, and dried to give a first crop (217 mg) of **3**. The filtrate and washings were combined and concentrated *in vacuo*, and the residue was triturated with H_2O (2 ml). The insoluble solid that resulted was filtered off, washed with a little H_2O, and dried to yield a second crop (33 mg). The total yield of **3** was 250 mg (70% from **14a**). Recrystallization of the crude **3** from H_2O provided an analytical sample as faintly yellowish plates, mp 208—220 °C (dec.) [lit.[7] mp 230—235 °C (dec.)]; MS *m/z*: 168 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 287 nm (ε 6400); $\lambda_{max}^{H_2O}$ (pH 1) 246 (4700), 279 (9500); $\lambda_{max}^{H_2O}$ (pH 7) 289 (9400); $\lambda_{max}^{H_2O}$ (pH 13) 289 (9200); IR ν_{max}^{Nujol} cm^{-1}: 3300, 3190 (NH, OH), 1620 (lactam CO); ^{1}H-NMR (D_2O) δ (relative to external Me_4Si): 3.11 [1H, d, J=14 Hz, C(5)-H], 3.69 [1H, dd, J=6 and 14 Hz, C(5)-H], 5.14 [1H, d, J=6 Hz, C(6)-H], 7.58 [1H, s, C(2)-H]; ^{1}H-NMR (0.1 N DCl in D_2O) δ (relative to external Me_4Si): 3.24 [1H, d, J=14 Hz, C(5)-H], 3.81 [1H, dd, J=6 and 14 Hz, C(5)-H], 5.22 [1H, d, J=6 Hz, C(6)-H], 8.43 [1H, s, C(2)-H]. *Anal.* Calcd for $C_6H_8N_4O_2$: C, 42.86; H, 4.80; N, 33.32. Found: C, 42.57; H, 4.90; N, 33.06.

The UV [H_2O (pH 1 or 7)], IR (KBr), and ^{1}H-NMR (D_2O or DCl in D_2O) spectra and TLC mobility of this sample matched those of natural azepinomycin.[6]

ii) From **4a**: A slution of **4a** (246 mg, 0.952 mmol) in MeOH (80 ml) was hydrogenated over 10% Pd–C (350 mg) at atmospheric pressure and 50 °C for 10 h. The catalyst was removed by filtration and washed with MeOH (150 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave **3** (74 mg, 46%) as a colorless solid. Recrystallization of the solid from H_2O yielded a pure sample as a slightly yellowish solid, mp 208—220 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by method (i).

iii) From **4b**: A stirred mixture of **4b**·1/3H_2O (638 mg, 2.92 mmol) and 5% aqueous H_3PO_4 (30 g) was heated under reflux for 10 h. After cooling, the reaction mixture was passed through a column of Amberlite IRA-402 (HCO_3^-) (37 ml), and the column was eluted with H_2O (300 ml). The eluates were combined and concentrated *in vacuo*, and the residue was triturated with H_2O (2 ml). The colorless solid that resulted was filtered off, washed with a little H_2O, and dried to give **3** (100 mg, 20%). Recrystallization from H_2O furnished a pure sample of **3** as slightly brownish minute plates, mp 208—220 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC behavior) with the one obtained by method (i).

iv) From **4c**: A solution of **4c** (301 mg, 1.00 mmol) in 5% aqueous H_3PO_4 (9.80 g) was heated at 95 °C for 10 h. After cooling, the reaction mixture was passed through a column of Amberlite IRA-402 (HCO_3^-) (12 ml), and the column was eluted with H_2O (200 ml). The eluates were combined and worked up in a manner similar to that described above under method (iii), giving **3** (81 mg, 48%) as a grayish solid, mp 208—220 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

5(4)-(2,2-Diethoxyethylamino)imidazole-4(5)-carboxamidine Hydrochloride (16) A solution of **12a** (1.84 g, 4.90 mmol) in a mixture of H_2O (60 ml) and 1 N aqueous HCl (4.9 ml) was hydrogenated over Raney Ni W-2 catalyst[24] (3.7 ml) at atmospheric pressure and room temperature for 6 h. The catalyst was removed by filtration and washed with H_2O (500 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave **13a**·HCl as a reddish oil, which was dissolved in H_2O (65 ml). The resulting solution was hydrogenated over 10% Pd–C (2.6 g) at atmospheric pressure and 50 °C for 15 h. The catalyst was removed by filtration and washed with H_2O (350 ml). The filtrate and washings were combined and concentrated *in vacuo*, and the residue was dried to give crude **16** (1.01 g) as a yellowish oil, ^{1}H-NMR (Me_2SO-d_6) δ: 1.09 (6H, t, J=7 Hz, $OCH_2\underline{Me}$'s), 3.57 (m, $NHC\underline{H}_2CH$ and $OC\underline{H}_2Me$'s), 4.62 (1H, t, J=5.5 Hz, $NHCH_2C\underline{H}$), 6.94 (1H, br, $N\underline{H}CH_2CH$), 7.41 [1H, s, C(2)-H], 7.97 (4H, dull s, protonated amidine), 12.25 (1H, br, imidazole NH).

This sample was directly used in the next cyclization step without purification.

3,4,5,6,7,8-Hexahydro-8-iminoimidazo[4,5-*e*][1,4]diazepin-6-ol Dihydrochloride (17) A solution of the crude **16** (*vide supra*) (960 mg) in 1 N aqueous HCl (46 ml) was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* to leave a slightly yellowish solid, which was triturated with EtOH–ether (1 : 1, v/v) (3 × 10 ml). The insoluble solid that resulted was filtered off and dried to give **17** (597 mg, 53% overall yield from **12a**). The crude **17** was recrystallized by dissolving it in MeOH and adding ether to the resulting methanolic solution, affording an analytical sample as a colorless microcrystalline solid, mp 229.5—235 °C (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 304 nm (ε 12900); $\lambda_{max}^{H_2O}$ (pH 1) 226 (7900), 300 (12700); $\lambda_{max}^{H_2O}$ (pH 7) 302 (12200); $\lambda_{max}^{H_2O}$ (pH 13) 246 (6900), 312 (9500); IR ν_{max}^{Nujol} cm^{-1}: 3250 (br, OH and NH), 1650 ($C=N^+$), 1580 (NH_2^+); ^{1}H-NMR (Me_2SO-d_6) δ: 3.05 [1H, d, J=14 Hz, C(5)-H], 3.53 [1H, dd, J=5 and 14 Hz, C(5)-H], 5.14 [1H, m, C(6)-H], 7.12 [4H, m, NH's and C(6)-OH or N(7)-H], 7.79 [1H, s, C(2)-H], 8.06 (2H, dull s, NH_2^+), 9.26 [1H, dull d, J=5 Hz, N(7)-H or C(6)-OH]; ^{1}H-NMR (D_2O) δ (relative to external Me_4Si): 3.26 [1H, d, J=14 Hz, C(5)-H], 3.82 [1H, dd, J=5.5 and 14 Hz, C(5)-H], 5.42 [1H, d, J=5.5 Hz, C(6)-H], 7.91 [1H, s, C(2)-H]. *Anal.* Calcd for $C_6H_9N_5O \cdot 2HCl$: C, 30.02; H, 4.62; N, 29.17. Found: C, 29.81; H, 4.69; N, 29.04.

3,4,5,6,7,8-Hexahydro-8-imino-3-β-D-ribofuranosylimidazo[4,5-*e*]-[1,4]diazepin-6-ol Dihydrochloride (18) A solution of **12c** (2.19 g, 4.57 mmol) in a mixture of H_2O (20 ml) and 1 N aqueous HCl (4.6 ml) was hydrogenated over 10% Pd–C (2.2 g) at atmospheric pressure and 50 °C for 6 h. The catalyst was removed by filtration and washed with H_2O (600 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave **13c**·HCl (1.47 g) as a brown foam. A portion (514 mg) of the crude **13c**·HCl was treated with 1 N aqueous HCl (8 ml) at room temperature for 4 h. The reaction mixture was concentrated *in vacuo* to leave a brownish solid, which was triturated with cold EtOH (5 ml). The insoluble solid that resulted was filtered off and dried to give a diastereomeric mixture of **18**·3/4H_2O (357 mg, 58% overall yield from **12c**), mp 149—154 °C (dec.). Recrystallization from MeOH and drying over P_2O_5 at 2 mmHg and room temperature for 8 h furnished an analytical sample of **18**·3/4H_2O as colorless minute crystals, mp 163.5—185 °C (dec.); $[\alpha]_D^{19}$ −32.3° (c=0.099, H_2O); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 303 nm (ε 11700); $\lambda_{max}^{H_2O}$ (pH 1) 300 (11700); $\lambda_{max}^{H_2O}$ (pH 7) 232 (sh) (8100), 300 (11300); $\lambda_{max}^{H_2O}$ (pH 13) 298 (9700); ^{1}H-NMR (D_2O) δ (relative to external Me_4Si): 3.37 [1H, d, J=14 Hz, C(5)-H], 3.82 [3H, m, C(5)-H and C(5′)-H's], 4.28 [2H, m, C(4′)-H and C(3′)-H], 4.5—4.8 [m, C(2′)-H], 5.69 [2H, m, C(6)-H and C(1′)-H], 7.70 [1H, s, C(2)-H].[23] *Anal.* Calcd for $C_{11}H_{17}N_5O_5 \cdot 2HCl \cdot 3/4H_2O$: C, 34.25; H, 5.36; N, 18.16. Found: C, 34.18; H, 5.11; N, 18.42.

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References and Notes

1) Paper LXII in this series, T. Fujii, M. Ohba, H. Kawamura, Y. Nakashio, K. Honda, S. Matsubara, *Chem. Pharm. Bull.*, **42**, 1045 (1994).
2) *a*) R. S. Hosmane, V. S. Bhadti, B. B. Lim, *Synthesis*, **1990**, 1095, and references cited therein; *b*) J. W. Daly, I. Hide, P. K. Bridson, *J. Med. Chem.*, **33**, 2818 (1990), and references cited therein.
3) *a*) H. Nakamura, G. Koyama, Y. Iitaka, M. Ohno, N. Yagisawa, S. Kondo, K. Maeda, H. Umezawa, *J. Am. Chem. Soc.*, **96**, 4327 (1974); *b*) M. Ohno, N. Yagisawa, S. Shibahara, S. Kondo, K. Maeda, H. Umezawa, *ibid.*, **96**, 4326 (1974).
4) P. W. K. Woo, H. W. Dion, S. M. Lange, L. F. Dahl, L. J. Durham, *J. Heterocycl. Chem.*, **11**, 641 (1974).
5) For related natural products, see *a*) S. Ōmura, N. Imamura, H. Kuga, H. Ishikawa, Y. Yamazaki, K. Okano, K. Kimura, Y. Takahashi, H. Tanaka, *J. Antibiot.*, **38**, 1008 (1985); *b*) J. B. Tunac, M. Underhill, *ibid.*, **38**, 1344 (1985); *c*) S. Ōmura, H. Tanaka, H. Kuga, N. Imamura, *ibid.*, **39**, 309 (1986); *d*) B. D. Bush, G. V. Fitchett, D. A. Gates, D. Langley, *Phytochemistry*, **32**, 737 (1993).
6) H. Umezawa, T. Takeuchi, H. Iinuma, M. Hamada, S. Nishimura, Japan. Patent 159494 (1983) [83159494] [*Chem. Abstr.*, **100**, 137362*x* (1984)].
7) K. Isshiki, Y. Takahashi, H. Iinuma, H. Naganawa, Y. Umezawa, T. Takeuchi, H. Umezawa, S. Nishimura, N. Okada, K. Tatsuta, *J. Antibiot.*, **40**, 1461 (1987).
8) *a*) For a review, see T. Fujii, T. Itaya, T. Saito, *Yuki Gosei Kagaku Kyokai Shi*, **41**, 1193 (1983); *b*) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, T. Fujisawa, *Chem. Pharm. Bull.*, **39**, 301 (1991), and earlier references cited therein;

c) T. Fujii, T. Saito, K. Tamura, *ibid.*, **39**, 2855 (1991); *d*) T. Fujii, T. Saito, T. Suzuki, M. Kunugi, *ibid.*, **42**, 151 (1994).
9) *a*) T. Fujii, T. Itaya, C. C. Wu, F. Tanaka, *Tetrahedron*, **27**, 2415 (1971); *b*) T. Itaya, F. Tanaka, T. Fujii, *ibid.*, **28**, 535 (1972); *c*) T. Fujii, C. C. Wu, T. Itaya, S. Moro, T. Saito, *Chem. Pharm. Bull.*, **21**, 1676 (1973); *d*) T. Itaya, T. Saito, S. Kawakatsu, T. Fujii, *ibid.*, **23**, 2643 (1975); *e*) T. Fujii, T. Itaya, T. Saito, S. Kawakatsu, *ibid.*, **32**, 4842 (1984); *f*) T. Fujii, T. Saito, T. Itaya, K. Kizu, Y. Kumazawa, S. Nakajima, *ibid.*, **35**, 4482 (1987).
10) T. Fujii, T. Saito, T. Fujisawa, *Heterocycles*, **27**, 1163 (1988).
11) T. Fujii, T. Itaya, T. Saito, K. Mohri, M. Kawanishi, T. Nakasaka, *Chem. Pharm. Bull.*, **37**, 1504 (1989).
12) T. Fujii, S. Sakurai, T. Uematsu, *Chem. Pharm. Bull.*, **20**, 1334 (1972).
13) T. Fujii, C. C. Wu, T. Itaya, *Chem. Pharm. Bull.*, **19**, 1368 (1971).
14) T. Fujii, T. Itaya, T. Saito, M. Kawanishi, *Chem. Pharm. Bull.*, **26**, 1929 (1978).
15) *a*) T. Fujii, T. Saito, T. Nakasaka, *Chem. Pharm. Bull.*, **37**, 2601 (1989); *b*) *Idem*, *ibid.*, **37**, 3243 (1989); *c*) T. Fujii, T. Saito, Y. Kumazawa, *ibid.*, **38**, 1392 (1990).
16) T. Itaya, T. Saito, T. Harada, S. Kagatani, T. Fujii, *Chem. Pharm. Bull.*, **37**, 3200 (1989).
17) M. Larchevêque, G. Valette, T. Curvigny, *Tetrahedron*, **35**, 1745 (1979).
18) Until the tautomeric structure is established, we prefer to use the exocyclic C(8)=NH structure for convenience.
19) W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
20) See ref. 8*b* for the basis of this assignment.
21) The observed complexity of the proton signals is interpretable in terms of *cis–trans* isomerism of the formamido moiety, as we have experienced in similar structures.[9a,11,15)]
22) The enhanced complexity of the N–CHO and C(2)-H signals with the appearance of minor peaks is suggestive of the coexistence of atropisomers due to restricted rotation about the C(5)–N bond in the chiral 1,4,5-trisubstituted imidazole system.[15a)]
23) For convenience, each carbon of the sugar moiety is indicated by a primed number.
24) R. Mozingo, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, New York, 1955, p. 181.