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Nucleosides and Nucleotides 179. Ring-expanded Purine Nucleosides. The Synthesis and Cytotoxicity of Imidazo[4,5-*c*]azepine Nucleosides

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Abstract: The synthesis of ring-expanded imidazo[4,5-*c*]azepine nucleosides (**3**-**6**) is described. Treatment of 5-iodoimidazole derivative **9** with methyl acrylate in the presence of a palladium catalyst gave (*E*)-5-(2-carbomethoxyvinyl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**10**), appropriate manipulation of which gave 1-β-D-ribofuranosyl-1,5-dihydroimidazo[4,5-*c*]azepin-4,6-dione (**3**). The ring-expanded guanosine derivative **4** was prepared in a manner similar to the synthesis of **3**. The ring-expanded inosine derivatives **5** and **6** were obtained from 6-acetoxy-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5,6-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (**21**) through palladium-catalyzed hydrogenolysis. The cytotoxicity of these ring-expanded nucleosides is also described.

Keyword: Antitumor compounds; Bicyclic heterocyclic compounds; Nucleosides; purines

We have recently been studying the design and synthesis of a series of inhibitors of purine nucleotide biosynthesis.[1] In a previous article in this series,[2] we reported the synthesis and antileukemic activity of 6-hydroxy-1-β-D-ribofuranosyl-5,6-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (**1**), which was expected to inhibit guanosine 5'-monophosphate (GMP) synthase.[3] This compound has a new 5:7-fused imidazo[4,5-*c*]azepine ring system in its structure and is interesting because this ring-expanded nucleoside analogue exhibited antileukemic activity, although there was no obvious evidence that the nucleoside inhibited GMP synthase as a transition-state analogue. To date, nucleoside analogues with 5:7-fused ring-expanded nucleobases such as naturally occurring coformycin[4] and pentostatine (2'-deoxycoformycin)[5] which contain an imidazo[4,5-*d*][1,3]diazepine ring skeleton are well known as potent transition-state analogue inhibitors of adenosine deaminase.[6] Several nucleosides have also been synthesized and evaluated as transition-state analogues.[7-9] All of these are known to be inhibitors of nucleoside and nucleobase catabolic pathways, and hence need not be phosphorylated by intracellular enzyme(s), such as kinase(s), to exhibit their biological activities. On the other hand, **1** should be converted to the corresponding 5'-monophosphate to exhibit the expected GMP synthase

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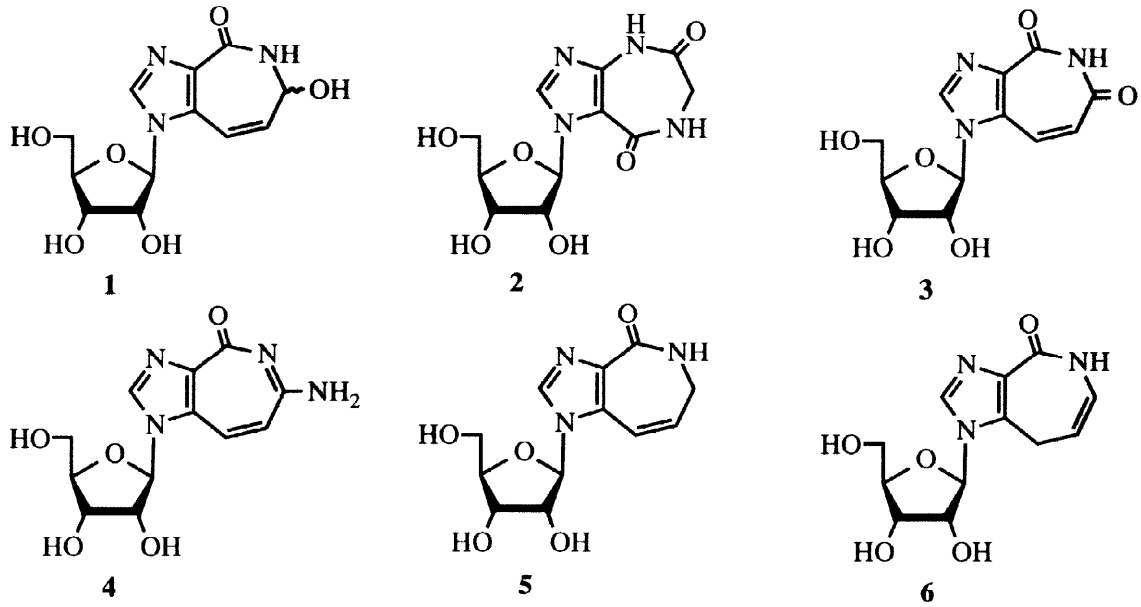
inhibition. Therefore, the antileukemic activity of **1** suggested that this compound may be phosphorylated by intracellular kinase(s), which implies that imidazo[4,5-*c*]azepine nucleosides might act as inhibitors of ***de novo*** purine nucleotide biosynthesis.

Recently, Hosmane *et al.* reported the synthesis of two isomeric imidazo[4,5-*e*][1,4]diazepine nucleosides, and one of them, **2**, inhibited reverse transcriptase of murine leukemia virus in tissue culture systems.[10] Coformycins possess a tetrahedral geometry at the 8 position of their seven-membered ring. The same structural feature has been observed in **1**, which is therefore expected to be a transition-state analogue inhibitor. In contrast, as can be seen from its structure, **2** would not be a transition-state analogue inhibitor, and it has been speculated that **2** also inhibits purine nucleotide biosynthesis after conversion to the corresponding phosphate analogue(s). These results prompted us to synthesize and evaluate new imidazo[4,5-*c*]azepine nucleosides as potential inhibitors of *de novo* purine nucleotide biosynthesis. In this paper, we describe the synthesis of four imidazo[4,5-*c*]azepine nucleosides **3**-**6** related to ring-expanded xanthosine, guanosine, and inosine derivatives, which are structurally comparable to the natural purine nucleosides.

Chart 1

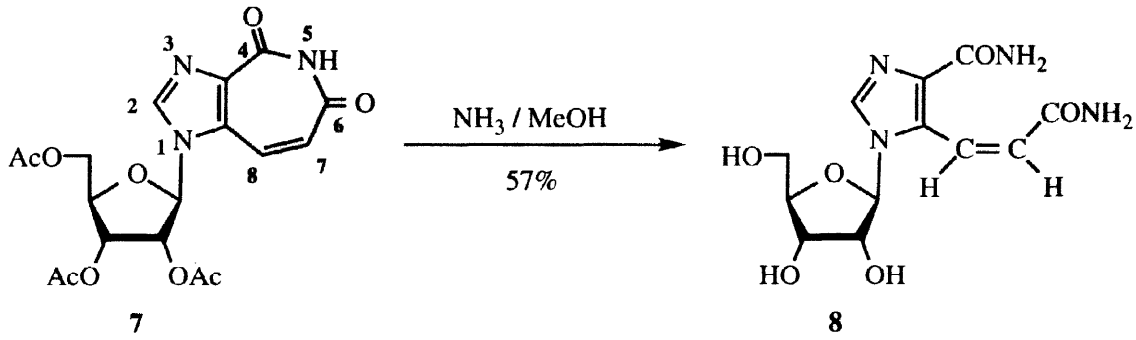


For the synthesis of ring-expanded xanthosine derivative **3**, we previously isolated protected derivative **7** as an over-oxidation product during the synthesis of **1**.[2] Therefore, **7** was subjected to usual deprotection conditions of the acetyl groups, i.e., methanolic ammonia at room temperature. Consequently, (*Z*)-acrylamide derivative **8** was obtained in 57% yield, but not the desired **3** (Scheme 1). The nucleophilic addition of ammonia to the C=O bond at either the 4 or 6 position may give ring-opening product **8**. In the report of Hosmane *et al.*,[10] the X-ray crystal structure of **2** showed that the imidazole and diazepine rings are almost coplanar except for C(6), which lies out of the plane due to its structurally strained conformation relative to the purine ring. Latypov *et al.* also reported the conformational analysis of imidazodiazepine and pyrroloazepine skeletons including **2** using NMR experiments and MM and AM1 calculations in which **2** showed a high degree of conformational similarity to the results of its X-ray crystal structure.[11] A similar structural feature would be expected in the case of the imidazo[4,5-*c*]azepine nucleus, namely the C(4)-N(5) fragment and the olefinic

portion between C(7) and C(8) lie above the plane of the imidazole ring, while C(6) would be located out of the

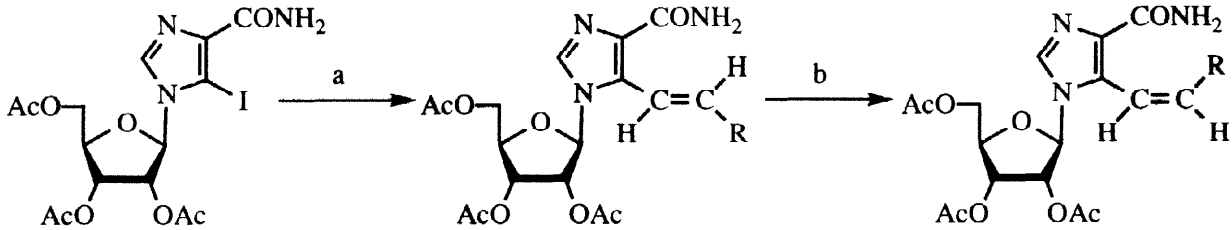
NMR spectrum (DMSO-d_6), in which four NH proton signals appeared at 7.66, 7.27, 7.09, and 7.05 as broad singlets, respectively. The Z-geometry of **8** was determined from the coupling constant of the olefinic protons (J = 12.1 Hz).

Scheme 1



7 **8**

Scheme 2[a]



9

10: R = CO_2Me
11: R = CN

12: R = CO_2Me
13: R = CN

[a] a) H_2C=CHR, $(PhCN)_2PdCl_2$, Et_3N in CH_3CN, 100 °C; b) 100 W-high pressure Hg lamp in CH_3CN

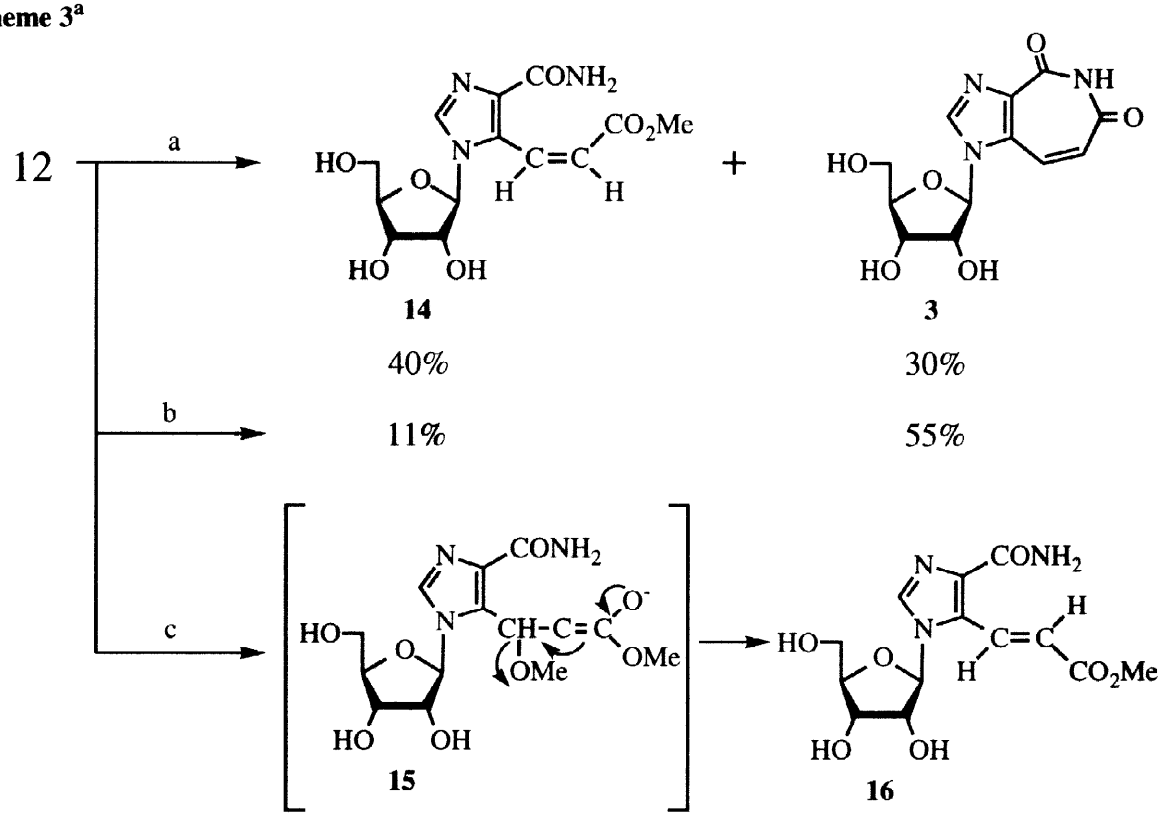
Table 1. Summary of coupling reaction and isomerization.

comp.	yield (%)	uv λmax (nm)	J_{vinyl} (Hz)	comp.	yield (%)	uv λmax (nm)	J_{vinyl} (Hz)
10	65	300	16.4	**12**	80	291	12.1
11	59	300	16.6	**13**	89	290	11.7

Based on these considerations, we planned to synthesize **3** from (*E*)-5-carbomethoxyvinyl derivative **10** *via* isomerization to the (*Z*)-isomer, followed by ring closure. In this method, ring-expanded guanosine derivative **4** would also be obtained from (*E*)-5-cyanovinyl derivative **11**. We previously reported the palladium-catalyzed cross-coupling reaction of **9** with methyl acrylate to give **10** with *E*-geometry.[12] When **9**

was treated with acrylonitrile in the presence of triethylamine and bis(benzonitrile)palladium dichloride, the desired (*E*)-5-cyanovinyl derivative **11** was obtained in 59% yield. Conversion of the *E*-derivative to the corresponding *Z*-isomer was carried out by photo irradiation using a 100W high-pressure mercury lamp through a Pyrex filter (Scheme 2). The resulting *E*- and *Z*-isomers were easy to separate from each other by column chromatography, although this isomerization reached equilibrium, and the starting *E*-isomer was not consumed completely. The chemical yields of the coupling reaction and the isomerization, the λmax of UV spectra, and the coupling constants of olefinic protons are listed in Table 1.

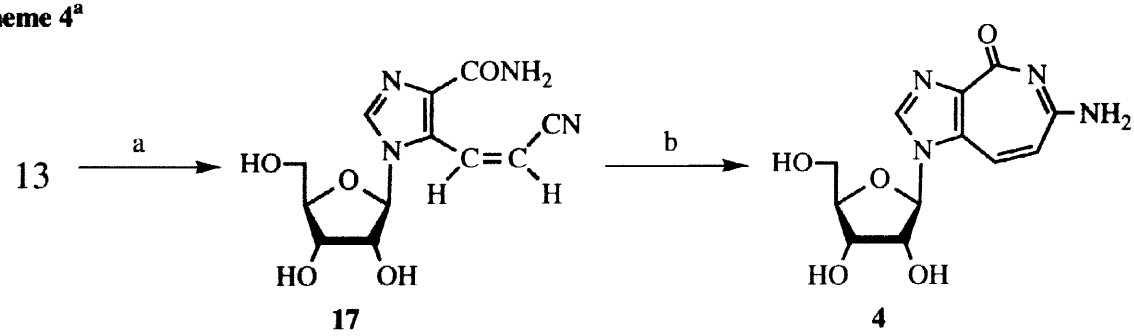
Scheme 3[a]



[a]a) Et_3N in MeOH, r.t; b) Et_3N in MeOH, 60 °C; c) Et_3N in MeOH, 80 °C, 70%

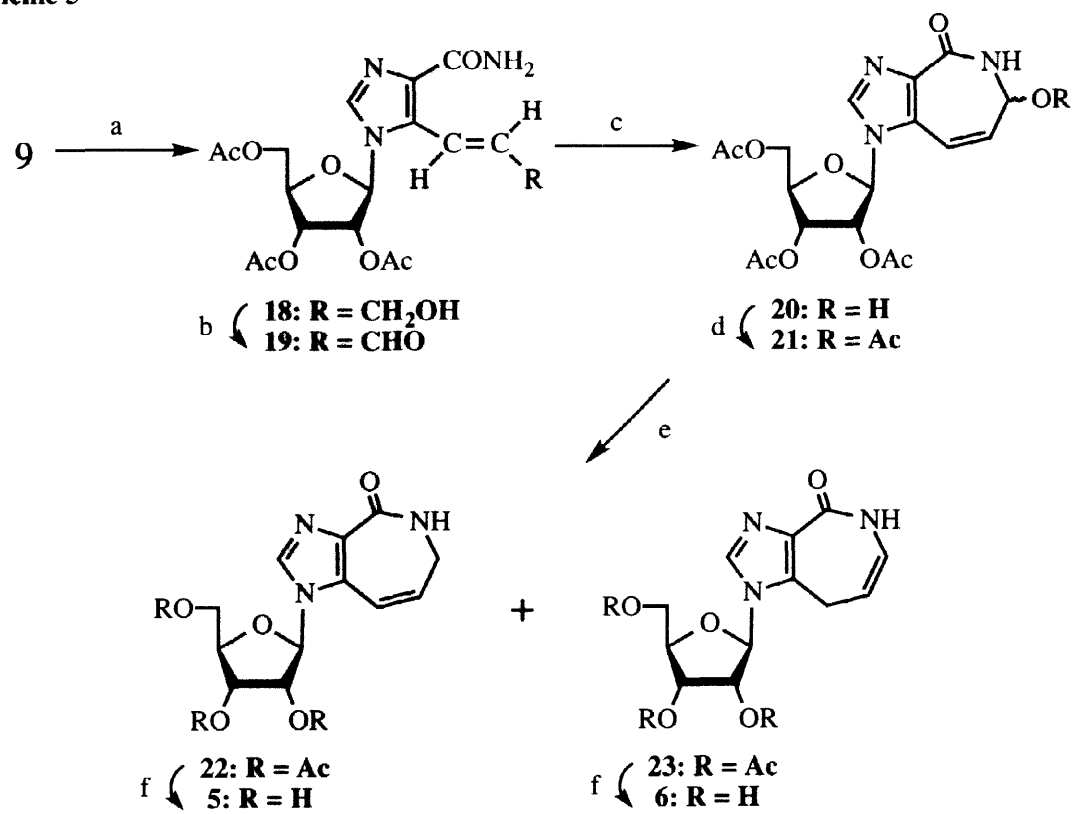
As mentioned above, treatment of **7** with methanolic ammonia predominantly gave ring-opened **8**. Thus, (*Z*)-5-carbomethoxyvinyl derivative **12** was treated with triethylamine in methanol at room temperature to give the desired ring-closed compound **3** in 30% yield along with 40% of **14**. When **12** was heated at 60 °C under the same conditions, **3** was isolated in 55% yield and the formation of **14** was suppressed to 11% yield. Either prolongation of the reaction time or an increase in the temperature resulted in the formation of thermodynamically favored *E*-derivative **16** through Michael addition of a methoxy anion, followed by elimination of the methoxy anion from resulting enolate **15** (Scheme 3). Ring closure and isomerization did not take place when **12** was heated in methanol without adding a base. As in the synthesis of **3**, **13** was treated with triethylamine in methanol. Under these conditions, however, deprotected (*E*)-cyanovinyl derivative **17** was obtained as a single product. Compound **17** was subsequently treated with 5% aqueous $NaHCO_3$ to afford ring-expanded guanosine derivative **4** in 36% yield after HPLC purification (Scheme 4).

Scheme 4[a]



[a]a) Et_3N in MeOH, r.t, 68%; b) 5% aq. $NaHCO_3$, 80 °C, 36%

Scheme 5[a]



[a]a) (*E*)-tributylstannylprop-1-en-3-ol, $(PhCN)_2PdCl_2$ in CH_3CN, 100 °C, 68%; b) $BaMnO_4$ in CH_2Cl_2, r.t, 81%; c) 100W-high pressure Hg lamp in MeOH, 87%; d) Ac_2O in pyridine, 71%; e) Et_3N, HCOOH, $Pd(OAc)_2$, Bu_3P in CH_3CN, 90 °C; f) NH_3 / MeOH

For the synthesis of inosine derivatives **5** and **6**, we tried palladium-catalyzed hydrogenolysis[13] of allylic acetate **21**, as shown in Scheme 5. The palladium-catalyzed cross-coupling reaction of **9** with (*E*)-tributylstannylprop-1-en-3-ol[2,14] gave (*E*)-hydroxypropenyl derivative **18** in 68% yield. Conversion of **18** to **19** in 81% yield was achieved using barium manganate, which was preferable to activated manganese dioxide for this oxidation. The resulting (*E*)-formylvinyl derivative **19** was photo-irradiated in methanol in a manner similar to that for **10** to give a 1:1 mixture of the 6*R* and 6*S* diastereomeric alcohols **20** in 87% yield. After the conversion of **20** to allylic acetate **21**, hydrogenolysis was carried out with triethylammonium formate in the

presence of palladium acetate. Consequently, ring-expanded inosine derivatives **22** and **23** were obtained in yields of 20% and 62%, respectively. The structure of each compound was confirmed after deprotection of the acetyl groups with methanolic ammonia. In the ^{1}H NMR spectrum of **5** in DMSO-d_6, olefinic protons appeared at 6.89 and 6.25 ppm as a doublet and a double triplet, respectively. On the other hand, **6** had olefinic proton signals at 5.82 and 4.84 ppm (double triplet), and the former was changed to a doublet by the addition of D_2O. Furthermore, their UV spectra strongly suggested their respective structures, i.e., **5** has its maximum at 273 nm, while **6** has its maximum at 241 nm due to splitting of the conjugated system at C(8).

The synthetic nucleosides **3-6** were screened for their cytotoxicity against murine L1210 cells in culture. The ring-expanded xanthosine and guanosine derivatives (**3** and **4**) did not significantly inhibit tumor cell growth at up to 100 μg/mL. Furthermore, compound **6** also showed no inhibitory activity at the same concentration. Interestingly, **5** had an IC_{50} value of 20 μg/mL. Although this activity is not very high, it does represent a difference in the cytotoxicities of **5** and **6** despite their very similar structures. The same tendency was observed for **2** (active) and its regio isomer (inactive).[10] Although the reason for this difference is not clear, Hosmane *et al.* assumed that it may be related to the conformational differences between the compounds. For example, **2** has been shown to prefer the *syn* conformation in both the solid state and in solution, while its regio isomer assumes the *anti* conformation in both phases. The sugar pucker geometry in **2** was $C_{2'}$-endo–$C_{3'}$-exo, whereas that in its regio isomer was $C_{2'}$-exo–$C_{3'}$-endo. Since there is little information available regarding the interrelationships of the conformation about the glycosyl bond, sugar pucker, and biological activity, it would be interesting to perform a detailed conformational analysis of **5** and **6**.

Experimental section.

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

(*Z*)-5-(2-Carbamoylvinyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (8). Compound **7** (90 mg, 0.21 mmol) was dissolved in methanolic ammonia (10 mL, saturated at 0 °C), and the mixture was kept at room temperature for 7 h. The solvent was removed *in vacuo*, and the residue was purified by a silica gel column (1.7 x 9 cm), which was eluted with 10–40% EtOH in $CHCl_3$ to give **8** (38 mg, 57% as a white solid). The solid was crystallized from MeOH as white crystals: mp 180–181 °C; MS *m/z* 312 (M^+); UV λ_{max} (H_2O) 285 nm (sh) (ε 3200); UV λ_{max} (0.5 N NaOH) 285 nm (sh) (ε 3700); ^{1}H NMR (DMSO-d_6) 8.02 (s, 1 H, H-2), 7.66, 7.27, 7.09, 7.05 (each br s, each 1 H, NH_2), 6.73, 6.20 (each d, each 1 H, vinyl protons, J = 12.1 Hz), 5.45 (d, 1 H, H-1', $J_{1',2'}$ = 3.3 Hz), 5.27 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 4.8 Hz), 5.08–5.01 (m, 2 H, 3'-OH, 5'-OH), 4.08–3.99 (m, 2 H, H-2', 3'), 3.84–3.82 (m, 1 H, H-4'), 3.70–3.49 (m, 2 H, H-5'a, b). *Anal.* Calcd for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.12; H, 5.18; N, 17.82.

(*E*)-5-(2-Cyanovinyl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (11). A solution of **9** (495 mg, 1 mmol), bis(benzonitrile)palladium dichloride (36 mg, 10 mol%), triethylamine (0.16 mL, 1.2 mmol), and acrylonitrile (80 μL, 1.2 mmol) in dry acetonitrile (5 mL) was heated at 100 °C under argon atmosphere in a sealed glass tube. After the starting material was completely consumed, judged by TLC, the reaction mixture was filtered through a Celite pad, which was washed well with ethanol. The combined filtrate and washings were concentrated to dryness *in vacuo*, and the residue was purified by a silica gel column (2.7 x 15 cm), which was eluted with 66–100% AcOEt in hexane to give **11** (247 mg, 59% as a white solid). An analytical sample was prepared by recrystallization from $CHCl_3$–ether as white crystals: mp 90–93 °C; MS *m/z* 420 (M^+); IR 2200 cm^{-1}; ^1H NMR ($CDCl_3$) 7.82 (s, 1 H, H-2), 7.62 (d, 1 H, vinyl proton, J = 16.6 Hz), 7.21 (br s, 1 H, NHa), 7.12 (d, 1 H, vinyl proton, J = 16.6 Hz), 5.85 (d, 1 H, H-1', $J_{1',2'}$ = 6.4 Hz), 5.62–5.37 (m, 3 H, H-2', 3', NHb), 4.51–4.34 (m, 3 H, H-4', 5'a, b), 2.19, 2.14, 2.12 (each s, each 3 H, acetyl). *Anal.* Calcd for $C_{18}H_{20}N_4O_8$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.54; H, 4.78; N, 13.15.

(*Z*)-5-(2-Carbomethoxyvinyl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (12). A solution of **10** (300 mg, 0.66 mmol)) in dry acetonitrile (300 mL) was irradiated with a 100W high-pressure mercury lamp through Pyrex filter for 26 h at room temperature under argon atmosphere. After removal of the solvent *in vacuo*, the residue was purified by a silica gel column (1.8 x 11 cm), which was eluted with 50–100% AcOEt in hexane to give **12** (240 mg, 80% as a bright yellow oil) and unchanged **10** (59 mg, 20%): MS *m/z* 453 (M^+); ^1H NMR ($CDCl_3$) 7.78 (s, 1 H, H-2), 7.09 (d, 1 H, vinyl proton, J = 12.0 Hz), 6.98 (br s, 1 H, NHa), 6.29 (d, 1 H, vinyl proton, J = 12.0 Hz), 5.73 (d, 1 H, H-1', $J_{1',2'}$ = 4.4 Hz), 5.50–5.38 (m, 3 H, H-2', 3', NHb), 4.35 (br s, 3 H, H-4', 5'a, b), 3.64 (s, 3 H, methyl), 2.15, 2.11, 2.08 (each s, each 3 H, acetyl).

(*Z*)-5-(2-Cyanovinyl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (13). A solution of **11** (300 mg, 0.71 mmol) in dry acetonitrile (300 mL) was irradiated in a similar manner to that described above to give **13** (266 mg, 89% as a bright yellow oil) and unchanged **11** (33 mg, 11%): MS *m/z* 420 (M^+); IR 2200 cm^{-1}; ^1H NMR ($CDCl_3$) 7.86 (s, 1 H, H-2), 7.44 (d, 1 H, vinyl proton, J = 11.7 Hz), 7.05 (br s, 1 H, NHa), 5.88 (d, 1 H, H-1', $J_{1',2'}$ = 4.9 Hz), 5.84 (d, 1 H, vinyl proton, J = 11.7 Hz), 5.53–5.32 (m, 3 H, H-2', 3', NHb), 4.45–4.34 (m, 3 H, H-4', 5'a, b), 2.15, 2.14, 2.11 (each s, each 3 H, acetyl).

(*Z*)-5-(2-Carbomethoxyvinyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (14) and 1-β-D-ribofuranosyl-1,5-dihydroimidazo[4,5-*c*]azepin-4,6-dione (3). A solution of **12** (530 mg, 1.17 mmol) in a mixture of methanol (30 mL) and triethylamine (1 mL) was stirred for 3 h at room temperature. The solvent was removed *in vacuo*, and the residue was purified by a short silica gel column (2.7 x 5 cm), which was eluted with 5–20% EtOH in $CHCl_3$, to give **14** and **3** as a mixture. The mixture was separated by HPLC (YMC-D-ODS-5, flow 8 mL/min, retention time 20 min for **14** and 34 min for **3**) with 10% MeOH–H_2O as an eluent to give **14** (152 mg, 40% as a white foam) and **3** (101 mg, 30% as a white solid), which was crystallized from MeOH–H_2O as white crystals.

Physical data for **14**: MS *m/z* 296 (M^+-OMe); UV λ_{max} (H_2O) 296 nm (ε 3900); UV λ_{max} (0.5 N NaOH) 305 nm (sh) (ε 5500); ^1H NMR (DMSO-d_6) 8.06 (s, 1 H, H-2), 7.29, 7.05 (each br s, each 1 H, NH_2), 7.03 (d, 1 H, vinyl proton, J = 12.1 Hz), 6.20 (d, 1 H, vinyl proton, J = 12.1 Hz), 5.40 (d, 1 H, H-1', $J_{1',2'}$ = 5.9 Hz), 5.38 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 5.8 Hz), 5.15 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 5.1 Hz), 5.04 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'a} = J_{5'\text{-OH},5'b}$ = 5.3 Hz), 4.13–4.01 (m, 2 H, H-2', 3'), 3.85 (dt, 1 H, H-4', J = 3.7, 4.0 Hz), 3.69–3.49 (m, 2 H, H-5'a, b), 3.54 (s, 3 H, methyl). *Anal.* Calcd for $C_{13}H_{17}N_3O_7$: C, 47.71; H, 5.24; N, 12.84. Found: C, 47.72; H, 5.30; N, 12.73.

Physical data for **3**: mp >280 °C (colored at 230 °C); FAB-MS *m/z* 296 (M^++1); UV λ_{max} (H_2O) 316 nm (ε 6400), 235 nm (ε 12000); UV λ_{max} (0.5 N HCl) 297 nm (ε 4700); ^1H NMR (DMSO-d_6) 11.21 (br s, 1 H, NH), 8.38 (s, 1 H, H-2), 7.54, (d, 1 H, H-8, $J_{8,7}$ = 12.6 Hz), 6.34 (d, 1 H, H-7, $J_{7,8}$ = 12.6 Hz), 5.85 (d, 1 H, H-1', $J_{1',2'}$ = 5.5 Hz), 5.63 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 6.0 Hz), 5.27 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.9 Hz), 5.15 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'a} = J_{5'\text{-OH},5'b}$ = 5.2 Hz), 4.22 (ddd, 1 H, H-2', $J_{2',1'}$ = 5.5, $J_{2',2'\text{-OH}}$ = 6.0, $J_{2',3'}$ = 4.9 Hz), 4.08 (dt, 1 H, H-3', $J_{3',2'} = J_{3',3'\text{-OH}}$ = 4.9, $J_{3',4'}$ = 3.3 Hz), 4.00–3.99 (m, 1 H, H-4'), 3.69–3.54 (m, 2 H, H-5'a,b). *Anal.* Calcd for $C_{12}H_{13}N_3O_6 \cdot 1/4H_2O$: C, 48.08; H, 4.54; N, 14.02. Found: C, 48.21; H, 4.47; N, 13.97.

(*E*)-5-(2-Carbomethoxyvinyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (16). A solution of **12** (349 mg, 0.77 mmol) in a mixture of methanol (15 mL) and triethylamine (1 mL) was heated at 80 °C overnight. The solvent was removed *in vacuo*, and the residue was purified by a silica gel column (2.7 x 7 cm), which was eluted with 5–20% EtOH in $CHCl_3$ to give **16** (176 mg, 70%) as a bright yellow foam. The foam was crystallized from EtOH–hexane as white crystals: mp 169–170 °C; MS *m/z* 327 (M^+); UV λ_{max} (H_2O) 301 nm (ε 14200); UV λ_{max} (0.5 N HCl) 275 nm (ε 9900); UV λ_{max} (0.5 N NaOH) 290 nm (ε 12600); ^1H NMR (DMSO-d_6) 8.31 (s, 1 H, H-2), 8.24 (d, 1 H, vinyl proton, J = 16.6 Hz), 7.59, 7.38 (each br s, each 1 H, NH_2), 6.73 (d, 1 H, vinyl proton, J = 16.6 Hz), 5.67 (d, 1 H, H-1', $J_{1',2'}$ = 5.4 Hz), 5.60 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 5.9 Hz), 5.32 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 5.1 Hz), 5.09 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'a} = J_{5'\text{-OH},5'b}$ = 5.5 Hz), 4.36 (ddd, 1 H, H-2', $J_{2',1'}$ = 5.1, $J_{2',2'\text{-OH}}$ = 5.9, $J_{2',3'}$ = 5.5 Hz), 4.09 (ddd, 1 H, H-3', $J_{3',2'}$ = 5.5, $J_{3',3'\text{-OH}}$ = 5.1, $J_{3',4'}$ = 4.8 Hz), 3.98–3.94 (m, 1 H, H-4'), 3.74 (s, 3 H, methyl), 3.69–3.53 (m, 2 H, H-5'a, b). *Anal.* Calcd for $C_{13}H_{17}N_3O_7$: C, 47.71; H, 5.24; N, 12.84. Found: C, 47.44; H, 5.32; N, 12.54.

(*Z*)-5-(2-Cyanovinyl)-1-β-D-ribofuranosylimidazole-4-carboxamide (17). In the same manner as for **3**, treatment of **13** (490 mg, 1.17 mmol) with triethylamine (1 mL) in methanol (20 mL) gave **17** as a bright yellow foam (260 mg, 76%). An analytical sample was purified by a HPLC (YMC-D-ODS-5, flow 8 mL/min, retention time 8 min) with 20% MeOH–H_2O as eluent: MS *m/z* 294 (M^+); IR 2230 cm^{-1}; UV λ_{max} (H_2O) 291 nm (ε 5200); UV λ_{max} (0.5 N HCl) 265 nm (ε 4800); UV λ_{max} (0.5 N NaOH) 287 nm (ε 5600); ^1H NMR (DMSO-d_6) 8.16 (s, 1 H, H-2), 7.40 (d, 1 H, vinyl proton, J = 11.7 Hz), 7.38, 7.21 (each br s, each 1 H, NH_2), 6.15 (d, 1 H, vinyl proton, J = 11.7 Hz), 5.52 (d, 1 H, H-1', $J_{1',2'}$ = 6.2 Hz), 5.51 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 5.5 Hz), 5.21 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 5.1 Hz), 5.09 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'a} = J_{5'\text{-OH},5'b}$ = 5.3 Hz), 4.13 (ddd, 1 H, H-2', $J_{2',1'}$ = 6.2, $J_{2',2'\text{-OH}}$ = 5.5, $J_{2',3'}$ = 5.1 Hz), 4.06–3.89 (m, 2

H, H-3', 4'), 3.68–3.51 (m, 2 H, H-5'a, b). *Anal.* Calcd for $C_{12}H_{14}N_4O_5 \cdot 1/2H_2O$: C, 47.56; H, 4.99; N, 18.49. Found: C, 47.60; H, 4.84; N, 18.49.

6-Amino-1-β-D-ribofuranosylimidazo[4,5-*c*]azepin-4(1*H*)-one (4). A solution of **17** (150 mg, 0.51 mmol) in 5% aqueous $NaHCO_3$ (9 mL) was heated for 1.5 h at 80 °C. The reaction mixture was neutralized by addition of 1 N HCl, and the solvent was removed *in vacuo*. The residue was purified by HPLC (YMC-D-ODS-5, flow 9 mL/min, retention time 24 min) with 5% MeOH–H_2O as eluent to give **4** (50 mg, 33% as a white solid, which was crystallized from H_2O): mp >200 °C; FAB-MS *m/z* 295 (M^++1); UV λ_{max} (H_2O) 324 nm (ε 5600), 240 nm (ε 22700); UV λ_{max} (0.5 N HCl) 331 nm (ε 5000), 257 nm (ε 10600); UV λ_{max} (0.5 N NaOH) 316 nm (ε 4700); ^1H NMR (DMSO-d_6) 8.27 (s, 1 H, H-2), 7.51 (d, 1 H, H-8, J = 11.7 Hz), 7.49 (br s, 2 H, NH_2), 6.45 (d, 1 H, H-7, J = 11.7 Hz), 5.77 (d, 1 H, H-1', $J_{1',2'}$ = 5.9 Hz), 5.55 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 5.9 Hz), 5.23 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.8 Hz), 5.12 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'a}$ = $J_{5'\text{-OH},5'b}$ = 5.1 Hz), 4.20 (dt, 1 H, H-2', $J_{2',1'}$ = $J_{2',2'\text{-OH}}$ = 5.9, $J_{2',3'}$ = 5.1 Hz), 4.09 (ddd, 1 H, H-3', $J_{3',2'}$ = 5.1, $J_{3',3'\text{-OH}}$ = 4.8, $J_{3',4'}$ = 4.4 Hz), 3.96 (ddd, 1 H, H-4', $J_{4',3'}$ = 4.4, $J_{4',5'a}$ = 3.3, $J_{4',5'b}$ = 3.7 Hz), 3.64 (ddd, 1 H, H-5'a, $J_{5'a,4'}$ = 3.3, $J_{5'a,5'b}$ = 12.1, $J_{5'a,5'\text{-OH}}$ = 5.1 Hz), 3.57 (ddd, 1 H, H-5'b, $J_{5'b,4'}$ = 3.7, $J_{5'b,5'a}$ = 12.1, $J_{5'b,5'\text{-OH}}$ = 5.1 Hz). *Anal.* Calcd for $C_{12}H_{14}N_4O_5 \cdot 1/4H_2O$: C, 48.28; H, 4.81; N, 18.77. Found: C, 48.15; H, 4.97; N, 18.58.

(*E*)-5-(3-Hydroxy-1-propenyl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (18). Compound **9** (990 mg, 2 mmol), bis(benzonitrile)palladium dichloride (36 mg, 10 mol%), and (*E*)-1-tributylstannylprop-1-en-3-ol[12] in dry acetonitrile (7 mL) was heated at 100 °C under argon atmosphere in a sealed glass tube. After 12 h, the reaction mixture was filtered through a Celite pad, which was washed with ethanol. The combined filtrate and washings were concentrated to dryness *in vacuo*, and the residue was purified by a silica gel column (2.7 x 24 cm), which was eluted with 0–8% EtOH in $CHCl_3$ to give **18** (576 mg, 68% as a yellow foam): MS *m/z* 425 (M^+); ^1H NMR ($CDCl_3$) 7.75 (s, 1 H, H-2), 7.13 (br s, 1 H, NHa), 6.96 (dt, 1 H, vinyl proton, J = 1.8, 16.5 Hz), 6.53 (dt, 1 H, vinyl proton, J = 4.8, 16.5 Hz), 5.90 (d, 1 H, H-1', $J_{1',2'}$ = 5.5 Hz), 5.71 (br s, 1 H, NHb), 5.63 (dd, 1 H, H-2', $J_{2',1'}$ = 5.5, $J_{2',3'}$ = 5.1 Hz), 5.42 (dd, 1 H, H-3', $J_{3',2'}$ = 5.1, $J_{3',4'}$ = 4.4 Hz), 4.41–4.34 (m, 5 H, H-4', 5'a, b, CH_2OH), 3.35 (br s, 1 H, $CH_2O\mathit{H}$), 2.15, 2.14, 2.10 (each s, each 3 H, acetyl).

(*E*)-5-(2-Formylvinyl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (19). Barium manganate (5.4 g, 21.2 mmol) was added to a solution of **18** (900 mg, 2.12 mmol) in dichloromethane (50 mL), and the whole was stirred for 13 h at room temperature. The reaction mixture was filtered through a Celite pad, which was washed with ethanol. The combined filtrate and washings were concentrated to dryness *in vacuo*, and the residue was purified by a silica gel column (3.2 x 15 cm), which was eluted with 0–4% EtOH in $CHCl_3$ to give **19** (726 mg, 81% as a yellow solid). An analytical sample was prepared by recrystallization from EtOH as pale yellow crystals: mp 78–80 °C; MS *m/z* 423 (M^+); ^1H NMR ($CDCl_3$) 9.72 (d, 1 H, C*H*O, J = 7.6 Hz), 8.38 (d, 1 H, vinyl proton, J = 16.8 Hz), 7.92 (s, 1 H, H-2), 7.17 (br s, 1 H, NHa), 6.70 (dd, 1 H, vinyl proton, J = 7.6, 16.8 Hz), 5.95 (d, 1 H, H-1', $J_{1',2'}$ = 5.9 Hz), 5.67 (dd, 1 H, H-2', $J_{2',1'}$ = 5.9, $J_{2',3'}$ = 5.4 Hz), 5.47–5.38 (m, 2 H, H-3', NHb), 4.47–4.33 (m, 3 H, H-4',

5'a, b), 2.15, 2.14, 2.12 (each s, each 3 H, acetyl). *Anal.* Calcd for $C_{18}H_{21}N_3O_9$: C, 51.06; H, 5.00; N, 9.93. Found: C, 50.86; H, 5.15; N, 9.64.

6-Hydroxy-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5,6-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (20). A solution of **19** (423 mg, 1.0 mmol) in dry methanol (350 mL) was irradiated with a 100W high-pressure mercury lamp through Pyrex filter for 40 min at room temperature under argon atmosphere. After removal of the solvent *in vacuo*, the residue was purified by a silica gel column (3.2 x 7 cm), which was eluted with 0–16% EtOH in $CHCl_3$ to give **20** (366 mg, 87% as a pale yellow oil): FAB-MS *m/z* 424 (M^++1); ^{1}H NMR ($CDCl_3$) 7.88 (s, 0.5 H, H-2 of isomer A), 7.87 (s, 0.5 H, H-2 of isomer B), 6.70 (d, 0.5 H, H-1' of isomer A or B, $J_{1',2'}$ = 6.6 Hz), 6.66 (d, 0.5 H, H-1' of isomer A or B, $J_{1',2'}$ = 6.2 Hz), 6.38–6.31 (m, 1 H, H-8), 5.87–5.84 (m, 1 H, H-2'), 5.51–5.37 (m, 3 H, H-6, 7, 3'), 4.45–4.32 (m, 3 H, H-4', 5'a, b), 2.15, 2.14, 2.10 (each s, each 3 H, acetyl).

6-Acetoxy-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5,6-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (21). A solution of **20** (270 mg, 0.64 mmol) in dry pyridine (10 mL) was treated with acetic anhydride (0.3 mL, 3.2 mmol) at room temperature for 24 h. The reaction was quenched by addition of ethanol, and the solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$, and the organic layer was washed successively with saturated aqueous $NaHCO_3$, water, and saturated brine. The separated organic layer was dried (Na_2SO_4), concentrated *in vacuo* and coevaporated three times with toluene. The residue was purified by a silica gel column (2.7 x 5 cm), which was eluted with 0–4% EtOH in $CHCl_3$ to give **21** (211 mg, 71% as a yellow oil): FAB-MS *m/z* 424 (M^+-OAc+1); ^{1}H NMR ($CDCl_3$) 7.92 (s, 0.4 H, H-2 of isomer A), 7.86 (s, 0.6 H, H-2 of isomer B), 7.01 (d, 0.4 H, NH of isomer A, J = 5.0 Hz), 6.79 (d, 0.6 H, NH of isomer B, J = 4.4 Hz), 6.75 (d, 0.6 H, H-1' of isomer B, $J_{1',2'}$ = 8.8 Hz), 6.71 (d, 0.4 H, H-1' of isomer A, $J_{1',2'}$ = 8.2 Hz), 6.27 (dd, 0.6 H, H-8 of isomer B, J = 1.7, 7.2 Hz), 6.23 (dd, 0.4 H, H-8 of isomer A, J = 1.1, 6.6 Hz), 5.86 (m, 1 H, H-2'), 5.50–5.36 (m, 2 H, H-7, 3'), 4.95 (m, 1 H, H-6), 4.48-4.36 (m, 3 H, H-4', 5'a, b), 2.15, 2.14, 2.11, 2.10 (each s, each 3 H, acetyl).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-5,6-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (22) and 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5,8-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (23). A mixture of **21** (220 mg, 0.47 mmol) in dry acetonitrile including tributylphosphine (22 μL, 0.09 mmol), triethylamine (0.13 mL, 0.94 mmol), formic acid (36 μL, 0.94 mmol), and palladium acetate (12 mg, 10 mol%) was heated at 90 °C for 1 h under argon atmosphere. The reaction mixture was filtered through a Celite pad, which was washed with ethanol. The combined filtrate and washings were concentrated *in vacuo*, and the residue was purified by a silica gel column (1.8 x 13 cm), which was eluted with 0–8% EtOH in $CHCl_3$ to give **22** (40 mg, 20% as a foam) and **23** (120 mg, 62% as a foam).

Physical data for **22**: FAB-MS *m/z* 408 (M^++1); ^{1}H NMR ($CDCl_3$+D_2O) 7.91 (s, 1 H, H-2), 6.80 (d, 1 H, H-8, J = 10.4 Hz), 6.27 (dt, 1 H, H-7, J = 6.0, 10.4 Hz), 5.84 (d, 1 H, H-1', $J_{1',2'}$ = 5.5 Hz), 5.47–5.39 (m, 2 H, H-2',3'), 4.45–4.31 (m, 3 H, H-4', 5'a, b), 3.69 (t, 2 H, H-6, J = 6.0 Hz), 2.16, 2.13, 2.10 (each s, each 3 H, acetyl).

Physical data for **23**: FAB-MS *m/z* 408 (M^++1); ^{1}H NMR ($CDCl_3$) 7.81 (s, 1 H, H-2), 7.69 (d, 1 H, NH, *J* = 6.1 Hz), 5.96 (dd, 1 H, H-6, *J* = 6.1, 9.3 Hz), 5.71 (d, 1 H, H-1', $J_{1',2'}$ = 4.9 Hz), 5.45 (dd, 1 H, H-2', $J_{2',1'}$ = 4.9, $J_{2',3'}$ = 5.5 Hz), 5.39 (dd, 1 H, H-3', $J_{3',2'}$ = 5.5, $J_{3',4'}$ = 4.4 Hz), 4.92 (dt, 1 H, H-7, *J* = 2.2, 9.3 Hz), 4.44–4.38 (m, 3 H, H-4', 5'a,b), 4.36 (d, 2 H, H-8, *J* = 2.2 Hz), 2.15, 2.14, 2.12 (each s, each 3 H, acetyl).

1-β-D-Ribofuranosyl-5,6-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (5). Compound **22** (100 mg, 0.25 mmol) was dissolved in methanolic ammonia (5 mL, saturated at 0 °C), and the mixture was kept at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was purified by a silica gel column (1.8 x 9 cm), which was eluted with 4–40% EtOH in $CHCl_3$ to give **5** (53 mg, 77%). An analytical sample was purified by HPLC (YMC-D-ODS-5, flow 9 mL/min, retention time 14 min) with 10% MeOH–H_2O as eluent to give a white solid: FAB-MS *m/z* 282 (M^++1); UV λ_{max} (H_2O) 274 nm (ε 3200); UV λ_{max} (0.5 N NaOH) 273 nm (ε 3100); ^{1}H NMR (DMSO-d_6+D_2O) 8.10 (s, 1 H, H-2), 6.89 (d, 1 H, H-8, *J* = 10.4 Hz), 6.24 (dt, 1 H, H-7, *J* = 6.6, 10.4 Hz), 5.59 (d, 1 H, H-1', $J_{1',2'}$ = 6.0 Hz), 4.19 (dd, 1 H, H-2', $J_{2',1'}$ = 6.0, $J_{2',3'}$ = 5.5 Hz), 4.04 (dd, 1 H, H-3', $J_{3',2'}$ = 5.5,$J_{3',4'}$ = 3.3 Hz), 3.92 (dt, 1 H, H-4', $J_{4',3'}$ = $J_{4',5'b}$ = 3.3, $J_{4',5'a}$ = 3.8 Hz), 3.63 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 3.8, $J_{5'a,5'b}$ = 12.1 Hz), 3.55 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 3.3, $J_{5'b,5'a}$ = 12.1 Hz), 3.46 (m, 2 H, H-6); HRMS (FAB) Calcd for $C_{11}H_{13}N_3O_4$: 282.1090. Found: 282.1116.

1-β-D-Ribofuranosyl-5,8-dihydroimidazo[4,5-*c*]azepin-4(1*H*)-one (6). In the same manner as for **5**, treatment of **23** (100 mg, 0.25 mmol) with methanolic ammonia (5 mL, saturated at 0 °C) gave **6** (42 mg, 61% as a foam). An analytical sample was purified by HPLC (YMC-D-ODS-5, flow 9 mL/min, retention time 20 min) with 10% MeOH–H_2O as eluent to give a white solid: FAB-MS *m/z* 282 (M^++1); UV λ_{max} (H_2O) 241 nm (ε 3200); UV λ_{max} (0.5 N HCl) 282 nm (ε 1800), 233 nm (ε 7700); UV λ_{max} (0.5 N NaOH) 242 nm (ε 8900); ^{1}H NMR (DMSO-d_6) 8.87 (br d, 1 H, H-5), 7.99 (s, 1 H, H-2), 5.82 (dd, 1 H, H-6, *J* = 6.6, 9.5 Hz), 5.50 (d, 1 H, 2'-OH, $J_{2'\text{-OH},\ 2'}$ = 5.9 Hz), 5.47 (d, 1 H, H-1', $J_{1',2'}$ = 5.5 Hz), 5.20 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.8 Hz), 5.05 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'}$ = 5.3 Hz), 4.84 (dt, 1 H, H-7, *J* = 4.8, 9.5 Hz), 4.17 (ddd, 1 H, H-2', $J_{2',1'}$ = 5.5, $J_{2',2'\text{-OH}}$ = 5.9, $J_{2',3'}$ = 5.1 Hz), 4.03 (ddd, 1 H, H-3', $J_{3',2'}$ = 5.5,$J_{3',3'\text{-OH}}$ = 4.8, $J_{3',4'}$ = 3.7 Hz), 3.61–3.48 (m, 4 H, H-8, H-5'a, b). *Anal.* Calcd for $C_{12}H_{15}N_3O_5$•1/4H_2O: C, 50.43; H, 5.47; N, 14.70. Found: C, 50.41; H, 5.49; N, 14.38.

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