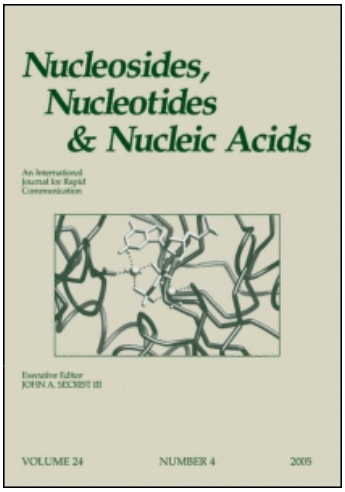

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Nucleosides and Nucleotides. 130. The Synthesis of Imidazo[4, 5-*e*][1, 4] Diazepine Nucleosides From N^1-Substituted Inosines

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NUCLEOSIDES AND NUCLEOTIDES. 130. THE SYNTHESIS OF IMIDAZO[4,5-*e*][1,4]DIAZEPINE NUCLEOSIDES FROM N^1-SUBSTITUTED INOSINES#, 1

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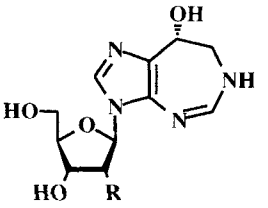
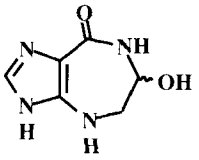
Abstract: New synthetic methods for pyrimidine ring-expanded xanthosine, guanosine, and inosine analogues containing imidazo[4,5-*e*][1,4]diazepine nucleus are described. Treatment of N^1-substituted inosine derivatives **5**, **12**, **19** with aqueous NaOH gave 5-amino-4-(*N*-substituted carbamoyl)imidazole derivatives, followed by appropriate manipulations to cyclize these to constitute imidazo[4,5-*e*][1,4]diazepine nucleosides **11**, **17**, **22**.

Nucleoside analogues with a 5:7-fused imidazodiazepine nucleus as a nucleobase have considerable interest in their structural and biological properties.[2-6] Imidazo[4,5-*d*][1,3]diazepine nucleosides such as coformycin (**1**)[2] and pentostatin (**2**),[3] which are naturally occurring antibiotics, have been recognized as potent inhibitors of adenosine deaminase.[7] Azepinomycin (**3**),[5] which has an imidazo[4,5-*e*][1,4]diazepine nucleus, was also isolated and showed inhibitory activity toward guanine deaminase. They are known to be tight-binding inhibitors of these enzymes due to resemblance to transition states in the enzyme reactions.[8] Although such ring-expanded nucleosides would be

This paper is dedicated to Dr. Morio Ikehara on the occasion of his 70th birthday.



1: R = OH, coformycin
2: R = H, pentostatin



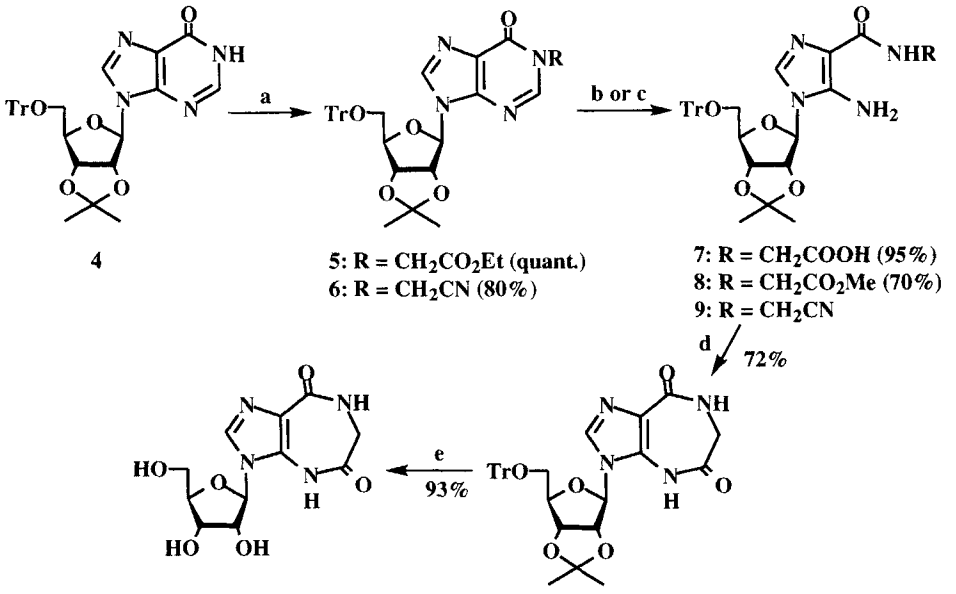
3: azepinomycin

Chart I

expected to a new class of antimetabolites, almost all of the synthetic studies so far reported used condensation reactions with ring-expanded purines and appropriately protected sugars.[9-12]

Quite recently, Hosmane *et al.* reported the synthesis of two imidazo[4,5-*e*][1,4]diazepine nucleosides and found that one of them inhibits the reverse transcriptase of murine leukemia virus in tissue culture systems.[13] We designed an imidazo[4,5-*c*]azepine nucleoside as a GMP synthase inhibitor, which is a deaza analogue of the title imidazo[4,5-*e*][1,4]diazepine nucleoside and had a potent cytotoxicity against mouse leukemia cells *in vitro*.[14] These results prompt us to find a new general route to synthesize imidazo[4,5-*e*][1,4]diazepine ribosides, related to pyrimidine ring-expanded xanthosine, guanosine, and inosine derivatives, which are structurally comparable to the natural purine nucleosides and are expected to act as inhibitors of purine nucleotide biosynthesis.

N^1-Alkylinosines have been known in which the pyrimidine ring was readily cleaved by aqueous alkali to produce 5-amino-4-(*N*-alkylcarbamoyl)imidazole ribosides.[15] We have already reported the synthesis of 3-alkyl-3-deazainosines from N^1-substituted inosines via ring opening of the pyrimidine moiety by alkali, followed by Pd catalyzed cyclization.[16] We planned to use this method to synthesize the imidazo[4,5-*e*][1,4]diazepine nucleosides (Scheme I). When 2',3'-*O*-isopropylidene-5'-*O*-triphenylmethylinosine (**4**)[17] was treated with ethyl bromoacetate and K_2CO_3 in the presence of 18-crown-6 in THF, N^1-ethoxycarbonylmethylinosine derivative **5** was exclusively obtained in a quantitative yield without formation of the corresponding O^6-alkylated derivative. Ring opening of the pyrimidine moiety of **5** was then done using 5 N NaOH in EtOH at reflux temperature, followed by esterification of the carboxyl group of **7** by CH_2N_2 to

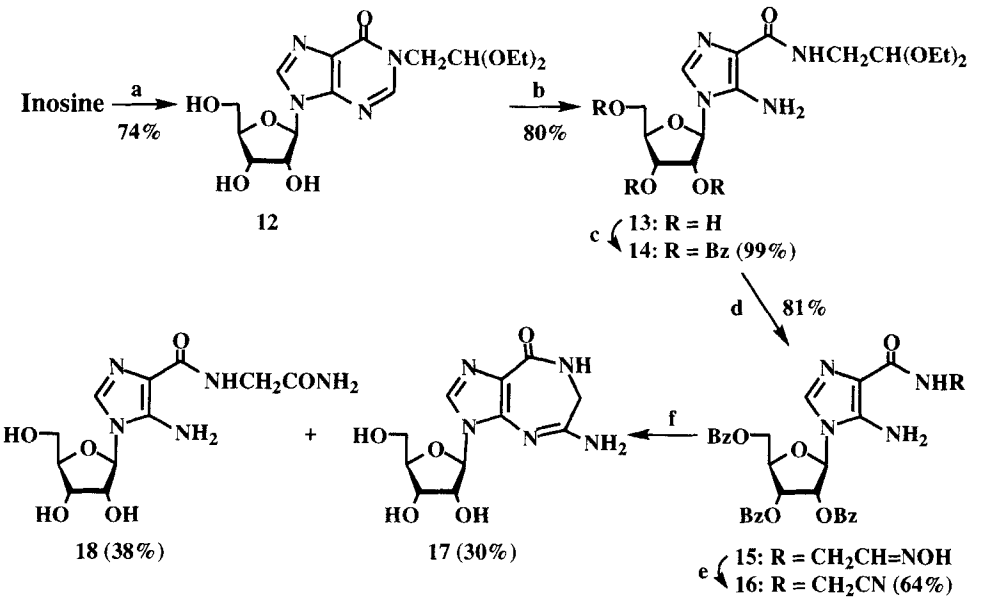


[a]a) RBr, K_2CO_3, 18-crown-6 in THF, room temperature; b) 5 N NaOH in EtOH, reflux, then CH_2N_2 in MeOH; c) 5 N NaOH in EtOH, reflux; d) 1 N NaOMe in MeOH, reflux; e) 70% aqueous TFA, room temperature.

Scheme I[a]

give 5-aminoimidazole-4-[*N*-(methoxycarbonyl)methyl]carboxamide derivative **8** in 70% yield from **5**. Hosmane *et al.* have already reported the synthesis of a benzoylated derivative of **8** having the same aglycon by using the condensation, which was converted to ring-expanded xanthosine derivative **11** by treatment with NaOMe / MeOH.[13] In the same manner, **8** was converted to imidazo[4,5-*e*][1,4]diazepine-5,8-dione derivative **10** in 72% yield. In this reaction, the ring-opened *N*-carboxymethyl derivative **7** was concomitantly obtained with **10**. Compound **10** was then deprotected with aqueous trifluoroacetic acid (TFA) to afford **11**, that analytical data were identical with those of reported by Hosmane (see experimental section).

The ring-expanded guanosine derivative **17** could be prepared if *N*-cyanomethyl derivative **9** is available. Compound **6** was similarly obtained from **4** by using bromoacetonitrile. Treatment of **6** with aqueous alkali, however, gave **7** in 95% yield but not the desired **9**. Therefore we next examined another route as shown in Scheme II, that is, reaction of inosine with bromoacetaldehyde diethyl acetal in DMF was first done to give



[a]a) $BrCH_2CH(OEt)_2$, NaI, K_2CO_3, 18-crown-6 in DMF, 70 °C; b) 5 N NaOH in EtOH, reflux; c) benzoic anhydride, Et_3N, DMAP in CH_3CN; d) 0.2 N HCl in THF, room temperature, then NH_2OH•HCl in pyridine; e) acetic anhydride, Et_3N, DMAP in CH_3CN, then EtOH, reflux; f) NH_3 / MeOH, 100 °C.

Scheme II[a]

12. Ring opening of the pyrimidine moiety of **12** by 5 N NaOH gave *N*-diethoxyethyl derivative **13** in 80% yield. Protection of the sugar hydroxyls of **13** by benzoyl groups was necessary to convert the *N*-diethoxyethyl group to *N*-cyanomethyl group. Compound **14** was treated with 0.2 N HCl, followed by hydroxylamine hydrochloride to give *N*-hydroxyiminomethyl derivative **15** in 81% yield, which was further converted to 5-aminoimidazole-4-(*N*-cyanomethyl)carboxamide derivative **16** by dehydration. When **16** was treated with methanolic ammonia at 100 °C in a sealed tube, the desired 5-amino-6,7-dihydro-3-β-D-ribofuranosylimidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one (**17**) was obtained in 30% yield after HPLC purification. In this reaction, however, a considerable amount of ring-opened *N*-carbamoylmethyl derivative **18** was obtained. It is not clear that whether the formation of ring opened derivatives **7** and **18** took place by hydrolysis of the ring-closed products **10** and **17** or of the methoxycarbonyl and cyano groups of **8** and **16**, respectively.

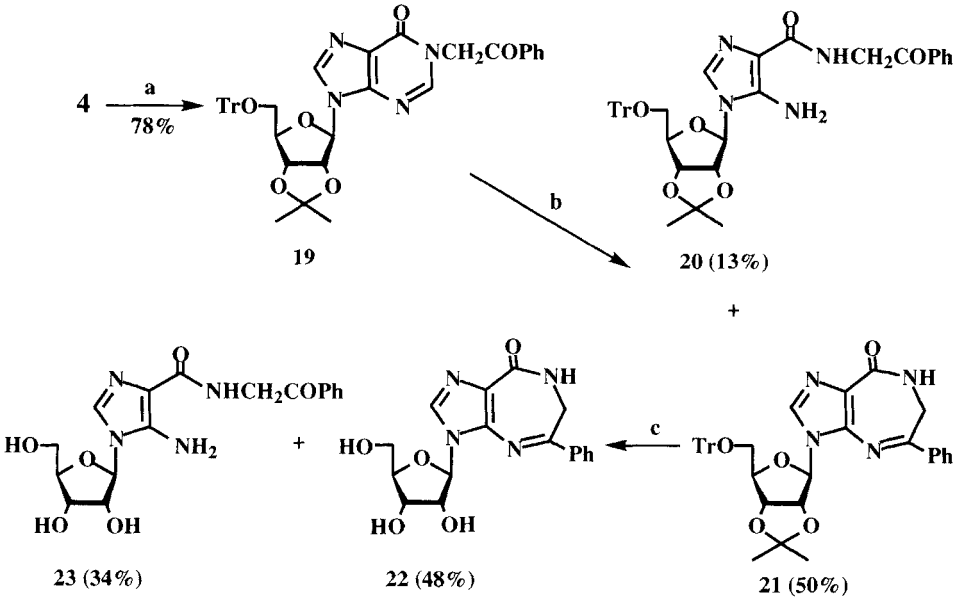
We further examined the synthesis of an aryl substituted ring-expanded inosine derivative (Scheme III). Introduction of a phenacyl group at N^1 position of **4** was done with phenacyl bromide to give **19** in a similar manner to that described above. When **19** was treated with 5 N NaOH, the expected *N*-phenacyl derivative **20** was obtained in only 13% yield along with a spontaneously cyclized product, 5-phenylimidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one derivative **21** in 50% yield. Compound **21** was treated with aqueous TFA to remove acid labile protecting groups giving the desired 6,7-dihydro-5-phenyl-3-β-D-ribofuranosylimidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one (**22**) and ring-opened derivative **23** in 48% and 34% yields, respectively. Furthermore, it was found that when **21** was treated with 5 N NaOH, the ring-opening was again observed to give **20**. Therefore, the ring system of imidazo[4,5-*e*][1,4]diazepine was sensitive both to acidic and basic conditions.

In conclusion, we developed new synthetic methods for pyrimidine ring-expanded xanthosine, guanosine, and inosine derivatives containing imidazo[4,5-*e*][1,4]diazepine nucleus from inosine. Further work is now in progress and the biological activities will be reported elsewhere.

Experimental Section

Melting points were measured on a Yanagimoto MP-3 micro melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL JNM FX-100 or JEOL JNM 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), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV spectra were recorded with a Shimadzu UV-260 or UV-2100S spectrometer. Mass spectra were recorded on a JEOL JMS DX-303 or JEOL JMS HX-110 spectrometer. TLC was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70-230 mesh). Materials not soluble in the solvent system used for column chromatography were coevaporated onto YMC gel 60A, using a suitable solvent. The dry materials were then put on the top of a silica gel chromatography column.

2',3'-*O*-Isopropylidene-5'-*O*-triphenylmethyl-1-[(ethoxycarbonyl)-methyl]-inosine (5). Ethyl bromoacetate (0.45 mL, 4.0 mmol) was added to a



[a]a)$BrCH_2COPh$, K_2CO_3, 18-crown-6 in THF, room temperature; b) 5 N NaOH in EtOH, reflux; c) 70% aqueous TFA, room temperature.

Scheme III[a]

solution of **4** (1.10 g, 2.0 mmol) in dry THF (10 mL) containing K_2CO_3 (553 mg, 4.0 mmol) and 18-crown-6 (52 mg, 0.2 mmol) and the resulting mixture was stirred for 4 hr at room temperature. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.8 x 10 cm), eluted with hexane : AcOEt (1:1-1:2), to give **5** (1.27 g, 100%) as a yellow oil. An analytical sample was crystallized from EtOH as white crystals: mp 170-173 °C; MS *m/z* 637 (M^++1); ^{1}H-NMR ($CDCl_3$) 7.86, 7.72 (each s, each 1 H, H-2, 8), 7.65-7.19 (m, 15 H, trityl), 6.08 (d, 1 H, H-1', $J_{1',2'}$ = 2.4 Hz), 5.25 (dd, 1 H, H-2', $J_{2',1'}$ = 2.4, $J_{2',3'}$ = 6.3 Hz), 4.89 (dd, 1 H, H-3', $J_{3',2'}$ = 6.3, $J_{3',4'}$ = 3.4 Hz), 4.74 (d, 2 H, CH_2, J = 6.4 Hz), 4.51 (m, 1 H, H-4'), 4.26 (q, 2 H, CH_2CH_3, J = 7.3 Hz), 3.33 (m, 2 H, H-5'a, b), 1.62, 1.38 (each s, each 3 H, isoPr), 1.26 (t, 3 H, CH_2CH_3, J = 7.3 Hz). *Anal.* Calcd for $C_{36}H_{36}N_4O_7$: C, 67.91; H, 5.70; N, 8.80. Found: C, 68.08, H, 5.71, N, 8.80.

5-Amino-1-(2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-β-D-ribofuranosyl)imidazole-4-[*N*-(methoxycarbonyl)methyl]carboxamide (8). Five N NaOH (3 mL) was added to a solution of **5** (368 mg, 0.58 mmol) in EtOH (20 mL) and the solution was heated under reflux for 3 hr. The cooled mixture was neutralized by addition of Dowex 50W (H^+ form) and the resin was filtered and washed with EtOH. The combined filtrate and washings were concentrated to dryness *in vacuo* giving **7**. The residue was dissolved in MeOH (20 mL) and treated with CH_2N_2 (prepared from *N*-nitroso-*N*-methylurea). The reaction was quenched by addition of AcOH and the solvent was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.2 x 9 cm), eluted with 1% EtOH in $CHCl_3$, to give **8** (248 mg, 70%) as a white foam: MS *m/z* 553 (M^+-COOMe); ^{1}H-NMR ($CDCl_3$) 7.38-7.24 (m, 15 H, trityl), 7.05 (t, 1 H, NH, J = 5.9 Hz), 7.04 (s, 1 H, H-2), 5.57 (d, 1 H, H-1', $J_{1',2'}$ = 3.9 Hz), 5.17 (br s, 2 H, NH_2), 5.04 (dd, 1 H, H-2', $J_{2',1'}$ = 3.9, $J_{2',3'}$ = 6.8 Hz), 4.93 (dd, 1 H, H-3', $J_{3',2'}$ = 6.8, $J_{3',4'}$ = 3.9 Hz), 4.22 (m, 1 H, H-4'), 4.16 (d, 2 H, CH_2, J = 5.9 Hz), 3.76 (s, 3 H, CO_2Me), 3.50 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 3.4, $J_{5'a,b}$ = 10.8 Hz), 3.41 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 3.4, $J_{5'a,b}$ = 10.8 Hz), 1.53, 1.37 (each s, each 3 H, isoPr).

4,5,7,8-Tetrahydro-6*H*-3-(2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-β-D-ribofuranosyl)imidazo[4,5-*e*][1,4]diazepine-5,8-dione (10). One N NaOMe (0.49 mL, 0.49 mmol) was added to a solution of **8** (202 mg, 0.33 mmol) in absolute MeOH (10 mL) and maintained under an Ar atmosphere. The mixture was heated under reflux for 6 hr. The cooled mixture was neutralized by addition of Dowex 50W (H^+ form) and the resin was filtered and washed with MeOH. The combined filtrate and washings were concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.2 x 5 cm), eluted with 4-8% EtOH in $CHCl_3$, to give **10** (137 mg, 72%) as a white foam. An analytical sample was crystallized from EtOH as white crystals: mp 162-165 °C; MS *m/z* 580 (M^+); ^{1}H-NMR ($CDCl_3$) 8.49 (br s, 1 H, N^4-H), 7.55 (s, 1 H, H-2), 7.35-7.22 (m, 15 H, trityl), 6.46 (t, 1 H, N^7-H, J = 5.4 Hz), 5.64 (d, 1 H, H-1', $J_{1',2'}$ = 3.9 Hz), 4.92 (dd, 1 H, H-2', $J_{2',1'}$ = 3.9, $J_{2',3'}$ = 5.9 Hz), 4.64 (dd, 1 H, H-3', $J_{3',2'}$ = 5.9, $J_{3',4'}$ = 2.0 Hz), 4.49 (dt, 1 H, H-4', $J_{4',3'}$ = 2.0, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.4 Hz), 3.88 (d, 2 H, H-6, J = 5.4 Hz), 3.41 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 4.4, $J_{5'a,b}$ = 10.8 Hz), 3.26 (d, 1 H, H-5'b, $J_{5'b,4'}$ = 4.4, $J_{5'a,b}$ = 10.8 Hz), 1.60, 1.36 (each s, each 3 H, isoPr). *Anal.* Calcd for $C_{33}H_{32}N_4O_6 \cdot 1/2H_2O$: C, 67.22; H, 5.64; N, 9.50. Found: C, 67.46, H, 5.70, N, 9.28.

4,5,7,8-Tetrahydro-6*H*-3-β-D-ribofuranosylimidazo[4,5-*e*][1,4]-diazepine-5,8-dione (11). An aqueous TFA solution (70%, 10 mL) containing **10** (201 mg, 0.35 mmol) was stirred for 1.5 hr at room temperature. The solvent was removed *in vacuo* and coevaporated several times with EtOH. The residue was purified by a silica gel column (3.2 x 4 cm), eluted with 15% MeOH in $CHCl_3$, to give **11** (96 mg, 93%) as light yellow crystals. An analytical sample was crystallized from $CHCl_3$-MeOH as white crystals: mp 163 °C (dec.) (lit.[13] mp 170 °C dec); FAB-MS *m/z* 299 (M^++1); UVλ_{max} (H_2O) 263 nm (ε 6100); UVλ_{max} (0.5 N NaOH) 294 nm (ε 6800), 247 nm (ε 8400); ^{1}H-NMR (DMSO-d_6) 10.62 (br s, 1 H, N^7-H), 7.89 (s, 1 H, H-2), 7.70 (br s, 1 H, N^4-H), 5.67 (d, 1 H, H-1', $J_{1',2'}$ = 6.0 Hz), 5.42 (m, 2 H, 2'-OH, 5'-OH), 5.24 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.4 Hz), 4.23 (dd, 1 H, H-2', $J_{2',1'}$ = 6.0, $J_{2',3'}$ = 5.0 Hz), 4.07 (ddd, 1 H, H-3', $J_{3',2'}$ = 5.0, $J_{3',3'\text{-OH}}$ = 4.4, $J_{3',4'}$ = 2.8 Hz), 3.95 (m, 1 H, H-4'), 3.64 (m, 4 H, H-5'a, b, H-6). *Anal.* Calcd for $C_{11}H_{14}N_4O_6 \cdot 1/4H_2O$: C, 43.63; H, 4.83; N, 18.79. Found: C, 43.60, H, 4.71, N, 18.43.

2',3'-*O*-Isopropylidene-5'-*O*-triphenylmethyl-1-cyanomethylinosine (6). Bromoacetonitrile (0.40 mL, 5.74 mmol) was added to a solution of **4** (1.58 g, 2.87 mmol) in dry THF (20 mL) containing K_2CO_3 (793 mg, 5.74 mmol) and 18-crown-6 (152 mg, 0.57 mmol) and the resulting mixture was stirred for 3 hr at room temperature. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (3.2 x 11 cm), eluted with 1-2% EtOH in $CHCl_3$, to give **6** (1.35 g, 80%) as a white foam: MS *m/z* 346 (M^+-trityl); ^{1}H-NMR ($CDCl_3$) 7.91, 7.90 (each s, each 1 H, H-2, 8), 7.37-7.20 (m, 15 H, trityl), 6.08 (d, 1 H, H-1', $J_{1',2'}$ = 2.6 Hz), 5.25 (dd, 1 H, H-2', $J_{2',1'}$ = 2.6, $J_{2',3'}$ = 6.3 Hz), 4.94, 4.93 (each s, each 1 H, CH_2), 4.90 (dd, 1 H, H-3', $J_{3',2'}$ = 6.3, $J_{3',4'}$ = 2.8 Hz), 4.53 (ddd, 1 H, H-4', $J_{4',3'}$ = 2.8, $J_{4',5'a}$ = 5.7, $J_{4',5'b}$ = 4.3 Hz), 3.35 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 5.7, $J_{5'a,b}$ = 10.2 Hz), 3.31 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 4.3, $J_{5'b,a}$ = 10.2 Hz), 1.62, 1.39 (each s, each 3 H, isoPr).

5-Amino-1-(2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-β-D-ribofuranosyl)imidazole-4-(*N*-carboxymethyl)carboxamide (7). Five N NaOH (5 mL) was added to a solution of **6** (300 mg, 0.51 mmol) in EtOH (10 mL) and the solution was heated under reflux for 6 hr. The cooled mixture was neutralized by addition of Dowex 50W (H^+ form) and the resin was filtered and washed with EtOH. The combined filtrate and washings were concentrated to dryness *in vacuo*. The residue was purified by

a silica gel column (2.8 x 4 cm), eluted with 10-25% EtOH in $CHCl_3$, to give **7** (288 mg, 95%) as a orange solid: MS *m/z* 598 (M^+); ^{1}H-NMR ($CDCl_3$) 7.48 (t, 1 H, NH, J = 5.4 Hz), 7.38-7.24 (m, 16 H, H-2, trityl), 5.88 (br s, 2 H, NH_2), 5.84 (d, 1 H, H-1', $J_{1',2'}$ = 2.9 Hz), 5.14 (dd, 1 H, H-2', $J_{2',1'}$ = 2.9, $J_{2',3'}$ = 6.4 Hz), 4.85 (dd, 1 H, H-3', $J_{3',2'}$ = 6.4, $J_{3',4'}$ = 3.9 Hz), 4.15 (ddd, 1 H, H-4', $J_{4',3'}$ = 3.9, $J_{4',5'a}$ = 6.1, $J_{4',5'b}$ = 4.1 Hz), 3.74 (d, 2 H, CH_2, J = 5.4 Hz), 3.18 (dd, 1H, H-5'a, $J_{5'a,4'}$ = 6.1, $J_{5'a,b}$ = 10.8 Hz), 3.08 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 4.1, $J_{5'b,a}$ = 10.8 Hz), 1.51, 1.31 (each s, each 3 H, isoPr).

1-(2,2-Diethoxyethyl)inosine (12). A mixture of NaI (4.45 g, 30 mmol) and bromoacetaldehyde diethyl acetal (4.5 mL 30 mmol) in dry DMF was stirred for 30 min at room temperature. Then to the mixture, inosine (2.68 g, 10 mmol), K_2CO_3 (4.15 g, 30 mmol), and 18-crown-6 (264 mg, 1.0 mmol) were added, and the resulting mixture was heated at 70 °C overnight. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.8 x 12 cm), eluted with 8-10% EtOH in $CHCl_3$, to give **12** (2.83 g, 74%) as a white solid: MS *m/z* 384 (M^+); ^{1}H-NMR (DMSO-d_6) 8.37 (s, 1 H, H-8), 8.29 (s, 1 H, H-2), 5.86 (d, 1 H, H-1', $J_{1',2'}$ = 5.9 Hz), 5.50 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 5.5 Hz), 5.21 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.8 Hz), 5.07 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'}$ = 5.5 Hz), 4.72 (dt, 1 H, H-2', $J_{2',1'}$ = 5.9, $J_{2',3'}$ = $J_{2',2'\text{-OH}}$ = 5.5 Hz), 4.48 (m, 1 H, H-3', $J_{3',2'}$ = 5.5, $J_{3',3'\text{-OH}}$ = 4.8 Hz), 4.11 (m, 3 H, CH_2CH), 3.94 (m, 1 H, H-4'), 3.69-3.41 (m, 6 H, H-5'a, b, OCH_2CH_3 x 2), 1.06 (t, 6 H, OCH_2CH_3 x 2, J = 7.0 Hz).

5-Amino-1-β-D-ribofuranosylimidazole-4-[*N*-(2,2-diethoxyethyl)]-carboxamide (13). Five N NaOH (5 mL) was added to a solution of **12** (1.0 g, 2.6 mmol) in EtOH (20 mL) and the solution was heated under reflux for 4 hr. The cooled mixture was neutralized with 1 N HCl and concentrated to dryness *in vacuo*. A small amount of MeOH was added to the residue and the insoluble salt was filtered and washed with MeOH. The combined filtrate and washings were concentrated to dryness *in vacuo* and the residue was purified by a silica gel column (3.2 x 7 cm), eluted with 10-15% EtOH in $CHCl_3$, to give **13** (783 mg, 80%) as a white foam. An analytical sample was crystallized from acetone as white crystals: mp 155-158 °C; MS *m/z* 374 (M^+); ^{1}H-NMR (DMSO-d_6) 7.32 (s, 1 H, H-2), 7.13 (t, 1 H, NH, J = 5.9 Hz), 5.90 (br s, 2 H, NH_2), 5.46 (d, 1 H, H-1', $J_{1',2'}$ = 6.2 Hz), 5.34 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 6.6 Hz), 5.24 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'}$ = 4.9 Hz), 5.15 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.4 Hz), 4.56 (t, 1 H,

CH_2CH, J = 5.5 Hz), 4.27 (dt, 1 H, H-2', $J_{2',1'} = J_{2',2'\text{-OH}}$ = 6.6, $J_{2',3'}$ = 5.1 Hz), 4.03 (ddd, 1 H, H-3', $J_{3',2'}$ = 5.1, $J_{3',3'\text{-OH}}$ = 4.4, $J_{3',4'}$ = 2.9 Hz), 3.89 (m, 1 H, H-4'), 3.68-3.04 (m, 6 H, H-5'a, b, OCH_2CH_3 x 2), 3.27 (dd, 2 H, CH_2CH, J = 5.5, 5.9 Hz), 1.11 (t, 6 H, OCH_2CH_3 x 2, J = 7.0 Hz). *Anal.* Calcd for $C_{15}H_{26}N_4O_7$: C, 48.12; H, 7.00; N, 14.97. Found: C, 47.98, H, 7.01, N, 14.95.

5-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-[*N*-(2,2-diethoxyethyl)]carboxamide (14). Benzoic anhydride (1.69 g, 7.49 mmol) was added to a solution of **13** (700 mg, 1.87 mmol) in dry CH_3CN (15 mL) containing triethylamine (1.04 mL, 7.49 mmol) and DMAP (15 mg). The reaction mixture was stirred for 2 hr at room temperature and MeOH (10 mL) was added to the mixture to decompose an excess of benzoic anhydride. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in AcOEt, which was washed with saturated aqueous $NaHCO_3$, followed by saturated aqueous NaCl. The separated organic layer was dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (3.2 x 7.5 cm), eluted with hexane : AcOEt (1 : 1 to 1 : 2), to give **14** (1.27 g, 99%) as a bright orange foam: MS *m/z* 686 (M^+); ^{1}H-NMR ($CDCl_3$) 8.10-7.75, 7.63-7.38 (m, 15 H, Bz x 3), 7.22 (s, 1 H, H-2), 6.77 (t, 1 H, NH, J = 6.3 Hz), 5.97 (d, 1 H, H-1', $J_{1',2'}$ = 2.0 Hz), 5.96 (dd, 1 H, H-2', $J_{2',1'}$ = 2.0, $J_{2',3'}$ = 2.4 Hz), 5.85 (m, 1 H, H-3', $J_{3',2'}$ = 2.4 Hz), 4.78 (m, 3 H, H-4', 5'a, b), 4.54 (t, 1 H, CH_2CH, J = 5.4 Hz), 3.72, 3.61 (each q, each 2 H, OCH_2CH_3, J = 6.8 Hz), 3.55 (m, 2 H, CH_2CH), 1.22 (t, 6 H, OCH_2CH_3, J = 6.8 Hz).

5-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-(*N*-hydroxyiminomethyl)carboxamide (15). Two-tenths N HCl (40 mL) was added to a solution of **14** (1.50 g, 2.19 mmol) in THF (40 mL) and the resulting mixture was stirred for 2 days at room temperature. Pyridine (10 mL) was added to the reaction mixture and concentrated to dryness *in vacuo*. The residue was further coevaporated twice with pyridine. The residue was dissolved in dry pyridine (20 mL) and NH_2OH•HCl (304 mg, 0.58 mmol) was added to the solution. The mixture was stirred for 2 hr at room temperature and the reaction was quenched by addition of acetone (1 mL). The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed three times with H_2O. The separated organic layer was dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was coevaporated three times with toluene and the residue was purified by a silica gel column (2.8 x 10 cm),

eluted with 1-4% EtOH in $CHCl_3$, to give **15** (1.11 g, 81%) as a brown foam: MS *m/z* 609 (M^+-H_2O); ^{1}H-NMR ($CDCl_3$) 8.09-7.95, 7.61-7.02 (m, 16 H, Bz x 3, H-2), 7.83 (m, 1 H, NH), 7.10 (m, 0.4 H, C*H*=NOH cis), 6.81 (m, 0.6 H, C*H*=NOH trans), 5.95 (m, 2 H, H-1', 2'), 5.83 (m, 1 H, H-3'), 5.51 (br s, 2 H, NH_2), 5.40 (br s, 1 H, CH=NO*H*), 4.80 (m, 3 H, H-4', 5'a, b), 4.13 (m, 2 H, CH_2).

5-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-(*N*-cyanomethyl)carboxamide (16). Acetic anhydride (0.24 mL, 2.54 mmol) was added to a solution of **15** (796 mg, 1.27 mmol) in dry CH_3CN (15 mL) containing triethylamine (0.35 mL, 2.54 mmol) and DMAP (15 mg). The reaction mixture was stirred for 6 hr at room temperature and EtOH (10 mL) was added to the mixture to decompose an excess of acetic anhydride. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in $CHCl_3$, which was washed with saturated aqueous $NaHCO_3$, followed by saturated aqueous NaCl. The separated organic layer was dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was dissolved in EtOH (50 mL) and the solution was heated under reflux for 2 days. The solution was concentrated to dryness *in vacuo* and the residue was purified by a silica gel column (2.8 x 7 cm), eluted with hexane : AcOEt (1 : 1), to give **16** (495 mg, 64%) as a white solid: MS *m/z* 609 (M^+); ^{1}H-NMR ($CDCl_3$) 8.09-7.96, 7.65-7.24 (m, 16 H, Bz x 3, H-2), 6.99 (t, 1 H, NH, *J* = 5.9 Hz), 5.94 (m, 2 H, H-1', 2'), 5.83 (m, 1 H, H-3'), 5.45 (br s, 2 H, NH_2), 4.81 (m, 3 H, H-4', 5'a, b), 4.28 (d, 2 H, CH_2, *J* = 5.9 Hz).

5-Amino-6,7-dihydro-3-β-D-ribofuranosylimidazo[4,5-*e*][1,4]-diazepin-8(3*H*)-one (17) and 5-amino-1-β-D-ribofuranosylimidazole-4-(*N*-carbamoylmethyl)carboxamide (18). Compound **16** (200 mg, 0.29 mmol) was dissolved in methanolic ammonia (saturated at 0 °C, 15 mL) and the mixture was heated at 100 °C for 18 hr in a sealed tube. The solvent was concentrated to dryness *in vacuo* and the residue was purified by a HPLC (YMC-D-ODS-5, 250 x 20.0 mm, flow 9.9 mL / min) eluted with 2.5% MeOH in H_2O. The fractions having retention times of 8 min were collected, and the solvent was removed *in vacuo* to give **17** (28.8 mg, 30%) as a white glass. The fractions having retention times of 14 min were collected, and the solvent was removed *in vacuo* to give **18** (39.1 mg, 38%) as a white glass.

Physical data for **17**: FAB-MS *m/z* 298 (M^++1); UVλ_{max} (H_2O) 297 nm (ε 6700); UVλ_{max} (0.5 N HCl) 287 nm (ε 6900), 261 nm (ε 7300); UVλ_{max} (0.5 N NaOH) 296 nm (ε 6600); ^{1}H-NMR (DMSO-d_6) 7.73 (s, 1 H, H-2), 7.51 (t, 1 H, NH, *J* = 4.9

Hz), 7.40 (br s, 1 H, NH_2), 5.66 (d, 1 H, H-1', $J_{1',2'}$ = 5.4 Hz), 5.30 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 5.5 Hz), 5.07 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.4 Hz), 4.96 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'a} = J_{5'\text{-OH},5'b}$ = 5.5 Hz), 4.28 (ddd, 1 H, H-2', $J_{2',1'}$ = 5.4, $J_{2',3'}$ = 4.9, $J_{2',2'\text{-OH}}$ = 5.5 Hz), 4.09 (m, 1 H, H-3', $J_{3',2'}$ = 4.9, $J_{3',4'}$ = 3.9, $J_{3',3'\text{-OH}}$ = 4.4 Hz), 3.88 (m, 1 H, H-4'), 3.58 (d, 2 H, CH_2, J = 4.9 Hz), 3.58-3.46 (m, 2 H, H-5'a, b). *Anal.* Calcd for $C_{11}H_{15}N_5O_5 \cdot 3/4H_2O$: C, 42.51; H, 5.35; N, 22.54. Found: C, 42.81; H, 5.12; N, 22.49.

Physical data for **18**: FAB-MS *m/z* 316 (M^++1); UVλ_{max} (H_2O) 269 nm (ε 12700); UVλ_{max} (0.5 N HCl) 270 nm (ε 10800), 249 nm (ε 8900); UVλ_{max} (0.5 N NaOH) 271 nm (ε 13200); ^{1}H-NMR (DMSO-d_6) 7.44 (t, 1 H, NH, J = 5.5 Hz), 7.34 (s, 1 H, H-2), 7.31, 7.02 (each br s, each 1 H, $CONH_2$), 5.91 (br s, 2 H, NH_2), 5.47 (d, 1 H, H-1', $J_{1',2'}$ = 6.6 Hz), 5.39 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 6.6 Hz), 5.30 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'a} = J_{5'\text{-OH},5'b}$ = 5.1 Hz), 5.20 (d, 1 H, 3'-OH, $J_{3'\text{-OH},3'}$ = 4.4 Hz), 4.27 (m, 1 H, H-2'), 4.04 (m, 1 H, H-3'), 3.90 (m, 1 H, H-4'), 3.75 (d, 2 H, CH_2, J = 5.5 Hz), 3.59 (m, 2 H, H-5'a, b). *Anal.* Calcd for $C_{11}H_{17}N_5O_6 \cdot 3/2H_2O$: C, 38.60; H, 5.89; N, 20.46. Found: C, 38.92; H, 5.62; N, 20.45.

2',3'-*O*-Isopropylidene-5'-*O*-triphenylmethyl-1-phenacylinosine (19). Phenacyl bromide (1.08 g, 5.44 mmol) was added to a solution of **4** (1.50 g, 2.72 mmol) in dry THF (20 mL) containing K_2CO_3 (750 mg, 5.44 mmol) and 18-crown-6 (71 mg, 0.27 mmol) and the resulting mixture was stirred for 5 hr at room temperature. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.8 x 9 cm), eluted with hexane : AcOEt (1:1-1:2), to give **19** (1.42 g, 78%) as a yellow oil. An analytical sample was crystallized from EtOH-$CHCl_3$ as white crystals: mp 246-248 °C; MS *m/z* 669 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.11-8.01 (m, 2 H, *o*-Ph), 7.86, 7.72 (each s, each 1 H, H-2, 8), 7.63-7.02 (m, 18 H, *m*, *p*-Ph, trityl), 6.10 (d, 1 H, H-1', $J_{1',2'}$ = 2.4 Hz), 5.53 (s, 1 H, CHa), 5.44 (s, 1 H, CHb), 5.29 (dd, 1 H, H-2', $J_{2',1'}$ = 2.4, $J_{2',3'}$ = 6.4 Hz), 4.90 (dd, 1 H, H-3', $J_{3',4'}$ = 3.2, $J_{3',2'}$ = 6.4 Hz), 4.50 (m, 1 H, H-4'), 3.35 (m, 2 H, H-5'a, b), 1.63, 1.40 (each s, each 3 H, isoPr). *Anal.* Calcd for $C_{40}H_{36}N_4O_6$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.76; H, 5.37; N, 8.35.

5-Amino-1-(2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-β-D-ribofuranosyl)imidazole-4-(*N*-phenacyl)carboxamide (20) and 6,7-dihydro-5-phenyl-3-(2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-β-D-ribofuranosyl)-

imidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one (21). Five N NaOH (3 mL) was added to a solution of **19** (600 mg, 0.90 mmol) in EtOH (10 mL) and the solution was heated under reflux for 2 hr. The cooled mixture was neutralized with 1 N HCl and concentrated to dryness *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O. The separated organic layer was dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was purified by a silica gel column (2.2 x 7 cm), eluted with 1-4% EtOH in $CHCl_3$, to give **20** (76.6 mg, 13%) as a yellow oil and **21** (289 mg, 50%) as a yellow foam.

Physical data for **20**: MS *m/z* 658 (M^+); ^{1}H-NMR ($CDCl_3$) 8.03-7.99, 7.63-7.23 (m, 21 H, trityl, Ph, NH), 7.07 (s, 1 H, H-2), 5.59 (d, 1 H, H-1', $J_{1',2'}$ = 3.7 Hz), 5.18 (br s, 2 H, NH_2), 5.05 (dd, 1 H, H-2', $J_{2',1'}$ = 3.7, $J_{2',3'}$ = 6.6 Hz), 4.94 (dd, 1 H, H-3', $J_{3',4'}$ = 4.0, $J_{3',2'}$ = 6.6 Hz), 4.88 (d, 2 H, CH_2, J = 4.8 Hz), 4.22 (m, 1 H, H-4'), 3.45 (m, 2 H, H-5'a, b), 1.57, 1.37 (each s, each 1 H, isoPr).

Physical data for **21**: MS *m/z* 640 (M^+); ^{1}H-NMR ($CDCl_3$) 7.80 (s, 1 H, H-2), 7.95-7.21 (m, 21 H, Ph, trityl, NH), 6.17 (d, 1 H, H-1', $J_{1',2'}$ = 2.8 Hz), 5.10 (dd, 1 H, H-2', $J_{2',1'}$ = 2.8, $J_{2',3'}$ = 6.0 Hz), 4.73 (dd, 1 H, H-3', $J_{3',4'}$ = 3.3, $J_{3',2'}$ = 6.0 Hz), 4.44 (dt, 1 H, H-4', $J_{4',3'}$ = 3.3, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.7 Hz), 4.26 (dd, 1 H, H-5'a, $J_{5'a,4'}$ = 4.7, $J_{5'a,b}$ = 15.4 Hz), 4.00 (dd, 1 H, H-5'b, $J_{5'b,4'}$ = 4.7, $J_{5'a',b}$ = 15.4 Hz), 3.27 (d, 2 H, H-6, J = 5.4 Hz), 1.62, 1.37 (each s, each 3 H, isoPr).

6,7-Dihydro-5-phenyl-3-β-D-ribofuranosylimidazo[4,5-*e*][1,4]diazepin-8(3*H*)-one (22) and 5-amino-1-β-D-ribofuranosylimidazole-4-(*N*-phenacyl)carboxamide (23). An aqueous TFA solution (70%, 5 mL) containing **21** (309 mg, 0.48 mmol) was stirred for 2 hr at 0 °C. The solvent was removed *in vacuo* and coevaporated several times with EtOH. The residue was purified by a silica gel column (1.8 x 10 cm), eluted with 8-16% MeOH in $CHCl_3$, to give **23** (62.9 mg, 34%) as a yellow solid and **22** (82.5 mg, 48%) as an orange solid. Compound **22** was crystallized from MeOH-H_2O as white crystals and **23** was crystallized from MeOH as bright yellow crystals.

Physical data for **22**: mp 204-205 °C; UVλ_{max} (H_2O) 337 nm (ε 10500); UVλ_{max} (0.5 N HCl) 320 nm (ε 10800), 245 nm (ε 8800); UVλ_{max} (0.5 N NaOH) 341 nm (ε 7600), 248 nm (ε 11900); FAB-MS *m/z* 359 (M^++1); ^{1}H-NMR (DMSO-d_6) 8.20 (s, 1 H, H-2), 8.10 (m, 2 H, *o*-Ph), 7.79 (t, 1 H, NH, J = 5.4 Hz), 7.57 (m, 3 H, *m*, *p*-Ph), 5.89 (d, 1 H, H-1', $J_{1',2'}$ = 4.9 Hz), 5.48 (d, 1 H, 2'-OH, $J_{2'\text{-OH},2'}$ = 5.9 Hz), 5.20

(d, 1 H, 3'-OH, $J_{3'\text{-OH},\ 3'}$ = 4.9 Hz), 5.05 (m, 1 H, 5'-OH), 4.37 (dt, 1 H, H-2', $J_{2',\ 1'} = J_{2',\ 3'}$ = 4.9, $J_{2',\ 2'\text{-OH}}$ = 5.9 Hz), 4.11 (m, 3 H, H-3', CH_2, $J_{3',\ 2'} = J_{3',\ 3'\text{-OH}}$ = 4.9, $J_{3',\ 4'}$ = 3.9 Hz), 3.92 (dt, 1 H, H-4', $J_{4',\ 3'}$ = 3.9, $J_{4',\ 5'a} = J_{4',\ 5'b}$ = 3.4 Hz), 3.65 (m, 1 H, H-5'a, $J_{5'a,\ 4'}$ = 3.4, $J_{5'a,\ b}$ = 12.2 Hz), 3.55 (m, 1 H, H-5'b, $J_{5'b,\ 4'}$ = 3.4, $J_{5'a,\ b}$ = 12.2 Hz). *Anal.* Calcd for $C_{17}H_{18}N_4O_5 \cdot 1/2H_2O$: C, 55.58; H, 5.21; N, 15.25. Found: C, 55.35; H, 5.28; N, 15.18.

Physical data for **23**: mp 192-194 °C; UVλ_{max} (H_2O) 259 nm (ε 18600); UVλ_{max} (0.5 N HCl) 250 nm (ε 19600); UVλ_{max} (0.5 N NaOH) 341 nm (ε 7500), 248 nm (ε 12500); MS *m/z* 376 (M^+); ^{1}H-NMR (DMSO-d_6) 8.01 (m, 2 H, *o*-Ph), 7.70-7.41 (m, 5 H, H-2, NH, *m*, *p*-Ph), 5.93 (br s, 2 H, NH_2), 5.50 (d, 1 H, H-1', $J_{1',\ 2'}$ = 6.2 Hz), 5.21 (m, 3 H, 2', 3', 5'-OH), 4.70 (d, 2 H, CH_2, *J* = 5.5 Hz), 4.30 (m, 1 H, H-2', $J_{2',\ 1'}$ = 6.2, $J_{2',\ 3'}$ = 5.1 Hz), 4.06 (m, 1 H, H-3', $J_{3',\ 2'}$ = 5.1, $J_{3',\ 4'}$ = 2.9 Hz), 3.91 (m, 1 H, H-4'), 3.59 (m, 2 H, H-5'a, b). *Anal.* Calcd for $C_{17}H_{20}N_4O_6 \cdot 1/2H_2O$: C, 52.98; H, 5.49; N, 14.54. Found: C, 52.81; H, 5.31; N, 14.30.

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