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Synthesis of L-ribofuranosyl *C*-nucleosides

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Abstract

C-Nucleosides, 4-amino-8-(β-L-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine (**12**) and 4-amino-7-(β-L-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (L-9-deazaadenosine, **22**), were synthesized from the key intermediate, 3-dimethylamino-2-(2,3-*O*-isopropylidene-5-*O*-trityl-L-ribofuranosyl)acrylonitrile (**8**), which was prepared from L-xylose in 11 steps. © 1997 Elsevier Science Ltd.

Keywords: L-9-Deazaadenosine; L-*C*-Nucleoside; Antiviral agents

1. Introduction

Recently, a number of L-nucleosides have been synthesized as potential antiviral agents, in which (−)-(2′*R*,5′*S*)-1-(2-hydroxymethyloxathiolan-5-yl)cytosine (3TC, lamivudine) [1–3], (−)-β-L-2′,3′-dideoxy-5-fluoro-3′-thiocytidine (FTC) [4], β-L-2′,3′-dideoxy-5-fluorocytidine (L-FddC) [5,6] and 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-methyluracil (L-FMAU) [7] have been found to be the most interesting and promising L-nucleosides. 3TC has been already approved as an anti-HIV drug by the FDA, and several L-nucleosides are currently undergoing preclinical and clinical trials as anti-HIV and/or anti-HBV agents. [1]

C-Nucleosides have been of interest as a unique class of compounds that contain a C–C bond instead of the C–N bond between the carbohydrate and heterocyclic moiety, which stabilizes the glycosylic bond, resulting in a different biological profile. Some of the *C*-nucleosides have shown very interesting biological activities [8]. For example, 9-deazaadenosine was reported to be a potent antibacterial and antifungal agent [9], and another isostere of adenosine, 4-amino-8-β-D-ribofuranosylpyrazolo[1,5-*a*]-1,3,5-triazine (D-APTR), has also shown antileukemic activity [10,11]. As part of our ongoing drug discovery program, herein we wish to report the synthesis of L-APTR and L-9-deazaadenosine.

2. Results and discussion

Chemistry.—The synthesis of L-APTR was accomplished from the key intermediate **8** according to the methodology developed for its D-isomer by Tam et al. [10,11] (Scheme 1). Due to the limited availability of L-ribose, we have developed an efficient synthetic procedure for the preparation of **8** from the

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[1] HIV = Human immunodeficiency virus, and HBV = hepatitis B virus.

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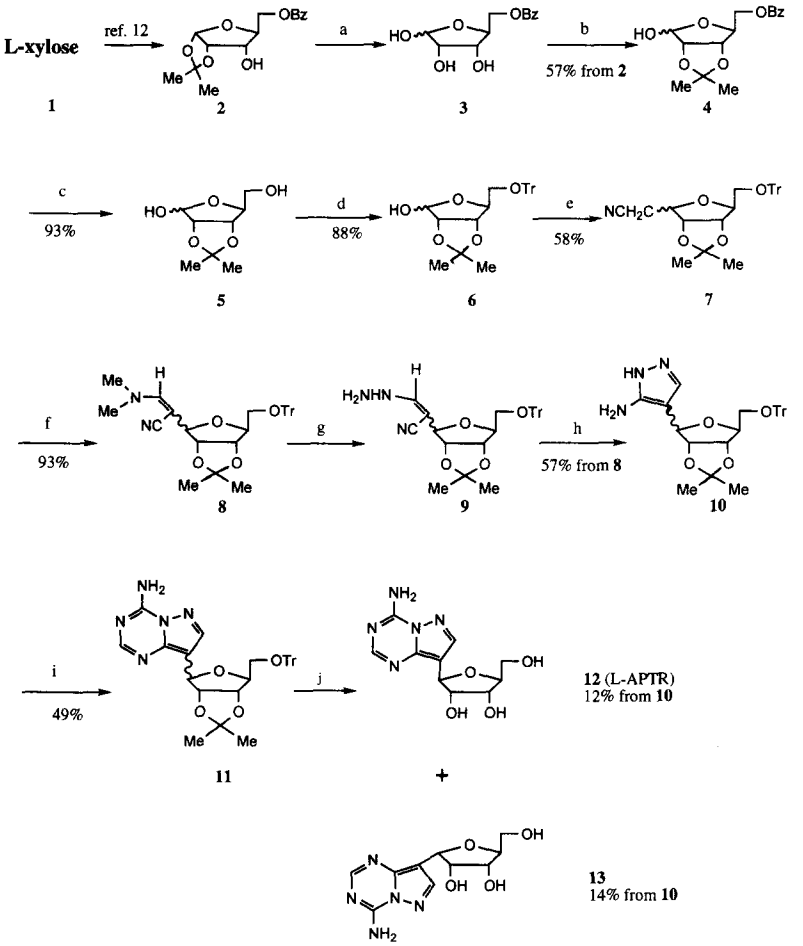
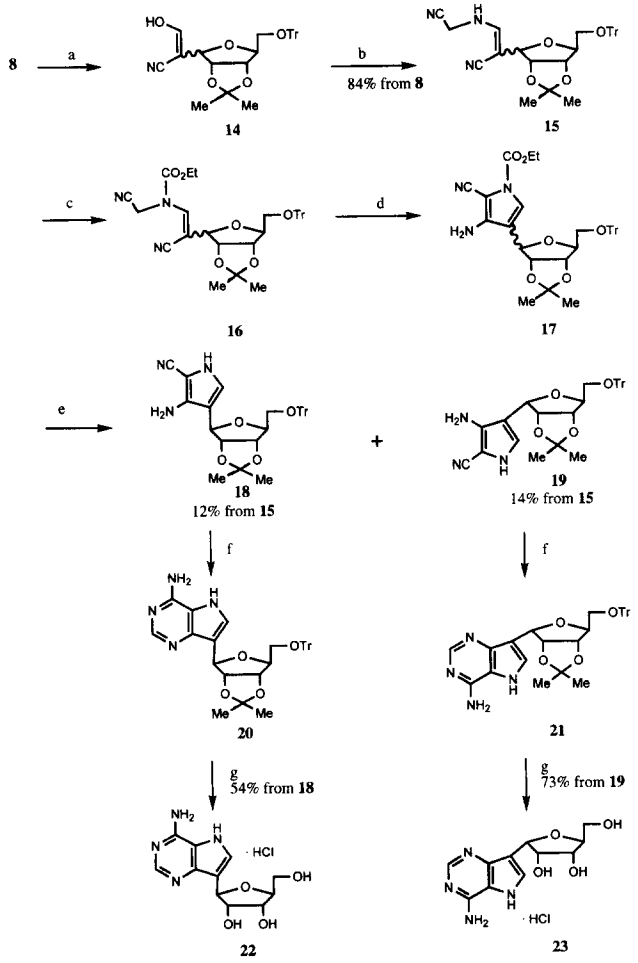
readily available starting material, L-xylose. Thus, 5-*O*-benzoyl-1,2-*O*-isopropylidene-L-ribofuranose (**2**) was prepared from L-xylose (**1**) in five steps using the procedure recently reported by us [12]. The hydrolysis of the 1,2-*O*-isopropylidene group of **2** in formic acid (85%) gave 5-*O*-benzoyl-L-ribofuranose (**3**), which was subjected to the selective 2,3-*O*-isopropylidenation in acetone catalyzed by concentrated H_2SO_4 in the presence of 2,2-dimethoxypropane to give 5-*O*-benzoyl-2,3-*O*-isopropylidene-L-ribofuranose (**4**). Compound **5**, obtained by debenzoylation of **4** with NaOH, was treated with trityl chloride in pyridine to give the protected L-ribose **6**, which was further treated with diethyl cyanomethylenephosphonate, followed by the formylation with bis(dimethylamino)-*tert*-butyloxymethane, to give the key intermediate **8** in good yield. A silica gel column pretreated with Et_3N was used for the purification of **8** due to its instability in acid, even in silica gel. The treatment of **8** with hydrazine and hydrazine monohydrochloride in refluxing aqueous ethanol gave compound **9**, which was cyclized in refluxing acetonitrile to yield aminopyrazole **10** as a mixture of α and β anomers. The reaction of **10** with methyl *N*-cyanoformimidate in refluxing benzene gave an anomeric mixture of **11**, which was deprotected with methanolic hydrogen chloride to obtain the free nucleosides, L-APTR (**12**) and its α isomer **13**, after column chromatography. The structure and stereochemistry were assigned based on the comparison of their spectroscopic and physical data to those of the known D-isomers [10,11].

The procedure published by Lim et al. [9] was utilized for the synthesis of L-9-deazaadenosine. Selective hydrolysis of **8** with aqueous trifluoroacetic acid gave **14**, which was condensed with aminoacetonitrile hydrochloride in the presence of sodium acetate to obtain enamine **15** (Scheme 2). *N*-Protec-



Scheme 1. Reagents and conditions: (a) 85% HCO_2H; (b) acetone, concd H_2SO_4, $CH_3C(OMe)_2CH_3$; (c) NaOH, MeOH; (d) TrCl, py; (e) $(EtO)_2OPCH_2CN$, DME; (f) *t*-BuOCH[$N(CH_3)_2$]$_2$, Me_2NCHO, CH_2Cl_2; (g) NH_2NH_2, $NH_2NH_2 \cdot HCl$, MeOH, H_2O; (h) CH_3CN, reflux; (i) $NCNHCHOCH_3$; (j) 10% HCl, MeOH.



Scheme 2. Reagents and conditions: (a) CF_3CO_2H, $CHCl_3$; (b) $NCCH_2NH_2 \cdot HCl$, NaOAc; (c) $ClCO_2Et$, DBN; (d) DBN, MeOH; (e) Na_2CO_3, MeOH; (f) $NH_2CH = NH \cdot AcOH$, EtOH; (g) 12% HCl, MeOH.

tion of **15** by reaction of ethyl chloroformate in the presence of 1,5-diazabicyclo[4,3,0]non-5-ene (DBN), followed by cyclization catalyzed with DBN, yielded aminopyrrole **17** as a mixture of α and β anomers. The individual isomers **18** and **19** were obtained by the treatment of **17** with sodium carbonate in methanol, followed by silica gel chromatography. The assignment of stereochemistry of **18** and **19** was based on the comparison of their ^1H NMR spectra to those of the corresponding D-isomers, in which the difference of chemical shifts ($\Delta\delta$ 0.18) between the two methyl groups of the *O*-isopropylidene moiety in the α-isomer **19** is smaller than that of the β-isomer **18** ($\Delta\delta$ 0.21). Condensation of **18** and **19** with formamidine acetate in absolute ethanol gave the corresponding pyrrolo[3,2-*d*]pyrimidine derivatives **20** and **21**, respectively. A smaller difference of chemical shifts between the two methyl groups in α-isomer **21** ($\Delta\delta$ 0.19) compared to that in β-isomer **20** ($\Delta\delta$ 0.22) was also observed, which was consistent with those described above as well as others reported for D-ribofuranosylpurine nucleosides [9,13]. The desired nucleosides L-9-deazaadenosine hydrochloride salt (**22**) and its α isomer (**23**) were obtained by deprotection of **20** and **21** with methanolic hydrogen chloride at room temperature, followed by recrystallization from ethanol.

Biological studies.—The anti-HBV and anti-HIV activities of the synthesized L-*C*-nucleosides were evaluated in 2.2.15 and PBM cells, respectively. No significant activities were observed up to 100 μM. The toxicities of the synthesized nucleosides were also assessed in CEM and PBM cells, and these compounds did not exhibit any significant toxicities with concentrations up to 100 μM.

3. Experimental

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker 250 or 300 MHz spectrometer with tetramethylsilane as the internal reference, and chemical shifts (δ) are reported in parts per million. UV spectra were obtained on a Beckman DU-7 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. TLC was performed on Uniplates (silica gel) purchased from Analtech Co.

5-O-Benzoyl-2,3-O-isopropylidene-L-ribofuranose (**4**).—A mixture of **2** [12] (10.0 g, 34.0 mmol) in formic acid (85%, 250 mL) was stirred at rt for 16 h and then concentrated to dryness under reduced pressure. The residue was coevaporated with toluene twice to obtain crude **3** as a syrup. Acetone (150 mL), sulfuric acid (0.5 mL) and 2,2-dimethoxypropane (50 mL) were added to the crude **3**, and the mixture was stirred at rt for 2 h and quenched with saturated $NaHCO_3$. Solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by silica gel column chromatography (1:3 EtOAc–hexanes) to give **4** as a mixture of α and β anomers: ^1H NMR ($CDCl_3$): δ 8.11, 7.43 (m, 5 H, Ar), 5.90 and 5.52 (d, *J* 3.6 Hz and s, 1 H, H-1), 4.90, 4.34 (m, 5 H, H-2, H-3, H-4, H-5), 3.25 (br s, 1 H, D_2O exchangeable, anomeric OH), 1.59, 1.51, 1.37, 1.35 (4 × s, 6 H, CMe_2). Anal.

Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.12. Found: C, 61.28; H, 6.10.

2,3-O-Isopropylidene-L-ribofuranose (**5**).—To a suspension of NaOH (15.0 g, 380 mmol) in MeOH (150 mL), compound **4** (25.0 g, 85.0 mmol) was added and stirred at rt for 6 h and then concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (20:1 $CHCl_3$–MeOH) to give **5** (15 g, 92.8%) as a mixture of α and β anomers: ^{1}H NMR (DMSO-d_6): δ 6.48 and 5.00 (d, 1 H, D_2O exchangeable, anomeric OH), 5.64 and 5.14 (d, J 3.6 Hz and s, 1 H, H-1), 4.92 and 4.65 (t, 1 H, D_2O exchangeable, 5-OH), 4.66 and 4.42 (br d, 1 H, H-2), 4.03, 3.60 (m, 2 H, H-3, H-4), 3.44, 3.29 (m, 2 H, H-5), 1.42, 1.35, 1.24, 1.22 (4 × s, 6 H, CMe_2). Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.37. Found: C, 50.48; H, 7.29.

2,3-O-Isopropylidene-5-O-trityl-L-ribofuranose (**6**).—To a solution of **5** (15.0 g, 80.0 mmol) in pyridine (100 mL), trityl chloride (27.0 g, 100 mmol) was added and heated at 80 °C for 6 h. Pyridine was evaporated under reduced pressure, and the residue was redissolved in EtOAc (250 mL). The solution was washed successively with H_2O, brine and dried (Na_2SO_4). The solvent was removed, and the residue was chromatographed on a silica gel column (4:1 hexanes–EtOAc) to obtain **6** (30.0 g, 87.9%) as a mixture of α and β anomers: ^{1}H NMR ($CDCl_3$): δ 7.47, 7.29 (m, 15 H, Ar), 5.89 and 5.33 (d, J 3.8, 7.9 Hz, 1 H, H-1), 4.79, 4.58 (m, 1 H, H-2), 4.02, 3.89 (m, 2 H, H-3, H-4), 3.44, 3.26 (m, 2 H, H-5), 2.30 (br s, 1 H, D_2O exchangeable, anomeric OH), 1.57, 1.48, 1.37, 1.34 (4 × s, 6 H, CMe_2). Anal. Calcd for $C_{27}H_{28}O_5$: C, 75.00; H, 6.48. Found: C, 75.03; H, 6.49.

3,6-Anhydro-2-deoxy-4,5-O-isopropylidene-7-O-trityl-L-allo- and L-altro-septononitrile (**7**).—To a suspension of NaH (95%, 2.5 g, 100 mmol) in dry 1,2-dimethoxyethane (DME, 500 mL), diethyl cyanomethylenephosphonate (20 mL, 126 mmol) was added dropwise at 0 °C under argon within 20 min. After evolution of H_2 ceased, compound **6** (30.0 g, 69 mmol) in dry DME (200 mL) was added to the resulting solution within 30 min and then stirred at rt for 2 h under argon. The reaction mixture was partitioned between Et_2O (2 L) and H_2O (1 L), and the aqueous layer was extracted with Et_2O (1 L). The combined extracts were washed with H_2O and dried (Na_2SO_4). The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (4:1 hexanes–EtOAc) to give **7** as a syrup of a mixture of α and β anomers (18.4 g, 58.2%), which was used directly for the next reaction without further separation. Anal. Calcd for $C_{29}H_{29}NO_4$: C, 76.48; H, 6.37; N, 3.07. Found: C, 76.40; H, 6.41; N, 3.01.

(2E)-3,6-anhydro-2-deoxy-2-C-[(N,N-dimethylamino)methylidene]-4,5-O-isopropylidene-7-O-trityl-L-allo- and L-altro-septononitrile (**8**).—To a mixture of **7** (11.0 g, 24.0 mmol) in CH_2Cl_2 (50 mL) and dry DMF (2 mL), bis(dimethylamino)-*tert*-butoxymethane (16.7 g, 96.0 mmol) was added and stirred at rt for 20 h. After removal of the solvents, the residue was chromatographed on a silica gel column pretreated with Et_3N (20:1 CH_2Cl_2–MeOH) to obtain **8** (11.5 g, 93.4%) as a hygroscopic syrup of a mixture of α and β anomers: ^{1}H NMR ($CDCl_3$): δ 7.50–7.28 (m, 15 H, Ar), 6.60, 6.55 (2 × s, 1 H, CHN), 4.64 (m, 2 H, H-1′, H-4′), 4.52 (m, 2 H, H-2′, H-3′), 4.13 (2 m, 2 H, CH_2OTr), 3.17 (s, 3 H, NCH_3), 3.08 (s, 3 H, NCH_3), 1.56, 1.53, 1.25, 1.22 (4 × s, 6 H, CMe_2). Anal. Calcd for $C_{32}H_{34}N_2O_4 \cdot 0.6H_2O$: C, 73.67; H, 6.77; N, 5.36. Found: C, 73.57; H, 6.86; N, 5.08.

3-Amino-4-(2,3-O-isopropylidiene-5-O-trityl-L-ribofuranosyl)pyrazole (**10**).—A mixture of dimethylaminoacrylonitrile **8** (2.2 g, 4.3 mmol), MeOH (15 mL), anhydrous hydrazine (3.2 mL, 0.10 mol), H_2O (0.5 mL) and hydrazine monohydrochloride (0.43 g, 6.3 mmol) was heated at reflux for 20 h and concentrated to dryness in vacuo, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed to afford the hydrazine **9** as a yellow syrup that was redissolved in CH_3CN (50 mL) and heated at reflux for 16 h. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was purified by silica gel column chromatography (100:3 CH_2Cl_2–MeOH) to give **10** as a mixture of α and β mixture (1.12 g, 57.1%), which was used directly for the next reaction without further purification. Anal. Calcd for $C_{30}H_{31}N_3O_4 \cdot H_2O$: C, 69.82; H, 6.40; N, 8.15. Found: C, 69.87; H, 6.25; N, 8.21.

4-Amino-8-(β-L-ribofuranosyl)pyrazolo[1,5-a]-1,3,5-triazine (**12**) *and 4-amino-8-(α-L-ribofuranosyl)pyrazolo[1,5-a]-1,3,5-triazine* (**13**).—To a solution of methyl *N*-cyanoformimidate (800 mg, 8.8 mmol) in benzene (8 mL), a solution of **10** (1.0 g, 2.0 mmol) in benzene (20 mL) was slowly added and heated at reflux for 5 h. The solvent was evaporated to afford a syrup that was treated with H_2O (10 mL). After stirring for 5 min, the aqueous layer was discarded. The resulting solid was redissolved in $CHCl_3$

(50 mL), washed with H_2O, brine and dried (Na_2SO_4). Evaporation of the solvent gave a syrup that was purified by silica gel column chromatography (4:1 EtOAc–hexanes) to afford **11** (0.54 g, 48.9%) as a mixture of α and β anomers. A solution of HCl in MeOH (10%, 5 mL) was slowly added to a solution of **11** (600 mg, 1.10 mmol) in MeOH (5 mL), and the solvent was immediately evaporated to dryness under reduced pressure at rt. The residue was redissolved in MeOH (20 mL), neutralized with $NaHCO_3$ and filtered. The MeOH was evaporated, and the residue was purified by silica gel column chromatography (1:5 MeOH–$CHCl_3$) to obtain **12** (36 mg, 12%) as white crystals and **13** (42 mg, 14%) as a white solid after recrystallization from MeOH.

Compound **12**: mp 218–220 °C; $[\alpha]_D^{27}$ +47.17° (*c* 0.11, H_2O); UV (H_2O) λ_{max} 273.0 nm (ε 9484, pH 11), 273.5 nm (ε 9302, pH 7), 268.5 nm (ε 6078, pH 2); ^1H NMR (DMSO-d_6): δ 8.48 (br s, 2 H, NH_2, D_2O exchangeable), 8.19 (s, 1 H, H-7), 8.06 (s, 1 H, H-2), 4.84 (d, 1 H, *J* 7.0 Hz, H-1′), 4.21 (dd, 1 H, *J* 7.0 Hz, 5.3 Hz, H-2′), 3.96 (m, 1 H, H-3′), 3.80 (m, 1 H, H-4′), 3.54 (m, 2 H, H-5′). Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.91; H, 4.99; N, 26.13.

Compound **13**: mp 142–143 °C; $[\alpha]_D^{27}$ +41.16° (*c* 0.09, H_2O); UV (H_2O) λ_{max} 273.0 nm (ε 8185, pH 11), 272.7 nm (ε 7108, pH 7), 264.2 nm (ε 4743, pH 2); ^1H NMR (DMSO-d_6): δ 8.51 (br s, 2 H, NH_2, D_2O exchangeable), 8.17 (s, 1 H, H-7), 8.05 (s, 1 H, H-2), 5.21 (d, 1 H, *J* 3.0 Hz, H-1′), 4.22 (m, 1 H, H-3′), 3.96 (m, 1 H, H-2′), 3.80 (m, 1 H, H-4′), 3.54 (m, 2 H, H-5′). Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C, 43.44; H, 5.06; N, 25.64. Found: C, 43.28; H, 4.97; N, 25.84.

(2E)-3,6-anhydro-2-deoxy-2-C-[(cyanomethyleneamino)methylidene]-4,5-O-isopropylidene-7-O-trityl-L-allo- *and* L-altro-*septononitrile* (**15**).—To a solution of dimethylaminoacrylonitrile (**8**, 6.0 g, 11.8 mmol) in chloroform (120 mL), a solution of trifluoroacetic acid (3 mL) in water (200 mL) was added, and the mixture was stirred vigorously at rt for 16 h. The organic layer was washed with water and dried (Na_2SO_4). Removal of solvent afforded 2-formylacetonitrile **14** as a foam which was redissolved in a mixture of methanol (50 mL) and water (3 mL). To this solution, aminoacetonitrile hydrochloride (1.4 g, 15.3 mmol) and sodium acetate trihydrate (2.4 g, 17.6 mmol) were added and stirred at rt for 16 h. Solvents were evaporated, and the residue was redissolved in $CHCl_3$ (100 mL), washed with water and dried (Na_2SO_4). Pure compound **15** (5.2 g, 83.8%) was obtained after silica gel column chromatography (20:1 $CHCl_3$–MeOH) and used in the next reaction without further purification.

*3-Amino-2-cyano-4-(2,3-O-isopropylidene-5-O-trityl-β-*L*-ribofuranosyl)pyrrole* (**18**) *and 3-amino-2-cyano-4-(2,3-O-isopropylidene-5-O-trityl-α-*L*-ribofuranosyl)pyrrole* (**19**).—To a magnetically stirred solution of enamine **15** (5.2 g, 0.01 mol) and 1,5-diazabicyclo[4,3,0]non-5-ene (DBN, 0.6 g, 16.5 mmol) in dichloromethane (60 mL) was added ethyl chloroformate (1.78 g, 16.5 mmol), and the mixture was stored at 0 °C for 16 h to give **16**. Additional DBN (4 mL) was added to the reaction mixture, and the mixture was stirred at rt for 20 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography (3:1 hexanes–EtOAc) to obtain **17** as an oil, which was treated with Na_2CO_3 (1.5 g) in MeOH (50 mL) at rt for 1 h. The solvent was evaporated, and the residue was chromatographed on a silica gel column (3:1 hexanes–EtOAc) to give **18** (0.6 g, 11.5%) as a foam and **19** (0.7 g, 13.5%) as white crystals.

Compound **18**: $[\alpha]_D^{25}$ +28.73° (*c* 0.23, MeOH); UV (MeOH) λ_{max} 248.0 nm; ^1H NMR ($CDCl_3$): δ 7.87 (s, 1 H, NH, D_2O exchangeable), 7.22–7.43 (m, 15 H, Ar), 6.62 (d, 1 H, *J* 3.29 Hz, H-5), 4.79 (m, 2 H, H-2′, H-3′), 4.74 (d, 1 H, *J* 4.05 Hz, H-1′), 4.17 (m, 1 H, H-4′), 4.00 (br s, 2 H, NH_2, D_2O exchangeable), 3.42 (dd, 1 H, *J* 3.2, 10.3 Hz, H-5′$_a$), 3.32 (dd, 1 H *J* 3.8, 10.3 Hz, 1 H, H-5′$_b$), 1.57, 1.36, (2 × s, 3 H, CH_3). Anal. Calcd for $C_{32}H_{31}N_3O_4$: C, 73.61; H, 5.94; N, 8.05. Found: C, 73.89; H, 6.12; N, 7.88.

Compound **19**: mp 176–178 °C; $[\alpha]_D^{25}$ +8.84°(*c*, 0.14, MeOH); UV (MeOH) λ_{max} 247.7 nm; ^1H NMR ($CDCl_3$): δ 7.89 (s, 1 H, NH, D_2O exchangeable), 7.21–7.44 (m, 15 H, Ar), 6.78 (d, 1 H, *J* 3.3 Hz, H-5), 5.15 (d, 1 H, *J* 3.5 Hz, H-1′), 4.79 (m, 2 H, H-2′, H-3′), 4.27 (m, 1 H, H-4′), 4.03 (br s, 2 H, NH_2, D_2O exchangeable), 3.35 (dd, 1 H, *J* 4.0, 10.1 Hz, H-5′$_a$), 3.21 (dd, 1 H, *J* 4.5, 10.1 Hz, H-5′$_b$), 1.52, 1.34, (2 × s, 3 H, CH_3). Anal. Calcd for $C_{32}H_{31}N_3O_4$: C, 73.61; H, 5.94; N, 8.05. Found: C, 73.78; H, 6.10; N, 7.86.

*4-Amino-7-(β-*L*-ribofuranosyl)-5H-pyrrolo[3,2-d]pyrimidine hydrochloride* (**22**).—A mixture of **18** (0.6 g, 1.15 mmol) and formamidine acetate (0.36 g, 3.45 mmol) in anhydrous EtOH (15 mL) was heated at reflux for 5 h. The EtOH was evaporated, and the residue was chromatographed on a silica gel column (20:1 $CHCl_3$–MeOH) to give **20** (0.6 g, 95.2%) as a syrup. A suspension of **20** (0.5 g, 0.91 mmol) in methanolic hydrogen chloride (12%, 10 mL) was

stirred at rt for 2 h, and the precipitate was collected by filtration. The white solid was recrystallized from EtOH to afford **22** (0.22 g, 57.0%): $[\alpha]_D^{25}$ +39.97° (*c* 0.19, MeOH); UV (MeOH) λ_{max} 273.7 nm (ε 6579, pH 2), 273.5 nm (ε 6330, pH 7), 274.0 nm (ε 6304, pH 11); ^{1}H NMR (DMSO-d_6): δ 11.51 (br s, 1 H, NH, D_2O exchangeable), 8.93 (br s, 2H, NH_2, D_2O exchangeable), 8.49 (s, 1 H, H-2), 7.85 (s, 1 H, H-6), 4.86 (d, 1 H, *J* 6.50 Hz, H-1′), 3.87–4.00 (m, 3 H, H-2′, H-3′, H-4′), 3.62 (d, 2 H, H-5). Anal. Calcd for $C_{11}H_{15}ClN_4O_4$: C, 43.63; H, 4.95; N, 18.51. Found: C, 43.40; H, 4.95; N, 18.29.

*4-Amino-7-(α-*L*-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine hydrochloride* (**23**).—The title compound was obtained by using a procedure similar to that described for **22**. From **19** (0.50 g, 0.96 mmol) compound **21** was obtained as a syrup (0.50 g, 94.3%); compound **23**, as a solid after recrystallization from EtOH (0.20 g, 72.8%): $[\alpha]_D^{25}$ 43.17° (*c* 0.15, MeOH); UV (H_2O) λ_{max} 273.5 nm (ε 6881, pH 2), 268.0 nm (ε 5029, pH 7), 273.5 nm (ε 5389, pH 11); ^{1}H NMR (DMSO-d_6): δ 11.39 (br s, 1 H, NH, D_2O exchangeable), 8.99, 8.92 (2s, 2 H, NH_2, D_2O exchangeable), 8.45 (s, 1 H, H-2), 7.78 (d, 1 H, H-6), 5.15 (d, 1 H, *J* 3.25 Hz, H-1′), 3.97–4.21 (m, 3 H, H-2′, H-3′, H-4′), 3.58–3.62 (m, 2 H, H-5′). Anal. Calcd for $C_{11}H_{15}ClN_4O_4$: C, 43.63; H, 4.95; N, 18.51. Found: C, 43.70; H, 4.93; N, 18.40.

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