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Synthesis of Several Pyrimidine L-Nucleoside Analogues as Potential Antiviral Agents

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Abstract: β-L-5-Iodo-2'-deoxyuridine (β-L-IUdR, **7**) and 1-[(β-L-arabinofuranosyl)-*E*-5-(2-bromovinyl)]uracil (β-L-BV-ara-U, **10**) have been synthesized via a multi-step synthesis from L-arabinose. 2',3'-Dideoxy-β-L-5-azacytidine (**18**), 2',3'-dideoxy-β-L-2-thiocytidine (**20**) and their respective α-anomers, compounds **19** and **21**, also were synthesized by direct coupling of 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (**13**) with the corresponding silylated bases, in the presence of $EtAlCl_2$ in CH_2Cl_2, followed by separation of the α- and β-isomers and deblocking of the 5'-protecting groups. In addition, 2',3'-dideoxy-β-L-5-fluorocytidine (**34**), a potent anti-HIV and anti-HBV agent, was synthesized by an alternative methodology from 2',3'-dideoxy-β-L-5-fluorouridine (**31**) via a 4-triazolylpyrimidinone intermediate. These L-nucleoside analogues were tested *in vitro* against HIV, HBV, HSV-1, and HSV-2. Among these compounds, 2',3'-dideoxy-β-L-5-azacytidine (**18**) was found to show significant activity against HBV *in vitro* at approximately the same level as 2',3'-dideoxy-β-D-cytidine (ddC), which is a known potent anti-HBV agent.

INTRODUCTION

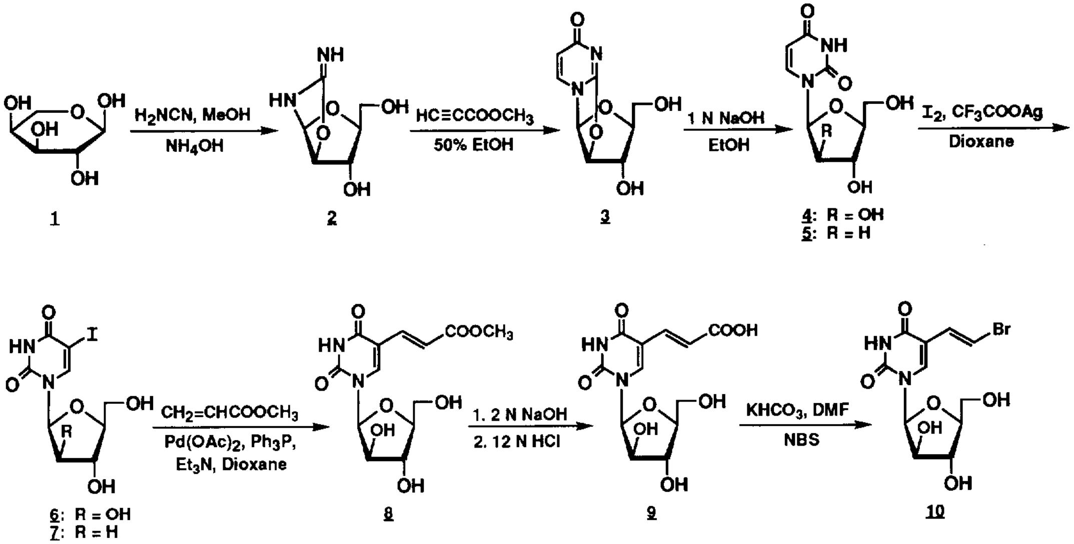
β-D-5-Iodo-2'-deoxyuridine (Idoxuridine, IUdR) was first synthesized by Prusoff[1] in 1959 and shown to be active *in vitro* against various DNA viruses.[2] Later, Idoxuridine was approved by FDA as the first nucleoside antiviral chemotherapeutic agent to be licensed for human use for the topical treatment of herpes infections. β-D-*E*-5-(2-Bromovinyl)-2'-deoxyuridine (BVdU) was first synthesized by Jones, Verhelst, and Walker[3] in 1979 and shown by De Clercq *et al.*[4] to be a potent and selective inhibitor of herpes simplex virus type-1 (HSV-1). 1-[(β-D-Arabinofuranosyl)-*E*-5-(2-bromovinyl)]uracil (BV-ara-U) was synthesized by Sakata *et al.*[5] and demonstrated comparable activity to that of BVdU against HSV-1 infection *in vivo*.[6] Furthermore, BV-ara-U is more potent than BVdU against varicella-zoster virus with ID_{50} values of 0.00026 μg/mL and 0.008 μg/mL, respectively,[7] and is currently in clinical trial for the treatment of varicella-zoster infection.[8]

In comparison to the natural D-nucleoside analogues, only a relatively few studies have reported on the biological activity of L-nucleosides. Earlier, Simuth and Holy[9] reported the interaction of some β-L-nucleoside derivatives, such as L-adenosine diphosphate (L-ADP), with bacterial polynucleotide phosphorylase. Spadari *et al.*[10] reported that L-thymidine is not recognized by human thymidine kinase, but functions as specific substrates for the HSV-1 viral enzyme and demonstrates anti-HSV-1 activity in HeLa cells. Recently, a number of the unnatural L-configuration nucleoside analogues have been synthesized and biologically evaluated against human immunodeficiency virus (HIV) and hepatitis B virus (HBV) by our laboratory[11-13] and by others.[14-20] Among these compounds, 2',3'-dideoxy-β-L-fluorocytidine (β-L-FddC), (–)-2',3'-dideoxy-3'-thiacytidine [(–)SddC or (–)-3TC], and (–)-5-fluoro-2',3'-dideoxy-3'-thiacytidine [(–)FSddC or (–)-FTC] were found to demonstrate more potent activity against both HIV and HBV than their corresponding D-configuration counterparts with much less host toxicity. Based on these findings, the L-counterparts of IUdR, BV-ara-U, 2',3'-dideoxy-β-D-5-azacytidine, and 2',3'-dideoxy-β-D-thiocytidine were synthesized as potential antiviral agents, with the hope that these compounds would retain their antiviral activity with a reduction of the host toxicity.

SYNTHESIS

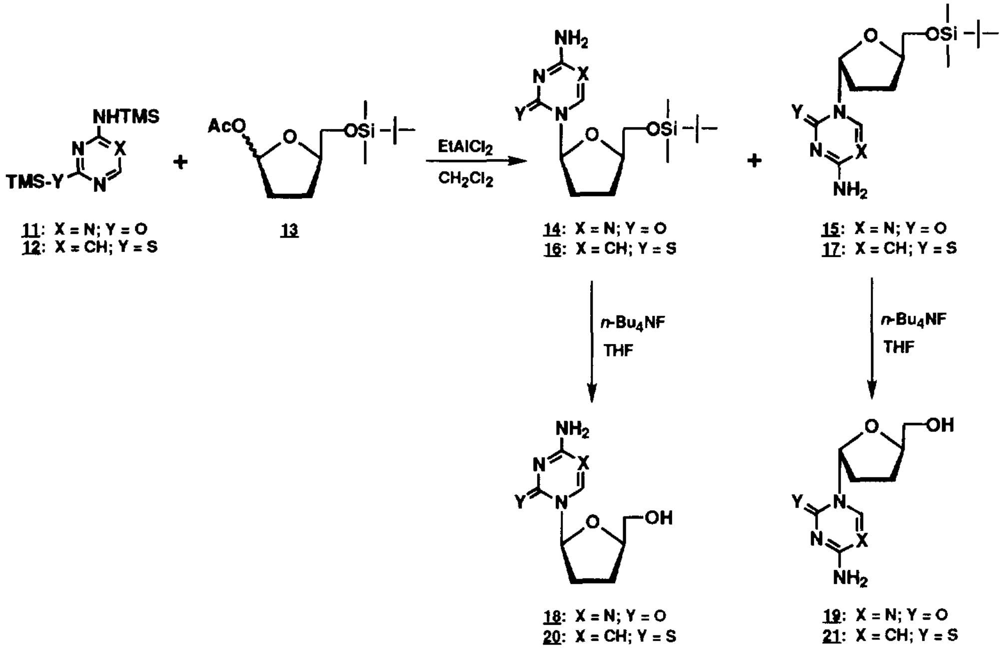
The synthesis of β-L-5-iodo-2'-deoxyuridine (β-L-IUdR, **7**) and 1-[(β-L-arabinofuranosyl)-*E*-5-(2-bromovinyl)]uracil (β-L-BV-ara-U, **10**) are described in **Scheme 1**. The anhydro derivative **3** was synthesized from L-arabinose by the methodology of Holy.[21] Treatment of compound **3** with 1 N NaOH in aqueous ethanol gave 1-β-L-arabinofuranosyluracil (**4**). β-L-2'-Deoxyuridine (**5**) was also synthesized from compound **3** by the methodology of Holy[21] with minor modification. Iodination[22,23] of compounds **4** and **5** with silver trifluoroacetate and iodine in dry dioxane produced the corresponding 5-iodo analogues, **6** and **7**. Reaction[24] of 5-iodo derivative **6** with palladium acetate, methyl acrylate, and triphenylphosphine in the presence of triethylamine afforded 1-[(β-L-arabinofuranosyl)-*E*-5-(2-methoxycarbonylvinyl)]uracil (**8**), which was then hydrolyzed with 2 N NaOH solution at room temperature to give the corresponding acid derivative **9**. Treatment of compound **9** with $KHCO_3$ and *N*-bromosuccinimide in DMF produced the target compound, 1-[(β-L-arabinofuranosyl)-*E*-5-(2-bromovinyl)]uracil (**10**).

Scheme 1



Coupling of the silylated derivatives of 5-azacytosine and 2-thiocytosine, **11** and **12**, with 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (**13**)[12] in the presence of ethylaluminum dichloride ($EtAlCl_2$) gave the corresponding nucleosides, **14** and **15**, and, **16** and **17**, both as a mixture of α- and β-anomers (**Scheme 2**). The anomeric mixture of the nucleoside derivatives, **14** and **15**, and, **16** and **17**, were separated by repeated silica gel chromatography due to the small difference in their R_f values. Treatment of compounds **14-17** with tetra-*n*-butylammonium fluoride in tetrahydrofuran afforded the deblocked target nucleosides **18-21**, as shown in **Scheme 2**.

Scheme 2



The assignment of the anomeric configuration of these nucleosides was made on the basis of characteristic proton NMR spectra. The H-4' protons of the α-anomers appear at a lower field than those of the β-anomers. Conversely, the H-5' protons of the α-anomers appear at a higher field than those of the β-anomers. These findings were consistent with the earlier report of Okabe *et al.*[25] concerning the D-nucleosides. For example, the difference in chemical shifts of the H-4' protons of compound **18** (β-L-5-aza-ddC) and compound **19** (α-L-5-aza-ddC) is -0.39 ppm, and the difference in chemical shifts of the H-5' protons of compound **18** (β-L-5-aza-ddC, 3.39 δ) and compound **19** (α-L-5-aza-ddC, 3.61 δ: average value of 5-H_A and 5-H_B) is 0.22 ppm (**Table 1**). These shifts are attributed to the effects that protons at a syn-position relative to the base are more deshielded than those in anti-position to the base. Furthermore, inspection of **Table 1** reveals that the chemical shift values of the two H-5' protons in the molecules of β-anomers **14**, **16**, **18**, and **20** are multiplets at 3.68 (5'-H_A) and 4.03 (5'-H_B) ppm; 3.70 (5'-H_A) and

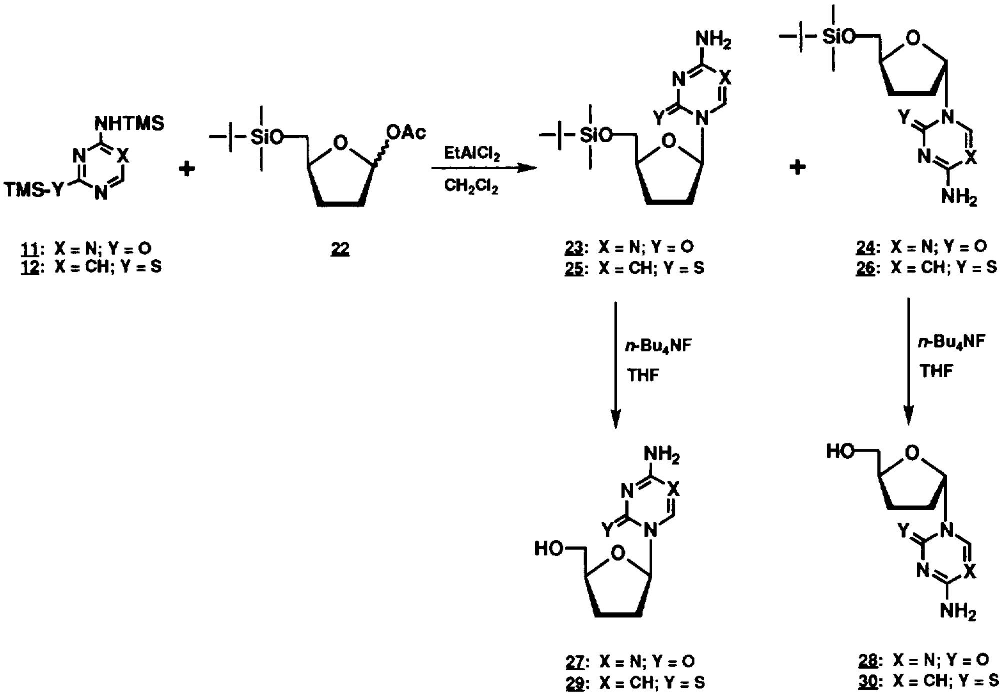
4.10 (5'-H_B) ppm; 3.50 (5'-H_A) and 3.71 (5'-H_B) ppm; and 3.55 (5'-H_A) and 3.75 (5'-H_B) ppm, respectively. On the contrary, the two protons of H-5' for the corresponding α-anomers, **15**, **17**, **19**, and **21**, show a doublet at 3.62, 3.65, 3.39, and 3.42, respectively. These differences might be due to the asymmetric features of H-5' protons in β-anomers **14**, **16**, **18**, and **20**, which are located in the vicinity of the base, or to the restricted rotation due to the base being on the β-face.

Table 1. Proton NMR Chemical Shifts δ (ppm)

Compound (abbr)	H-4'	Δ δ	H-5'
14 (TBS-β-L-5-aza-ddC)	4.18	-0.25	3.68 (H_A), 4.03 (H_B)
15 (TBS-α-L-5-aza-ddC)	4.43		3.62
16 (TBS-β-L-2-thio-ddC)	4.25	-0.20	3.70 (H_A), 4.10 (H_B)
17 (TBS-α-L-2-thio-ddC)	4.45		3.65
18 (β-L-5-aza-ddC)	4.03	-0.39	3.50 (H_A), 3.71 (H_B)
19 (α-L-5-aza-ddC)	4.42		3.39
20 (β-L-2-thio-ddC)	4.10	-0.40	3.55 (H_A), 3.75 (H_B)
21 (α-L-2-thio-ddC)	4.50		3.42

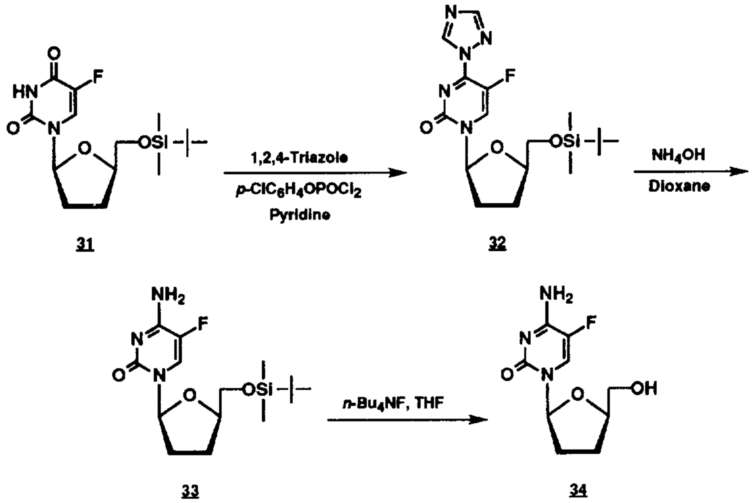
For the purpose of comparison, the D-enantiomers of 2',3'-dideoxy-β-L-5-azacytidine (**18**) and 2',3'-dideoxy-α-L-5-azacytidine (**19**); 2',3'-dideoxy-β-L-2-thiocytidine (**20**) and 2',3-dideoxy-α-L-2-thiocytidine (**21**), compounds, **27**-**30**, were synthesized by direct coupling of 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-D-ribofuranose (**22**)[25] with the respective silylated bases as described in **Scheme 3**. The 2-thio nucleoside analogues, **29** and **30**, were unknown compounds, and 2',3'-dideoxy-β-D-5-azacytidine (**27**) was synthesized previously by Kim *et al.*[26] by a different methodology, employing 5-azacytidine as the starting material.

Scheme 3



An alternative route for the synthesis of 2',3'-dideoxy-β-L-fluorocytidine (β-L-FddC) was also developed as depicted in **Scheme 4**. Treatment of 1-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]-5-fluorouracil (**31**)[12] with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole in anhydrous pyridine at room temperature yielded the 4-triazolylpyrimidinone derivative **32**. Subsequent treatment of compound **32** with a mixture of ammonium hydroxide/dioxane (2:1, v/v) gave the respective 2',3'-dideoxycytidine derivative **33**, which was then deblocked by reaction with tetra-*n*-butylammonium fluoride in THF to afford 2',3'-dideoxy-β-L-5-fluorocytidine (**34**, β-L-FddC).

Scheme 4



BIOLOGICAL EVALUATIONS AND DISCUSSION

The synthesized L-nucleoside analogues were tested *in vitro* against HIV-1, HBV, HSV-1, HSV-2, L1210, P388, S-180, and CCRF-CEM cells by previously reported methodology.[12] Among these compounds, 2',3'-β-L-dideoxy-5-azacytidine (**18**) was found to demonstrate potent anti-HBV activity at approximately the same level as 2',3'-dideoxy-β-D-cytidine (ddC) with ED_{50} values of 1.5 and 1 μM, respectively. ddC is known to have both potent anti-HIV and anti-HBV activity and is currently used clinically as a drug to treat AIDS. On the contrary, 2',3'-dideoxy-β-D-5-azacytidine, the D-enantiomer, demonstrated no antiviral activity against HBV. Replacement of the 5-carbon in the pyrimidine ring of β-L-ddC with a nitrogen to form β-L-5-aza-ddC (**18**) resulted in the retention of the anti-HBV activity to the level of ddC but loss of the anti-HIV-1 activity. Substitution of the 2-oxygen of β-L-ddC in the base moiety with a sulfur produced β-L-2-thio-ddC (**20**) and led to the total loss of both anti-HBV and -HIV activity. The α-anomeric counterparts of β-L-5-aza-ddC (**18**) and β-L-2-thio-ddC (**20**), compounds **19** and **21**, were not active. In conclusion, 2',3'-dideoxy-β-L-5-azacytidine (**18**) was found to be a selective inhibitor of HBV and demonstrated no cytotoxicity against L1210, P388, S-180, and CEM cells at concentration up to 100 μM, may warrant further studies. Compounds **6**, **7**, and **10** were tested against HSV-1 and HSV-2 *in vitro* and found not to be active up to 100 μM.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) NMR spectrometer or a Bruker WM-250

(250 MHz) spectrometer. Mass spectra were recorded on a VG-ZAB spectrometer. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer Model 241 polarimeter at 25 °C. The UV spectra were recorded on a Beckman-25 spectrophotometer. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT, U.S.A.

1-(β-L-Arabinofuranosyl)uracil (4). A suspension of 2,2'-anhydro-L-β-uridine (**3**, 5.0 g, 22 mmol), 1 N NaOH (20 mL) and 50% ethanol (130 mL) was stirred at room temperature for 4 h, then neutralized with HOAc/EtOH (1:1, v/v) to ~pH 7. The resulting solution was evaporated *in vacuo* to a small volume, and purified on a silica gel column (CH_2Cl_2/EtOH, 2:1, v/v, R_f 0.60) to give 5.2 g (96%) of product: mp 210-212 °C; ^1H NMR (Me_2SO-d_6, 90 MHz) δ 3.50-4.10 (m, 6 H, 2'-H, 3'-H, 4'-H, 5'-H and OH, D_2O exchangeable), 5.30-6.30 (br s, 2 H, 2 OH, D_2O exchangeable), 5.45-5.55 (d, 1 H, 5-H, J = 7.5 Hz), 5.95 (d, 1 H, 1'-H, J = 3.5 Hz), 7.60 (d, 1 H, 6 H, J = 7.5 Hz), 11.20 (br s, 1 H, 3-NH, D_2O exchangeable). Anal. Calcd. for $C_9H_{12}N_2O_6{\cdot}H_2O$: C, 41.18; H, 5.38; N, 10.68. Found: C, 41.06; H, 5.08; N, 10.28.

1-(β-L-Arabinofuranosyl)-5-iodouracil (6). 1-(β-L-Arabinofuranosyl)uracil (**4**, 4.20 g, 17.2 mmol) and silver trifluoroacetate (4.20 g, 18.9 mmol) were stirred in dioxane (70 mL) at 5 °C (ice-water bath) and a solution of iodine (4.80 g, 18.9 mmol) in dioxane (60 mL) was slowly added at 5-10 °C. The resulting mixture was stirred at room temperature overnight, after which a saturated sodium bicarbonate solution (20 mL) was added. The mixture was filtered through celite, which was washed with dioxane. The combined filtrate and washings were evaporated *in vacuo* to dryness. The remaining residue was chromatographed on a silica gel column, using CH_2Cl_2/EtOH (10:1, v/v) as eluting solvent to give 4.2 g (66%) of product: mp 212-214 °C; R_f 0.80 (CH_2Cl_2/EtOH, 4:1, v/v); ^1H NMR (Me_2SO-d_6, 90 MHz) δ 3.20-3.55 (m, 1 H, OH, D_2O exchangeable), 3.60-3.80 (m, 3 H, 4'-H and 5'-H), 3.90-4.15 (m, 2 H, 2'-H and 3'-H), 5.10-5.40 (br s, 1 H, OH, D_2O exchangeable), 5.40-5.65 (br s, 1 H, OH, D_2O exchangeable), 5.90-6.00 (d, 1 H, 1'-H, J = 3.6 Hz), 8.10 (s, 1 H, 6 H), 11.60 (s, 1 H, 3-NH, D_2O exchangeable).

2'-Deoxy-L-5-iodouridine (7). This compound was synthesized from β-L-2'-deoxyuridine[21] (**5**) by the same procedure as for the synthesis of compound **6**. Yield: 0.6 g (74.3%); mp 188-190 °C; R_f 0.79 (CH_2Cl_2/EtOH, 4:1, v/v); $[\alpha]_D^{25}$ -10.3° (c = 0.12, MeOH); UV (MeOH) λ_{max} 284 nm, λ_{min} 244 nm; ^1H NMR (Me_2SO-d_6, 90 MHz) δ 2.08-2.12 (t, 2 H, 2'-H), 3.56-3.60 (m, 2 H, 5'-H), 3.77-3.78 (m, 1 H, 4'-H), 4.22 (t, 1 H, 3'-H), 5.12 (t, 1 H, 5'-OH, D_2O exchangeable), 5.20-5.22 (d, 1 H, 3'-OH, D_2O exchangeable), 6.05-6.10 (t, 1 H, 1'-H, J = 3.6 Hz), 8.37 (s, 1 H, 6 H), 11.65 (s, 1 H, 3-NH, D_2O exchangeable). Anal. Cacld. for $C_9H_{11}N_2O_5I$: C, 30.53; H, 3.13; N, 7.91. Found: C, 30.55; H, 3.20; N, 7.72.

1-[(β-L-Arabinofuranosyl)-*E*-5-(2-methoxycarbonylvinyl)]uracil (8). A mixture of triethylamine (1.4 g, 14 mmol), triphenylphosphine (0.2 g, 0.76 mmol) and palladium acetate (0.1 g, 0.4 mmol) in dioxane (11.5 mL) was refluxed to form a homogeneous dark-red solution. The reaction temperature was then reduced to just below reflux, and methyl acrylate (1.7 g, 20 mmol), compound **6** (1.5 g, 4 mmol) and triethylamine (0.53 g, 5.3 mmol) were added subsequently with stirring. The reaction mixture was then refluxed for about 30 min until TLC showed the starting material had disappeared. The reaction mixture was filtered hot through celite, which was washed with dioxane. The combined filtrate and washings were evaporated *in vacuo* to a small volume and chromatographed on a silica gel column (CH_2Cl_2/MeOH, 4:1, v/v). The fractions containing the desired product (R_f 0.64) were pooled together, and the solvent was removed *in vacuo* to afford 0.8 g (62%) of product as white crystals: mp 196-198 °C; ^{1}H NMR (Me_2SO-d_6, 90 MHz) δ 3.35 (s, 3 H, CH_3), 3.60-3.70 (m, 3 H, 4'-H and 5'-H), 3.90-4.15 (m, 2 H, 2'-H and 3'-H), 5.15-5.30 (t, 1 H, 5'-OH, D_2O exchangeable), 5.45-5.50 (d, 1 H, OH, D_2O exchangeable), 5.55-5.60 (d, 1 H, OH, D_2O exchangeable), 5.95-6.05 (d, 1 H, 1'-H, J = 3.6 Hz), 6.85 (d, 1 H, vinyl H_A, J = 16 Hz), 7.40 (d, 1 H, vinyl H_B, J = 16 Hz), 8.20 (s, 1 H, 6-H), 11.50 (br s, 1 H, 3-NH, D_2O exchangeable). Anal. Cacld. for $C_{13}H_{16}N_2O_8 \cdot MeOH$: C, 46.66; H, 5.60; N, 7.78. Found: C, 46.68; H, 5.83; N, 7.83.

1-[(β-L-Arabinofuranosyl)-*E*-5-(2-carboxyvinyl)]uracil (9). Compound **8** (0.35 g, 1.1 mmol) was stirred in 10 mL of 2 N NaOH solution for 1.5 h at room temperature until the TLC showed the starting material had disappeared. The reaction mixture was cooled in an ice bath and carefully acidified with concentrated hydrochloric acid to pH 1. The resultant white solid was collected by filtration and washed with water and acetone. After drying, the product weighed 0.25 g (74%): mp 272-273 °C (dec); TLC, R_f 0.29 (CH_2Cl_2/MeOH/HOAc, 8:1:1, v/v); ^{1}H NMR (Me_2SO-d_6, 90 MHz) δ 3.50-3.85 (m, 4 H, 3'-H, 4'-H and 5'-H), 3.90-3.95 (m, 1 H, 2'-H), 4.00-4.15 (t, 1 H, 5'-OH, D_2O exchangeable), 5.10-5.30 (br s, 1 H, OH, D_2O exchangeable), 5.45-5.65 (br s, 1 H, OH, D_2O exchangeable), 6.00 (d, 1 H, 1'-H, J = 3.4 Hz), 6.70 (d, 1 H, vinyl H_A, J = 18 Hz), 7.25 (d, 1 H, vinyl H_B, J = 18 Hz), 8.10 (s, 1 H, 6-H), 11.45 (s, 1 H, 3-NH, D_2O exchangeable), 11.5-11.6 (br s, 1 H, COOH, D_2O exchangeable). Anal. Cacld. for $C_{12}H_{14}N_2O_8$: C, 45.86; H, 4.49; N, 8.92. Found: C, 45.85; H, 4.62, N, 8.74.

1-[(β-L-Arabinofuranosyl)-*E*-5-(2-bromovinyl)]uracil (10). To a stirred slurry of compound **9** (0.21 g, 0.67 mmol) in DMF (1 mL) was added potassium hydrogen carbonate (0.21 g, 0.67 mmol). The reaction mixture was stirred for 20 min at room temperature, and then a solution of *N*-bromosuccinimide (0.13 g, 0.70 mmol) in DMF (0.4 mL) was added dropwise. Evolution of carbon dioxide occurred during the addition. The resultant pale-yellow mixture was stirred for 1 h at room temperature and then filtered to remove the insoluble material. The filtrate was evaporated *in vacuo* to dryness, and the residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 4:1, v/v, R_f 0.74) to afford 120 mg (52%) of product as white crystals: mp 175-176 °C; $[\alpha]_D^{25}$ -2.7° (c = 0.12, MeOH); UV (MeOH) λ_{max} 292 nm, λ_{min} 272 nm; ^{1}H NMR (Me_2SO-d_6, 250 MHz) δ 3.61 (m, 2 H, 5'-H), 3.74 (m, 1 H, 4'-H), 3.91 (m, 1 H, 3'-H), 4.05 (m, 1 H, 2'-H), 5.00 (t, 1 H, 5'-OH, D_2O exchangeable), 5.45 (d, 1 H, OH, D_2O exchangeable), 5.55 (d, 1 H, OH, D_2O exchangeable), 6.00 (d, 1 H, 1'-H, J = 4.5 Hz), 6.84 (d, 1 H, vinyl H_A, J = 13.5 Hz), 7.22 (d, 1 H, vinyl H_B, J = 13.5 Hz), 7.88 (s, 1 H, 6-H), 11.43 (s, 1 H, 3-NH, D_2O exchangeable). EIMS: *m/e* (%) 349 (^{79}Br M$^+$+1, 40), 351 (^{81}Br M$^+$+1, 39), 333 (12), 259 (10). HRMS: $C_{11}H_{14}O_6N_2Br$ (M$^+$+1): Calcd. 349.0075; found 349.0066.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-β-L-ribofuranosyl)-5-azacytosine (14) and 1-(5-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-α-L-ribofuranosyl)-5-azacytosine (15). A suspension of 5-azacytosine (2.5 g, 22.5 mmol) and ammonium sulfate (60 mg) in 1,1,1,3,3,3-hexamethyldisilazane (19 mL) was refluxed for 2.5 h to form a clear solution. The reaction mixture was cooled to room temperature and evaporated *in vacuo* to give an oily residue, to which a solution of 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose[12] (**13**, 5.3 g, 18.7 mmol) in anhydrous methylene chloride (50 mL) was added, followed by the addition of a 1.8 M solution of ethylaluminum dichloride ($EtAlCl_2$) in toluene (10.4 mL, 18.7 mmol) over a period of 30 min at room temperature. The reaction mixture was stirred overnight and then slowly poured into an ice-cooled mixture of methylene chloride and saturated sodium bicarbonate solution with stirring. The mixture was stirred for 15 min and filtered. The organic layer was washed with sodium bicarbonate solution, brine, and water and then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* and the residue was first purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1, v/v) to give 600 mg (10%) of a mixture of β-anomer (**14**) and α-anomer (**15**) with a ratio of 5:3 (estimated by ^1H NMR spectra for the integration values of 6-H at δ 8.26 ppm and 7.38 ppm, respectively, for β- and α-anomers). The mixture was separated by silica gel chromatography (CH_2Cl_2/MeOH, 20:1, v/v) again to afford 230 mg (3.8%) of compound **14** (β-anomer) and 130 mg (2.1%) of compound **15** (α-anomer).

Compound **14** was isolated as a white solid: mp 202-204 °C; TLC, R_f 0.55 (CH_2Cl_2/MeOH, 10:1, v/v); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.10 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.75-2.55 (m, 4 H, 2'-H and 3'-H), 3.78 (m, 1 H, 5'-H_A), 4.03 (m, 1 H, 5'-H_B), 4.18 (m, 1 H, 4'-H), 5.80-5.95 (br s, 1 H, 4-NH_A, D_2O exchangeable), 5.95 (m, 1 H, 1'-H), 7.90-8.25 (br s, 1 H, 4-NH_B, D_2O exchangeable), 8.60 (s, 1 H, 6-H). Anal. Cacld. for $C_{14}H_{26}N_4O_3Si{\cdot}0.4C_2H_5OH$: C, 51.54; H, 8.29; N, 16.24. Found: C, 51.86; H, 7.94; N, 15.92.

Compound **15** was isolated as a white solid: mp 185-187 °C; TLC, R_f 0.50 (CH_2Cl_2/MeOH, 10:1, v/v); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.10 [s, 6 H, $Si(CH_3)_2$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 1.85-2.60 (m, 4 H, 2'-H and 3'-H), 3.62 (m, 2 H, 5'-H), 4.43 (m, 1 H, 4'-H), 5.80-5.90 (br s, 1 H, 4-NH_A, D_2O exchangeable), 5.96 (m, 1 H, 1'-H), 7.10-7.30 (br s, 1 H, 4-NH_B, D_2O exchangeable), 8.08 (s, 1 H, 6-H). Anal. Cacld. for $C_{14}H_{26}N_4O_3Si$: C, 51.50; H, 8.03; N, 17.16. Found: C, 51.60; H, 8.11; N, 16.91.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-β-L-ribofuranosyl)-2-thiocytosine (16) and 1-(5-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-α-L-ribofuranosyl)-2-thiocytosine (17). Compounds **16** and **17** were synthesized by the similar methodology as described for the preparation of compounds **14** and **15** except that 2-thiocytosine (2.5 g, 19.7 mmol) was used as the starting material instead of 5-azacytosine.

Compound **16** was isolated as a white solid (600 mg, 11%): mp 106-108 °C; TLC, R_f 0.36 (CH_2Cl_2/MeOH, 15:1, v/v); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.10 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.80-2.60 (m, 4 H, 2'-H and 3'-H), 3.75 (m, 1 H, 5'-H_A), 4.05 (m, 1 H, 5'-H_B), 4.25 (m, 1 H, 4'-H), 6.00 (d, 1 H, 5-H, J = 7.2 Hz), 6.70 (m, 1 H, 1'-H), 6.80-8.00 (br s, 2 H, 4-NH_2, D_2O

exchangeable), 8.30 (d, 1 H, 6-H, *J* = 7.2 Hz). Anal. Cacld. for $C_{15}H_{27}N_3O_2SSi{\cdot}0.3H_2O$: C, 51.92; H, 8.02; N, 12.11. Found: C, 51.73; H, 7.95; N, 12.17.

Compound **17** was isolated as a white solid (465 mg, 8.3%): mp 150-152 °C; TLC, R_f 0.29 (CH_2Cl_2/MeOH, 15:1, v/v); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.10 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.80-2.60 (m, 4 H, 2'-H and 3'-H), 3.65 (m, 2 H, 5'-H), 4.45 (m, 1 H, 4'-H), 6.03 (d, 1 H, 5-H, *J* = 7.2 Hz), 6.70 (m, 1 H, 1'-H), 6.30-6.80 (br s, 2 H, 4-NH_2, D_2O exchangeable), 7.53 (d, 1 H, 6-H, *J* = 7.2 Hz). Anal. Cacld. for $C_{15}H_{27}N_3O_2SSi$: C, 52.75; H, 7.97; N, 12.30. Found: C, 52.79; H, 7.98; N, 12.58.

2',3'-Dideoxy-β-L-5-azacytidine (18). To a stirred solution of compound **14** (0.21 g, 0.64 mmol) in 15 mL of THF was added dropwise 2.8 mL of tetra-*n*-butylammonium fluoride (1 M solution in THF, 3.7 mmol) at ambient temperature. The reaction was complete after 30 min and the solvent was evaporated in vacuo to dryness. The residue was dissolved in 15 mL of water and extracted with methylene chloride (2 x 10 mL). The water layer was evaporated with 5 g of silica gel to dryness and the residue was chromatographed on a silica gel column (EtOAc/EtOH, 6:1, v/v) to afford 60 mg (42%) of product as white solid: mp 260 °C (dec); TLC, R_f 0.56 (EtOAc/EtOH, 6:1, v/v); $[\alpha]_D^{25}$ -45° (*c* = 0.1, MeOH); UV (MeOH) λ_{max} 246 nm (ε 5178), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 254 nm (ε 4499), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 246 nm (ε 5602), λ_{min} 236 nm; ^{1}H NMR (Me_2SO-d_6, 250 MHz) δ 1.80-2.33 (m, 4 H, 2'-H and 3'-H), 3.50 (m, 1 H, 5'-H_A), 3.71 (m, 1 H, 5'-H_B), 4.05 (m, 1 H, 4'-H), 5.09 (t, 1 H, 5'-OH, D_2O exchangeable), 5.85 (m, 1 H, 1'-H), 7.40 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.62 (s, 1 H, 6-H). Anal. Cacld. for $C_8H_{12}N_4O_3{\cdot}0.2CH_2Cl_2{\cdot}0.3CH_3COOC_2H_5$: C, 44.16; H, 5.83; N, 21.92. Found: C, 44.46; H, 5.90; N, 21.44.

Compounds **19-21** were synthesized by the similar methodology as described for the synthesis of compound **18**.

2',3'-Dideoxy-α-L-5-azacytidine (19). Compound **19** was isolated as a white solid (30 mg, 43%): mp 135-137 °C; TLC, R_f 0.50 (EtOAc/EtOH, 6:1, v/v); $[\alpha]_D^{25}$ -59.7° (*c* = 0.07, MeOH); UV (MeOH) λ_{max} 248 nm (ε 4630), λ_{min} 233 nm; UV (0.01 N HCl) λ_{max} 251 nm (ε 3936), λ_{min} 228 nm; UV (0.01 N NaOH) λ_{max} 246 nm (ε 4707), λ_{min} 236 nm; ^{1}H NMR (Me_2SO-d_6, 250 MHz) δ 1.73-2.36 (m, 4 H, 2'-H and 3'-H), 3.39 (m, 2 H, 5'-H), 4.42 (m, 1 H, 4'-H), 4.78 (t, 1 H, 5'-OH, D_2O exchangeable), 5.88 (m, 1 H, 1'-H), 7.44 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.21 (s, 1 H, 6-H). Anal. Cacld. for $C_8H_{12}N_4O_3{\cdot}0.1CH_2Cl_2{\cdot}0.35CH_3COOC_2H_5$: C, 45.35; H, 6.00; N, 22.27. Found: C, 45.01; H, 5.60; N, 21.95.

2',3'-Dideoxy-β-L-2-thiocytidine (20). Compound **20** was isolated as a white solid (0.20 g, 56%): mp 250 °C (dec, turned brown at 122 °C); TLC, R_f 0.39 (CH_2Cl_2/EtOH, 6:1, v/v); $[\alpha]_D^{25}$ -36.5° (*c* = 0.12, MeOH); UV (MeOH) λ_{max} 274 nm (ε 14453), λ_{min} 254 nm; UV (0.01 N HCl) λ_{max} 276 nm (ε 11730), λ_{min} 250 nm; UV (0.01 N NaOH) λ_{max} 264 nm (ε 10682), λ_{min} 250 nm; ^{1}H NMR (Me_2SO-d_6, 90 MHz) δ 1.64-2.45 (m, 4 H, 2'-H and 3'-H), 3.55 (m, 1 H, 5'-H_A), 3.75 (m, 1 H, 5'-H_B), 4.10 (m, 1 H, 4'-H), 4.95-5.10 (t, 1 H, 5'-OH, D_2O exchangeable), 6.00 (d, 1 H, 5-H, *J* = 7.0 Hz), 6.62 (m, 1 H, 1'-H), 7.40-7.60 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.20 (d, 1 H, 6-H, *J* = 7.0 Hz). Anal. Cacld. for $C_9H_{13}N_3O_2S{\cdot}0.1CH_2Cl_2$: C, 46.35; H, 5.64; N, 17.82. Found: C, 46.59; H, 5.21; N, 17.34.

2',3'-Dideoxy-α-L-2-thiocytidine (21). Compound **21** was isolated as a white solid (0.16 g, 73%): mp 233-236 °C (dec, turned brown at 200 °C); TLC, R_f 0.32 (CH_2Cl_2/EtOH, 6:1, v/v); $[\alpha]_D^{25}$ +63.3° (*c* = 0.1, MeOH); UV (MeOH) λ_{max} 276 nm (ε 18837), λ_{min} 260 nm; UV (0.01 N HCl) λ_{max} 278 nm (ε 18512), λ_{min} 250 nm; UV (0.01 N NaOH) λ_{max} 270 nm (ε 14875), λ_{min} 260 nm; ^1H NMR (Me_2SO-d_6, 90 MHz) δ 1.75-2.15 (m, 4 H, 2'-H and 3'-H), 3.42 (m, 2 H, 5'-H), 4.50 (m, 1 H, 4'-H), 4.70-4.85 (t, 1 H, 5'-OH, D_2O exchangeable), 6.10 (d, 1 H, 5-H, *J* = 7.0 Hz), 6.72 (m, 1 H, 1'-H), 7.45-7.65 (br s, 2 H, 4-NH_2, D_2O exchangeable), 7.70 (d, 1 H, 6-H, *J* = 7.0 Hz). Anal. Cacld. for $C_9H_{13}N_3O_2S\cdot0.1H_2O$: C, 46.10; H, 5.95; N, 17.92. Found: C, 46.17; H, 5.86; N, 17.56.

Compounds **23** and **24** were synthesized by the similar methodology as described for the synthesis of compounds **14** and **15** except that the coupling employed 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-D-ribofuranose (**22**)[25] instead of 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (**13**)[12] with 5-azacytosine.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-β-D-ribofuranosyl)-5-azacytosine (23). Compound **23** was isolated as a white solid (0.96 g, 20%): mp 196-198 °C; TLC, R_f 0.32 (CH_2Cl_2/MeOH, 15:1, v/v); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.10 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.80-2.60 (m, 4 H, 2'-H and 3'-H), 3.60-4.20 (m, 2 H, 5'-H), 4.20-4.30 (m, 1 H, 4'-H), 5.70-5.90 (br s, 1 H, 4-NH_A, D_2O exchangeable), 5.90-6.05 (m, 1 H, 1'-H), 7.90-8.20 (br s, 1 H, 4-NH_B, D_2O exchangeable), 8.65 (s, 1 H, 6-H). EIMS: *m/e* (%) 327 (M^++1, 65), 269 (M-CMe_3, 30), 215 (sugar, 100). HRMS: $C_{14}H_{27}O_3N_4Si$ (M^++1): Calcd. 327.1868; found 327.1854.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-α-D-ribofuranosyl)-5-azacytosine (24). Compound **24** was isolated as a white solid (0.74 g, 15%): mp 191-193 °C; TLC, R_f 0.24 (CH_2Cl_2/MeOH, 10:1, v/v); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.10 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.95-2.65 (m, 4 H, 2'-H and 3'-H), 3.65-3.80 (m, 2 H, 5'-H), 4.35-4.55 (m, 1 H, 4'-H), 5.95-6.05 (m, 1 H, 1'-H), 6.10-6.30 (br s, 1 H, 4-NH_A, D_2O exchangeable), 7.50-7.70 (br s, 1 H, 4-NH_B, D_2O exchangeable), 8.04 (s, 1 H, 6-H). Anal. Cacld. for $C_{14}H_{26}N_4O_3Si$: C, 51.50; H, 8.03; N, 17.16. Found: C, 51.81; H, 8.25; N, 16.88.

Compounds **25** and **26** were synthesized by the similar methodology as described for the synthesis of compounds **14** and **15** except that the coupling employed 2-thiocytosine (2.0 g, 15.7 mmol) with 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-D-ribofuranose (**22**)[25] instead of 5-azacytosine with 1-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-L-ribofuranose (**13**).[12]

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-β-D-ribofuranosyl)-2-thiocytosine (25). Compound **25** was isolated as a foam (0.51 g, 10%): TLC, R_f 0.31 (CH_2Cl_2/MeOH, 15:1, v/v); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.10 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.80-2.65 (m, 4 H, 2'-H and 3'-H), 3.55-4.10 (m, 2 H, 5'-H), 4.10-4.30 (m, 1 H, 4'-H), 6.05 (d, 1H, 5-H, *J* = 7.2 Hz), 6.65-6.80 (m, 1 H, 1'-H), 7.30-8.10 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.30 (d, 1 H, 6-H, *J* = 7.2 Hz). Anal. Cacld. for $C_{15}H_{27}N_3O_2SSi$: C, 52.75; H, 7.97; N, 12.30. Found: C, 52.53; H, 7.63; N, 12.63.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-α-D-ribofuranosyl)-2-thiocytosine (26). Compound **26** was isolated as a foam (0.34 g, 6.4%): TLC, R_f 0.27 (CH_2Cl_2/MeOH, 10:1, v/v); ^1H NMR

($CDCl_3$, 90 MHz) δ 0.05 [s, 6 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 1.90-2.80 (m, 4 H, 2'-H and 3'-H), 3.60-3.70 (m, 2 H, 5'-H), 4.50-4.70 (m, 1 H, 4'-H), 6.08 (d, 1 H, 5-H, *J* = 7.2 Hz), 6.65-6.80 (m, 1 H, 1'-H), 7.30-7.80 (br s, 2 H, 4-NH_2, D_2O exchangeable), 7.68 (d, 1 H, 6-H, *J* = 7.2 Hz). Anal. Cacld. for $C_{15}H_{27}N_3O_2SSi$: C, 52.75; H, 7.97; N, 12.30. Found: C, 52.38; H, 7.92; N, 12.37.

Compounds **27**-**30** were synthesized by the similar methodology as described for the synthesis of compound **18**.

2',3'-Dideoxy-β-D-5-azacytidine (27). Compound **27** was isolated as a white solid (0.10 g, 36%): mp 245 °C (dec) [lit.[26] 247 °C]; ^{1}H NMR (Me_2SO-d_6, 90 MHz) δ 1.70-2.20 (m, 4 H, 2'-H and 3'-H), 3.52-3.74 (m, 2 H, 5'-H), 4.15 (m, 1 H, 4'-H), 5.12 (t, 1 H, 5'-OH, D_2O exchangeable), 5.86 (m, 1 H, 1'-H), 7.30 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.61 (s, 1 H, 6-H).

2',3'-Dideoxy-α-D-5-azacytidine (28). Compound **28** was isolated as a white solid (60 mg, 18%): mp 132-134 °C; TLC, R_f 0.52 (EtOAc/EtOH, 6:1, v/v); UV (MeOH) λ_{max} 244 nm (ε 4999), λ_{min} 228 nm; UV (0.01 N HCl) λ_{max} 254 nm (ε 8394), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 245 nm (ε 11035), λ_{min} 233 nm; ^{1}H NMR (Me_2SO-d_6, 90 MHz) δ 1.70-2.40 (m, 4 H, 2'-H and 3'-H), 3.40-3.50 (m, 2 H, 5'-H), 4.40-4.50 (m, 1 H, 4'-H), 4.78 (t, 1 H, 5'-OH, D_2O exchangeable), 5.85 (m, 1 H, 1'-H), 7.40-7.55 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.20 (s, 1 H, 6-H). EIMS: *m/e* (%) 213 (M^++1, 32), 113 (B^++1, 55), 101 (sugar, 15). HRMS: $C_8H_{13}O_3N_4$ (M^++1): Calcd. 213.0913; found 213.0906.

2',3'-Dideoxy-β-D-2-thiocytidine (29). Compound **29** was isolated as a white solid (0.13 g, 32%): mp 246 °C (dec turned brown at 120-122 °C); TLC, R_f 0.33 (CH_2Cl_2/EtOH, 6:1, v/v); UV (MeOH) λ_{max} 274 nm (ε 13636), λ_{min} 260 nm; UV (0.01 N HCl) λ_{max} 272 nm (ε 13409), λ_{min} 243 nm; UV (0.01 N NaOH) λ_{max} 270 nm [shoulder] (ε 13977); ^{1}H NMR (Me_2SO-d_6, 90 MHz) δ 1.75-2.50 (m, 4 H, 2'-H and 3'-H), 3.55-3.80 (m, 2 H, 5'-H), 4.10 (m, 1 H, 4'-H), 5.00-5.10 (t, 1 H, 5'-OH, D_2O exchangeable), 6.00 (d, 1 H, 5-H, *J* = 7.2 Hz), 6.60-6.75 (m, 1 H, 1'-H), 7.40-7.60 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.20 (d, 1 H, 6-H, *J* = 7.2 Hz). EIMS: *m/e* (%) 228 (M^++1, 40), 128 (B^++1, 60), 101 (sugar, 20). HRMS: $C_9H_{14}N_3O_2S$ (M^++1): Calcd. 228.0807; found 228.0806.

2',3'-Dideoxy-α-D-2-thiocytidine (30). Compound **30** was isolated as a white solid (0.13 g, 35%): mp 230-233 °C (dec, turned brown at 200 °C); TLC, R_f 0.63 (CH_2Cl_2/EtOH, 6:1, v/v); UV (MeOH) λ_{max} 276 nm (ε 18666), λ_{min} 262 nm; UV (0.01 N HCl) λ_{max} 277 nm (ε 16242), λ_{min} 249 nm; UV (0.01 N NaOH) λ_{max} 270 nm [shoulder] (ε 18060); ^{1}H NMR (Me_2SO-d_6, 90 MHz) δ 1.40-2.10 (m, 4 H, 2'-H and 3'-H), 3.40-3.60 (m, 2 H, 5'-H), 4.50 (m, 1 H, 4'-H), 4.70-4.85 (t, 1 H, 5'-OH, D_2O exchangeable), 6.10 (d, 1 H, 5-H, *J* = 7.2 Hz), 6.65 (m, 1 H, 1'-H), 7.40-7.65 (br s, 2 H, 4-NH_2, D_2O exchangeable), 7.65 (d, 1 H, 6-H, *J* = 7.2 Hz). EIMS: *m/e* (%) 228 (M^++1, 65), 128 (B^++1, 100), 101 (sugar, 33). HRMS: $C_9H_{14}N_3O_2S$ (M^++1): Calcd. 228.0807; found 228.0806.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]-5-fluorocytosine (33). To a cooled (ice-water bath) solution of 1-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-L-ribofuranosyl]-5-fluorouracil[12] (**31**, 3.0 g, 8.7 mmol) and 1,2,4-triazole (7.9 g, 0.12 mol) in 60 mL of anhydrous pyridine was added dropwise 4-chlorophenyl phosphorodichloridate (6.2 mL, 38 mmol). The reaction mixture was stirred at 0-5 °C for 2 h, and at room temperature overnight, then evaporated *in vacuo* to dryness. The residue was co-evaporated with toluene twice and mixed with 110 mL of ammonium hydroxide and 220 mL of dioxane. The mixture was stirred at room temperature for 2 h and then evaporated *in vacuo* to dryness. The residue was dissolved in methylene chloride (200 mL) and filtered. The filtrate was evaporated to a small volume and chromatographed on a silica gel column (CH_2Cl_2/MeOH, 15:1, v/v) to produce 1.2 g (40%) of product as a white solid: mp 174-176 °C; TLC, R_f 0.33 (CH_2Cl_2/MeOH, 15:1, v/v); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.15 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.80-2.20 (m, 4 H, 2'-H and 3'-H), 3.55-4.00 (m, 2 H, 5'-H), 4.10-4.25 (m, 1 H, 4'-H), 5.85-6.00 (m, 1 H, 1'-H), 7.20-7.60 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.10-8.20 (d, 1 H, 6-H, J = 6.0 Hz).

2,3-Dideoxy-β-L-ribofuranosyl-5-fluorocytosine (34). Compound **34** was synthesized by the similar methodology as described for the preparation compound **18** and isolated as white crystals (0.20 g, 85%): mp 148-149 °C; TLC, R_f 0.32 (EtOAc/EtOH, 4:1, v/v); $[\alpha]_D^{25}$ -108° (c = 0.13, MeOH); UV (MeOH) λ_{max} 285 nm (ε 6480), λ_{min} 263 nm; UV (0.01 N HCl) λ_{max} 290 nm (ε 10980), λ_{min} 250 nm; UV (0.01 N NaOH) λ_{max} 283 nm (ε 7974), λ_{min} 260 nm; ^{1}H NMR (Me_2SO-d_6, 250 MHz) δ 1.85-2.35 (m, 4 H, 2'-H and 3'-H), 3.40-3.82 (m, 2 H, 5'-H), 3.95-4.10 (m, 1 H, 4'-H), 5.11-5.15 (t, 1 H, 5'-OH, D_2O exchangeable), 5.95 (m, 1 H, 1'-H), 7.35-7.60 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.20-8.30 (d, 1 H, 6-H, J = 6.2 Hz).

Compounds **33** and **34**, prepared by these procedures, were identical to the same compounds previously synthesized in our laboratory by using a different methodology.[12]

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