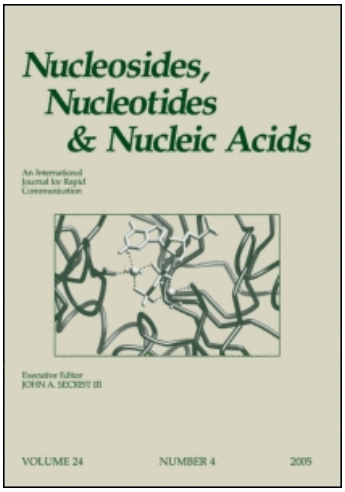

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Synthesis and Anti-HIV Activity of β-D-3'-Azido-2',3'-unsaturated Nucleosides and β-D-3'-Azido-3'-deoxyribofuranosylnucleosides

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SYNTHESIS AND ANTI-HIV ACTIVITY OF β-D-3′-AZIDO-2′,3′-UNSATURATED NUCLEOSIDES AND β-D-3′-AZIDO-3′-DEOXYRIBOFURANOSYLNUCLEOSIDES

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□ *Since the discovery of 3′-azido-3′-deoxythymidine (AZT) and 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T) as potent and selective inhibitors of the replication of human immunodeficiency virus (HIV), there has been a growing interest for the synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides with electron withdrawing groups on the sugar moiety. Here we described an efficient method for the synthesis of such nucleoside analogs bearing structural features of both AZT and d4T. The key intermediate, 3-azido-1,2-bis-O-acetyl-5-O-benzoyl-3-deoxy-D-ribofuranose,* **5** *was synthesized from commercially available D-xylose in five steps, from which a series of pyrimidine and purine nucleosides were synthesized in high yields. The resultant protected nucleosides were converted to target nucleosides using appropriate chemical modifications. The final nucleosides were evaluated as potential anti-HIV agents.*

Keywords Nucleosides; β-D-3′-azido-2′,3′-unsaturated nucleosides; β-D-3′-azido-3′-deoxyribofuranosylnucleosides; Anti-HIV activity

INTRODUCTION

Nucleoside analogs have been extensively used as chemotherapeutic agents for the treatment of HIV infection. Since the discovery of 3′-azido-3′-deoxythymidine (AZT)[1] and 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T)[2] as potent and selective inhibitors of the replication of HIV,

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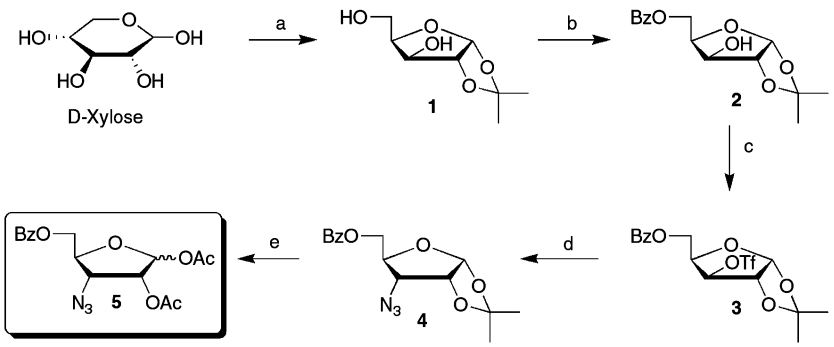
several 2′,3′-unsaturated and 2′,3′-dideoxy nucleoside analogs have been synthesized and evaluated. For example, most of the FDA approved nucleoside reverse transcriptase inhibitors[3] for the treatment of AIDS can be considered as 2′,3′-unsaturated and/or 2′,3′-dideoxy nucleoside analogs. In addition, the nucleoside analogs with electron withdrawing groups like azide[1] or fluorine[4–11] on the carbohydrate moiety have been proven as potent antiviral agents.

In recent years, we have extensively explored the synthesis and biological activity of such substituents, particularly F or CN groups in 2′,3′-dideoxy-2′,3′-didehydro-nucleoside analogs.[4–12] For example, synthesis and evaluation of D- and L-2′(or 3′)-fluoro-2′,3′-unsaturated nucleosides [D- and L-2′(or 3′)-F-d4Ns],[5–8] D- and L-2′,3′-unsaturated 2′(or 3′)-fluoro-4′-thionucleosides [D- and L-2′(or 3′)-F-4′Sd4Ns][9–11] and L-3′-*C*-cyano-2′,3′-unsaturated nucleosides (L-3′-*C*-CN-d4Ns)[12] have been reported by our group and a number of nucleosides from the above classes displayed moderate to potent anti-HIV activity and anti-hepatitis B virus (HBV) activities. Particularly in the D-2′-F-d4Ns series, the adenine and hypoxanthine derivatives exhibited potent anti-HIV-1 activities (EC_{50} 0.04 and 0.5 μM, respectively) and showed favorable cross-resistance profiles with respect to the 2′,3′-dideoxy-3′-thiacytidine (3TC) resistant viral isolates.[6] Furthermore, the cytosine and 5-fluorocytosine derivatives from the L-2′-F-d4Ns series displayed potent HBV (EC_{50} = 0.002 and 0.004 μM, respectively) as well as anti-HIV-1 activities without significant cytotoxicities.[5]

In view of these interesting biological results, we were prompted to explore the synthesis and biological activity of a series of β-D-3′-azido-2′,3′-unsaturated nucleosides and β-D-3′-azido-3′-deoxyribofuranosylnucleosides. To our knowledge, β-D-3′-azido-2′,3′-unsaturated nucleosides were unknown except 3′-azido-2′,3′-dideoxy-2′,3′-didehydrothymidine,[13] of which a synthetic method was not amenable for the synthesis of the same series of compounds. Herein, we report a general synthetic method and biological evolution of 3′-azido-2′,3′-didehydro-2′,3′-dideoxynucleoside analogs and 3′-azido-3′-deoxyribofuranosylnucleosides.

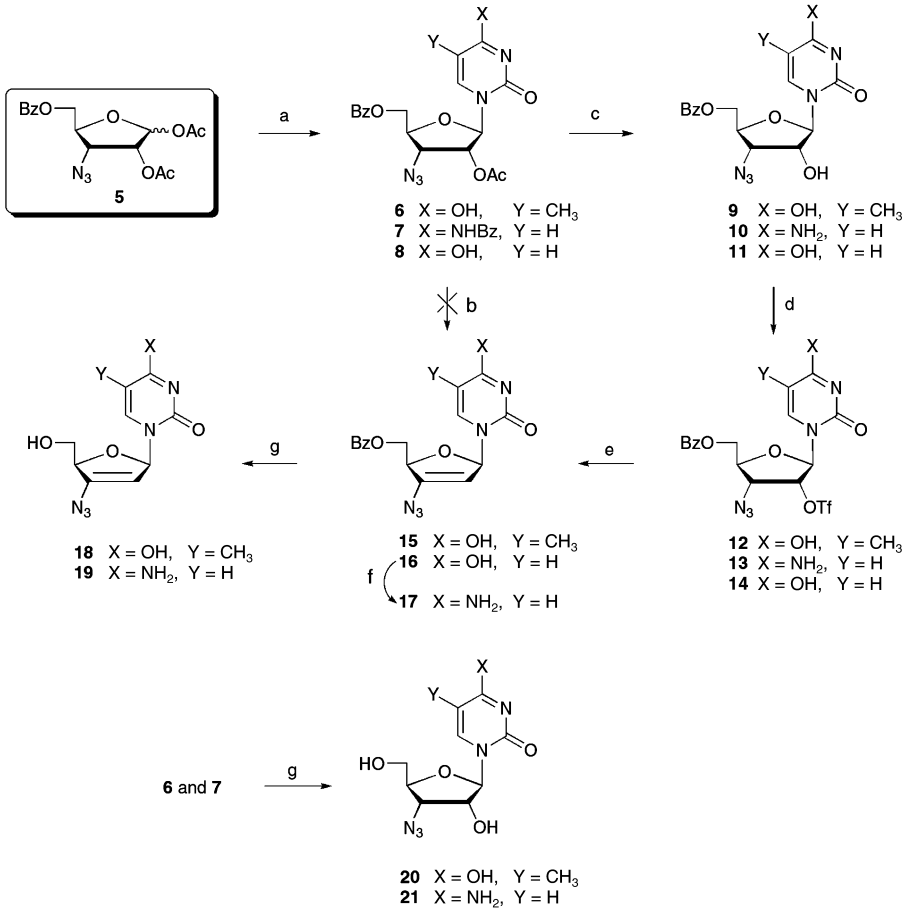
RESULTS AND DISCUSSION

To synthesize the target compounds, a versatile carbohydrate precursor **5** was used as a key intermediate, which was prepared in five steps from D-xylose (Scheme 1). The conversion of D-xylose to 1,2-*O*-isopropylidene-β-D-xylofuranose **1** was achieved in 90% yield by the reported procedure.[14] The primary hydroxyl group of compound **1** was selectively protected with benzoyl chloride and pyridine to produce the benzoyl derivative **2** in 85% yield. In order to introduce an 3-azido group, the 3-hydroxy group of compound **2** was converted to a triflate **3** with trifluoromethanesulfonic anhy-



SCHEME 1 Reagents and conditions: (a) H_2SO_4, $CuSO_4$, acetone, rt; (ii) 0.1 M HCl solution in MeOH, 40°C; (b) BzCl, Py, CH_2Cl_2, 0°C; (c) Tf_2O, Py, CH_2Cl_2, −10°C; (d) NaN_3, Bu_4NCl (cat), DMF, 60°C; (e) (i) 75% HCOOH, 50°C; (ii) Ac_2O, Py, rt.

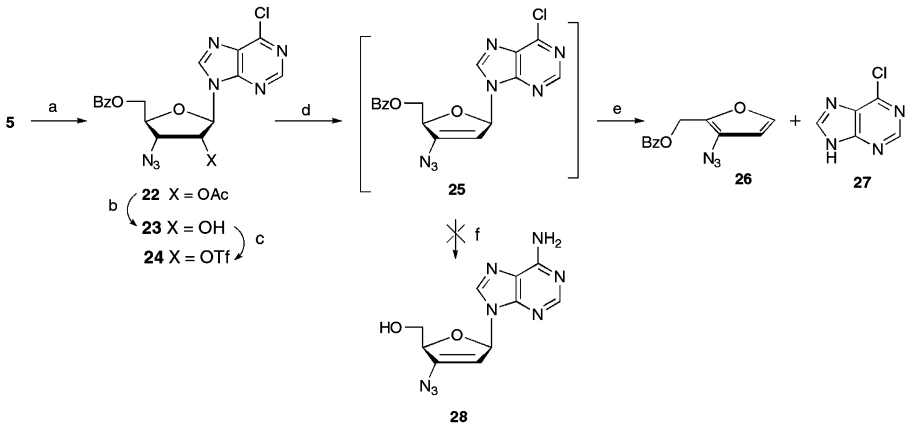
dride, which was subsequently converted to an 3-azido derivative **4** in approximately 52% yield with sodium azide and catalytic amount of phase transfer catalyst (Bu_4NCl) in DMF at 60°C.[15] The azide **4** was converted to 3-azido-1,2-*bis*-*O*-acetyl-5-*O*-benzoyl-3-deoxy-D-ribofuranose **5** in 75% yield as an epimeric mixture with 75% formic acid, followed by acetylation with acetic anhydride in pyridine.[16] Condensation of the key intermediate **5** with persilylated pyrimidines with trimethylsilyl triflate as Lewis acid gave the corresponding nucleosides **6**, **7**, and **8** in 79–83% yield (Scheme 2). The condensation reaction gave exclusively the β-anomer, which can be explained by the neighboring 2-acetyl group participation. Then we attempted the elimination reaction on the compound **6** to obtain the intermediate **15** with DBU and DMAP in CH_2Cl_2.[12] It was thought that the 3′-β-proton would be acidic enough to be abstracted by base (DBU or DMAP) and subsequently the 2′-acetyl group would be expected to leave. Unfortunately, this reaction did not proceed and only starting material was isolated. However, Hasegawa et al.[17] reported a similar elimination reaction on 2-*O*-triflate sugar derivative with tetrabutyl ammonium fluoride. Thus, a similar protocol was used for the introduction of 2′,3′-unsaturation in our target nucleosides. In order to synthesize the 2′-*O*-triflate derivatives **12**, **13**, and **14**, compounds **6**, **7**, and **8** were treated with hydrazine hydrate in buffered acetic acid and pyridine to produce the desired nucleosides **9** and **11** in 84% and 86% yields, respectively. In the case of compound **7**, in addition to the 2′-*O*-acetyl group, the *N*-benzoyl group was also affected under the reaction conditions and compound **10** was obtained in 71% yield. The resulting nucleosides **9**, **10**, and **11** were treated with trifluoromethanesulfonic anhydride and pyridine in CH_2Cl_2 at −40°C to produce triflate derivatives **12** and **14** in 78% and 82% yields, respectively. In the case of compound **10**, an undesired black mass was observed under similar reaction conditions due to the presence of a primary amino group. Since the cytosine analog **10** did not give the



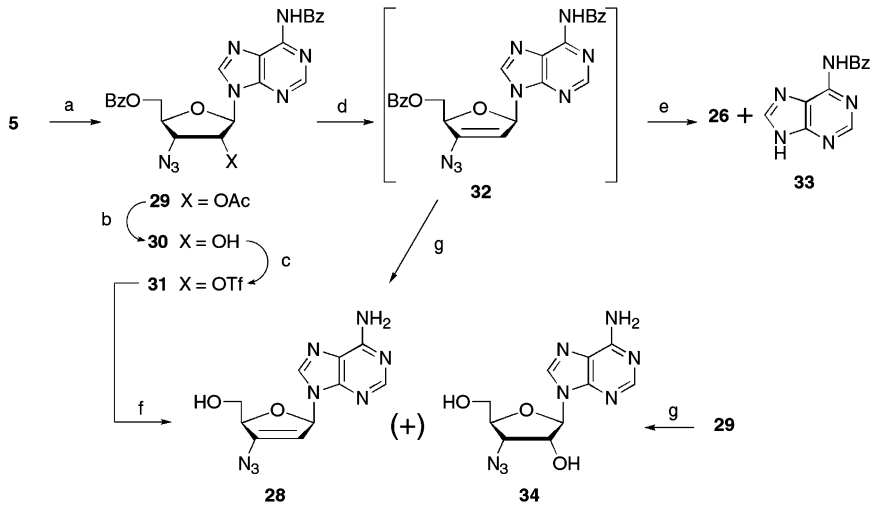
SCHEME 2 Reagents and conditions: (a) BSA, pyrimidines, TMSOTf, CH_3CN, 50–70°C; (b) DBU, DMAP, CH_2Cl_2, rt; (c) $N_2H_4.H_2O$, AcOH-Py, rt; (d) Tf_2O, Py, CH_2Cl_2, −40°C; (e) TBAF, THF, rt; (f) (i) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, Et_3N, CH_3CN, rt; (ii) 30% NH_4OH, rt; (g) NH_3/MeOH, rt.

expected triflate derivative **13**, we decided to synthesize the cytosine analog **19** from the uracil analog **11**. The nucleosides **12** and **14** were treated with 2 equivalents of tetrabutylammonium fluoride (TBAF) in THF to give the desired compounds **15** and **16** in 87% and 85% yields, respectively. The resulting 2′,3′-unsaturated uracil analog **16** was converted to the cytosine analog **17** by amination with triisopropylbenzenesulfonyl chloride, DMAP and triethylamine.[18] Finally, compounds **15** and **17** were treated with saturated methanolic ammonia to afford the desired nucleosides **18** and **19** in 84% and 82% yields, respectively. On the other hand, compounds **6** and **7** were treated with saturated methanolic ammonia to obtain the final nucleosides **20** and **21** in 79% and 75% yields, respectively.

For the synthesis of purine nucleosides, we first attempted the synthesis of adenine analog **28**. Key intermediate **5** was treated with 6-chloropurine under similar reaction conditions used for the pyrimidine nucleosides to obtain nucleoside **22** exclusively as the N-9 glycosylation product in 90% yield (Scheme 3). Since the preparation of the triflate of cytosine (**13**) was problematic, it was of interest to convert compound **22** to **25** by a similar sequence of reactions used for pyrimidines, and it was expected that amination and deprotection would give final compound **28** in a single step. Accordingly, compound **22** was treated with hydrazine hydrate in buffered acetic acid and pyridine to give the desired compound **23** in only 20% yield. Alternatively, compound **22** was converted to the desired compound **23** in 86% yield with partially saturated methanolic ammonia at 0°C. Compound **23** was converted to the triflate derivative **24**, and subsequently treated with TBAF in THF to give only hydrolyzed products **26** and **27**. TLC studies revealed that the expected product was formed in the reaction medium, but unfortunately it was not stable enough to be isolated. We also tried to convert **25** to desired compound **28** in situ by treating with saturated methanolic ammonia in a steel bomb at 100°C but without success. In an alternative approach, key intermediate **5** was treated with silylated *N*-benzoyladenine under similar reaction conditions with trimethylsilyltriflate as Lewis acid to give the desired compound **29** in only 30% yield along with unidentified side products. However, much improved yields were achieved when the key intermediate **5** was treated with *N*-benzoyladenine in the presence of tin(IV) chloride in anhydrous acetonitrile (Scheme 4). The resulting compound **29** was first chemo-selectively deacylated with partially saturated methanolic ammonia to give compound **30**. Compound **30** was treated with trifluoro-



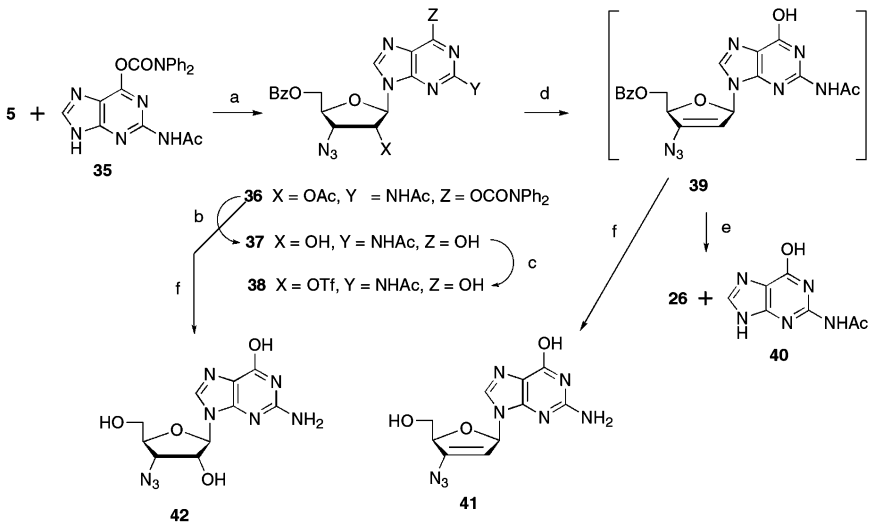
SCHEME 3 Reagents and conditions: (a) 6-Chloropurine, BSA, TMSOTf, CH_3CN, 50–70°C; (b) partially saturated NH_3/MeOH, 0°C; (c) Tf_2O, Py, CH_2Cl_2, −40°C; (d) TBAF, THF, rt; (e) work up; (f) NH_3/MeOH, steel bomb, 100°C.



SCHEME 4 Reagents and conditions: (a) N-Benzoyladenine, $SnCl_4$, CH_3CN, rt; (b) partially saturated NH_3/MeOH, 0°C; (c) Tf_2O, Py, CH_2Cl_2, −40°C; (d) TBAF, THF, rt; (e) work up; (f) K_2CO_3, MeOH, rt; (g) NH_3/MeOH, rt.

methanesulfonic anhydride in a mixture of pyridine and methylene chloride at −40°C to obtain triflate derivative **31**, which was treated with TBAF in THF. After usual work up and purification, a similar cleavage product **26** was obtained along with the corresponding free base N^6-benzoyladenine. Since the elimination product was not stable enough to isolate, we searched for an alternative method where both elimination and deprotection would take place in a single step. Such triflate elimination reaction was reported with potassium carbonate in methanol[19] and it was also known in the literature that the same potassium carbonate would work for the deprotection of a benzoyl group. The same method was applied to the triflate sugar **31**, which gave the desired final product **28** along with the deprotected product **34** in 30% and 22% yields, respectively. Since the yield of the final nucleoside **28** was poor, an alternative method was tried in which the unstable eliminated compound **32** was treated with saturated methanolic ammonia in situ without work up to give the desired final compound **28** in 75% yield. On the other hand, compound **29** was treated with saturated methanolic ammonia to give the final nucleoside **34** in 87% yield.

For the synthesis of guanine analogs **41** and **42** (Scheme 5), initially the condensation of persilylated-protected guanine with the key intermediate **5** was carried out using (trimethylsilyl) trifluoromethane sulfonate in acetonitrile to give compound **36** in 74% yield. In order to obtain the final compound **41**, a similar sequence of reactions were followed, in which compound **36** was first treated with hydrazine hydrate in buffered acetic acid and pyridine to give compound **37** in 78% yield. Compound **37** was converted



SCHEME 5 Reagents and conditions: (a) **35**, BSA, TMSOTf, CH_3CN, 50–70°C; (b) $N_2H_4.H_2O$, AcOH-Py; (c) Tf_2O, Py, CH_2Cl_2, −40°C; (d) TBAF, THF, rt; (e) work up; (f) NH_3/MeOH, rt.

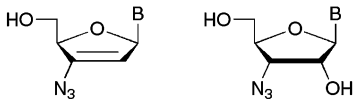
to the triflate derivative **38** in 81% yield, which was subsequently treated with TBAF in THF. After work up, similar elimination product **26** and the corresponding free base **40** were observed. To obtain the final compound, a similar strategy (i.e., compound **32** to **28**) was followed, where the elimination compound **39** was treated with saturated methanolic ammonia to afford the final nucleoside **41** in 72% yield. Compound **36** was directly converted to the final nucleoside **42** with saturated methanolic ammonia in 83% yield.

ANTI-HIV ACTIVITY

The synthesized β-D-3′-azido-2′,3′-unsaturated nucleosides (**18**, **19**, **28**, and **41**) and β-D-3′-azido-3′-deoxyribofuranosylnucleosides (**20**, **21**, **34**, and **42**) were evaluated against HIV-1 in human PBM cells in vitro, as well as their cytotoxicity and the results are summarized in Table 1. Among these nucleosides, compounds **42** (9.03 μM), **34** (13.9 μM), **18** (31.0 μM), **19** (44.9 μM), and **41** (46.5 μM) exhibited moderate anti-HIV activity with significant cytotoxicity in PBM, CEM and vero cells. Adenine analog **28** exhibited weak anti-HIV activity with significant cytotoxicity. Compounds **20** and **21** exhibited weak anti-HIV activities without significant cytotoxicity.

In summary, we have developed an efficient synthetic methodology for the synthesis of β-D-3′-azido-2′,3′-unsaturated nucleosides and β-D-3′-azido-3′-deoxyribofuranosylnucleosides and evaluated their anti-HIV activities. Some of the synthesized compounds exhibited moderate anti-HIV activity.

TABLE 1 In Vitro Anti-HIV-1 Activity and Toxicity of β-D-3′-Azido-2′,3′-Unsaturated Nucleosides and β-D-3′-Azido-3′-Deoxyribofuranosylnucleosides



18, **19**, **28** & **41** **20**, **21**, **34** & **42**

	Anti-HIV-1 activity (PBM)		Toxicity (μM)		
Comp. (B)	EC_{50} (μM)	EC_{90} (μM)	PBM	CEM	VERO
Thymine (**18**)	31.0	83.5	24.2	11.7	>100
Cytosine (**19**)	44.9	>100	~100	20.7	>100
Adenine (**28**)	>100	>100	42.4	4.1	>100
Guanine (**41**)	46.5	>100	28	11.3	15.5
Thymine (**20**)	>100	>100	>100	>100	>100
Cytosine (**21**)	91.0	>100	>100	>100	>100
Adenine (**34**)	13.9	48.3	59.4	>100	84.1
Guanine (**42**)	9.03	>100	14.5	33.8	>100
AZT	0.0024	0.014	>100	14.3	28

EXPERIMENTAL

Melting points were determined on a Mel-temp II apparatus and were uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker 500 AMX spectrophotometer at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR with tetramethylsilane as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (single), d (double), t (triple), q (quartet), m (multiplet), br (broad singlet), and dd (doublet of doublets). UV spectra were recorded on a Beckman DU-650 spectrophotometer. Optical rotation was measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a LCT premier electrospray ionization high-resolution mass spectrometer. TLC was performed on uniplates (silica gel) purchased from Analtech Co. Silica gel G (TLC grade, >440 mesh) was used for vacuum column chromatography as well as for flash column chromatography. Elemental analysis were performed by Atlantic Microlab Inc., Norcross, Georgia.

3′-Azido-2′-*O*-acetyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosylthymine (6). *N,O-Bis*(trimethylsilyl)acetamide (BSA, 2.0 mL, 8.0 mmol) was added at room temperature to a mixture of compound **5** (1.0 g, 2.74 mmol) and thymine (0.40 g, 3.20 mmol) in anhydrous acetonitrile (30 mL) under argon, then stirred for 1 h at 50–60°C to form a clear solution. After being cooled to room temperature, trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.54 mL, 3.0 mmol) was added and the resulting mixture was

heated to 65–70°C for 6 h. The reaction mixture was cooled to room temperature, then quenched with saturated aqueous sodium bicarbonate solution (15 mL) and stirred until the evolution of CO_2 ceased. The resulting mixture was diluted with ethyl acetate (80 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (100:1 v/v) to give compound **6**[20] (0.98 g, 83%) as a white foam. mp 58–60°C; $[\alpha]_D^{25}$ 31.3° (c, 0.56, $CHCl_3$); UV (MeOH) λ_{max} 264.0 nm; IR (neat): 2111.82 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 1.68 (s, 3 H, 5-CH_3), 2.21 (s, 3 H, 2′-OAc), 4.27 (m, 1 H, 4′-H), 4.48 (t, $J = 6$ Hz, 1 H, 3′-H), 4.60 (dd, $J = 4$, 12 Hz, 1 H, 5′-H_a), 4.74 (dd, $J = 3$, 12 Hz, 1 H, 5′-H_b), 5.54 (dd, $J = 5$, 6 Hz, 1 H, 2′-H), 5.85 (d, $J = 4.5$ Hz, 1 H, 1′-H), 7.03 (d, $J = 1.5$ Hz, 1 H, 6-H), 7.47–7.50 (m, 2 H, Ar-H), 7.60–7.64 (m, 1 H, Ar-H), 8.07 (dd, $J = 1.5$, 8 Hz, 2 H, Ar-H), 8.54 (bs, 1 H, 4-OH), ^{13}C NMR ($CDCl_3$) δ 12.24, 20.51, 60.17, 63.36, 74.98, 79.79, 89.47, 111.86, 128.77, 129.16, 129.69, 133.74, 135.98, 150.14, 163.67, 166.05, 170.09; MS (ESI) m/z 452 (M+Na).

3′-Azido-2′-*O*-acetyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-N^4-benzoyl Cytosine (7). Using the same procedure as described for **6**, compound **5** (1.10 g, 3.0 mmol) was condensed with N^4-benzoyl cytosine (0.75 g, 3.5 mmol) using BSA (2.21 mL, 9.0 mmol) and TMSOTf (0.60 mL, 3.3 mmol) for 4 h to produce compound **7** (1.23 g, 79%) as a white foam. $R_f = 0.55$ (CH_2Cl_2/MeOH, 10:1); mp 80-82°C; $[\alpha]_D^{25}$ 46.3° (c, 0.51, $CHCl_3$); UV (MeOH) λ_{max} 261.0 nm; IR (neat): 2115.47 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H, 2′-OAc), 4.32–4.35 (m, 1 H, 4′-H), 4.42 (dd, $J = 5$, 9 Hz, 1 H, 3′-H), 4.65 (dd, $J = 4$, 12 Hz, 1 H, 5′-H_a), 4.73 (dd, $J = 3$, 12.5 Hz, 1 H, 5′-H_b), 5.76 (dd, $J = 2.5$, 5.5 Hz, 1 H, 2′-H), 5.92 (d, $J = 2$ Hz, 1 H, 1′-H), 7.44–7.54 (m, 5 H, 5,6-H, Ar-H), 7.60–7.66 (m, 2 H, Ar-H), 7.93 (dd, $J = 7$, 28 Hz, 3 H, Ar-H), 8.07–8.09 (m, 2 H, Ar-H), 8.88 (bs, 1 H, NH), ^{13}C NMR ($CDCl_3$) δ 20.51, 59.79, 62.82, 75.57, 80.17, 91.53, 127.70, 128.77, 129.02, 129.19, 129.72, 133.26, 133.76, 144.60, 162.81, 166.09, 169.58; ES HRMS calcd $C_{25}H_{22}N_6O_7$ [M+H^+] 519.1629, found 519.1601.

3′-Azido-2′-*O*-acetyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyluracil (8). Using the same procedure as described for **6**, compound **5** (1.95 g, 5.37 mmol) was condensed with uracil (0.69 g, 6.20 mmol) using BSA (3.71 mL, 15.0 mmol) and TMSOTf (1.0 mL, 5.60 mmol) for 4 h to produce compound **8**[20] (1.78 g, 80%) as a white foam. $R_f = 0.6$ (CH_2Cl_2/MeOH, 10:1); mp 73–75°C; $[\alpha]_D^{25}$ 56.3° (c, 1.3, MeOH); UV (MeOH) λ_{max} 258.0 nm; IR (neat): 2115.30 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 2.22 (s, 3 H, 2′-OAc), 4.27–4.29 (m, 1 H, 4′-H), 4.42 (dd, $J = 6.5$, 7.5 Hz, 1 H, 3′-H), 4.56

(dd, $J = 4$, 12.5 Hz, 1 H, 5′-H_a) 4.70 (dd, $J = 3$, 13 Hz, 1 H, 5′-H_b), 5.55 (dd, $J = 4$, 6 Hz, 1 H, 2′-H), 5.60 (dd, $J = 2.5$, 8.5 Hz, 1 H, 5-H), 5.79 (d, $J = 3.5$ Hz, 1 H, 1′-H), 7.31 (d, $J = 8.5$ Hz, 1 H, 6-H), 7.47-7.50 (m, 2 H, Ar-H), 7.61–7.64 (m, 1 H, Ar-H), 8.05–8.07 (m, 2 H, Ar-H), 8.85 (bs, 1 H, 4-OH); ^{13}C NMR ($CDCl_3$) δ 20.46, 60.02, 63.08, 75.19, 79.94, 90.32, 103.07, 128.71, 129.18, 129.69, 133.70, 140.39, 150.01, 163.14, 166.05, 169.89.

3′-Azido-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosylthymine (9). Hydrazine hydrate (0.7 mL, 12.0 mmol) was added to a stirred solution of compound **6** (0.86 g, 2.0 mmol) in an acetic acid-pyridine (10 mL, v/v, 1:4) mixture. After being stirred for 24 h, acetone (5 mL) was added and stirred further for 30 min. The resulting mixture was diluted with chloroform (100 mL) and washed with saturated aqueous sodium hydrogen carbonate (20 mL) followed by water (30 mL). The organic layer was dried over sodium sulfate, evaporated to dryness and coevaporated with anhydrous toluene (20 mL). The residue was purified by silica gel column chromatography using dichloromethane/methanol (100:1 v/v) obtained compound **9** (0.65 g, 84%) as a white foam. mp 78–80°C; $[\alpha]_D^{25}$ 26.6° (c, 1.2, $CHCl_3$); UV (MeOH) λ_{max} 266.0 nm; IR (neat): 2109.62 cm^{-1} (azide); ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 3 H, 5-CH_3), 4.16 (t, $J = 6$ Hz, 1 H, 3′-H), 4.49–4.51 (m, 1 H, 4′-H), 4.59 (dd, $J = 4$, 12.5 Hz, 1 H, 5′-H_a), 4.76 (dd, $J = 2.5$, 12.5 Hz, 1 H, 5′-H_b), 4.63 (t, $J = 5$ Hz, 1 H, 2′-H), 5.10 (bs, 1 H, 2′-OH), 5.86 (d, $J = 3.5$ Hz, 1 H, 1′-H), 7.26 (s, 1 H, 6-H), 7.48 (t, $J = 8$ Hz, 2 H, Ar-H), 7.61–7.64 (m, 1 H, Ar-H), 8.06 (d, $J = 8$ Hz, 2 H, Ar-H), 10.41 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 12.27, 60.48, 63.61, 75.92, 80.01, 90.40, 111.06, 128.81, 129.29, 129.67, 133.71, 134.89, 151.51, 163.79, 166.10; ES HRMS calcd $C_{17}H_{17}N_5O_6$ [M+H^+] 388.1258, found 388.1277.

3′-Azido-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosylcytosine (10). Using the same procedure as described for **9**, compound **7** (1.20 g, 2.30 mmol) was deprotected with hydrazine hydrate (0.7 mL, 12.0 mmol) in acetic acid-pyridine (10 mL, 1:4 v/v) to give compound **10** (0.61 g, 71%) as a white solid. R_f = 0.50 (CH_2Cl_2/MeOH, 10:1); mp 182-184°C; $[\alpha]_D^{25}$ 30.15° (c, 0.73, MeOH); UV (MeOH) λ_{max} 272.0 nm; IR (neat): 2112.64 cm^{-1} (azide); ^{1}H NMR (DMSO-d6) δ 4.20 (t, $J = 5.5$ Hz, 1 H, 3′-H), 4.24–4.26 (m, 1 H, 4′-H), 4.45–4.47 (m, 1 H, 2′-H), 4.49 (dd, $J = 5$, 12.5 Hz, 1 H, 5′-H_a) 4.60 (dd, $J = 3$, 12 Hz, 1 H, 5′-H_b), 5.63 (d, $J = 7.5$ Hz, 1 H, 2′-OH), 5.80 (d, $J = 3.5$ Hz, 1 H, 1′-H), 6.25 (d, $J = 5.5$ Hz, 1 H, 5-H), 7.23 (d, $J = 13.5$ Hz, 2 H, NH_2), 7.55–7.58 (m, 3 H, 6-H, and Ar-H), 7.70-7.73 (m, 1 H, Ar-H), 8.02–8.04 (m, 2 H, Ar-H); ^{13}C NMR (DMSO-d6) δ 60.97, 64.42, 74.57, 78.42, 91.23, 94.82, 129.29, 129.75, 129.79, 134.07, 141.83, 155.55, 165.98, 166.11; MS (ESI) m/z 373 (M+H^+); ES HRMS calcd $C_{16}H_{16}N_6O_5$ [M+H^+] 373.1261, found 373.1220.

3′-Azido-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyluracil (11). Using the same procedure as described for **9**, compound **8** (1.66 g, 4.0 mmol) was deprotected with hydrazine hydrate (1.1 mL, 18.0 mmol) in acetic acid-pyridine (15 mL, 1:4 v/v) to give compound **11** (1.28 g, 86%) as a white foam. $R_f = 0.55$ (CH_2Cl_2/MeOH, 10:1); mp 99–101°C; $[\alpha]_D^{25}$ 48.4° (c, 1.0, MeOH); UV (MeOH) λ_{max} 261.0 nm; IR (neat): 2111.36 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 4.16 (dd, $J = 6$, 7 Hz, 1 H, 3′-H), 4.53–4.55 (m, 1 H, 4′-H), 4.64 (dd, $J = 3.5$, 12.5 Hz, 1 H, 5′-H_a), 4.68–4.70 (m, 1 H, 2′-H), 4.70–4.73 (m, 1 H, 5′-H_b), 5.16 (bs, 1 H, 2′-OH), 5.36 (d, $J = 8$ Hz, 1 H, 5-H), 5.87 (d, $J = 3.5$ Hz, 1 H, 1′-H), 7.45–7.48 (m, 2 H, Ar-H), 7.55–7.60 (m, 2 H, Ar-H, and 6-H), 8.06–8.08 (m, 2 H, Ar-H), 10.62 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 60.14, 63.41, 75.74, 79.98, 90.66, 102.53, 128.69, 129.32, 129.70, 133.69, 139.39, 151.63, 163.25, 166.06; ES HRMS calcd $C_{16}H_{15}N_5O_6$ [M+H^+] 374.1101, found 374.1163.

3′-Azido-2′-*O*-triflyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosylthymine (12). Trifluoromethanesulfonic anhydride (0.22 mL, 1.30 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise during 5 min. to a stirred solution of compound **9** (0.39 g, 1.0 mmol) and anhydrous pyridine (0.16 mL, 2.0 mmol) in anhydrous CH_2Cl_2 (15 mL) at −40°C (acetone/dry ice bath). After being stirred for 30 min. at 20–30°C, the reaction temperature was allowed to 0°C and diluted with CH_2Cl_2 (50 mL), washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), and dried (Na_2SO_4). After evaporation of the solvent the crude was purified by silica gel column chromatography with CH_2Cl_2/MeOH (100:3) as eluent, afforded nucleoside **12** (0.40 g, 78%) as a pale red solid. UV (MeOH) λ_{max} 263.0 nm; IR (neat): 2117.34 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 1.88 (s, 3 H, 5-CH_3), 4.30–4.36 (m, 2 H, 5′-H), 4.51 (dd, $J = 4$, 6 Hz, 1 H, 3′-H), 5.41 (dd, $J = 2$, 6 Hz, 1 H, 2′-H), 4.53–4.55 (m, 1 H, 4′-H), 6.30 (d, $J = 6$ Hz, 1 H, 1′-H), 7.22 (d, $J = 1.5$, 1 H, 6-H), 7.44 (t, $J = 7$ Hz, 2 H, Ar-H), 7.57–7.60 (m, 1 H, Ar-H), 7.93 (dd, $J = 1$, 8.5 Hz, 2 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.01, 62.73, 65.99, 83.04, 86.50, 90.30, 119.61, 128.65, 128.82, 129.65, 130.19, 133.73, 158.93, 165.73, 172.00.

3′-Azido-2′-*O*-triflyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosylcytosine (13). Using the same procedure as described for **12**, compound **10** (0.37 g, 1.0 mmol) was also reacted with trifluoromethanesulfonic anhydride (0.22 mL, 1.30 mmol) under similar reaction conditions. After standard work up desired compound was not obtained.

3′-Azido-2′-*O*-triflyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyluracil (14). Using the same procedure as described for **12**, trifluoromethanesulfonic anhydride (0.44 mL, 2.60 mmol) was added dropwise to a stirred solution of

compound **11** (0.75 g, 2.0 mmol) and anhydrous pyridine (0.4 mL, 5 mmol) in anhydrous CH_2Cl_2 (25 mL) under similar reaction conditions. After standard work up and purification produced compound **14** (0.83 g, 82%) as a light red solid. $R_f = 0.53$ (CH_2Cl_2/MeOH, 10:1); UV (MeOH) λ_{max} 257.0 nm; IR (neat): 2112.28 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 4.32 (d, $J = 6$ Hz, 2 H, 5′-H), 4.51–4.53 (m, 1 H, 3′-H), 4.53–4.55 (m, 1 H, 4′-H), 5.50 (dd, $J = 1.5$, 6 Hz, 1 H, 2′-H), 5.97 (d, $J = 7.5$ Hz, 1 H, 5-H), 6.41 (d, $J = 6$ Hz, 1 H, 1′-H), 7.42–7.45 (m, 3 H, 6-H, and Ar-H), 7.56–7.59 (m, 1 H, Ar-H), 7.93–7.95 (m, 2 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 62.83, 65.79, 83.13, 86.83, 90.25, 110.40, 128.63, 128.86, 129.68, 133.68, 135.10, 159.40, 165.77, 171.60.

3′-Azido-5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosylthymine (15). To a stirred solution of nucleoside **12** (0.35 g, 0.67 mmol) in anhydrous tetrahydrofuran (20 mL) was added TBAF in THF solution (1 M) (1.34 mL, 1.34 mmol). The mixture was stirred for 20 h at room temperature and then evaporated to dryness. The resulting residue was dissolved in chloroform (100 mL) and washed with water (30 mL). The organic layer was dried and evaporated to dryness under reduced pressure. The crude was purified by silica gel column chromatography with dichloromethane/MeOH (100:3) afforded the title compound **15** (0.22 g, 87%) as a white foam. mp 68–70°C; $[\alpha]_D^{25}$ −119.9° (c, 1.6, $CHCl_3$) UV (MeOH) λ_{max} 261.0 nm; IR (neat): 2119.86 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 1.43 (s, 3 H, 5-CH_3), 4.40 (dd, $J = 4$, 13 Hz, 1 H, 5′-H_a), 4.70 (dd, $J = 2$, 12.5 Hz, 1 H, 5′-H_b), 4.90–4.95 (m, 1 H, 4′-H), 5.54 (t, $J = 2$ Hz, 1 H, 1′-H), 7.04 (dd, $J = 1.5$, 4 Hz, 1 H, 2′-H), 7.20 (d, $J = 1$ Hz, 1 H, 6-H), 7.46–7.48 (m, 2 H, Ar-H), 7.59–7.62 (m, 1 H, Ar-H), 7.99–8.02 (m, 2 H, Ar-H), 9.18 (bs, 1 H, 4-OH); ^{13}C NMR ($CDCl_3$) δ 11.83, 63.37, 80.52, 88.05, 108.05, 111.58, 128.77, 129.51, 129.61, 133.63, 134.83, 143.95, 150.67, 163.60, 165.96; ES HRMS calcd $C_{17}H_{15}N_5O_5$ [M+Na^+] 392.0970, found 392.0919.

3′-Azido-5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyluracil (16). Using the same procedure as described for **15**, compound **14** (0.75 g, 1.50 mmol) was treated with TBAF/THF (1 M) solution (3 mL, 3.0 mmol) in anhydrous THF obtained compound **16** (0.45 g, 85%) as a white foam. $R_f = 0.56$ (CH_2Cl_2/MeOH, 10:1); mp 122–124°C; $[\alpha]_D^{25}$ −146.5° (c, 1.1, $CHCl_3$); UV (MeOH) λ_{max} 259.0 nm; IR (neat): 2110.28 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 4.45 (dd, $J = 3$, 13 Hz, 1 H, 5′-H_a), 4.69 (dd, $J = 2.5$, 13.5 Hz, 1 H, 5′-H_b), 4.89–4.4.91 (m, 1 H, 4′-H), 5.23 (dd, 1.5, 8 Hz, 1 H, 5-H), 5.49 (t, $J = 1.5$ Hz, 1 H, 1′-H), 7.05 (dd, $J = 1.5$, 3.5 Hz, 1 H, 2′-H), 7.47–7.50 (m, 3 H, 6-H, and Ar-H), 7.60–7.64 (m, 1 H, Ar-H), 7.97–7.99 (m, 2 H, Ar-H), 9.54 (bs, 1 H, 4-OH); ^{13}C NMR ($CDCl_3$) δ 62.91, 80.75, 88.06, 102.84, 107.63, 128.77, 129.44, 129.54, 133.74, 139.72, 144.23, 150.68, 163.26, 165.88; ES HRMS calcd $C_{16}H_{13}N_5O_5$ [M+Na^+] 378.0814, found 378.0746.

3′-Azido-5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosylcytosine (17). A mixture of **16** (0.36 g, 1.0 mmol), 4-dimethylamino pyridine (0.24 g, 2.0 mmol), triethylamine (0.20 g, 2.0 mmol) and 2,4,6-triisopropylbenzene sulfonyl chloride (0.61 g, 2.0 mmol) in anhydrous acetonitrile (30 mL) was stirred at room temperature for 24 h. After the addition of 30% NH_4OH (7 mL), the mixture was further stirred for 5 h, then $CHCl_3$ (150 mL) and water (35 mL) were added and the resulting mixture was partitioned. The organic phase was washed with saturated aqueous NH_4Cl solution, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography with dichloromethane/MeOH (100:4) and obtained the desired nucleoside **17** (0.28 g, 78%) as a white solid. mp 104–106°C; $[\alpha]_D^{25}$ −148.4° (c, 0.55, MeOH), UV (MeOH) λ_{max} 272.0 nm; IR (neat): 2121.96 cm^{-1} (azide); ^1H NMR (CD_3OD) δ 4.44 (dd, 3.5, 13 Hz, 1 H, 5′-H_a), 4.70 (dd, $J = 2.5$, 13 Hz, 1 H, 5′-H_b), 4.98–5.00 (m, 1 H, 4′-H), 5.45 (d, 8 Hz, 1 H, 5-H), 5.75 (t, $J = 2$ Hz, 1 H, 1′-H), 7.03 (dd, $J = 2$, 3.5 Hz, 1 H, 2′-H), 7.54 (t, 8 Hz, 2 H, Ar-H), 7.66–7.69 (m, 2 H, 6-H, and Ar-H), 8.01 (dd, 1.5, 8 Hz, 2 H, Ar-H); ^{13}C NMR (CD_3OD) δ 61.53, 79.08, 87.69, 93.42, 106.84, 126.86, 127.66, 128.06, 131.71, 139.52, 141.83, 155.46, 164.39, 164.67; Anal. calcd for $C_{16}H_{14}N_6O_4$: C, 54.24; H, 3.98; N, 23.72; Found C, 53.91; H, 4.40; N, 23.47.

3′-Azido-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosylthymine (18). A solution of compound **15** (0.17 g, 0.46 mmol) in methanolic ammonia (previously saturated at 0°C) (20 mL) was stirred for 16 h at room temperature. Upon completion of the reaction, the solvent was removed under reduced pressure. The resulting crude was purified by silica gel column chromatography with dichloromethane/MeOH (100:4) afforded the target nucleoside **18** (0.10 g, 84%) as a white solid. $R_f = 0.45$ (CH_2Cl_2/MeOH, 10:1); mp 52–54°C, [lit.[13] mp 145°C (Decomposition)]; $[\alpha]_D^{25}$ −265.2° (c, 0.6, MeOH); UV (MeOH) λ_{max} 261.0 nm, (ε 14,813) (pH 2), 261.0 nm, (ε 15,190) (pH 7), 260.0 nm, (ε 13,116) (pH 11); IR (neat): 2112.32 cm^{-1} (azide); ^1H NMR (DMSO-D6) δ 1.76 (d, $J = 0.5$ Hz, 3 H, 5-CH_3), 3.56–3.64 (m, 2 H, 5′-Hs), 4.64–4.67 (m, 1 H, 4′-H), 5.25 (t, $J = 2.5$ Hz, 1 H, 5′-OH, D_2O exch), 5.73 (t, $J = 1.75$ Hz, 1 H, 2′-H), 6.86 (dd, $J = 1.75$, 3.25 Hz, 1 H, 1′-H), 7.86 (d, $J = 1.5$ Hz, 1 H, 6-H), 11.35 (bs, 1 H, NH, D_2O exch); ^{13}C NMR (CD_3OD) δ 11.09, 60.80, 61.06, 74.82, 82.41, 89.10, 110.21, 136.80, 151.22, 165.00; MS (ESI) m/z 288 ($M+Na^+$); Anal. calcd for $C_{10}H_{11}N_5O_4$: C, 45.28; H, 4.18; N, 26.41; Found C, 45.06; H, 4.44; N, 26.17.

3′-Azido-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosylcytosine (19). Using the same procedure as described for **18**, compound **17** (0.20 g, 0.57 mmol) was treated with saturated methanolic ammonia (20 mL) obtained

the title nucleoside **19** (0.12 g, 82%) as a white solid. $R_f = 0.35$ (CH_2Cl_2/MeOH, 10:1); mp 123–125°C; $[\alpha]_D^{25}$ −102.2° (c, 0.6, MeOH); UV (MeOH) λ_{max} 265.0 nm (ε 16,333) (pH 7), 268.0 nm (ε 2586) (pH 2) 265.0 nm (ε 16,233) (pH 11); IR (neat): 2124.26 cm^{-1} (azide); ^1H NMR (CD_3OD) δ 3.72 (dd, $J = 2.5$, 13 Hz, 1 H, 5′-H_a), 3.77 (dd, $J = 2$, 13 Hz, 1 H, 5′-H_b), 4.64–4.66 (m, 1 H, 4′-H), 5.62 (t, $J = 2$ Hz, 1 H, 1′-H), 5.89 (d, $J = 7$ Hz, 1 H, 5-H), 7.05 (dd, $J = 1.25$, 2.5 Hz, 1 H, 2′-H), 8.10 (d, $J = 7$ Hz, 1 H, 6-H); ^{13}C NMR (CD_3OD) δ 60.58, 83.61, 88.93, 94.69, 108.16, 142.30, 144.02, 157.27, 166.40; Anal. calcd for $C_9H_{10}N_6O_3$, 0.1 H_2O: C, 42.89; H, 4.08; N, 33.35; Found C, 42.95; H, 4.04; N, 32.98.

3′-Azido-3′-deoxy-β-D-ribofuranosylthymine (20). Using the same procedure as described for **18**, compound **6** (0.15 g, 0.39 mmol) was treated with saturated methanolic ammonia (15 mL) produced the title compound **20**[21] (0.087 g, 79%) as a white solid. $R_f = 0.34$ (CH_2Cl_2/MeOH, 10:1); mp 56–58°C; $[\alpha]_D^{25}$ 62.2° (c, 0.47, MeOH); UV (MeOH) λ_{max} 266.0 nm.

3′-Azido-3′-deoxy-β-D-ribofuranosylcytosine (21). Using the same procedure as described for **18**, compound **7** (0.30 g, 0.58 mmol) was treated with saturated methanolic ammonia (30 mL) produced the title compound **21** (0.12 g, 75%) as a white solid. $R_f = 0.30$ (CH_2Cl_2/MeOH, 10:1); mp 70–72°C; $[\alpha]_D^{25}$ 99.3° (c, 0.32, MeOH); UV (MeOH) λ_{max} 270.0 nm (ε 11,086) (pH 7), 270.0 nm (ε 10,523) (pH 11) 271.0 nm (ε 10,953) (pH 2); ^1H NMR (DMSO-d6) δ 3.55–3.59 (m, 1 H, 5′-H_a), 3.66–3.70 (m, 1 H, 5′-H_b), 3.89–3.92 (m, 1 H, 4′-H), 3.95 (t, $J = 6$ Hz, 1 H, 3′-H), 4.35 (q, $J = 5$ Hz, 1 H, 2′-H), 5.24 (t, $J = 5.5$ Hz, 1 H, 5′-OH, D_2O exch), 5.72 (d, $J = 7.5$ Hz, 1 H, 5-H), 5.77 (d, $J = 4$ Hz, 1 H, 1′-H), 6.12 (d, $J = 5.5$ Hz, 1 H, 2′-OH, D_2O exch), 7.17 (d, $J = 25$ Hz, 2 H, NH_2, D_2O exch), 7.82 (d, $J = 7.5$ Hz, 1 H, 6-H); ^{13}C NMR (DMSO-d6) δ 61.05, 74.86, 81.83, 89.87, 94.59, 141.86, 142.33, 155.78, 166.07; ES HRMS calcd $C_9H_{12}N_6O_4$ [M+H^+] 269.0999, found 269.0972; Anal. calcd for $C_9H_{12}N_6O_4$ 0.3 H_2O: C, 39.50; H, 4.64; N, 30.71; Found C, 39.93; H, 4.64; N, 30.33.

3′-Azido-2′-*O*-acetyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-6-chloro-9*H*-purine (22). Using the same procedure as described for **6**, compound **5** (1.27 g, 3.50 mmol) was condensed with 6-chloropurine (0.62 g, 4.0 mmol) using BSA (1.10 mL, 4.50 mmol) and TMSOTf (0.68 mL, 3.80 mmol) for 4 h to produce compound **22** (1.44 g, 90%) as a white foam. $R_f = 0.6$ (EtOAc/hexane, 4:6); mp 113–114°C; $[\alpha]_D^{25}$ 12.2° (c, 0.72, $CHCl_3$); UV (MeOH) λ_{max} 264.0 nm; IR (neat): 2114.36 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 2.22 (s, 3 H, 2′-OAc), 4.40–4.43 (m, 1 H, 4′-H), 4.58 (dd, $J = 4$, 13 Hz, 1H, 5′-H_a), 4.78 (dd, $J = 3.25$, 12.5 Hz, 1H, 5′-H_b), 4.93 (dd, $J = 6$, 7.5 Hz, 1 H, 3′-H), 6.09–6.13 (m, 2 H, 1′-H, and 2′-H), 7.41–7.44 (m, 2 H,

Ar-H), 7.57–7.62 (m, 1 H, Ar-H), 7.94–7.96 (m, 2 H, Ar-H), 8.17 (s, 1 H, 8-H), 8.52 (s, 1 H, 2-H); ^{13}C NMR ($CDCl_3$) δ 20.44, 60.07, 62.58, 74.97, 80.48, 88.07, 128.55, 129.05, 129.56, 132.41, 133.61, 144.58, 150.82, 151.57, 152.14, 166.01, 169.79; ES HRMS calcd $C_{19}H_{16}ClN_7O_5$ [M+H$^+$] 458.0980, found 458.1075.

3′-Azido-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-6-chloro-9*H*-purine (23). To a solution of compound **22** (0.73 g, 1.60 mmol) in methanol (40 mL) was added a saturated methanolic ammonia (6 mL) at 0°C and stirred at the same temperature for 10 min. The solvent was evaporated to dryness under reduced pressure and the residue was purified by silica gel column chromatography with 35% EtOAc/hexane as eluent, afforded the compound **23** (0.57 g, 86%) as a white foam. R_f = 0.50 (EtOAc/hexane, 4:6); mp 142–144°C; $[\alpha]_D^{25}$ 20.6° (c,1.0, $CHCl_3$); UV (MeOH) λ_{max} 263.0 nm; IR (neat): 2113.03 cm^{-1} (azide); ^{1}H NMR ($CDCl_3$) δ 4.12 (bs, 1 H, 2′-OH), 4.50–4.53 (m, 1 H, 4′-H), 4.58 (dd, J = 3.5, 13 Hz, 1H, 5′-H$_a$), 4.67 (t, 5.5 Hz, 1 H, 3′-H), 4.74 (dd, J = 3.5,12 Hz, 1 H, 5′-H$_b$), 5.10–5.12 (m, 1 H, 2′-H), 5.99 (d, J = 4 Hz, 1 H, 1′-H), 7.35–7.38 (m, 2 H, Ar-H), 7.53–7.57 (m, 1 H, Ar-H), 7.83–7.86 (m, 2 H, Ar-H,), 8.24 (s, 1 H, 8-H), 8.55 (s, 1 H, 2 H, 2-H); ^{13}C NMR ($CDCl_3$) δ 62.30, 63.19, 75.17, 81.23, 90.59, 128.55, 128.89, 129.50, 132.10, 133.68, 144.49, 150.58, 151.38, 151.86, 166.06; ES HRMS calcd $C_{17}H_{14}ClN_7O_4$ [M+Na$^+$] 438.0693, found 438.0753.

3′-Azido-2′-*O*-triflyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-9*H*-6-chloropurine (24). Using the same procedure as described for **12**, trifluoromethanesulfonic anhydride (0.25 mL, 1.50 mmol) was added dropwise to a stirred solution of compound **23** (0.46 g, 1.10 mmol) and anhydrous pyridine (0.5 mL, 6.0 mmol) in anhydrous CH_2Cl_2 (20 mL) under similar reaction conditions obtained compound **24** (0.51 g, 84%) as a light red color solid. R_f = 0.5 (EtOAc/hexane, 4:6); UV (MeOH) λ_{max} 263.0 nm; IR (neat): 2122.90 cm^{-1} (azide); ^{1}H NMR ($CDCl_3$) δ 4.44-4.47 (m, 1 H, 4′-H), 4.65 (dd, J = 3.25, 12.75 Hz, 1 H, 5′-H$_a$), 4.79 (dd, J = 3, 13 Hz, 1 H, 5′-H$_b$), 5.12 (dd, J = 5.5, 8.25 Hz, 1 H, 3′-H), 6.17 (dd, J = 2, 5.5 Hz, 1 H, 2′-H), 6.20 (d, J = 2.5 Hz, 1 H, 1′-H), 7.40–7.43 (m, 2 H, Ar-H), 7.59–7.63 (m, 1 H, Ar-H), 7.86 (dd, J = 1.5, 8 Hz, 2 H, Ar-H), 8.21 (s, 1 H, 8-H), 8.44 (s, 1 H, 2-H); ^{13}C NMR ($CDCl_3$) δ 59.92, 61.43, 80.50, 85.45, 88.04, 128.63, 128.74, 129.53, 132.54, 133.87, 144.26, 150.38, 152.24, 152.35, 165.93.

COMPOUNDS 26 AND 27

Using the same procedure as described for **15**, compound **24** (0.48 g, 0.87 mmol) was treated with TBAF/THF (1 M) solution (0.87 mL, 0.87 mmol) in anhydrous THF, after usual work up and purification obtained

compound **26** (0.18 g, 84%) as a colorless oil (0.11 g, 82%) and 6-chloropurine **27** as a yellow solid, respectively. Compound **26**: $R_f = 0.7$ (EtOAc/hexane, 1:9); MS (ESI) m/z (M+Na) $^+$266; IR (neat): 2122.72 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 5.25 (s, 2 H), 6.40 (d, $J = 2$ Hz, 1 H), 7.38–7.44 (m, 3 H), 7.53–7.57 (m, 1 H), 8.03–8.06 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 55.50, 104.98, 126.13, 128.37, 129.80, 133.13, 138.02, 143.36, 165.35, 166.19.

3′-Azido-2′-*O*-acetyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-N^6-benzoyl Adenine (29). To a stirred solution of compound **5** (1.45 g, 4.0 mmol) and N^6-benzoyladenine (1.20 g, 5.0 mmol) in anhydrous acetonitrile (35 mL) was added 1 M stannic chloride solution in dichloromethane (9 mL, 9 mmol) at room temperature and the mixture was stirred for 2 h at same temperature. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and stirred until the evolution of CO_2 ceased. The reaction mixture was diluted with EtOAc (75 mL) and the organic phase was separated and the aqueous phase was back extracted with an additional amount of EtOAc (100 mL). The combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$ (40 mL) H_2O (45 mL), dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography with dichloromethane/MeOH (100:1) as eluent to give nucleoside **29**[20] (1.54 g, 71%) as a white foam. mp 108–110°C; $[\alpha]_D^{25}$ 6.6° (c, 0.68, $CHCl_3$); UV (MeOH) λ_{max} 279.0 nm; IR (neat): 2113.39 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 2.21 (s, 3 H, 2′-OAc), 4.39–4.42 (m, 1 H, 4′-H), 4.58 (dd, $J = 4.5$, 12.5 Hz, 1 H, 5′-H_a), 4.77 (dd, $J = 3.5$, 12.5 Hz, 1 H, 5′-H_b), 4.98 (dd, $J = 6$, 7 Hz, 1 H, 3′-H), 6.11 (d, $J = 3.5$ Hz, 1 H, 1′-H), 6.14 (dd, 3.25, 6 Hz, 1 H, 2′-H), 7.40–7.44 (m, 2 H, Ar-H), 7.50 (t, $J = 8$ Hz, 2 H, Ar-H), 7.54–7.61 (m, 2 H, Ar-H), 7.97–8.02 (m, 4 H, Ar-H), 8.07 (s, 1 H, 8-H), 8.61 (s, 1 H, 2-H), 9.15 (bs, 1 H, N^6HCOPh); ^{13}C NMR ($CDCl_3$) δ 20.50, 60.20, 62.89, 75.10, 80.29, 87.90, 123.73, 127.93, 128.58, 128.90, 129.16, 129.68, 132.91, 133.46, 133.57, 142.27, 149.84, 151.25, 152.89, 164.64, 166.11, 169.85.

3′-Azido-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-N^6-benzoyl Adenine (30). To a solution of compound **29** (1.39 g, 2.55 mmol) in methanol (30 mL) was added a saturated methanolic ammonia (10 mL) at 0°C and stirred at the same temperature for 1 h. The solvent was evaporated to dryness under reduced pressure and the residue was purified by silica gel column chromatography with dichloromethane/MeOH (100-2 mL) as eluent, afforded the compound **30** (0.96 g, 75%) as a white foam. mp 102–104°C; $[\alpha]_D^{25}$ 4.1° (c, 0.54, $CHCl_3$); UV (MeOH) λ_{max} 279.0 nm; IR (neat): 2110.31 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 4.49–4.53 (m, 1 H, 4′-H), 4.55 (dd, $J = 4$, 12.5 Hz, 1 H, 5′-H_a), 4.60 (t, $J = 5$ Hz, 1 H, 3′-H), 4.71 (dd, $J = 3.5$, 12.5 Hz, 1 H, 5′-H_b), 5.00 (bs, 1 H, 2′-OH), 5.15 (t, $J = 4.5$ Hz, 1 H,

2′-H), 6.01 (d, $J = 5$ Hz, 1 H, 1′-H), 7.36 (t, $J = 8$ Hz, 2 H, Ar-H), 7.52–7.55 (m, 3 H, Ar-H), 7.63 (t, $J = 7.5$ Hz, 1 H, Ar-H), 7.90 (dd, $J = 1$, 8.5 Hz, 2 H, Ar-H), 7.99 (d, $J = 2.5$ Hz, 2 H, Ar-H), 8.09 (s, 1 H, 8-H), 8.62 (s, 1 H, 2-H), 9.07 (bs, 1 H, N^6HCOPh); ^{13}C NMR ($CDCl_3$) δ 62.09, 63.70, 75.00, 80.65, 89.67, 122.74, 127.91, 128.55, 128.89, 129.15, 129.16, 129.62, 133.03, 133.25, 133.52, 142.23, 149.16, 151.02, 152.40, 166.13; ES HRMS $(M+H)^+$ calcd $C_{24}H_{20}N_8O_5$, 501.1636, found 501.1703.

3′-Azido-2′-*O*-triflyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-N^6-benzoyl Adenine (31). Using the same procedure as described for **12**, trifluoromethanesulfonic anhydride (0.43 mL, 2.60 mmol) was added dropwise to a stirred solution of compound **30** (0.65 g, 1.30 mmol) and anhydrous pyridine (0.5 mL, 6.0 mmol) in anhydrous CH_2Cl_2 (25 mL) under similar reaction conditions obtained compound **31** (0.74 g, 90%) as a pale yellow solid. $R_f = 0.6$ (CH_2Cl_2/MeOH, 10:1 mL); UV (MeOH) λ_{max} 279.0 nm; IR (neat): 2128.52 cm^{-1} (azide); ^{1}H NMR ($CDCl_3$) δ 4.42–4.45 (m, 1 H, 4′-H), 4.62 (dd, $J = 3.5$, 13 Hz, 1 H, 5′-H_a), 4.79 (dd, $J = 3$, 13 Hz, 1 H, 5′-H_b), 5.23 (dd, $J = 5.5$, 8.5 Hz, 1 H, 3′-H), 6.19 (d, $J = 2$ Hz, 1 H, 1′-H), 6.22 (d, $J = 5.5$ Hz, 1 H, 2′-H), 7.39–7.43 (m, 2 H, Ar-H), 7.52–7.59 (m, 3 H, Ar-H), 7.61–7.63 (m, 1 H, Ar-H), 7.90–7.92 (m, 2 H, Ar-H), 8.00 (d, $J = 7.5$ Hz, 2 H, Ar-H), 8.09 (s, 1 H, 8-H), 8.55 (s, 1 H, 2-H), 8.97 (bs, 1 H, N^6HCOPh); ^{13}C NMR ($CDCl_3$) δ 60.03, 61.79, 80.13, 85.83, 87.96, 123.66, 127.91, 128.59, 128.89, 128.98, 129.63, 133.05, 133.31, 133.70, 142.21, 150.07, 150.82, 153.04, 164.51, 165.99.

3′-Azido-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyladenine (28) and 3′-Azido-3′-deoxy-β-D-ribofuranosyladenine (34). To a stirred solution of compound **31** (0.68 g, 1.10 mmol) in MeOH (30 mL) was added K_2CO_3 (0.30 g, 2.17 mmol) at room temperature. After stirring for 6 h, the reaction was neutralized with acetic acid (0.025 mL). After removal of the solvent the residue was purified by silica gel column chromatography with MeOH/dichloromethane (2:100–4:100 mL) obtained compound **28** (0.09 g, 30%) as a white solid and then compound **34** (0.07 g, 22%) as a spongy solid. Compound **28**: mp 128–130°C; $[\alpha]_D^{25}$ −96.5° (c, 0.7, MeOH); UV (MeOH) λ_{max} 258.0 nm (ε 21,726) (pH 7), 258.0 nm (ε 20,376) (pH 11), (unstable in pH 2); IR (neat): 2197.05 cm^{-1} (azide); ^{1}H NMR ($CDCl_3$) δ 3.75 (dd, $J = 2.5$, 12.5 Hz, 1 H, 5′-H_a), 3.79 (dd, $J = 2.5$, 13 Hz, 1 H, 5′-H_b), 4.77–4.79 (m, 1 H, 4′-H), 5.83 (t, $J = 2$ Hz, 1 H, 1′-H), 7.09 (t, $J = 2$ Hz, 1 H, 2′-H), 8.23 (s, 1 H, 2-H), 8.43 (s, 1 H, 8-H); ^{13}C NMR ($CDCl_3$) δ 61.56, 84.26, 86.42, 108.81, 119.15, 139.87, 143.17, 149.51, 153.04, 156.47; Anal. calcd for $C_{10}H_{10}N_8O_2$: C, 43.80; H, 3.68; N, 40.86; Found C, 43.54; H, 3.94; N, 40.61. Compound **34**: mp 210–213°C, (lit.[22] mp 208–212), $[\alpha]_D^{25}$ 19.5° (c, 0.2, MeOH); UV (MeOH) λ_{max} 258 nm.

3′-Azido-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosyladenine (28). Using the same procedure as described for **15**, compound **31** (0.25 g, 0.39 mmol) was treated with TBAF/THF (1 M) solution (0.39 mL, 0.39 mmol) in anhydrous THF (15 mL), after being stirred for 45 min, the solvent was removed under reduced pressure and the resulting residue was treated with saturated methanolic ammonia (20 mL) for 20 h. After removal of the solvent the crude was purified by silica gel column chromatography with dichloromethane/MeOH (100:3 mL) afforded the desired nucleoside **28** (0.08 g, 75%) as a white solid. The mp, UV and NMR spectral data were similar to the previously obtained compound **28**.

3′-Azido-3′-deoxy-β-D-ribofuranosyladenine (34). Using the same procedure as described for **18**, compound **29** (0.35 g, 0.65 mmol) was treated with saturated methanolic ammonia (25 mL) obtained the title compound **34** (0.17 g, 87%) as a white spongy solid. The spectral data was similar to the previously obtained compound **34**.

3′-Azido-2′-*O*-acetyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-N^2-acetyl-6-*O*-diphenylcarbamoylguanine (36). Using the same procedure as described for **6**, compound **5** (0.73 g, 2.0 mmol) was condensed with N^2-acetyl-6-*O*-diphenylcarbamoyl guanine[23] (0.85 g, 2.20 mmol) using BSA (1.1 mL, 4.50 mmol) and TMSOTf (0.40 mL, 2.20 mmol) for 4 h to produce compound **36** (1.02 g, 74%) as a white foam. $R_f = 0.6$ (CH_2Cl_2/MeOH, 10:1); mp 110–112°C; $[\alpha]_D^{25}$ −2.4° (c, 0.58, $CHCl_3$); UV (MeOH) λ_{max} 277.0 nm; IR (neat): 2117.40 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 2.21 (s, 6 H, NHAc, and 2′-OAc), 4.34–4.42 (m, 1 H, 4′-H), 4.62 (dd, $J = 5$, 13 Hz, 1 H, 5′-H_a), 4.71 (dd, $J = 3.5$, 13 Hz, 1 H, 5′-H_b), 5.30 (s, 1 H, 3′-H), 5.91 (d, $J = 1.5$ Hz, 1 H, 1′-H), 5.95 (dd, $J = 1.5$, 6 Hz, 1 H, 2′-H), 7.22–7.51 (m, 13 H, Ar-H), 7.79 (s, 1 H, 8-H), 7.86–7.88 (m, 2 H, Ar-H), 8.57 (bs, 1 H, 2-NHAc); ^{13}C NMR ($CDCl_3$) δ 20.63, 25.00, 53.49, 59.52, 63.23, 76.13, 80.37, 88.75, 121.22, 126.51, 128.32, 129.26, 129.47, 129.57, 133.17, 143.56, 150.08, 151.74, 153.55, 156.03, 166.11, 170.04; Anal. calcd for $C_{34}H_{29}N_9O_8$: C, 59.04; H, 4.23; N, 18.23; Found C, 59.05; H, 4.27; N, 18.02.

3′-Azido-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-N^2-acetyl-guanine (37). Using the same procedure as described for **9**, compound **36** (1.0 g, 1.45 mmol) was deprotected with hydrazine hydrate (0.7 mL, 12.0 mmol) in acetic acid–pyridine (10 mL, 1:4 v/v) to give compound **37** (0.51 g, 78%) as a white solid. $R_f = 0.4$ (CH_2Cl_2/MeOH, 10:1); mp 98–100°C; $[\alpha]_D^{25}$ 14.7° (c, 0.58, $CHCl_3$); UV (MeOH) λ_{max} 278.0 nm, 257.0 nm; IR (neat): 2110.62 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 2.41 (s, 3 H, 2-NHAc), 4.32 (d, $J = 5.5$ Hz, 1 H, 5′-H_a), 4.48–4.52 (m, 2 H, 5′-H_b, and 4′-H), 5.20 (dd, $J = 10$, 12.5 Hz, 1 H, 3′-H), 5.58 (t, $J = 6.5$ Hz, 1 H, 2′-H), 5.74 (d, $J = 7$ Hz, 1 H, 1′-H), 6.85

(bs, 1 H, 2′-OH), 7.44 (t, $J = 8$ Hz, 2 H, Ar-H) 7.48 (s, 1 H, 8-H), 7.56–7.60 (m, 1 H, Ar-H), 7.99 (dd, $J = 1.5$, 8 Hz, 2 H, Ar-H), 9.70 (s, 1 H, 2-NHAc), 11.92 (bs, 1 H, 6-OH); ^{13}C NMR ($CDCl_3$) δ 24.25, 62.93, 65.38, 73.65, 80.84, 91.27, 121.33, 128.65, 129.18, 129.74, 133.79, 139.42, 147.02, 147.26, 154.76, 167.77, 173.04; ES HRMS $(M+H)^+$ calcd $C_{19}H_{18}N_8O_6$, 453.1270, found 453.1208.

3′-Azido-2′-*O*-triflyl-5′-*O*-benzoyl-3′-deoxy-β-D-ribofuranosyl-N^2-acetyl Guanine (38). Using the same procedure as described for **12**, trifluoromethanesulfonic anhydride (0.25 mL, 1.40 mmol) was added drop wise to a stirred solution of compound **37** (0.32 g, 0.70 mmol) and anhydrous pyridine (0.5 mL, 6.0 mmol) in anhydrous CH_2Cl_2 (20 mL) under similar reaction conditions obtained compound **38** (0.33 g, 81%) as a yellow solid. $R_f = 0.5$ (CH_2Cl_2/MeOH, 10:1 mL); UV (MeOH) λ_{max} 278.0 nm, 256.0 nm; ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3 H, 2-NHAc), 4.42–4.46 (m, 1 H, 4′-H), 4.59 (dd, $J = 5$, 12 Hz, 1 H, 5′-H_a), 4.99 (dd, $J = 6$, 12 Hz, 1 H, 3′-H), 5.26–5.30 (m, 1 H, 5′-H_b), 5.89 (d, $J = 5.5$ Hz, 1 H, 2′-H), 6.07 (d, $J = 2$ Hz, 1 H, 1′-H), 7.44 (t, $J = 8$ Hz, 2 H, Ar-H), 7.59–7.62 (m, 1 H, Ar-H), 7.69 (s, 1 H, 8-H), 7.97–7.99 (m, 2 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 24.28, 60.12, 62.73, 79.65, 87.30, 88.38, 121.98, 128.54, 128.94, 129.62, 133.73, 138.51, 147.95, 148.30, 155.99, 166.50, 172.94.

3′-Azido-2′,3′-didehydro-2′,3′-dideoxy-β-D-ribofuranosylguanine (41). Using the same procedure as described for **28**, compound **38** (0.30 g, 0.51 mmol) was treated with TBAF/THF (1 M) solution (0.51 mL, 0.51 mmol) in anhydrous THF (15 mL), after being stirred for 45 min, the solvent was removed under reduced pressure and the resulting residue was treated with saturated methanolic ammonia (25 mL) for 20 h. After removal of the solvent the crude was purified by silica gel column chromatography with MeOH/dichloromethane (12%) afforded the desired nucleoside **41** (0.11 g, 72%) as a white solid. mp 180–182°C; $[\alpha]_D^{25}$ −86.5° (c, 0.34, DMSO); UV (MeOH) λ_{max} 250.0 nm (ε 15,551) (pH 7), 253.0 nm (ε 12,356) (pH 11) (unstable in pH 2). ^{1}H NMR (DMSO-d6) δ 3.53–3.57 (m, 2 H, 5′-H), 4.71 (t, $J = 2.5$ Hz, 1 H, 4′-H), 5.12 (bs, 1 H, 5′-OH, D_2O exch), 5.88 (t, $J =$ 2 Hz, 1 H, 1′-H), 6.53 (bs, 2 H, 2-NH_2, D_2O exch), 6.71 (t, $J = 2.5$ Hz, 1 H, 2′-H), 7.89 (s, 1 H, 8-H); ^{13}C NMR (DMSO-d6) δ 61.63, 84.09, 85.86, 108.75, 116.83, 136.13, 143.10, 151.23, 154.25, 157.20; Anal. calcd for $C_{10}H_{10}N_8O_3$ 1.3 H_2O: C, 38.29; H, 4.05; N, 35.72; Found C, 38.44; H, 4.02; N, 35.46.

3′-Azido-3′-deoxy-β-D-ribofuranosylguanine (42). Using the same procedure as described for **18**, compound **36** (0.30 g, 0.63 mmol) was treated with saturated methanolic ammonia (30 mL) obtained the title nucleoside **42** (0.16 g, 83%) as a white solid. $R_f = 0.25$ (CH_2Cl_2/MeOH, 10:1); mp

246–248°C; $[\alpha]_D^{25}$ 56.9° (c, 0.37, DMSO); UV (MeOH) λ_{max} 250.0 nm (ε 11,428) (pH 7), 256.0 nm (ε 9760) (pH 11), (unstable in pH 2); ^{1}H NMR (DMSO-d6) δ 3.56 (dd, $J = 3.5, 9$ Hz, 1 H, 5′-H_a), 3.63 (dd, $J = 4, 12$ Hz, 1 H, 5′-H_b), 3.92 (q, $J = 4$ Hz, 1 H, 4′-H), 4.25 (dd, $J = 4, 5.5$ Hz, 1 H, 3′-H), 4.82 (q, $J = 5$ Hz, 1 H, 2′-H), 5.22 (t, $J = 5.5$ Hz, 1 H, 5′-OH, D_2O exch), 5.72 (d, $J = 6.5$ Hz, 1 H, 1′-H), 6.21 (d, $J = 5.5$ Hz, 1 H, 2′-OH, D_2O exch), 6.52 (bs, 2 H, 2-NH_2, D_2O exch), 7.96 (s, 1 H, 8-H), 10.67 (s, 1 H, 1-NH, D_2O exch); ^{13}C NMR (DMSO-d6) δ 61.88, 62.48, 74.73, 82.81, 86.94, 117.18, 136.00, 151.76, 154.23, 157.20; ES HRMS $(M+H)^+$ calcd $C_{19}H_{18}N_8O_6$, 453.1270, found 453.1208. Anal. calcd for $C_{10}H_{12}N_8O_4$ 1.0 H_2O: C, 36.81; H, 4.32; N, 34.34; Found C, 36.96; H, 4.34; N, 34.12.

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