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New Isomeric Analogues of Anti-HIV Active Azidonucleosides

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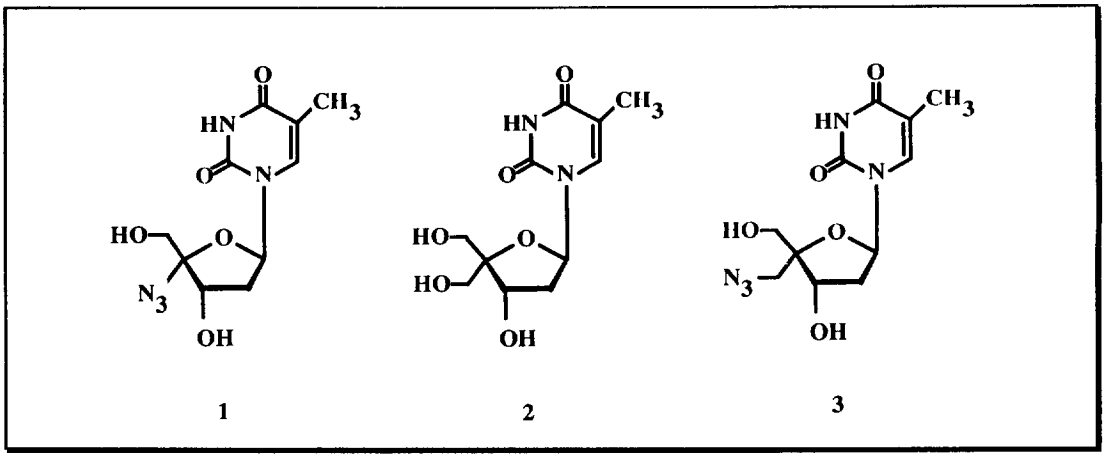
Key words: azido isodideoxynucleosides, synthesis, anti-HIV

Abstract: Synthesis and antiviral studies of novel 2'-isomeric dideoxynucleosides of the D-related class are described. The target compounds are analogues of anti-HIV active 4'-azido-2'-deoxynucleosides.

INTRODUCTION

Although nucleoside and nucleotide analogues such as 3'-azido-3'-deoxythymidine (AZT), dideoxycytidine (ddC), and dideoxyinosine (ddI) have shown remarkable activity as inhibitors of the human immunodeficiency virus (HIV), their long-term usefulness is somewhat limited by their toxicities which include bone marrow toxicity, peripheral neuropathy, pancreatitis and hepatotoxicity.[1-14] The development of resistant strains on prolonged clinical use of these compounds and their cross resistance to related nucleosides are major concerns in the development of new nucleoside antiviral agents. For this reason, the synthesis of new and distinctly different nucleosides is of considerable significance in this area. Additionally, if the new nucleosides are structurally unlike the currently used antiviral agents, the probability of cross resistance to AZT or other nucleoside resistant strains would be expected to be diminished. However, the nucleoside structural modification cannot be so major that either the new nucleoside is not recognized by cellular kinases, or that its triphosphate, if cellularly produced, does not bind competitively to HIV reverse transcriptase.

Recently, a few selective inhibitors of HIV have been found among a rare class of nucleosides, the 4'-substituted analogues.[15,16] Prisbe and coworkers[15] have suggested that 2'-deoxynucleosides bearing an azido group at the 4'-α-position (**1**) show potent anti-HIV-1 activity in CD-4$^+$ (A 3.01) cell lines [IC_{50} 0.01 μM and CC_{50} 8 μM]. 4'-Hydroxymethylthymidine (**2**) and 4'-azidomethylthymidine (**3**) synthesized by Walker et al. both show good activity against HIV.[16] Of these, the compound with the azidomethyl group at the 4'-position exhibits more potent activity than the compound with the 4'-hydroxymethyl group against HIV-1 in CD-4$^+$ (A 3.01) cell lines [IC_{50} 2.1 μM, CC_{25} >333 μM versus IC_{50} 12.5 μM, CC_{25} >200 μM].[16] However, the corresponding dideoxy analogues show only moderate to low antiviral activity.[17] Thus, the role of the oxygen at the 3'-position appears to be critical in terms of antiviral activity. Whether this role could be assumed by an endocyclic oxygen appeared worthy of investigation. This paper reports on the synthesis and antiviral studies

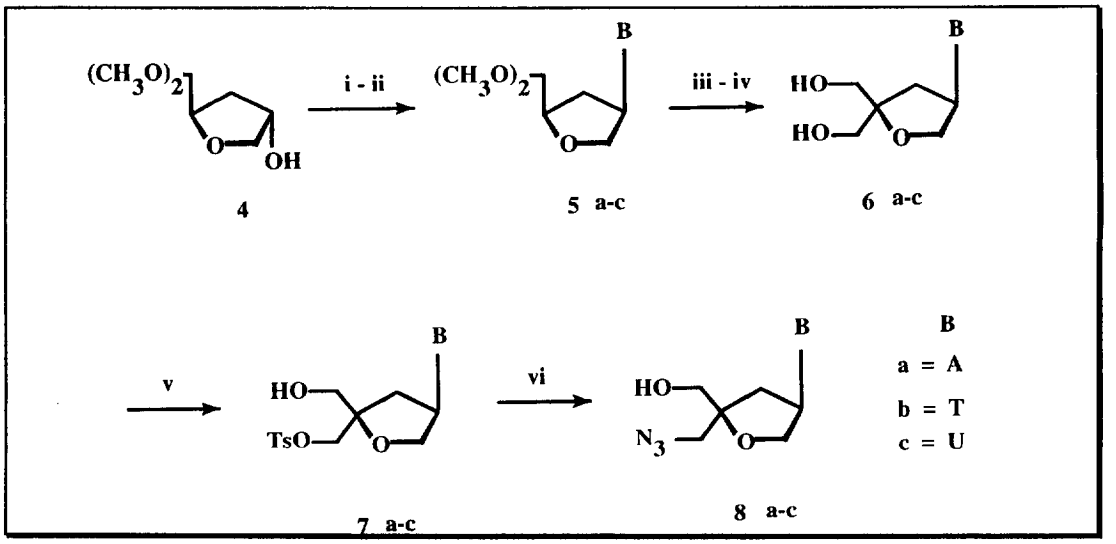


of 4'-azidomethyldeoxynucleosides with an endocyclic oxygen at the 3'-position. Of relevance to this work is the observation by us and others that isomeric dideoxynucleosides of both the (*S,S*) and (*R,R*) absolute stereochemistry, where the endocyclic oxygen has been transposed to the 3'-position, exhibit potent activity against HIV-1 and HIV-2.[18-21]

RESULTS AND DISCUSSION

The synthesis was approached with the rearranged deoxy sugar, 2(*R*)-(dimethoxymethyl)tetrahydrofuran-4(*S*)-ol, **4** (Scheme 1) prepared from the acid-catalyzed rearrangement of 1,2-O-isopropylidene-5-O-(p-toluenesulfonyl)-α-D-xylofuranose.[18,22] Coupling of the nucleic acid bases with the tosylate of **4** in the presence of potassium carbonate and 18-crown-6 in DMF gave the β-nucleosides **5** cleanly and in good yields (~70%). Hydrolysis of **5** with 0.1 M aqueous oxalic acid followed by a sequential aldol condensation and Cannizzaro reaction[22,23] gave the desired *bis*-hydroxymethyl compounds **6** in about 30 % yield.

Tosylation of the 4'-hydroxymethyl dideoxyisonucleoside analogues **6** with limiting amounts of tosyl chloride in pyridine resulted in the formation of **7** (major product) and its isomeric β–tosylate (minor product) in a combined yield of about 60%. The ratios of **7** and its β–isomer depended in part on the size of the nucleobase and were found to be 1.8:1, 1.4:1, and 1.2:1 for adenine, thymine, and uracil, respectively. Thus, the most sterically bulky base, adenine, afforded the largest amount of α-tosylated derivative and the least bulky base, uracil, afforded the least amount of α-tosylated derivative. The distinction between **7** and its β–isomer was made by differential NOE experiments. Treatment of **7** with sodium azide in the presence of catalytic amounts of 18-crown-6 in DMF at 110 °C[24] gave the desired target compounds **8** in yields of >80 %.



Reagents and Conditions: (i) TsCl, pyridine, 25°C; (ii) nucleoside base, K_2CO_3, 18-crown-6, DMF, 75°C; (iii) 0.1 M oxalic acid (aq), 80°C; (iv) 2N NaOH, 37 % formaldehyde (aq), 1,4-dioxane, 25°C; (v) TsCl, pyridine, 25°C; (vi) NaN_3, 18-crown-6, DMF, 110°C.

Scheme 1

Establishment of the structure of **8** including regiochemistry and stereochemistry was made through extensive ^1H and ^{13}C NMR studies. For example, stereochemical confirmation of the structure of **8b** was established by differential NOE experiments (Fig. 1). Thus, irradiation of 4'-H_α resulted in the enhancement of

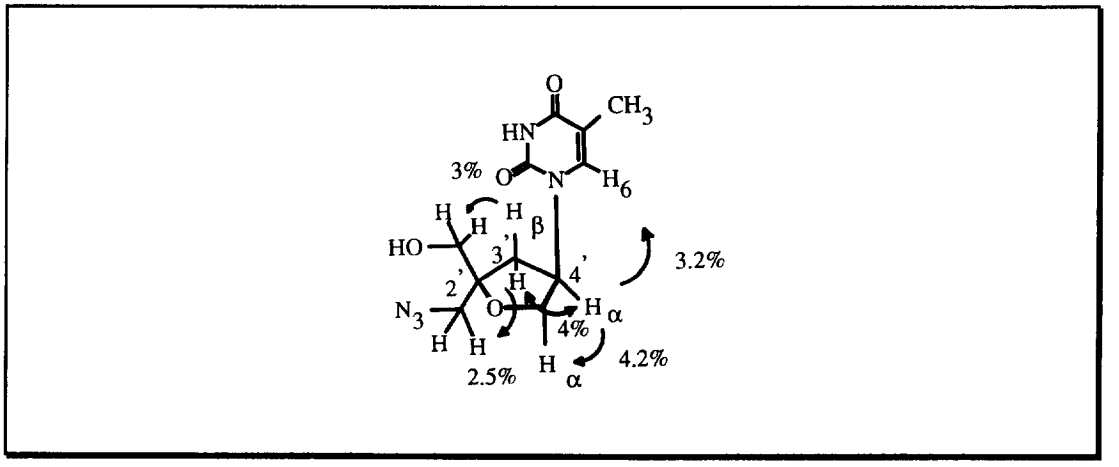


Figure 1

3'-H_α (4%), 5'-H_α (4.2%), and 6-H (3.2%). Irradiation of 3'-H_α resulted in enhancement of the signal for 4'-H_α (8.7%), the methylene protons on the azidomethyl group (2.5%), and 3'-H_β (5%). Irradiation of 3'-H_β resulted in the enhancement of the signal for the methylene protons on the hydroxymethyl group (3%), 3'-H_α (5%), and 6-H (4.5%). The larger *cis*-coupling constants ($J_{3',4'}$ = 9.1 Hz and $J_{4',5'}$ = 7.2 Hz) compared to the *trans*-coupling constants ($J_{3',4'}$ = 6.0 Hz and $J_{4',5'}$ = 4.9 Hz) are also consistent with the stereochemistry of **8b**.

The isomeric azidomethyldideoxynucleosides described in this paper, although structurally related to other active isomeric dideoxynucleosides and to other active 4'-substituted dideoxynucleosides, exhibited low *in vitro* inhibitory activity (IC_{50} > 100 μM, CC_{50} > 200 μM). The cell line used was the human T-cell lymphotropic virus type I-transformed cell line, MT4, infected with HIV-1 (strain IIIB).[25] It is unclear whether the low activity of these compounds is due to the difficulty associated with intracellular conversion to their triphosphates or to the weak competitive inhibition of the HIV RT by the triphosphate or both. Further studies to delineate this are in progress.

Experimental

Melting points were determined on a Thomas-Hoover open stage melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ or Me_2SO-d_6. Chemical shift values are reported in parts per million relative to the internal standard, TMS. Elemental analyses were carried out at the University of Iowa on a Perkin-Elmer 2400 Series II Elemental Analyzer. UV spectra were recorded on a Gilford Response spectrometer. Preparative TLC plates were made from E. Merck PF_{254} silica gel. TLC plates were visualized by ultraviolet absorbance or by charring for several minutes after exposure to either a 20% sulfuric acid/methanol solution or a 12% phosphomolybdic acid/methanol solution. HPLC separations were carried out with a Pharmacia-based HPLC system at medium pressures using an Amberlite XAD-4 resin as the stationary phase and ethanol/water as the mobile phase.

4(R)-(6-Amino-9H-purin-9-yl)-2-hydroxymethyltetrahydro-2-furanmethanol (6, B = A). 1,2-O-Isopropylidene-5-O-(p-toluenesulfonyl)-α-D-xylofuranose (4.86 mmol) in 1% acetic acid/methanol (80 mL) was converted to **4** in 80 % yield as described previously.[18] To a solution of 2(R)-[(dimethoxy)-methyl]tetrahydrofuran-4(S)-ol **4** (0.958 g, 5.91 mmol) in pyridine (10 mL) was added p-toluenesulfonyl chloride (7.68mmol) and the mixture was stirred at rt for 47 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel with hexane followed by 75% hexane/ethyl acetate to give 2(R)-[(dimethoxy)methyl]-4(S)-[O-(p-toluenesulfonyl)]tetrahydrofuran in 90% yield: ^{1}H NMR

($CDCl_3$) δ 2.01 (m, 2H), 2.41 (s, 3H), 3.38 (s, 6H), 3.85 (m, 1H), 3.91 (dd, 1H), 4.14 (m, 1H), 4.20 (d, 1H), 5.07 (m, 1H), 7.31 (m, 2H), 7.74 (m, 2H). 2(R)-[(Dimethoxy)methyl]-4(S)-O-(p-toluenesulfonyl)-tetrahydrofuran (1.100 mmol) was coupled with adenine (2.210 mmol) in the presence of potassium carbonate (2.200 mmol), 18-crown-6 (1.660 mmol) in dimethylformamide (5 mL) at 75 °C for 20 h. The solvent was evaporated and the residue was chromatographed on silica gel with chloroform followed by 3% methanol/chloroform to produce 4(R)-(6-amino-9H-purin-9-yl)-2(R)-[(dimethoxy)methyl]-tetrahydrofuran in 70% yield. This compound was hydrolyzed to 4(R)-(6-amino-9H-purin-9-yl)-2(R)-tetrahydrofuranal almost quantitatively by treatment with 0.1M aqueous oxalic acid at 80 °C. The aldehyde was subjected to an aldol/Cannizzarro reaction as previously described by us[23] to give 4(R)-(6-amino-9H-purin-9-yl)-2-hydroxymethyltetrahydro-2-furanmethanol (**6**, B = A) in 30% yield: mp 202-203 °C; ^1H NMR (Me_2SO-d_6) δ 2.22 (dd, 1H), 2.46 (dd, 1H), 3.40 (d, 2H), 3.46 (d, 2H), 4.00 (dd, 1H), 4.21 (dd, 1H), 4.90 (br s, 2H), 5.12 (m, 1H), 7.21 (s, 2H), 8.13 (s, 1H), 8.26 (s, 1H); UV (H_2O) λ_{max} 260 nm (ε 12,464). Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.71; N, 26.39. Found: C, 49.69; H, 5.75; N, 26.42.

4(*R*)-(6-Amino-9(*H*)-purin-9-yl)-2(*R*)-azidomethyltetrahydro-2-furanmethanol (8a). To a chilled (0°C) solution of 4(*R*)-[6-amino-9(*H*)purin-9-yl]-2-hydroxymethyltetrahydro-2-furanmethanol **6a** (0.33g, 1.22 mmol) in pyridine (15 mL) was added *p*-toluenesulfonyl chloride (0.30g, 1.40 mmol) at 0°C for 24 h. The reaction was quenched with methanol. After coevaporating the solvent with toluene, the residue was purified with chloroform followed by 15 % methanol/ chloroform by silica gel column chromatography, followed by preparative TLC to afford **7a** (117 mg, 0.28 mmol, 23 %) and its isomer (75 mg, 0.18 mmol, 15 %). Data for **7a**: ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3 of Ts), 2.54 (m, 2H, H-3'), 3.68 (m, 2H, CH_2OH), 4.03 (m, 2H, H-5'), 4.26 (m, 2H, CH_2OTs), 5.21 (m, 1H, H-4'), 6.07 (s, 2H, NH_2, exchangeable), 7.34 (d, 2H, Ph), 7.76 (d, 2H, Ph), 8.00 (s, 1H, H-8), 8.24 (s, 1H, H-2); Data for isomer: ^1H NMR ($CDCl_3$) δ 2.35(dd, 1H, H-3'), 2.45 (s, 3H, CH_3), 2.51 (dd, 1H, H-3') 3.70 (m, 3H, CH_2OH, OH, exchangeable), 4.23 (m, 4H, CH_2OTs, H-5'), 5.20 (m, 1H, H-4'), 5.83 (br s, 2H, NH_2, exchangeable) 7.30 (d, 2H, Ph), 7.74 (d, 2H, Ph) 7.93 (s, 1H, H-8), 8.27 (s, 1H, H-2). 4(*R*)-[6-Amino-9(*H*)-purin-9-yl]-2(*R*)-*O*-(*p*-toluene-sulfonyl)tetrahydro-2-furanmethanol **7a** (100mg, 0.24 mmol) was treated with sodium azide (46.4 mg, 0.713 mmol) and 18-crown-6 (trace amount) in DMF (10 mL) at 110°C with stirring for 16 h. The solvent was removed under reduced pressure using a high vacuum pump and the residue was purified by column chromatography and then by preparative TLC with chloroform followed by 15 % methanol/ chloroform as the eluting solvent to give 4(*R*)-[6-amino-9(*H*)-purin-9-yl]-2(*R*)-azidomethyltetrahydro-2-furanmethanol **8a** (64 mg, 0.22 mmol, 94%): mp 182-183°C; ^1H NMR (Me_2SO-d_6) δ 2.34(m, 2H, H-3'), 3.42 (m, 4H, CH_2OH, CH_2N_3) 4.18 (dd, 1H, H-5'), 4.27 (dd, 1H, H-5'), 5.08 (t, 1H, OH, exchangeable), 5.18 (m, 1H, H-4), 7.24 (br s, 2H, NH_2, exchangeable), 8.13 (s, 1H, H-8), 8.23 (s, 1H, H-2); ^{13}C NMR (Me_2SO-d6) δ 36.60 (C-3'), 54.14 (CH_2N_3, C-4'), 63.91 (CH_2OH), 70.33 (C-5'), 85.76 (C-2'),

118.93 (C-5), 139.05 (C-8), 149.40 (C-4), 152.36 (C-2), 156.00 (C-6); UV (H_2O) λ_{max} 259.5 nm (ε 15,413); FTIR 3500-3200, 2107 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_8O_2$: C, 45.52; H, 4.87; N, 38.59. Found: C, 45.55; H, 4.84; N, 38.50.

4(*R*)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2(*R*)-azidomethyltetrahydro-2-furanmethanol (8b). 4(*R*)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2-hydroxy-methyltetrahydro-2-furanmethanol (**6b**) (0.311g, 1.214mmol) was prepared and tosylated as described above for the preparation of **7a**. Purification by preparative TLC afforded **7b** (206 mg, 0.502 mmol, 41 %) and its isomer (140 mg, 0.341 mmol, 28 % for **6b** to **7b**). Data for **7b**: ^1H NMR ($CDCl_3$) δ 1.84 (s, 3H, CH_3), 2.19 (dd, 1H, H-3'), 2.38 (dd, 1H, H-3') 2.43 (s, 3H, CH_3 of Ts), 3.09 (br s, 1H, OH, exchangeable), 3.69 (m, 2H, CH_2OH), 4.02 (m, 4H, CH_2OTs, H-5'), 5.11 (m, 1H, H-4'), 7.34 (m, 3H, H-6, Ph), 7.77 (d, 2H, Ph), 9.61 (br s, 1H, NH, exchangeable); Data for isomer: ^1H NMR ($CDCl_3$) δ 1.94 (s, 3H, CH_3) 2.00 (dd, 1H, H-3'), 2.35 (dd, 1H, H-3'), 2.45 (s, 3H, CH_3 of Ts) 3.03 (s, 1H, OH, exchangeable), 3.58 (m, 2H, CH_2OH) 3.93 (dd, 1H, H-5'), 4.14 (m, 3H, CH_2OTs, H-5'), 5.26 (m, 1H, H-4') 7.32 (m, 3H, H-6, Ph), 7.73 (d, 2H, Ph), 9.63 (s, 1H, NH, exchangeable). 4(*R*)-[3,4-Dihydro-2,4-dioxo-5-methyl-1-(2*H*)-pyrimidinyl]-2(*R*)-*O*-(*p*-toluenesulfonyl)methyltetrahydro-2-furanmethanol **7b** (107 mg, 0.206 mmol) was treated with sodium azide (33.9 mg, 0.521 mmol) as described for conversion of **7a** to **8a**. Purification of the crude product by preparative TLC afforded **8b** (55 mg, 0.195 mmol, 75%). Data for **8b** (hygroscopic solid): ^1H NMR (Me_2SO-d_6) δ 1.90 (s, 3H, CH_3 of Ts), 2.20 (dd, 1H, H-3') 2.36 (dd, 1H, H-3'), 2.56 (br s, 1H, OH, exchangeable), 3.38 (dd, 2H, CH_2N_3), 3.72 (dd, 2H, CH_2OH) 4.05 (dd, 1H, H-5'), 4.26 (dd, 1H, H-5'), 5.25 (m, 1H, H-4'), 7.33 (s, 1H, H-6), 9.14 (s, 1H, NH, exchangeable); ^{13}C NMR (Me_2SO-d_6) δ 12.54 (CH_3), 35.87 (C-3'), 54.84 (CH_2N_3), 56.32 (C-4'), 65.27 (CH_2OH), 70.69 (C-5'), 86.07 (C-2'), 110.63 (C-5), 137.16 (C-6), 150.99 (C-2), 163.67 (C-4); UV (H_20) 270.5 nm (ε 13,936); FTIR 3500~3200, 2107 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.39; N, 24.88, Found: C, 47.85; H, 5.52; N, 24.69.

4(*R*)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pryimidinyl]-2(*R*)-azidomethyltetrahydro-2-furanmethanol(8c). 4(*R*)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (0.39 g, 1.61 mmol) (**6c**) in pyridine was tosylated as described for the conversion of **6a** to **7a** to give **7c** (110 mg, 0.277 mmol, 17 %) and its isomer (89 mg, 0.224 mmol, 14%). Data for **7c**: ^1H NMR ($CDCl_3$) δ 2.07 (dd, 1H, H-3'), 2.39 (dd, 1H, H-3'), 2.45 (s, 3H, CH_3 of Ts), 3.64 (m, 2H, CH_2OH), 4.03 (m, 3H, CH_2OTs, H-5'), 4.11 (m, 1H, H-5') 5.13 (m, 1H, H-4'), 5.71 (d, 1H, H-5) 7.35 (d, 2H, Ph), 7.47 (d, 1H, H-6), 7.78 (d, 2H, Ph), 8.45 (br s, 1H, NH, exchangeable); Data for isomer: ^1H NMR ($CDCl_3$) δ 1.93 (dd, 1H, H-3'), 2.34 (m, 1H, H-3'), 2.39 (s, 3H, CH_3 of Ts), 3.4 6 (m, 2H, CH_2OH), 3.88 (dd, 1H, H-5'), 4.10 (m, 3H, CH_2OTs, H-5'), 5.17 (m, 1H, H-4'), 5.62 (d, 1H, H-5), 7.28 (d, 2H, Ph) 7.39 (d, 1H, H-6), 7.70 (d, 2H, Ph), 9.79 (br s, 1H, NH, exchangeable). 4(*R*)-[3,4-

Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2(*R*)-*O*-(*p*-toluenesulfonyl)methyltetrahydrofuran-2-methanol (**7c**) (110 mg, 0.277 mmol) was treated with sodium azide (54 mg, 0.832 mmol) as described for the conversion of **7a** to **8a** to give **8c** (60 mg, 0.224 mmol, 81%): m.p 133°C (hygroscopic solid); ^{1}H NMR ($CDCl_3$) δ 2.01 (dd, 1H, H-3'), 2.15 (dd, 1H, H-3'), 3.20 (m, 2H, CH_2N_3), 3.45 (m, 2H, CH_2OH), 3.82 (dd, 1H, H-5'), 4.05 (dd, 1H, H-5'), 4.36 (t, 1H, OH), 5.12 (m, 1H, H-4'), 5.51 (dd, 1H, H-5), 7.48 (d, 1H, H-6), 10.26 (br s, 1H, NH, exchangeable); ^{13}C NMR ($CDCl_3$) δ 12.54 (CH_3), 35.87 (C-3'), 54.84 (CH_2N_3), 56.31 (C-4'), 65.27 (CH_2OH), 70.59 (C-5'), 86.07 (C-2'), 111.63 (C-5), 137.16 (C-6), 150.99 (C-2), 163.67 (C-4); UV (H_2O) λ max 263.0 nm (ε 20,905). Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.91; N, 26.20. Found: C, 45.13; H, 4.99; N, 26.03.

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