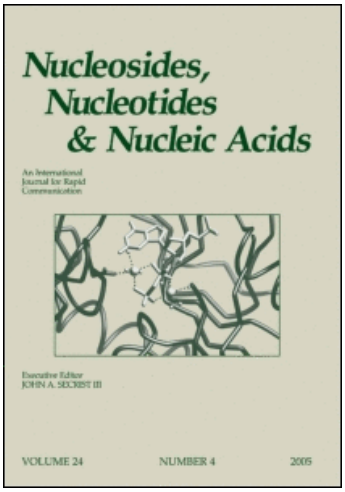

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Homologues of Isomeric Dideoxynucleosides as Potential Antiviral Agents: Synthesis of Isodideoxy-Nucleosides with a Furanethanol Sugar Moiety

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HOMOLOGUES OF ISOMERIC DIDEOXYNUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS: SYNTHESIS OF ISODIDEOXY-NUCLEOSIDES WITH A FURANETHANOL SUGAR MOIETY

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ABSTRACT: The synthesis of a homologues series of compounds related to (R, S)-isodideoxynucleosides has been completed by coupling a variety of natural purine and pyrimidine bases with a modified sugar intermediate. This sugar precursor was prepared regiospecifically and stereospecifically from D-glucose.

INTRODUCTION

The FDA approval of 3′-azido-3′-deoxythymidine (AZT)[1,2] for the treatment of AIDS was followed by licensing of other nucleoside anti-HIV therapeutic agents such as 2′,3′-dideoxyinosine (ddI) and 2′,3′-dideoxycytidine (ddC)[3,4] and subsequently 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T)[5-7] and (-) 2′,3′-dideoxy-3′-thiacytidine [(-)3TC]. [8,9] As has been demonstrated with AZT, all of these dideoxynucleosides (ddNs) act in a similar fashion; that is, following intracellular phosphorylation to the 5′-triphosphate forms, they serve as enzyme inhibitors and/or alternate substrates for HIV reverse transcriptase.[10, 11] While these ddNs appear to be successful prodrugs, their long-term usefulness is limited because of their toxicities which include bone marrow toxicity, peripheral neuropathy, pancreatitis and hepatotoxicity.[12] In addition, it is known that HIV can develop resistance (ie., reduced susceptibility) to various ddN analogues.[13,14] Along with their toxicity problem, these ddNs and their analogs, particularly those of the purine family, have inherent instability of the glycosidic bond.[15] This inherent chemical property, which results from both the absence of the 2′- and 3′-hydroxyl groups (-I effect) and the presence of the proximal endocyclic oxygen,[15] limits the usefulness of these

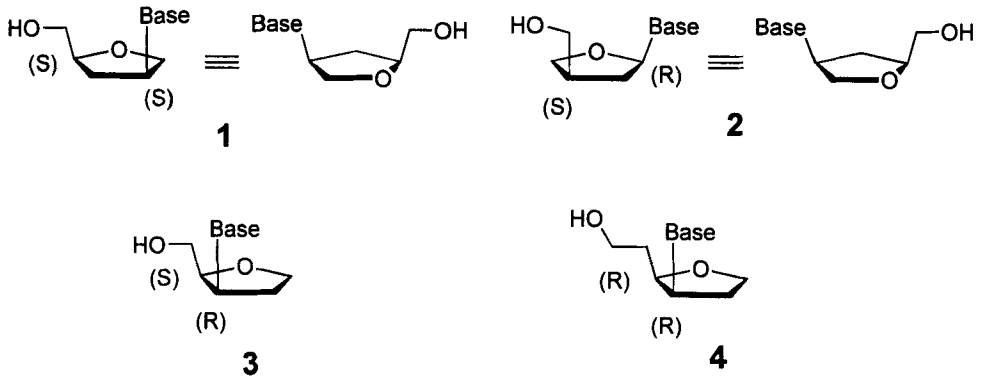


FIGURE 1

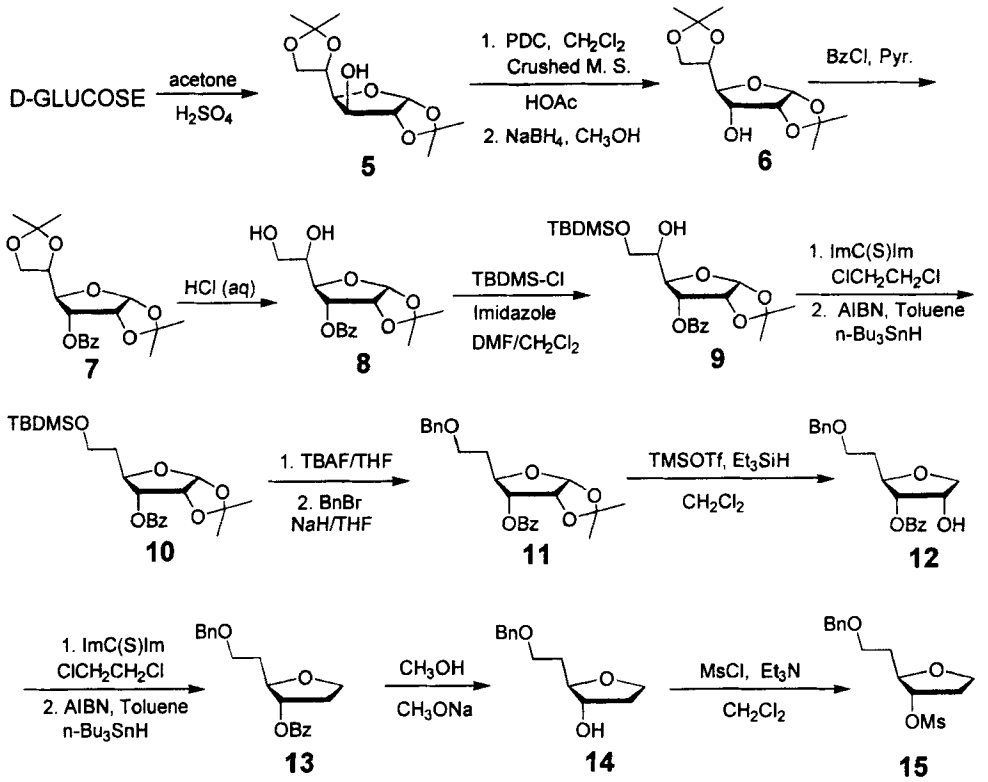
compounds as antiviral agents. For these reasons, the synthesis of new and distinctly different nucleosides is of considerable significance in this field.

The recent surge of interest in *L*-dideoxynucleosides was spurred by the expectation that they would be recognized, not by normal mammalian enzymes, but by virus-encoded or bacterial enzymes. The synthesis of several 2′,3′-*L*-dideoxynucleosides has been accomplished and a few have been found to have anti-HIV activity.[16-22] The synthesis and antiviral studies of L-related isonucleosides (e.g., **1, 2**, and others) have been pursued in our laboratory.[23-28] Among them was 4(*S*)-(6-amino-9H-purin-9-yl)tetrahydro-2(*S*)-furanmethanol, [(*S,S*)-isoddA], which shows potent activity against HIV-1 and HIV-2 (HIV-1, EC_{50} =0.67 μM in PBM cells; CC_{50} > 100 μM in MT-4 and CEM cells).[29]

As a continuation of our pursuit of the discovery of novel antiviral nucleosides and their structure-activity relationships, dideoxynucleosides **4** (**Figure 1**), homologues of (*R, S*)-isodideoxynucleosides **3,** have been synthesized and are the focus of this paper. Insertion of a methylene carbon may add a greater degree of lipophilicity to this kind of molecule, which is an important contribution in the delivery of potential prodrugs across cellular membranes.

RESULTS AND DISCUSSION

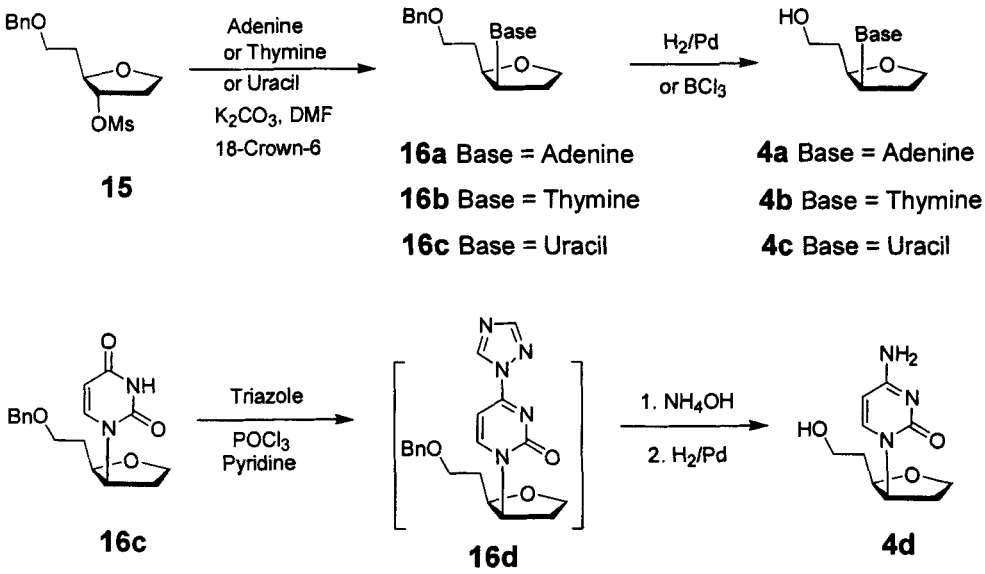
Synthesis of these target compounds was achieved by coupling of the desired nucleobases with the appropriately modified sugar moiety. Thus, 1,2:5,6-O-bis-



SCHEME 1

isopropylidene-*D*-glucofuranose, prepared from *D*-glucose[30] (see **Scheme 1**), was oxidized with PDC to the corresponding ketone[31,32] which was reduced with $NaBH_4$ to afford, stereospecifically, 1,2:5,6-O-bis-isopropylidene-*D*-allofuranose (**6**).[33] Conversion of the 3-hydroxyl group in compound **6** to its benzoyl ester **7** followed by selective hydrolysis of the 5,6-O-isopropylidene group[30] yielded compound **8**. Masking of the 6-hydroxyl group selectively in **8** with TBDMS-Cl allowed the specific Barton deoxygenation [34,35] at C-5 of compound **9** to give compound **10**.

As the TBDMS protecting group in **10** could not survive the strong Lewis acid conditions (TMSOTf or BF_3) of the next step, it was replaced by the benzyl (Bn) group (**11**). Reductive cleavage[23,36,37] of the 1,2-O-isopropylidene group of **11** gave compound **12** which was deoxygenated through a second Barton deoxygenation to afford **13**.



SCHEME 2

Deprotection of the benzoyl ester in **13** with catalytic NaOMe in MeOH freed the 3-hydroxyl group (see **14**) which was mesylated to provide the desired coupling sugar moiety (**15**). The key coupling reaction was carried out by displacement of the leaving group on the modified sugar by the desired nucleobase anion generated by K_2CO_3 in the presence of 18-crown-6. Thus, isoadenosine (**4a**), isothymidine (**4b**), and isouridine (**4c**) were synthesized by direct coupling of adenine, thymine and uracil with the mesylate **15.** Isocytidine (**4d**) was made by converting isouridine to the 4-triazole intermediate followed by ammonolysis of this intermediate with ammonium hydroxide (**Scheme 2**).[38] Deprotection of the benzyl ether either with trichloroborane or by catalytic hydrogenation with 10% palladium on charcoal provided the targets: (*R*,*R*)-isodideoxynucleosides **4a, 4b, 4c, 4d**.

The data shown in **Table 1** indicate that all target compounds were optically active with positive rotations. The molar absorptivities and the wavelength maxima of the major bands in the UV spectra are consistent with expected data. Proton assignments for the key intermediate mesylate **15** and the target compounds (for example, **4a**) were

TABLE 1. Optical rotation and UV data of homologous isodideoxynucleosides **4**

Compound	$[\alpha]_D^{25}$	UV λ_{max} (MeOH)
4a	+25.0 (C 0.20 M, MeOH)	260 (ε=14,200)
4b	+17.2 (C 0.12 M, MeOH)	270 (ε=9,200)
4c	+30.1 (C 0.15 M, MeOH)	266 (ε=8,700)
4d	+54.1 (C 0.021 M, MeOH)	275 (ε=8,500)

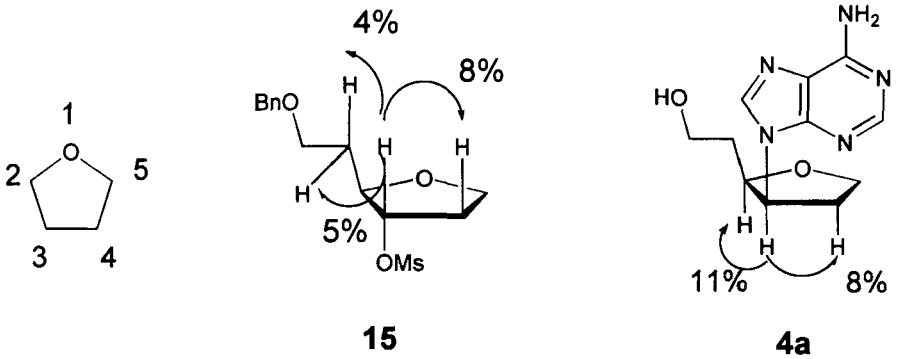


FIGURE 2. NOESY NMR correlations of compounds **15** and **4a**

determined on the basis of HETCOR and COSY two dimensional NMR spectra. The results of the differential NOE studies for mesylate **15** and target compound **4a** (**Figure 2**) provide illustrations of the confirmation of the stereochemistry of these and other compounds. For example, the NOE correlation of H-3α with H-2α and H-4α in compound **4a** was clearly observed. In the precursor, compound **15**, H-3β showed NOE correlations with H-4β and the methylene protons of the hydroxyethyl group. These data indicated that the adenine moiety and the hydroxyethyl group were *cis* while the mesylate leaving group and the hydroxyethyl group were *trans*. The results are also consistent with the expected S_N2 mechanism of the coupling reaction.

In summary, a new class of optically active, homologous, isomeric dideoxynucleosides with (*R, R*)-stereochemistry has been regiospecifically and stereospecifically synthesized from a new coupling sugar, deoxygenated allofuranose (**15**), prepared in a number of steps from *D*-glucose. Preliminary biological data suggest that none of the target compounds showed significant anti-HIV activity.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Brüker Model AC-300 spectrometer. Chemical shifts (δ, ppm) are relative to TMS. Mass spectra were determined on a VG ZAB-HF instrument. UV spectra were recorded on a Gilford Response spectrophotometer. Optical rotations were measured on a Perkin Elmer Model 141 Polarimeter at 25 °C. Melting points reported are uncorrected and were determined on a Thomas Hoover apparatus fitted with a microscope. Preparative layer chromatography used plates prepared with E. Merck PF_{254} silica gel. Flash chromatography was carried out on columns packed with 240-400 mesh silica gel. Elemental analyses were determined at Desert Analytics, Tucson, AZ and NuMega Resonance Labs., Inc., San Diego, CA.

Coupling Reaction: Procedure A. To a solution of coupling sugar **15** (10 mmol) in DMF (20 mL) at room temperature under N_2 were added, sequentially, purine or pyrimidine nucleobase (20 mmol), potassium carbonate (15 mmol), and 18-crown-6 (15 mmol). The reaction mixture was stirred overnight at 50 °C under N_2. The solvent was removed under reduced pressure and the residue was stirred in chloroform (50 mL), filtered and the undissolved solid was washed with chloroform (3 x 20 mL). The chloroform portions were concentrated and the residue was purified by column chromatography gel and/or preparative TLC plates eluted with 2-6 % MeOH/$CHCl_3$.

Debenzylation with Trichloroborane: Procedure B. To a solution of the O-benzylated isomeric nucleoside (1.0 mmol) in 10 mL of dry methylene chloride was added 6 equiv. of trichloroborane at -78 °C. The reaction was stirred at -78 °C under N_2 for 2 h then allowed to stir at -20 °C for another 4 h. Methanol (2 mL) was added at this point and the mixture was stirred at room temperature for 14 h. The mixture was concentrated and

coevaporated with methanol (3 x 2 mL) and the residue was purified by flash chromatography and preparative TLC plates using 2-10 % MeOH/$CHCl_3$.

Debenzylation with Palladium on Charcoal: Procedure C. To a solution of the O-benzylated isomeric nucleosides (1.0 mmol) in 40 mL of absolute ethanol were added 10% palladium on charcoal (50% by weight based on nucleosides) and 1.0 mL of 1M aqueous HCl. Hydrogenation was carried out under 30 psi of hydrogen for 12 h. Palladium catalyst was filtered, ethanol was removed under reduced pressure, and the residue was purified on preparative plates.

1,2:5,6-O-Bis-isopropylidene-*D*-allofuranose (6). This precursor was prepared in multigram quantities using a modification of the literature method.[33] Data for **6**: mp 74 - 76 °C; $[\alpha]_D$ +35.4° (1.0 M in MeOH); ^1H NMR ($CDCl_3$) δ 5.80 (1H, d), 4.60 (1H, t), 4.31(1H, dd), 4.13 (1H, dd), 4.10-3.98(2H, m), 3.84 (1H, dd), 3.00 (1H, s); 1.57 (3H, s), 1.45 (3H, s), 1.36 (3H, s), 1.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ 112.2, 109.2, 103.3, 79.1, 78.7, 75.0, 71.9, 65, 26.1, 26.0, 25.8, 24.8. Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.38; H, 7.73. Found : C, 55.53; H, 7.72.

3-O-Benzoyl-1,2-O-isopropylidene-*D*-allofuranose (8). To a solution of compound **6** (28.8 g, 111 mmol) in 220 mL of pyridine, was added benzoyl chloride (18.7 g, 133 mmol) at 0 °C. The reaction was stirred for 6 h at room temperature and then quenched with methanol. Pyridine was removed by coevaporating with toluene (3 x 20 mL). The syrup was then taken up in 300 mL of diethyl ether, and the pyridinium salt was filtered and washed with diethyl ether (3 x 50 mL). The combined ether portion was concentrated and the residue was purified on a silica gel column (ethyl acetate/hexanes) to afford compound **7** as a colorless oil (38.3 g, 105 mmol 95% yields): ^1H NMR ($CDCl_3$) δ 8.07 (2H, m), 7.54 (1H, m) 7.43 (2H, m), 5.90 (1H, d), 5.09 (1H, dd), 4.98 (1H, dd), 4.37 (2H, m), 4.10 (1H, m), 3.98 (1H, m), 1.54 (3H, s), 1.40 (3H, s), 1.32 (3H, s), 1.30 (3H, s); ^{13}C NMR ($CDCl_3$) δ 165.1, 132.7, 129.6, 127.3, 128.1, 112.6, 109.8, 104.0, 77.5, 75.0, 73.0, 65.4, 26.0, 26.3, 26.0, 24.7.

To a solution of compound **7** (40.0 g, 110 mmol) in 200 mL of acetonitrile was added 50 mL of 0.4 % HCl (aq). The reaction mixture was stirred at room temperature for 8 h and then quenched by neutralization with 1M NaOH. Acetonitrile was removed on the rotovap and the aqueous residue was extracted with chloroform (4 x 100 mL). The organic layer was dried with sodium sulfate and then concentrated. The residue was purified on a silica gel column (0-6% methanol/chloroform) to afford compound **8** as white crystals (27.1 g, 83.5 mmol, 76%): mp 164-166 °C; $[\alpha]_D$ +32.7 (1.50M in MeOH); ^{1}H NMR($CDCl_3$) δ 8.02 (2H, m), 7.54 (1H, m) 7.41 (2H, m), 5.86 (1H, d), 5.11(1H, dd), 4.94 (1H, t), 4.32 (1H, d), 4.04 (1H, q), 3.70 (1H, dd), 3.62 (1H, dd), 2.7-2.1 (2H, OH), 1.52 (3H, s), 1.30 (3H, s); ^{13}C NMR ($CDCl_3$) δ 166.9, 134.4, 130.6 129.5, 113.9, 105.9, 79.7, 79.2, 73.9, 72.6, 63.8 27.0, 26.9. Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.21. Found : C, 59.35; H, 6.09.

6-O-Benzyl-3-O-benzoyl-5-deoxy-1,2-O-isopropylidene-*D*-allofuranose (11). To compound **8** (8.54 g, 26.4 mmol) in dry DMF (13 mL) at room temperature, imidazole (2.23 g, 32.9 mmol) was added. The mixture was cooled to -15 °C and TBDMS-Cl (3.98 g, 29.2 mmol) in 120 mL of methylene chloride was added dropwise over 2 h. The reaction mixture was allowed to warm to 0 °C, stirred for 6 h, diluted with methylene chloride (200 mL), and then quenched by the addition of saturated aqueous sodium bicarbonate (100 mL). The separated aqueous layer was extracted with methylene (3 x 200 mL) and the combined methylene chloride layers were washed with 10% LiCl (aq) (2 x 50 mL), dried (Na_2SO_4), and concentrated. Purification of the product residue on a silica gel column (ethyl acetate/hexanes) afforded compound **9** (10.7 g, 24.5 mmol) as a colorless oil in 92% yield: ^{1}H NMR($CDCl_3$) δ: 8.02 (2H, m), 7.54 (1H, m) 7.41 (2H, m), 5.89 (1H, d), 5.14 (1H, dd), 4.98 (1H, t), 4.36 (1H, d), 3.94 (1H, q), 3.77 (1H, dd), 3.66 (1H, dd), 2.58 (1H, d), 1.54 (3H, s), 1.33 (3H, s), 0.84 (9H, s), 0.024 (3H, s) 0.012 (3H, s); ^{13}C NMR ($CDCl_3$) δ 165.6, 133.2, 129.8, 129.5, 128.3, 113.0, 104.3, 77.9, 77.7, 72.9, 71.6, 63.5 26.8, 26.6, 25.8, 18.2, -5.5.

To a solution of compound **9** (20.10 g, 45.8 mmol) in dichloroethane (240 mL), thiocarbonyl diimidazole (10.2 g, 57.2 mmol) was added and the reaction mixture was

refluxed under N_2 for 4 h. The solvent was removed and the residue was purified on a silica gel column (5-20% ethyl acetate/hexanes) to afford the thiocarbonylimidazole ester intermediate as a pale yellow glassy material (22.3 g, 40.7 mmol, 89%): ^{1}H NMR ($CDCl_3$) δ 8.23 (1H, s), 7.90 (2H, m), 7.54 (2H, m) 7.37 (1H, m), 6.87 (1H, d), 5.94 (1H, d), 5.87 (1H, d), 5.14 (1H, dd), 4.95 (1H, t), 4.68 (1H, m), 3.99 (1H, q), 3.86 (1H, dd), 3.74 (1H, dd), 1.54 (3H, s), 1.31 (3H, s), 0.84 (9H, s), 0.026 (3H, s), 0.012 (3H, s); ^{13}C NMR ($CDCl_3$) δ 183.2, 165.4, 136.5, 136.1, 132.8, 130.4, 129.2, 128.9, 128.1, 117.6, 113.0, 104.8, 81.9, 77.5, 74.8, 74.0, 60.6, 26.6, 26.5, 25.6, 18.0, -5.6, -5.7.

To a refluxing solution of thiocarbonylimidazole ester intermediate (25.0 g, 45.6 mmol) in 150 mL of anhydrous toluene under N_2 was added over 45 min, *n*-tributyltin hydride (15.9 g, 54.6 mmol) and AIBN (4.49 g, 27.3 mmol) in toluene (250 mL). The reaction mixture was heated under reflux under N_2 for 3 h. Toluene was removed on the rotovap and the residue was dissolved in acetonitrile (400 mL), extracted with hexanes (5 x100 mL), and the acetonitrile portion was concentrated. The residue was purified on a silica gel column (hexanes followed by 10-30% ethyl acetate/hexanes) to afford compound **10** as a colorless oil (16.9 g, 40.1 mmol, 87%): ^{1}H NMR ($CDCl_3$) δ 8.0 (2H, d), 7.54 (1H, t) 7.41 (2H, t), 5.85 (1H, d), 4.92 (1H, t), 4.69 (1H, dd), 4.42 (1H, dt), 3.78 (2H, m), 1.93 (1H, m), 1.85 (1H, m), 1.52 (3H, s), 1.33 (3H, s), 0.88 (9H, s), 0.043 (6H, s); ^{13}C NMR ($CDCl_3$) δ 165.8, 133.2, 129.9, 129.6, 128.4, 112.7, 104.0, 77.4, 76.6, 74.0, 59.3, 35.3, 26.6, 26.3, 25.8, 18.2, -5.5, -5.4.

To a solution of compound **10** (13.60 g, 32.1 mmol) in 100 mL of THF was added at room temperature TBAF (48.18 ml of 1.0 M solution in THF). The mixture was stirred for 3 h, diluted with diethyl ether (100 mL) and quenched with 5% $NaCO_3$ (100 ml). The water layer was extracted with diethyl ether (2 x 100 mL). The organic layers were combined and concentrated and the residue was purified on a silica gel column (0-3% methanol/chloroform) to afford the corresponding alcohol (7.72 g, 25.1 mmol, 78%) as a colorless oil: ^{1}H NMR (chloroform-d_3) δ 8.02 (2H, d), 7.54(1H, t) 7.41 (2H, t), 5.80 (1H, d), 4.57-4.42 (3H, m), 3.90 (1H, m), 3.70 (1H, m), 2.64 (1H, d), 2.221(1H, m), 2.02 (1H, m), 1.54 (3H, s), 1.35 (3H, s). ^{13}C NMR ($CDCl_3$) δ 166.3, 132.7, 130.2, 129.4, 128.2, 112.3, 103.7, 78.4, 76.8, 75.6, 61.5, 31.1, 26.4, 26.2.

To the above alcohol (5.27 g, 17.1 mmol) in dry THF (170 mL) under N_2, NaH (440 mg, 18.8 mmol) was added at 0 °C followed by benzyl bromide (4.38 g, 20.5 mmol). The mixture was stirred overnight at room temperature. It was quenched with 5% $NaHCO_3$ (100 mL) and extracted with diethyl ether (3x 100 mL). The solvent was removed and the residue was chromatographed on a silica gel column (0-20% ethyl acetate/hexanes) to afford compound **11** (6.07 g, 15.2 mmol) as a colorless oil in 89% yield: ^{1}H NMR ($CDCl_3$) δ 8.02 (2H, m), 7.54 (1H, t), 7.41-7.27 (7H, m), 5.72 (1H, d), 4.80 (1H, d), 4.57-4.40 (4H, m), 4.21 (1H, dt), 3.49 (1H, dd), 2.20 (1H, m), 1.90 (1H, m), 1.58 (3H, s), 1.35 (3H, s); ^{13}C NMR($CDCl_3$) δ 166.3, 137.3, 132.7, 130.2, 129.4, 128.3, 128.1, 127.9, 127.8, 112.6, 103.9, 81.6, 74.8, 71.9, 61.5, 31.3, 26.5, 26.4. Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33 ; H, 6.58. Found : C, 69.39; H, 6.79.

6-O-Benzyl-3-O-benzoyl-1,5-dideoxy-*D*-allofuranose (12). To a solution of **11** (9.82 g, 24.6 mmol) in 80 mL of anhydrous methylene chloride under N_2, 8.9 mL of TMSOTf (49.3 mmol) in 40 mL of methylene chloride was added dropwise at -15 °C over 30 min under N_2. The reaction mixture was warmed to room temperature and kept stirring for 30 min and then cooled to 0 °C again and 14.4 mL of triethylsilane (90.6 mmol) was added. The mixture was warmed to room temperature and stirred at room temperature under N_2 for 18 h and then quenched with 100 mL of 5% sodium bicarbonate, and extracted with dichloromethane (3x 100mL). The organic layer was combined and concentrated on a rotovap and the residue was purified on a silica gel column which was eluted with 0-3% methanol/chloroform to afford **11** as a colorless oil (5.33 g, 15.8 mmol, 64%): ^{1}H NMR ($CDCl_3$) δ 8.02 (2H, m), 7.52 (1H, t), 7.41--7.27 (7H, m), 4.62 (2H, dd), 4.43 (2H, m), 4.22 (1H, dt), 4.07-3.99 (2H, m), 3.78 (1H, dd), 3.68 (1H, dd), 2.68 (1H, d), 2.04 (1H, m), 1.90 (1H, m); ^{13}C NMR ($CDCl_3$) δ 166.3,137.0, 132.7, 130.2, 129.4, 128.6, 128.3, 127.9, 82.9, 77.0, 73.1, 72.8, 69.5, 61.7, 32.7. Anal. Calcd for $C_{20}H_{22}O_6$: C, 70.16; H, 6.48. Found : C, 69.85; H, 6.14.

6-O-Benzyl-3-O-mesyl-1,2,5-trideoxy-*D*-allofuranose (15). To the solution of compound **12** (4.15 g, 12.3 mmol) in dichloroethane (50 mL) was added thiocarbonyl

diimidazole (3.28 g, 18.4 mmol). The reaction mixture was heated under reflux for 3 h under N_2. The solvent was then removed and the residue was purified on a silica gel column (10-30% ethyl acetate/ hexanes) to afford the thiocarbonylimidazole ester intermediate as a light yellow oil (4.51 g, 10.1 mmol, 82%): ^{1}H NMR ($CDCl_3$) δ 8.24 (1H, s), 8.0(2H, m), 7.51 (1H, t), 7.4-7.27 (7H, m), 5.94 (1H, d), 5.87 (1H, d), 4.62 (2H, dd), 4.47 (2H, m), 4.24 (1H, dt), 4.07-4.01 (2H, m), 3.78 (1H, dd), 3.68 (1H, dd), 2.04 (1H, m), 1.90 (1H, m); ^{13}C NMR ($CDCl_3$) δ 183.0, 166.1, 136.8, 136.3, 136.0, 132.4, 130.0, 129.3, 128.6, 128.3, 127.9, 117.7, 82.9, 77.0, 73.1, 72.8, 69.5, 61.7, 32.6.

To a refluxing solution of the thiocarbonylimidazole ester (4.16 g, 9.27 mmol) in toluene (40 mL) under N_2, *n*-tributyltin hydride (3.23 g, 11.1 mmol) and AIBN (0.91 g, 5.56 mmol) in toluene (50 mL) were added dropwise over 30 min. The reaction was heated under reflux for 3 h and toluene was removed and the residue was taken up in 200 mL of acetonitrile and washed with hexanes (5 x 50 mL). The acetonitrile portion was concentrated and the residue was purified on a silica gel column (hexanes followed by 10-30% ethyl acetate/ hexanes) to afford compound **13** as a colorless oil in 88% yield: ^{1}H NMR ($CDCl_3$) δ 8.02 (2H, m), 7.52(1H, t), 7.41-7.27 (7H, m), 4.56-4.37 (3H, m), 4.07-3.84 (5H, m), 2.04-1.63 (4H, m); ^{13}C NMR ($CDCl_3$) δ 166.1, 137.8, 132.7, 130.2, 129.4, 128.3, 128.1, 127.4, 83.0, 80.4, 71.0, 66.5, 61.7, 32.8, 31.8.

To a solution of compound **13** (0.765 g, 2.21 mmol) in 22 mL of methanol was added sodium methoxide (0.06 g, 1.16 mmol). The mixture was stirred at room temperature for 6 h and then neutralized with 1M HCl to pH = 7. Methanol and water were removed on a rotovap and the residue was washed with chloroform (3x 30 mL). The chloroform portions were combined and concentrated and the residue was purified by flash chromatography to afford **14** as a colorless oil (0.484 g, 2.00 mmol, 90%): ^{1}H NMR ($CDCl_3$) δ 7.37-7.27 (5H, m), 4.52 (2H, dd), 4.02-3.72 (6H, m), 2.76 (1H, OH peak), 2.08-1.69 (4H, m); ^{13}C NMR ($CDCl_3$) δ 137.8, 128.4, 127.7, 127.6, 83.3, 83.1, 71.4, 66.8, 60.9, 35.7, 31.8.

To a solution of compound **14** (0.200 g, 0.825 mmol) in 16 mL of methylene chloride, triethylamine (0.399 g, 0.46 mL) was added, followed by addition of mesyl chloride (0.225 g, 1.98 mmol) at -15 °C. The reaction mixture was stirred at 0 °C for 6 h

and then quenched with 4 mL of methanol. All of the solvents were removed and the residue was taken up in EtOAc (100 mL), and then washed with water (2x 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified on a silica gel column (10-30% EtOAc/hexanes) to afford **15** as a colorless oil (0.219 g, 0.684 mmol, 83 %): ^1H NMR ($CDCl_3$) δ 8.01 (2H, m), 7.55 (1H, m), 7.42 (2H, m), 5.02 (1H, dt), 4.49 (2H, m), 4.21 (1H, m), 4.05 (1H, m), 3.94 (1H, m), 3.02 (3H, s), 2.28 (2H, m), 2.15 (1H, m), 1.92 (1H, m); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.6, 127.7, 127.6, 83.1, 79.6, 71.4, 67.2, 66.8. 37.1, 33.3, 31.9. Anal. Calcd for $C_{15}H_{24}O_5S$: C, 55.94 ; H, 6.64. Found : C, 55.96; H, 6.42.

3-(*R*)-(6-Amino-9H-purin-9-yl)tetrahydro-2-(*R*)-furanethanol (4a). Compound **15** was coupled with adenine using Procedure A to afford compound **16a** as a colorless oil in 61% yield: ^1H NMR ($CDCl_3$) δ 8.37 (1H, s), 7.82 (1H, s), 7.37-7.27 (5H, m), 5.92 (2H, NH_2 peak), 4.50 (2H, m), 4.32 (2H, m), 3.95 (2H, m), 3.75 (2H, m), 2.24-1.86 (4H, m); ^{13}C NMR ($CDCl_3$) δ 156.0, 152.9, 149.9, 137.9, 128.7, 127.7, 127.6, 119.7, 83.3, 80.5, 71.5, 66.9, 40.9, 33.8, 32.0. Compound **16a** was debenzylated using Procedure B to afford **4a** as a white solid in 68% yield. Further purification was done on preparative TLC plates: mp 140-142 °C; ^1H NMR ($CDCl_3$) δ 8.29 (1H, s), 7.82 (1H, s), 6.14 (2H, s), 4.43--4.24 (3H, m), 4.14 (1H, m), 3.75 (2H, m), 3.62 (1H, m), 2.18 (2H, m), 1.95(2H, m); ^{13}C NMR ($CDCl_3$) δ 155.5, 152.8, 149.7, 140.9, 119.4, 82.6, 75.8, 66.7, 40 8, 35.0, 33.7. UV λ_{max} = 260 nm (ε = 14200); $[\alpha]_D$ +25.0° (0.20 M in MeOH). Anal. Calcd for $C_{11}H_{15}N_5O_2$. 0.5 H_2O: C, 51.18; H, 6.25; N, 27.16. Found: C, 51.46; H, 6.38; N, 27.46.

3-(*R*)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2H)-pyrimidinyl]tetrahydro-2-(*R*)-furanethanol (4b). Thymine was condensed with mesylate **15** using Procedure A to give 6-O-benzylethyl-3-(*R*)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2H)-pyrimidinyl]tetrahydro-2-(*R*)-furanethanol (**16b**) in 34% yield: ^1H NMR ($CDCl_3$) δ 8.90 (1H, s, NH peak), 7.37-7.26 (5H, m), 7.05 (1H, d), 4.49 (2H, m), 3.98-3.62 (6H, m), 2.21 (2H, m), 1.99 (3H, s), 1.87 (2H, m); ^{13}C NMR ($CDCl_3$) δ 164.4, 150.8, 141.3, 137.7, 128.5, 128.3, 127.8, 127.7, 110.2, 83.4, 80.4, 71.6, 66.8, 46.0, 32.7, 31.9. Compound **16b** was deprotected using Procedure C to afford **4b** as a white solid in 92% yield: mp 129-130 °C; ^1H NMR

(CD_3OD) δ 7.42 (1H, s), 4.02 (1H, m), 3.92-3.85 (3H, m), 3.74 (1H, m), 3.62 (1H, m), 2.18 (2H, m), 2.0 (3H, s), 1.92 (1H, m), 1.72 (1H, m); ^{13}C NMR (CD_3OD) δ 163.5, 151.9, 136.4, 111.7, 82.8, 75.9, 66.9, 47.9, 34.8, 34.7, 13.1; UV λ_{max} = 270nm (ε = 9200); $[\alpha]_D$ +17.2° (0.12 M in MeOH). Anal. Calcd for $C_{11}H_{16}N_2O_4$. 0.5 H_2O: C, 53.15; H, 6.87; N, 11.23. Found : C, 53.41; H, 6.84; N, 12.42.

3-(*R*)-[3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahydro-2-(*R*)-furanethanol (4c). Procedure A was followed for the coupling of mesylate **15** with uracil to provide 6-O-benzyl isonucleoside **16c** as a clear oil in 31 % yield: ^1H NMR ($CDCl_3$) δ 9.14 (1H, br, NH peak), 7.38-7.29 (6H, m), 5.65 (1H, d), 4.47 (2H, m),4.03-3.65 (6H, m), 2.05 (2H, m), 1.72 (2H, m); ^{13}C NMR ($CDCl_3$) δ 163.7, 150.7, 145.3, 128.5, 127.8, 127.7, 126.9, 101.7, 83.3, 80.3, 71.6, 66.9, 46.3, 32.6, 31.9. Compound **16c** was deprotected by using general procedure (C) to provide **4c** as a hygroscopic white solid in 94% yield: ^1H NMR ($CDCl_3$) δ 7.30 (1H, d), 5.68 (1H, d), 4.12 (1H, m), 4.10-3.96 (3H, m), 3.75 (2H, m), 3.62 (1H, m), 2.14 (2H, m), 1.91(1H, m), 1.68(1H, m); ^{13}C NMR ($CDCl_3$) δ 164.1, 151.2, 145.4, 102.0, 82.6, 75.8, 66.6, 46.4, 34.7, 32.2; UV λ_{max} = 266 nm (ε = 8700); $[\alpha]_D$ +30.1° (0.15 M in MeOH). Anal. Calcd for $C_{10}H_{14}N_2O_4$. 0.5 H_2O: C, 51.01; H, 6.42; N, 11.90. Found : C, 50.29; H, 6.35; N, 11.84.

3-(*R*)-[4-Amino-2-dioxo-1(2H)-pyrimidinyl]tetrahydro-2-(*R*)-furanethanol (4d). The 6-O-benzyl isonucleoside **16c** (0.582 g, 1.86 mmol) was dissolved in 14 mL of dry pyridine and a solution of 0.460 ml (3.73 mmol) of $POCl_3$ and 0.386 g (5.59 mmol) of triazole in 10 mL of pyridine was added dropwise to it at 0 °C under N_2. The reaction mixture was warmed to room temperature and allowed to stir for 18 h to provide the triazole intermediate which was not isolated but immediately dissolved in 17 mL of dioxane. Conc NH_4OH solution (6 mL) was added at room temperature and the clear yellow solution was allowed to stir for 5 h. Solvents were removed under reduced pressure and the residue was extracted with chloroform (3 x 10 mL) and the chloroform layers were concentrated. The yellow residue was purified on a silica gel column to afford **16d** as a colorless oil in 48 % yield: ^1H NMR ($CDCl_3$) δ 7.34-7.22 (6H, m), 5.73

(1H, d), 4.47 (2H, q), 4.00-3.65 (6H, m), 2.05 (3H, m), 1.72 (1H, m); ^{13}C NMR ($CDCl_3$) δ 166.2, 156.7, 146.0, 137.8, 128.4, 127.7, 127.6, 94.2, 83.3, 80.5, 71.3, 66.9, 47,3, 32.7, 31.9. Compound **16d** was deprotected using Procedure B to give **4d** as a white solid in 60 % yield: mp 117-120 °C; ^1H NMR (CD_3OD) δ 7.56 (1H, d), 5.83 (1H, d), 4.04 (1H, m), 4.01-3.91 (3H, m), 3.75 (1H, m), 3.62 (1H, m), 2.14 (1H, m), 1.97(1H, m), 1.84 (1H, m), 1.68 (1H, m); ^{13}C NMR ($CDCl_3$) δ 166.5, 155.2, 145.4, 101.1, 81.6, 75.3, 66.1, 46.1, 34.3, 32.1; UV λ_{max} = 275 nm (ε =8500); $[\alpha]_D$ +54.1° (0.021M in MeOH). Anal. Calcd for $C_{10}H_{15}N_3O_3 \cdot 0.5\ H_2O$: C, 51.27; H, 6.81. Found : C, 51.20; H, 6.72.

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REFERENCES

1. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; Gallo, R. C. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 7096-7100.
2. Yarchoan, R.; Klecker, R. W.; Weinhold, K. J.; Broder, S. *Lancet* **1986**, *1*, 575-580.
3. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1911-1915.
4. Yarchoan, R.; Pluda, J. M.; Thomas, R. V.; Mitsuya, H.; Broder, S. *Lancet* **1986**, *1*, 526-529.
5. Lin, T.-S.; Schinazi, R. F.; Chen, M. S.; Prusoff, W. H. *Biochem. Pharmacol.* **1987**, *36*, 311-316.
6. Lin, T.-S.; Schinazi, R. F.; Griffith, B. P.; Zheng, D.-K.; Huang, L. *Biochem. Pharmacol.* **1987**, *36*, 2713-2718.
7. Browne, M. J.; Mayer, K. H.; Chafee, S. B. D.; Dudley, M. N. *J. Infect. Dis.* **1993**, *167*, 21-29.
8. Soudeyns, H.; Yao, X.-J.; Gao, Q,; Belleau, B.; Kraus, J.-L.; Nguyen-Ba, N.; Spira, B.; Wainberg, M. A. *Antimicrob. Agents Chemother.* **1991**, *35*, 1386-1390.
9. Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillian, A.; Mathis, R.; Cannon, D.; Jeong, L-S.; Beach, J. W.: Choi, W-B.; Yeola, S.; Liotta, D. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 672-676.

10. Cooney, D. A.; Ahluwalia, G.; Mitsuya, H.; Fridland, A.; Johnson, M.; Dalal, M.; Balzarini, J.; Broder, S.; Johns, D. G. *Biochem. Pharmacol.* **1987**, *36*, 1765-1768.
11. Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533-1544.
12. Richman, D. D. *Antimicrob. Agents Chemother.* **1993**, *37*, 1207-1213.
13. St. Clair, M. H.; Martin, H., J.; Tudor-Williams, G.; Bach, M. C.; Vavro, C. L.; King, D. M.; Kellam, P.; Kemp, S. D.; Larder, B. A. *Science,* **1991**, *253*, 1557-1559.
14. De Clercq, E. *Biochem. Pharmacol.* **1994**, 47, 155-169.
15. Nair, V.; Buenger, G. S. *J. Org. Chem.* **1990**, *55*, 3695-3697.
16. Gosselin, G.; Schinazi, R. F.; Sommadossi, J.-P.; Mathe, C.; Bergogne, M.-C. *Antimicrob. Agents Chemother.* **1994,** *38*, 1292-1297.
17. Liu, T.-S.; Luo, M. Z.; Liu, M. C.; Pai, S. B.; Butschman, G. E.; Cheng, Y.-C. *Biochem. Pharmacol.* **1994**, *47*, 171-174.
18. Liu, T.-S.; Luo, M. Z.; Liu, M. C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem.* **1994**, *37*, 798-803.
19. Kim, H. O.; Schinazi, R. F.; Nampalli, S.; Shanmuganathan, K.; Cannon, D. L.; Alves, A. J.; Jeong, L. S.; Beach, J. W.; Chu, C. K. *J. Med. Chem.* **1993**, *36*, 30-37.
20. Mansuri, M. M.; Farina, V.; Starrett, Jr., J. E.; Benigni, D. A.; Brankovan, V.; Martin, J. C. *Bioorg. Med.Chem. Lett.* **1991**, *1*, 65-68.
21. Van Draanen, N. A.; Koszalka, G. W. *Nucleosides Nucleotides* **1994**, *13*, 1679-1693.
22. De Clercq, E. *Clinical Microbiology Rev.* **1997**, *10*, 674.
23. Nair, V.; Bolon, P.; Sells, T. B.; Nuesca, Z. M.; Purdy, D. F. *Tetrahedron* **1994**, *50*, 7747- 7764.
24. Nair, V.; Jahnke, T. S. *Antimicrobial Agents and Chemother.* **1995**, *39*, 1017-1029.
25. Nair, V.; Sells, T. B. *Tetrahedron Lett.* **1992**, *33*, 7639-7642.
26. Nair, V.; Sells, T. B. *Tetrahedron* **1994**, *50*, 117-138.
27. Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951-7953.
28. Nair, V.; Bolon, P.; Jahnke, T. S. *Tetrahedron* **1995**, *51*, 10443-10452.
29. Nair, V.; St. Clair, M. H.; Reardon, J. E.; Krasny, H. C.; Hazen, R. J.; Paff, M. T.; Boone, L. R.; Tisdale, M.; Najera, I.; Dornsife, R. E.; Averett, D. R.; Borroto-Esoda, K.; Yale, J. L.; Zimmerman, T. P.; Rideout, J. L. *Antimicrob. Agents Chemother.* **1995**, *39*, 1993-1999.

30. Nair, V.; Emanuel, D. J. *J. Am. Chem. Soc.* **1977**, *99,* 1571-1576.

31. Johnson, C. R.; Bhumralkar, D. R.; De Clercq, E. *Nucleosides & Nucleotides* **1995**, *14,* 185-194.

32. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399-402.

33. Machado, I. C.; Alonso, O. M.; Bencomo, V. V. *J. Carbohydr. Chem.* **1994**, *13*, 465-474.

34. Barton, D. H. R.; Subramanian, R. *J. Chem. Soc. Perkin Trans. I* **1977**, 1718-1723.

35. Nair, V.; Buenger, G. S. *J. Am. Chem Soc.* **1989**, *111*, 8502-8504.

36. Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892-897.

37. Kakefuda, A.; Shuto, S.; Nagahata, T.; Seki, J.; Sasaki, T.; Matsuda, A. *Tetrahedron* **1994**, *34,* 10167-10182.

38. Reese, C. B.; Ubasawa, A. *Nucleic Acid Res.* **1980** Symposium Series 7, 5-21.

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