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Homologues of Anti-HIV Active Isodideoxynucleosides

Pascal Bolon, Tamera S. Jahnke and Vasu Nair*

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242, USA

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Abstract: *The synthesis of a homologous series of compounds related to the anti-HIV active class of compounds known as (S,S)-isodideoxynucleosides has been completed by a convergent route using a modified carbohydrate intermediate. This precursor, synthesized from D-glucose, was coupled with a variety of natural purine and pyrimidine bases to regiospecifically and stereospecifically afford the desired new class of compounds.*

INTRODUCTION

Nucleoside analogs remain the primary source of antiviral prodrugs with the mechanism of action of these compounds being through their triphosphates which act as enzyme inhibitors or alternate substrates for HIV reverse transcriptase.[1-8] If the triphosphate is an alternate substrate then it is incorporated into the growing viral DNA chain and may thus act as a viral DNA chain terminator. The "normal-D" dideoxynucleosides, **1**, are a well-established class of compounds, a few of which have been approved by the FDA for anti-HIV chemotherapy (Figure 1). Attention has been focused in the last few years on the L-dideoxynucleosides, **2**, and some of these compounds have been synthesized and a few have been discovered to have anti-HIV activity.[9-13] Recent focus has also been directed at antiviral nucleosides belonging to the isomeric series. In this family of compounds, transposition of the hydroxymethyl functionality from the normal C-4' position to the C-3' carbon gives rise to a series referred to as the apiodideoxynucleosides **3** (Figure 1).[14-16] This class of compounds showed low toxicity but no anti-HIV activity at concentrations up to 200 μM. However, the transposition of the base moiety from the traditionally numbered C-1' to the C-2' carbon on the dideoxygenated glycon portion of the nucleoside gives rise to the antivirally more interesting 2'-isodideoxynucleosides, **4**.[17-19] One of these compounds, 4(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol [(S,S)-IsoddA], synthesized previously by us, has been shown to have potent anti-HIV activity. As seen in Figure 1, the (S,S)-isomeric nucleosides are related to the L-nucleosides in their absolute stereochemistry. Because of the location of the base moiety at the 2'-position which is not the anomeric position, these isodideoxynucleosides are very stable with respect to "glycosidic" bond hydrolysis, unlike their normal counterparts. The chemotherapy of HIV infections by RT inhibitors is hindered by the fact that the virus is capable of mutating to drug-resistant strains,[20] so the search for new nucleosides with anti-HIV activity will continue to be an important area of research. In our pursuit of producing novel, active dideoxynucleosides we have tried to assemble what may be the important characteristics of the aforementioned three classes of compounds in the form of the title compounds of this paper. This new class of compounds represented in Figure 2 resembles the L-dideoxynucleosides. Additionally, this class of compounds is expected to exhibit the glycosidic bond

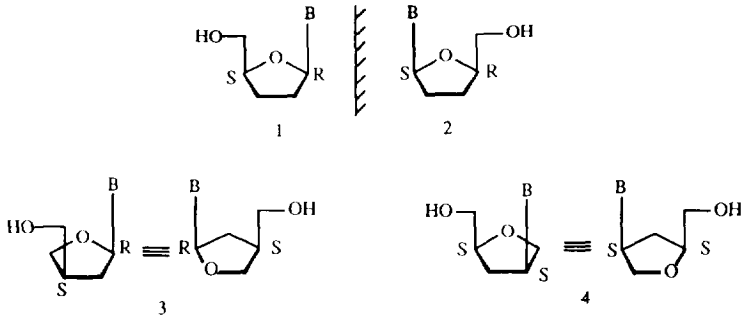


Figure 1. General structure representations of dideoxynucleosides, **1** and **2**, dideoxyapionucleosides, **3**, and isodideoxynucleosides, **4**.

stability of isonucleosides due in part to the absence of the proximal endocyclic ring oxygen which in the case of normal dideoxynucleosides contributes to their hydrolytic instability.[17,18,21] (S,S)-IsoddA is known to be resistant to adenosine deaminase, a degradative pathway of the antiviral prodrug dideoxyadenosine which converts it to dideoxyinosine. These new homologous compounds are also not expected to be substrates in this degradative pathway. Finally, the insertion of a methylene carbon adds a degree of hydrophobicity to the molecule which is an important contributing factor in the delivery of potential prodrugs across cellular membranes. The role of the O-4' furan oxygen has been investigated in the design of novel dideoxynucleosides. This site does not seem to be implicitly necessary to enzyme recognition, as carbocyclic dideoxynucleosides have been shown to possess anti-HIV activity.[22]

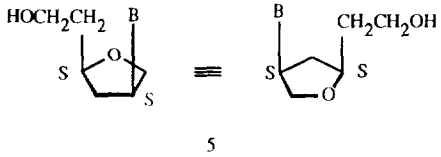
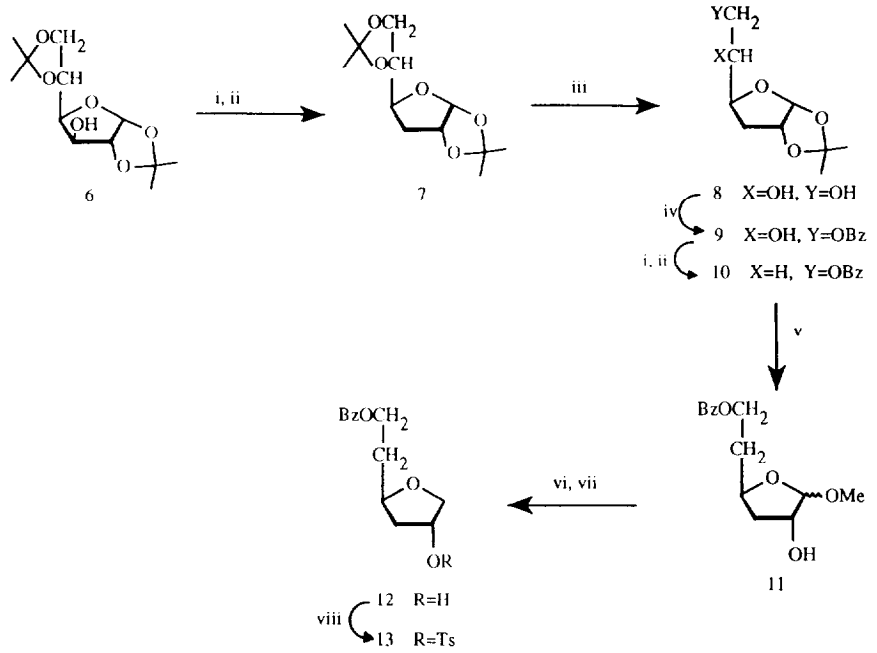


Figure 2. Structural Representations of Homologous Isodideoxynucleosides

RESULTS AND DISCUSSION

An efficient synthesis of the title compounds summarized in Figure 2 was achieved by a convergent pathway involving the coupling of the desired nucleobases to the appropriately deoxygenated coupling sugar. 1,2:5,6-O-bis-isopropylideneglucofuranose (**6**), prepared from D-glucose,[23] was allowed to undergo a modified Barton deoxygenation of the C-3 hydroxyl group to give compound **7**.[24] This was followed by selective hydrolysis of the 5,6-O-isopropylidene moiety and protection of the C-6 hydroxyl group as the benzoate ester which allowed a second modified Barton deoxygenation to take place at C-5 to yield compound **10**. Methanolysis of the remaining 1,2-O-isopropylidene to the methyl acetal, **11**, was followed by reductive cleavage of the methyl acetal to provide the benzoate ester of (2S,4R) 4-hydroxytetrahydrofuran-2-ethanol (**12**).[25] Tosylation of the secondary hydroxyl group provided the desired coupling sugar **13**. This coupling

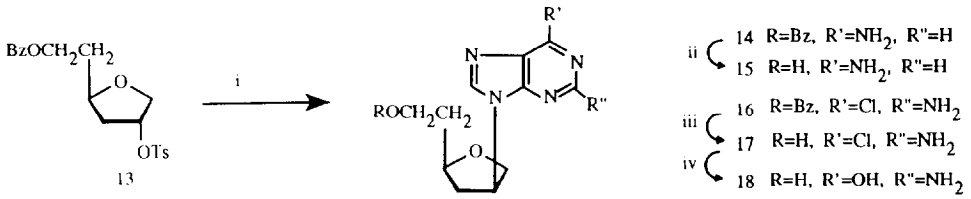
sugar is a novel deoxygenated furoglucitol derivative.



i. Im_2CS, $ClCH_2CH_2Cl$; ii. Bu_3SnH, AIBN, toluene; iii. 0.2% aq. HCl; iv. BzCl, pyridine, -15°C; v. HCl, MeOH; vi. HMDS, TMSCl; vii. Et_3SiH, TMSOTf, CH_2Cl_2; viii. TsCl, pyridine.

Scheme 1

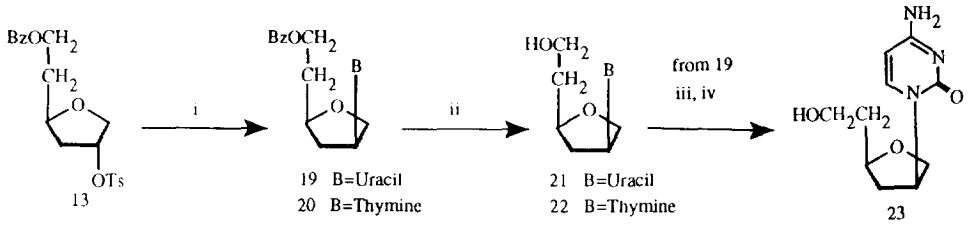
In general terms, the coupling reaction was carried out by the addition of the desired nucleobase to the coupling sugar in the presence of 18-crown-6 and K_2CO_3 followed by deprotection in the presence of NaOMe in dry MeOH to provide the desired target nucleosides. Condensation with the appropriate heterocyclic bases provided the purine analogs (Scheme 2). Thus, the adenosine analogue was synthesized by direct coupling with adenine, followed by deprotection with NaOMe in dry MeOH. The guanosine analogue was synthesized by coupling 2-amino-6-chloropurine followed by displacement of the 6-Cl group with hydroxide ion and deprotection.



i. purine base, K_2CO_3, 18-crown-6, DMF, 70°C; ii. NaOMe, MeOH; iii. NH_3, MeOH; iv. 1N NaOH.

Scheme 2

Coupling of the pyrimidine bases with carbohydrate intermediate **13** followed by deprotection gave the modified pyrimidine nucleosides (Scheme 3). These couplings gave reduced yields of the desired products due to side reactions which gave O-coupled products. These N and O isomeric products can be separated and distinguished by selective INEPT NMR experiments[26] with irradiation of the proton on C-2', to enhance the pyrimidine carbon resonances of C-2 and C-6. Irradiation of H-6 on the pyrimidine base provided confirmation of the site of coupling by the enhancement of the C-2' carbon signal on the glycon. Due to the synthetic inefficiency of pyrimidine base couplings, the cytidine analog was synthesized from the protected uridine (Scheme 3, see also data in Table 1). This was achieved by conversion of the protected uridine analog to the 4-triazole intermediate followed by conversion of this intermediate to the cytidine analog by ammonolysis with ammonium hydroxide.[27] Full deprotection of the benzoate ester was accomplished by removal of the solvent and addition of NaOMe in dry MeOH.



i. pyrimidine, K_2CO_3, 18-crown-6, DMF, 70°C; ii. NaOMe, MeOH; iii. $POCl_3$, triazole, pyridine; iv. NH_4OH.

Scheme 3

Table 1. Optically Active, Homologous Isodideoxynucleosides

Compound	$[\alpha]^{25}_D$	UV λ_{max} (H_2O)
15	-28.4° (c 0.1, MeOH)	259.5 (ε 12,500)
18	-27.4° (c 0.1, MeOH)	252.5 (ε 11,300)
21	+31.1° (c 0.12, MeOH)	266 (ε 8,700)
22	+24.9° (c 0.1, MeOH)	271 (ε 9,300)
23	+85.9° (c 0.06, MeOH)	275 (ε 8,800)

In summary, a new class of optically active, homologous, isomeric dideoxynucleosides with (*S,S*) absolute stereochemistry has been regiospecifically and stereospecifically synthesized from a new coupling sugar. The latter is prepared in a number of steps from readily available glucose. These novel nucleosides are hydrolytically stable and have stability toward degradative enzymes (for example, the A analogue is resistant to

hydrolytic deamination by adenosine deaminase). Preliminary biological data suggest that, unlike the parent (S,S)-isodideoxynucleosides, their one carbon homologues have no significant anti-HIV activity. However, further antiviral studies against other viruses are in progress and will be reported elsewhere.

EXPERIMENTAL SECTION

NMR spectra were recorded on Brüker Models AC-300 and WM-360 spectrometers. Chemical shifts are reported in parts per million, δ, relative to TMS or DSS. UV spectra were recorded on a Gilford Response spectrophotometer. Optical rotations were measured on a Perkin Elmer Model 141 polarimeter at 25°C. Lyophilizations were performed with a Virtis Freezemobile 3 unit. Preparative layer chromatography used plates prepared with E. Merck PF_{254} silica gel. Flash chromatography was carried out on columns packed with 230-400 mesh silica gel. HPLC separations were performed on a Waters automated 600E system using Delta-Pak C_{18} and Hamilton PRP-1 columns. Elemental analyses were performed at the University of Iowa, Iowa City, IA and Desert Analytics Laboratory, Tucson, AZ.

General Procedure for the Glycosylation Reaction. A mixture of purine or pyrimidine base (2 equiv), potassium carbonate (2 equiv), 18-crown-6 (1-2 equiv), and coupling sugar **13** (1 equiv) in DMF were stirred at 70°C. Typically 0.5-1 mmol of coupling sugar was used in this procedure. The reaction was monitored by TLC. The solvent was removed under reduced pressure and the residue was purified by preparative layer or flash chromatography on silica gel with 0-10% MeOH/$CHCl_3$.

General Procedure for the Debenzoylation with Sodium Methoxide. To a solution of O-benzoylated isomer nucleoside (0.25 mmol) in anhydrous methanol (3 mL) was added sodium methoxide (0.50 mmol). After stirring at room temperature for 2 h, the reaction mixture was neutralized. The residue was purified by preparative layer or flash chromatography on silica gel with 0-10% MeOH/$CHCl_3$.

α-D-1,2:5,6-bis-O-isopropylidene-glucofuranose (6) To 800 mL of dry acetone was added 160 g (1 mole) of anhydrous $CuSO_4$ followed by the dropwise addition of 8.9 mL (0.16 moles) of H_2SO_4, and 100 g (0.55 moles) of D-glucose. The reaction was vigorously shaken at room temperature for 24 h and then the reaction contents were filtered. The reaction mixture was neutralized with NH_4OH and the solution was refiltered. The volume was reduced. The syrup was taken up in EtOAc and extracted with H_2O to remove the remaining inorganic salts and starting material. The solvent was evaporated to yield 45% of **6**. Spectral data directly matched those in the literature.[28]

α-D-1,2:5,6-O-bis-O-isopropylidene-3-deoxy-glucofuranose (7). Compound **6** (18.34 g, 70.45 mmol) was dissolved in 168 mL (2.11 mol) of dichloroethane and then 13.81 g (77.50 mmol) of thiocarbonyl diimidazole was added. The reaction was allowed to reflux under an inert atmosphere for 4 h. The solvent was then removed and the dark syrup was purified by flash chromatography using $CHCl_3$ as eluant to give α-D-1,2:5,6-bis-O-isopropylidene-3-O-thiocarbonylimidazoleglucofuranose (80%): ^1H NMR ($CDCl_3$): δ 1.29 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.57 (s, 3H), 4.08 (dd, J = 4.2, 9.0 Hz, 1H), 4.16 (dd, J = 5.4, 8.7 Hz, 1H),

4.29 (m, 2H), 4.76 (d, J = 3.9 Hz, 1H), 5.84 (d, J = 2.4 Hz, 1H), 5.95 (d, J = 3.9 Hz, 1H), 7.06 (s, 1H), 7.61 (s, 1H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.1, 26.2, 26.6, 26.9, 67.6, 72.4, 79.8, 82.7, 84.5, 105.1, 109.9, 112.8, 117.9, 131.2, 136.8, 182.5. A portion of the thiocarbonylimidazole intermediate 0.8459 g (2.28 mmol) was dried, dissolved in 30 mL anhydrous toluene, and then purged with N_2. To a dried constant addition funnel was added 100 mL of anhydrous toluene, 0.365 g (2.28 mmol) of AIBN, and 2.45 mL (9.13 mmol) of Bu_3SnH. The solution in the addition funnel was also purged with N_2. The second solution was allowed to drip into the refluxing reaction mixture over 2 h. The reaction mixture was allowed to reflux for 3 h following the addition and then the solvents were removed. The residue was dissolved in CH_3CN and extracted with hexanes. The CH_3CN was removed and the product was purified by flash column chromatography with $CHCl_3$ to give 0.2230 g (40%) of the deoxygenated product: ^1H NMR: δ 1.26 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.70 (m, 2H), 2.15 (m, 1H), 3.77 (m, 1H), 4.09 (m, 2H), 4.69 (t, J = 4.5 Hz, 1H), 5.76 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 25.1, 26.0, 26.4, 26.7, 35.2, 67.1, 76.8, 78.5, 80.3, 105.5, 109.5, 111.2; Anal. Calcd for $C_{12}H_{20}O_5$: C, 58.99; H, 8.25. Found: C, 58.46; H, 8.34.

α-D-3-deoxy-1,2-O-isopropylidene-glucofuranose (8). Compound **7** (4.54 g, 18.58 mmol) was dissolved in 22 mL 0.2% aqueous HCl and was allowed to stir at room temperature for 16 h. The solution was then neutralized with 1N NaOH and purified by flash chromatography with 0-5% MeOH:$CHCl_3$ to yield 3.035 g (80%) of product: ^1H NMR ($CDCl_3$): δ 1.23 (s, 3H), 1.41 (s, 3H), 1.74 (m, 1H), 1.98 (m, 1H), 3.44 (dd, J = 6.9, 7.2 Hz, 1H), 3.61 (dd, J = 3.3, 11,4 Hz, 1H), 3.69 (br s, 1H), 3.76 (m, 2H), 4.08 (m, 1H), 4.65 (t, J = 4.2 Hz, 1H), 5.72 (d, J = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 25.9, 26.5, 33.6, 63.4, 72.2, 78.3, 80.3, 105.0, 111.1; Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.89. Found: C, 52.76; H, 7.73.

α-D-6-O-benzoyl-3-deoxy-1,2-O-isopropylidene-glucofuranose (9). Compound **8** (1.5364 g, 7.52 mmol) was dissolved in 60.8 mL (752 mmol) of anhydrous pyridine and cooled to -15°C. To 304 mL (3.76 mol) of anhydrous pyridine in a constant addition funnel was added 0.87 mL (7.52 mmol) of benzoyl chloride. The benzoyl chloride and pyridine mixture is allowed to stand for 15 minutes for complexation to occur (noted color change from clear to orange/brown). The contents of the addition funnel are added dropwise over a period of 2 h, while the reaction temperature was maintained at -15°C. The reaction was allowed to stir for an additional 2 h and then was quenched with MeOH. The volatile components were removed by evaporation under reduced pressure followed by coevaporation with toluene three additional times. The crude product was then purified by column chromatography, using $CHCl_3$ to yield 1.8557 g (80%) of **9**: ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.49 (s, 3H), 1.97 (m, 1H), 2.12 (dd, J = 4.5, 13.5 Hz, 1H), 2.60 (br s, 1H), 4.19 (m, 1H), 4.33 (m, 2H), 4.48 (dd, J = 3.6, 11.7 Hz, 1H), 4.75 (t, J = 4.2 Hz, 1H), 5.81 (d, J = 3.3 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 8.00 (d, J = 6.9 Hz, 2H); Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.53. Found: C, 62.35; H, 6.40.

α-D-6-O-benzoyl-3,5-dideoxy-1,2-O-isopropylidene-glucofuranose (10). Compound **9** (0.2521 g, 0.78 mmol) was dissolved in 186 mL (2.3 mol) of anhydrous dichloroethane. To the stirring solution under a nitrogen atmosphere was added 0.2077 g (1.17 mmol) of thiocarbonyldiimidazole. The reaction mixture was allowed to stir at reflux temperatures under N_2 for 5 h. The solvent was removed and the crude

thiocarbonylimidazole intermediate was dissolved in 224 mL (2.11 mol) of anhydrous toluene. To a dry constant addition funnel was added 374 mL (3.52 mol) of anhydrous toluene, 5.63 g (35.22 mmol) of AIBN, and 28.4 mL (105.6 mmol) of Bu_3SnH. Each vessel was purged for 10 minutes with N_2, and then the contents of the constant addition funnel were added dropwise to the refluxing solution over 3 h. The reaction was allowed to reflux for an additional 2 h and then the solvents were removed. The crude mixture was taken up in CH_3CN, and extracted with hexanes. The solvent was evaporated and the residue purified by column chromatography with $CHCl_3$ to yield 0.1590 g (70%) of the desired product: ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.49 (s, 3H), 1.85 (m, 2H), 1.93 (m, 1H), 2.12 (dd, J = 4.5, 13.5 Hz, 1H), 4.72 (m, 3H), 4.83 (t, J = 3 Hz, 1H), 6.14 (d, J = 3 Hz, 1H), 6.96 (m, 2H), 7.47 (m, 1H), 7.98 (d, J = 6 Hz, 2H); Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.89. Found: C, 65.55; H, 6.74.

6-O-benzoyl-3,5-dideoxy-1-O-methoxy-glucofuranose (11). Compound **10** (0.1632 g, 0.56 mmol) was dissolved in 2.25 mL (55.84 mmol) of anhydrous MeOH and 0.0020 g (0.056 mmol) of anhydrous HCl was bubbled into the stirring solution. The solution was kept under a N_2 atmosphere and allowed to stir for 16 hours at room temperature before neutralization with basic Dowex. The Dowex was filtered and then the solvent was removed. The crude mixture was purified by preparative layer chromatography to give 0.0966 g (65%) of **11**: ^1H NMR ($CDCl_3$): δ 1-78-2.03 (m, 3H), 3.24 (s, 3H), 3.53 (br s, 1H), 4.18 (d, J = 4.2 Hz, 1H), 4.31-4.51 (m, 4H), 4.74 (s, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.96 (d, J = 3 Hz, 2H); Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.75; H, 6.48.

6-O-benzoyl-1,3,5-trideoxy-glucofuranose (12). To a solution of 1.1980 g (4.50 mmol) of compound **11** in 9.49 mL (44.99 mmol) of HMDS was added 0.28 mL (2.25 mmol) of TMSCl . The solution was heated to reflux for 4 h to allow for all material to react. The reaction was then cooled to room temperature and the volatiles were removed *in vacuo*. The residue was dissolved in 34 mL (650 mmol) of dry CH_3CN. The solution was cooled to 0°C and 2.15 mL (13.50 mmol) of Et_3SiH was added. This was followed by the dropwise addition of TMSOTf (2.61 mL, 13.50 mmol) by syringe. The reaction was allowed to stir at room temperature for 16 h prior to being neutralized with 0.1 N NaOH. The solvents were then removed and the product was purified by column chromatography using $CHCl_3$ to give 0.4251 g (40%) of **12**: ^1H NMR ($CDCl_3$): δ 1.58-1.76 (m, 1H), 1.88-2.08 (m, 3H), 2.66 (br s, 1H), 3.69 (d, J = 9.9 Hz, 1H), 3.99 (dd, J = 4.5, 9.9 Hz, 1H), 4.23-4.73 (m, 4H), 7.38 (t, J = 7.8 Hz, 2H), 7.51 (t, J = 6.9 Hz, 1H), 8.05 (d, J = 8.1 Hz, 2H); Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 66.13; H, 7.12.

6-O-benzoyl-2-O-tosyl-1,3,5-trideoxy-glucofuranose (13). Compound **12** (0.1997 g, 0.85 mmol) was dissolved in 6.8 mL (84.52 mmol) of anhydrous pyridine. The solution was cooled to 0°C and 0.4834 g (2.54 mmol) of tosyl chloride was added under a N_2 atmosphere. The reaction mixture was warmed to room temperature, allowed to stir for 16 h, and then quenched with MeOH. The volume was reduced and residue was taken up in $CHCl_3$ and purified by preparative layer chromatography with 2% MeOH:$CHCl_3$ to provide 0.2144 g (65%) of the target coupling sugar: ^1H NMR ($CDCl_3$): δ 1.72 (m, 1H), 1.96 (m, 2H), 2.28 (dd, J = 5.4, 14.1 Hz, 1H), 2.49 (s, 3H), 3.81 (d, J = 11.4 Hz, 1H), 4.05 (dd, J = 4.8, 11.1 Hz, 1H), 4.14-4.24 (m, 1H),

4.32-4.45 (m, 2H), 5.11 (m, 1H), 7.33 (m, 2H), 7.45 (m, 2H), 7.57 (m, 1H), 7.78 (m, 2H), 8.01 (d, J = 5.4 Hz, 2H); Anal. Calcd for $C_{20}H_{22}O_6S$: C, 61.52; H, 5.67. Found: C, 61.24; H, 5.33.

4(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanethanol (15) The general glycosylation procedure was followed. The reaction time was 18 h. The solvents were removed and the product was purified by preparative layer chromatography with 5% MeOH:$CHCl_3$ to give the desired product **14** contaminated with 18-crown-6. The yield based on NMR integration data was 50%. Deprotection with the general debenzoylation procedure provided 0.0563 g (40% for both steps) of the target compound **15**: $[\alpha]_D$: -28.4 (*c* 0.1, MeOH); UV (H_2O): λ_{max} 259.5 nm (ε 12500); ^1H NMR (DMSO-d_6): δ 1.84 (m, 3H), 2.74 (m, 1H), 3.51 (d, J = 6.6 Hz, 1H), 3.54 (d, J = 6.6 Hz, 1H), 4.00 (m, 3H), 4.46 (t, J = 5.1 Hz, 1H), 5.16 (m, 1H), 7.19 (br s, 2H), 8.14 (s, 1H), 8.29 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 37.6, 53.6, 57.4, 70.6, 75.6, 78.6, 118.3, 138.1, 148.8, 151.8, 155.4; Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 52.96; H, 6.06; N, 28.09. Found: C, 52.54; H, 5.95; N, 27.65.

4(S)-(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)tetrahydro-2(S)-furanethanol (18) The general glycosylation procedure was followed to give 4(S)-(2-amino-6-chloro-9H-purin-9-yl)-2(S)-(O-benzoylethyl)tetrahydrofuran, **16**. The solvents were removed and the product was purified by preparative layer chromatography to give 0.1994 g (50%) of the protected nucleoside **16**: UV (MeOH): λ_{max} 247, 309 nm; ^1H NMR ($CDCl_3$): δ 1.89 (m, 1H), 2.14 (m, 1H), 2.76 (m, 2H), 4.11 (m, 2H), 4.45 (m, 2H), 4.98 (m, 1H), 5.09 (m, 1H), 5.56 (br s, 2H), 7.39 (m, 2H), 7.52 (m, 1H), 7.88 (s, 1H), 7.97 (d, 2H); ^{13}C NMR ($CDCl_3$): δ 34.2, 39.0, 54.3, 61.8, 70.3, 72.1, 76.4, 128.2, 129.3, 129.9, 132.9, 139.8, 153.3, 159.3, 166.3. The nucleoside **16** (0.1901 g, 0.49 mmol) was dissolved in 10 mL MeOH, cooled to 0°C and then saturated with anhydrous ammonia. The debenzoylation reaction was warmed to room temperature and allowed to stir for 48 h. Excess ammonia was removed and then the solvent was removed under reduced pressure. The residue was purified by preparative layer chromatography with 10% MeOH/$CHCl_3$ to give 0.0695 g (60%) 4(S)-(2-amino-6-chloro-9H-purin-9-yl)-2(S)-furanethanol **17**: UV (MeOH): λ_{max} 247, 309 nm; ^1H NMR ($CDCl_3$): δ 1.96 (m, 3H), 2.55 (br s, 1H), 2.73 (m, 1H), 3.68 (m, 2H), 4.04 (m, 1H), 4.17 (m, 2H), 5.13 (m, 1H), 5.31 (br s, 2H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 36.7, 38.9, 54.6, 60.2, 72.5, 78.6, 125.2, 140.4, 151.5, 153.3, 159.0. A solution of the 6'-deprotected nucleoside **17** (0.0652 g, 0.23 mmol) in 2 mL of 1N NaOH was stirred for 1 h at 95°C. The reaction mixture was then neutralized with 1N HCl. Removal of the solvent under reduced pressure and purification of the residue by reversed-phase HPLC gave 0.042 g (70%) of the desired compound: $[\alpha]_D$: -27.4 (*c* 0.1, MeOH); UV (H_2O): λ_{max} 252.5 nm (11300), 271.5 (7906); ^1H NMR (DMSO-d_6): δ 1.81 (m, 4H), 2.57 (m, 3H), 3.92 (m, 3H) 4.52 (br s, 1H), 4.89 (m, 1H), 6.56 (br s, 2H), 7.67 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 37.7, 40.8, 53.2, 57.6, 70.9, 75.6, 119.0, 134.2, 150.6, 153.7, 157.4; Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.69; N, 26.39. Found: C, 49.47; H, 5.98; N, 25.77.

4(S)-[3,4-Dihydro-2,4-dioxo-5-methyl-1-(2H)-pyrimidinyl]tetrahydro-2(S)-furanethanol (22). The general glycosylation procedure was followed to give 2(S)-(O-benzoylethyl)-4(S)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2H)-pyrimidinyl]tetrahydrofuran **20**. The solvent was removed and the residue was purified by preparative layer chromatography to give 0.1077 g (35%) of protected nucleoside **20**: ^1H NMR ($CDCl_3$): δ

1.54 (m, 1H), 1.93 (s, 3H), 2.12 (m, 2H), 2.70 (m, 1H), 3.87 (m, 1H), 3.96 (m, 2H), 4.48 (m, 2H), 5.33 (m, 1H), 7.41 (m, 2H), 7.52 (m, 2H), 7.99 (m, 2H), 9.76 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 12.6, 33.9, 39.5, 54.6, 61.9, 72.0, 76.8, 112.2, 128.2, 129.3, 129.4, 128.9, 132.9, 136.0, 151.0, 163.8, 166.3. The protected nucleoside **20** was then debenzoylated according to the general procedure to afford 0.0593 g (85%) of the title compound **22** as a very hygroscopic white solid: $[\alpha]_D$: +24.9 (*c* 0.1, MeOH); UV (H_2O): λ_{max} 271 nm (ε 9300); ^{1}H NMR ($CDCl_3$): δ 1.27 (m, 1H), 1.66 (s, 3H), 1.79 (br s, 1H), 2.26 (m, 1H), 2.41 (m, 1H), 3.67 (m, 6H), 5.06 (m, 1H), 6.98 (s, 1H), 9.21 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ 12.6, 37.0, 39.6, 54.5, 60.7, 72.3, 78.9, 112.3, 136.2, 150.9, 163.5; Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.65. Found: C, 54.30; H, 6.30; N, 11.05.

4(S)-[4-Amino-2-oxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanethanol (23). The general glycosylation procedure was followed to give 2(S)-O-benzoylethanol-4(S)-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl] tetrahydrofuran **19**. The reaction was complete in 8 h. The solvent was removed and purification was achieved by multiple elution on preparative layer chromatography with 5% MeOH:$CHCl_3$ to give 0.0633 g (35%) of the desired protected nucleoside **19** (bis-glycosylated and O-glycosylated side products were also produced): ^{1}H NMR ($CDCl_3$): δ 1.54 (m, 1H), 2.15 (m, 2H), 2.73 (m, 1H), 3.80 (m, 3H), 4.44 (m, 2H), 5.34 (m, 1H), 5.77 (m, 1H), 7.47 (m, 4H), 8.01 (m, 2H), 10.01 (br s, 1H). The general debenzoylation procedure was followed to give 0.0345 g (80%) of the desired target compound **21**: $[\alpha]_D$: +31.7 (*c* 0.12, MeOH); UV (H_2O): λ_{max} 266 nm (ε 8700); ^{1}H NMR (DMSO-d_6): δ 1.53 (m, 1H), 2.13 (m, 2H), 2.71 (m, 1H), 3.91 (m, 4H), 4.45 (m, 2H), 5.32 (m, 1H), 5.77 (m, 1H), 7.97 (m, 1H), 10.10 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ 37.8, 38.1, 54.9, 58.0, 70.9, 76.3, 102.1, 141.5, 150.9, 163.2.

The uridine analog **19** (0.083 g, 0.25 mmol) was dissolved in 2.0 mL (25.13 mmol) of pyridine. A solution of 0.04 mL (0.38 mmol) of $POCl_3$ and 0.0521 g (0.75 mmol) of triazole in 3 mL of pyridine was added dropwise at 0°C. The reaction mixture was warmed to room temperature and allowed to stir for 18 h to provide the triazole intermediate. This intermediate was not isolated but immediately dissolved in 1.95 mL of dioxane. 0.65 mL (9.75 mmol) of a concentrated NH_4OH solution was added at room temperature and the solution was allowed to stir for 5 h. Although some deprotection occurred with this hydrolysis the product mixture was fully deprotected by the addition of 0.0135 g (0.22 mmol) of NaOMe to the crude product. The reaction was neutralized and the product was purified by preparative layer chromatography with 5% MeOH:$CHCl_3$ to give 0.0152 (27%) of the target compound **23**: $[\alpha]_D$: +85.9 (*c* 0.06, MeOH); UV (H_2O): λ_{max} 275 nm (ε 8775); ^{1}H NMR (D_2O): δ 1.62 (m, 1H), 1.89 (m, 2H), 2.65 (m, 1H), 3.67 (m, 2H), 3.96 (m, 3H), 5.15 (m, 1H), 6.02 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H); ^{13}C NMR (D_2O): δ 39.1, 40.7, 59.4, 61.5, 73.9, 79.9, 99.1, 145.6, 160.7, 168.3. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.65. Found: C, 53.02; H, 6.42 ; N, 18.20.

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REFERENCES

1. De Clercq, E. *Nucleosides & Nucleotides* **1994**, *13*, 1271-1295.
2. Herdewijn, P. A. M. M. *Antiviral Res.* **1992**, *19*, 1-14.
3. Mitsuya, H.; Weindhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.*, **1985**, *82*, 7096-7100.
4. Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533-1544.
5. Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Broder, S. *Science* **1989**, *245*, 412-415.
6. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911-1915.
7. Coates, J. A. V.; Cammack, N.; Jenkinson, J. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202-205.
8. Schinazi, R. F.; Mead, J. R.; Feorino, P. M. *AIDS Res. Human Retroviruses* **1992**, *8*, 963-990.
9. Lin, T.-S.; Luo, M.-Z.; Liu, M.-C. *Tetrahedron* **1995**, *51*, 1055-1068.
10. Lin, T.-S.; Luo, M.-Z.; Liu, M.-C. *Tetrahedron Lett.* **1994**, *35*, 3477-3480.
11. Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y. C. *J. Med. Chem.* **1994**, *37*, 798-803.
12. 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.
13. Chu, C. K.; Beach, W. J.; Jeong, L. S.; Choi, B. G.; Comer, F. I.; Alves, A. J.; Schinazi, R. F. *J. Org. Chem.* **1991**, *56*, 6503-6505.
14. Sells, T. B.; Nair, V. *Tetrahedron* **1994**, *50*, 117-138.
15. Sells, T. B.; Nair, V. *Tetradedron Lett.* **1992**, *33*, 7639-7642.
16. Bamford, M. J.; Humber, D. C.; Storer, R. *Tetrahedron Lett.* **1991**, *32*, 271-274.
17. Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951-7953.
18. Bolon, P. J.; Sells, T. B.; Nuesca, Z. M.; Purdy, D. F.; Nair, V. *Tetrahedron* **1994**, *50*, 7747-7764.
19. Nair, V. Approaches to Novel Isomeric Nucleosides as Antiviral Agents. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K.; Baker, D. C. Eds.; Plenum Press: New York, 1993, pp. 127-140.
20. De Clercq, E. *Biochem. Pharmacol.* **1994**, *47*, 155-169.
21. Nair, V.; Buenger, G. S. *J. Org. Chem.* **1990**, *55*, 3695-3697.
22. Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611-10670.
23. Nair, V.; Emanuel, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 1571-1576.
24. Barton, D. H. R.; Subramanian, R. *J. Chem. Soc. Perkin Trans. I* **1977**, 1718-1723.
25. Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892-897.
26. Bax, A. *J. Magn. Reson.* **1984**, *57*, 314-318.
27. Reese, C. B.; Ubasawa, A. *Nucleic Acid Res.* **1980**, Symposium Series 7, 5-21.
28. *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*; Pouchert, C. J.; Behnke, J. Eds.; Aldrich Chemical Co., Inc.: USA, 1993, p 314b.

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