THE SYNTHESIS OF (*S*) AND (*R*) ENANTIOMERS OF NOVEL HYDROXYMETHYLATED ISODIDEOXYNUCLEOSIDES

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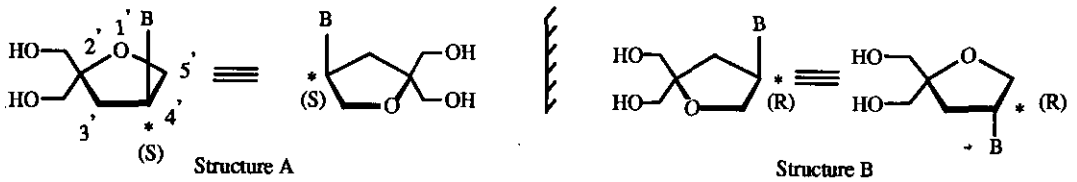
Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday

Abstract- Novel isomeric dideoxynucleosides, with symmetry introduced at the 2'-position (4'-position using normal nucleoside numbering) through the introduction of an additional hydroxymethyl group, have been synthesized. Both (*R*) and (*S*) enantiomeric series were investigated. The methodologies developed have generality and the presence of the hydroxymethyl group trans to the base may be used to introduce a wide variety of functionalities at this position.

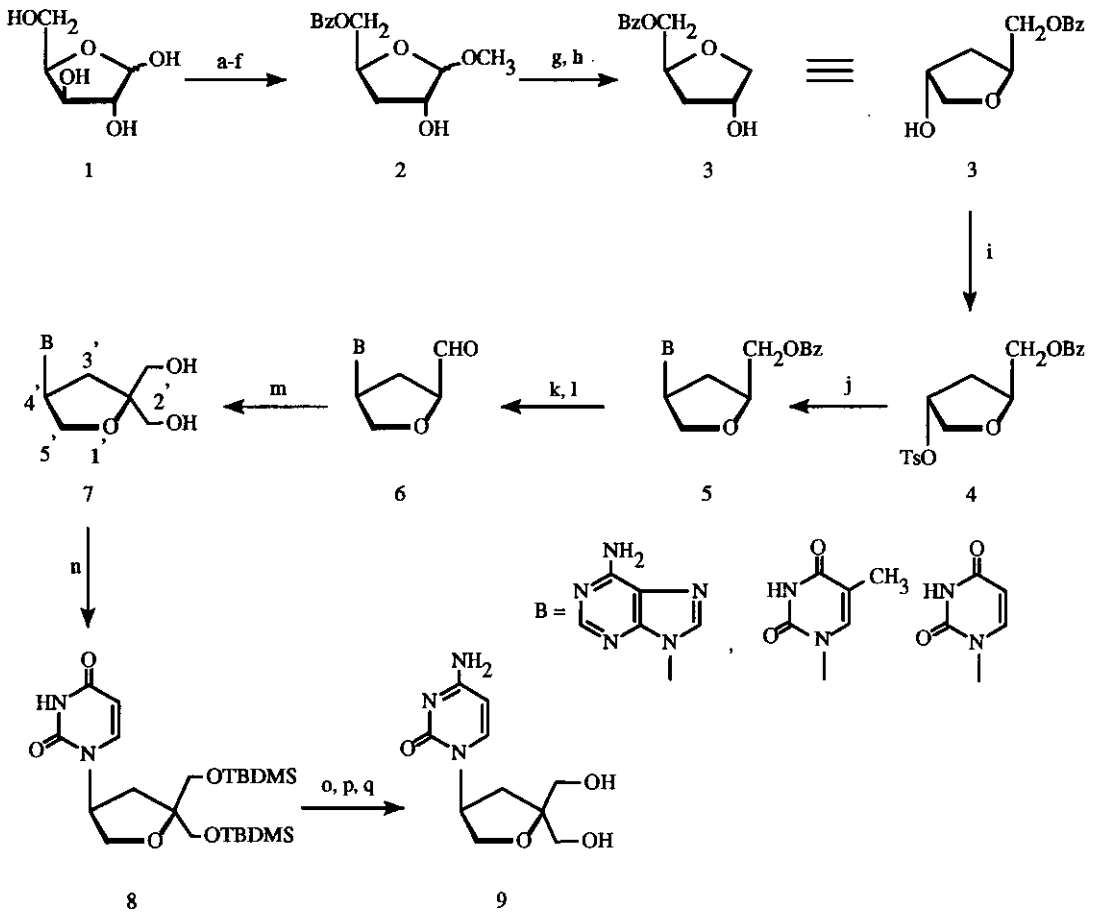
The synthesis of novel modified dideoxynucleosides has received considerable attention in the last few years because of the potential of these types of compounds to inhibit the cytopathic effect of HIV, the etiologic agent of acquired immunodeficiency syndrome (AIDS).[1-3] In these modifications, the carbohydrate ring has been extensively studied in terms of alterations at the 2'- and 3'-positions. Much less attention has been focused on 4'-substituted deoxy- and dideoxynucleosides. However, recent work on 4'-substituted nucleosides as anti-HIV and anti-HSV agents suggest that this family may have significant antiviral potential.[4,5] For example, 4'-cyano and 4'-azido derivatives of some pyrimidine 2'-deoxynucleosides show high anti-HIV activity with EC_{50} values in the low to sub micromolar range, but in some cases with considerable toxicity.[4-7] The 4'-modifications of guanine carbocyclic nucleosides have resulted in compounds with activity against HSV-1 and HSV-2.[8] However, the synthesis of 4'-substituted dideoxynucleosides with isomeric modifications have not been investigated. This paper reports on the development of synthetic approaches to novel, optically active regioisomers of 4'-hydroxymethyl dideoxynucleosides (Scheme 1, structures A and B). Because of the symmetry introduced at this position (designated as the 2'-position in the new numbering), these molecules have only one asymmetric center.



Scheme 1.

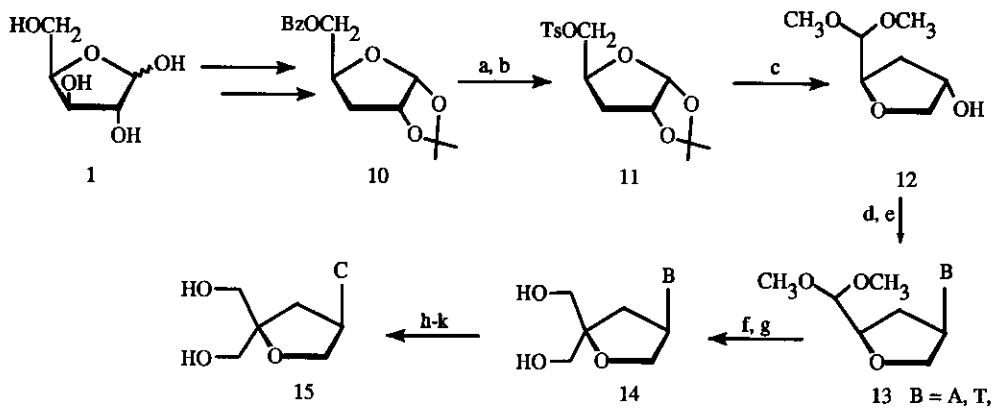
Synthesis of the (*S*)-enantiomeric series of the 2'-hydroxymethyl isodideoxynucleosides bearing both purine and pyrimidine bases (Scheme 2) will be illustrated with the preparation of 4(*S*)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]tetrahydro-2(*S*)-furanmethanol (**7**, B = thymine). This compound was prepared by the glycosylation of thymine with the modified carbohydrate (**4**) which was derived from D-xylose (**1**) in the following manner. D-Xylose was protected as its bis-isopropylidene derivative and specifically deprotected to produce 1,2-*O*-isopropylidene-D-xylose which was selectively 5-*O*-benzoylated, 3-deoxygenated (using the Barton procedure) and converted into its methyl acetal (**2**). [9,10] Demethoxylation of **2** by treatment with HMDS/TMSCl followed by reduction with triethylsilane in the presence of TMS triflate[11] gave compound (**3**).[12] The 4-(*R*)-hydroxyl group of **3** was tosylated to give **4** which was glycosylated with thymine in the presence of potassium carbonate and 18-crown-6 in DMF with heating to give deoxyisothymidine (**5**) (B = T). The strategy for the introduction of the hydroxymethyl group was through the aldehyde, using in tandem, an aldol and a Cannizzaro reaction.[5] The aldehyde (**6**) needed for these reactions was prepared by deprotection of **5** and oxidation of the resulting compound using Moffatt conditions (DCC, DMSO, dichloroacetic acid). Aldol condensation of aldehyde (**6**) with formaldehyde, followed under the conditions of the reaction by a Cannizzaro reduction, yielded the desired target hydroxymethyldeoxyisothymidine (**7**) (**B = T**). The structure of this compound was confirmed by uv, ir, ms, optical rotation and nmr data. Synthesis of the adenine analog was carried out using a similar approach. Dideoxyisouridine (**7**) (B = U) was converted to dideoxyisocytidine *via* the triazole derivative followed by ammonolysis.[13,14]

The (*R*)-enantiomeric series (Scheme 3) was approached through the glycosylation of the desired nucleic acid base with the tosylate of modified carbohydrate (**12**) which was prepared from D-xylose (**1**). Thus, **1** was converted in several steps to 1,2-*O*-isopropylidene-3-deoxy-5-*O*-benzoyl-D-xylose (**10**) which was debenzoylated and tosylated to yield 1,2-*O*-isopropylidene-3-deoxy-5-*O*-(*p*-toluenesulfonyl)-D-xylose (**11**).[9,12]



Scheme 2. Reagents and conditions: a, acetone, H_2SO_4, room temperature; b, 0.2% HCl, room temperature; c, BzCl, pyridine, -10 °C; d, 1,1'-thiocarbonyldiimidazole, 1,2-dichloroethane, reflux; e, AIBN, Bu_3SnH, toluene, reflux; f, HCl (cat.), CH_3OH; g, HMDS, TMSCl, reflux; h, TMSOTf, $(C_2H_5)_3SiH$, CH_3CN, room temperature; i, TsCl, pyridine, 0 °C; j, nucleoside base, K_2CO_3, 18-crown-6, DMF, 75 °C; k, $NaOCH_3$, CH_3OH, room temperature; l, DMSO, DCC, DCAA, room temperature; m, 2N NaOH, 37% aq. formaldehyde, 1,4-dioxane, room temperature; n, *t*-$C_4H_9(CH_3)_2SiCl$, imidazole, DMF; o, 1,2,4-triazole, $POCl_3$, pyridine, 0 °C; p, NH_4OH; q, $(C_2H_5)_4NF$, CH_3CN, room temperature (Bz = benzoyl; AIBN = azobisisobutyronitrile; HMDS = 1,1,1,3,3,3-hexamethyldisilazane; TMSCl = chlorotrimethylsilane; TMSOTf = trimethylsilyl trifluoromethanesulfonate; Ts = *p*-toluenesulfonyl; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; DCC = 1,3-dicyclohexylcarbodiimide; DCAA = dichloroacetic acid).

Treatment of **11** with a 1% acetic acid/ methanol solution[15] yielded the rearranged 2(*R*)-(dimethoxymethyl)-tetrahydrofuran-4-(*S*)-ol (**12**) which was subsequently tosylated to yield 2(*R*)-(dimethoxymethyl)-4(*S*)-[*O*-(*p*-toluenesulfonyl)]tetrahydrofuran. Coupling of the latter with adenine, thymine and uracil gave 4(*R*)-(nucleoside base)-2(*R*)-(dimethoxymethyl)tetrahydrofuran (**13**). Hydrolysis of the dimethyl acetal using aqueous oxalic acid followed by a sequential aldol condensation and Cannizzaro reduction of the resulting aldehyde gave the desired 4(*R*)-(nucleoside base)-2-hydroxymethyl-2-furanmethanol (**14**). The cytidine analog was prepared from the uridine precursor in the same manner as described previously to produce 4(*R*)-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (**15**).



Scheme 3. Reagents and conditions: a, $NaOCH_3$, CH_3OH, room temperature; b, TsCl, pyridine, 0 °C; c, 1% acetic acid/CH_3OH, 70 °C; d, TsCl, pyridine, room temperature; e, nucleoside base, K_2CO_3, 18-crown-6, DMF, 75 °C; f, 0.1M oxalic acid, 80 °C; g, 2N NaOH, 37% aq. formaldehyde, 1,4-dioxane, room temperature; h, *t*-$C_4H_9(CH_3)_2SiCl$, imidazole, DMF; i, 1,2,4-triazole, $POCl_3$, pyridine, 0 °C; j, NH_4OH; k, $(C_2H_5)_4NF$, CH_3CN, room temperature (Ts = *p*-toluenesulfonyl; DMF = dimethylformamide).

In summary, methodologies for the synthesis of isomeric dideoxynucleosides bearing an additional hydroxymethyl group have been developed. Final target compounds of both the *(R)*- and (*S*)-enantiomeric families were synthesized and their structures confirmed by uv, nmr and elemental analysis data. Introduction of the additional hydroxymethyl group trans to the existing base allows entry to a wide variety of functionalities at this position (e.g. α-azido, α-amino, α-halo, etc.). Further extension of these synthetic studies to other stereochemically defined regioisomeric analogs and evaluations of biological activities are still in progress.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover open stage melting point apparatus and are uncorrected. The ^1H nmr were recorded on either a Bruker MSL 300, AC 300, or a WM 360 in $CDCl_3$ or Me_2SO-d_6. Chemical shift values are reported in δ, parts per million, relative to the internal standard. Elemental analysis were carried out at the University of Iowa on a Perkin-Elmer 2400 Series II Elemental Analyzer. Uv spectra were recorded on a Varian Cary 3 or a Gilford Response spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Preparative layer chromatography plates were made from E. Merck PF_{254} silica gel. Tlc plates were visualized by ultraviolet absorbance or charring for several minutes after exposure to either a 20% sulfuric acid/methanol solution or a 12% phosphomolybdic acid/ethanol solution. Hplc separations were carried out on Pharmacia or Waters instruments at medium pressures using an Amberlite XAD-4 resin or Hamilton PRP-1 resin as the stationary phase and ethanol/water as the mobile phase.

General Synthetic Procedures (A-I). Procedure A: Glycosylation reactions - S series. To a solution of 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol (2.349 g, 6.240 mmol) in dry dimethylformamide (15 ml) was added potassium carbonate (1.725 g, 12.48 mmol), 18-crown-6 (1.649 g, 6.240 mmol) and nucleoside base (9.360 mmol). The resulting mixture was stirred at 70 °C for 20 h. The solvent was evaporated and the residue was purified on silica gel with chloroform followed by 2% methanol/chloroform.

Procedure B: Deprotection of benzoate. To a solution of 4(S)-(nucleoside base)tetrahydro-2(S)-furan-methylbenzoate (4.056 mmol) in anhydrous methanol (10 ml) was added sodium methoxide (0.329 g, 6.084 mmol), the resulting solution was stirred at room temperature under nitrogen for 2 h. The solvent was evaporated and the residue was purified on silica gel with chloroform followed by 6% methanol/chloroform.

Procedure C: Oxidation of -CH_2OH group. A solution of 4(S)-(nucleoside base)tetrahydro-2(S)-furan-methanol (1.007 mmol), dicyclohexylcarbodiimide (0.8311 g, 4.028 mmol) and dichloroacetic acid (0.0649 g, 0.5035 mmol) in dimethyl sulfoxide (10 ml) was stirred at room temperature under nitrogen for 24 h. The solvent was evaporated under reduced pressure and the residue was dissolved in petroleum ether (75 ml) and extracted with water (3 x 50 ml). The water layer was filtered and concentrated under reduced pressure and taken without further purification to procedure D.

Procedure D: Aldol/Cannizzaro reactions. To a solution of 4(S)-(nucleoside base)tetrahydro-2(S)-furanmethanal (1.007 mmol) in 1,4-dioxane (10 ml) was added a 37% solution of formaldehyde (0.3019 ml, 4.028 mmol) and 2N NaOH (2.014 ml, 4.028 mmol). The resulting mixture was stirred at room temperature for 24 h, neutralized with 1N HCl, and the solvents were evaporated under reduced pressure. The residue was purified on silica gel with chloroform followed by 15% methanol/chloroform.

Procedure E: Protection by silylation. A mixture of 4(S or R)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (0.1783 g, 0.7357 mmol), *tert*-butyldimethylsilyl chloride (0.2439 g, 1.618 mmol), and imidazole (0.1503 g, 2.207 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 20 h. The solvent was evaporated and the residue was chromatographed on silica gel with 5% methanol/chloroform.

Procedure F: Conversion of isouridine to isocytidine analogs. A nitrogen purged solution of 1,2,4-triazole (0.2265 g, 3.280 mmol) and phosphorus oxychloride (0.1257 g, 0.8200 mmol) in anhydrous pyridine (5 ml) was added dropwise to a 0 ^{o}C solution of 4(S or R)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol-di-(*tert*-butyldimethylsilyl) (0.1930 g, 0.4100 mmol) in anhydrous pyridine (5 ml). The resulting mixture was warmed to room temperature and stirred for 5 h at which time ammonium hydroxide (3.5 ml) was added and stirred overnight. The solvent was evaporated and the residue was purified on silica gel with 2% methanol/chloroform.

Procedure G: Desilylation. The 4(S or R)-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol-di-(*tert*-butyldimethylsilyl) (0.1279 g, 0.2723 mmol) was dissolved in acetonitrile (5 ml) and tetraethylammonium fluoride (0.1219 g, 0.8169 mmol) was added and the mixture was stirred at room temperature for 2 h. Water (5 ml) was added and stirring continued for 20 min. The solvents were evaporated and the residue was purified by preparative tlc (30% methanol/chloroform) and hplc (water) to provide the cytidine analog.

Procedure H: Glycosylation procedure for R series. A mixture of 2(R)-(dimethoxymethyl)-4(S)-*O*-(*p*-toluenesulfonyl)tetrahydrofuran (0.3479 g, 1.100 mmol), potassium carbonate (0.3041 g, 2.200 mmol), 18-

crown-6 (0.4388 g, 1.660 mmol), and nucleoside base (2.210 mmol) in dimethylformamide (5 ml) was stirred 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.

Procedure I: Hydrolysis of dimethylacetal. A solution of (2R,4R)-[2-(dimethoxymethyl)tetrahydrofuran-4-yl] nucleoside (0.6800 mmol) in 0.1 M oxalic acid (50 ml) was stirred at 80 °C for 16 h. The mixture was neutralized with 2N NaOH and taken directly to procedure D.

4(S)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (7, B = T). Glycosylation of thymine with 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol **(4)** by procedure A (29% yield) produced 4(S)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]tetrahydro-2(S)-furanmethanol benzoate **(5)**: ^{1}H Nmr (Me_2SO-d_6) δ 1.63 (s, 3H), 1.83 (m, 1H), 2.50 (m, 1H), 3.82 (dd, 1H, J= 5.00, 9.59 Hz), 3.95 (dd, 1H, J = 6.85, 9.56 Hz), 4.19 (m, 1H), 4.39 (dd, 1H, J = 4.82, 12.20 Hz), 4.55 (dd, 1H, J = 2.99, 12.23 Hz), 5.10 (m, 1H), 7.39 (s, 1H), 7.49 (m, 2H), 7.65 (m, 1H), 7.94 (m, 2H), 11.26 (s, 1H); uv (EtOH) λ_{max} 271.5 nm. The protected isonucleoside was debenzoylated by procedure B (95% yield) to produce 4(S)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]tetrahydro-2(S)-furanmethanol **(6)** as a hygroscopic solid: ^{1}H Nmr (Me_2SO-d_6) δ 1.76 (s, 3H), 1.76 (m, 1H), 2.38 (m, 1H), 3.51 (m, 1H), 3.63 (m, 1H), 3.76 (m, 1H), 3.85 (m, 2H), 4.94 (t, 1H, J = 5.68 Hz), 5.11 (m, 1H), 7.61 (s, 1H), 11.20 (s, 1H). 4(S)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]tetrahydro-2(S)-furanmethanol was converted to 4(S)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (7, B = T) by using in sequence procedures C and D (45% yield, hygroscopic solid): $[\alpha]_D^{25}$ + 45.3° (c 0.265, MeOH); ^{1}H nmr (Me_2SO-d_6) δ 1.77 (s, 3H), 1.85 (dd, 1H, J = 6.07, 13.46 Hz), 2.18 (dd, 1H, J = 8.92, 13.32 Hz), 3.30 (m, 2H), 3.42 (m, 2H), 3.80 (dd, 1H, J = 4.96, 9.57 Hz), 4.01 (dd, 1H, J = 5.52, 12.37 Hz), 4.78 (br t, 1H), 4.90 (br t, 1H), 5.09 (m, 1H), 7.65 (s, 1H), 11.22 (br, 1H); uv (H_2O) λ_{max} 271 nm (ε 8019). Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.41; H, 6.39; N, 10.81.

4(S)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (7, B = U). Glycosylation of uracil with 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol **(4)** by procedure A (26% yield) produced 4(S)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]tetrahydro-2(S)-furanmethanol benzoate **(5)**:

^{1}H Nmr (Me_2SO-d_6) δ 1.81 (m, 1H), 2.50 (m, 1H), 3.86 (m, 1H), 3.98 (m, 1H), 4.20 (m, 1H), 4.48 (m, 2H), 5.10 (m, 1H), 5.50 (d, 1H, J = 6.16 Hz), 7.58 (m, 2H), 7.60 (d, 1H, J = 6.09 Hz), 7.65 (m, 1H), 7.95 (m, 2H), 11.28 (s, 1H); uv (EtOH) λ_{max} 265 nm. The protected isonucleoside was debenzoylated by procedure B (95% yield) to produce 4(S)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (**6**): ^{1}H Nmr (Me_2SO-d_6) δ 1.72 (m, 1H), 2.40 (m, 1H), 3.48 (m, 1H), 3.63 (m, 1H), 3.78 (m, 1H), 3.86 (m, 2H), 4.91 (t, 1H, J = 5.68 Hz), 5.09 (m, 1H), 5.58 (d, 1H, J = 8.09 Hz), 7.73 (d, 1H, J = 8.05 Hz), 11.23 (s, 1H). 4(S)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]tetrahydro-2(S)-furanmethanol was converted to 4(S)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (**7**, B = U) by using in sequence procedures C and D (35% yield): mp 173 °C; $[\alpha]_D^{25}$ + 63.1° (c 0.070, MeOH); ^{1}H nmr (Me_2SO-d_6) δ 1.85 (dd, 1H, J = 5.55, 14.52 Hz), 2.21 (dd, 1H, J = 9.32, 14.23 Hz), 3.31 (m, 2H), 3.41 (m, 2H), 3.79 (dd, 1H, J = 4.50, 10.01 Hz), 4.02 (dd, 1H, J = 6.69, 10.41 Hz), 4.76 (br, 1H), 4.85 (br, 1H), 5.08 (m, 1H), 5.58 (d, 1H, J = 7.86 Hz), 7.76 (d, 1H, J = 8.00 Hz), 11.20 (s, 1H); uv (H_2O) λ_{max} 265 nm (ε 9644). Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.59; H, 5.83; N, 11.56. Found: C, 49.47; H, 5.92; N, 11.43.

4(S)-(6-Amino-9*H*-purin-9-yl)-2-hydroxymethyltetrahydro-2-furanmethanol (**7**, B = A). Glycosylation of adenine with 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol (**4**) by procedure A (65% yield) produced 4(S)-(6-amino-9*H*-purin-9-yl)tetrahydro-2(S)-furanmethanol benzoate (**5**): ^{1}H Nmr ($CDCl_3$) δ 2.21 (m, 1H), 2.82 (m, 1H), 4.13 (dd, 1H, J = 6.00, 10.13 Hz), 4.30 (dd, 1H, J = 3.06, 9.93 Hz), 4.44 (m, 2H), 4.59 (dd, 1H, J = 3.01, 11.58 Hz), 5.31 (m, 1H), 5.65 (br, 2H), 7.42 (m, 2H), 7.55 (m, 1H), 7.89 (m, 2H), 8.02 (s, 1H), 8.32 (s, 1H). The protected isonucleoside was debenzoylated by procedure B (95% yield) to produce 4(S)-(6-amino-9*H*-purin-9-yl)tetrahydro-2(S)-furanmethanol as a white solid: mp 180-182 °C; ^{1}H nmr (Me_2SO-d_6) δ 2.09 (m, 1H), 2.58 (m, 1H), 3.40 (m, 1H), 3.58 (m, 1H), 4.00 (m, 3H), 4.93 (t, 1H, J = 5.63 Hz), 5.16 (m, 1H), 7.21 (s, 2H), 8.13 (s, 1H), 8.25 (s, 1H); uv (H_2O) λ_{max} 260 nm. 4(S)-(6-Amino-9*H*-purin-9-yl)tetrahydro-2(S)-furanmethanol was converted to 4(S)-(6-amino-9*H*-purin-9-yl)-2-hydroxymethyltetrahydro-2-furanmethanol (**7**, B = A) by using in sequence procedures C and D (13.6% yield): mp 195-196 °C; ^{1}H nmr (Me_2SO-d_6) δ 2.23 (dd, 1H, J = 6.76, 13.00 Hz), 2.43 (dd, 1H, J = 8.30, 13.16 Hz), 3.39 (t, 2H, J = 5.26 Hz), 3.44 (t, 2H, J = 5.26 Hz), 4.05 (dd, 1H, J = 6.08, 8.96 Hz), 4.21 (dd, 1H, J = 6.38, 8.93 Hz), 4.83 (m, 2H), 5.12 (m, 1H), 7.21 (s, 2H), 8.13 (s, 1H), 8.27 (s, 1H); uv (H_2O) λ_{max} 258 nm (ε 12625). Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot H_2O$: C, 46.64; H, 6.05; N, 24.72. Found: C, 46.56; H, 5.89; N, 24.74.

4(S)-[4-Amino-2-oxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (9). 4(S)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimdinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (**7**, B = U) was converted to 4(S)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol-di-(*tert*-butyldimethylsilyl) (**8**) by procedure E: ^{1}H Nmr ($CDCl_3$) δ 0.02 (s, 12H), 0.84 (s, 18H), 1.98 (dd, 1H, J = 4.42, 14.17 Hz), 2.44 (dd, 1H, J = 9.32, 14.23 Hz), 3.48 (s, 2H), 3.61 (s, 2H), 3.86 (dd, 1H, J = 3.06, 13.07 Hz), 4.17 (dd, 1H, J = 6.69, 10.38 Hz), 5.29 (m, 1H), 5.69 (d, 1H, J = 8.07 Hz), 7.68 (d, 1H, J = 8.09 Hz), 8.42 (br, 1H) followed by procedure F to produce 4(S)-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol-di-(*tert*-butyldimethylsilyl) (66% yield) as an oil: ^{1}H Nmr ($CDCl_3$) δ 0.03 (s, 12H), 0.86 (s, 18H), 1.92 (dd, 1H, J = 4.51, 14.47 Hz), 2.43 (dd, 1H, J = 8.94, 14.31 Hz), 3.48 (s, 2H), 3.64 (s, 2H), 3.87 (dd, 1H, J = 2.60, 10.37 Hz), 4.17 (dd, 1H, J = 6.41, 10.51 Hz), 5.40 (br, lH), 5.67 (d, 1H, J = 7.3 Hz), 7.22 (br, 2H), 7.80 (d, 1H, J = 7.31 Hz); uv (EtOH) λ_{max} 274 nm. The protected isocytidine analog was desilylated by procedure G to produce 4(S)-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (**9**) (90% yield): mp 186-187 °C; $[\alpha]_D^{25}$ + 82.6° (c 0.118, MeOH); ^{1}H nmr (Me_2SO-d_6) δ 1.83 (dd, 1H, J = 5.86, 13.33 Hz), 2.19 (dd, 1H, J = 8.82, 13.32 Hz), 3.32 (m, 4H), 3.73 (dd, 1H, J = 4.99, 9.31 Hz), 4.00 (dd, 1H, J = 6.81, 9.42 Hz), 4.76 (br t, lH), 4.81 (br t, 1H), 5.10 (m, 1H), 5.69 (d, 1H, J = 7.36 Hz), 6.96 (br, 2H), 7.69 (d, 1H, J = 7.37 Hz); uv (H_2O) λ_{max} 273 (ε 8295). Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.92; H, 6.25; N, 17.23.

4(R)-(6-Amino-9*H*-purin-9-yl)-2-hydroxymethyltetrahydro-2-furanmethanol (14, B = A). 1,2-*O*-Isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-xylofuranose (1.599 g, 4.860 mmol) in 1% acetic acid/methanol (80 ml) was stirred at 70 °C for 70 h. After neutralizing the solution with sodium methoxide the solvent was evaporated. The residue was chromatographed on silica gel with 5% methanol/chloroform to give 2(R)-(dimethoxymethyl)tetrahydrofuran-4(S)-ol in 80% yield (0.6300 g) as an oil: ^{1}H Nmr ($CDCl_3$) δ 1.90 (m, 2H), 2.78 (br d, 1H), 3.38 (s, 6H), 3.69 (d, 1H, J = 10.66 Hz), 3.85 (dd, 1H, J = 4.20, 10.65 Hz), 4.19 (m, 2H), 4.41 (m, 1H). To a solution of 2(R)-(dimethoxymethyl)tetrahydrofuran-4(S)-ol (0.9580 g, 5.907 mmol) in pyridine (10 ml) was added *p*-toluenesulfonyl chloride (1.464 g, 7.680 mmol) and the mixture was stirred at room temperature 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)-(dimethoxymethyl)-4(S)-*O*-(*p*-toluenesulfonyl)tetrahydrofuran in 90% yield (1.681 g): ^{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, J = 4.19, 10.66 Hz), 4.14 (m, 1H), 4.20 (d, 1H, J = 4.73 Hz), 5.07 (m, 1H), 7.31 (m, 2H), 7.74 (m, 2H). 2(R)-(Dimethoxymethyl)-4(S)-*O*-(*p*-toluenesulfonyl)tetrahydrofuran (0.3480 g, 1.100 mmol) was coupled with adenine (0.2990 g, 2.200 mmol) to produce 4(R)-(6-amino-9*H*-purin-9-yl)-2(R)-(dimethoxymethyl)tetrahydrofuran (**13,** B = A) by procedure H in 70% yield (0.2150 g): ^{1}H Nmr ($CDCl_3$) δ 2.24 (m, 1H), 2.66 (m, 1H), 3.46 (s, 3H), 3.38 (s, 3H), 4.09 (m, 3H), 4.48 (d, 1H, J = 4.34 Hz), 5.28 (m, 1H), 5.69 (br s, 1H), 8.13 (s, 1H), 8.33 (s, 1H); uv (MeOH) λ_{max} 262.0 nm. 4(R)-(6-Amino-9*H*-purin-9-yl)-2(R)-(dimethoxymethyl)tetrahydrofuran (**13,** B = A) (0.151 g, 0.540 mmol) was hydrolyzed to 4(R)-(6-amino-9*H*-purin-9-yl)-2(R)-tetrahydrofuranal by procedure I. The latter was converted to 4(R)-(6-amino-9*H*-purin-9-yl)-2-hydroxymethyltetrahydro-2-furanmethanol (**14**, B = A) by procedure D in 30% yield: mp 202-203 °C; ^{1}H nmr (Me_2SO-d_6) δ 2.22 (dd, 1H, J = 6.30, 13.11 Hz), 2.46 (dd, 1H, J = 8.26, 13.82 Hz), 3.40 (m, 2H), 3.46 (m, 2H), 4.00 (dd, 1H, J = 5.93, 8.94 Hz), 4.21 (dd, 1H, J = 6.45, 8.99), 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 12464). 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)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (14, B = T). 2(R)-(Dimethoxymethyl)-4(S)-*O*-(*p*-toluenesulfonyl)tetrahydrofuran (0.6010 g, 1.900 mmol) was coupled with thymine (0.4790 g, 3.800 mmol) to produce 4(R)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2(R)-(dimethoxymethyl)tetrahydrofuran (**13**, B = T) by procedure H in 28% yield (0.1440 g): ^{1}H Nmr ($CDCl_3$) δ 1.87 (s, 3H), 1.93 (m, 1H), 2.50 (m, 1H), 3.43 (s, 3H), 3.46 (s, 3H), 3.80 (m, 3H), 4.46 (d, 1H, J = 6.05 Hz), 5.28 (m, 1H), 7.45 (s, 1H), 9.64 (s, 1H); uv (MeOH) λ_{max} 269 nm. 4(R)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2(R)-(dimethoxymethyl)tetrahydrofuran (0.1300 g, 0.4800 mmol) was hydrolyzed to 4(R)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2(R)-tetrahydrofuranal by procedure I which was used in the next step without purification. 4(R)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2(R)-tetrahydrofuranal was converted to 4(R)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-2-hydroxymethyl-tetrahydro-2-furanmethanol (**14,** B = T) by procedure D in 35% yield as a hygroscopic solid: $[\alpha]_D^{25}$ - 52.2° (c 0.255, MeOH); ^{1}H nmr (Me_2SO-d_6) δ 1.77 (s, 3H), 1.85 (dd, 1H, J = 6.08, 13.40 Hz), 2.17 (dd, 1H, J = 8.90, 13.30 Hz), 3.30 (m, 2H), 3.42 (m, 2H), 3.78 (dd, 1H, J = 4.95, 9.40 Hz), 4.00 (dd, 1H, J = 5.48, 12.33 Hz), 4.77 (m, 1H), 4.89 (m, 1H), 5.06 (m, 1H), 7.64 (s, 1H), 11.20 (s, 1H); uv (H_2O) λ_{max} 270.5 nm (ε 9690). Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.38; H, 6.29; N, 10.83.

4(R)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (14, B = U). 2(R)-(Dimethoxymethyl)-4(S)-*O*-(*p*-toluenesulfonyl)tetrahydrofuran (0.6700 g, 2.120 mmol) was coupled with uracil (0.4640 g, 4.140 mmol) to afford 4(R)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2(R)-(dimethoxymethyl)tetrahydrofuran by procedure H in 20% yield (0.1090 g): ^{1}H Nmr ($CDCl_3$) δ 1.95 (m, 1H), 2.56 (m, 1H), 3.47 (s, 3H), 3.50 (s, 3H), 4.00 (m, 1H), 4.50 (m, 1H), 5.32 (m, 1H), 5.76 (d, 1H, J = 8.07 Hz), 7.68 (dd, 1H, J = 2.22, 8.06 Hz), 10.10 (s, 1H); uv (MeOH) λ_{max} 265 nm. 4(R)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2(R)-(dimethoxymethyl)tetrahydrofuran (0.3460 g, 1.420 mmol) was hydrolyzed to 4(R)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2(R)-tetrahydrofuranal by procedure I which was used in next step without further purification. 4(R)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2(R)-tetrahydrofuranal was converted to 4(R)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol **(14,** B = U) by procedure D in 40% yield: mp 172-174 °C; $[\alpha]_D^{25}$ -56.1° (c 0.57, MeOH); ^{1}H nmr (Me_2SO-d_6) δ 1.89 (dd, 1H, J = 5.63, 13.55 Hz), 2.23 (dd, 1H, J = 8.95, 13.52 Hz), 3.30 (m, 2H), 3.41 (m, 2H), 3.80 (dd, 1H, J = 4.45, 9.68 Hz), 4.06 (dd, 1H, J = 6.70, 9.79 Hz), 4.75 (t, 1H, J = 5.75 Hz), 4.80 (t, 1H, J = 5.75 Hz), 5.05 (m, 1H), 5.58 (d, 1H, J = 8.02 Hz), 7.75 (d, 1H, J = 8.04 Hz), 11.23 (s, 1H); uv (H_2O) λ_{max} 265 nm (ε 9500). Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.59; H, 5.83; N, 11.56. Found: C, 49.52; H, 5.86; N, 11.50.

4(R)-[4-Amino-2-oxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (15). 4(R)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2-hydroxymethyltetrahydro-2-furanmethanol (0.1140 g, 0.4690 mmol) was converted to 4(R)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-di-(*tert*-butyldimethylsilyl)-2-hydroxymethyl-tetrahydro-2-furanmethanol by procedure E in 83% yield: ^{1}H Nmr ($CDCl_3$) δ 0.07 (s, 12H), 0.90 (s, 18H), 2.01 (dd, 1H, J = 4.53, 14.48 Hz), 2.47 (dd, 1H, J = 9.16, 14.16 Hz), 3.46 (s, 2H), 3.52 (d, 2H, J = 1.92 Hz), 3.85 (dd, 1H, J = 3.15, 10.31 Hz), 4.15 (dd, 1H, J = 6.68, 10.33 Hz), 5.01 (m, 1H), 5.79 (d, 1H, J = 8.06 Hz), 7.67 (d, 1H, J = 8.10 Hz), 9.30 (s, 1H). 4(R)-[3,4-Dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-di-(*tert*-butyldimethylsilyl)-2-hydroxymethyltetrahydro-2-furanmethanol was converted to 4(R)-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-di-(*tert*-butyldimethylsilyl)-2-hydroxymethyltetrahydro-2-furanmethanol by procedure F in 80% yield as an oil: ^{1}H Nmr ($CDCl_3$) δ 0.02 (s, 12H), 0.85 (s, 18H), 1.93 (dd, 1H, J = 2.75, 14.02 Hz), 2.41 (dd, 1H, J = 8.99, 14.06 Hz), 3.46 (s, 2H), 3.60 (s, 2H), 3.85 (d, 1H, J = 10.17 Hz), 4.14 (m, 1H), 5.30 (m, 1H), 5.70 (d, 1H, J = 9.34 Hz), 7.23 (s, 2H), 7.67 (d, 1H, J = 9.38 Hz). 4(R)-[4-Amino-2-oxo-1(2*H*)-pyrimidinyl]-di-(*tert*-butyldimethylsilyl)-2-hydroxymethyltetrahydro-2-furanmethanol was converted to 4(R)-[4-amino-2-oxo-1(2*H*)-pyrimidinyl]-2-

hydroxymethyltetrahydro-2-furanmethanol by procedure G in 44% yield: mp 188-190 °C; $[\alpha]_D^{25}$ -85.1° (c 0.069, MeOH); ^{1}H nmr (Me_2SO-d_6) δ 1.82 (dd, 1H, J = 5.94, 13.30 Hz), 2.18 (dd, 1H, J = 8.90, 13.35 Hz), 3.29 (m, 2H), 3.39 (m, 2H), 3.71 (dd, 1H, J = 4.95, 9.44 Hz), 4.00 (dd, 1H, J = 6.72, 9.00 Hz), 4.77 (m, 2H), 5.08 (m, 1H), 5.67 (d, 1H, J = 7.37 Hz), 7.00 (m, 2H), 7.68 (d, 1H, J = 7.38 Hz); uv (H_2O) λ_{max} 273.0 nm (ε 9,600). Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.90; H, 6.26; N, 17.47.

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