Pergamon

Tetrahedron Vol. 50, No. 26, pp. 7747-7764, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00397-1

Novel Isomeric Dideoxynucleosides as Potential Antiviral Agents

Pascal J. Bolon, Todd B. Sells, Zoraida M. Nuesca, David F. Purdy and Vasu Nair*

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

Abstract: Novel isomeric dideoxynucleosides with *S,S* absolute stereochemistry and involving the transposition of the base moiety from the normal 1'- to the 2'-position have been regiospecifically and stereospecifically synthesized. The synthetic approaches involved either direct coupling with inversion at the 2-position of a preformed dideoxygenated sugar using the base moiety as nucleophile (for purine isodideoxynucleosides) or construction of the base moiety onto a stereochemically defined amino sugar precursor (pyrimidine isodideoxynucleosides). These compounds possess extremely high stability with respect to "glycosidic" bond cleavage and enzymatic deamination. Antiviral data suggest that the most active compound was levorotatory *S,S*-isodideoxyadenosine.

The discovery that the human immunodeficiency virus (HIV) requires the multifunctional viral enzyme, reverse transcriptase (RT) for its replication has focused attention on inhibitors of this enzyme.[1] A few deoxygenated analogs of the natural purine and pyrimidine nucleosides are known to be inhibitors, as their triphosphates, of HIV RT.[2] However, dideoxynucleosides of "natural origin", particularly those of the purine family, are inherently unstable with respect to cleavage of the glycosidic bond,[3] because of the absence of the -I effect of the OH groups and the involvement of the proximal ring oxygen in hydrolytic cleavage. The molecular design and synthesis of antiviral nucleosides that are stable, both with respect to glycosidic bond cleavage and enzymatic deamination, would be of significance in this area. While many dideoxynucleoside analogs with the "natural" glycosidic bonding between the base and sugar moieties have been prepared,[4] the synthesis of regioisomeric structures involving the glycosidic bond has received much less attention.[5] We wish to report on the design and synthesis of one family of stereochemically defined, optically active isomeric dideoxynucleosides that involve transposition of the base moiety from the natural 1'- to the 2'-position (using normal nucleoside

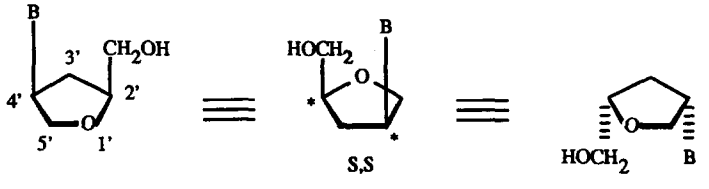
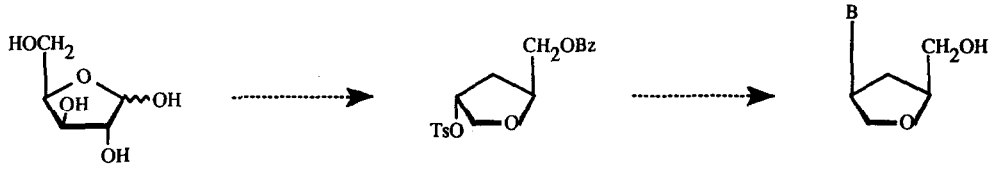


Figure 1

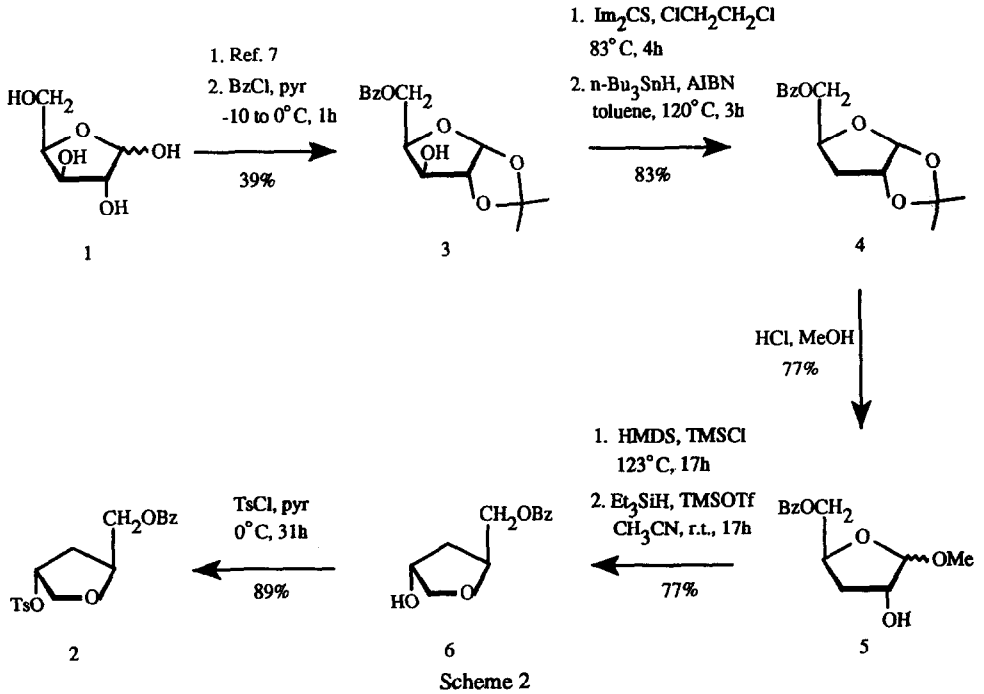
numbering) while maintaining the cis-relationship with the CH_2OH (Figure 1, S,S absolute configuration).[6]

Our strategy for the synthesis of one series of compounds of this class involved utilization of the novel sugar unit **2** (Scheme 1). Condensation of sugar **2** with a range of nucleic acid bases *via* direct displacement of the tosyl group could provide the target isodideoxynucleosides after elaboration and/or



Scheme 1

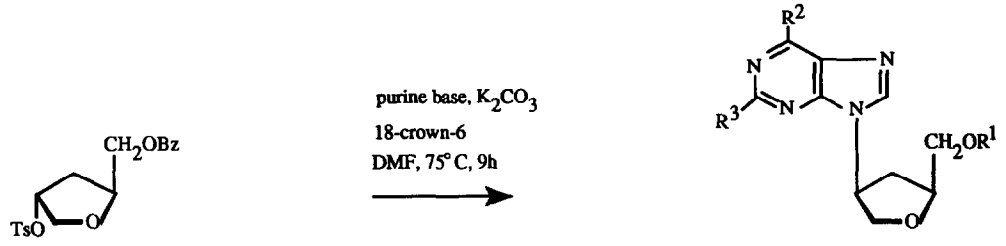
deprotection. The approach for another series of compounds involved construction of the base moiety on a stereochemically defined amino sugar precursor.



Scheme 2

The required carbohydrate moiety **2** was prepared from D-xylose (**1**) in eight steps in 17% overall

yield (Scheme 2). The procedure involved initial formation of the *bis*-isopropylidene derivative of D-xylose **1**, selective deprotection of the six-membered isopropylidene ring,[6] and selective benzoylation of the primary 5-hydroxyl group to provide the ester **3** in 39% overall yield. Compound **3** was deoxygenated at the 3-position by conversion of the 3-hydroxyl group to its imidazole thiocarbonyl ester and subsequent treatment with tributyltin hydride and AIBN in refluxing toluene (83% yield, 2 steps).[7] Acid-catalyzed methanolysis of the remaining acetonide group afforded the α and β-methyl glycosides **5**. Reductive demethoxylation of the latter utilized a methodology which first involved protection of the 2-hydroxyl group by silylation (HMDS, TMSCl) followed *in situ*, by treatment of this product with triethylsilane and TMS-triflate[8] in acetonitrile which produced the tetrahydrofuran **6** in 60% yield for the two steps. Tosylation of compound **6** generated the key carbohydrate intermediate **2**. Condensation of the tosylate **2** with the appropriate heterocyclic base provided the desired products in good yields and with the expected complete inversion of stereochemistry at the 2-position (Scheme 3).



2 7 - 17

	7	8	9	10	11	12	13	14	15	16	17
R^1	Bz	H	Ac	Bz	H	Bz	H	H	H	Bz	H
R^2	NH_2	NH_2	NH_2	Cl	OH	Cl	Cl	OCH_3	OH	NHC_3H_5	NHC_3H_5
R^3	H	H	H	H	H	NH_2	NH_2	NH_2	NH_2	H	H

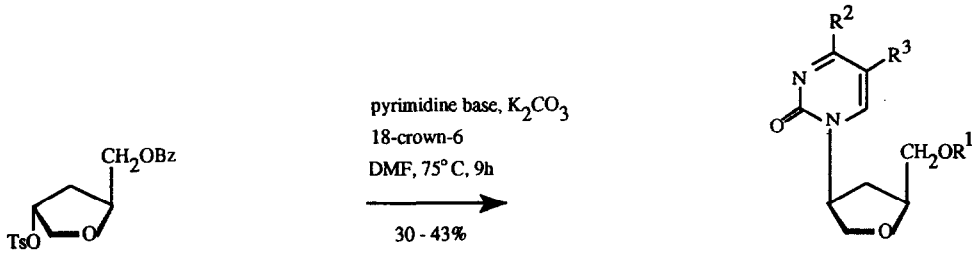
Conversion of 7 to 8: NaOMe, MeOH, r.t., 2h, 85%; **8 to 9:** DMAP, Et_3N, Ac_2O, CH_3CN, r.t., 1h, 75%; **10 to 11:** 1N NaOH, 95°C, 45 min, 69%; **12 to 13:** NH_3, EtOH, 0°C to r.t., 5h, 52%; **12 to 14:** NaOMe, MeOH, r.t., 5h, 69%; **12 to 15:** 1N NaOH, 95°C, 45 min, 69%; **10 to 16:** CPA, Et_3N, EtOH, 110°C, 15h, 87%; **16 to 17:** NaOMe, MeOH, r.t., 2h, 88%.

Scheme 3

For example, 4(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**8**) was synthesized by heating compound **2** and adenine in DMF in the presence of potassium carbonate and 18-crown-6 (64%

purified yield, 86% conversion), followed by deprotection with sodium methoxide. IsoddA (**8**) and the other isodideoxynucleosides prepared were fully characterized by FTIR, UV, NMR, and optical rotation. Conversion of 6-chloropurine and 2-amino-6-chloropurine isonucleosides **10** and **12** into the corresponding isoddI (**11**) and isoddG (**15**) analogs, respectively, was carried out by refluxing **10** and **12** with aqueous NaOH. Additional lipophilic or pro-drug purine isonucleosides of antiviral interest were also synthesized (e.g. **9**, **14**, **17**).

The pyrimidine analogs, isoddU (**19**) and isoddT (**21**) were prepared analogously (Scheme 4) but in lower yields (43% and 30%, respectively in the coupling step) but the desired condensation was also accompanied by bis-alkylated nucleosides as side products.



2 18 - 21

	R^1	R^2	R^3			R^1	R^2	R^3	
18	Bz	OH	H	NH_3, EtOH 0°C to r.t. 59%	20	Bz	OH	CH_3	NaOMe, MeOH r.t. 1h 82%
19	H	OH	H		21	H	OH	CH_3	

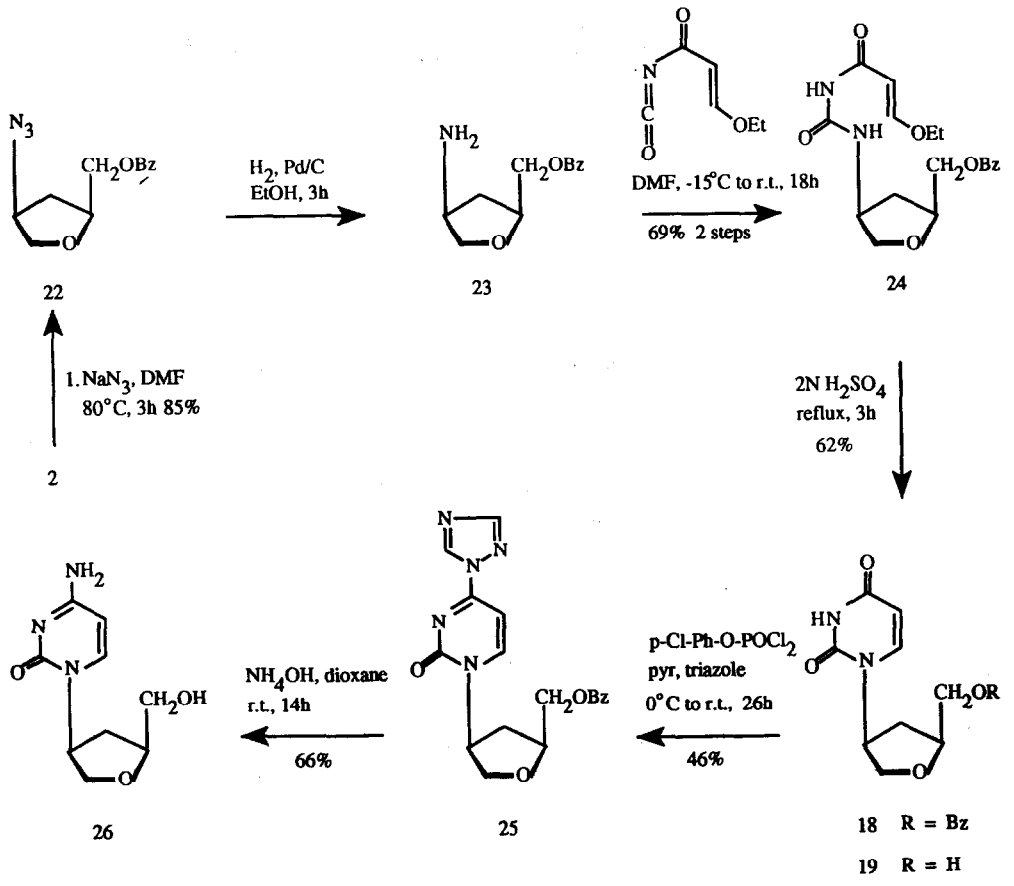
Scheme 4

Total synthesis of isoddU (and isoddT) confirmed unequivocally both the structure and site of glycosylation. For example, the synthesis of isoddU was accomplished *via* the amino sugar intermediate **23** (see Scheme 5). Compound **23** could be prepared easily from the tosylate **2** by heating the latter with sodium azide for three hours and subsequently reducing the resulting azide intermediate to afford the amino sugar **23** in 83% overall yield for the two steps. Synthesis of the uracil ring from **23** was achieved by treatment with 3-ethoxy-2-propenoyl isocyanate[9] to generate the acryloylurea derivative **24** which underwent cyclization and deprotection in refluxing 2N sulfuric acid to produce the desired isodideoxyuridine derivative **19** (43% yield, 2 steps).

An attempt to prepare the dideoxycytidine analog **26** *via* the direct displacement reaction on **2**

with cytosine under previously described conditions was unsuccessful and generated only the O^2-alkylated product **27**. However, isoddC (**26**) could be synthesized from its isoddU counterpart **18** in good yields (see Scheme 5). Thus, treatment of compound **18** with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine produced the 4-triazolylpyrimidinone derivative **25**.[10] Reaction of **25** with aqueous ammonia in dioxane and subsequent deprotection with sodium methoxide afforded the desired product **26**.

Unequivocal differentiation between the N^1- and O^2- alkylated products, **26** and **27**, respectively,



Scheme 5

could not be made from their UV spectra or their ^1H or ^{13}C NMR data. However, application of the selective INEPT NMR technique[11] confirmed the position of attachment of the sugar to the aglycone

(Figure 2). Thus, irradiation of H-4' of isomer **26** (optimized for 3-bond coupling, J = 4 Hz) led to selective enhancements of the C-2, C-6, and C-2' resonances at 155.8, 142.3 and 79.8 ppm, respectively

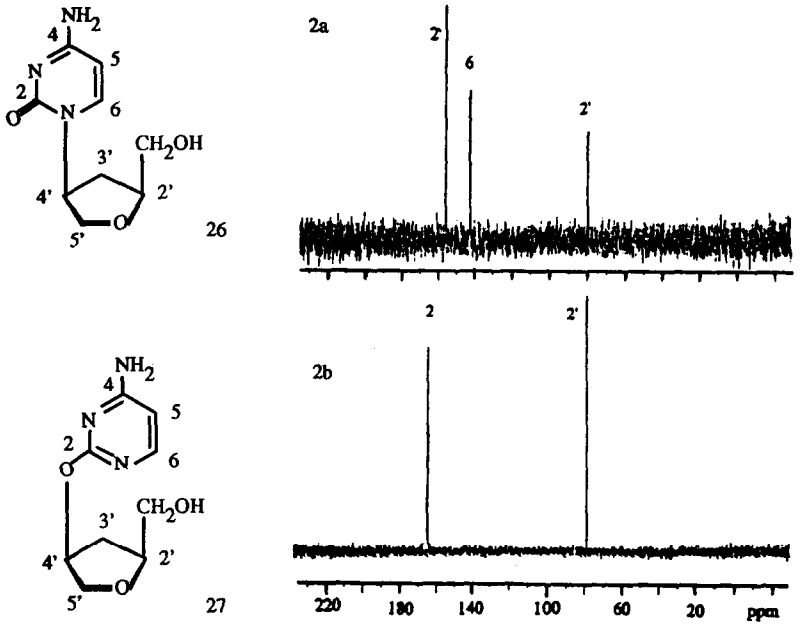


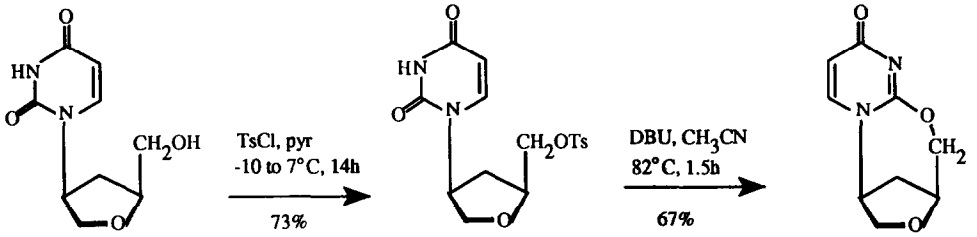
Figure 2. One dimensional J-modulated selective INEPT ^{1}H - ^{13}C NMR correlations that differentiate between structures **26** and **27**. Irradiation at H-4', using J_{CH} = 4 Hz provided the spectra above. Figure 2a, spectrum for **26**; figure 2b, spectrum for **27**. DMSO-d_6 as solvent.

(Figure 2a). Analogous irradiation on isomer **27**, enhanced only the C-2 and C-2' carbons at 156.2 and 79.3 ppm, respectively (Figure 2b). Similarly, in isomer **26**, irradiation of H-6 (spectra not shown), optimized for 3-bond coupling, enhanced C-4 (165.3 ppm), C-2 (155.8 ppm) and C-4' (55.0 ppm), whereas in isomer **27**, irradiation of H-6 enhanced only the signals corresponding to C-2 and C-4 (164.4 and 165.5 ppm, respectively).

Chemical support for the cis-stereochemical relationship between the heterocyclic base and the CH_2OH of the isonucleosides synthesized, was provided by the successful preparation of the corresponding cyclonucleosides. For example, facile conversion of isoddU (**19**) to its tosylate derivative **28** under conventional tosylation conditions and subsequent treatment of **28** with DBU in acetonitrile afforded the O^2,6'-anhydroisonucleoside **29** in 50% overall yield (Scheme 6).

In the case of isoddA (**8**), a single-crystal X-ray diffraction analysis gave structural confirmation

and supportive evidence for the structural assignments of this and other isonucleosides synthesized, as well as conformational data (Figure 3). The orientation of the adenine base relative to the sugar ring is *anti*, with a glycosyl torsion angle of -46.8° [C(3')-C(4')-N(9)-C(8)], and the sugar pucker is C-5'-exo / O-1'-endo.[12] The glycosyl bond length, 1.472Å, is about the same to that found in dideoxyadenosine



19 28 29

Scheme 6

(1.467Å), but its base-CH_2OH (N9-C6') distance is 0.36 Å wider than that found in dideoxyadenosine.[13] Because the absolute configuration of the carbon bearing the CH_2OH in the starting compound was known, and did not change during synthesis, the absolute configuration of the entire molecule was established by the X-ray data.

The hydrolytic stabilities of the dideoxynucleosides were also studied. These studies were monitored by differential UV spectroscopy[14] or by HPLC. For example, in the case of (-)-isodideoxyadenosine (**8**), no detectable hydrolysis was observed even at pH 1 for 36h. However, at pH 3, 2',3'-dideoxyadenosine is completely hydrolyzed in less than 3h. Compound **8** was also resistant to deamination by mammalian adenosine deaminase and was only deaminated with very large excesses of the enzyme (V_{max} at 5.8 x 10^{-5} µmol /unit /min with 39 units of enzyme compared to adenosine at 1 µmol /unit /min with 0.009 units/mL of enzyme). (-)-Isodideoxyadenosine (**8**) was a moderate to weak competitive inhibitor of this enzyme with a K_i of 8.2 x 10^{-5} M. The most biologically active compound in this series was also **8** which exhibited anti-HIV activity in the low micromolar range in MT-4 cells.

In summary, optically active isomeric dideoxynucleosides with S,S absolute stereochemistry, where the base is transposed from the normal 1'- to the 2'-position, have been regiospecifically and stereospecifically synthesized and their structure and stereochemistry were established by chemical and physical methods including single crystal X-ray data. These isomeric dideoxynucleosides are extremely stable with respect to glycosidic bond hydrolysis in both acid and base. Stability with respect to enzymatic deamination was also found. Preliminary biological data suggest that there is significant antiviral potential with this family of compounds.

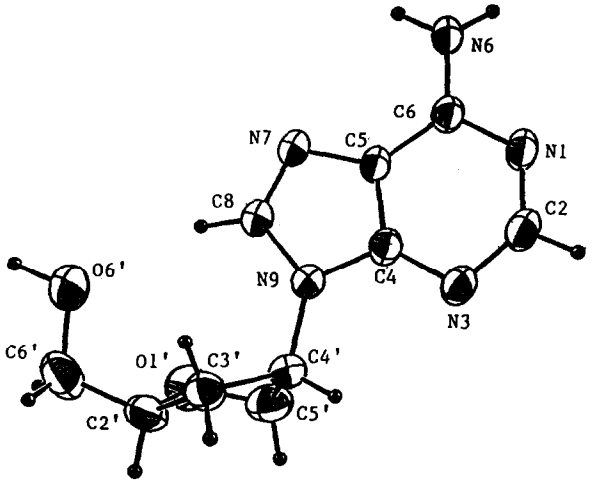


Figure 3. ORTEP plot showing the structure, configuration and conformation of (-)-isodideoxyadenosine. Phase angle P = 106.7°, using conventional calculation methods for natural nucleosides; V_{max} = 44.2°, C6'-N9 = 4.25Å, glycosyl torsion (C3'-C4'-N9-C8) = -46.8°.

EXPERIMENTAL

Melting points reported are uncorrected and were determined on a Thomas Hoover apparatus fitted with a microscope. NMR spectra were recorded on Bruker Models AMX-600 and AC-300 pulse Fourier transform spectrometers. Mass spectra were determined on a VG TRIO GC/MS system. Ultraviolet spectra were recorded on a Varian Cary 3 or a Gilford Response spectrophotometer. IR spectra were recorded on a Mattson Cygnus 25 Fourier transform instrument. Lyophilizations were performed with a Virtis freezemobile 3 unit. Preparative layer chromatography was carried out on plates prepared with E. Merck PF_{254} silica gel. Flash chromatography was carried out using glass columns packed with 230-400 mesh silica gel. HPLC separations were done using a Waters automated 600E system with photodiode array detector and FOXY fraction collector using Delta-Pak C_{18} and Hamilton PRP-1 columns. Elemental analyses were performed at Galbraith Laboratories, Inc., Knoxville, TN.

GENERAL SYNTHETIC PROCEDURES

Procedure A: Glycosylation: A mixture of purine or pyrimidine base (1.96 mmol), potassium carbonate (2.62 mmol), 18-crown-6 (2.62 mmol), and 2(S)-(O-benzoylmethyl)-4(R)-(*p*-O-toluenesulfonyl)tetrahydrofuran (1.31 mmol) (2) in DMF (11 mL) was stirred at 75°C for 11h. The solvent was

removed under reduced pressure and the residue was purified by flash chromatography on silica gel with 0-10% MeOH/$CHCl_3$.

Procedure B: Debenzoylation by Ammonia: A solution of the 6'-O-benzoylated isodideoxynucleoside (0.44 mmol) in methanol (10 mL) was cooled down to 0°C and saturated with ammonia. The reaction mixture was allowed to stand at 0°C for 2h and then at room temperature for 46h. Excess ammonia was purged out with nitrogen and then the solvent was removed under reduced pressure. The residue was purified by preparative TLC with 10% MeOH/$CHCl_3$.

Procedure C: Debenzoylation by Sodium methoxide: To a solution of the 6'-O-benzoylated isonucleoside (0.31 mmol) in methanol (15 mL), was added sodium methoxide (0.46 mmol). After stirring for 2h at room temperature, the reaction mixture was neutralized by stirring with DOWEX ion exchange resins (H^+ form). The resin was filtered and the filtrate was then concentrated under reduced pressure. The residue was purified on silica gel plates with 10% MeOH/$CHCl_3$.

5-O-Benzoyl-1,2-O-isopropylidene-α-D-xylofuranose (3): D-Xylose was converted to 1,2-O-isopropylidene-α-D-xylofuranose in two steps (58-80% overall yield). A solution of 1,2-O-isopropylidene-α-D-xylofuranose (15.95 g, 83.86 mmol) in anhydrous pyridine (54 mL) was cooled down to -20°C. At this temperature, a solution of benzoyl chloride (9.73 mL, 83.86 mmol) in 20 mL of pyridine was added dropwise into the sugar solution over a period of 30 min. The reaction was continously stirred for an additional 30 min while allowing the mixture to warm to 0°C and then was poured into 200 mL of ice-water mixture. The mixture was extracted with $CHCl_3$ (4 x 75 mL). The organic extracts were combined, washed, dried with Na_2SO_4, filtered, evaporated, and coevaporated with several small portions of toluene. The residue was purified by column chromatography with 0-5% MeOH/$CHCl_3$ as the eluting solvent to yield 18.75 g (63.71 mmol, 76%) of **3** as a clear light yellow viscous oil.[7] ^1H NMR ($CDCl_3$): δ 1.28 (s, 3H), 1.47 (s, 3H), 3.69 (s, 1H), 4.21 (m, 1H), 4.39 (m, 1H), 4.44 (m, 1H), 4.69 (m, 2H), 5.94 (d, 1H), 7.46 (t, 3H), 8.01 (d, 2H).

2(S)-(O-Benzoylmethyl)tetrahydrofuran-4(R)-ol (6):

5-O-Benzoyl-3-deoxy-1,2-isopropylidene-α -D-xylofuranose (4): A solution of **3** (7.08 g, 24.06 mmol) and 1,1'-thiocarbonyldiimidazole (6.43 g, 36.08 mmol) in dry dichloroethane (75 mL) was stirred at reflux for 4h. The solvent was evaporated and the residue was purified by flash chromatography using 0-10% MeOH/$CHCl_3$ to provide 8.88 g (21.96 mmol, 91%) of 5-O-benzoyl-3-O-(1-imidazolylthiocarbonyl)-1,2-O-isopropylidene-α-D-xylofuranose as a clear, light yellow viscous oil. To a refluxing solution of the latter compound in toluene (175 mL), a nitrogen-purged solution of Bu_3SnH (8.86 mL, 32.93 mmol) and 2,2'-azobis(2-methylpropionitrile) (2.8 g, 17.56 mmol) in toluene (100 mL) was added dropwise over a period of 45 min. The reaction mixture was stirred at reflux for 2h. The solvent was

then evaporated under reduced pressure. The residue was partitioned between CH_3CN (225 mL) and hexanes (150 mL). The CH_3CN portion was washed several times with hexanes (4 x 50 mL). Evaporation of the acetonitrile portion gave an oily residue which was purified by flash chromatography using hexanes followed by $CHCl_3$ to afford 5.56 g (19.98 mmol, 91%) of **4** as a viscous oil. ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.51 (s, 3H), 1.74 (m, 1H), 2.16 (dd, 1H), 4.53 (m, 4H), 5.84 (d, 1H), 7.47 (t, 3H), 8.03 (d, 2 H).

Methyl 5-O-benzoyl-3-deoxy-α -D-erythro-pentofuranose and Methyl 5-O-benzoyl-3-deoxy-β -D-erythro-pentofuranose (5): Hydrogen chloride (0.004 g, 0.1 mmol) was bubbled through a solution of the benzoylated sugar **4** (0.577 g, 2.07 mmol) in MeOH (10 mL). The reaction mixture was stirred at room temperature for 12h and was then neutralized by stirring with DOWEX (OH^- form) ion-exchange resin. The resin was filtered and the filtrate concentrated. Purification of the residue by flash chromatography using 5% MeOH/$CHCl_3$ as eluting solvent afforded 0.402 g (1.59 mmol, 77%) of **5** as a viscous, clear, light yellow oil: ^1H NMR ($CDCl_3$): δ 2.07 (m, 2H), 3.3 (s, 3H), 3.68 (s, 1H), 4.28 (m, 2H), 4.44 (dd, 1H), 4.72 (m, 1H), 4.87 (s, 1H), 7.42 (t, 2H), (t, 1H), 8.08 (d, 2H).

2(S)-(O-Benzoylmethyl)tetrahydrofuran-4(R)-ol (6): A mixture of sugar **5** (5.03 g, 19.9 mmol) and chlorotrimethylsilane (1.26 mL, 9.97 mmol) in 1,1,1,3,3,3-hexamethyldisilazane (63 mL, 299 mmol) was refluxed for 17h. Unreacted HMDS was evaporated under reduced pressure to afford a clear, yellow viscous oil. Dry CH_3CN (25 mL) was added to this residue followed by the addition of triethylsilane (9.55 mL, 59.8 mmol) and TMS-triflate (11.6 mL, 59.8 mmol). The reaction mixture was stirred at room temperature for 17h. Excess TMS-triflate in the reaction was quenched by stirring the mixture with 8 mL of H_2O. Reaction mixture was neutralized by dropwise addition of 5N NaOH while stirring the mixture vigorously. The solvent was removed under reduced pressure. The residue was purified by flash chromatography using 8% MeOH/$CHCl_3$ as eluting solvent to give 3.44 g (15.47 mmol, 77.6%) of **6** as a clear, viscous, light yellow oil. ^1H NMR ($CDCl_3$): δ 1.83 (m, 1H), 2.01 (m, 1H), 3.1 (s, 1H), 3.76 (d, 1H), 3.94 (dd, 1H), 4.23 (dd, 1H), 4.38 (dd, 1H), 4.48 (m, 2H), 7.37 (t, 2H), 7.49 (t, 1H), 7.98 (d, 2H). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.62; H, 6.15.

2(S)-(O-Benzoylmethyl)-4(R)-(*p*-O-toluenesulfonyl)tetrahydrofuran (2). A solution of the benzoylated sugar **6** (3.44 g, 15.4 mmol) in dry pyridine (20 mL) was cooled down to -10°C for 1h. At this temperature, tosyl chloride (4.43 g, 23 mmol) was added to the sugar solution. The reaction mixture was allowed to stand at 5°C for 31h. The solvent was evaporated under reduced pressure. The residue was taken up in dichloromethane then washed with H_2O (3 x 20 mL). The organic portion was dried with Na_2SO_4, filtered and concentrated. Purification of the residue by flash chromatography using 3% MeOH/$CHCl_3$ as eluting solvent afforded 5.15 g (13.7 mmol, 89%) of **2** as a clear, light yellow viscous oil: ^1H NMR ($CDCl_3$): δ 1.97 (m, 1H), 2.25 (m, 1H), 2.45 (s, 3H), 3.98 (m, 2H), 4.29 (m, 1H), 4.42 (m, 2H), 5.17 (m, 1H), 7.45 (m, 5H), 7.80 (d, 2H), 8.01 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 21.6, 35.2, 65.6, 72.8, 75.9, 81.3, 127.6, 128.3, 129.5, 129.6, 129.9, 133.1, 133.6, 145.1, 166.2. Anal. Calcd for

$C_{19}H_{20}O_6S$: C, 60.62; H, 5.36. Found: C, 60.54; H, 5.43.

4(S)-(6-Amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (8):

4(S)-(6-Amino-9H-purin-9-yl)-2(S)-(O-benzoylmethyl)tetrahydrofuran (**7**): Adenine was coupled with the tosylate **2** using procedure A to afford **7** as a white solid in 64% yield. Melting point 193-195° C. UV (MeOH) λ_{max} 260 nm. ^{1}H NMR ($CDCl_3$): δ 2.17 (m, 1H), 2.79 (m, 1H), 4.12(dd, 1H), 4.29 (dd, 1H), 4.45 (m, 2H), 4.59 (dd, 1H), 5.32 (m, 1H), 6.00 (s, 2H), 7.40 (t, 2H), 7.53 (t, 1H), 7.98 (d, 1H), 8.02 (s, 1H), 8.31 (s, 1H).

4(S)-(6-Amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**8**): Compound **7** was deprotected with procedure C. Final purification of the product was done by reversed-phase HPLC on Amberlite XAD-4 resin using 10% EtOH/H_2O as the eluting solvent to give the title compound as a white solid (85% yield). Melting point 180-182°C. Mass spectrum, m/z 235 (M^+). $[\alpha]_D$ -26.6 (c = 1.0 in MeOH). UV (H_2O) λ_{max} 260 nm (ε 13788). ^{1}H NMR (Me_2SO-d_6): δ 2.09 (m, 1H), 2.58 (m, 1H), 3.55 (m, 2H), 3.99 (m, 3H), 4.95 (m, 1H), 5.17 (m, 1H), 7.25 (s, 2H), 8.15 (s, 1H), 8.26 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 33.9, 53.9, 62.4, 71.8, 79.6, 118.7, 138.9, 149.3, 152.3, 155.9. Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.40; H, 5.56; N, 29.66.

2(S)-(O-Acetylmethyl)-4-(S)-(6-amino-9H-purin-9-yl)tetrahydrofuran (9): To a suspension of 4-(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**8**) (0.029 g, 0.12 mmol) and 4-dimethylaminopyridine (0.001 g, 0.008 mmol) in anhydrous CH_3CN (2.5 mL), triethylamine (0.03 mL, 0.21 mmol) and acetic anhydride (0.014 mL, 0.15 mmol) were added. The reaction mixture was stirred at room temperature for 23 minutes. Excess acetic anhydride was quenched by addition of MeOH (0.5 mL). The solvent was removed under reduced pressure. The residue was purified on a silica gel plate with 5% MeOH/$CHCl_3$ as developing solvent. The band at R_f 0.55 afforded 0.026 g (0.09 mmol, 75%) of **9** as a white solid. Melting point 158-160°C. Mass spectrum, m/z 277 (M^+). UV (MeOH) λ_{max} 260 nm (ε 10668). ^{1}H NMR (Me_2SO-d_6): δ 1.99 (s, 3H), 2.09 (m, 1H), 2.61 (m, 1H), 4.11 (m, 5H), 5.16 (m, 1H), 7.23 (s, 2H), 8.13 (s, 1H), 8.18 (s, 1H).

4(S)-(1,6-Dihydro-6-oxo-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (11):

2(S)-(O-Benzoylmethyl)-4(S)-(6-chloro-9H-purin-9-yl)tetrahydrofuran (**10**): The tosylate **2** and 6-chloropurine were coupled using procedure A to provide the protected nucleoside **10** as a white solid in 36% yield. Melting point 125-127°C; UV (MeOH) λ_{max} 264 nm; ^{1}H NMR ($CDCl_3$): δ 2.22 (m, 1H), 2.83 (m, 1H), 4.16 (dd, 1H), 4.35 (dd, 1H), 4.48 (m, 2H), 4.62 (dd, 1H), 5.39 (m, 1H), 7.42 (t, 2H), 7.56 (t, 1H), 7.96 (d, 2H), 8.35 (s, 1H), 8.70 (s,1H).

4(S)-(1,6-Dihydro-6-oxo-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**11**): A suspension of the protected compound **10** (0.085 g, 0.24 mmol) in 1N NaOH (15 mL) was stirred at 95°C for 1h and then was neutralized with 1N acetic acid. The solvent was removed under reduced pressure. Purification of

the residue by reversed-phase HPLC on Amberlite XAD-4 resin using 8% EtOH/H_2O as eluting solvent afforded 0.021 g (0.09 mmol, 38%) of the title compound as a white solid. Melting point 205-208°C. Mass spectrum, m/z 236 (M^+). $[\alpha]_D$ -27.0 (c = 1.0 in MeOH). UV (H_2O) λ_{max} 249 nm (ε 10027). ^1H NMR (Me_2SO-d_6): δ 2.05 (m, 1H), 2.50 (m, 1H), 3.58 (dd, 2H), 3.97 (m, 3H), 4.94 (m, 1H), 5.15 (m, 1H), 8.02 (s, 1H), 8.16 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 34.1, 54.2, 62.4, 71.9, 79.6, 123.9, 137.6, 148.2, 150.5, 157.8. Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 29.77.
Found: C, 50.32, H, 5.08, N, 23.39.

4(S)-(6-Cyclopropylamino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (17):

2(S)-(O-Benzoylmethyl)-4(S)-(6-cyclopropylamino-9H-purin-9-yl)tetrahydrofuran (**16**): To a solution of the 6'-benzoylated nucleoside **10** (0.110 g, 0.31 mmol) in absolute EtOH (8 mL) was added triethylamine (0.13 mL, 0.92 mmol) and cyclopropylamine (0.11 mL, 1.53 mmol). The resulting mixture was stirred at 110°C for 15h. All volatiles were removed under reduced pressure, and the residue was purified by preparative TLC with 5% MeOH/$CHCl_3$. The band at R_f 0.4 afforded 0.101 g (0.27 mmol, 87%) of the title compound as a light yellow viscous oil. UV (MeOH) λ_{max} 269 nm. ^1H NMR ($CDCl_3$): δ 0.56 (m, 2H), 0.83 (q, 2H), 2.12 (m, 1H), 2.25 (m, 1H), 2.72 (m, 1H), 4.06 (dd, 1H), 4.23 (dd, 1H), 4.37 (m, 2H), 4.51 (dd, 1H), 5.23 (m, 1H), 6.46 (br s, 1H), 7.32 (t, 2H), 7.45 (t, 1H), 7.92 (m, 3H), 8.37 (s, 1H).

4(S)-(6-Cyclopropylamino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**17**): Compound **16** (0.095 g, 0.25 mmol) was debenzoylated using procedure C to afford 0.060 g (0.22 mmol, 88%) of the title compound as a hygroscopic white solid. Mass spectrum, m/z 275 (M^+). UV (MeOH) λ_{max} 269 nm (ε 16813). ^1H NMR ($CDCl_3$): δ 0.64 (m, 2H), 0.89 (m, 2H), 1.24 (m, 1H), 2.33 (m, 1H), 2.64 (m, 1H), 3.05 (t, 1H), 3.72 (m, 1H), 4.01 (m, 1H), 4.07 (dd, 1H), 4.16 (m, 1H), 5.25 (m, 1H), 5.94 (br s, 1H), 7.99 (s, 1H), 8.45 (s, 1H). Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.22; N, 25.44. Found: C, 56.46; H, 6.24; N, 25.70.

4(S)-(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (15):

4(S)-(2-Amino-6-chloro-9H-purin-9-yl)-2(S)-(O-benzoylmethyl)tetrahydrofuran (**12**): The tosylate **2** was condensed using procedure A with 2-amino-6-chloropurine to give **12** as a colorless viscous oil in 54% yield. UV (MeOH) λ_{max} 247, 309 nm. ^{1}NMR ($CDCl_3$): δ 2.08 (m, 1H), 2.65 (m, 1H), 4.01 (dd, 1H), 4.18 (dd, 1H), 4.31 (m, 1H), 4.46 (m, 2H), 5.04 (m, 1H), 5.60 (s, 2H), 7.30 (t, 2H), 7.43 (t, 2H), 7.86 (m, 3H).

4(S)-(2-Amino-6-chloro-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**13**): Nucleoside **12** was debenzoylated using procedure B. The band at R_f 0.2 afforded compound **13** as a white solid in 52% yield. Melting point 194-196°C. Mass spectrum, m/z 269 (M^+). UV (MeOH) λ_{max} 247 (ε 5596), 309 nm (ε 6313). ^1H NMR (Me_2SO-d_6): δ 2.04 (m, 1H), 2.5 (m, 1H), 3.59 (m, 2H), 3.99 (m, 3H),4.94 (m, 1H), 5.02 (m, 1H), 6.91 (s, 2H), 8.25 (s, 1H). Anal. Calcd for $C_{10}H_{21}ClN_5O_2$: C, 44.54; H, 4.48, N,

25.97. Found: C, 44.24; H, 4.24, N, 25.56.

4(S)-(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**15**): A solution of the 6'-deprotected nucleoside **12** (0.043 g, 0.16 mmol) in 1N NaOH (11 mL) was stirred at 95°C for 45 min. The reaction mixture was then neutralized with 1N acetic acid. Removal of the solvent under reduced pressure and purification of the residue by reversed-phase HPLC on Amberlite XAD-4 using 4% EtOH/H_2O as eluting solvent afforded 0.0289 g (0.11 mmol, 69%) of **15** as a white solid. Melting point 261-263°C. Mass spectrum, m/z 251 (M^+). $[\alpha]_D$ -27.0 (c = 1.0 in MeOH). UV (H_2O) λ_{max} 252 nm (ε 11583), 271 nm (ε 8320). ^1H NMR (Me_2SO-d_6): δ 1.97 (m, 1H), 2.50 (m, 1H), 3.52 (m, 2H), 3.91 (m, 3H), 4.91 (m, 2H), 6.45 (s, 2H), 7.81 (s, 1H), 10.60 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 34.0, 53.4, 62.5, 72.0, 79.6, 116.4, 135.2, 150.9, 153.5, 156.9. Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.21; N, 27.87. Found: C, 47.42; H, 5.03; N, 27.38.

4(S)-(2-Amino-6-methoxy-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (14): A solution of compound **12** (0.205 g, 0.548 mmol) and NaOMe (0.098 g, 1.81 mmol) in methanol (8 mL), was stirred at room temperature for 5h. The reaction mixture was then neutralized by stirring the mixture with NH_4Cl. The solvent was removed under reduced pressure and the residue was purified on a silica gel plate with 8% MeOH/$CHCl_3$. The band at R_f 0.4 afforded 0.100 g (0.38 mmol, 69%) of the title compound as a white solid. Mass spectrum, m/z 265 (M^+). UV (MeOH) λ_{max} 247 (ε 5596), 309 nm (ε 6313). ^1H NMR (Me_2SO-d_6): δ 2.04 (m, 1H), 2.55 (m, 1H), 3.54 (m, 2H), 3.94 (m, 6H), 4.92 (m, 1H), 5.01 (m, 1H), 6.41 (br s, 2H), 7.99 (s, 1H). Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.19; H, 5.78; N, 26.63.

4(S)-[3,4-Dihydro-2,4-dioxo-5-methyl-1 (2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (21):

2-(S)-(O-Benzoylmethyl)-4(S)-[3,4-dihydro-2,4-dioxo-5-methyl-1(2H)-pyrimidinyl]tetrahydrofuran (**20**): Thymine was condensed with 2(S)-(O-benzoylmethyl)-4(R)-(*p*-O-toluenesulfonyl)tetrahydrofuran (**2**) using procedure A to give the 6'-benzoate of the title compound in 30% yield: UV (MeOH) λ_{max} 271 nm. ^1H NMR (Me_2SO-d_6): δ 1.63 (s, 3H), 1.84 (m, 1H), 2.5 (m, 1H), 3.84 (dd, 1H), 3.97 (dd, 1H), 4.21 (m, 1H), 4.40 (m, 1H), 4.55 (dd, 1H), 5.13 (m, 1H), 7.41 (s, 1H), 7.52 (t, 2H), 7.67 (t, 1H), 7.95 (d, 2H), 11.27 (s, 1 H).

4(S)-[3,4-Dihydro-2,4-dioxo-5-methyl-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (**21**): The protected nucleoside **20** was debenzoylated with procedure C to afford the title compound as a very hygroscopic white solid in 82% yield. Mass spectrum, m/z 226 (M^+). $[\alpha]_D$ +26.0 (c = 1.0 in MeOH). UV (H_2O) λ_{max} 271 nm (ε 9554). FTIR (KBr): 1670 cm^{-1}. ^1H NMR (Me_2SO-d_6): δ 1.76 (m, 4H), 2.35 (m, 1H), 3.48 (m, 1H), 3.65 (m, 1H), 3.80 (m, 3H), 4.95 (t, 1H), 5.10 (m, 1H), 7.61 (s, 1H), 11.21 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 12.3, 35.0, 54.2, 61.8, 71.6, 79.8, 109.3, 137.8, 151.0, 163.9. Anal Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.85; H, 6.48; N, 12.21.

4(S)-[3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (19):

Preparation via direct displacement: 2(S)-(O-Benzoylmethyl)-4(S)-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahdrofuran (**18**): The tosylate **2** was condensed using procedure A with uracil to provide **18** as a white solid in 43% yield. Melting point 154-156°C. UV (MeOH) λ_{max} 266. UV (0.1N NaOH) λ_{max} 265 nm. ^{1}H NMR (Me_2SO-d_6): δ 1.81 (m, 1H), 2.5 (m, 1H), 3.92 (m, 2H), 4.20 (m, 2H), 4.45 (m, 2H), 5.10 (m, 1H), 5.51 (d, 1H), 7.61 (m, 4H), 7.96 (d, 2H).

4(S)-[3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (**19**): Nucleoside **18** was debenzoylated with procedure B to afford **19** as a very hygroscopic white solid in 59% yield. Mass spectrum, m/z 212 (M^+). $[\alpha]_D$ +31.0 (c = 1.0 in MeOH). UV (H_2O) λ_{max} 266 nm (ε 8786). FTIR (KBr): 1682 cm^{-1}. ^{1}H NMR (Me_2SO-d_6): δ 1.73 (m, 1H), 2.42 (m, 1H), 3.52 (dd, 2H), 3.81 (m, 3H), 4.91 (m, 1H), 5.09 (m, 1H), 5.58 (d, 1H), 7.72 (d, 1H), 11.23 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 33.4, 54.6, 61.8, 71.6, 79.7, 101.7, 141.9, 150.9, 163.1. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.77; H, 5.52; N, 12.97.

Total Synthesis of 4(S)-[3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (19):

4(S)-Azido-2(S)-(O-benzoylmethyl)tetrahydrofuran (**22**): A mixture of the tosylate **2** (1.97 g, 5.23 mmol) and sodium azide (0.41 g, 6.27 mmol) in wet DMF (5 mL) was stirred at 80°C for 3h. The reaction mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic portion was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by preparative TLC using $CHCl_3$ as the eluting solvent to give the title compound (4.44 mmol, 85%) as a viscous oil. FTIR (KBr): 2955, 2253, 2105, 1719 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 1H), 2.42 (m, 1H), 3.95 (m, 1H), 3.98 (m, 1H), 4.20 (m, 1H), 4.40 (m, 3H), 7.50 (dt, 3H), 8.08 (d, 2H).

N-[[[(2S,4S)-2-(O-Benzoylmethyl)tetrahydrofuranyl]amino]carbonyl]-3-ethoxy-2-propenamide (**24**): A suspension of compound **22** (0.182 g, 0.736 mmol) and 0.052 g of 5% Pd/C in absolute EtOH (15 mL) was shaken under 40 psi of H_2 for 3h. The reaction mixture was filtered and the filtrate evaporated. The residue was used for the next step without purification. To a solution of the crude amino sugar (0.207 g, 1.472 mmol) in dry DMF (5 mL), 3-ethoxy-2-propenoyl isocyanate[9] (0.163 g, 0.736 mmol) was added dropwise at -15°C. The temperature was not allowed to exceed -10°C during the addition. After the addition, the reaction mixture was slowly warmed to room temperature and was stirred for an additional 18h. The mixture was filtered and the filtrate was evaporated under reduced pressure. Ethanol was added to the residue and then evaporated. Purification of the residue by preparative TLC on silica gel with 5% MeOH/$CHCl_3$ afforded compound **24** in 69% yield. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3 H), 1.77 (m, 1 H), 2.53 (m, 1 H), 3.86 (m, 1H), 3.98 (m, 1 H), 4.34 (m, 1H), 4.50 (m, 2H), 5.30 (d, 1H), 7.50 (dt, 3H), 7.79 (d, 1H), 8.09 (d, 2H), 9.12 (br s, 1H).

4(S)-[3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (**19**): Compound

24 (0.182 g, 0.502 mmol) was refluxed in 2N H_2SO_4 (10 mL) for 3h. The reaction mixture was then neutralized with 2N NaOH. The solvent was evaporated under reduced pressure and the residue was purified on a silica gel plate with 9% MeOH/$CHCl_3$ to provide 0.100 g of the deprotected nucleoside **19** (0.31 mmol, 62%) as a white solid. The physical data obtained for this product was identical to the data collected for the directly coupled product.

4(S)-[4-Amino-2-oxo-1 (2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (26):

2(S)-(O-Benzoylmethyl)-4(S)-[4-(1,2,4-triazolyl)-2-oxo-1(2H)-pyrimidinyl]tetrahydrofuran (**25**): To a stirred solution of the nucleoside **18** 0.187 g, 0.59 mmol) in pyridine (7 mL), 4-chlorophenylphosphorodichloridate (0.2 mL, 1.2 mmol) was added dropwise at 0°C. After the addition, 1,2,4-triazole (0.163 g, 2.36 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 26h. The solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 then washed with H_2O (3 x 25 mL). The organic portion was dried with Na_2SO_4, filtered, concentrated and purified on a silica gel plate with 6% MeOH/$CHCl_3$ to afford 0.101 g (0.27 mmol, 46%) of **25** as a viscous yellow oil. UV (MeOH) λ_{max} 252, 316 nm. ^1H NMR ($CDCl_3$): δ 1.93 (m, 1H), 2.81 (m, 1H), 3.96 (dd, 1H), 4.15 (d, 1H), 4.30 (m, 1H), 4.40 (dd, 1H), 4.68 (dd, 1H), 5.46 (m, 1H), 6.78 (d, 1H), 7.33 (t, 2H), 7.45 (t, 1H), 7.90 (d, 2H), 8.05 (s, 1H), 8.18 (d, 1H), 9.17 (s, 1H).

4(S)-[4-Amino-2-oxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (**26**): A solution of nucleoside **25** (0.098 g, 0.27 mmol) in 1:6 (v/v) of NH_4OH/dioxane (4 mL) was stirred at room temperature for 14h. The solvent was removed under reduced pressure and the residue was purified on a silica gel plate with 8% MeOH/$CHCl_3$ to afford 0.056 g (0.18 mmol, 66%) of 4(S)-[4-amino-2-oxo-1(2H)-pyrimidinyl]-2(S)-(O-benzoylmethyl)tetrahydrofuran as a colorless viscous oil. This nucleoside was deprotected with procedure C to afford 0.014 g (0.07 mmol, 39%) of the title compound as a white hygroscopic solid. Mass spectrum, m/z 211 (M^+). $[\alpha]_D$ +87.0 (c = 1.0 in MeOH). UV (H_2O) λ_{max} 274 nm (ε 9040). FTIR (KBr): 1652 cm^{-1}. ^1H NMR (Me_2SO-d_6): δ 1.67 (m, 1H), 2.38 (m, 1H), 3.50 (dd, 2H), 3.81 (m, 3H), 4.85 (m, 1H), 5.14 (m, 1H), 5.68 (d, 1H), 7.02 (s, 2H), 7.68 (d, 1H). ^{13}C NMR (Me_2SO-d_6): δ 33.9, 55.0, 62.3, 71.9, 79.7, 94.0, 142.3, 155.7, 165.3. Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 50.71; H, 5.79; N, 19.40.

O^2,6'-Anhydro-4(S)-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (29):

4(S)-[3,4-Dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2(S)-(p-O-toluenesulfonylmethyl)tetrahydrofuran (**28**): A solution of the nucleoside **19** (0.025 g, 0.117 mmol) in dry pyridine (3 mL) was cooled down to -10°C. At this temperature, tosyl chloride (0.029 g, 0.15 mmol) was added to the nucleoside solution. The reaction mixture was allowed to stand at 7°C for 14h. Ice-water (0.5 mL) was added with stirring into the reaction mixture. The solvent was removed under reduced pressure. The residue was purified on a silica gel plate using 5% MeOH/$CHCl_3$ as the eluting solvent. The band at R_f 0.4

afforded 0.023 g (0.063 mmol, 72.5%) of **28** as a colorless viscous oil. UV (MeOH) λ_{max} 262 nm. ^1H NMR ($CDCl_3$): δ 1.76 (m, 1H), 2.42 (s, 3H), 2.55 (m, 1H), 3.88 (m, 2H), 4.11 (m, 2H), 4.30 (m, 1H), 5.28 (m, 1H), 5.61 (d, 1H), 7.32 (d, 2H), 7.39 (d, 1H), 7.74 (d, 2H).

O^2,6'-Anhydro-4(S)-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]tetrahydro-2(S)-furanmethanol (**29**): To a solution of the nucleoside **28** (0.02 g, 0.054 mmol) in acetonitrile (1.8 mL), was added DBU (0.01 mL, 0.075 mmol). The reaction mixture was refluxed for 1.5h. The solvent was removed under reduced pressure. The residue was purified on a silica gel plate using 5% MeOH/$CHCl_3$ to afford 0.007 g (0.036 mmol, 67%) of the nucleoside **29**. Mass spectrum, m/z 194 (M^+). UV (MeOH) λ_{max} 252 nm. ^1H NMR ($CDCl_3$): δ 2.03 (m, 1H), 2.51 (m, 1H), 3.92 (m, 5H), 5.12 (m, 1H), 5.98 (d, 1H), 7.74 (d, 1H). Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.42. Found: C, 55.48; H, 5.03; N, 14.17.

Deamination of 8 by Adenosine Deaminase: A solution of **8** (2.7×10^{-4} M) in phosphate buffer (0.05 M, pH 7.4) was treated with ADA (Sigma, Type VII) to give an enzyme concentration of 39 units/mL. The deamination was monitored at 265 nm ($\Delta\varepsilon = 8100$) and a velocity of 5.8×10^{-5} μmole/unit/min was observed. Under identical conditions a solution of adenosine (2.7×10^{-4} M) was deaminated with a 0.009 units/mL solution of ADA and exhibited a velocity of 1 μmole/unit/min.

Inhibition of the Deamination of Adenosine by 8: The deamination of adenosine (20 to 80 μM) in phosphate buffer (0.05 M, pH 7.4) with adenosine deaminase (0.004 units/mL) was inhibited by the addition of **8** (100, 125 and 150 μM). The kinetic data was fitted to the Michaelis-Menten equation by a computer program using linear least-squares analysis. An inhibition constant of $K_i = 8.2 \times 10^{-5}$ M was calculated from the following equation: $\text{slope} = (1 + [I]/K_i)K_m/V_{max}$, where slope = slope of inhibited reaction, [I] is inhibitor concentration and K_m and V_{max} are the constants for the deamination with no inhibitor present.

Acid Catalyzed Hydrolysis of 8: The hydrolysis of **8** (2×10^{-4} M) at pH 3 (0.001 M HCl) and 25°C was monitored by differential UV spectroscopy. While no evidence for the hydrolysis of **8** was observed under these conditions, 2',3'-dideoxyadenosine was completely hydrolyzed to adenine within 3h. Under more stringent conditions the hydrolysis of **8** (0.1 M) at pH 1 (1 M HCl) and 90°C was monitored by HPLC (10 μm, Hamilton PRP-1, linear gradient H_2O to EtOH) after neutralization with 1M NaOH. Upon prolonged exposure (36h) no hydrolysis of **8** ($t_r = 23$ min) to adenine ($t_r = 6$ min) was observed.

Single Crystal X-ray Structure Determination of (-)-Isodideoxyadenosine 8: A colorless crystal, 0.22mm x 0.55mm x 0.65mm mounted on a glass filter with [1,0,0] roughly parallel to the phi rotation axis on an Enraf-Nonius CAD-4 diffractometer, graphite monochromator, Mo K_α, α (average = 0.7107 Å; 295K data collection; scan ratio (Ω/θ) = 1, scan range ($^\circ$ Ω) = 0.7 + 0.35 Tan θ; scan speed ($^\circ$/min) = 1.5 - 5.0; θ range = $2 < \theta < 30$. Lorentz and polarization corrections were made but absorption

corrections were not (μ = 0.9 cm^{-1}). The three standard reflections used to monitor decay showed a decrease of only 1.006 %. A total of 9881 reflections were measured of which 1943 were unique reflections and 1265 were reflections with $F > 2*\sigma_F$. Cell dimensions were obtained from 25 reflections with θ range $2 < 2\theta < 24$ were used to determine the orientation matrix, a = 8.538(4), c = 27.078 (15) Å. The crystal belongs to the $P3_121$ space group. The cell volume was 1709(3) $Å^3$. For Z = 6, F.W. = 235.25, the calculated density = 1.37 g/cm^3.

The structure was solved by direct methods and refined by full matrix least squares. All hydrogen atoms were located from difference maps and refined. Anisotropic refinement on all non-hydrogen atoms and isotropic refinement on hydrogen atoms gave R = 0.035, R_w = 0.044. The estimated standard deviation of an observation of unit weight = 1.153. Weights used in the refinement were P = 0.04 and Q = 0.0, where $W = [\sigma F^2 + (P*F)^2 + Q]^{-1}$. The last parameter shift/error was less than 0.09. The final difference map had a maximum residual electron density of 0.148 $e^-/Å^3$. All crystallographic calculations were made using the SDP set of programs of Enraf-Nonius Corp.

Supplementary Material Available: A list of refined coordinates and estimated standard deviations, bond distances, and bond angles for (-)-isodideoxyadenosine are available through any current masthead page.

Acknowledgments. We thank the National Institutes of Health for support of this research through AI32851 and the Burroughs Wellcome Company for the collaborative antiviral studies. The high-field NMR spectrometers (Bruker AC-300 and AMX-600) used in this work were purchased in part from funds provided by the N.S.F. and the N.I.H. We thank Dr. Dale Swenson for help with the X-ray structure determination.

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(*Received in USA* 15 *March* 1994; *accepted* 2 *May* 1994)