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NOVEL DIDEOXYNUCLEOSIDE ISOSTERES[1]

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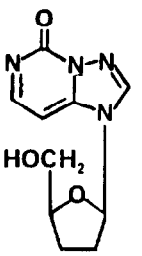
Abstract: Novel 5-aza-7-deaza isosteres of the anti-HIV compounds, dideoxyinosine (ddI) and dideoxyguanosine (ddG), have been prepared by glycosylation of the corresponding isosteric bases with appropriately tailored dideoxyribose components. The glycosylation reactions were regiospecific and the position of glycosylation was established by UV and high-field NMR data. However, attempted preparation of the 3-deaza-5-aza isostere of dideoxyinosine led to a different regioisomer, a ring-extended dideoxycytidine analogue, whose structure was established by X-ray crystallographic data. The 5-aza-7-deaza isosteres of ddI and ddG were more stable with respect to hydrolytic cleavage than ddI and ddG.

The synthesis of modified dideoxynucleosides continues to receive considerable attention because of the potential of this family of compounds to inhibit the cytopathic effect of HIV, the etiologic agents of AIDS.[2-6] Dideoxyinosine (ddI), the metabolic product of the action of adenosine deaminase on dideoxyadenosine (ddA), and dideoxyguanosine (ddG) are both inhibitors of HIV reverse transcriptase, a viral DNA polymerase, through the incorporation of these dideoxynucleosides *via* their triphosphates.[6-8] The detailed mechanism of inhibition is still not fully understood. Although many modified purine dideoxynucleosides have been synthesized and examined for anti-HIV activity (see for example, references 9-12), it has been discovered that major alterations in the structures of both the base

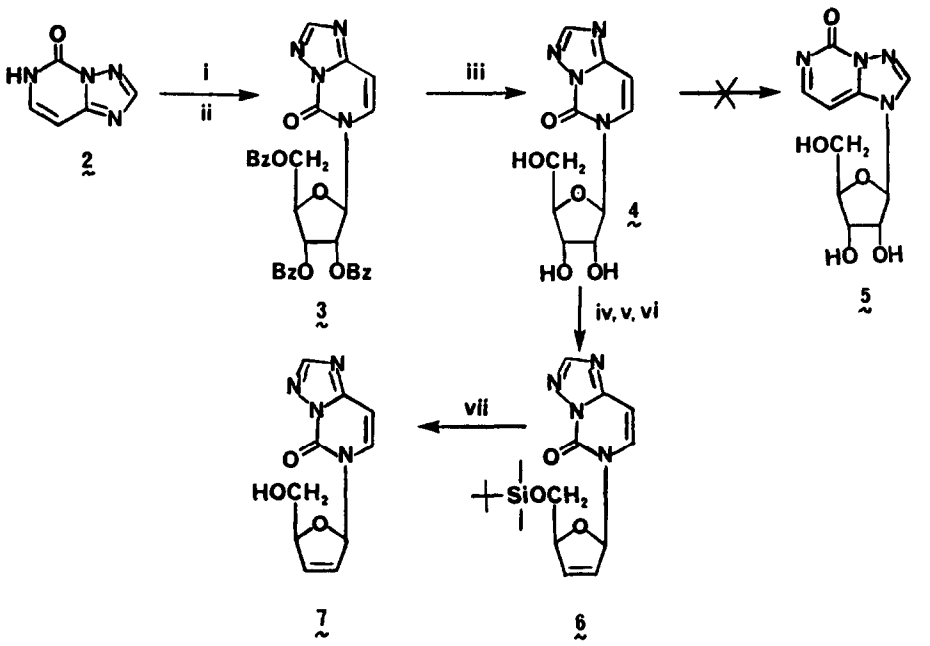
and carbohydrate moieties usually lead to target compounds with low or little activity. Also, one of the inherent structural drawbacks of many of these compounds is the instability of the glycosidic bond.[13] Within the context of the last two statements, it should be mentioned that few examples of dideoxypurine nucleosides with isosteric modifications are known.[14-16] This paper reports on the synthesis and structural studies of novel isosteres of ddI and ddG.

The strategy for the synthesis of the isosteres involved glycosylation of the appropriately modified carbohydrate precursor with the separately synthesized base isostere. An alternative approach involved selective dideoxygenation of the appropriate isosteric ribonucleoside. For example, synthesis of isostere **1** was



1

attempted through the ribonucleoside, 1-(ß-D-ribofuranosyl)-s-triazolo [1,5-c]pyrimidine-5-one. The heterocyclic base for the ribonucleoside, s-triazolo[1,5-c]-pyrimidin-5-one (i.e. 5-aza-3-deazahypoxanthine) **2** was prepared in several steps from uracil with a Dimroth rearrangement being the key step.[17] Glycosylation of **2** with 1-O-acetyl-2,3,5-tri-O-benzoylribose in 1,2-dichloroethane was accomplished by generation of the silylated base *in situ* using either bis(trimethylsilyl)trifluoro-acetamide or bis(trimethylsilyl)acetamide[18,19] followed by condensation with the sugar derivative in the presence of TMS triflate (Scheme 1). The product of this glycosylation (82% yield) was not



i) BSA, CH_3CN, Δ ; ii) ABR, $TMST_f$, CH_3CN, Δ ; iii) NH_3, CH_3OH ;
iv) TBDMSCl, DMAP, CH_2Cl_2, DMF ; v) NaOH, CS_2, CH_3I, DMSO ;
vi) *n*-Bu_3SnH, AIBN, toluene, Δ ; vii) Et_4NF, CH_3CN .

Scheme 1

the isostere of inosine (protected) but rather the compound with the glycosidic bond formed at the 6-position of the heterocyclic base, i.e. the ring-extended cytidine derivative **3**. The regiochemistry of the glycosylation reaction was established by the spectroscopic data of the deprotected nucleoside **4**, particularly the 2D NOESY NMR spectrum. Attempted conversion of **4** to **5** by thermal isomerization was discovered to be unattainable even under a variety of conditions. Nucleoside **4** was converted in three steps to the ring extended d^4 compound **6** which could be desilylated to **7**. Both the complete structure of this compound and the regiochemistry of the original glycosylation reaction were fully confirmed by single crystal X-ray data (see Fig. 1). Attempted catalytic (H_2, Pd/C) hydrogenation of **7**

resulted in cleavage of the glycosidic bond and very low yields of the saturated dideoxycytidine analogue **10**.

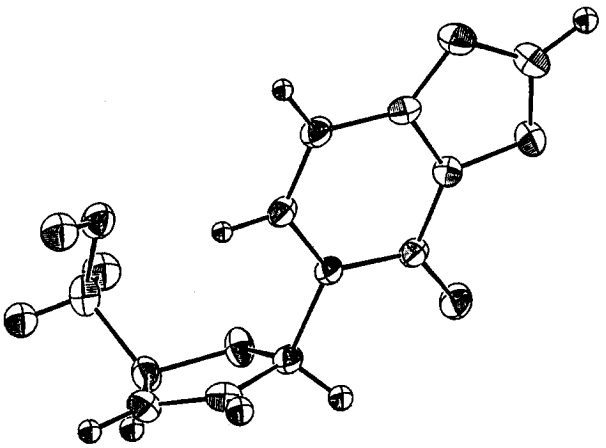
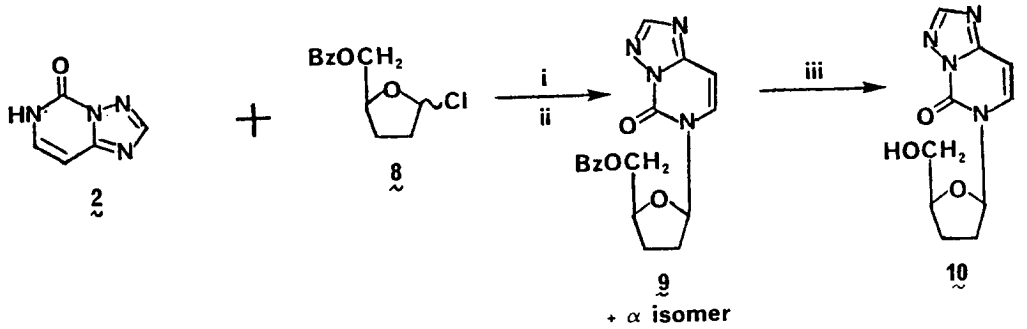


Figure 1. ORTEP plot of the single crystal X-ray structure of **7**

This saturated compound could be prepared by direct glycosylation of the silylated form of **2** with 1-chloro-5-O-benzoyl-2,3-dideoxy-D-glycero-pentofuranose **8** in the presence of a catalytic amount of pyridine (Scheme 2). Although this procedure is said to yield an



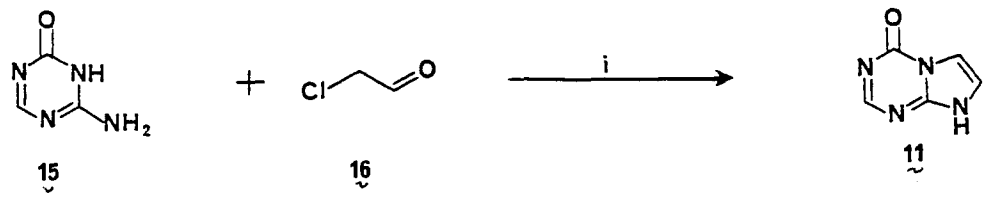
i) BSA, CH_3CN, Δ; ii) $CHCl_3$, pyridine; iii) $NaOCH_3$, CH_3OH.

anomeric ratio favoring the ß-isomer,[20] analysis of the glycosylation product mixture by high-field ^1H NMR indicated an approximately 1:1 ratio of the two isomers. The products were separated chromatographically, deprotected, and characterized. This is the first example of a ring extended dideoxycytidine analogue. Attempted synthesis of the 5-aza isostere of ddI from the glycosylation of s-triazolo[2,3-a]-s-triazin-5(6H)-one[21] with 1-O-acetyl-2,3,5-tri-O-benzoylribose in the presence of TMS triflate resulted in a complex mixture of products which could not be separated, and deprotection led to decomposition.

The isosteric dideoxyinosine **14** (5-aza-7-deazadideoxyinosine) was synthesized by glycosylation of **11** with the appropriately protected dideoxy sugar **12** (Scheme 3) as initial attempts to deoxygenate the isosteric ribonucleoside thionocarbonate with tributyltin hydride and AIBN resulted in decomposition rather than deoxygenation. The isosteric base of hypoxanthine (i.e. imidazo[1,2-a]-s-triazin-4-one, **11**), a new heterocyclic system, was prepared in 86% yield from the reaction of chloroacetaldehyde with 5-azacytosine (Scheme 3). The dideoxy carbohydrate precursor **12** can be prepared from L-glutamic acid[22] or it can be also conveniently prepared from **17** as shown in Scheme 3. The latter approach has not been previously described.

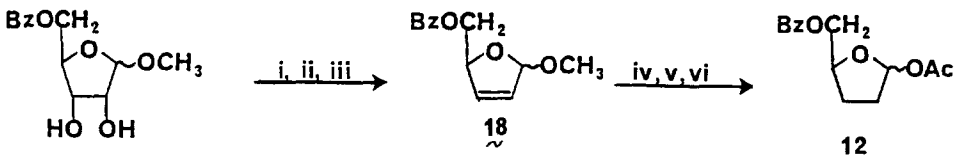
Glycosylation of **11** (silylated with BSA) with **12** in CH_3CN in the presence of TMS triflate gave **13** as a mixture of α- and ß-isomers (1:1) in 76% yield. This mixture was deprotected with methanolic ammonia and the α- and ß-isomers separated on silica gel plates. The higher R_f material was the less polar ß-isomer, **14**. The high-field ^1H NMR spectra of the two compounds showed differences in the chemical shifts of the 1', 4' and 5' hydrogens. In particular, the chemical shift of the 4'- hydrogen in the α-isomer (4.60 ppm) is about 0.5 ppm further downfield as compared to the ß-isomer (4.12 ppm)

because of the deshielding effect of the heterocyclic base. Further confirmation of these assignments came from NOE experiments.



15 16 11

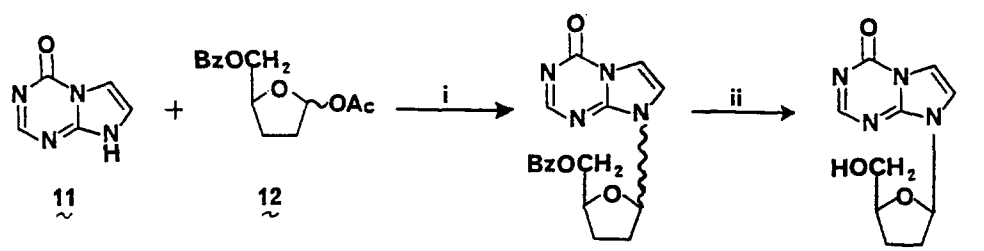
i) H_2O, 5 days, 45°



17 18 12

i) CS_2, NaOH ; ii) CH_3I, DMSO ; iii) n-Bu_3SnH, AIBN, Toluene, △ ;

iv) H_2, PtO_2 ; v) HCl, dioxane, △ ; vi) Ac_2O, Et_3N, DMAP, CH_3CN



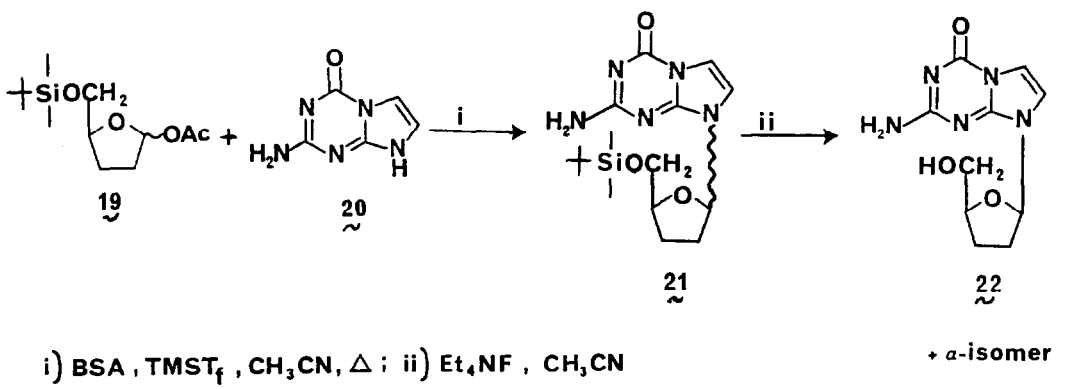
11 12 13 14

i) BSA, $TMST_f$, CH_3CN, △ ; ii) NH_3, CH_3OH, 0°C + α isomer

Scheme 3

Synthesis of the dideoxyguanosine isostere **22** involved the same approach as for **14** except the carbohydrate moiety used for the coupling was **19**[23] instead of **12**. The reason for the difference in the

choice of the carbohydrate precursor was the instability of the benzoylated isosteric product under the conditions of deprotection of the 5'-benzoate. The base for the glycosylation reaction (i.e. the guanine isostere **20**) was synthesized in five steps from 2,4,6-trichloro-1,3,5-triazine.[24] As produced in the final step of this reaction, the isostere **20** is contaminated with considerable amounts of inorganic salts from which it is not easily separated. Purification was achieved, however, by preparative HPLC on a Hamilton PRP-1 column followed by careful crystallization from water. Glycosylation of **20** with **19** as described above gave a 56% yield of an approximately 1:1 α/ß mixture of **21**. Deprotection of **21** with fluoride ions and separation of the product mixture gave a 20% isolated yield of the desired ß-isomer **22** (Scheme 4). Characterization of this compound was carried out as described above for isostere **14**.



Scheme 4

The stability of the ddI and ddG isosteres with respect to hydrolytic bond cleavage was also studied. One rationale for the synthesis of these isosteres was that they would be hydrolytically more stable than their counterpart structures where the anti-HIV activity is limited by the instability of the glycosidic bond. These

studies were carried out by differential UV spectroscopy at pH 3 and 25 ^{o}C where easily observable rates could be obtained. Samples were monitored at appropriate time intervals by adjusting the pH to 13, thus separating the absorption of the unchanged nucleoside from that of the bathochromically shifted hydrolyzed base anion. The apparent first order rate constants were calculated from the slopes of the appropriate log plots as described by Garrett and Mehta.[25] The relative rates of hydrolysis were compared to ddA, ddI and ddG. As expected, the isostere of ddI derived by transposing the nitrogen at the 7-position to the 5-position was hydrolytically more stable than ddI with relative rates being: ddA (100), ddG (84), ddI (74), ddI isostere, **14** (33), ddG isostere **22** (37).[26]

In summary, novel isosteres of the anti-HIV active compounds, ddI and ddG, have been prepared by glycosylation of the appropriate bases with dideoxy sugar components. In one case, attempted preparation of a 3-deaza-5-aza isostere of dideoxyinosine led to a totally different regioisomer, i.e. a ring-extended dideoxycytidine analogue whose structure was established by X-ray crystallographic data. It was also discovered that isosteres containing an additional nitrogen at the 5-position were unstable with respect to ring opening of the heterocyclic base under basic conditions. However, the ddI and ddG isosteres successfully synthesized were more stable than their counterparts bearing unmodified bases.

Experimental Section

Melting points reported are uncorrected and were determined on a Thomas-Hoover melting point apparatus fitted with a microscope. Nuclear magnetic resonance spectra were recorded on Bruker Models AMX-600, MSL-300, and AC-300 pulse Fourier transform spectrometers. Mass

spectra were determined on a VG ZAB-HF high resolution mass spectrometer with FAB capability or a VG TRIO single quadrupole GC/MS system. Ultraviolet spectra were recorded on a Varian Cary Model 219 or a Gilford Response spectrophotometer. Infrared 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. High performance liquid chromatography was done at 80 psi using Altex columns packed with 40-60 μm Amberlite XAD-4 resin (Rohm and Haas). Fractions were monitored by a Pharmacia UV-2 ultraviolet monitor and products were collected on a Gilson FC-100 fraction collector. Analytical and Preparative HPLC separations were also carried out with a Waters automated 600E system with photodiode array detector and FOXY fraction collector using Delta-Pak C_{18} and Hamilton PRP-1 columns. X-ray crystallographic data were obtained using an Enraf-Nonius CAD-4 diffractometer. Elemental analyses were performed at Galbraith Laboratories, Inc., Knoxville, TN.

s-Triazolo[1,5-c]pyrimidin-5(6)H-one (2). This isosteric base was prepared from thiouracil[27] in 54% overall yield using a modification of the procedure of Brown and Shinozuka[17]: mp >340°C (lit.[17] mp >340°C dec); ^{13}C NMR (Me_2SO-d_6) δ 95.7, 134.7, 145.3, 154.2, 154.4; ^{1}H NMR (Me_2SO-d_6) δ 6.75 (d, 1H; J = 7.3 Hz), 7.57 (d, 1H; J = 7.3 Hz), 8.40 (s, 1H); UV (H_2O) 242 (sh), 248, 261.5, 270 (sh), 282 (sh).

6-(ß-D-Ribofuranosyl)-s-triazolo[1,5-c]pyrimidin-5-one (4). A mixture of **2** (0.318 g, 2.33 mmol) and bis(trimethylsilyl) trifluoroacetamide (0.80 mL, 3.04 mmol) in dry 1,2-dichloroethane (15 mL) was refluxed under a N_2 atmosphere with stirring for 1.5 h, then

cooled to room temperature. To the silylated base was added 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose (1.120 g, 2.22 mmol) and trimethylsilyl triflate in 1,2-dichloroethane (0.52 M, 2.25 mL) via a syringe and needle. Additional 1,2-dichloroethane (15 mL) was added. The reaction mixture was refluxed under a N_2 atmosphere with stirring for 3.5 h and concentrated in vacuo. The resulting solid was dissolved in warm chloroform (40 mL), washed with saturated aqueous sodium bicarbonate (10 mL) , water (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography with 2-5% methanol/chloroform afforded **3** as a white solid (1.053 g, 1.81 mmol, 82%) which contained a minor amount of lower R_f material (< 5%): ^1H NMR (Me_2SO-d_6) δ 4.74 (m, 2H), 4.86 (m, 1H), 6.00 (m, 1H), 6.06 (m, 1H), 6.50 (d, 1H; J = 3.8 Hz), 6.93 (d, 1H; J = 7.8 Hz), 7.41-8.03 (m, 16H, aromatics and H7), 8.48 (s, 1H).

A chilled (0°C) suspension of nucleoside **3** (0.598 g, 1.03 mmol) in dry methanol (75 mL) was saturated with NH_3 gas. The reaction was allowed to proceed for 48 h at room temperature. The reaction mixture was concentrated under reduced pressure to 1/4 volume, adsorbed onto silica gel and purified by flash chromatography with chloroform followed by 15-20% methanol/chloroform to afford **4** (0.260 g, 0.97 mmol, 94%) as white crystals (from EtOH): mp 187-189 °C (EtOH); (lit.[28] mp 182-185 °C; reported after this work was completed); ^{13}C NMR (Me_2SO-d_6) δ 60.5, 69.6, 74.7, 85.3, 89.7, 96.2, 133.5, 145.0, 153.2, 154.8; ^1H NMR (Me_2SO-d_6) δ 3.62 (m, 1H), 3.72 (m, 1H), 3.96 (m, 1H), 4.04 (dd, 1H), 4.15 (dd, 1H), 5.14 (d, 1H; J = 5.2 Hz), 5.23 (t, 1H; J = 4.8 Hz), 5.51 (d, 1H; J = 5.1 Hz), 6.03 (d, 1H; J = 4.5 Hz), 6.91 (d, 1H; J = 7.8 Hz), 8.14 (d, 1H; J = 7.8 Hz), 8.44 (s, 1H); UV (H_2O) 243 (sh) (ϵ 5000), 250 (sh) (5800), 266.5, (7880), 274 (sh) (7200), 286 nm (sh) (3800).

6-(2,3-didehydro-2,3-dideoxy-ß-D-glycero-pentofuranosyl)-s-triazolo [1,5-c]pyrimidin-5-one (7). A mixture of nucleoside **4** (0.288 g, 1.07 mmol), tert-butyldimethylsilyl chloride (0.178 g, 1.18 mmol), DMAP (0.020 g, 0.16 mmol), triethylamine (0.15 mL, 1.07 mmol), CH_2Cl_2 (4 mL), and DMF (8 mL) was stirred at room temperature for 21 h. The solvents were removed under reduced pressure and the residue adsorbed onto silica gel. Purification by flash chromatography with chloroform followed by 5% methanol/chloroform afforded the mono-silylated derivative (0.332g, 0.87 mmol, 81%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.92 (s, 9H), 3.84 (dd, 1H), 4.02 (dd, 1H), 4.30 (m, 2H), 4.32 (m, 1H), 6.14 (d, 1H; J = 4.0 Hz), 6.71 (d, 1H; J = 7.8 Hz), 8.08 (d, 1H; J = 7.8 Hz), 8.25 (s, 1H).

To a chilled (0-5°C) solution of the monosilylated nucleoside (0.324 g, 0.847 mmol) and CS_2 (0.18 mL, 2.96 mmol) in DMSO (5 mL) was added aqueous sodium hydroxide (5M, 0.37 mL) dropwise with stirring. After 20 min, methyl iodide (0.11 mL, 1.78 mmol) was added dropwise and the mixture stirred for an additional 1 h. The reaction mixture was poured into H_2O (40 mL) and extracted with ethyl acetate (2 X 20 mL). The combined extracts were washed with H_2O (3 X 40 mL), dried (Na_2SO_4), and concentrated <u>in vacuo</u>. The residue was purified by flash chromatography with chloroform to afford the bis-xanthate derivative (0.363 g, 0.64 mmol, 76%) as an off-white foam: ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 6H), 0.97 (s, 9H), 2.53 (s, 3H), 2.60 (s, 3H), 3.97 (dd, 1H; J = 1.8, 11.4 Hz), 4.07 (dd, 1H; J = 1.7, 11.4 Hz), 4.52 (m, 1H), 6.15 (dd, 1H; J = 5.6, 7.3 Hz), 6.27 (dd, 1H; J = 1.4, 5.6 Hz), 6.71 (d, 1H; J = 7.8 Hz), 6.87 (d, 1H; J = 7.3 Hz), 8.03 (d, 1H; J = 7.8 Hz), 8.25 (s, 1H); UV (EtOH) 277 nm.

To a refluxing solution of the bis-xanthate (0.345 g, 0.61 mmol) in toluene (25 mL) under N_2 was added a mixture of tributyltin hydride (0.66 mL, 2.45 mmol) and AIBN (0.04 g, 0.24 mmol) in N_2 purged toluene

(25 mL) over a 90 min period. The reaction mixture was refluxed an additional 30 min then concentrated in vacuo. The residue was dissolved in chloroform and eluted through a short scrubber column with hexanes followed by ethyl acetate. Further purification by flash chromatography with chloroform afforded **6** (0.187 g, 0.54 mmol, 87%) as a white solid: ^{1}H NMR (Me_2SO-d_6) δ 0.05 (s, 6H), 0.86 (s, 9H), 3.84 (dd, 2H), 4.94 (m, 1H), 6.06 (m, 1H), 6.48 (dt, 1H), 6.80 (d, 1H; J = 7.8 Hz), 7.08 (m, 1H), 7.84 (d, 1H; J = 7.8 Hz), 8.46 (s, 1H).

The silylated nucleoside **6** (0.097 g, 0.28 mmol) was dissolved in dry CH_3CN (7 mL) and treated with a 0.5 M tetraethylammonium fluoride (TEAF) solution (0.83 mL, 0.42 mmol) in CH_3CN. The reaction proceeded at room temperature for 1h. Water (1 mL) was added and stirring continued for 5 min. The solvent was removed under reduced pressure and the residue purified by preparative TLC with 8% methanol/chloroform as the developing solvent. The band at R_f 0.47 afforded 0.056 g (0.24 mmol, 86%) of product which was recrystallized from methanol to afford the title nucleoside **7** as clear prisms: mp 262-264°C (sublimes); ^{13}C NMR (Me_2SO-d_6) δ 62.1, 88.1, 90.9, 96.0, 126.0, 134.2, 135.3, 145.2, 153.3, 154.8; ^{1}H NMR (Me_2SO-d_6) δ 3.65 (m, 2H), 4.89 (m, 1H), 5.06 (t, 1H), 6.03 (ddd, 1H), 6.48 (ddd, 1H), 6.86 (d, 1H; J = 7.8 Hz), 7.09 (m, 1H), 7.98 (d, 1H; J = 7.8 Hz), 8.45 (s, 1H); UV (H_2O) 243 (sh) (ϵ 5200), 250 (sh) (6300), 266.5 (7900), 274.5 (sh) (7200), 286 nm (sh) (3500). Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.27; H, 4.31; N, 23.92. Found C, 51.30; H, 4.38; N, 24.14

1-Chloro-5-O-benzoyl-2,3-dideoxy-D-glycero-pentofuranose (8). This compound was prepared from 5-O-Benzoyl-2,3-dideoxy-D-glycero-pentofuranose according to the method of Kawakami, et al.[20] and used without further purification.

6-(2,3-Dideoxy-ß-D-glycero-pentofuranosyl)-s-triazolo[1,5-c]-pyrimidin-5-one (10). A mixture of **2** (0.161 g, 1.19 mmol) and bis(trimethylsilyl)acetamide (0.37 mL, 1.48 mmol) in acetonitrile was refluxed under a N_2 atmosphere with stirring for 30 min, cooled to room temperature, and concentrated under high vacuum. To the silylated base dissolved in dry chloroform (3 mL) was added **8** (0.142 g, 0.59 mmol) in chloroform (3 mL) and pyridine (0.02 mL, 0.29 mmol) and stirred under a N_2 atmosphere for 16 h at room temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 mL) and extracted with chloroform (4 X 10 mL). The combined extracts were dried (Na_2SO_4), concentrated in vacuo, and the residue purified by preparative TLC with 5% methanol/chloroform as the developing solvent. The band at R_f 0.38 afforded **9** (0.102 g, 0.30 mmol, 51%) as a clear glass, ratio of α:ß anomers = 44:56. Separation of the anomers was achieved by preparative TLC with 5% methanol/chloroform as the developing solvent (6 immersions). Data for **9** (α anomer) : R_f 0.57; ^{13}C NMR ($CDCl_3$) δ 26.2, 32.9, 65.9, 79.5, 89.3, 96.6, 128.5-133.3, 133.5, 144.5, 153.2, 154.8, 166.2; ^1H NMR ($CDCl_3$) δ 2.04 (m, 1H), 2.20 (m, 2H), 2.72 (m, 1H), 4.36 (dd, 1H; J = 5.4, 11.9 Hz), 4.45 (dd, 1H; J = 3.7, 11.9 Hz), 4.81 (m, 1H), 6.34 (dd, 1H; J = 3.6, 6.1 Hz), 6.71 (d, 1H; J = 7.8 Hz), 7.42-7.57 (m, 5H), 8.01 (d, 1H; J = 7.8 Hz), 8.20 (s, 1H). Data for **9** (ß anomer): R_f 0.63; ^{13}C NMR ($CDCl_3$) δ 25.3, 33.2, 64.6, 79.8, 87.8, 96.3, 128.5-133.4, 133.5, 144.6, 153.2, 154.7, 167.1; ^1H NMR ($CDCl_3$) δ 1.94 (m, 1H), 2.18 (m, 2H), 2.60 (m, 1H), 4.50 (m, 1H), 4.58 (dd, 1H; J = 4.2, 12.3 Hz); 4.66 (dd, 1H; J = 2.2, 12.3 Hz), 6.28 (dd, 1H; J = 2.8, 6.4 Hz), 6.48 (d, 1H; J = 7.8 Hz), 7.40-7.59 (m, 3H), 7.81 (d, 1H; J = 7.8 Hz), 7.99 (m, 2H), 8.19 (s, 1H).

A mixture of the protected nucleoside **9** (0.032, 0.09 mmol) and sodium methoxide (0.006 g, 0.11 mmol) in anhydrous MeOH (2 mL) was

stirred for 5 h at room temperature under N_2. The solution was neutralized with Dowex resin (H^+), filtered and the filtrate concentrated in vacuo. The residue was purified by preparative TLC with 7% MeOH/$CHCl_3$ as the developing solvent. The band at R_f 0.39 afforded 0.017 g (0.07 mmol, 77%) of **10**: mp 126-128 °C; ^{13}C NMR (Me_2SO-d_6) δ 24.4, 33.3, 64.2, 82.5, 87.7, 96.2, 133.1, 144.6, 153.2, 154.6; ^1H NMR (Me_2SO-d_6) δ 1.91 (m, 2H), 2.17 (m, 1H), 2.41 (m, 1H), 3.59 (m, 1H), 3.79 (m, 1H), 4.14 (m, 1H), 5.18 (t, 1H; J = 5.0 Hz), 6.18 (dd, 1H, J = 2.7, 6.7 Hz), 6.86 (d, 1H, J = 7.8 Hz), 8.22 (d, 1H, J = 7.8 Hz) 8.42 (s, 1H); UV (H_2O) 243 (sh) (ϵ 5400), 250 (sh) (6200), 266.5 (7900), 274 (sh) (7500), 286 nm (sh) (3400). Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.83; H, 5.13; N, 23.72. Found: C, 50.62; H, 5.13; N, 23.04.

Imidazo[1,2-a]-s-triazin-4-one (**11**). A mixture of 5-azacytosine (**15**) (1.00 g, 8.92 mmol) and chloroacetaldehyde (13.0 mL, 82.6 mmol) in distilled water (200 mL) was heated at 45°C for 5 days. The reaction mixture was neutralized with 5M NaOH. The solution was extracted with diethyl ether (3 x 50 mL), then concentrated under reduced pressure. The residue was purified on HPLC with water as the eluting solvent to give 1.04 g (7.67 mmol, 86%) of **11** as a white solid: mp 200°C (dec.); ^1H NMR (Me_2SO-d_6) δ 7.37 (d, 1H, J = 1.4 Hz), 7.68 (d, 1H, J = 1.4 Hz), 8.11 (s, 1H); UV (H_2O) 249 (ϵ 5500), 271 nm (6600); mass spectrum, m/z (rel. intensity) 136 (M^+, 100%); Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.16. Found: C, 44.51; H, 3.15; N, 40.61.

8-(2,3-dideoxy-ß-D-glycero-pentofuranosyl)imidazo[1,2-a]-s-triazin-4-one (**14**). Imidazo[1,2-a]-s-triazin-4-one (**11**) (0.071 g, 0.521 mmol) was placed in a 100 mL RBF containing 30.0 mL of acetonitrile. The suspension was purged (N_2, 15 min), followed by the addition of BSA

(0.20 mL, 0.782 mmol). The resulting solution was stirred at 25°C for 1 h. A solution of 0.124 g (0.469 mmol) of **12** in 20 mL of acetonitrile was added to the base solution, followed by the addition of 0.03 mL (0.172 mmol) of TMS-triflate (neat). The resulting solution was stirred for 4 h at 25°C. The solvent was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ (20.0 mL) and saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was washed with $CHCl_3$ (25 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel flash chromatography (7% MeOH/$CHCl_3$) to give 0.134 g (0.394 mmol, 76%) of a 1:1 mixture of the α,ß isomers of **13** as an oil: ^1H NMR ($CDCl_3$) δ 2.00-2.80 (m, 4H), 4.50 (m, 3H), 6.30 (m, 1H), 7.45 (m, 5H), 8.01 (m, 2H), 8.32 (m, 1H); UV (EtOH) 273, 279 nm; mass spectrum, m/z (rel. intensity) 341 (M^+, 0.38), 340 [$(M-H)^+$, 1.86], 205 ($sugar^+$, 87.13), 136 ($base^+$, 50.88).

To 40 mL of dry methanol saturated with anhydrous ammonia gas at ice-salt bath temperatures was added 0.043 g (0.126 mmol) of **13**. The solution was allowed to stand for 12 h at this temperature. The solvent was removed under reduced pressure and the residue was partitioned between $CHCl_3$ (20 mL) and H_2O (20 mL). The organic layer was re-extracted with 2 x 20 mL of H_2O. The combined aqueous layers were concentrated and the residue was chromatographed on silica gel plates (10% MeOH/$CHCl_3$) to separate the α and ß isomers, followed by HPLC (8% EtOH/H_2O) to give 0.009 g (0.038 mmol, 30%) of the α anomer and 0.009 g (0.038 mmol, 30%) of the ß anomer of **14** (total conversion based on starting material, 82%) as a white solid: (data for α anomer) mp 85-88 °C (hygroscopic); ^1H NMR (Me_2SO-d_6) δ 2.00-2.40 (m, 4H), 3.30 (m, 2H), 4.60 (m, 1H), 4.84 (m, 1H) 6.31 (m, 1H), 7.81 (dd, 2H; J = 2.5 Hz), 8.24 (s, 1H); UV (H_2O) 236 (ε 2950), 280 nm (6800): (data for ß anomer) mp 112-113°C; ^1H NMR (Me_2SO-d_6) δ 1.78-

2.50 (m, 4H); 3.50 (m, 2H), 4.12 (m, 1H), 5.04 (m, 1H), 6.25 (m, 1H), 7.69 (d, 1H, J = 2.6 Hz), 7.92 (d, 1H, J = 2.6 Hz), 8.22 (s, 1H); UV (H_2O) 237 (ε 2800), 280 nm (6400); Anal. Calcd for $C_{10}H_{12}N_4O_3.0.5H_2O$: C, 48.98; H, 4.93; N, 22.84. Found: C, 48.72; H, 4.67; N, 22.50.

2-Amino-8-(2,3-dideoxy-ß-D-glycero-pentofuranosyl)imidazo-[1,2-a]-s-triazin-4-one (22). 2-Aminoimidazo[1,2-a]-s-triazin-4-one (**20**) was synthesized in 41% overall yield from cyanuric chloride according to the method of Robins et al.[24]

5-O-Tert-butyldimethylsilyl-1-O-acetyl-2,3-dideoxy-ß-D-glycero-pentofuranose (**19**) was synthesized in 29% overall yield from L-glutamic acid according to the method of Okabe, M. et al.[23]

The isosteric base **20** (0.06 g, 0.397 mmol) was placed in a 100 mL RBF containing 30 mL of acetonitrile. The suspension was purged (N_2, 15 min), followed by the addition of 0.15 mL (0.596 mmol) of BSA. The resulting solution was stirred at 25°C for 1 h. A solution of 0.110 g (0.397 mmol) of **19** in 20 mL of acetonitrile was added to the base solution, followed by the addition of 0.04 mL (0.20 mmol) of TMS-Triflate (neat). The resulting solution was stirred at 25°C for 4.5 h. The solvent was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ (20 mL) and aqueous saturated $NaHCO_3$ (20 mL). The aqueous layer was washed with 2 x 25 mL of $CHCl_3$. The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by silica gel flash chromatography (7% MeOH/$CHCl_3$) to give 0.081 g (0.222 mmol, 56%) of a 1:1 mixture of the α,ß isomers of **21** as a light brown oil: ^1H NMR ($CDCl_3$) δ 0.08 (m, 6H), 0.90 (m, 9H), 2.00 (m, 2H), 3.50 (m, 2H), 4.15 (m, 1H), 5.80 (m, 2H), 6.20 (m, 1H), 7.15 (m, 2H); UV (EtOH) 253 nm; mass spectrum, m/z (rel. intensity) 368 (M^+, 0.41) 307 [$(M-tBu)^+$, 0.97], 149 (base$^+$, 55.1).

A solution of 0.04 g (0.109 mmol) of **21** in 15 mL of acetonitrile was treated with 0.033 g (0.219 mmol) of Et_4NF at 25°C for 3 h. The solvent was removed, and the residue was partitioned between $CHCl_3$ (20 mL) and H_2O (20 mL). The aqueous layer was re-extracted with ether (20 mL). The combined organics were back extracted with 20 mL of H_2O. The combined aqueous layers were concentrated, then purified on silica gel plates (15% MeOH/$CHCl_3$) to separate α,β isomers, followed by HPLC (6% EtOH/H_2O) to give 0.005 g (0.020 mmol, 20%) of the α anomer and 0.005 g (0.020 mmol, 20%) of the β anomer of **22** (total conversion based on starting material, 50%) as a white solid: (data for α anomer) mp 72-75°C; ^1H NMR (Me_2SO-d_6) δ 2.00-2.40 (m, 4H), 3.36 (m, 2H), 4.70 (m, 1H), 4.91 (m, 1H), 6.34 (m, 1H), 7.00 (br s, 2H), 7.49 (s, 1H), 7.54 (s, 1H); UV (H_2O) 254 nm (ε 14200): (data for β anomer) mp 87-90°C; ^1H NMR (Me_2SO-d_6) δ 2.00-2.50 (m, 4H), 3.50 (m, 2H), 4.25 (m, 1H), 5.15 (m, 1H), 6.25 (m, 1H), 7.08 (s, 2H), 7.45 (s, 1H), 7.60 (s, 1H); UV (H_2O) 254 nm (ε 14000); Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.22; N, 27.87. Found: C, 47.51; H, 5.59; N, 26.99.

5-O-Benzoyl-1-O-acetyl-2,3-dideoxy-D-glycero-pentofuranose (12). Methyl 5-O-Benzoyl-β-D-ribofuranose **17**[29] was converted to its 2,3-bis-xanthate in 92% by treatment with carbon disulfide, sodium hydroxide and methyl iodide in DMSO. The bis-xanthate was converted to the dideoxy didehydro analogue **18** in 82% yield by treatment with n-Bu_3SnH, AIBN, in refluxing toluene.[30] The olefin was reduced by catalytic hydrogenation over PtO_2 in 90% yield, and subsequently demethylated with HCl in dioxane at 110 °C in quantitative yield. The demethylated sugar was acetylated in 96% yield using acetic annhydride, triethylamine, and DMAP in acetonitrile to afford the dideoxy carbohydrate precursor **12**[22] as an oil: ^1H NMR ($CDCl_3$) δ 1.95-2.21 (m, 7H), 4.30-4.50 (m, 3H), 6.35 (d, 1H), 7.39-8.07 (m, 5H).

Single Crystal X-ray Structure Determination of 6-(2,3-Didehydro-2,3-dideoxy-ß-D-glycero-pentofuranosyl)-s-triazolo-[1,5-C]-pyrimidin-5-one. X-ray diffraction intensity data were obtained from a colorless triangular plate-like crystal with thickness 0.16mm, three sides measuring 0.33mm x 0.26mm x 0.25mm, mounted on a glass fiber with [1,0,0] perpendicular to the triangular face, on an Enraf-Nonius CAD-4 diffractometer; graphite monochromator, CuKalpha radiation, alpha(ave) = 1.5418; 295K data collection; omega/two theta scan, 0.70 + 0.14tan(theta); background counts, 25% below and above range; peak counting time/background counting time = 2/1; horizontal aperture, 2.4 to 5.0 mm depending on the angle; scan speed, 0.7 to 5.5 deg/min depending on the intensity; reflections collected to 2 theta(max) = 140. Lorentz, polarization and empirical absorption corrections were made [abs.corr (on F) max = 1.00, min = 0.95, mu = 9.7 cm^{-1}]. The three standard reflections used to monitor decay showed a decrease of only 1.6 % so reflections were not corrected for decay. A total of 2119 reflections were measured (+/-h,-k,+/-1) of which only 54 were classed as absent. Net average reflections = 1063 of which 1058 exceeded 3 sigma. Agreement among equivalent reflections observed is 2.2% based on F, and 3.5% based on F*F. Cell dimensions were obtained from 25 reflections used to determine the orientation matrix, a = 8.225 (2), b = 7.349 (2), c+ 9.646 (2) Å, beta = 106.73(2). The cell volume is 523.6 $Å^3$. For Z = 2, FW = 234.24, the calculated density is 1.486 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 of hydrogem atoms gave R(1) = 0.039, R(2) = R(w) = 0.045 (number of parameters = 193). The standard deviation of an observation of unit weight = 1.08. Weights used in the refinement

are those of Killean and Lawrence[31] with P = 0.03, Q = 0.0. The last parameter shift/error was 0.10. The final difference map has a maximum residual electron density = 0.24 el/Å^3. All crystallographic calculations used the SDP set of programs from Enraf-Nonius Corp.

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Supplementary Material Available: Tables of atomic coordinates, bond angles, bond lengths, positional parameters and standard deviations.

References and Notes

1. Presented in part at the 201st National Meeting of the American Chemical Society, Atlanta, Georgia, April 14-19, 1991.
2. AIDS; Broder, S., Ed.; Dekker: New York, 1987.
3. Fauci, A.S. Science **1988**, 239, 617.
4. Mitsuya, H.; Broder, S. Nature **1987**, 325, 773.
5. DeClercq, E. J. Med. Chem. **1986**, 29, 1561.
6. Mitsuya, H.; Broder, S. Proc. Natl. Acad. Sci. USA **1986**, 83, 1911.
7. Mitsuya, H.;Jarrett, R.F.; Matsukura, M.; Veronese, F.; DeVico, A.L.; Sarngadharan, M.G.; Johns, D.G.; Reitz, M.S.; Broder, S. Proc. Natl. Acad. Sci. USA **1987**, 84, 2033.
8. Hao, Z.; Cooney, D.A.; Hartman, N.R.; Perno, C.F.; Fridland, A.; DeVico, A.L.; Sarngadharan, M.G.; Broder, S.; Johns, D.G. Mol. Pharmacol. **1988**, 34, 431.
9. Herdewijn, P.; Pauwels, R.; Baba, M.; Balzarini, J.; De Clercq, E. J. Med. Chem. **1987**, 30, 2131.
10. a. Buenger, G.S.; Nair, V. Synthesis **1990**, 962.
b. Nair, V.; Buenger, G.S. J. Am. Chem. Soc., **1989**, 111, 8502.

11. Chu, C.K.; Ullas, G.V.; Jeong, L.S.; Ahn, S.K.; Doboszewski, B.; Lin, Z.X.; Beach, J.W.; Schinazi, R.F. J. Med. Chem. **1990**, 33, 1553.

12. Barchi, Jr., J.J.; Marquez, V.E.; Driscoll, J.S.; Ford, Jr., H.; Mitsuya, H.; Shirasaki, T.; Aoki, S.; Kelley, J.A. J. Med. Chem. **1991**, 34, 1647.

13. Nair, V.; Buenger, G.S. J. Org. Chem. **1990**, 55, 3695.

14. Seela, F.; Muth, H.-P.; Bindig, U. Synthesis **1988**, 670.

15. Seela, F.; Muth, H.-P. Liebigs Ann. Chem. **1990**, 227.

16. Serafinowski, P. Synthesis **1990**, 411.

17. Brown, D.J.; Shinozuka, K. Aust. J. Chem. **1980**, 33, 1147.

18. Dudycz, L.W.; Wright, G.E. Nucleosides & Nucleotides **1984**, 3, 33.

19. Imazawa, M.; Eckstein, F. J. Org. Chem. **1979**, 44, 2039.

20. Kawakami, H.; Ebata, T.; Koseki, K.; Matsumoto, K.; Matsushita, H.; Naoi, Y.; Itoh, K. Heterocycles **1990**, 31, 2041.

21. Taylor, E.C.; Hendess, R.W. J. Am. Chem. Soc. **1965**, 87, 1980.

22. Farina, V.; Benigni, D.A. Tetrahedron Lett. **1988**, 29, 1239.

23. Okabe, M.; Sun, R.C.; Tam, S. Y.-K.; Todaro, L.J.; Coffen, D.L. J. Org. Chem. **1988**, 53, 4780.

24. Kim, S.-H.; Bartholomew, D.G.; Allen, L.B.; Robins, R.K.; Revankar,G.R.; Dea, P. J. Med. Chem. **1978**, 21, 883.

25. Garrett, E.R.; Mehta, P.J. J. Am. Chem. Soc. **1972**, 94, 8532.

26. Value for the ddG isostere **21** was obtained via extrapolation because of the significant overlap of the absorption maxima in the UV spectrum between the sodium salt of the guanine isostere base and the ddG isostere.

27. Mizuno, Y.; Ikehara, M.; Watanabe, K.A. Chem. Pharm. Bull. **1962**, 10, 647.

28. Singh, K.; Hasan, A.; Pratap, R.; Guru, P.Y.; Bhakuni, D.S. J. Indian Chem. Soc., **1989** 66, 686.

29. Montgomery, J.A.; Thomas, H.J. J. Am. Chem. Soc. **1965**, 87, 5442.

30. Barrett, A.G.M.; Barton, D.H.R.; Bielski, R. J. Chem. Soc., Perkin Trans. I. **1979**, 2378.

31. Killean, R.C.G.; Lawrence, J.L. Acta Cryst. B. **1969**, 25, 1750.