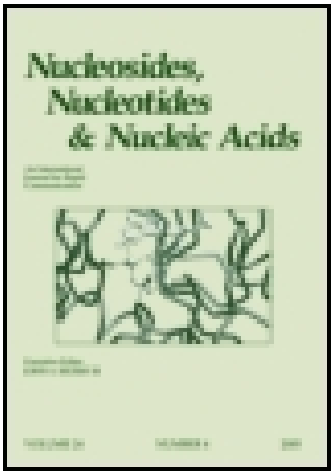

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Synthesis and Conformational Studies of New Purine Isodideoxynucleosides

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SYNTHESIS AND CONFORMATIONAL STUDIES OF NEW PURINE ISODIDEOXYNUCLEOSIDES#

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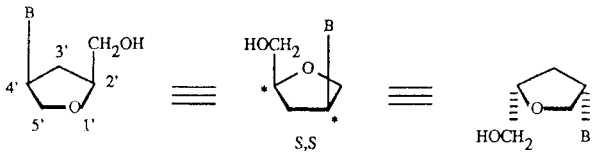
Abstract: The synthesis and NMR conformational correlations (preferred *syn* or *anti*) of new isomeric dideoxynucleosides of potential antiviral interest are described. These compounds are related to the potently active anti-HIV compound, (*S,S*)-isodideoxyadenosine.

INTRODUCTION

One of the goals of antiviral research continues to be focused on the development of modified purine and pyrimidine nucleosides.[1-3] A number of nucleoside derivatives, especially the dideoxynucleosides (ddNs), have been shown to be inhibitors of reverse transcriptase (RT), a key enzyme in the replication of the human immunodeficiency virus (HIV).[1,2,4,5] These "natural" ddNs, where the base is at the anomeric carbon of the carbohydrate portion, are inherently unstable with respect to cleavage of the glycosyl bond, because of the absence of the -I effect of the 2'- and 3'-hydroxyl groups and the involvement of the proximal ring oxygen in the hydrolytic cleavage.[6-7] The molecular design and synthesis of antiviral nucleosides that are stable, both with respect to glycosyl bond cleavage and enzymatic deamination, would be of interest in this area.[8] Recently, regioisomeric analogues of ddNs involving the transposition of the glycosyl bond from the 1'- to the 2'-position (normal nucleoside numbering) have been synthesized (Scheme 1), and several of these isomeric dideoxynucleosides (isoddNs) have been shown to exhibit activity against both HIV-1 and HSV.[8-12] However, there are no reports of base-modified isodideoxynucleosides. This paper describes the synthesis of new base-modified purine isodideoxynucleosides related to the potent anti-HIV active isomeric nucleoside, 4(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol or isoddA (**1**).[13] In addition, the use

 # Dedicated to Dr. Yoshihisa Mizuno on the occasion of his 75th birthday



Scheme 1

of carbon-13 NMR spectral data to infer the preferred glycosyl bond conformation of these isomeric nucleosides in solution is also discussed together with a comparison of the data for the "natural" dideoxynucleosides.

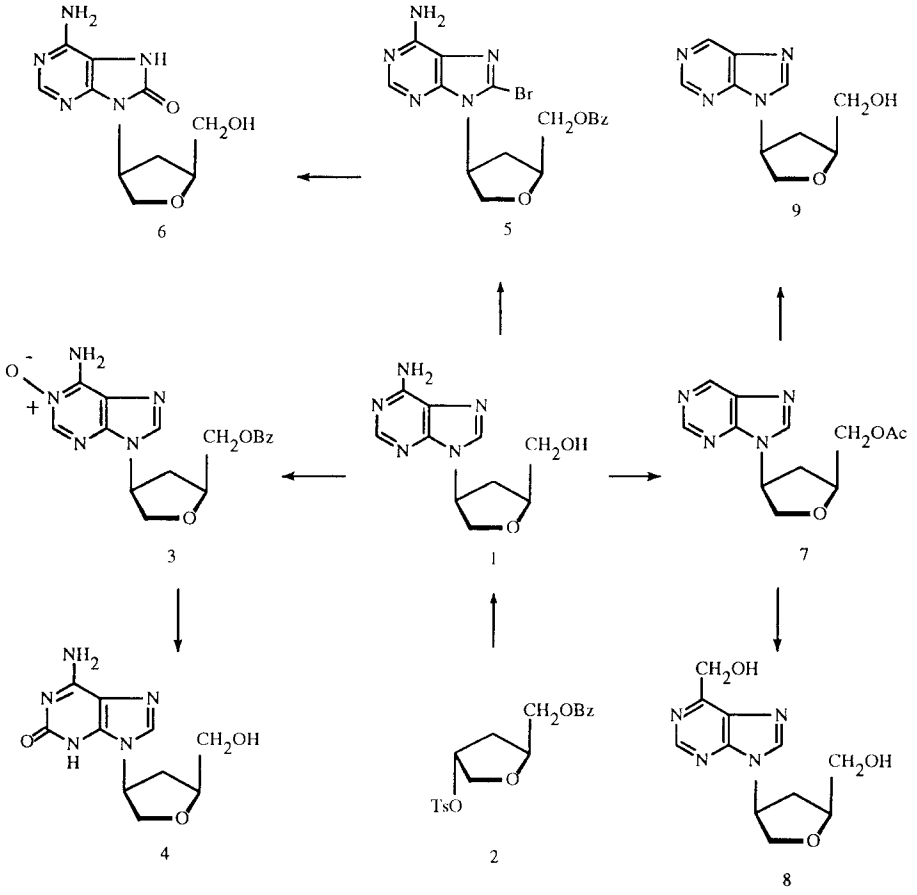
RESULTS AND DISCUSSION

Synthesis

The ribonucleoside isoguanosine bearing the modified base, 2-hydroxyadenine, is one of only a few naturally occurring analogues of guanosine.[14-15] The dideoxy isomeric analogue of isoguanosine [4(S)-(2-hydroxy-6-amino-9H-purin-9-yl)-tetrahydro-2(S)-furanmethanol or isodideoxyisoguanosine] was of interest because this compound could be viewed as the 2-hydroxy derivative of isoddA. A photochemical procedure was chosen for the synthesis of this compound as the parent, isoddA (**1**), prepared by coupling adenine to the modified sugar **2**[8] could be used as a convenient starting material. Oxidation at N-1 of isoddA was accomplished with *m*-chloroperoxybenzoic acid in a biphasic mixture of a NaOAc/HOAc buffered solution of EtOAc. The resulting N-1 oxide **3** exhibited a characteristically strong UV absorption at 232 nm (ε 28,700) which could be taken advantage of in its photochemical rearrangement. Thus, irradiation of the N-1 oxide in water with UV light of maxima 254 nm for 6 h (monitored by the decrease in the peak at 232 nm) produced isodideoxyisoguanosine (**4**) as a white solid in low yields (Scheme 2).

Synthesis of the related 8-hydroxyisoddA **6** (Scheme 2) was accomplished *via* the 8-bromo compound.[16-17] Bromination involved stirring the benzoate of **1** in a buffered solution (NaOAc/AcOH) containing bromine at 50 °C for three days to produce 4(*S*)-(6-amino-8-bromo-9H-purin-9-yl)tetrahydro-2(*S*)-furanmethylbenzoate (**5**). Substitution and deprotection to **6** occurred when compound **5** in dioxane was treated with 5N NaOH. Target compound **6** is the isomeric analogue of 8-hydroxydideoxyadenosine previously synthesized by Buenger and Nair[17] and found to exhibit some anti-HIV activity.

Very few nucleosides with a hydroxymethyl group at the 6-position are known. The known 6-hydroxymethylpurine ribonucleoside is derived from the oxidation of the related compound, 1,6-dihydro-6-hydroxymethylnebularine. This latter compound, the photo-addition product of methanol to 9-(β-D-ribofuranosyl)-9H-purine (nebularine), is a strong reversible inhibitor of adenosine deaminase functioning as a transition-state analogue.[18-19]



Scheme 2

The corresponding 6-hydroxymethylisodideoxypurine nucleoside was prepared as an example of modification of isoddA at the 6-position. The starting material was another 6-modified isonucleoside, **7**, prepared from **1**-OAc by a reductive deamination reaction with n-pentyl nitrite in THF. Irradiation of **7** (254 nm) in dry degassed methanol for 4 h produced the 1,6-dihydro-6-hydroxymethylpurine addition product in 60% yield.[20] Oxidation of this intermediate using phenyltrimethyl ammonium tribromide in methanol (71% yield) followed by deprotection with sodium methoxide (76%) gave the 6-hydroxymethyl product **8.** The deaminated compound **7** could be deprotected to the new purine isodideoxynucleoside (isodideoxynebularine) **9.** 9-(β-D-Ribofuranosyl)-9H-purine (nebularine) and its 2'-deoxy and 2',3'-dideoxy analogues[21] are inhibitors of adenosine deaminase.[22-23] Nebularine, for example, also has antileukemic activity.[24-26]

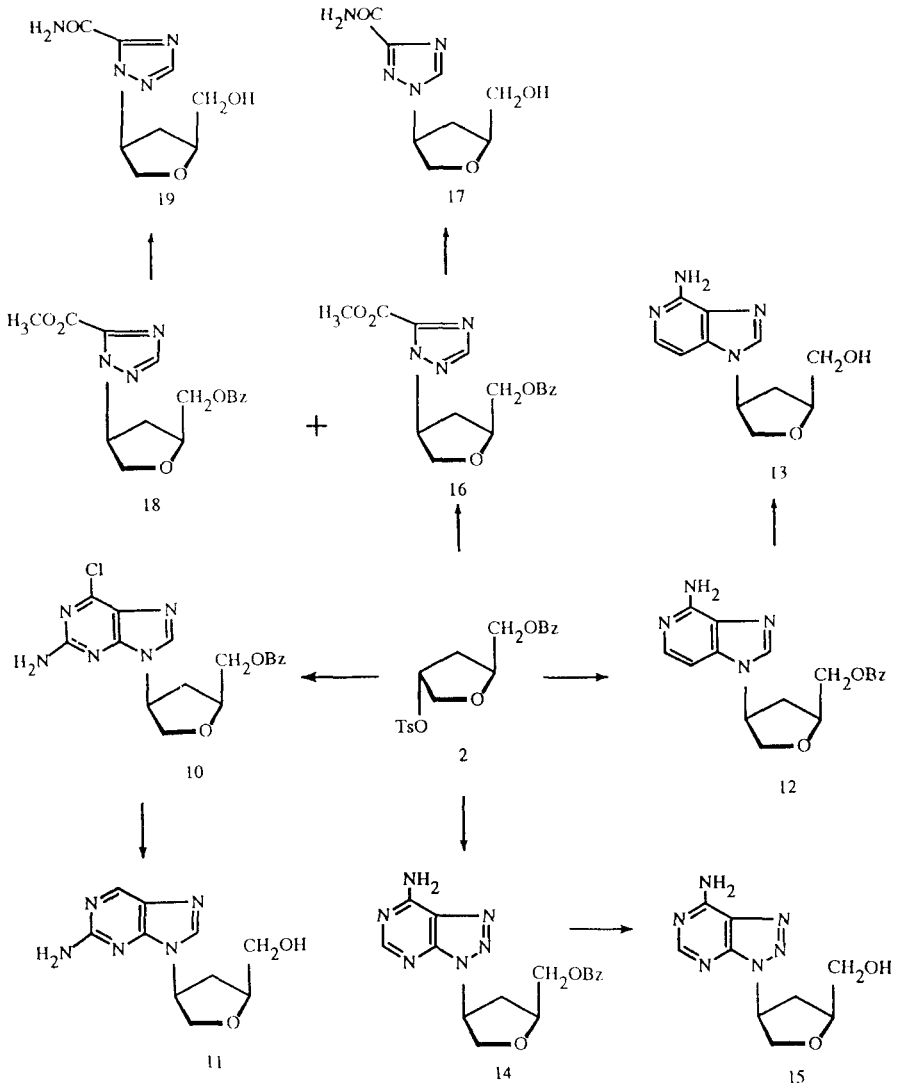
2-Aminopurine isodideoxynucleoside **11** [4(S)-(2-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol] is an isomer of isoddA which is of potential interest as a pro-drug of isoddG through the action of cellular enzymes (e.g. xanthine oxidase). Compound **11** was synthesized by first coupling the modified sugar **2** with 2-amino-6-chloropurine to produce **10** (Scheme 3). This coupled product was reductively dehalogenated using 10% Pd/C under a hydrogen atmosphere in a NaOAc buffered solution. Photochemical reductive dehalogenation of the corresponding 6-iodo compound is also possible using a procedure previously described by Nair and co-workers.[27] Deprotection of the dehalogenated compound with sodium methoxide in methanol produced the desired product **11.**

In addition to modifications of the adenine ring at the 2, 6, and 8 positions of isodideoxyadenosine, alterations involving removal or addition of nitrogen were also investigated. Both 8-azadideoxyadenosine and 3-deazadideoxyadenosine have been synthesized and are of antiviral interest.[28] The modified purines, 3-deazaadenine and 8-azaadenine, were coupled to 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol **2** to produce the benzoylated adducts **12** and **14** which were deprotected using sodium methoxide in methanol to produce the target compounds **13** and **15** (Scheme 3). The characteristic UV absorbance of 276 nm of the 9-substituted 8-azaadenosine reported in the literature[29] was also observed for the iso 8-aza analog **15**.

Isomeric dideoxynucleoside analogues related to ribavirin have also been synthesized as potential antiviral agents. Ribavirin, synthesized by Robins and coworkers,[30] was discovered to have broad spectrum antiviral activity against DNA and RNA viruses.[31,32] The synthesis of the ribavirin base, 1,2,4-triazole-3-methylcarboxylate, was carried out by a procedure by Chipen and Grinshtein.[33] Coupling of the triazole with 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol produced two structural isomers, 4(*S*)-(3-carboxymethyl-1H-1,2,4-triazol-1-yl)tetrahydro-2(*S*)-furanmethylbenzoate (**16,** 24% yield) and 4(*S*)-(5-carboxymethyl-1H-1,2,4-triazol-1-yl)tetrahydro-2(*S*)-furanmethyl-benzoate (**18,** 19% yield), which were easily separated on silica gel preparative layer chromatography with 2% MeOH/$CHCl_3$ (Scheme 3). Compounds **16** and **18** were treated with saturated methanolic ammonia to yield the desired products, 4(*S*)-(3-carboxamido-1H-1,2,4-triazol-1-yl)tetrahydro-2(*S*)-furanmethanol (**17**) and 4(*S*)-(5-carboxamido-1H-1,2,4-triazol-1-yl)tetrahydro-2(*S*)-furanmethanol (**19**), respectively. The ^1H NMR chemical shift of the triazole ring proton of the 3-carboxamide (**17**) appeared at 8.68 ppm which is distinctly different from the chemical shift of this proton in the 5-carboxamide (**19**) (δ 8.07 ppm), and this is consistent with the literature values for related compounds.[30]

Conformational Analyses

In addition to strategic modifications of the base and sugar moieties, the conformation of the glycosyl bond and sugar ring puckering of nucleosides have been suggested to be important factors in determining biological activity.[34] The crystal structures of ddA and other active anti-HIV agents have been reported.[35-37] While ddA



Scheme 3

exists in the *anti* conformation in the solid state, the data on the preferred conformation of ddA and other ddNs in solution are of considerable interest. Several methods have been used to study the orientation of the glycosyl bond of nucleosides in solution such as circular dichroism,[38] pD studies,[39] fast Fourier transform ^{1}H-(^{31}P) NMR,[40] and proton and carbon-13 NMR spectroscopy.[41-42] These studies have shown that purine nucleosides with bulky C-8 substituents prefer the *syn* conformation while most other purine nucleosides prefer the *anti* conformation.

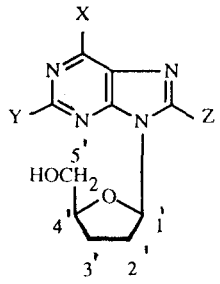
The most practical procedure for determining the preferred conformations of purine nucleoside analogues in solution is by carbon-13 NMR spectroscopy. A study with purine ribonucleosides found that the C-2' carbon resonance of purine ribonucleosides in the *syn* conformation was found to be shifted upfield by 2-3 ppm when compared to the C-2' carbon resonance of a nucleoside in the *anti* conformation.[41] In addition, the difference in chemical shifts of the C-2' and C-3' carbon signals can be correlated to the preferred glycosyl bond conformation. A difference of 1.5 ppm or less (C-2' ppm minus C-3' ppm) correlates with a *syn* conformation while a difference of more than 2.3 ppm suggests a preference for the *anti* conformation. Interestingly, a review of the carbon-13 NMR spectral data of dideoxynucleosides in DMSO-d_6 indicates that correlations also exist to suggest preferred conformations in these compounds (Table 1). The C-2' carbon resonance of purine ddNs in the *syn* conformation is found to be shifted upfield by 2-3 ppm when compared to the C-2' carbon resonances of these nucleosides in the *anti* conformation. A chemical shift difference of 3.0 ppm or less (C-2' - C-3') suggests a preferred *syn* conformation while a difference of more than 5.5 ppm suggests a greater population in the *anti* conformation. Note for example that the C-8 substituted purines which are presumed to prefer the *syn* conformation, all show carbon-13 resonances of C-2' that are shifted upfield. The preferred conformation of ddA in solution found to be *anti* by carbon-13 NMR (Table 1), is consistent with the X-ray crystallographic data for ddA.[36]

The glycosyl bond conformations of purine isodideoxynucleosides may also be predictable using carbon-13 NMR data. It should be noted that for purposes of comparison, the numbering around the sugar ring of isoddNs (Table 2) is maintained the same as for the "natural" dideoxynucleosides and therefore the base in the isoddNs is now attached to C-2'. The carbon-13 NMR data in DMSO-d_6 for a number of isoddNs described in this article and elsewhere by us[8] have been compiled (Table 2). Although it is not possible to look at differences in chemical shifts between two resonances like the examples of the ribonucleosides and the ddNs, it is possible to suggest trends based on chemical shift data. In the examples studied, a chemical shift for C-1' >71.5 ppm and for C-3' $\geq$ 34 ppm is suggestive of a preferred *anti* conformation whereas a chemical shift for C-1' < 69 ppm and for C-3' $\leq$ 32 ppm is suggestive of a greater population in the *syn* conformation. The preferred conformation of isoddA in solution found to be *anti* by carbon-13 NMR (Table 2), is consistent with the X-ray crystallographic data for isoddA.[8] In addition, the C-8 substituted purine compound **6** which is presumed to be in the *syn* conformation shows the carbon-13 resonance of C-1' at 67.8 ppm and that for C-3' at 32.1 ppm, both shifted upfield compared to the *anti* compounds. The correlation for the iso-8-azaadenosine derivative **15** is less clear cut although the data seem to indicate a preferred high *anti* conformation. 8-Azapurine nucleosides are known to adopt an extreme (or high) *anti* conformation.[47]

Summary

In summary, we have synthesized a series of new isomeric dideoxynucleosides related to the anti-HIV compound, 4(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furan-

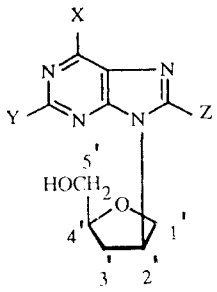
Table 1. Carbon-13 NMR Data[a] of ddNs (C-1'-C-5' only)[17, 43-46]



ddN	X	Y	Z	C-1'	C-2'	C-3'	C-4'	C-5'	*syn/anti*
ddA	NH_2	H	H	84.9	32.2	26.2	82.1	63.4	*anti*
ddI	OH	H	H	84.9	32.6	25.9	82.5	63.1	*anti*
ddG	OH	NH_2	H	83.7	32.0	25.7	81.7	62.9	*anti*
ddN	H	H	H	84.4	31.7	25.4	82.1	62.5	*anti*
ddN	OCH_3	H	H	84.6	31.8	25.4	82.0	62.5	*anti*
ddN	OCH_3	CH_2CH_3	H	84.6	31.8	25.8	82.0	62.9	*anti*
ddN	NH_2	C≡N	H	84.7	32.0	25.4	82.3	62.6	*anti*
ddN	NH_2	CH_2CH_3	H	84.5	31.6	26.0	81.5	63.3	*anti*
ddN	NH_2	SCH_3	H	84.2	31.5	26.0	81.7	63.1	*anti*
ddN	NH_2	NH_2	H	83.8	31.6	25.4	81.6	62.6	*anti*
ddN	NH_2	CF_3	H	84.5	31.8	25.7	82.1	62.8	*anti*
ddN	NH_2	H	OH	82.3	28.0	27.0	80.6	64.1	*syn*
ddN	NH_2	H	NH_2	83.9	29.0	26.0	79.5	63.1	*syn*
ddN	NH_2	H	OCH_3	83.3	28.9	27.0	81.1	64.0	*syn*
ddN	NH_2	H	SCH_3	85.3	29.1	26.9	81.1	63.9	*syn*
ddN	NH_2	H	OCH_2Ph	83.1	28.8	26.9	81.0	63.9	*syn*

[a]All spectra run in DMSO with TMS reference.

Table 2. Carbon-13 NMR data[a] of IsoddNs (sugar carbons only)[8]



IsoddN	X	Y	Z	C-1'	C-2'	C-3'	C-4'	C-5'	*syn/anti*
isoddA	NH_2	H	H	71.8	53.9	33.9	79.6	62.4	*anti*
isoddI	OH	H	H	71.9	54.2	34.1	79.6	62.4	*anti*
isoddG	OH	NH_2	H	72.0	53.4	34.0	79.6	62.5	*anti*
4	NH_2	OH	H	71.9	53.2	33.8	79.5	62.4	*anti*
11	H	NH_2	H	71.8	53.2	33.7	79.5	62.4	*anti*
9	H	H	H	71.7	54.2	33.7	79.6	62.3	*anti*
8	CH_2OH	H	H	71.8	54.3	33.8	79.6	62.2	*anti*
13				71.6	55.6	34.1	79.9	62.4	*anti*
15				70.6	57.4	33.3	79.7	63.1	*anti*
6	NH_2	H	OH	68.7	51.4	31.6	79.8	63.8	*syn*
5	NH_2	H	Br	68.6	57.2	31.7	77.1	65.5	*syn*
Deprotected **5**	NH_2	H	Br	67.8	56.6	32.1	79.8	63.3	*syn*

[a]All spectra run in DMSO with TMS reference.

methanol [(*S*,*S*)-isoddA]. The preferred glycosidic bond conformations of these compounds as *anti* or *syn* have been studied by carbon-13 NMR chemical shift correlations and comparisons with the data for "natural" dideoxynucleosides have been made. X-ray crystallographic data provide support for the correlations. These new isomeric dideoxynucleosides, however, showed low or no activity toward HIV-1 in MT-4 cells. Antiviral studies against other viruses are in progress.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover open stage melting point apparatus and are uncorrected. The ^{1}H NMR were recorded on either a Bruker MSL 300, AC 300, or a WM 360 instrument 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. Infrared spectra were recorded on a Mattson Cygnus 25 Fourier transform instrument. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Low resolution electron impact (EI) mass spectra were recorded on a VG TRIO-1 single quadrupole GC/MS and EI-DIP system operating at 70 eV. Lyophilizations were performed with a Virtis Freezemobile 3 unit. Preparative layer chromatography plates were made from E. Merck PF_{254} silica gel. TLC plates were visualized by ultraviolet light 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. Common reagents were ACS reagent grade or better.

4(S)-(2-Hydroxy-6-amino-9H-purin-9-yl)-tetrahydro-2(S)-furanmethanol (4). A mixture of isodideoxyadenosine (**1**) (0.691 g, 2.94 mmol) and 3-chloroperoxybenzoic acid (1.88 g, 10.86 mmol) was stirred for 24 h at room temperature in a NaOAc/HOAc buffered solution of EtOAc (25 mL). The residue was purified by column chromatography with 20% MeOH/$CHCl_3$ as the eluting solvent to afford 1.576 g (78%) of 4(S)-(1-N-oxide-6-amino-9H-purin-9-yl)-tetrahydro-2(S)-furanmethanol **3** as a white solid; mp 225°C; $[\alpha]_D^{25}$ -37.7° (c 0.10, MeOH); UV (H_2O) λ_{max} 231.5 nm (ε 28700), 261 nm (ε 6700); ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 2.09 (m, 1H), 2.59 (m, 1H), 3.57 (m, 2H), 4.00 (m, 3H), 4.92 (br, 1H), 5.17 (m, 1H), 8.10 (br s, 2H), 8.41 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz) δ 33.8, 54.2, 62.2, 71.8, 79.6, 118.3, 141.8, 141.9, 142.9, 148.1. A solution of **3** (0.451 g, 1.79 mmol) in water (70 mL) was irradiated at 254 nm for 6 h at which time the solvent was removed and the residue was purified by preparative layer chromatography with 25% MeOH/$CHCl_3$ as the developing solvent and by HPLC with water as solvent to afford 0.071 g (15.7%) **4** as a white solid: mp 169-171 °C; $[\alpha]_D^{25}$

- 24.4° (c 0.10, MeOH); UV λ_{max} (H_2O) 291 nm (ε 9500), 245 nm (ε 6500), 213 nm (ε 19300); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 1.97 (m, 1H), 2.49 (m, 1H), 3.56 (m, 2H), 3.88 (m, 3H), 4.91 (m, 2H, 1H exchangeable), 7.52 (br 2H), 7.88 (s, 1H), 10.5 (br, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz): δ 33.8, 53.2, 62.4, 71.9, 79.5, 108.9, 137.0, 152.1, 156.4, 169.0. Anal. Calcd for $C_{10}H_{13}N_5O_3$.1.5 H_20: C, 43.16; H, 5.80; N, 25.17. Found: C, 43.00; H, 5.83; N, 25.12.

4(S)-(6-Amino-8-hydroxy-9H-purin-9-yl)-tetrahydro-2(S)-furanmethanol (6). A mixture of 5'-benzoylated-isoddA (0.473 g, 1.39 mmol) and bromine (2.34 mL, 4.60 mmol) in a buffered solution of NaOAc/AcOH was stirred for 3 days at 50 °C. Sodium bisulfite was then added and solvents were removed and the residue was purified by column chromatography (5% MeOH/$CHCl_3$) to yield 0.281 g (48%) of 4(S)-(6-amino-8-bromo-9H-purin-9-yl)tetrahydro-2(S)-furanmethylbenzoate (**5**): UV (EtOH) λ_{max} 265 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (m, 1H), 3.0 (m, 1H), 4.15 (m, 1H), 4.54 (m, 2H), 4.65 (m, 2H), 5.31 (m, 1H), 5.72 (br s, 2H), 7.43 (m, 2H), 7.55 (m, 1H), 8.11 (m, 2H), 8.16 (s, 1H). To a solution of **5** (0.240 g, 0.574 mmol) in dioxane (10 mL) was added 5N NaOH (15 mL). The mixture was stirred for 4 days at which time the mixture was neutralized with 2N HCl and the residue was purified by column and preparative layer chromatography (15% MeOH/$CHCl_3$) to produce 0.047 g (32%) of **6** as a white hygroscopic solid: UV (H_2O) λ_{max} 270 nm (ε 9800); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.18 (m, 1H), 2.39 (m, 1H), 3.52 (m, 2H), 3.88 (t, J = 8.2 Hz, 1H), 4.00 (m, 1H), 4.09 (t, J = 8.2 Hz, 1H), 4.75 (br t, 1H), 4.95 (m, 1H), 6.45 (s, 2H), 8.01 (s, 1H), 10.45 (br, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz) δ 31.6, 51.4, 63.8, 68.7, 79.8, 103.1, 147.0, 147.4, 150.5, 151.8. Anal. Calcd for $C_{10}H_{13}N_5O_3$. C, 47.81; H, 5.18; N, 27.89. Found: C, 47.39; H, 5.09; N, 27.51.

4(S)-(6-Hydroxymethyl-9H-purin-9-yl)-tetrahydro-2(S)-furanmethanol (8). A solution of 4(S)-(9H-purin-9-yl)tetrahydro-2(S)-furanmethylacetate (**7**) (1.329 g, 5.07 mmol) in dry degassed MeOH (75 mL) was irradiated at 254 nm for 4 h at which time the solvent was removed and the residue was purified by column chromatography with 10% MeOH/$CHCl_3$ to produce 0.892 g (60%) of 4(S)-(6-hydroxymethyl-9H-1,6-dihydropurin-9-yl)tetrahydro-2(S)-furanmethylacetate: UV (EtOH) λ_{max} 296 nm ; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.93 (m, 1H), 2.02 (s, 3H), 2.47 (m, 1H), 3.40 (m, 1H), 3.58 (m, 1H), 3.89 (m, 2H), 4.14 (m, 3H), 4.78 (m, 3H), 6.90 (d, J = 2.8 Hz, 1H), 7.35 (s, 1H), 7.56 (br, 1H). A solution of 4(S)-(6-hydroxymethyl-9H-1,6-dihydropurin-9-yl)tetrahydro-2(S)-furanmethylacetate (0.275 g, 0.935 mmol) and phenyltrimethyl ammonium tribromide (0.387 g, 1.03 mmol) in MeOH (20 mL) was stirred at room temperature for 5 min at which time a solution of sodium bisulfite was added and the solvents evaporated. The residue was purified by column chromatography (5% MeOH/$CHCl_3$) to produce 0.193 g (71%) of the acetylated isodideoxynucleoside: UV (EtOH) λ_{max} 263 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (m, 1H), 2.78 (m, 1H), 2.05 (s, 3H), 4.11 (dd, J = 5.6, 10.4 Hz, 1H), 4.40 (m, 1H),

4.28 (m, 3H), 5.02 (s, 3H, 1H exchangeable), 5.42 (m, 1H), 8.41 (s, 1H), 8.96 (s, 1H). To a solution of the acetylated isodideoxynucleoside (0.098 g, 0.335 mmol) in MeOH (10 mL) was added NaOMe (0.054 g, 1.01 mmol). The reaction mixture was stirred for 3 h at room temperature and then neutralized with 2N NaOH and the dried residue was purified by preparative layer chromatography (18% MeOH/$CHCl_3$) to produce 0.064 g (76%) of the target compound **8**: mp 122-124 °C; $[\alpha]_D^{25}$ -22.8° (c. 0.16, MeOH); UV (MeOH) λ_{max} 211 (ε 8600), 263 (ε 7700); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.13 (m, 1H), 2.63 (m, 1H), 3.60 (m, 2H), 4.03 (m, 2H), 4.09 (dd, J = 3.2, 9.7 Hz, 1H), 4.89 (s, 2H), 4.94 (br s, 1H), 5.34 (m, 1H), 5.39 (br s, 1H), 8.67 (s, 1H), 8.88 (s, 1H); ^{13}C (Me_2SO-d_6, 75.48 MHz) δ 33.8, 54.3, 59.9, 62.2, 71.8, 79.6, 130.9, 144.1, 150.8, 151.5, 159.2. Anal. Calcd for $C_{11}H_{14}N_4O_3$: C, 52.80; H, 5.60; N, 22.40. Found: C, 52.33; H, 5.69; N, 21.98.

4(S)-(9H-Purin-9-yl)tetrahydro-2(S)-furanmethanol (9). To a solution of the 5'-OAc of isoddA (2.26 g, 8.15 mmol) in THF (25 mL) *n*-pentyl nitrite (24.3 mL, 180.9 mmol) was added over 3 days and the mixture was stirred at 50 °C. The solvents were removed and the residue was purified by column chromatography (2% MeOH/$CHCl_3$) to yield 4(S)-(9H-purin-9-yl)tetrahydro-2(S)-furanmethylacetate (**7**) (1.32 g, 4.52 mmol, 55.4%). The acetylated 2'-isodideoxynebularine analogue (**7**) (0.137 g, 0.521 mmol) was deprotected with NaOMe (0.084 g, 1.56 mmol) in MeOH (20 mL) in 3 h at room temperature. The isonebularine dideoxynucleoside was purified by HPLC with 5% EtOH/water to yield 0.087 g (76.2%) of the target compound **9**: mp 90-91 °C; $[\alpha]_D^{25}$ -17.3° (c 0.32, MeOH); UV (H_2O) λ_{max} 262 nm (ε 6100); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.15 (m, 1H), 2.63 (m, 1H), 3.60 (m, 2H), 4.02 (m, 2H), 4.11 (m, 1H), 4.95 (br s, 1H), 5.34 (m, 1H), 8.73 (s, 1H), 8.94 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz) δ 33.7, 54.2, 62.3, 71.7, 79.6, 133.6, 145.1, 147.8, 150.9, 151.8. Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.55; H, 5.45; N, 25.45 Found: C, 54.42; H, 5.58; N, 24.86.

4(S)-(2-Amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (11). A solution of **2** (0.887 g, 2.36 mmol), 2-amino-6-chloropurine (0.599 g, 3.53 mmol), 18-crown-6 (0.622 g, 2.36 mmol), K_2CO_3 (0.651 g, 4.71 mmol) and DMF (15 mL) was stirred at 70 °C overnight. The residue was purified by column chromatography (3% MeOH/$CHCl_3$) to afford 0.446 g (58.1%) of 4(S)-(2-amino-6-chloro-9H-purin-yl)tetrahydro-2(S)-furanmethylbenzoate **10** as an oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.19 (m, 1H), 2.73 (m, 1H), 4.12 (dd, J = 6.2, 10.1 Hz, 1H), 4.27 (dd, J = 3.7, 10.1 Hz, 1H), 4.57 (m, 2H), 4.43 (m, 1H), 5.05 (br s, 2H), 7.43 (m, 2H), 5.12 (m, 1H), 7.54 (m, 1H), 7.94 (s, 1H), 7.97 (m, 2H). A solution of **10** (0.338 g, 0.907 mmol), sodium acetate (0.171 g, 2.08 mmol), and 10% Pd/C (0.05 g) in EtOH (25 mL) was shaken under hydrogen (40 psi) overnight, at which time the Pd/C was filtered off and the residue was purified by column chromatography (3% MeOH/$CHCl_3$) to afford 0.257 g (83%) of dehalogenated product: UV (EtOH) λ_{max} 308 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.19 (m, 1H), 2.75 (m, 1H),

4.12 (dd, J = 6.2, 10.0 Hz, 1H), 4.26 (dd, J = 3.9, 10.0 Hz, 1H), 4.41 (m, 1H), 4.57 (m, 2H), 5.07 (br s, 2H), 5.18 (m, 1H), 7.42 (m, 2H), 7.55 (m, 1H), 7.94 (s, 1H), 8.01 (m, 2H), 8.65 (s, 1H). A solution of the dehalogenated product (0.220 g, 0.648 mmol) and NaOMe (0.175 g, 3.24 mmol) in MeOH (10 mL) was stirred for 2 h at room temperature and then neutralized with 1N HCl and the residue was purified by preparative layer chromatography ($MeOH/CHCl_3$) to give a very hygroscopic solid **11** (0.142 g, 93%): UV (EtOH) λ_{max} 303 nm (ε 6400), 242 nm (ε 4700); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.04 (m, 1H),2.53 (m, 1H), 3.56 (m, 2H), 3.97 (m, 3H), 4.91 (br s, 1H), 5.06 (m, 1H), 6.48 (br s, 2H), 8.19 (s, 1H), 8.56 (s, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz): δ 33.7, 53.2, 62.4, 71.8, 79.5, 126.8, 140.5, 149.0, 152.7, 160.4. Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 50.06; H, 5.53; N, 29.79. Found: C, 50.11; H, 5.68; N, 29.24.

4(S)-(4-Amino-1H-imidazo[4,5-c]pyrimidin-1-yl)-tetrahydro-2(S)-furan-methanol (13). A solution of 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol, (**2**), (0.669 g, 1.77 mmol), 3-deazaadenine phosphate (0.618 g, 2.66 mmol), 18-crown-6 (1.41 g, 5.33 mmol) and K_2CO_3 (1.47 g, 10.66 mmol) in DMF (20 mL) was stirred at 70 °C for 20 h at which time the solvent was removed and the residue was purified by silica gel column chromatography to give benzoylated 3-deaza analogue (**12**): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (m, 1H), 2.73 (m, 1H), 4.15 (dd, J = 6.7, 10.4 Hz, 1H), 4.35 (m, 2H), 4.44 (dd, J = 5.4, 12.0 Hz, 1H), 4.65 (dd, J = 3.1, 12.0 Hz, 1H), 5.04 (m, 1H), 6.86 (d, J = 5.9 Hz, 1H), 7.41 (m, 2H), 7.56 (m, 1H), 7.76 (d, J = 6.0 Hz, 1H), 7.90 (s, 1H), 7.97 (m, 2H). Deprotection of **12** with NaOMe in MeOH and then purification by preparative layer chromatography with 10% $MeOH/CHCl_3$ gave 0.069 g (17% for two steps) of the 3-deaza analogue (**13**) mp: 199-201 °C; $[\alpha]_D^{25}$ -18.3° (c 0.087, MeOH); UV (H_2O) λ_{max} 266 nm (ε 7900); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.00 (m, 1H), 2.54 (m, 1H), 3.57 (m, 2H), 4.00 (m, 3H), 4.91 (t, J = 5.7 Hz, 1H), 5.15 (m, 1H), 6.11 (br s, 2H), 6.89 (d, J = 5.8 Hz, 1H), 7.66 (d, J = 5.8 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz) δ 34.1, 55.6, 62.4, 71.6, 79.9, 97.0, 126.8, 137.5, 140.1 (2), 152.4. Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.39; H, 6.02; N, 23.92. Found: C, 56.20 ; H, 5.82; N; 23.56.

4(S)-(7-Amino-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-tetrahydro-2(S)-furan-methanol (15). A solution of **1** (0.767 g, 2.04 mmol), 8-azaadenine (0.277 g, 3.06 mmol), 18-crown-6 (1.08 g, 2.04 mmol), and K_2CO_3 (0.563 g, 4.08 mmol) in DMF (20 mL) was stirred at 70 °C for 20 h and then the solvent was removed and the residue was purified by silica gel column chromatography with 1% $MeOH/CHCl_3$ to produce both the 9- (**14**) and 8- coupled isodideoxynucleoside analogues. The 9-isodideoxynucleoside analogue (**14**) had a slightly higher R_f than the 8 substituted isonucleoside and gave 0.273 g (39%) of product: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65 (m, 2H), 4.28 (dd, J = 6.7, 9.5 Hz, 1H), 4.49 (dd, J = 5.0, 9.5 Hz, 1H), 4.54 (m, 1H), 4.62 (m, 2H), 5.54 (m, 1H), 6.75 (br s, 2H), 7.41 (m, 2H), 7.54 (m, 1H), 8.05 (m, 2H), 8.38 (s, 1H). The protected isonucleoside (**14**) (0.273 g,

0.803 mmol) was stirred with NaOMe (0.043 g, 0.80 mmol) in MeOH (40 mL) for 4 h and the residue was purified by silica gel column chromatography and preparative layer chromatography with 5% MeOH/$CHCl_3$ followed by HPLC with 5% EtOH/water to give 0.081 g (43%) of the target molecule (**15**): mp 201-202 °C; $[\alpha]_D^{25}$ -34.9° (c 0.13, MeOH); UV (H_2O) λ_{max} 276 (ε 11500); ^1H NMR (Me_2SO-d_6, 300 MHz) δ 2.44 (m, 1H), 2.63 (m, 1H), 3.55 (m, 2H), 4.05 (m, 1H), 4.13 (dd, J = 6.7, 9.2 Hz, 1H), 4.21 (dd, J = 4.8, 9.2 Hz, 1H), 4.81 (br t, 1H), 5.46 (m, 1H), 8.38 and 8.07 (s, 2H, exchangeable), 8.29 (s, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz) δ 33.3, 57.4, 63.1, 70.6, 79.7, 124.2, 148.7, 156.2, 156.5. Anal. Calcd for $C_9H_{12}N_6O_2$: C, 45.76; H, 5.12; N, 35.57. Found: C, 45.66; H, 5.04; N; 35.76.

4(S)-(3-Carboxamido-1H-1,2,4-triazol-1-yl)tetrahydro-2(S)-furanmethanol (17). A solution of 2-*O*-(*p*-toluenesulfonyl)-3-deoxy-5-*O*-benzoyl-D-ribitol (**2**) (0.592 g, 1.77 mmol), 3-methylcarboxylate-1,2,4-triazole (0.30 g, 2.36 mmol), 18-crown-6 (0.468 g, 1.77 mmol), and K_2CO_3 (0.489 g, 3.54 mmol) in DMF (20 mL) was stirred at 70 °C overnight at which time the solvents were removed and the residue was purified by column and preparative layer chromatography (2% MeOH/$CHCl_3$, multiple elution for PLC) to give the separted isomers: The lower band was 4(S)-(3-methylcarboxylate-1H-1,2,4-triazol-1-yl)-tetrahydro-2(S)-furanmethylbenzoate (**16**) (0.145 g, 0.437 mmol, 25%) and the top band was 5-methylcarboxylate (**18**) (0.116 g, 0.349 mmol, 20%). 3-Methylcarboxylate (**16**): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (m, 1H), 2.79 (m, 1H), 4.00 (s, 3H), 4.14 (dd, J = 6.0, 10.3 Hz, 1H), 4.33 (dd, J = 3.3 10.3 Hz, 1H), 4.45 (m, 2H), 4.58 (m, 1H), 5.15 (m, 1H), 7.44 (m, 2H), 7.57 (m, 1H), 7.99 (m, 2H), 8.32 (s, 1H). 5-Methylcarboxylate analogue (**18**): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (m, 1H), 2.71 (m, 1H), 4.02 (s, 3H), 4.22 (m, 2H), 4.46 (m, 1H), 4.60 (m, 2H), 5.99 (m, 1H), 7.44 (m, 2H), 7.56 (m, 1H), 7.98 (s, 1H), 8.09 (m, 2H). A solution of the 5-methylcarboxylate analogue (**18**) (0.116 g, 0.349 mmol) in MeOH (20 mL) was saturated with NH_3. The solution was kept at RT for 20 h at which time the solvent was removed and the residue was purified by preparative layer chromatography with 10% MeOH/$CHCl_3$ to yield 0.05 g (93%) the target molecule **19**: mp: 97 °C; $[\alpha]_D^{25}$ -19.0° (c. 0.14, MeOH); UV (H_2O) λ_{max} 221 nm (ε 7770); ^1H NMR (Me_2SO-d_6, 300 MHz): δ 2.15 (m, 1H), 2.45 (m, 1H), 3.53 (m, 2H), 3.89 (m, 1H), 3.98 (dd, J = 4.8, 9.2 Hz, 2H), 4.76 (t, J = 5.8 Hz, 1H), 5.97 (m, 1H), 7.97 (br s, 1H), 8.07 (s, 1H), 8.18 (br s, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz): δ 34.1, 59.2, 63.1, 71.6, 79.9, 146.5, 149.5, 159.0. Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.66; N, 26.41. Found: C, 44.88; H, 5.46; N, 26.04. A solution of 3-methylcarboxylate analogue (**16**) (0.145 g, 0.437 mmol) in MeOH (20 mL) was saturated with NH_3. The solution was kept at room temperature for 20 h at which time the solvent was removed and the residue was purified by preparative layer chromatography with 10% MeOH/$CHCl_3$ to yield 0.069 g (95%) of the target molecule (**17**): mp 124-126 °C; $[\alpha]_D^{25}$: -29.6° (c. 0.29, MeOH); UV (H_2O) λ_{max} 215.5 nm (ε 7774); ^1H NMR (Me_2SO-d_6, 300 MHz): δ 2.11 (m, 1H), 2.53 (m,

1H), 3.50 (m, 2H), 3.98 (m, 3H), 4.84 (br, 1H), 5.14 (m, 1H), 7.73 and 7.54 (d, 2H, amide), 8.68 (s, 1H); ^{13}C NMR (Me_2SO-d_6, 75.48 MHz): δ 33.8, 59.9, 62.6, 71.4, 79.6, 144.0, 155.7, 160.5; Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.66; N, 26.41. Found: C, 44.79; H, 5.76; N, 26.02.

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REFERENCES

1. a. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 7096-7100. b. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1911-1915. c. Mitsuya, H.; Jarrett, R. F.; Matsukura, M.; Veronese, F. D. M.; DeVico, A. L.; Sarngadharan, M. G.; Johns, D. G.; Reitz, M. S.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 2033-2037. d. Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J. P.; Johns, D. G.; Broder, S. *Science*, **1989**, *245*, 412-415.
2. De Clercq, E. *Nucleosides & Nucleotides* **1994**, *13*, 1271-1295.
3. a. Coates, J. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202-205. b. Liang, C.; Lee, D. W.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1995**, *60*, 1546-1553. c. Schinazi, R. F.; Mead, J. R.; Feorino, P. M. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 963-990.
4. Ahluwalia, G.; Cooney, D. A.; Mitsuya, H.; Fridland, A.; Flora, K. P.; Hao, Z.; Dalal, M.; Broder, S.; Johns, D. G. *Biochem. Pharmacol.* **1987**, *36*, 3797-3800.
5. Chen, M. S.; Suttman, R. T.; Papp, E.; Cannon, P. D.; McRoberts, M. J.; Bach, C.; Copeland, W. C.; Wang, T. S-F. *Biochemistry* **1993**, *32*, 6002-6010.
6. York, J. L. *J. Org. Chem.* **1981**, *46*, 2171-2173.
7. Nair, V.; Buenger, G. S. *J. Org. Chem.* **1990**, *55*, 3695-3697.
8. Bolon, P. J.; Sells, T. B.; Nuesca, Z. M.; Purdy, D. F.; Nair, V. *Tetrahedron* **1994**, *50*, 7747-7764.
9. Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951-7953.
10. Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1992**, *35*, 2347-2354.
11. Zahler, R.; Goodfellow, V. S.; Ahmad, S. Eur. Pat. Appl. EP 464,769; *Chem. Abstr.* **1992**, *116*, 194800.
12. Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Rubin, B.; Slusarchyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari,

A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221-1229.

13. Nair, V. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K.; Baker, D. C., Eds.; Plenum Press: New York, 1993; pp. 127-140.
14. Nair, V.; Young, D. A. *J. Org. Chem.* **1985**, *50*, 406-408.
15. Kazimierczuk, Z.; Shugar, D. *Acta Biochimica Polonica* **1973**, *20*, 395-402.
16. Holmes, R. E.; Robins, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 1242-1245.
17. Buenger, G. S.; Nair, V. *Synthesis* **1990**, 962-966.
18. Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10-18.
19. Frieden, C.; Kurz, L. C.; Gilbert, H. R. *Biochemistry* **1980**, *19*, 5303-5309.
20. a. Evans, B.; Wolfenden, R. *J. Am. Chem. Soc.* **1970**, *92*, 4751-4752.
    b. Nair, V.; Wiechert. R. J. *Bioorg. Chem.* 1980, 9, 423-433.
21. Suhadolnik, R. J. *Nucleosides as Biological Probes;* John Wiley & Sons: New York, 1979; pp 244-245.
22. Siaw, M. F. E.; Coleman, M. S. *J. Biol. Chem.* **1984**, *259*, 9426-9433.
23. Zielke, C. L.; Suelter, C. H. In *"The Enzymes"*; 3rd ed.: Boyer, P. D., Ed.; Academic Press: New York, 1971; Vol. IV, pp. 47-78.
24. Cory, J. G.; Suhadolnik, R .J. *Biochemistry* **1965**, *4*, 1729-1732.
25. Suhadolnik, R. J. *Nucleoside Antibiotics* Wiley, New York, 1970, 264.
26. Lynch, T. P.; Paran, J. H.; Paterson, A. R. P. *Cancer Research* **1981**, *41*, 560-565.
27. Nair, V.; Young, D. A.; DeSilvia, R. Jr. *J. Org. Chem.* **1987**, *52*, 1344-1347.
28. Montgomery, J. A. In *Nucleosides, Nucleotides, and Their Biological Applications*; Rideout, J. L.; Henry, D. W.; Beacham, L. M., Eds.; Academic Press: New York, 1983, pp 19-46.
29. Montgomery, J. A.; Elliot, R. D. in *Nucleoside Chemistry, Part II*; Townsend, L. B.; Tipson, R. S., Eds. John Wiley and Sons: New York, New York, 1978, 687-691.
30. Witkowski, J. T.; Robins, R. K.; Sidwell, R. W.; Simon, L. N. *J. Med. Chem.* **1972**, *15*, 1150-1154.
31. Sidwell, R. W.; Simon, L. N.; Witkowski, J. T.; Robins, R. K. *Prog. Chemother. Proc. Int. Congr. Chemother.*, 8th. **1980**, *2*, 889.
32. Smith, R. A. Mechanism of Action of Ribavirin, in *Ribavirin: A Broad Spectrum Antiviral Agent*, Smith, R. A. and Kirkpatrick, W., Eds Academic Press: New York, NY. 1980 pp. 99-145.
33. Chipen, G. I.; Grinshtein, V. Y. *Khimiya Geterotsiklicheskikh Soedinenii* **1965**, *1*, 624-626.
34. Taylor, E. W.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. *Antiviral Chem. & Chemother.* **1990**, *1*, 163-173.
35. Van Roey, P.; Salerno, J. M.; Duax, W. L.; Chu, C. K.; Ahn, M. A.; Schinazi, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 2277-2282.

36. Silverton, J. V.; Quinn, F. R.; Haugwitz, R. D.; Todaro, L. J. *Acta Cryst.* **1988**, *C44*, 321-324.
37. Van Roey, P.; Salerno, J. M.; Chu, C. K.; Schinazi, R. F. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 3929-3933.
38. Ikehara, M.; Uesugi, S.; Yoshida, K. *Biochemistry* **1972**, *11*, 830-836.
39. Ts'o, P. O. P.; Kondo, N. S.; Schweizer, M. P.; Hollis, D. P. *Biochemistry* **1969**, *8*, 997-1029.
40. Sarma, R. H.; Lee, C.-H.; Evans, F. E.; Yathindra, N.; Sundaralingam, M. *J. Am. Chem. Soc.* **1974**, *96*, 7337-7348.
41. Nair, V.; Young, D. A. *Magn. Reson. Chem.* **1987**, *25*, 937-940.
42. Stolarski, R.; Hagberg, C.-E.; Shugar, D. *Eur. J. Biochem.* **1984**, *138*, 187-192.
43. Nair, V.; Buenger, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 8502-8504.
44. Buenger, G. S. Ph.D. Thesis, University of Iowa, 1990.
45. Buchanan, G. W.; Bourque, K. *Magn. Reson. Chem.* **1989**, *27*, 200-201.
46. Seela, F.; Muth, H.-P. *Leibigs Ann. Chem.* **1988**, 215-219.
47. Saenger, W. In *Nucleoside Analogues*; Walker, R. T.; De Clercq, E.; Eckstein, F., Eds.; Plenum Press: New York, 1979, pp 1-13.