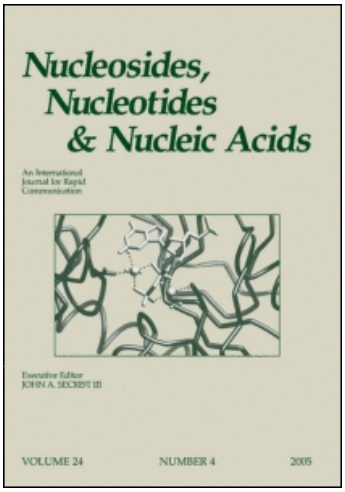

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SYNTHESIS OF 2'-C-α-METHYL-2',3'-DIDEOXYNUCLEOSIDES

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Abstract: A general method for the synthesis of 2'-C-α-methyl-2',3'-dideoxynucleosides is presented. Stereofacial selectivity of the 2-C-methylation reaction of γ–lactone has been investigated, in which the presence of a bulky group at the 5-hydroxymethyl produced the α–isomer as a major product. During glycosylation, the α-methyl group directed the formation of nucleosides in favor of the ß-isomer. This methodology is applied to the synthesis of some new pyrimidine and purine nucleosides.

The identification of human immunodeficiency virus (HIV) as the etiological agent of acquired immunodeficiency syndrome (AIDS), has generated considerable effort to the design and synthesis of compounds that would inhibit the replication of HIV and related viruses. An important focus has been on inhibitors of reverse transcriptase (RT), a key enzyme encoded by the virus for its replication. Since 3'-azido-3'-deoxythymidine (AZT) has been found to be effective against HIV-1,[1] a number of 2',3'-dideoxynucleosides have been synthesized as potential RT inhibitors.[2-4] Currently, AZT, 2',3'-dideoxycytidine (ddC),[5] 2',3'-dideoxyinosine (ddI)[6] and 3'-deoxy-2',3'-didehydrothymidine (d4T)[7] have been approved by the FDA and are being used clinically for the treatment of AIDS and HIV infected individuals while other 2',3'-dideoxynucleosides such as ß-*L*-(2-hydroxymethyl-1,3-oxathiolan-4-yl)cytosine (3TC)[8] and ß-*L*-(2-hydroxymethyl-1,3-oxathiolan-4-yl)-5-fluorocytosine (FTC)[9] are in various stages of clinical trials as anti-HIV and anti-HBV agents. As a result, a number of laboratories, including ours, have become interested in developing new dideoxynucleosides as potential anti-HIV and anti-HBV agents.

Ioannidis *et al* [10] reported the synthesis of 2'-C-α-methyl cytosine from 2'-C-α-acetoxymethyl cytosine. Kakefuda *et al* [11] also reported the synthesis of several 2',3'-dideoxy-2'-C-β-methyl-ß-*D-threo*-pentofuranosyl pyrimidines and adenine nucleosides

This manuscript is dedicated to the celebration of Prof. Yoshihisa Mizuno's 75th birthday.

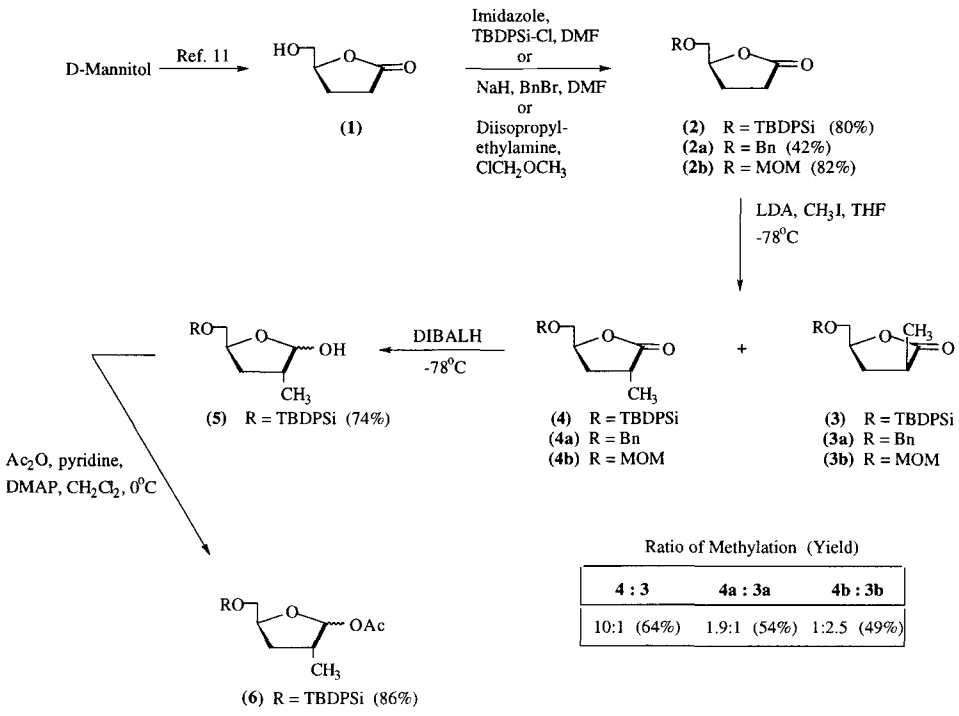
from 3'-deoxy-ß-*D-erythro*-pentofuran-2'-ulosyl nucleosides as starting materials. Among these compounds only 1-(2',3'–dideoxy-2-C-methyl-ß-*D-threo*-pentofuranosyl)uracil has shown moderate anticancer activity (IC_{50}=16.5 µg/mL against mouse leukemic L1210 cells and IC_{50}=33 µg/mL against human oral epidermoid carcinoma KB cells).[11] Kakefuda *et al* suggested that inactivity of 2'-C-methyl-ß-*D-threo* -pyrimidines and -purines might be related to the insusceptibility to nucleoside kinases, due to the presence of a bulky group at 2'-ß-position.

As part of our effort to develop practical synthetic routes to dideoxynucleosides, we have previously reported a general synthetic method for 2',3'-dideoxy and 2',3'-didehydro-2',3'-dideoxynucleosides from corresponding ribonucleosides[12] and a highly stereoselective synthesis of 2',3'-dideoxy and 2',3'-didehydro-2',3'-dideoxy-nucleosides from 1,2:5,6-di-*O*-isopropylidine-*D*-mannitol.[13] We would now like to report a new synthetic method for 2'-C-α-methyl-2',3'-dideoxynucleosides.

RESULTS AND DISCUSSION

Compound **1** was synthesized from 1,2:5,6-di-*O*-isopropylidine-*D*-mannitol as previously reported.[13] Our initial attempt to introduce a methyl group at C-2 position of lactone **2** by *in situ* generation of a lithium enolate with lithium hexamethyldisilazane at –78°C followed by addition of trimethylsilyl chloride[13,14] and then subsequent addition of CH_3I to obtain the desired products **3** and **4**, failed. However, *in situ* generation of an enolate using lithium diisopropylamine (LDA) followed by the addition of CH_3I gave a mixture of products **4** and **3** (10:1) with a 64% overall yield.[15, 16] Variation of the protecting group on the 5 hydroxyl group had a direct effect on the stereofacial selectivity of the methylation reaction (Scheme 1). Use of benzyl and methoxymethyl protecting groups instead of the more bulky TBDPSi protecting group resulted in an increased yield of ß-methyl lactone, 1.9:1 (**4a**:**3a**), and 1:2.5 (**4b**:**3b**), respectively. The reduction of compound **4** with DIBALH at –78°C followed by acetylation with acetic anhydride and pyridine at 0°C provided the key intermediate **6** in 86% overall.

The condensation of acetate **6** with different silylated pyrimidines was conducted at 5°C in 1,2-dichloroethane, whereas couplings of silylated purines were carried out at -20°C. Reaction times were typically 20-25 min using trimethylsilyl trifluoromethane sulfonate (TMSOTf) as a Lewis acid. The condensations resulted in mixtures of α and ß anomers. Deprotection with tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran at room temperature, followed by purification, provided an anomeric mixture of pure final products. For example, for the synthesis of 2'-C-α-methyl-*D-erythro*-glyceropentonic-5'-



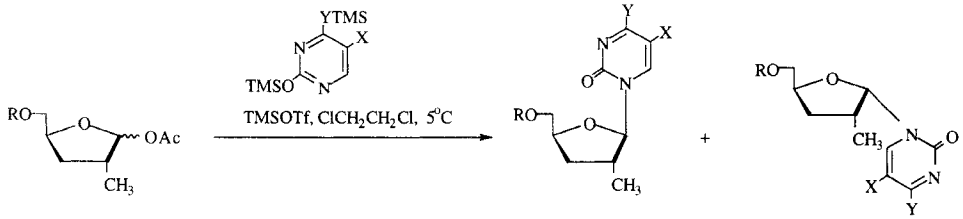
Ratio of Methylation (Yield)

4 : 3	4a : 3a	4b : 3b
10:1 (64%)	1.9:1 (54%)	1:2.5 (49%)

SCHEME 1

tert-butyldiphenylsilyl uracil (**7** and **10**), the key intermediate **6** was condensed with silylated uridine in the presence of TMSOTf (Scheme 2). Compounds **7** and **10** were easily separated by silica gel column chromatography and were deprotected with TBAF to obtain compounds **13** and **17**, respectively. The synthesis of the thymine analogues **9** and **12** was achieved by coupling silylated thymine with compound **6**, to obtain an inseparable mixture of α and β anomers. Deprotection with TBAF facilitated the separation of anomers, but could only be achieved by multiple elution preperative TLC (2% MeOH/$CHCl_3$, 5% MeOH/$CHCl_3$, and 33% EtOAc/hexanes) to provide the desired compounds **16** and **20**. The synthesis of cytidine analogues was simplified by coupling N^4-benzoylated silylated cytosine bases to avoid difficult separation of isomers. The two isomers **8** and **11** were separated by silica gel column chromatography. Desilylation with TBAF, followed by debenzoylation of the crude compounds **14** and **18** with methanolic ammonia, gave the desired anomers, **15** and **19**, respectively.

Purine nucleosides were similarly synthesized. For example, the synthesis of 2'-C-methyl adenosine derivative **21** and **27** was achieved by coupling the intermediate **6**



(6) R = TBDPSi

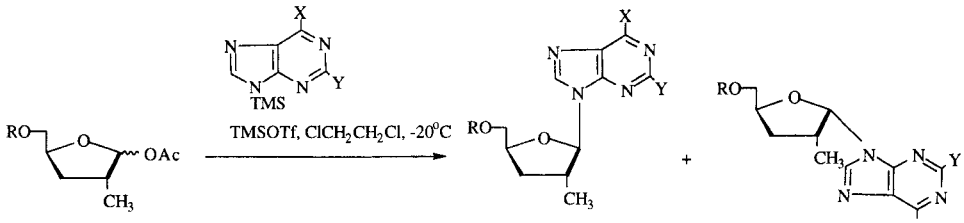
(7) - (9)
(13) - (16)

(10) - (12)
(17) - (20)

Reaction	Product	Yield (Ratio)	R	X	Y
X = H, Y = O	(7)	35% (1.8:1) + (10)	TBDPSi	H	OH
X = H, Y = NBz	(8)	41% (1.4:1) + (11)	TBDPSi	H	NHBz
X = CH_3, Y = O	(9)	28% (2.2:1) + (12)	TBDPSi	CH_3	OH
X = H, Y = O	(10)	19% (1:1.8) + (7)	TBDPSi	H	OH
X = H, Y = NBz	(11)	29% (1:1.4) + (8)	TBDPSi	H	NHBz
X = CH_3, Y = O	(12)	12.8% (1:2.2) + (9)	TBDPSi	CH_3	OH
(7) + TBAF / THF	(13)	80%	H	H	OH
(8) + TBAF / THF	(14)	> 100%	H	H	NHBz
(14) + NH_3 / MeOH	(15)	84%	H	H	NH_2
(9), (12) + TBAF / THF	(16)	47% + (20)	H	CH_3	OH
(10) + TBAF / THF	(17)	70%	H	H	OH
(11) + TBAF / THF	(18)	> 100%	H	H	NHBz
(18) + NH_3 / MeOH	(19)	80%	H	H	NH_2
(12), (9) + TBAF / THF	(20)	16% + (16)	H	CH_3	OH

SCHEME 2

directly with silylated adenosine using 2 equivalents of TMSOTf to provide an inseparable mixture. After deprotection with TBAF, the two isomers were separated by column chromatography to give desired **34** and **39**. The ß isomer **34** was converted to the corresponding inosine derivative **35** enzymatically with adenosine deaminase (ADA)[17] (Scheme 3). The α isomer failed to be converted to the corresponding derivative under the same conditions, which supported the α and ß assignments of the final products. Condensation of compound **6** with silylated 6-chloropurine resulted in an inseparable anomeric mixture of **22** and **28**. The 6-chloro substituted anomeric mixture was hydrolyzed by refluxing the mixture in the presence of 2–mercaptoethanol, and sodium methoxide/MeOH for 16 h to obtain a mixture of protected hypoxanthine derivatives **23** and **29**. Desilylation (TBAF) allowed the two isomers of the inosine derivative **35** and **40** to be separated. For the synthesis of 2,6-disubstituted purine analogues, the key intermediate acetate **6** was condensed with silylated 2-fluoro-6-chloropurine[18] to give **24**



Reaction	Product	Yield (Ratio)	R	X	Y
X = NH_2, Y = H	(21)	39.1% (2:1) + (27)	TBDPSi	NH_2	H
X = Cl, Y = H	(22)	44.6% (2:1) + (28)	TBDPSi	Cl	H
(22) + $HSCH_2CH_2OH$ / NaOMe	(23)	37.1% (1.8:1) + (29)	TBDPSi	OH	H
X = Cl, Y = F	(24)	47.5% (1.3:1) + (30)	TBDPSi	Cl	F
(24) + NH_3/MeOH	(25)	25%	TBDPSi	Cl	NH_2
(24) + NH_3/MeOH	(26)	33% + (32)	TBDPSi	NH_2	F
X = NH_2, Y = H	(27)	19.6% (1:2) + (21)	TBDPSi	NH_2	H
X = Cl, Y = H	(28)	23.3% (1:2) + (22)	TBDPSi	Cl	H
(28) + $HSCH_2CH_2OH$ / NaOMe	(29)	20.6% (1:1.8) + (23)	TBDPSi	OH	H
X = Cl, Y = NH_2	(30)	36.5% (1:1.3) + (24)	TBDPSi	Cl	F
(30) + NH_3 / MeOH	(31)	23%	TBDPSi	Cl	NH_2
(30) + NH_3 / MeOH	(32)	33% + (26)	TBDPSi	NH_2	F
	(33)		TBDPSi	OH	NH_2
(21) + TBAF / THF	(34)	46.6%	H	NH_2	H
(23) + TBAF / THF or (34) + ADA	(35)	39.6% / 83%	H	OH	H
(25) + TBAF / THF	(36)	64%	H	Cl	NH_2
(26) + TBAF / THF	(37)	40%	H	NH_2	F
(36) + ADA	(38)	75%	H	OH	NH_2
(27) + TBAF / THF	(39)	29%	H	NH_2	H
(39) + ADA	(39)	no reaction	H	NH_2	H
(29) + TBAF / THF	(40)	18.9%	H	OH	H
(31) + TBAF / THF	(41)	60%	H	Cl	NH_2
(32) + TBAF / THF	(42)	33%	H	NH_2	F
(41) + $HSCH_2CH_2OH$ / NaOMe	(43)	75%	H	OH	NH_2

SCHEME 3

and **30** as an inseparable anomeric mixture. After treatment with ammonia in DME for 18 h, the mixture resulted in two pairs of α and ß anomers **25**, **31** and **26**, **32**. Desilylation with TBAF provided the desired 2-amino-6-chloro derivatives **36** and **41**, and 6-amino-2-fluoro derivatives **37** and **42**, respectively. Compound **36** was enzymatically dechlorinated[19-21] with adenosine deaminase to obtain the guanosine derivative **38**. The α anomer **43** was synthesized from **41** by treatment with 2-mercaptoethanol and sodium methoxide, desilylated with TBAF, and purified by column chromatography.

Assignment of the anomeric configuration for *D-erythro* nucleoside analogues was based on the chemical shift of the ß-anomeric proton in the ^{1}H NMR spectra, which appeared upfield relative to the α-anomeric signal. The 4'-proton of the ß-nucleoside appeared upfield of the 4'-proton of the α-nucleoside because of the shielding/deshielding effect by the heterocyclic base. Additionally the 2'α-methyl signal for the ß-nucleoside appeared further upfield than the corresponding α-nucleoside due to same effect.[22] Comparison of the data for compound **13** and **15** with the published data[18,23] have also supported our assignment. Additional proof of these assignments was based on NOESY experiments, which revealed the presence of NOE between H-4' and H-1' protons for the ß-nucleoside, whereas for the α-nucleoside an NOE between the H-4' and H-6 was observed.

In summary, a new synthetic route for 2'-C-α-methyl-2',3'-dideoxynucleosides has been developed and the synthesis of some new dideoxynucleosides has been described. Both chemical and enzymatic methods have been used. Synthesized compounds have been evaluated against HIV and HBV, however, no significant antiviral activities have been detected.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp II and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q fourier transform spectrometer or on a Bruker AM 250, AC 300 or AMX 400 spectrometer with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet) or (m) multiplet. IR spectra were measured on a Nicolet 510P FT-IR Spectrometer. Optical rotations were performed on a Jasco DIP-370 Digital Polarimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel-60 (220-440 mesh) for flash chromatography or silica gel G (TLC grade >440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU-7 or on a Beckman DU 650 Spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Adenosine deaminase was purchased from Sigma Chemical Company as the crude extract from calf intestine.

5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-γ-lactone (2).[13] Imidazole (18.5 g, 258 mmol) and *tert*-butyldiphenylsilyl chloride (42.6 g, 154 mmol) were added to a solution of ribonolactone **1** (15 g, 129 mmol) in DMF (300 mL) and the mixture was stirred for 1 h at rt. Solvent was removed under reduced pressure, the resulting yellow residue dissolved in $CHCl_3$, washed with water, brine, and dried over Na_2SO_4. The

organic layer was filtered and the filtrate concentrated to produce a viscous yellow syrup. Crystallization from hot hexane afforded compound **2** (36.5 g, 80%): IR (KBr) 1772 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 9 H, *t*-butyl), 2.10-2.40 (m, 2 H, H-3_a, H-2_a), 2.50-2.80 (m, 1 H, H-3_b), 3.70-3.80 (m, 2 H, H-5), 4.00 (m, 1 H, H-2_b), 4.30-4.50 (m, 1 H, H-4), 7.20-7.70 (m, 10 H, 2xPh).

5-*O*-Benzyl-2,3-dideoxy-*D*-glyceropentonic-γ-lactone (2a).[24] 2.01 g (18.0 mmol) of dried compound **2** was dissolved in anhydrous DMF (80 mL) and NaH (60%, 1.2 g, 27.0 mmol) was added to the stirring solution. The mixture was stirred for 20 min before BnBr (3.21 mL, 27.0 mmol) in DMF (10 mL) was added dropwise. The mixture was stirred at room temperature for 2 hours, was quenched with MeOH, and concentrated *in vacuo*. The residue was taken up in $CHCl_3$, washed with H_2O, dried over Na_2SO_4, and purified by column chromatography with EtOAc/hexanes 1:3 (42% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.99 (m, 1 H, H-3_a), 2.14 (m, 1 H, H-2_a), 2.31 (m, 1 H, H-3_b), 2.48 (m, 1 H, H-2_b), 3.61 (dd, 1 H, H-5_a, *J*=4.0, 10.6 Hz), 3.69 (dd, 1 H, H-5_b, *J*=3.6, 10.6 Hz), 4.58 (br s, 2 H, O$\underline{CH_2}$Ph), 4.69 (m, 1 H, H-4), 7.32 (m, 5 H, Ph)

5-*O*-Methoxymethyl-2,3-dideoxy-*D*-glyceropentonic-γ-lactone (2b). Compound **1** (8.0 g, 68.8 mmol) was dissolved in diisopropylethylamine (70 mL) and stirred at rt for 1 h under argon. The reaction mixture was cooled to –5°C and chloromethylmethyl ether (15.67 mL, 206.4 mmol) was added dropwise over 30 min. The reaction mixture was stirred at -5°C for 4 h, quenched with H_2O, the compound extracted with methylene chloride, washed with $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated to obtain **2a** which was purified by column chromatography with 0-60% EtOAc/hexanes gradient. Compound **2a** (9.1 g, 82%) was recovered as an oil. ^1H NMR ($CDCl_3$, 90 MHz) δ 2.1-2.4 (m, 2 H, H-3_a, H-2_a), 2.5-2.8 (m, 1 H, H-3_b), 3.0 (br s, 3 H, O$\underline{CH_3}$), 3.7-3.8 (m, 2 H, H-5), 4.0 (m, 1 H, H-2_b), 4.3-4.5 (m, 1 H, H-4), 4.5 (br s, 2 H, O$\underline{CH_2}$); Anal Calcd for $C_7H_{12}O_4$, 0.05 C_6H_{14}: C, 53.31; H, 7.78. Found: C, 53.32; H, 7.65.

5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-*D*-*erythro*-pentonic-γ-lactone (3) and 5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-*D*-*threo*-pentonic-γ-lactone (4). Compound **2** (30.1 g, 84.75 mmol) was dissolved in dry THF (200 mL) under nitrogen and LDA (63.3 mL, 95 mmol) was added to the stirring solution at -78°C over a period of 15 min, and stirred for 30 min. CH_3I (5.27 mL, 84.75 mmol) was then rapidly added to the mixture and stirred for 2 h at -78°C. The reaction mixture was then warmed to rt, diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$, sodium sulfite solution, 10% HCl, then brine. The organic layer was separated, dried, filtered, concentrated *in vacuo*, and purified by silica gel column

chromatography with 0-20% EtOAc/hexanes to obtain the desired compound **3** (18.4 g, 58.7%) as white crystals: IR (KBr) 1768 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (br s, 9 H, *t*-butyl), 1.27-1.29 (d, 3 H, CH_3, $J_{CH3,2H}$=7.0 Hz), 1.91-2.04 (m, 1 H, H_a-3), 2.39-2.48 (m, 1 H, H_b-3), 2.81-2.89 (m, 1 H, H-2), 3.62-3.68 and 3.82-3.87 (dd and dd, 2 H, H-5_a, H-5_b), 4.52-4.56 (m, 1 H, H-4), 7.20-7.70 (m, 10 H, 2xPh); Anal Calcd for $C_{22}H_{28}SiO_3$, C; 71.69, H; 7.65, Found, C; 71.46, H; 7.75 and the ß isomer **4** (1.8 g, 5.8%) as a white crystal: IR (KBr) 1768 cm^{-1}(C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (br s, 9 H, *t*-butyl), 1.27-1.30 (d, 3 H, CH_3, $J_{CH3,2H}$=7.1 Hz), 1.79-1.91 (m, 1 H, H-3_a), 2.34-2.43 (m, 1 H, H-3_b), 2.68-2.71 (m, 1 H, H-2), 3.70-3.75 and 3.83-3.88 (m and m, 2 H, H-5_a, H-5_b), 4.43-4.47 (m, 1 H, H-4), 7.25-7.70 (m, 10 H, 2xPh); Anal Calcd for $C_{22}H_{28}SiO_3$, C; 71.69, H; 7.65, Found, C; 71.61, H; 7.73.

5-*O*-Benzyl-2,3-dideoxy-2-C-methyl-*D*-*erythro*-pentonic-γ-lactone (3a) and 5-*O*-Benzyl-2,3-dideoxy-2-C-methyl-*D*-*threo*-pentonic-γ-lactone (4a). Compound **2a** (2.53 g, 12.26 mmol) was dissolved in dry THF (10 mL), cooled to -78°C and LDA (9.0 mL, 13.49 mmol) was added dropwise over 15 min. The solution was stirred for 30 min and CH_3I (8.17 mL, 12.26 mmol) was rapidly added and the solution stirred for and additional 2 hours at -78°C. The reaction mixture was then allowed to warm to rt, diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$, sodium sulfite solution, 10% HCl and brine. The organic layer was dried, filtered, concentrated *in vacuo* and purified by silica gel column chromatography using 0-20% EtOAc/hexanes gradient to obtain the desired compound **3a** and **4a** (1:1.9) in 54.6% yield. ^1H NMR (DMSO-d_6, 300 MHz) δ 3a: 1.29 (d, 3 H, $J_{CH3,H2}$=7.0 Hz), 1.66-1.78 (m, 1 H, H-3_a), 2.38-2.47 (m, 1 H, H-3_b), 2.64-2.70 (m, 1 H, H-2), 3.60 (dd, 1 H, *J*=5.2, 10.5 Hz), 3.68 (dd, 1 H, *J*=3.5, 10.6 Hz), 4.53 (m, 1 H, H-4), 4.59 (s, 2 H, O$\underline{CH_2}$Ph), 7.13-7.37 (m, 5 H, Ph). Compound 4a: ^1H NMR (DMSO-d_6, 250 MHz) δ 1.27 (d, 3 H, *J*=7.2 Hz), 1.91-2.04 (m, 1 H, H-3_a), 2.32-2.42 (m, 1 H, H-3_b), 2.81-2.84 (m, 1 H, H-2), 3.58 (dd, 1H, H-5_a, *J*=4.0, 10.7 Hz), 3.65 (dd, 1 H, H-5_b, *J*=3.1, 10.4 Hz), 4.55 (d, 2 H, *J*=3.1), 4.64 (m, 1 H, H-4), 7.12-7.36 (m, 5 H, Ph).

5-*O*-Methoxymethyl-2,3-dideoxy-2-C-methyl-*D*-*erythro*-pentonic-γ-lactone (3b) and 5-*O*-Methoxymethyl-2,3-dideoxy-2-C-methyl-*D*-*threo*-pentonic-γ-lactone (4b). LDA (38.79 mL, 58 mmol) was added to a solution of **2a** (8.5 g, 53 mmol) in dry THF (200 mL) at -78°C over a period of 15 min, and stirred for 30 min under argon. CH_3I (7.5 g, 53 mmol) was then added rapidly to the mixture (-78°C) and stirred for 2 h. The reaction mixture was then allowed to warm to rt, diluted with 100 mL of EtOAc and washed with saturated $NaHCO_3$, sodium sulfite solution, 10% HCl, then brine. The organic layer was separated, dried over Na_2SO_4, and concentrated *in*

vacuo. The residue was purified by column chromatography with 0-60% EtOAc/hexanes gradient to obtain the desired α isomer **3b** (3.28 g, 35.9%) as an oil and the ß isomer **4b** (1.22 g, 13.1%) as an oil. Compound **3b**: IR (neat) 1768 cm^{-1}(C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.27-1.29 (d, 3 H, 2-CH_3, $J_{CH3,H2}$=7.8 Hz), 1.95-2.04 (m, 1 H, H-3_a), 2.32-2.41 (m, 1 H, H-3_b), 2.80-2.83 (m, 1 H, H-2), 3.37 (br s, 3 H, OCH_3), 3.59-3.64 (dd, 1 H, H-5_a), 3.72-3.77 (dd, 1 H, H-5_b), 4.11-4.13 (m, 1 H, H-4), 4.63 (br s, 2 H, $CH_3O\underline{CH_2}$); Anal Calcd for $C_8H_{14}O_4$, 0.22 H_2O C; 53.9, H; 7.97, Found, C; 53.85, H; 8.08 and ß isomer **4b**: IR (neat) 1768 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.29-1.31 (d, 3 H, CH_3, $J_{CH3,H2}$=6.9 Hz), 1.68-1.79 (m, 1 H, H-3_a), 2.40-2.47 (m, 1 H, H-3_b), 2.69-2.73 (m, 1 H, H-2), 3.37 (br s, 3 H, $O\underline{CH_3}$), 3.70-3.75 and 3.83-3.88 (dd and dd, 2 H, H-5_a, H-5_b), 4.52-4.56 (m, 1 H, H-4), 4.63 (br s, 2 H, $CH_3O\underline{CH_2}$); Anal Calcd for $C_8H_{14}O_4$: C; 55.16, H; 8.1, Found, C; 55.02, H; 8.17.

1-*O*-Hydroxyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-and-ß-*D*-*erythro*-pentofuranose (5). 1 M DIBALH (69.44 mL, 69.44 mmol) was added to a solution of compound **3** (16 g, 43.4 mmol) in dry methylene chloride (150 mL) under argon and at -78°C over a period of 15 min, and stirred for 2 h. The reaction was quenched with MeOH (20 mL) and the mixture stirred at -30°C for 20 min. The mixture was then diluted with $CHCl_3$ (100 mL), and washed with sodium tartrate solution, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and solvents removed *in vacuo*. Purification by silica gel column chromatography with 20% EtOAc/hexanes gradient, provided compound **5** (12 g, 74.6%) as a syrup: IR (neat) 3418 cm^{-1}(OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98-1.00 (d, 3 H, CH_3, $J_{CH3,H2}$=6.9), 1.07 (br s, 9 H, *t*-butyl), 1.53-2.20 (m, 2 H, H-3), 2.20-2.30 (m, 1 H, H-2), 2.57 and 3.35-3.37 (d, OH, D_2O exchangeable), 3.50-3.78 (m, 2 H, H-5_a, H-5_b), 4.43-4.36 (m, 1 H, H-4), 7.25-7.70 (m, 10 H, 2xPh).

1-*O*-Acetoxy-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α and-ß-*D*-*erythro*-pentofuranose (6). The syrup **5** (8.5 g, 22.9 mmol) was dissolved in methylene chloride (60 mL) and acetic anhydride (5.40 mL, 57.3 mmol), pyridine (9.22 mL, 114 mmol), DMAP (6 mg, 0.049 mmol) sequentially added at 0°C. The mixture stirred in an ice-water bath for 2 h, and the solvent removed *in vacuo*, providing compound **6** as clear yellow viscous liquid. Purification by silica gel column chromatography with 0-20% EtOAc/hexanes gradient afforded a colorless syrup as a mixture of α - and ß -anomers (8.2 g, 86.6%): IR (Neat) 1740 cm^{-1} (OAc); ^1H NMR ($CDCl_3$, 300 MHz), δ 1.05-1.06 (d, 3 H, CH_3), 1.06 (br s, 9 H, *t*-butyl), 1.66-1.72 (m, 1 H, H-3_a),1.89 (br s, 3 H, OAc), 2.05-2.09 (m, 1 H, H-3_b), 2.33-2.39 (m, 1 H, H-2), 3.62-3.72 (m, 2 H, H-5), 4.36-4.37 (m, 1 H, H-4), 5.92 and 6.22 (d, 1 H, H-1), 7.25-

7.73 (m, 10 H, 2xPh). Anal Calcd for $C_{24}H_{32}O_4Si$: C, 69.86; H, 7.82;. Found: C, 71.06; H, 8.28.

1-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]uracil (7) and 1-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]uracil (10). A suspension of uracil (0.55 g, 4.8 mmol) and ammonium sulfate (0.01 g, 0.076 mmol) in HMDS (30 mL) was refluxed for 4 h under argon until a clear solution was obtained. The mixture was cooled to rt and HMDS evaporated under reduced pressure to obtain silylated uracil. The residue was dissolved in dry 1,2-dichloroethane (10 mL) and a solution of acetate **6** (0.99 g, 2.42 mmol) in dry 1,2-dichloroethane (20 mL) was added. The reaction mixture was cooled to 5°C, TMSOTf (0.5 mL, 2.58 mmol) was added dropwise, and the mixture stirred for 10 min. The mixture was then brought back to rt and stirred for 20 min. The reaction mixture was poured into a stirring EtOAc and saturated $NaHCO_3$ solution, and the organic layer washed with water, brine, and dried over Na_2SO_4. The organic layer was then filtered and the filtrate concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with EtOAc/hexanes (0-10% gradient) and then (50% EtOAc/hexanes) to obtain 390 mg (35%) of the ß anomer (**7**) and 220 mg (19.5%) of α anomer (**10**). Compound **7**: $[\alpha]_D^{25}$ 8.14° (c 0.25, MeOH); UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (br s, 9 H, *t*-butyl), 1.15-1.17 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.64-1.72 (m, 1 H, H-3'$_b$), 2.21-2.28 (m, 1 H, H-3'$_a$), 2.31-2.39 (m, 1 H, H-2'), 3.65-3.70 (dd, 1 H, H-5'$_b$, $J_{H5'a,\ H5'b}$=11.5 Hz, $J_{H5'b,\ H4'}$=2.6 Hz), 4.04-4.09 (dd, 1 H, H-5'$_a$, $J_{H5'a,\ H5'b}$=11.6 Hz, $J_{H5'a,\ H4'}$=4.3 Hz), 4.25-4.29 (m, 1 H, H-4'), 5.42-5.44 (d, 1 H, H-5, $J_{H5,H6}$=8.0 Hz), 5.72-5.73 (d, 1 H, H-1', $J_{H1',\ H2'}$=4.5 Hz), 7.25-7.28 (m, 10 H, 2xPh), 7.90-7.93 (d, 1 H, H-6, $J_{H5,H6}$=7.6 Hz), 8.47 (s, NH, D_2O exchangeable); Anal Calcd for $C_{26}H_{32}N_2SiO_4$: C, 67.15; H, 6.95; N, 6.02. Found: C, 67.15; H, 7.28; N, 5.65. Compound (**10**): $[\alpha]_D^{25}$ -8.59° (c 0.35, MeOH); UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89-0.91 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=7.0 Hz), 1.07 (br s, 9 H, *t*-butyl), 1.60-1.73 (m, 1 H, H-3'$_b$), 2.15-2.23 (m, 1 H, H-3'$_a$), 2.81-2.86 (m, 1 H, H-2'), 3.60-3.73 (m, 2 H, H-5'$_b$, H-5'$_a$), 4.47-4.51 (m, 1 H, H-4'), 5.70-5.74 (d, 1 H, H-5, $J_{H5,H6}$=8.1 Hz), 6.10-6.12 (d, 1 H, H-1', $J_{H1',H2'}$=6.0 Hz), 7.23-7.40 (m, 10 H, 2xPh), 7.65-7.67 (d, 1 H, H-6, $J_{H5,H6}$=7.7 Hz), 8.51 (s, NH, D_2O exchangeable); Anal Calcd for $C_{26}H_{32}N_2SiO_4$, 0.25 H_2O: C, 66.48; H, 6.97; N, 5.96. Found: C, 66.18; H, 7.00; N, 5.71.

N^4-Benzoyl-1-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]cytosine (8) and N^4-Benzoyl-1-[(5-O-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pento-

furanosyl]cytosine (11). A mixture of N^4-benzoyl cytosine (0.86 g, 4.0 mmol) and ammonium sulfate (0.01 g, 0.076 mmol) in HMDS (30 mL) was refluxed under argon for 3 h until a clear solution was obtained. HMDS was evaporated under reduced pressure to obtain silylated N^4-benzoyl cytosine as a white solid. A solution of acetate **6** (0.82 g, 2.0 mmol) in dry 1,2-dichloroethane (20 mL) was added to the residue under nitrogen. TMSOTf (0.8 mL, 4.12 mmol) was added dropwise to the reaction mixture, and then stirred for 35 min at rt before saturated $NaHCO_3$ solution was added. The solution was stirred for 30 min and the reaction mixture then poured into EtOAc, the organic layer was washed with saturated $NaHCO_3$ solution, water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel using EtOAc/hexanes (33%) to obtain 460 mg, 40.9% of compound **8** as a white foam: UV (MeOH) λ_{max} 306 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (br s, 9 H, *t*-butyl), 1.28-1.30 (d, 3 H, 2'-CH_3, $J_{CH3',H2'}$=7.1 Hz), 1.56-1.63 (m, 1 H, H-3'$_b$), 2.12-2.25 (m, 1 H, H-3'$_a$), 2.48-2.53 (m, 1 H, H-2'), 3.70-3.74 (dd, 1 H, H-5'$_b$), 4.13-4.18 (dd, 1 H, H-5'$_a$), 4.34-4.39 (m, 1 H, H-4'), 5.78-5.79 (d, 1 H, H-1'), 7.26 (d, 1 H, H-5, $J_{H5,H6}$=8.4 Hz), 8.45-8.47 (d, 1 H, H-6, $J_{H5,H6}$=8.6 Hz), 8.80 (s, NH, D_2O exchangeable), 7.30-7.75 (m, 15 H, 3xPh) and 330 mg, 29.4% compound **11** as a white foam: $[\alpha]_D^{25}$ -35.64° (c 0.31, MeOH); UV (MeOH) λ_{max} 305 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82-0.84 (d, 3 H, 2'-CH_3, $J_{CH3',H2'}$=7.0 Hz), 1.07 (br s, 9 H, *t*-butyl), 1.71-1.76 (m, 1 H, H-3'$_a$), 2.15-2.24 (m, 1 H, H-3'$_b$), 2.97-3.00 (m, 1 H, H-2'), 3.64-3.77 (dd, 2 H, H-5'), 4.50-4.54 (m, 1 H, H-4'), 6.19-6.21 (d, 1 H, H-1'), 7.25 (s, 1 H, H-5), 7.88-7.90 (d, 1 H, H-6), 7.30-7.75 (m, 15 H, 3xPh), 8.67 (s, NH, D_2O exchangeable).

1-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]thymine (9) and 1-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]thymine (12). A suspension of thymine (0.6 g, 4.84 mmol) and ammonium sulfate (0.01 g, 0.076 mmol) in HMDS (30 mL) was refluxed for 4 h under argon until a clear solution was obtained. HMDS was evaporated under reduced pressure to obtain silylated thymine as a white residue. A solution of acetate **6** (0.99 g, 2.42 mmol) in dry 1,2-dichloroethane (20 mL) was added to the silylated thymine in 1,2-dichloroethane (10 mL), under nitrogen. The reaction mixture was cooled to 5°C in an ice bath, TMSOTf (0.5 mL, 2.58 mmol) added dropwise and the solution allowed to stir for 10 min at 5°C. The reaction mixture was then stirred at rt for 20 min, and the reaction mixture poured into EtOAc and saturated $NaHCO_3$ solution. The layers were separated, and the organic layer washed with saturated $NaHCO_3$ solution, water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with EtOAc/hexanes (75%) to obtain an inseparable

mixture of ß (**9**) (28.2%) and α (**12**) (12.8%) anomer (2.2:1, 41%): UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89-0.91 (d, 3 H, 2'-CH_3, $J_{2'CH3,\ H2'}$=6.9 Hz), 1.08 and 1.11 (br s, 9 H, *t*-butyl), 1.16-1.17 (d, 3 H, 2'-CH_3, $J_{2'CH3,H2'}$=6.5 Hz), 1.64 and 1.94 (s, 3 H, 5-CH_3), 1.73-1.83 (m, 1 H, H-3'$_a$), 2.05-2.41 (m, 1 H, H-3'$_b$), 2.82 (m, 1 H, H-2'), 3.65-3.71 (dd, 1 H, H-5'$_a$), 3.98-4.04 (dd, 1 H, H-5'$_b$), 4.25 (m, 1 H, H-4'), 5.76-5.78 (d, 1 H, H-1', $J_{H1',H2'}$=6.3 Hz), 6.11-6.14 (d, 1 H, H-1', $J_{H1',H2'}$=6.1 Hz), 7.27 (s, 1 H, H-6), 7.27-7.76 (m, 10 H, 2xPh), 8.54 (s, 1 H, NH, D_2O exchangeable).

1-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)uracil (13). Compound **7** (86 mg, 0.178 mmol) was deprotected following a similar method (TBAF) as reported for the thymidine derivatives to obtain 32 mg, 80% compound **13** as a white solid: mp 158-160°C; $[\alpha]_D^{25}$ 104.43° (c 0.3, MeOH); UV (H_2O) λ_{max} 262 nm (ε 4,154) (pH 11), 262.5 nm (ε 3,312) (pH 7), 262.5 nm (ε 3,033) (pH 2); ^{1}H NMR (DMSO-*d* $_6$, 300 MHz) δ 1.01-1.04 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.54-1.68 (m, 1 H, H-3'$_a$), 1.95-2.05 (m, 1 H, H-3'$_b$), 2.27-2.40 (m, 1 H, H-2'), 3.40 -3.65 (m, 2 H, H-5'$_a$ and H-5'$_b$), 4.08-4.20 (m, 1 H, H-4'), 5.03 (t, 5'-OH, D_2O exchangeable), 5.55-5.57 (d, 1 H, H-1', $J_{H1',H2'}$=5.9 Hz), 5.60 -5.63 (d, 1 H, H-5, $J_{H5,H6}$=8.2 Hz), 7.91-7.94 (d, 1 H, H-6, $J_{H5,H6}$=8.1 Hz), 11.37 (s, 1 H, NH, D_2O exchangeable); Anal Calcd for $C_{10}H_{14}N_2O_4$, 0.25 H_2O: C, 52.01; H, 6.33; N, 12.13. Found: C, 51.97; H, 6.13; N, 12.01.

1-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)cytosine (15). A 1 M solution of TBAF (0.53 mL, 0.53 mmol) was added to a solution of **8** (300 mg, 0.53 mmol) in THF (15 mL) and stirred at rt for 3 h. The solvent was removed under reduced pressure, and the residue (crude compound **14**) was dissolved in a saturated solution of NH_3 in methanol and the mixture was stirred for 18 h. The solvent was removed *in vacuo*, and the residue chromatographed over silica gel with 10% MeOH/$CHCl_3$ to obtain 100 mg, 84% compound **15** as a white foam: $[\alpha]_D^{25}$ 38.55° (c 0.18, MeOH); UV (H_2O) λ_{max} 271 nm (ε 6,759) (pH 11), 271.0 nm (ε 5,828) (pH 7), 280.0 nm (ε 7,686) (pH 2); ^{1}H NMR (DMSO-*d* $_6$, 300 MHz) δ 1.01-1.04 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.57-1.63 (m, 1 H, H-3'$_a$), 1.94-2.00 (m, 1 H, H-3'$_b$), 2.17-2.21 (m, 1 H, H-2'), 3.16-3.19 (m, 1 H, H-5'$_a$), 3.48-3.60 (dd, 1 H, H-5'$_b$), 4.12 (m, 1 H, H-4'), 5.06 (br s, 5'-OH, D_2O exchangeable), 5.57-5.59 (d, 1 H, H-1', $J_{H1',H2'}$=4.7 Hz), 5.70-5.72 (d, 1 H, H-5, $J_{H5,H6}$=7.4 Hz), 7.05 and 7.18 (s, NH_2, D_2O exchangeable), 7.86-7.88 (d, 1 H, H-6, $J_{H5,H6}$=7.4 Hz). Physical data in accordance with that reported by Ioannidis.[10]

1-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)thymine (16) and 1-(2,3-Dideoxy-2-C-methyl-α-*D-erythro*-pentofuranosyl)thymine (20).

A 1 M solution of TBAF (1 mL, 1 mmol) was added to a solution of **9** and **12** (0.490 g, 1.0 mmol) in THF (20 mL) and the reaction mixture stirred at rt for 3 h. Solvent was then removed under reduced pressure and the residue was chromatographed over silica gel to obtain 181 mg, 75% mixture of **16** and **20**. The mixture was separated by preparative TLC by using three developing systems: 2% MeOH/CHCl3, 5% MeOH/$CHCl_3$ and then 30% EtOAc/hexanes to give 85 mg of **16**: mp 118-122.5°C; $[\alpha]_D^{25}$ 51.52° (c 0.2, MeOH); UV (H_2O) λ_{max} 267.5 nm (ε 6,031) (pH 11), 267.5 nm (ε 6,551) (pH 7), 267.5 nm (ε 5,103) (pH 2); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.99-1.03 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=7.1 Hz), 1.62-1.69 (m, 1 H, H-3'$_a$), 1.77 (s, 3 H, 5-CH_3), 2.02-2.09 (m, 1 H, H-3'$_b$), 2.11-2.32 (m, 1 H, H-2'), 3.47-3.52 (m, 1 H, H-5'$_a$), 3.59-3.65 (m, 1 H, H-5'$_b$), 4.08-4.13 (m, 1 H, H-4'), 5.02-5.05 (t, 5'-OH, D_2O exchangeable), 5.56-5.58 (d, 1 H, H-1', $J_{H1',H2'}$=5.9 Hz), 7.78 (s, 1 H, H-6), 11.2 (s, 1 H, NH, D_2O exchangeable); Anal Calcd for $C_{11}H_{16}N_2O_4$, 0.25 H_2O : C, 53.97; H, 6.79; N, 11.44. Found: C, 53.91; H, 6.58; N, 11.26 and 30 mg of **20**: mp 120-124°C; $[\alpha]_D^{25}$ -41.43° (c 0.75, MeOH); UV (H_2O) λ_{max} 267.5 nm (ε 4,385) (pH 11), 270 nm (ε 4,875) (pH 7.0), 269.5 nm (ε 5,557) (pH 2.0); ^{1}H NMR (DMSO-d_6, 300 MHz), δ 0.77-0.79 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.63-1.73 (m, 1 H, H-3'$_a$), 1.80 (s, 3 H, 5-CH_3), 1.85-2.00 (m, 1 H, H-3'$_b$), 2.69-2.72 (m, 1 H, H-2'), 3.25-3.4 (m, 2 H, H-5'), 4.51 (m, 1 H, H-4'), 4.79-4.83 (pseudo t, 5'-OH, D_2O exchangeable), 6.02-6.04 (d, 1 H, H-1', $J_{H1',H2'}$=6.5 Hz), 7.29 (s, 1 H, H-6), 11.27 (s, NH, D_2O exchangeable); Anal Calcd for $C_{11}H_{16}N_2O_4$, 0.12 $CHCl_3$, 0.65 CH_3OH : C, 51.37; H, 6.85; N, 10.18. Found: C, 51.34; H, 6.56; N, 10.17.

1-(2,3-Dideoxy-2-C-methyl-α-*D-erythro*-pentofuranosyl)uracil (17). Compound **10** (72 mg, 0.15 mmol) was deprotected as described previously (TBAF) to obtain 20 mg, 70% of compound **17** as a foam: $[\alpha]_D^{25}$ -53.22° (c 0.5, MeOH); UV(H_2O) λ_{max} 261.5 nm (ε 5,694) (pH 11), 263.0 nm (ε 3,830) (pH 7), 262.5 nm (ε 4,409) (pH 2); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.78-0.80 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.59-1.70 (m, 1 H, H-3'$_a$), 1.98-2.06 (m, 1 H, H-3'$_b$), 2.68-2.71 (m, 1 H, H-2'), 3.26-3.45 (m, 2 H, H-5'), 4.46-4.50 (m, 1 H, H-4'), 4.80-4.84 (pseudo t, 5'-OH, D_2O), 5.56-5.58 (d, 1 H, H-5, $J_{H5,H6}$=8.0 Hz), 6.02-6.05 (d, 1 H, H-1', $J_{H1',H2'}$=6.4 Hz), 7.48-7.51 (d, 1 H, H-6, $J_{H5,H6}$=8.0 Hz), 11.30 (s, NH, D_2O exchangeable); Anal Calcd for $C_{11}H_{16}N_2O_4$, 0.25 H_2O, 0.2 C_6H_{14}: C, 54.67; H, 6.63; N, 10.58. Found: C, 54.67; H, 6.75; N, 10.9.

1-(2,3-Dideoxy-2-C-methyl-α-*D-erythro*-pentofuranosyl)cytosine (19). A 1 M solution of TBAF (0.44 mL, 0.44 mmol) was added to a solution of **11** (250 mg, 0.44 mmol) in THF (20 mL) and stirred at rt for 3 h. Solvent was removed under reduced pressure, the residue **18** was dissolved in a saturated solution of NH_3 in methanol and the

mixture was stirred for 18 h. The solvent was removed under reduced pressure, and the residue chromatographed over silica gel with 10% MeOH/$CHCl_3$ to produce 80 mg, 80% compound **19** as a white solid: mp 192°C; $[\alpha]_D^{25}$ -126.55° (c 0.35, H_2O); UV (H_2O) λ_{max} 271 nm (ε 9,271) (pH 11), 271 nm (ε 5,781) (pH 7), 280.5 nm (ε 7,628) (pH 2); ^1H NMR (DMSO-d_6, 300 MHz) δ 0.70-0.72 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.23-1.34 (m, 1 H, H-3'$_a$), 1.45-1.66 (m, 1 H, H-3'$_b$), 1.95-2.03 (m, 1 H, H-2'), 2.62-2.72 (m, 1 H, H-5'$_a$), 3.13-3.19 (m, 1 H, H-5'$_b$), 4.40-4.44 (m, 1 H, H-4'), 4.82 (br s, 5'-OH, D_2O exchangeable), 5.69-5.72 (d, 1 H, H-5, $J_{H5,H6}$=7.3 Hz), 6.05-6.07 (d, 1 H, H-1', $J_{H1',H2'}$=6.3 Hz), 7.01 and 7.14 (s, NH_2, D_2O exchangeable), 7.43-7.46 (d, 1 H, H-6, $J_{H5,H6}$=7.4 Hz).

9-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]adenine (21) and 9-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]adenine (27). A suspension of adenine (0.65 g, 4.8 mmol) and ammonium sulfate (0.01 g, 0.076 mmol) in HMDS (50 mL) was refluxed for 4 h under argon until a clear solution was obtained. HMDS was then evaporated under reduced pressure to obtain silylated adenine as a white solid. Acetate **6** (0.98 g, 2.42 mmol) in dry 1,2-dichloroethane (20 mL)was added to the residue under nitrogen. The reaction mixture was cooled to -20°C, TMSOTf (0.45 mL, 2.32 mmol) added dropwise, and the solution stirred for 20 min at rt. The reaction mixture was poured into EtOAc/saturated $NaHCO_3$ solution, the layers were separated, and the organic layer washed with water, brine and dried over Na_2SO_4, filtered and the filtrate evaporated to dryness. The residue was chromatographed over silica gel with EtOAc/hexanes (20%) to obtain a mixture of ß (**21**) and α (**27**) (680 mg, 58.77%, 2:1) as a foam: UV (MeOH) λ_{max} 258 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75-0.80 (d, 3 H, 2'-CH_3), 1.07 (br s, 9 H, *t*-butyl), 1.16-1.17 (d, 3 H, 2'-CH_3), 1.63-2.50 (m, 2 H, H-3'), 2.70-3.00 (m, 1 H, H-2'), 3.60-4.00 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.24-4.48 and 4.60-4.70 (m, 1 H, H-4'), 5.70-5.80 (d, 6-NH, D_2O exchangeable), 6.25 and 6.39 (d, 1 H, H-1'), 7.27-7.76 (m, 10 H, 2xPh), 8.10 (s, 1 H, H-8), 8.25 (s, 1 H, H-2).

6-Chloro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]-9H-purine (22) and 6-Chloro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]-9H-purine (28). A suspension of 6-chloropurine (0.5 g, 3.23 mmol) and ammonium sulfate (0.01 g, 0.076 mmol) in HMDS (40 mL) was refluxed for 3 h. HMDS was evaporated under reduced pressure to obtain silylated 6-chloropurine as a yellow solid. Acetate **6** (0.85 g, 2.05 mmol) in dry 1,2-dichloroethane (20 mL) was added to the crude silylated base under nitrogen. The reaction mixture was cooled to -22°C, TMSOTf (0.8

mL, 4.12 mmol) added dropwise, and the solution stirred for 15 min (-22°C) and then an additional 20 min at rt. The reaction mixture was poured into ice cold EtOAc/saturated $NaHCO_3$ solution, and the organic layer washed once with saturated $NaHCO_3$ solution, water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with EtOAc/hexanes (33%) to produce a mixture of ß (**22**) and α (**28**) anomer (750 mg, 70%, 2:1) as a foam: UV (MeOH) λ_{max} 265.5 nm; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.75-0.80 (d, 3 H, 2'-CH_3), 1.10 (br s, 9 H, *t*-butyl), 1.16-1.17 (d, 3 H, 2'-CH_3), 1.80-2.50 (m, 2 H, H-3'), 2.70-3.00 (m, 1 H, H-2'), 3.70-4.00 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.20-4.70 (m, 1 H, H-4'), 6.00 and 6.50 (d, 1 H, H-1'), 7.27-7.76 (m, 10 H, 2xPh), 8.10 (s, 1 H, H-8), 8.25 (s, 1 H, H-2).

9-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]hypoxanthine (23) and 9-[(5-*O*-*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]hypoxanthine (29). 2–Mercaptoethanol (0.36 mL, 5.7 mmol) and NaOMe (0.033 g, 0.611 mmol) were added to a solution of **23** and **29** in MeOH (60 mL) and the mixture refluxed for 4 h. The mixture was then cooled, neutralized with acetic acid, diluted with water (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water (50 mL), saturated $NaHCO_3$, dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the residue column chromatographed with EtOAc/hexanes (35%) to obtain an inseparable mixture of **23** and **29** as white foam (410 mg, 57.7%, 1.8:1): UV (MeOH) λ_{max} 250 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71-0.73 (d, 3 H, 2'-CH_3), 1.08 (br s, 9 H, *t*-butyl), 1.18-1.20 (d, 3 H, 2'-CH_3), 1.77-1.84 (m, 1 H, H-3'$_a$), 2.27-2.36 (m, 1 H, H-3'$_b$), 2.73-2.91 (m, 1 H, H-2'), 3.60-3.93 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.60 (m, 1 H, H-4'), 5.81-5.83 (d, 1 H, H-1', $J_{H1',H2'}$=4.6 Hz), 6.31-6.33 (d, 1 H,H-1', $J_{H1',H2'}$=6.1 Hz), 7.27-7.76 (m, 10 H, 2xPh), 8.08 (s, 1 H, H-8), 8.11 (s, 1 H, H-2).

6-Chloro-2-fluoro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]-9H-purine (24) and 6-Chloro-2-fluoro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]-9H-purine (30). A suspension of 6-chloro-2-fluoropurine (2.5 g, 14.8 mmol) and ammonium sulfate (10 mg, 0.076 mmol) in HMDS (50 mL) was refluxed for 4 h under nitrogen until a clear solution was obtained. The mixture was cooled to rt and HMDS evaporated under reduced pressure to obtain silylated 6-chloro-2-fluoropurine as a white solid. Acetate **6** (2.6 g, 6.3 mmol) in dry methylene chloride (40 mL) was added to silylated base dissolved in dry methylene chloride (15 mL) under nitrogen. The reaction mixture was cooled to -22°C, TMSOTf (2 mL, 10 mmol) added dropwise, and stirred for 30 min (-22°C) followed by 20 min at rt. The reaction mixture was poured into ice cold

EtOAc/saturated $NaHCO_3$ solution, the organic layer washed once with saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with EtOAc/hexanes (33%) to obtain an inseparable mixture of **24** and **30** (2.5 g, 84%, 1.3:1): UV (MeOH) λ_{max} 269 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.74-0.76 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.10 (br s, 9 H, *t*-butyl), 1.24-1.26 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=7.0 Hz), 1.77-2.36 (m, 1 H, H-3'), 2.73-2.90 (m, 1 H, H-2'), 3.60-3.93 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.40 and 4.60 (m, 1 H, H-4'), 5.81-5.83 and 6.33 (d, 1 H, H-1'), 7.27-7.76 (m, 10 H, 2xPh), 8.08 (s, 1 H, H-8), 8.43 (s, 1 H, H-2).

2-Amino-6-chloro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]-9H-purine (25), 2-Amino-6-chloro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]-9H-purine (31), 6-Amino-2-fluoro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-ß-*D*-*erythro*-pentofuranosyl]-9H-purine (26), and 6-Amino-2-fluoro-9-[(5-*O*-*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-C-methyl-α-*D*-*erythro*-pentofuranosyl]-9H-purine (32). Anhydrous ammonia was bubbled through a stirred solution of the mixture of **24** and **30** (2.2 g, 4.69 mmol) in DME for 15 min, and the solution stirred for 18 h at rt. The solvent was then removed under reduced pressure, and the residue was column chromatographed with EtOAc/hexanes (50%) to obtain 550 mg, 25% of compound **25** as a white foam and 500 mg, 23% of compound **31** as white foam. Compound **25**: UV (MeOH) λ_{max} 310 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (br s, 9 H, *t*-butyl), 1.17-1.19 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.81-1.86 (m, 1 H, H-3'$_a$), 2.28-2.33 (m, 1 H, H-3'$_b$), 2.78-2.81 (m, 1 H, H-2'), 3.71-3.75 (dd, 1 H, H-5'$_a$, $J_{4',5'a}$=4.2 Hz, $J_{5'b,5'a}$=10.9 Hz), 4.33-4.37 (m, 1 H, H-4'), 5.68-5.69 (d, 1 H, H-1', $J_{1',2'}$=5.5 Hz), 6.31-6.33 (d, 1 H, H-1', $J_{H1',H2'}$=6.1 Hz), 7.27-7.76 (m, 10 H, 2xPh), 7.80 (s, 1 H, H-8), 8.00 (s, 1 H, H-2); and compound **31**: UV (MeOH) λ_{max} 311 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73-0.75 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.10 (br s, 9 H, *t*-butyl), 1.91-1.95 (m, 1 H, H-3'$_a$), 2.27-2.31 (m, 1 H, H-3'$_b$), 2.88 (m, 1 H, H-2'), 3.60-3.93 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.60 (m, 1 H, H-4'), 6.19-6.21 (d, 1 H, H-1', $J_{1',2'}$=6.1 Hz), 7.27-7.76 (m, 10 H, 2xPh), 7.65 (s, 1 H, H-8), 7.87 (s, 1 H, H-2). Further elution with EtOAc/hexanes (33%) gave 740 mg, 33% of compounds **26** and **32** as an inseparable mixture, as a white foam: UV (MeOH) λ_{max} 262 nm, 270 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.10 (br s, 9 H, *t*-butyl), 1.24-1.26 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=7.0 Hz), 1.79-1.82 (m, 1 H, H-3'$_a$), 2.31-2.34 (m, 1 H, H-3'$_b$), 2.73-2.90 (m, 1 H, H-2'), 3.73-3.76 (dd, 1 H, H-5'$_a$, $J_{H5'a,H5'b}$=11.0 Hz, $J_{H5'b,H4'}$=5.1 Hz), 3.91-3.94 (dd, 1 H, H-5'$_a$, J

$_{H5'a,H5'b}$=11.0 Hz, $J_{H5'b,H4'}$=5.1 Hz), 4.35 and 4.60 (m, 1 H, H-4'), 5.75-5.78 and 6.00 (d, 1 H, H-1'), 5.78 (br s, 2 H, NH_2), 7.27-7.76 (m, 10 H, 2xPh), 8.01 (s, 1 H, H-8).

9-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)adenine (34) and 9-(2,3-Dideoxy-2-C-methyl-α-*D-erythro* -pentofuranosyl)adenine (39). A 1 M solution of TBAF (1.1 mL, 1.1 mmol) was added to a mixture of **21** and **27** (520 mg, 1.06 mmol) in THF (20 mL) and the reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure, the residue chromatographed over silica gel with 6% MeOH/$CHCl_3$ to obtain 118 mg, 46.7% of compound **34**, which was crystallized from MeOH/$CHCl_3$ to provide a white solid: mp 210-212°C; $[\alpha]_D^{25}$ -6.87° (c 0.5, MeOH); UV (H_2O) λ_{max} 257.5 nm (ε 8,545) (pH 11), 258.5 nm (ε 9,378) (pH 7), 255.0 nm (ε 8,546) (pH 2); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 1.04-1.07 (d, 3 H, 2'-CH_3, $J_{CH3',H2'}$=6.6 Hz), 1.78-1.88 (m, 2 H, H-3'$_a$), 2.50 (m, 1 H, H-3'$_b$) 2.82-2.85 (m, 1 H, H-2'), 3.47-3.60 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.20 (m, 1 H, H-4'), 5.19-5.21 (m, 5'-OH, D_2O exchangeable), 5.70-5.73 (d, 1 H, H-1', $J_{H1',H2'}$=6.0 Hz), 7.38 (br s, 2 H, NH_2, D_2O exchangeable), 8.12 (s, 1 H, H-8), 8.35 (s, 1 H, H-2); Anal Calcd for $C_{11}H_{15}N_5O_2$, 0.25 H_2O: C, 50.43; H, 6.31; N, 26.74. Found: C, 50.29; H, 5.92; N, 26.39 and compound **39** (74 mg, 29 %), crystallized from MeOH/hexanes to produce a white solid: mp 180°C; $[\alpha]_D^{25}$ 97.75° (c 0.2, MeOH); UV (H_2O) λ_{max} 260 nm (ε 2,772) (pH 11), 257.5 nm (ε 2,954) (pH 7), 258.5 nm (ε 2,163) (pH 2); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 0.59-0.61 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.7 Hz), 1.90-2.09 (m, 2 H, H-3'$_a$, H-3'$_b$), 2.79 (m, 1 H, H-2'), 3.30-3.45 (m, 2 H, H-5'$_a$, H-5'$_b$,), 4.59 (m, 1 H, H-4'), 4.82-4.86 (m, 5'-OH, D_2O exchangeable), 6.25 -6.26 (d, 1 H, H-1', $J_{H1',H2'}$=6.4 Hz), 7.38 (br s, 2 H, NH_2, D_2O exchangeable), 8.13 (s, 1 H, H-8), 8.17 (s, 1 H, H-2); Anal Calcd for $C_{11}H_{15}N_5O_2$, 0.2 CH_3OH: C, 52.28; H, 6.2; N, 27.22. Found: C, 52.39; H, 5.98; N, 27.00.

9-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)hypoxanthine (35) and 9-(2,3-Dideoxy-2-C-methyl-α-*D-erythro*-pentofuranosyl) hypoxanthine (40). A mixture of **23** and **29** (340 mg, 0.68 mmol) was deprotected using the same procedure (TBAF) as for adenosine derivatives and purified over silica gel with 10% MeOH/$CHCl_3$. Fractional recrystallization from EtOAc, produced 69 mg, 39.6% of the ß-anomer, compound **35** as a white solid and 33 mg of α-anomer compound **40** (18.9%) as a white solid. Compound **35**: mp 205°C (dec); $[\alpha]_D^{25}$ 71.76° (c 0.22, MeOH); UV (H_2O) λ_{max} 248.5 nm (ε 7,403) (pH 11), 249.0 nm (ε 6,482) (pH 7), 249.0 nm (ε 6,043) (pH 2); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.07-1.09 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.8 Hz), 1.74-1.83 (m, 1 H, H-3'$_a$), 2.16-2.53 (m, 1 H, H-3'$_b$), 2.71-2.77 (m, 1 H, H-2'), 3.56-3.64 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.22 (m, 1 H, H-4'), 4.99 (m, 5'-OH, D_2O exchangeable), 5.71-5.73 (d, 1 H, H-1', $J_{H1',H2'}$=5.4 Hz), 8.05 (s, 1 H, H-8), 8.34 (s, 1

H, H-2), 12.4 (s, 1 H, NH, D_2O exchangeable); Anal Calcd for $C_{11}H_{14}N_4O_3$, 0.5 H_2O, 0.5 CH_3OH: C, 50.0; H, 5.84; N, 20.29. Found: C, 49.66; H, 5.80; N, 19.90 and compound **40**: mp 203°C (dec); $[\alpha]^{25}$ -9.51° (c 0.2, MeOH); UV (H_2O) λ_{max} 249 nm (ε 11,137) (pH 11), 248.0 nm (ε 8,574) (pH 7), 249.5 nm (ε 6,431) (pH 2); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.59-0.61 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.7 Hz), 1.90-2.09 (m, 2 H, H-3'$_a$, H-3'$_b$), 2.79 (m, 1 H, H-2'), 3.30-3.45 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.59 (m, 1 H, H-4'), 4.82-4.86 (m, 5'-OH, D_2O exchangeable), 6.25-6.26 (d, 1 H, H-1', $J_{H1',H2'}$=6.4 Hz), 8.13 (s, 1 H, H-8), 8.17 (s, 1 H, H-2), 12.36 (s, 1 H, NH, D_2O exchangeable); Anal Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.63; N, 22.39. Found: C, 52.57; H, 5.97; N, 20.96.

Enzymatic conversion to 9-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)hypoxanthine (35) from 9-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)adenine (34). Compound **34** (30 mg, 0.12 mmol) was dissolved in distilled water (10 mL) and added to a solution of 7 mg of adenosine deaminase (1.5 units/ mg) in 3 mL of distilled water. The mixture was stirred at rt for 4 h, diluted with MeOH, and the solution evaporated to dryness. The residue was redissolved in methanol and filtered. The filtrate was concentrated and purified by prep. TLC with 10% MeOH/$CHCl_3$ to obtain 25 mg, 83% of the desired product **35**. Spectroscopic data was identical to that reported above.

2-Amino-6-chloro-9-(2,3-dideoxy-2-C-methyl-ß-*D-erythro* -pento furanosyl)-9H-purine (36). Compound **25** (400 mg, 0.79 mmol) was deprotected as previously described (TBAF) and purified over silica gel with 10% MeOH/$CHCl_3$, and recrystallized from EtOAc/hexanes to obtain 146 mg of **36** (64%): mp (softens 120°C, dec. 200°); UV(H_2O) λ_{max} 308.0 nm (ε 8,041) (pH 11), 313.5 nm (ε 7,585) (pH 7), 309.7 nm (ε 5,468) (pH 2) ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.07-1.09 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.7 Hz), 1.74-1.81 (m, 1 H, H-3'$_a$), 2.20-2.25 (m, 1 H, H-3'$_b$), 2.78-2.82 (m, 1 H, H-2'), 3.44-3.64 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.18-4.22 (m, 1 H, H-4'), 4.93-4.97 (pseudo t, 5'-OH, J =5.4, 5.6 Hz, D_2O exchangeable), 5.62-5.64 (d, 1 H, H-1', $J_{H1',H2'}$=5.4 Hz), 6.94 (br s, 2 H, NH_2, D_2O exchangeable), 8.38 (s, 1 H, H-2); Anal Calcd for $C_{11}H_{14}N_5O_2Cl$, 0.18 $CHCl_3$, 0.45 $C_4H_8O_2$: C, 45.77; H, 5.22; N, 20.39. Found: C, 45.41; H, 4.85; N, 20.16.

2-Fluoro-9-(2,3-dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl) adenine (37) and 2-Fluoro-9-(2,3-dideoxy-2-C-methyl-α-*D-erythro*-pento furanosyl)adenine (42). The mixture of compounds **26** and **32** (600 mg, 1.2 mmol) was deprotected as stated before (TBAF) and purified over silica gel with 10% MeOH/$CHCl_3$ to obtain 120 mg of **37** (40%) as white solid: mp >250°C (dec); UV (H_2O)

λ_{max} 261.0 nm (ε 9,112), 268.5 nm sh (ε 6,527) (pH 11), 261.0 nm (ε 9,515), 267.5 nm sh (ε 7,985) (pH 7), 263.5 nm (ε 9,962), 269.5 nm sh (8,926) (pH 2); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.03-1.05 (d, 3 H, 2'-CH_3, $J_{2'CH3,\ H2'}$=6.8 Hz), 1.70-1.81 (m, 1 H, H-3'$_a$), 2.13-2.20 (m, 1 H, H-3'$_b$), 2.70-2.81 (m, 1 H, H-2'), 3.13-3.64 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.14-4.17 (m, 1 H, H-4'), 5.09 (pseudo t, 5'-OH, J =4.7, 5.5 Hz, D_2O exchangeable), 5.62-5.64 (d, 1 H, H-1', $J_{H1',H2'}$=5.5 Hz), 7.84 (br s, 2 H, NH_2, D_2O exchangeable), 8.35 (s, 1 H, H-2); Anal Calcd for $C_{11}H_{14}N_5O_2F$, 0.45 H_2O: C, 47.95; H, 5.45; N, 25.42. Found: C, 47.84; H, 5.22; N, 25.42 and 100 mg of compound **42** (33%) as a white solid: mp 142-144°C; UV (H_2O) λ_{max} 261.0 nm (ε 9,455) , 267.5 nm sh (ε 7,877) (pH 11), 261.0 nm (ε 8,715), 267.0 nm sh (ε 8,315) (pH 7), 263.0 nm (ε 10,661), 269 nm sh (ε 9,226) (pH 2); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.60-0.63 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.8 Hz), 1.90-2.11 (m, 2 H, H-3'$_a$, H-3'$_b$), 2.78 (m, 1 H, H-2'), 3.31-3.44 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.58 (m, 1 H, H-4'), 4.81-4.84 (dd, 5'-OH, J =4.2, 5.60 Hz, D_2O exchangeable), 6.13-6.15 (d, 1 H, H-1', $J_{H1',H2'}$=6.3 Hz), 7.82 (br s, 2 H, NH_2), 8.15 (s, 1 H, H-2); Anal Calcd for $C_{11}H_{14}N_5O_2F$, 0.11 $CHCl_3$, 1.0 CH_3OH: C, 46.48; H, 5.83; N, 22.39. Found: C, 46.30; H, 5.55; N,22.44.

9-(2,3-Dideoxy-2-C-methyl-ß-*D-erythro*-pentofuranosyl)guanosine (38). Compound **36** (50 mg, 0.17 mmol) was dissolved in 25 mL of distilled water and added to a solution of 10 mg of adenosine deaminase (1.5 units/mg) in 3 mL of distilled water. The mixture was stirred at rt for 6 h, then quenched by adding MeOH, and evaporated to dryness. The residue was dissolved in methanol and filtered. The filtrate was concentrated andpurified by prep. TLC with 10% MeOH/$CHCl_3$ to obtain the desired product **38** which was further recrystallized from ether/chloroform (35 mg, 75%): mp >200°C; UV (H_2O) λ_{max} 256.5 nm (ε 9,005) (pH 11), 253.0 nm (ε 9,510) (pH 7), 248.0 nm (ε 5,173) (pH 2); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.06-1.08 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.9 Hz), 1.74-1.81 (m, 1 H, H-3'$_a$), 2.17-2.25 (m, 1 H, H-3'$_b$), 2.77-2.82 (m, 1 H, H-2'), 3.46-3.64 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.18-4.22 (m, 1 H, H-4'), 5.09 (pseudo t, 5' OH, D_2O exchangeable), 5.48-5.50 (d, 1 H, H-1', $J_{H1',H2'}$=6.0 Hz), 6.61 (br s, 2 H, NH_2, D_2O exchangeable), 8.53 (s, 1 H, H-2), 10.90 (br s, 1 H, NH, D_2O exchangeable); Anal Calcd for $C_{11}H_{15}N_5O_3$, 2.47 $C_4H_{10}O$, 0.3 $CHCl_3$: C, 52.52; H, 8.26; N, 14.41. Found: C, 52.85; H,7.87; N, 14.3.

2-Amino-6-chloro-9-(2,3-dideoxy-2-C-methyl-α-*D-erythro*-pento furanosyl)-9H-purine (41). Compound **31** (200 mg, 0.395 mmol) was deprotected as before (TBAF) and then purified by prep. TLC with 10% MeOH/$CHCl_3$ to obtain 69 mg of **41** which was recrystallized from EtOAc to obtain 60 mg (60%) as a white solid: mp 140-145°C; UV (H_2O) λ_{max} 307.0 nm (ε 7,411) (pH 11), 313.0 nm (ε 7,415) (pH 7),

307.0 nm (ε 4,782) (pH 2); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.63-0.66 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.8 Hz), 1.51-2.09 (m, 2 H, H-3'$_a$, H-3'$_b$), 2.76-2.82 (m, 1 H, H-2'), 3.13-3.44 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.59-4.61 (m, 1 H, H-4'), 4.82-4.86 (m, 5'-OH, J =4.8 and 5.6 Hz D_2O), 6.14-6.16 (d, 1 H, H-1', $J_{H1',H2'}$=6.4 Hz), 6.94 (br s, 2 H, NH_2), 8.38 (s, 1 H, H-2); Anal Calcd for $C_{11}H_{14}N_5O_2Cl$, 0.6 H_2O, 0.47 $C_4H_8O_2$: C, 46.43; H, 5.43; N, 21.02; Cl, 10.65. Found: C, 46.36; H, 5.78; N, 20.68; Cl, 10.81.

9-(2,3-Dideoxy-2-C-methyl-α-*D-erythro*-pentofuranosyl)guanosine (43). 2-Mercaptoethanol (0.24 mL ,3.6 mmol) and NaOMe (0.025 g, 0.463 mmol) were added to a solution of **41** (150 mg, 0.30 mmol) in MeOH (15 mL) and the mixture was refluxed for 24 h. Then the mixture was cooled, acidified with acetic acid to pH 8, and evaporated to dryness. The residue was column chromatographed to obtain a white foam (120 mg, 83%). 90 mg of this residue was dissolved in 10 mL of THF and 1M TBAF solution (0.18 mL, 0.18 mmol) was then added to the stirring mixture. After 4 h, and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel using 10% MeOH/$CHCl_3$ to obtain 36 mg (75%) of **43**, and crystallized from EtOAc: mp >200°C; UV (H_2O) λ_{max} 259.5 nm (ε 6,500) (pH 11), 251.5 nm (ε 3,779) (pH 7), 253.5 nm (ε 4,225) (pH 2); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.61-0.64 (d, 3 H, 2'-CH_3, $J_{CH3,H2'}$=6.8 Hz), 1.90-2.11 (m, 2 H, H-3'$_a$, H-3'$_b$), 2.78 (m, 1 H, H-2'), 3.31-3.44 (m, 2 H, H-5'$_a$, H-5'$_b$), 4.58 (m, 1 H, H-4'), 4.81-4.84 (m, 5'-OH, J =4.2 and 5.6 Hz, D_2O exchangeable), 6.13-6.15 (d, 1 H, H-1', $J_{H1',H2'}$=5.5 Hz), 6.60 (br s, 2 H, NH_2, D_2O exchangeable), 8.35 (s, 1 H, H-2), 10.85 (br s, 2 H, NH_2, D_2O exchangeable); Anal Calcd for $C_{11}H_{14}N_5O_3$, 1.1 $C_4H_8O_2$, 0.3 $CHCl_3$: C, 50.68; H, 6.51; N, 19.16. Found: C, 50.37; H, 5.67; N, 19.04.

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