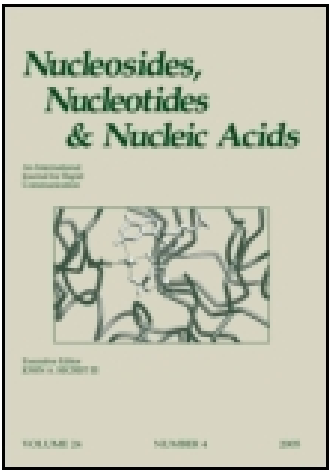

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Stereoselective Synthesis of β-L-2′, 3′-Dideoxy-and L-2′,3′-Didehydro-2′,3′-Dideoxy Purine Nucleosides

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STEREOSELECTIVE SYNTHESIS OF β-L-2',3'- DIDEOXY- AND L-2',3'-DIDEHYDRO-2',3'-DIDEOXY PURINE NUCLEOSIDES

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ABSTRACT: β-L-2',3'-Dideoxy- and L-2',3'-didehydro-2',3'-dideoxy purine nucleosides have been synthesized *via* a highly stereoselective method of glycosylation by the condensation of L-2-(phenylselenyl)-2,3-dideoxyribose derivative with silylated heterocyclic base.

Introduction

Since the identification of human immunodeficiency virus (HIV) as the causative agent of AIDS, intensive efforts have been made toward the discovery of clinically useful anti-HIV agents. To date, there are five nucleosides reverse transcriptase inhibitors (AZT, ddC, ddI, d4T and 3TC) approved by the FDA for the treatment of AIDS. However, drug resistance and toxicity of the existing regimens limit their long-term usefulness, which prompts the development of additional anti-HIV agents to overcome these drawbacks.

Previously, β–D-2',3'-dideoxynucleosides (ddN) and β–D-2',3'-dideoxy-2',3'-didehydronucleosides (d4N) have shown significant anti-HIV activity.[1] Of the purine nucleosides, β–D-2',3'-dideoxyadenosine (D-ddA)[2] and β–D-2',3'-dideoxy-2',3'-didehydroadenosine (D-d4A)[3] exhibited significant anti-HIV activity. However, D-ddA is susceptible to the action of adenosine deaminase[4] (ADA) and purine nucleoside phosphorylase[5] (PNP), leading to inactive metabolites.

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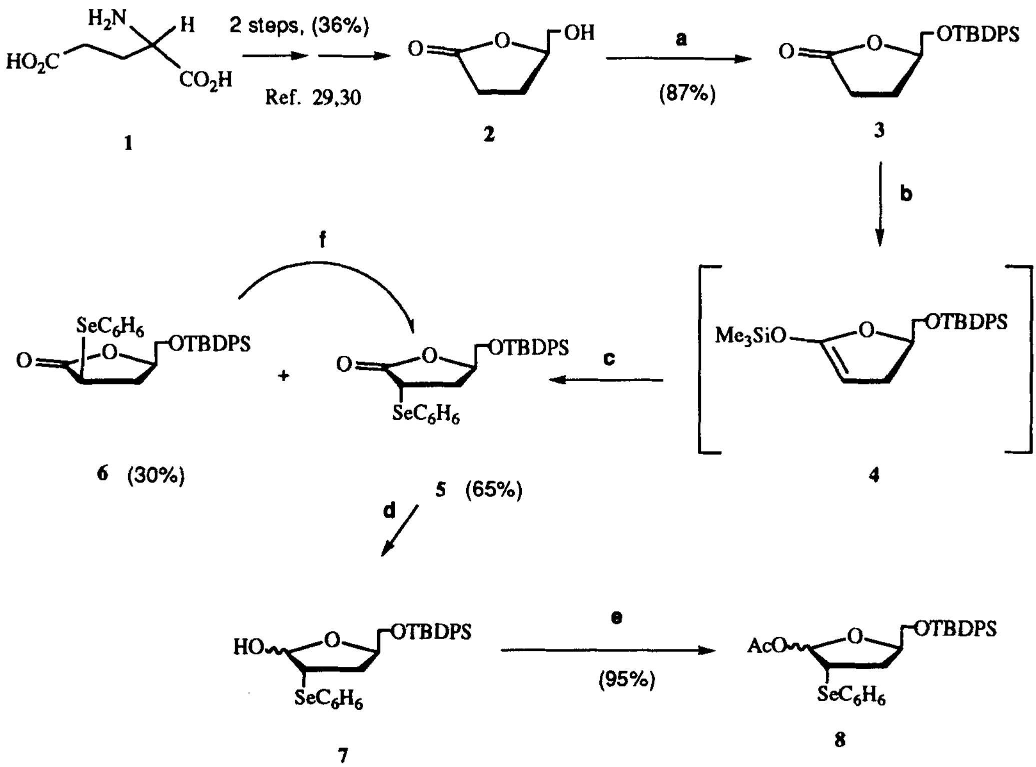
Recently, a number of L-nucleosides including (–)-(2'*R*,5'*S*)-1-(2-hydroxymethyl-oxathiolan-5-yl)cytosine (3TC),[6,7] (–)-β-L-2',3'-dideoxy-5-fluoro-3'-thiacytidine (FTC),[8] β-L-2',3'-dideoxy-5-fluorocytidine (L-FddC),[9,10] (–)-cis-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (OddC)[11] and β-L-2'-fluoro-5-methylarabinofuranosyl uracil (L-FMAU)[12] have been synthesized as antiviral and/or anticancer agents. Both 3TC and FTC have shown more potent antiviral activity against HIV and hepatitis B virus (HBV) and less toxicity than their D-counterparts.[13,14] Furthermore, it has been reported that unlike their D-enantiomers, 3TC and L-FTC were resistant against cytidine deaminase which may be related to their increased anti-HIV and anti-HBV activity.[14,15] As D-ddA, d_4A and their analogs exhibited potent anti-HIV activity, it is of interest to synthesize the corresponding L-nucleosides in anticipation of promising antiviral agents.

For the preparation of 2',3'-unsaturated-D-nucleosides, several synthetic methods have been reported. The syntheses of these compounds followed two principal routes. One method is to use a nucleoside as starting material. For example, Horwitz and co-workers reported the method that involved the elimination of 3'-*O*-sulfonyl esters of 2'-deoxynucleosides.[16,17] Some 2',3'-unsaturated-D-nucleosides were obtained directly from the corresponding ribonucleosides by treating with acetoxyisobutyryl halides followed by the reductive elimination of 2'-acetoxy-3'-halogeno or 3'-acetoxy-2'-halogeno derivatives.[18,19] Barton and co-workers[20,21] reported the synthesis of olefinic compounds from the corresponding *vic*-diols through their bisxanthates. Chu and co-workers reported[22] a general method for 2',3'-unsaturated nucleosides from the corresponding ribonucleosides *via* bisxanthates followed by the reductive elimination with tributyl tin hydride or *via* cyclic thiocarbonates followed by deoxygenated with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.

Another method is to condense 2',3'-dideoxyribose analog with a nucleobase in the presence of a Lewis acid (Hilbert-Johnson reaction) to obtain the desired nucleoside as a mixture of α- and β- anomers, which can be separated. A major drawback is the production of varying ratios of α,β-mixtures.[23,24] Introducing a phenylselenenyl group at the 2-position of the sugar moiety results in the desired β stereoselectivity during the condensation of the sugar moiety and heterocycle by providing steric hindrance as well



Scheme 1: Reagents and conditions: **a**: TBDPSCl/imidazole, CH_2Cl_2, rt, 3 h. **b**: LiHMDS/Me_3SiCl, THF, -78 °C, 30 min. **c**: PhSeBr/THF, -78 °C. **d**: DIBAL-H, toluene, 1.5 h, -78 °C. **e**: Ac_2O/Et_3N, DMAP, CH_2Cl_2, rt, 2 h. **f**: DBU or diethylamine

as a neighboring group effect.[25,26] This method has been applied to the synthesis of D-ddT, D-d_4T and other D-form nucleosides, such as ddC, ddI, ddA and d_4A.[27] Recently, we have applied this method to the synthesis of L-purine nucleosides and their antiviral activities have been reported as a communication.[28] We now report the full account of synthetic procedures of purine derivatives.

Results and Discussion

Compound **2** was synthesized from D-glutamic acid in 2 steps by reported procedures.[29,30] Silylation of **2** with *tert*-butyldiphenylsilyl chloride afforded **3** in 87% yield (Scheme 1). Treatment of the lactone **3** at -78 °C with lithium bis(trimethylsilyl)-

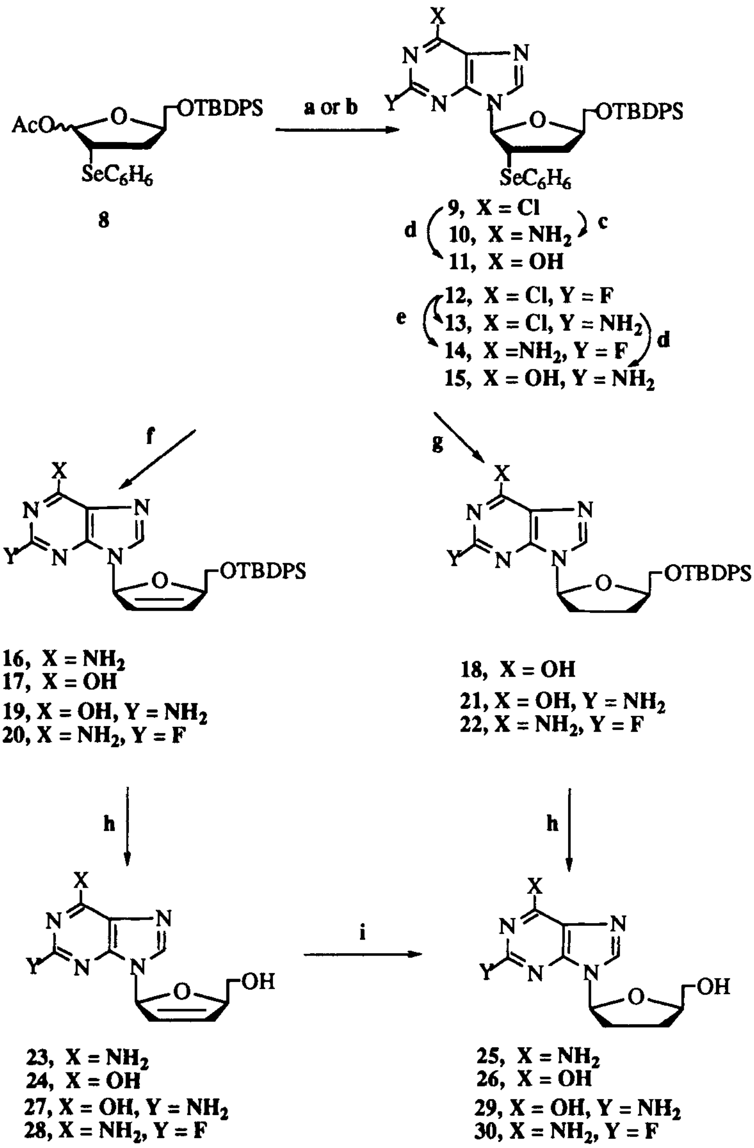
amine followed by the addition of chlorotrimethylsilane gave silyl enol ether **4**, which was reacted with phenylselenenyl bromide to give the major C_2 α phenylselenenyl lactone **5** (63%) and the minor C_2 β isomer **6** (30%). Compound **6** could be equilibrated to a mixture of the α- and β-isomer (α:β ≈ 3:2) by the treatment of DBU or diethylamine. Reduction of C_2α-isomer **5** with DIBAL-H at -78 °C followed by acetylation with Ac_2O/Et_3N/DMAP in CH_2Cl_2 at room temperature gave the key intermediate **8** in quantitative yield.

The stereoselectivity for the β-anomer was high (95%) during the coupling of the acetate **8** with purine bases (Scheme 2). The condensations of acetate **8** with silylated 6-chloropurine and 6-chloro-2-fluoropurine[31] using 1.7 equivalents of TMSOTf were conducted at -25 °C in 1,2-dichloroethane and gave exclusively the desired β-anomers of 6-chloropurine selenenyl nucleoside **9** and 6-chloro-2-fluoropurine selenenyl nucleoside **12** as solids in 88% and 78% yield, respectively after recrystallization.

6-Chloropurine nucleoside **9** was refluxed with 2-mercaptoethanol and sodium methoxide in MeOH to provide the hypoxanthine derivative **11**. Careful deprotection of **11** by treatment with H_2O_2/pyridine followed by desilylation with TBAF provided L-d_4I (**24**). Compound **11** was converted to L-ddI (**26**) by treating with Bu_3SnH/Et_3B in benzene followed by silyl deprotection.

Introducing ammonia into a solution of compound **12** in DME at room temperature gave the 2-amino-6-chloropurine derivative **13** and the 6-amino-2-fluoropurine derivative **14** in 59% and 35% yields, respectively.[27] Compound **13** was treated with sodium methoxide and 2-mercaptoethanol in methanol to give the guanine derivative **15** which were carefully reacted with H_2O_2/pyridine to give **19** in a low yield. Desilylation of compound **19** with TBAF gave the target compound **27** (L-d_4G, 14%). Compound **14** was converted to compound **28** by treating with H_2O_2/pyridine followed by silyl deprotection. Treatment of compounds **14** and **15** with n-Bu_3SnH/Et_3B followed by deprotection with TBAF gave the target compounds **30** and **29**, respectively.

The nucleosides obtained were characterized by spectroscopic methods in comparison to those of known D-isomers. Furthermore, the configuration of β-D-2',3'-dideoxy-2',3'-didehydroadenosine **23** (L-d4A) has been unambiguously determined by a



Scheme 2: Reagents and conditions: **a**: TMS-6-chloropurine, TMSOTf, $ClCH_2CH_2Cl$, -22 °C. **b**: TMS-6-chloro-2-fluoropurine, TMSOTf, $ClCH_2CH_2Cl$, 0 °C. **c**: NH_3/MeOH, 80 °C. **d**: $HSCH_2CH_2OH$, MeOH, reflux, 24 h. **e**: NH_3/DME. **f**: H_2O_2, pyridine, CH_2Cl_2, 0 °C. **g**: Bu_3SnH, Et_3B, benzene, rt. **h**: 1M TBAF/THF, rt. **i**: 15 psi H_2, 10% Pd/C, rt.

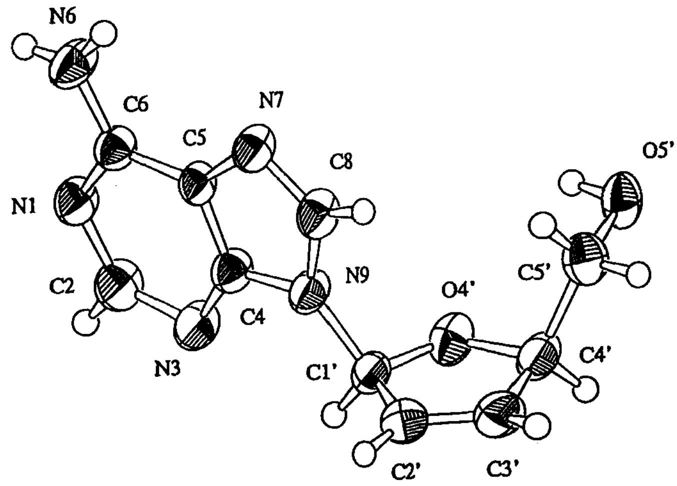


Figure 1. ORTEP Drawing of Compound 23 (L-D4A)

single crystal X-ray crystallography (Figure 1).[32] The X-ray study indicated that L-d4A (**23**) adopts a sugar puckering with the pseudorotational phase angle P = 62.29° and ν_{max} = 7.74°, the 5'-OH orientation γ = 179.7° (C3'–C4'–C5'–O5') and the base orientation χ = 99.7° (O4'–C1'–N9–C4).

It was observed that 2-fluoro-9-(2,3-dideoxy-ß-L-*glycero*-pent-2-enofuranosyl) adenine (**28**) was not stable. It decomposed to give the heterocyclic base and the half-life of **28** is around 24 h under experimental conditions (phosphate buffer, pH7.4, 37 °C). The instability of **28** is probably due to the strong electron withdrawing effect of fluorine atom, which facilitates the cleavage of the glycosidic bond.

Experimental

Melting points were determined on a Mel-temp II apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker 400 AMX spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR with tetramethylsilane as the internal standard (δ in ppm, J in Hz). UV spectra were recorded on a Beckman DU-650 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using silica gel G (TLC grade, >440 mesh) for vacuum flash column chromatography. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-L-*glycero*-pentonic acid-γ -lactone (3) Imidazole (21.44g, 0.315 mol) and *tert*-butyldiphenylsilyl chloride (54.7 mL, 0.21 mol) were added to a solution of the lactone **2** [29,30](16.25 g, 0.14 mol) in dry CH_2Cl_2 (180 mL) under nitrogen at room temperature. The reaction mixture was stirred for 3 h at room temperature, diluted with CH_2Cl_2 (100 mL), washed with water (3 X 100 mL) and brine (2 X 100 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude product as an oil which was crystallized from hexanes (100 mL) to give **3** (43 g, 87%). mp. 73-75 °C; ^{1}H NMR ($CDCl_3$): δ 1.06 (m, 9 H), 2.26 (m, 2 H), 2.51 (m , 1 H), 2.67 (m , 1 H), 3.70 (dd, J = 3.3, 11.4, 1 H), 3.88 (dd, J = 3.3, 11.4, 1 H), 4.60 (m, 1 H) , 4.71 (m, 6 H), 7.67 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.58, 26.68, 28.53, 65.41, 79.93, 127.80, 129.87, 132.46, 132.88, 135.48, 135.59, 177.47; Anal. Calcd for $C_{21}H_{26}O_3Si$: C, 71.15; H, 7.39. Found: C, 70.92; H, 7.35.

5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-L-*erythro*-pentonic acid-γ-lactone (5) Conversion of **3** (10 g, 28.22 mmol) to **5** was accomplished using a procedure similar to that described for the D enantiomers.[27] The resulting oil residue, which contained the major C_2 α isomer **5** and minor C_2 β isomer **6**, was purified by silica gel chromatography. Elution with ethyl acetate (0-5%) in hexanes gave the desired C_2 α isomer **5** (9.0 g, 62.6%) as a syrup. ^{1}H NMR ($CDCl_3$) δ 1.02(s, 9 H), 2.29 (m, 1 H), 2.68 (m, 1 H), 3.61 (dd, J = 3.2, 11.5, 1 H), 3.84 (dd, J = 3.2, 11.4, 1 H), 4.11 (m, 1 H), 4.36 (m, 1 H), 7.30-7.45 (m, 9 H), 7.60-7.68 (m, 6 H); Anal. Calcd for $C_{27}H_{30}O_3SeSi$: C, 63.64; H, 5.93. Found: C, 63.47; H, 6.02.

1-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-α-and-β-*L*-*erythro*-pentofuranose (8) Conversion of **5** (7.8 g, 15.31 mmol) to **7** was accomplished using a procedure similar to that described for the D enantiomers.[27] The resulting crude lactol 7, without further purification, was acetylated by treatment with acetic anhydride (3.75 g, 36.76 mmol), triethylamine (9.27 g, 91.61 mmol) and DMAP

(2.5 mg) in CH_2Cl_2 (40 mL) at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (3 X 50 mL), brine (2 X 50 mL), dried ($MgSO_4$), filtered, and concentrated. Compound **8** (8.5 g, quantitative yield) was obtained as yellow syrup (mixture of a-and ß-anomers); ^1H NMR ($CDCl_3$): δ 0.96 and1.05 (s, 9 H, *t*-Bu), 2.11 (s, 3 H, Ac), 1.85 - 2.65 (m, 2 H, 3-H), 3.50 - 3.82 (m, 3 H, 2- and 5-H), 4.40 (m, 1 H, 4-H), 6.27 (s, 0.66 H, 1-H), 6.45 (d, 0.33 H, 1-H), 7.25-7.67 (m, 15 H, 3 X C_6H_5).

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-β-L-*erythro*-pentofuranosyl]-6-chloro-9H-purine (9) Conversion of **8** (1.5 g, 2.7 mmol) to **9** was accomplished using a procedure similar to that described for the D enantiomers.[27] The resulting residue was separated by silica gel chromatography using $CHCl_3$ as the eluant to give **9** (1.55 g, 88%) as crystalline solid from hexanes. mp 110-112 °C; UV(MeOH) λ_{max}265 nm; ^1H NMR ($CDCl_3$) δ 1.08 (s, 9 H, t-Bu), 2.20 (m, 1 H, 3'-H_a), 2.69 (m, 1 H, 3'-H_b), 3.76 (dd, *J* = 3.6, 11.3 Hz, 1 H, 5'-H_a), 4.00 (dd, *J* = 3.4, 11.3, 1 H, 5'-H_b), 4.36 (m, 1 H, 2'-H), 4.42 (m, 1 H, 4'-H), 6.28 (d, *J* = 5.7, 1 H, 1'-H), 7.07 - 7.76 (m, 15 H, 3 X C_6H_5), 8.18 (s, 1H, 8-H), 8.60 (s, 1 H, 2-H); Anal. Calcd for $C_{32}H_{33}N_4O_2SiClSe$: C, 59.31; H, 5.10; N, 8.65. Found: C, 59.19; H, 5.14; N, 8.67.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-β-L-*glycero*-pent-2-enofuranosyl]adenine (17) A steel bomb containing **9** (1.1 g, 1.8 mmol) and NH_3 in MeOH (36 mL) was heated at 80 °C for 20 h. After cooling, the solvent was removed and the residue was purified by silica gel column chromatography with 5% MeOH in chloroform to give **10** (0.87 g, 69%) as a white solid (mp 155-156 °C; UV(MeOH) λ_{max} 259 nm). Compound **10** (0.78 g, 1.24 mmol) was dissolved in CH_2Cl_2 (8 mL) containing a catalytic amount of pyridine (1 drop), and the solution was cooled in an ice-water bath. A 30% solution of hydrogen peroxide (0.77 mL, 6.84 mmol) in water (1.7 mL) was added dropwise to the above solution with stirring. Meanwhile, the temperature of the reaction mixture was allowed to come to room temperature. The reaction mixture was stirred at room temperature for 1 h and then diluted with CH_2Cl_2 (10 mL) and ice water (10 mL). The organic layer was separated and dried ($MgSO_4$). The solvent was removed to dryness and the residue was purified by preparative TLC (6% MeOH in

$CHCl_3$) to give **16** (0.39 g, 66%) as a white solid. mp 155-156 °C; UV(H_2O) λ_{max} 261 nm ; ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9 H, *t*-Bu), 3.81 (m, 2 H, 5'-H), 5.02 (m, 1 H, 4'-H), 5.64 (br s, 2 H, NH_2), 6.06 (m, 1 H, 2'-H), 6.44 (m, 1 H, 3'-H), 7.09 (br s, 1 H, 1'-H), 7.32 - 7.61 (m, 10 H, 2 X C_6H_5), 7.88 (s, 1 H, 8-H), 8.37 (s, 1 H, 2-H). Anal. Calcd for $C_{26}H_{29}N_5O_2Si$: C, 66.21; H, 6.19; N, 14.85. Found: C, 65.96; H, 6.25; N, 14.78.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-β-L-*erythro*-pentofuranosyl]hypoxanthine (11) Mercaptoethanol (0.36 mL, 5.13 mmol) and NaOMe powder (292 mg, 5.4 mmol) were added to a solution of **9** (0.93 g, 1.435 mmol) in MeOH (80 mL) and the mixture was heated at reflux for 4 h. The reaction mixture was cooled, acidified with acetic acid, diluted with water (300 mL) and extracted with EtOAc (300 mL). The organic layer was washed with water and sat. $NaHCO_3$ solution (150 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed over a flash silica gel column using MeOH (0-3%) in $CHCl_3$ as the eluent to give **11** (0.863 g, 95.5%) as a solid. UV(MeOH) γ_{max} 245 nm, (pH 11) 256.5 nm; ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9 H, t-Bu), 2.18 (m, 1 H, 3'-H_a), 2.67 (m, 1 H, 3'-H_b), 3.75 (dd, *J* = 3.8, 11.2, 1 H, 5'-H_a), 3.96 (dd, *J* = 3.8, 11.3, 1 H, 5'-H_b), 4.21 (q, *J* = 6.7, 12.5, 1 H, 2'-H), 4.40 (m, 1 H, 4'-H), 6.16 (d, *J* = 5.3, 1 H, 1'-H), 7.16 - 7.67 (m, 15 H, 3 X C_6H_5), 7.88 (s, 1H, 8-H), 7.93 (s, 1 H, 2-H). Anal. Calcd for $C_{32}H_{34}N_4O_3SiSe \cdot 0.6CHCl_3$: C, 55.85; H, 4.97; N, 7.99. Found: C, 55.80; H, 5.27; N, 7.72.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-β-L-*glycero*-pentofuranosyl] hypoxanthine (18) 1M Et_3B in hexane (1.2 mL, 1.2 mmol) and n-Bu_3SnH (0.43 mL, 1.58 mmol) were added to a solution of **11** (0.240 g, 0.38 mmol) in dry benzene (5 mL) and the reaction mixture stirred for 1 h at room temperature. The solvent was evaporated and the residue was dissolved in acetonitrile (20 mL) and washed with hexanes (3 X 5 mL). The acetonitrile layer was evaporated and the residue was chromatographed over a flash silica gel column using (0-3%) MeOH in $CHCl_3$ as eluent to give **18** as syrup which was crystallized from hexanes/CH_2Cl_2 (0.127 g, 70.4%). mp 156-158 °C; UV(MeOH) λ_{max} 249.5 nm, (pH 11) 255.5 nm; ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9 H, *t*-Bu), 2.13 (m, 2 H, 3'-H), 2.48 (m, 2 H, 2'-H), 3.78 (dd, *J* = 4.3, 11.2, 1 H, 5'-H_a), 3.94 (dd, *J* = 3.8, 11.2, 1 H, 5'-H_b), 4.27 (m, 1 H, 4'-H), 6.28 (q, *J* = 2.8, 6.5, 1 H, 1'-H), 7.35 - 7.70 (m, 10 H, 2 X C_6H_5), 8.11 (s, 1 H, 8-H), 8.14 (s, 1 H, 2-H). Anal. Calcd for $C_{26}H_{30}N_4O_3Si{\cdot}0.5H_2O$: C, 65.47; H, 6.46; N, 11.58. Found: C, 64.64; H, 6.46; N, 11.52.

9-(2,3-Dideoxy-β-L-*glycero*-pentofuranosyl)hypoxanthine (L-ddI, 26) Conversion of **18** (100 mg, 0.21 mmol) to **26** was accomplished using a procedure similar to that described for **23**. The obtained residue was purified by silica gel column chromatography (0-9% MeOH: $CHCl_3$) to give **26** (45 mg, 90.7%) as a white crystal. mp 170-173 °C soften; UV(H_2O) λ_{max} (pH 7) 248.5 nm (ε 15,200), (pH 2) 248 nm (ε 13,600), (pH 11) 253.5 nm (ε 14,200); $[\alpha]_D^{27}$ 24.9 (c 0.15, H_2O). ^1H NMR (DMSO-d_6): δ 2.05 (m, 2 H, 3'-H), 2.41 (m, 2 H, 2'-H), 3.58 (m, 2 H, 5'-H), 4.13 (m, 1 H, 4'-H), 5.01 (br s, 1 H, 5'-OH), 6.21 (dd, J= 3.3 and 6.8 Hz, 1 H, 1'-H_a), 8.06 (s, 1 H, 8-H), 8.34 (s, 1 H, 2-H). Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.88; H, 5.11; N, 23.61. MS m/e 237$(M+1)^+$.

9-(2,3-Dideoxy-β-L-*glycero*-pent-2-enofuranosyl)adenine (L-d_4A, 23) A solution of TBAF in THF(1 M, 0.82 mL, 0.82 mmol) was added to a mixture of **16** (352 mg, 0.746 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 3 h and the solvent was removed under reduced pressure. The residue was purified by preparative TLC with 8% MeOH in $CHCl_3$ to give **23** (134 mg, 77%) as a white solid. mp 187-188 °C; $[\alpha]^{25}{}_D$ = 24.5 (c 0.5, DMSO); UV (MeOH) λ_{max} (pH 7) 259.5 nm (ε 13,400), (pH 2) 258 nm (ε 13,000), (pH 11) 260 nm (ε 13,000); ^1H NMR (DMSO-d_6) δ 3.59 (t, J = 4.6 Hz, 2 H, 5'-H), 4.90 (m, 1 H, 4'-H), 5.07 (t, J = 5.5 Hz, 1H, OH), 6.15 (ddd, J = 1.5, 1.8, 5.9 Hz, 1 H, 2'-H), 6.48 (ddd, J = 1.5, 1.8, 5.9 Hz, 1 H, 3'-H), 6.95 (m, 1H, 1'-H), 7.30 (br s, 2H, NH_2), 8.16 (s, 1H, 8-H), 8.23 (s, 1H, 2-H). Anal. Calcd for $C_{10}H_{11}N_5O_2$: C, 51.49; H, 4.75; N, 30.03. Found: C, 51.54; H, 4.77; N, 30.00. MS m/e 235 $(M+1)^+$.

9-(2,3-Dideoxy-β-*L-glycero*-pentofuranosyl)adenine (L-ddA, 25). Compound **23** (82 mg, 0.35 mmol) in MeOH (21 mL) was reacted with 10% Pd/C at 15 psi at rt for 1.5 h. The reaction mixture was filtered and concentrated. The residue was purified by crystallization from MeOH to give **25** (80 mg, 97%) as a solid. mp 182-183 °C; $[\alpha]^{28}{}_D$ = 13.18 (c 0.44, MeOH); UV(H_2O) λ_{max} (pH 7) 259.5 nm (ε 15,600), (pH 2) 259 nm (ε

14,900), (pH 11) 259.5 nm (ε 16,900); ^{1}H NMR (DMSO-d_6) δ 2.05 (m, 2 H, 3'-H), 2.41 (m, 2 H, 2'-H), 3.54 (m, 2 H, 5'-H), 4.11 (m, 1 H, 4'-H), 5.05 (br s, 1 H, 5'-OH), 6.21 (m, 1 H, 1'-H), 7.25 (br s, 2H, NH_2), 8.12 (s, 1 H, 8-H), 8.34 (s, 1 H, 2-H). Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.05; H, 5.57; N, 29.77. Found: C, 51.07; H, 5.57; N, 29.74. MS m/e 236 $(M+1)^+$.

9-(2,3-Dideoxy-β-L-*glycero*-pent-2-enofuranosyl)hypoxanthine (L-d$_4$I, 24) Compound **11** (0.23 g, 0.366 mmol) was dissolved in CH_2Cl_2 (2.3 mL) containing a catalytic amount of pyridine (1 drop) and the solution was cooled in an ice-water bath. A 30% solution of hydrogen peroxide (0.23 mL, 2.01 mmol) was diluted with water (0.45 mL) and was added dropwise to the above solution over a period of 20 min while stirring. The temperature of the reaction mixture was allowed to reach to 20 °C slowly, the reaction mixture was stirred at room temperature for 30 min and was diluted with CH_2Cl_2 (10 mL) and ice water (10 mL). The organic layer was separated and dried ($MgSO_4$). The solvent was removed to dryness to give a crude product of **17**, which was dissolved in THF (2.8 mL). A 1 M solution of TBAF in THF (0.29 mL, 0.29 mmol) was added to the above solution and the reaction mixture was stirred at room temperature until TLC showed complete disappearance of **17** (ca. 2 h). The solvent was removed under reduced pressure and flash silica gel chromatography with MeOH in $CHCl_3$ (3-10%) gave **24** (36 mg, 42% from **11**) as a white solid. mp >310 °C; $[\alpha]^{27}_D$ = 35.0 (c 0.05, H_2O); UV (MeOH) λ_{max} (pH 7) 249 nm (ε 9,440), (pH 2) 249 nm (ε 9,530), (pH 11) 259 nm (ε 10,200); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.58 (m, 2 H, 5'-H), 4.93 (m, 2 H, 4'-H and OH), 6.16 (br d, J = 6.0, 1 H, 2'-H), 6.51 (br d, J = 6.0, 1 H, 3'-H), 6.92 (m, 1H, 1'-H), 8.09 (s, 1H, 8-H), 8.13 (s, 1H, 2-H). Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.41; H, 4.33; N, 23.65. MS m/e 235 $(M+1)^+$.

9-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-β-L-*erythro*-pentofuranosyl]-6-chloro-2-fluoro-9*H*-purine (12). Conversion of **8** (2.87 g, 5.17 mmol) to **12** was accomplished using a procedure similar to that described for the D enantiomers.[27] The resulting residue was separated by chromatography over silica using EtOAc in hexanes (3-6%) as the eluant to give **12** (2.7 g, 78.3%) as crystalline solid from MeOH. Mp 107-108 °C; UV (MeOH) λ_{max} 269.5 nm; ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 9 H, *t*-Bu), 2.18 (m, 1 H, 3'-H_a), 2.64 (m, 1 H, 3'-H_b), 3.76 (dd, *J*= 3.6, 11.4, 1 H, 5'-H_a), 4.01 (dd, *J*= 3.3, 11.4, 1 H, 5'-H_b), 4.25 (m, 1 H, 2'-H), 4.42 (m, 1 H, 4'-H), 6.14 (d, *J*= 5.8, 1 H, 1'-H), 7.08 - 7.66 (m, 15 H, 3 X C_6H_5), 8.20 (s, 1H, 8-H). Anal. Calcd for $C_{32}H_{32}N_4O_2FClSiSe$: C, 57.70; H, 4.84; N, 8.41; F, 2.77. Found: C, 57.80; H, 4.89; N, 8.48; F, 2.85.

2-Amino-9-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-β-L-*erythro*-pentofuranosyl]-6-chloro-9H-purine (13) and 9-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-β-L-*erythro*-pentofuranosyl]-2-fluoro-9H-adenine (14). Dry ammonia gas was bubbled into a stirred solution of **12** (2.2 g, 3.3 mmol) in DME (80 mL) for 18 h. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel. Elution with 15-25% EtOAc in hexanes gave **13** (1.28 g, 58.67%) as a solid. mp 64-66 °C; UV(MeOH) λ_{max} 309.5 nm; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H, *t*-Butyl), 2.17 (m, 1 H, 3'-H_a), 2.64 (m, 1 H, 3'-H_b), 3.74 (dd, *J*= 3.8, 11.2 Hz, 1 H, 5'-H_a), 3.96 (dd, *J*= 4.0, 11.2, 1 H, 5'-H_b), 4.27 (m, 1 H, 2'-H), 4.39 (m, 1 H, 4'-H), 4.87 (br s, 2 H, NH_2), 6.04 (d, *J*= 5.7, 1 H, 1'-H), 7.13 -7.67 (m, 15 H, 3 X C_6H_5), 7.83 (s, 1H, 8-H). Anal. Calcd for $C_{32}H_{34}N_5O_2ClSiSe$: C, 57.96; H, 5.17; N, 10.56. Found: C, 58.06; H, 5.19; N, 10.58. Elution with 40-50% EtOAc in hexanes gave **14** (0.75 g, 35.14%) as white solid. mp 184-185 °C; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 9 H, *t*-Butyl), 2.19 (m, 1 H, 3'-H_a), 2.70 (m, 1 H, 3'-H_b), 3.78 (dd, *J*= 3.9, 11.3 Hz, 1 H, 5'-H_a), 4.01 (dd, *J*= 3.8, 11.3, 1 H, 5'-H_b), 4.30 (m, 1 H, 2'-H), 4.41 (m, 1 H, 4'-H), 5.87 (br s, 2 H, NH_2), 6.12 (d, *J*= 5.6, 1 H, 1'-H), 7.16 - 7.70 (m, 15 H, 3 X C_6H_5), 7.89 (s, 1 H, 8-H). Anal. Calcd for $C_{32}H_{34}N_5O_2FSiSe$: C, 59.43; H, 5.30; N, 10.83. Found: C, 59.45; H, 5.37; N, 10.93.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-β-L-*erythro*-pentofuranosyl]guanine (15) Compound **13** (0.388 g, 0.585 mmol) in MeOH (30 mL) was treated with mercaptoethanol (0.21 mL, 2.97 mmol) and NaOMe powder (0.26 g, 4.8 mmol) and the reaction mixture heated at reflux for 18 h. The reaction mixture was cooled, acidified with acetic acid, and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography (1-4% MeOH: CHCl3) to give **15**

(0.335 g, 88.8%) as a foam. UV(MeOH) λ_{max} 256 nm; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H, *t*-Bu), 2.15 (m, 1 H, 3'-H_a), 2.64 (m, 1 H, 3'-H_b), 3.74 (dd, *J* = 3.7, 11.1, 1 H, 5'-H_a), 3.97 (dd, *J* = 3.6, 11.3, 1 H, 5'-H_b), 4.17 (m,1 H, 2'-H), 4.38 (m, 1 H, 4'-H), 6.02 (d, *J* = 5.1, 1 H, 1'-H), 7.19 - 7.67 (m, 15 H, 3 X C_6H_5), 7.64 (s, 1 H, 8-H). MS m/e 646 $(M+1)^+$.

9-(2,3-Dideoxy-β-*L-glycero*-pent-2-enofuranosyl)guanine (L-d$_4$G, 27). Compound **15** (0.28 g, 0.434 mmol) was dissolved in CH_2Cl_2 (4.8 mL) containing a catalytic amount of pyridine (1 drop), and the solution was cooled in an ice-water bath. A 30% solution of hydrogen peroxide (0.27 mL, 2.39 mmol) was diluted with water (1 mL) which was added dropwise to the above solution over a period of 20 min while stirring. The temperature of the reaction mixture was allowed to reach to 20 °C, the reaction mixture was stirred at room temperature for 30 min and then diluted with CH_2Cl_2 (20 mL) and ice water (10 mL). The organic layer was separated and dried ($MgSO_4$). The solvent was removed to dryness and the residue was chromatographed over flash silica gel column using MeOH (1-6%) in $CHCl_3$ as the eluent to give **19** (0.03 g, 14.18%) as a foam (UV (H_2O) λ_{max} 255 nm). Conversion of **19** (30 mg, 0.062 mmol) to **27** was accomplished using a procedure similar to that described for **23**. The obtained residue was purified by silica gel chromatography (5-10% MeOH: $CHCl_3$) to give **27** (14 mg, 95%) as a white solid. mp> 250 °C; UV (MeOH) λ_{max} (pH 7) 253.5 nm (ε16,000), (pH 2) 252 nm (ε14,4000), (pH 11) 255.5 nm (ε15,200); ^{1}H NMR (DMSO-d_6) δ 3.52 (m, 2 H, 5'-H), 4.82 (m, 1 H, 4'-H), 4.92 (t, 1 H, OH), 6.08 (d, *J* = 5.9, 1 H, 2'-H), 6.43 (d, *J* = 5.9, 1 H, 3'-H), 6.49 (br s, 2 H, NH_2), 6.67 (m, 1H, 1'-H), 7.70 (s, 1 H, 8-H), 10.60 (br s, 1 H, NH). Anal. Calcd for $C_{10}H_{11}N_5O_3 \cdot 0.15MeOH \cdot 0.5H_2O$: C, 46.35; H, 4.83; N, 26.62. Found: C, 46.78; H, 5.08; N, 26.50. MS m/e 250 $(M+1)^+$.

9-(2,3-Dideoxy-β-L-*glycero*-pentofuranosyl)guanine (L-ddG, 29). Conversion of **15** (0.25 g, 0.388 mmol) to **21** was accomplished using a procedure similar to that described for **18**. The obtained residue was purified by silica gel chromatography (1-6% MeOH: $CHCl_3$) to give **21** (0.148 g, 78%) as a solid (UV(MeOH) λ_{max} 254.5 nm). Conversion of **21** (0.1 g, 0.398 mmol) to **29** was accomplished using a procedure similar to that described for **23**. The obtained residue was purified by silica gel chromatography (5-10% MeOH: $CHCl_3$) to give **29** (42 mg, 42%) as a white solid. mp >250 °C; $[\alpha]^{25}_D$ = 6.3 (c 0.1, MeOH). UV(MeOH) λ_{max} (pH 7) 253.5 nm (ε 15,100), (pH 2) 256.5 nm (ε 13,500), (pH 11) 255.5 nm (ε 13,800); ^{1}H NMR (DMSO-d_6) δ 1.99 (m, 2 H, 3'-H), 2.30 (m, 2 H, 2'-H), 3.56 (m, 2 H, 5'-H), 4.06 (m, 1 H, 4'-H), 4.95 (br s, 1 H, 5'-OH), 5.99 (dd, *J* = 3.4, 6.7, 1 H, 1'-H), 6.45 (br s, 2 H, NH_2), 7.96 (s, 1 H, 8-H), 10.59 (br s, 1 H, NH). Anal. Calcd for $C_{10}H_{13}N_5O_3 \cdot 0.2H_2O$: C, 47.13; H, 5.30; N, 27.48. Found: C, 47.00; H, 5.25; N, 27.26. MS m/e 252 $(M+1)^+$.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-β-L-*glycero*-pent-2-enofuranosyl]-2-fluoroadenine (20) Conversion of **14** (0.35 g, 0.541 mmol) to **20** was accomplished using a procedure similar to that described for **19**. The obtained residue was purified by silica gel chromatography (1% MeOH: $CHCl_3$) to give **20** (0.235 g, 88.7%) as a white solid which was recrystallized from MeOH. mp >250 °C; UV(H_2O) λ_{max} 261.5 nm ; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9 H, *t*-Bu), 3.75 (dd, *J* = 1.0, 4.1, 2 H, 5'-H), 4.94 (m, 1 H, 4'-H), 5.85 (br s, 2 H, NH_2), 5.97 (d, *J* = 5.9, 1 H, 2'-H), 6.35 (d, *J* = 5.9, 1 H, 3'-H), 6.90 (br s, 1H, 1'-H), 7.24 - 7.55 (m, 10 H, 2 X C_6H_5), 7.80 (s,1 H, 8-H). Anal. Calcd for $C_{26}H_{28}FN_5O_2Si \cdot 0.5H_2O$: C, 62.63; H, 5.86; N, 14.05. Found: C, 62.61; H, 5.84; N, 14.04.

9-(2,3-Dideoxy-ß-L-*glycero*-pent-2-enofuranosyl)-2-fluoroadenine (28). Conversion of **20** (0.17 g, 0.35 mmol) to **28** was accomplished using a procedure similar to that described for **23**. The obtained residue was purified by silica gel chromatography (1-5% MeOH: $CHCl_3$) to give **28** (0.082 g, 94%) as a white solid. mp > 310 °C; $[\alpha]^{25}_D$ -18.17 (c 0.34, MeOH). UV (MeOH) λ_{max} (pH 7) 261 nm (ε 21,500), (pH 2) 266.5 nm (ε 19,000), (pH 11) 261 nm (ε 24,100); ^{1}H NMR (DMSO-d_6) δ 3.56 (t, *J* = 4.5, 2 H, 5'-H), 4.87 (m, 1 H, 4'-H), 4.94 (t, *J* = 5.4, 5'-OH), 6.12 (d, *J* = 5.9, 1 H, 2'-H), 6.47 (d, *J* = 6.0, 1 H, 3'-H), 6.81 (m, 1 H, 1'-H), 7.82 (br s, 2 H, NH_2), 8.13 (s, 1 H, 8-H). Anal. Calcd for $C_{10}H_{10}N_5O_2F$: C, 47.81; H, 4.01; N, 27.88; F, 7.56. Found: C, 47.72; H, 4.09; N, 27.77; F, 7.75. MS m/e 252 $(M+1)^+$.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-β-L-*glycero*-pentofuranosyl]-2-fluoroadenine (22) Conversion of **14** (0.35 g, 0.54 mmol) to **22** was_accomplished using a procedure similar to that described for **18**. The obtained residue was purified by silica gel chromatography (1% MeOH: $CHCl_3$) to give **22** (0.263 g, 97%) as a white solid which was recrystallized from MeOH. mp 185-186 °C; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9 H, *t*-Bu), 2.04 (m, 2 H, 3'-H), 2.41 (m, 2 H, 2'-H), 3.70 (dd, *J*= 4.0, 11.3, 1 H, 5'-H_a), 3.90 (dd, *J*= 3.6, 11.4, 1 H, 5'-H_b), 4.18 (m, 1 H, 4'-H), 5.82 (br s, 2 H, NH_2), 6.16 (q, *J*= 3.1, 6.4, 1 H, 1'-H), 7.28 - 7.62 (m, 10 H, 2 X C_6H_5), 8.06 (s, 1 H, 8-H). Anal. Calcd for $C_{26}H_{30}N_5O_2SiF$: C, 63.52; H, 6.15; N, 14.25. Found: C, 63.60; H, 6.20; N, 14.35.

9-(2,3-Dideoxy-β-L-*glycero*-pentofuranosyl)-2-fluoroadenine (30). Conversion of **22** (0.22 g, 0.45 mmol) to **30** was accomplished using a procedure similar to that described for **23**. The obtained residue was purified by silica gel chromatography (1-4% MeOH: $CHCl_3$) to give **30** (0.111 g, 97.9%) as a white solid. mp> 250 °C; $[\alpha]^{25}_D$ 11.9 (c 0.38, MeOH). UV (MeOH) λ_{max}(pH 7) 261 nm (ε 23,900), (pH 2) 263 nm (ε 21,300), (pH 11) 261.5 nm (ε 23,500); ^{1}H NMR (DMSO-d_6) δ 2.06 (m, 2 H, 3'-H), 2.40 (m, 2 H, 2'-H), 3.57 (m, 2 H, 5'-H), 4.11 (m, 1 H, 4'-H), 4.95 (br s, 1 H, 5'-OH), 6.12 (dd, *J*= 3.7, 6.4, 1 H, 1'-H), 7.82 (br s, 2 H, NH_2), 8.35 (s, 1 H, 8-H). Anal. Calcd for $C_{10}H_{12}N_5O_2SiF$: C, 47.43; H, 4.78; N, 27.66; F, 7.50. Found: C, 47.64; H, 4.82; N, 27.44; F, 7.56. MS m/e 254 $(M+1)^+$.

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