Enantiomeric Synthesis of Novel Apiosyl Nucleosides as Potential Antiviral Agents

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A series of 2',3'-dideoxy-3'-fluoro-D-apiosyl nucleosides **15**, **16**, **17** and **18** were synthesized enantiomerically with L-Gulonic-γ-lactone as the starting material. The reduction of butenolide **1** with DIBAL-H followed by the Luche procedure afforded the allylic alcohol **2**. Ozonolysis and the reduction of compound **4** induced the cyclized lactol, which was acetylated to give the acetate **7**. Condensation of the acetate **7** with silylated pyrimidine (N^4-benzoyl cytosine) and a purine base (6-chloropurine) under Vorbrüggen conditions and deblocking afforded a series of fluorinated apiosyl nucleosides.

Key Words : Apiosyl nucleosides, Claisen rearrangement, Luche procedure, Antiviral agents

Introduction

The discovery of novel nucleosides for use as antiviral and anticancer agents has been the goal of nucleoside chemists for several decades. In particular, since the emergence of the HIV pandemic, extensive efforts have been concentrated on various modifications in the sugar moiety of the nucleosides, resulting in FDA approved anti-HIV agents such as AZT,[1] ddC,[2] ddI,[3] d4T,[4] 3TC,[5] and Abacavir.[6] In connection with these efforts, the introduction of a fluorine atom to the carbohydrate moiety was found to confer interesting biological activities, as shown in FLT,[7] FIAU,[8] and L-2'-F-d4N.[9] The electronegativity of fluorine (4 *vs* 3.5 for oxygen) can have pronounced effects on the electron distribution in the molecule, effecting either the alkalinity or acidity of the neighboring groups, the dipole moments within the molecule and the overall reactivity and stability of the neighboring functional groups.[10] While there has been considerable interest in modifications at the 2'- and 3'-position of nucleosides, much less is known about 4'-modified compounds.[11] Recently, Ahn *et al.* reported the synthesis of fluoroapiosyl pyrimidine nucleosides as a racemate.[12] We have also published preliminary accounts of the asymmetric synthesis of the 3'-fluoro-L-apionucleosides, of which the configuration was analogous to the natural D-nucleosides (Figure 1).[13] This paper reports the full enantioselective synthesis of fluorinated apionucleosides in a D-series with the modified strategies.

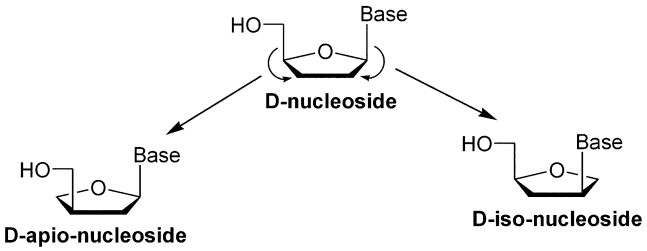

Figure 1

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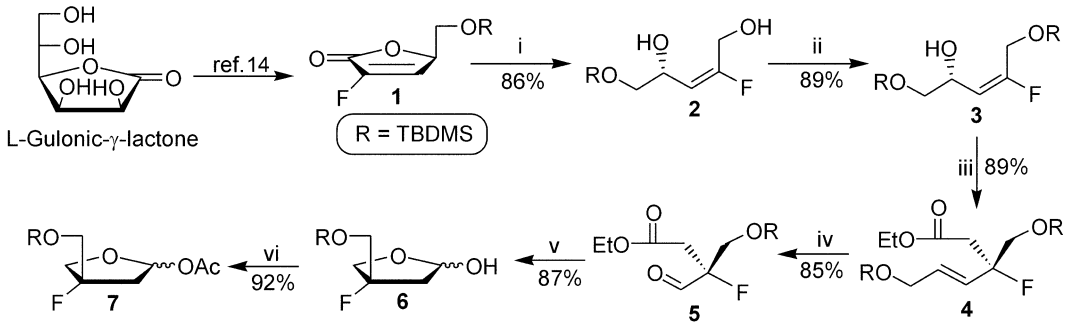
Results and Discussion

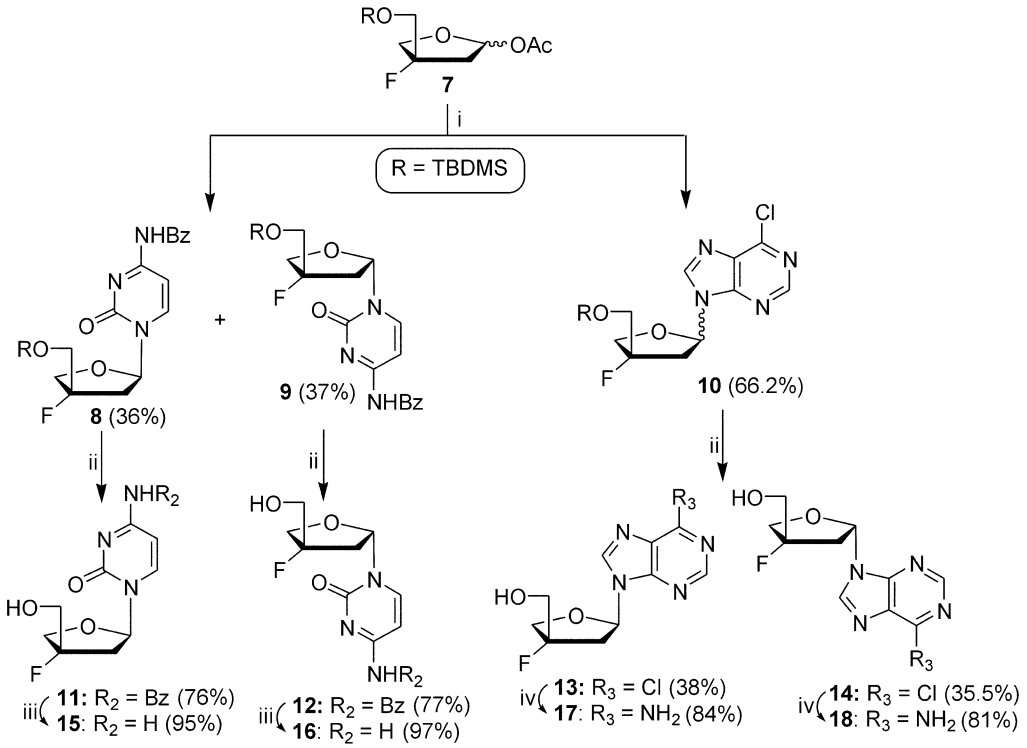
The key strategy for the synthesis of the target compounds was based on the implementation of a [3,3]-sigmatropic rearrangement to generate an optically active fluoroester **4**, which provides two useful functionalities, such as alkene and carbonyl groups, to obtain the fluorinated apiosyl moiety **6**. However, due to the difficulties in preparing the (*E*) or (*Z*)-fluorinated olefin in a large scale, the planning for the preparation of the intermediate for the Claisen rearrangement, was guided using the difference in the geometry between the (*E*)- and (*Z*)-isomers. Therefore, this study attempted to synthesize the (*E*)-isomer **2** *via a* 2-fluorobutenolide formation **1**, which could be readily prepared from L-Gulonic γ-Lactone in a large scale by the known procedure (Scheme 1).[14]

Usually, the lactones are rapidly reduced to the diol by various reducing agents such as LAH, $LiAlH(OMe)_3$, DIBAL-H, and $NaBH_4$. However, to our knowledge, there are only a few examples of the direct reduction of butenolide to the diol.[15] In order to identify the optimal conditions of **1** for the conversion into the allylic diol **2**, several reducing conditions were screened at various temperatures. Among the investigated conditions, the LAH and DIBALH reduction did not give satisfactory yields in several conditions. The use of DIBALH followed by a combination of $CeCl_3 \cdot 7H_2O$[16] and $NaBH_4$, gave the best yield (86%). The selective monosilylation of the allylic diol **2** and the subsequent Claisen rearrangement generated the α,β-unsaturated fluoroester **4** *via* the orthoester intermediate in an 89% yield. Ozonolysis of compound **4**, followed by a DIBALH reduction furnished the lactol **6**, which was further converted into the key intermediate **7** in a 68% three-step yield**.**

Condensation of compound **7** with silylated N^4-benzoyl-cytosine gave compounds **8** and **9**, which were readily separated using normal column chromatography (Scheme



Scheme 1. i) (a) Dibal-H, -78 °C, (b) $CeCl_3 \cdot 7H_2O$, NaBH4, 0 °C, ii) TBDMSCI, imidazole, CH_2Cl_2; iii) Triethylorthoacetate, propionic acid, 140 °C; iv) O_3/DMS; v) Dibal-H, toluene, -78 °C; vi) Ac_2O, pyridine.



Scheme 2. Reagents: i) silylated N^4-Bz-cytosine, or 6-Cl-purine, TMSOTf, DCE; ii) TBAF, CH_3CN; iii) sat. NH_3/MeOH, rt; iv) sat. NH_3/MeOH, 90-100 °C.

2). The separate treatment of compound **8** and **9** with TBAF in CH_3CN afforded the cytosine derivatives **11** and **12**. Debenzoylation was performed under the condition of saturated ammonia in MeOH to give the compounds **15** and **16**. The 6-chloropurine derivatives were obtained by condensation with compound **7** under the same conditions to give the anomeric mixtures **10**, which were separated after desilylation with TBAF to give compounds **13** and **14**. Compounds **13** and **14** were treated separately with NH_3/MeOH in a steel bomb at 90-100 °C to give the adenine derivatives **17** and **18** in an 84 and 81% yield, respectively. The stereochemical assignments of the synthesized compounds were easily determined based on the spectroscopic data (^{1}H NMR and ^{13}C NMR). In addition, the specific rotations of the synthesized nucleoside **15** ($[\alpha]_D^{24}$ +41.1° (*c* 0.48, MeOH) was in good agreement with those of the reported antipode ($[\alpha]_D^{27}$ -40.7° (*c* 0.70, MeOH).[13]

The antiviral activities of the synthesized compounds were evaluated against HIV-1, HSV-1 HSV-2 and polio virus, respectively. However, none of them showed significant antiviral activity or cytotoxicity at concentrations up to 100 μM.

In conclusion, this report described the synthesis of 3'-fluoro apionucleosides of the D-series, using a Claisen rearrangement of the allylic alcohol **3**, which was readily prepared from 2-fluoro-butenolide **1** by a reduction with a combination of DIBAL-H and the Luche procedure.

Experimental Section

The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra

were recorded on a Bruker 300 Fourier transform spectrometer; the chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. The optical rotations were measured on an Autopol-IV digital polarimeter. The elemental analyses were performed using an Elemental Analyzer System (Profile HV-3). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Dry 1,2-dichloro-ethane (DCE), dichloromethane, acetonitrile and pyridine were distilled from CaH_2 prior to use. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(*E*)(*R*)-5-(*tert*-Butyldimethylsiloxy)-2-fluoropent-2-en-1,4-diol (2). To a solution of **1** (10 g, 40.59 mmol) in CH_2Cl_2 (150 mL), 1 M solution of DIBALH in CH_2Cl_2 (60.88 mL, 60.88 mmol) was added dropwise at -78 °C and the mixture was then stirred at -78 °C for 2 h. The reaction was treated with dilute nitric acid. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and evaporated to a pale yellow oil, which was used for the next step without further purification.

To a solution of the crude lactol in MeOH, $CeCl_3 \cdot 7H_2O$ (14.9 g, 40 mmol) and $NaBH_4$ (1.51 g, 40 mmol) was added at 0 °C and stirred for 1 h at rt. The mixture was quenched with saturated NH_4Cl and extracted using ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a column chromatography (hexane : EtOAc, 3 : 1) to give compound **2** (8.74 g, 86%) as a colorless oil: $[\alpha]_D^{25}$ = +3.31° (*c* 1.56, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.24 (dd, *J* = 8.4, 20.0 Hz, 1H), 4.11-4.42 (m, 2H), 3.51-3.65 (m, 2H), 3.14. 3.33 (2s, 2H), 0.92 (s, 9H), 0.09 (s, 6H); Anal. Calcd for $C_{11}H_{23}FO_3Si$: C, 52.77; H, 9.26. Found: C, 52.52; H, 9.48.

(*E*)(*R*)-1,5-Bis-(*tert*-butyldimethylsiloxy)-2-fluoropent-2-en-4-ol (3). To a mixture of the diol **2** (8 g, 31.95 mmol) and imidazole (4.35 g, 61.9 mmol) in CH_2Cl_2 (200 mL), a solution of TBDMSCl (5.29 g, 35.14 mmol) in anhydrous CH_2Cl_2 (100 mL) was added drop wise at 0 °C. The mixture was stirred at 0 °C for 3 h and then washed with water (2 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified on a silica gel column (hexane : EtOAc, 2 : 1) to give compound **3** (10.36 g, 89%) as a colorless oil: $[\alpha]_D^{24}$ = +2.7° (*c* 2.5, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.21 (dd, *J* = 8.8, 20.0 Hz), 4.24-4.43 (m, 2 H), 3.63 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.48 (dd, *J* = 7.6, 9.6 Hz, 1H), 2.64 (d, *J* = 2.8 Hz, 1H), 0.91 (s, 18H), 0.08, 0.11 (2s, 12H); Anal. Calcd for $C_{17}H_{37}FO_3Si_2$: C, 55.99; H, 10.23. Found: C, 56.25; H, 10.10.

(*E*)-6-*O*-*tert*-Butyldimethylsilyloxy-(*S*)(*tert*-butyldimethylsiloxymethyl)-3-fluoro-hex-4-enoic acid ethyl ester (4). A mixture of **3** (11 g, 30.0 mmol), propionic acid 1.5 mL, triethyl orthoacetate (200 mL) was heated at 140 °C for overnight using a Claisen apparatus. The excess triethyl orthoacetate was removed under reduced pressure. The residue was purified by column chromatography (hexane : EtOAc, 80 : 1) to yield compound **4** (11.6 g, 89%) as a colorless oil: $[\alpha]_D^{24}$ = -40.25° (*c* 1.45, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.83-5.95 (m, 2H), 4.21 (s, 2H, H-6), 4.12 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 1H), 3.78 (dd, *J* = 10.8, 18.4 Hz, 1H), 2.73-2.93 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.89, 0.91 (s, 9H), 0.05, 0.06 (s, 12H); Anal. Calcd for $C_{21}H_{43}FO_4Si_2$: C, 58.02; H, 9.97. Found: C, 57.82; H, 9.78.

(*R*)-3-(*tert*-Butyldimethylsilyloxymethyl)-3-fluoro-4-oxo-butyric acid ethyl ester (5). A solution of compound **4** (3.5 g, 8.05 mmol) in methanol (30 mL) was treated with O_3 at -78 °C until a slight blue color persisted. The solution was degassed with N_2 and brought to 0 °C, whereupon methyl sulfide (2.0 mL, 22.7 mmol) was added. The mixture was stirred at 0 °C for 1 h. The mixture was concentrated and taken up into water. The water was washed with ethyl acetate (2 × 100 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by a column chromatography (hexane : EtOAc, 8 : 1) to give compound **5** (2.0 g, 85%) as a colorless oil: $[\alpha]_D^{24}$ = -42.1° (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.90 (d, *J* = 4.4 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.74-3.93 (m, 2H), 2.90-3.04 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.06, 0.07 (2s, 6H); Anal. Calcd for $C_{13}H_{25}FO_4Si$: C, 53.40; H, 8.62. Found: C, 53.54; H, 8.68.

1-*O*-Acetyl-3-*C*-(*tert*-butyldimethylsiloxy)-3-deoxy-3-fluoro-D-erythro-tetrafuranose (7). To a solution of compound **5** (4.5 g, 15.38 mmol) in toluene (50 mL), a 1 M solution of DIBALH in hexane (32.3 mL, 32.3 mmol) was added dropwise at -78 °C and the mixture was stirred at the same temperature for 0.5 h. The reaction was quenched with methanol (30 mL) and then allowed warm to room temperature. The resulting white solid was filtered and the filtrate was concentrated to a pale yellowish oil, which was used for the next step without further purification.

To a solution of the crude lactol **6** (3.35 g, 13.37 mmol, 87%) in anhydrous pyridine (30 mL), acetic anhydride (2 mL, 19.76 mmol) was added at 0 °C and then the mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, which was washed with saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by a column chromatography (hexane : EtOAc, 15 : 1) to give compound **8** as an anomeric mixture in pale yellow oil (3.59 g, 92%): ^{1}H NMR ($CDCl_3$) δ 6.45 (dd, *J* = 2.0, 6.0 Hz, 1H), 6.33 (d, *J* = 5.2 Hz, 1H), 3.70-4.25 (m, 2H), 2.22-2.59 (m, 1H), 2.04, 2.09 (2s, 3H), 0.89, 0.91 (s, 9H), 0.08, 0.09 (2s, 6H); Anal. Calcd for $C_{13}H_{25}FO_4Si$: C, 53.40; H, 8.62. Found: C, 53.26; H, 8.59.

***N*^{4}-Benzoyl-1-[3-*C*-(*tert*-butyldimethylsilyloxymethyl)-2,3-deoxy-3-fluoro-β-D-erythro-tetrafuranosyl] cytosine (8) and *N*^{4}-benzoyl-1-[3-*C*-(*tert*-Butyldimethylsilyloxymethyl)-2,3-deoxy-3-fluoro-α-D-erythro-tetrafuranosyl] cytosine (9).** A suspension of *N*^{4}-benzoyl cytosine (420 mg, 1.95 mmol), HMDS (20 mL), and ammonium sulfate (catalytic amount) was refluxed overnight under a nitrogen atmosphere, and excess HMDS was removed under a high vacuum. To the residue, dry 1,2-dichloroethane (DCE) (10

mL), a solution of the acetates **26** (456.54 mg, 1.56 mmol) in dry DCE (10 mL), and trimethylsilyl trifluoromethane sulfonate (TMSOTf) (0.4 mL, 1.92 mmol) was added at rt and the resulting reaction mixture was stirred for 1 h at rt. Sat.$NaHCO_3$ (5 mL) was added to the reaction mixture and stirred another 30 min, which was extracted with methylene chloride (30 mL × 2). The combined organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue of the anomeric mixture was separated by silica gel column chromatography (hexane : EtOAc = 2 : 1) to give **8** (313.93 mg, 36%) and **9** (322.9 mg mg, 37%) as a foam, respectively: Compound **8**: ^{1}H NMR ($CDCl_3$) δ 8.78 (br s, 1H, D_2O exchangeable), 7.64-7.26 (m, 7H), 6.20 (t, J = 6.4 Hz, 1H), 4.53-4.22 (m, 2H), 3.76-3.61 (m, 2H), 3.10 (m, H), 2.36 (m, 1H), 0.9 (s, 9H), 0.08 (s, 6H); Anal. Calcd for $C_{22}H_{30}FN_3O_4Si$: C, 59.04; H, 6.76; N, 9.39. Found: C, 58.77; H, 6.69; N, 9.22. Compound **9**: ^{1}H NMR ($CDCl_3$) δ 8.70 (br s, 1H, D_2O exchangeable), 8.00-7.30 (m, 7H), 6.23 (d, J = 7.1 Hz, 1H), 4.49-4.21 (m, 2H), 3.77-3.56 (m, 2H), 2.79-2.49 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H); Anal. Calcd for $C_{22}H_{30}FN_3O_4Si$: C, 59.04; H, 6.76; N, 9.39. Found: C, 58.91; H, 6.79; N, 9.43.

6-Chloro-9-[3-*C*-(*tert*-butyldimethylsilyloxymethyl)-2,3-deoxy-3-fluoro-D-erythro-tetrafuranosyl] purine (10). The suspension of 6-Cl-purine (1.59 g, 10.3 mmol) in HMDS (50 mL), and ammonium sulfate (catalytic amount) was refluxed under a nitrogen atmosphere for 4 h and excess HMDS was removed under a high vacuum under anhydrous conditions to yield a yellow solid, which was dissolved in dry CH_2Cl_2 (10 mL). To the solution, the acetates **7** (1.6 g, 4.14 mmol) in dry CH_2Cl_2 (20 mL) and TMSOTf (2 mL, 10.3 mmol) were added at 0 °C and the resulting reaction mixture was stirred for 2 h at rt. Sat $NaHCO_3$ (20 mL) was then added to the reaction mixture, which was extracted with methylene chloride (2 × 20 mL). The combined organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue of the anomeric mixture was purified by silica gel column chromatography (hexane : EtOAc = 4 : 1) to give an inseparable anomeric mixture **10** (1.06 g, 66.2%): UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.44 (s, 1H), 8.27 (s, 1H), 6.60 (d, J = 7.6, 1H), 6.53 (t, J = 6.8, 1H), 4.16-4.49 (m, 1H), 3.83-3.99 (m, 1H), 2.65-3.17 (m, 1H), 0.9, 0.92 (2 s, 18H), 0.1, 0.11 (2s, 12H); Anal. Calcd for $C_{16}H_{24}ClFN_4O_2Si$: C, 49.67; H, 6.25; N, 14.48. Found: C, 49.45; H, 6.12; N, 14.56.

***N*^{4}-Benzoyl-1-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-β-D-erythro-tetrafuranosyl] cytosine (11).** A solution of compound **8** (250 mg, 0.558 mmol) in CH_3CN (7 mL) was treated with TBAF (1 M solution in THF, 0.67 mL) and then stirred at rt for 1 h. After concentrating the mixture, the residue was purified by silica gel column chromatography (hexane : EtOAc = 1 : 3) to give compound **11** (141 mg, 76%) as a white solid: mp: 156-158 °C; $[\alpha]_D^{24}$ +44.9° (*c* 1.3, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.64-7.26 (m, 6H), 7.29 (br d, 2H, D_2O exchangeable), 6.18 (t, J = 6.9 Hz, 1H), 5.80 (d, J = 7.4 Hz, 1H), 5.33 (t, J = 5.7 Hz, 1H, D_2O exchangeable), 4.32 (dd, J = 10.4, 35.1 Hz, 1H), 4.06 (dd, J = 10.4, 21.7 Hz, 1H), 3.78-3.70 (m, 2H), 2.53-2.21 (m, 2H); Anal. Calcd for $C_{16}H_{16}F\ N_3O_4$: C, 57.65; H, 4.84; N, 12.61. Found: C, 57.42; H, 4.71; N, 12.67.

***N*^{4}-Benzoyl-1-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-α-D-erythro-tetrafuranosyl] cytosine (12).** Compound **12** was prepared from compound **9** using the method for the preparation of compound **11**: Yield 77%; mp: 160-163 °C; $[\alpha]_D^{24}$ -72.4° (*c* 0.77, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.17-7.29 (m, 6H), 6.03 (dd, J = 1.6, 7.4 Hz, 1H), 4.37-3.94 (m, 2H), 3.71 (m, 2H), 2.87-2.77 (m, 1H), 2.30-2.17 (m, 1H); Anal.

Calcd for $C_{16}H_{16}FN_3O_4$: C, 57.65; H, 4.84; N, 12.61. Found: C, 57.44; H, 4.90; N, 12.72.

1-[3-*C*-(Hydroxymethyl)-2,3-deoxy-3-fluoro-β-D-erythro-tetrafuranosyl] cytosine (15). Compound **11** (420 mg, 1.26 mmol) was dissolved in 20 mL of saturated methanolic ammonia and the resulting solution was stirred overnight at rt. The reaction solvent was removed under reduced pressure and the residue was purified by column chromatography ($CHCl_3$: MeOH = 7 : 1) to give compound **15** as a foam (274 mg, 95%): $[\alpha]_D^{24}$ +41.1° (*c* 0.48, MeOH); UV (H_2O) λ_{max} 271.0 nm ; ^{1}H NMR (DMSO-d_6) δ 7.62 (d, J = 7.4 Hz, 1H), 7.15, 7.24 (2 br s, 2H, D_2O exchangeable), 6.12 (t, J = 6.9 Hz, 1H), 5.73 (d, J = 7.4 Hz, 1H), 5.12 (t, J = 5.7 Hz, 1H, D_2O exchangeable), 4.20 (dd, J = 10.4, 35.1 Hz, 1H), 3.96 (dd, J = 10.4, 21.7 Hz, 1H), 3.59-3.72 (m, 2H), 2.15-2.47 (m, 2H); Anal. Calcd for $C_9H_{12}FN_3O_3$: C, 47.16; H, 5.28; N, 18.33. Found: C, 47.35; H, 5.52; N, 18.25.

1-[3-*C*-(Hydroxymethyl)-2,3-deoxy-3-fluoro-α-D-erythro-tetrafuranosyl] cytosine (16). Compound **16** was prepared from compound **12** using the method for the preparation of compound **15**: yield 97%; mp 181-183 °C; $[\alpha]_D^{24}$ -75.8° (*c* 0.50, MeOH); UV (H_2O) λ_{max} 271 nm; ^{1}H NMR (DMSO-d_6) δ 7.55 (d, J = 7.4 Hz, 1H), 7.07, 7.16 (2 br d, 2H, D_2O exchangeable), 6.04 (dd, J = 2.3, 7.5 Hz, 1H), 5.72 (d, J = 7.4 Hz, 1H), 5.28 (s, 1H, D_2O exchangeable), 4.00 (dd, J = 3.5, 5.6 Hz, 1H), 3.92 (dd, J = 5.2, 5.6 Hz, 1H), 3.56-3.66 (m, 2H), 2.53-2.64 (m, 1H), 2.10 (dd, J = 2.4, 5.6 Hz, 1H); Anal. Calcd for $C_9H_{12}FN_3O_3$: C, 47.16; H, 5.28; N, 18.33. Found: C, 47.35; H, 5.30; N, 18.27.

6-Chloro-9-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-β-D-erythro-tetrafuranosyl] purine (13) and 6-chloro-9-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-α-D-erythro-tetrafuranosyl] purine (14). A solution of compound **11** (1.14 g, 2.95 mmol) in CH_3CN (50 mL) was treated with TBAF (1 M solution in THF, 3.5 mL) and stirred at rt for 1 h. After concentrating the mixture, the residue was purified by silica gel column chromatography to give compounds **13** (305 mg, 38%) and **14** (285mg, 35.5%) as a white solid, respectively. **13**: mp 102-104 °C; $[\alpha]_D^{24}$ -36.5° (*c* 1.12, MeOH); UV (MeOH) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 1H), 8.82 (s, 1H), 6.62 (t, J = 6.8 Hz, 1H), 5.40 (t, J = 5.6 Hz, 1H, D_2O exchangeable), 4.34 (dd, J = 10.8, 35.6 Hz, 1H), 4.12 (dd, J = 10.8, 20.4 Hz, 1H), 3.81-3.88 (m, 2H), 2.92-3.04 (m, 1H), 2.73-2.84 (m, 1H); Anal. Calcd for $C_{10}H_{10}ClFN_4O_2$: C, 44.05; H, 3.70; N, 20.55. Found: C, 43.80; H, 3.56; N, 20.36. **14**: mp 121-123 °C; $[\alpha]_D^{24}$ +22.2°

(*c* 1.40, MeOH); UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 8.15 (s, 1H), 7.30 (br s, 2H, D_2O exchangeable), 6.39 (dd, *J* = 3.0, 7.3 Hz, 1H), 5.39 (t, *J* = 5.3, 1H, D_2O exchangeable), 4.33 (dd, *J* = 10.7, 20.9, 1H), 4.11 (dd, *J* = 10.8, 30.8, 1H), 3.74-3.67 (m, 2H), 2.88-2.72 (m, 2H); Anal. Calcd for $C_{10}H_{10}ClFN_4O_2$: C, 44.05; H, 3.70; N, 20.55. Found: C, 43.80; H, 3.67; N, 20.52.

9-[3-*C*-(Hydroxymethyl)-3-deoxy-3-fluoro-β-D-erythro-tetrafuranosyl] adenine (17). Compound **13** (132 mg, 0.484 mmol) was dissolved in saturated methanolic ammonia (15 mL) and the resulting solution was stirred overnight at 90-100 °C in a steel bomb. After removing the reaction solvent, the yellowish residue was purified by column chromatography ($CHCl_3$: MeOH = 7 : 1) to give **17** as a solid (102 mg, 84%): mp 195-197 °C; $[\alpha]_D^{24}$ -85.5° (*c* 0.78, MeOH); UV (H_2O) λ_{max} 259.0 nm; ^{1}H NMR (DMSO-d_6) δ 8.34 (s, 1H), 8.16 (s, 1H), 7.32 (br s, 2H, D_2O exchangeable), 6.47 (t, *J* = 7.0 Hz, 1H), 5.37 (t, *J* = 5.7 Hz, 1H, D_2O exchangeable), 4.37-4.25 (dd, *J* = 10.5, 35.4 Hz, 1H), 4.09-4.02 (dd, *J* = 10.4, 20.1 Hz, 1H), 3.88 (dd, *J* = 5.5, 20.5 Hz, 2H), 3.05-2.91 (ddd, *J* = 6.9, 14.9, 34.6 Hz, 1H), 2.76-2.65 (m, 1H); Anal. Calcd for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.26; H, 4.76; N, 27.62.

9-[3-*C*-(Hydroxymethyl)-3-deoxy-3-fluoro-α-D-erythro-tetrafuranosyl] adenine (18). Compound **18** was prepared from compound **14** using the method for the preparation of compound **17**: Yield; 81%; mp 198-200 °C; $[\alpha]_D^{24}$ +56.2° (*c* 1.04, MeOH); UV (H_2O) λ_{max} 260 nm; ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 8.15 (s, 1H), 7.30 (br s, 2H, D_2O exchangeable), 6.39 (dd, *J* = 3.0, 7.3 Hz, 1H), 5.39 (t, *J* = 5.3 Hz, 1H, exchangeable), 4.33 (dd, *J* = 10.7, 20.9 Hz, 1H), 4.11 (dd, *J* = 10.8, 30.8 Hz, 1H), 3.74-3.67 (m, 2H), 2.88-2.72 (m, 2H); Anal. Calcd for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.67; H, 4.57; N, 27.48.

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