PERKIN 1

Synthesis of 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro apionucleosides as potential antiviral agents

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Synthesis of novel 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro apionucleosides which combine the properties of 2′,3′-didehydro-2′,3′-dideoxy nucleosides and apionucleosides on the basis of a bioisosteric rationale is described.

Introduction

2′,3′-Didehydro-2′,3′-dideoxynucleosides[1] have played a major role in the development of antiviral agents, especially anti-AIDS agents. Among this class of compounds, 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, Stavudine)[2] is being clinically used for the treatment of AIDS and AIDS-related complex (ARC). This compound exhibits anti-AIDS activity by inhibiting reverse transcriptase and/or terminating the viral DNA chain, after being converted into its corresponding triphosphate.[3] However, this compound suffers from side effects such as peripheral neuropathy and from the appearance of d4T-resistant strains.[4]

Recently, Chu and coworkers have published the synthesis and antiviral activity of D- and L-2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro nucleosides (**1**)[5] (Fig. 1). Among them, the

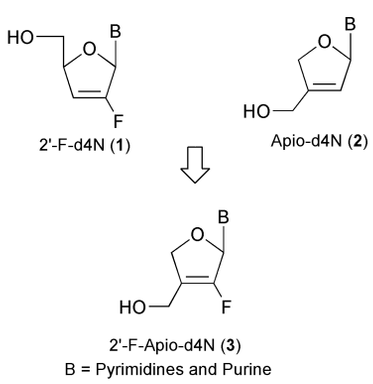


Fig. 1 The rationale for the design of the desired nucleosides.

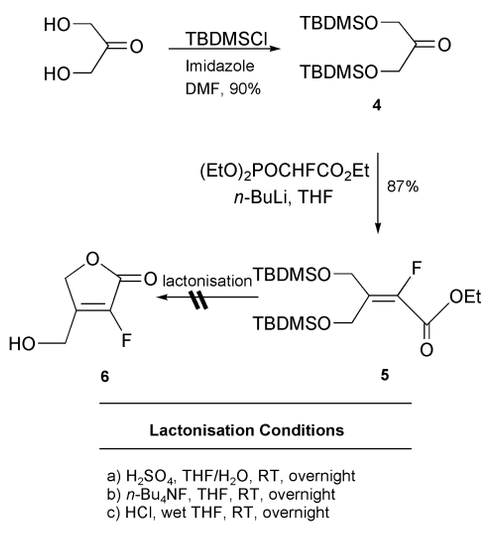
D-cytidine, D-thymidine, and D-uridine analogues showed weak to moderate anti-HIV-1 activity, while L-cytidine, L-5-fluorocytidine and L-adenosine derivatives exhibited moderate to potent anti-HIV-1 activity in PBM cells.

A nucleoside resulting from moving the 4′-hydroxymethyl group of 2′,3′-dideoxynucleosides to the C3′-position is called an apiodideoxynucleoside.[6] Among this class of nucleosides, the adenine derivative was reported to show anti-HIV-1 activity comparable to 2′,3′-dideoxyadenosine (ddA)[7] and the 2′,3′-didehydro-2′,3′-dideoxy apio analogue (**2**)[8] was found to show potent anti-HCMV activity.

Therefore, based on these findings, it was of interest to us to synthesize the target compound **3** which would combine the properties of 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro nucleosides and apio nucleosides based on a bioisosteric rationale. While synthesizing our target nucleosides, we encountered different chemistry from that experienced in the synthesis of **2**. Herein, we report the synthesis of 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro apionucleosides and their related chemistry.

Results and discussion

Our original plan to synthesize the target nucleosides was to utilize the method used in the synthesis of 2′,3′-didehydro-2′,3′-dideoxy apionucleosides (**2**),[8] as shown in Scheme 1, but this was not successful.



Scheme 1

1,3-Dihydroxyacetone dimer was protected as the disilyl ether **4**, which was converted into the fluoro ester **5**[9] (87%), using a Horner–Emmons olefination. However, lactonisation of **5** under aqueous acidic conditions or in the presence of *n*-tetrabutylammonium fluoride failed to give the desired α,β-unsaturated fluorolactone **6**, but instead resulted in extensive decomposition. This finding is in sharp contrast with the case of no fluorine at the α position of α,β-unsaturated fluoroester **5**.

Since the unsuccessful lactonisation is probably due to the low reactivity of the ester group, we decided to change the ester group to the more reactive aldehyde, as shown in Scheme 2.

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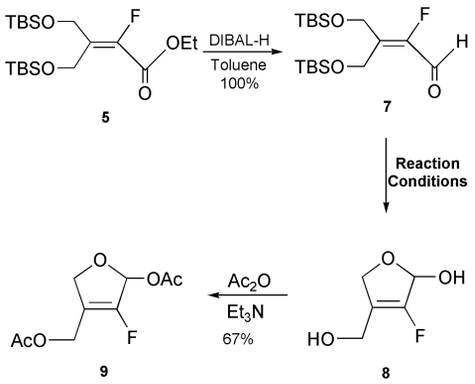
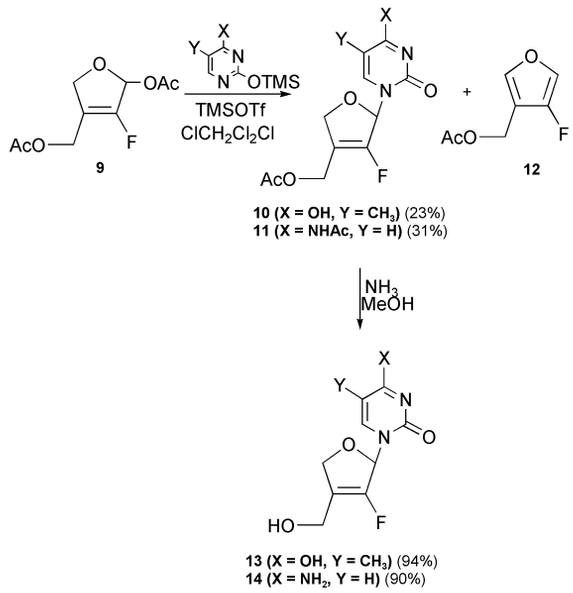


Reaction Conditions	Yields
a) *p*-TsOH, THF/H_2O, RT, 15 h b) *n*-Bu_4NF, THF, RT, 20 min c) Et_3N-3HF, CH_2Cl_2, RT, 3 h	trace 30-52% 63%

Scheme 2

Reduction of ester **5** with DIBAL-H gave the aldehyde **7** in quantitative yield. Cyclisation of **7** using *p*-TsOH in aqueous THF gave the dihydrofuran derivative as the main product, instead of producing the desired lactol **8**. Use of *n*-tetrabutylammonium fluoride in the cyclisation resulted in many spots due to decomposed products on TLC, and in low yield; however, the use of triethylamine trihydrofluoride gave the desired lactol **8** in 63% yield. The lactol **8** was treated with acetic anhydride and triethylamine to afford the diacetate **9** (67%). Since the diacetate **9** was unstable during storage or during the silica gel column purification, it was used directly for the condensation after aqueous work-up or purification by short-pad silica gel column chromatography. It is interesting to note that phenylselenenyl chemistry was utilised to insert the double bond when the fluorine atom was absent at α position of fluorolactone **6** as the reduction of this lactone with DIBAL-H yielded the linear allylic alcohol, instead of giving the required lactol. This clearly indicates that the electronegative fluorine atom in this case reported herein played a major role in lactol formation.[8]

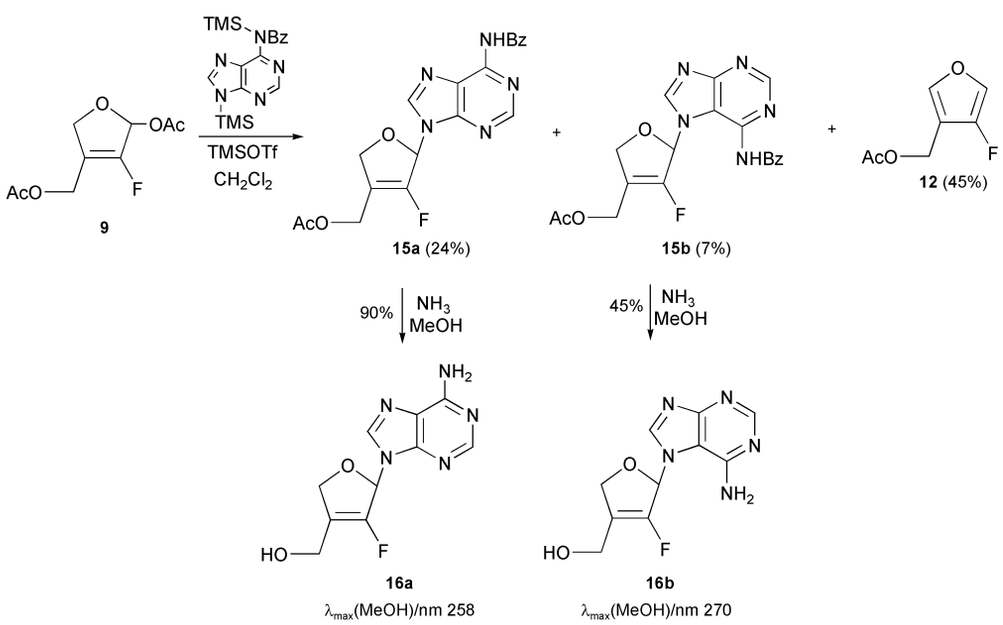
Diacetate **9** was condensed with silylated thymine and N^4-acetylcytosine in the presence of TMSOTf at 0 °C to give the protected nucleosides **10** (23%) and **11** (31%), respectively (Scheme 3). Low yields of condensation are attributed to the



Scheme 3

aromatisation of the diacetate **9**, forming the dihydrofuran derivative **12** as the major product. Treatment of **10** and **11** with methanolic ammonia at RT afforded the final nucleosides **13** and **14**, respectively.

For the synthesis of the purine nucleoside (Scheme 4), diacetate **9** was condensed with silylated N^6-benzoyladenine in the presence of TMSOTf at 0 °C to give the protected nucleoside **15a** (24%) and the N-7 isomer **15b** (7%). As in the case of pyrimidine nucleosides, the aromatized compound **12** was also produced as a major product (45%). Deprotection of **15a** and **15b** with methanolic ammonia afforded the desired N-9 isomer **16a** and the N-7 isomer **16b**, respectively. The regioisomers were easily confirmed by the comparison of the UV literature data[10] of N-9 isomer **16a** [λ_{max}(MeOH)/nm 258] and N-7 isomer **16b** [λ_{max}(MeOH)/nm 270]. It is also of interest to note that in the case of 2′,3′-dideoxy-2′,3′-didehydro apionucleosides, cytosine



Scheme 4

and adenine derivatives could not be obtained due to the decomposition at the final deprotection step,[8] indicating that the electronegative fluorine played a major role in stabilizing the final nucleosides in the 2′-fluoro substituted nucleosides.[11]

The final nucleosides **13**, **14**, and **16a** were tested for antiviral activity against several viruses such as HIV-1, HSV-1, HSV-2, and polio virus. All tested compounds exhibited neither antiviral activity nor cytotoxicity up to 100 μg ml^{-1}.

In summary we have synthesized novel 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro apionucleosides *via* lactol formation from an α,β-unsaturated fluoroaldehyde as a key step, starting from 1,3-dihydroxyacetone. While synthesizing the final nucleosides, we found that the synthetic method is very different from that of the reported 2′,3′-didehydro-2′,3′-dideoxy apionucleosides with regard to lactonisation, lactol formation and stability of the final nucleosides, which are caused by the presence of the electronegative fluorine atom.

Experimental

General methods

^{1}H NMR (250, 400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were measured for samples in $CDCl_3$ or MeOH-d_4 and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. Coupling constants (J) are given in Hz. Elemental analyses were performed at the general instrument laboratory of Ewha Womans University, Korea. TLC was performed on Merck precoated $60F_{254}$ plates. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). All anhydrous solvents were distilled over CaH_2, P_2O_5 or Na-benzophenone prior to use.

1,3-Bis-(*tert*-butyldimethylsilyloxy)propan-2-one (4)

tert-Butyldimethylsilyl chloride (8.25g, 55 mmol) was added to a stirred solution of 1,3-dihydroxyacetone dimer (2 g, 11 mmol) and imidazole (6.0 g, 28 mmol) in *N,N*-dimethylformamide (40 cm^3) at RT and the mixture was stirred at RT for 48 h. Water (100 cm^3) and hexane (300 cm^3) were added to the reaction mixture and the organic layer was washed with brine (20 cm^3), dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane and ethyl acetate (15 : 1) as the eluent to give *the title compound* **4** (3.1 g, 90%) as a colourless oil. δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.09 (12 H, s, 4 × CH_3), 0.92 [18 H, s, 2 × $(CH_3)_3C$], 4.41 (4 H, s, 2 × TBSOCH_2); *m*/*z* (EI-LR) 319 (M^+ + 1), 261, 115, 103, 89, 73.

4-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)-2-fluorobut-2-enoic acid ethyl ester (5)

n-Butyllithium (13.5 cm^3, 21.6 mmol, 1.6 M solution in hexane) was added dropwise to a stirred solution of triethyl 2-fluoro-2-phosphonoacetate (4.2 cm^3, 20.71 mmol) in tetrahydrofuran (30 cm^3) at −78 °C and the reaction mixture was stirred for 30 min at the same temperature. A solution of compound **4** (5.981 g, 18.77 mmol) in tetrahydrofuran (10 cm^3) was added to the above reaction mixture and the mixture was stirred at −78 °C for 30 min and allowed to warm slowly to RT. The mixture was quenched carefully with water (10 cm^3) and then extracted with ethyl acetate (100 cm^3). The extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane and ethyl acetate (50:1) as the eluent to give *the title compound* **5** (6.776 g, 87%) as a colourless oil. (Found: C, 56.12; H, 9.87. $C_{19}H_{39}FO_4Si_2$ requires C, 56.11; H, 9.67%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.08 (6 H, s, 2 × CH_3), 0.08 (6 H, s, 2 × CH_3), 0.90 [18 H, s, 2 × $(CH_3)_3C$], 1.35 (3 H, t, J 7.2, OCH_2CH_3), 4.30 (2 H, q, J 7.2, OCH_2CH_3), 4.44 (2 H, d, J 3.6, TBSOCH_2), 4.74 (2 H, d, J 2.0, TBSOCH_2); *m*/*z* (EI-LR) 349 (M^+ − C_4H_9), 115, 105, 91, 73; δ_F(376 MHz; MeOH-d_4) −124.73.

4-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)-2-fluorobut-2-enal (7)

Diisobutylaluminium hydride (1.6 cm^3, 1.6 mmol, 1.0 M solution in toluene) was added dropwise to a stirred solution of compound **5** (572 mg, 1.41 mmol) in toluene (6 cm^3) at −78 °C and the reaction mixture was stirred at the same temperature for 1 h. After the successive addition of methanol (1.6 cm^3), hexane (3 cm^3) and ethyl acetate (3 cm^3), the mixture was allowed to warm to RT and stirred for 5 h. The mixture was then filtered through Celite and the filtrate evaporated under reduced pressure. The colourless oil was purified by silica gel column chromatography using hexane and ethyl acetate (25 : 1) as the eluent to give *the title compound* **7** (509 mg, 100%) as a colourless oil. (Found: C, 56.45; H, 9.98. $C_{17}H_{35}FO_3Si_2$ requires C, 56.31; H, 9.73%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.09 (6 H, s, 2 × CH_3), 0.11 (6 H, s, 2 × CH_3), 0.91 [18 H, s, 2 × $(CH_3)_3C$], 4.48 (2 H, d, J 3.2, TBSOCH_2), 4.65 (2 H, d, J 3.6, TBSOCH_2), 9.99 [1 H, d, J 18.4, C(O)H].

(±)-Acetic acid 5-acetoxy-4-fluoro-2,5-dihydrofuran-3-ylmethyl ester (9)

Triethylamine trihydrofluoride (2.71 cm^3, 16.63 mmol) was added dropwise to a stirred solution of compound **7** (1.004 g, 2.77 mmol) in methylene chloride (22 cm^3) at 0 °C and the reaction mixture was stirred at RT overnight to produce the lactol **8** (239 mg, 63%) as a colourless syrup. (Found: C, 44.38; H, 5.07. $C_5H_7FO_3$ requires C, 44.78; H, 5.26%); δ_H(400 MHz; MeOH-d_4; Me_4Si) 4.16 (1 H, d, J 13.2, HOCHH), 4.23 (1 H, d, J 13.2, HOCHH), 4.47 (1 H, dd, J 5.6 and 12.0, OCHH), 4.62 (1 H, dt, J 4.8 and 12.0, OCHH), 5.69 (1 H, t, J 4.4, anomeric H).

Triethylamine (15.3 cm^3, 110.49 mmol) and acetic anhydride (5.3 cm^3, 56.17 mmol) were added to **8** (239 mg, 1.78 mmol) at 0 °C and the reaction mixture was stirred at RT overnight. The mixture was extracted with ethyl acetate (100 cm^3). The organic layer was dried and evaporated under reduced pressure. The pale yellow syrup was purified by short-pad silica gel column chromatography using hexane and ethyl acetate (3 : 1) as the eluent to give *the title compound* **9** (260 mg, 67%) as a colourless oil and the monoacetylated lactol (107 mg) as a colourless oil. (Found: C, 49.32; H, 4.87. $C_9H_{11}FO_5$ requires C, 49.54; H, 5.08%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.09 (3 H, s, $COCH_3$), 2.12 (3 H, s, $COCH_3$), 4.60 (1 H, dd, J 6.0, and 12.4, OCHH), 4.73–4.82 (3 H, m, OCHH, AcOCH_2), 6.71 (1 H, t, J 3.6, anomeric H); δ_F(376 MHz; MeOH-d_4) −142.55.

(±)-Acetic acid 4-fluoro-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrohydropyrimidin-1-yl)-2,5-dihydrofuran-3-ylmethyl ester (10)

A solution of compound **9** (77 mg, 0.35 mmol) in dichloroethane (3 cm^3) and trimethylsilyl trifluoromethanesulfonate (0.13 cm^3, 0.71 mmol) were added dropwise at 0 °C successively to a stirred solution of persilylated thymine in dichloroethane (3 cm^3) [prepared from refluxing thymine (89 mg, 0.71 mmol) and hexamethyldisilazane (5 cm^3) in the presence of catalytic amount of ammonium sulfate] and the reaction mixture was stirred at the same temperature for 30 min. After being quenched with saturated aqueous sodium bicarbonate (2 cm^3), the mixture was filtered through a Celite and the filtrate extracted with methylene chloride (3 × 50 cm^3). The organic layer was dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (1 : 1.5) as the eluent to give *the title compound* **10** (23 mg, 23%) as a white solid and the dihydrofuran derivative **12** (19 mg, 34%) as a colourless oil.

Compound 10. Mp 124–126 °C; (Found: C, 50.75; H, 4.87; N, 9.47. $C_{12}H_{13}FN_2O_5$ requires C, 50.71; H, 4.61; N, 9.86%); λ_{max}(MeOH)/nm 272; ν_{max}/cm^{-1} 1696 (COO); δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.95 (3 H, s, CH_3), 2.12 (3 H, s, $COCH_3$), 4.68 (1 H, ddd, *J* 2.4, 5.6, and 12.4, OC*H*H), 4.74–4.79 (2 H, m, HOCH*H*, AcOC*H*H), 4.85 (1 H, d, *J* 13.6, AcOCH*H*), 6.88 (1 H, br s, anomeric H), 6.92 (1 H, s, H-6), 8.97 (1 H, br s, NH); *m*/*z* (FAB-LR) 285 ($M^+ + 1$), 225, 154, 136, 127, 99, 77.

Compound 12. δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.08 (3 H, s, $COCH_3$), 4.97 (2 H, s, CH_2), 7.30–7.31 (1 H, m, vinylic H), 7.36 (1 H, dd, *J* 1.6 and 5.2, vinylic H).

(±)-Acetic acid 5-(4-acetamido-2-oxo-1,2-dihydropyrimidin-1-yl)-4-fluoro-2,5-dihydrofuran-3-ylmethyl ester (11)

A solution of compound **9** (120 mg, 0.55 mmol) in dichloroethane (4 cm^3), and trimethylsilyl trifluoromethanesulfonate (0.22 cm^3, 1.24 mmol) were added dropwise at 0 °C successively to a stirred solution of persilylated N^4-acetylcytosine in dichloroethane (3 cm^3) [prepared from refluxing N^4-acetylcytosine (190 mg, 1.24 mmol) and hexamethyldisilazane (6 cm^3) in the presence of a catalytic amount of ammonium sulfate] and the reaction mixture was stirred at the same temperature for 20 min. After being quenched with saturated aqueous sodium bicarbonate (3 cm^3), the mixture was filtered through a pad of Celite and the filtrate extracted with methylene chloride (3 × 50 cm^3). The organic layer was dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using methylene chloride and methanol (25 : 1) as the eluent to give the *title compound* **11** (52.4 mg, 31%) as a white solid and the dihydrofuran derivative **12** (36.5 mg, 42%) as a colourless oil.

Compound 11. Mp 249 °C (decomp.); (Found: C, 50.23; H, 4.44; N, 13.65. $C_{13}H_{14}FN_3O_5$ requires C, 50.16; H, 4.53; N, 13.50%); λ_{max}(MeOH)/nm 249 and 299; ν_{max}/cm^{-1} 1732 (COO); δ_H(400 MHz; MeOH-d_4; Me_4Si) 2.09 (3 H, s, $COCH_3$), 2.19 (3 H, s, $NHCOCH_3$), 4.74 (1 H, ddd, *J* 2.4, 6.0, and 12.4, OC*H*H), 4.83 (2 H, s, AcOCH_2), 4.85–4.92 (1 H, m, OCH*H*), 6.96 (1 H, br s, anomeric H), 7.48 (1 H, d, *J* 8.0, H-5), 7.90 (1 H, d, *J* 7.2, H-6); *m*/*z* (FAB-LR) 312 ($M^+ + 1$), 252, 136, 99, 77.

(±)-1-(3-Fluoro-4-hydroxymethyl-2,5-dihydrofuran-2-yl)-5-methylpyrimidine-2(1*H*),4(3*H*)-dione (13)

A solution of compound **10** (22 mg, 0.08 mmol) in saturated methanolic ammonia (3 cm^3) was stirred at RT for 2 h and the mixture was evaporated under reduced pressure to give an oil. This was purified by silica gel column chromatography using hexane and ethyl acetate (1 : 3.5) as the eluent to give the *title compound* **13** (17.6 mg, 94%) as a white solid. Mp 175–177 °C; (Found: C, 49.99; H, 4.17; N, 11.33. $C_{10}H_{11}FN_2O_4$ requires C, 49.59; H, 4.58; N, 11.57%); λ_{max}(MeOH)/nm 263; δ_H(400 MHz; MeOH-d_4; Me_4Si) 1.90 (3 H, d, *J* 1.2, CH_3), 4.31 (1 H, d, *J* 13.6, HOC*H*H), 4.37 (1 H, d, *J* 13.2, HOCH*H*), 4.72 (1 H, ddd, *J* 2.4, 5.6, and 12.0, OC*H*H), 4.86–4.90 (1 H, m, OCH*H*), 6.83 (1 H, br s, anomeric H), 7.31 (1 H, s, H-6); δ_C(100 MHz; MeOH-d_4; Me_4Si) 11.05, 52.66, 71.99 (d, *J* 8.4), 84.44 (d, *J* 28.8), 111.75, 119.44 (d, *J* 6.3), 135.59, 146.32 (d, *J* 274.9), 151.49, 164.94; δ_F(376 MHz; MeOH-d_4) −150.11; *m*/*z* (FAB-LR) 243 ($M^+ + 1$), 154, 136, 117, 89, 77.

(±)-4-Amino-1-(3-fluoro-4-hydroxymethyl-2,5-dihydrofuran-2-yl)pyrimidin- 2(1*H*)-one (14)

A solution of compound **11** (40 mg, 0.13 mmol) in saturated methanolic ammonia (5 cm^3) was stirred at RT for 2 h and the mixture was evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography using methylene chloride and methanol (5.5 : 1) as the eluent to give the *title compound* **14** (26 mg, 90%) as a white solid. Mp 82–83 °C; (Found: C, 47.99; H, 4.14; N, 18.11. $C_9H_{10}FN_3O_3$ requires C, 47.58; H, 4.44; N, 18.50%); λ_{max}(MeOH)/nm 266; δ_H(400 MHz; MeOH-d_4; Me_4Si) 4.30 (1H, d, *J* 14.0, HOC*H*H), 4.34 (1H, d, *J* 14.8, HOCH*H*), 4.72 (1 H, ddd, *J* 2.0, 5.6, and 12.0, OC*H*H), 4.82–4.88 (1 H, m, OCH*H*), 5.95 (1 H, d, *J* 7.6, H-5), 6.91 (1 H, br s, anomeric H), 7.52 (1 H, d, *J* 7.2, H-6); δ_C(100 MHz; MeOH-d_4; Me_4Si) 53.99, 73.26 (d, *J* 8.3), 86.62 (d, *J* 28.5), 97.55, 120.36 (d, *J* 6.2), 142.24, 148.48 (d, *J* 275.1), 158.71, 167.89; δ_F(376 MHz; MeOH-d_4) −148.24.

(±)-Acetic acid 5-(6-benzamidopurin-9-yl)-4-fluoro-2,5-dihydrofuran-3-ylmethyl ester (15a)

A solution of compound **9** (72 mg, 0.33 mmol) in dichloroethane (3 cm^3) and trimethylsilyl trifluoromethanesulfonate (0.09 cm^3, 0.50 mmol) were added dropwise at 0 °C successively to a stirred solution of persilylated N^6-benzoyladenine in dichloroethane (3 cm^3) [prepared from refluxing N^6-benzoyladenine (119 mg, 0.50 mmol) and hexamethyldisilazane (5 cm^3) in the presence of catalytic amount of ammonium sulfate], and the reaction mixture was stirred at the same temperature for 20 min. After being quenched with saturated aqueous sodium bicarbonate (2 cm^3), the mixture was filtered through a pad of Celite, and extracted with methylene chloride (3 × 50 cm^3). The organic layer was dried and evaporated under reduced pressure to give a syrup, which was purified by silica gel column chromatography using methylene chloride and methanol (30 : 1) as the eluent to give *the title compound* **15a** (23 mg, 24%) as a sticky syrup, N-7 glycosylated nucleoside **15b** (7 mg, 7%) as a sticky syrup and the dihydrofuran derivative **12** (45%).

Compound 15a. (Found: C, 57.44; H, 4.25; N, 17.32. $C_{19}H_{16}FN_5O_4$ requires C, 57.43; H, 4.06; N, 17.62%); λ_{max}(MeOH)/nm 279; δ_H(400 MHz; MeOH-d_4; Me_4Si) 2.12 (3 H, s, $COCH_3$), 4.79–4.84 (1 H, m, OC*H*H), 4.91 (2 H, br s, AcOCH_2), 5.01–5.06 (1 H, m OCH*H*), 7.04 (1 H, br t, *J* 3.8, anomeric H), 7.55–8.10 (5 H, m, Ph), 8.52 (1 H, s, H-2), 8.74 (1 H, s, H-8).

Compound 15b. λ_{max}(MeOH)/nm 279; δ_H(400 MHz; MeOH-d_4; Me_4Si) 2.02 (3 H, s, $COCH_3$), 4.68–4.86 (4 H, m, OCH_2, AcOCH_2), 7.44–8.08 (6 H, m, anomeric H, and Ph), 8.63 (2 H, br s, H-2 and H-8).

(±)-[5-(6-Aminopurin-9-yl)-4-fluoro-2,5-dihydrofuran-3-yl]methanol (16a)

A solution of the N^9-isomer **15** (30 mg, 0.08 mmol) in saturated methanolic ammonia (5 cm^3) was stirred at RT for 1.5 h. The mixture was evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography using methylene chloride and methanol (12:1) as the eluent to give *the title compound* **16a** (17 mg, 90%) as a white solid. Mp 205–206 °C; (Found: C, 47.88; H, 4.03; N, 27.91. $C_{10}H_{10}FN_5O_2$ requires C, 47.81; H, 4.01; N, 27.88%); λ_{max}(MeOH)/nm 258; δ_H(400 MHz; MeOH-d_4; Me_4Si) 4.39 (2 H, s, HOCH_2), 4.80–4.84 (1 H, m, OC*H*H), 4.97–5.02 (1 H, m, OCH*H*), 6.90 (1 H, br t, *J* 4.4, anomeric H), 8.22 (1 H, s, H-2), 8.25 (1 H, s, H-8); δ_C(100 MHz; MeOH-d_4; Me_4Si) 51.13, 73.77 (d, *J* 8.3), 84.80 (d, *J* 29.1), 120.49, 120.55, 140.79, 147.37 (d, *J* 274.5), 150.81, 154.48, 157.59; δ_F(376 MHz; MeOH-d_4) –148.84 (s); *m*/*z* (FAB-LR) 252 ($M^+ + 1$), 176, 136, 107, 89.

(±)-[5-(6-Aminopurin-7-yl)-4-fluoro-2,5-dihydrofuran-3-yl] methanol (16b)

A solution of the N^7-isomer **15b** (7 mg, 0.019 mmol) in saturated methanolic ammonia (3 cm^3) was stirred at RT for 16 h. The mixture was evaporated under reduced pressure to give an

oil, which was purified by silica gel column chromatography using methylene chloride and methanol (12 : 1) as the eluent to give *the title compound* **16b** (2.1 mg, 45%) as a white solid; λ_{max}(MeOH)/nm 270; δ_H(400 MHz; MeOH-d_4; Me_4Si) 4.39 (1 H, s, HOC*H*H), 4.57 (1 H, s, HOC*H*H), 4.49–4.89 (1 H, m, OC*H*H), 4.97–5.02 (1 H, m, OCH*H*), 6.89 (1 H, m, anomeric H), 8.22 (1 H, s, H-2), 8.25 (1 H, s, H-8); δ_F(376 MHz; MeOH-d_4) −149.00 (s).

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References

1 (*a*) M. Nasr, C. Litterst and J. McGowan, *Antiviral Res.*, 1990, **14**, 125; (*b*) E. De Clercq, *AIDS Res. Hum. Retroviruses*, 1992, **8**, 119.
2 T.-S. Lin, R. F. Schinazi and W. H. Prusoff, *Biochem. Pharmacol.*, 1987, **36**, 2713.
3 F. Sanger, S. Nicklen and A. R. Coulson, *Proc. Natl. Acad. Sci. USA*, 1977, **75**, 5463.
4 (*a*) T.-S. Lin, R. F. Schinazi and W. H. Prusoff, *Biochem. Pharmacol.*, 1987, **36**, 2713; (*b*) Y. Hamamoto, H. Nakashima, T. Matsui, A. Matsuda, T. Ueda and N. Yamamoto, *Antimicrob. Agents Chemother.*, 1987, **31**, 907.
5 (*a*) K. Lee, Y. Choi, E. Gullen, S. Schlueter-Wirtz, R. F. Schinazi, Y.-C. Cheng and C. K. Chu, *J. Med. Chem.*, 1999, **42**, 1320; (*b*) K. Lee, Y. Choi, G. Gumina, R. F. Schinazi and C. K. Chu, *J. Med. Chem.*, 2002, **45**, 1313.
6 V. Nair and T. S. Jahnke, *Antimicrob. Agents Chemother.*, 1995, **39**, 1017.
7 Y. Terao, M. Akamatsu and K. Achiwa, *Chem. Pharm. Bull.*, 1991, **39**, 823.
8 L. S. Jeong, H. O. Kim, H. R. Moon, J. H. Hong, S. J. Yoo, W. J. Choi, M. W. Chun and C.-K. Lee, *J. Med. Chem.*, 2001, **44**, 806.
9 J. H. Hong, H. O. Kim, H. R. Moon and L. S. Jeong, *Arch. Pharm. Res.*, 2001, **24**, 95.
10 (*a*) R. P. Panzica, R. J. Rousseau, R. K. Robins and L. B. Townsend, *J. Am. Chem. Soc.*, 1972, **94**, 4708; (*b*) R. J. Rousseau, R. K. Robins and L. B. Townsend, *J. Am. Chem. Soc.*, 1968, **90**, 2661.
11 V. E. Marquez, C. K.-H. Tseng, H. Mitsuya, S. Aoki, J. A. Kelley, H. Ford Jr., J. S. Roth, S. Broder, D. G. Johns and J. S. Driscoll, *J. Med. Chem.*, 1990, **33**, 978.