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Synthesis and Antiviral Activity of 2'-Fluorohexopyranosyl Nucleosides

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2'-Fluorohexopyranosyl nucleosides **1a** and **1b** which contained a bioisosteric double bond and a fluorine were synthesized in 12 steps, starting from D-galactose. During diethylaminosulfur trifluoride (DAST) fluorination, retention of stereochemistry was observed through the participation of methoxy or chloro group at the 6-position of the purine base. The final nucleosides **1a** and **1b** were found to be inactive against HIV-1 and HSV-1,2.

Key words : Bioisosteric, DAST fluorination, Antiviral, Retention of configuration

INTRODUCTION

1,3-Oxathiolanyl nucleosides show potent *in vitro* anti-HIV activity in both T-lymphoid and monocytoid cell lines as well as in primary cultures of human peripheral lymphocytes (Belleau *et al.*, 1990, Soudeyns *et al.*, 1991). Especially, 1,3-oxathiolanyl cytosine is less toxic than AZT in tissue culture. This relatively low toxicity compensates in large part for lower specific anti-HIV-1 activity of 1,3-oxathiolanyl cytosine, in comparison with that of AZT, in the same system (Belleau *et al.*, 1990, Soudeyns *et al.*, 1991). It has been shown that both enantiomers of racemic 1,3-oxathiolanyl cytosine (BCH-189) are very potent against HIV-1 and 2 *in vitro* (Coates *et al.*, 1992, Schinazi *et al.*, 1991). However, (-)-L-enantiomer (3TC, Lamivudine), which is the unnatural form, is considerably less toxic than (+)-D-enantiomer (Beach *et al.*, 1992, Jeong *et al.*, 1993) and is being currently used clinically in combination with AZT for the treatment of AIDS and AIDS related complex (ARC).

On the other hand, many 2'-fluoro-substituted nucleosides like 2'-fluoro-*ara*-ddA (Marquez *et al.*, 1987) were reported to be very potent anti-HIV agents. Since fluorine and hydrogen have similar Van Der Waals radii, but they possess very different electronegative character, a number of fluorine containing nucleosides have played a major role for the development of new antiviral and antitumor agents. In addition, it is known that the glycosyl bond of nucleosides containing fluorine at 2'-position is greatly stabilized chemically and metabolically due to the fluorine atom (Marquez *et al.*, 1990).

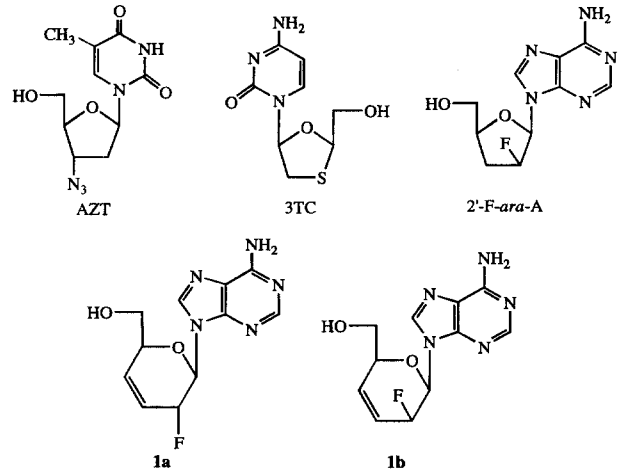

Fig. 1.

Based on these findings, it was interesting to synthesize the 2'-fluorohexopyranosyl nucleosides **1a** and **1b**, where sulfur atom of 1,3-oxathiolanyl nucleosides is substituted by a bioisosteric double bond and fluorine is substituted at the 2-position of the hexopyranose because of potent activity of 2'-F-*ara*-ddA (Fig. 1). Here, we wish to report synthesis and antiviral activity of 2'-fluorohexopyranosyl nucleosides.

MATERIALS AND METHODS

^{1}H NMR spectra were recorded on a Bruker DPX (250 MHz or 300 MHz) spectrometer using $CDCl_3$ or

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DMSO-d_6 with TMS as internal standard. Ultra Violet (UV) spectra were recorded on a DU-68 spectrometer. TLC was performed on Merck precoated $60F_{254}$ plates. Elemental analyses were performed by the general instrument laboratory of Ewha Womans University. Flash column chromatography was performed using silica gel 60 (230~400 mesh, Merck). All reagents were purchased from Aldrich. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to reaction.

2,3,4,5-Di-*O*-isopropylidene-α-D-galactopyranose (3)

Anhydrous zinc chloride (30 g, 0.22 mol) was added to a 500 ml of round-bottom flask followed by acetone and c-H_2SO_4 (0.60 ml). D-Galactose (**2**) (15.0 g, 0.83 mol) was added and the mixture was stirred at room temperature for 6 h. After the reaction was completed, the suspension of Na_2CO_3 (30.0 g) in water was added and the mixture was stirred vigorously for 4 h. The suspension was filtered and washed with acetone thoroughly. The combined filtrates were evaporated until most of acetone was removed. The residue was extracted with diethyl ether, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and evaporated to give crude product **3**. The residue was purified by silica gel column chromatography (Hx:EtOAc=3:1) to give **3** (20.7 g, 95%), as a yellow syrup: R_f=0.33 ($CHCl_3$:MeOH=20:1); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 2.16 (br s, 1 H, OH), 3.67~3.70 (m, 1 H, 5-H), 3.88 (dd, 2 H, *J*=7.0, 7.3 Hz, 6-H), 4.28 (dd, 2 H, *J*=1.4, 6.5 Hz, 3-H), 4.34 (dd, 1 H, *J*=2.4, 2.7 Hz, 4-H), 4.62 (dd, 1 H, *J*=2.4, 5.6 Hz, 2-H), 5.57 (d, 1 H, *J*=5.0 Hz, 1-H).

6-*O*-Benzyl-2,3,4,5-di-*O*-isopropylidene-α-D-galactopyranose (4)

60% NaH (2.86 g, 0.12 mol) was added all at once to the solution of **3** (20.7 g, 0.79 mol) in dry THF and BnBr (14.2 ml, 0.12 mol) was then added dropwise followed by Bu_4NI (2.93 g, 8.0 mmol) at 0°C. The mixture was stirred at room temperature under nitrogen overnight and neutralized with glacial acetic acid. The whole mixture was diluted with water and ethyl acetate, and the organic layer was washed with water, dried ($MgSO_4$) and filtered. The residue was purified by silica gel column chromatography (Hx:EtOAc=7:1) to give **4** (27.4 g, 99%) as a pale yellow oil: R_f=0.45 ($CHCl_3$:MeOH=10:1); ^{1}H NMR ($CDCl_3$) δ 1.34~1.60 (m, 12 H, 4×$OCOCH_3$), 3.40-3.48 (m, 1 H, 5-H), 3.59~3.69 (m, 1 H, 6-H), 4.06~4.09 (m, 1 H, 3-H), 4.29~4.33 (m, 1 H, 2-H), 4.57~4.69 (m, 2 H, CH_2-Ar), 5.55 (d, 1 H, *J*=5.0 Hz, 1-H).

6-*O*-Benzyl-2,3,4,5-tetra-*O*-acetyl-D-galactopyranose (6)

A solution of **4** (5.71 g, 16.3 mmol) in 80% acetic acid was heated overnight at 90°C. The reaction mixture was evaporated and coevaporated with toluene and ethanol. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH=7:1) to give 5 (3.46 g, 70%) as an ivory foam: R_f=0.30 ($CHCl_3$:MeOH =7:1).

Acetic anhydride (5.90 ml, 3.08 mmol) was added to a solution of **5** (2.08 g, 7.70 mmol) in pyridine and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated and the residue was coevaporated with ethanol. The residue was purified by silica gel column chromatography (Hx:EtOAc =2:1) to give 6 (3.42 g, 100%) as a yellow syrup: R_f= 0.65 (Hx:EtOAc=1:1); ^{1}H NMR ($CDCl_3$) δ 1.99~2.15 (m, 24 H, 4 $OCOCH_3$), 3.97~4.02 (m, 2 H, 5-H), 4.40 (dd, 4 H, *J*=2.8, 9.2 Hz, 6-H), 4.53 (s, 2 H, β-CH_2-Ar), 4.58 (s, 2 H, α-CH_2-Ar), 5.08 (dd, 2 H, *J*=3.4, 7.1 Hz, 3-H), 5.51 (d, 1 H, *J*=3.2 Hz, β-4-H), 5.57-5.67 (m, 1 H, α-4-H), 5.69 (d, 2 H, *J*=4.4 Hz, 2-H), 6.32 (d, 1 H, *J*=4.7 Hz, β-1-H), 6.37 (d, 1 H, *J*=2.5 Hz, α-1-H), 7.26-7.37 (m, 10 H, 2 Ar-H).

6-Chloro-9-[6-*O*-benzyl-3,4,5-tri-*O*-acetyl-β-D-galactopyranosyl]-9*H*-purine (7a) and its α-isomer (7b)

A suspension of 6-chloropurine (0.74 g, 4.81 mmol) and catalytic amount of ammonium sulfate (0.01 g) in hexamethyldisilazane (HMDS) (20.0 ml) was heated at 140~150°C for 1 h until a clear solution was obtained. The reaction mixture was cooled to room temperature and HMDS was removed under reduced pressure under anhydrous conditions to give the residue. To a solution of this residue in 1,2-dichloroethane was added acetate **6** (1.00 g, 3.20 mmol) in dry 1,2-dichloroethane under nitrogen followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.87 ml, 4.81 mmol) at 5°C and the mixture was stirred at 5°C for 10 min and at room temperature for 24 h. The reaction mixture was neutralized with saturated sodium bicarbonate ($NaHCO_3$) solution and poured into EtOAc. The organic layer was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (Hx:EtOAc=3:2) to give **7a** (0.72 g, 59%) and **7b** (0.21 g, 17%).

β-isomer (**7a**): R_f=0.45 ($CHCl_3$:MeOH=20:1); UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3 H, $OCOCH_3$), 2.01 (s, 3 H, $OCOCH_3$), 2.16 (s, 3 H, $OCOCH_3$), 3.47~3.60 (m, 2 H, 6'-H), 4.19 (m, 1 H, 5'-H), 4.47 (dd, 2 H, *J*=12.0, 21.2 Hz, CH_2-Ar), 5.30 (dd, 1 H, *J*= 3.3, 6.8 Hz, 3'-H), 5.65 (d, 1 H, *J*=2.5 Hz, 4'-H), 5.71 (d, 1 H, *J*=9.9 Hz, 2'-H), 5.90 (d, 1 H, *J*=9.4 Hz, 1'-H), 7.23~7.37 (m, 5 H, Ar-H), 8.36 (s, 1 H, H-2), 8.77 (s,

1 H, H-8).

α-isomer (**7b**): R_f=0.40 ($CHCl_3$:MeOH=20:1); UV (MeOH) λ_{max} 265 nm; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3 H, $OCOCH_3$), 2.09 (s, 3 H, $OCOCH_3$), 2.16 (s, 3 H, $OCOCH_3$), 3.66 (d, 2 H, *J*=5.9 Hz, 6'-H), 4.51 (s, 2 H, CH_2-Ar), 4.81 (t, 1 H, *J*=4.5 Hz, 5'-H), 5.29~5.35 (m, 1 H, 3'-H), 5.47~5.50 (m, 1 H, 4'-H), 5.89 (t, 1 H, *J*=3.42 Hz, 2'-H), 6.28 (d, 1 H, *J*=3.4 Hz, 1'-H), 7.23~7.33 (m, 5 H, Ar-H), 8.27 (s, 1 H, H-2), 8.78 (s, 1 H, H-8).

6-Methoxy- and 6-Chloro-9-[6-*O*-benzyl-3,4,5-tri-*O*-hydroxyl-β-D-galactopyranosyl]-9*H*-purine (8)

To a stirred solution of **7a** (0.66 g, 1.25 mmol) in MeOH were added potassium carbonate (K_2CO_3) (1.03 g, 7.48 mmol) and 1 drop of water and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized with acetic acid and passed through a silica gel pad to remove excess K_2CO_3. Solvent was evaporated and the residue was purified by column chromatography over silica gel ($CHCl_3$:MeOH=10:1) to give **8** (0.50 g, 100%) as an inseparable mixture of 6-methoxy- and 6-chloropurine derivatives whose ratio was variable depending on the reaction time: R_f=0.41 ($CHCl_3$:MeOH=10:1) (6-Methoxypurine derivative); ^1H NMR (DMSO) δ 3.43 (br s, 3 H, 3 OH), 3.58~3.65 (m, 1 H, 5'-H), 3.68~3.73 (m, 2 H, 6'-H), 3.87 (d, 1 H, *J*=2.6 Hz, 3'-H), 4.07~4.12 (m, 1 H, 4'-H), 4.21 (s, 3 H, OCH_3), 4.30~4.37 (m, 1 H, 2'-H), 4.55 (s, 2 H, CH_2-Ar), 5.62 (d, 1 H, *J*=9.3 Hz, 1'-H), 7.29~7.43 (m, 5 H, Ar-H), 8.62 (s, 1 H, H-2), 8.65 (s, 1 H, H-8).

6-Methoxy-9-[6-*O*-benzyl-5-hydroxyl-3,4-isopropylidene-β-D-galactopyranosyl]-9*H*-purine (9A) and 6-Chloro-9-[6-*O*-benzyl-5-hydroxyl-3,4-isopropylidene-β-D-galactopyranosyl]-9*H*-purine (9B)

To a solution of **8** (0.36 g, 0.88 mmol) in acetone were added 2,2-dimethoxypropane (0.66 ml, 5.30 mmol) and p-toluenesulfonic acid (17.0 mg, 0.09 mmol) and the reaction mixture was stirred at room temperature for 1 h, neutralized with triethylamine and evaporated to give the residue, which was purified by silica gel column chromatography (Hx:EtOAc=1:2 to EtOAc only) to give 6-methoxy derivative **9A** (0.27 g, 70%) as an ivory foam and 6-chloro derivative **9B** (0.09 g, 23%) as an ivory foam.

6-methoxypurine derivative (**9A**): R_f=0.20 (Hx:EtOAc=1:1); ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 3.52~3.55 (m, 1 H, 5-H), 3.74~3.83 (m, 1 H, 6'-H), 4.13 (s, 3 H, OCH_3), 4.26~4.32 (m, 3 H, 2', 3',4'-H), 4.57 (dd, 2 H, *J*=7.0, 12.1 Hz, CH_2-Ar), 4.95 (s, 1 H, OH), 5.51 (d, 1 H, *J*=8.1 Hz, 1'-H), 7.24~7.37 (m, 5 H, Ar-H), 8.13 (s, 1 H, H-2), 8.49 (s, 1 H, H-8).

6-chloropurine derivative (**9B**): R_f=0.11 (Hx:EtOAc=1:1); ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 3.47 (d, 1 H, *J*=3.5 Hz, 5'-H), 3.75~3.82 (m, 2 H, 6'-H), 4.29~4.36 (m, 3 H, 2',3',4'-H), 4.58 (dd, 2 H, *J*=6.6, 12.0 Hz, CH_2-Ar), 5.57 (d, 1 H, *J*=8.4 Hz, 1'-H), 7.26~7.34 (m, 5 H, Ar-H), 8.36 (s, 1 H, H-2), 8.76 (s, 1 H, H-8).

6-Methoxy-9-[6-*O*-benzyl-2-deoxy-2-α,β-fluoro-3,4-*O*-isopropylidene-β-D-galactopyranosyl]-9*H*-purine (10a and 10b).

To a solution of **9A** (0.14 g, 0.31 mmol) in anhydrous methylene chloride, diethylaminosulfur trifluoride (DAST) was added (0.08 ml, 0.63 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH=40:1) to give a mixture (0.11 g, 78%) of 6-methoxy fluoro-down **10a** and 6-methoxy fluoro-up **10b**. Analytical sample was purified by preparative TLC for the ^1H NMR.

10a: R_f=0.40 ($CHCl_3$:MeOH=10:1); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 3.61 (dd, 1 H, *J*=6.7, 3.8 Hz, 6'-Ha), 3.78 (dd, 1 H, *J*=4.8, 5.8 Hz, 6'-Hb), 4.20 (s, 3 H, OCH_3), 4.28~4.31 (m, 1 H, 1'-H), 4.48 (d, 2 H, *J*=4.1 Hz, CH_2-Ar), 4.70~4.78 (m, 1 H, 5'-H), 4.86 (dd, 1 H, *J*=3.9, 2.1 Hz, 4'-H), 5.09 (d, 1 H, *J*=6.0 Hz, 3'-H), 6.56 (dd, 1 H, *J*=6.8, 41.7 Hz, 2'-H), 7.23~7.38 (m, 5 H, Ar-H), 8.19 (s, 1 H, H-2), 8.60 (s, 1 H, H-8).

10b: R_f=0.43 ($CHCl_3$:MeOH=10:1); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.78 (dd, 1 H, *J*=6.9, 3.5 Hz, 6'-Ha), 3.88 (dd, 1 H, *J*=4.5, 6.1 Hz, 6'-Hb), 4.21 (s, 3 H, OCH_3), 4.43~4.59 (m, 2 H, 1'-H, 2'-H), 4.49~4.59 (m, 1 H, 5'-H), 4.64 (dd, 2 H, *J*=12.1, 11.4 Hz, CH_2Ar), 4.90~4.94 (m, 1 H, 4'-H), 5.05 (d, 1 H, *J*=5.6 Hz, 3'-H), 6.80 (dd, 1 H, *J*=1.8, 45.2 Hz, 2'-H), 7.33~7.38 (m, 5 H, Ar-H), 8.56 (s, 1 H, H-2), 8.60 (s, 1 H, H-8).

6-Chloro-9-[6-*O*-benzyl-2-deoxy-2-α,β-fluoro-3,4-*O*-isopropylidene-β-D-galactopyranosyl]-9*H*-purine (10c and 10d)

To a solution of **9B** (0.14 g, 0.32 mmol) in anhydrous methylene chloride, diethylaminosulfur trifluoride (DAST) was added (0.08 ml, 0.64 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH=40:1) to give a mixture (0.10 g, 72%) of 6-chloro fluoro-down **10c** and 6-chloro fluoro-up **10d**. Analytical sample was purified by preparative TLC for the ^1H NMR.

10c: R_f=0.41 ($CHCl_3$:MeOH=10:1); ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 3.61 (dd, 1 H, *J*=6.7, 3.8 Hz, 6'-Ha), 3.78 (dd, 1 H, *J*=4.8, 5.7 Hz, 6'-Hb), 4.16 (dd, 1 H, *J*=2.2, 1.9 Hz, 1'-H), 4.49 (dd, 2 H, *J*=12.0, 3.3 Hz, CH_2-Ar), 4.87 (dd, 1 H, *J*=3.8, 2.1 Hz, 5'-H), 5.07 (dd, 1 H, *J*=1.5, 3.0 Hz, 3'-H), 6.56 (dd, 1 H, *J*=7.1, 40.7 Hz, 2'-H), 7.22~7.32 (m, 5 H, Ar-H), 8.39 (s, 1 H, H-2), 8.78 (s, 1 H, H-8).

10d: R_f=0.43 ($CHCl_3$:MeOH=10:1); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.75 (dd, 1 H, *J*=7.1, 3.4 Hz, 6'-Ha), 3.87 (dd, 1 H, *J*=4.3, 6.3 Hz, 6'-Hb), 4.41~4.49 (m, 2 H, 1-H, 5'-H), 4.63 (dd, 2 H, *J*=12.0, 11.8 Hz, CH_2-Ar), 4.94 (dd, 1 H, *J*=3.9, 2.1 Hz, 4'-H), 5.09 (d, 1 H, *J*=5.9 Hz, 3'-H), 6.85 (dd, 1 H, *J*=1.5, 45.2 Hz, 2'-H), 7.26~7.39 (m, 5 H, Ar-H), 8.80 (d, 2 H, *J*=4.2 Hz, H-8, H-2).

6-Methoxy- or 6-Chloro-9-[6-*O*-benzyl-2-deoxy-2-α,β-fluoro-3,4-dihydroxy-β-D-galactopyranosyl]-9*H*-purine (11)

Compound **10** (0.35 g, 0.77 mmol) was treated with 90% HCOOH (10.0 mL) and CH_2Cl_2 (10.0 mL) and the mixture was stirred at room temperature for 72 h. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography to give **11** (0.27 g, 92%): R_f=0.42 ($CHCl_3$:MeOH=15:1); ^1H NMR ($CDCl_3$) δ 3.53~3.82 (m, 4 H, α,β-F-6-H), 4.22 (s, 6 H, 2 OCH_3), 4.51 (s, 2 H, α-CH_2-Ar), 4.64 (s, 2 H, β-CH_2-Ar), 4.76 (dd, 2H, *J*=6.6, 6.7 Hz, 3'-H), 5.22 (br s, 2 H, 3'-OH), 5.48 (br s, 2 H, 4'-OH), 6.73 (dd, 1 H, *J*=5.8, 43.2 Hz, β-2'-H), 6.80 (dd, 1 H, *J*=6.1, 41.0 Hz, α-2'-H), 7.31~7.50 (m, 10 H, 2 Ar-H), 7.76~7.78 (m, 2 H, 1'-H), 8.68 (s, 1 H, β-H-2), 8.72 (s, 1 H, β-H-8), 8.73 (s, 1 H, α-H-2), 8.76 (s, 1 H, α-H-2).

6-Methoxy- or 6-Chloro-9-[6-*O*-benzyl-2-deoxy-2-α,β-fluoro-3,4-dideoxydidehydro-β-D-galactopyranosyl]-9*H*-purine (12)

To a solution of **11** (0.43 g, 1.06 mmol) in anhydrous toluene and DMF (4:1) were added iodoform (0.92 g, 2.33 mmol), triphenylphosphine (1.11 g, 4.24 mmol), and imidazole (0.29 g, 4.24 mmol) and the mixture was heated at 100°C for 3 h. The reaction mixture was poured into CH_2Cl_2 and washed with 10% sodium thiosulfate ($Na_2S_2O_3$) solution. The organic layer was dried over magnesium sulfate, filtered and evaporated. The residue was purified by silica gel column chromatography (Hx:EtOAc=2:1) to give **12** (0.27 g, 69%). Analytical samples of 6-methoxy derivative were purified by preparative TLC for the ^1H NMR.

fluoro-down (**12a**): R_f=0.72 ($CHCl_3$:MeOH=10:1); ^1H NMR ($CDCl_3$) δ 3.51 (d, 2 H, *J*=4.6 Hz, 6'-H), 4.20 (s, 3 H, OCH_3), 4.55 (s, 2 H, CH_2-Ar), 4.91~4.95 (m, 1 H, 5'-H), 5.62~5.68 (m, 1 H, 1'-H), 5.91~5.97 (t, 2 H, *J*= 7.2 Hz, 3,4-vinyl-H), 6.51 (dd, 1 H, *J*=4.6, 49.0 Hz, 2'-H), 7.27~7.37 (m, 5 H, Ar-H).

fluoro-up (**12b**): R_f=0.70 ($CHCl_3$:MeOH=10:1); ^1H NMR ($CDCl_3$) δ 3.60 (d, 2 H, 6'-H), 4.21 (s, 3 H, OCH_3), 4.58 (s, 2 H, CH_2-Ar), 5.12~5.15 (m, 1 H, 5'-H), 5.40~5.48 (m, 1 H, 1'H), 5.87~5.91 (m, 1 H, 4'-H), 6.17 (d, 1 H, *J*=6.18 Hz, 3'-H), 6.59 (dd, 1 H, *J*= 2.9, 43.9 Hz, 2'-H), 7.25~7.38 (m, 5 H, Ar-H), 8.44 (s, 1 H, H-2), 8.56 (s, 1 H, H-8).

6-Methoxy- or 6-Chloro-9-[6-hydroxyl-2-deoxy-2-α,β-fluoro-3,4-dideoxydidehydro-β-D-galactopyranosyl]-9*H*-purine (13)

Boron trichloride (BCl_3) (1 M solution in THF, 2.30 ml, 2.30 mmol) was added to a solution of **12** (0.14 g, 0.39 mmol) in dry methylene chloride at -78°C for 2 h. MeOH was added and the mixture was neutralized with pyridine and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$: MeOH=35:1 to 25:1) to give **13** (98.0 mg, 91%): R_f= 0.55 ($CHCl_3$:MeOH=10:1); ^1H NMR ($CDCl_3$) δ 3.48~3.51 (m, 2 H, 6'-H) 4.22 (s, 3 H, OCH_3) 4.81~4.93 (m, 2 H, 5'-H, OH) 5.83~5.91 (m, 1 H, 1'-H) 6.18~6.26 (m, 2 H, 3,4-vinyl-H) 6.54~6.79 (m, 1 H, 2'-H) 8.76~8.86 (m, 2 H, H-8, H-2).

6-Amino-9-[6-hydroxyl-2-α-fluoro-3,4-dideoxydidehydro-β-D-galactopyranosyl]-9*H*-purine (1α) and 6-Amino-9-[6-hydroxyl-2-β-fluoro-3,4-dideoxydidehydro-β-D-galactopyranosyl]-9*H*-purine (1b)

A solution of **13** (98.0 mg, 34.8 mmol) in methanolic ammonia was heated at 100°C for 48 h. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography ($CHCl_3$: MeOH=10:1) to give **1a** (50.0 mg, 50%) as a white solid and **1b** (10.0 mg, 10%) as a white solid:

fluoro-down (**1a**); MS (*m/e*) 265 (M^+); R_f=0.35 ($CHCl_3$: MeOH=10:1); UV (MeOH) λ_{max} 260 nm; ^1H NMR (D_2O) δ 3.69 (s, 2 H, 6'-H), 4.80~4.89 (m, 1 H, 5'-H), 5.72 (dd, 1 H, *J*=5.4, 4.8 Hz, 1'-H), 5.95~5.98 (m, 1 H, 4'-H), 6.06~6.09 (m, 1 H, 3'-H), 6.56 (dd, 1 H, *J*=4.5, 39.6 Hz, 2'-H), 8.22 (s, 1 H, H-2), 8.38 (s, 1 H, H-8). Calcd for $C_{11}FH_{12}N_5O_2$: C, 49.81; H, 4.53; N, 26.42. Found: C, 49.84; H, 4.45; N, 26.22.

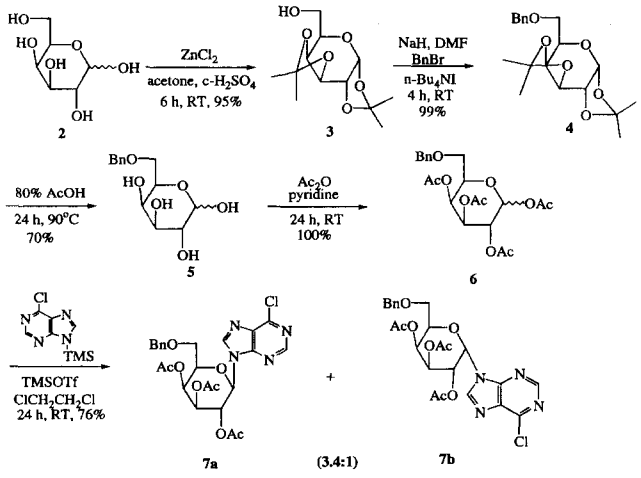
fluoro-up (**1b**); MS (*m/e*) 265 (M^+); R_f=0.33 ($CHCl_3$: MeOH=10:1); UV (MeOH) λ_{max} 260 nm; ^1H NMR (D_2O) δ 3.69 (m, 2 H, 6'-H), 5.00~5.10 (m, 1 H, 5'-H), 5.69~5.75 (m, 1 H, 1'-H), 5.89 (d, 1 H, *J*=6.3 Hz, 4'-H), 6.16 (d, 1 H, *J*=6.4 Hz, 3'-H), 6.47 (dd, 1 H, *J*=4.8, 42.5 Hz, 2'-H), 8.29 (s, 1 H, H-2), 8.47 (s, 1 H, H-8). Calcd for $C_{11}FH_{12}N_5O_2$: C, 49.81; H, 4.53; N, 26.42. Found: C, 49.65; H, 4.65; N, 26.31.

RESULTS AND DISCUSSION

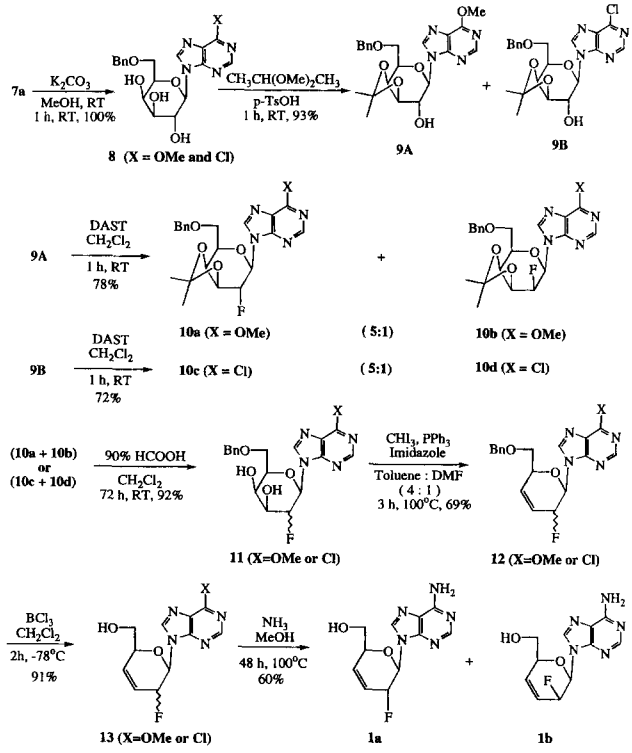
Synthesis

To prepare 2'-fluorohexopyranosyl nucleosides, D-galactose (**2**) was used as starting material (Scheme 1). D-Galactose (**2**) was protected as diacetonide **3** by the treatment with $ZnCl_2$ and acetone. The remaining hydroxyl group was benzylated using NaH and BnBr in THF to give benzylate **4**. We first tried the selective deprotection of 3,4-isopropylidene group over 1,2-isopropylidene group for the proper functionlization, but it resulted in no selectivity at all. Therefore, two isopropylidene groups were removed using 80% AcOH at 100°C to afford tetraol **5**. Tetraol **5** was peracetylated with Ac_2O and pyridine to give tetraacetate **6**, which is ready for the condensation with nucleosidic base to yield the target nucleosides. The acetate **6** was condensed with silylated 6-chloropurine in the presence of TMSOTf in 1,2-dichloroethane to produce **7a** and its α-isomer **7b** in 3.4 to 1 ratio in 74% yield, which were separated by silica gel column chromatography.

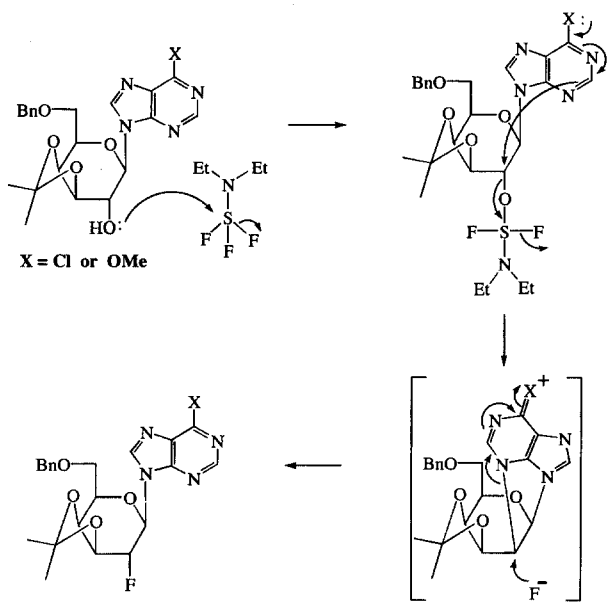
Conversion of protected nucleoside **7a** to the target nucleosides **1a** and **1b** is shown in Scheme 2. Triacetyl group of **7a** was deprotected with K_2CO_3 in MeOH to get triol. However, under this reaction conditions, an inseparable mixture of 6-chloro- and 6-methoxypurine derivatives **8** was always formed, although their ratio was variable on the reaction time. An inseparable mixture of 6-chloro- and 6-methoxypurine derivatives **8** was treated with 2,2-dimethoxypropane and and p-TsOH to give the isopropylidene analogue **9**, which could be separated by silica gel column chromatography to afford 6-chloropurine analogue **9A** and 6-methoxypurine analogue **9B**. To insert the fluorine atom at the 2'-position, DAST (diethylaminosulfur trifluoride) fluorination was carried out. When each analogue **9A** or **9B** was independently treated with DAST in CH_2Cl_2 at room temperature, two fluorinated products were always formed in 5 to 1 ratio, regardless of which analogue was used as starting material. Since DAST fluorination generally proceeds with inversion of stereochemistry (Herdewijn *et al.*, 1989), **10b** or **10d** was expected to be formed predominantly, but **10a** or **10c** turned out to be the major product by means of participation of electron-releasing methoxy or chlorine group at the 6-position of the purine, whose mechanism is well illustrated in Scheme 3. The introduction of the fluorine atom was easily confirmed by the geminal coupling constants ($J_{2'\text{-H},2'\text{-F}}$=40~50 Hz) between 2'-H and 2'-F. The stereochemistries of the fluorines in **10a** and **10b** were also confirmed by the vicinal coupling constants between 2'-H and 1'-H since $J_{axial,axial}$ value (6.8 Hz) is bigger than $J_{equatorial,axial}$ value (1.8 Hz). It is interesting to note that purine bases are in general not participated in the formation of anhydronucleosides in case of furanosylpurine nucleosides (Herdewijn *et al.*, 1989), while in our pyranosyl nucleosides, purine bases played a major role in the retention of stereochemistry during DAST reaction. Since **10a** and **10b** were too difficult to be separated by silica gel column chromatography, we decided to separate these isomers at the late stage. Isopropylidene group of **10** was removed by treating it with 90% formic acid in CH_2Cl_2 to yield diol **11**. The diol derivative **11** was converted to the olefinic



Scheme 1.



Scheme 2.



Scheme 3.

compound **12**, after treatment with iodoform-triphenylphosphine-imidazole system in 69% yield (Halmos *et al.*, 1986). Benzyl protecting group was easily deprotected using excess BCl_3 at -78°C to afford **13**. Treatment of 6-methoxy or 6-chloropurine analogue **13** independently with methanolic ammonia at 100°C produced the same final products **1a** and **1b**, which were purified by silica gel column chromatography.

Antiviral activity of 2'-fluorohexopyranosyl nucleosides

The final adenine derivatives **1a** and **1b** were tested against HIV-1 and HSV-1,2 and found to be inactive when tested up to 100 μg/ml. It is presumed that no antiviral activity is due to lack of affinity to nucleoside kinases, resulting in no formation of triphospahtes which is the active species for the antiviral activity.

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