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ADDITION OF MOLECULAR FLUORINE TO 7-OXABICYCLO[2.2.1]HEPT-5-ENE DERIVATIVE AND CONVERSION TO FLUORINE SUBSTITUTED DEOXYHEXOFURANOSIDES

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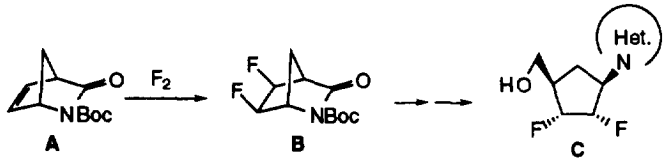
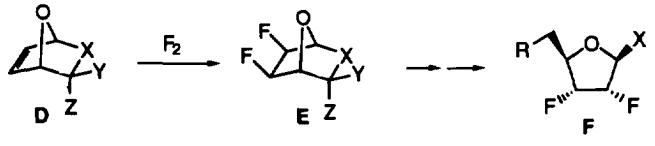
Abstract: Addition of molecular fluorine to 7-oxabicyclo[2.2.1]hept-2-ene derivative (**1**) has been found to give *exo,exo*-difluoro adduct in fair yield. The adduct was converted to various 2,3-difluoro ribofuranosides and 2,3-difluoro ribofuranosyl acetate derivatives were transformed selectively to β-pyrimidine nucleoside analogs *via* unique glycosilation process in the presence of TMSBr.

Addition of molecular fluorine to 2-azabicyclo[2.2.1]hept-5-en-3-ones (**A**) has been shown to give *exo,exo*-difluoro adducts (**B**)[1] which are converted to 2,3-difluorinated carbocyclic nucleosides. The cyclopentane ring of the nucleosides thus obtained were found to prefer $C_{2'}$-*endo* conformation by NMR study.[2]



Scheme 1

In an extension of the above work to the synthesis of 2,3-difluoro-2,3-dideoxy-ribonucleoside derivatives, we have studied fluorination of 7-oxabicyclo[2.2.1]hept-5-enes (**D**). We now report successful fluorination of readily available 2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetate[3] (**D**: X = CH_2, Y = CN, Z = OAc) and conversion of the difluoro adduct (**E**) to fluorine substituted furanoside and nucleoside analogs (**F**) (Scheme 2).

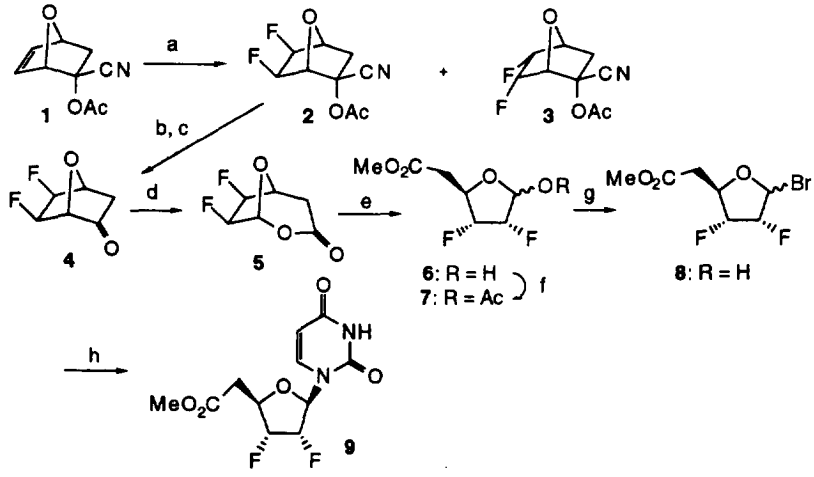


Scheme 2

RESULTS AND DISCUSSION

Addition of fluorine (5% F_2 / N_2) to **1** in $CFCl_3$-$CHCl_3$-EtOH (5:4:1)[4] at -78 °C furnished the *exo* (**2**) and *endo* difluoro adducts (**3**) in 53% and 9% yields, respectively. The *exo* configuration of two fluorine atoms in **2** was evident from the larger coupling (J = 12 Hz) of C_1-H with C_6-H compared to the absence of the corresponding coupling in **3**.[1] The *exo* selectivity (*exo*/*endo* = 5.9) in **1** is slightly lower than the corresponding selectivity (8.6)[1] in **A** probably due to stereoelectronic repulsion of oxygen atom at C_7 position. Saponification of **2** with MeONa/ MeOH followed by treatment with formalin[3] furnished **4** (78%). Baeyer-Villiger oxidation[5] of **4** with *m*-CPBA afforded lactone **5** (81%). Treatment of **5** with catalytic amount of NaOMe in MeOH at -25 °C → -15 °C gave **6** (β/α = 3) in quantitative yield. Acetylation of **6** (β/α = 3) with Ac_2O in the presence of equimolar amount of DMAP gave **7** (β/α = 19) in quantitative yield. The β–configuration of the major acetyl furanoside with N-type conformation of the furanoside ring (as described later) was obvious from the vicinal coupling constant $^3J_{H1',F2'}$ = 10.3 Hz compared to the absence of the corresponding coupling in the α–acetyl furanoside with S-type conformation[6] of the sugar ring .

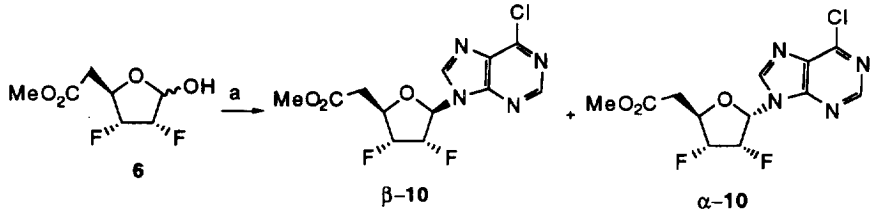
Direct coupling of **7** (β/α = 19) with the bissilylated uracil in the presence of TMSOTf[7] afforded **9** only in 10% yield. We thought that formation of oxonium cation derived from the acetate (**7**) led to ring opening followed by dehydrofluorination. According to the usual procedure to prepare 1-α-bromo-2-β-fluoro sugar,[8] **7** was treated with HBr-AcOH to give bromo sugar (**8**) (β/α = 1.3). Reaction of **8** with the bissilylated uracil gave **9** in 38% yield. The β–configuration of **9** with the N-type sugar was deduced from the vicinal coupling constant $^3J_{H1',F2'}$ = 16.5 Hz,[9] since the corresponding coupling in the α-anomer with S-type sugar[6] should be much smaller. Alternatively, treatment of the acetate (**7**) with 2 equivalents of TMSBr[10] followed by condensation with the bissilylated uracil in the presence of TMSBr furnished **9** in 96% yield. Since the bromide (**8**) is a mixture (3 : 1) of β- and α-anomers as evidenced by the NMR spectrum, selective formation of **9**



Scheme 3. a, 5%F_2/N_2, $CFCl_3$-$CHCl_3$-EtOH = 5 : 4 : 1, -78 °C; b, NaOMe, MeOH; c, aq. HCHO; d, *m*-CPBA, CH_2Cl_2; e, NaOMe, MeOH, -25 °C→15 °C; f, Ac_2O, DMAP, CH_2Cl_2; g, TMSBr, $CDCl_3$; h, bissilylated uracil.

deserves to comment. Assuming that the bissilylated uracil could only attack the α-bromide from β-side due to the repulsion with the fluorine atom at C_2 position, it is reasonable to conclude that isomerization of the β-anomer to the α-bromide is facilitated by reaction with TMSBr.

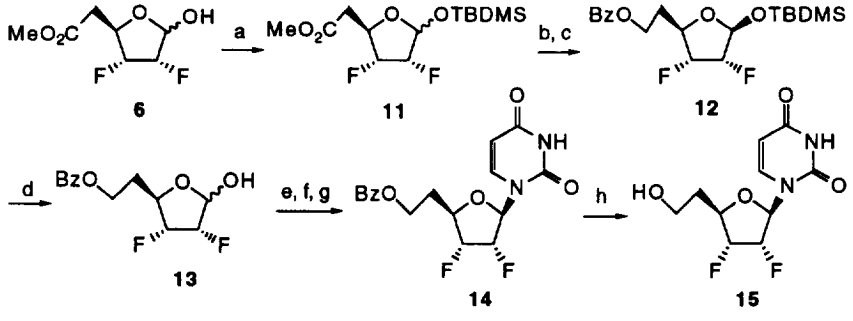
In order to synthesize their purine nucleoside analog more easily, **6** was reacted with 6-chloropurine under Mitsunobu conditions.[11] Though most of **6** was decomposed under these conditions (Ph_3P, DEAD, -35 °C→15 °C, THF), **β-10** and **α-10** were formed in 27% and 13% yields, respectively.



Scheme 4. a, Ph_3P, DEAD, 6-chloropurine, THF.

For the synthesis of 2,3-difluoro homoribose and its nucleoside derivatives, the hemiacetal (**6**) was treated with TBDMSOTf in the presence of 2,6-lutidine[12] to give **11** (β/α = 3.7) in 94% yield. Reduction of the anomeric mixture (**β-11**) with $LiBH_4$ followed by benzoylation with BzCl gave **12** in 90% yield. Treatment of **12** with Bu_4NF facilitated the ring opening. When the reaction was carried out in the presence of 1 equivalent of AcOH at -25 °C→-15 °C, the hemiacetal (**13**) (β/α = 3) was obtained in quantitative yield. Similar acetylation of **13** followed by coupling with the bissilylated uracil *via* bromide gave **14** in 83% yield. Compound **14** was treated with methanolic ammonia to provide **15** in 84% yield.

The coupling constants 0, 0, 3.5, 0, 0, 0, 3.5 and 7 Hz of $C_{2'}$-H with $C_{3'}$-F and 18, 19, 18, 20, 21, 19.5, 18, and 15 Hz of $C_{2'}$-F with $C_{3'}$-H were observed in the spectra of the β-furanoside analogs (**7**, **8**, **9**, **11**, **12**, **13**, **14** and **15**). The result could be correlated with N-type conformation of the furanoside ring. Preference of such conformation can be explained by the O4'-C1'-X1' (X = O, Br or N) anomeric effect over the gauche effect of F2'-C2'-C1'-X1' (X = O, Br or N), if the gauche effects of 2'-F and 3'-F with O4' oppose each other with identical magnitude and are therefore mutually cancelled.[13] The conformational



Scheme 5. a, TBDMSOTf, 2,6-lutidine, CH_2Cl_2; b, $LiBH_4$,THF; c, BzCl, pyridine; d, Bu_4NF, AcOH, THF; e, Ac_2O, DMAP, CH_2Cl_2; f, TMSBr, $CDCl_3$; g, bissilylated uracil; h, NH_3, MeOH.

preference was not observed in purine nucleoside analog (β-**10**), in which the corresponding coupling constants were $^3J_{H2',F3'}$ = 11.4 Hz and $^3J_{F2',H3'}$ = 8.7 Hz. This fact is in good accordance with relative efficiency of the anomeric effects: that of purine nucleoside is weaker than that of pyrimidine nucleoside.[14]

In conclusion, we have found that fluorination of 7-oxabicyclo[2.2.1]hept-2-ene (**1**) by molecular fluorine affords the *exo*-difluoro adduct in fair yield. The adduct (**2**) was converted to various 2,3-difluoro ribofuranosides and 2,3-difluoro ribofuranosyl acetate derivatives were transformed selectively to β-pyrimidine nucleoside analogs *via* unique glycosilation process in the presence of TMSBr.

Acknowledgment. This work is supported in part by a Grant-in-Aid from the Tokyo Biochemical Research Foundation.

Experimental Section

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. IR spectra were measured on a JASCO A-102 spectrophotometer and UV spectra were measured on a Hitachi 320 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI, Hitachi R-300 or JEOL JNM-GX 500 spectrometer with tetramethylsilane as an internal standard. If otherwise noted, all spectra were mesured by 60 MHz. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 or JMS-AX-500 spectrometer.

The fluorine gas [5% (v/v) in N_2] was donated from Asahi Glass Co., Ltd. and the amount of fluorine was determined by means of Kusano KG-2 flowmeter. Merck Silicagel 60 (230-400 mesh ASTM) was employed for flash chromatography.

2-*endo*-Acetoxy-5-*exo*,6-*exo*-difluoro-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (2) and 2-*endo*-Acetoxy-5-*endo*,6-*endo*-difluoro-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (3) 5% F_2/N_2 was passed into a solution of **1** (567 mg, 3.15 mmol) in $CFCl_3$ (79 ml)-$CHCl_3$ (63 ml)-EtOH (16 ml) at -78 °C until 10 mmol of F_2 had passed through the flowmeter (*ca.* 100 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (13 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (3 : 1)] to give **2** (363 mg, 53%) as colorless prisms, mp 142-143 °C (Et_2O), and **3** (62 mg, 9%) as a colorless oil.

2: IR ($CHCl_3$): 1765, 1370, 1230, 1190, 1070 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.76 (1H, d, J = 14.6 Hz, C_3-H$_\alpha$), 2.20 (3H, s, Ac), 2.82 (1H, m, C_3-H$_\beta$), 4.82 (1H, m, C_4-H), 4.83 (1H, ddd, J = 52, 5 and 2 Hz, C_5-H), 5.05 (1H, ddd, J = 51, 5 and 2.6 Hz, C_6-H), 5.18 (1H, d, J = 12 Hz, C_1-H). High-resolution MS *m/z* Calcd for $C_7H_7F_2NO_2$ (M^++1-CH_3CO): 175.0445. Found: 175.0399. *Anal.* Calcd for $C_9H_9F_2NO_3$: C, 49.77; H, 4.18; N, 6.45. Found: C, 49.62; H, 4.17; N, 6.51.

3: ^{1}H-NMR ($CDCl_3$) δ: 2.18 (1H, d, J = 15.5 Hz, C_3-H$_\alpha$), 2.15 (3H, s, Ac), 2.31 (1H, dd, J = 15.5 and 6.5 Hz, C_3-H$_\beta$), 2.97 (1H, m, C_4-H), 4.84 (1H, s), 5.05 (1H, dd, J = 52.5 and 1.5 Hz, C_5-H), 5.64 (1H, d, J = 67 Hz, C_6-H).

5-*exo*,6-*exo*-Difluoro-7-oxabicyclo[2.2.1]heptan-2-one (4)

To a stirred sloution of **2** (706 mg, 3.25 mmol) in MeOH (19 ml) was added NaOMe (10 mg, 0.18 mmol) at room temperature. After 22 h, the resulting mixture was treated with formalin (1.6 ml, 37% solution in H_2O; 0.63g, 21 mmol) and then stirred for 22 h. After evapolation of MeOH, the residue was diluted with H_2O (15 ml) and extracted with CH_2Cl_2 (3 x 48 ml). The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-Et_2O (2 : 1)] to give **4** (374 mg, 78%) as a colorless oil. IR ($CHCl_3$): 1780, 1145, 1070 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ: 1.97 (1H, d, J = 18 Hz, C_3-H_α), 2.58 (1H, dm, J = 18 Hz, C_3-H_β), 4.55 (1H, dd, J = 11.7, and 1.5 Hz, C_1-H), 4.98 (1H, ddd, J = 59, 5.5 and 3 Hz, C_5-H), 4.98 (1H, ddd, J = 50, 5.5 and 5 Hz, C_6-H), 5.12 (1H, m, C_4-H).High-resolution MS *m/z* Calcd for $C_6H_6F_2O_2$ (M^+): 148.0336. Found: 148.0314.

6-*exo*,7-*exo*-Difluoro-2,8-dioxabicyclo[3.2.1]octan-3-one (5)

To a solution of **4** (105 mg, 0.71 mmol) in CH_2Cl_2 (5 ml) was added *m*-CPBA (148 mg, 0.86 mmol) at room temperature. After 19 h of stirring at the same temperature, the mixture was diluted with CH_2Cl_2 (5 ml) and washed with 2% aq. K_2CO_3 (5 ml) and H_2O (5 ml). The aqueous layers were extracted with CH_2Cl_2 (5 ml) and the combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (3 : 1)] to give **5** (94 mg, 81%) as colorless prisms, mp 96-98 °C (Et_2O). IR ($CHCl_3$): 1772, 1190, 1080 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ: 2.62 (1H, d, J = 18.7 Hz, C_4-H_α), 3.18 (1H, ddd, J = 18.7, 7 and 3 Hz, C_4-H_β), 4.90 (1H, m, C_5-H), 5.15 (1H, ddd, J = 51, 5 and 3 Hz, C_6-H), 5.26 (1H, ddd, J = 51, 5 and 3 Hz, C_7-H), 5.96 (1H, ddd, J = 6.5, 2 and 1.5 Hz, C_1-H). High-resolution MS *m/z* Calcd for $C_6H_7F_2O_3$ (M^++ 1): 165.0363. Found: 165.0346. *Anal.* Calcd for $C_6H_6F_2O_3$: C, 43.91; H, 3.69. Found: C, 44.11; H, 3.72.

Methyl 2,3-Difluoro-2,3,5-trideoxy-*ribo*-hexofuranuronate (6)

To a stirred sloution of **5** (151 mg, 0.92 mmol) in MeOH (13 ml) was added portionwise NaOMe (4.4 mg, 0.08 mmol) at -25 °C and the mixture was stirred at -25 °C→-15 °C for 40 min. After neutralization with sat. aq. NH_4Cl (1.3 ml) and removal of methanol, the residue was extracted with CH_2Cl_2 (4 x 35 ml). The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give **6** (β/α = 3) (180 mg, 100%) as a colorless oil. IR ($CHCl_3$): 3600, 1740, 1440, 1060 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) **β-6:** δ: 2.73 (1H, dd, J = 16.3 and 7 Hz, C_5-H), 2.90 (1H, dd, J = 16.3 and 4.6 Hz, C_5-H'), 3.74 (3H, s, OMe), 4.55 (1H, dddd, J = 17, 7, 6.6 and 4.6 Hz, C_4-H), 4.90 (1H, dd, J = 53 and 4 Hz, C_2-H), 5.22 (1H, dddd, J = 51.5, 19.7, 6.6, and 4 Hz, C_3-H), 5.35-5.5 (1H, m, C_1-H). **α-6:** δ: 2.67 (1H, dd, J = 17 and 5.5 Hz, C_5-H), 2.75 (1H, dd, J = 17 and 6 Hz, C_5-H'), 3.71 (3H, s, OMe), 4.68 (1H, dddd, J = 22, 6, 5.5 and 3 Hz, C_4-H), 5.04 (1H, dddd, J = 47, 15, 8 and 4 Hz, C_2-H), 5.07 (1H, ddd, J = 50, 4 and 3 Hz, C_3-H), 5.35-5.5 (1H, m, C_1-H). High-resolution MS *m/z* Calcd for $C_6H_7F_2O_3$ (M^+-CH_3O): 165.0363. Found: 165.0366.

Methyl 1-Acetyl-2,3-difluoro-2,3,5-trideoxy-β-*ribo*-hexofuranuronate (β-7) and Methyl 1-Acetyl-2,3-difluoro-2,3,5-trideoxy-α-*ribo*-hexofuranuronate (α-7)

To a solution of **6** (β/α = 3) (98 mg, 0.50 mmol) in CH_2Cl_2 (6 ml) was added Ac_2O (0.060 ml, 0.64 mmol) and DMAP (61 mg, 0.50 mmol) at 0 °C and the mixture was stirred at the same temperature for 75 min. After neutralization with sat. aq. NH_4Cl (3 ml), the mixture was extracted with CH_2Cl_2 (4 x 25 ml). The

organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give β-**7** (113 mg, 95%) as colorless prisms, mp 42.5-44.5 °C (Et_2O), and α-**7** (6 mg, 5%) as a colorless oil.

β-**7**: IR ($CHCl_3$): 1750, 1530, 1210, 1040 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ: 2.09 (3H, s, Ac), 2.71 (1H, dd, J = 15.5 and 7 Hz, C_5-H), 2.78 (1H, dd, J = 15.5 and 6 Hz, C_5-H'), 3.73 (3H, s, OMe), 4.68 (1H, dddd, J = 16, 7, 6.2 and 6 Hz, C_4-H), 4.98 (1H, ddd, J = 51.5, 4.2 and 1.8 Hz, C_2-H), 5.10 (1H, dddd, J = 51, 18, 6.2, and 4.2 Hz, C_3-H), 6.24 (1H, dd, J = 10.3 and 1.8 Hz, C_1-H). High-resolution MS *m/z* Calcd for $C_7H_9F_2O_4$ (M^+- CH_3CO): 195.0469. Found: 195.0424. *Anal.* Calcd for $C_9H_{12}F_2O_5$: C, 45.38; H, 5.08. Found: C, 45.31; H, 4.96.

α-**7**: IR ($CHCl_3$): 1745, 1440, 1375, 1220, 1130, 1050 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ: 2.15 (3H, s, Ac), 2.73 (1H, dd, J = 17 and 5 Hz, C_5-H), 2.79 (1H, dd, J = 17 and 5.5 Hz, C_5-H'), 3.71 (3H, s, OMe), 4.68 (1H, dm, J = 26.5 Hz, C_4-H), 5.10 (1H, ddd, J = 56.5, 5.5 and 2.2 Hz, C_3-H), 5.20 (1H, dddd, J = 48.7, 17.6, 5.5, and 5 Hz, C_2-H), 6.40 (1H, d, J = 5 Hz, C_1-H). High-resolution MS *m/z* Calcd for $C_7H_9F_2O_4$ (M^+- CH_3CO): 195.0469. Found: 195.0458.

1-(2',3'-Difluoro-5'-methoxycarbonyl-2',3',5'-trideoxy-β-*ribo*-furanosyl)uracil (9)

To a solution of β-**7** (24 mg, 0.10 mmol) in $CDCl_3$ (0.20 ml) was added TMSBr (0.020 ml, 0.15 mmol) at 0 °C and the mixture was stirred at the same temperature for 100 min. After standing at room temperature for 14 days, the resulting mixture was diluted with $CDCl_3$ (0.50 ml) and observed by ^1H-NMR to form **8** (β/α = 3). To the solution of **8** (β/α = 3) was added bis(trimethylsilyl)uracil (51 mg, 0.20 mmol) and the mixture was stirred at room temperature for 3 days. After diluted with AcOEt (6 ml) and H_2O (0.5 ml), the mixture was neutralized with sat. aq. $NaHCO_3$. The mixture was extracted with AcOEt (3 x 10 ml) and the organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **9** (28 mg, 96%) as colorless prisms, mp 171.5-173 °C (MeOH).

β-**8**: ^1H-NMR (300 MHz, $CDCl_3$) δ: 3.07 (2H, d, J = 7 Hz, C_5-H_2), 3.91 (3H, s, OMe), 5.01 (1H, ddt, J = 17, 7 and 7 Hz, C_4-H), 5.48 (1H, ddd, J = 53.8, 4 and 3.3 Hz, C_2-H), 5.71 (1H, dddd, J = 51, 19, 7, and 4 Hz, C_3-H), 6.54 (1H, dd, J = 11.5 and 3.3 Hz, C_1-H).

α-**8**: ^1H-NMR (300 MHz, $CDCl_3$) δ: 3.02 (2H, d, J = 4.8 Hz, C_5-H_2), 3.86 (3H, s, OMe), 4.89 (1H, dm, J = 27 Hz, C_4-H), 5.30 (1H, ddd, J = 57, 6 and 2.5 Hz, C_3-H), 5.34 (1H, dddd, J = 51, 16, 6, and 4.4 Hz, C_2-H), 6.72 (1H, d, J = 4.4 Hz, C_1-H).

9: UV (MeOH) λmax: 257.5. ^1H-NMR (300 MHz, $CDCl_3$) δ: 2.72 (1H, dd, J = 17 and 6.8 Hz, $C_{5'}$-H), 2.89 (1H, dd, J = 17 and 4 Hz, $C_{5'}$-H'), 3.76 (3H, s, OMe), 4.78 (1H, dddd, J = 15, 7.5, 6.8 and 4 Hz, $C_{4'}$-H), 5.20 (1H, dddd, J = 50.5, 18, 7.5 and 4 Hz, $C_{3'}$-H), 5.32 (1H, dddd, J = 53, 4, 3.5, and 3.3 Hz, $C_{2'}$-H), 5.79 (1H, dd, J = 8 and 2.2 Hz, C_5-H), 6.28 (1H, dd, J = 16.5 and 3.3 Hz, $C_{1'}$-H), 7.43 (1H, dd, J = 8 and 1.5 Hz, C_6-H), 8.55-8.7 (1H, br, NH). High-resolution MS *m/z* Calcd for $C_{11}H_{12}F_2N_2O_5$ (M^+): 290.0714. Found: 290.0717. *Anal.* Calcd for $C_{11}H_{12}F_2N_2O_5$: C, 45.52; H, 4.17; N, 9.65. Found: C, 45.82; H, 4.31; N, 9.35.

6-Chloro-9-(2',3'-difluoro-5'-methoxycarbonyl-2',3',5'-trideoxy-β-*ribo*-furanosyl)-9H-purine (β-10) and 6-Chloro-9-(2',3'-difluoro-5'-methoxycarbonyl-2',3',5'-trideoxy-α-*ribo*-furanosyl)-9H-purine (α-10)

To a solution of **6** (β/α = 3) (20 mg, 0.10 mmol), 6-chloropurine (15.5 mg, 0.10 mmol) and Ph_3P (53 mg, 0.20 mmol) in THF (2.7 ml) was added dropwise DEAD (0.020 ml, 0.13 mmol) at -35 °C and the stirred mixture was gradually warmed to room temperature over 100 min. After 1 h of stirring at room temperature, the solvent was evapolated. The residue was purified by flash chromatography [hexane-AcOEt (3 : 1)] to give β-**10** (8 mg, 27%) as a colorless foam. UV (MeOH) λmax: 264. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.89 (1H, dd, *J* = 17 and 6.6 Hz, $C_{5'}$-H), 2.98 (1H, dd, *J* = 17 and 5 Hz, $C_{5'}$-H'), 3.72 (3H, s, OMe), 4.76 (1H, dm, *J* = 21.5 Hz, $C_{4'}$-H), 5.50 (1H, dddd, *J* = 52.7, 8.7, 4.8 and 3.7 Hz, $C_{3'}$-H), 5.99 (1H, dddd, *J* = 51, 11.4, 5, and 4.8 Hz, $C_{2'}$-H), 6.28 (1H, ddd, *J* = 15, 5 and 1.1 Hz, $C_{1'}$-H), 8.26 (1H, s, C_2-H), 8.78 (1H, s, C_8-H). High-resolution MS *m/z* Calcd for $C_{12}H_{11}ClF_2N_4O_3$ (M^+): 332.0487. Found: 332.0457.

Further elution with hexane-AcOEt (5 : 3) gave α-**10** (4 mg, 13%) as a colorless foam. UV (MeOH) λmax : 263.5. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.81 (1H, dd, *J* = 17 and 5.1 Hz, $C_{5'}$-H), 2.93 (1H, dd, *J* = 17 and 4.8 Hz, $C_{5'}$-H'), 3.76 (3H, s, OMe), 4.88 (1H, ddddd, *J* = 20, 5.1, 5, 4.8 and 1.5 Hz, $C_{4'}$-H), 5.48 (1H, dddd, *J* = 53.5, 10.6, 5 and 5 Hz, $C_{3'}$-H), 5.57 (1H, dddd, *J* = 51.6, 9, 5, and 4.8 Hz, $C_{2'}$-H), 6.76 (1H, dd, *J* = 11.7 and 4.8 Hz, $C_{1'}$-H), 8.41 (1H, d, *J* = 2.6 Hz, C_2-H), 8.76 (1H, s, C_8-H). High-resolution MS *m/z* Calcd for $C_{12}H_{10}ClFN_4O_3$ (M^+-HF): 312.0425. Found: 332.0450.

Methyl 1-*tert*-Butyldimethylsilyl-2,3-difluoro-2,3,5-trideoxy-β-*ribo*-hexofuranuronate (β-11) and Methyl 1-*tert*-Butyldimethylsilyl-2,3-difluoro-2,3,5-trideoxy-α-*ribo*-hexofuranuronate (α-11)

To a solution of **6** (β/α = 3) (42 mg, 0.21 mmol) in CH_2Cl_2 (3.2 ml) was added TBDMSOTf (0.089 ml, 0.39 mmol) and 2,6-lutidine (0.095 ml, 0.82 mmol) at 0 °C and the mixture was stirred at the same temperature for 20 min. After 5 h of standing at room temperature, the reaction mixture was quenched with H_2O (2 ml) and extracted with CH_2Cl_2 (3 x 9 ml). The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (3 : 1)] to give β-**11** (48 mg, 74%) and α-**11** (13 mg, 20%) as a colorless oil respectively.

β-**11**: IR ($CHCl_3$): 1740, 1255, 1115, 1045 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.11 (6H, s, $SiMe_2$), 0.88 (9H, s, *t*-Bu), 2.67 (1H, dd, *J* = 15.5 and 8 Hz, C_5-H), 2.75 (1H, dd, *J* = 15.5 and 5.5 Hz, C_5-H'), 3.73 (3H, s, OMe), 4.59 (1H, dddd, *J* = 16, 8, 6.6 and 5.5 Hz, C_4-H), 4.76 (1H, ddd, *J* = 53.8, 4 and 2 Hz, C_2-H), 5.02 (1H, dddd, *J* = 51.5, 20, 6.6, and 4 Hz, C_3-H), 5.36 (1H, dd, *J* = 9 and 2 Hz, C_1-H). High-resolution MS *m/z* Calcd for $C_9H_{15}F_2O_4Si$ (M^+-*t*-Bu): 253.0708. Found: 253.0698.

α-**11**: IR ($CHCl_3$): 1740, 1255, 1165, 1100 cm^{-1}.^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.13 (3H, s, SiMe), 0.14 (3H, s, SiMe'), 0.92 (9H, s, *t*-Bu), 2.68 (1H, dd, *J* = 16.5 and 5.5 Hz, C_5-H), 2.75 (1H, dd, *J* = 16.5 and 5.5 Hz, C_5-H'), 3.70 (3H, s, OMe), 4.60 (1H, dddd, *J* = 25.5, 5.5, 5.5 and 3 Hz, C_4-H), 4.83 (1H, dddd, *J* = 49.4, 17.2, 5.9 and 4 Hz, C_2-H), 4.95 (1H, ddd, *J* = 56.6, 5.9 and 3 Hz, C_3-H), 5.42 (1H, d, *J* = 4 Hz, C_1-H). High-resolution MS *m/z* Calcd for $C_9H_{15}F_2O_4Si$ (M^+-*t*-Bu): 253.0708. Found: 253.0714.

1-*tert*-Butyldimethylsilyl-2,3-dideoxy-2,3-difluoro-β-*ribo*-hexofuranose

To a solution of **β-11** (174 mg, 0.56 mmol) in THF (11 ml) was added portionwise $LiBH_4$ (210 mg, 9.64 mmol) at room temperature and the mixture was stirred at the same temperature for 8 h. After neutralization with 10% aq. HCl (2 ml), the mixture was extracted with AcOEt (2 x 50 ml). The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (7 : 1)] to give the alcohol (143 mg, 90%) as a colorless oil. IR ($CHCl_3$): 3560, 1260, 1110, 1060 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.13 (6H, s, $SiMe_2$), 0.89 (9H, s, *t*-Bu), 1.90 (1H, ddt, *J* = 14.5, 8 and 6 Hz, C_5-H), 2.20 (1H, dtd, *J* = 14.5, 6 and 5 Hz, C_5-H'), 3.84 (2H, t, *J* = 6 Hz, C_6-H_2), 4.33 (1H, dm, *J* = 16 Hz, C_4-H), 4.75 (1H, ddd, *J* = 54, 3.7 and 2.2 Hz, C_2-H), 4.98 (1H, dddd, *J* = 51.5, 20.5, 7, and 3.7 Hz, C_3-H), 5.38 (1H, dd, *J* = 9.5 and 2.2 Hz, C_1-H). High-resolution MS *m/z* Calcd for $C_8H_{15}F_2O_3Si$ (M^+-*t*-Bu): 225.0759. Found: 225.0759.

6-Benzoyl-1-*tert*-butyldimethylsilyl-2,3-dideoxy-2,3-difluoro-β-*ribo*-hexofuranose (12)

To a solution of the above alcohol (143 mg, 0.50 mmol) in pyridine (1.8 ml) was added BzCl (0.069 ml, 0.60 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. After quenched with H_2O (1 ml), the mixture was extracted with Et_2O (2 x 9ml) . The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (20 : 1)] to give **12** (196 mg, 100%) as a colorless oil. IR ($CHCl_3$): 1720, 1275, 1110, 1070 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.12 (6H, s, $SiMe_2$), 0.88 (9H, s, *t*-Bu), 2.08 (1H, dddd, *J* = 14, 8.5, 5.5 and 5.5 Hz, C_5-H), 2.24 (1H, m, C_5-H'), 4.36 (1H, dddd, *J* = 16, 8.5, 7 and 4.5 Hz, C_4-H), 4.4-4.55 (2H, m, C_6-H_2), 4.78 (1H, ddd, *J* = 53.8, 3.7 and 2 Hz, C_2-H), 5.00 (1H, dddd, *J* = 52, 21, 7, and 3.7 Hz, C_3-H), 5.38 (1H, dd, *J* = 9.5 and 2 Hz, C_1-H), 7.44 (2H, t, *J* = 7.5 Hz, Ph-H x 2), 7.56 (1H, t, *J* = 7.5 Hz, Ph-H x 1), 8.04 (2H, d, *J* = 7.5 Hz, Ph-H x 2). High-resolution MS *m/z* Calcd for $C_{15}H_{19}F_2O_4Si$ (M^+-*t*-Bu): 329.1021. Found: 329.1003.

6-Benzoyl-2,3-dideoxy-2,3-difluoro-β-*ribo*-hexofuranose (13)

To a solution of **12** (196 mg, 0.500 mmol) in THF (6 ml) was added AcOH (0.03 ml, 0.5 mmol) and Bu_4NF (0.5 ml, 0.5 mmol) at -25 °C and the mixture was stirred at the same temperature for 30 min. To the reaction mixture was added AcOH (0.03 ml, 0.5 mmol) and Bu_4NF (0.5 ml, 0.5 mmol) at -25 °C and the mixture was stirred at -25 °C→-10 °C for 12 h. After diluted with Et_2O (10 ml) and H_2O (2 ml), the mixture was neutralized with 10% aq. HCl and extracted with Et_2O (2 x 10 ml). The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give **13** (β/α = 3) (138 mg, 100%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) **β-13:** δ: 2.14 (1H, ddt, *J* = 14, 8.5 and 5.5 Hz, C_5-H), 2.2-2.35 (1H, m, C_5-H'), 4.35-4.45 (1H, m, C_4-H), 4.45-4.6 (2H, m, C_6-H_2), 4.91 (1H, ddd, *J* = 52, 4 and 2 Hz, C_2-H), 5.05 (1H, dddd, *J* = 51.5, 19.5, 6.5, and 4 Hz, C_3-H), 5.49 (1H, dd, *J* = 8 and 2 Hz, C_1-H), 7.45 (2H, t, *J* = 7.5 Hz, Ph-H x 2), 7.58 (1H, t, *J* = 7.5 Hz, Ph-H x 1), 8.04 (2H, d, *J* = 7.5 Hz, Ph-H x 2). **α-13:** δ: 2.00 (1H, ddt, *J* = 14, 8 and 5.5 Hz, C_5-H), 2.1-2.2 (1H, m, C_5-H'), 4.45-4.6 (2H, m, C_6-H_2), 4.55-4.65 (1H, m, C_4-H), 4.85 (1H, dddd, *J* = 53, 8.5, 4.5 and 4.5 Hz, C_3-H), 4.93 (1H, dddd, *J* = 51, 12.5, 4.5 and 4 Hz, C_2-H), 5.46 (1H, dd, *J* = 4 and 4 Hz, C_1-H), 7.45 (2H, t, *J* = 7.5 Hz, Ph-H x 2), 7.58 (1H, t, *J* = 7.5 Hz, Ph-H x 1), 8.04 (2H, d, *J* = 7.5 Hz, Ph-H x 2).

1-Acetyl-6-benzoyl-2,3-dideoxy-2,3-difluoro-β-*ribo*-hexofuranose

To a solution of **13** (β/α = 3) (138 mg, 0.50 mmol) in CH_2Cl_2 (6 ml) was added Ac_2O (0.057 ml, 0.6 mmol) and DMAP (61 mg, 0.50 mmol) at 0 °C and the mixture was stirred at the same temperature for 1 h. After neutralization with sat. aq. $NaHCO_3$ (3 ml), the mixture was extracted with CH_2Cl_2 (2 x 15 ml). The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (5 : 1)] to give the acetate (144 mg, 92%) as a colorless oil. IR ($CHCl_3$): 1715, 1280, 1110 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ: 2.09 (3H, s, Ac), 2.0-2.35 (2H, m, C_5-H_2), 4.42 (1H, ddd, *J* = 12, 7, 5.5 Hz, C_4-H), 4.4-4.6 (2H, m, C_6-H_2), 4.99 (1H, ddd, *J* = 51, 4 and 2 Hz, C_2-H), 5.02 (1H, dddd, *J* = 51.5, 19, 7, and 4 Hz, C_3-H), 6.27 (1H, dd, *J* = 10.6 and 2 Hz, C_1-H), 7.45 (2H, t, *J* = 7.5 Hz, Ph-H x 2), 7.58 (1H, t, *J* = 7.5 Hz, Ph-H x 1), 8.03 (2H, d, *J* = 7.5 Hz, Ph-H x 2). High-resolution MS *m/z* Calcd for $C_{13}H_{13}F_2O_3$ (M^+- CH_3CO_2): 255.0833. Found: 255.0825.

1-(6-Benzoyl-2',3'-difluoro-2',3'-dideoxy-β-*ribo*-hexofuranosyl)uracil (14)

To a solution of the above acetate (31 mg, 0.10 mmol) in $CDCl_3$ (0.20 ml) was added TMSBr (0.035 ml, 0.27 mmol) at 0 °C and the mixture was stirred at the same temperature for 15 min. After standing at room temperature for 18 days, the mixture was diluted with $CDCl_3$ (0.20 ml). To the resulting solution was added bis(trimethylsilyl)uracil (51 mg, 0.20 mmol) and the mixture was stirred at room temperature for 8 days. After diluted with AcOEt (6 ml) and H_2O (0.5 ml), the mixture was neutralized with sat. aq. $NaHCO_3$. The mixture was extracted with AcOEt (3 x 20 ml) and the organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **14** (33 mg, 90%) as colorless prisms, mp 174.5-176 °C (hexane-AcOEt = 1 : 1). UV (MeOH) λmax: 259. ^1H-NMR (300 MHz, $CDCl_3$-CD_3OD = 40 : 1) δ: 2.13 (1H, ddt, *J* = 14.5, 9 and 6 Hz, C_5'-H), 2.29 (1H, dtd, *J* = 14.5, 6 and 5 Hz, C_5'-H'), 4.54 (2H, t, *J* = 6 Hz, C_6-H_2), 4.55-4.65 (1H, m, C_4'-H), 4.97 (1H, dddd, *J* = 50, 18, 7 and 3.5 Hz, C_3'-H), 5.29 (1H, dddd, *J* = 53, 3.5, 3.5, and 3.3 Hz, C_2'-H), 5.74 (1H, d, *J* = 8 Hz, C_5-H), 6.23 (1H, dd, *J* = 16.8 and 3.3 Hz, C_1'-H), 7.41 (1H, dd, *J* = 8 and 1 Hz, C_6-H), 7.47 (2H, t, *J* = 8 Hz, Ph-H x 2), 7.60 (1H, t, *J* = 8 Hz, Ph-H x 1), 8.04 (2H, d, *J* = 8 Hz, Ph-H x 2). High-resolution MS *m/z* Calcd for $C_{17}H_{15}FN_2O_5$ (M^+-HF): 346.0965. Found: 346.0935. *Anal.* Calcd for $C_{17}H_{16}F_2N_2O_5$: C, 55.74; H, 4.40; N, 7.65. Found: C, 55.77; H, 4.45; N, 7.59.

1-(2',3'-Difluoro-2',3'-dideoxy-β-*ribo*-hexofuranosyl)uracil (15)

A solution of **14** (25 mg, 0.068 mmol) in MeOH (3 ml) saturated with NH_3 at 0 °C was stirred at room temperature for 7 h. The residue obtained after evaporation of the solvent *in vacuo* was purified by flash chromatography [AcOEt-MeOH (10 : 1)] to give **15** (15 mg, 84%) as colorless prisms, mp 185-187 °C (MeOH). UV (MeOH) λmax: 258.5. ^1H-NMR (300 MHz, $CDCl_3$-CD_3OD = 40 : 1) δ: 1.85-2.05 (2H, m, C_5'-H_2), 3.75-3.8 (2H, m, C_6-H_2), 4.6-4.7 (1H, m, C_4'-H), 5.05 (1H, dddd, *J* = 51, 15, 6 and 4 Hz, C_3'-H), 5.32 (1H, dddd, *J* = 53, 7, 4, and 4 Hz, C_2'-H), 5.76 (1H, d, *J* = 8 Hz, C_5-H), 6.26 (1H, dd, *J* = 15 and 4 Hz, C_1'-H), 7.50 (1H, dd, *J* = 8 and 1.4 Hz, C_6-H). High-resolution MS *m/z* Calcd for $C_{10}H_{12}F_2N_2O_4$ (M^+): 262.0765. Found: 262.0808. *Anal.* Calcd for $C_{10}H_{12}F_2N_2O_4 \cdot 0.1H_2O$: C, 45.49; H, 4.66; N, 10.61. Found: C, 45.48; H, 4.52; N, 10.52.

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