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Synthesis of 4'-*C*-Fluoromethylnucleosides as Potential Antineoplastic Agents

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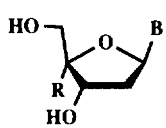
Abstract: 2-Deoxy-D-*erythro*-, *ribo*-, and *arabino*-pentofuranosylcytosines, which have a fluoromethyl group at the 4'-position, were synthesized. Introduction of fluorine was achieved by DAST treatment of 4-*C*-hydoxymethyl-D-ribofuranose, the key intermediate of 4'-*C*-methyl-nucleosides. Among these nucleosides, the 2'-deoxy derivative exhibited potent antineoplastic activity *in vitro*. © 1997 Published by Elsevier Science Ltd.

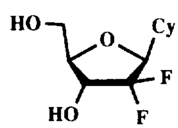
INTRODUCTION

Many sugar-modified nucleosides have been synthesized for the clinical treatment of cancer and viral diseases. Compared to 2'- and 3'-substituted derivatives, which are easily modified, only a few 4'-substituted derivatives have been produced.[1] However, interesting findings have been reported with 4'-substituted nucleosides; 4'-azidothymidine (**1**)[2] and 4'-cyanothymidine (**2**)[3] showed significant anti-human immunodeficiency virus (HIV) activity, and 2'-deoxy-4'-*C*-methylcytidine (**3**)[4] revealed potent antitumor activity *in vivo*, which was superior to that of araC.

It has been shown that the introduction of fluorine atoms increases a drug activity.[5] To create new drugs, many nucleosides with a fluorinated sugar have been synthesized.[6] Some of these have shown notable biological activities. For example, 2'-deoxy-2',2'-difluorocytidine (**4**)[7] exhibited broad cytotoxicity toward a variety of tumor cell lines which contained solid tumors, and was recently approved as an anticancer agent in Europe. Hence, we designed 2'-deoxy-4'-*C*-fluoromethylcytidine (**5**) as a novel 4'-substituted nucleoside and a possible anticancer agent. This compound was expected to have greater antitumor activity than **3** due to the specific effects of a fluorine atom, which was introduced as a hydrogen mimic. In this paper, we describe the synthesis of **5** , ribo (**6**) and ara (**7**) derivatives, and discuss cytotoxicities against tumor cell lines.



1:B=Th, R=N_3
2:B=Th, R=CN
3:B=Cy, R=Me



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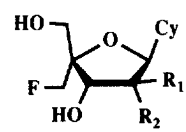
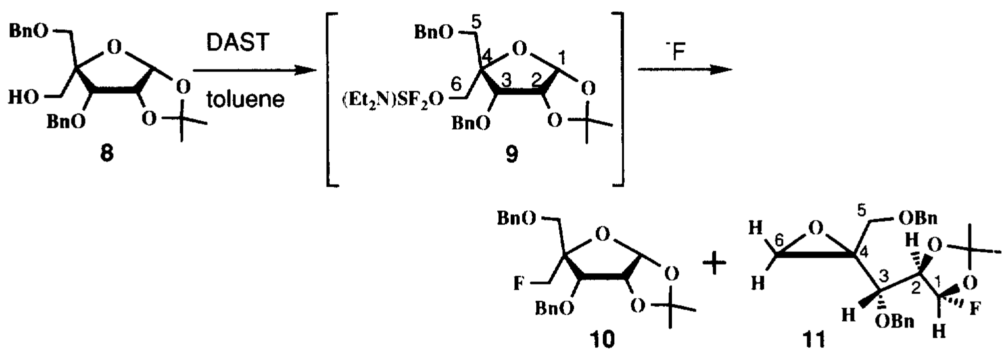


5:R_1=R_2=H
6:R_1=H, R_2=OH
7:R_1=OH, R_2=H

Figure 1

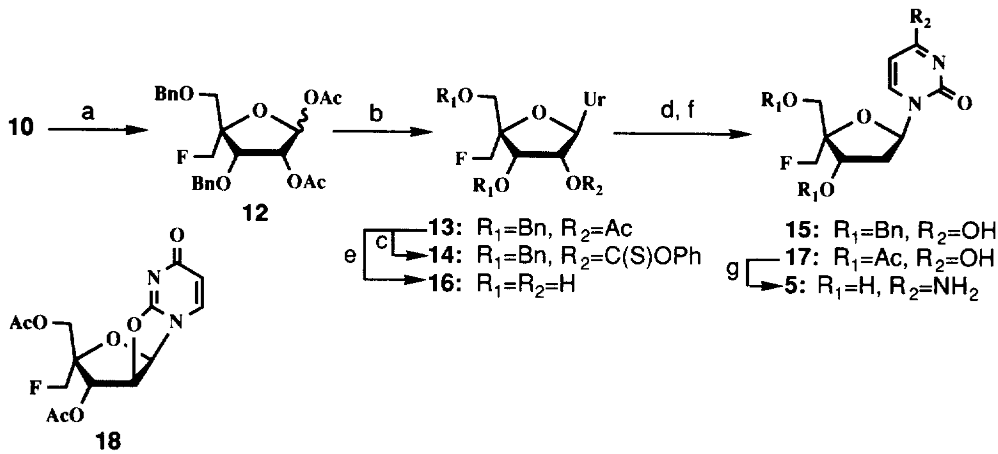
RESULTS AND DISCUSSION

Compound **8**, the synthetic intermediate of 4'-*C*-methylnucleosides,[8] was initially treated with DAST[9] in dichloromethane at room temperature to be clearly consumed. However, the yield of the desired compound **10** was very low (12%). On the other hand, DAST treatment in toluene at 60 °C gave **10** in moderate yield (55%) and a three-membered compound **11** in 12% yield.[10] Fluorination at the 6-position of intermediate **9** under mild reaction conditions would be difficult because the hydroxy group of **8** is neopentylic, and is *cis* to the 3-benzyloxy group. The structure of **11** depicted in Scheme 1 was determined based on its ^{1}H-NMR spectrum in which the two protons of the oxirane ring showed doublet peaks at 2.80 and 2.92 ppm (^2J = 4.4 Hz), and the double of doublet peak of C_1-H at 5.75 ppm reflected a large coupling constant between C_1-H and fluorine (^2J = 68.8 Hz) and a small one between C_1-H and C_2-H (^3J = 1.0 Hz). The stereochemistry of the 1-position was confirmed to be *R* by an NOE experiment: an NOE of 7.1% was observed between C_1-H and C_3-H. Compound **11** was probably produced by the selective attack of fluoride ion from the less-hindered β-side at the 1-position of **9**.



Scheme 1

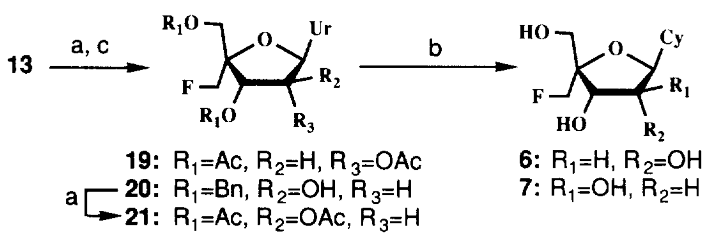
Acetolysis of **10** gave **12** (α/β = *ca.* 1/7.5)[11] in 83% yield. Glycosylation of **12** with silylated uracil in 1,2-dichloroethane in the presence of TMSOTf gave the protected nucleoside **13** in 91% yield. In this reaction, only the β anomer was produced due to participation of the 2-acetoxy group of **12**. To synthesize 2'-deoxy derivative **5**, we tried radical reduction[12] of the phenoxythiocarbonate compound **14**. However, **15** was not obtained in high yield because of the unexpected instability of **14**. Therefore, we planned to convert **13** to **5** according to the synthesis of **3**.[4] Thus, treatment of **13** with BBr_3 in dichloromethane at -45 °C, followed by quenching with MeOH, gave 4'-*C*-fluoromethyluridine (**16**) in 95% yield. Incidentally, when the deprotection was conducted at -78 °C, only the 5'-*O*-benzyl group was removed. Treatment of **16** with AcBr gave a 2'-bromo compound, which was reduced by Bu_3SnH in the presence of AIBN to yield **17**. However, the reduced compound **17** could not be separated from **18** which was made in the reaction of **16** with AcBr. Therefore, the mixture of **17** and **18** was used in the next step. The uracil moiety of **17** was transformed to cytosine by the triazole method[13] to give the target compound **5** in moderate yield.



a) AcOH, Ac_2O, H_2SO_4, b) TMS-Ur, TMSOTf/$ClCH_2CH_2Cl$, c) ClC(S)OPh, DMAP/MeCN, d) Bn_3SnH, AIBN/toluene, e) BBr_3/CH_2Cl_2, then MeOH, f) AcBr/MeCN, then Bu_3SnH, AIBN/toluene, g) $Cl_2P(O)C_6H_4Cl$, triazole/pyridine, then NH_4OH/dioxane

Scheme 2

The ribo derivative **6** was easily prepared from **13**. Protective groups of **13** were removed as described above, followed by acetylation with Ac_2O and DMAP in pyridine to give triacetate **19** in 90% yield. Conversion to cytosine using the triazole method produced the desired compound **6** in 54% yield. On the other hand, ara derivative **7** was synthesized as follows. Treatment with DAST[14] after deacetylation of **13** with anhydrous K_2CO_3 in MeOH gave a cyclo compound, which was hydrolyzed under alkali conditions to afford **20** in 71% yield. In contrast to the case of the deprotection of **13**, two benzyl groups of **20** were removed at -78 °C to give **21** in 93% yield after acetylation as described above. The deacetylated cytosine derivative **7** was obtained in 74% yield from **21** using the triazole method.



a) i) BBr_3/CH_2Cl_2, then MeOH, ii) Ac_2O, DMAP/pyridine, b) $Cl_2P(O)OC_6H_4Cl$, triazole/pyridine, then NH_4OH/dioxane, c) i) K_2CO_3/MeOH, ii) DAST/CH_2Cl_2, iii) 1N NaOH/EtOH

Scheme 3

The three synthesized 4'-C-fluoromethylnucleosides were subjected to an evaluation of antitumor activity. Antitumor activity was evaluated in terms of their cytotoxicities toward the human T-cell lines, CCRF-HSB-2 and KB cells using the MTT method.[15] The results are summarized in Table 1. Only the 2'-deoxy derivative **5** showed potent cytotoxicity toward CCRF-HSB-2. Compound **3**, which was synthesized as a positive control, exhibited higher activities toward the two cell lines than **5**. Thus, the introduction of a fluorine atom into **3** reduced its activity.

Table 1. Antineoplastic Activities of 4'-*C*-Fluoromethyl Nucleosides (IC_{50}, μg/mL).

compound	5	6	7	araC	3
CCRF-HSB-2	0.27	86	4.6	0.013	0.12
KB	>100	59	>100	0.24	0.27

In summary, we derived three 4'-*C*-fluoromethylnucleosides from the key intermediate of 4'-*C*-methylnucleosides. Among them, the 2'-deoxy derivative showed potent antineoplastic activity. However, its activity was lower than that of the 4'-*C*-methyl derivative of the lead compound. Further investigation of other 4'-*C*-fluoromethylnucleosides with different bases is now in progress.

EXPERIMENTAL SECTION

All melting points were determined on a Yanagimoto MP-500D micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX-400 instrument in $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as an internal standard. UV-specra were recorded with a Shimadzu UV-160A spectrophotometer. Mass specra were taken on a JEOL JMS-AX500 spectrometer.

Merck Kieselgel 60 was used for column chromatography and Merck Kieselgel $60F_{254}$ for analytical thin layer chromatography. Reversed-phase column chromatography was carried out on Wakosil 40C18. The ratios of mixtures of solvents for chromatography are shown as volume/volume.

(1*R*)-4,6-Anhydro-3,5-di-*O*-benzyl-1-*C*-fluoro-4-*C*-hydroxymethyl-1,2-*O*-isopropyridne-D-ribitol (11) and 3,5-Di-*O*-benzyl-4-*C*-fluoromethyl-1,2-*O*-isopropyridene-α-D-ribofuranose (10). To a toluene solution (18.0 mL) of DAST (2.39 mL, 18.0 mmol) was added a toluene solution (18.0 mL) of **8** (3.60 g, 9.0 mmol) at 0 °C under Ar atmosphere, and the mixture was stirred for 30 min at room temperature and then for 5 h at 60 °C. After allowed to cool to room temperature, the mixture was poured into sat. $NaHCO_3$ solution and followed by stirring for 30 min. The whole was extracted with AcOEt x 2, and the organic phase was washed with water and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was purified over silica gel chromatography [AcOEt-hexane (1:5)] to give **11** (418 mg, 12%) as a yellow oil and **10** (2.0 g, 55%) as a yellow oil. **11**: ^{1}H-NMR ($CDCl_3$) δ 1.44 (3H, s, Me), 1.50 (3H, s, Me), 2.80 (1H, d, *J* = 4.4 Hz, 6-*H*H'), 2.92 (1H, d, *J* = 4.9 Hz, 6-H*H'*), 3.29 (1H, d, *J* = 7.8 Hz, 3-H), 3.50 (1H, d, *J* = 10.7 Hz, 5-*H*H'), 3.95 (1H, d, J = 10.7 Hz, 5-H*H'*), 4.50 (1H, ddd, *J* = 17.6, 7.8, 1.0 Hz, 2-H), 4.54 (1H, d, *J* = 11.7 Hz, C*H*H'Ph), 4.57 (1H, d, *J* = 11.2 Hz, CH*H'*Ph), 4.59 (1H, d, *J* = 11.7 Hz, C*H*H'Ph), 4.78 (1H, d, *J* = 11.7 Hz, CH*H'*Ph), 5.75 (1H, d, *J* = 68.8, 1.0 Hz, 1-H), 7.26-7.37 (10H, m, 2 x Ph); EI-MS *m/z* 402 (M^+). Anal. Calcd for $C_{23}H_{27}FO_5$: C, 68.64; H, 6.76. Found: C, 68.44; H, 6.79. **10**: ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, s, Me), 1.63 (3H, s, Me), 3.54 (1H, dd, *J* = 10.5, 1.8 Hz, 5-*H*H'), 3.61 (1H, dd, *J* = 10.5, 2.0 Hz, 5-H*H'*), 4.26 (1H, dd, *J* = 4.9, 1.7 Hz, 3-H), 4.48 (1H, d, *J* = 12.0 Hz, C*H*H'Ph), 4.54 (1H, d, *J* = 12.2 Hz, CH*H'*Ph), 4.56 (1H, d, *J* = 12.0 Hz, C*H*H'Ph), 4.61 (1H, ddd, *J* = 4.9, 3.4, 1.5 Hz, 2-H), 4.68 (1H, dd, *J* = 47.1, 10.2 Hz, 6-*H*H'), 4.73 (1H, d, *J* = 12.0 Hz, CH*H'*Ph), 4.87 (1H, dd, *J* = 48.6, 10.0 Hz, 6-H*H'*), 5.76 (1H, d, *J* = 3.4 Hz), 7.23-7.37 (10H, m, 2 x Ph); EI-MS *m/z* 402 (M^+). Anal. Calcd for $C_{23}H_{27}FO_5$: C, 68.64; H, 6.76. Found: C, 68.54; H, 6.69.

1,2-Di-*O*-acetyl-3,5-di-*O*-benzyl-4-*C*-fluoromethyl-α and β-D-ribofuranose (12). A mixture of **10** (1.87 g, 4.65 mmol), Ac_2O (4.70 mL), and conc. H_2SO_4 (40 μL) in AcOH (42.0 mL) was stirred for 5 h at room temperature. The mixture was poured into ice-cooled water and followed by stirring for 30 min. The whole was extracted with $CHCl_3$ x 3, using sat. NH_4Cl solution as an additive. The organic phase was washed with water, sat. $NaHCO_3$ solution, and brine. After dryness ($MgSO_4$), the filtrate was concentrated under reduced pressure, and the residue was co-distilled with toluene x 2. The residue was purified over silica gel column chromatography [AcOEt-hexane (1:5)] to give **12** (α/β = *ca.* 1/7.5) (1.73 g, 83%) as a pale yellow oil.^{1}H-NMR ($CDCl_3$) δ 1.90 (0.88 x 3H, s, Me), 1.92 (0.12 x 3H, s, Me), 2.04 (0.12 x 3H, s, Ac), 2.10 (0.88 x 3H, s , Ac), 3.50 (1H, dd, *J* = 9.9, 2.6 Hz, 5-*H*H'), 3.63 (0.12 x 1H, dd, *J* = 10.3, 2.2 Hz, 5-H*H'*), 3.69 (0.88 x 1H, dd, *J* = 9.9, 1.8 Hz, 5-H*H'*), 4.43 (1H, dd, *J* = 5.1, 1.1 Hz, 3-H), 4.49 (1H, d, *J* = 11.7 Hz, C*H*H'Ph), 4.52 (2H, s, CH_2Ph), 4.58 (1H, d, *J* = 11.4 Hz, C*H*H'Ph), 4.59 (1H, dd, *J* = 46.9, 9.9 Hz, 6-*H*H'), 4.64 (1H, dd, *J* = 46.9, 9.9 Hz, 6-H*H'*), 5.22 (0.12 x 1H, dd, *J* = 6.2, 4.8 Hz, 2-H), 5.35 (0.88 x 1H, d, *J* = 5.1 Hz, 2-H), 6.17 (0.88 x 1H, s, 1-H), 6.42 (0.12 x 1H, d, *J* = 4.4 Hz, 1-H), 7.22-7.38 (10H, m, 2 x Ph); EI-MS *m/z* 446 (M^+). Anal. Calcd for $C_{24}H_{27}FO_7$: C, 64.56; H, 6.10. Found: C, 64.69; H, 6.11.

2'-*O*-Acetyl-3',5'-di-*O*-benzyl-4'-*C*-fluoromethyluridine (13). A mixture of uracil (47 mg, 0.42 mmol), hexamethyldisilazane (1.50 mL), and $(NH_4)_2SO_4$ (1.5 mg) was refluxed for 3 h and concentrated under reduced pressure. To a 1,2-dichloroethane solution (1.50 mL) of the silylated uracil and **12** (156 mg, 0.35 mmol) was added TMSOTf (0.11 mL, 0.57 mmol) at 0 °C under Ar atmosphere. The mixture was stirred at room temperature for 2 h and followed by quenching with sat. $NaHCO_3$ solution. After filtration through a pad of Celite, the filtrate was extracted with $CHCl_3$ x 3. The organic phase was washed with brine and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was purified over silica gel chromatography [AcOEt-hexane (1:1)] to give **13** (158 mg, 91%) as a foam. ^{1}H-NMR ($CDCl_3$) δ 2.09 (3H, s, Ac), 3.64 (1H, dd, *J* = 10.3, 2.6 Hz, 5'-*H*H'), 3.81 (1H, dd, *J* = 10.3, 2.2 Hz, 5-H*H'*), 4.42 (1H, d, *J* = 5.5 Hz, 3'-H), 4.45-4.65 (6H, m, 2 x 6'-H, 2 x CH_2Ph), 5.35 (1H, t, *J* = 5.9 Hz, 2'-H), 5.37 (1H, dd, *J* = 8.1, 2.6 Hz, 5-H), 6.23 (1H, d, *J* = 5.9 Hz, 1'-H), 7.25-7.42 (10H, m, 2 x Ph), 7.66 (1H, d, *J* = 8.4 Hz, 6-H), 8.18 (1H, br s, NH); FAB-MS *m/z* 499 (M^++H). Anal. Calcd for $C_{26}H_{27}FN_2O_7$: C, 62.64; H, 5.46; N, 5.62. Found: C, 62.70; H, 5.51; N, 5.61.

4'-*C*-Fluoromethyluridine (16). To a CH_2Cl_2 solution (3.60 mL) of **13** (261 mg, 0.52 mmol) was added BBr_3 (0.50 mL, 5.24 mmol) at -78 °C under Ar atomsphere and the mixture was stirred for 3 h at -45 °C. After addition of MeOH-CH_2Cl_2 solution (3.70-3.70 mL) to the mixture at the same temperature, the solution was allowed to warm to room temperature. The solvent was removed under reduced pressure, and the residue was co-distilled with MeOH x 4. The residue was purified over silica gel chromatography [$CHCl_3$-MeOH (5:1)] to give **16** (137 mg, 95%) as an amorphous crystal, mp 196-197 °C (EtOH). UV (H_2O) λ_{max} = 206 nm (ε 6503) and 261 nm (ε 8085); ^{1}H-NMR (DMSO-d_6) δ 3.49-3.61 (2H, m, 2 x 5'-H), 4.11 (1H, t, J = 4.9 Hz, 3'-H), 4.20-4.27 (1H, m, 2'-H), 4.46 (1H, dd, *J* = 49.3, 9.8 Hz, 6-*H*H'), 4.57 (1H, dd, *J* = 46.9, 9.8 Hz, 6-H*H'*), 5.27-5.32 (2H, m, 2 x OH), 5.41 (1H, d, *J* = 6.3 Hz, OH), 5.69 (1H, d, *J* = 8.3 Hz, 1'-H), 5.90 (1H, d, *J* = 7.8 Hz, 5-H), 7.82 (1H, d, *J* = 7.8 Hz, 6-H), 11.34 (1H, br s, NH); FAB-MS *m/z* 277 (M^++H). Anal. Calcd for $C_{10}H_{13}FN_2O_6$: C, 43.48; H, 4.74; N, 10.14. Found: C, 43.56; H, 4.81; N, 10.10.

2'-Deoxy-4'-*C*-fluoromethylcytidine (5). To an acetonitrile suspension (22.0 mL) of **16** (490 mg, 1.78 mmol) was added dropwise AcBr (0.76 mL, 10.30 mmol) at reflux under Ar atmosphere and the mixture was kept to be refluxed for 30 min. After allowed to cool to room temperature, the solvent was evaporated under reduced pressure. The residue was partitioned between AcOEt and brine, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure.

A mixture of the bromination residue, AIBN (294 mg, 1.79 mmol), and Bu_3SnH (0.96 mL, 3.56 mmol) in toluene (36.0 mL) was stirred for 3 h at 80 °C under Ar atmosphere. The mixture was allowed to cool to room temperature and followed by evaporation of the solvent under reduced pressure. The residue was purified over silica gel chromatography [AcOEt-hexane-EtOH (30:20:1)] to give the mixture of **17** and **18** (560 mg) as a foam.

To a pyridine solution (11.0 mL) of the mixture of **17** and **18** was added 4-chlorophenyl phosphorodichloride (0.58 mL, 3.60 mmol) at 0 °C under Ar atmosphere. And then 1,2,4-triazole (849 mg, 12.30 mmol) was added at a stretch to the mixture, which was followed by stirring for 12 h at room temperature. After water was added to it, the solution was stirred for 15 min. The solvent was removed under reduced pressure , and the residue was partitioned between $CHCl_3$ and sat. $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was passed through short silica gel column chromatography to give a yellow oil. To a dioxane solution (14.0 mL) of the oil was added NH_4OH (28.0 mL) and the mixture was stirred for 2.5 d at room temperature. After the solvent was removed under reduced pressure, the residue was purified over silica gel chromatography [$CHCl_3$-MeOH (3:1)] to give **5** (250 mg, 54% from **16**) as colorless prisms, mp 219-221 °C (MeOH). UV (H_2O) λ_{max} = 271 nm (ε 7795); UV (0.1N HCl) λ_{max} = 279 nm (ε 11804); ^{1}H-NMR (DMSO-d_6) δ 2.05-2.19 (2H, m, 2'-H), 3.47 (1H, ddd, *J* = 11.7, 4.9, 2.0 Hz, 5'-*H*H'), 3.55 (1H, dd, *J* = 11.2, 4.8 Hz, 5'-H*H'*), 4.34-4.39 (1H, m, 3'-H), 4.49 (1H, dd, *J* = 48.3, 9.8 Hz, 6-*H*H'), 4.55 (1H, dd, *J* = 47.4, 9.8 Hz, 6'-H*H'*), 5.15 (1H, t, *J* = 5.4 Hz, OH), 5.34 (1H, d, *J* = 4.4 Hz, OH), 5.72 (1H, d, *J* = 7.3 Hz, 5-H), 6.25 (1H, t, *J* = 7.0 Hz, 1'-H), 7.11 (2H, br s, NH_2), 7.74 (1H, d, *J* = 7.3 Hz, 6-H); FAB-MS *m/z* 260 (M^++H). Anal. Calcd for $C_{10}H_{14}FN_3O_4$: C, 46.33; H, 5.44; N, 16.21. Found: C, 46.17; H, 5.55; N, 15.85.

2',3',5'-Tri-*O*-acetyl-4'-*C*-fluoromethyluridine (19). To a CH_2Cl_2 solution (0.70 mL) of **13** (50 mg, 0.10 mmol) was added BBr_3 (95 μL, 1.0 mmol) at -78 °C under Ar atmosphere and the mixture was stirred for 3 h at -45 °C. After the addition of MeOH-CH_2Cl_2 solution (0.75-0.75 mL) to the mixture at the same temperature, the solution was allowed to warm to room temperature. The solvent was removed under reduced pressure, and the residue was co-distilled with MeOH x 3 and $CHCl_3$ x 2. The residue was dissolved in pyridine (2.50 mL), and to this solution was added Ac_2O (0.13 mL) and DMAP (1.9 mg). After the mixture was stirred at room temperature for 4 h under Ar atmosphere, water was added. Stirring for 15 min before evaporation of the solvent was followed by partition between AcOEt and water. The organic phase was washed with brine and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was co-distilled with toluene x 2. The residue was purified over silica gel chromatography [AcOEt-hexane (3:2)] to give **19** (36 mg, 90%) as an amorphous crystal, mp 175-177 °C (AcOEt). ^{1}H-NMR ($CDCl_3$) δ 2.07 (3H, s, Ac), 2.17 (6H, s, 2 x Ac), 4.24 (1H, dd, *J* = 11.7, 2.0 Hz, 5'-*H*H'), 4.49 (1H, dd, *J* = 12.2, 2.4 Hz, 5'-H*H'*), 4.54 (1H, dd, *J* = 46.9, 10.3 Hz, 6'-*H*H'), 4.60 (1H, dd, *J* = 46.4, 9.8 Hz, 6'-H*H'*), 5.48 (1H, t, *J* = 6.3 Hz, 2'-H), 5.80 (1H, dd, *J* = 8.3, 2.4 Hz, 5-H), 6.10 (1H, d, *J* = 6.8 Hz, 1'-H), 7.37 (1H, d, *J* = 8.3 Hz, 6-H), 8.37 (1H, br s, NH); FAB-MS *m/z* 403 (M^++H). Anal. Calcd for $C_{16}H_{19}FN_2O_9$: C, 47.77; H, 4.76; N, 6.96. Found: C, 47.69; H, 4.78; N, 6.94.

4'-*C*-Fluoromethylcytidine (6). The compound **19** (54 mg, 0.13 mmol) was treated as described in the synthesis of **5**. After purification by reversed-phase column chromatography (H_2O as an eluent), **6** (20 mg, 54%) was obtained as a colorless solid. UV (H_2O) λ_{max} = 237 (ε 6137) and 271 nm (ε 7800); UV (0.1N HCl) λ_{max} = 279 nm (ε 11771); ^{1}H-NMR (DMSO-d_6) δ 3.48-3.58 (2H, m, 2 x 5'-H), 4.11 (1H, t, *J* = 4.9 Hz, 3'-H), 4.19 (1H, dt, *J* = 6.8, 5.4 Hz, 2'-H), 4.47 (1H, dd, *J* = 49.3, 10.3 Hz, 6-*H*H'), 4.56 (1H, dd *J* = 46.9, 10.3 Hz, 6-H*H'*), 5.21 (1H, t, *J* = 4.9 Hz, OH), 5.24 (1H, d, *J* = 4.9 Hz, OH), 5.25 (1H, d, *J* = 6.8 Hz, OH), 5.75 (1H, d, *J* = 6.8 Hz, 5-H), 5.93 (1H, d, *J* = 7.8 Hz, 1'-H), 7.17 (2H, br d, NH_2), 7.74 (1H, d, *J* = 7.3 Hz, 6-H); FAB-MS *m/z* 276 (M^++H). Anal. Calcd for $C_{10}H_{14}FN_3O_5$.0.5EtOH: C, 44.29; H, 5.74; N, 14.09. Found: C, 44.17; H, 5.51; N, 14.33.

1-(3,5-Di-*O*-benzyl-4-*C*-fluoromethyl-β-D-arabinofuranosyl)uracil (20). To a MeOH solution (1.10 mL) of **13** (100 mg, 0.20 mmol) was added anhydrous K_2CO_3 (83 mg, 0.60 mmol) and the mixture was stirred for 2.5 h at room temperature. After neutraliazed with AcOH, the solvent was evapolated under reduced pressure. The residue was partitioned between AcOEt and water, and the organic phase was washed with sat. $NaHCO_3$ solution and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was passed through silica gel chromatography to give a foam.

To a CH_2Cl_2 solution (2.80 mL) of the foam was added DAST (54 μL, 0.40 mmol) at 0 °C under Ar atmosphere and the mixture was stirred for 30 min at room temperature. After Et_3N (0.11 mL) was added, the solution was stirred for 15 min. The solvent was removed under reduced pressure, and the residue was co-distilled with CH_2Cl_2 x 3.

The cyclized product was dissolved in EtOH (6.30 mL), and to this solution was added 1N NaOH (0.86 mL, 0.86 mmol). After the mixture was refluxed for 5 h, the same amount of 1N NaOH was added. The mixture was refluxed further for 1.5 h, and the solution was allowed to cool to room temperature and neutralized with AcOH. After the solvent was removed under reduced pressure, the residue was partitioned between AcOEt and water. The organic phase was washed with sat. $NaHCO_3$ solution and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was purified over silica gel chromatography [AcOEt-hexane-EtOH (20:20:1)] to give **20** (65 mg, 71%) as a foam. ^{1}H-NMR ($CDCl_3$) δ 3.63 (1H, d, *J* = 10.3 Hz, 5'-*H*H'), 3.79 (1H, dd, *J* = 10.3, 1.5 Hz, 5'-H*H'*), 3.89 (1H, d, *J* = 8.8 Hz, OH), 4.18 (1H, d, *J* = 2.9 Hz, 3'-H), 4.45-4.50 (1H, m, 2'-H), 4.50 (1H, d, *J* = 46.9, 9.8 Hz, 6'-*H*H'), 4.53 (1H, d, *J* = 11.2 Hz, C*H*H'Ph), 4.54 (1H, d, *J* = 11.2 Hz, CH*H'*Ph), 4.58 (1H, d, *J* = 11.7 Hz, C*H*H'Ph), 4.60 (1H, dd, *J* = 46.4, 10.3 Hz, 6'-H*H'*), 4.77 (1H, d, *J* = 11.7 Hz, CH*H'*Ph), 5.45 (1H, d, *J* = 8.3 Hz, 5-H), 6.17 (1H, d, *J* = 3.9 Hz, 1'-H), 7.24-7.42 (10H, m, 2 x Ph), 7.59 (1H, d, *J* = 8.3 Hz, 6-H), 8.41 (1H, br s, NH); FAB-MS *m/z* 457 (M^++H). Anal. Calcd for $C_{24}H_{25}FN_2O_6$.0.25H_2O: C, 62.53; H, 5.58; N, 6.08. Found: C, 62.77; H, 5.73; N, 5.96.

1-(2,3,5-Tri-*O*-acetyl-4-*C*-fluoromethyl-β-D-arabinofuranosyl)uracil (21). To a CH_2Cl_2 solution (3.0 mL) of **20** (142 mg, 0.31 mmol) was added BBr_3 (0.18 mL, 1.87 mmol) at -78 °C under Ar atmosphere and the mixture was stirred at the same temperature for 2 h. After the addition of MeOH-CH_2Cl_2 solution (3.9-2.0 mL) to the mixture at the same temperature, the solution was allowed to warm to room temperature. The solvent was removed under reduced pressure, and the residue was co-distilled with MeOH x 3 and $CHCl_3$ x 2. The residue was acetylated as described in the synthesis of **19**. After purification by silica gel column chromatography [AcOEt-hexane (3:2)], **21** (116 mg, 93%) was obtained as a foam. ^{1}H-NMR ($CDCl_3$) δ 2.05 (3H, s, Ac), 2.14 (3H, s, Ac), 2.17 (3H, s, Ac), 4.28 (1H, dd, *J* = 12.2, 1.0 Hz, 5'-*H*H'), 4.46 (1H, dd, *J* = 12.2, 2.0 Hz, 5'-H*H'*), 4.52 (1H, dd, *J* = 46.9, 9.8 Hz, 6'-*H*H'), 4.59 (1H, dd, *J* = 45.9, 10.3 Hz, 6'-H*H'*), 5.51 (1H, ddd, *J* = 3.9, 3.4, 1.5

Hz, 2'-H), 5.55 (1H, br s, 3'-H), 5.74 (1H, dd, *J* = 7.8, 2.0 Hz, 5-H), 6.37 (1H, br s, 1'-H), 7.40 (1H, d, *J* = 8.3 Hz, 6-H), 8.34 (1H, br s, NH); FAB-MS *m/z* 403 (M^++H). Anal. Calcd for $C_{16}H_{19}FN_2O_9$: C, 47.77; H, 4.76; N, 6.96. Found: C, 47.71; H, 4.91; N, 7.01.

1-(4-*C*-Fluoromethyl-β-D-arabinofuranosyl)cytosine (7). The compound **21** (79 mg, 0.20 mmol) was treated as described in the synthesis of **5**. After purification by reversed-phase column chromatography (H_2O as an eluent), **7** (40 mg, 74%) was obtained as a colorless crystal, mp 256-259 °C (dec.). UV (H_2O) λ_{max} = 272 nm (ε 8233); UV (0.1N HCl) λ_{max} = 280 nm (ε 12280); ^{1}H-NMR (DMSO-d_6) δ 3.54 (1H, ddd, *J* = 10.8, 5.4, 1.5 Hz, 5'-*H*H'), 3.61 (1H, dd, *J* = 11.7, 5.4 Hz, 5'-H*H'*), 4.01-4.06 (1H, m, 2'-H), 4.10 (1H, dd, *J* = 4.9, 2.9 Hz, 3'-H), 4.51 (2H, d, *J* = 47.9 Hz, 2 x 6'-H), 5.14 (1H, t, *J* = 5.4 Hz, OH), 5.53 (1H, d, *J* = 5.4 Hz, OH), 5.58 (1H, d, *J* = 4.4 Hz, OH), 5.66 (1H, d, *J* = 7.3 Hz, 5-H), 6.14 (1H, d, *J* = 4.4 Hz, 1'-H), 7.06 (2H, br s, NH_2), 7.55 (1H, d, *J* = 7.8 Hz, 6-H); FAB-MS *m/z* 276 (M^++H). Anal. Calcd for $C_{10}H_{14}FN_3O_5$: C, 43.64; H, 5.13; N, 15.27. Found: C, 43.38; H, 4.85; N, 15.03.

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