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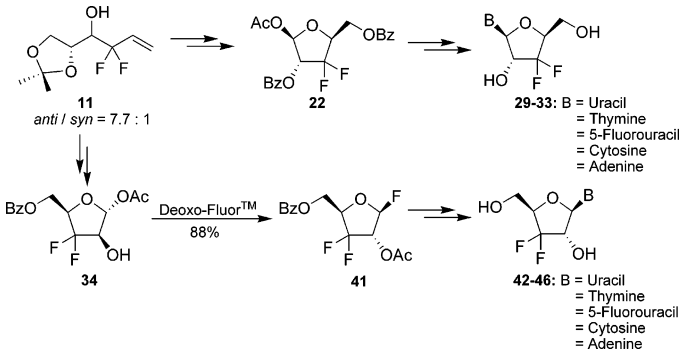
Synthesis of L- and D-β-3′-Deoxy-3′,3′-difluoronucleosides

Xiu-Hua Xu,[†] Xiao-Long Qiu,[†] Xingang Zhang,[†] and Feng-Ling Qing*[,†,‡]

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Lu, Shanghai 200032, China, and Institute of Biological Sciences and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

flq@mail.sioc.ac.cn

Received December 26, 2005



Both L- and D-β-3′-deoxy-3′,3′-difluoronucleosides were synthesized starting from the key intermediate difluorohomoallyl alcohol **11**. Deoxo-Fluor was accidentally found to be efficient in reversing the hydroxyl configuration of **34**, and the desired product **41** was provided in good yield.

Introduction

Nucleoside analogues have been the cornerstone of antiviral and anticancer chemotherapy over the past three decades. In an effort to discover effective antiviral and anticancer agents against various cancers and viral infections, a large number of nucleoside analogues have been synthesized and evaluated.[1−4] Continual endeavors of organic and medicinal chemists endowed human beings with great benefits, and to date, eight clinically useful nucleosides and nucleotides have been approved by the FDA for the treatment of HIV infection that are being used as part of the highly bioactive antiretroviral treatment.[5] Despite certain improvements against viruses and cancer, there is an intense demand to develop novel antiviral and anticancer nucleoside analogues. Nucleoside analogues with good stability, excellent absorption ability (good solubility), low toxicity, and highly bioactivity are always the targets of organic and medicinal chemists. It is well-known that introduction of fluorine atom(s) or a fluorine-containing group into an organic compound can bring about remarkable changes in the physical, chemical, and biological properties.[6] Thus, fluorinated nucleosides containing fluorine atom(s) or fluorine-containing groups in the sugar moiety or the base moiety of nucleosides[7] have drawn increasing attention, and many investigations have shown that fluorinated nucleosides had high antiherpes activity as well as antitumor activity in some cases. Moreover, Gemcitabine[8] (2′-deoxy-2′, 2′-difluorocytidine) has been approved by the FDA for treatment

[†] Chinese Academy of Science.

[‡] Donghua University.

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10.1021/jo052652h CCC: $33.50
Published on Web 03/09/2006

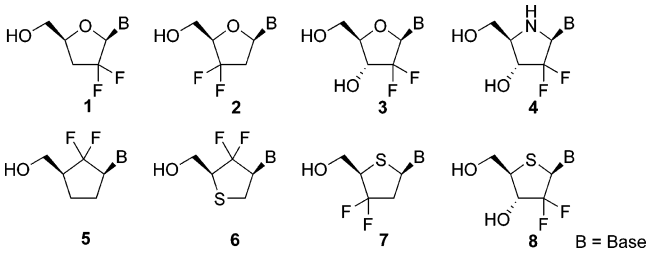
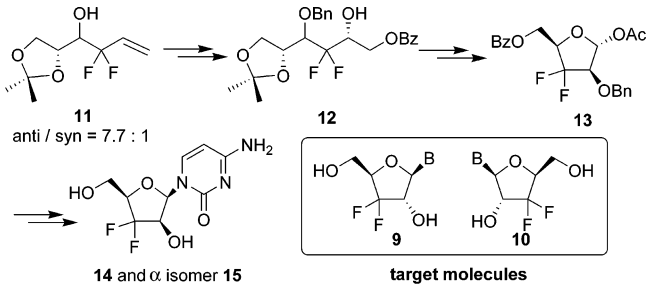


FIGURE 1. Some synthesized gem-difluoromethylenated nucleosides.

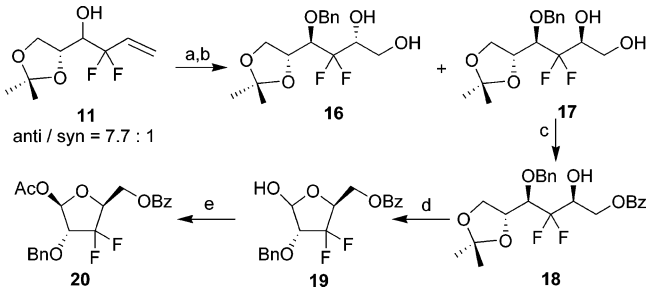
of inoperable pancreatic cancer and of 5-fluorouracial resistant pancreatic cancer.

The high antiviral and antineoplastic activities of Gemcitabine reveal the special influences of the CF_2 group on biological activities of nucleosides. Thus, a number of nucleosides containing the CF_2 group at the sugar moiety have been synthesized and biologically evaluated. The nucleosides included 2′,3′-dideoxy-2′,2′-difluoronucleoside series **1**,[9] 2′,3′-dideoxy-3′,3′-difluoronucleoside series **2**,[10] 2′-deoxy-2′,2′-difluoronucleoside series **3**,[8a,11] 2′-deoxy-2′,2′-difluoroazanucleoside series **4**,[12] 2′,3′-dideoxy-6′,6′-difluorocarbocyclic nucleoside series **5**,[13] 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleoside series **6**,[14] 2′,3′-dideoxy-3′,3′-difluoro-6′-thionucleoside series **7**[15] and 2′-deoxy-2′,2′-difluoro-6′-thionucleoside series **8**,[16] and so forth (Figure 1). Recently, we synthesized N^1-(3-deoxy-3,3-difluoro-*β*-D-*threo*-arabinofuranosy)cytosine **14** and its α isomer **15** starting from the key difluorohomoallyl alcohol **11** (Scheme 1).[17] As part of our ongoing and continual efforts to prepare fluorinated-sugar nucleosides, it interests us to convert the *R* configuration of the hydroxyl group at C2′ of compound **14** to *S* configuration to obtain nucleosides **9** (Scheme 1). In addition, in view of the fact that among some fluorinated nucleosides, L-isomers have potent antiviral activity with no toxicity or less toxicity than their D-counterparts,[18] it was more significant to synthesize L-isomers **10** of nucleosides **9**. Herein, we described the synthesis of the L- and D-*β*-3′-deoxy-3′,3′-difluoronucleosides **9** and **10** starting from difluorohomoallyl alcohol **11**.

SCHEME 1



SCHEME 2 [a]



[a] Reagents and conditions: (a) NaH (0.8 equiv), BnBr, TBAI, THF; (b) OsO_4, NMNO, acetone/H_2O; (c) BzCl, Py, CH_2Cl_2; (d) i. 75% AcOH, 50 °C; ii. $NaIO_4$, acetone/H_2O, room temperature; (e) Ac_2O, DMAP, CH_2Cl_2.

Results and Discussion

The starting material difluorohomoallyl alcohol **11** was first prepared from 1-(*R*)-glyceraldehyde acetonide and 3-bromo-3,3-difluoropropene according to our recent report.[17] Utilizing the kinetic resolution method and optimized reaction condition, we easily accomplished benzylation by treatment with sodium hydride (0.8 equiv) and catalytic TBAI, followed by benzyl bromide. The desired single anti-isomer was afforded in 78.5% yield. Then, the Os-catalyzed dihydroxylation of the resulting benzyl ether gave the mixture of diol compounds **16** and **17** in 95% yield and in 1:1 ratio (Scheme 2), which could be easily separated by column chromatography. Selective benzoylation of the primary hydroxyl group in diol **17** gave the benzoate **18** in 90% yield. The conversion of **18** to furanose **19** was achieved in 94% yield by acidic hydrolysis with 75% acetic acid and oxidation with sodium periodate, followed by subsequent cyclization. The ratio of two diastereoisomers in compound **19** is 1:1 according to ^{19}F NMR, and they could not be separated on silica gel chromatography. O-Acetylation of furanose **19** with Ac_2O/DMAP/CH_2Cl_2 afforded the corresponding product in 94% yield, which was obtained nearly as single *β* anomer **20** ($\alpha/\beta = 1:17$) due to the assistance of neighboring large group participation.[17,19]

Vorbrüggen proposed that, for furanose substrate with an acyloxy group in the C-2′ position, the glycosylation reaction would involve the oxonium intermediate, which might induce the attack of the silylated base from the contrary face of C-2′ acyloxy group.[20] Thus, it is our assumption that conversion of the benzyloxy group in acetate **20** into an acyloxy group would

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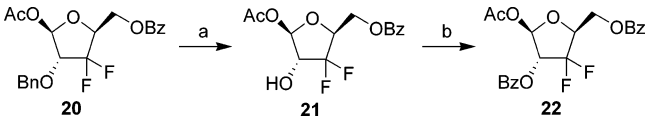
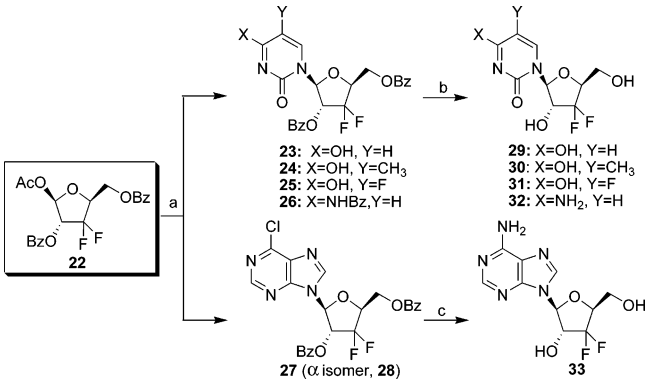
SCHEME 3 [a]



[a] Reagents and conditions: (a) $NaBrO_3$, $Na_2S_2O_4$, ethyl acetate/H_2O; (b) Bz_2O, DMAP, Et_3N, CH_2Cl_2.

SCHEME 4 [a]



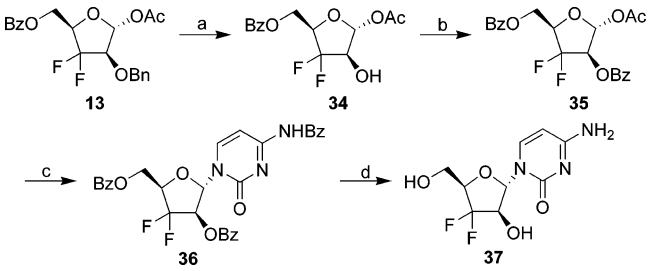
[a] Reagents and conditions: (a) *N*,*O*-bis(trimethylsilyl)acetamide, pyrimidine (3.0 equiv), TMSOTf, CH_3CN; (b) *N*,*O*-bis(trimethylsilyl)acetamide, 6-chloropurine (1.0 equiv), TMSOTf, CH_3CN; (c) NH_3, MeOH; (d) NH_3, MeOH, steel boom, 110 °C, 5 d.

benefit the formation of our desired β anomer necleosides in glycosylation reaction. In view of this case and the conveniency following removal of the protecting group, we decided to replace the benzyloxy group in compound **20** with a benzoyloxy group. Thus, treatment of acetate **20** with $NaBrO_3/Na_2S_2O_4$[21] smoothly provided the alcohol **21** in 94% yield, which was then benzoylated with Bz_2O/DMAP/Et_3N to produce the key intermediate **22** in 92% yield (Scheme 3).

With compound **22** in hand, couplings with various persilylated pyrimidines and 6-chloropurine were carried out in refluxed acetonitrile using Vorbrüggen conditions (Scheme 4).[22] As expected, all the reactions gave the β anomers as the main products. As to pyrimidine bases, the coupling reactions resulted in only β anomers **23**−**26** because of neighboring group participation, while in the case of 6-chloropurine the glycosylation reaction afforded the mixture of β and α anomers **27** and **28** with a 4.4:1 ratio, which might be due to the large steric hinderance of persilylated 6-chloropurine. The diastereoisomers **27** and **28** were readily separated by column chromatography. Finally, removal of the benzoyl groups of compounds **23**−**26** with saturated methanolic ammonia smoothly produced the desired free nucleosides **29**−**32**. In addition, conversion of compound **27** to the corresponding adenine derivative by ammonolysis in a steel bomb at 110 °C proceeded well, and the desired product **33** was afforded in 92% yield.

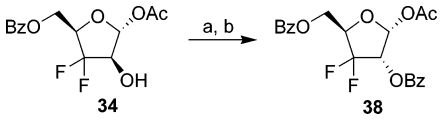
Very recently, N^1-(3-deoxy-3,3-difluoro-D-arabinofuranosyl)-cytosine **14** was synthesized in our group.[17] How to reverse the configuration of the C-2′ substitution group in compound **14** is the key for the synthesis of our other target molecules **9**. In view of the fact that the Mitsunobu reaction is frequently used to reverse the configuration of the hydroxyl group,[23] we decided to first try this method. Thus, treatment of compound **13**[17] with $NaBrO_3/Na_2S_2O_4$ smoothly provided the alcohol **34** in 94% yield, which was then subject to Mitsunobu reaction condition to afford the compound **35** in 68% yield (Scheme 5). Coupling of compound **35** with silylated cytosine furnished the benzoyl-protected α anomer nucleoside **36** as the only isomer, which was subsequently treated with saturated methanolic ammonia to produce the corresponding free nucleoside **37**. However, what surprised us was that all the characterization data of compound **37** were identical to our reported compound N^1-(3-deoxy-3,3-difluoro-α-D-arabinofuranosyl)cytosine,[17] which indicated the failure of reversing the configuration of the hydroxyl group via Mitsunobu reaction.

SCHEME 5 [a]



[a] Reagents and conditions: (a) $NaBrO_3$, $Na_2S_2O_4$, ethyl acetate/H_2O; (b) Ph_3P, DEAD, $PhCO_2H$, toluene; (c) *N*,*O*-bis(trimethylsilyl)acetamide, N^4-benzoylcytosine, TMSOTf, CH_3CN; (d) NH_3, MeOH, room temperature.

SCHEME 6 [a]



[a] Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2; (b) $PhCO_2Na$, toluene, 60 °C.

In view of the above failure of reversing configuration, we subsequently attempted S_N2 substitution reaction to reverse the configuration (Scheme 6). Reaction of compound **34** with trifluoromethanesulfonic anhydride in CH_2Cl_2 afforded the corresponding triflate; treatment with sodium benzoate in toluene at 60 °C then gave the desired product **38**. Comparing the characterization data of compound **38** with that of **35**, it was doubtless that the configuration of the hydroxyl group had been successfully reversed. However, the yield of this procedure was only 30%, and the product could not be easily purified due to similar polarity of some byproducts to the product, which urged us to explore a novel route.

During the research of synthesizing polyfluorinated nucleosides, we accidentally found that treatment of compound **34** with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) failed to give the expected compound **39**, but the acetate **41** was obtained in 88% yield (Scheme 7). It delighted us that the configuration of the hydroxyl group had been reversed during the reaction, which resulted from the formation of the pentatomic oxonium intermediate **40**.[24] That is, the attack of fluorine anion

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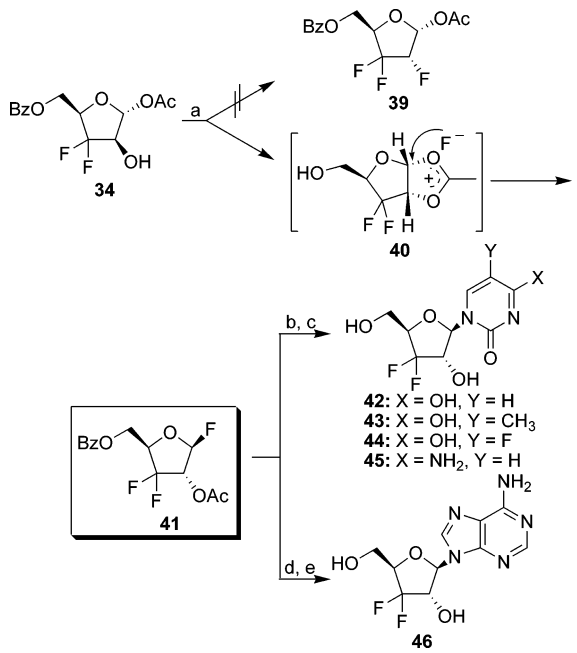
SCHEME 7 [a]



[a] Reagents and conditions: (a) Deoxo-Fluor, toluene; (b) *N*,*O*-bis(trimethylsilyl)acetamide, pyrimidine (3.0 equiv), TMSOTf, CH_3CN; (c) NH_3, MeOH; (d) *N*,*O*-bis(trimethylsilyl)acetamide, 6-chloropurine (1.0 equiv), TMSOTf, CH_3CN; (e) NH_3, MeOH, steel boom, 110 °C, 36 h.

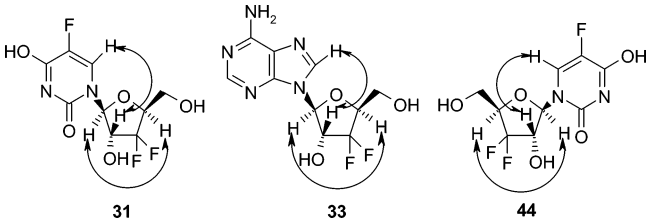


FIGURE 2. NOE correlations of compounds **31**, **33**, and **44**.

on the C-1′ position of intermediate **40** brought about the production of compound **41**. Finally, coupling of acetate **41** with various persilylated pyrimidines and 6-chloropurine using Vorbrüggen glycosylation conditions smoothly provided the acyl-protected nucleosides, which were subsequently treated with saturated methanolic ammonia to afford the desired free nucleosides **42**−**46** as *β* anomers.

The stereochemistry of products **31**, **33**, and **44** has been established by 2D NMR NOESY experiments. As show in Figure 2, correlations between H1′ and H4′ were clearly observed in these three compounds. In addition, all the H2′ protons in nucleosides **31**, **33**, and **44** strongly correlated with H6 or H9 protons of base. All of these showed that nucleosides **31**, **33**, and **44** are *β* anomers, which was as anticipated. Moreover, it should be noticed that nucleosides **21**−**33** and **42**−**46** are enantiomers whose ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, and IR are identical to each other, but the optical rotation values of which are opposite to each other.

In summary, we have addressed the syntheses of L- and D-*β*-3′-deoxy-3′,3′-difluoronucleosides. Starting from key intermediate difluorohomoallyl alcohol **11**, diastereoisomers **16** and **17** were readily afforded via kinetic resolution and dihydroxylation. Selectively protecting the primary hydroxyl in compound **17** followed by oxidation, cyclization, and a series of transformations of protecting groups smoothly gave the L-ribose **22**, which was then subjected to Vorbrüggen glycosylation to provide the L-3′-deoxy-3′,3′-difluoronucleosides **29**−**33** with *β* anomers as the main isomers. In addition, D-arabinofuranose **34** was also conveniently prepared in a straightforward fashion from diol **16**. Mitsunobu reaction and S_N2 substitution reaction were used to reverse the configuration of the C-2′ hydroxyl group in **34**; however, the former failed to give the expected products and the latter only gave desired compound in low yield (30%). Finally, Deoxo-Fluor was accidentally found to be efficient in reversing the hydroxyl configuration of **34**, and the desired product **41** was provided in good yield. Coupling of compound **41** with silylated pyrimidines and purine successfully gave target molecules D-*β*-3′-deoxy-3′,3′-difluoronucleosides **42**−**46**. Antiviral and cytotoxicity evaluations of herein synthesized L- and D-*β*-3′-deoxy-3′,3′-difluoronucleosides (**29**−**33** and **42**−**46**) are currently in progress and will be reported soon.

Experimental Section

1-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-3,3-difluoro-D-arabinofuranose (34). Compound **13** (3.64 g, 8.95 mmol) was dissolved in ethyl acetate (89.6 mL), and then a solution of $NaBrO_3$ (8.10 g, 53.71 mmol) in water (67.2 mL) was added dropwise. To the well-stirred two-phase system, an aqueous portion of $Na_2S_2O_4$ (9.35 g, dissolved in 134.4 mL water) was added dropwise over 1 h at room temperature. After the reaction mixture was stirred for 5 h, the mixture was diluted with EtOAc and the organic phase was washed with aqueous sodium thiosulfate. The crude product was then purified by silica gel chromatography (petroleum ether/ethyl acetate = 3:1) to give compound **34** (2.62 g, 92%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 6.19 (d, J = 5.4 Hz, 1H), 4.64 (m, 2H), 4.53 (m, 1H), 4.33 (d, J = 10.5 Hz, 1H), 2.98 (br, 1H), 2.14 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −106.3 (dt, J = 248.4, 11.8 Hz, 1F), −129.8 (dd, J = 249.6, 11.0 Hz, 1F); IR(KBr) $_{max}$ 3465, 3070, 2962, 1727, 1603, 1585, 1453, 1277 cm^{-1}; MS (ESI) *m*/*z* 334.1 ($M^+ + H_2O$); Anal. Calcd for $C_{14}H_{14}O_6F_2$: C, 53.17; H, 4.46. Found: C, 53.20; H, 4.70.

2-*O*-Acetyl-5-*O*-benzoyl-1-fluoro-3-deoxy-3,3-difluoro-D-ribose (41). To a stirred solution of compound **34** (2.28 g, 7.209 mmol) in anhydrous toluene (48 mL) at room temperature, Deoxo-Fluor (3.0 mL, 16.2 mmol) was added dropwise. The resulting reaction mixture was refluxed for 12 h. After removal of the volatile materials, the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 4:1) to give compound **41** (2.04 g, 88%) as a clear oil: $[\alpha]^{25}_D$ +16.4° (*c* 0.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.1 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 5.75 (dd, J = 60.3, 2.7 Hz, 1H), 5.40 (dd, J = 9.6, 6.3 Hz, 1H), 4.72 (m, 2H), 4.57 (m, 1H), 2.20 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.6 (ddd, J = 254.6, 22.3, 11.3 Hz, 1F), −119.3 (d, J = 61.8 Hz, 1F), −121.0 (dd, J = 255.5, 10.2 Hz, 1F); IR(KBr) $_{max}$ 3068, 3008, 1764, 1729, 1603, 1453, 1375, 1274 cm^{-1}; MS (ESI) *m*/*z* 341.1 (M^+ + Na), 336.2 ($M^+ + H_2O$); Anal. Calcd for $C_{14}H_{13}O_5F_3$: C, 52.87; H, 4.12. Found: C, 52.97; H, 4.01.

1-(3-Deoxy-3,3-difluoro-*β*-D-ribofuranosyl)uracil (42). To a stirred solution of compound **41** (227 mg, 0.713 mmol) and uracil (243 mg, 2.168 mmol) in anhydrous acetonitrile (24 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (1.08 mL, 4.32 mmol). The reaction mixture was stirred at reflux for 30 min. After reaction mixture was cooled to 0 °C, TMSOTf (0.57 mL, 2.52 mmol) was added dropwise. After that, the solution was heated to 80 °C and stirred for 80 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/

ethyl acetate = 1:1) to the corresponding nucleoside (160 mg) as a crude product (β anomer; very little α anomer can also be obtained). The crude product was dissolved in saturated methanolic ammonia (40 mL) and methanol (20 mL).The resulting reaction mixture was stirred for 12 h. After removal of the volatile materials, the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 9:1) to give compound **42** (87 mg, 46% from **41**) as a white solid: mp 66−68 °C; $[\alpha]^{19}_D$ −14.0° (*c* 0.350, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.03 (d, J = 8.1 Hz, 1H), 6.03 (d, J = 6.9 Hz, 1H), 5.82 (d, J = 8.1 Hz, 1H), 4.48 (m, 1H), 4.28 (m, 1H), 3.89 (d, J = 2.7 Hz, 2H); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 165.8, 152.4, 142.0, 124.1 (dd, J_{C-F} = 257.3, 251.8 Hz), 103.6, 87.0 (d, J_{C-F} = 11.1 Hz), 82.0 (dd, J_{C-F} = 27.4, 24.9 Hz), 75.1 (dd, J_{C-F} = 27.4, 18.3 Hz), 60.1 (t, J_{C-F} = 6.2 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −117.9 (dt, J = 241.4, 11.6 Hz, 1F), −132.3 (dt, J = 240.8, 5.6 Hz, 1F); IR $(KBr)_{max}$ 3369, 2816, 1701, 1471, 1389, 1284 cm^{-1}; MS *m*/*z* 287.2 (M^+ + Na), 265.2 (M^+ + 1); HRMS Calcd for $C_9H_{10}O_5N_2F_2Na$ (M^+ + Na): 287.0450. Found: 287.0449.

Acknowledgment. National Natural Science Foundation of China, Ministry of Education of China, and Shanghai Municipal Scientific Committee are greatly acknowledged for funding this work.

Supporting Information Available: Detailed experimental procedures and analytical data for compounds **18**−**33**, **35**−**36**, **38**, and **43**−**46**. Copies of ^{1}H NMR and ^{13}C NMR spectra of all the compounds. Copies of ^{19}F NMR spectra of compounds **20** and **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052652H