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Synthesis of 2′,3′-dideoxy-6′,6′-difluoro-3′-azanucleosides

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ABSTRACT

The straightforward synthesis of four novel 2′,3′-dideoxy-6′,6′-difluoro-3′-azanucleosides **1a–d** is described. Efficient construction of the fluorine-containing pyrrolidine ring through two different ways and installation of pyrimidine rings using the amino groups in the intermediates **12**, **26** were the key steps of our synthesis.

1. Introduction

Over the past three decades, nucleosides and nucleoside analogues have been the cornerstone of antiviral and anticancer chemotherapy. Nucleoside analogues with good stability and high bioactivity are popular targets of organic and medicinal chemists. Accordingly a large number of nucleoside analogues have been synthesized and evaluated [1]. Continuing endeavors of organic and medicinal chemists have endowed human beings with great benefits, and to date, several clinically useful nucleosides and nucleotides have been approved by the FDA for the treatment of HIV infection [2]. Perhaps the best known of the nucleosides against HIV are (−)-β-L-(2*R*, 5*S*)-1,3-oxathiolanylcytosine (3TC) [3] and its 5-fluorocytosine analogue (−)-FTC [4] (Fig. 1), both of which are approved as antiviral drugs that reduce the amount of HIV in the body. However, clinical experiments demonstrated that both 3TC and (−)-FTC can cause some common side effects including headache, diarrhea, vomiting, rare cases of hair loss, etc. Thus, there is an intense demand to develop new novel nucleoside analogues effective against HIV. In view of the fact that the *gem*-difluoromethylene (CF_2) group has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen [5] and the fact that the introduction of fluorine atoms to a nucleoside may enhance its clinical efficacy by altering drug metabolism and lipophilicity [6], recently we have designed and synthesized a series of new 3TC analogues—6′,6′-difluoromethylenated thionucleosides [7]. Additionally, conformational studies have demonstrated that the pyrrolidine rings in proline and 4-hydroxyproline have substantial similarity to the furan and cyclopentyl structures [8]. Taking all the above considerations together and as part of our efforts to develop novel potential fluorinated sugar nucleosides, we designed new types of 3TC analogues by replacing the oxygen atom with a difluoromethylene group (CF_2) based on bioisosteric rationale, and by substitution of nitrogen atom for the sulfur atom, which would provide the system with more conformational flexibility (Fig. 1). Herein we would like to describe our synthesis of the 2′,3′-dideoxy-6′,6′-difluoro-3′-azanucleosides **1a–d** starting from our reported *gem*-difluoromethylenated intermediate.

2. Results and discussion

Our retrosynthetic analysis (Fig. 2) was based on the idea that the target molecules **1a–d** could be derived from a precursor of type **A** by building a base moiety at the C1 position using the procedure of Shaw and Warrener [9] and by converting the isopropylidene ketal moiety to a hydroxyl-methyl group. Transformation of the alcohol **B** into the amine **A** could be realized by an S_N2 substitution reaction. The pyrimidine ring in **B** should be constructed via cyclization of the mesylate **C**, which was accessed starting from our reported *gem*-difluoromethylenated azide **D** [7].

According to the retrosynthetic analysis, our synthesis embarked from the *gem*-difluoromethylenated homoallylazide **2**, which was initially converted to the diol **3** in three steps [7b] (Scheme 1). Selective mesylation of the primary hydroxyl group in **3** afforded the compound **4** in 92% yield, which was further benzoylated to give compound **5** in almost quantitative yield. Delightfully, the desired ring-closed product **6** was delivered in

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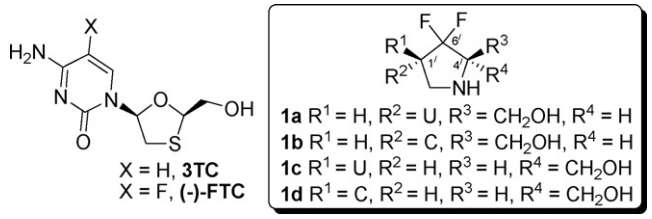


Fig. 1. Structures of 3TC, (−)-FTC and rationale for the design of the target compounds ***1a*–d**.

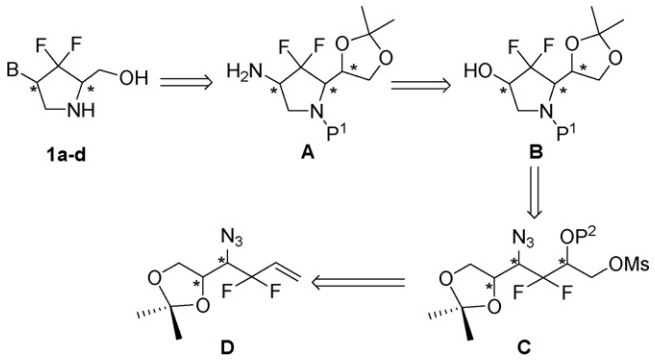


Fig. 2. Retrosynthetic analysis of our target molecules.

high yield upon treatment of the mesylate **5** with *t*-BuOK in THF. The conversion of isopropylidene ketal moiety in compound **6** to the hydroxymethyl group of compound **7** was accomplished by the following steps: (1) acid hydrolysis of the isopropylidene group via exposure to 75% aqueous AcOH at 50 °C; (2) oxidative scission of the resultant diol with $NaIO_4$/acetone; (3) then, the yielded aldehyde was directly reduced to the desired alcohol **7** with $NaBH_4$/MeOH. Silylation of the alcohol **7** gave compound **8** in 95% yield, which was further subjected to treatment with NH_3/MeOH to deliver compound **9**. Subsequent exposure of the alcohol **9** to trifluoromethanesulfonic anhydride in dichloromethane at −55 °C generated the corresponding triflate **10** in 99% yield. Reaction of compound **10** with NaN_3 in DMF at room temperature smoothly provided the azide **11**, which was reduced by using Ph_3P as the reducing agent to afford the desired amine **12** in 97% yield.

With the precursor amine **12** in hand, attention was turned to construction of the nucleoside base, which is outlined in Scheme 2. The construction of pyrimidine base utilized the procedure reported by Shaw and Warrener [9]. Thus, condensation of the

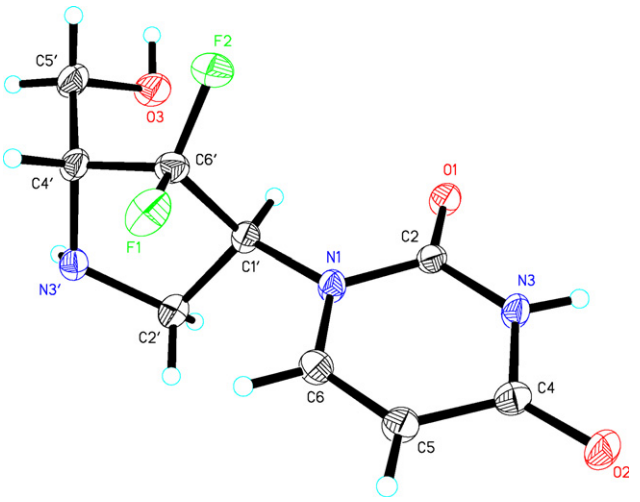
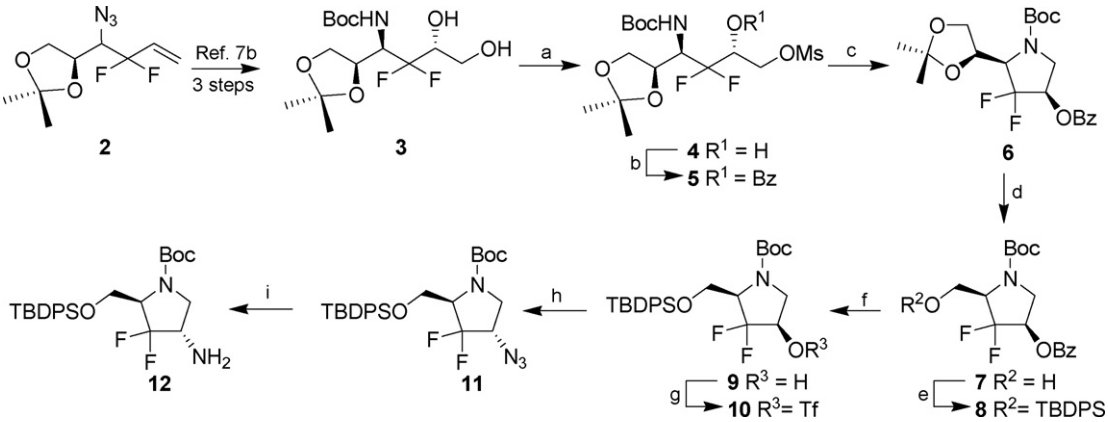


Fig. 3. ORTEP drawing of the X-ray crystallographic structure of compound ***1a***.

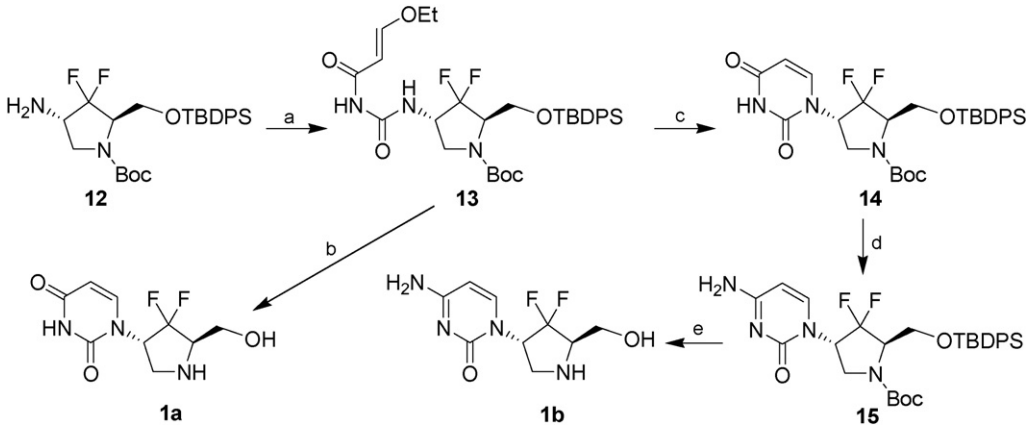
amine **12** with 3-ethoxy-2-propenoyl isocyanate in DMF at −45 °C yielded compound **13**, which was further treated with 2N H_2SO_4 in dioxane to give the target nucleoside **1a**. The structure of the target compound **1a** was unambiguously established by X-ray crystallographic analysis (Fig. 3) [10]. Interestingly, we found that ring closure of compound **13** could be achieved via treatment with concentrated $NH_3{\cdot}H_2O$, affording compound **14** in 78% yield. The uracil compound **14** was further converted to the cytosine derivative **15** by isopropylbenzene-sulfonylation of the *O*-4 position followed by treatment with concentrated $NH_3{\cdot}H_2O$. Finally, deprotection of the Boc and TBDPS protecting groups of **15** in one step with 2N H_2SO_4 afforded the cytosine nucleoside **1b**.

At this stage, we noted that six steps were needed to build the pyrrolidine ring derivative **6** starting from the azide **2**. To improve the synthesis efficiency, we decided to develop a novel and short-step route to access the *gem*-difluoromethenated pyrrolidine ring intermediate. Our new synthetic route was based on the idea that the pyrrolidine ring skeletons **17** could be conveniently constructed by hydrogenation of the mesylated azide derivatives **16** followed by spontaneous cyclization (Fig. 4).

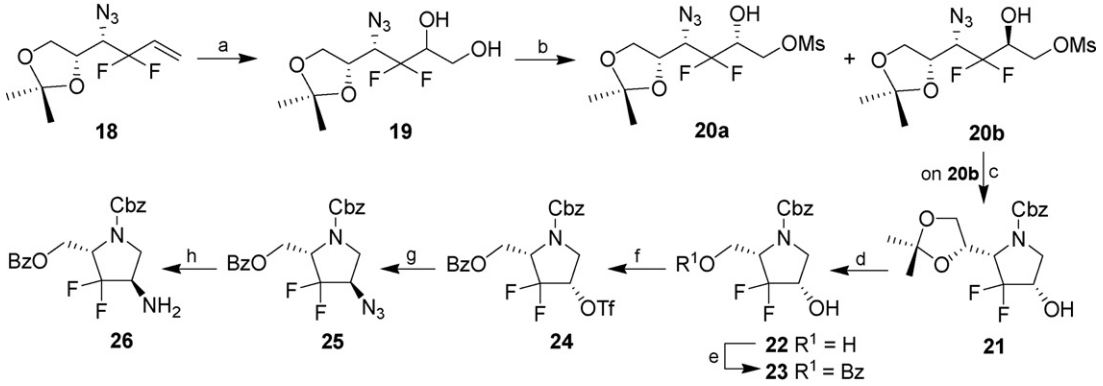
According to the new synthetic route, we first subjected the azide derivative **18** [7a] to dihydroxylation to give the diol **19** in 83% yield (Scheme 3). Then, selective mesylation of the primary hydroxyl group in **19** gave a mixture of the diastereoisomers **20a** and **20b** in 82% yield. Fortunately, the diastereoisomers **20a** and **20b** could be separated by column chromatography. At this stage,



Scheme 1. Reagents and conditions: (a) MsCl, 2,4,6-collidine, CH_2Cl_2, 0 °C, 24 h, 92%; (b) BzCl, Et_3N, DMAP, CH_2Cl_2, 99%; (c) *t*-BuOK, THF, 89%; (d) (I) 75% AcOH, 50 °C, 3 h; (II) $NaIO_4$, acetone; (III) $NaBH_4$, MeOH, 0 °C, 73%; (e) TBDPSCl, imidazole, DMF, 95%; (f) sat. NH_3/MeOH, overnight, 67%; (g) Tf_2O, pyridine, CH_2Cl_2, −35 °C, 99%; (h) NaN_3, DMF, overnight, 85%; (i) (I) Ph_3P, THF, rt, 6 h; (II) H_2O, reflux, 12 h, 97%.



Scheme 2. Reagents and conditions: (a) 3-ethoxy-2-propenoyl isocyanate in benzene, DMF, overnight, 97%; (b) (I) 2N H_2SO_4, dioxane, reflux, 3.5 h; (II) 20% aq. NaOH, 66%; (c) conc. $NH_3{\cdot}H_2O$, MeOH, 78%; (d) (I) TPSCl, Et_3N, DMAP, MeCN; (II) conc. $NH_3{\cdot}H_2O$, 98%; (e) 2N H_2SO_4, dioxane, reflux, 3.5 h, 87%.



Scheme 3. Reagents and conditions: (a) OsO_4, NMNO, acetone, H_2O, 83%; (b) MsCl, 2,4,6-collidine, CH_2Cl_2, 0 °C, 29 h, 82%; (c) (I) Ph_3P, THF, rt, 18 h; (I) Sat. $NaHCO_3$, reflux, 30 h; (III) CbzCl, rt, 21 h, 43%; (d) (I) 75% AcOH, 50 °C, 3 h; (II) $NaIO_4$, acetone; (III) $NaBH_4$, MeOH, 0 °C, 80%; (e) BzCl, Py, −78 °C, 81%; (f) Tf_2O, pyridine, CH_2Cl_2, −60 °C, 3 h, 89%; (g) NaN_3, DMF, rt, overnight, 81%; (h) (I) Ph_3P, THF, rt, 24 h; (II) H_2O, reflux, 24 h, 96%.

it was obvious that the isomer **20b** was our desired compound required to access the target nucleosides **1d**–**c**. Thus, just as expected in Fig. 4, the pyrrolidine ring intermediate **21** was smoothly produced in 43% overall yield by hydrogenation of the mesylated azide **20b** using PPh_3 as reducing reagent followed by *in situ* protection of the resultant amine group with Cbz. The conversion of the ispropylidene ketal moiety in the alcohol **21** to the hydroxymeythyl group was conveniently fulfilled using the same procedures as described for the access of the alcohol **7** from the compound **6**, and our desired diol **22** was provided in 80% yield. Selective protection of the primary hydroxyl group in **22** with BzCl delivered compound **23** in 81% yield, which upon treatment with Tf_2O/pyridine provided the triflate **24** in excellent yield. Subsequent reaction of compound **24** with NaN_3 in DMF furnished the azide **25**. Finally, PPh_3-mediated reduction of the azide **25** gave the key amine **26** in 96% yield.

With the amine **26** in hand, the next goal was to install the pyrimidine base using a traditional linear method. Thus, reaction of the amine **26** with 3-ethoxy-2-propenoyl isocyanate in DMF provided compound **27** in 92% yield (Scheme 4). 2N sulfuric acid-mediated ring closure of the amide **27** followed by debenzoylation with saturated NH_3 in MeOH gave the desired uracil derivative **28** in 53% overall yield. Then, removal of the Cbz group via Pd-catalyzed hydrogenation afforded the target nucleoside **1c** in good yield. In addition, conversion of the uracil derivative **28** to the cytosine derivative **29** was accomplished in 50% yield via treatment with Ac_2O/pyridine/DMAP and TPSCl/Et_3N/DMAP. Upon removal of the Cbz group of **29** via hydrogenation, the desired nucleoside **1d** was provided in 70% yield. The structure of uracil nucleoside **1c** was further confirmed by X-ray crystal analysis (Fig. 5) [10].

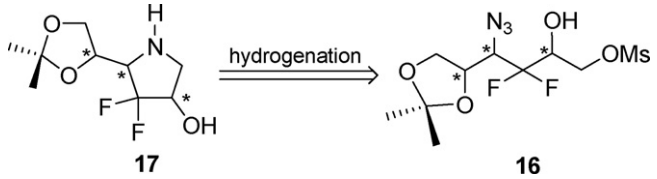


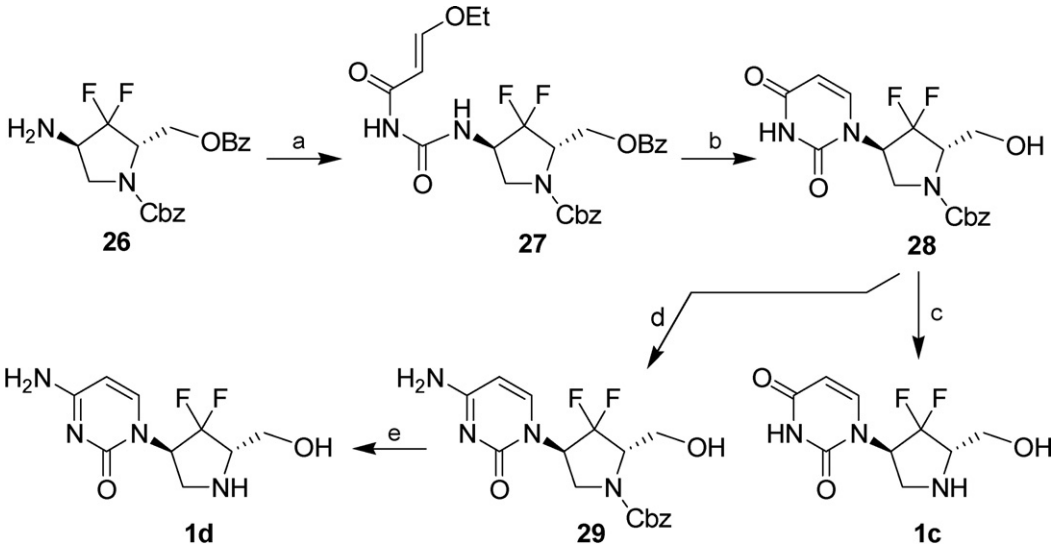
Fig. 4. New route to construct the pyrrolidine ring skeleton ***17***.

In conclusion, based on a bioisosteric rationale, we successfully synthesized four novel 3TC analogues **1a**–**d**, which featured replacement of the oxygen atom with a difluoromethylene group (CF_2) and substitution of a nitrogen atom for the sulfur atom. Efficient construction of the fluorine-containing pyrrolidine ring through two different ways and installation of pyrimidine rings using the amino groups in the intermediates **12** and **26** were the key steps of our synthesis. Antiviral and cytotoxicity evaluations of the herein reported nucleosides **1a**–**d** are currently in progress.

3. Experimental

3.1. General

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Tetrahydrofuran was distilled from sodium and



Scheme 4. Reagents and conditions: (a) 3-ethoxy-2-propenoyl isocyanate, DMF, benzene, overnight, 92%; (b) (I) 2N H_2SO_4, dioxane, reflux, 3.5 h; (II) 20% aq. NaOH; (III) sat. $NH_3{\cdot}H_2O$ 53%; (c) 10% Pd/C, 1 atm. H_2, MeOH, 85%; (d) (I) Ac_2O, Py, DMAP; (II) TPSCl, Et_3N, DMAP, MeCN; (III) conc. $NH_3{\cdot}H_2O$, 50%; (e) 10% Pd/C, 1 atm. H_2, MeOH, 70%.

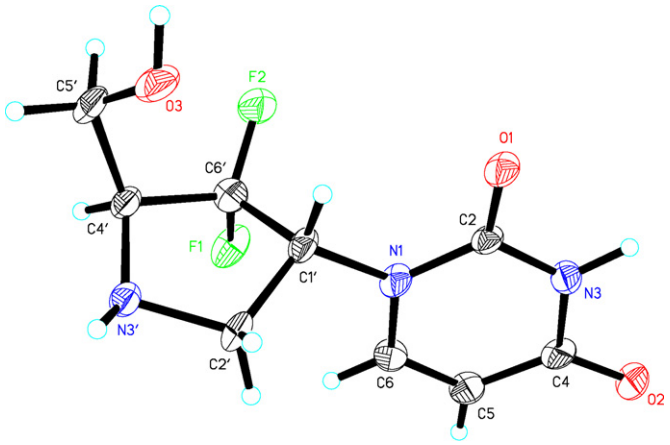


Fig. 5. ORTEP drawing of the X-ray crystallographic structure of compound ***1c***.

benzophenone immediately before use. Dichloromethane was distilled from CaH_2. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM300 spectrometer. ^{19}F NMR was recorded on a Bruker AM300 spectrometer ($CFCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

3.2. (2R,4R)-4-(tert-Butoxycarbonylamino)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoro-2-hydroxybutyl methanesulfonate (4)

Collidine (4.8 mL, 35.2 mmol) was added to a solution of the diol **2** (1.20 g, 3.52 mmol) in CH_2Cl_2 (70 mL) at room temperature. The mixture was cooled to 0 °C and MsCl (441 mg, 3.86 mmol) in CH_2Cl_2 (6 mL) was added dropwise. The reaction mixture was stirred for 24 h at 0 °C and quenched with aq. $NaHCO_3$ (9 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give compound **4** (1.36 g, 92% yield): white solid, mp 109–111 °C; $[\alpha]_D^{27}$ = +1.2° (*c* 0.76, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (d, J = 8.7 Hz, 1H), 4.61–4.51 (m, 2H), 4.43–4.36 (m, 1H), 4.21–4.04 (m, 3H), 3.70 (t, J = 7.5 Hz, 1H), 3.11 (s, 3H), 1.50 (s, 9H), 1.48 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.7 (d, J = 7.2 Hz), 121.6 (dd, J = 192.0 Hz, 125.4 Hz), 110.4, 82.1 (d, J = 20.0 Hz), 70.6 (d, J = 2.2 Hz), 68.4, 67.2 (d, J = 19.8 Hz), 63.6, 51.1 (t, J = 17.4 Hz), 37.6, 28.2, 26.1, 25.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.3 (dd, J = 255.8 Hz, 25.4 Hz, 1F), −123.5 (dd, J = 255.5 Hz, 25.1 Hz, 1F); IR (KBr) υ_{max} 3512, 3420, 1708, 1513, 1177 cm^{-1}; MS (ESI) *m/z* 442 $(M+Na)^+$, 458 $(M+K)^+$; Anal. Calcd. for $C_{15}H_{27}NO_8F_2S$: C, 42.95; H, 6.49; N, 3.34; found: C, 42.97; H, 6.51; N, 3.08.

3.3. (2R,4R)-4-(tert-Butoxycarbonylamino)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoro-1-(methylsulfonyloxy)butan-2-yl benzoate (5)

Et_3N (0.50 mL) and DMAP (12 mg, 0.10 mmol) were added to a solution of the compound **4** (850 mg, 2.03 mmol) in dry CH_2Cl_2 (20 mL). After the reaction mixture was cooled to 0 °C, BzCl (388 mg, 2.28 mmol) was added dropwise. Then, the mixture was stirred at room temperature until the reaction was completed. The reaction was quenched with water and the organic layer was separated. The aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give compound **5** (1.05 g, 99% yield): white solid, mp 55–57 °C; $[\alpha]_D^{22}$ = −13.1° (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H), 7.53 (t, J = 6.9 Hz, 1H), 7.40 (t, J = 8.1 Hz, 2H), 5.79–5.71 (m, 1H), 5.00 (d, J = 10.5 Hz, 1H), 4.64 (dd, J = 12.0 Hz, 3.6 Hz, 1H), 4.52–4.44 (m, 2H), 4.24–4.14 (m, 1H), 4.04–3.99 (m, 1H), 3.51 (t, J = 7.8 Hz, 1H), 2.93 (s, 3H), 1.32 (s, 9H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.3, 155.3, 133.4, 130.0, 129.9, 128.9, 128.6, 128.4, 128.9 (t, J = 190.0 Hz), 110.2, 80.8, 71.5, 68.3 (dd, J = 24.7 Hz, 20.1 Hz), 66.7, 65.1, 51.4 (t, J = 19.3 Hz), 37.8, 28.1, 25.8, 25.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.3 to 115.5 (m, 2F); IR (KBr) υ_{max} 3375, 1720, 1603, 1368, 1178 cm^{-1}; MS (ESI) *m/z* 541 $(M+NH_4)^+$; Anal. Calcd. for $C_{22}H_{31}NO_9F_2S$: C, 50.47; H, 5.97; N, 2.68; found: C, 50.95; H, 5.91; N, 2.43.

3.4. (2R,4R)-tert-Butyl-4-(benzoyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoropyrrolidine-1-carboxylate (6)

To a solution of the compound **5** (1.05 g, 2.01 mmol) in anhydrous THF (18 mL) was added potassium *tert*-butoxide

(787 mg, 7.02 mmol) in several portions at 0 °C. Then, the reaction mixture was stirred at 0 °C for 1 h. After that, saturated aq. NaCl was added to quench the reaction and the resulting mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give compound **6** (763 mg, 89% yield): clear oil, $[\alpha]_D^{25} = -15.0^\circ$ (*c* 3.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.56–7.51 (m, 1H), 7.39 (t, *J* = 8.1 Hz, 2H), 5.50–5.43 (m, 1H), 4.41–4.38 (m, 1H), 4.25 (d, *J* = 18.0 Hz, 2H), 4.04 (t, *J* = 8.4 Hz, 1H), 3.95 (br, 1H), 3.50 (dd, *J* = 12.9 Hz, 3.9 Hz, 1H), 1.61 (s, 9H), 1.42 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0, 154.2, 133.6, 129.9, 129.8, 128.9, 128.6, 128.4, 123.9 (dd, *J* = 201.4 Hz, 186.9 Hz), 109.7, 81.1, 73.4 (d, *J* = 5.1 Hz), 71.3, 66.7 (d, *J* = 1.3 Hz), 62.3 (t, *J* = 20.4 Hz), 50.2, 30.7, 26.0, 25.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.0 (dm, *J* = 205.9 Hz, 1F), −120.6 (dm, *J* = 229.8 Hz, 1F); IR (thin film) υ_{max} 1733, 1705, 1454, 1270, 1117 cm^{-1}; MS (ESI) *m/z* 450 $(M+Na)^+$; Anal. Calcd. for $C_{21}H_{27}NO_6F_2$: C, 59.01; H, 6.37; N, 3.28; found: C, 59.10; H, 6.44; N, 3.11.

3.5. (2*R*,4*R*)-*tert*-Butyl-4-(benzoyloxy)-3,3-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (7)

A mixture of compound **6** (867 mg, 2.03 mmol) and 75% of aq. AcOH (9 mL) was stirred at 50 °C for 3 h. Then, the solvent was removed in vacuo. The residue was dissolved in acetone (8 mL), followed by treatment with a solution of $NaIO_4$ (651 mg, 3.05 mmol) in water (9 mL) at room temperature with stirring. After stirring for 3 h, the mixture was filtered and the filtrate was washed with acetone. The solvent was removed in vacuo and the residue was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was dissolved in MeOH (22 mL). To the solution was added $NaBH_4$ (228 mg, 6.01 mmol) in several portions at 0 °C. After stirring for 30 min, 75% of aq AcOH was added until no gas was produced. The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4 and filtered. After the solvent was removed in vacuo, the residue was purified by silica gel column chromatography to give 530 mg of compound **7** (73% yield, three steps): clear oil, $[\alpha]_D^{25} = -36.5^\circ$ (*c* 8.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.61 (t, *J* = 6.9 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 5.53 (br, 1H), 4.26 (d, *J* = 16.5 Hz, 1H), 4.07–3.94 (m, 3H), 3.62 (dt, *J* = 12.9 Hz, 2.7 Hz, 1H), 1.49 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −99.8 (d, *J* = 248.2 Hz, 0.24F), −103.2 (dm, *J* = 248.7 Hz, 0.76F), −124.8 (d, *J* = 250.4 Hz, 0.24F), −125.5 (d, *J* = 249.0 Hz, 0.76F); IR (thin film) υ_{max} 3428, 1733, 1705, 1405, 1270 cm^{-1}; MS (ESI) *m/z* 380 $(M+Na)^+$; Anal. Calcd. for $C_{17}H_{21}NO_5F_2$: C, 57.14; H, 5.92; N, 3.92; found: C, 57.18; H, 6.02; N, 3.94.

3.6. (2*R*,4*R*)-*tert*-Butyl-4-(benzoyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoropyrrolidine-1-carboxylate (8)

To a solution of compound **7** (160 mg, 0.45 mmol) in DMF (1 mL) was added imidazole (76 mg, 2.5 mmol) followed by TBDPSCl (285 mg, 1.04 mmol). The reaction mixture was stirred at room temperature for 24 h and water was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic layer was washed with 1N HCl, saturated $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, after filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography to give compound **8** (253 mg, 95% yield): clear oil, $[\alpha]_D^{19} = -40.5^\circ$ (*c* 4.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.59 (br, 4H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.33–7.24 (m, 6H), 7.21–7.16 (m, 2H), 5.45 (br, 1H), 4.30–4.16 (m, 1H), 4.01–3.87 (m, 3H), 3.46–3.40 (m, 1H), 1.38–1.27 (m, 9H), 0.96 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0, 153.9,135.6, 135.5, 133.6, 133.2, 129.9, 129.7, 128.7, 128.5, 127.7, 124.5 (t, *J* = 219.9 Hz), 81.1, 71.5, 62.7, 61.2, 48.9, 28.3, 26.7, 19.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.2 (dm, *J* = 250.1 Hz, 1F), −124.4 (dd, *J* = 249.3 Hz, 30.7 Hz, 1F); IR (thin film) υ_{max} 3073, 1736, 1708, 1389, 1112 cm^{-1}; MS (ESI) *m/z* 618 $(M+Na)^+$; Anal. Calcd. for $C_{33}H_{39}NO_5F_2Si$: C, 66.53; H, 6.60; N, 2.35; found: C, 66.42; H, 6.62; N, 2.24.

3.7. (2*R*,4*R*)-*tert*-Butyl-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-4-hydroxypyrrolidine-1-carboxylate (9)

Compound **8** (903 mg, 1.52 mmol) was dissolved in saturated NH_3 solution in MeOH and the resultant mixture was stirred at room temperature for 24 h. After removal of the solvent in vacuo, the residue was purified by silica gel column chromatography to give compound **9** (492 mg, 66% yield): clear oil, $[\alpha]_D^{19} = -44.0^\circ$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 4H), 7.35 (d, *J* = 7.5 Hz, 6H), 5.11 (br, 1H), 4.09 (t, *J* = 10.2 Hz, 2H), 3.94–3.83 (m, 1H), 3.76–3.63 (m, 1H), 3.56–3.52 (m, 2H), 1.21 (s, 9H), 0.99 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −101.0 (dm, *J* = 245.3 Hz, 1F), −125.2 (dd, *J* = 280.0, 244.8 Hz, 1F); IR (thin film) υ_{max} 3387, 1706, 1367, 1113 cm^{-1}; MS (ESI) *m/z* 492 $(M+H)^+$, 514 $(M+Na)^+$; Anal. Calcd. for $C_{26}H_{35}NO_4F_2Si$: C, 63.52; H, 7.18; N, 2.85; found: C, 64.14; H, 7.39; N, 2.82.

3.8. (2*R*,4*R*)-*tert*-Butyl-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-4-(trifluoromethylsulfonyloxy)pyrrolidine-1-carboxylate (10)

Compound **9** (440 mg, 0.90 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and freshly distilled pyridine (1.2 mL, 14.9 mmol) was added. The resulting mixture was cooled to −35 °C. Then, trifluoromethanesulfonic anhydride (1.3 mL, 7.49 mmol) was added dropwise with stirring. After that, the reaction mixture was stirred for about 2 h at about −25 °C. Water was added to quench the reaction. The mixture was warmed to room temperature. The mixture was extracted with CH_2Cl_2 and the combined organic phases were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography to afford compound **10** (550 mg, 99% yield): clear oil, $[\alpha]_D^{20} = -20.8^\circ$ (*c* 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.51 (m, 4H), 7.33–7.30 (m, 6H), 5.13 (t, *J* = 3.0 Hz, 1H), 4.08–4.04 (m, 2H), 3.80 (br, 2H), 3.58–3.55 (m, 1H), 1.27–1.15 (br, 9H), 0.97 and 0.96 (two singlets, 9H, amide isomers); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −74.4 (s, 3F), −98.4 (d, *J* = 256.9 Hz, 0.39F), −99.0 (d, *J* = 253.8 Hz, 0.61F), −120.7 (d, *J* = 254.6 Hz, 0.39F), −121.0 (d, *J* = 251.5 Hz, 0.61F); IR (thin film) υ_{max} 3074, 1711, 1428, 1221, 1144 cm^{-1}; MS (ESI) *m/z* 646 $(M+Na)^+$, 662 $(M+K)^+$; Anal. Calcd. for $C_{27}H_{34}NO_6F_5SSi$: C, 51.99; H, 5.49; N, 2.25; found: C, 52.26; H, 5.60; N, 2.05.

3.9. (2*R*,4*S*)-*tert*-Butyl-4-azido-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoropyrrolidine-1-carboxylate (11)

A solution of compound **10** (540 mg, 0.87 mmol) in DMF (20 mL) was cooled to 0 °C. Then, sodium azide (303 mg, 4.66 mmol) was added carefully with stirring. The reaction mixture was stirred overnight at room temperature. Water was added to quench the reaction. The combined organic layers were

washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was quickly purified by silica gel column chromatography to afford compound **11** (382 mg, 85% yield): clear oil, $[\alpha]_D^{22} = -36.8^\circ$ (*c* 3.70, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.58 (m, 4H), 7.48–7.35 (m, 6H), 4.54–4.37 (m, 1H), 4.10–4.03 (m, 1H), 3.98–3.78 (m, 3H), 3.45–3.30 (m, 1H), 1.52 (s, 4.5 H), 1.34 (s, 4.5H), 1.05 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −111.3 (dt, *J* = 232.1 Hz, 19.7 Hz, 0.51F), −111.5 (dt, *J* = 231.8 Hz, 18.3 Hz, 0.49F), −118.0 (dd, *J* = 232.9 Hz, 7.9 Hz, 0.51F), −119.6 (dd, *J* = 232.7 Hz, 7.6 Hz, 0.49F); IR (thin film) υ_{max} 2113, 1709, 1401, 1169, 1114 cm^{-1}; MS (ESI) *m/z* 539 $(M+Na)^+$, 555 $(M+K)^+$; Anal. Calcd. for $C_{26}H_{34}N_4O_3F_2Si$: C, 60.44; H, 6.63; N, 10.84; found: C, 60.73; H, 6.68; N, 10.77.

3.10. (2*R*,4*S*)-*tert*-Butyl-4-amino-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoropyrrolidine-1-carboxylate (12)

A solution of Ph_3P (372 mg, 1.42 mmol) in THF (5 mL) was slowly added at room temperature to a solution of compound **11** (360 mg, 0.70 mmol) in THF (30 mL). Then, the reaction mixture was monitored by TLC. When the starting material was completely consumed, water (5 mL) was added and the reaction mixture was reflux for 12 h. The reaction mixture was cooled to room temperature and brine was added. The resultant mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography to give compound **12** (330 mg, 97% yield): clear oil, $[\alpha]_D^{25} = -16.1^\circ$ (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.55 (m, 4H), 7.34–7.32 (m, 6H), 4.04–3.69 (m, 5H), 3.03–2.92 (m, 1H), 1.43 (s, 5H), 1.19 (s, 4H), 0.97 and 0.96 (two singlets, 9H, amide isomers); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −114.3 (dt, *J* = 229.5 Hz, 19.2 Hz, 0.51F), −114.5 (dt, *J* = 229.8 Hz, 19.5 Hz, 0.49F), −122.4 (dd, *J* = 229.5 Hz, 7.1 Hz, 0.51F), −123.9 (dd, *J* = 229.8 Hz, 6.2 Hz, 0.49F); IR (thin film) υ_{max} 3413, 1702, 1402, 1168, 1114 cm^{-1}; MS (ESI) *m/z* 491 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{36}N_2O_3F_2Si$: C, 63.64; H, 7.40; N, 5.71; found: C, 63.65; H, 7.39; N, 5.47.

3.11. (2*R*,4*S*,*E*)-*tert*-Butyl-2-((*tert*-butyldiphenylsilyloxy)methyl)-4-(3-(3-ethoxyacryloyl)ureido)-3,3-difluoropyrrolidine-1-carboxylate (13)

To a solution of compound **12** (210 mg, 0.43 mmol) in DMF (4 mL) at −25 °C, a solution of 3-ethoxy-2-propenoyl isocyanate (181 mg, 0.42 mmol) in benzene (4 mL) was added slowly enough to cause no rise in temperature. After addition, the reaction mixture was stirred overnight at room temperature. EtOH and toluene were then added to form a low-boiling ternary azeotrope that was evaporated under reduced pressure while the temperature was maintained below 40 °C. The solid residue was purified by silica gel column chromatography to give compound **13** (248 mg, 97% yield): white solid, mp 78–80 °C; $[\alpha]_D^{24} = -15.4^\circ$ (*c* 1.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.25 (d, *J* = 9.3 Hz, 1H), 9.11 (d, *J* = 15.3 Hz, 1H), 7.69–7.62 (m, 5H), 7.41–7.26 (m, 6H), 5.35–5.24 (m, 2H), 4.08–3.96 (m, 2H), 3.90–3.75 (m, 4H), 3.30–3.22 (m, 1H), 1.51 (s, 4.5H), 1.33 (s, 4.5H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.08 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −110.7 (dm, *J* = 234.6 Hz, 1F), −119.7 (dd, *J* = 230.7 Hz, 5.9 Hz, 0.49F), −121.1 (dd, *J* = 234.6 Hz, 6.2 Hz, 0.51F); IR (KBr) υ_{max} 3236, 1707, 1681, 1552, 1401, 1115 cm^{-1}; MS (ESI) *m/z* 632 $(M+H)^+$, 654 $(M+Na)^+$, 670 $(M+K)^+$; HRMS Calcd. for $C_{32}H_{43}N_3O_6SiF_2Na$: 654.2781; found: 654.2763; Anal. Calcd. for $C_{32}H_{43}N_3O_6F_2Si$: C, 60.83; H, 6.86; N, 6.65; found: C, 60.90; H, 6.94; N, 6.51.

3.12. 2′,3′-Dideoxy-6′,6′-difluoro-3′-aza-α-L-uridine (1a)

A mixture of compound **13** (100 mg, 0.16 mmol) in dioxane (2 mL) and 2N sulfuric acid (5 mL) was refluxed for 4 h. The mixture was cooled to 0 °C and neutralized with diluted aq. NaOH. After filtration and removal of the solvent in vacuo, the residue was dissolved in methanol and the product was extracted into methanol solution, then the methanol was removed in vacuo and the residue was purified by silica gel column chromatography to give compound **1a** (26 mg, 66% yield): white solid, mp 197–199 °C; $[\alpha]_D^{24} = 0.85^\circ$ (*c* 0.90, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 7.60 (dd, *J* = 7.8 Hz, 2.1 Hz, 1H), 5.63 (d, *J* = 8.1 Hz, 1H), 5.22–5.07 (m, 1H), 3.74–3.63 (m, 2H), 3.43–3.30 (m, 2H), 3.27–3.14 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 165.2, 151.9, 143.6 (d, *J* = 3.9 Hz), 126.7 (t, *J* = 260.9 Hz), 101.5, 64.0 (q, *J* = 25.8 Hz), 59.5 (q, *J* = 18.3 Hz), 58.5 (q, *J* = 2.8 Hz), 45.6 (d, *J* = 6.2 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −108.8 (dm, *J* = 236.6 Hz, 1F), −114.9 (dm, *J* = 236.3 Hz, 1F); IR (KBr) υ_{max} 3432, 3300, 3095, 1703, 1673, 1448, 1389 cm^{-1}; MS (ESI) *m/z* 248 $(M+H)^+$, 270 $(M+Na)^+$; HRMS Calcd. for $C_9H_{11}N_3O_3F_2Na$: 270.0673; found: 270.0666.

3.13. 2′,3′-Dideoxy-6′,6′-difluoro-5′-*tert*-butyldiphenylsilyl-3′-aza-*tert*-butoxycarbonyl-α-L-uridine (14)

A mixture of compound **13** (90 mg, 0.14 mmol) in MeOH (2 mL) and concentrated $NH_3{\cdot}H_2O$ (4 mL) in a sealable tube was heated to 75 °C for 12 h. Solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography to give 65 mg (78%) of compound **14**: white solid, mp 100–102 °C; $[\alpha]_D^{23} = -47.5^\circ$ (*c* 0.86, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD) δ 7.88–7.81 (m, 1H), 7.74–7.67 (m, 4H), 7.50–7.39 (m, 6H), 6.27–6.13 (m, 1H), 5.75 (d, *J* = 7.8 Hz, 1H), 4.17–4.01 (m, 2H), 3.99–3.74 (m, 3H), 1.55 (s, 4H), 1.31 (s, 5H), 1.10 (d, *J* = 4.2 Hz, 9H); ^{19}F NMR (282 MHz, CD_3OD) (two rotamers) δ −109.2 (dt, *J* = 232.4 Hz, 22.8 Hz, 1F), −119.1 (dd, *J* = 232.9 Hz, 7.1 Hz, 0.56F), −120.4 (dd, *J* = 232.7 Hz, 7.9 Hz, 0.44F); IR (KBr) υ_{max} 3213, 1702, 1378, 1165, 1108 cm^{-1}; MS (ESI) *m/z* 586 $(M+H)^+$, 608 $(M+Na)^+$, 624 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{37}N_3O_5F_2Si$: C, 61.52; H, 6.37; N, 7.17; found: C, 61.48; H, 6.46; N, 7.04.

3.14. 2′,3′-Dideoxy-6′,6′-difluoro-5′-*tert*-butyldiphenylsilyl-3′-aza-*tert*-butoxycarbonyl-α-L-cytidine (15)

To a 0 °C solution of compound **14** (60 mg, 0.10 mmol) in MeCN (2 mL) under argon, TPSCl (63 mg, 0.21 mmol), Et_3N (29 μL, 0.21 mmol) and DMAP (24 mg, 0.20 mmol) were added subsequently. Then, the reaction mixture was warmed to room temperature and stirred for 12 h. After that, concentrated $NH_3{\cdot}H_2O$ H_2O (28%, 1.3 mL) was added and the whole reaction mixture was stirred overnight. The solvent was removed and the residue was purified by silica gel column chromatography to give compound **15** (58 mg, 98% yield): white solid, mp 233–235 °C; $[\alpha]_D^{25} = -43.5^\circ$ (*c* 0.81, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.64 (m, 4H), 7.42–7.40 (m, 7H), 6.44–6.30 (m, 1H), 6.22–6.13 (m, 1H), 4.14–3.75 (m, 4H), 3.60–3.45 (m, 1H), 1.52 (s, 4H), 1.34 (s, 5H), 1.25 (s, 2H), 1.08 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −108.1 (dt, *J* = 231.0 Hz, 22.6 Hz, 1F), −117.8 (d, *J* = 234.3 Hz, 0.57F), −119.0 (d, *J* = 232.4 Hz, 0.43F); IR (KBr) υ_{max} 3481, 3149, 1702, 1664, 1645, 1166 cm^{-1}; MS (ESI) *m/z* 585 $(M+H)^+$, 607 $(M+Na)^+$, 623 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{33}N_4O_4F_2Si$: C, 61.62; H, 6.55; N, 9.58; found: C, 61.73; H, 6.94; N, 9.20.

3.15. 2′,3′-Dideoxy-6′,6′-difluoro-3′-aza-α-L-cytidine (1b)

A mixture of compound **15** (60 mg, 0.10 mmol) in dioxane (1.2 mL) and 2N sulfuric acid (3 mL) was refluxed for 4 h. After

that, the mixture was cooled to 0 °C and neutralized with dilute aq. NaOH. After filtration and removal of the solvent in vacuo, the residue was dissolved in methanol and the product was extracted into methanol solution. Then, the methanol was removed and the residue was purified by silica gel column chromatography to give compound **1b** (22 mg, 87% yield): white solid, mp 148–150 °C; $[\alpha]_D^{24} = -5.1°$ (*c* 0.44, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 6.37 (d, *J* = 6.3 Hz, 1H), 4.62 (d, *J* = 7.2 Hz, 1H), 4.09–4.01 (m, 1H), 2.48–2.42 (m, 2H), 2.21–2.14 (m, 2H), 2.02–1.92 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 166.0, 157.3, 144.0 (d, *J* = 4.4 Hz), 126.8 (t, *J* = 258.4 Hz), 94.9, 64.3 (t, *J* = 23.6 Hz), 60.1 (q, *J* = 18.6 Hz), 58.5 (d, *J* = 6.9 Hz), 46.0 (d, *J* = 4.9 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −109.0 (dt, *J* = 237.4 Hz, 11.6 Hz, 1F), −114.6 (dt, *J* = 236.3 Hz, 16.9 Hz, 1F); IR (KBr) υ_{max} 3357, 1655, 1497, 1397, 787 cm^{-1}; MS (ESI) *m/z* 247 $(M+H)^+$; HRMS Calcd. for $C_9H_{12}N_4O_2F_2Na$: 269.0821; found: 269.0824.

3.16. (4*S*)-4-Azido-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluorobutane-1,2-diol (19)

To a solution of compound **18** (7.50 g, 32.2 mmol) in acetone (160 mL) was added NMNO·H_2O (8.26 g, 61.2 mmol), followed by water (30 mL) at room temperature with stirring. Then, a catalytic amount of OsO_4 solution (4%) in water was added. After the reaction mixture was stirred at room temperature for 48 h, the reaction was quenched with saturated aq. $NaHSO_3$ and extracted with ethyl acetate. The combined organic layers were washed with 1N HCl and brine, and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography to give compound **19** (7.20 g, 83% yield): clear oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55–4.49 (m, 1H), 4.19–4.07 (m, 2H), 3.95–3.80 (m, 3H), 3.73 (td, *J* = 11.1 Hz, 5.1 Hz, 1H), 3.52 (br, 2H), 1.49 (s, 3H), 1.40 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.1 (dm, *J* = 263.4 Hz, 0.82F), −117.1 (dm, *J* = 291.3 Hz, 0.82F), −118.0 (dm, *J* = 259.2 Hz, 0.18F), −119.1 (dm, *J* = 261.7 Hz, 0.18F); IR (thin film) υ_{max} 3412, 2122, 1376, 1261, 1215, 1064 cm^{-1}; MS (ESI) *m/z* 285 $(M+NH_4)^+$, 290 $(M+Na)^+$; Anal. Calcd. for $C_9H_{15}N_3O_4F_2$: C, 40.45; H, 5.66; N, 15.72; found: C, 40.57; H, 5.73; N, 15.42.

3.17. (2*S*,4*S*)-4-Azido-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoro-2-hydroxybutyl methanesulfonate (20b) and (2*R*,4*S*)-4-Azido-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoro-2-hydroxybutyl methanesulfonate (20a)

Compounds **20a** and **20b** were prepared using the same condition as described for the compound **4**. **20b**: white solid, mp 95–98 °C; $[\alpha]_D^{25} = -12.8°$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55–4.36 (m, 4H), 4.21–4.16 (m, 1H), 3.95–3.84 (m, 2H), 3.13 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.7 (dd, *J* = 263.7 Hz, 19.5 Hz, 1F), −118.2 (dd, *J* = 262.0 Hz, 22.3 Hz, 1F); IR (KBr) υ_{max} 3406, 2126, 1355, 1174 cm^{-1}; MS (ESI) *m/z* 363 $(M+NH_4)^+$, 368 $(M+Na)^+$; Anal. Calcd. for $C_{10}H_{17}N_3O_6F_2S$: C, 34.78; H, 4.96; N, 12.17; found: C, 34.90; H, 4.97; N, 11.97. **20a**: White solid, mp 87–91 °C; $[\alpha]_D^{22} = -7.5°$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49–4.26 (m, 3H), 4.11(t, *J* = 8.4 Hz, 1H), 3.87 (t, *J* = 7.8 Hz, 1H), 3.73 (td, *J* = 11.1 Hz, 5.1 Hz, 1H), 3.04 (d, *J* = 1.2 Hz, 3H), 3.04 (d, *J* = 1.2 Hz, 3H), 1.42 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 120.4 (dd, *J* = 188.0 Hz, 191.9 Hz), 110.2, 73.2, 68.4, 66.5, 63.3 (t, *J* = 19.5 Hz), 37.2, 30.6, 25.8, 25.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.0 (dm, *J* = 265.9 Hz, 1F), −116.9 (dm, *J* = 264.2 Hz, 1F); IR (KBr) υ_{max} 3375, 2122, 1635, 1351 cm^{-1}; MS (ESI) *m/z* 363 $(M+NH_4)^+$; Anal. Calcd. for $C_{10}H_{17}N_3O_6F_2S$: C, 34.78; H, 4.96; N, 12.17; found: C, 33.95; H, 5.08; N, 11.88.

3.18. (2*S*,4*S*)-Benzyl 2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoro-4-hydroxypyrrolidine-1-carboxylate (21)

To a solution of compound **20b** (2.47 g, 7.16 mmol) in THF (150 mL) was added a solution of PPh_3 (3.75 mg, 14.3 mmol) in THF (33 mL) dropwise at room temperature. After the starting material was completely consumed, saturated aq. $NaHCO_3$ (33 mL) was added and the reaction mixture was heated to reflux for 30 h. The reaction mixture was cooled to the room temperature and CbzCl (1.34 g, 7.88 mmol) was added. The reaction mixture was stirred for further 21 h, the phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford compound **21** (1.10 g, 43% yield): clear oil, $[\alpha]_D^{23} = 61.6°$ (*c* 1.41, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.23–5.13 (m, 2H), 4.45–4.37 (m, 1H), 4.34–4.15 (m, 3H), 4.05–3.91 (m, 1H), 3.48–3.41 (m, 1H), 1.38 and 1.25 (two singlets, 6H, amide isomers); ^{13}C NMR (75.5 MHz, $CDCl_3$) (two rotamers) δ 156.28, 136.00, 128.61 and 128.54, 128.46 and 128.31, 127.83 and 126.96, 127.61 (t, *J* = 211.4 Hz), 110.55, 74.02 and 73.51, 71.29 and 71.01, 68.13 and 67.82, 66.32 and 65.33, 61.51 (t, *J* = 15.2 Hz), 54.35, 29.67 and 29.33, 25.70 and 25.59; ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −100.7 (dt, *J* = 243.4 Hz, 16.6 Hz, 0.34F), −101.0 (dm, *J* = 244.5 Hz, 0.66F), −124.6 (d, *J* = 249.9 Hz, 0.34F), −125.3 (d, *J* = 245.6 Hz, 0.66F); IR (thin film) υ_{max} 3417, 1709, 1412, 1345, 1115 cm^{-1}; MS (ESI) *m/z* 358 $(M+H)^+$, 380 $(M+Na)^+$; Anal. Calcd. for $C_{17}H_{21}NO_5F_2$: C, 57.14; H, 5.92; N, 3.92; found: C, 57.18; H, 6.14; N, 4.00.

3.19. (2*S*,4*S*)-Benzyl 3,3-difluoro-4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (22)

The compound **22** was prepared from the compound **21** using the same procedure as described for the compound **7**. Colorless oil: $[\alpha]_D^{23} = 47.8°$ (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.32 (m, 5H), 5.18–5.08 (m, 2H), 4.17–4.13 (m, 3H), 4.05–3.98 (m, 1H), 3.87–3.71 (m, 2H), 3.58 (d, *J* = 12.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −101.7 (dm, *J* = 246.2 Hz, 0.39F), −102.3 (dm, *J* = 246.5 Hz, 0.61F), −125.1 (d, *J* = 246.2 Hz, 0.39F), −126.7 (d, *J* = 247.0 Hz, 0.61F); IR (thin film) υ_{max} 3342, 1689, 1425, 1353, 1110 cm^{-1}; MS (ESI) *m/z* 288 $(M+H)^+$, 310 $(M+Na)^+$; Anal. Calcd. for $C_{13}H_{15}NO_4F_2$: C, 54.35; H, 5.26; N, 4.88; found: C, 54.52; H, 5.55; N, 4.74.

3.20. (2*S*,4*S*)-Benzyl 2-(benzoyloxymethyl)-3,3-difluoro-4-hydroxypyrrolidine-1-carboxylate (23)

To a solution of compound **22** (382 mg, 1.33 mmol) in anhydrous CH_2Cl_2 (10 mL) was added pyridine (3.7 mL) followed by BzCl (0.20 mL, 1.65 mmol) in CH_2Cl_2 (1.2 mL) at −78 °C. After the mixture was stirred at the same temperature for 2 h, MeOH (2 mL) was added and the mixture was stirred for 30 min. Then water was added to quench the reaction. The aqueous layer was extracted with ether. The combined organic layers were washed with 1N HCl, saturated aq. $NaHCO_3$, and brine and further dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography to give compound **23** (420 mg, 81% yield): clear oil, $[\alpha]_D^{23} = 0.92°$ (*c* 4.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (br, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.45–7.40 (m, 2H), 7.33–7.26 (m, 4H), 5.20–5.00 (m, 2H), 4.75–4.33 (m, 4H), 3.91–3.85 (m, 1H), 3.59 (d, *J* = 12.3 Hz, 1H), 2.84 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −103.2 (dm, *J* = 246.5 Hz, 1F), −127.0 (d, *J* = 245.1 Hz, 0.48F), −128.4 (d, *J* = 247.3 Hz, 0.52F); IR (thin film) υ_{max} 3433, 1719, 1419, 1276, 1113 cm^{-1}; MS (ESI) *m/z* 392 $(M+H)^+$, 409

$(M+NH_4)^+$, 414 $(M+Na)^+$; Anal. Calcd. for $C_{20}H_{19}NO_5F_2$: C, 61.38; H, 4.89; N, 3.58; found: C, 61.43; H, 4.95; N, 3.34.

3.21. (2S,4S)-Benzyl 2-(benzoyloxymethyl)-3,3-difluoro-4-(trifluoromethylsulfonyloxy)pyrrolidine-1-carboxylate (24)

The compound **24** was prepared from compound **23** using the same procedure as described for **10**: clear oil, $[\alpha]_D^{23} = 15.2^\circ$ (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 6.9 Hz, 2H), 7.52–7.47 (m, 1H), 7.35 (t, *J* = 8.1 Hz, 2H), 7.26 (s, 5H), 5.21–5.16 (m, 1H), 5.13–5.03 (m, 2H), 4.56–4.45 (m, 3H), 4.12–4.07 (m, 1H), 3.77–3.72 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −74.3 (s, 3F), −100.5 (dm, *J* = 253.2 Hz, 1F), −120.8 (d, *J* = 256.1 Hz, 0.50F), −122.4 (d, *J* = 254.9 Hz, 0.50F); IR (thin film) υ_{max} 1719, 1604, 1425, 1274, 1220, 1141 cm^{-1}; MS (ESI) *m/z* 524 $(M+H)^+$, 541 $(M+NH_4)^+$, 546 $(M+Na)^+$; Anal. Calcd. for $C_{21}H_{18}NO_7F_5S$: C, 48.19; H, 3.47; N, 2.68; found: C, 48.31; H, 3.74; N, 2.70.

3.22. (2S,4R)-Benzyl 4-azido-2-(benzoyloxymethyl)-3,3-difluoropyrrolidine-1-carboxylate (25)

Compound **25** was prepared from compound **24** using the same procedure as described for **11**: clear oil, $[\alpha]_D^{23} = 32.2^\circ$ (*c* 3.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.62–7.57 (m, 1H), 7.49–7.44 (m, 2H), 7.35–7.32 (m, 5H), 5.22–5.13 (m, 2H), 4.76–4.67 (m, 1H), 4.59–4.36 (m, 2H), 4.21–4.12 (m, 1H), 3.87–3.81 (m, 1H), 3.56–3.54 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −111.8 (dt, *J* = 237.7 Hz, 13.8 Hz, 0.49F), −112.2 (dt, *J* = 237.2 Hz, 14.7 Hz, 0.51F), −115.1 (d, *J* = 236.3 Hz, 0.49F), −116.6 (d, *J* = 236.9 Hz, 0.51F); IR (thin film) υ_{max} 3067, 2115, 1724, 1415, 1272, 1113 cm^{-1}; MS (ESI) *m/z* 417 $(M+H)^+$, 434 $(M+NH_4)^+$, 439 $(M+Na)^+$, 455 $(M+K)^+$; Anal. Calcd. for $C_{20}H_{18}N_4O_4F_2$: C, 57.69; H, 4.36; N, 13.46; found: C, 57.88; H, 4.40; N, 13.42.

3.23. (2S,4R)-Benzyl 4-amino-2-(benzoyloxymethyl)-3,3-difluoropyrrolidine-1-carboxylate (26)

Compound **26** was prepared from compound **25** using the same procedure as described for compound **12**: clear oil, $[\alpha]_D^{25} = 42.0^\circ$ (*c* 0.76, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.61–7.56 (m, 1H), 7.48–7.43 (m, 2H), 7.36–7.31 (m, 5H), 5.17–5.16 (m, 2H), 4.80–4.70 (m, 1H), 4.46–4.40 (m, 2H), 3.92–3.89 (m, 2H), 3.18–3.15 (m, 1H), 1.55 (br, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 154.6, 136.0, 135.9, 133.3, 129.5, 128.6, 128.3, 127.9, 122.4 (t, *J* = 103.7 Hz), 67.8, 67.5, 60.7 (d, *J* = 21.8 Hz), 54.6, 49.7; ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −115.3 (dm, *J* = 233.8 Hz, 1F), −121.9 (d, *J* = 234.3 Hz, 0.47F), −123.7 (d, *J* = 232.9 Hz, 0.53F); IR (thin film) υ_{max} 3399, 1719, 1417, 1274, 1112 cm^{-1}; MS (ESI) *m/z* 391 $(M+H)^+$, 408 $(M+NH_4)^+$; Anal. Calcd. for $C_{20}H_{20}N_2O_4F_2$: C, 61.53; H, 5.16; N, 7.18; found: C, 61.50; H, 5.06; N, 7.22.

3.24. (2S,4R,E)-Benzyl 2-(benzoyloxymethyl)-4-(3-(3-ethoxyacryloyl)ureido)-3,3-difluoropyrrolidine-1-carboxylate (27)

Compound **27** was prepared from compound **26** using the same procedure as described for compound **13**: white solid, mp 62–64 °C; $[\alpha]_D^{24} = 19.9^\circ$ (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, *J* = 19.5 Hz, 1H), 9.28 (d, *J* = 9.0 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 2H), 7.65–7.55 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.34 (s, 5H), 5.28–5.16 (m, 4H), 4.90 (t, *J* = 12.0 Hz, 1H), 4.50–4.29 (m, 2H), 4.01 (t, *J* = 10.2 Hz, 1H), 3.78–3.66 (m, 2H), 3.35–3.31 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) (two rotamers) δ −110.9 (dt, *J* = 235.2 Hz, 19.7 Hz, 1F), −119.1 (d, *J* = 234.9 Hz, 0.45F), −120.9 (d, *J* = 235.2 Hz, 0.55F); IR (KBr) υ_{max} 3248, 1716, 1680, 1550, 1272, 1108 cm^{-1}; MS (ESI) *m/z* 532 $(M+H)^+$, 549 $(M+NH_4)^+$; Anal. Calcd. for $C_{26}H_{27}N_3O_7F_2$: C, 58.75; H, 5.12; N, 7.91; found: C, 58.40; H, 5.12; N, 7.63.

3.25. 2′,3′-Dideoxy-6′,6′-difluoro-3′-aza-benzyloxycarbonyl-α-D-uridine (28)

A mixture of compound **27a** (180 mg, 0.34 mmol) in dioxane (2.2 mL) and 2N sulfuric acid (5.1 mL) was heated at reflux for 4 h. After that, the mixture was cooled to 0 °C and neutralized with diluted aq. NaOH. Then, the resulting mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration and removal of all the solvent, the residue was dissolved in saturated NH_3 in MeOH (5 mL). The resultant mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give compound **28** (68 mg, 53% yield): white solid, mp 97–100 °C; $[\alpha]_D^{23} = 35.4^\circ$ (*c* 0.46, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 7.77 (dd, *J* = 8.1 Hz, 2.7 Hz, 1H), 7.41–7.33 (m, 5H), 6.06–5.90 (m, 1H), 5.72 (d, *J* = 7.8 Hz, 1H), 5.27–5.16 (m, 2H), 4.18 (d, *J* = 19.8 Hz, 1H), 4.03–3.89 (m, 2H), 3.83–3.76 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 164.2, 154.6, 151.4, 142.8 (d, *J* = 6.0 Hz), 136.2, 128.2, 127.9, 127.8, 123.9 (t, *J* = 259.0 Hz), 101.6, 67.3, 63.3 (q, *J* = 26.5 Hz), 57.5 (d, *J* = 66.4 Hz), 54.2 (t, *J* = 17.4 Hz), 44.8; ^{19}F NMR (282 MHz, CD_3OD) (two rotamers) δ −109.3 (dt, *J* = 233.5 Hz, 20.0 Hz, 1F), −119.7 (dd, *J* = 232.4 Hz, 7.9 Hz, 0.45F), −121.2 (dd, *J* = 233.2 Hz, 5.4 Hz, 0.55F); IR (KBr) υ_{max} 3439, 3066, 1697, 1458, 1422, 1345 cm^{-1}; MS (ESI) *m/z* 382 $(M+H)^+$, 404 $(M+Na)^+$; HRMS Calcd. for $C_{17}H_{17}N_3O_5F_2Na$: 404.1029; found: 404.1033.

3.26. 2′,3′-Dideoxy-6′,6′-difluoro-3′-aza-α-D-uridine (1c)

A mixture of **28** (20 mg, 0.053 mmoL) and 10% Pd/C (13 mg) in MeOH (5 mL) was vigorously stirred under H_2 atmosphere (1atm). After 40 min, the solution was filtered over celite and evaporated, the residue was purified by silica gel column chromatography to give the nucleoside **1c** (11 mg, 85% yield) as a white solid: mp 192–194 °C; $[\alpha]_D^{23} = -2.7^\circ$ (*c* 0.27, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 7.70 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H), 5.70 (d, *J* = 7.8 Hz, 1H), 5.28–5.14 (m, 1H), 3.81–3.70 (m, 2H), 3.51–3.42 (m, 2H), 3.26–3.22 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 164.5, 151.4, 143.6 (d, *J* = 2.6 Hz), 126.7 (t, *J* = 258.5 Hz), 101.4, 64.1 (t, *J* = 27.1 Hz), 59.5 (q, *J* = 18.0 Hz), 58.4 (q, *J* = 2.9 Hz), 45.5 (d, *J* = 7.3 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −107.9 (dm, *J* = 237.2 Hz, 1F), −114.1 (dm, *J* = 237.7 Hz, 1F); IR (KBr) υ_{max} 3431, 3300, 3095, 1702, 1673, 1448, 1389 cm^{-1}; MS (ESI) *m/z* 248 $(M+H)^+$, 270 $(M+Na)^+$; HRMS Calcd. for $C_9H_{11}N_3O_3F_2Na$: 270.0661; found: 270.0664.

3.27. 2′,3′-Dideoxy-6′,6′-difluoro-3′-aza-benzyloxycarbonyl-α-D-cytidine (29)

To a solution of compound **28** (10 mg, 0.026 mmol) in pyridine (0.60 mL), DMAP (2 mg, 0.016 mmol) and Ac_2O (0.10 mL, 1.06 mmol) were added subsequently. After being stirred for 12 h, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined and washed with 1N HCl, saturated aq $NaHCO_3$, and brine. The organic phase was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was dissolved in CH_3CN (1.5 mL) at 0 °C. Then, TPSCl (15 mg, 0.050 mmol), DMAP (6 mg, 0.048 mmol), and Et_3N (7 μL, 0.048 mmol) were added subsequently. The reaction mixture was warmed to room temperature and stirred for 12 h. After that, concentrated $NH_3{\cdot}H_2O$ (28%, 0.40 mL) was added and the whole reaction mixture was stirred overnight. The resulting mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed in vacuo. The residue was dissolved in the saturated NH_3 in MeOH (3 mL) and the reaction mixture was stirred at room temperature for 36 h. After that, the solvent was removed in vacuo

and the residue was purified by silica gel column chromatography to give compound **29** (5 mg, 50% yield): white solid, mp 145–147 °C; $[\alpha]_D^{25}$ = 26.4° (*c* 1.70, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.74 (dd, *J* = 7.2 Hz, 2.4 Hz, 1H), 7.44–7.33 (m, 5H), 6.23–6.06 (m, 1H), 5.92 (d, *J* = 8.4 Hz, 1H), 5.20–5.16 (m, 2H), 4.16 (d, *J* = 20.4 Hz, 1H), 4.02–3.90 (m, 2H), 3.80–3.73 (m, 2H); ^{19}F NMR (282 MHz, CD_3OD) (two rotamers) δ −109.3 (dm, *J* = 232.4 Hz, 1F), −119.7 (dd, *J* = 231.0 Hz, 5.4 Hz, 0.46F), −121.2 (dd, *J* = 232.7 Hz, 7.3 Hz, 0.54F); IR (KBr) υ_{max} 3327, 1655, 1496, 1342, 1106 cm^{-1}; MS (ESI) *m/z* 381 (M+H)$^+$; HRMS Calcd. for $C_{17}H_{19}N_4O_4F_2$: 381.1369; found: 381.1372.

*3.28. 2′,3′-Dideoxy-6′,6′-difluoro-3′-aza-α-D-cytidine (**1d**)*

The nucleoside **1d** was prepared from compound **29** using the same procedure as described for **1c**: white solid, mp 138–140 °C; $[\alpha]_D^{25}$ = 11.9° (*c* 0.08, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.68 (dd, *J* = 7.8 Hz, 2.1Hz, 1H), 5.92 (d, *J* = 7.2 Hz, 1H), 5.42–5.28 (m, 1H), 3.84–3.73 (m, 2H), 3.52–3.36 (m, 2H), 3.29–3.22 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 166.0, 157.3, 144.0 (d, *J* = 2.0 Hz), 126.8 (t, *J* = 242.9 Hz), 94.8, 64.3 (t, *J* = 21.8 Hz), 60.1 (q, *J* = 19.9 Hz), 58.5 (t, *J* = 6.9 Hz), 46.0 (d, *J* = 5.4 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −107.7 (dm, *J* = 236.0 Hz, 1F), −113.3 (dm, *J* = 236.9 Hz, 1F); IR (KBr) υ_{max} 3355, 3195, 1655, 1488, 1399, 1198 cm^{-1}; MS (ESI) *m/z* 247 (M+H)$^+$; HRMS Calcd. for $C_9H_{12}N_4O_2F_2Na$: 269.0821; found: 269.0824.

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References

[1] (a) C.K. Chu, D.C. Baker (Eds.), Nucleosides and Nucleotides as Antitumor and AntiViral Agents, Plenum Press, New York, 1993;
(b) M.T. Crimmins, Tetrahedron 54 (1998) 9229–9272;
(c) A.D. Borth-wick, K. Biggadike, Tetrahedron 48 (1992) 571–623;
(d) L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S.R. Challand, R.A. Earl, R. Guedj, Tetrahedron 50 (1994) 10611–10670;
(e) M. Yokoyama, Synthesis (2000) 1637–1655;
(f) M. Yokoyama, A. Momotake, Synthesis (1999) 1541–1554.
[2] E.J. De Clercq, Clin. Virol. 30 (2004) 115–133, Nucleosides/nucleotide are zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (1596U89), emtricitabine (FTC), and tenofovir disoproxil fumarate..
[3] (a) C.N. Chang, S.L. Doong, J.H. Zhou, J.W. Beach, L.S. Jeong, C.K. Chu, C.H. Tasi, Y.C. Cheng, J. Biol. Chem. 267 (1992) 13938–13942;
(b) S.L. Doong, C.H. Tasi, R.F. Schinazi, D.C. Liotta, Y.C. Cheng, Proc. Natl. Acad. Sci. U.S.A. 88 (1991) 8495–8499.
[4] (a) L.W. Frick, C.U. Lambe, L. St. John, L.C. Taylor, D.J. Nelson, Antimicrob. Agents Chemother. 38 (1994) 2722–2729;
(b) L.W. Frick, L.St. John, L.V. Taylor, G.R. Painter, P.A. Furman, D.C. Liotta, E.S. Furfine, D.J. Nelson, Antimicrob. Agents Chemother. 37 (1993) 2285–2292.
[5] C.M. Blackburn, D.A. England, F. Kolkmann, J. Chem. Soc., Chem. Commun. (1981) 930–932.
[6] For recent examples, see:
(a) W. Zhou, G. Gumina, Y. Chong, J. Wang, R.F. Schinazi, C.K. Chu, J. Med. Chem. 47 (2004) 3399–3408;
(b) G. Gumina, R.F. Schinazi, C.K. Chu, J. Med. Chem. 46 (2003) 3245–3256;
(c) K. Lee, Y. Choi, G. Gumina, W. Zhou, R.F. Schinazi, C.K. Chu, J. Med. Chem. 45 (2002) 1313–1320.
[7] (a) Y.-Y. Wu, X. Zhang, W. Meng, F.-L. Qing, Org. Lett. 6 (2004) 3941–3944;
(b) X. Yue, Y.-Y. Wu, F.-L. Qing, Tetrahedron 63 (2007) 1560–1567.
[8] D.F. DeTar, N.P. Luthra, J. Am. Chem. Soc. 99 (1977) 1232–1244.
[9] G. Shaw, R.N. Warrener, J. Chem. Soc. (1958) 157–161.
[10] Crystal data have been deposited at the Cambridge Crystallographic Data Center with reference numbers: compound **1a**, CCDC 666126; compound **1c**, CCDC 666127.