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Synthesis of a series of novel 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleosides

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Abstract—A series of novel 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleosides **1a**–**d**, analogues of 3TC that has high biological activities against HIV and HBV, have been synthesized from the *gem*-difluorohomoallyl amine **7** in a straightforward fashion. Our synthesis featured the construction of thiofuranose skeleton through ring closure of key intermediates and installation of pyrimidine ring with amino group in compounds **13a**,**b**.

1. Introduction

2′,3′-Dideoxynucleosides (ddNs) have far proven to be the most effective therapeutic agents against human immunodeficiency virus (HIV) and hepatitis B virus (HBV).[1] Among them, 3′-azido-2′,3′-dideoxythymidine (AZT),[2] 2′,3′-dideoxyinosine (DDI),[3] and 2′,3′-dideoxycytidine (DDC)[4] have been approved for the treatment of AIDS. In spite of the initial success obtained with these modified nucleosides, the instability of the glycosidic bond of the 4′-oxonucleosides under physiological conditions[5] as well as undesirable side effects of certain nucleosides has prompted the search for further novel nucleosides with improved biological and chemical properties. Consequently, extensive modifications have been made to both the heterocyclic base and the sugar moiety of nucleosides.[6] Sulfur-containing dideoxynucleosides, (−)-β-L-(2*R*,5*S*)-1,3-oxathiolanylcytosine (3TC)[7] and its 5-fluorocytosine analogue (−)-FTC (Fig. 1),[8] showed higher biological activity than conventional ddNs and were approved by the FDA for the treatment of HIV infection. As the *gem*-difluoromethylene (CF_2) group has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen,[9] recently we have designed and synthesized a new difluoromethylenated thionucleoside **A**.[10] To investigate the structure–activity relationship of this novel analogue of 3TC, a series of 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleosides are needed. Herein, we wish to report the preparation of stereoisomers **1c** and **1d** of compound **A** (Fig. 1).

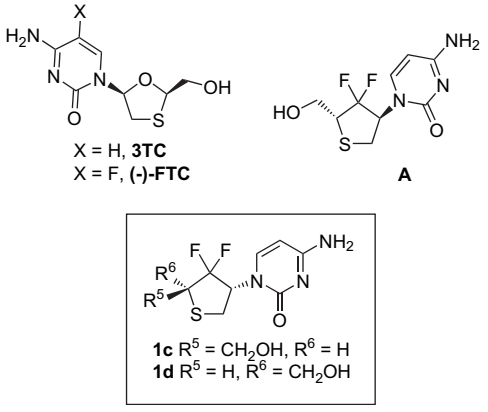

Figure 1.

2. Results and discussion

On the basis of our retrosynthetic analysis (Scheme 1), the target molecules **1a**–**d** can be reached from the *gem*-difluoromethylenated cyclic amine **B** by installing the pyrimidine base moiety at C1 position through the reported methodology.[11] As the *gem*-difluoromethylenated thiofuranose could be smoothly constructed via ring closure of the corresponding dimesylate,[12] we envisioned that the *gem*-difluoromethylenated diols **C** could be suitable precursors for **B**. Compounds **C** could be afforded by removal of the isopropylidene ketal of intermediate **D** followed by oxidation of the dihydroxyl moiety and subsequent reduction. Conversion of hydroxyl group of homoallyl alcohol **E** to amino group followed by dihydroxylation would furnish the amino alcohol **D**. To obtain the desired base configuration of target nucleosides

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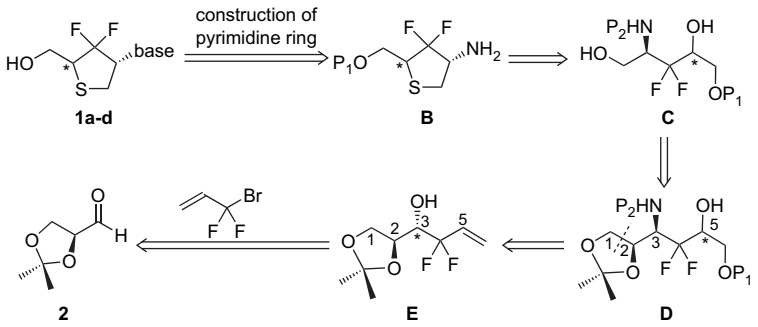
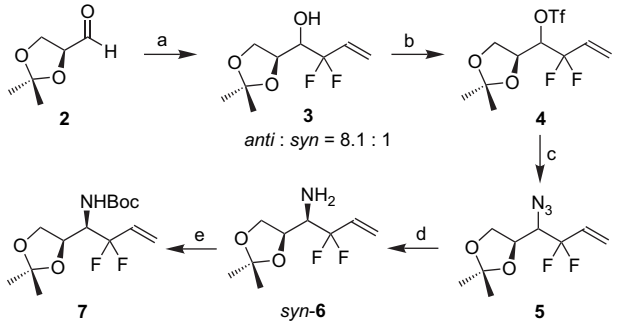


Scheme 1. Retrosynthetic analysis of target molecules **1a**–**d**.

1a–**d**, the configuration of amino group (C3 position) of compound **D** must be *R* and thus the hydroxyl group of homoallyl alcohol **E** should be formed with *S* configuration. We have reported that the allylation of chiral aldehyde with 3-bromo-3,3-difluoropropylene in the presence of indium provided the *anti*-isomer of homoallyl alcohol as the major product.[13] Therefore, (*S*)-glyceraldehyde acetonide **2** was chosen for the preparation of the desired *gem*-difluoromethylenated homoallyl alcohol **E**.

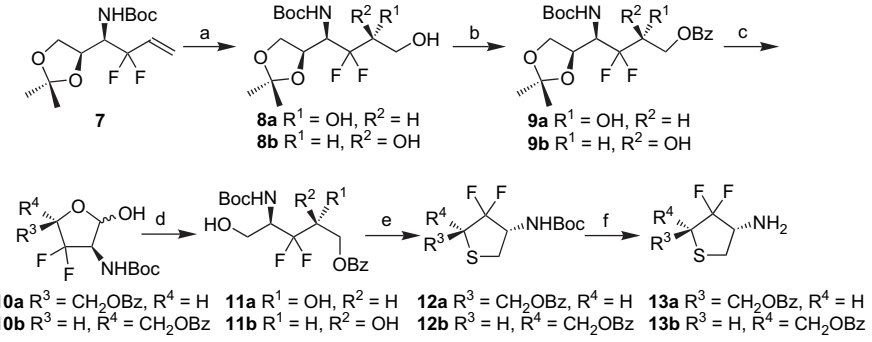
Accordingly, the coupling of 1-(*S*)-glyceraldehyde acetonide **2** with 3-bromo-3,3-difluoropropene in DMF in the presence of indium provided *gem*-difluorohomoallyl alcohol **3** in 73% yield. The ratio of *anti*/*syn* is 8.1:1 determined by ^{19}F NMR. Notably, *anti*-**3** was our desired compound (Scheme 2). Then, reaction of compound **3** with Tf_2O in CH_2Cl_2 at −25 °C gave triflate **4**. Subsequent treatment of compound **4** with NaN_3 in DMF provided azide **5**. Reduction of compound **5** with Ph_3P in THF produced our desired amine *syn*-**6**, which could be easily separated through column chromatography. Finally, protection of amine *syn*-**6** with Boc_2O gave amide **7** in 94% yield.



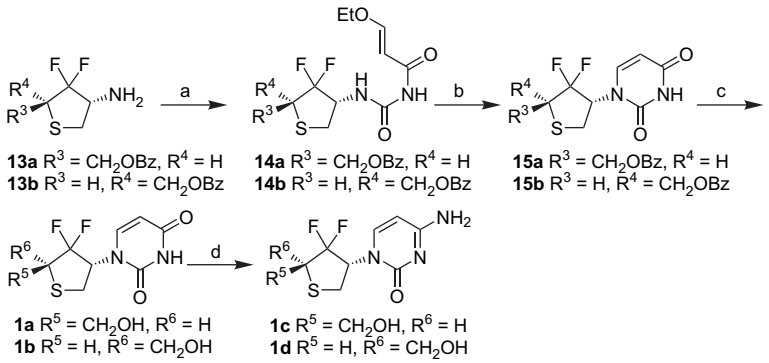
Scheme 2. Reagents and conditions: (a) In powder, $CH_2{=}CHCF_2Br$, DMF, 22 h, 73%; (b) Tf_2O, pyridine, CH_2Cl_2, −25 °C, 1 h, 92%; (c) NaN_3, DMF, 12 h, rt, overnight, 75%; (d) (i) Ph_3P, THF, rt, 6 h; (ii) H_2O, 50 °C, 40 h, 57%; (e) Boc_2O, Et_3N, THF, CH_2Cl_2, 94%.

With the difluorohomoallyl amide **7** in hand, key intermediates **13a** and **13b** were synthesized in a straightforward fashion (Scheme 3). The Os-catalyzed dihydroxylation of compound **7** gave a mixture of the diastereoisomers **8a** and **8b** in 83% yield (**8a**/**8b**=1:1). Luckily, the diastereoisomers **8a** and **8b** were easily separated by column chromatography. Benzoates **9a** and **9b** were obtained by selective benzoylation of the primary hydroxyl groups of diols **8a** and **8b**, respectively. The conversions of benzoates **9a** and **9b** to their respective difluoromethylenated furanoses **10a** and **10b** were achieved by the following two steps: (1) the acidic hydrolysis of the isopropylidene groups by treatment with 75% aqueous AcOH at 50 °C and (2) the oxidative scission of the resulting diols with $NaIO_4$ and subsequent cyclization. Difluorinated furanoses **10a** and **10b** were directly reduced by $NaBH_4$ in MeOH to give the diols **11a** and **11b** both in 77% yields from **9a** and **9b**, respectively. Mesylations at C1 and C4 positions of diols **11a** and **11b**, followed by treatment with Na_2S in DMF, resulted in a ring closure to provide thiofuranoses **12a** and **12b** as single stereoisomers, respectively. Finally, removal of Boc group of thiofuranoses **12a** and **12b** gave the key intermediates **13a** and **13b** in high yields, respectively.

The construction of pyrimidine was followed by the procedure reported by Shaw and Warrener (Scheme 4).[11] Condensation of amines **13a** and **13b** with 3-ethoxy-2-propenoyl



Scheme 3. Reagents and conditions: (a) OsO_4, NMNO, acetone, H_2O, 48 h; (b) BzCl, pyridine, CH_2Cl_2, −78 °C, 2 h; (c) (i) AcOH (aq 75%), 50 °C, 3 h; (ii) $NaIO_4$, H_2O, rt, 3 h; (d) $NaBH_4$, MeOH, 0 °C, 20 min; (e) (i) MsCl, pyridine, 0 °C–rt, overnight; (ii) $Na_2S{\cdot}9H_2O$, DMF, 80 °C, 10 min; (f) CF_3CO_2H, CH_2Cl_2, rt, 15 min.



Scheme 4. Reagents and conditions: (a) 3-ethoxy-2-propenoyl isocyanate, DMF, benzene, −25 °C, overnight; (b) 2 N H_2SO_4, reflux, 3 h; (c) satd NH_3/MeOH, rt, overnight; (d) (i) Ac_2O, pyridine, DMAP, rt, 12 h; (ii) TPSCl, DMAP, Et_3N, rt, 4 h; (iii) concd $NH_3 \cdot H_2O$, rt, overnight.

isocyanate in DMF at −25 °C gave the compounds **14a** and **14b** followed by ring closure with 2 N H_2SO_4 in dioxane to afford the compounds **15a** and **15b**, respectively. Deprotection of the compounds **15a** and **15b** was accomplished by ammonolysis to give the corresponding 2′,3′-dideoxy-6′,6′-difluoro-3′-thiouridine **1a** and **1b**. Thiouridines **1a** and **1b** were further converted into the cytosine derivatives **1c** and **1d**, respectively, by isopropylbenzene-sulfonylation of the O-4 position followed by treatment with concentrated $NH_3 \cdot H_2O$.

The absolute configuration of the target molecules **1a**–**d** was assigned on the basis of the X-ray crystal structures of compounds **1a**,**b** (Fig. 2).[14]

In summary, based on the bioisosteric rationale, we have synthesized a series of 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleosides. Our synthesis featured the construction of thiofuranose skeleton through ring closure of key intermediates and construction of pyrimidine ring with amino group in compounds **13a**,**b**. Antiviral and cytotoxicity evaluations of herein synthesized 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleosides **1a**–**d** are currently in progress.

3. Experimental section

3.1. General

Tetrahydrofuran (THF) was distilled from sodium metal. Dichloromethane (CH_2Cl_2) and pyridine were distilled from CaH_2. ^1H NMR spectra were recorded on a Bruker AM300 spectrometer. ^{19}F NMR spectra were recorded on a Bruker AM300 spectrometer ($FCCl_3$ as external standard and low field is positive). All the melting points and optical rotations are uncorrected. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

3.1.1. 1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-but-3-en-1-ol (3). A suspension consisting of an aldehyde **2** (9.900 g, 76.15 mmol), 3-bromo-3,3-difluoropropene (17.100 g, 108.92 mmol), powdered indium (9.700 g, 84.49 mmol), and DMF (500 mL) was stirred for 22 h at room temperature. The reaction mixture was then quenched with 1 N HCl and extracted with ether. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=3:1) to give 11.500 g (72.6% yield) of compound **3** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.12–5.94 (m, 1H), 5.74 (dt, J=17.4 Hz, 2.7 Hz, 1H), 5.60 (d, J=11.1 Hz, 1H), 4.33–4.27 (m, 1H), 4.06–3.99 (m, 3H), 2.38 (s, 1H), 1.44 (s, 3H), 1.37 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −106.36 (dm, J=253.8 Hz, 0.11F), −108.01 (dm, J=250.0 Hz, 0.89F), −110.23 (dm, J=256.6 Hz, 0.89F), −111.29 (dm, J=248.2 Hz, 0.11F); IR (thin film) ν_{max} 3444, 1652, 1219 cm^{-1}; MS m/z 209 (M^++1, <1), 193 (14), 101 (77), 43 (100). Anal. Calcd for $C_9H_{14}O_3F_2$: C, 51.92; H, 6.78. Found: C, 51.45; H, 6.72.

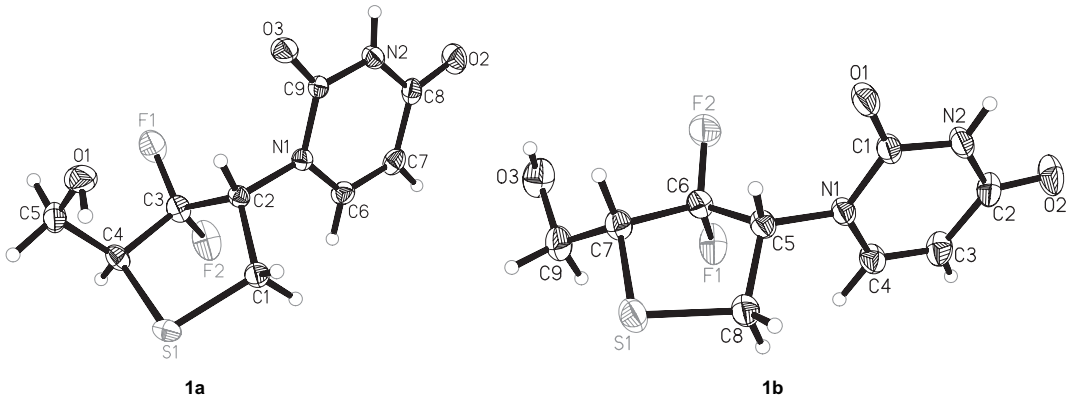


Figure 2. ORTEP drawing of the X-ray crystallographic structures of compounds **1a** and **1b**.

3.1.2. Trifluoromethanesulfonic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-difluorobut-3-enyl ester (4). Compound **3** (10.000 g, 48.08 mmol) was dissolved in dry CH_2Cl_2 (144 mL), after that freshly distilled pyridine (7.8 mL, 96.21 mmol) was added. The resulting mixture was cooled to −35 °C. Then, trifluoromethanesulfonic anhydride (12.1 mL, 72.12 mmol) was added dropwise to the solution with stirring. After that, the reaction mixture was stirred for about 1 h at about −25 °C. Water and $NaHCO_3$ solution were added successively after the mixture was warmed to the room temperature. Then the mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and purified by silica gel column chromatography (petroleum ether/ethyl acetate=8:1) to afford compound **4** (15.000 g, 91.8% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02–5.82 (m, 2H), 5.73–5.70 (m, 1H), 5.20–5.12 (m, 1H), 4.41 (td, J=6.9 Hz, 2.7 Hz, 1H), 4.08–3.93 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.1 (s, 3F), −102.19 (dm, J=269.9 Hz, 0.06F), −106.38 (dm, J=254.1 Hz, 0.94F), −107.29 (dm, J=219.7 Hz, 0.94F), −108.41 (dm, J=265.1 Hz, 0.06F); IR (thin film) ν_{max} 1421, 1214, 1143 cm^{-1}; MS m/z 325 (M^+−CH_3, 24), 101 (12), 77 (14), 43 (100). Anal. Calcd for $C_{10}H_{13}O_5F_5S$: C, 35.30; H, 3.85. Found: C, 35.23; H, 3.83.

3.1.3. 4-(1-Azido-2,2-difluoro-but-3-enyl)-2,2-dimethyl-[1,3]dioxolane (5). A solution of compound **4** (15.000 g, 44.12 mmol) in DMF (120 mL) was cooled to 0 °C in an ice bath. Then, sodium azide (13.192 g, 202.95 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 layer was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was quickly purified by silica gel column chromatography (petroleum ether/ethyl acetate=8:1) to afford compound **5** (7.700 g, 74.9% yield): clear oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06–5.92 (m, 1H), 5.81–5.73 (m, 1H), 5.60 (d, J=11.1 Hz, 1H), 4.32–4.26 (m, 1H), 4.13–4.08 (m, 1H), 3.91–3.85 (m, 1H), 3.57–3.51 (m, 1H), 1.47 (s, 3H), 1.40 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.84 (dm, J=253.5 Hz, 0.95F), −103.70 (dm, J=252.7 Hz, 0.05F), −106.07 (dm, J=249.6 Hz, 0.05F), −106.62 (dm, J=253.8 Hz, 0.95F); IR (thin film) ν_{max} 2120, 1263, 1216, 1065 cm^{-1}; MS m/z 218 (M^+−CH_3, 41), 101 (49), 77 (16), 43 (100). Anal. Calcd for $C_9H_{13}O_2F_2N_3$: C, 46.35; H, 5.62; N, 18.02. Found: C, 46.69; H, 5.79; N, 17.72.

3.1.4. 1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-difluoro-but-3-enylamine (6). A solution of Ph_3P (14.701 g, 56.05 mmol) in THF (20 mL) was slowly added at room temperature to a solution of compound **5** (7.700 g, 33.05 mmol) in THF (93 mL), and then, the reaction mixture was monitored by TLC. When the starting material was completely consumed, water (70 mL) was added and the reaction mixture was stirred for 40 h at 50 °C. The reaction mixture was cooled to room temperature and brine was added. 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 (petroleum ether/ethyl acetate=4:1) to give compound **6** (3.870 g, 56.6% yield) as a yellow oil: $[\alpha]_D^{26}$ +4.7 (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08–5.94 (m, 1H), 5.74–5.67 (m, 1H), 5.55 (d, J=10.8 Hz, 1H), 4.26–4.20 (m, 1H), 4.10–4.05 (m, 1H), 3.87 (t, J=7.5 Hz, 1H), 3.04 (td, J=10.2 Hz, 4.5 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 130.38 (t, J_{C-F}= 25.8 Hz), 121.00 (t, J_{C-F}=9.5 Hz), 120.99 (t, J_{C-F}= 227.93 Hz), 109.35, 73.94, 67.19, 57.72 (t, J_{C-F}=27.6 Hz), 26.34, 25.49; ^{19}F NMR (282 MHz, $CDCl_3$) δ −106.00 (dm, J=249.3 Hz), −106.82 (dm, J=247.3 Hz); IR (thin film) ν_{max} 3408, 1608, 1065 cm^{-1}; MS (ESI) m/z 208 (M^++H). Anal. Calcd for $C_9H_{15}NO_2F_2$: C, 52.17; H, 7.29; N, 6.76. Found: C, 52.30; H, 7.34; N, 6.31.

3.1.5. [1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-difluoro-but-3-enyl]-carbamic acid *tert*-butyl ester (7). A solution of compound **6** (3.870 g, 18.70 mmol) in CH_2Cl_2 (152 mL) was added to di-*tert*-butyl dicarbonate (20.500 g, 94.04 mmol) dropwise at room temperature with vigorous stirring. After the starting material completely disappeared, water was added to quench the reaction and the mixture was stirred for another 10 min. The organic layer was washed with brine and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=8:1) to give compound **7** (5.410 g, 94.3% yield) as a yellow oil: $[\alpha]_D^{20}$ −32.7 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05–5.91 (m, 1H), 5.72 (dd, J=17.4 Hz, 1.2 Hz, 1H), 5.57 (d, J=10.8 Hz, 1H), 4.99 (d, J=10.8 Hz, 1H), 4.49 (t, J=6.6 Hz, 1H), 4.13–4.07 (m, 2H), 3.69–3.63 (m, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.74, 130.58 (t, J_{C-F}=17.7 Hz), 121.09 (t, J_{C-F}=6.2 Hz), 119.46 (t, J_{C-F}=184.1 Hz), 110.00, 80.28, 72.03, 66.86, 54.39 (t, J_{C-F}=21.7 Hz), 28.23, 26.07, 25.33; ^{19}F NMR (282 MHz, $CDCl_3$) δ −105.30 (dm, J=248.7 Hz), −107.81 (dm, J=248.7 Hz); IR (thin film) ν_{max} 3458, 3352, 1721, 1503 cm^{-1}; MS m/z 330 (M^++Na). Anal. Calcd for $C_{14}H_{23}NO_4F_2$: C, 54.71; H, 7.54; N, 4.56. Found: C, 55.10; H, 7.65; N, 4.13.

3.1.6. [1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2,2-difluoro-3,4-dihydroxy-butyl]-carbamic acid *tert*-butyl esters 8a and 8b. To a solution of compound **7** (5.410 g, 17.62 mmol) in acetone (107 mL) was added NMNO (4.502 g, 33.34 mmol), followed by addition of water (24 mL) at room temperature with stirring. Then, a catalytic amount of OsO_4 (5–10 mol %) solution in water (4% solution) 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 1 N 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 (petroleum ether/ethyl acetate=2:1) to give compound **8a** (2.700 g, 46.7% yield) as a white solid and compound **8b** (2.101 g, 36.3% yield).

*Compound **8a***: white solid, mp 91–93 °C; $[\alpha]_D^{23}$ −4.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (d, J=9.0 Hz, 1H), 4.58 (td, J=6.9 Hz, 1.8 Hz, 1H), 4.18–4.08 (m, 2H), 3.88–3.84 (m, 3H), 3.68 (t, J=8.1 Hz, 1H), 1.46 (s, 9H), 1.39 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.53, 121.57 (t, J_{C-F}=190.9 Hz), 110.25, 81.84, 70.80, 70.18 (dd, J_{C-F}=23.6, 18.0 Hz), 67.33, 60.10 (d, J_{C-F}=3.4 Hz), 51.32 (dd, J_{C-F}=22.9 Hz, 18.0 Hz), 28.20,

26.12, 25.19; ^{19}F NMR (282 MHz, $CDCl_3$) δ −122.61 (dm, J=254.9 Hz), −123.26 (dm, J=255.5 Hz); IR (KBr) ν_{max} 3332, 1710, 1533, 1017 cm^{-1}; MS (ESI) m/z 364 (M^++Na). Anal. Calcd for $C_{14}H_{25}O_6NF_2$: C, 49.26; H, 7.38; N, 4.10. Found: C, 49.06; H, 7.17; N, 3.72.

*Compound **8b***: white solid, mp 88–91 °C; $[\alpha]_D^{24}$ −25.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (d, J=12.6 Hz, 1H), 4.54 (t, J=6.3 Hz, 1H), 4.26–4.11 (m, 2H), 4.10–3.85 (m, 3H), 3.68 (t, J=7.5 Hz, 3H), 1.46 (s, 12H), 1.38 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.3 (dm, J=253.8 Hz), −119.64 (dm, J=260.0 Hz); IR (KBr) ν_{max} 3234, 1698, 1513, 1163 cm^{-1}; MS (ESI) m/z 364 (M^++Na). Anal. Calcd for $C_{14}H_{25}O_6NF_2$: C, 49.26; H, 7.38; N, 4.10. Found: C, 48.95; H, 7.34; N, 3.83.

3.1.7. Benzoic acid 4-*tert*-butoxycarbonylamino-4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3,3-difluoro-2-hydroxy-butyl ester (9a). To a solution of compound **8a** (1.390 g, 4.08 mmol) in anhydrous CH_2Cl_2 (23 mL) and pyridine (9.9 mL) was added BzCl (0.50 mL, 4.08 mmol) in CH_2Cl_2 (3 mL) slowly at −78 °C. After the mixture was stirred at the same temperature for 2 h, MeOH (5 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 1 N HCl, saturated aq $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=4:1) to give compound **9a** (1.696 g, 93.5% yield).

*Compound **9a***: white solid, mp 90–91 °C; $[\alpha]_D^{23}$ −6.0 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J=8.4 Hz, 2H), 7.56 (t, J=7.2 Hz, 1H), 7.44 (t, J=7.8 Hz, 2H), 5.32 (d, J=9.3 Hz, 1H), 4.69–4.48 (m, 4H), 4.25–4.14 (m, 3H), 3.70 (t, J=7.8 Hz, 1H), 1.47 (s, 12H), 1.40 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.53, 157.48, 133.09, 129.93, 129.78, 128.36, 121.49 (t, J_{C-F}=192.1 Hz), 110.30, 81.85, 70.86, 68.30 (dd, J_{C-F}=23.3 Hz, 17.5 Hz), 67.34, 62.81 (d, J_{C-F}=4.5 Hz), 51.27 (dd, J_{C-F}=23.3 Hz, 17.4 Hz), 28.20, 26.13, 25.20; ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.12 (dd, J=256.1 Hz, 25.4 Hz), −123.57 (dd, J=255.2 Hz, 24.8 Hz); IR (KBr) ν_{max} 3313, 1733, 1674, 1550, 1450 cm^{-1}; MS (ESI) m/z 468 (M^++Na). Anal. Calcd for $C_{21}H_{29}O_7NF_2$: C, 56.62; H, 6.56; N, 3.14. Found: C, 56.98; H, 6.64; N, 2.97.

*Compound **9b***: it was prepared using the same condition as described for compound **9a**; white solid, mp 100–103 °C; $[\alpha]_D^{26}$ −22.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.05 (m, 2H), 7.58–7.56 (m, 1H), 7.48–7.42 (m, 2H), 5.13 (d, J=10.2 Hz, 1H), 4.68–4.56 (m, 3H), 4.34–4.29 (m, 2H), 4.14 (t, J=8.4 Hz, 1H), 3.70 (t, J=7.5 Hz, 1H), 1.47 (s, 12H), 1.38 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.73 (dm, J=260.9 Hz), −119.19 (dm, J=267.1 Hz); IR (KBr) ν_{max} 3494, 3382, 1707, 1506, 717 cm^{-1}; MS (ESI) m/z 468 (M^++Na). Anal. Calcd for $C_{21}H_{29}O_7NF_2$: C, 56.62; H, 6.56; N, 3.14. Found: C, 56.13; H, 6.72; N, 2.78.

3.1.8. Benzoic acid 4-*tert*-butoxycarbonylamino-3,3-difluoro-5-hydroxy-tetrahydrofuran-2-ylmethyl ester (11a). A mixture of compound **9a** (1.120 g, 2.52 mmol) and 75% of aq AcOH (13 mL) was stirred at 50 °C for 3 h. The solvent was then removed in vacuo. The residue was dissolved in acetone (11 mL), followed by treatment with a solution of $NaIO_4$ (0.810 g, 3.78 mmol) in water (13 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 aqueous layer 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 (20 mL). To the solution of compound **10a** was added $NaBH_4$ (0.187 g, 5.00 mmol) in portions at 0 °C. After stirring for 20 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, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1) to give 0.730 g of compound **11a** (77.3% yield, three steps).

*Compound **11a***: white solid, mp 106–110 °C; $[\alpha]_D^{26}$ +8.7 (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.05 (m, 2H), 7.59–7.54 (m, 1H), 7.47–7.41 (m, 2H), 5.52 (d, J=8.1 Hz, 1H), 5.01 (br, 1H), 4.71–4.67 (m, 1H), 4.52–4.46 (m, 1H), 4.22–4.11 (m, 3H), 3.87–3.85 (m, 1H), 1.75 (br, 1H), 1.47 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.29 (dd, J=253.8 Hz, 25.1 Hz), −122.76 (dd, J=253.2 Hz, 23.1 Hz); IR (KBr) ν_{max} 3286, 1728, 1680, 1557, 713 cm^{-1}; MS (ESI) m/z 398 (M^++Na). Anal. Calcd for $C_{17}H_{23}O_6NF_2$: C, 54.39; H, 6.18; N, 3.73. Found: C, 54.45; H, 6.17; N, 3.18.

*Compound **11b***: it was prepared using the same condition as described for compound **11a**; white solid, mp 84–86 °C; $[\alpha]_D^{26}$ −7.2 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.03 (m, 2H), 7.58–7.54 (m, 1H), 7.45–7.40 (m, 2H), 5.35 (d, J=9.3 Hz, 1H), 4.68–4.52 (m, 2H), 4.35–4.29 (m, 2H), 3.94–3.76 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.84, 156.18, 133.18, 129.66, 129.42, 128.28, 121.52 (t, J_{C-F}=191.8 Hz), 80.70, 69.51 (t, J_{C-F}=21.2 Hz), 63.70, 60.03, 53.65 (t, J_{C-F}=16.2 Hz), 28.10; ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.16 (dm, J=260.0 Hz), −118.90 (dm, J=234.1 Hz); IR (KBr) ν_{max} 3367, 1704, 1278, 713 cm^{-1}; MS (ESI) m/z 398 (M^++Na), 414 (M^++K). Anal. Calcd for $C_{17}H_{23}O_6NF_2$: C, 54.39; H, 6.18; N, 3.73. Found: C, 54.52; H, 6.13; N, 3.42.

3.1.9. Benzoic acid 4-*tert*-butoxycarbonylamino-3,3-difluoro-tetrahydro-thiophen-2-ylmethyl ester (12a). To a solution of compound **11a** (0.730 g, 1.95 mmol) in anhydrous CH_2Cl_2 (6 mL) and pyridine (5.7 mL) was added MsCl (0.62 mL, 7.79 mmol) slowly at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was quenched with water. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl, saturated aq $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was dissolved in DMF (24 mL) and $Na_2S\cdot 9H_2O$ (0.700 g, 2.93 mmol) was added. Then, the reaction mixture was heated to 80 °C. After stirring for 20 min, the reaction mixture was cooled to room temperature and water was added.

The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=6:1) to give compound **12a** (0.468 g, 64.5% yield, two steps).

*Compound **12a***: white solid, mp 94–95 °C; $[\alpha]_D^{25}$ −72.2 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J*=8.1 Hz, 2H), 7.61–7.55 (m, 1H), 7.48–7.43 (m, 2H), 4.99 (d, *J*=7.8 Hz, 1H), 4.63–4.57 (m, 2H), 4.44 (dd, *J*=11.7 Hz, 6.0 Hz, 1H), 3.88–3.80 (m, 1H), 3.17–3.11 (m, 1H), 2.67 (t, *J*=9.6 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.97, 154.84, 133.28, 129.79, 129.53, 128.48, 126.21 (dd, J_{C-F}=175.5 Hz, 152.3 Hz), 80.71, 63.19, 55.78 (t, J_{C-F}=13.7 Hz), 45.13 (t, J_{C-F}= 16.5 Hz, 12.8 Hz), 29.10, 28.25; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.54 (dm, *J*=234.9 Hz), −115.87 (dm, *J*=234.6 Hz); IR (KBr) ν_{max} 3368, 1729, 1696, 1523, 1283, 709 cm^{-1}; MS (ESI) *m/z* 391 (M^++NH_4). Anal. Calcd for $C_{17}H_{21}O_4NSF_2$: C, 54.68; H, 5.67; N, 3.75. Found: C, 54.85; H, 5.81; N, 3.63.

*Compound **12b***: it was prepared using the same condition as described for compound **12a**; white solid, mp 116–118 °C; $[\alpha]_D^{26}$ +41.9 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.60–7.55 (m, 1H), 7.47–7.41 (m, 2H), 4.97 (d, *J*=8.7 Hz, 1H), 4.67–4.60 (m, 2H), 4.51–4.45 (m, 2H), 4.06–3.92 (m, 1H), 3.08 (t, *J*=10.2 Hz, 1H), 2.77 (t, *J*=10.2 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.92, 154.81, 133.26, 129.76, 129.55, 128.44, 124.65 (dd, J_{C-F}=196.5 Hz, 189.3 Hz), 80.76, 62.42 (d, J_{C-F}=8.0 Hz), 56.65 (t, J_{C-F}=16.4 Hz), 44.10 (t, J_{C-F}=17.1 Hz), 29.14 (d, J_{C-F}=4.8 Hz), 28.24; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.21 (dm, *J*= 231.2 Hz), −125.85 (dm, *J*=231.0 Hz); IR (KBr) ν_{max} 3369, 1730, 1695, 1529, 708 cm^{-1}; MS (ESI) *m/z* 396 (M^++Na), 391 (M^++NH_4). Anal. Calcd for $C_{17}H_{21}O_4NSF_2$: C, 54.68; H, 5.67; N, 3.75. Found: C, 54.66; H, 5.56; N, 3.59.

3.1.10. Benzoic acid 4-amino-3,3-difluoro-tetrahydro-thiophen-2-ylmethyl ester (13a). Trifluoroacetic acid (4 mL) was added in one portion to a solution of compound **12a** (0.373 g, 1.23 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred at room temperature for 15 min. Volatiles were evaporated and the residue was dissolved in ether and washed with $NaHCO_3$. The aqueous layer was extracted with ether. The combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1) to give compound **13a** (0.322 g, 95.6% yield).

*Compound **13a***: clear oil, $[\alpha]_D^{20}$ −102.5 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.60–7.55 (m, 1H), 7.45 (t, *J*=7.8 Hz, 2H), 4.64–4.58 (m, 1H), 4.48–4.42 (m, 1H), 4.00–3.88 (m, 1H), 3.67–3.65 (m, 1H), 3.12 (dd, *J*=11.4 Hz, 6.3 Hz, 1H), 2.67–2.61 (m, 1H), 1.55 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.97, 133.24, 129.71, 129.65, 128.46, 127.34 (t, J_{C-F}=193.7 Hz), 63.10 (dd, J_{C-F}=5.7 Hz, 2.4 Hz), 57.89 (dd, J_{C-F}=21.3 Hz, 17.9 Hz), 45.11 (dd, J_{C-F}=20.3 Hz, 16.5 Hz), 31.27 (t, J_{C-F}=2.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −114.08 (dm, *J*=233.8 Hz), −116.77 (dm, *J*=233.5 Hz); IR (KBr) ν_{max} 3394, 1720, 1273, 713 cm^{-1}; MS (ESI) *m/z* 274 (M^++H), 291 (M^++NH_4).

*Compound **13b***: it was prepared using the same condition as described for compound **13a**; clear oil, $[\alpha]_D^{24}$ +14.7 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.59–7.54 (m, 1H), 7.46–7.41 (m, 2H), 4.70–4.63 (m, 1H), 4.52–4.46 (m, 1H), 3.99–3.90 (m, 1H), 3.62 (br, 1H), 2.99 (t, *J*=9.9 Hz, 1H), 2.72 (t, *J*=10.5 Hz, 1H), 1.55 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.88, 133.12, 129.64, 129.58, 128.34, 125.13 (t, J_{C-F}=188.0 Hz), 62.80 (d, J_{C-F}=7.4 Hz), 58.96 (t, J_{C-F}=18.8 Hz), 44.77 (t, J_{C-F}= 18.0 Hz), 30.99 (t, J_{C-F}=4.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.09 (dm, *J*=222.5 Hz), −129.67 (dm, *J*= 219.1 Hz); IR (thin film) ν_{max} 3394, 1720, 1452, 1278, 1115 cm^{-1}; MS (ESI) *m/z* 274 (M^++H).

3.1.11. Benzoic acid 4-[3-(3-ethoxy-acryloyl)-ureido]-3,3-difluoro-tetrahydro-thiophen-2-ylmethyl ester (14a). To a solution of compound **13a** (0.060 g, 0.22 mmol) in DMF (3 mL) at −25 °C, a solution of 3-ethoxy-2-propenoyl isocyanate (0.059 g, 0.42 mmol) in benzene (1.6 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 (petroleum ether/ethyl acetate= 3:1) to give compound **14a** (0.125 g, 82.4% yield).

*Compound **14a***: white solid, mp 146–148 °C; $[\alpha]_D^{26}$ −76.4 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, *J*=8.7 Hz, 1H), 9.13 (s, 1H), 8.06 (d, *J*=8.1 Hz, 2H), 7.68 (d, *J*=11.7 Hz, 1H), 7.58 (t, *J*=7.8 Hz, 1H), 7.45 (t, *J*=7.2 Hz, 2H), 5.28 (d, *J*=12.0 Hz, 1H), 4.93–4.88 (m, 1H), 4.64 (dd, *J*=11.7 Hz, 6.3 Hz, 1H), 4.45 (dd, *J*= 11.7 Hz, 6.0 Hz, 1H), 3.95–3.87 (m, 3H), 3.20 (dd, *J*=10.5 Hz, 6.9 Hz, 1H), 2.80 (t, *J*=8.4 Hz, 1H), 1.33 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.29, 165.93, 163.64, 155.08, 133.32, 129.78, 129.49, 128.50, 126.39 (dd, J_{C-F}=195.7 Hz, 192.4 Hz), 97.55, 67.75, 62.92 (d, J_{C-F}=8.0 Hz), 55.09 (dd, J_{C-F}=22.3 Hz, 16.1 Hz), 45.28 (dd, J_{C-F}=20.5 Hz, 16.1 Hz), 29.35 (t, J_{C-F}= 2.6 Hz), 14.43; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.34 (dm, *J*=234.9 Hz), −115.17 (dm, *J*=234.6 Hz); IR (KBr) ν_{max} 3242, 1738, 1706, 1677, 1541 cm^{-1}; MS (ESI) *m/z* 415 (M^++H), 437 (M^++Na).

*Compound **14b***: it was prepared using the same condition as described for compound **14a**; white solid, mp 150–153 °C; $[\alpha]_D^{27}$ −13.1 (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.32 (d, *J*=8.7 Hz, 1H), 9.23 (s, 1H), 8.05–8.02 (m, 2H), 7.67 (d, *J*=12.3 Hz, 1H), 7.60–7.54 (m, 1H), 7.47–7.41 (m, 2H), 5.30 (d, *J*=12.3 Hz, 1H), 4.93–4.81 (m, 1H), 4.65 (dd, *J*=11.4 Hz, 7.8 Hz, 1H), 4.55–4.49 (m, 1H), 4.08–3.95 (m, 3H), 3.11 (dd, *J*=10.2 Hz, 6.9 Hz, 1H), 2.91 (t, *J*=10.8 Hz, 1H), 1.35 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.18, 165.90, 163.64, 154.94, 133.23, 129.73, 129.51, 128.39, 124.75 (t, J_{C-F}= 195.5 Hz), 97.63, 67.97, 62.44 (d, J_{C-F}=7.9 Hz), 55.61 (t,

J_{C-F}=15.6 Hz), 44.35 (t, J_{C-F}=17.6 Hz), 29.14 (d, J_{C-F}=4.8 Hz), 14.47; ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.82 (dm, J=231.5 Hz), −124.50 (dm, J=231.5 Hz); IR (KBr) ν_{max} 3248, 1697, 1683, 1620, 1270, 715 cm^{-1}; MS (ESI) m/z 415 (M^++H), 437 (M^++Na). Anal. Calcd for $C_{18}H_{20}O_5N_2SF_2$: C, 52.17; H, 4.86; N, 6.76. Found: C, 52.73; H, 4.79; N, 6.40.

3.1.12. 1-(4,4-Difluoro-5-hydroxymethyl-tetrahydro-thiophen-3-yl)-1*H*-pyrimidine-2,4-dione (1a). A solution of compound **14a** (0.125 g, 0.30 mmol) in dioxane (2 mL) and 2 N sulfuric acid (5 mL) was refluxed for 3 h. The mixture was cooled to room temperature and neutralized by diluted aq NaOH. The mixture was extracted by ethyl acetate. The organic layers were dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was dissolved in saturated solution of ammonia in methanol (8 mL) and stirred overnight at room temperature. The solvent was removed and the residue was purified by silica gel column chromatography (dichloromethane/methanol=35:1) to give compound **1a** (0.063 g, 79.0% yield, two steps).

*Compound **1a***: white solid, mp 86–88 °C; $[\alpha]_D^{26}$ −48.3 (*c* 0.4, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (d, J=8.1 Hz, 1H), 5.63 (d, J=8.1 Hz, 1H), 5.59–5.49 (m, 1H), 3.70–3.68 (m, 2H), 3.58–3.48 (m, 1H), 3.21–3.02 (m, 3H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 165.92, 152.99, 144.18 (d, J_{C-F}=3.4 Hz), 127.96 (dd, J_{C-F}=157.0 Hz, 152.4 Hz), 103.39, 62.28 (t, J_{C-F}=3.2 Hz), 59.27 (dd, J_{C-F}=17.4 Hz, 11.6 Hz), 50.71 (dd, J_{C-F}=14.9 Hz, 12.6 Hz), 26.37 (d, J_{C-F}=4.1 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −106.14 (dm, J=232.9 Hz), −116.41 (dm, J=230.7 Hz); IR (KBr) ν_{max} 3384, 1730, 1386, 1095 cm^{-1}; MS (ESI) m/z 265 (M^++H), 282 (M^++NH_4), 287 (M^++Na).

*Compound **1b***: it was prepared using the same condition as described for compound **1a**; white solid, mp 206–214 °C; $[\alpha]_D^{28}$ +88.4 (*c* 0.2, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.80 (dd, J=8.1 Hz, 2.7 Hz, 1H), 5.74 (d, J=8.4 Hz, 1H), 5.70–5.58 (m, 1H), 4.05–3.99 (m, 1H), 3.92–3.87 (m, 1H), 3.84–3.68 (m, 1H), 3.43–3.36 (m, 1H), 3.14–3.08 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 165.87, 152.97, 144.04 (d, J_{C-F}=4.4 Hz), 126.79 (dd, J_{C-F}=195.3 Hz, 191.1 Hz), 103.29, 61.88 (d, J_{C-F}=7.6 Hz), 59.56 (dd, J_{C-F}=20.3 Hz, 14.7 Hz), 49.23 (t, J_{C-F}=17.2 Hz), 26.78 (t, J_{C-F}=5.4 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −109.63 (dm, J=230.4 Hz), −125.00 (dm, J=229.0 Hz); IR (KBr) ν_{max} 3386, 3172, 1718, 1667, 1383 cm^{-1}; MS (ESI) m/z 265 (M^++H), 287 (M^++Na).

3.1.13. 4-Amino-1-(4,4-difluoro-5-hydroxymethyl-tetrahydro-thiophen-3-yl)-1*H*-pyrimidin-2-one (1d). To a solution of compound **1b** (0.020 g, 0.076 mmol) in pyridine (2 mL), DMAP (0.002 g, 0.016 mmol) and Ac_2O (0.20 mL, 1.59 mmol) were added. 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 1 N HCl, saturated aq $NaHCO_3$, brine, dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was dissolved in CH_3CN (2 mL) at 0 °C. After that, TPSCl (0.042 g, 0.14 mmol), DMAP (0.017 g, 0.14 mmol), and Et_3N (0.019 g, 0.14 mmol) were added. Then, the reaction mixture was warmed to room temperature and stirred for 4 h. After that concd $NH_3\cdot H_2O$ (28%, 1 mL) was added and the whole reaction mixture kept stirring overnight. Then, the solvent was removed and the residue was purified by silica gel column chromatography (dichloromethane/methanol=10:1) to give compound **1d** (0.010 g, 50.2% yield, three steps).

*Compound **1d***: white solid, mp 234–238 °C; $[\alpha]_D^{27}$ +90.1 (*c* 0.6, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.66 (dd, J=7.8 Hz, 2.4 Hz, 1H), 5.82 (d, J=7.5 Hz, 1H), 5.79–5.62 (m, 1H), 3.91 (dd, J=11.4 Hz, 6.3 Hz, 1H), 3.80–3.75 (m, 1H), 3.72–3.69 (m, 1H), 3.62–3.50 (m, 1H), 3.00–2.94 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 167.64, 158.81, 144.50 (d, J_{C-F}=4.9 Hz), 126.77 (dd, J_{C-F}=195.4 Hz, 190.8 Hz), 96.74, 64.62, 61.95 (d, J_{C-F}=7.9 Hz), 60.02 (dd, J_{C-F}=20.1 Hz, 14.6 Hz), 27.24 (d, J_{C-F}=5.4 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −109.49 (dm, J=229.3 Hz), −124.91 (dm, J=229.3 Hz); IR (KBr) ν_{max} 3398, 1663, 1181, 1016 cm^{-1}; MS (ESI) m/z 264 (M^++H).

*Compound **1c***: it was prepared using the same condition as described for compound **1d**; white solid, mp 210–214 °C; $[\alpha]_D^{29}$ −27.6 (*c* 0.2, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (dd, J=7.5 Hz, 2.1 Hz, 1H), 5.85 (d, J=7.5 Hz, 1H), 5.79–5.64 (m, 1H), 3.75–3.66 (m, 2H), 3.61–3.50 (m, 1H), 3.14–3.02 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 167.66, 158.85, 144.67 (d, J_{C-F}=4.2 Hz), 128.04 (dd, J_{C-F}=195.9 Hz, 190.6 Hz), 96.83, 62.55 (t, J_{C-F}=4.0 Hz), 59.78 (dd, J_{C-F}=21.7 Hz, 14.6 Hz), 50.90 (dd, J_{C-F}=18.6 Hz, 15.5 Hz), 26.89 (d, J_{C-F}=5.3 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −106.29 (dm, J=231.8 Hz), −116.35 (dm, J=230.1 Hz); IR (KBr) ν_{max} 3419, 1659, 1499, 1395 cm^{-1}; MS (ESI) m/z 264 (M^++H).

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14. Crystal data have been deposited at the Cambridge Crystallographic Data Center with reference numbers: compound **1a**, CCDC 628402; compound **1b**, CCDC 628403.