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Synthesis of 2′,3′-dideoxy-2′-monofluoromethyl azanucleosides

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Abstract—(2*S*,4*S*)-Methyl-*N*-*tert*-butoxycarbonyl-4-monofluoromethylpyroglutamate **6** was synthesized via a key dehydrofluorination followed by hydrogenation. Compound **6** was converted to (5*S*,3*S*)-*N*-benzyloxycarbonyl-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethyl-2-pyrrolidone **12** over four steps in 62% yield, which was used as a precursor for the synthesis of 2′,3′-dideoxy-2′-monofluoromethyl azanucleosides **17**–**18**.

1. Introduction

In the last two decades, nucleosides and nucleotides, known to be DNA and RNA subunits, have become an important subject of research in the field of pharmaceutical science. Modification of the ribose moiety and base moiety of nucleosides exhibits two important ways to new high bioactive nucleoside analogues.[1] Recently, many modified sugar nucleosides,[2] including thionucleosides,[3] carbocyclic nucleosides,[4] and azanucleosides[5] were synthesized and studied. In connection with special properties of fluorine, fluorinated nucleosides have received a great interest for their biological and medical applications.[6] In fluorinated sugar nucleosides, fluorine stabilizes the glycosidic bond toward hydrolysis by alteration of the conformation of the sugar moiety.[7] Some highly bioactive fluorinated nucleosides have been synthesized and used in cancer and herpes therapies, for example, 2′-deoxy-2′,2′-difluorocytidine (Gemcitabine) has been approved as a drug for solid tumor treatment.[8] Interestingly, sugar moieties of several high bioactive fluorinated nucleosides FMAU,[9] FLT,[10] FIAC,[9b] F-ddC,[11] SFDC,[12] and DFDT[13] contain a fluorine atom, which in some degree, reveals the special influences of monofluoro groups on the biological activities of nucleosides (Fig. 1). Azanucleosides, in which the oxygen atom of pyranose or furanose ring is replaced by nitrogen atom, represent an important class of modified nucleosides. The synthesis and biological activities of azanucleosides were summarized by Yokoyama and Momotake.[5] However, to the best of our knowledge, few fluorinated azanucleosides have been synthesized[14] and up to date there is no corresponding report on the monofluorinated azanucleosides. Considering all these aspects and in connection with our studies on fluorinated sugar nucleosides, we decided to synthesize monofluorinated azanucleosides: 2′,3′-dideoxy-2′-monofluoromethyl azanucleosides and investigate their biological activities.

2. Results and discussion

During the synthesis of 2′,3′-dideoxy-2′-difluoromethyl azanucleosides,[14b] we accidentally found that the dehydrofluorination reaction occurred when the amino group of 5-*tert*-butyldimethylsilyloxymethyl-3-difluoromethyl-pyrrolidin-2-one **1** was protected with *tert*-butoxycarbonyl group (Boc) (Scheme 1). The dehydrofluorinated compound **2** was obtained in 25% yield. The dehydrofluorination was induced by the enhancement of acidity of 3-H as a result of the protection of the amino groups with electron-withdrawing group (Boc). In our opinion, compound **2** could be used as a precursor for the preparation of target molecules: 2′,3′-dideoxy-2′-monofluoromethyl azanucleosides.

So, according to our previous reports,[14b,15] the methyl (2*S*)-*N*-*tert*-butoxycarbonyl-4-difluoromethylpyroglutamate **4** were synthesized from the *trans*-4-hydroxy-L-proline **3** in 22% yield over six steps (Scheme 2). Dehydrofluorination of the compound **4** under the

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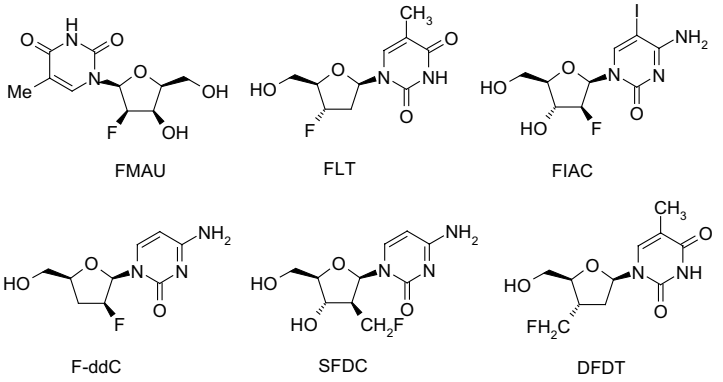
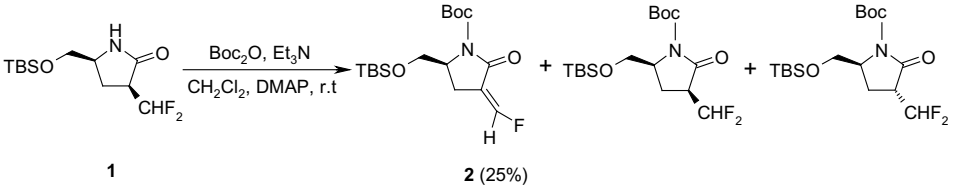
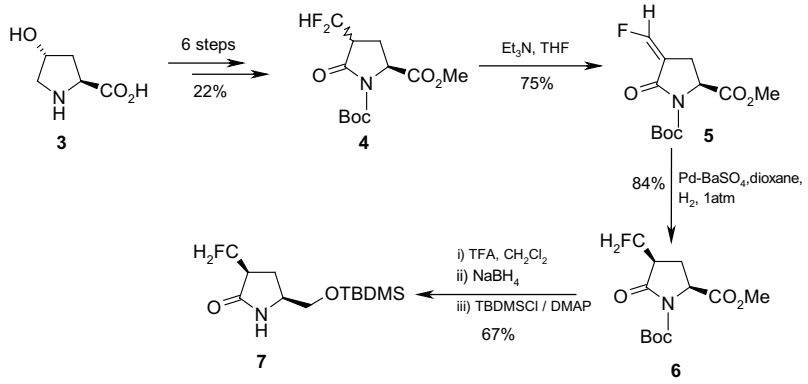


Figure 1. Several high bioactive monofluorinated nucleosides.



Scheme 1.

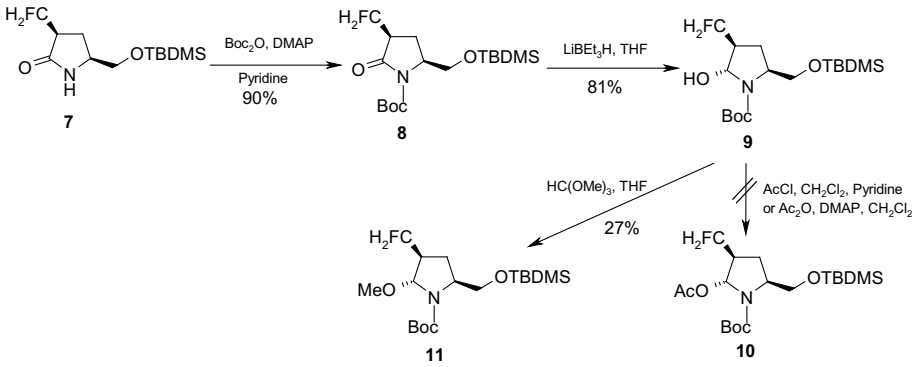


Scheme 2.

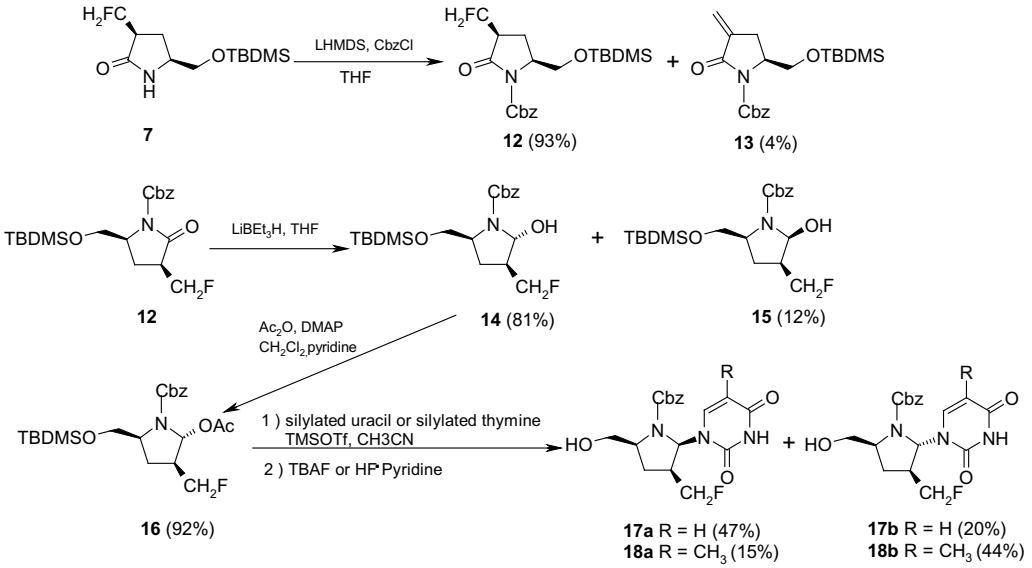
optimized condition (Et_3N, THF) smoothly provided the monofluoro olefin **5** in 75% yield. Hydrogenation of the compound **5** with Pd–$BaSO_4$ in dioxane gave the desired product **6** in 84% yield. Then deprotection of *N*-Boc group of **6** with trifluoroacetic acid in CH_2Cl_2 followed by reduction of the ester with $NaBH_4$, and further protection of the resulting hydroxyl group with TBDMSCl afforded the compound **7** in 67% yield over three steps.

Treatment of the lactam **7** with Boc_2O/pyridine/CH_2Cl_2 under the catalyst of DMAP provided (5*S*,3*S*)-*N*-*tert*-butoxycarbonyl-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethyl-2-pyrrolidione **8** in 90% yield and a few defluorinated byproduct could be detected by TLC (Scheme 3). Then, reduction of the compound **8** with Li-BEt_3H in THF at −78 °C yielded the desired compound **9** in 81% yield. However, acetylation of compound **9** under two reaction conditions (Ac_2O/DMAP/pyridine/CH_2Cl_2 and AcCl/pyridine/CH_2Cl_2) failed to give the desired compound **10**. Protection of hydroxyl group of **9** with methyl group only gave the desired product **11** in 27% yield.[16] In our opinion, the big block of the *tert*-butoxycarbonyl group along with the existence of monofluoromethyl group may be responsible for the failure of the acetylation reaction and the low yield in preparation of the compound **11**.

In view of above failure, the protection of the amino group of compound **7** by benzyloxycarbonyl (Cbz) group instead of Boc group was investigated. We were pleased to find that treatment of **7** with CbzCl and 1.0 equiv LHMDS in THF at −78 °C for 10 min smoothly gave the desired lactam **12** in 93% yield along



Scheme 3.



Scheme 4.

with the dehydrofluorination product **13** in 4% yield (Scheme 4).[17] Similarly, reduction of lactam **12** with $LiBEt_3H$ yielded two diastereoisomers **14** (81% yield) and **15** (12% yield) (**14/15** = 6.8:1.0). The two diastereoisomers could be separated on silica gel chromatography. As we expected, O-acetylation of the major diastereoisomer **14** with Ac_2O/DMAP/pyridine smoothly afforded the desired compound **16** in 92% yield. Finally, coupling of **16** with silylated uracil and thymine under Vorbrüggen's condition (glycosylation reaction)[18] gave the silyl-protected azanucluosides. Deprotection of the silyl protection groups with TBAF or HF·pyridine afforded target molecules **17a**, **17b**, **18a**, and **18b**. The ratio of **17a/17b** and that of **18a/18b** were different and opposite. The absolute configuration of compound **17b** was confirmed by X-ray (Fig. 2).[19]

We investigated the biological activities of the target molecules **17a**, **17b**, and **18b** to the tumor cell U2OS. The experiments were carried out in the effects of **17a**, **17b**, and **18b** on the cell life cycle of U2OS. Mimosine

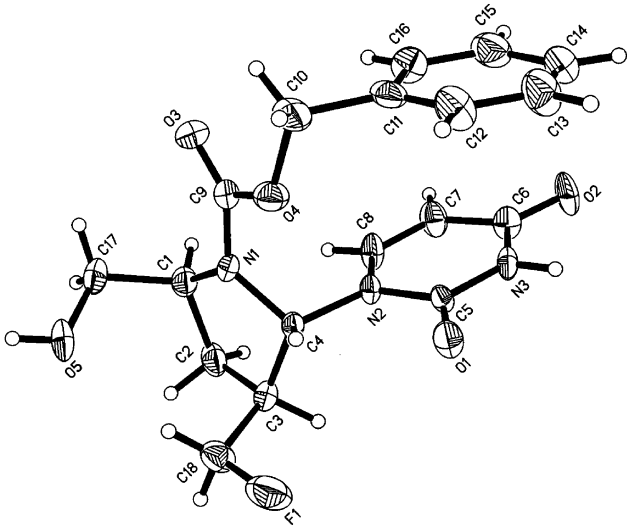


Figure 2. ORTEP drawing of the X-ray crystallographic structure of **17b**.

Table 1. Effects of azanucleosides **17a**, **17b**, and **18b** to the cell cycles of U2OS

Cell cycles	Control	Mimosine	**17a**	**17b**	**18b**
Dip G1 (%)	46.20	76.78	47.18	49.16	49.16
Dip S (%)	43.23	20.93	45.33	41.73	41.73
Dip G2/M (%)	10.58	2.29	7.49	9.11	9.11

(500 μM) was used as S phase block drug in control experiment and the sample concentrations (**17a**, **17b**, and **18b**) were 10 mmol/L. The biological results were summarized in Table 1. As shown in Table 1, the cell cycles had no evident change after azanucleosides **17a**, **17b**, and **18b** were injected. So, none of azanucleosides **17a**, **17b**, and **18b** exhibited a significant biological effect on the tumor cell U2OS.

In summary, we synthesized the novel fluorinated azanucleosides: 2′,3′-dideoxy-2′-monofluoromethyl azanucleosides **17**–**18** from *trans*-4-hydroxy-L-proline via a novel dehydrofluorination found accidentally. Active tests shown that none of the synthesized azanucleosides **17a**, **17b**, and **18b** had significant activity against U2OS. The related modified fluorinated analogues are in intensive synthesis and to be reported soon.

3. Experimental

3.1. (2*S*)-Methyl-*N*-*tert*-butoxycarbonyl-4-[(*Z*)-fluoromethylidene]-pyroglutamate (5)

To a solution of **4** (3.162 g, 10.79 mmol) in CH_3CN (100 mL), Et_3N (7.0 mL) was added dropwise at room temperature. The mixture was stirred overnight at room temperature. Removal of the solvent in vacuo gave a residue and H_2O (50 mL) and CH_2Cl_2 (50 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the resulting residue was purified by silica gel chromatography (hexane/ethyl acetate, 6:1) to give **5** as a white solid (2.082 g, 75%): mp 118–119 °C; $[\alpha]_D^{20}$ −8.6 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dt, J = 78.3, 2.7 Hz, 1H), 4.66 (dd, J = 3.3, 3.6 Hz, 1H), 3.80 (s, 3H), 3.11–3.00 (m, 1H), 2.76 (dq, J = 18.0, 3.0 Hz, 1H), 1.51 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −119.76 to −120.07 (dt, J = 78.5, 3.7 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9, 165.0 (d, J = 19.3 Hz), 154.9 (d, J = 276.1 Hz), 149.0, 114.4 (d, J = 12.7 Hz), 83.7, 55.8, 52.4, 29.4, 27.6, 22.7 (d, J = 1.5 Hz). IR (thin film) 3109, 1790, 1747, 1706, 1687, 1288, 1152 cm^{-1}; MS (ESI) *m*/*z* 296.0 (M^++Na); Anal. Calcd for $C_{12}H_{16}FNO_5$: C, 52.75; H, 5.86; N, 5.13. Found: C, 52.82; H, 5.89; N, 5.10.

3.2. (2*S*,4*S*)-Methyl-*N*-*tert*-butoxycarbonyl-4-monofluoromethylpyroglutamate (6)

To a solution of compound **5** (1.028 g, 3.77 mmol) in dioxane (60 mL), Pd–$BaSO_4$ (250 mg) was added. Then, the mixture was hydrogenated at room temperature for 24 h. Filtration and removal of the solvent gave a residue, which was purified by silica gel chromatography (hexane/ethyl acetate, 8:1 then 6:1) to give **6** as a white solid (871 mg, 84%): mp 83–84 °C; $[\alpha]_D^{20}$ −29.3 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (ddd, J = 26.1, 6.0, 5.7 Hz, 1H), 4.65–4.52 (m, 2H), 3.79 (s, 3H), 3.03–2.85 (m, 1H), 2.64–2.53 (m, 1H), 2.12–2.03 (m, 1H), 1.50 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −228.01 to −228.44 (m, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.4, 171.2 (d, J = 8.8 Hz), 148.9, 83.9, 81.7 (d, J = 170.1 Hz), 57.2, 52.4, 43.7 (d, J = 21.1 Hz), 29.5, 27.7, 23.7 (d, J = 3.2 Hz); IR (thin film) 1776, 1745, 1702, 1339, 1296 cm^{-1}; MS (EI) *m*/*z* 276 (M^++1, <1), 260 (M^+−15, <1), 57 (100); MS (ESI) *m*/*z* 298 (M^++Na); EI-HRMS *m*/*z* 260.09538 (M^+−CH_3, $C_{11}H_{15}FNO_5$ required 260.09343).

3.3. (5*S*,3*S*)-5-*tert*-Butyldimethylsilyloxymethyl-3-monofluoromethylpyrolidin-2-one (7)

TFA (1.0 mL) was added dropwise to a solution of **6** (813 mg, 2.96 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The mixture was then warmed up to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was dissolved in MeOH (30 mL) and the solution was cooled to −78 °C. $NaBH_4$ (145 mg, 3.82 mmol) was added. The mixture was then warmed up to 0 °C and stirred for 1.5 h. The reaction was quenched with concentrated HCl. The mixture was then filtered and concentrated to give a yellowish solid. To a cooled solution of DMAP (26 mg, 0.21 mmol) and imidazole (900 mg, 13.24 mmol) in CH_2Cl_2 (50 mL), a solution of above yellowish solid in DMF (1 mL) was added. Then, a solution of TBDMSCl (2.0 g, 13.27 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After the mixture was stirred overnight at room temperature, it was quenched with saturated aqueous NH_4Cl (10 mL) in cooled ice-bath. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 3:2) to give **7** as a clear oil (516 mg, 67%). $[\alpha]_D^{20}$ +51.4 (*c* 1.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (br, 1H), 4.60 (ddd, J = 92.5, 4.2, 4.2 Hz, 1H), 4.62–4.60 (m, 1H), 3.76–3.68 (m, 1H), 3.62 (dd, J = 3.9, 3.9 Hz, 1H), 3.42 (dd, J = 7.8, 7.8 Hz, 1H), 2.82–2.63 (m, 1H), 2.32 (ddd, J = 15.3, 7.2, 6.0 Hz, 1H), 1.70 (ddd, J = 14.7, 7.5, 3.6 Hz, 1H), 0.85 (s, 9H), 0.02 (2s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −228.52 to −228.96 (m, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.4 (d, J = 7.5 Hz), 82.3 (d, J = 169.7 Hz), 66.7, 53.9, 42.6 (d, J = 21.7 Hz), 25.7, 25.3 (d, J = 3.2 Hz), 18.1 (d, J = 0.5 Hz), −5.6 (d, J = 0.8 Hz); IR (thin film) 3223, 1708, 1464, 1256, 1104 cm^{-1}; MS (EI) *m*/*z* 262 (M^++1, 3), 260 (M^+−1, <1), 246 (M^+−

15, 2), 110 (100); EI-HRMS *m/z* 246.13041 (M^+-CH_3, $C_{11}H_{21}FNO_2Si$ required 246.13256).

3.4. (5*S*,3*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethyl-2-pyrrolidone (8)

To a cooled solution of **7** (178 mg, 0.68 mmol), DMAP (5 mg, 0.04 mmol), and pyridine (0.31 mL) in CH_2Cl_2 (10 mL), Boc_2O (500 mg, 2.29 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was warmed up to room temperature and stirred for 3 h. Then the reaction was quenched with H_2O and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (2×30 mL) and the combined organic phases were washed with diluted aqueous HCl, brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 7:1) to give **8** as a white solid (222 mg, 90%): mp 65–66 °C; $[\alpha]_D^{20}$ −53.2 (*c* 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (ddd, J = 23.3, 5.1, 5.7 Hz, 1H), 4.59 (ddd, J = 22.5, 5.7, 5.4 Hz, 1H), 4.18–4.11 (m, 1H), 3.92 (dd, J = 4.8, 4.8 Hz, 1H), 3.72 (dd, J = 2.4, 2.7 Hz, 1H), 3.01–2.83 (m, 1H), 2.32 (ddd, J = 16.5, 8.9, 2.3 Hz, 1H), 2.09 (ddd, J = 13.7, 5.1, 5.3 Hz, 1H), 1.54 (s, 9H), 0.88 (s, 9H), 0.05 (2s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −226.23 to −226.65 (m, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.3 (d, J = 10.1 Hz), 150.0, 83.1, 83.0 (d, J = 170.2 Hz), 63.4 (d, J = 0.6 Hz), 57.1, 43.9 (d, J = 21.7 Hz), 28.0, 25.8, 22.7 (d, J = 2.5 Hz), 18.3, −5.5 (d, J = 0.8 Hz); IR (thin film) 1765, 1689, 1473, 1369, 836, 779 cm^{-1}; MS (EI) *m/z* 288 ($M^+-C_4H_9O$, 7), 248 (51), 204 (100); MS (ESI) *m/z* 384.2 (M^++Na); ESI-HRMS *m/z* 384.19792 (M^++Na, $C_{17}H_{32}FNO_4SiNa$ required 384.19768).

3.5. *tert*-Butyl (2*R*,3*S*,5*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethyl-2-hydroxypyrrolidine-1-carboxylate (9)

To a solution of **8** (222 mg, 0.62 mmol) in THF (10 mL) at −78 °C was added $LiBEt_3H$ (1.70 mL, 1 M in THF, 1.70 mmol) dropwise. The mixture was stirred at −78 °C for 30 min. The reaction was then quenched with H_2O (3 mL) and warmed up to room temperature. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 20:1, then 15:1) to give **9** as a clear oil (181 mg, 81%). $[\alpha]_D^{20}$ −51.2 (*c* 1.05, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 5.44 (d, J = 12.6 Hz, 1H), 4.61 (dt, J = 46.5, 8.1 Hz, 1H), 4.40 (ddd, J = 47.1, 5.7, 6.0 Hz, 1H), 3.95–3.54 (m, 3H), 2.47–2.30 (m, 1H), 2.23–2.10 (m, 1H), 1.79–1.65 (m, 1H), 1.44 (s, 9H), 0.89 (s, 9H), 0.08, 0.07 (2s, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −221.72 to −222.34 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 153.3 (d., J = 37.0 Hz), 82.6 (d, J = 81.6 Hz), 80.7 (d, J = 5.7 Hz), 79.4, 65.4, 63.6, 57.9, 43.5, 27.7, 27.1, 25.4, 17.9. IR (thin film) 3441, 1700, 1474, 1390, 839 cm^{-1}; MS (ESI) *m/z* 386.2 (M^++Na); Anal. Calcd for $C_{17}H_{34}FNO_4Si$: C, 56.20; H, 9.37; N, 3.86. Found: C, 56.35; H, 9.71; N, 3.70.

3.6. *tert*-Butyl (2*R*,3*S*,5*S*)-2-methoxy-5-*tert*-butyldimethylsilyloxy-3-monofluoromethylpyrrolidine-1-carboxylate (11)

To a cooled mixture of **9** (86 mg, 0.24 mmol) and 4 Å MS (131 mg, powder) in Et_2O (5 mL), $CH(OMe)_3$ (0.06 mL) was added dropwise followed by $BF_3{\cdot}Et_2O$ (10 μL, 1 M in Et_2O, 0.01 mmol). The mixture was then stirred at room temperature for 20 min. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent gave a residue, which was purified by flash chromatography to give **11** as an oil (24 mg, 27%). $[\alpha]_D^{20}$ −59.3 (*c* 0.87, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 5.14 (br, 1H), 4.67–4.29 (m, 2H), 3.97–3.82 (m, 2H), 3.47 (br, 1H), 3.27 (2s, 3H), 2.51–2.34 (m, 1H), 2.15 (br, 1H), 1.74–1.63 (m, 1H), 1.46 (s, 9H), 0.89 (s, 9H), 0.07, 0.05 (2s, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −221.04 to −221.63 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 154.2 (d, J = 32.8 Hz), 88.4 (d, J = 5.0 Hz), 82.3 (d, J = 162.0 Hz), 79.5, 65.6, 64.8, 58.5, 54.6, 43.4, 27.6, 25.3, 17.8, −6.1; IR (thin film) 1705, 1473, 1381, 839 cm^{-1}; MS (ESI) *m/z* 400.2 (M^++Na); ESI-HRMS *m/z* 400.22817 (M^++Na, $C_{18}H_{36}FNO_4SiNa$ required 400.22898).

3.7. (5*S*,3*S*)-*N*-Benzyloxycarbonyl-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethyl-2-pyrrolidone (12) and (5*S*)-*N*-benzyloxycarbonyl-5-*tert*-butyldimethylsilyloxymethyl-3-methylene-2-pyrrolidone (13)

To a solution of **7** (516 mg, 2.00 mmol) in THF (20 mL) at −78 °C was added LHMDS (2.0 mL, 1 M in THF, 2.0 mmol) dropwise. After the mixture was stirred for 10 min, CbzCl (0.45 mL, 3.16 mmol) was added dropwise. The mixture was stirred for further 10 min at −78 °C and quenched with saturated aqueous NH_4Cl (5 mL). The mixture was then warmed up to room temperature and extracted with EtOAc (3×40 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 10:1) to give **13** as a white solid (less polar, 28 mg, 4%) and **12** as a white solid (more polar, 727 mg, 93%). Compound **12**: mp 80–82 °C; $[\alpha]_D^{20}$ −57.2 (*c* 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.32 (m, 5H), 5.34–5.23 (m, 2H), 4.76 (ddd, J = 28.1, 5.3, 5.0 Hz, 1H), 4.61 (ddd, J = 27.2, 5.3, 5.4 Hz, 1H), 4.24–4.17 (m, 1H), 3.90 (dd, J = 4.8, 4.8 Hz, 1H), 3.70 (dd, J = 2.7, 2.4 Hz, 1H), 3.02–2.84 (m, 1H), 2.40–2.32 (m, 1H), 2.17–2.04 (m, 1H), 0.84 (s, 9H), −0.02, −0.03 (2s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −226.31 to −226.72 (m, 1F); IR (thin film) 2955, 1714, 1289, 834 cm^{-1}; MS (ESI) *m/z* 418.2 (M^++Na); Anal. Calcd for $C_{20}H_{30}FNO_4Si$: C, 60.76; H, 7.59; N, 3.54. Found: C, 60.70; H, 7.87; N, 3.40. Compound **13**: mp 41–43 °C; $[\alpha]_D^{20}$ −33.8 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.32 (m, 5H), 6.16 (t,

J = 2.4 Hz, 1H), 5.46 (t, J = 2.1 Hz, 1H), 5.37–5.23 (m, 2H), 4.28–4.22 (m, 1H), 3.77 (dd, J = 4.8, 4.5 Hz, 1H), 3.69–3.66 (dd, J = 2.4, 2.7 Hz, 1H), 2.81–2.77 (m, 2H), 0.81 (s, 9H), −0.04, −0.07 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.2, 152.1, 139.0, 135.4, 128.6, 128.3, 128.1, 119.3, 68.1, 63.7, 55.7, 27.8, 25.7, 18.1, −5.7; IR (thin film) 2956, 2929, 1739, 1700, 1658, 1301, 1014, 838 cm^{-1}; MS (ESI) m/z 376.2 (M^++1); ESI-HRMS m/z 398.17538 (M^++Na, $C_{20}H_{29}NO_7SiNa$ required 398.17581).

3.8. Benzyl (2*R*,3*S*,5*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethyl-2-hydroxypyrrolidine-1-carboxylate (14) and benzyl (2*S*,3*S*,5*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethyl-2-hydroxypyrrolidine-1-carboxylate (15)

To a solution of **12** (727 mg, 1.84 mmol) in THF (25 mL) at −78 °C was added $LiBEt_3H$ (6.0 mL, 1 M in THF, 6.0 mmol) dropwise. The mixture was stirred at −78 °C for 1 h. The reaction was quenched with H_2O (10 mL) and warmed up to room temperature. The mixture was extracted with Et_2O (3 × 40 mL) and the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 5:1) to give **14** (less polar) as a clear oil (589 mg, 81%) and **15** (more polar) as a clear oil (90 mg, 12%). Compound **14**: $[\alpha]_D^{20}$ −48.1 (c 0.76, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.42–7.31 (m, 5H), 5.56 (t, J = 5.4 Hz, 1H), 5.21–5.05 (m, 2H), 4.75–4.34 (m, 3H), 4.02–3.90 (m, 2H), 3.78–3.56 (br, 1H), 2.51–2.42 (m, 1H), 2.27–2.15 (m, 1H), 1.82–1.70 (m, 1H), 0.90 (s, 9H), 0.08, 0.01 (2s, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −221.99 to −222.37 (m, 1F); IR (thin film) 3429, 2956, 1708, 1412, 1101, 838 cm^{-1}; MS (ESI) m/z 380.2 (M^+−OH); MS (MALDI) m/z 420.2 (M^++Na); Anal. Calcd for $C_{20}H_{32}FNO_4Si$: C, 60.45; H, 8.06; N, 3.53. Found: C, 60.87; H, 8.20; N, 3.85. Compound **15**: $[\alpha]_D^{20}$ −47.6 (c 0.47, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.44–7.34 (m, 5H), 5.45–5.07 (m, 4H), 4.61–4.34 (m, 2H), 3.99–3.60 (m, 3H), 2.46–2.36 (m, 2H), 1.79 (br, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −218.77 to −220.47 (m, 1F); IR (thin film) 3426, 2956, 1710, 1409, 1101, 838 cm^{-1}; MS (ESI) m/z 420.1 (M^++Na), 398.3 (M^++1), 380.2 (M^+−OH); Anal. Calcd for $C_{20}H_{32}FNO_4Si$: C, 60.45; H, 8.06; N, 3.53. Found: C, 60.60; H, 8.37; N, 3.42.

3.9. Benzyl (2*R*,3*S*,5*S*)-2-acetyloxy-5-*tert*-butyldimethylsilyloxymethyl-3-monofluoromethylpyrrolidine-1-carboxylate (16)

To a mixture of **14** (589 mg, 1.48 mmol), DMAP (16 mg, 0.13 mmol), pyridine (2.0 mL, 24.56 mmol) in CH_2Cl_2 (25 mL) was added Ac_2O (1.30 mL, 13.89 mmol). After the mixture was stirred overnight at room temperature, the reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with dilute HCl, brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 5:1) to afford **16** as a white solid (597 mg, 92%): mp 74–76 °C; $[\alpha]_D^{20}$ −53.2 (c 0.98, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.39–7.34 (m, 5H), 6.78 (d, J = 5.1 Hz, 1H), 5.14 (br, 2H), 4.55 (dd, J = 4.2, 3.0 Hz, 1H), 4.39 (dd, J = 3.6, 3.6 Hz, 1H), 3.96–3.54 (m, 3H), 2.76–2.65 (m, 1H), 2.27–2.15 (m, 1H), 2.04–1.87 (m, 4H), 0.90 (s, 9H), 0.03 (s, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −223.55 to −223.87 (m, 1F); IR (thin film) 2937, 1736, 1716, 1401, 1213, 1086, 837 cm^{-1}; MS (ESI) m/z 478.2 (M^++K), 462.2 (M^++Na); Anal. Calcd for $C_{22}H_{34}FNO_5Si$: C, 60.14; H, 7.74; N, 3.19. Found: C, 60.27; H, 7.73; N, 2.98.

3.10. Benzyl (2*S*,3*S*,5*S*)-5-hydroxymethyl-2-[2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl]-3-(monofluoromethyl)-pyrrolidine-1-carboxylate (17a) and benzyl (2*R*,3*S*,5*S*)-5-hydroxymethyl-2-[2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl]-3-(monofluoromethyl)-pyrrolidine-1-carboxylate (17b)

Typical procedure: To a stirred solution of **16** (128 mg, 0.29 mmol) and uracil (96 mg, 0.86 mmol) in anhydrous acetonitrile (30 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (0.44 mL, 1.33 mmol). The reaction mixture was stirred under reflux for 30 min. After cooled to 0 °C, TMSOTf (0.15 mL, 0.72 mmol) was added dropwise and the solution was stirred at room temperature for further 40 min. The reaction was quenched with cold saturated aqueous $NaHCO_3$ (6 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 3:2) to give two compounds, the less polar compound (75 mg, white foam) and more polar compound (34 mg, white foam). A stirred solution of above less polar compound (42 mg) in THF (4.5 mL) was treated with 1.0 M solution of TBAF (0.11 mL, 0.11 mmol) at 0 °C. After stirred at room temperature for 8.5 h, the reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 1:3) to give **17a** as a white foam (29 mg, 47% from **16**). The more polar compound (34 mg) was also treated with TBAF under the same conditions to give **17b** as a white foam (22 mg, 20% from **16**). Deprotection of the silyl protection groups was also conveniently achieved using HF·pyridine in CH_2Cl_2. Compound **17a**: $[\alpha]_D^{20}$ −5.3 (c 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.46 (br, 1H), 7.29 (br, 5H), 6.44 (d, J = 7.2 Hz, 1H), 5.56 (d, J = 7.8 Hz, 1H), 5.21–5.17 (m, 1H), 5.10–4.97 (br, 1H), 4.56 (ddd, J = 25.0, 4.2, 4.2 Hz, 1H), 4.47–4.34 (m, 2H), 3.92 (t, J = 9.0 Hz, 1H), 3.66 (d, J = 11.4 Hz, 1H), 2.93–2.74 (m, 1H), 2.33–2.18 (m, 1H), 2.10–2.00 (m, 1H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −228.87 to −229.45 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 166.3, 156.5, 152.9, 144.0, 137.4, 129.6, 129.3, 128.9, 101.9, 82.1 (d, J = 168.1 Hz), 72.2, 68.7, 61.8, 61.0, 43.5 (d,

$J = 19.5$ Hz), 27.8; IR (thin film) 3448, 3199, 1685, 1466, 1400, 1275 cm^{-1}; MS (EI) *m/z* 266 (M^+−uracil, 14), 222 (16), 91 (100); MALDI-HRMS *m/z* 400.1319 (M^++Na, $C_{18}H_{20}N_3O_5FNa$ required 400.1279). Compound **17b**: $[\alpha]_D^{20}$ −25.2 (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, MeOH-d_4) δ 7.54–7.23 (m, 6H), 5.86 (br, 1H), 5.42–5.30 (m, 1H), 5.11 (br, 1H), 4.84–4.80 (m, 1H), 4.62–4.59 (m, 1H), 4.47–4.44 (m, 1H), 4.22 (br, 1H), 3.99–3.79 (m, 1H), 3.67–3.63 (m, 1H), 2.73 (br, 1H), 2.48–2.37 (m, 1H), 1.88–1.75 (m, 1H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −222.53 to −222.65 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 166.0, 155.2, 151.9, 143.5, 137.2, 129.7, 129.6, 129.5, 102.9, 84.6 (d, $J = 170.3$ Hz), 75.8, 68.7, 62.8, 61.8, 46.1 (d, $J = 18.5$ Hz), 28.5; IR (thin film) 3510, 3152, 3033, 1677, 1627, 1461, 1402, 1262, 699 cm^{-1}; MS (EI) *m/z* 346 (M^+−CH_2OH, <1), 266 (M^+−uracil, 17), 222 (16), 91 (100); MALDI-HRMS *m/z* 400.1301 (M^++Na, $C_{18}H_{20}N_3O_5FNa$ required 400.1279).

3.11. Benzyl (2*S*,3*S*,5*S*)-5-hydroxymethyl-2-[5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl]-3-(monofluoromethyl)-pyrrolidine-1-carboxylate (18a) and benzyl (2*R*,3*S*,5*S*)-5-hydroxymethyl-2-[5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl]-3-(monofluoromethyl)-pyrrolidine-1-carboxylate (18b)

Compounds **18a** (27 mg, 15%) and **18b** (78 mg, 44%) were prepared as white foams from compound **16** (119 mg, 0.45 mmol) and thymine (178 mg, 1.41 mmol) using the same conditions as described for compounds **17a** and **17b**. Compound **18a**: $[\alpha]_D^{20}$ +9.4 (*c* 0.72, $CHCl_3$); ^1H NMR (300 MHz, MeOH-d_4) δ 8.41 (br, 1H), 7.28 (br, 5H), 6.43 (d, $J = 5.1$ Hz, 1H), 5.23–4.99 (m, 2H), 4.60–4.33 (m, 3H), 3.90 (t, $J = 9.0$ Hz, 1H), 3.66 (d, $J = 11.7$ Hz, 1H), 2.93–2.74 (m, 1H), 2.34–2.22 (m, 1H), 2.10–2.01 (m, 1H), 1.79 (s, 3H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −229.95 to −230.72 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 166.5, 156.3, 153.0, 139.9, 137.5, 129.6, 129.3, 128.8, 110.7, 82.1 (d, $J = 168.1$ Hz), 71.8, 68.6, 61.8, 60.8, 43.5 (d, $J = 19.6$ Hz), 27.7, 12.4; IR (thin film) 3448, 3192, 3064, 1685, 1472, 1404, 1273 cm^{-1}; MS (EI) *m/z* 391 (M^+, <1), 266 (M^+−thymine, 16), 222 (18), 91 (100); MALDI-HRMS *m/z* 414.1468 (M^++Na, $C_{19}H_{22}N_3O_5FNa$ required 414.1436). Compound **18b**: $[\alpha]_D^{20}$ −24.7 (*c* 0.62, $CHCl_3$); ^1H NMR (300 MHz, MeOH-d_4) δ 7.27 (m, 5H), 7.07 (br, 1H), 5.83 (br, 1H), 5.35–5.31 (d, $J = 11.4$ Hz, 1H), 4.78–4.75 (m, 1H), 4.60–4.55 (m, 1H), 4.44–4.43 (m, 1H), 4.24 (br, 1H), 3.99–3.95 (m, 1H), 3.79–3.63 (m, 1H), 2.72 (br, 1H), 2.47–2.37 (m, 1H), 1.86–1.64 (m, 4H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −220.83 to −223.35 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ166.2, 155.2, 152.0, 139.2, 137.1, 129.7, 129.6, 129.5, 111.8, 84.5 (d, $J = 169.7$ Hz), 76.7, 75.5, 68.6, 62.7, 46.0 (d, $J = 18.6$ Hz), 28.6, 12.4; IR (thin film) 3440, 3188, 3038, 1689, 1470, 1404 cm^{-1}; MS (EI) *m/z* 391 (M^+, <1), 266 (M^+−thymine, 19), 222 (21), 91 (100); MALDI-HRMS *m/z* 414.1474 (M^++Na, $C_{19}H_{22}N_3O_5FNa$ required 414.1436).

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