Supporting Information

Stereoselective Reformatskii-Claisen Rearrangement: Synthesis of 2′,3′-Dideoxy-6′,6′-difluoro-2′-thionucleosides

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(2S, $E$)-1,5-Bis(benzyloxy)pent-3-en-2-ol (7) To a suspension of NaH (60% in oil, 1.79 g, 44.75 mmol) and Bu$_4$NI (1.65 g, 4.47 mmol) in anhydrous THF (200 mL) was added a solution of compound 6 (12.41 g, 59.66 mmol) in anhydrous THF (70 mL) slowly at 0 °C. After the mixture was stirred for 20 min at the same temperature, it was allowed to warm to room temperature and stirred for 60 min. Then the resulting reaction mixture was cooled to 0 °C, treated with BnBr (5.3 mL, 44.72 mmol) in anhydrous THF (90 mL) and stirred at room temperature. Water was added when the side product (2S,$E$)-1,2,5-tri-O-benzyl-3-penten-1,2,3-triol appeared. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 5 : 1) to give compound 7 (10.4 g, 59% yield) as a clear oil and 4.78g of recovered compound 6. The recovered compound 6 repeated the reaction procedure as above and afforded another 3.95g of compound 7 (22% yield).

The overall yield of the reaction was 81%. $\left[\alpha\right]^{26}_D = +22.0^\circ$ (c 1.50, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36-7.25 (m, 10H), 5.98-5.89 (m, 1H), 5.80-5.65 (m, 1H), 4.70-4.41 (m, 4H), 4.43-3.97 (m, 1H), 3.63-3.36 (m, 2H), 2.29 (s, 1H); IR (KBr) $\text{max}$ 3440, 3029, 2856, 1496, 1071, 696 cm$^{-1}$; MS (ESI) $m/z$ 321.2 (M$^++$Na); Anal. Calcd for C$_{19}$H$_{22}$O$_3$: C, 76.48; H, 7.43 Found: C, 76.16; H, 7.51. The chiral HPLC analytical data: Chiralpak IC column, detected at $\lambda$=220nm, eluent: n-hexane/i-PrOH (80:20), 0.7ml/ min, $t_R$ (minor) =12.6 min, $t_R$ (major)=13.3 min, 99% ee.
(R,E)-methyl 6-(benzyloxy)-3-(benzyloxymethyl)-2,2-
difluorohex-4-enoate (10) To a solution of chlorodifluoroacetic acid (7.36 g, 56.39 mmol) and oxalyl chloride (7.16 g, 56.38 mmol) in anhydrous CH₂Cl₂ (70 mL) were added catalytic DMF at 0 °C. After the reaction mixture was stirred for 60 min at room temperature, the reaction mixture was cooled to −5 °C, and a mixture of compound 7 (5.60 g, 18.79 mmol), NEt₃ (13 mL, 92.52 mmol) in anhydrous CH₂Cl₂ (50 mL) was added dropwise. The reaction mixture was warmed to ambient temperature and was stirred for 1 h. Then the reaction was quenched with water. The resultant mixture was extracted with Et₂O. The combined organic layer was washed with water and brine. After the resultant solution was dried over anhydrous Na₂SO₄ and filtered, the solvent was removed in vacuo. Flash chromatography (petroleum ether: ethyl acetate = 10:1) afforded the crude product 8 (7.61 g, 18.51 mmol) as a clear yellow oil. Then a mixture of 8 (7.61 g, 18.51 mmol), chlorotrimethyl silane (4.7 mL, 37.08 mmol), dry pyridine (3.0 mL, 37.11 mmol) and freshly activated zinc dust (12.03 g, 185.07 mmol) in dry acetonitrile (70 mL) was heated to 120 °C over a period of 20 min and stirred for 5 h at the same temperature. After the reaction mixture cooled to room temperature, the mixture was filtered and the residue was washed by MeOH (20 mL × 2). To the combined organic solution, SOCl₂ (5 mL) was added slowly and then stirred for 1 h. Water was added to quench the reaction and the solvent was partially removed in vacuo. The resultant mixture was extracted with Et₂O. The combined organic layer was washed with brine, and dried over anhydrous
Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (petroleum ether: ethyl ether = 40:1) to give compound 10 (3.06 g, 41% yield for three steps, $ee$ 90%) as a clear oil: $[\alpha]^{26}_D = -15.7^\circ$ (c 2.00, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.37-7.26 (m, 10H), 5.87 (dt, $J = 15.6$, 5.7 Hz, 1H), 5.65 (dd, $J = 15.6$, 9.0 Hz, 1H), 4.50 (s, 2H), 4.44 (s, 1H), 4.03 (d, $J = 5.7$ Hz, 2H), 3.64 (s, 3H), 3.69-3.54 (m, 2H), 3.40-3.22 (m, 1H); $^{13}$C NMR (100.7 MHz, CDCl$_3$) $\delta$164.3, 138.1, 137.5, 133.8, 131.2, 128.4 (d, $J = 4.0$ Hz), 127.8 (d, $J = 4.3$ Hz), 127.7, 123.8 (t, $J = 3.4$ Hz), 115.4 (dd, $J = 255.9$, 251.1 Hz), 73.5, 72.1, 70.0, 68.1 (dd, $J = 5.3$, 3.1 Hz), 53.0, 47.6 (t, $J = 22.2$ Hz); $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$-107.4 (dd, $J = 257.7$, 9.0 Hz, 1F), -116.2 (dd, $J = 257.7$, 20.3 Hz, 1F); IR (KBr) max 3031, 2858, 1766, 1496, 1454, 1362, 1095, 697 cm$^{-1}$; MS (ESI) $m/z$ 408.3 (M$^+$+NH$_4$), 413.2 (M$^+$+Na); HRMS Calcd for C$_{22}$H$_{24}$O$_4$F$_2$Na$^+$ (M$^+$ + Na): 413.1536. Found: 413.1535. The chiral HPLC analytical data: Chiralpak IC column, detected at $\lambda$=214nm, eluent: $n$-hexane/i-PrOH (95:5), 0.4ml/min, $t_R$ (major) =18.0 min, $t_R$ (minor)=19.3 min, 90% $ee$.

(R)-3-(benzyloxymethyl)-2,2-difluorobutane-1,4-diol (11) A solution of compound 10 (1.89 g, 4.85 mmol) in CH$_2$Cl$_2$ (50 mL) was ozonized at –78 $^\circ$C for 30 min. Then a suspension of NaBH$_4$ (850 mg, 22.36 mmol) in C$_2$H$_5$OH (15 mL) was added to the reaction mixture. The reaction mixture was warmed to room temperature and was stirred for 30 min. Then the reaction was quenched with water. The resultant mixture was extracted with EtOAc. The combined organic layers were
washed with brine, dried over anhydrous Na$_2$SO$_4$, 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 compound 11 (1.09 g, 92 % yield) as a clear oil: [α]$^27_D$ = -1.9° (c 1.10, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$), δ 7.39-7.29 (m, 5H), 4.53 (s, 2H), 3.93-3.82 (m, 2H), 3.81-3.45 (m, 4H), 3.03 (s, 2H), 2.57-2.40 (m, 1H) ; $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ137.2, 128.7, 128.2, 127.9, 123.2 (t, $J$ = 246.3 Hz), 73.8, 66.7 (t, $J$ = 5.7 Hz), 63.5 (t, $J$ = 33.2 Hz), 59.3 (t, $J$ = 5.8 Hz), 46.1 (t, $J$ = 22.5 Hz) ; $^{19}$F NMR (282 MHz, CDCl$_3$) δ-108.4 (ddd, $J$ = 257.7, 27.1, 14.4 Hz, 1F), -109.4 (ddd, $J$ = 257.2, 27.1, 15.2 Hz, 1F); IR ( KBr ) $\text{max}$ 3391, 2879, 1454, 1367, 1072, 906, 698 cm$^{-1}$; MS (ESI) $m/z$ 269.0 (M$^+$+Na); HRMS Calcd for C$_{12}$H$_{16}$O$_3$F$_2$Na$^+$ (M$^+$+Na): 269.0960. Found: 269.0959.

(R)-4-Benzoxymethyl-3,3-difluoro-tetrahydrothiophene (12). To a compound 11 (1.07 g, 4.35 mmol) in anhydrous CH$_2$Cl$_2$ (15 mL), and pyridine (5 mL) was added MsCl (1.35 mL, 17.45 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 1N HCl, saturated NaHCO$_3$ solution, water and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent was removed in vacuo. The residue was dissolved in DMF (40 mL) and Na$_2$S·9H$_2$O (2.01 g, 8.38 mmol) was added. Then the reaction mixture was heated to 90 °C. After stirring for 30 min, the reaction mixture was cooled to room temperature and water was added. The
resulting mixture was extracted with ether. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 40 : 1) to give compound 12 (851 mg, 81 % yield for two steps) as a light yellow oil: [α]²⁷_D = +20.0° (c 1.20, CHCl₃) ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.26 (m, 5H), 4.53 (dd, J = 14.1, 12.0 Hz, 2H) 3.74 (dd, J =9.3, 4.2 Hz, 1H), 3.54 (t, J =8.7 Hz, 2H), 3.27-3.06 (m, 3H), 2.91-2.71 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ137.9, 130.0 (t, J = 252.6 Hz), 128.6, 127.9, 127.7, 73.5, 67.1 (d, J = 5.7 Hz), 48.2 (t, J = 22.0 Hz), 36.3 (t, J = 27.8 Hz), 30.1 (d, J = 4.8 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ–100.1 (ddd, J = 231.2, 21.4, 9.6 Hz, 1F ), –108.6 (ddd, J = 230.4, 33.3, 18.1 Hz, 1F); IR (KBr ) max 3030, 2866, 1454, 1100, 1028, 697 cm⁻¹; MS (ESI) m/z 245.0 (M⁺+H), 266.9 (M⁺+Na); HRMS Calcd for C₁₂H₁₄OF₂S⁺ (M⁺): 244.0733. Found: 244.0739.

(R,E)-6-Benzylxy-3-benzyloxymethyl-2,2-difluorohex-4-en-1-ol (13) Compound 10 (2.12 g, 5.43 mmol) was dissolved in CH₃OH (15 mL) and then NaBH₄ (310 mg, 8.16 mmol) was added at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 30 min. Then the reaction was quenched with water. The resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, 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 compound 13 (1.85 g,
94 % yield) as a clear oil: $[\alpha]^{27}_D = -14.8^\circ$ (c 0.48, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.38-7.29 (m, 10H), 5.85 (dt, $J = 15.9$, 5.7 Hz, 1H), 5.70 (dd, $J = 15.9$, 8.4 Hz, 1H), 4.54 (s, 2H), 4.51 (s, 2H), 4.03 (d, $J = 5.4$ Hz, 2H), 3.88-3.58 (m, 4H), 3.15-2.98 (m, 1H), 2.36 (br, 1H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ –106.6 (dm, $J = 253.0$ Hz, 1F), –114.4 (dm, $J = 253.2$ Hz, 1F); IR( KBr )$_{\text{max}}$ 3430, 2925, 1453, 1261, 1074, 698 cm$^{-1}$; MS (ESI) $m/z$ 385.2 (M$^+$+ Na), 380.3 (M$^+$+NH$_4$); Anal. Calcd for C$_{21}$H$_{24}$O$_3$F$_2$: C, 69.60; H, 6.67. Found: C, 69.10; H, 6.70.

\[(R,E)-1,6-O-Dibenyl-3-benzylxymethyl-2,2-difluoro-4-hexen-1,6-diol \ (14)\]

To a suspension of NaH (60% in oil, 258 mg, 6.45 mmol) and Bu$_4$NI (236 mg, 0.64 mmol) in anhydrous THF (40 mL) was added a solution of compound 13 (1.78 g, 4.92 mmol) in anhydrous THF (10 mL) slowly at 0 °C. After the mixture was stirred for 20 min at the same temperature, it was allowed to warm to room temperature and stirred for 20 min. Then the resulting reaction mixture was cooled to 0 °C, treated with BnBr (0.9 mL, 7.49 mmol) in anhydrous THF (10 mL) and stirred at room temperature for 3 h. Then water was added to quench the reaction and the resulting mixture was extracted with Et$_2$O. The combined organic layer was washed with water and brine. Then, the resultant organic phase was dried over anhydrous Na$_2$SO$_4$ and filtered, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 10: 1) to give compound 14 (2.05 g, 91%) as a clear oil: $[\alpha]^{27}_D = -3.4^\circ$ (c 0.40, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.32-7.28 (m, 15H), 5.83 (dt, $J = 15.9$, 5.7 Hz, 1H), 5.67
\((\dd, J = 15.9, 8.7 \text{ Hz}, 1\text{H}), 4.56 (\dd, J = 15.6, 12.0 \text{ Hz}, 2\text{H}), 4.50-4.44 (\text{m}, 4\text{H}), 4.01 (\text{d}, J = 5.4 \text{ Hz}, 2\text{H}), 3.78-3.57 (\text{m}, 4\text{H}), 3.23-3.06 (\text{m}, 1\text{H}); \) \(^{13}\text{C NMR} (100.7 \text{ MHz, CDCl}_3) \delta 138.2, 137.9, 137.2, 132.4, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 126.9, 122.4 (t, J = 247.3 \text{ Hz}), 73.8, 73.3, 71.9, 69.9, 67.9 (t, J = 4.5 \text{ Hz}), 66.9, 46.7 (t, J = 22.6 \text{ Hz}); \(^{19}\text{F NMR} (282 \text{ MHz, CDCl}_3) \delta -108.9 (\text{ddd}, J = 255.4, 25.9, 14.4 \text{ Hz}, 1\text{F}), -109.7 (\text{ddd}, J = 257.4, 26.8, 13.0 \text{ Hz}, 1\text{F}); \text{IR} (\text{KBr}) \max 3031, 2864, 1454, 1106, 1028, 698 \text{ cm}^{-1}; \text{MS (ESI) } m/z 470.4 (\text{M}^+ + \text{NH}_4), 475.3 (\text{M}^+ + \text{Na}); \text{HRMS Calcd for C}_{28}\text{H}_{30}\text{O}_3\text{F}_2\text{Na}^+ (\text{M}^+ + \text{Na}): 475.2047. \text{Found: 475.2055.}

**(R)-4-Benzyl oxy-2-benzyl oxymethyl-3,3-difluorobutan-1-ol (15)** Compound 15 (1.39 g, 92%) was prepared from compound 14 (2.05 g, 4.53 mmol) using the same conditions as described for compound 11. Clear oil: \([\alpha]^{27}_D = +5.9^\circ \) (c 0.89, CHCl\(_3\)); \(^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 7.38-7.25 (\text{m}, 10 \text{H}), 4.59 (\text{s}, 2\text{H}), 4.51 (\text{s}, 2\text{H}), 3.90 (\text{d}, J = 5.1 \text{ Hz}, 2\text{H}), 3.80-3.62 (\text{m}, 4\text{H}), 2.66-2.49 (\text{m}, 1\text{H}), 2.21 (\text{br}, 1\text{H}); \(^{13}\text{C NMR} (75.5 \text{ MHz, CDCl}_3) \delta 137.7, 137.0, 128.7, 128.6, 128.3, 128.0, 127.8, 127.1, 122.9 (t, J = 245.5 \text{ Hz}), 74.1, 73.6, 69.9 (t, J = 31.9 \text{ Hz}), 67.2 (t, J = 5.5 \text{ Hz}), 60.1 (t, J = 5.4 \text{ Hz}), 45.9 (t, J = 20.7 \text{ Hz}); \(^{19}\text{F NMR} (282 \text{ MHz, CDCl}_3) \delta -106.2 (\text{ddd}, J = 261.1, 26.2, 13.8 \text{ Hz}, 1\text{F}), -106.7 (\text{ddd}, J = 261.4, 27.6, 17.6 \text{ Hz}, 1\text{F}); \text{IR} (\text{KBr}) \max 3448, 3032, 2873, 1453, 1273, 1105, 697 \text{ cm}^{-1}; \text{MS (ESI) } m/z 359.1 (\text{M}^+ + \text{Na}), \text{HRMS Calcd for C}_{19}\text{H}_{22}\text{O}_3\text{F}_2\text{Na}^+ (\text{M}^+ + \text{Na}): 359.1427. \text{Found: 359.1429.}

**(S)-3-(tert-Butyldimethylsilyloxy)methyl-2,2-difluorobutane-1,4-diol (18)** To a solution of compound 15 (1.38 g, 4.11 mmol) and
imidaxole (558 mg, 8.21 mmol) in DMF (8 mL) was added TBDMSCl (1.12 g, 7.44 mmol) 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 Et₂O. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 40:1) to give compound 17 (1.63 g, 88%). Then a mixture of compound 17 (1.63 g, 3.62 mmol) and 10% palladium/carbon (320 mg) in ethanol (160 mL) was hydrogenated at room temperature and atmospheric pressure for 20 h. The mixture was filtered, and the filtrate evaporated at reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 3:1) to give compound 18 (818 mg, 84% yield) as a clear oil: [α]28D = -0.91° (c 0.69, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 3.86-3.61 (m, 6H), 2.72 (br, 2H), 2.33-2.16 (m, 1H), 0.80 (s, 9H), 0.00 (s, 6H); ¹³C NMR (100.7 MHz, CDCl₃) δ 123.2 (t, J=246.3 Hz), 63.6 (t, J=32.5 Hz), 60.1 (t, J=5.6 Hz), 59.4 (t, J=5.2 Hz), 48.0 (t, J=21.7 Hz), 25.8, 18.1, -5.7; ¹⁹F NMR (282 MHz, CDCl₃) δ -108.3 (ddd, J=258.3, 28.2, 12.4 Hz, 1F), -110.3 (ddd, J=257.5, 28.2, 15.2 Hz, 1F); IR (KBr) max 3366, 2955, 2859, 1472, 1257, 1079, 837, 778 cm⁻¹; MS (ESI) m/z 271.2 (M⁺+H), 293.2 (M⁺+Na), HRMS Calcd for C₁₁H₂₅O₃F₂Si⁺ (M⁺+H): 271.1541. Found: 271.1536.

(S)-(4,4-difluorotetrahydrothiophen-3-yl)methyl 4-bromobenzoate (20) The compound 19 (643 mg, 81%) was prepared from
compound 18 (801 mg, 2.97 mmol) using the same condition as described for the compound 12. Then, to a solution of compound 19 (643 mg, 2.40 mmol) in dry THF (15 mL) was added a solution of TABF (1M in THF, 2.5 mL) and stirred for 2 h. The solvent was evaporated at reduced pressure. The crude product was dissolved in dry CH2Cl2 (12 mL) and pyridine (5 mL), and p-BrBzCl (1.05 g, 4.78 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with water. The resulting mixture was extracted with CH2Cl2. The combined organic layers were washed with 1N HCl, saturated NaHCO3 solution, water and brine, dried over anhydrous Na2SO4. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 40: 1) to give compound 20 (668 mg, 83 %) as a clear oil: [α]27D = -13.9° (c 0.18, CHCl3); 1H NMR (300 MHz, CDCl3) δ 7.90 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 4.58 (dd, J = 11.4, 5.4 Hz, 1H), 4.44 (dd, J = 11.4, 6.6 Hz, 2H), 3.36-2.89 (m, 5H); 13C NMR (100.7 MHz, CDCl3) δ 165.4, 131.8, 131.1, 129.5 (t, J = 255.5 Hz ), 128.5 (d, J = 4.5 Hz), 61.6, 47.0 (t, J = 22.5 Hz), 36.1 (t, J = 29.2 Hz), 29.1 (dd, J = 5.9, 1.5 Hz); 19F NMR (282 MHz, CDCl3) δ –100.6 (ddd, J = 233.2, 18.8, 8.7 Hz, 1F), –108.3 (ddd, J = 233.2, 32.7, 17.8 Hz, 1F); IR( KBr ) max 2926, 1725, 1591, 1269, 1116, 1012, 756 cm⁻¹; MS (EI) m/z 136 (M+-C7H5O2Br), HRMS Calcd for C5H7F2S+: 137.0237. Found: 137.0231, HRMS Calcd for C7H4OBr+: 182.9446.  Found: 182.9449.

1-((2S,4R)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydrothiophen-2-yl)-5-fluoro uracill (21a) and 1-((2R,4R)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydro
thiophen-2-yl)-5-fluorouracil (21b). A solution of \textit{m}-CPBA (80\%, 154 mg, 0.71 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise to the solution of compound 12 (174 mg, 0.71 mmol) in CH$_2$Cl$_2$ (8 mL) at $-70$ °C. The reaction mixture was stirred at $-70$ °C for 40 min. Then the mixture was quenched with saturated NaHCO$_3$ solution, the resulting mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with 10\% of aqueous Na$_2$SO$_3$ and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent was removed in vacuo to give the sulfoxide, which was used directly in next step without purification. To a solution of silylated 5-fluorouracil, prepared from refluxing 5-fluorouracil (278 mg, 2.14 mmol) and ammonium sulfate (catalytic amount) in HMDS (6 mL), in anhydrous DCE (2 mL) was added a solution of the sulfoxide in anhydrous DCE (6 mL) followed by addition of TMSOTf (258 $\mu$l, 1.42 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was quenched with saturated aqueous NaHCO$_3$ solution, filtered and poured into CH$_2$Cl$_2$. The organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, 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 $\alpha$ isomer of protected 5-fluorouridine (69 mg) and $\beta$ isomer of protected 5-fluorouridine (43 mg). To a solution of $\alpha$ isomer (69 mg, 0.18 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) was added BCl$_3$ (1M in CH$_2$Cl$_2$, 3.7 mL, 3.7 mmol) at $-70$ °C. After the reaction mixture was stirred for 2h, the mixture was quenched with MeOH (5 mL), and the solvent was removed in vacuo. The residue was purified by silica gel column
chromatography (CH$_2$Cl$_2$: MeOH = 20: 1) to give compound 21a (41mg, 20 % yield for three steps) as a white solid.

Compound 21a: m. p. 193-195 °C; [α]$^2_{D}$ = +22.1 °(c 1.00 MeOH); $^1$H NMR (300 MHz, MeOH-d$_4$) δ 8.22 (d, $J$ = 6.3 Hz, 1H), 6.28 (dd, $J$ = 12.0, 3.6 Hz, 1H), 3.83 (dd, $J$ = 11.1, 5.1 Hz, 1H), 3.69 (dd, $J$ = 11.7, 7.8 Hz, 1H), 3.37 (dd, $J$ = 10.5, 7.8 Hz, 1H), 2.85 (t, $J$ = 10.5 Hz, 1H), 2.79-2.62 (m, 1H); $^{13}$C NMR (100.7 MHz, MeOH-d$_4$) δ 157.6 (d, $J$ = 26.4 Hz), 149.8, 140.1(d, $J$ = 235.0 Hz), 127.4 (t, $J$ = 257.5 Hz), 125.3 (d, $J$ = 35.8 Hz), 63.1 (dd, $J$ =39.5, 21.3 Hz), 57.9 (d, $J$ = 4.9 Hz), 27.4 (d, $J$ =6.9 Hz); $^{19}$F NMR (282 MHz, MeOH-d$_4$) δ −110.3 (ddd, $J$ =236.9, 8.7, 3.9 Hz, 1F), −112.9 (ddd, $J$ = 236.3, 20.6, 11.2 Hz, 1F), -166.5 (d, $J$ =7.9 Hz, 1F); IR (KBr) max 3462, 3020, 1723, 1690, 1387, 1099 cm$^{-1}$; MS m/z 587.0 (2M$^+$+Na); HRMS Calcd for C$_9$H$_9$O$_3$N$_2$F$_3$SNa (M$^+$+ Na): 305.0190. Found: 305.0178.

Compound 21b (27 mg, 14 % yield for three steps) was prepared from the β isomer of protected 5-fluorouridine using the same conditions as for compound 21a. white solid: m. p. 200-202 °C; [α]$^2_{D}$ = +14.3 °(c 0.51 MeOH); $^1$H NMR (300 MHz, MeOH-d$_4$) δ 8.11 (dd, $J$ = 6.9, 3.0 Hz, 1H), 6.61 (dd, $J$ = 15.0, 8.4 Hz, 1H), 3.88 (dd, $J$ = 11.1, 5.1 Hz, 1H), 3.67 (dd, $J$ = 11.1, 7.5 Hz, 1H), 3.25-3.10 (m, 2H), 3.05-2.86 (m, 1H); $^{13}$C NMR (100.7 MHz, MeOH-d$_4$) δ 157.6 (d, $J$ = 26.2 Hz), 149.8, 139.8 (d, $J$ = 234.6 Hz), 126.41 (t, $J$ = 258.1 Hz), 126.42 (dd, $J$ = 35.9,
4.5 Hz), 61.9 (dd, $J = 29.2, 19.5$ Hz), 57.9 (d, $J = 5.9$ Hz), 49.0 (t, $J = 21.8$ Hz), 28.9 (d, $J = 8.3$ Hz); $^{19}$F NMR (282 MHz, MeOH-d$_4$) $\delta$ –109.6 (dt, $J = 230.4, 6.2$ Hz, 1F), –121.8 (dm, $J = 230.9$ Hz, 1F), –167.2 (d, $J = 6.8$ Hz, 1F); IR (KBr) $\text{max}$ 3461, 3051, 1701, 1664, 1389, 1225 cm$^{-1}$; MS $m/z$ 283.1 (M$^+$+H); HRMS Calcd for C$_9$H$_9$O$_3$N$_2$F$_3$SNa (M$^+$ + Na): 305.0179. Found: 305.0178.

1-((2S,4R)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydrothiophen-2-yl)thymine (22a) and 1-((2R,4R)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydrothiophen-2-yl)thymine (22b) Conversion of 12 (181 mg, 0.74 mmol) to 22 was accomplished using the same procedure as described above. Compound 22a (29 mg, 16% yield for three steps) was obtained as a white solid and compound 22b (16 mg, 9% yield for three steps) was obtained as a white solid too.

**Compound 22a:** m. p. 186-188 °C; [$\alpha$]$^D_{27}$ = +33.9° (c 0.70, MeOH); $^1$H NMR (300 MHz, MeOH-d$_4$) $\delta$ 7.84 (s, 1H), 6.34 (dd, $J = 12.3, 4.5$ Hz, 1H), 3.87 (dd, $J = 11.1, 4.8$ Hz, 1H), 3.73 (dd, $J = 11.4, 7.2$ Hz, 1H), 3.40 (dd, $J = 18.3, 10.2$ Hz, 1H), 2.89 (t, $J = 10.5$ Hz, 1H), 2.83-2.66 (m, 1H), 1.93 (s, 3H); $^{13}$C NMR (100.7 MHz, MeOH-d$_4$) $\delta$164.6, 151.4, 136.8, 127.6 (t, $J = 256.4$ Hz), 110.7, 62.5 (dd, $J = 39.0, 21.1$ Hz), 58.1 (d, $J = 5.2$ Hz), 27.5 (d, $J = 6.1$ Hz), 11.0; $^{19}$F NMR (282 MHz, MeOH-d$_4$) $\delta$ –107.3 (ddd, $J = 236.9, 8.4, 3.9$ Hz, 1F), –109.6 (ddd, $J = 236.9, 20.3, 12.9$ Hz, 1F); IR (KBr) $\text{max}$ 3414, 3045, 1693, 1466, 1377, 1220 cm$^{-1}$; MS
m/z 301.0 (M⁺+Na); HRMS Calcd for C₁₀H₁₃O₃N₂F₂S⁺ (M⁺+H): 279.0609. Found: 279.0609.

Compound 22b: m. p. 204-205 °C; [α]°D = +2.8° (c 0.41, MeOH); ¹H NMR (300 MHz, MeOH-d₄) δ 7.70 (d, J = 2.7 Hz, 1H), 6.59 (dd, J = 15.3, 8.4 Hz, 1H), 3.84 (dd, J = 11.1, 5.4 Hz, 1H), 3.63 (dd, J = 11.4, 7.5 Hz, 1H), 3.21-3.08 (m, 2H), 2.99-2.81 (m, 1H), 1.87 (s, 3H); ¹³C NMR (100.7 MHz, MeOH-d₄) δ 166.3, 153.1, 139.8 (d, J = 5.2 Hz), 128.1 (dd, J = 263.1, 254.9 Hz), 111.9, 62.9 (dd, J = 29.2, 19.5 Hz), 59.7 (d, J = 5.9 Hz), 50.8 (t, J = 22.4 Hz), 30.6 (d, J = 8.3 Hz), 12.7; ¹⁹F NMR (282 MHz, MeOH-d₄) δ -109.8 (dt, J = 231.2, 7.6 Hz, 1F), -121.9 (ddddd, J = 230.7, 26.5, 15.5, 3.4 Hz, 1F); IR (KBr) max 3417, 3179, 3044, 1693, 1466, 1379, 1220 cm⁻¹; MS m/z 279.0 (M⁺+H), 301.0 (M⁺+Na); HRMS Calcd for C₁₀H₁₃O₃N₂F₂S⁺ (M⁺+H): 279.0614. Found: 279.0610.

1-((2R,4S)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydrothiophen-2-yl)-5-fluorouracil (23a) and 1-((2S,4S)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydrothiophen-2-yl)-5-fluorouracil (23b) Under the same conditions of Pummerer reaction as described above, Compound 20 (130 mg, 0.38 mmol) was condensed with silylated 5-fluorouracil to give α isomer of protected 5-fluorouridine (47 mg) and β isomer of protected 5-fluorouridine (30 mg). Then the α isomer was dissolved in saturated methanolic ammonia (8 mL) and methanol (4 mL) and stirred for 8 h. After removal of the volatile materials, the residue was purified by silica gel
chromatography (CH$_2$Cl$_2$: MeOH = 10: 1) to give compound **23a** (24 mg, 23% yield for three steps) as a white solid.

![Compound 23a](image)

**Compound 23a**: m.p. 212-213 °C; [α]$^27_D$ = -31.1° (c 0.85 MeOH); $^1$H NMR (300 MHz, MeOH-d$_4$) δ 8.28 (d, $J$ = 6.6 Hz, 1H), 6.32 (ddd, $J$ = 11.7, 3.9, 1.2 Hz, 1H), 3.86 (dd, $J$ = 11.4, 5.1 Hz, 1H), 3.72 (dd, $J$ = 11.4, 7.2 Hz, 1H), 3.41 (dd, $J$ = 10.5, 7.5 Hz, 1H), 2.87 (t, $J$ = 9.9 Hz, 1H), 2.82-2.65 (m, 1H); $^{13}$C NMR (100.7 MHz, MeOH-d$_4$) δ 157.6 (d, $J$ = 26.4 Hz), 149.9, 140.1 (d, $J$ = 235.2 Hz), 127.5 (dd, $J$ = 261.4, 257.1 Hz), 125.3 (d, $J$ = 35.9 Hz), 63.1 (dd, $J$ = 39.1, 21.1 Hz), 58.0 (d, $J$ = 5.0 Hz), 27.5 (t, $J$ = 7.3 Hz); $^{19}$F NMR (282 MHz, MeOH-d$_4$) δ -111.3 (ddd, $J$ = 236.1, 9.6, 4.5 Hz, 1F), -113.8 (ddd, $J$ = 236.3, 20.5, 11.5 Hz, 1F), -167.4 (d, $J$ = 8.4 Hz, 1F); IR (KBr) max 3401, 3018, 1724, 1688, 1386, 1099 cm$^{-1}$; MS m/z 283.0 (M$^+$+H); HRMS Calcd for C$_9$H$_{10}$O$_3$N$_2$F$_3$S (M$^+$ + H): 283.0361. Found: 283.0359.

![Compound 23b](image)

**Compound 23b** (16 mg, 15% yield for three steps) was prepared from the β isomer of protected 5-fluorouridine using the same conditions as for compound **23a**. white solid: m.p. 218-220 °C; [α]$^27_D$ = -18.9° (c 0.45 MeOH); $^1$H NMR (300 MHz, MeOH-d$_4$) δ 8.08 (dd, $J$ = 6.9, 3.0 Hz, 1H), 6.58 (dd, $J$ = 15.0, 8.1 Hz, 1H), 3.85 (dd, $J$ = 11.7, 4.8 Hz, 1H), 3.64 (dd, $J$ = 11.4, 7.5 Hz, 1H), 3.22-3.07 (m, 2H), 3.02-2.83 (m, 1H); $^{13}$C NMR (100.7 MHz, MeOH-d$_4$) δ 158.1 (d, $J$ = 29.9 Hz, 1H).
Hz), 150.1, 140.4 (d, $J = 235.1$ Hz), 126.4 (t, $J = 261.2$ Hz), 126.5 (dd, $J = 35.5$, 4.6 Hz), 61.9 (dd, $J = 28.7$, 20.0 Hz), 57.9 (d, $J = 6.5$ Hz), 49.1 (t, $J = 22.0$ Hz), 28.9 (d, $J = 8.6$ Hz); $^{19}$F NMR (282 MHz, MeOH-$_d$$_4$) $\delta$ −109.5 (dd, $J =$230.1, 6.2 Hz, 1F), −121.7 (ddd, $J =$ 230.9, 21.4, 13.8 Hz, 1F), −167.1 (s, 1F); IR (KBr) $\text{max}$ 3460, 3057, 1704, 1665, 1390, 1390, 1116 cm$^{-1}$; MS $m/z$ 305.2 (M$^+$+Na); HRMS Calcd for C$_9$H$_9$N$_2$O$_3$F$_3$Na (M$^+$+Na): 305.0188. Found: 305.0178.
Chiral HPLC analytical data of compound 7

authentic racemic 99% ee
Chiral HPLC analytical data of compound 10

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**authentic racemic**

90% ee
Supplementary Material (ESI) for Chemical Communications

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X-ray crystal structure of compound 23a

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Supplementary Material (ESI) for Chemical Communications

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23b

\[ ^{13}\text{C} \]

\[
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Chiral HPLC analytical data of compound 21a

The chiral HPLC analytical data: Chiralpak OD column, detected at $\lambda=214$nm, eluent: $n$-hexane/i-PrOH (70:30), 0.4ml/min, $t_R(21a) = 19.8$ min, $t_R(23a) = 17.8$ min.

*authentic* racemic 21a  ee 70%

The chiral HPLC analytical data: Chiralpak OD column, detected at $\lambda=214$nm, eluent: $n$-hexane/i-PrOH (70:30), 0.4ml/min, $t_R(21a) = 19.8$ min, $t_R(23a) = 17.8$ min.
Chiral HPLC analytical data of compound 21b and 23b

\[ \text{Chiralpak IC column, detected at } \lambda = 214\text{nm, eluent:} \]
\[ n\text{-hexane/i-PrOH (70:30), 0.7ml/min, } t_R (23b) = 21.3 \text{ min, } t_R (21b) = 23.2 \text{ min} \]

**authentic racemic**

**21b ee 70%**

**23b ee 87%**