

## Supporting Information

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

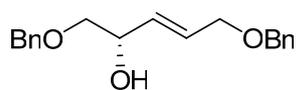
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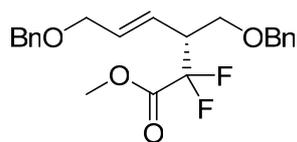
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(2*S*, *E*)-1,5-Bis(benzyloxy)pent-3-en-2-ol (**7**)

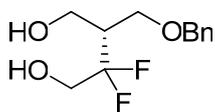
To a suspension of NaH (60% in oil, 1.79 g, 44.75 mmol) and Bu<sub>4</sub>NI (1.65 g, 4.47 mmol) in anhydrous THF (200 mL) was added a solution of compound **6** (12.41 g, 59.66 mmol) in anhydrous THF (70 mL) slowly at 0 °C. After the mixture was stirred for 20 min at the same temperature, it was allowed 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 (2*S*,*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<sub>2</sub>SO<sub>4</sub>, 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%. :  $[\alpha]_D^{26} = +22.0^\circ$  (*c* 1.50, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 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) <sub>max</sub> 3440, 3029, 2856, 1496, 1071, 696 cm<sup>-1</sup>; MS (ESI) *m/z* 321.2 (M<sup>+</sup>+Na); Anal. Calcd for C<sub>19</sub>H<sub>22</sub>O<sub>3</sub>: C, 76.48; H, 7.43 Found: C, 76.16; H, 7.51. The chiral HPLC analytical data: Chiralpak IC column, detected at λ=220nm, eluent: n-hexane/*i*-PrOH (80:20), 0.7ml/ min, *t*<sub>R</sub> (minor) =12.6 min, *t*<sub>R</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (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), NEt<sub>3</sub> (13 mL, 92.52 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (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 Et<sub>2</sub>O. The combined organic layer was washed with water and brine. After the resultant solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> 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, SOCl<sub>2</sub> (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 Et<sub>2</sub>O. The combined organic layer was washed with brine, and dried over anhydrous

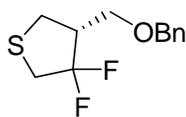
Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (petroleum ether: ethyl ether = 40:1) to give compound **10** (3.06 g, 41% yield for three steps, *ee* 90%) as a clear oil:  $[\alpha]_D^{26} = -15.7^\circ$  (*c* 2.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100.7 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -107.4 (dd, *J* = 257.7, 9.0 Hz, 1F), -116.2 (dd, *J* = 257.7, 20.3 Hz, 1F); IR (KBr)  $\nu_{\max}$  3031, 2858, 1766, 1496, 1454, 1362, 1095, 697 cm<sup>-1</sup>; MS (ESI) *m/z* 408.3 (M<sup>+</sup>+NH<sub>4</sub>), 413.2 (M<sup>+</sup>+Na); HRMS Calcd for C<sub>22</sub>H<sub>24</sub>O<sub>4</sub>F<sub>2</sub>Na<sup>+</sup> (M<sup>+</sup> + 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<sub>R</sub>* (major) =18.0 min, *t<sub>R</sub>* (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<sub>2</sub>Cl<sub>2</sub> (50 mL) was ozonized at -78 °C for 30 min. Then a suspension of NaBH<sub>4</sub> (850 mg, 22.36 mmol) in C<sub>2</sub>H<sub>5</sub>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

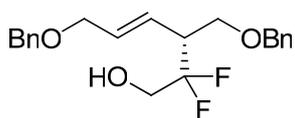
washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 3 : 1) to give compound **11** (1.09 g, 92 % yield) as a clear oil:  $[\alpha]_D^{27} = -1.9^\circ$  (*c* 1.10, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  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); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  137.2, 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); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -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)  $\nu_{\max}$  3391, 2879, 1454, 1367, 1072, 906, 698 cm<sup>-1</sup>; MS (ESI) *m/z* 269.0 (M<sup>+</sup>+Na); HRMS Calcd for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>F<sub>2</sub>Na<sup>+</sup> (M<sup>+</sup>+Na): 269.0960. Found: 269.0959.



**(R)-4-Benzyloxymethyl-3,3-difluoro-tetrahydrothiophene (12).**

To a compound **11** (1.07 g, 4.35 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> solution, water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed in vacuo. The residue was dissolved in DMF (40 mL) and Na<sub>2</sub>S·9H<sub>2</sub>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

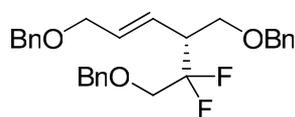
resulting mixture was extracted with ether. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 40 : 1) to give compound **12** (851 mg, 81 % yield for two steps) as a light yellow oil:  $[\alpha]_D^{27} = +20.0^\circ$  (*c* 1.20, CHCl<sub>3</sub>) <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 137.9, 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); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) 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) <sub>max</sub> 3030, 2866, 1454, 1100, 1028, 697 cm<sup>-1</sup>; MS (ESI) *m/z* 245.0 (M<sup>+</sup>+H), 266.9 (M<sup>+</sup>+Na); HRMS Calcd for C<sub>12</sub>H<sub>14</sub>OF<sub>2</sub>S<sup>+</sup> (M<sup>+</sup>): 244.0733. Found: 244.0739.



**(*R,E*)-6-Benzyloxy-3-benzyloxymethyl-2,2-difluorohex-**

**4-en-1-ol (13)** Compound **10** (2.12 g, 5.43 mmol) was dissolved in CH<sub>3</sub>OH (15 mL) and then NaBH<sub>4</sub> (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 Na<sub>2</sub>SO<sub>4</sub>, 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 ,

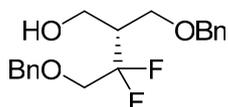
94 % yield) as a clear oil:  $[\alpha]_D^{27} = -14.8^\circ$  ( $c$  0.48,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.29 (m, 10H), 5.85 (dt,  $J = 15.9, 5.7$  Hz, 1H), 5.70 (dd,  $J = 15.9, 8.4$  Hz, 1H), 4.54 (s, 2H), 4.51 (s, 2H), 4.03 (d,  $J = 5.4$  Hz, 2H), 3.88-3.58 (m, 4H), 3.15-2.98 (m, 1H), 2.36 (br, 1H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -106.6 (dm,  $J = 253.0$  Hz, 1F), -114.4 (dm,  $J = 253.2$  Hz, 1F); IR (KBr)  $\nu_{\text{max}}$  3430, 2925, 1453, 1261, 1074, 698  $\text{cm}^{-1}$ ; MS (ESI)  $m/z$  385.2 ( $\text{M}^+ + \text{Na}$ ), 380.3 ( $\text{M}^+ + \text{NH}_4$ ); Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{O}_3\text{F}_2$ : C, 69.60; H, 6.67. Found: C, 69.10; H, 6.70.



**(*R,E*)-1,6-*O*-Dibenzyl-3-benzyloxymethyl-2,2-difluoro-4-hexen-1,6-diol (**14**)**

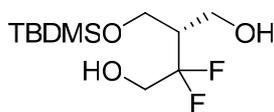
To a suspension of NaH (60% in oil, 258 mg, 6.45 mmol) and  $\text{Bu}_4\text{NI}$  (236 mg, 0.64 mmol) in anhydrous THF (40 mL) was added a solution of compound **13** (1.78 g, 4.92 mmol) in anhydrous THF (10 mL) slowly at 0 °C. After the mixture was stirred for 20 min at the same temperature, it was 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  $\text{Et}_2\text{O}$ . The combined organic layer was washed with water and brine. Then, the resultant organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$  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:  $[\alpha]_D^{27} = -3.4^\circ$  ( $c$  0.40,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.28 (m, 15H), 5.83 (dt,  $J = 15.9, 5.7$  Hz, 1H), 5.67

(dd,  $J = 15.9, 8.7$  Hz, 1H), 4.56 (dd,  $J = 15.6, 12.0$  Hz, 2H), 4.50-4.44 (m, 4H), 4.01 (d,  $J = 5.4$  Hz, 2H), 3.78- 3.57 (m, 4H), 3.23-3.06 (m, 1H);  $^{13}\text{C}$  NMR (100.7 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $J = 247.3$  Hz), 73.8, 73.3, 71.9, 69.9, 67.9 (t,  $J = 4.5$  Hz), 66.9, 46.7 (t,  $J = 22.6$  Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -108.9 (ddd,  $J = 255.4, 25.9, 14.4$  Hz, 1F), -109.7 (ddd,  $J = 257.4, 26.8, 13.0$  Hz, 1F); IR (KBr)  $\text{max}$  3031, 2864, 1454, 1106, 1028, 698  $\text{cm}^{-1}$ ; MS (ESI)  $m/z$  470.4 ( $\text{M}^+ + \text{NH}_4$ ), 475.3 ( $\text{M}^+ + \text{Na}$ ); HRMS Calcd for  $\text{C}_{28}\text{H}_{30}\text{O}_3\text{F}_2\text{Na}^+$  ( $\text{M}^+ + \text{Na}$ ): 475.2047. Found: 475.2055.



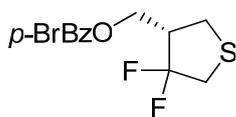
**(R)-4-Benzyloxy-2-benzyloxymethyl-3,3-difluorobutan-1-ol**

**(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:  $[\alpha]_{\text{D}}^{27} = +5.9^\circ$  ( $c$  0.89,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.25 (m, 10 H), 4.59 (s, 2H), 4.51 (s, 2H), 3.90 (d,  $J = 5.1$  Hz, 2H), 3.80-3.62 (m, 4H), 2.66-2.49 (m, 1H), 2.21 (br, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  137.7, 137.0, 128.7, 128.6, 128.3, 128.0, 127.8, 127.1, 122.9 (t,  $J = 245.5$  Hz), 74.1, 73.6, 69.9 (t,  $J = 31.9$  Hz), 67.2 (t,  $J = 5.5$  Hz), 60.1 (t,  $J = 5.4$  Hz), 45.9 (t,  $J = 20.7$  Hz);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -106.2 (ddd,  $J = 261.1, 26.2, 13.8$  Hz, 1F), -106.7 (ddd,  $J = 261.4, 27.6, 17.6$  Hz, 1F); IR (KBr)  $\text{max}$  3448, 3032, 2873, 1453, 1273, 1105, 697  $\text{cm}^{-1}$ ; MS (ESI)  $m/z$  359.1 ( $\text{M}^+ + \text{Na}$ ), HRMS Calcd for  $\text{C}_{19}\text{H}_{22}\text{O}_3\text{F}_2\text{Na}^+$  ( $\text{M}^+ + \text{Na}$ ): 359.1427; 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

imidazole (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 Et<sub>2</sub>O. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, 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:  $[\alpha]_D^{28} = -0.91^\circ$  (*c* 0.69, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100.7 MHz, CDCl<sub>3</sub>) 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; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) 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 )<sub>max</sub> 3366, 2955, 2859, 1472, 1257, 1079, 837, 778 cm<sup>-1</sup>; MS (ESI) *m/z* 271.2 (M<sup>+</sup>+H), 293.2 (M<sup>+</sup>+Na), HRMS Calcd for C<sub>11</sub>H<sub>25</sub>O<sub>3</sub>F<sub>2</sub>Si<sup>+</sup> (M<sup>+</sup> +H): 271.1541. Found: 271.1536.



**(S)-(4,4-difluorotetrahydrothiophen-3-yl)methyl**

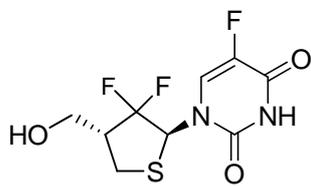
**4-bromobenzoate (20)** The compound **19** (643 mg, 81%) was prepared from

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 CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with 1N HCl, saturated NaHCO<sub>3</sub> solution, water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. 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:  $[\alpha]_D^{27} = -13.9^\circ$  (*c* 0.18, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100.7 MHz, CDCl<sub>3</sub>) 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); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) 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)  $\nu_{\max}$  2926, 1725, 1591, 1269, 1116, 1012, 756 cm<sup>-1</sup>; MS (EI) *m/z* 136 (M<sup>+</sup>-C<sub>7</sub>H<sub>5</sub>O<sub>2</sub>Br), HRMS Calcd for C<sub>5</sub>H<sub>7</sub>F<sub>2</sub>S<sup>+</sup>: 137.0237. Found: 137.0231, HRMS Calcd for C<sub>7</sub>H<sub>4</sub>OBr<sup>+</sup>: 182.9446. Found: 182.9449.

**1-((2*S*,4*R*)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydrothiophen-2-yl)-5-fluorouracil (21a) and 1-((2*R*,4*R*)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydro**

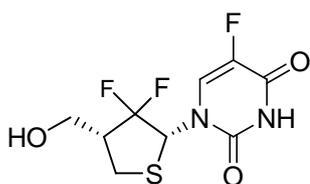
**thiophen-2-yl)-5-fluorouracil (21b)**. A solution of *m*-CPBA (80%, 154 mg, 0.71 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added dropwise to the solution of compound **12** (174 mg, 0.71 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at -70 °C. The reaction mixture was stirred at -70 °C for 40 min. Then the mixture was quenched with saturated NaHCO<sub>3</sub> solution, the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with 10% of aqueous Na<sub>2</sub>SO<sub>3</sub> and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, 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 μL, 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<sub>3</sub> solution, filtered and poured into CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, 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 α isomer of protected 5-fluorouridine (69 mg) and β isomer of protected 5-fluorouridine (43 mg). To a solution of α isomer (69 mg, 0.18 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added BCl<sub>3</sub> (1M in CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub>: MeOH = 20: 1) to give compound **21a** (41mg, 20 % yield for three steps) as a white solid.



Compound **21a**: m. p. 193-195 °C;  $[\alpha]_D^{27} = +22.1$  (c 1.00

MeOH); <sup>1</sup>H NMR (300 MHz, MeOH-d<sub>4</sub>) 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); <sup>13</sup>C NMR (100.7 MHz, MeOH-d<sub>4</sub>) 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); <sup>19</sup>F NMR (282 MHz, MeOH-d<sub>4</sub>) 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<sup>-1</sup>; MS *m/z* 587.0 (2M<sup>+</sup>+Na); HRMS Calcd for C<sub>9</sub>H<sub>9</sub>O<sub>3</sub>N<sub>2</sub>F<sub>3</sub>SNa (M<sup>+</sup>+ Na): 305.0190. Found: 305.0178.

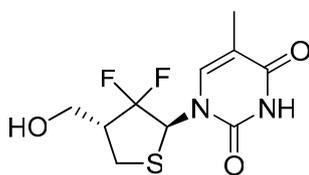


Compound **21b** (27 mg, 14 % yield for three steps) was

prepared from the β isomer of protected 5-fluorouridine using the same conditions as for compound **21a**. white solid: m. p. 200-202 °C;  $[\alpha]_D^{27} = +14.3$  (c 0.51 MeOH); <sup>1</sup>H NMR (300 MHz, MeOH-d<sub>4</sub>) 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); <sup>13</sup>C NMR (100.7 MHz, MeOH-d<sub>4</sub>) 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,

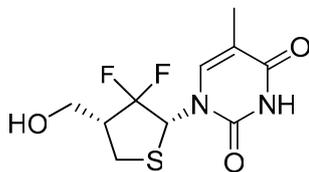
4.5 Hz), 61.9 (dd,  $J=29.2, 19.5$  Hz), 57.9 (d,  $J = 5.9$  Hz), 49.0 (t,  $J = 21.8$  Hz), 28.9 (d,  $J = 8.3$  Hz);  $^{19}\text{F}$  NMR (282 MHz, MeOH- $d_4$ )  $\delta$  -109.6 (dt  $J = 230.4, 6.2$  Hz, 1F), -121.8 (dm,  $J = 230.9$  Hz, 1F), -167.2 (d,  $J = 6.8$  Hz, 1F); IR (KBr)  $\text{max}$  3461, 3051, 1701, 1664, 1389, 1225  $\text{cm}^{-1}$ ; MS  $m/z$  283.1 ( $\text{M}^+ + \text{H}$ ); HRMS Calcd for  $\text{C}_9\text{H}_9\text{O}_3\text{N}_2\text{F}_3\text{SNa}$  ( $\text{M}^+ + \text{Na}$ ): 305.0179. Found: 305.0178.

**1-((2*S*,4*R*)-3,3-Difluoro-4-(hydroxymethyl)-tetrahydrothiophen-2-yl)thymine (22a) and 1-((2*R*,4*R*)-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;  $[\alpha]_D^{27} = +33.9^\circ$  ( $c$  0.70, MeOH);  $^1\text{H}$  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);  $^{13}\text{C}$  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;  $^{19}\text{F}$  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  $\text{cm}^{-1}$ ; MS

$m/z$  301.0 ( $M^+ + Na$ ); HRMS Calcd for  $C_{10}H_{13}O_3N_2F_2S^+$  ( $M^+ + H$ ): 279.0609. Found: 279.0609.

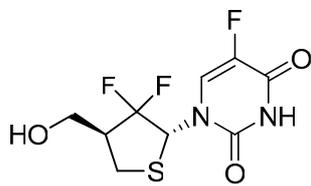


Compound **22b**: m. p. 204-205 °C;  $[\alpha]_D^{27} = +2.8^\circ$  ( $c$  0.41,

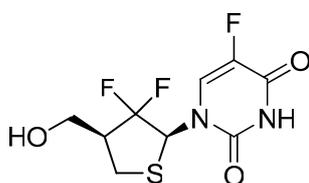
MeOH);  $^1H$  NMR (300 MHz, MeOH- $d_4$ )  $\delta$  7.70 (d,  $J = 2.7$  Hz, 1H), 6.59 (dd,  $J = 15.3, 8.4$  Hz, 1H), 3.84 (dd,  $J = 11.1, 5.4$  Hz, 1H), 3.63 (dd,  $J = 11.4, 7.5$  Hz, 1H), 3.21-3.08 (m, 2H), 2.99-2.81 (m, 1H), 1.87 (s, 3H);  $^{13}C$  NMR (100.7 MHz, MeOH- $d_4$ )  $\delta$  166.3, 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;  $^{19}F$  NMR (282 MHz, MeOH- $d_4$ )  $\delta$  -109.8 (dt,  $J = 231.2, 7.6$  Hz, 1F), -121.9 (dddd,  $J = 230.7, 26.5, 15.5, 3.4$  Hz, 1F); IR (KBr)  $\nu_{max}$  3417, 3179, 3044, 1693, 1466, 1379, 1220  $cm^{-1}$ ; MS  $m/z$  279.0 ( $M^+ + H$ ), 301.0 ( $M^+ + Na$ ); HRMS Calcd for  $C_{10}H_{13}O_3N_2F_2S^+$  ( $M^+ + H$ ): 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  $\alpha$  isomer of protected 5-fluorouridine (47 mg) and  $\beta$  isomer of protected 5-fluorouridine (30 mg). Then the  $\alpha$  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<sub>2</sub>Cl<sub>2</sub>: MeOH = 10: 1) to give compound **23a** (24 mg, 23% yield for three steps) as a white solid.

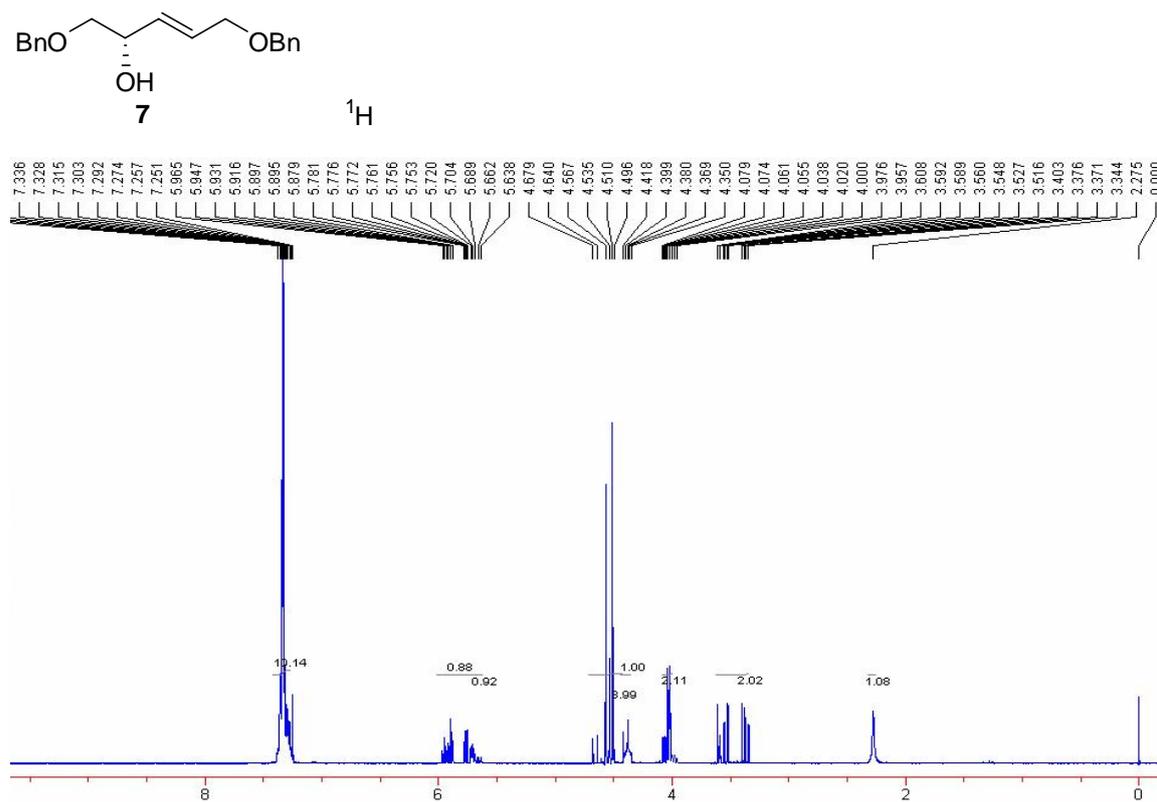


Compound **23a**: m.p.212-213 °C;  $[\alpha]_D^{27} = -31.1^\circ$  (*c* 0.85 MeOH); <sup>1</sup>H NMR (300 MHz, MeOH-d<sub>4</sub>) δ 8.28 (d, *J* = 6.6 Hz, 1H), 6.32 (ddd, *J* = 11.7, 3.9, 1.2 Hz, 1H), 3.86 (dd, *J* = 11.4, 5.1 Hz, 1H), 3.72 (dd, *J* = 11.4, 7.2 Hz, 1H), 3.41 (dd, *J* = 10.5, 7.5 Hz, 1H), 2.87 (t, *J* = 9.9 Hz, 1H), 2.82-2.65 (m, 1H); <sup>13</sup>C NMR (100.7 MHz, MeOH-d<sub>4</sub>) 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); <sup>19</sup>F NMR (282 MHz, MeOH-d<sub>4</sub>) 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<sup>-1</sup>; MS *m/z* 283.0 (M<sup>+</sup>+H); HRMS Calcd for C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>N<sub>2</sub>F<sub>3</sub>S (M<sup>+</sup> + H): 283.0361. Found: 283.0359.

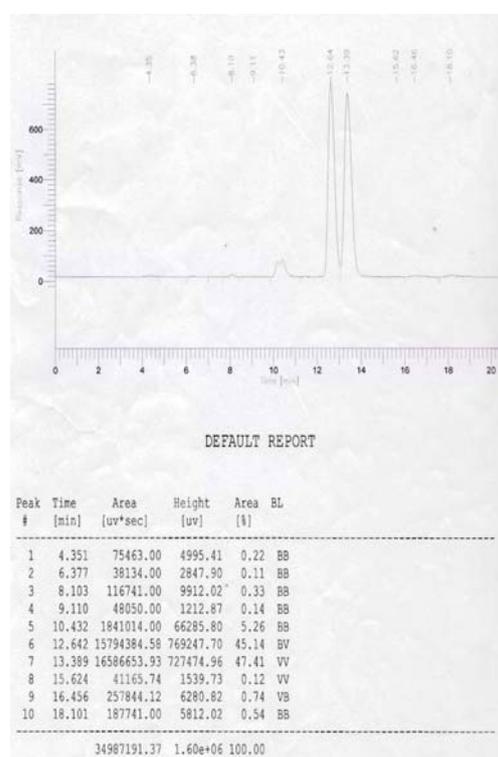


Compound **23b** (16 mg, 15% yield for three steps) was prepared from the β isomer of protected 5-fluorouridine using the same conditions as for compound **23a**. white solid: m.p. 218-220 °C;  $[\alpha]_D^{27} = -18.9^\circ$  (*c* 0.45 MeOH); <sup>1</sup>H NMR (300 MHz, MeOH-d<sub>4</sub>) δ 8.08 (dd, *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); <sup>13</sup>C NMR (100.7 MHz, MeOH-d<sub>4</sub>) δ 158.1 (d, *J* = 29.9

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);  $^{19}\text{F}$  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  $\text{cm}^{-1}$ ; MS  $m/z$  305.2 ( $\text{M}^+ + \text{Na}$ ); HRMS Calcd for  $\text{C}_9\text{H}_9\text{N}_2\text{O}_3\text{F}_3\text{SNa}$  ( $\text{M}^+ + \text{Na}$ ): 305.0188. Found: 305.0178.



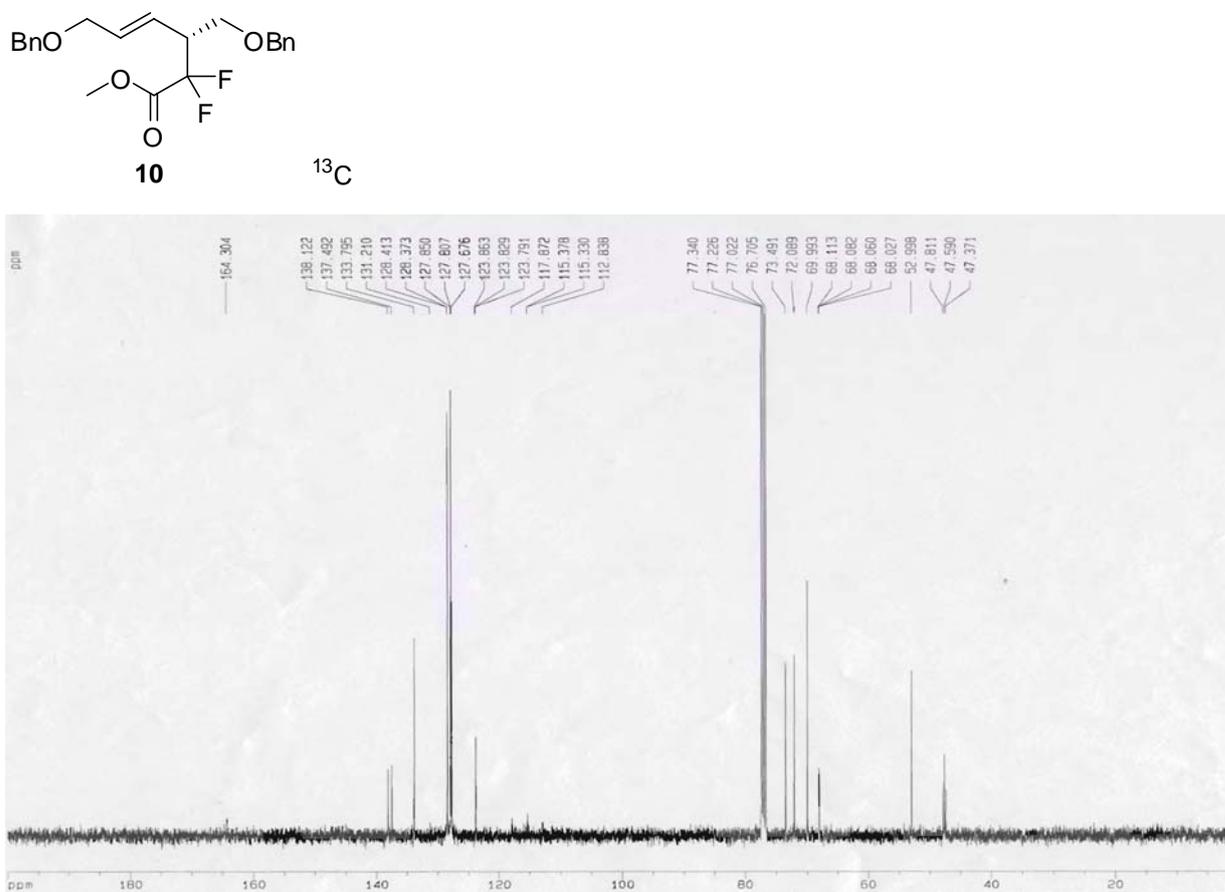
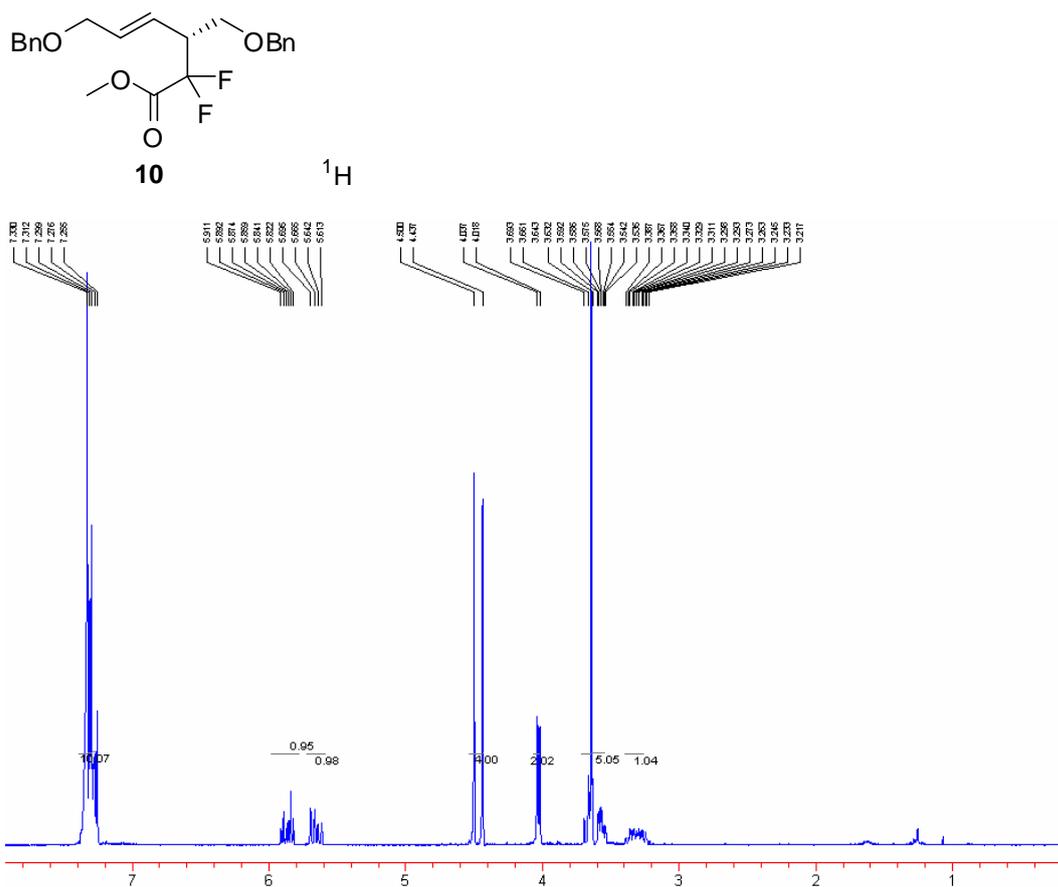
Chiral HPLC analytical data of compound **7**



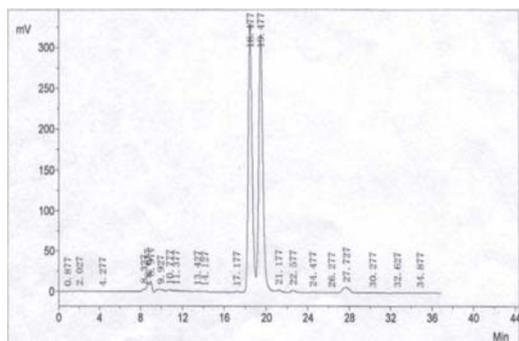
*authentic racemic*



99% *ee*

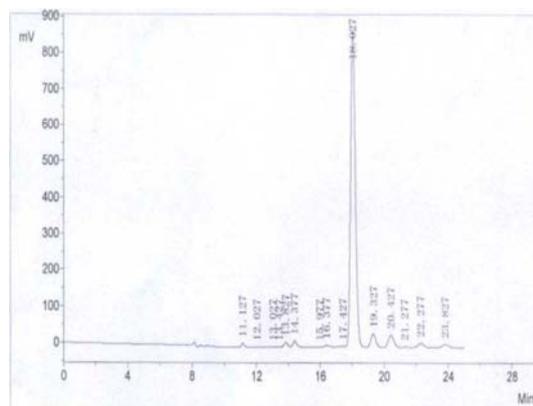


Chiral HPLC analytical data of compound **10**



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		0.877	76.1	1987.4	0.0106
2	2		2.027	972.3	54203.7	0.2887
3	3		4.277	191.8	7837.7	0.0417
4	4		8.327	3590.8	82187.4	0.4377
5	5		8.677	10702.5	166056.3	0.8844
6	6		8.977	12742.5	184861.8	0.9845
7	7		9.927	3662.2	173942.5	0.9264
8	8		10.777	2896.2	113252.4	0.6031
9	9		11.377	2201.1	151056.2	0.8045
10	10		13.427	982.3	32984.9	0.1757
11	11		14.127	345.8	9089.3	0.0484
12	12		17.177	608.2	22545.3	0.1201
13	13		18.477	329347.4	8428113.3	44.8853
14	14		19.477	317762.6	8875231.1	47.2665
15	15		21.177	1603.8	37072.7	0.1974
16	16		22.577	2147.4	65110.6	0.3468
17	17		24.477	531.7	16917.3	0.0901
18	18		26.277	267.0	6719.8	0.0358
19	19		27.727	6462.8	313049.3	1.6672
20	20		30.277	207.9	6228.8	0.0332
21	21		32.627	416.6	14040.3	0.0748
22	22		34.877	248.3	14527.0	0.0774
合计:				697967.3	18777015.2	100.0000

*authentic racemic*



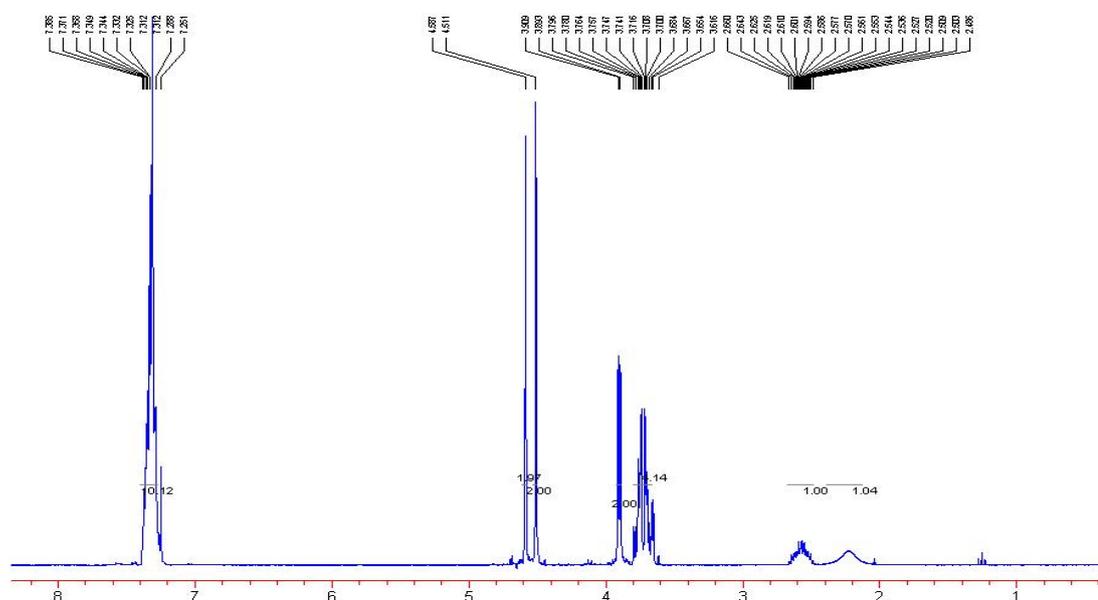
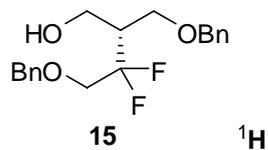
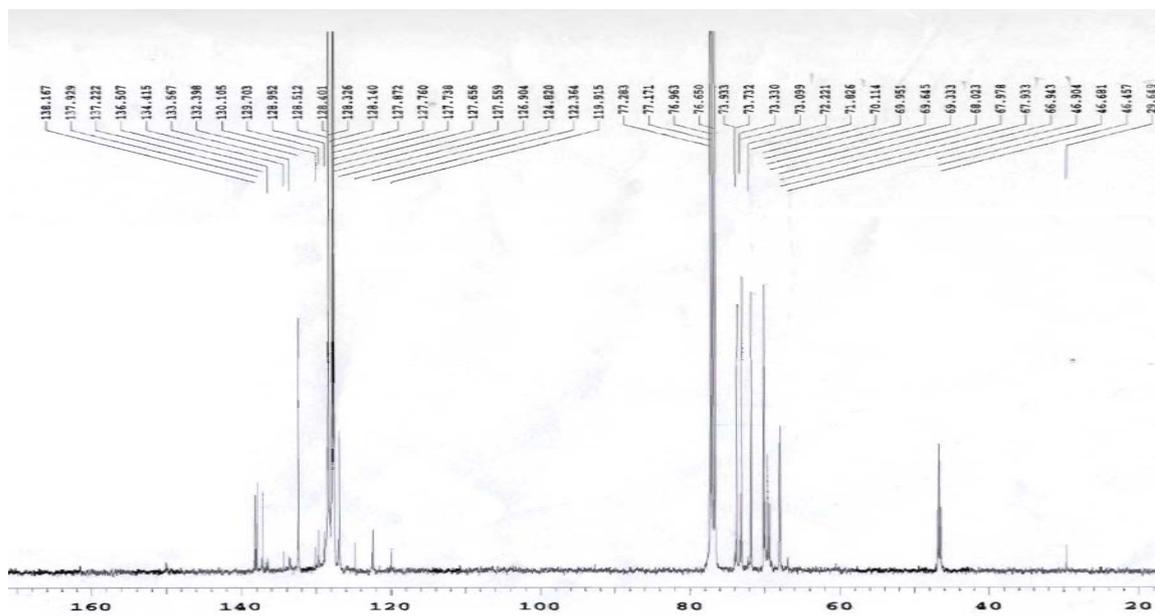
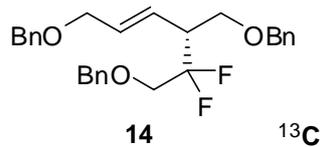
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		11.127	10214.1	125408.3	0.5958
2	2		12.027	374.3	7468.2	0.0355
3	3		13.027	1060.0	16484.5	0.0783
4	4		13.427	720.8	10641.2	0.0506
5	5		13.827	13683.9	213498.6	1.0143
6	6		14.377	16898.5	296095.2	1.4067
7	7		15.977	743.9	10322.8	0.0490
8	8		16.377	5214.2	120404.9	0.5720
9	9		17.427	3142.8	80600.7	0.3829
10	10		18.027	862443.0	17971485.3	85.3769
11	11		19.327	36646.3	799102.0	3.7963
12	12		20.427	33357.5	833011.4	3.9574
13	13		21.277	1484.9	29696.2	0.1411
14	14		22.277	11278.2	285794.2	1.3577
15	15		23.827	9110.5	249562.2	1.1856
合计:				1006372.9	21049575.7	100.0000

*90% ee*

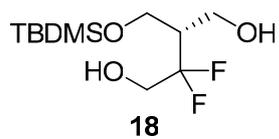




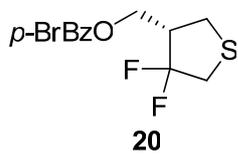
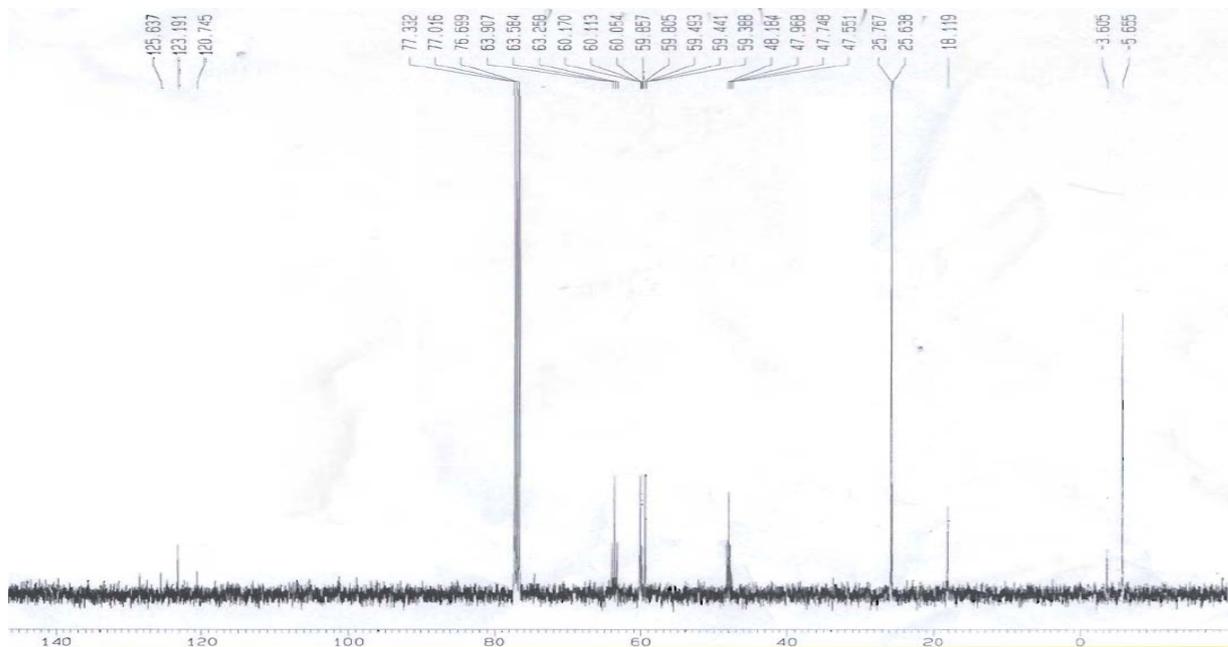




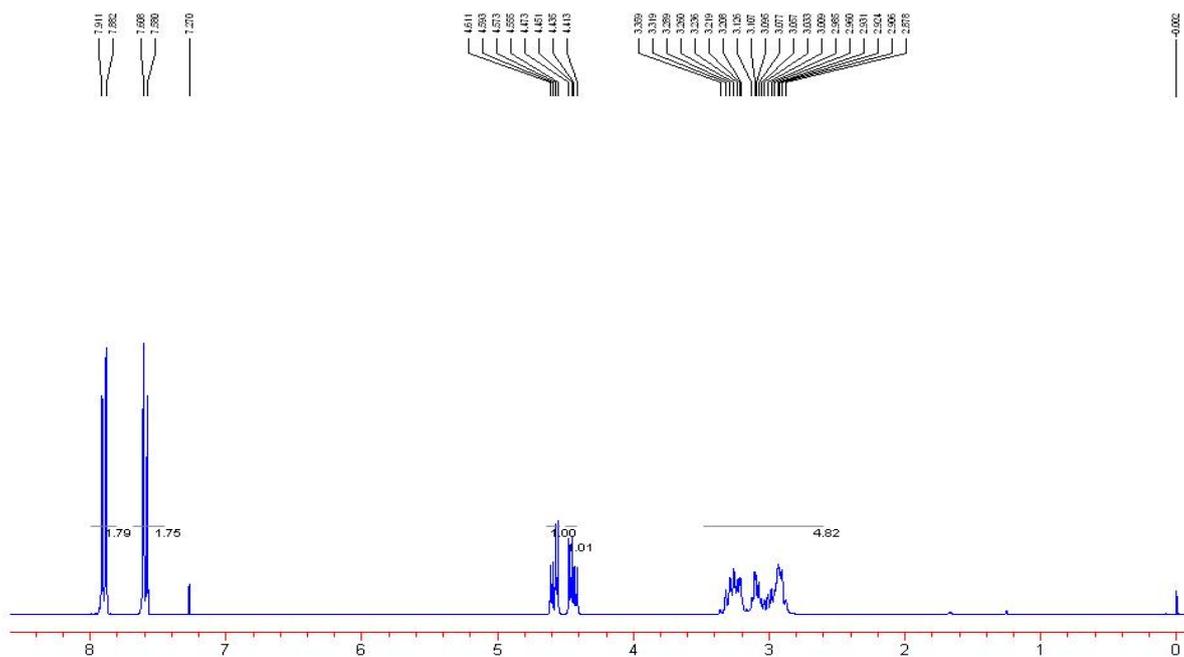


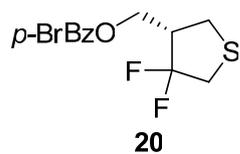


<sup>13</sup>C

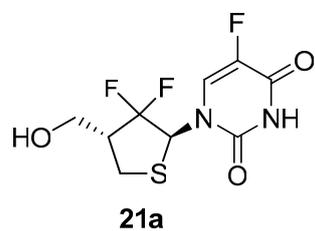
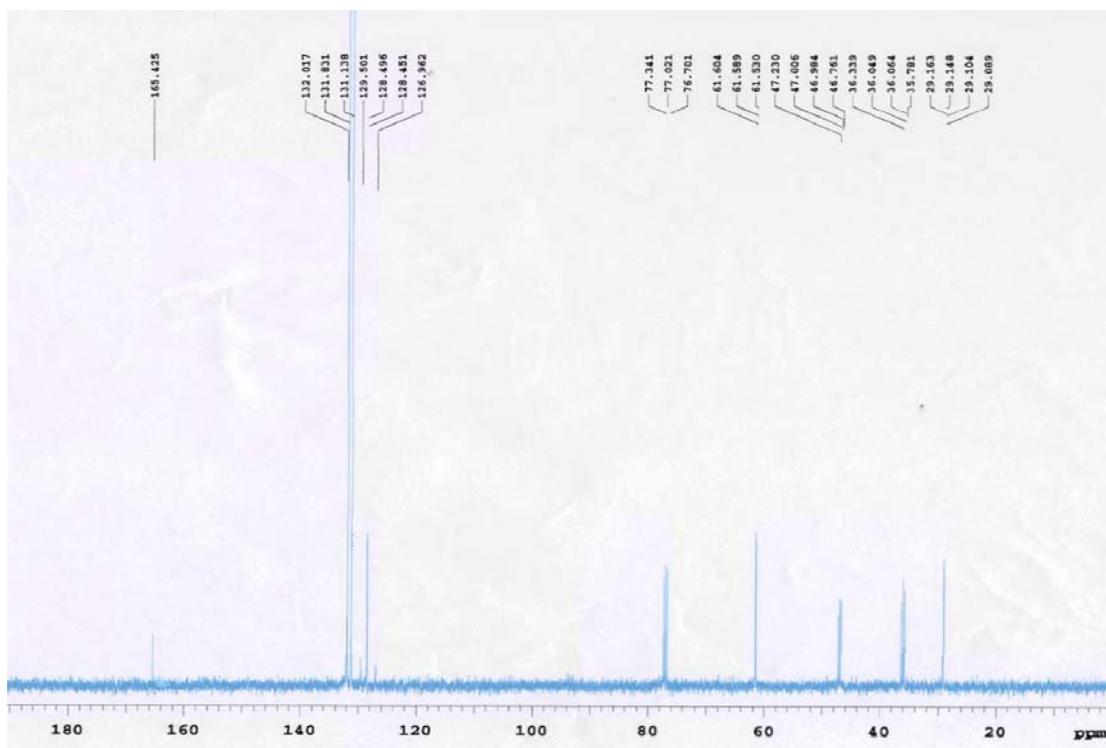


<sup>1</sup>H

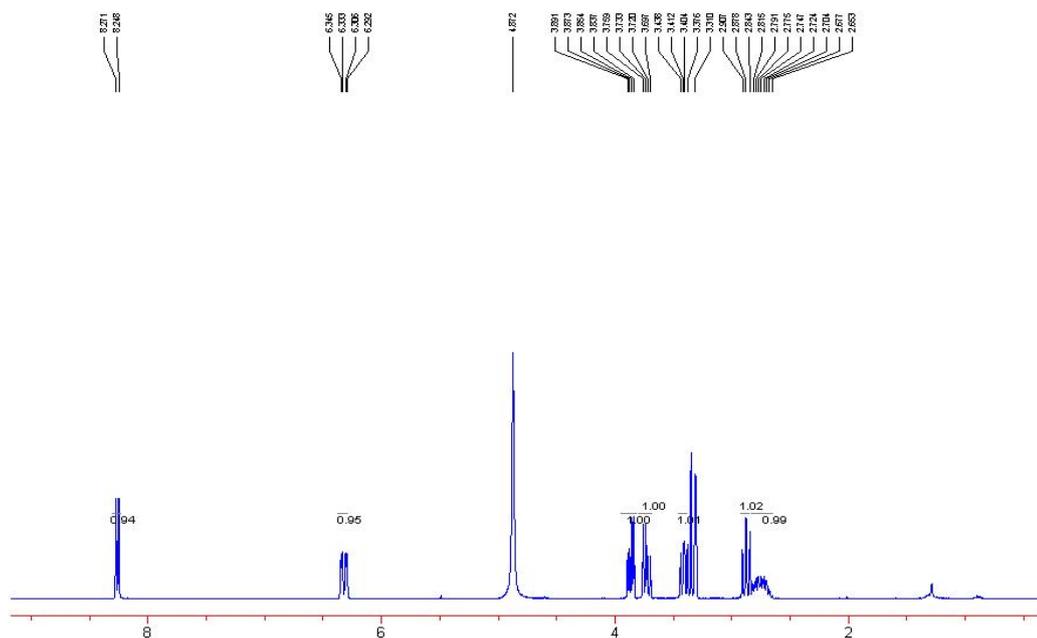


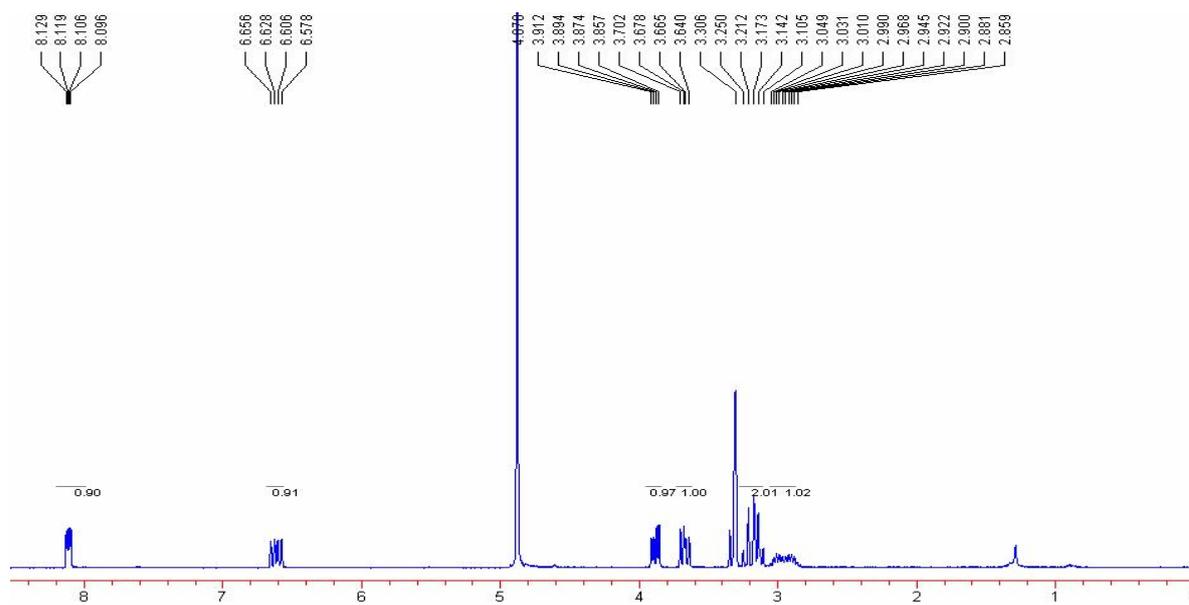
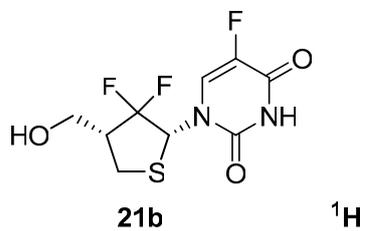
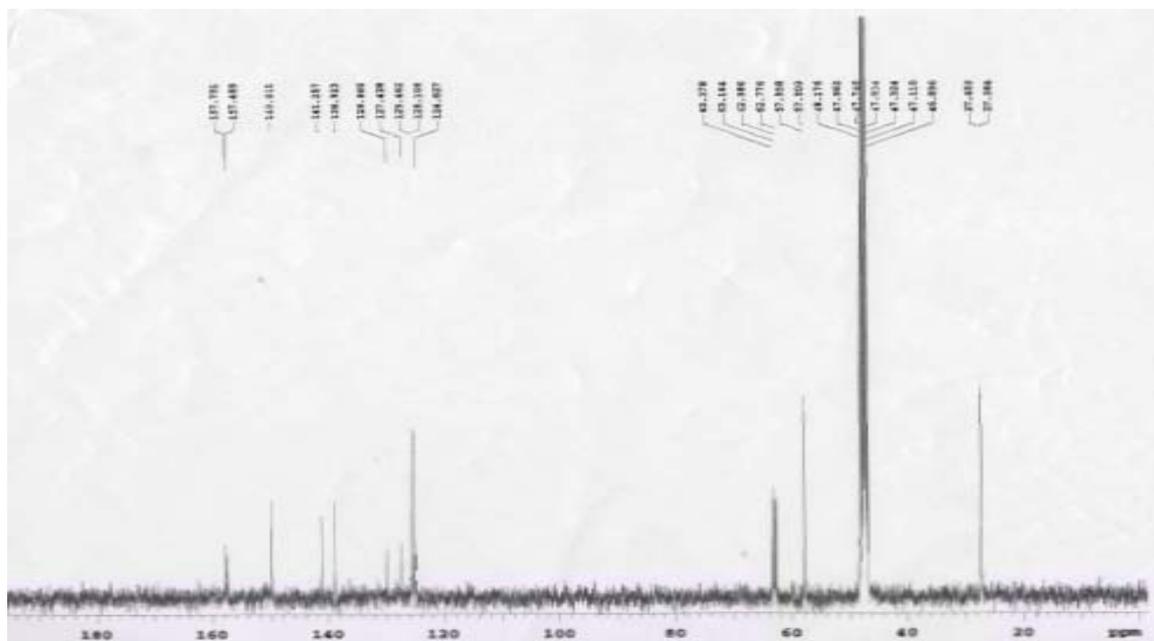
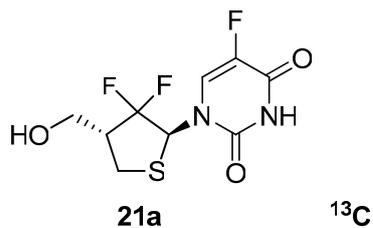


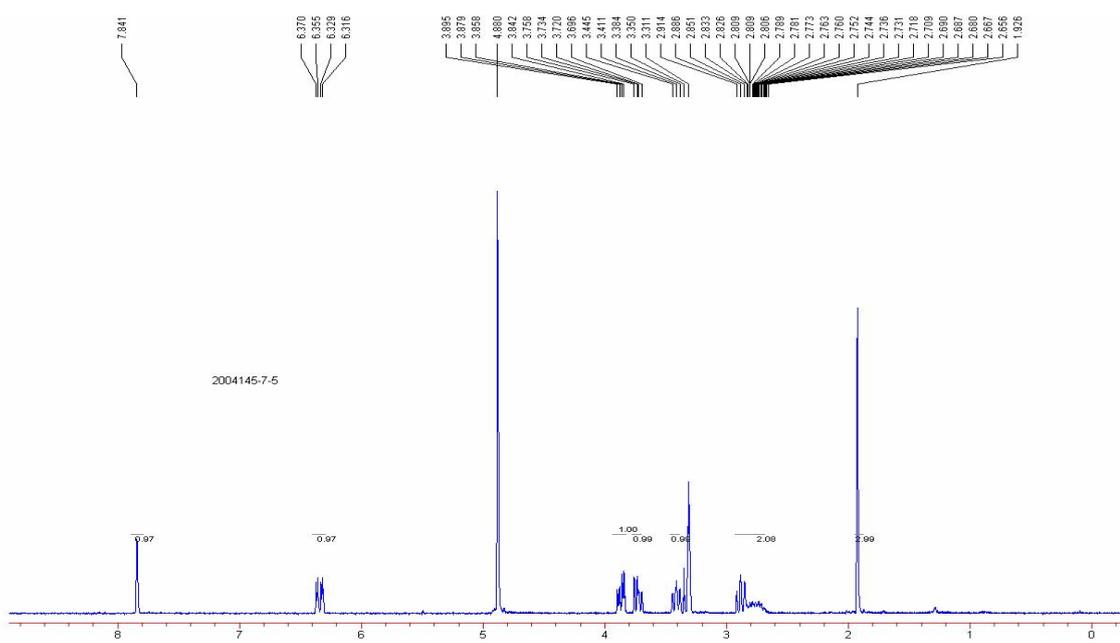
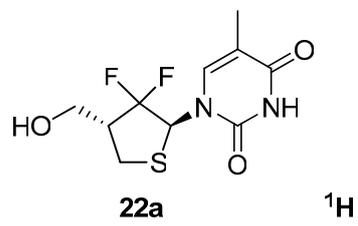
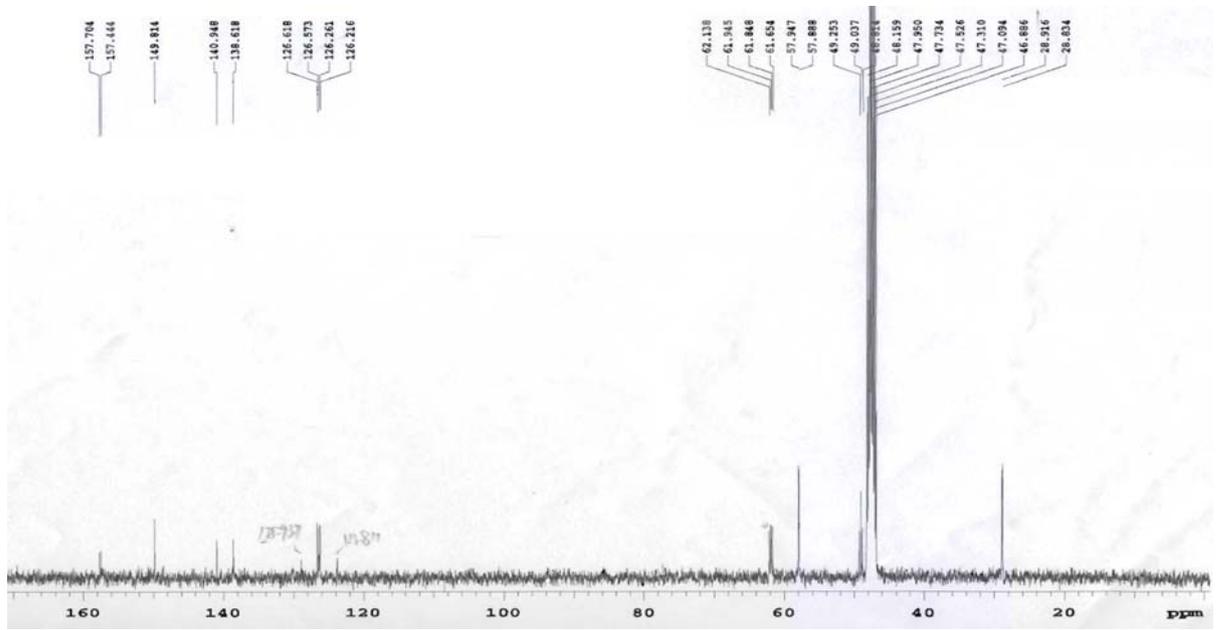
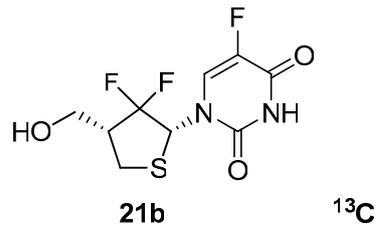
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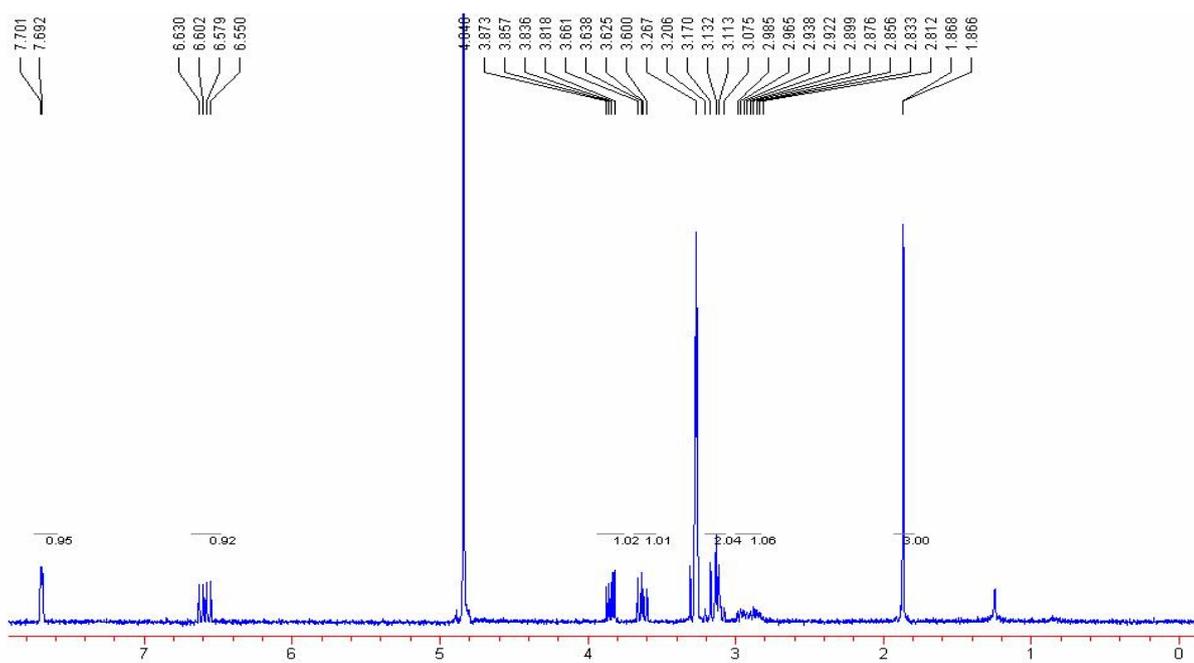
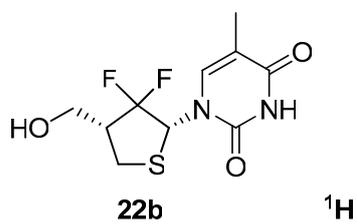
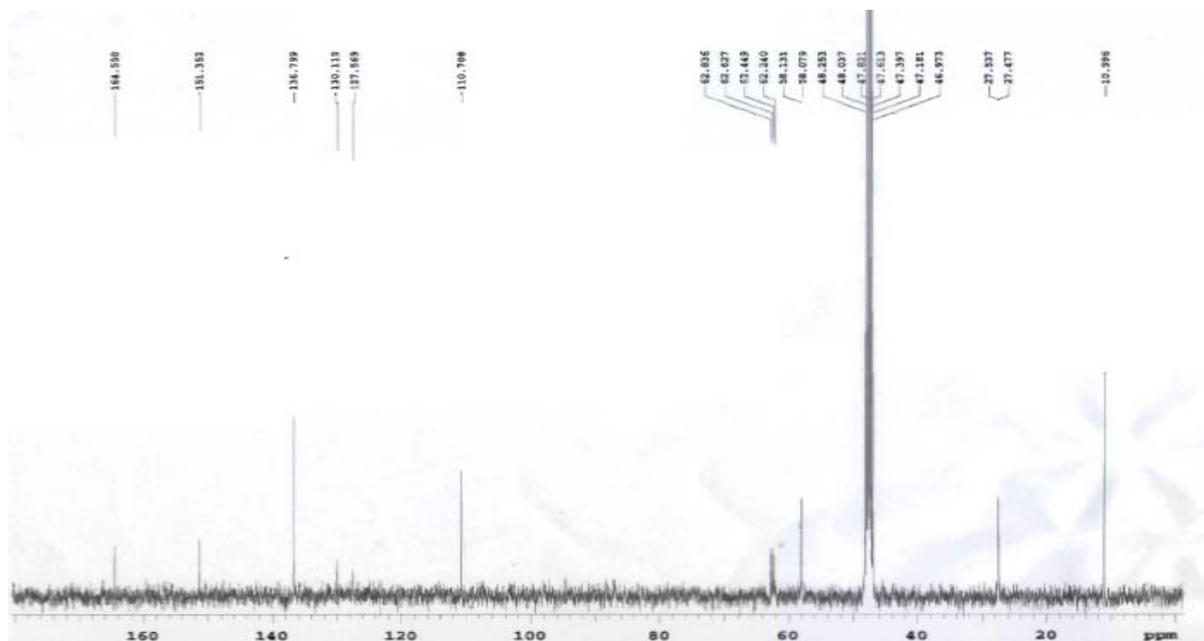
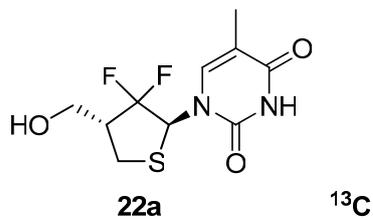


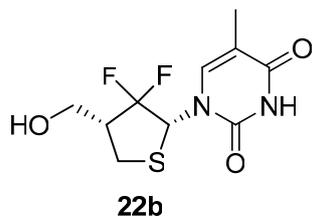
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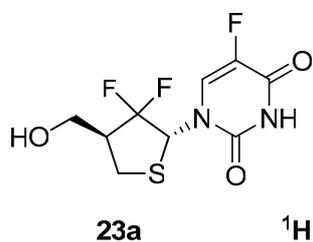
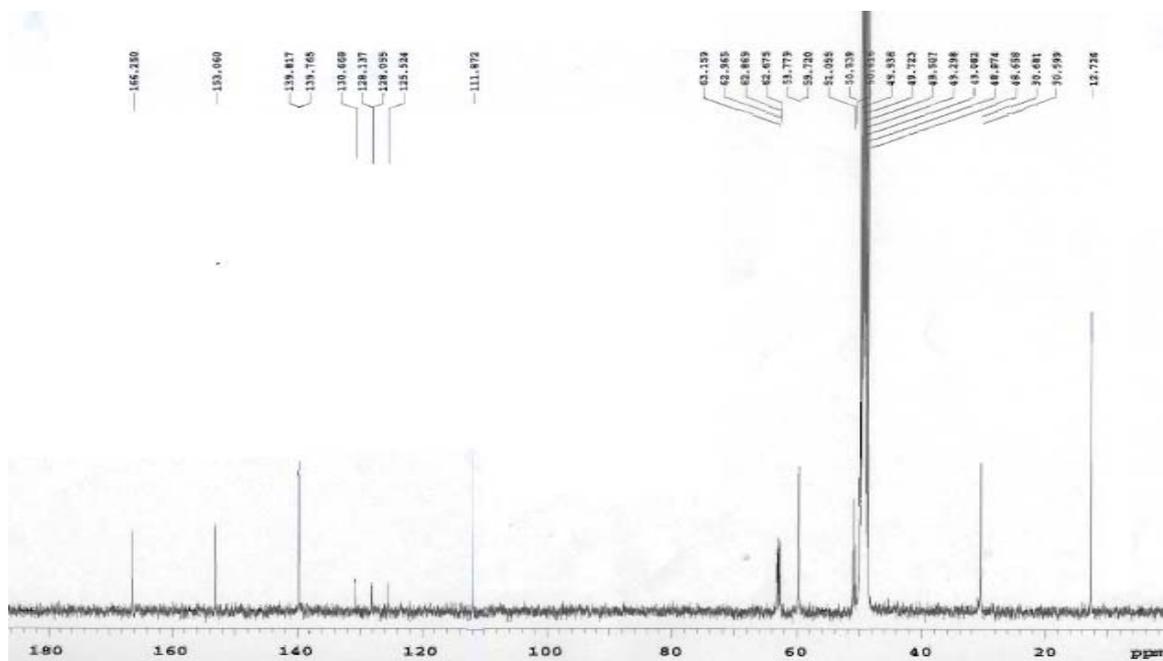




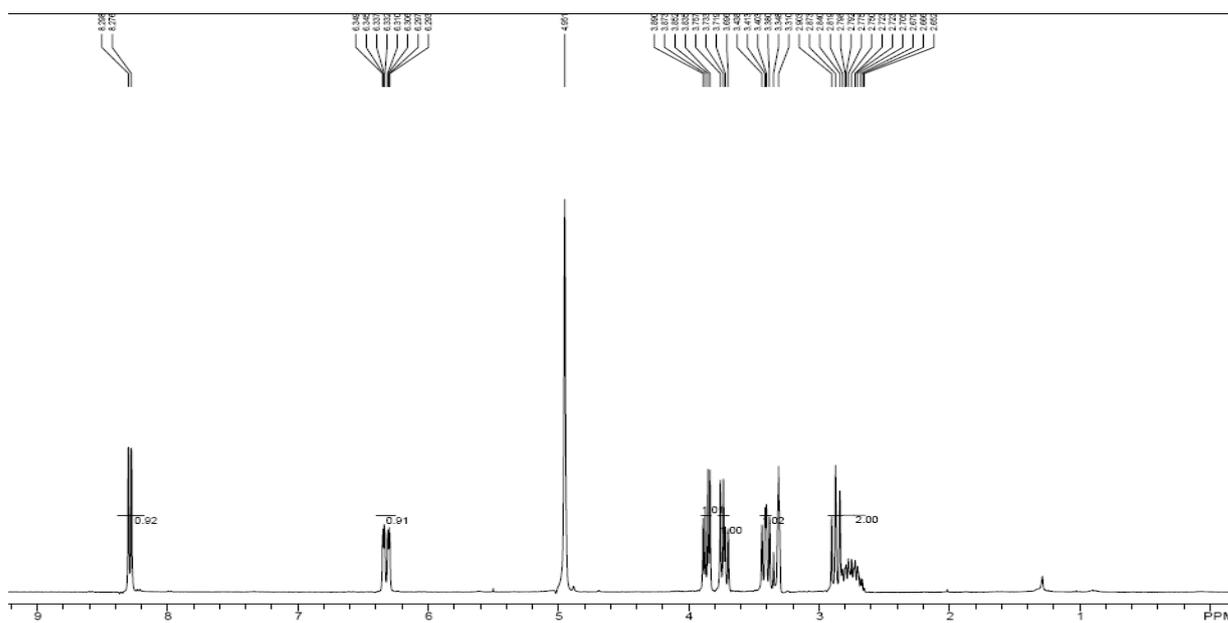


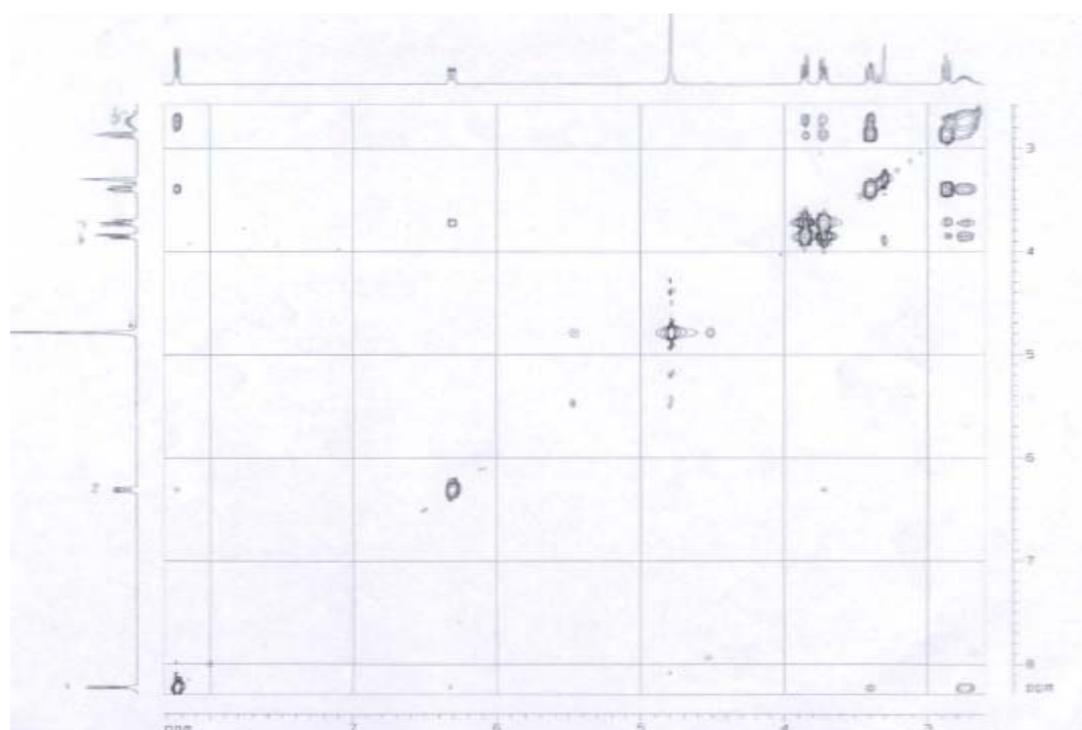
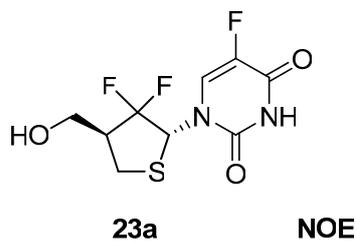
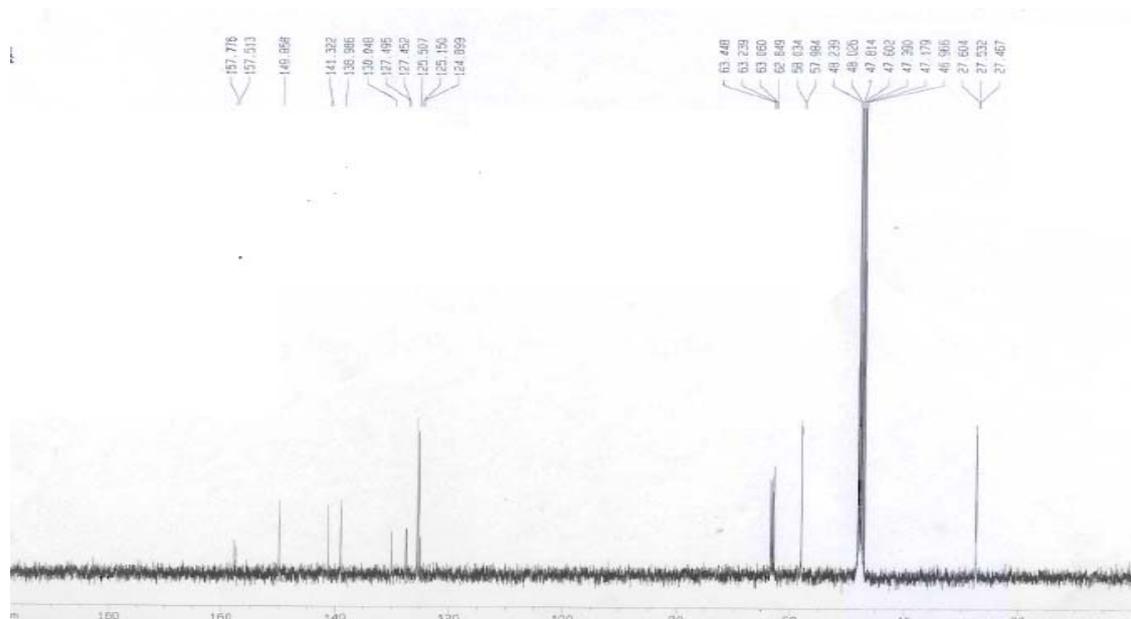
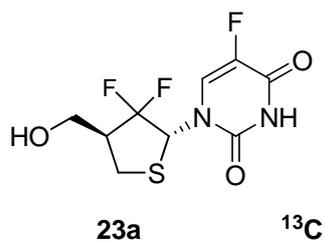


<sup>13</sup>C

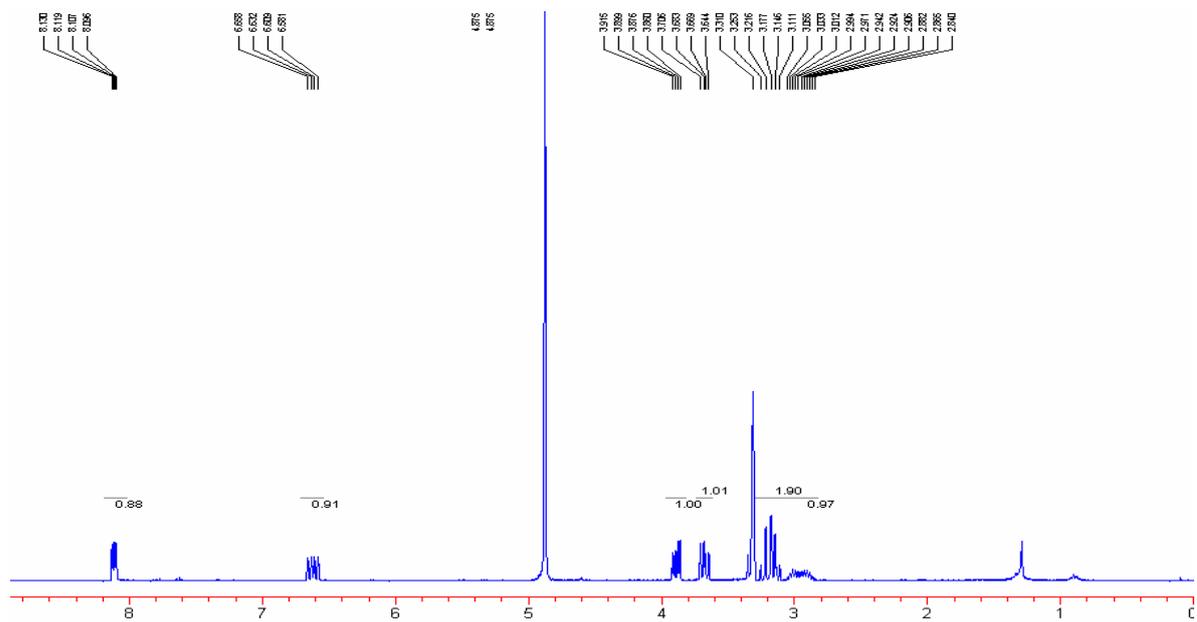
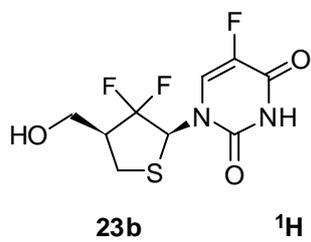
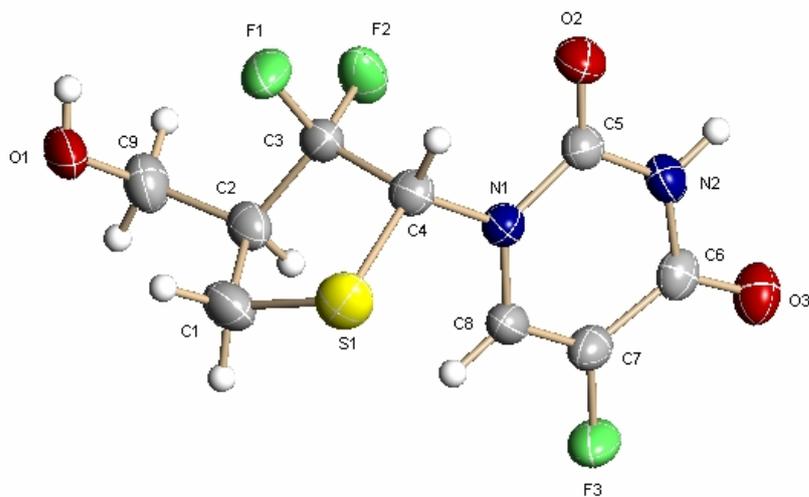


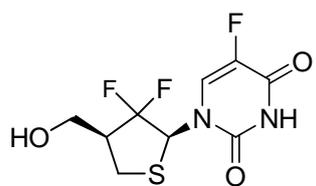
<sup>1</sup>H





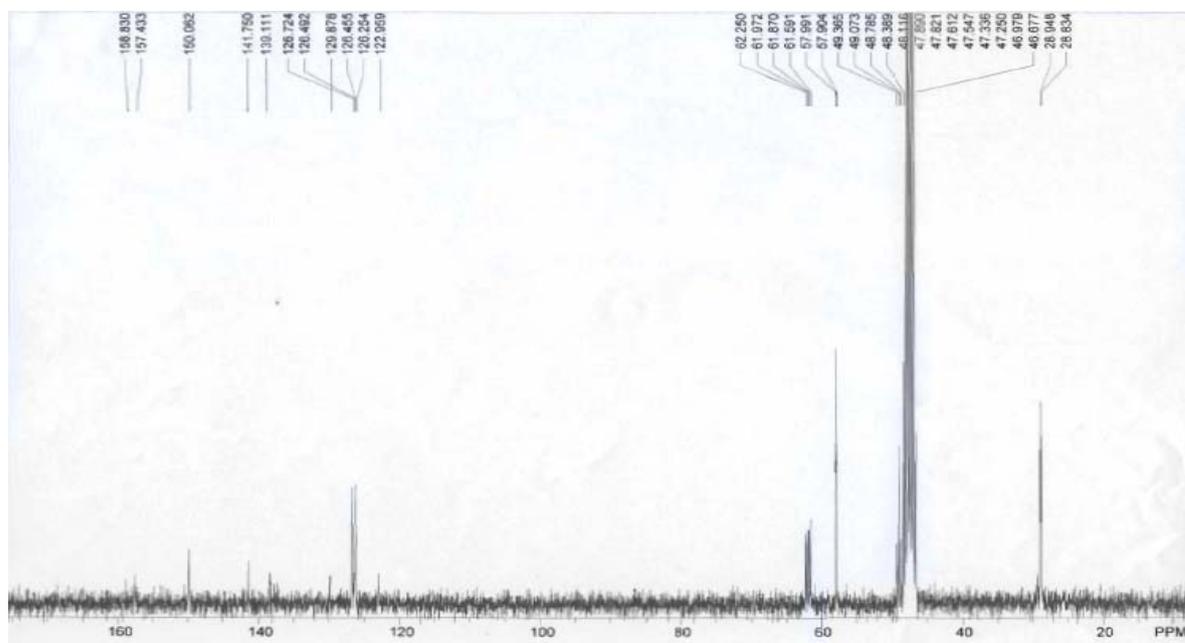
X-ray crystal structure of compound **23a**



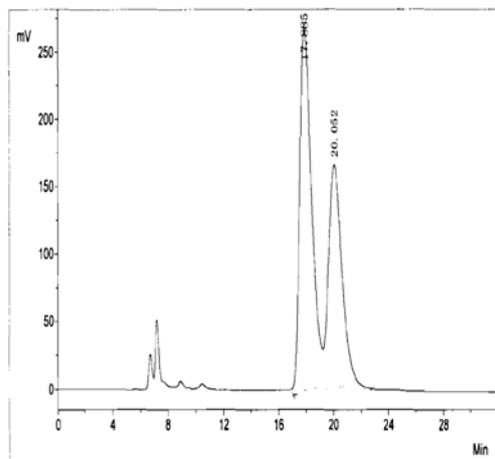


**23b**

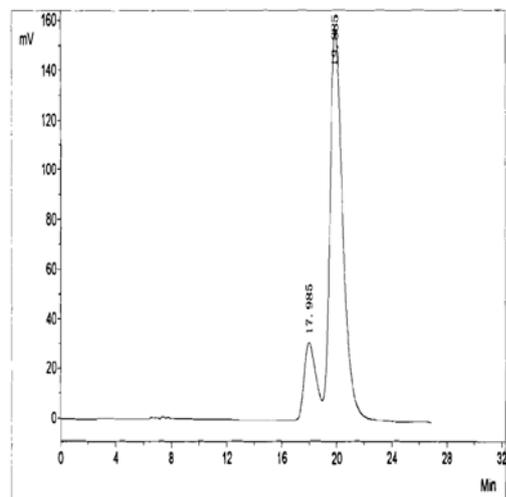
**<sup>13</sup>C**



Chiral HPLC analytical data of compound **21a**



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		17.885	268768.3	16268980.9	57.8470
2	2		20.052	166843.6	11855157.5	42.1530
合计:				435611.9	28124138.4	100.0000



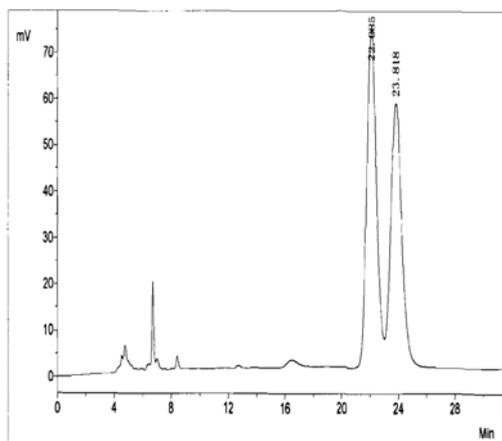
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		17.985	31234.2	1874549.2	15.4644
2	2		19.885	156928.8	10247132.7	84.5356
合计:				188163.0	12121681.9	100.0000

*authentic racemic*

**21a** *ee* 70%

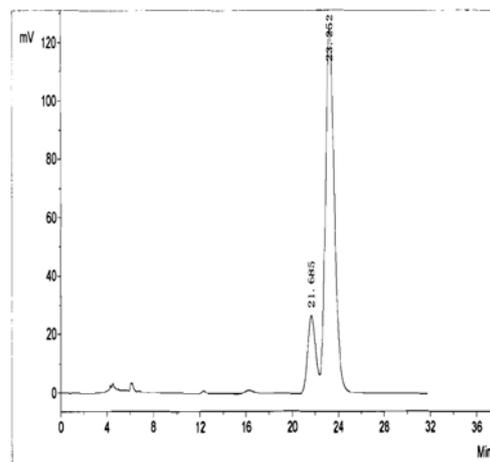
The chiral HPLC analytical data: Chiralpak OD column, detected at  $\lambda=214\text{nm}$ , eluent: *n*-hexane/*i*-PrOH (70:30), 0.4ml/min,  $t_R$  (21a)=19.8 min,  $t_R$  (23a)=17.8 min.

Chiral HPLC analytical data of compound **21b** and **23b**



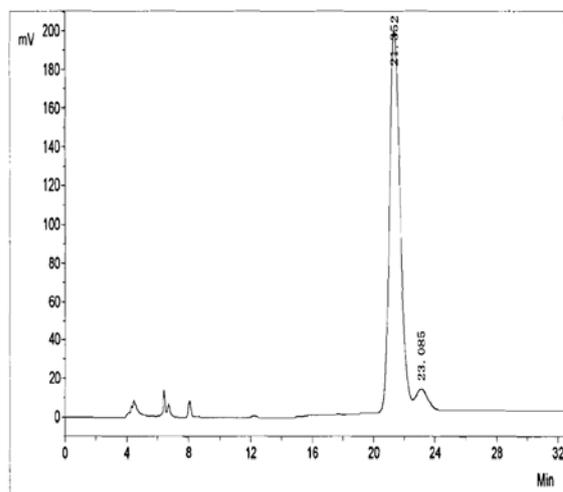
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		22.085	73075.4	3517359.5	53.0495
2	2		23.818	57120.9	3112980.4	46.9505
合计:				130196.3	6630339.9	100.0000

*authentic racemic*



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		21.685	26477.6	1279096.9	15.9350
2	2		23.252	124681.1	6747869.2	84.0650
合计:				151158.7	8026966.2	100.0000

**21b** *ee* 70%



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		21.352	197471.6	9569684.9	93.5022
2	2		23.085	11798.4	665032.7	6.4978
合计:				209270.0	10234717.7	100.0000

**23b** *ee* 87%

The chiral HPLC analytical data: Chiralpak IC column, detected at  $\lambda=214\text{nm}$ , eluent: *n*-hexane/*i*-PrOH (70:30), 0.7ml/min,  $t_R$  (23b) = 21.3 min,  $t_R$  (21b) = 23.2 min