# 2'-*C*-Branched Ribonucleosides II: The Synthesis of 2'-*C*-β-Trifluoromethyl Ribonucleosides

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## Experimental

All reagents and anhydrous solvents were purchased from Aldrich; other solvents were from Fisher unless otherwise noted. All reactions using air sensitive or moisture sensitive reagents were run under an argon atmosphere. $^1$H, $^{19}$F and $^{13}$C NMR spectra were recorded on Bruker 500 or Bruker 400 MHz NMR spectrometer. $^1$H chemical shifts are reported in δ (ppm) relative to tetramethylsilane, $^{19}$F chemical shift are recorded in δ (ppm) relative to $CFCl_3$ and $^{13}$C chemical shifts δ (ppm) relative to the solvent used. $^{19}$F-$^1$H NOE experiments were recorded on Bruker 400 spectrometer. High Resolution Mass Spectra were obtained from the Department of Chemistry, University of California at Riverside on VG-ZAB instrument. Merck silica gel (9385 grade, 230-400 mesh, 60 Å, Aldrich) was used for column chromatography. Silica gel on glass with fluorescent indicator (Sigma) was used for TLC.

**1,3,5-Tri-*O*-benzoyl-α-D-2-ketoribofuranose (2):** Under argon atmosphere, 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose **1** (10.0 g, 21.6 mmol) was added to the mixture of Dess-Martin periodinane (20.0 g, 47.2 mmol) in dry $CH_2Cl_2$ (100 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The solvent was removed and the residue was triturated with diethyl ether (200mL). Following filtration through a pad of silica gel and anhydrous $MgSO_4$ (w/w=1:1), the organic solution was washed with a solution of sodium thiosulfate pentahydrate (25 g) in water (150 mL), then ice cooled saturated $NaHCO_3$ (100 mL), brine (100 mL) and dried over $MgSO_4$. The solvent was removed and the residue was dried under high vacuum to give pure **2** as white foam: 9.835 g (97% yield). $^1H$ NMR ($CDCl_3$) δ 8.11-8.08 (m, 4H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.65-7.35 (m, 9H), 6.18 (s, 1H), 5.86 (d, 1H, *J* = 8.8 Hz), 5.04-5.01 (m, 1H), 4.82 (dd, *J* = 3.4, 12.5 Hz), 4.63 (dd, *J* = 4.5, 12.5 Hz).

**1,2,3,5-Tetra-*O*-benzoyl-2-*C*-β-trifluoromethyl-α-D-ribofuranose (3)**: Under argon atmosphere, a catalytic amount of TBAF (1 M solution in THF, 1.1 mL, 1.1 mmol) was added into the mixture of 1,3,5-tri-*O*-benzoyl-α-D-2-ketoribofuranose **2** (9.95 g, 21.6 mmol) with trifluoromethyltrimethylsilane (0.5 M solution in THF, 75.0 mL, 37.5 mmol) at -78 °C. The reaction mixture was allowed to warm to ambient temperature. The solution became yellow immediately upon the addition of TBAF and became dark brown eventually. After the reaction mixture was stirred for 18 h at room temperature, TBAF (1M solution in THF, 20 mL, 20 mmol) was added into the mixture. The mixture was stirred at room temperature for another 10 minutes. Following removal of THF under vacuum, $CH_2Cl_2$ was added and the mixture was washed with saturated aqueous NaCl. After the organic layer was dried over $MgSO_4$, the solvent was removed and the residue was dried under high vacuum. This material was dissolved in dry dichloromethane (300 mL). To the resulting solution at 0 °C, *N,N*-dimethylaminopyridine (3.96 g, 32.4 mmol), $Et_3N$ (40 mL), and benzoyl chloride (7.52 mL, 64.8 mmol) were added. After 5 h at ambient temperature, the reaction mixture was poured into 500 mL of ethyl ether and washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 15% ethyl acetate in hexanes to give **3** (10.0 g, 73% overall yield from **2**) as a white foam. The sterochemistry of **3** was confirmed by $^{19}F$-$^1H$ NOE.

$^1$H NMR ($CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* =7.5 Hz, 1H), 7.53 (t, *J* =8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.41-7.46 (m, 4H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 2H), 6.15 (d, *J* = 5.0 Hz, 1H), 4.97 (m, 1H), 4.77 (dd, *J* = 4.4, 12.1 Hz, 1H), 4.68 (dd, *J* = 5.8, 12.1 Hz, 1H). $^{19}$F NMR ($CDCl_3$) δ -73.4. $^{13}$C NMR ($CDCl_3$) δ 166.0, 164.7, 163.6, 162.8, 133.9, 133.8, 133.7, 133.2, 129.9, 129.8, 129.7, 129.3, 128.8, 128.6, 128.3, 127.9, 123.2 (q, *J* = 287.0 Hz), 94.3, 83.0 (q, *J* = 29.9 Hz) 81.0, 70.7, 62.8. HMRS calcd for $C_{34}H_{29}F_3NO_9$ $[M+NH_4]^+$ 652.1794; Found: 652.1794.

**2',3',5'-Tri-*O*-benzoyl-2'-*C*-β-trifluoromethyl-D-uridine (4a and 4b)**: A stirred suspension of uracil (280 mg, 2.5 mmol) and $(NH_4)_2SO_4$ (10 mg) in 1,1,1,3,3,3-hexamethyldisilazane (25 mL) was heated to reflux under argon until a clear solution formed. The clear solution was evaporated under vacuum to remove the excess 1,1,1,3,3,3-hexamethyldisilazane. The residue was dried under high vacuum (< 0.1 mm Hg) for 2 h. The crude bis(trimethylsilyl)uracil (2.5 mmol) obtained was dissolved in dry acetonitrile (25 mL), which was then transferred *via* cannula to a heavy-wall pressure tube containing 1,2,3,5-tetra-*O*-benzoyl-2-*C*-trifluoromethyl-α-D-ribofuranose **3** (0.50 g, 0.79 mmol). Under an argon atmosphere, trimethylsilyl trifluoromethansulfonate (0.45 mL, 2.5 mmol) was added in one portion to the solution with exclusion of moisture. The reaction mixture was heated to 120 °C for 3 days. The reaction was quenched by carefully pouring the mixture into 25 mL of 10% $NaHCO_3$ and stirred for 15 min. The mixture was extracted with methylene chloride, and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent under vacuum, the residue was purified by silica gel chromatography eluting with 25% ethyl acetate in hexanes. The reaction gave the β-anomer **4b** (157 mg, 32%; the fast isomer) and the α-anomer **4a** (7 mg, 1%; the slow isomer) as white solids in a combined yield of 33% along with the recovery of a large amount of starting material **3** (283 mg, 57%). The stereochemistry of **4a** and **4b** was determined by $^{19}$F-$^{1}$H NOE. β-isomer (**4b**): $^{1}$H NMR ($CDCl_3$) δ 9.60 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.46 (m, 5H), 7.30 (s, 1H), 7.19 (t, *J* = 8.0 Hz, 2H), 6.24 (d, *J* = 8.0 Hz, 1H), 5.62 (dd, *J* = 2.0, 8.5 Hz, 1H), 5.17-5.19 (m, 1H), 4.93 (dd, *J* = 2.5, 12.8 Hz, 1H), 4.61 (dd, *J* = 3.5, 12.8 Hz, 1H). $^{19}$F NMR ($CDCl_3$) δ -76.5. $^{13}$C NMR ($CDCl_3$) δ 165.9, 164.9, 164.1, 163.1, 149.9, 139.0, 134.3, 133.9, 133.5, 130.2, 129.8, 129.5, 129.2, 128.6, 128.4, 128.2, 127.5, 125.8, 123.4 (q, *J* = 283.8 Hz), 102.1, 85.5 (q, *J* = 28.9 Hz), 84.5, 79.7, 67.6, 62.0. HMRS calcd for $C_{31}H_{24}F_3N_2O_9$ $[M+H]^+$ 625.1434; Found: 625.1415. α-isomer (**4a**): $^{1}$H NMR ($CDCl_3$) δ 9.31 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.57-7.65 (m, 3H), 7.43-7.50 (m, 5H), 7.21(t, *J* = 8.5 Hz, 2H), 6.92 (s, 1H), 6.43 (d, *J* = 5.5 Hz, 1H), 5.70 (dd, *J* = 2.5, 8.3 Hz, 1H), 5.21 (m, 1H), 4.80 (dd, *J* = 4.0, 12.5 Hz, 1H), 4.69 (dd, *J* = 4.5, 12.5 Hz, 1H). $^{19}$F NMR ($CDCl_3$) δ -75.3. $^{13}$C NMR ($CDCl_3$) δ 166.0, 164.1, 163.5, 162.8, 149.8, 139.8, 134.7, 134.0, 133.4, 130.1, 129.73, 129.71, 129.2, 129.0, 128.5, 127.64, 127.59, 123.0 (q, *J* = 285.6 Hz), 102.1, 86.3, 85.3 (q, *J* = 29.5 Hz), 83.1, 70.8, 63.5, 60.4. HMRS calcd for $C_{31}H_{24}F_3N_2O_9$ $[M+H]^+$ 625.1434; Found: 625.1396.

**3,5-Di-*O*-benzoyl-2-*C*-β-trifluoromethyl-α-D-1-ribofuranosyl bromide (5):** A mixture of 1,2,3,5-tetra-*O*-benzoyl-2-*C*-trifluoromethyl-α-D-ribofuranose **3** (1.62 g, 2.56 mmol) and 30% HBr in AcOH (10 mL) was stirred and heated to 80-85 °C for 5 h in a dry sealed heavy-wall pressure tube. After it was cooled, the reaction mixture was diluted with methylene chloride (110 mL) and transferred to a separating funnel containing ice. The organic layer was washed subsequently with ice water (45 mL), ice cooled saturated $NaHCO_3$ (2x45 mL) and ice water (45 mL). After the organic layer was dried by anhydrous $MgSO_4$ and the solvent was removed, the residue was purified by silica gel chromatography eluting with 10% ethyl acetate in hexane to give **5** (0.965 g, 77%). The stereochemistry of **5** was determined by $^{19}F$-$^{1}H$ NOE. $^{1}H$ NMR ($CDCl_3$) δ (d, *J* = 7.7 Hz, 2H), 8.01 (d, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* =7.7 Hz, 2H), 6.93 (s, 1H), 5.67 (d, *J* = 5.4 Hz), 4.75-4.85 (m, 2H), 4.63 (dd, *J* = 6.9, 13.3 Hz, 1H), 3.56 (br s, 1H). $^{19}F$ NMR ($CDCl_3$) δ -78.6. $^{13}C$ NMR ($CDCl_3$) δ 165.9, 164.5, 134.1, 133.3, 130.0, 129.7, 129.1, 128.7, 128.4, 128.1, 122.9 (q, *J* = 279.7 Hz), 94.0, 82.7, 81.1 (q, *J* = 28.7 Hz), 68.9, 61.9. HMRS calcd for $C_{20}H_{17}O_6F_3Br$ $[M+H]^+$ 489.0161; Found: 489.0166.

**3',5'-Di-*O*-benzoyl-4-*N*-benzoyl-2'-*C*-β-trifluoromethyl-β-D-Cytidine (6)**: A mixture of **3** (2.39 g, 3.77 mmol) and 30% HBr in acetic acid (30 mL) was stirred and heated to 80-85 °C in a heavy-wall pressure tube overnight. After it cooled, the reaction mixture was diluted with methylene chloride (360 mL) and transferred to a separating funnel containing ice. After mixing and separating, the organic layer was washed successively with ice $H_2O$ (150 mL), ice cooled saturated aqueous $NaHCO_3$ (2x150 mL), ice water (150 mL). After the organic layer was dried over $MgSO_4$, the solvent was removed and the residue was dried under reduced pressure to give **5** as a pale-yellow oil which was used without further purification. **5** was then taken up in dry toluene (100 mL) and transferred *via* cannula to the reaction flask containing persilylated 4-*N*-

benzoylcytosine (8.74 mmol), which was prepared *in situ* from 4-*N*-benzoylcytosine (1.88 g, 8.74 mmol), $(NH_4)_2SO_4$ (30 mg) in 1,1,1,3,3,3-hexamethyldisilazane (100 mL) as described above for the synthesis of **4a** and **4b**. To this solution was added HgO (1.15 g) and $HgBr_2$ (1.15 g). The reaction mixture was heated to reflux under an argon atmosphere overnight. When TLC indicated that **5** was completely consumed, the reaction was quenched by addition of methanol (10 mL) and water (5 mL). The mixture was stirred for another 15 min at rt and extracted with methylene chloride. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel chromatography eluting with 0.5% methanol in chloroform to provide the **6** (0.99 g, 42% yield) as the only isomer. The stereochemistry of **6** was determined by the $^{19}F$-$^{1}H$ NOE experiment. $^{1}H$ NMR ($CDCl_3$) δ 9.20 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 2H), 8.04 (m, 3H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.72 (m, 1H), 7.57 (m, 3H), 7.40-7.50 (m, 7H), 6.55 (br s, 1H), 5.85 (d, *J* = 5 Hz, 1H), 4.89 (m, 1H), 4.70-4.75 (m, 2H). $^{19}F$ NMR ($CDCl_3$) δ -77.2. $^{13}C$ NMR ($CDCl_3$) δ 166.4, 166.0, 164.8, 163.2, 156.8, 143.9, 133.6, 133.3, 133.2, 132.7, 130.0, 129.6 129.2, 128.9, 128.7, 128.4, 127.6, 123.9 (q, *J* = 286.9 Hz), 97.7, 90.9, 80.1, 79.8 (q, *J* = 28.0 Hz), 70.7, 62.4. HRMS calcd for $C_{31}H_{25}N_3O_8F_3$ $(M+H)^+$ 624.1594; Found: 624.1588.

**3',5'-Di-*O*-benzoyl-2'-*C*-β-trifluoromethyl-β-D-uridine (7):** A mixture of **3** (2.32 g, 3.66 mmol) and 30% HBr in acetic acid (20 mL) was stirred and heated to 80-85 °C in a heavy-wall pressure tube overnight. After it cooled, the reaction mixture was diluted with methylene chloride (240 mL) and transferred to a separating funnel containing ice. After mixing and separating, the organic layer was washed successively with ice $H_2O$ (100 mL), ice cooled saturated aqueous $NaHCO_3$ (2x100 mL), ice water

(100 mL). After the organic layer was dried over $MgSO_4$, the solvent was removed and the residue was dried under reduced pressure to give **5** as a pale-yellow oil which was used without further purification. **5** was then taken up in dry benzene (70 mL) and transferred *via* cannula to the reaction flask containing bis(trimethylsilyl)uracil (8.03 mmol), which was prepared *in situ* from uracil (0.90 g, 8.03 mmol), $(NH_4)_2SO_4$ (30 mg) in 1,1,1,3,3,3-hexamethyldisilazane (80 mL) as described above for the synthesis of **4a** and **4b**. To this solution was added HgO (1.00 g) and $HgBr_2$ (1.00 g), the reaction mixture was then heated to reflux under an argon atmosphere for 8 h. When TLC indicated that **5** was completely consumed, the reaction was quenched by addition of methanol (15 mL) and water (6 mL). The mixture was stirred for another 30 min at rt and extracted with methylene chloride. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel chromatography eluting with 0.5% methanol in chloroform to provide the **7** (0.894 g, 47% yield) as the only isomer. The stereochemistry of **7** was determined by the $^{19}F$-$^{1}H$ NOE experiment. $^{1}H$ NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* =8.0 Hz, 2H), 7.51-7.63 (m, 3H), 7.43-7.47 (m, 4H), 6.33 (s, 1H), 5.96 (d, *J* = 5.0 Hz, 1H), 5.85 (br s, 1H), 5.58 (d,*J* = 8.0 Hz, 1H), 4.92 (dd, *J* = 4.0, 12.0 Hz, 1H), 4.57-4.66 (m, 1H), 4.55 (dd, *J* = 4.0, 12.0 Hz, 1H). $^{19}F$ NMR ($CDCl_3$) δ -76.7. $^{13}C$ NMR ($CDCl_3$) δ 165.8, 164.7, 163.2, 150.7, 139.3, 133.9, 133.5, 130.1, 129.5, 129.1, 128.6, 128.5, 128.2, 123.5 (q, *J* = 284.7 Hz), 102.9, 89.5, 79.7 (q, *J* = 27.8 Hz), 78.0, 69.0, 61.6. HRMS calcd for $C_{24}H_{20}N_2O_8F_3$ $(M+H)^+$ 521.1172; Found: 521.1162.

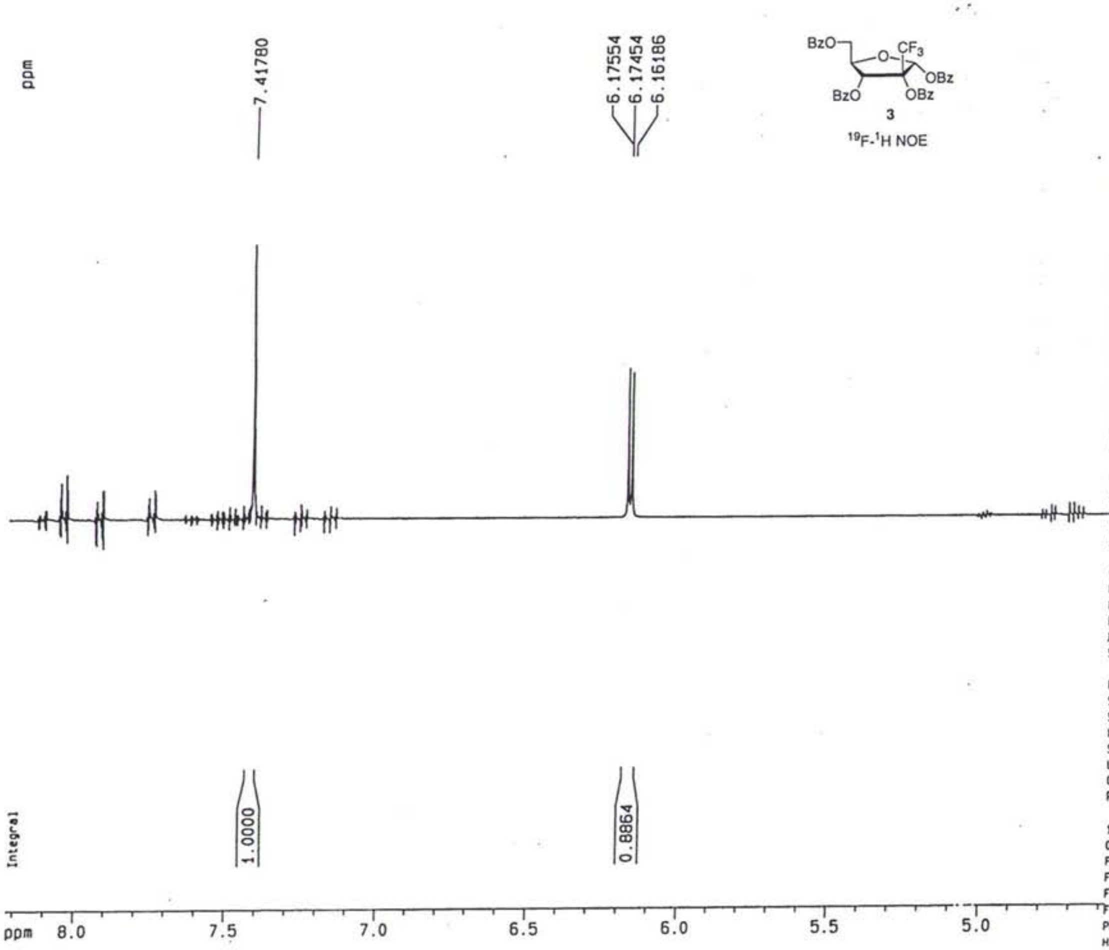
**3',5'-Di-*O*-benzoyl-5-methyl-2'-*C*-β-trifluoromethyl-β-D-uridine (8):** A mixture of **3** (1.694 g, 2.67 mmol) and 30% HBr in acetic acid (15 mL) was stirred and heated to 80-85 °C in a heavy-wall pressure tube for 5 h. After it cooled, the reaction mixture was diluted with methylene chloride (175 mL) and transferred to a separating funnel containing ice. After mixing and separating, the organic layer was washed successively with ice $H_2O$ (75 mL), ice cooled saturated aqueous $NaHCO_3$ (2x75 mL), ice water (75 mL). After the organic layer was dried over $MgSO_4$, the solvent was removed and the residue was dried under reduced pressure to give **5** as a pale-yellow oil which was used without further purification. **5** was then taken up in dry benzene (70 mL) and transferred *via* cannula to the reaction flask containing persilylated thymine (6.0 mmol), which was prepared *in situ* from thymine (0.76 g, 6.0 mmol) and $(NH_4)_2SO_4$ (20 mg) in 1,1,1,3,3,3-hexamethyldisilazane (60 mL) as described above for the synthesis of **4a** and **4b**. To this solution was added HgO (0.77 g) and $HgBr_2$ (0.77 g). The reaction mixture was heated to reflux under an argon atmosphere overnight. After it was cooled down, the reaction was quenched by addition of methanol (10 mL) and water (4 mL). The mixture was stirred for another 15 min at rt and extracted with methylene chloride. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel chromatography eluting with 0.5% methanol in chloroform to provide the **8** (0.817 g, 57% yield) as the only isomer. The stereochemistry of **8** was determined by the $^{19}F$-$^{1}H$ NOE experiment. $^{1}H$ NMR ($CDCl_3$) δ 10.46 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 8.07 (d, *J* =8.0 Hz, 2H), 7.55-7.65 (m, 2H), 7.45 (m, 4H), 7.29 (s, 1H), 6.36 (s, 1H), 6.08 (s, 1H), 5.98 (d, *J* = 8.0 Hz, 1H), 4.95 (dd, *J* = 4.0, 12.0, 1H), 4.66 (m, 1H), 4.56 (dd, *J* = 3.2, 12.0, 1H), 1.66 (s, 3H). $^{19}F$ NMR ($CDCl_3$) δ -76.1. $^{13}C$ NMR ($CDCl_3$) δ 165.9, 164.8, 163.9, 150.8, 134.8, 133.8, 133.5, 130.1, 129.5, 129.2, 128.6, 128.5, 128.3, 123.6 (q, *J* = 281.7 Hz), 111.6, 89.5, 79.6 (q, *J* = 29.2

Hz), 69.0, 61.6, 12.0. HRMS calcd for $C_{25}H_{22}N_2O_8F_3$ $(M+H)^+$ 535.1328; Found: 535.1311.

**2'-*C*-β-trifluoromethyl-β-D-cytidine (9):** Ammonia was bubbled into a solution of **6** (128 mg, 0.205 mmol) in methanol (25 mL) at 0 °C for half an hour. The solution was kept at 4 °C for 2 days and then concentrated under vacuum. The residue was redissolved in water (20 mL) and washed with $CCl_4$ (3x20 mL). The aqueous layer was concentrated and the residue was purified by silica gel chromatography eluting with ethyl acetate and methanol (4:1) to give **9** (58 mg, 91%) as a white solid. $^1$H NMR (DMSO) δ 7.78 (d, $J$ = 7.5 Hz, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 6.45 (s, 1H), 6.21 (s, 1H), 5.95 (d, $J$ = 7.0 Hz, 1H), 5.71 (d, $J$ = 7.5 Hz, 1H), 5.23 (t, $J$ = 4.5 Hz, 1H), 4.32 (t, $J$ = 7.5 Hz, 1H), 3.77-3.83 (m, 2H), 3.61-3.65 (m, 1H). $^{13}$C NMR (DMSO) δ 165.4, 154.6, 141.7, 124.5 (q, $J$ = 285.1 Hz), 93.9, 88.2, 81.1, 79.8 (q, $J$ = 27.1Hz), 67.7, 58.5. HRMS calcd for $C_{10}H_{13}F_3N_3O_5$ $[M+H]^+$ 312.0807; Found 312.0804.

**2'-*C*-β-trifluoromethyl-β-D-uridine (10):** A solution of **7** (186 mg, 0.36 mmol) in ammonia-saturated methanol (0 °C; 25 mL) was kept at 4 °C for 2 days. Whe TLC indicated that the reaction was complete, the solvent was removed under vacuum. The residue was purified by chromatography eluting with 12% methanol in chloroform to provide **10** (109 mg, 98%) as a white solid. $^1$H NMR (DMSO) δ 7.90 (d, $J$ = 8.0 Hz, 1H), 6.65 (s, 1H), 6.08 (s, 1H), 6.06 (d, $J$ = 6.5 Hz, 1H), 5.66 (d, $J$ =8.0 Hz, 1H), 5.34 (br s, 1H), 4.38 (t, $J$ = 7.8 Hz, 1H), 3.81-3.83 (m, 2H), 3.63-3.66 (m, 1H). $^{13}$C NMR (DMSO) δ 162.8, 149.9, 140.8, 124.4 (q, $J$ = 284.6 Hz), 101.5, 87.6, 81.4, 80.0 (q, $J$ = 27.5 Hz), 67.3, 58.1. HRMS calcd for $C_{10}H_{12}F_3N_2O_6$ $[M+H]^+$ 313.0647; Found 313.0650.

**2'-*C*-β-trifluoromethyl-5-methyl-β-D-uridine (11):** A solution of **8** (346 g, 0.65 mmol) in ammonia-saturated methanol (0 ºC; 50 mL) was kept at 4 ºC for 2 days. When TLC indicated that the reaction was complete, the solvent was removed under vacuum. The residue was purified by chromatography eluting with 10% methanol in chloroform to provide **11** (210 mg, 99%) as a white solid. $^1$H NMR (DMSO) δ 7.84 (s, 1H), 6.64 (br s, 1H), 6.07 (s, 1H), 6.03 (br s, 1H), 5.42 (br s, 1H), 4.43 (d, *J* = 8.5 Hz, 1H), 3.81-3.86 (m, 2H), 3.65-3.67 (m, 1H), 1.75 (s, 3H). $^{13}$C NMR (DMSO) δ 163.5, 150.0, 136.5, 124.4 (q, *J* = 285.4 Hz), 108.8, 87.5, 81.4, 78.0 (q, *J* = 27.3 Hz), 67.2, 58.1, 12.2. HRMS calcd for $C_{11}H_{14}F_3N_2O_6$ [M+H]$^+$ 327.0804; Found 327.0819.



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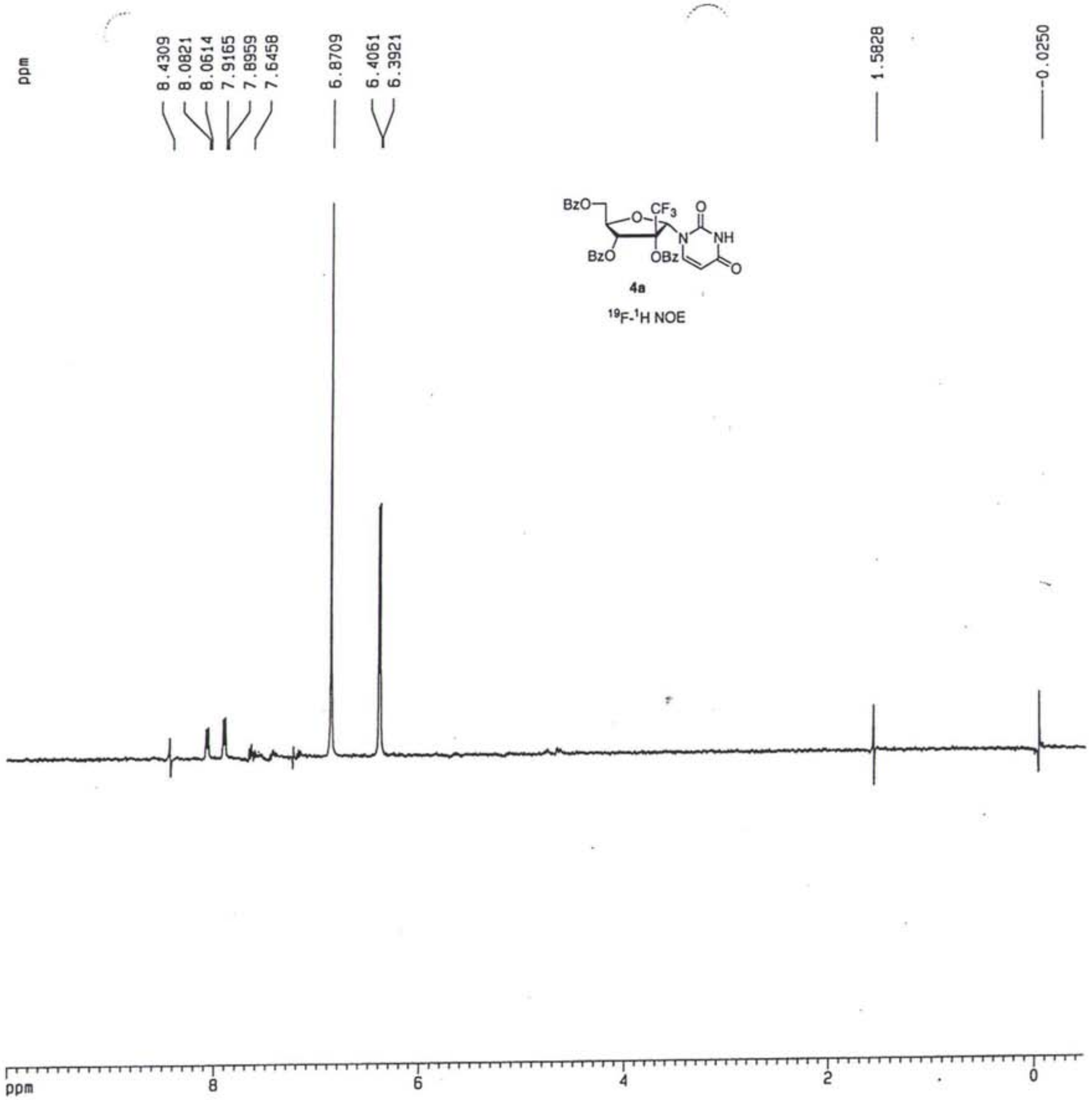

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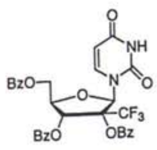
TE               300.0 K
D1         1.00000000 sec
d11        0.03000000 sec
d12        0.00002000 sec
D20        3.00000000 sec
L4                   1
NUC1                1H
P1                7.30 usec
PL1              -6.00 dB
SFO1       400.1319246 MHz
FQ2LIST          f19.1
NUC2               19F
PL2             120.00 dB
PL14             50.00 dB
SFO2       376.4694828 MHz

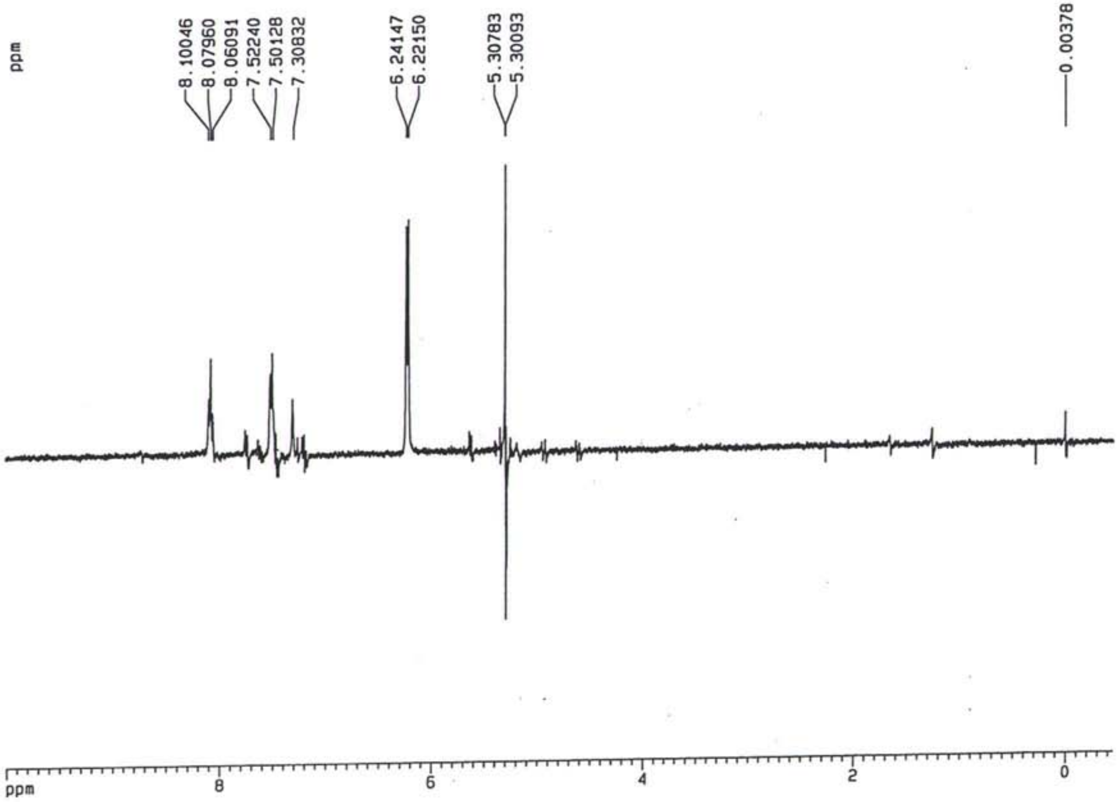
F2 - Processing parameters
SI               65536
SF         400.1300179 MHz
WDW                 EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.00

1D NMR plot parameters
CX               20.00 cm
F1P             10.007 ppm
F1             4003.97 Hz
F2P             -0.476 ppm
F2             -190.66 Hz
PPMCM          0.52416 ppm/cm
HZCM         209.73154 Hz/cm
```



**4b**

$^{19}F$-$^{1}H$ NOE

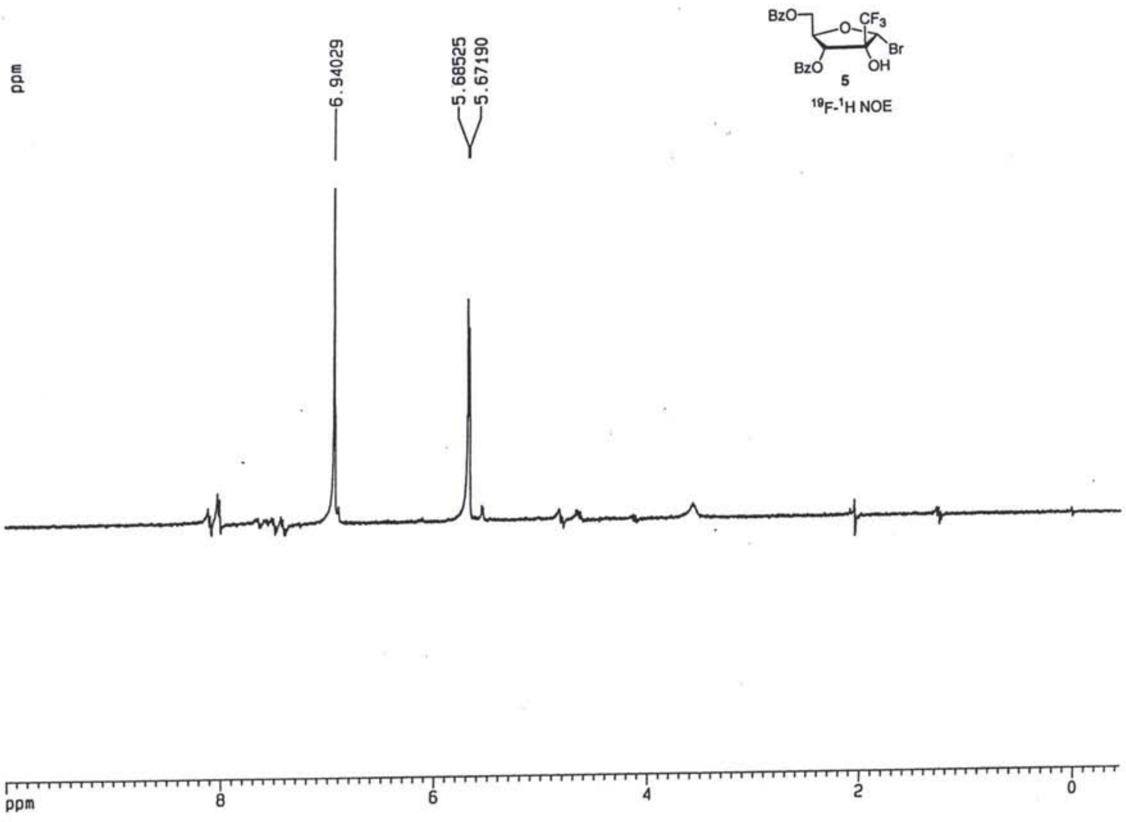


```
Current Data Parameters
NAME          junk-2.f19
EXPNO                  3
PROCNO                 2

F2 - Acquisition Parameters
Date_             991103
Time               16.25
INSTRUM            spect
PROBHD     5 mm QNP  1H
PULPROG       noemul.f19
TD                 65536
SOLVENT            CDCl3
NS                    24
DS                     8
SWH          4194.631 Hz
FIDRES       0.064005 Hz
AQ          7.8119411 sec
RG                  71.8
DW           119.200 usec
DE              4.50 usec
TE               300.0 K
D1        1.00000000 sec
d11       0.03000000 sec
d12       0.00002000 sec
D20       3.00000000 sec
L4                     1
NUC1                  1H
P1              7.40 usec
PL1             -6.00 dB
SF01     400.1319246 MHz
F02LIST            f19.1
NUC2                 19F
PL2             120.00 dB
PL14             54.00 dB
SF02     376.4698323 MHz

F2 - Processing parameters
SI                 65536
SF       400.1300081 MHz
WDW                   EM
SSB                    0
LB               0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX              20.00 cm
F1P           10.007 ppm
F1            4004.18 Hz
F2P           -0.476 ppm
F2            -190.45 Hz
PPMCM      0.52416 ppm/cm
HZCM       209.73154 Hz/cm
```



5

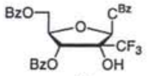
$^{19}F$-$^{1}H$ NOE

```
Current Data Parameters
NAME           p-100.f19
EXPNO                  3
PROCNO                 2

F2 - Acquisition Parameters
Date_             991022
Time               14.43
INSTRUM            spect
PROBHD      5 mm QNP  1H
PULPROG       noemul.f19
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     8
SWH             4194.631 Hz
FIDRES          0.064005 Hz
AQ             7.8119411 sec
RG                  71.8
DW               119.200 usec
DE                  4.50 usec
TE                 300.0 K
D1            1.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec
D20           3.00000000 sec
L4                     1
NUC1                  1H
P1                  7.40 usec
PL1                -6.00 dB
SFO1         400.1319246 MHz
FQ2LIST            f19.1
NUC2                 19F
PL2               120.00 dB
PL14               50.00 dB
SFO2         376.4698323 MHz

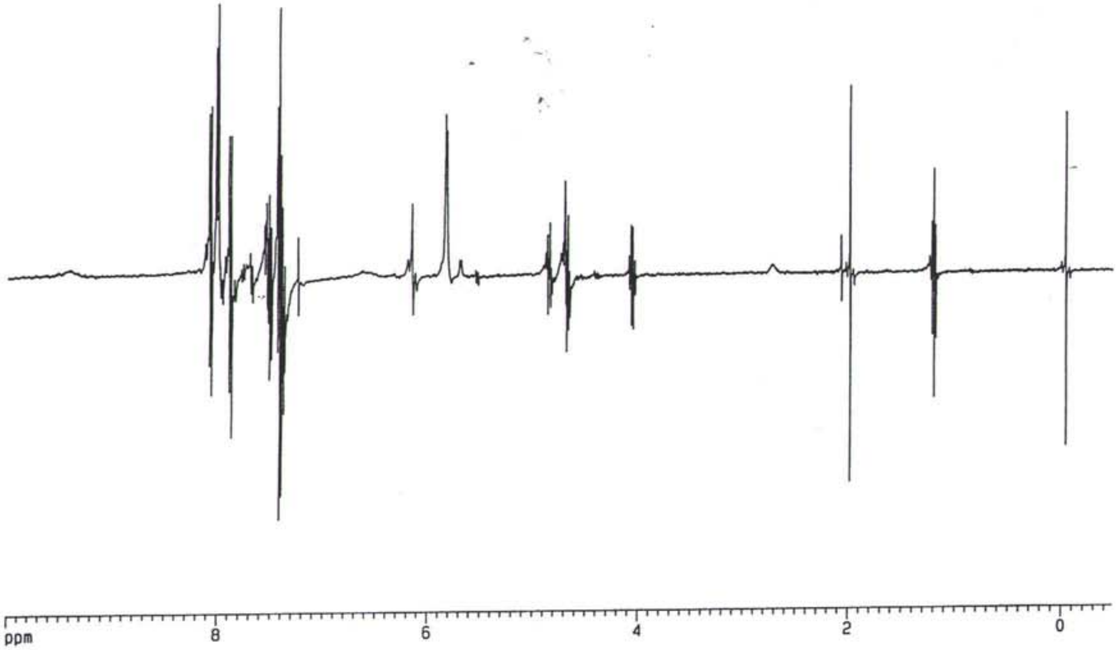
F2 - Processing parameters
SI                 65536
SF           400.1300042 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P               10.007 ppm
F1               4004.18 Hz
F2P               -0.476 ppm
F2               -190.45 Hz
PPMCM            0.52416 ppm/cm
HZCM           209.73154 Hz/cm
```



**6**

$^{19}F$-$^{1}H$ NOE



```
Current Data Parameters
NAME           test.f19
EXPNO                 2
PROCNO                2

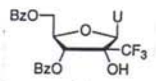
F2 - Acquisition Parameters
Date_            990812
Time              15.23
INSTRUM           spect
PROBHD     5 mm QNP  1H
PULPROG      noemul.f19
TD                25166
SOLVENT           CDCl3
NS                   64
DS                    8
SWH            4194.631 Hz
FIDRES         0.166678 Hz
AQ            2.9998372 sec
RG                 11.3
DW              119.200 usec
DE                 4.50 usec
TE                300.0 K
D1           1.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec
D20          3.00000000 sec
L4                    1

============ CHANNEL f1 ============
NUC1                 1H
P1                 7.30 usec
PL1               -6.00 dB
SFO1        400.1319246 MHz

============ CHANNEL f2 ============
FQ2LIST           f19.1
NUC2                19F
PL2              120.00 dB
PL14              52.00 dB
SFO2        376.4694828 MHz

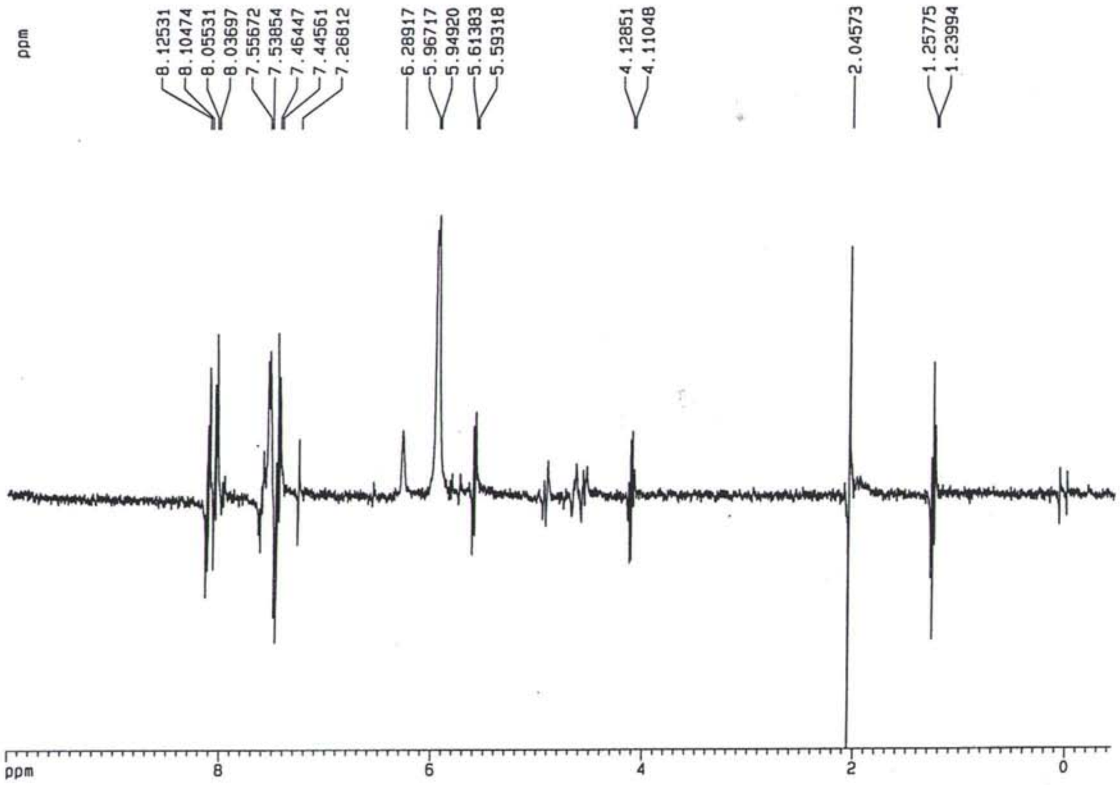
F2 - Processing parameters
SI                16384
SF          400.1300179 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P              10.007 ppm
F1              4003.97 Hz
F2P              -0.476 ppm
F2              -190.66 Hz
PPMCM           0.52416 ppm/cm
HZCM          209.73154 Hz/cm
```



**7**

$^{19}F$-$^{1}H$ NOE

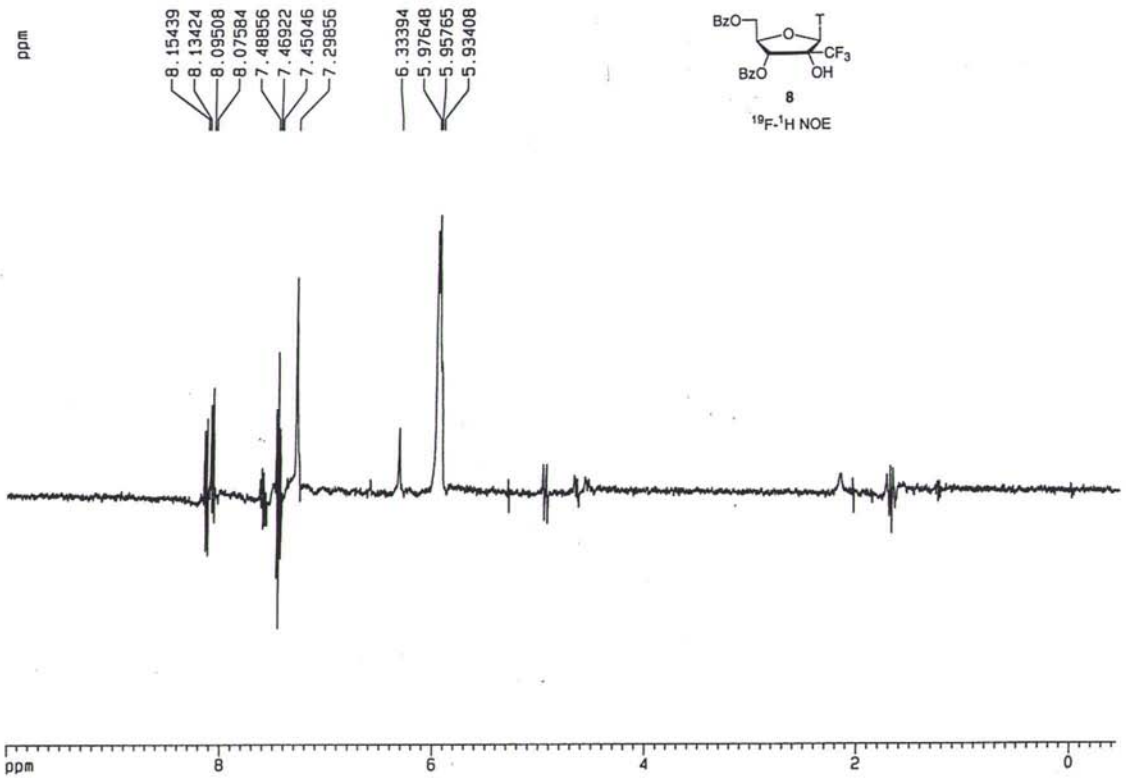


```
Current Data Parameters
NAME            p-77.f19
EXPNO                  3
PROCNO                 2

F2 - Acquisition Parameters
Date_             991022
Time               13.12
INSTRUM            spect
PROBHD     5 mm QNP  1H
PULPROG       noemul.f19
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     8
SWH          4194.631 Hz
FIDRES       0.064005 Hz
AQ          7.8119411 sec
RG                  71.8
DW           119.200 usec
DE              4.50 usec
TE               300.0 K
D1         1.00000000 sec
d11        0.03000000 sec
d12        0.00002000 sec
D20        3.00000000 sec
L4                     1
NUC1                  1H
P1              7.40 usec
PL1             -6.00 dB
SF01      400.1319246 MHz
FQ2LIST            f19.1
NUC2                 19F
PL2             120.00 dB
PL14             50.00 dB
SF02      376.4698323 MHz

F2 - Processing parameters
SI                 65536
SF        400.1300042 MHz
WDW                   EM
SSB                    0
LB               0.70 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX              20.00 cm
F1P           10.007 ppm
F1           4004.18 Hz
F2P           -0.476 ppm
F2           -190.45 Hz
PPMCM     0.52416 ppm/cm
HZCM     209.73154 Hz/cm
```



**8**

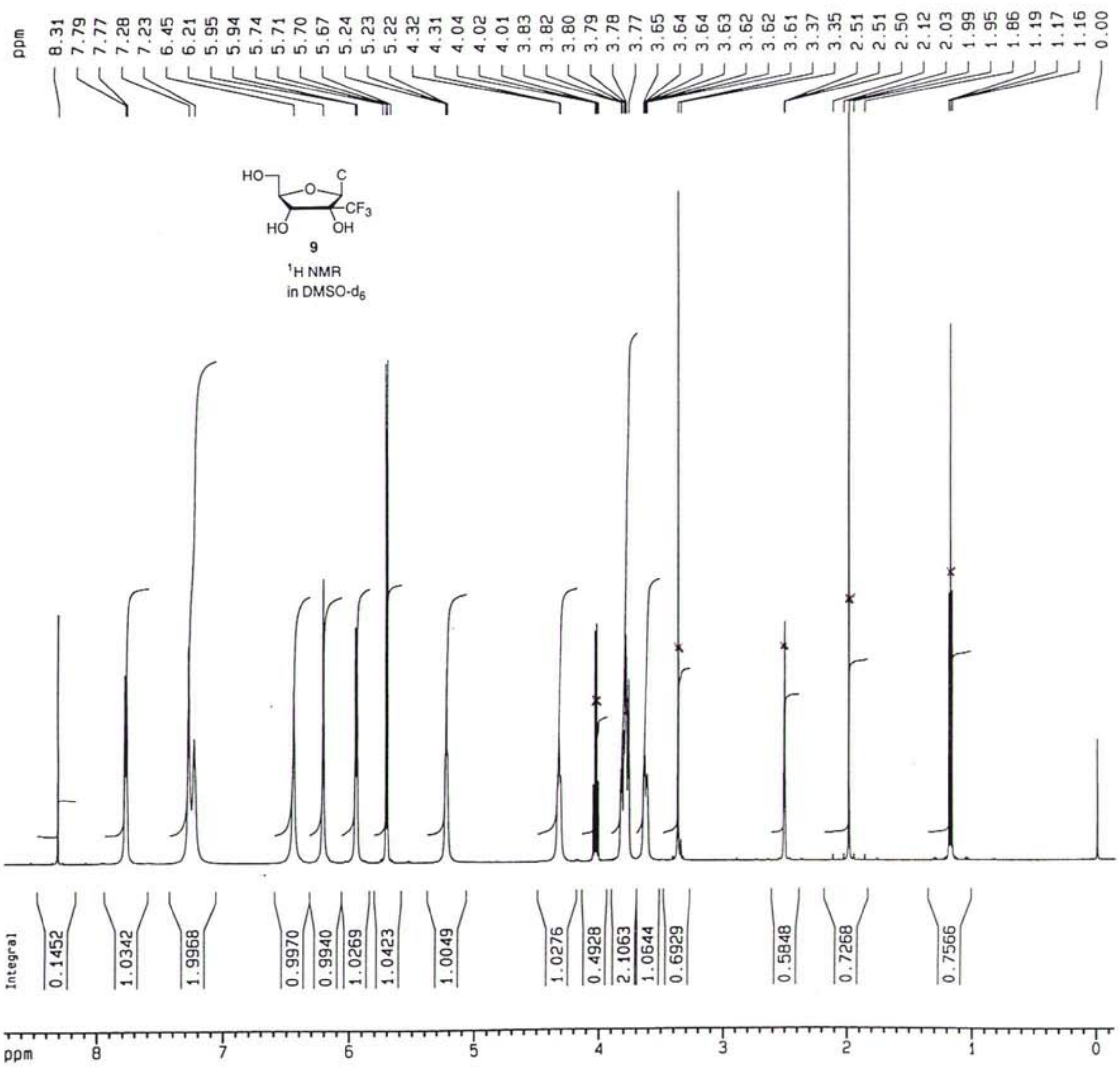
$^{19}$F-$^{1}$H NOE

```
Current Data Parameters
NAME             p-78.f19
EXPNO                   3
PROCNO                  2

F2 - Acquisition Parameters
Date_              991022
Time                13.56
INSTRUM             spect
PROBHD       5 mm QNP  1H
PULPROG        noemul.f19
TD                  65536
SOLVENT             CDCl3
NS                     32
DS                      8
SWH              4194.631 Hz
FIDRES           0.064005 Hz
AQ              7.8119411 sec
RG                   71.8
DW                119.200 usec
DE                   4.50 usec
TE                  300.0 K
D1             1.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec
D20            3.00000000 sec
L4                      1
NUC1                   1H
P1                   7.40 usec
PL1                 -6.00 dB
SFO1          400.1319246 MHz
FQ2LIST             f19.1
NUC2                  19F
PL2                120.00 dB
PL14                50.00 dB
SFO2          376.4698323 MHz

F2 - Processing parameters
SI                  65536
SF            400.1300042 MHz
WDW                    EM
SSB                     0
LB                   0.70 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
F1P                10.007 ppm
F1                4004.18 Hz
F2P                -0.476 ppm
F2                -190.45 Hz
PPMCM             0.52416 ppm/cm
HZCM            209.73154 Hz/cm
```



**9**

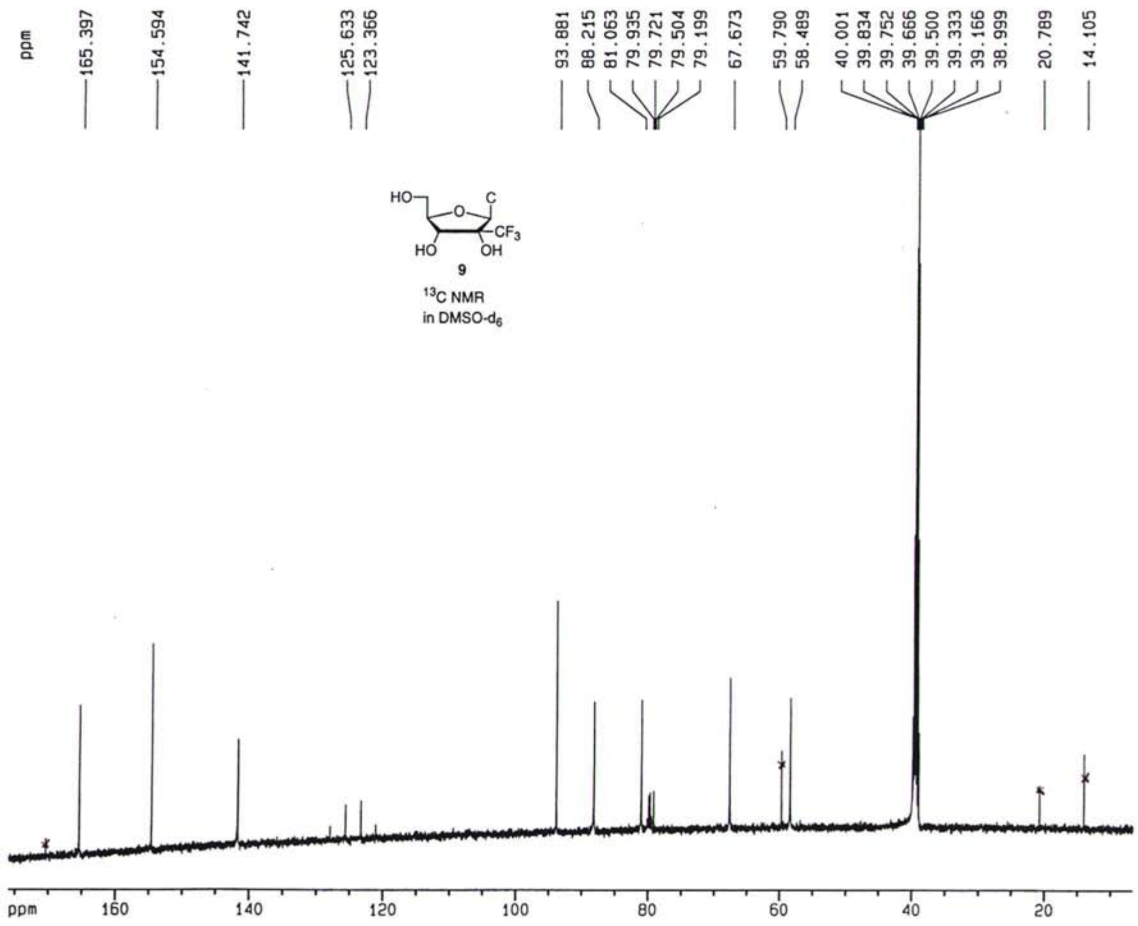
$^1$H NMR
in DMSO-$d_6$

```
Current Data Parameters
NAME                CF3
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_            971007
Time              15.51
INSTRUM           spect
PROBHD     5 mm QNP  1H
PULPROG              zg
TD                32768
SOLVENT            DMSO
NS                   32
DS                    0
SWH           5580.357 Hz
FIDRES        0.170299 Hz
AQ           2.9360628 sec
RG                  128
DW               89.600 usec
DE                 4.50 usec
TE                300.0 K
D1           1.00000000 sec
P1                 5.00 usec
DE                 4.50 usec
SFO1        500.1325364 MHz
NUC1                 1H
PL1                0.00 dB

F2 - Processing parameters
SI                16384
SF          500.1300020 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P               8.737 ppm
F1              4369.87 Hz
F2P              -0.142 ppm
F2               -71.01 Hz
PPMCM           0.44397 ppm/cm
HZCM          222.04401 Hz/cm
```



9

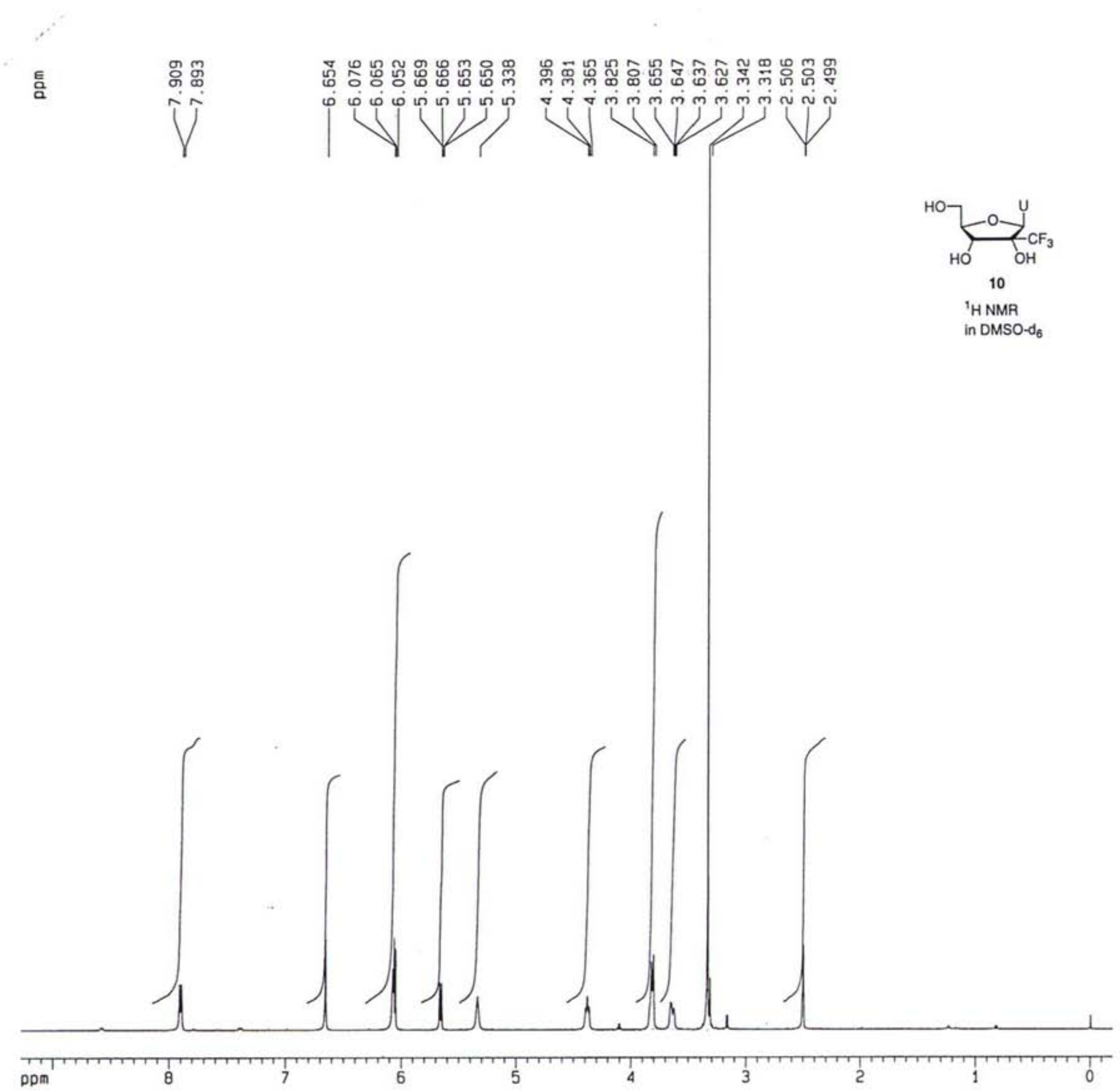
$^{13}$C NMR
in DMSO-d$_6$

```
Current Data Parameters
NAME              CF3
EXPNO               2
PROCNO              2

F2 - Acquisition Parameters
Date_          971007
Time            16.03
INSTRUM         spect
PROBHD   5 mm QNP  1H
PULPROG          zgdc
TD              65536
SOLVENT         CDCl3
NS                701
DS                  1
SWH         39682.539 Hz
FIDRES       0.605507 Hz
AQ          0.8258036 sec
RG               1024
DW             12.600 usec
DE               4.50 usec
TE              300.0 K
d11         0.0300000 sec
PL12            23.00 dB
CPDPRG2       waltz16
PCPD2          100.00 usec
SF02      500.1320005 MHz
NUC2               1H
PL2            120.00 dB
D1         1.50000000 sec
P1               5.00 usec
DE               4.50 usec
SF01      125.7736214 MHz
NUC1              13C
PL1              0.00 dB

F2 - Processing parameters
SI              32768
SF        125.7578445 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.40

1D NMR plot parameters
CX              20.00 cm
F1P           175.957 ppm
F1           22127.92 Hz
F2P             6.690 ppm
F2             841.26 Hz
PPMCM         8.46335 ppm/cm
HZCM       1064.33289 Hz/cm
```



10

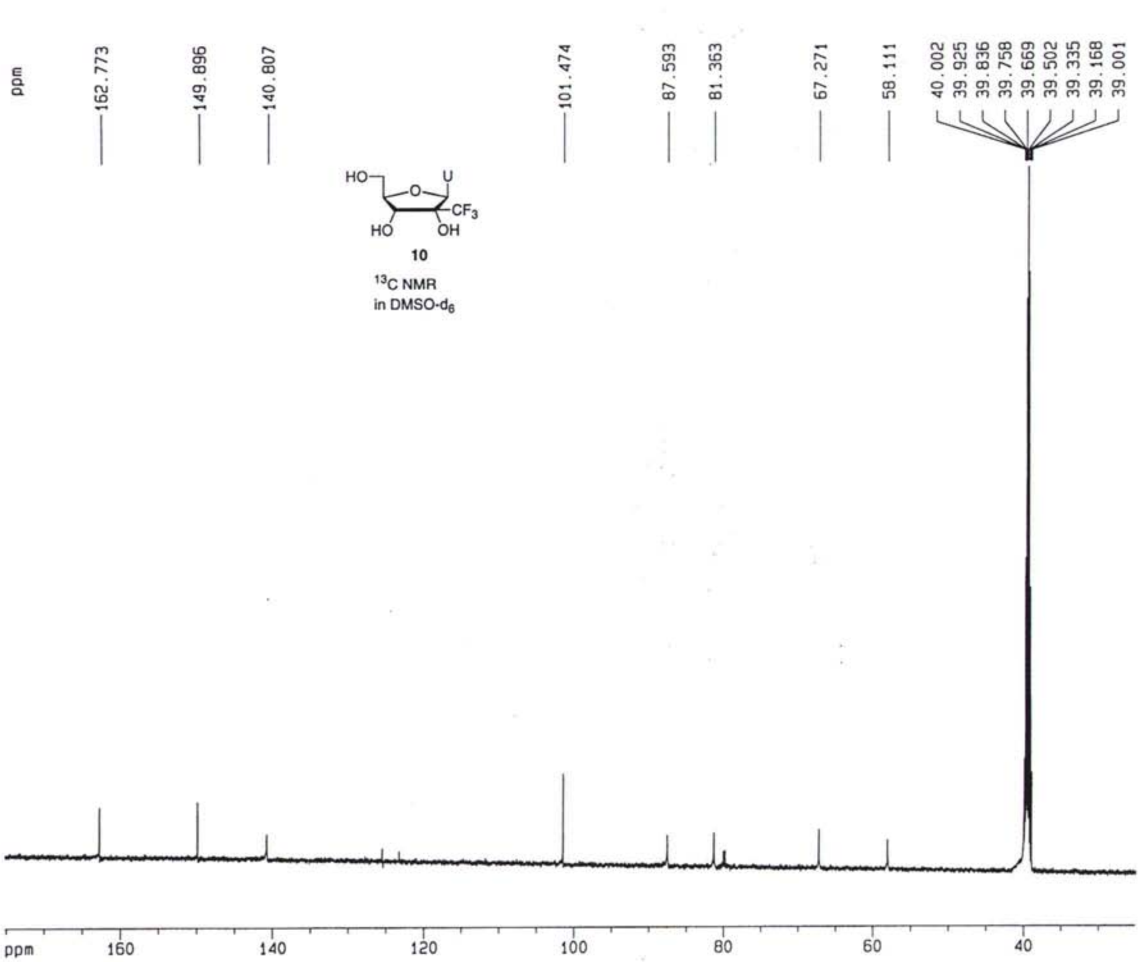
$^1$H NMR
in DMSO-d$_6$

```
Current Data Parameters
NAME          U-CF3-1H
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_           980728
Time             18.17
INSTRUM          spect
PROBHD    5 mm QNP  1H
PULPROG             zg
TD               32768
SOLVENT           DMSO
NS                  16
DS                   0
SWH           5580.357 Hz
FIDRES        0.170299 Hz
AQ           2.9360628 sec
RG                 128
DW              89.600 usec
DE                4.50 usec
TE               300.0 K
D1          1.00000000 sec
P1                8.80 usec
SFO1       500.1325364 MHz
NUC1                1H
PL1              -6.00 dB

F2 - Processing parameters
SI               16384
SF         500.1300037 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00

1D NMR plot parameters
CX               20.00 cm
F1P              9.276 ppm
F1             4639.18 Hz
F2P             -0.195 ppm
F2              -97.35 Hz
PPMCM          0.47353 ppm/cm
HZCM         236.82642 Hz/cm
```



**10**

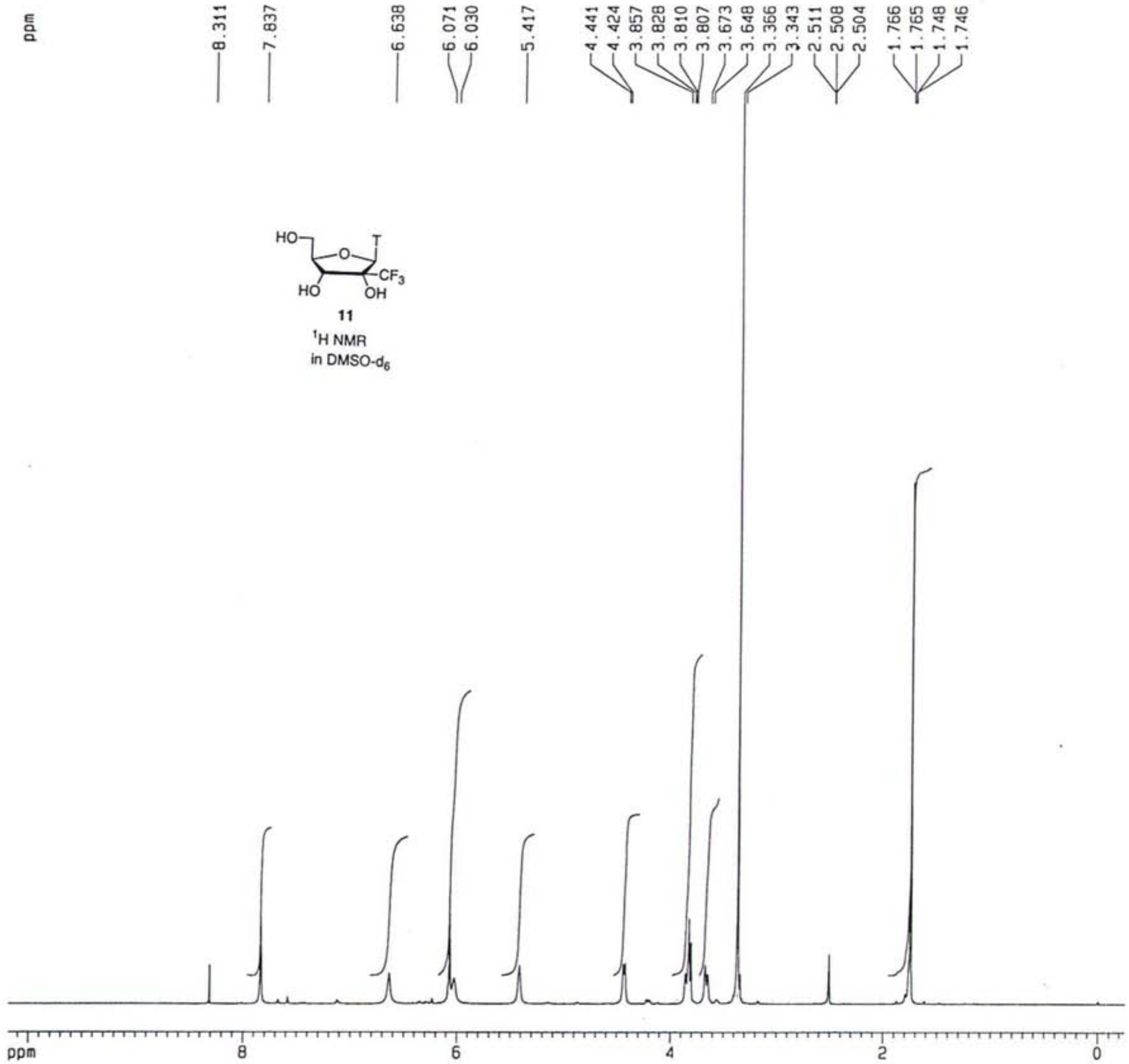
$^{13}$C NMR
in DMSO-$d_6$

```
Current Data Parameters
NAME             U-CF3-13C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_               980728
Time                 18.22
INSTRUM              spect
PROBHD      5 mm QNP  1H
PULPROG               zgdc
TD                   65536
SOLVENT              CDCl3
NS                    1093
DS                       0
SWH             39682.539 Hz
FIDRES           0.605507 Hz
AQ              0.8258036 sec
RG                    2048
DW                  12.600 usec
DE                    7.50 usec
TE                   300.0 K
d11             0.03000000 sec
PL12                 20.00 dB
CPDPRG2            waltz16
PCPD2               100.00 usec
SFO2          500.1320005 MHz
NUC2                    1H
PL2                 120.00 dB
D1              2.00000000 sec
P1                    5.00 usec
SFO1          125.7736214 MHz
NUC1                   13C
PL1                   0.00 dB

F2 - Processing parameters
SI                   32768
SF            125.7578493 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                175.221 ppm
F1                22035.47 Hz
F2P                 25.110 ppm
F2                 3157.79 Hz
PPMCM              7.50557 ppm/cm
HZCM             943.88379 Hz/cm
```



**11**

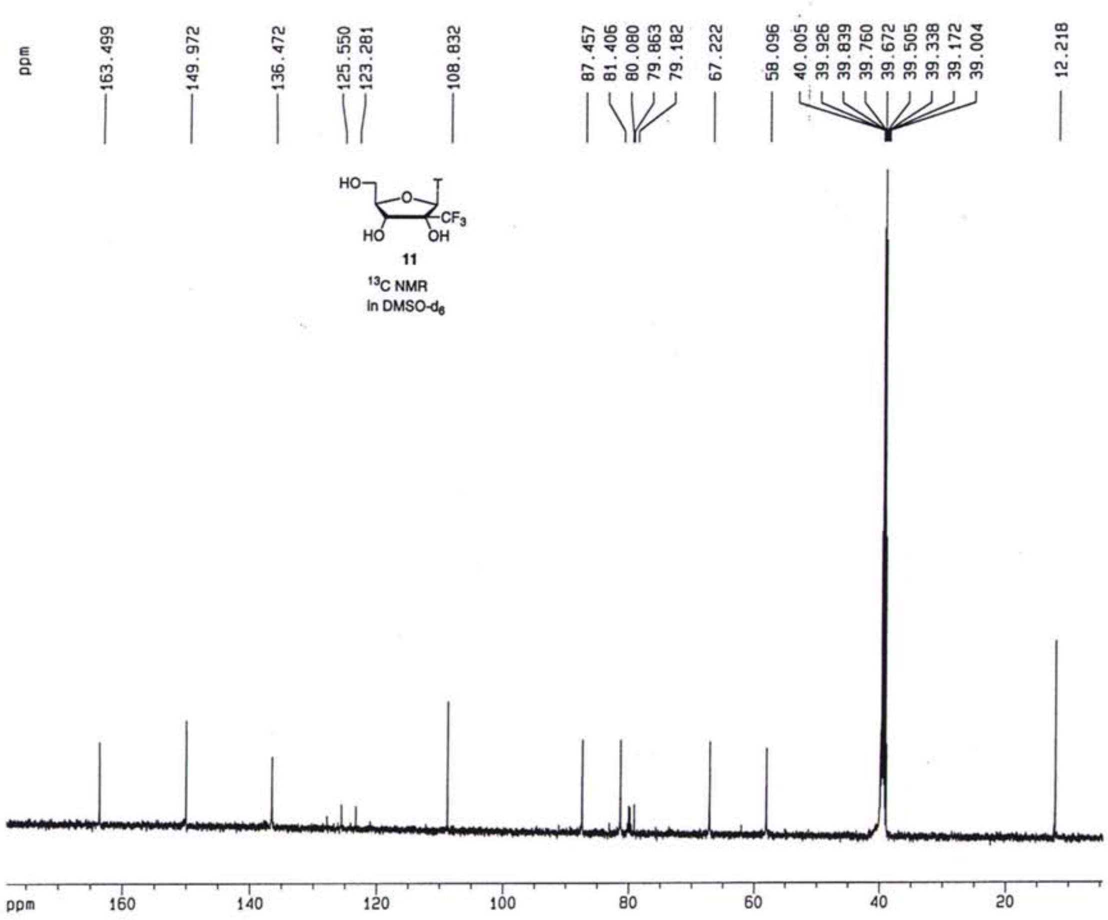
$^1$H NMR
in DMSO-$d_6$

```
Current Data Parameters
NAME            T-CF3-1H
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_             980728
Time               17.01
INSTRUM            spect
PROBHD      5 mm QNP  1H
PULPROG               zg
TD                 32768
SOLVENT             DMSO
NS                    16
DS                     0
SWH             5580.357 Hz
FIDRES          0.170299 Hz
AQ             2.9360628 sec
RG                    64
DW                89.600 usec
DE                  4.50 usec
TE                 300.0 K
D1            1.00000000 sec
P1                  8.80 usec
SFO1        500.1325364 MHz
NUC1                  1H
PL1                -6.00 dB

F2 - Processing parameters
SI                 16384
SF          500.1300010 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P               10.193 ppm
F1               5097.69 Hz
F2P               -0.251 ppm
F2               -125.42 Hz
PPMCM            0.52218 ppm/cm
HZCM           261.15579 Hz/cm
```



11

$^{13}C$ NMR
In DMSO-$d_6$

```
Current Data Parameters
NAME               test
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_            980728
Time              17.45
INSTRUM           spect
PROBHD     5 mm QNP  1H
PULPROG            zgdc
TD                65536
SOLVENT           CDCl3
NS                  499
DS                    0
SWH          39682.539 Hz
FIDRES        0.605507 Hz
AQ           0.8258036 sec
RG                 8192
DW               12.600 usec
DE                 7.50 usec
TE                300.0 K
d11          0.03000000 sec
PL12              20.00 dB
CPDPRG2         waltz16
PCPD2            100.00 usec
SFO2       500.1320005 MHz
NUC2                 1H
PL2              120.00 dB
D1           2.00000000 sec
P1                 5.00 usec
SFO1       125.7736214 MHz
NUC1                13C
PL1                0.00 dB

F2 - Processing parameters
SI                32768
SF         125.7578457 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P             178.037 ppm
F1             22389.50 Hz
F2P               4.590 ppm
F2               577.24 Hz
PPMCM           8.67233 ppm/cm
HZCM         1090.61292 Hz/cm
```