Electronic Supplementary Material (ESI) for RSC Advances


**Supporting Information**

# Synthesis of 6,6'-(*S*)-cyclo-2'-deoxyuridine Featuring a Unique Barbier Style Cyclization

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## A) Nucleoside synthesis

**Compound 4:** 2'-deoxyuridine (10.01 g, 43.82 mmol), tert-butyldimethylsilyl chloride (15.83 g, 105.2 mmol), and imidazole (7.150 g, 105.2 mmol) were dissolved in 300 mL of DMF and stirred for 12 hrs. The reaction mixture was partitioned between brine and ethyl acetate. The organic layer was washed again with brine and then dried over $NaSO_4$. This crude material was of sufficient purity to use in further reactions. For standardization and for characterization the crude was purified by flash chromatography (3:2 hexanes to ethyl acetate) to yield **4** as a white solid (18.81 g, 41.19 mmol, 94%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.06 (s,6H), 0.87 (s, 9H), 0.90 (s, 9H), 2.04 (p, *J*=6.4 Hz, 1H), 2.31 (m, 1H), 3.74 (dd, *J*=11.2, 1.6 Hz, 1H), 3.89 (m, 3H), 4.39 (m, 1H), 5.66 (d, *J*=8.4 Hz, 1H), 6.26 (t, *J*=6.0 Hz, 1H), 7.88 (d, *J*=8.0 Hz, 1H), 8.33 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$), δ -4.65, -4.41, 18.19, 18.57, 25.93, 26.08, 42.07, 62.65, 71.42, 85.41, 88.00, 102.34, 140.41, 150.23, 163.14. HRMS (DART) Calcd for $C_{21}H_{41}N_2O_5Si_2$ 457.25540; Found, 457.25651.

**Compound 5:** Diisopropyl amine (14.8 mL, 104 mmol) was added to 200 mL of THF and the mixture was cooled to -78 $^{o}$C. A solution of *n*-BuLi (2.6M in hexanes, 39.6 mL, 104 mmol) was slowly added and the mixture was allowed to stir at 0 $^{o}$C for 20 min. The flask was cooled back to -78 $^{o}$C and a solution of **2** (9.45 g, 20.7 mmol) in 200 mL of THF was slowly added. After 2.5 hrs, DMF (40.1 mL, 517 mmol) was added and the reaction was stirred for 2.5 hrs. Acetic acid (15.5, 271 mmol) was added and the reaction was warmed to ambient temperature. The mixture was diluted with EtOH (200 mL) and

$NaBH_4$ was slowly added (2.34 g, 61.9 mmol). The reaction was stirred for 30 min before the solvents were removed by rotary evaporation. The crude mixture was dissolved in EtOAc and washed twice with brine before being dried over $NaSO_4$. The material was purified by flash chromatography (3:2 ethyl acetate to hexanes) to yield a mixture of the starting material, **4** (3.89 g, 8.49 mmol, 41%), and the product, **5** (4.43 g, 9.12 mmol, 44%), as a clear oil/white foam. If impurities remain, the material can be "recrystallized" from an ethanol water mixture to a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.07 (s, 6H), 0.86 (s, 6H), 0.88 (s, 6H), 2.14 (m, 1H), 2.65 (m, 1H), 3.79 (m, 2H), 3.86 (m, 1H), 4.86 (m, 1H), 5.77 (s, 1H), 6.19 (t, *J*=6.5 Hz, 1H), 9.34 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$), δ -4.91, -4.65, 17.83, 18.45, 25.67, 25.92, 39.32, 61.40, 62.82, 71.05, 85.49, 87.39, 102.59, 150.40, 155.47, 163.15. HRMS (DART) Calcd for $C_{22}H_{43}N_2O_6Si_2$ 487.26596; Found, 487.26819.

**Compound 6:** *N,N*-Diisopropylethylamine (1.05 mL, 6.01 mmol) and **3** (1.46 g, 3.00 mmol) were dissolved in THF (40 mL) and cooled to 0 $^o$C. Mesyl chloride (0.785 mL, 4.51 mmol) was added and the reaction was stirred for 1.5 hrs. A solution of LiBr (522 mg, 6.01 mmol) in DMF (5.60 mL) was added drop wise and the mixture was allowed to warm to ambient temperature. After 3 hrs the reaction was quenched with sat. $NaHCO_3$. Ethyl acetate was added to help partition the mixture. The organic layer was washed with brine and the combined aqueous layers were back extracted with ethyl acetate. The product was purified by flash chromatography (2:1 hexanes to ethyl acetate) to yield the product as a tan oil (1.16 g, 2.12 mmol, 71%). This compound has some stability issues and we recommend immediately setting up the following reaction. $^1$H NMR (500 MHz,

$CDCl_3$) δ 0.04 (s, 6H), 0.07 (s, 6H), 0.88 (s, 18 H), 2.15 (m, 1H), 2.95 (p, *J*=5.5 Hz, 1H), 3.73 (dd, *J*=12.0, 7.0 Hz, 1H), 3.80 (m, 1H), 4.26 (q, *J*=11.5 Hz, 1H), 4.51 (m, 1H), 5.74 (s, 1H), 6.09 (t, *J*=7.0 Hz, 1H), 8.74 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$), δ -5.11, -4.75, 18.06, 18.68, 25.91, 26.19, 38.60, 41.69, 43.42, 63.38, 71.81, 86.12, 87.98, 105.30, 150.29, 151.54, 162.65. HRMS (DART) Calcd for $C_{22}H_{42}BrN_2O_5Si_2$ 549.18156; Found, 549.18261.

**Compound 7:** Compound **6** (1.16 g, 2.12 mmol) and PPTS (150 mg, 0.597 mmol) were dissolved in ethanol (25 mL) and stirred for 12 hrs. The reaction was quenched with saturated $NaHCO_3$ and the ethanol was removed by rotary evaporation. The crude product was extracted with ethyl acetate and washed with brine. The combined aqueous layers were back extracted with ethyl acetate and the organic layers were dried over $NaSO_4$. The material was purified by flash chromatography (7:3 ethyl acetate to hexanes) to yield **7** as a white solid (840 mg, 1.93 mmol, 91%). $^1$H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.87 (s, 9H), 2.13 (m, 1H), 3.00 (p, *J*=7.0 Hz, 1H), 3.45 (dd, *J*=9.0, 2.5 Hz, 1H), 3.70 (dt, *J*=9.5, 3.0 Hz, 1H), 3.84 (dt, *J*=12.0, 2.5 Hz, 1H), 3.94 (q, *J*=3.5 Hz, 1H), 4.26 (d, *J*=13.0 Hz, 1H), 4.46 (d, *J*=13.0 Hz), 4.66 (m, 1H), 5.76 (s, 1H), 5.98 (t, *J*=7.0Hz, 1H) 9.20 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$), δ -4.51, 18.13, 25.94, 38.94, 42.05, 62.59, 72.27, 87.54, 88.95, 105.43, 150.76, 150.85, 162.06. HRMS (DART) Calcd for $C_{16}H_{28}BrN_2O_5Si$ 435.09509; Found, 435.09683.

**Compound 9:** Compound **7** (526 mg, 1.21 mmol) and Dess-Martin Periodinane (1.28 g, 3.02 mmol) were dissolved in dichloromethane (35 mL) and stirred for 2.5 hrs. The

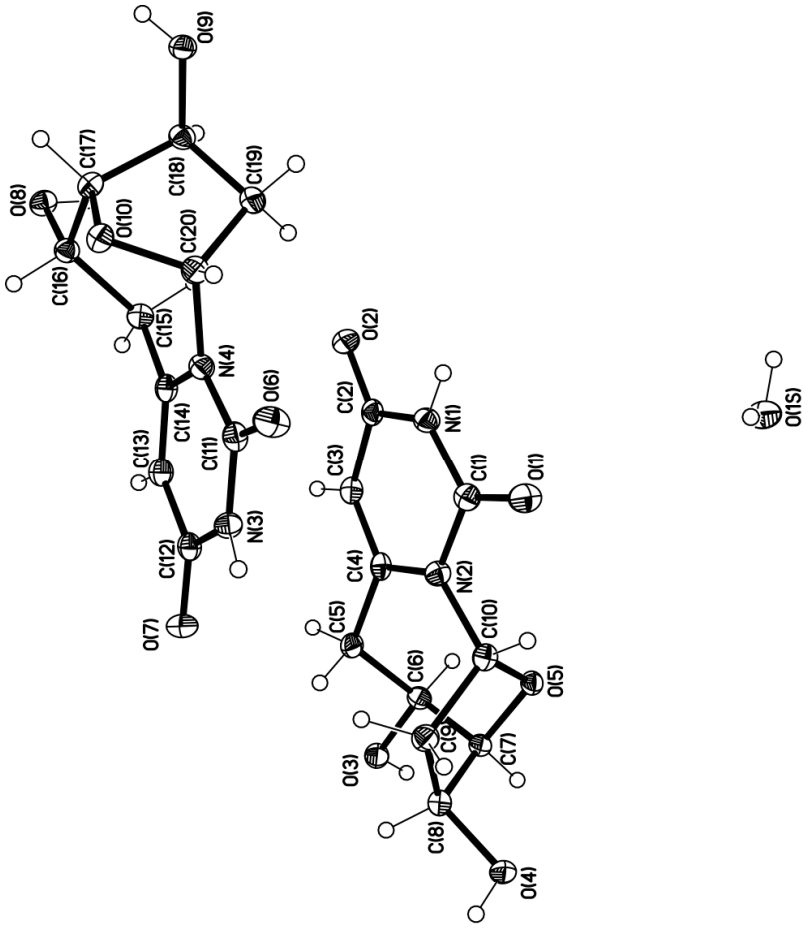
reaction was quenched with equal parts saturated $Na_2S_2O_3$ and saturated $NaHCO_3$. The organic layer was washed with brine and the combined aqueous layers were washed with ethyl acetate. The solvent was removed by rotary evaporation and the crude material was carried on to the next reaction as it decomposes on silica.

The crude aldehyde **8** and zinc (1.97 g, 30.2 mmol) were dissolved in DMF (100 mL) and sonicated for 3 hrs. The reaction mixture was filtered through Celite and the Celite was rinsed several times with ethyl acetate. The mixture was partitioned between brine and ethyl acetate. The ethyl acetate layer was washed a second time with brine and the combined aqueous layers were back extracted with ethyl acetate. The organic layers were dried over $NaSO_4$ and the solvent was removed by rotary evaporation. The crude material was purified by column chromatography (65:35 ethyl acetate to hexane) to yield **9** as a white solid (559 mg, 1.58 mmol, 56%). $^1$H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 2.37 (ddd, *J*=15.5, 6.5, 2.5 Hz, 1H), 2.56 (dd, *J*=15.5, 9.0 Hz, 1H), 2.71 (m, 2H), 4.02 (m, 1H), 4.25 (d, *J*=4.0 Hz, 1H), 4.70 (d, *J*=6.0 Hz, 1H), 5.60 (s, 1H), 7.02 (dd, *J*=9.0, 3.0 Hz, 1H), 8.52 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$), δ -4.55, 18.25, 25.97, 39.30, 43.72, 67.80, 72.03, 79.35, 85.10, 90.29, 105.24, 151.08, 162.39. HRMS (DART) Calcd for $C_{16}H_{27}N_2O_5Si$ 355.16892; Found, 355.16813. $[\alpha]_D^{23}$ -151.36° (*c*= 1.33, Acetone).

**Compound 1:** The cyclized product, **9** (35.0 mg, 98.7 μmol), was dissolved in THF (5.00 mL). TBAF (495 μL of 1M solution in THF, 495 μmol) was added and the reaction was stirred for 1.5 hrs. The reaction was quenched with water. The mixture was partitioned between water and ethyl acetate. The organic layer was washed three times

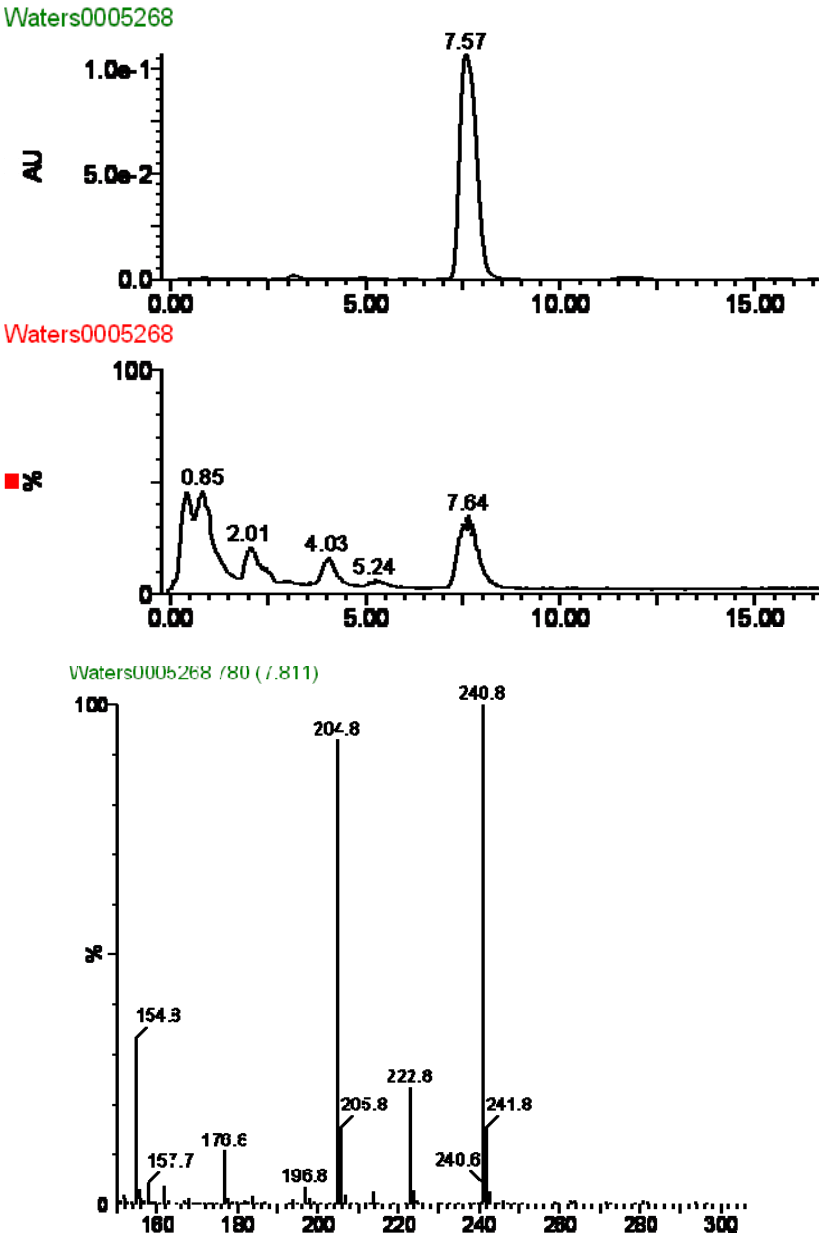
with water and the aqueous layer was concentrated by rotary evaporation. The crude material was purified by flash chromatography (1:1 acetone to ethyl acetate) to yield **1** as a white solid (19.4 mg, 80.9 μmol, 82%). $^{1}$H NMR (MHz, $D_5$-Pyridine) δ 2.76 (ddd, *J*=15.5, 7.0, 3.0 Hz, 1H), 2.92 (dd, *J*=15.5, 9.0 Hz, 1H), 3.12 (m, 2H), 4.38 (m, 1H), 4.94 (d, *J*=3.5 Hz), 5.35 (d, *J*=6.5 Hz, 1H), 5.90 (s, 1H), 7.61 (dd, *J*=9.0, 2.5 Hz), 13.32 (s, 1H). $^{13}$C NMR (125 MHz, $D_5$-Pyridine), δ 40.30, 43.69, 68.67, 71.75, 85.45, 92.05, 105.69, 152.23, 153.14, 163.97. HRMS (DART) Calcd for $C_{10}H_{13}N_2O_5$ 241.08245; Found, 241.08255. $[\alpha]_D^{23}$ -7.50° (*c*= 0.33, $H_2O$).

**B) <u>Thermal Ellipsoid Plot of Compound 1</u>**

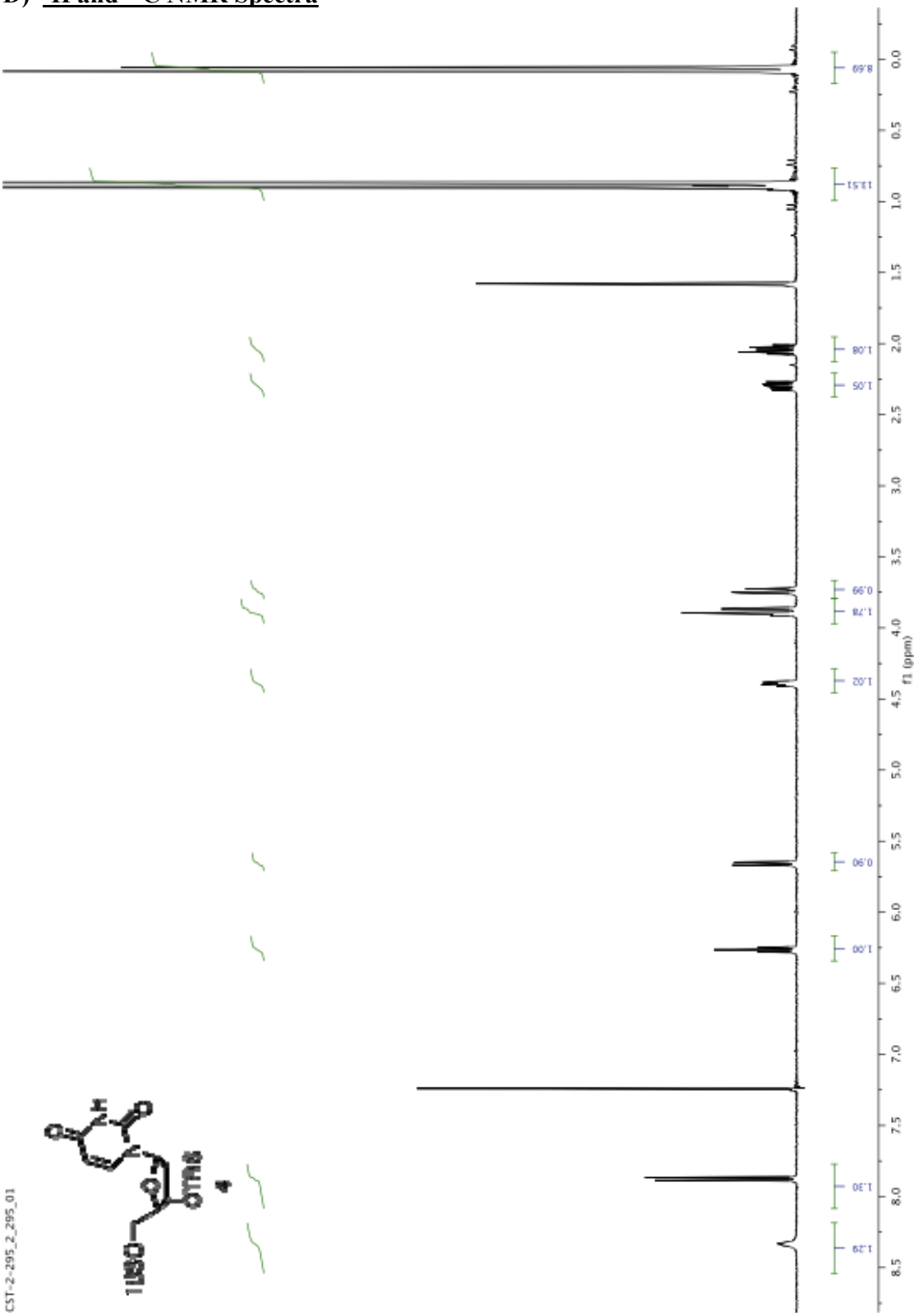


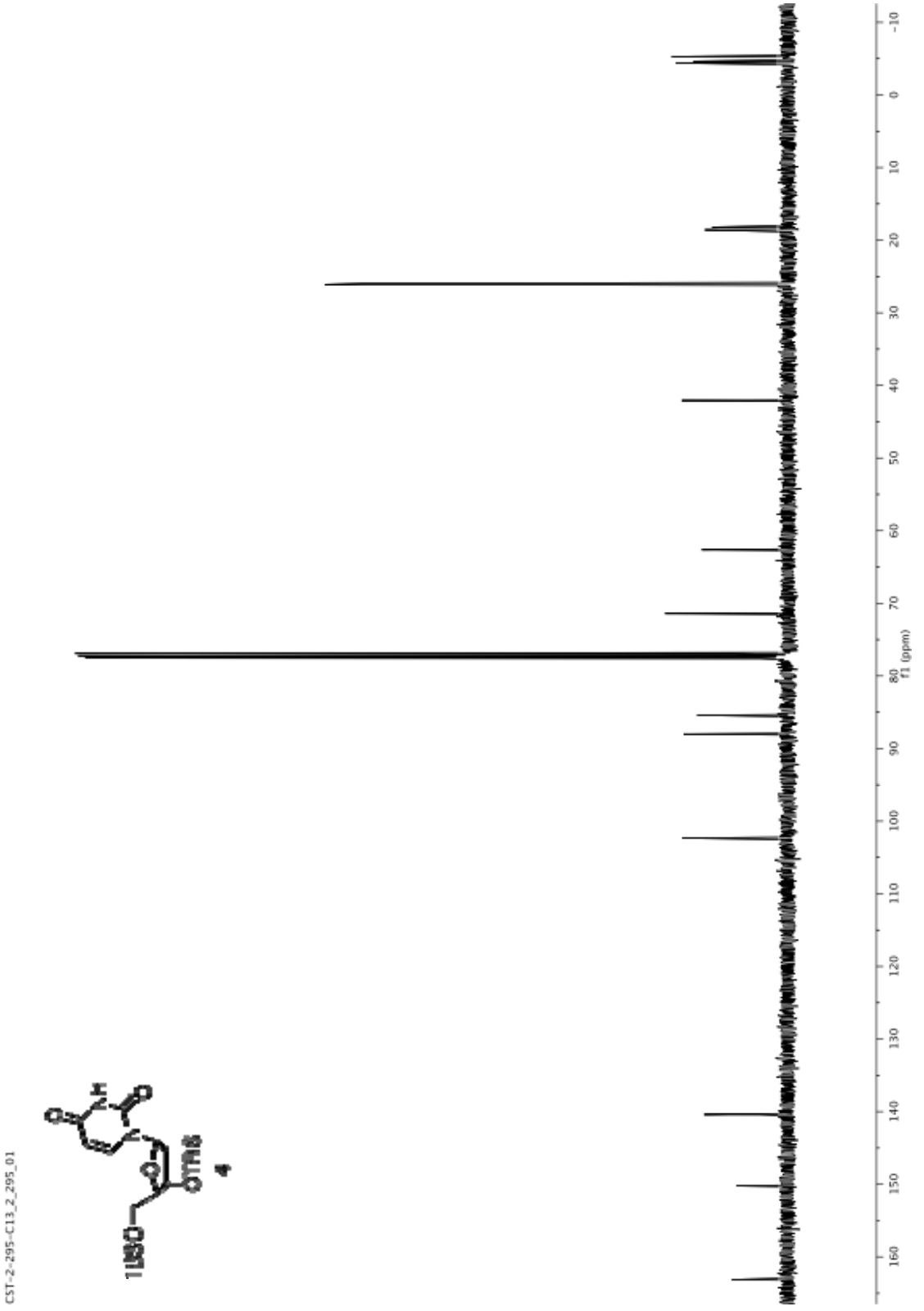
## C) LC-MS analysis of Compound 1

The top chromatogram shows absorbance detection at 260 nm, while the bottom chromatogram shows mass detection. The compound was eluted with water using a $C_{18}$ analytical column. The spectrum below the chromatograms shows a peak at 240.8, corresponding to compound **1**. None of other minor peaks in the chromatogram had masses corresponding to the desired product.



**D) $^{1}$H and $^{13}$C NMR Spectra**

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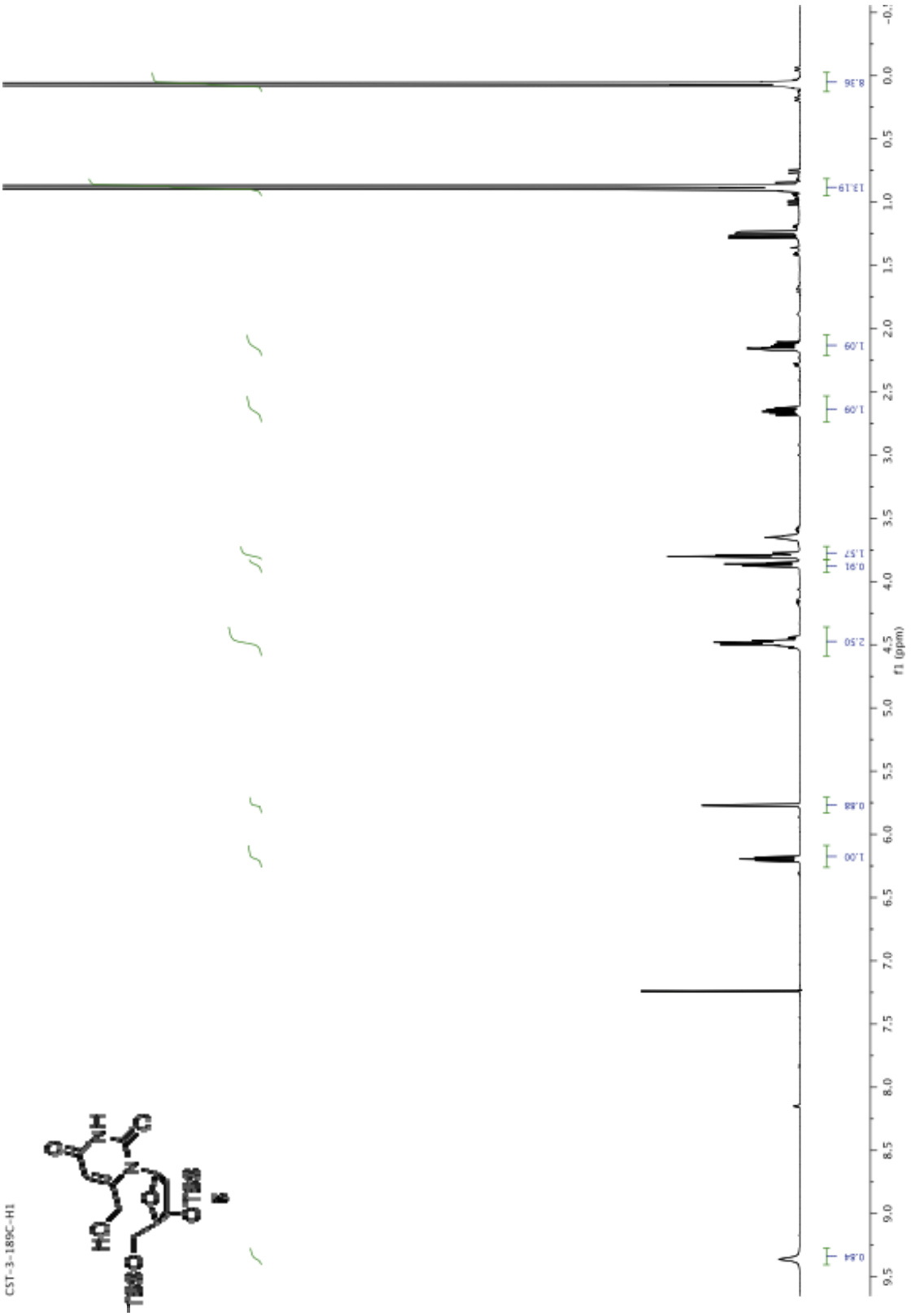
f1 (ppm)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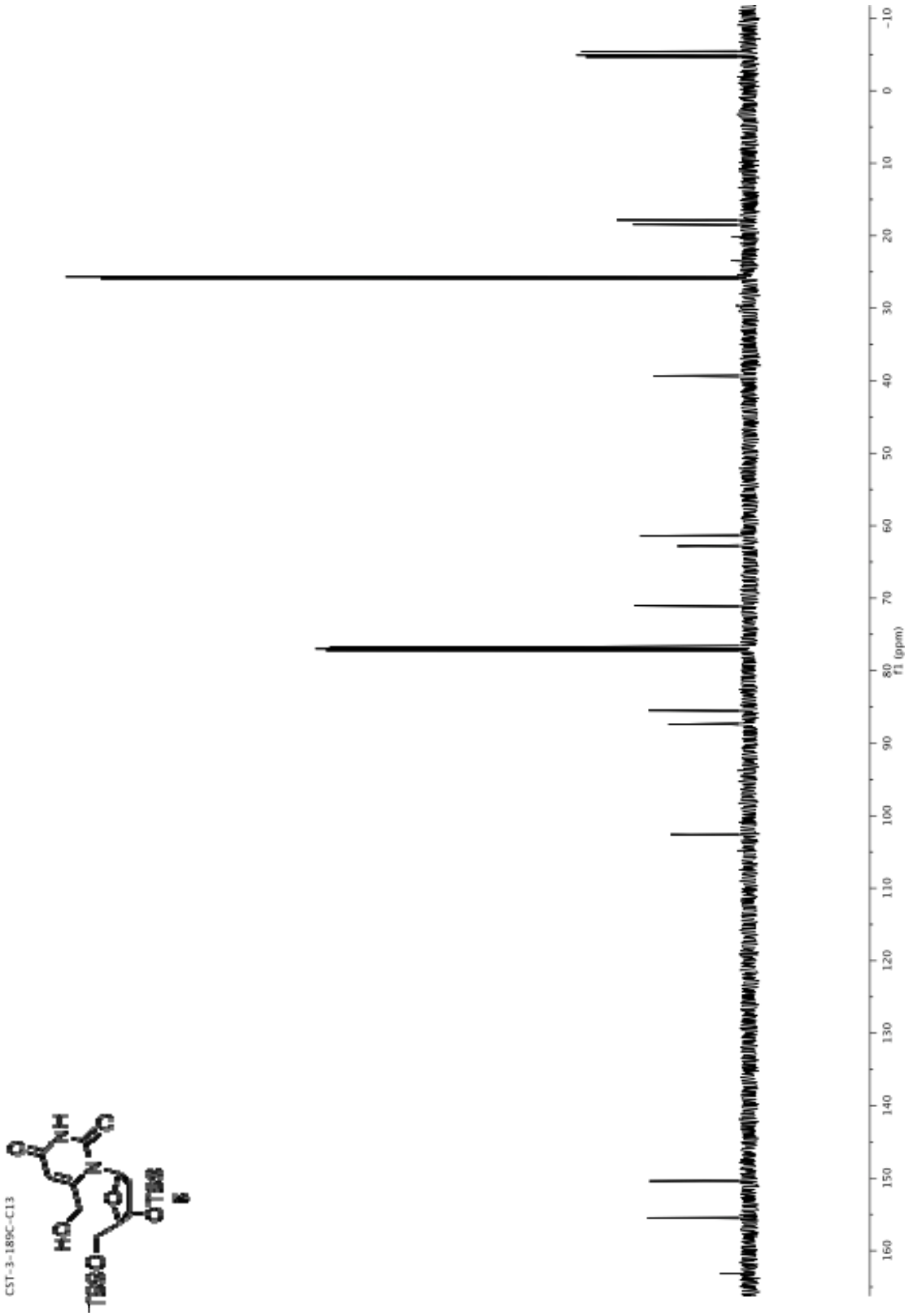
1.00
0.84
f1 (ppm)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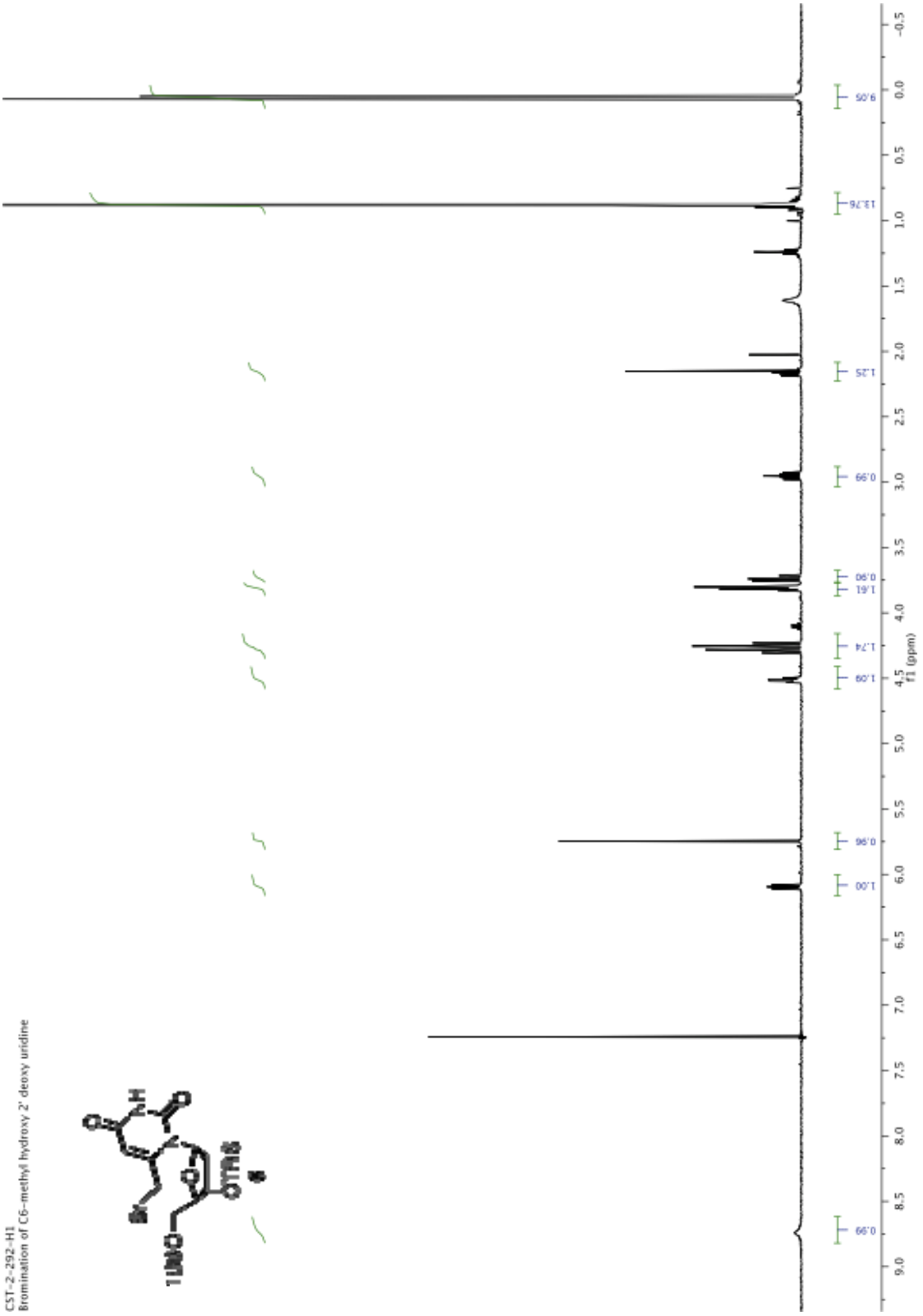
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Bromination of C6-methyl hydroxy 2' deoxy uridine
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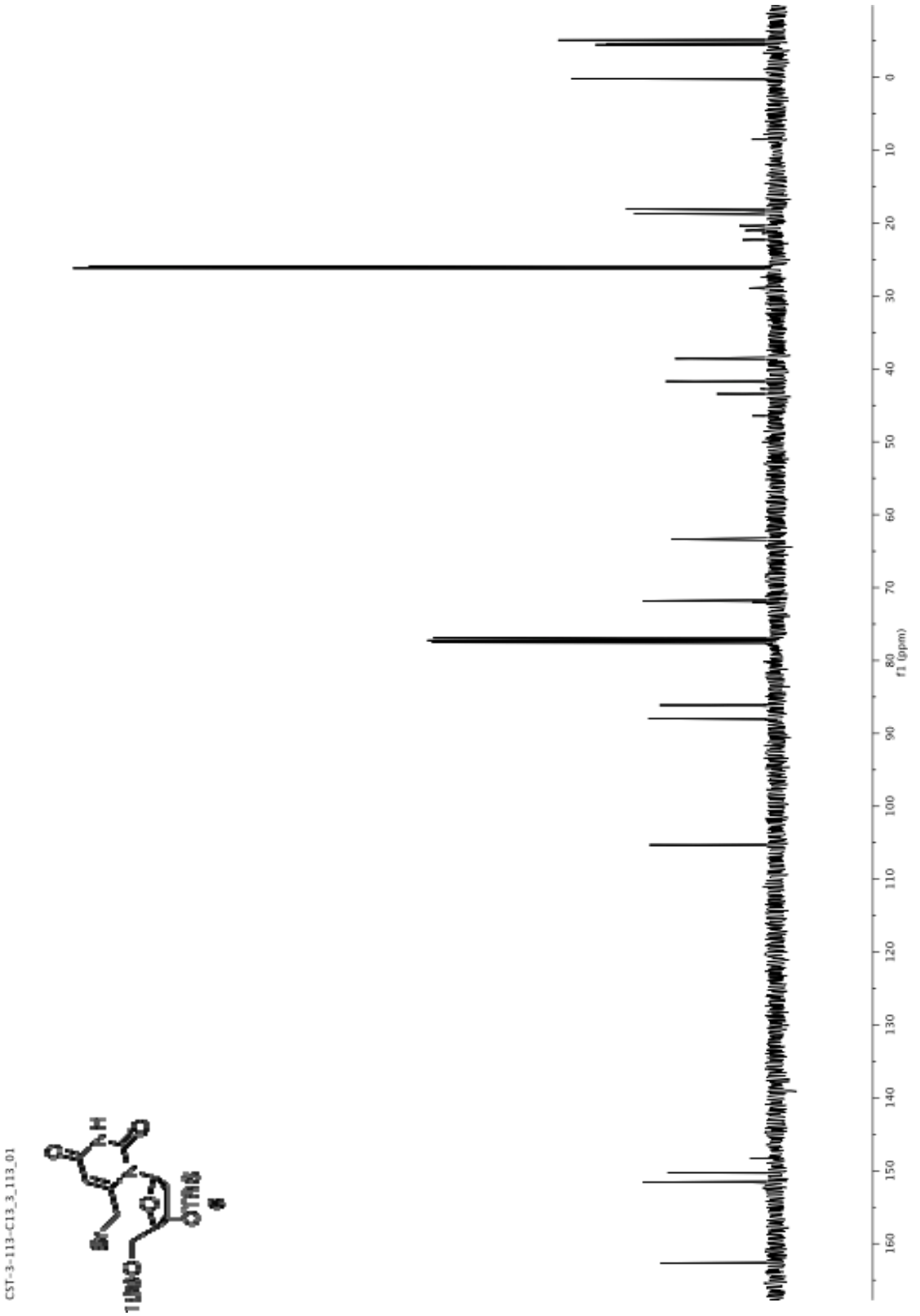
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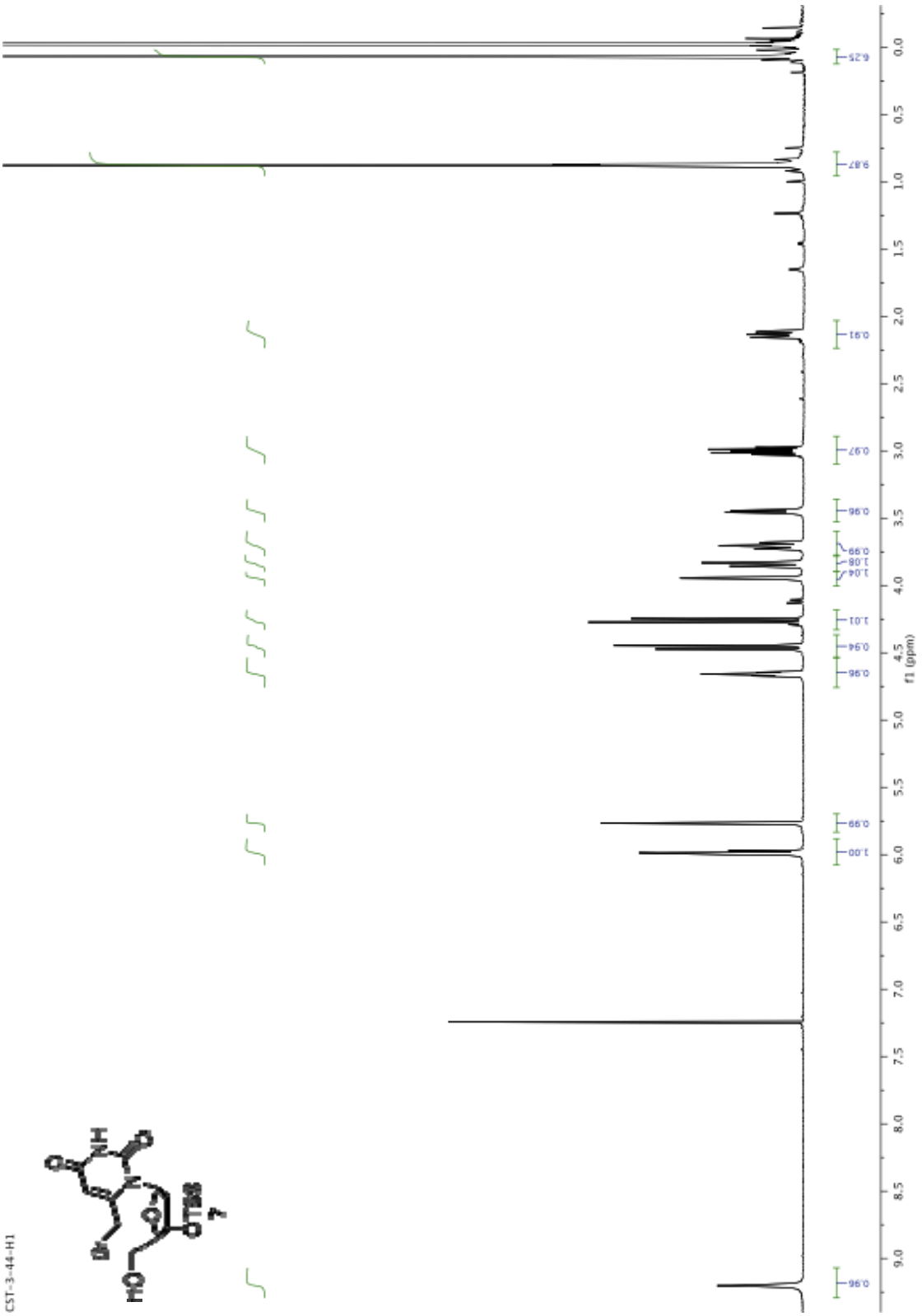
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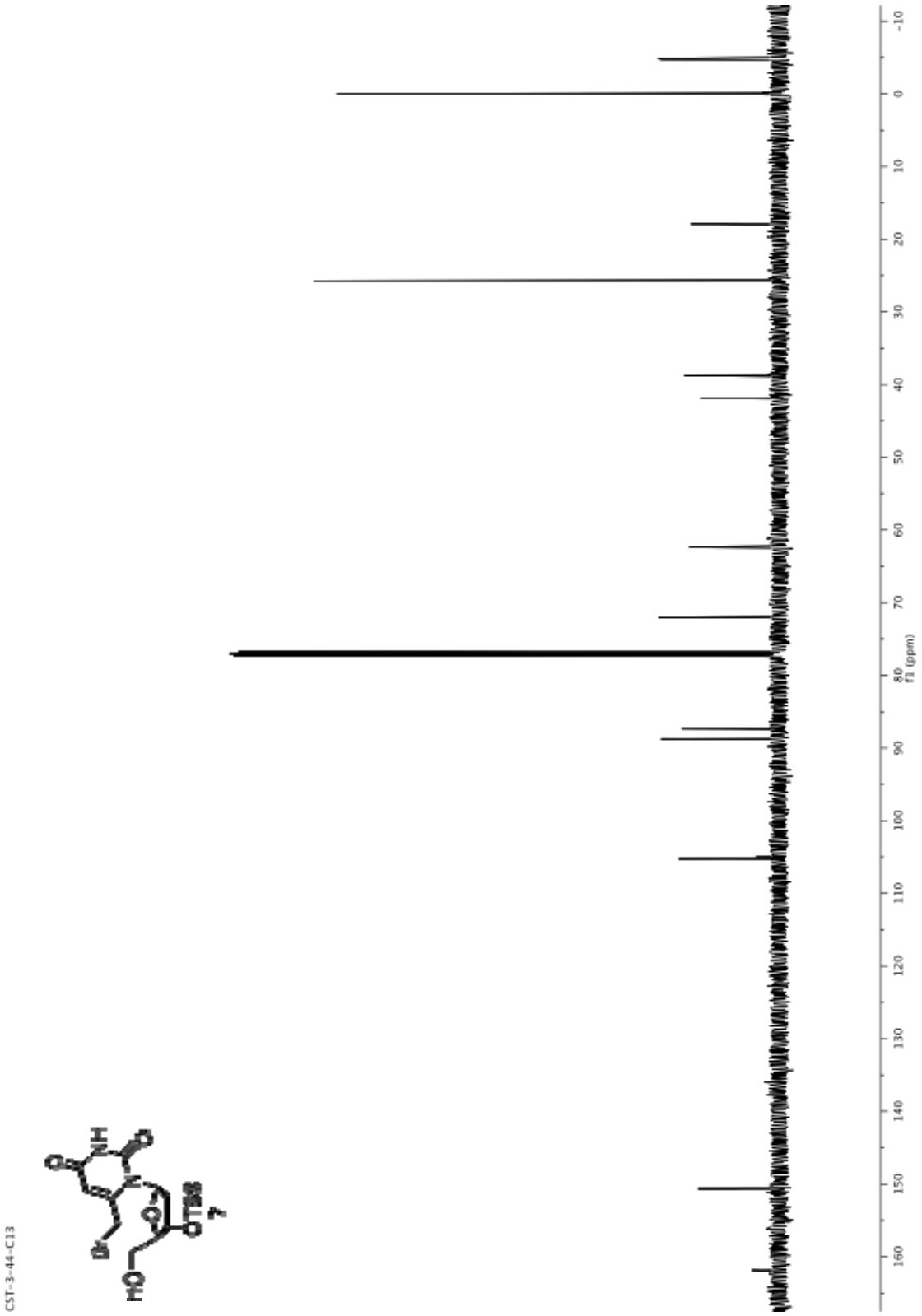
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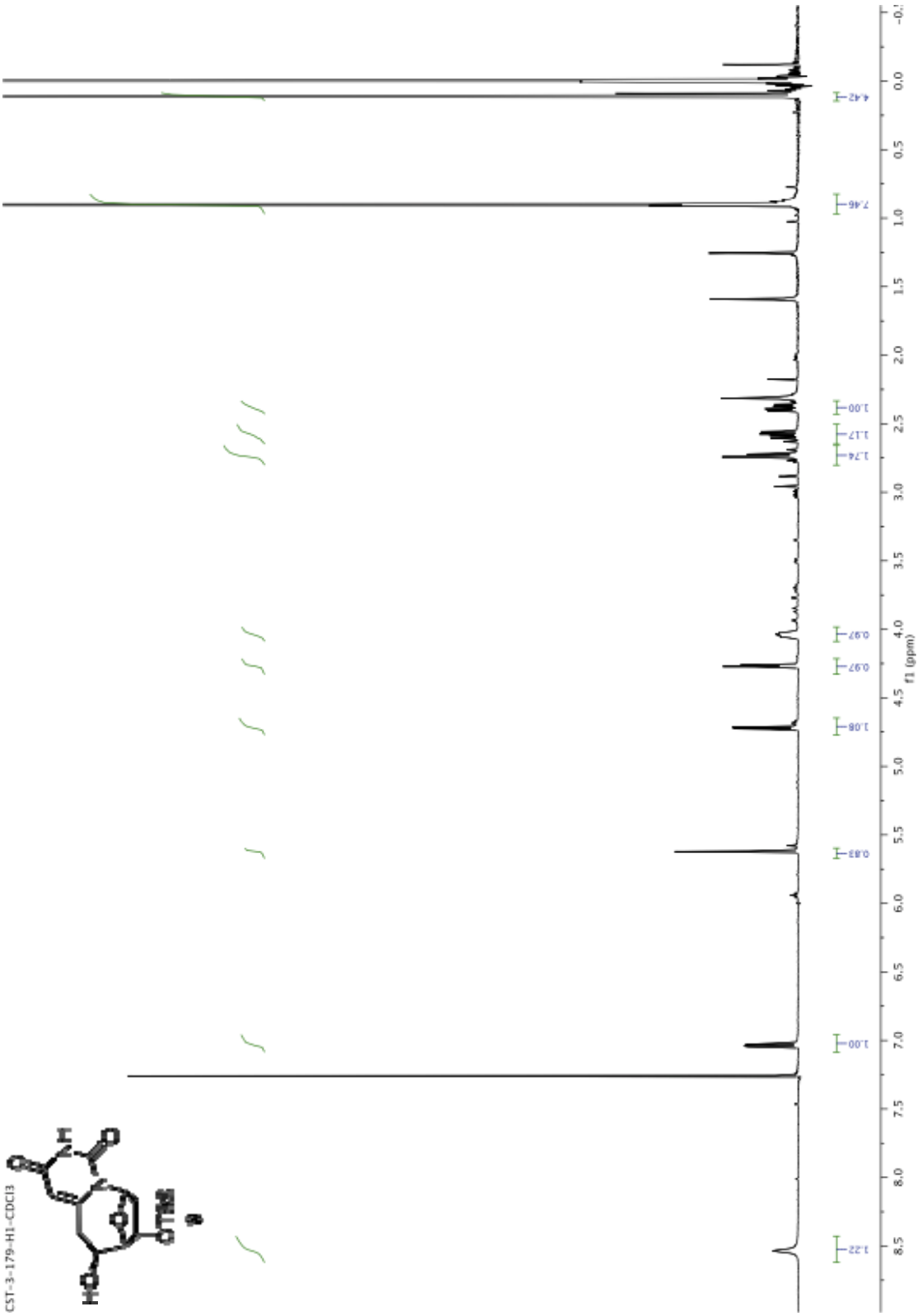
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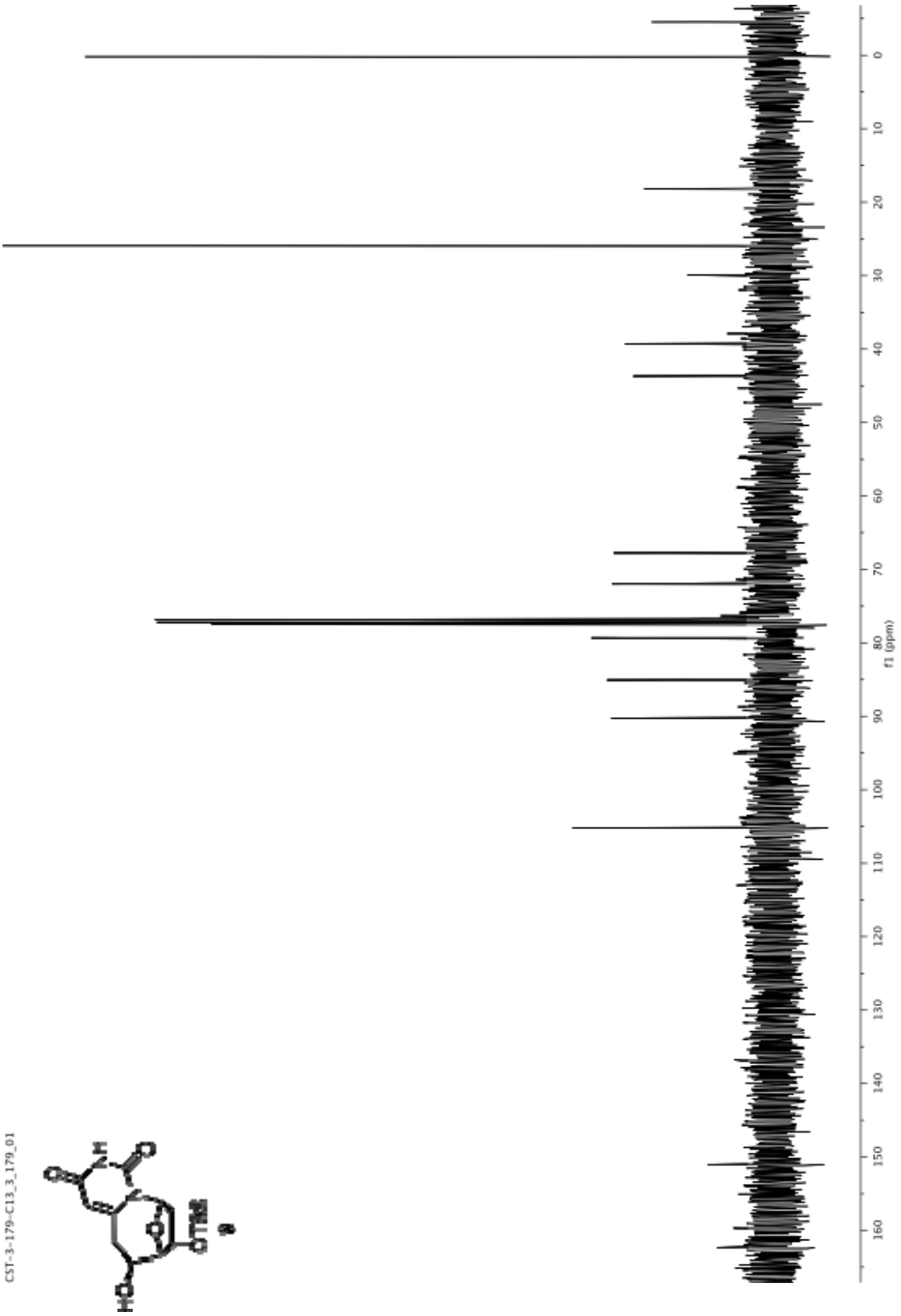
f1 (ppm)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150
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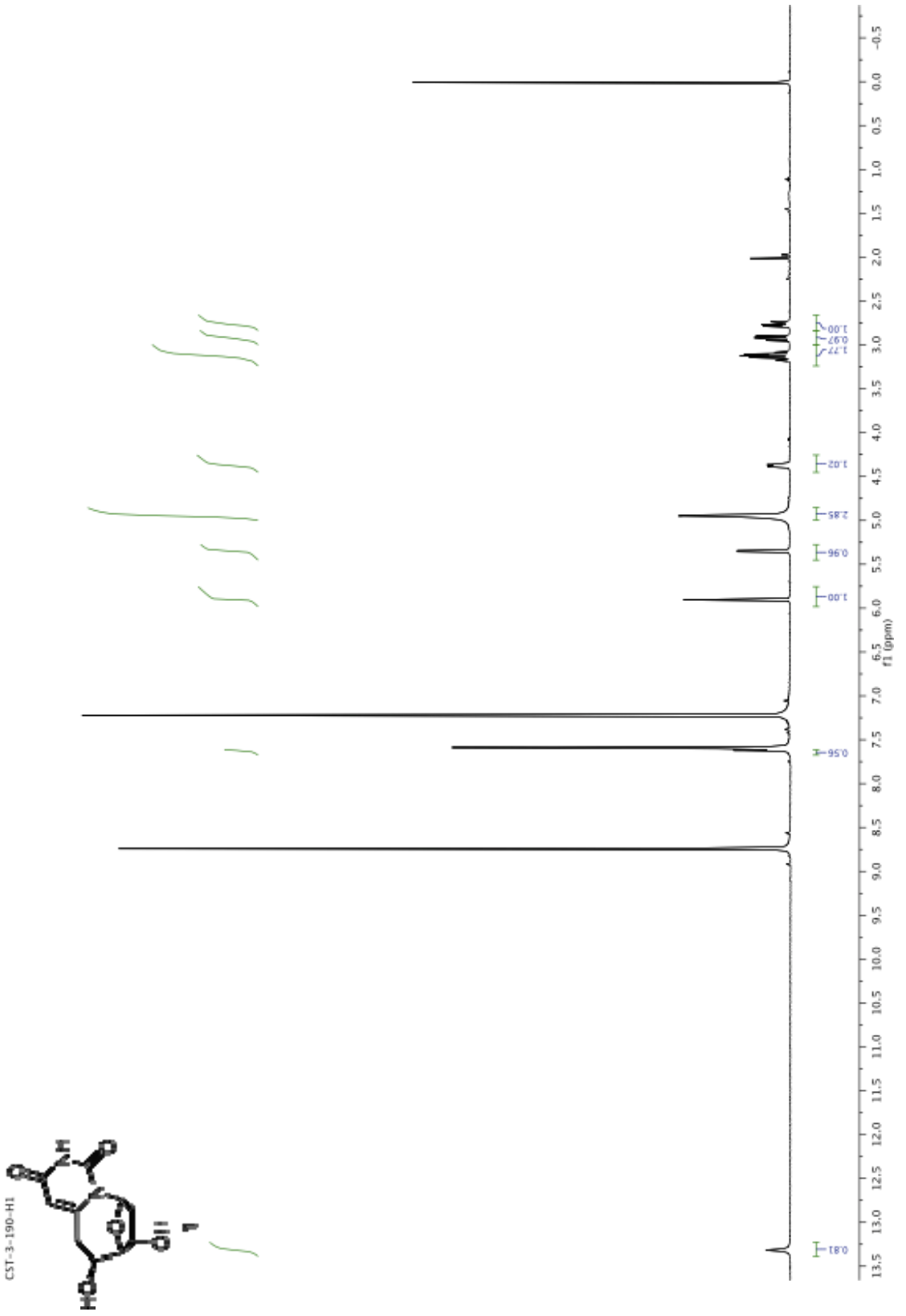
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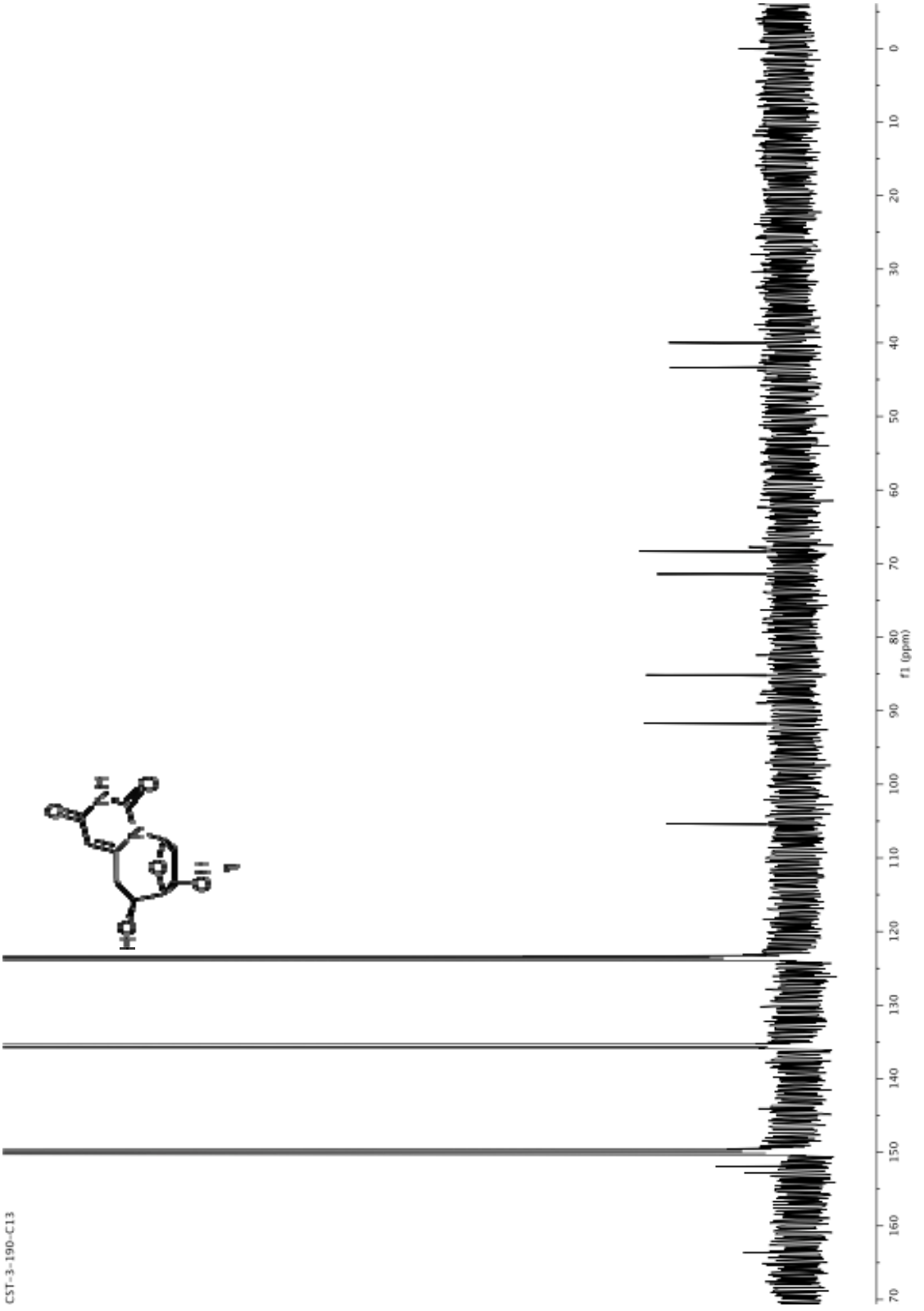
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f1 (ppm)