

Supporting Information for

## A simple, rapid method for the preparation of [ $^{11}\text{C}$ ] formaldehyde

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**General.** All chemicals were purchased from Sigma-Aldrich (USA) and used without additional purification. Reactions were carried out in anhydrous solvents (unless otherwise noted).

**Carbon-11 Chemistry:** [ $^{11}\text{C}$ ]Carbon dioxide was generated by an EBCO cyclotron by the nuclear reaction,  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ , using a nitrogen/oxygen (1000 ppm) target and transferred in a nitrogen stream to a PETtrace MeI Microlab for automated synthesis of [ $^{11}\text{C}$ ]methyl iodide. During radiosynthesis, carbon-11 was measured using a Capintec CRC-712MV radioisotope calibrator (Capintec Inc., Ramsey, NJ, USA). For dimedone precipitation experiments,  $^{11}\text{C}$  radioactivity was measured by a Packard MINAXI  $\gamma$  5000 automated gamma counter (Packard Instrument, Meriden, CT). All measurements were decay corrected.

**Chromatography:** Semipreparative and analytical high performance liquid chromatography (HPLC) were performed using a Knauer HPLC system (Sonntek Inc., Woodcliff Lake, NJ, USA) with a model K-5000 pump, a model 87 variable wavelength monitor and NaI radioactivity detector. Specific activity was determined by measuring the radioactivity and the mass; the latter is derived from a standard curve at UV (254 nm) using different concentrations of the authentic reference compounds. (Column and eluent conditions are given in the experimental section). Radiochemical purity was also determined by thin-layer chromatography (TLC) using Macherey–Nagel polygram sil G/UV254 plastic-backed TLC plates and measuring radioactivity distribution on with Bioscan system 200 imaging scanner (Bioscan Inc., Washington, DC).

**Nuclear Magnetic Resonance.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured with a Bruker DRX 400 MHz spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts are reported as  $\delta$  in units of parts per million (ppm) relative to acetonitrile- $d_3$  ( $^1\text{H}$ :  $\delta$  1.95, pentet;  $^{13}\text{C}$ :  $\delta$  1.39, septet).

### Experimental

#### NMR Monitored reactions of trimethylamine-*N*-oxide (TMAO) with methyl iodide (MeI):

**Excess MeI:** TMAO (7.5 mg, 0.1 mmol, 1 eqv x 2) was dissolved in 1.25 mL of  $d_3$ -MeCN. The sample was divided into two portions, which were added to either 35.5 mg [ $^{12}\text{C}$ ]-MeI (0.5 mmol, 10 eqv) or 36.7 mg [ $^{13}\text{C}$ ]-MeI (0.5 mmol, 10 eqv). While the initial stoichiometry was carefully controlled, the final stoichiometry was

approximate due to the volatility of MeI. Each solution was mixed using a Pasteur pipette and transferred to an NMR tube, which was subsequently flame sealed.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded.

**Excess TMAO:** TMAO (37.6 mg, 0.5 mmol, 5 eqv x 2) was dissolved in 1.25 mL of  $\text{d}_3\text{-MeCN}$ . The sample was divided into two portions which were added to either 7.3 mg [ $^{12}\text{C}$ ]-MeI (0.05 mmol, 1.0 eqv) or 7.6 mg [ $^{13}\text{C}$ ]-MeI (0.05 mmol, 5.0 eqv) in a dram vial. The vial was capped and heated to 70 °C for 1 min then cooled to RT. A small amount of white, crystalline precipitate was observed (determined to be  $\text{Me}_3\text{NHI}$ ). The mixture was transferred to an NMR tube, which was subsequently flame sealed.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded.

**[ $^{11}\text{C}$ ]Formaldehyde reaction condition screens.** [ $^{11}\text{C}$ ]-MeI in a stream of nitrogen gas was trapped in 1.0 mL of a given solvent (DMF at -40 °C, DMSO at RT, or MeCN at 0 °C, THF at -40 °C). This solution was subsequently divided into three 300  $\mu\text{L}$  aliquots (typically 0.5-1.0 mCi), which were added to three vials containing TMAO (masses given in Table 1). Each vial was capped placed in a heating block at 70 °C for a given reaction time. At the end of the reaction time, the vials were removed from the heating block and immediately placed into an ice/water bath. Analysis of the samples was accomplished by dimedone precipitation.

**Dimedone precipitation:** An aliquot (10  $\mu\text{L}$ ) of the crude [ $^{11}\text{C}$ ]formaldehyde solution was added to an aqueous solution of formaldehyde (400  $\mu\text{L}$ , 30% w/w). To this solution was added a solution of dimedone (160 mg in 30:70 MeOH:H $_2$ O). After measuring the radioactivity, the vessel was sealed and heated to 100 °C for 10 min. After cooling to RT, the precipitate was separated from the supernatant by either centrifugation or filtration and the radioactivity of each was measured.

**Pictet-Spengler Reaction of tryptamine and [ $^{11}\text{C}$ ]formaldehyde to form [ $^{11}\text{C}$ ]-2,3,4,9-tetrahydro-1H-beta-carboline:** A mixture of trimethylamine-*N*-oxide or its hydrate (4 mg, ~0.05 mmol) and DMF (300  $\mu\text{L}$ ) cooled to -40 °C in a tall thin reaction vial was used to capture  $^{11}\text{CH}_3\text{I}$  from a stream of nitrogen gas. The sealed vessel was heated to 70 °C for 2 min. The solution was then treated with a solution of DMF (100  $\mu\text{L}$ ) containing tryptamine (8 mg, 0.05 mmol) and *p*-toluene sulfonic acid (29 mg, 0.15 mmol) and heating was continued for 5 min. To the solution was added 1.0 mL of HPLC solvent (15% MeCN / 85% 0.1M aqueous ammonium formate) and the entire contents were loaded onto a Phenomenex Gemini C18 column (250 x 10 mm, 5  $\mu$ ). [ $^{11}\text{C}$ ]-2,3,4,9-tetrahydro-1H-beta-carboline, eluting at 22 min, was collected and the radioactivity measured. A portion of eluted product was subjected to analytical HPLC (C18 Luna, same eluent) and TLC ( $\text{Et}_3\text{N}:\text{MeOH}$ ), each indicating greater than 99% radiochemical purity.

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 NS 64  
 DS 2

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 FIDRES 0.187800 Hz  
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 RG 574.7  
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 TE 297.2 K

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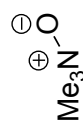
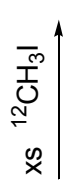
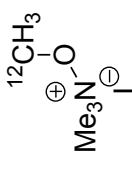
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Hooker (Standard Proton Parameters)  
 TMAO + [12C]MeI (excess)

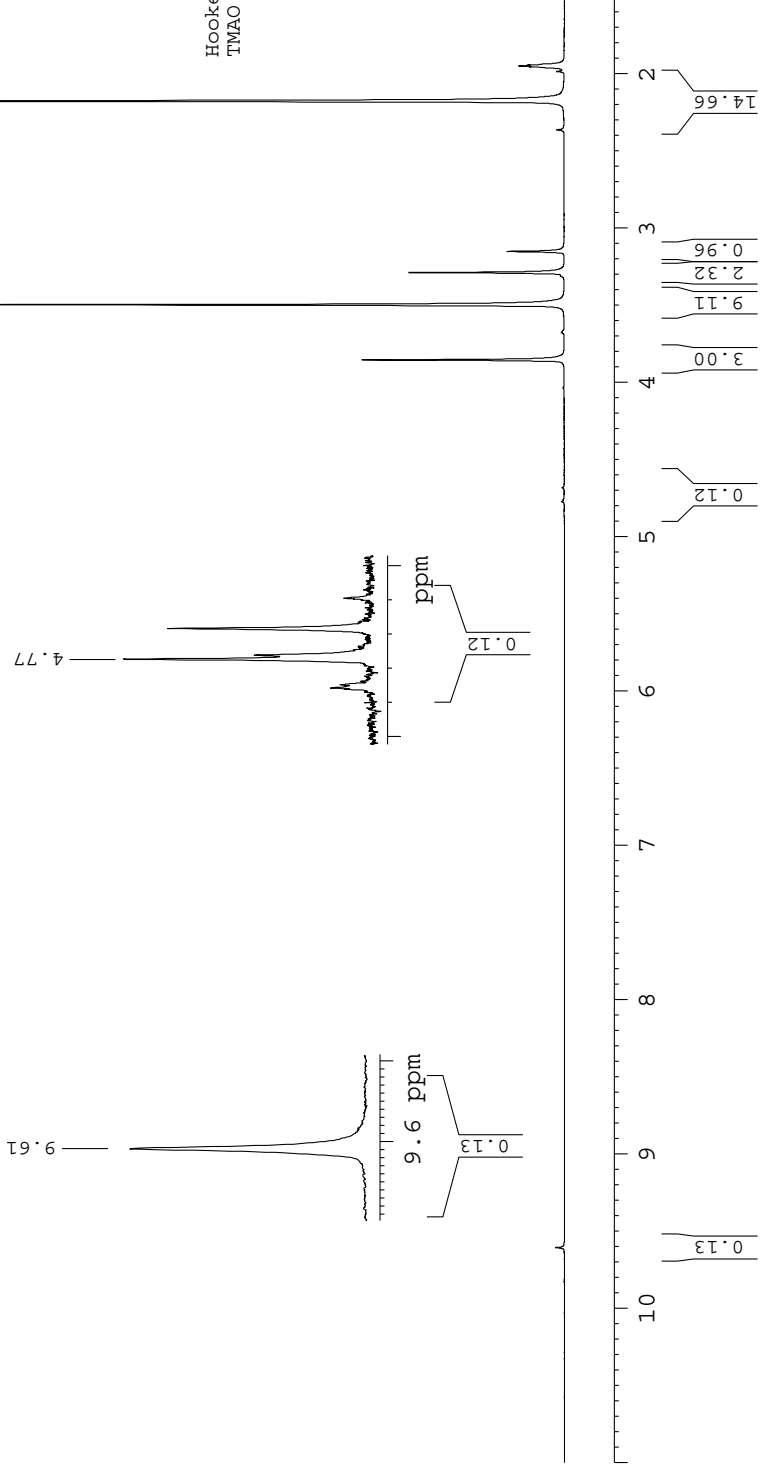
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3.15  
3.29

4.77

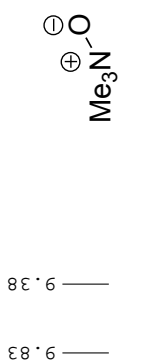


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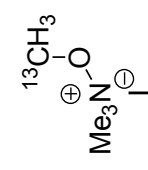
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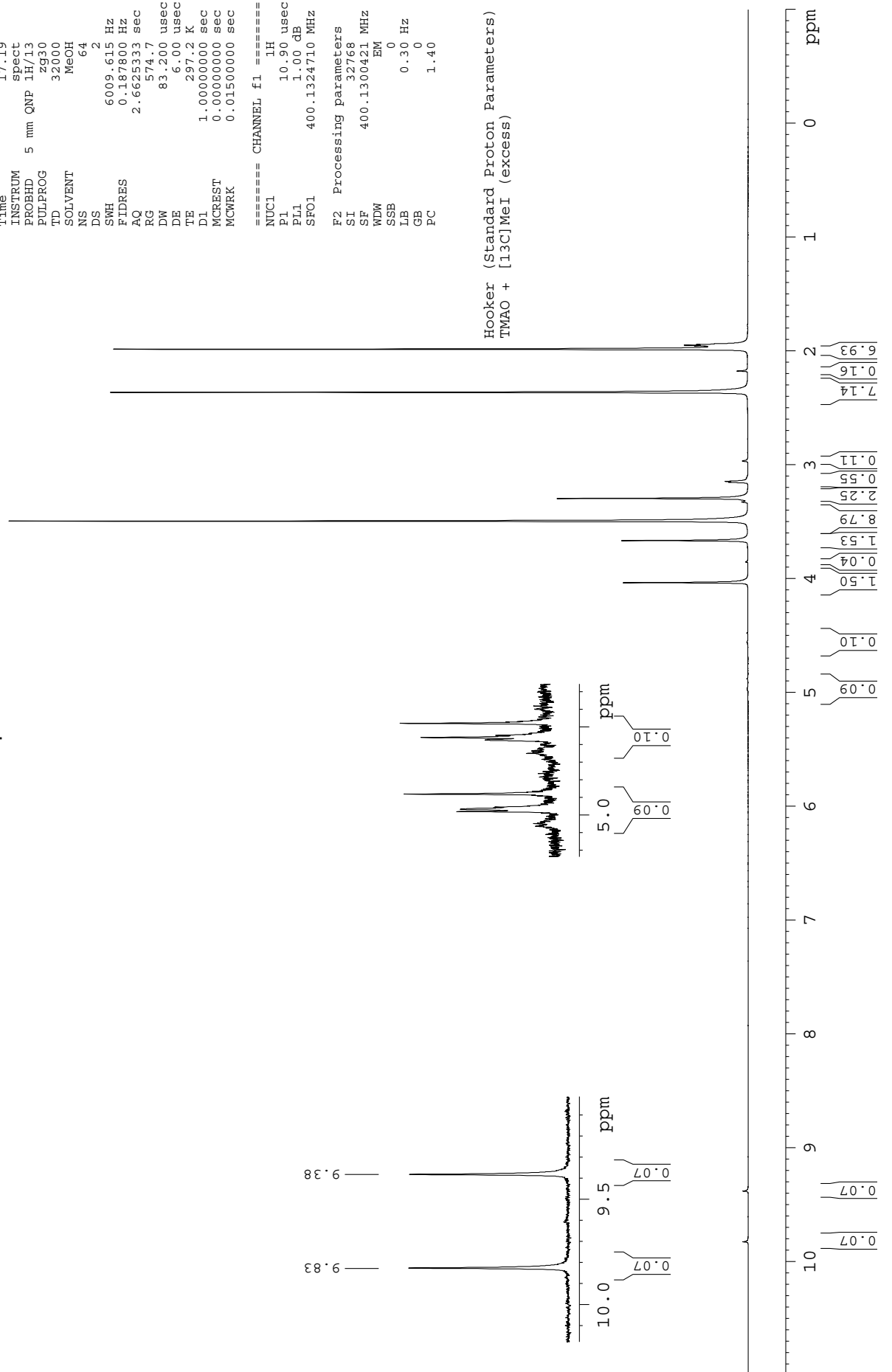
xs  $^{13}\text{CH}_3\text{I}$



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 4.04  
 3.85  
 3.67  
 3.50  
 3.33  
 3.30  
 3.15  
 3.15  
 2.97  
 2.36  
 2.18  
 1.99  
 1.96  
 1.96  
 1.95  
 1.94

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 SOLVENT MeOH  
 NS 64  
 DS 2  
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 AQ 2.6625333 sec  
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Hooker (Standard Proton Parameters)  
 TMAO +  $^{13}\text{C}$ MeI (excess)



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F2 Acquisition Parameters

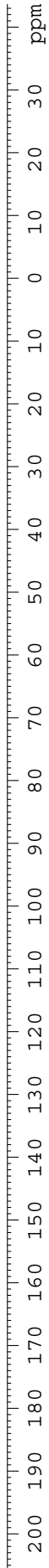
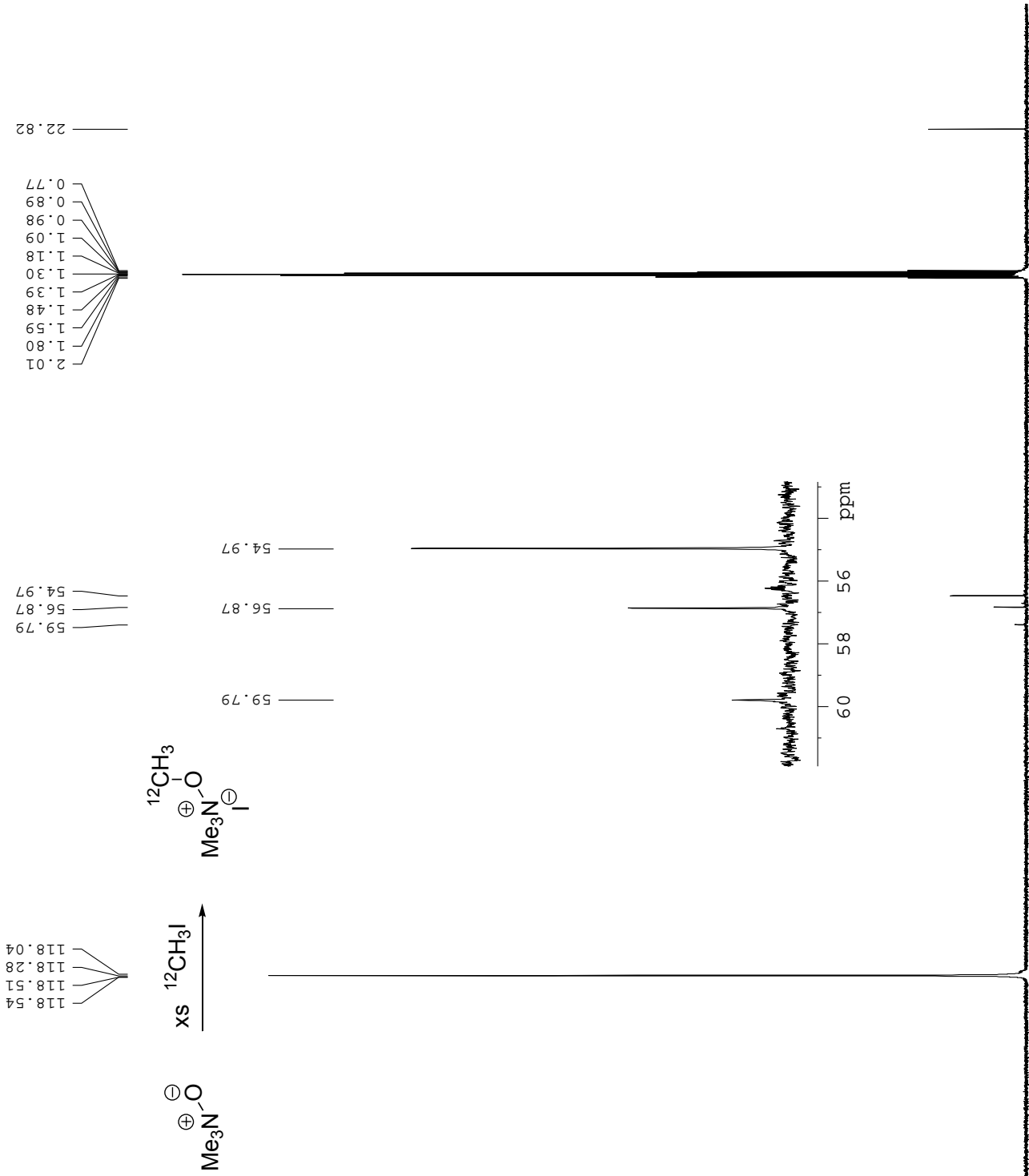
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TWAO + [12C]MeI (excess)



Current Data Parameters  
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 AQ 1.3075131 sec  
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 DE 6.00 usec  
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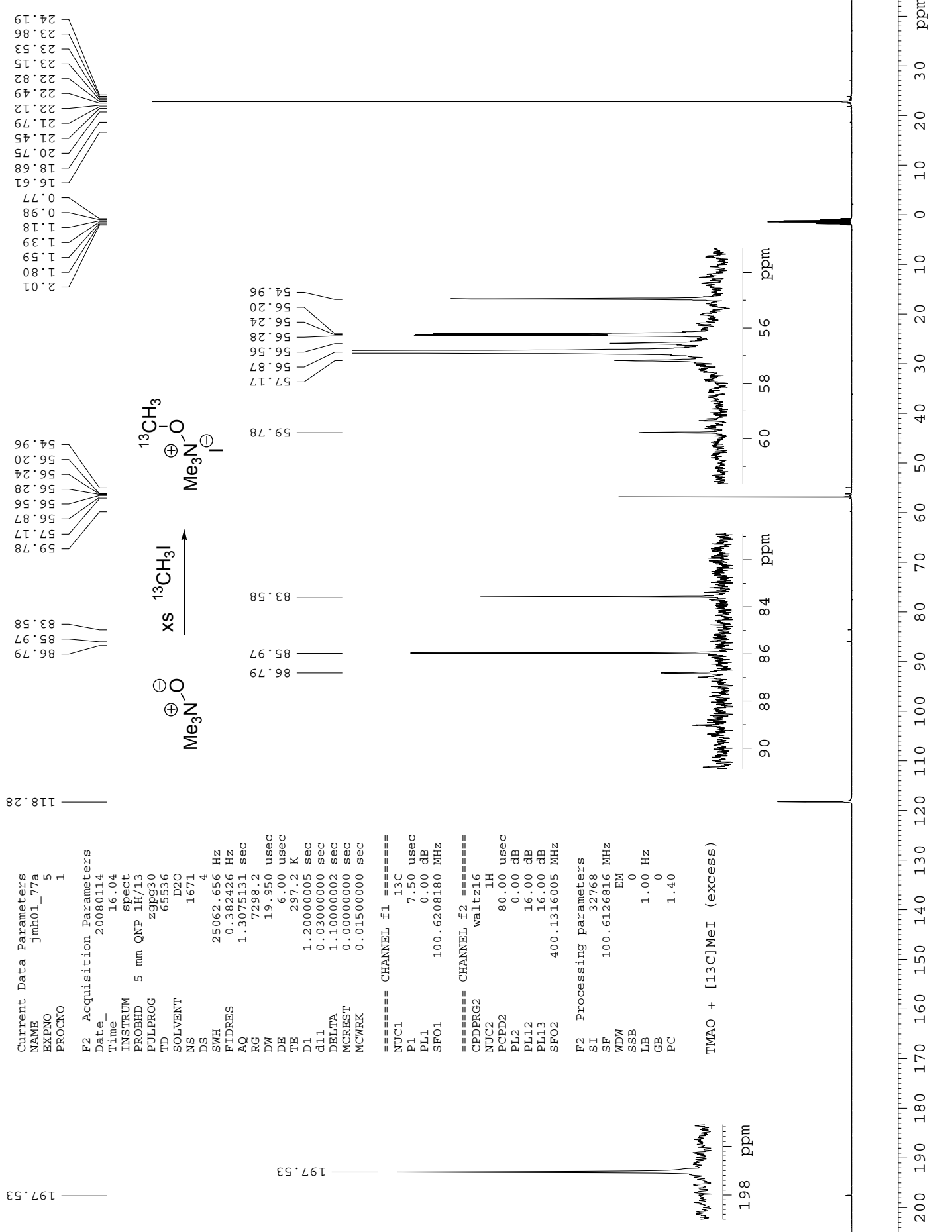
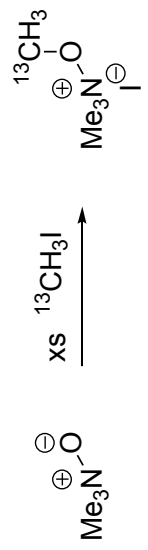
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TMAO + [13C]MeI (excess)

197.53  
 118.28  
 86.79  
 85.97  
 83.58  
 59.78  
 57.17  
 56.87  
 56.56  
 56.28  
 56.24  
 56.20  
 54.96  
 2.01  
 1.80  
 1.59  
 1.39  
 1.18  
 0.98  
 0.77  
 16.61  
 18.68  
 20.75  
 21.45  
 21.79  
 22.12  
 22.49  
 22.82  
 23.15  
 23.53  
 23.86  
 24.19



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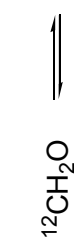
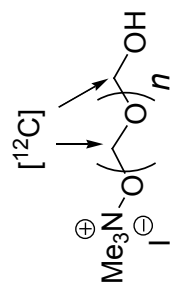
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1.94  
1.94  
1.95  
1.96  
1.96  
1.96  
2.12  
2.28

2.98  
3.16  
3.24  
3.33

4.70  
4.73  
4.74  
4.76  
4.83  
4.83

4.83  
4.83  
4.76  
4.74  
4.73  
4.70



9.60

9.60

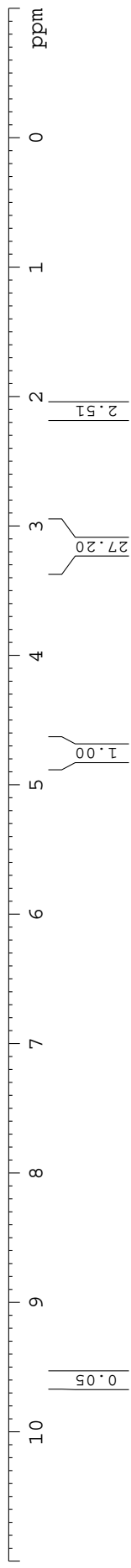
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ppm

1.00

4.8 4.7 ppm

Hooker (Standard Proton Parameters)  
 TMAO (excess) + [12C]MeI



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Hooker (Standard Proton Parameters)  
 TMAO (excess) + [13C]MeI

1.94  
1.95  
1.96  
2.12  
2.20  
2.28  
2.77  
2.89  
2.98  
3.16  
3.33

4.50  
4.52  
4.54  
4.55  
4.56  
4.61  
4.62  
4.63  
4.64  
4.89  
4.93  
4.95  
4.96  
4.96  
5.02  
5.04  
5.05

4.50  
4.52  
4.54  
4.55  
4.56  
4.61  
4.62  
4.63  
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4.89  
4.93  
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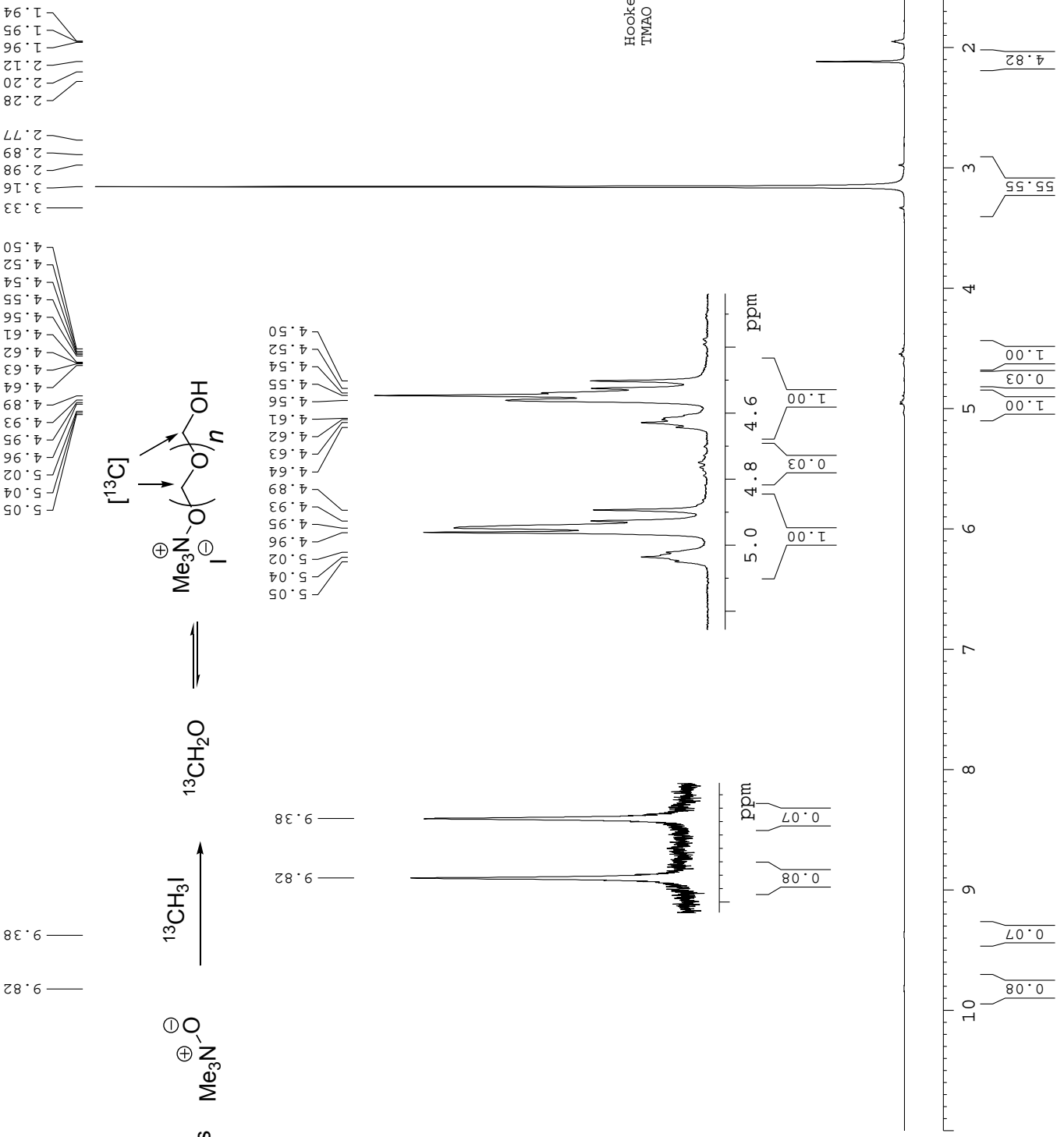
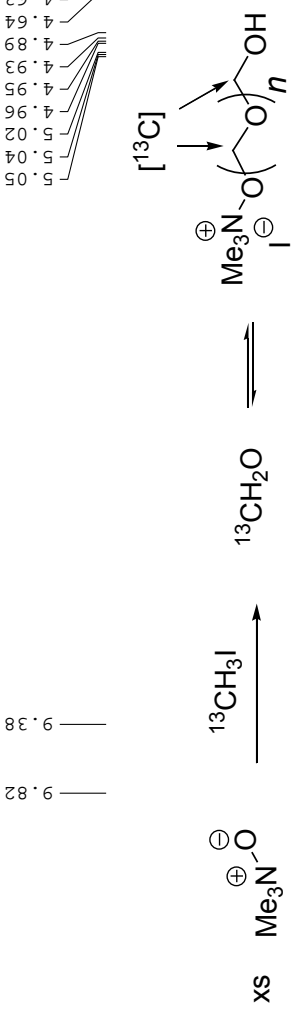
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0.07  
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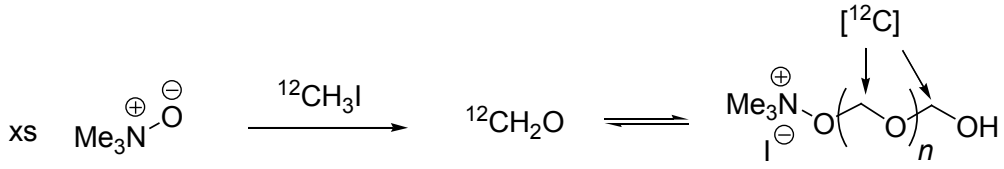
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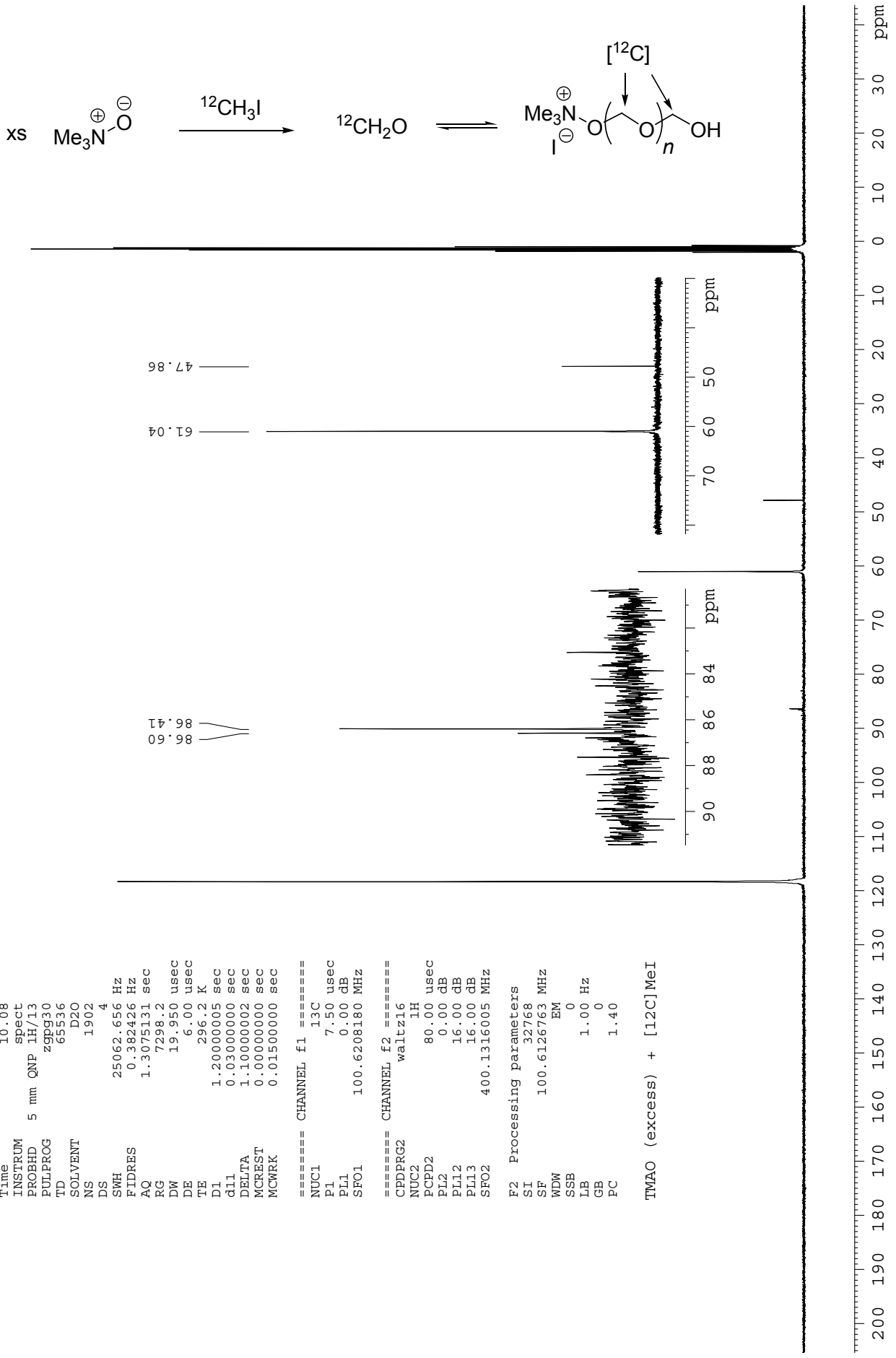
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F2 Processing parameters  
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 PC 1.40

TMAO (excess) + [12C]MeI



118.35  
 86.60  
 86.41  
 61.04  
 47.86  
 2.18  
 2.01  
 1.81  
 1.60  
 1.39  
 1.19  
 0.98  
 0.77



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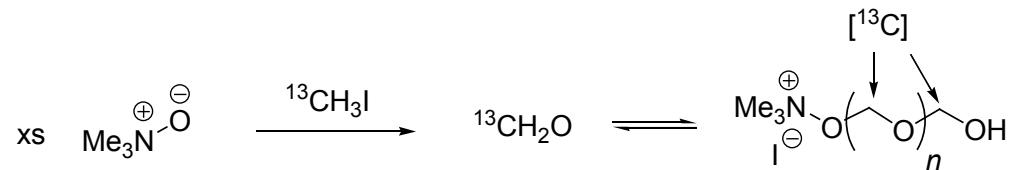
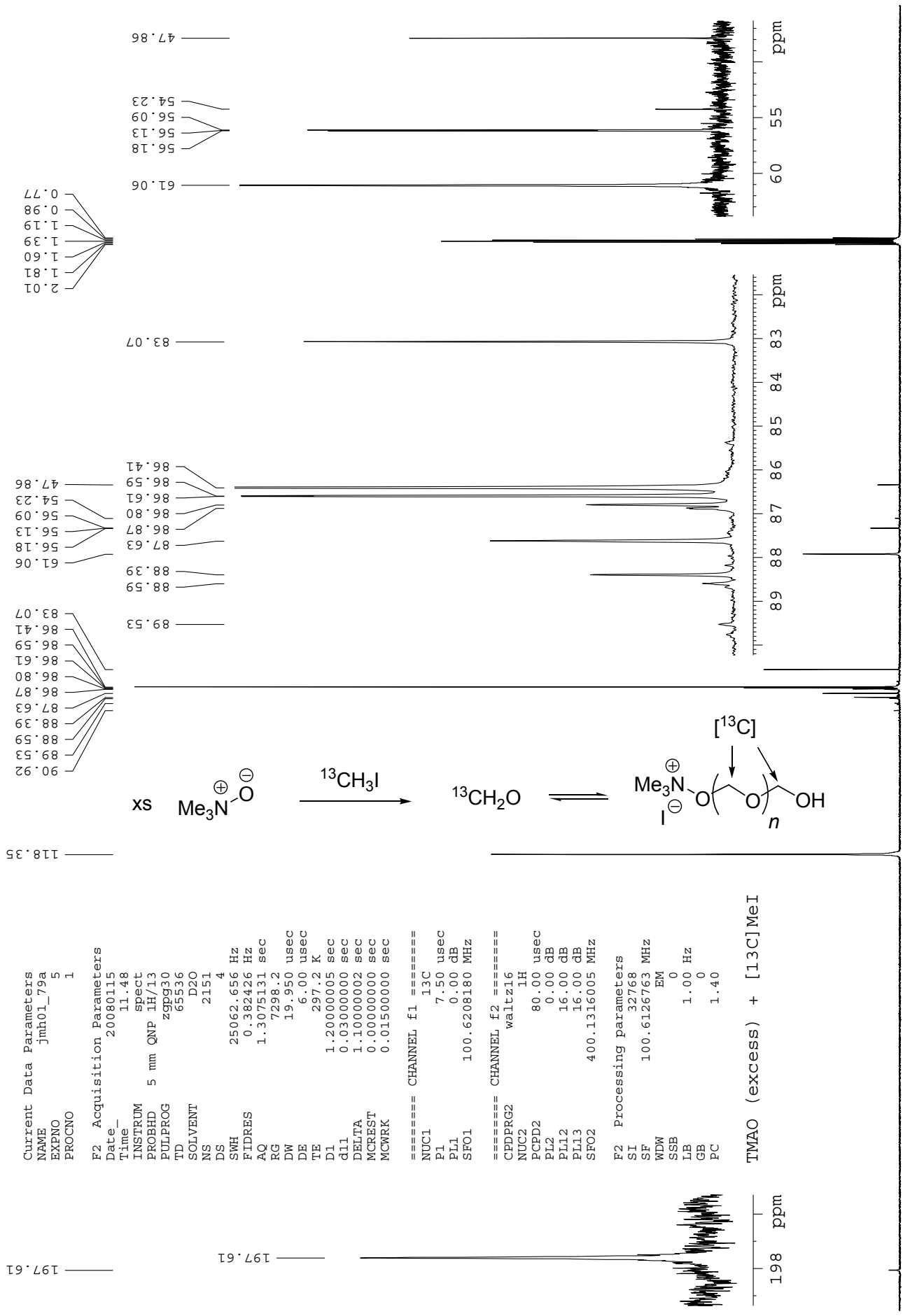
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 PC 1.40

TMAO (excess) + [13C]MeI



2.01  
1.81  
1.60  
1.39  
1.19  
0.98  
0.77

61.06

83.07  
88.59  
88.39  
61.06  
56.18  
56.13  
56.09  
54.23  
47.86  
86.59  
86.61  
86.80  
86.87  
87.63

89.53

83.07  
86.41  
86.59  
86.61  
86.80  
86.87  
87.63  
88.39  
88.59  
89.53  
90.92  
89.53  
88.59  
88.39  
87.63  
86.87  
86.80  
86.61  
86.59  
86.41

89.53

197.61

197.61

198 ppm