

# Mechanistic Analysis and Optimization of the Copper-Catalyzed Enantioselective Intramolecular Alkene Aminooxygenation

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## Supporting Information

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## Kinetics Experiments

**General Information:** All reagents were used out of the bottle as purchased from the supplier without further purification unless otherwise specified.  $\text{Cu}(\text{OTf})_2$  was handled in dry atmosphere (glove box). The  $\text{Cu}(\text{OTf})_2$  and ligand were complexed under rigorously anhydrous conditions. Reactions were monitored using High Performance Liquid Chromatography. Data analysis was performed using Microsoft Office Excel 2007 software and data were plotted using SigmaPlot for Window's v. 10.0 (Systat Software, Inc, San Jose, CA).

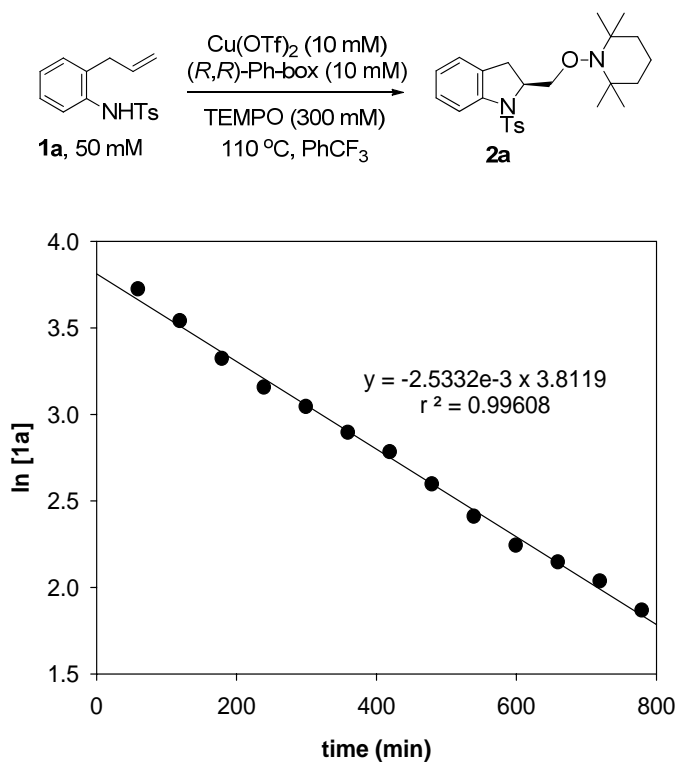
### General Procedure for Kinetics Experiments

$\text{Cu}(\text{OTf})_2$  and (*R,R*)-Ph-Box were pre-complexed in  $\text{CF}_3\text{Ph}$  under Argon for 2 h at 60 °C in an oven-dried 10 mL round bottom flask equipped with magnetic stir bar and sealed with septa. The solution was cooled to room temperature and treated with substrate **1a** and TEMPO. The reaction mixture was heated to 110 °C using a temperature regulated oil bath. It was taken out of the oil bath every hour and a 20  $\mu\text{L}$  aliquot was collected using gas-tight syringe. The aliquots collected were dried under vacuum and the residue was dissolved in 200  $\mu\text{L}$  acetonitrile. The samples were analyzed using HPLC in a Microsorb-MV 100 C8 column by gradient elution (65-100%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$ ). Calibration plots for substrate **1a** and the TEMPO adduct **2a** were used to calculate the concentrations of **1a** and **2a** as a function of time.

Reactions were run up to 80-90% conversion for higher catalyst loading (20-40 mol% or 10-20 mM). We observed that at low catalyst loading (5-10 mol% or 2.5-5 mM), reactions do not go to completion and the rate tails off at 40-60% conversion presumably due to catalyst decomposition. Therefore, initial reaction rates were measured for these catalyst loadings.

**Order in substrate 1a:** The general procedure above was followed using 20 mol% each of  $\text{Cu}(\text{OTf})_2$  and  $(R,R)$ -PhBox, 50 mM of substrate **1a** and 300 mM of TEMPO in  $\text{CF}_3\text{Ph}$  (1.04 mL). Unique kinetics experiments were performed three times and in each case a plot of  $\ln[1\mathbf{a}]$  versus time gave a straight line ( $r^2 = 0.996$ ), indicating first-order dependence in substrate **1a**. A representative plot of  $\ln[1\mathbf{a}]$  versus time is shown in Figure S-1. Figure S-2 shows the simultaneous disappearance of **1a** and appearance of **2a** as determined by HPLC analysis.

**Figure S-1.** A representative plot of  $\ln[1\mathbf{a}]$  (mM) versus time (min) showing first-order kinetics in substrate **1a**



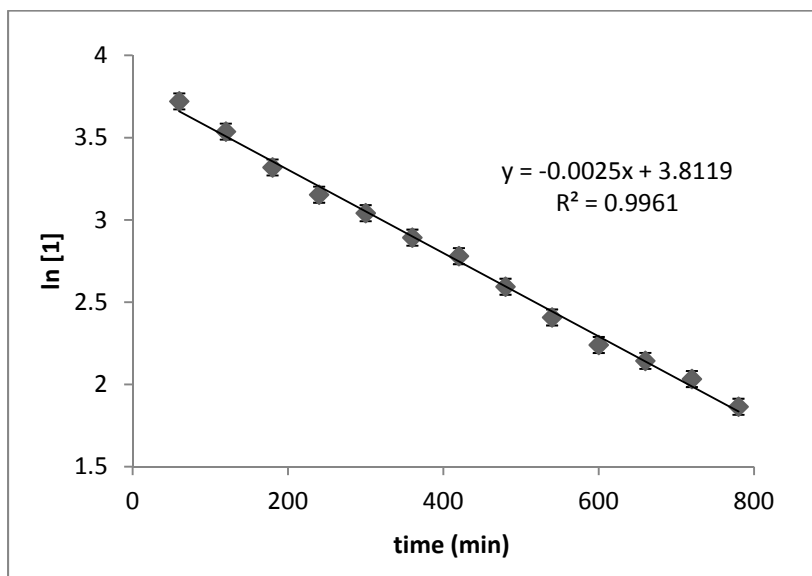
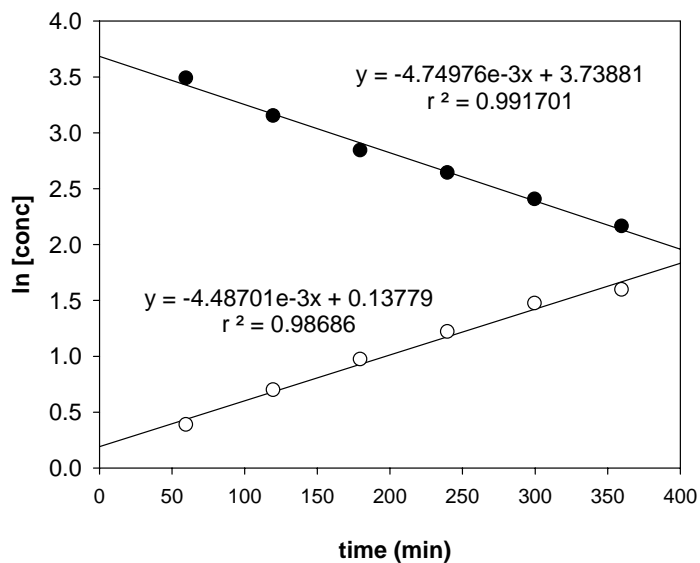
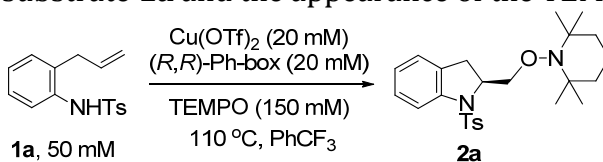


Figure S-1 with error bars.

Figure S-2. The loss of alkene substrate **1a** and the appearance of the TEMPO adduct **2a**



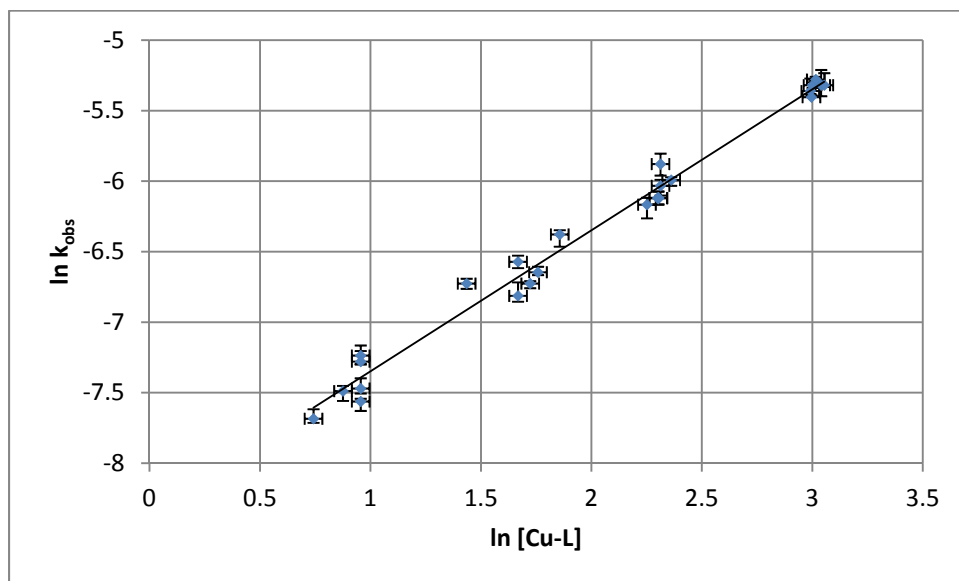
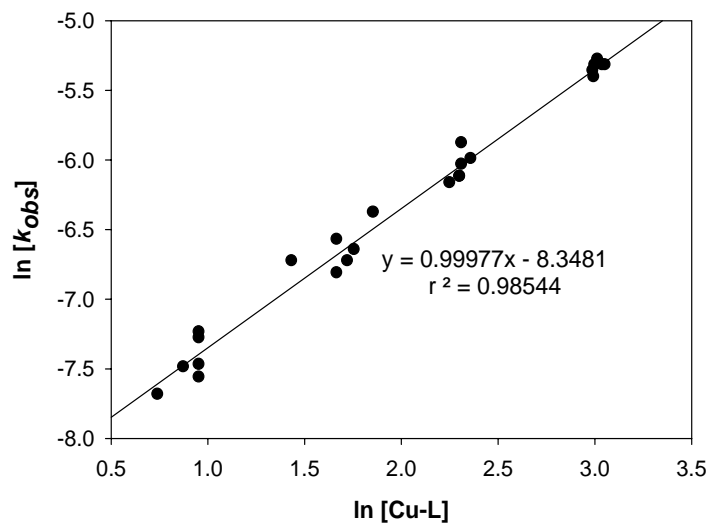
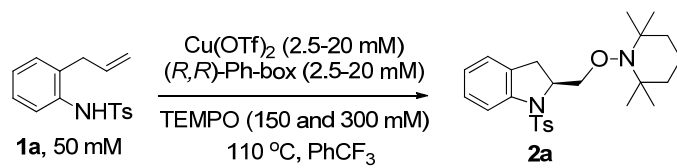
**Order in Copper-bisoxazoline complex (Cu-L) and TEMPO:** The order in Cu-L complex ( $\text{Cu}(\text{OTf})_2$  complexed with  $(R,R)\text{-PhBox}$ ) was determined by performing a series of experiments using different

concentrations of Cu-L complex (2.5-20.4 mM), substrate **1a** (50 mM) and TEMPO (150 and 300 mM) in CF<sub>3</sub>Ph (1.04 mL). The disappearance of **1a** was monitored and the observed rate constant was determined from the slope of the plot of ln[**1a**] against time. Kinetic data is given in Table S-1. The first-order dependence in the Cu-L complex was determined from the plot of ln[*k<sub>obs</sub>*] versus ln[Cu-L] (*m* = 0.99 ± 0.02) (Figure S-3). The data from the experiments showed no significant change in the rate constant upon changing the concentration of TEMPO (Table S-1, e.g. compare entry 1 and 4), which suggests zero-order dependence in TEMPO.

**Table S-1.** Kinetic data for determining the order of the reaction in Cu-L complex and TEMPO.

Entry	Cu-L (mM)	TEMPO (mM)	$k_{obs}$ (min <sup>-1</sup> )
1	2.6	161.8	$5.7(0.4) \times 10^{-4}$
2	2.6	147.1	$5.2(0.1) \times 10^{-4}$
3	2.4	150.2	$5.6(0.2) \times 10^{-4}$
4	2.6	296.7	$7.2(0.5) \times 10^{-4}$
5	2.6	299.8	$6.9(0.5) \times 10^{-4}$
6	2.1	297.9	$4.6(0.3) \times 10^{-4}$
7	5.6	171.6	$1.2(0.2) \times 10^{-3}$
8	6.4	149.0	$1.7(0.05) \times 10^{-3}$
9	4.2	150.0	$1.2(0.04) \times 10^{-3}$
10	5.3	303.4	$1.1(0.1) \times 10^{-3}$
11	5.8	300.0	$1.3(0.05) \times 10^{-3}$
12	5.3	297.9	$1.4(0.06) \times 10^{-3}$
13	10.6	150.2	$2.5(0.05) \times 10^{-3}$
14	10.0	150.0	$2.2(0.1) \times 10^{-3}$
15	10.1	152.6	$2.4(0.1) \times 10^{-3}$
16	10.0	304.7	$2.2(0.1) \times 10^{-3}$
17	10.1	297.3	$2.8(0.2) \times 10^{-3}$
18	9.5	296.7	$2.1(0.1) \times 10^{-3}$
19	19.9	149.6	$4.7(0.4) \times 10^{-3}$
20	20.9	152.0	$4.9(0.5) \times 10^{-3}$
21	20.1	149.6	$4.9(0.1) \times 10^{-3}$
22	21.2	301.0	$4.9(0.4) \times 10^{-3}$
23	20.4	297.9	$5.1(0.1) \times 10^{-3}$
24	20.0	298.5	$4.5(0.06) \times 10^{-3}$

**Figure S-3.** Plot of  $\ln[k_{obs}]$  against  $\ln[\text{Cu-L}]$  showing first-order dependence in copper.

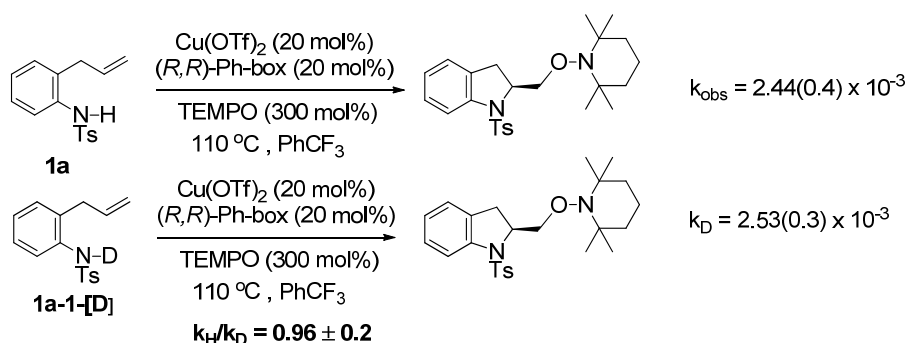


**Figure S-3 with error bars.**

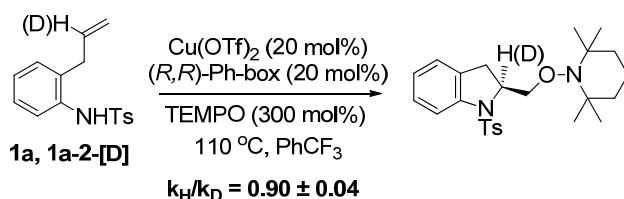
## Kinetic Isotope Effect (KIE)

The deuterated compounds **1a-1-[D]** and **1a-2-[D]** were obtained following our reported procedure.<sup>1</sup>

**Primary Kinetic Isotope Effect:** The primary kinetic isotope effect was determined by comparing the rate of reactions of substrate **1a** and **1a-1-[D]**. The general procedure on for the catalytic aminooxygenation reaction was followed using a pre-complexed solution of Cu(OTf)<sub>2</sub> (20 mol%) and (*R,R*)-PhBox (20 mol%), substrate **1a** or **1a-1-[D]** (0.05 mmol, 1 equiv), TEMPO (24.4 mg, 0.16 mmol, 3 equiv) and CF<sub>3</sub>Ph (1.04 mL). Reactions were conducted at 110 °C and the reported value of *k*<sub>obs</sub> represents an average of three unique kinetics experiments.



## Secondary Kinetic Isotope Effect



Following the previously reported procedure,<sup>1</sup> a mixture of substrates **1a** (25.0 mg) and **1a-2-[D]** (25.0 mg) was dissolved in CF<sub>3</sub>Ph (1.16 mL). An aliquot (0.232 mL) was taken from this solution *via* micropipet and was subjected to mass spectrometry to determine the isotopic ratio prior to reaction (R<sub>0</sub>) (representative data is given in Table S-2). The remaining solution was added to a pre-complexed Cu(OTf)<sub>2</sub> (10.1 mg, 27.8 μmol, 0.2 equiv) and (*R,R*)-PhBox (0.56 mL of 0.05 M solution in CF<sub>3</sub>Ph, 27.8 μmol, 0.2 equiv) followed by TEMPO (65.2 mg, 417 μmol, 3 equiv) and 0.56 mL CF<sub>3</sub>Ph. The solution was



heated to 110 °C under partial conversion. The remaining mixture of starting olefins (**1a** and **1a-2-[D]**) was isolated by flash chromatography (5% EtOAc in hexanes) and the isotopic ratio was determined by mass spectroscopy (R). Fractional conversion (F) which was corrected (Fc) using the equation given in Table S-3 was determined by HPLC analysis. Four separate reactions were performed and kinetic isotope effect was determined for each case. The reported KIE is the average of these 4 experiments ( $0.90 \pm 0.04$ ).<sup>2,3</sup>

**Table S-2.** Representative data of isotopic ratio as determined by mass spectrometry

Trial	Ro	R	R/Ro
1	0.96	0.88	
2	0.96	0.84	
3	0.98	0.82	
4	0.99	0.84	
Ave	$0.97 \pm 0.01$	$0.84 \pm 0.01$	$0.86 \pm 0.02$

**Table S-3.** Calculated KIE data and errors<sup>2,3</sup>

$$F_c = 1 - \frac{(1-F)(1+R_o)}{1+R}$$

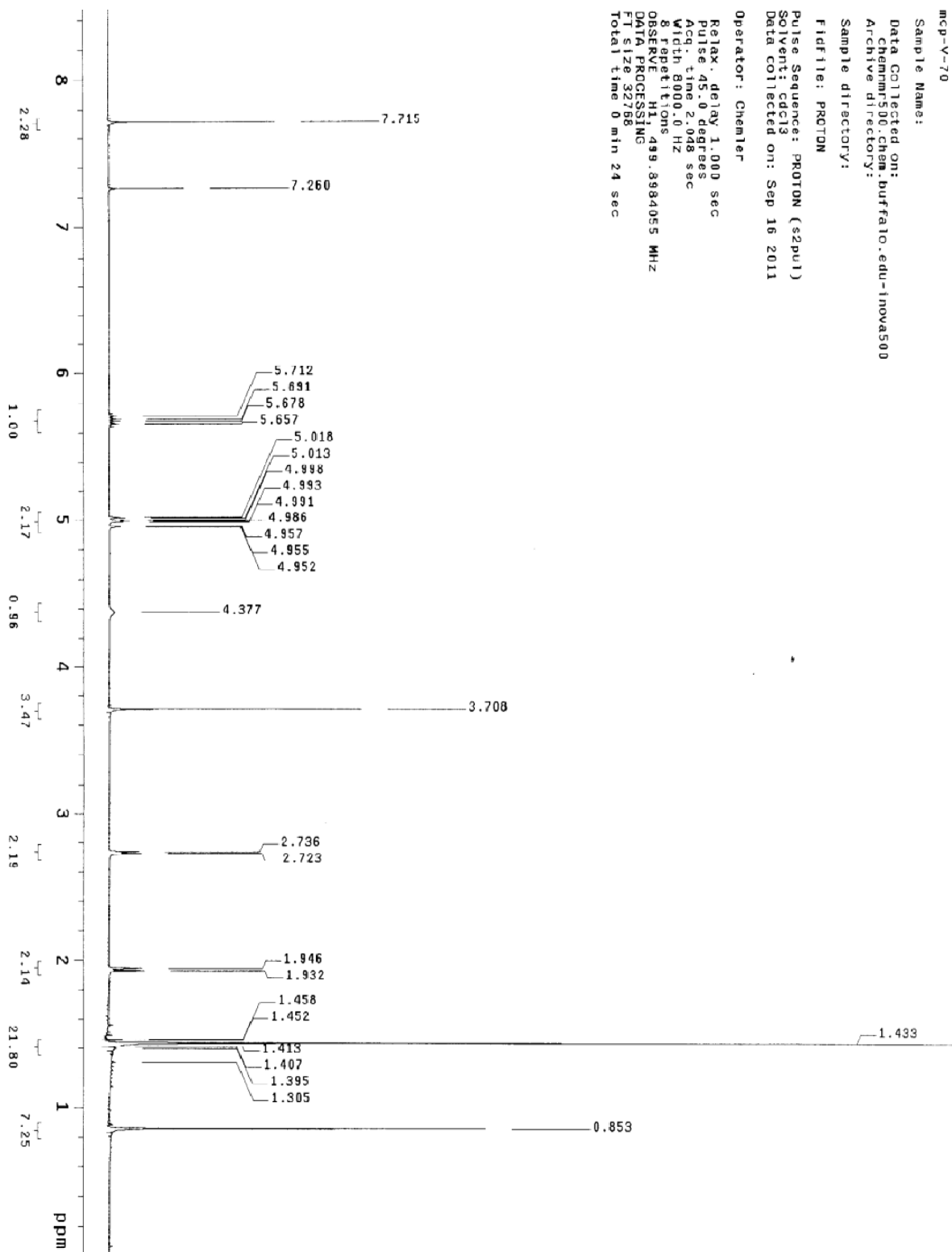
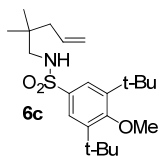
$$KIE = \frac{k_H}{k_D} = \frac{\ln(1-F_c)}{\ln[(1-F)(R/R_o)]}$$

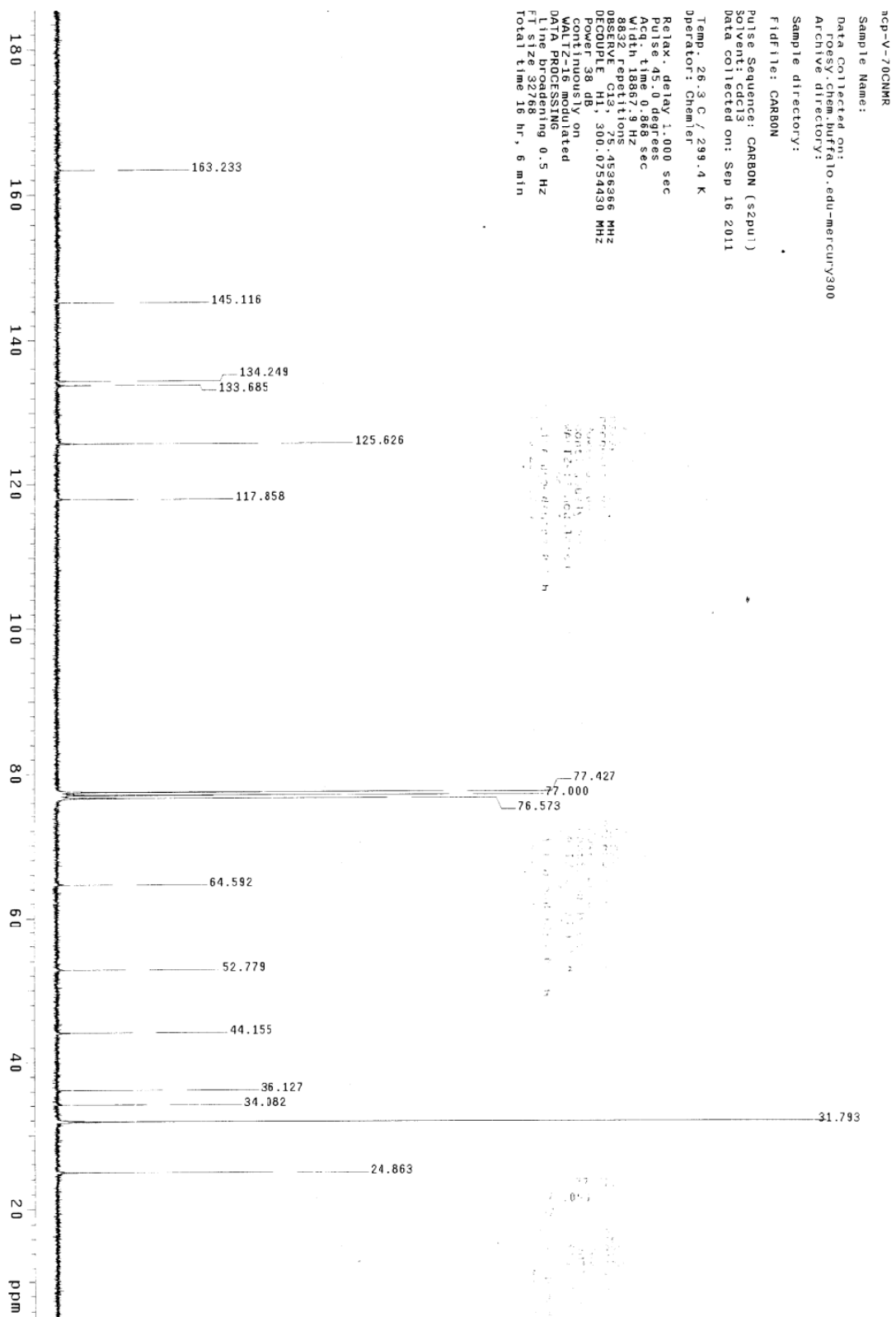
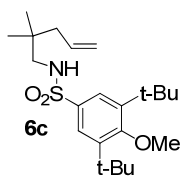
$$\Delta KIE = \frac{-(\Delta R/R_o) \ln(1-F_c)}{(R/R_o) \ln^2[(1-F_c)(R/R_o)]}$$

Entry	1-F	1-Fc	R/Ro	$\Delta R/R_o$	KIE	$\Delta KIE$
1	0.2427	0.2602	0.8637	0.02	0.9018	0.0139
2	0.1605	0.1752	0.8222	0.02	0.8990	0.0113
3	0.4699	0.4897	0.9184	0.09	0.8934	0.1095
4	0.1112	0.1210	0.8350	0.07	0.9214	0.0337
				Ave. KIE	0.9039	0.04

**References**

- (1) Paderes, M. C.; Belding, L.; Fanovic, B.; Dudding, T.; Keister, J. B.; Chemler, S. R. *Chem. Eur. J.* **2012**, *18*, 1711-1726.
- (2) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; John Wiley and Sons, 1979.
- (3) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357-9358.





mcp-v-53

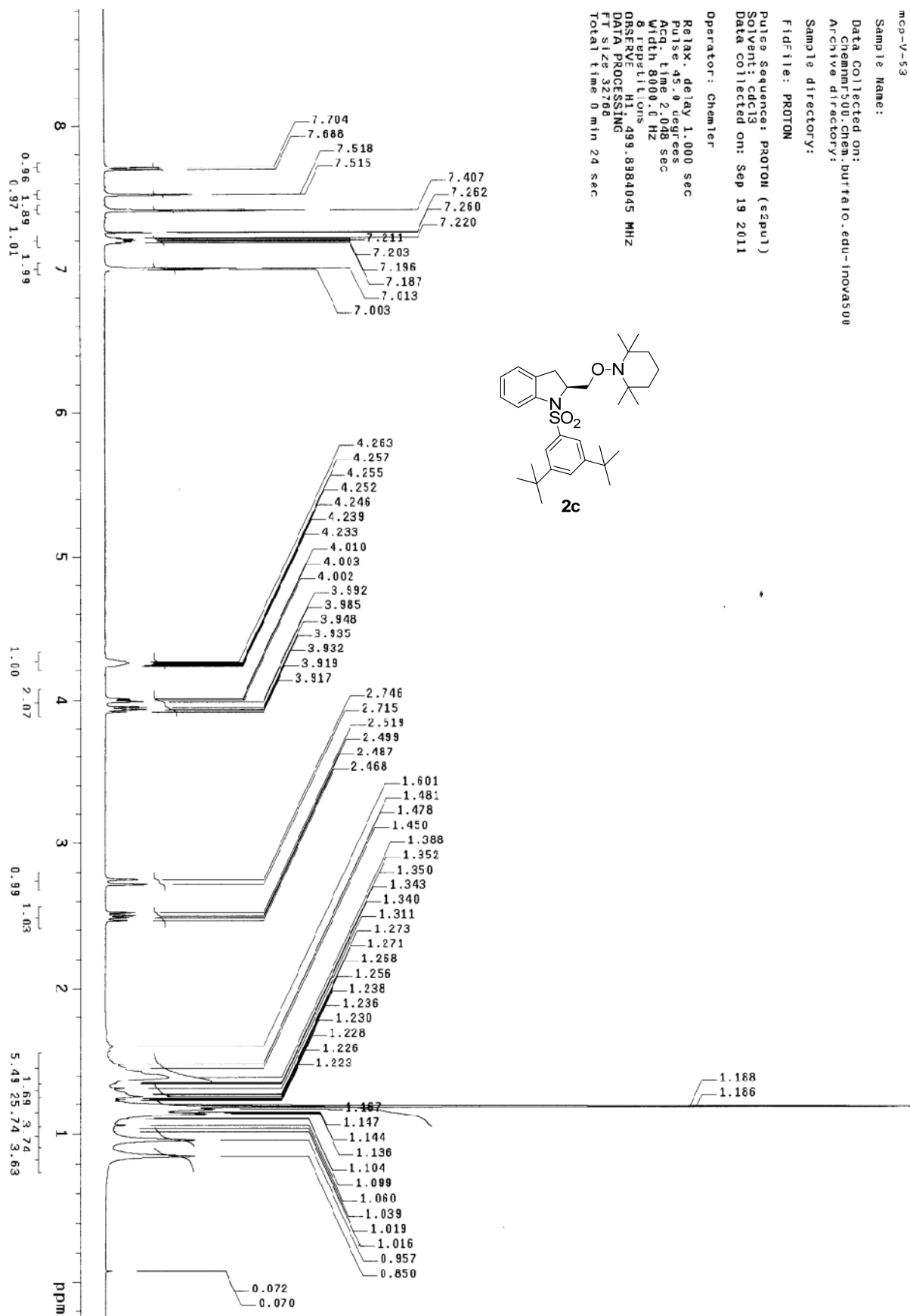
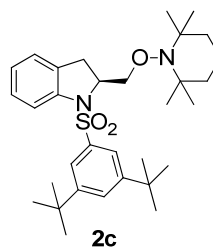
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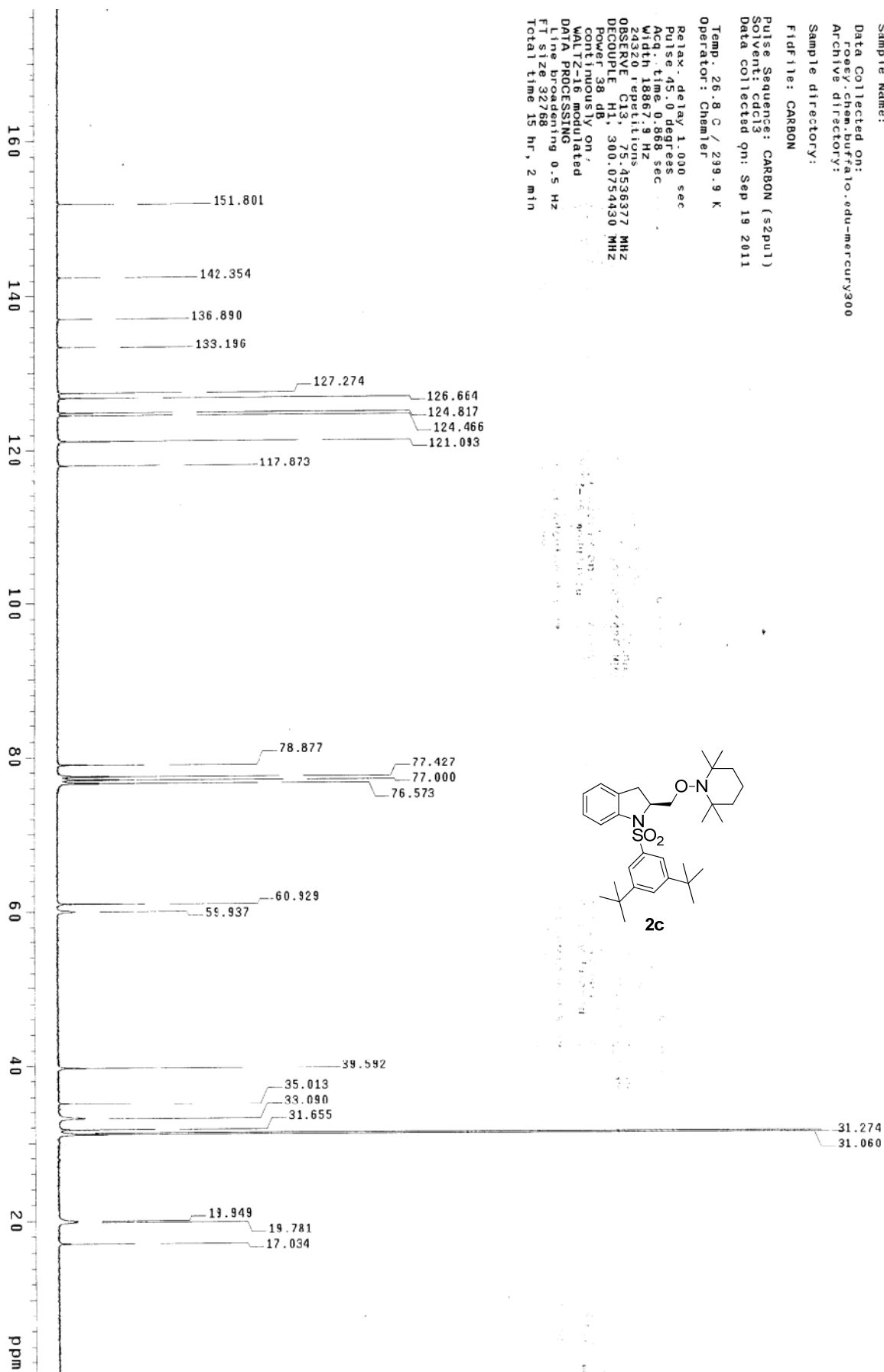
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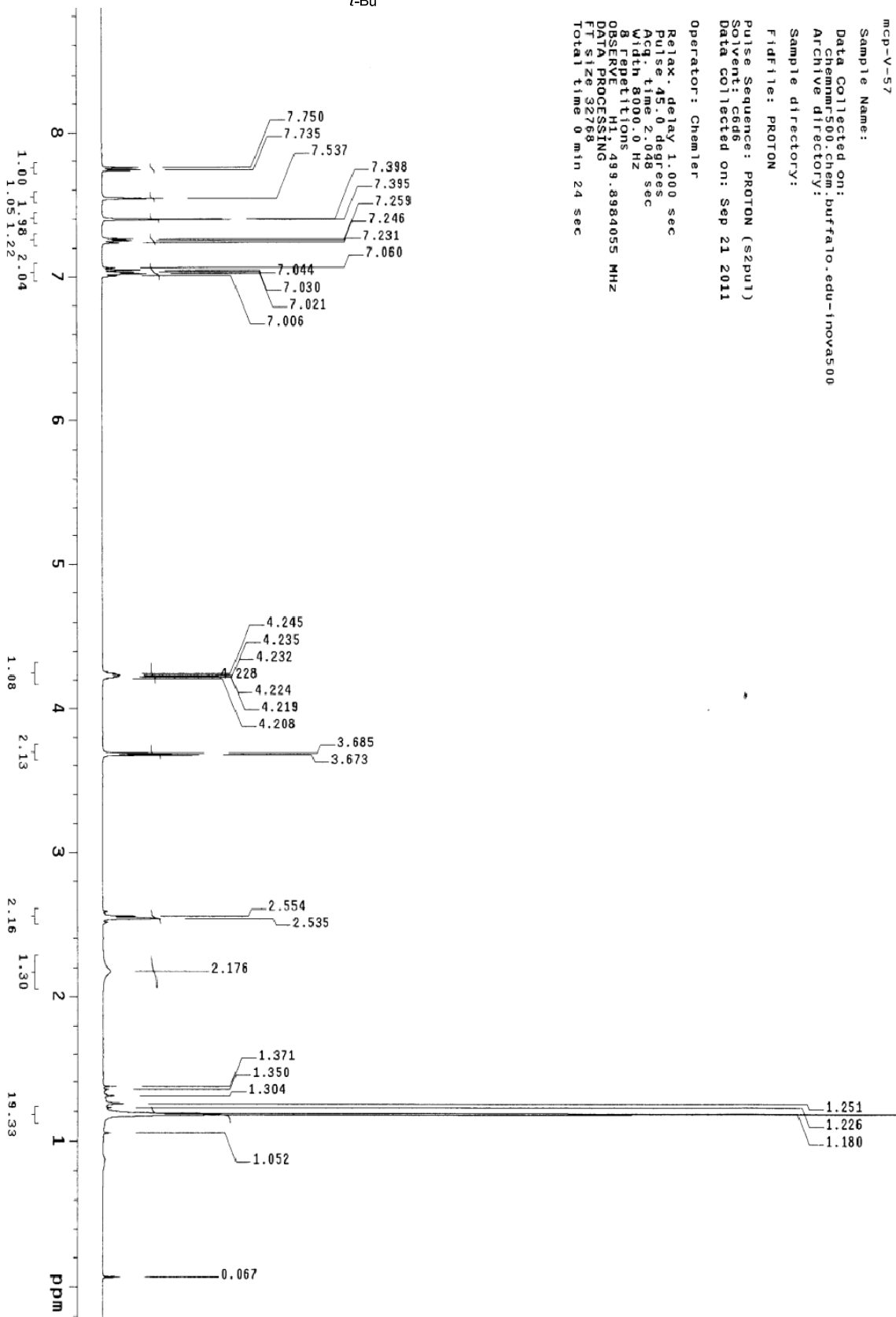
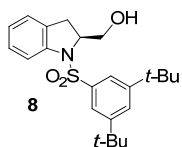
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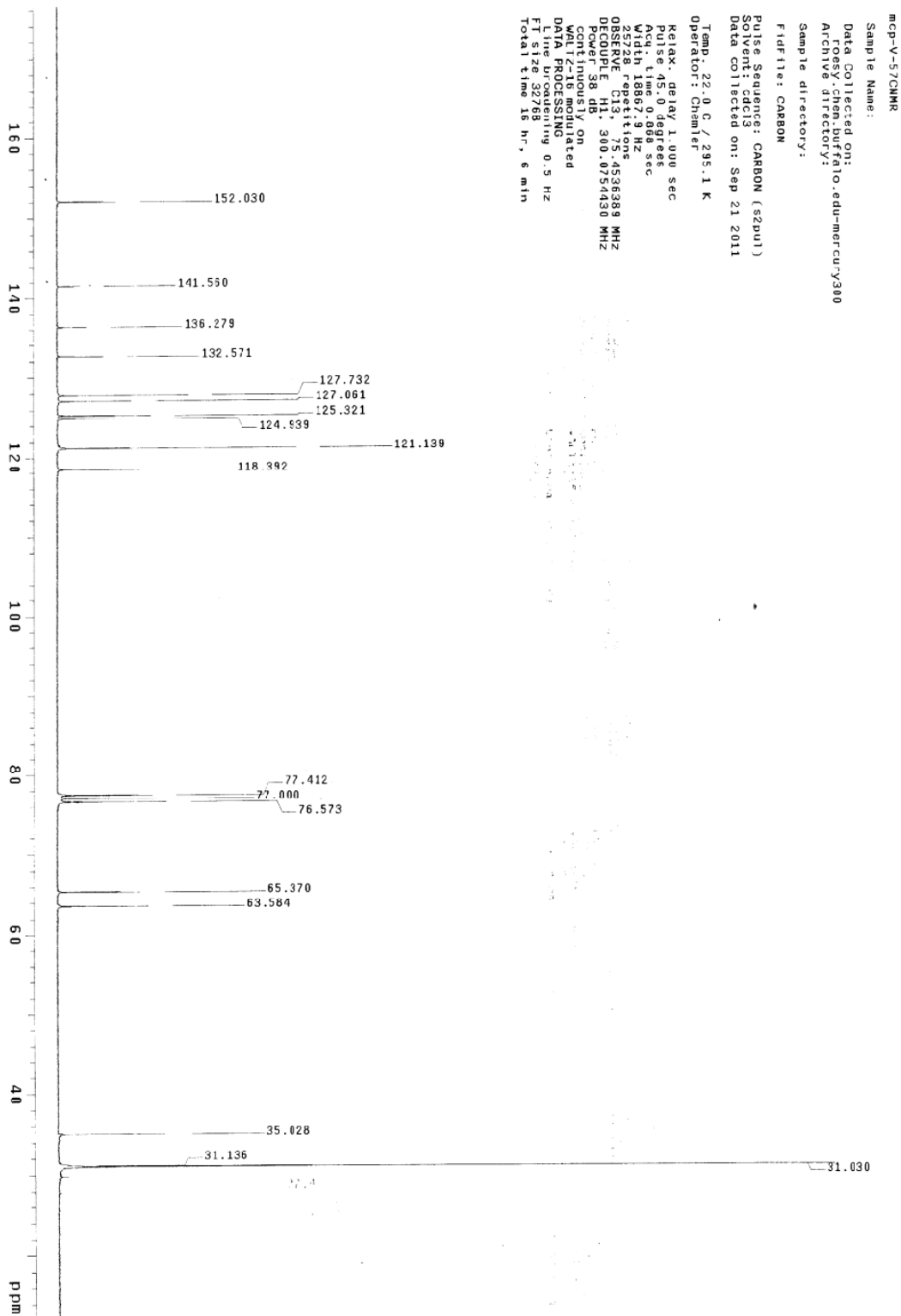
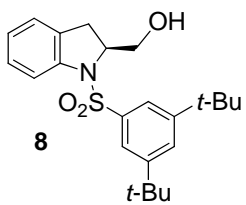
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mcp-V-50

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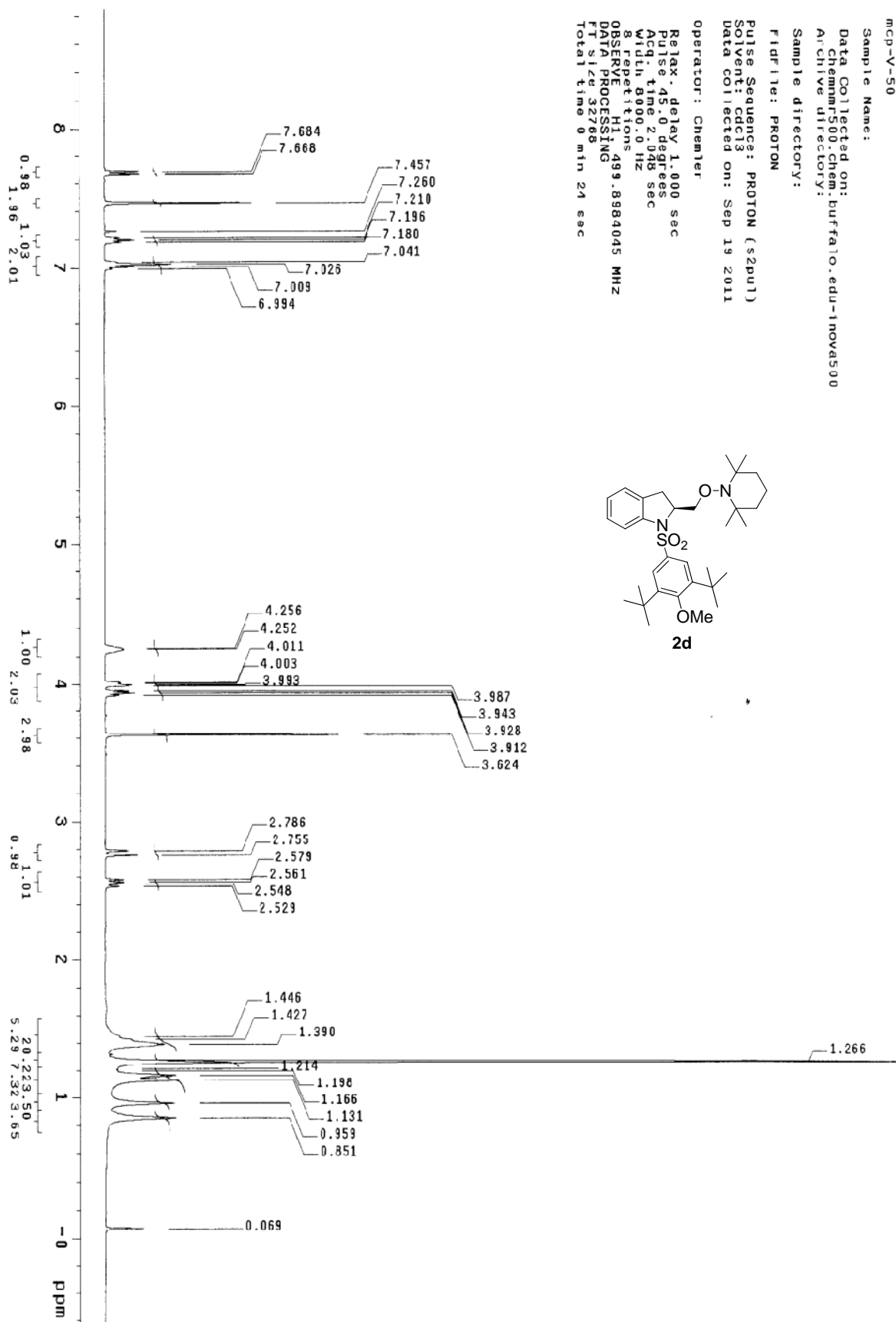
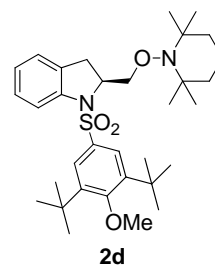
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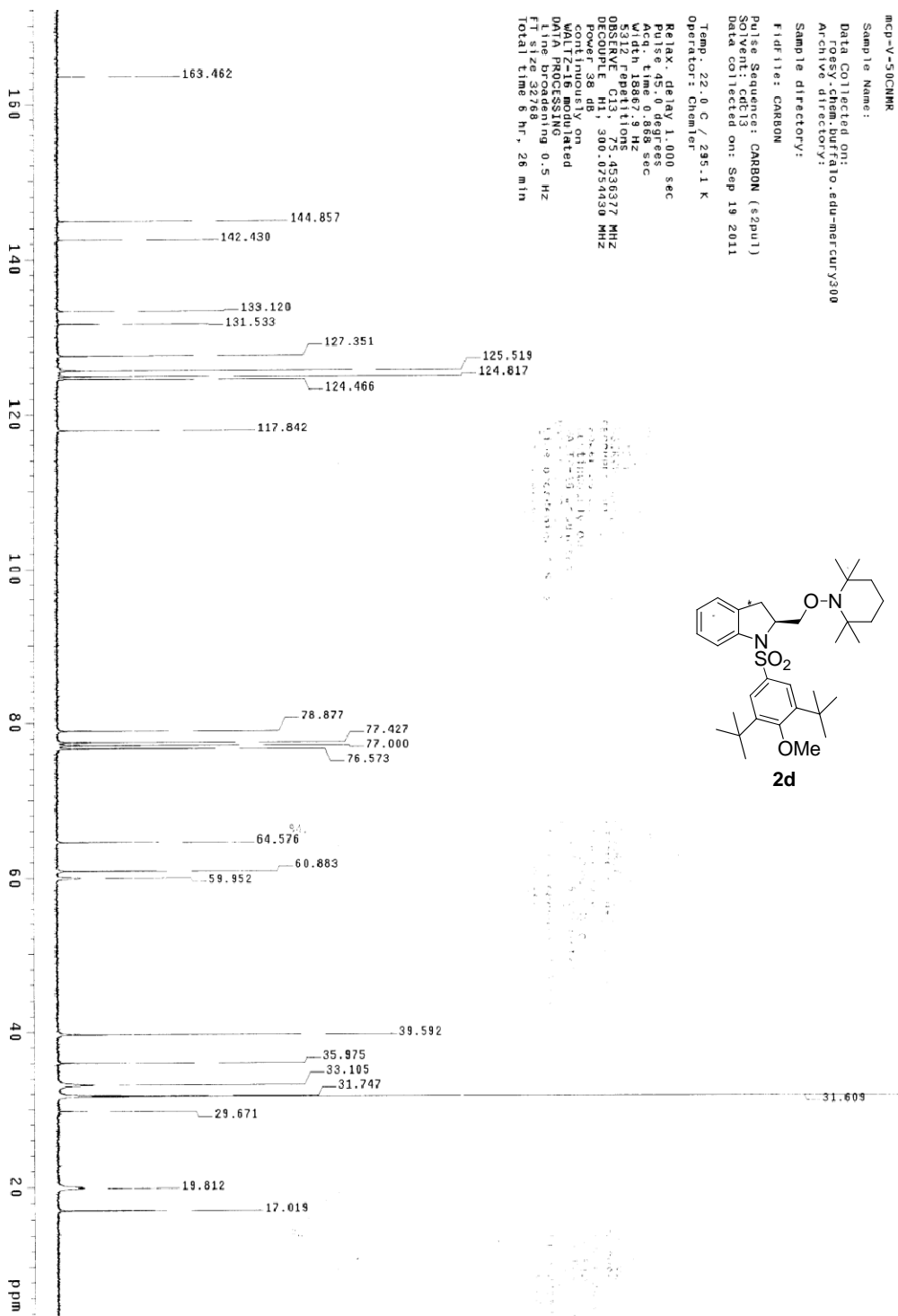
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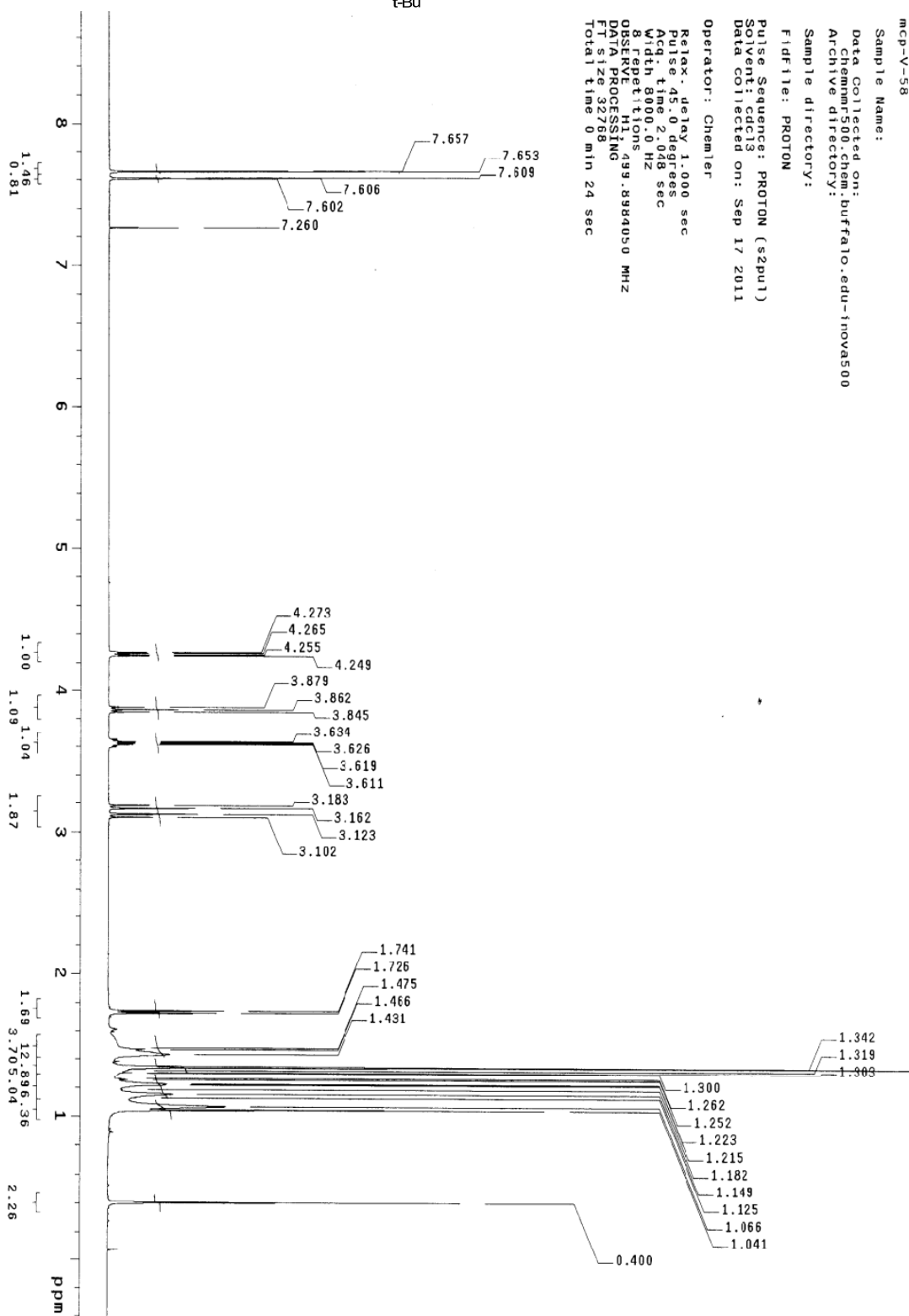
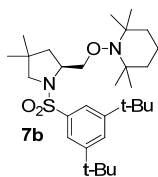
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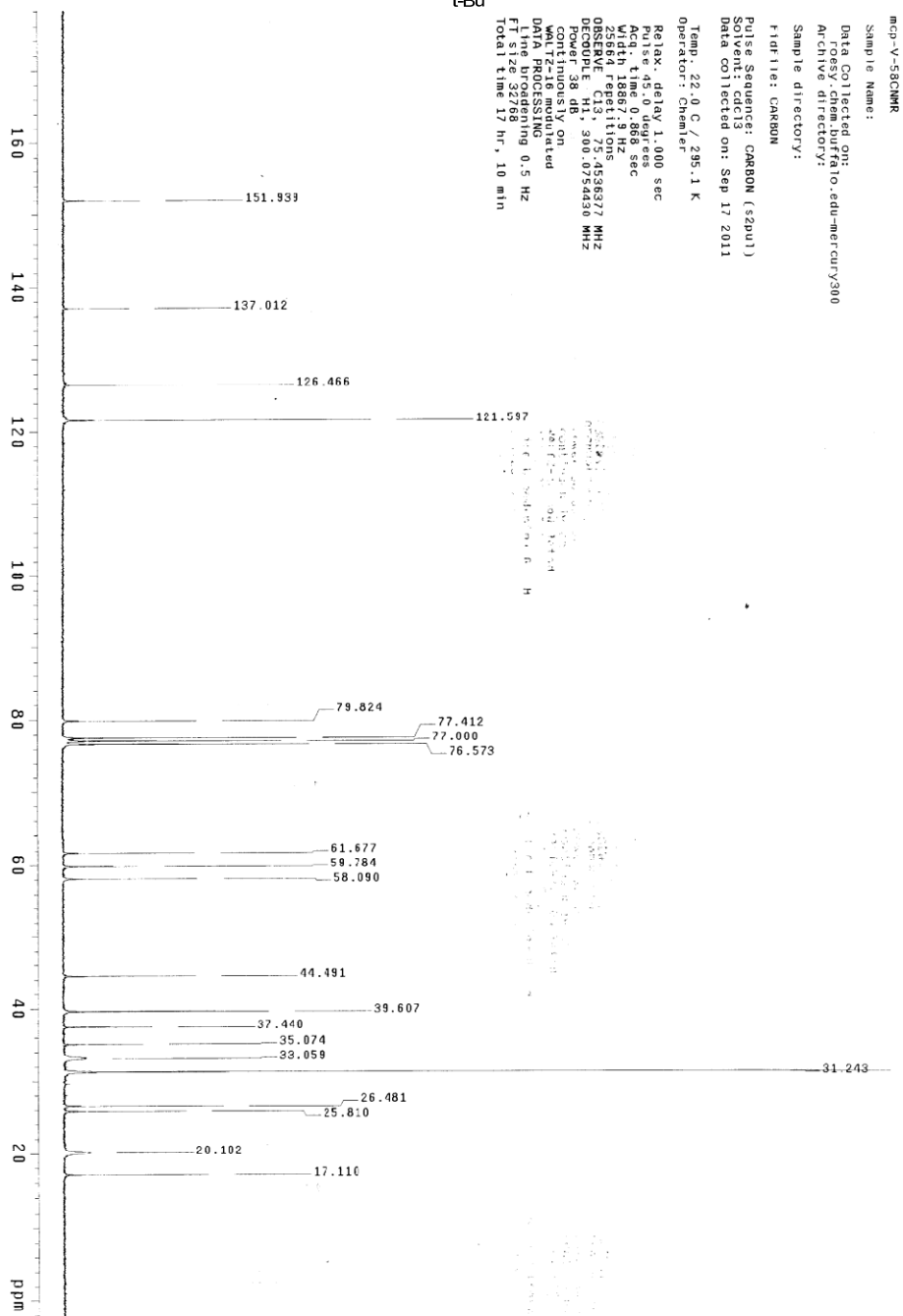
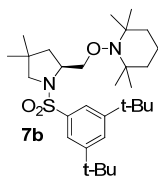
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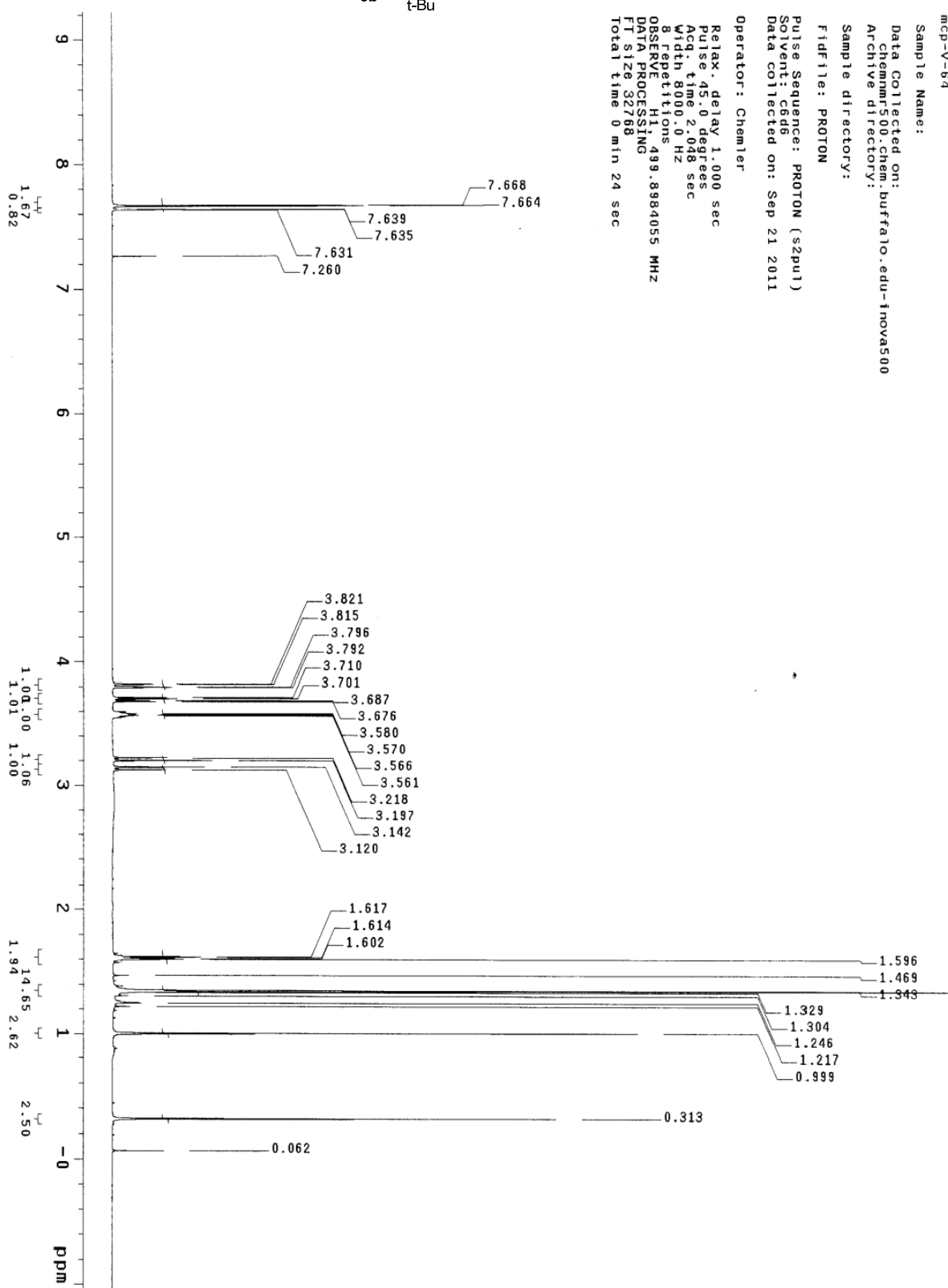
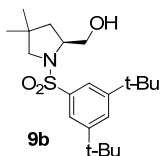
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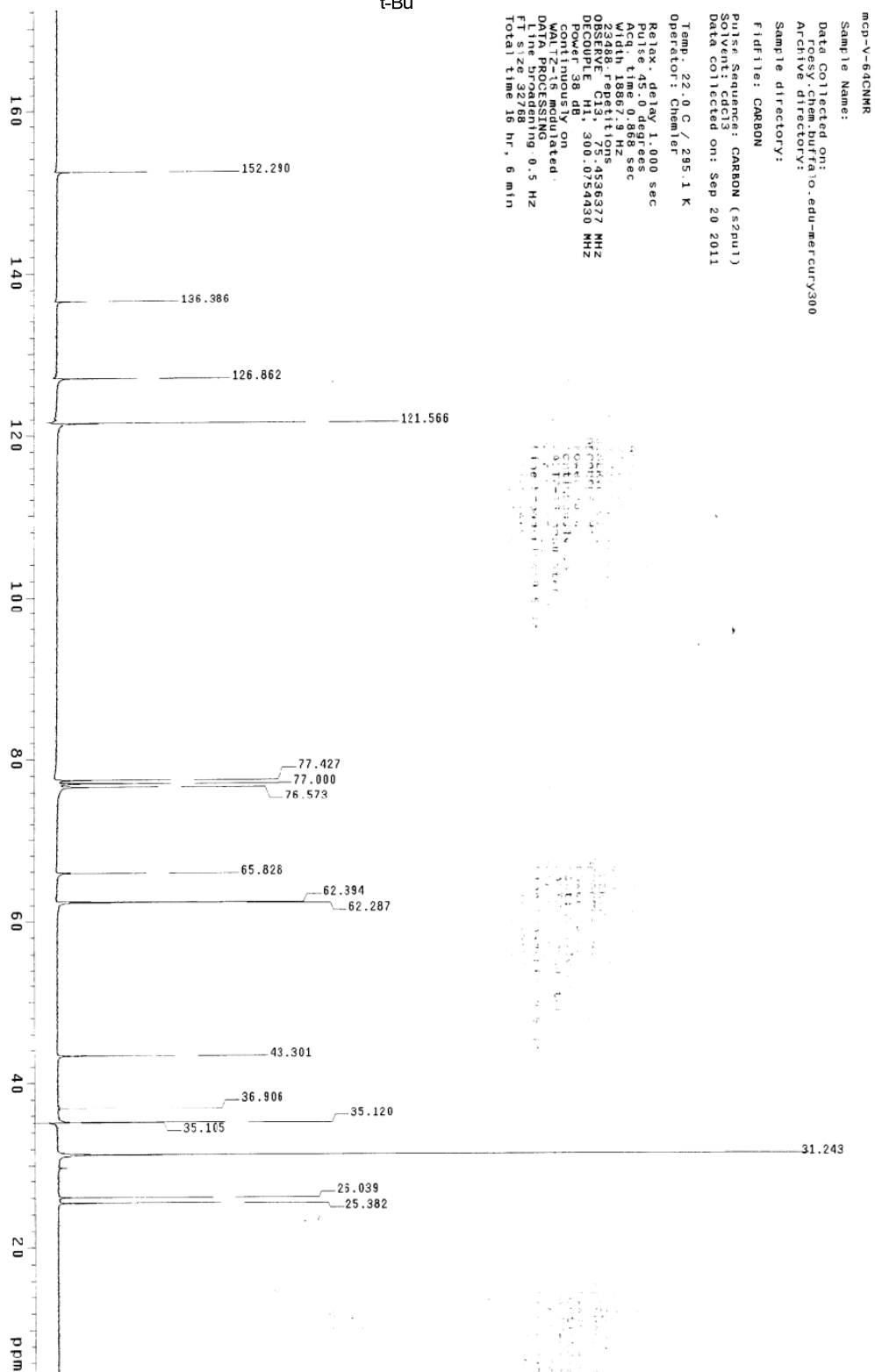
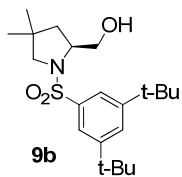
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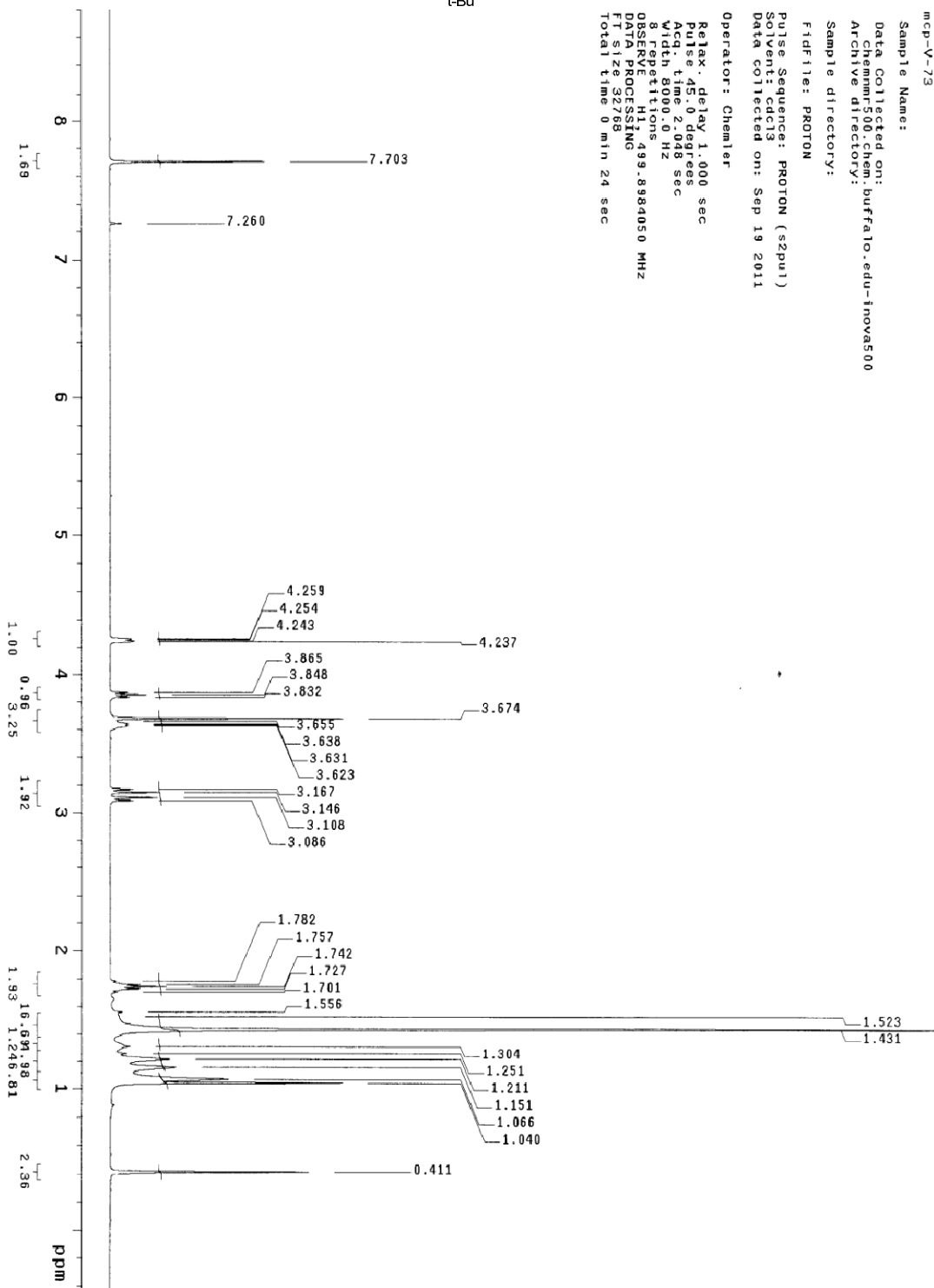
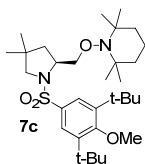
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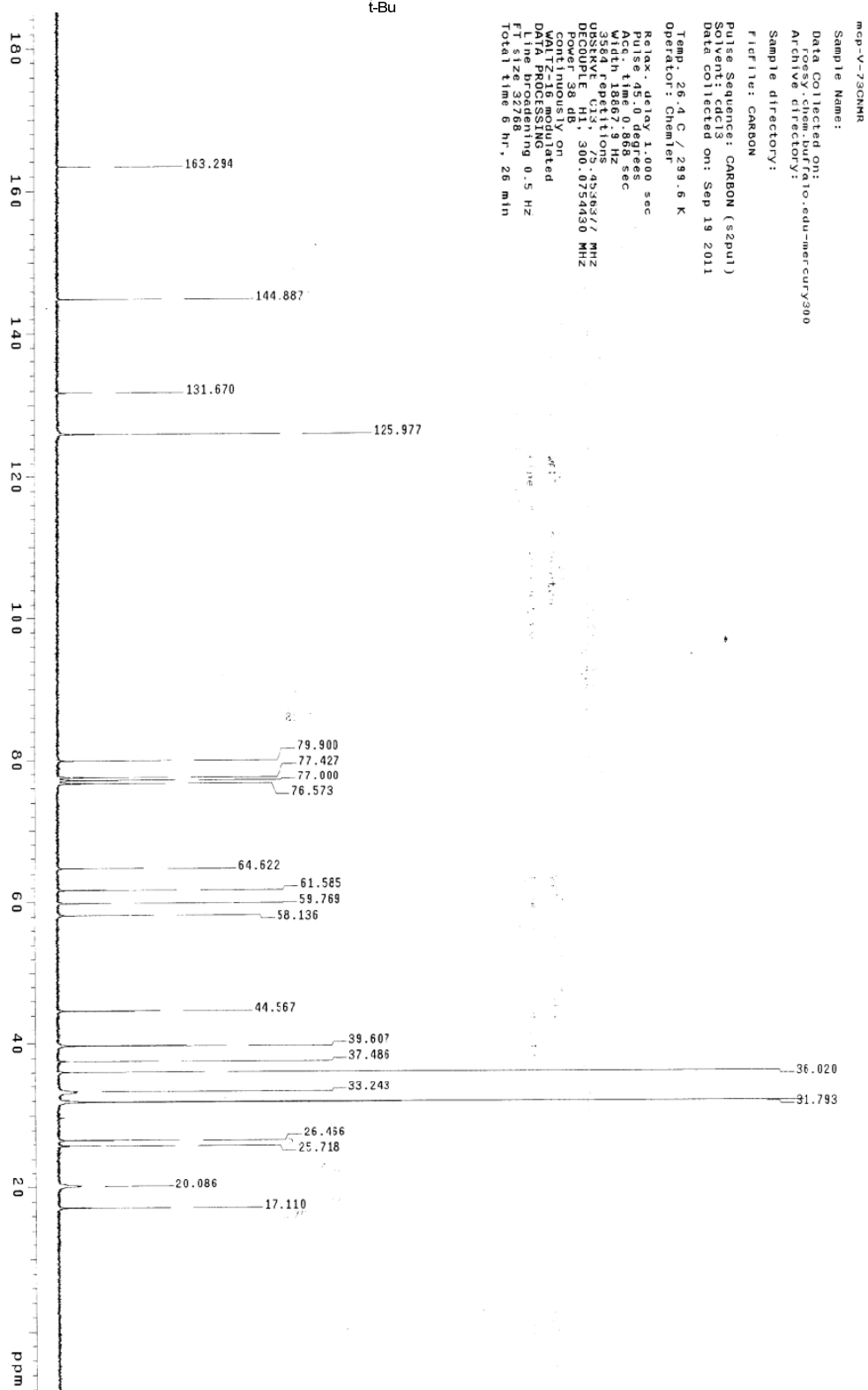
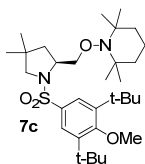
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Operator: Chemler

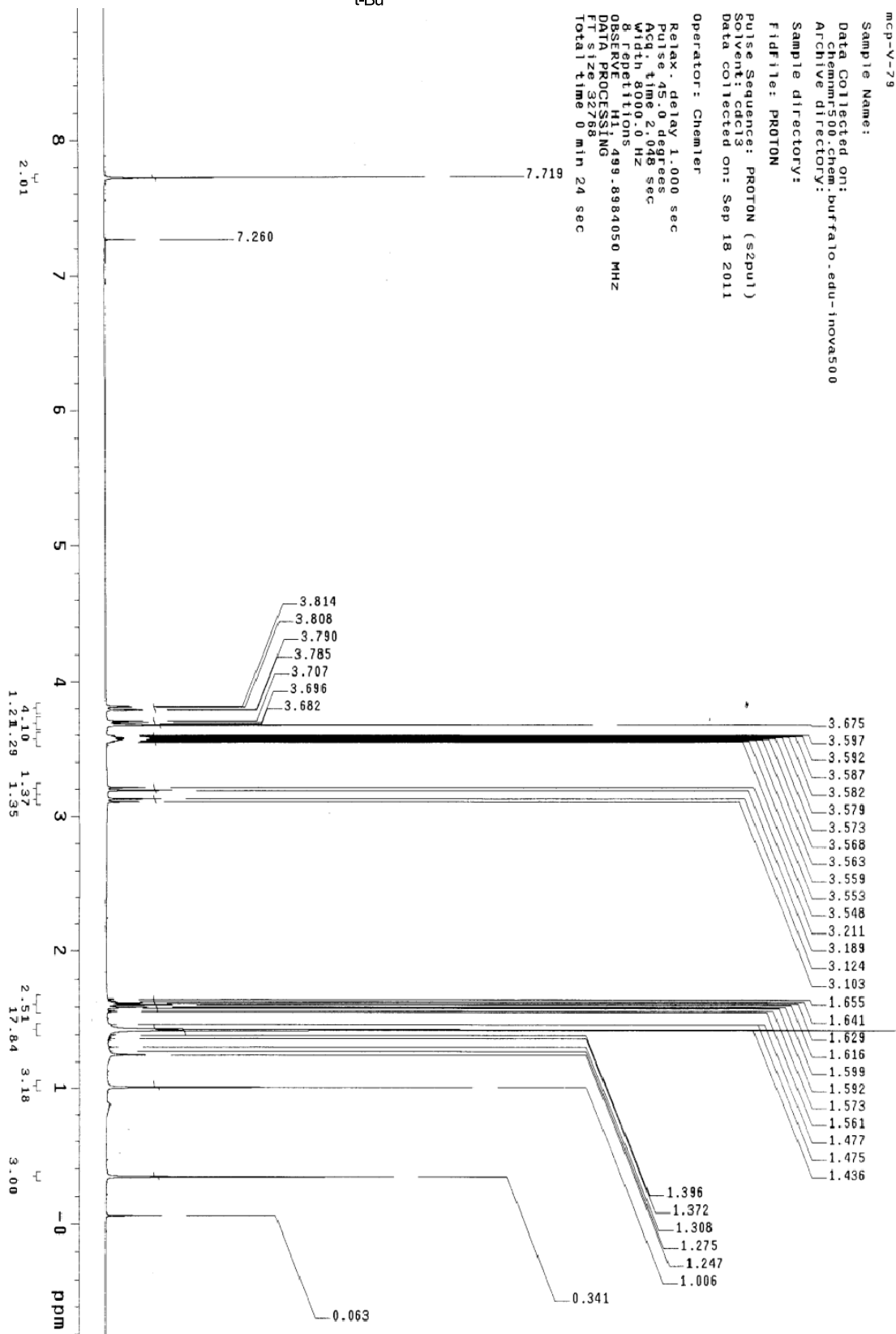
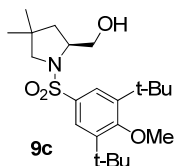
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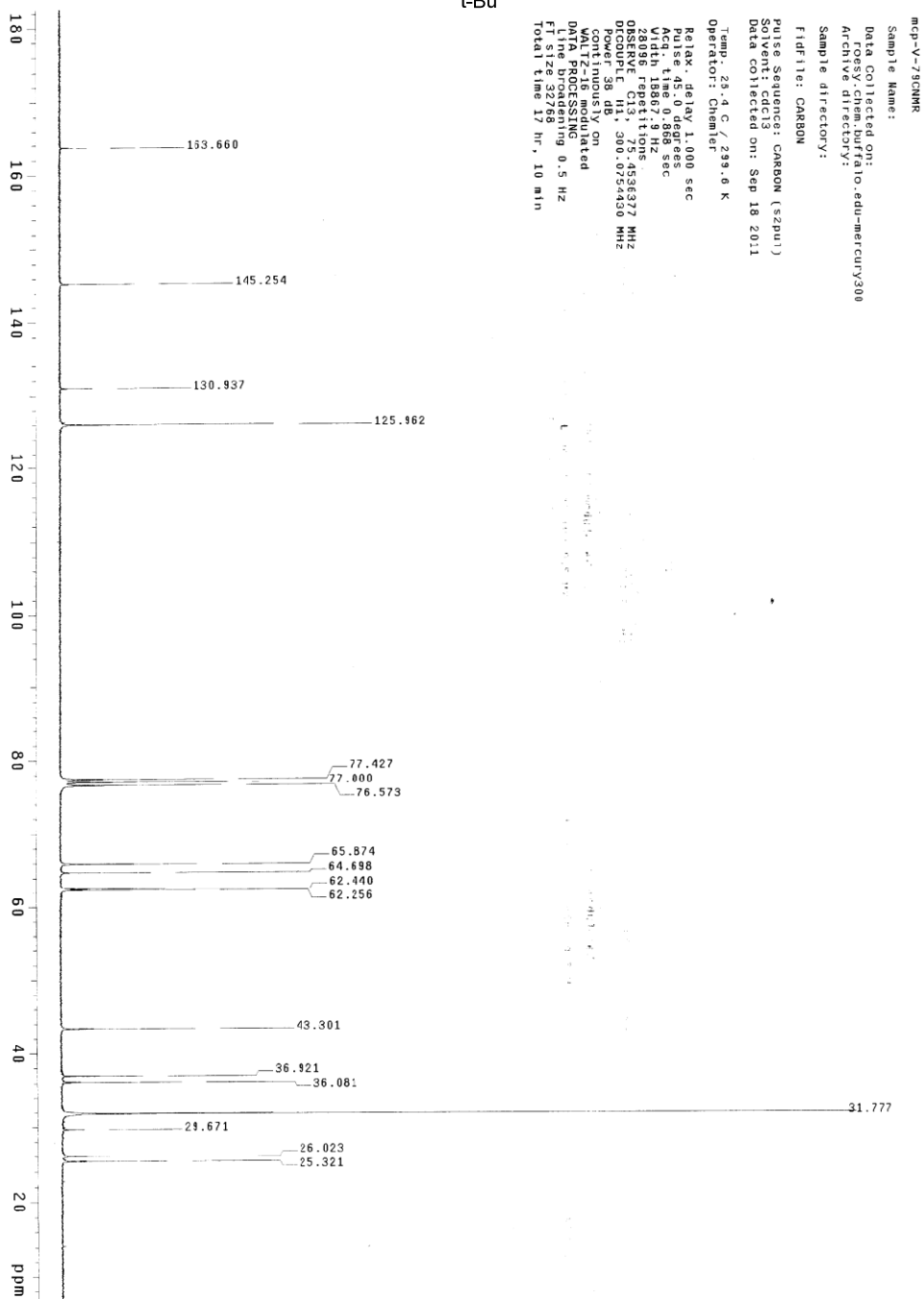
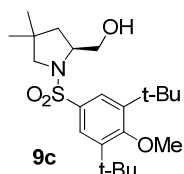












Crude  $^1\text{H}$  NMR of di-Ph-box +  $\text{Cu}(\text{OTf})_2$  + TEMPO run at rt for 15 min

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Sample directory:

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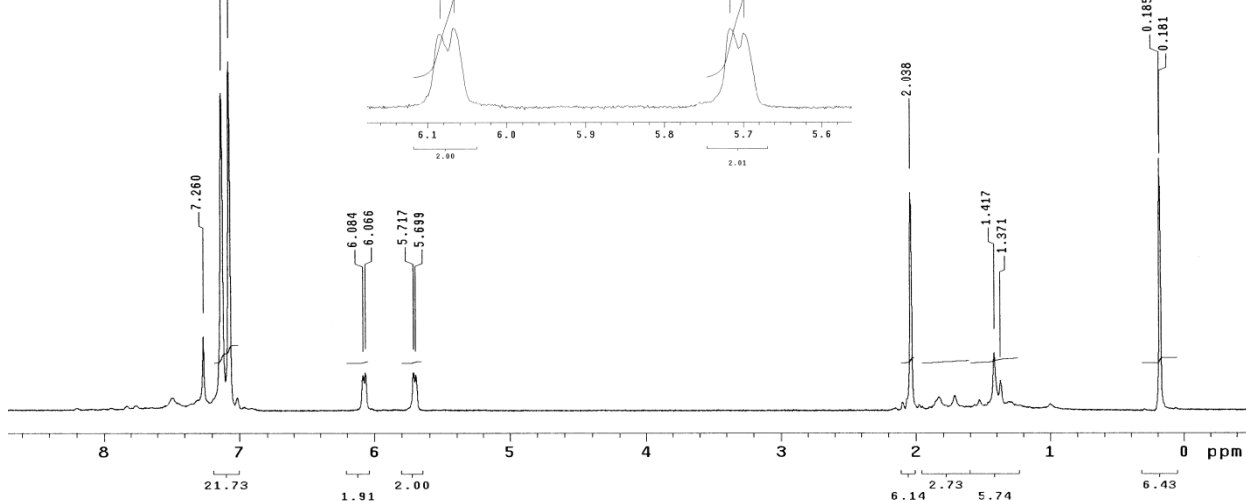
8 repetitions

OBSERVE H1, 499.8984074 MHz

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Total time 0 min 24 sec

Crude  $^1\text{H}$  NMR of di-Ph-box +  $\text{Cu}(\text{OTf})_2$  + TEMPO at 110  $^\circ\text{C}$  for 6 h

mcp-V-180crude-4

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Sample directory:

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Solvent: cdc13

Data collected on: Apr 22 2012

Operator: Chemler

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.048 sec

Width 8000.0 Hz

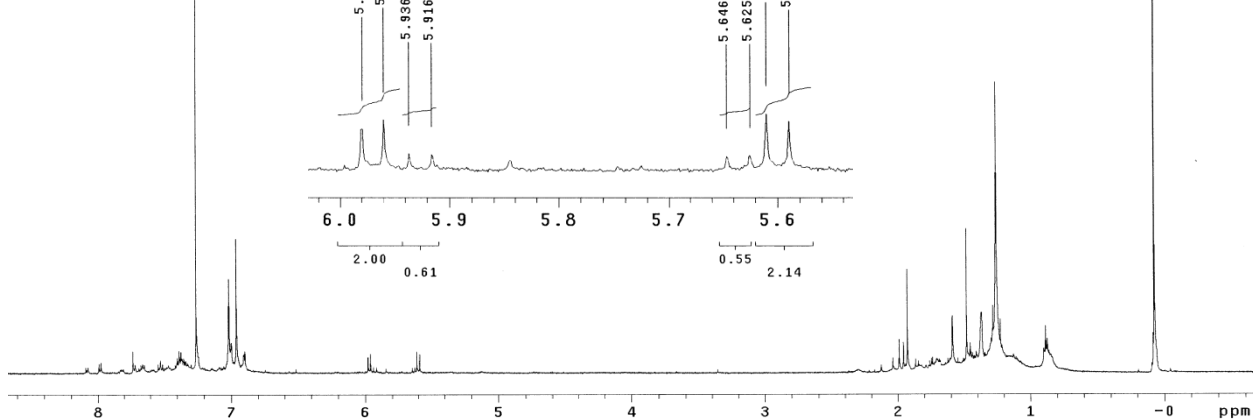
8 repetitions

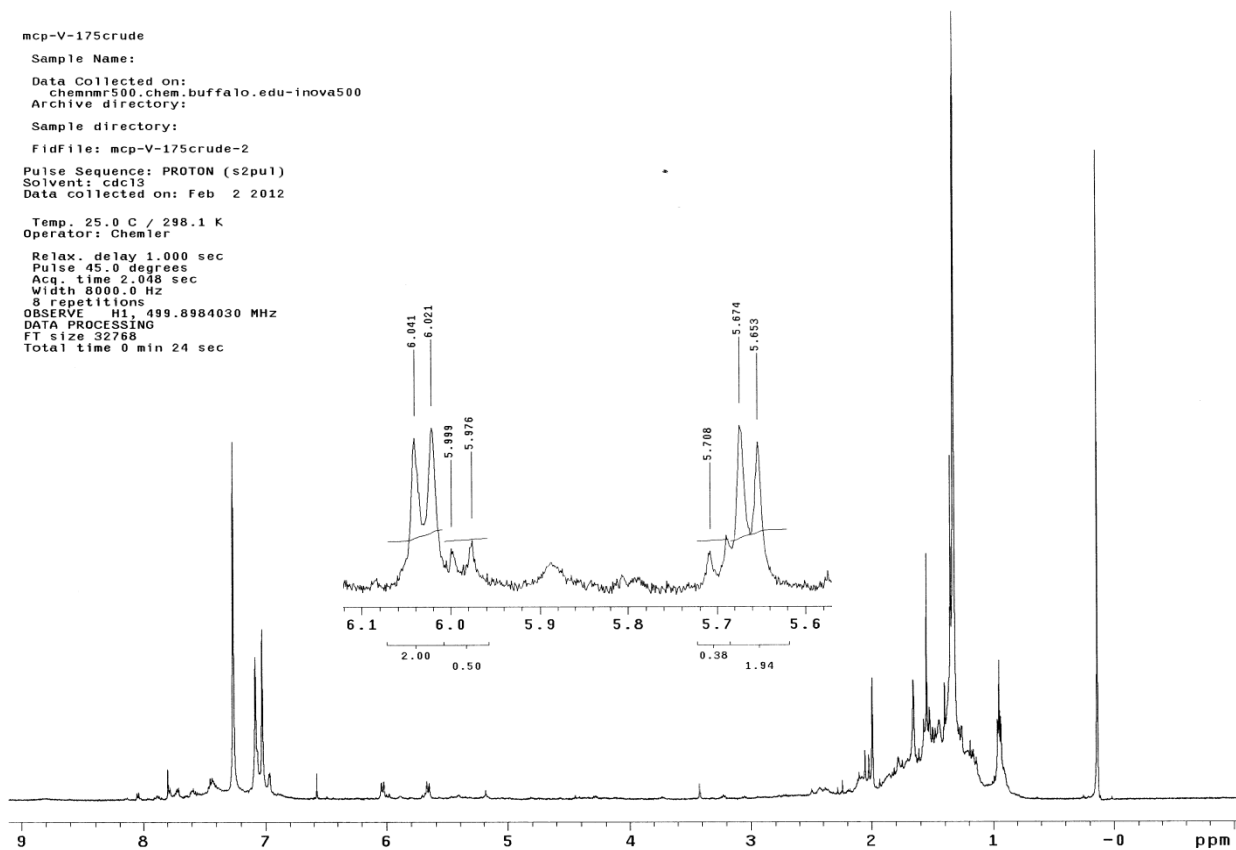
OBSERVE H1, 499.8984050 MHz

DATA PROCESSING

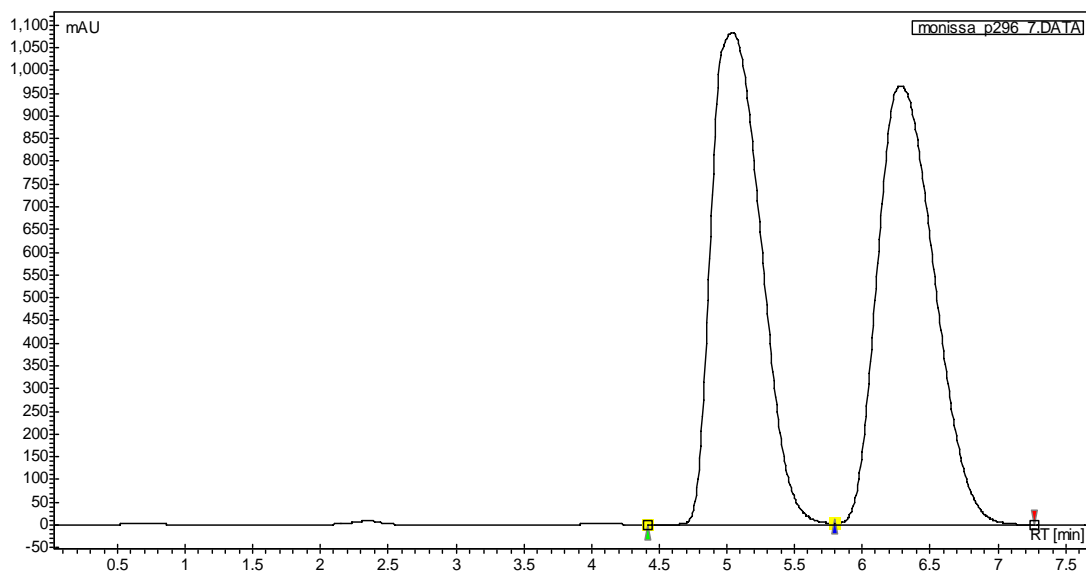
FT size 32768

Total time 0 min 24 sec

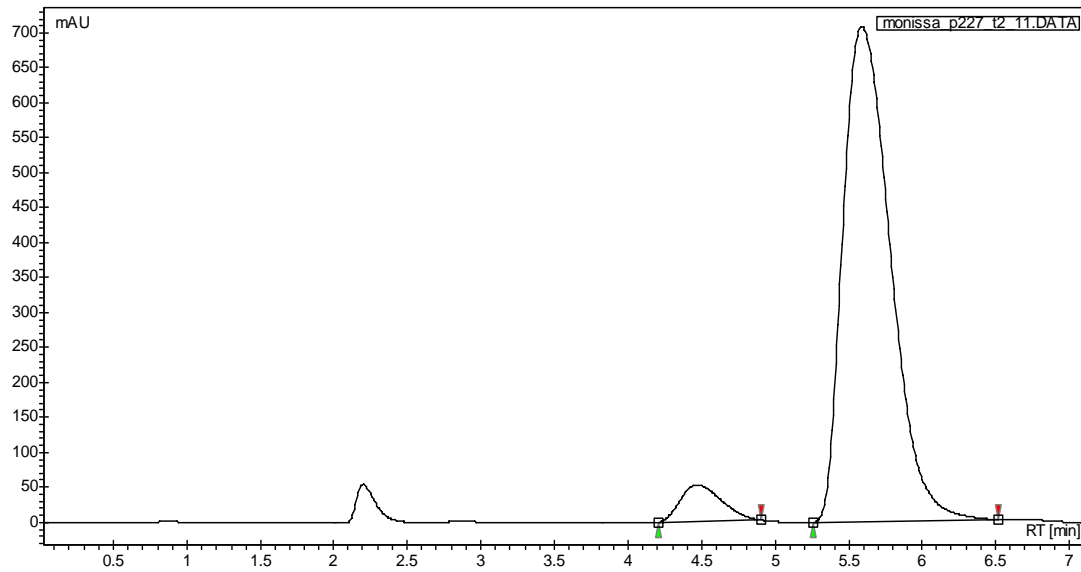
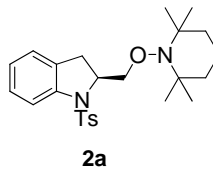


Crude  $^1\text{H}$  NMR of di-Ph-Box +  $\text{Cu}(\text{OTf})_2$  + TEMPO at  $120^\circ\text{C}$  for 6 h

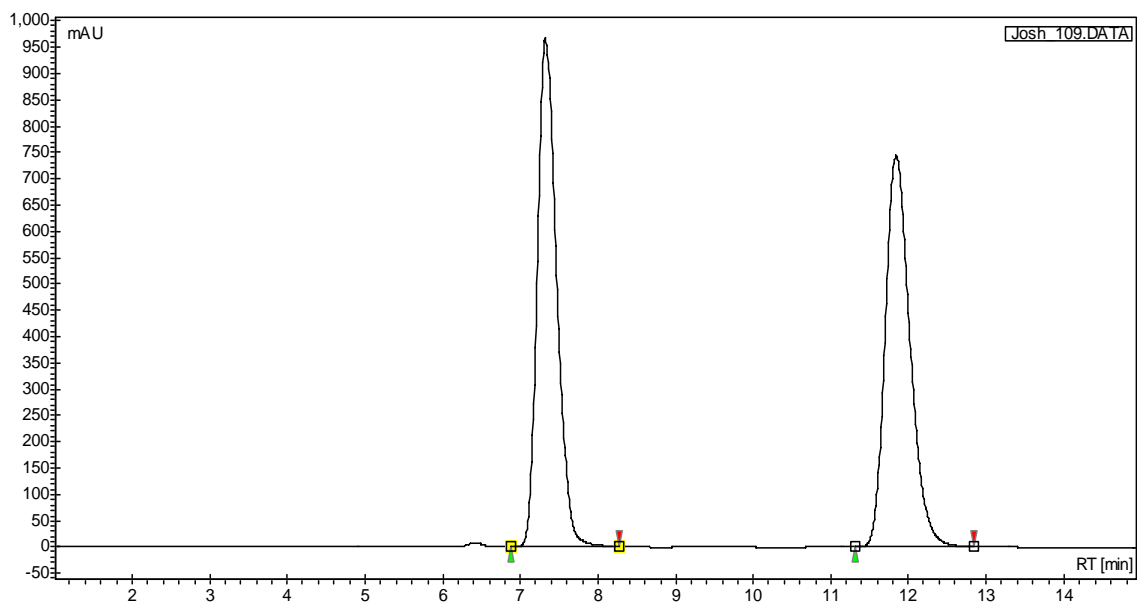
## HPLC Traces



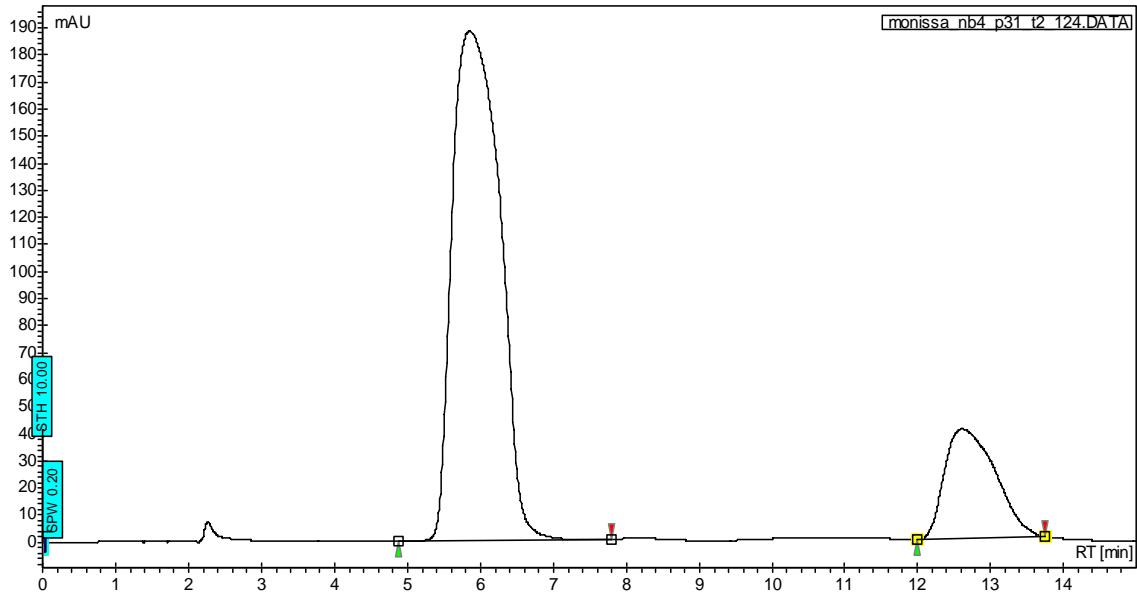
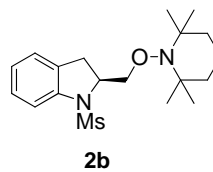
#	Time (min)	Area (%)
1	5.04	49.35
2	6.29	50.66



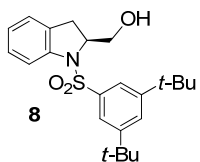
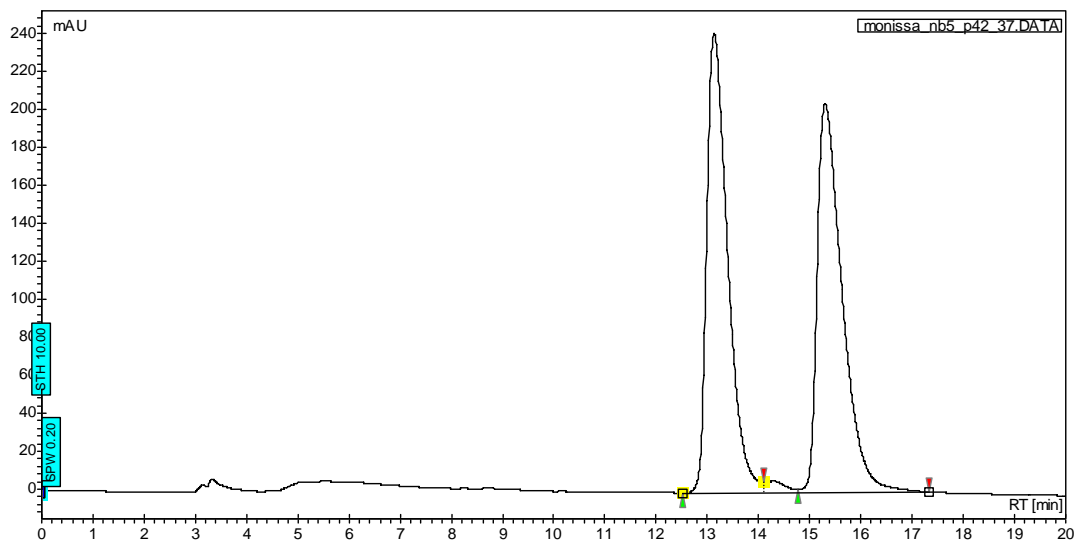
#	Time (min)	Area (%)
1	4.47	6.04
2	5.59	93.96



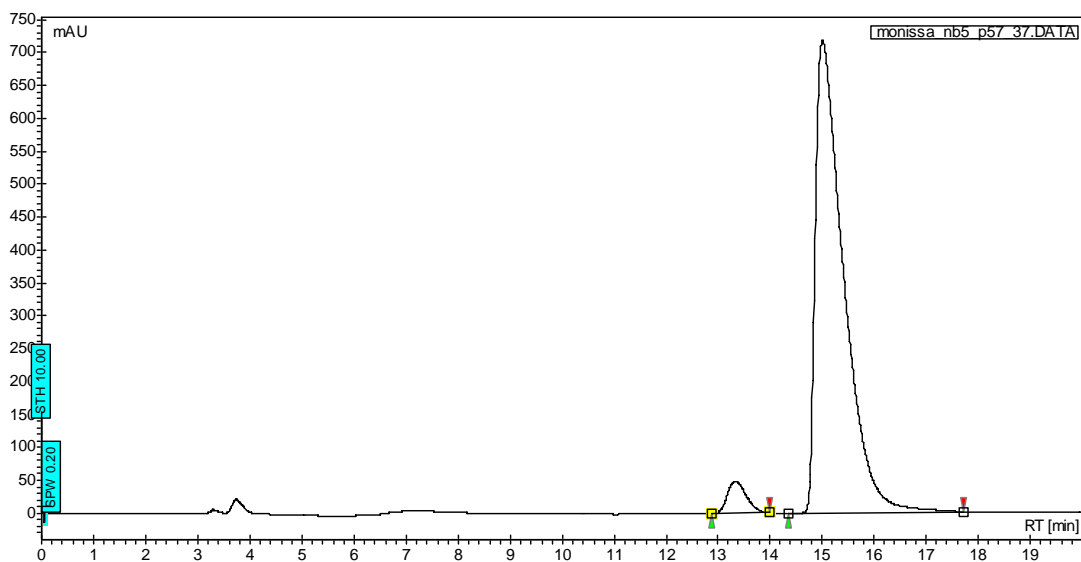
#	Time (min)	Area (%)
1	7.00	50.27
2	11.84	49.73



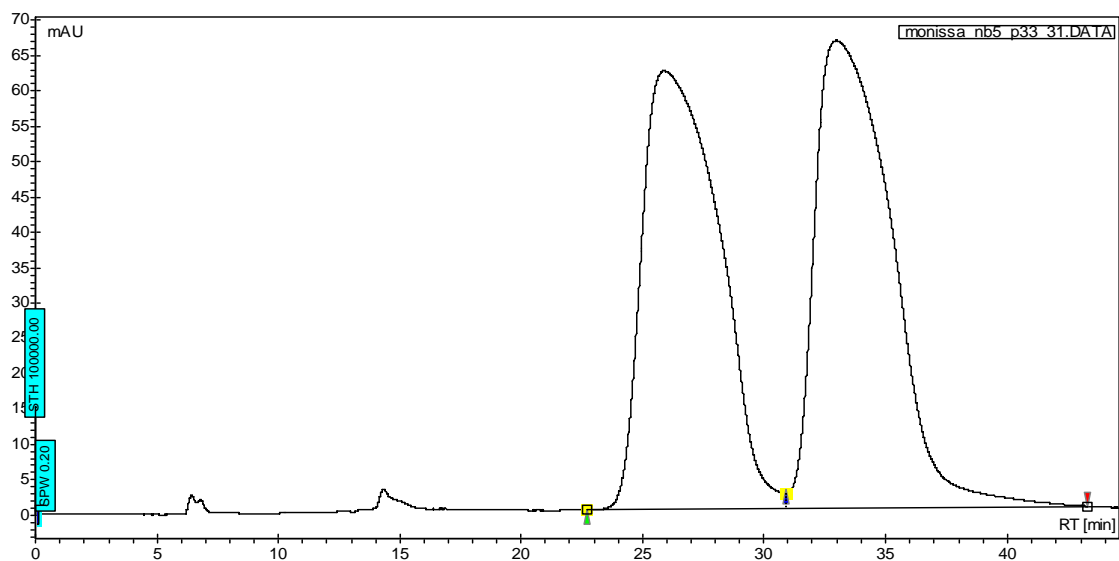
#	Time (min)	Area (%)
1	5.85	81.30
2	12.00	18.69



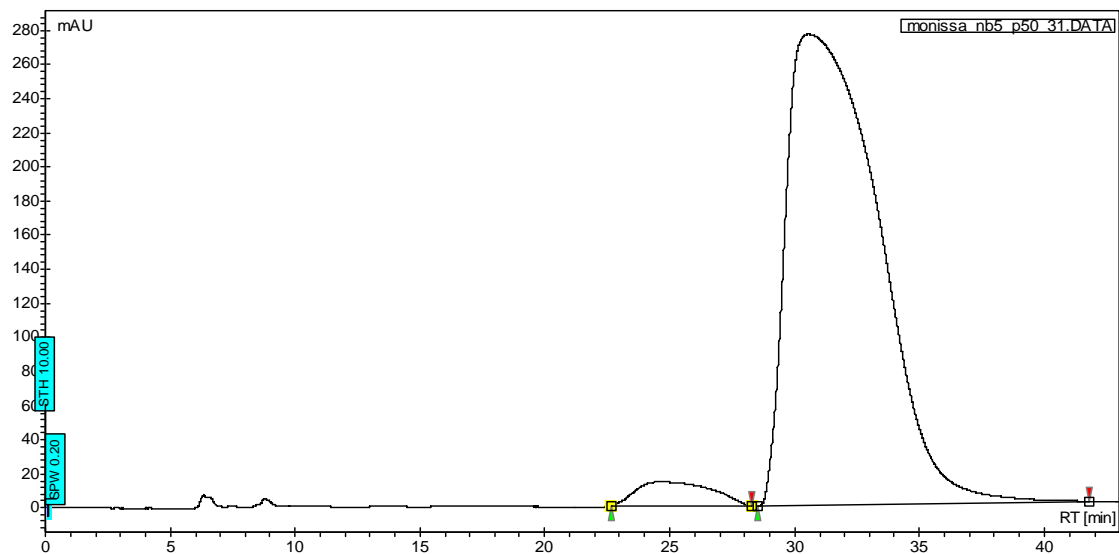
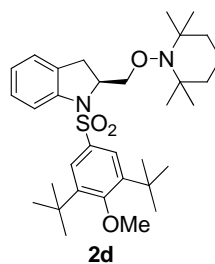
#	Time (min)	Area (%)
1	13.13	49.70
2	15.30	50.30



#	Time (min)	Area (%)
1	13.33	4.39
2	15.00	95.60

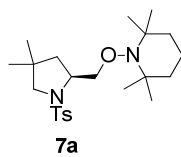
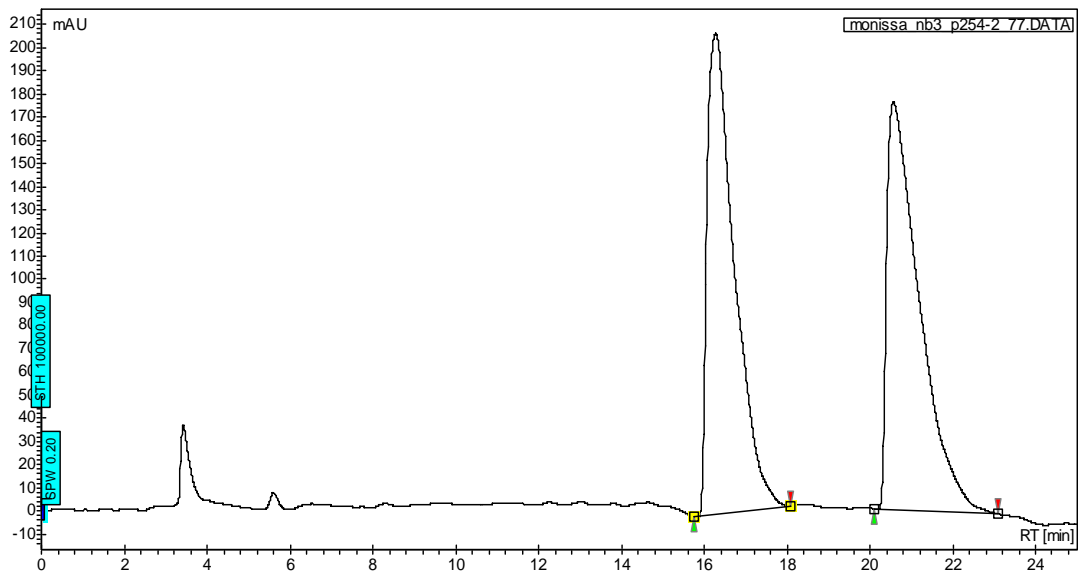


#	Time (min)	Area (%)
1	25.87	48.46
2	32.97	51.54

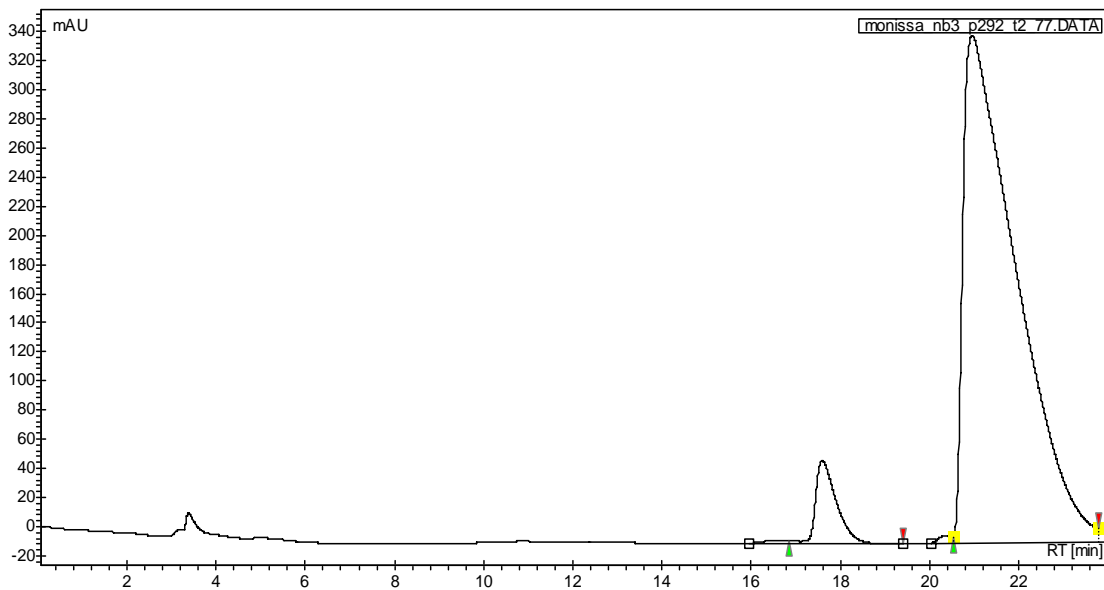


#	Time (min)	Area (%)
1	24.74	3.98
2	30.56	96.02

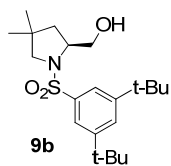
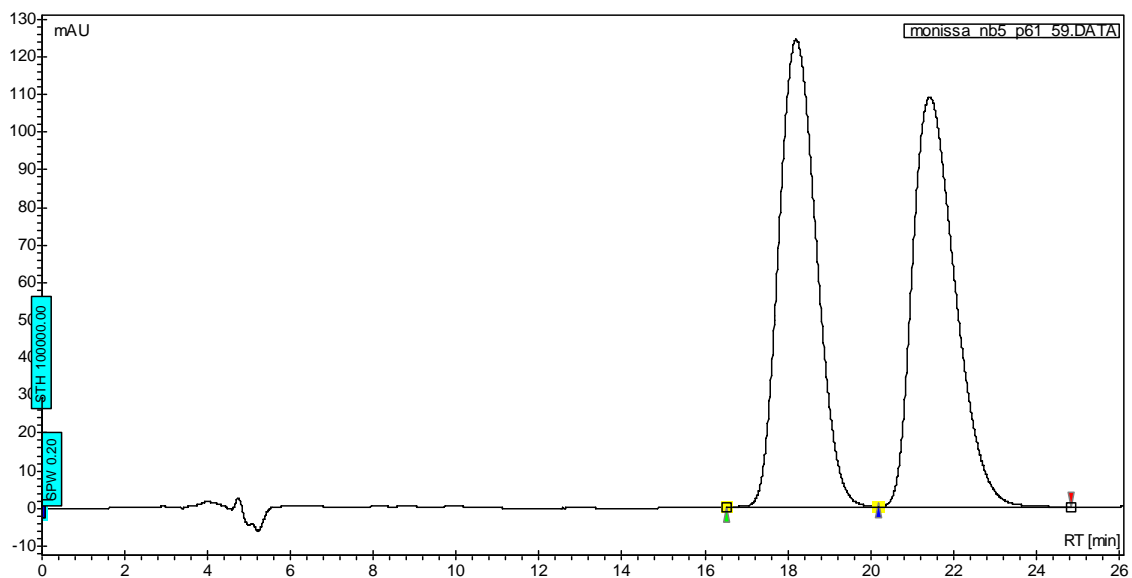




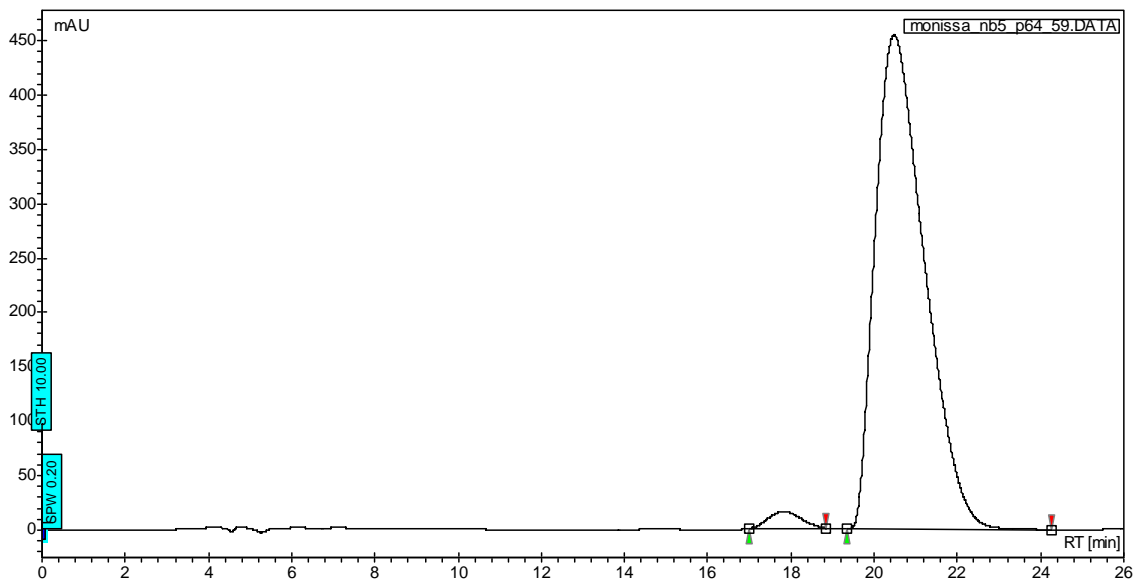
#	Time (min)	Area (%)
1	16.27	49.89
2	20.56	50.11



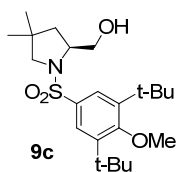
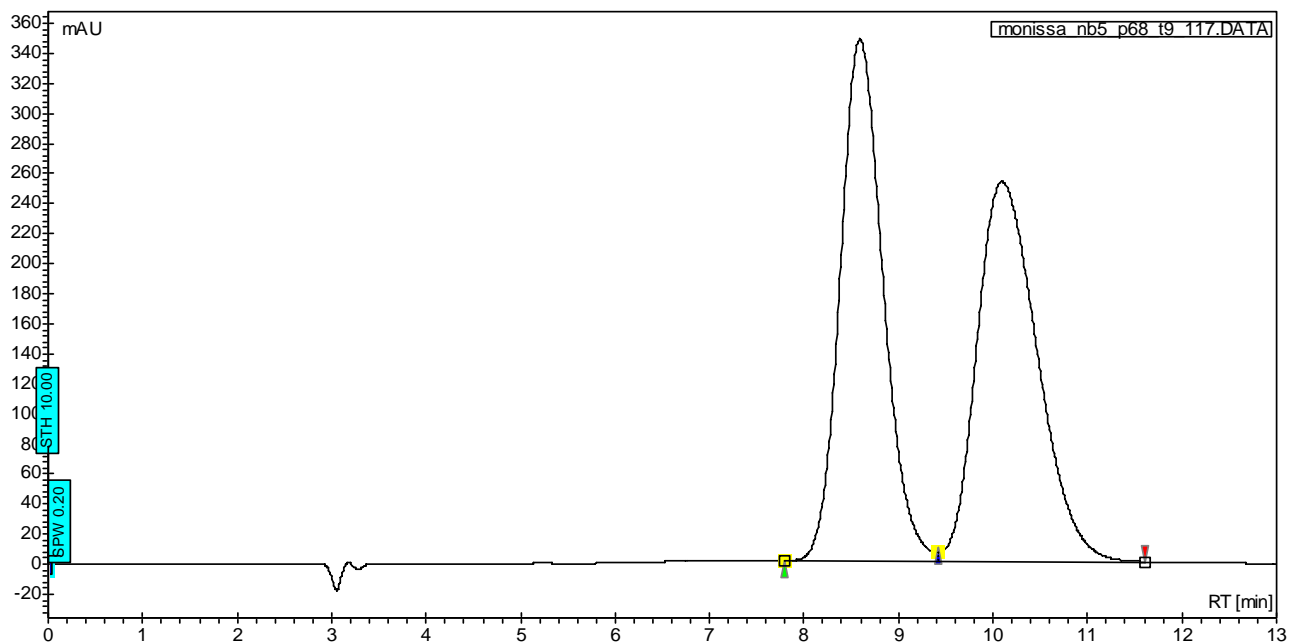
#	Time (min)	Area (%)
1	17.59	6.06
2	20.95	93.94



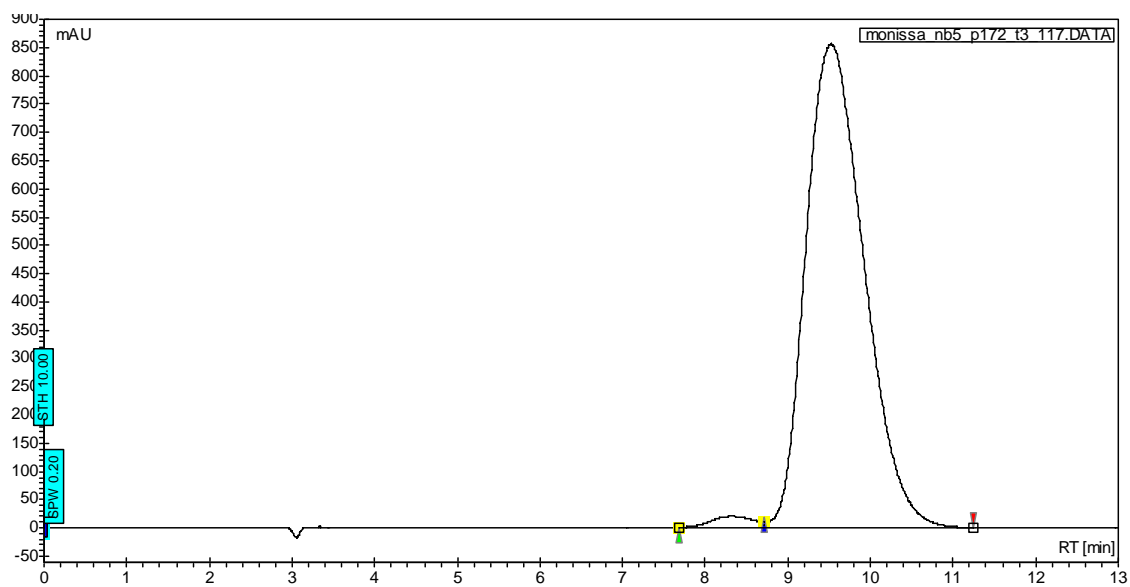
#	Time (min)	Area (%)
1	18.21	49.99
2	21.43	50.01



#	Time (min)	Area (%)
1	17.82	2.21
2	20.48	97.79



#	Time (min)	Area (%)
1	8.36	49.62
2	9.82	50.38



#	Time (min)	Area (%)
1	8.35	1.63
2	9.61	98.37