Supplementary Information

Enantioselective Synthesis of β-Amino Acid Derivatives via Nickel-Promoted Regioselective Carboxylation of Ynamides and Rhodium-Catalyzed Asymmetric Hydrogenation

Nozomi Saito,[a,b]* Iman Abdullah,[a] Kayoko Hayashi,[a] Katsuyuki Hamada,[a]

Momoko Koyama[a] and Yoshihiro Sato[a]*

[a] Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

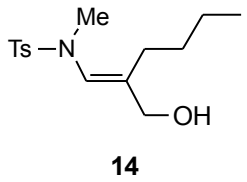
[b] Current Address: Meiji Pharmaceutical University, Kiyose, Tokyo 204-8588, Japan

General Information

All reactions were performed under an atmosphere of argon (1 atm) unless otherwise stated. Solvents were purified under argon using The Ultimate Solvent System (Glass Counter Inc.) (THF, toluene, and DMF), and were distilled from CaH_2 (chlorobenzene and 1,2-dichloroethane). Anhydrous CH_2Cl_2 was purchased from Kanto Chemical Co. Inc., and used as received. All other reagents were purified by standard procedures. Column chromatography was performed on silica gel 60 N (spherical, neutral, Kanto Chemical, Co. Inc., 45-50 μm) with the indicated solvent as an eluent. Analytical thin-layer chromatography was performed on Silica gel 60 PF_{254a}(Merck).

Infrared (IR) spectra were recorded on a JASCO FT/IR 4100 infrared spectrometer.^{1}H NMR spectroscopy was recorded on JEOL ECA500 (500 MHz) NMR spectrometer. Chemical shifts are reported in ppm from the solvent resonance as an internal standard ($CDCl_3$: δ = 7.26 ppm). NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. ^{13}C NMR spectroscopy was recorded on JEOL ECA500 (125 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the internal reference ($CDCl_3$: δ = 77.00 ppm). Mass spectra were obtained on JEOL JMS-T100GCv mass spectrometer. GPC was performed on HPLC LC-9201 (Japan Analytical Industry Co., Ltd). Optical rotations were measured on a Jasco P-1030 digital polarimeter at the sodium D line (589 nm). Chiral HPLC analyses were carried out using a Jasco PU-980 and using indicated chiral column. Autoclave (Portable reactor, TVS-1, 10 cm^3) was purchased from TAIATSU TECHNO.

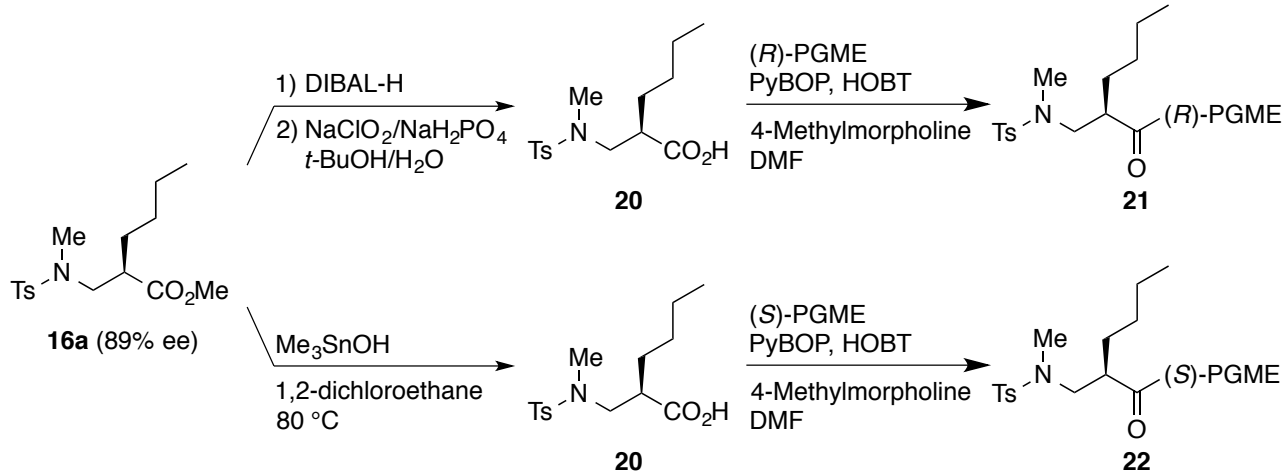
(*E*)-*N*-[3-(Hydroxymethyl)hept-2-en-2-yl]-*N*-methyl-*p*-toluenesulfonamide (14). To a solution of **13a** (56.9 mg, 0.175 mmol) in toluene (0.4 mL) was added a solution of DIBAL-H in toluene (1.01 M, 0.5 mL, 0.505 mmol) at -78 °C, and the mixture was stirred at the same temperature for 3 hours. To the mixture was added a saturated aqueous solution of potassium sodium tartrate, and the mixture was stirred at room temperature for 20 h. After the aqueous layer was extracted with AcOEt, the organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. A crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **14** (41.0 mg, 75%) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.4 Hz, 3H), 1.18-1.34 (m, 4H), 1.92 (br s, 1H), 2.23 (t, *J* = 7.7, 2H), 2.36 (s, 3H), 2.70 (s, 3H), 4.03 (s, 2H), 5.43 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.9, 21.5, 22.9, 27.5, 29.6, 38.1, 63.9, 123.6, 127.7 (2C), 129.6 (2C), 133.4, 143.6, 144.6; IR (film, $CHCl_3$) 3487, 2957, 2928 cm^{-1}; EI-LRMS *m/z* 312 [(M+H)$^+$]; EI-HRMS calcd for $C_{16}H_{26}NO_3S$ 312.1633, found 312.1637.



14

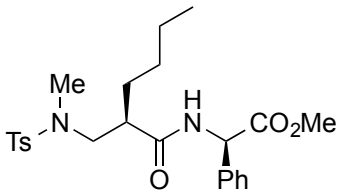
Determination of Absolute Configuration of 16a (Scheme S1)

Absolute configuration of the C2 position of **16a** was determined by a similar manner to that of **16c** (Scheme S1).



Scheme S1.

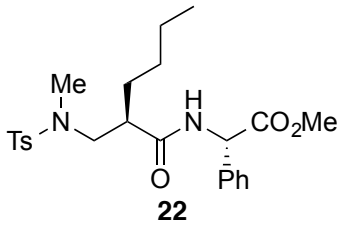
(*R*)-PGME amide (21). To a solution of **13a** (33.0 mg, 0.10mmol) in CH_2Cl_2 (0.5 mL) was added a solution of DIBAL-H in hexane (1.02 M, 0.11mmol, 0.11 mL) at -78 °C, and the mixture was stirred at the same temperature for 1 hour. To the mixture was added saturated



21

aqueous solution of NH_4Cl, and the aqueous layer was extracted with AcOEt. The organic layer was dried over Na_2SO_4, and concentrated. The crude product was dissolved in *tert*-butyl alcohol (1.9 mL), and 2-methylbut-2-ene (0.5 mL) was added to the solution. To the mixture was added a mixed solution of $NaClO_2$ (77.9 mg, 0.86 mmol) and NaH_2PO_4 (77.5 mg, 0.65 mmol) in H_2O (0.9 mL), and the mixture was stirred at room temperature for 9 hours. After acidification with aqueous solution of HCl (10%), the aqueous layer was extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was dissolved in DMF (0.5 mL), (*R*)-phenylglycine methyl ester (21.5 mg, 0.11 mmol), PyBOP (55.4 mg, 0.11 mmol) and HOBT (14.4 mg, 0.11mmol) were added to the DMF solution. To the mixture was added 4-methylmorpholine (34 μL, 0.31mmol) at 0 °C, and the mixture was stirred at room temperature for 16 hours. After the mixture was diluted with AcOEt, the resulting organic layer washed by 10% HCl aqueous solution and saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to afford the (*R*)-PGME amide **21** (13.4 mg, 29% in 3 steps) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 1.12-1.18 (m, 2H), 1.20-1.24 (m, 2H), 1.43 (m, 1H), 1.53 (m, 1H), 2.43 (s, 3H), 2.77 (s, 3H), 2.59-2.65 (m, 1H), 2.99 (dd, *J* = 14.1, 9.2 Hz, 1H), 3.15 (dd, *J* = 14.1, 5.7 Hz, 1H), 3.74 (s, 3H), 5.55 (d, *J* = 6.9 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.41-7.34 (m, 5H), 7.68 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8 21.5, 22.6, 29.2, 30.2, 37.4, 47.5, 52.8, 52.9, 56.7, 127.3, 127.5, 128.6, 129.0, 129.7, 134.0, 136.3, 143.5, 171.0, 173.3; IR (film, $CHCl_3$) 1742 cm^{-1}; EI-LRMS *m/z* 401 [$(M-CO_2CH_3)^+$], 198, 155, 140, 91, 77; EI-HRMS calcd for $C_{22}H_{29}N_2O_3S$ 401.1899, found 401.1892.

(*S*)-PGME amide (22). To a solution of **13a** (33.0 mg, 0.10 mmol) in 1,2-dichloroethane (2.3 mL), was added trimethyltin hydroxide (273.5 mg, 1.50 mmol), and the mixture was stirred at 80 °C for 89 hours. After the mixture was cooled to room temperature, volatiles were evaporated and the residue was taken up in AcOEt. The solution was washed with aqueous solution of $KHSO_4$ (0.01 M) three times, dried over Na_2SO_4, and concentrated to give a crude carboxylic acid **20**. Similar to the synthesis of **21** from **20**, (*S*)-PGME amide **22** (31.3 mg, 67% in 2 steps) was obtained from the crude carboxylic acid **20** (34.6 mg) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.24-1.34 (m, 4H), 1.40 (m, 1H), 1.55 (m, 1H), 2.41 (s, 3H), 2.45 (s, 3H), 2.66 (m, 1H), 2.81 (dd, *J* = 14.3, 9.7 Hz, 1H), 3.19 (dd,



22

J = 14.3, 5.2 Hz, 1H), 3.74 (s, 3H), 5.59 (d, J = 6.9 Hz, 1H), 6.81 (d, J = 6.9 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 6.9 Hz, 1H), 7.37 (dd, J = 7.2, 7.2 Hz, 2H), 7.42 (d, J = 6.9 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 21.4, 22.6, 29.1, 30.0, 37.3, 48.0, 52.8, 53.2, 56.5, 127.3, 127.4, 128.4, 128.9, 129.7, 133.9, 136.3, 143.4, 171.0, 173.4; IR (film, $CHCl_3$) 1746 cm^{-1}; EI-LRMS m/z 401 [(M-CO_2CH_3)$^+$], 198, 155, 140, 91, 77; EI-HRMS calcd for $C_{22}H_{29}N_2O_3S$ 401.1899, found 401.1889.

The values of Δδ = $\delta_{(S)\text{-PGME amide}}$ **22** - $\delta_{(R)\text{-PGME amide}}$ **21** in the 500 MHz ^{1}H NMR spectra were calculated as shown in Figure S1. These data were considered by applying Kusumi's PGME method, and the configuration at the C2 position of **16a** was determined to be 2*R*.

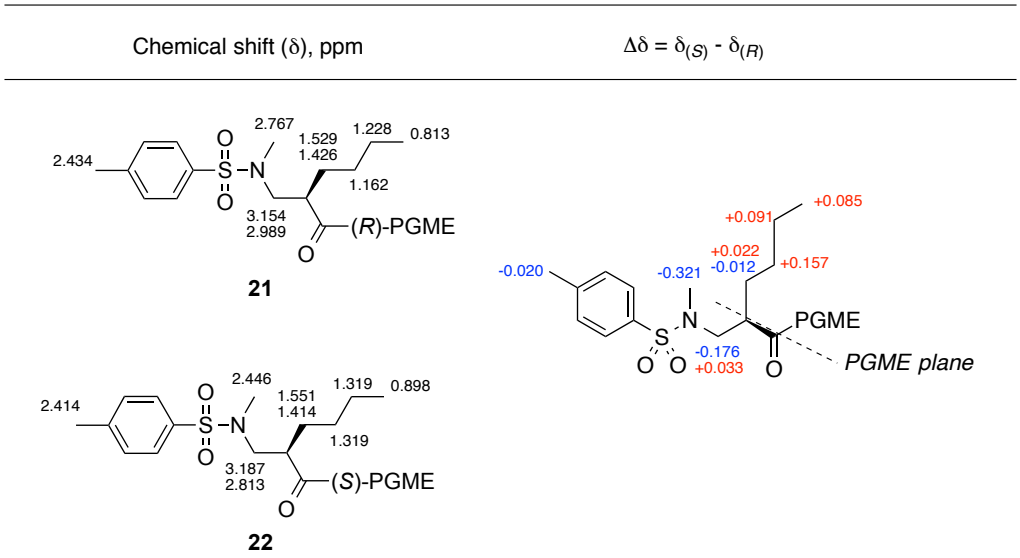
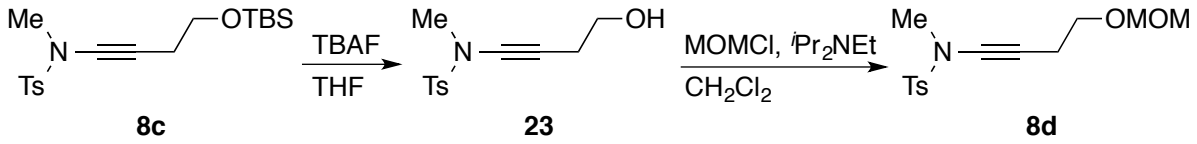


Figure S1.

Preparation of Ynamides

All new ynamides were synthesized via following procedure.

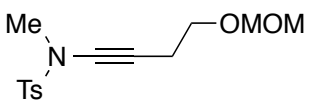
Preparation of Ynamide 8c.



8c **23** **8d**

Scheme S2.

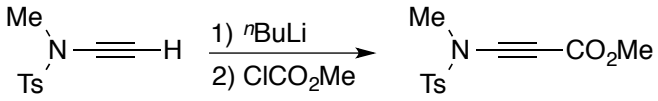
Ynamide 8d. To a solution of **8c** (733.3 mg, 2.00 mmol) in THF (2.0 mL) was added a solution of TBAF in THF (1.0 M, 1.0 mL, 1.000 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 hours. To the mixture was added water at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on short silica gel pad (hexane/AcOEt = 2/1) to give **23**[1] in quantitative yield (510.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (br, 1H), 2.45 (s, 3H), 2.52 (t, *J* = 6.3 Hz, 2H), 3.03 (s, 3H), 3.68 (q, *J* = 6.3, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.6, 22.8, 39.1, 61.2, 65.4, 76.8, 127.7 (2C), 129.8 (2C), 133.0, 144.7. To a solution of **23** (252.6 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) were successively added ^{i}Pr$_2$NEt (0.9 mL, 5.17 mmol) and MOMCl (0.2 mL, 2.63 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 hours. To the mixture was added a saturated aqueous solution of $NaHCO_3$ at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 3/1) to give **8d** (251.8 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.51 (t, *J* = 6.9, 2H), 2.97 (s, 3H), 3.31 (s, 3H), 3.56 (t, *J* = 6.9, 2H), 4.59 (s, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 19.8, 21.5, 39.1, 55.1, 65.3, 66.1, 75.6, 96.3, 127.7 (2C), 129.6 (2C), 133.0, 144.5; IR (neat) 2257, 1363, 1173 cm^{-1}; EI-LRMS *m/z* 266 [(M-OCH_3)$^+$], 155, 91, 82; EI-HRMS calcd for $C_{13}H_{16}NO_3S$ 266.0851, found 266.0845.



8d

[1] Fujino, D.; Yorimitsu, H.; Osuka, A. *J. Am. Chem. Soc.* **2014**, *136*, 6255–6258.

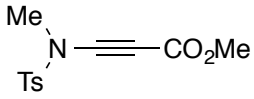
Preparation of Ynamide 8e.



8g **8e**

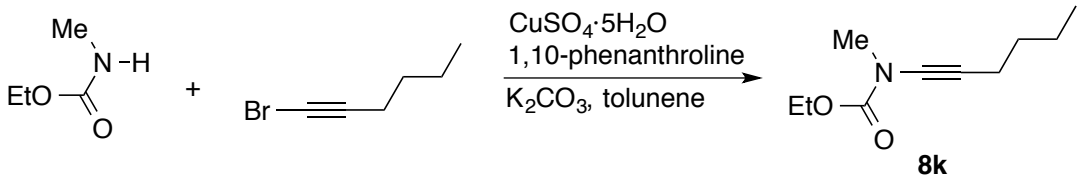
Scheme S3

Ynamide 8e. To a solution of **8g** (422.0 mg, 2.02 mmol) in THF (15.0 mL) was added a solution of ^{n}BuLi in hexane (1.64 M, 1.3 mL, 2.132 mmol) at -78 °C, and the mixture was stirred at the same temperature for 1 hour. To the mixture was added methyl chloroformate (190 μl, 2.459 mmol), and the mixture was stirred at the same temperature for another 1 hour. The temperature was raised to room temperature and the mixture was stirred for 12 hours. To the mixture was added a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **8e** (492.1 mg, 90%) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.16 (s, 3H), 3.76 (s, 3H), 7.39 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.7, 38.6, 52.4, 65.7, 83.9, 127.8 (2C), 130.1 (2C), 133.0, 145.7, 154.5; IR (film, $CHCl_3$) 2223, 1709 cm^{-1}; EI-LRMS m/z 267 $(M)^+$; EI-HRMS calcd for $C_{12}H_{13}NO_4S$ 267.0565, found 267.0562.



8e

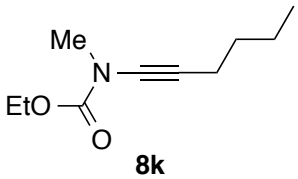
Preparation of Ynamide 8k.



8k

Scheme S4

Ynamide 8k. To a solution of 1-bromohex-1-yne (1.94 g, 12.0 mmol)[2] in toluene (56 mL) were added 1,10-phenanthroline (483.4 mg, 2.44 mmol), $CuSO_4.5H_2O$ (431.3 mg, 1.727 mmol), K_3PO_4 (4.20 g, 19.8 mmol),

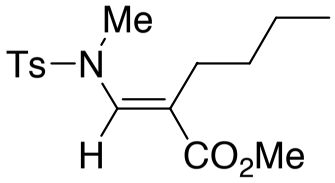


8k

[2] Niggemann, M.; Jelonek, A.; Biber, N.; Wuchrer, M.; Plietker, B. *J. Org. Chem.* **2008**, *73*, 7028-7036.

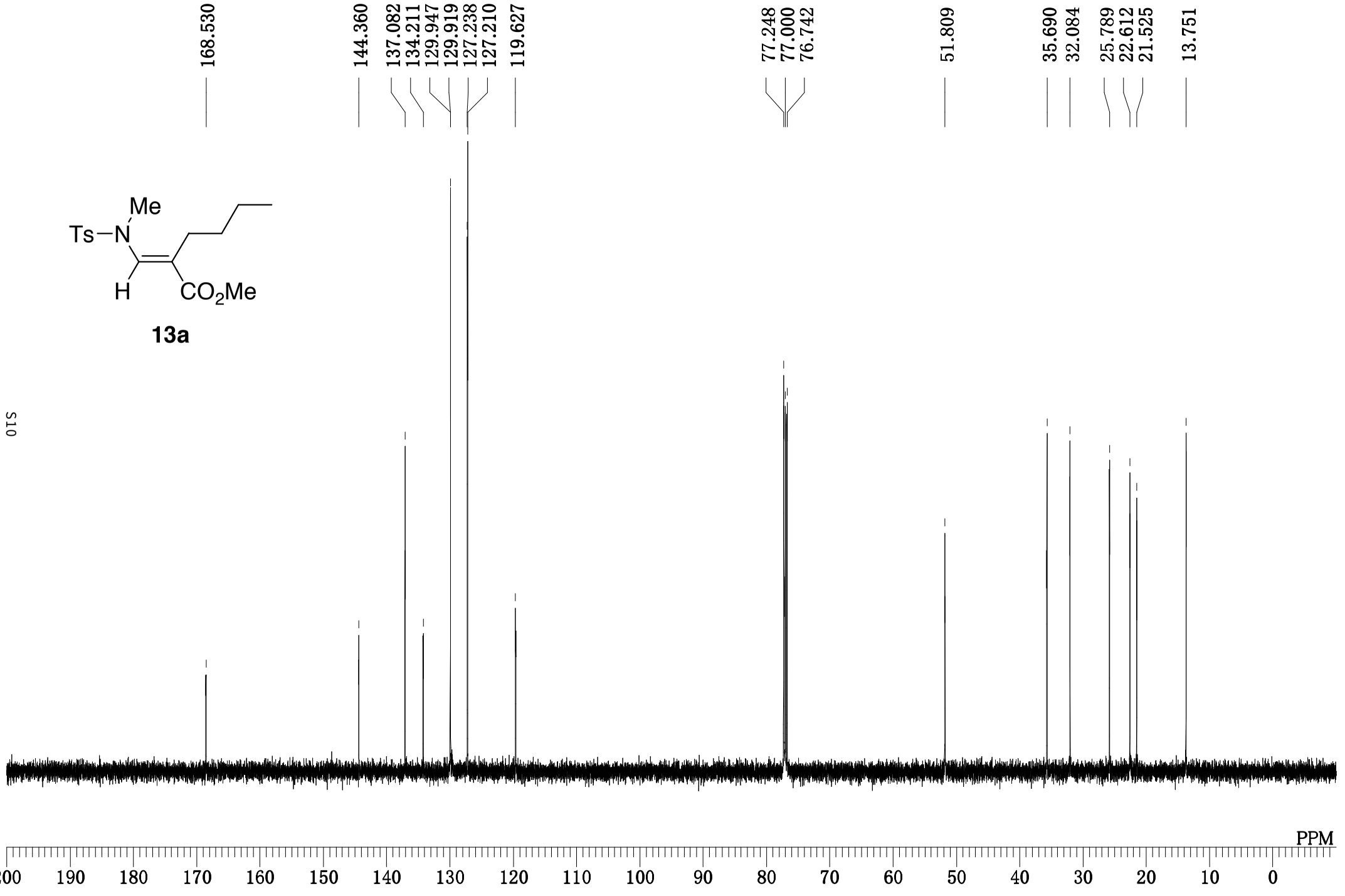
and ethyl methylcarbamate (1.0 mL, 9.90 mmol) at room temperature. The mixture was stirred at 135 °C for 46 hours. After the mixture was filtered through Celite® pad, the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 8/1) to give **8k** (1.17 g, 65%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.30 (t, *J* = 7.2, 3H), 1.38-1.44 (m, 2H), 1.47-1.52 (m, 2H), 2.28 (t, *J* = 6.9, 2H), 3.11 (s, 3H), 4.21 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.3, 14.2, 17.8, 21.6, 30.9, 37.4, 62.6, 68.3, 74.8, 155.8; IR (neat) 2265, 1725 cm^{-1}; EI-LRMS *m/z* 168 [$(M-CH_3)^+$], 154, 110, 81; EI-HRMS calcd for $C_9H_{14}NO_2$ 168.1025, found 168.1021.

CDCl3, 500 MHz

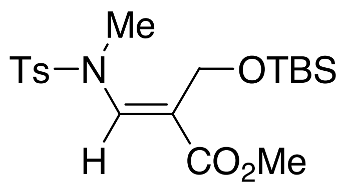


13a

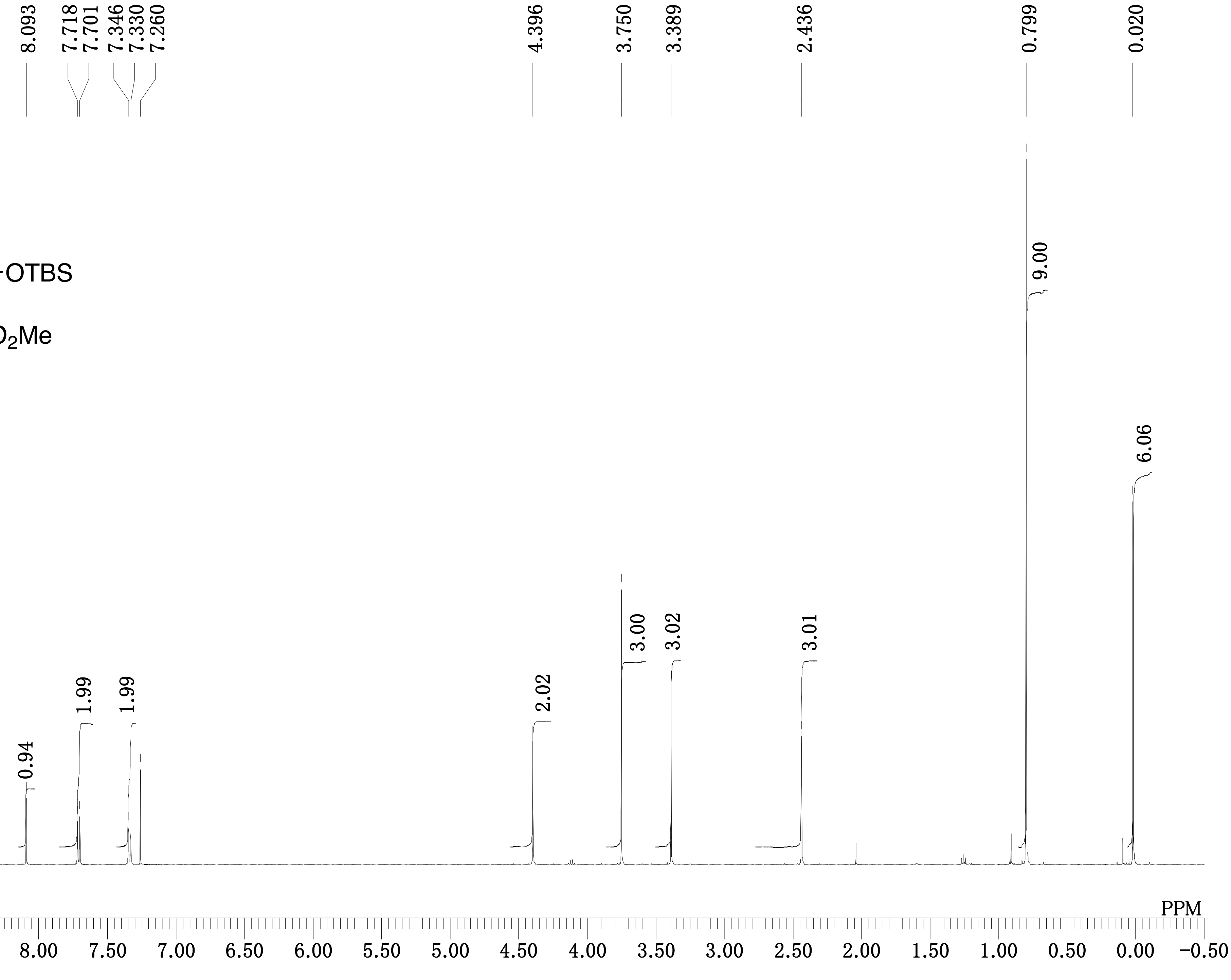
CDCl3, 125 MHz



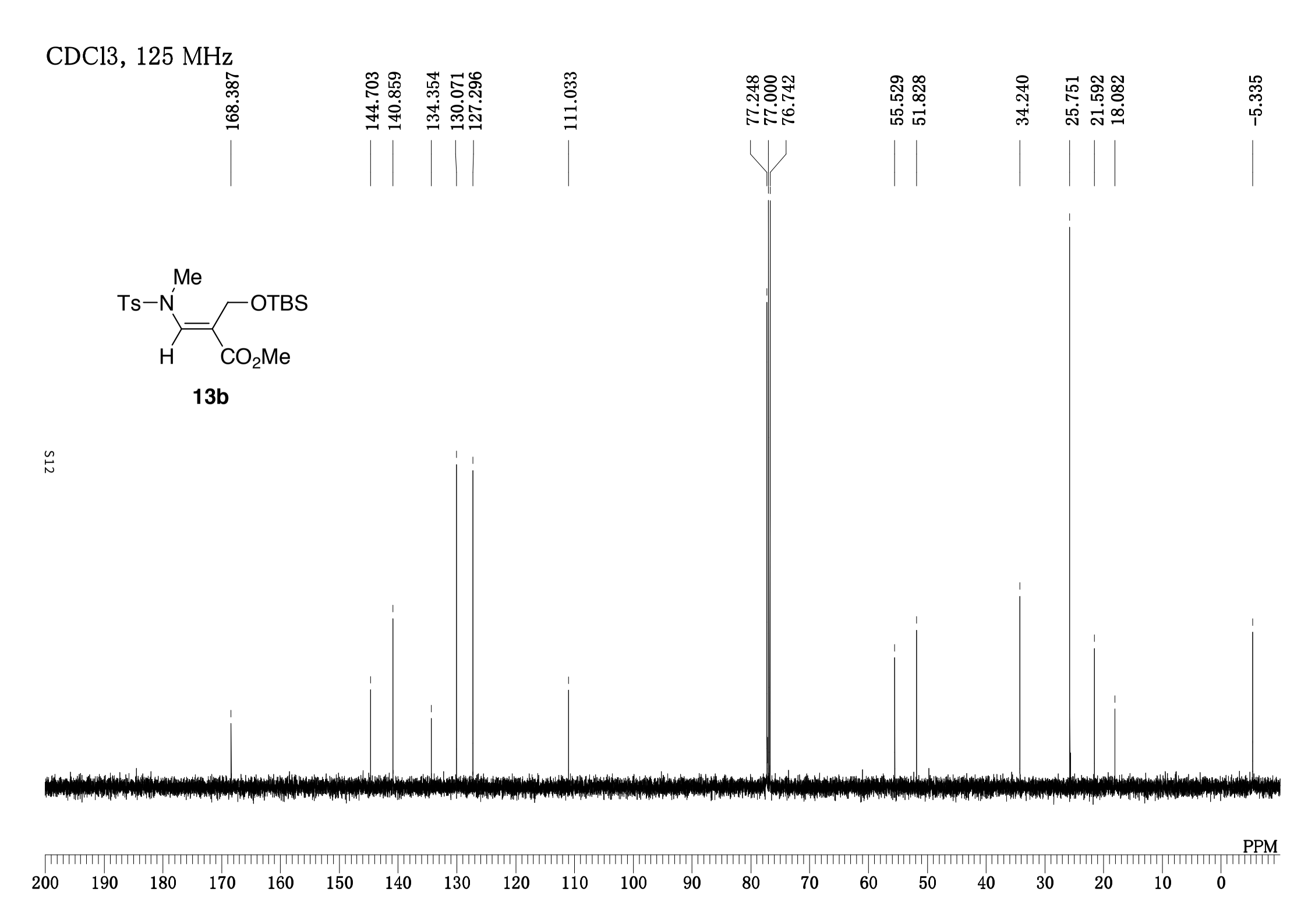
CDCl3, 500 MHz



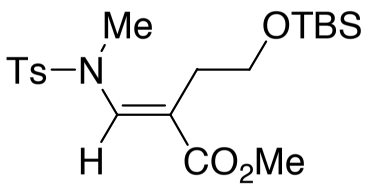
13b



CDCl3, 125 MHz

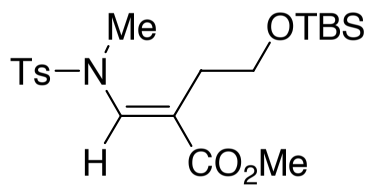


CDCl3, 400 MHz



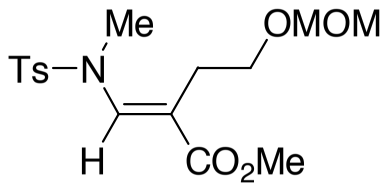
13c

CDCl3, 125 MHz



13c

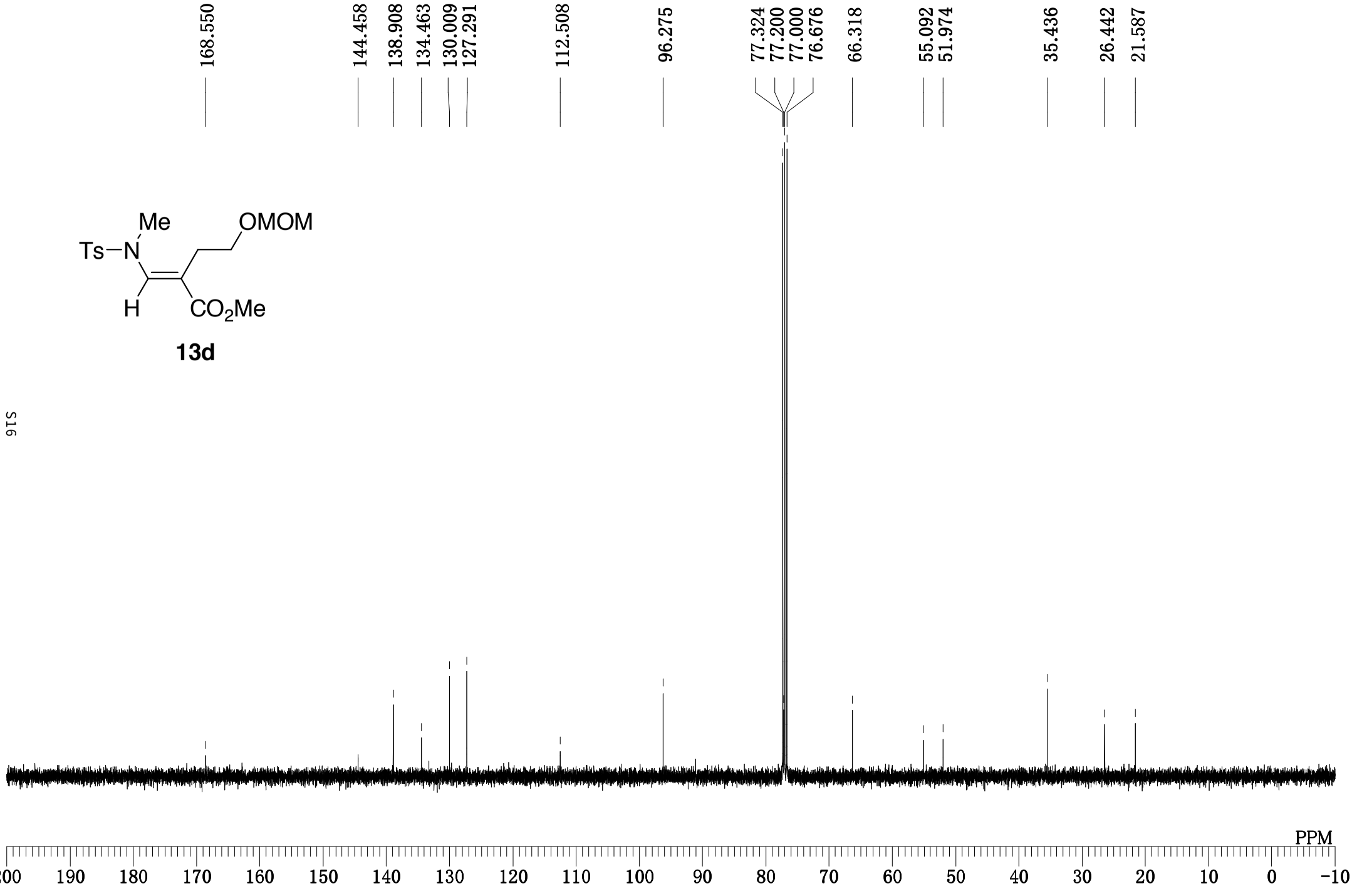
CDCl3, 400 MHz



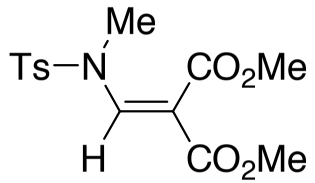
13d

PPM

CDCl3, 100 MHz



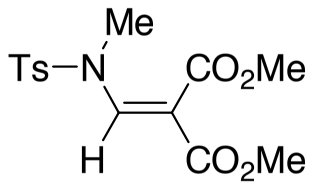
CDCl3, 500 MHz



13e

CDCl3, 125 MHz

166.107
165.001
145.104
140.220
133.724
130.043
127.067
104.671
77.000
76.952
76.742
76.494
52.305
52.086
32.599
21.382

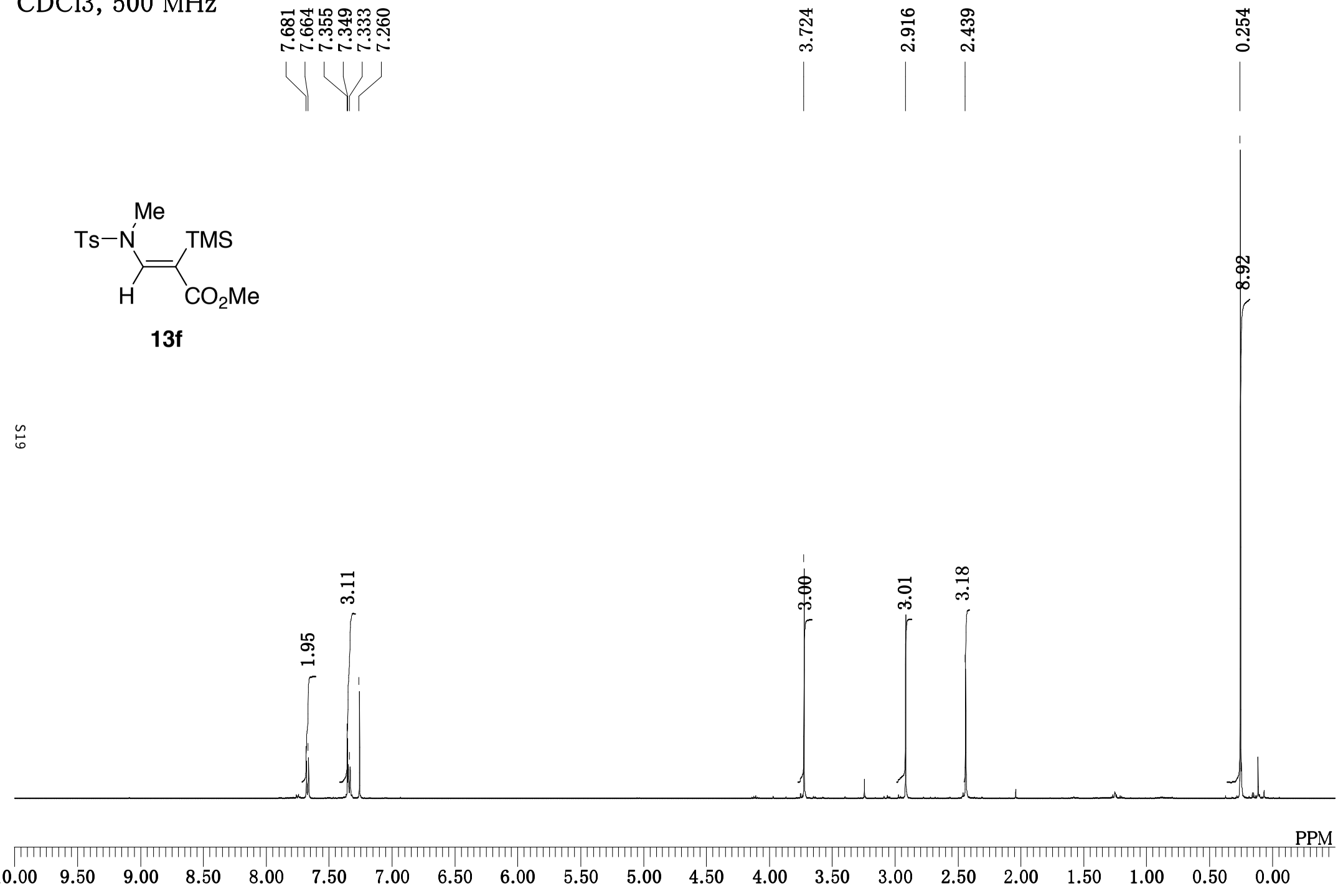


13e

PPM

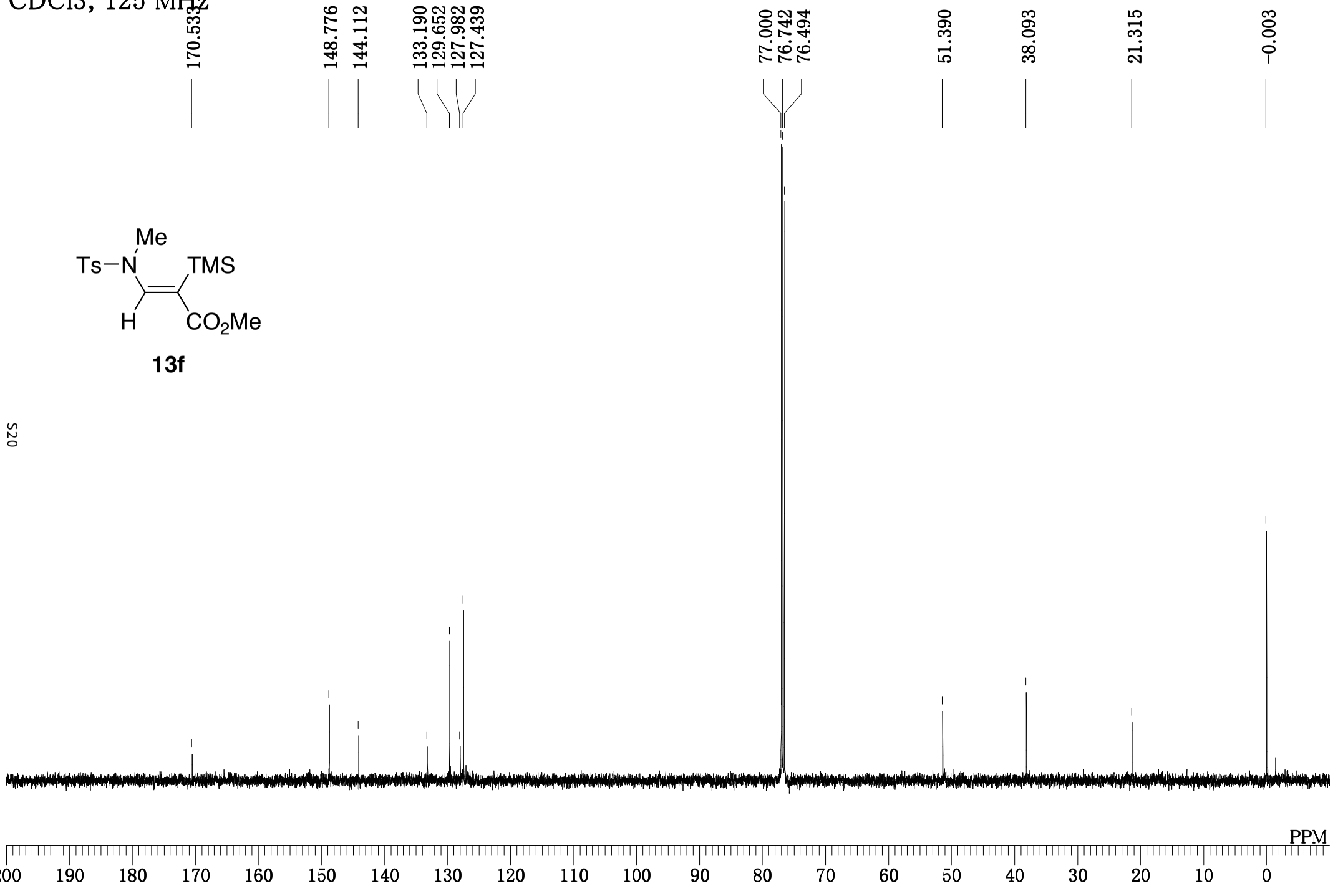
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

CDCl3, 500 MHz

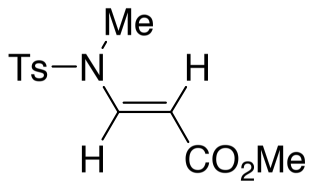


13f

CDCl3, 125 MHz

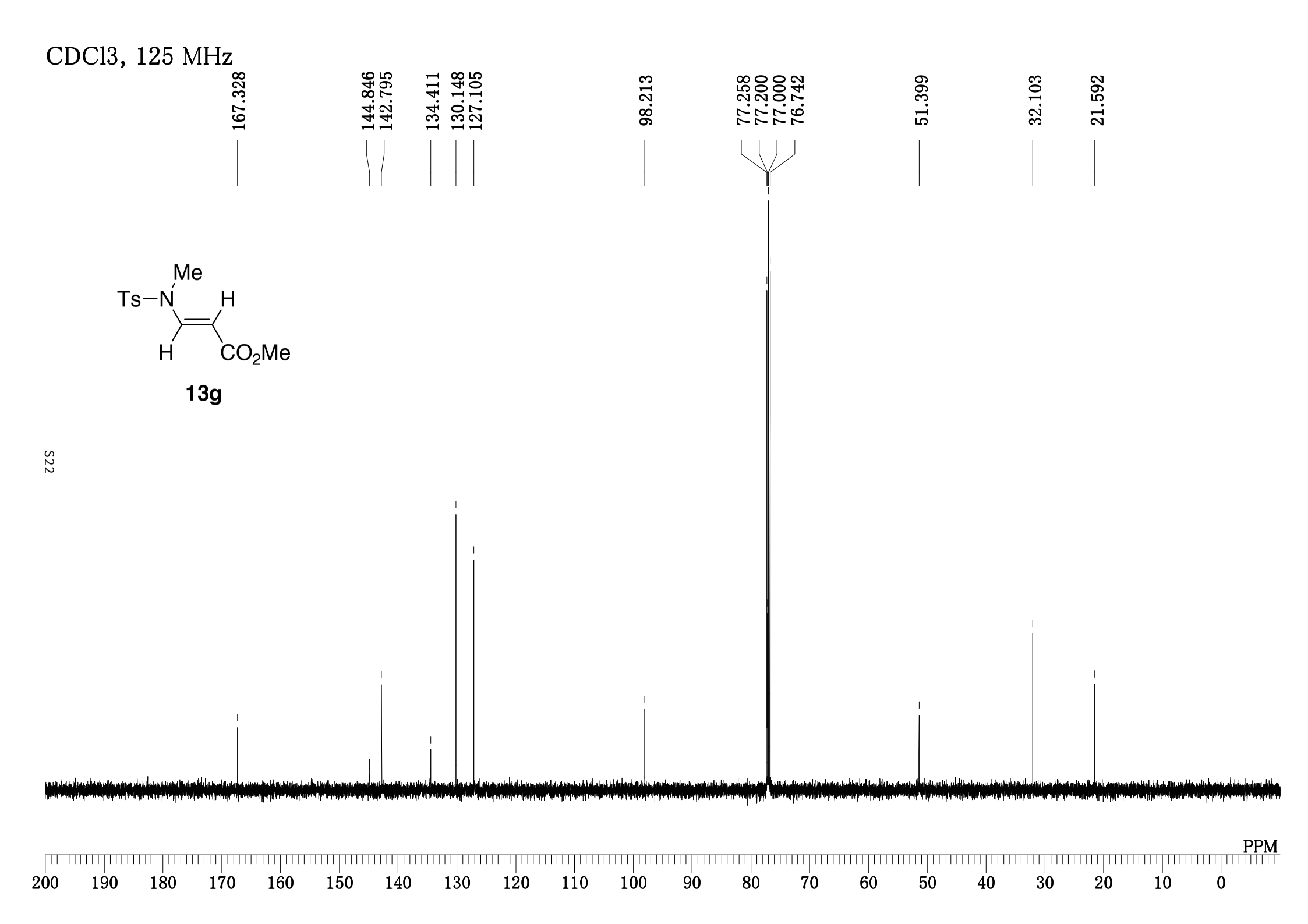


CDCl3, 500 MHz

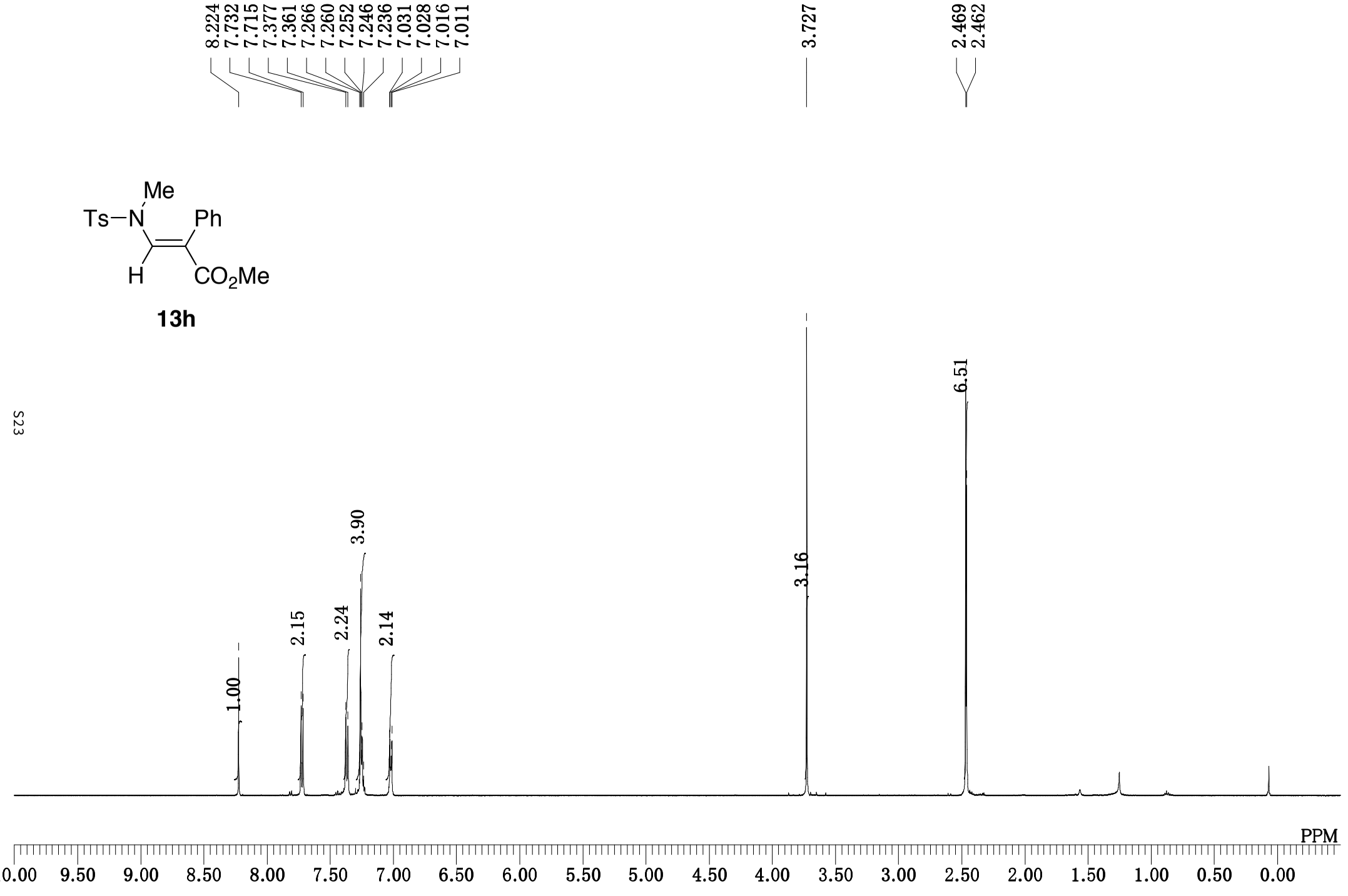


13g

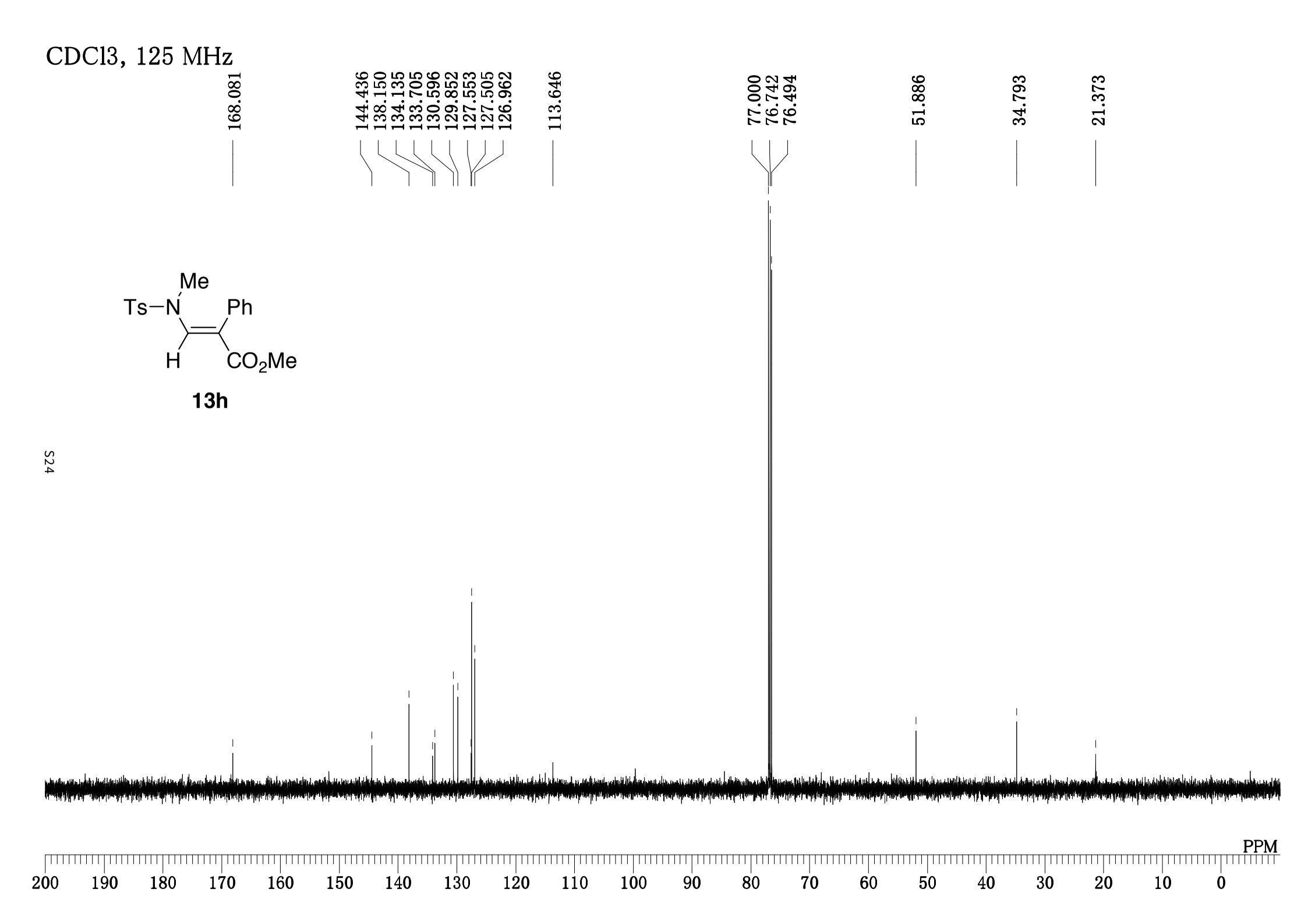
CDCl3, 125 MHz



CDCl3, 500 MHz

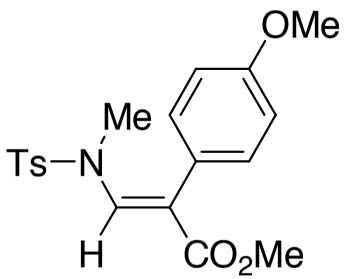


CDCl3, 125 MHz



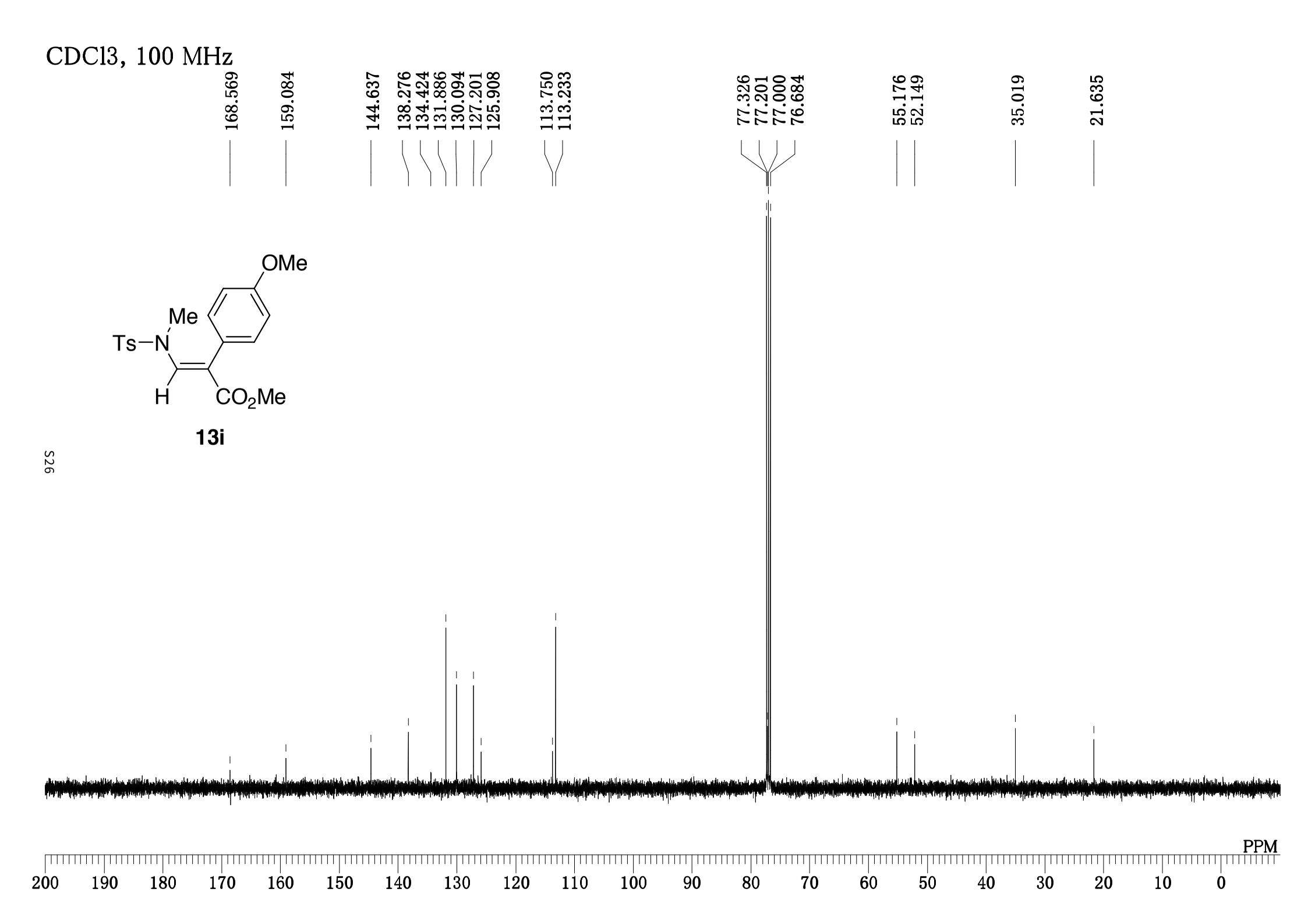
13h

CDCl3, 500 MHz



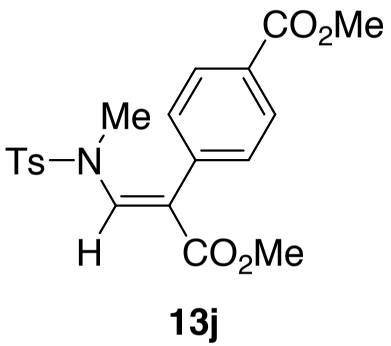
13i

CDCl3, 100 MHz



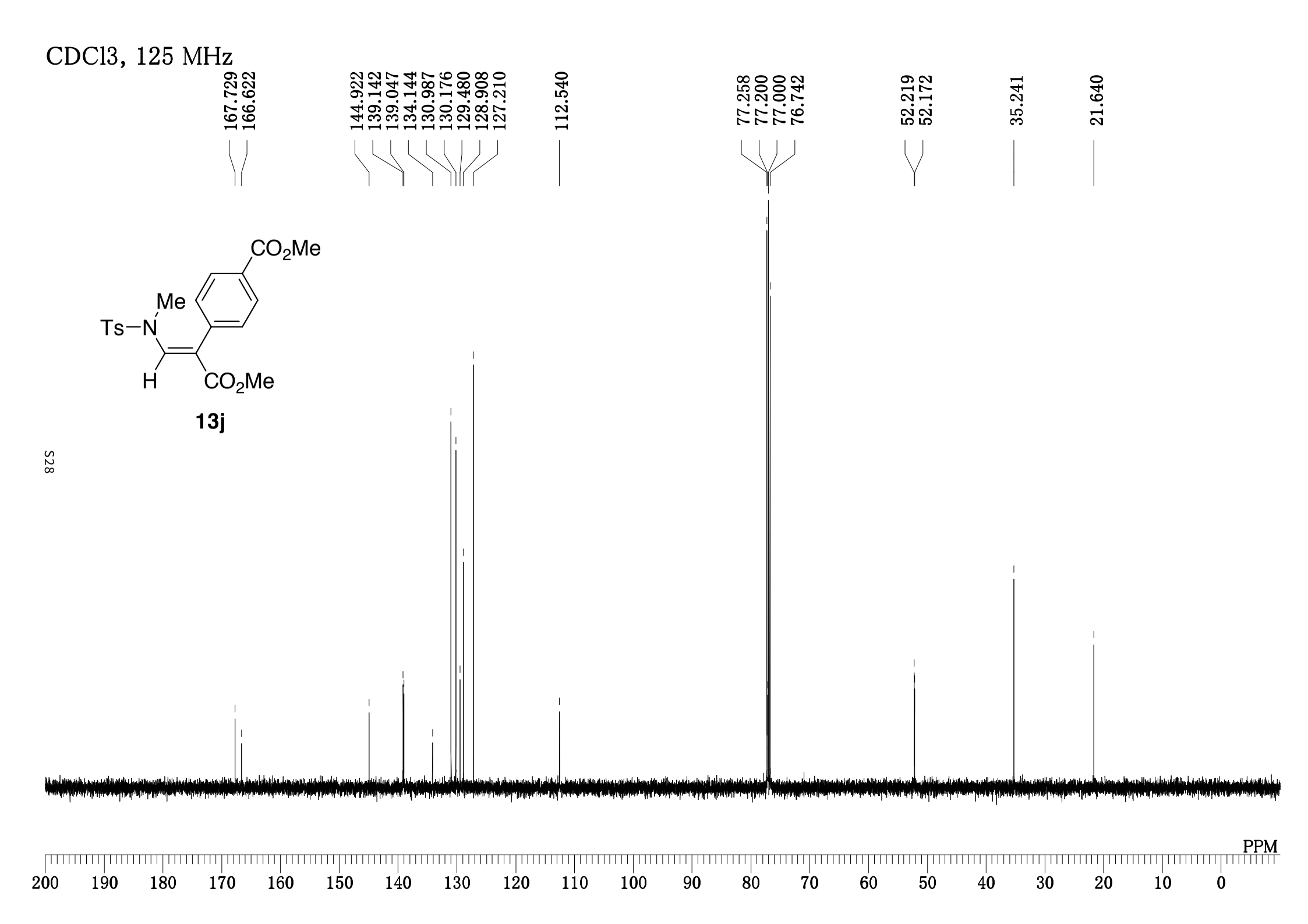
13i

CDCl3, 500 MHz



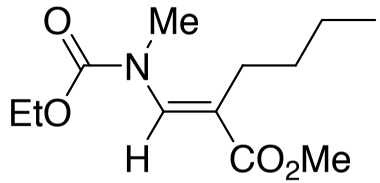
13j

CDCl3, 125 MHz



13j

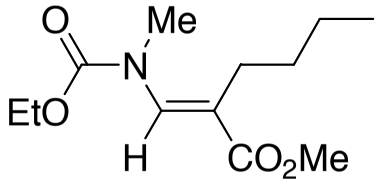
CDCl3, 500 MHz



13k

CDCl3, 125 MHz

169.207
154.985
138.703
116.813
77.248
77.200
77.000
76.742
62.893
51.714
35.279
31.941
26.199
22.841
14.476
13.809



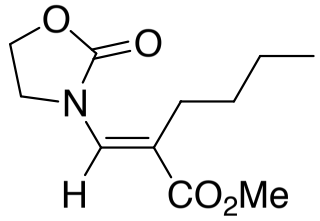
13k

S30

PPM

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

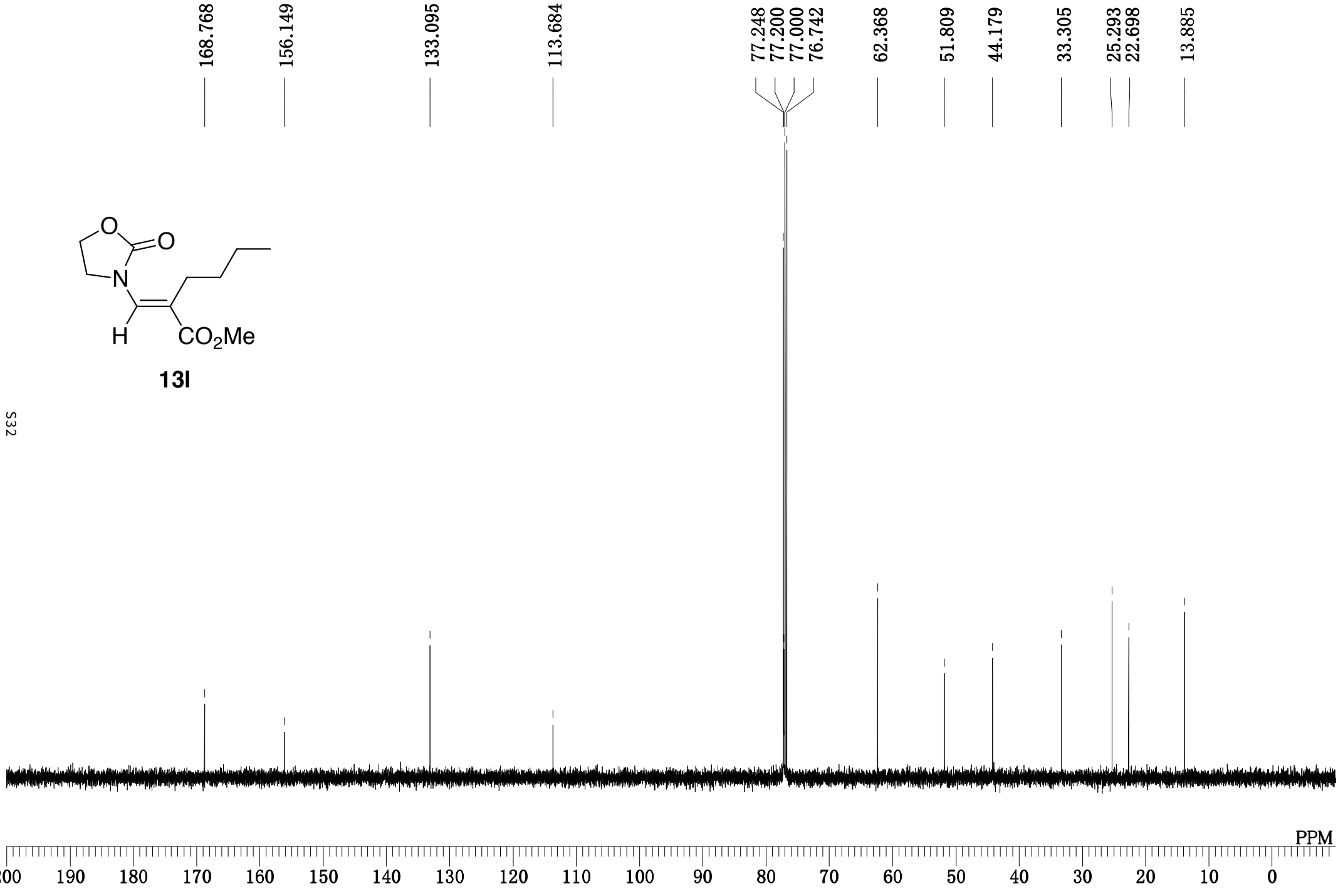
CDCl3, 500 MHz



13l

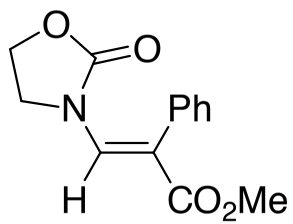
S31

CDCl3, 125 MHz



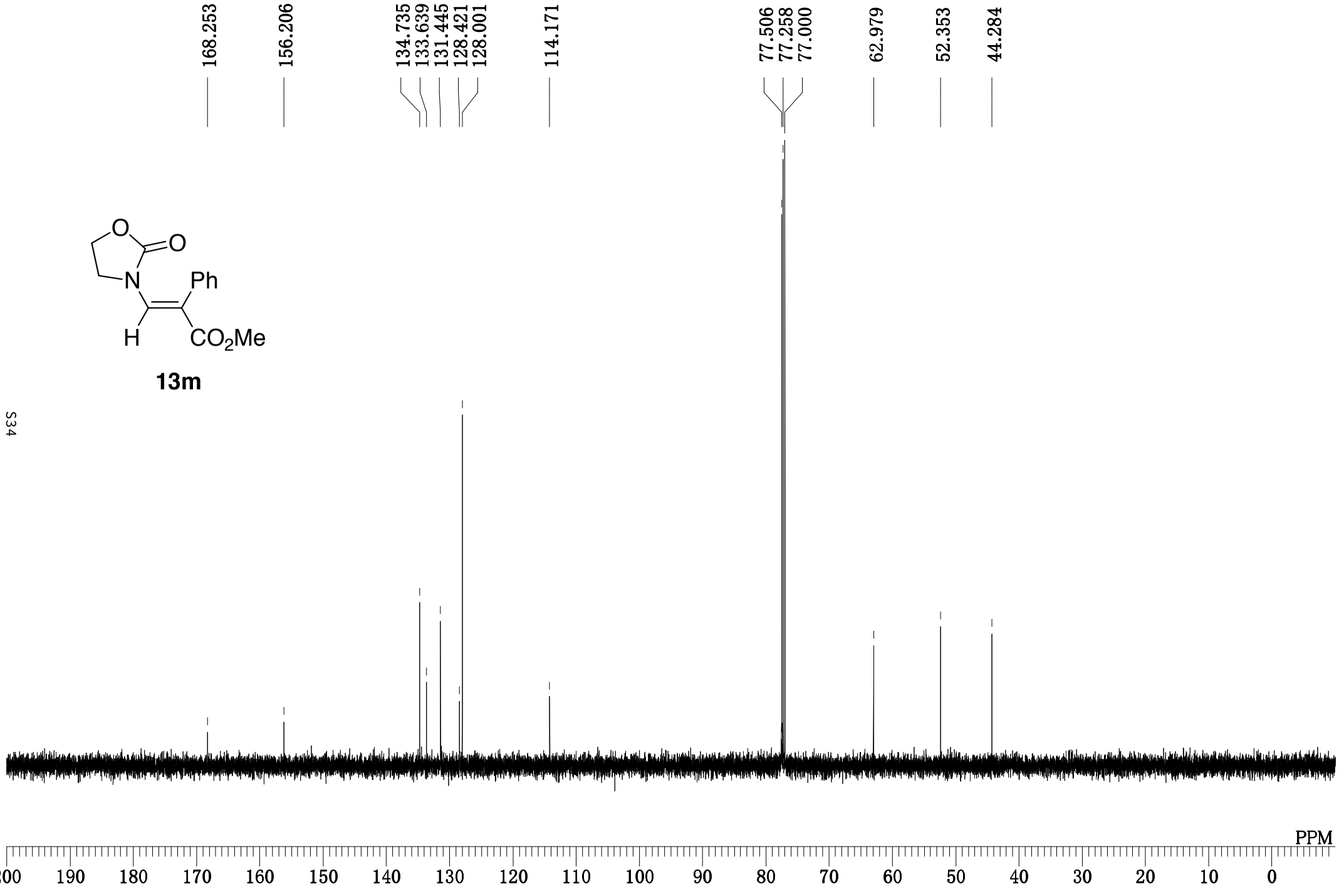
13l

CDCl3, 500 MHz

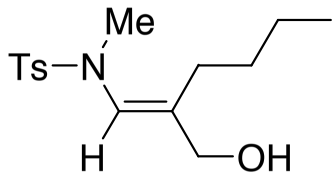


13m

CDCl3, 125 MHz

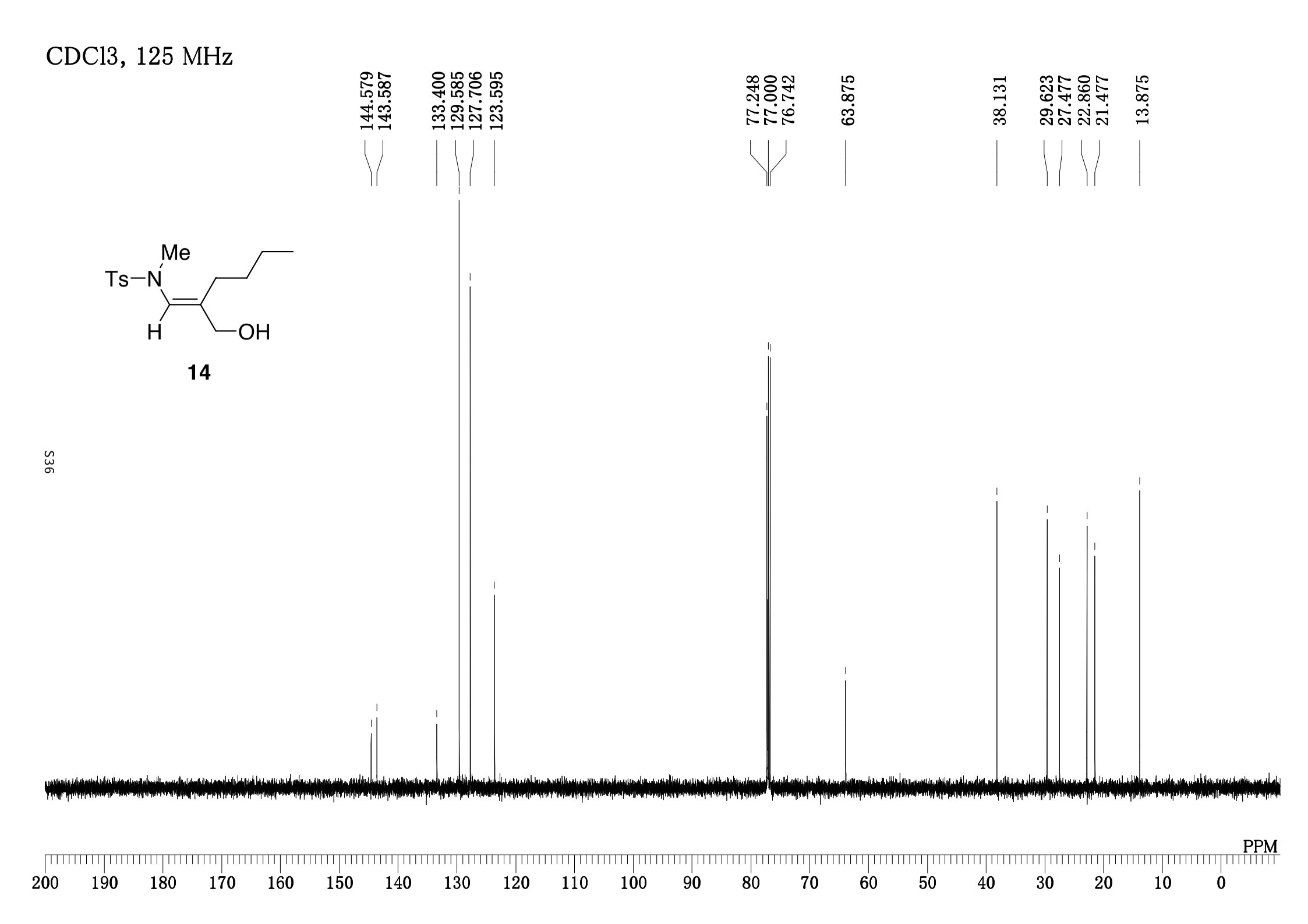


CDCl3, 500 MHz

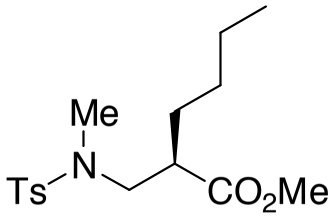


14

CDCl3, 125 MHz

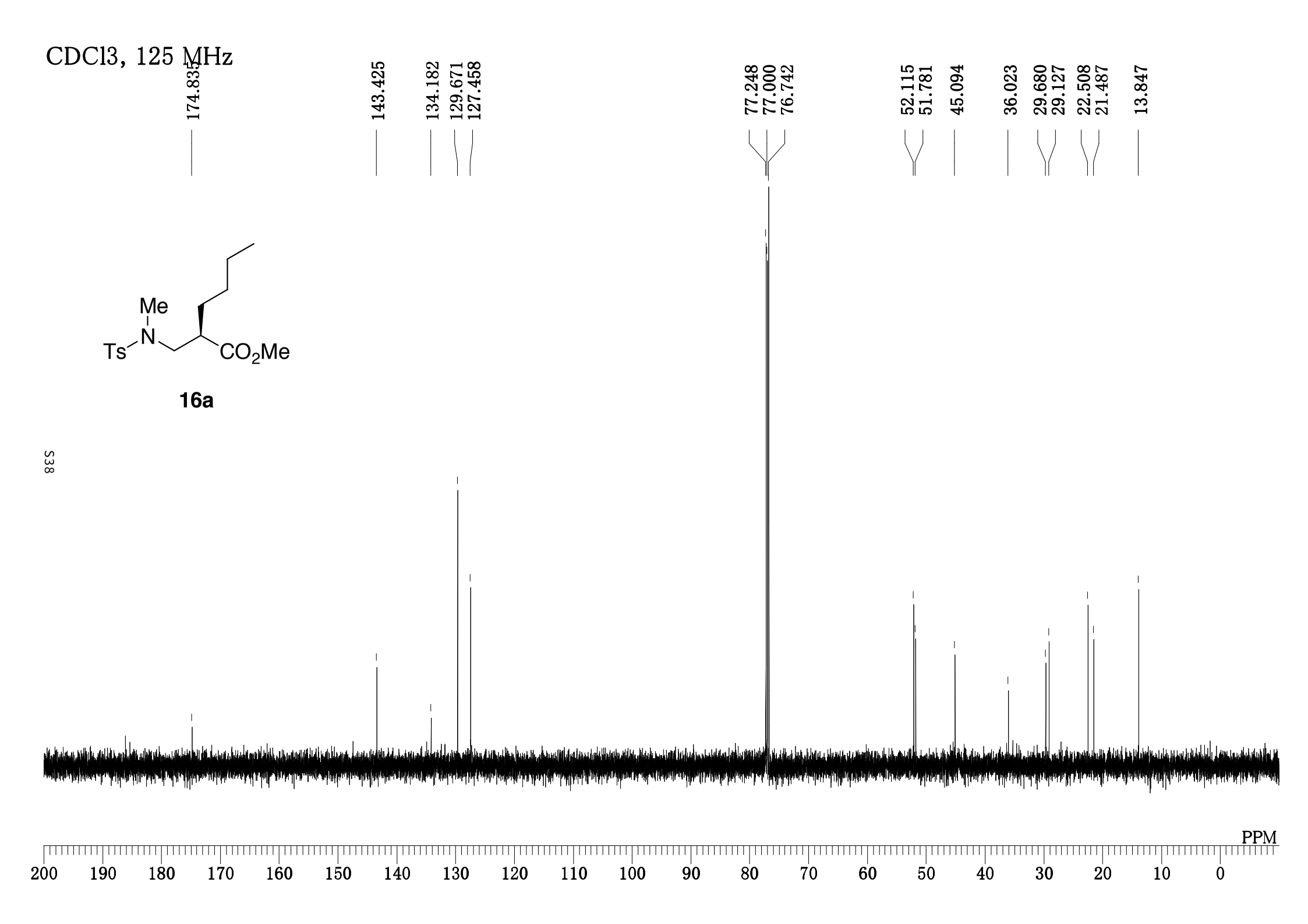


CDCl3, 500 MHz

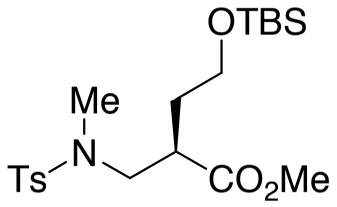


16a

CDCl3, 125 MHz

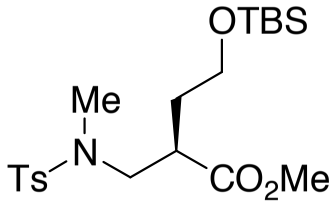


CDCl3, 500 MHz



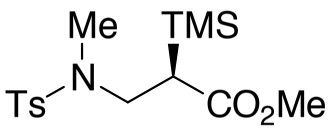
16c

CDCl3, 125 MHz



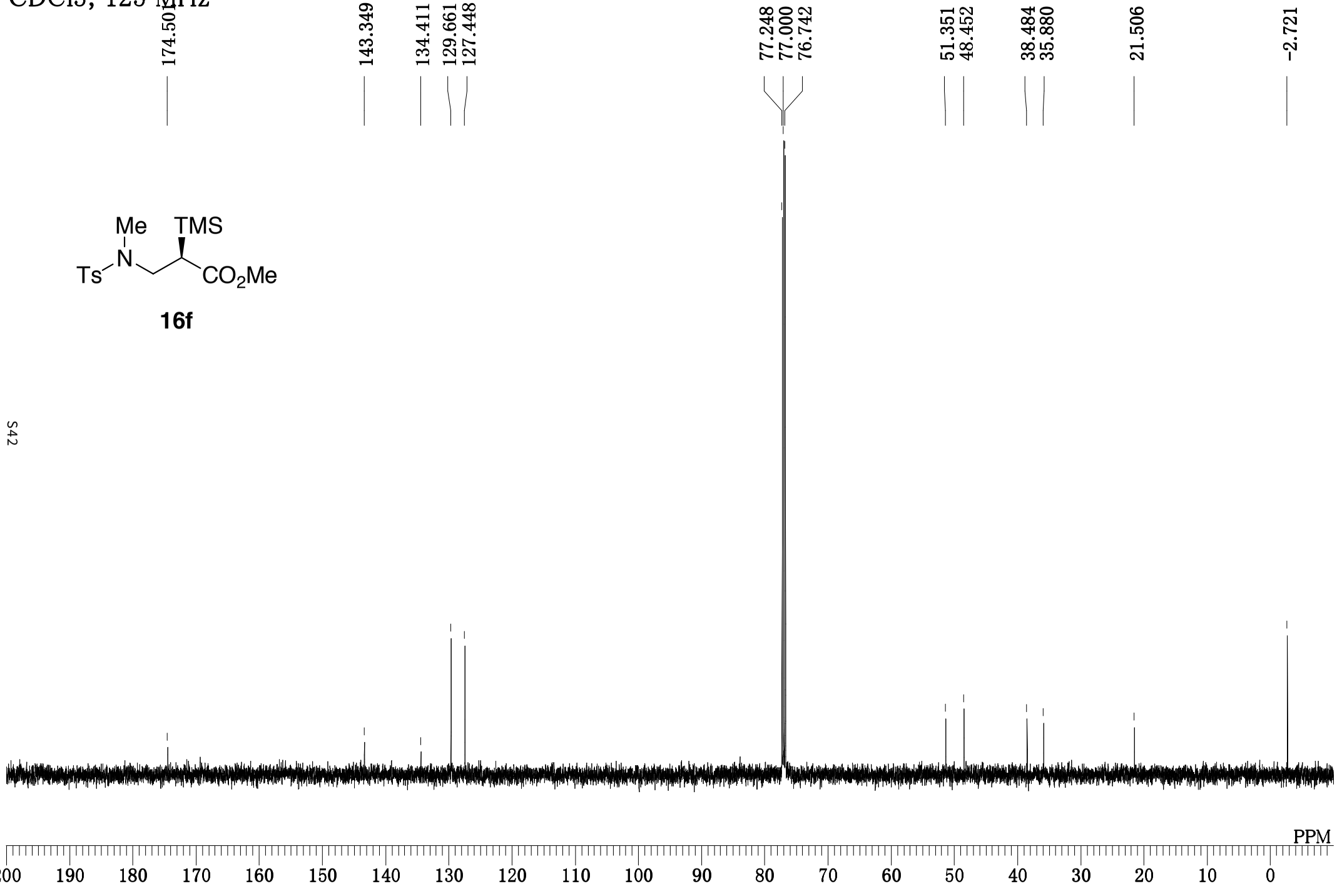
16c

CDCl3, 500 MHz



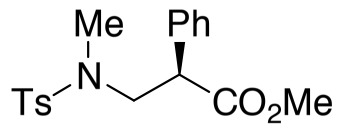
16f

CDCl3, 125 MHz



16f

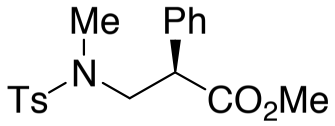
CDCl3, 500 MHz



16h

CDCl3, 125 MHz

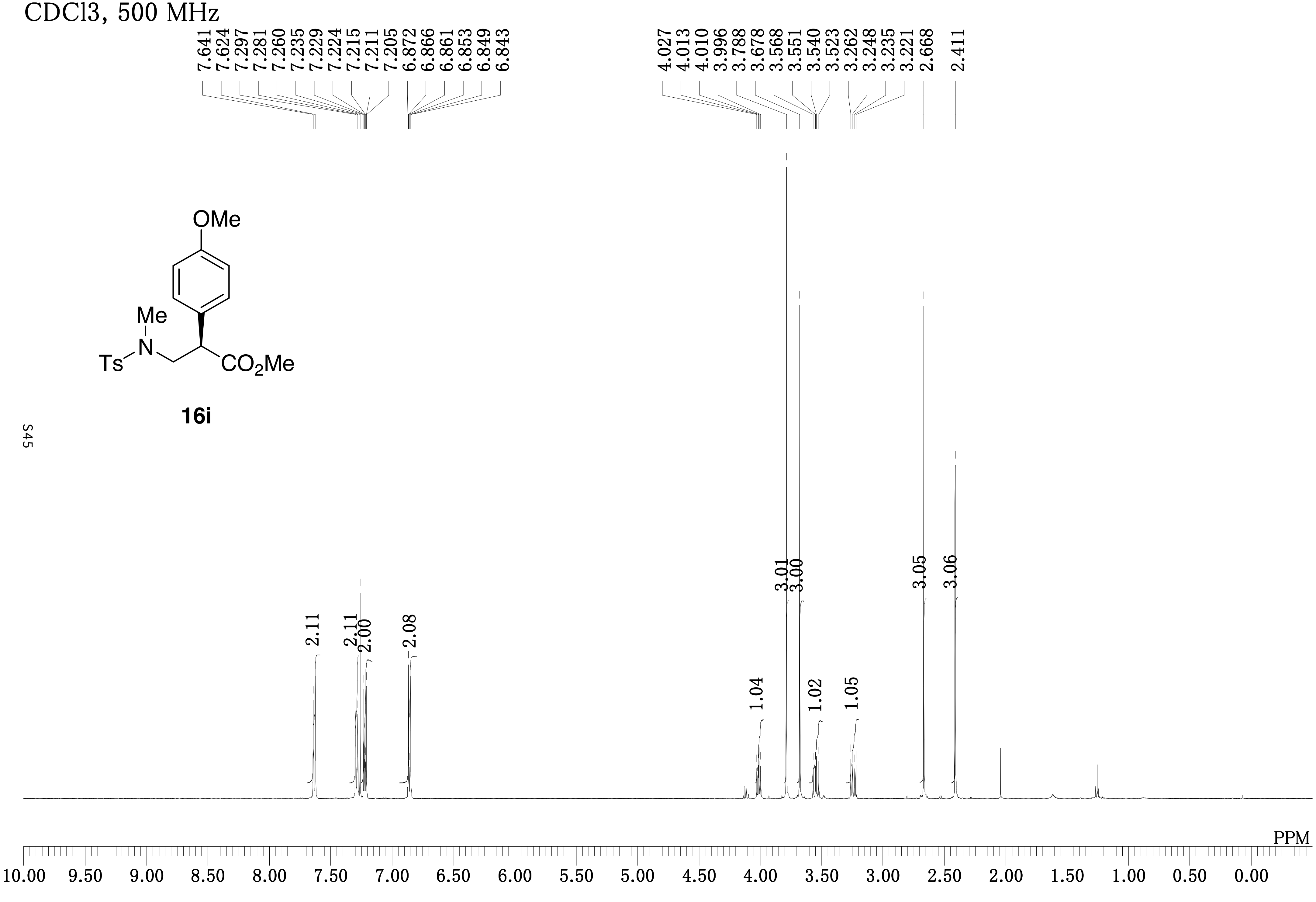
172.889
143.482
136.109
134.154
129.690
128.908
128.049
127.887
127.448
77.248
77.000
76.742
53.555
52.277
51.924
37.044
21.477



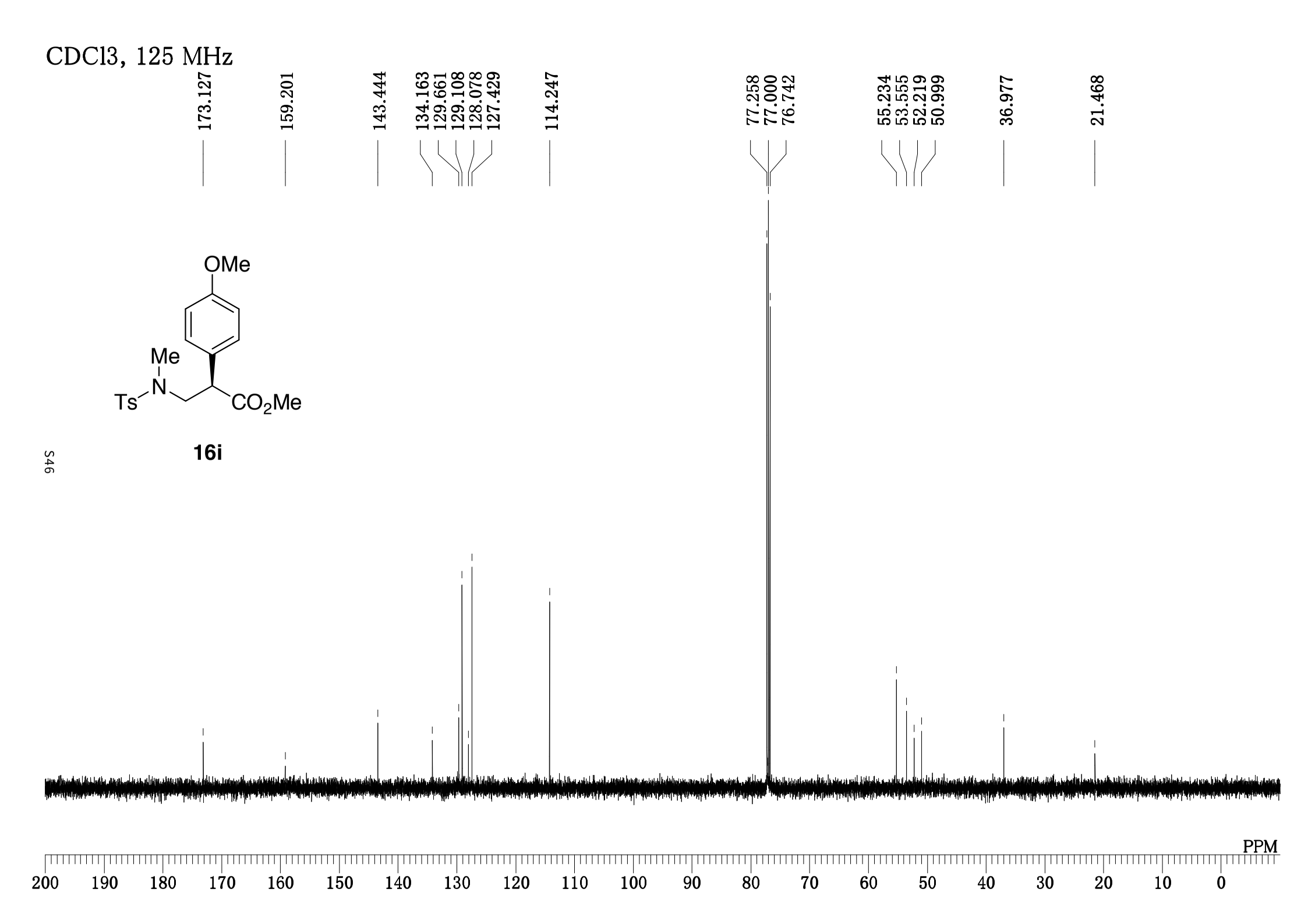
16h

PPM

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

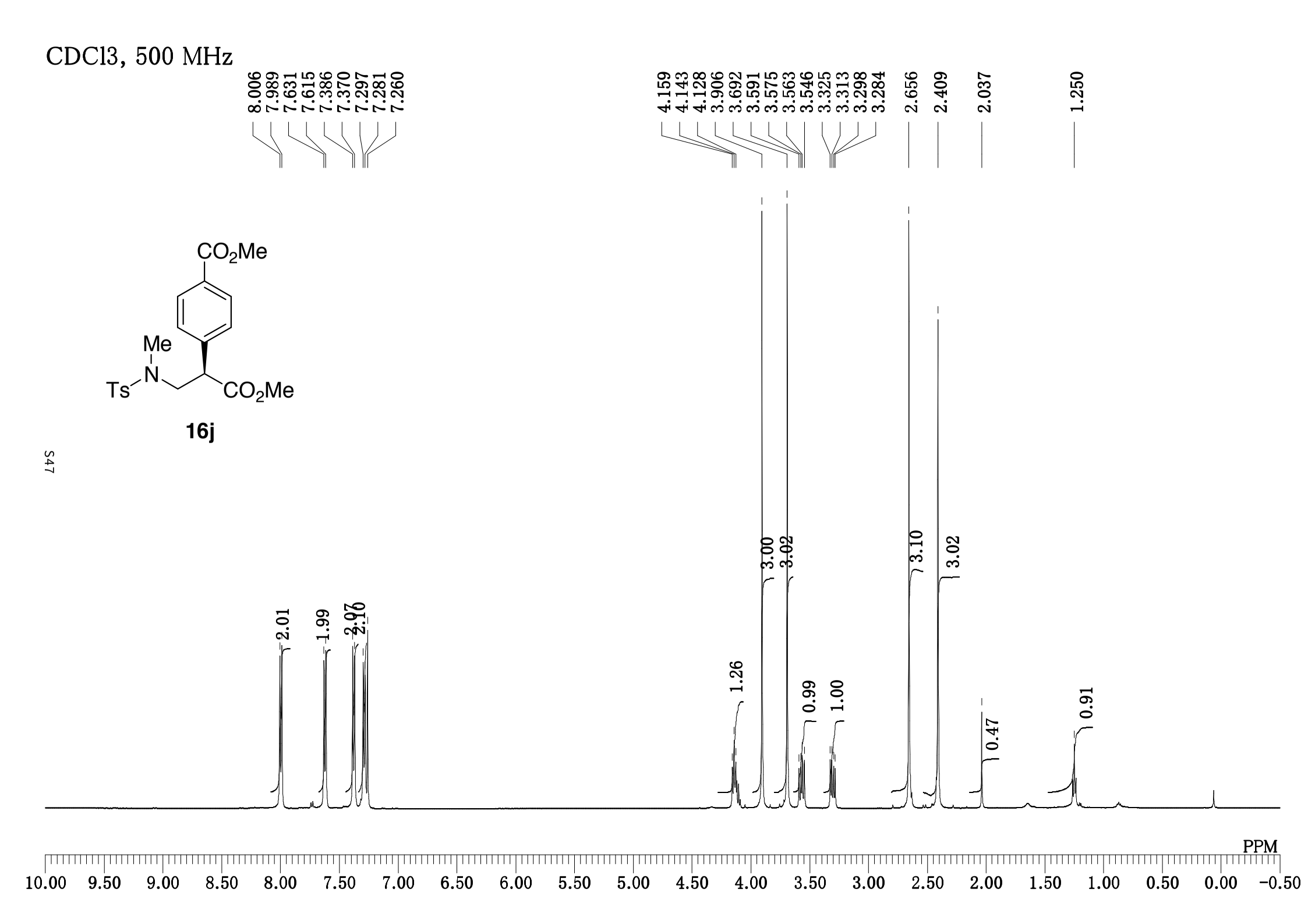

CDCl3, 500 MHz
7.641 7.624 7.297 7.281 7.260 7.235 7.229 7.224 7.215 7.211 7.205 6.872 6.866 6.861 6.853 6.849 6.843
4.027 4.013 4.010 3.996 3.788 3.678 3.568 3.551 3.540 3.523 3.262 3.248 3.235 3.221 2.668
2.411
OMe
Me
N
Ts
CO_2Me
16i
2.11
2.11
2.00
2.08
1.04
3.01
3.00
1.02
1.05
3.05
3.06
PPM
10.00 9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00

CDCl3, 125 MHz

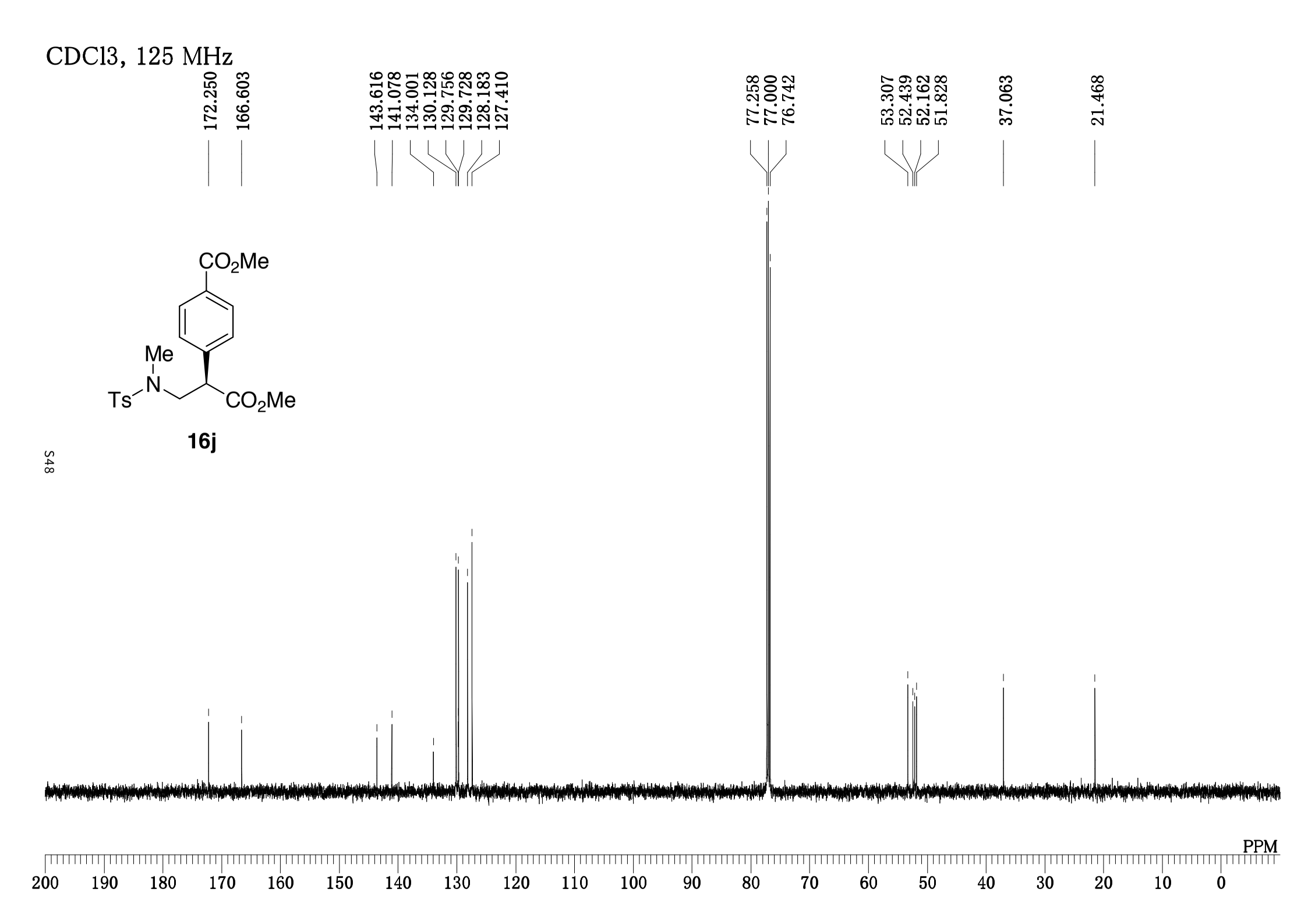


16i

CDCl3, 500 MHz

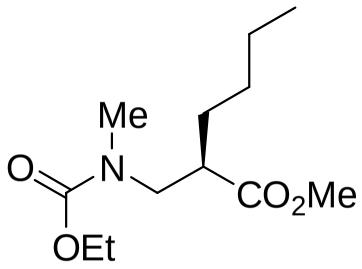


CDCl3, 125 MHz



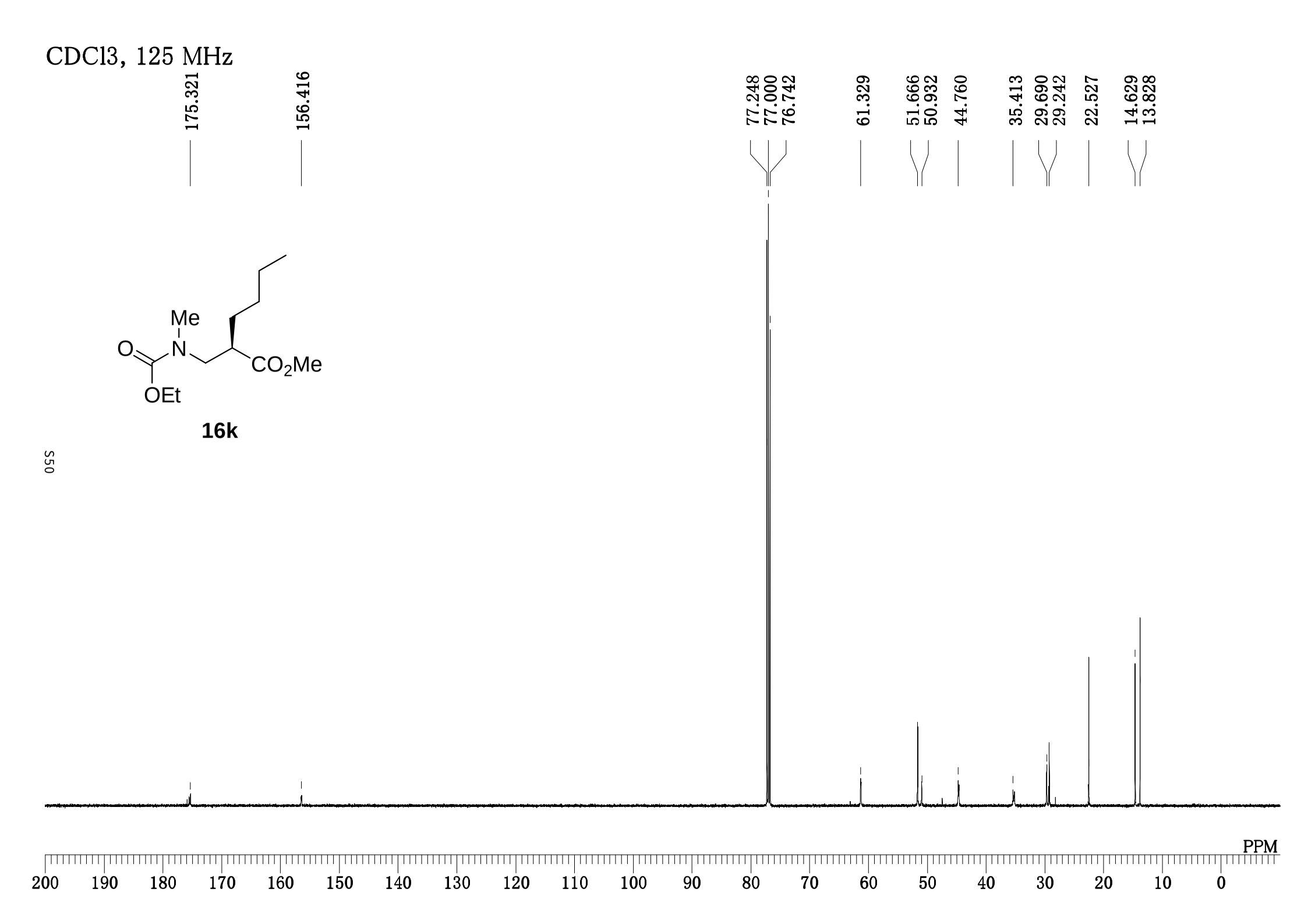
16j

CDCl3, 500 MHz

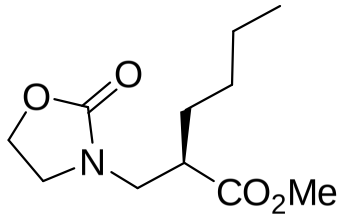


16k

CDCl3, 125 MHz

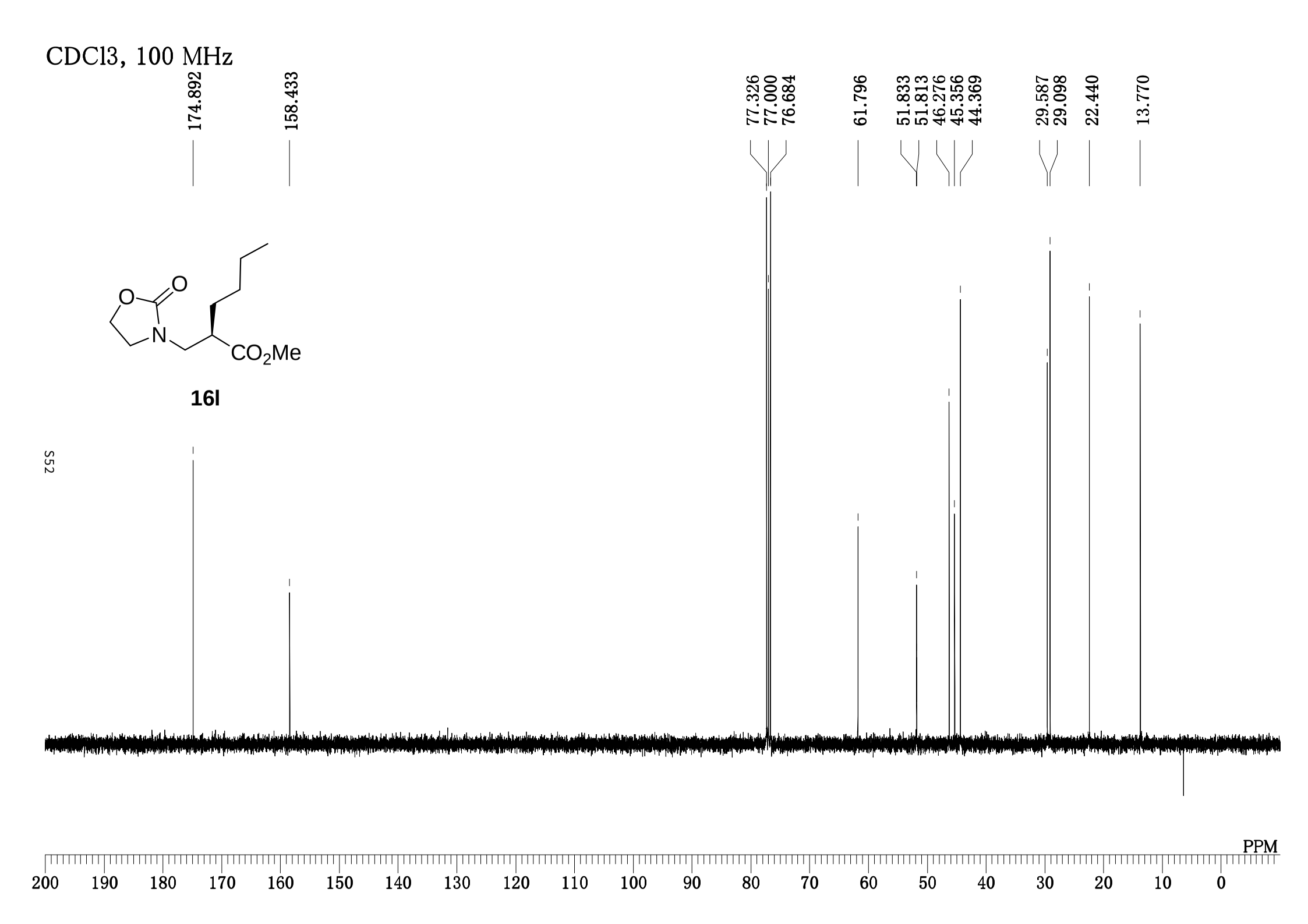


CDCl3, 400 MHz

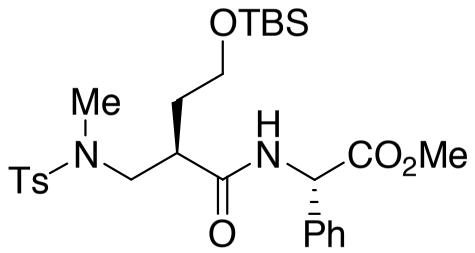


16l

CDCl3, 100 MHz

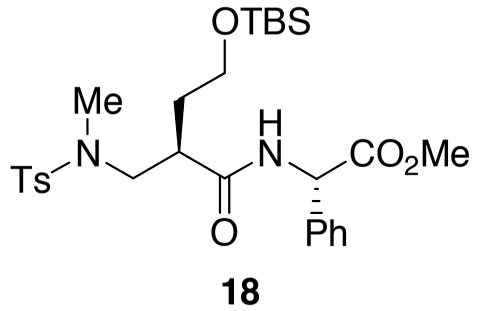


CDCl3+tms, 500 MHz



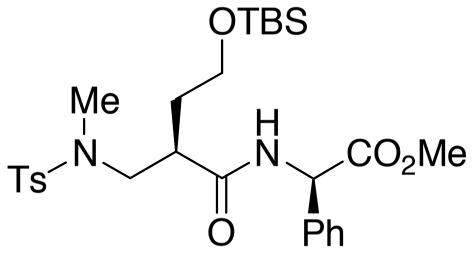
18

CDCl3+tms, 500 MHz



18

CDCl3+tms, 500 MHz

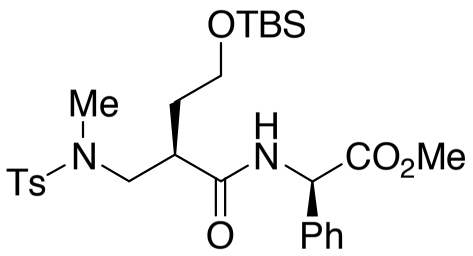


19

S55

CDCl3+tms, 125 MHz

172.917
170.924
143.434
136.357
134.125
129.699
128.984
128.593
127.496
127.343
77.258
77.000
76.752
60.108
56.683
52.735
52.439
42.509
36.729
33.181
25.865
21.506
18.177
−0.022
−5.383



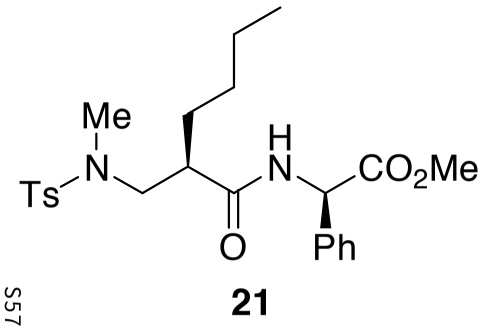
19

S56

PPM

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

CDCl3+tms, 500 MHz



21

S57

7.684 7.668 7.411 7.389 7.376 7.373 7.364 7.348 7.340 7.333 7.317 7.263 6.717 6.699 5.552 5.538 3.744 3.173 3.162 3.146 3.134 3.012 2.994 2.983 2.965 2.767 2.650 2.639 2.630 2.620 2.610 2.602 2.593 2.434 1.565 1.548 1.522 1.508 1.490 1.459 1.433 1.418 1.406 1.390 1.255 1.241 1.235 1.228 1.214 1.199 1.184 1.169 1.154 1.139 1.122 0.827 0.813 0.798 0.000

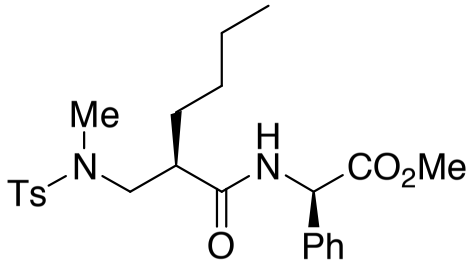
4.98 2.36 2.00 0.89 0.99 3.13 0.96 1.00 3.16 1.04 3.24 0.86 0.99 2.23 2.17 3.03

PPM

10.00 9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00 −0.50

CDCl3+tms, 125 MHz

173.308
170.972
143.530
136.338
133.972
129.718
128.993
128.564
127.477
127.324
77.248
77.000
76.742
56.712
52.897
52.801
47.469
37.359
30.272
29.146
22.584
21.525
13.828
−0.022



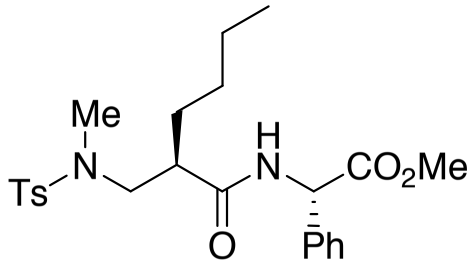
21

S58

PPM

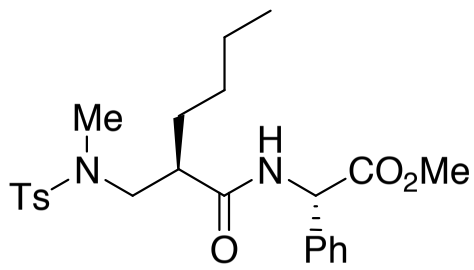
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

CDCl3+tms, 500 MHz



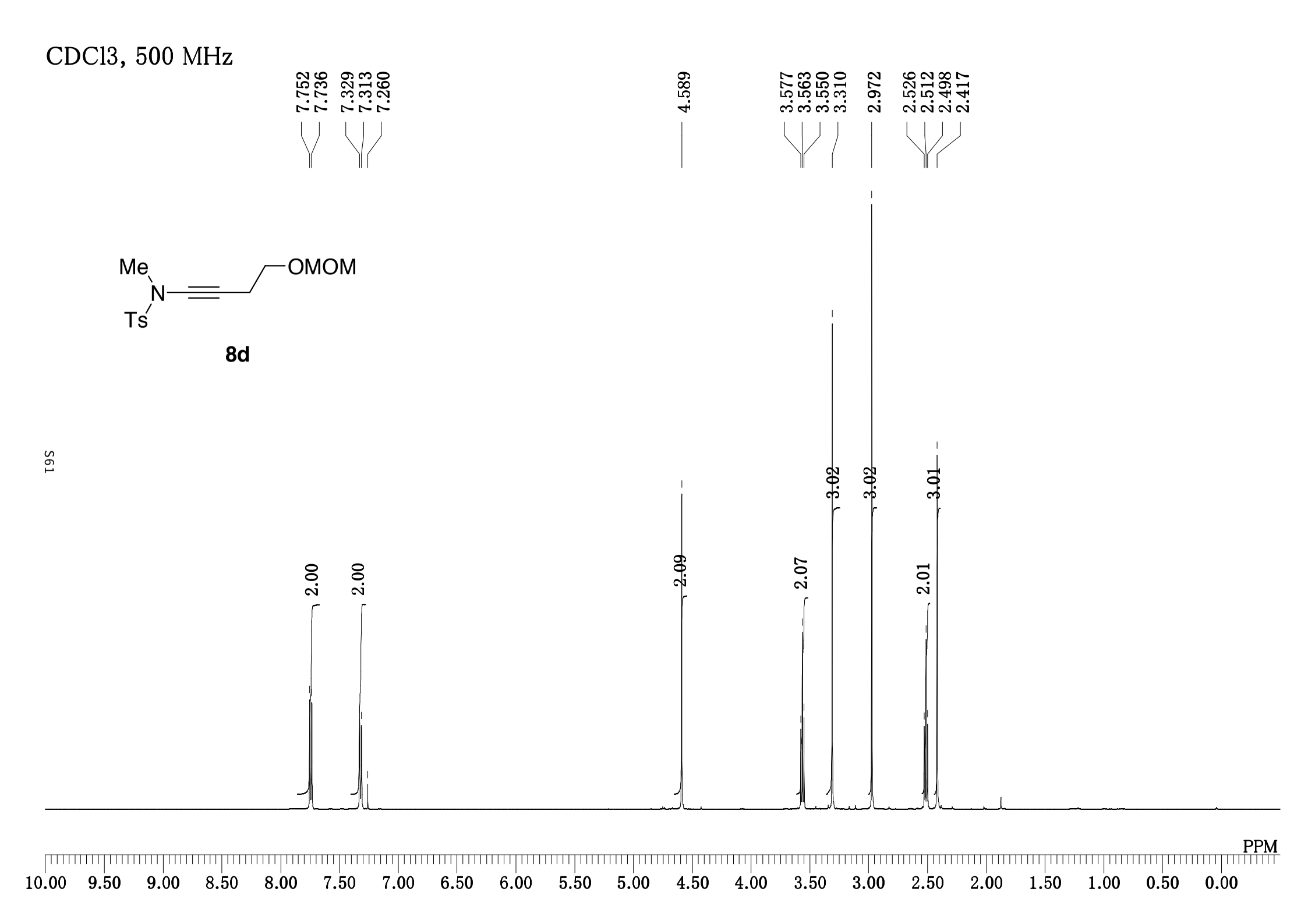
22

CDCl3+tms, 500 MHz

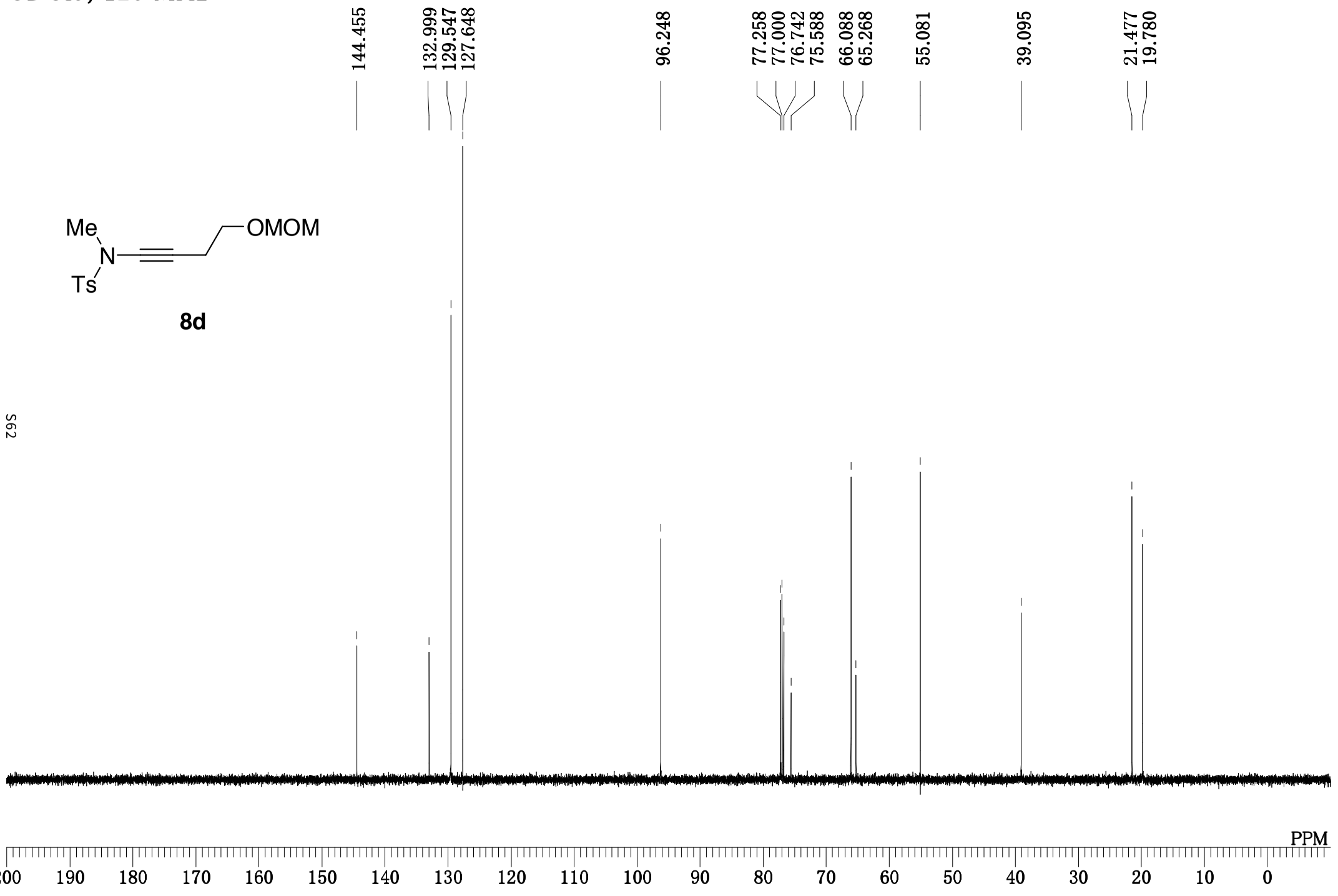


22

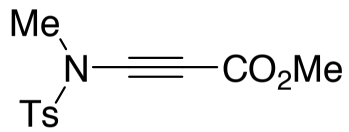
CDCl3, 500 MHz



CDCl3, 125 MHz

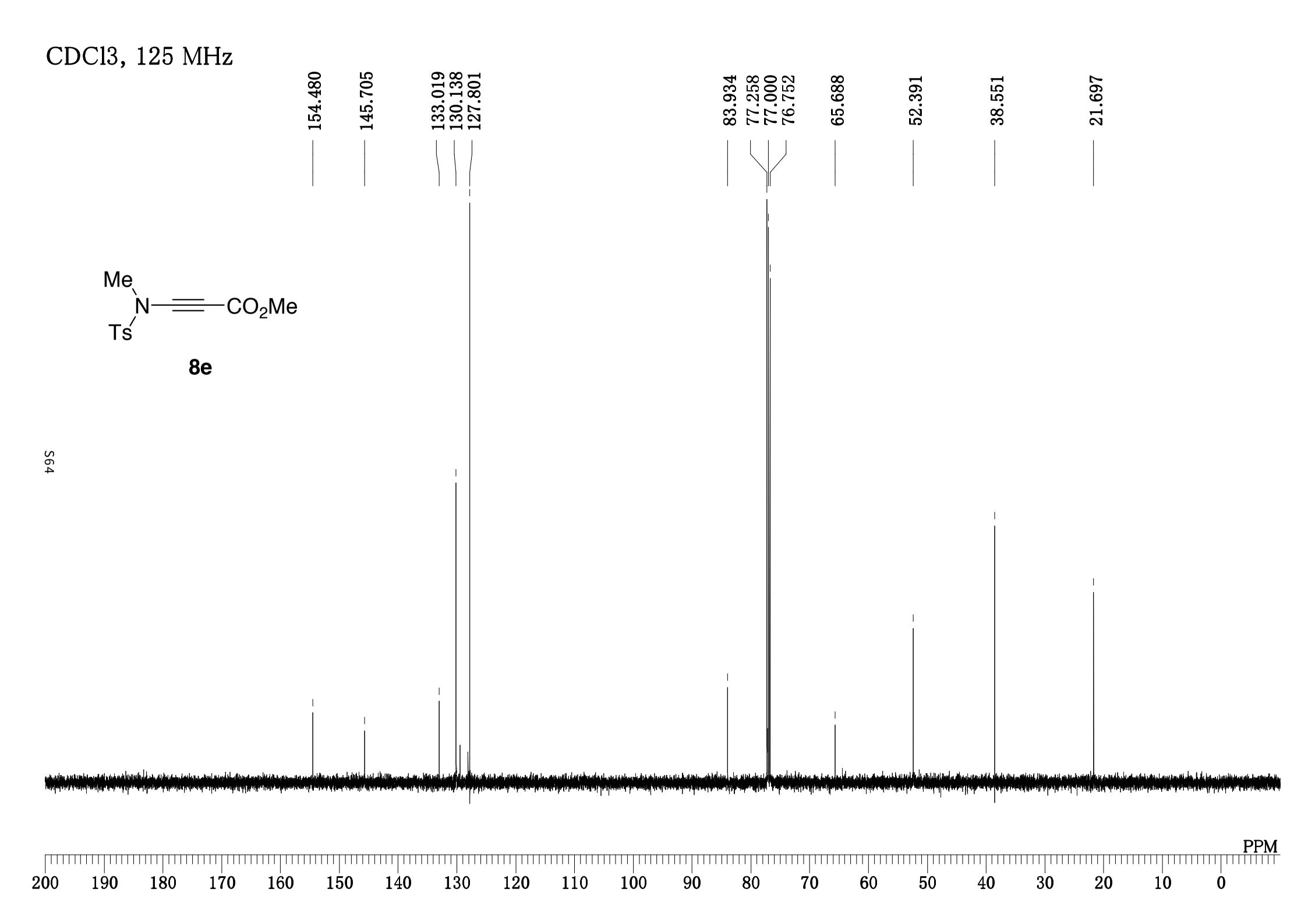


CDCl3, 500 MHz

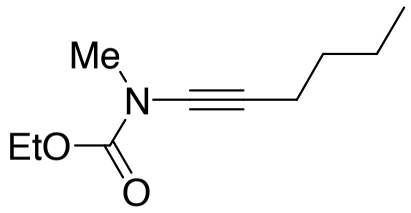


8e

CDCl3, 125 MHz



CDCl3, 500 MHz



8k

CDCl3, 125 MHz