Novel synthesis of various orthogonally protected C^{α}-methyl lysine analogues and biological evaluation of a Vapreotide analogue containing (*S*)-α-methyl lysine

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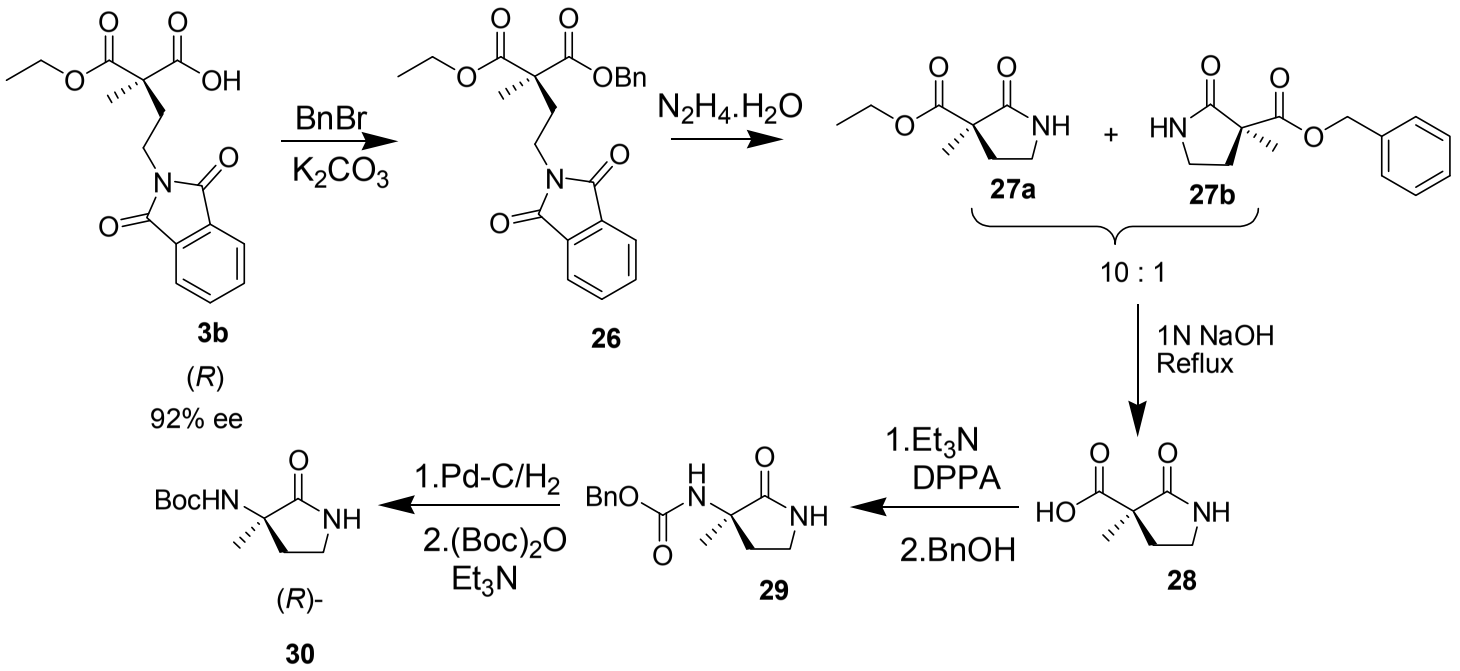
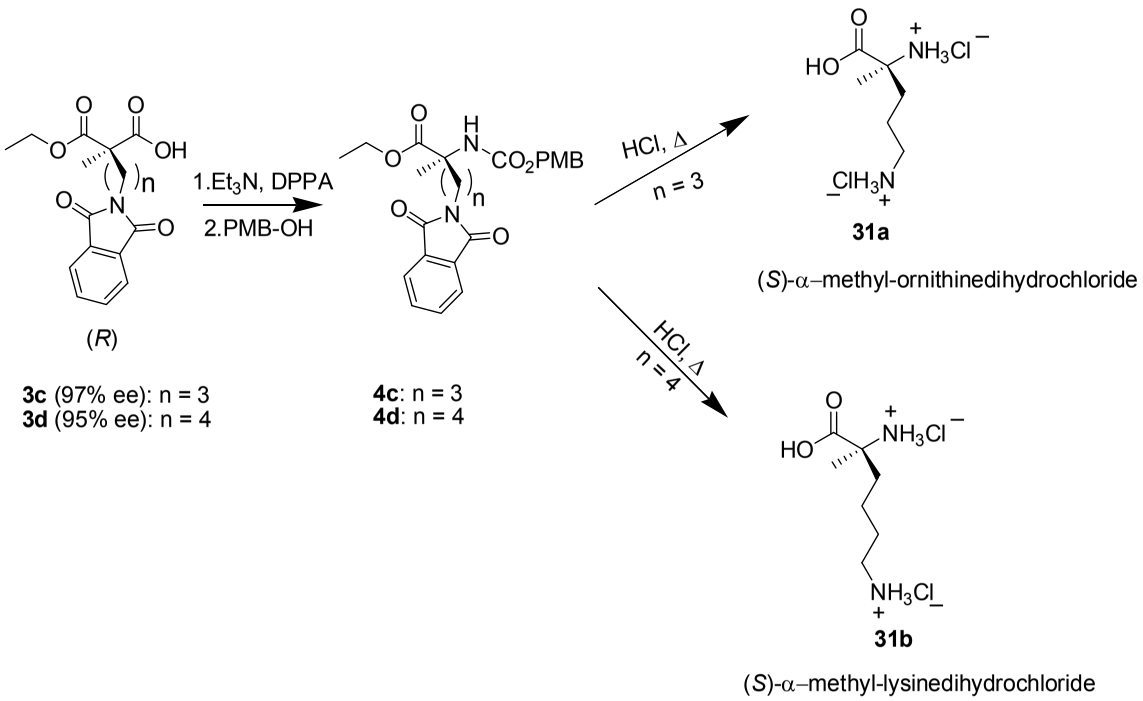
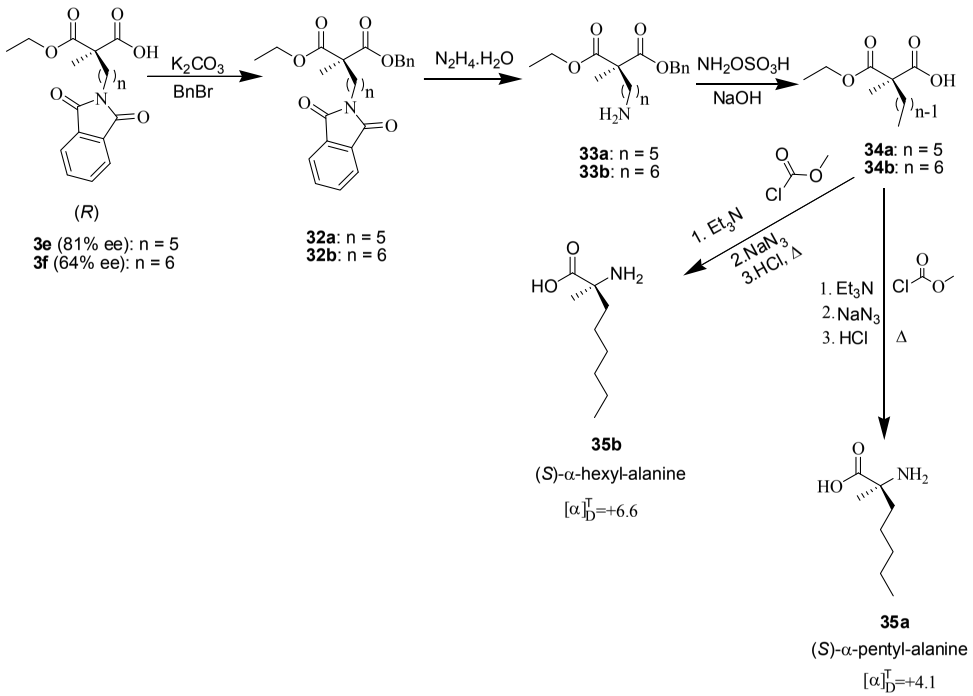
Supporting Information



Scheme 8: Stereochemical Configuration of **3b**



Scheme 9: Absolute configuration of **3c** and **3d**



Scheme 10: Absolute configuration of **3e** and **3f**

Synthesis of (*S*) – 1-benzyl -3-ethyl-2-methyl-2-(2-(1,3—dioxoisoindolin-2-yl)malonate (26): A 250 mL round bottom flask was charged with 10g of **2b** (31 mmol), 4.3 g of K_2CO_3 (31 mmol), 100 mL of anhydrous DMF, and a stirbar. A solution of 4.8g benzyl bromide (28 mmol) in 20 mL anhydrous DMF was slowly added over 15 minutes. The reaction was allowed to stir approximately 12 hr. under a nitrogen atmosphere. The reaction mixture was then diluted with 100 mL of water and the resulting mixture was washed with Et_2O (3 x 100 mL). The combined ether layer was washed with water (5 x 100 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by flash chromatography (40% Et_2O/Hexanes) providing 11g of **26** (27 mmol, 96%) as a colorless liquid. R_f= 0.2 (40% Et_2O/Hexanes). $[\alpha]_D^{24}$ = -3.08 (c = 1, $CHCl_3$). IR (cm^{-1}): 2980, 1773, 1708. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.33 (m, 5H), 5.15 (m, 2H), 4.10 (m, 2H), 3.74 (m, 2H), 2.28 (m, 2H), 1.56 (s, 3H), 1.16 (t, 3H, *J* = 7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 171.4, 171.3, 168.0, 135.5, 134.0, 132.0, 128.5, 128.3, 128.1, 123.0, 67.0, 61.0, 52.0, 33.8, 33.8, 20.0, 14.0. HRMS [$C_{23}H_{23}NO_6Na^+$]: calculated = 432.1417, found = 432.1406.

Synthesis of (*R*)-ethyl-3-methyl-2-oxopyrrolidine-3-carboxylate (27): A volume of 930 µL (10.2 mmol) 35% hydrazine in water was added to a solution of 3.8g (9.3 mmol) of **26** in 50 mL MeOH. The mixture was heated to reflux solvent overnight. A white precipitate was observed within an hour of reflux. The reaction mixture was allowed to cool to RT, and the resulting mixture was filtered. The filtrate was evaporated under reduced pressure. The resulting residue was taken up in CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography using 30%

Hexanes/EtOAc giving 1.2 g of a 10:1 mixture of **27a:27b** as a white solid. The mixture was recrystallized in cold Et_2O giving 1g (6 mmol, 64.5%) of pure **27a** as white crystals. R_f (**27a**) = 0.31 (30% Hexanes/EtOAc). MP = 63 ^{0}C. $[\alpha]_D^{23}$= +19.0 (c = 2, MeOH). IR (cm^{-1}): 3245, 2985, 1726, 1698, 1660. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.06 (bs, 1H), 4.20 (m, 2H), 3.47 (m, 1H), 3.36 (m, 1H), 2.64 (m, 1H), 2.02 (m, 1H), 1.45 (s, 3H), 1.28 (t, 3H, *J* = 7 Hz), ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 177.0, 172.0, 61.0, 51.0, 40.0, 34.0, 20.0, 14.0. HRMS [$C_8H_{13}NO_3Na^+$]: calculated = 194.0788, found = 194.0795.

(*R*) – 3- methyl-2-oxopyrrolidine- 3- carboxylic acid (28): An amount of 1.6g (9.4 mmol) of **27a** was dissolved in 15 mL ethanol. A volume of 7 mL 1N NaOH was added to the reaction mixture. The solution was brought to reflux solvent for an hour. The solution was cooled and acidified with HCl to pH 4. The water layer was concentrated at 35 ^{0}C under high vacuum. A volume of 10 mL MeOH was added to the residue and stirred for 5 min. The MeOH layer was decanted from the remaining solid and concentrated in vacuo giving 1g of **28** (6.9 mmol, 73%) as a white solid. MP = 155 ^{0}C. IR (cm^{-1}) = 3363, 3368, 2975, 2906, 1749, 1722, 1704, 1636, 1485. R_f = 0.17 (5% MeOH/ CH_2Cl_2). ^{1}H-NMR (CD_3OD, 400 MHz): δ 3.35 (m, 1H), 3.25 (m, 1H), 2.49 (m, 1H), 1.95 (m, 1H), 1.27 (s, 3H). ^{13}C-NMR (CD_3OD, 100 MHz): δ 179.6, 175.7, 52.1, 40.7, 35.0, 20.3. ESI-MS $[C_6H_{10}NO_3]^+$ = 143.1, observed = 143.2.

Benzyl (*R*)- 3- methyl- 2- oxopyrrolidin- 3- ylcarbamate (29): An amount of 1.77g (12.4 mmol) of **28** was dissolved in 50 mL of dry dichloroethane. A volume of 3.6 mL (26 mmol) Et_3N was added followed by 3.1 mL (13.6 mmol) diphenylphosphorylazide (DPPA). The solution was allowed to stir for 2 hrs at RT and then heated to reflux solvent for 2 hr. A volume of 1.8 mL (17.4 mmol) benzyl alcohol was then added and the solution was allowed to reflux solvent over night. The dichloroethane layer was concentrated in

vacuo and the residue was purified by flash chromatography (40% EtOAc/Hexanes) giving 1.97g of **29** as a white wax (7.9 mmol, 64%). R_f = 0.10 (40% EtOAc/Hexanes). IR (cm^{-1}) = 3225, 1725, 1693, 1657, 1536. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.33 (m, 5H), 6.75 (bs, 1H), 5.55 (bs, 1H), 5.06 (m, 2H), 3.34 (m, 2H), 2.52 (m, 1H), 2.31 (m, 1H), 1.40 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 178.2, 155.2, 136.2, 128.7, 128.3, 128.2, 66.7, 57.2, 39.0, 34.8, 22.3. HRMS [$C_{13}H_{16}N_2O_3Na^+$] = 271.1053, observed = 271.1047.

(*R*)- *tert*-butyl- 3- methyl- 2- oxopyrrolidin-3- ylcarbamate (30): An amount of 1.6 g (6.4 mmol) of **29** was dissolved in 25 mL MeOH in a pressure bottle. An amount of 0.16g Pd-C (10%) was added to the reaction mixture. The reaction mixture was allowed to shake under 20 psi H_2 pressure for 12 hr. The MeOH layer was filtered off through a Celite bed. The filtrate was concentrated *in vacuo* giving 0.66g of the free amine (5.8 mmol), which was then dissolved in 20 mL THF. A volume of 1.7mL (11.6 mmol) Et_3N was added to the reaction mixture. A solution of 1.5g $(BOC)_2O$ (6.9 mmol) in 10 mL THF was added to the reaction mixture drop wise. The reaction mixture was allowed to stir over night at RT. The THF was concentrated and the resulting residue was extracted with Et_2O and water. The ether layer was concentrated and the residue was rinsed with hexane giving 0.83g of the **30** (3.9 mmol, 61% over two steps) as a white solid. The characterization of **30** complied with the literature.[1] $[\propto]_D^{22}$ = -16 (c = 0.35, $CHCl_3$).

Synthesis of (*S*)- 2- methyl-ornithinedihydrochloride (31a): A volume of 30 mL 6N HCl solution was added to 1g of **4c** (2.1 mmol) in a round bottom flask. The reaction mixture was heated to reflux solvent for 24 hr. The aqueous layer was evaporated to dryness under reduced pressure. The resulting gummy solid was triturated with EtOAc multiple times leading to 0.4g (1.8 mmol, 86%) of **31a** as a white solid. All the characterization data of the product complied with the literature.[2] $[\alpha]_D^{24}$ = + 6.86 (c = 0.7, 4N HCl).

Synthesis of (*S*)- 2- methyl-lysinedihydrochloride (31b): A volume of 30 mL 6N HCl solution was added in 1g of **4d** (2.1 mmol) in a round bottom flask. The reaction mixture was heated to reflux solvent for 24 hr. The aqueous layer was evaporated to dryness under reduced pressure. The resulting gummy solid was triturated with EtOAc multiple times leading to 0.36g (1.5 mmol, 71%) of **31b** as a white solid. All the characterization data of the product complied with the literature.[2] $[\alpha]_D^{24} = +7.25$ (c = 1, 4N HCl).

General synthetic procedure for the formation 32a, and 32b: An amount of **3e**/**3f** (1 equivalent) was dissolve in DMF under N_2. A calculated amount of K_2CO_3 (1.2 equivalent) was added to the solution. A measured volume of benzyl bromide (0.95 equivalents) was added to the reaction mixture. The reaction was allowed to stir over night under N_2. Water was added to the reaction mixture and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined ether layer was given a water wash (10 x 50 mL). The Et_2O layer was dried over $MgSO_4$, concentrates, and the residue was purified by flash chromatography (40% Et_2O/ Hexanes) giving the product as a colorless oil.

(*S*)- 1- benzyl 3- ethyl-2- methyl-2-(5-(1,3-dioxoisoindolin-2-yl)pentyl)malonate (32a): 32a was synthesized following the general synthetic procedure for the formation of **32a/32b** using 5g (14 mmol) of **3e**. An amount of 5.2g of **32a** (11.5 mmol, 82%) was obtained as a colorless viscous oil after purification (40% Et_2O/Hexanes). R_f = 0.16 (40% Et_2O/Hexanes). IR (cm^{-1}) = 2938, 1770, 1700. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.32 (m, 5H), 5.15 (m, 2H), 4.11 (q, 2H, *J* = 7Hz), 3.64 (t, 2H, *J* = 7Hz), 1.85 (m, 2H), 1.64 (m, 2H), 1.41 (s, 3H), 1.28 (m, 4H), 1.15 (t, 3H, *J* = 7Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 172.2, 172.0,

168.4, 136.0, 134.0, 132.2, 128.4, 128.2, 128.0, 123.2, 66.6, 61.1, 54.0, 38.0, 35.4, 28.2, 27.0, 24.0, 20.0, 14. HRMS [$C_{26}H_{29}NO_6Na^+$] calculated = 474.1887, observed = 474.1905.

(*S*)- 1- benzyl 3- ethyl-2-methyl-2-(6-(1,3-dioxoisoindolin-2-yl)hexyl)malonate (32b): 32b was synthesized following the general synthetic procedure for the formation of **32a/32b** using 5g (13.3 mmol) of **3f**. An amount of 5.3g of **32b** (11.4 mmol, 86%) was obtained as a colorless viscous oil after purification (40% Et_2O/Hexanes). R_f = 0.30 (40% Et_2O/Hexanes). IR (cm^{-1}) = 2936, 1771, 1706. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.32 (m, 5H), 5.15 (m, 2H), 4.11 (q, 2H, *J* = 7Hz), 3.64 (t, 2H, *J* = 7Hz), 1.85 (m, 2H), 1.64 (m, 2H), 1.41 (s, 3H), 1.30 (m, 4H), 1.17 (m, 5H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 172.3, 172.1, 168.4, 136.0, 134.0, 132.2, 128.5, 128.2, 128.0, 123.2, 66.7, 61.1, 54.0, 38.0, 35.5, 29.4, 28.5, 26.5, 24.2, 20.0, 14. HRMS [$C_{27}H_{31}NO_6Na^+$] calculated = 488.2043, observed = 488.2030.

General synthetic procedure for the formation of 33a, and 33b: A measured amount of **32a/32b** (1 equivalent) was dissolved in methanol. A calculated amount of 35% $N_2H_4.H_2O$ in water (1.2 equivalents) was added to the reaction mixture. The reaction mixture was heated to reflux solvent for 6 hrs. The reaction mixture was cooled to RT and the white precipitate was filtered off. The MeOH layer was concentrated *in vacuo* and the gummy solid was taken up in CH_2Cl_2 leading to more white precipitate. The white precipitate is again removed by filtration and the CH_2Cl_2 layer was again concentrated *in vacuo* giving pure product as colorless oil.

(*S*)-1-benzyl-3-ethyl-2-(5-aminopentyl)-2-methylmalonate (33a): 33a was prepared from **32a** following the general synthetic procedure for the formation of **33a/33b** using 5g of **32a** (11 mmol). An amount of 3.3g (10.3 mmol, 94%) of **33a** was obtained as a

colorless viscous oil. R_f = 0.12 (3% MeOH/CH_2Cl_2). IR (cm^{-1}) = 3100, 3000, 2938, 1724. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.32 (m, 5H), 5.15 (m, 2H), 4.11 (q, 2H, *J* = 7Hz), 2.65 (t, 2H, *J* = 7Hz), 1.87 (t, 2H, *J* = 8Hz), 1.61 (bs, 2H), 1.41 (m, 5H), 1.24 (m, 7H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 172.3, 172.2, 136.0, 128.5, 128.2, 128.0, 67, 61.2, 54.0, 42.0, 35.4, 33.5, 27.0, 24.0, 20.0, 14.0. HRMS [$C_{18}H_{27}NO_4Na^+$] calculated = 344.1832, observed = 344.1823.

(*S*)-1-benzyl-3-ethyl-2-(6-aminohexyl)-2-methylmalonate (33b): 33b was prepared from **32b** following the general synthetic procedure for the formation of **33a/33b** using 5g of **32b** (10.7 mmol). An amount of 3g (8.9 mmol, 83%) of **33b** was obtained as a colorless viscous oil. R_f = 0.14 (3% MeOH/CH_2Cl_2). IR (cm^{-1}) = 3300, 2932, 1726. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.25 (m, 5H), 5.07 (m, 2H), 4.04 (q, 2H, *J* = 7Hz), 2.68 (bs, 2H), 2.61 (t, 2H, *J* = 7Hz), 1.77 (t, 2H, *J* = 7Hz), 1.33 (m, 5H), 1.14 (m, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 171.3, 171.2, 135.0, 127.5, 127.2, 127.0, 66.0, 60.1, 53.0, 41.0, 34.5, 32.0, 28.5, 25.5, 23.1, 19.0, 13.0. HRMS [C19H29NO4Na$^+$] calculated = 358.1988, observed = 358.1983.

General synthetic procedure for the formation of 34a, and 34b: **34a/34b** were synthesized from **33a/33b** following a literature procedure.[3] A measured amount of **33a/33b** (1 equivalent) was dissolved in 24 mL 2:1 2.5M NaOH/EtOH mixture. The solution was cooled to 0 ^{0}C and a measured amount of NH_2OSO_3H (2 equivalent) was added to the solution. The solution was stirred at 0 ^{0}C for 35 minutes. At that point an additional amount of NH_2OSO_3H (1 equivalent) and 5 mL 2.5 M NaOH were added to the reaction mixture. The reaction was allowed to stir at 0 ^{0}C foranother 90 minutes and then allowed to warm to RT overnight. The reaction mixture was

acidified to pH 1. The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and purified in 1:1 Et_2O/Hexanes giving the product as a colorless oil.

(*R*)- 2-(ethoxycarbonyl)-2-methylheptanoic acid (34a): **34a** was prepared from **33a** following the general synthetic procedure of making **34a/34b** using 3g of **33a** (9.3 mmol). An amount of 1.2g of **34a** was obtained (5.5 mmol, 59%) after purification. R_f = 0.49 (50% Et_2O/Hexanes). IR (cm^{-1}) = 2956, 2930, 2871, 1705. $[\propto]_D^{25}$ = + 3.15 (c = 2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.38 (bs, 1H), 4.21 (q, 2H, *J* = 7Hz), 1.87 (m, 2H), 1.44 (s, 3H), 1.27 (m, 9H), 0.88 (t, 3H, *J* = 7Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 178.0, 172.5, 61.5, 53.6, 35.7, 32.0, 24.0, 22.3, 20.0, 14.0, 13.9. HRMS [$C_{11}H_{20}O_4Na^+$] calculated = 239.1255, observed = 239.1253.

(*R*)- 2-(ethoxycarbonyl)-2-methyloctanoic acid (34b): **34b** was prepared from **33b** following the general synthetic procedure of making **34a/34b** using 3g of **33b** (8.9 mmol). An amount of 1.3g pure **34b** was obtained (5.6 mmol, 63%) after purification. R_f = 0.51 (50% Et_2O/Hexanes). IR (cm^{-1}) = 2955, 2927, 2858, 1705. $[\propto]_D^{22}$ = + 2.2 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 400MHz): δ 4.21 (q, 2H, *J* = 7Hz), 1.87 (m, 2H), 1.44 (s, 3H), 1.28 (m, 11H), 0.88 (t, 3H, *J* = 7Hz). ^{13}C-NMR ($CDCl_3$, 100MHz): δ 178.0, 172.6, 61.6, 53.6, 35.8, 31.4, 29.4, 24.2, 22.6, 20.0, 14.1. 14.0. HRMS [$C_{12}H_{22}O_4Na^+$] calculated = 253.1410, observed = 253.1409.

General synthetic procedure for the formation of 35a, and 35b: A measured amount of **34a/34b** (1 equivalent) was dissolved in 3 mL of H_2O, and 1 mL of acetone was added to the solution. A solution of Et_3N (1.2 equivalent) in 1 mL acetone was added to the reaction mixture drop wise followed by a solution of methylchloroformate (1.55 equivalent) in 1 mL acetone. The reaction was allowed to stir for 30 minutes at RT. A solution of NaN_3 (1.56 equivalent) in 3 mL H_2O was added to the reaction mixture and the

mixtures was stirred for 2hr. The reaction mixture was then poured into 25 mL of ice cold water. The water layer was extracted with ether (3 x 50 mL). The combined ether layer was dried over $MgSO_4$, concentrated *in vacuo* giving the acylazide as a colorless oil. The acylazide was dissolved in toluene and heated to reflux solvent for 2 hr. The toluene was concentrated *in vacuo* giving the isocyanate as yellowish oil. A volume of 10 mL 4M HCl was added to the isocyanate and the mixture was heated to reflux solvent for 4 hr. The water layer was concentrated under reduced pressure giving the (*S*)-α-alkyl-alaninehydrochloride as a pale yellowish solid. The **35a/35b** HCl salt was then dissolved in MeOH and $NaHCO_3$ was added portion wise to neutralize it to (S)-α-alkyl-alanine (**35a/35b**). The MeOH layer was filtered and concentrated giving **35a/35b** as a white solid.

Synthesis of (*S*)-α-pentylalanine (35a): 35a was prepared following the general synthetic procedure for the formation of **35a/35b** using 1g of **34a** (5 mmol). An amount of 0.5g (3 mmol, 60%) of (*S*)-α-pentylalanine (**35a**) was obtained as a white solid after neutralization. All the characterization data of **35a** complied with the literature.[4, 5] $[\propto]_D^{25} = +4.1$ (c = 1, MeOH).

Synthesis of (*S*)-α-hexylalanine (35b): 35b was prepared following the general synthetic procedure for the formation of **35a/35b** using 1g of **34b** (4.6 mmol). An amount of 0.55g (3.4 mmol, 74%) of (*S*)-α-pentylalanine (**35b**) was obtained as a white solid after neutralization. All the characterization data of **35b** complied with the literature.[4, 5] $[\propto]_D^{25} = +6.7$ (c = 0.15, MeOH).

Specific Binding of Vapreotide analogue (25) against IMR 32 cells: Table 2 illustrates the specific binding experiments of Vapreotide analogue (**25**) against IMR 32 human neuroblastoma cells that are known to over express SSTR2.[6] In the binding assay ^{111}In-Pentetreotide, which is known to effectively bind to SSTR2, was used as the radio ligand (Hot ligand). In addition, Octreotide

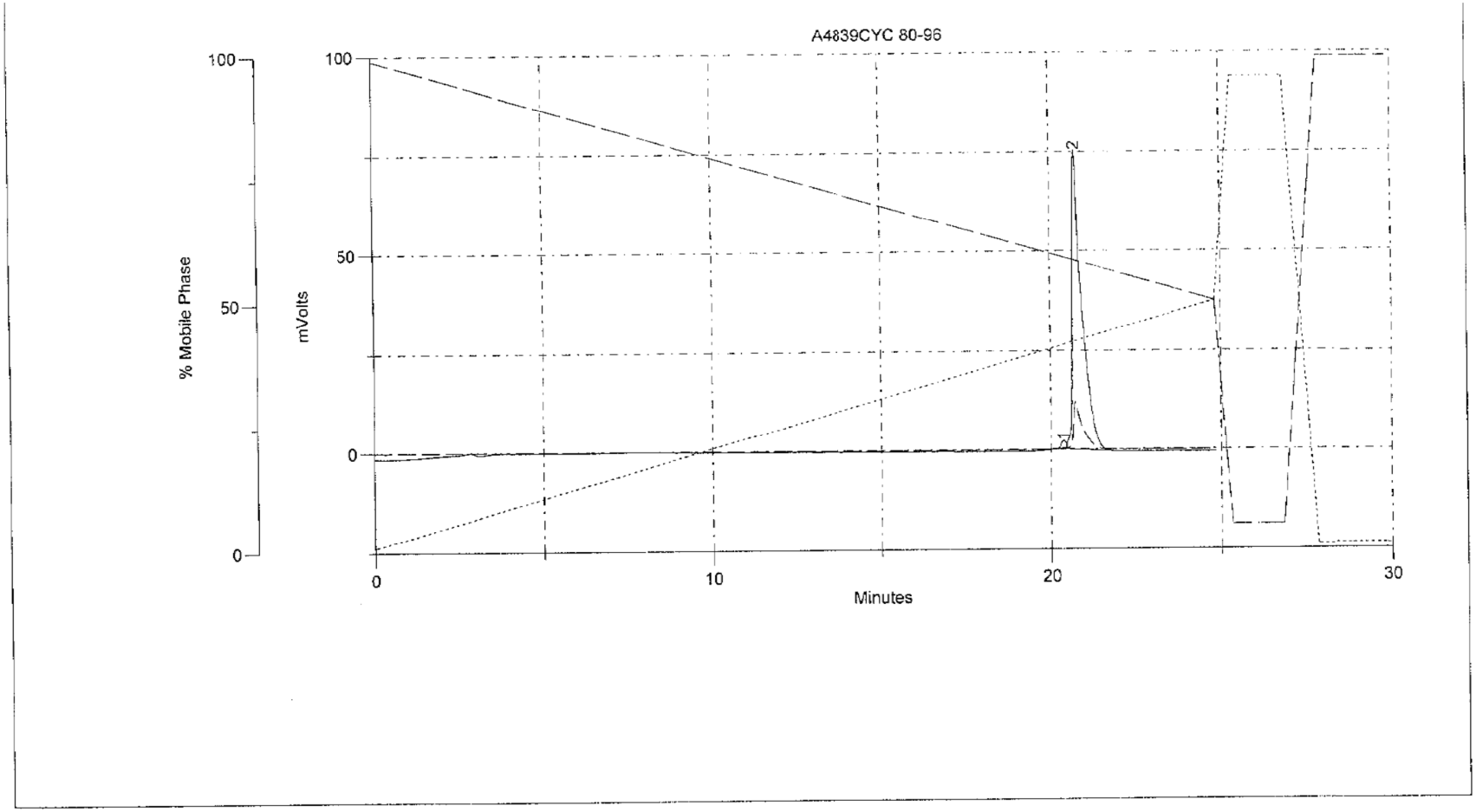
acetate, which is known to have high selectivity for SSTR2, was used as a positive control (Cold ligand 1) to compete with the ^{111}In-Pentetreotide.[6] The Vapreotide analogue (**25**, Cold ligand 2) was allowed to compete with the ^{111}In-Petetreotide as well (Cold ligand 2). Cells were harvested, washed and counted in gamma counter to determine the quantity of the ^{111}In-Pentetreotide (CPM) bound to the cells. The specific binding of each cold ligand was determined from the equation below based on the amount of ^{111}In-Pentetreotide bound to the IMR 32 cells as obtained from the gamma counter.

Specific binding of Octreotide Acetate in CPM (cold ligand 1) = competitive binding of ^{111}In-Pentetreotide and Octreotide Acetate in CPM (Hot + Cold 1) – binding of ^{111}In-Pentetreotide in CPM (Hot)

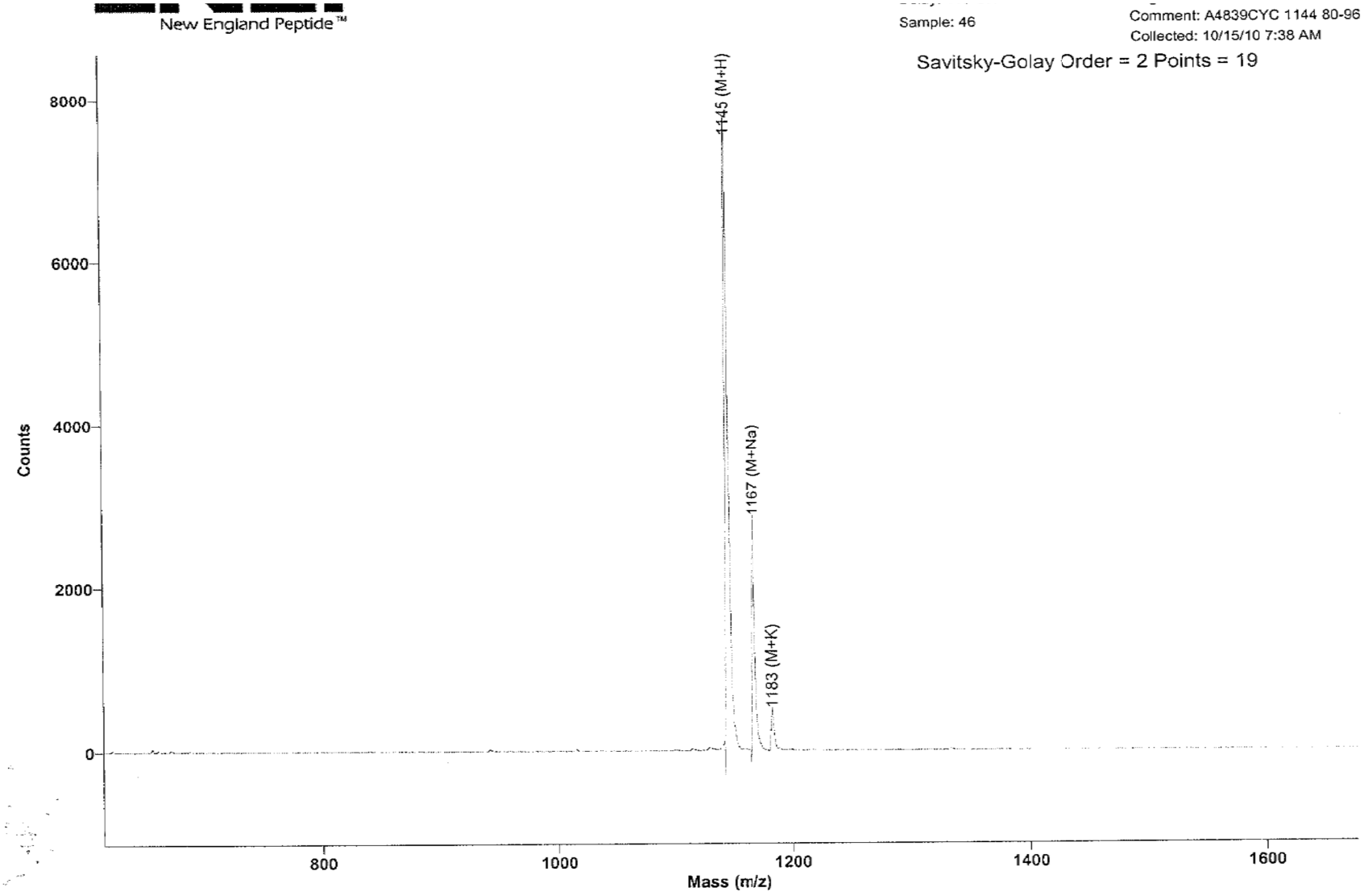
Specific Binding of Vapreotide analogue (**25**, cold ligand 2) = competitive binding of ^{111}In-Pentetreotide and Vapreotide (**35**) in CPM (Hot + Cold 2) – binding of ^{111}In-Pentetreotide in CPM (Hot)

Competitor: Octreotide Acetate (Cold 1)	CPM (Hot)	CPM (Hot + Cold)	CPM Specific binding (Hot - Hot + Cold)
	2591	317	2663.0
	3096	332	
	3238	287	
Mean CPM	2975	312	
Standard Deviation	340	22.9	
Competitor: Vapreotide (Cold 2) (**25**, **Figure 2**) with (*S*)-α-methyl-α-lysine	3272	4284	-78.3
	4062	3415	
	3574	3444	
Mean CPM	3636	3714.3	
Standard Deviation	398.6	493.6	
Total CPM added			348,315
Background CPM			40
Radio Ligand Used			^{111}In-Pentetreotide (Hot)

Table 2: Specific binding assay of the Vapreotide (**25**) against IMR 32 cell line



	Inj. Number	Peak Name	R. Time	Area	Area %	Sample Descrip.							
1	12.00	1	20.36	32855.40	1.34	4839CYC 80-9							
2	12.00	2	20.73	2419931.00	98.66	4839CYC 80-9							



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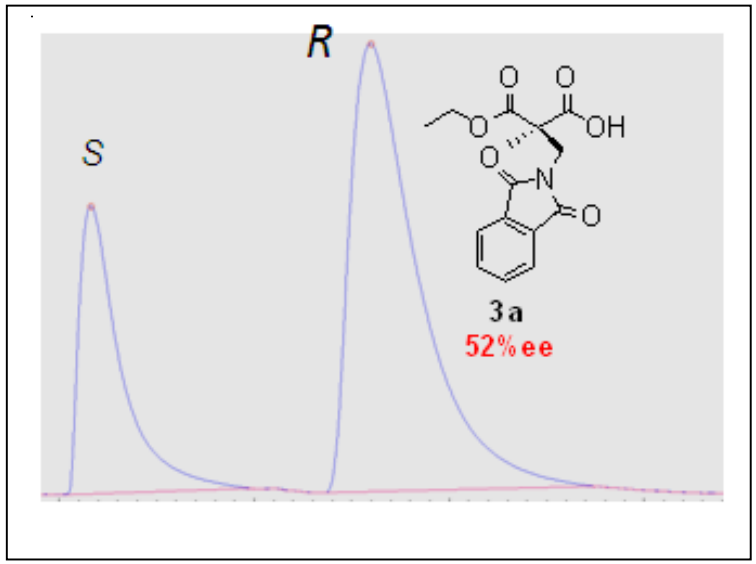
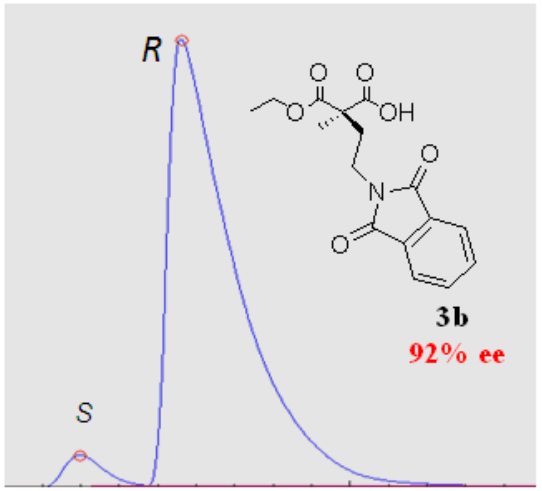
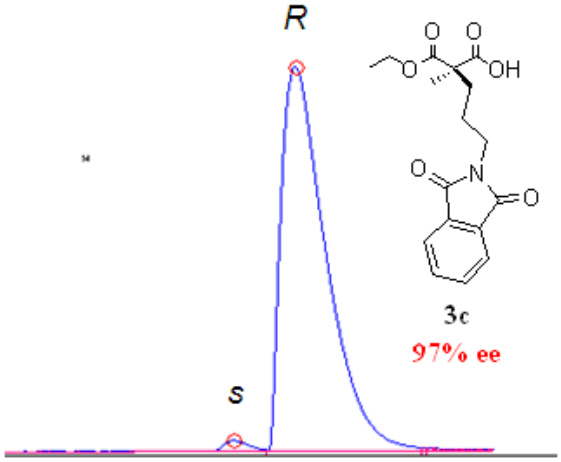
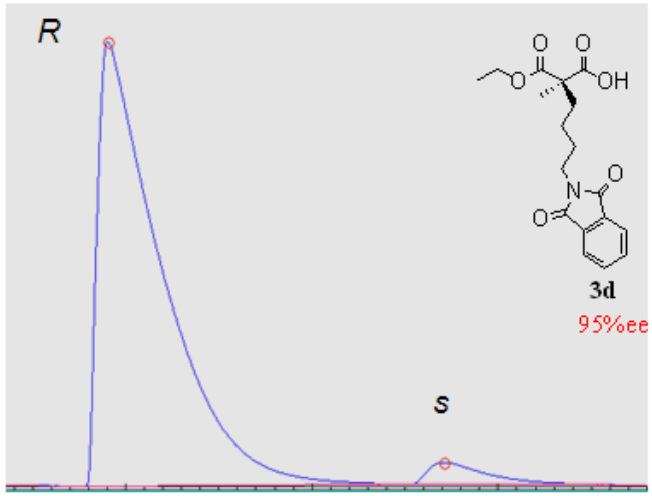
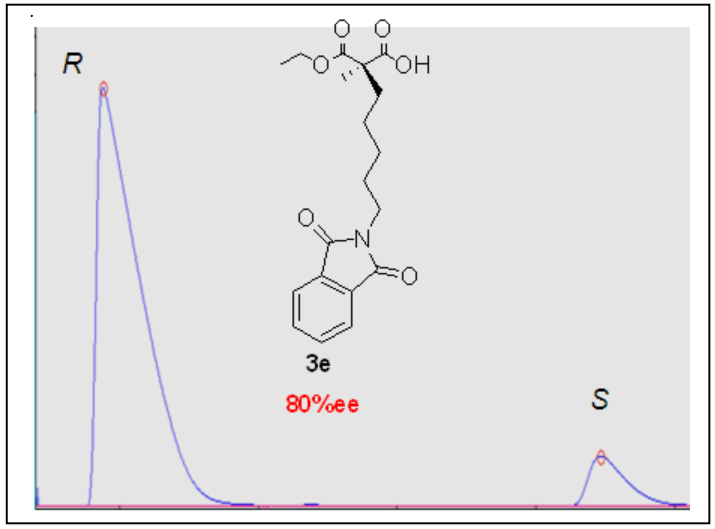


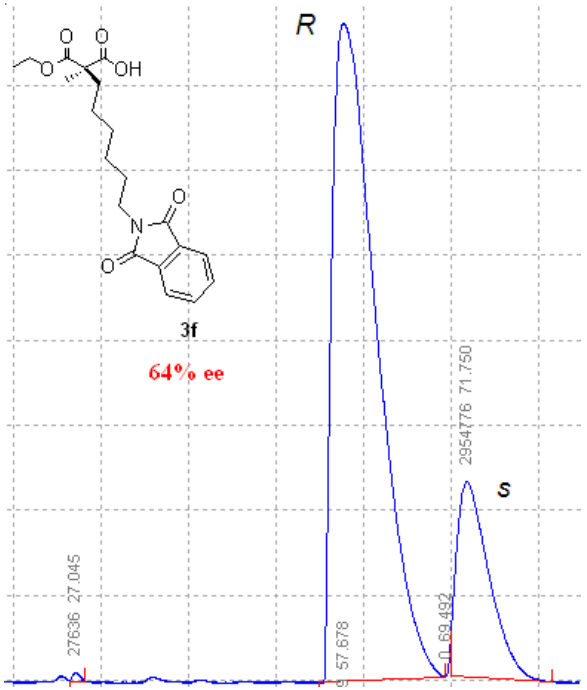




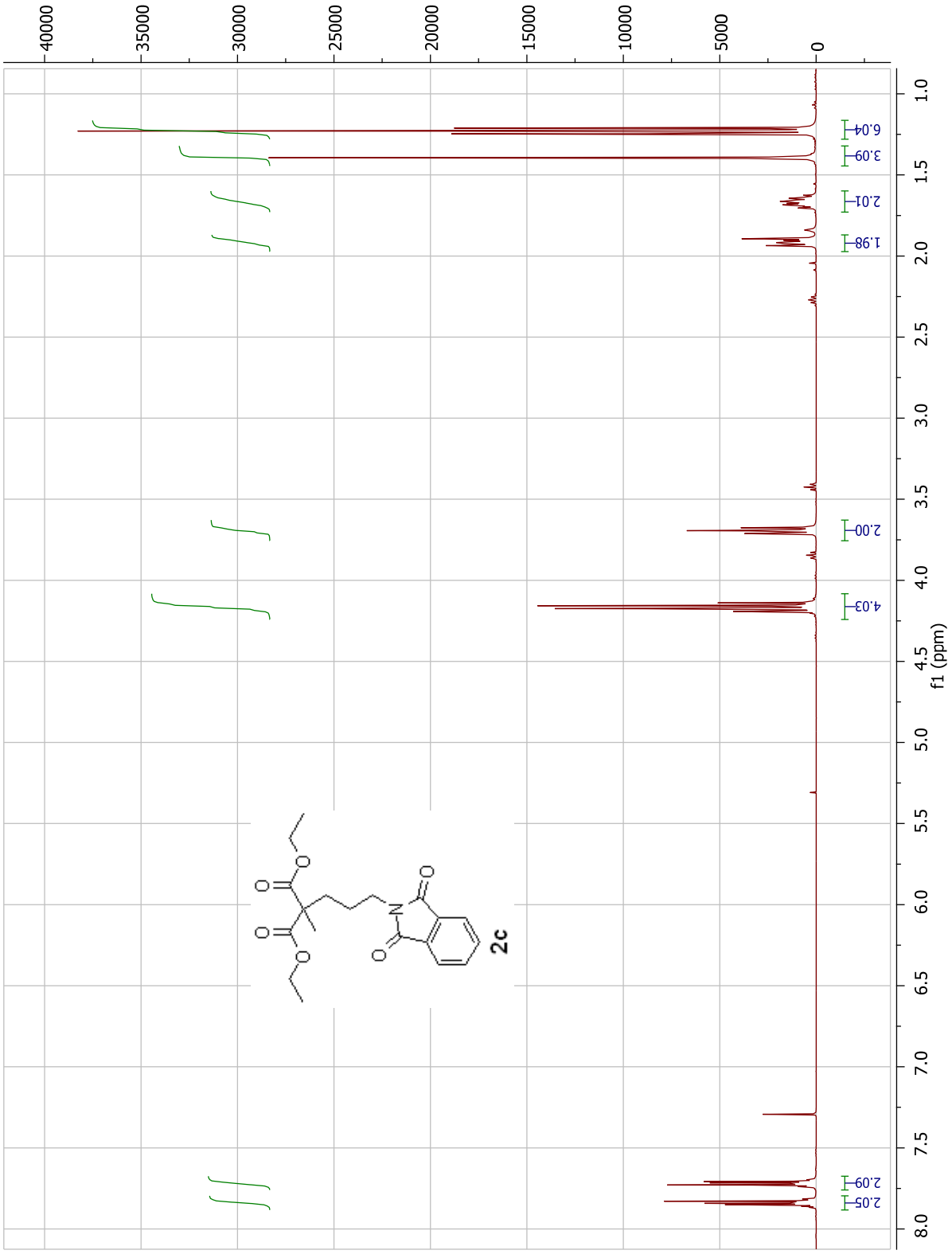


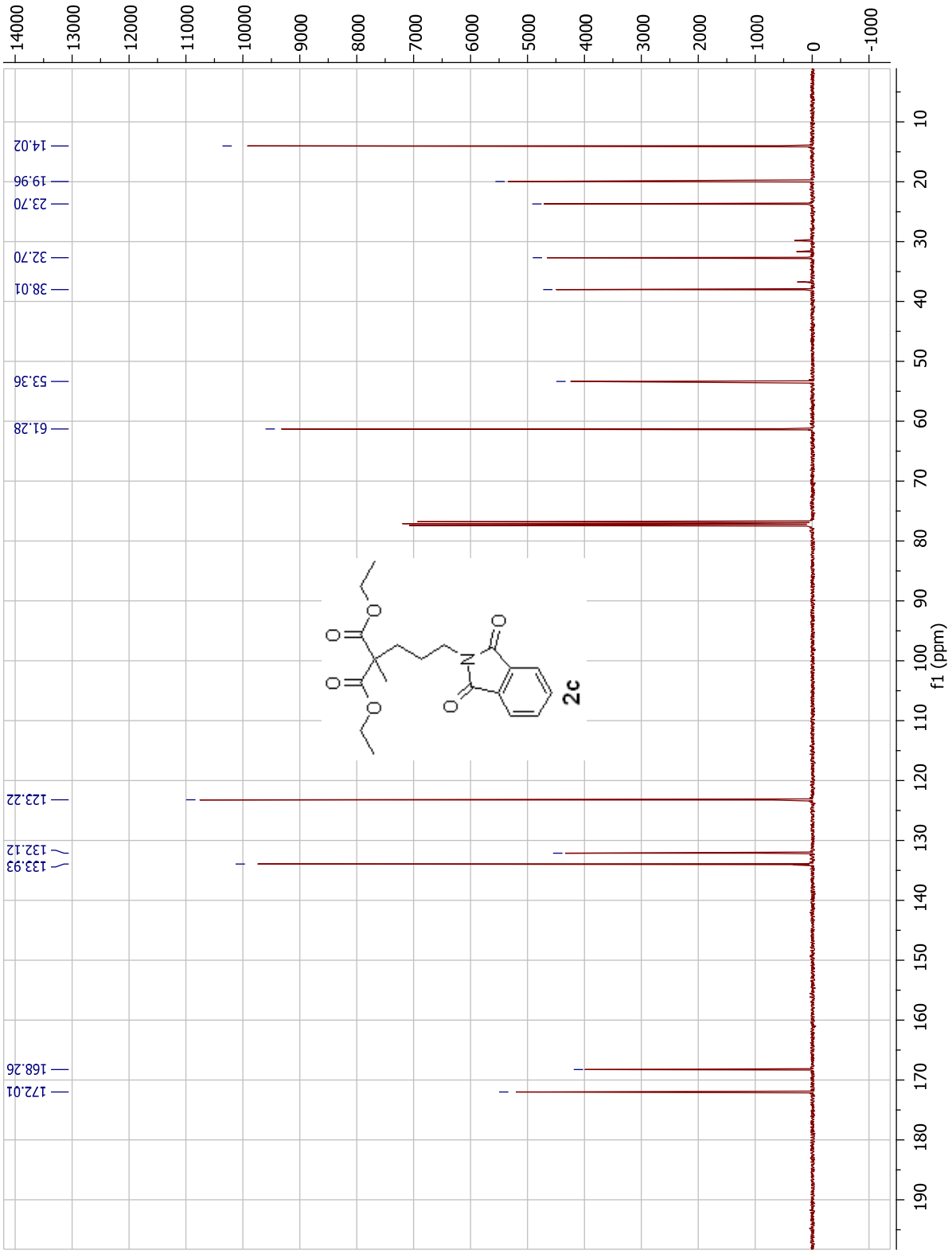
Chiral HPLC traces of PLE hydrolyzed half-esters

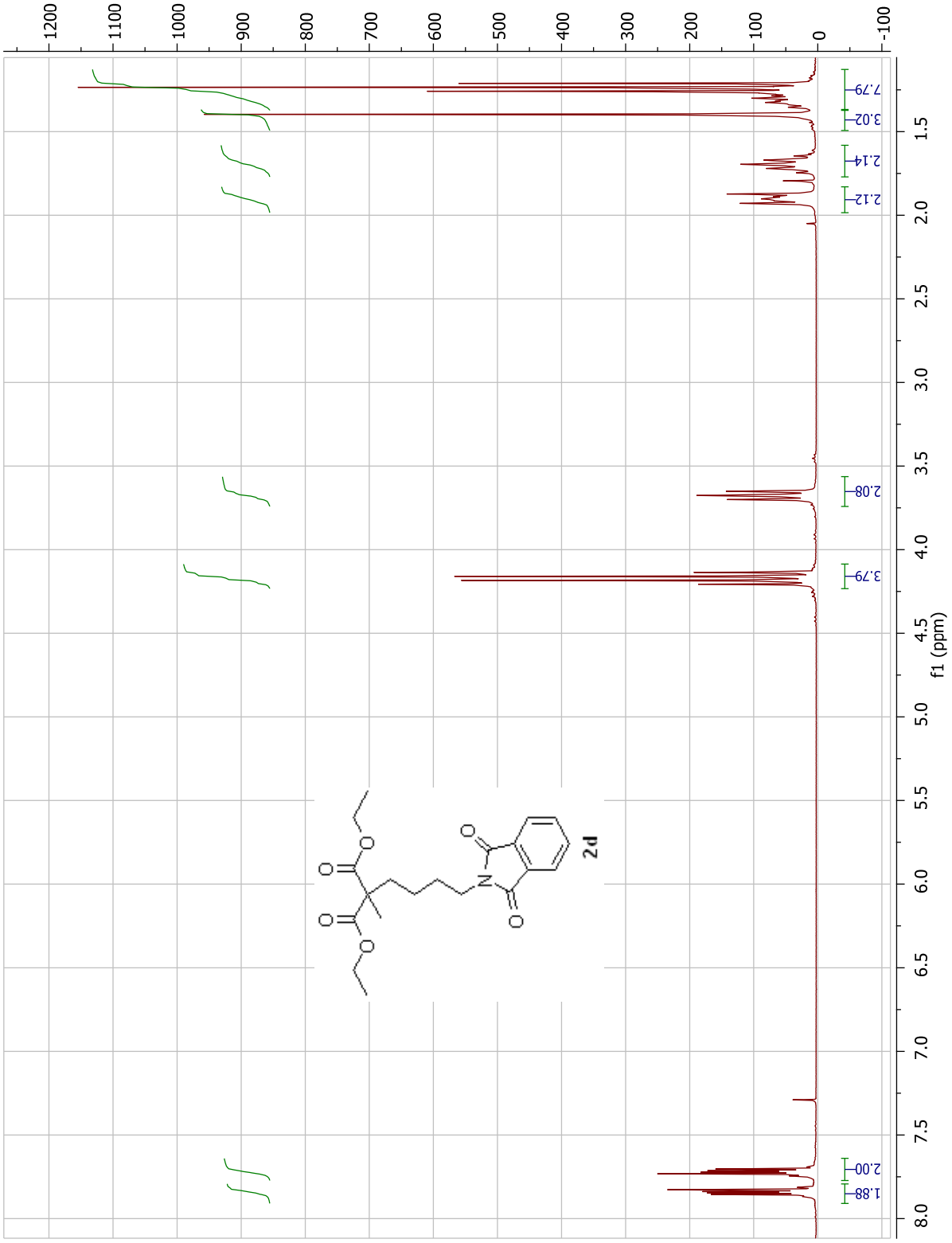


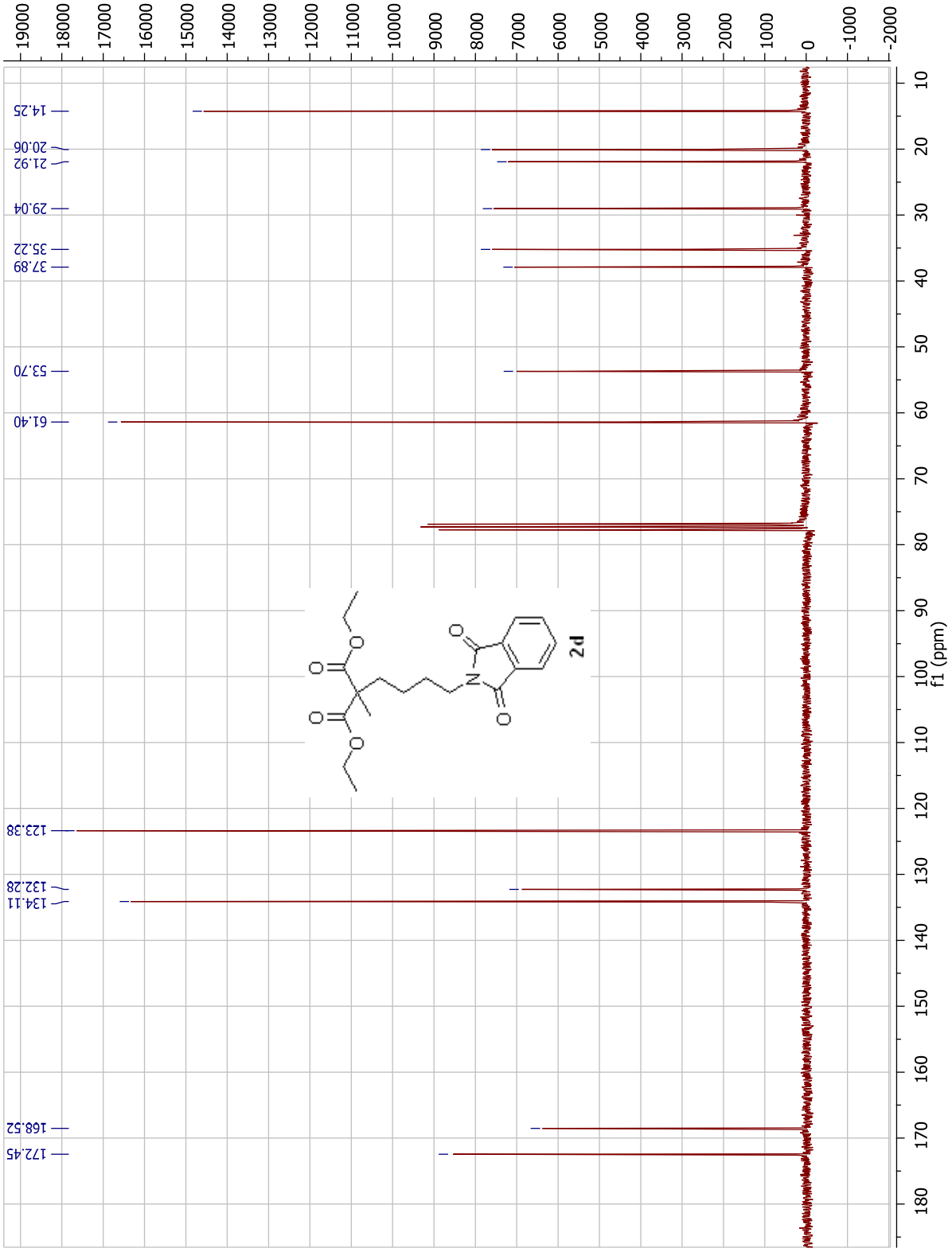


HPLC traces of PLE hydrolyzed half-esters





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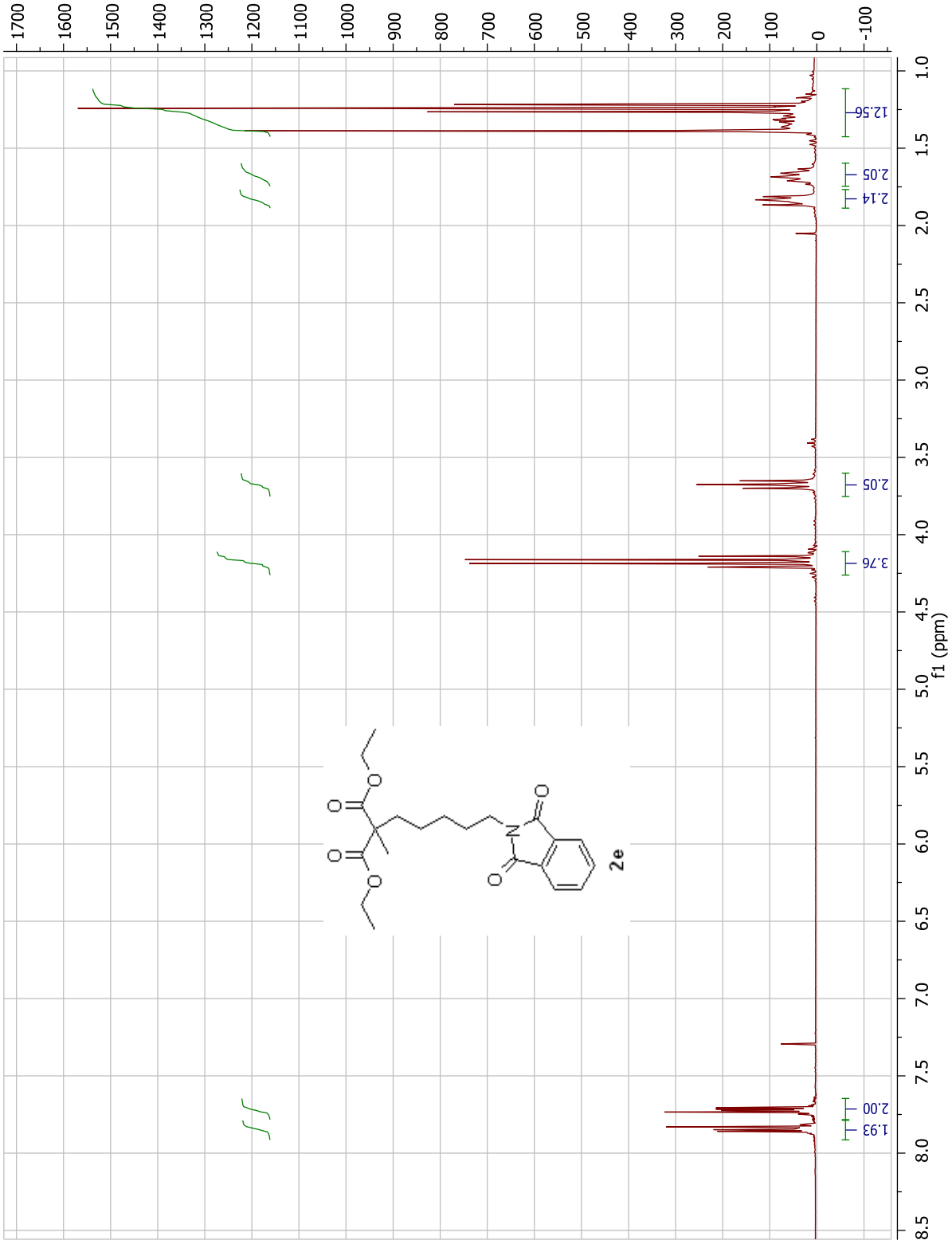
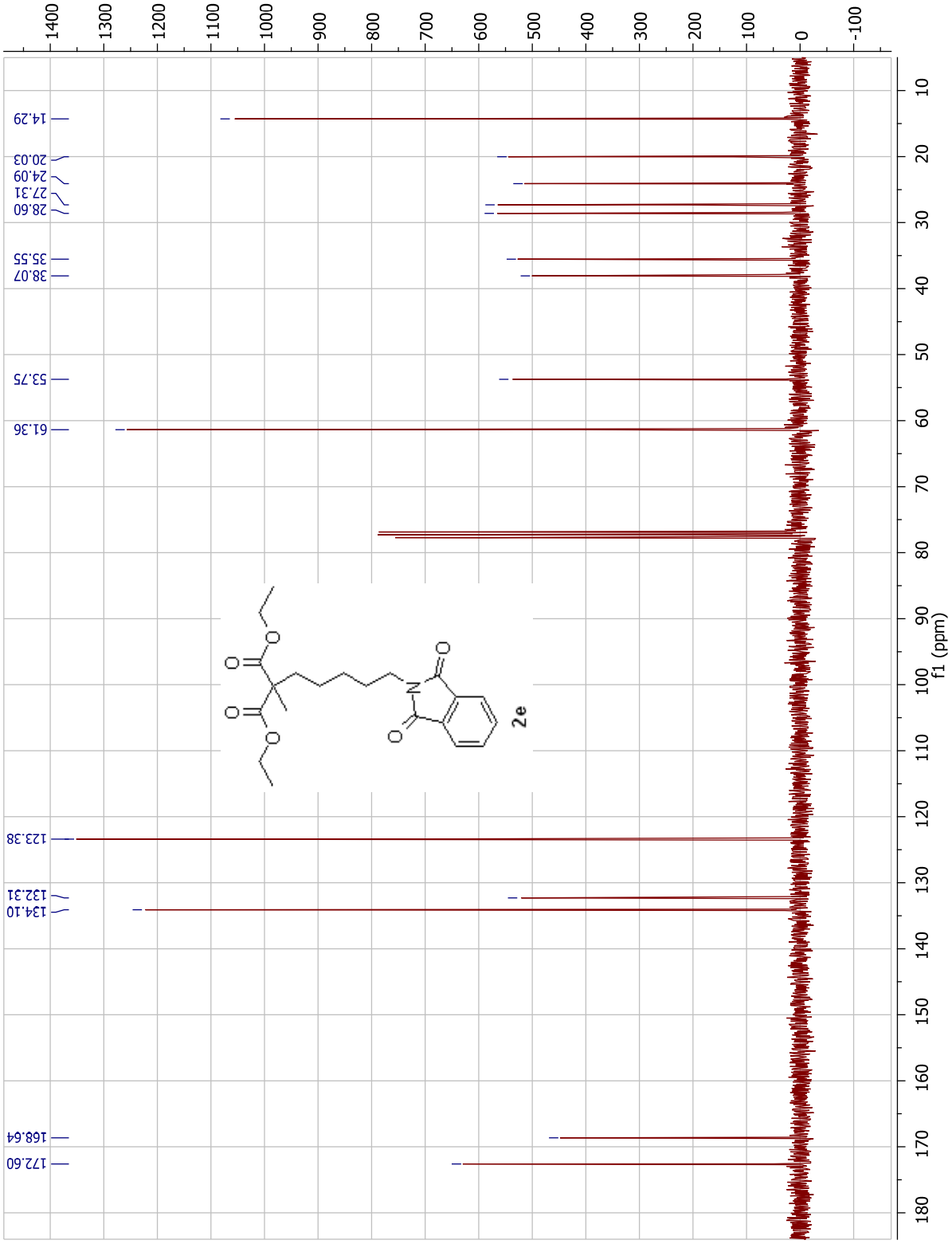
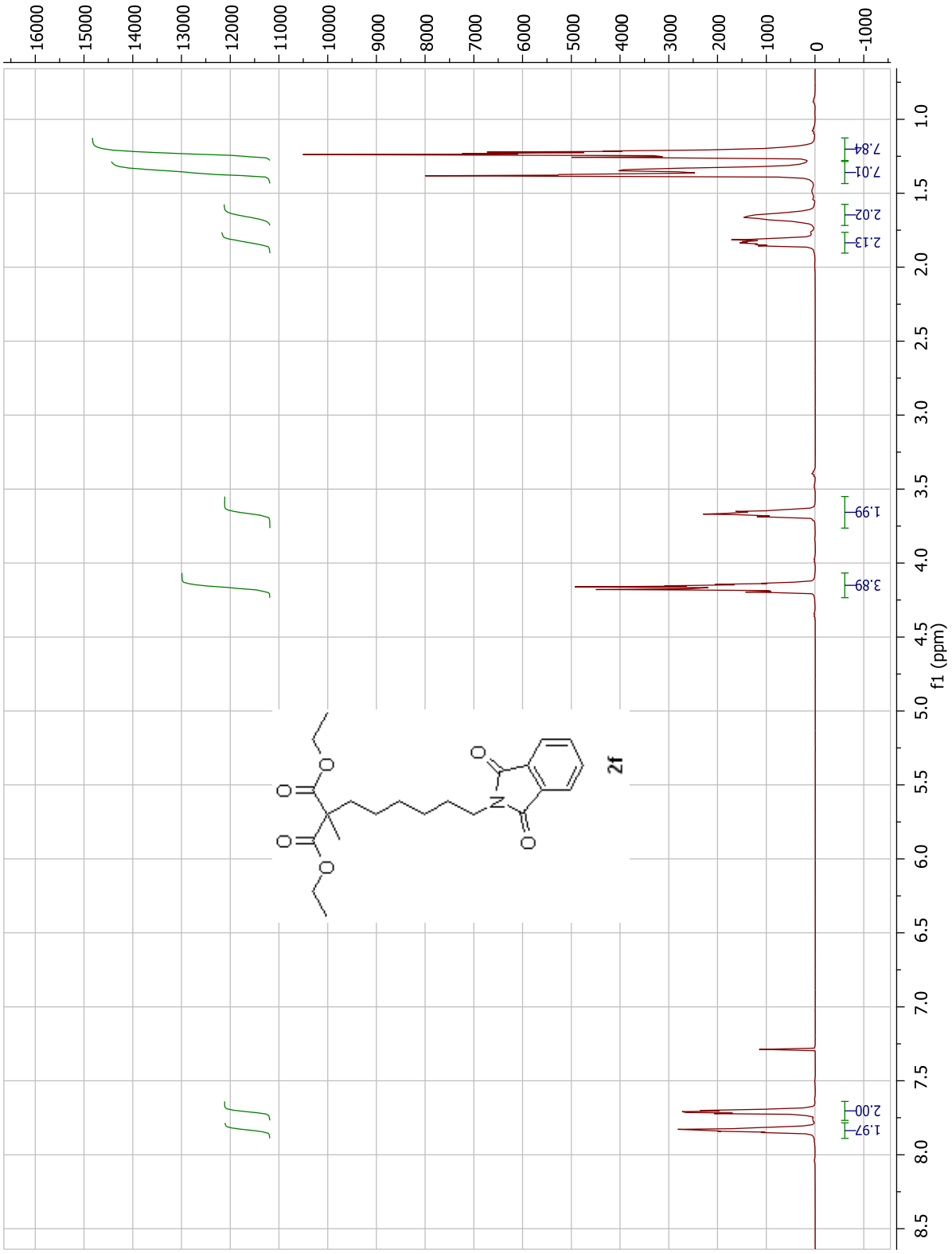
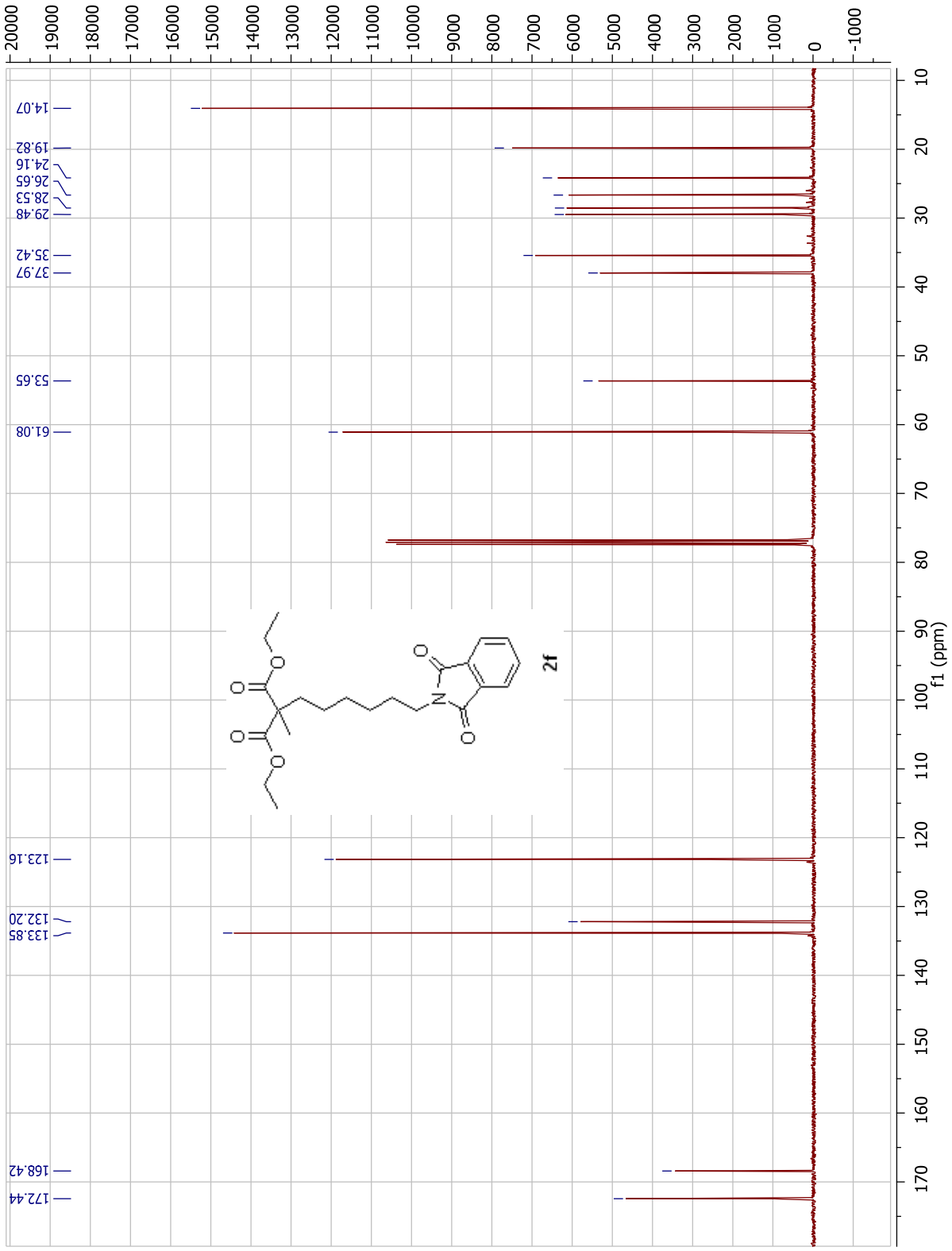
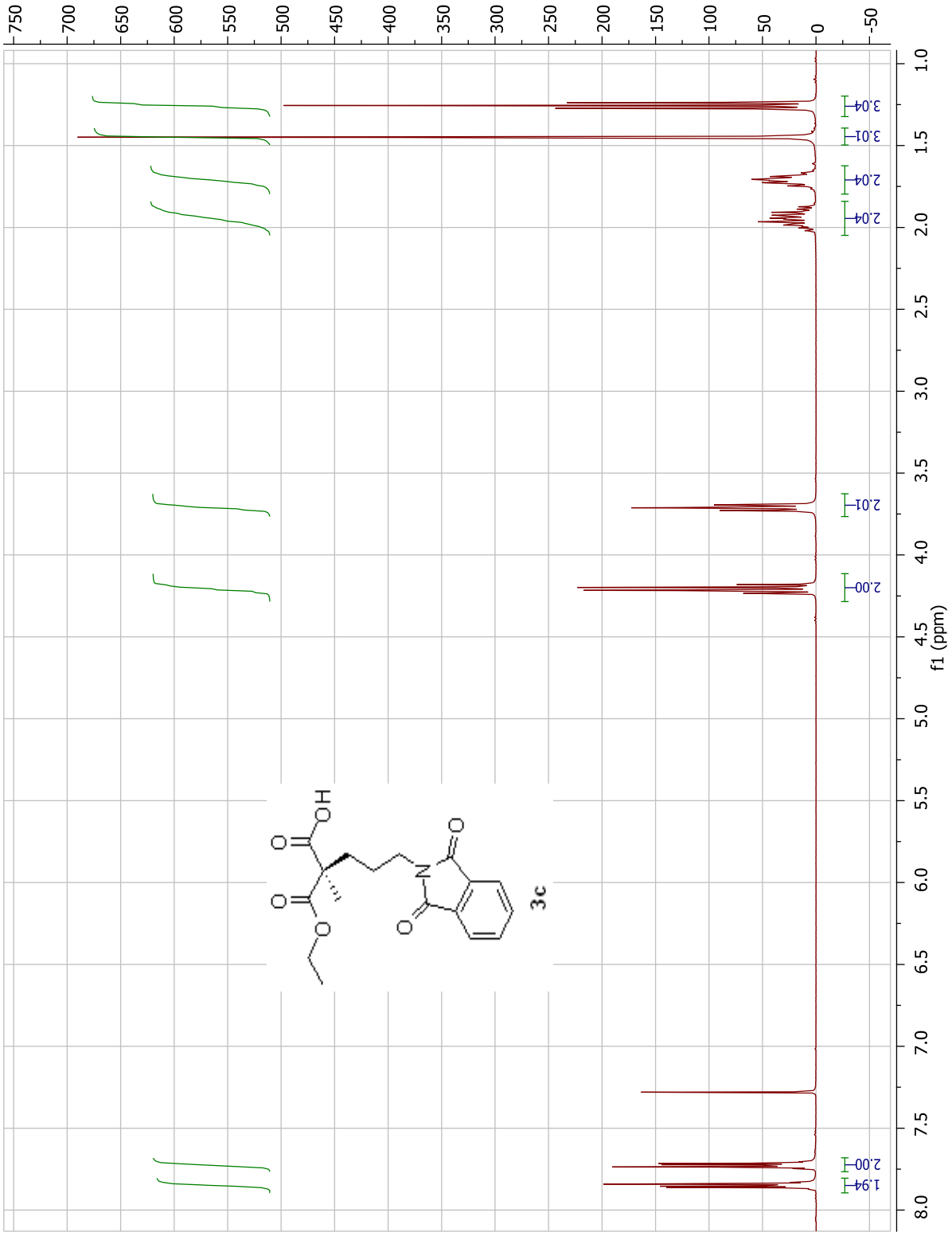
20.06
21.92
29.04
35.22
37.89
53.70
61.40
123.38
132.28
134.11
168.52
172.45
2d
f1 (ppm)

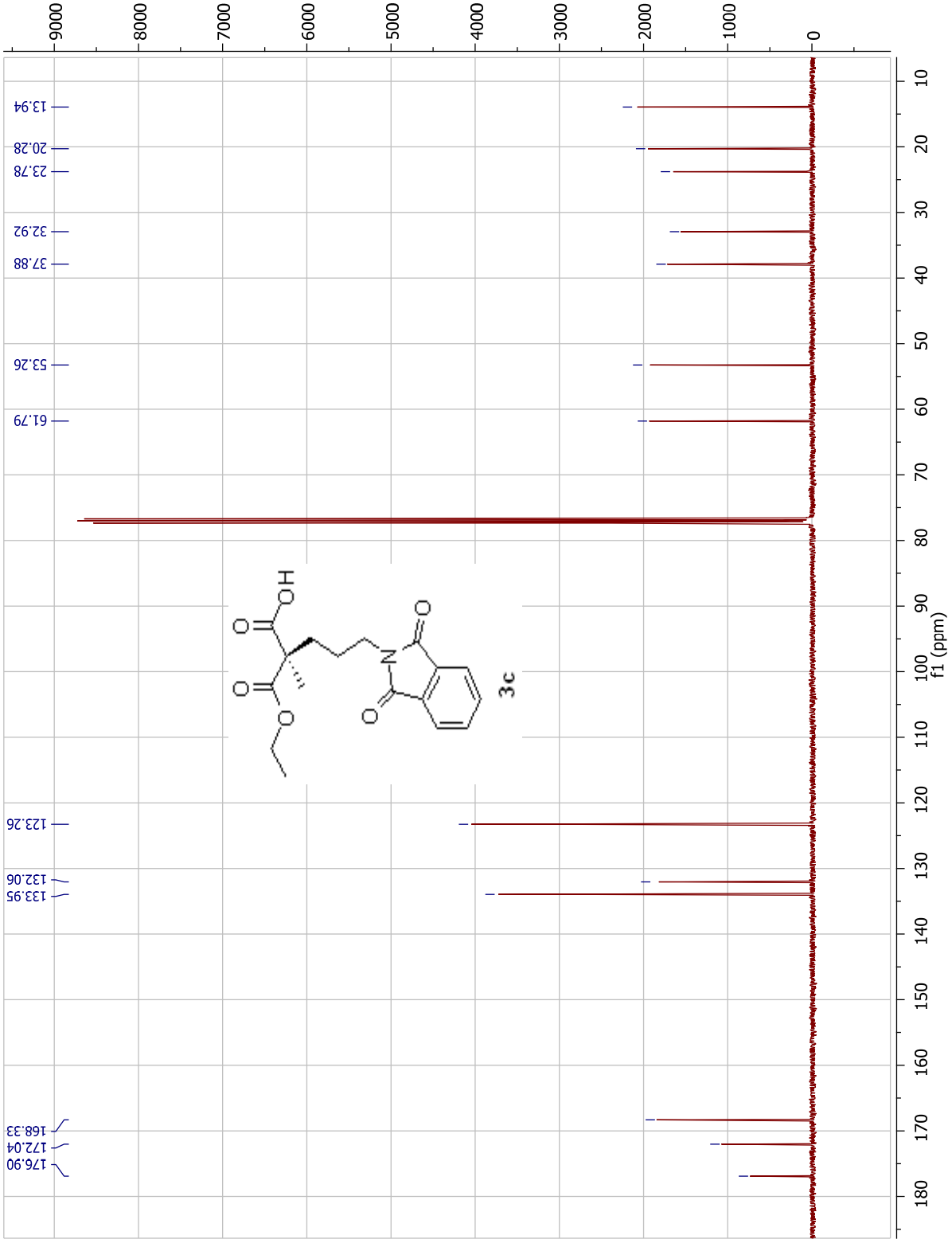

12.56
2.05
2.14
2.05
3.76
2.00
1.93
f1 (ppm)
2e

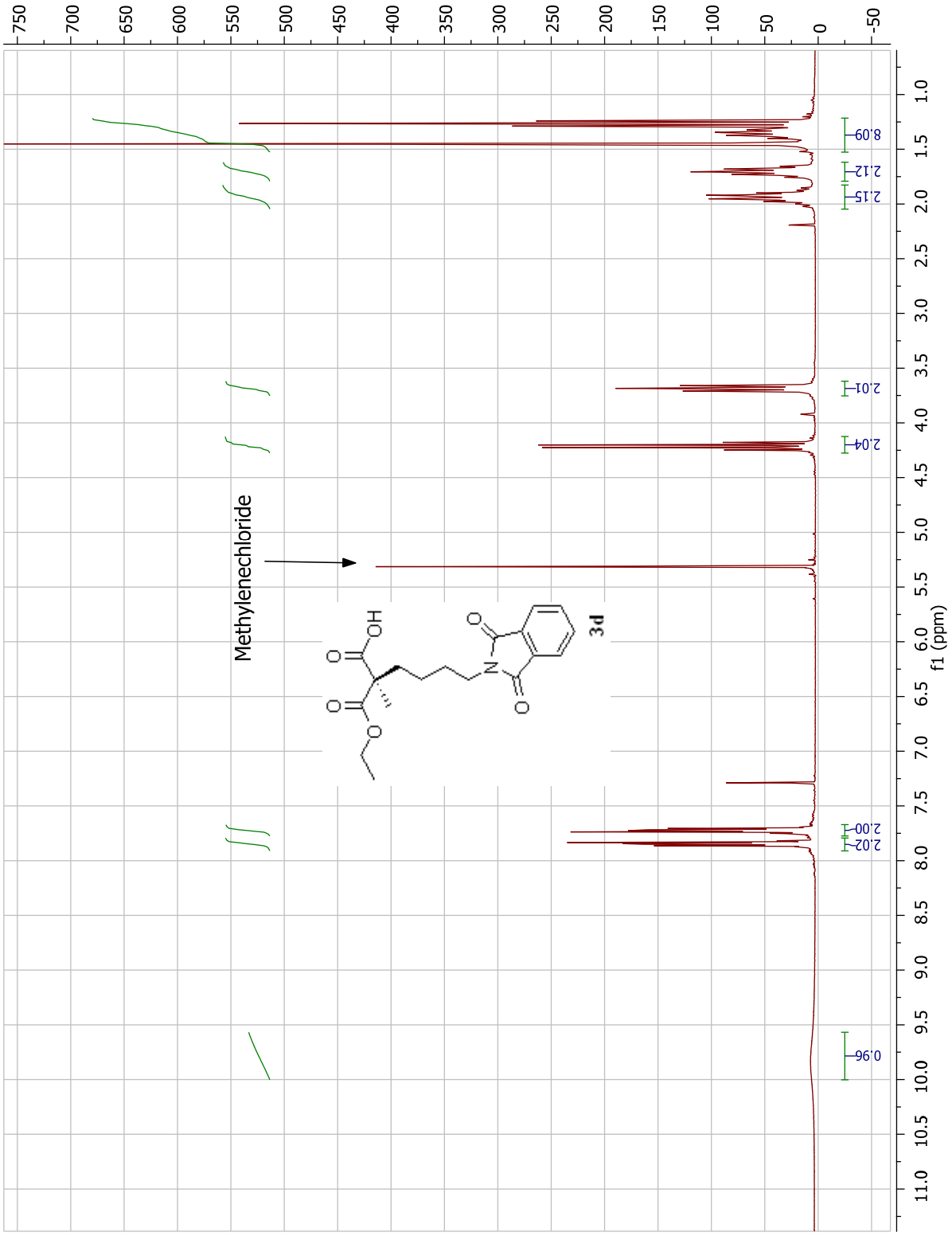


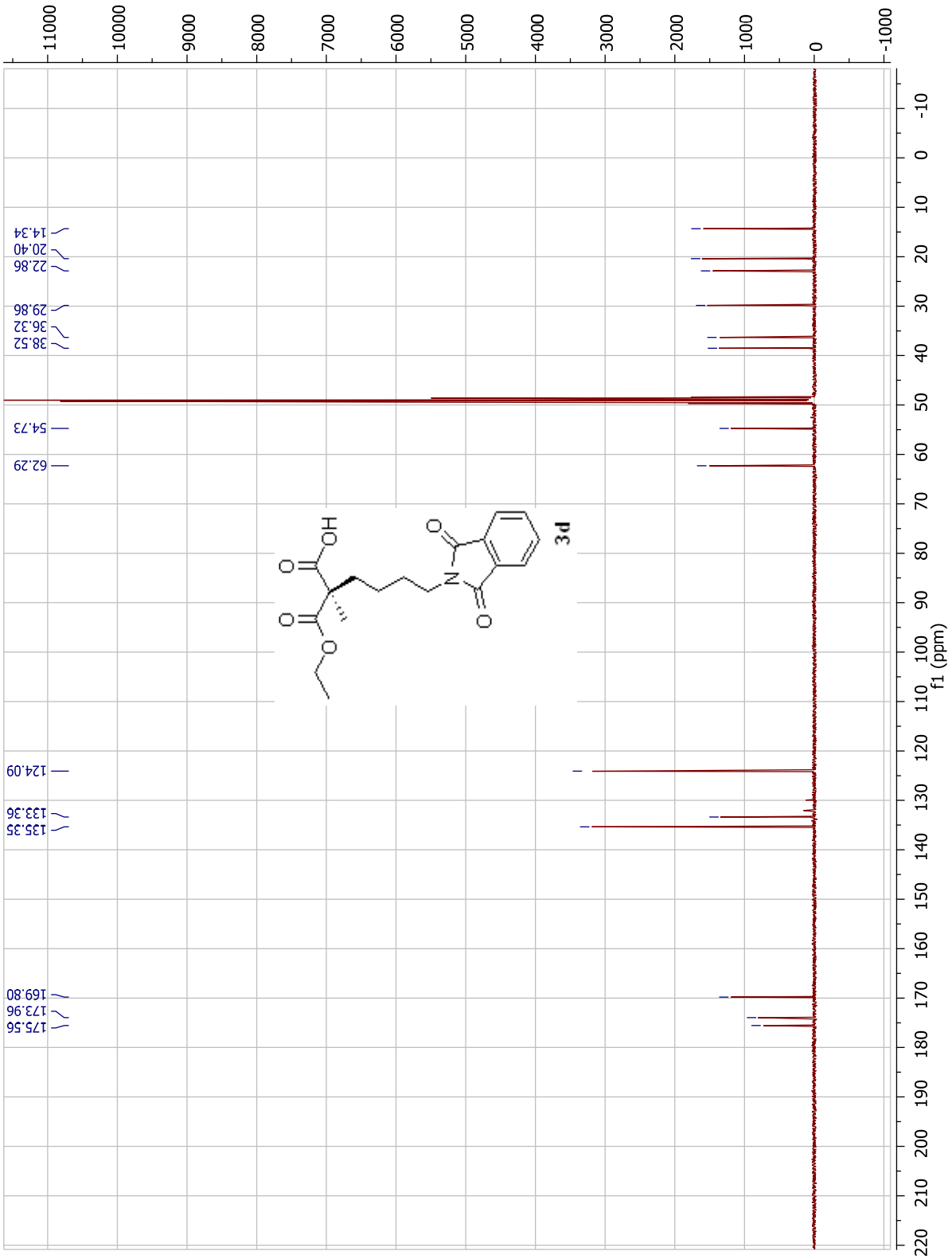


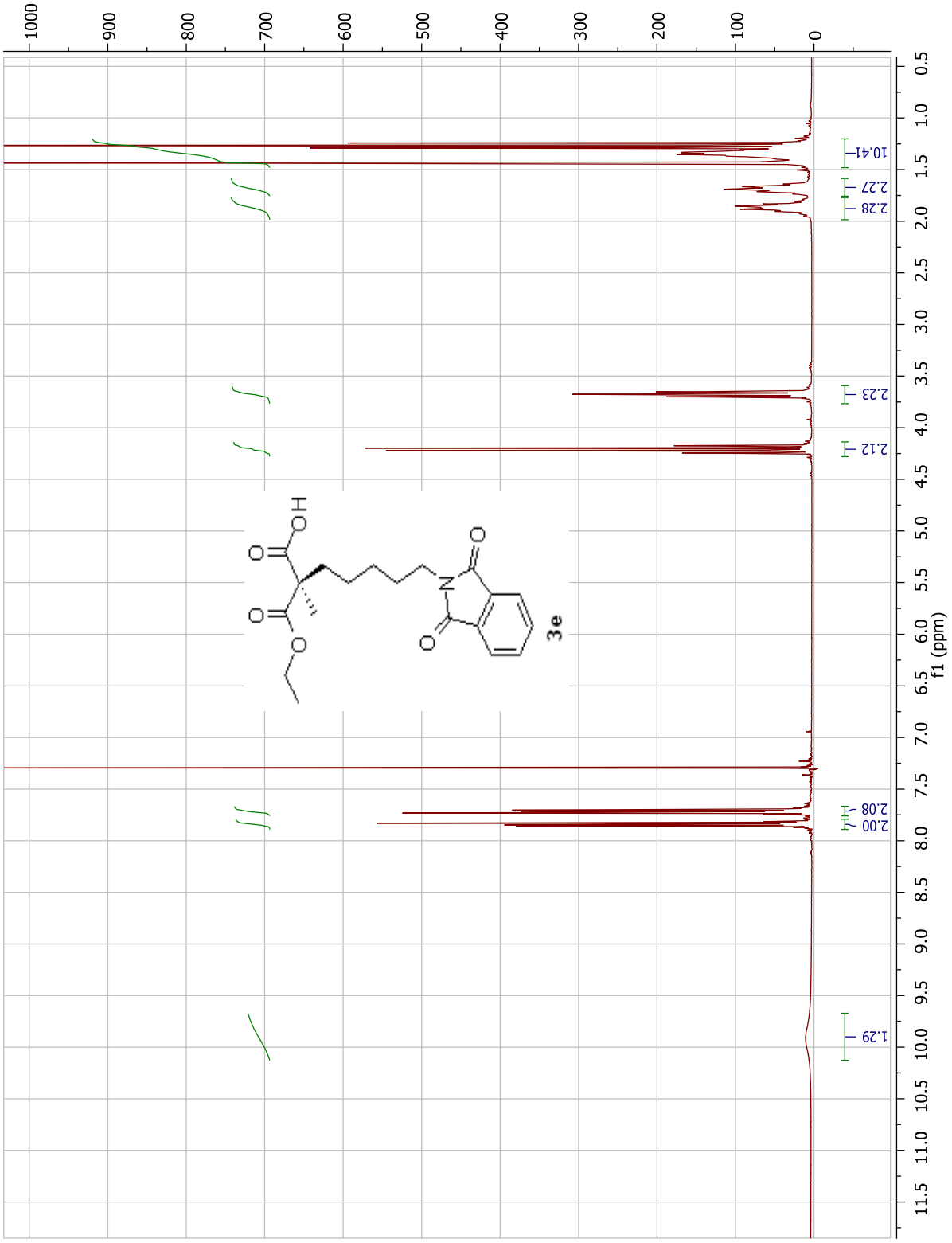


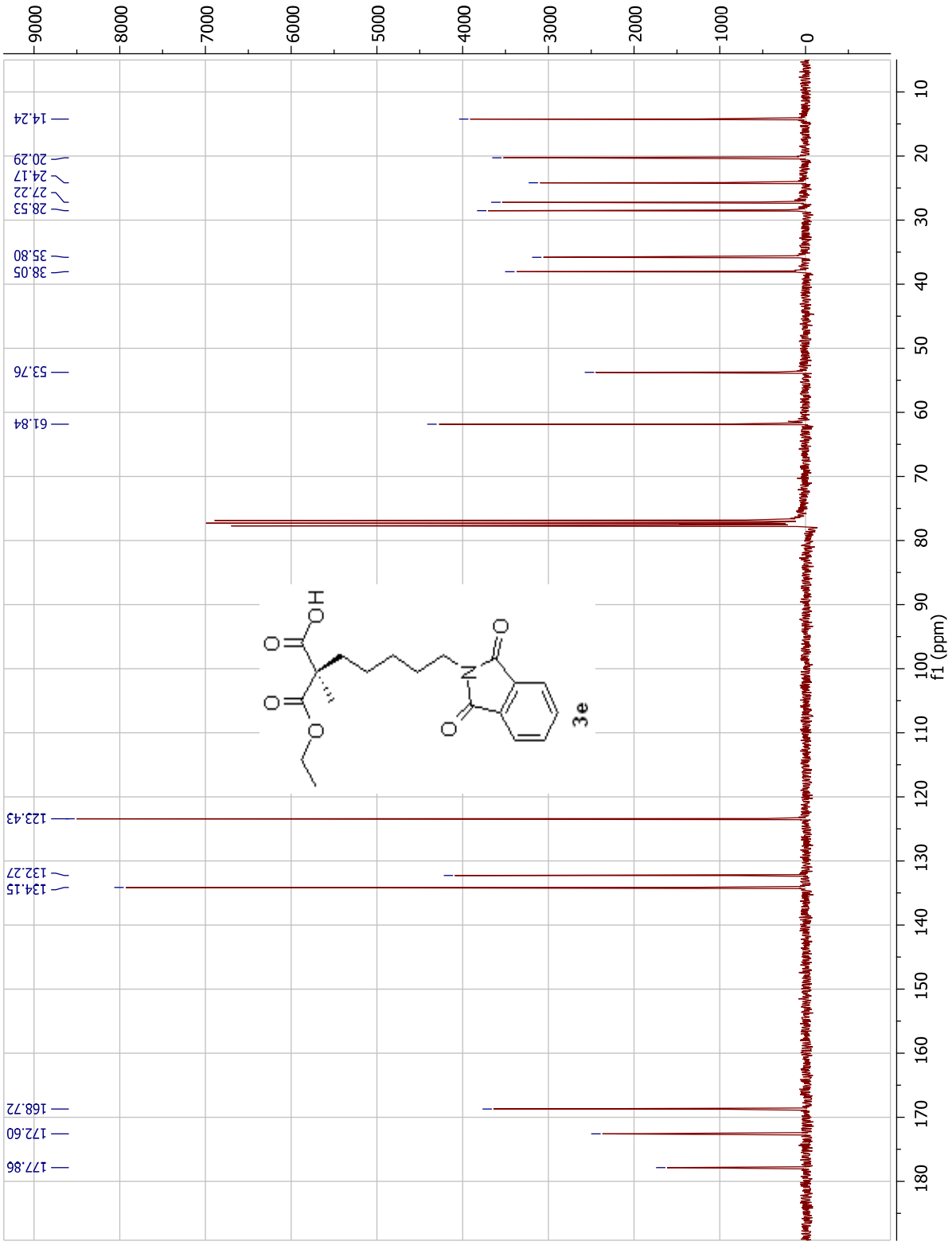


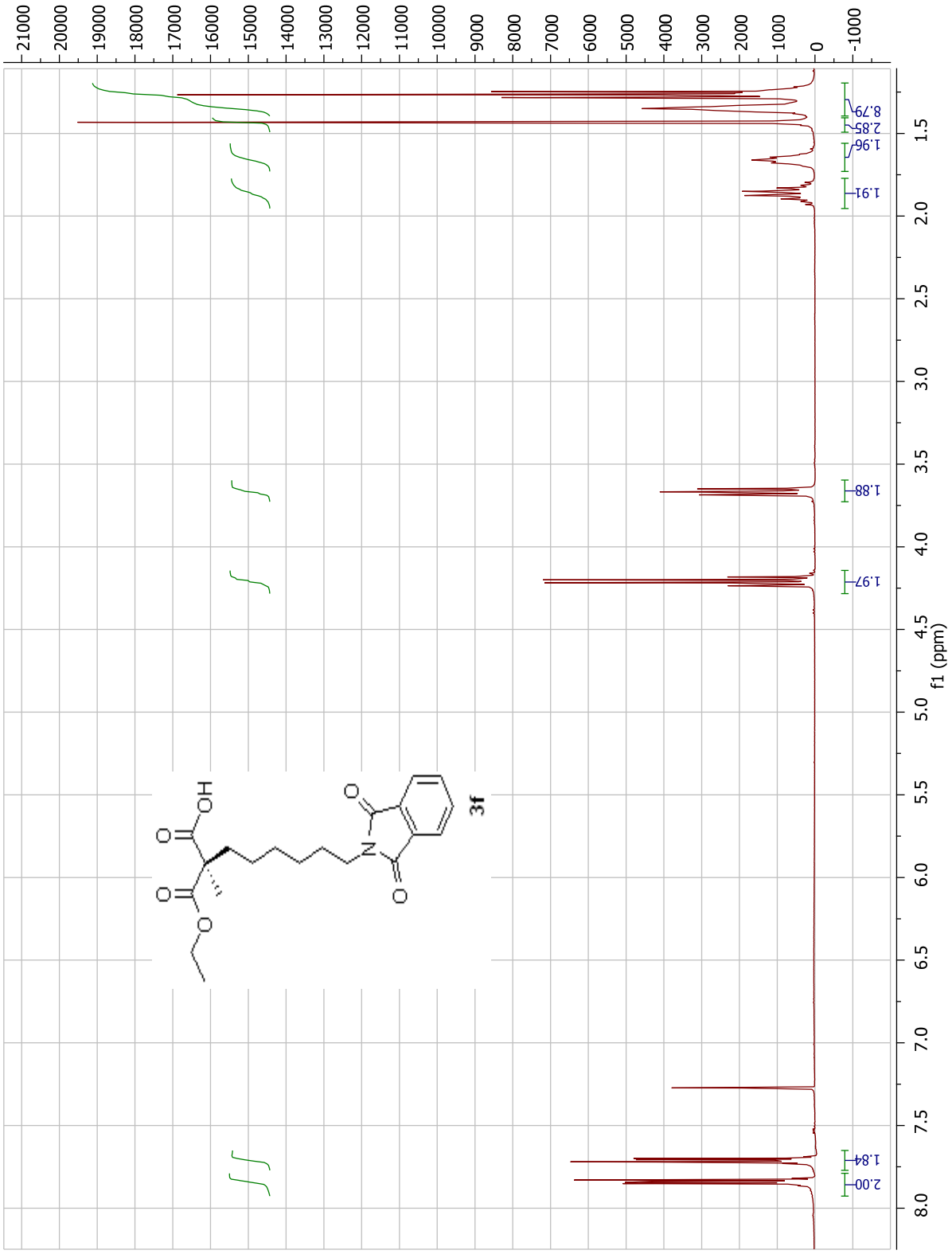


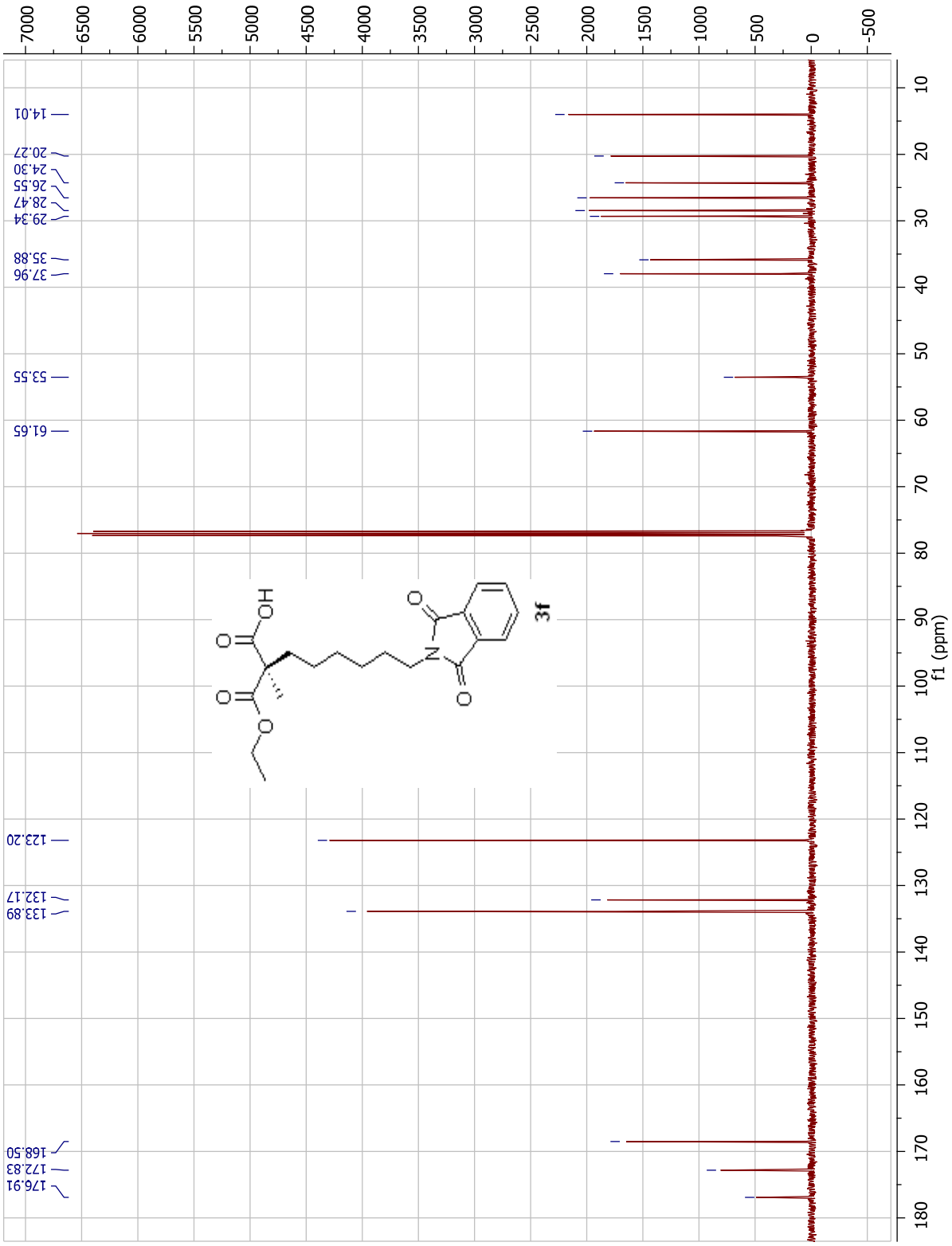


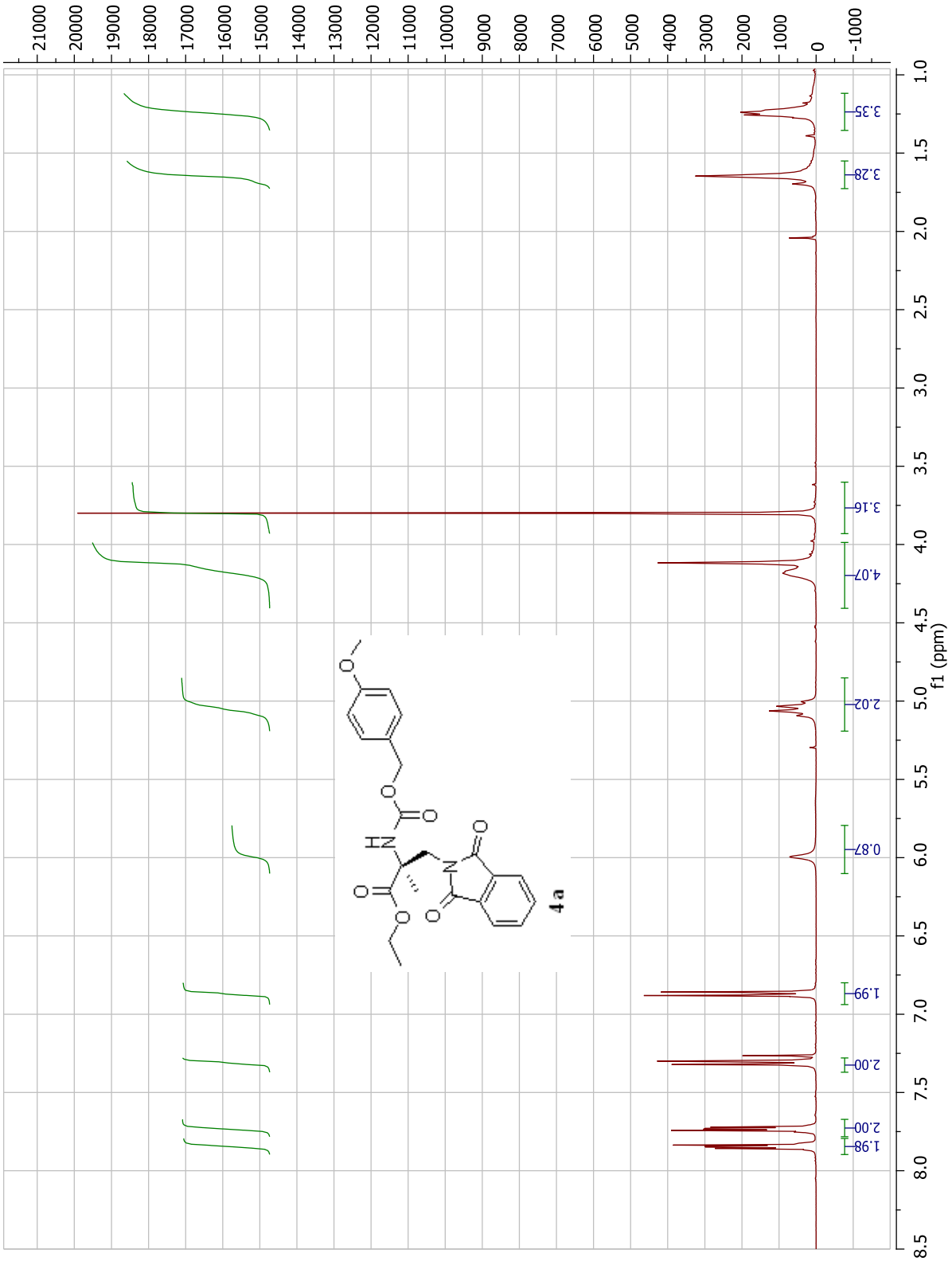


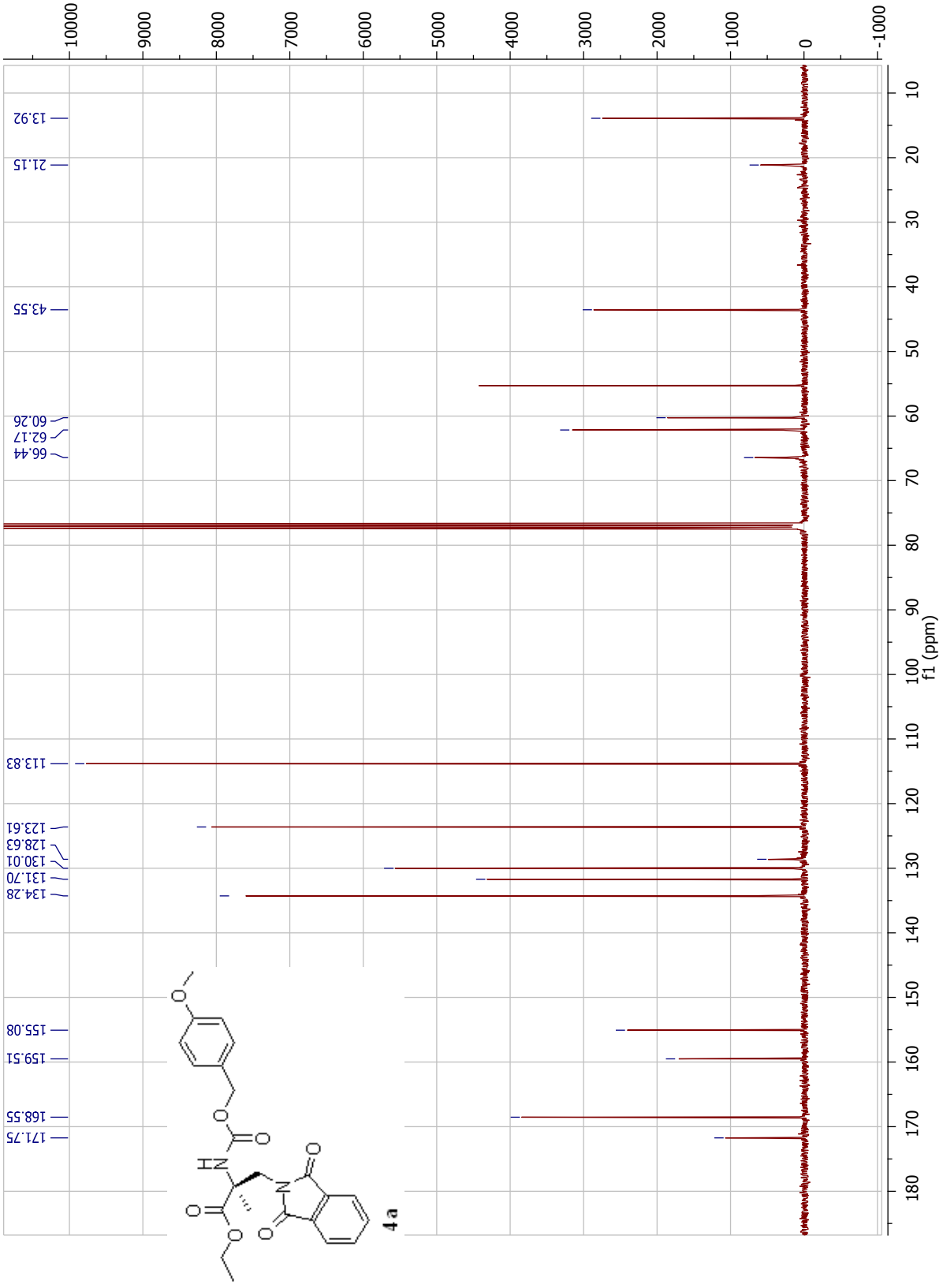


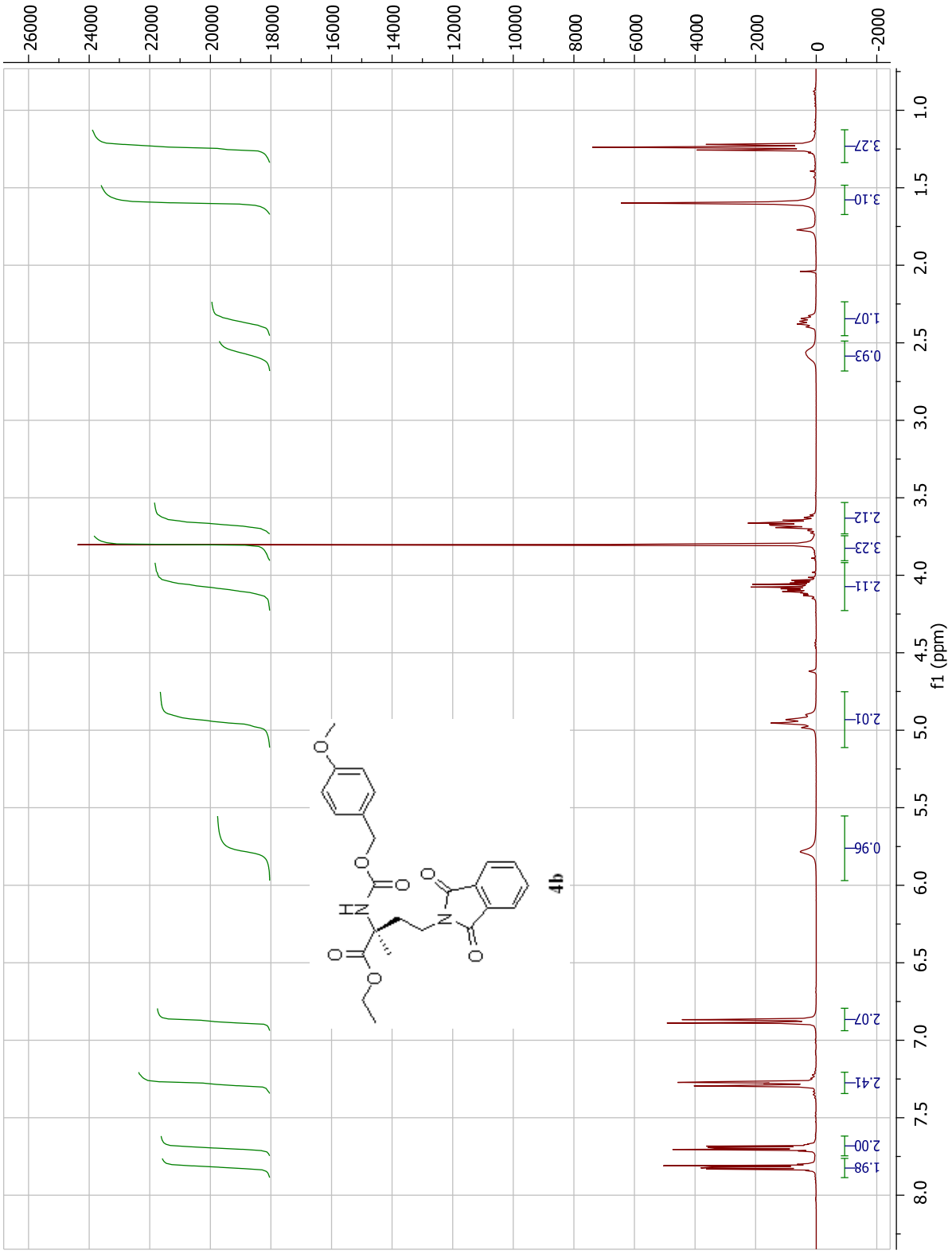


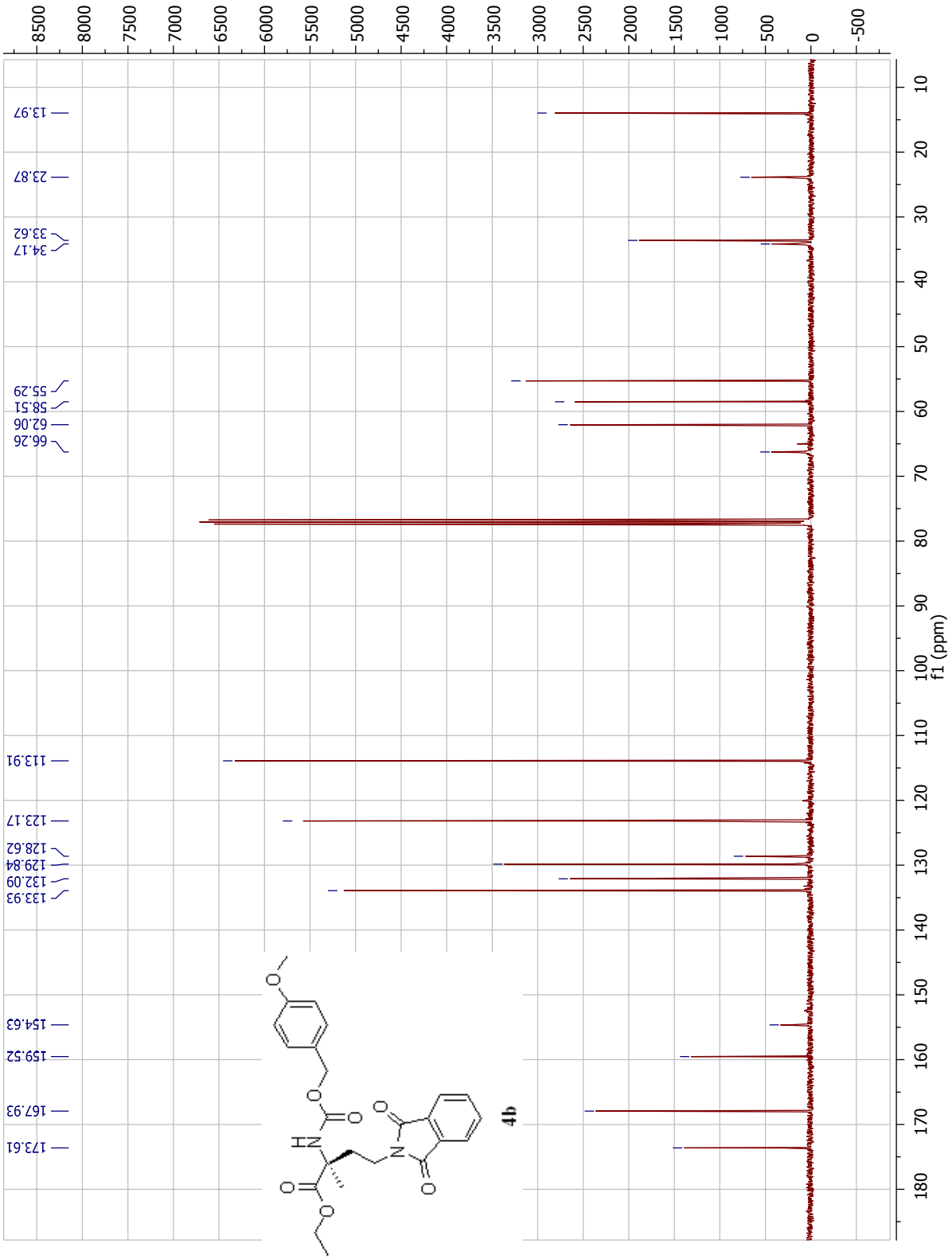


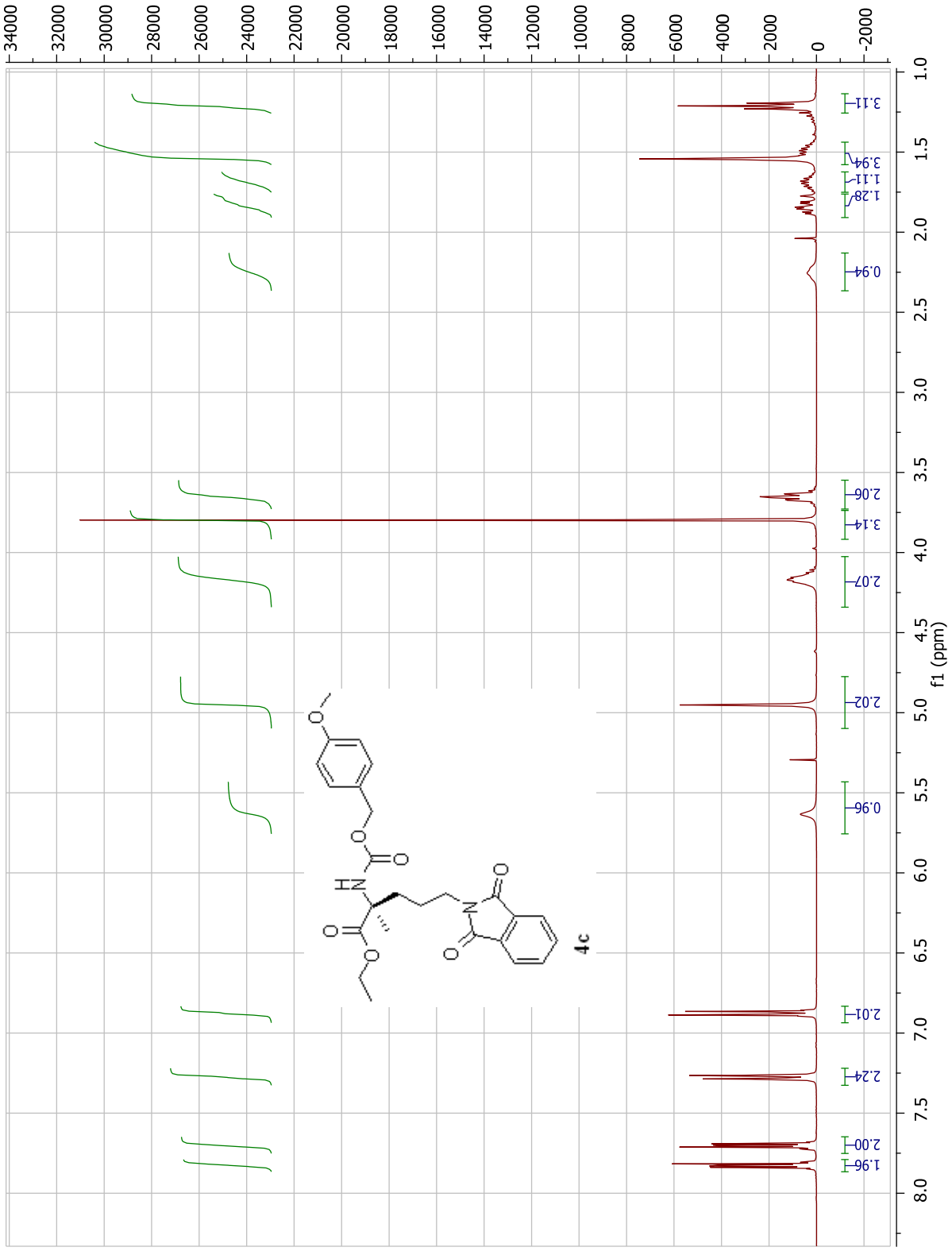


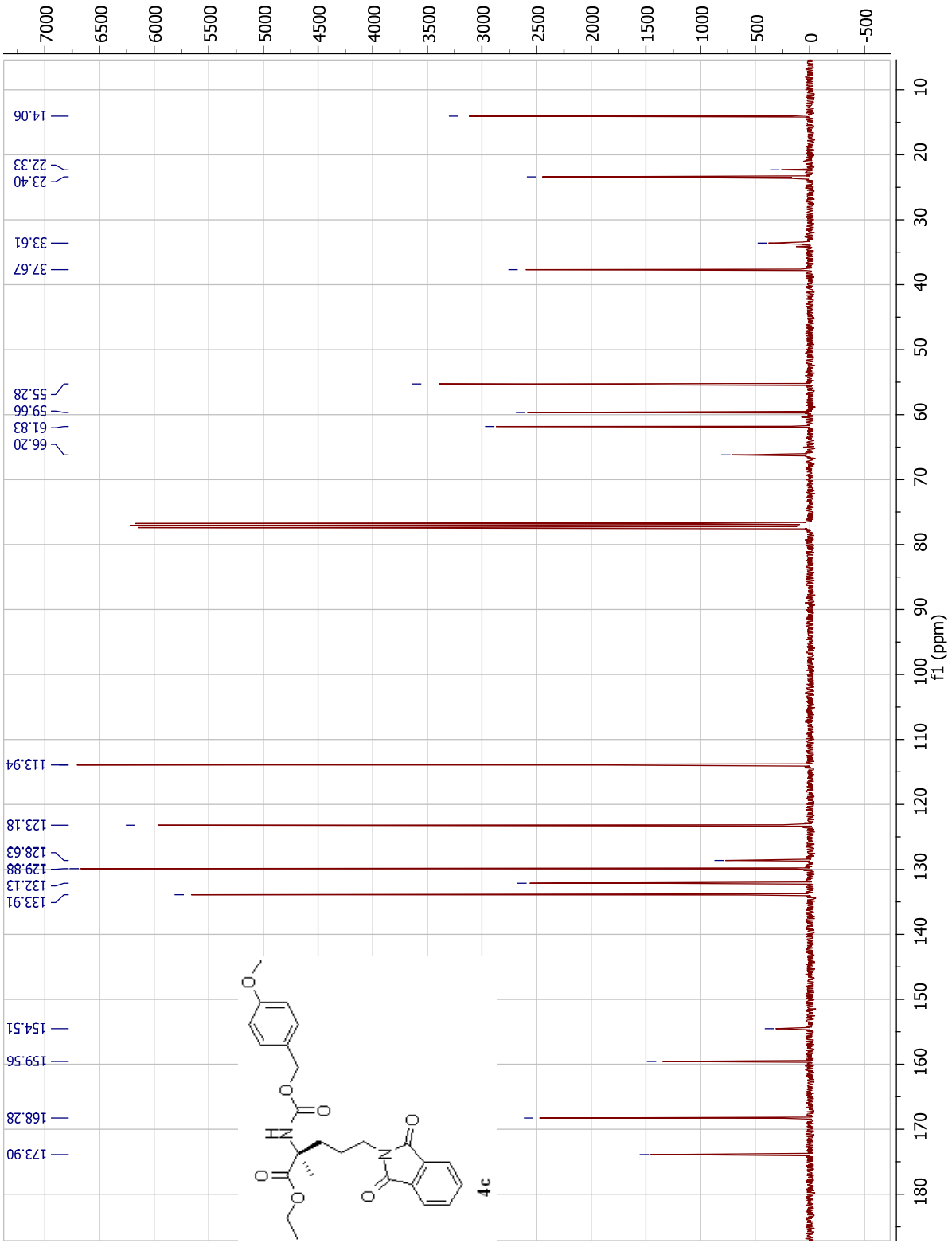


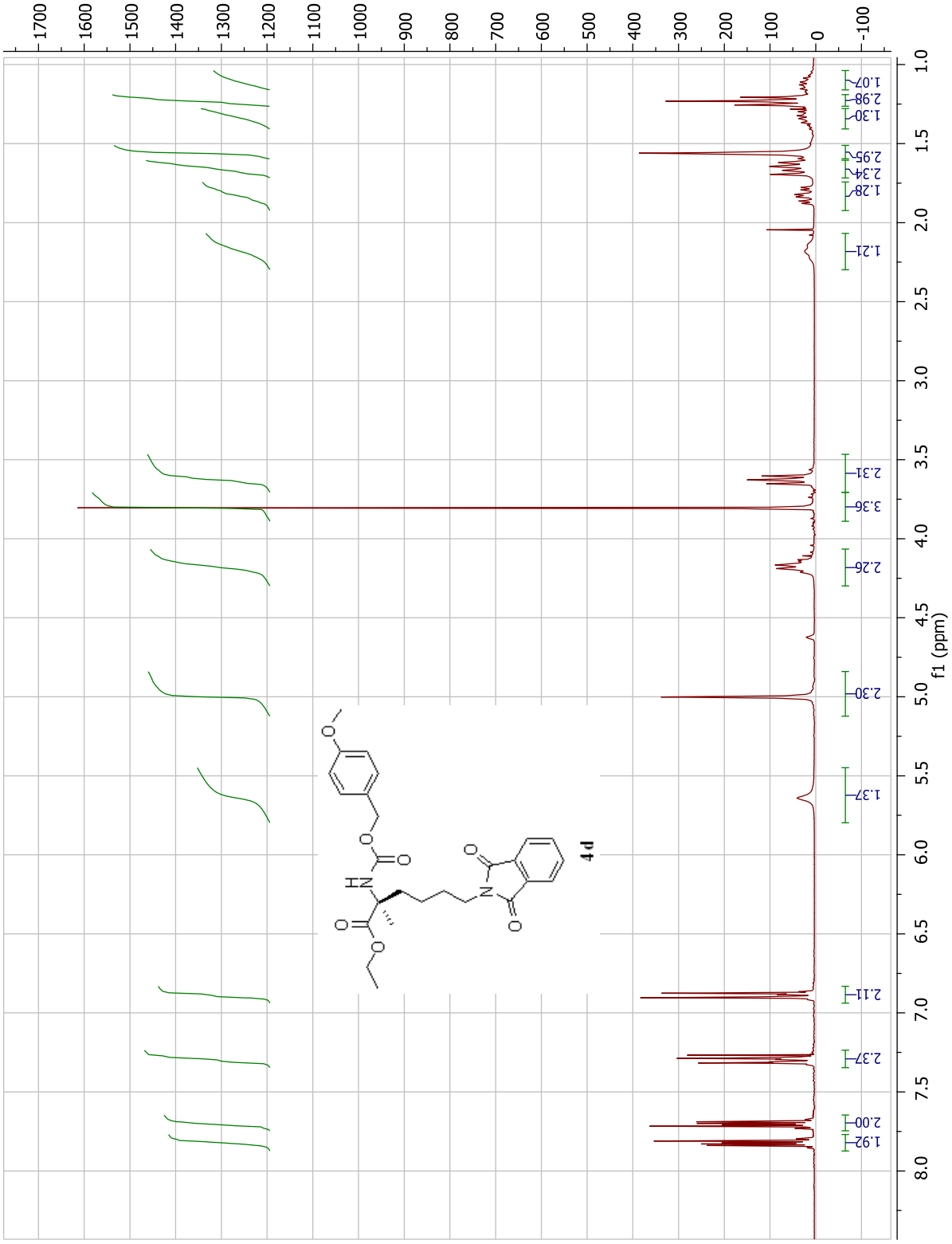


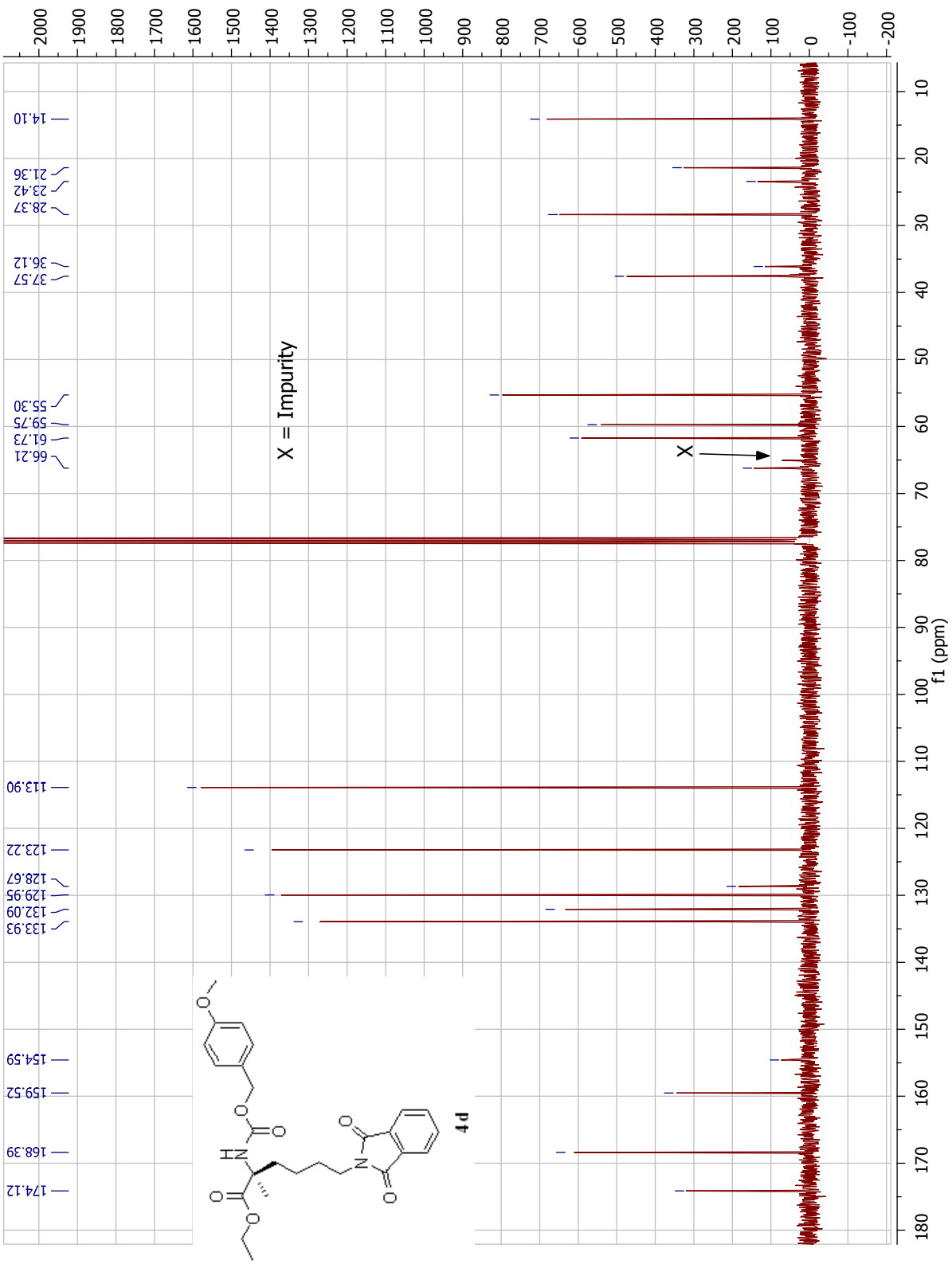


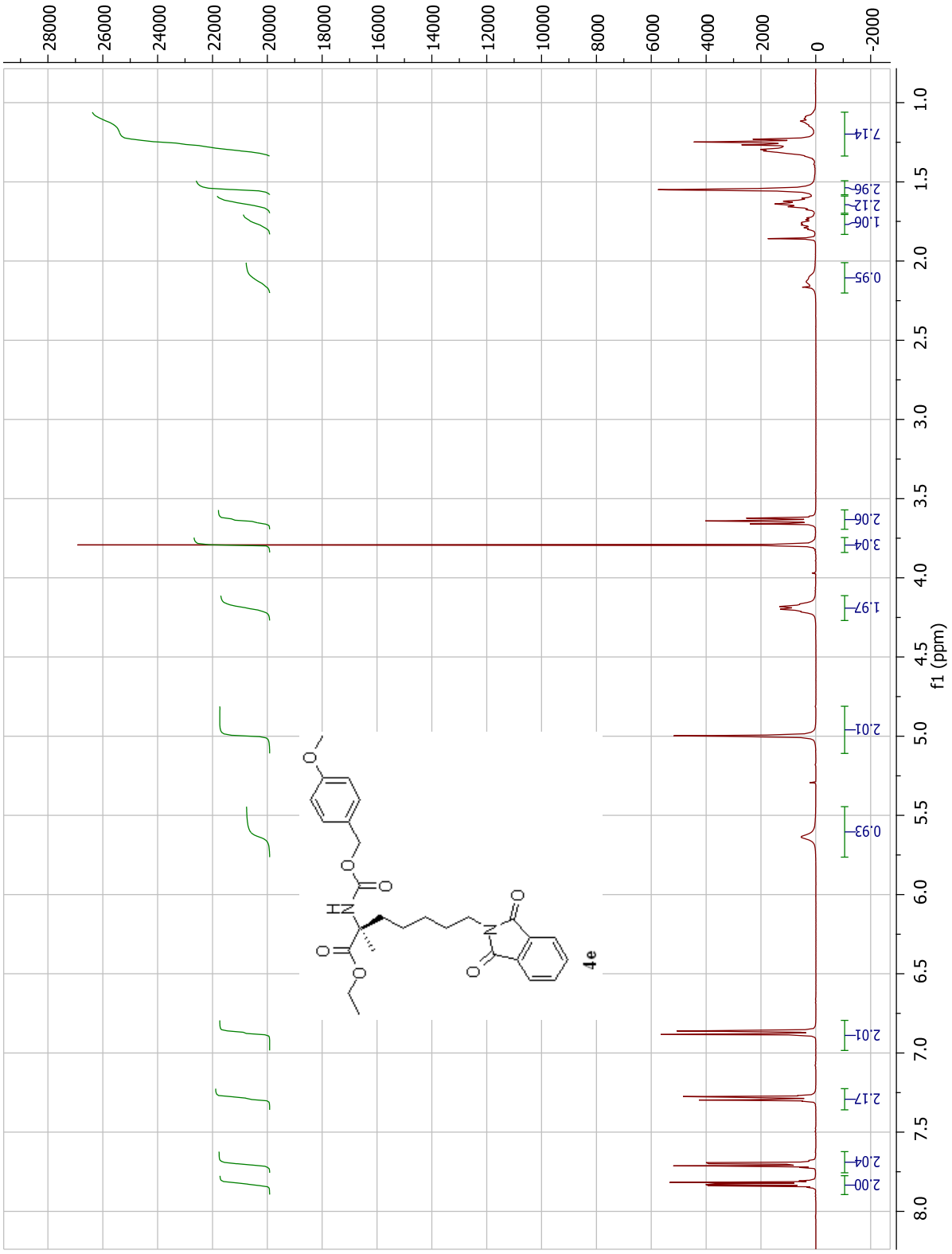


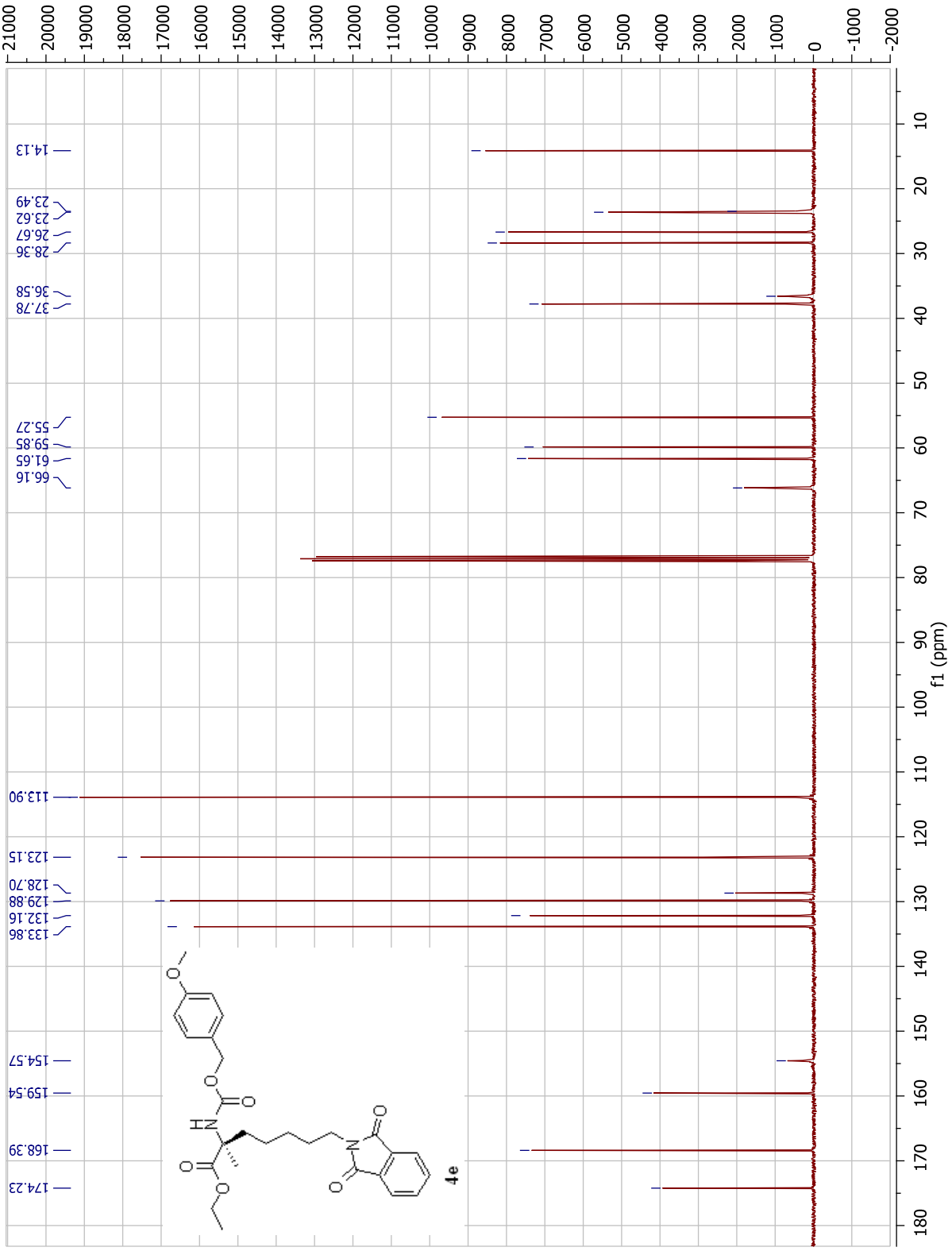


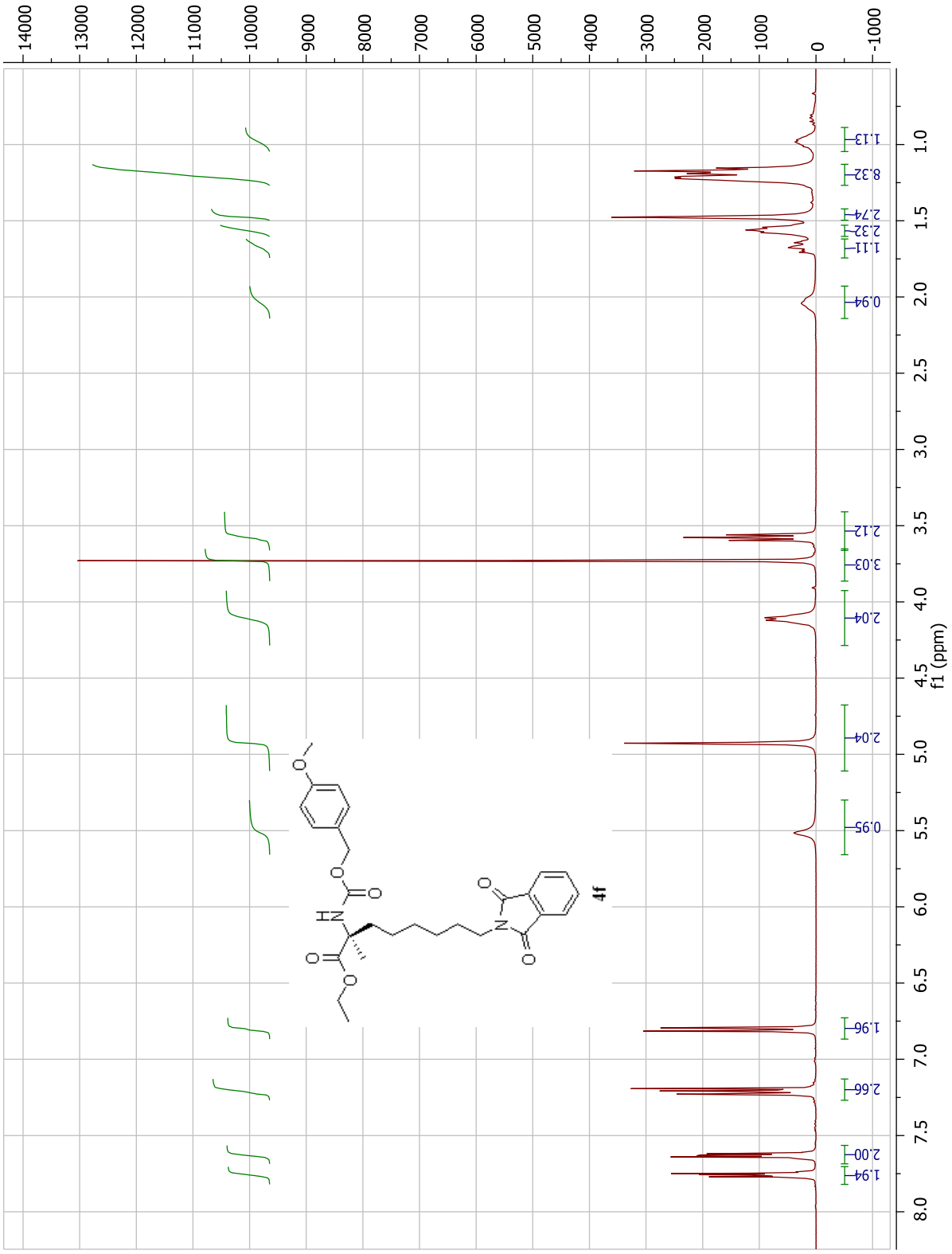


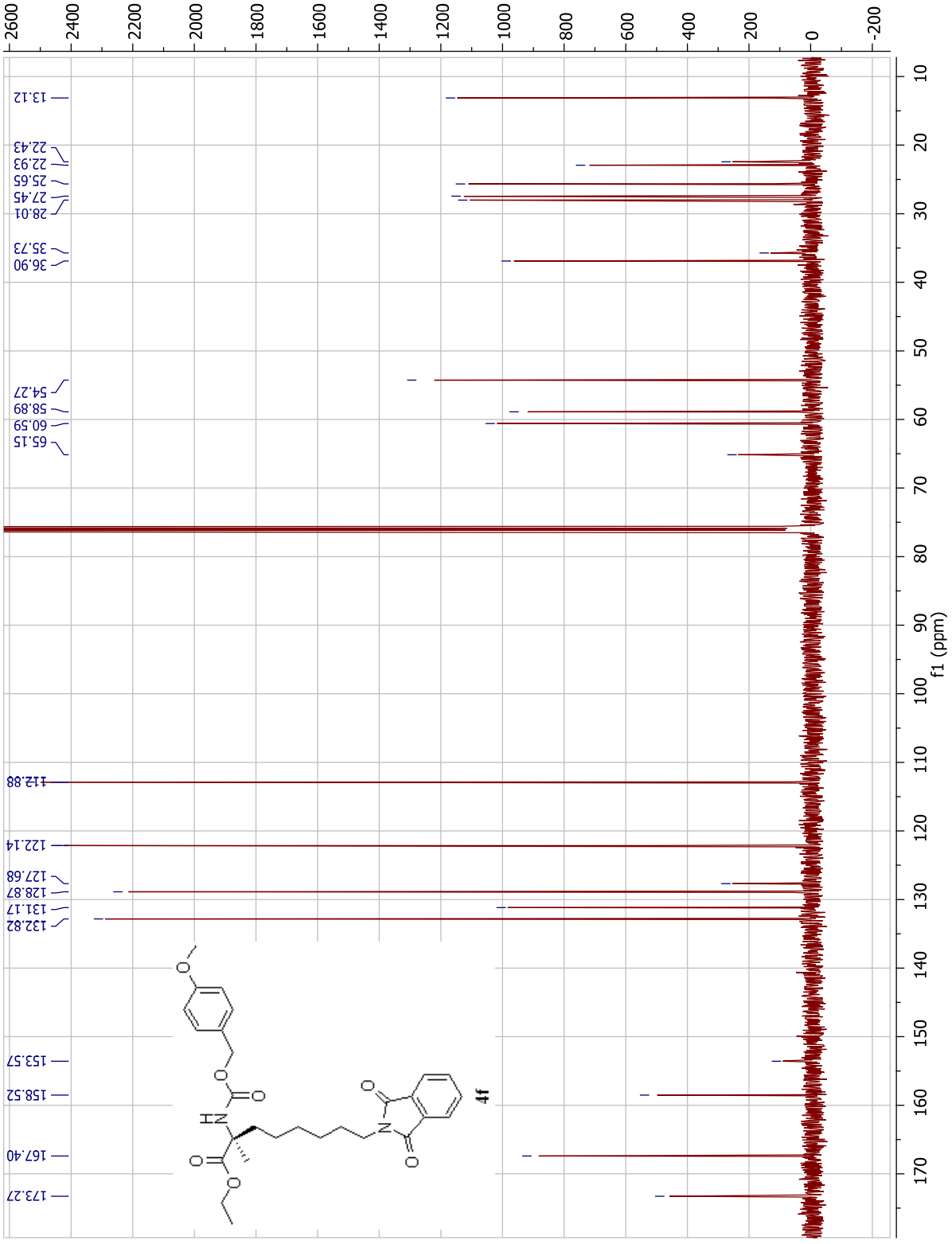


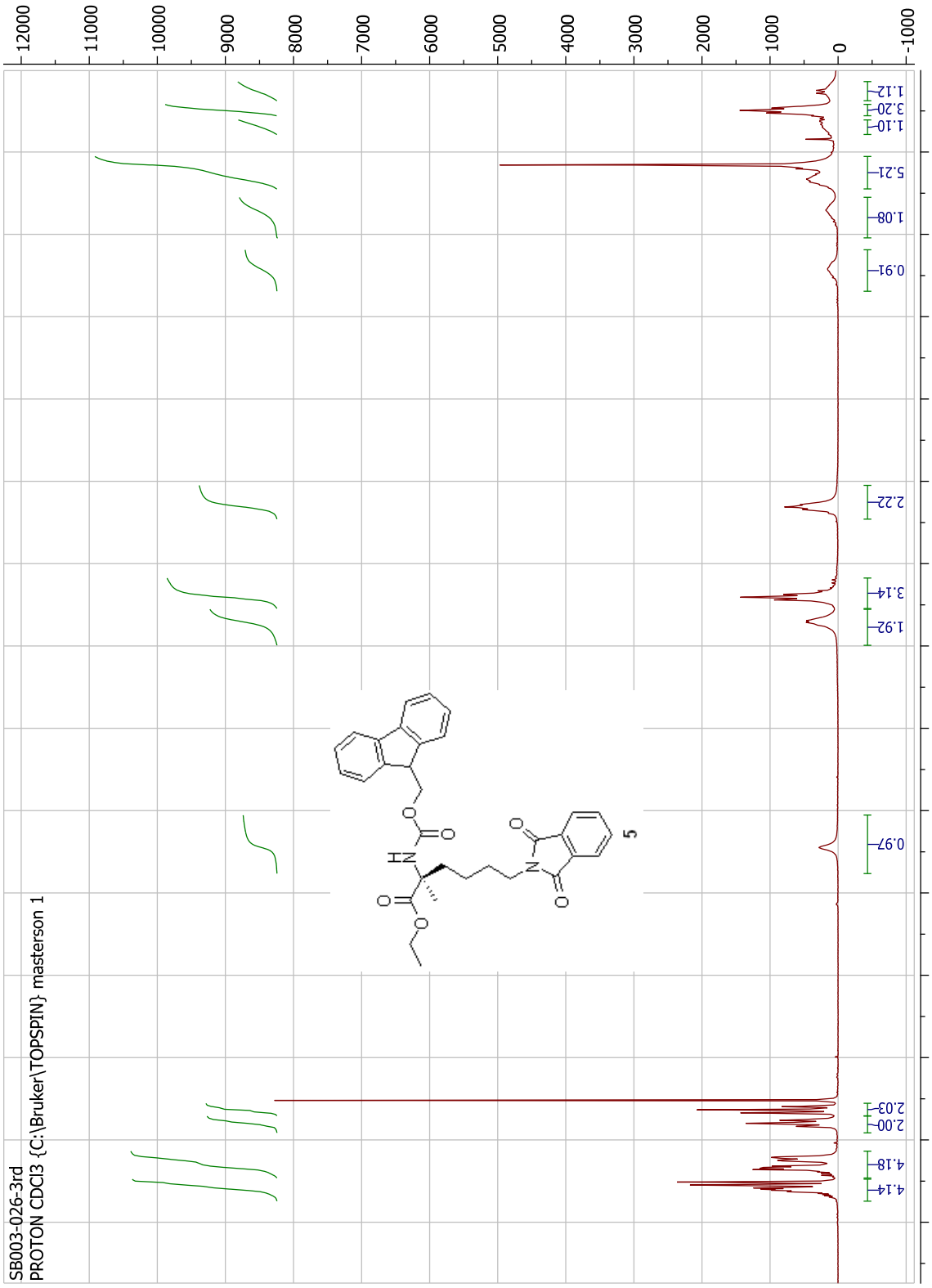


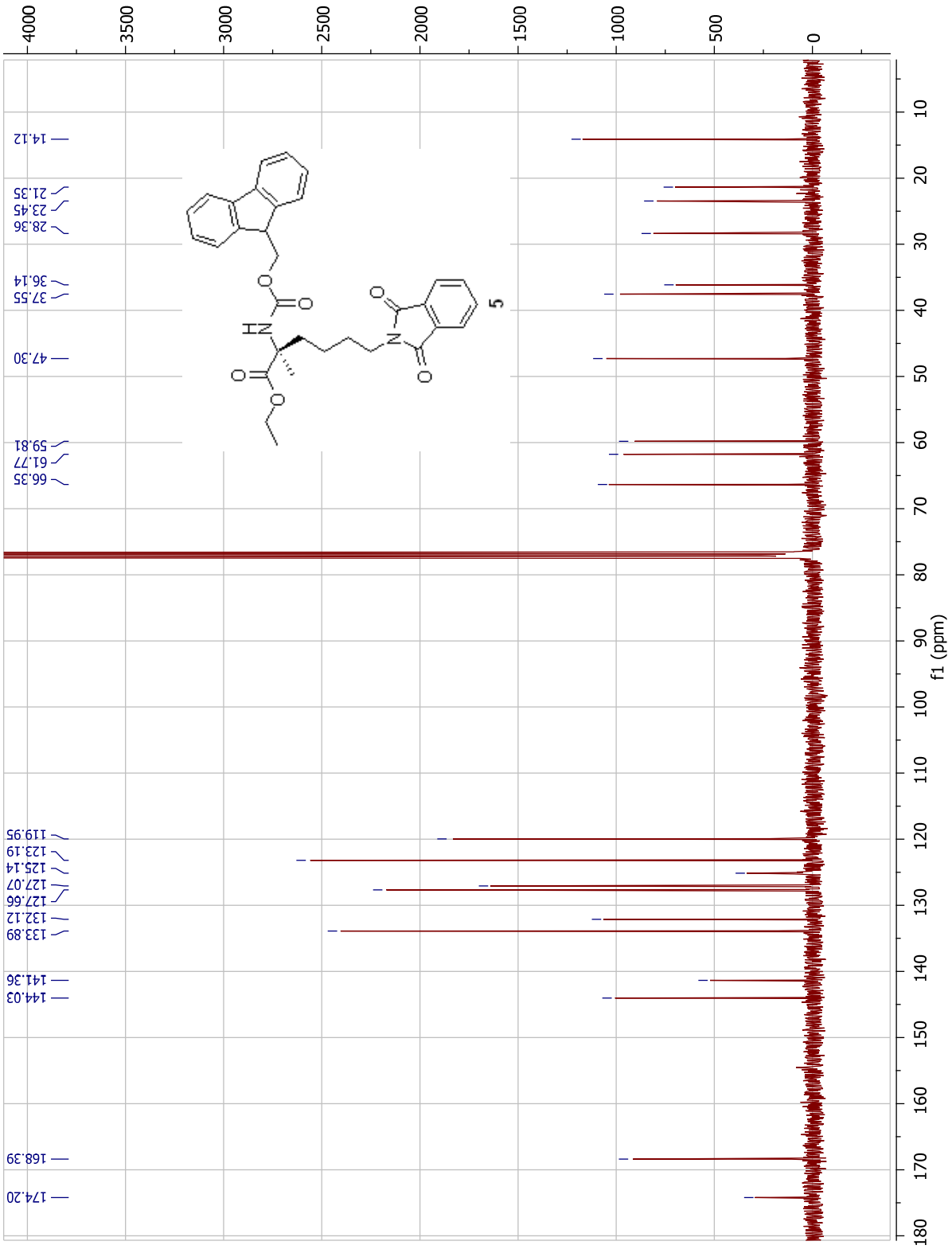


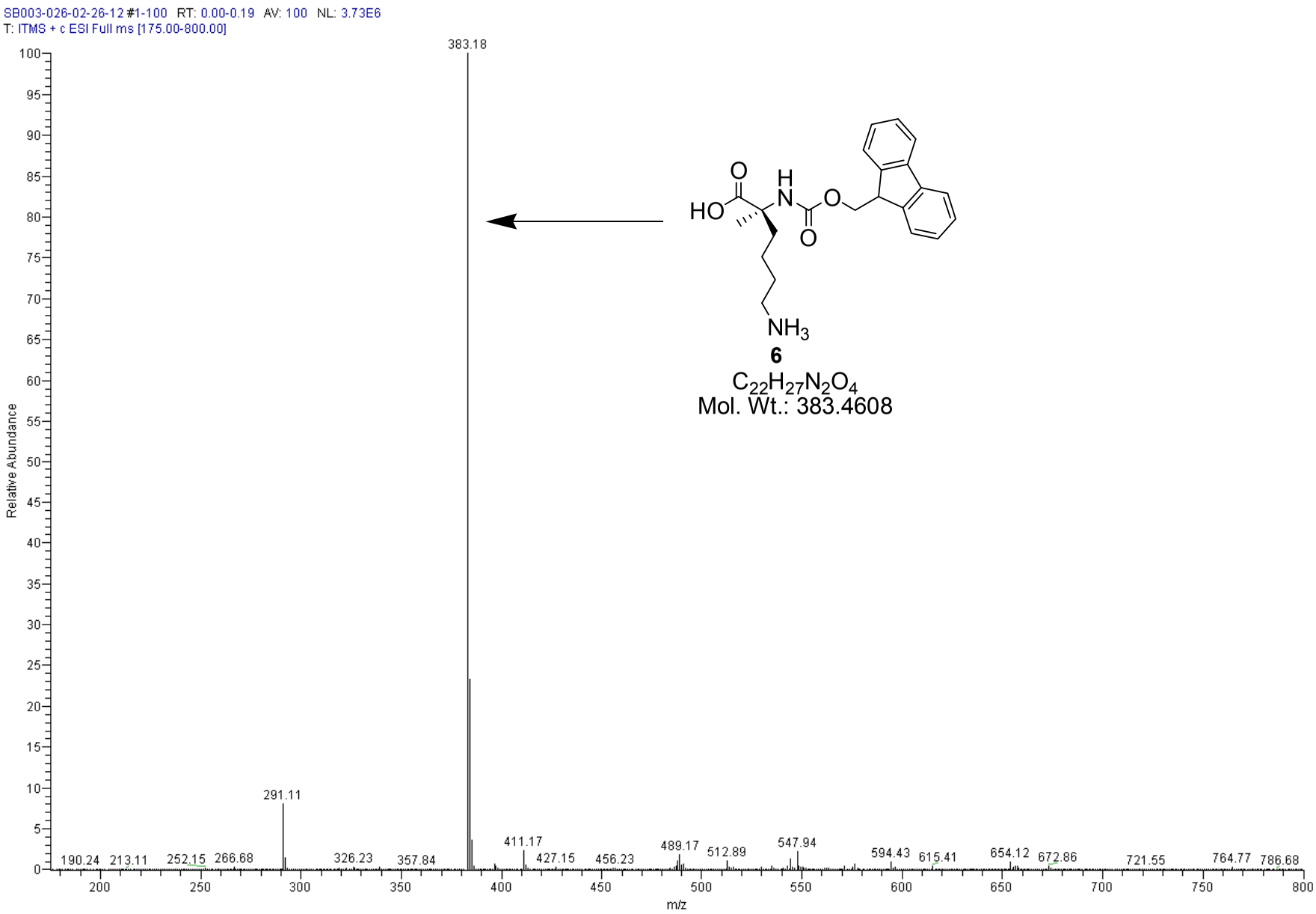


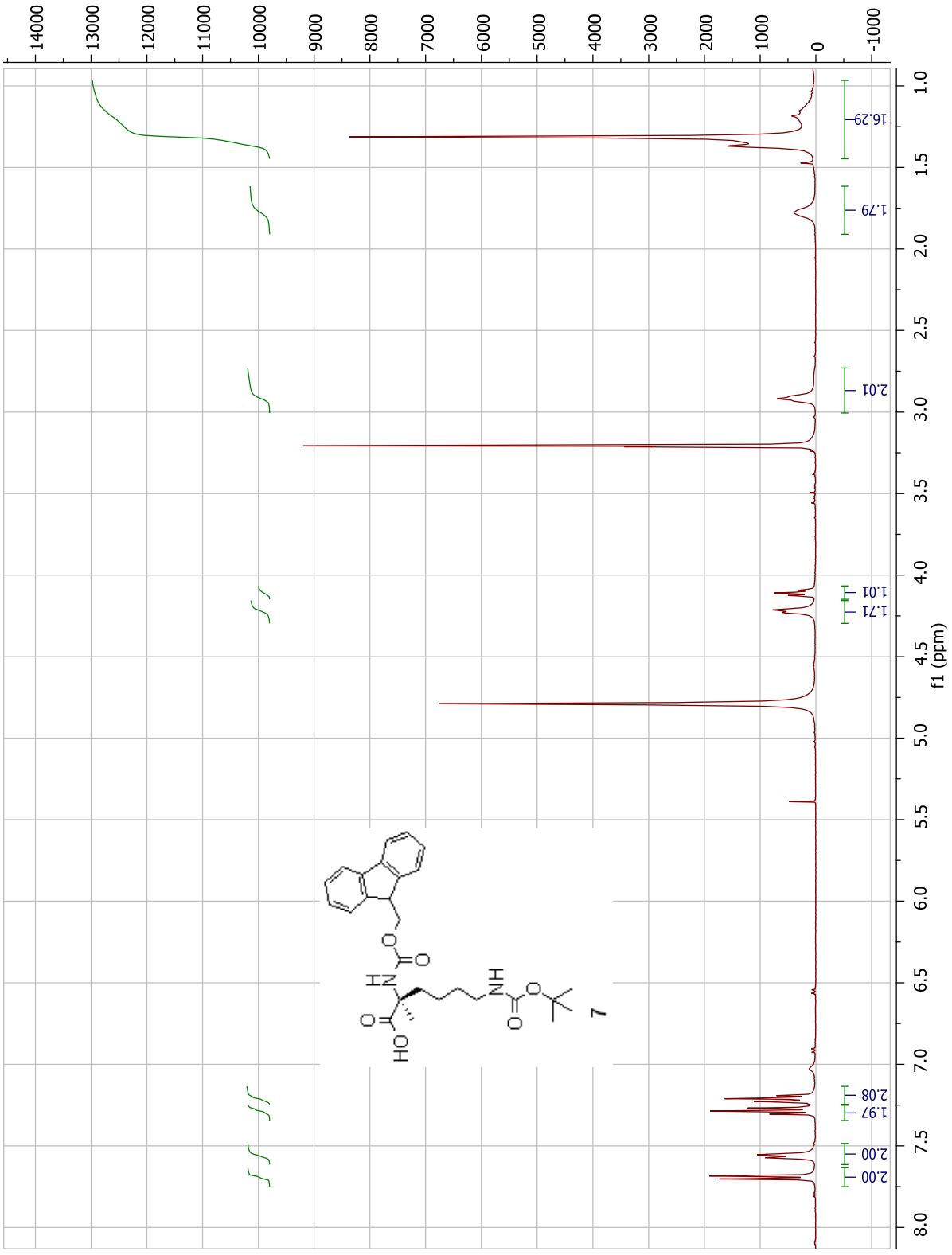


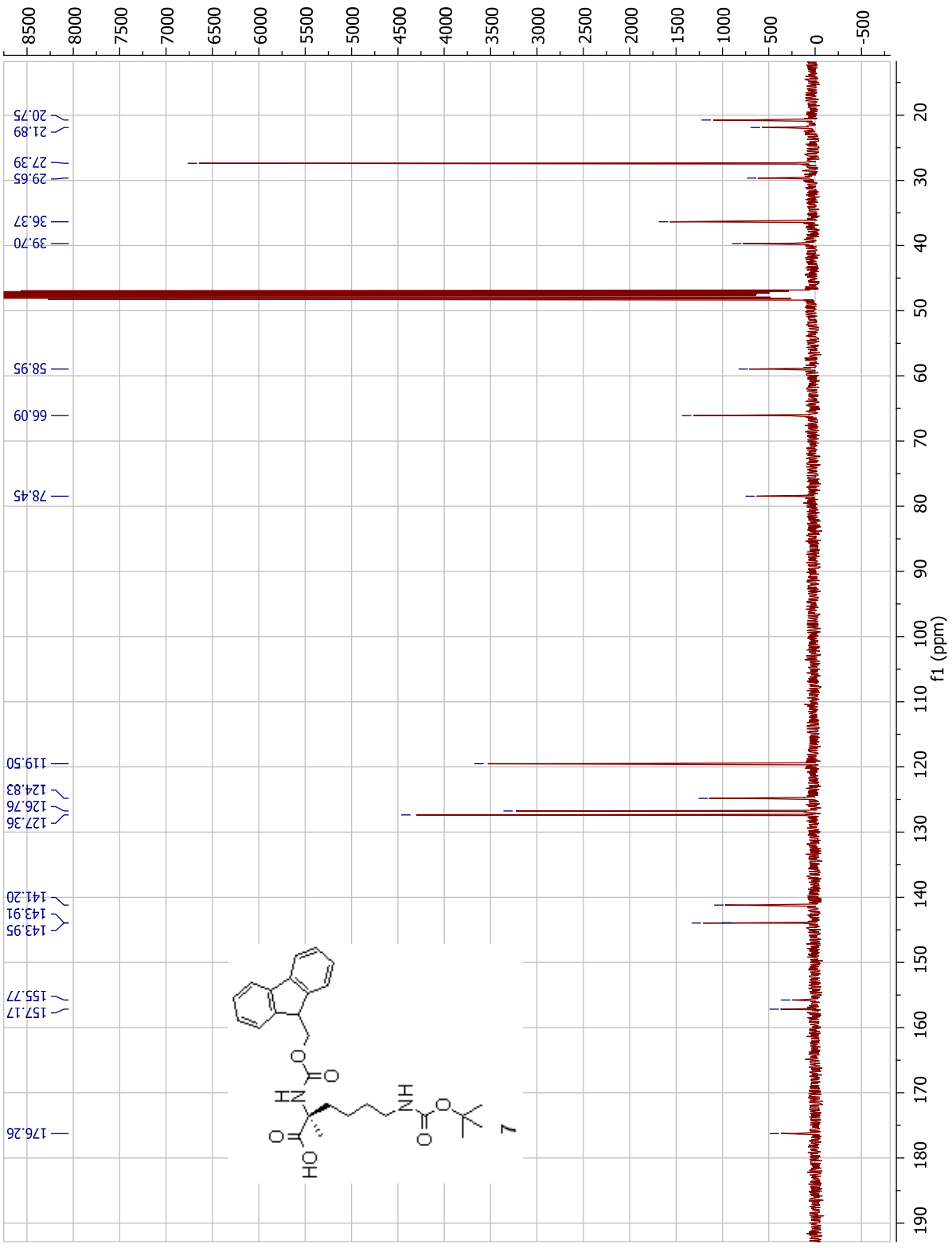


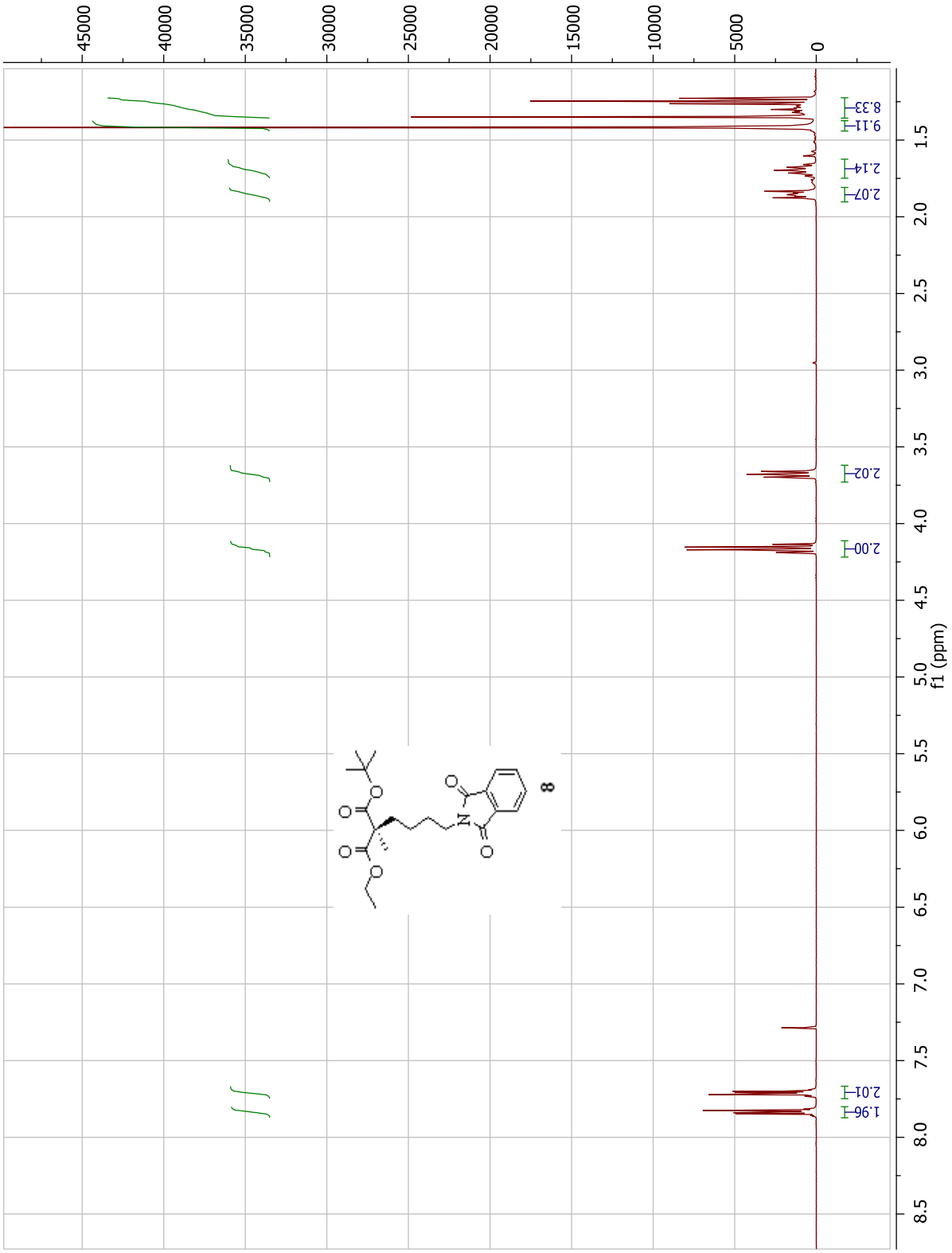

SB003-026-3rd
PROTON CDCl3 {C:\Bruker\TOPSPIN} masterson 1
f1 (ppm)
5
1.12
3.20
1.10
5.21
1.08
0.91
2.22
3.14
1.92
0.97
2.03
2.00
4.18
4.14

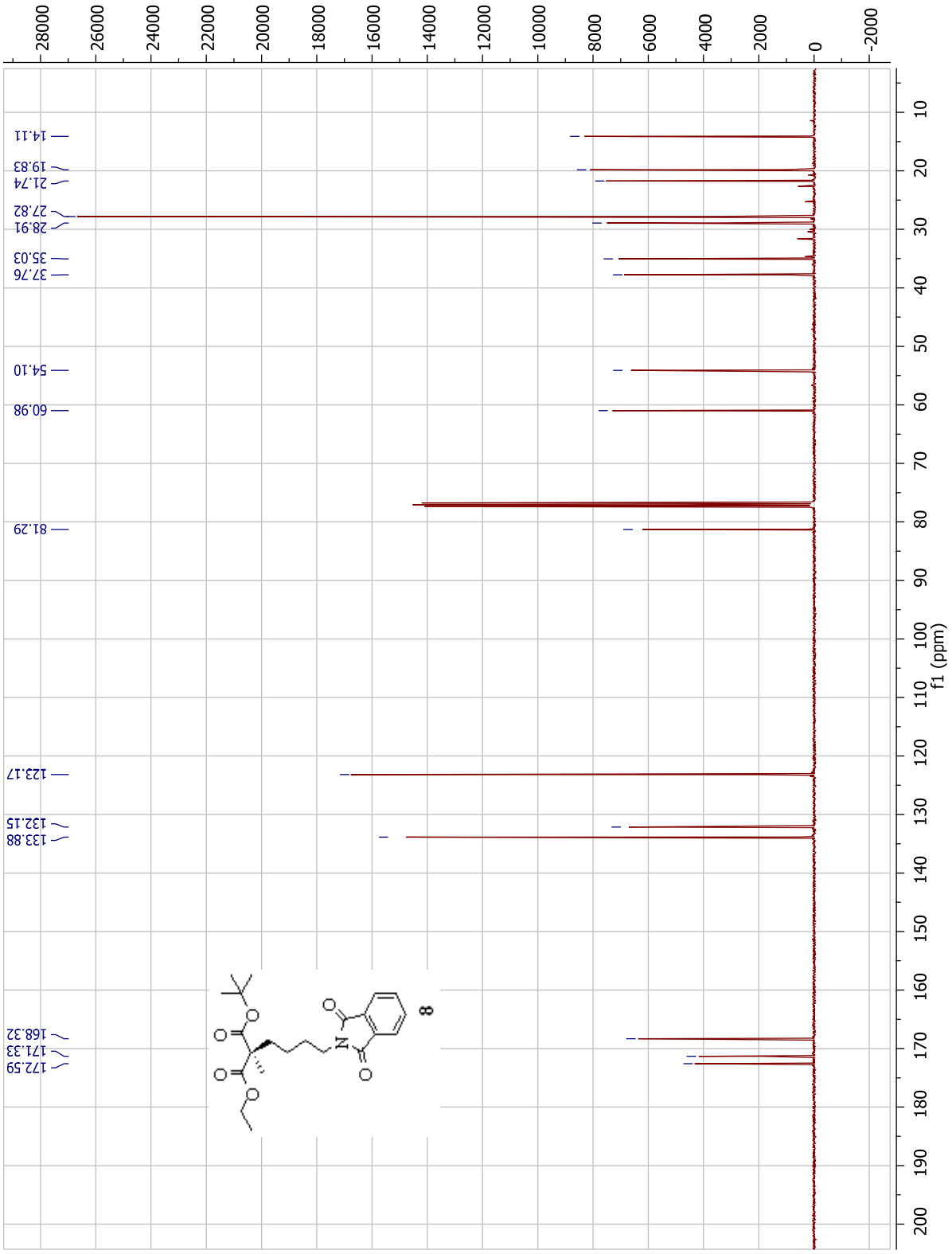


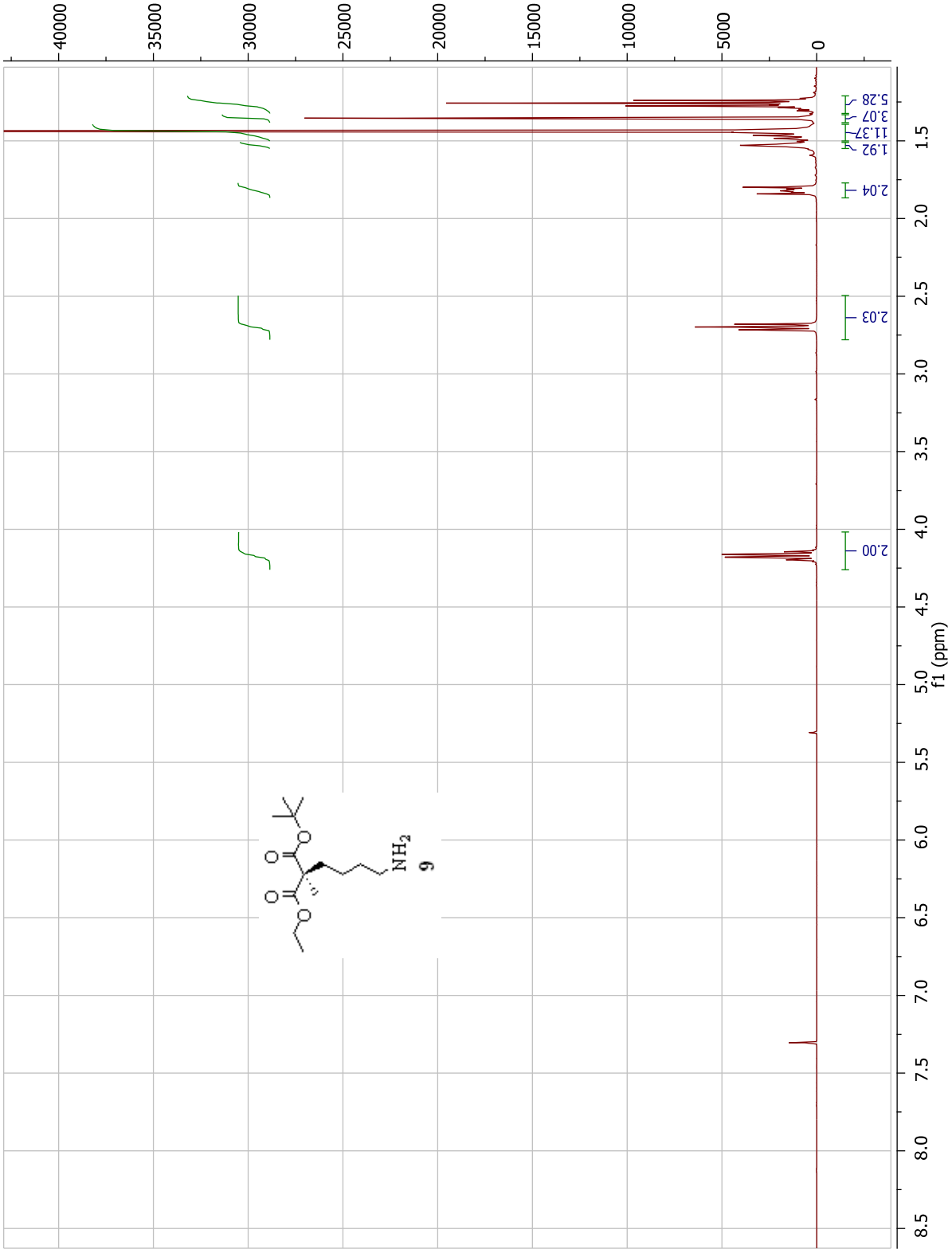


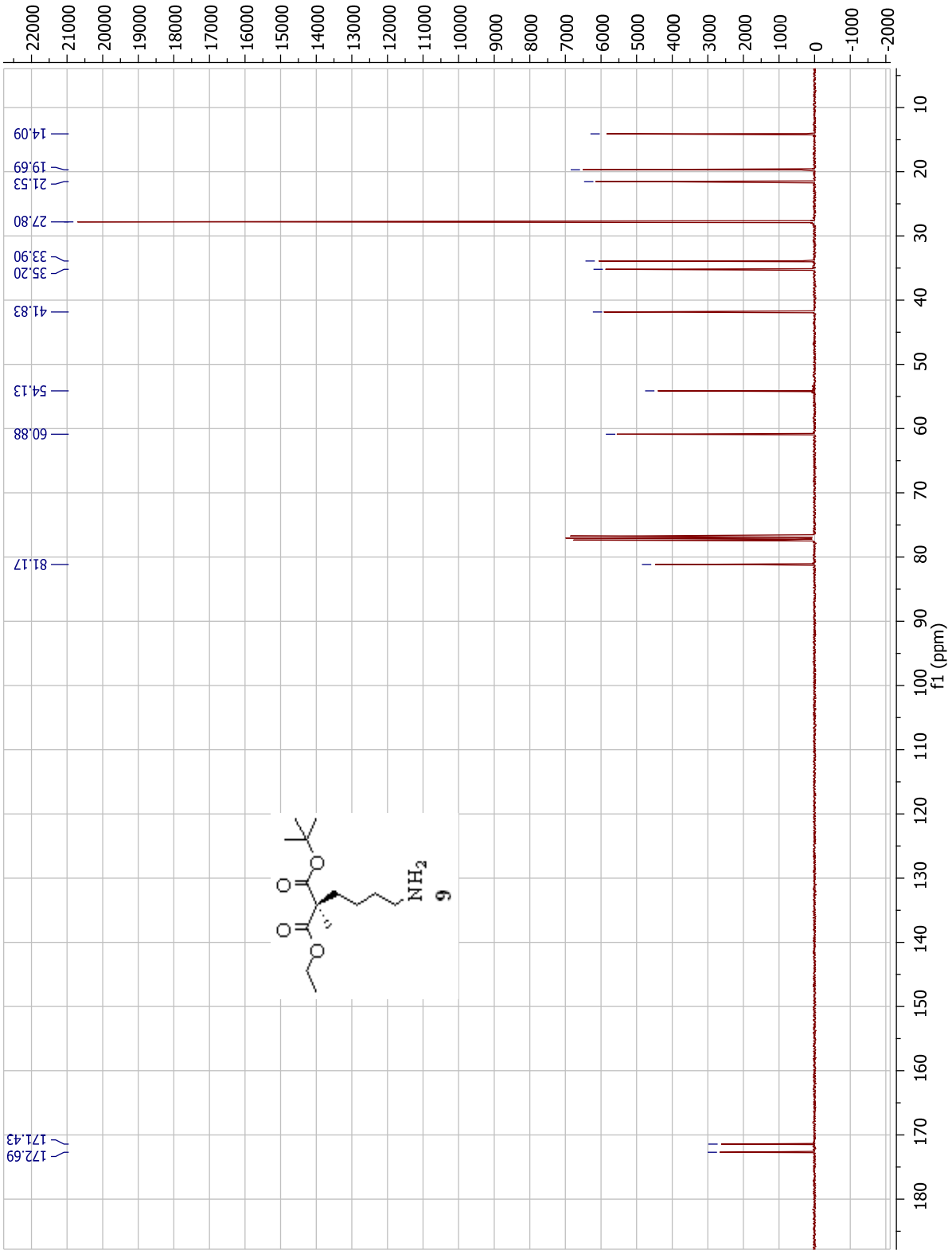


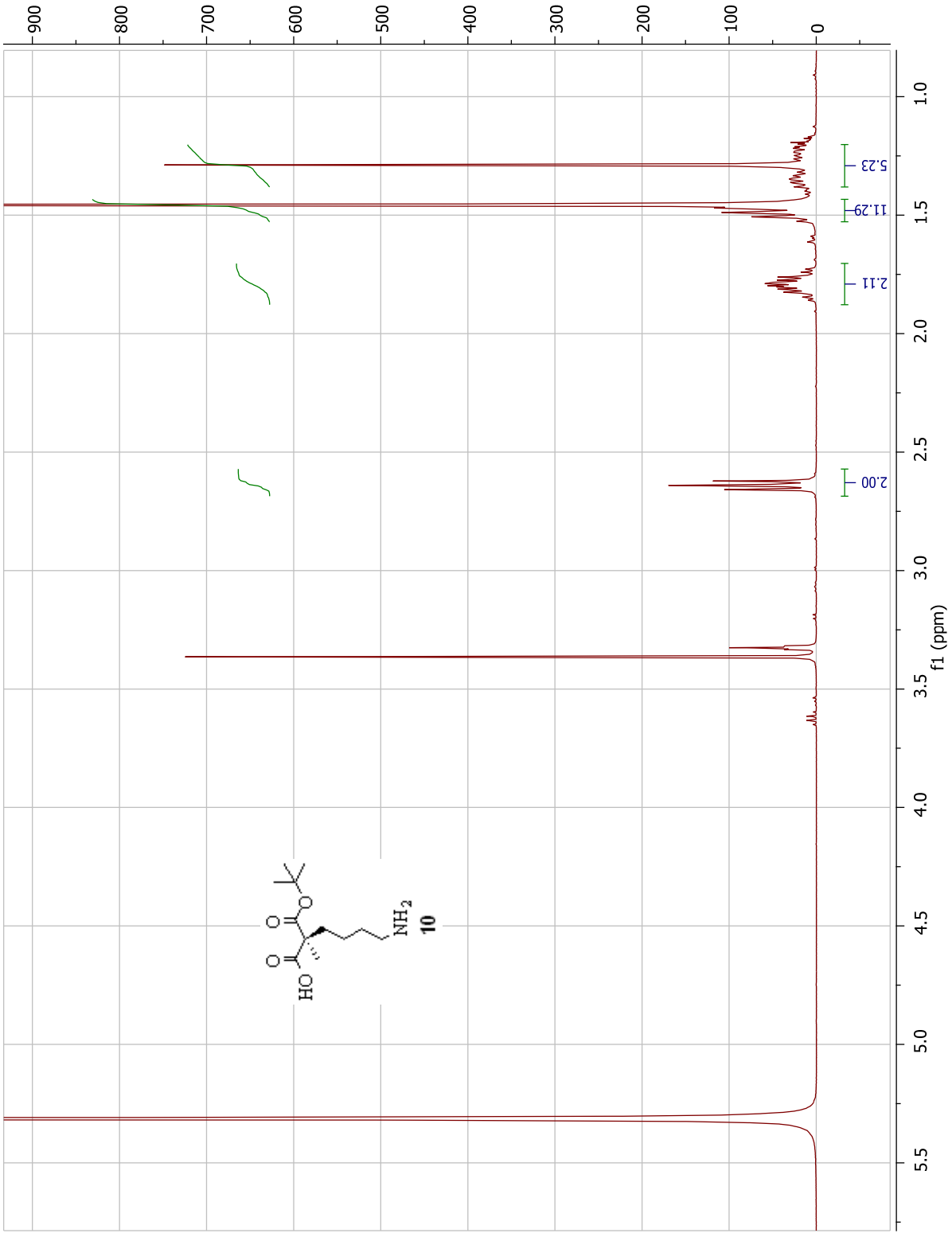

20.75
21.89
27.39
29.65
36.37
39.70
58.95
66.09
78.45
119.50
124.83
126.76
127.36
141.20
143.91
143.95
155.77
157.17
176.26
f1 (ppm)
7

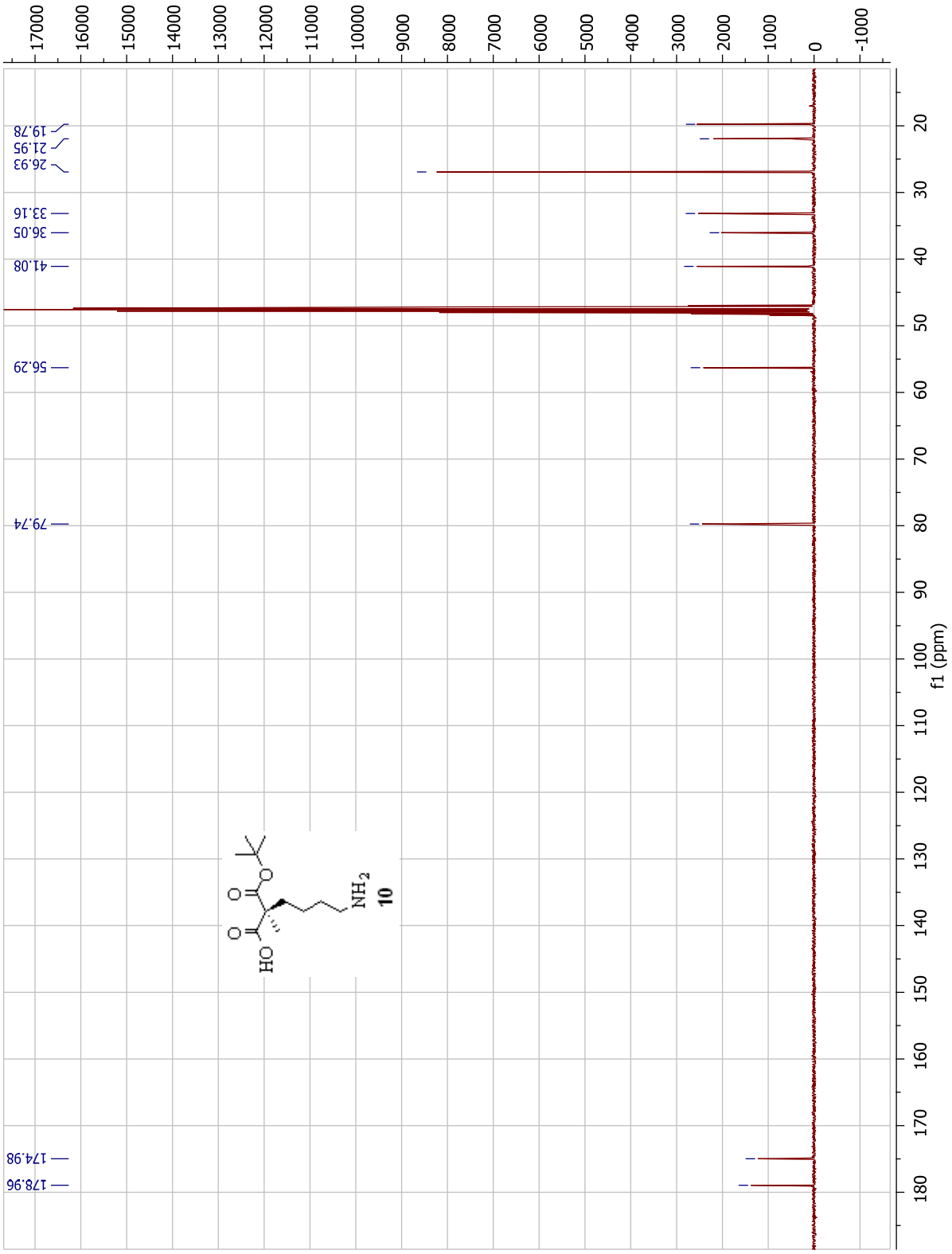


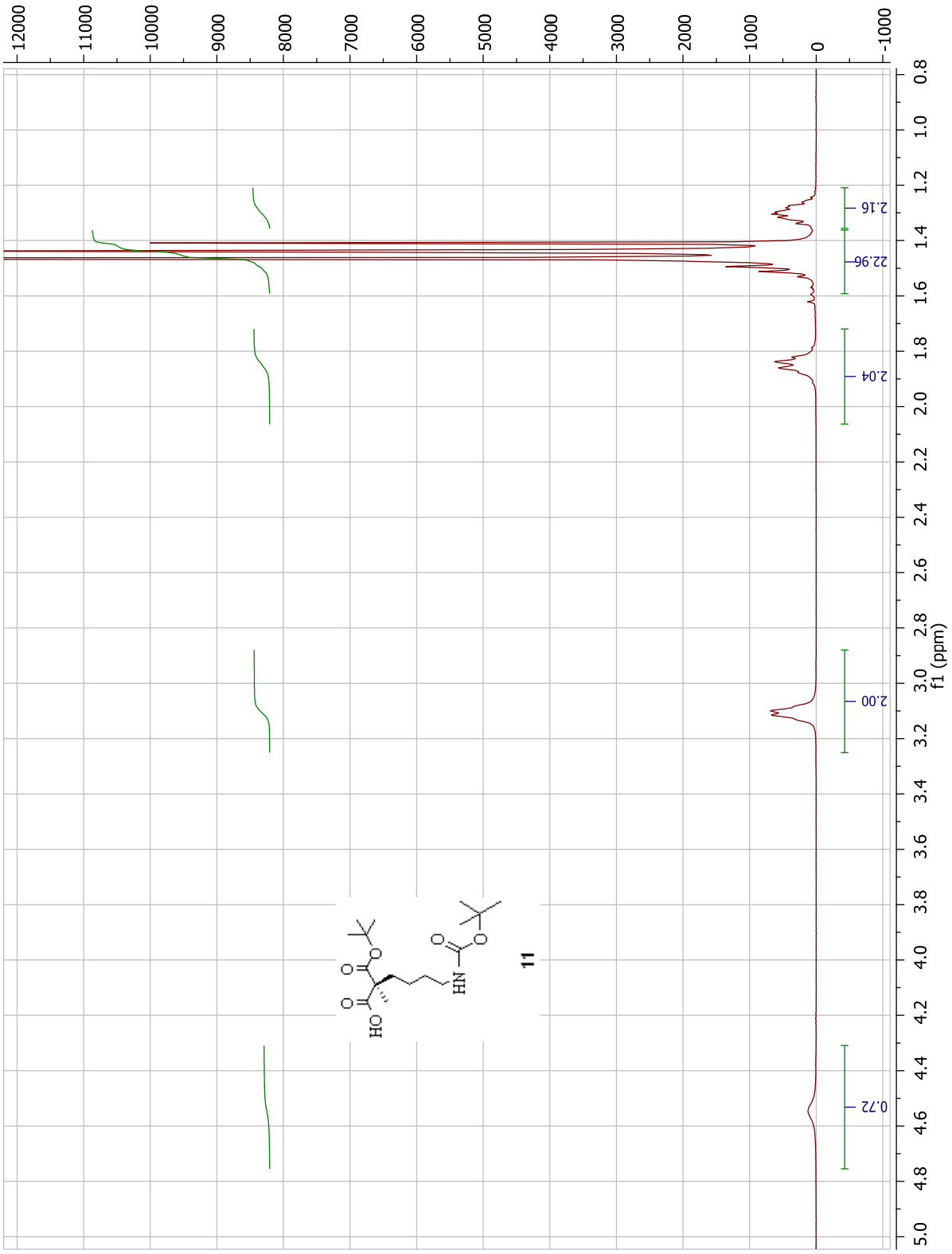


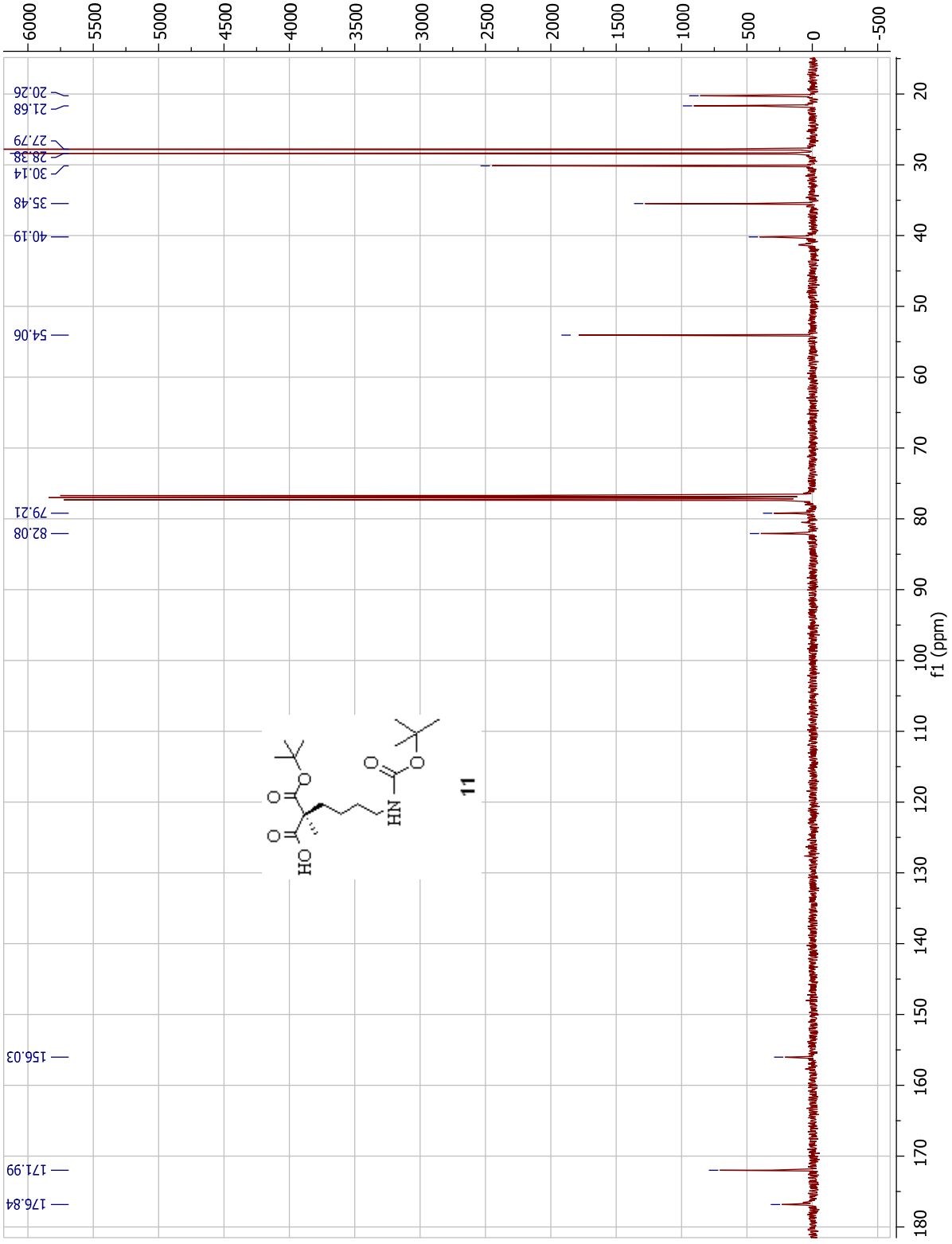


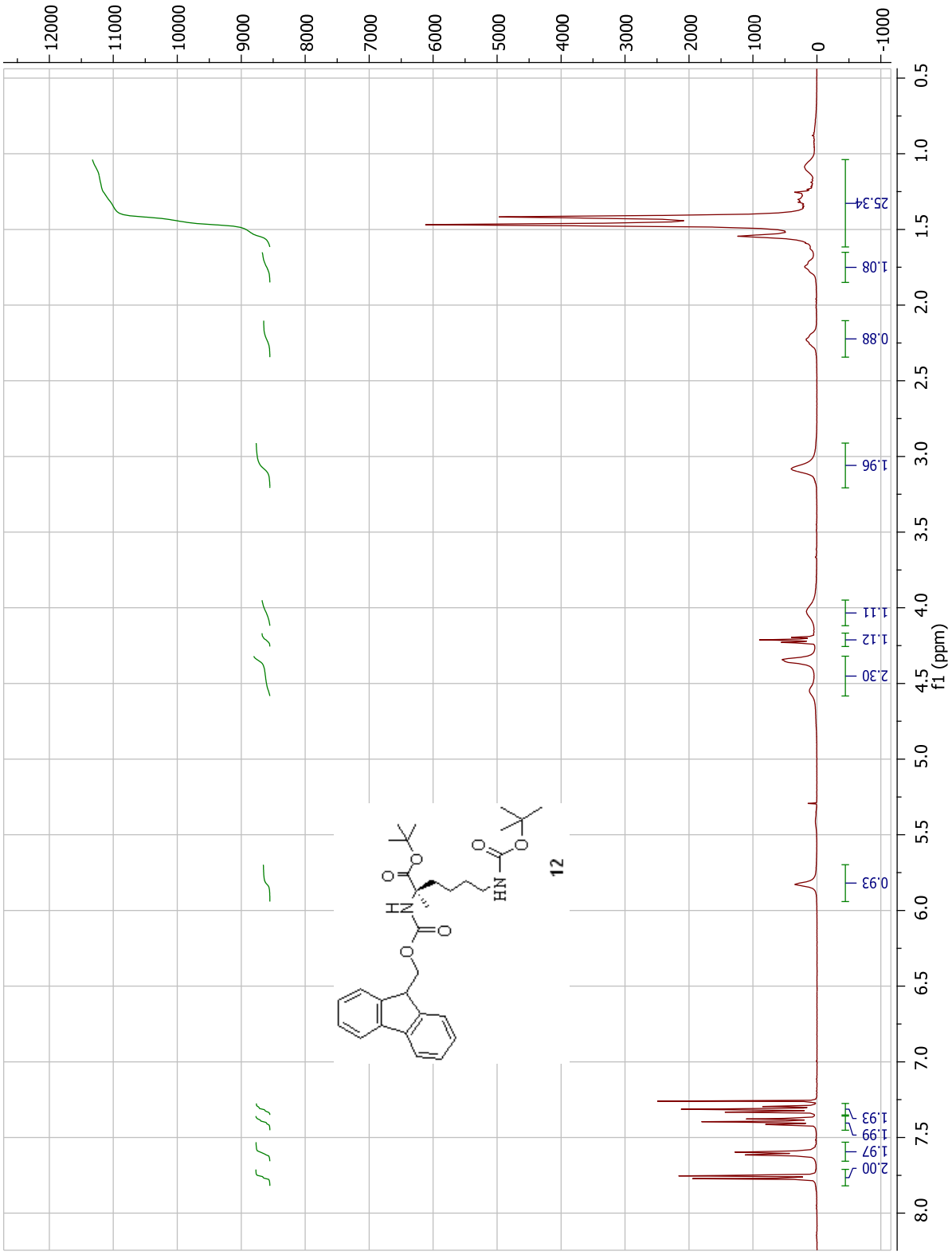


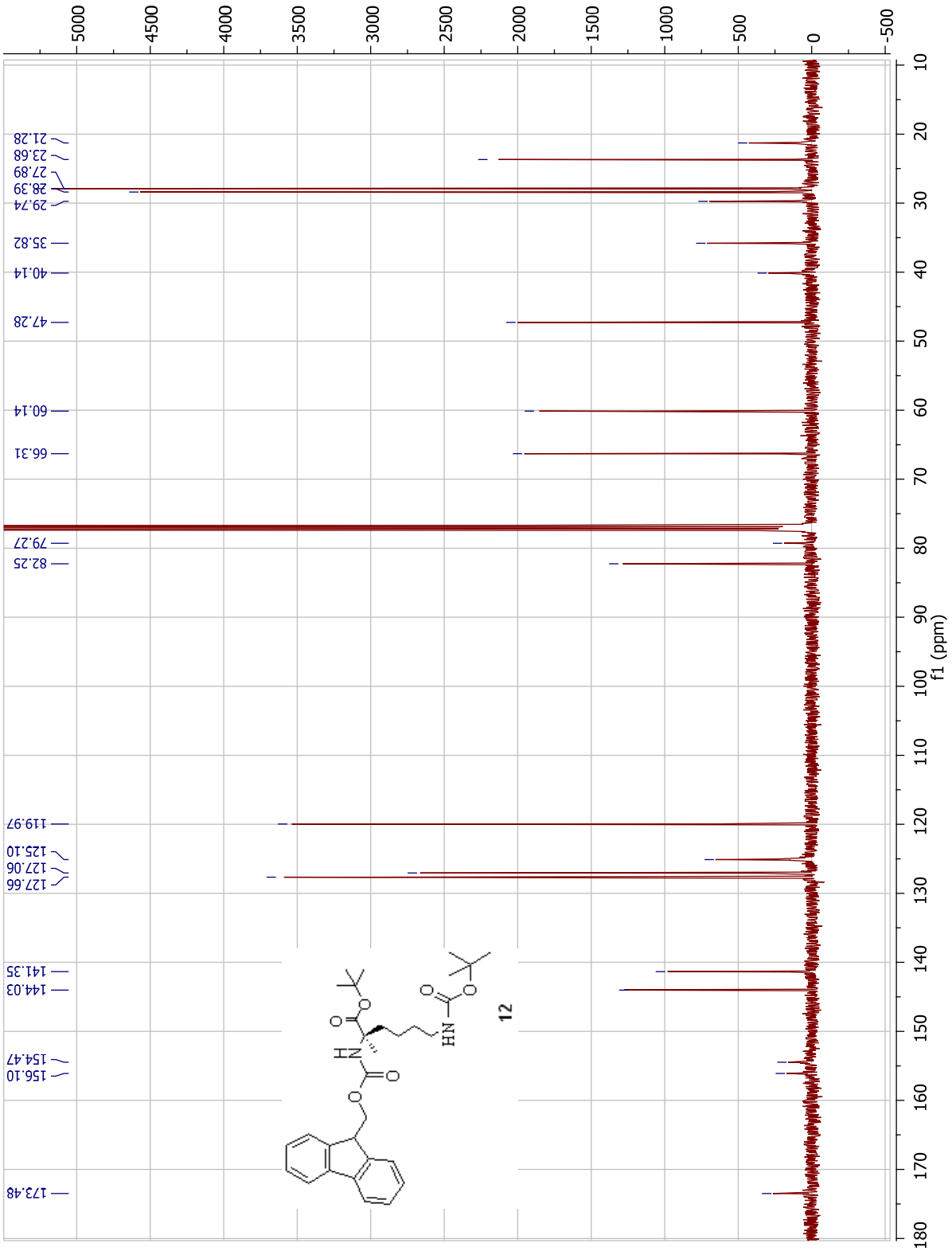


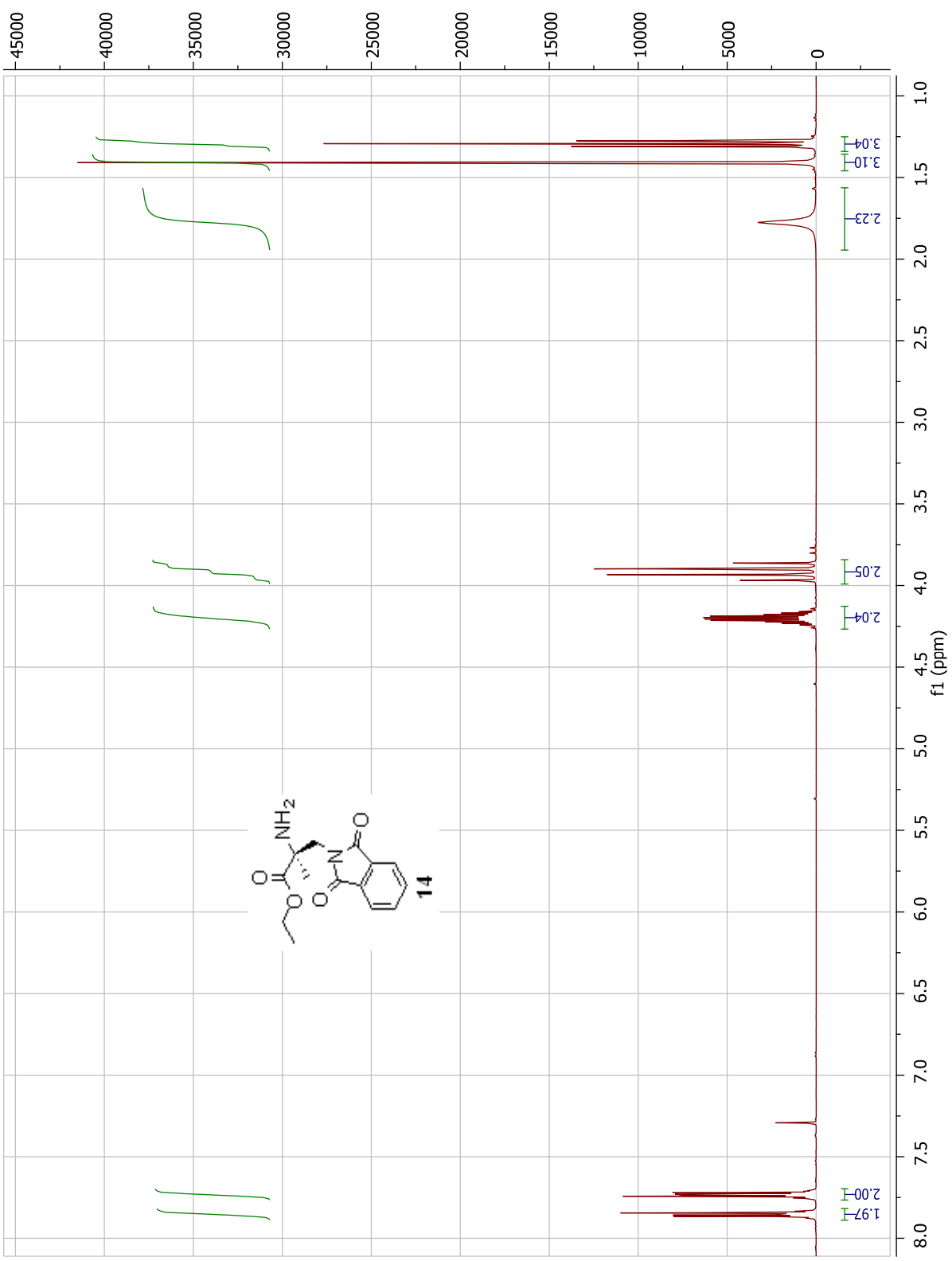


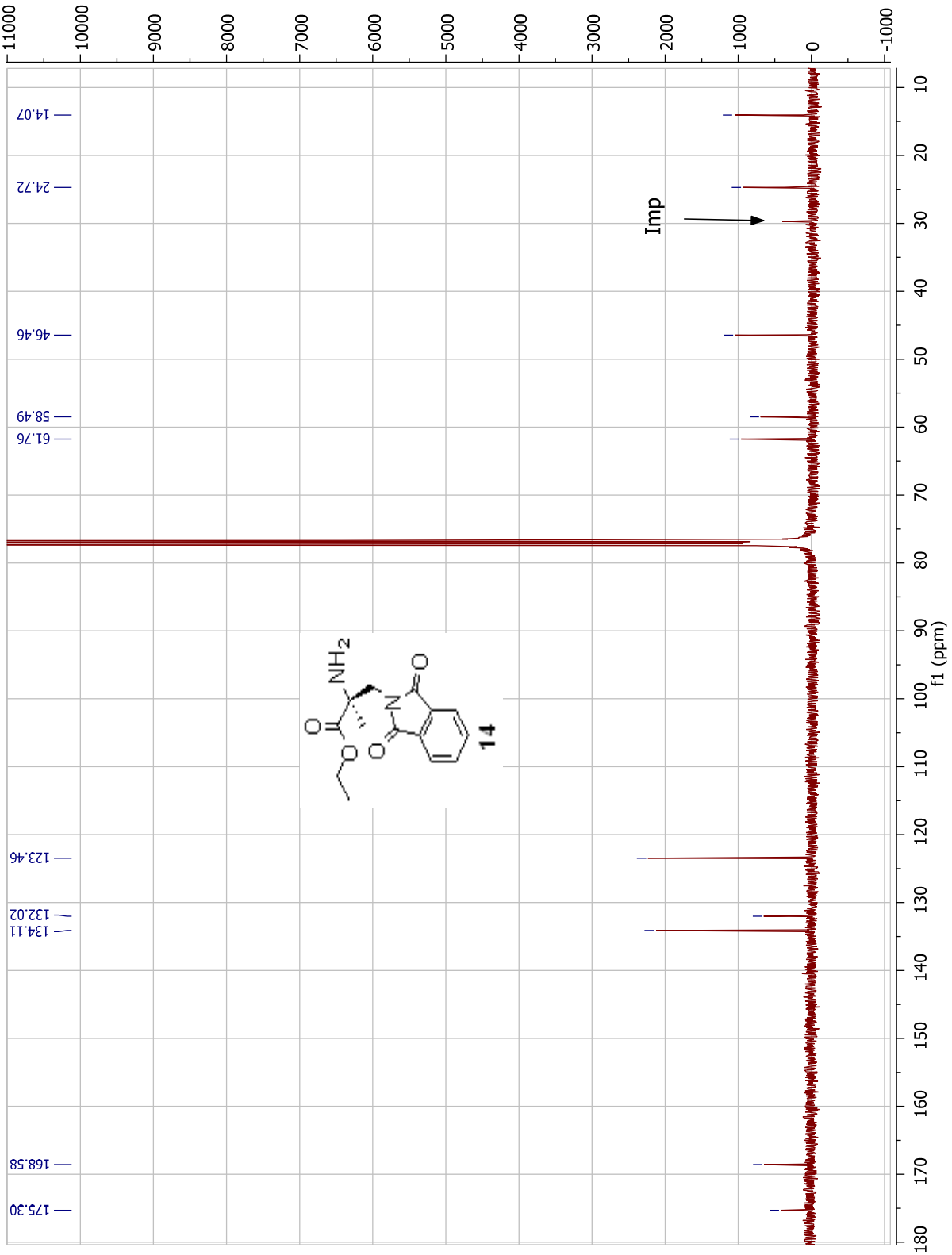


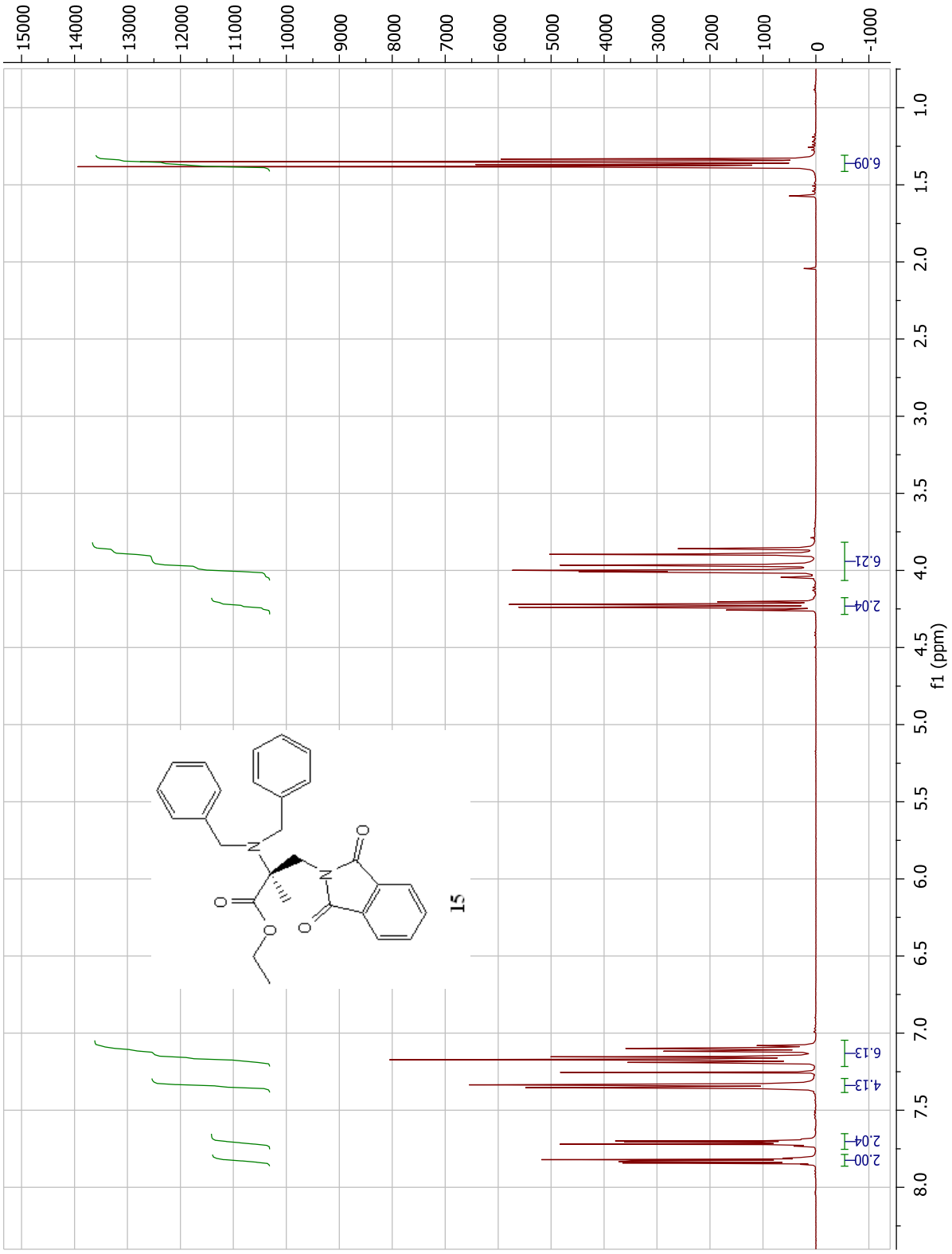


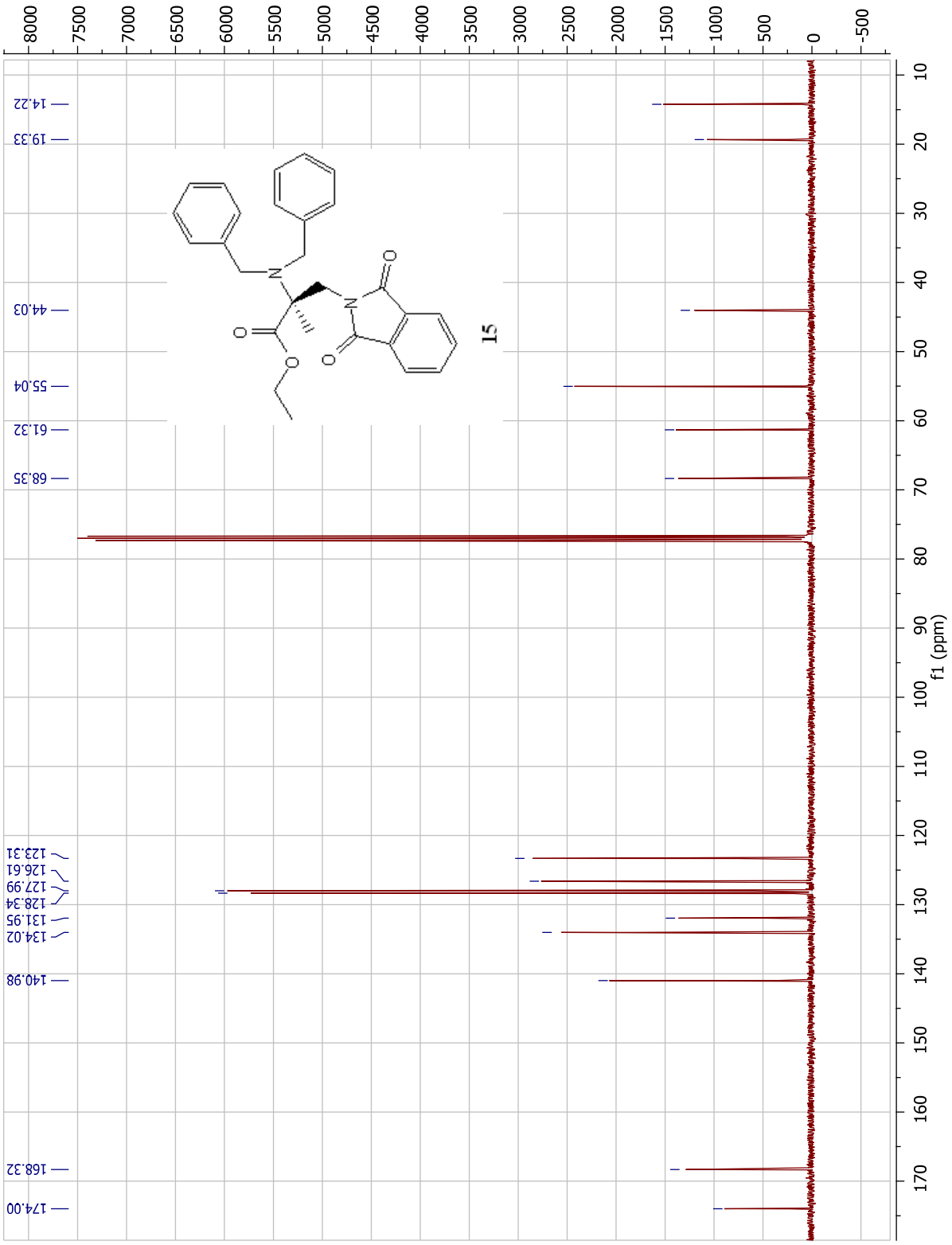


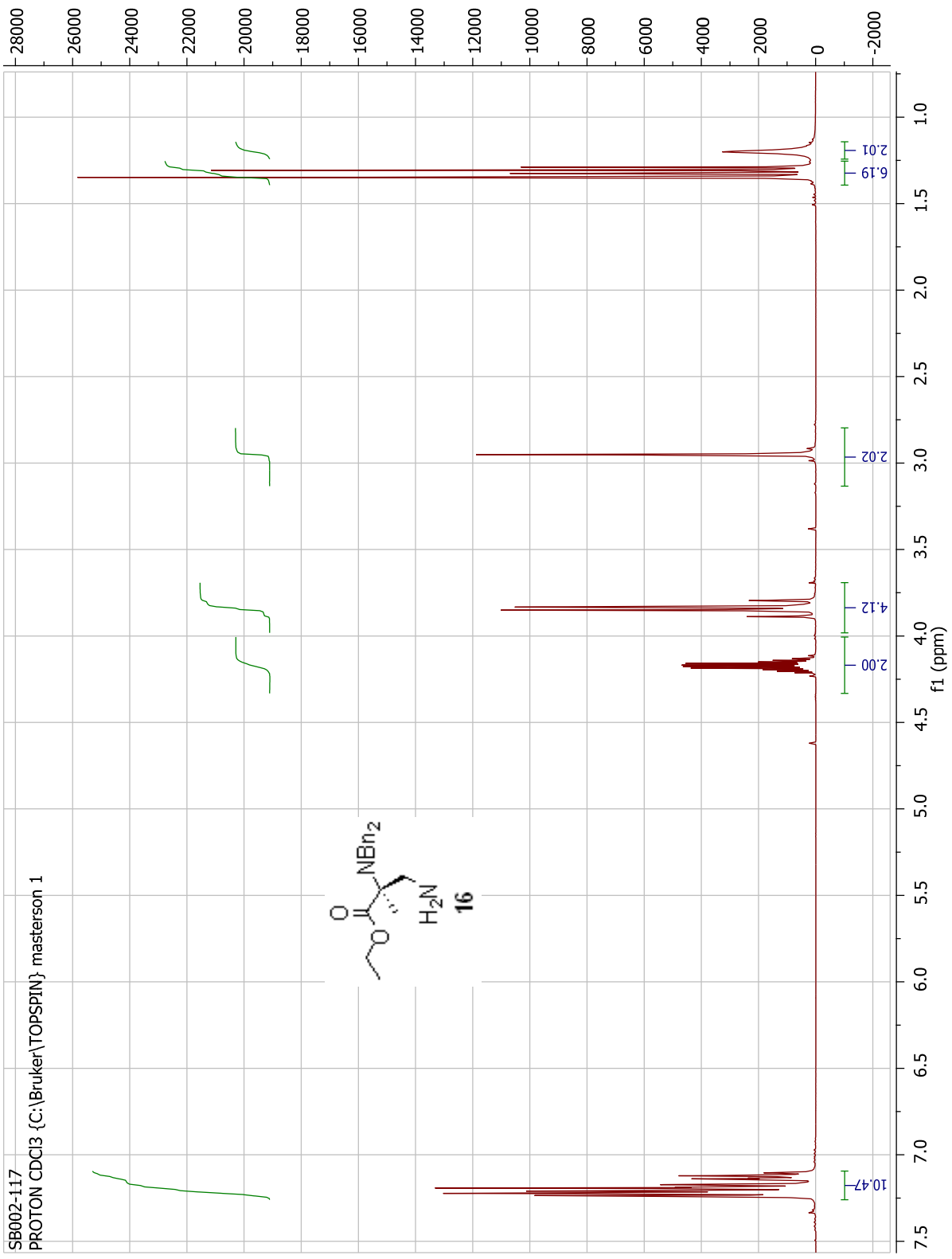


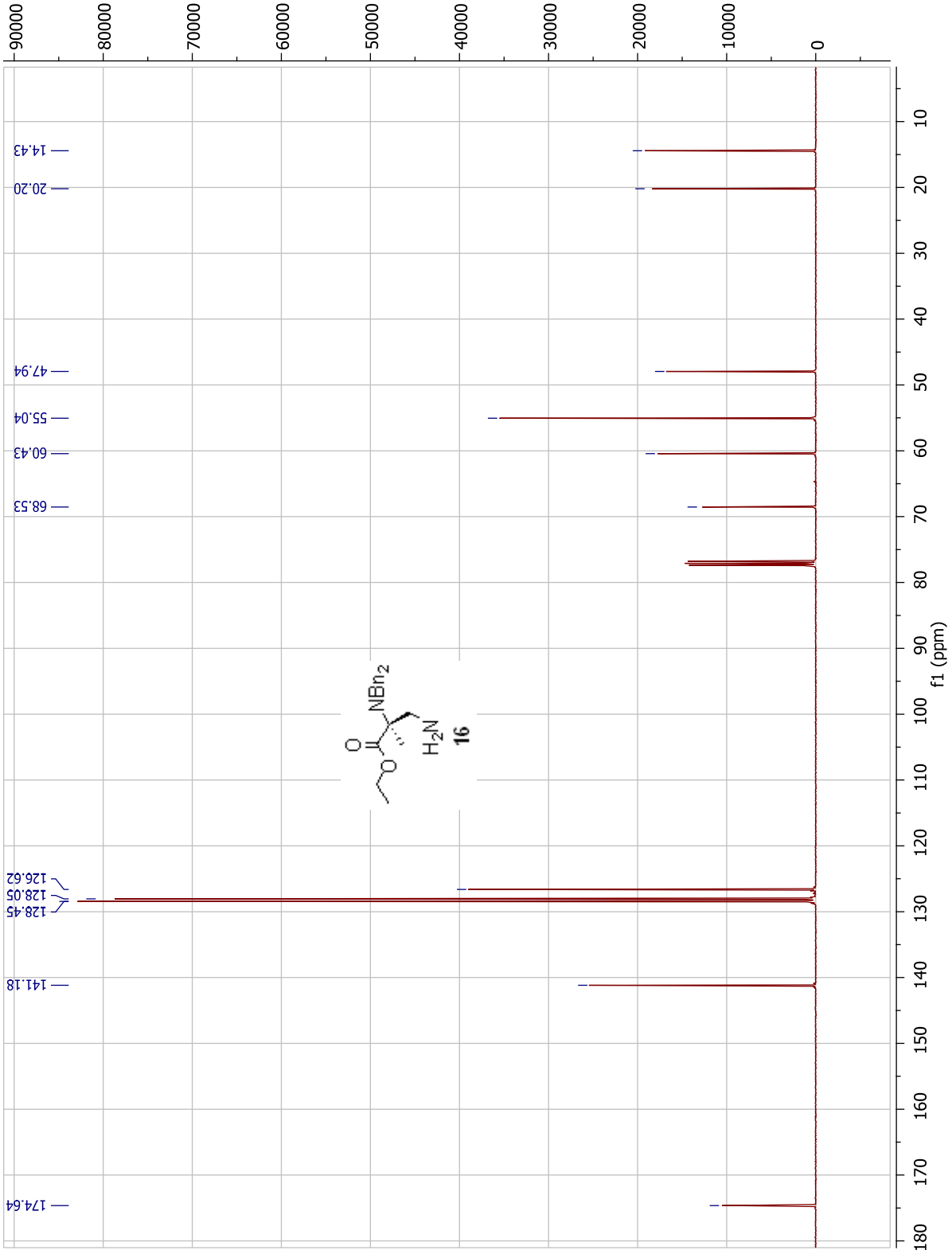

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
3.04
3.10
2.23
2.05
2.04
2.00
1.97
NH2
O
O
O
N
O
O
14

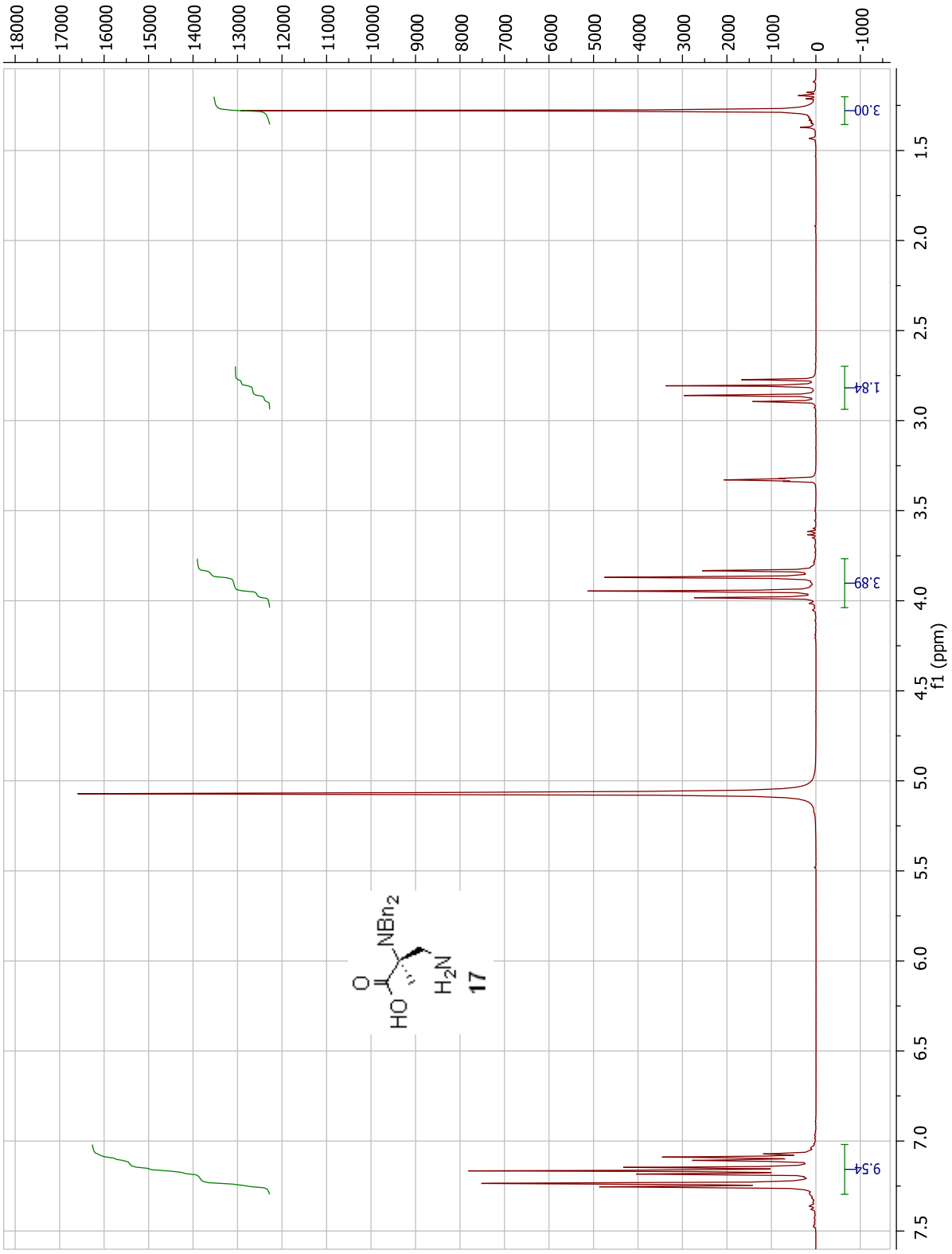


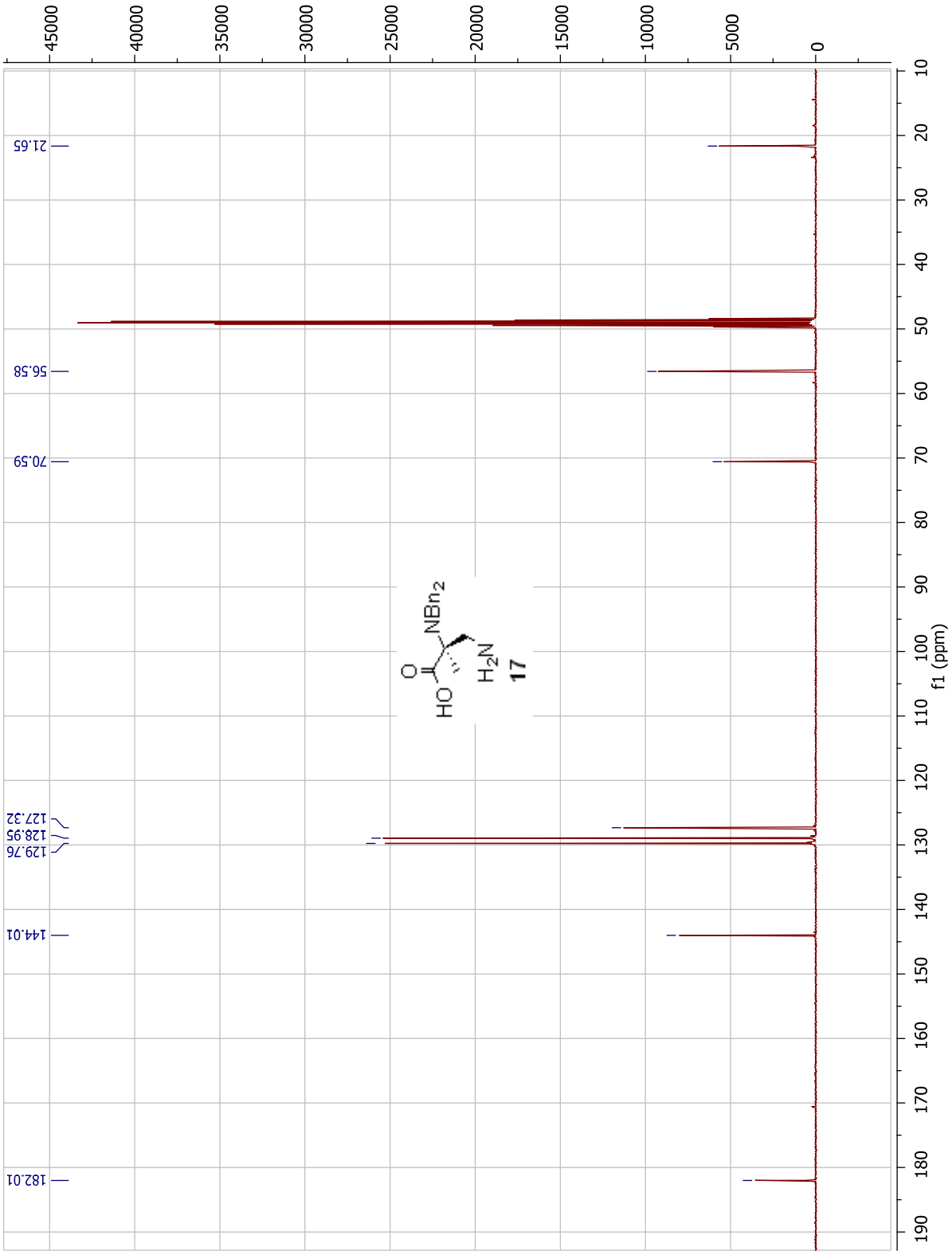


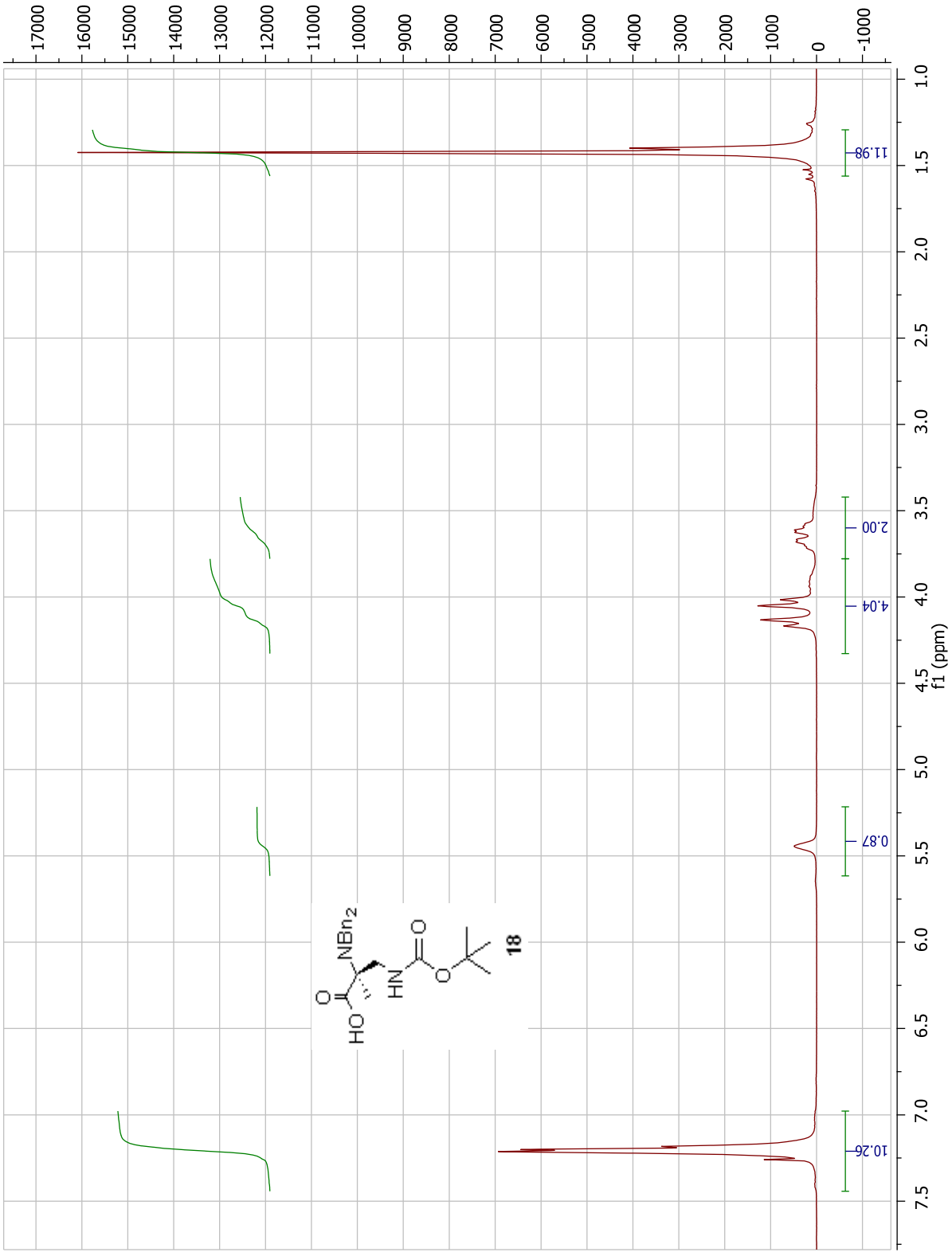


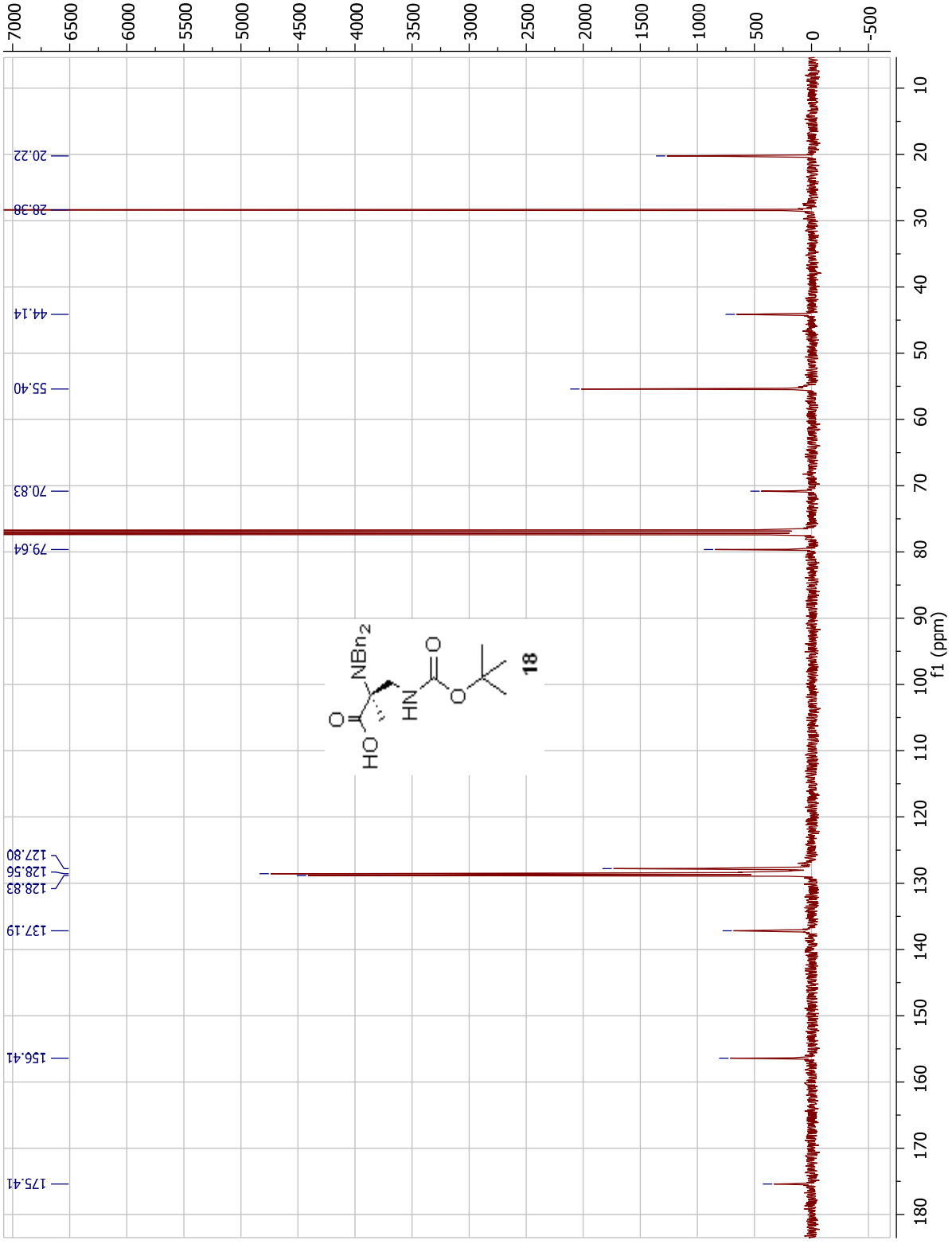

SB002-117
PROTON CDCl3 {C:\Bruker\TOPSPIN} masterson 1
NBn2
H2N
O
O
16
10.47
2.00
4.12
2.02
6.19
2.01
f1 (ppm)

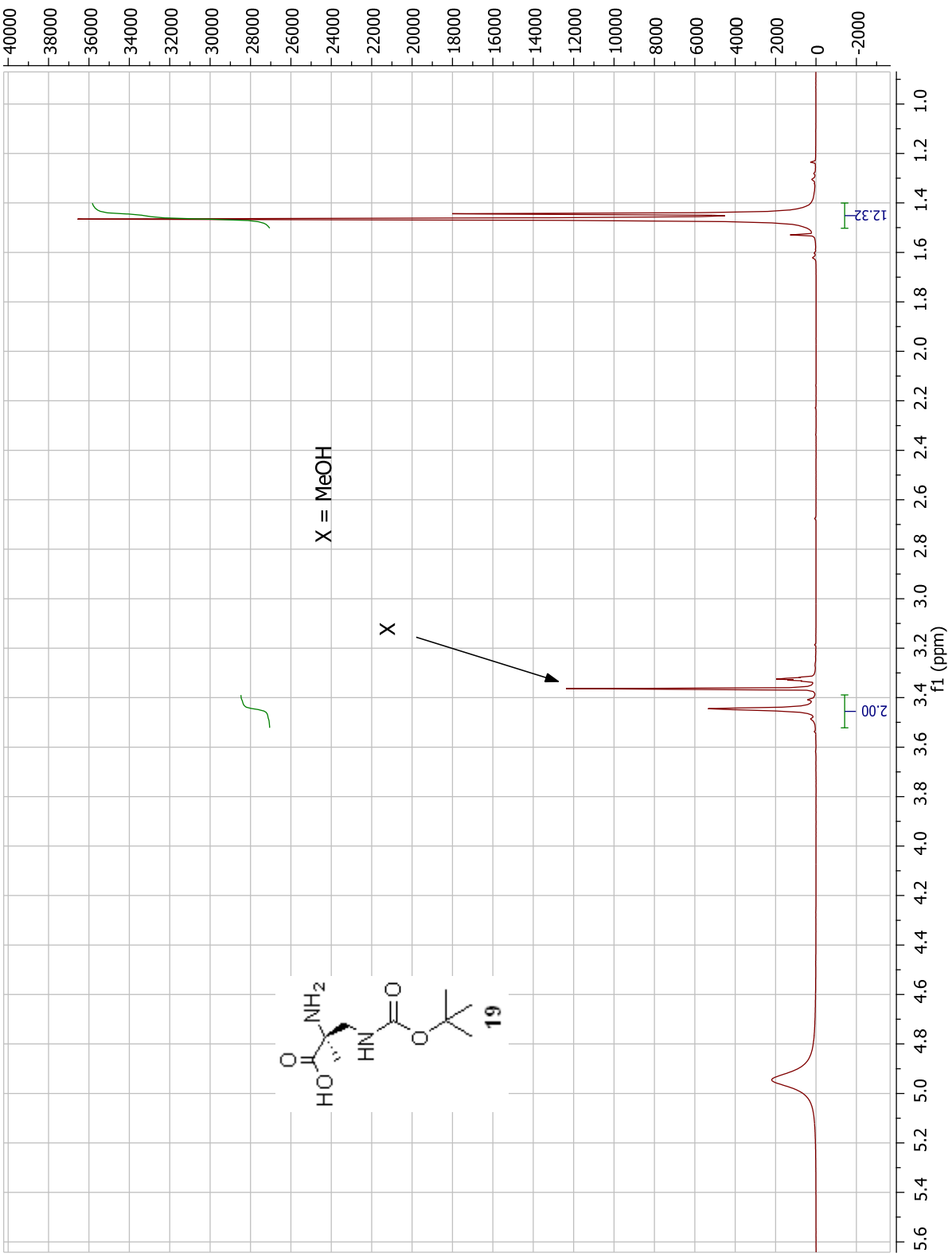


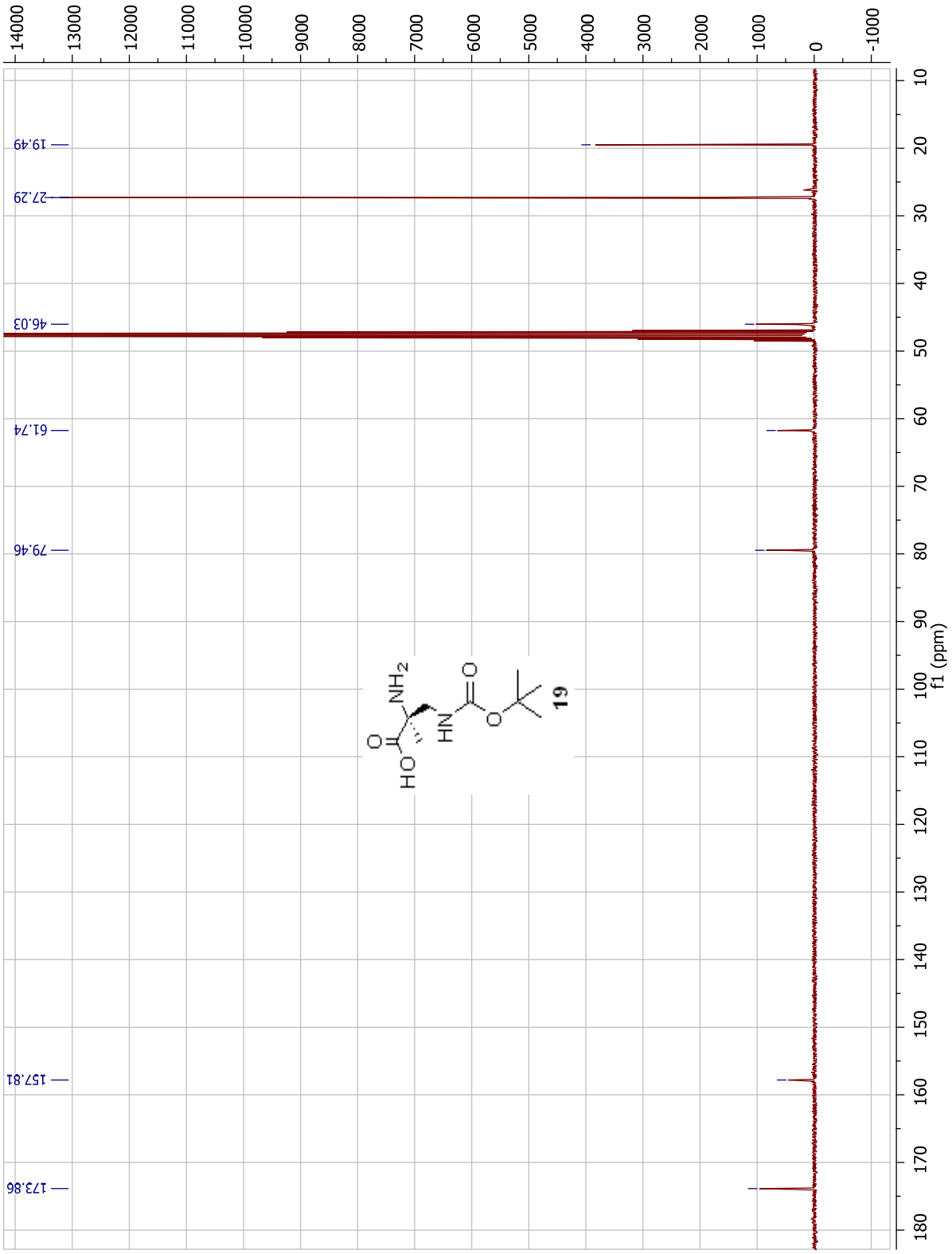


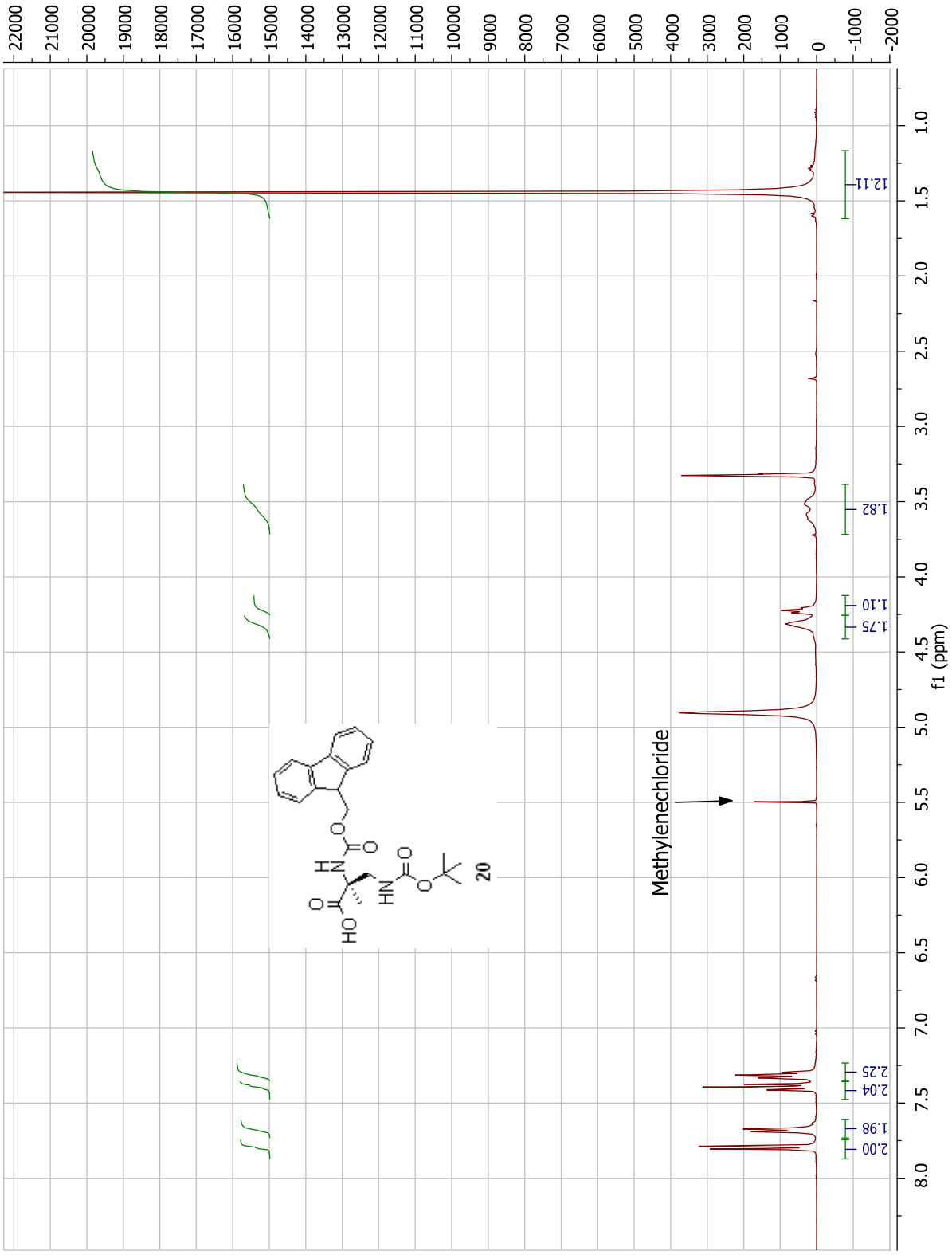


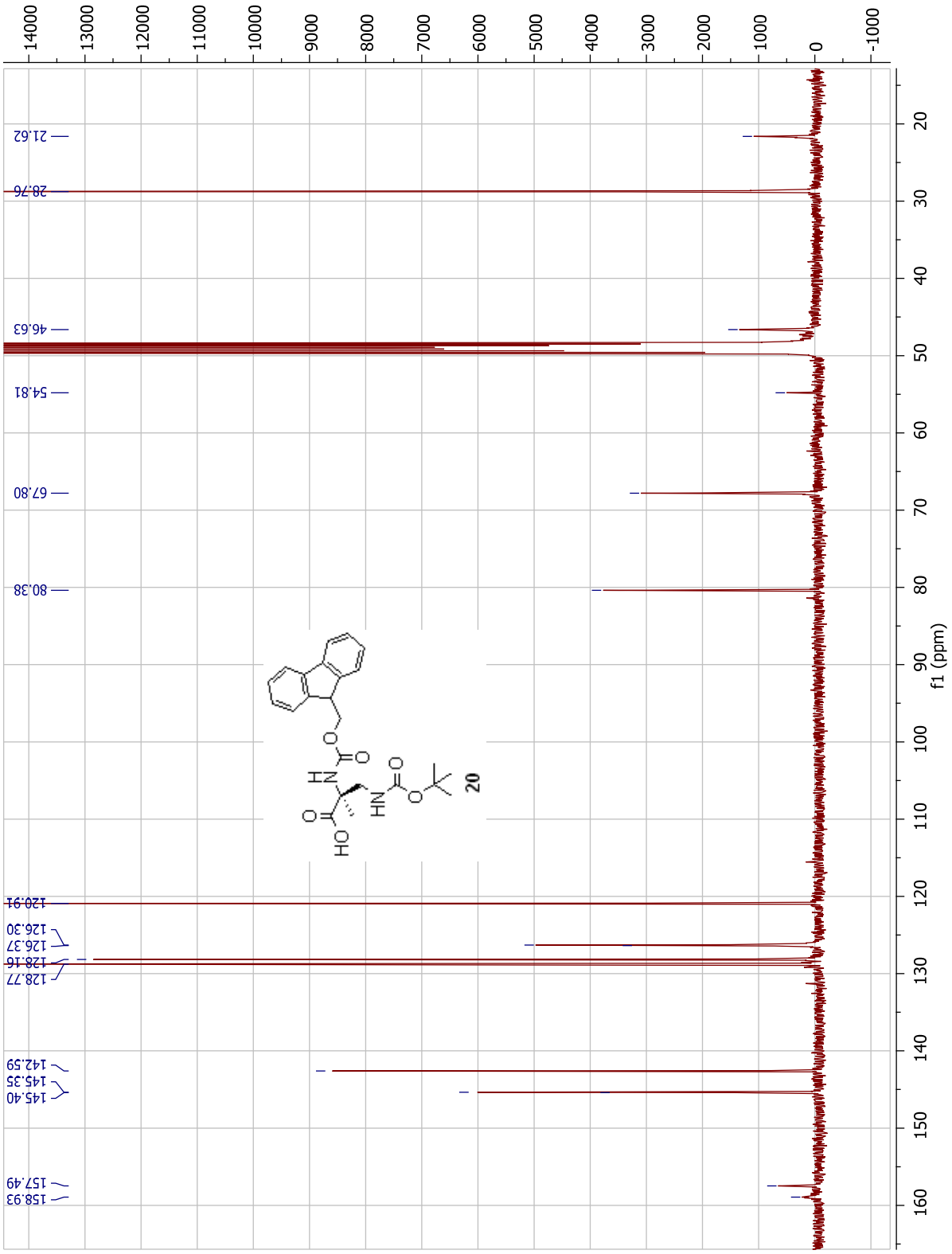


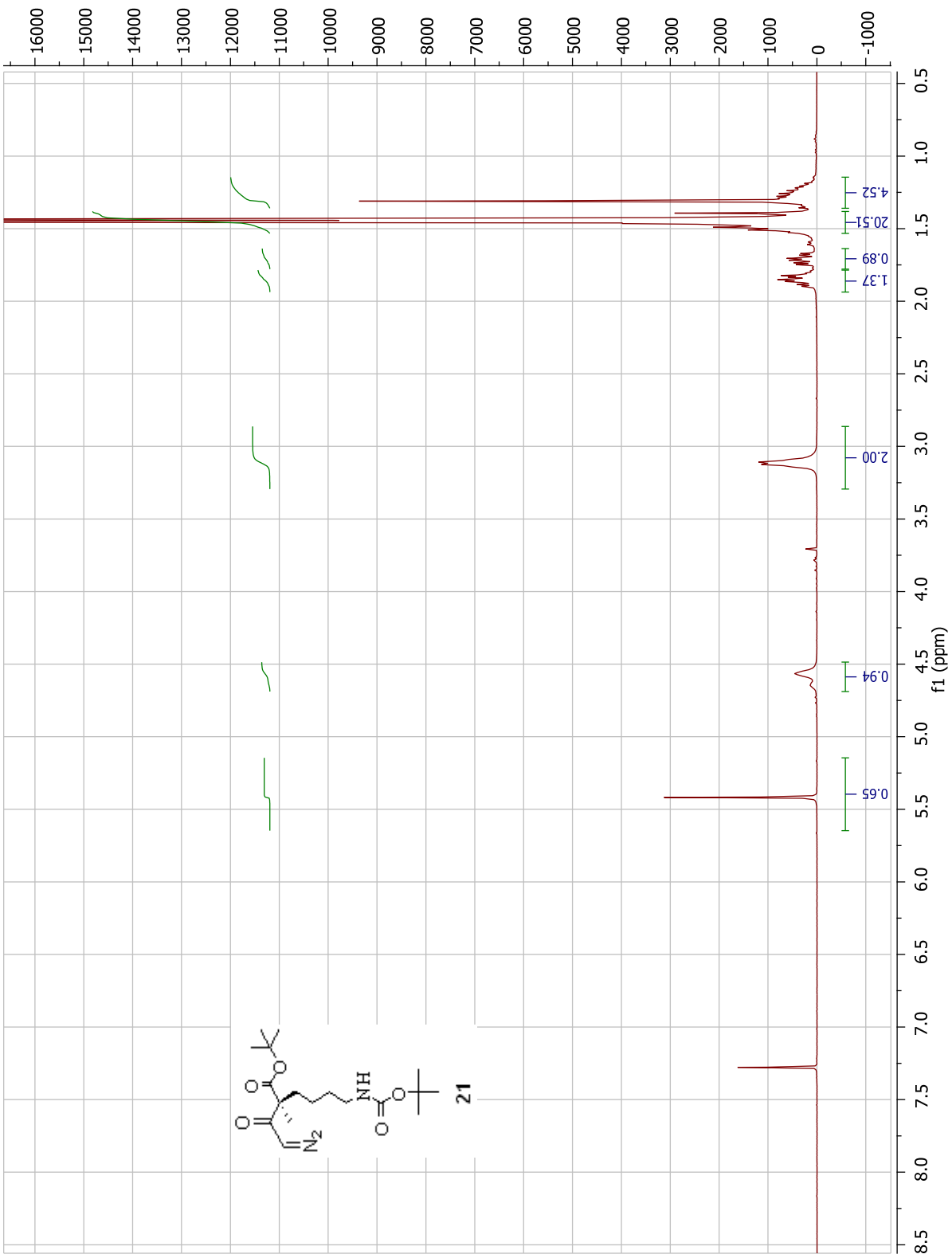


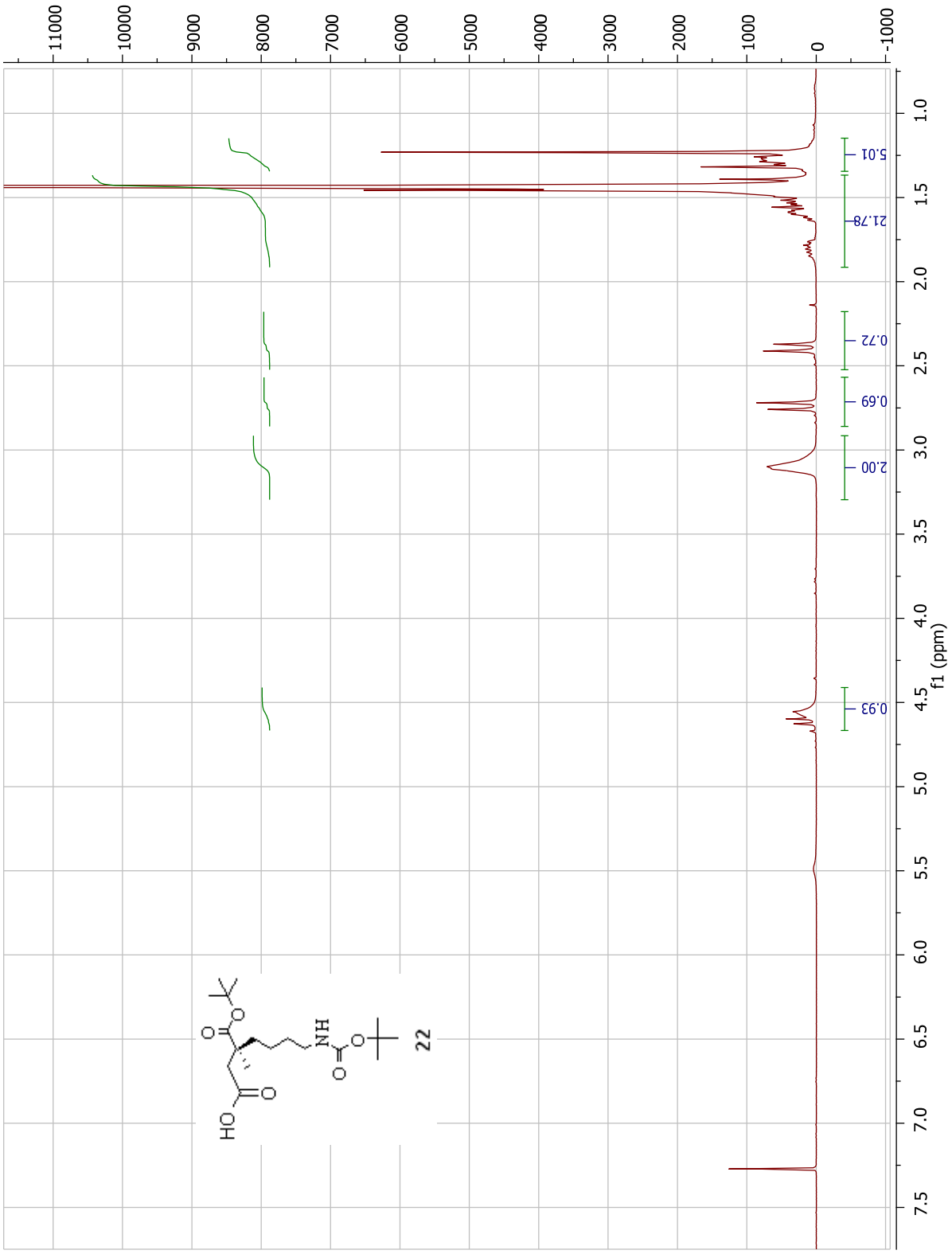

X = MeOH
X
19
12.32
2.00
f1 (ppm)

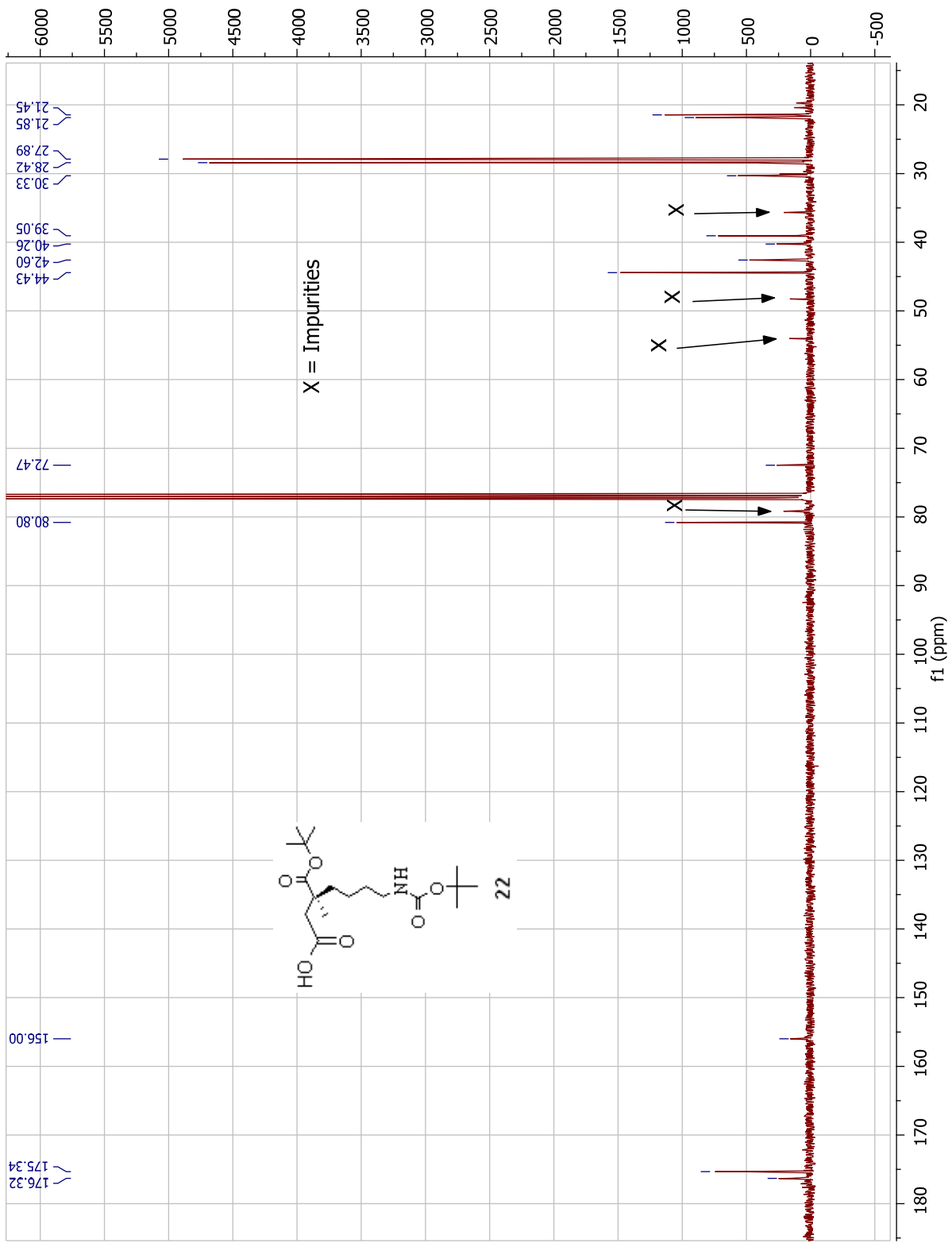

19.49
27.29
46.03
61.74
79.46
157.81
173.86
19
f1 (ppm)

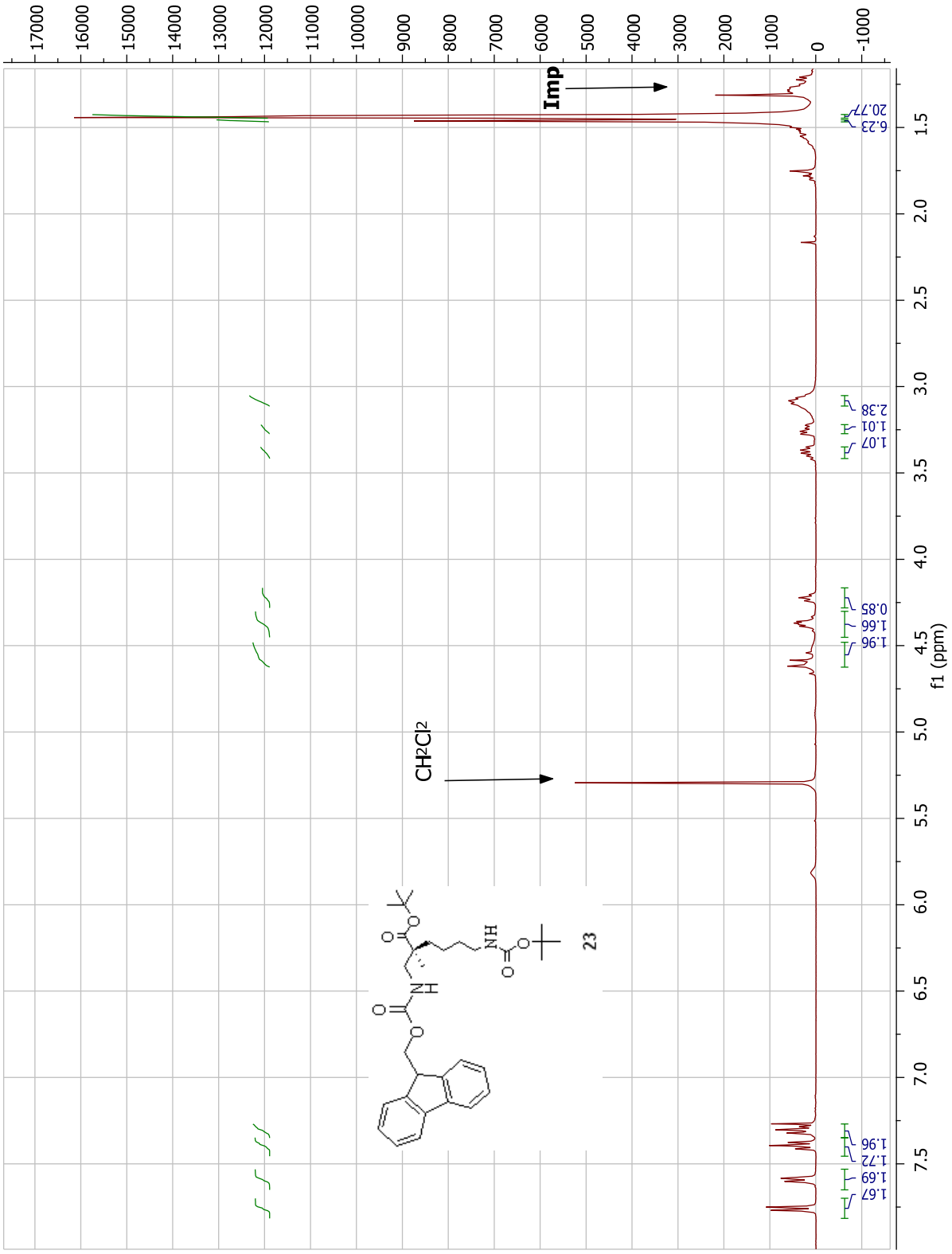


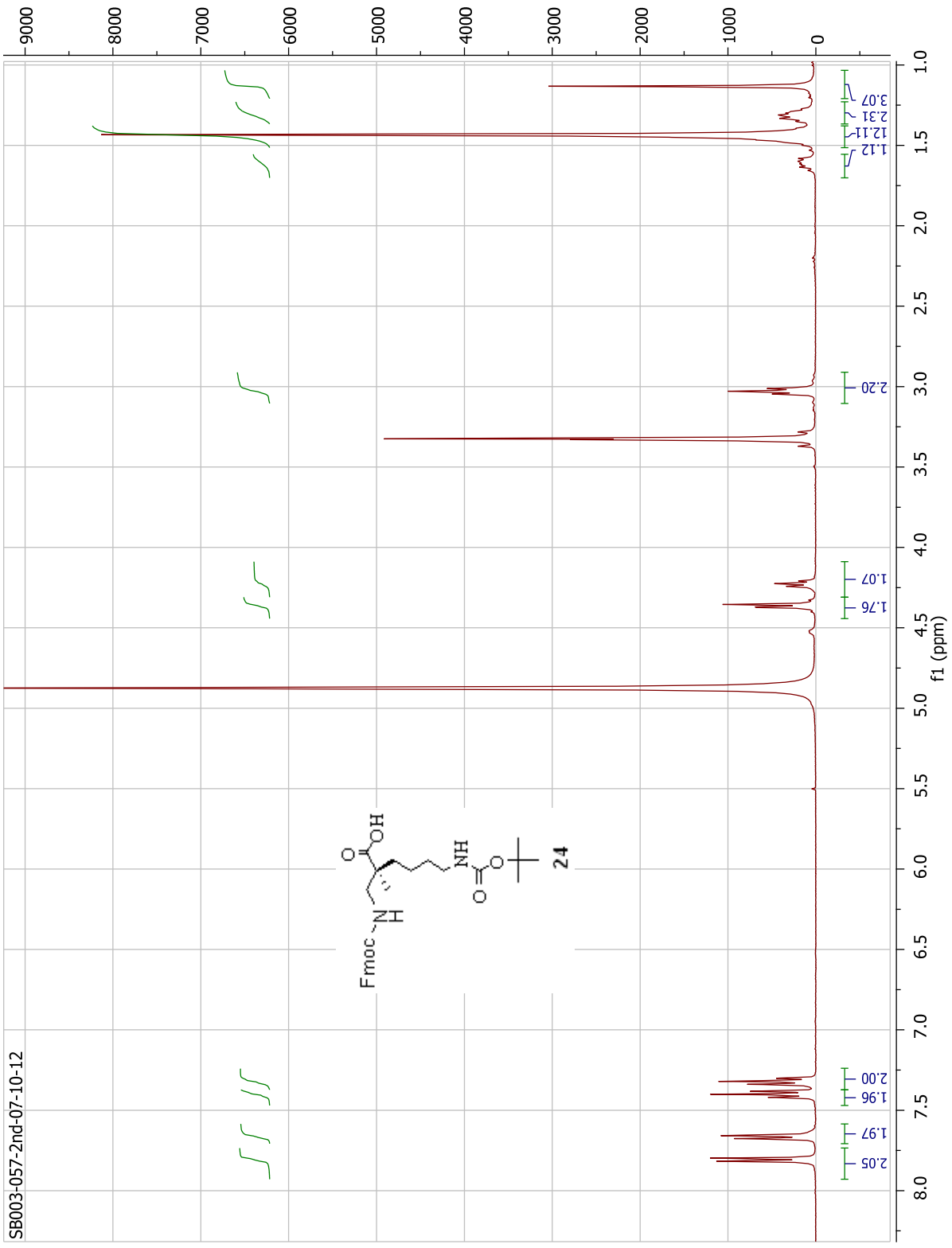


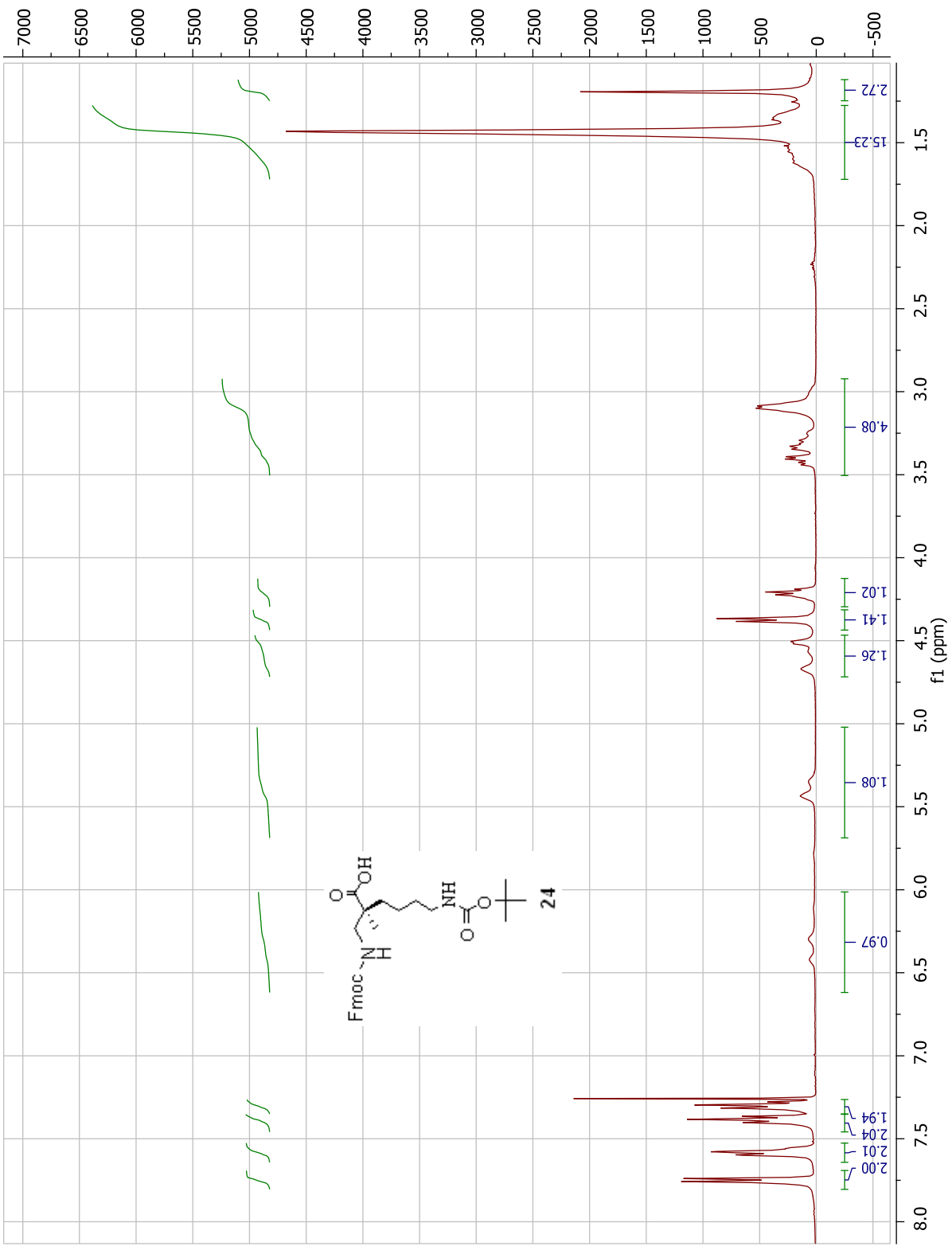

16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)
4.52
20.51
0.89
1.37
2.00
0.94
0.65
NH
O
N2
21

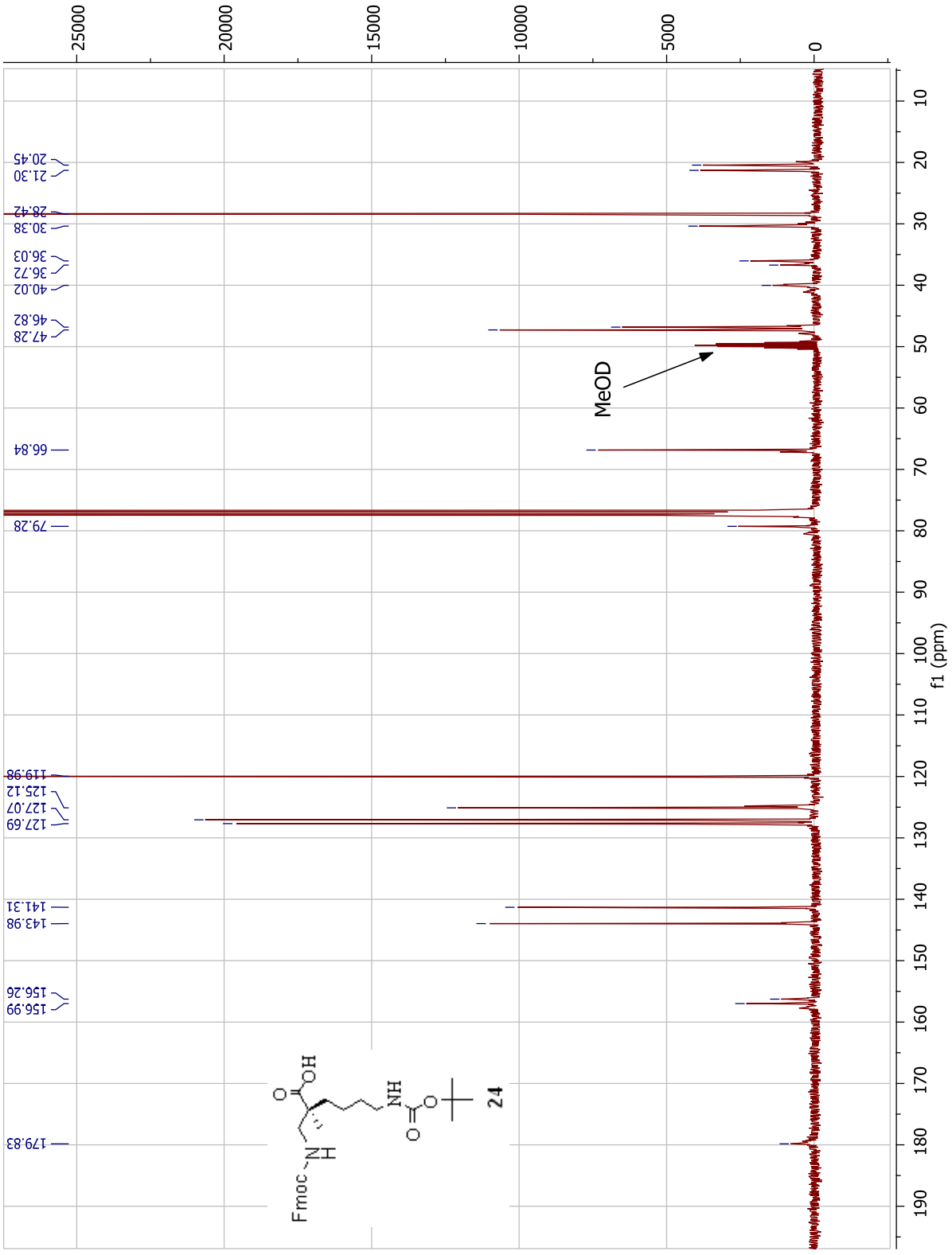


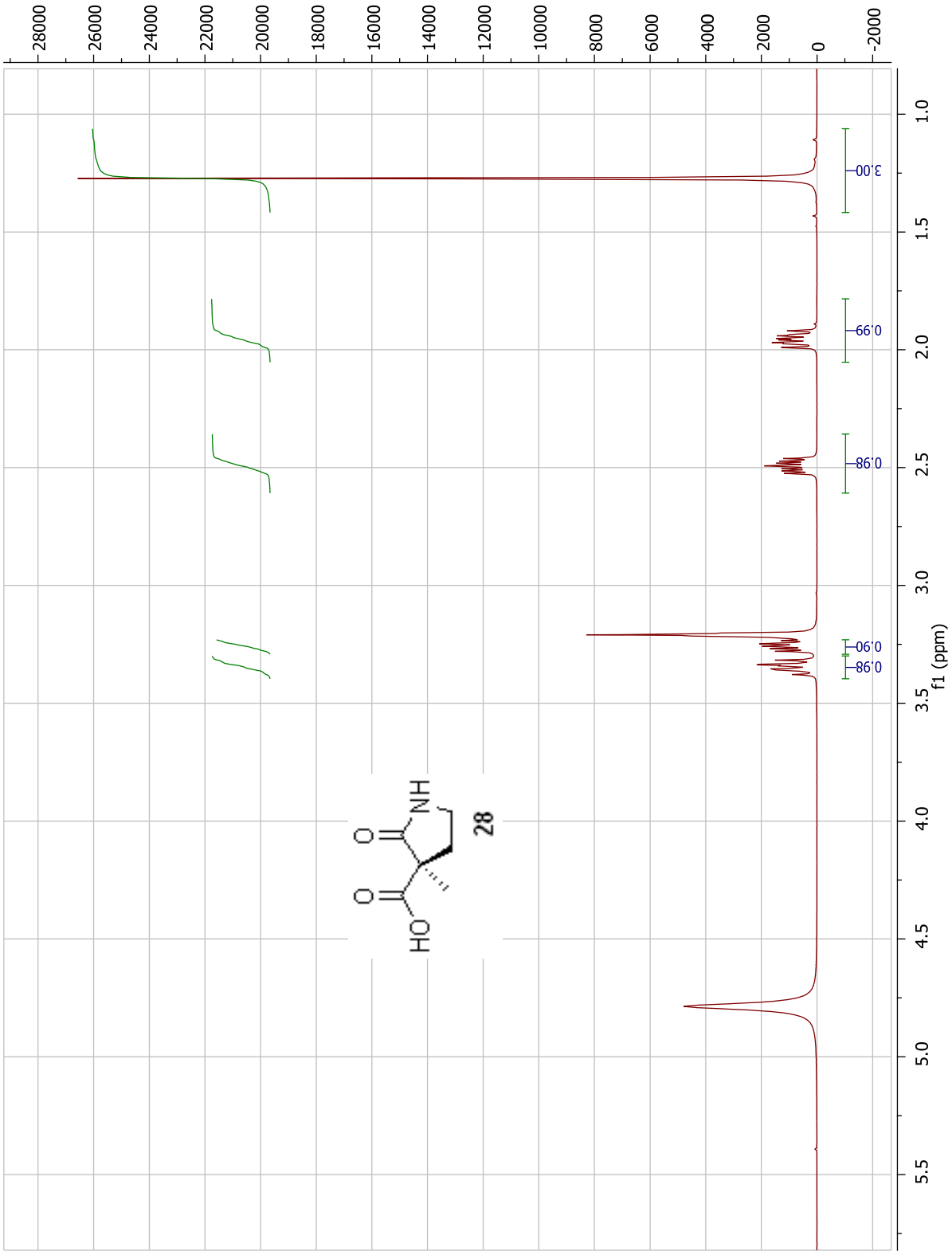


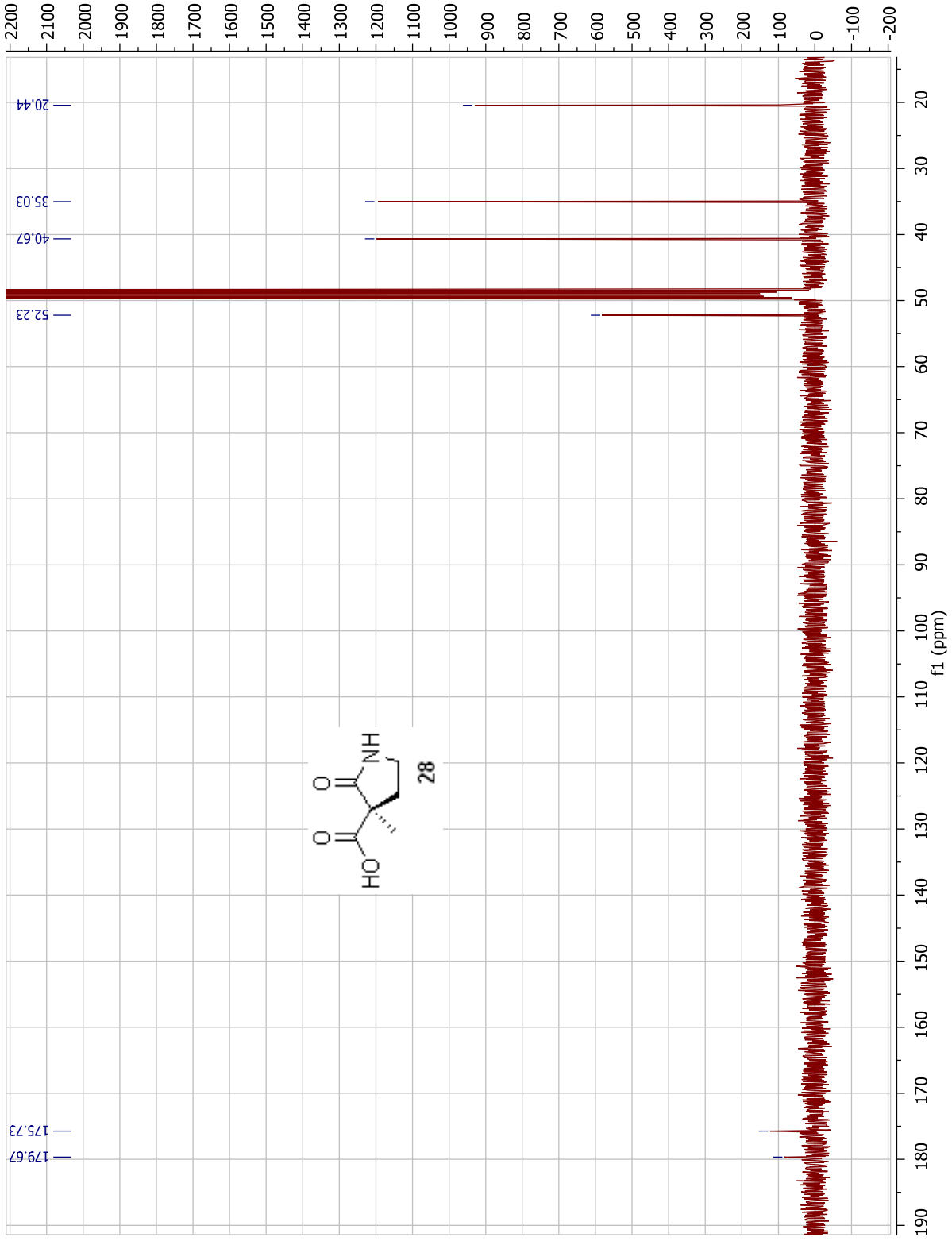


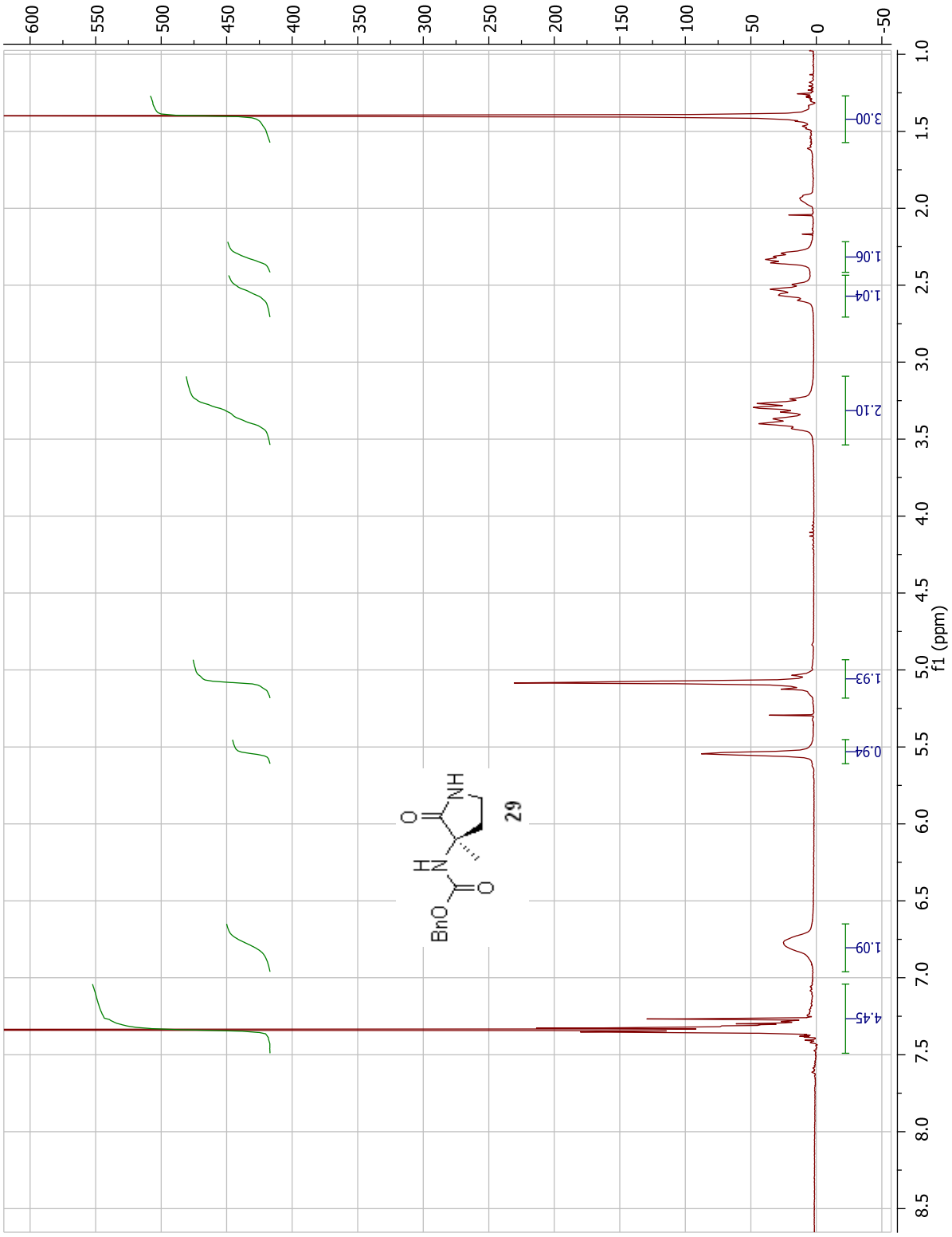


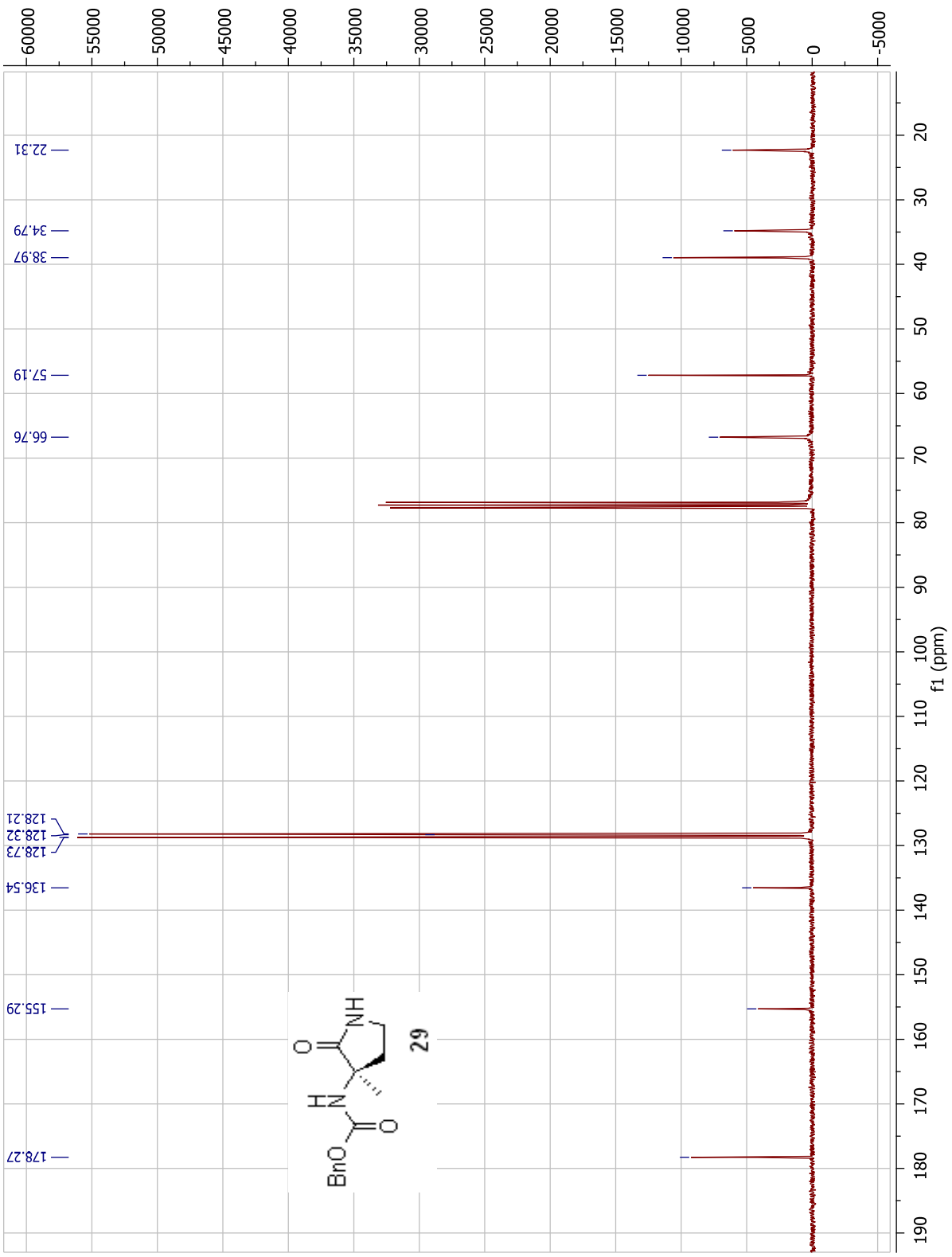


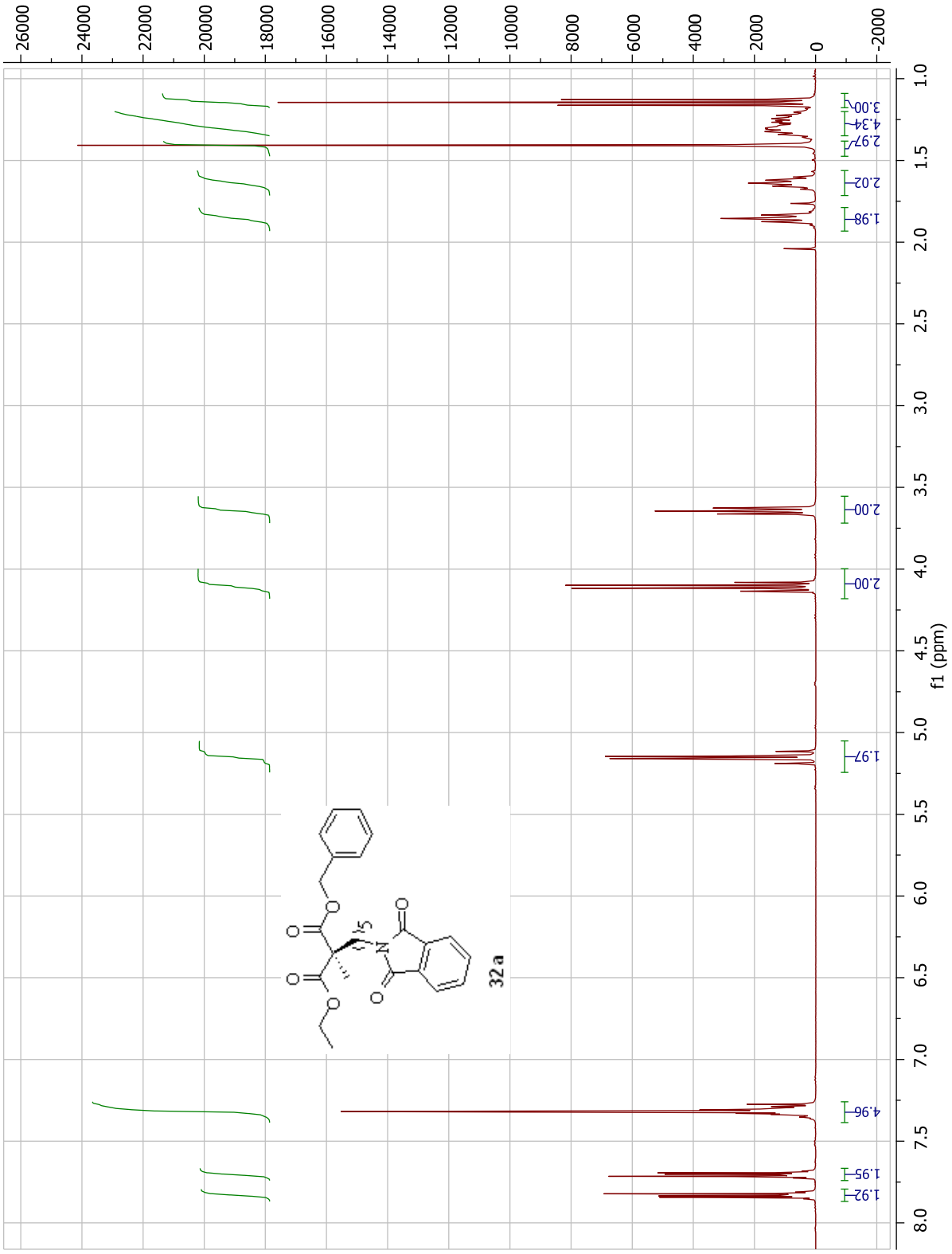


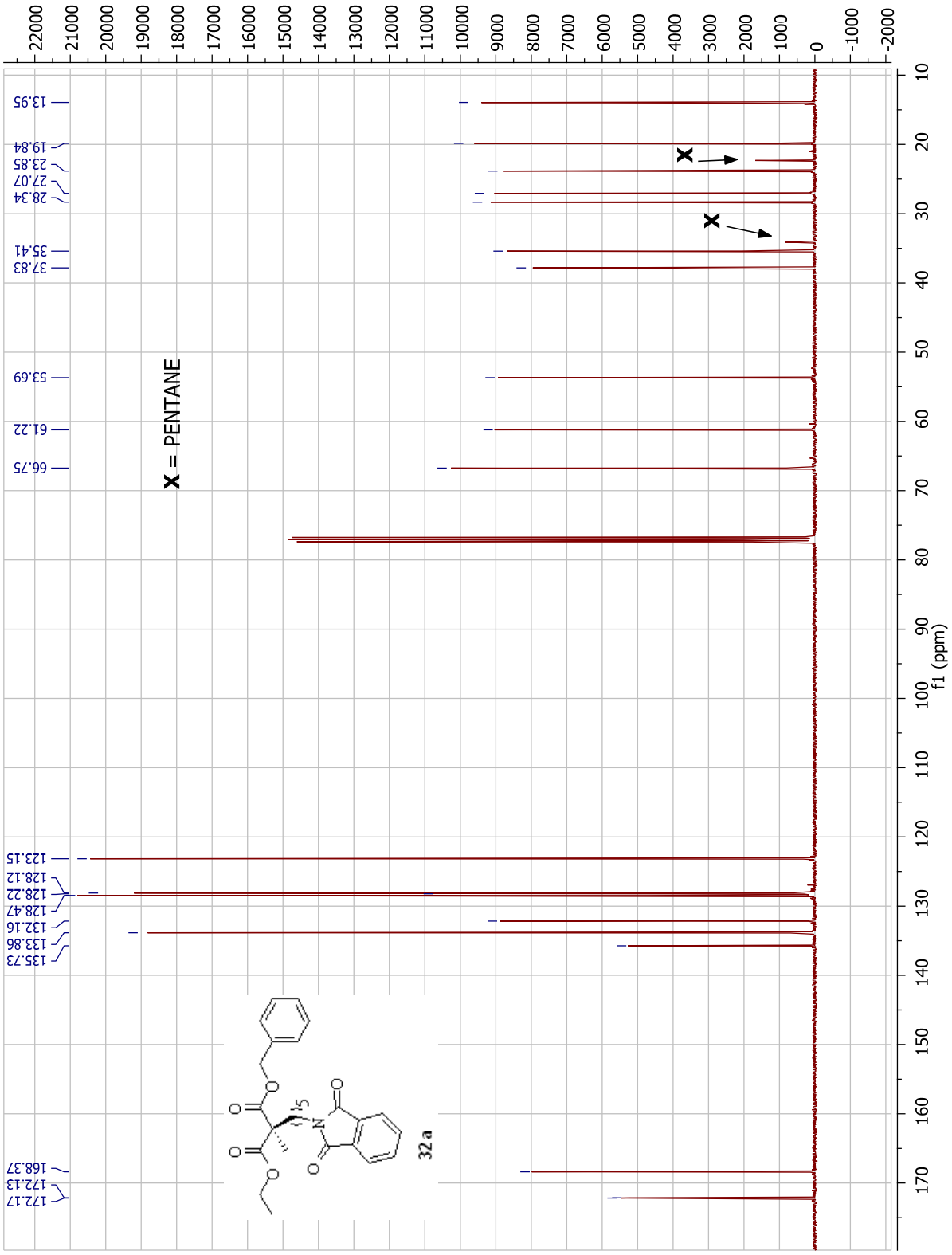


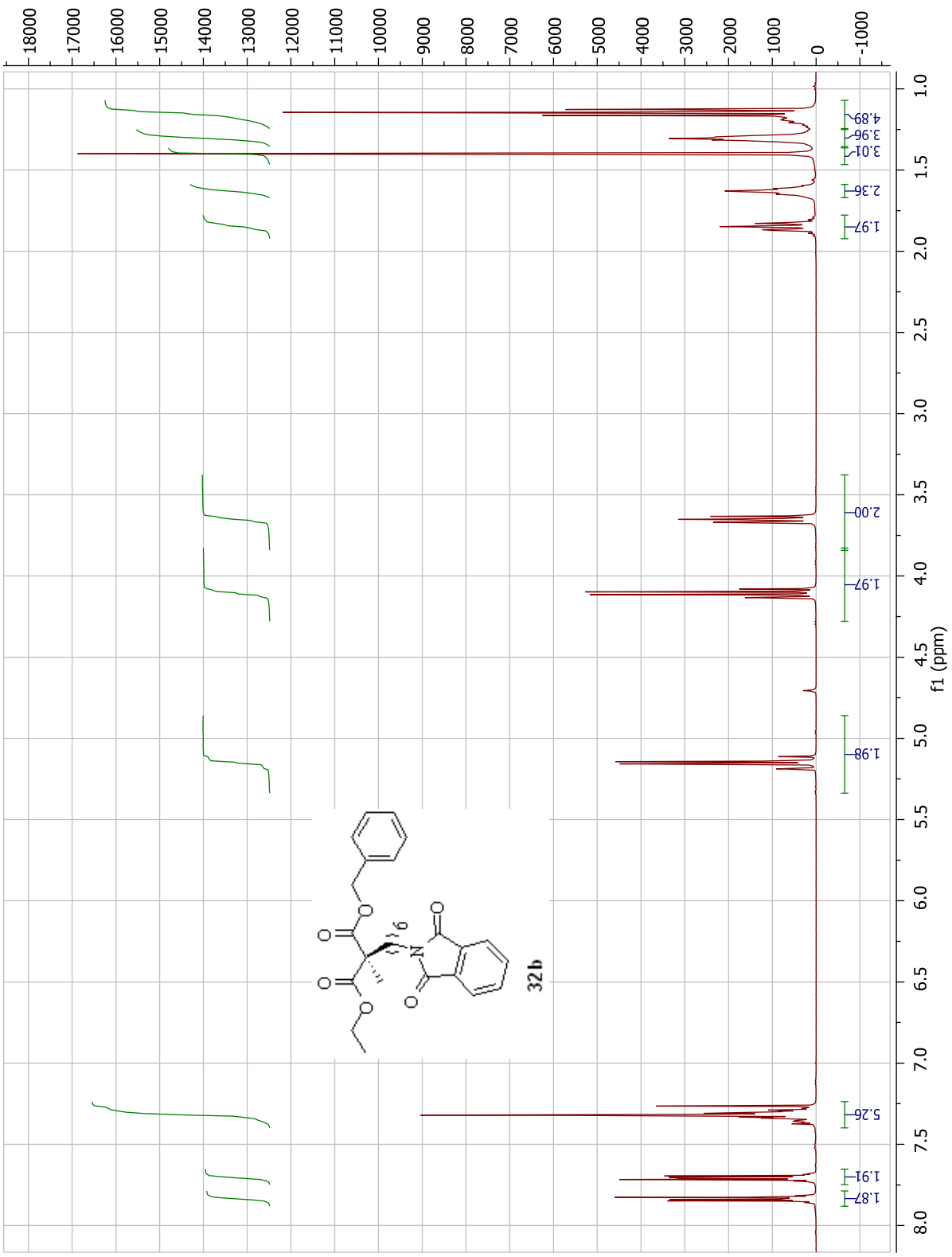


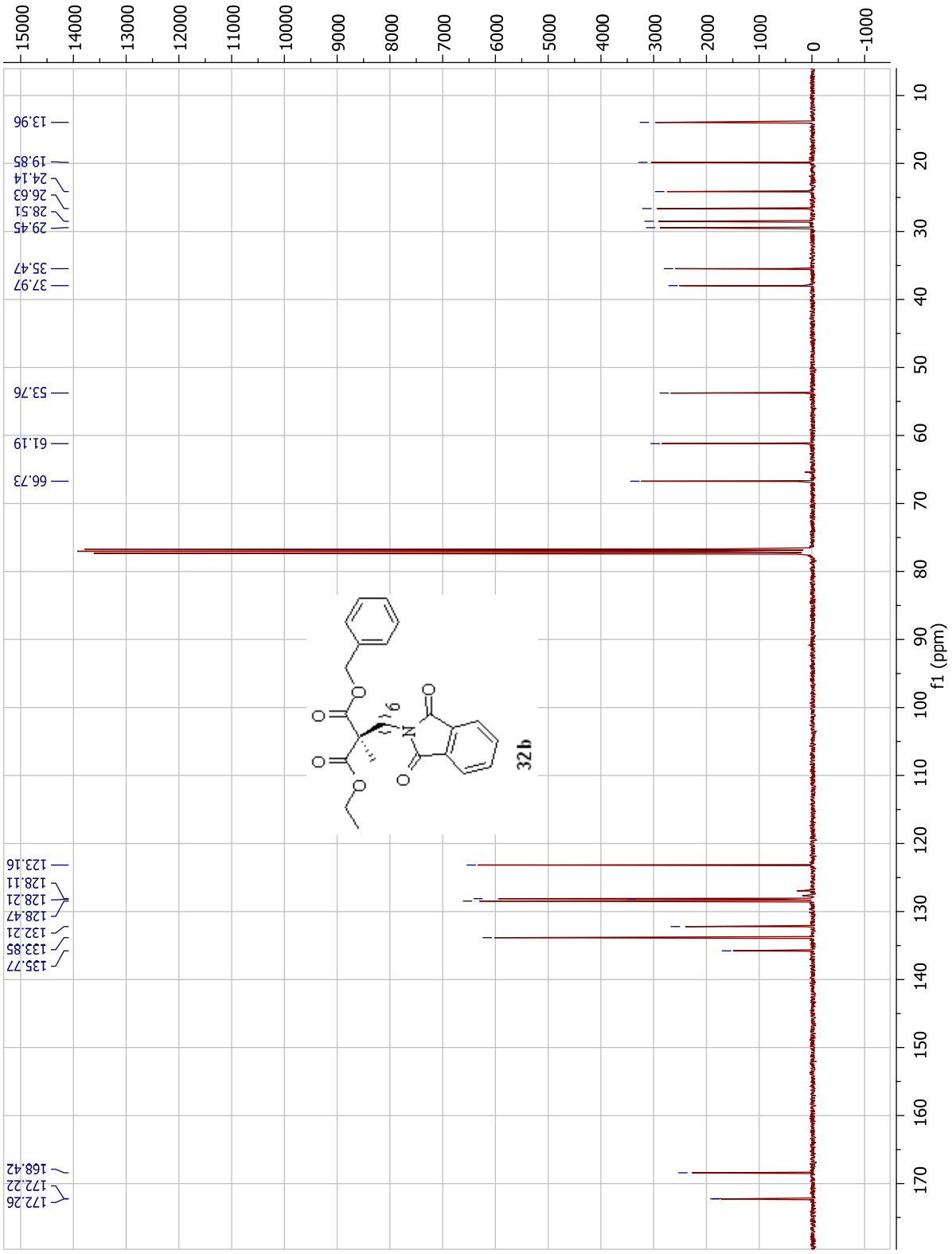

600
550
500
450
400
350
300
250
200
150
100
50
0
-50
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)
3.00
1.06
1.04
2.10
1.93
0.94
1.09
4.45
BnO
NH
O
O
29

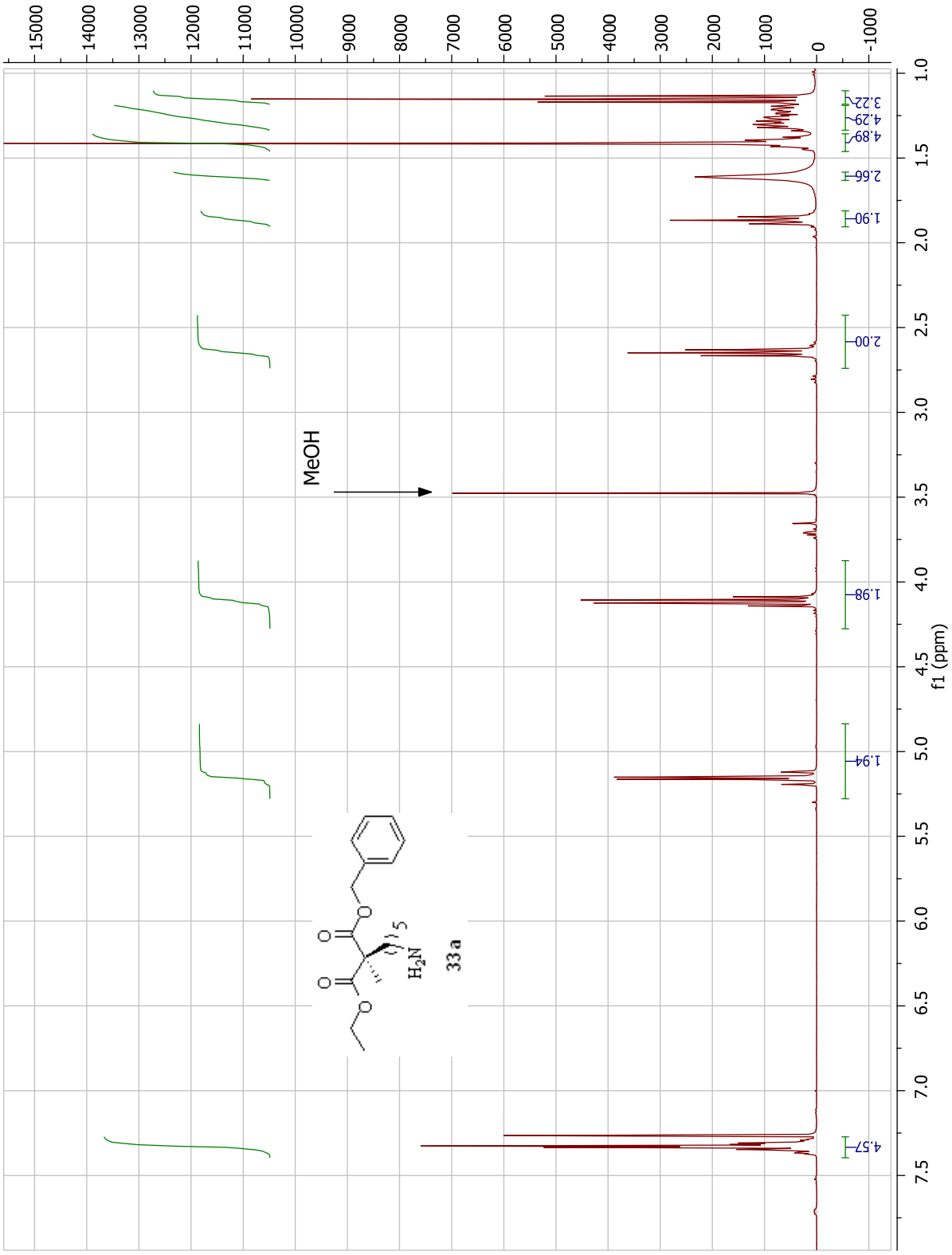

22.31
34.79
38.97
57.19
66.76
128.21
128.32
128.73
136.54
155.29
178.27
29
BnO
NH
O
HN
O
f1 (ppm)

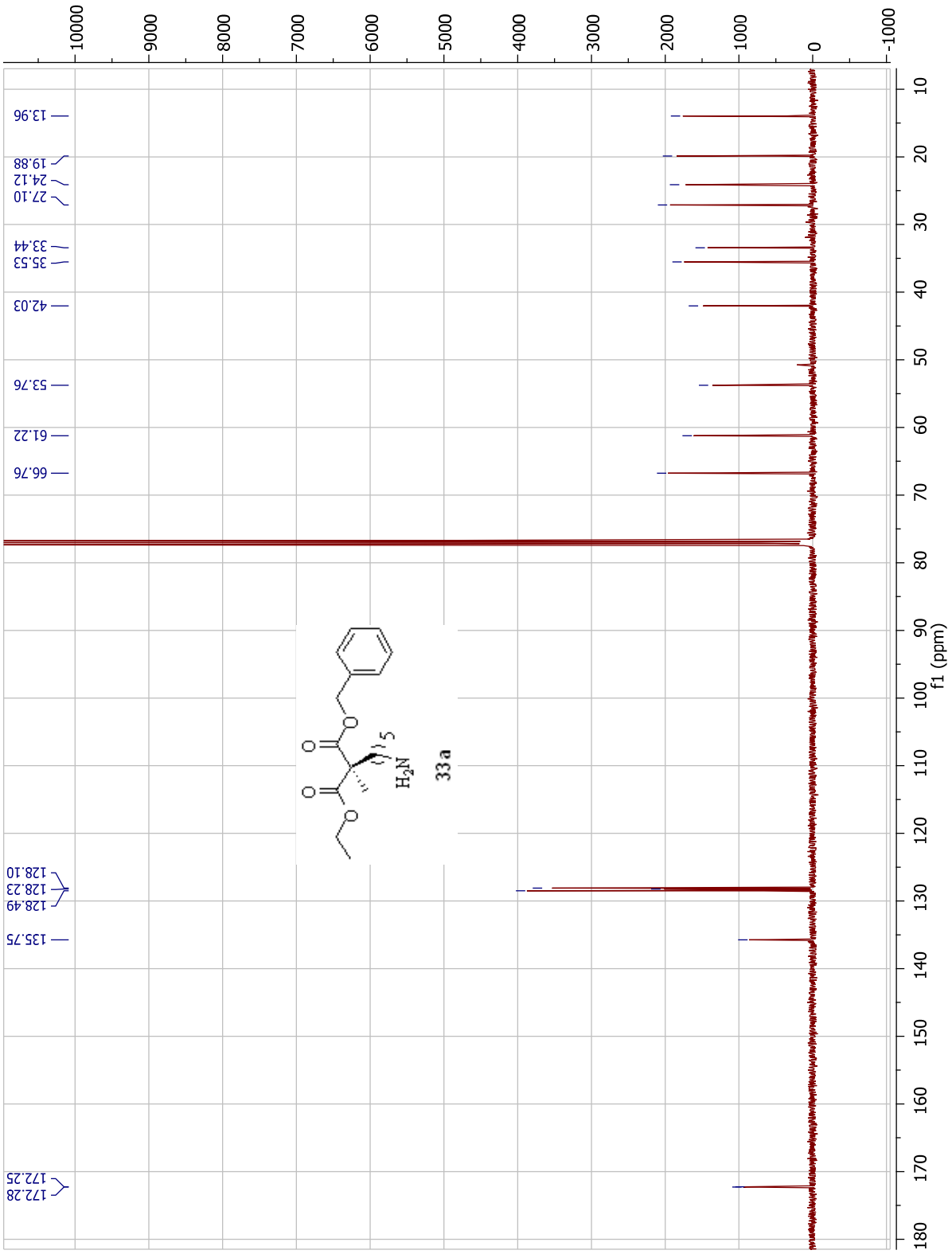


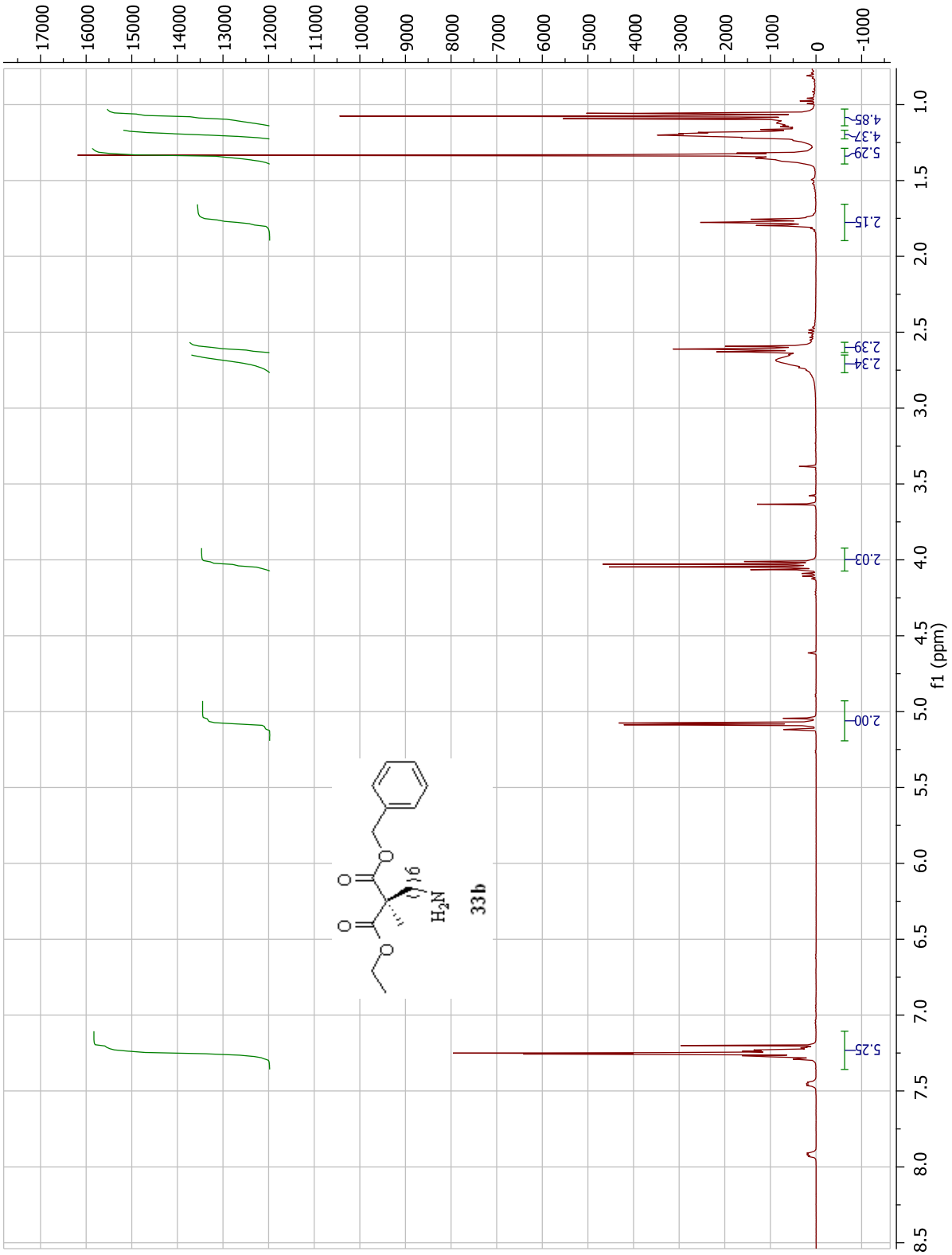


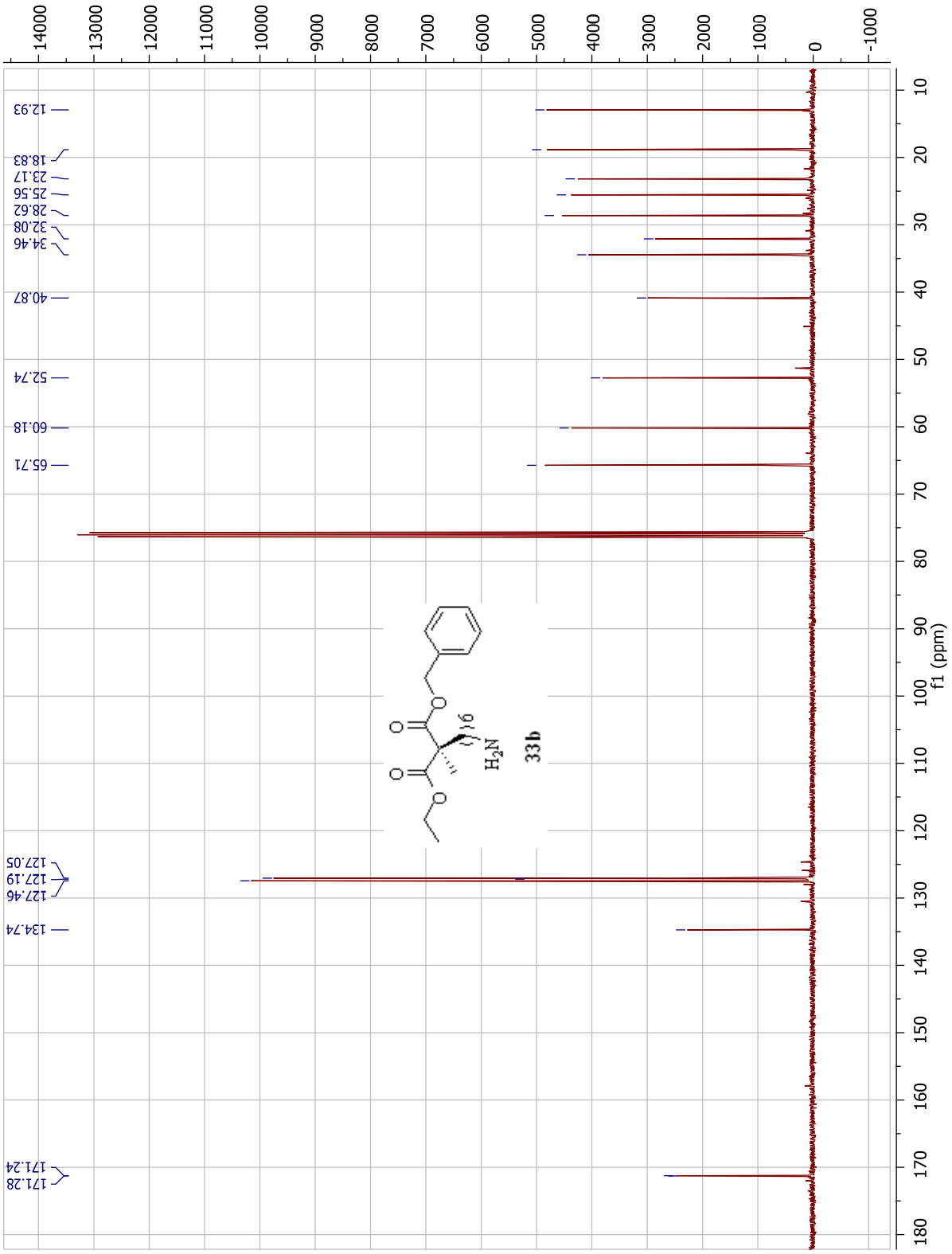


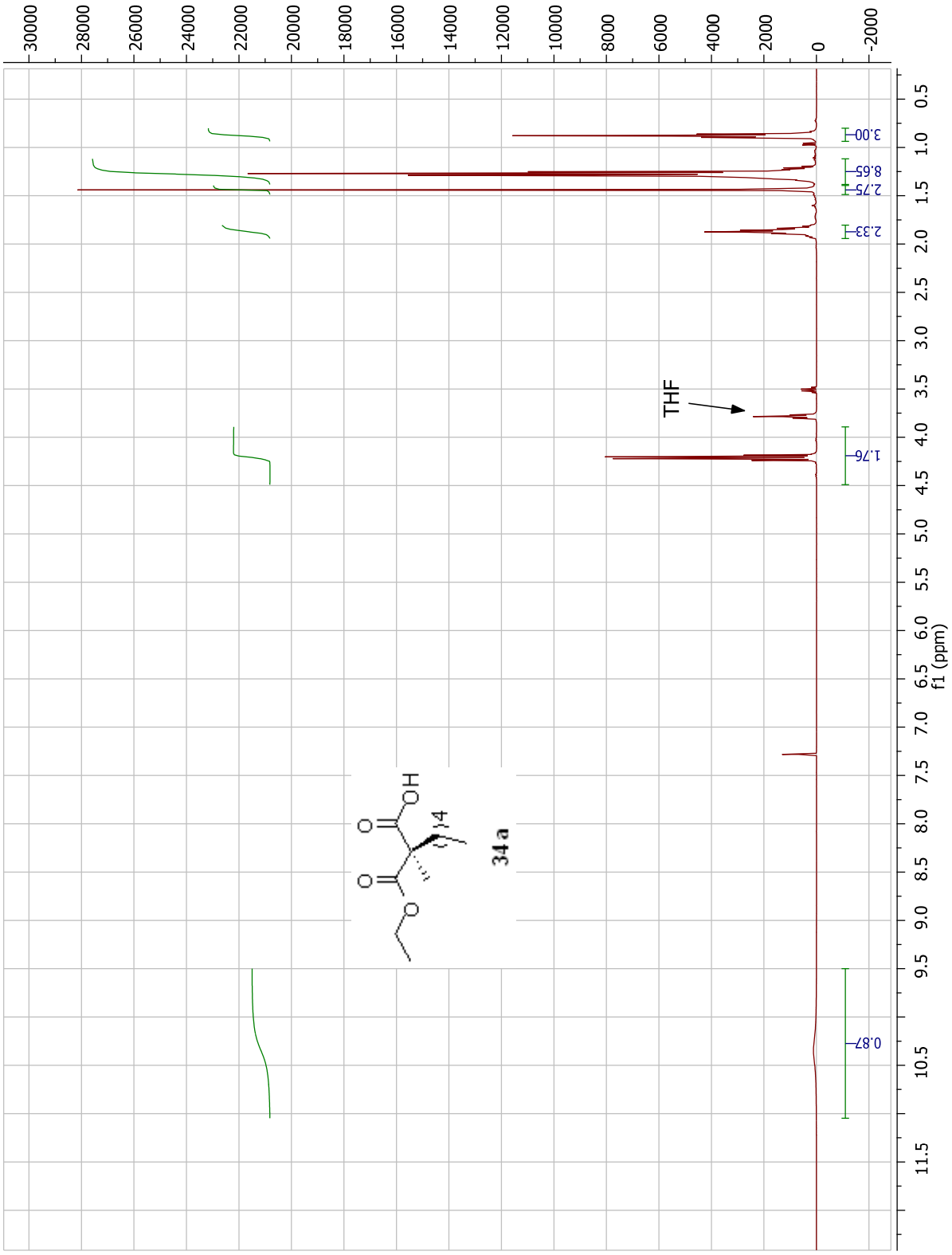


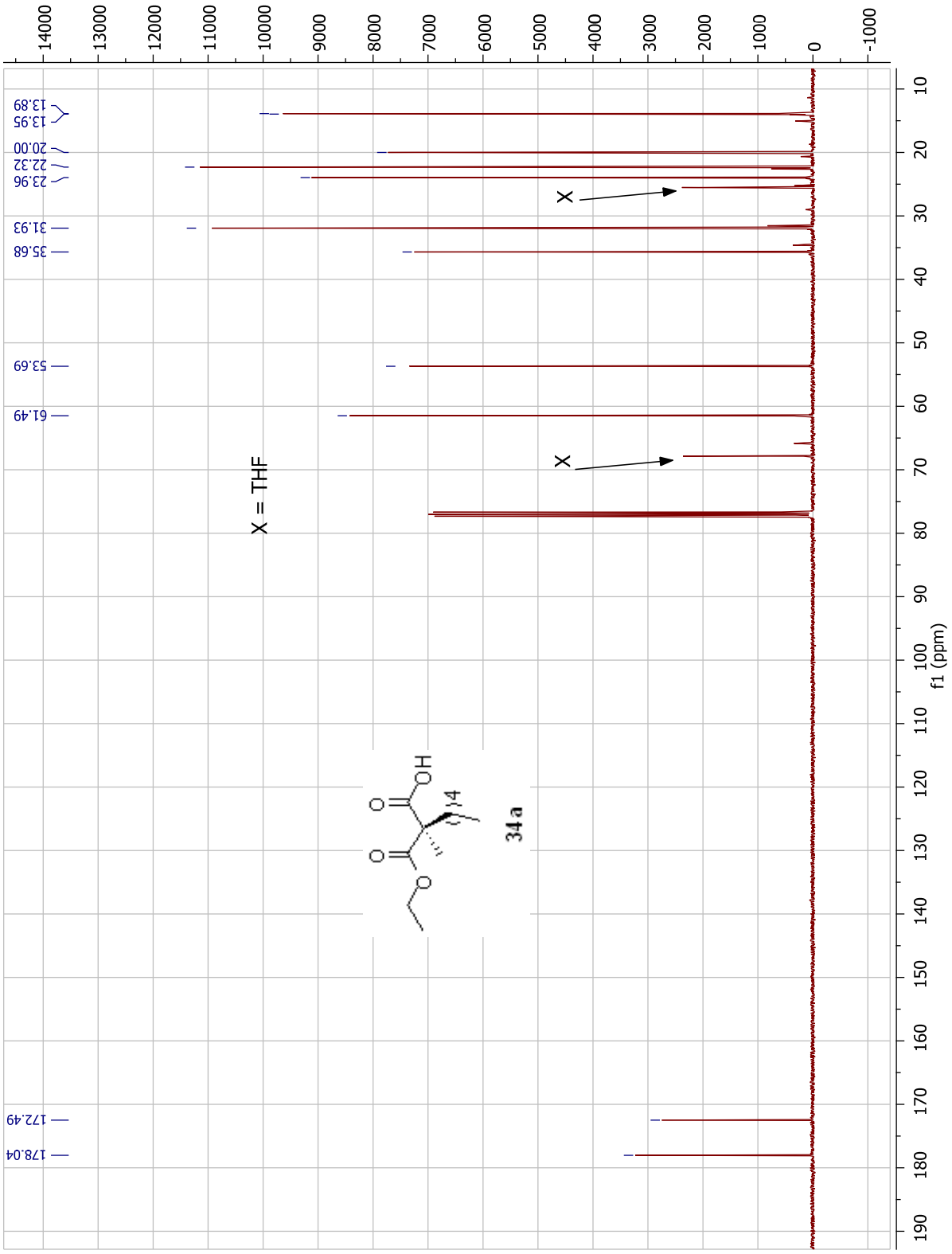


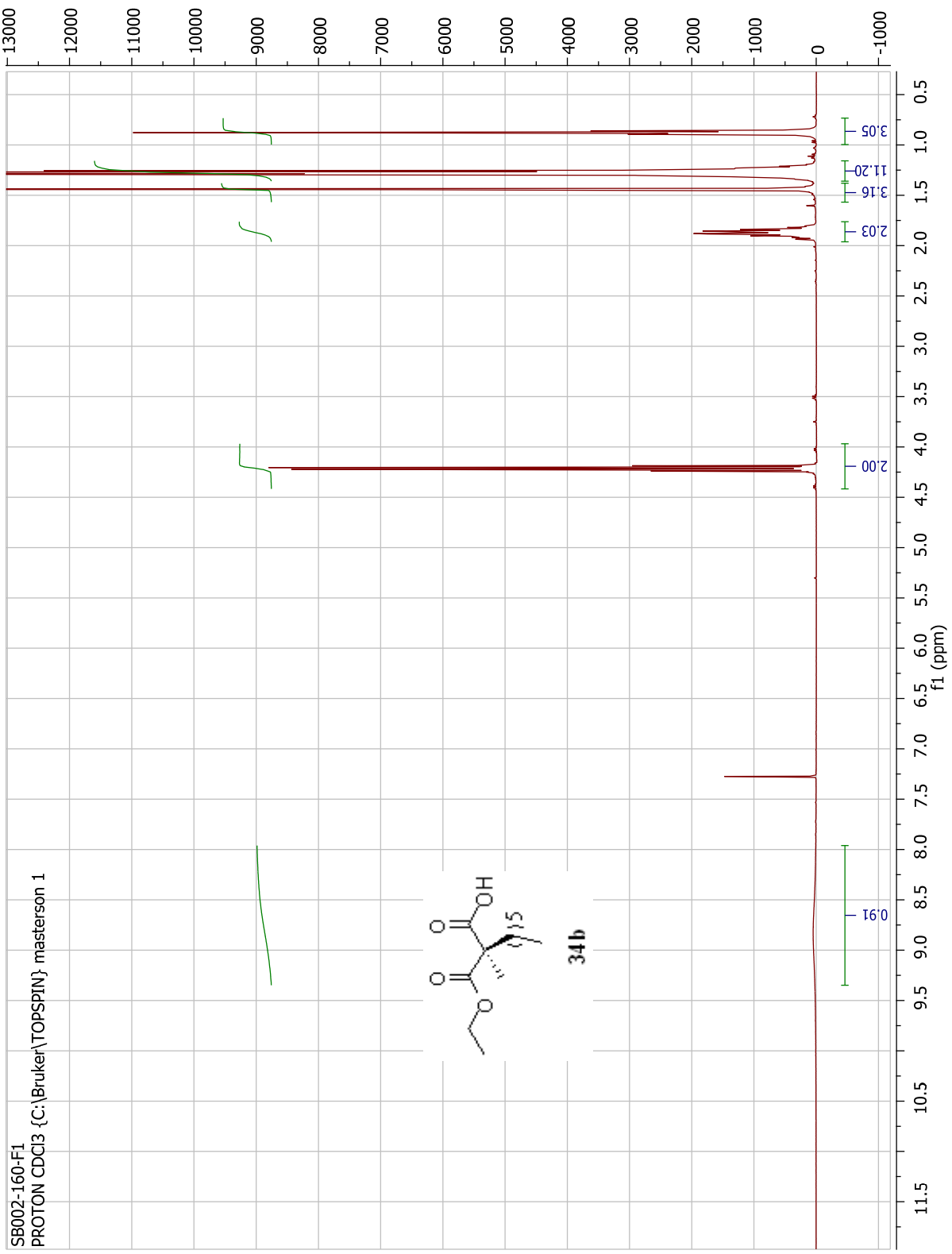











SB002-160-F1
PROTON CDCl3 {C:\Bruker\TOPSPIN} masterson 1
34b
3.05
11.20
3.16
2.03
2.00
0.91
f1 (ppm)