Much Improved Conditions for the Negishi Cross-Coupling of Iodoalanine Derived Zinc Reagents with Aryl Halides

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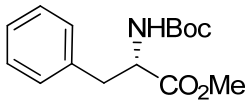
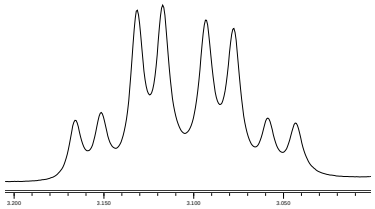
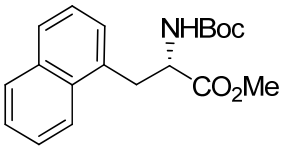
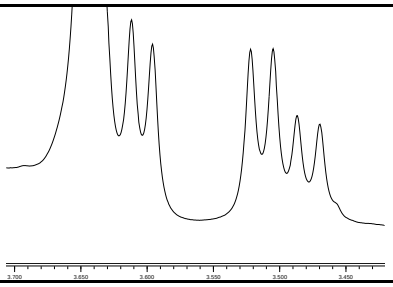
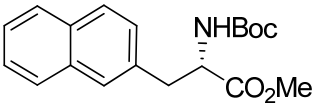
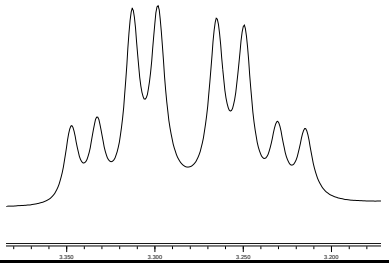
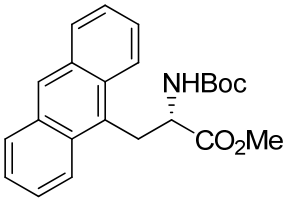
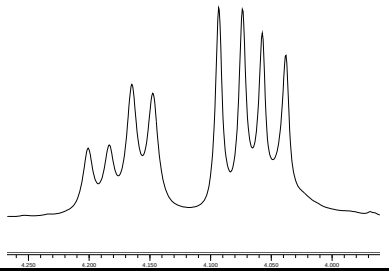
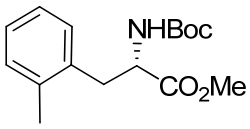
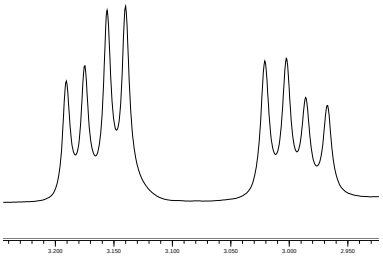
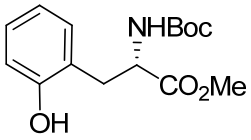
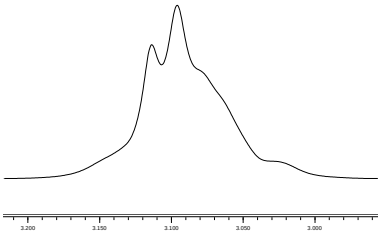
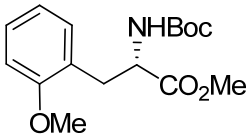
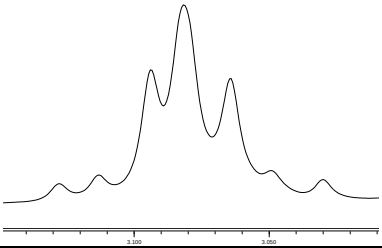
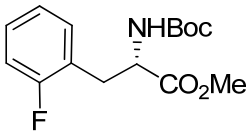
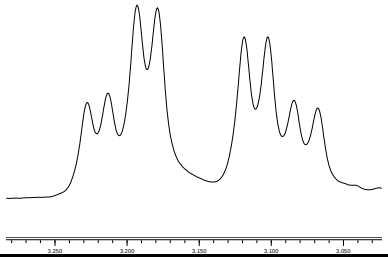
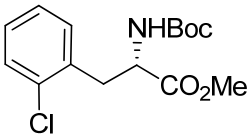
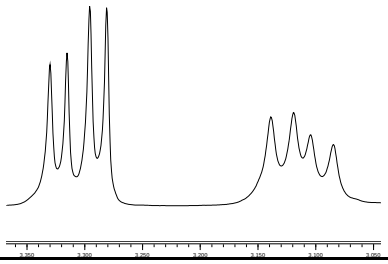
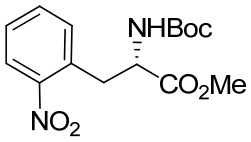
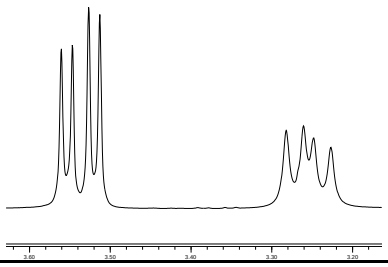
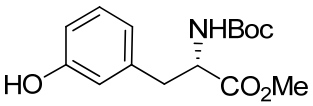
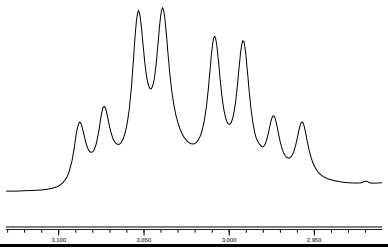
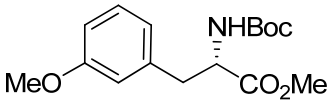
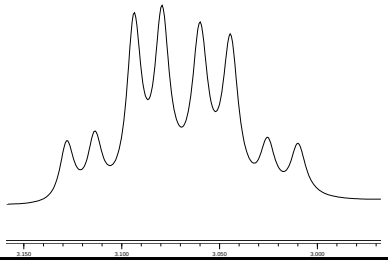
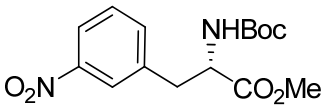
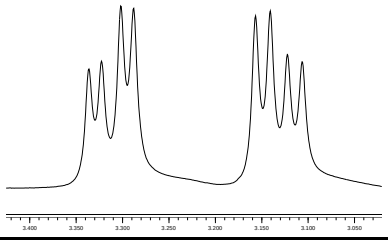
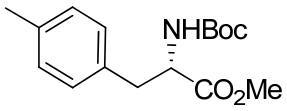
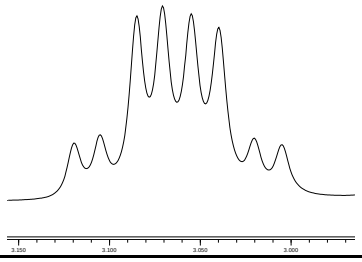
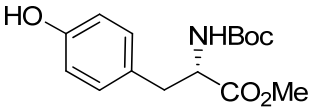
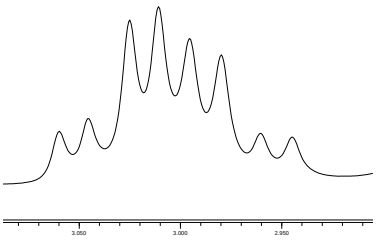
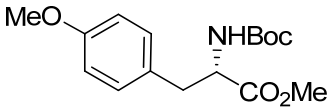
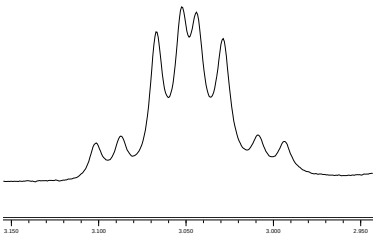
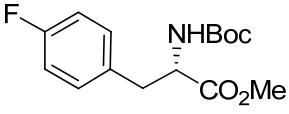
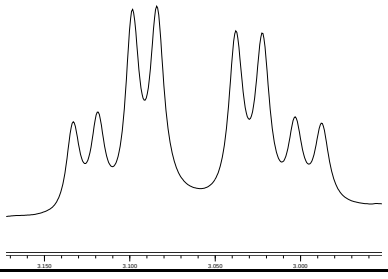
Supporting information

Table 4: Comparison of NMR chemical shift for the diastereotopic protons of substituted phenylalanine derivatives

Product	Structure	Diastereotopic CH_2	Δδ (ppm)	Hammett value
4a			0.07	0
4b			0.14	-
4c			0.08	
4d			0.11	-
4e			0.17	-

4f			0	-
4g			0.06	-
4h			0.11	-
4i			0.19	-
4j			0.28	-
4k			0.08	0.12

4l			0.07	0.12
4m			0.18	0.71
4n			0.07	-0.17
4o			0.07	-0.37
4p			0.07	-0.27
4q			0.09	0.06

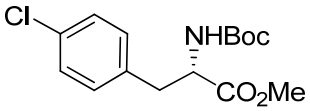
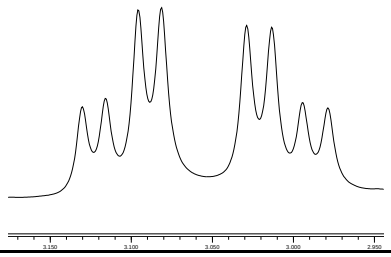
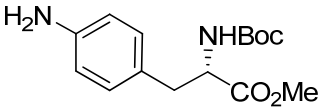
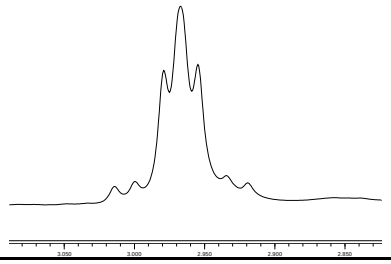
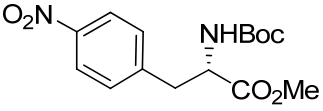
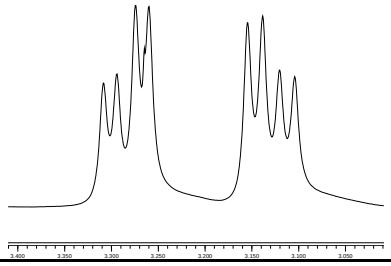
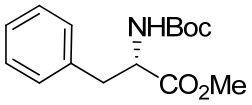
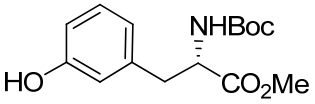
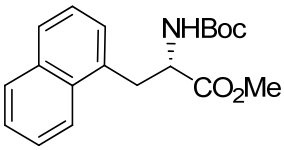
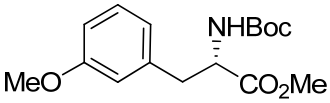
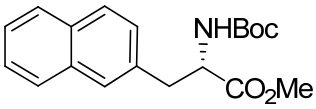
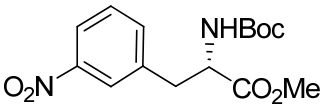
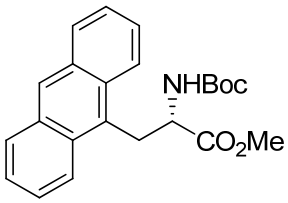
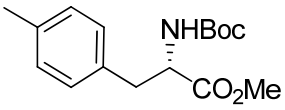
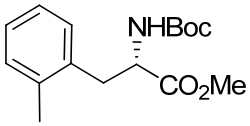
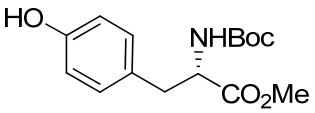
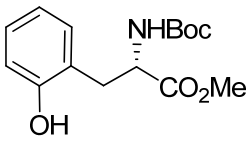
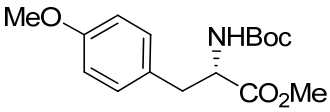
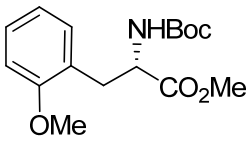
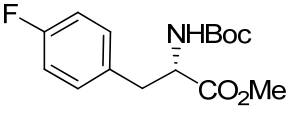
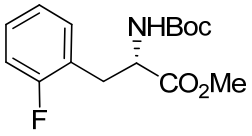
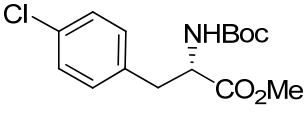
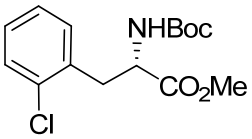
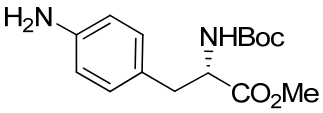
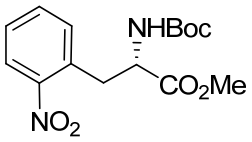
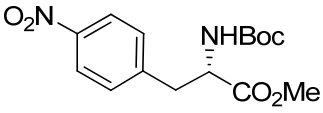
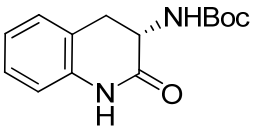
4r			0.10	0.23
4s			0.05	-0.66
4t			0.15	0.78

Table 5: Comparison of optical rotations of phenylalanine derivatives at c = 1.0 in $CHCl_3$

Product	Product	α_D^{20}	Product	Product	α_D^{20}
4a		+47.0	**4k**		+37.5
4b		+20.0	**4l**		+46.1
4c		+60.0	**4m**		+49.5
4d		+28.7	**4n**		+56.7
4e		+26.9	**4o**		+46.0
4f		+10.0	**4p**		+60.3
4g		+24.0	**4q**		+45.2

4h		+45.1	**4r**		+50.0
4i		+18.0	**4s**		+42.0
4j		+20.0	**4t**		+53.0
			12		+5.0

General experimental

All the reagents used were obtained commercially and were not purified further. The SPhos was obtained from two sources, Alfa Aesar® and Aldrich®, the SPhos obtained from Aldrich® was ground before use. All solvents used were of HPLC quality and purchased from Fischer Scientific®. Petroleum ether refers to the fraction that boils in the range of 40-60 °C. The DMF was distilled from calcium hydride and kept under inert atmosphere with 4Å molecular sieves.

All columns were monitored using TLC, on pre-coated silica plates, TLC plates visualised by Ultra Violet light and ninhydrin dip. Flash column chromatography was performed under pressure, using silica gel 60 from Davisil Fluorochem.

^{1}H and ^{13}C-NMR spectra were recorded on a 400 MHz spectrometer at room temperature. Samples were dissolved in $CDCl_3$. Coupling constants are measured in hertz and are quoted to the nearest 0.1 Hz and chemical shifts are quoted in ppm relative to the residual chloroform peak.

Melting points are reported uncorrected.

Optical rotations were determined using a Polarimeter, at 589nm.

Infra red spectra were measured in wavenumbers and are quoted to the nearest whole number.

General experimental procedures

General cross coupling **Method A**:

Zinc dust (190 mg, 3 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (1 mL) was added *via* syringe followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A colour change of the DMF was observed from colourless to yellow and back again. Iodoalanine (329 mg, 1 mmol) was added immediately followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at room temperature and gave a noticeable exotherm. In a separate flame dried nitrogen purged flask Pd_2dba_3 (11 mg, 0.0125 mmol), was added followed by dry DMF (0.5 mL). In a separate flame dried nitrogen purged flask, SPhos (11 mg, 0.025 mmol) was added followed by dry DMF (0.5 mL). Once the zinc insertion has cooled the palladium solution (100 µL, 0.0025 mmol) and SPhos solution (100 µL, 0.005 mmol) were added *via* syringe followed by aryl iodide (1.3 mmol). The reaction was allowed to stir at room temperature overnight under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

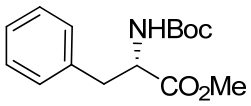
General cross coupling **Method B**:

Zinc dust (190 mg, 3 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (1 mL) was added *via* syringe followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A colour change of the DMF was observed from colourless to yellow and back again. Iodoalanine (329 mg, 1 mmol) was added immediately followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at room temperature and gave a noticeable exotherm. When the solution had cooled Pd_2dba_3 (22 mg, 0.025 mmol), SPhos (21 mg, 0.05 mmol) and aryl iodide (1.3 mmol) were added to the flask and left to stir at room temperature overnight, under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

General cross coupling **Method C**:

Zinc dust (190 mg, 3 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (1 mL) was added *via* syringe followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A colour change of the DMF was observed from colourless to yellow and back again. Iodoalanine (329 mg, 1 mmol) was added immediately followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at room temperature and gave a noticeable exotherm. When the solution had cooled Pd_2dba_3 (22 mg, 0.025 mmol), SPhos (21 mg, 0.05 mmol) and aryl bromide (1.3 mmol) were added to the flask. The reaction was heated at 50^{o}C for 3 hours, under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

(S)-methyl 2-(tert-butoxycarbonylamino)-3-phenylpropanoate, ***(4a)***



Following general cross coupling **Method A** using iodobenzene (145 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (221 mg, 80 %) as a yellow oil.

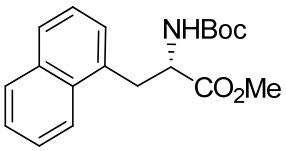
Following general cross coupling **Method B** using iodobenzene (145 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (220 mg, 79 %) as a yellow oil.

Following general cross coupling **Method C** using bromobenzene (137 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (215 mg, 77 %) as a yellow oil.

R_f 0.5 (30 % EtOAc in petrol); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s), 3.10 (2H, dd, *J* 14.0 and 6.1), 3.75 (3H, s), 4.61 (1H, dd, *J* 14.0 and 6.1), 5.00 (1H, d, *J* 7.8), 7.15 (2H, d, *J* 6.9), 7.36-7.23 (3H, m); δ_C (101 MHz, $CDCl_3$) 18.6, 27.3, 28.3, 38.3, 52.2, 54.4, 79.9, 127.0, 128.5, 129.3, 136.1, 155.1, 172.3; $[\alpha]_D^{22}$ +47.0 (c 1.0, $CHCl_3$) , $[\alpha]_D^{22}$ +43.5 (c 3.68 CH_2Cl_2), lit[1] value $[\alpha]_D^{22}$ +46.9 (c 3.43, CH_2Cl_2).

Spectroscopic data is consistent with that previously reported.[1]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(naphthalen-1-yl)propanoate, ***(4b)***

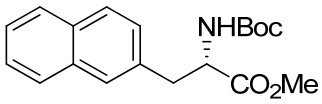


Following general cross coupling **Method A** using 1-iodonapthalene (190 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (95 mg, 29 %) as a yellow oil.

Following general cross coupling **Method B** using 1-iodonapthalene (190 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (278 mg, 84 %) as a yellow oil.

R_f 0.6 (30 % EtOAc in toluene); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 3.72-3.56 (4H, m), 3.50 (1H, dd, *J* 14.2 and 6.9), 4.75 (1H, dd, *J* 14.2 and 6.9), 5.10 (1H, d, *J* 7.8), 7.30 (1H, d, *J* 7.0), 7.44-7.39 (1H, m), 7.54 (2H, td, *J* 14.7 and 7.0), 7.79 (1H, d, *J* 8.1), 7.88 (1H, d, *J* 8.1), 8.11 (1H, d, *J* 8.1); δ_C (101 MHz, $CDCl_3$) 28.3, 35.7, 52.2, 54.4, 79.9, 123.6, 125.3, 125.7, 126.3, 127.5, 127.9, 128.8, 132.2, 132.5, 133.9, 155.0, 172.6; $[\alpha]_D^{22}$ +20.0 (c 1.0, $CHCl_3$), $[\alpha]_D^{22}$ +27.6 (c 1.45, CH_2Cl_2), lit[1] value $[\alpha]_D^{22}$ +27.5 (c 1.47, CH_2Cl_2).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(naphthalen-2-yl)propanoate, ***(4c)***

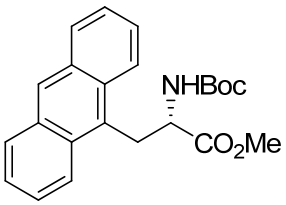


Following general cross coupling **Method C** using 2-bromonapthalene (190 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (258 mg, 79 %) as a yellow solid.

m.p. 82-84 °C, lit. value[2] 85-86 °C; R_f 0.53 (30 % EtOAc in toluene); δ_H (400 MHz; $CDCl_3$) 1.43 (9H, s), 3.24 (1H, dd, *J* 14.0 and 6.5), 3.32 (1H, dd, *J* 14.0 and 6.5), 3.74 (3H, s), 4.70 (1H, dd, *J* 14.0 and 6.5), 5.05 (1H, d, *J* 8.0), 7.29 (1H, d, *J* 8.5), 7.53-7.45 (2H, m), 7.62 (1H, s), 7.86-7.78 (3H, m); δ_C (101 MHz; $CDCl_3$ 28.3, 38.5, 52.3, 54.5, 78.0, 125.7, 126.2, 127.3, 127.6, 127.7, 128.1, 128.3, 132.5, 133.5, 133.6, 155.1, 172.4; $[\alpha]_D^{21}$ +60.0 (c 1.0, $CHCl_3$), $[\alpha]_D^{21}$ +52.0 (c 2.6, $CHCl_3$), lit. value[2] $[\alpha]_D^{32}$ +59.9 (2.62, $CHCl_3$).

Spectroscopic data correlates with that recorded in the literature.[2]

(S)-methyl 3-(anthracen-9-yl)-2-(tert-butoxycarbonylamino)propanoate, ***(4d)***

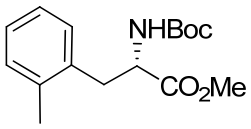


Following general cross coupling **Method C** using 9- bromoanthracenene (334 mg, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (150 mg, 40 %) as a yellow solid.

m.p. 161-163 °C, lit. value[3] 159.8-160 °C; R_f 0.62(30 % EtOAc in toluene); δ_H (400 MHz; $CDCl_3$) 1.40 (9H, s), 3.33 (3H, s), 4.07 (1H, dd, *J* 14.5 and 8.0), 4.17 (1H, dd, *J* 14.5 and 7.5), 4.80 (1H, dd, *J* 15.0 and 7.5), 5.33 (1H, d, *J* 7.5), 7.52-7.45 (2H, m), 7.61-7.54 (2H, m), 8.03 (2H, d, J 8.5 Hz), 8.33 (2H, d, J 9.0 Hz), 8.41 (1H, s); δ_C (101 MHz; $CDCl_3$) 28.3, 31.2, 52.1, 54.6, 79.9, 123.9, 124.9, 126.2, 127.1, 128.4, 129.3, 130.6, 131.5, 154.9, 172.7; $[\alpha]_D^{21}$ +28.7 (c 1.0, $CHCl_3$), $[\alpha]_D^{22}$ +18.0 (c 2.22, CH_2Cl_2) lit. value[3] $[\alpha]_D^{22}$ +21.4 (c 2.24, CH_2Cl_2).

Spectroscopic data correlates with that recorded in the literature.[3]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-o-tolylpropanoate, ***(4e)***



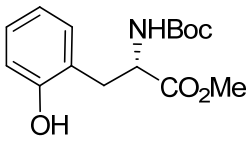
Following general cross coupling **Method A** using 2-iodotoluene (166 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (67mg, 23 %) as a white solid.

Following general cross coupling **Method B** using 2-iodotoluene (166 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (194mg, 66 %) as a white solid.

Following general cross coupling **Method C** using 2-bromotoluene (156 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (194mg, 66 %) as a white solid.

m.p. 49-50 ^{o}C; R_f 0.49 (20 % EtOAc in toluene); ν_{max}(film)/cm^{-1} 2956, 2928, 2854, 1739, 1714, 1513; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s), 2.37 (3H, s), 3.08 (2H, dd, *J* 14.4 and 7.2), 3.71 (3H, s), 4.59 (1H, dd, *J* 14.4 and 7.2), 5.04 (1H, d, *J* 8.1), 7.07 (1H, d, *J* 6.8), 7.21-7.11 (3H, m); δ_C (101 MHz, $CDCl_3$) 19.4, 28.3, 36.1, 52.2, 53.7, 79.9, 125.9, 127.1, 129.9, 130.5, 134.5, 136.7, 155.0, 172.8; *m/z* (ES) Found: MH^+ 294.1699. $C_{16}H_{24}NO_4$ requires MH^+ 294.1705; $[\alpha]_D^{22}$ +26.9 (c 1.04 $CHCl_3$).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(2-hydroxyphenyl)propanoate, ***(4f)***

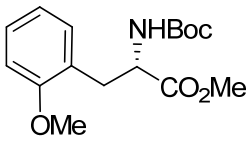


Following general cross coupling **Method A** using 2-iodophenol (285 mg, 1.3 mmol) gave, after purification by silica gel column (3 column volumes 20 % EtOAc in petrol followed by 30 % EtOAc in petrol) the title compound (148 mg 50 %) as a yellow oil.

Following general cross coupling **Method B** using SPhos 2-iodophenol (285 mg, 1.3 mmol) gave, after purification by silica gel column (3 column volumes 20 % EtOAc in petrol followed by 30 % EtOAc in petrol) the title compound (221 mg 75 %) as a yellow oil.

R_f 0.29 (30 % EtOAc in toluene); ν_{max}(film)/cm^{-1} 3352 br, 2979, 2916, 1713, 1682, 1509; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 2.97-3.19 (2H, m), 3.73 (3H, s), 4.61 (1H, d, *J* 5.4), 5.67 (1H, d, *J* 5.4), 6.82 (2H, t, *J* 7.4), 7.16-6.99 (3H, m), 8.01 (1H, d, *J* 21.62); δ_C (101 MHz, $CDCl_3$) 28.3, 34.0, 52.4, 54.1, 80.4, 115.8, 119.9, 122.6, 128.6, 131.2, 155.1, 155.9, 173.3; *m/z* (ES) Found: MH^+ 296.1507. $C_{15}H_{22}NO_5$ requires MH^+ 296.1498; $[\alpha]_D^{22}$ +10.0 (c 1.0 $CHCl_3$).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(2-methoxyphenyl)propanoate, ***(4g)***



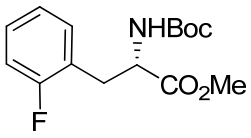
Following general cross coupling **Method A** using 2-iodoanisole (169 µL, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (25 mg, 8 %) as an orange oil.

Following general cross coupling **Method B** using 2-iodoanisole (169 µL, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (204 mg, 66 %) as an orange oil.

Following general cross coupling **Method C** using 2-bromoanisole (163 µL, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (180 mg, 58 %) as an orange oil.

R_f 0.64 (30 % EtOAc in toluene); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s), 3.13-3.02 (2H, m), 3.71 (3H, s), 3.84 (3H, s), 4.52 (1H, dd, *J* 13.7 and 7.5), 5.26 (1H, d, *J* 7.5), 6.89 (2H, dd, *J* 15.8 and 7.5), 7.10 (1H, dd, *J* 7.5 and 1.6), 7.29-7.21 (m, 1H); δ_C (101 MHz, $CDCl_3$) 28.3, 32.8, 52.0, 54.0, 55.3, 79.5, 110.4, 120.6, 124.7, 128.4, 131.2, 155.3, 157.6, 172.9; $[\alpha]_D^{22}$ +24.0 (c 1.0, $CHCl_3$) , $[\alpha]_D^{22}$ +16.5 (c 1.09, CH_2Cl_2), lit[1] value $[\alpha]_D^{22}$ +14.9 (c 0.68, CH_2Cl_2).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(2-fluorophenyl)propanoate, ***(4h)***



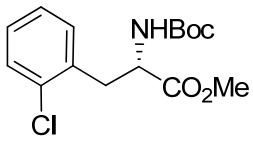
Following general cross coupling **Method A** using 1-iodo-2- fluorobenzene (150 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (62 mg, 21 %) as a yellow oil.

Following general cross coupling **Method B** using 1-iodo-2- fluorobenzene (150 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (209 mg, 70 %) as a yellow oil.

Following general cross coupling **Method C** using 1-bromo-2- fluorobenzene (141 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (192 mg, 65 %) as a yellow oil.

R_f 0.48 (30 % EtOAc in toluene); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s), 3.09 (1H, dd, *J* 13.8 and 6.4), 3.20 (1H, dd, *J* 13.8 and 6.4), 3.75 (3H, s), 4.60 (1H, dd, *J* 14.0 and 6.4), 5.08 (1H, d, *J* 7.7), 7.31-7.02 (5H, m); δ_C (101 MHz, $CDCl_3$) 28.3, 31.9, 52.3, 53.6, 79.9, 115.4 (d, *J* 22), 123.2 (d, *J* 16), 124.1, 128.9 (d, *J* 8), 131.7 (d, *J* 4), 160.2, 162.6, 172.2, $[\alpha]_D^{22}$ +45.1 (c 1.02, $CHCl_3$) , $[\alpha]_D^{22}$ +35.6 (c 1.01, CH_2Cl_2), lit[1] value $[\alpha]_D^{22}$ +40.0 (c 1.02, CH_2Cl_2).
Spectroscopic data is consistent with that previously reported.[4]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(2-chlorophenyl)propanoate, ***(4i)***

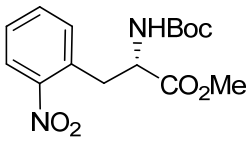


Following general cross coupling **Method A** using 1-iodo-2- chlorobenzene (159 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (74 mg, 24 %) as a white solid.

Following general cross coupling **Method B** using 1-iodo-2- chlorobenzene (159 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (242 mg, 76 %) as a white solid.

m.p. 53-55 ^{o}C; R_f 0.63 (30 % EtOAc in toluene); ν_{max}(film)/cm^{-1} 2978, 2944, 1742, 1715, 1508; δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s), 3.11 (1H, dd, *J* 13.8 and 7.9), 3.31 (1H, dd, *J* 13.8, 7.9), 3.72 (3H, s), 4.65 (1H, dd, *J* 13.8 and 7.9), 5.12 (1H, d, *J* 7.9), 7.20 (3H, s), 7.37 (1H, dd, *J* 6.63 and 2.57); δ_C (101 MHz, $CDCl_3$) 28.2, 36.2, 52.3, 53.5, 79.9, 126.8, 128.4, 129.6, 131.4, 134.3, 134.5, 155.0, 172.4; *m/z* (ES) Found: MH^+ 314.1147. $C_{15}H_{21}NO_4Cl$ requires MH^+ 314.1159; $[\alpha]_D^{22}$ +18.0 (c 1.0, $CHCl_3$).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(2-nitrophenyl)propanoate, ***(4j)***

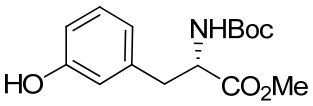


Following a variation of general cross coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using 1-iodo-2-nitrobenzene (323 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in petrol) the title compound (158 mg, 49 %) as a yellow solid.

Following a variation of general cross coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using and 1-iodo-2-nitrobenzene (323 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in petrol) the title compound (214 mg, 66 %) as a yellow solid.

m.p. 77-79 ^{o}C, lit[1] value 83-84 ^{o}C; R_f 0.17 (20% EtOAc in petrol); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s), 3.25 (1H, dd, *J* 13.6 and 8.6), 3.54 (1H, dd, *J* 13.6 and 8.6), 3.74 (3H, s), 4.69 (1H, dd, *J* 13.6 and 8.6), 5.24 (1H, d, *J* 8.1), 7.41 (2H, dd, *J* 12.0 and 7.8), 7.56 (1H, t, *J* 7.8), 7.96 (1H, d, *J* 7.8); δ_C (101 MHz, $CDCl_3$) 28.2, 35.6, 52.6, 54.0, 80.0, 125.0, 128.1, 131.8, 132.9, 133.0, 149.7, 155.0, 172.0; $[\alpha]_D^{22}$ +36.0 (c 1.0, $CHCl_3$), $[\alpha]_D^{22}$ +27.8 (c 0.18, CH_2Cl_2), lit[1] value $[\alpha]_D^{22}$ +42.7 (c 0.19, CH_2Cl_2).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(3-hydroxyphenyl)propanoate, ***(4k)***

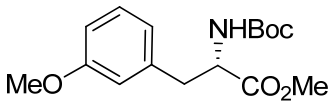


Following general cross coupling **Method A** using 3-iodophenol (287 mg, 1.3 mmol) gave, after purification by silica gel column (3 column volumes 20 % EtOAc in petrol followed by 30 % EtOAc in petrol) the title compound (206 mg, 70 %) as a colourless oil.

Following general cross coupling **Method B** using 3-iodophenol (287 mg, 1.3 mmol) gave, after purification by silica gel column (3 column volumes 20 % EtOAc in petrol followed by 30 % EtOAc in petrol) the title compound (260 mg, 88 %) as a colourless oil.

R_f 0.20 (30 % EtOAc in petrol); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 2.98 (1H, dd, *J* 13.8, 6.7), 3.06 (1H, dd, *J* 13.8, 5.7 Hz), 3.70 (3H, s), 4.58 (1H, dd, *J* 13.8, 6.7), 5.16 (1H, d, *J* 8.3 Hz), 6.70-6.64 (2H, m), 6.79-6.73 (1H, m), 7.14 (1H, t, *J* 8.0); δ_C (101 MHz, $CDCl_3$) 28.3, 38.1, 52.4, 54.4, 80.4, 114.3, 116.2, 121.1, 129.8, 137.5, 156.5, 172.7; $[\alpha]_D^{22}$ +37.5 (c 1.04 $CHCl_3$) lit[5] value $[\alpha]_D^{22}$ +38.6 (c 1.04 $CHCl_3$).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(3-methoxyphenyl)propanoate, ***(4l)***

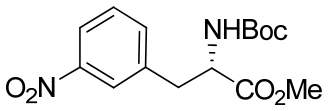


Following general cross coupling **Method A** using 3-iodoanisole (155 µL, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (208 mg, 67 %) as an orange oil.

Following general cross coupling **Method B** using 3-iodoanisole (155 µL, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (219 mg, 71 %) as an orange oil.

R_f 0.46 (20 % EtOAc in toluene); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 3.07 (2H, dd, *J* 13.9 and 6.0), 3.73 (3H, s), 3.79 (3H, s), 4.59 (1H, dd, *J* 13.9 and 6.0), 5.04 (1H, d, *J* 8.0), 6.68 (1H, d, *J 2.2*), 6.72 (1H, d, *J* 7.5), 6.80 (1H, dd, *J* 8.1 and 2.2), 7.21 (1H, t, *J* 8.1); δ_C (101 MHz, $CDCl_3$) 28.3, 38.3, 52.2, 54.4, 55.1, 79.9, 112.5, 115.0, 121.6, 129.5, 137.5, 155.1, 159.7, 172.3; $[\alpha]_D^{22}$ +46.1 (c 1.02, $CHCl_3$), $[\alpha]_D^{22}$ +43.5 (c 2.07, $CHCl_3$) , lit[6] value $[\alpha]_D^{22}$ +24.7 (c 1.9, $CHCl_3$). Spectroscopic data is consistent with that previously reported.[6]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(3-nitrophenyl)propanoate, ***(4m)***

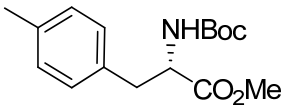


Following a variation of general cross coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using 1-iodo-3-nitrobenzene (324 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in petrol) the title compound (110 mg, 34 %) as a yellow solid.

Following a variation of general cross coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using 1-iodo-3-nitrobenzene (323 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in petrol) the title compound (172 mg, 53 %) as a yellow solid.

m.p. 102-103 ^{o}C; R_f 0.16 (20 % EtOAc in petrol); ν_{max} (film)/cm^{-1} 3346, 2962, 2926, 1735, 1686, 1522, 1438, 1351, 1249; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s), 3.13 (1H, dd, *J* 13.8 and 5.9), 3.31 (1H, dd, *J* 13.8 and 5.9), 3.77 (3H, s), 4.64 (1H, dd, *J* 13.4 and 6.3), 5.12 (1H, d, *J* 7.6), 7.54-7.46 (2H, m), 8.02 (1H, s), 8.10-8.16 (1H, m), δ_C (101 MHz, $CDCl_3$) 28.2, 38.1, 52.5, 54.2, 80.3, 122.1, 123.3, 124.3, 129.4, 130.3, 135.6, 138.4, 148.3, 154.9, 171.6; *m/z* (ES) Found: MNa^+ 347.1209. $C_{15}H_{20}N_2O_6Na$ requires MNa^+ 347.1219; $[\alpha]_D^{22}$ +49.5 (c 1.0, $CHCl_3$).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-p-tolylpropanoate, ***(4n)***



Following general cross coupling **Method A** using 4-iodotoluene (283 mg, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (156 mg, 53 %) as a colourless oil, which solidified on standing.

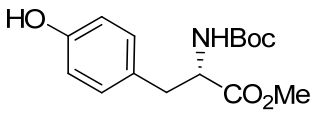
Following general cross coupling **Method B** using 4-iodotoluene (283 mg, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (244 mg, 83 %) as a colourless oil, which solidified on standing.

Following general cross coupling **Method C** using 4-bromotoluene (222 mg, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (125 mg, 43 %) as a colourless oil, which solidified on standing.

m.p. 37-39 ^{o}C, lit[7] value 27-29 ^{o}C; R_f 0.6 (30 % EtOAc in toluene); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s), 2.33 (3H, s), 3.06 (2H, dd, *J* 13.9 and 5.9), 3.73 (3H, s), 4.58 (1H, dd, *J* 13.9 and 5.9), 5.03 (1H, d, *J* 8.00 Hz), 7.02 (2H, d, *J* 7.84), 7.12 (2H, d, *J* 7.84); δ_C (101 MHz, $CDCl_3$) 21.0, 28.3, 37.8, 52.1, 54.5, 79.8, 129.2, 132.9, 136.6, 155.1, 172.4; $[\alpha]_D^{22}$ +56.7 (c 1.04 $CHCl_3$) lit[7] value $[\alpha]_D^{22}$ +52.1 (c 1.0 $CHCl_3$).

Spectroscopic data is consistent with that previously reported.[4]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(4-hydroxyphenyl)propanoate, ***(4o)***



Following general cross coupling **Method A** using 4-iodophenol (287 mg, 1.3 mmol) gave, after purification by silica gel column (3 column volumes 20 % EtOAc in petrol followed by 30 % EtOAc in petrol) the title compound (229 mg, 77 %) as a colourless oil, which solidified on standing.

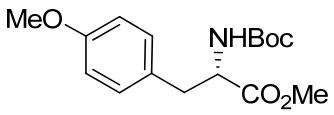
Following general cross coupling **Method B** using 4-iodophenol (287 mg, 1.3 mmol) gave, after purification by silica gel column (3 column volumes 20 % EtOAc in petrol followed by 30 % EtOAc in petrol) the title compound (242 mg, 82 %) as a colourless oil, which solidified on standing.

Following general cross coupling **Method C** using 4-bromophenol (225 mg, 1.3 mmol) gave, after purification by silica gel column (3 column volumes 20 % EtOAc in petrol followed by 30 % EtOAc in petrol) the title compound (148 mg, 51 %) as a colourless oil, which solidified on standing.

m.p. 100-102 ^{o}C, lit[5] value 106-107 ^{o}C; R_f 0.26 (30 % EtOAc in petrol); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 3.00 (2H, dd, *J* 14.0 and 6.0), 3.72 (3H, s), 4.55 (1H, dd, *J* 14.0 and 6.0), 5.09 (1H, d, *J* 8.3), 6.75 (2H, d, *J* 8.3), 6.96 (2H, d, *J* 8.3); δ_C (101 MHz, $CDCl_3$) 28.3, 37.5, 52.3, 52.5, 54.7, 80.3, 115.6, 127.2, 130.3, 155.4, 172.7; $[\alpha]_D^{22}$ +46.0 (c 1.0, $CHCl_3$) , lit[8] value $[\alpha]_D^{22}$ +48.0 (c 1.0, $CHCl_3$).

Spectroscopic data is consistent with that previously reported.[5]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(4-methoxyphenyl)propanoate, ***(4p)***



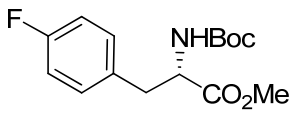
Following general cross coupling **Method A** using 4-iodoanisole (155 µL, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (201 mg, 65 %) as a yellow oil.

Following general cross coupling **Method B** using 4-iodoanisole (304 mg, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (235 mg, 76 %) as a yellow oil.

Following general cross coupling **Method C** using 4-bromoanisole (163 µL, 1.3 mmol) gave, after purification by silica gel column (3 % EtOAc in toluene) the title compound (210 mg, 69 %) as a yellow oil.

R_f 0.47 (15 % EtOAc in toluene); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s), 3.05 (2H, dd, *J* 14.0 and 5.9), 3.74 (3H, s), 3.81 (3H, s), 4.56 (1H, dd, *J* 14.0 and 5.9), 4.98 (1H, d, *J* 8.2), 6.87-6.83 (2H, m), 7.06 (2H, d, *J* 8.5); δ_C (101 MHz, $CDCl_3$) 28.3, 37.5, 52.2, 54.5, 55.2, 76.7, 77.0, 77.3, 114.0, 127.9, 130.3, 158.7, 172.4; $[\alpha]_D^{22}$ +60.3 (c 1.16, $CHCl_3$) , $[\alpha]_D^{22}$ +51.1 (c 1.76, $CHCl_3$), lit[9] value $[\alpha]_D^{22}$ +59.2 (c 1.8, $CHCl_3$).
Spectroscopic data is consistent with that previously reported.[4, 9]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(4-fluorophenyl)propanoate, ***(4q)***



Following general cross coupling **Method A** using 1-iodo-4- fluorobenzene (150 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (230 mg, 77 %) as a yellow oil, which solidified on standing.

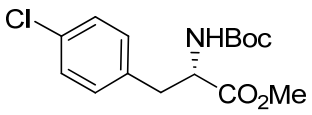
Following general cross coupling **Method B** using 1-iodo-4- fluorobenzene (150 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (238 mg, 80 %) as an orange oil, which solidified on standing.

Following general cross coupling **Method C** using 1-bromo-4- fluorobenzene (141 µL, 1.3 mmol) gave, after purification by silica gel column (5 % EtOAc in toluene) the title compound (223 mg, 75 %) as an orange oil, which solidified on standing.

m.p. 63-65 ^{o}C, lit[1] value 38-41 ^{o}C; R_f 0.57 (30 % EtOAc in toluene); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s), 3.01 (1H, dd, *J* 13.9 and 6.0), 3.11 (1H, dd, *J* 13.9 and 6.0), 3.72 (3H, s), 4.57 (1H, dd, *J* 13.9 and 6.0), 5.04 (1H, d, *J* 7.8 Hz), 7.03-6.94 (2H, m), 7.10 (2H, dd, *J* 8.3 and 5.5); δ_C (101 MHz, $CDCl_3$) 28.3, 37.6, 52.2, 54.4, 80.0, 115.2, 115.5, 130.8 (d, *J* 8), 131.8 (d, *J* 3), 155.0, 160.8, 163.2, 172.2; $[\alpha]_D^{22}$ +45.2 (c 1.2, $CHCl_3$) , $[\alpha]_D^{22}$ +45.8 (c 0.72, CH_2Cl_2) lit[6] value $[\alpha]_D^{22}$ +44.1 (c 0.72, CH_2Cl_2).

Spectroscopic data is consistent with that previously reported.[4]

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(4-chlorophenyl)propanoate, ***(4r)***

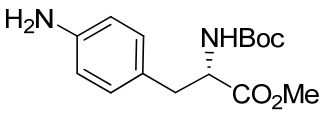


Following general cross coupling **Method A** using 1-iodo-4- chlorobenzene (309 mg, 1.3 mmol) gave, after purification by silica gel column (10 % EtOAc in toluene) the title compound (182 mg, 58 %) as a white solid.

Following general cross coupling **Method B** using 1-iodo-4- chlorobenzene (309 mg, 1.3 mmol) gave, after purification by silica gel column (10 % EtOAc in toluene) the title compound (217 mg, 69 %) as a white solid.

m.p. 69-71 ^{o}C; R_f 0.58 (30 % EtOAc in toluene); ν_{max}(film)/cm^{-1} 2963, 2960, 1737, 1707, 1512, 1491; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s), 3.00 (1H, dd, *J* 13.8 and 5.9), 3.11 (1H, dd, *J* 13.8 and 5.9), 3.71 (3H, s), 4.57 (1H., dd, *J* 13.8 and 5.9), 5.06 (1H, d, *J* 8.0), 7.06 (2H, d, *J* 8.2), 7.26 (2H, d, *J* 8.2); δ_C (101 MHz, $CDCl_3$) 28.3, 37.7, 52.3, 54.3, 80.0, 128.6, 130.6, 132.9, 134.6, 155.0, 172.1; *m/z* (ES) Found: MH^+ 314.1146. $C_{15}H_{21}NO_4Cl$ requires MH^+ 314.1159; $[\alpha]_D^{22}$ +50.0 (c 1.04, $CHCl_3$).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(4- aminophenyl)propanoate, ***(4s)***

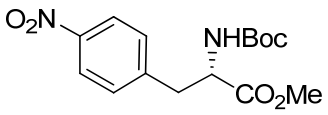


Following general cross coupling **Method A** using 4-iodoaniline (285 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in toluene) the title compound (145 mg, 49 %) as a yellow oil.

Following general cross coupling **Method B** using 4-iodoaniline (285 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in toluene) the title compound (232 mg, 79 %) as a yellow oil.

R_f 0.24 (30 % EtOAc in toluene); ν_{max} (film)/cm^{-1} 3423 br, 2973, 2081 br, 1663, 1650, 1633, 1518; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s), 2.99-2.95 (2H, m), 3.52 (2H, bs), 3.70 (3H, s), 4.50 (1H, dd, *J* 13.9 and 5.9), 5.01 (1H, d, *J* 8.1), 6.61 (2H, d, *J* 8.4), 6.89 (2H, d, *J* 8.4); δ_C (101 MHz, $CDCl_3$) 28.3, 37.4, 52.1, 54.6, 79.8, 115.3, 125.6, 130.1, 145.4, 155.2, 172.6; *m/z* (ES) Found: MNa^+ 317.1465. $C_{15}H_{22}N_2O_4Na$ requires MNa^+ 317.1477; $[\alpha]_D^{22}$ +42.0 (c 1.0, $CHCl_3$).

(S)-methyl 2-(tert-butoxycarbonylamino)-3-(4-nitrophenyl)propanoate, ***(4t)***



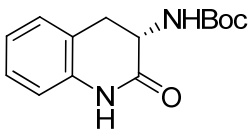
Following a variation of general cross coupling **Method A**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using 1-iodo-4-nitrobenzene (323 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in petrol) the title compound (106 mg, 33 %) as a yellow solid.

Following a variation of general cross coupling **Method B**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using 1-iodo-4-nitrobenzene (324 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in petrol) the title compound (165 mg, 51 %) as a yellow solid.

Following a variation of general cross coupling **Method C**, (after zinc insertion the zinc was allowed to settle and the liquid removed into a separate flame dried, nitrogen purged side arm round bottom flask) using 1-bromo-4-nitrobenzene (265 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in petrol) the title compound (167 mg, 52 %) as a yellow solid.

m.p. 99-101 ^{o}C;, lit[1] value 95-97 ^{o}C; R_f 0.15 (20 % EtOAc in petrol); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s), 3.13 (1H, dd, *J* 13.7 and 6.3), 3.28 (1H, dd, *J* 13.7 and 6.3), 3.75 (3H, s), 4.64 (1H, dd, *J* 13.6 and 6.4), 5.11 (1H, d, *J* 7.7), 7.33 (2H, d, *J* 8.6), 8.17 (2H, d, *J* 8.6); δ_C (101 MHz, $CDCl_3$) 28.2, 38.4, 52.5, 54.1, 76.7, 77.1, 77.4, 80.3, 123.6, 130.2, 144.1, 147.1, 154.9, 171.6; $[\alpha]_D^{22}$ +53.0 (c 1.0, $CHCl_3$), $[\alpha]_D^{22}$ +39.0 (c 1.02, CH_2Cl_2), lit[1] value $[\alpha]_D^{22}$ +30.4 (c 1.01, CH_2Cl_2).

(S)-tert-butyl 2-oxo-1,2,3,4-tetrahydroquinolin-3-ylcarbamate, ***(12)***



Produced as the only product from the attempted synthesis of (S)-methyl 3-(2-aminophenyl)-2-(tert-butoxycarbonylamino)propanoate.[10]

Following general cross coupling **Method A** using 2-iodoaniline (287 mg, 1.3 mmol) gave, after purification by silica gel column (20 % EtOAc in toluene) the title compound (224 mg, 85 %) as a yellow oil.

R_f 0.26 (30 % EtOAc in toluene); ν_{max} (film)/cm^{-1} 3254 (br), 2979, 2930, 2361, 1683, 1617, 1596, 1491; δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s), 2.85 (1H, dd, *J* 14.8 and 6.0), 3.48 (1H, dd, *J* 14.8 and 6.0), 4.47-4.29 (1H, m), 5.75 (1H, d, *J* 4.4), 6.89 (1H, d, *J* 7.7), 7.02 (1H, t, *J* 7.3), 7.18 (2H, d, *J* 7.9 Hz), 9.42 (1H, s); δ_C (101 MHz, $CDCl_3$) 28.4, 32.4, 50.0, 80.0, 115.7, 122.9, 123.6, 127.9, 128.5, 136.3, 155.7, 170.4; *m/z* (ES) Found: MNa^+ 285.1205. $C_{14}H_{18}N_2O_3Na$ requires MNa^+ 285.1215; $[\alpha]_D^{22}$ +5.0 (c 1.2, $CHCl_3$).

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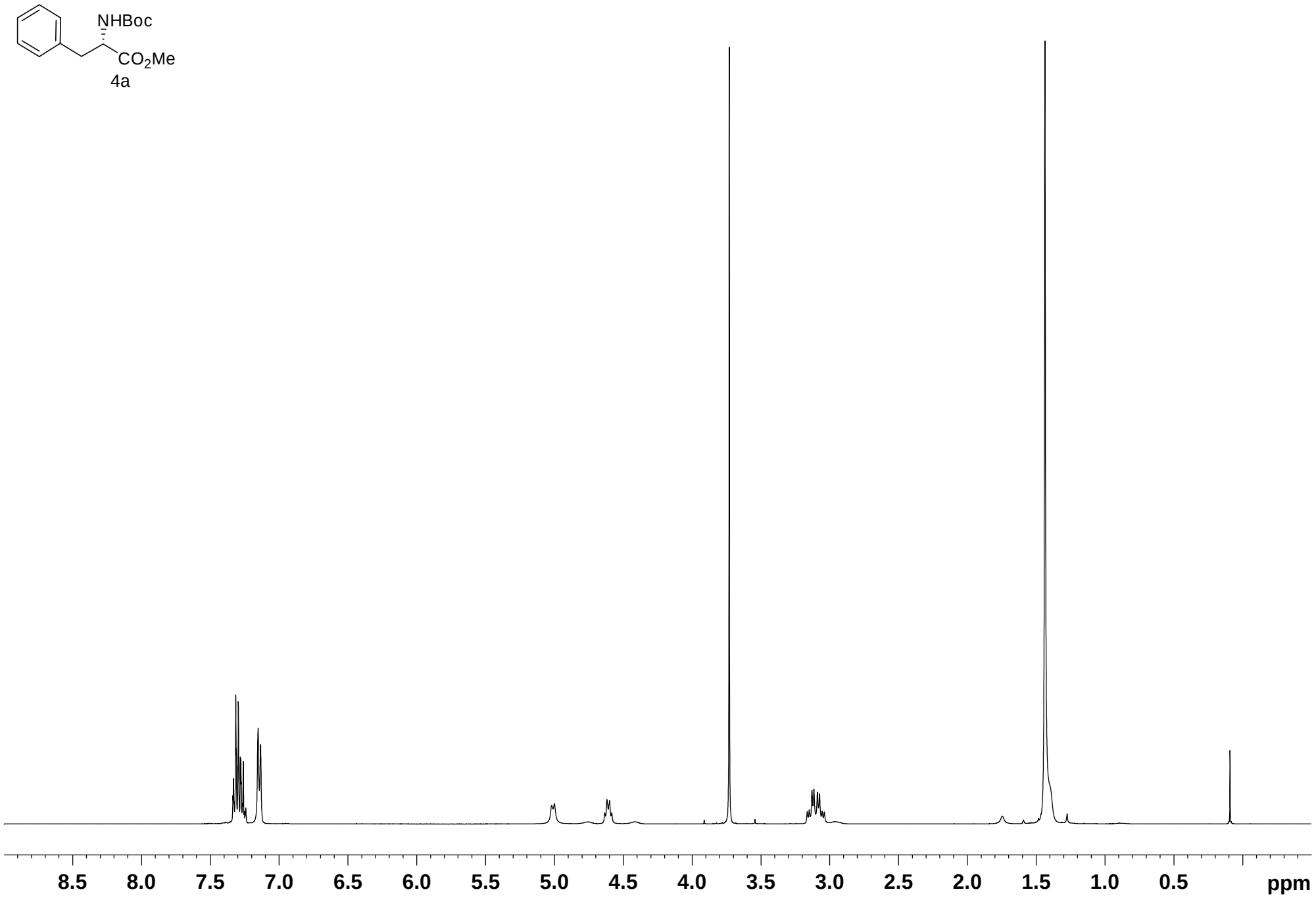
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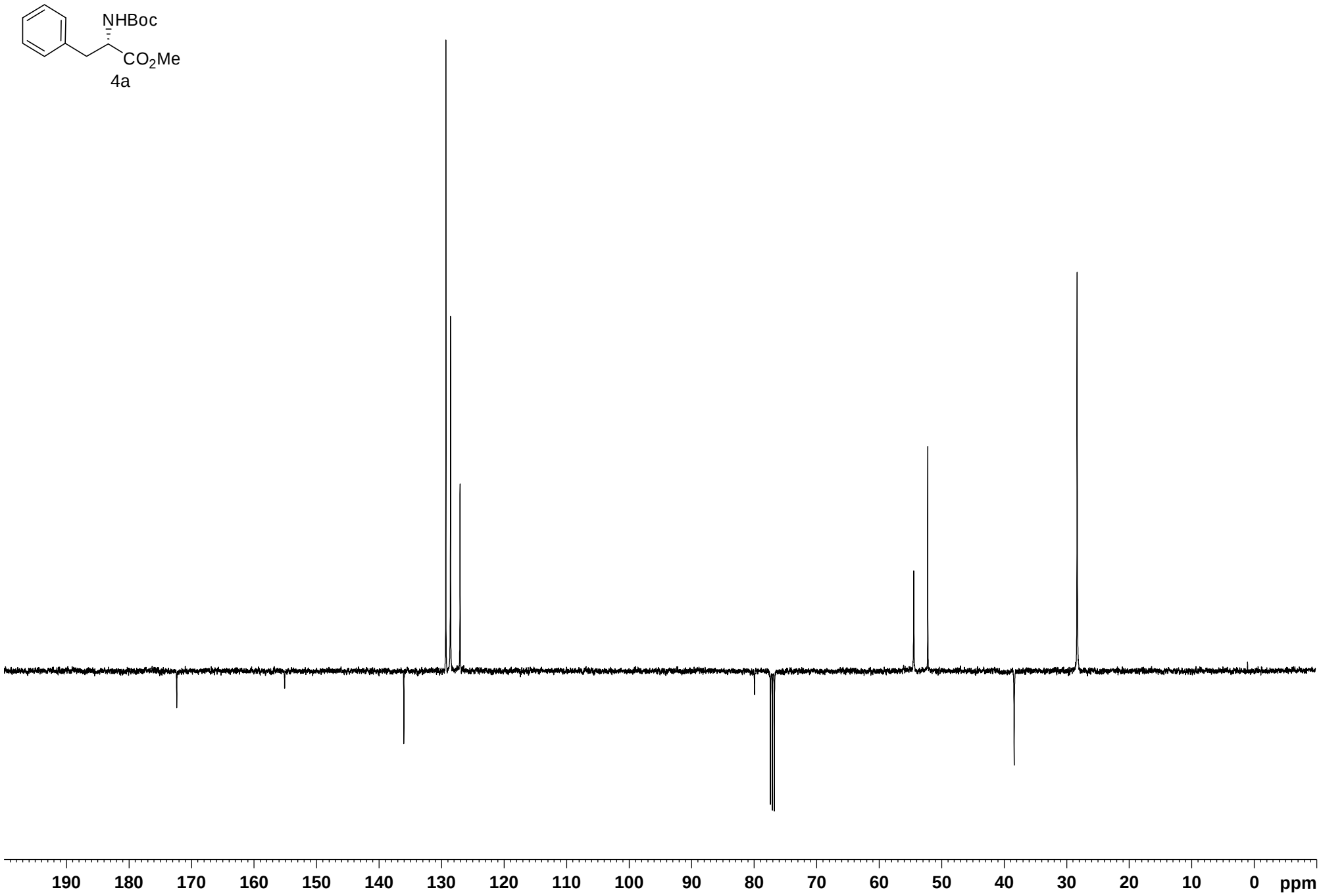
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CO2Me
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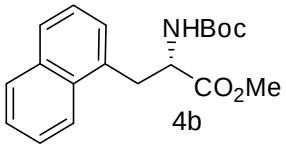

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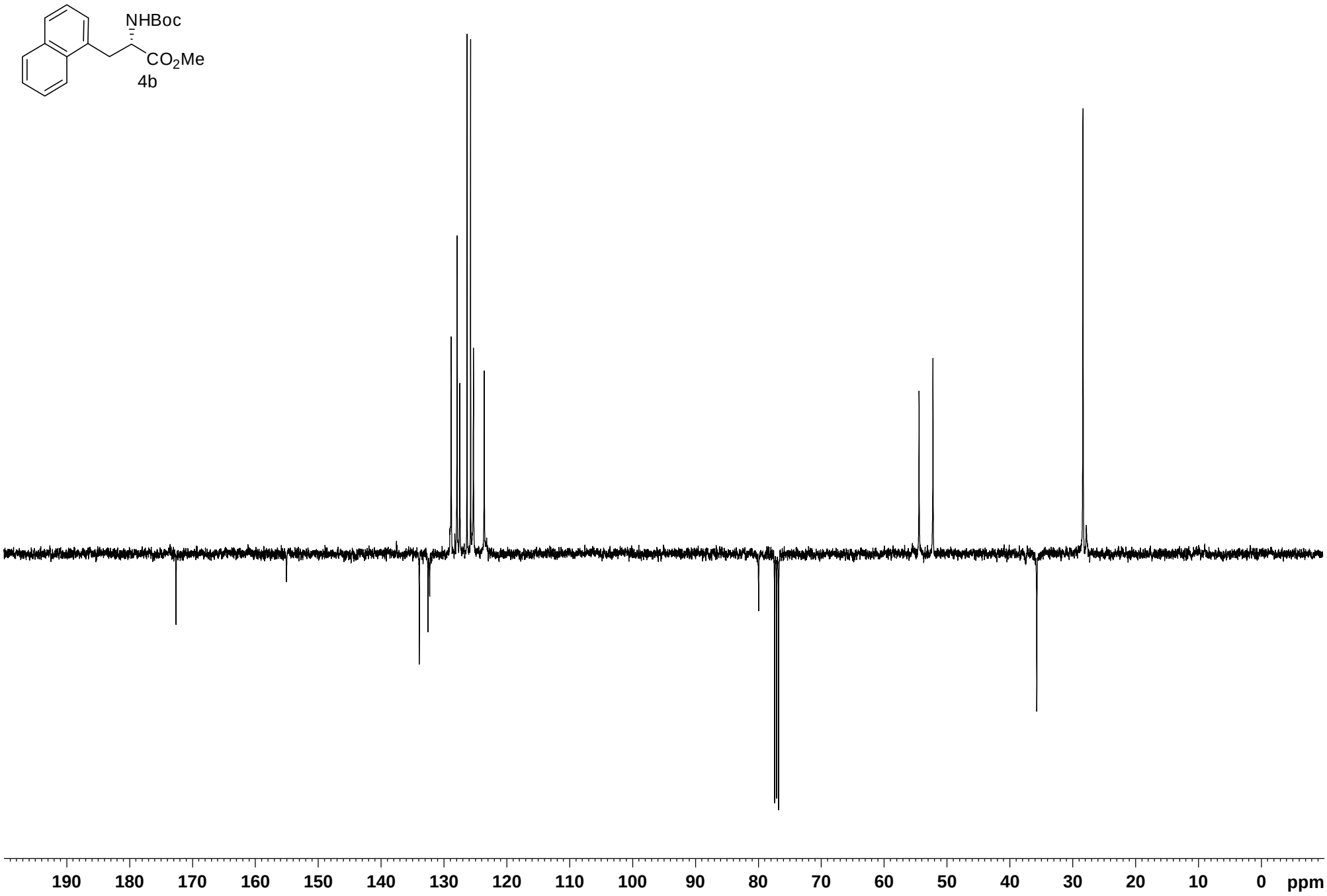
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CO2Me
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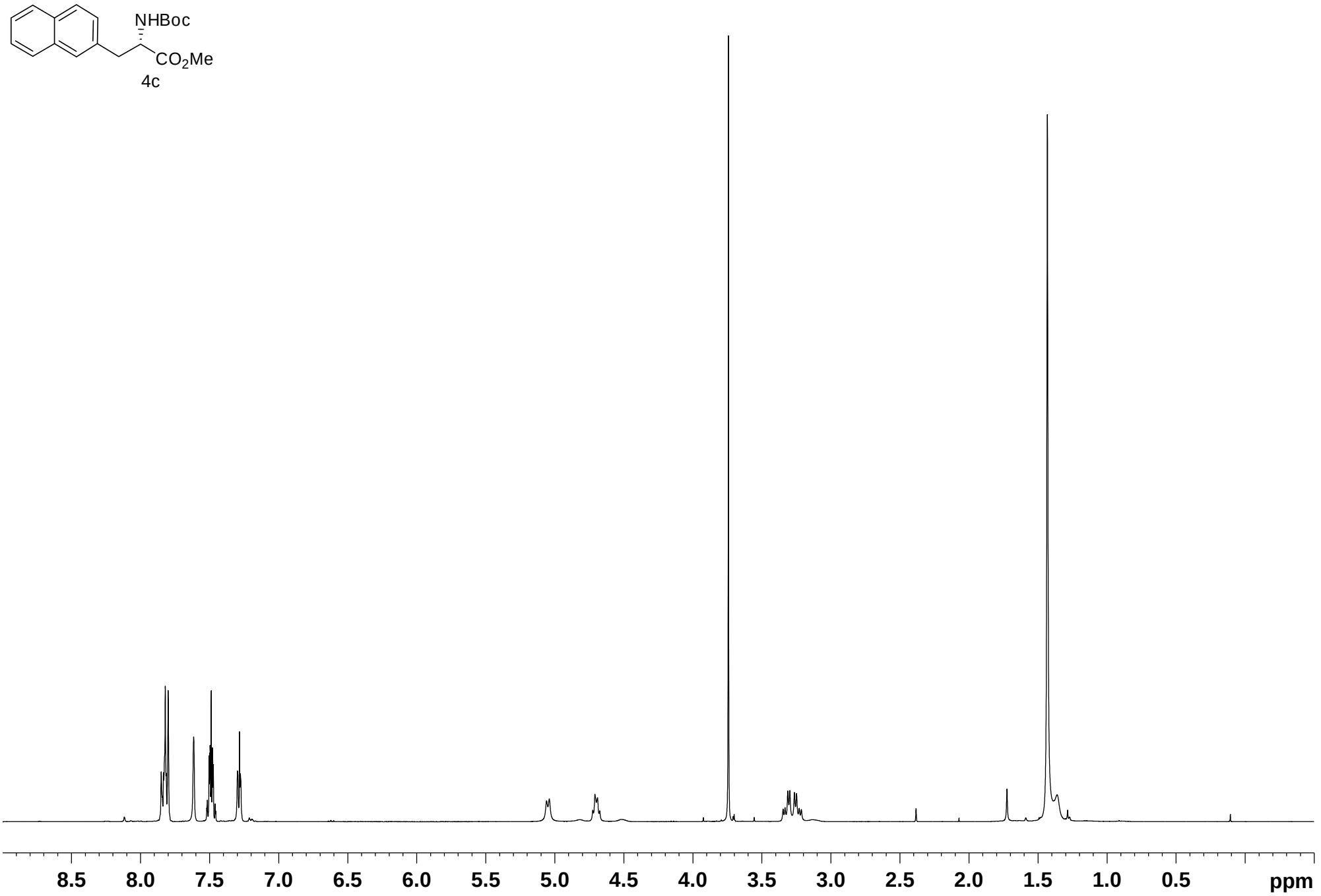
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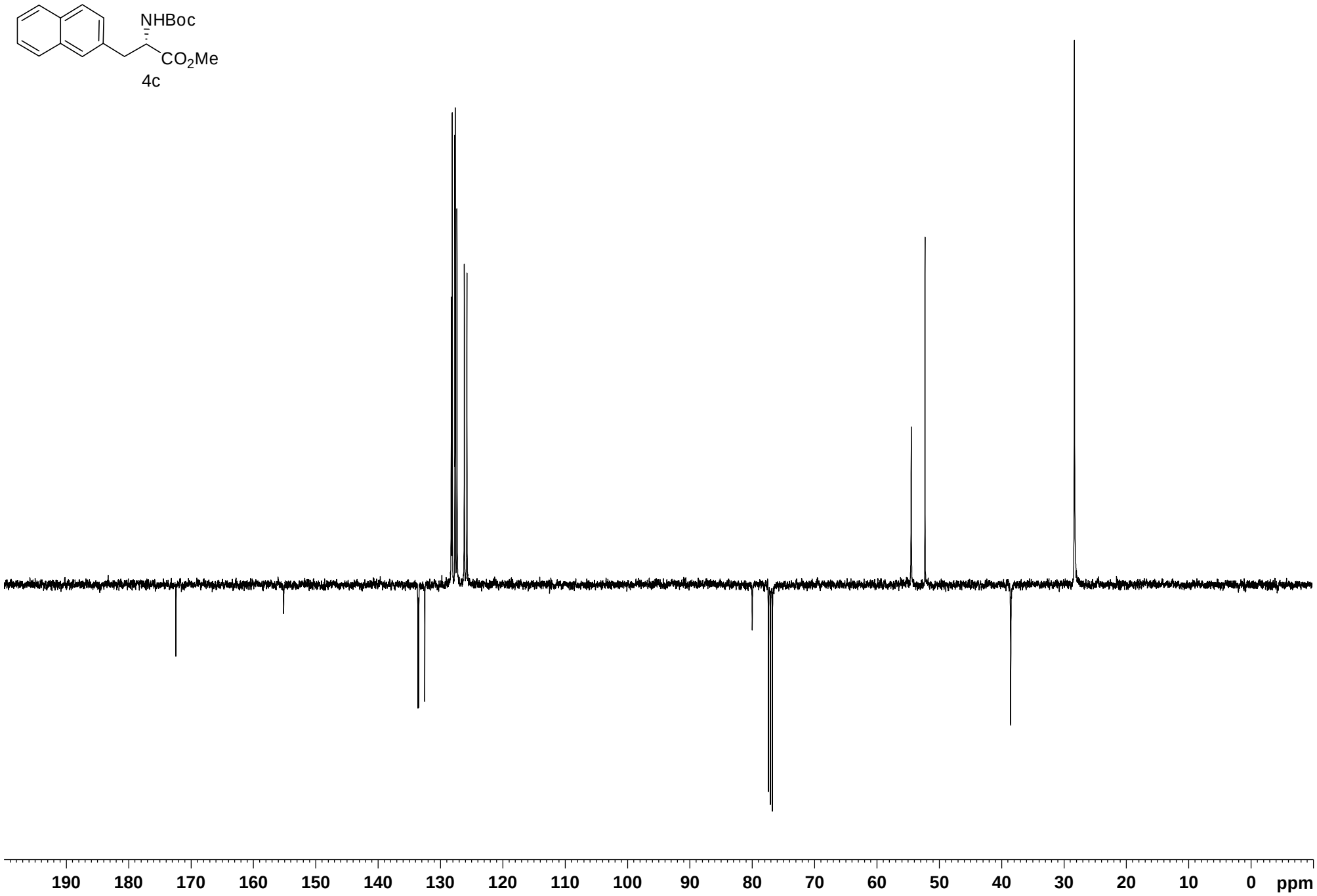
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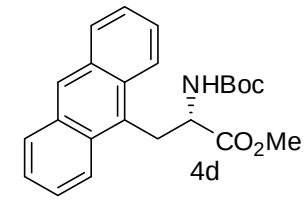

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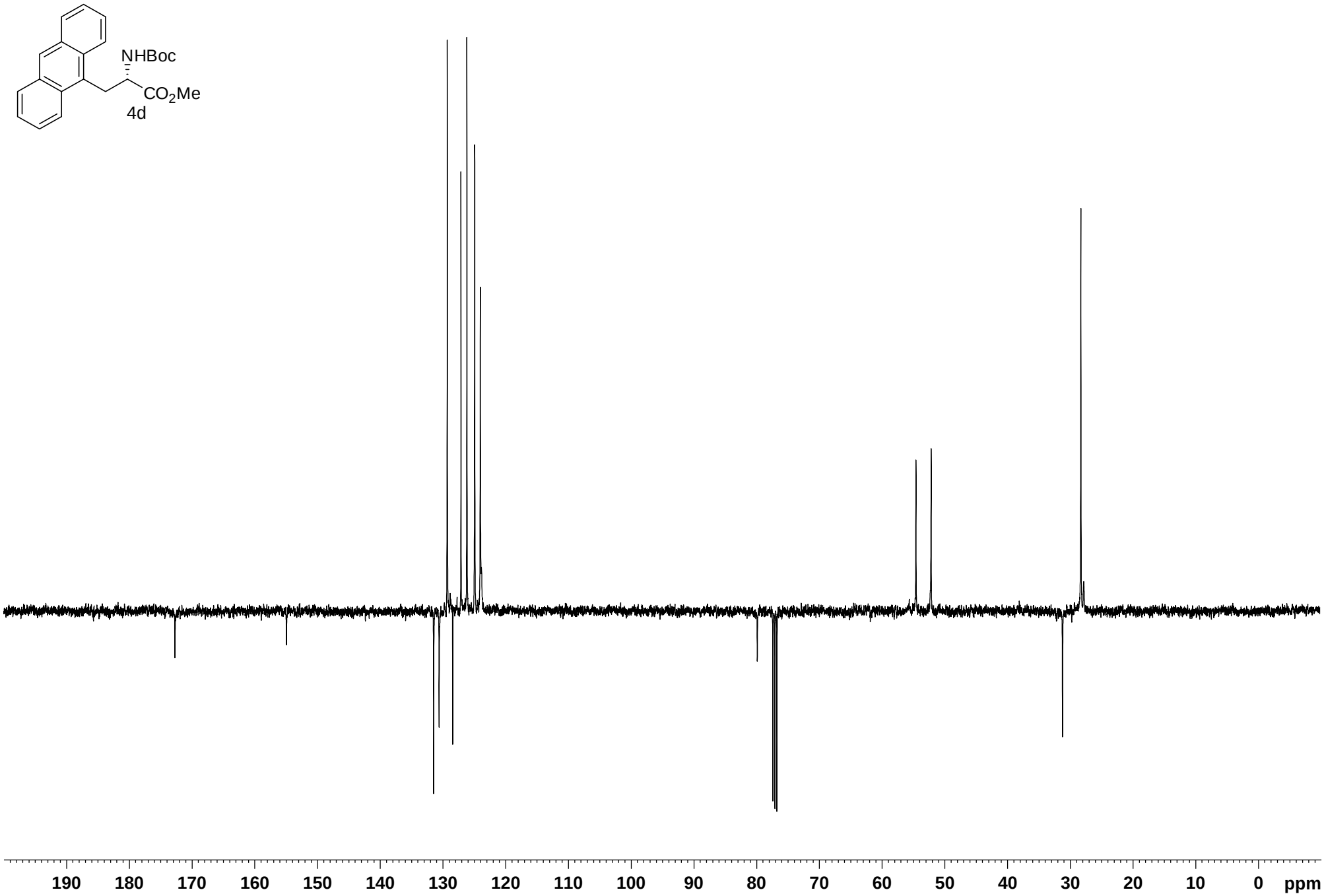
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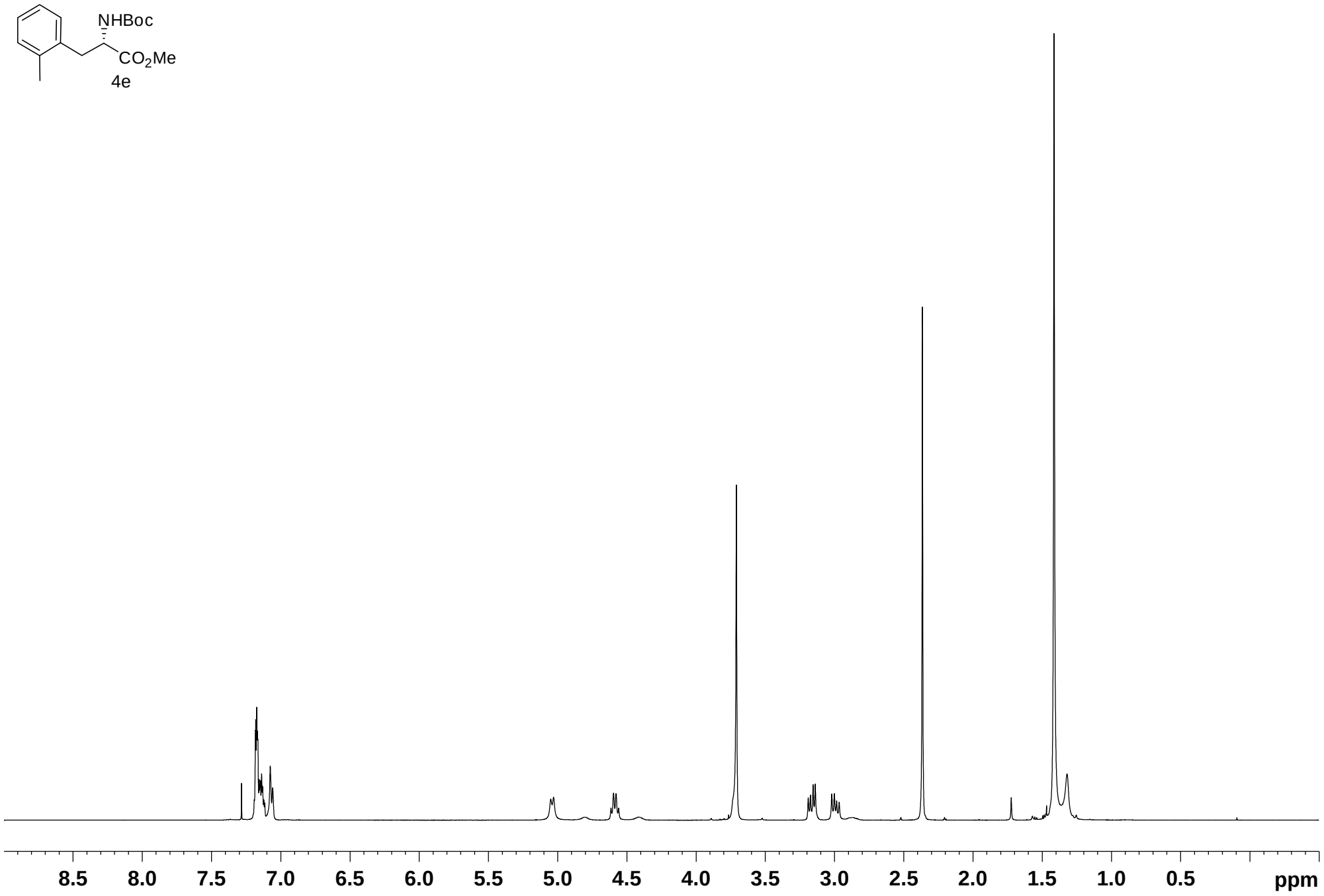
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7.0
6.5
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
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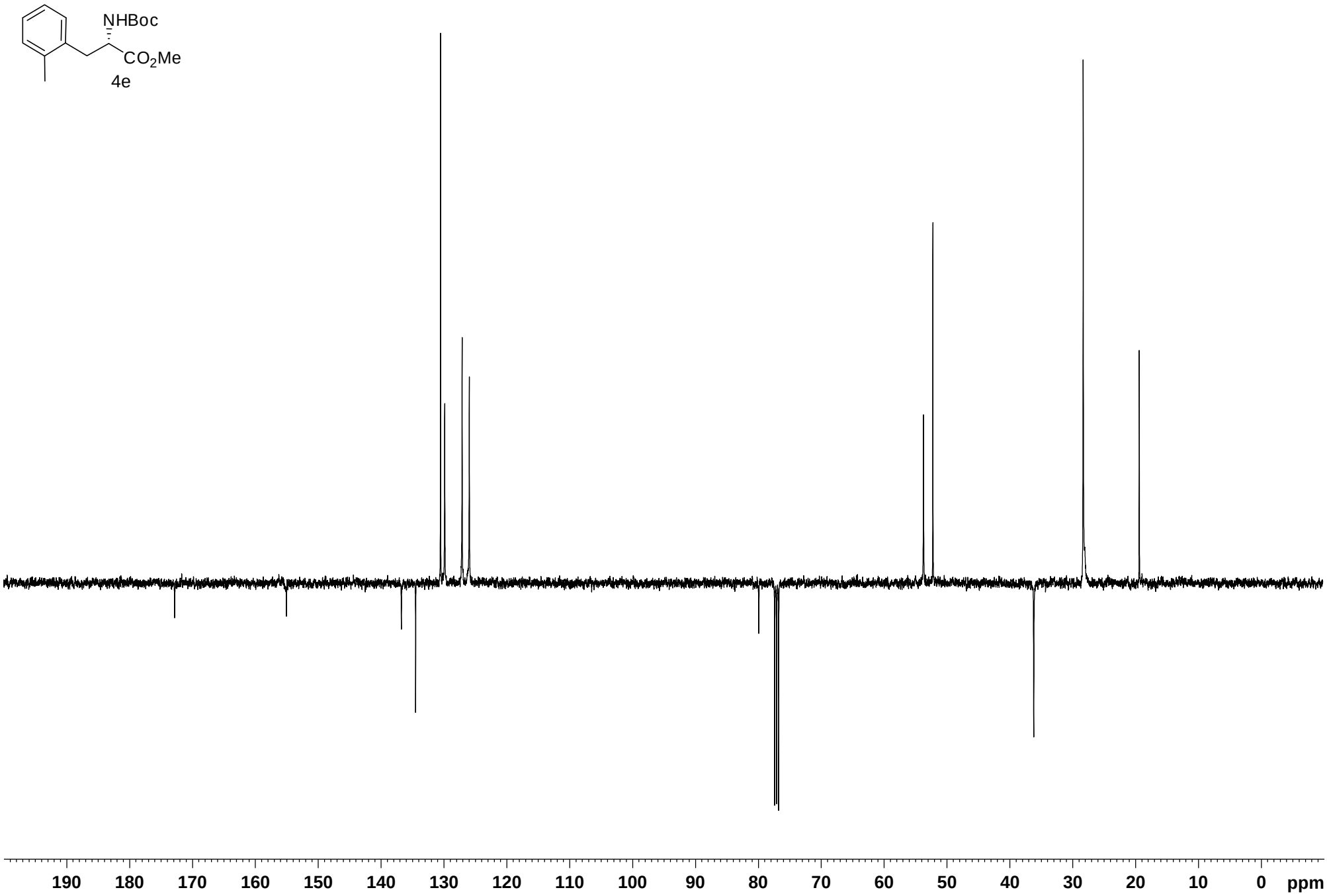
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4e
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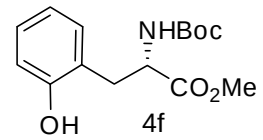
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CO2Me
OH

4f

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4.0
3.5
3.0
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2.0
1.5
1.0
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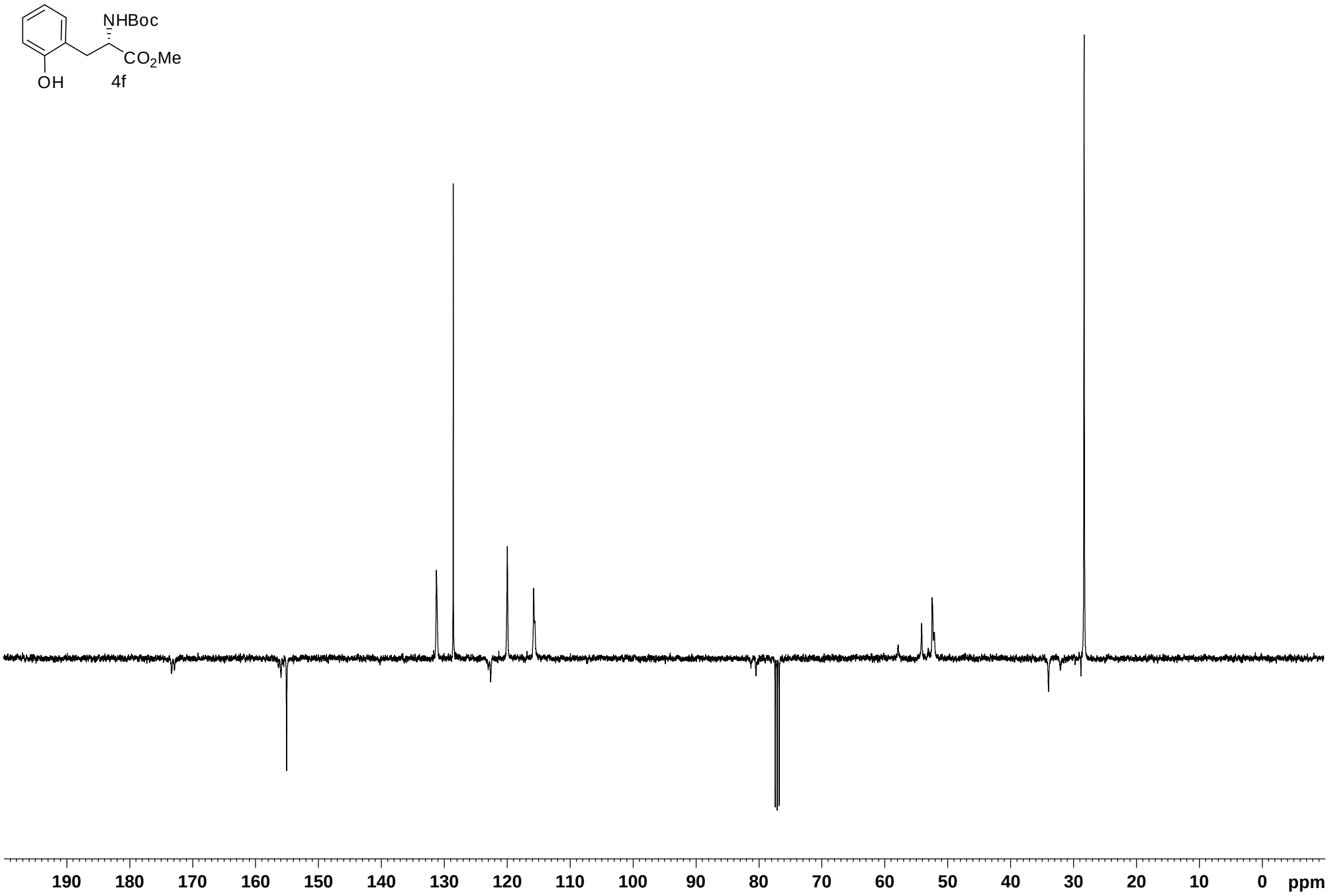
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CO2Me
OH
4f
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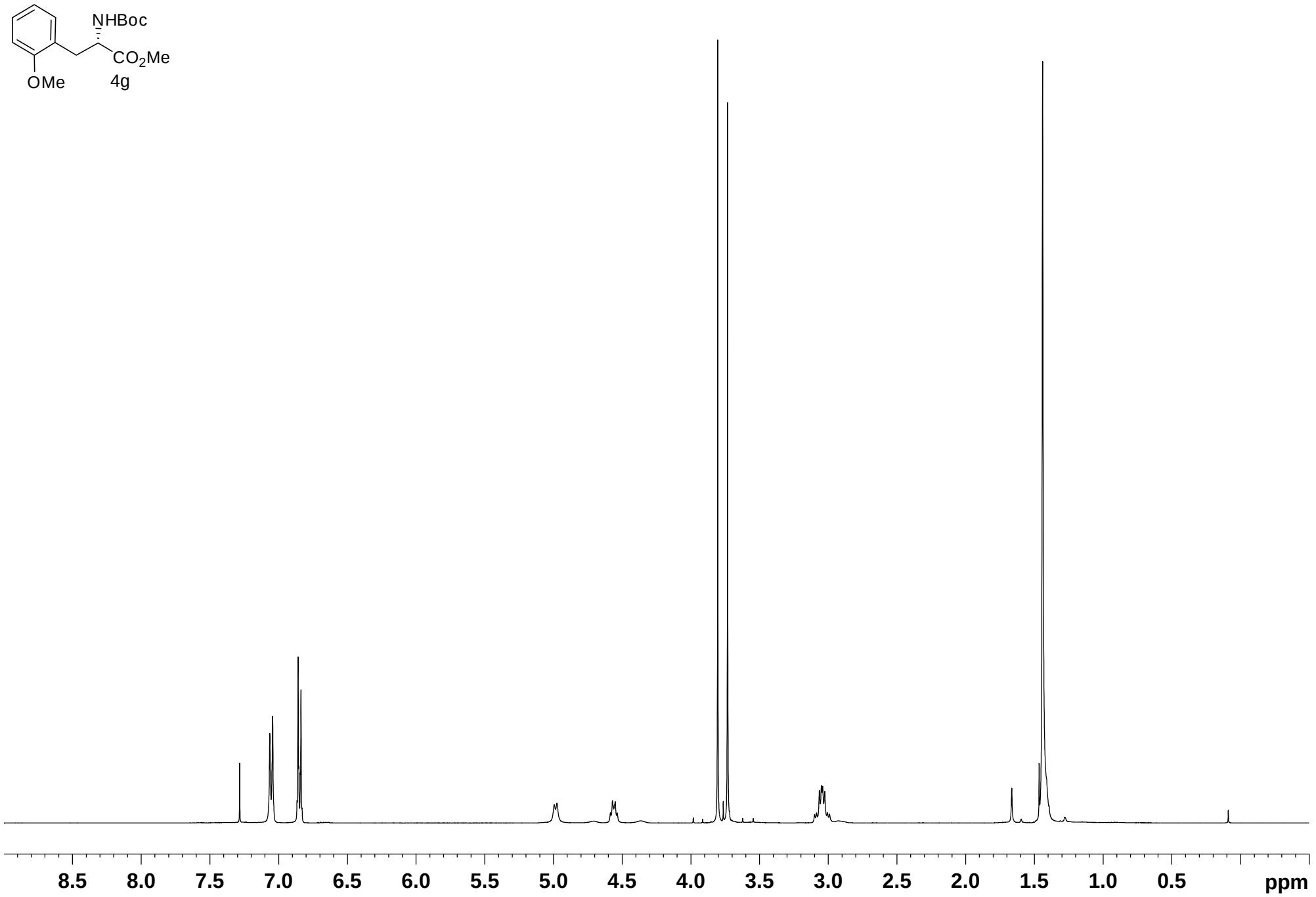
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OMe
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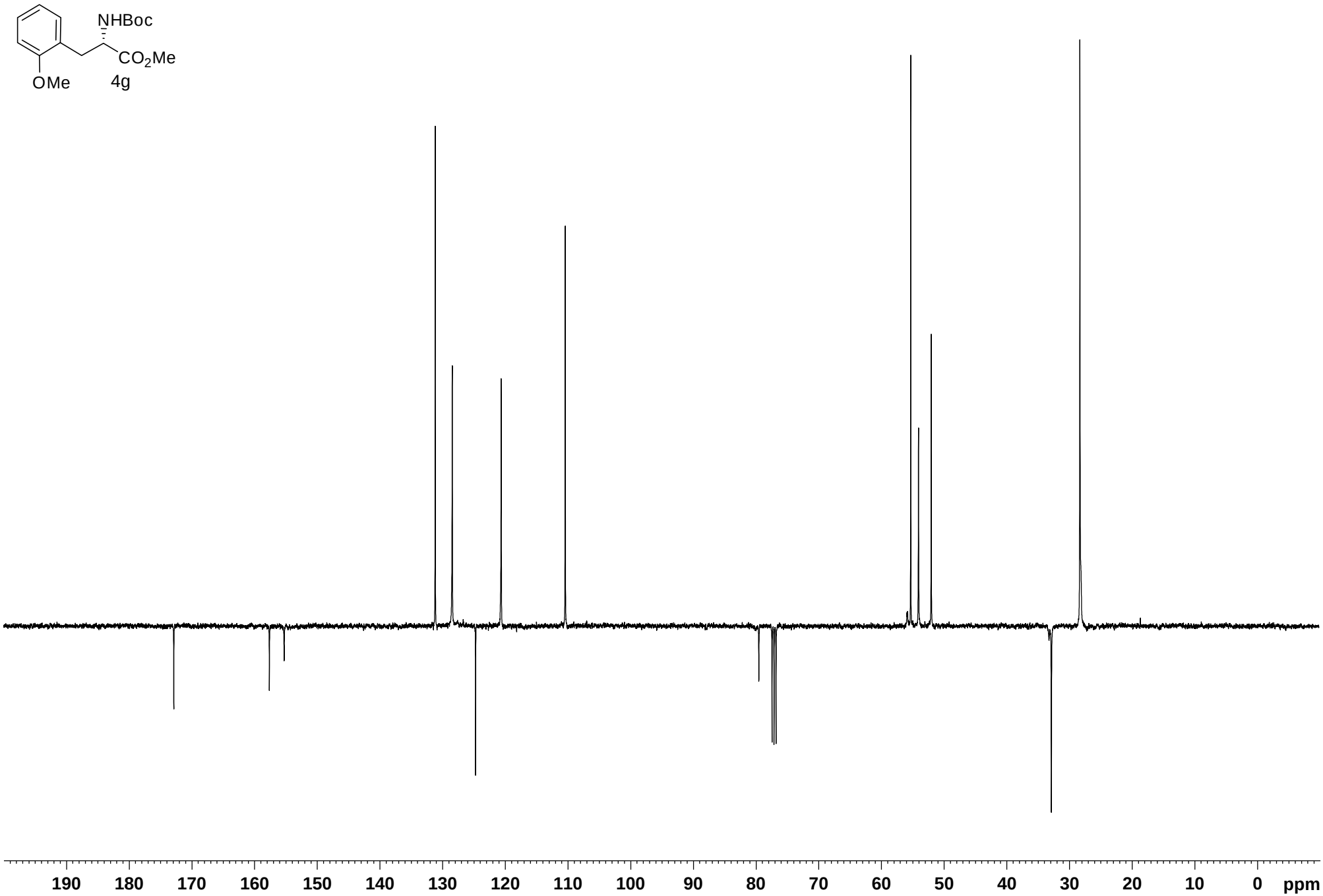
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CO2Me
OMe
4g
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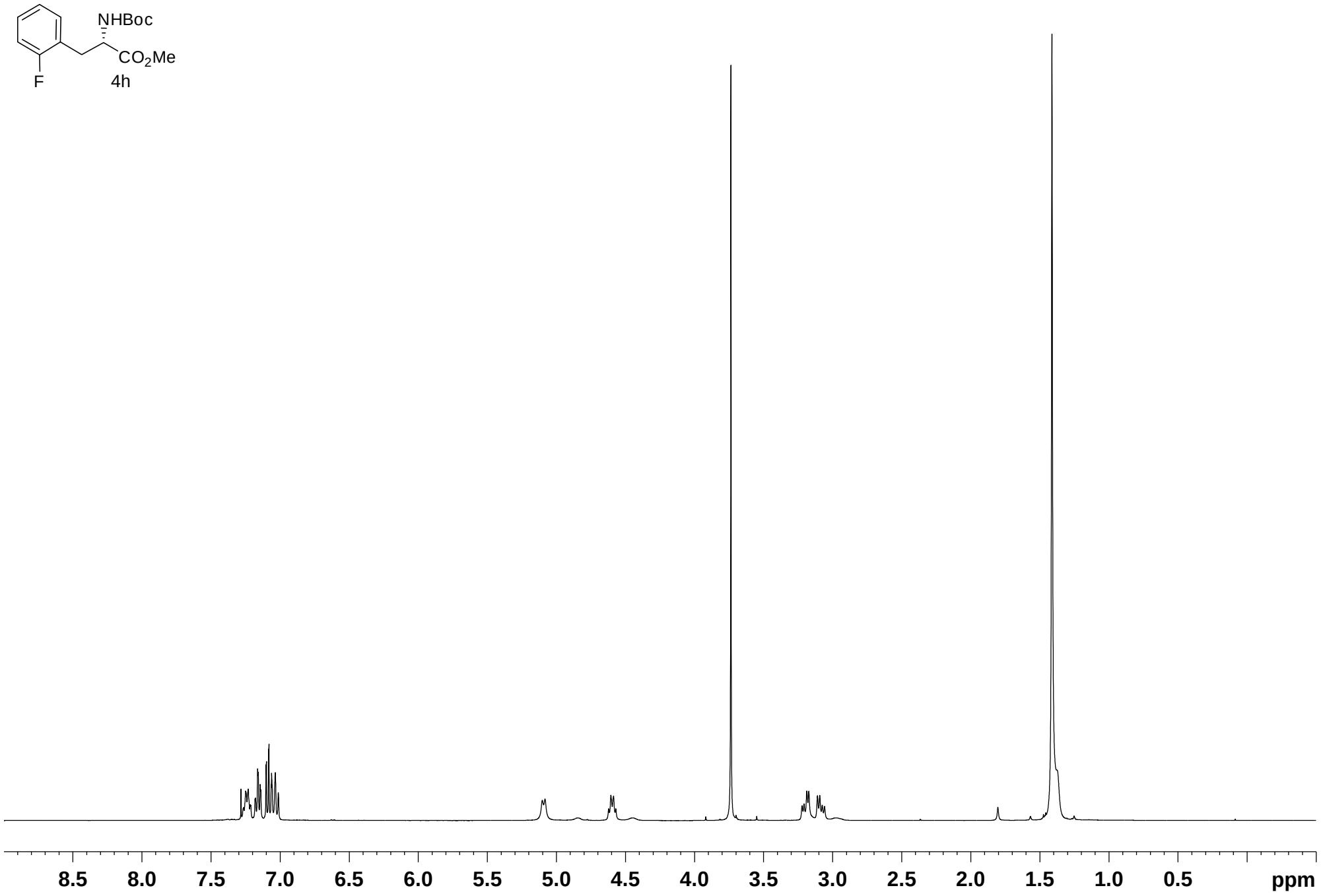
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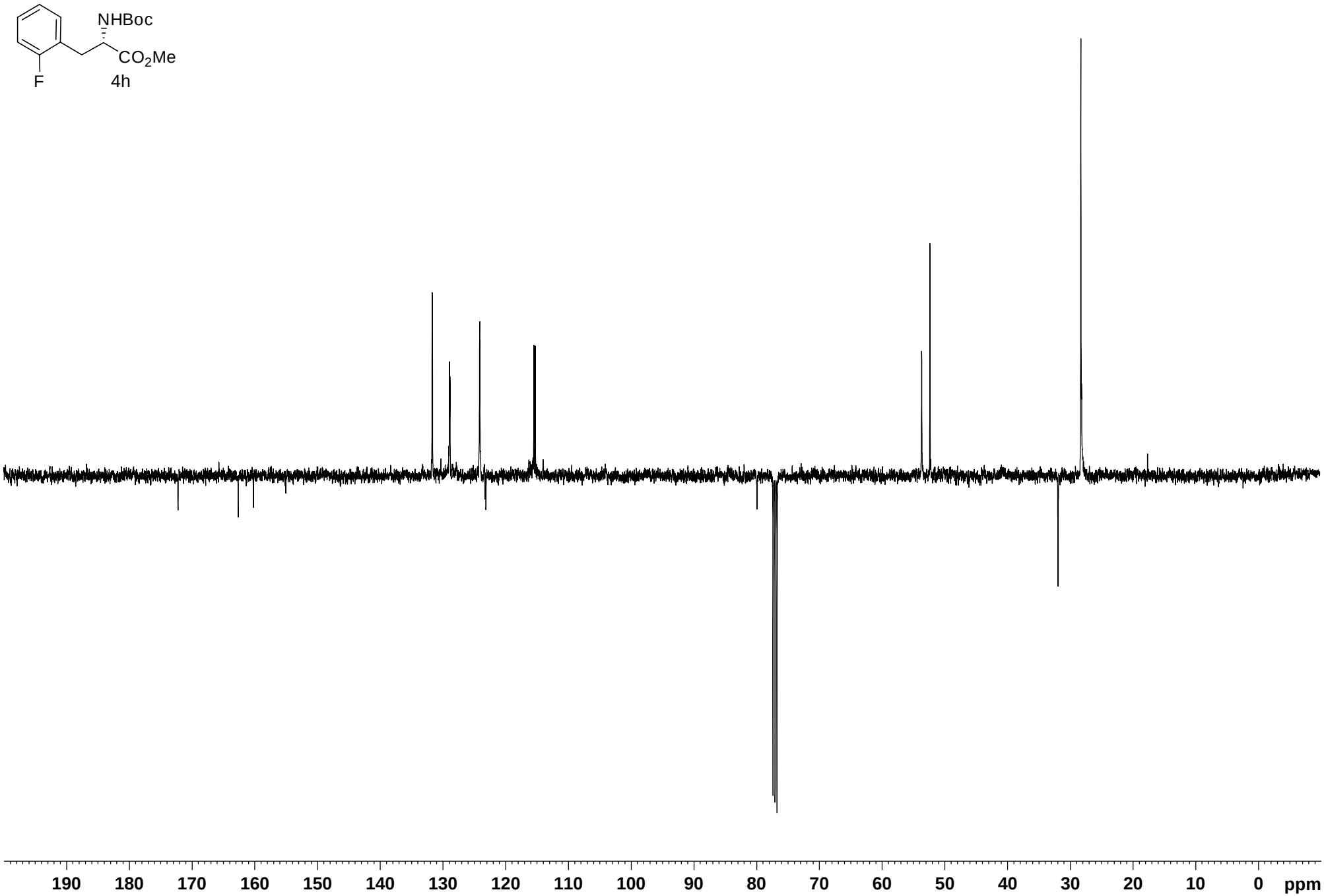
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CO2Me
F
4h
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100
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10
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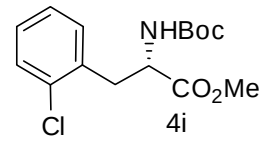
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CO2Me
Cl
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3.5
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1.0
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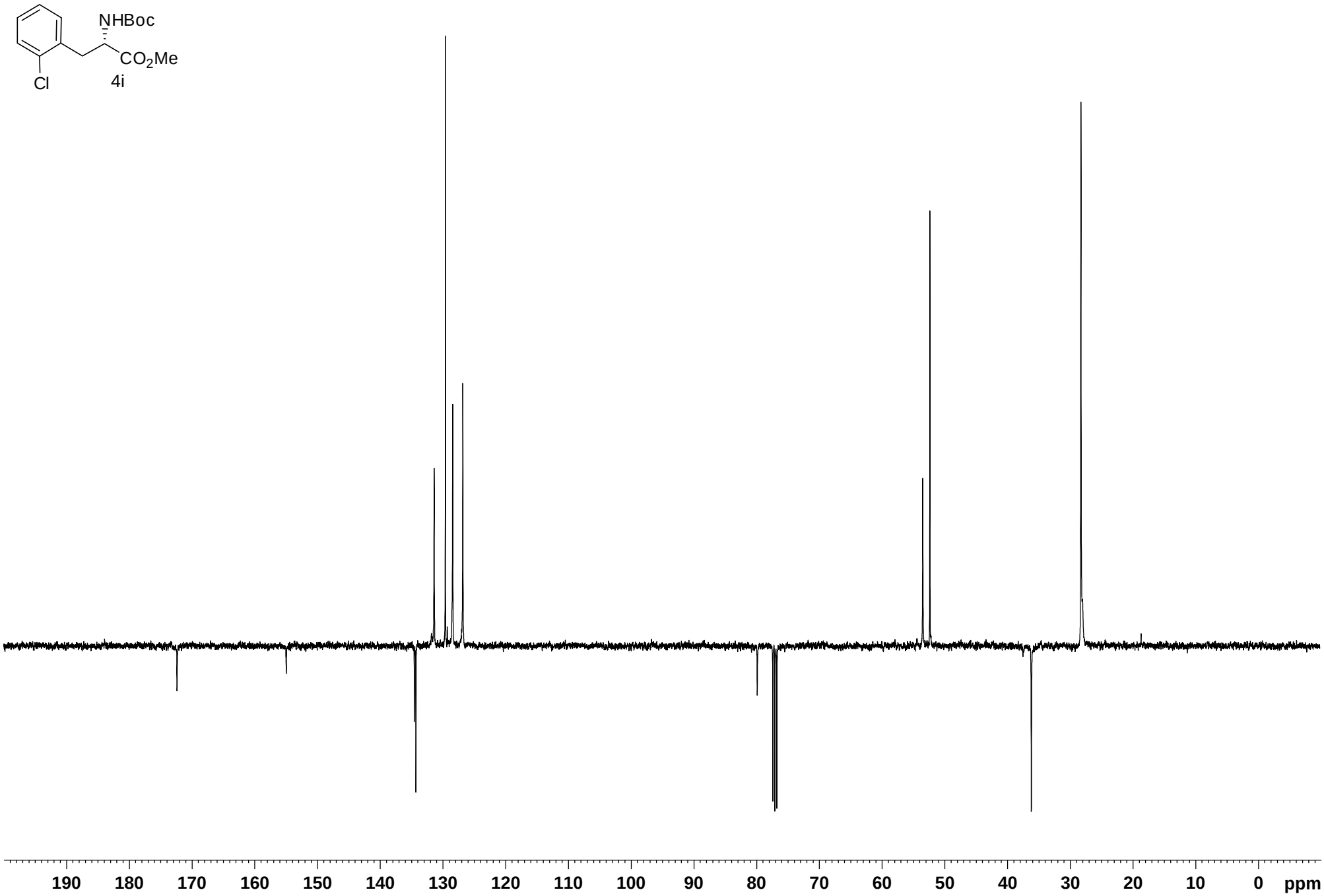
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CO2Me
Cl
4i
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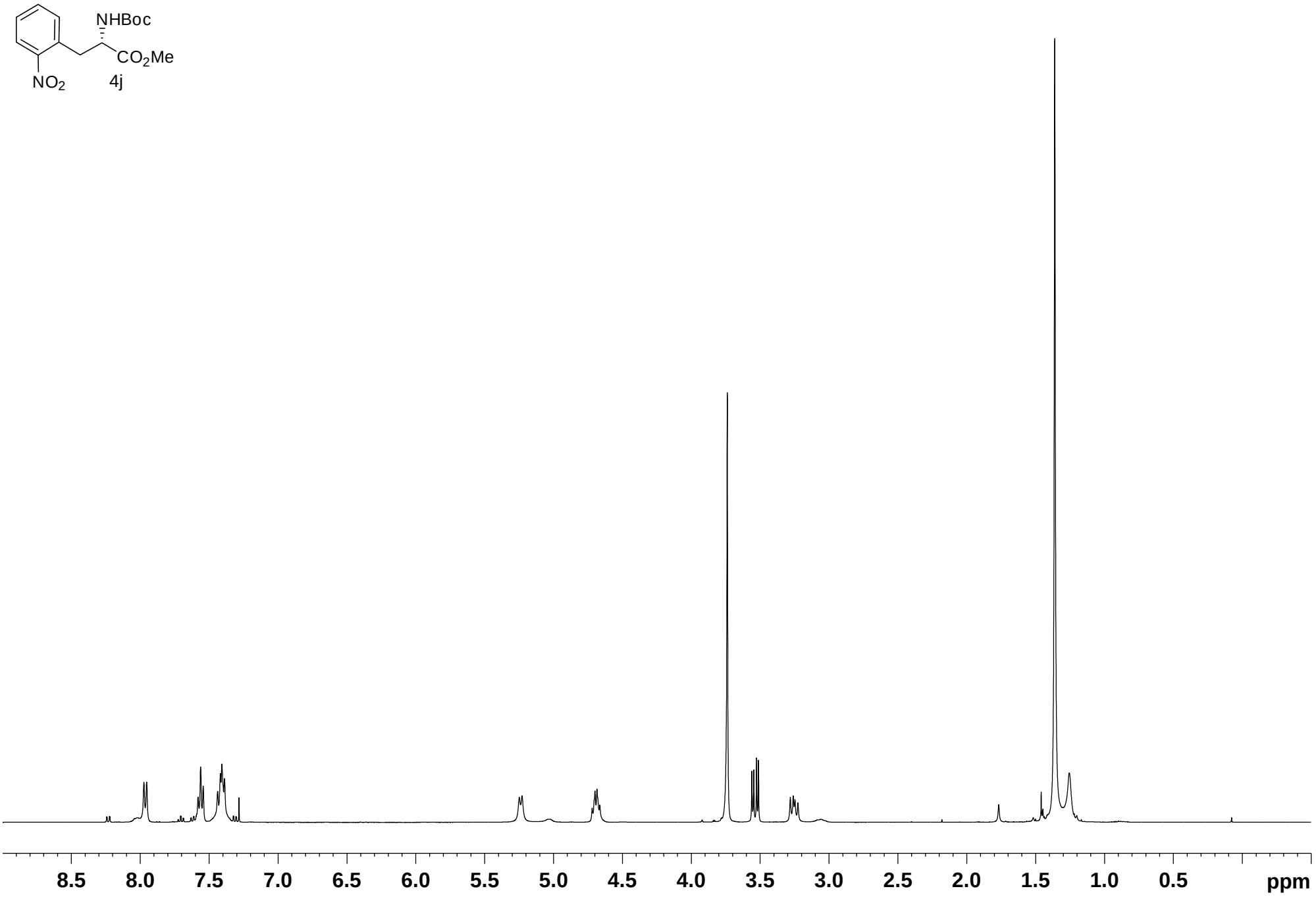
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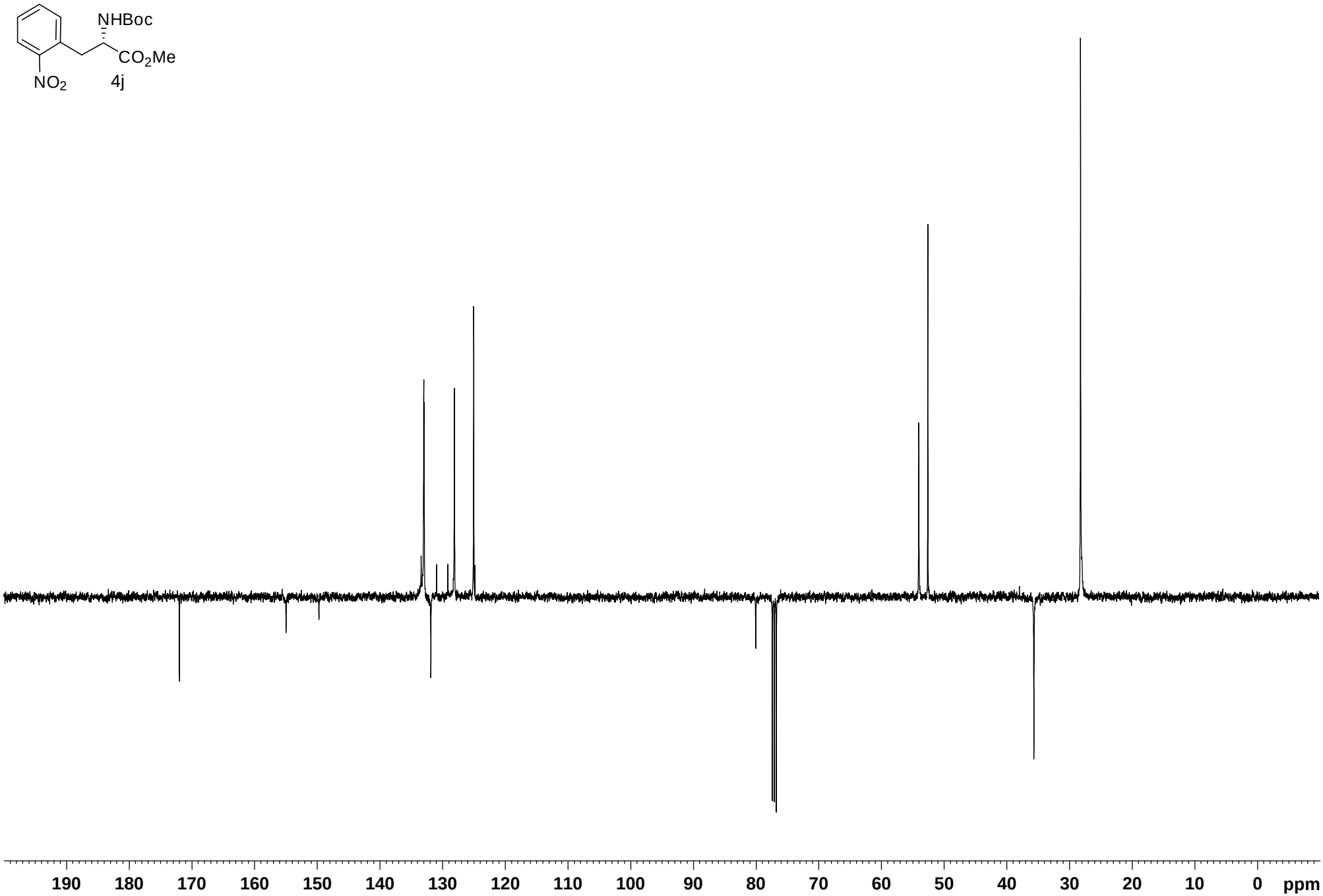
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CO2Me
NO2
4j
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0
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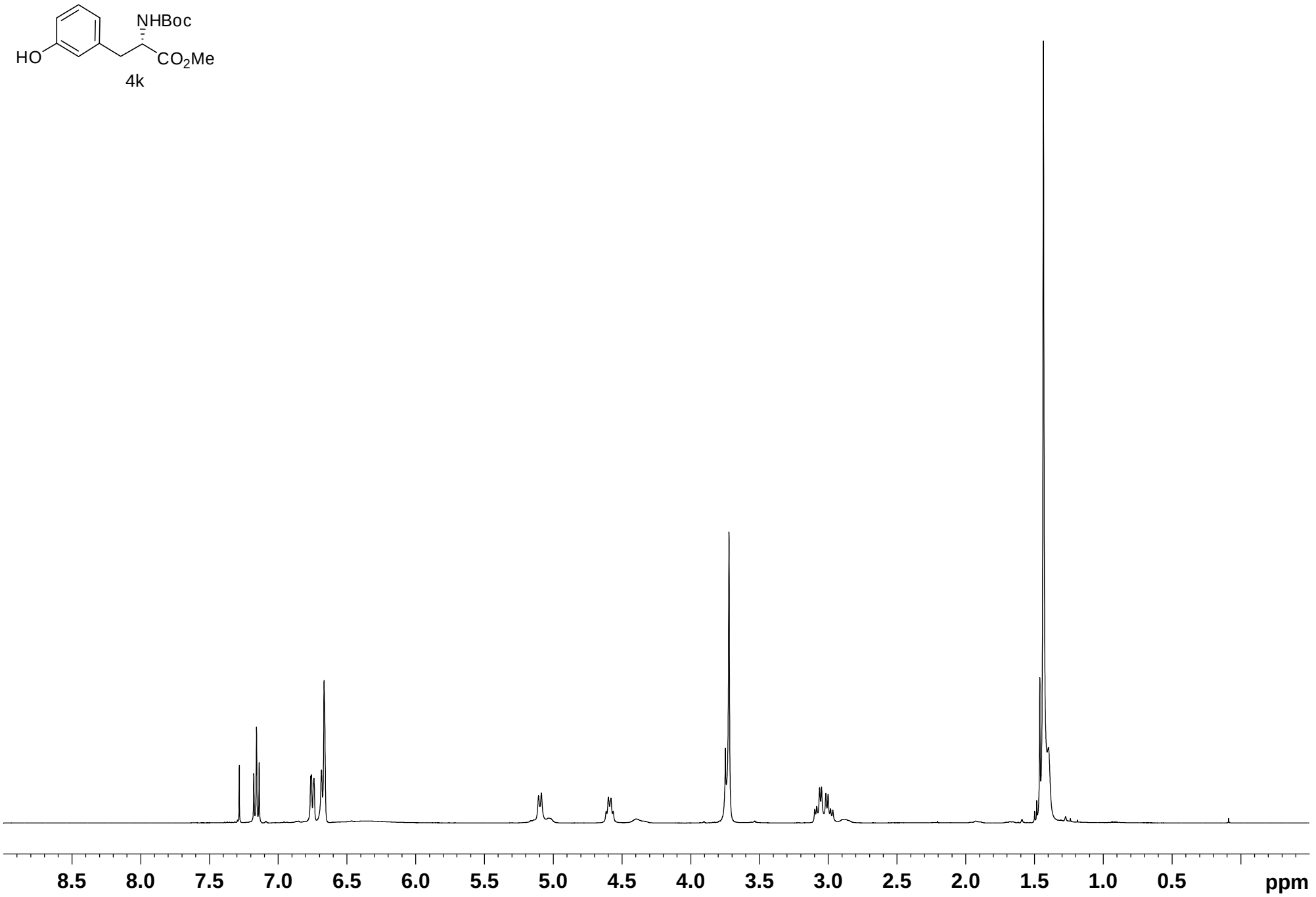
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1.0
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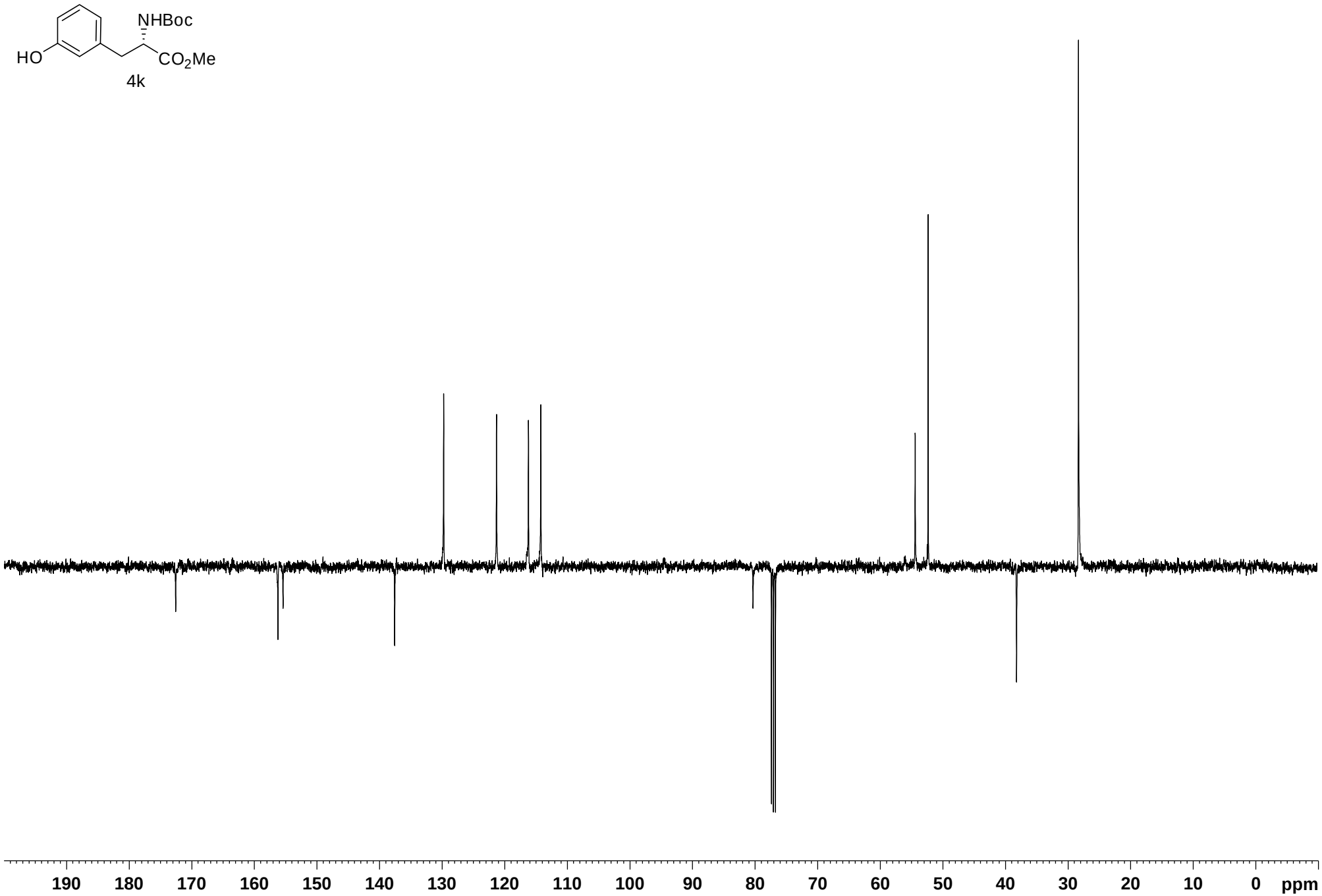
ppm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HO
CO2Me
4k
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100
90
80
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60
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20
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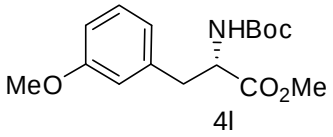
0
ppm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CO2Me

4l

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6.5
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4.5
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3.0
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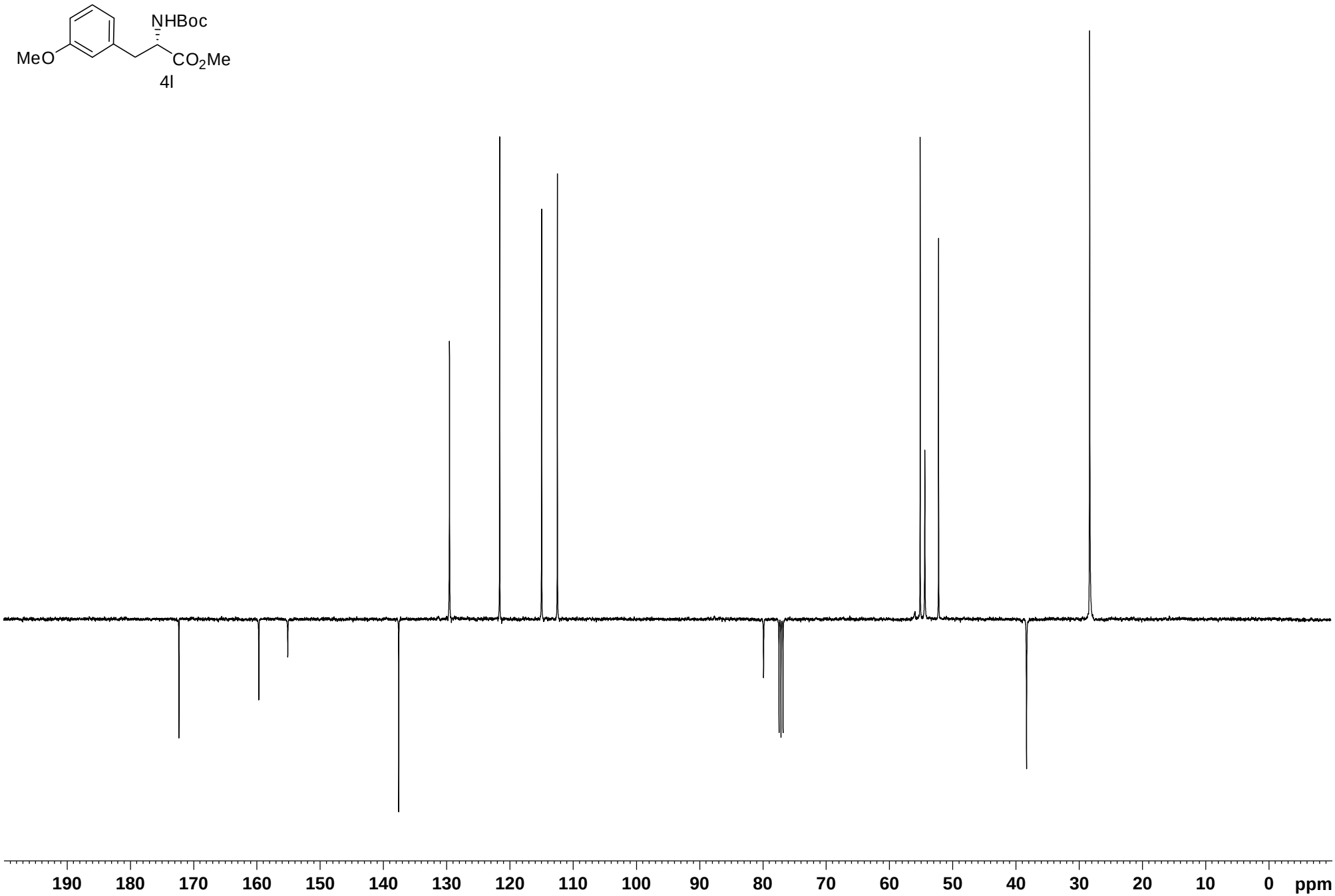
2.0
1.5
1.0
0.5
ppm


NHBoc
MeO
CO2Me
4l
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140
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110
100
90
80
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60
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30
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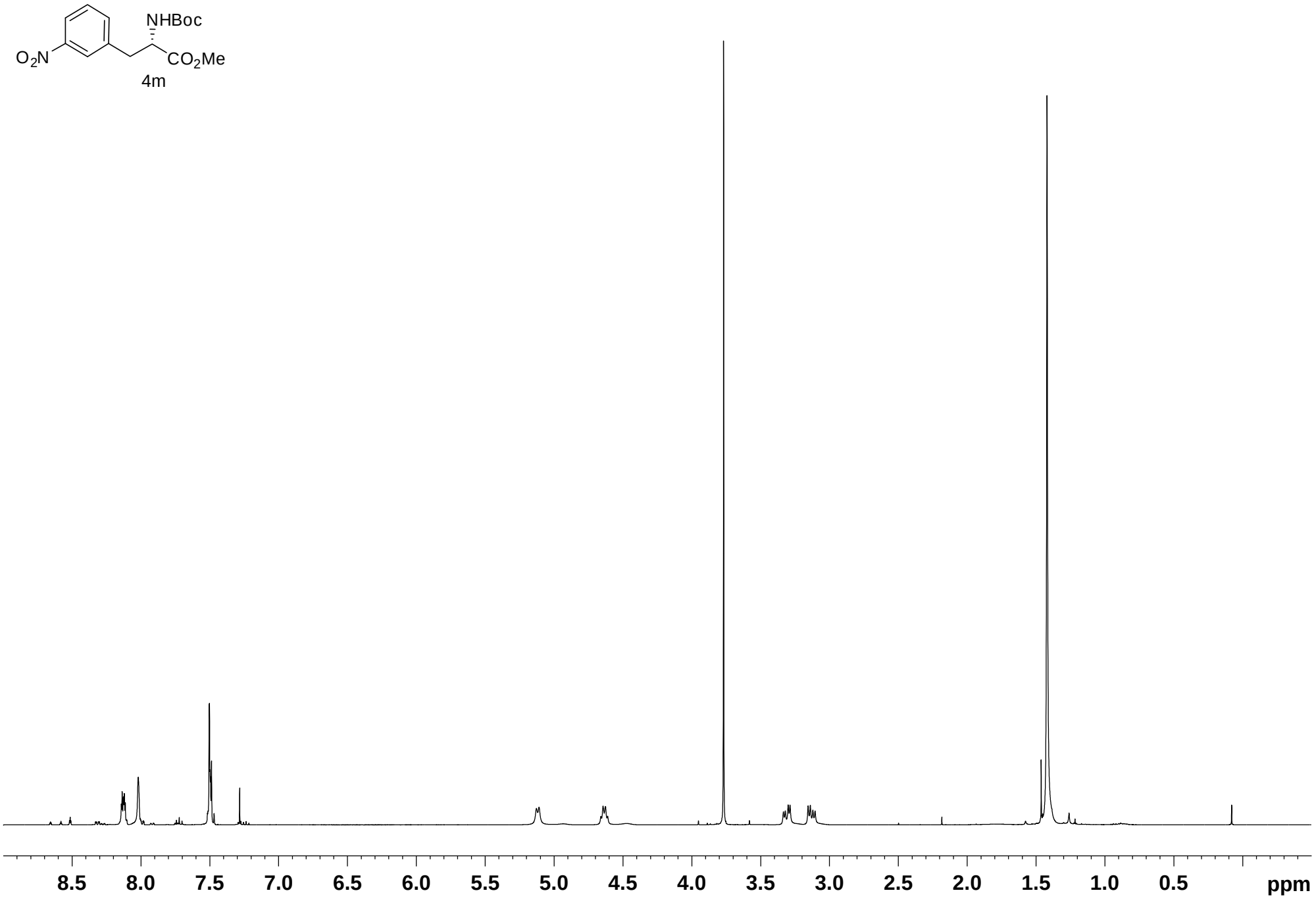
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CO_2Me
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7.0
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4.5
4.0
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2.0
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1.0
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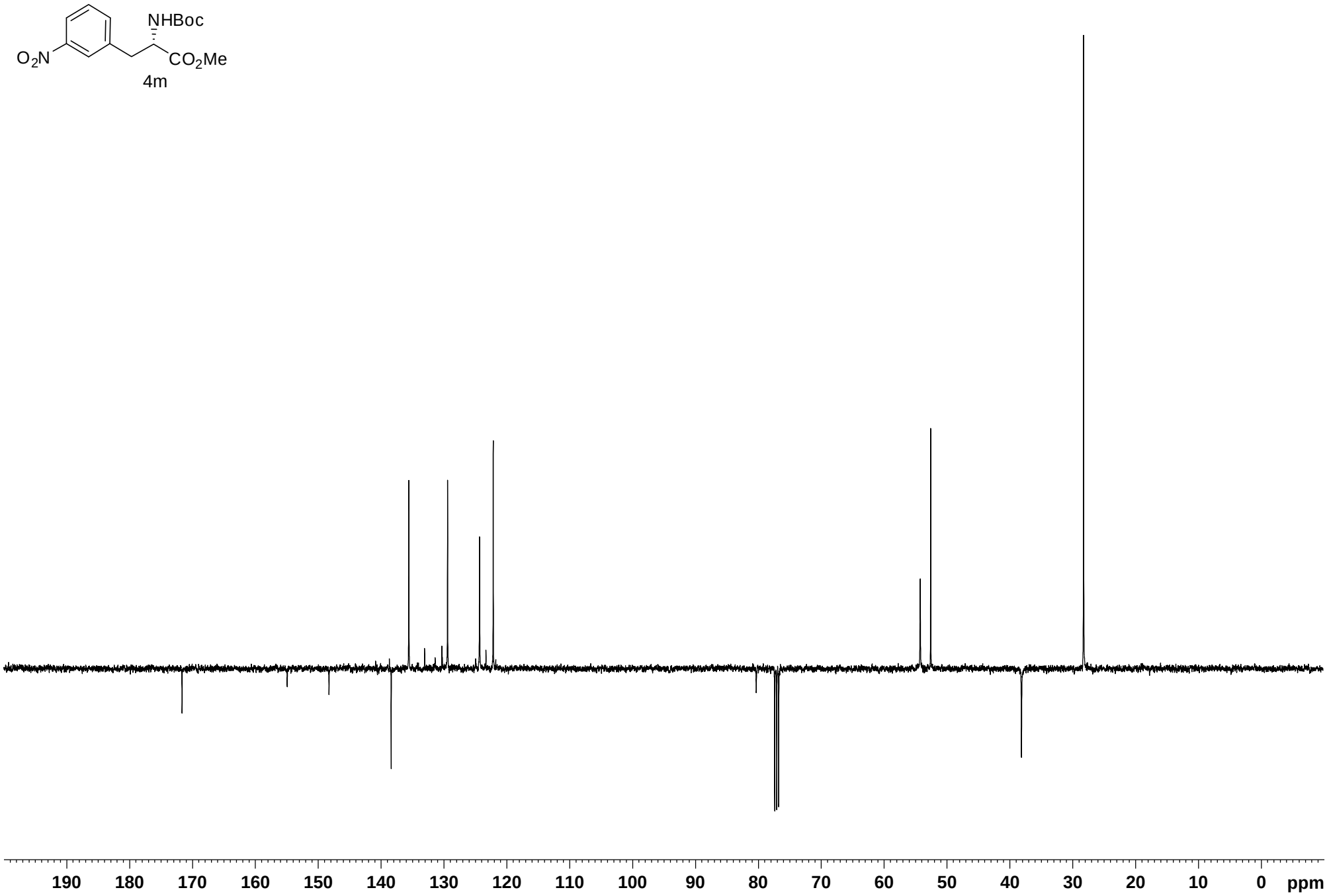
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O2N
CO2Me
4m
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100
90
80
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60
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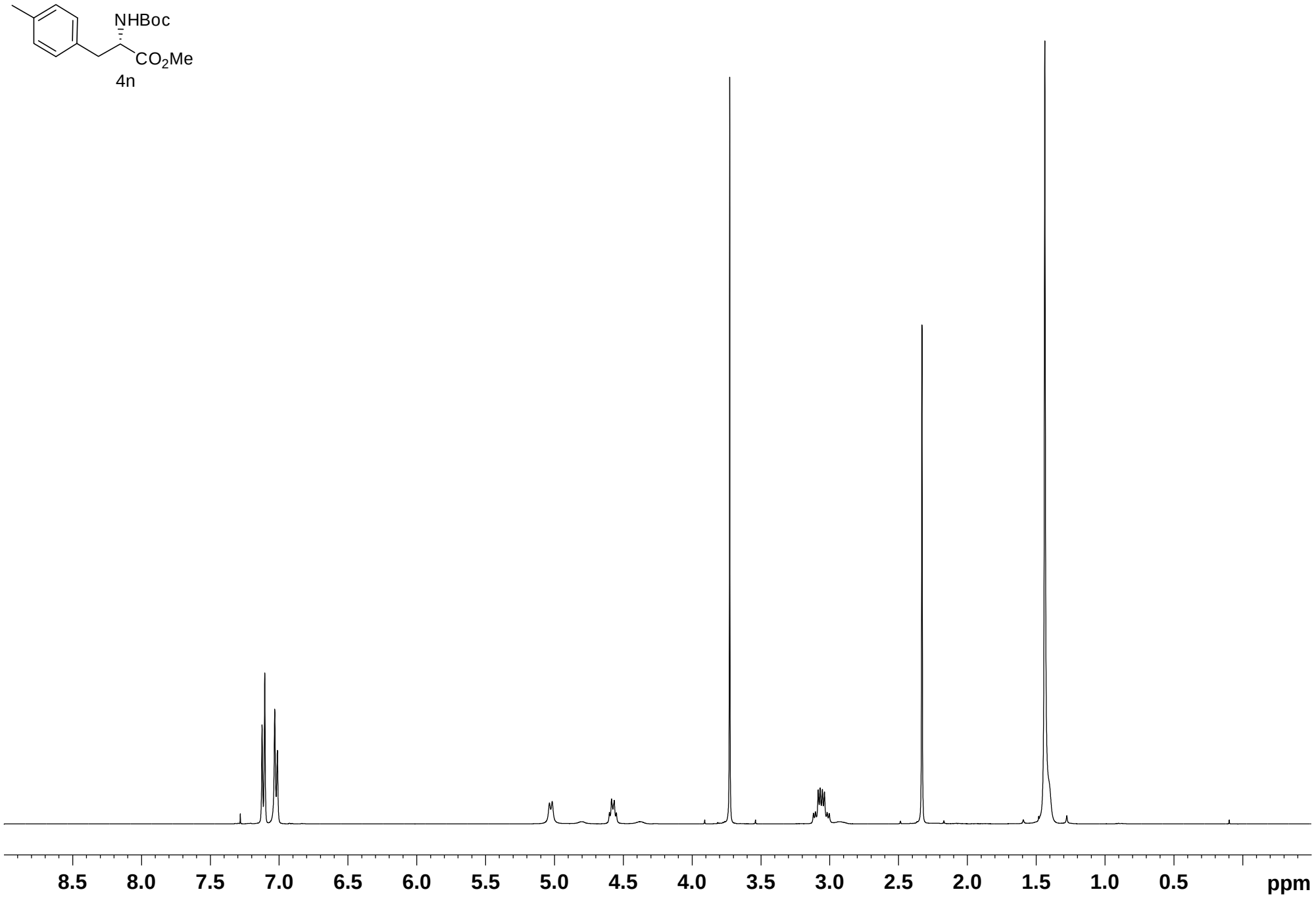
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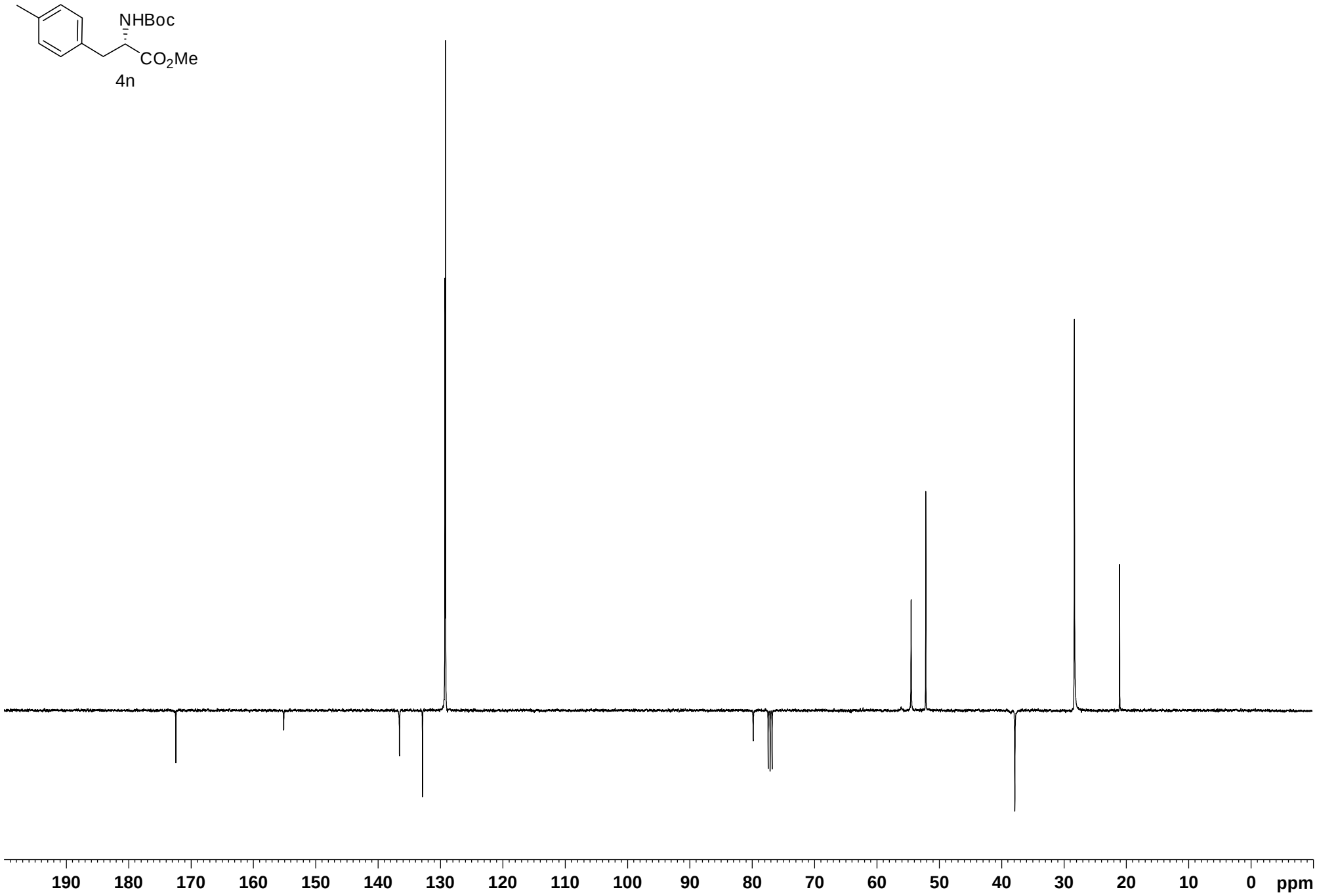
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CO2Me
4n
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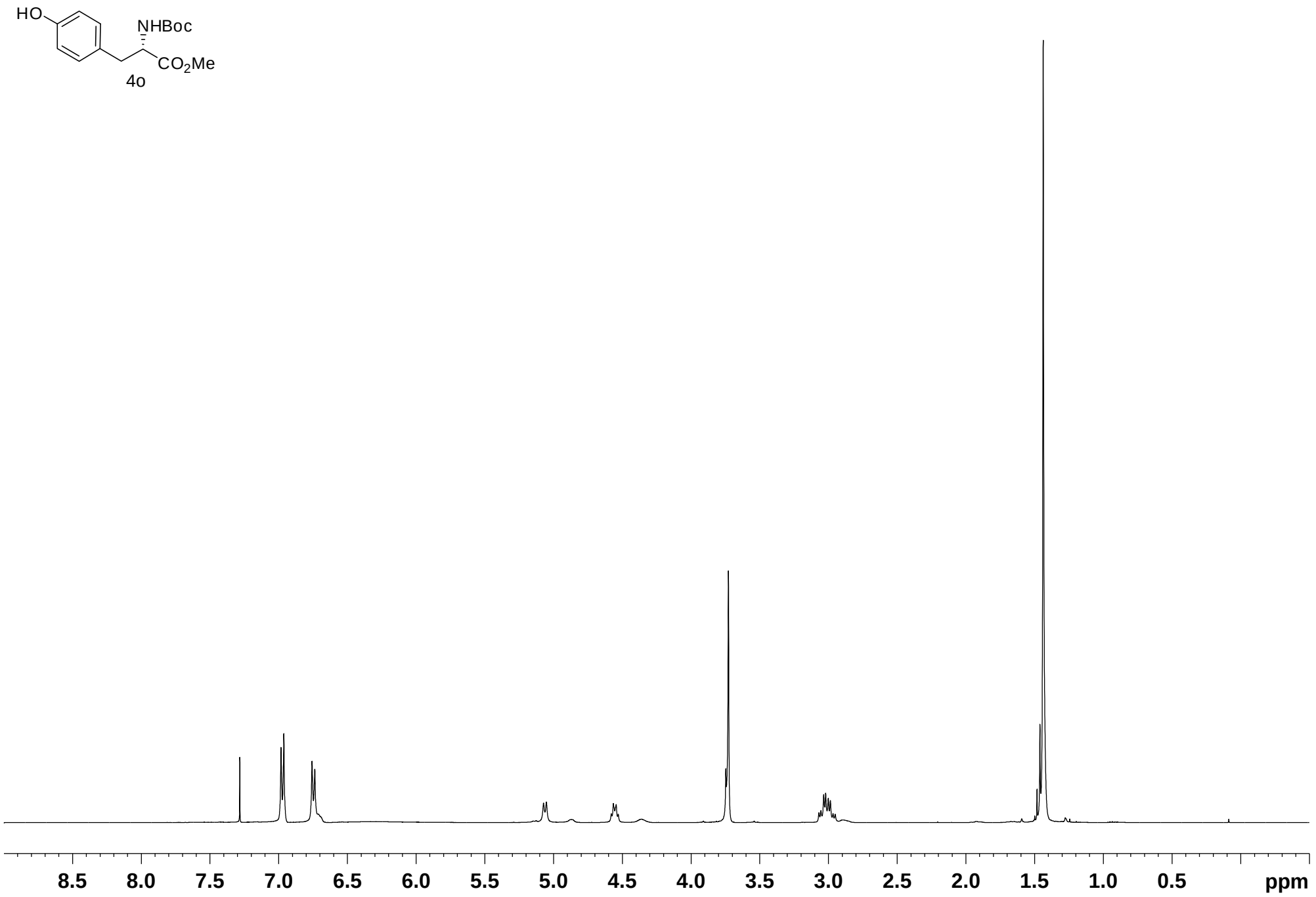
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CO2Me
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3.0
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1.5
1.0
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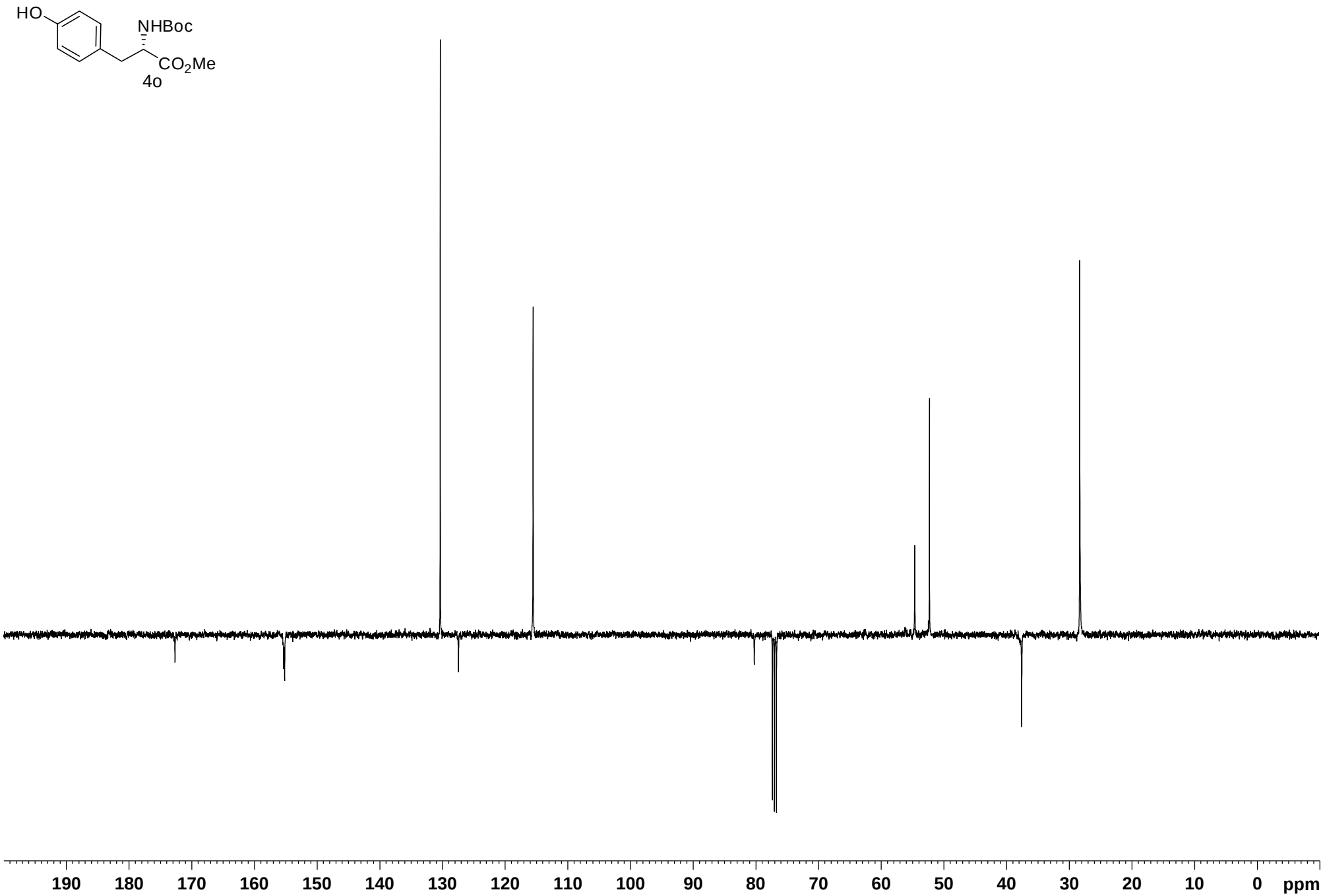
ppm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CO2Me
4o
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90
80
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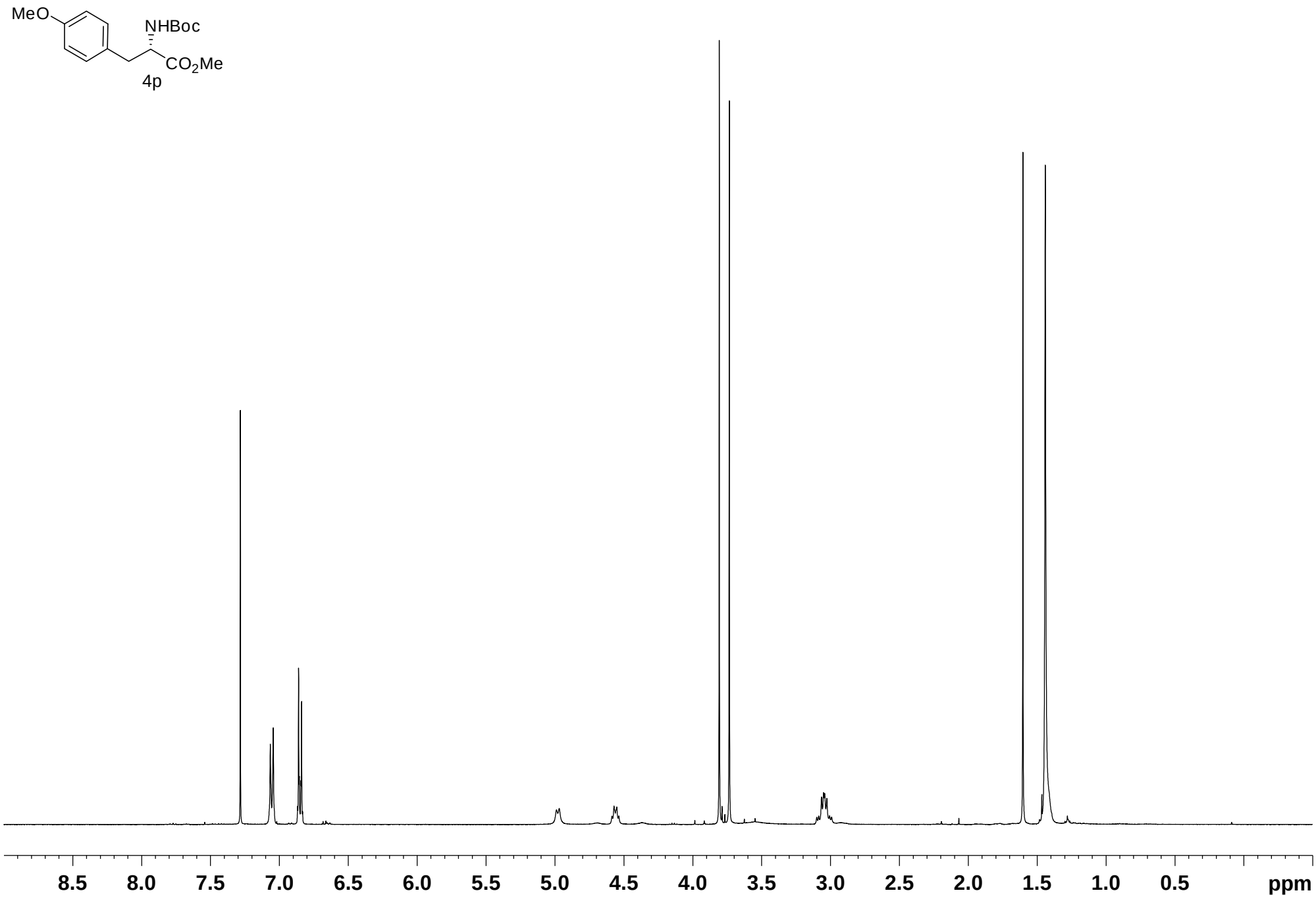
60
50
40
30
20
10
0
ppm


MeO
NHBoc
CO2Me
4p
8.5
8.0
7.5
7.0
6.5
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4.5
4.0
3.5
3.0
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2.0
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1.0
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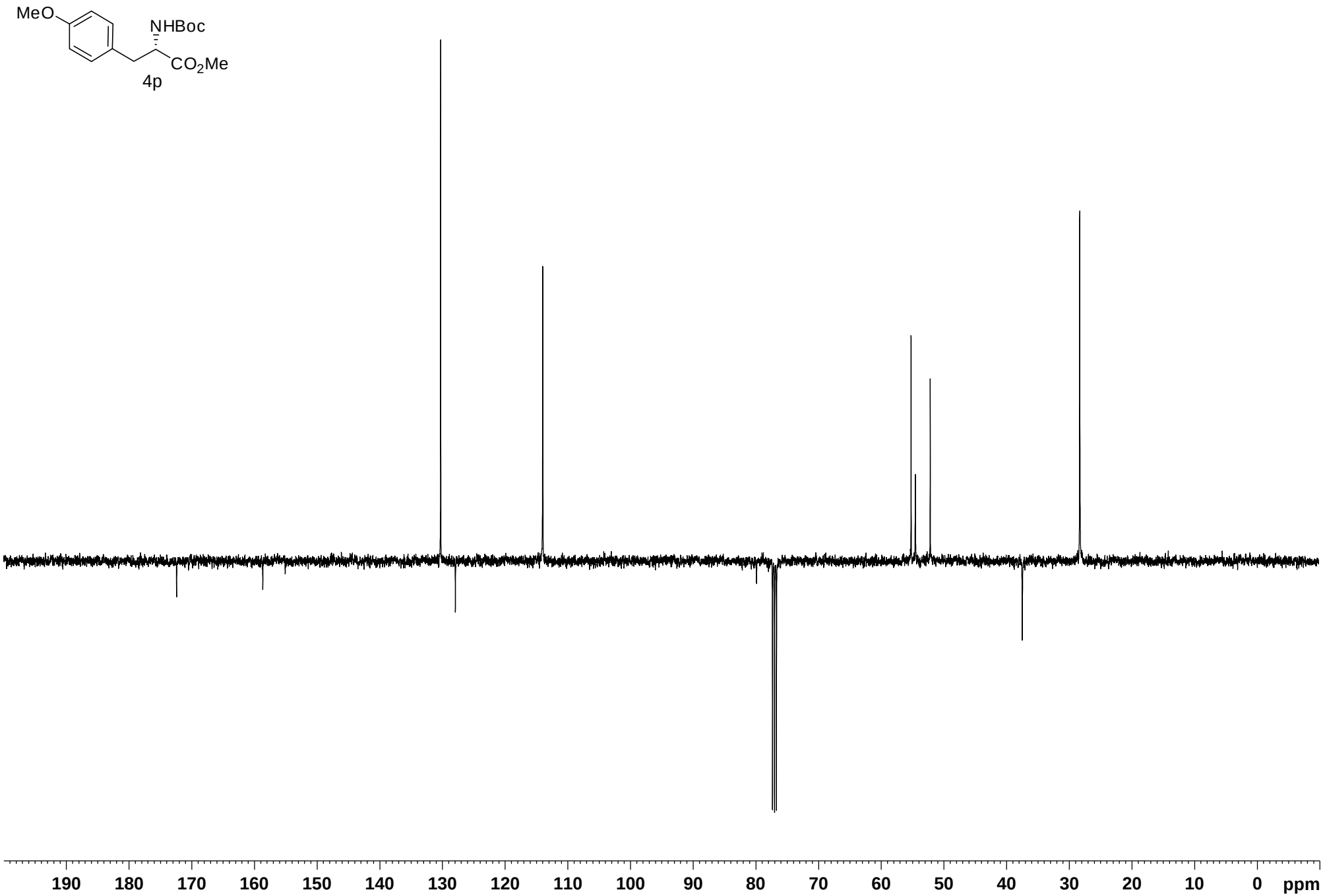
ppm


MeO
NHBoc
CO2Me
4p
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100
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30
20
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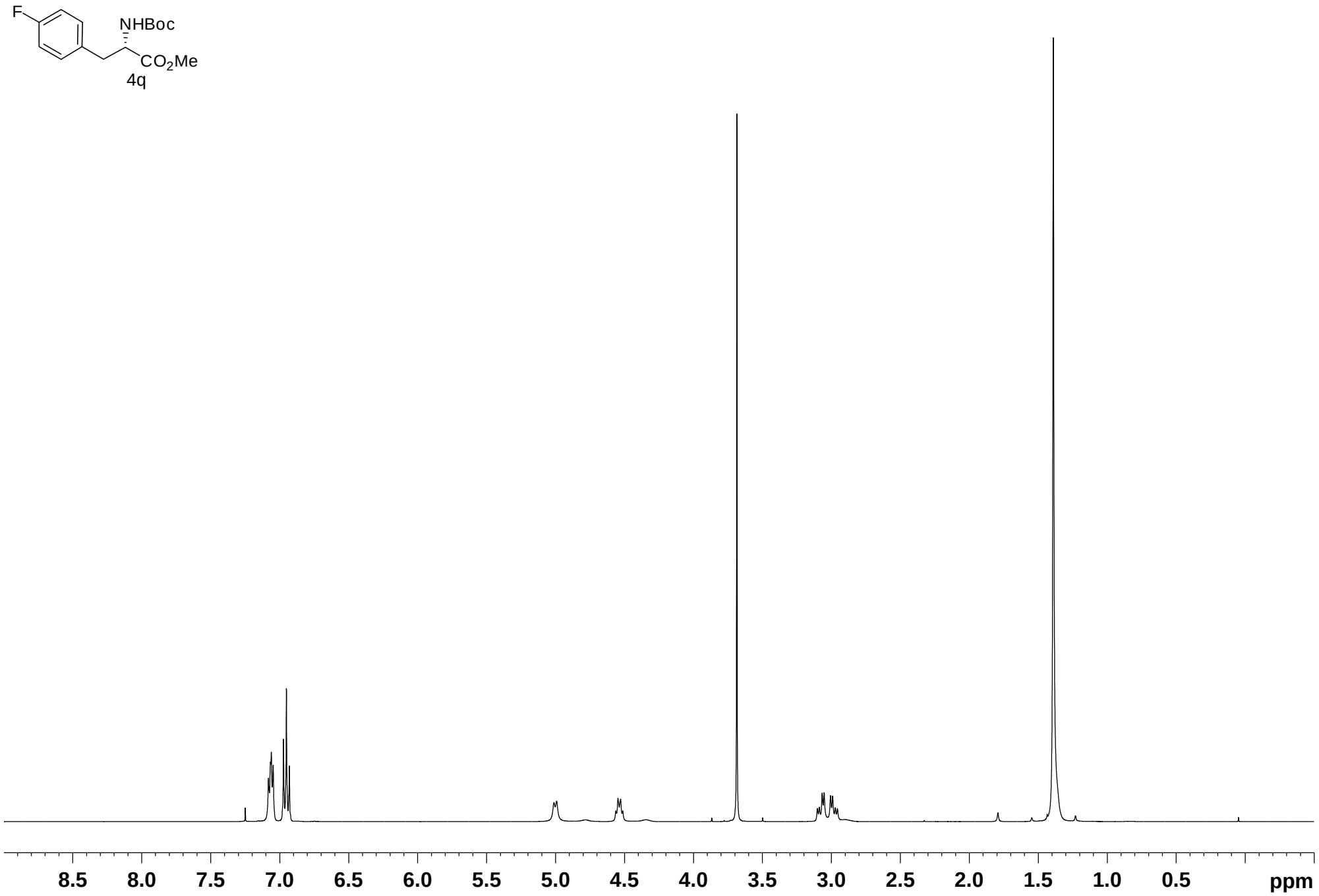
0
ppm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NHBoc
CO2Me
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6.5
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2.0
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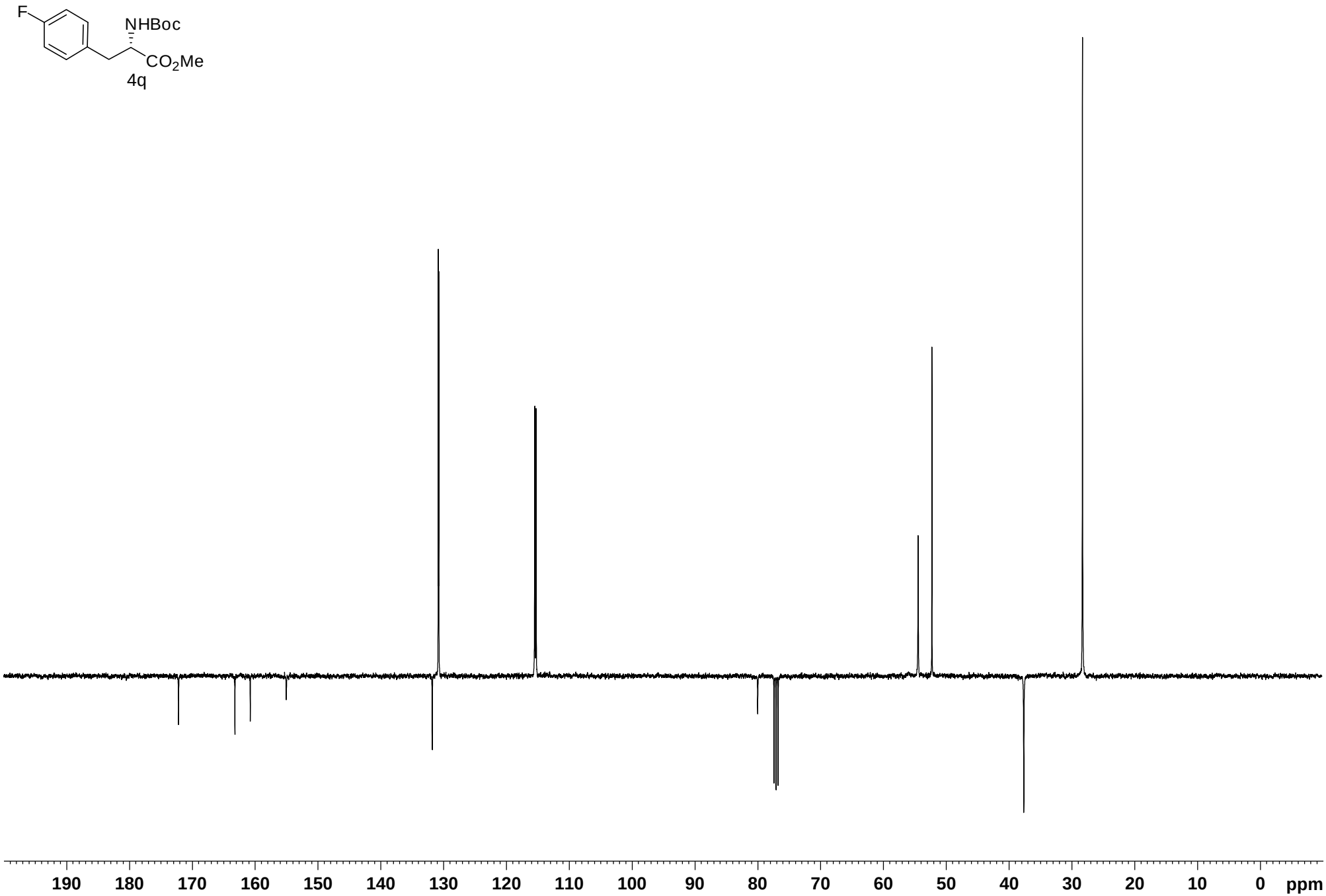
1.0
0.5
ppm


F
NHBoc
CO2Me
4q
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100
90
80
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60
50
40
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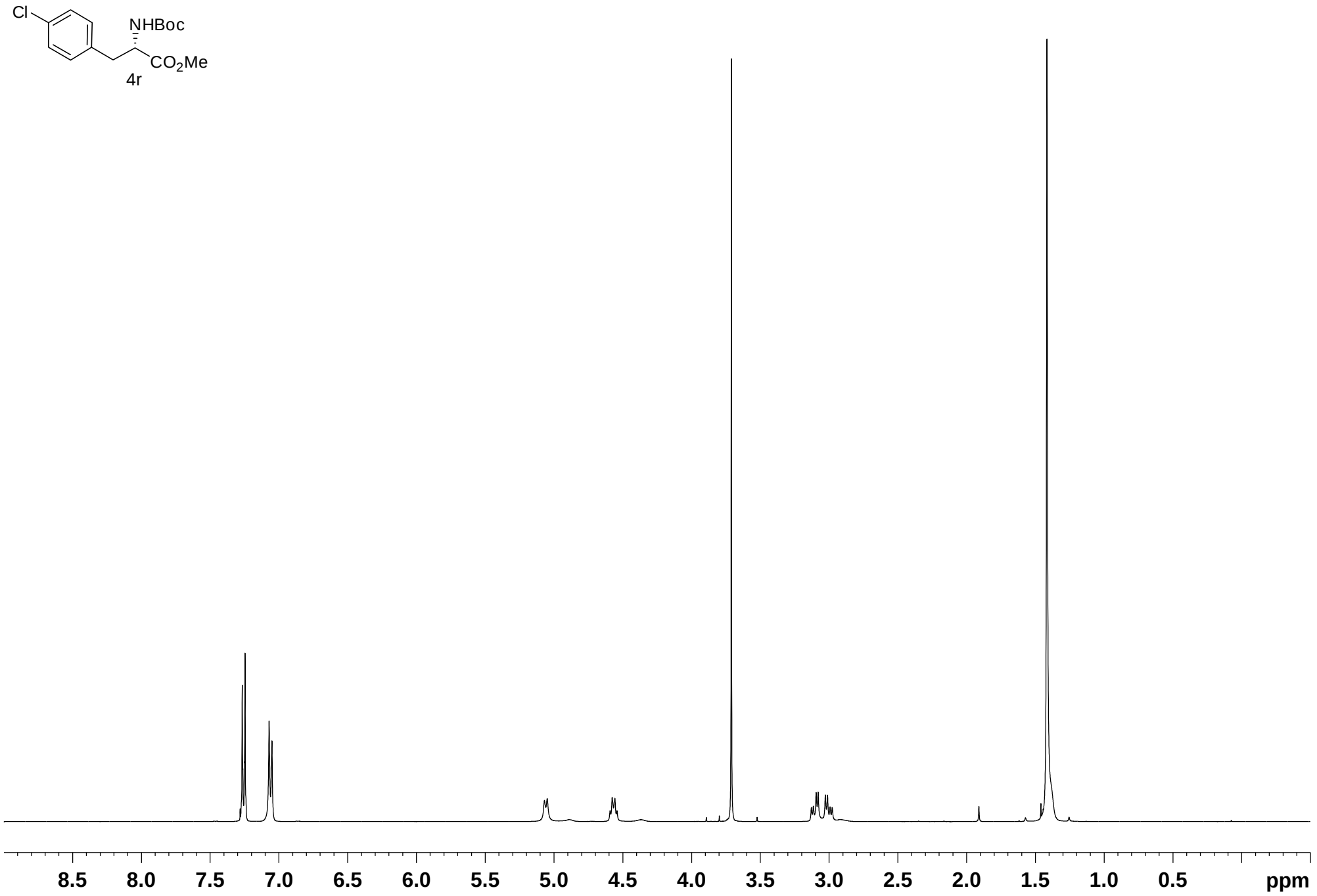
20
10
0
ppm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NHBoc
CO2Me
4r
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7.5
7.0
6.5
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4.0
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3.0
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2.0
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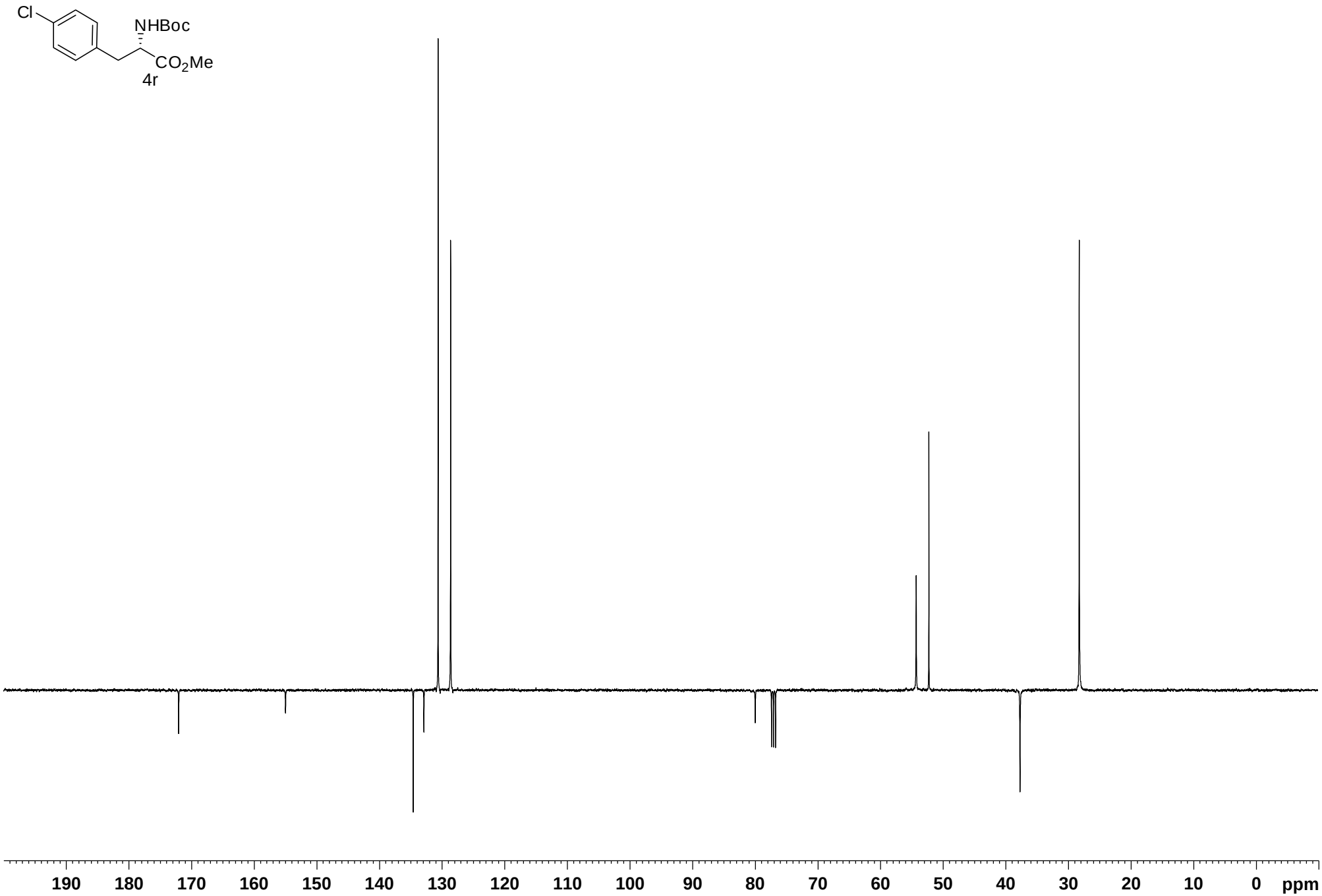
1.0
0.5
ppm


Cl
NHBoc
CO2Me
4r
190
180
170
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50
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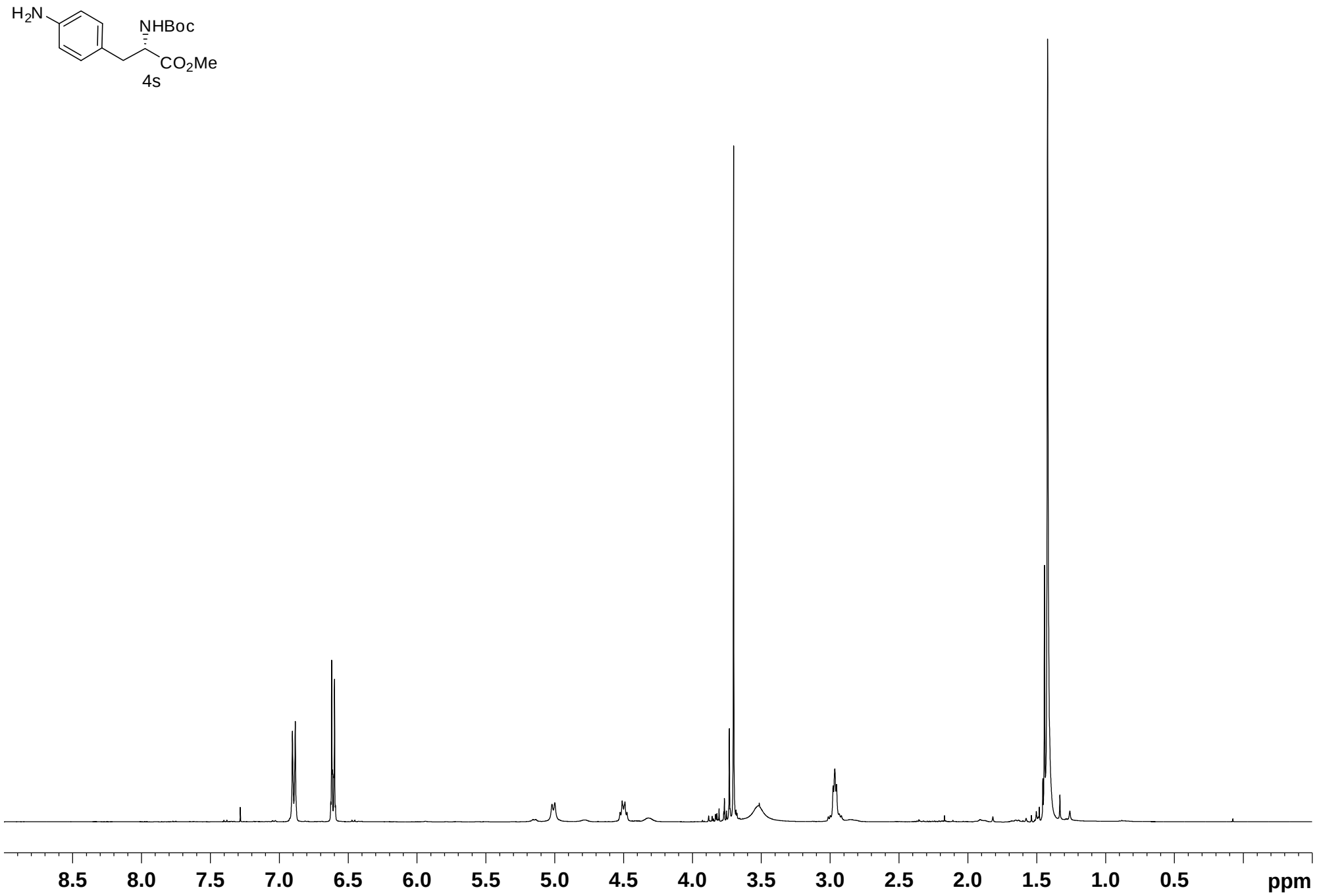
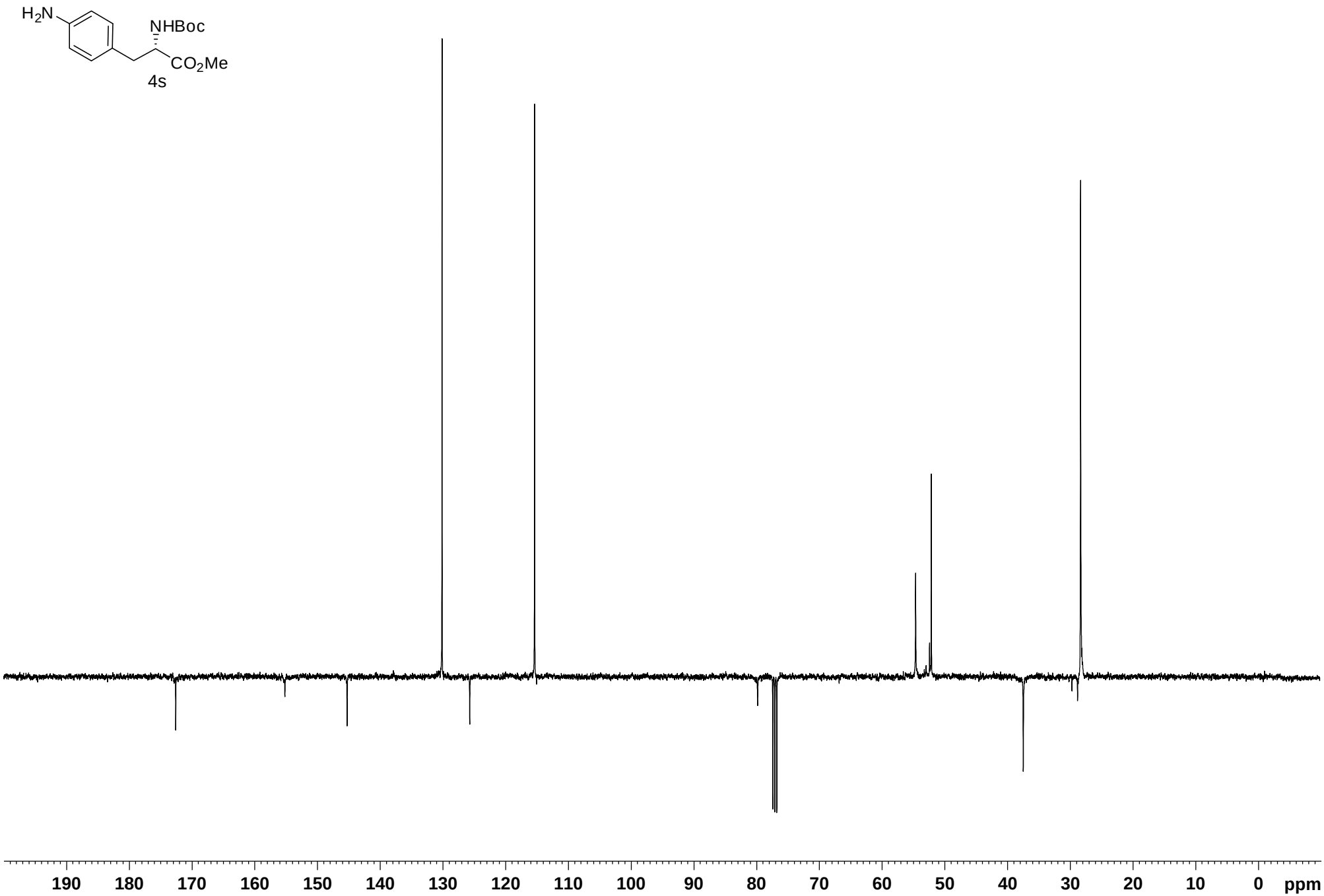
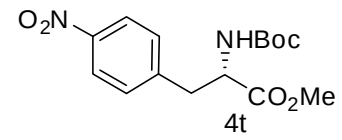
ppm


H2N
NHBoc
CO2Me
4s
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


H2N
NHBoc
CO2Me
4s
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


O2N
NHBoc
CO2Me

4t

8.5
8.0
7.5
7.0
6.5
6.0
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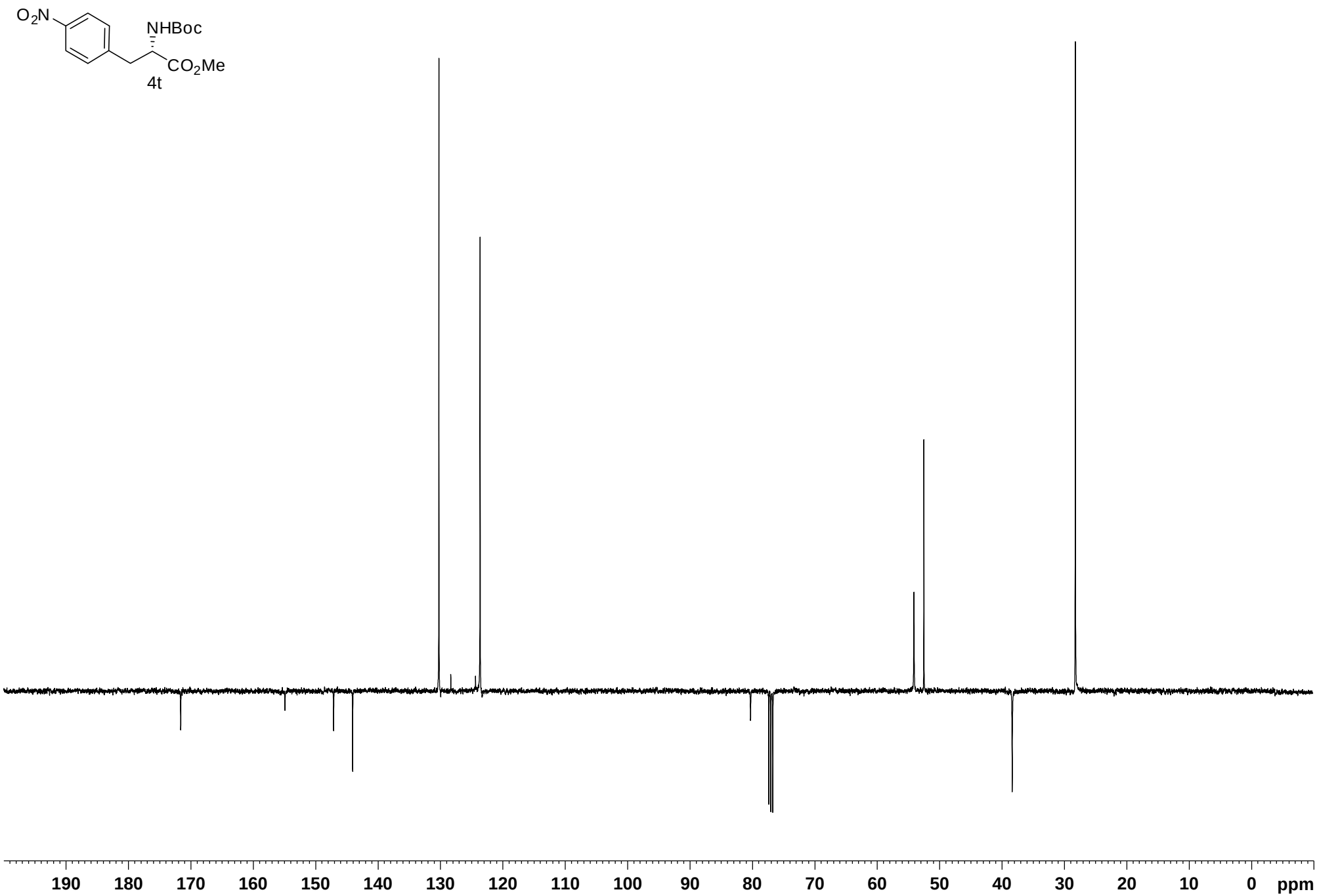
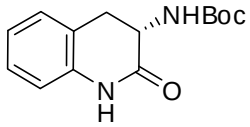
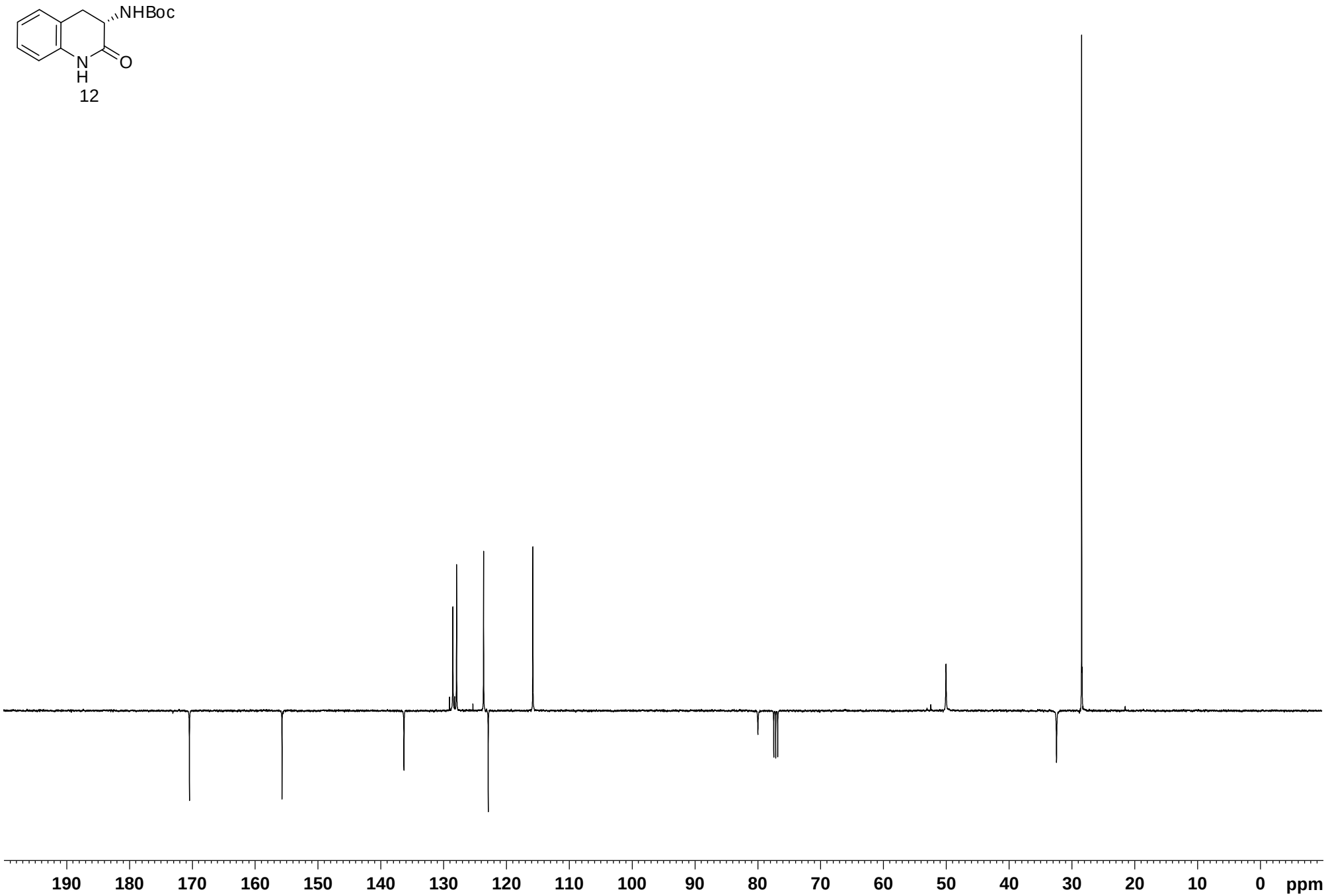
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


O2N
NHBoc
CO2Me
4t
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



12


NHBoc
N
H
O
12
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm