Copper-Mediated Cross-Coupling of Functionalized Arylmagnesium Reagents with Functionalized Alkyl and Benzylic Halides

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Supporting Information

Procedures:

The following starting materials were obtained from commercial sources: methyl 4-iodobenzoate (precursor to **1a**), ethyl 4-iodobenzoate (precursor to **1b**), ethyl 3-iodobenzoate (precursor to **1c**), and 1-chloro-4-iodobutane (**2b**).

The following starting materials were prepared according to literature procedures: *N*,*N*-dimethyl-2-iodoaniline[1] (precursor to **1f**), ethyl 4-iodobutanoate[2] (**2a**), and 4-iodobutyl pivaloate[3] (**2b**).

Ethyl 4-*N*,*N*-diallylamino-3-iodobenzoate (precursor to **1d**):

To a solution of ethyl-4-amino-3-iodobenzoate (2.91 g, 10 mmol, 1 eq) in DMF (20 mL) was added sodium carbonate (4.24 g, 40 mmol, 4 eq) and allyl bromide (7.2 mL, 80 mmol, 8 eg) and the reaction mixture was heated to 100 °C for 8 h. After cooling down to room temperature the reaction mixture was poured into water (50 mL), then extracted with ether (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (19:1 pentane/ether) to yield the product as a pale yellow oil (2.74 g, 74%).

R_f = 0.59 (19:1 pentane/ether)
IR (KBr): 3412 (w), 3078 (m), 2980 (m), 2932 (m), 2821 (m), 2571 (w), 1976 (w), 1913 (w), 1715 (s), 1643 (m), 1590 (s), 1483 (s), 1444 (m), 1367 (s), 1285 (s), 1252 (s), 1159 (m), 1112 (s), 1040 (m), 1020 (m), 992 (m), 923 (s), 770 (m), 724 (m) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, J =7.2 Hz, 3H), 3.71 (d, J = 5.7 Hz, 4H), 4.34 (q, J = 7.2 Hz, 2H), 5.11-5.21 (m, 4H), 5.73-5.86 (m, 2H),6.99 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = (.4 Hz, J = 2.1 Hz, 1H), 8.51 (d, J = 2.1 Hz, 1H)
^{13}C NMR ($CDCl_3$,75 MHz): δ 14.3, 55.4, 60.9, 97.2, 118.2, 122.8, 126.7, 129.8, 134.3, 141.6, 156.0, 165.0
HRMS (EI): $C_{15}H_{18}NO_2I$ required 371.0382 found 371.0369 (M^+)

Piperidino 4-iodobenzamide (precursor to **1e**):

[1] Bunnett, J.F.; Mitchel, E.; Galli, C.; *Tetrahedron* **1985**, *41*, 4119
[2] Thompson, C.M.; Frick, J.A. *J. Org. Chem.* **1989**, *54*, 890.
[3] Wu, Y.; Ahlberg, P. *Acta Chem. Scand.* **1995**, *49*, 364.

4-iodobenzoic acid (4.96 g, 20 mmol, 1 eq) and thionyl chloride (28.58 g, 240 mmol, 12 eq) were heated to reflux overnight. After the reaction mixture was cooled down to room temperature the excess of thionyl chloride was distilled off to give the pure acid chloride which was added directly into piperidine (8.52 g, 100 mmol, 5 eq) stirring at 0 °C. After 30 min of stirring at 0 °C the white precipitate was filtered and washed with water (3 x 20 mL), ether (3 x 20 mL) and pentane (3 x 20 mL). Finally the product was dried for 1 h *in vacuo* at 50 °C to give 5.47 g (17.4 mmol, 87% yield) as a white solid.

mp: 128-129 °C
IR: 3436 (w), 2938 (m), 2853 (m), 1621 (s), 1588 (m), 1442 (s), 1388 (m), 1288 (m), 1275 (m), 1108 (m), 1002 (m), 827 (m), 752 (m) cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz): δ 1.45-1.71 (m, 6H), 3.21-3.75 (m, 4H), 7.09-7.14 (m, 2H), 7.70-7.75 (m, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.4, 26.0, 26.0, 43.1, 48.5, 95.4, 128.5, 135.8, 137.5, 169.2
HRMS (EI): $C_{12}H_{14}NOI$: required 315.0120; found 315.0109 (M^+)

3-iodopropiophenone (**2e**):
Compound **2e** was prepared according to literature procedure[4].

mp: 64-65 °C
IR (KBr): 3438 (w), 1675 (s), 1594 (w), 1447 (m), 1413 (m), 1338 (m), 1230 (m), 1163 (m), 976 (w), 730 (m), 688 (m), 550 (m) cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz): δ 3.46 (t, J = 5.2 Hz, 2H), 3.62 (t, J = 5.2 Hz, 2H), 7.45-7.52 (m, 2H), 7.56-7.61 (m, 1H), 7.93-7.96 (m, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.0, 42.5, 128.0, 128.7, 133.5, 136.1, 197.5
HRMS (EI): C_9H_9OI: required 259.9698; found 259.9716 (M^+)

9-Iodononanonitrile (**2d**):

To a solution of 1,8-diiodooctane (15 g, 41 mmol, 1 eq.) in DMSO (16 mL) was added potassium cyanide (2.13 g, 3.28 mmol, 0.8 eq) and the reaction mixture heated to 50 ºC for 16 h. The reaction mixture was then poured into water (100 mL) and extracted with ether (3 × 100 mL). The combined extracts were dried over Na_2SO_4 and the solvents removed *in vacuo*. The resiude was purified by flash column chromatography (9:1 pentane/ether) to give 3.26 g of product as a pale yellow liquid (30% yield).

R_f = 0.33 (9:1 pentane/ether)
IR (film): 2930 (s), 2856 (m), 2246 (w), 1723 (w), 1656 (w), 1463 (w), 1426 (w), 1184 (w), 722 (w), 598 (w) cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz): d 1.33-1.49 (m, 8H), 1.59-1.70 (m, 2H), 1.76-1.86 (m, 2H), 2.33 (t, J=7.1 Hz, 2H), 3.18 (d, J=7.1 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 7.0, 17.1, 25.2, 28.1, 28.5 (2C), 30.2, 33.3, 119.7
HRMS (EI): $C_9H_{17}IN$ required 266.0406; found 266.0396 ($M^+ + H^+$)

General Procedure for cross-couplings using stochiometric CuCN·2LiCl (Method A):

[4] Sakuraba, S; Nakajima, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1457.

The aryl iodide (2.5 mmol, 1eq.) was dissolved in dry THF (2.5 mL) under argon. The solution was cooled to –25 ºC in a dry ice/*iso*-propanol bath and *iso*-propylmagnesium bromide (5.1 mL, 0.54 M in THF, 2.75 mmol, 1.1 eq) was added slowly over 5 min, keeping the temperature below –20 ºC. On completion of the addition, the reaction mixture was stirred at –20 ºC until exchange was complete (as indicated by TLC or GC), usually 30 min to 1 h. A solution of CuCN·2LiCl (2.75 mL, 1 M in THF, 2.75 mmol, 1.1 eq) was then added, again keeping the temperature below –20 ºC, and on completion of the addition the reaction mixture was warmed up to room temperature within 30 min. Then trimethyl phosphite (4.8 mmol, 1.9 eq) was added and the clear solution was stirred for an additional 5 min. The alkyl iodide was then added (2 mmol, 0.8 eq.) *via* syringe and the reaction mixture was stirred under argon at this temperature until all the alkyl iodide was consumed (as indicated by TLC or GC), usually 2-8 h. The reaction was then quenched by the addition of a solution of saturated NH_4Cl(aq) and poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organics washed with water (50 mL) and dried over $MgSO_4$. After removal of the solvents *in vacuo*, the residue was purified by flash column chromatography using the specified solvent system.

General Procedure for cross-couplings using catalytic CuCN·2LiCl (Method B):

The aryl iodide (2.5 mmol, 1eq.) was dissolved in dry THF (2.5 mL) under argon. The solution was cooled to –25 ºC in a dry ice/*iso*-propanol bath and *iso*-propylmagnesium bromide (2.1 mL, 1.3 M in THF, 2.73 mmol, 1.1 eq) was added slowly over 5 min, keeping the temperature below –20 ºC. On completion of the addition, the reaction mixture was stirred at –20 ºC until exchange was complete (as indicated by TLC or GC), usually 30 min. A solution of CuCN·2LiCl (0.5 mL, 1 M in THF, 0.5 mmo,, 0.2 eq) was then added, again keeping the temperature below –20 ºC, and on completion of the addition the reaction mixture was stirred for a further 15 min at –20 ºC. The alkyl iodide was then added (2 mmol, 0.8 eq.) *via* syringe and the reaction placed in a cryostatically controlled cooling bath at –5 ºC. The reaction mixture was stirred under argon at this temperature until all the alkyl iodide was consumed (as indicated by TLC or GC), usually 20-24 h. The reaction was then quenched by the addition of a 9:1 solution of saturated NH_4Cl(aq) and 25% NH_3(aq) and poured into water (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organics washed with water (40 mL) and dried over Na_2SO_4. After removal of the solvents *in vacuo*, the residue was purified by flash column chromatography using the specified solvent system.

General Procedure for cross-couplings with benzylic bromides using catalytic CuCN·2LiCl (Method C):

The aryl iodide (2.5 mmol, 1eq.) was dissolved in dry THF (2.5 mL) under argon. The solution was cooled to –25 ºC in a dry ice/*iso*-propanol bath and *iso*-propylmagnesium bromide (2.1 mL, 1.3 M in THF, 2.73 mmol, 1.1 eq) was added slowly over 5 min, keeping the temperature below –20 ºC. On completion of the addition, the reaction mixture was stirred at –20 ºC until exchange was complete (as indicated by TLC or GC), usually 30 min. A solution of CuCN·2LiCl (0.5 mL, 1 M in THF, 0.5 mmol, 0.2 eq) was then added, again keeping the temperature below –20 ºC, and on completion of the

addition the reaction mixture was stirred for a further 15 min at –20 ºC. The benzylic bromide was then added (2 mmol, 0.8 eq.) *via* syringe and the reaction placed in a cryostatically controlled cooling bath at –20 ºC. The reaction mixture was stirred under argon at this temperature until all the benzylic bromide was consumed (as indicated by TLC or GC), usually 2 h. The reaction was then quenched by the addition of a 9:1 solution of saturated NH_4Cl(aq) and 25% NH_3(aq) and poured into water (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organics washed with water (40 mL) and dried over Na_2SO_4. After removal of the solvents *in vacuo*, the residue was purified by flash column chromatography using the specified solvent system.

Methyl 4-(4-ethoxycarboynlpropyl)benzoate (**4a**)

Compound **4a** was isolated (Method A, 75% yield; Method B, 60% yield) as a colourless oil after flash column chromatography using CH_2Cl_2 as eluent.

R_f = 0.43 (CH_2Cl_2)
IR (film): 2982 (m), 2953 (m), 1724 (s), 1611 (m), 1436 (m), 1281 (s), 1180 (m), 1112 (m), 1021 (m), 857 (w), 834 (w), 764 (w), 705 (w) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.25 (t, J=7.1 Hz, 3H), 1.91-2.01 (m, 2H), 2.31 (t, J=7.5 Hz, 2H), 2.70 (t, J=7.7 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 7.95 (d, J=8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 14.2, 26.1, 33.5, 35.1, 52.0, 60.3, 128.0, 128.5, 129.7, 146.9, 167.1, 173.2
HRMS (EI): $C_{14}H_{18}O_4$ required 250.1205; found 250.1187 (M^+)

Methyl 4-(4-chlorobutyl)benzoate (**4b**)

Compound **4b** was isolated (Method A, 81% yield; Method B, 63% yield) as a colourless oil after flash column chromatography using 2:1 pentane/CH_2Cl_2 as eluent.

R_f = 0.30 (2:1 pentane/CH_2Cl_2)
IR (film): 2996 (w), 2950 (m), 2863 (w), 1721 (s), 1610 (m), 1435 (m), 1310 (m), 1280 (s), 1179 (m), 1112 (s), 1020 (m), 968 (w), 857 (w), 764 (m), 704 (w), 653 (w) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.77-1.82 (m, 4H), 2.68-2.72 (m, 2H), 3.52-3.56 (m, 2H), 3.90 (s, 3H), 7.24 (d, J=8.8 Hz, 2H), 7.96 (d, J=8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 28.2, 32.0, 35.1, 44.7, 52.0, 128.0, 128.4, 129.7, 147.3, 167.1
HRMS (EI): $C_{12}H_{15}ClO_2$ required 226.0761; found 226.0777 (M^+; ^{35}Cl)

Methyl 4-(4-pivaloyloxybutyl)benzoate (**4c**):

Compound **4c** was isolated (Method A, 89% yield; Method B, 57% yield) as a pale yellow oil after flash column chromatography using 2:1 CH_2Cl_2/pentane as eluent.

R_f = 0.51 (CH_2Cl_2)
IR (film): 2956 (s), 2871 (m), 1727 (s), 1611 (m), 1481 (m), 1461 (m), 1436 (m), 1309 (m), 1281 (s), 1178 (s), 1157 (s), 1109 (s), 1020 (m), 763 (m), 705 (w) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz): d 1.12 (s, 9H), 1.64-1.73 (m, 4H), 2.70 (t, J=7.3 Hz, 2H), 3.90 (s, 3H), 4.07 (t, J=6.2 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 7.95 (d, J=8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 27.2, 27.4, 28.2, 35.4, 38.7, 51.9, 63.9, 127.9, 128.4, 129.7, 147.6, 167.1, 178.6
HRMS (EI): $C_{17}H_{24}O_4$ required 292.1675; found 292.1670 (M^+)

Methyl 4-(8-cyanooctyl)benzoate (**4d**):

Compound **4d** was isolated (Method A, 81% yield; Method B, 55% yield) as a pale yellow solid after flash column chromatography using 2:1 CH_2Cl_2/pentane as eluent.

mp = 37-38 ºC
R_f = 0.49 (CH_2Cl_2)
IR (KBr): 3417 (w), 2929 (m), 2855 (m), 2246 (w), 1718 (s), 1610 (m), 1467 (m), 1425 (m), 1277 (s), 1186 (m), 1177 (m), 1105 (s), 1018 (m), 760 (m) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.22 –1.46(m, 8H), 1.55 – 1.66 (m, 4H), 2.29 (t, J = 7.2 Hz, 2H), 2.63 (t, 7.8 Hz, 2H), 3.87 (s, 3H), 7.21 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 16.9, 25.2, 28.4, 28.5, 28.9, 29.0, 30.8, 35.8, 51.8, 119.7, 127.5, 128.3, 129.5, 148.1, 167.0
HRMS (EI): $C_{17}H_{23}NO_2$ required 273.1729; found 273.1711 (M^+)

Methyl 4-(3-oxo-3-phenylpropyl)benzoate (4e):

Compound **4e** was isolated in 56% yield according to Method A as a white solid after flash column chromatography using 9:1 pentane/ethylacetate as eluent.

mp: 88-89 °C
R_f = 0.36 (9:1 pentane/ethylacetate)
IR (KBr): 3432 (m), 2962 (m), 1715 (s), 1684 (s), 1608 (m), 1449 (m), 1436 (m), 1283 (s), 1262 (s), 1204 (m), 1179 (m), 1112 (s), 1101 (s), 1019 (s), 802 (s), 770 (m), 744 (m) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 3.02 (t, J = 7.2 Hz, 2H), 3.21 (t, J = 7.2 Hz, 2H), 3.79 (s, 3H), 7.20-7.24 (m, 2H), 7.31-7.42 (m, 2H), 7.42-7.46 (m, 1H), 7.82- 7.89 (m, 4H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 29.9, 39.6, 51.9, 127.9, 128.0, 128.4, 128.5, 129.7, 133.1, 136.6, 146.7, 166.9, 198.5
HRMS (EI): $C_{17}H_{16}O_3$ required 268.1099; found 268.1102 (M^+)

Ethyl 3-(4-ethoxycarbonylpropyl)benzoate (4f):

Compound **4f** was isolated in 71% yield according to Method A as a colourless oil after flash column chromatography using 9:1 pentane/ethylacetate as eluent.

R_f = 0.53 (9:1 pentane/ethylacetate)
IR (film): 2982 (m), 2938 (m), 2872 (w), 1732 (s), 1607 (m), 1588 (m), 1478 (m), 14664 (m), 1445 (m), 1368 (m), 1280 (s), 1198 (s), 1147 (s), 1107 (s), 1085 (m), 1025 (m), 752 (m), 697 (m) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz): d 1.17 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.89 (quin, J = 7.5 Hz, 2H), 2.23 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 4.04 (q, J = 7.2 Hz; 2H), 4.29 (q, J = 7.2 Hz, 2H), 7.24-7.29 (m, 2H), 7.76-7.82 (m, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 14.1, 14.2, 26.3, 33.4, 34.8, 60.2, 60.8, 127.2, 128.3, 129.4, 130.5, 132.9, 141.6, 166.6, 173.2
HRMS (EI): $C_{15}H_{20}O_4$ required 264.1362; found 264.1348 (M^+)

Ethyl 3-(4-chlorobutyl)-4-(*N*,*N*-diallylamino)benzoate (4g):

Compound **4g** was isolated in 69% yield according to Method A as a colourless oil after flash column chromatography using 19:1 pentane/ether as eluent.

R_f = 0.44 (19:1 pentane/ether)
IR (film): 3425 (m), 3079 (m), 2980 (m), 2935 (m), 2869 (m), 1714 (m), 1643 (m), 1606 (s), 1580 (m), 1524 (m), 1497 (m), 1446 (m), 1418 (m), 1367 (m), 1291 (s), 1264 (s), 1244 (s), 1184 (s), 1115 (s), 1026 (s), 992 (m), 922 (s), 772 (m), 744 (m), 652 (m) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.37 (t, J = 7.2 Hz, 3H), 1.75-1.85 (m, 4H), 2.67-2.77 (m, 2H), 4.34 (q, 7.2 Hz, 2H), 5.10-5.22 (m, 4H), 5.69-5.84 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.81 (dd, J = 8.4 Hz, J = 1.8 Hz, 2H), 7.89 (d, J = 1.8 Hz, 1H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 14.4, 27.5, 30.1, 32.4, 44.8, 56.0, 60.5, 117.7, 121.9, 125.2, 127.7, 131.2, 134.5, 137.1, 154.2, 166.6
HRMS (EI): $C_{19}H_{26}NO_2Cl$ required 335.1652; found 335.1658 (M^+; ^{35}Cl)

Ethyl 4-*N*,*N*-diallylamino-3-(4-ethoxycarbonylpropyl)benzoate (4h):

Compound **4h** was isolated in 65% yield according to Method A as a colourless oil after flash column chromatography using 9:1 pentane/ether as eluent.

R_f = 0.34 (9:1 pentane/ether)
IR (film): 3396 (m), 3080 (w), 2981 (m), 2938 (m), 2874 (m), 1714 (s), 1644 (m), 1607 (s), 1526 (m), 1368 (m), 1280 (s), 1184 (s), 1114 (s), 1024 (m), 922 (m), 772 (m), 746 (w) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.24 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.98 (quin, 7.5 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 2.73 (t, J = 7.5 Hz, 2H), 3.58 (d, J = 5.7 Hz, 4H), 4.11 (q, J = 7.2, 2H), 4.32 (q, J = 7.2 Hz, 2H), 5.08-5.19 (m, 4H), 5.67-5.82 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 7.79 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H)
^{13}C NMR ($CDCl_3$, 75MHz): d 14.1, 14.3, 25.4, 30.3, 34.0, 55.9, 60.1, 60.5, 117.5, 121.8, 125.1, 127.7, 131.2, 134.4, 136.7, 154.1, 166.5, 173.3
HRMS (EI): $C_{21}H_{29}NO_4$ required 359.2097,; found 359.2085 (M^+)

Piperidino 4-(4-chlorobutyl)benzamide (4i):

Compound **4i** was isolated in 69% yield according to Method A as a colourless oil after flash column chromatography using 1:1 pentane/ethylacetate as eluent.

R_f = 0.47 (1:1 pentane/ethylacetate)

IR (film): 3481 (w), 3243 (w), 2998 (m), 2937 (s), 2856 (s), 1631 (s), 1578 (m), 1512 (m), 1494 (m), 1434 (s), 1370 (m), 1351 (m), 1275 (s), 1238 (m), 1182 (m), 1109 (m), 1026 (m), 1003 (m), 853 (m), 788 (m), 760 (m), 709 (m), 636 (w), 532 (w) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.32-1.78 (m, 10H), 2.50- 2.63 (m, 2H), 3.16-3.74 (m, 6H), 7.09-7.15 (m, 2H), 7.21-7.26 (m, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 24.5, 25.6, 26.3, 28.3, 31.8, 34.8, 43.0, 44.7, 48.6, 126.9, 128.2, 134.0, 143.2, 170.2
HRMS (EI): $C_{16}H_{22}NOCl$ required 279.1390; found 279.1394 (M^+; ^{35}Cl)

Piperidino 4-(4-ethoxycarbonylpropyl)benzamide (4j):

Compound **4j** was isolated in 63% yield according to Method A as a colourless oil after flash column chromatography using 1:1 pentane/ethylacetate as eluent.

R_f = 0.39 (1:1 pentane/ethylacetate)
IR (film): 3474 (w), 2937 (m), 2856 (m), 1731 (m), 1631 (s), 1433 (s), 1372 (w), 1276 (m), 1181 (m), 1109 (w), 1026 (m), 1004 (m)
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.18 (t, J = 7.2 Hz, 3H), 1.36-1.68 (m, 6H), 1.88 (quin, J = 7.5 Hz, 2H), 2.24 (t, J =7.2 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 3.18-3.73 (m, 4H), 4.05 (q, J = 7.2 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 14.1, 24.5, 25.6, 26.2, 26.2, 33.4, 34.8, 43.1, 48.7, 60.2, 126.9, 128.3, 134.0, 142.8, 170.2, 173.2
HRMS (EI): $C_{18}H_{25}NO_3$ required 303.1834; found 303.1826

***N*,*N*-Dimethylamino-2-(4-ethoxycarbonylpropyl)benzene (4k)**:

Compound **4k** was isolated in 73% yield according to Method A as a colourless oil after flash column chromatography using 4:1 pentane/ether as eluent.

R_f = 0.55 (4:1 pentane/ether)
IR (film): 3447 (w), 3060 (w), 2979 (s), 2938 (s), 2860 (m), 2825 (m), 2783 (m), 1732 (s), 1598 (m), 1578 (w), 1494 (s), 1453 (s), 1374 (m), 1304 (m), 1247 (m), 1189 (s), 1149 (s), 1099 (m), 1048 (m), 947 (m), 767 (m), 750 (m)
^{1}H NMR ($CDCl_3$, 300 MHz): d 1.16 (t, J = 7.2 Hz, 3H), 1.89 (quin, J = 7.5 Hz, 2H), 2.26 (t, J = 7.5 Hz, 2H), 2.57 (s, 6H), 2.65 (t, J = 7.5 Hz, 2H), 4.03 (q, J = 7.2 Hz, 2H), 6.88-7.13 (m, 4H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 14.2, 25.7, 29.9, 34.0, 45.1, 60.0, 119.5, 123.4, 126.6, 129.6, 136.3, 152.8, 173.6
HRMS (EI): $C_{14}H_{21}NO_2$ required 235.1572; found 235.1568

Methyl 4-benzylbenzoate (**6a**):

Compound **6a** was isolated in 72% yield according to Method C as a colourless oil after flash column chromatography using 2:1 pentane/CH_2Cl_2 as eluant.

R_f = 0.36 (2:1 pentane/CH_2Cl_2)

IR (film): 3321 (m), 3269 (w), 3028 (m), 2951 (m), 1722 (s), 1612 (m), 1496 (m), 1454 (m), 1435 (m), 1415 (m), 1280 (s), 1179 (m), 1109 (s), 755 (m), 743 (m), 706 (m), 585 (w), 562 (w) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 3.90 (s, 3H), 4.03 (s, 2H), 7.17-7.33 (m, 7H), 7.97 (d, J=8.0 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 41.9 (CH), 52.0 (CH3), 126.3 (CH), 128.1 (C), 128.6 (CH), 128.9 (2CH), 129.8 (CH), 140.1 (C), 146.5 (C), 167.0 (C)

Methyl 4-(2-trifluoromethylbenzyl)benzoate (**6b**):

Compound **6b** was isolated in 71% yield according to Method C as a colourless oil after flash column chromatography using 2:1 pentane/CH_2Cl_2 as eluant.

R_f = 0.38 (2:1 pentane/CH_2Cl_2)
IR (film): 3006 (w), 2954 (w), 2845 (w), 1723 (s), 1611 (m), 1450 (m), 1436 (m), 1333 (s), 1283 (s), 1165 (s), 1124 (s), 1075 (s), 788 (m), 744 (m), 702 (m), 660 (w) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 3.82 (s, 3H), 4.00 (s, 2H), 7.16 (d, J=8.4 Hz, 2H), 7.25-7.42 (m, 4H), 7.90 (d, J=8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 41.6, 52.0, 123.3 (q, $^{3}J_{C-F}$=3.7 Hz), 124.1 (q, $^{1}J_{C-F}$=272.3 Hz), 125.6 (q, $^{3}J_{C-F}$=3.7 Hz), 128.5, 128.9, 129.0, 130.0, 130.9 (q, $^{2}J_{C-F}$=130.9 Hz), 132.3, 141.0, 145.2, 166.9
HRMS (EI): $C_{16}H_{13}F_3O_2$ required 294.0868; found 294.0871 (M^+)

Methyl 4-(4-bromobenzyl)benzoate (**6c**):

Compound **6c** was isolated in 61% yield according to Method C as a white crystalline solid after flash column chromatography using 2:1 pentane/CH_2Cl_2 as eluant.

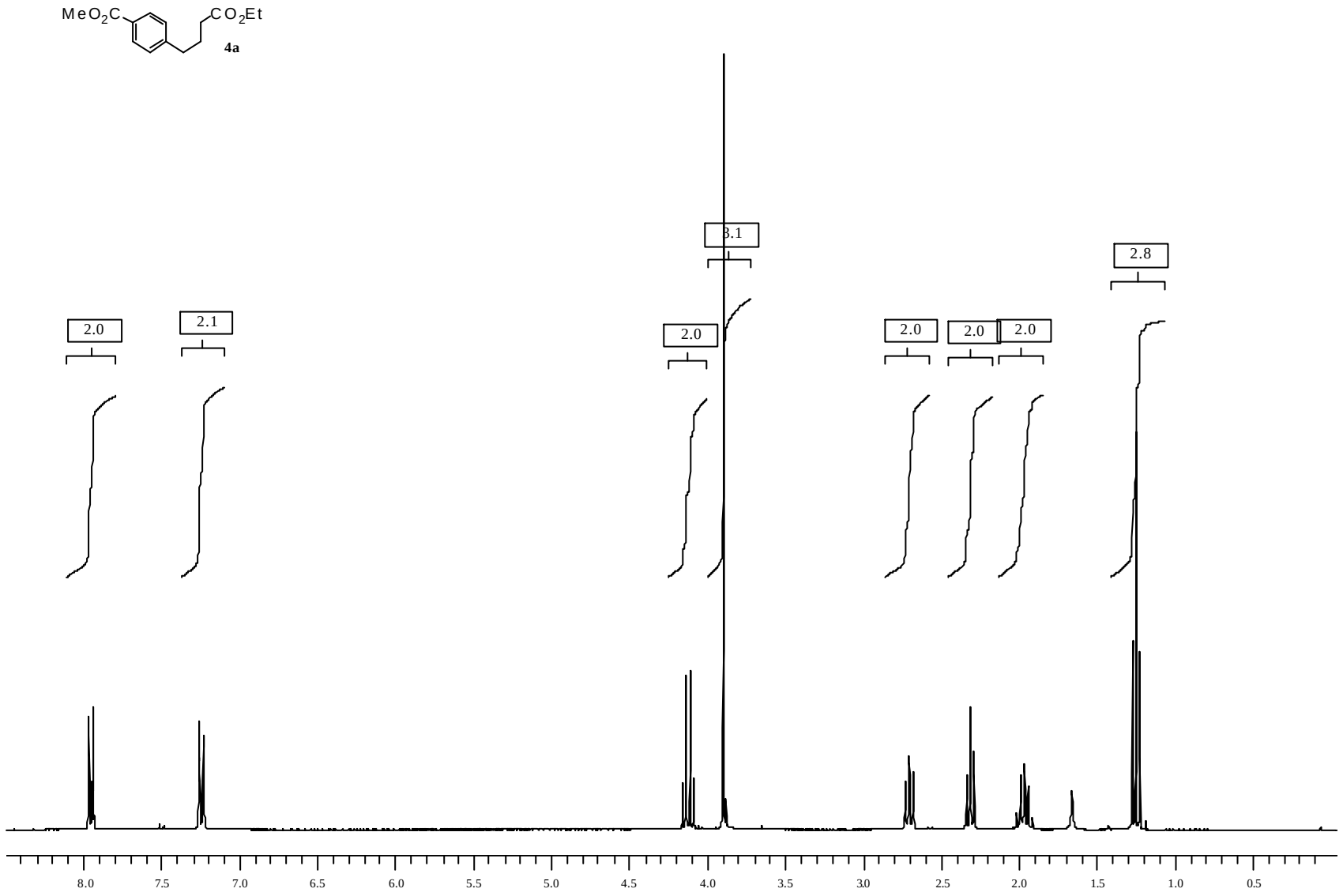
mp = 60-61 °C
R_f = 0.38 (2:1 pentane/CH_2Cl_2)
IR (KBr disc): 2948 (w), 1716 (s), 1611 (m), 1488 (m), 1430 (m), 1284 (s), 1183 (m), 1110 (m), 1070 (m), 1013 (m), 787 (m), 758 (m), 719 (m), 696 (w), 506 (m) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 3.90 (s, 3H), 3.97 (s, 2H), 7.04 (d, J=8.4 Hz, 2H), 7.22 (d, J=8.4 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H), 7.96 (d, J=8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 41.2, 52.0, 120.3, 128.3, 128.8, 129.9, 130.6, 131.6, 139.0, 145.7, 166.9
Microanalysis: $C_{15}H_{13}BrO_2$ required C, 59.04; H, 4.29; Br, 26.18; found C, 59.18; H, 4.28; Br, 26.20%
HRMS (EI): $C_{15}H_{13}BrO_2$ required 304.0099; found 304.0072 (M^+ ; ^{79}Br)

Methyl 4-(2,4-difluorobenzyl)benzoate (**6d**):

Compound **6d** was isolated in 67% yield according to Method C as a white crystalline solid after flash column chromatography using 2:1 pentane/CH_2Cl_2 as eluant.

R_f = 0.40 (2:1 pentane/CH_2Cl_2)

IR (film): 3078 (w), 2954 (w), 1723 (s), 1612 (m), 1505 (s), 1436 (m), 1280 (s), 1180 (m), 1138 (m), 1110 (m), 969 (m), 851 (m), 751 (m), 712 (w), 696 (w), 534 (w) cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz): d 3.90 (s, 3H), 4.00 (s, 2H), 6.77-6.85 (m, 2H), 7.05-7.13 (m, 1H), 7.25 (d, J=8.4 Hz, 2H), 7.96 (d, J=8.4 Hz, 2H)
^{13}C NMR ($CDCl_3$, 75 MHz): d 33.9 (d, $^{3}J_{C-F}$=2.3 Hz), 51.6, 103.4 (app t, $^{2}J_{C-F}$=25.8 Hz), 110.8 (dd, $^{2}J_{C-F}$=21.1 Hz, $^{4}J_{C-F}$=3.5 Hz), 122.6 (dd, $^{2}J_{C-F}$=16.4 Hz, $^{4}J_{C-F}$=3.5 Hz), 128.0, 128.2, 129.5, 131.0 (dd, $^{3}J_{C-F}$=9.4 Hz, $^{3}J_{C-F}$=6.5 Hz), 144.5, 160.4 (dd, $^{1}J_{C-F}$=248.2 Hz, $^{3}J_{C-F}$=11.7 Hz), 161.4 (dd, $^{1}J_{C-F}$=247.6 Hz, $^{3}J_{C-F}$=11.7 Hz), 166.5
HRMS (EI): $C_{15}H_{12}F_2O_2$ required 262.0805; found 262.0811 (M^+)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2.0
3.1
2.0
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2.0
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8.0
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6.5
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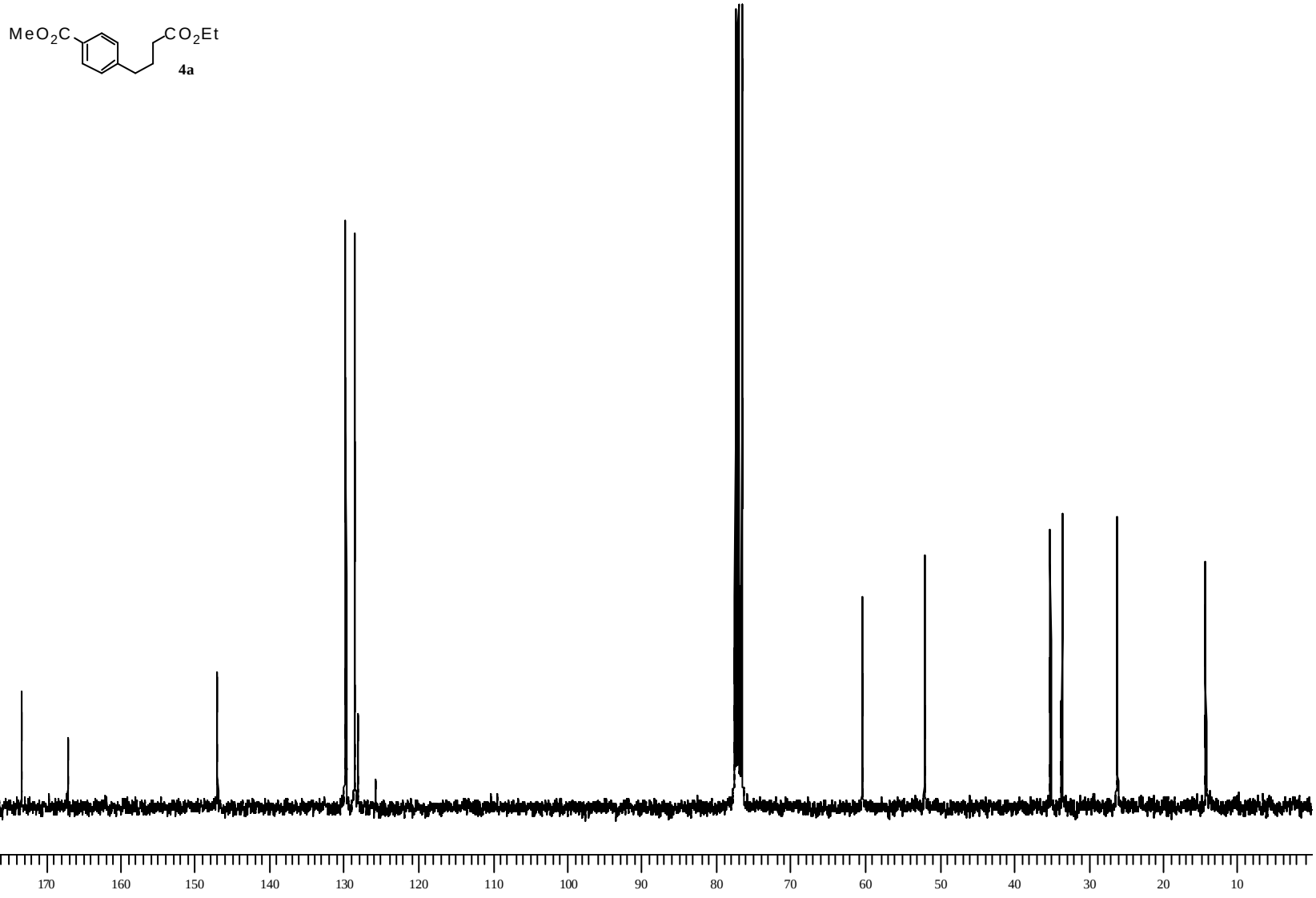
0.5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CO2Et
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20
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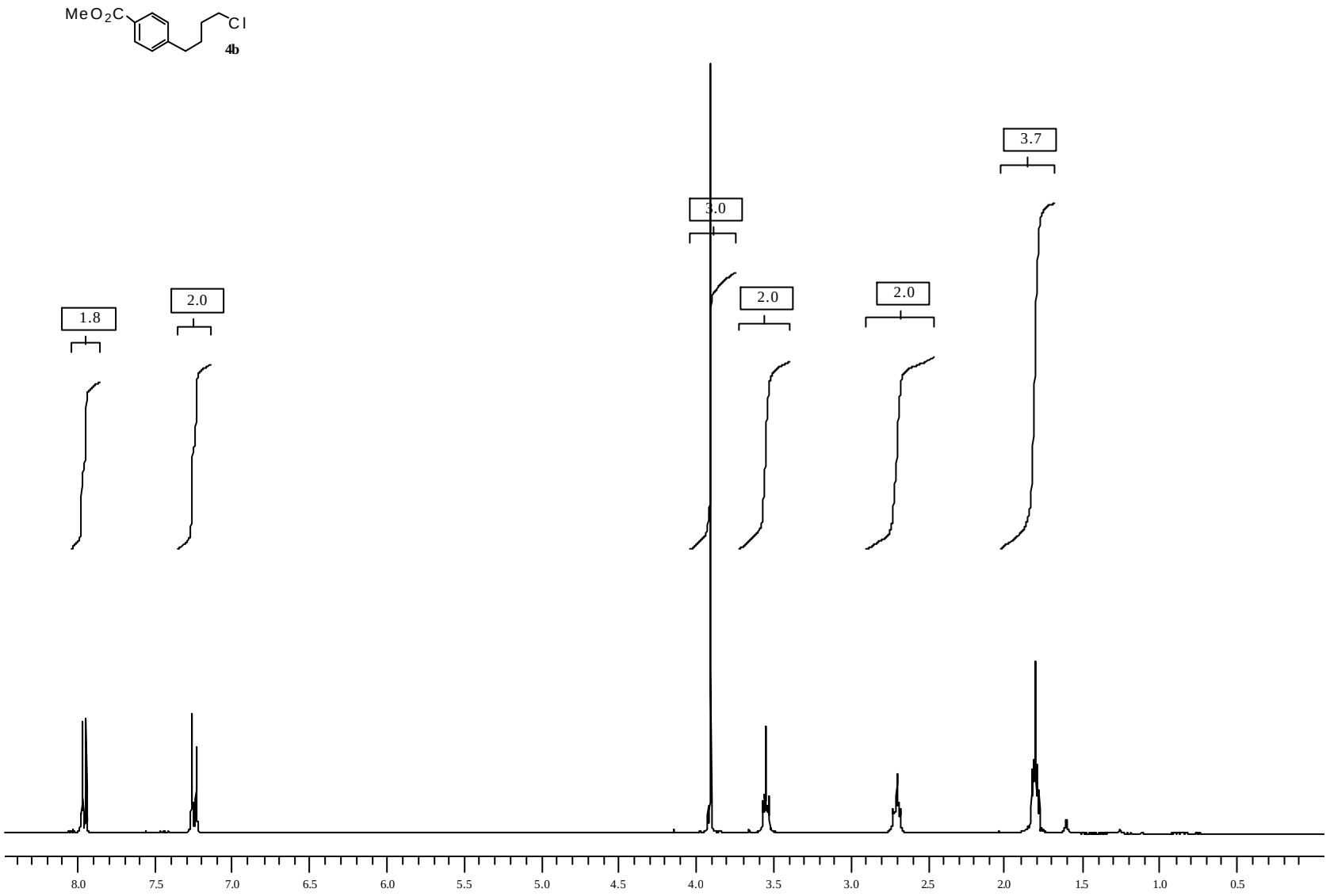
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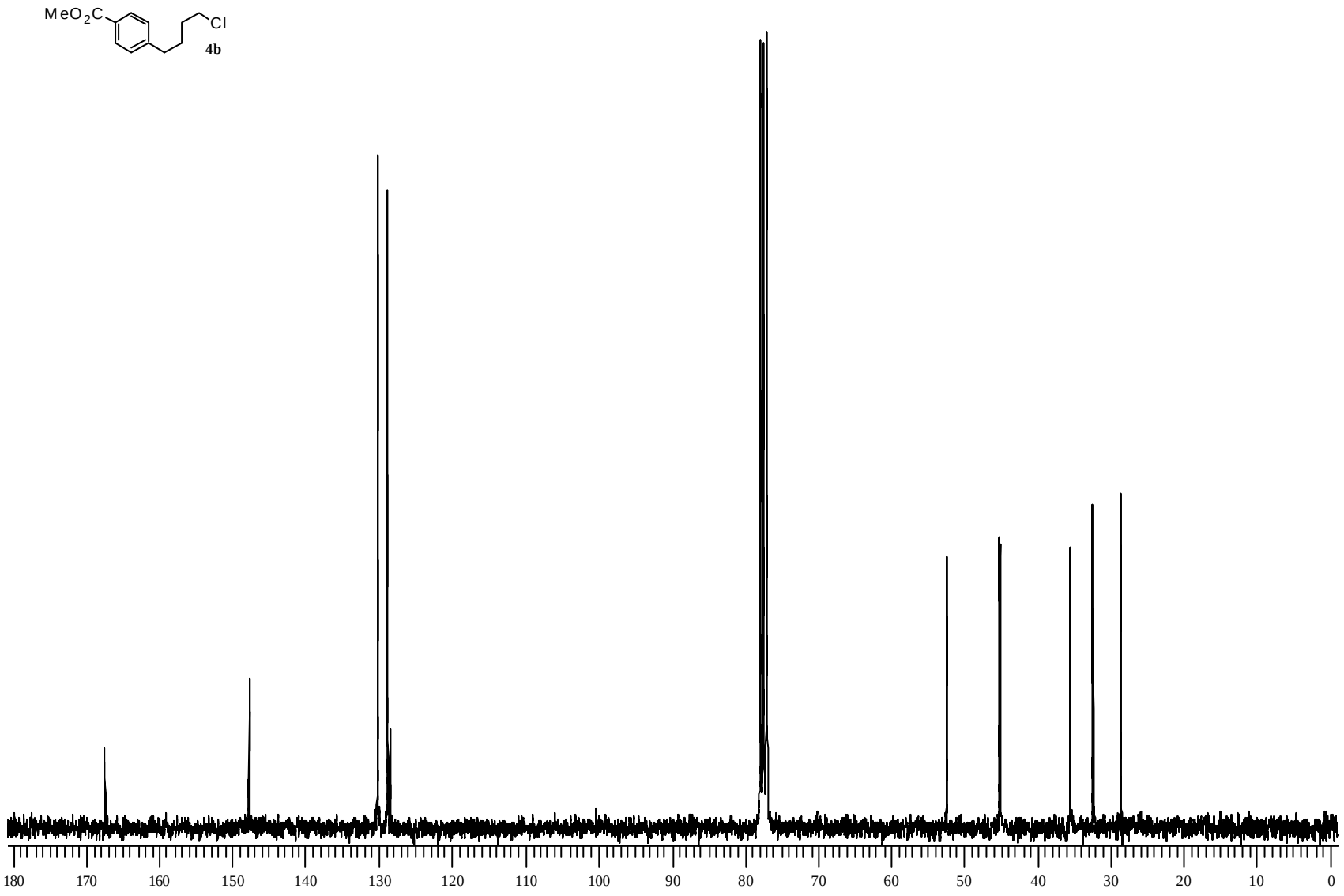
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Cl
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150
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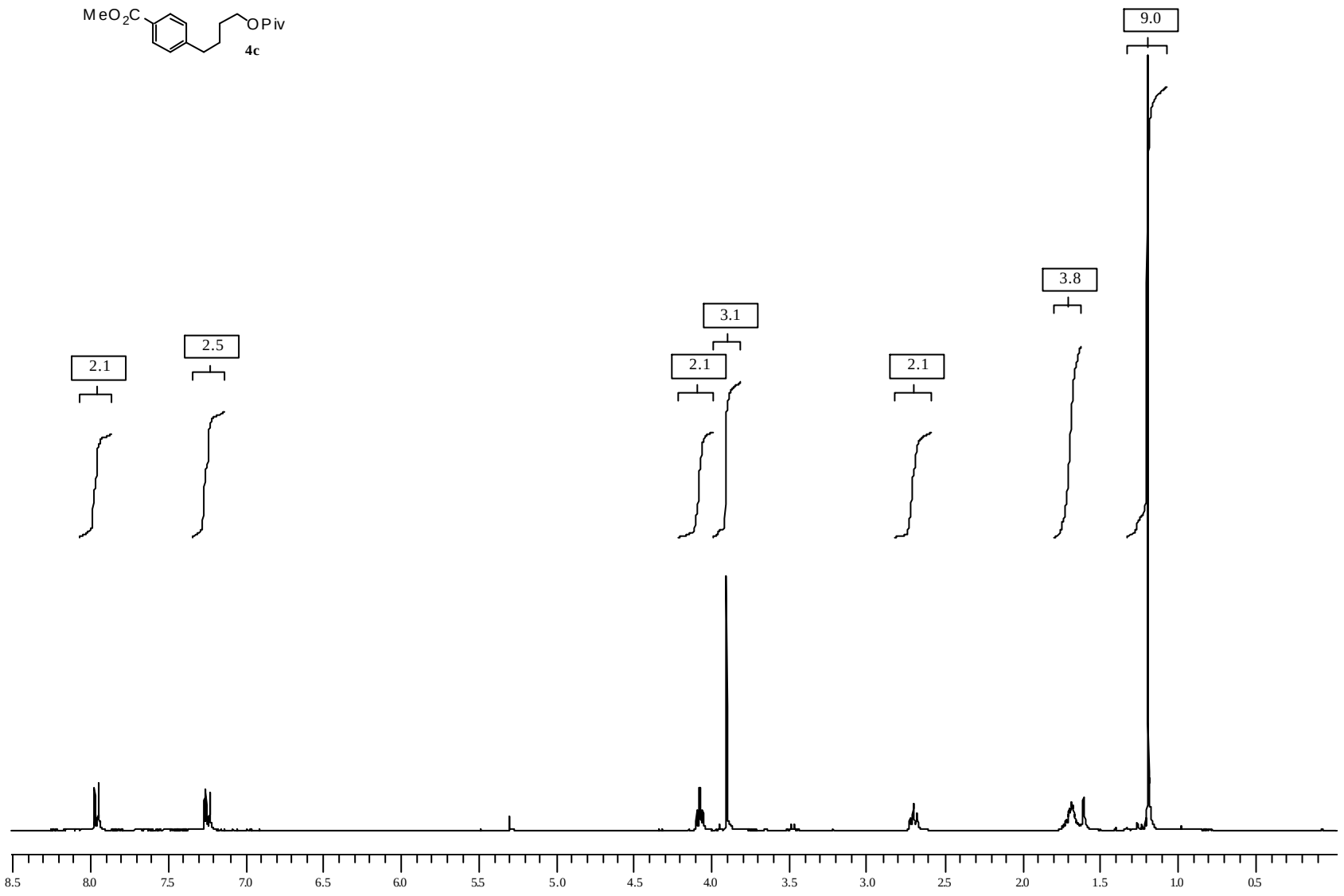
10
0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7.0
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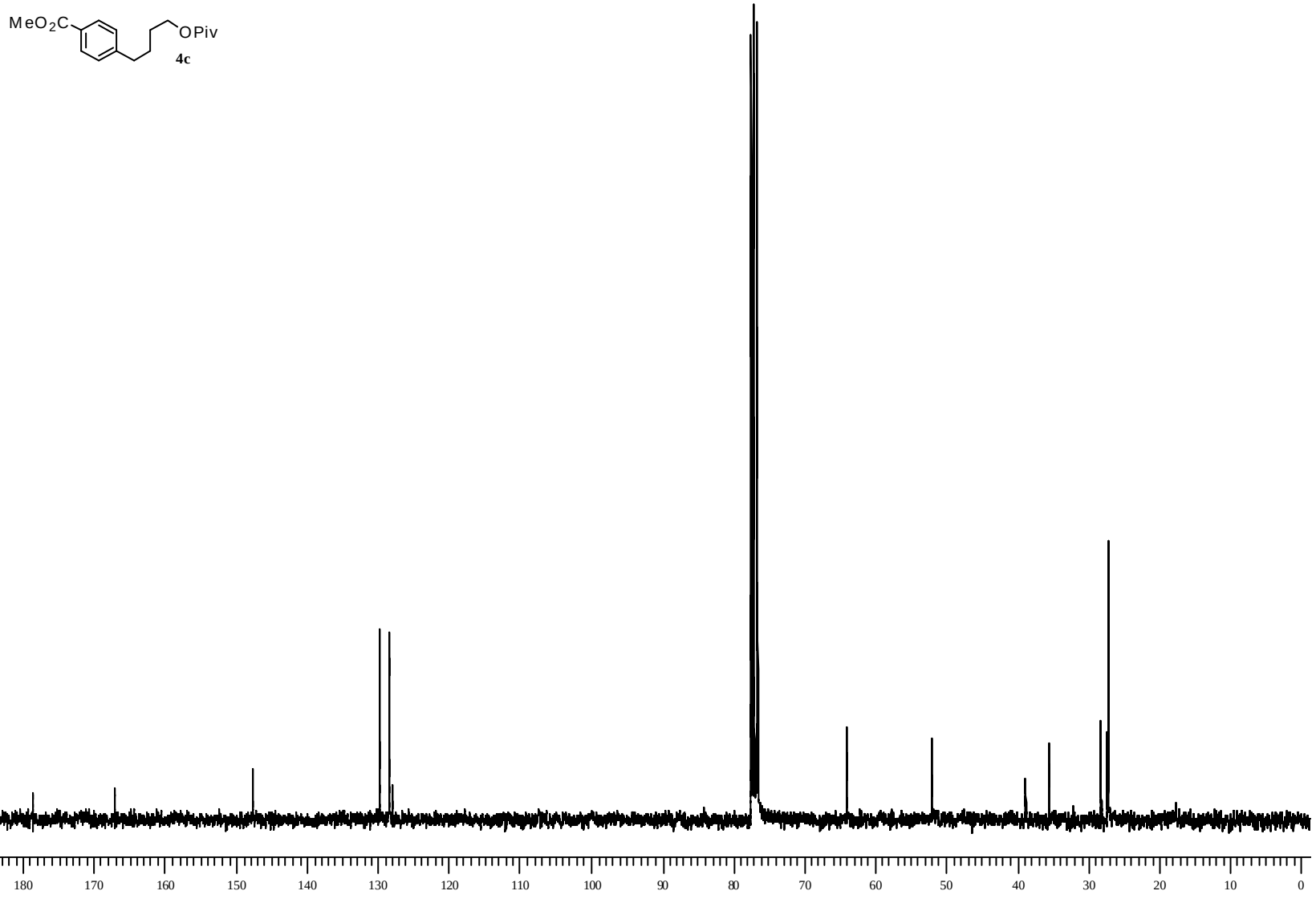
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4c
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30
20
10
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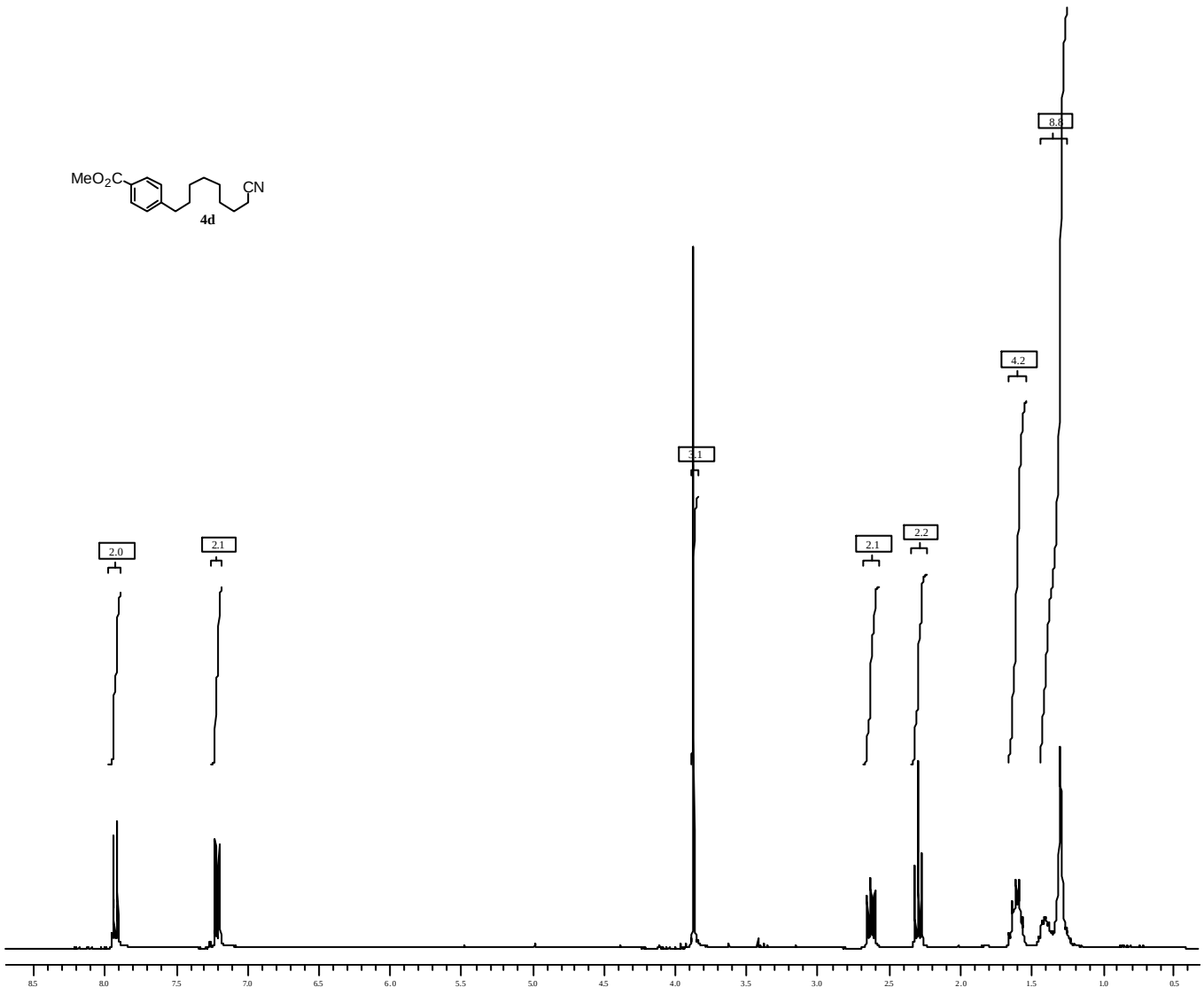
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CN
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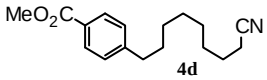
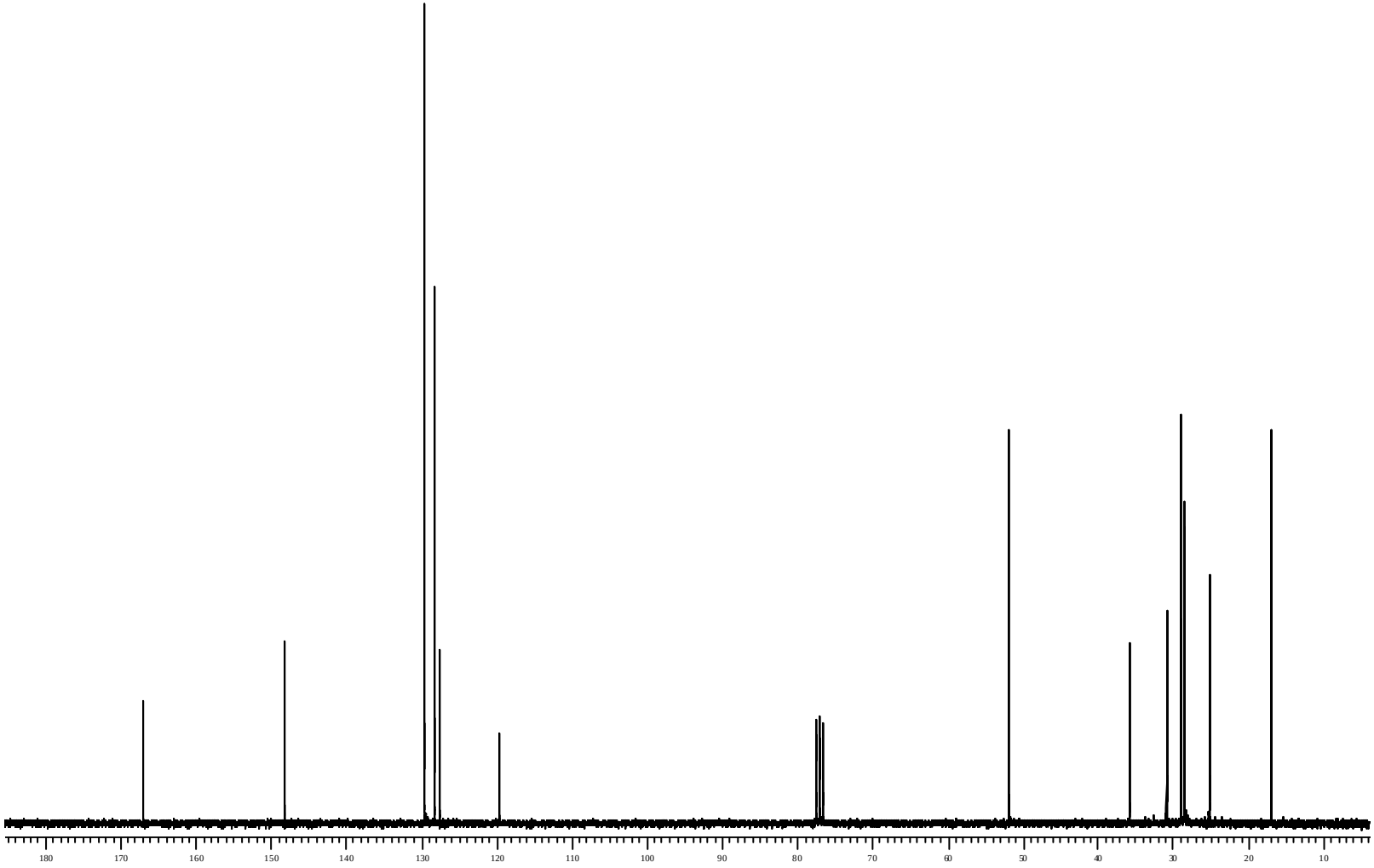

MeO2C
CN

4d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20
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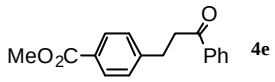
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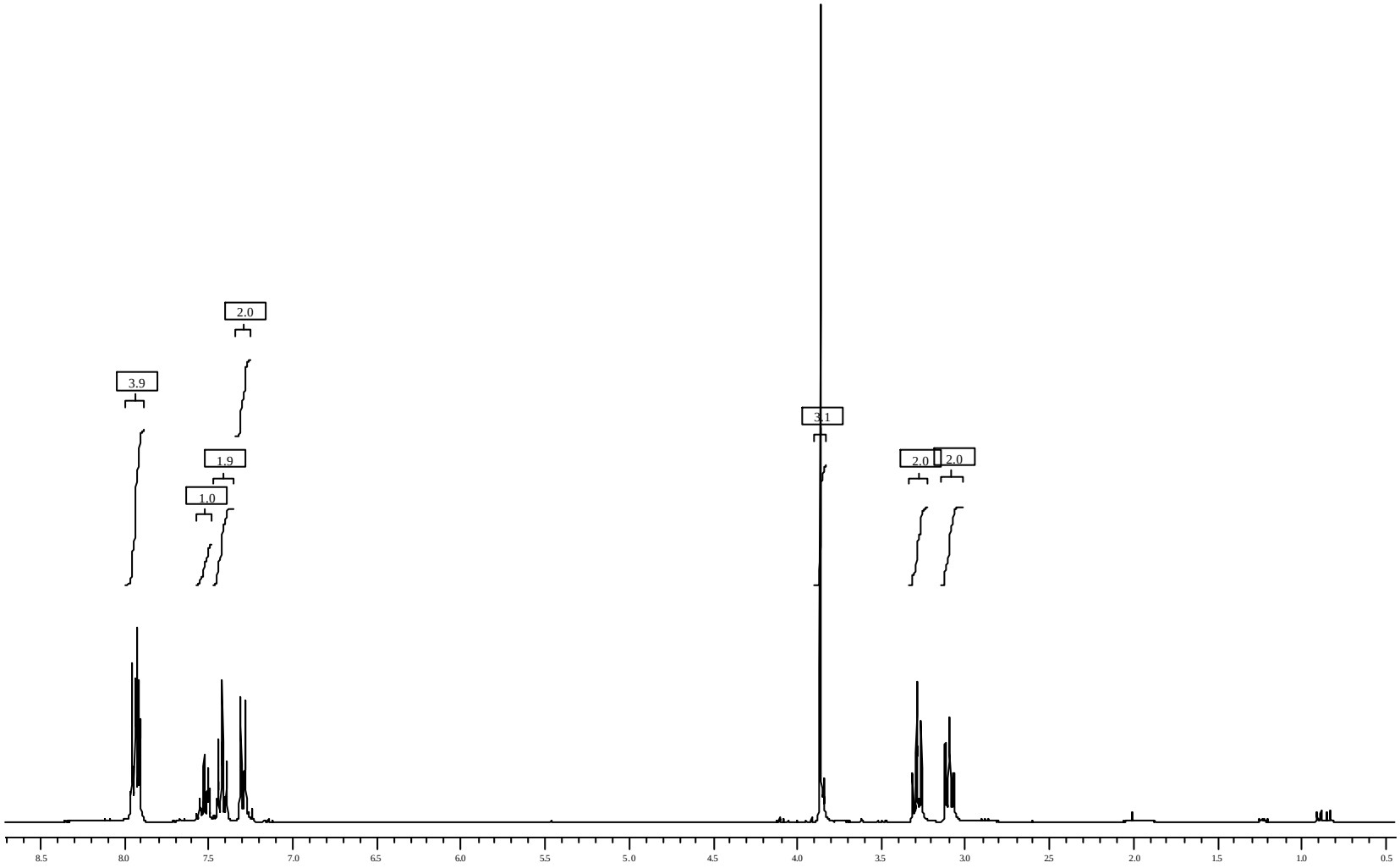
O
Ph

4e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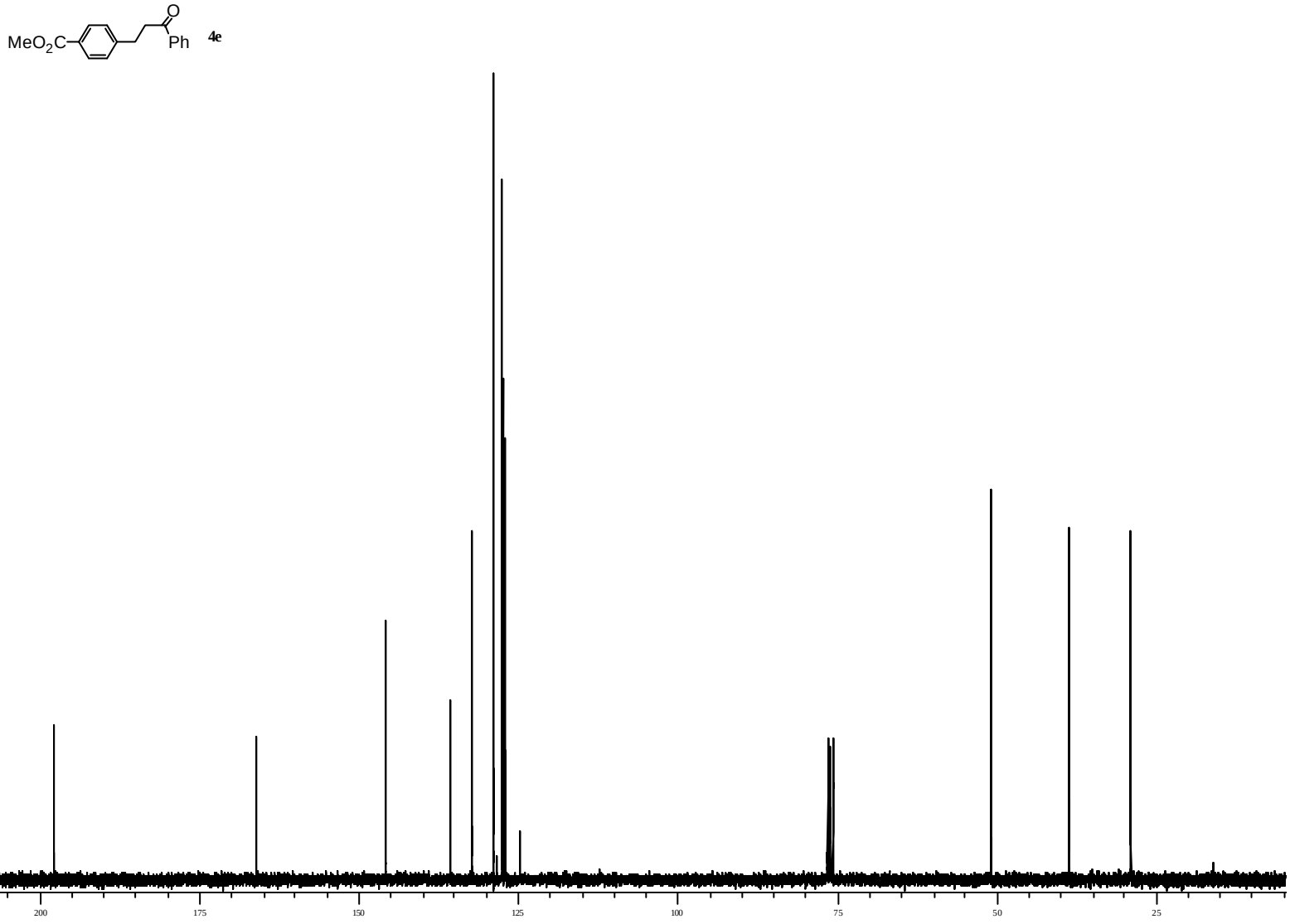
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Ph
4e
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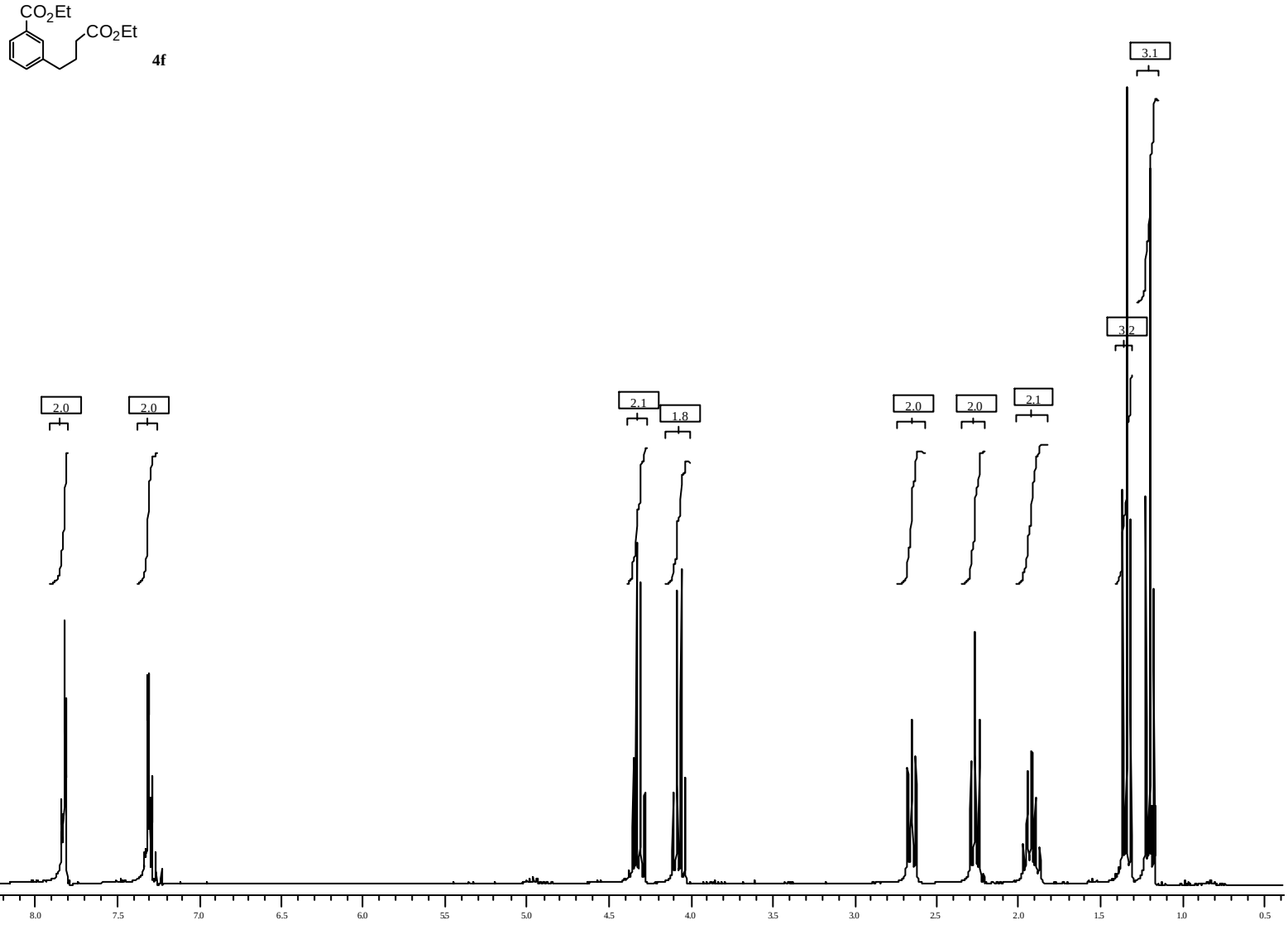
175
150
125
100
75
50
25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CO2Et
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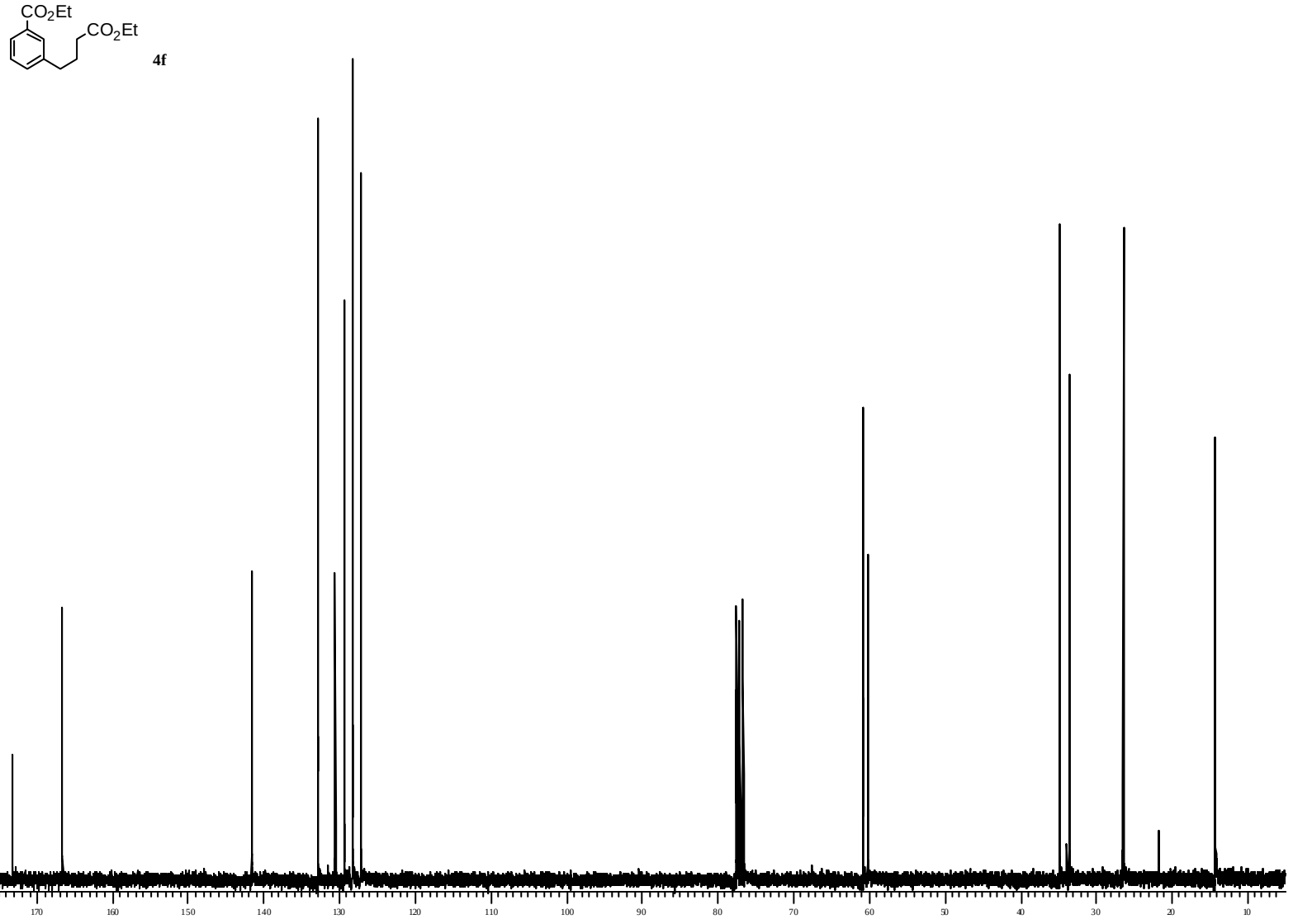
CO2Et
CO2Et
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150
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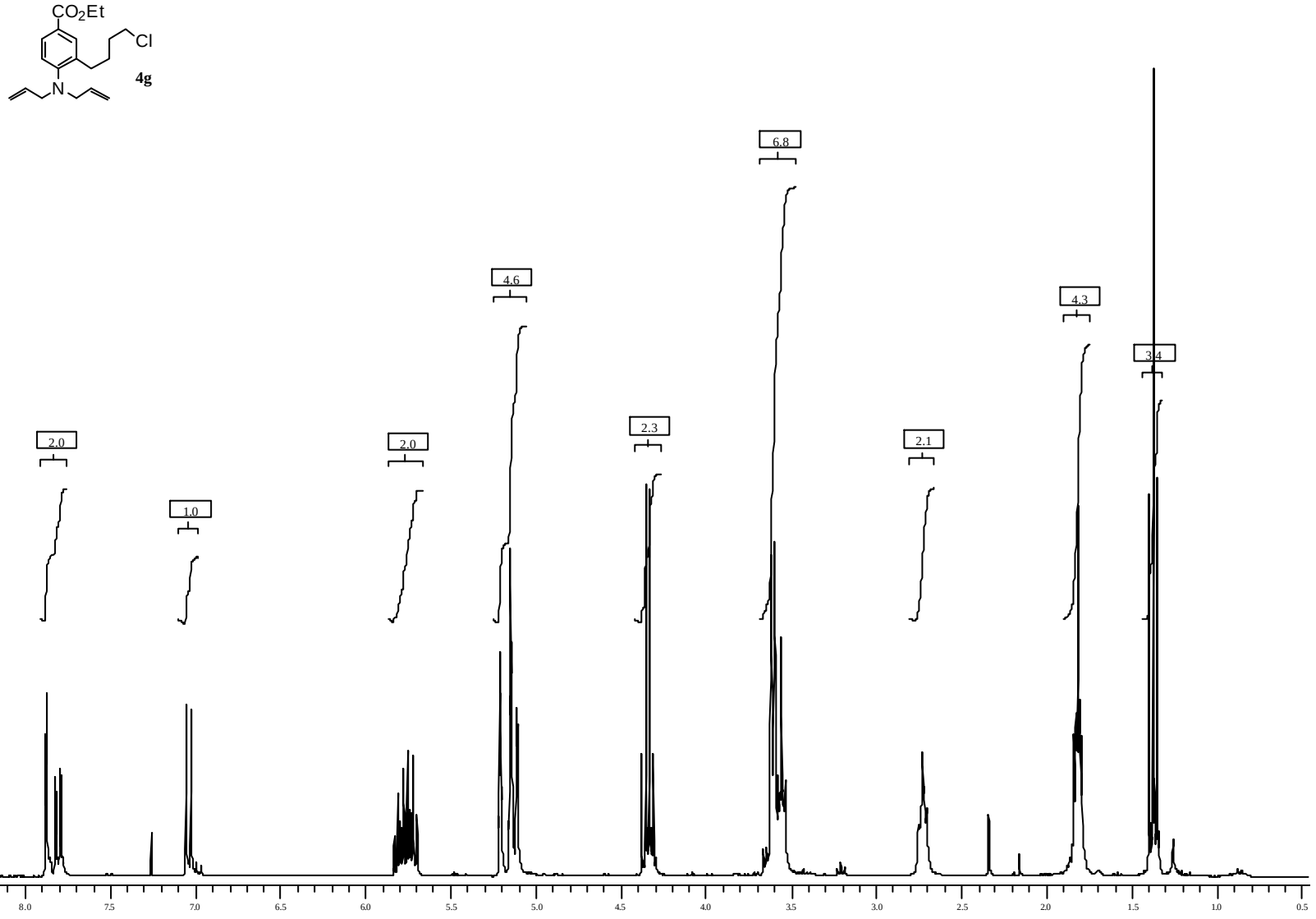
120
110
100
90
80
70
60
50
40
30
20
10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Cl
N
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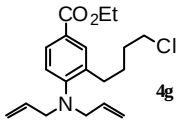
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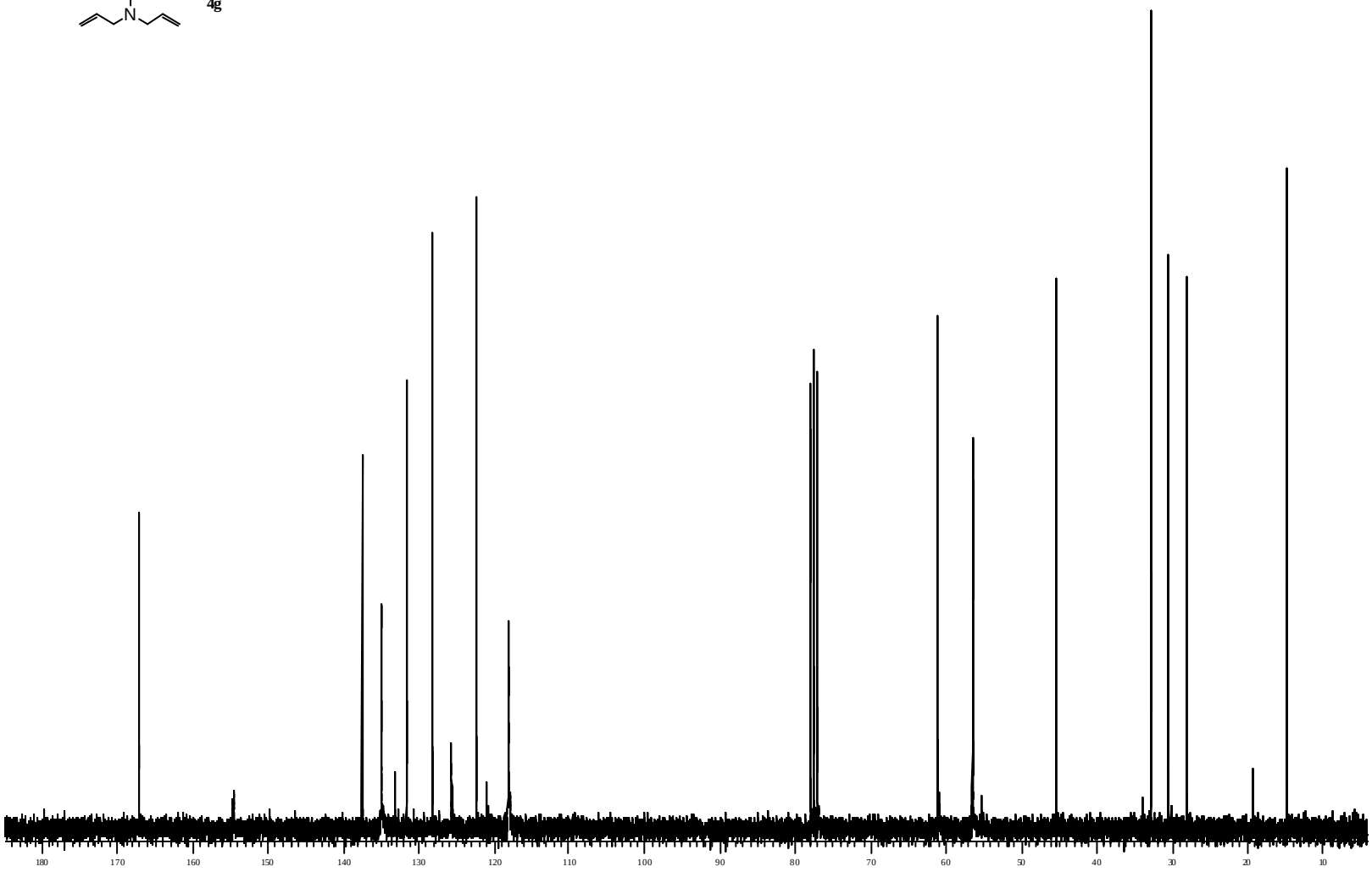
Cl
N

4g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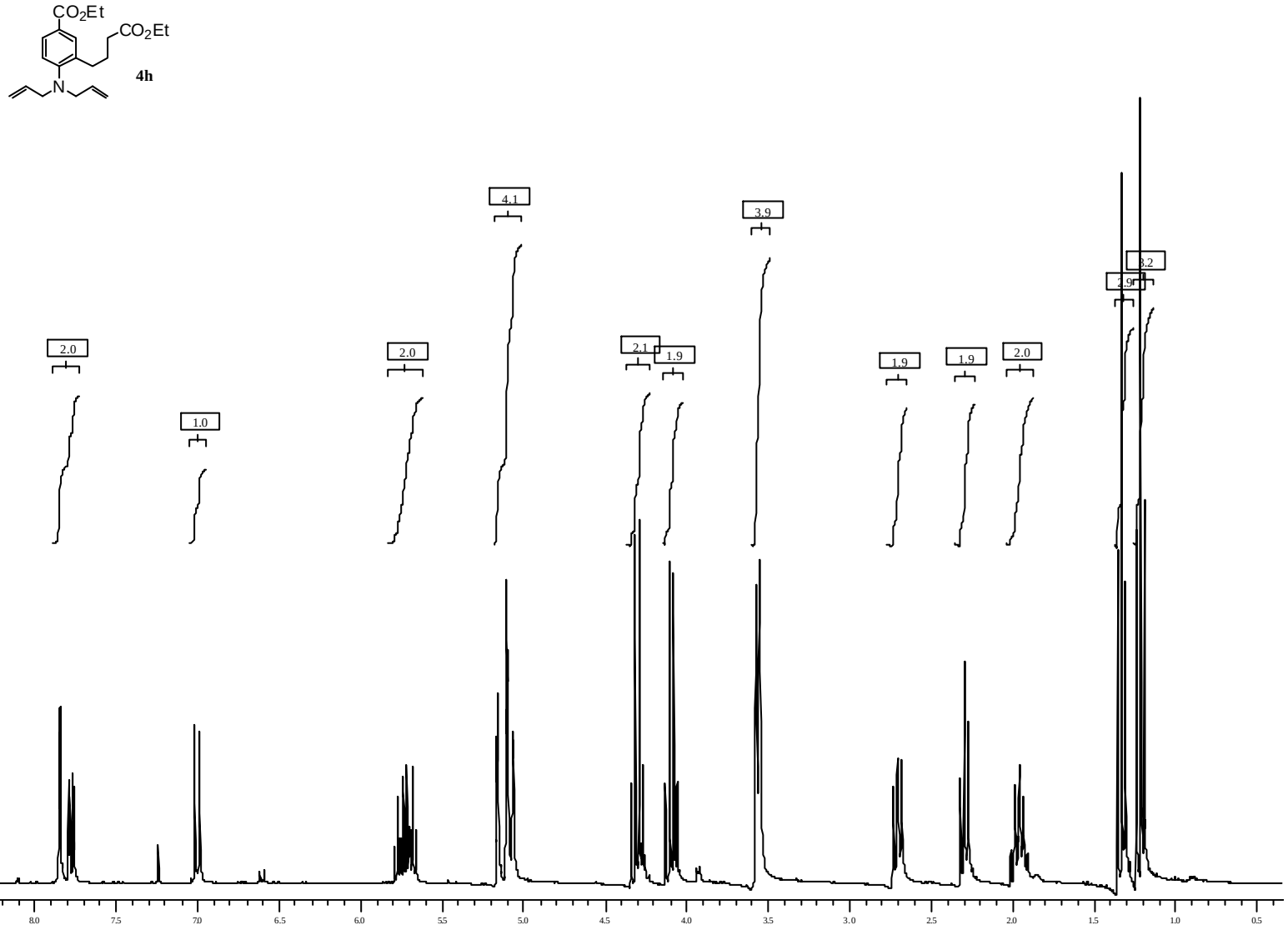
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CO2Et
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2.0
3.2
2.9
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7.5
7.0
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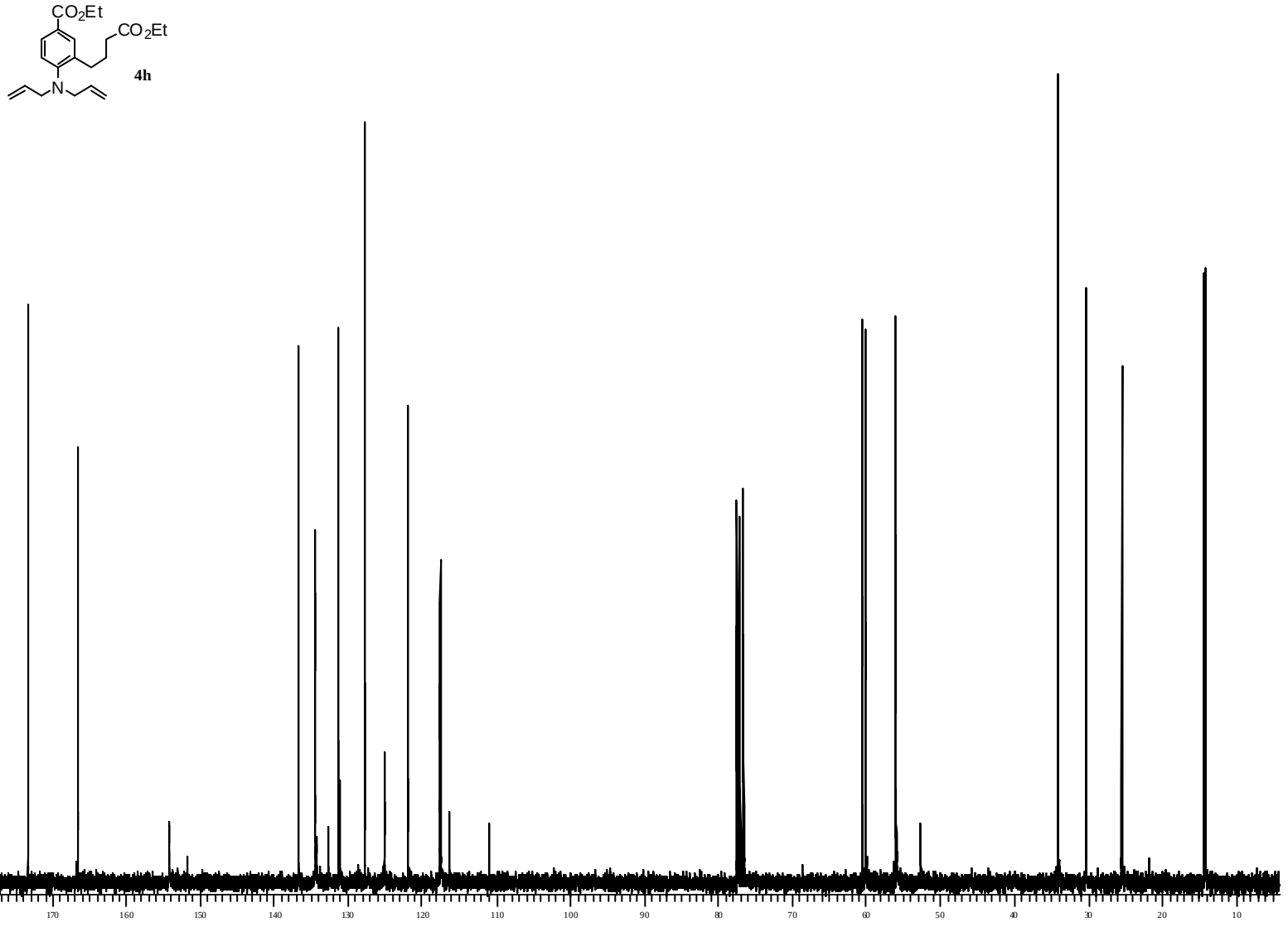
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CO2Et
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4h
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160
150
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80
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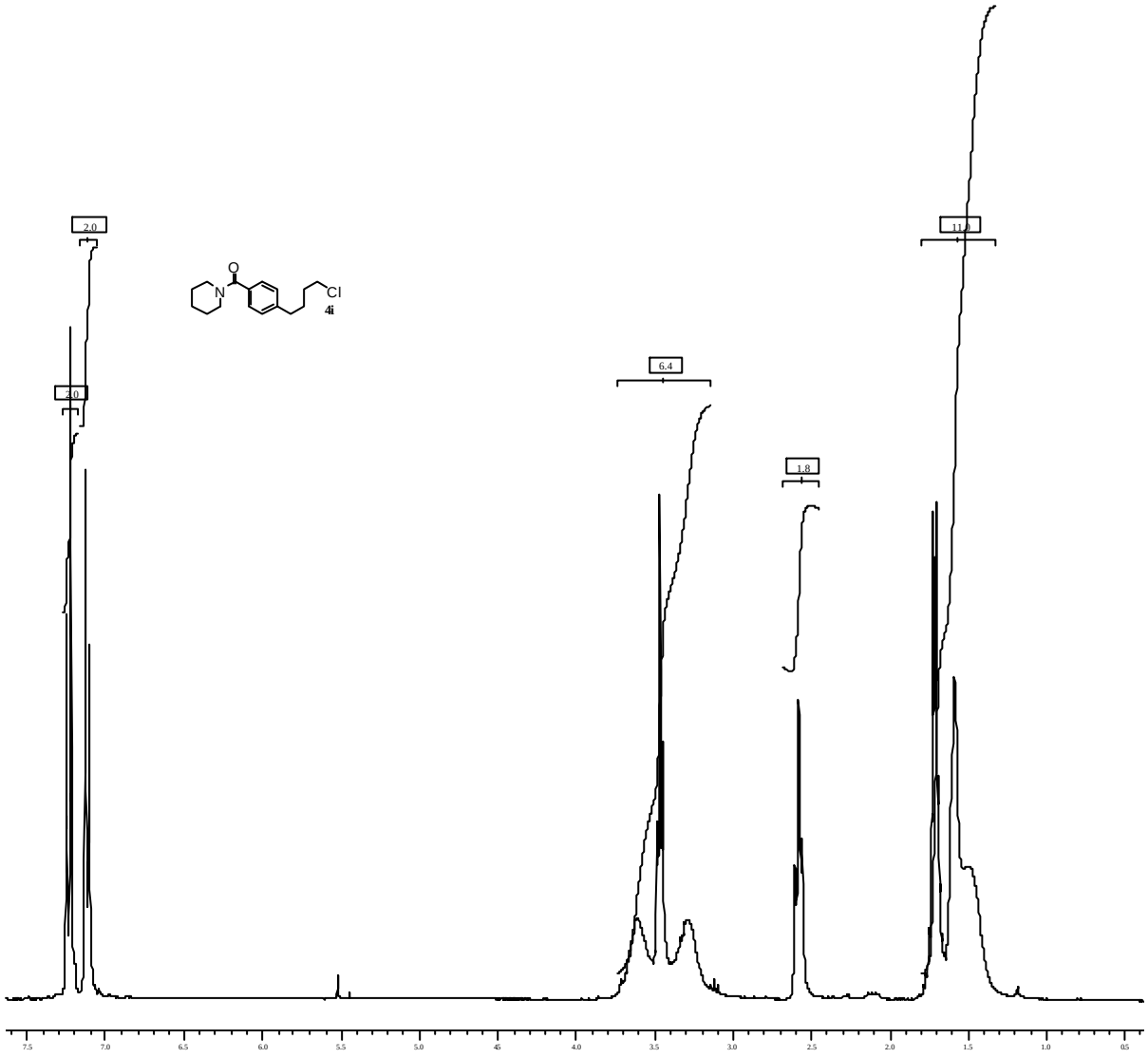
40
30
20
10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Cl
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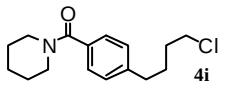
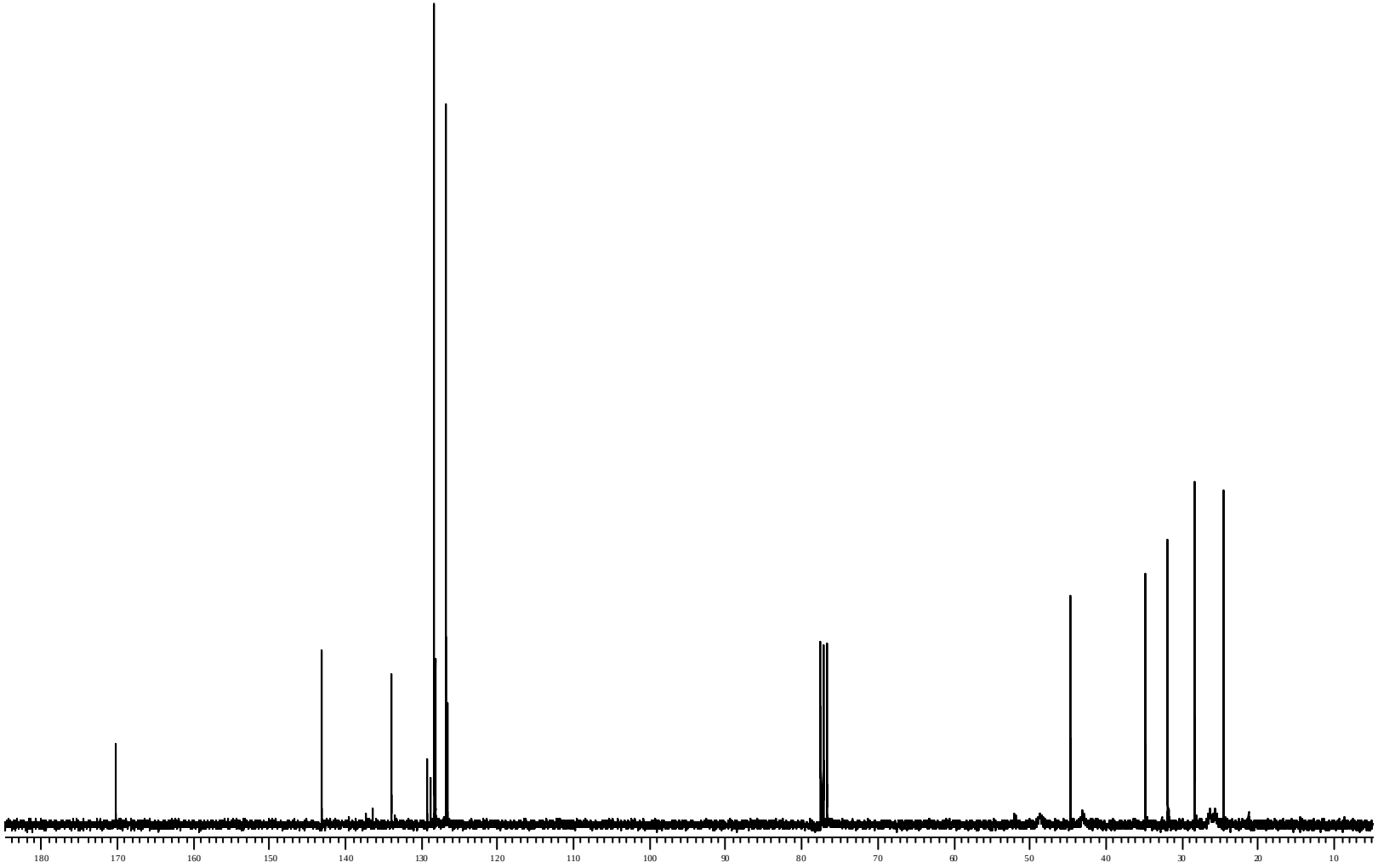
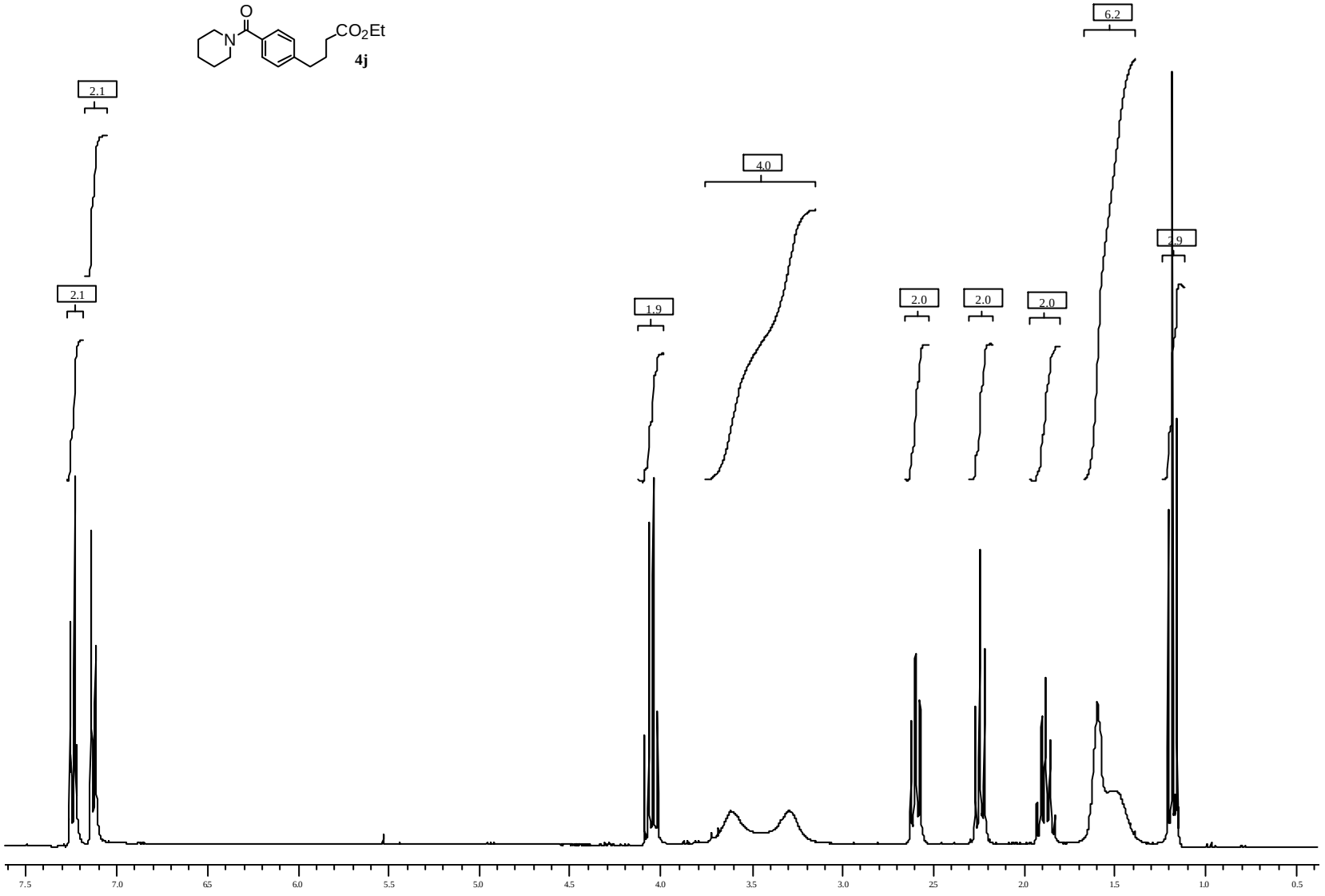


4i

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CO2Et
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6.5
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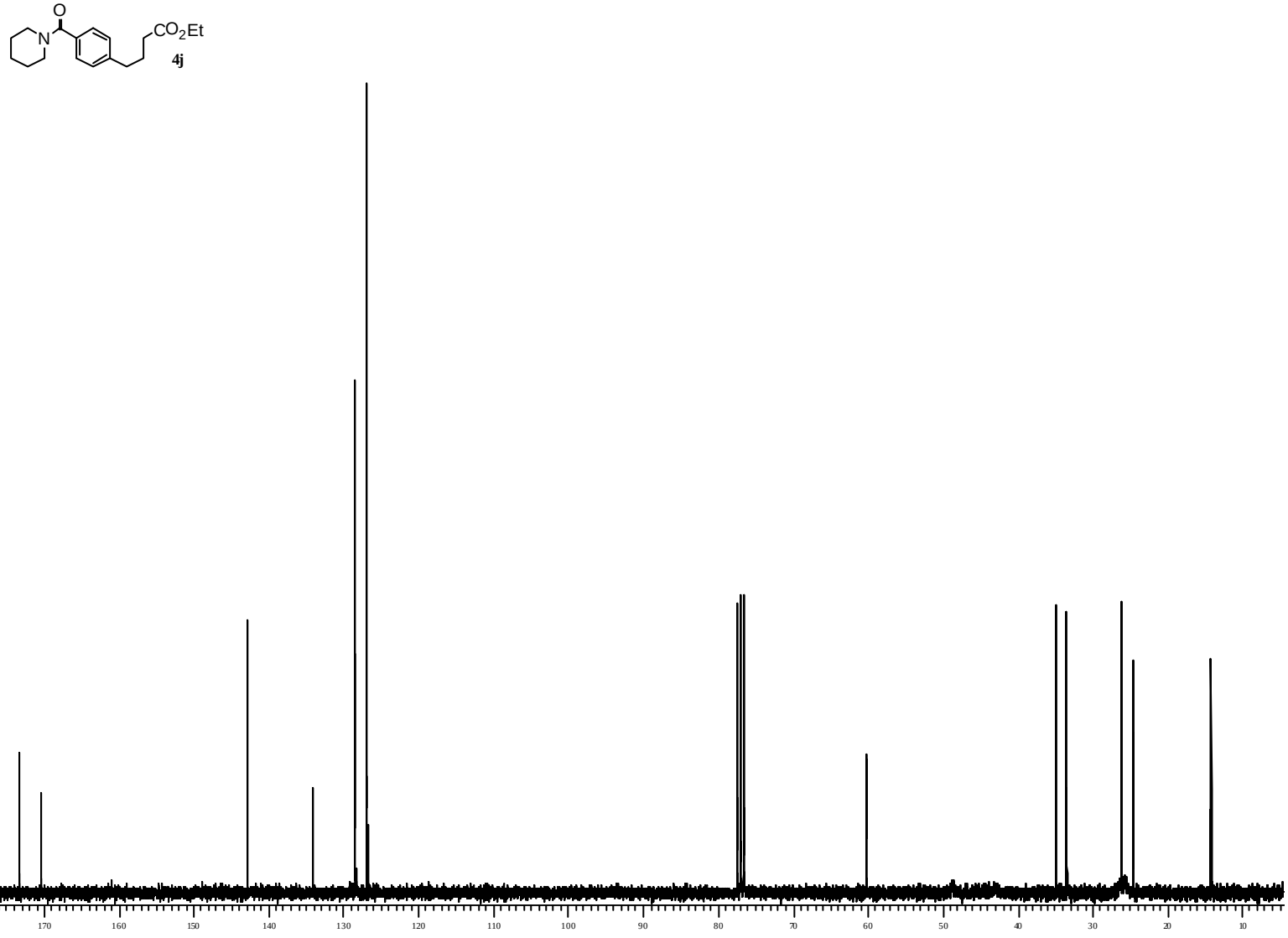
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N
CO2Et
4j
180
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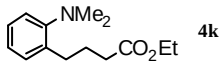
20
10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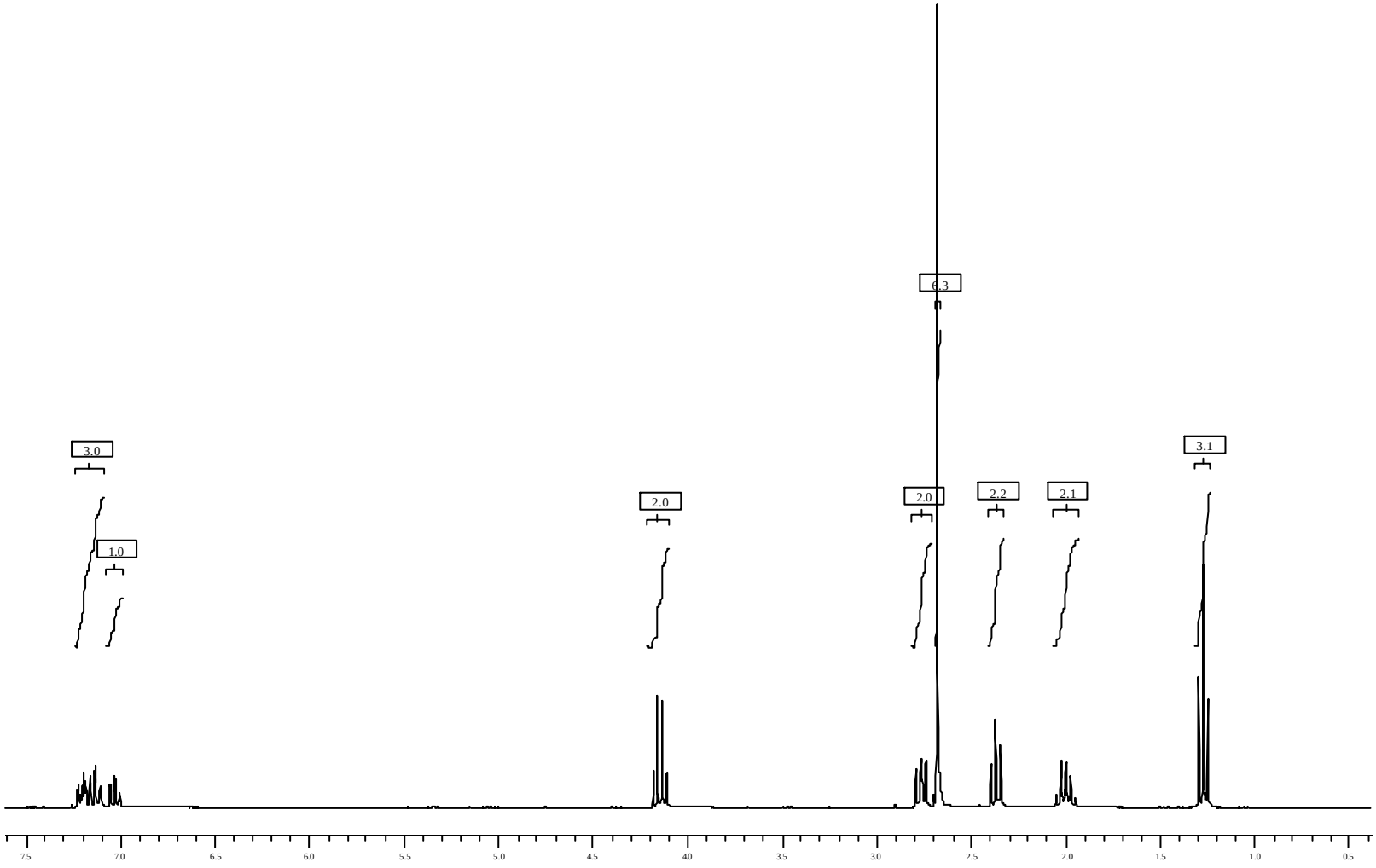
CO2Et

4k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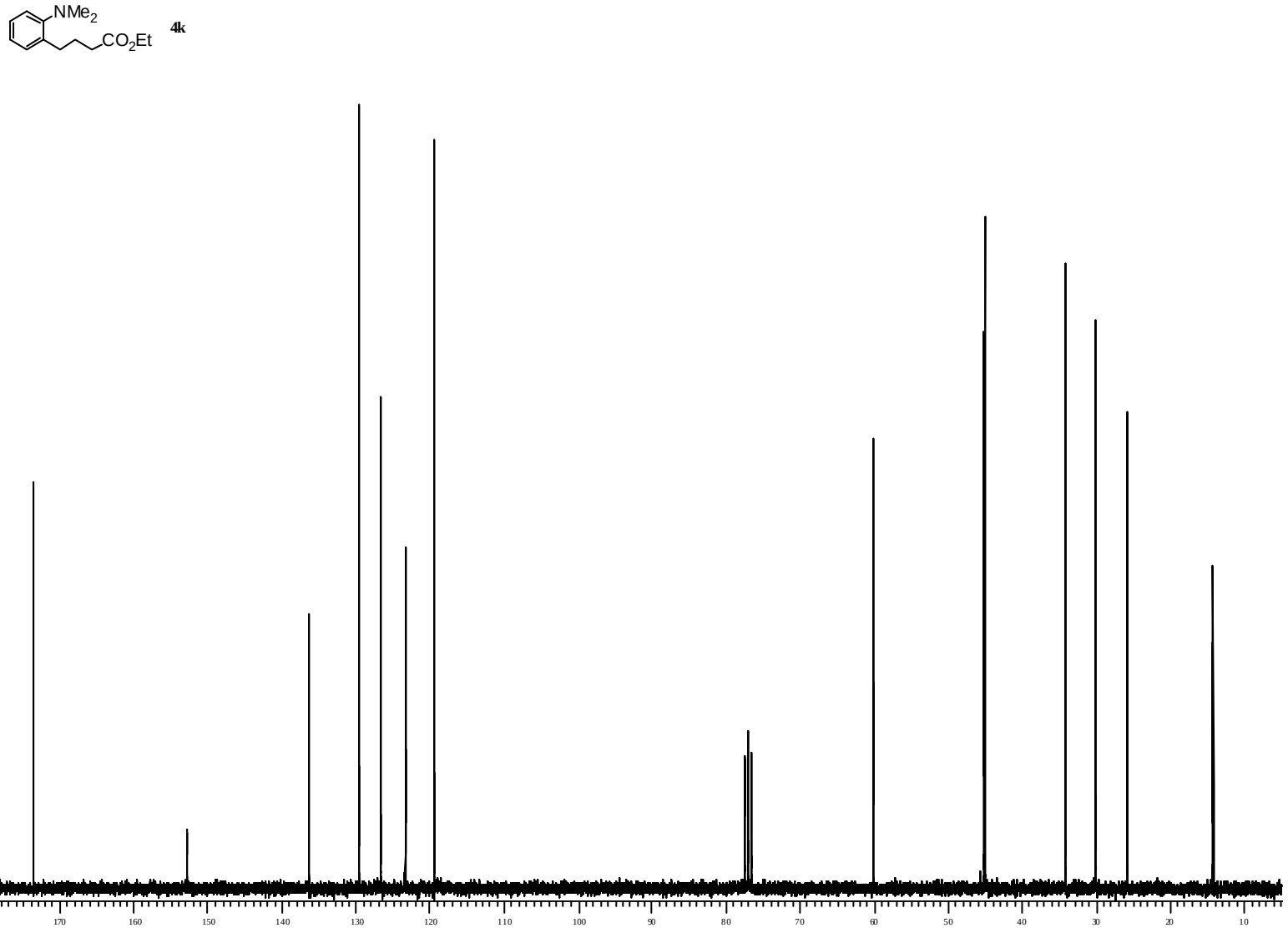
NMe2
CO2Et
4k
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150
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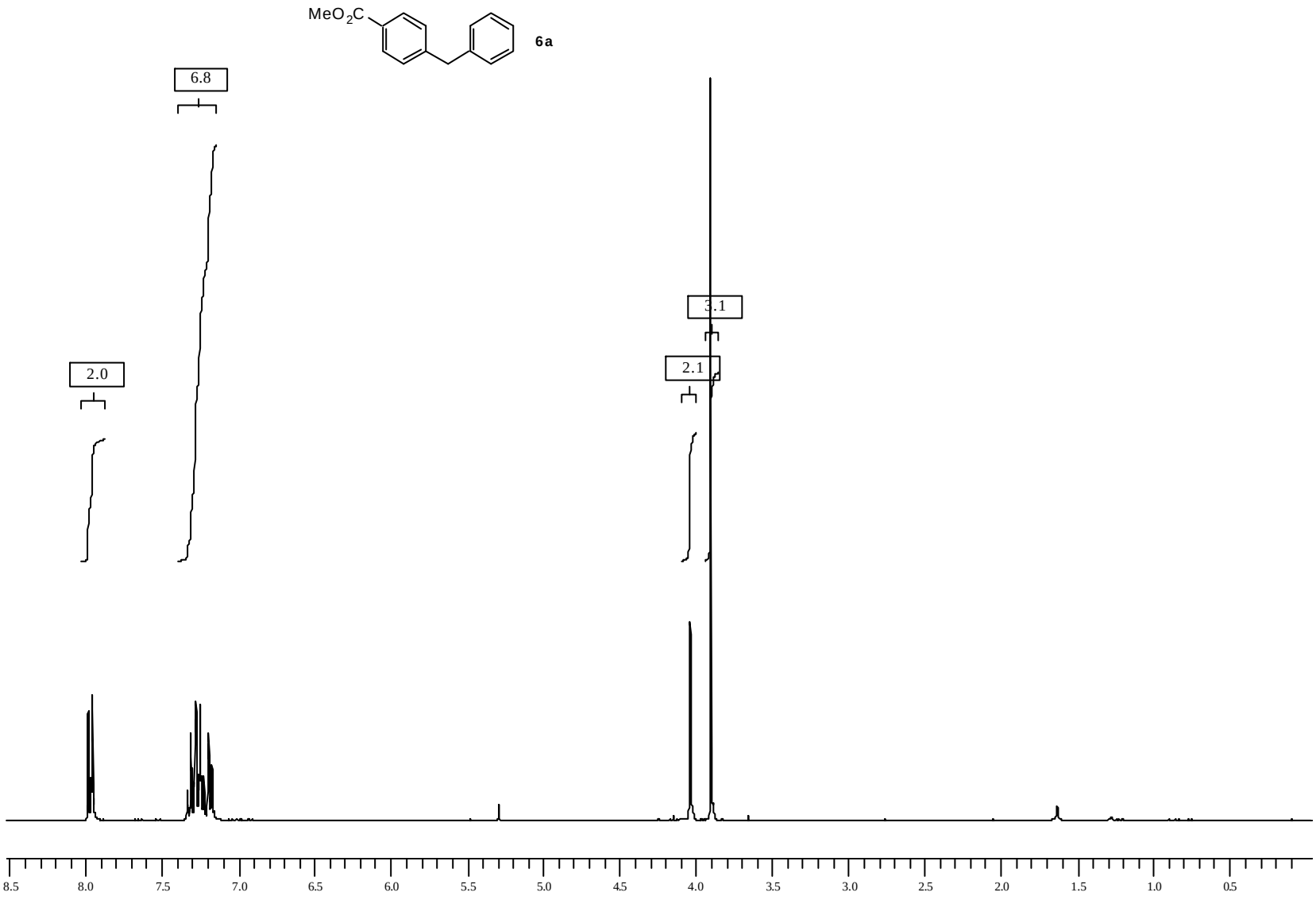
130
120
110
100
90
80
70
60
50
40
30
20
10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6a
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2.1
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8.0
7.5
7.0
6.5
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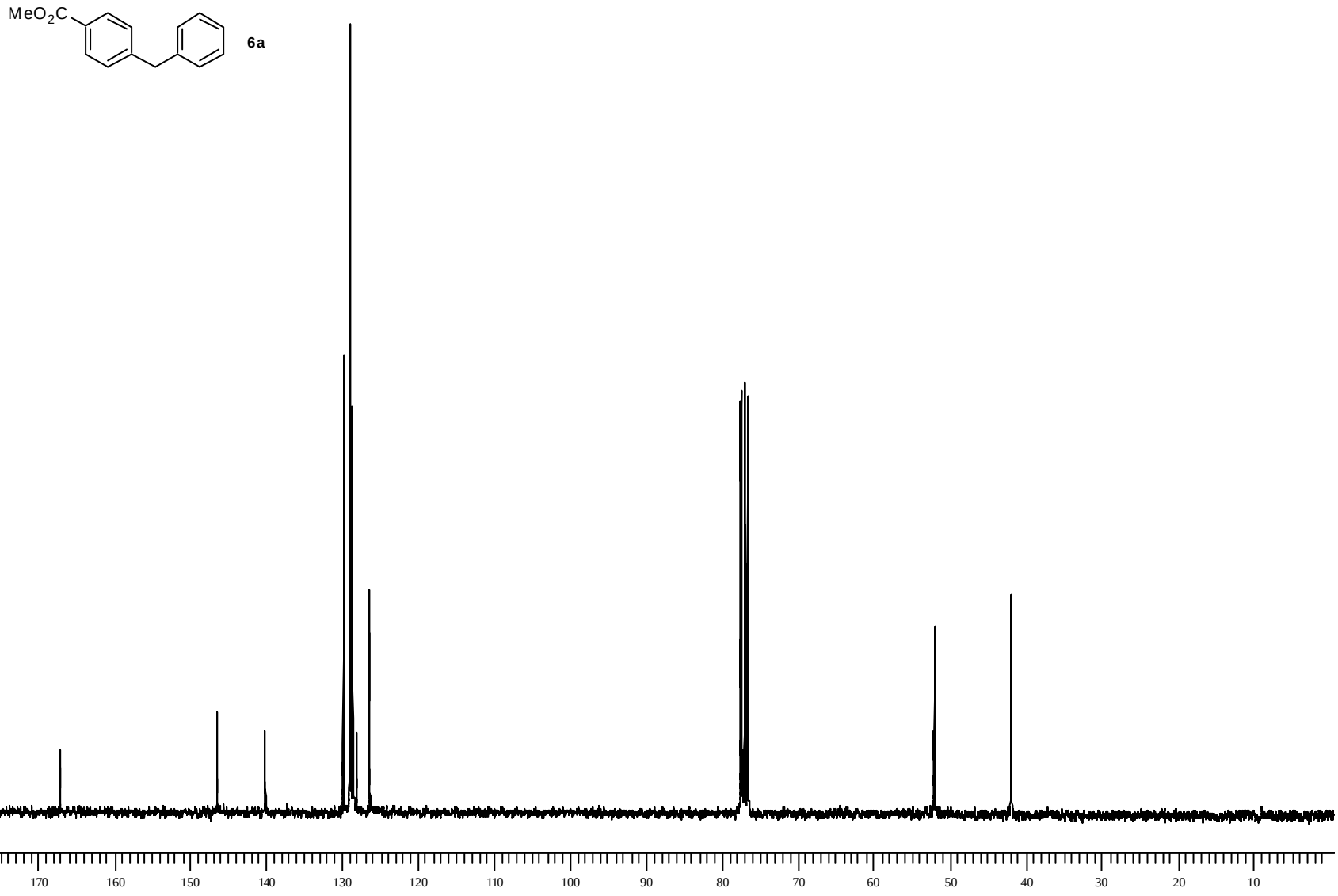
MeO2C
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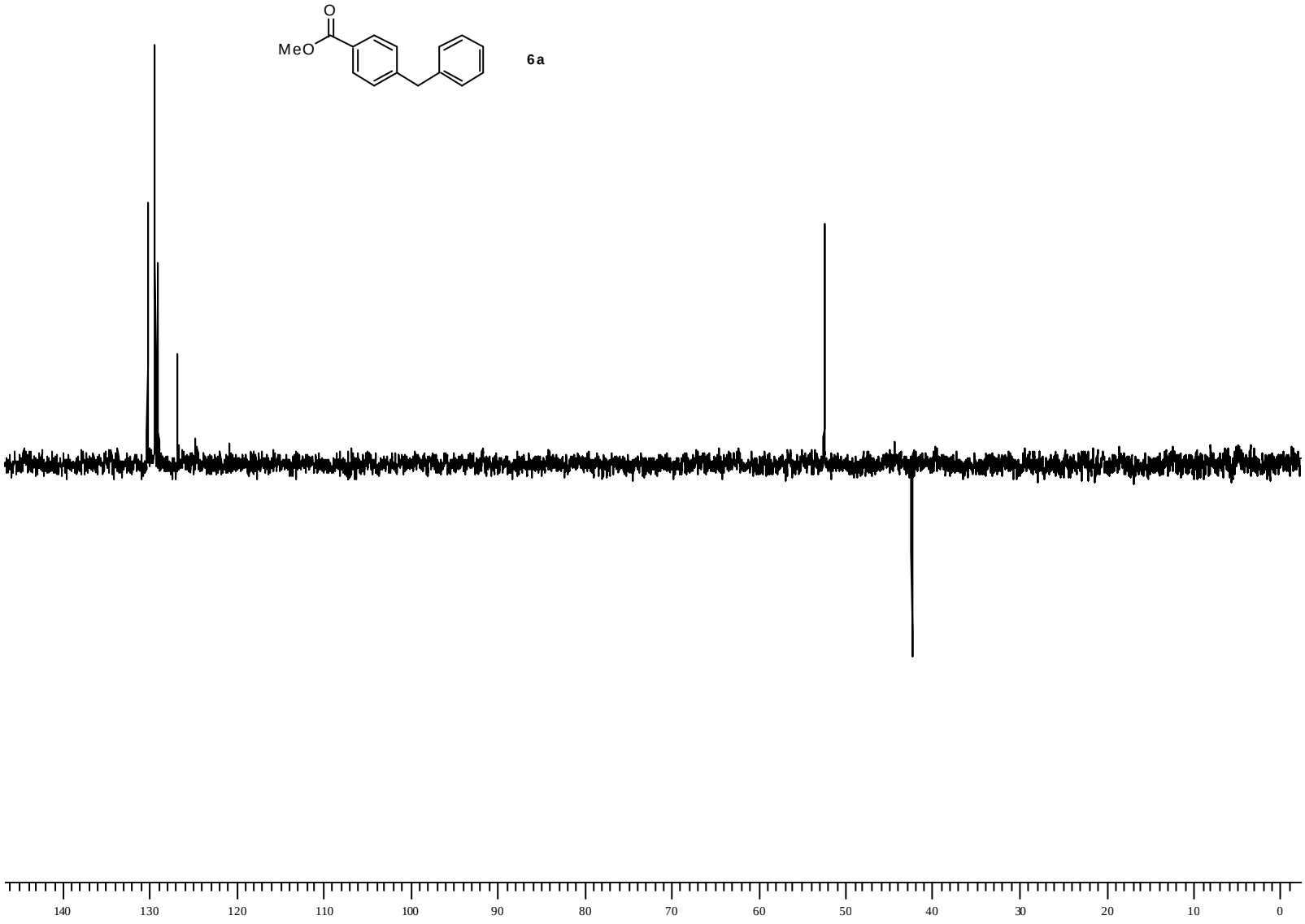
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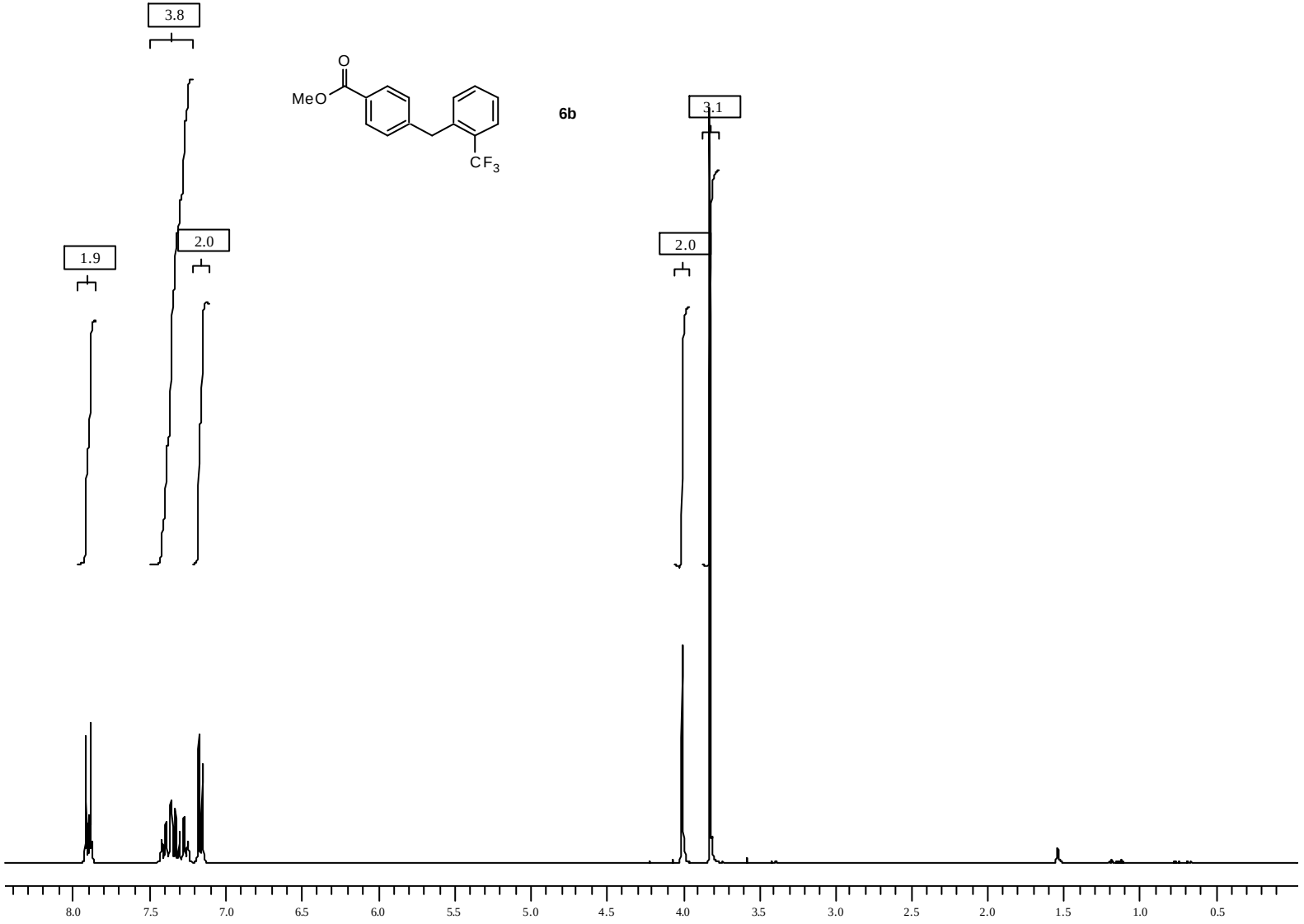
3.8
1.9
2.0
2.0
3.1
MeO
O
CF3
6b
8.0
7.5
7.0
6.5
6.0
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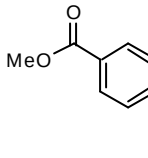
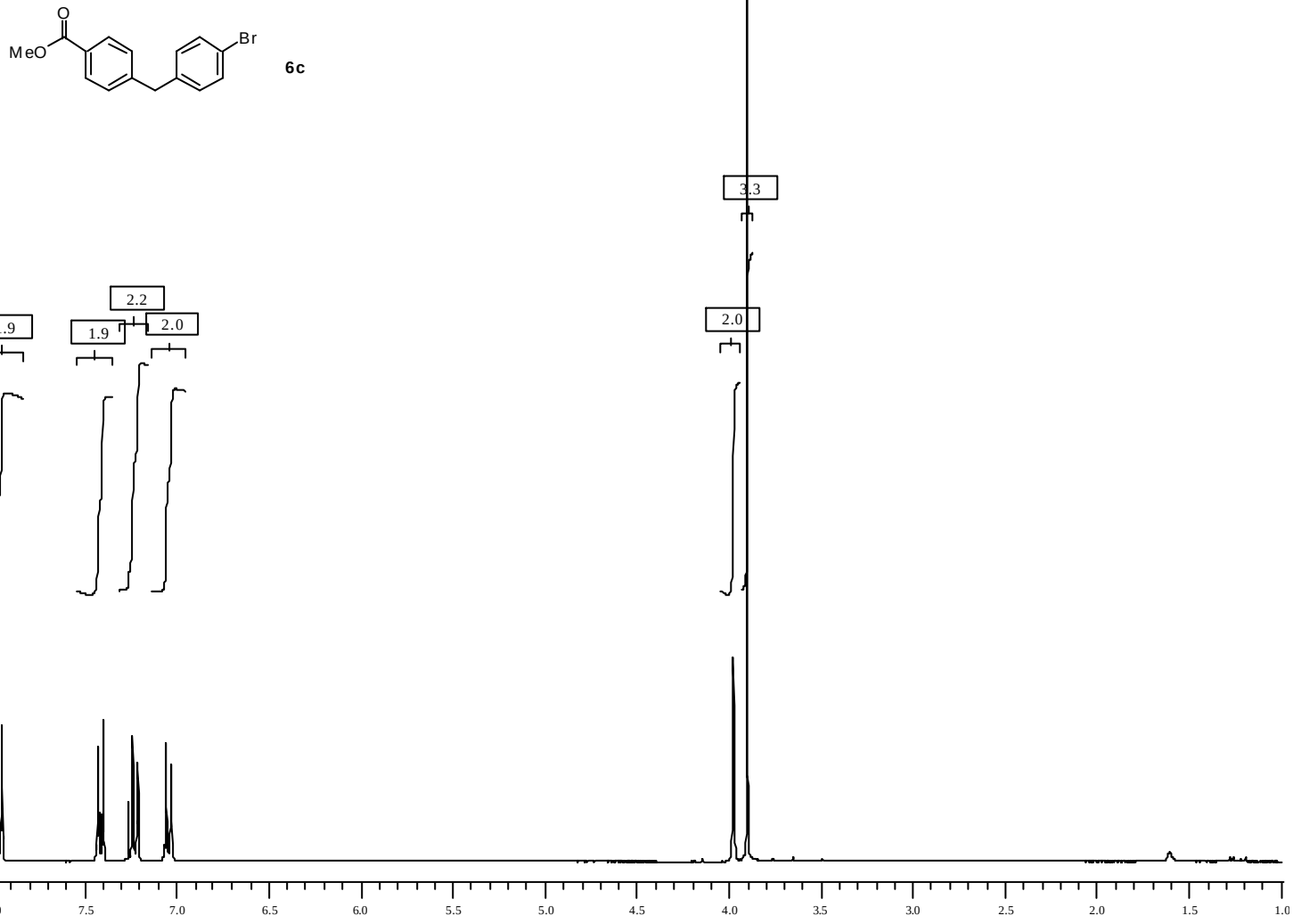
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


O
MeO
CF3

6b

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


O
MeO
Br
6c
3.3
2.2
1.9
1.9
2.0
2.0
8.0
7.5
7.0
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6.0
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5.0
4.5
4.0
3.5
3.0
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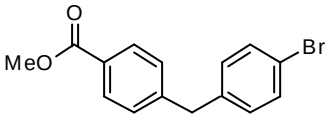
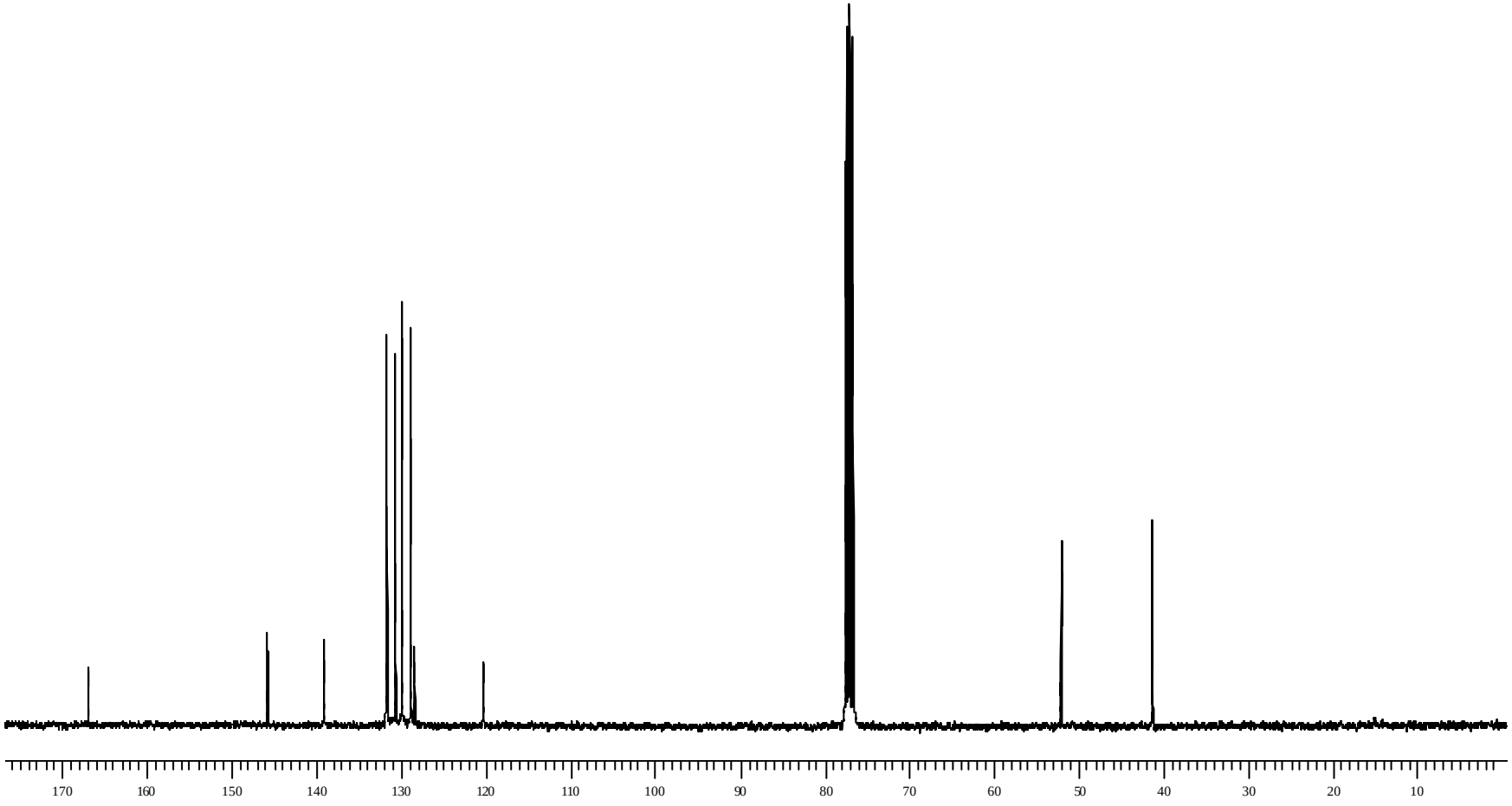
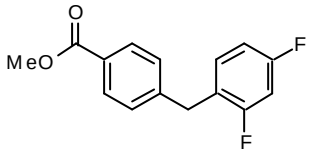
2.0
1.5
1.0

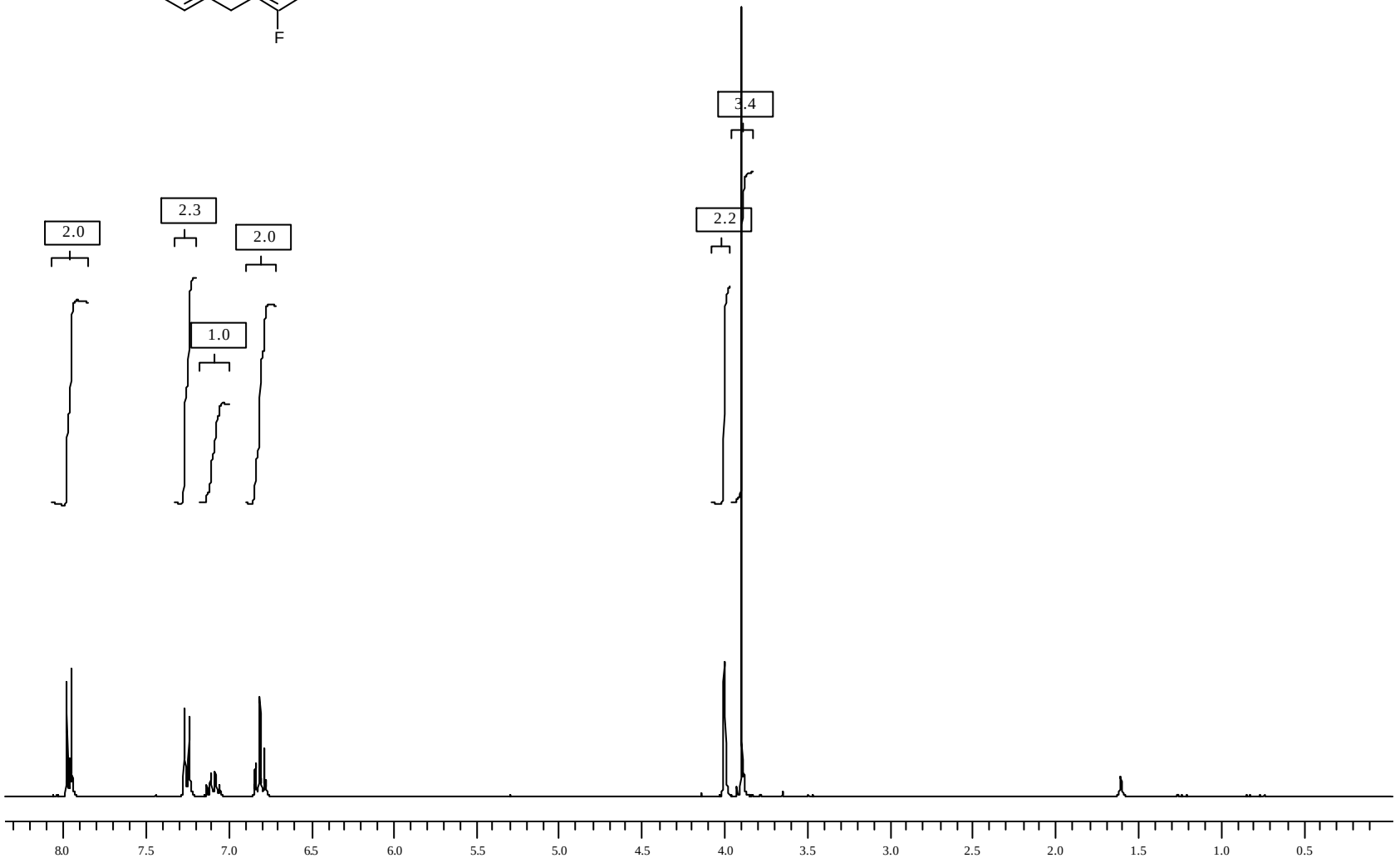


6c




O
MeO
F
F

6d


2.0
2.3
2.0
1.0
2.2
3.4
8.0
7.5
7.0
6.5
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3.5
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2.5
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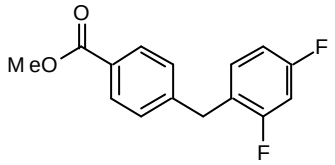
1.0
0.5



6d