SUPPORTING INFORMATION

Diastereoselective Alkylations of a Protected Cysteinesulfenate

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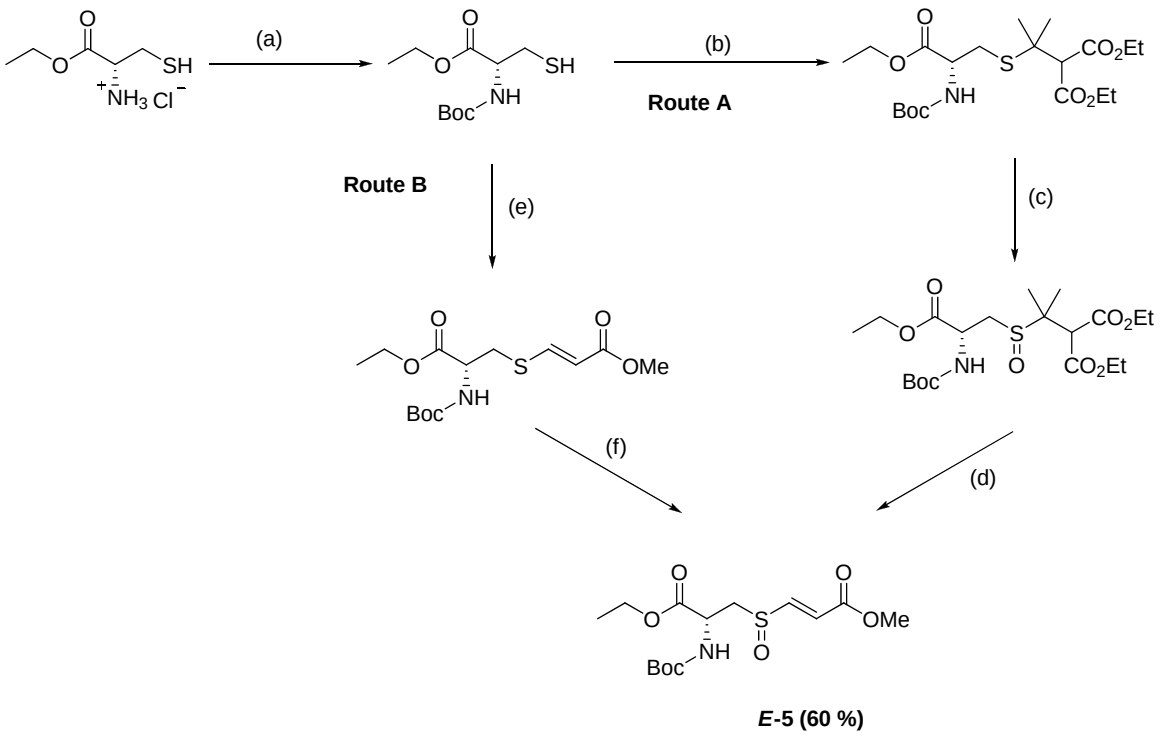
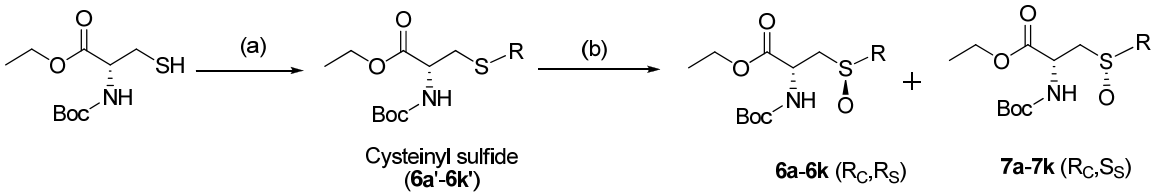


Scheme 1. Synthesis of Boc-Cys((O)-*E*-Carbomethoxyethenyl)-OEt (***E*-5**); **Route A**[1] : (a) Et_3N, Boc_2O, THF (b) Diethyl isopropylidenemalonate, Triton B, THF (c) m-CPBA, CH_2Cl_2 (d) methyl propiolate, CH_2Cl_2, **Route B:** (e) Et_3N, methyl propiolate, CH_2Cl_2 (f) m-CPBA, CH_2Cl_2



Scheme 2. Synthesis of sulfoxide through oxidation of sulfides; (a) *N*,*N*-diisopropylethylamine, CH_2Cl_2 (b) m-CPBA, CH_2Cl_2.

Synthesis of Boc-Cys((O)-*E*-Carbomethoxyethenyl)-OEt (*E*-5)

Triethylamine (2.10 g, 20.5 mmol) was added to a stirred cold solution (0 °C) of methyl propiolate (2.20 g, 26.6 mmol) in dry CH_2Cl_2 (30 mL) under N_2 gas. N-(*t*-butoxycarbonyl)-L-cysteine ethyl ester (5.10 g, 20.5 mmol) was added to the reaction immediately. The mixture was stirred for 4 min then 1.0 M HCl (10 mL) was added to the reaction and the organic layer was extracted. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. *E*-isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 15.3 Hz, 1H), 5.82 (d, *J* = 15.3 Hz, 1H), 5.39 (br d, 1H), 4.59 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 3.28 (br m, 2H), 1.41 (s, 9H), 1.27 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.9, 165.4, 154.9, 146.4, 114.8, 80.4, 62.2, 53.1, 51.4, 35.2, 28.0, 14.0; IR ($CDCl_3$) cm^{-1}: 3432, 2987, 1747, 1718, 1690.

The sulfide (**4**) was taken to the next step without further purification. MCPBA (3.38 g, 19.6 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a stirred solution of the sulfide in CH_2Cl_2 (30 mL) at -70 °C for 15 min. The reaction was washed with a saturated solution of $Na_2S_2O_3$ (10 mL). The organic layer was extracted and washed with $NaHCO_3$ (3 x 10 mL) and water (3 x 10 mL). The combine organic layers where dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexanes 50:50)

to afford compound ***E*-5** (4.28 g, 60 %, epimeric ratio 1.2:1) as a yellow solid. The major diastereomers can be resolved by recrystallization from EtOAc/hexanes as white crystals. *Major* diastereomer: Mp: 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.63 (d, J = 15.0 Hz, 1H), 6.63 (d, J = 15.0 Hz, 1H), 5.78 (br s, 1H), 4.58 (br s, 1H), 4.18 (q, J = 6.9 Hz, 2H), 3.76 (s, 3H), 3.33 (ABX, J_{AX} = 8.6 Hz, J_{BX} = 5.5 Hz, J_{AB} = 13.3 Hz, 2H), 1.39 (s, 9H), 1.24 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.9, 163.9, 155.2, 149.6, 126.0, 80.5, 62.2, 54.3, 52.3, 49.7, 28.1, 14.0; IR ($CDCl_3$) cm^{-1} 3428, 3058, 2983, 1746, 1715, 1695, 1061; MS (EI), m/z (%): no M^+ peak, 276 (5), 249 (7), 217 (7), 176 (7), 160 (94), 159 (10), 116 (17), 114 (8), 102 (8), 57 (100); Analysis calc'd for $C_{14}H_{23}NO_7S$: C, 48.13; H, 6.64; Found: C, 48.13; H, 6.56. *Minor* diastereomer: Mp: 58-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.53 (d, J = 15.0 Hz, 1H), 6.43 (d, J = 15.0 Hz, 1H), 5.64 (br s, 1H), 4.44 (m, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.58 (s, 3H), 3.20 (ABX, J_{AX} = 4.3 Hz, J_{BX} = 6.5 Hz, J_{AB} = 13.0 HZ, 2H), 1.21 (s, 9H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.7, 163.9, 155.0, 149.5, 125.9, 80.5, 62.3, 54.6, 52.2, 49.0, 28.1, 14.0; IR ($CDCl_3$) cm^{-1} 3422, 3058, 2980, 1751, 1701, 1651, 1028.

Preparation of sulfoxides via oxidation of sulfide

A solution of a RX (methyl iodide, allyl bromide or (substituted) benzyl bromide, 1.2 eq), *N*,*N*-diisopropylethylamine (2.0 eq) and CH_2Cl_2 (5 mL) was stirred for 5 min at 0 °C, under N_2 gas. A solution of N-(*t*-butoxycarbonyl)-L-cysteine ethyl ester (1.0 eq) in CH_2Cl_2 (5 mL) was added to the reaction. The mixture was warmed to RT and stirred for 18 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexanes 10:90 to 30:70) to afford the cysteinyl sulfides in 48-94% yield (Scheme 2, **6a'**-**6k'**).

A solution of MCPBA dissolved in CH_2Cl_2 (6 mL) was added dropwise to a stirred solution of the cysteinyl sulfide (**6a'-6k'**) in CH_2Cl_2 (5 mL) at -70 °C for the 30 min. The reaction was washed with a saturated solution of $Na_2S_2O_3$ (10 mL). The organic layer was extracted and washed with $NaHCO_3$ (3 x 10 mL) and water (3 x 10 mL). The combine organic layers where dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexanes 50:50) to give desired sulfoxide as a mixture of diastereomers (**6a/7a-6k/7k**) in 55-79% yield (*dr* 0.6-1.8/1.0). (Scheme 2)

Data for the sulfoxide diastereomers is reported in the next section.

Preparation of Sulfoxides via Sulfenate Anion Alkylation. The general procedure and data for **Boc-Cys((O)-Bn)-OEt** (**6a/7a**) are in the main body of the paper. The scales and data for the remaining sulfoxides are presented below.

Synthesis of Boc-Cys((O)-4-MeBn)-OEt (6b/7b)

Sulfoxide ***E*-5** (187 mg, 0.536 mmol) in anhydrous THF (10 mL) was treated with a CySH (64.0 μL, 0.509 mmol)/*n*-BuLi (31.0 μL, 0.493 mmol) solution, followed by the addition of 4-methylbenzyl bromide (198 mg, 1.07 mmol) in THF (1 mL). Sulfoxides **6b/7b** (136 mg, 75 %) were recovered as a white solid after flash chromatography (EtOAc/hexanes 90:10 up to 50:50) as a mixture of diastereomers (*dr* 92:8). Recrystallization from EtOAc/hexanes yielded the major diastereomer. *Major* diastereomer: Mp: 149-150 °C; $[\alpha]_D^{25}$: -73.3 (*c* = 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 5H), 5.71 (br d, *J* = 7.2 Hz, 1H), 4.66 (br m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.05 (AB_q, *J* = 13.5 Hz, 2H), 3.09 (ABX, J_{AX} = 7.6 Hz, J_{BX} = 3.8 Hz, J_{AB} = 13.1

Hz, 2H), 1.42 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 155.3, 138.5, 130.0, 129.8, 126.0, 80.2, 62.0, 58.7, 51.7, 50.2, 28.2, 21.2, 14.0; IR (CH_2Cl_2) cm^{-1} 3363, 3271, 2979, 1741, 1714, 1515, 1367, 1025; Analysis calc'd for $C_{18}H_{27}NO_5S$: C, 58.56; H, 7.31; Found: C, 58.46; H, 7.18. HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 21.6 min. *Minor* diastereomer: partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (br d, *J* = 6.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.4, 155.3, 138.1, 129.9, 129.6, 126.0, 80.2, 62.2, 57.9, 52.6, 49.7, 28.2, 21.1, 14.0; HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 18.9 min.

Synthesis of Boc-Cys((O)-4-BrBn)-OEt (6c/7c)

Sulfoxide ***E*-5** (256 mg, 0.733 mmol) in anhydrous THF (10 mL) was treated with a CySH (88.0 μL, 0.697 mmol)/*n*-BuLi (42.0 μL, 0.675 mmol) solution, followed by the addition of 4-bromobenzyl bromide (366 mg, 1.47 mmol) in THF (1 mL). Sulfoxide **6c/7c** (209 mg, 72 %) were recovered as a white solid after flash chromatography (EtOAc/hexanes 90:10 up to 50:50) as a mixture of diastereomers (*dr* 92:8). Recrystallization from EtOAc/hexanes yielded the major diastereomer. *Major* diastereomer: Mp: 151-152 °C; $[\alpha]_D^{25}$: -25.5 (*c* = 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 5.68 (br d, *J* = 7.6 Hz, 1H), 4.57 (br m, 1H), 4.15 (m, 2H), 3.92 (AB_q, *J* = 11.2 Hz, 2H), 3.04 (ABX, J_{AX} = 7.7 Hz, J_{BX} = 3.8 Hz, J_{AB} = 13.0 Hz, 2H), 1.36 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2, 155.3, 132.1, 131.7, 128.4, 122.8, 80.4, 62.2, 57.9, 52.2, 50.0, 28.2, 14.0; IR (CH_2Cl_2) cm^{-1} 3264, 2979, 2931, 1734, 1713, 1488, 1216, 1165, 1013; Analysis calc'd for $C_{17}H_{24}BrNO_5S$: C, 47.04; H, 5.53; Found: C, 47.25; H, 5.37. HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 24.3 min. *Minor* diastereomer: partial ^{1}H NMR (400 MHz,

$CDCl_3$) δ 5.60 (br d, *J* = 6.1 Hz, 1H), 1.40 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.8, 155.2, 132.0, 131.7, 128.4, 122.7, 80.3, 62.0, 56.9, 53.0, 49.5, 28.1, 13.9; HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 23.0 min.

Synthesis of Boc-Cys((O)-3-MeOBn)-OEt (6d/7d)

Sulfoxide ***E*-5** (231 mg, 0.660 mmol) in anhydrous THF (10 mL) was treated with a CySH (79.0 μL, 0.628 mmol)/*n*-BuLi (38.0 μL, 0.608 mmol) solution, followed by the addition of 3-methoxybenzyl bromide (184 μL, 1.32 mmol). Sulfoxides **6d/7d** (122 mg, 52 %) were recovered as a white solid after flash chromatography (EtOAc/hexanes 90:10 up to 50:50) as a mixture of diastereomers (*dr* 91:9). Recrystallization from EtOAc/hexanes yielded the major diastereomer. *Major* diastereomer: Mp: 130-132 °C; $[\alpha]_D^{25}$: -57.8 (*c* =1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.9 Hz, 1H), 6.89-6.84 (m, 3H), 5.71 (br d, *J* = 7.7 Hz, 1H), 4.70 (br d *J* = 3.4 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.05 (AB_q, *J* = 13.0 Hz, 2H), 3.83 (s, 1H), 3.12 (ABX, J_{AX} = 7.7 Hz, J_{BX} = 3.6 Hz, J_{AB} = 13.0 Hz, 2H), 1.45 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 159.8, 155.2, 130.6, 130.0, 122.2, 115.4, 114.0, 80.2, 61.9, 59.0, 55.2, 52.0, 50.1, 28.1, 14.0; IR (CH_2Cl_2) cm^{-1} 3377, 2978, 2933, 1734 , 1713, 1600, 1491, 1269, 1165, 1045; Analysis cal'd for $C_{18}H_{27}NO_6S$ C, 56.08; H, 7.06; Found C, 55.91; H, 6.96. HPLC (10% iPrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 31.0 min. *Minor* diastereomer: partial ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (br d, *J* = 6.0 Hz, 1H), 4.61 (br d *J* = 5.6 Hz, 1H), 3.80(s, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.0, 159.8, 155.3, 131.5, 129.9, 122.2, 115.5, 113.9, 80.2, 61.9, 57.4, 55.2, 53.0, 49.7, 28.2, 14.0; HPLC (10% iPrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 27.3 min.

Synthesis of Boc-Cys((O)-3-NO_2Bn)-OEt (6e/7e)

Sulfoxide ***E*-5** (222 mg, 0.637 mmol) in anhydrous THF (10 mL) was treated with a CySH (76.0 μL, 0.604 mmol)/*n*-BuLi (36.0 μL, 0.585 mmol) solution, followed by the addition of 3-nitrobenzyl bromide (275 mg, 1.27 mmol) in THF (1 mL). Sulfoxides **6e/7e** (155 mg, 66 %) were recovered as a white solid after flash chromatography (EtOAc/ hexanes 90:10 up to 50:50) as a mixture of diastereomers (*dr* 89:11). Recrystallization from EtOAc/hexanes yielded the major diastereomer. *Major* diastereomer: Mp: 147-150 °C; $[\alpha]_D^{25}$: +13.7 (*c* = 1.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.22 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 5.83 (br d, *J* = 7.3 Hz, 1H), 4.66 (m, 1H), 4.26 (dq, *J* = 2.8 & 7.2 Hz, 2H), 4.19 (d, *J* = 13.1 Hz, 2H), 4.08 (d, *J* = 13.1 Hz, 2H), 3.23 (ABX, J_{AX} = 7.9 Hz, J_{BX} = 3.9 Hz, J_{AB} = 12.6 Hz, 2H), 1.46 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.1, 155.3, 148.3, 136.3, 131.9, 129.8, 125.0, 123.4, 80.5, 62.4, 57.4, 52.9, 49.8, 28.1, 14.0; IR (CH_2Cl_2) cm^{-1} 3338, 2982, 2933, 1734, 1701, 1529, 1351, 1163, 1026, 808; Analysis cal'd for $C_{17}H_{24}N_2O_7S$ C, 50.99; H, 6.04; Found C, 51.06; H, 5.95. HPLC (10% *i*PrOH/hexanes, gradient flow rate, 0.4 mL/min up to 1 mL/min, OJ-H Column): 63.0 min. *Minor* diastereomer: partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (br d, *J* = 7.1 Hz, 1H), 1.43 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.6, 155.2, 148.3, 136.3, 132.1, 129.6, 125.0, 123.2, 80.4, 62.1, 56.7, 54.0, 49.5, 28.1, 13.9; HPLC (10% *i*PrOH/hexanes, gradient flow rate, 0.4 mL/min up to 1 mL/min, OJ-H Column): 53.7 min.

Synthesis of Boc-Cys((O)-4-CNBn)-OEt (6f/7f)

Sulfoxide ***E*-5** (228 mg, 0.653 mmol) in anhydrous THF (10 mL) was treated with a CySH (78.0 μL, 0.620 mmol)/*n*-BuLi (37.0 μL, 0.600 mmol) solution, followed by the addition of α-Bromo-p-tolunitrile (256 mg, 1.31 mmol) in THF (1 mL). Sulfoxides **6f/7f** (169 mg, 74 %) were recovered as a white solid after flash chromatography (EtOAc/ hexanes 90:10 up to 50:50) as a mixture of diastereomers (*dr* 89:11). Recrystallization from EtOAc/hexanes yielded the major diastereomer. *Major* diastereomer: Mp: 127-130 °C; $[\alpha]_D^{25}$: +15.6 (*c* = 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 5.74 (br d, *J* = 7.6 Hz, 1H), 4.64 (br m, 1H), 4.24 (dq, *J* = 5.2 & 7.1 Hz, 2H), 4.13 (d, *J* = 13.0 Hz, 1H), 4.05 (d, *J* = 13.0 Hz, 2H), 3.18 (ABX, J_{AX} = 8.4 Hz, J_{BX} = 3.6 Hz, J_{AB} = 13.0 Hz, 2H), 1.36 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.1, 155.2, 135.0, 132.5, 130.9, 118.2, 112.4, 80.5, 62.3, 62.1, 57.9, 52.7, 49.7, 28.1, 14.0; IR (CH_2Cl_2) cm^{-1} 3356, 3276, 2980, 2230, 1742, 1711, 1607, 1506, 1165, 1024, 854; Analysis cal'd for $C_{18}H_{24}N_2O_5S$ C, 56.82; H, 6.36; Found C, 57.04; H, 6.47. HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 69.8 min. *Minor* diastereomer partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (br d, *J* = 6.6 Hz, 1H), ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.6, 155.2, 135.3, 132.3, 131.0, 118.3, 112.2, 80.6, 62.3, 57.2, 53.8, 49.5, 28.1, 13.9; HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 54.0 min.

Synthesis of Boc-Cys((O)-2-CNBn)-OEt (6g/7g)

Sulfoxide ***E*-5** (241 mg, 0.690 mmol) in anhydrous THF (10 mL) was treated with a CySH (83.0 μL, 0.656 mmol)/*n*-BuLi (40.0 μL, 0.636 mmol) solution, followed by the addition of α-Bromo-o-tolunitrile (270 mg, 1.38 mmol) in THF (1 mL). Sulfoxides **6g/7g** (129 mg, 53 %) were recovered as a white solid after flash chromatography (EtOAc/ hexanes 90:10 up to 50:50) as a mixture of diastereomers (*dr* 89:11). Recrystallization from EtOAc/hexanes yielded the

major diastereomer. *Major* diastereomer: Mp: 147-150 °C; $[\alpha]_D^{25}$: +26.8 (*c* = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.7 & 1.0 Hz, 1H), 7.65-7.50 (m, 3H), 5.74 (br d, *J* = 7.0 Hz, 1H), 4.71 (br m, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.18 (d, *J* = 13.2 Hz, 1H), 3.24 (ABX, J_{AX} = 8.0 Hz, J_{BX} = 3.8 Hz, J_{AB} = 13.2 Hz, 2H), 1.45 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.1, 155.2, 133.5, 133.1, 131.7, 129.0, 117.3, 113.4, 80.3, 62.1, 56.5, 53.1, 49.8, 28.1, 14.0; IR (CH_2Cl_2) cm^{-1} 3359, 2980, 2933, 2227, 1736, 1714, 1517, 1392, 1165, 1029, 862, 772; Analysis cal'd for $C_{18}H_{24}N_2O_5S$ C, 56.82; H, 6.36; Found C, 56.56; H, 6.54. HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 47.9 min. *Minor* diastereomer: partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (br d, *J* = 5.8 Hz, 1H), 1.43 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.7, 155.2, 133.7, 133.1, 131.6, 128.9, 117.3, 113.6, 80.5, 62.2, 56.0, 53.6, 49.6, 28.2, 13.9; HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 38.9 min.

Synthesis of Boc-Cys((O)-2-BrBn)-OEt (6h/7h)

Sulfoxide ***E*-5** (0.132 mg, 0.378 mmol) in anhydrous THF (10 mL) was treated with a CySH (45.0 μL, 0.356 mmol)/*n*-BuLi (103 μL, 0.347 mmol) solution, followed by the addition of 2-Bromobenzylbromide (188 mg, 755 mmol) in THF (1 mL). Sulfoxides **6h/7h** (110 mg, 73 %) were recovered as a white solid after flash chromatography (EtOAc/hexanes 90:10 to 50:50) as a mixture of diastereomers (*dr* 95:5). Recrystallization from EtOAc/hexanes yielded the major diastereomer as a white solid. *Major* diastereomer: Mp: 124-125 °C; $[\alpha]_D^{25}$: -24.4 (*c* = 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.31-7.16 (br m, 3H), 5.60 (br d, *J* = 7.7 Hz, 1H), 4.64 (br m, 1H), 4.24 (d, *J* = 12.9 Hz, 1H), 4.17 (m, 3H), 3.16 (ABX, J_{AX} = 7.7 Hz, J_{BX} = 3.7 Hz, J_{AB} = 13.1Hz, 2H), 1.36 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6

MHz, $CDCl_3$) δ 170.2, 155.4, 133.3, 132.5, 130.3, 129.8, 128.0, 125.1, 80.4, 62.1, 59.3, 52.5, 50.3, 28.3, 14.1; IR (CH_2Cl_2) cm^{-1} 3356, 3268, 2979, 1742, 1713, 1515, 1367, 1166, 1027, 763; Analysis cal'd for $C_{17}H_{24}BrNO_5S$ C, 47.01; H, 5.57; Found C, 47.17; H, 5.66. HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 22.7 min. *Minor* diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 1H), 7.37 (m, 1H), 7.29 (m, 1H), 7.19 (m, 1H), 5.54 (d, J = 7.7 Hz, 1H), 4.64 (br m, 1H), 4.24 (d, J = 12.9 Hz, 1H), 4.17 (m, 3H), 3.27 (ABX, J_{AX} = 7.7 Hz, J_{BX} = 3.7 Hz, J_{AB} = 13.1Hz, 2H), 1.36 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.9, 155.0, 133.1, 132.4, 130.0, 129.9, 127.7, 125.0, 80.3, 62.0, 58.6, 52.9, 49.7, 28.1, 13.9; HPLC (10% *i*PrOH/hexanes, 0.4 mL/min flow rate, OJ-H Column): 18.9 min.

Synthesis of Boc-Cys((O)-2-CHOBn)-OEt (6i/7i)

Sulfoxide ***E*-5** (280 mg, 0.800 mmol) in anhydrous THF (10 mL) was treated with a CySH (88.0 μL, 0.758 mmol)/*n*BuLi (150 μL, 0.758 mmol) solution, followed by the addition of 2–(bromomethyl)benzaldehyde (300 mg, 1.51 mmol) in THF (1 mL). Sulfoxide (**6i/7i**) (145 mg, 58 %) was recovered as a white solid after flash chromatography (EtOAc/hexanes 90:10 to 50:50) as a mixture of diastereomers. (*dr* 93:7) Recrystallization from EtOAc/hexanes yielded the major diastereomer. *Major* diastereomer: Mp: 94-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.51 (br m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 5.82 (br d, J = 8.2 Hz, 1H), 4.75 (d, J = 12.4 Hz, 1H), 4.63 (br m, 1H), 4.15 (d, J = 12.4 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.19 (ABX, J_{AX} = 8.3 Hz, J_{BX} = 3.2 Hz, J_{AB} = 12.9 Hz, 2H), 1.34 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 193.2, 170.3, 155.3, 135.3, 133.8, 133.77, 133.1, 131.7, 129.0, 80.0, 61.9, 56.3, 52.6, 49.9, 28.0, 13.9; IR (CH_2Cl_2) cm^{-1} 3418, 1691, 1634,

1524, 1161, 1021, 774; Analysis cal'd for $C_{18}H_{25}NO_6S$ C, 56.38; H, 6.57; Found C, 56.42; H, 6.70. HPLC (10% iPrOH/hexanes, 1.0 mL/min flow rate, OJ-H Column): 16.5 min. *Minor* diastereomer: partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 5.72 (br d, *J* = 5.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ193.0, 169.9, 155.2, 134.9, 133.9, 133.7, 133.1, 131.5, 128.9, 80.0, 61.7, 55.7, 53.2, 49.6, 28.0, 14.0; HPLC (10% iPrOH/hexanes, 1.0 mL/min flow rate, OJ-H Column): 13.7 min.

Synthesis of Boc-Cys((O)-Me)-OEt (6j/7j)

Sulfoxide ***E*-5** (260 mg, 0.745 mmol) in anhydrous THF (10 mL) was treated with a CySH (86.0 μL, 0.745 mmol)/*n*-BuLi (476.0 μL, 0.760 mmol) solution, followed by the addition of methyl iodide (37 mg, 0.745 mmol) in THF (1 mL). Sulfoxides **6j/7j** (97 mg, 51 %) were recovered as an oil, after flash chromatography (EtOAc/ hexanes 90:10 up to 50:50) as a mixture of diastereomers (*dr* 83:17). Recrystallization from EtOAc/hexanes yielded the major diastereomer as a solid. *Major* diastereomer: Mp: 100-101 °C; $[\alpha]_D^{25}$: -75.2 (*c* = 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (br d, *J* = 10.4 Hz, 1H), 4.72 (br m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.22 (m, 2H), 2.73(s, 3H), 1.46 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2, 155.4, 80.8, 62.4, 56.7, 49.7, 39.1, 28.3, 14.2; IR (CH_2Cl_2) cm^{-1} 3370, 2979, 2931, 1742, 1713, 1522, 1165, 1026. Analysis cal'd for $C_{11}H_{21}NO_5S$ C, 47.29; H, 7.58; Found C, 47.40; H, 7.43. *Minor* diastereomer: partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (br d, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ170.2, 155.4, 80.8, 62.1, 56.7, 50.3, 39.4, 28.3, 14.2.

Synthesis of Boc-Cys((O)- prop-2-ene)-OEt (6k/7k)

Sulfoxide ***E*-5** (184 mg, 0.529 mmol) in anhydrous THF (10 mL) was treated with a CySH (63.0 μL, 0.502 mmol)/*n*-BuLi (102 μL, 0.486 mmol) solution, followed by the addition of allyl bromide (91.0 μL, 1.06 mmol). Sulfoxides **6k/7k** (87 mg, 60 %) were recovered as oil after flash chromatography (EtOAc/ hexanes 90:10 to 50:50) as a mixture of diastereomers (*dr* 83:17). Recrystallization from EtOAc/hexanes yielded the major diastereomer as a white solid (20 %). *Major* diastereomer: Mp: 78-80 °C; $[\alpha]_D^{25}$: -85.0 (*c* = 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97-5.83 (m, 1H), 5.73 (br d, *J* = 8.2 Hz, 1H), 5.50-5.39 (m, 2H), 4.68 (br m, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.54 (ABX, J_{AX} = 8.3 Hz, J_{BX} = 3.2 Hz, J_{AB} = 12.9 Hz, 2H), 3.19 (ABX, J_{AX} = 7.5 Hz, J_{BX} = 7.3 Hz, J_{AB} = 12.9 Hz, 2H), 1.46 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2, 155.2, 125.1, 124.0, 80.2, 62.0, 56.4, 52.0, 50.0, 28.2, 14.0; IR (CH_2Cl_2) cm^{-1} 3356, 3274, 2979, 2932, 1715, 1637, 1523, 1367, 1167, 1026. Analysis cal'd for $C_{13}H_{23}NO_5S$ C, 51.13; H, 7.59; Found C, 51.30; H, 7.79. *Minor* diastereomer: partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (br d, *J* = 5.2 Hz, 1H), 4.62 (br m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ169.8, 155.0, 125.1, 123.7, 80.0, 61.6, 55.4, 51.8, 49.2, 28.0, 14.1.

S-Benzyl *(R)*-cysteinol (*R*)-sulfoxide (8)

To a solution of *N*-(*tert*-butyloxycarbonyl)-*S*-methyl-*S*-oxo-L-cysteine ethyl ester **6a/7a** (860 mg, 2.42 mmol) in THF (20 mL) cooled at 0°C was added dropwise a solution of $LiBH_4$ in THF (2 M, 1.81 mL, 3.63 mmol) and the resulting mixture was stirred for 30 min at rt. A few drops of H_2O were added and the was solvent evaporated under vacuum. Flash chromatography (ethyl acetate/methanol 80:20) of the crude reaction mixture afforded *N*-(*tert*-butyloxycarbonyl)-*S*-methyl-*S*-oxo-L-cysteinol as a white solid (542 mg, 72%) and as a mixture of diastereomers (*dr*

92:8, based on 600 MHz ^{1}H NMR). Mp: 179-180 °C. Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 5.43 (br d, J = 6.2 Hz, 1H), 4.06 (br s, 3H), 3.95-3.86 (m, 1H), 3.80-3.72 (m, 1H), 3.21 (s, 1H), 3.05 (ABX, J_{AX} = 6.4 Hz, J_{BX} = 4.6 Hz, J_{AB} = 13.6 Hz, 1H), 2.84 (ABX, J_{AX} = 6.4 Hz, J_{BX} = 6.2 Hz, J_{AB} = 13.5 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6, 130.1, 129.3, 129.0, 128.6, 80.1, 64.1, 58.7, 55.0, 49.6, 28.3; Mixture of isomers: IR (CH_2Cl_2) cm^{-1} 3441 (broad), 2981, 2863, 1639, 1520, 1458, 1394, 1368, 1315, 1249, 1160, 1069, 1043, 1016, 1002. To a solution of *N*-(*tert*-butyloxycarbonyl)-*S*-benzyl-*S*-oxo-L-cysteinol (200 mg, 0.638 mmol) in CH_2Cl_2 (5 mL) cooled at 0°C, was added trifluoroacetic acid (2 ml) and the reaction mixture was allowed to warm to rt for 2h. The solvent evaporated under vacuum and the residue was dissolved in ethyl acetate, which was extracted with aq. $NaHCO_3$. Aqueous layer was evaporated under vacuum to give a mixture of desired compound and inorganic salts. Flash chromatography (4:1 EtOAc/MeOH and then 1:1) afforded a white crystalline powder consisting of impure diasteromers **8**. This white crystalline powder was dissolved in acetone and filtered and washed with acetone. Filtrate was evaporated to give **8** (80 mg, 59% yield) as a mixture of diastereomers (*dr* 92:8, based on ^{1}H NMR). Recrystallization from ethanol/CH_2Cl_2 yielded pure (R_C,R_S)-**8**. Mp: 126-127 °C; lit.[2] mp. 128-129 °C. $[\alpha]_D^{25}$: +16.2 (c = 0.9, EtOH); lit.[2] $[\alpha]^{20}_D$: +16 (c = 0.9, EtOH).

Preparation of Sulfoxides via Sulfenate Anion Alkylation in the Presence of 12-crown-4. General Procedure.

A solution of cyclohexyl mercaptan (0.95 eq.) and *n*-BuLi (0.92 eq.) in anhydrous THF (2 mL), under N_2 gas, was stirred at RT for 5 min and was then cooled to -78 °C. The CySLi solution

was transferred via syringe into the solution of the α,β-unsaturated sulfoxide ***E*-5** (1 eq.) stirring in anhydrous THF (10 mL) at -78 °C, under N_2 gas. 12-Crown-4 (0.3-2.5 eq. in separate experiments) was added almost immediately and the reaction was stirred for 1 min followed by the addition of benzyl bromide (2 eq.). The reaction was left to stir overnight, slowly warming to room temperature. The solution was evaporated under vacuum or concentrated by N_2 gas and the residue was purified by flash chromatography (EtOAc/hexanes 90:10 to 50:50) as a mixture of diastereomers (*dr* 92:8 to 85:15).[3]

References and Notes:

1. Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *J. Org. Chem.* **2005**, *70*, 1986-1992.

2. Petra, D.G.I.; Kamer, P.C.J.; Spek, A.L.; Schoemaker, H.E.; van Leeuwen, P.W.N.M. *J. Org. Chem.* **2000,** *65,* 3010-3017.

3. For diastereomeric ratio of individual experiments see Table 2 in the article.

NMR spectra

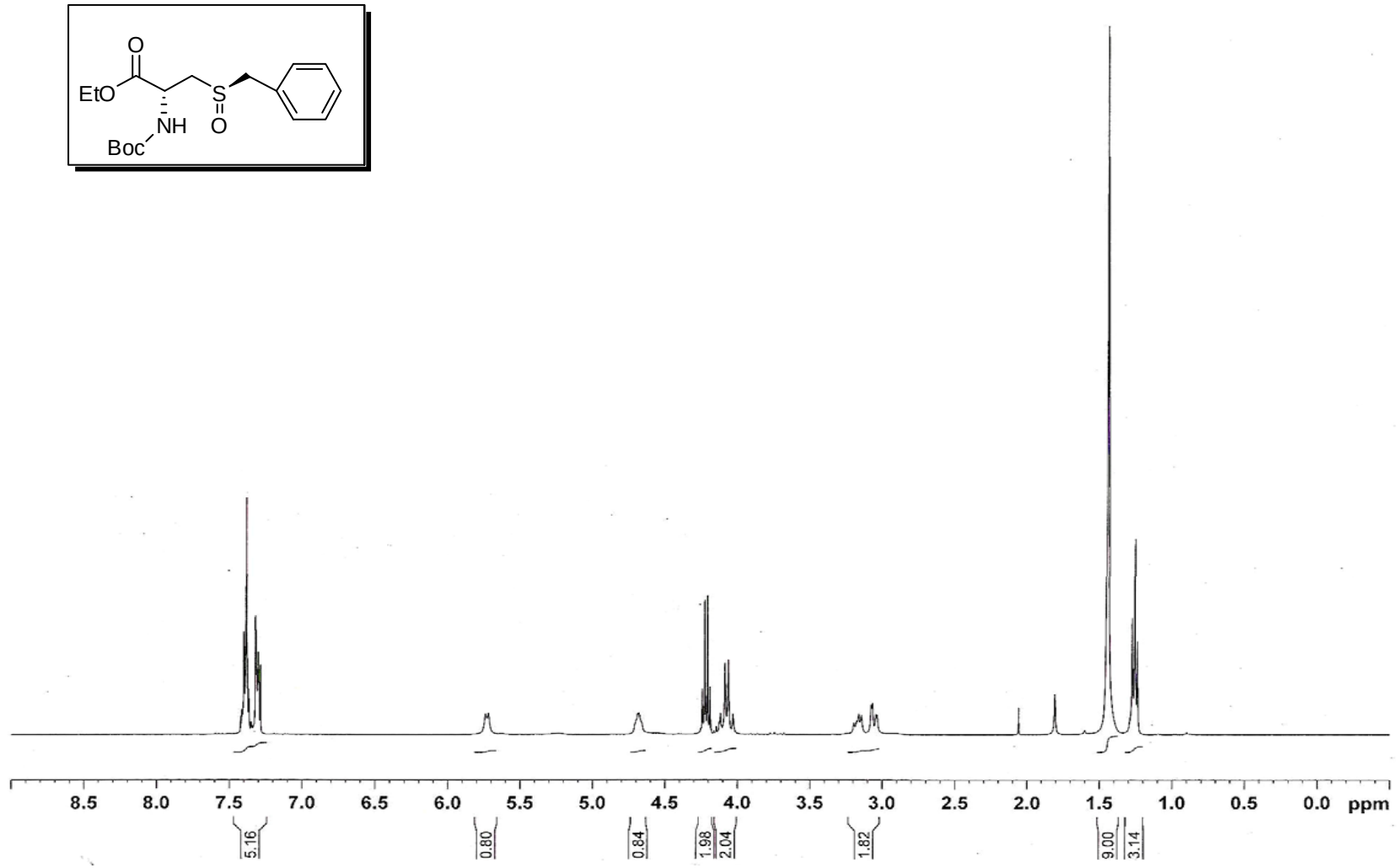


Figure 1. ^{1}H NMR spectrum of **6a** in $CDCl_3$ (400 MHz)

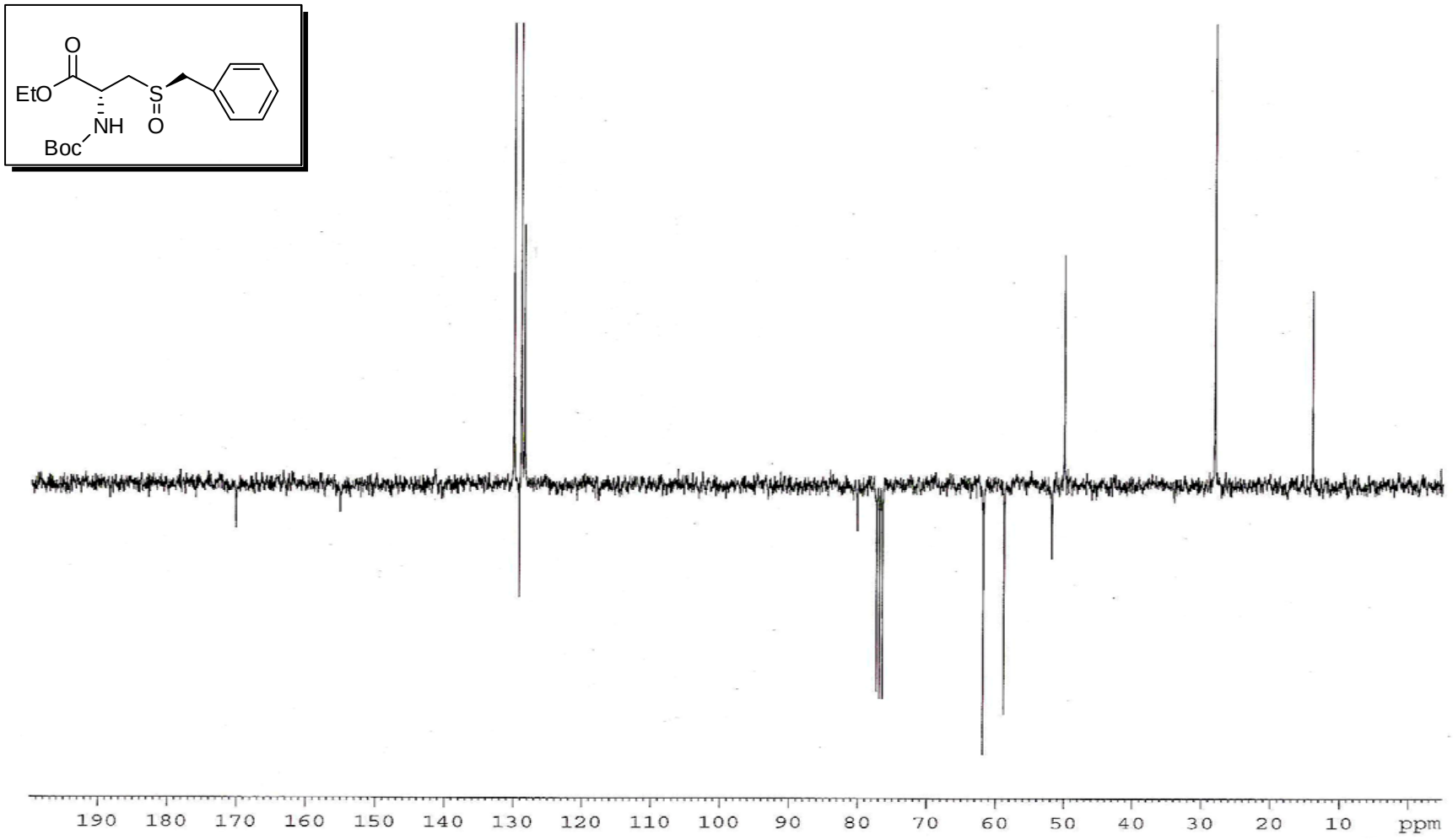


Figure 2. ^{13}C (JMOD) NMR spectrum of **6a** in $CDCl_3$ (100.6 MHz)

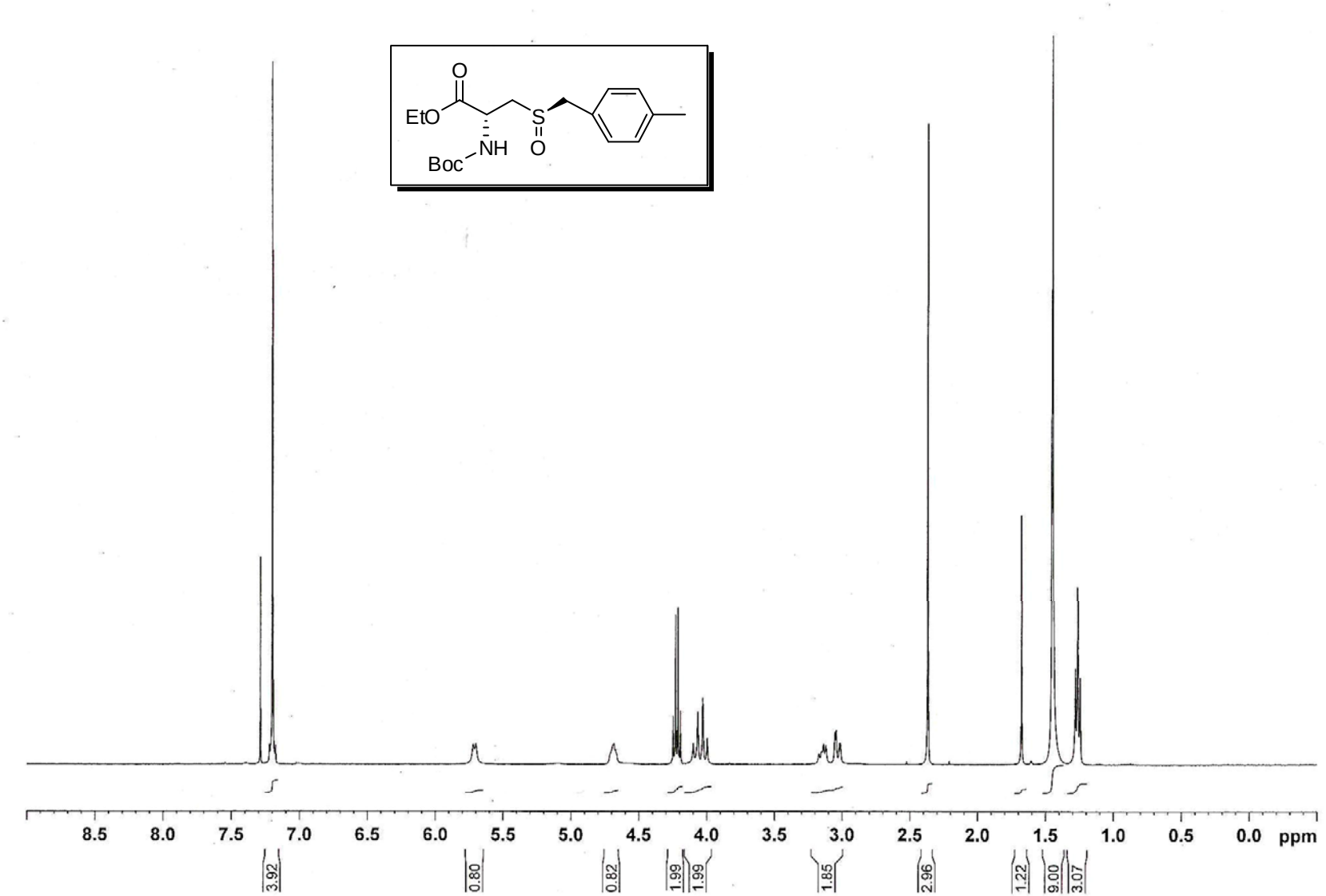


Figure 3. ^{1}H NMR spectrum of **6b** in $CDCl_3$ (400 MHz)

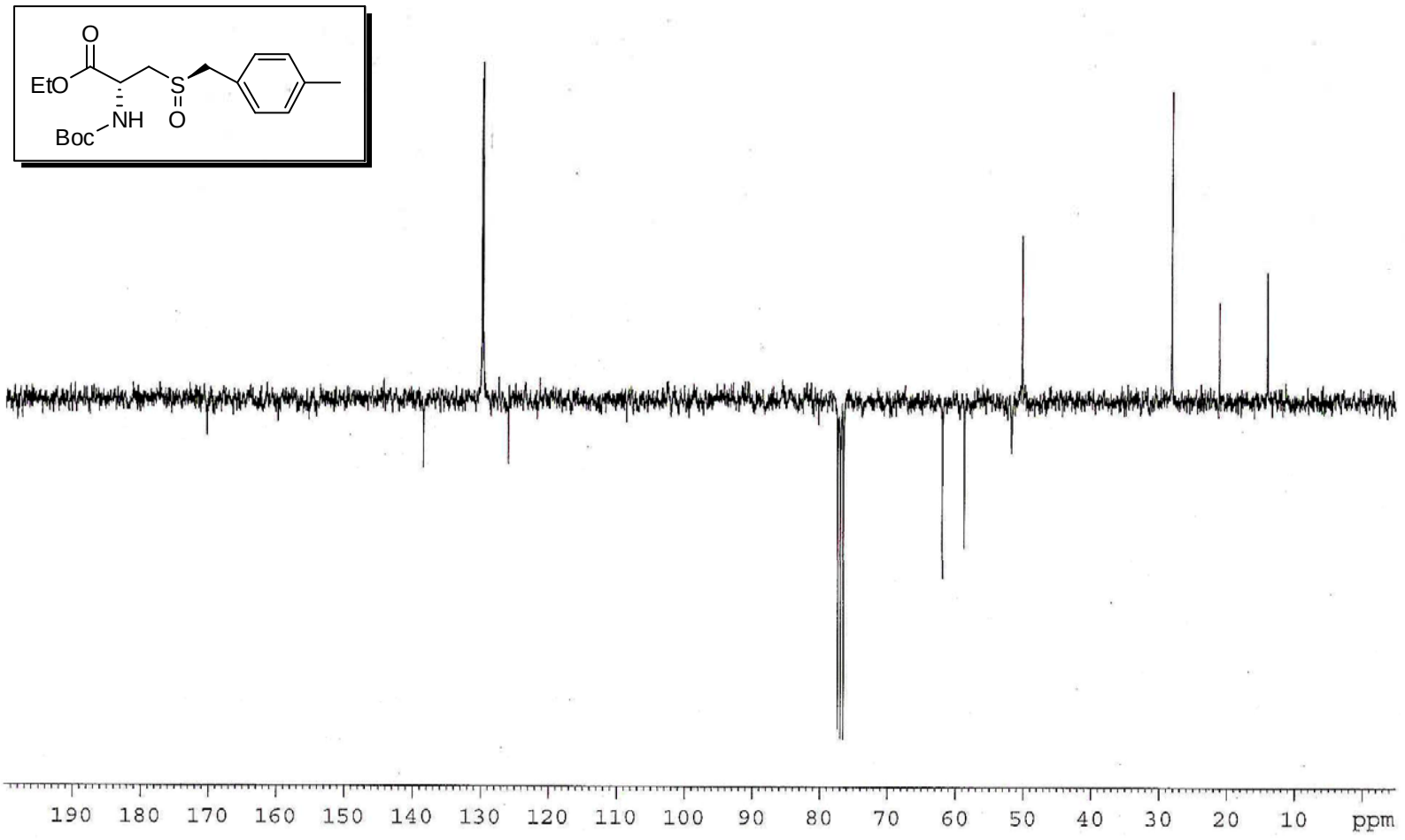


Figure 4. ^{13}C (JMOD) NMR spectrum of **6b** in $CDCl_3$ (100.6 MHz)

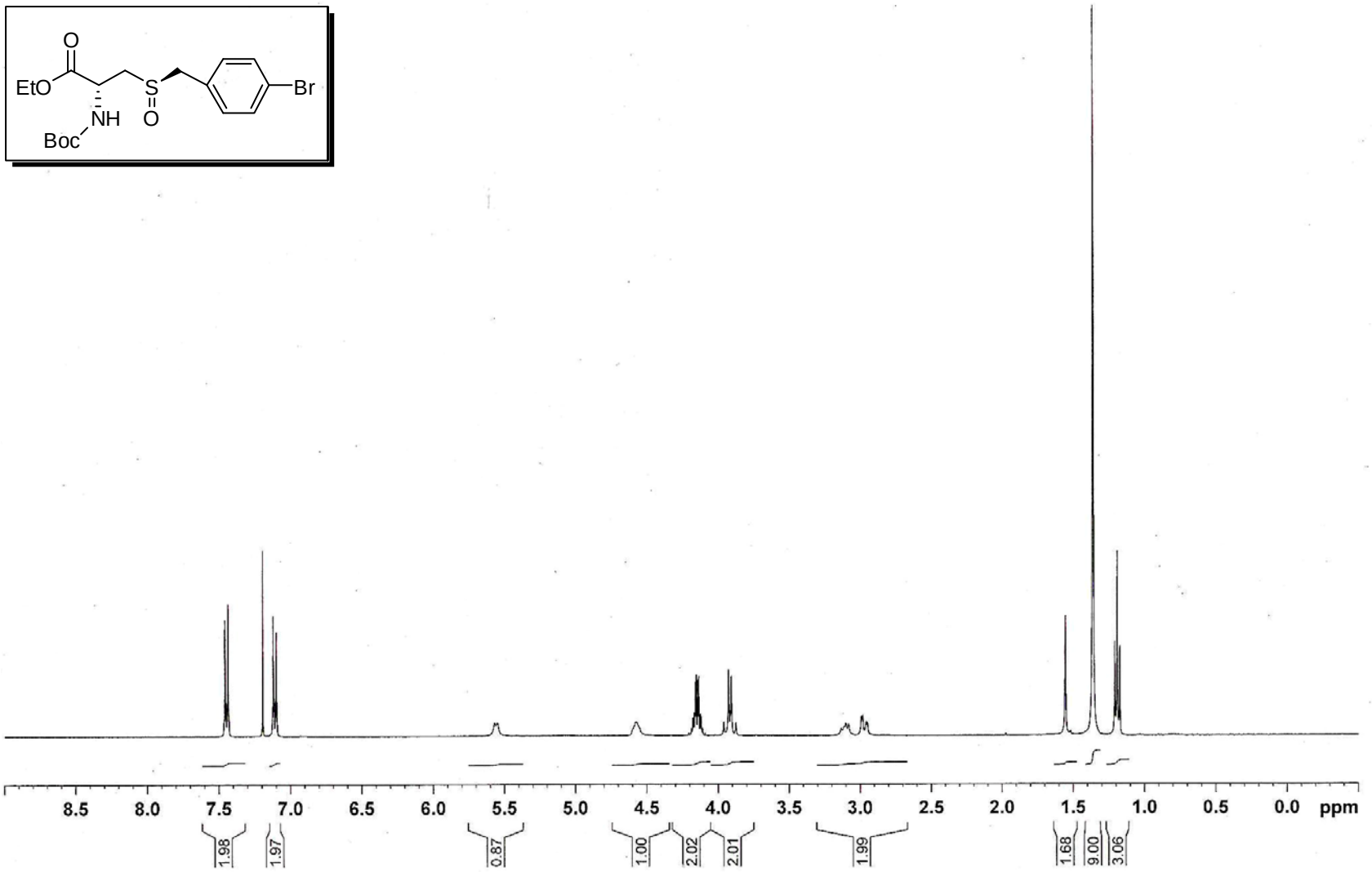


Figure 5. ^{1}H NMR spectrum of **6c** in $CDCl_3$ (400 MHz)

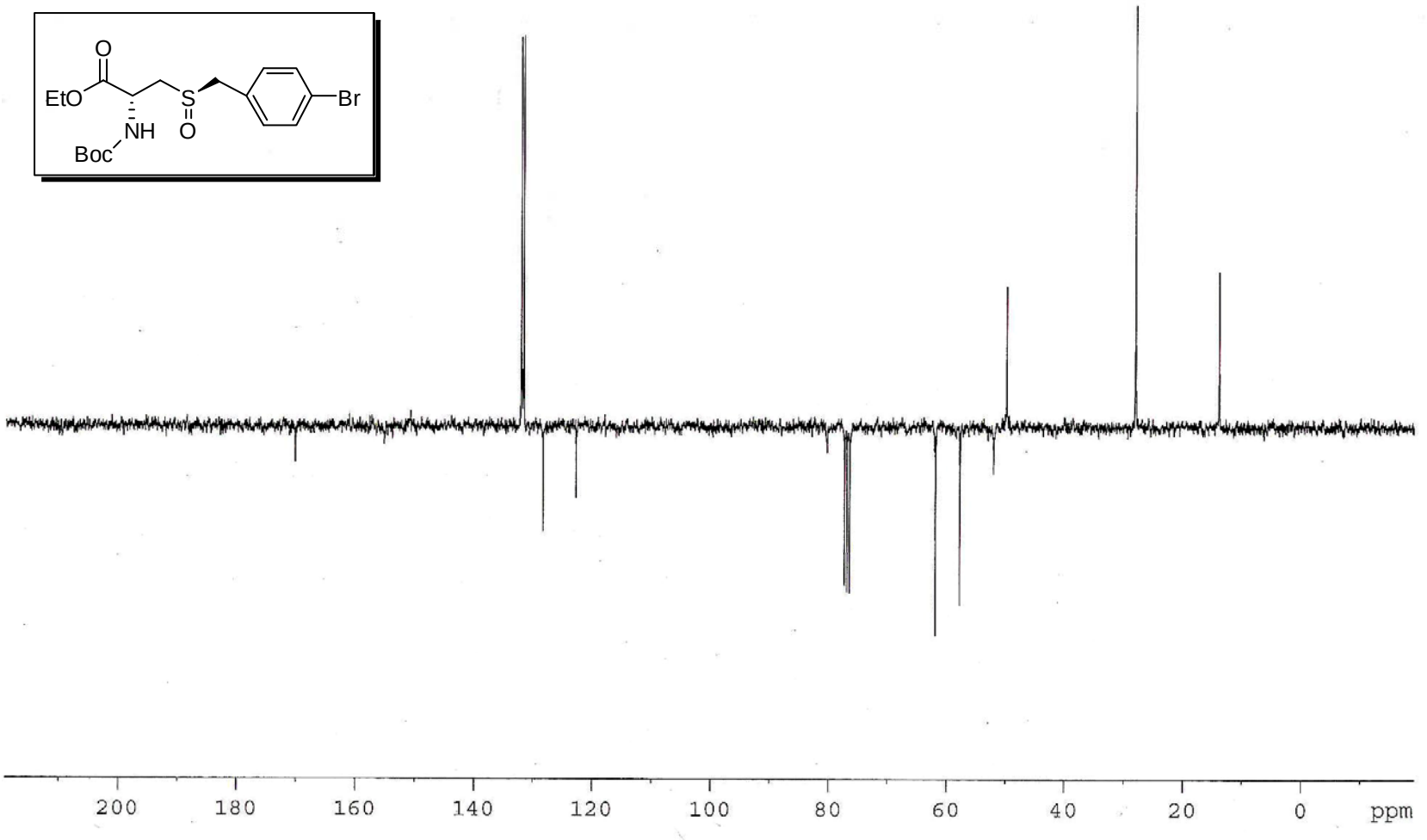


Figure 6. ^{13}C (JMOD) NMR spectrum of **6c** in $CDCl_3$ (100.6 MHz)

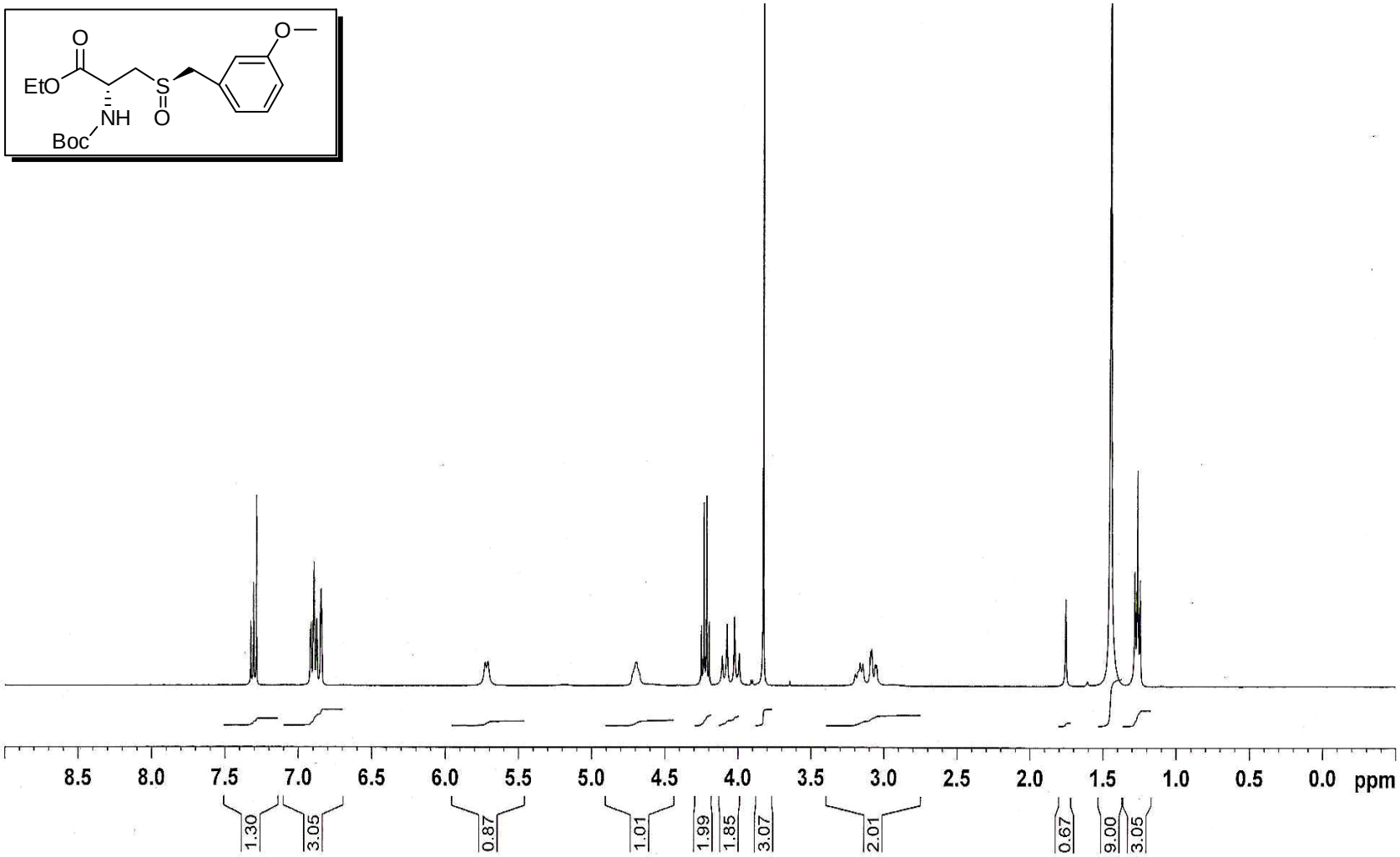


Figure 7. ^{1}H NMR spectrum of **6d** in $CDCl_3$ (400 MHz)

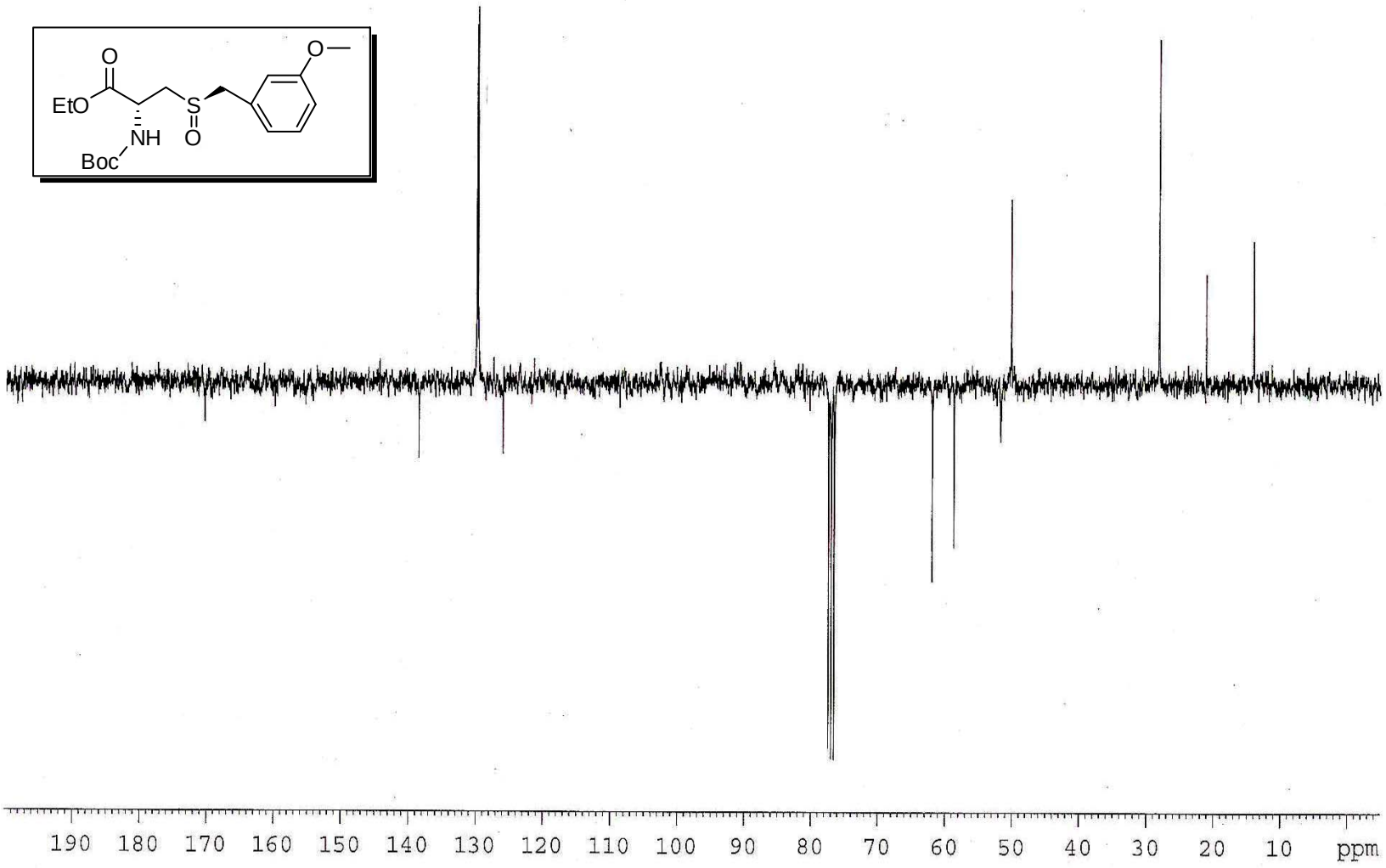


Figure 8. ^{13}C (JMOD) NMR spectrum of **6d** in $CDCl_3$ (100.6 MHz)

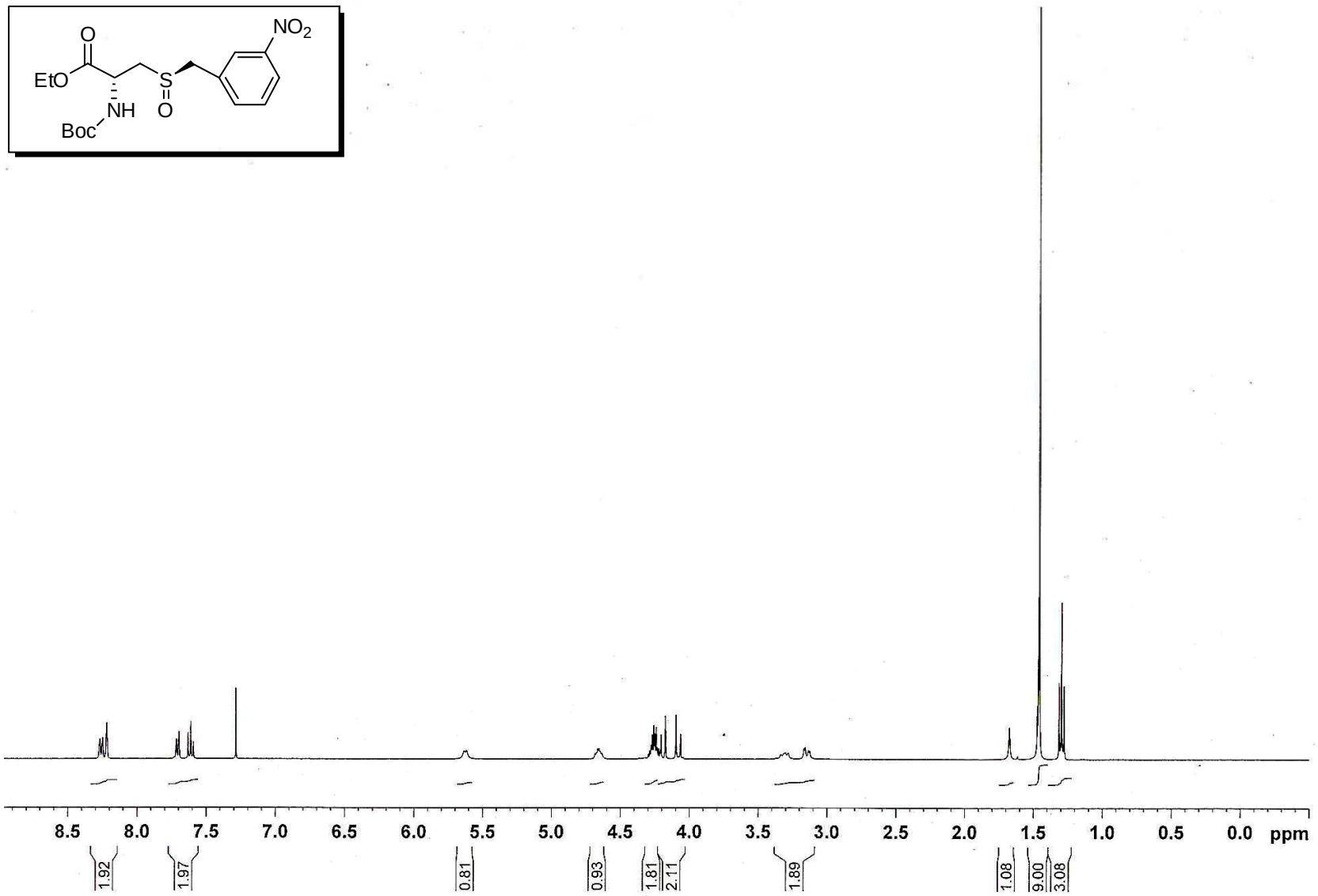


Figure 9. ^{1}H NMR spectrum of **6e** in $CDCl_3$ (400 MHz)

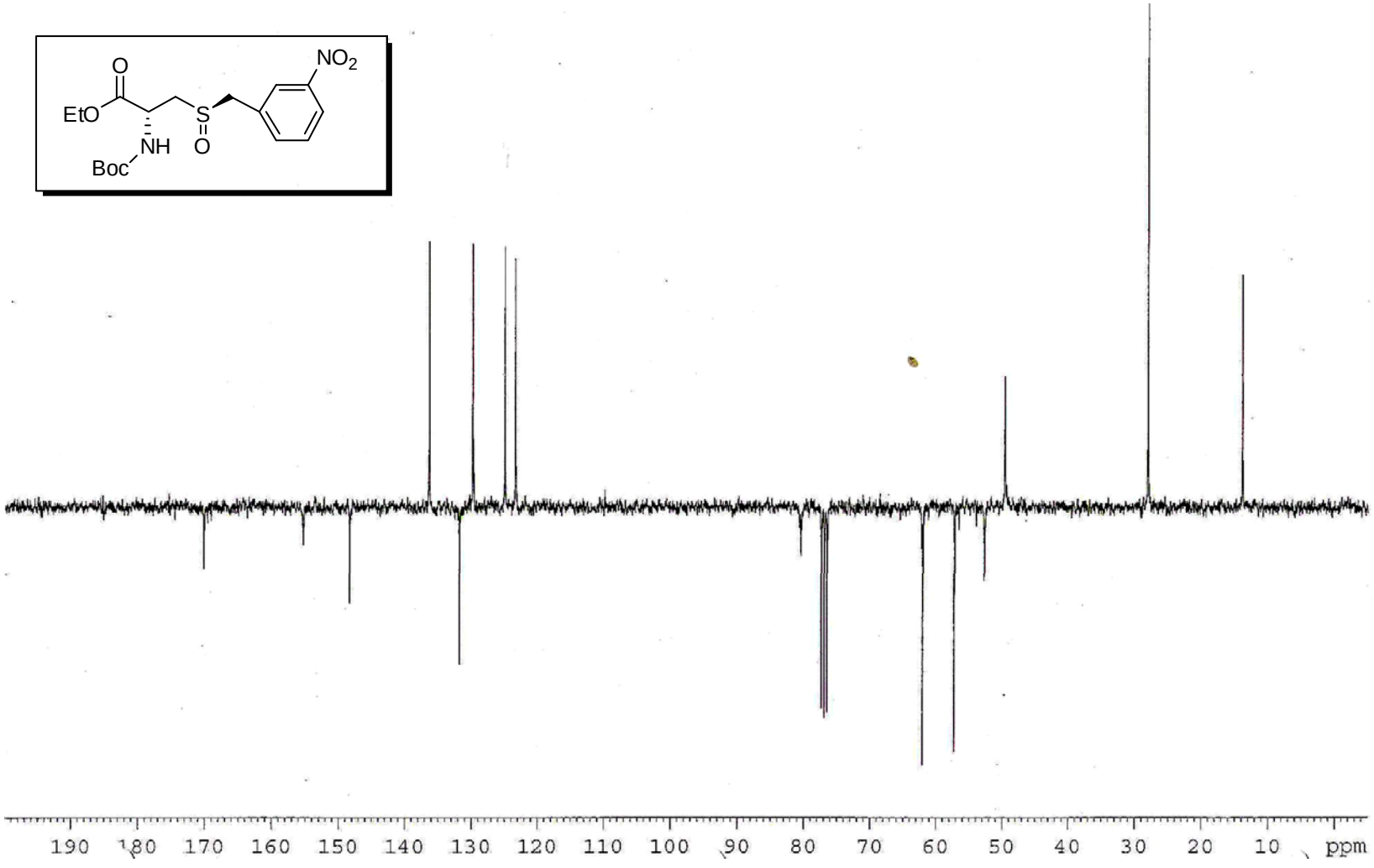


Figure 10. ^{13}C (JMOD) NMR spectrum of **6e** in $CDCl_3$ (100.6 MHz)

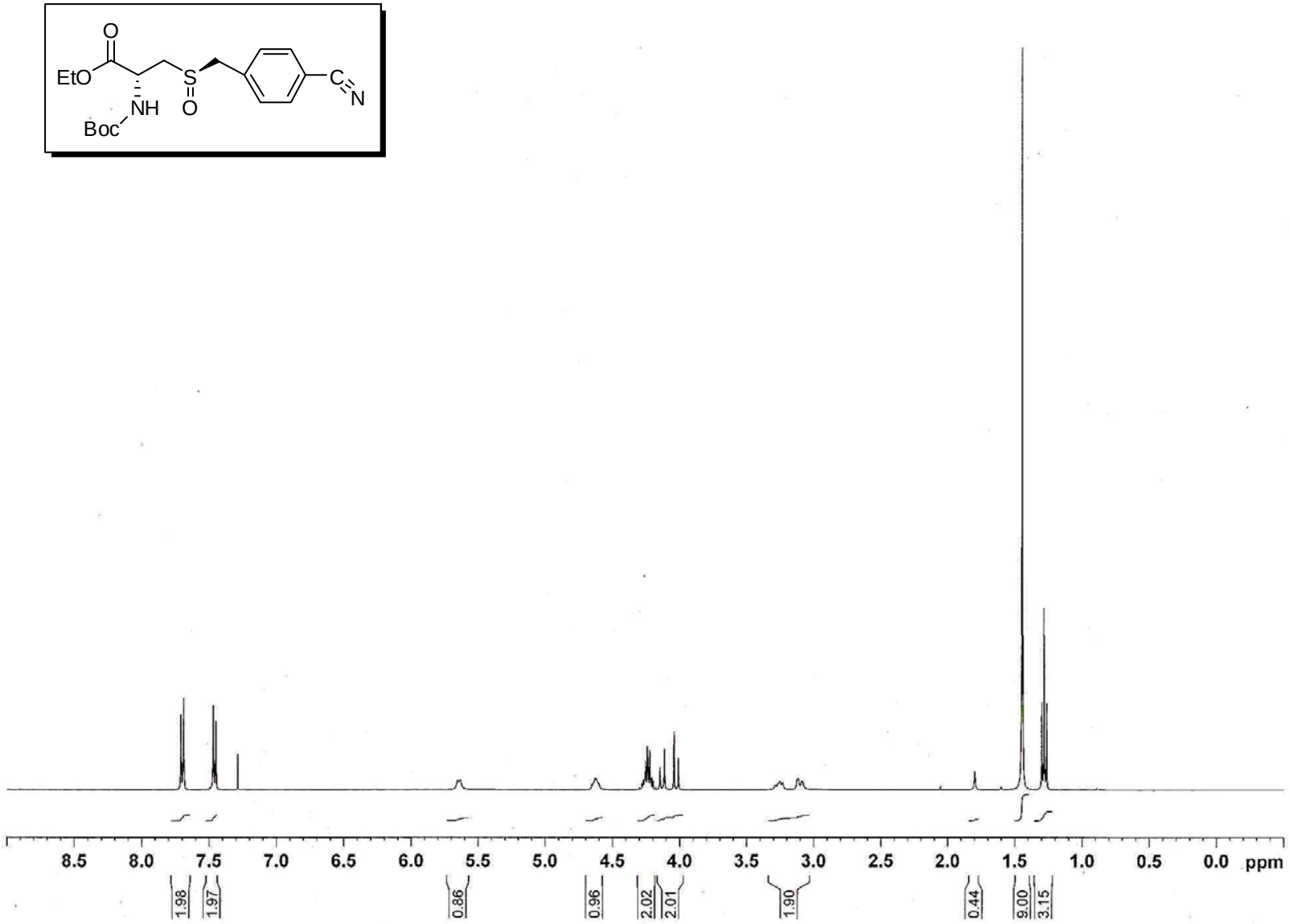


Figure 11. ^{1}H NMR spectrum of **6f** in $CDCl_3$ (400 MHz)

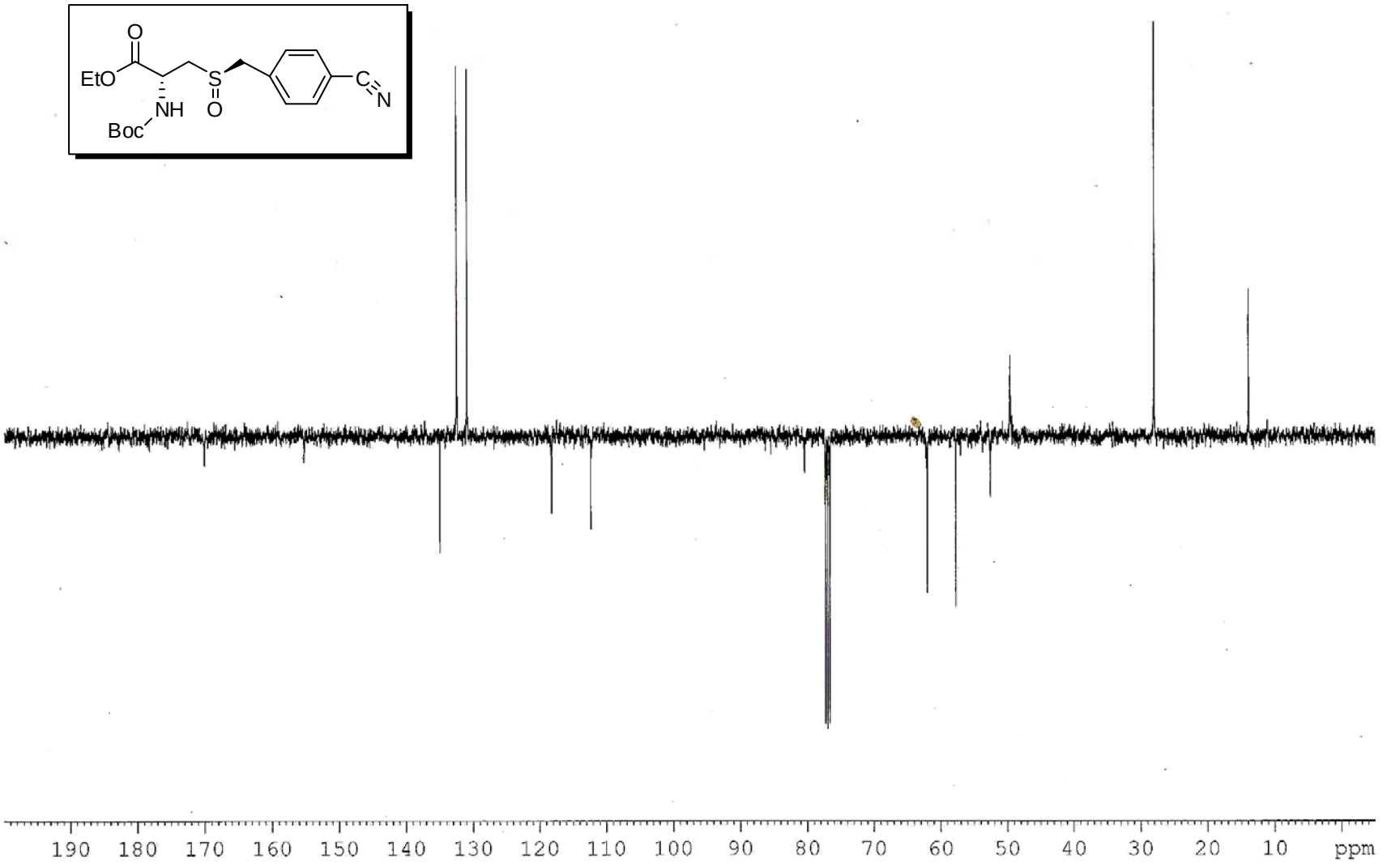


Figure 12. ^{13}C (JMOD) NMR spectrum of **6f** in $CDCl_3$ (100.6 MHz)

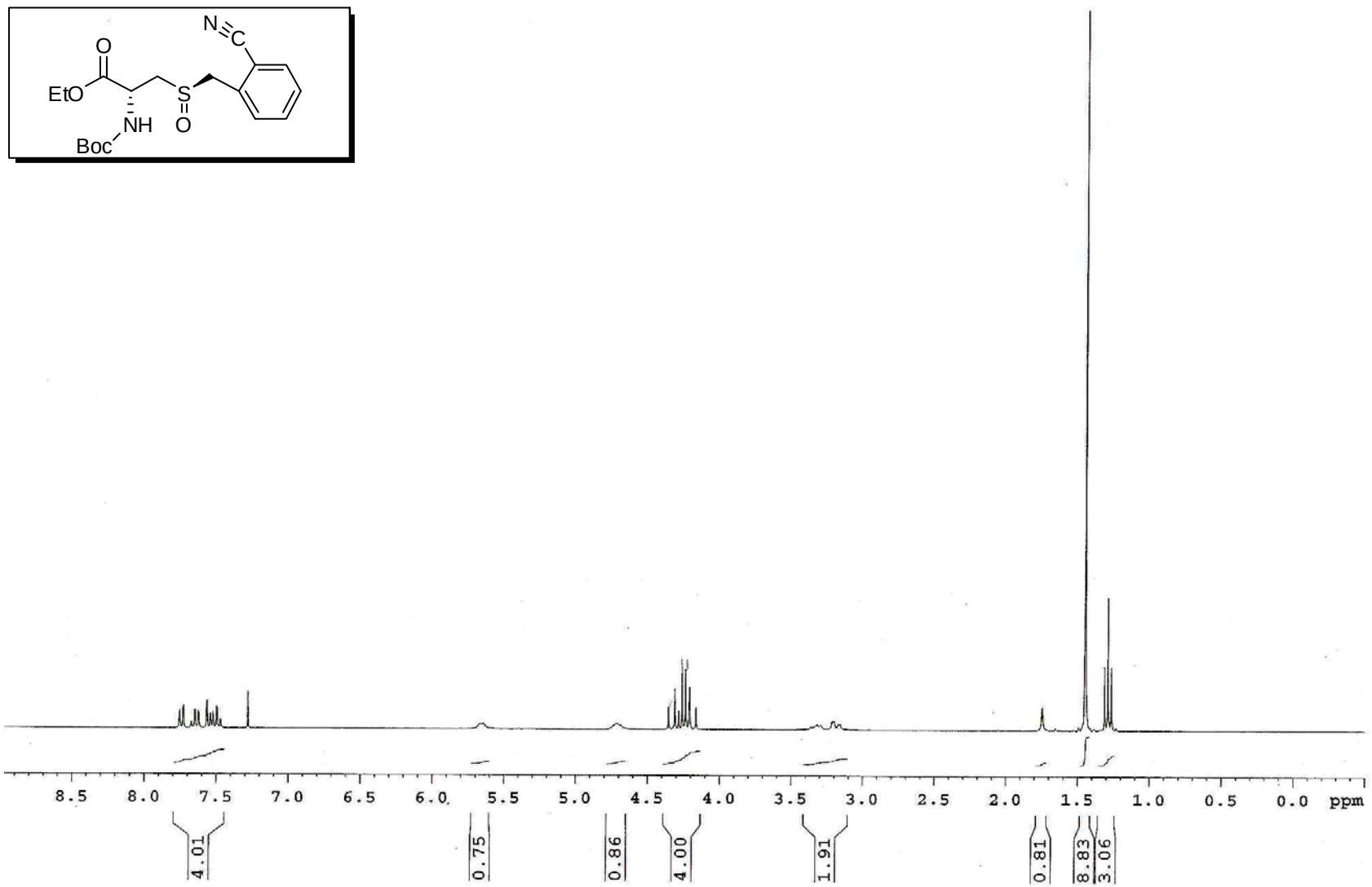


Figure 13. ^{1}H NMR spectrum of **6g** in $CDCl_3$ (400 MHz)

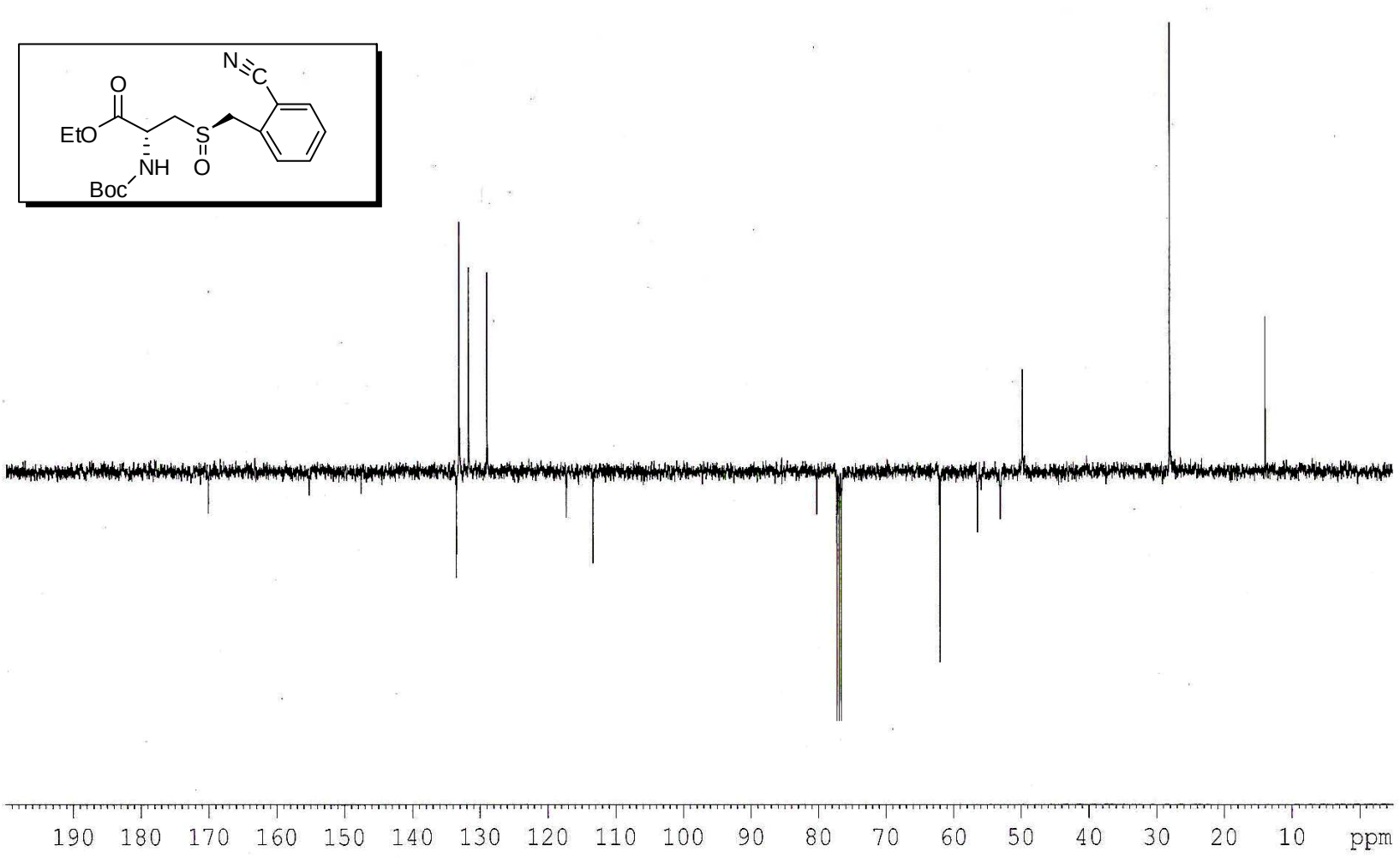


Figure 14. ^{13}C (JMOD) NMR spectrum of **6g** in $CDCl_3$ (100.6 MHz)

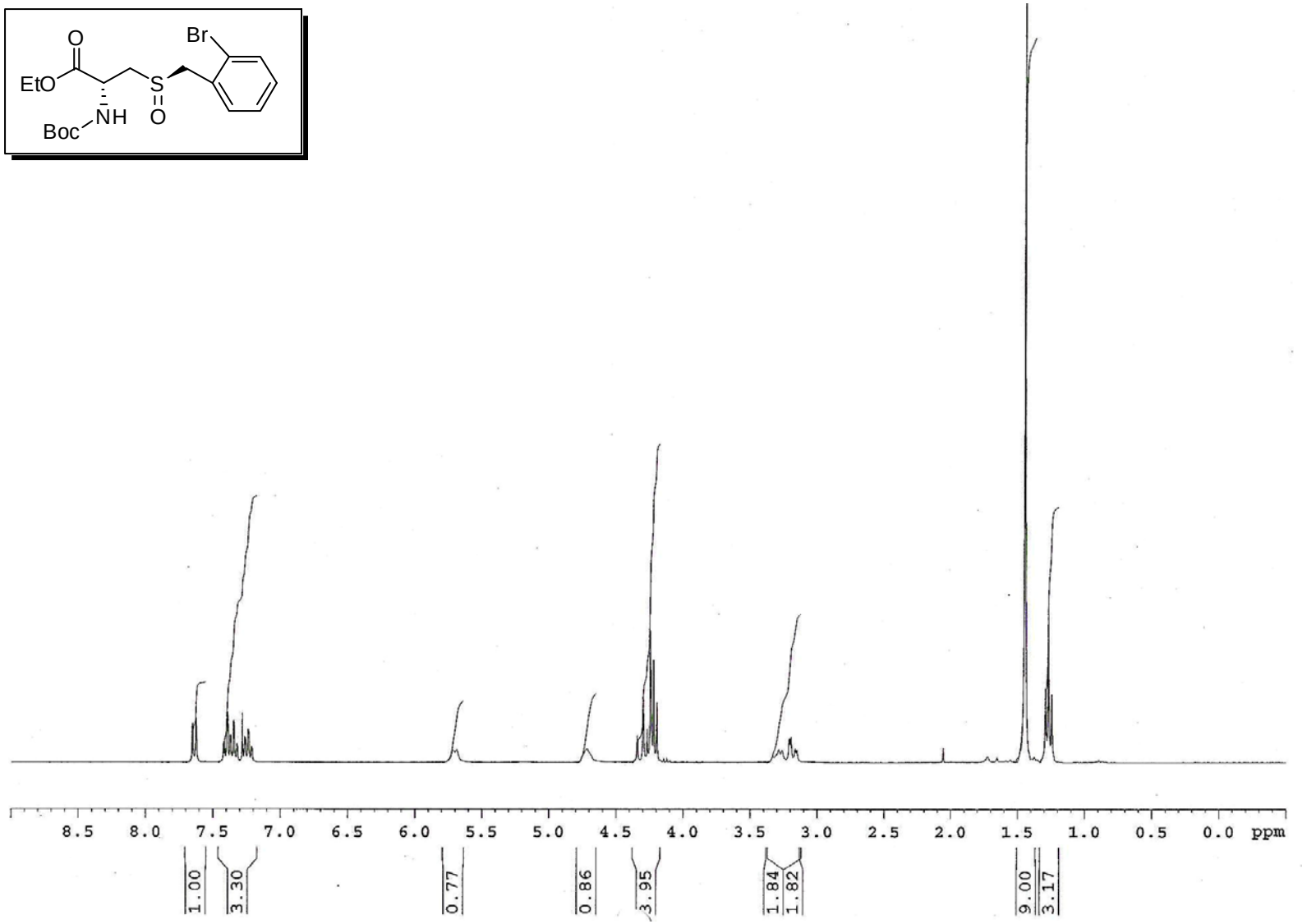


Figure 15. ^{1}H NMR spectrum of **6h** in $CDCl_3$ (400 MHz)

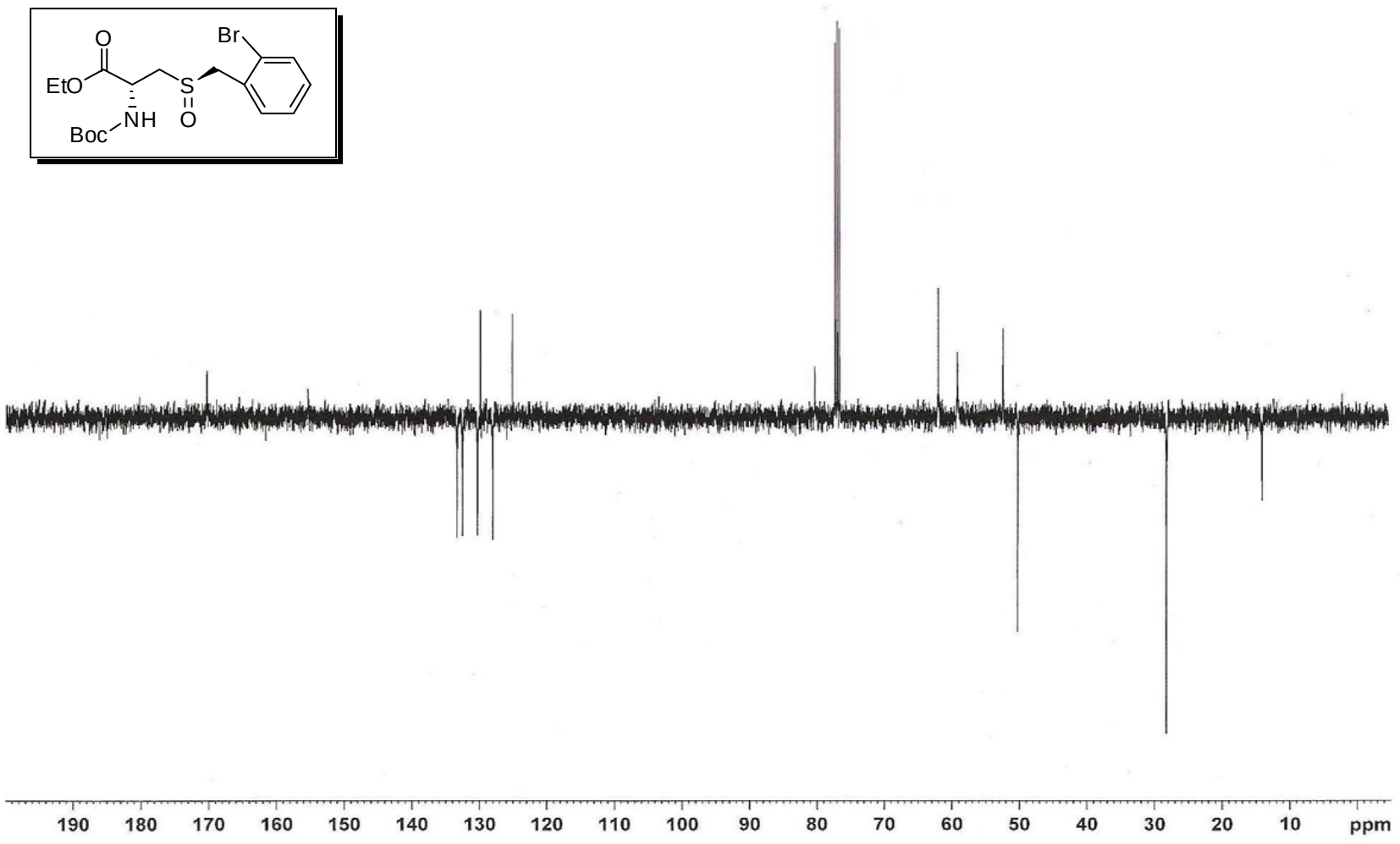


Figure 16. ^{13}C (JMOD) NMR spectrum of **6h** in $CDCl_3$ (100.6 MHz)

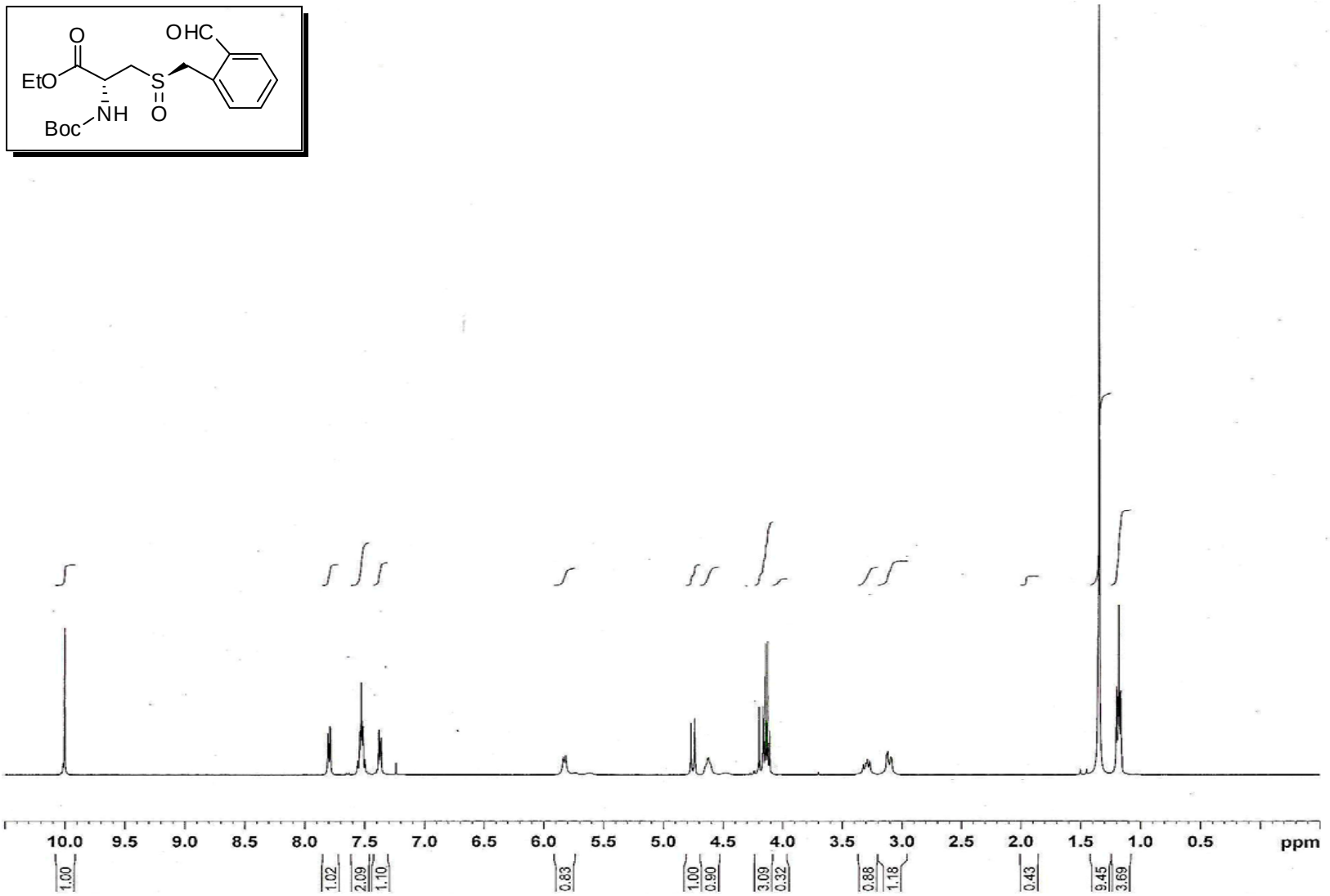


Figure 17. ^{1}H NMR spectrum of **6i** in $CDCl_3$ (400 MHz)

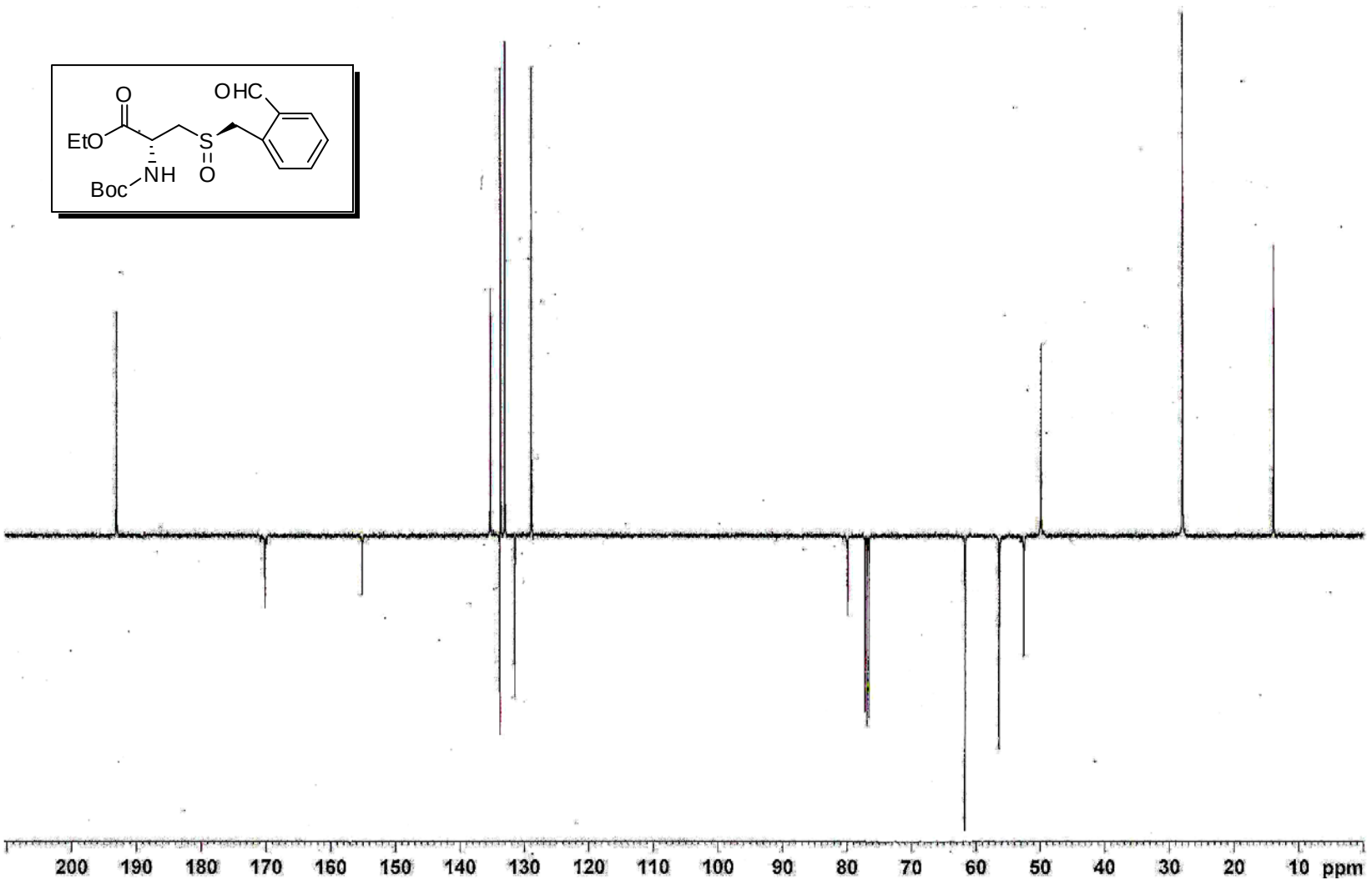


Figure 18. ^{13}C (JMOD) NMR spectrum of **6i** in $CDCl_3$ (100.6 MHz)

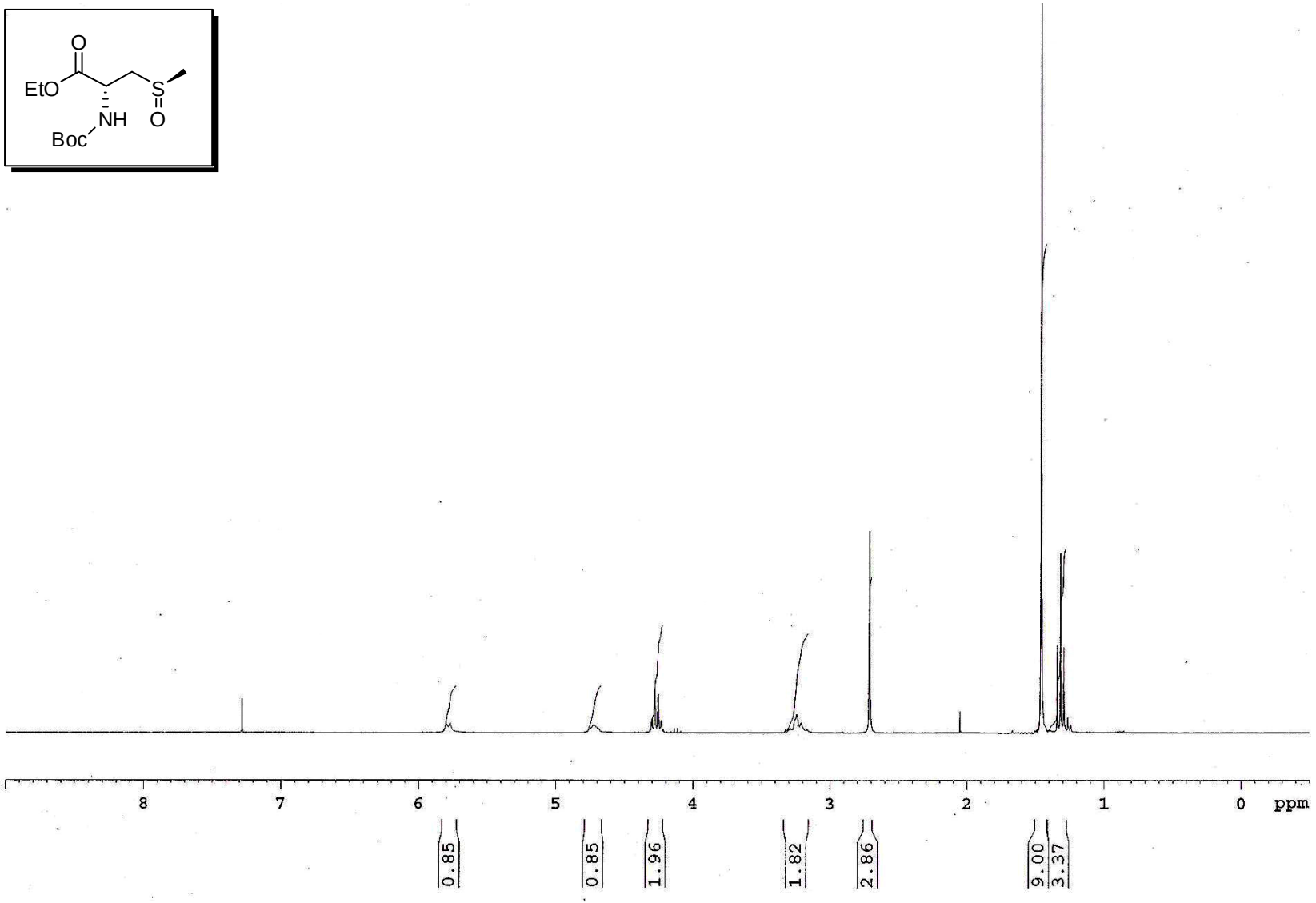


Figure 19. ^{1}H NMR spectrum of **6j** in $CDCl_3$ (400 MHz)

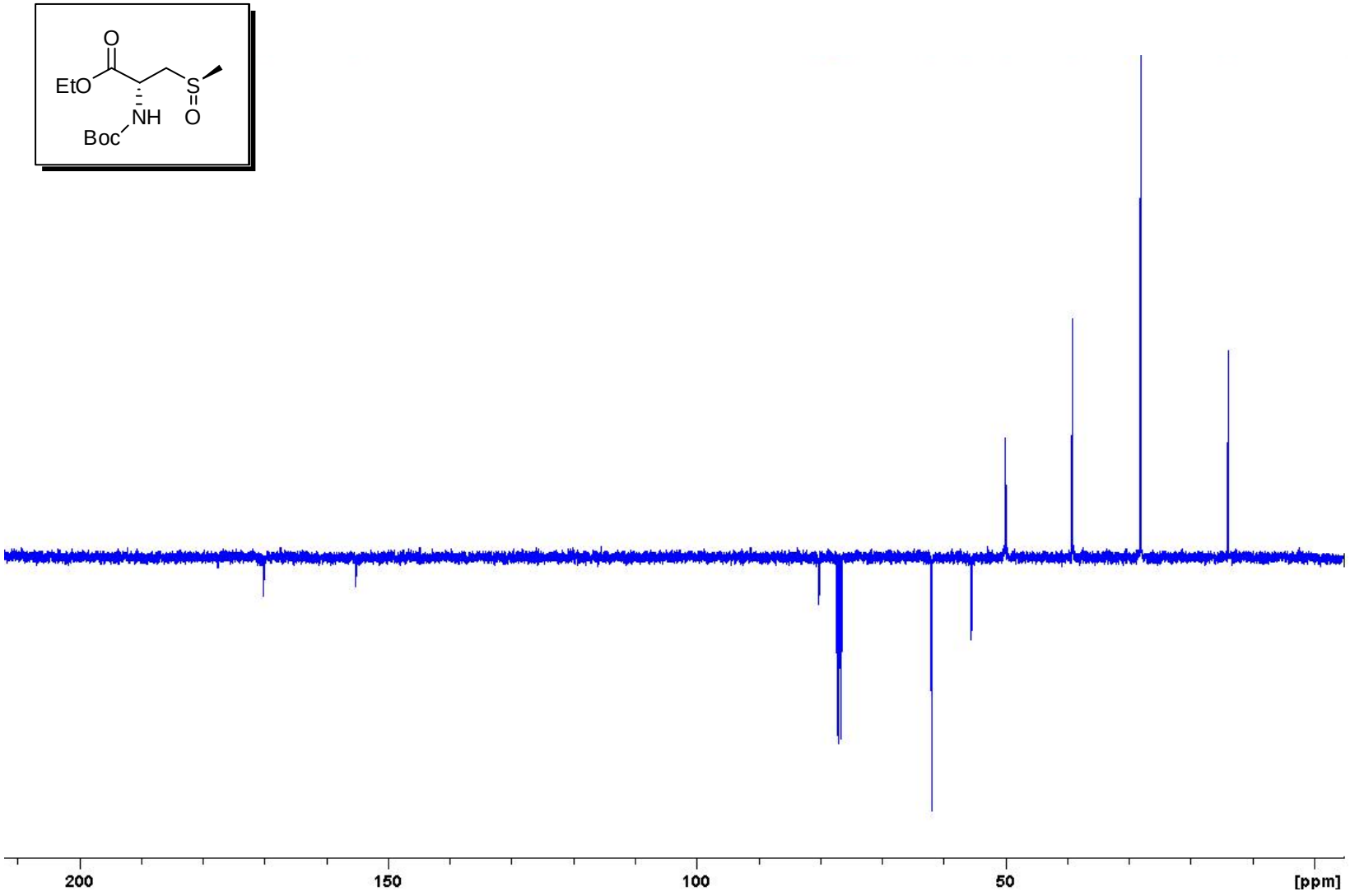


Figure 20. ^{13}C (JMOD) NMR spectrum of **6j** in $CDCl_3$ (100.6 MHz)

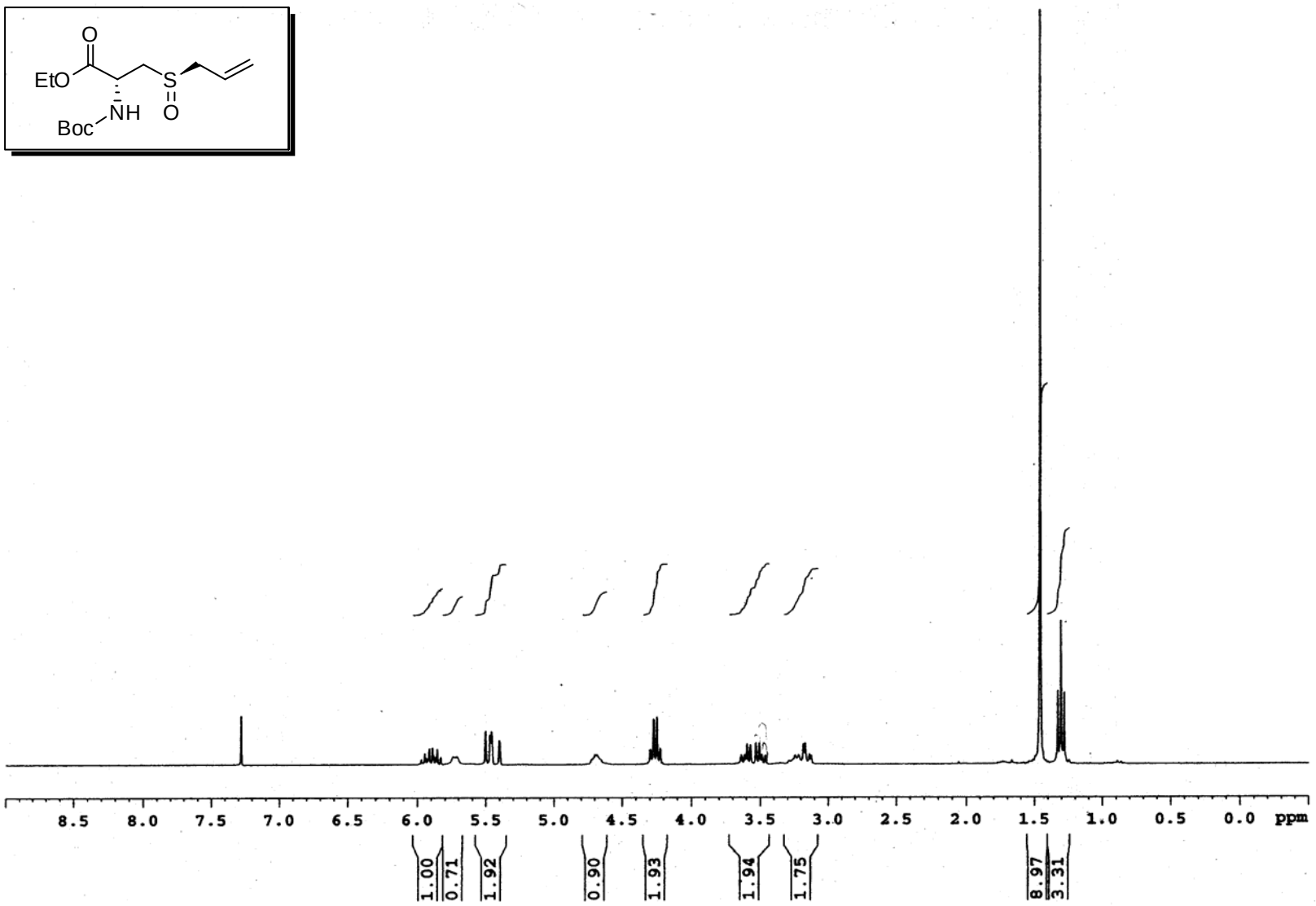


Figure 21. ^{1}H NMR spectrum of **6k** in $CDCl_3$ (400 MHz)

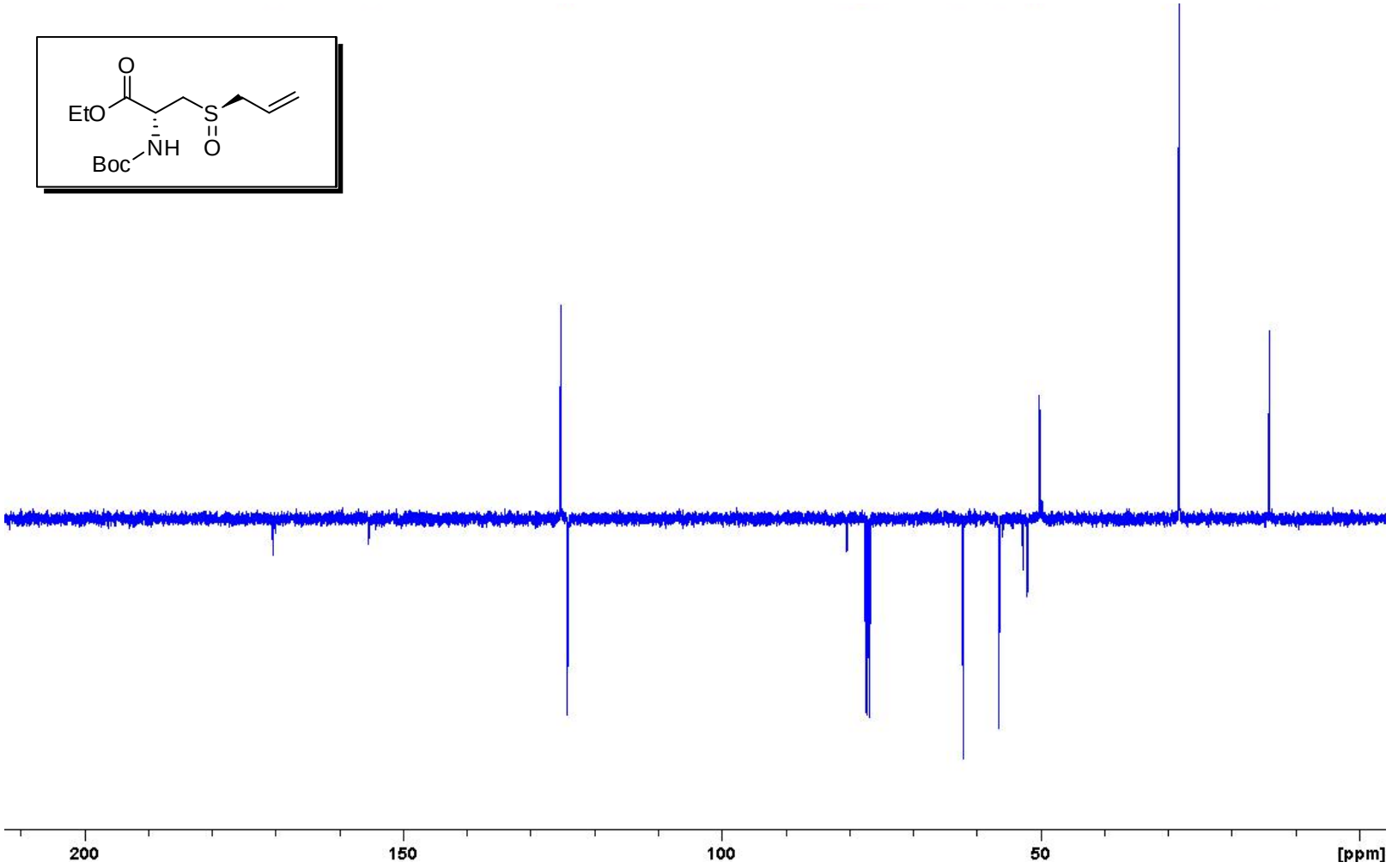


Figure 22. ^{13}C (JMOD) NMR spectrum of **6k** in $CDCl_3$ (100.6 MHz)