Scalable asymmetric synthesis of a key fragment of Bcl-2 / Bcl-x_L inhibitors

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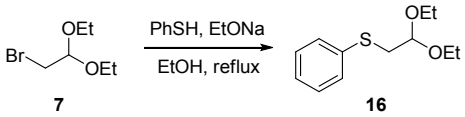
I. GENERAL METHODS

Solvent was purchased as dehydrated solvent and toluene was distilled on CaH_2. All reagents were used as received unless otherwise indicated. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm).[1] Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^1H NMR spectra were recorded on a Bruker AVANCE 300 MHz or Brucker AVANCE III 400 MHz. Data appear in the following order: chemical shifts in ppm, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J* in Hz. ^{13}C NMR spectra were acquired at 75.4 MHz or 100 MHz operating with broad band ^1H decoupling. Hydrogen multiplicity was obtained using DEPT135 or Attached Proton Test (APT) using JMOD pulse program. Reference for $CDCl_3$ was fixed at 77 ppm for ^{13}C NMR and 7.26 ppm for ^1H NMR. IR spectra were recorded on a Perkin Elmer IRTF 100 spectrometer using an ATR (Attenuated Total Reflectance) neat. Mp's stand uncorrected. HRMS analyses were measured on a Q-TOF Micro WATERS spectrometer. HPLC analyses were performed with with Daicel Chiralpak® columns (4.6 mm × 25 cm. A spectrosystemUV 1000 thermofisher detector and a chiral detector (polarimeter) JACSCO OR-1590 were used. Elemental analysis was conducted with Thermo Scientific Flash 2000 (Thermo Fisher).

[1]W. C.Still, M.Kahn and A. Mitra, *J. Org. Chem.*,1978, **43**, 2923.

II. EXPERIMENTAL SESSION ON SMALL SCALES

(2,2-Diethoxyethyl)(phenyl)sulfane (16)

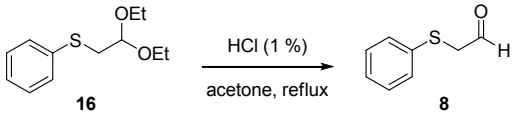


7 **16**

To a solution of sodium ethoxide (1.5 g, 66 mmol, 1.2 equiv.) at 0 °C, was slowly added thiophenol (6.7 mL, 66 mmol, 1.2 equiv.) over 15 min. The mixture was stirred for 15 min and bromoacetaldehyde diethylacetal **7** (8.1 mL, 53 mmol, 1.0 equiv.) was then added dropwise at 0 °C. The mixture was stirred under reflux for 1 h. The resulting mixture was allowed to cool and aqueous saturated $NaHCO_3$ (20 mL) was added. The aqueous solution was extracted with AcOEt (3 x 20 mL). The combined organic layers were dried ($MgSO_4$). The volatiles were rotary evaporated and chromatographed (ACOEt : PE, 5 : 95) to afford (2,2-diethoxyethyl)(phenyl)sulfane **16** as a colorless oil (11.74 g, 98 %).

R*f* = 0.62 (AcOEt : PE, 1 : 9); IR (neat) ν_{max} 2975, 2880, 1584, 1480, 1439, 1372, 1343, 1299, 1205, 1120, 1014, 998 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 7.40-7.37 (2 H, m), 7.29-7.23 (2 H, m), 7.19-7.14 (1 H, m), 4.65 (1 H, t, *J* = 5.6 Hz), 3.67 (2 H, dq, *J* = 9.1, 7.1 Hz), 3.54 (2 H, dq, *J* = 9.1, 7.1 Hz), 3.13 (2 H, d, *J* = 5.6 Hz), 1.19 (6 H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 136.3 (C), 129.2 (CH), 128.8 (CH), 126.0 (CH), 101.6 (CH), 62.0 (CH_2), 37.3 (CH_2), 15.2 (CH_3). HRMS (EI^+): Calcd for $C_{12}H_{18}O_2S$ [M^+]: 226.1028; Found: 226.1037.

2-(phenylthio)acetaldehyde (8)



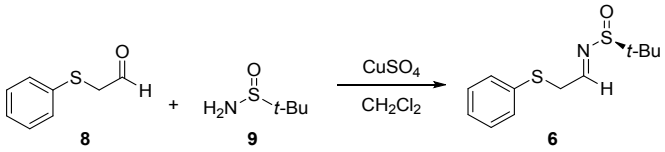
16 **8**

To a mixture of acetone (25 mL) and aqueous solution of HCl (1 %) (50 mL) at 25 °C was added acetal **16** (5.65 g, 25 mmol, 1.0 equiv.). The mixture was stirred at reflux for 2 h. The reaction mixture was allowed to cool down and solid $NaHCO_3$ was added until neutralization. Acetone was evaporated under reduced pressure and the residual aqueous solution was extracted with AcOEt (3x 30 mL). The combined organic layers were dried ($MgSO_4$) and the volatiles were rotary evaporated to afford 2-(phenylthio)acetaldehyde **8** as a colorless oil (3.80 g, 25 mmol, quant.). The crude mixture was pure enough for the next step without further purification.[2]

R*f* = 0.89 (AcOEt : PE, 1 : 9); IR (film) ν max/cm^{-1}: 3058, 2822, 2721, 1717, 1581, 1480, 1439, 1384, 1162, 1087, 1024, 975; ^1H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 9.54 (1 H, t, *J* = 3.2 Hz), 7.42-7.15 (5 H, m), 3.60 (2 H, d, *J* = 5.6 Hz), 1.19 (6 H, t, *J* = 3.2 Hz); ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 194.8 (CH), 133.4 (C), 129.7 (CH), 129.1 (CH), 127.0 (CH), 43.4 (CH_2). HRMS (EI^+): Calcd for C_8H_8OS [M^+]: 152.0296; Found: 152.0305.

[2] The product could be purified by distillation: bp 105 °C (7 Torr) (*J. Org. Chem.*, 1995, **60**, 1276).

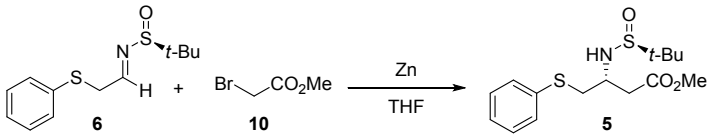
(*S*,*E*)-2-methyl-*N*-(2-(phenylthio)ethylidene)propane-2-sulfinamide (6)



To a mixture of (*S*)-(-)-1-methyl-2-propanesulfinamide **9** (954 mg, 7.67 mmol, 1.0 equiv.) and anhydrous $CuSO_4$ (3.78 g, 23.7 mmol, 3 equiv.) in CH_2Cl_2 (75 mL) was added aldehyde **8** (1.2 g, 7.88 mmol, 1.0 equiv.) dropwise. The mixture was stirred at 25 °C for 14 h and the reaction mixture was filtered under celite. The resulting organic mixture was washed with brine (3 x 20 mL), dried ($MgSO_4$) and the volatiles were rotary evaporated and chromatographed (AcOEt : PE, 1 : 9) to provide sulfinamide **6** (1.40 g, 70 %) as a brownish oil.

R*f* =0.48 (AcOEt : PE, 2 : 8); $[\alpha]_{589}^{25}$ = -202, (*c* = 1.0, $CHCl_3$); IR (film) ν max/cm^{-1}: 3057, 2960, 2925, 1613, 1581, 1476, 1456, 1439, 1363, 1179, 1084, 1024; ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 8.03 (1 H, dd, *J* = 6.1, 4.8 Hz), 7.46-7.42 (2 H, m), 7.36-7.23 (3 H, m), 3.99 (1 H, dd, *J* = 14.8, 6.1 Hz), 3.88 (1 H, dd, *J* = 14.8, 4.8 Hz), 1.10 (9 H, s); ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 163.7 (CH), 133.7 (C), 130.3 (CH), 129.1 (CH), 127.0 (CH), 56.9 (C), 37.9 (CH_2), 22.1 (CH_3); HRMS (ESI$^+$): Calcd for $C_{13}H_{17}NOS_2$ [M + H]$^+$: 256.0824; Found: 256.0821.

(*R*)-methyl 3-((*S*$_S$)-1,1-dimethylethylsulfinamido)-4-(phenylthio)butanoate (5)



A slurry of granular Zn, previously activated[3] (422 mg, 6.46 mmol, 2.2 equiv.) in THF (15 mL) was refluxed. A mixture of sulfinamide **6** (750 mg, 2.94 mmol, 1.0 equiv.) and methylbromoacetate **10** (0.69 mL, 7.34 mmol, 2.5 equiv.) in THF (5 mL) was added dropwise. The mixture was refluxed for 1 h and then cooled to 25 °C. Aqueous solution of NH_4Cl (30 mL) was added. The contents were extracted with EtOAc (4 x 15 mL). The combined layers were dried ($MgSO_4$), rotary evaporated and chromatographed (AcOEt : PE, 1 : 1) to afford **5** as a yellowish oil (823 mg, 85 %).

R*f*= 0.54 (AcOEt); $[\alpha]_{589}^{25}$ = +31, (*c* = 0.25, $CHCl_3$); IR (film) ν max/cm^{-1}: 3212, 2954, 1731, 1583, 1477, 1437, 1412, 1363, 1292, 1253, 1199, 1047; ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 7.37-7.33 (2 H, m), 7.31-7.28 (2 H, m), 7.22-7.16 (1 H, m), 4.29 (1 H, d, *J* = 8.5 Hz), 3.86-3.69 (1 H, m), 3.65 (3 H, s), 3.25 (1 H, dd, *J* = 13.8, 6.1 Hz), 3.12 (1 H, dd, *J* = 13.8, 6.9 Hz), 2.92 (1 H, dd, *J* = 16.7, 5.5 Hz), 2.82 (1 H, dd, *J* = 16.7, 5.3 Hz), 1.18 (9 H, s); ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 172.0 (C), 135.4 (C), 129.8 (CH), 129.1 (CH), 126.6 (CH), 56.1 (C), 53.3 (CH), 51.8 (CH_3), 39.4 (CH_2), 38.3 (CH_2), 22.5 (CH_3); HRMS (ESI$^+$): Calcd for $C_{15}H_{24}NO_3S_2$ [M + H$^+$]: 330.1192; Found: 330.1203.

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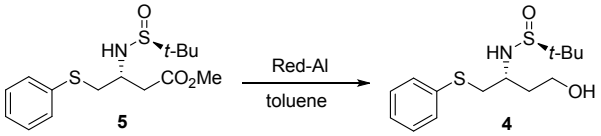
[3] Commercial zinc dust (10 g) was washed successively with 2% HCl (50 mL), distilled water (25 mL), 95% EtOH (25 mL) and absolute Et_2O (25 mL) and dried under vacuum before use. W. L. F. Armarego and C. L. L. Chai, 2003, *Purification of Laboratory Chemicals Fifth Edition*, Butterworth Heinemann, Elsevier, 497.

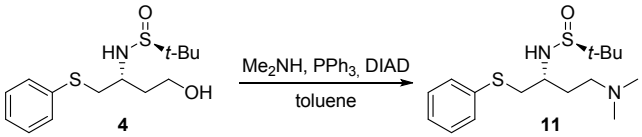
(S_S)-N-((*R*)-4-hydroxy-1-(phenylthio)butan-2-yl)-2-methylpropane-2-sulfinamide (4)



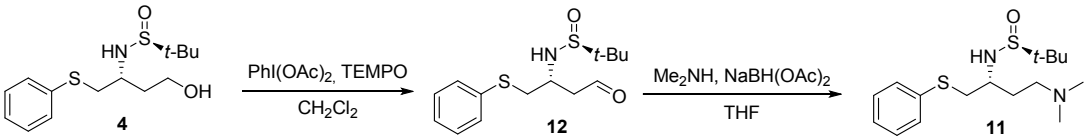
To a solution of Red-Al (65 % in toluene)(1.0 mL, 3.35 mmol, 1.7 equiv.) in toluene (2 mL) at 0 °C was added ester **5** (650 mg, 1.97 mmol, 1.0 equiv.) in toluene (5 mL) dropwise. After 10 min stirring at 0 °C was added an aqueous solution of NaOH (5 %) (7 mL) within 10 min. The reaction mixture was stirred for 15 min and was filtered under celite. Toluene (20 mL) was added and the organic phase was washed twice with brine (2 x 15 mL). The combined organic layers were dried $MgSO_4$ and the volatiles were rotary evaporated and chromatographed (AcOEt) to provide alcohol **4** as a brownish oil (415 g, 70 %).

R*f* = 0.38 (AcOEt); $[\alpha]_{589}^{25}$ = +15, (*c* = 1.0, $CHCl_3$); IR (film) ν max/cm^{-1}: 3222, 2955, 2927, 2871, 1583, 1477, 1438, 1364, 1175, 1040; ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 7.36-7.32 (2 H, m), 7.31-7.28 (2 H, m), 7.22-7.16 (1 H, m), 4.14 (1 H, d, *J* = 6.7 Hz), 3.83-3.81 (3 H, m), 3.64 (1 H, m), 3.10 (1 H, dd, *J* = 13.4, 6.2 Hz), 3.02 (1 H, dd, *J* = 13.4, 6.2 Hz), 2.06-1.99 (1 H, m), 1.81 (1 H, m), 1.21 (9 H, s); ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 136.0 (C), 129.5 (CH), 129.1 (CH), 126.3 (CH), 60.0 (CH_2), 56.1 (C), 55.8 (CH), 41.5 (CH_2), 36.9 (CH_2), 22.7 (CH_3); HRMS (ESI$^+$) : Calcd for $C_{14}H_{24}NO_2S_2$ [M + H^+]: 302.1243; Found: 302.1255.

(S_S)-N-((*R*)-4-(dimethylamino)-1-(phenylthio)butan-2-yl)-2-methylpropane-2-sulfinamide (11)



In a mixture of triphenylphosphine (740 mg, 2.82 mmol, 1.7 equiv.), alcohol **4** (500 mg, 1.66 mmol, 1 equiv.) and dimethylamine (solution 2M in THF) (2.5 mL, 4.98 mmol, 3 equiv.) in toluene (5 mL) at 0 °C was added DIAD (diisopropylazodicarboxylate) (0.49 mL, 2.49mmol, 1.5 equiv.) dropwised. The mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with AcOEt (30 mL) and washed with a saturated aqueous solution of Na_2CO_3 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (AcOEt to CH_2Cl_2 : MeOH, 9 : 1) to provide amine **11** as a brownish oil (234 mg, 43 %).

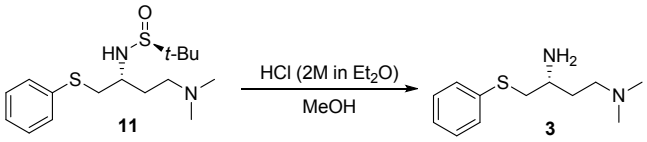


To a solution of alcohol **4** (151 mg, 0.5 mmol, 1.0 equiv.) in CH_2Cl_2 at 25 °C was added TEMPO (17.2 mg, 0.11 mmol, 0.22 equiv.) and $PhI(OAc)_2$ ((diacetoxyiodo)benzene) (354 mg, 1.1 mmol, 2.2 equiv.). The reaction mixture was stirred for 6 h at 25 °C and an aqueous solution Na_2SO_3 10 % (10 mL) was added. The content was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with saturated solution of NaHCO3 (10 mL) and brine (10 mL), dried ($MgSO_4$) and rotary evaporated to provide

aldehyde **12** as a crude yellowish oil (150 mg, quant.), pure enough to be used for the next step without further purification.
To a solution of aldehyde **12** (150 mg, 0.5 mmol, 1.0 equiv.) in THF (2.5 mL) was added dimethylamine (solution 2M in THF) (0.5 mL, 1.0 mmol, 2 equiv.). After 10 min stirring at 25 °C was added $NaBH(OAc)_3$. (148 mg, 0.7 mmol, 1.4 equiv.). The mixture was stirred 2 h at 25 °C and was diluted with AcOEt (10 mL). The mixture was added to a saturated solution of $NaHCO_3$ (10 mL) and the phases were separated. The aqueous layer was extracted with AcOEt (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (CH_2Cl_2 : MeOH, 2 : 8) to provide **11** as a pure yellowishoil (118 mg, 72 %).

R*f* = 0.41; $[\alpha]_{589}^{25}$ = +23, (*c* = 0.25, $CHCl_3$); IR (film) ν max/cm^{-1}: 2957, 2674, 1734, 1583, 1472, 1439, 1390, 1366, 1241, 1176, 1043; ^{1}H NMR (DMSO-d_6, 25 °C, 400 MHz): δ_H 7.34-7.28 (4 H, m), 7.19-7.15 (1 H, m), 5.80 (1 H, d, *J* = 6.8 Hz), 3.38-3.32 (1 H, m), 3.08 (2 H, d, J = 6.5 Hz), 2.44-2.38 (1 H, m), 2.31-2.25 (1 H, m), 2.12 (6 H, s), 1.86-1.78 (1 H, m), 1.72-1.64 (1 H, m), 1.11 (9 H, s); ^{13}C NMR (DMSO-d_6, 25 °C, 100 MHz): δ_C 136.6 (C), 129.0 (CH), 127.9 (CH), 125.5 (CH), 55.8 (C), 55.2 (CH_2), 54.9 (CH_2), 44.8 (CH_3), 38.8 (CH_2), 31.4 (CH_2), 22.6 (CH_3); ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 7.36-7.32 (2 H, m), 7.32-7.30 (2 H, m), 7.19-7.14 (1 H, m), 6.44 (1 H, bs), 3.66-3.57 (1 H, m), 3.20 (1 H, dd, *J* = 13.3, 4.8 Hz), 3.02 (1 H, dd, *J* = 13.3, 7.7 Hz), 2.58-2.41 (2 H, m), 2.25 (6 H, s), 2.02-1.91 (1 H, m), 1.17-1.65 (1 H, m), 1.20 (9 H, s) ; ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 136.3 (C), 129.1 (CH), 129.0 (CH), 126.0 (CH), 57.0 (CH_2), 55.4 (C), 55.3 (CH), 44.8 (CH_3), 39.8 (CH_2), 29.7 (CH_2), 22.8 (CH_3); HRMS (ESI$^+$) : Calcd for $C_{16}H_{29}N_2OS_2$ [M + H$^+$]: 329.1716; Found: 329.1728.

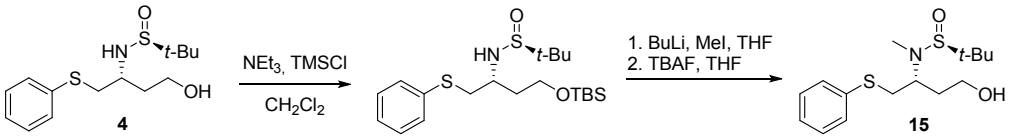
(*R*)-*N*^{1},*N*^{1}-dimethyl-4-(phenylthio)butane-1,3-diamine (3)



To a solution of amine **11** (200 mg, 0.61 mmol, 1.0 equiv.) in dry MeOH (10 mL) was added a solution of HCl (2 M in Et_2O) (0.91 mL, 1.83 mmol, 3.0 equiv.). The reaction was stirred 2 h at 25 °C and was diluted with AcOEt (10 mL). Aqueous solution of NaOH (2 M) was added until pH > 9. The phases were separated and the aqueous layer was washed with AcOEt (4 x 15 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated to afford the desired product **3** as a yellowish oil (119 mg, 87 %).

R*f* = 0.38 (CH_2Cl_2 : MeOH, 7 : 3); $[\alpha]_{589}^{25}$ = -328, (*c* = 0.5, $CHCl_3$); IR (film) ν max/cm^{-1}: 2940, 2857, 2816, 2766, 1583, 1479, 1462, 1439, 1260, 1041, 1025, 935; ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 7.37-7.34 (2 H, m), 7.28-7.23 (2 H, m), 7.18-7.14 (1 H, m), 3.10 (1 H, dd, *J* = 13.0, 4.1 Hz), 3.02-2.93 (1 H, m), 2.76 (1 H, dd, *J* = 13.0, 8.1 Hz), 2.38-2.32 (2 H, m), 2.19 (6 H, s), 1.82 (2 H, bs), 1.74-1.63 (1 H, m), 1.57-1.44 (1 H, m); ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 136.2 (C), 129.4 (CH), 128.9 (CH), 126.0 (CH), 56.9 (CH_2), 49.4 (CH), 45.5 (CH_3), 42.7 (CH_2), 34.5 (CH_2); HRMS (ESI$^+$) : Calcd for $C_{12}H_{21}N_2S$ [M + H$^+$]: 225.1425; Found: 225.1427.

(*S*)-*N*-((*R*)-4-hydroxy-1-(phenylthio)butan-2-yl)-*N*,2-dimethylpropane-2-sulfinamide (15)



To a solution of alcohol **4** (1 g, 3.32 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added triethylamine (1.0 mL, 7.3 mmol, 2.2 equiv.) and TBSCl (600 mg, 3.98 mmol, 1.2 equiv.). The mixture was stirred at 25 °C for 2 h and aqueous saturated solution of $NaHCO_3$ (15 mL) was added. The phases were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (AcOEt : PE, 2 : 8) to provide the corresponding TBS protected alcohol as a yellowish oil (1.30 g, 94 %).

To a solution of the TBS protected alcohol (1 g, 2.4 mmol) in THF (10 mL) was added BuLi (solution 1.6 M in hexanes) (1.7 mL, 2.64 mmol, 1.1 equiv.) dropwise at 0 °C. After 30 min stirring at 0 °C was added MeI (0.3 mL, 4.8 mmol, 2.0 equiv.) dropwise. The content was stirred at 25 °C for 2 h and a saturated aqueous solution of NH_4Cl was added (30 mL). The aqueous phase was washed with AcOEt (4 x 15 mL). The combined organic phases were dried and rotary evaporated to provide a crude oil, directly used in the next step. The oil was diluted in THF (10 mL) and TBAF (1 M solution in THF) (2.6 mL, 2.64 mmol, 1.2 equiv.) was added. The mixture was stirred at 25 °C for 2 h. AcOEt (20 mL) and brine (20 mL) was added. The phases were separated and the aqueous layer was washed with AcOEt (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (AcOEt) to afford alcohol **15** as a yellowish oil (681 mg, 90 % for two steps).

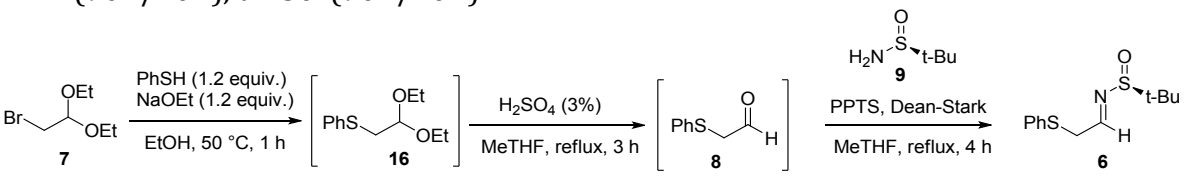
R*f*= 0.40 (AcOEt); $[\alpha]_{589}^{25}$ = -71, (*c* = 1.0, $CHCl_3$); IR (film) ν max/cm^{-1}: 3394, 2950, 2869, 1583, 1478, 1458, 1439, 1362, 1190, 1174, 1043, 932; ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ_H 7.34-7.25 (4 H, m), 7.21-7.16 (1 H, m), 3.77-3.72 (2 H, m), 3.70-3.61 (1 H, m), 3.43 (1 H, m), 3.16 (1 H, dd, *J* = 13.2, 7.7 Hz), 2.99 (1 H, dd, *J* = 13.2, 6.6 Hz), 2.55 (3 H, s), 1.89-1.82 (2 H, m), 1.24 (9 H, s); ^{13}C NMR ($CDCl_3$, 25 °C, 75.4 MHz): δ_C 136.0 (C), 129.3 (CH), 129.0 (CH), 126.3 (CH), 62.7 (CH), 59.4 (CH_2), 59.3 (C), 38.5 (CH_2), 34.0 (CH_2), 24.8 (CH_3), 24.2 (CH_3); HRMS (ESI$^+$) : Calcd for $C_{15}H_{26}NO_2S_2$ [M + H$^+$]: 316.1405; Found: 316.1412.

III. LARGE SCALE PROCEDURES

The crude yield corresponds to yield calculated from the obtained weight of product with respect to the expected theoretical mass. As an indication, the purity of this crude product is estimated by HPLC, considering the integration of the desired product with regard to the sum of all products integration at wavelength-210 nm.

HPLC Method: An aliquot (1 mg) of the product was dissolved in eluent and subjected to HPLC analysis (injection 5 µL) (HP Agilent 1100 series, mobile phase: A (water containing 0.1% methanesulfonic acid) and B : acetonitrile – Method : Initial time 90A/10B for 5 min, increase to 10A/90B with a 3.2% gradient and hold at 10A/90B for

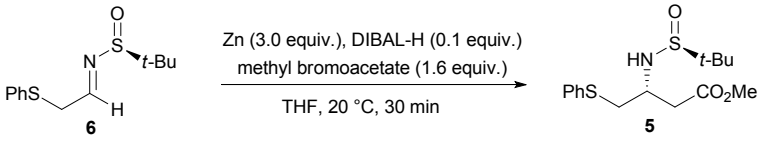
10 min – flow rate: 1 mL/min - column temp 40 °C – Column : Xbridge C18 (100 mm × 4.6 mm) – wavelength : 210 nm). For compound **17** specifically, the conditions are the following. An aliquot (2.5 mg) of the product was dissolved in 10ml CH_3CN/H_2O (1/1). Mobile phase : t = 0 (97A/3B), t = 5 (90A/10B), t = 30 (10A/90B), t = 40 (10A/90B), t = 41 (90A/10B), t = 50 (90A/10B).



A 21% solution of sodium ethoxide in ethanol (3.95 kg, 12.2 mol, 1.2 equiv.) was charged to a 12 L reactor under nitrogen atmosphere. Thiophenol (1.34 kg, 12.2 mol, 1.2 equiv.) was added over 1 h at 20 °C with a dropping funnel. The funnel was rinsed with ethanol (0.2 kg). After stirring for 20 minutes, the mixture was heated to 50 °C and bromoacetaldehyde diethyl acetal **7** (2.00 kg, 10.2 mol, 1 equiv.) was added over 1 h. The dropping funnel was rinsed with ethanol (0.2 kg) and the mixture was heated to reflux. After stirring for 1 h, the suspension was cooled to 40 °C and H_2O (3 kg) was added over 20 minutes. The resulting solution was concentrated by vacuum distillation and MeTHF (2.63 kg) was added. The aqueous layer was removed and a 1 N solution of NaOH (0.8 L) was added. The aqueous phase was removed to leave a solution of the title compound **16** as a solution in MeTHF with 95% HPLC purity (product **16** retention time : t_R = 20.9 min).

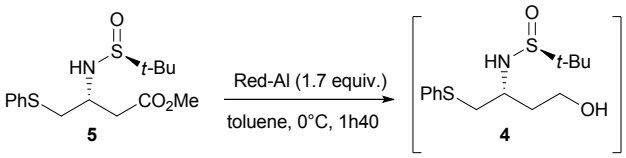
A 3% w solution of H_2SO_4 was prepared by adding concentrated H_2SO_4 (1.1 kg) to H_2O (35 L) in a 70 L reactor. After stirring for 5 minutes at 20 °C, solution containing **16** (2.28 kg in MeTHF, 10.1 mol, 1.0 equiv.) was added over 30 minutes followed by a line wash with MeTHF (0.4 kg). The reaction mixture was heated to reflux and vigorously stirred for 2 h then cooled to 20 °C over 1 h. MeTHF (0.7 kg) was added, the aqueous phase was removed to leave a MeTHF solution of **8** with 89% HPLC purity (product **8** retention time : t_R = 12.2 min).

(*S*)-(-)-1-methyl-2-propanesulfinamide (1.22 kg, 1 equiv.) was charged under nitrogen to a 12 L reactor equipped with a Dean-Stark apparatus followed by PPTS (0.38 kg, 0.15 equiv.) and MeTHF (1.46 kg). The reaction mixture was vigorously stirred for 30 minutes at 20 °C and the MeTHF solution of **8** was added over 45 minutes followed by a line wash with MeTHF (0.27 kg). After 4 h at reflux, the reaction mixture was cooled to 20 °C over 45 minutes and H_2O was added (1.37 kg). The aqueous phase was removed, toluene (1.4 kg) was added followed by H_2O (1.6 kg). The aqueous phase was removed and H_2O was added (1.4 kg). The aqueous phase was removed and the organic phase was concentrated to dryness under vacuum to give **6** as an oil (1.73 kg, 68% crude yield over three steps, 69% HPLC purity (product **6** retention time : t_R = 18.7 min)).

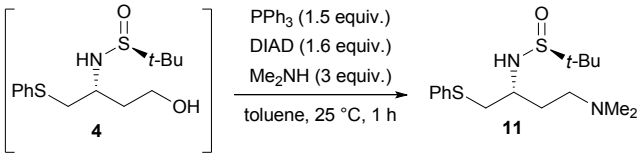


Activated zinc (23.1 g, 353 mmol, 3 equiv.) was charged to a 0.5 L reactor under nitrogen followed by THF (100 mL) with good stirring. The suspension was heated to 35 °C and methyl bromoacetate (1.1 mL, 11.7 mmol, 0.1 equiv.) was added. DibalH (1 M in toluene) (10.6 mL, 10.6 mmol, 0.09 eq) was added over 10 minutes and the reaction mixture was heated to 50 °C. Methyl bromoacetate (18.2 mL, 189 mmol, 1.6 equiv.) was added over 1

h followed by washing with THF (4 mL). After stirring 1 h at 50 °C, the reaction mixture was cooled to 20 °C. A solution of **6** (30 g, 118 mmol, 1 equiv.) in THF (105 mL) was added over 1 h followed by washing with THF (5 mL). After 30 minutes, an aqueous solution of NaCl (26% w/w) (11 mL, 59 mmol, 0.5 equiv.) was added over 10 minutes followed by an aqueous citric acid solution (10% w/w) (120 mL, 59 mmol, 0.5 equiv.) added over 20 minutes. An aqueous solution of NaCl (26% w/w) (44 mL, 236 mmol, 2 equiv.) was then added over 15 minutes and the reaction mixture was stirred for 30 minutes. The suspension was filtered on a bed of Celite and the filter washed with toluene (2 x 100 mL). The aqueous phase was removed, the organic phase was washed with H_2O (2 x 120 mL). The organic phase was concentrated to dryness to provide **5** as an oil with a crude yield of 80% (31 g) and 68% purity (R/S 94/6). This product was chromatographed (silicagel Merck grade (15111), pore size 60 Å, particle size 15-40 µm) (toluene : AcOEt 1:1 to toluene : AcOEt 3:7) to provide product **5** with HPLC purity of 82% (product **5** retention time : t_R = 17.9 min).

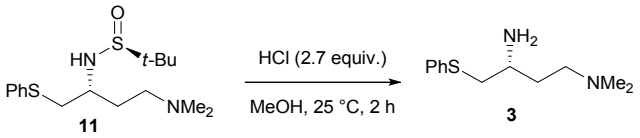


In a 500 mL reactor was charged a solution of Red-Al (65 % in toluene) (70.7 mL, 236 mmol, 1.55 equiv.) and toluene (100 mL) at 0 °C. The solution of ester **5** (50 g, 151.7 mol, 1.0 equiv.) in toluene (150 mL) over 90 min followed by a line wash with toluene (10 mL). The mixture was stirred at 0 °C for 40 min and then 1 h at 25 °C. Aqueous solution of NaOH (5 % w/w) (520 mL, 685 mmol, 4.5 equiv.) was added slowly over 10 min. The line was washed with toluene (15 mL) and the reaction mixture was stirred for 1 hour at 25 °C. The phases were separated and the aqueous phase was extracted with toluene (100 mL). The combined organic layers were washed with H_2O (2 x 100 mL). The product was kept in solution for the next step. A sample concentrated to dryness gave **4** as an oil with 80% crude yield and 89% HPLC purity (product **4** retention time : t_R = 15.5 min).

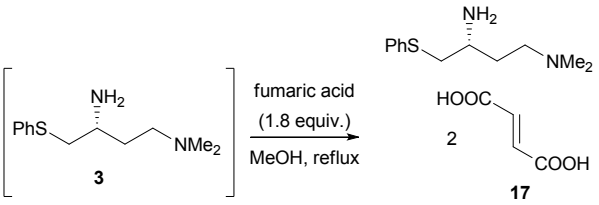


In a 500 mL reactor is added to the solution of alcohol **11** in toluene (35 g, 116 mmol, 1 equiv.), PPh_3 (51.7 g, 197 mmol, 1.7 equiv.) and dimethylamine (2M in THF) (174 mL, 348 mmol, 3.0 equiv.). The mixture was cooled down to 0 °C and DIAD (36.7 mL, 186 mmol, 1.6 equiv.) was added slowly over 90 min. The mixture was stirred at 0 °C for 90 min and at 20 °C for 75 min. An aqueous solution of $NaHCO_3$ (10 %) (135 mL) was added and the phases were separated. The organic phase was washed with water (2 x 100 mL). The organic phases were concentrated under reduced pressure and methylcyclohexane (200 mL) was added. The mixture was stirred at 20 °C for 1 h and the temperature cooled down to 0 °C. The content was filtrated using a Buchner apparatus. The solid was washed with methylcyclohexane (15 mL). The solvent was rotary evaporated to provide a brownish oil (m = 69.5 g) with a purity of 72%. A fraction of this oil (63.5 g) was purified by column chromatography (2 kg silicagel Merck grade (15111), pore size 60 Å, particle size 15-40 µm) (Flow rate : 600 mL/min - CH_2Cl_2 : MeOH 7 : 3) to provide pure

11 as a brownish oil (22 g) with a 99.6% of HPLC purity (product **11** retention time : t_R = 12.5 min). Yield 64%.



To a solution of **11** (12.5 g, 38.1 mmol, 1.0 equiv.) in MeOH 12.5 mL was added a solution of HCl (1.37 M in MeOH) (75 mL, 103 mmol, 2.7 equiv.) at 22 °C over 40 min. The mixture was stirred 1 h at 25 °C. MeOH was distilled out by heating under atmospheric pressure and an aqueous solution of NaOH (10 M) (10.3 mL, 103 mmol, 2.7 equiv.) and toluene (94 mL) was added to the reaction mixture. The phases were separated and the aqueous layers were washed with toluene (22 mL). The combined organic layers were used directly for the next step. A sample was concentrated to dryness to give **3** as a yellowish oil with 98% yield and 95.6% HPLC purity (product **3** retention time : t_R = 1.3 min).

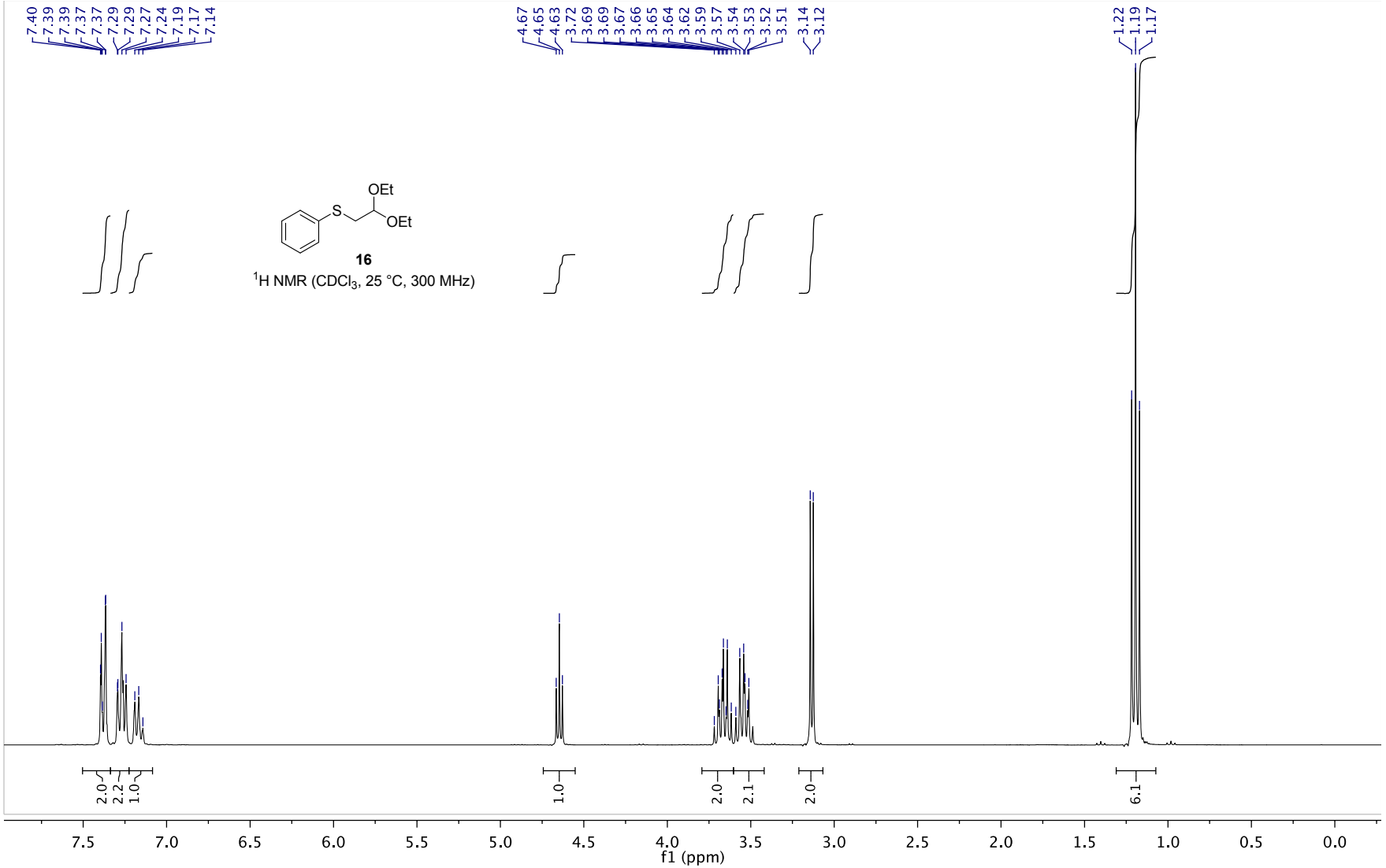


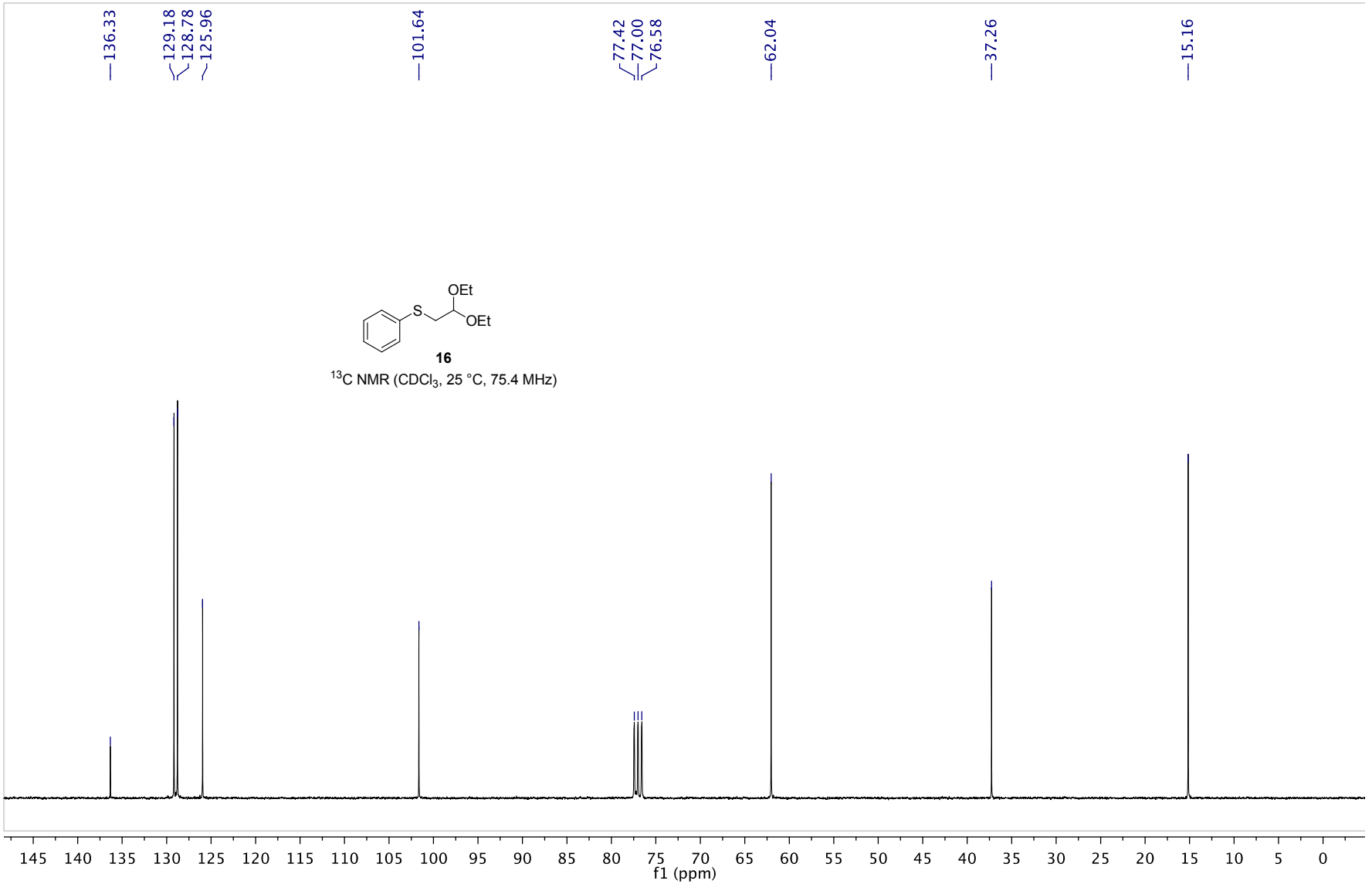
In a 25 mL flask, a solution of fumaric acid (7.66 g, 65.9 mmol, 1.8 equiv.) in MeOH (57.4 mL) was heated under reflux for 15 min and the mixture was cooled down to 60 °C. A solution of diamine **3** (8.2 g, 36.6 mmol, 1 equiv.) in toluene (109 mL) was added over 45 min. The mixture was stirred 20 min at 60 °C and the mixture was cooled down to 50 °C and the content was kept at 50 °C for two hours. The mixture was cooled down at 5 °C and the solid was filtered. The solid was washed with cold EtOH (13 mL) and with MTBE (34 mL). The solid was dried through drying oven at 50 °C to provide pure *R* diamine difumarate salt **17** as a white solid (13.8 g, 80 %). 99.5% ee. Optical purity was determined using chiral HPLC : Chiralpak AD column. λ = 254 nm (CH_3CN/IpOH/DEA 900/100/1, flow rate 1 mL/min) ; *R* isomer t_R = 6.7 min (major enantiomer) and *S* isomer t_R = 8.2 min. (minor enantiomer).

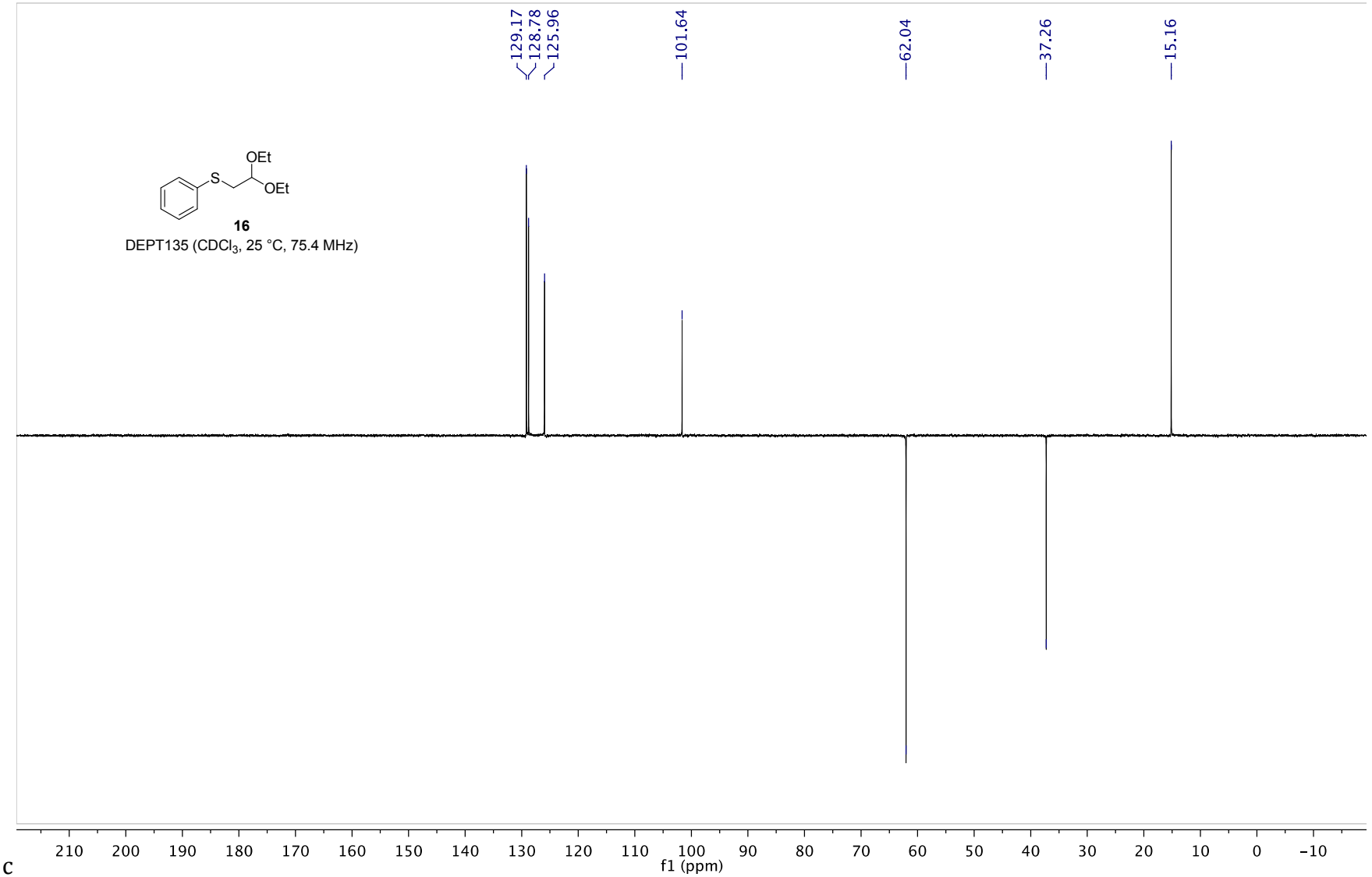
Mp = 151-153 °C; IR (film) ν max/cm^{-1}: 3448, 2991, 2955, 2903, 2666, 2333, 1702, 1653, 1530, 1396, 1251, 1172, 1025, 972; ^{1}H NMR (D_2O, 25 °C, 300 MHz): δ_H 7.49-7.44 (2 H, m), 7.38-7.26 (3 H, m), 6.59 (4 H, s), 3.50-3.37 (1 H, m), 3.30 (1 H, dd, *J* = 15.1, 4.9 Hz), 3.17 (1 H, dd, *J* = 15.1, 6.4 Hz), 3.16-2.98 (2 H, m), 2.75 (3 H, s), 2.70 (3 H, s), 1.98-2.20 (2 H, m); ^{13}C NMR (D_2O, 25 °C, 100 MHz): δ_C 172.1 (C), 135.3 (CH), 133.6 (C), 131.7 (CH), 130.4 (CH), 128.7 (CH), 54.1 (CH_2), 49.3 (CH), 43.5 (CH_3), 43.2 (CH_3), 36.5 (CH_2), 27.1 (CH_2).^{1}H NMR (DMSO-d_6, 25 °C, 400 MHz): δ_H 7.42-7.39 (2 H, m), 7.35-7.31 (2 H, m), 7.25-7.20 (1 H, m), 6.52 (4 H, s), 3.26-3.16 (3 H, m), 2.73-2.61 (2 H, m), 2.33 (6 H, s), 1.96-1.90 (1 H, m),1.84-1.76 (1 H, m); ^{13}C NMR (DMSO-d_6, 25 °C, 100 MHz): δ_C 167.8 (C), 135.1 (CH), 135.0 (C), 129.5 (CH), 128.8 (CH), 126.5 (CH), 54.5 (CH_2), 49.0 (CH), 43.7 (CH_3), 35.8 (CH_2), 28.1 (CH_2); HRMS (ESI$^+$) : Calcd for $C_{12}H_{21}N_2S$ [M + H$^+$]: 225.1425; Found: 225.1423; Elemental analysis for $C_{20}H_{28}N_2O_8S$ (456.51): Calcd C 52.62, H 6.18, N 6.14; found C 52.28, H 6.21, N 6.08.

IV. NMR SPECTROSCOPIC CHARACTERIZATION

(2,2-Diethoxyethyl)(phenyl)sulfane (16)

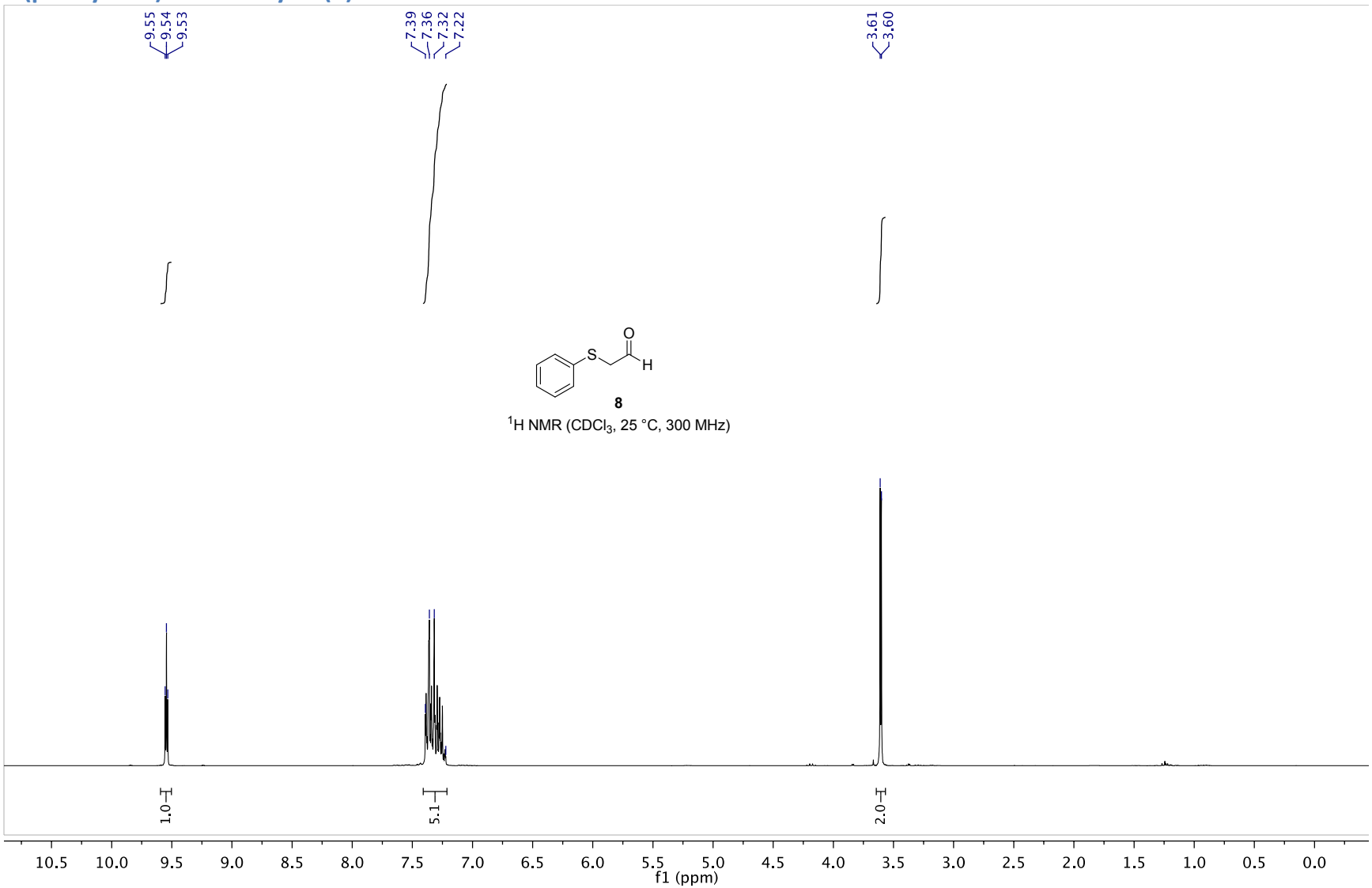


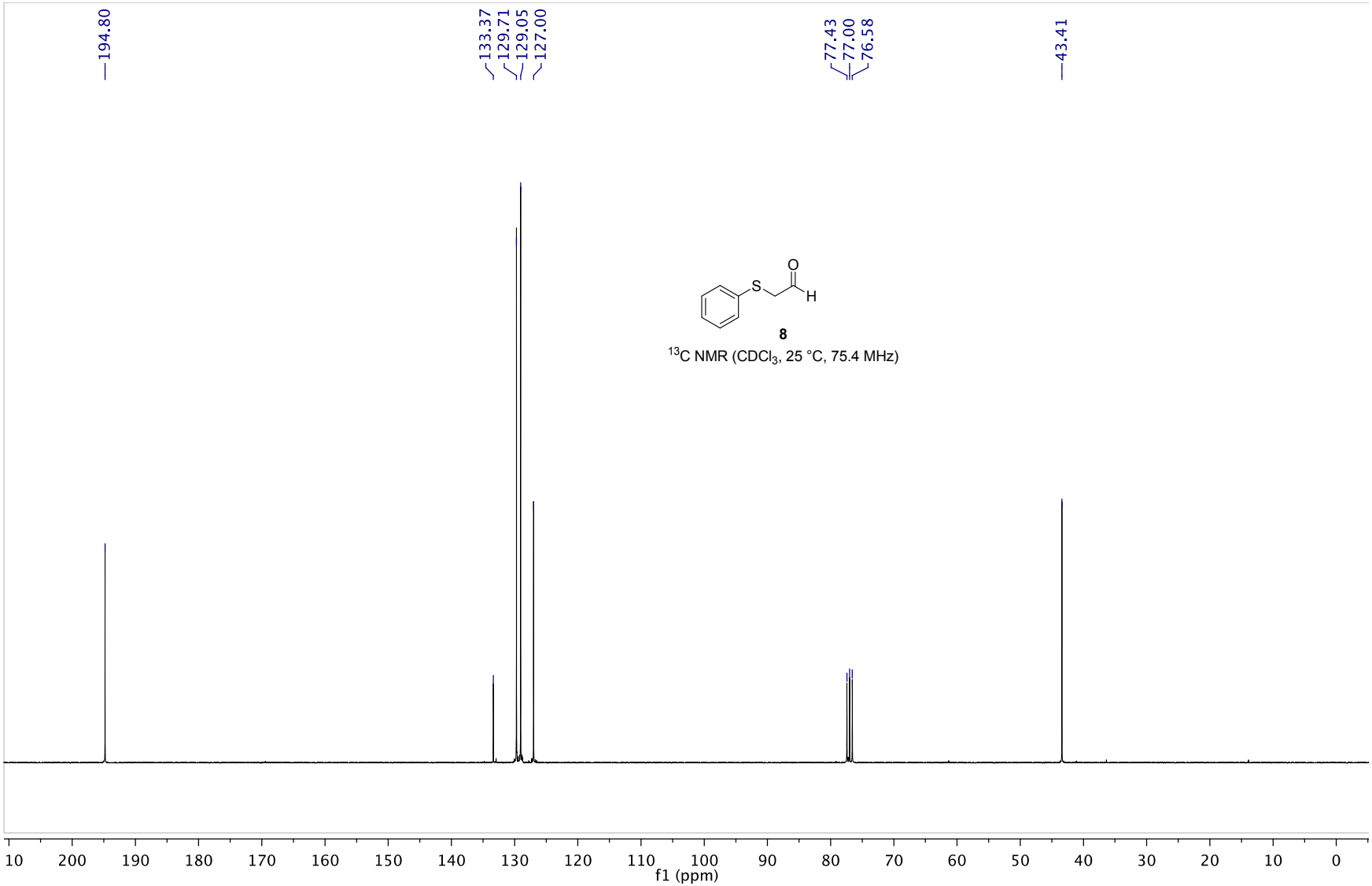

136.33
129.18
128.78
125.96
101.64
77.42
77.00
76.58
62.04
37.26
15.16
OEt
S
OEt
16
13C NMR (CDCl3, 25 °C, 75.4 MHz)
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

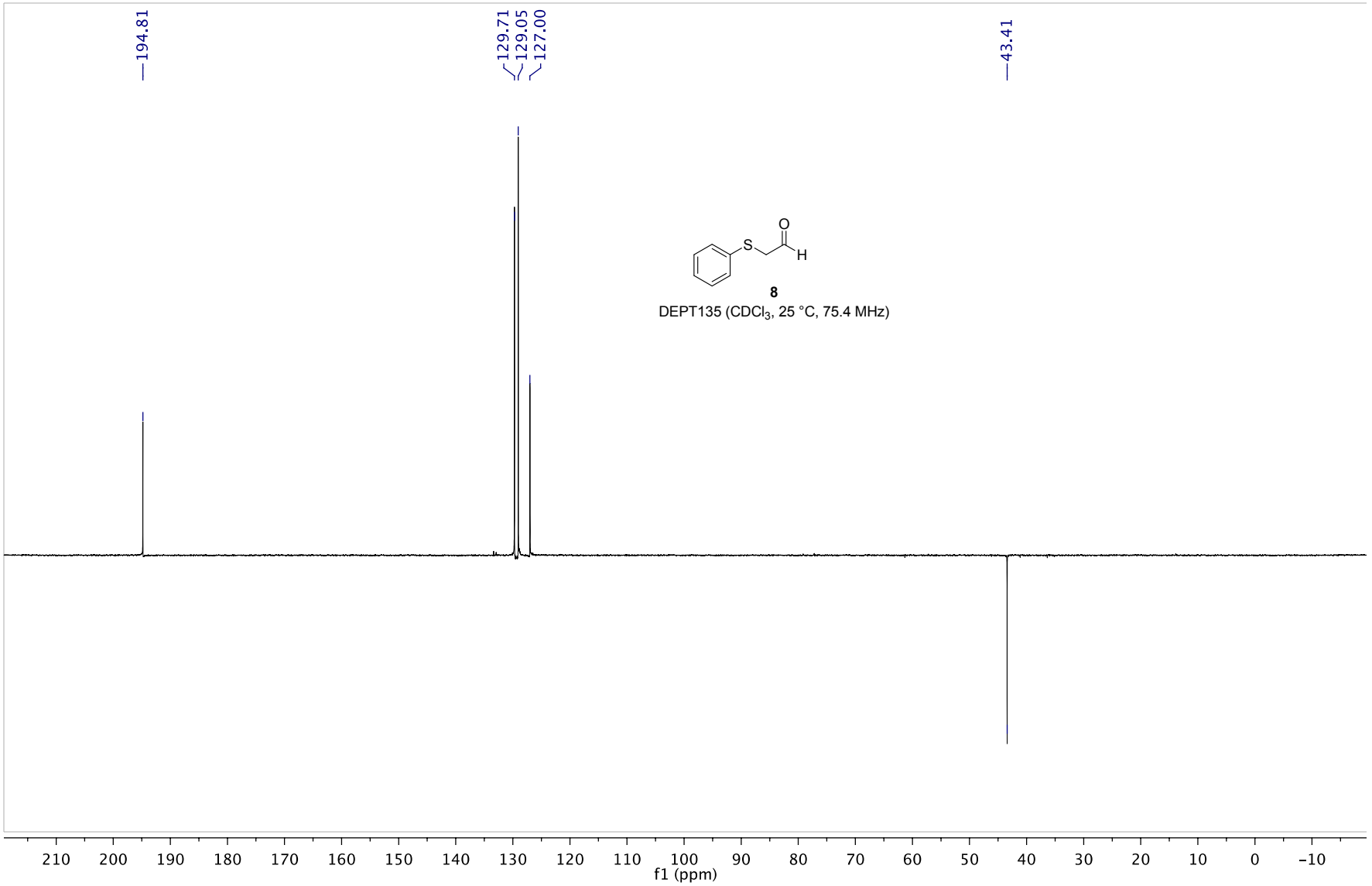

129.17
128.78
125.96
101.64
62.04
37.26
15.16
OEt
OEt
S
16
DEPT135 (CDCl3, 25 °C, 75.4 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

c

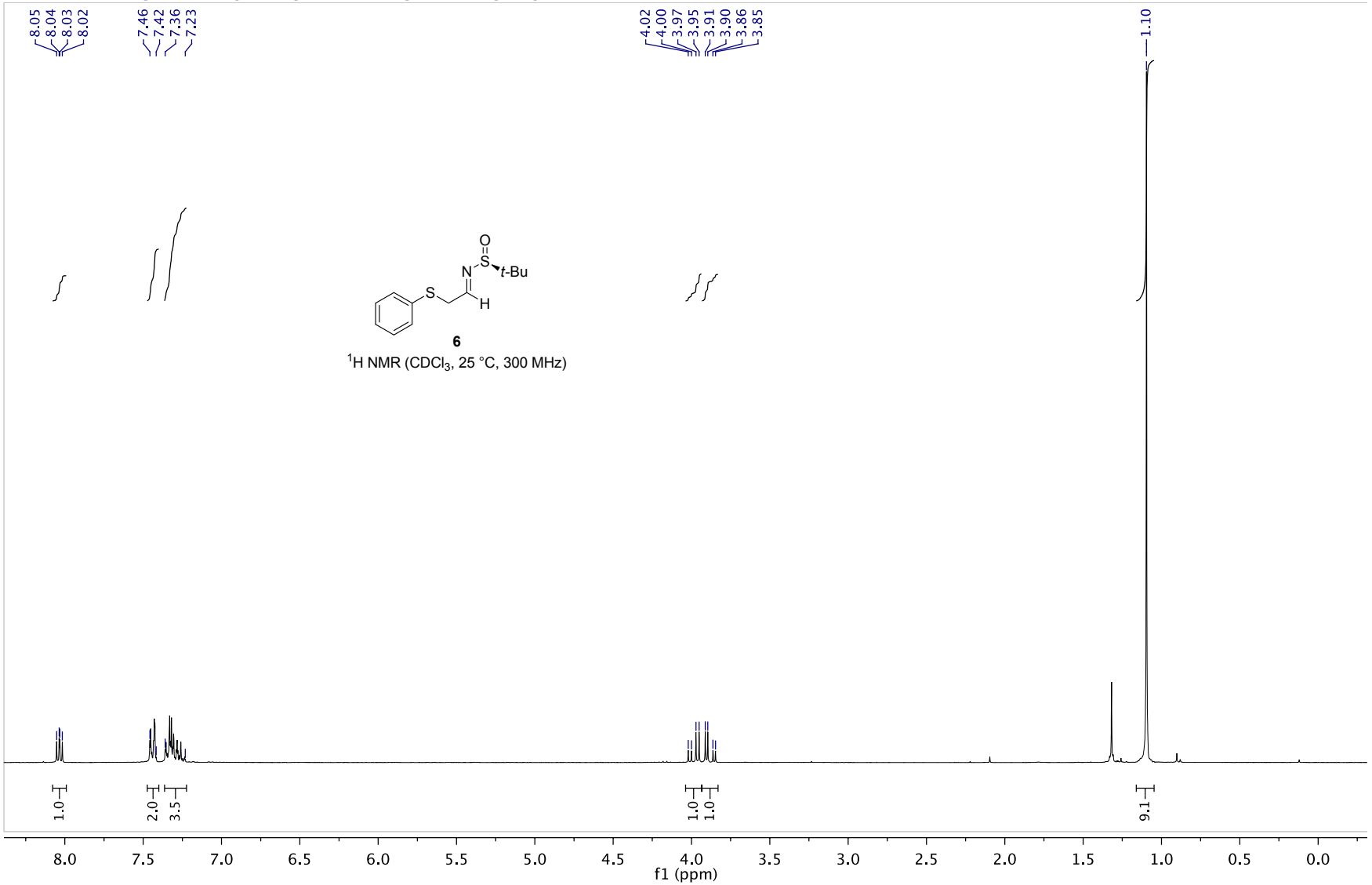
2-(phenylthio)acetaldehyde (8)

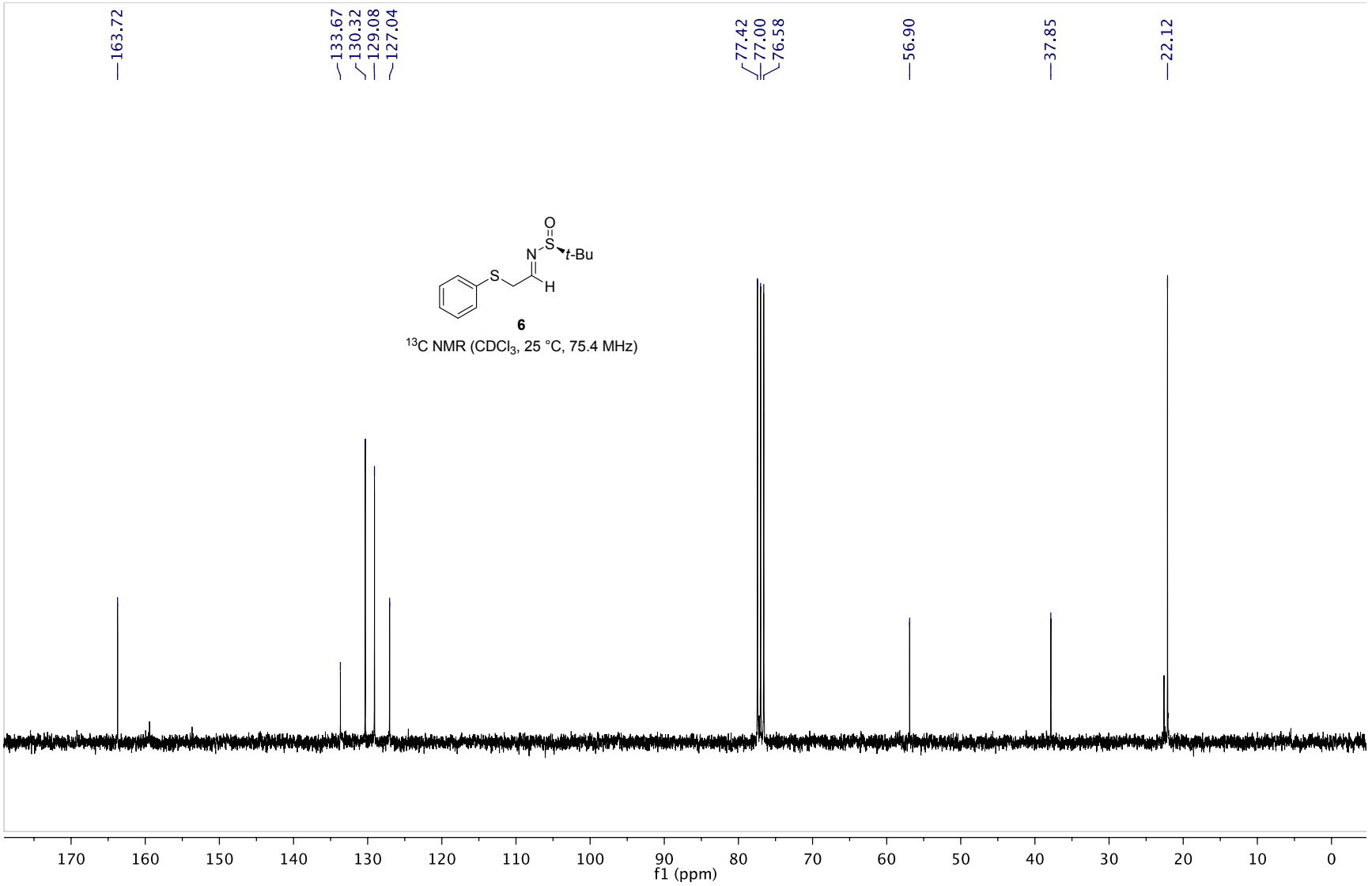


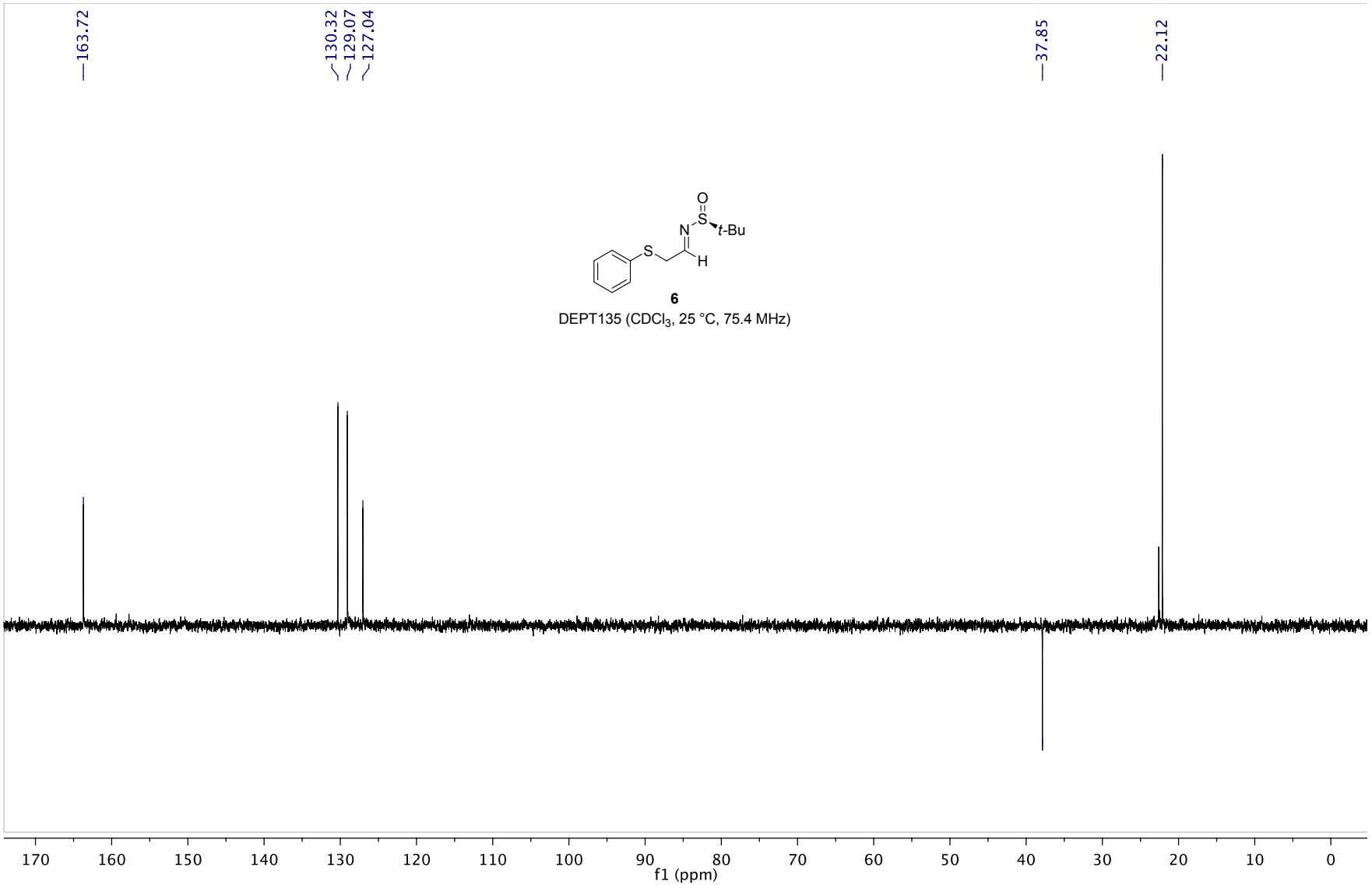

194.80
133.37
129.71
129.05
127.00
77.43
77.00
76.58
43.41
O
S
H
8
13C NMR (CDCl3, 25 °C, 75.4 MHz)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


194.81
129.71
129.05
127.00
43.41
S
O
H
8
DEPT135 ($CDCl_3$, 25 °C, 75.4 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

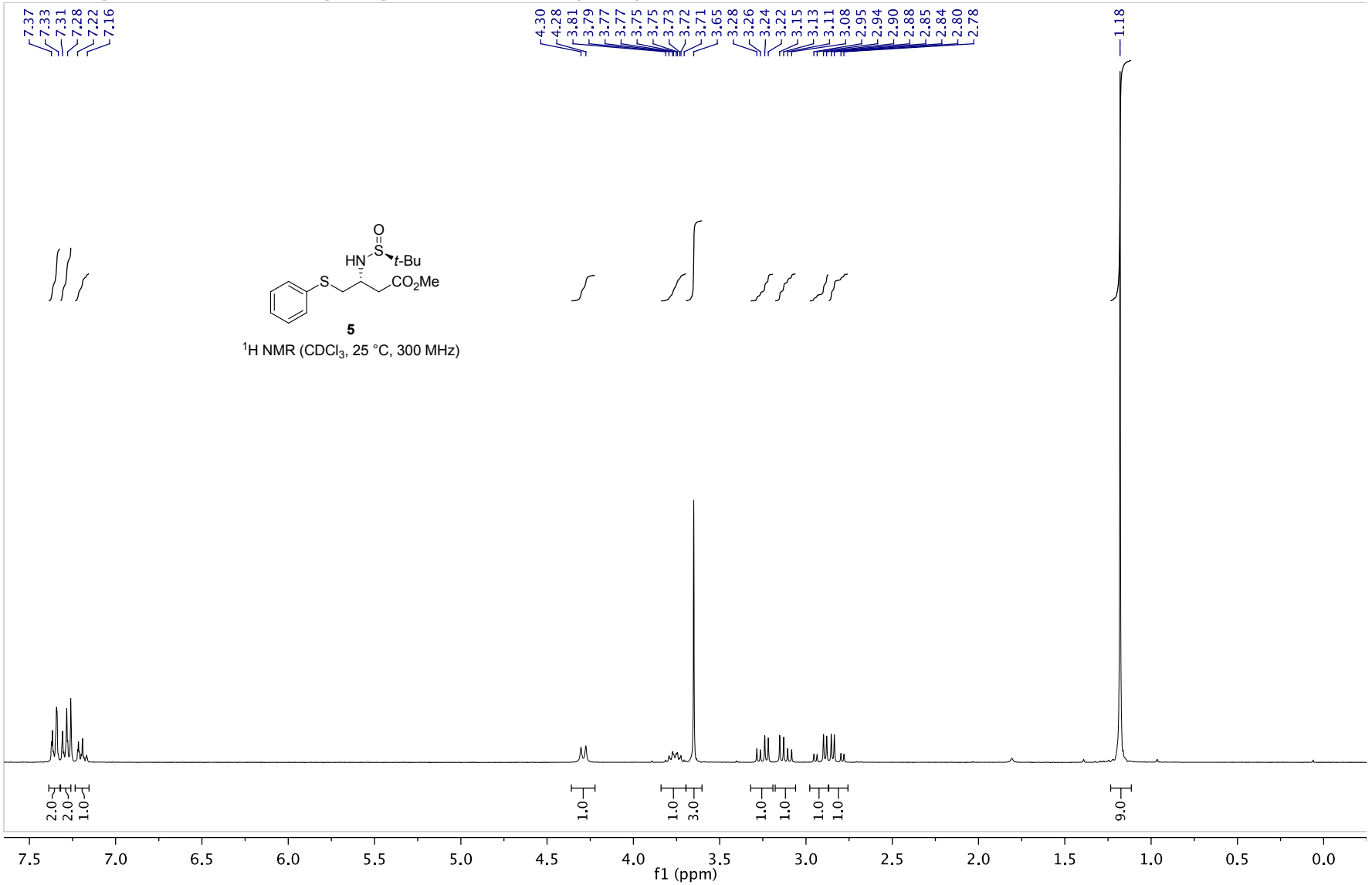
(*S*,*E*)-2-methyl-*N*-(2-(phenylthio)ethylidene)propane-2-sulfinamide (6)

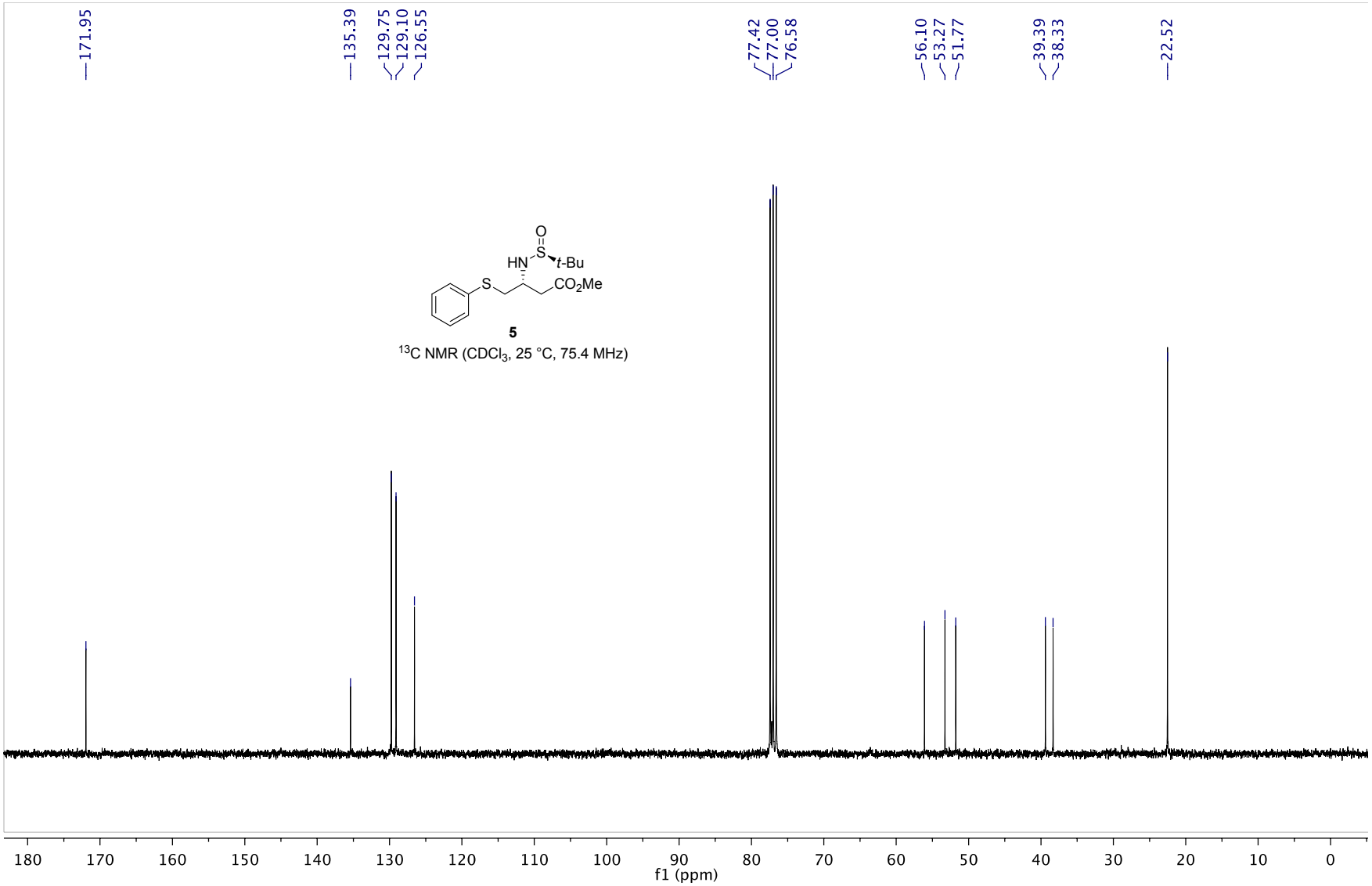


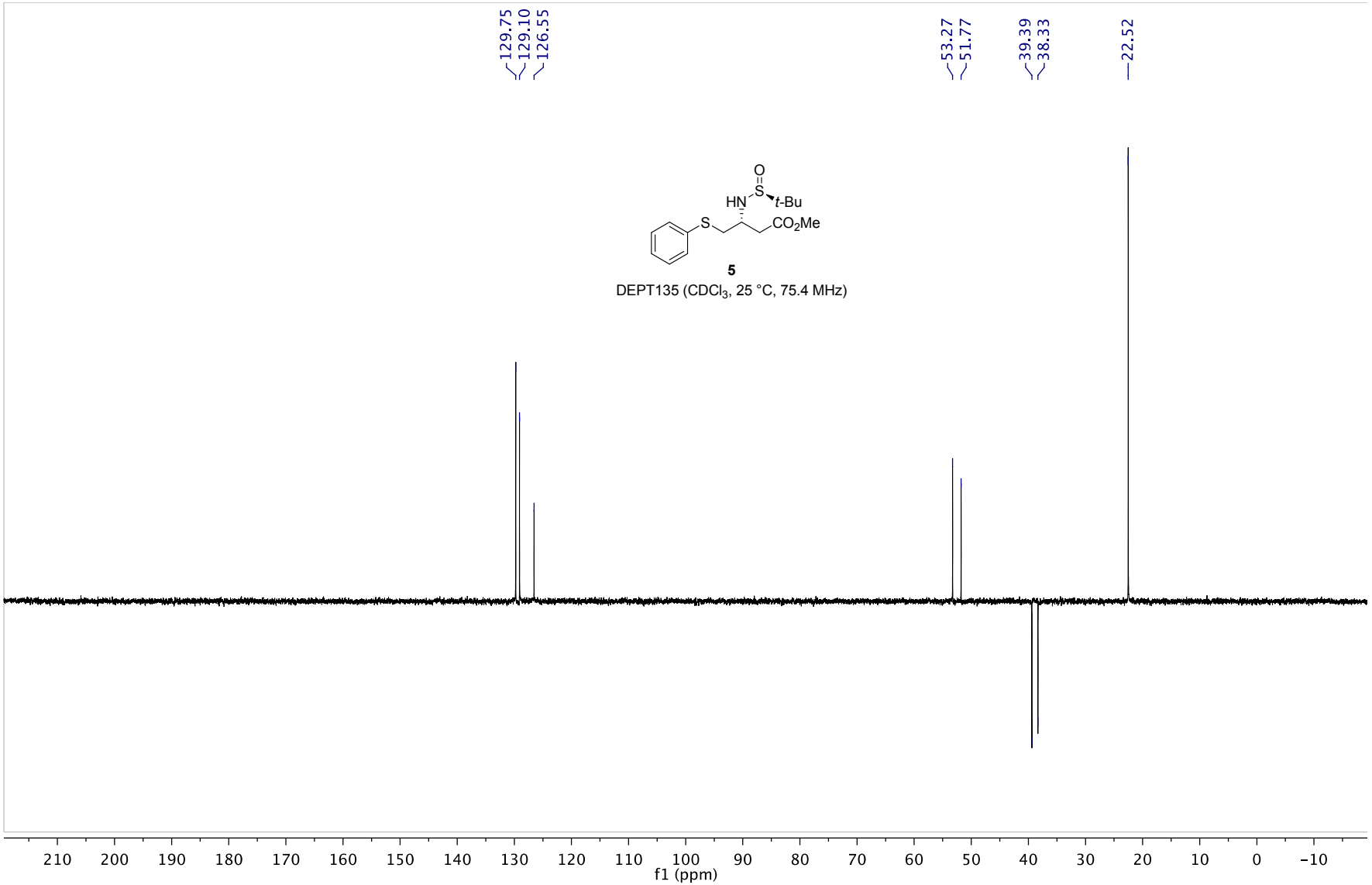

163.72
133.67
130.32
129.08
127.04
77.42
77.00
76.58
56.90
37.85
22.12
O
S
N
t-Bu
S
H
6
13C NMR (CDCl3, 25 °C, 75.4 MHz)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


163.72
130.32
129.07
127.04
37.85
22.12
O
S
N
t-Bu
S
H
6
DEPT135 (CDCl3, 25 °C, 75.4 MHz)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

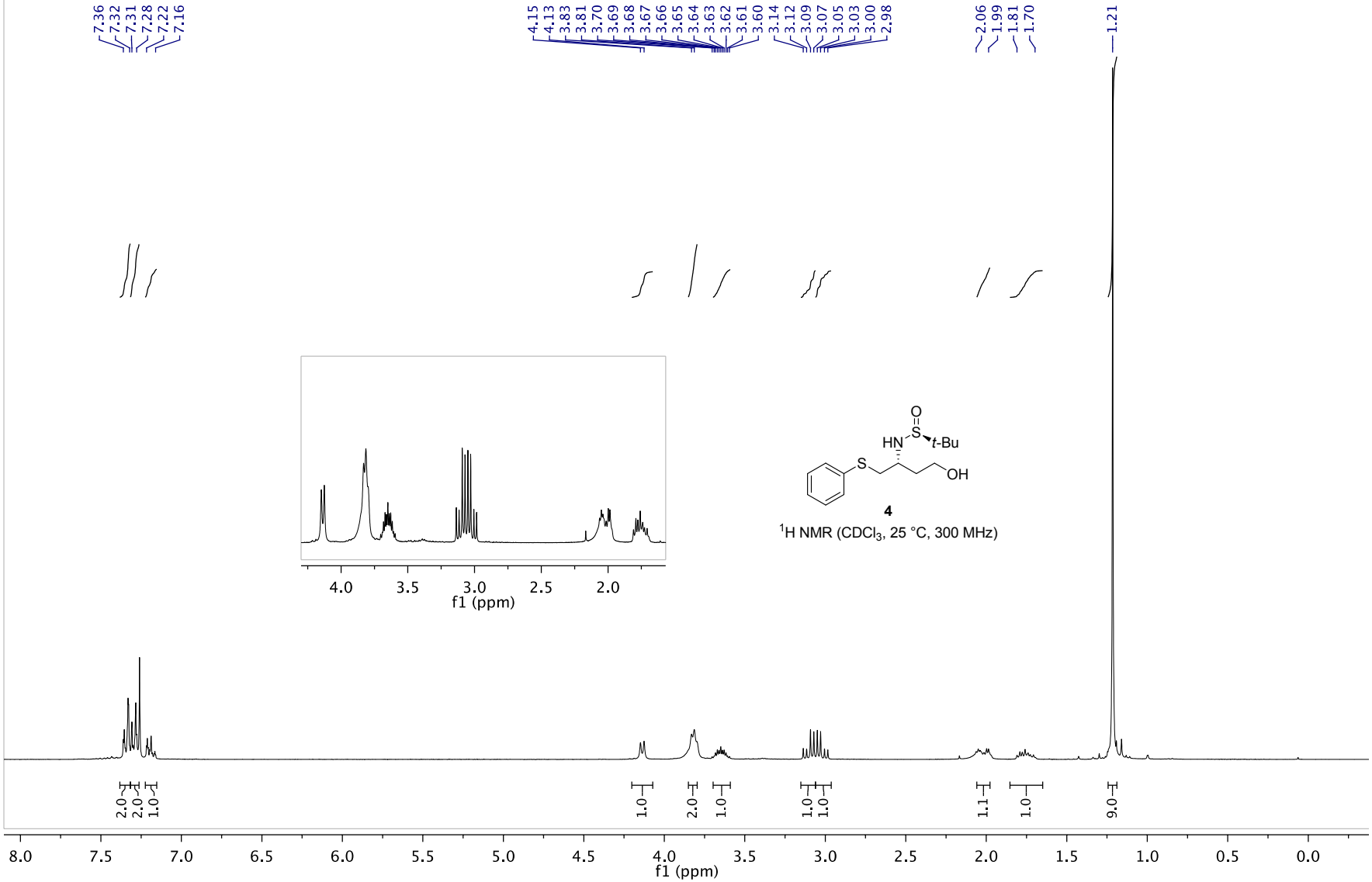
(*R*)-methyl 3-((*S*$_S$)-1,1-dimethylethylsulfinamido)-4-(phenylthio)butanoate (5)

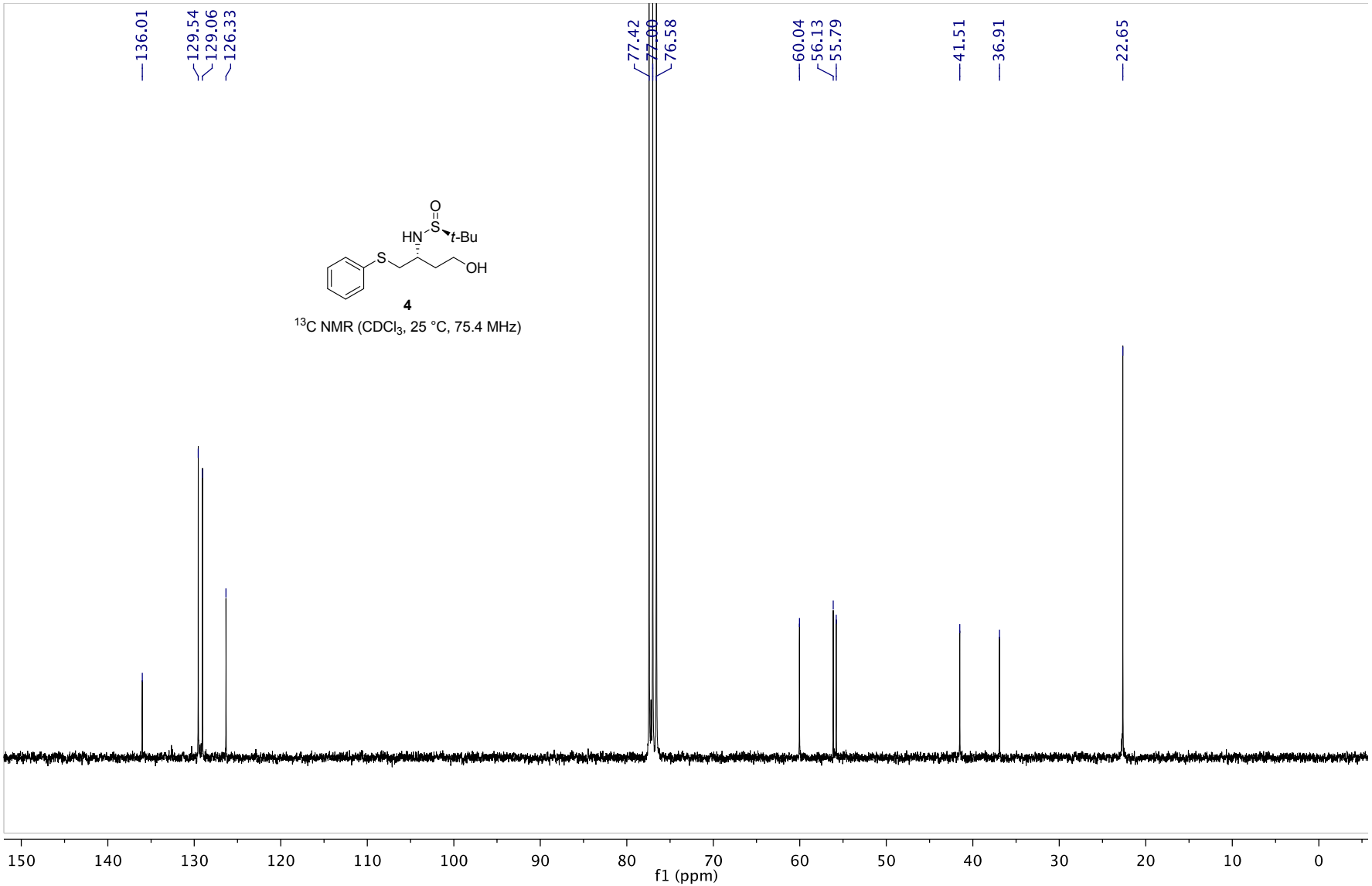


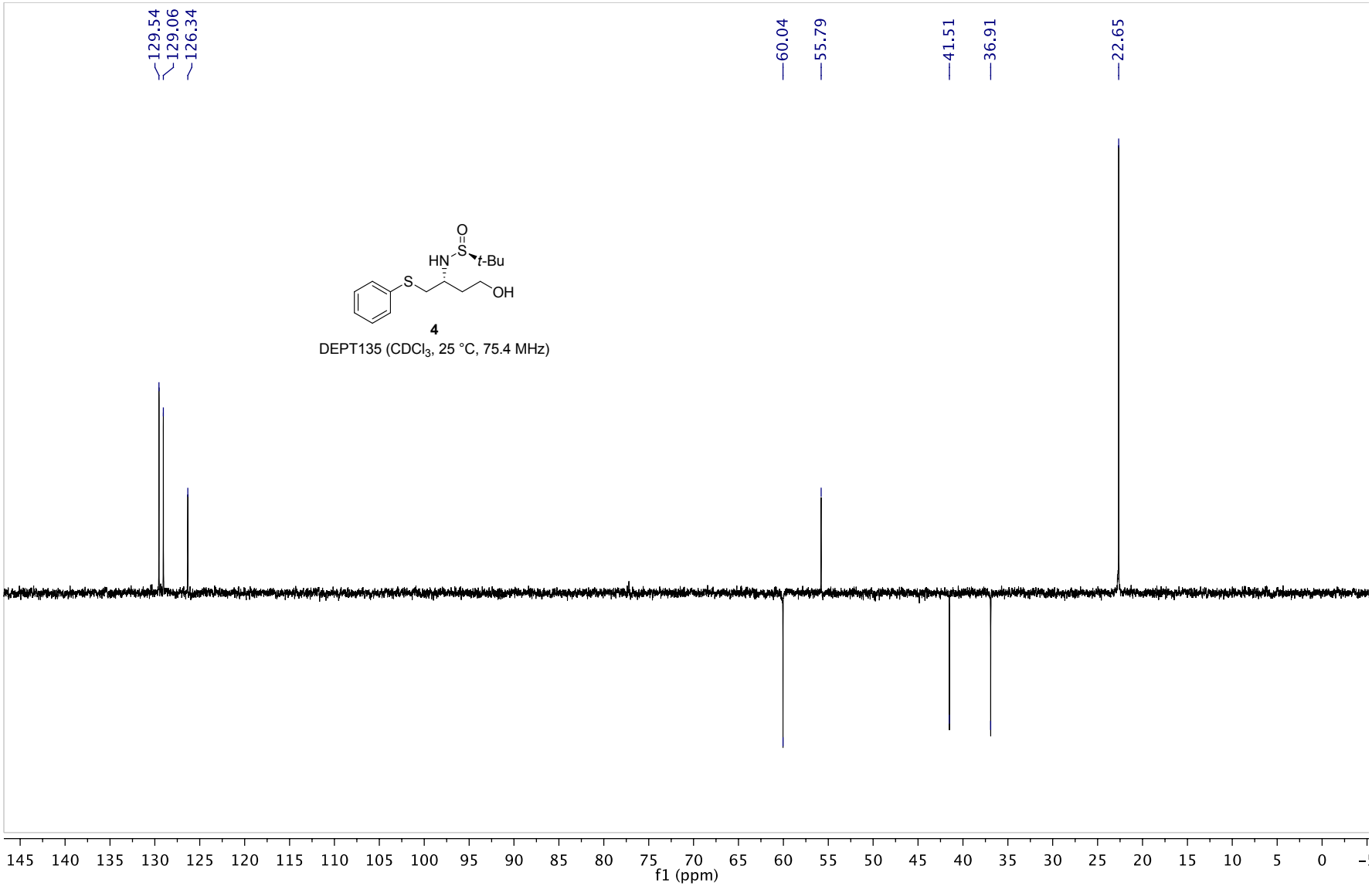

171.95
135.39
129.75
129.10
126.55
77.42
77.00
76.58
56.10
53.27
51.77
39.39
38.33
22.52
O
S
HN
t-Bu
S
CO2Me
5
13C NMR (CDCl3, 25 °C, 75.4 MHz)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


129.75
129.10
126.55
53.27
51.77
39.39
38.33
22.52
O
S
HN
t-Bu
S
CO2Me
5
DEPT135 (CDCl3, 25 °C, 75.4 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

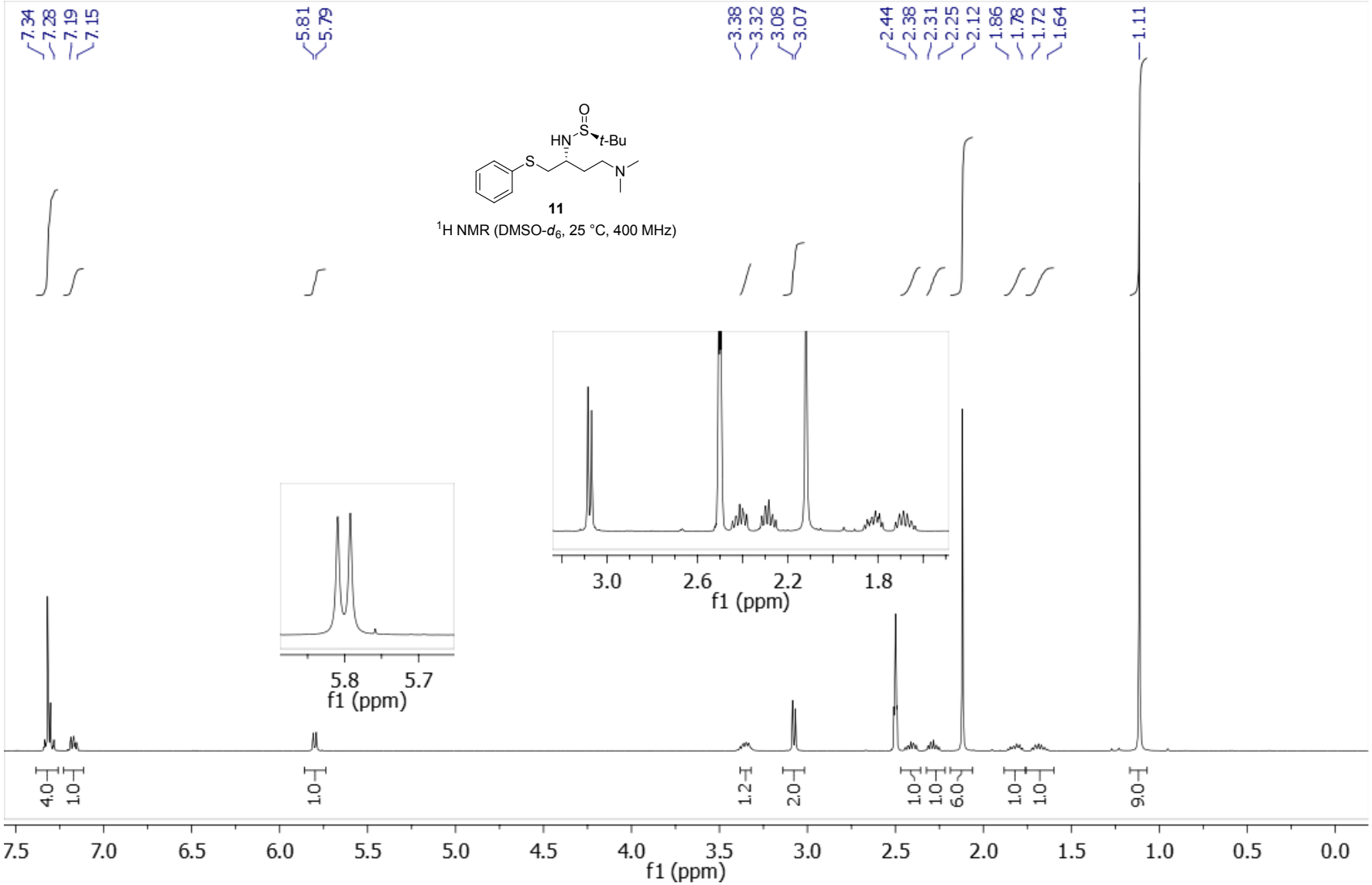
(S_S)-*N*-((*R*)-4-hydroxy-1-(phenylthio)butan-2-yl)-2-methylpropane-2-sulfinamide (4)

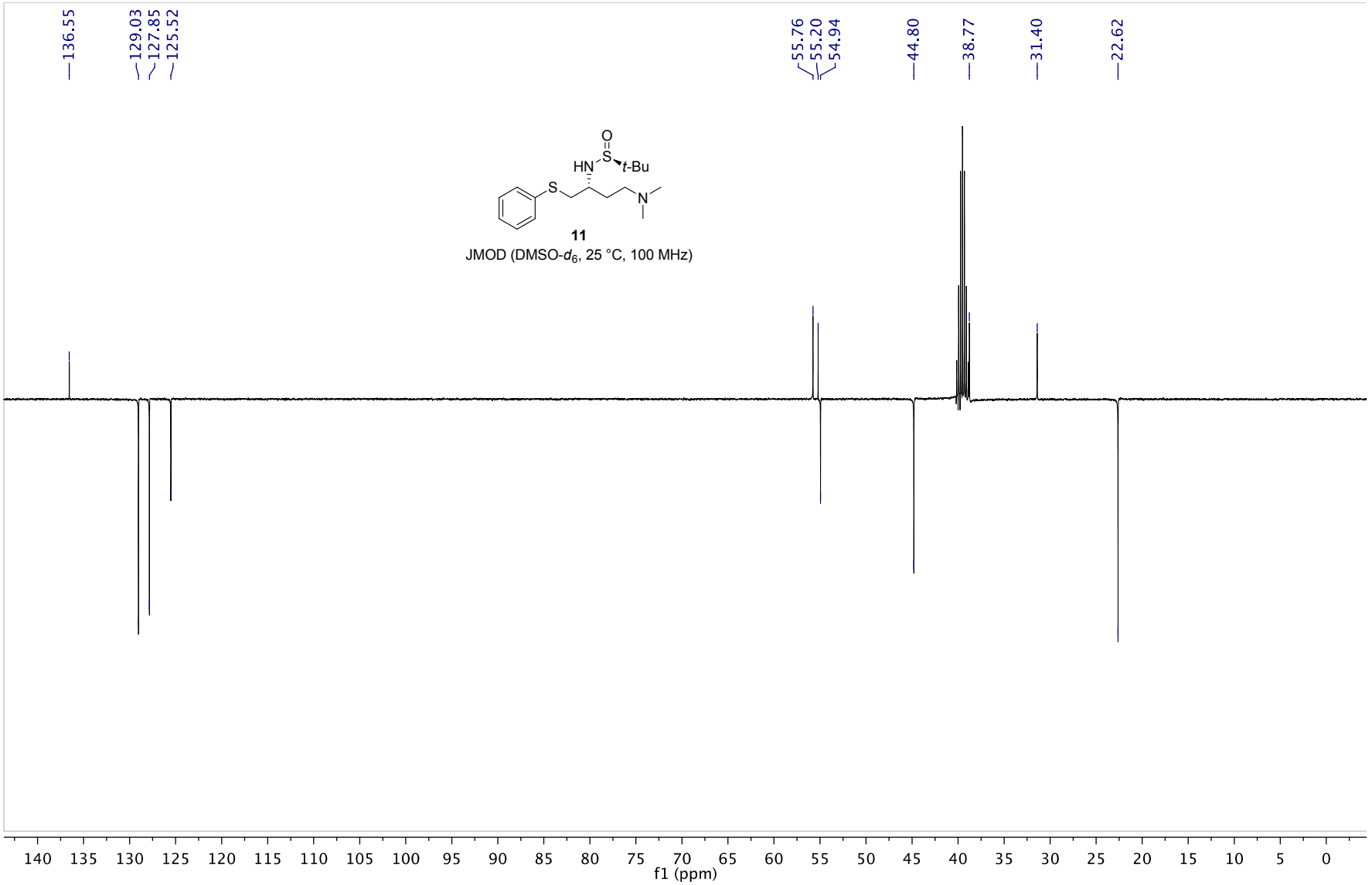


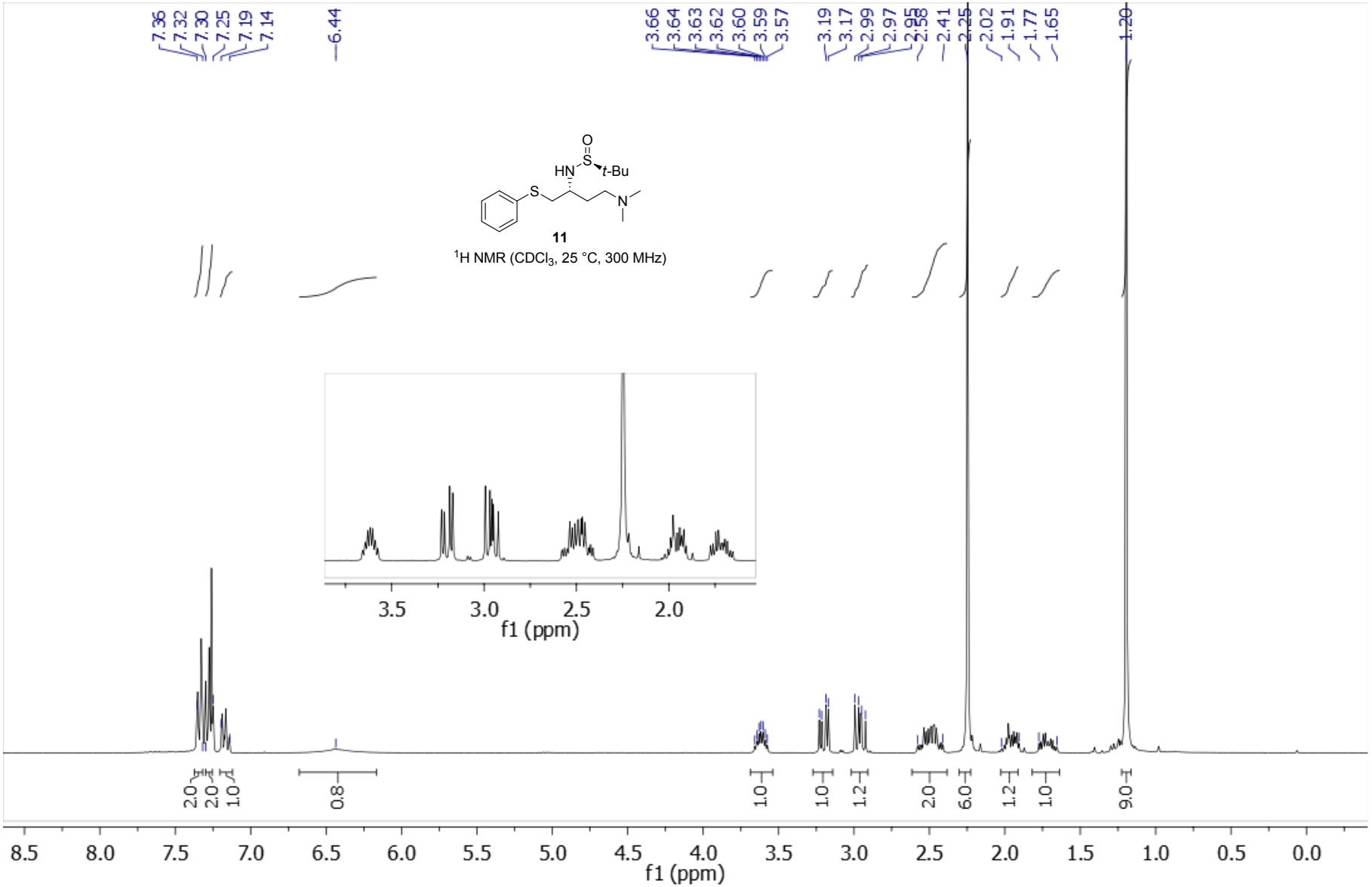

136.01
129.54
129.06
126.33
77.42
77.00
76.58
60.04
56.13
55.79
41.51
36.91
22.65
O
S
HN
t-Bu
S
OH
4
13C NMR (CDCl3, 25 °C, 75.4 MHz)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

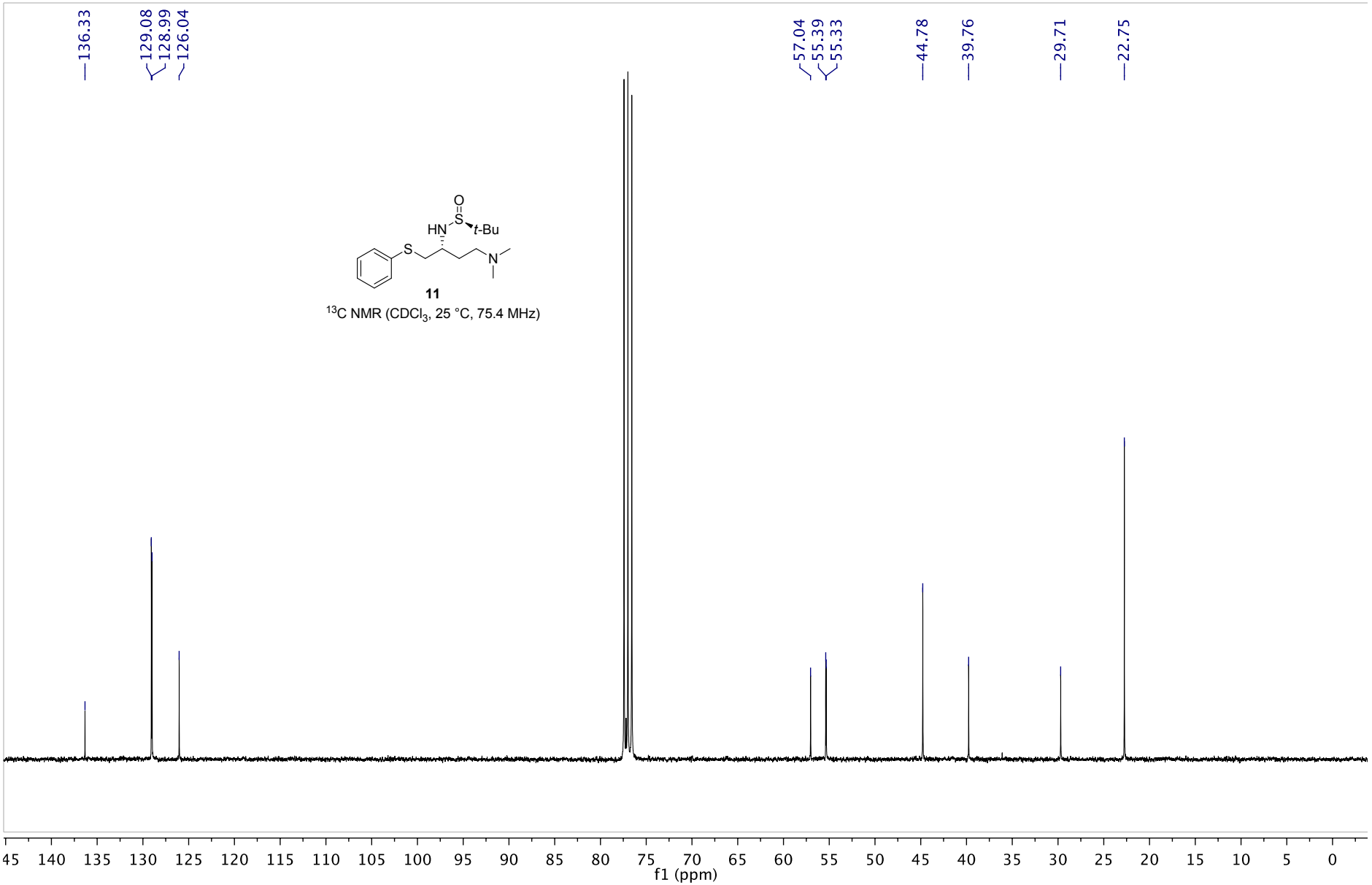

129.54
129.06
126.34
60.04
55.79
41.51
36.91
22.65
O
S
HN
t-Bu
S
OH
4
DEPT135 (CDCl3, 25 °C, 75.4 MHz)
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

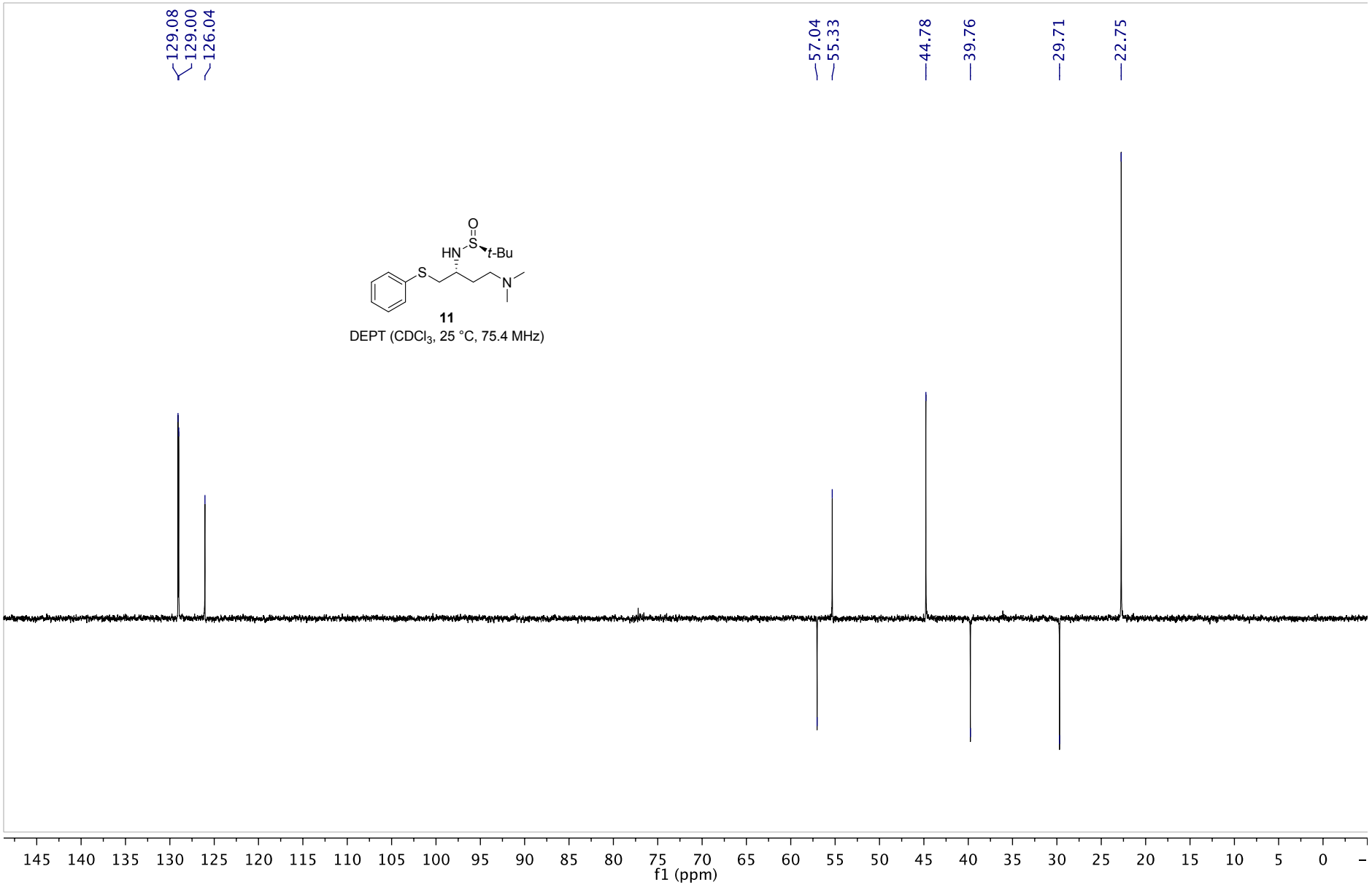
(S_S)-*N*-((*R*)-4-(dimethylacccmino)-1-(phenylthio)butan-2-yl)-2-methylpropane-2-sulfinamide (11)



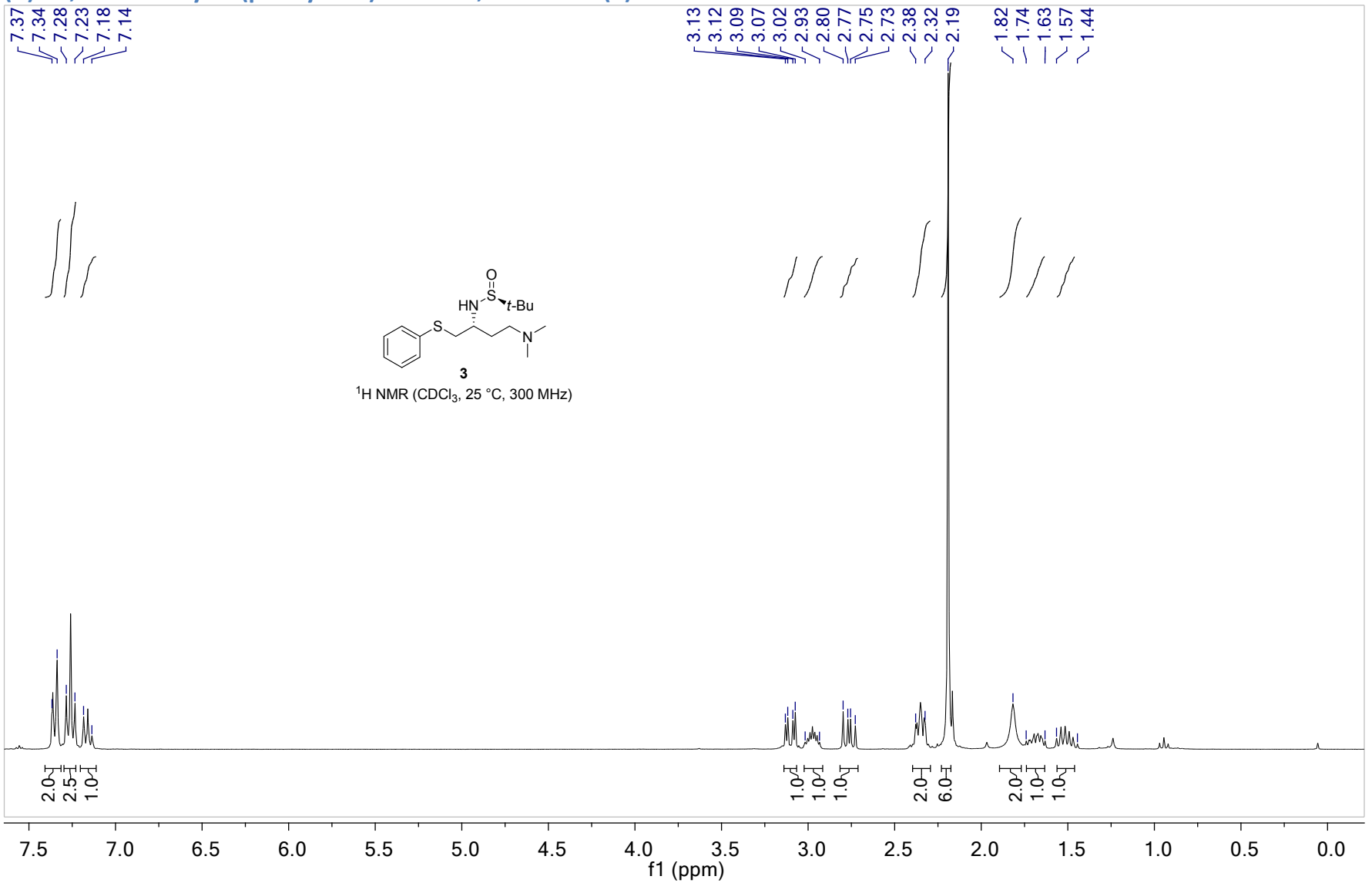

136.55
129.03
127.85
125.52
55.76
55.20
54.94
44.80
38.77
31.40
22.62
O
S
HN
t-Bu
S
N
11
JMOD (DMSO-d6, 25 °C, 100 MHz)
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

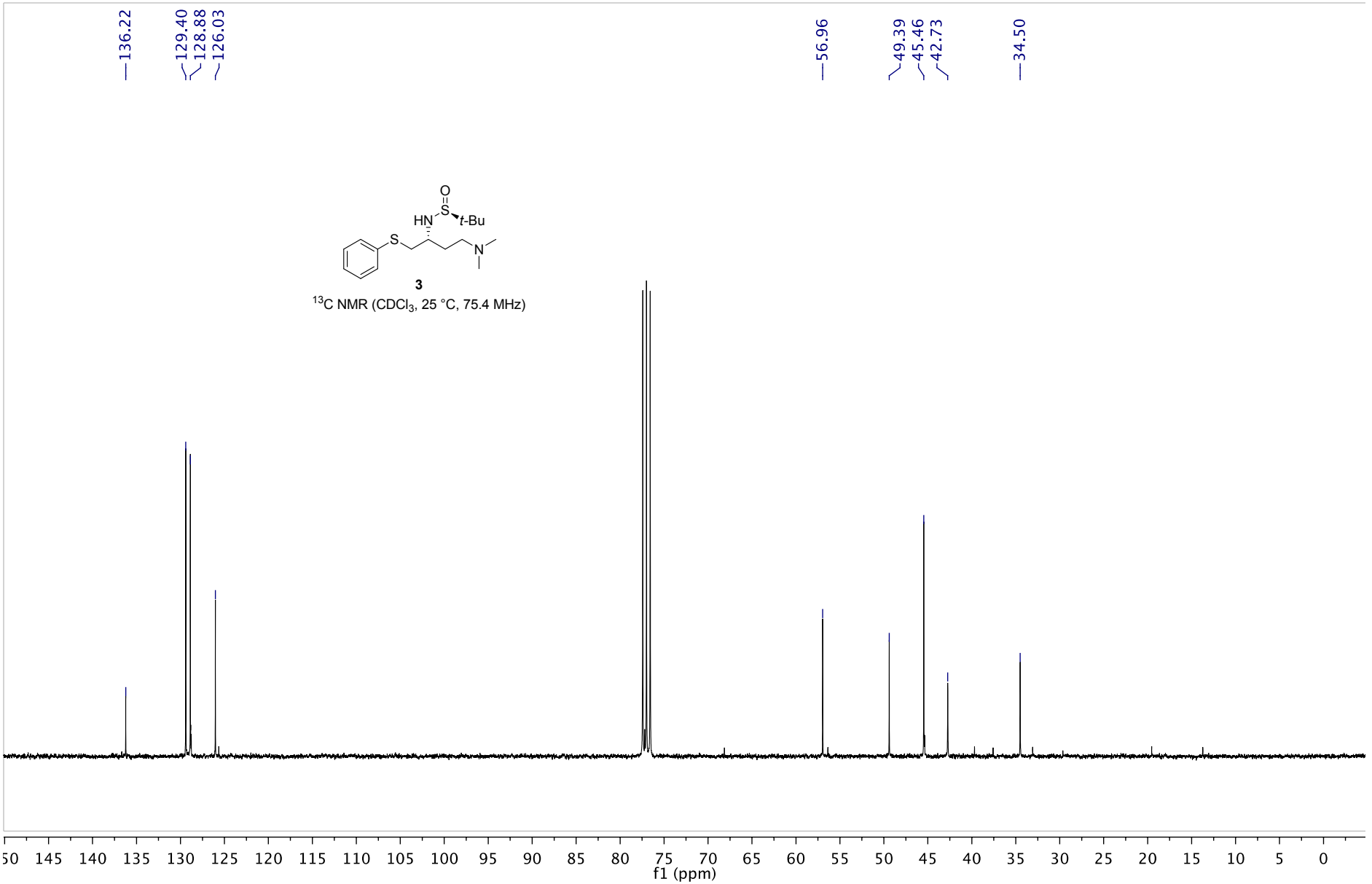

7.36
7.32
7.30
7.25
7.19
7.14
6.44
3.66
3.64
3.63
3.62
3.60
3.59
3.57
3.19
3.17
2.99
2.97
2.95
2.58
2.41
2.25
2.02
1.91
1.77
1.65
1.20
HN
S
O
t-Bu
S
N
11
1H NMR (CDCl3, 25 °C, 300 MHz)
3.5
3.0
2.5
2.0
f1 (ppm)
2.0
2.0
1.0
0.8
1.0
1.0
1.2
2.0
6.0
1.2
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

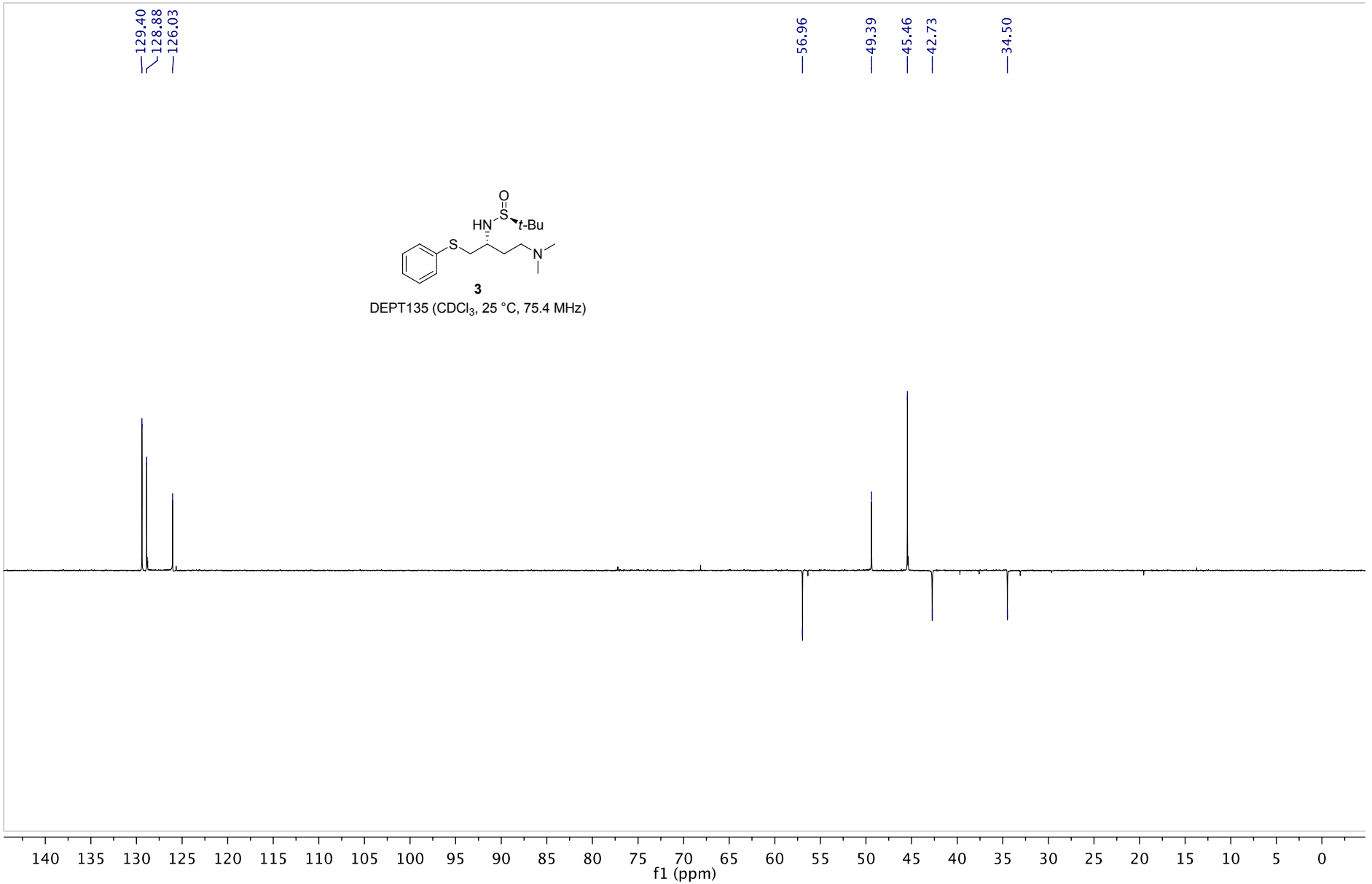

136.33
129.08
128.99
126.04
57.04
55.39
55.33
44.78
39.76
29.71
22.75
HN
S
O
t-Bu
S
N
11
13C NMR (CDCl3, 25 °C, 75.4 MHz)
f1 (ppm)


129.08
129.00
126.04
57.04
55.33
44.78
39.76
29.71
22.75
O
S
HN
t-Bu
S
N
11
DEPT (CDCl3, 25 °C, 75.4 MHz)
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

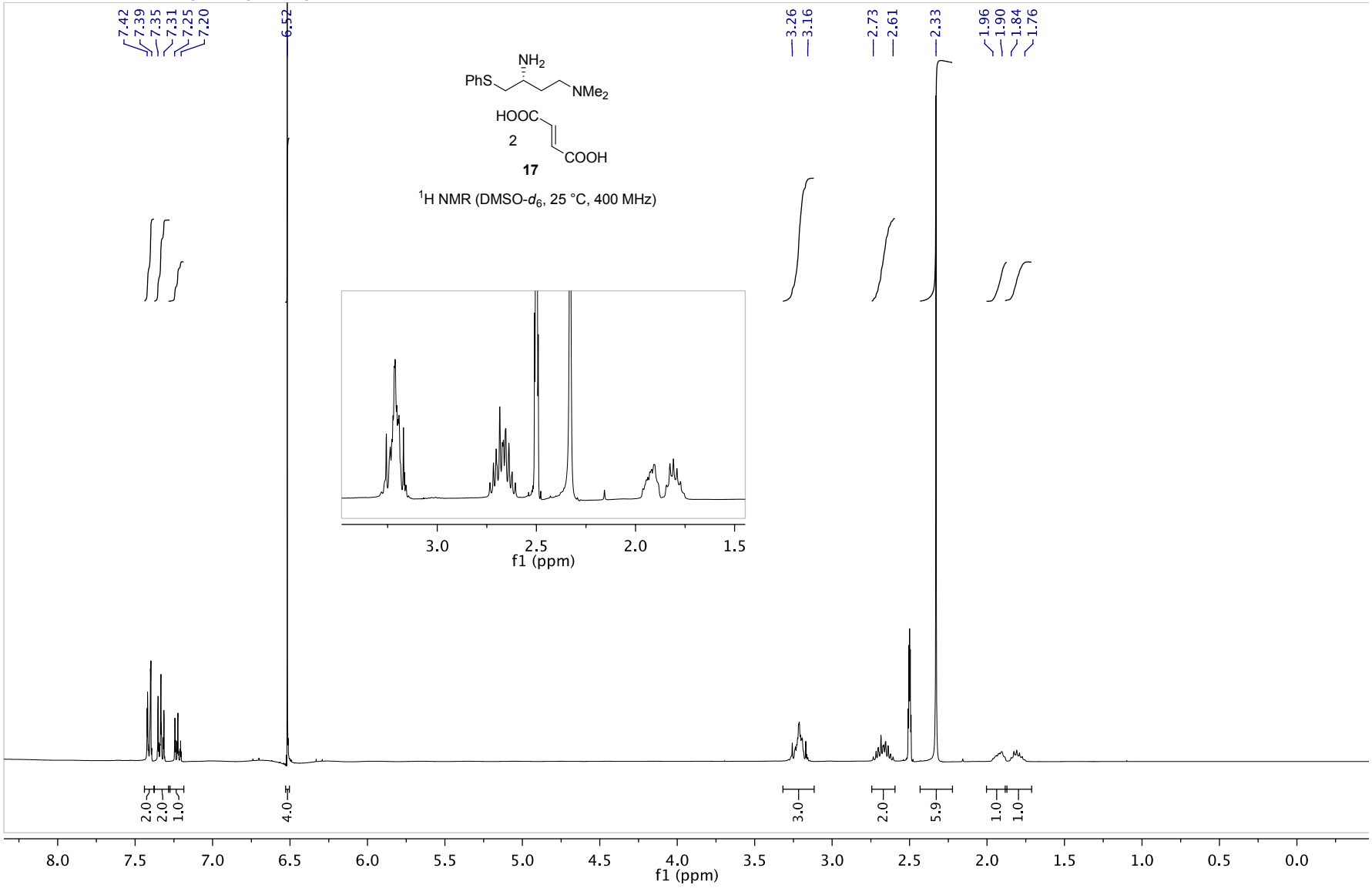
(*R*)-N^1,N^1-dimethyl-4-(phenylthio)butane-1,3-diamine (3)

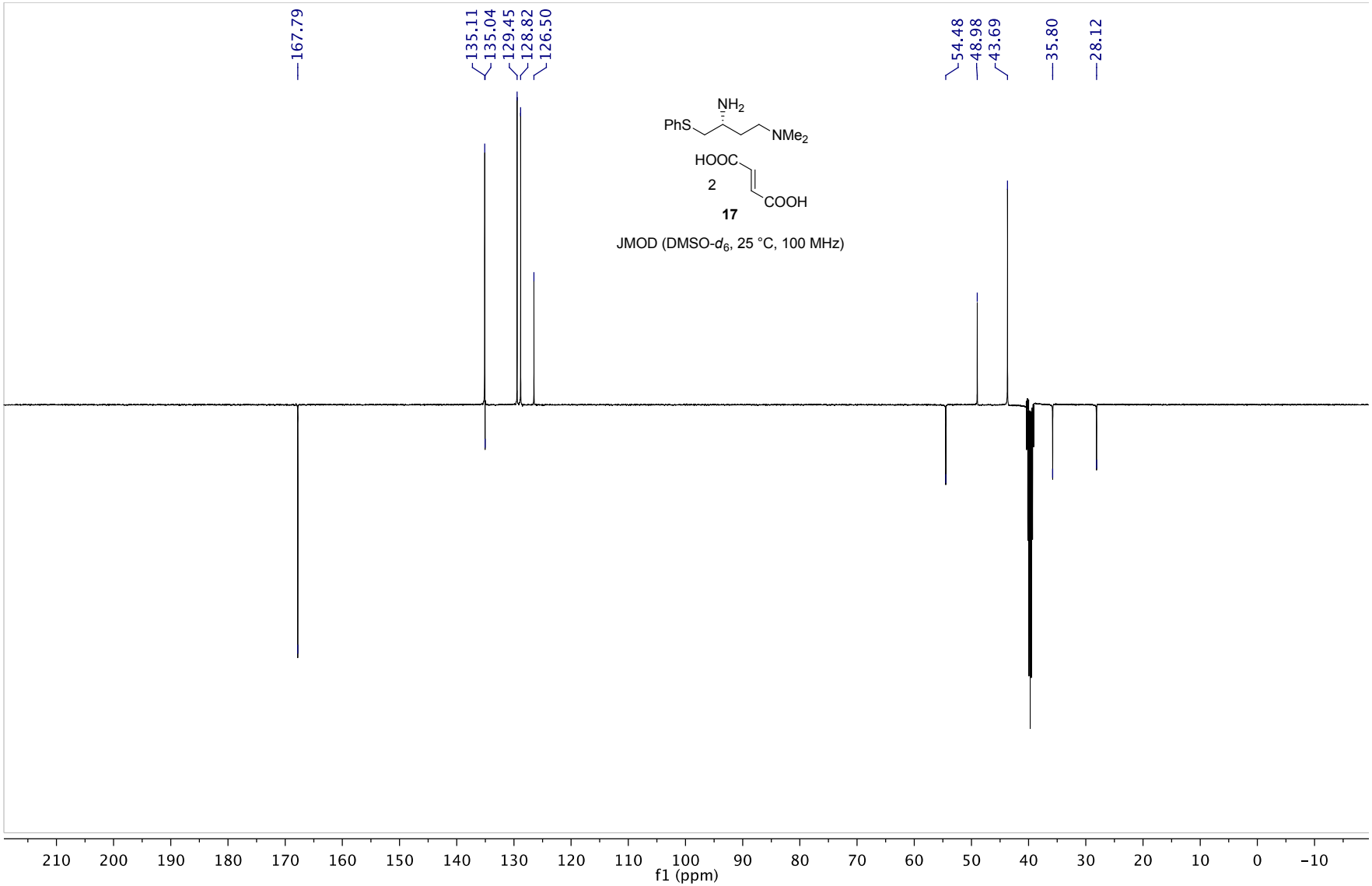


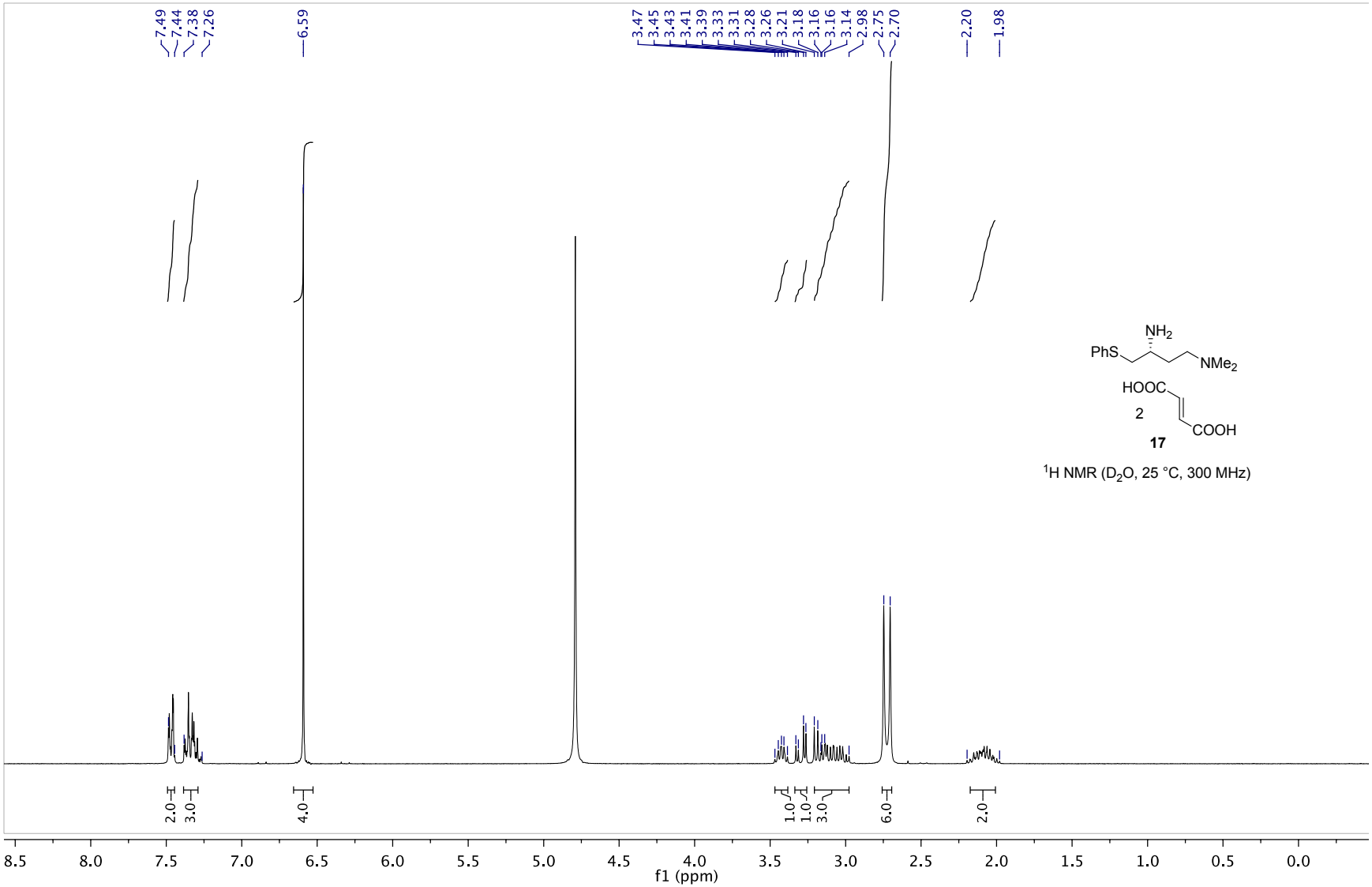

136.22
129.40
128.88
126.03
56.96
49.39
45.46
42.73
34.50
O
S
HN
t-Bu
S
N
3
13C NMR (CDCl3, 25 °C, 75.4 MHz)
f1 (ppm)

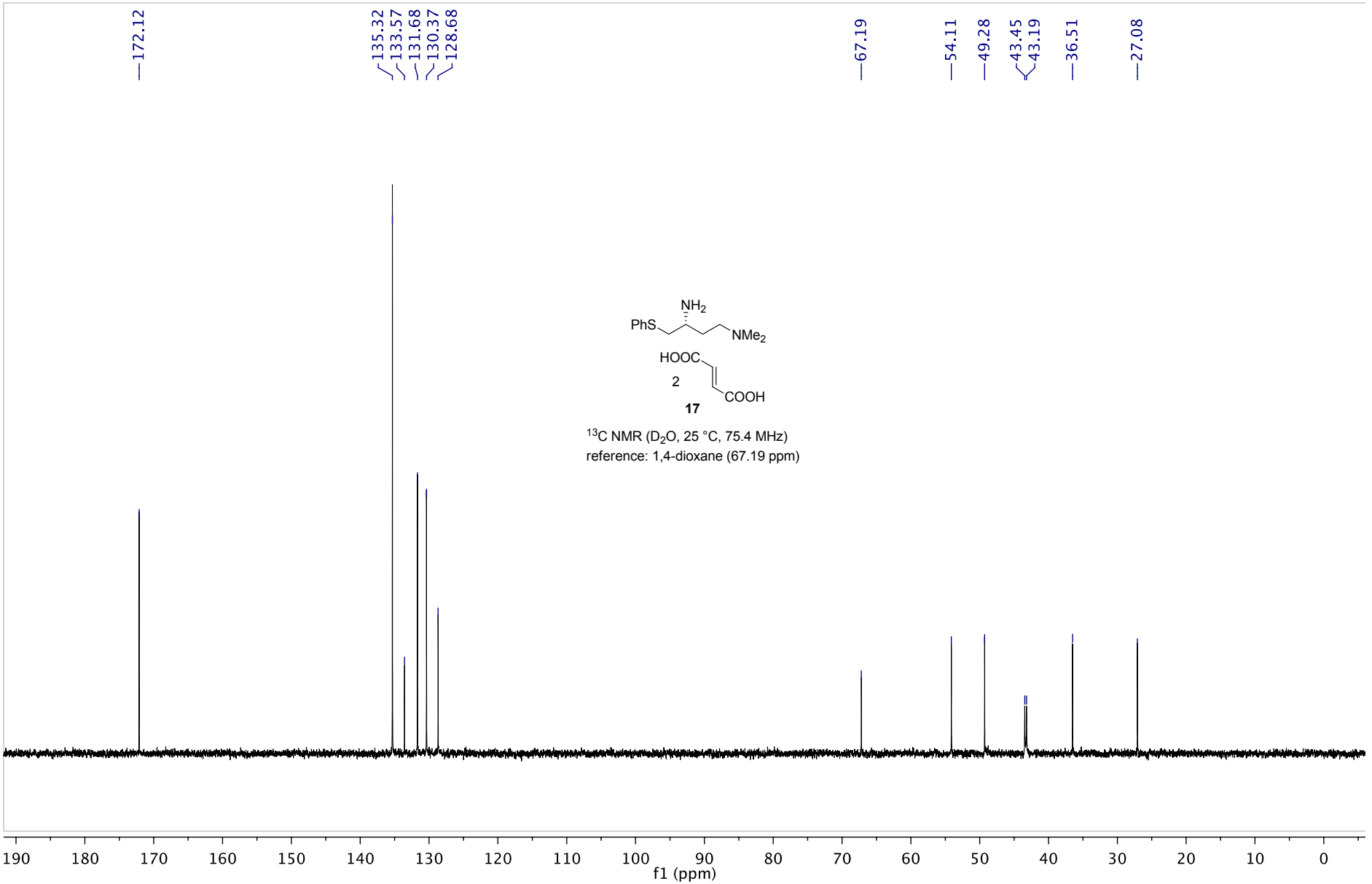

129.40
128.88
126.03
56.96
49.39
45.46
42.73
34.50
HN
S
O
t-Bu
S
N
3
DEPT135 (CDCl3, 25 °C, 75.4 MHz)
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

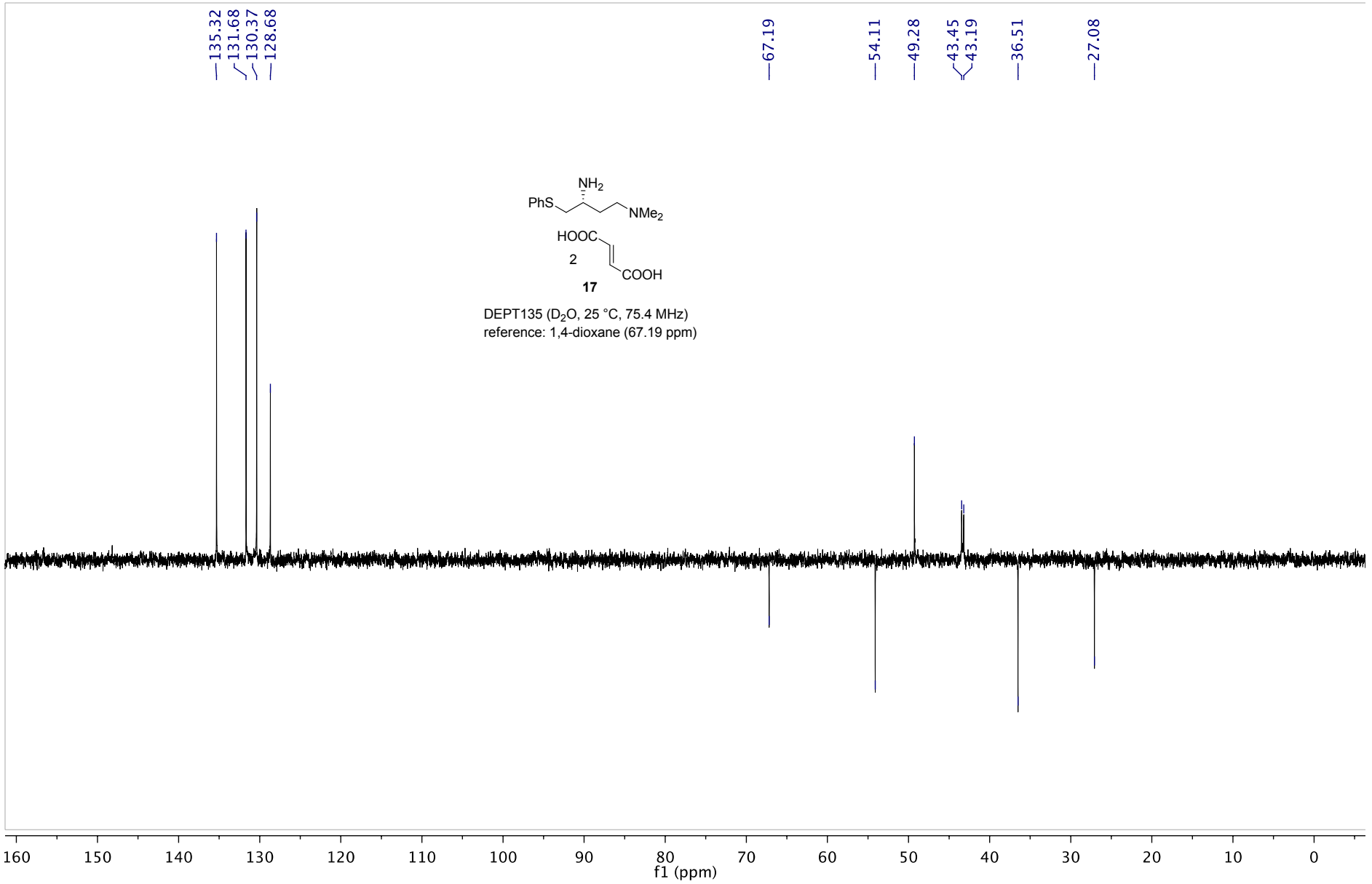
(*R*)-N^1,N^1-dimethyl-4-(phenylthio)butane-1,3-diamine difumarate salt (17)

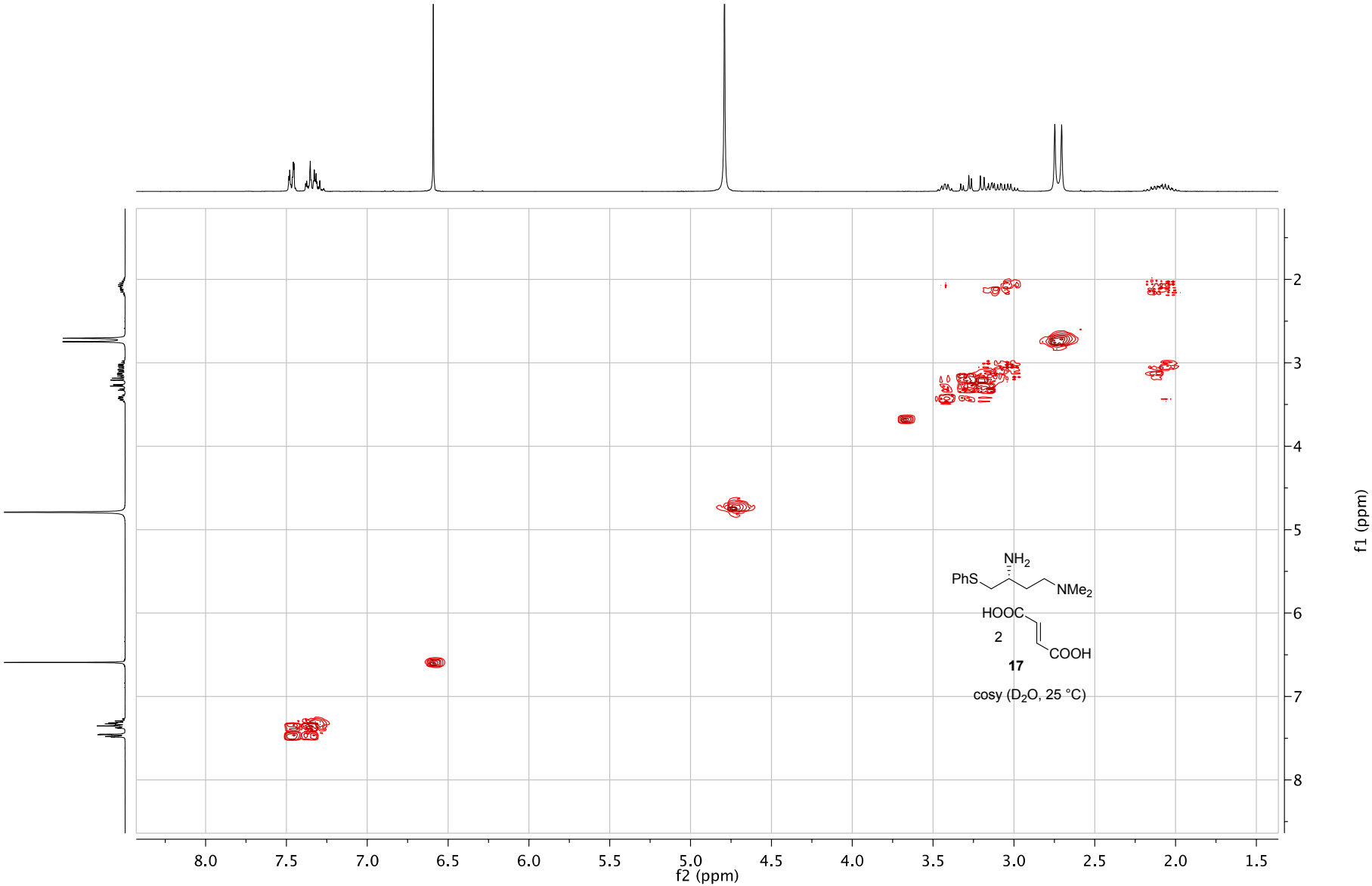


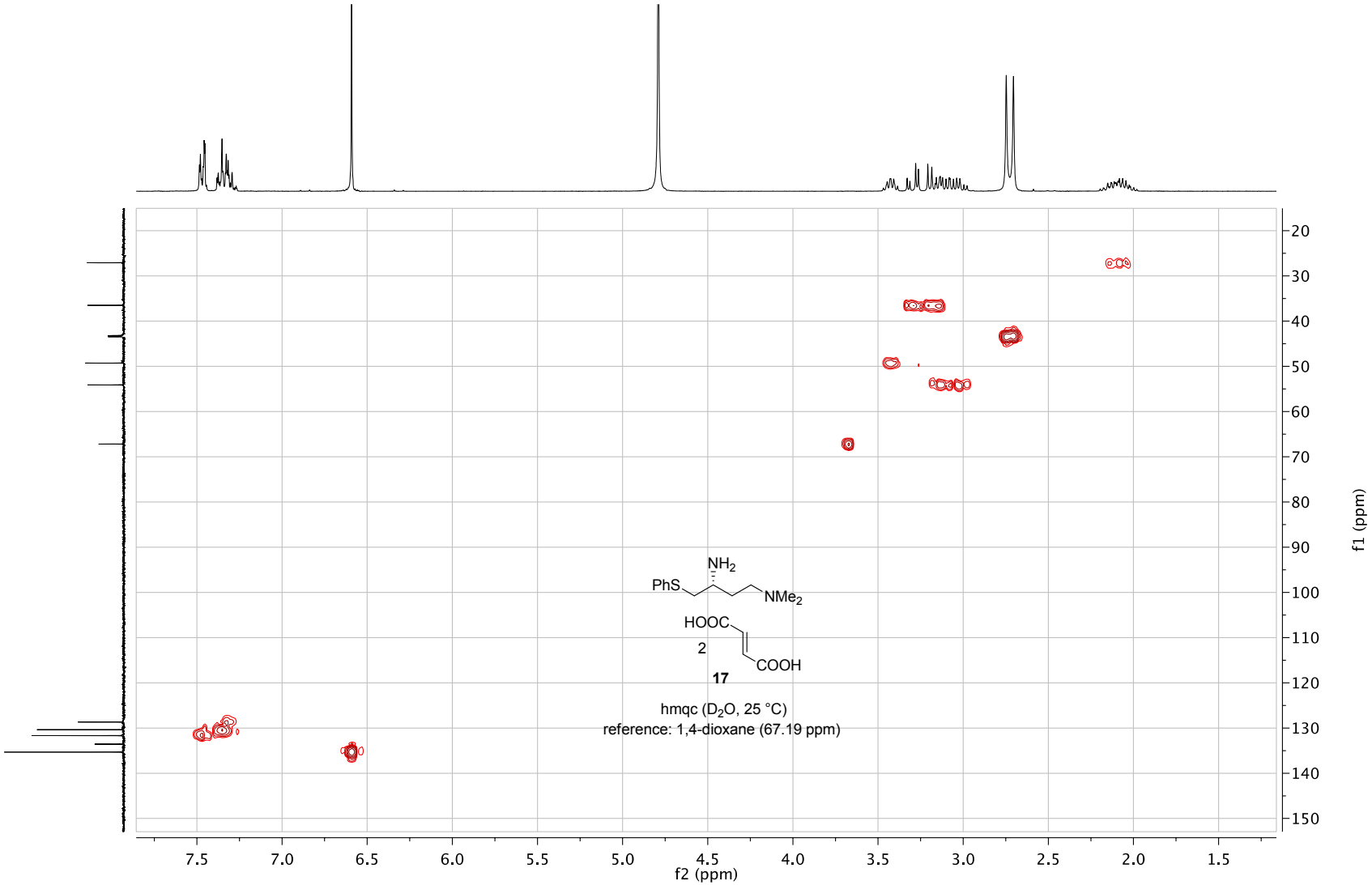

167.79
135.11
135.04
129.45
128.82
126.50
54.48
48.98
43.69
35.80
28.12
NH2
PhS
NMe2
HOOC
2
COOH
17
JMOD (DMSO-d6, 25 °C, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.49
7.44
7.38
7.26
6.59
3.47
3.45
3.43
3.41
3.39
3.33
3.31
3.28
3.26
3.21
3.18
3.16
3.16
3.14
2.98
2.75
2.70
2.20
1.98
NH2
PhS
NMe2
HOOC
2
COOH
17
1H NMR (D2O, 25 °C, 300 MHz)
2.0
3.0
4.0
1.0
1.0
3.0
6.0
2.0
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
0.0
f1 (ppm)

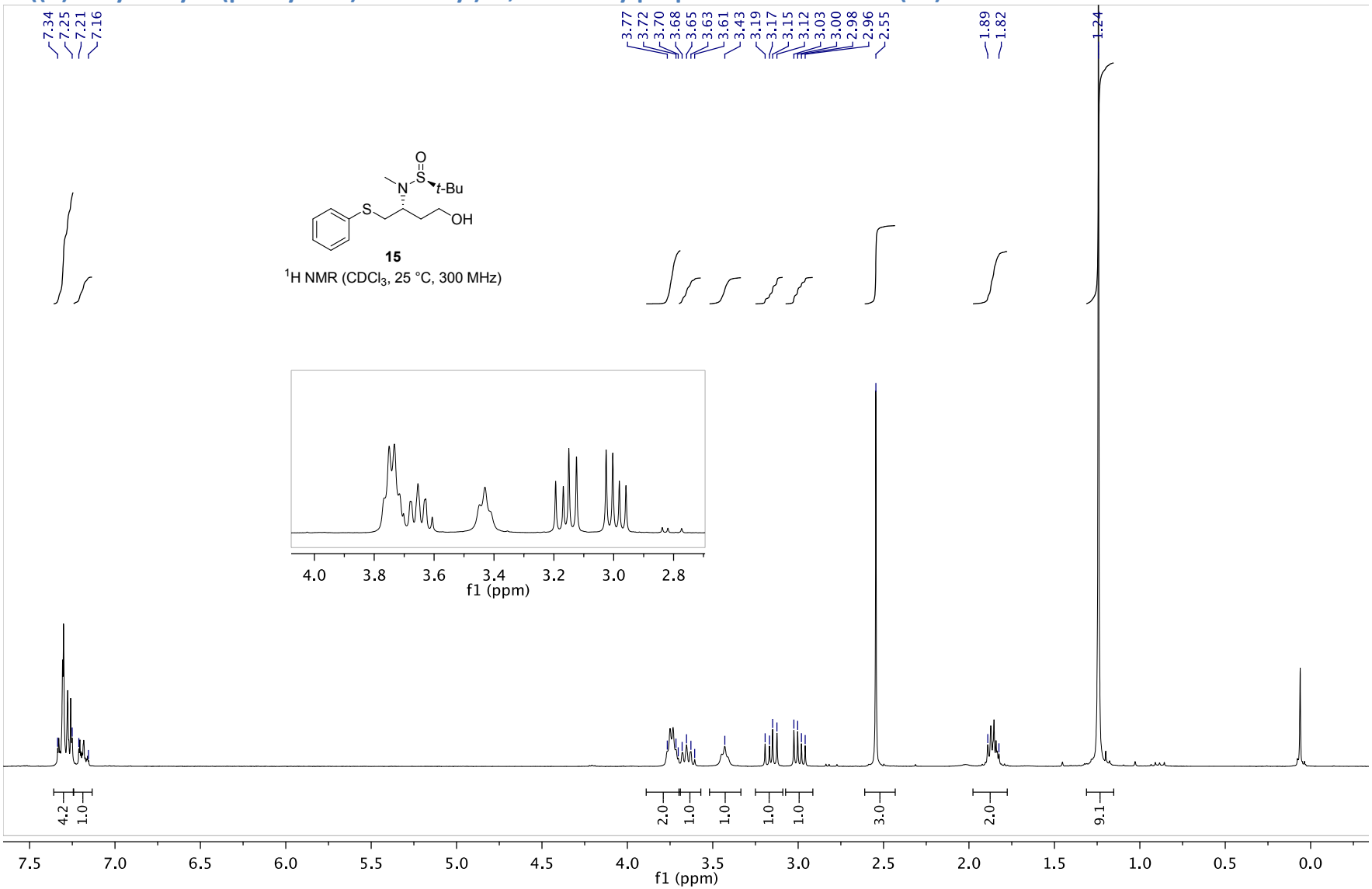

172.12
135.32
133.57
131.68
130.37
128.68
67.19
54.11
49.28
43.45
43.19
36.51
27.08
NH2
PhS
NMe2
HOOC
2
COOH
17
13C NMR (D2O, 25 °C, 75.4 MHz)
reference: 1,4-dioxane (67.19 ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

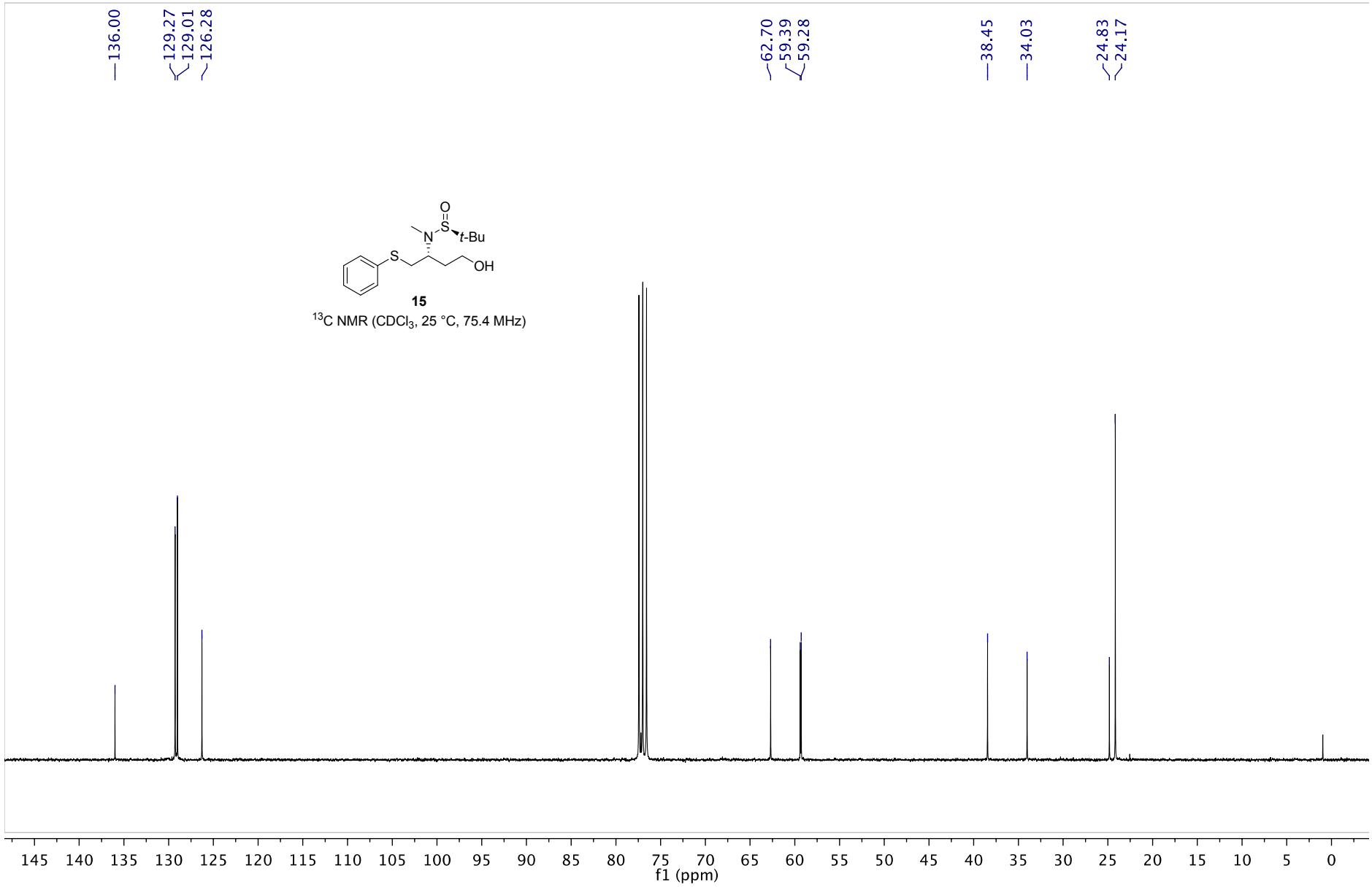

135.32
131.68
130.37
128.68
67.19
54.11
49.28
43.45
43.19
36.51
27.08
NH2
PhS
NMe2
HOOC
2
COOH
17
DEPT135 (D2O, 25 °C, 75.4 MHz)
reference: 1,4-dioxane (67.19 ppm)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

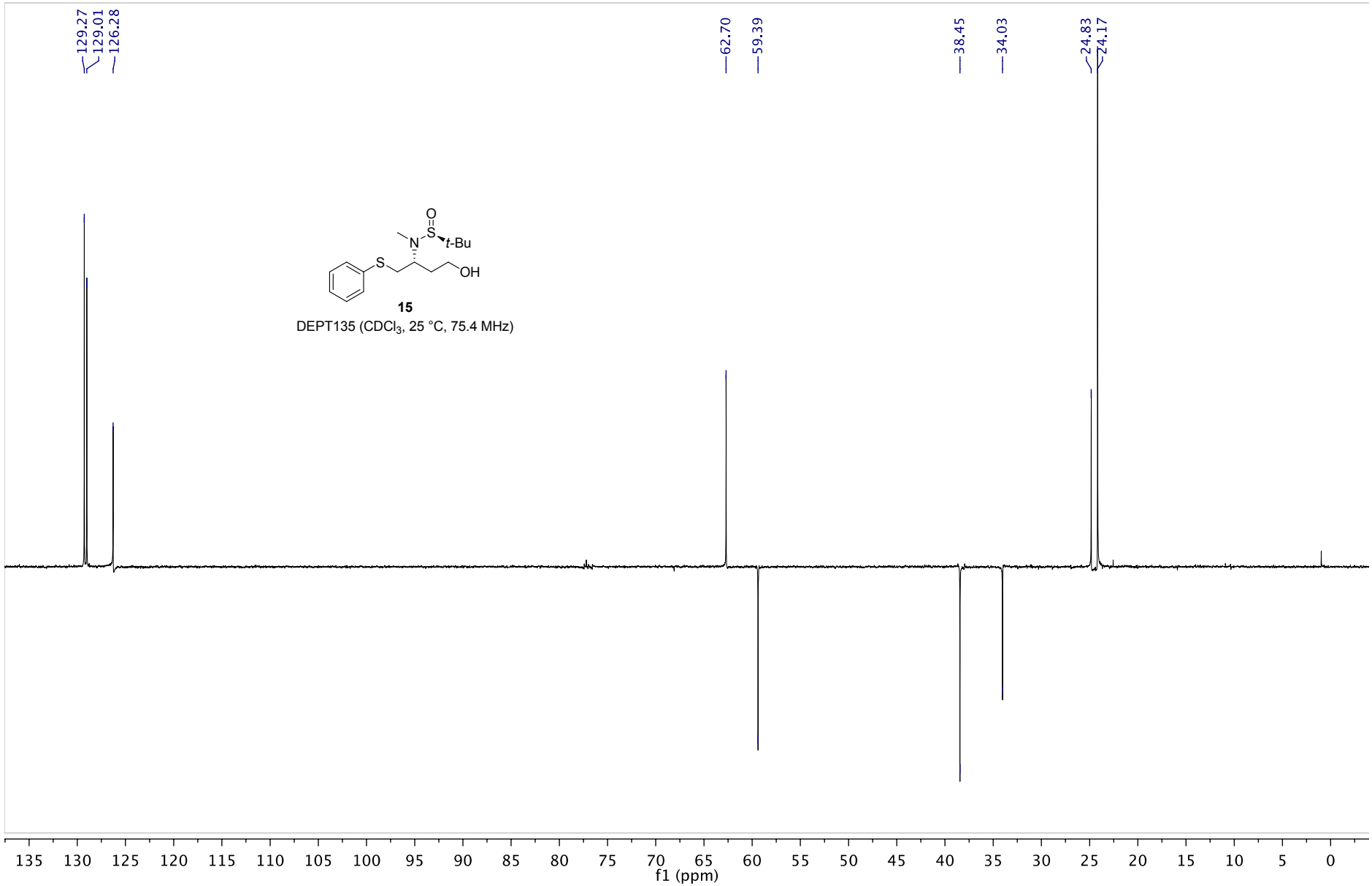

NH2
PhS
NMe2
HOOC
2
COOH
17
cosy (D2O, 25 °C)
f2 (ppm)
f1 (ppm)


NH2
PhS
NMe2
HOOC
2
COOH
17
hmqc (D2O, 25 °C)
reference: 1,4-dioxane (67.19 ppm)
f2 (ppm)
f1 (ppm)

(*S*)-*N*-((*R*)-4-hydroxy-1-(phenylthio)butan-2-yl)-*N*,2-dimethylpropane-2-sulfinamide (15)




136.00
129.27
129.01
126.28
62.70
59.39
59.28
38.45
34.03
24.83
24.17
O
S
N
t-Bu
S
OH
15
13C NMR (CDCl3, 25 °C, 75.4 MHz)
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)


129.27
129.01
126.28
62.70
59.39
38.45
34.03
24.83
24.17
O
S
N
t-Bu
S
OH
15
DEPT135 (CDCl3, 25 °C, 75.4 MHz)
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)