Improved Total Synthesis of the Potent HDAC Inhibitor FK228 (FR-901228)

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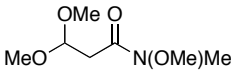
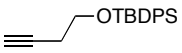
General Methods. All air or moisture sensitive reactions were performed under a positive pressured of argon in flame-dried glassware. Tetrahydrofuran (THF), toluene, diethyl ether (Et_2O), N,N-dimethylformamide (DMF), dichloromethane, acetonitrile, and triethylamine were obtained from a dry solvent system (activated alumina columns, positive pressure of argon). Column chromatography was performed on Merck silica gel Kieselgel 60 (230-400 mesh). Melting points were determined in open-end capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300, 400 or 500 MHz spectrometers. Chemical shifts are reported in ppm relative to $CHCl_3$ at δ 7.27 (^{1}H NMR) and δ 77.23 (^{13}C NMR) or DMSO-d_6 at δ 2.5 (^{1}H NMR) and δ 39.51 (^{13}C NMR) or MeOH-d_4 δ 3.31 (^{1}H NMR) and δ 49.15 (^{13}C NMR). Mass spectra were obtained on Fisons VG Autospec. IR spectra were obtained from thin films on a NaCl plate using a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were collected at 589 nm on a Rudolph Research automatic polarimeter Autopol III.



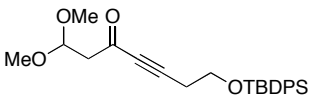
***N,O*-Dimethyl-1,1-dimethoxypropylhydroxylamide** (**9**). To a solution of methyl 3,3-dimethoxypropionate **8** (55.0 g, 0.37 mol) and *N,O*-dimethylhydroxylamine hydrochloride (39.8 g, 0.408 mol) in THF (750 mL) was added *i*PrMgCl (408 mL, 2.0 M in THF, 0.817 mol) over 1 hour at -10 ºC to create a homogeneous reaction mixture. After stirring for 1.5 hours at 0 ºC, the reaction was poured into a mixture of ice and saturated *aq.* NH_4Cl. The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness *in vacuo* to give crude mixture (colorless oil containing 30% MeOH elimination byproduct by ^1H NMR). To a solution of the crude mixture in MeOH (400 mL) was added anhydrous K_2CO_3 (9.5 g, 69.3 mmol) at room temperature. After stirring for 1.5 days, the solution was evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 and washed with H_2O and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated to dryness *in vacuo* The crude product was purified by sílica gel chromatography (2 : 1 to 4 : 1 EtOAc/hexanes) affording **9** as a yellow oil. It was subsequently found that the product can be purified by distillation under HVAC (65 - 75 ºC). The methyl ester starting material distills at 42 ºC under the same HVAC pressure. The mixed fractions were purified by distillation under HVAC pressure to provide additional desired product, which was combined with the product above to provide **9** as a mixture of amide rotamers (43.8 g, 247 mmol, 67%); ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (t, J = 6 Hz, 1 H), 3.61 (s, 3 H), 3.31 (s, 6 H), 3.10 (s, 3 H), 2.69 (d, J = 6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 161.6, 102.3, 61.4, 60.4, 54.2, 36.4, 31.9; IR (neat) 3565, 2940, 2833, 1663, 1601, 1444, 1389, 1191, 1124,

1069, 998, 921, 844, 785 cm^{-1}; ESI/APCI-HRMS (M-OCH_3) calcd for $C_6H_{12}NO_3$ 146.0812, found 146.0805.

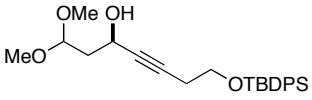


4-*tert*-Butyldiphenylsilyloxy-1-butyne (**10**).[1] To a solution of 3-butyn-1-ol (10.8 g, 0.154 mol), DMAP (1.85 g, 15.1 mmol), and triethylamine (23 mL, 0.166 mol) in CH_2Cl_2 (250 mL) was added TBDPSCl (44.3 g, 0.161 mol) *via* canula at rt. After stirring at rt for 15 hours, the mixture was quenched with saturated *aq.* NH_4Cl (100mL), and extracted with CH_2Cl_2 (100 mL). The organic extract was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography (hexanes to 9 : 1 hexanes/EtOAc) to give compound **10** as colorless oil (46.9 g, 0.15 mmol, 99 %), which is consistent with reported characterization data. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 - 7.68 (m, 4 H), 7.47 - 7.39 (m, 6 H), 3.81 (t, J = 7 Hz, 2 H), 2.47 (dt, J = 3, 7 Hz, 2 H), 1.97 (t, J = 3 Hz, 1 H), 1.08 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.8, 133.7, 129.9, 127.9, 81.7, 69.5, 62.5, 27.0, 22.8, 19.4; IR (neat) 3307, 3071, 3050, 2958, 2931, 2858, 1472, 1428, 1389, 1112, 1059, 823, 701, 613 cm^{-1}.

[1] Sinha, S. C.; Sinha, S. C.; Keina, E. *J. Org. Chem*. **1999**, *64*, 7067-7073. Delorme, D.; Girard, Y.; Rokach, J. *J. Org. Chem*. **1989**, *54*, 3635-3640.

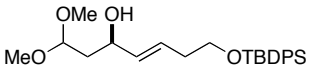


7-(*tert*-butyldiphenylsilyloxy)-1,1-dimethoxyhept-4-yn-3-one (**11**). To a solution of alkyne **10** (26.9 g, 87.3 mmol) in THF (430 mL) cooled to -78 ºC was added *n*-BuLi (52 mL, 96 mmol, 1.84 M solution in hexanes) over 1 hour. The reaction was stirred an additional 30 min at -78 ºC, and then amide **9** (17.0 g, 96.0 mmol) in THF (50 mL) at -78 ºC was added quickly via canula. The reaction was allowed to slowly warm to 0 ºC over 14 hours. It was then poured onto a saturated *aq.* NH_4Cl solution, diluted with EtOAc and extracted 3 x 50 mL EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by silica gel chromatography (20 : 1 hexanes/EtOAc + 1% Et_3N) to afford **11** (27.9 g, 65.5 mmol, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 - 7.63 (m, 4 H), 7.44 - 7.35 (m, 6 H), 4.91 (t, J = 6 Hz, 1 H), 3.80 (t, J = 7 Hz, 2 H), 3.31 (s, 6 H), 2.83 (d, J = 6 Hz, 2 H), 2.60 (t, J = 7 Hz, 2 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 135.7, 133.3, 130.0, 128.0, 100.8, 92.3, 81.9, 61.7, 53.6, 49.0, 26.9, 23.3, 19.4; IR (neat) 3071, 2956, 2932, 2858, 2215, 1676, 1619, 1428, 1226, 1113, 1057, 703, 505 cm^{-1}; FAB-MS (MH^+) calcd for $C_{25}H_{33}O_4Si$ 425.2, found 425.2.



(*R,E*)-5-hydroxy-7,7-dimethoxyhept-3-enyl 4-methylbenzenesulfonate (**S-1**). To a solution of propargyl ketone **11** (14.0 g, 32.9 mmol) in *i*PrOH (300 mL) at rt was added

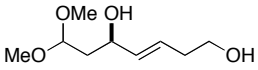
(*R,R*)-Ru-(TSDPEN) **12**[2] (505 mg, 0.82 mmol) as a solution in *i*PrOH (10 mL). The reaction mixture was stirred for 18 hours. Additional aliquots of **12** (505 mg, 0.82 mmol) as a solution in *i*PrOH (10 mL) were added after 18, 24, and 42 hours. Most of the starting material was consumed by TLC analysis after 4 days and the reaction was concentrated to a viscous oil. The mixture was purified by silica gel chromatography (10 : 1 hexanes/EtOAc, and then 4 : 1 hexanes/EtOAc) to afford the title compound **S-1** (11.9 g, 27.9 mmol, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.67 (m, 4 H), 7.46 - 7.37 (m, 6 H), 4.68 (t, *J* = 6 Hz, 1 H), 4.49 (br t, *J* = 5 Hz, 1 H), 3.77 (t, *J* = 7 Hz, 2 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.86 (br s, 1 H), 2.50 (dt, *J* = 2, 7 Hz, 2 H), 1.99 (dt, *J* = 2, 7 Hz, 2H), 1.06 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 133.8, 129.9, 127.9, 103.1, 82.7, 81.6, 62.6, 59.6, 53.8, 53.4, 39.9, 27.0, 23.1, 19.4; IR (neat) 2933, 2858, 1471, 1427, 1389, 1111, 1086, 1057, 915, 703, 511 cm^{-1}; ESI/APCI-MS (MNa^+) calcd for $C_{25}H_{34}O_4SiNa$ 449.21, found 449.27; $[\alpha]^{20}_D$ = +7.7 (*c* 1.3, $CHCl_3$).



(*R,E*)-7-(*tert*-butyldiphenylsilyloxy)-1,1-dimethoxyhept-4-en-3-ol (**13**). To a solution of sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®) (0.53 mL, 2.67 mmol) in Et_2O (10 mL) cooled to 0 ºC was added alkyne **S-1** (758 mg, 1.78 mmol) as a solution in Et_2O (8 mL) dropwise. The reaction was stirred an additional 30 min at 0 ºC, additional Red-Al (0.53, 2.67 mmol) was added, stirred for 30 min at 0 ºC, and then 1 hour at rt. The reaction was quenched by the addition of saturated *aq.* NH_4Cl, diluted with EtOAc,

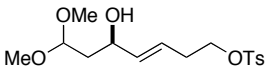
[2] Haak, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285-287.

and extracted 3 x 10 mL with EtOAc. The organic layers were combined, washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by silica gel chromatography (10 : 1 hexanes/EtOAc + 1% Et_3N) to afford **13** (0.76 g, 1.78 mmol, quant.) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.62 (m, 4 H), 7.42 - 7.33 (m, 6 H), 5.66 (dt, *J* = 7, 15 Hz, 1 H), 5.49 (dd, *J* = 7, 15 Hz, 1 H), 4.54 (t, *J* = 6 Hz, 1 H), 4.22 (m, 1 H), 3.68 (t, *J* = 7 Hz, 2 H), 3.33 (s, 3 H), 3.31 (s, 3 H), 2.64 (br s, 1 H), 2.27 (q, *J* = 7 Hz, 2 H), 1.84 - 1.73 (m, 2 H), 1.02 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.3, 134.1, 129.8, 128.2, 127.8, 103.6, 69.5, 63.7, 53.7, 53.2, 39.7, 35.8, 27.1, 19.4; IR (neat) 3457, 3070, 3047, 2931, 2858, 1471, 1427, 1387, 1189, 1110, 969, 938, 822, 703 cm^{-1}; ESI/APCI-MS (MNa^+) calcd for $C_{25}H_{36}O_4Si$ 451.23, found 451.27; $[\alpha]^{20}_D$ = +2.9 (*c* 2.25, $CHCl_3$).

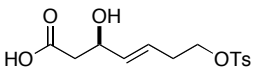


(*R,E*)-7,7-dimethoxyhept-3-ene-1,5-diol (**S-2**). To a solution of silyl ether **13** (202 mg, 0.66 mmol) in THF (7 mL) was added TBAF (1.0 M in THF, 1.00 mL, 1.00 mmol) at room temperature. After stirring for 3.5 hours, the mixture was concentrated to dryness *in vacuo*. The crude product was purified by sílica gel chromatography (7 : 1 EtOAc/hexanes to 2 : 98 MeOH/EtOAc) affording the title compound **S-2** (126 mg, 0.66 mmol, 99%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dt, *J* = 7, 15 Hz, 1 H), 5.56 (dd, *J* = 7, 15 Hz, 1 H), 4.55 (t, *J* = 6 Hz, 1 H), 4.24 (m, 1 H), 3.62 (m, 2 H), 3.38 (br s, 1 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 2.69 (s, 1 H), 2.26 (q, *J* = 7 Hz, 2 H), 1.87 - 1.75 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 128.0, 103.3, 69.3, 61.7, 53.6, 53.3, 39.6,

35.7; IR (neat) 3393, 2931, 2833, 2360, 2340, 1420, 1387, 1191, 1126, 1052, 969 cm^{-1}; ESI/APCI-HRMS (MNa^+) calcd for $C_9H_{18}O_4Na$ 213.1097, found 213.1095; $[\alpha]_D^{25}$ -8.7 (*c* 2.7, $CHCl_3$).

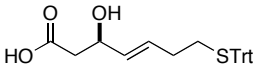


(*R*,*E*)- 1, 1-dimethoxy-7-*p*-toluenesulfonyl-4-hepten-3-ol (**14**). To a solution of TsCl (4.12 g, 21.6 mmol), DMAP (176 mg, 1.44 mmol), and Et_3N (3.0 mL, 21.6 mmol) in CH_2Cl_2 (25 mL) at room temperature was added the diol **S-2** (2.75 g, 14.4 mmol) in CH_2Cl_2 (5 mL). After stirring for 2 hours, the reaction mixture was poured onto a mixture of *aq.* $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by sílica gel chromatography (2 : 1 to 1 : 1 CH_2Cl_2/EtOAc) affording **14** as a pale yellow oil (3.50 g, 10.2 mmol, 71%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8 Hz, 2 H), 7.33 (d, J = 8 Hz, 2 H), 5.63 - 5.54 (m, 2 H), 4.54 (t, J = 5 Hz, 1 H), 4.20 (m, 1 H), 4.04 (t, J = 7 Hz, 2 H), 3.37 (s, 3 H), 3.35 (s, 3 H), 2.84 (br s, 1 H), 2.45 (s, 3 H), 2.38 (q, J = 7 Hz, 2 H), 1.78 (t, J = 5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 145.0, 136.0, 130.1, 128.1, 124.9, 103.6, 69.7, 69.1, 53.9, 53.4, 39.5, 31.9, 21.8; IR (neat) 3447, 2955, 2832, 1598, 1456, 1359, 1176, 1189, 1123, 1056, 966, 918, 816, 664, 555 cm^{-1}; FABHRMS (MH^+) calcd for $C_{16}H_{24}O_6{}^{33}S$ 345.1287, found 345.1292; $[\alpha]^{20}_D$ = -4.6 (*c* 1.94, CH_2Cl_2).

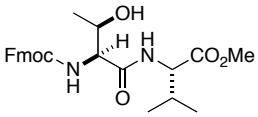


***(R,E)*-3-hydroxy-7-(tosyloxy)hept-4-enoic acid** (**S-4**). To a solution of **14** (2.34 g, 6.79 mmol) in wet CH_3CN (55 mL, 2% water by volume) at rt was added $LiBF_4$ (100 mg, 1.07 mmol) as a solution in wet CH_3CN (3 mL) dropwise. Additional $LiBF_4$ (100 mg, 1.07 mmol x 19) was added over 10 days. The reaction was quenched by the addition of water, followed by saturated *aq.* $NaHCO_3$, diluted with CH_2Cl_2, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (5 : 1 to 1 : 2 hexanes/EtOAc) to provide the corresponding aldehyde **S-3** (2.02 g, 6.77 mmol, 99.7%), which was immediately carried on to the acid. To a solution of the aldehyde (1.77 g, 5.93 mmol) in *t*BuOH (22.5 mL) was added a solution of NaH_2PO_4 (8.18 g, 59.3 mmol) dissolved in water (7.5 mL). The reaction was cooled to 0 ºC and a solution of 2-methyl-2-butene (22 mL, 44 mmol, 2 M in THF) was added, followed by gradual addition of $NaClO_2$ (2.68 g, 29.6 mmol). The reaction was stirred for 1.5 hours at 0 ºC and 2 hours at room temperature. The reaction was cooled to 0 ºC and additional NaH_2PO_4 (4.1 g, 29.7 mmol) and $NaClO_2$ (1.34 g, 14.8 mmol) were added. The reaction was allowed to warm to rt and stirred 8 hours. The reaction was quenched with 2 M HCl and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Water was removed from the crude product by concentrating from toluene. The crude oil was purified by silica gel chromatography (1 : 1 hexanes/EtOAc + 1% HOAc) to afford the title acid **S-4** (1.24 g, 3.95 mmol, 67%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2 H), 5.66 - 5.54 (m, 2 H), 4.48 (m, 1

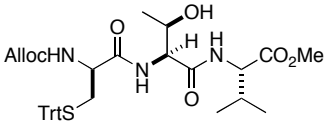
H), 4.37 (br s, 1 H), 4.08 - 4.03 (m, 2 H), 2.55 – 2.30 (m, 4 H), 2.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 145.1, 145.0, 134.2, 133.2, 130.1, 128.1, 69.5, 68.5, 41.3, 31.8, 21.0; IR (neat) 3508, 2973, 2929, 1732, 1598, 1495, 1358, 1308, 1189, 1176, 1122, 1020, 967, 919, 706, 690, 665, 574, 555 cm^{-1}; ESI/APCI-MS ($M-H^+$) calcd for $C_{14}H_{17}O_6Si$ 313.07, found 313.13; $[\alpha]^{20}_D$ = +2.6 (*c* 2.95, CH_2Cl_2).



(*R*,*E*)-3-hydroxy-7-(tritylthio)hept-4-enoic acid (**5**). To a solution of the tosylate **S-4** (1.36 g, 4.32 mmol) in THF (20 mL) at 0 ºC was slowly added a mixture of $HSCPh_3$ (1.79, 6.48 mmol) and KO*t*Bu (1.45 g, 13.0 mmol) in THF (25 mL) via canula. The reaction was stirred for 3 hours at 0 ºC. The reaction mixture was acidified to pH 2 by the addition of 2 M HCl and extracted with EtOAc. The combined extracts were filtered through celite and concentrated. The crude product was purified by silica gel chromatography (2 : 1 hexanes/EtOAc + 1% HOAc) to afford **5** (1.75 g, 4.19 mmol, 97%) and matches reported spectroscopic data; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 - 7.17 (m, 15 H), 5.56 (dt, *J* = 7, 15 Hz, 1 H), 5.40 (dd, *J* = 7, 15 Hz, 1 H), 4.43 (m, 1 H), 2.62 - 2.41 (m, 2 H), 2.18 (m, 2 H), 2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 145.0, 131.7, 131.0, 129.8, 128.1, 126.8, 68.7, 66.8, 41.3, 31.6, 31.5; IR (neat) 3056, 2924, 1709, 1490, 1443, 1181, 1034, 972 cm^{-1}; ESI/APCI-HRMS (MNa^+) calcd for $C_{26}H_{26}O_3SNa$ 441.1495, found 441.1498; $[\alpha]^{20}_D$ = +6.3 (*c* 0.30, $CHCl_3$).



***N*-α-[(fluorenylmethoxy)carbonyl]-L-threonyl-L-valine, methyl ester** (**15**).[3] To a solution of *N*-Fmoc-L-Thr (8.59 g, 25.2 mmol) and L-Val-OMe HCl (4.22 g, 25.2 mmol) in CH_3CN (252 mL) was added BOP (16.7 g, 37.8 mmol) and *i*Pr_2NEt (13.2 mL, 75.5 mmol) at rt. After stirring for 30 min, the mixture was concentrated *in vacuo* to give the crude product. Purification by sílica gel chromatography (1 : 1 to 2 : 3 hexanes/EtOAc) afforded compound **15** as an amorphous white powder (10.8 g, 22.9 mmol, 91%), which matches reported characterization data; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2 H) 7.58 (d, *J* = 7.5 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 6.95 (d, *J* = 8.7 Hz, 1 H), 5.81 (d, *J* = 7.8 Hz, 1 H), 4.50 (dd, *J* = 8.7, 4.8 Hz, 1 H), 4.45 - 4.35 (m, 4 H) 4.25 - 4.17 (m, 2 H), 3.74 (s, 3 H), 2.19 (m, 1 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H); FABHRMS (MH^+) calcd for $C_{25}H_{31}N_2O_6$ 455.2182, found 455.2181.

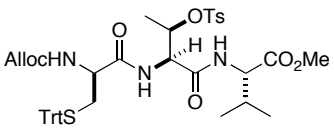


***N*-(Allyloxycarbonyl)-D-Cysteinyl-(*S*-triphenylmethyl)-L-threonyl-L-valine methyl ester** (**16**). A solution of *N*-Fmoc-L-Thr-L-Val-OMe **15** (12.1 g, 26.7 mmol) and Et_2NH (53.4 mL) in CH_2Cl_2 (121 mL) was stirred at rt for 4.5 hours. The reaction mixture was concentrated *in vacuo* to give the crude product (14.4 g). The crude amine (14.4 g) was

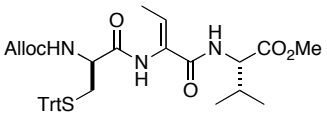
[3] Li, K. W.; Wu, J; Xing, W.; Simon, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 7237-7238.

dissolved in DMF (20 mL) and CH_2Cl_2 (120 mL) and treated with *N*-Alloc-S-Trt-D-Cys[4] (12.3 g, 27.5 mmol), HOBt (4.33 g, 32.1 mmol) and EDCI (6.14 g, 32.1 mmol) at 0ºC. The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo*, poured into water (150 mL) and extracted with EtOAc (200 mL). The organic extract was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by sílica gel chromatography (2 : 1 to 1 : 1 CH_2Cl_2/EtOAc) to give compound **16** as an amorphous white solid (11.9 g, 17.9 mmol, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.40 (m, 6 H), 7.33 - 7.20 (m, 10 H), 7.08 (br d, *J* = 9 Hz, 1 H), 6.80 (br d, *J* = 7 Hz, 1 H), 5.85 (ddt, *J* = 5, 11, 17 Hz, 1 H), 5.29 (d, *J* = 17 Hz, 1 H), 5.22 (d, *J* = 11 Hz, 1 H), 5.09 (d, *J* = 7 Hz, 1 H), 4.51 (d, *J* = 6 Hz, 2 H), 4.43 (dd, *J* = 2, 8 Hz, 1 H), 4.35 (m, 1 H), 4.29 (dd, *J* = 2, 8 Hz, 1 H), 3.80 (m, 1 H), 3.73 (s, 3 H), 2.76 (dd, *J* = 7, 13 Hz, 1 H), 2.58 (dd, *J* = 6, 13 Hz, 1 H), 2.15 (m, 1 H), 1.09 (d, *J* = 6 Hz, 3 H), 0.86 (d, *J* = 7 Hz, 3 H), 0.84 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.5, 171.0, 144.4, 132.5, 129.7, 128.3, 127.2, 118.3, 67.6, 66.3, 66.2, 57.5, 56.8, 54.3, 52.4, 34.0, 30.9, 19.3, 18.2, 17.8; IR (neat) 3289, 3059, 2966, 1733, 1647, 1444, 1213, 733, 700, 503 cm^{-1}; FABHRMS ($M\text{-}H^+$) calcd for $C_{36}H_{42}N_3O_7S$ 660.2743, found 660.2741; Anal. calcd C: 65.33; H: 6.55; N: 6.35; S: 4.85. Obs, C: 64.98; H: 6.60; N: 6.54; S: 5.13; $[\alpha]^{20}_D$ = -50.0 (*c* 0.68, $CHCl_3$).

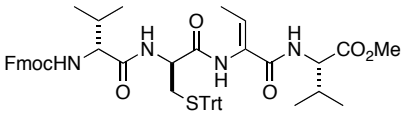
[4] Kruse, C. H.; Holden, K. G. *J. Org. Chem*. **1985**, *65*, 1192-1194.



***N*-(Allyloxycarbonyl)-D-Cysteinyl-(*S*-triphenylmethyl)-L-threonyl-(*O*-*p*-toluenesulfonyl)-L-valine methyl ester** (**S-5**). To a solution of *N*-Alloc-S-Trt-D-Cys-L-Thr-L-Val-OMe **16** (11.5 g, 17.3 mmol) in pyridine (86 mL) was added tosylanhydride (17.0 g, 52.0 mmol) at 0°C. The mixture was stirred at 0 °C for 40 min. The resulting solution was quenched with saturated *aq.* $NaHCO_3$ (200 mL) and extracted with EtOAc (250 mL). The combined extracts were washed with aqueous 1 M HCl (150 mL x 6), brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography (2 : 1 to 3 : 2 hexanes/EtOAc) to give compound **S-5** as a white powder (13.4 g, 16.5 mmol, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8 Hz, 2 H), 7.45 - 7.21 (m, 17 H), 6.86 (d, J = 8 Hz, 1 H), 6.62 (d, J = 8 Hz, 1 H), 5.88 (ddt, J = 5, 11, 17 Hz, 1 H), 5.28 (d, J = 17 Hz, 1 H), 5.21 (d, J = 11 Hz, 1 H), 5.14 (m, 1 H), 5.00 (d, J = 5 Hz, 1 H), 4.54 (dd, J = 4, 8 Hz, 1 H), 4.50 (m, 2 H), 4.31 (dd, J = 6, 8 Hz, 1 H), 3.69 (s, 3 H), 3.54 (m, 1 H), 2.77 (dd, J = 7, 13 Hz, 1 H), 2.62 (dd, J = 6, 13 Hz, 1 H), 2.45 (s, 3 H), 2.10 (m, 1H), 1.19 (d, J = 6 Hz, 3 H), 0.87 (d, J = 7 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.8, 167.5, 156.0, 145.3, 144.4, 133.5, 132.5, 130.1, 129.7, 128.4, 128.3, 127.2, 118.3, 67.6, 66.4, 58.0, 56.5, 54.4, 52.3, 33.4, 30.8, 21.9, 19.1, 18.2, 17.3; FABHRMS (MH^+) calcd for $C_{43}H_{50}N_3O_9S_2$ 816.2988, found 816.2987; Anal. calcd C: 63.29; H: 6.05; N: 5.15; S: 7.86. Obs. C: 63.36; H: 6.39; N: 5.40; S: 7.65; $[\alpha]^{20}_D$ = +5.1 (*c* 0.70, $CHCl_3$).

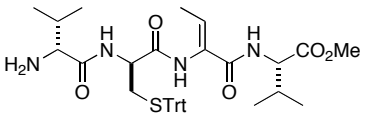


***N*-(Allyloxycarbonyl)-D-Cysteinyl-(*S*-triphenylmethyl)-*(Z)*-dehydrobutyrinyl-L-valine methyl ester** (**17**). To a solution of *N*-Alloc-S-Trt-D-Cys-L-Thr(*O*-Ts)-L-Val-OMe **S-5** (12.5 g, 15.3 mmol) in CH_3CN (306 mL) was added DABCO (17.2 g, 153 mmol) at rt. After stirring for 18 hours, the mixture was concentrated and rediluted with EtOAc and 1 M aqueous HCl (200 mL). The aqueous layer was extracted with EtOAc. The combined extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the crude product. The crude product was purified by sílica gel chromatography (2 : 1 hexanes/EtOAc) to give compound **17** as a white powder (9.84 g, 153 mmol, quant.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 - 7.22 (m, 15 H), 7.04 (br s, 1 H), 6.77 (br q, *J* = 7 Hz, 1 H), 6.71 (br d, *J* = 7 Hz, 1 H), 5.90 (ddt, *J* = 5, 11, 17 Hz, 1 H), 5.31 (d, *J* = 17 Hz, 1 H), 5.24 (d, *J* = 17 Hz, 1 H), 5.02 (br s, 1 H), 4.55 (d, *J* = 5 Hz, 2 H), 4.50 (dd, *J* = 6, 8 Hz, 1 H), 3.73 (q, *J* = 6 Hz, 1 H), 3.68 (s, 3 H), 2.80 (dd, J = 7 Hz, 13 Hz, 1 H), 2.71 (dd, J = 7 Hz, 14 Hz, 1 H), 2.11 (m, 1 H), 1.69 (d, *J* = 7 Hz, 3 H), 0.91 (d, *J* = 7 Hz, 3 H), 0.89 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 169.2, 164.0, 156.5, 144.3, 133.0, 132.4, 129.7, 128.6, 128.4, 127.3, 118.6, 67.8, 66.6, 58.0, 54.8, 52.2, 33.2, 31.2, 19.2, 18.4, 13.9; IR (neat) 3278, 3083, 2964, 2875, 1740, 1700, 1518, 1444, 1245, 1185, 1149, 1035, 912, 733, 701 cm^{-1}; FABHRMS (MH^+) calcd for $C_{36}H_{42}N_3O_6S$ 644.2794, found 644.2778; Anal. calcd C: 67.16; H: 6.42; N: 6.53; S: 4.98. Obs. C: 66.77; H: 6.76; N: 6.74; S 5.34; $[\alpha]^{20}_D$ = +7.1 (*c* 0.80, $CHCl_3$).



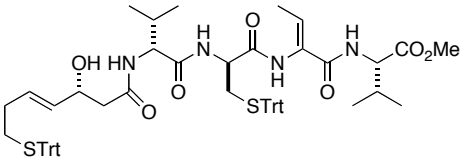
***N*-α-[(Fluorenylmethoxy)carbonyl]-D-Valyl-D-Cysteinyl-(*S*-triphenylmethyl)-*(Z)*-dehydrobutyrinyl-L-valine methyl ester** (**18**). To a mixture of *N*-Alloc-tripeptide **17** (9.16 g, 14.2 mmol), $PdCl_2(PPh_3)_2$ (200 mg, 0.29 mmol) and AcOH (1.95 mL, 34.2 mmol) in CH_2Cl_2 (142 mL) was added $SnBu_3H$ (4.15 mL, 15.7 mmol) at rt. After stirring for 3 hours, saturated *aq.* $NaHCO_3$ (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give crude amide (14.2 g). The crude amine was dissolved in DMF (20 mL) and CH_2Cl_2 (142 mL), and then treated with *N*-Fmoc-D-Valine (5.29 g, 15.6 mmol), HOBt (2.31 g, 17.1 mmol), and EDCI (3.27 g, 17.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 19 hours and then concentrated *in vacuo*. The residue was diluted with water (100 mL), and extracted with EtOAc (100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by sílica gel chromatography (1 : 1 to 1 : 2 hexanes/EtOAc) to give compound **18**. This solid was washed with Et_2O – hexanes to remove the Bu_3SnH residue, and dried under vacuum to give **18** as a white powder (10.4 g, 11.8 mmol, 83% from **17**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7 Hz , 2 H), 7.54 (d, *J* = 7 Hz , 2 H), 7.48 - 7.15 (m, 20 H), 6.85 (m, 2 H), 6.27 (br s, 1 H), 5.29 (br s, 1 H), 4.52 (dd, *J* = 6, 8 Hz, 1 H), 4.43 (dd, *J* = 7, 11 Hz, 1 H), 4.26 (dd, *J* = 7, 10 Hz, 1 H), 4.12 (m, 1 H), 4.02 - 3.95 (m, 2 H), 3.67 (s, 3 H), 2.94 (dd, *J* = 6, 13 Hz, 1 H), 2.61 (dd, *J* = 6, 13 Hz, 1 H),

2.19 - 2.07 (m, 2 H), 1.74 (d, *J* = 7 Hz, 3 H), 1.00 - 0.84 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 172.0, 168.7, 164.1, 157.0, 144.3, 143.9, 141.5, 132.5, 129.6, 128.8, 128.3, 128.0, 127.2, 125.2, 125.1, 120.2, 67.4, 60.7, 58.0, 53.3, 52.1, 47.3, 32.8, 31.3, 30.7, 19.5, 19.2, 18.4, 17.8, 13.8; IR (neat) 3293, 360, 2963, 2875, 1740, 1645, 1506, 1448, 1244, 910, 738, 701 cm^{-1}; FABHRMS (MH^+) calcd for $C_{52}H_{57}N_4O_7S$ 881.3948, found 881.3972; Anal. calcd C: 70.88; H: 6.41; N: 6.36; S: 3.64. Obs. C: 70.92; H: 6.80; N: 6.45; S: 4.02; $[\alpha]^{20}_D$ = -3.6 (*c* 1.0, CH_2Cl_2).



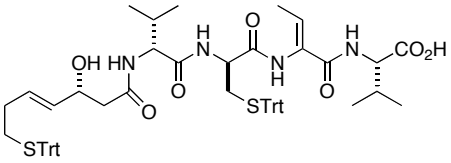
***D*-Valyl-*D*-Cysteinyl-(*S*-triphenylmethyl)-*(Z)*-dehydrobutyrinyl-L-valine methyl ester** (**4**).[2] To a solution of Fmoc-tetrapeptide **18** (800 mg, 0.91 mmol) in anhydrous CH_3CN (36 mL) at 0 ºC was added Et_2NH (470 μL, 4.54 mmol). The mixture was warmed to rt and stirred for 2 h. The resulting solution was concentrated and purified by silica gel chromatorgraphy (30 : 1, CH_2Cl_2/MeOH) to afford **4** (595 mg, 0.91 mmol, quant.), which matched the reported spectroscopic data. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7 Hz, 1 H), 7.51 (s, 1 H), 7.42 - 7.17 (m, 15 H), 6.69 (q, *J* = 7 Hz, 1 H), 6.67 (d, *J* = 8 Hz, 1 H), 4.46 (dd, *J* = 6, 8 Hz, 1 H), 3.75 (q, *J* = 7 Hz, 1 H), 3.63 (s, 3 H), 3.23 (d, *J* = 4 Hz, 1 H), 2.76 (dd, *J* = 7, 13 Hz, 1 H), 2.61 (dd, *J* = 7, 13 Hz, 1 H), 2.15 (m, 1 H), 2.07 (m, 1 H), 1.63 (d, *J* = 7 Hz, 3 H), 0.92 (d, *J* = 7 Hz, 3 H), 0.86 (d, *J* = 7 Hz, 3 H), 0.85 (d, *J* = 7 Hz, 3 H), 0.76 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 172.7, 169.1, 164.0, 144.5, 132.6, 129.7, 128.6, 128.3, 127.1, 67.4, 60.0, 57.8, 53.0,

52.1, 32.4, 31.3, 30.9, 19.7, 19.1, 18.4, 16.5, 13.8; IR (neat) 3310, 3057, 2962, 2873, 1741, 1647, 1496, 1444, 1372, 1267, 1207, 742, 701, 671 cm^{-1}; ESI/APCI-HRMS (MH^+) calcd for $C_{37}H_{47}N_4O_5S$: 659.3262, found 659.3254; $[\alpha]^{20}_D$ = +40.6 (*c* 1.0, CH_2Cl_2).



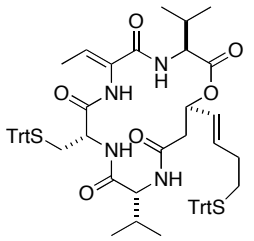
Pentapeptide (**19**).[2] To a mixture of tetrapeptide **4** (3.34 g, 5.02 mmol) and acid **5** (1.67 g, 3.99 mmol) in CH_3CN (40 mL) and CH_2Cl_2 (10 mL) maintained at rt by a water bath was added BOP (3.71 g, 8.38 mmol) and iPr$_2$NEt$_2$ (2.9 mL, 16.8 mmol). The reaction was stirred at rt for 15 hours. The resulting solution was quenched with *aq.* citric acid and extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by sílica gel chromatography (1 : 1 to 1 : 4, hexanes/EtOAc) to afford **19** (4.23 g, 3.99 mmol, quant.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.43 - 7.12 (m, 30 H), 6.80 (d, *J* = 8 Hz, 1 H), 6.75 – 6.69 (m, 2 H) 6.64 (q, *J* = 7 Hz, 1 H), 5.49 (dt, *J* = 6, 15 Hz, 1 H), 5.34 (dd, *J* = 5, 15 Hz, 1 H), 4.45 (dd, *J* = 8.3, 6.1 Hz, 1 H), 4.33 (s, 1 H), 4.09 (t, *J* = 6.2 Hz, 1 H), 3.92 (m, 1 H), 3.64 (s, 3 H), 3.30 (d, *J* = 4.0 Hz, 1 H), 2.80 (dd, *J* = 7.0, 13.0 Hz, 1 H), 2.62 (dd, *J* = 6.0, 13.0 Hz, 1 H), 2.40 (dd, *J* = 3, 15 Hz, 1 H), 2.28 (dd, *J* = 9, 15 Hz, 1 H), 2.20 - 2.10 (m, 6 H), 1.68 (d, *J* = 6 Hz, 3 H), 0.94 - 0.81 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 173.0, 172.0, 169.4, 164.4, 144.9, 144.3, 132.33, 132.30, 129.6, 129.5, 128.9, 128.3, 127.1, 126.8, 69.5, 67.5, 66.7, 59.6, 58.2, 53.3, 52.2, 42.9, 32.7, 31.52, 31.45, 31.1, 30.2, 19.5, 19.2, 18.5, 18.0, 13.7; IR (neat) 3395, 3294, 3057, 2963,

2930, 1738, 1640, 1522, 1491, 1443, 848, 742, 700, 669 cm^{-1}; FABHRMS (MNa^+) calcd for $C_{63}H_{70}N_4O_7S_2Na$ 1081.4584, found 1081.4617; $[\alpha]^{20}_D$ = -2.6 (*c* 1.0, CH_2Cl_2).

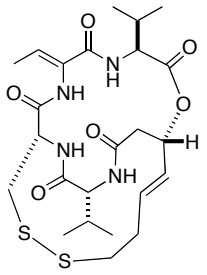


Hydroxyacid pentapeptide (**S-6**). To a solution of ester **19** (2.16 g, 2.04 mmol) in THF (4 mL) under argon at 0 ºC was added a solution of $LiOH{\cdot}H_20$ (146 mg, 6.13 mmol) in H_2O (1 mL). After stirring for 2 hours at 0 ºC, the reaction was poured into a mixture of EtOAc (25 mL) and 2N HCl (5 mL). The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, filtered through cotton, and concentrated. The crude oil was purified by silica gel chromatography (1 : 1 to 1 : 8 hexanes/EtOAc + 1% HOAc). Excess HOAc was azeotropically removed by concentrating from toluene. The product was further purified by recrystallization from hexanes/EtOAc to provide **S-6** (1.56 g, 1.49 mmol, 73%) as an off-white powder that is consistent with reported spectroscopic data; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 34 H), 6.66 (q, *J* = 7 Hz, 1 H), 5.44 (dt, *J* = 7, 15 Hz, 1 H), 5.32 (dd, *J* = 7, 15 Hz, 1 H), 4.38 - 4.25 (m, 2 H), 4.08 (d, *J* = 6 Hz, 1 H), 3.91 (t, *J* = 7 Hz, 1 H), 2.35 - 2.23 (m, 2 H), 2.15 - 1.98 (m, 4 H), 1.64 (d, *J* = 7 Hz, 3 H), 0.88 - 0.78 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.3, 170.9, 169.7, 164.8, 144.8, 144.2, 132.5, 129.5, 128.5, 128.2, 128.1, 127.9, 127.0, 126.6, 69.0, 67.2, 66.6, 58.1, 53.2, 53.1, 42.8, 32.5, 31.5, 31.2, 30.6, 30.3, 21.4, 19.2, 19.0, 18.1, 17.6, 13.5; IR (neat) 3304, 3056, 2964, 2928, 2875,

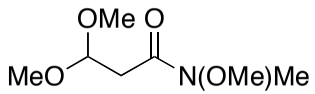
1717, 1445, 419, 1393, 1265, 1034, 847, 781, 701 cm^{-1}; ESI/APCI-HRMS (MNa^+) calcd for $C_{62}H_{68}N_4O_7S_2Na$ 1067.4422, found 1067.4398; $[\alpha]^{20}_D$ = +6.8 (*c* 1.0, CH_2Cl_2).



Depsipeptide (**3**).[3] To a solution of PPh_3 (188 mg, 0.72 mmol) in THF (25 mL) was added *p*-TsOH (27.0 mg, 0.14 mmol) and DIAD (113 μL, 0.57 mol) at rt. The mixture was stirred at rt for 20 min and then cooled to 0 ºC. To the resulting solution at 0 ºC was added acid **S-6** (30 mg, 0.028 mmol) in THF (5 mL) dropwise via syringe pump over 2 h. The mixture was then stirred an additional 2 h at 0 ºC and concentrated. Purification by silica gel chromatography (2 : 1 to 1 : 1 to 1 : 2 to 1 : 4, hexanes/EtOAc) afforded depsipeptide **3** as a colorless oil (7.0 mg, 0.0068 mmol, 24%); ^{1}H NMR (400 MHz, $CDCl_3$: CD_3OD, 10 : 1) δ 7.75 (d, *J* = 7 Hz, 1H), 7.72 (d, *J* = 7 Hz, 1 H), 7.39 - 7.05 (m, 32 H), 6.79 (q, *J* = 7 Hz, 1 H), 5.53 (dt, *J* = 15 Hz, 7 Hz, 1 H), 5.45 - 5.40 (m, 1 H), 5.23 (dd, *J* = 15 Hz, 7 Hz, 1 H), 4.51 (d, *J* = 5 Hz, 1 H), 4.18 - 4.12 (m, 1 H), 3.93 - 3.83 (m, 1 H), 2.57 – 2.38 (m, 1 H), 2.31 - 2.23 (m, 4 H), 2.20 - 2.10 (m, 2 H), 2.02 - 1.91 (m, 2 H), 1.93 - 1.83 (m, 1 H), 1.64 (d, *J* = 7 Hz, 3 H), 0.92 (d, *J* = 7 Hz, 3 H), 0.88 (d, *J* = 7 Hz, 3 H), 0.85 - 0.77 (m, 6 H); ESI/APCI-HRMS (MH^+) calcd for $C_{62}H_{67}N_4O_6S_2$ 1027.4502, found 1027.4487.

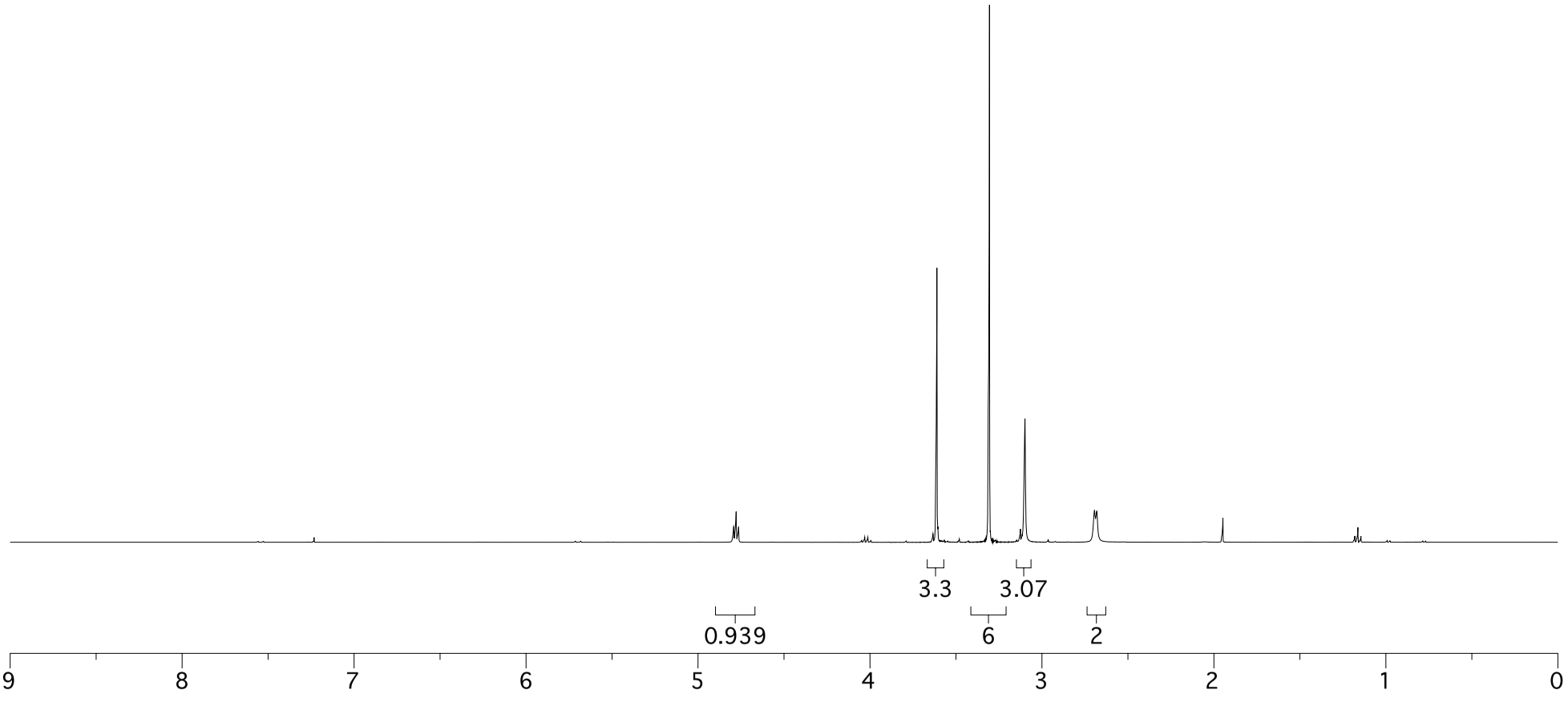


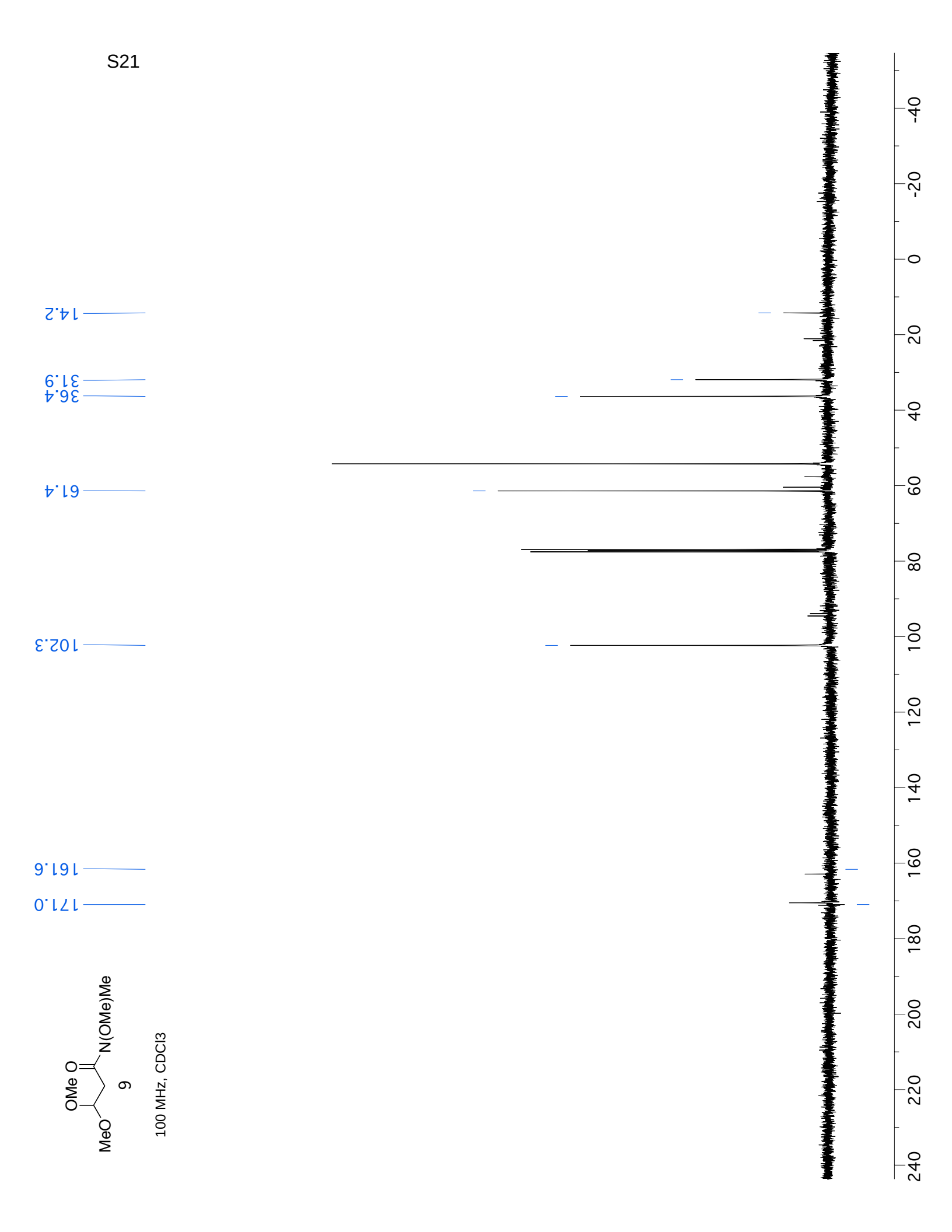
FK228 (**1**).[3] To a solution of I_2 (14.8 mg, 0.058 mmol) in MeOH (19 mL) at rt was added depsipeptide **3** (20.0 mg, 0.019 mmol). The mixture was stirred at rt for 10 min. The resulting solution was quenched with 0.2 M aqueous citrate/ 0.2 M aqueous ascorbate pH 4 buffer (10 mL). The mixture was poured onto brine and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (1 : 20, MeOH/CH_2Cl_2) afforded FK228 **1** as a thin film (8.5 mg, 0.016 mmol, 81%); ^{1}H NMR (400 MHz, $CDCl_3$: CD_3OD, 10 : 1) δ 8.00 (br s, 1 H), 7.73 (d, *J* = 7 Hz, 1 H), 7.53 (d, *J* = 8 Hz, 1 H), 6.30 (q, *J* = 7 Hz, 1 H), 5.76 - 5.60 (m, 3 H), 4.67 (dt, *J* = 7, 10 Hz, 1 H), 4.49 (dd, *J* = 4, 8 Hz, 1 H), 3.94 (m, 1 H), 3.36 (d, *J* = 2 Hz, 1 H), 3.14 - 3.04 (m, 3 H), 2.94 - 2.87 (m, 1 H), 2.74 - 2.56 (m, 4 H), 2.36 - 2.29 (m, 1 H), 2.20 - 2.13 (m, 1 H), 1.68 (d, *J* = 7 Hz, 3 H), 1.06 (d, *J* = 7 Hz, 3 H), 1.04 (d, *J* = 7 Hz, 3 H), 0.97 (d, *J* = 7 Hz, 3 H), 0.94 (d, *J* = 7 Hz, 3 H); ESI/APCI-MS (MNa^+) calcd for $C_{24}H_{36}N_4O_6S_2Na$ 563.40, found 563.40.



9

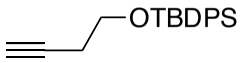
400 MHz, CDCl3





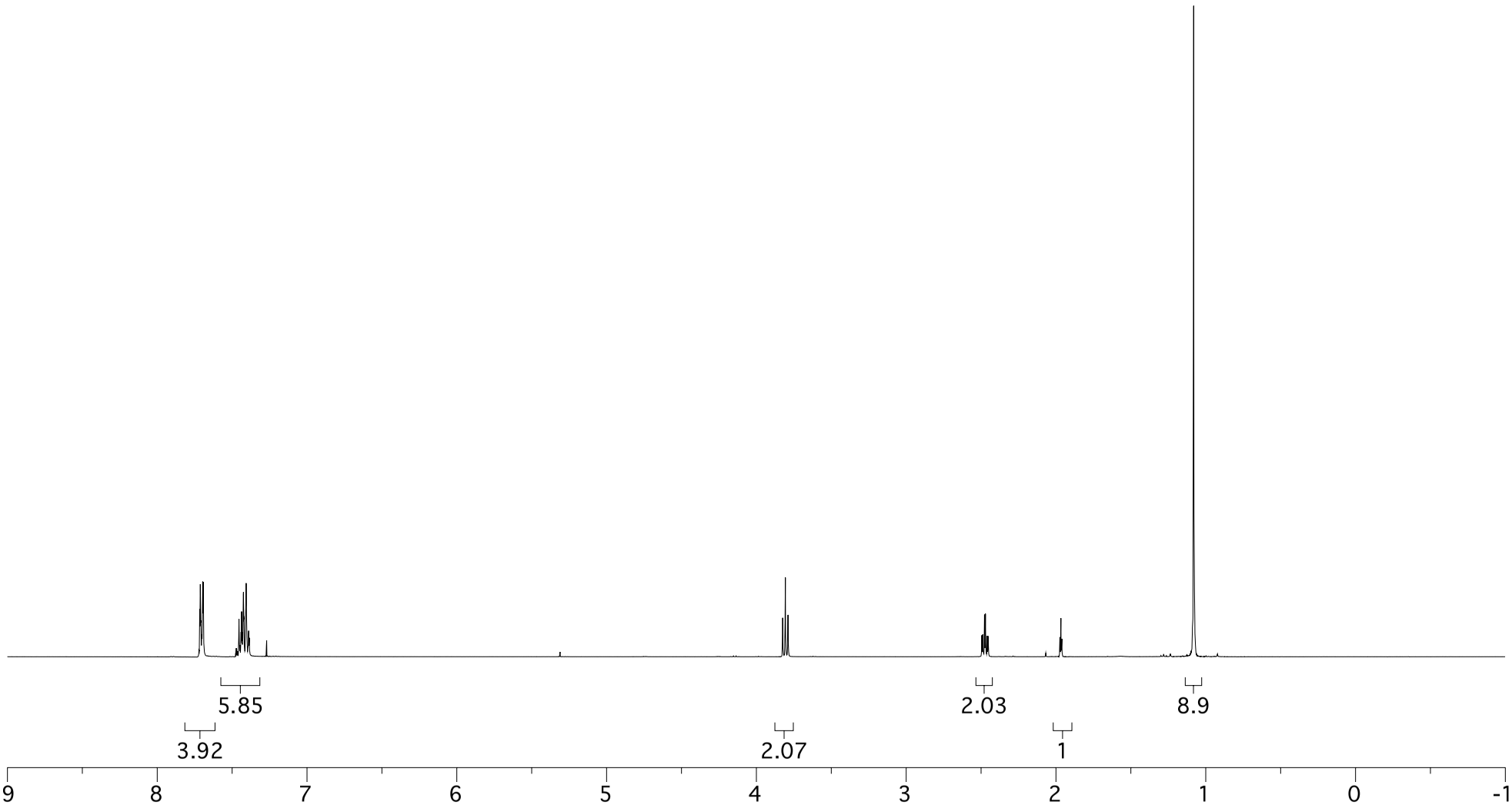
9

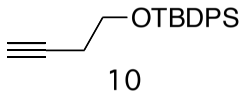
100 MHz, CDCl3



10

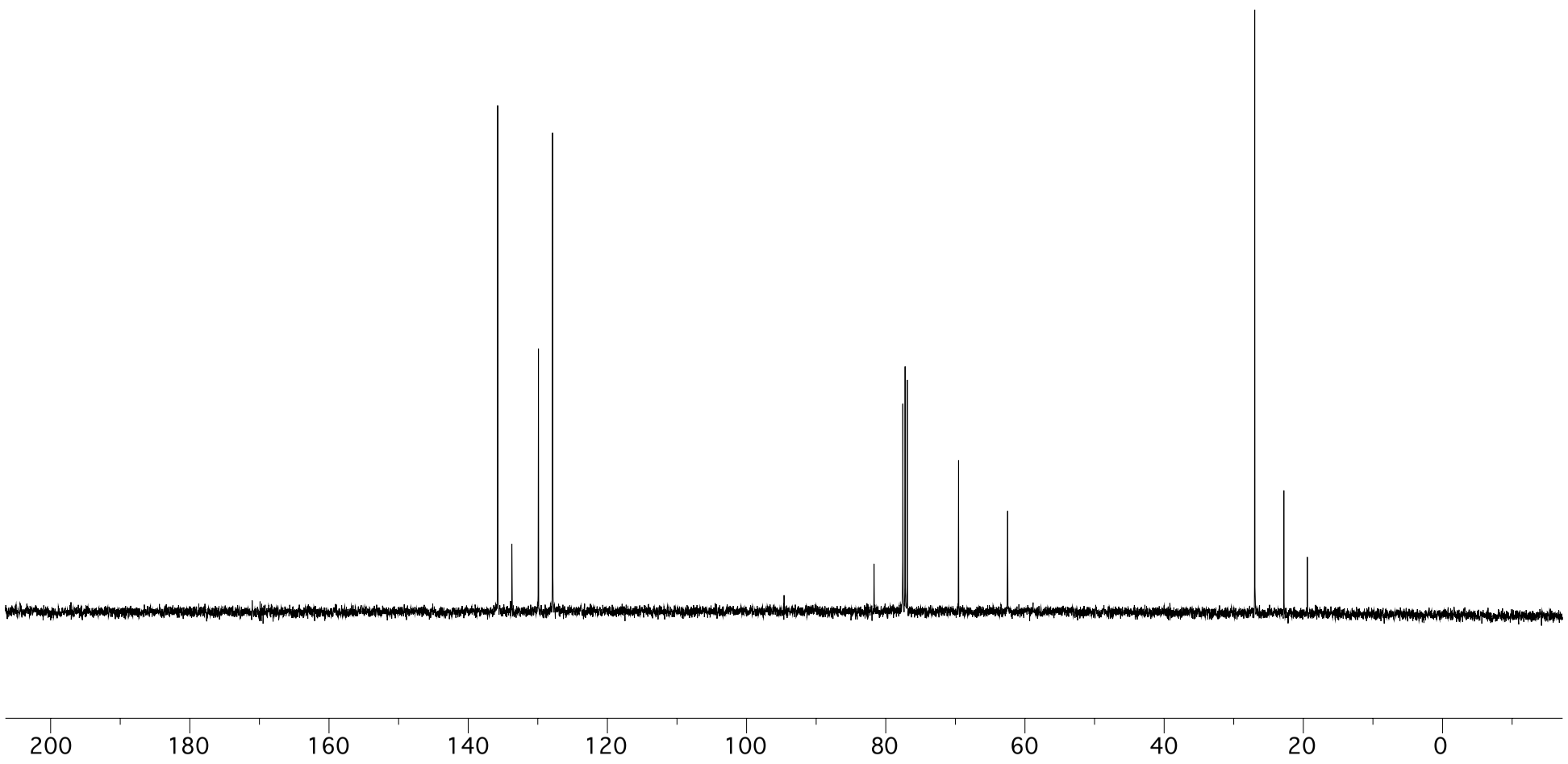
400 MHz, CDCl3

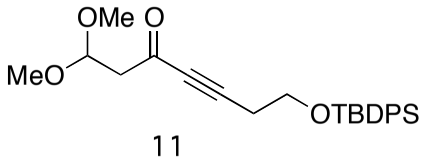




10

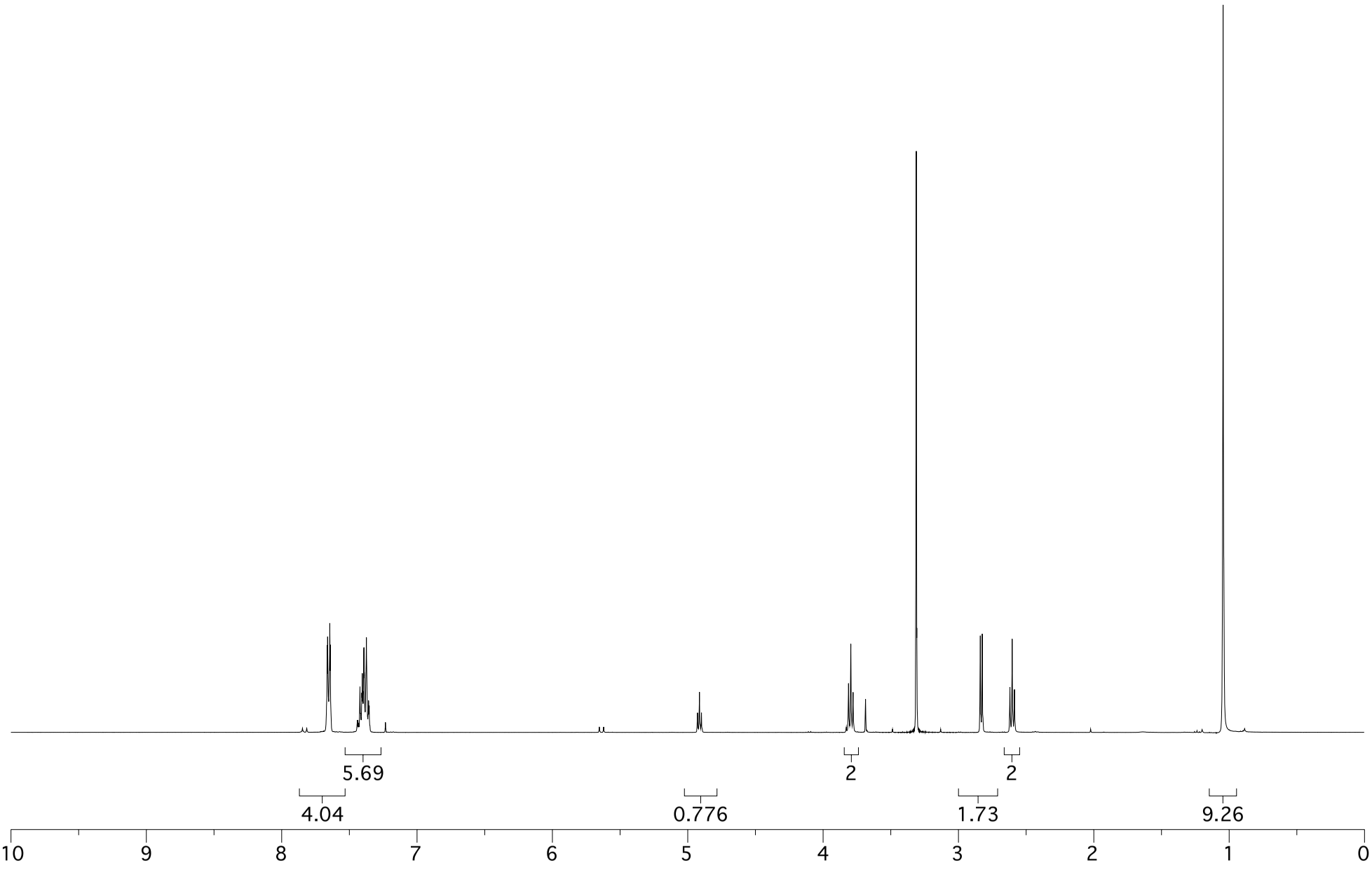
100 MHz, CDCl3

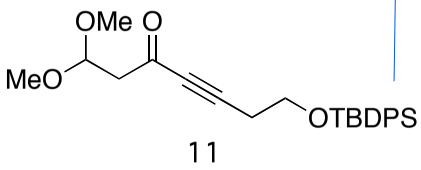




11

400 MHz, CDCl3



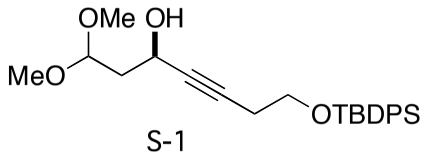


11

100 MHz, CDCl3

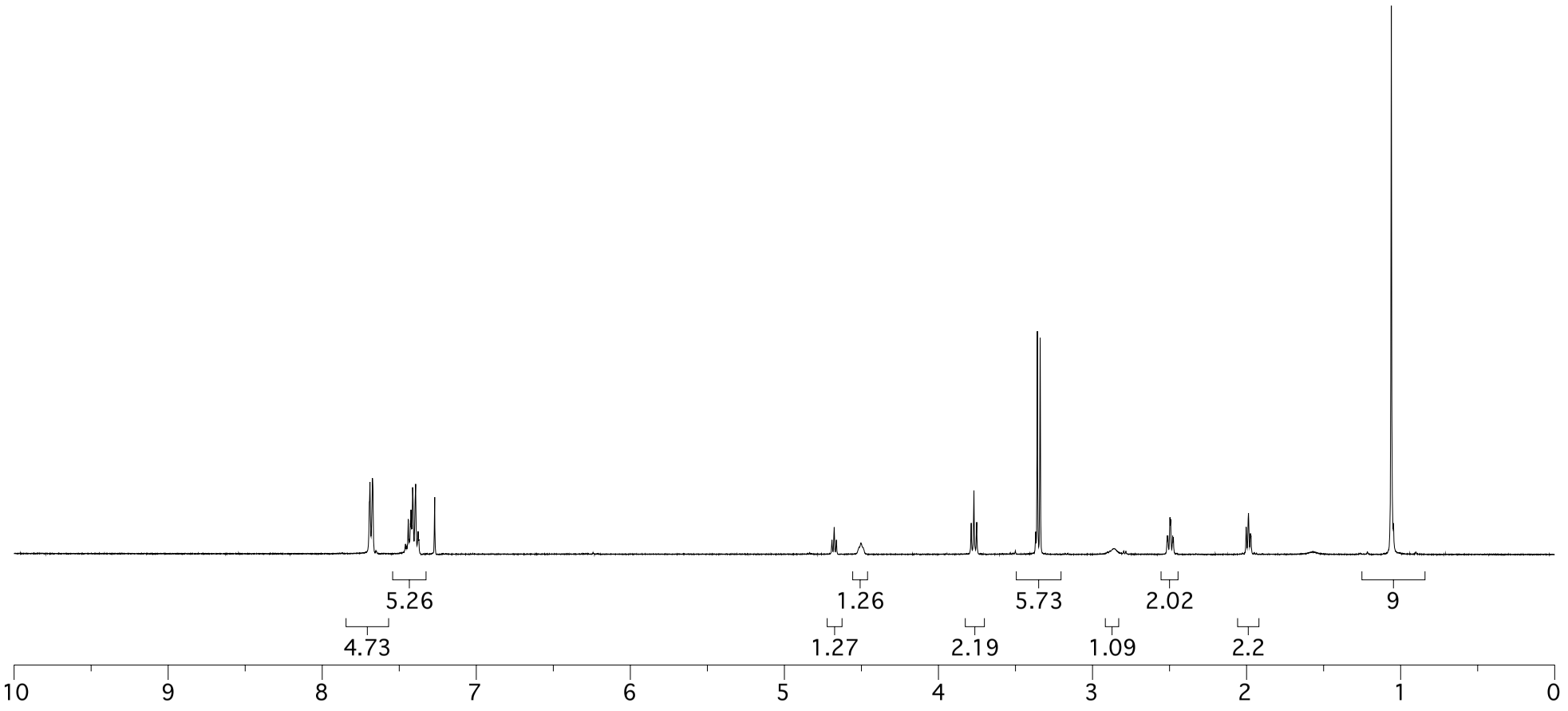
183.6
135.7
133.3
130.0
128.0
100.7
92.3
81.9
61.5
53.6
49.0
26.9
23.3
19.4

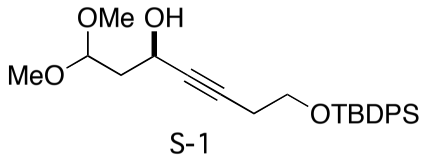
240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40



S-1

400 MHz, CDCl3



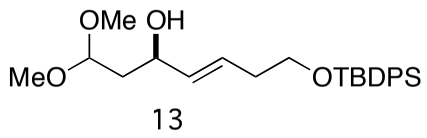


S-1

100 MHz, CDCl3

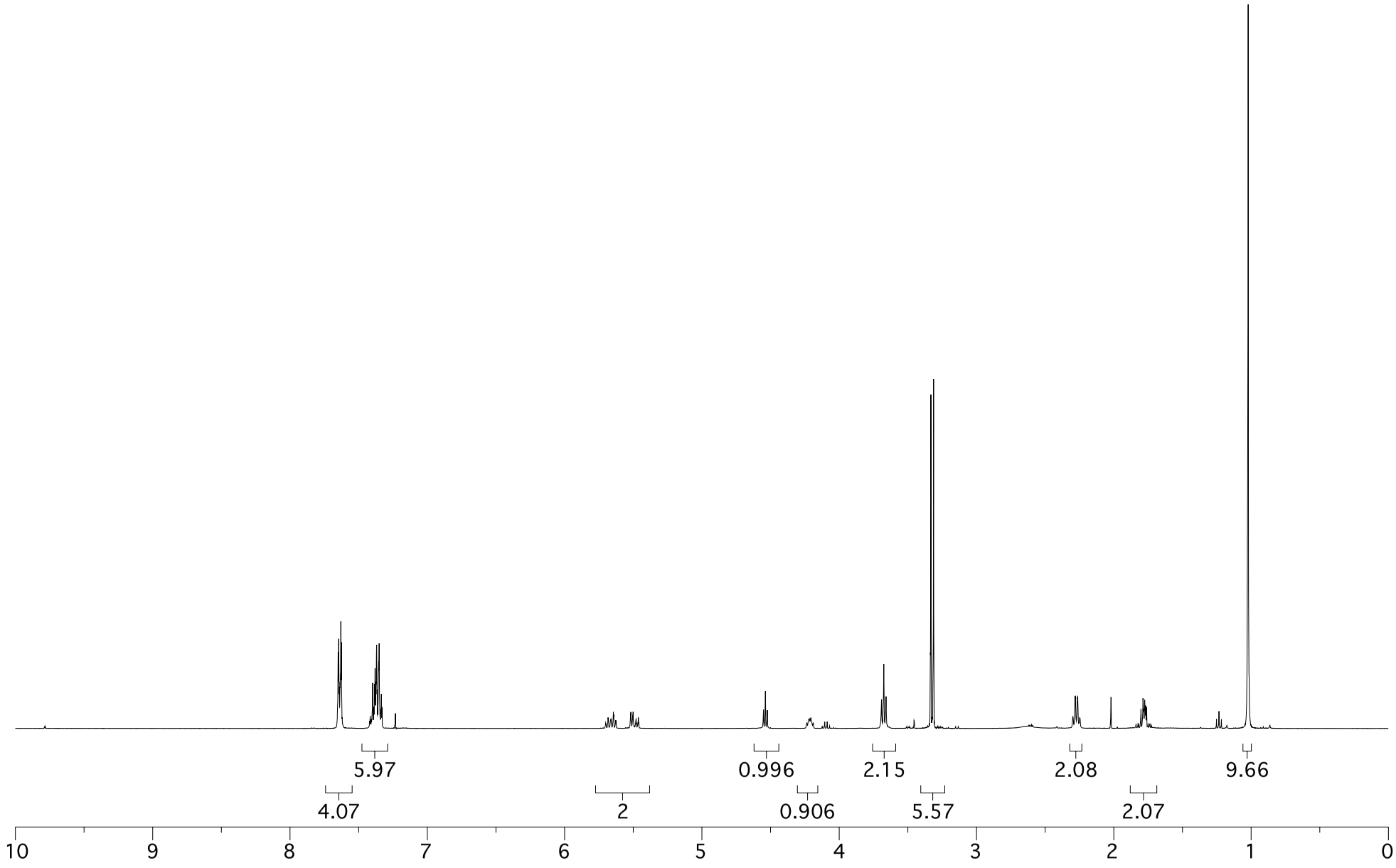
135.8
133.8
129.9
127.9
103.1
82.6
81.6
62.6
59.6
53.8
53.4
40.0
27.0
23.1
19.4

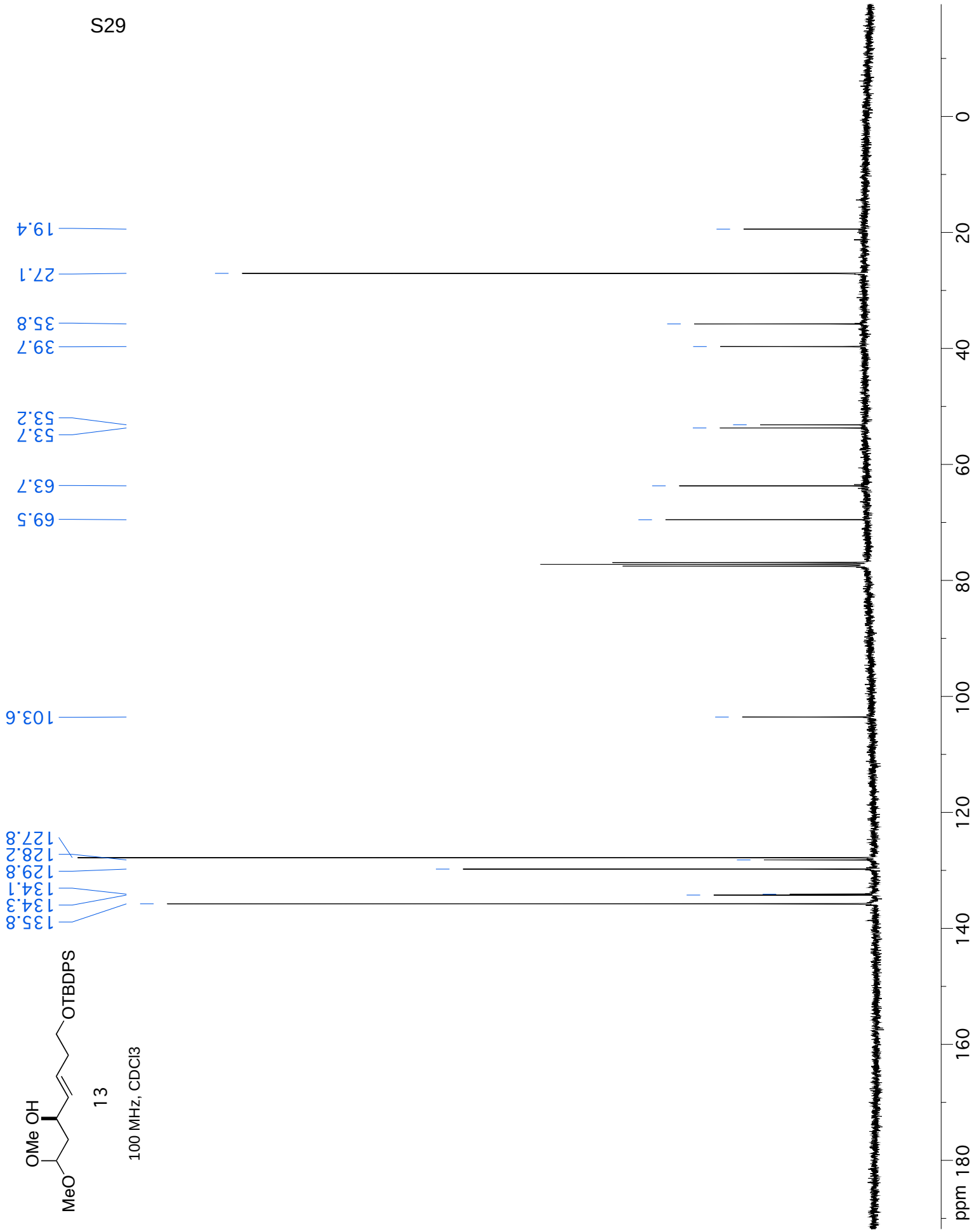
ppm 180 160 140 120 100 80 60 40 20 0

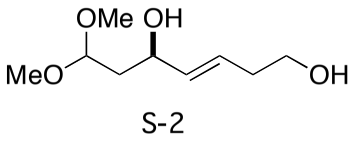


13

400 MHz, CDCl3

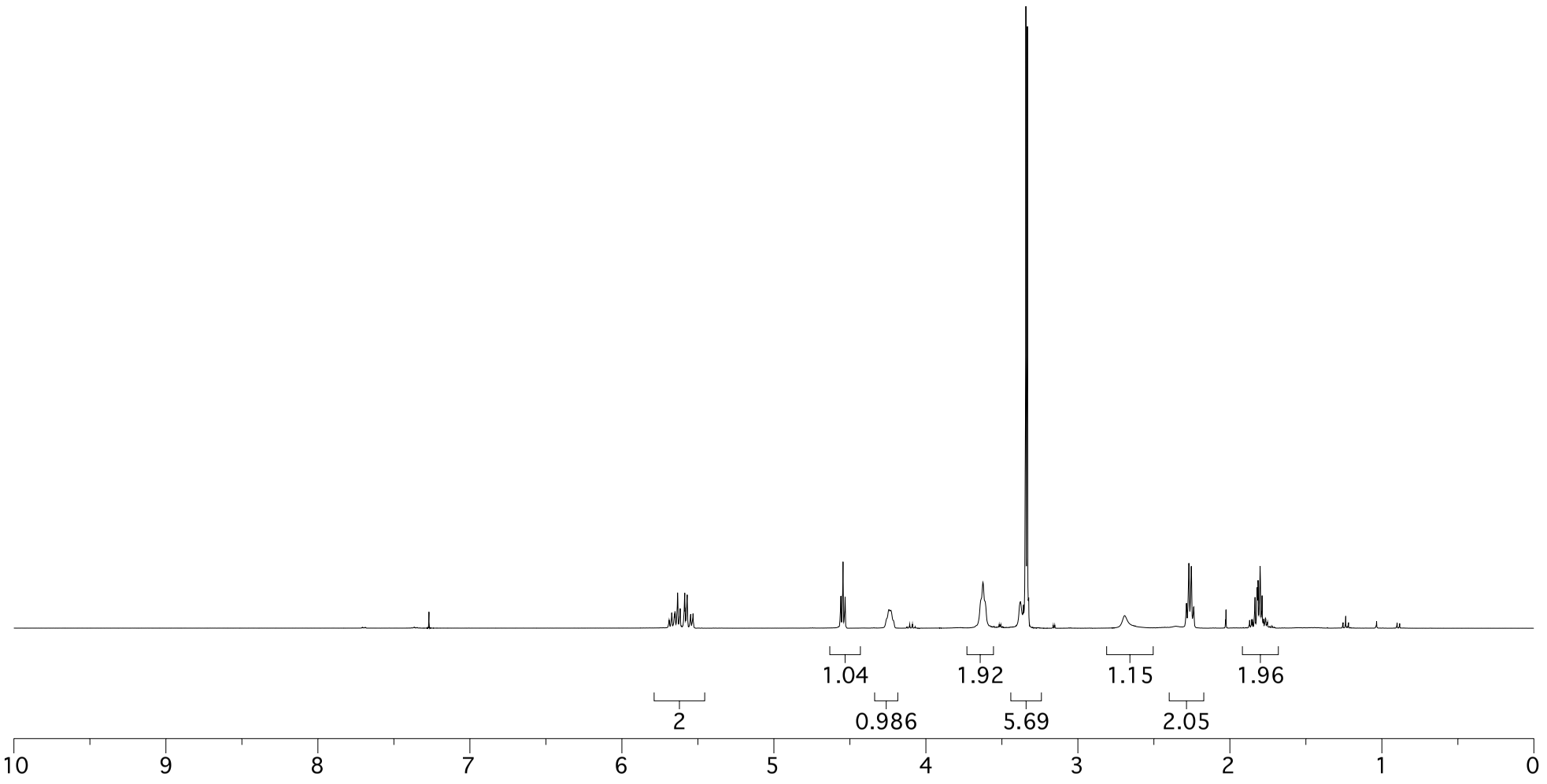


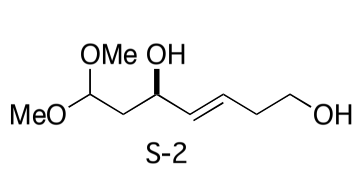

19.4
27.1
35.8
39.7
53.2
53.7
63.7
69.5
103.6
127.8
128.2
129.8
134.1
134.3
135.8
ppm
0
20
40
60
80
100
120
140
160
180
OMe OH
MeO
OTBDPS
13
100 MHz, CDCl3



S-2

400 MHz, CDCl3



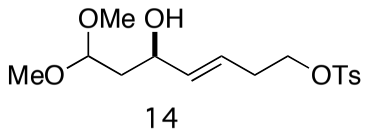


S-2

100 MHz, CDCl3

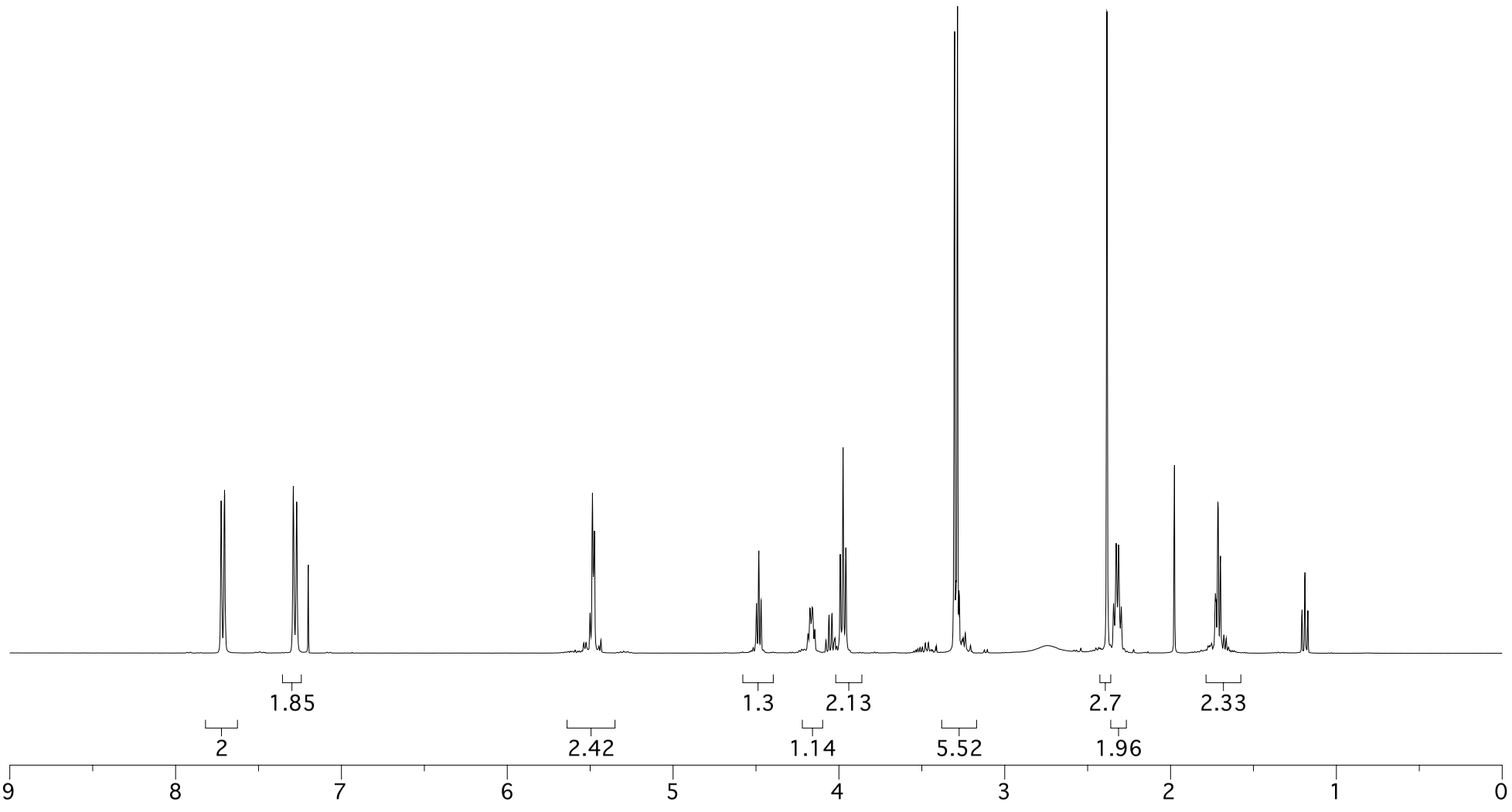
135.2
128.0
103.3
69.3
61.8
53.6
53.3
39.6
35.7

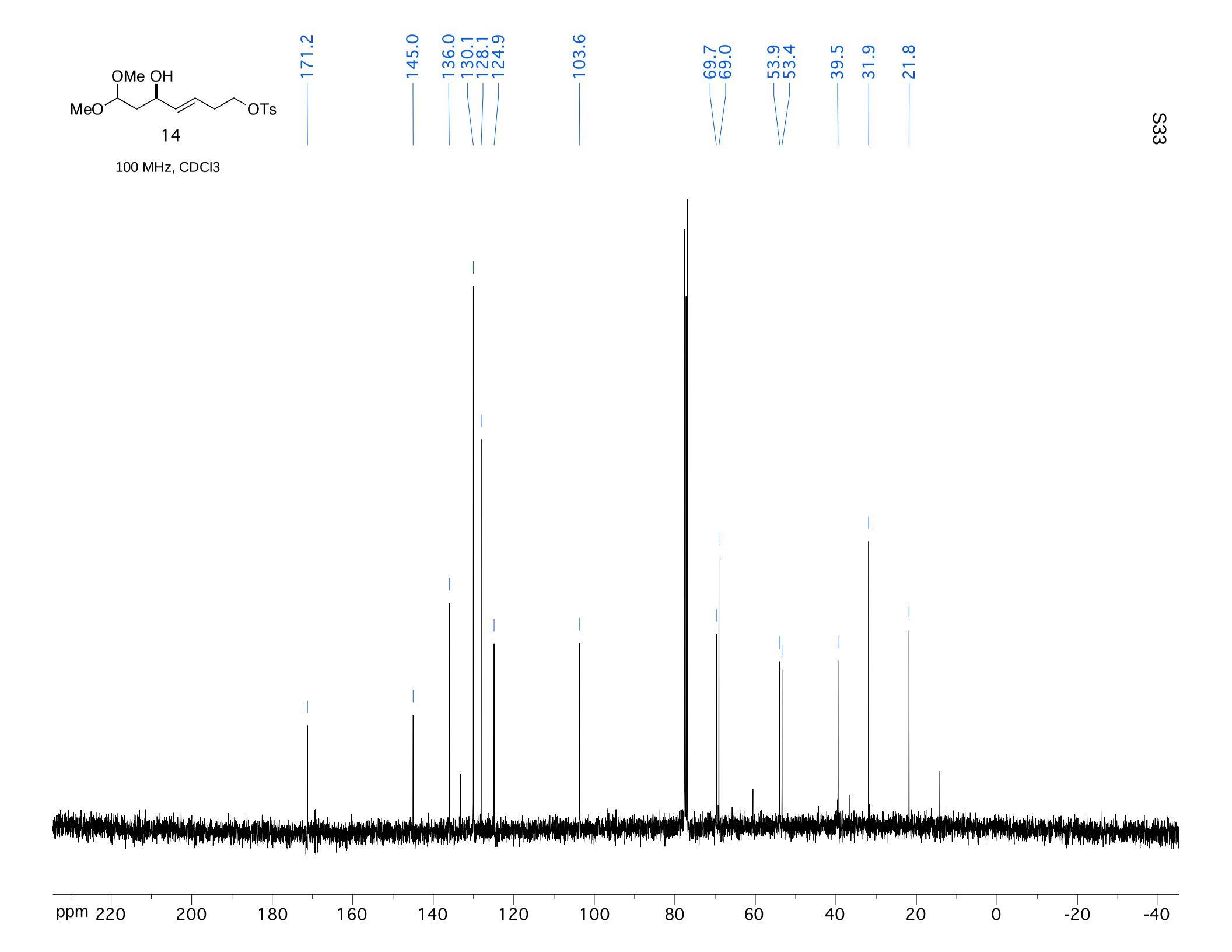
220 200 180 160 140 120 100 80 60 40 20 0 -20 -40

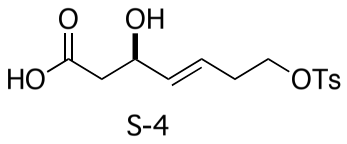


14

400 MHz, CDCl3

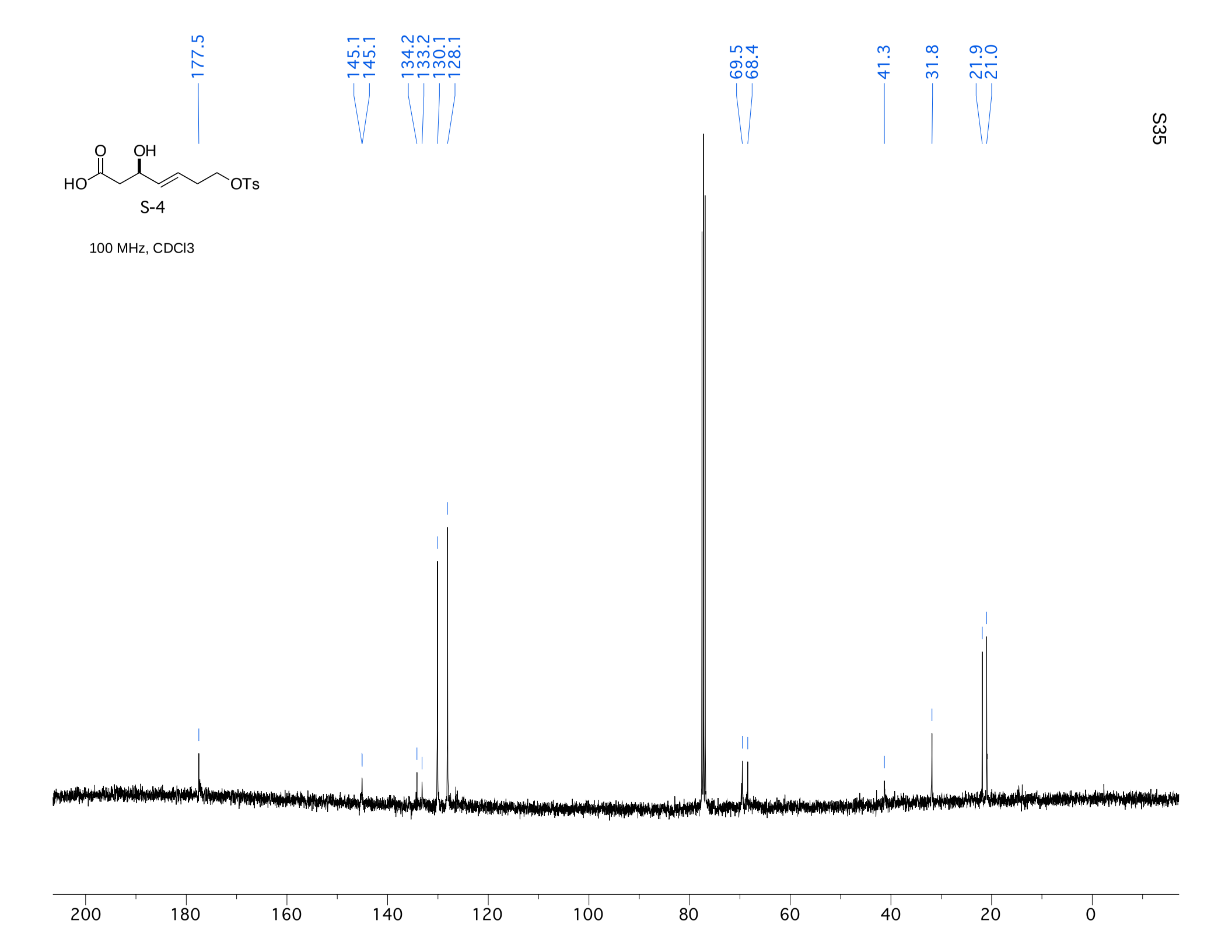


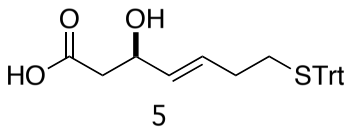

OMe OH
MeO
OTs
14
100 MHz, CDCl3
171.2
145.0
136.0
130.1
128.1
124.9
103.6
69.7
69.0
53.9
53.4
39.5
31.9
21.8
ppm 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40



S-4

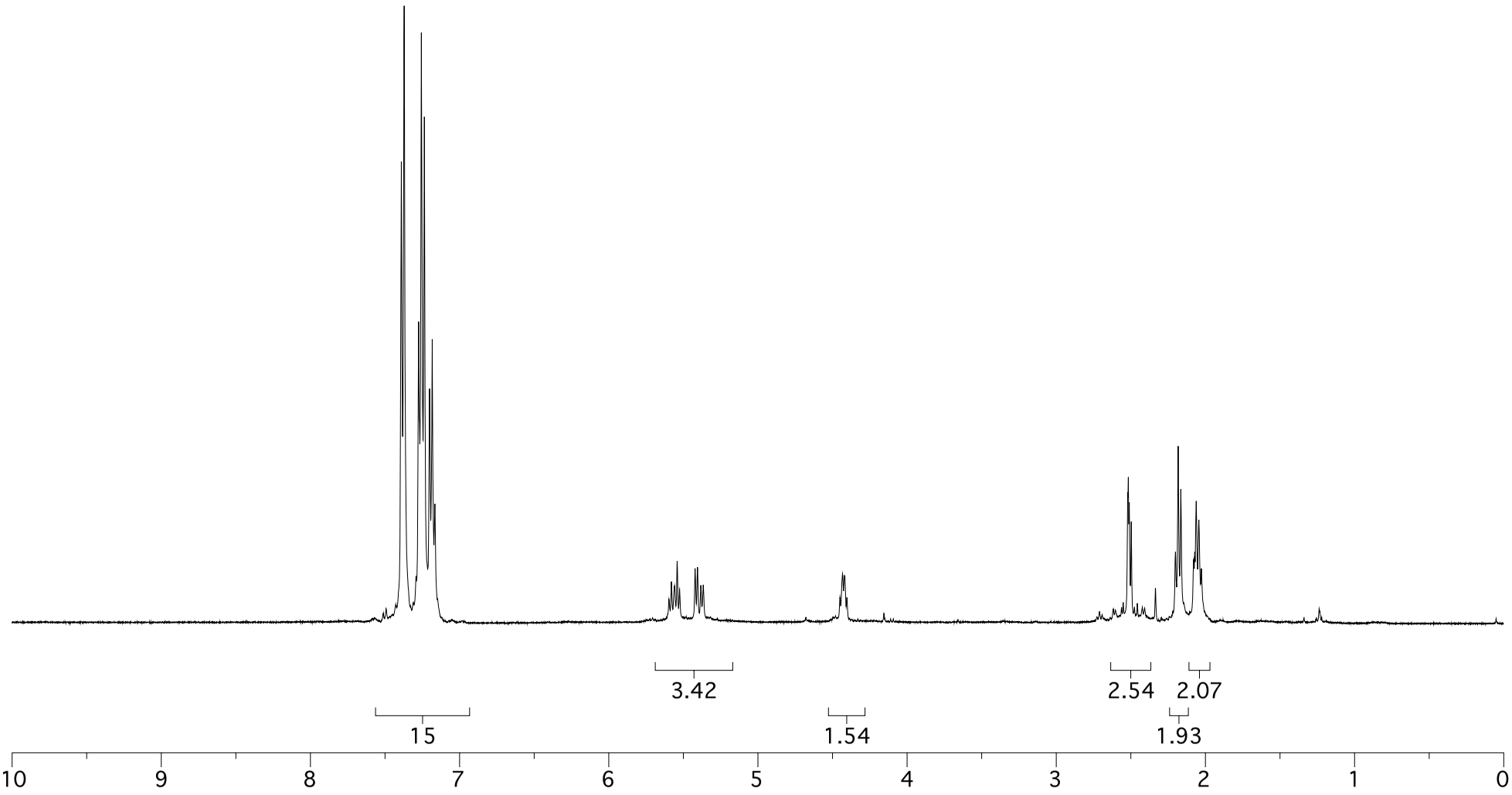
400 MHz, CDCl3

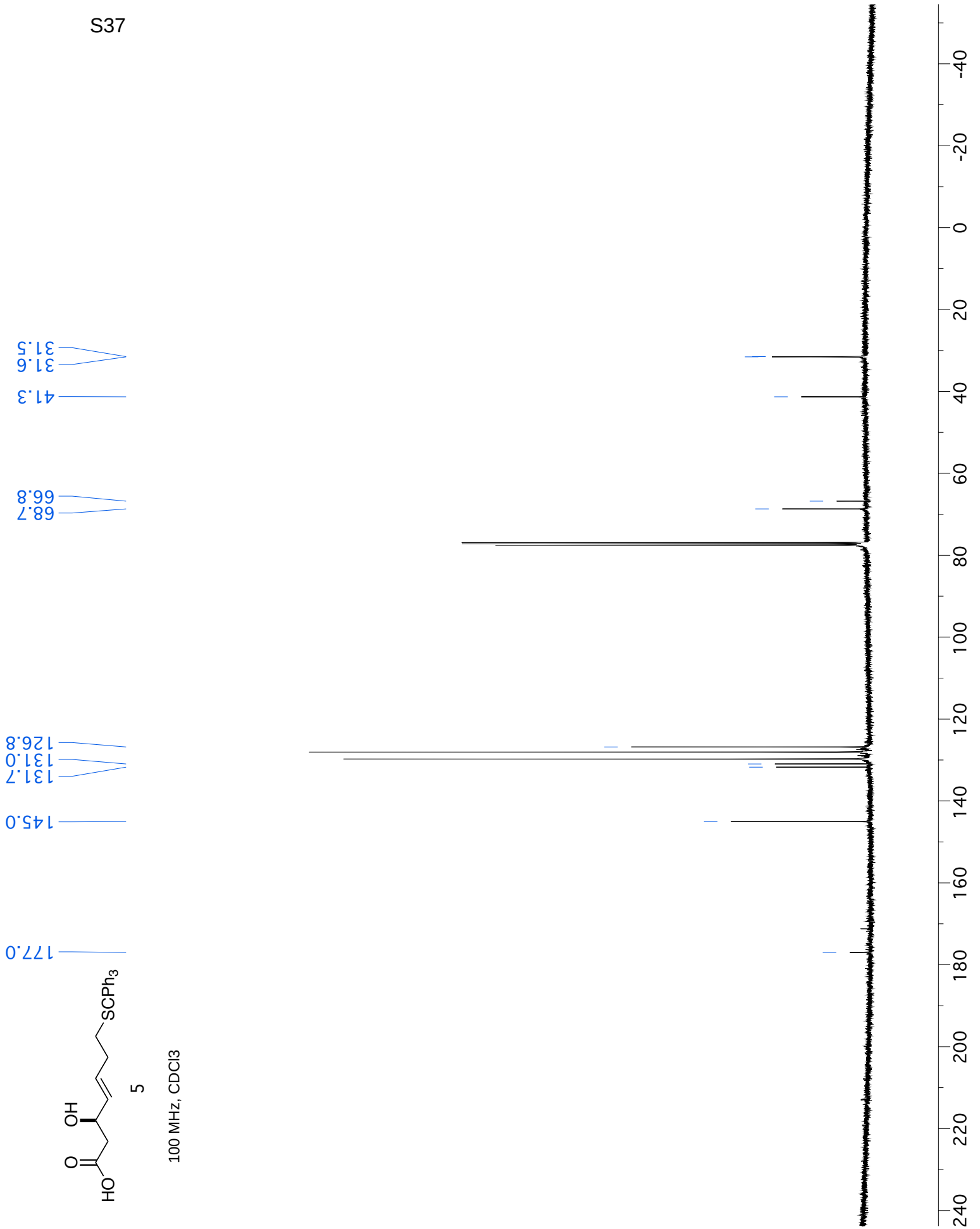

177.5
145.1
145.1
134.2
133.2
130.1
128.1
69.5
68.4
41.3
31.8
21.9
21.0
O
OH
HO
OTs
S-4
100 MHz, CDCl3
S35
200
180
160
140
120
100
80
60
40
20
0

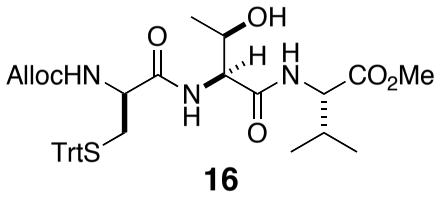


5

300 MHz, CDCl3

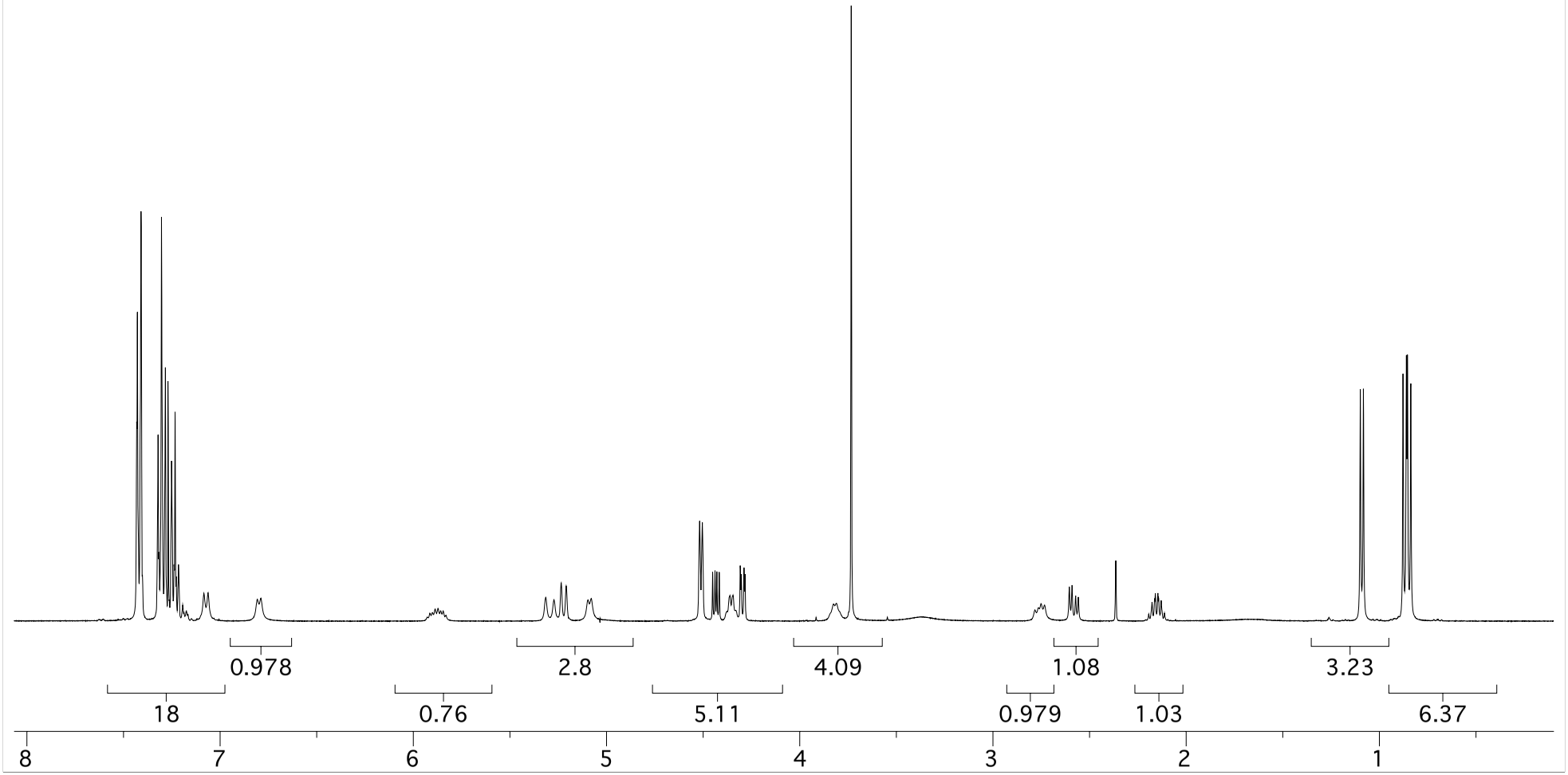


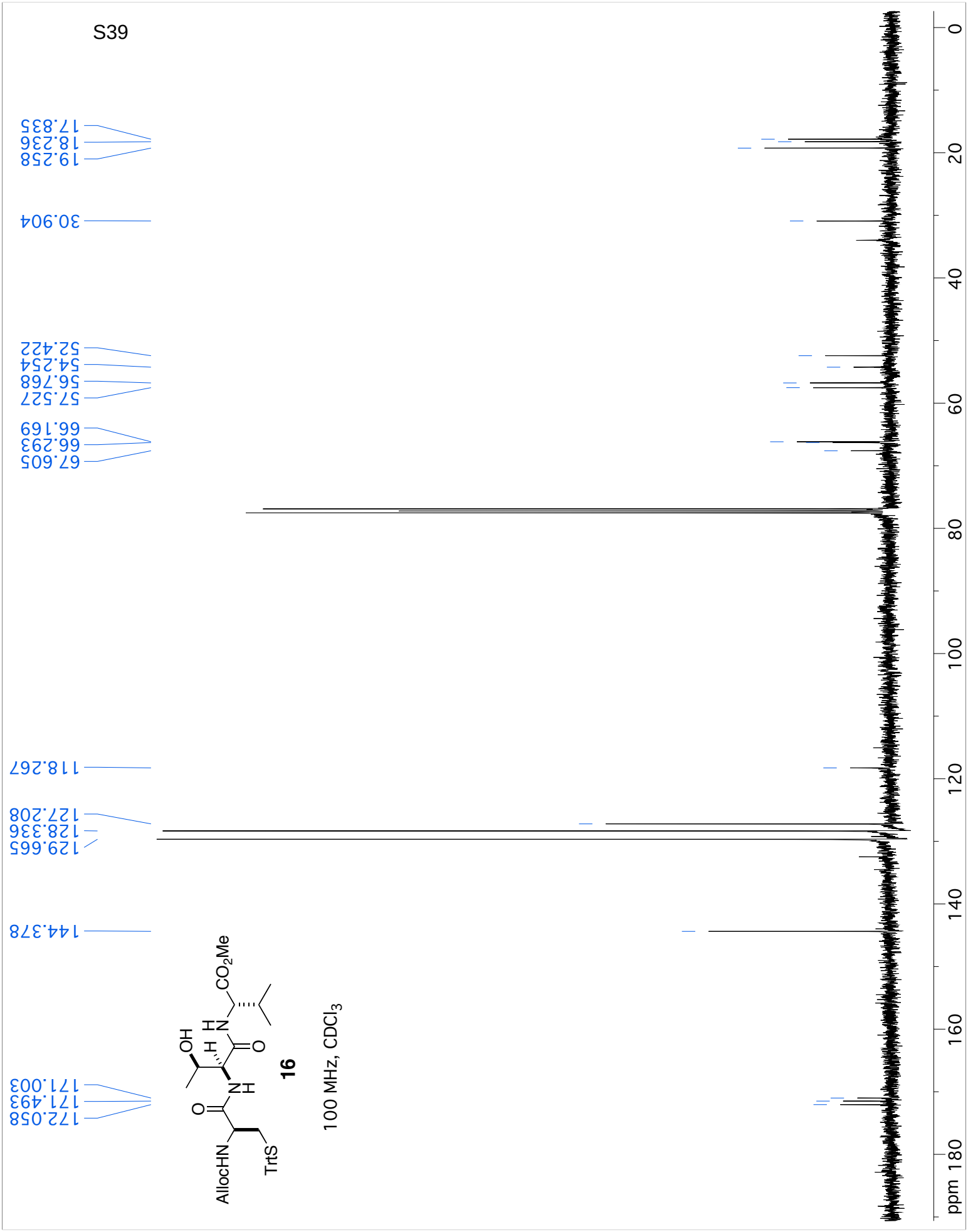

177.0
145.0
131.7
131.0
126.8
68.7
66.8
41.3
31.6
31.5
HO
O
OH
SCPh3
5
100 MHz, CDCl3
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40

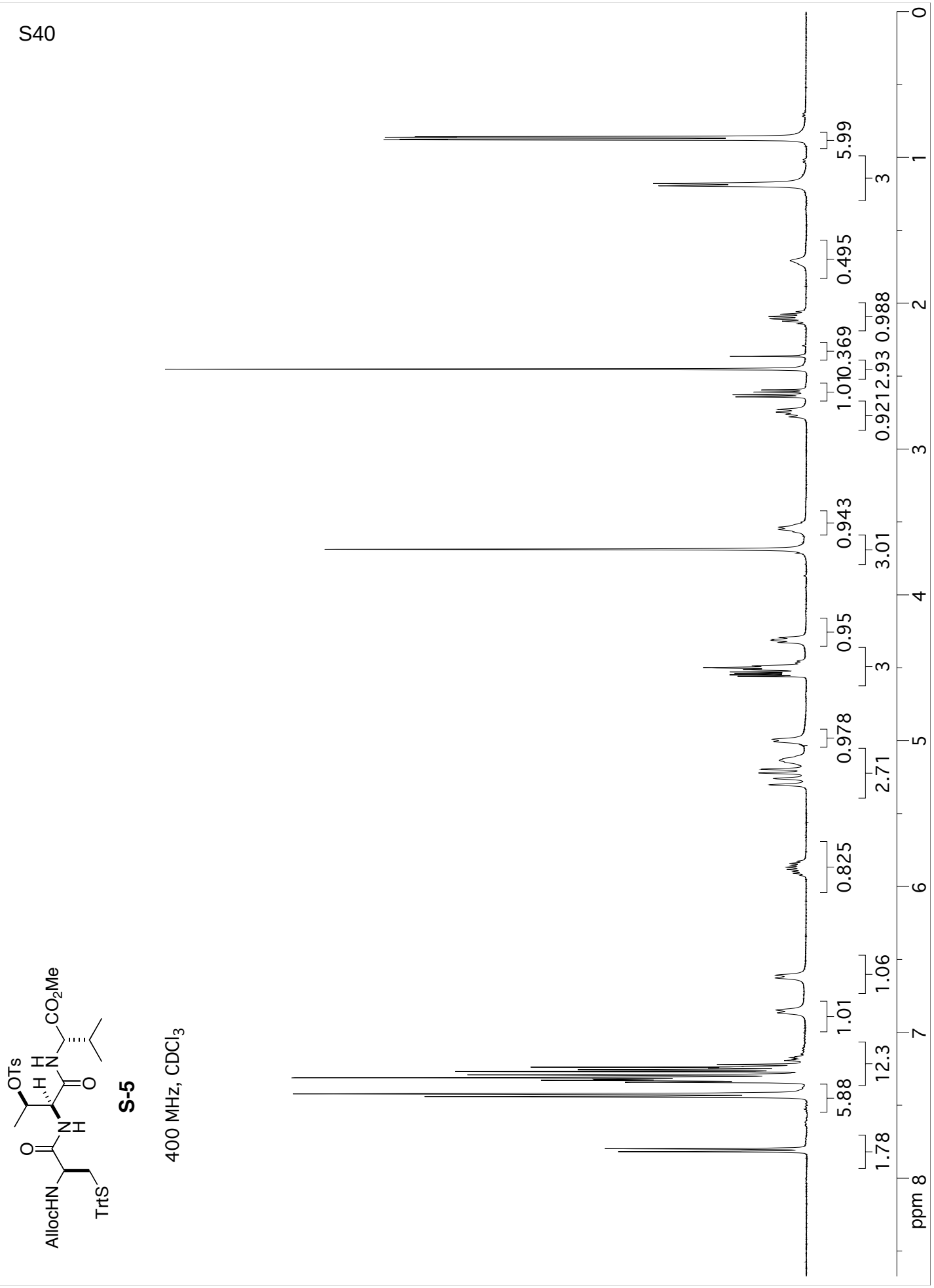


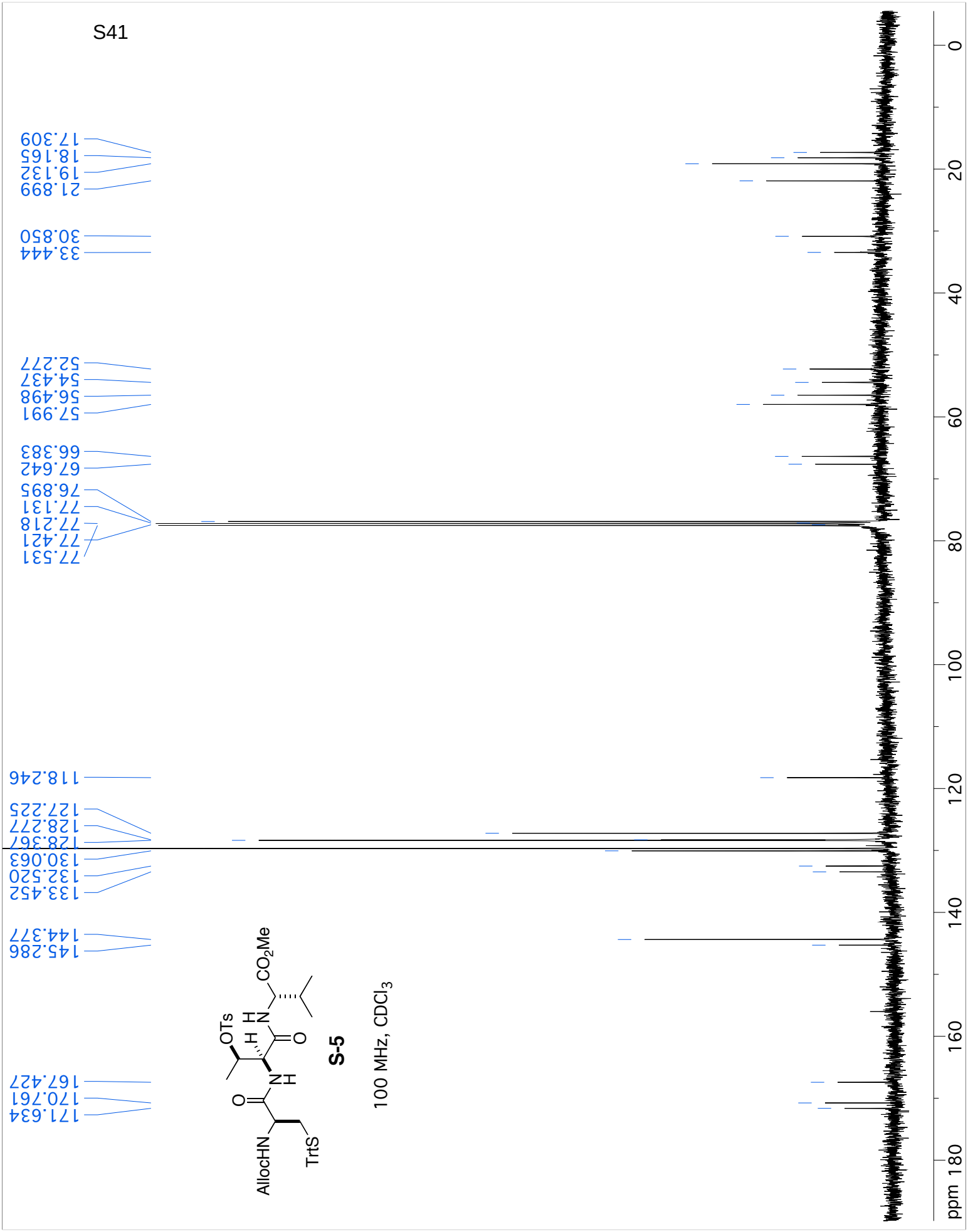
16

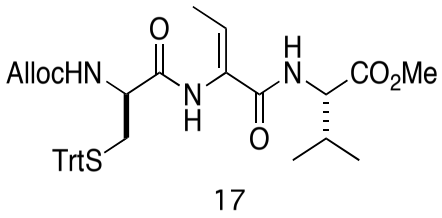
400 MHz, $CDCl_3$




17.835
18.236
19.258
30.904
52.422
54.254
56.768
57.527
66.169
66.293
67.605
118.267
127.208
128.336
129.665
144.378
171.003
171.493
172.058
ppm
0
20
40
60
80
100
120
140
160
180
16
100 MHz, CDCl3

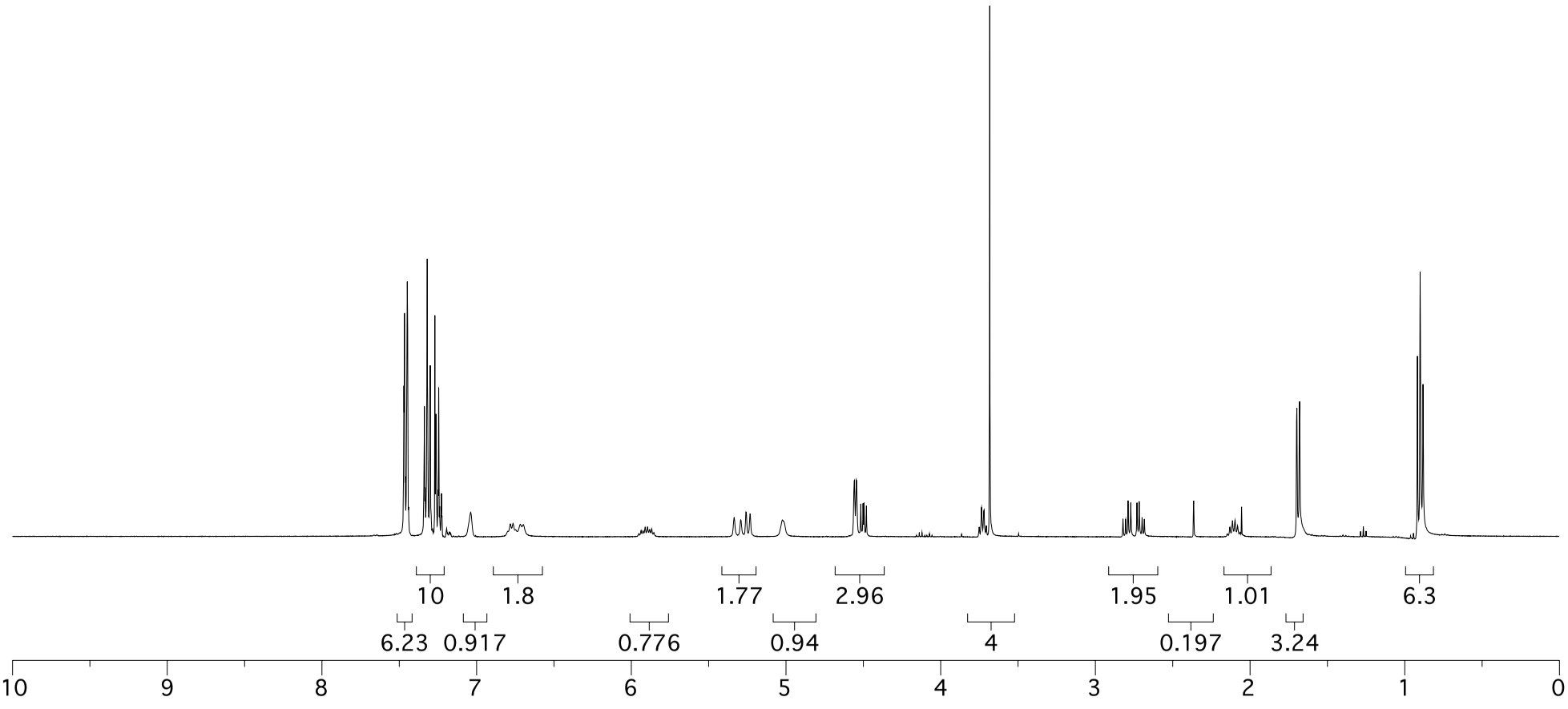

OTs
H
N
CO2Me
H
N
O
O
H
N
AllocHN
TrtS
S-5
400 MHz, CDCl3
5.88
1.01
12.3
1.06
1.78
0.825
0.978
2.71
0.95
3
3.01
0.943
1.01
0.369
0.921
2.93
0.988
0.495
5.99
ppm 8
7
6
5
4
3
2
1
0

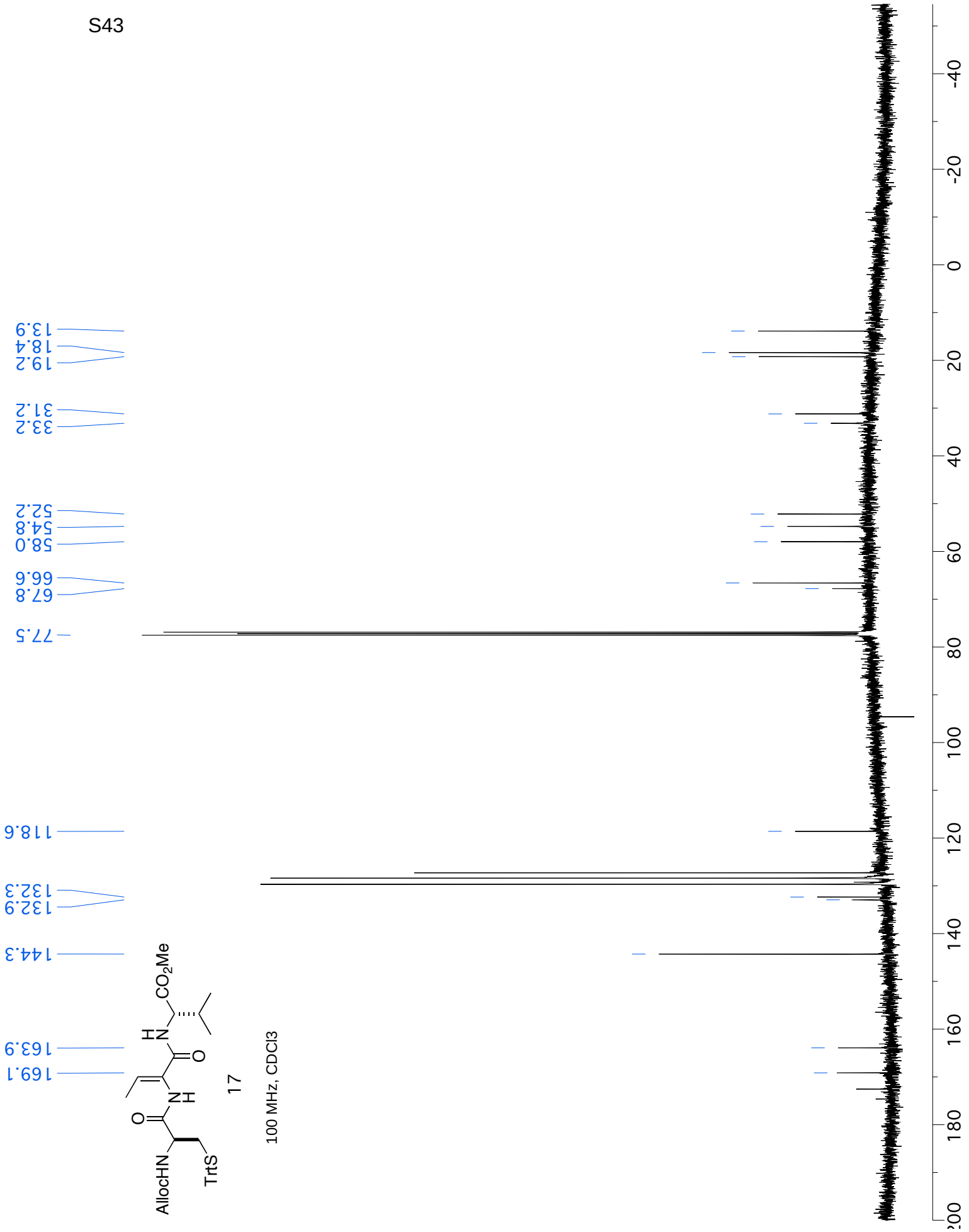

17.309
18.165
19.132
21.899
30.850
33.444
52.277
54.437
56.498
57.991
66.383
67.642
76.895
77.131
77.218
77.421
77.531
118.246
127.225
128.277
128.367
130.063
132.520
133.452
144.377
145.286
167.427
170.761
171.634
OTs
H
N
H
N
O
O
CO2Me
H
N
O
AllocHN
TrtS
S-5
100 MHz, CDCl3
ppm
0
20
40
60
80
100
120
140
160
180

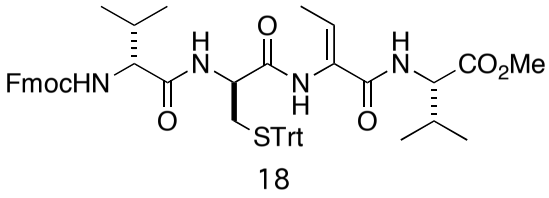


17

400 MHz, CDCl3

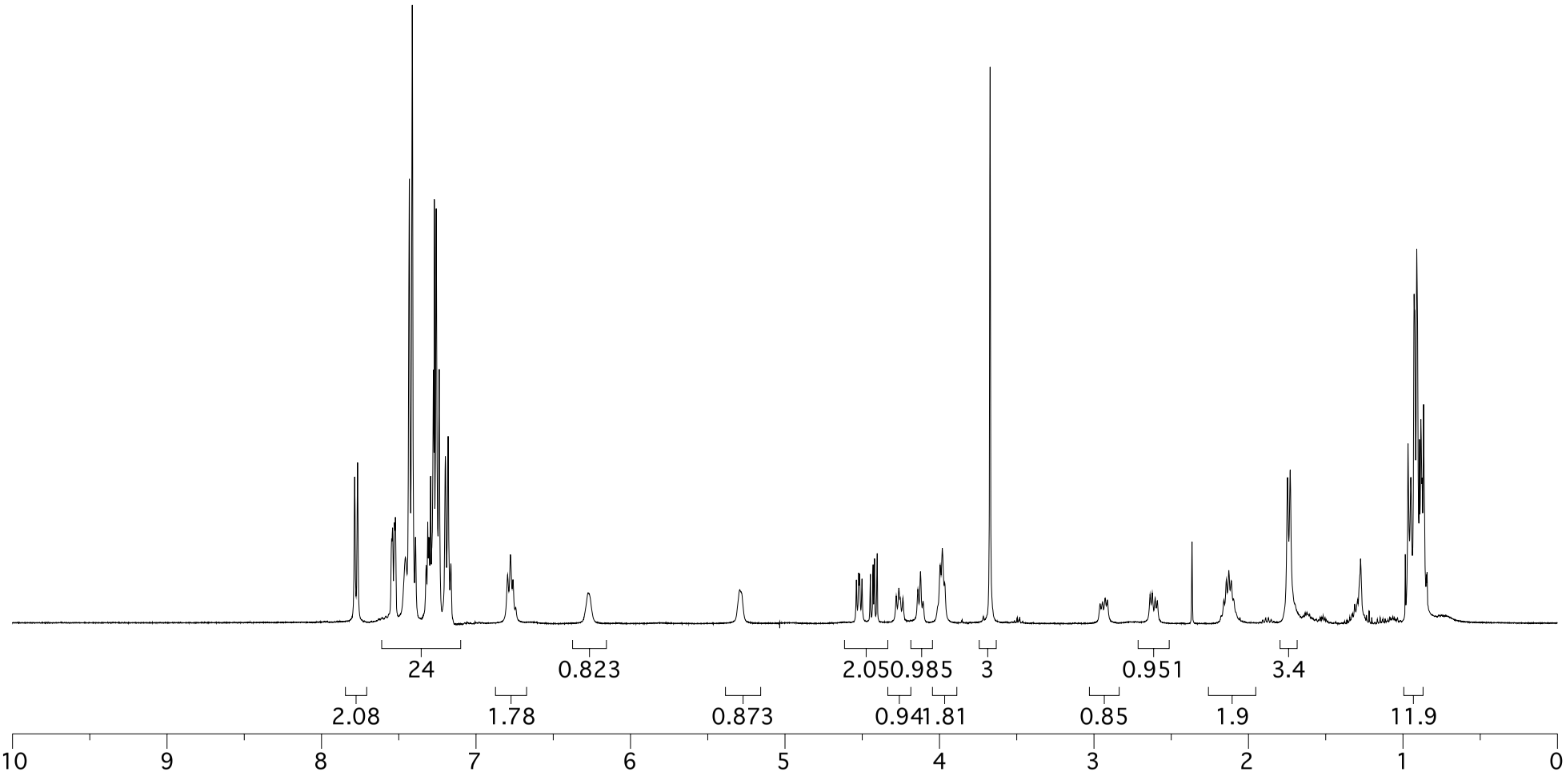


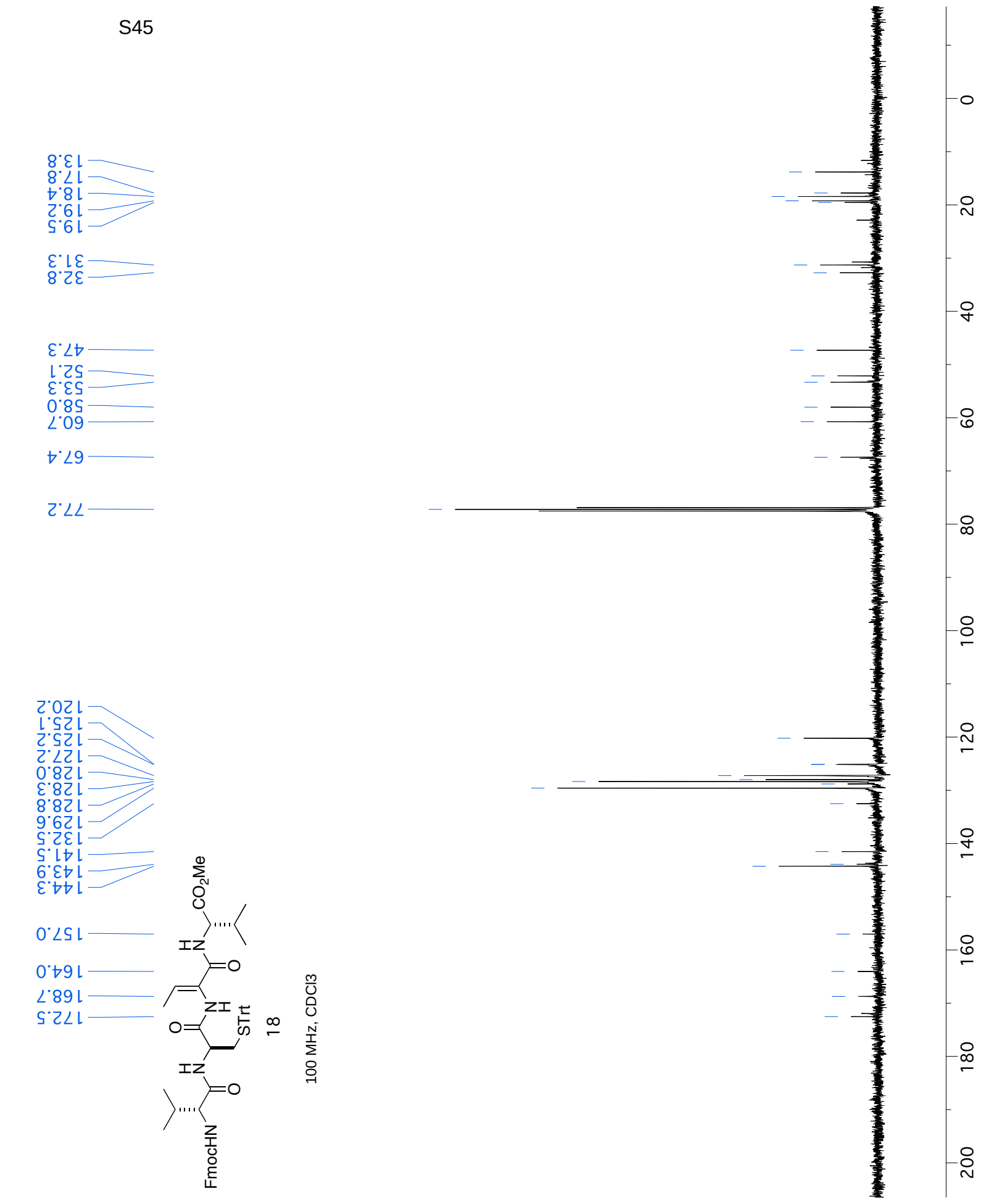

13.9
18.4
19.2
31.2
33.2
52.2
54.8
58.0
66.6
67.8
77.5
118.6
132.3
132.9
144.3
163.9
169.1
AllocHN
TrtS
CO2Me
17
100 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
-40

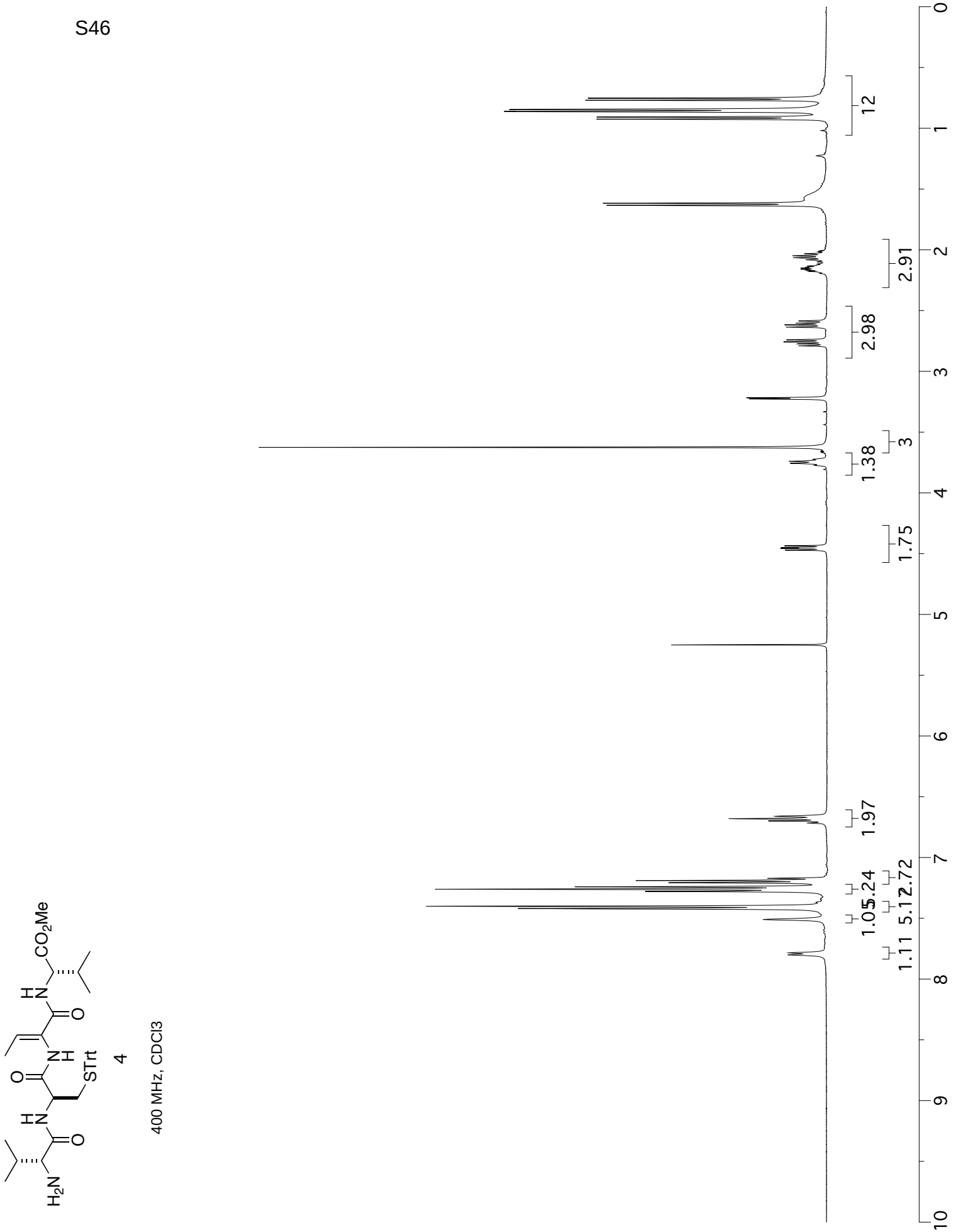


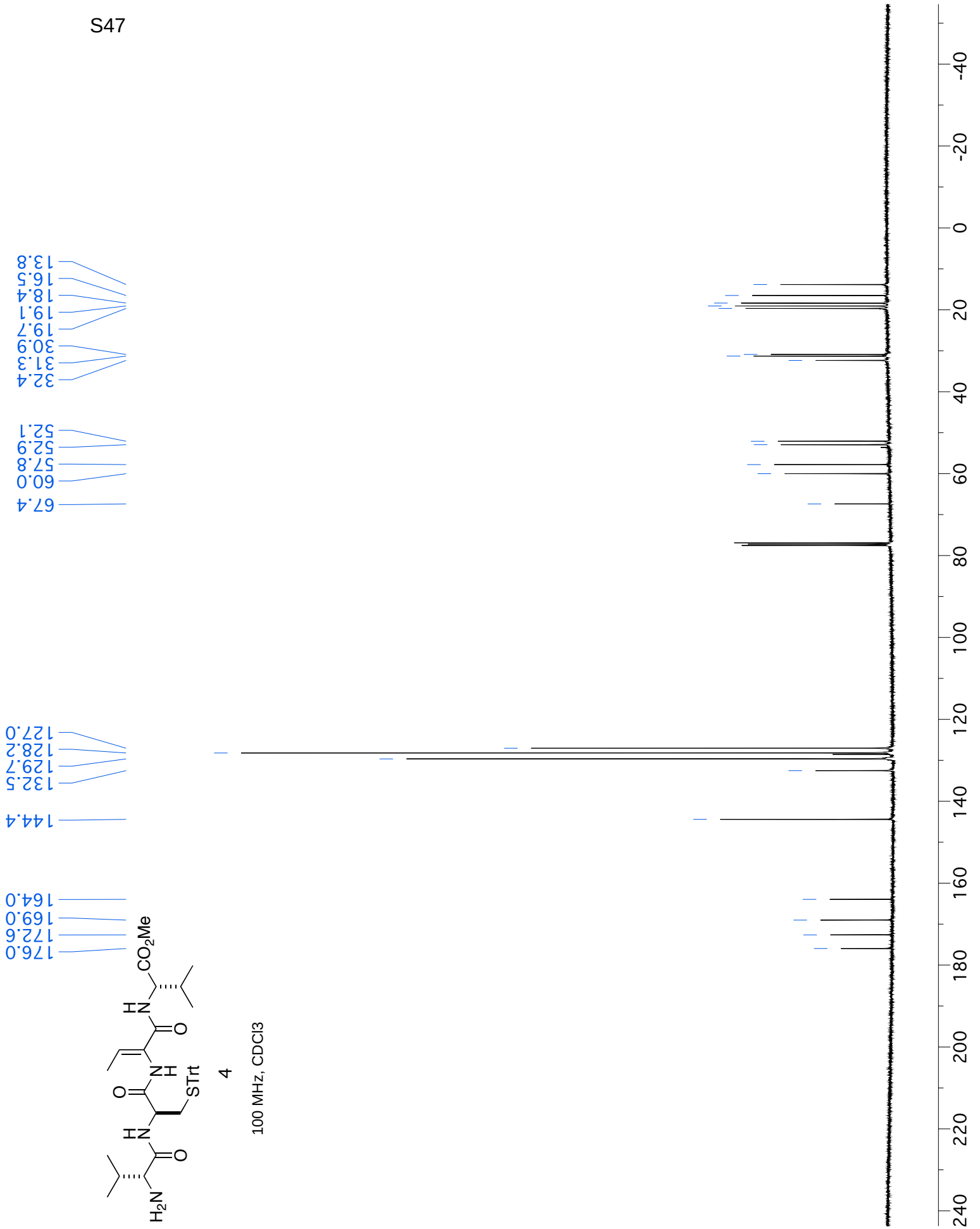
18

400 MHz, CDCl3

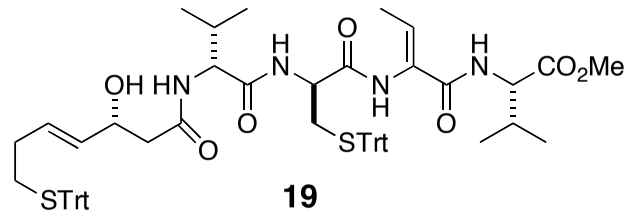



13.8
17.8
18.4
19.2
19.5
31.3
32.8
47.3
52.1
53.3
58.0
60.7
67.4
77.2
120.2
125.1
125.2
127.2
128.0
128.3
128.8
129.6
132.5
141.5
143.9
144.3
157.0
164.0
168.7
172.5
FmocHN
STrt
CO2Me
18
100 MHz, CDCl3
0
20
40
60
80
100
120
140
160
180
200

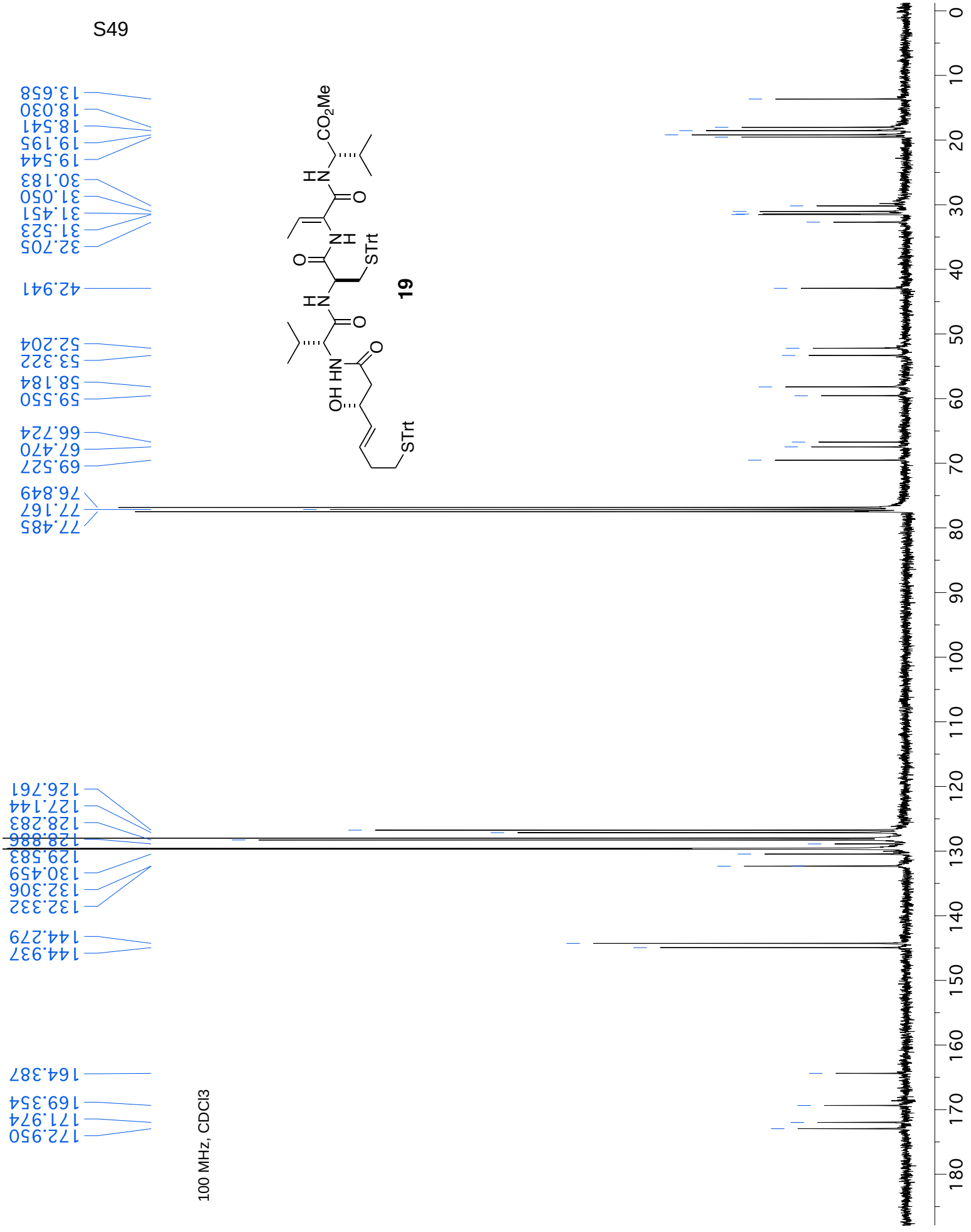

H2N
O
H
N
O
H
N
O
STrt
N
H
O
H
N
CO2Me
4
400 MHz, CDCl3
1.11
5.12
1.05
5.24
2.72
1.97
1.75
1.38
3
2.98
2.91
12
0
1
2
3
4
5
6
7
8
9
10


13.8
16.5
18.4
19.1
19.7
30.9
31.3
32.4
52.1
52.9
57.8
60.0
67.4
127.0
128.2
129.7
132.5
144.4
164.0
169.0
172.6
176.0
CO2Me
STrt
4
100 MHz, CDCl3
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40

400 MHz, CDCl3

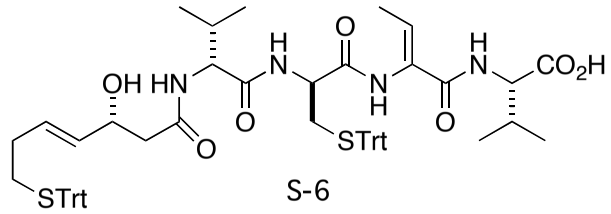


19


13.658
18.030
18.541
19.195
19.544
30.183
31.050
31.451
31.523
32.705
42.941
52.204
53.322
58.184
59.550
66.724
67.470
69.527
76.849
77.167
77.485
126.761
127.144
128.283
128.886
129.583
130.459
132.306
132.332
144.279
144.937
164.387
169.354
171.974
172.950
100 MHz, CDCl3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

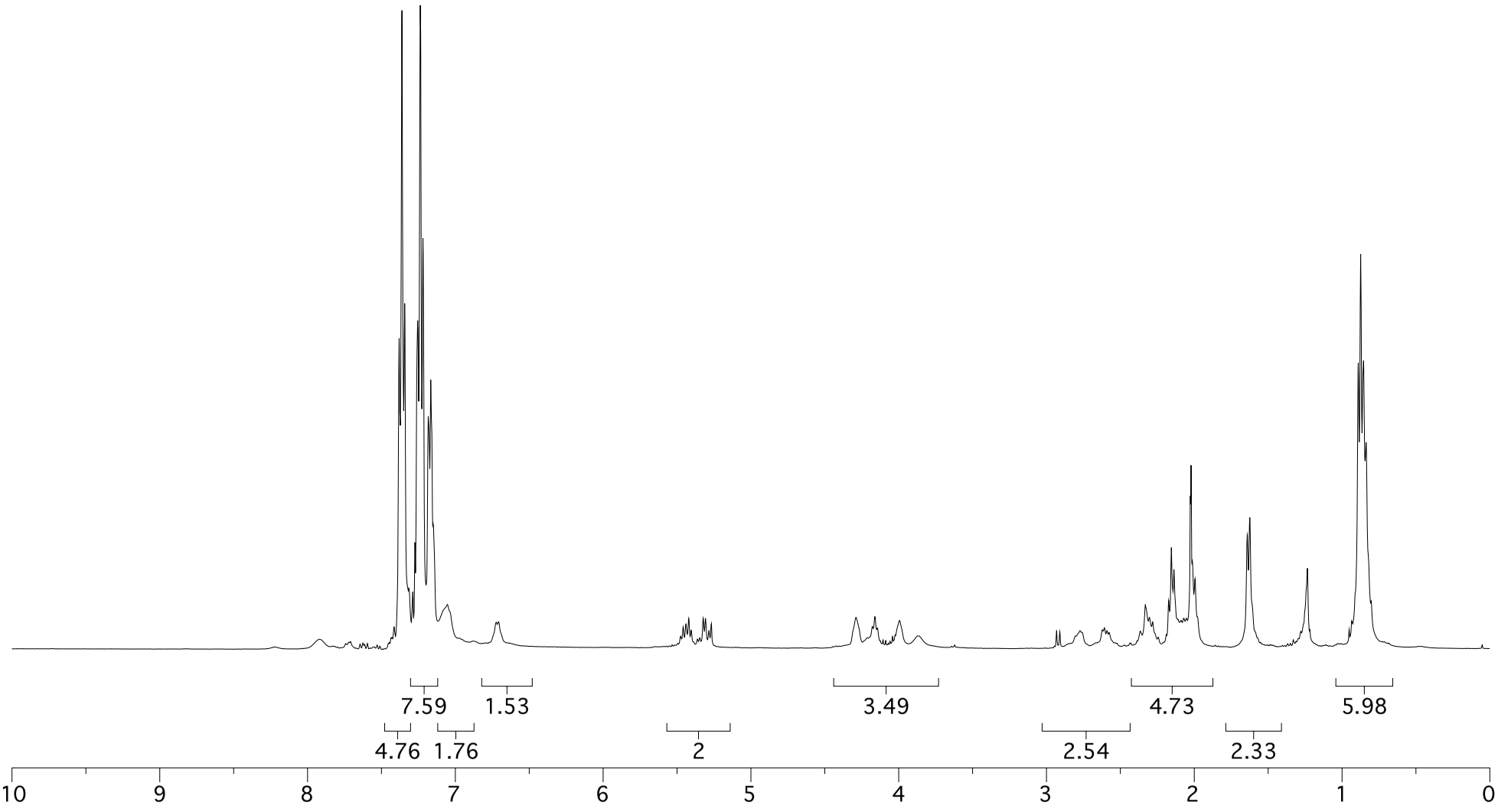
CO2Me
H N
O
N H
O
STrt
H N
O
OH HN
O
STrt

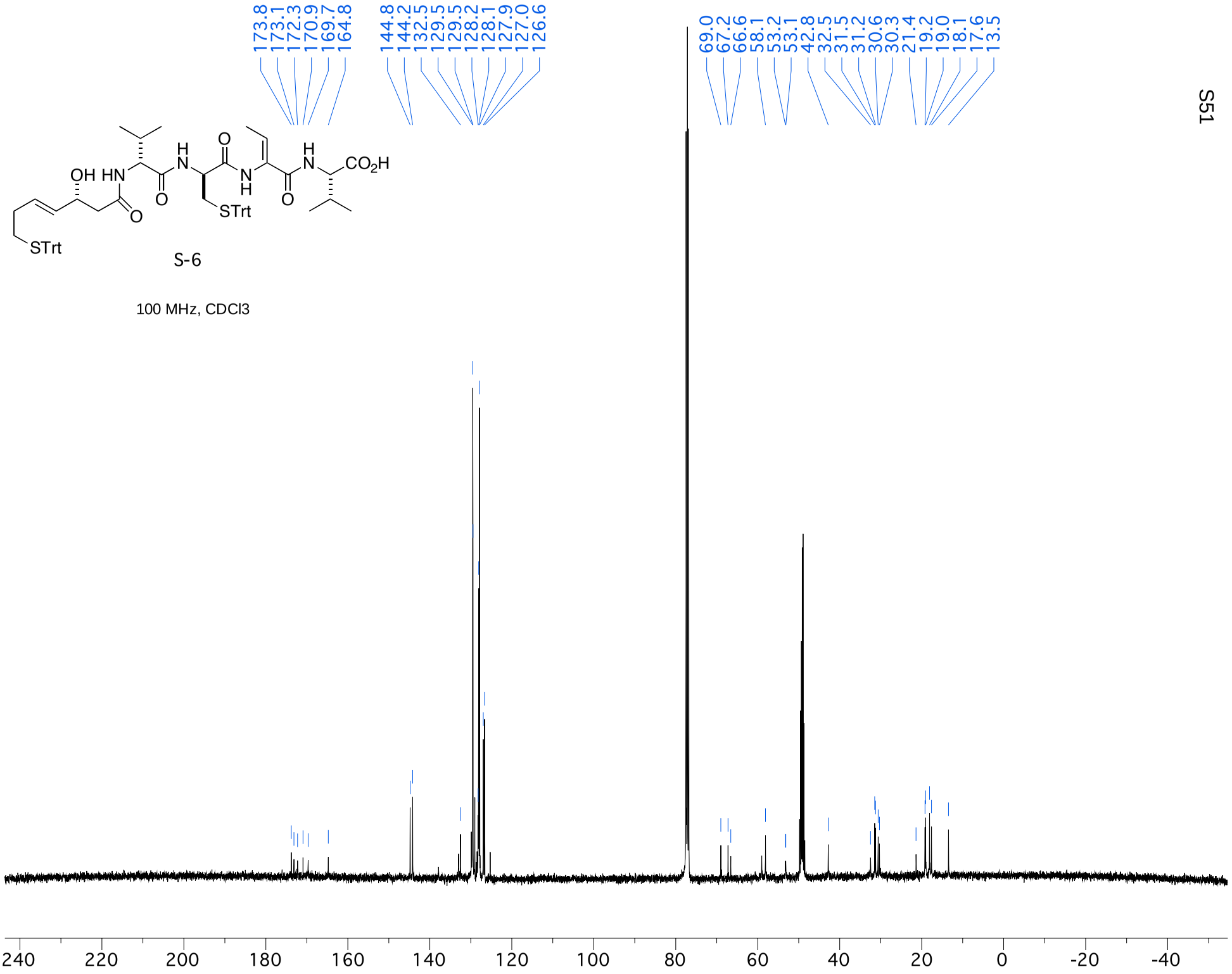
19

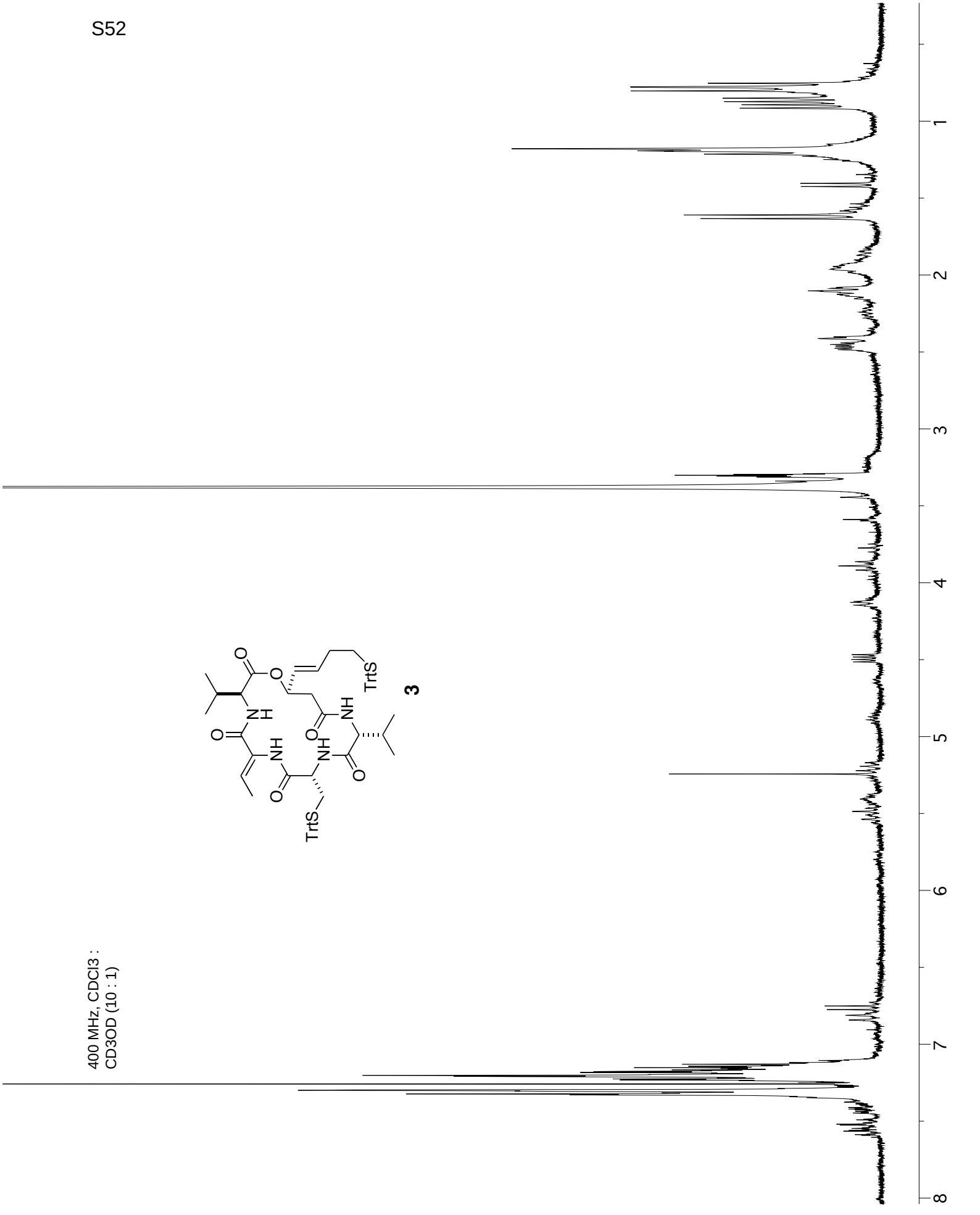


S-6

400 MHz, CDCl3

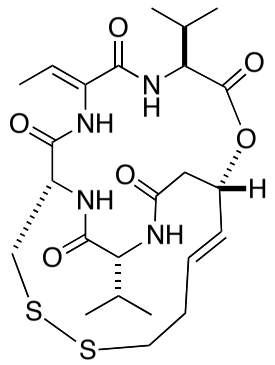



173.8
173.1
172.3
170.9
169.7
164.8
144.8
144.2
132.5
129.5
129.5
128.2
128.1
127.9
127.0
126.6
69.0
67.2
66.6
58.1
53.2
53.1
42.8
32.5
31.5
31.2
30.6
30.3
21.4
19.2
19.0
18.1
17.6
13.5
OH HN
O
H
N
O
N
H
O
H
N
CO2H
STrt
STrt
S-6
100 MHz, CDCl3
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40


400 MHz, CDCl3 :
CD3OD (10 : 1)
1
2
3
4
5
6
7
8
TrtS
TrtS
NH
NH
NH
NH
O
O
O
O
O
O
O
O

3

400 MHz, CDCl3 :
CD3OD (10 : 1)



1

ppm 8 7 6 5 4 3 2 1 0