Concise Synthesis of (+)-Fastigiatine

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Supporting Information

I. General experimental and laboratory conditions

All glassware was flame- or oven-dried and cooled under argon unless otherwise stated. All reactions and solutions were conducted under argon unless otherwise stated. All commercially available reagents were used as received, unless otherwise stated. Toluene (PhMe), tetrahydrofuran (THF), dimethylformamide (DMF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were degassed and dried by filtration through activated alumina under vacuum according to the procedure by Grubbs.[1] Diisopropylamine (DIPA), acetonitrile (MeCN), 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) were distilled from CaH_2 prior to use. All reactions involving LiDBB were conducted with glass stirbars. Thin layer chromatography (TLC) was performed with Millipore 60 F_{254} glass-backed silica gel plates and visualized using potassium permanganate, Dragendorff-Munier, ceric ammonium molybdate (CAM) or vanillin stains. Flash column chromatography was performed according to the method by Still, Kahn, and Mitra[2] using Millipore Geduran Silica 60 (40-63 μm).

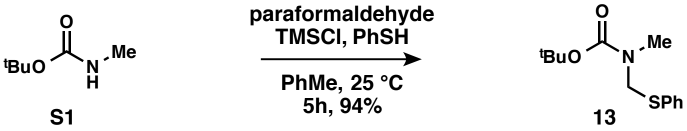
II. Instrumentation

All data collected at ambient temperature unless noted. ^1H NMR spectra were taken at 500 or 600 MHz, calibrated using residual NMR solvent or TMS and interpreted on the δ scale. Peak abbreviations are listed: s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, dd = doublet of doublets, ddd = doublet of doublet of doublets dt = doublet of triplets, ddt = doublet of doublet of triplets, dq = doublet of quartets, m = multiplet, app = apparent, br = broad. ^{13}C NMR spectra were taken at 125 MHz, calibrated using the NMR solvent, and interpreted on the δ scale. Some samples were analyzed above room temperature to minimize line broadening due to rotamers.

III. Experimental Section

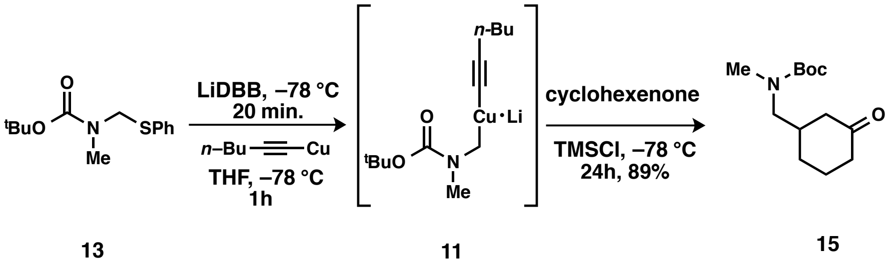
General procedure for preparation of LiDBB stock solution.

A round-bottom flask equipped with a glass stir bar was charged with 4,4'-di-*tert*-butylbiphenyl (1 equiv) and the flask was flame-dried under vacuum until 4,4'-di-*tert*-butylbiphenyl melted, at which point it was cooled to room temperature under argon. Lithium wire (10 equiv) was clipped in a stream of argon. Dry THF (0.5 M) was added and the solution stirred to give a dark green solution within 2-3 min. The mixture was cooled to 0 °C and stirred for 5 h to produce lithium di-*tert*-butylbiphenyl (LiDBB) at full molarity.



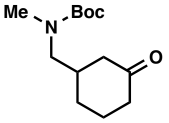
Thioether 13:

Dry toluene (149 mL) was added to a 500 mL round-bottom flask containing *tert*–butyl methyl carbamate **S1** (5.86 g, 0.044 mol, 1 equiv), paraformaldehyde (1.55 g, 0.051 mol, 1.15 equiv) and magnesium sulfate (15 g) at room temperature. After 5 min, TMSCl (16.9 mL, 0.134 mol, 3 equiv) was added dropwise via syringe. The solution was allowed to stir for 15 min and then thiophenol (5.07 mL, 0.025 mol, 1.1 equiv) was added, and the resulting mixture was allowed to stir until starting material was consumed as observed by TLC. After 5 h, the crude reaction mixture was filtered, concentrated and purified via chromatography (15% EtOAc in hexanes) to afford product **13** (10.62 g, 94%) as a crystalline white solid. **^{1}H NMR** (500 MHz, $CDCl_3$, 65 °C) δ 7.49 (d, *J* = 7.0 Hz, 1H), 7.31–7.20 (m, 3H), 4.75 (s, 2H), 2.90 (s, 3H), 1.33 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$, 65 °C) δ 155.0, 134.5, 133.4, 129.0, 127.6, 80.2, 55.5, 33.3, 28.3; **IR** (thin film) 2972, 2929, 1699, 1478, 1443, 1389, 1265, 1230, 1172, 1133, 1052, 869, 745 cm^{-1}; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{13}H_{19}NO_2SNa$ (M + Na)$^+$: 276.1034, found: 276.1029. **mp** = 60–63 °C; **TLC** (20% EtOAc in hexanes) R_f = 0.42 ($KMnO_4$ stain).



Cyclohexanone 15:

A round bottom flask containing **13** (211 mg, 0.83 mmol) and 1,10-phenanthroline (2-3 crystals) was dried by azeotroping three times with freshly distilled benzene. The flask was then equipped with a glass stir bar and THF (15 mL) was introduced under Ar. The mixture was cooled to –78 °C and *n*–BuLi/hexanes (2-3 M) was added until a brown dark color persisted (~0.3–0.4 mL). This procedure was performed to quench adventitious proton sources. LiDBB (4.7 mL, 1.86 mmol, 2.2 equiv) was then added dropwise over 10 min at –78 °C until a dark-green color persisted, and the mixture was allowed to stir for 20 min. A separate flask containing 1-hexynyl copper (240 mg, 1.67 mmol) and tetrahydrofuran (3 mL) was cooled to –78 °C and trimethyl phosphite (0.44 mL, 3.75 mmol) was introduced; the mixture was stirred until a clear solution developed. The resulting homogeneous solution was added via syringe to the organolithium reagent down the flask wall over 3 min and stirring was continued for 1 h to produce **15** as deep red solution. The cyclohexenone (40 mg, 0.42 mmol) was added as a solution in THF (0.3 mL) with freshly distilled TMSCl (263 μL, 2.08 mmol). The resulting mixture was stirred at –78 °C for 24 h and quenched with 10% concentrated ammonium hydroxide/saturated ammonium chloride (20 mL), followed by warming to room temperature. After 1 h, the organic layers were separated and the aqueous layers were extracted with ethyl acetate (20 mL) three times. The organic layers were combined, dried and concentrated under vacuum. The resulting mixture was filtered through a plug silica with 20% CH_2Cl_2 in hexanes to remove excess of 4,4'-di-*tert*-butylbiphenyl, at which point ethyl acetate was used to flushed the plug. The material was concentrated under vacuum. The mixture was concentrated, loaded onto silica gel with DCM and purified by column chromatography, eluting with 25% EtOAc/hexanes gradient, to afford **16** (89.2 mg, 89%).



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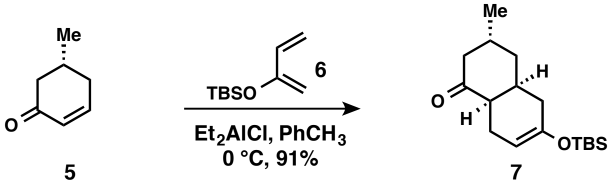
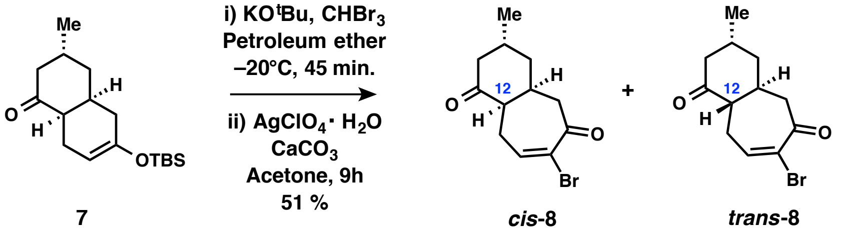
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24–3.03 (m, 2H), 2.84–2.74 (m, 3H), 2.39–2.28 (m, 2H), 2.27–2.18 (m, 1H), 2.11–1.90 (m, 3H), 2.67 (s, 3H), 1.88–1.75 (m, 1H), 1.67–1.53 (m, 1H), 1.40 (s, 9H), 1.38–1.27 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 211.3, 210.9, 156.2, 155.8, 79.8, 79.6, 54.5, 53.9, 45.8, 45.7, 41.5, 38.5, 38.1, 35.2, 29.1, 28.5, 25.3, 25.2; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{13}H_{23}NO_3Na$ $(M + Na)^+$: 264.1576, found: 264.1572; **TLC** (25 % EtOAc in Hexanes) R_f = 0.33 (CAM stain). Spectral data matched those reported in the literature.[3]



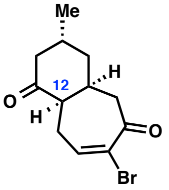
Decalin 7:

A round-bottom flask was charged with (+)-5-methylcyclohex-2-en-1-one (2.01 g, 18.26 mmol) and 2-*tert*-butyldimethylsiloxy-1,3-butadiene (4.68 g, 25.44 mmol) and purged 4 times via vacuum/argon cycles. Dry toluene (75 mL) was added and the solution was cooled to 0 °C. Diethyl aluminum chloride (19.1 mL, 1.0 M in toluene 19.1 mmol) was then added dropwise over a 10 min period. The resulting mixture was allowed to reach room temperature with stirring. After 1.5 h, the mixture was cooled to 0 °C and the reaction was quenched by addition of saturated $NaHCO_3$ (250 mL) and 10% potassium sodium tartrate (20 mL). The aqueous layer was separated and extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (3 x 200 mL), brine (3 x 200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Volatile materials were removed under high vacuum (ca. 1 Torr) overnight to afford the desired product **7** (4.91 g, 91%) as light yellow oil. Spectral data were consisted with those reported in the literature.[4] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.81–4.78 (app. m, 1H), 2.61 (t, *J* = 5.8 Hz, 1H), 2.57–2.48 (m, 2H), 2.39 (ddd, *J* = 13.5, 4.8, 2.0 Hz, 1H), 2.25–2.17 (m, 1H), 2.20–1.95 (m, 2H), 1.86 (app. dd, *J* = 8.0, 1.5 Hz, 2H), 1.80 (d, *J* = 14.5 Hz, 1H), 1.64 (ddd, *J* = 13.5, 11.5, 4.0 Hz, 1H), 1.03 (d, *J* = 6 Hz, 3H), 0.89 (s, 9H), 0.11, 0.08; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 211.1, 148.2, 102.0, 49.7, 47.0, 38.2, 36.1, 31.9, 30.8, 25.9, 22.6, 22.2, 18.1, -4.1, -4.4; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{17}H_{31}O_2Si$ $(M + H)^+$: 295.2093, found: 295.2095. **TLC** (10% EtOAc in hexanes) R_f = 0.60 (CAM Stain).



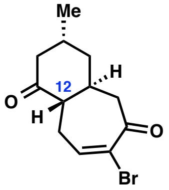
Bromo enone 8:

To a solution of decalin **7** (1.21 g, 4.12 mmol) in petroleum ether (110 mL) at –20 °C was added potassium *tert*-butoxide (1.39 g, 12.37 mmol) in 3 portions. The heterogeneous mixture turned yellow within 2 min. After 2 min, freshly distilled bromoform (1.08 mL, 12.37 mmol) was added dropwise in petroleum ether (20 mL) over 4 min. The reaction mixture was allowed to stir at –20 °C until starting material was consumed as observed by TLC. After 45 min, the mixture was removed from the cooling bath and filtered through a silica plug with 25% EtOAc in petroleum ether. The filtrate was concentrated under vacuum and the resulting yellow oil was dissolved in acetone (45 mL). Calcium carbonate (2.06 g, 20.63 mmol) and silver perchlorate monohydrate (1.85 g, 8.25 mmol) were added. The reaction was allowed to stir at 25 °C for 9 h, during which time a dark precipitate developed. The reaction was quenched by addition of Et_3N (1.15 mL, 8.25 mmol) and silica gel (1.5 g), and the mixture concentrated under vacuo. The resulting crude mixture was flushed through a plug of silica using Et_2O. The material was concentrated under vacuo and purified via chromatography (eluent, gradient 15% → 25% EtOAc in hexanes) to afford a mixture of diastereomers of **8** (0.57 g, 51%) as yellow oil (~3:1 *cis*/*trans* mixture of C-12 epimers). A small sample of the mixture was purified by MPLC to separate the cis and trans isomers for characterization.



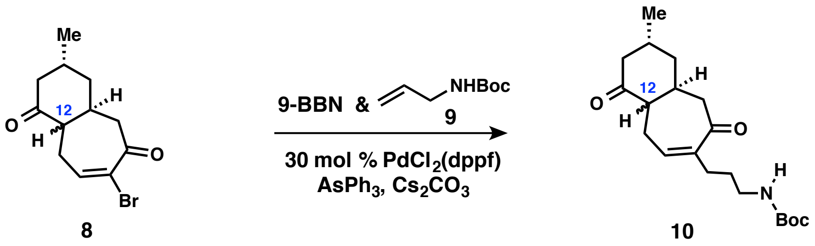
***cis*-8**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 10.5, 4.8 Hz, 1H), 2.75–2.65 (m, 3H), 2.57–2.46 (m, 3H), 2.4 (dd, *J* = 16.3, 10.3 Hz, 1H), 2.07 (t, *J* = 12.8 Hz, 1H), 1.97–1.87 (m, 1H), 1.84 (dt, *J* = 13.5, 3.3 Hz, 1H), 1.75 (ddd, *J* = 14.8, 11.5, 4.3 Hz, 1H), 1.05 (d, *J* = 6.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.8, 195.7, 144.1, 125.6, 49.7, 47.4, 45.3, 39.4, 34.7, 29.9, 27.0, 22.1; **IR** (thin film) 3444, 2955, 2924, 1705, 1685, 1600, 1452, 1379, 1231, 1111, 1041, 916 cm^{-1}; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{12}H_{15}BrO_2Na$ $(M + Na)^+$: 293.0153, found: 293.0161. **TLC** (20% EtOAc in hexanes) R_f = 0.33 (CAM Stain).



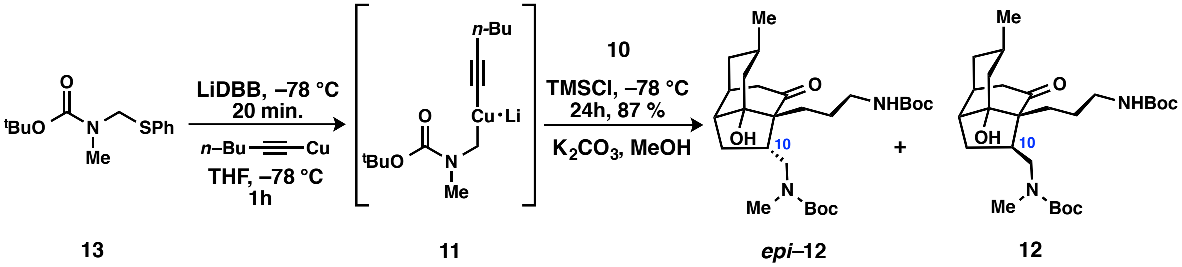
***trans*-8**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.3, 4.3 Hz, 1H), 2.92 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.87–2.78 (m, 1 Hz), 2.60 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.53–2.36 (m, 3H), 2.27–2.21 (m, 1H), 2.18 (d, *J* = 13 Hz, 1H), 1.94 (td, *J* = 13.0, 4.8 Hz, 1H), 1.68 (d, J = 14.5 Hz, 1H), 0.98 (d, J = 7Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.4, 195.3, 145.3, 125.9, 54.9, 48.0, 46.9, 38.3, 35.6, 29. 8, 28.4, 20.0; **IR** (thin film) 3437, 2957, 2826, 1602, 1711, 1687, 1459, 1385, 1238, 1090, 912 cm^{-1}; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{12}H_{15}BrO_2Na$ $(M + Na)^+$: 293.0153, found: 293.0161. **TLC** (20% EtOAc in hexanes) R_f = 0.32 (CAM Stain).



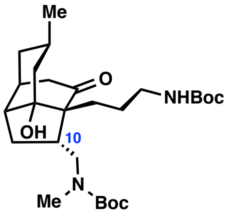
Carbamate 10:

To a solution of *tert*–butyl allylcarbamate **9** (402 mg, 2.56 mmol) in degassed THF (4.3 mL) was added a solution of 9-BBN (0.5 M in THF, 7.2 mL, 3.58 mmol) at room temperature. After stirring for 4 h, the solution was treated with degassed water (615 μL, 34.14 mmol) for 20 min. In a separate Schlenk flask, bromo enone **8** (461 mg, 1.71 mmol), $CsCO_3$ (1.22 g, 3.76 mmol), $AsPh_3$ (157 mg, 0.51 mmol), and $Pd(dppf)Cl_2$ (375 mg, 0.51 mmol) were degassed via high-vacuum/argon cycles (4x) and diluted in degassed DMF (11 mL). The resulting mixture was then stirred for 15 min before the borane solution was added. The reaction was stirred for 4 h at 80 °C, at which point the mixture turned black. The mixture was cooled to room temperature, diluted with Et_2O (15 mL) and filtered through a plug of alumina. Concentration in *vacuo* followed by purification via flash column chromatography (eluent, gradient 30% → 40% EtOAc in hexanes) afforded inseparable diastereomers (494 mg, 83%) of **7** as a colorless oil (~ 3:2 *trans*/*cis* epimers at C-12). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.50–6.40 (m, 1H), 4.67–4.55 (br. s, 1H), 3.13–3.01 (app. m, 2H), 2.83–2.73 (app. m, 1H), 2.66–2.60 (m, 0.5H), 2.59–2.54 (m, 1H), 2.49–2.40 (m, 2.5H), 2.34–2.25 (m, 2.5H), 2.20–2.11 (m, 2H), 2.03 (t, J = 12.5 Hz, 0.5H), 1.97–1.87 (m, 1H), 1.82–1.75 (m, 0.5H), 1.73–1.69 (m, 0.5H), 1.68–1.64 (m, 1H), 1.54 (p, J = 5.9 Hz, 2H), 1.42 (s, 9H), 1.02 (d, J = 6.5 Hz, 1.5H), 0.97 (d, J = 7.0, Hz, 1.5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 211.1, 210.5, 204.6, 204.1, 156.2, 142.6, 139.5, 138.4, 79.3, 55.6, 53.3, 49.8, 49.1, 48.0, 47.04, 46.99, 40.5, 40.1, 39.5, 39.0, 38.3, 36.0, 34.8, 30.5, 29.99, 29.97, 29.92, 29.6, 28.6, 26.7, 25.6, 22.1, 20.1; **IR** (thin film) 3373, 2953, 2921, 2881, 1708, 1664, 1517, 1454, 1391, 1363, 1252, 1173, 875 cm^{-1}; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{20}H_{31}NO_4Na$ $(M + Na)^+$: 372.2151, found: 372.2157. **TLC** (40% EtOAc in hexanes) R_f = 0.32 (CAM Stain).



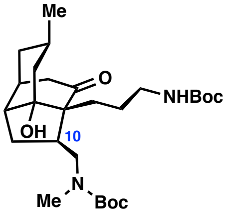
Tricycle 12 and its C10 epimer:

A round bottom flask containing **13** (0.62 g, 2.44 mmol) and 1,10-phenanthroline (2-3 crystals) was dried by azeotroping three times with freshly distilled benzene. The flask was then equipped with a glass stir bar and THF (27 mL) was introduced under Ar. The mixture was cooled to –78 °C and *n*–BuLi/hexanes (2-3 M) was added until a brown dark color persisted (~0.3–0.4 mL). This procedure was performed to quench adventitious proton sources. LiDBB (12.8 mL, 5.12 mmol, 2.1 equiv) was then added dropwise over 10 min at –78 °C until a dark-green color persisted, and the mixture was allowed to stir for 20 min. A separate flask containing 1-hexynyl copper (0.71 g, 4.94 mmol) and tetrahydrofuran (6.2 mL) was cooled to –78 °C and trimethyl phosphite (1.8 mL, 14.6 mmol) was introduced; the mixture was stirred until a clear solution developed. The resulting homogeneous solution was added via syringe to the organolithium reagent down the flask wall over 3 min and stirring was continued for 1 h to produce **15** as deep red solution. The carbamate **10** (213 mg, 0.61 mmol) was added as a solution in THF (0.5 mL) with freshly distilled TMSCl (0.39 mL, 3.05 mmol). The resulting mixture was stirred at –78 °C for 24 h and quenched with 10% concentrated ammonium hydroxide/saturated ammonium chloride (120 mL), followed by warming to room temperature. After 1 h, the organic layers were separated and the aqueous layers were extracted with ethyl acetate (40 mL) three times. The organic layers were combined, dried and concentrated under vacuum. The resulting mixture was filtered through a plug silica with 20% CH_2Cl_2 in hexanes to remove excess of 4,4'-di-*tert*-butylbiphenyl, at which point ethyl acetate was used to flushed the plug. The material was concentrated under vacuum. The crude product was dissolved in methanol (15 mL) with potassium carbonate (627 mg, 4.54 mmol) and stirred for 4 h. The mixture was concentrated, loaded onto silica gel with DCM and purified by MPLC, eluting with 20% to 40% EtOAc/hexanes gradient, to deliver tricycle **12** (126.1 mg, 42%) and its C10 epimer (134.5 mg, 45%)**.**



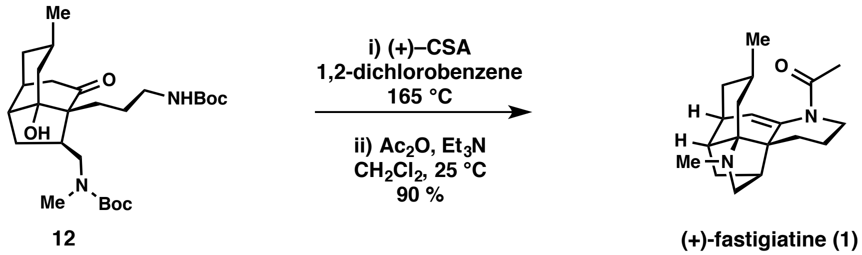
***epi*–12**

^{1}H NMR (500 MHz, tol-d$_8$, 85 °C) δ 4.46–4.37 (br s, 1H), 3.42–3.27 (br s, 1H), 3.10 (m, 2H), 2.77–2.72 (m, 1H), 2.71–2.68 (m, 1H), 2.67 (s, 3H), 2.63–2.52 (m, 1H), 2.25 (ddd, *J* = 13.5, 11.2, 7.6 Hz, 1H), 2.01 (d, *J* = 17.5 Hz, 1H), 1.87 (app d, *J* = 13.6 Hz, 1H), 1.85–1.80 (m, 1H), 1.76–1.67 (m, 1H), 1.66–1.56 (m, 5H), 1.45 (s, 18H), 1.37–1.29 (m, 2H), 1.12–1.00 (br s, 1H), 0.86 (q, *J* = 13.7 Hz, 2H), 0.70 (d, *J* = 6.5 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$, 25 °C) δ 213.5, 213.3, 156.5, 156.3, 155.8, 80.1, 79.6, 79.3, 65.4, 48.4, 48.0, 47.1, 43.7, 43.2, 43.0, 42.7, 41.8, 41.1, 35.5, 35.3, 34.5, 34.2, 32.1, 29.9, 29.8, 29.6, 28.7, 28.6, 26.0, 25.5, 24.5, 22.9, 22.5, 14.3 ; **IR** (thin film) 3364, 2962, 2925, 1686, 1519, 1482, 1451, 1393, 1367, 1247, 1163, 1043, 870, 771 cm^{-1}; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{27}H_{46}N_2O_6Na$ (M + Na)$^+$: 517.3254, found: 517.3261; **TLC** (44 % EtOAc in Hexanes) R$_f$ = 0.34 (CAM stain); $[\alpha]^{24}_D$ = –74 (*c* 1.23, $CHCl_3$).



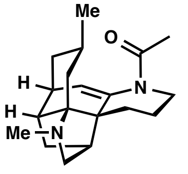
12

^{1}H NMR (500 MHz, tol-d_8, 85 °C) δ 4.51–4.43 (br s, 1H), 3.75 (dd, *J* = 13.3, 11.3 Hz, 1H), 3.17 (dd, *J* = 13.8, 4.3 Hz, 1H), 3.12–3.05 (m, 2H), 2.71 (s, 3H), 2.29 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.17 (ddd, *J* = 12.8, 7.0, 5.3 Hz, 1H), 2.03–1.96 (m, 1H), 1.91–1.85 (m, 1H), 1.79 (d, *J* = 16.5 Hz, 1H) 1.74 (dd, *J* = 14.0, 4.5 Hz, 1H), 1.69–1.64 (m, 1H), 1.61–1.51 (m, 4H), 1.46 (s, 9H), 1.43 (s, 9H), 1.34–1.26 (m, 3H), 1.06–1.00 (br s, 1H), 0.83 (td, *J* = 12.8, 3.0 Hz, 1H), 0.73 (t, *J* = 13.0 Hz, 1H), 0.65 (d, *J* = 6.0 Hz, 3H), 0.51–0.43 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, 25 °C) δ 214.4, 214.2, 156.8, 156.4, 156.22, 83.9, 83.8, 79.75, 79.66, 79.12, 79.06, 65.2, 65.1, 52.6, 51.7, 48.0, 43.0, 42.1, 41.9, 41.3, 40.7, 35.4, 35.3, 34.9, 32.1, 31.9, 31.6, 29.9, 29.8, 29.5, 28.6, 25.6, 22.9, 22.7, 21.8, 14.3; **IR** (thin film) 3380, 2957, 2920, 1961, 1514, 1456, 1393, 1362, 1252, 1168, 1033, 876, 771 cm^{-1}; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{27}H_{46}N_2O_6Na$ $(M + Na)^+$: 517.3254, found: 517.3234; **TLC** (44 % EtOAc in Hexanes) R_f = 0.38 (CAM stain); $[\alpha]^{24}_D$ = –41 (*c* 1.82, $CHCl_3$).



(+)-Fastigiatine:

A 10 mL Schlenk flask was charged with tricycle **12** (57.1 mg, 0.12 mmol) and purged three times with argon/vacuum. Freshly distilled and degassed 1,2-dichlorobenzene (5.9 mL) was introduced and the solution cooled to 0 °C, at which point (+)-10-camphorsulfonic acid (402.5 mg, 1.73 mmol) was added. The reaction was removed from the ice bath and warmed to 165 °C in a sealed atmosphere for 1 h. The mixture was cooled to 0 °C, quenched with saturated $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (5 mL) two times. The combined organic layers were dried over Na_2SO_4 and concentrated to remove $CHCl_3$. To the resulting solution were added Et_3N (0.16 mL, 1.16 mmol) and Ac_2O (0.11 mL, 1.16 mmol), and the mixture was stirred for 5 h. The reaction was quenched by addition of methanol (2 mL). Concentration under vacuum and purification by silica gel chromatography (gradient 1% → 10% MeOH in $CHCl_3$ with 0.5% Ammonium hydroxide) afforded (+)-fastigiatine (34.6 mg, 90% yield) as a white crystalline solid. The data for the synthetic natural product matched that reported by Shair.[5]


(+)-fastigiatine (1)

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 5.19 (d, *J* = 5.5 Hz, 1H), 3.82 (dt, *J* = 11.5, 6.0 Hz, 1H), 3.30–3.21 (m, 2H), 2.42–2.37 (m, 1H), 2.32 (s, 3H), 2.19 (d, 9.0 Hz, 1H), 2.18–2.16 (m, 1H), 2.15 (s, 3H), 2.07 (br. app. d, *J* = 14.5 Hz, 1H), 2.06–1.96 (m, 1H), 1.93–1.89 (m, 1H), 1.81–1.72 (m, 1H), 1.68 (dd, *J* = 14.0, 4.5 Hz, 1H), 1.63–1.53 (m, 3H), 1.43–1.32 (m, 2H), 1.20 (app. t, *J* = 12.0 Hz, 1H), 1.02 (app. dt, *J* = 12.8, 3.3 Hz, 1H), 0.91 (d, 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$, 25 °C) δ 170.5, 139.6, 123.6, 65.7, 60.0, 55.4, 45.9, 45.8, 40.6, 38.7, 37.8, 35.4, 35.0, 34.3, 25.9, 23.4, 22.7, 22.0, 21.6; **HRMS** (ESI/methanol) *m* / *z* calcd for $C_{19}H_{28}N_2ONa$ $(M + Na)^+$: 323.2099, found: 323.2106, **TLC** (10 % MeOH in $CHCl_3$) R_f = 0.33 (UV or $KMnO_4$);); $[\alpha]^{24}_D$= +310 (*c* 1.32, $CHCl_3$).

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[1] A. Pangborn, M. Giardello, R. Grubbs, R. Rosen, F. Timmers *Organometallics* 1996, **15**, 1518–1520.

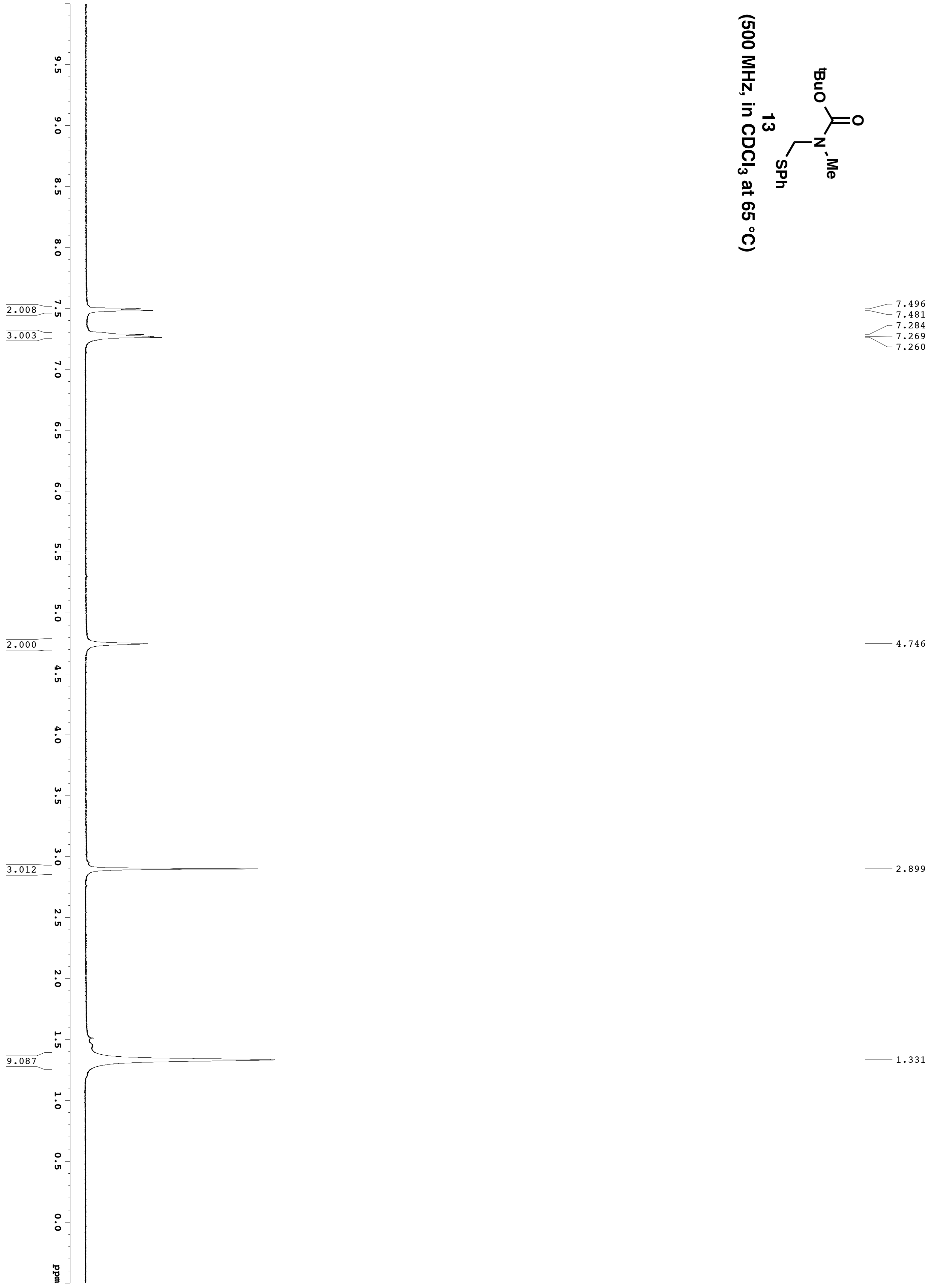
[2] W. Still, M. Khan, A. Mitra *J. Org. Chem.* 1978, **43**, 2923–2925.

[3] R. K. Dieter, C. W. Alexander, L. E. Nice *Tetrahedron*, 2000, **56**, 2767–2778.

[4] S. P. Waters, X. Cheng *Org. Lett.* 2010, **12**, 205-207.

[5] B. B. Liau, M. D. Shair *J. Am. Chem. Soc.* 2010, **132**, 9594–9595.

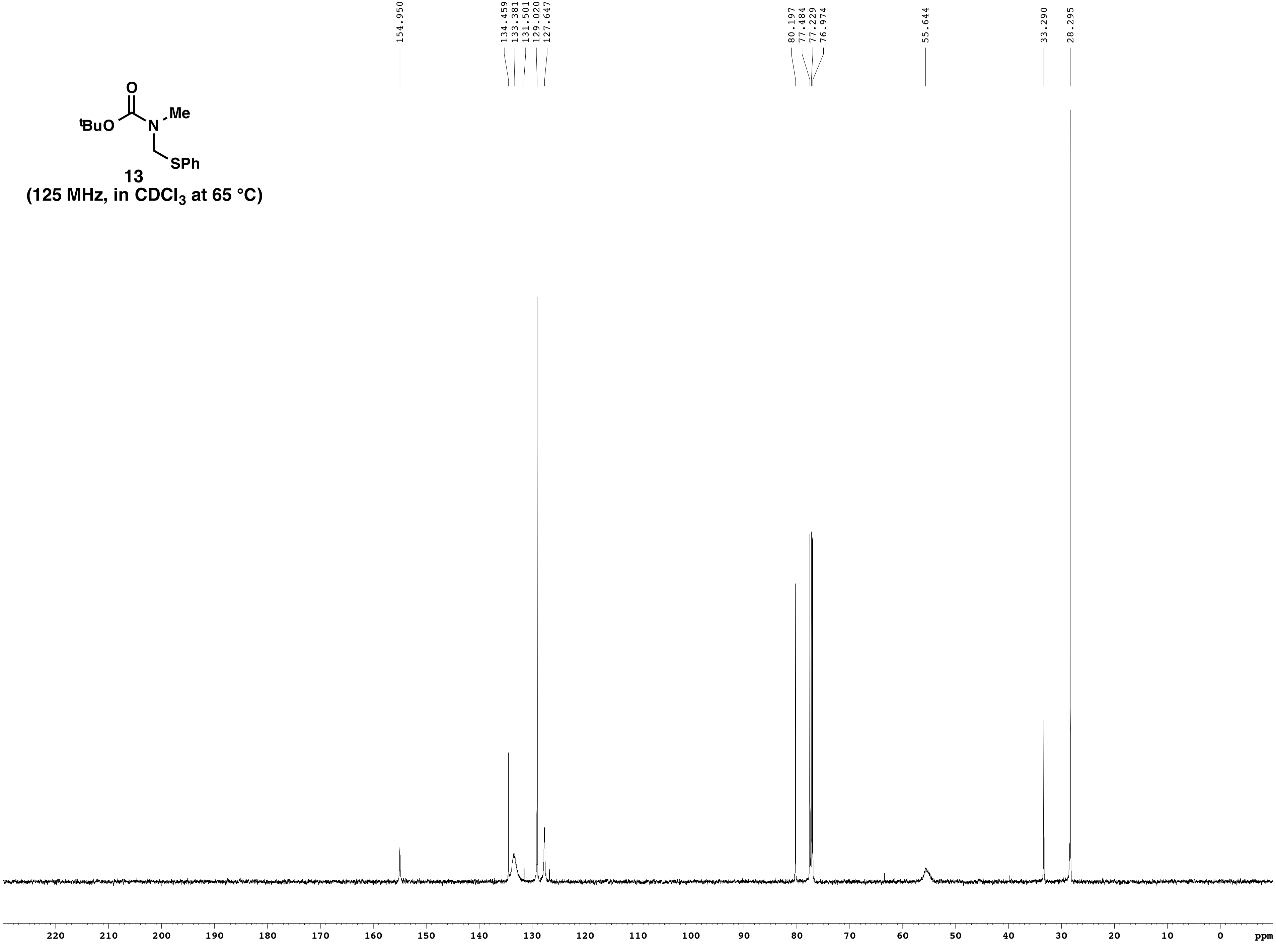
1H spectrum



13

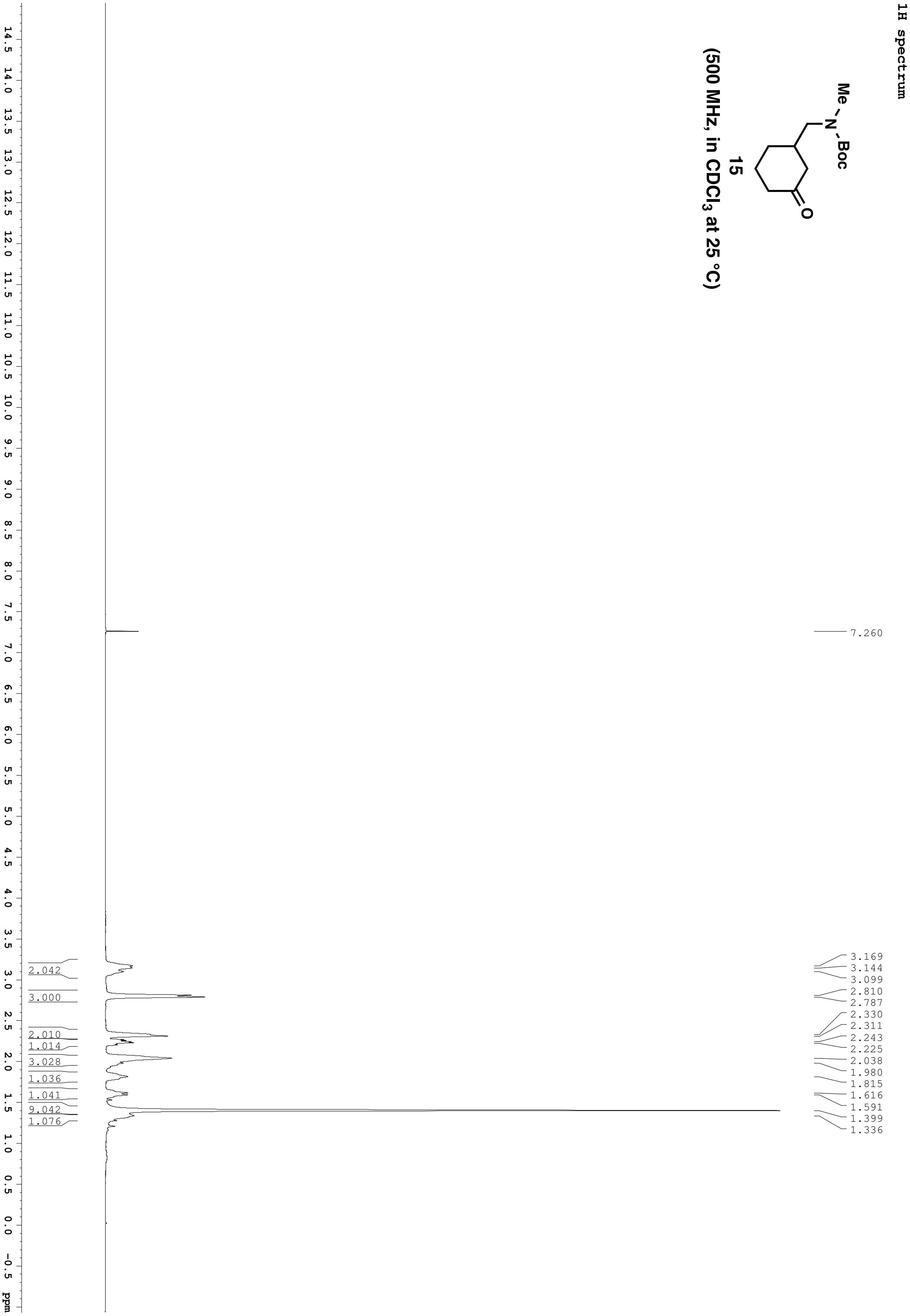
(500 MHz, in $CDCl_3$ at 65 °C)

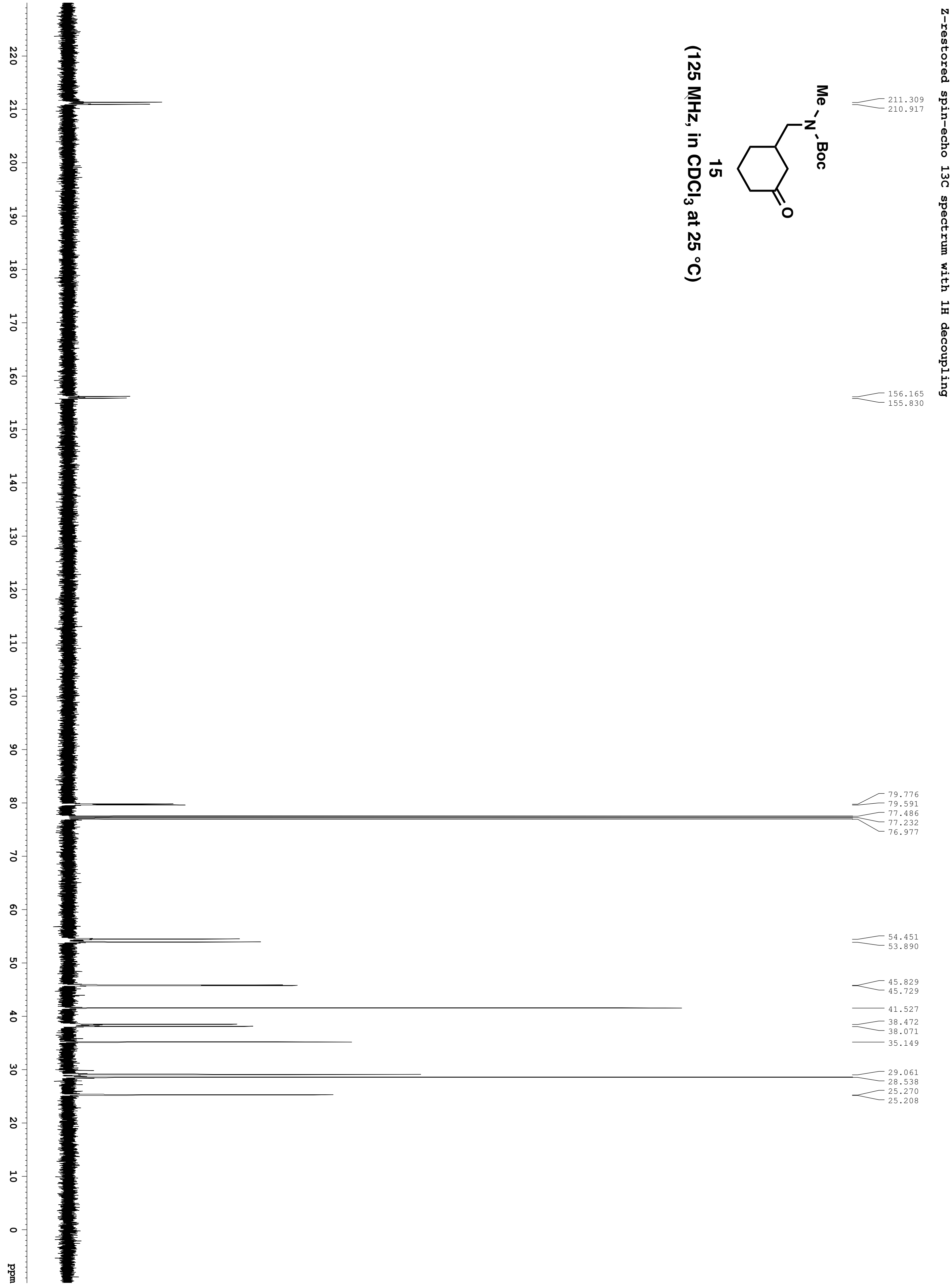
13C spectrum with 1H decoupling



13

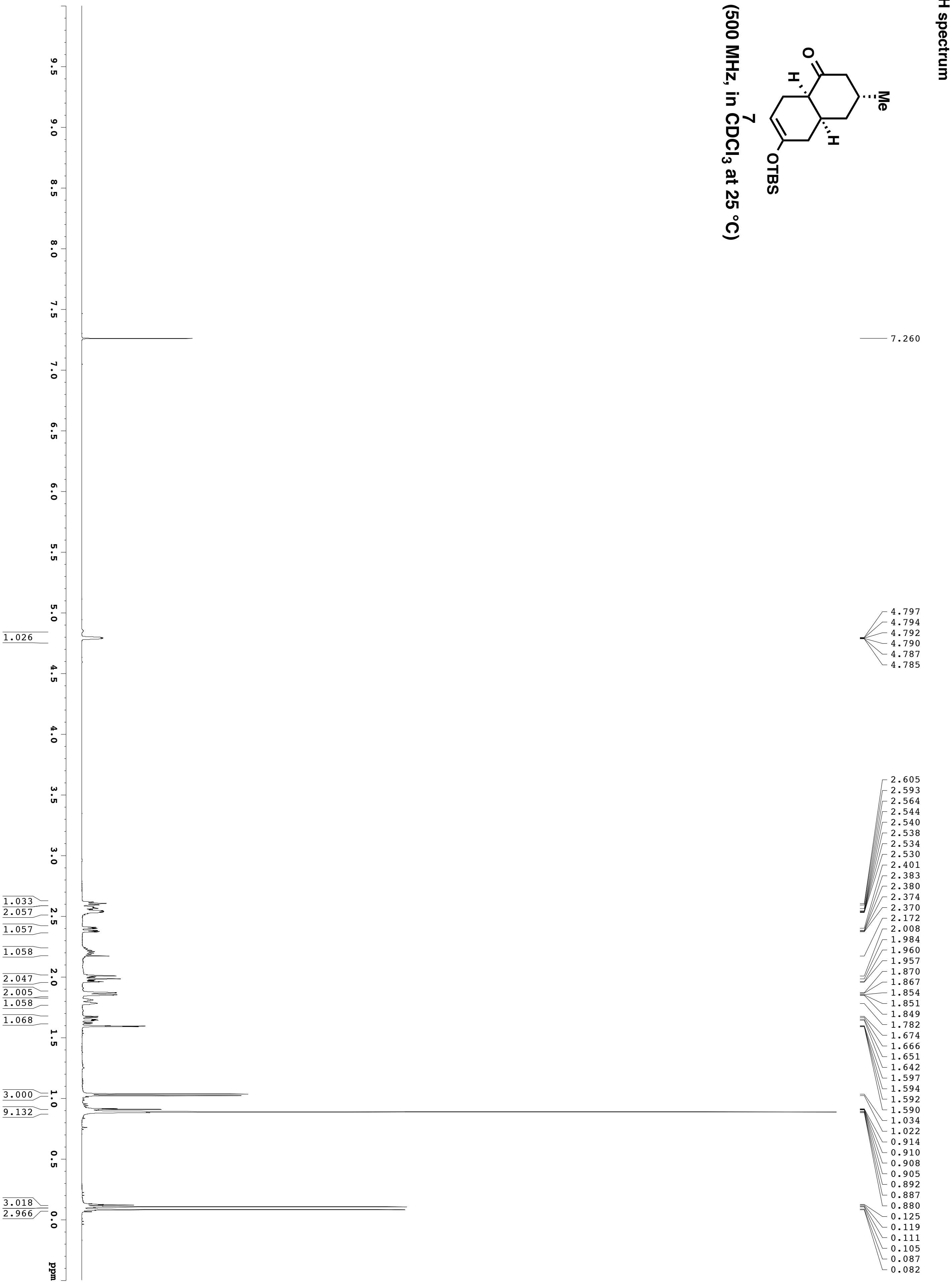
(125 MHz, in CDCl$_3$ at 65 °C)


1H spectrum
Me
N
Boc
O
15
(500 MHz, in CDCl$_3$ at 25 °C)
7.260
3.169
3.144
3.099
2.810
2.787
2.330
2.311
2.243
2.225
2.038
1.980
1.815
1.616
1.591
1.399
1.336
2.042
3.000
2.010
1.014
3.028
1.036
1.041
9.042
1.076
14.5
14.0
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
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
-0.5
ppm



15

(125 MHz, in CDCl$_3$ at 25 °C)

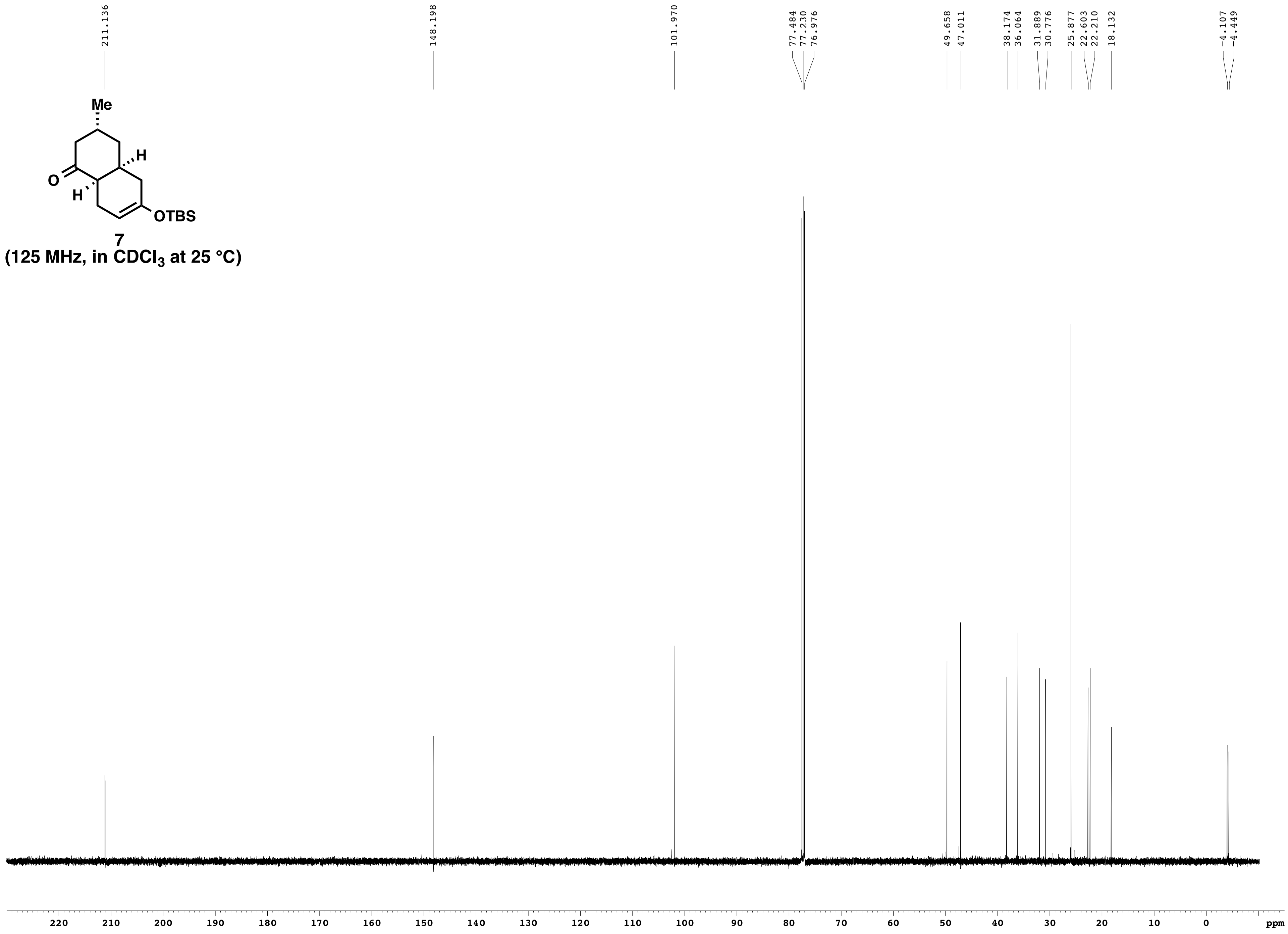


1H spectrum

7

(500 MHz, in $CDCl_3$ at 25 °C)

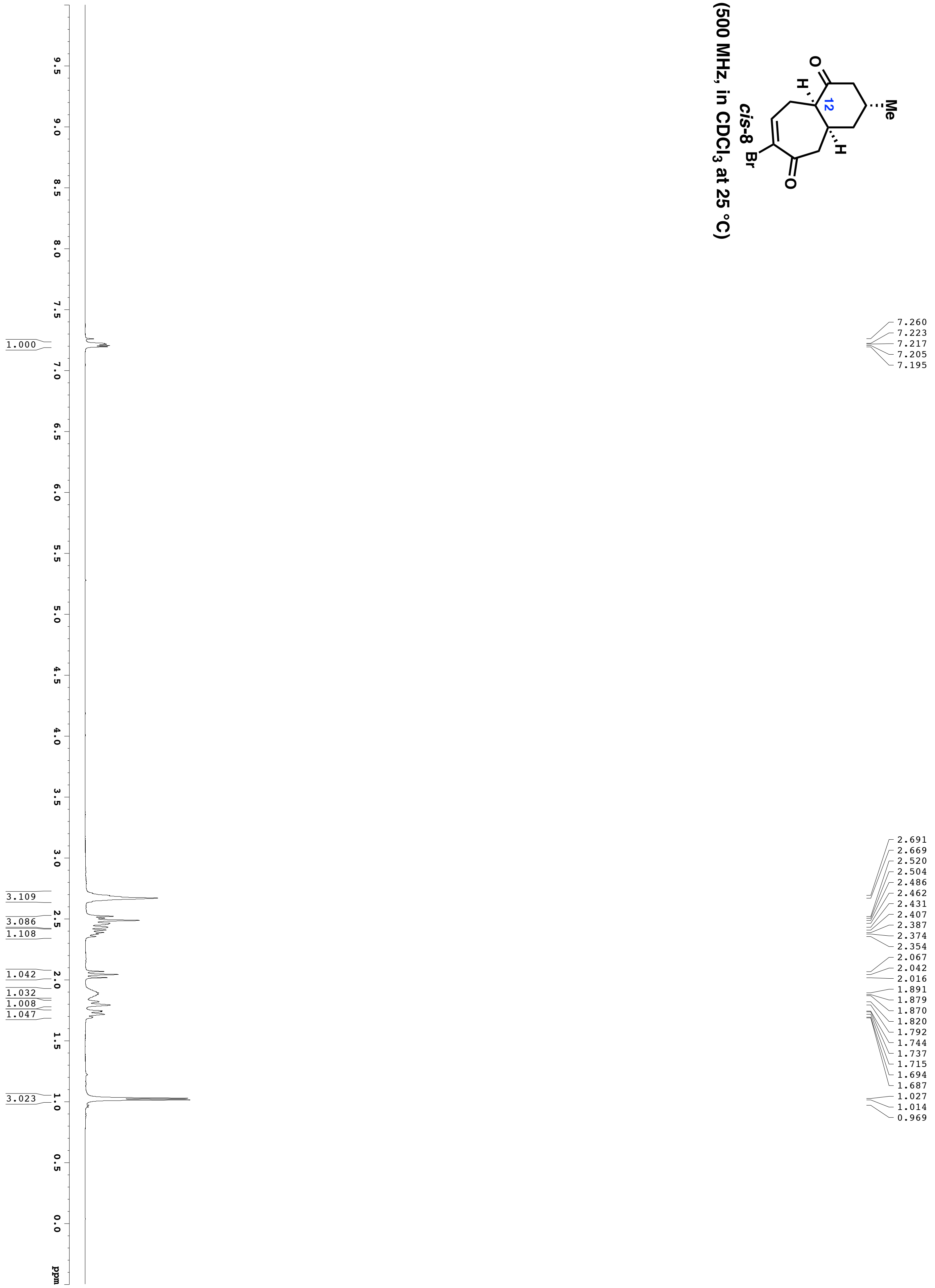
Z–restored spin–echo 13C spectrum with 1H decoupling



7

(125 MHz, in $CDCl_3$ at 25 °C)

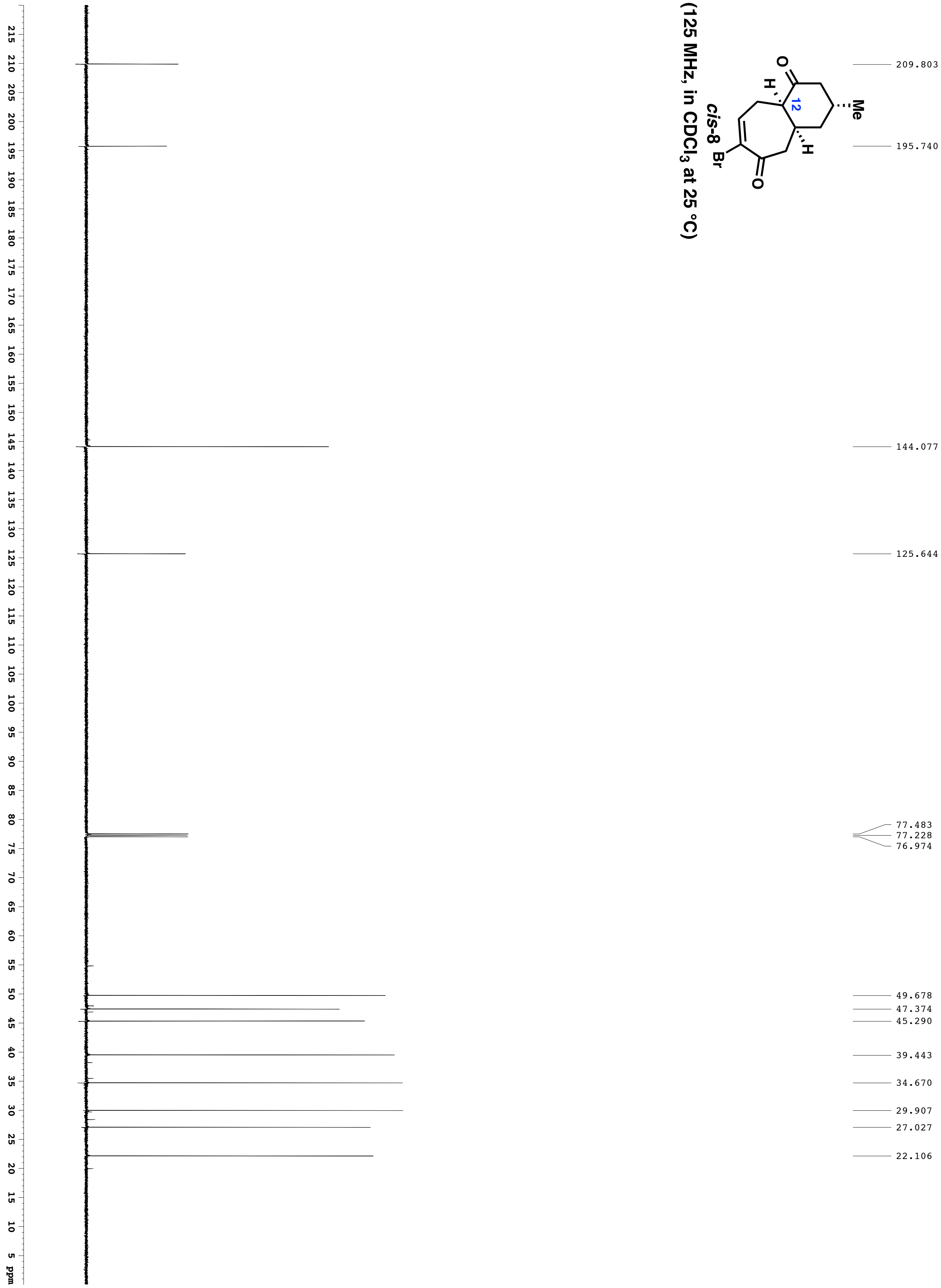
1H spectrum



cis-**8**

(500 MHz, in $CDCl_3$ at 25 °C)

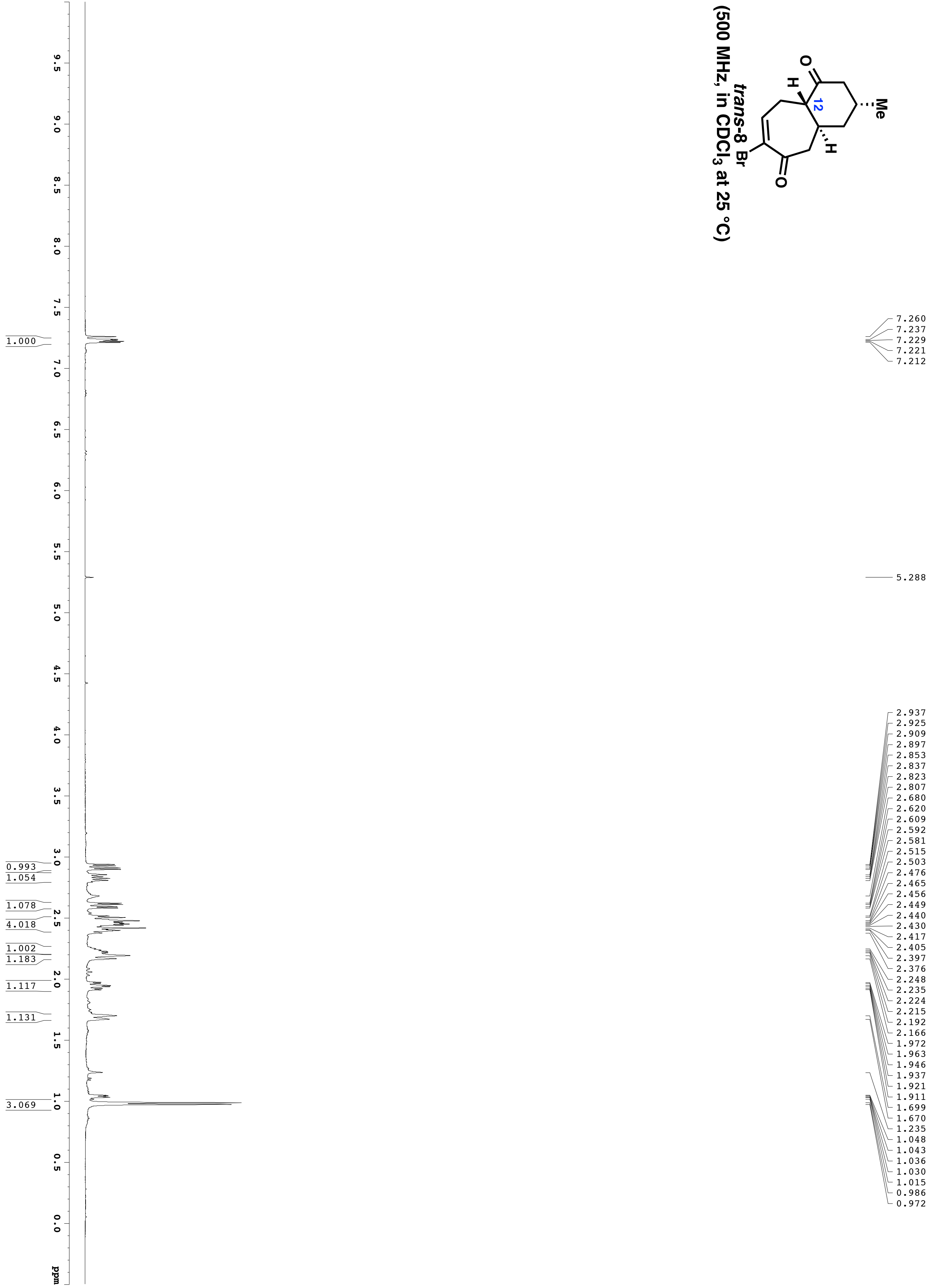
Z–restored spin–echo 13C spectrum with 1H decoupling



***cis*-8**

(125 MHz, in $CDCl_3$ at 25 °C)

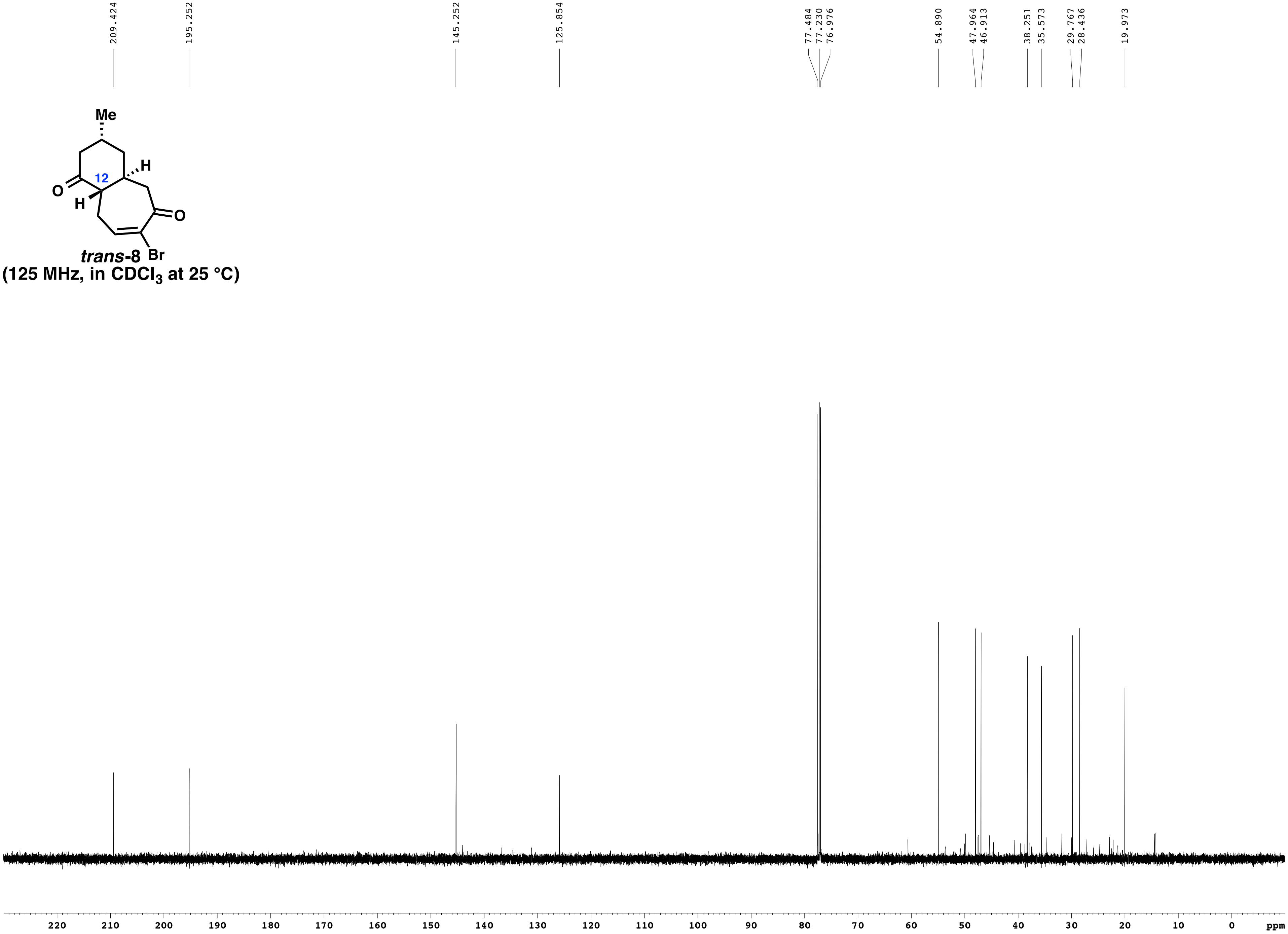
1H spectrum



trans-**8**

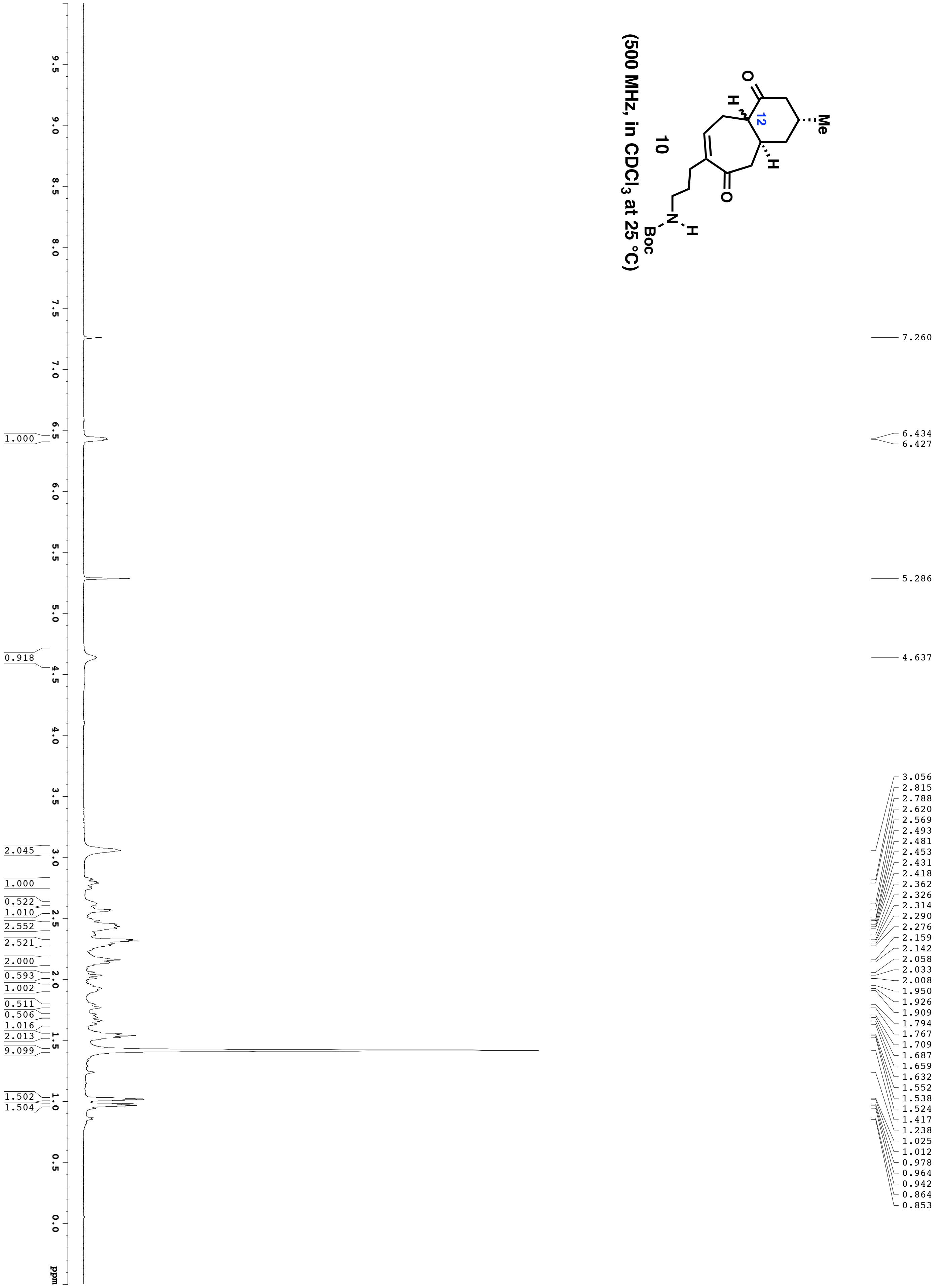
(500 MHz, in $CDCl_3$ at 25 °C)

Z–restored spin–echo 13C spectrum with 1H decoupling



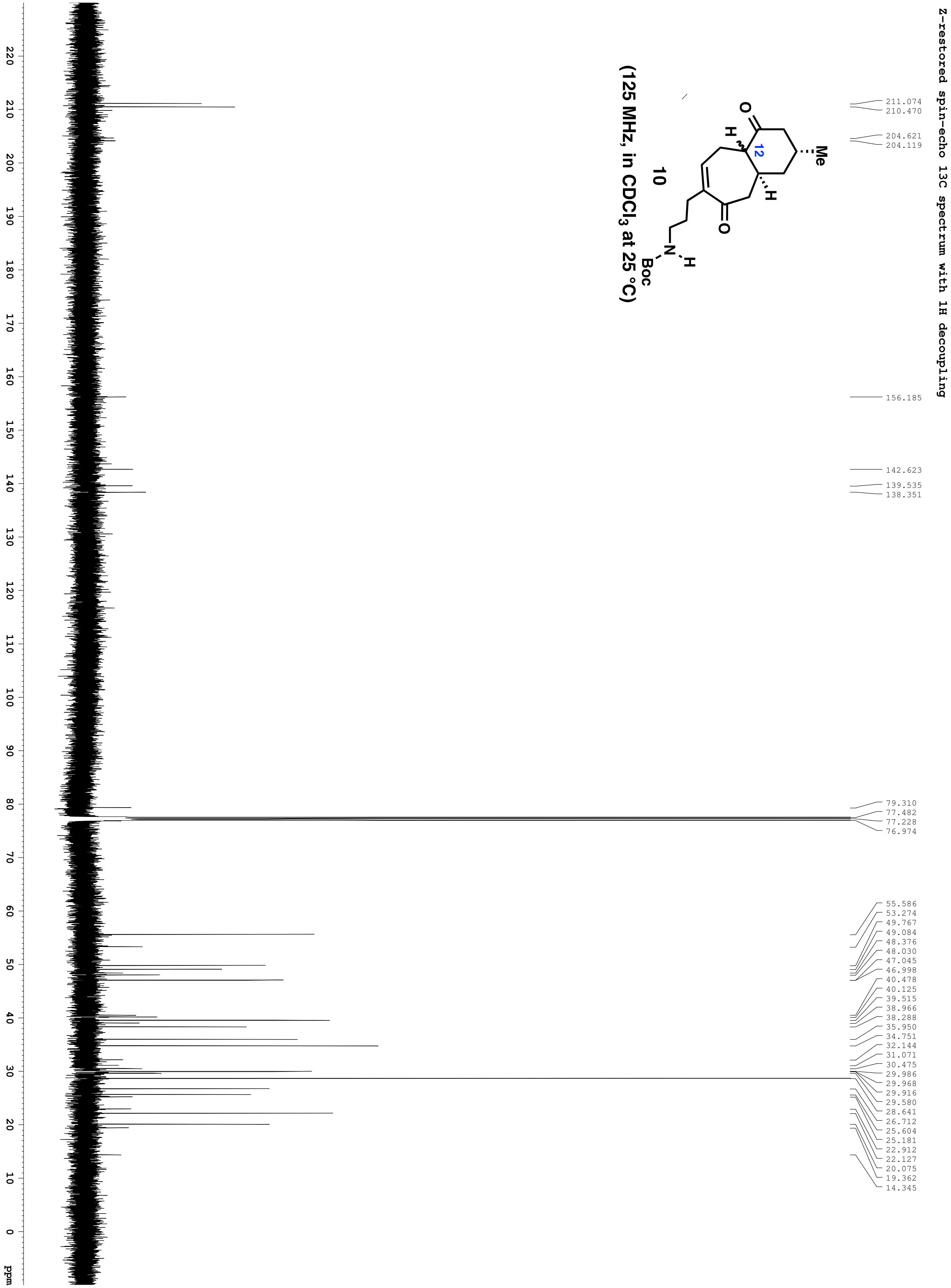
***trans*-8**
(125 MHz, in $CDCl_3$ at 25 °C)

1H spectrum



10

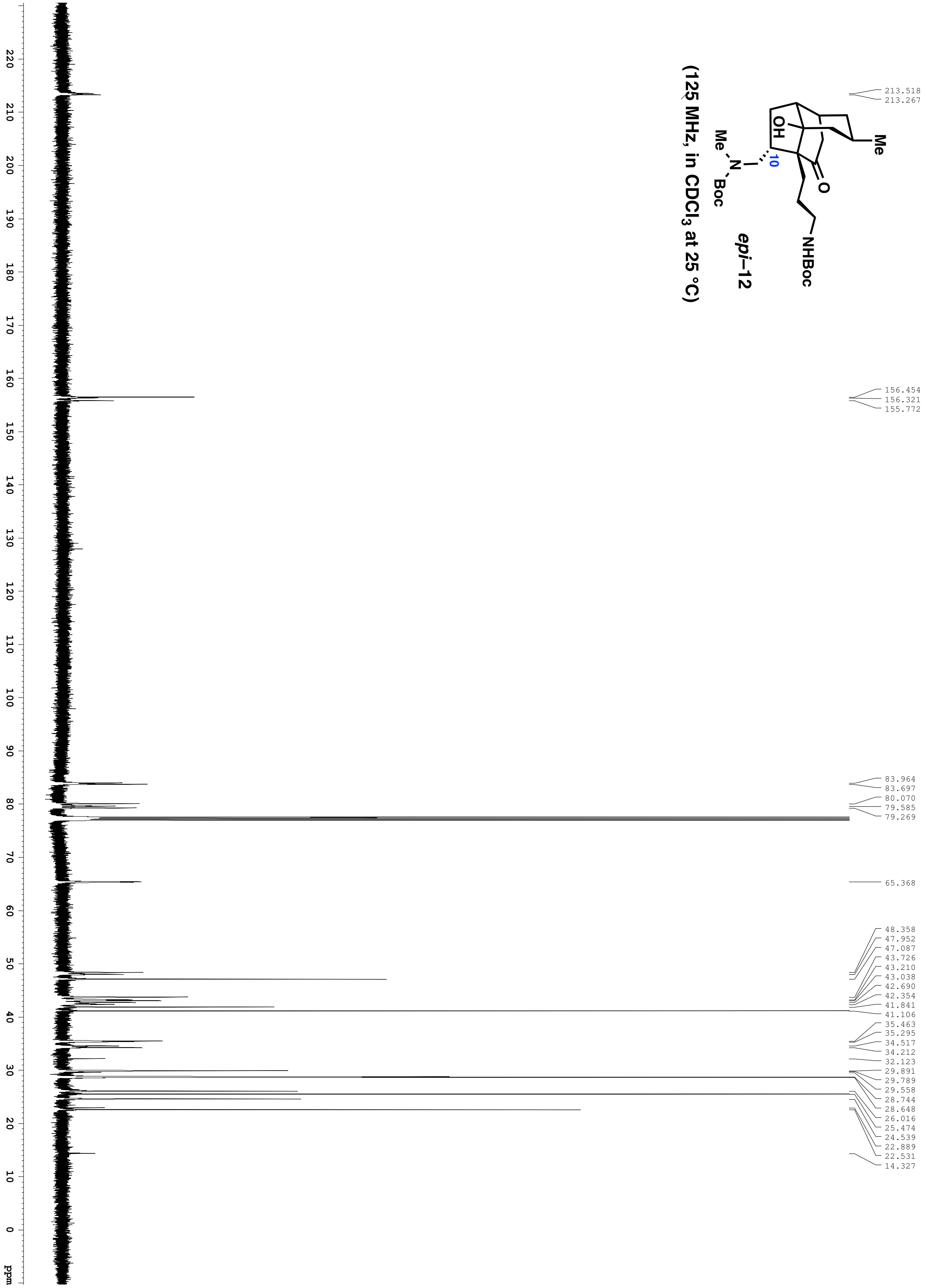
(500 MHz, in CDCl$_3$ at 25 °C)


Z-restored spin-echo 13C spectrum with 1H decoupling
10
(125 MHz, in CDCl$_3$ at 25 °C)
Me
H
H
O
O
12
N
H
Boc
211.074
210.470
204.621
204.119
156.185
142.623
139.535
138.351
79.310
77.482
77.228
76.974
55.586
53.274
49.767
49.084
48.376
48.030
47.045
46.998
40.478
40.125
39.515
38.966
38.288
35.950
34.751
32.144
31.071
30.475
29.986
29.968
29.916
29.580
28.641
26.712
25.604
25.181
22.912
22.127
20.075
19.362
14.345
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

epi–12

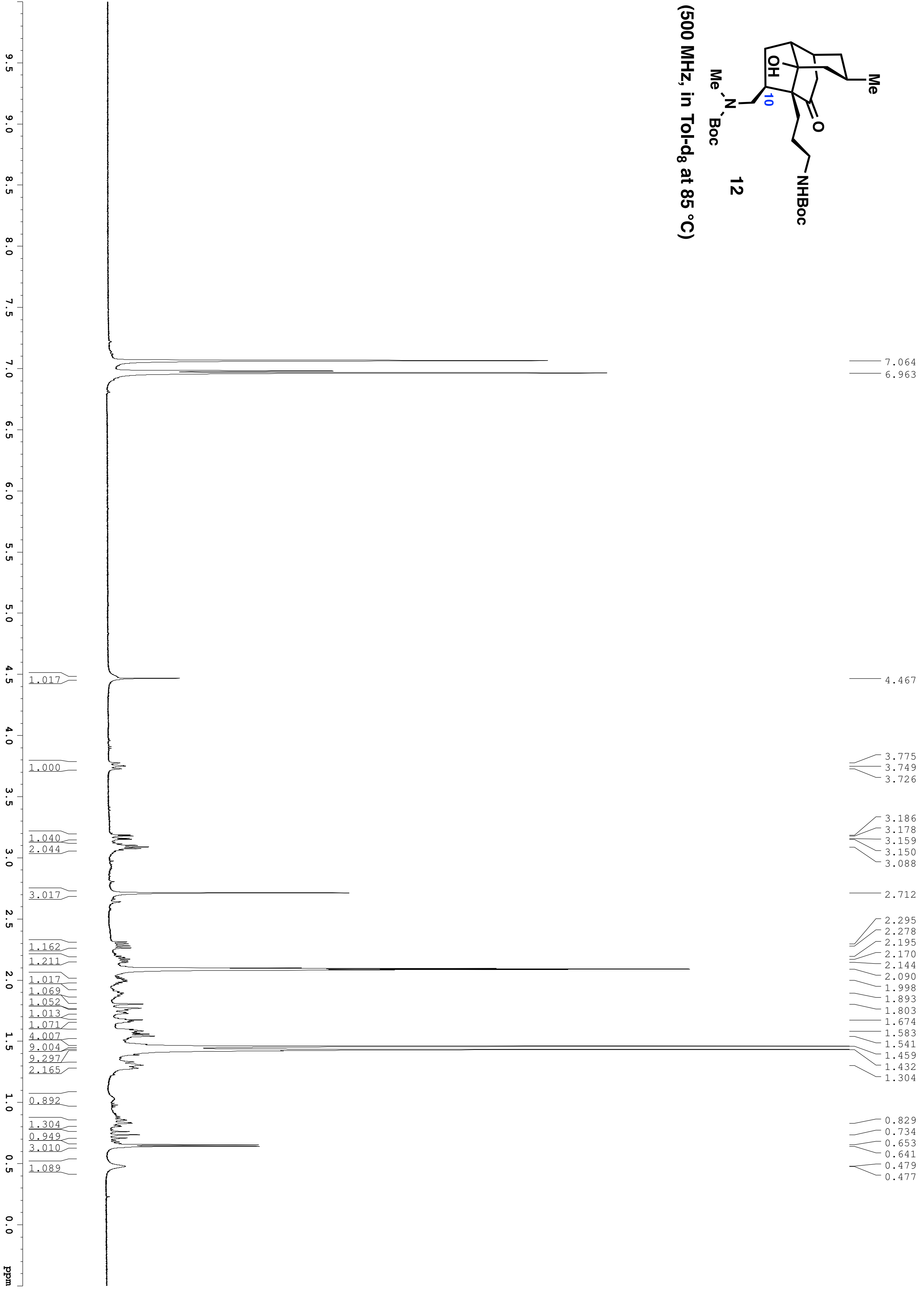
(500 MHz, in Tol-d_8 at 85 °C)

Z-restored spin-echo 13C spectrum with 1H decoupling



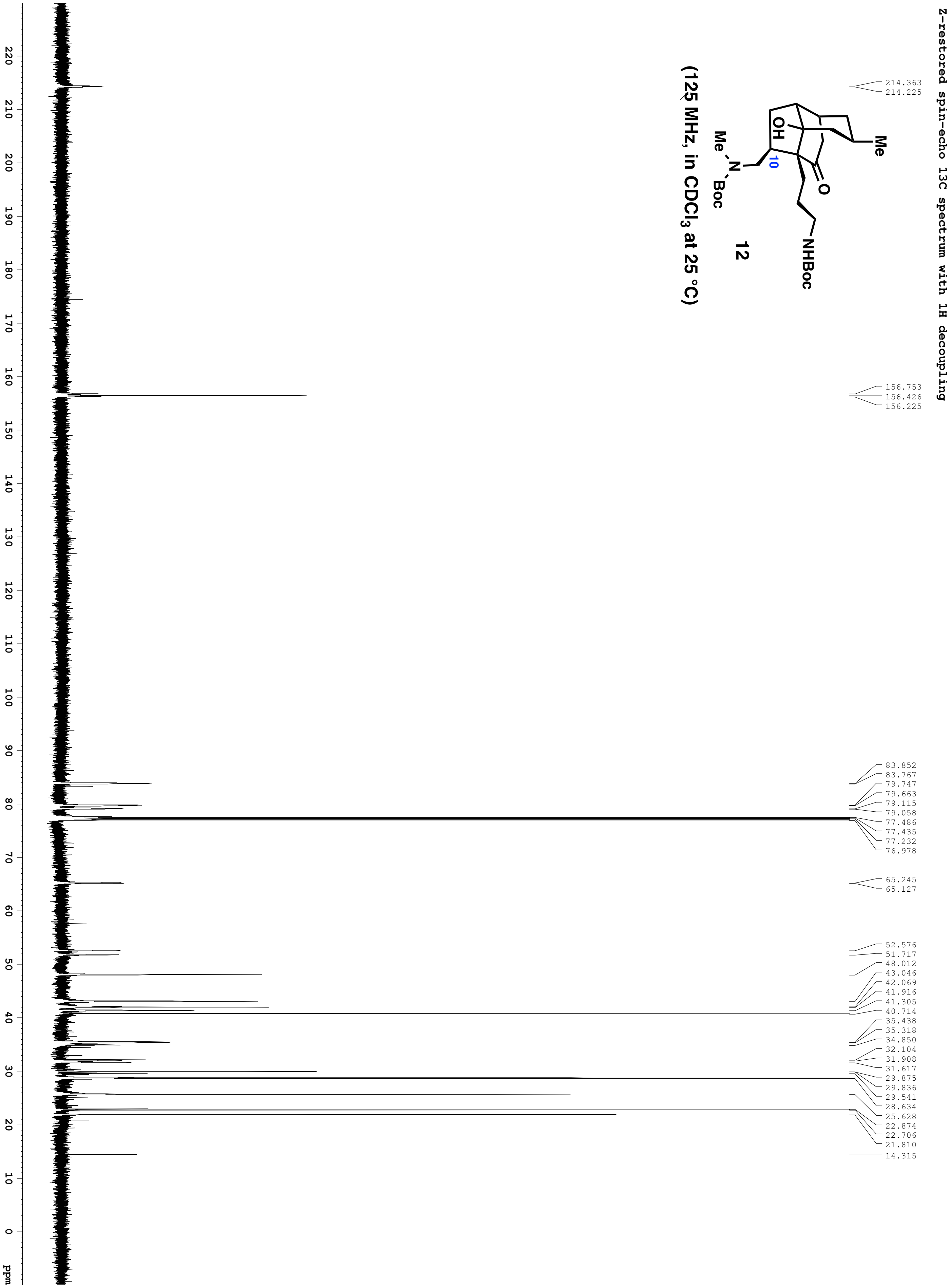
epi–12

(125 MHz, in $CDCl_3$ at 25 °C)



12

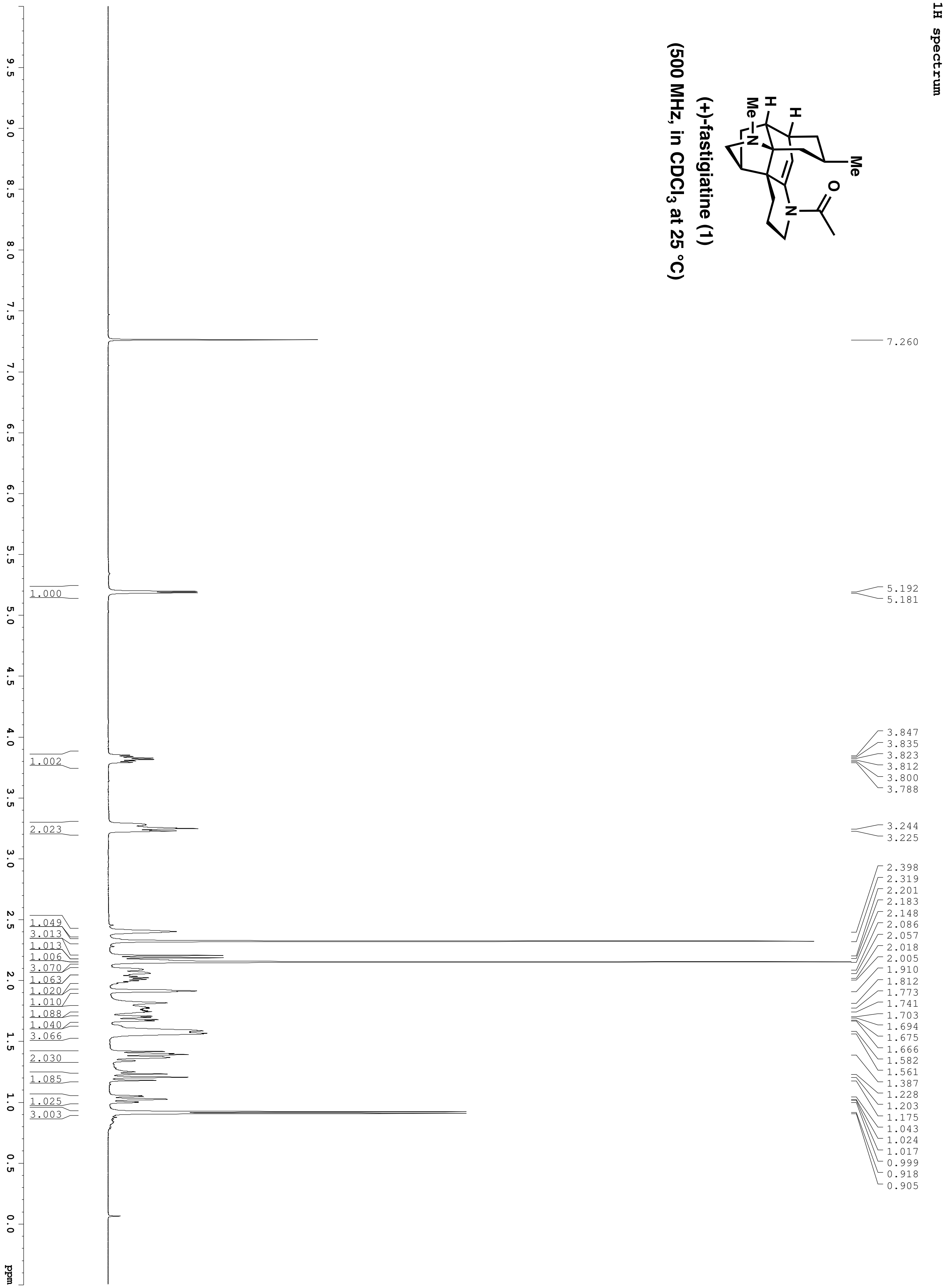
(500 MHz, in Tol-d_8 at 85 °C)



Z-restored spin-echo 13C spectrum with 1H decoupling

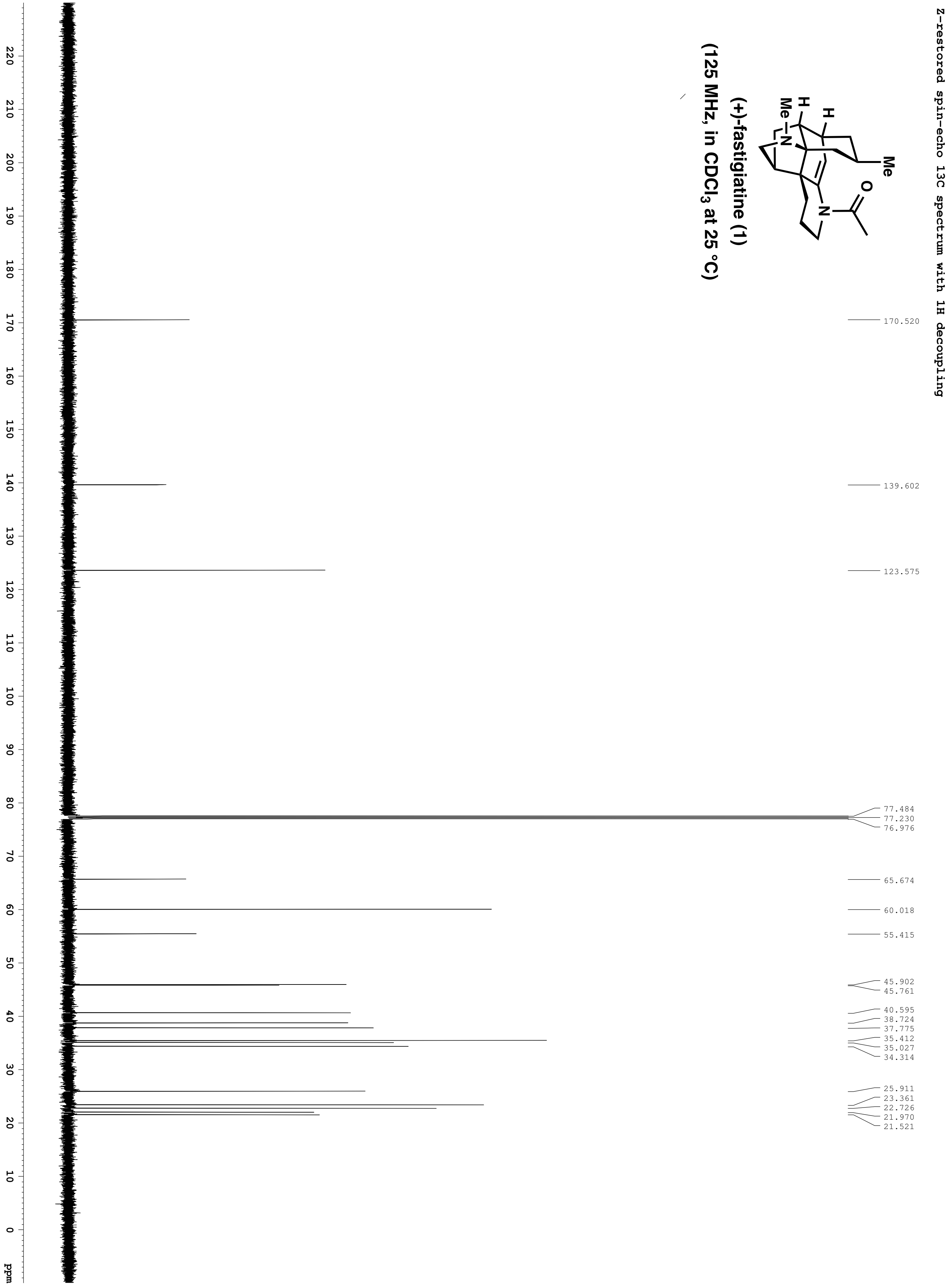
12

(125 MHz, in $CDCl_3$ at 25 °C)



1H spectrum

(+)-fastigiatine (1)
(500 MHz, in $CDCl_3$ at 25 °C)



(+)-fastigiatine (1)

(125 MHz, in $CDCl_3$ at 25 °C)