Supplemental Material

Oligomers of a 5-Carboxy-methanopyrrolidine β-Amino Acid. A Search for Order.

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Supplemental Section

General Procedures: Thin layer chromatography was performed on precoated plates of silica gel GF 250 microns (Analtec, Inc.). Column Chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). High Pressure Liquid Chromatography (HPLC) was performed on Shimadazu SCL-10A VP system equipped with vacuum degasser, quaternary pump, autosampler, a variable-wavelength UV detector, and reverse phase HPLC columns or Daicel ChiralPak columns. Mass spectra were performed either at Merck Research Laboratories (West Point, PA) or with a Waters Micromass ZQ system. X-Ray crystallography was performed by Dr. Patrick J. Carroll, Department of Chemistry, University of Pennsylvania. Circular dichroism (CD) measurements were obtained by Dr. Matthew Shoulders, University of Wisconsin, Madison. Optical rotations were recorded using Perkin Elmer Polarimetry Model 341 with Sodium D line. Chemical shifts in ^{1}H and ^{13}C NMR are reported in parts per million (δ) values and were recorded on 300, 400, or 500 MHz spectrometers. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Carbon nuclear magnetic resonance chemical shifts are reported in ppm (δ) relative to the central line of the $CDCl_3$ triplet (δ 77.0). Coupling constants (*J*) in ^{1}H NMR spectra are reported in Hertz. Reagent chemicals were obtained from commercial suppliers and chemical grade solvents were used without further purification.

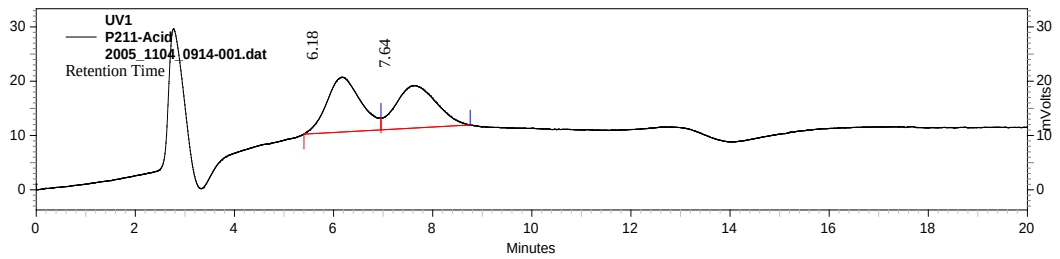
Resolution to give (-)-(1*S*, 4*R*, 5*R*)-5-*syn*-carboxylic-*N*-BOC-2-azabicyclo[2.1.1]-hexane (9). (*S*)-(-)-α-methylbenzylamine (0.5 g, 4.1 mmol) was slowly added to (±)-5-*syn*-acid **9** (1.0 g, 4.4 mmol) in THF (15.0 mL) solution. After stirring for 30 min at room temperature, a white slurry was gradually formed. Scratching the glass wall was needed if no solid formed during stirring. The slurry was stirred for an additional 6 h at room temperature. The salt was collected by vacuum filtration. The yield of the first crop was 0.67 g (1.93 mmol) or 44%. Chiral HPLC analysis of recovered acid indicated 75% ee of the resolved acid **9**, so one recrystallization was performed to improve the chiral purity. The salt (0.67 g, 1.93 mmol) was taken up in THF (7 mL). The mixture was heated to reflux until all solid was dissolved. The solution was slowly cooled to room temperature and the salt gradually precipitated. The slurry was stirred at room temperature for 2 h and the salt was collected by vacuum filtration. After drying, 0.53 g of salt was obtained. The yield was 35% based on (±)-5-*syn*-Acid **9** (See below).

Recovery of (-) acid 9 from its salt with (*S*)-(-)-α-methylbenzylamine. Recrystallized salt (0.53 g, 1.52 mmol) was partitioned between EtOAc (5.0 mL) and water (5.0 mL). The mixture was adjusted to pH 2.5 with 1.0 N HCl. The EtOAc layer was separated and the aqueous layer was extracted with 5.0 mL of EtOAc. The combined EtOAc solution was dried over anhydrous Na_2SO_4, then filtered and concentrated *in vacuo* to yield 0.34 g of free acid **9**, optical rotation $[\alpha]_D$ = -22.1 (20 ^{o}C, c = 1.8, 95% ethanol). Chiral HPLC analysis of recovered acid **9** gave evidence for only one enantiomer of **9.** For chiral HPLC analysis (ChiralPak AS-H®) of chiral acids (-)-**9** and (+)-**9** (Figure 4), an HPLC sample was prepared by dissolution of racemic acid **9** (1.0 mg) in 2-propanol (1.0 mL). After equilibration of the HPLC system had been achieved, 10 uL of sample solution was injected. The flow rate of the mobile phase, which consisted of 10

vol% of 2-propanol and 90 vol% n-heptane with 0.1% of trifluoroacetic acid additive, was set at 1.0 mL/min. Detection was achieved at 215 nm. Due to the lack of strong chromophores, UV signals were weak. The retention time for (-)-acid **9** was 6.15-6.21 min and the retention time for (+)-acid **9** was 7.60-7.69 min (Figure 4). Since the baseline is overlapped between two peaks, the peak areas of **(-)-9** and (+)- **9** are not exactly same.

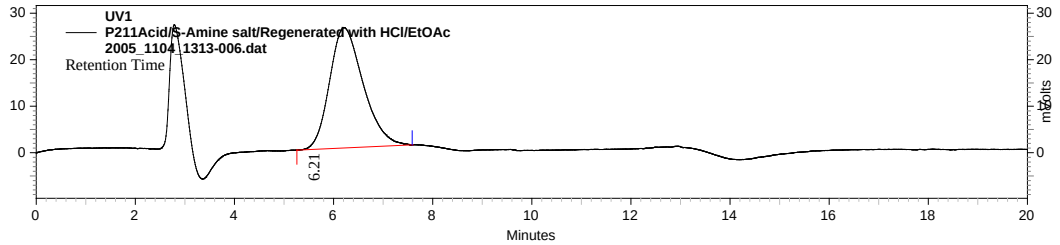
The same conditions were reproduced to analyze the resolved (-)-acid **9**. It should be noted that the existence of (*S*)-α-methylbenzyl amine interferes with the chiral HPLC analysis; so free acid **9** was freed from the diastereomeric salt prior to analysis. The HPLC trace of resolved (-)-**9** is shown in Figure 5.

Figure 4. Chiral HPLC spectrum of the racemic mixture of **(-)-9** and (+)- **9**.



peak	retention Time	area	area (%)
(-)-acid **9**	6.176	480807	51.892
(+)-acid **9**	7.640	445745	48.108
total		926552	100.00

Figure 5. Chiral HPLC spectrum of (-)-acid **9**



peak	retention Time	area	area (%)
(-)-acid **9**	6.211	1218135	100

Preparation of (1*S*, 4*R*, 5*R*)-(-)-5-*syn*-(*S*)-(1-phenylethylcarbamoyl)-*N*-Boc-2-azabicyclo[2.1.1]hexane (10). The salt from (*S*)-(-)-α-methylbenzylamine and (-)-**9** (0.5 g, 1.44 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide HCl salt (EDC or EDAC) (0.3 g, 1.58 mmol), and 1-

hydroxybenzotriazole (HOBt) (0.19 g, 1.44 mmol) were dissolved in DMF (5.0 mL). At room temperature, diisopropylethylamine (DIPEA) (0.21 g, 1.56 mmol) was slowly added. The reaction mixture was stirred at room temperature for 1 h. DMF was removed *in vacuo* and the residue was partitioned between 1.0 N HCl (5.0 mL) and EtOAc (8.0 mL). The bottom acidic aqueous layer was removed and the organic solution was washed with 20% potassium bicarbonate aqueous solution (2 x 5.0 mL). The EtOAc solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give (1*S*, 4*R*, 5*R*)-5-*syn*-(*S*)-(1-phenylethylcarbamoyl)-*N*-Boc-2-azabicyclo[2.1.1]hexane **10** (0.4 g, 1.21 mmol) as a white solid, mp 157-158 ^oC; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, 5H, Ph), 5.94 (br, 1H, NH), 5.06 (m, 1H), 4.50 (m, 1H), 3.39 (m, 1H), 3.31 (m, 1H), 3.14 (m, 1H), 2.73 (m, 1H), 1.74 (m, 1H), 1.48 (s, 9H), 1.44 (d, 3H, CH_3), 1.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 143.3, 129.0, 128.8, 127.7, 126.5, 80.1, 77.0, 52.4, 51.1, 48.9, 41.5, 28.9, 22.2; optical rotation $[\alpha]_D$ of **10**: -51.7 (20 ^oC, c = 1.0, chloroform). HRMS *m/z* (M + Na^+) calculated for $C_{19}H_{26}N_2O_3Na$ (M + Na^+) 353.1836, observed 353.1823.

Preparation of (1*S*, 4*R*, 5*R*)-(-)-5-*syn*-carboxymethyl-*N*-Boc-2-azabicyclo[2.1.1]hexane (11). The (-)-5-*syn*-acid **9** (0.64 g, 2.84 mmol) was dissolved in isopropanol (20 mL) and hexanes (20 mL) and trimethylsilyldiazomethane (1.5 mL, 3.0 mmol, 2 M in hexanes) was added. The mixture was stirred for 40 min at room temperature, then solvent was removed *in vacuo* to afford 0.66 g (100 %) of (-)-(1*S*, 4*R*, 5*R*)-5-*syn*-carboxymethyl-*N*-Boc-2-azabicyclo[2.1.1]hexane **11** as a colorless oil,[9] R_f = 0.40 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.52 (br, 1H, H_1), 3.56 (s, 3H, CH_3), 3.42 (br, 1H, H_3), 3.19 (d, *J* = 9.3 Hz, 1H, H_3), 2.93 (br, 1H, H_4), 2.70 (s, 1H, H_5), 1.71 (m, 1H, H_6), 1.39 (s, 9H, *t*-butyl), 1.25 (br, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 156.3, 79.7, 62.9 and 62.2, 51.8, 50.5 and 49.8, 47.4 and 46.6, 41.3, 37.0, 28.8; optical rotation $[\alpha]_D$ of **11**: -50.2 (20 ^oC, c = 1.8, chloroform).

Preparation of (1*S*, 4*R*, 5*R*)-(-)-5-*syn*-carboxymethyl-*N*-isobutyryl-2-azabicyclo[2.1.1]hexane (12). General Procedure. The (-)-*N*-Boc ester **11** (40.2 mg, 0.167 mmol) was dissolved in 4 *N* HCl/dioxane (1.0 mL) and stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and further dried under high vacuum to remove all solvent. To this residue, there was added CH_2Cl_2 (5 mL). The resulting solution was chilled in an ice bath and isobutyryl chloride (35.4 mg, 0.34 mmol) was added dropwise. The mixture was stirred in an ice bath for 15 min and then at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was chromatographed (gradient, 4:1 ethyl acetate/ hexanes) to afford 29.5 mg (84%) of amide **12** as a colorless oil, R_f = 0.19 (1:2 hexane/ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.96, 4.55 (2dt, *J* = 8.0, 2.0Hz, 1H, H_1), 3.75, 3.47 (2d, *J* = 8.0Hz, 1H, H_3), 3.56 (2s, 3H, OMe), 3.35, 3.31 (2d, *J* = 8.0Hz, 1H, H_3), 3.09 (br, 1H, H_4), 2.86, 2.77 (2s, 1H, H_5), 2.63, 2.50 (2hep, *J* = 8.0Hz, 1H, MeC<u>H</u>Me), 1.85 (2m, 1H, H_6), 1.35, 1.25 (2d, *J* = 8.0Hz, 1H, H_6), 1.08 (2t, *J* = 6.0Hz, 6H, 2Me); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 175.80, 175.27, 169.37, 169.17, 62.50, 60.43, 51.51, 51.38, 50.83, 48.90, 46.73, 45.81, 40.74, 40.05, 37.95, 37.25, 32.14, 31.93, 29.89, 19.36, 19.16, 18.84, 18.80. HRMS: *m/z* found 212.1281, calcd. for $C_{11}H_{17}NO_3$ (M + H) 212.1281; optical rotation $[\alpha]_D$ –67.0 (20 ^oC, c = 1.5, chloroform).

Preparation of (-)-*N*-Boc-dimer 13a from Ester 11. General Method. The 5-*syn*-ester **11** (120 mg, 0.5 mmol) was dissolved in 4 *N* HCl/Dioxane (2.0 mL) and stirred at room temperature for 2 h. The reaction was monitored by thin layer chromatography (9:1 CH_2Cl_2/MeOH). The solution was concentrated *in vacuo* and further dried under high vacuum to afford 86 mg (97 %) of (1*S*, 4*R*, 5*R*)-5-*syn*-carboxymethyl-2-azabicyclo[2.1.1]hexane HCl salt as an off-white solid that was used directly in the next step. (Method I) To (0.39 g, 2.2 mmol) of this salt there was added (-)-acid **9** (0.5 g, 2.2 mmol), EDC (0.46 g, 2.4 mmol) and HOBt (0.3 g, 2.2 mmol). A solution of diisopropylethyl amine (0.62 g, 4.8 mmol) in acetonitrile (1.5 mL) and EtOAc (0.5 mL) was added at 0 ^{o}C. The reaction solution was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with EtOAc (2.5 mL) and washed with 1 N HCl (2.0 mL) followed by 20% $KHCO_3$ aqueous solution (2 x 2.0 mL). The organic solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 0.64 g (83%) of (-)-dimer **13** as a yellow oil. (Method II) The above salt from ester **11** (24 mg, 0.13 mmol) was dissolved in anhydrous methylene chloride (4.5 mL) and (-)-acid **9** (30 mg, 0.13 mmol) was added, and the reaction mixture was cooled to 0 ºC. BopCl (66 mg, 0.26 mmol) and diisopropylethyl amine (0.13 mL, 0.78 mmol) were added, and the solution was stirred at room temperature for 44 h. The reaction solution was then washed with saturated $KHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (1:1 hexane/ethyl acetate) to afford 14 mg (34 %) of the (-)-dimer **13a**; R_f = 0.62 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.87 (m, 1H), 4.51 (d, *J* = 5.6 Hz, 1H), 3.70 (d, *J* = 7.2 Hz, 1H), 3.60 (d, *J* = 15.2 Hz, 3H), 3.35 (d, *J* = 9.6 Hz, 1H), 3.23 (mbr, 2H), 3.03 (br, 2H), 2.80 (m, 2H), 1.84 (m, 2H), 1.41 (m, 9H), 1.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 168.5, 168.3, 168.2, 168.1, 156.0, 79.2, 61.4, 60.9, 60.6, 53.7, 51.9, 51.5, 51.3, 51.0, 50.9, 50.7, 50.6, 48.3, 47.7, 46.5, 45.9, 41.9, 41.2, 40.6, 40.4, 38.4, 38.0, 37.9, 37.6, 36.9, 36.5, 36.1, 28.4, 18.7, 17.4; HRMS *m/z* (M + Na^+) calculated for $C_{16}H_{26}N_2O_5Na$ (M + Na^+) 373.1734, observed 373.1740; optical rotation $[\alpha]_D$ –37.8 (20 ^{o}C, c = 1.4, chloroform).

Preparation of (-)-*N*-isobutyryl-dimer 13b. According to the general procedure, (-)-*N*-Boc-dimer **13a** (60.0 mg, 0.167 mmol) was dissolved in 4 *N* HCl/dioxane (1.0 mL) and stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and further dried under high vacuum. To this residue in CH_2Cl_2 (5 mL) in an ice bath isobutyryl chloride (35 mg, 0.34 mmol) was added dropwise. The mixture was stirred in an ice bath for 15 min and then at room temperature for 2 h. Workup and chromatography (gradient, 4:1 ethyl acetate/ hexanes) afforded 42.2 mg (79%) of amide **13b** at R_f = 0.17 (1:2 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.06~3.89 (12dt, *J* = 8.0, 2.0Hz, 2H, $2H_1$), 3.76~3.55 (5d, *J* = 8.0Hz, 2H, $2H_3$), 3.53 (s, 3H, OMe), 3.31 (md, *J* = 8.0Hz, 2H, $2H_3$), 2.98 (m, 2H, $2H_4$), 2.76, 2.67 (2br, 2H, $2H_5$), 2.47 (hep, 1H), 1.86~1.70 (m, 2H, $2H_6$), 1.37~1.11 (8d, *J* = 8.0Hz, 2H, $2H_6$), 1.06 and 0.97 (2d, *J* = 8.0Hz, 6H, Me); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 176.1, 169.3, 168.1, 168.1, 60.9, 60.1, 51.6, 51.2, 50.7, 48.4, 47.4, 46.5, 41.2, 40.4, 37.7, 36.3, 36.0, 32.0, 19.4, 18.9; HRMS *m/z* found 321.1818, calcd. for $C_{17}H_{24}N_2O_4$ (M + H) 321.1809; optical rotation $[\alpha]_D$ –68.0 (20 ^{o}C, c = 2.0, chloroform).

Preparation of higher order oligomers.

(-)-*N*-Boc-Dimer acid 17. To the solution of (-)-dimer **13a** (0.35 g, 1.0 mmol) in THF (3.5 mL) there was added methanol (0.5 mL) and 2N NaOH aqueous solution (1.5 mL). The reaction solution was stirred at room temperature for 2 h until complete consumption of **13a**, as followed by reverse phase HPLC analysis [General method description: Column: Waters SymmetryShield 3.5μm 4.6 x 50 mm; mobile phase: Solvent A = 0.05% TFA in CH_3CN:water (5:95), Solvent B = 0.05% TFA in CH_3CN:water (95:5); gradient: 0 min 0% B, 12 min 100% B; flow Rate: 2 mL/min; wavelength: 205 nm]. The reaction solution was diluted with water (3.5 mL) and extracted with methyl *t*-butyl ether (5.0 mL) to remove any lipophilic impurity. The aqueous solution was adjusted to pH 2.5 with 2 N HCl and extracted with EtOAc (2 x 5.0 mL). The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford acid **17** (0.3 g, 0.9 mmol) at R_f = 0.13 (1:5 MeOH/CH_2Cl_2) that could be used without further purification; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.16~4.24 (m, 8H), 3.9~2.94 (m, 24H), 2.9~2.63 (m, 9H), 1.76 (m, 8H), 1.51~1.22 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 156.6, 155.8, 79.4, 62.9, 61.6, 51.7, 51.1, 48.6, 46.8, 45.8, 40.8, 38.4, 38.0, 37.3, 37.2, 28.5; HRMS: *m/z* found 555.2841, calcd. for $C_{30}H_{39}N_4O_7$ (M + H) 555.2813; optical rotation $[\alpha]_D$ of **17**: -2.7 (20 ^{o}C, c = 0.15, chloroform).

Preparation of (-)-*N*-Boc-tetramer 14a from Dimer 13a. According to the general procedure, the (-)-dimer **13a** (0.35 g, 1.0 mmol) was dissolved in 4 *N* HCl/dioxane (2.0 mL) and stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and further dried under high vacuum to afford 0.27 g (95 %) of (-) dimer amine HCl salt as an off-white solid that was used directly in the next step without further purification. To the amine salt (0.29g, 1.0 mmol), crude (-)-dimer acid **17** (0.34 g, 1.0 mmol), EDC (0.21 g, 1.1 mmol) and HOBt (0.14 g, 1.0 mmol) a solution of diisopropylethylamine (0.28 g, 2.2 mmol) in acetonitrile (1.5 mL) and EtOAc (0.5 mL) was added at 0 ^{o}C. The reaction solution was warmed to room temperature and stirred for 2 h. Workup afforded 0.43g (75%) of (-)-tetramer **14a** as a yellow solid, mp 215-216.5 ^{o}C; R_f = 0.54 (1:9 MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.95 (m, 1H), 4.85 (m, 1H), 4.47 (br, 2H), 3.53 (m, 7H), 2.98 (m, 6H), 2.65 (m, 3H), 1.67 (m, 6H), 1.51 (m, 1H), 1.38 (s, 9H), 1.37 (m 1H), 1.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.27, 168.22, 168.12, 168.06, 79.16, 60.89, 60.56, 50.74, 48.25, 47.35, 47.28, 46.46, 41.15, 40.56, 40.46, 40.36, 37.64, 36.46, 28.45; EI-MS *m/z* ($M+H^+$) calculated for $C_{30}H_{41}N_4O_7$ 569.30, observed 569.35; HRMS *m/z* ($M+Na^+$) calculated for $C_{30}H_{40}N_4O_7Na$ ($M+Na^+$) 591.2790, observed 591.2778; optical rotation $[\alpha]_D$ –36.5 (20 ^{o}C, c = 1.6, chloroform).

Preparation of a single crystal of (-)-tetramer 14a. In a small sample vial amorphous (-)-tetramer **14a** (15 mg) was dissolved in dichloromethane (1.0 mL) together with n-heptane (0.2 mL) and THF (0.2 mL). The solvents were slowly evaporated in an ambient environment to afford plate crystals, mp 215.5-216.5 ^{o}C, which were acceptable for X-ray crystallography analysis. When the same solution was slowly evaporated in an anhydrous environment, small needle-like crystals were obtained. Unfortunately, these crystals were too small for X-ray studies.

Preparation of (-)-*N*-isobutyryl-tetramer 14b. According to the general procedure, (-)-tetramer **14a** (45.5 mg, 0.08 mmol) was dissolved in 4 *N* HCl/dioxane (0.5 mL) and stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and further dried under high vacuum. To this residue in CH_2Cl_2 (5 mL) jn an ice bath isobutyryl chloride (17 mg, 0.16 mmol) was added dropwise. The mixture was stirred with ice bath for 15 min and at room temperature for 2 h. Workup and chromatography (gradient, 4:1 ethyl acetate/ hexanes) afforded amide **14b** (31.1 mg, 72%) at R_f = 0.18 (1:3 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.03~4.32 (mdt, *J* = 8.0, 2.0Hz, 4H, $4H_1$), 3.72, 3.55 (m, 4H, $4H_3$), 3.52 (s, 3H, OMe), 3.30 (m, 4H, $4H_3$), 3.04 (m, 4H, $4H_4$), 2.69 (m, 4H, $4H_5$), 2.46 (hep, *J* = 8.0Hz, 1H), 1.85~1.72 (m, 4H, $4H_6$), 1.33~1.09 (md, *J* = 8.0Hz, 6H, $6H_6$), 1.05, 0.97 (2d, *J* = 8.0Hz, 6H, 2Me); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 176.3, 169.3, 168.1, 61.0, 60.7, 60.2, 51.6, 51.1, 50.6, 50.5, 48.2, 47.7, 47.4, 46.5, 45.9, 41.2, 40.6, 40.4, 37.9, 37.7, 36.5, 36.3, 36.0, 32.0, 19.4, 18.8, 18.6; HRMS *m/z* found 539.2893, calcd. for $C_{29}H_{38}N_4O_6$ (M + H) 539.2864; optical rotation of **14b** $[\alpha]_D$ = -47.2 (20°C, c = 1.2, chloroform).

Preparation of (-)-*N*-Boc-tetramer acid 18. According to the general procedure, to a solution of (-)-tetramer **15a** (0.28 g, 0.5 mmol) in THF (2.5 mL) there were added methanol (0.5 mL) and 2N NaOH aqueous solution (0.2 mL). The reaction solution was stirred at room temperature for 2 h until complete consumption of ester **15a**. Workup afforded 0.22 g of acid **18** (84%) as yellow solid, R_f = 0.10 (1:5 MeOH/CH_2Cl_2), that could be used directly without further purification for subsequent reactions; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.16~4.24 (m, 8H), 3.9~2.94 (m, 24H), 2.9~2.63 (m, 9H), 1.76 (m, 8H), 1.51~1.22 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 168.3, 168.1, 167.9, 166.6, 156.0, 79.2, 62.2, 61.9, 61.5, 60.5, 60.4, 53.5, 53.0, 52.6, 51.6, 50.8, 48.0, 47.8, 47.3, 47.0, 46.4, 46.0, 45.6, 45.5, 42.0, 41.0, 40.5, 39.5, 38.4, 38.1, 37.7, 37.5, 37.0, 36.9, 36.5, 28.4; HRMS: *m/z* found 555.2841, calcd. for $C_{30}H_{39}N_4O_7$ (M + H) 555.2813; optical rotation $[\alpha]_D$ of **18**: -10.4 (20 ^{o}C, c = 0.25, chloroform).

Preparation of (-)-*N*-Boc-hexamer 15a. According to the procedure, the *N*-Boc group was removed from ester **13a** and this (-)-dimer amine HCl salt (28.7 mg, 0.1 mmol), the (-)-tetramer acid **18** (55.4 mg, 0.1 mmol), EDC (21 mg, 0.11 mmol) and HOBt (14 mg, 0.1 mmol) were added to a sample vial. A solution of diisopropylethylamine (28 mg, 0.22 mmol) in acetonitrile (1.0 mL) and EtOAc (0.2 mL) was added at 0 ^{o}C. The reaction solution was warmed to room temperature and stirred for 2 h. Workup afforded 48 mg (62%) of (-)-hexamer **15a** as a yellow solid; R_f = 0.49 (1:9 MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (m, 3H), 4.36 (br, 2H), 3.48 (m, 10H), 2.96 (m, 6H), 2.64 (m, 5H), 1.97 (m, 7H), 1.66 (m, 6H), 1.39 (s, 9H), 1.16 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 168.3, 168.0, 155.9, 79.1, 61.5, 61.4, 60.8, 60.5, 53.6, 51.8, 51.5, 51.4, 50.7, 50.4, 48.2, 47.2, 46.4, 45.8, 45.5, 41.2, 40.6, 40.5, 37.6, 36.9, 36.4, 29.7, 28.5, 28.4, 18.6, 17.4; EI-MS *m/z* (M + H) calculated for $C_{42}H_{55}N_6O_9$ 787.40, observed 787.59; HRMS *m/z* (M + Na^+) calculated for $C_{42}H_{54}N_6O_9Na$ (M + Na^+) 809.3845, observed 809.3831; optical rotation $[\alpha]_D$ –26.3 (20 ^{o}C, c = 1.0, chloroform).

Preparation of (-)-*N*-isobutyryl-hexamer 15b. According to the general procedure, hexamer (-)-**15a** (39 mg, 0.05 mmol) was dissolved in 4 N HCl/dioxane (0.4 mL) and stirred at room temperature for 2 h.

The solution was concentrated *in vacuo* and further dried under high vacuum. To this residue in CH_2Cl_2 (5 mL) chilled with an ice bath, isobutyryl chloride (15 mg, 0.14 mmol) was added. The mixture was stirred in the ice bath for 15 min and then at room temperature for 2 h. Workup afforded after chromatography (gradient, 1:10 MeOH/CH_2Cl_2) 28 mg (74%) of amide (-)-**15b** (100% pure by SB-C18 column, λ = 214 nm, flow rate = 1.0 mL/min) as a colorless oil; R_f = 0.48 (1:10 MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.10~4.40 (m, 6H), 3.79~3.22 (m, 12H), 3.61 (s, 3H, OMe), 3.18~3.04 (m, 6H), 2.77 (m, 6H), 2.55 (hep, *J* = 8.0 Hz, 1H, *iso*-H), 1.89~1.72 (m, 6H), 1.39~1.18 (m, 12H), 1.13, 1.04 (2d, *J* = 8.0 Hz, 6H, 2Me); HRMS *m/z* found 757.3895, calcd. for $C_{41}H_{53}N_6O_8$ (M + H) 757.3880; optical rotation $[\alpha]_D$ of (-)-**15b** -33.7 (20 °C, c = 1.0, chloroform).

Preparation of (-)-*N*-Boc-octamer 16a. According to the general procedure, the (-)-tetramer **14a** (0.14 g, 0.25 mmol) was dissolved in 4*N* HCl/dioxane (2.0 mL) and stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and further dried under high vacuum to afford 0.12 g (95 %) of (-)-tetramer amine HCl salt as a brownish solid that was used directly without further purification. The (-)-tetramer acid **18** (55.4 mg, 0.1 mmol), (-)-tetramer amine HCl salt (50.5 mg, 0.1 mmol), EDC (21 mg, 0.11 mmol) and HOBt (14 mg, 0.1 mmol) were added to a sample vial. A solution of diisopropylethylamine (28 mg, 0.22 mmol) in acetonitrile (1.0 mL) and EtOAc (0.2 mL) was added at 0 ^{o}C. The reaction solution was warmed to room temperature and stirred for 2 h. Workup afforded 60 mg (60%) of (-)-octamer **16a** as a brownish powder; R_f = 0.45 (1:9 MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.47 (m, br, 8H), 3.59 (m, 17H), 3.06 (m, 16H), 1.72 (m, 9H), 1.22 (m, 19H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 169.2, 168.0, 79.1, 72.3, 71.1, 61.7, 61.4, 60.9, 60.6, 53.6, 51.5, 51.4, 50.7, 50.4, 48.2, 47.7, 47.3, 46.5, 45.6, 42.9, 41.2, 40.5, 37.9, 37.6, 36.9, 36.4, 29.7, 28.6, 28.4, 18.6, 17.4; EI-MS *m/z* (M + H^+) calculated for $C_{54}H_{69}N_8O_{11}$ 1005.51, observed 1005.85; HRMS *m/z* (M + Na^+) calculated for $C_{54}H_{68}N_8O_{11}Na$ (M+Na^+) 1027.4900, observed 1027.4866; optical rotation $[\alpha]_D$ –47.6 (20 ^{o}C, c = 1.2, chloroform).

Preparation of (-)-*N*-isobutyryl-octamer 16b. According to the general procedure octamer (-)-**16a** (40 mg, 0.04 mmol) was dissolved in 4 N HCl/dioxane (0.4 mL) and stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and further dried under high vacuum to remove all solvent. To this residue, CH_2Cl_2 (5 mL) was added. The resulting solution was chilled with an ice bath and isobutyryl chloride (15 mg, 0.14 mmol) was added. The mixture was stirred with an ice bath for 15 min and then at room temperature for 2 hours. Workup afforded after chromatography (gradient, 1:10 MeOH/CH_2Cl_2) 28 mg (70%) of amide (-)-**16b** (100% pure by SB-C18 column, λ = 214 nm, flow rate = 1.0 mL/min) as a colorless oil at R_f = 0.43 (1:10 MeOH/ CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.03~4.31 (m, 8H), 3.71~3.14 (m, 16H), 3.52 (s, 3H, OMe), 3.08~2.97 (m, 8H), 2.72~2.62 (m, 8H), 2.45 (hep, *J* = 8.0 Hz, 1H, *iso*-H), 1.86~1.63 (m, 8H), 1.37~1.108 (m, 16H), 1.04, 0.96 (2d, *J* = 8.0 Hz, 6H, 2Me); HRMS**:** *m/z* found 975.4921, calcd. for $C_{53}H_{67}N_8O_{10}$ (M + H) 975.4935. Optical rotation $[\alpha]_D$ of (-)-**16b**: -37.4 (20 °C, c = 0.9, chloroform).

Table 4. Major ^{1}H NMR Resonances for Oligomers of Acid (-)-9.

entry	compound	Major H_1 (%)	Major H_1 (δ)	Minor H_1 (δ)[a]
1	**13a**	60[b]	4.85, 4.6	4.6-4.35
2	**13b**	62[c]	5.1, 4.9	4.85-4.4
3	**14a**	58-72[b]	5.0, 4.8	4.7-4.4
4	**14b**	72[c]	5.1, 4.97, 4.95, 4.87	4.6-4.3
5	**15a**	74[b]	5.0-4.6	4.55-4.35
6	**15b**	78[c]	5.13-4.80	4.65-4.35
7	**16a**	76[b]	4.97-4.6	4.55-4.35
8	**16b**	72[c]	5.1-4.85	4.65-4.35

[a]Some minor H_1 peaks are in the downfield region. [b]The most upfield major H_1 has the least overlap with minor peaks. The percentage is based upon this peak. [c]The most downfield H_1 of unit 1 has the least overlap with minor peaks. The percentage major isomer is calculated from this peak.

Table 5. Energy and Coordinates for the lowest energy *N*-acetyl tetramer methyl ester 14c.

Structure	Energy	zpe	Energy (corr)
Tetramer, lowest E	-1719.526582	0.589639	-1718.936943
1T4_2T4_3T4_4T4			

Candidates for the oligomer structures were sketched with each of the carbonyls oriented in approximately the manner one expects would be close to an energy minimum. These were optimized with the UFF molecular mechanics program, then further optimized with AM1. Single point energies were obtained at the B3LYP/6-31+G(2d,p) level of accuracy. Energies are reported below in hartrees as well as the zero point energies with which these initial energies were lastly corrected. The lowest energy tetramer is given in the table.

Tetramer 14c

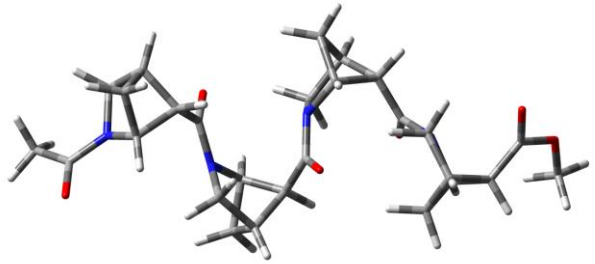
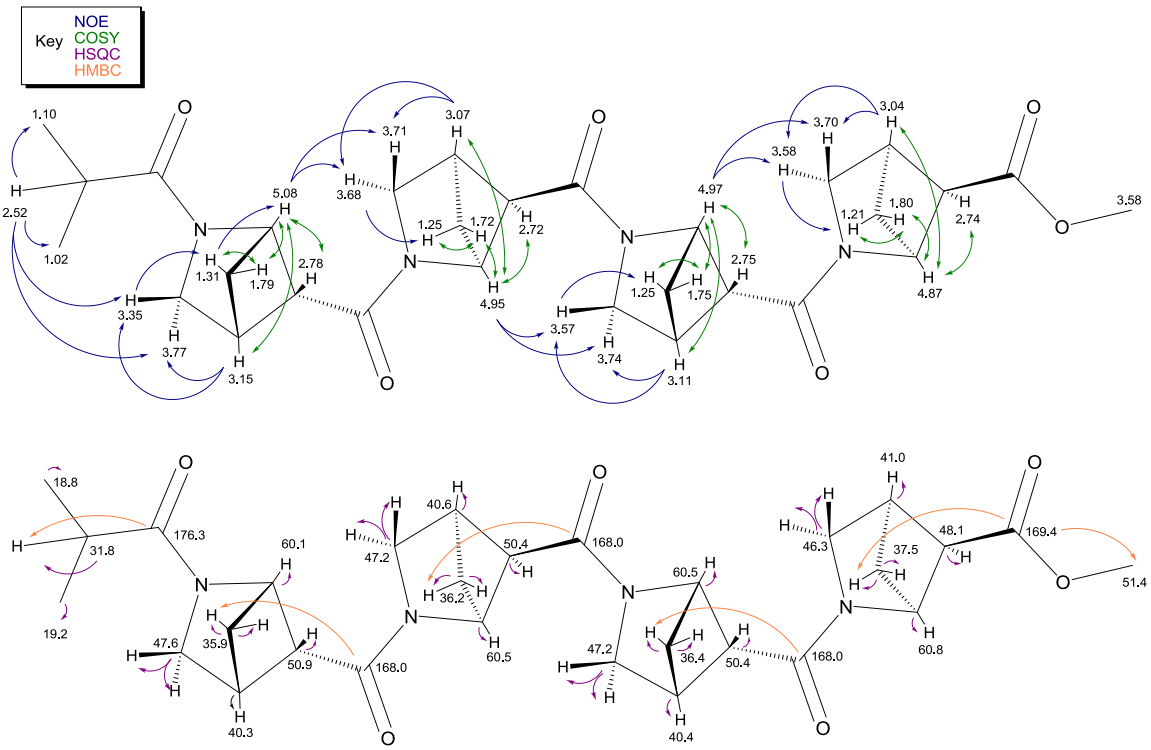


Table of Coordinates for tetramer **15c**

C	1.409586	-0.130816	-5.810716	H	-1.938727	-1.509300	0.434594
C	1.991898	0.920343	-4.795822	O	-0.881023	1.221540	0.656762
H	1.895670	-0.050917	-6.814623	N	0.790246	-0.280080	0.216503
H	1.498524	-1.175427	-5.416752	C	1.796378	0.404136	1.057007
N	-0.013748	0.283025	-5.828972	C	1.242846	-1.695029	0.293383
H	3.048898	0.848772	-4.530936	H	1.525430	-2.047492	-0.733442
C	-0.004570	1.456655	-4.932875	H	0.472668	-2.369356	0.745369
C	0.857213	0.915606	-3.704324	C	2.501144	-1.536071	1.220439
C	1.325890	2.226544	-5.349020	H	1.675394	1.491607	1.163417
C	-0.830005	0.206753	-6.950432	C	1.950413	-0.559697	2.324761
H	-0.969760	1.966261	-4.799836	C	3.146381	-0.269389	0.555600
H	1.518857	3.135626	-4.747944	H	3.066169	-2.434726	1.477619
H	1.464405	2.433688	-6.426188	H	4.045822	0.120754	1.069606
H	0.998919	1.685304	-2.911876	H	3.303255	-0.317270	-0.538774
C	0.504789	-0.397043	-3.065651	C	0.729805	-0.960101	3.102120
O	-1.845330	0.924847	-7.040271	H	2.744294	-0.208752	3.024654
C	-0.505530	-0.833211	-7.992803	O	0.247390	-2.110635	3.046318
O	1.340360	-1.317919	-2.946738	N	0.210048	-0.041508	4.000753
N	-0.799870	-0.583339	-2.649482	C	0.313860	1.433360	3.883738
H	-1.368108	-0.918082	-8.697567	H	1.221885	1.798404	4.426907
H	-0.317310	-1.827760	-7.521381	H	0.317839	1.776554	2.816747
H	0.403293	-0.523979	-8.564116	C	-1.111048	-0.208870	4.635770
C	-1.785968	0.485468	-2.373756	C	-1.018488	1.859607	4.603638
C	-1.219605	-1.644130	-1.717527	H	-1.216025	2.926570	4.728277
H	-2.371301	0.716990	-3.298569	C	-1.030460	0.862288	5.822803
H	-1.308931	1.415032	-1.971485	H	-1.975554	0.902836	6.411801
C	-1.549311	-0.845074	-0.370232	C	-2.016419	0.875544	3.902529
H	-0.604575	-2.555581	-1.713699	C	0.134846	0.856407	6.741228
C	-2.795924	-1.650719	-1.932747	O	1.093527	1.630348	6.749833
C	-2.670168	-0.228572	-1.284285	O	0.212362	-0.059424	7.764976
H	-3.155065	-1.685393	-2.978354	C	-0.832339	-1.014415	7.886914
H	-3.320233	-2.399937	-1.308843	H	-1.785736	-0.510187	8.179462
H	-3.516798	0.322360	-0.869063	H	-0.966002	-1.584018	6.935583
C	-0.544881	0.098295	0.222305	H	-0.480897	-1.692637	8.705686
H	-3.055044	0.916520	4.281823	H	-1.440330	-1.245689	4.796900
				H	-1.998317	0.875178	2.793973

Spectral Assignments for Tetramer **14b.**



Notes:

All NOE experiments were selective NOE (SELNOGP) as opposed to difference NOE.

H_3 protons are discussed as endo (syn) or exo (anti) to the bridge bearing the carbonyl, H_6 protons are discussed as syn or anti to nitrogen.

Trends noted:

H_{3exo} upfield, H_{3endo} downfield, H_{6syn} upfield, H_{6anti} downfield

NOE intensity by observation:

CH *i*-Pr → H_{3exo} unit 1 > CH *i*-Pr → H_{3endo} unit 1

H_1 Unit i → H_{3exo} unit i+1 < H_1 Unit i → H_{3endo} unit i+1

These results are predicted by the relative distances measured in the calculated and x-ray structures.

In addition to the NOE assignment of H_3 pairings shown above, each assignment is confirmed by COSY and HSQC measurements.

The chain of logic is as follows: **Bold,** in reference to NOE, signifies a larger intensity.

Unambiguous: δ 2.52 NOE to (3.35, 3.77), 3.35 NOE to 1.31, 1.31 NOE to 5.08, 5.08 NOE to (3.68, 3.71)

Tentative Ambiguity: What H_4 is in the same $H_{3,3'}$ unit as δ (3.68, 3.71)?

Solution:

COSY identifies the four major H_4-H_1 connectivities as δ 3.15-5.08, 3.11-4.97, 3.07-4.95, and 3.04-4.87. H_4-H_1 at δ 3.15-5.08 has already been identified as unit 1, leaving δ 3.11-4.97, 3.07-4.95, and 3.04-4.87.

NOE of H_4 peaks go as follows. Pulse of δ 3.15 shows peaks at δ **3.77**, 3.74, 3.57, **3.35**, where only a portion of the NOE pulse includes H_4 at δ 3.11. This supports H_4 at δ 3.15 connected with H_3 of unit 1 δ (3.77, 3.35), therefore H_4 δ 3.11 is associated with H_3 δ (3.74, 3.57). The next H_4 NOE pulse includes both δ 3.11 and 3.07 well. The H_3 peaks observed are δ 3.74, 3.71, 3.68, and 3.57. With δ (3.74, 3.57) now connected to H_4 δ 3.11, the NOE peaks at δ 3.71, 3.68, are then associated with H_4 δ 3.07.

As H_3 δ (3.68, 3.71) are known to be of unit 2 from an unambiguous NOE with H_1 of unit 1 at δ 5.08, H_4 δ 3.07 is now shown to belong to unit 2.

Tentative Ambiguity: with the first two units in order, how can the final two units be assigned?

Solution:

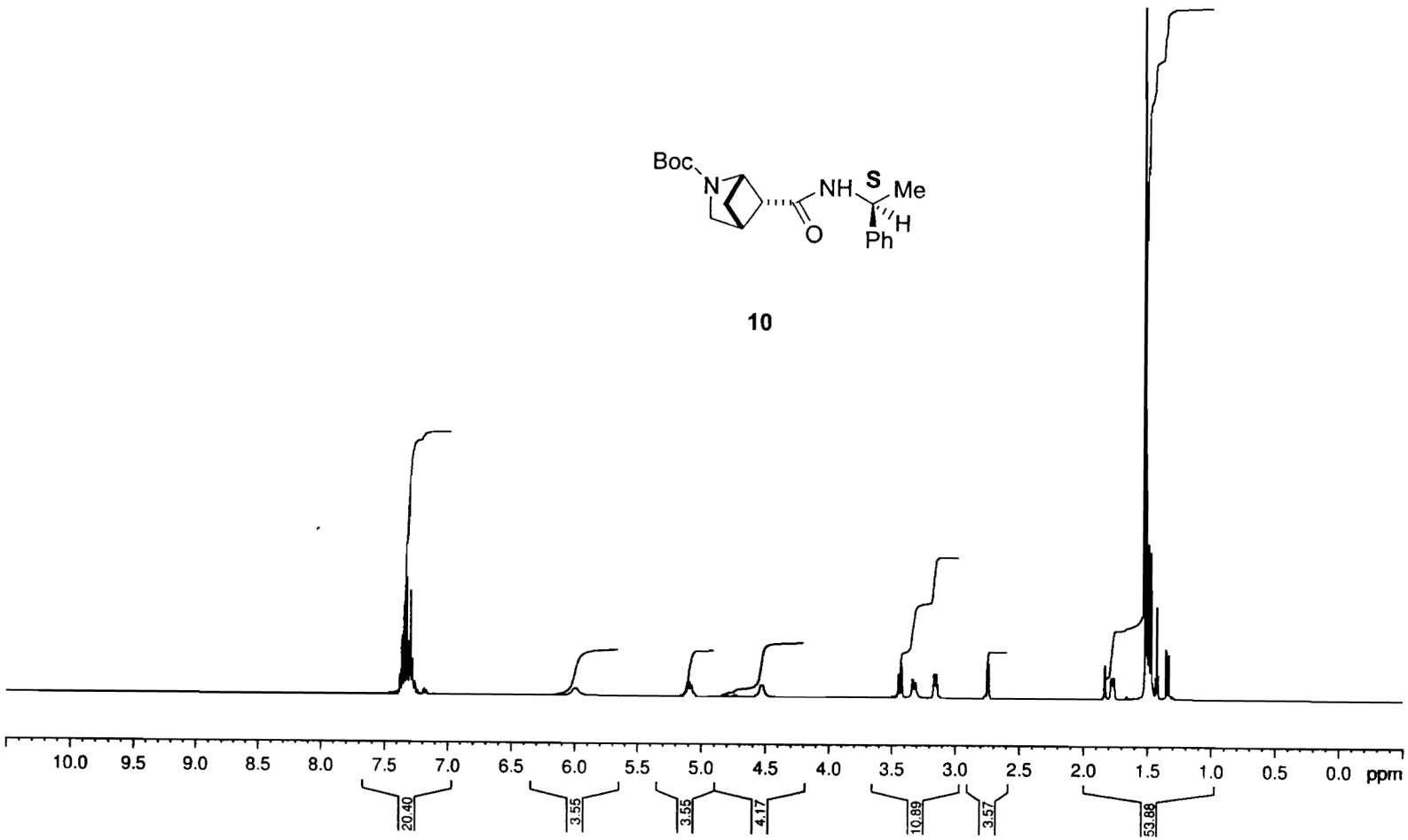
NOE of H_4 δ 3.04 is unambiguous, and shows peaks at δ 3.70, 3.58.

H_1 at δ 4.97 and 4.95 cannot be individually pulsed. Irradiating both H_1 peaks shows enhancements at δ 3.74, 3.70, and overlapping peaks at δ **3.58**, **3.57**.

The H_3 δ (3.57, 3.74) have already been shown to belong with H_4 δ 3.11 and H_1 δ 4.97. Likewise H_3 δ (3.58, 3.70) have already been shown to belong with H_4 δ 3.04 and H_1 δ 4.87.

As we have not yet observed H_1 enhancement of a non-adjacent H_3 of the *same* unit, H_1 unit 2 δ 4.95 must be enhancing H_3 unit 3 at δ (3.57, 3.74). Otherwise H_1 δ 4.97 of unit 3 would have an NOE to H_3 of the same unit.

Also, an unambiguous absence of an NOE for H_1 δ 4.87 with any H_3 peaks supports the assignment for this H_1 with unit 4 at the end of the oligomer chain.



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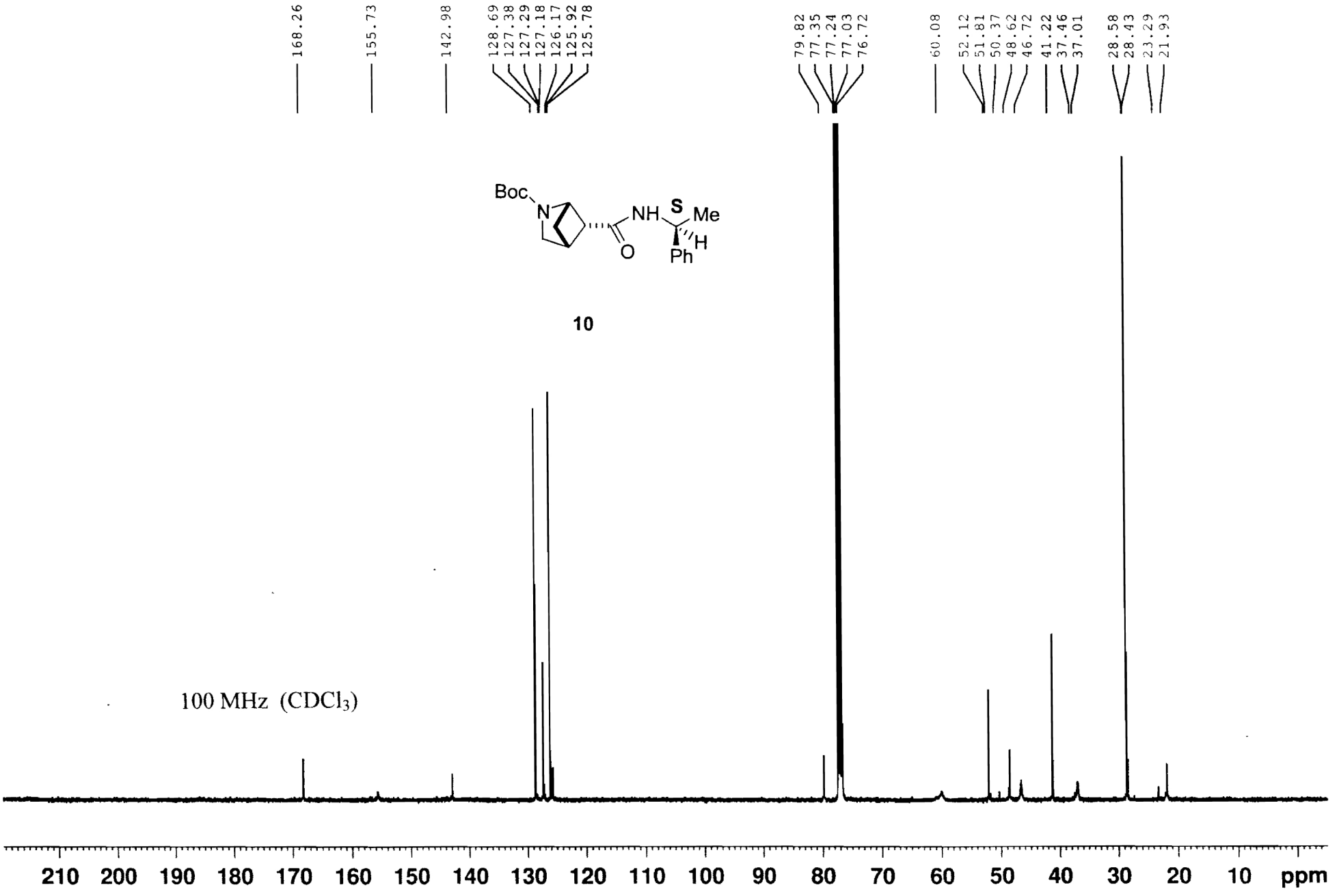
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128.69
127.38
127.29
127.18
126.17
125.92
125.78
79.82
77.35
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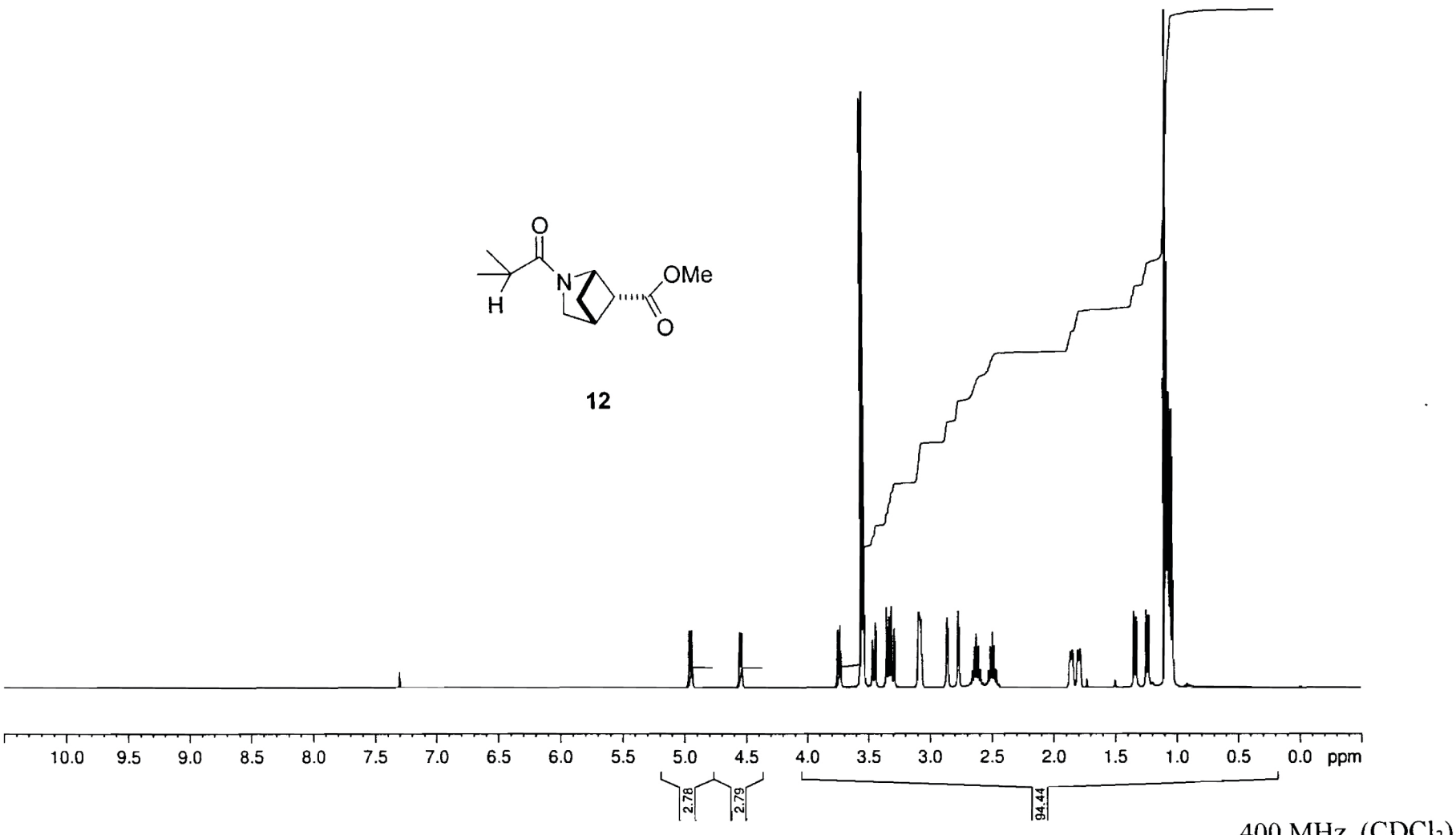
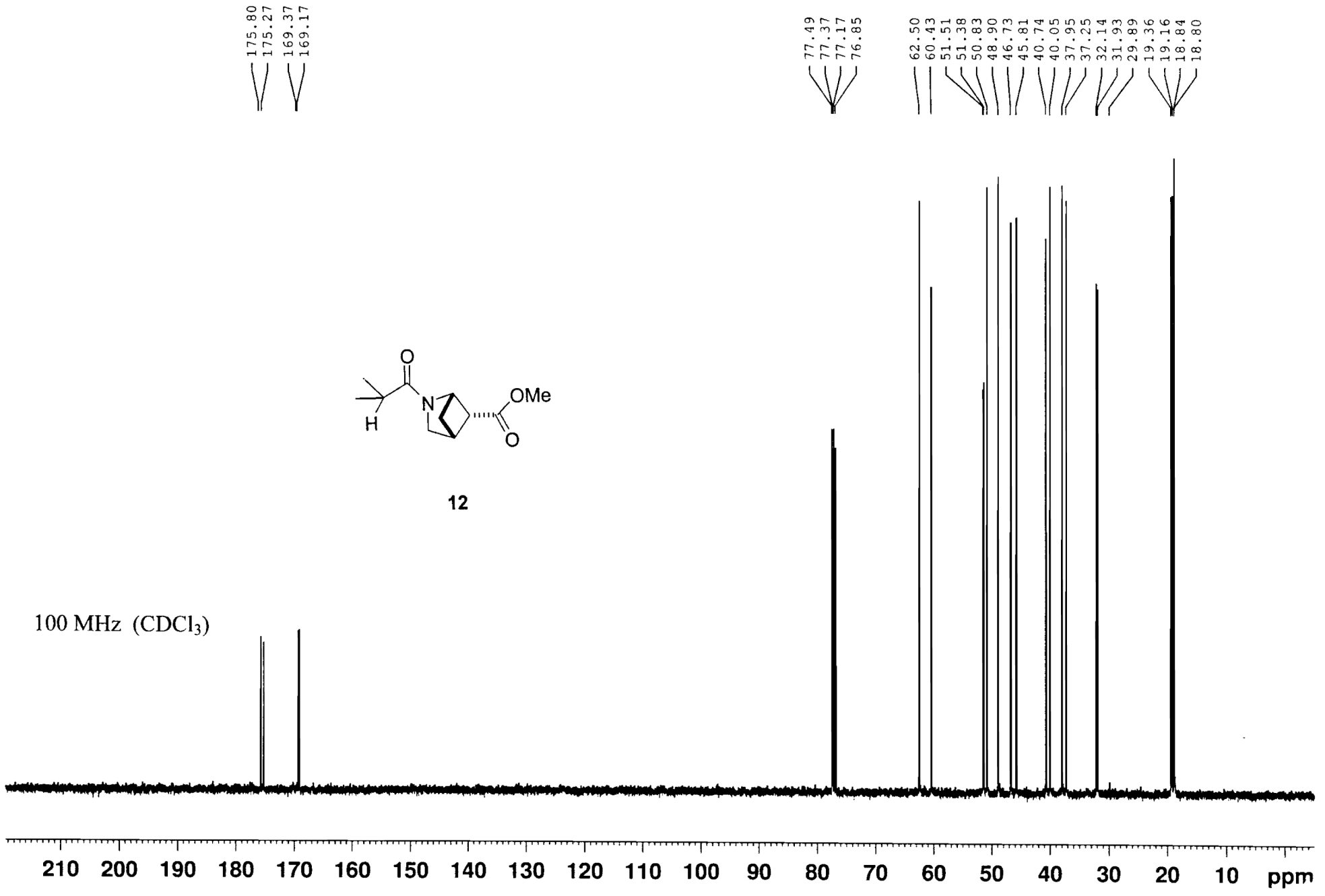
77.03
76.72
60.08
52.12
51.81
50.37
48.62
46.72
41.22
37.46
37.01
28.58
28.43
23.29
21.93
Boc
N
NH
S
Me
H
Ph
O
10
100 MHz (CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



400 MHz ($CDCl_3$)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175.27
169.37
169.17
77.49
77.37
77.17
76.85
62.50
60.43
51.51
51.38
50.83
48.90
46.73
45.81
40.74
40.05
37.95
37.25
32.14
31.93
29.89
19.36
19.16
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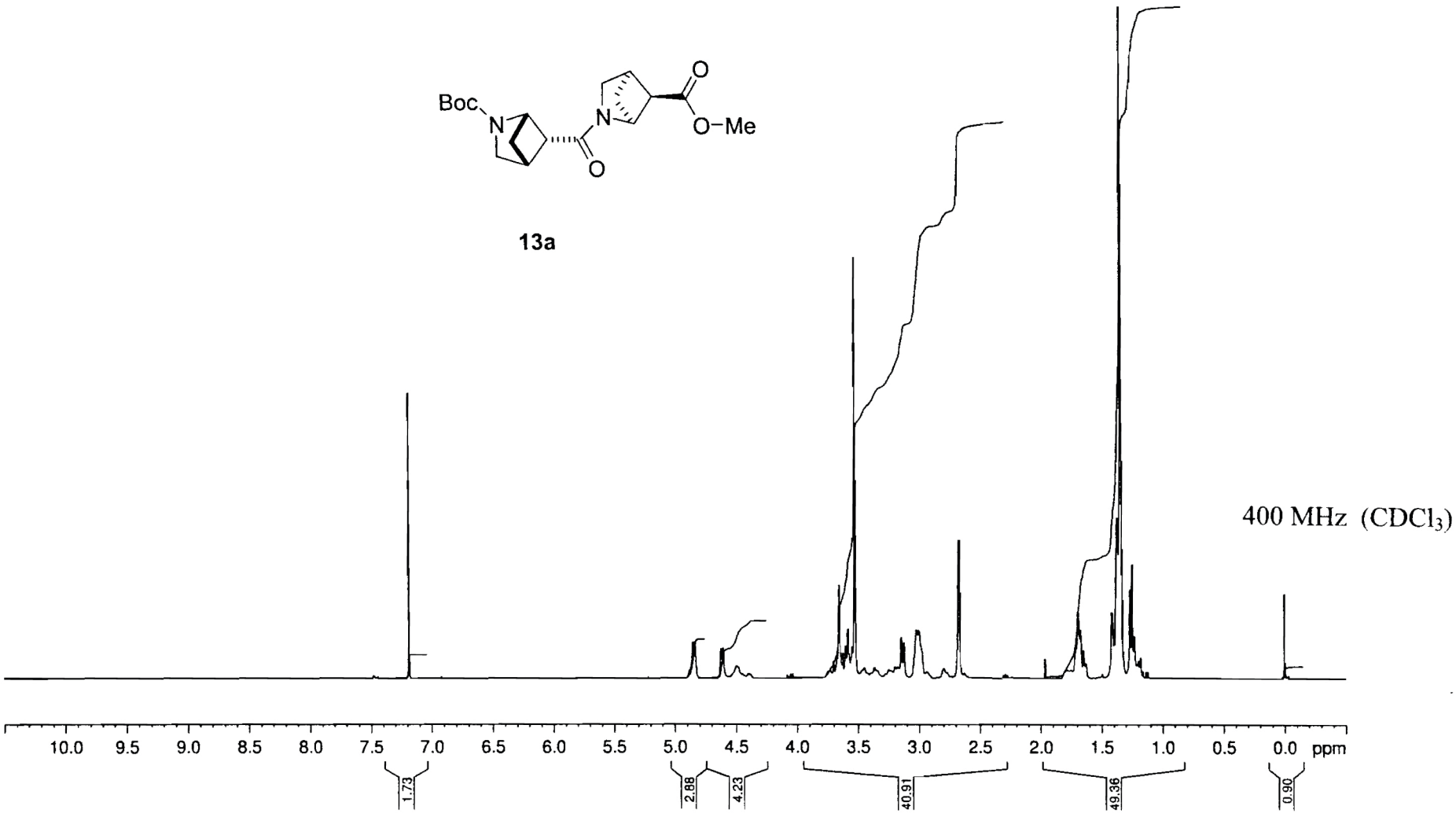
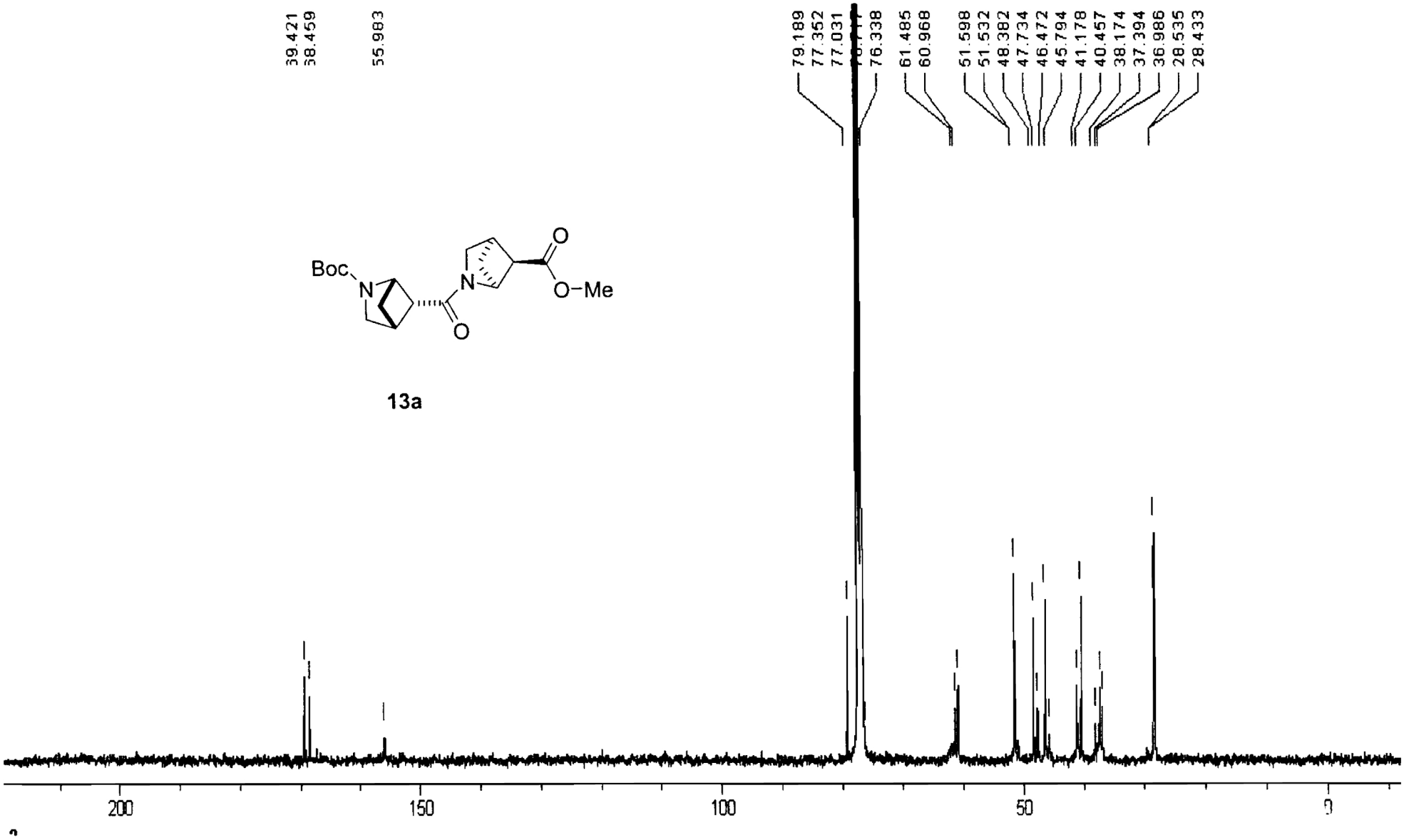
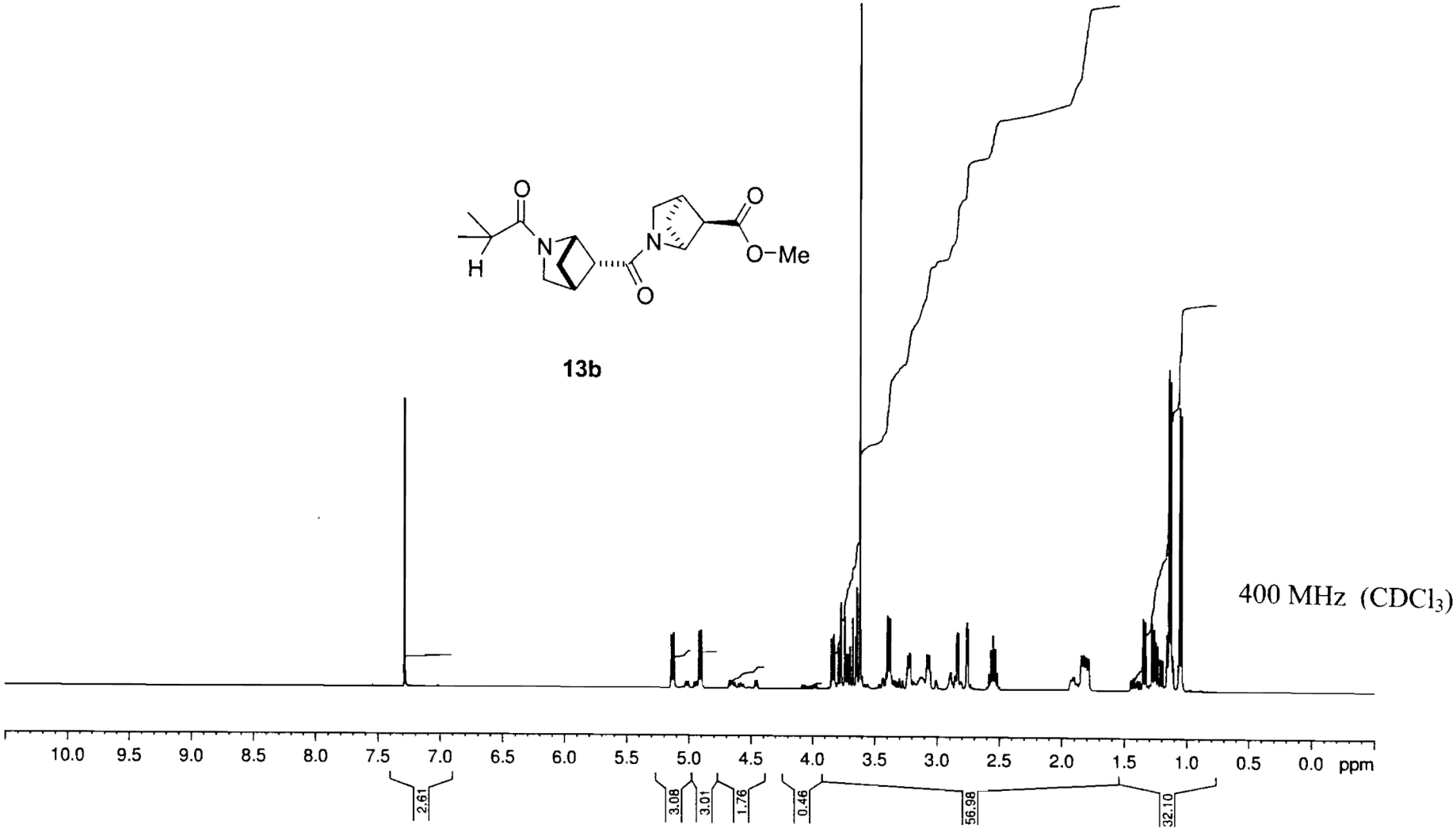
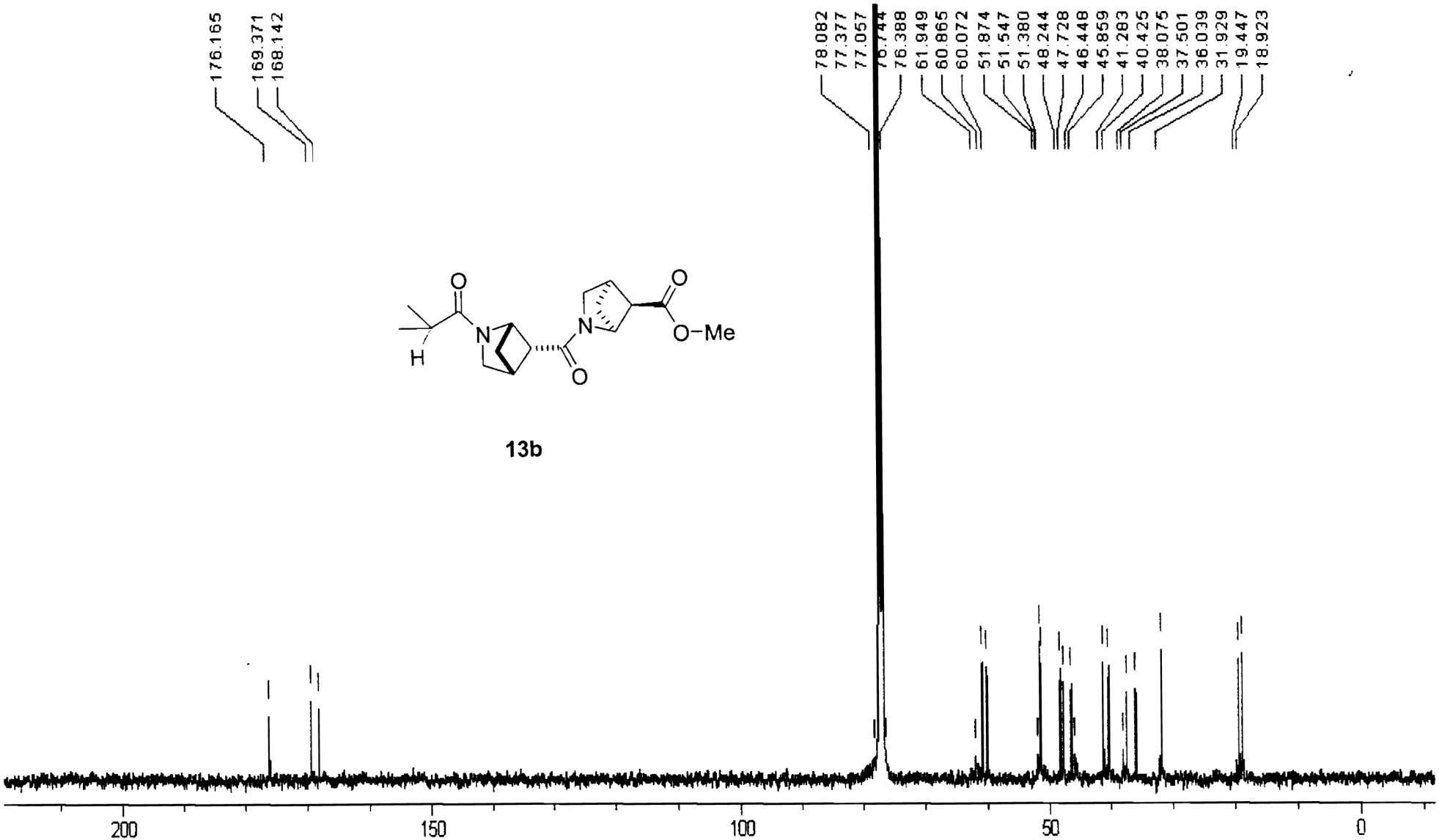
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Boc
N
N
O
O
O
O-Me
13a
400 MHz (CDCl3)
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 ppm
1.73
2.88
4.23
40.91
49.36
0.90



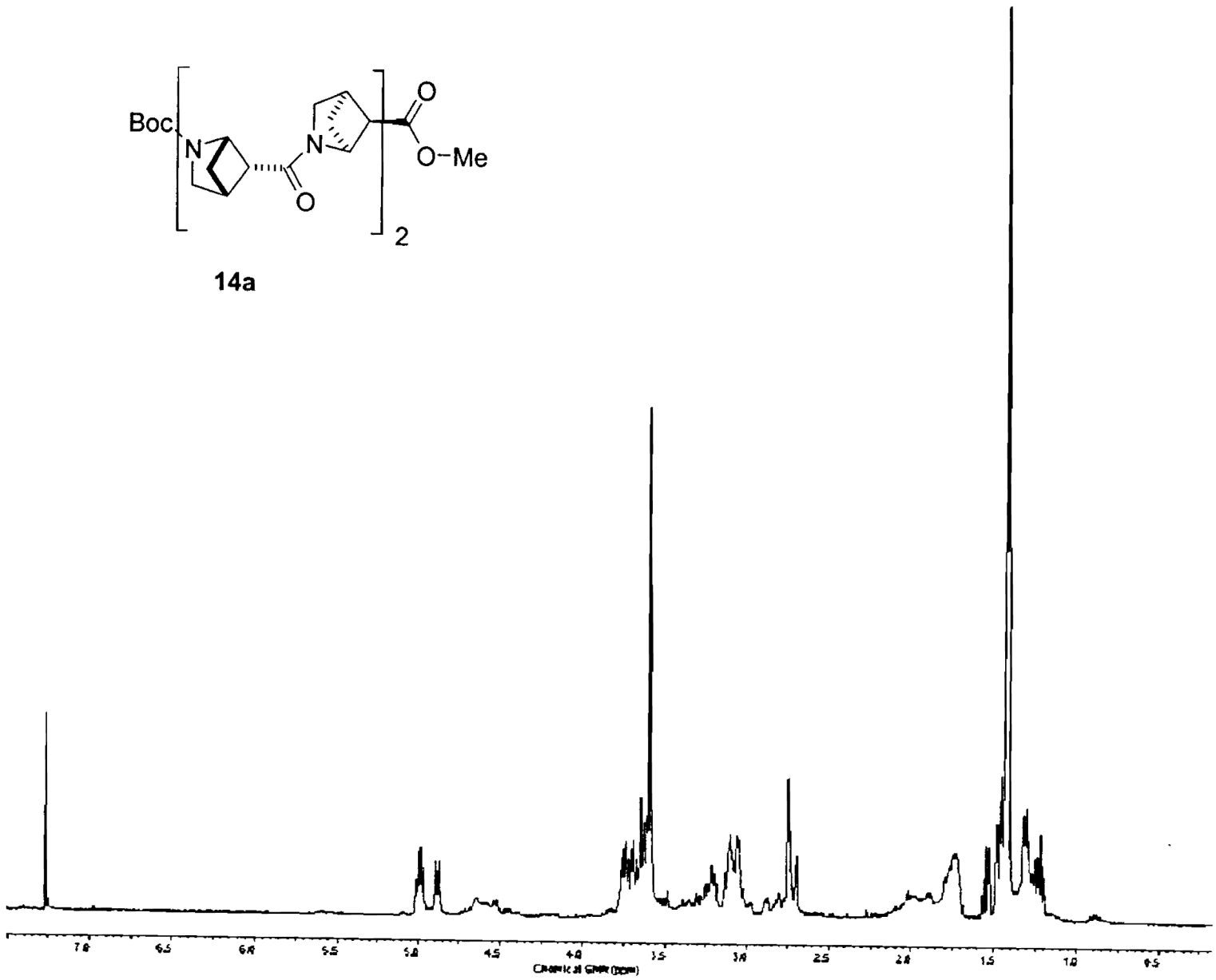
100 MHz ($CDCl_3$)


13b
400 MHz (CDCl3)
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 ppm
2.61
3.08
3.01
1.76
0.46
56.98
32.10

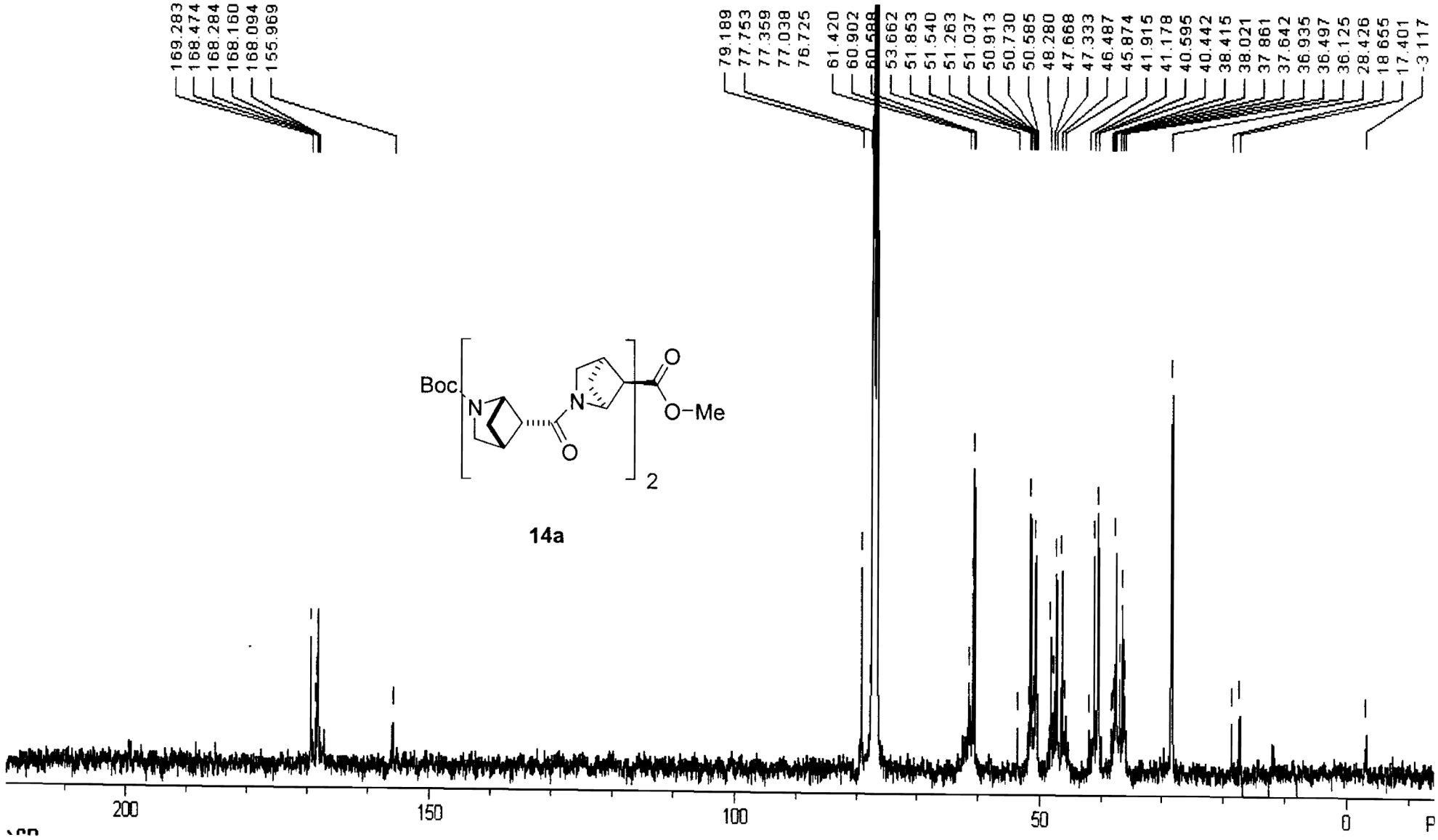


100 MHz ($CDCl_3$)

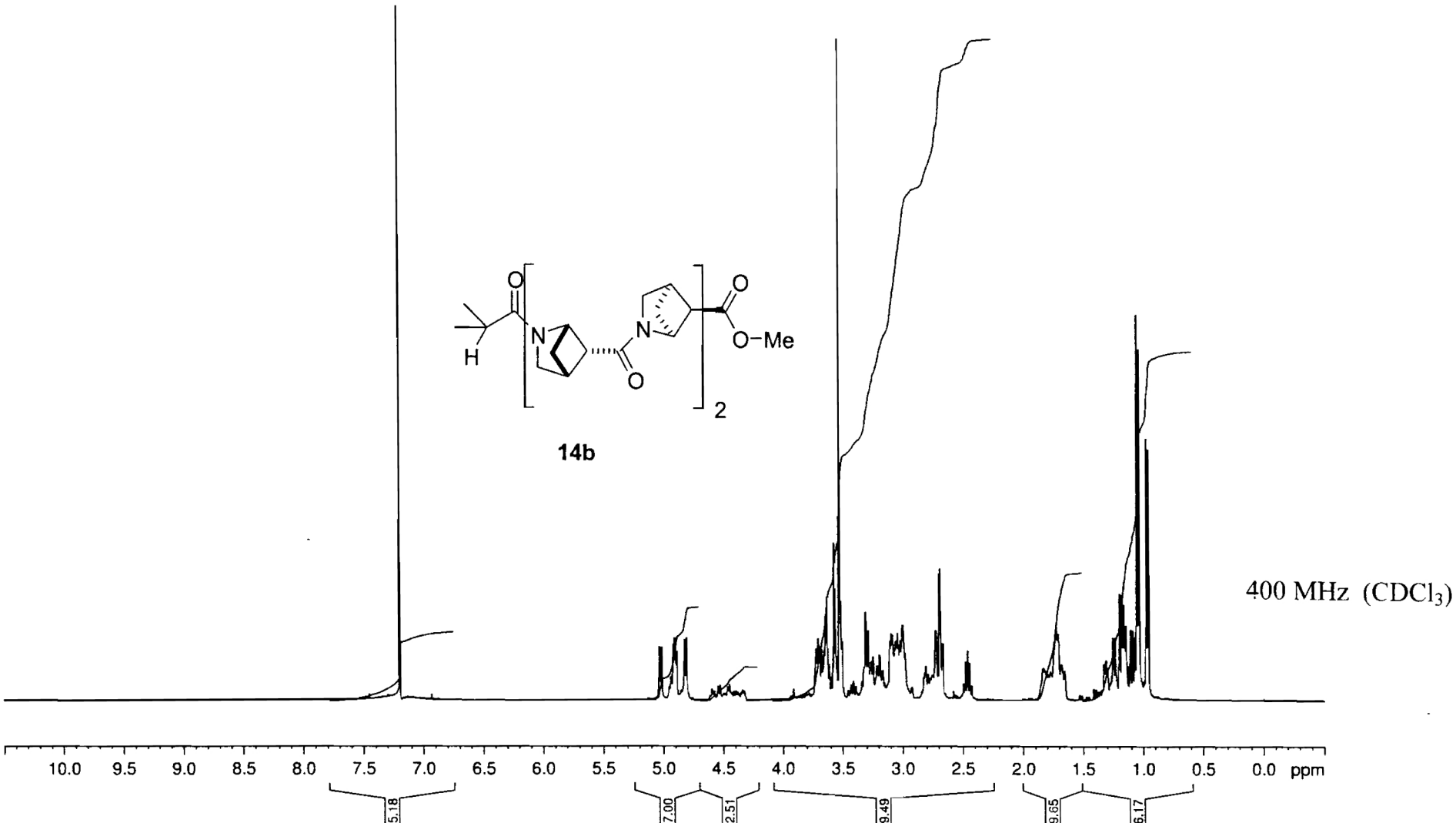
14a

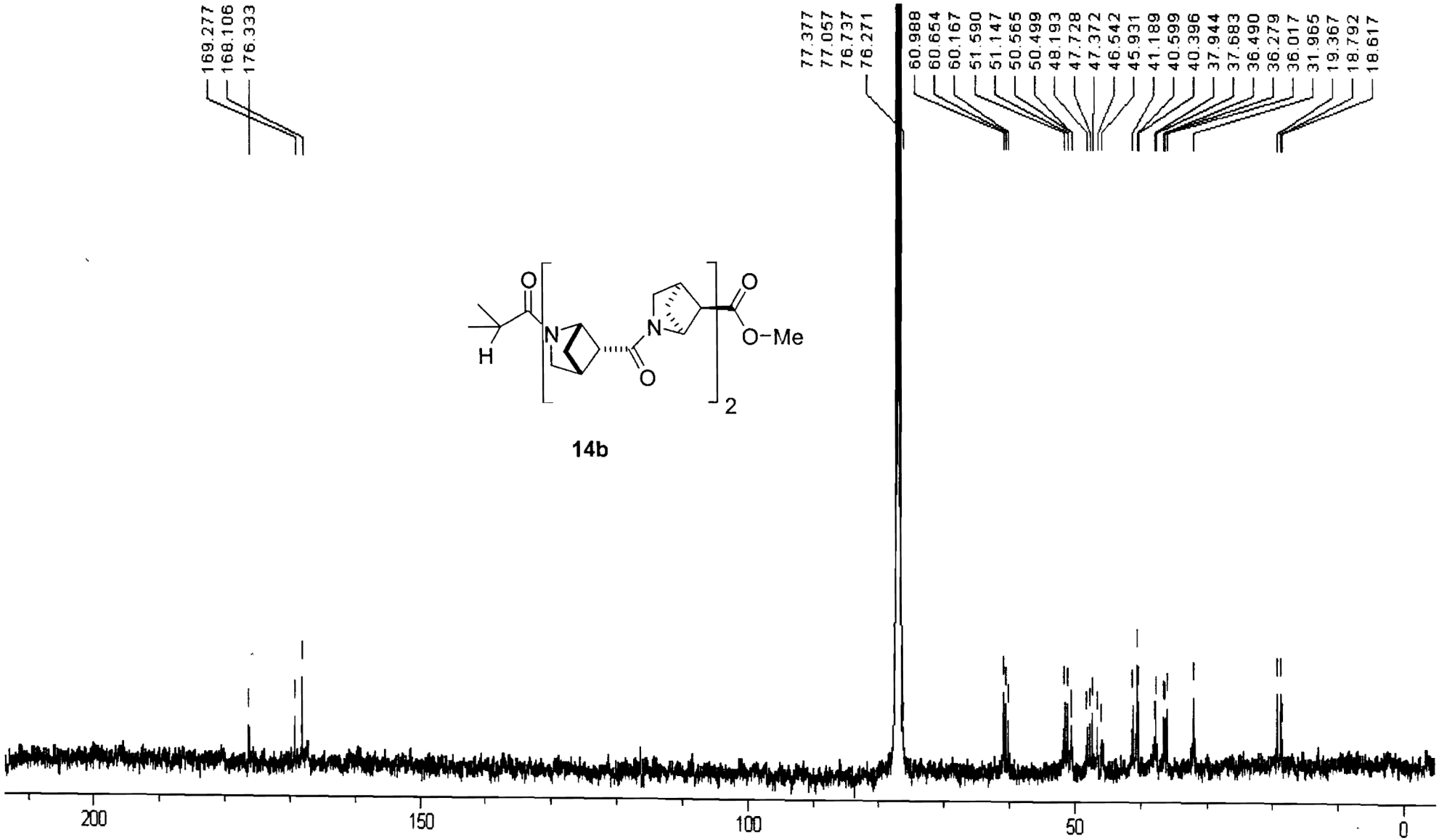


300 MHz ($CDCl_3$)

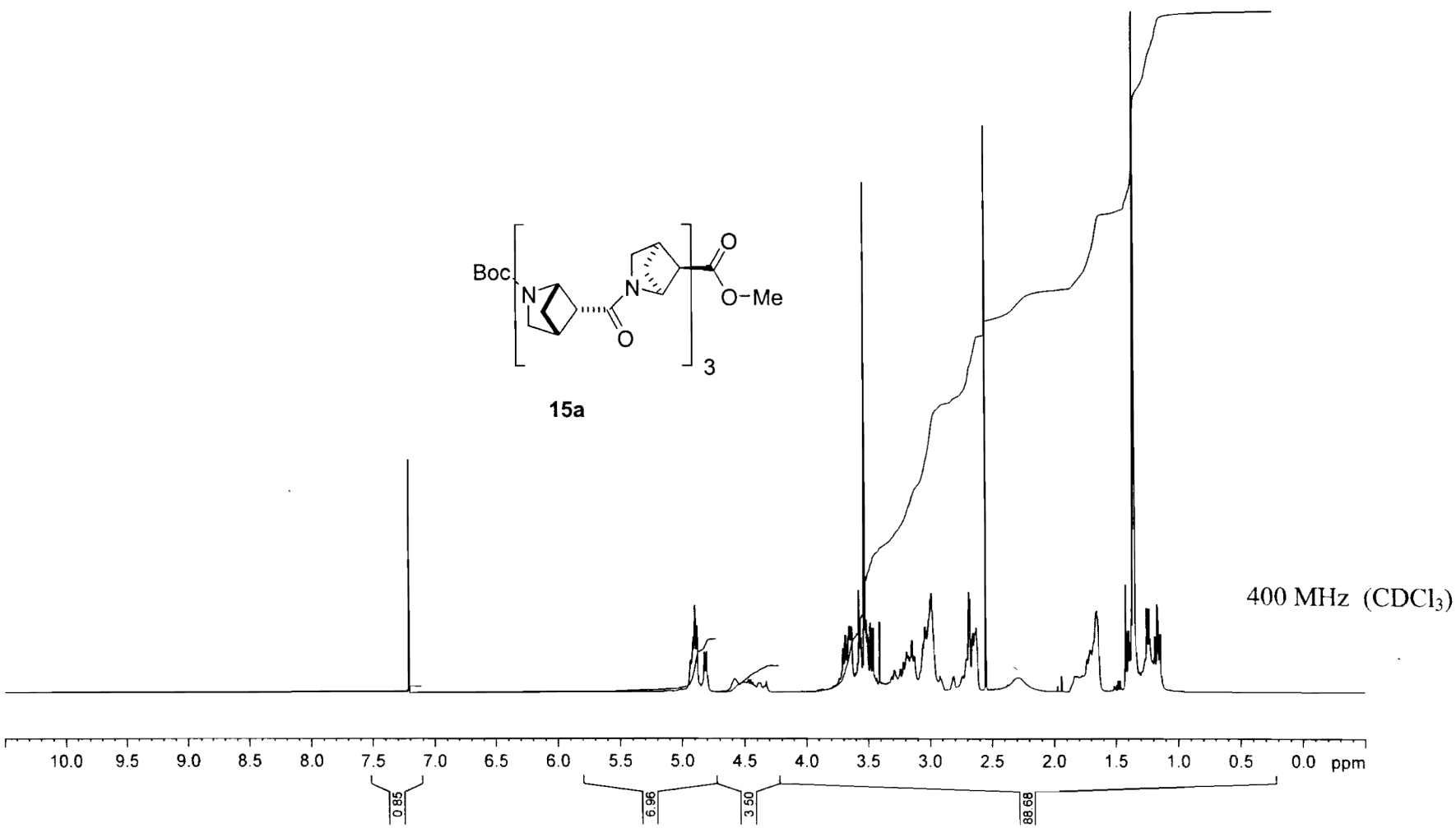


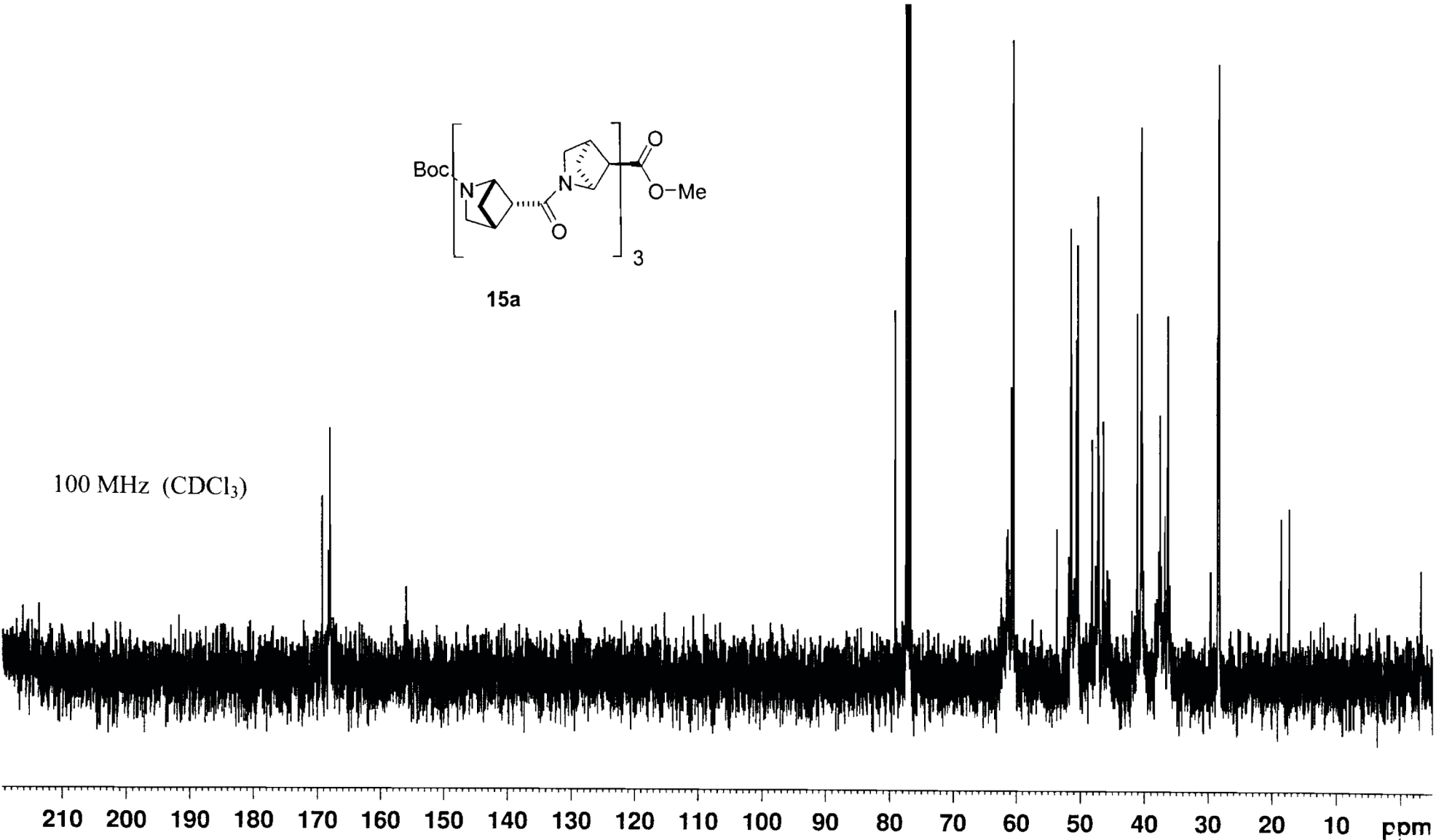
100 MHz ($CDCl_3$)

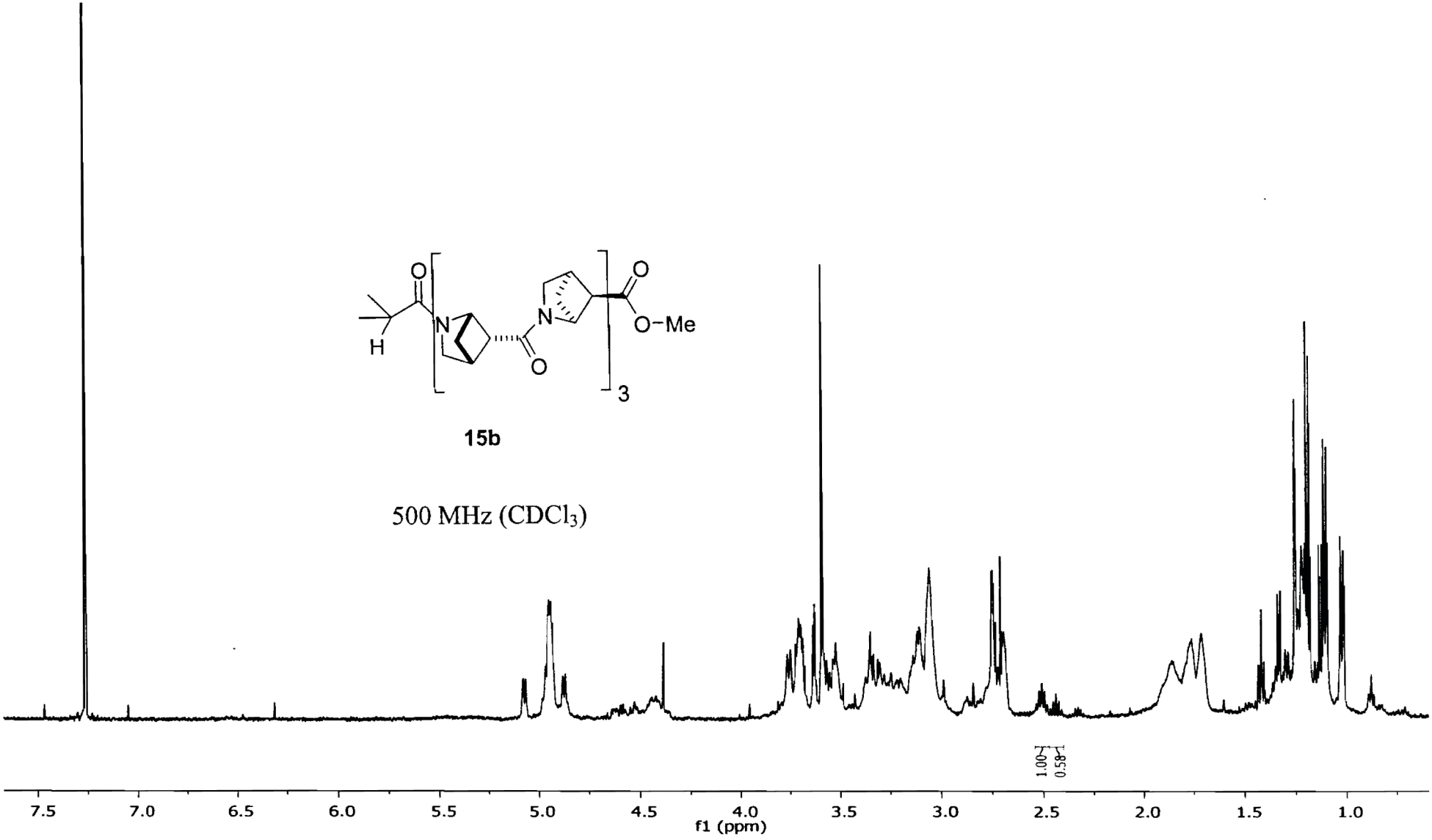

O
H
N
O
N
O
O
O-Me
2
14b
400 MHz (CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
5.18
7.00
2.51
49.49
9.65
26.17



100 MHz ($CDCl_3$)

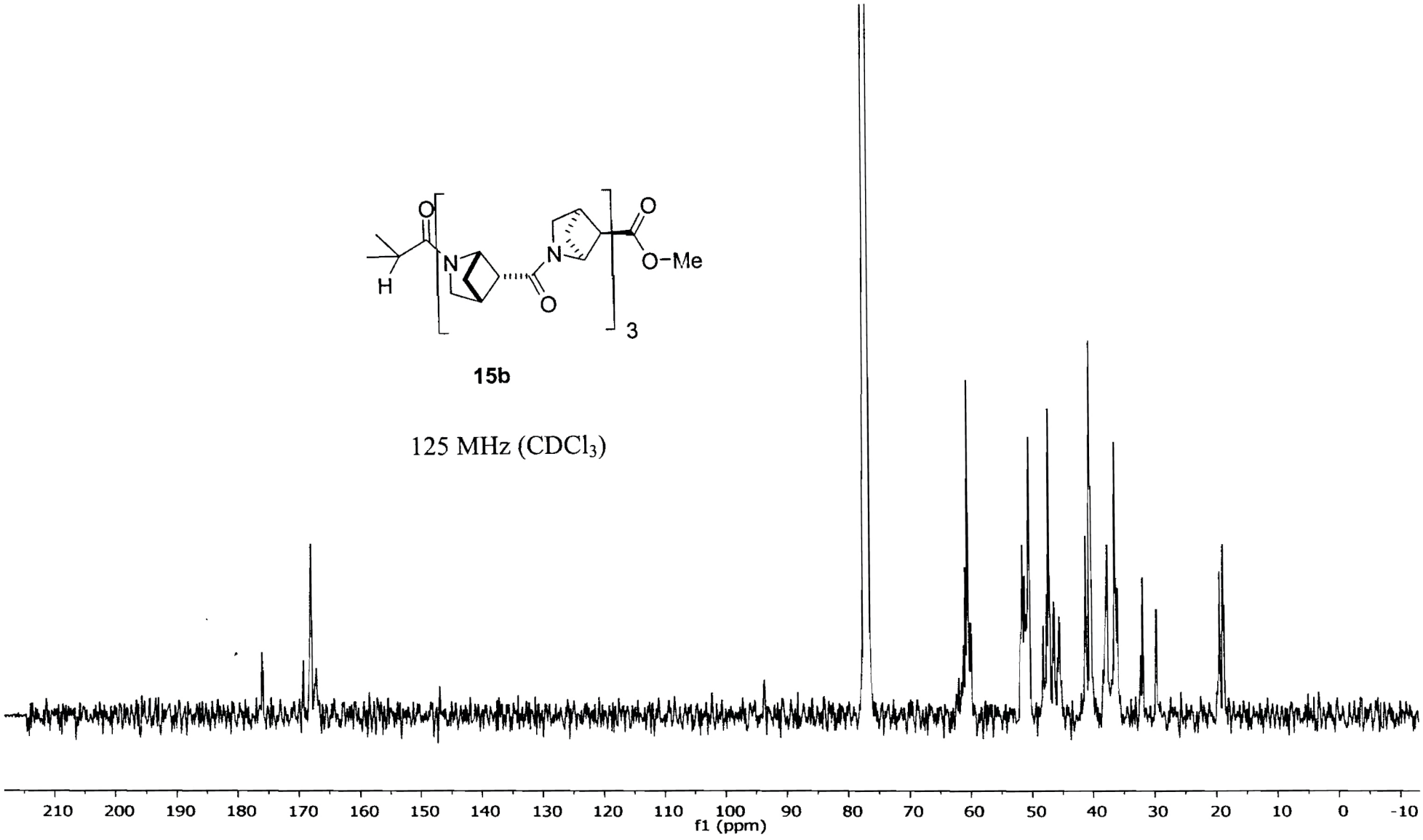

Boc
N
N
O
O
O
O-Me
3
15a
400 MHz (CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.85
6.96
3.50
88.68

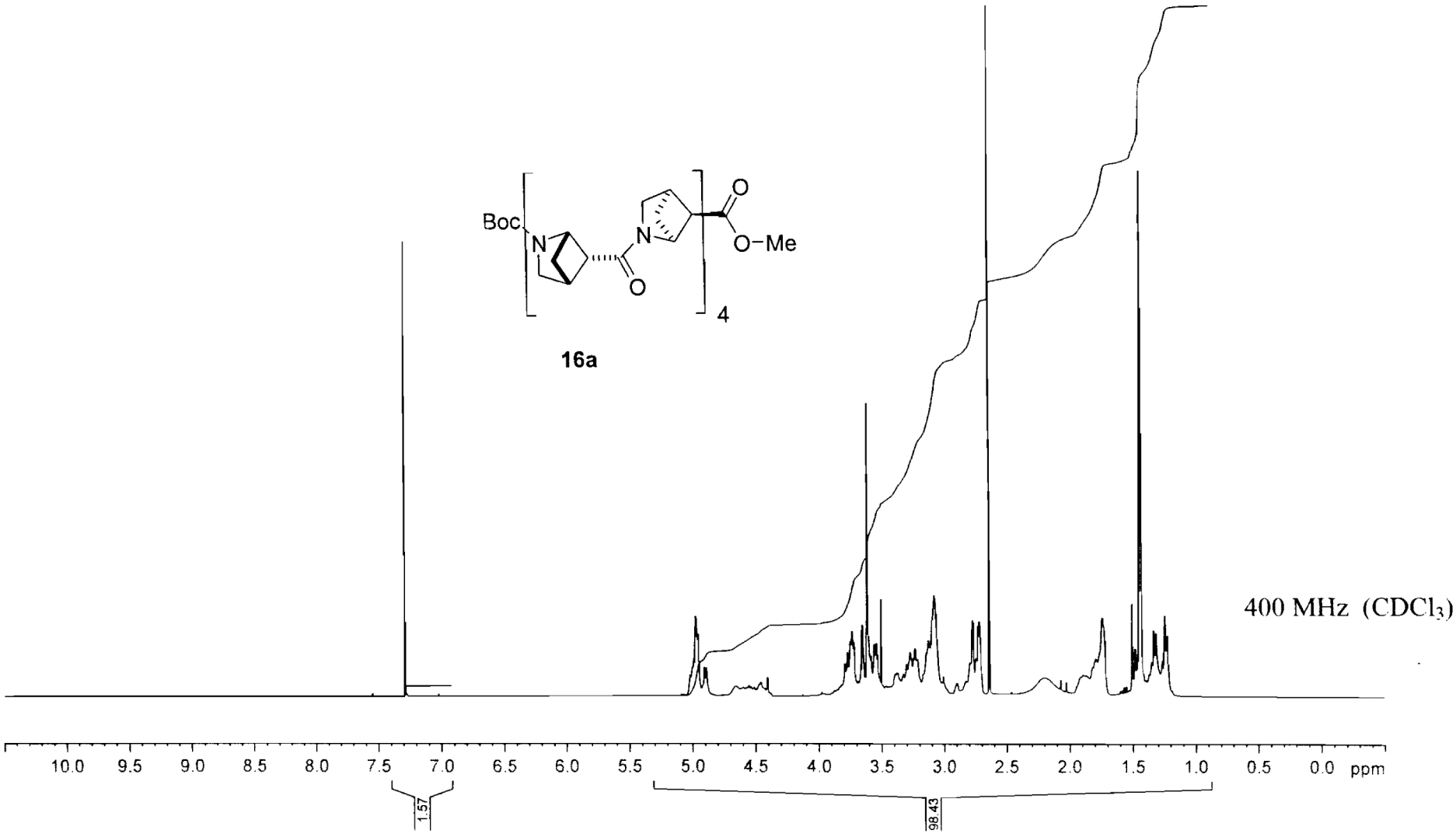

Boc
N
N
O
O
O
O−Me
3
15a
100 MHz (CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

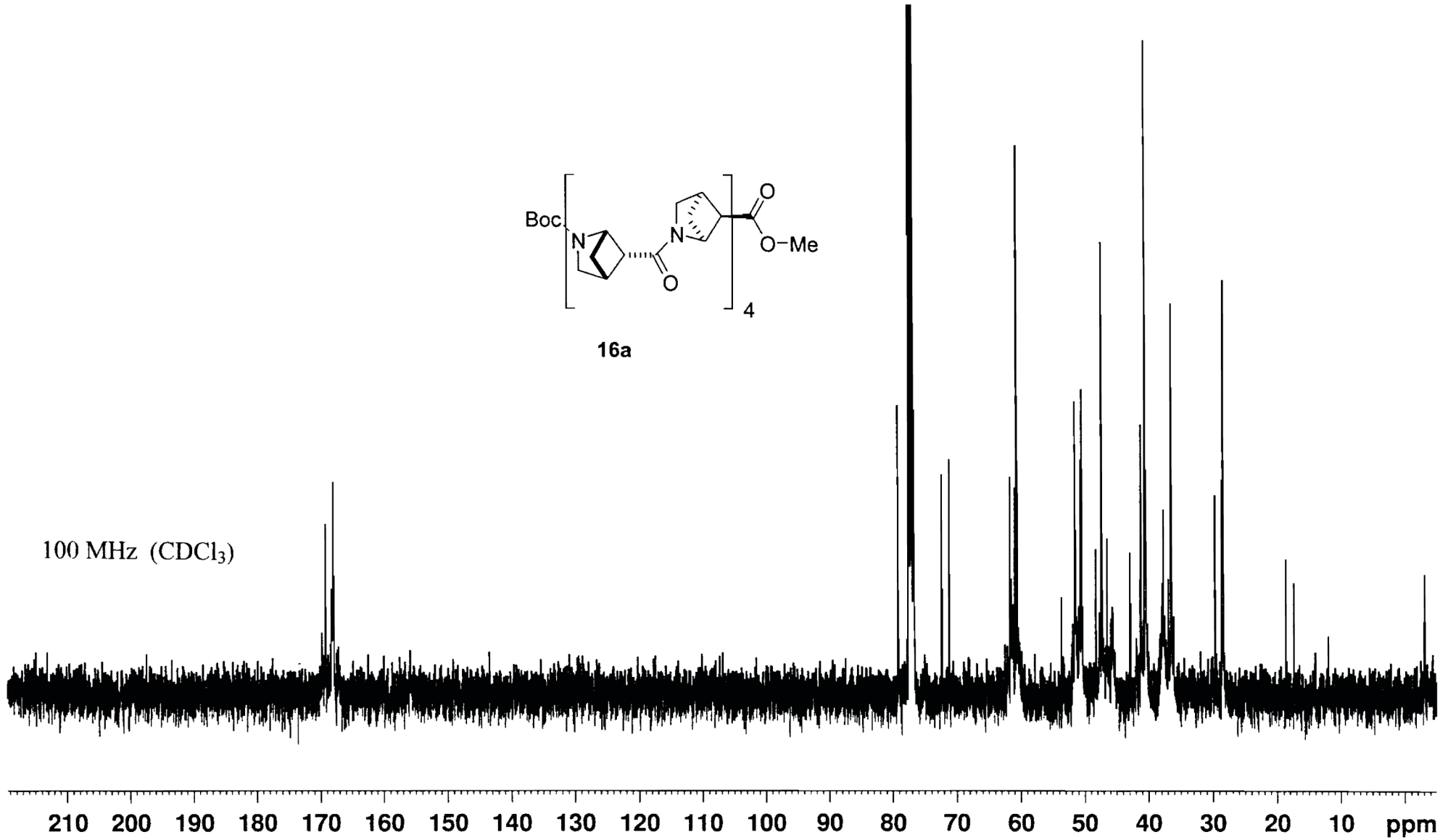

O
N
H
N
O
O
O-Me
3
15b
500 MHz (CDCl3)
1.00
0.58
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

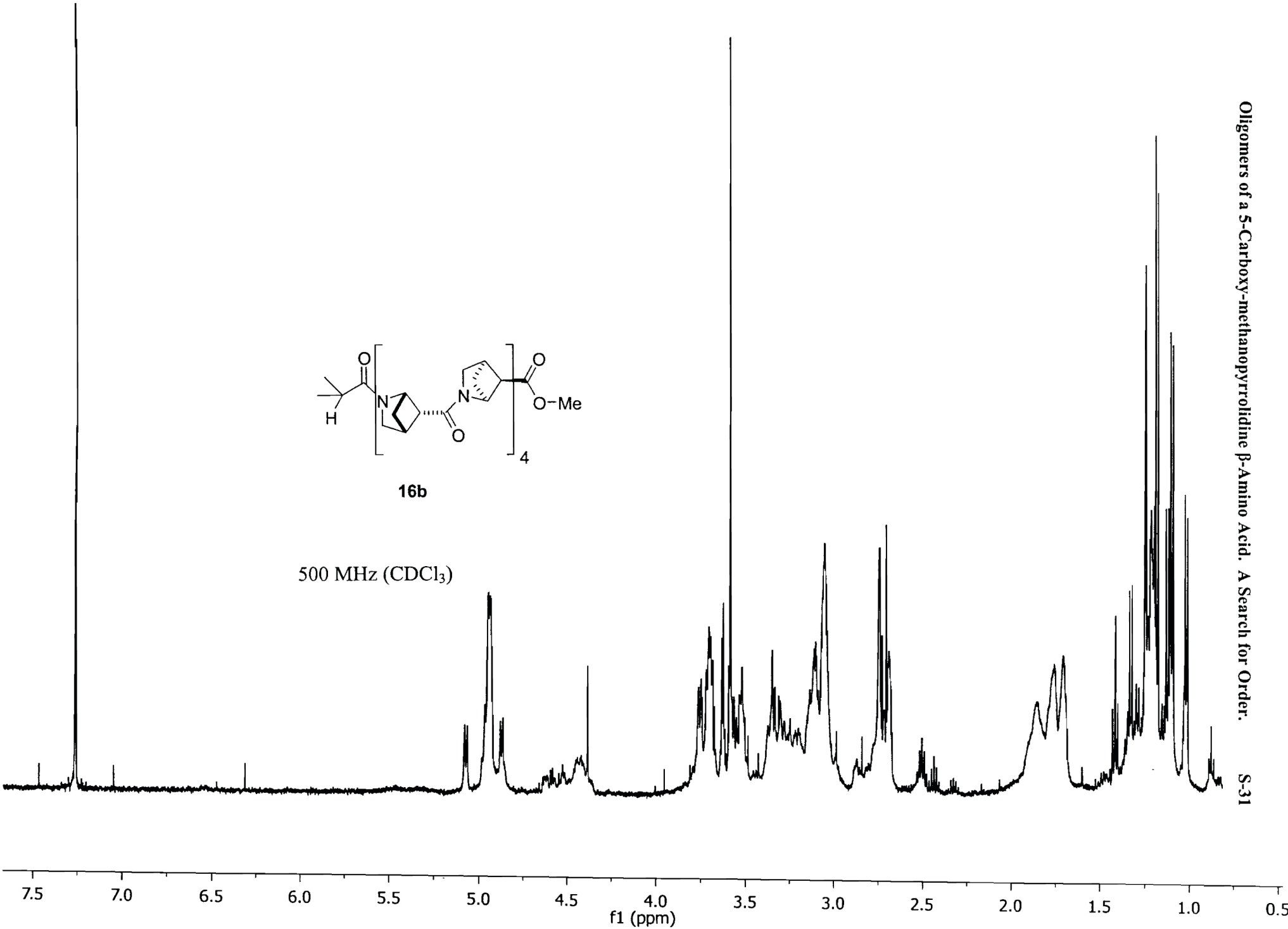
15b

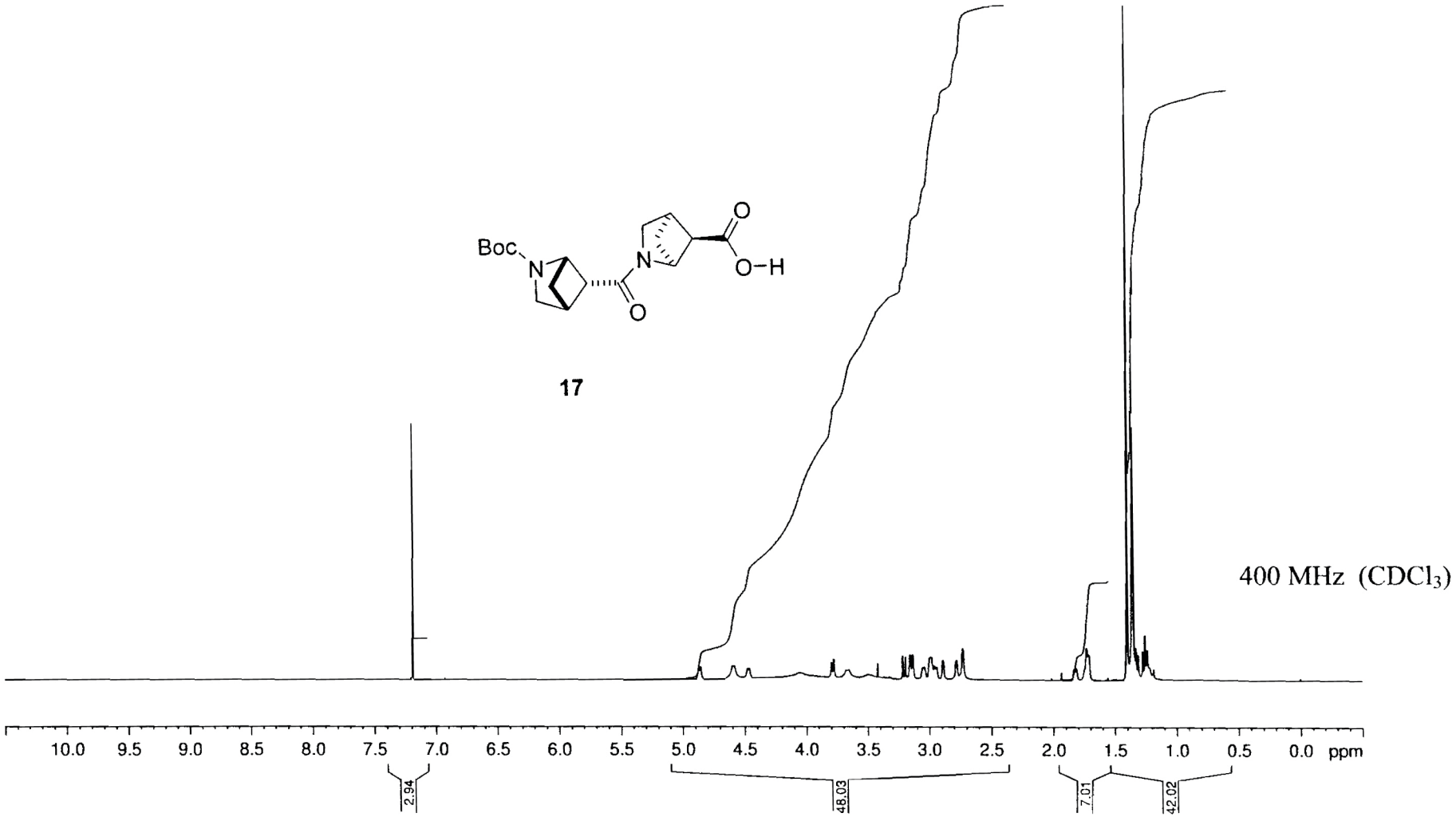
125 MHz ($CDCl_3$)

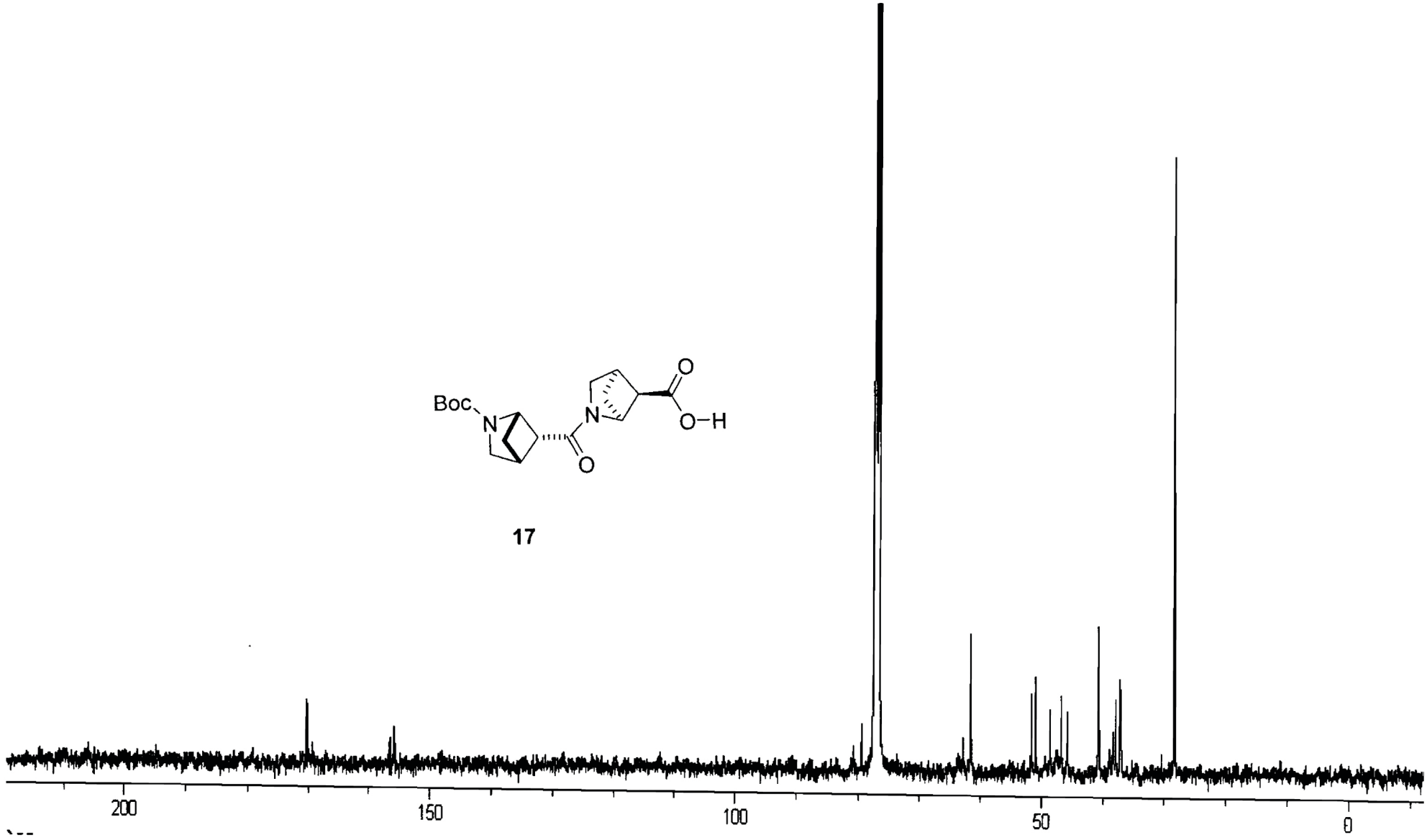



Boc
N
N
O
O
O
O−Me
4
16a
400 MHz (CDCl3)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.57
98.43

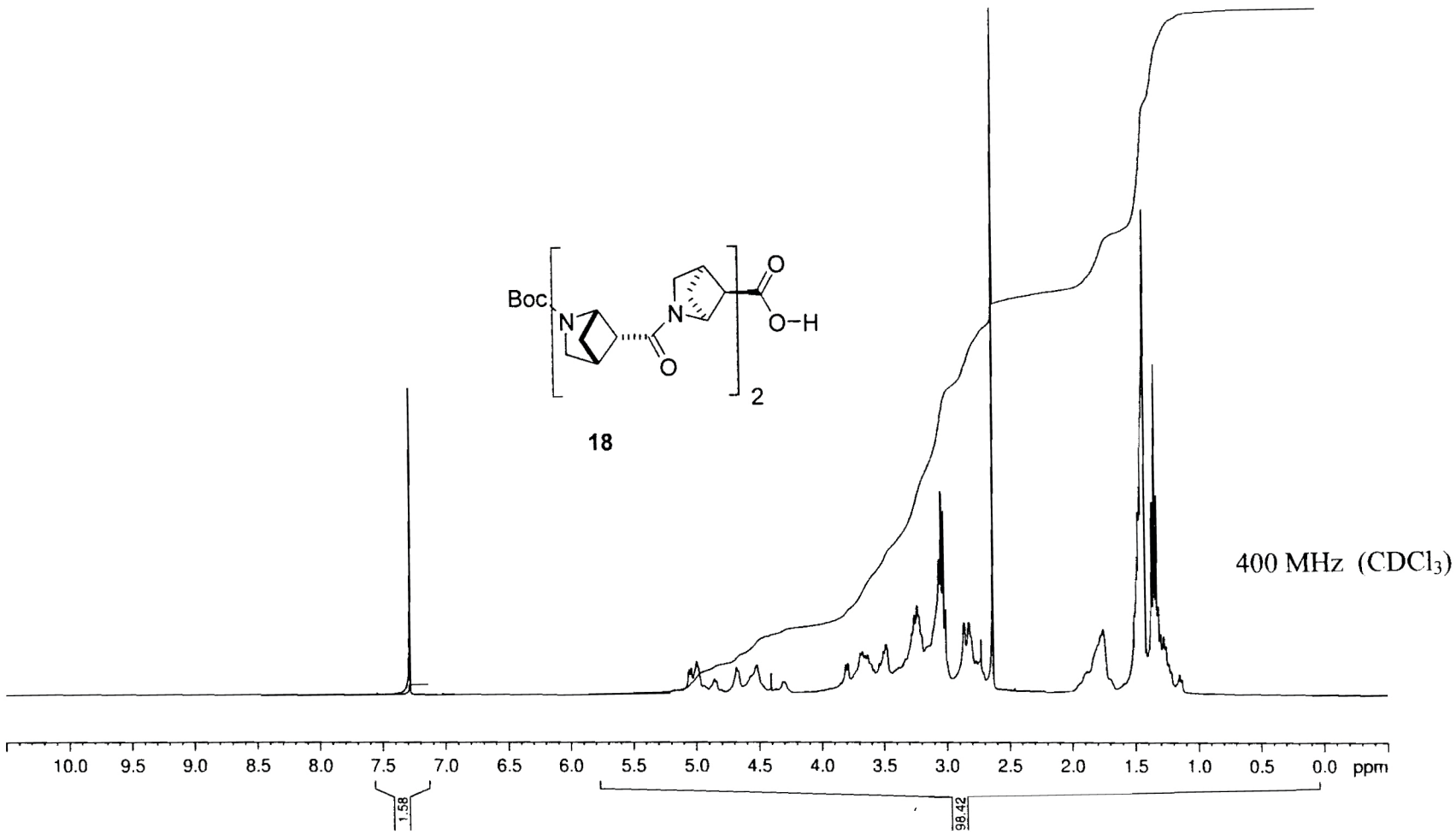

Boc
N
N
O
O
O
O−Me
4
16a
100 MHz (CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

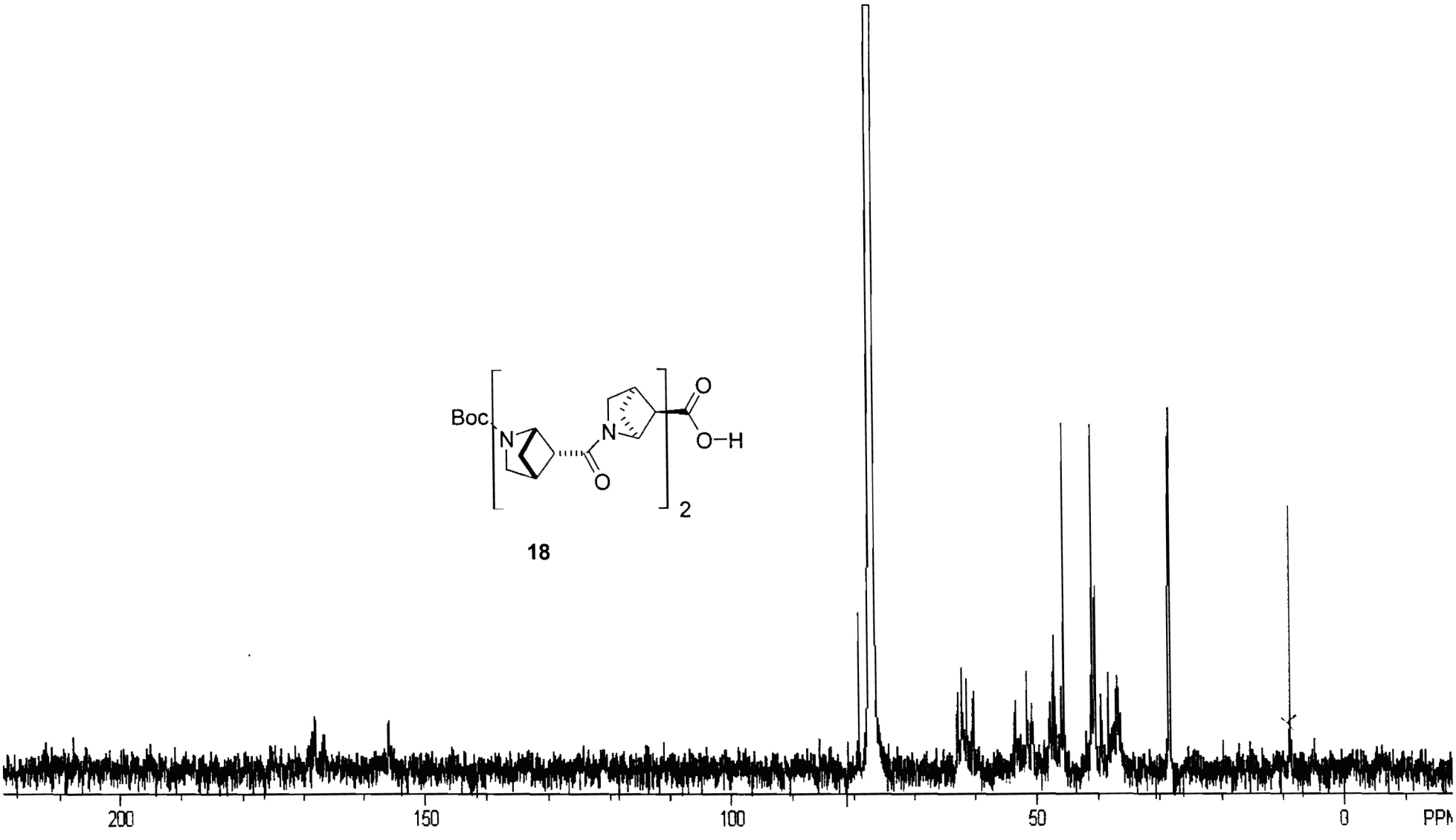

O
N
H
O
N
O
O
O-Me
4
16b
500 MHz (CDCl3)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Boc
N
N
O
O
O
O-H
17
400 MHz (CDCl3)
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 ppm
2.94
48.03
7.01
42.02



100 MHz ($CDCl_3$)


Boc
N
N
O
O
O
O−H
2
18
400 MHz (CDCl3)
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 ppm
1.58
98.42



100 MHz ($CDCl_3$)