Total Synthesis of (–)-Aplaminal

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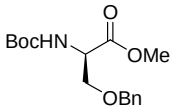
Supporting Information

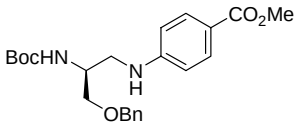
Materials and Methods: All solvents were reagent grade. Dichloromethane, tetrahydrofuran (THF), and toluene were filtered through activated alumina and copper purification system (Pure Solv. PS-400), while all reagents were purchased from Aldrich or Acros and used as received unless otherwise mentioned. Reactions were magnetically stirred under an argon atmosphere and monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040 - 0.062 mm) supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to either chloroform (δ 7.26), methanol (δ 3.31) or acetone (δ 2.05) for ^{1}H NMR and either chloroform (δ 77.23), or methanol (49.15) for ^{13}C NMR. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center.

Experimental Section.



(-)-**5**

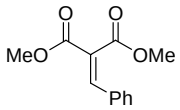
***N*-Boc-Serine methyl ester (–)-5.** To a solution of amino acid (-)-**SI 1** (2.95 g, 10 mmol) in CH_2Cl_2/MeOH (35 mL, 7/1) was added trimethylsilyldiazomethane (5.05 mL, 2.0 M in diethyl ether, 10.1 mmol) and the resultant solution was stirred for 0.5 h at room temperature. The mixtue was concentrated after the flask was open to air for 5 min and the residue was purified by flash chromatography (5:1 to 1:1 = hex: EtOAc) to give methyl ester (–)-**5** (3.06 g, 99%). $[\alpha]_D^{20}$ -15.0 (*c* 1.0, $CHCl_3$); IR (thin film, CH_2Cl_2) 3362 (br, w), 2977 (w), 1752 (s), 1715 (s), 1693 (s), 1499 (m), 1365 (m), 1165 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.29-7.25 (m, 3H), 5.39 (d, *J* = 8.1 Hz, 1H), 4.50 (ABq, *J* = 12.2 Hz, Δν = 28.4 Hz, 2H), 4.44-4.42 (m, 1H), 3.86 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, *J* = 9.4, 3.2 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 155.6, 137.7, 128.5, 127.9, 127.7, 80.1, 73.3, 70.1, 54.1, 52.5, 28.4; high resolution mass spectrum (ES+) *m/z* 332.1469 [$(M+Na)^+$; calcd for $C_{16}H_{23}NNaO_5$: 332.1474].



(-)-**3**

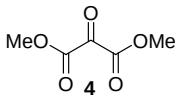
Diamine (–)-3. To a solution of methyl ester (–)-**5** (1.0 g, 3.24 mmol) in toluene (30 mL) was added DIBAL-H (6.5 mL, 1.0 M in hexanes, 6.5 mmol) slowly at -78 °C, maintaining an internal temperature below -70 °C. The mixture was stirred for additional 2 h at -78 °C before it was quenched by slowly adding MeOH (5 mL).

Then saturated Rochelle salt solution (30 mL) was added and the reaction was allowed to warm to room temperature. The mixture was stirred vigorously until the two layers were cleanly separated. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2X 50 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue dried on the vacuum. The crude aldehyde was taken forward without further purification. To a solution of the above aldehyde in MeOH (15 mL) was added methyl 4-aminobenzoate (489 mg, 3.24 mmol) and a few drops of acetic acid. The resultant mixture was stirred at room temperature for 24 h before the addition of $NaCNBH_3$ (529 mg, 8.4 mmol). After 6 h, water (10 mL) was added and the aqueous layer was extracted with diethyl ether (3X 30 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by flash chromatography (6:1 to 3:1 = hex: EtOAc) to provide diamine (–)-**3** (965 mg, 72% over two steps). $[\alpha]_D^{20}$ –10.6 (*c* 0.2, $CHCl_3$); IR (thin film, CH_2Cl_2) 3364 (br, w), 1698 (s), 1605 (s), 1280 (s), 1175 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.36-7.28 (m, 5H), 6.53 (d, *J* = 8.8 Hz, 2H), 5.29 (br s, 1H), 4.90 (br s, 1H), 4.48 (ABq, *J* = 11.9 Hz, Δν = 20.4 Hz, 2H), 3.99 (br s, 1H), 3.81 (s, 3H), 3.59-3.53 (m, 2H), 3.32 (br s, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 156.0, 152.1, 137.7, 131.5, 128.4, 127.9, 127.7, 117.9, 111.2, 79.6, 73.2, 69.8, 51.4, 49.6, 45.2, 28.3; high resolution mass spectrum (ES+) *m/z* 415.2225 $[(M+H)^+$; calcd for $C_{23}H_{31}N_2O_5$: 415.2233].



SI 2

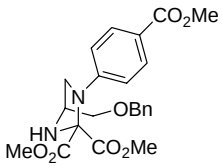
Dimethyl 2-benzylidenemalonate SI 2. To a solution of benzaldehyde (6.6 mL, 60 mmol) in DMSO (20 mL) was added proline (690 mg, 6.0 mmol) and the mixture was stirred for 5 min before the addition of dimethyl manolate (13.7 mL, 120 mmol). After stirring at room temperature for 24 h, the reaction was diluted with EtOAc (60 mL) and washed with water (2X 60 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by column to give dimethyl 2-benzylidenemalonate (12.9 g, 98%) as viscous oil, which is solidified standing in the refrigerator. Mp. 27-28 ºC. IR (thin film, CH_2Cl_2) 3002 (w), 2998 (m), 1731 (s), 1628 (m), 1436 (s), 1265 (s), 1221 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.74-7.34 (m, 5H), 3.84 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 164.7, 143.1, 132.9, 130.9, 129.6, 129.1, 125.7, 52.9s; high resolution mass spectrum (ES+) *m/z* 243.0667 $[(M+H)^+$; calcd for $C_{12}H_{12}O_4$: 243.0736].



4

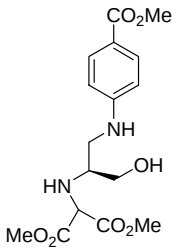
Dimethyl 2-oxomalonate 4. To a solution of dimethyl 2-benzylidenemalonate (4.0 g, 4.54 mmol) in CH_2Cl_2 (15 mL) was bubbled ozone at -78 °C until a dark blue solution was obtained. Excess ozone was removed by purging with argon for 10 min. Dimethyl sulfide (2 mL) was added to the mixture and the reaction was

warmed up slowly to room temperature. Then air was bubbled overnight and the mixture was concentrated and distilled (90-100 °C at 20 mm pressure) as a yellow liquid. The yellow liquid was then passed through a silica plug and eluted with diethyl ether. The solvent was removed and the residue was dehydrated by azeotropic removal of water by heating for 12 h in a Soxhlet apparatus equipped with a thimble filled with layers of basic alumina and phosphorous pentoxide. The solvent was finally removed and the residue was distilled under vacuum to give dimethyl 2-oxomalonate **4** (1.67 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 160.5, 53.9.



(+)-**6**

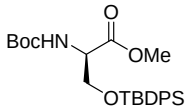
Imidazolidine (–)-6. To a solution of diamine **(–)-3** (300 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) was added TFA (1 mL, 13.4 mmol). The mixture was stirred at room temperature for 6 h and concentrated. The residue was dried over vacuum and the resulting amine was used directly in the next step. To the amine solution in CH_2Cl_2 (4 mL) was added $MgSO_4$ (300 mg) followed by the addition of dimethyl 2-oxomalonate **4** (118 mg, 0.72 mmol). The mixture was stirred at room temperature for 48 h and then concentrated. The residue was purified by flash chromatography (5:1 = toluene: EtOAc) to afford imidiazolidine (+)-**6** (224 mg, 70%) as a white solid. Mp. 94-95 ºC; $[\alpha]_D^{20}$ +35 (*c* 0.37, $CHCl_3$); IR (thin film, CH_2Cl_2) 3335 (br, w), 2951 (w), 1739 (s), 1709 (s), 1606 (s), 1283 (s), 1190 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.9 Hz, 2H), 7.36-7.30 (m, 5H), 6.72 (d, *J* = 8.9 Hz, 2H), 4.57 (s, 2H), 3.85 (s, 3H), 3.81-3.74 (m, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.67 (t, *J* = 7.8 Hz, 1H), 3.63 (dd, *J* = 9.5, 4.6 Hz, 1H), 3.58 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.49 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.2, 167.3, 148.2, 137.9, 130.8, 128.7, 128.0, 127.9, 113.8, 83.0, 73.7, 70.3, 55.7, 53.5, 52.0, 51.8; high resolution mass spectrum (ES+) m/z 465.1628 [(M+Na)+; calcd for $C_{23}H_{26}N_2NaO_7$: 465.1638]



(-)-**7**

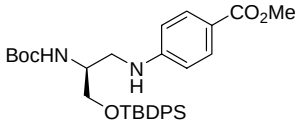
Amine (–)-7. To a solution of imidazolidine (+)-**6** (5.0 mg, 0.011 mmol) in EtOAc (1 mL) was $Pd(OH)_2/C$ (2 mg) under H_2 atmosphere (1 atm). The mixture was stirred at room temperature overnight and concentrated.

The residue was purified by flash chromatography (1:1 to 1:3 = hex: EtOAc) to afford amine (–)-**7** (3.0 mg, 75%). $[\alpha]_D^{20}$ -11.2 (*c* 0.2, $CHCl_3$); IR (thin film, CH_2Cl_2) 3371 (br, w), 2922 (w), 1737 (m), 1710 (m), 1605 (s), 1281 (s), 1176 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 4.93 (br s, 1H), 4,20 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.68 (dd, *J* = 11.5, 1.0 Hz, 1H), 3.57 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.31-3.21 (m, 2H), 1.15 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.4, 167.5, 152.0, 131.7, 118.8, 111.9, 62.9, 62.8, 57.2, 53.4, 53.4, 51.8, 44.6; high resolution mass spectrum (ES+) m/z 355.1518[(M+H)+; calcd for $C_{16}H_{23}N_2O_7$: 355.1505].



(-)-**9**

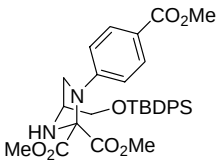
***N*-Boc-(D)-Serine methyl ester *tert*-butyldiphenylsilyl ether (–)-9.** To a solution of amino acid (–)-**8** (1.5 g, 7.3 mmol) in CH_2Cl_2/MeOH (28 mL, 7/1) was added trimethylsilyldiazomethane (3.7 mL, 2.0 M in diethyl ether, 7.4 mmol) and the resulting solution was stirred for 0.5 h at room temperature. The mixture was concentrated and the resultant methyl ester was used for the next step without further purification. To a solution of above methyl ester (1.6 g, 7.3 mmol) in DMF (12 mL) was added TBDPSCl (2.84 mL, 10.9 mmol) and imidazole (0.99 g, 14.6 mmol). The mixture was stirred at room temperature for 6 h before the addition of saturated NH_4Cl solution (30 mL). The mixture was extracted with diethyl ether (3 X 60 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (30:1 to 10: 1 = hex: EtOAc) to provide *tert*-butyldiphenylsilyl ether (–)-**9** (3.16 g, 95% over two steps) as viscous oil. $[\alpha]_D^{20}$ –14.3 (*c* 2.38, $CHCl_3$); IR (thin film, CH_2Cl_2) 3448 (br, w), 2954 (m), 2932 (m), 1751 (m), 1718 (s), 1498 (m), 1166 (s), 1113 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62-7.60 (m, 4H), 7.45-7.42 (m, 2H), 7.40-7.37 (m, 4H), 5.42 (d, *J* = 8.6 Hz, 1H), 4.41 (dd, *J* = 5.9, 2.9 Hz, 1H), 4.07 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.90 (dd, *J* = 10.1, 3.0 Hz, 1H), 3.75 (s, 3H), 1.47 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 155.6, 135.7, 135.7, 135.0, 133.2, 133.0, 130.1, 130.0, 130.0, 127.9, 80.1, 64.8, 55.7, 52.5, 28.5, 26.9, 26.8, 19.5; high resolution mass spectrum (ES+) *m/z* 480.2170 $[(M+Na)^+$; calcd for $C_{25}H_{35}NNaO_3Si^+$: 480.2182].



(-)-**10**

Diamine (–)-10. To a -78 ºC solution of methyl ester (–)-**9** (2.0 g, 4.4 mmol) in toluene (50 mL) was slowly added DIBAL-H (9.0 mL, 1.0 M in hexanes, 9.0 mmol), maintaining an internal temperature lower than -70 °C. The mixture was stirred for another 2 h at -78 °C after the completion of the addition before it was quenched by slowly adding MeOH (10 mL). Then saturated Rochelle salt solution (50 mL) was added and

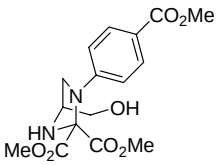
the reaction was allowed to warm to room temperature. The mixture was stirred vigorously until the two layers were cleanly separated. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2X 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was dried on the vacuum and was used for the next step without further purification. To the solution of the resulting aldehyde in MeOH (30 mL) was added methyl 4-aminobenzoate (660 mg, 4.4 mmol) and a few drops of acetic acid. The resulting solution was stirred at room temperature for 24 h before the addition of $NaCNBH_3$ (892 mg, 13.1 mmol). After 6 h water (10 mL) was added and the mixture was extracted with diethyl ether (3X 60 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by flash chromatography (8:1 to 3:1 = hex: EtOAc) to provide diamine (**–**)-**10** (1.85 g, 75%) as a white solid. Mp. 49-50 ºC; $[\alpha]_D^{20}$ –23 (*c* 0.9, $CHCl_3$); IR (thin film, CH_2Cl_2) 3370 (br, w), 2931 (w), 1706 (s), 1606 (s), 1280 (s), 1175 (s), 1113(s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 6.9 Hz, 2H), 7.51-7.39 (m, 6H), 6.45 (d, *J* = 8.1 Hz, 2H), 4.98 (d, *J* = 8.1 Hz, 1H), 4.37 (br s, 1H), 3.88 (br s, 1H), 3.84 (s, 3H), 3.80 (br s, 2H), 3.28-3.23 (m, 2H), 1.46 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 156.2, 152.0, 135.8, 135.7, 133.0, 132.9, 131.7, 130.3, 130.2, 128.2, 128.1, 118.4, 111.4, 80.0, 64.0, 51.7, 50.9, 45.4, 28.5, 27.2, 19.5; high resolution mass spectrum (ES+) *m/z* 563.2924 [$(M+H)^+$; calcd for $C_{32}H_{43}N_2O_7Si$: 563.2941].



(+)-**11**

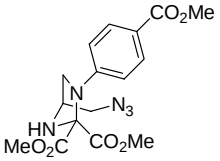
Imidazolidine(+)-11. To a solution of diamine (–)-**10** (400 mg, 0.71 mmol) in CH_2Cl_2 (8 mL) was added TFA (2 mL mL, 26.8 mmol). The solution was stirred at room temperature for 6 h, and azeotropied with toluene (3X 3 mL). The residue was dissolve in CH_2Cl_2 (5 mL) and Na_2SO_4 (400 mg) was added followed by the addition dimethyl 2-oxamonate **4** (116 mg, 0.71 mmol). The mixture was stirred for 48 h and then concentrated. The residue was purified by flash chromatography (6:1 to 3:1 = hex: EtOAc) to afford imidazolidine (+)-**11** (280 mg, 66%) as a white solid along with recovered dimethyl 2-oxamonate and amine. Fractions containing of dimethyl 2-oxamonate and amine were concentrated and the procedure repeated to give additional portion of imidazolidine (+)-**11** (55 mg, 14%, total yield 80%). Mp. 138-139 ºC; $[\alpha]_D^{20}$ +19.8 (*c* 0.71, $CHCl_3$); (thin film, CH_2Cl_2) 3334 (br, w), 2952 (m), 1740 (s), 1711 (s), 1607 (s), 1283 (s), 1190 (s), 1113 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.9 Hz, 2H), 7.67-7.65 (m, 4H), 7.47-7.43 (m, 2H), 7.42-7.38 (m, 4H), 6.71 (d, *J* = 8.9 Hz, 2H), 3.90-3.86 (partially observed, m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.77 (dd, *J* = 10.5, 4.3 Hz, 1H), 3.73 (s, 3H), 3.66-3.62 (m, 1H), 3.59 (t, *J* = 7.2 Hz, 1H), 3.51 (t, *J* = 7.8 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 169.0, 167.4, 148.3, 135.8, 135.8, 133.1, 133.0,

130.9, 130.2, 128.0, 119.8, 113.8, 83.2, 63.1, 57.4, 53.5, 51.9, 51.4, 27.0, 19.5; high resolution mass spectrum (ES+) *m/z* 591.2507 [$(M+H)^+$; calcd for $C_{32}H_{39}N_2O_7Si$: 591.2527].



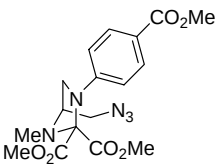
(+)-**2**

Alcohol (+)-2. To a solution of imidazolidine (+)-**11** (400 mg, 0.578 mmol) in THF (12 mL) was added TBAF-HOAc (1 M in THF, 0.8l mL, 0.81 mmol). The resulting mixture was stirred at room temperature for 2 h and then concentrated. The residue was purified by flash chromatography (1:1 to 1:3 = hex: EtOAc) to give alcohol (+)-**2** (202 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +103.1 (*c* 0.64, $CHCl_3$); IR (thin film, CH_2Cl_2) 3366 (br, w), 2952 (w), 1738 (s), 1707 (s), 1606 (s), 1520 (m), 1435 (m), 1284 (s),1191 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.76-3.71 (partially observed, m, 2H), 3.72 (s, 3H), 3.68-3.62 (m, 2H), 3.52 (t, *J* = 7.0 Hz, 1H), 2.79 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.7, 167.4, 148.1, 130.8, 119.9, 113.8, 82.9, 63.3, 56.9, 53.5, 53.5, 51.8, 51.0; high resolution mass spectrum (ES+) *m/z* 353.1346 [$(M+H)^+$; calcd for $C_{16}H_{21}N_2O_7^+$: 353.1349].



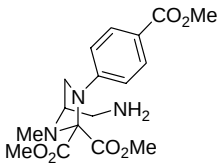
(+)-**12**

Azide (+)-12. To a solution alcohol (+)-**2** (120 mg, 0.34 mmol) in THF (10 mL) at 0 ºC was added PPh_3 (267 mg, 1.022 mmol) and diisopropyl azodicarboxylate (0.20 mL, 1.022 mmol). After stirring for 5 min, diphenylphosphoryl azide (0.22 mL, 1.022 mmol) was added. The mixture was slowly warmed up to room temperature and stirred over for 12 h. The volatile solvent was removed and the residue was purified by flash chromatography (8:1 to 2:1 = hex: EtOAc) to give azide (+)-**12** (90 mg, 70%) as a viscous oil. $[\alpha]_D^{20}$ +105.0 (*c* 0.48, $CHCl_3$); IR (thin film, CH_2Cl_2) 3366 (br, w), 2953 (w), 2104 (s), 1739 (s), 1709 (s), 1606 (s), 1284 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78-3.75 (partially observed, m, 1H), 3.76 (s, 3H), 3.72 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.67 (d, *J* = 6.3 Hz, 1H), 3.49 (d, *J* = 5.7 Hz, 1H), 3.46 (dd, *J* = 8.2, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.3, 167.2, 147.9, 130.8, 120.3, 114.0, 82.6, 55.3, 53.5, 53.5, 53.3, 52.3, 51.8; high resolution mass spectrum (ES+) *m/z* 378.1420 [$(M+H)^+$; calcd for $C_{16}H_{20}N_5O_6^+$: 378.1414].



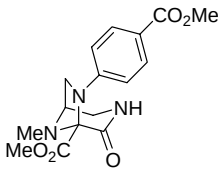
(+)-**13**

Azide (+)-13. To a solution of azide (+)-**12** (70 mg, 0.186 mmol) in CH_2Cl_2 (5.0 mL) was added K_2CO_3 (363 mg, 3.71 mmol) and MeOTf (0.12 mL, 1.10 mmol). The mixture was stirred at room temperature for 24 h before the addition of water (5.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3X 5.0 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (6:1 to 3:1 = hex: EtOAc) to give azide (+)-**13** (69 mg, 96%) as a viscous oil. $[\alpha]_D^{20}$ +123.2 (*c* 0.46, $CHCl_3$); IR (thin film, CH_2Cl_2) 2952 (w), 2102 (s), 1752 (s), 1709 (s), 1607 (s), 1283 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.80 (t, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.65 (t, *J* = 7.8 Hz, 1H), 3.59-3.56 (m, 1H), 3.53 (d, *J* = 5.2 Hz, 1H), 3.30 (dd, *J* = 12.4, 2.7 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 167.3, 167.3, 147.5, 131.1, 119.8, 112.7, 84.5, 61.5, 53.1, 52.6, 51.9, 51.1, 50.8, 34.0; high resolution mass spectrum (ES+) *m/z* 392.1576 $[(M+H)^+$; calcd for $C_{17}H_{22}N_5O_6^+$: 392.1570].



(+)-**14**

Amine (+)-14. To a solution of azide (+)-**13** (69 mg, 0.176 mmol) in EtOAc (5 mL) was added $Pd(OH)_2/C$ (10%, 10 mg). The mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 3 hr and filtrated through Celite. The filtrate was concentrated and the residue was purified by flash chromatography (50: 1 to 20:1= CH_2Cl_2: MeOH) to give amine (+)-**14** (58 mg, 90%) as an oil. $[\alpha]_D^{20}$ +72.0 (*c* 0.075, $CHCl_3$); IR (thin film, CH_2Cl_2) 3389 (br, w), 2952 (w), 1750 (s), 1706 (s), 1606 (s), 1284 (s), 1190 (s) cm^{-1}; 7.87 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H), 3.80-3.77 (partially observed, m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (t, *J* = 8.0 Hz, 1H), 3.44-3.40 (m, 1H), 2.95-2.88 (m, 2H), 2.51 (s, 3H), 2.41 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 167.7, 167.3, 147.7, 131.0, 119.5, 112.6, 84.8, 62.8, 53.0, 52.4, 51.8, 50.6, 40.8, 33.7; high resolution mass spectrum (ES+) *m/z* 366.1656 $[(M+H)^+$; calcd for $C_{17}H_{24}N_3O_6^+$: 366.1665].



(-)-**1**

Aplaminal (-)-1. To a solution of amine (+)-**14** (10 mg, 0.030 mmol) in toluene (3.0 mL) was added $AlMe_3$ (1.8 M in hexane, 20 μL, 0.036 mmol). The resulting solution was heated at 100 ºC for 15 h and another portion of $AlMe_3$ (10 μL, 0.018 mmol) was added. The mixture was continued stirring for additional 6 h and concentrated. The residue was purified on preparative TLC (20:1 = CH_2Cl_2: MeOH) to give aplaminal (6.0 mg, 66%) as a white solid. Mp. 233-235 ºC (decomposed) $[\alpha]_D^{20}$ –132.7 (*c* 0.04, MeOH); IR (thin film, CH_2Cl_2) 3389 (br, w), 1750 (s), 1684 (s), 1604 (s), 1277 (s), 1190 (s) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ

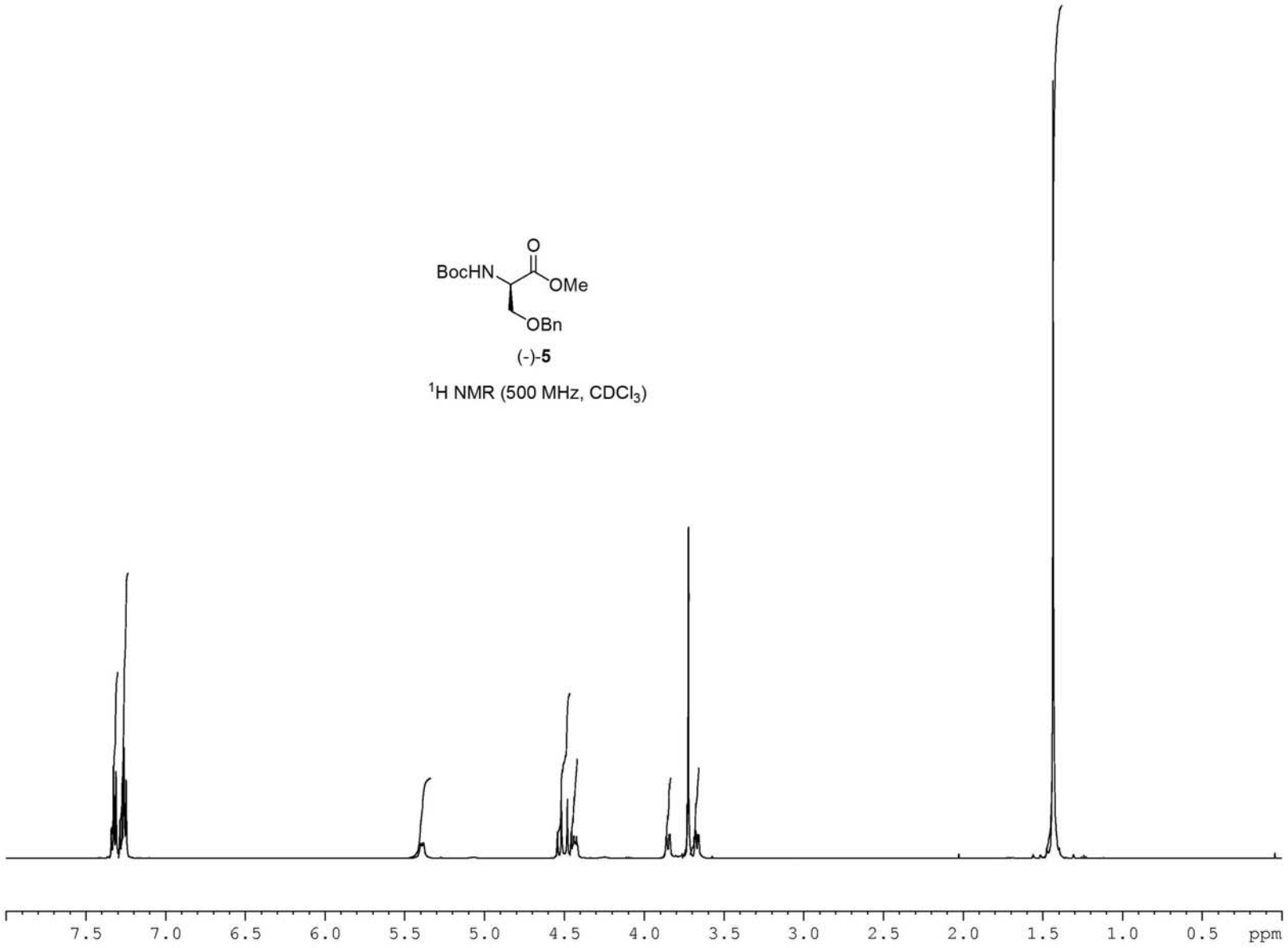
7.80 (dd, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 4.24 (ddd, *J* = 9.2, 5.7, 1.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75 (t, *J* = 5.0 Hz, 1H), 3.64 (ddd, *J* = 12.0, 4.4, 1.5 Hz, 1H), 3.34 (d, *J* = 9.3 Hz, 1H), 3.17 (d, *J* = 11.3 Hz, 1H), 2.47 (s, 3H); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.77 (dd, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 6.62 (br s, 1 H), 4.27 (ddd, *J* = 9.1, 5.7, 1.5 Hz, 1H), 3.86-3.76 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.67 (dd, *J* = 11.2, 4.5 Hz, 1H), 3.37 (d, *J* = 9.2 Hz, 1H), 3.24 (ddd, *J* = 11.1, 11.1, 1.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.1, 167.1, 167.0, 150.8, 131.3, 120.4, 116.4, 86.7, 59.1, 54.0, 53.4, 52.3, 47.6, 38.1; high resolution mass spectrum (ES+) *m/z* 356.1205 [$(M+Na)^+$; calcd for $C_{16}H_{19}N_3NaO_5^+$: 356.1222].

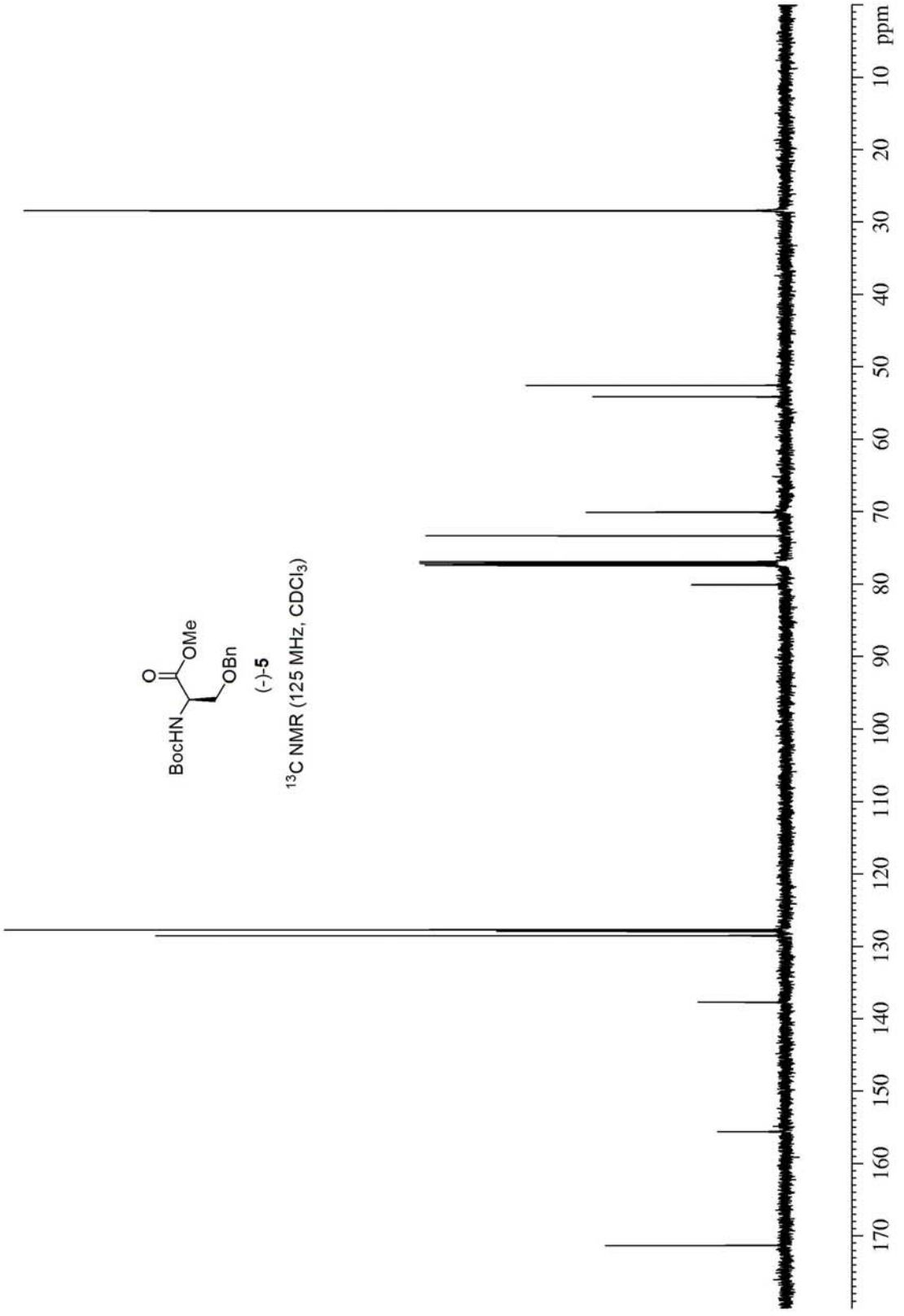
Comparison of the ^{1}H NMR spectra of the natural and synthesized (-)-Aplaminal

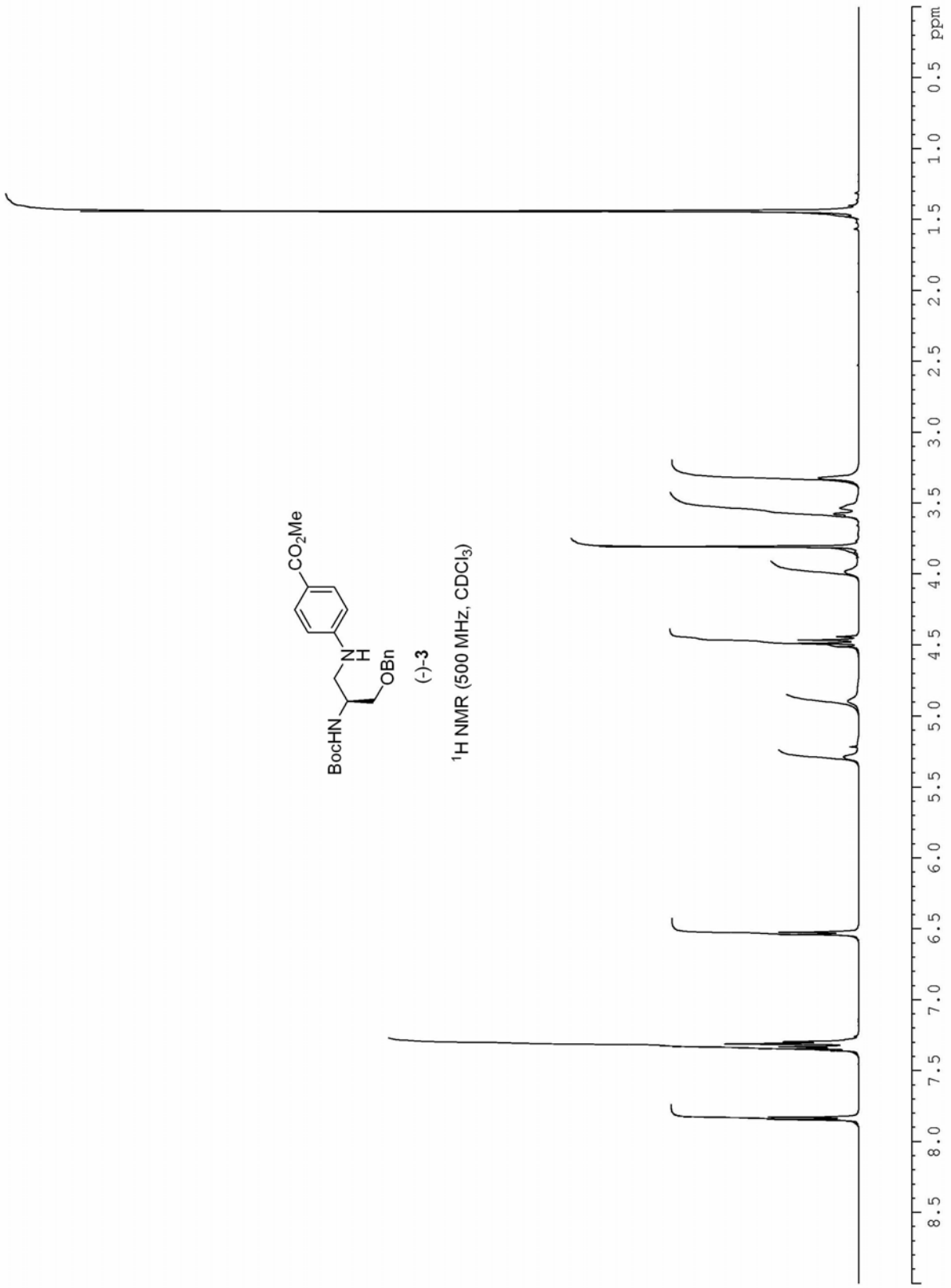
^{1}H in d_6-acetone	natural	Smith	Δδ (ppm)
10, 12	7.76 (d, *J* = 9.1 Hz, 2H)	7.77 (d, *J* = 9.1 Hz, 2H)	0.01
9,13	6.85 (d, *J* = 9.1 Hz, 2H)	6.86 (d, *J* = 9.1 Hz, 2H)	0.01
^{1}N-H	6.62 (br, s 1H)	6.62 (br, s 1H)	0
4	4.26 (ddd, *J* = 9.1, 5.7, 1.5 Hz, 1H)	4.27 (ddd, *J* = 9.1, 5.7, 1.5 Hz, 1H)	0.01
5	3.85-3.75 (m, 1H)	3.86-3.76 (m, 1H)	0.01
5’	3.66 (m, 1H)	3.67 (dd, *J* = 11.2, 4.5 Hz, 1H)	0.01
OMe	3.79 (s, 3H), 3.78 (s, 3H)	3.80 (s, 3H), 3.79 (s, 3H)	0.01
3	3.36 (d, *J* = 9.2 Hz, 1H)	3.37 (d, *J* = 9.2 Hz, 1H)	0.01
3’	3.23 (ddd, *J* = 11.1, 11.1, 1.2 Hz, 1H)	3.24 (ddd, *J* = 11.1, 11.1, 1.2 Hz, 1H)	0.01
N-Me	2.46 (s, 3H)	2.47 (s, 3H)	0.01

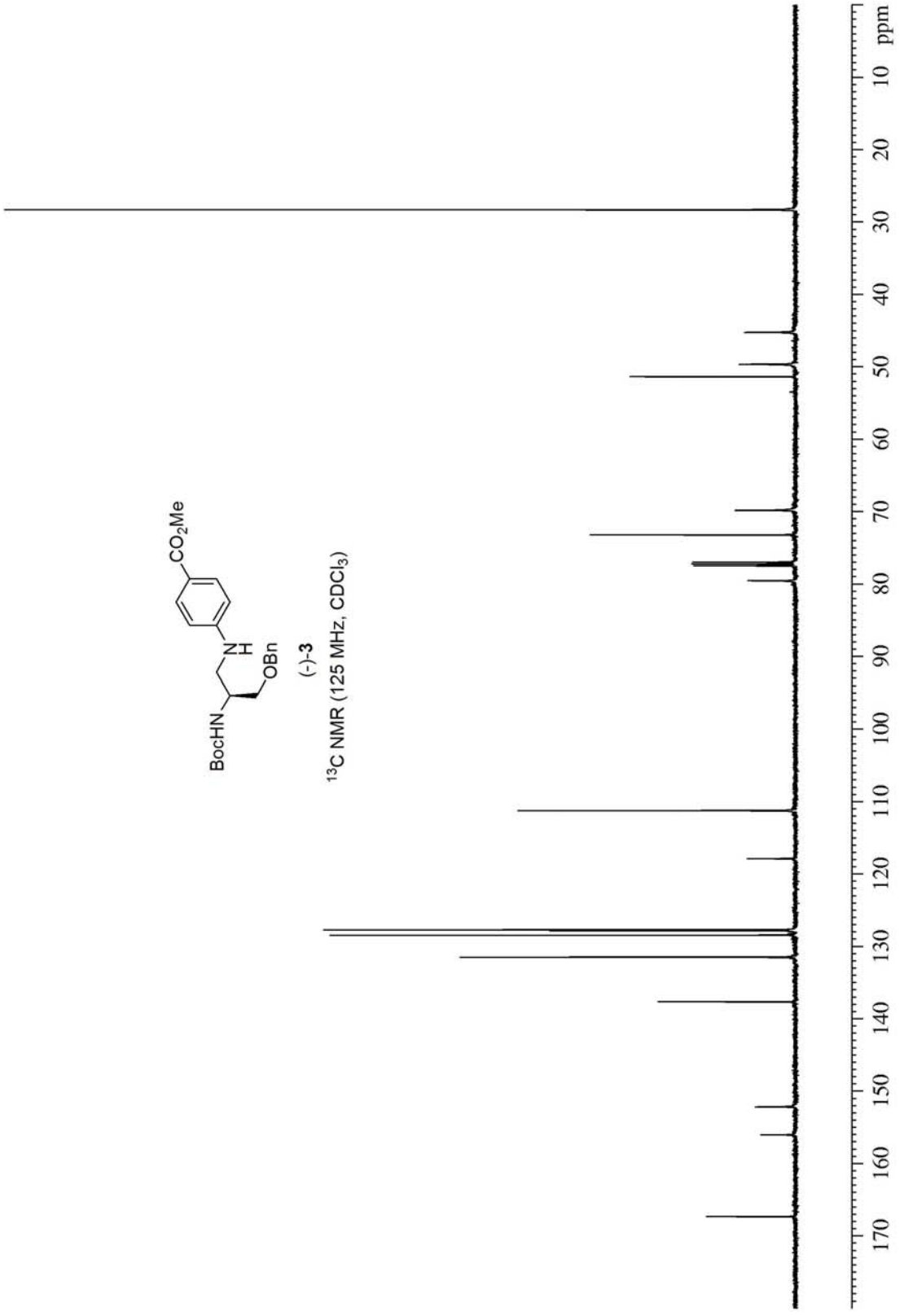
Comparison of the ^{13}C NMR spectra of the natural and synthesized (-)-Aplaminal

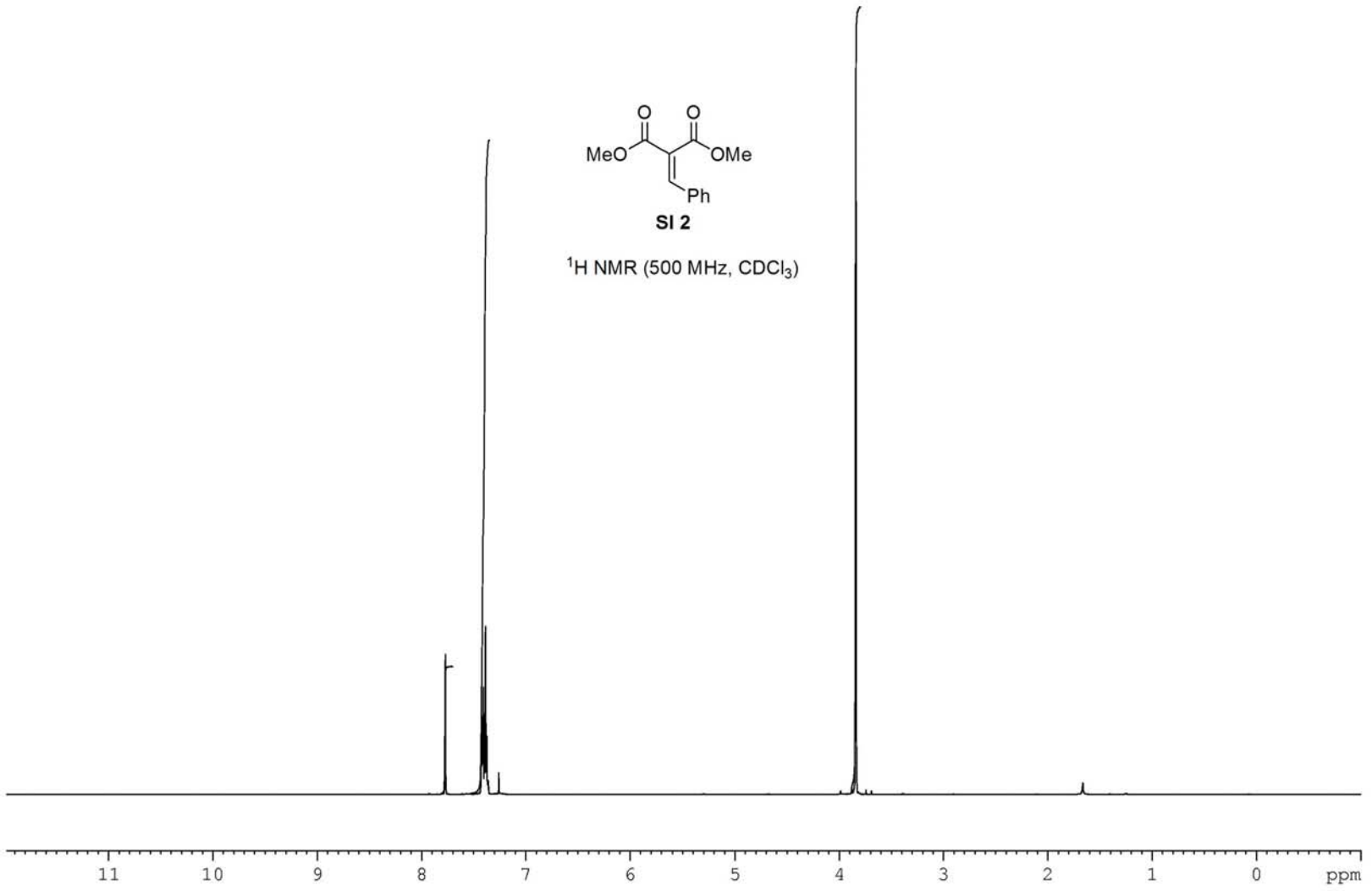
^{13}C in CD_3OD	natural	Smith	Δδ (ppm)
14	168.95	169.12	0.17
2	166.90	167.07	0.17
6	166.81	166.97	0.17
8	150.69	150.84	0.15
10,12	131.12	131.27	0.15
11	120.24	120.42	0.18
1,9	116.20	116.35	0.15
1	86.52	86.68	0.16
4	58.97	59.13	0.16
5	53.84	54.01	0.17
7	53.33	53.46	0.13
15	52.14	52.28	0.14
3	47.40	47.55	0.15
16	38.96	39.09	0.13

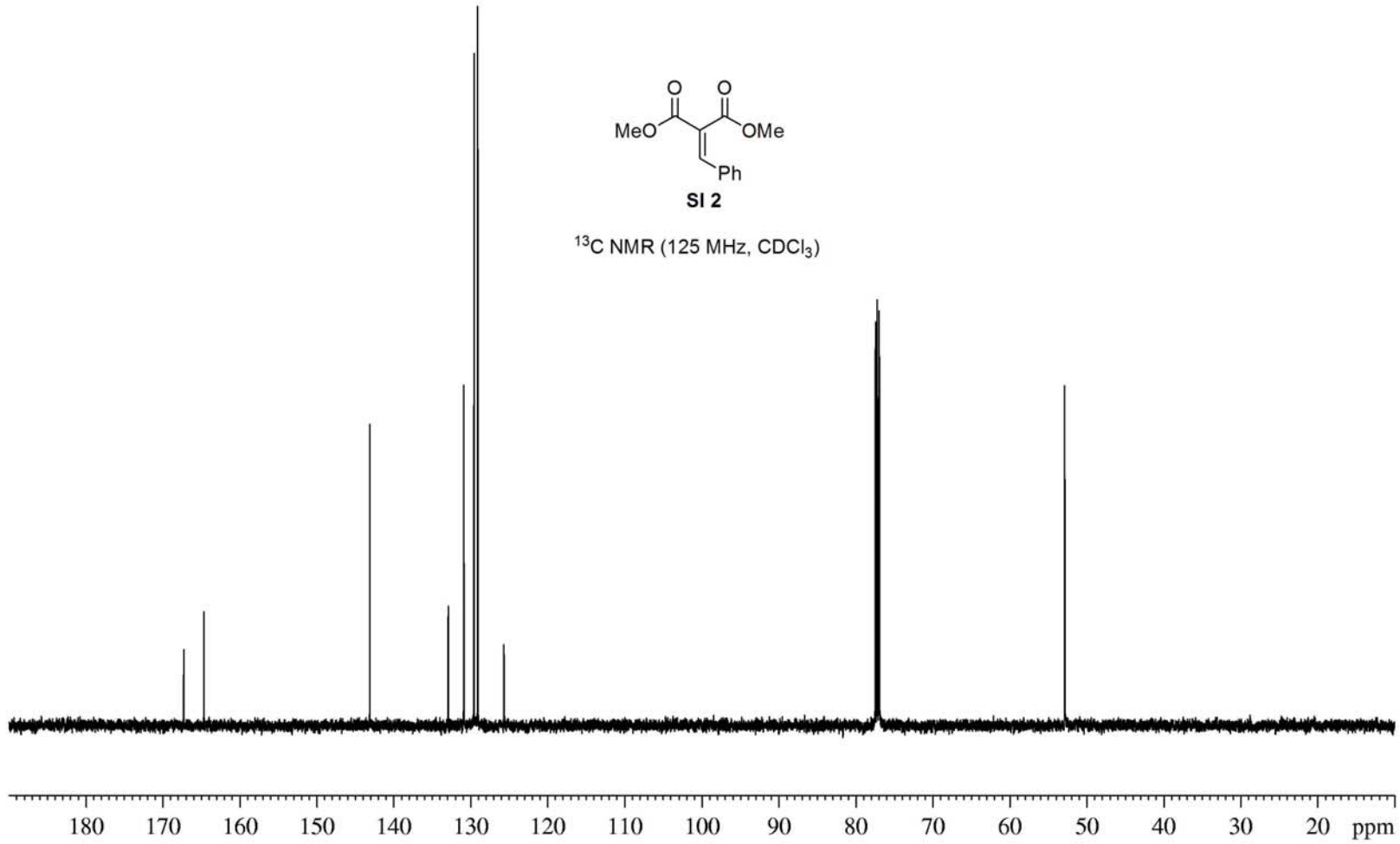

BocHN
O
OMe
OBn
(-)-5
1H NMR (500 MHz, CDCl3)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

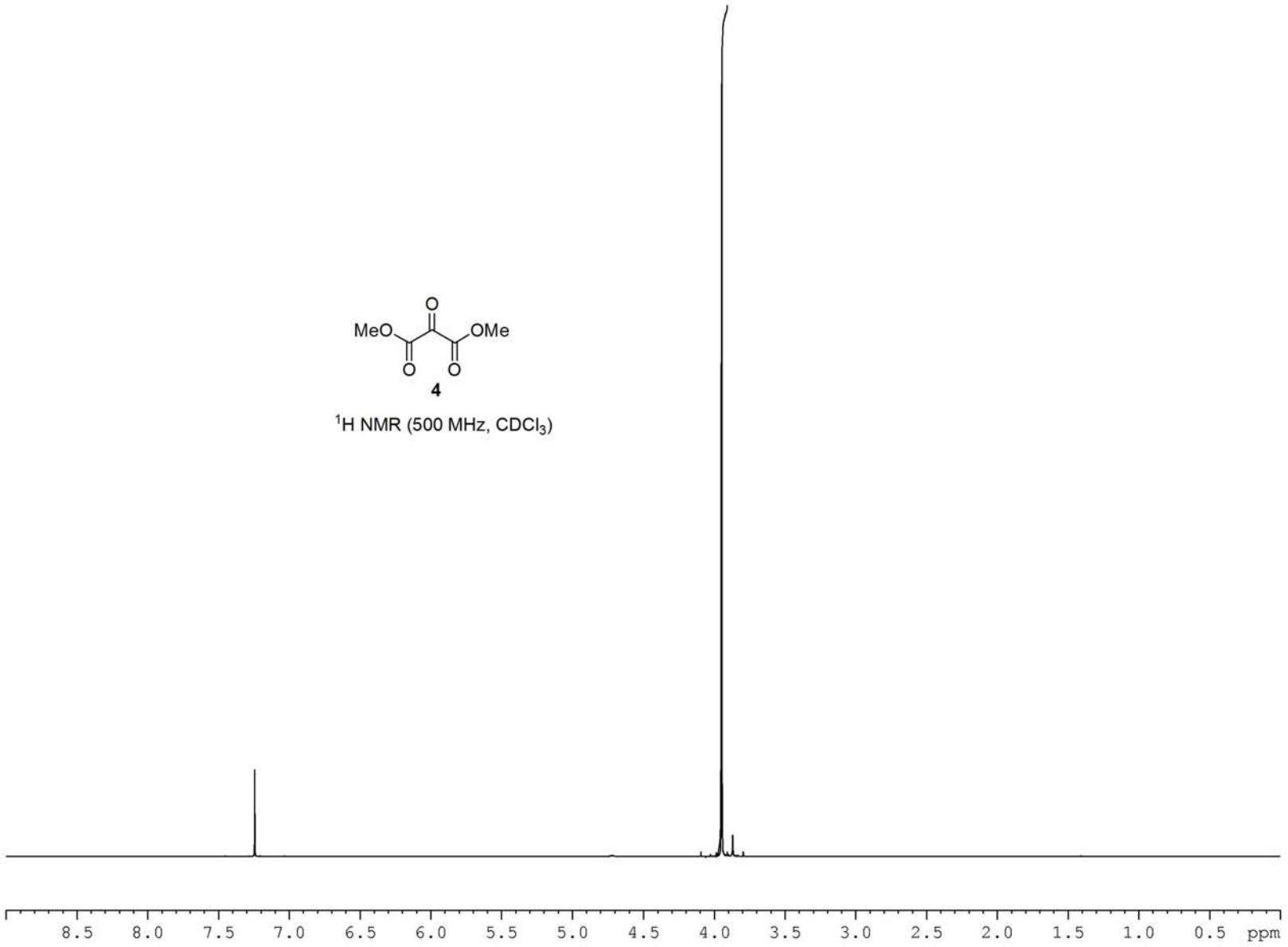

BocHN
O
OMe
OBn
(-)-5
^{13}C NMR (125 MHz, $CDCl_3$)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

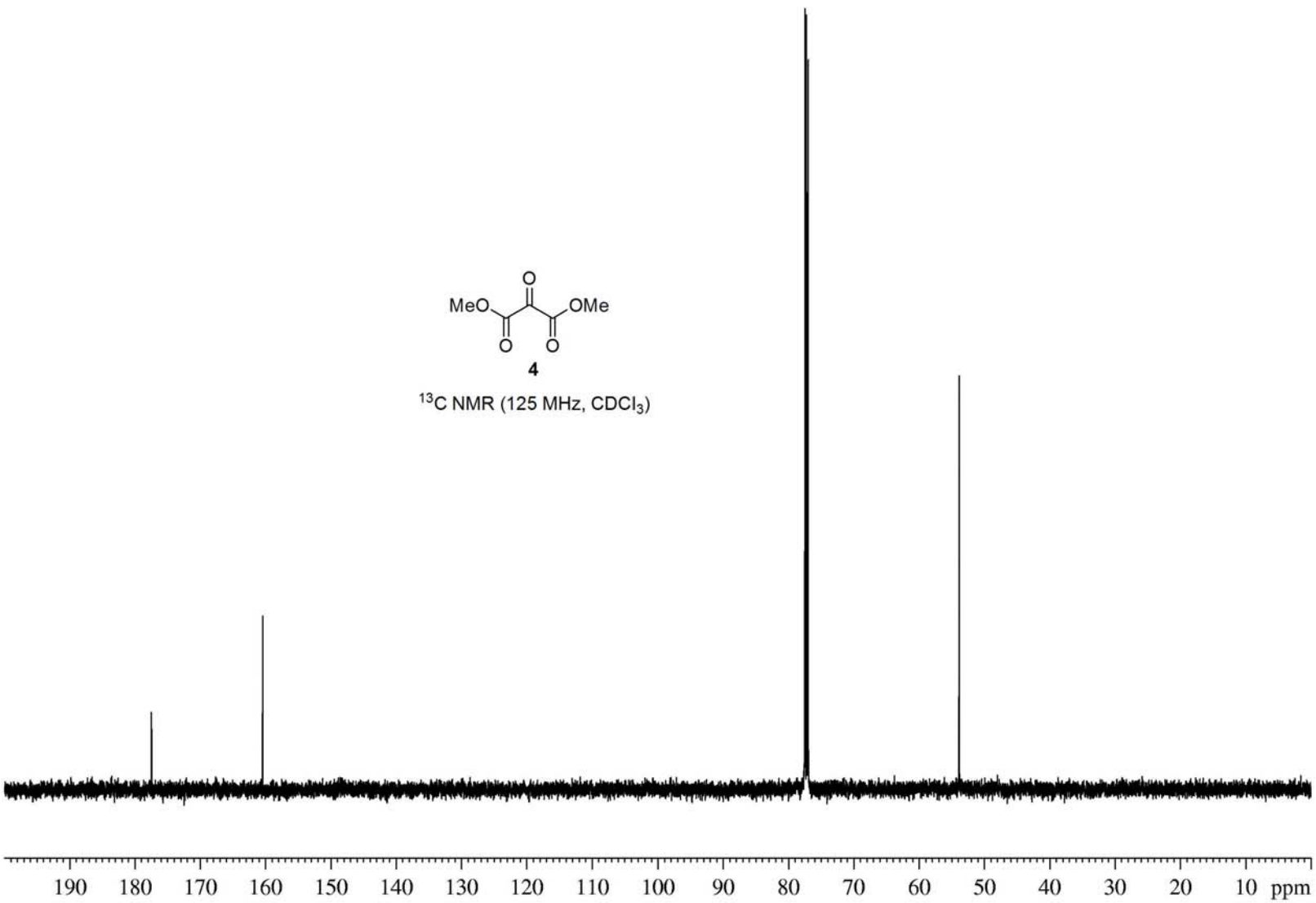

CO2Me
BocHN
N
H
OBn
(-)-3
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

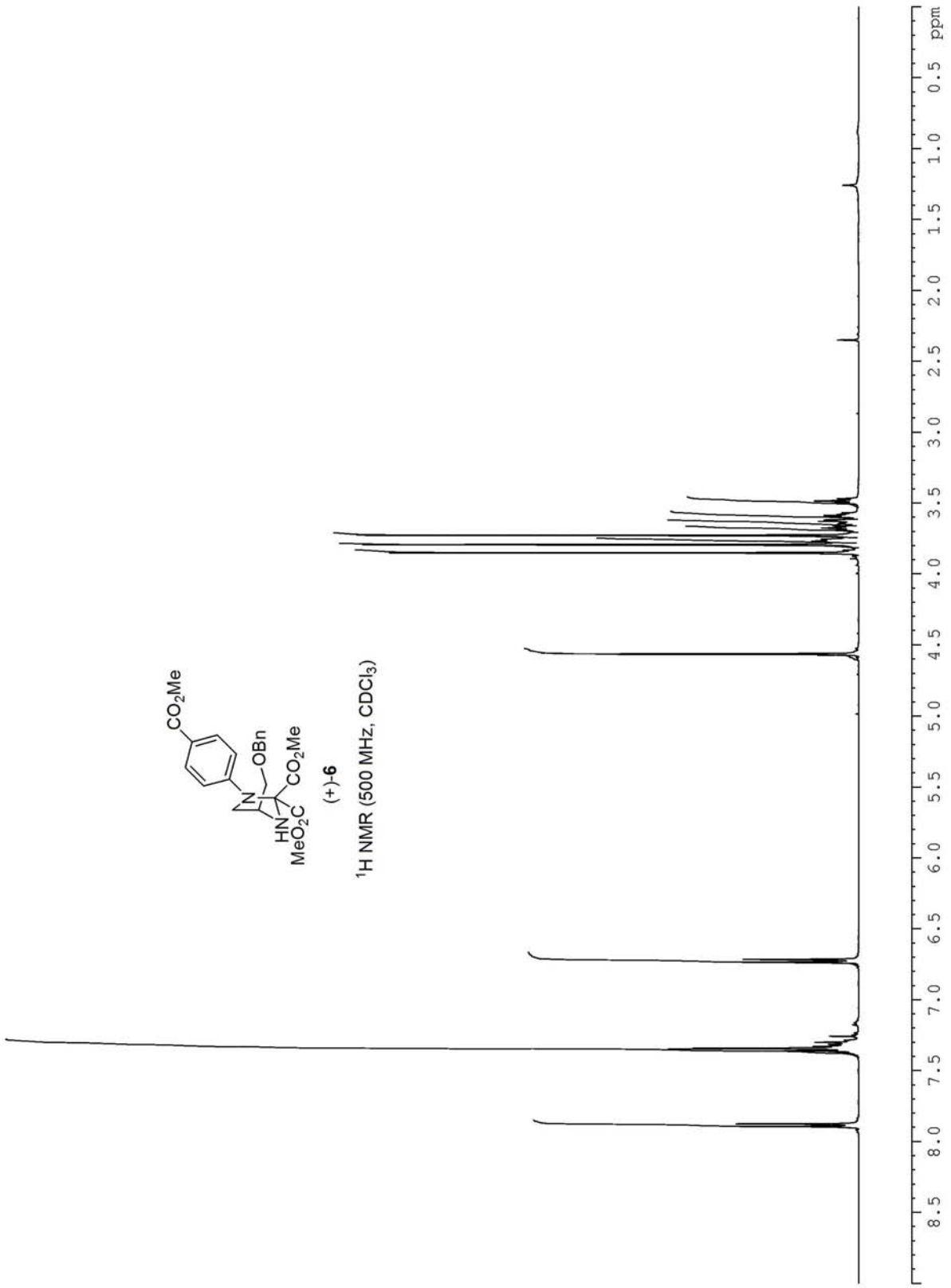

CO2Me
N
H
OBn
BocHN
(-)-3
13C NMR (125 MHz, CDCl3)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

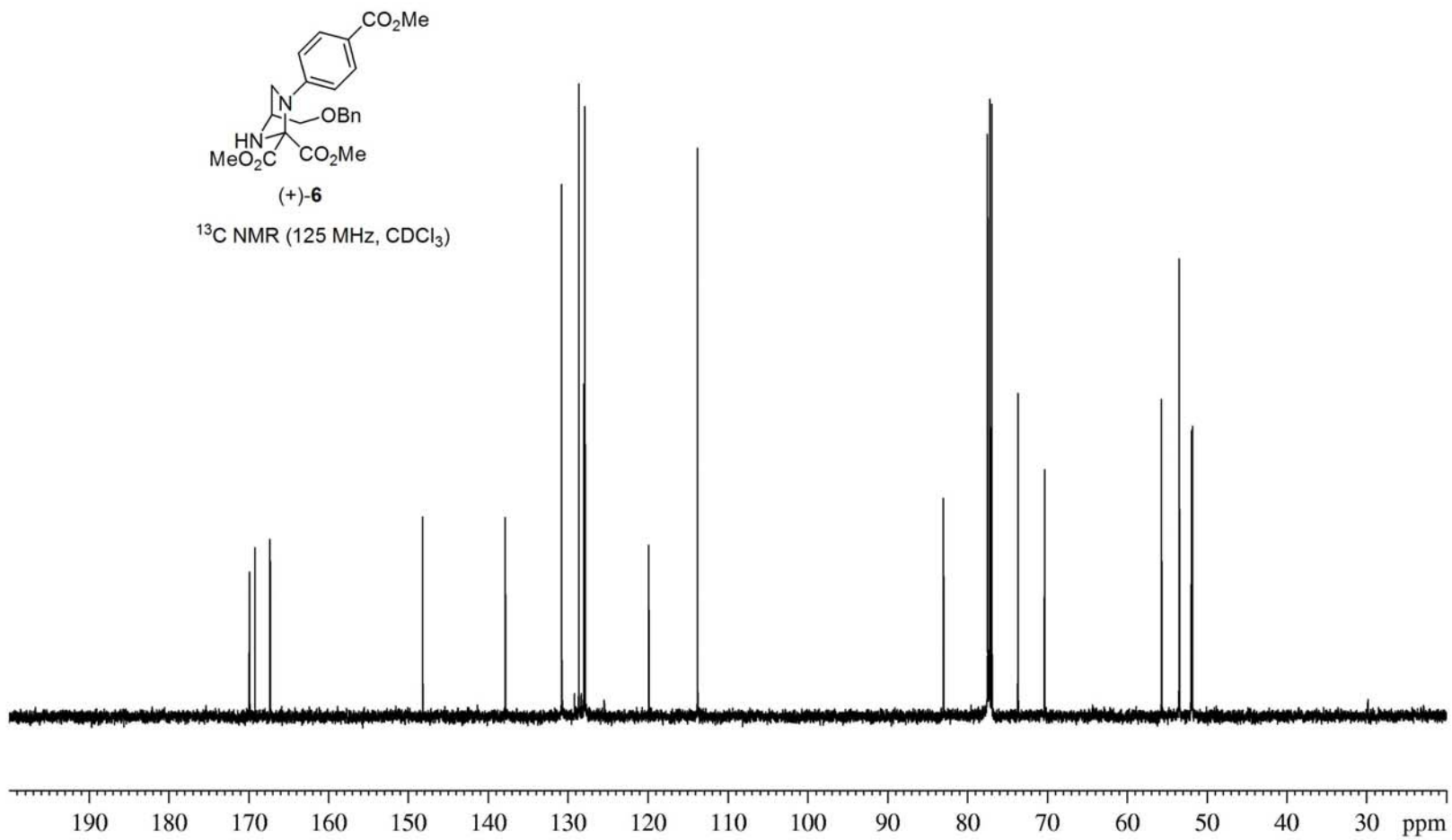

MeO
OMe
Ph
SI 2
^{1}H NMR (500 MHz, $CDCl_3$)
11
10
9
8
7
6
5
4
3
2
1
0
ppm

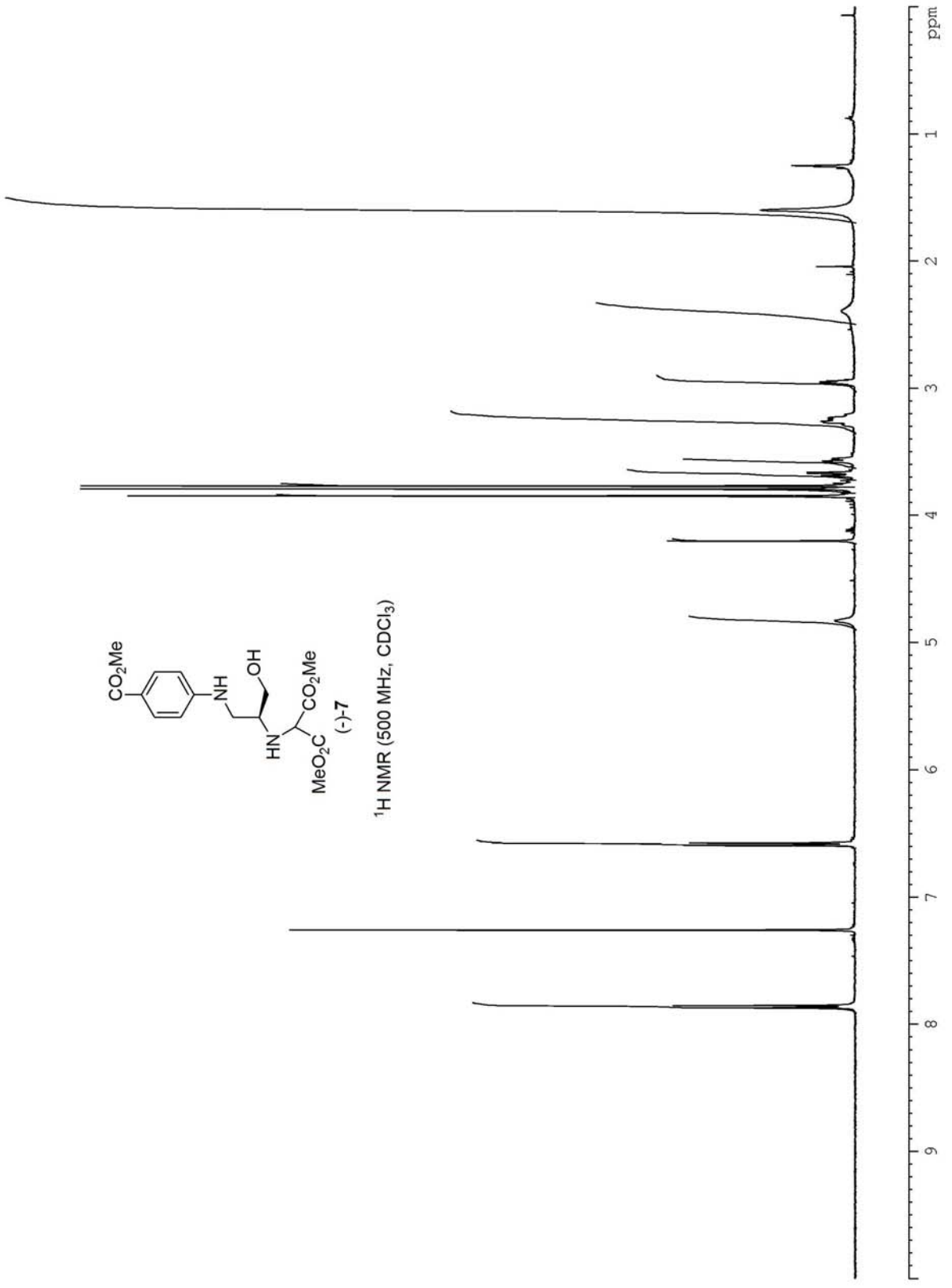

MeO
OMe
Ph
SI 2
^{13}C NMR (125 MHz, $CDCl_3$)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

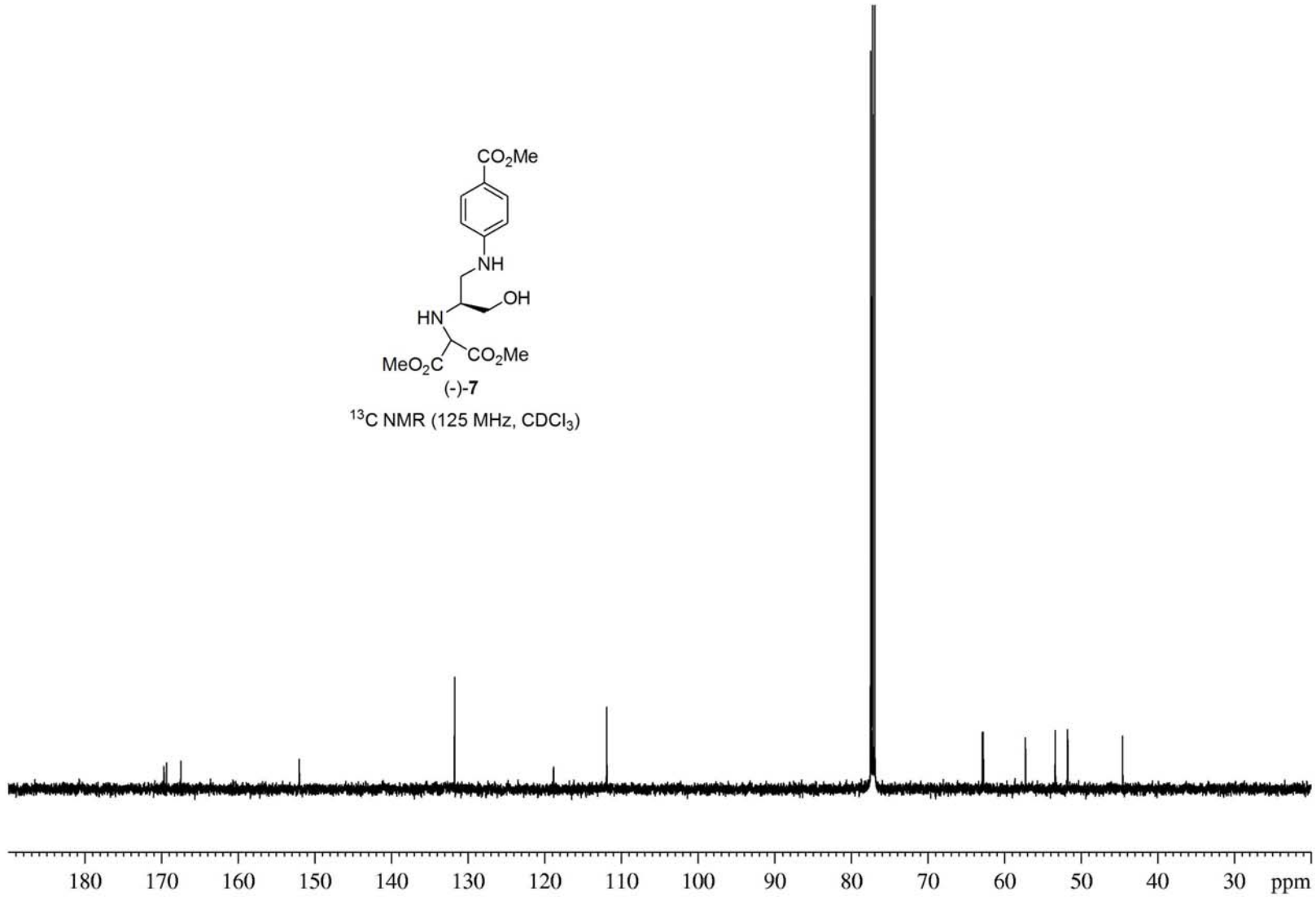

MeO
OMe
O
O
O
O
4
^{1}H NMR (500 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

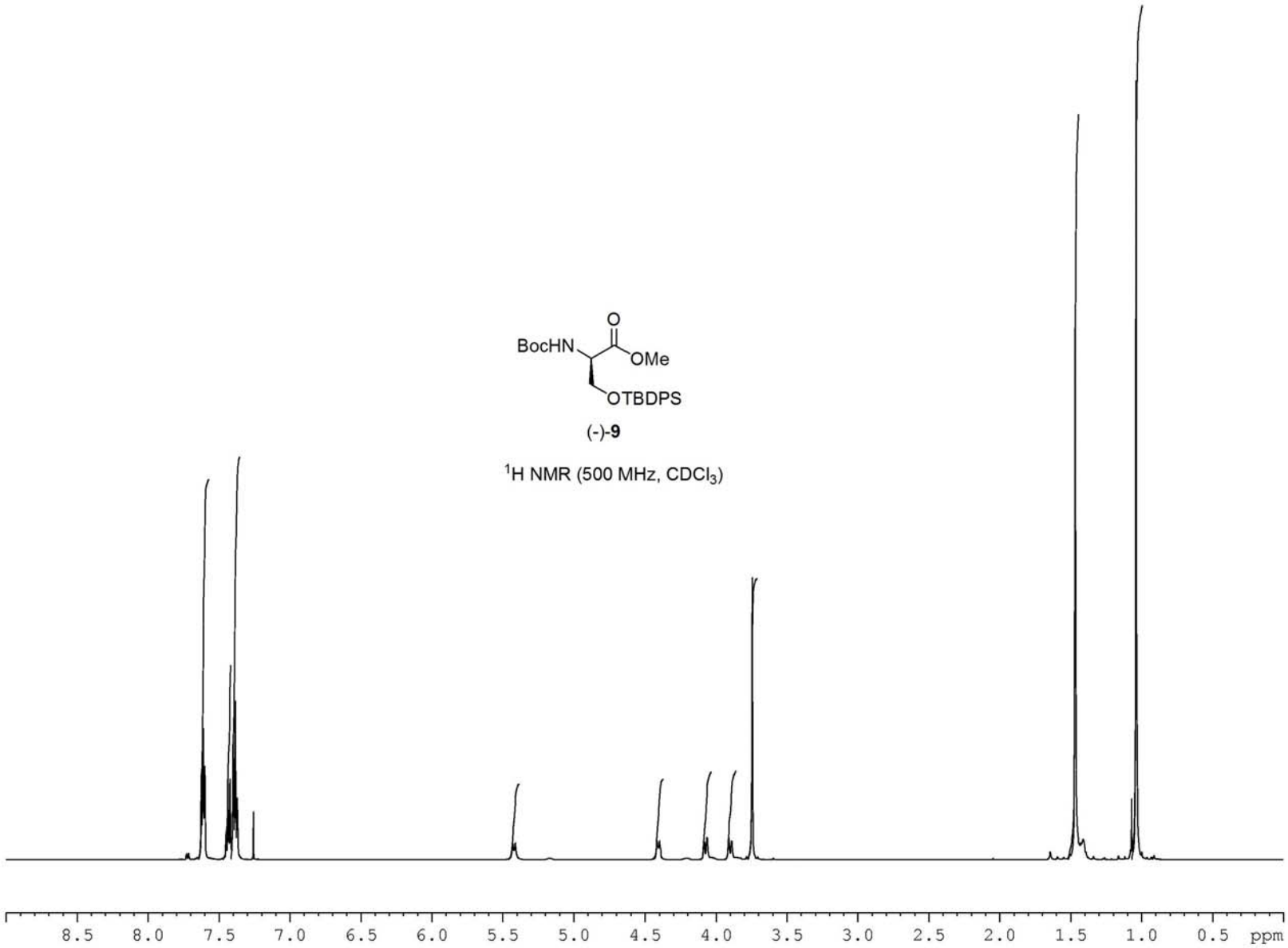

MeO
OMe
O
O
O
O
4
^{13}C NMR (125 MHz, $CDCl_3$)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

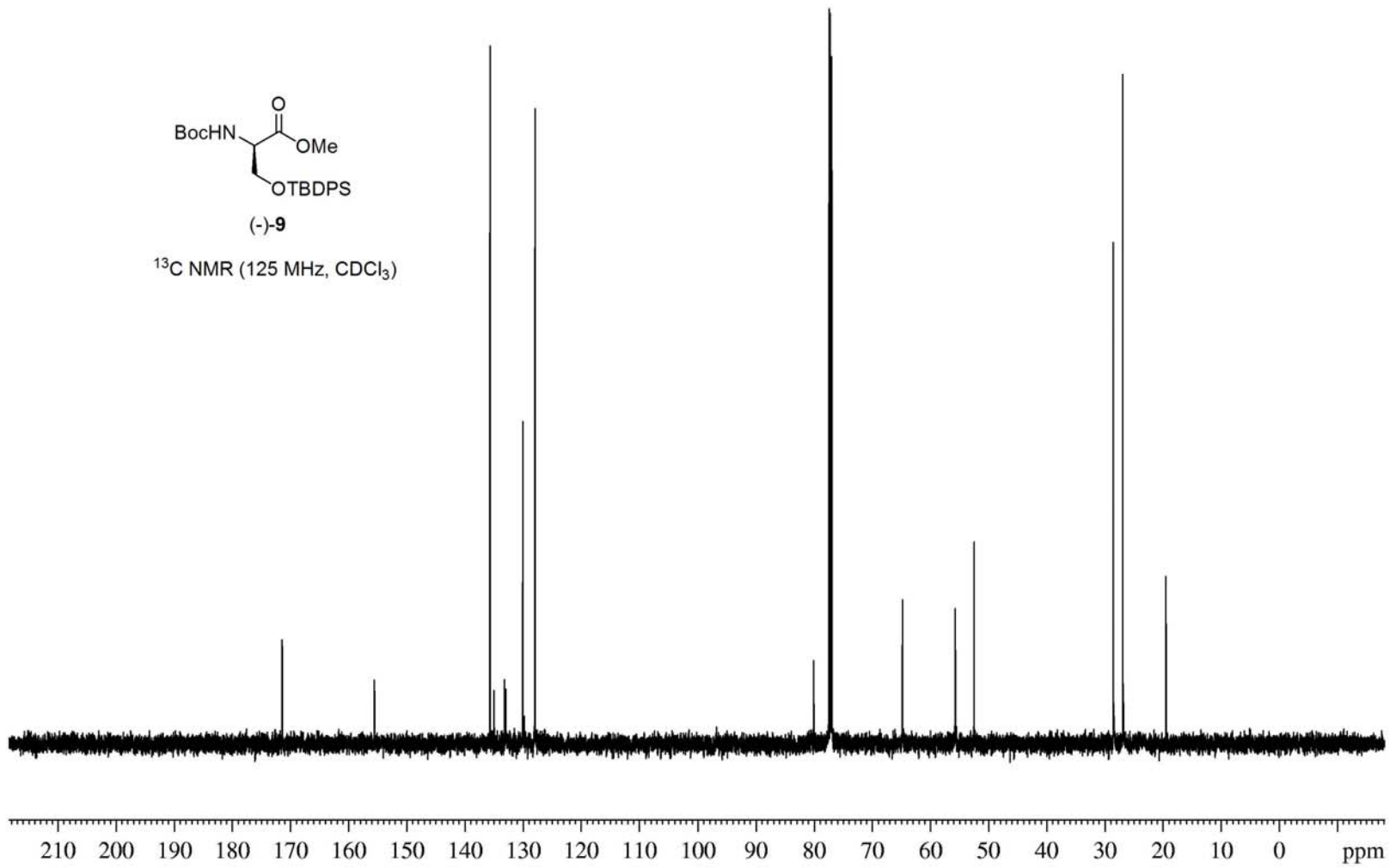

CO2Me
OBn
N
CO2Me
HN
MeO2C
(+)-6
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

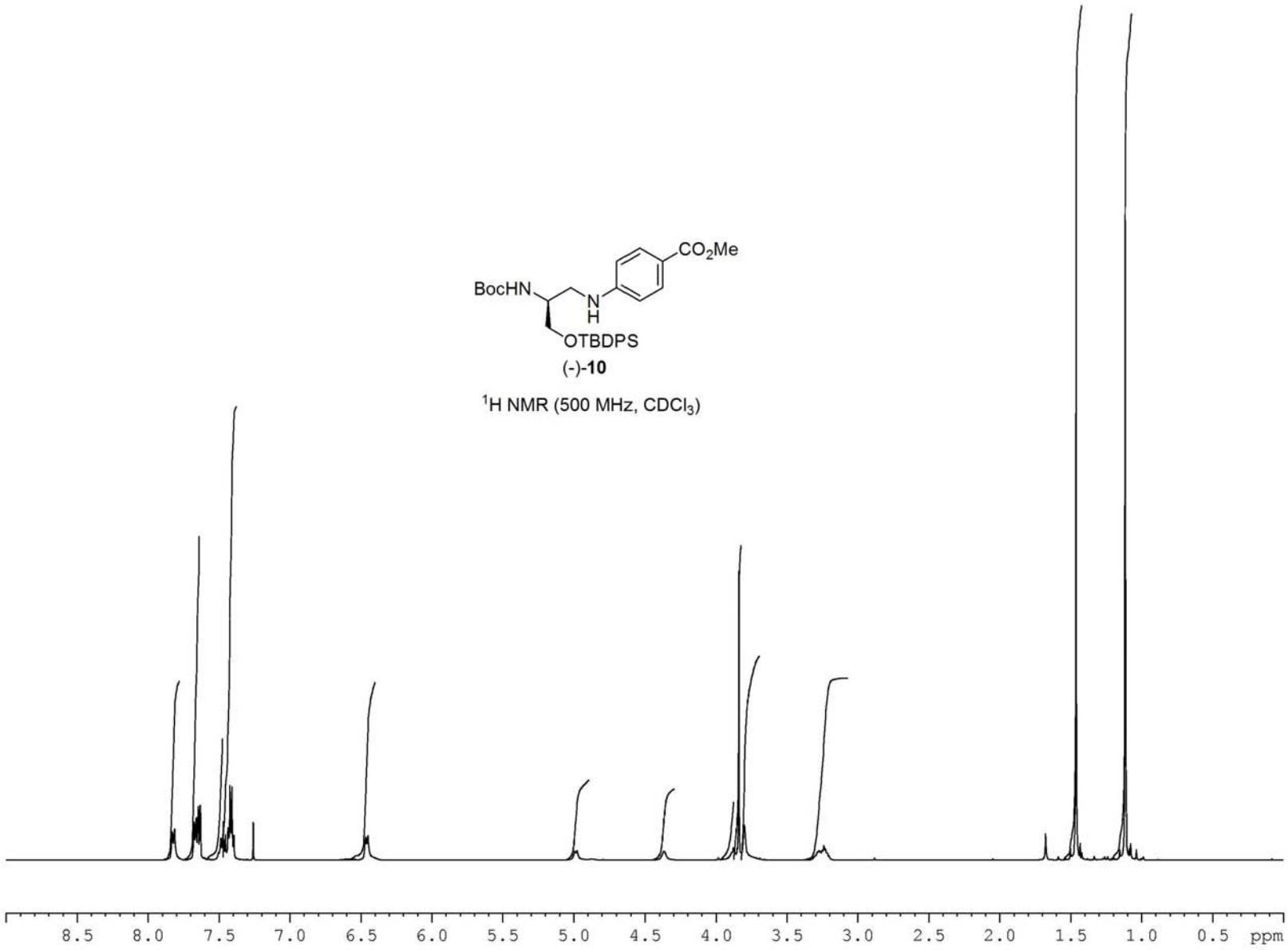

CO2Me
N
OBn
HN
MeO2C
CO2Me
(+)-6
13C NMR (125 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

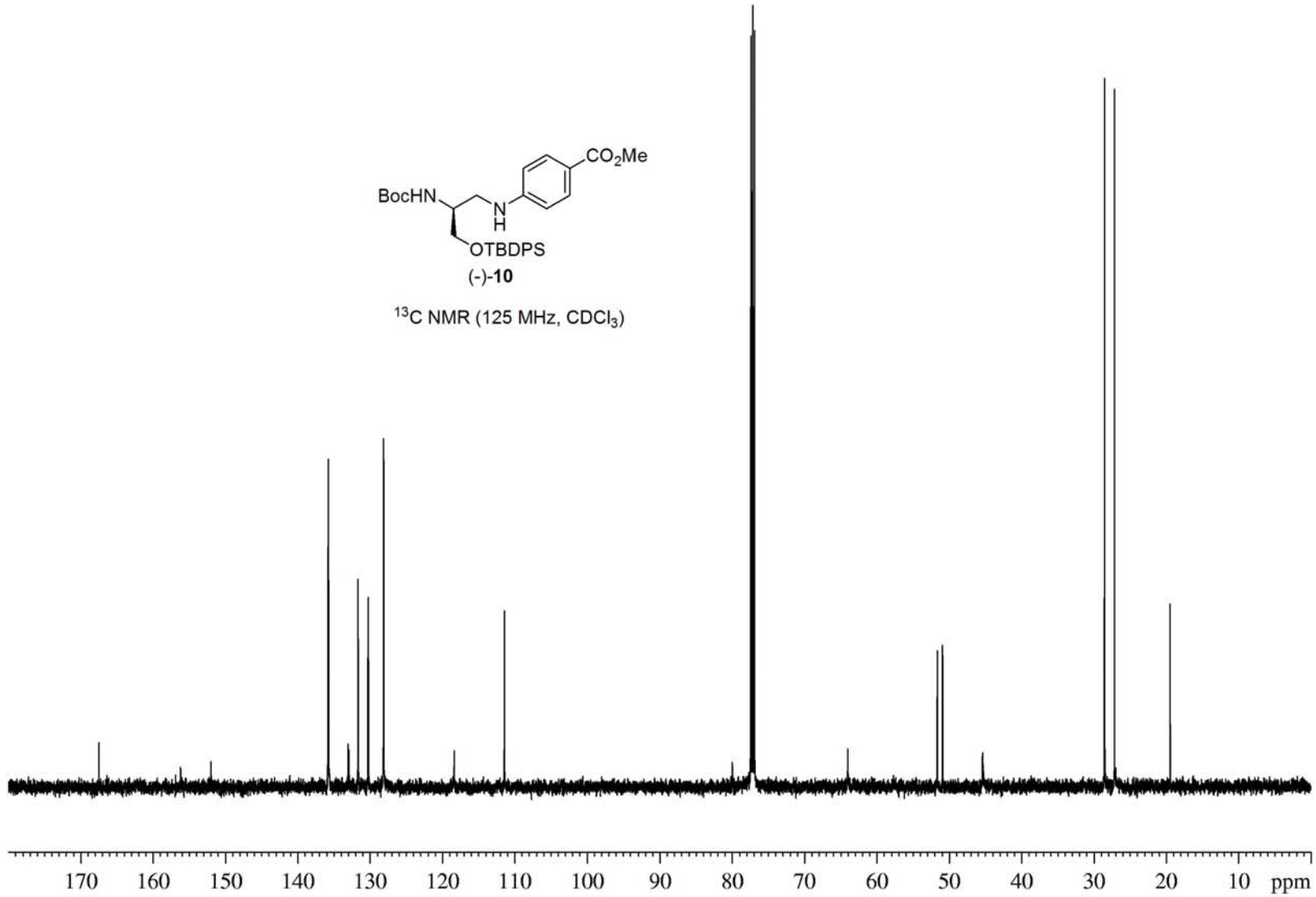

CO2Me
NH
OH
HN
CO2Me
MeO2C
(-)-7
1H NMR (500 MHz, CDCl3)
ppm
1
2
3
4
5
6
7
8
9

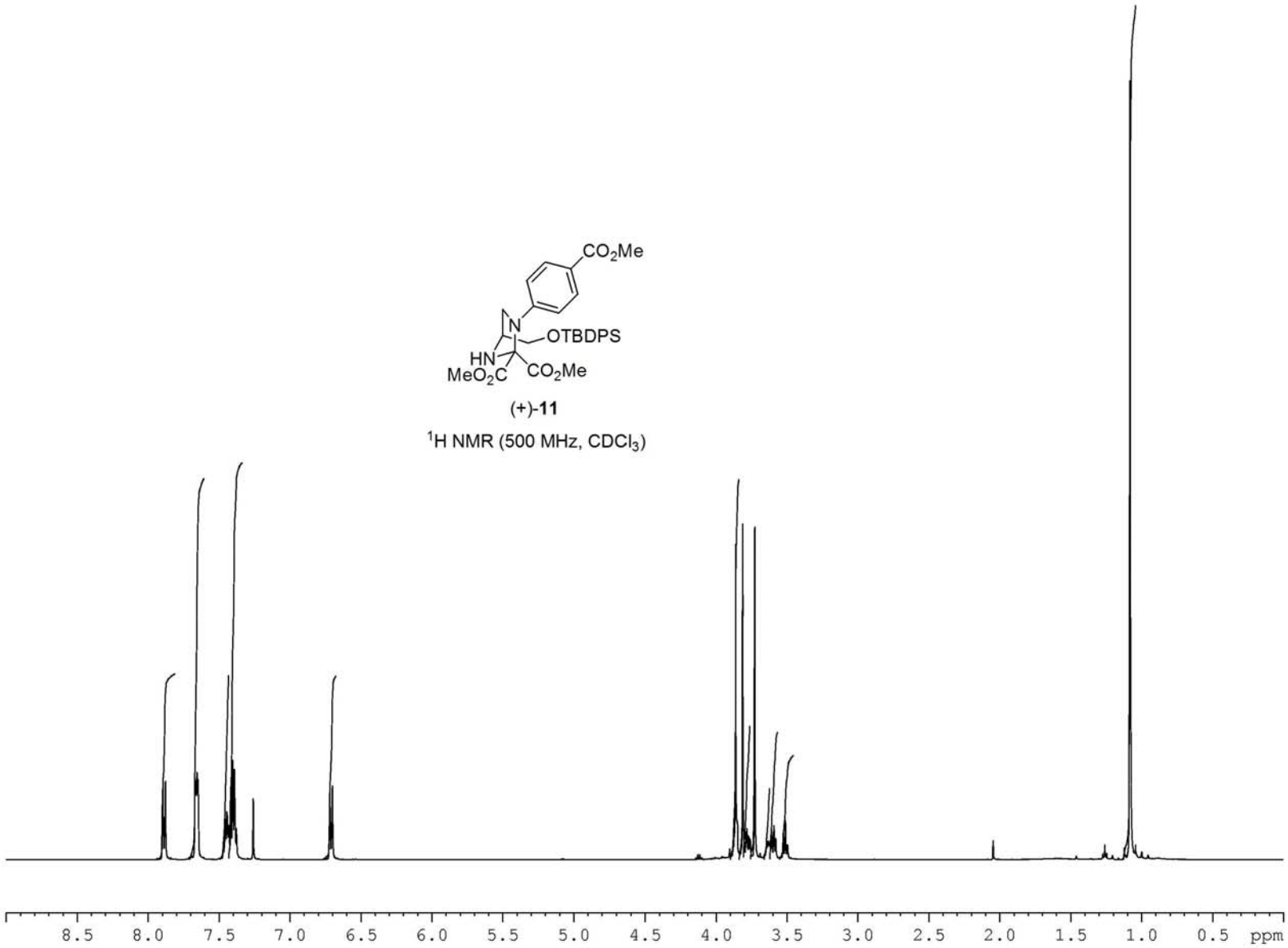

CO2Me
NH
OH
HN
MeO2C
CO2Me
(-)-7
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


BocHN
O
OMe
OTBDPS
(-)-9
^{1}H NMR (500 MHz, $CDCl_3$)
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
ppm

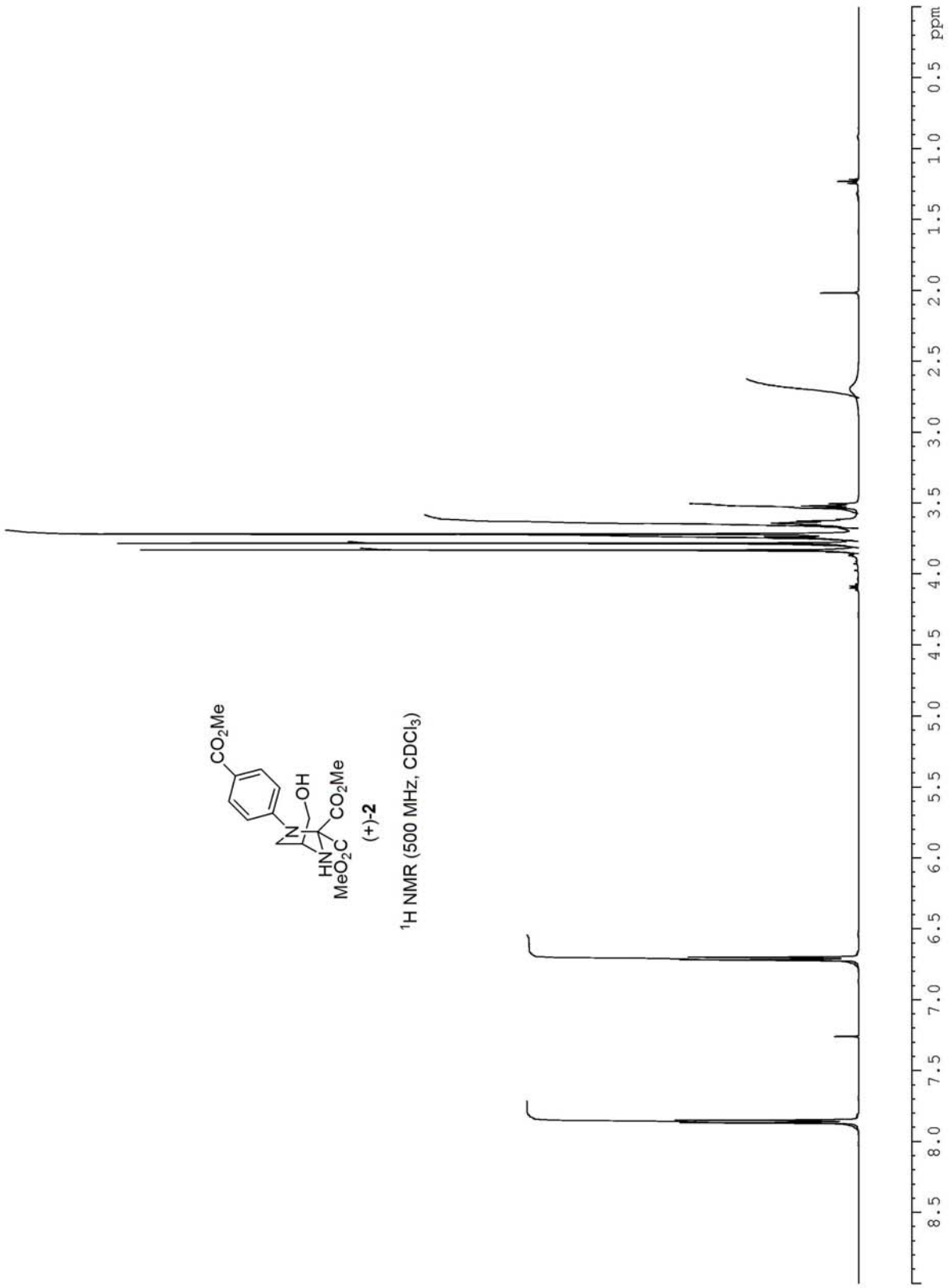

BocHN
O
OMe
OTBDPS
(-)-9
13C NMR (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


CO2Me
BocHN
N
H
OTBDPS
(-)-10
1H NMR (500 MHz, CDCl3)
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
ppm

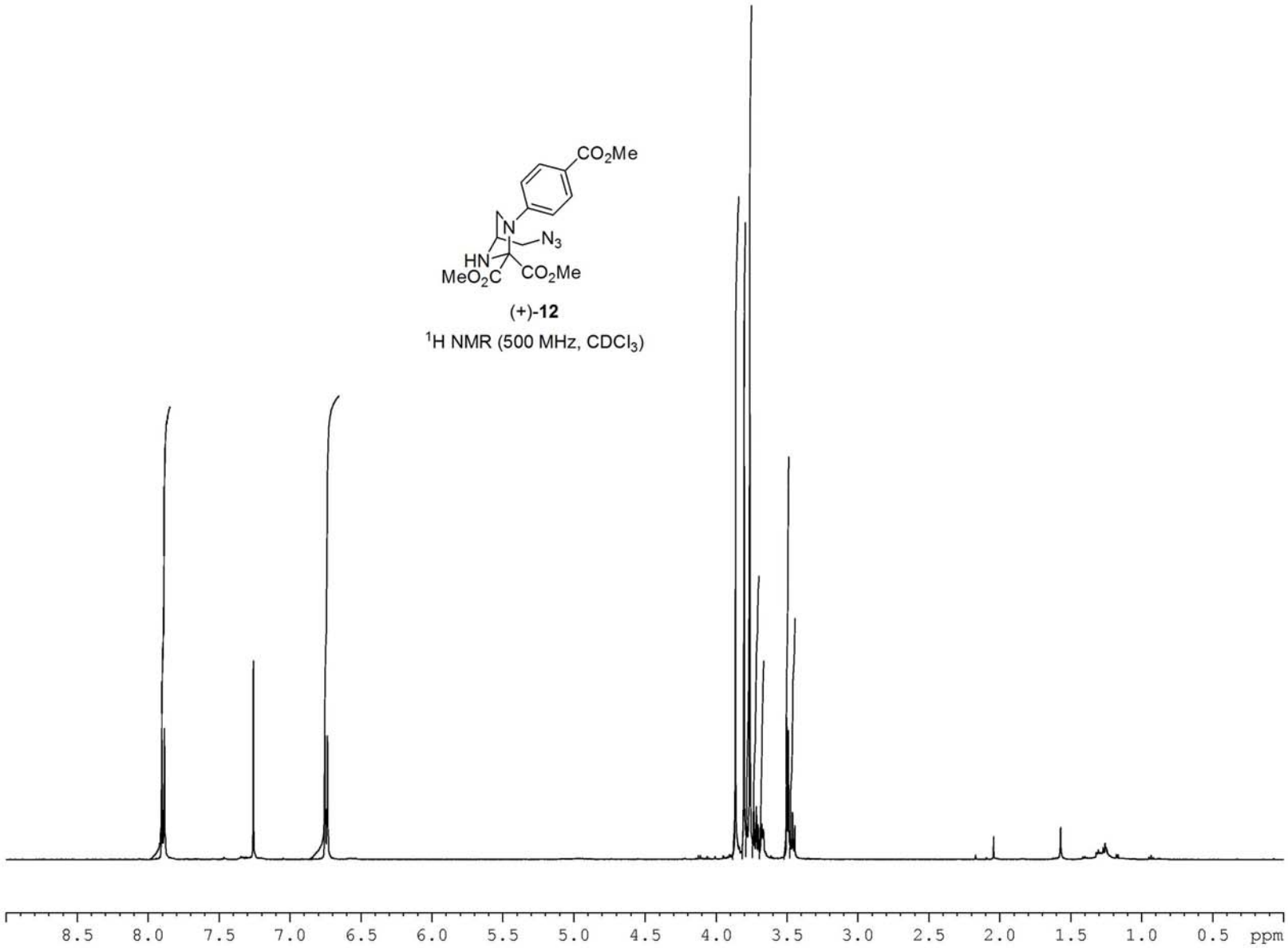

BocHN
N
H
OTBDPS
CO2Me
(-)-10
13C NMR (125 MHz, CDCl3)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Me
N
OTBDPS
HN
MeO2C
CO2Me
(+)-11
1H NMR (500 MHz, CDCl3)
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
ppm

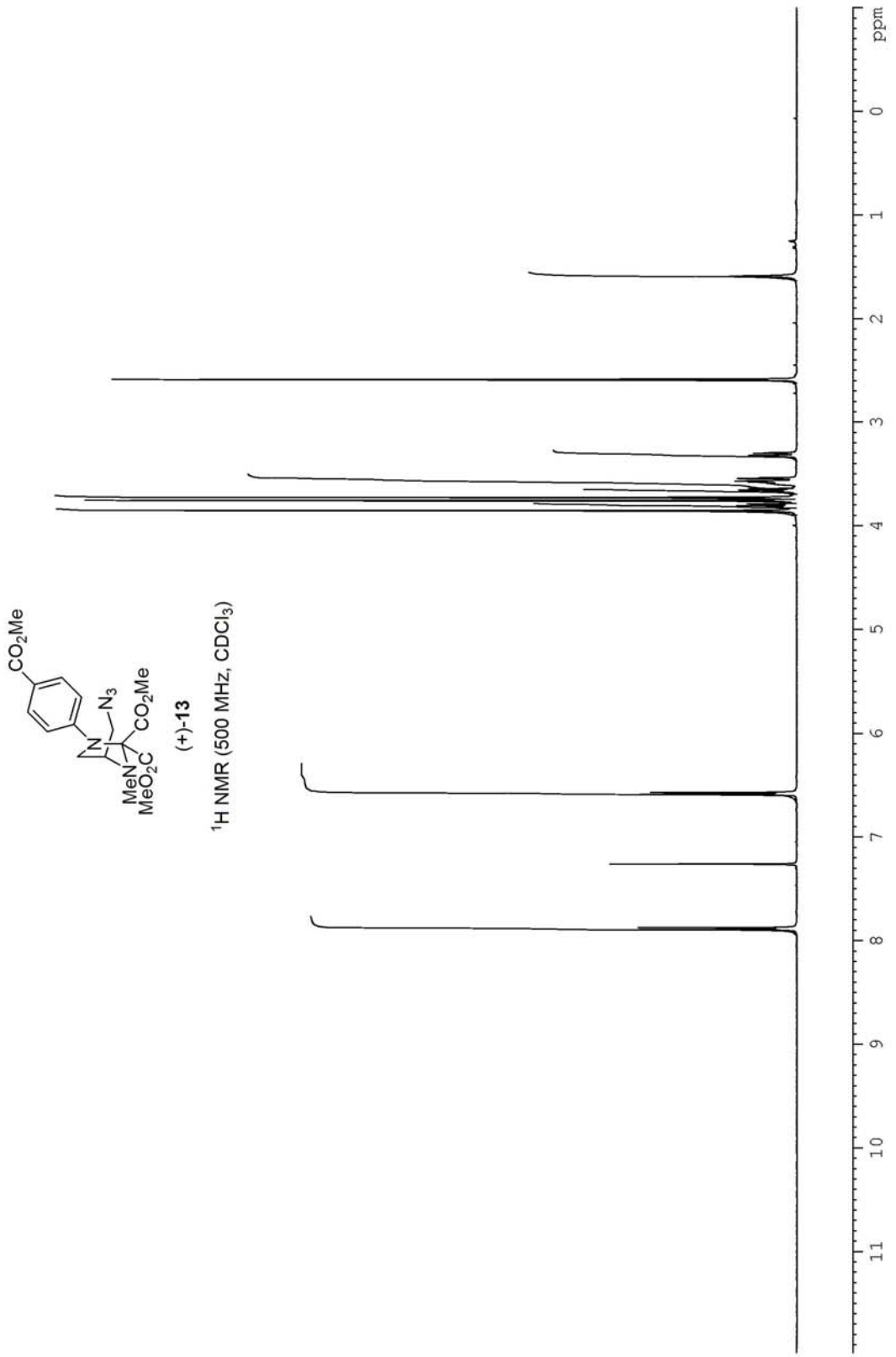
CO2Me
OTBDPS
CO2Me
HN
MeO2C
(+)-11
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

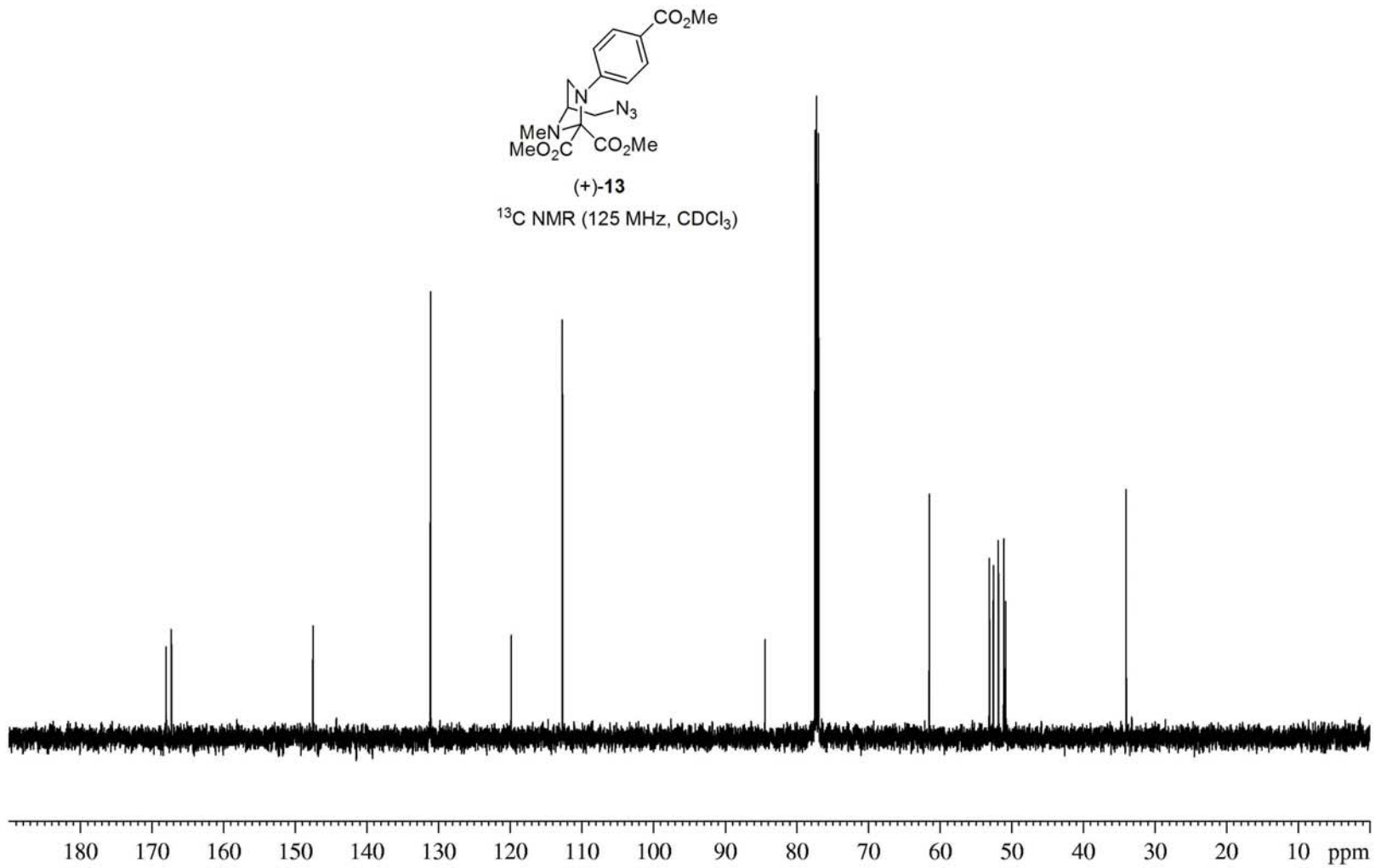

CO2Me
OH
N
HN
MeO2C
CO2Me
(+)-2
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

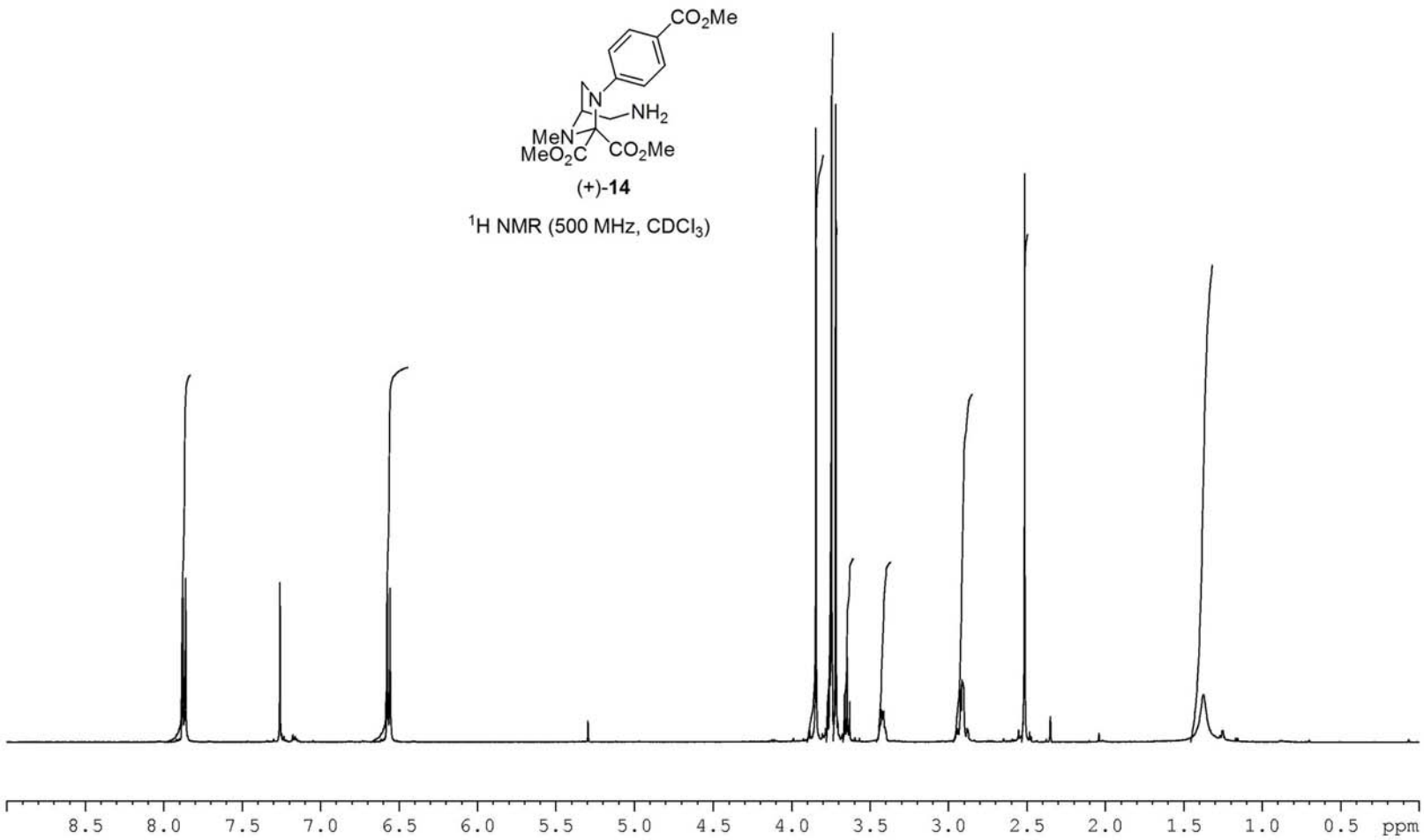
CO2Me
OH
N
HN
MeO2C
CO2Me
(+)-2
13C NMR (125 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

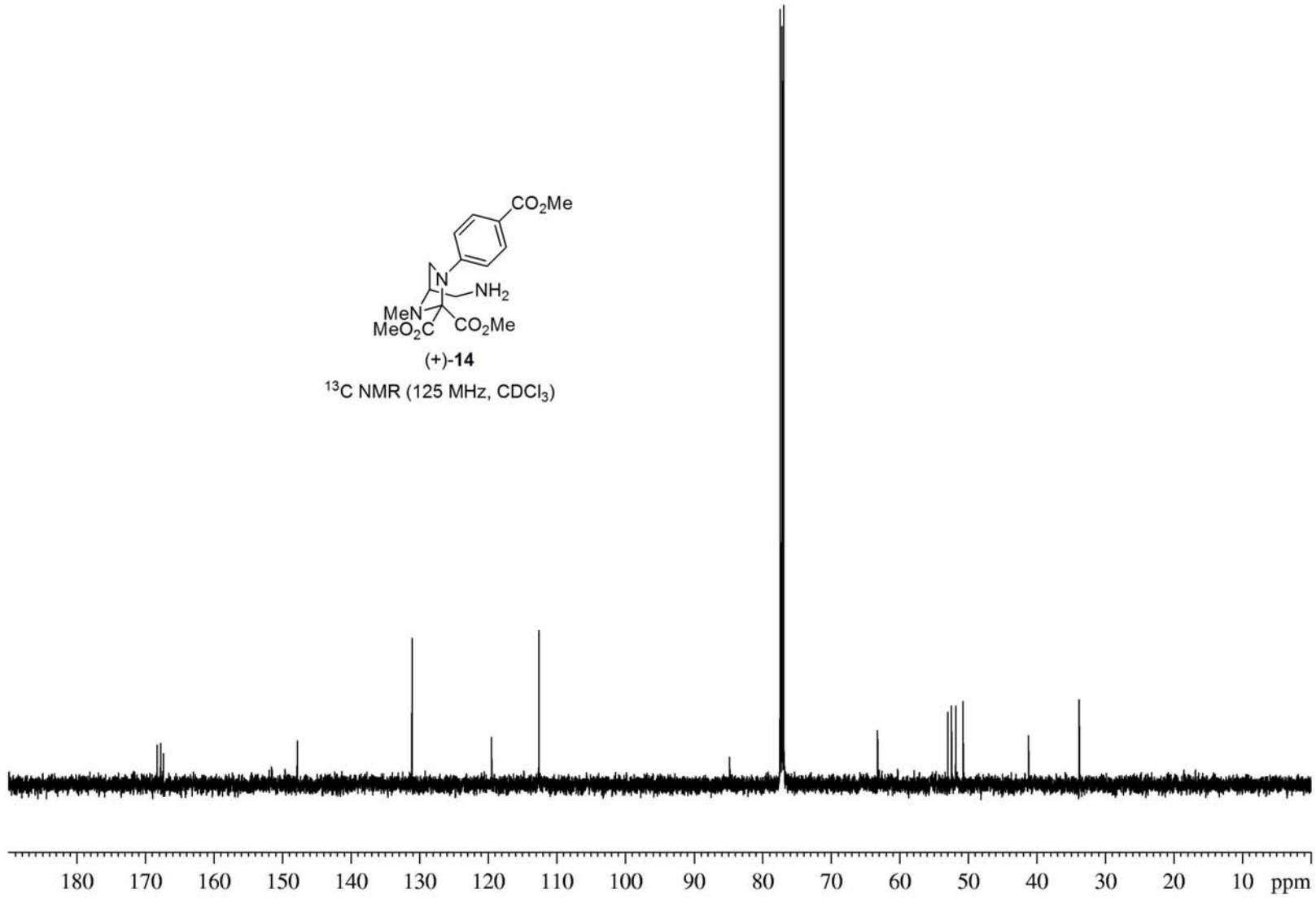

CO2Me
N
N3
HN
MeO2C
CO2Me
(+)-12
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

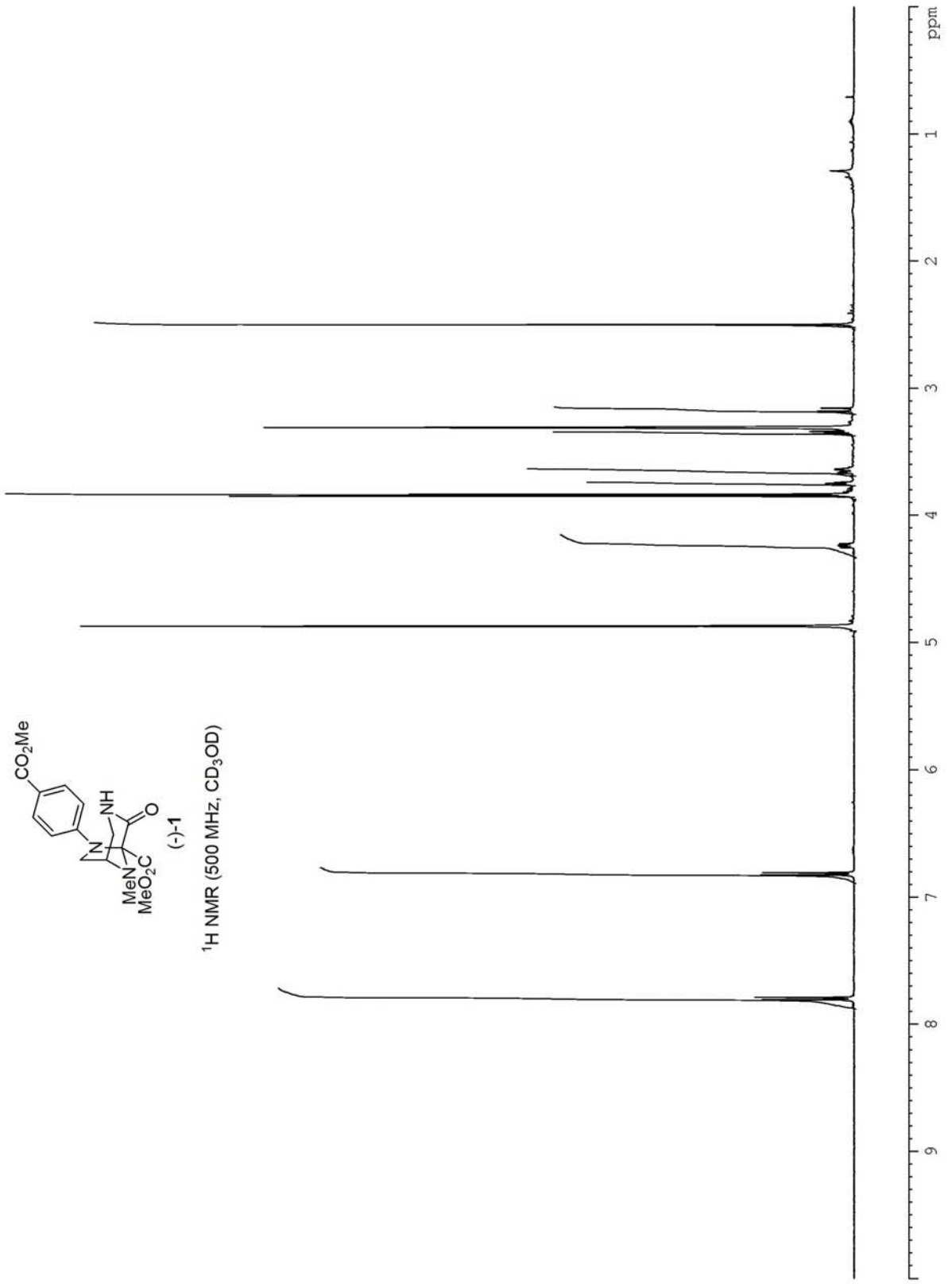
CO2Me
N3
CO2Me
HN
MeO2C
(+)-12
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


CO2Me
N3
CO2Me
MeN
MeO2C
(+)-13
1H NMR (500 MHz, CDCl3)
ppm
11
10
9
8
7
6
5
4
3
2
1
0

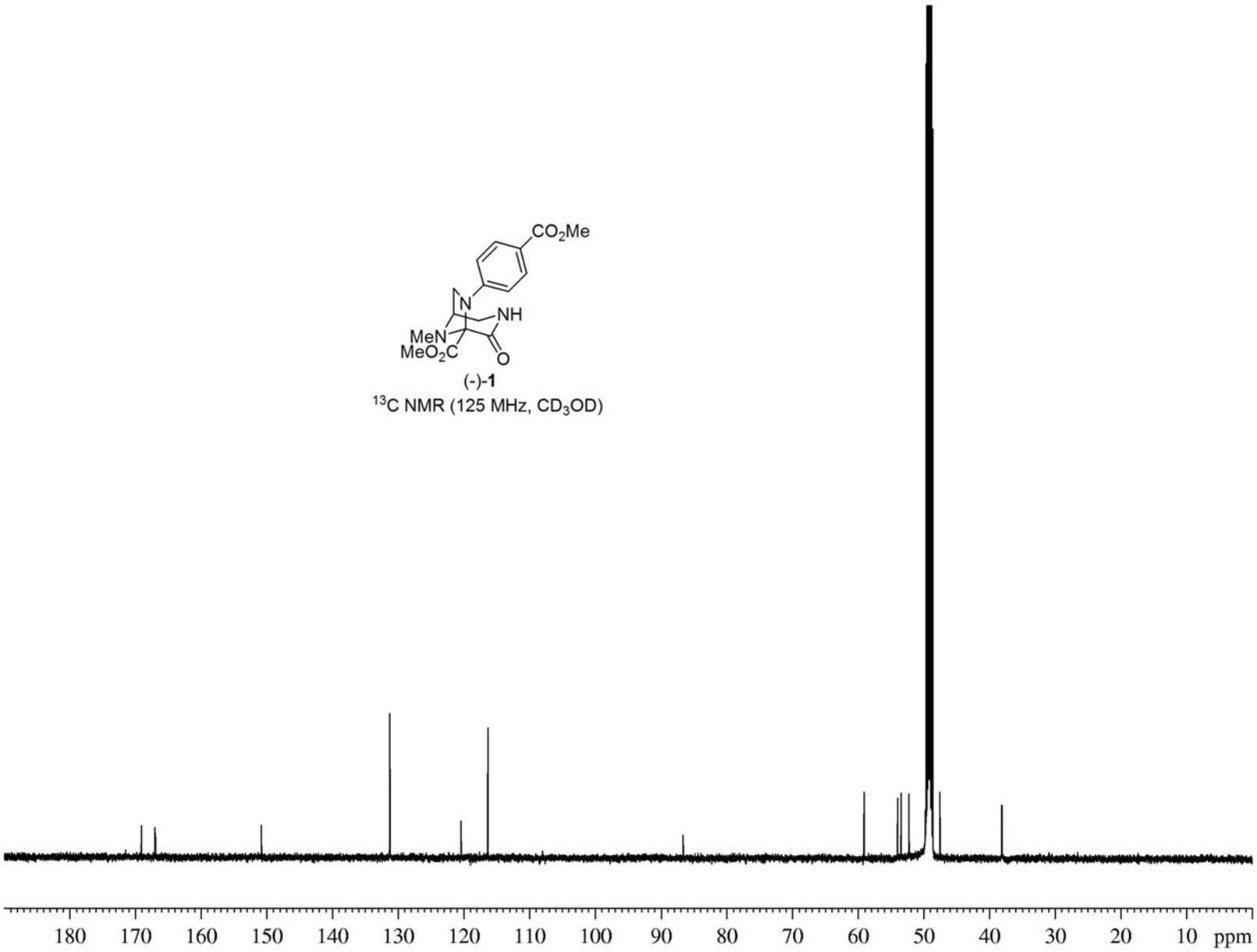

CO2Me
N
N3
MeN
MeO2C
CO2Me
(+)-13
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Me
N
NH2
MeN
MeO2C
CO2Me
(+)-14
1H NMR (500 MHz, CDCl3)
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
ppm


CO2Me
N
NH2
MeN
MeO2C
CO2Me
(+)-14
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Me
NH
O
N
MeN
MeO2C
(-)-1
1H NMR (500 MHz, CD3OD)
ppm
1
2
3
4
5
6
7
8
9

CO2Me
NH
O
N
MeN
MeO2C
(-)-1
1H NMR (500 MHz, CD3COCD3)
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
ppm


CO2Me
N
NH
MeN
MeO2C
O
(-)-1
13C NMR (125 MHz, CD3OD)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm