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Supporting Information

69451 Weinheim, Germany

Total Synthesis of the Biphenyl Alkaloid (−)-Lythranidine**

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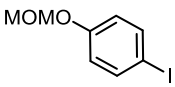
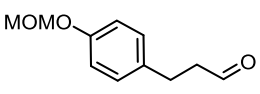
SUPPORTING INFORMATION

General. All reactions were carried out under Ar in flame-dried glassware. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, MeCN (CaH_2), hexane, toluene (Na/K), MeOH (Mg), DMF, EtOAc (MS 4Å). Flash chromatography: Merck silica gel 60 (40–63 μm), Merck silica gel 60 (15-40 μm) or Aldrich Alox (activated, neutral, 150 mesh). Preparative HPLC: Armen Instrument – Spot Prep Liquid Chromatography, Column: Merck NW50, Nucleodur-100-10-C18/A, 203x48 mm. NMR: Spectra were recorded on Bruker DPX 300, AV 400, AV 500 or AVIII 600 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C ≡ 77.16 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H ≡ 7.26 ppm; C_6D_6: δ_C ≡ 128.06 ppm; residual C_6D_5H: δ_H ≡ 7.16 ppm, $C_6D_5CD_3$: δ_C ≡ 20.43 ppm; residual $C_6D_5CD_2H$: δ_H ≡ 2.08 ppm). IR: Spectrum One (Perkin-Elmer) spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ 3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or MAT 95 (Finnigan). Unless stated otherwise, all commercially available compounds (ABCR, Acros, Aldrich, Strem) were used as received.

1-Iodo-4-(methoxymethoxy)benzene (6). NaH (1.2 g, 50 mmol) was added in portions over 30 min to a solution of 4-iodophenol (10.0 g, 45.5 mmol) in THF (50 mL) at 0°C. MOMCl (3.8 mL, 50 mmol) was then added dropwise at room temperature to the yellow solution. The resulting mixture was stirred for 16 h before the reaction was quenched with aqueous NaOH (1 M, 100 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated to afford the product as a colorless liquid (12.0 g, > 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 2H), 6.84-6.80 (m, 2H), 5.24 (s, 2H), 3.46 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 138.4 (2C), 118.7 (2C), 94.5, 84.4, 56.2 ppm; IR (film): $\tilde{\nu}$ = 2953, 2930, 2900, 2825, 1585, 1574, 1482, 1441, 1403, 1308, 1299, 1275, 1231, 1197, 1174, 1149, 1076, 985, 919, 818, 648, 609, 575, 504 cm^{-1}; MS (EI): *m/z* (%): 264 (37), 234 (13), 45 (100); HRMS (EI): *m/z*: calcd. for $C_8H_9O_2I$ $[M]^{+\bullet}$: 263.96473, found 263.96451.

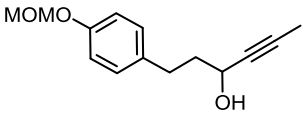


3-(4-(Methoxymethoxy)phenyl)propanal (7). A Schlenk tube was charged with $NaHCO_3$ (7.65 g, 91.0 mmol), Bu_4NCl (12.6 g, 45.5 mmol) and $Pd(OAc)_2$ (102 mg, 0.455 mmol) and the vessel was then evacuated and backfilled with Argon three times. A solution of iodide **6** (12.0 g, 45.5 mmol) in DMF (47 mL) and allyl alcohol (4.65 mL, 68.3 mmol) were successively added and the mixture was stirred for 16 h at 50°C. The

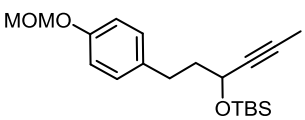


suspension was filtered through a plug of Celite which was rinsed with EtOAc (250 mL). The combined filtrates were washed with H_2O (2 x 200 mL) and brine (100 mL), and then dried over $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography (hexanes/EtOAc, 5:1) to afford the product as a yellow liquid (7.0 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (t, 1H, *J* = 1.4 Hz), 7.12-7.09 (m, 2H), 6.99-6.95 (m, 2H), 5.15 (s, 2H), 3.47 (s, 3H), 2.91 (t, 2H, *J* = 7.5 Hz), 2.77-2.73 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =201.8, 155.9, 133.8, 129.4 (2C), 116.6 (2C), 94.7, 56.1, 45.6, 27.5 ppm; IR (film): $\tilde{\nu}$ = 2898, 2826, 2725, 1720, 1611, 1510, 1443, 1407, 1388, 1312, 1230, 1198, 1176, 1149, 1110, 1076, 994, 920, 860, 813, 767, 732 cm^{-1}; MS (EI): *m/z* (%):194 (73), 164 (12), 121 (29), 108 (10), 77 (12), 45 (100); HRMS (ESI): *m/z*: calcd. for $C_{11}H_{14}O_3Na$ $[M+Na]^+$: 217.08352, found 217.08366.

1-(4-(Methoxymethoxy)phenyl)hex-4-yn-3-ol (8). Propynylmagnesium bromide (0.5 M in THF, 88 mL, 44 mmol) was added dropwise within 2 h to a solution of aldehyde **7** (4.27 g, 22.0 mmol) in THF (100 mL) at 0°C. The ice bath was removed and the mixture stirred for 15 h at room temperature. After quenching at 0°C with sat. aq. NH_4Cl (100 mL), the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 4:1 $\rightarrow$ 2:1) to yield the title compound as a colorless liquid (3.65 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15-7.11 (m, 2H), 6.98- 6.94 (m, 2H), 5.15 (s, 2H), 4.35-4.30 (m, 1H), 3.48 (s, 3H), 2.73 (t, 2H, *J* = 7.8 Hz), 2.00-1.92 (m, 2H), 1.86 ppm (d, 3H, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 135.0, 129.6 (2C), 116.5 (2C), 94.8, 81.6, 80.3, 62.2, 56.1, 39.9, 30.7, 3.7 ppm; IR (film): $\tilde{\nu}$ = 3412, 2920, 1611, 1509, 1442, 1406, 1311, 1230, 1197, 1175, 1150, 1076, 1000, 919, 826, 730 cm^{-1}; MS (EI): *m/z* (%): 234 (38), 216 (11), 107 (19), 43 (100); HRMS (ESI): *m/z*: calcd. for $C_{14}H_{18}O_3Na$ $[M+Na]^+$: 257.11482, found 257.11462.



***tert*-Butyl((1-(4-(methoxymethoxy)phenyl)hex-4-yn-3-yl)oxy)dimethylsilane (9)**. Imidazole (3.69 g, 54.3 mmol), DMAP (4.34 mmol, 0.530 g) and TBSCl (4.91 g, 32.6 mmol) were added to a solution of alcohol **8** (5.08 g, 21.7 mmol) in CH_2Cl_2 (100 mL) at 0°C. The mixture was stirred for 16 h at room temperature before the reaction was quenched with H_2O (100 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by



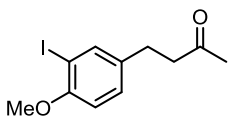
flash chromatography (hexanes/EtOAc, 5:1) to obtain the product as a pale yellow liquid (7.38 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13-7.09 (m, 2H), 6.97-6.93 (m, 2H), 5.14 (s, 2H), 4.34-4.31 (m, 1H), 3.48 (s, 3H), 2.69 (dt, 2H, *J* = 8.0, 4.0 Hz), 1.94-1.88 (m, 2H), 1.84 (d, 3 H, *J* = 2.0 Hz), 0.91 (s, 9 H), 0.12 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 135.6, 129.5 (2C), 116.4 (2C), 94.8, 80.9, 80.5, 62.7, 56.0, 40.9, 30.8, 26.0, 18.4, 3.7, –4.3, –4.8 ppm; IR (film): $\tilde{\nu}$ = 2953, 2928, 2894, 2856, 1612, 1510, 1472, 1463, 1360, 1311, 1249, 1231, 1198, 1175, 1151, 1078, 1004, 923, 833, 774, 666 cm^{-1}; MS (EI): *m/z* (%): 291 (16), 260 (21), 259 (100), 229 (17), 151 (23), 121 (24), 97 (11), 75 (15), 73 (10), 45 (50); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{32}O_3SiNa$ $[M+Na]^+$: 371.20191, found 371.20110.

Hept-5-ynal. To a solution of oxalyl chloride (4.83 mL, 56.3 mmol) in CH_2Cl_2 (235 mL) was added to DMSO (8.00 mL, 113 mmol) within 10 min at – 78°C. The mixture was stirred for 50 min at this temperature before hept-5-yn-1-ol (**12**) (5.27 g, 46.9 mmoL) was added within 15 min. Stirring was continued for 45 min at –78°C. NEt_3 (32.7 mL, 235 mmol) was then added within 1 h and the resulting slurry was allowed to reach room temperature within 13 h. Brine (100 mL) was introduced, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. Flash chromatography (pentanes/*tert*-butyl methyl ether, 7:1 $\rightarrow$ 5:1) afforded the title compound as a colorless liquid (4.67 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (t, 1H, *J* = 1.5 Hz), 2.56 (dt, 2H, *J* = 7.2, 1.6 Hz), 2.23-2.18 (tq, 2H, *J* = 7.1, 2.5 Hz), 1.80 (quint, 2H, *J* = 7.2 Hz), 1.77 ppm (t, 3H, *J* = 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2, 78.0, 76.9, 43.0, 21.6, 18.3, 3.5 ppm; IR (film): $\tilde{\nu}$ = 2921, 2844, 2724, 1721, 1437, 1411, 1390, 1364, 1335, 1243, 1177, 1071, 1032, 925, 866, 795, 689 cm^{-1}; MS (EI): *m/z* (%): 82 (25), 68 (100), 67 (12), 66 (65), 65 (20), 55 (17), 53 (42), 51 (14), 41 (30), 39 (32), 29 (11), 27 (28); HRMS (EI): *m/z*: calcd. for $C_7H_{10}O$ $[M]^{+\bullet}$: 110.07317, found 110.07307.

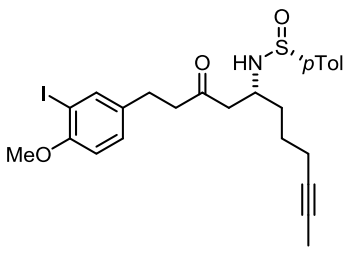
(*R*)-*N*-(Hept-5-yn-1-ylidene)-4-methylbenzenesulfinamide (13). A solution of hept-5-ynal (4.32 g, 39.2 mmol), (*R*)-(−)-*p*-toluenesulfinamide (6.09 g, 39.2 mmol) and $Ti(OEt)_4$ (41.1 mL, 196 mmol) in CH_2Cl_2 (500 mL) was stirred at 55°C for 15 h. The reaction was quenched with H_2O (100 mL), the suspension was filtered through a plug of Celite, eluting with H_2O (100 mL) and CH_2Cl_2 (100 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated, and the residue was purified by flash

chromatography (hexanes/EtOAc, 5:1) to give the desired product as a pale yellow liquid (8.94 g, 92%). $[\alpha]_{20}^{D} = -307.7$ (c = 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.26 (t, 1H, *J* = 4.5 Hz), 7.57-7.55 (m, 2H), 7.30 (d, 2H, *J* = 8.1 Hz), 2.62-2.57 (m, 2H), 2.40 (s, 3H), 2.19 (tq, 2H, *J* = 7.2, 2.6 Hz), 1.80 (quint, 2H, 7.2 Hz), 1.76 ppm (t, 3H, *J* = 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 166.8, 142.0, 141.8, 129.9 (2C), 124.7 (2C), 78.1, 77.4, 35.1, 24.8, 21.6, 18.4, 3.6 ppm; IR (film): $\tilde{\nu} =$ 2918, 1619, 1492, 1436, 1350, 1178, 1097, 1071, 1016, 808, 753, 704, 666 cm^{-1}; MS (EI): *m/z* (%): 184 (18), 140 (19), 139 (100), 92 (15), 91 (21), 67 (10), 65 (13); HRMS (ESI): *m/z*: calcd. for $C_{14}H_{17}NOSNa$ $[M+Na]^+$: 270.09230, found 270.09220.

4-(3-Iodo-4-methoxyphenyl)butan-2-one (11). Ag_2SO_4 (11.1 g, 35.8 mmol) and I_2 (9.07 g, 35.8 mmol) were added to a solution of 4-(4-methoxyphenyl)butan-2-one (**10**) (5.79 g, 32.5 mmol) in MeOH (290 mL). The initially dark brown suspension was vigorously stirred for 1.5 h, while turning bright yellow. The reaction was quenched with aq. sat. $Na_2S_2O_3$ (200 mL) and filtered through a pad of Celite, eluting with EtOAc (100 mL). The organic phase was evaporated and the aqueous layer was extracted with EtOAc (3 x 125 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1) yielded the title compound as a yellow liquid (8.78 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.60 (d, 1H, *J* = 2.0 Hz), 7.12 (dd, 1H, *J* = 8.3, 2.0 Hz), 6.73 (d, 1H, *J* = 8.3 Hz), 3.84 (s, 3H), 2.81-2.78 (m, 2H), 2.73-2.69 (m, 2H), 2.13 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 207.7, 156.7, 139.3, 135.5, 129.6, 111.0, 86.2, 56.6, 45.3, 30.2, 28.4 ppm; IR (film): $\tilde{\nu} =$ 3003, 2939, 2836, 1710, 1598, 1563, 1489, 1460, 1439, 1400, 1361, 1279, 1250, 1204, 1180, 1159, 1048, 1016, 891, 805, 747, 711, 662 cm^{-1}; MS (EI): *m/z* (%): 305 (12), 304 (100), 247 (86), 234 (10), 134 (15), 91 (10), 90 (10), 43 (26); HRMS (ESI): *m/z*: calcd. for $C_{11}H_{13}O_2INa$ $[M+Na]^+$: 326.98524, found 326.98506.



(*R*)-*N*-((*R*)-1-(3-Iodo-4-methoxyphenyl)-3-oxoundec-9-yn-5-yl)-4-methylbenzenesulfinamide (14). A solution of ketone **11** (2.59 g, 8.51 mmol) in Et_2O (27 mL) was added within 75 min to a solution of KHMDS (1.82 g, 9.12 mmol) in Et_2O (27 mL) at −78°C. After stirring for 2 h at this temperature, a solution of compound **13** (1.40 g, 5.66 mmol) in Et_2O (27 mL) was added within 20 min while keeping the temperature at −78°C. The resulting suspension was stirred for 2 h before the reaction was quenched with sat.



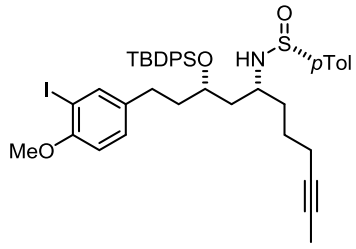
aq. NH_4Cl (75 mL) at the same temperature. The layers were separated, the aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined extracts were dried ($MgSO_4$) and evaporated. ^{1}H NMR analysis of the crude product indicated a diastereomeric ratio of 10:1 in favor of (*R*,R_S)-**14.** The crude product was purified by flash chromatography (CH_2Cl_2/EtOAc, 10:1, Merck silica gel 60 (15-40 µm)) to give product (*R*,R_S)-**14** as a colorless oil (2.00 g, 64%). $[\alpha]_{20}^{D} = -38.1$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$ (d, 1H, *J* = 1.6 Hz), 7.47 (d, 2H, *J* = 7.9 Hz), 7.20 (d, 2H, 7.9 Hz), 7.02 (dd, 1H, *J* = 8.3, 1.8 Hz), 6.64 (d, 1H, *J* = 8.4 Hz), 4.51 (d, 1H, *J* = 9.2 Hz), 3.75 (s, 3H), 3.62-3.57 (m, 1H), 2.68 (t, 2H, *J* = 7.4 Hz), 2.63 (m, 2H), 2.56 (t, 2H, *J* = 7.2 Hz), 2.32 (s, 3H), 2.10-2.06 (m, 2H), 1.69 (t, 3H, *J* = 2.2 Hz), 1.63-1.55 (m, 3H), 1.51-1.45 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.5$, 156.7, 142.6, 141.4, 139.2, 135.1, 129.6 (2C), 129.5, 125.5 (2C), 111.0, 86.1, 78.7, 76.1, 56.5, 52.4, 48.8, 45.1, 35.2, 28.1, 25.8, 21.4, 18.6, 3.6 ppm; IR (film): $\tilde{\nu} = 3220$, 2919, 1708, 1598, 1863, 1490, 1439, 1400, 1367, 1279, 1252, 1179, 1087, 1048, 1016, 907, 809, 726, 662 cm^{-1}; MS (EI): *m/z* (%): 503 (10), 428 (17), 413 (13), 412 (59), 304 (19), 260 (11), 247 (100), 140 (12), 139 (92), 134 (11), 124 (27), 110 (62), 108 (26), 93 (22), 91 (27), 90 (15), 77 (16), 43 (10); HRMS (ESI): *m/z*: calcd. for $C_{25}H_{30}NO_3ISNa$ $[M+Na]^+$: 574.08833, found 326.08824.

(*R*)-*N*-((3*S*,5*R*)-3-Hydroxy-1-(3-iodo-4-methoxyphenyl)undec-9-yn-5-yl)-4-methylbenzene-sulfinamide (15). A Schlenk tube was charged with pre-dried LiCl (1.92 g, 45.3 mmol) and then heated under vacuum (heatgun). After the vessel had reached room temperature, a solution of *β*-ketoamide **14** (2.50 g, 4.53 mmol) in Et_2O (226 mL) was introduced and the mixture sonicated in an ultrasonic bath for 15 min. The resulting suspension was cooled to –78°C before $LiAlH(OtBu)_3$ (1 M in THF, 13.6 mL, 13.6 mmol) was added dropwise at this temperature. Stirring was continued at –78°C for 13.5 h before the reaction was quenched with aq. sat. NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (3 x 200 mL), the combined extracts were dried ($MgSO_4$) and the solvent was evaporated. ^{1}H NMR analysis of the crude product showed a diastereomeric ratio of 4.5:1 in favor of (3*S*,5*R*,S_R)-**15**. Purification of the crude material by flash chromatography (CH_2Cl_2/EtOAc, 4:1 → 3:1) furnished *syn*-**15** as a colorless foam (1.99 g, 79%) as well as a second fraction containing the corresponding *anti*-configured product as a colorless foam (0.41 g, 16%). *Data of compound syn*-**15**: $[\alpha]_{20}^{D} = -40.5$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.61$ (d, 2H, *J* = 8.0

Hz), 7.61 (d, 1H, 2.2 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 7.13 (dd, 1H, *J* = 8.3, 2.1 Hz), 6.74 (d, 1H, *J* = 8.3 Hz), 4.21 (d, 1H, *J* = 7.3 Hz), 3.96 (d, 1H, *J* = 4.9 Hz), 3.90-3.83 (m, 1H), 3.85 (s, 3H), 3.59-3.52 (m, 1H); 2.74-2.67 (m, 1H), 2.61-2.54 (m, 1H), 2.41 (s, 3H), 2.21-2.17 (m, 2H), 1.78 (t, 3H, *J* = 2.5 Hz), 1.71-1.52 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 142.2, 141.7, 139.3, 136.7, 129.7 (2C), 129.6, 125.4 (2C), 111.0, 86.0, 78.8, 76.1, 70.3, 56.5, 56.3, 44.1, 40.1, 37.3, 30.5, 25.2, 21.5, 18.7, 3.6 ppm; IR (film): $\tilde{\nu}$ = 3211, 2916, 2858, 1597, 1562, 1489, 1439, 1398, 1278, 1250, 1179, 1086, 1045, 1015, 907, 807, 751, 730, 663 cm^{-1}; MS (EI): *m/z* (%): 505 (14), 430 (43), 415 (21), 414 (100), 247 (54), 154 (17), 140 (13), 139 (95), 110 (46), 93 (25), 91 (19), 90 (10); HRMS (ESI): *m/z*: calcd. for $C_{25}H_{32}NO_3ISNa$ $[M+Na]^+$: 576.10398, found 576.10453.

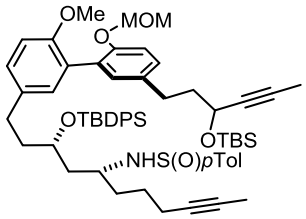
Data of compound anti-**15**: $[\alpha]_{20}^{D}$ = –33.1 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.54 (m, 3H), 7.25 (d, 2H, *J* = 8.2 Hz), 7.09 (dd, 1H, *J* = 8.4, 2.0 Hz), 6.69 (d, 2H, *J* = 8.4 Hz), 4.14 (d, 1H, 8.5 Hz), 3.81-3.75 (m, 1H), 3.79 (s, 3H), 3.70 (d, 1H, *J* = 5.0 Hz), 3.62-3.56 (m, 1H), 2.71-2.64 (m, 1H), 2.57-2.50 (m, 1H), 2.37 (s, 3H), 2.18-2.14 (m, 1H), 1.75 (t, 3H, *J* = 2.3 Hz), 1.73-1.53 (m, 7H), 1.42 ppm (ddd, 1H, *J* = 14.5, 9.7, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 142.3, 141.8, 139.5, 136.8, 129.8 (2C), 129.7, 125.5 (2C), 111.0, 86.0, 78.9, 76.2, 66.3, 56.5, 53.5, 43.5, 39.4, 36.9, 30.8, 25.8, 21.5, 18.8, 3.6 ppm; IR (film): $\tilde{\nu}$ = 3299, 2938, 2918, 2859, 1597, 1489, 1439, 1399, 1279, 1251, 1179, 1086, 1045, 1015, 909, 807, 729, 626, 528, 452 cm^{-1}; MS (pos. ESI): *m/z* (%): 554 (100), 576 (28); HRMS (ESI): *m/z*: calcd. for $C_{25}H_{33}NO_3IS$ $[M+H]^+$: 554.12204, found 554.12183.

(*R*)-*N*-((3*S*,5*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-1-(3-iodo-4-methoxyphenyl)undec-9-yn-5-yl)-4-methylbenzenesulfinamide (16). Imidazole (6.78 mmol, 461 mg), DMAP (0.54 mmol, 66 mg) and TBDPSCl (1.76 mL, 6.78 mmol) were successively added to a solution of compound **15** (1.5 g, 2.71 mmol) in CH_2Cl_2 (15.4 mL) at 0°C. The mixture was stirred for 15 h at room temperature before it was filtered, and the filtrate was evaporated. Flash chromatography (hexanes/EtOAc 2:1) gave the title compound as a pale yellow foam (1.93 g, 90%). $[\alpha]_{20}^{D}$ = –16.2 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 4H), 7.44 (d, 2H, *J* = 7.8 Hz), 7.38-7.35 (m, 7 H), 7.23 (d, 2H, *J* = 8.1 Hz), 6.92 (dd, 1H, *J* = 8.4, 1.7 Hz), 6.68 (d, 1H, *J* = 8.4 Hz), 3.83 (s, 3H), 3.81-3.75 (m, 1H), 3.38 (d, 1H, *J* = 8.3 Hz), 3.24-3.18 (m, 1H), 2.52-2.39 (m, 2H), 2.37 (s, 3H), 2.09-2.04 (m, 2H), 1.76 (t, 3H, *J* = 2.2



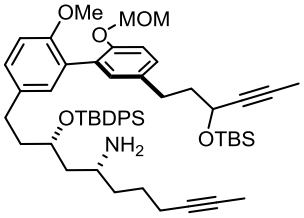
Hz), 1.66-1.56 (m, 2H), 1.55-1-37 (m, 6H), 1.06 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 156.4, 142.3, 141.2, 139.1, 136.7, 136.1 (4C), 134.3, 134.2, 129.9 (2C), 129.5 (2C), 129.3, 127.8 (4C), 125.9 (2C), 111.0, 86.0, 79.0, 76.0, 70.2, 56.5, 52.0, 43.2, 38.1, 36.6, 29.8, 27.2 (3H), 25.1, 21.5, 19.5, 18.9, 3.6 ppm; IR (film): $\tilde{\nu} =$ 3196, 2931, 2857, 1737, 1597, 1490, 1460, 1440, 1427, 1372, 1278, 1250, 1178, 1157, 1104, 1087, 1047, 1017, 909, 810, 731, 701, 686, 663 cm^{-1}; MS (EI): *m/z* (%): 736 (18), 735 (46), 734 (100), 653 (26), 652 (62), 595 (11), 594 (29), 396 (12), 247 (25), 224 (20), 199 (22), 139 (29); HRMS (ESI): *m/z*: calcd. for $C_{41}H_{50}NO_3ISSiNa$ $[M+Na]^+$: 814.22176, found 814.22162.

Diyne S1. A solution of compound **9** (2.81 g, 806 mmol) in Et_2O (40 mL) was carefully treated with *tert*-BuLi (1.7 M in pentanes, 4.74 mL, 8.06 mmol) at 0°C. The resulting dark yellow solution was stirred at this temperature for 40 min before $ZnCl_2$ (1 M in THF, 10.1 mL, 10.1 mmol) was introduced. A white precipitate was formed which quickly dissolved again. The mixture was stirred at room temperature for 1 h before it was transferred into a second Schlenk tube containing iodide **16** (2.39 g, 3.02 mmol) and $Pd(PPh_3)_4$ (87.0 mg, 0.076 mmol) in THF (41 mL). The flask was placed into a preheated oil bath at 60°C and the mixture was stirred at this temperature for 2 h under an argon stream to remove the Et_2O. After quenching with sat. aq. NH_4Cl (75 mL) and extraction of the aqueous phase with EtOAc (3 x 75 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Flash chromatography (hexanes/EtOAc 3:1) afforded a crude product which was further purified by preparative HPLC (MeCN/H_2O, 98:2) to yield the desired product as a colorless foam (2.29 g, 75%). $[\alpha]_{20}^{D} = -12.2$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.70-7.67 (m, 4H), 7.44 (d, 2H, *J* = 8.0 Hz), 7.38-7.30 (m, 6H), 7.22 (d, 2H, *J* = 7.8 Hz), 7.14 (s, 2H), 7.05 (s, 1H), 6.95 (dd, 1H, *J* = 8.2, 2.0 Hz), 6.87 (d, 1H, *J* = 1.8 Hz), 6.83 (d, 1H, *J* = 8.4 Hz), 5.03 (s, 2H), 4.40 (dt, 1H, *J* = 6.0, 2.0 Hz), 3.86-3.80 (m, 1H), 3.74 (s, 3H), 3.35 (s, 3H), 3.26-3.17 (m, 1H), 2.81-2.69 (m, 2H), 2.57 (dt, 1H, *J* = 11.0, 5.7 Hz), 2.48 (dt, 1H, *J* = 12.0, 5.0 Hz), 2.34 (s, 3H), 2.08-2.03 (m, 2H), 2.01-1.96 (m, 2H), 1.84 (d, 3H, *J* = 2.0 Hz), 1.75 (t, 3H, *J* = 2.2 Hz), 1.64-1.61 (m, 3H), 1.58-1.39 (m, 5H), 1.06 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$155.2, 153.3, 142.3, 141.1, 136.1 (5C), 135.3, 134.3, 134.0, 131.4, 131.3, 129.8 (2C), 129.5 (2C), 129.2, 128.5, 128.1, 128.0, 127.7 (4C), 125.8 (2C), 115.8, 110.8, 95.5, 81.0, 80.4, 75.9, 70.5, 62.8, 55.8, 55.8 (2C), 52.1, 43.2, 40.8, 38.4, 36.5, 30.9, 30.3, 27.2

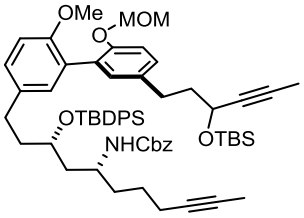


(3C), 26.0 (3C), 25.1, 21.4, 19.5, 18.8, 18.4, 3.7, 3.6, –4.3, –4.8 ppm; IR (film): $\tilde{\nu}$ = 2929, 2857, 1494, 1462, 1427, 1360, 1238, 1154, 1079, 1051, 1004, 922, 835, 812, 776, 740, 702 cm^{-1}; MS (pos. ESI): *m/z* (%): 1034.6 (100); HRMS (ESI): *m/z*: calcd. for $C_{61}H_{81}NO_6SSi_2Na$ $[M+Na]^+$: 1034.52154, found 1034.52082.

Amine S2. A solution of diyne **S1** (2.12 g, 2.09 mmol) and Dess-Martin periodinane (975 mg, 2.30 mmol) in a mixture of MeCN/CH_2Cl_2/H_2O (20.8 mL, 2.6 mL, 2.6 mL) was stirred for 20 h. The reaction was quenched with aq. sat. $NaHCO_3$ (50 mL) and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (hexanes/EtOAc, 3:1 + 1 vol.-% NEt_3) to give the title compound as a pale yellow foam (1.38 g, 76%). $[\alpha]_{20}^{D}$ = +16.6 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, 4H, *J* = 7.0 Hz), 7.41-7.32 (m, 6H), 7.13 (s, 2H), 7.93 (s, 1H), 6.97 (dd, 1H, *J* = 8.4, 1.9 Hz), 6.89 (d, 1H, *J* = 1.5 Hz), 6.81 (d, 1H, *J* = 8.4 Hz), 5.02 (s, 2H), 4.37 (m, 1H), 3.98-3.92 (m, 1H), 3.73 (s, 3H), 3.34 (s, 3H), 2.77-2.67 (m, 3H), 2.63-2.52 (m, 2H), 2.05-2.01 (m, 2H), 1.99-1.94 (m, 2H), 1.83 (d, 3H, *J* = 1.5 Hz), 1.83-1.75 (m, 2H), 1.75 (t, 3H, *J* = 2.2 Hz), 1.64-1.58 (m, 1H), 1.49-1.41 (m, 2H), 1.35-1.27 (m, 2H), 1.18-1.14 (m, 1H), 1.06 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.10 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 153.3, 136.1 (5C), 135.4, 134.5, 134.2, 131.5, 131.4, 129.7 (2C), 129.2, 128.5, 128.2, 128.0, 127.7 (4C), 115.8, 110.7, 95.5, 80.9, 80.4, 79.1, 75.8, 71.5, 62.8, 55.8 (2C), 48.5, 45.3, 40.7, 39.0, 38.0, 30.9, 30.4, 27.2 (3C), 26.0 (3C), 25.7, 19.6, 18.9, 18.4, 3.7, 3.6, –4.3, –4.8 ppm; IR (film): $\tilde{\nu}$ = 2929, 2856, 1500, 1471, 1462, 1427, 1389, 1361, 1238, 1198, 1154, 1104, 1078, 1005, 922, 836, 821, 776, 755, 741, 702, 686, 666 cm^{-1}; MS (pos. ESI): *m/z* (%): 874.7 (100); HRMS (ESI): *m/z*: calcd. for $C_{54}H_{76}NO_5Si_2$ $[M+H]^+$: 874.52566, found 874.52597.

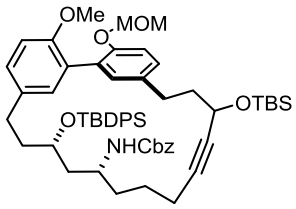


Compound 17. CbzCl (0.451 mL, 3.16 mmol) was added dropwise to a solution of amine **S2** (1.38 g, 1.58 mmol) in NEt_3 (0.661 mL, 4.74 mmol) and EtOAc (10 mL) at 0°C. The suspension was stirred for 30 min before the reaction was quenched with aq. sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography (hexanes/EtOAc, 3:1) afforded the product as a colorless liquid (1.16 g, 79%). $[\alpha]_{20}^{D}$ = +3.4 (c =



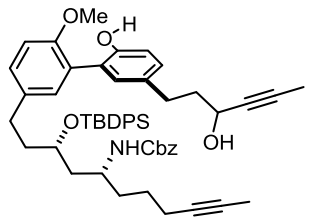
1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.69-7.65 (m, 4H), 7.04-7.32 (m, 11H), 7.14 (s, 2H), 7.06-7.05 (m, 2H), 6.97 (s, 1H), 6.84 (d, 1H, *J* = 8.4 Hz), 5.03 (s, 2H), 5.00 (s, 2H), 4.40-4.37 (m, 1H), 3.87-3.84 (m, 1H), 3.82 (d, 1H, *J* = 9.6 Hz), 3.73 (s, 3H), 3.63-3.55 (m, 1H), 3.36 (s, 3H), 2.81-2.66 (m, 3H), 2.63-2.56 (m, 1H), 2.03 (br s, 2H), 2.01-1.95 (m, 2H), 1.93-1.86 (m, 1H), 1.83 (d, 3H, *J* = 2.0 Hz), 1.81-1.77 (m, 1H), 1.74 (t, 3H, *J* = 2.4 Hz), 1.68-1.62 (m, 1H), 1.43-1.30 (m, 4H), 1.27-1.20 (1H, m), 1.07 (s, 9H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 155.9, 155.2, 153.3, 136.9, 136.0 (4C), 135.3, 134.6, 134.3, 134.2, 131.5 (2C), 129.8 (2C), 129.3, 128.6 (2C), 128.5, 128.2, 128.1 (3C), 128.0, 127.7 (4C), 115.8, 110.9, 95.5, 81.0, 80.4, 78.9, 75.9, 70.7, 66.5, 62.9, 55.8 (2C), 48.3, 42.6, 40.7, 38.2, 35.5, 30.9, 30.5, 27.2 (3C), 26.0 (3C), 25.2, 19.5, 18.7, 18.4, 3.7, 3.6, –4.3, –4.8 ppm; IR (film): $\tilde{\nu} =$ 2929, 2856, 1718, 1504, 1462, 1427, 1360, 1340, 1237, 1155, 1104, 1078, 1004, 921, 835, 821, 775, 754, 701, 666 cm^{-1}; MS (pos. ESI): *m/z* (%): 1030.6 (100); HRMS (ESI): *m/z*: calcd. for $C_{62}H_{81}NO_7Si_2Na$ $[M+Na]^+$: 1030.54438, found 1030.54369.

Cycloalkyne 18. A suspension of diyne **17** (1.37 g, 1.36 mmol) and activated molecular sieves (5Å, powder, 1.36 g) in toluene (680 mL) was stirred for 30 min at room temperature before the molybdenum complex **25** (71.0 mg, 0.068 mmol) was added. The mixture was stirred for 3 h before it was filtered through a plug of silica, eluting with EtOAc (300 mL). The combined filtrates were evaporated and the residue was purified by flash chromatography (hexanes/EtOAc, 6:1) to yield the title compound as a colorless foam (1.18 g, 91%). The ^{1}H and ^{13}C NMR spectra show 4 sets of signals even at elevated temperature ($C_6D_5CD_3$, 378 K), indicating that two diastereomers exist in solution, as two conformers each. $[\alpha]_{20}^{D} =$ +3.4 (c = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $C_6D_5CD_3$): $\delta =$ 7.81-7.64 (m, 4H), 7.23-7.16 (m, 9H), 7.13-7.10 (m, 2H), 7.07-7.04 (m, 2H), 7.0 (s, 2H), 6.98-6.94 (m, 1H), 6.88-6.50 (m, 1H), 5.03-4.92 (m, 2H), 4.90-4.82 (m, 2H), 4.47-4.36 (m, 1H), 4.05-3.74 (m, 3H), 3.38-3.33 (m, 3H), 3.16-3.13 (m, 3H), 2.78-2.66 (m, 3H), 2.59-2.31 (m, 2H), 2.11-1.94 (m, 5H), 1.87-1.78 (m, 1H), 1.55-1.44 (m, 2 H), 1.41-1.31 (m, 2H), 1.25-1.18 (m, 10H), 0.98-0.96 (m, 9H), 0.18-0.09 ppm (m, 6H); ^{13}C NMR (125 MHz, $C_6D_5CD_3$): $\delta =$ 155.5 (3C), 155.4 (4C), 155.3, 154.1 (3C), 154.0, 137.4, 137.3 (2C), 137.0, 136.3, 136.2 (3C), 136.1, 136.0, 135.1 (2C), 134.9, 134.4 (3C), 134.3, 133.8, 133.6, 133.4, 133.2, 132.7, 132.2, 132.1, 131.8, 131.6, 129.8 (3C), 129.7 (2C), 129.6 (2C), 129.4, 129.1, 128.4, 128.3 (5C), 127.8 (3C), 115.1, 115.0, 114.8, 110.7, 110.5, 110.2, 94.8, 94.7, 85.1, 85.0, 84.7, 82.2, 82.0, 81.8, 77.5,



71.4, 68.9, 68.6, 66.4 (2C), 66.1 (2C), 63.2, 63.1, 62.3, 62.2, 55.0 (3C), 54.6 (2C), 54.5, 48.7, 48.2, 47.9, 42.6, 42.4, 42.3, 40.5, 40.2, 39.3, 38.6, 37.2, 34.1, 32.5, 32.0, 31.4, 30.9, 30.7, 30.1, 29.9, 27.0 (2C), 26.9, 25.8 (2C), 25.5, 25.0, 19.5, 19.3, 19.3, 18.7, 18.4, 18.3, 18.2 (2C), 17.9, 1.2, –4.3 (3C), –4.4, –4.8, –4.9, –5.0 (2C), –5.1 ppm; IR (film): $\tilde{\nu}$ = 2931, 2856, 1721, 1501, 1462, 1427, 1340, 1238, 1155, 1077, 1004, 921, 834, 776, 739, 701, 667 cm^{-1}; MS (pos. ESI): *m/z* (%): 976.6 (100); HRMS (ESI): *m/z*: calcd. for $C_{58}H_{75}NO_7Si_2Na$ $[M+Na]^+$: 976.49743, found 976.49649.

Compound 19. A solution of diyne **17** (79.2 mg, 0.078 mmol) in HCl/EtOH (1% conc. HCl in EtOH, *w/w*, 1.2 mL) was stirred for 17 h at room temperature. Aq. sat. $NaHCO_3$ (8 mL) was added and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to give diol **19** as a colorless oil (51.3 mg, 77%).



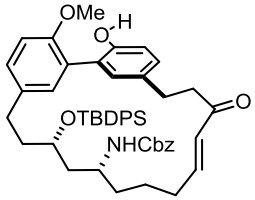
$[\alpha]_{20}^{D}$ = +4.9 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, 4H, *J* = 5.4 Hz), 7.40-7.26 (m, 10H), 7.13 (d, 1H, *J* = 8.2 Hz), 7.09-7.06 (m, 3H), 6.95 (d, 1H, *J* = 8.2 Hz), 6.89 (d, 1H, *J* = 8.0 Hz), 6.32 (s, 1H), 4.96 (m, 2H), 4.40-4.33 (m, 1H), 3.84 (s, 3H), 3.83-3.79 (m, 1H), 3.76 (dd, 1H, *J* = 9.0, 5.4 Hz), 3.60-3.51 (m, 1H), 2.78 (t, 2H, *J* = 7.6 Hz), 2.74-2.68 (m, 1H), 2.67-2.58 (m, 1H), 2.04-1.97 (m, 5H), 1.95-1.86 (m, 1H), 1.83-1.77 (m, 4H), 1.73 (t, 3H, *J* = 2.2 Hz), 1.66-1.59 (m, 2H), 1.38-1.32 (m, 4H), 1.07 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 153.8, 152.1, 136.8, 136.1 (4C), 134.6, 134.3 (2C), 132.6, 131.4 (2C), 129.9 (2C), 129.3, 129.1, 128.6 (2C), 128.2, 128.1 (3C), 127.8 (5C), 117.6, 111.6, 81.3, 80.3, 78.9, 76.0, 70.5, 66.7, 62.0, 56.5, 48.3, 42.7, 40.0, 38.2, 35.7, 30.8, 30.5, 27.2 (3C), 25.2, 19.5, 18.8, 3.7, 3.6 ppm; IR (film): $\tilde{\nu}$ = 3406, 3069, 2932, 2857, 1701, 1588, 1497, 1455, 1427, 1341, 1236, 1181, 1110, 1063, 1027, 909, 821, 773, 734, 702 cm^{-1}; MS (pos. ESI): *m/z* (%): 872.5 (100); HRMS (ESI): *m/z*: calcd. for $C_{54}H_{63}NO_6SiNa$ $[M+Na]^+$: 872.43169, found 872.43221.

Compound 20. *Procedure A:* A solution of diyne **18** (1.18 g, 1.23 mmol) in HCl/EtOH (1% conc. HCl in EtOH, *w/w*, 60 mL) was stirred for 15 h at room temperature. Aq. sat. $NaHCO_3$ (150 mL) was then added and the aqueous layer was extracted with EtOAc (3 x 250 mL). The combined extracts were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to give diol **20** as a colorless oil (880 mg, 89%). *Procedure B:* A suspension of diyne **19** (51.3 mg, 0.060 mmol) and activated molecular sieves (5Å, powder, 60 mg) in toluene (30 mL) was stirred for 15 min at room temperature before the molybdenum complex **25** (3.1 mg, 3.0 µmol) was added. The mixture was stirred for 3 h before it was filtered through a plug of silica, eluting with EtOAc (50 mL). The combined filtrates were evaporated and the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to give the title compound as a colorless oil (37.3 mg, 78%). For analytical purposes the diastereomeric mixture was separated by flash chromatography (hexanes/CH_2Cl_2/acetone, 10:10:1, Merck silica gel 60 (15-40 µm)). *Diastereomer A*: $[\alpha]_{20}^{D} = -50.0$ (c = 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.66-7.63 (m, 4H), 7.40-7.29 (m, 11H), 7.16 (s, 2H), 7.11 (dd, 1H, *J* = 8.2, 1.6 Hz), 7.06 (d, 1H, *J* = 8.0 Hz), 6.95 (d, 1H, *J* = 8.2 Hz), 6.92 (d, 1H, *J* = 8.4 Hz), 6.76 (s, 1H), 5.01 (d, 1H, *J* = 12.2 Hz), 4.94 (d, 1H, *J* = 12.2 Hz), 4.44-4.41 (m, 1H), 3.98-3.95 (m, 1H), 3.93 (s, 3H), 3.84-3.80 (m, 2H), 0.43-3.41 (br s, 1H), 2.86-2.68 (m, 3H), 2.65-2.60 (m, 1H), 2.28 (m, 1H), 2.20-2.15 (m, 1H), 2.12-2.05 (m, 1H), 2.01-1.94 (m, 1H), 1.90-1.80 (m, 2H), 1.76-1.71 (m, 1H), 1.58-1.49 (m, 1H), 1.46-1.40 (m, 2H), 1.32-1.23 (m, 2H), 1.07 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 156.1, 153.3, 152.3, 136.5, 136.2, 136.1 (2C), 136.0 (2C), 134.5, 134.3, 133.9 (2C), 132.8, 132.5, 129.9, 129.8, 129.5, 129.1, 128.6 (2C), 128.3 (3C), 127.8 (4C), 126.3, 118.3, 111.9, 85.1, 82.7, 70.5, 66.9, 60.8, 56.8, 48.3, 42.8, 38.9, 37.5, 35.3, 30.9, 30.5, 27.2 (3C), 23.6, 19.5, 18.8 ppm; IR (film): $\tilde{\nu} =$ 3399, 3353, 2932, 2857, 1700, 1498, 1454, 1427, 1342, 1263, 1236, 1180, 1110, 1083, 1062, 1021, 822, 737, 703, 612, 506 cm^{-1}; MS (pos. ESI): *m/z* (%): 818.5 (100); HRMS (ESI): *m/z*: calcd. for $C_{50}H_{57}NO_6SiNa$ $[M+Na]^+$: 818.38474, found 818.38551.

Diastereomer B: $[\alpha]_{20}^{D} = +47.7$ (c = 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.67 (d, 2H, *J* = 6.8 Hz), 7.63 (d, 2H, *J* = 7.0 Hz), 7.40-7.29 (m, 11H), 7.14 (dd, 1H, *J* = 8.7, 1.9 Hz), 7.07 (d, 1H, *J* = 8.6 Hz), 7.08 (s, 1H), 7.07 (s, 1H), 7.02 (d, 1H, *J* = 8.2 Hz), 6.96 (d, 1H, *J* = 8.2 Hz), 6.91 (d, 1H, *J* = 8.3 Hz), 6.62 (s, 1H), 4.97 (s, 2H), 4.30-4.26 (m, 1H), 3.90 (s, 3H), 3.87-3.85 (m, 2H), 3.59-3.52 (m, 1H), 2.85-2.80 (m, 1H), 2.76-2.69 (m, 2H), 2.67-2.61 (m, 1H), 2.28-2.15 (m, 2H), 2.05-1.98 (m, 3H), 1.87-1.76 (m, 2H), 1.49-1.46 (m, 2H), 1.41-1.30 (m, 3H), 1.07 ppm (s,

9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 153.4, 152.3, 136.7, 136.4, 136.1 (2C), 136.0 (2C), 134.3 (2C), 133.9, 132.7, 132.2, 129.9 (2C), 129.1, 128.9, 128.6, 128.2 (2C), 128.2 (2C), 127.8 (4C), 127.6, 126.4, 118.2, 112.1, 85.6, 81.7, 69.9, 66.7, 62.2, 56.8, 48.2, 41.9, 39.8, 37.6, 34.4, 30.8, 29.8, 27.2 (3C), 25.0, 19.5, 18.1 ppm; IR (film): $\tilde{\nu}$ = 3401, 3353, 2932, 2858, 1703, 1498, 1454, 1427, 1341, 1264, 1235, 1108, 1061, 1020, 895, 820, 733, 700, 611, 501, 438 cm^{-1}; MS (pos. ESI): *m/z* (%): 818.5 (100); HRMS (ESI): *m/z*: calcd. for $C_{50}H_{57}NO_6SiNa$ $[M+Na]^+$: 818.38474, found 818.38551.

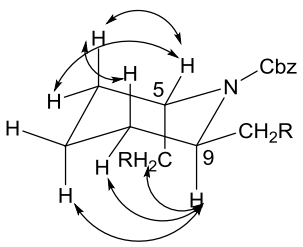
Enone 21. A solution of the propargylic alcohol **20** (413 g, 0.519 mmol), [(indenyl)Ru(PPh_3)$_2$Cl] (12.1 mg, 0.016 mmol) and CSA (12.1 mg, 0.052 mmol) in THF (49 mL) was stirred for 5 min before In(OTf)$_3$ (8.75 mg, 0.016 mmol) was introduced. The flask was placed in a preheated oil bath at 80°C and the mixture stirred at this temperature for 4 h. Additional [(indenyl)Ru(PPh_3)$_2$Cl] (12.1 mg, 0.016 mmol) and In(OTf)$_3$ (8.75 mg, 0.016 mmol) were added and stirring continued for another 1 h. The solution was filtered through a plug of silica, rinsing with EtOAc (50 mL). The filtrate was evaporated and the crude product purified by flash chromatography (hexanes/EtOAc, 3:1) to afford product **21** as a white solid (304 mg, 74%). $[\alpha]_{20}^{D}$ = +17.5 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, 2H, *J* = 7.2 Hz), 7.63 (d, 2H, *J* = 7.3 Hz), 7.41-7.28 (m, 11H), 7.12 (dd, 1H, *J* = 8.2, 1.9 Hz), 7.02 (d, 1H; *J* = 7.8 Hz), 6.98 (s, 1H), 6.94 (d, 1H, *J* = 7.9 Hz), 6.93 (s, 1H), 6.90 (d, 1H, *J* = 8.4 Hz), 6.73 (dt, 1H, *J* = 15.8, 7.0 Hz), 6.42 (s, 1H), 6.03 (d, 1H, *J* = 15.8 Hz), 4.96 (s, 2H), 3.96-3.94 (m, 1H), 3.88 (s, 3H), 3.85-3.82 (m, 1H), 3.53-3.45 (m, 1H), 2.99-2.92 (m, 2H), 2.90 (s, 2H), 2.74-2.67 (m, 1H), 2.61-2.54 (m, 1H), 2.20-2.07 (m, 2H), 2.01-1.91 (m, 1H); 2.83-1.74 (m, 2H), 1.45-1.37 (m, 2H), 1.35-1.23 (m, 4H), 1.08 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0, 155.8, 153.5, 152.4, 147.6, 136.3, 136.0 (4C), 134.0 (2C), 133.4, 133.2, 132.8, 131.5, 130.5, 129.9 (2C), 129.8, 129.0 (2C), 128.6 (2C), 128.2, 128.1, 127.8 (4C), 127.4, 126.5, 118.0, 112.0, 70.0, 66.6, 56.7, 48.3, 41.6, 40.7, 37.8, 34.8, 31.7, 30.6, 29.8, 27.1 (3C), 24.5, 19.5 ppm; IR (film): $\tilde{\nu}$ = 3347, 2932, 2858, 1715, 1668, 1499, 1454, 1427, 1338, 1237, 1110, 1085, 1027, 821, 740, 702 cm^{-1}; MS (pos. ESI): *m/z* (%): 818.4 (100); HRMS (ESI): *m/z*: calcd. for $C_{50}H_{57}NO_6SiNa$ $[M+Na]^+$: 818.38474, found 818.38440.



21

Piperidines 22 and 9-*epi*-22. A solution of PTSA (0.1 M in CH_2Cl_2, 0.250 mL, 0.025 mmol) was added to a solution of enone **21** (200 mg, 0.251 mmol) in $ClCH_2CH_2Cl$ (8.2 mL) and the mixture was stirred at 45°C for 14 h. After quenching the reaction with sat. aq. $NaHCO_3$ (20 mL) and extraction of the aqueous phase with EtOAc (3 x 50 mL), the combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (hexanes/CH_2Cl_2/acetone 10:10:1, Merck silica gel 60 (15-40 µm)) yielded **22** (93.5 mg, 47%, 67% brsm) and a second fraction consisting of **9-*epi*-22** (38.9 mg, 20%, 27% brsm) as white solids each. *Data of compound* **22:** $[\alpha]_{20}^{D} = +40.1$ (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6, 318 K): $\delta =$ 7.93-7.90 (m, 4H), 7.72-7.70 (m, 2H), 7.51 (d, 1H, *J* = 2.0 Hz), 7.27 (d, 1H, *J* = 2.0 Hz), 7.24-7.21 (m, 5H), 7.10-7.09 (m, 2H), 7.04-7.02 (m, 2H), 7.00 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.98-6.96 (m, 1H), 6.92 (s, 1H), 6.90 (dd, 1H, *J* = 8.3, 2.3 Hz), 6.49 (d, 1H, *J* = 8.3 Hz), 4.79-4.77 (m, 2H), 4.57-4.53 (m, 1H), 4.42 (d, 1H, *J* = 12.6 Hz), 3.45 (dddd, 1H, *J* = 11.8, 9.4, 5.3, 2.2 Hz), 3.34 (dd, 1H, *J* = 17.1, 9.3 Hz), 3.20 (ddd, 1H, *J* = 14.3, 11.8, 2.0 Hz), 3.13 (s, 3H), 3.02 (ddd, 1H, *J* = 15.5, 6.7, 5.7 Hz), 2.76 (ddd, 1H, *J* = 17.6, 12.0, 1.0 Hz), 2.72 (ddd, 1H, *J* = 15.4, 7.2, 5.8 Hz), 2.43 (ddd, 1H, *J* = 14.2, 7.1, 1.8 Hz), 2.34 (ddd, 1H, *J* = 14.3, 11.0, 2.9 Hz), 2.25 (dddd, 1H, *J* = 13.7, 7.1, 5.9, 3.4 Hz), 2.24 (ddd, 1H; *J* = 17.4, 7.0, 1.9 Hz), 2.03 (dd, 1H, *J* = 17.1, 5.3 Hz), 1.97 (ddd, 1H, *J* = 14.0, 7.5, 6.4 Hz), 1.40-1.34 (m, 1H), 1.25 (ddd, 1H, *J* = 14.3, 8.2, 3.5 Hz), 1.25 (s, 9H), 1.22-1.19 (m, 2H), 1.15 (qd, 1H, *J* = 12.0, 4.6 Hz), 1.06-1.01 ppm (m, 2H); ^{13}C NMR (150 MHz, C_6D_6, 318 K): $\delta =$ 205.1, 154.8, 153.6, 153.1, 137.9, 137.3, 136.7 (2C), 136.6 (2C), 136.0, 135.8, 135.2 (2C), 134.4, 133.7, 132.5, 129.8 (2C), 129.7, 129.6, 129.2, 129.1, 128.4, 128.1, 127.9, 127.7, 126.7, 117.9, 112.2, 71.5, 66.5, 56.1, 50.4, 48.1, 47.7, 43.5, 38.4, 37.3, 32.0, 30.9, 30.3, 30.1, 28.4, 27.6 (3C), 26.8, 20.5, 19.9 ppm; IR (film): $\tilde{\nu} =$ 3394, 2928, 2855, 1716, 1694, 1498, 1428, 1308, 1284, 1236, 1110, 1080, 1025, 821, 740, 702 cm^{-1}; MS (pos. ESI): *m/z* (%): 818.6 (100); HRMS (ESI): *m/z*: calcd. for $C_{50}H_{57}NO_6SiNa$ $[M+Na]^+$: 818.38474, found 818.38399.

nOe-analysis:



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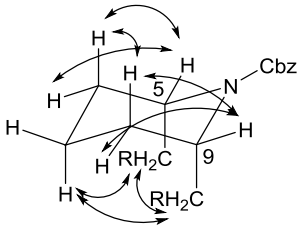
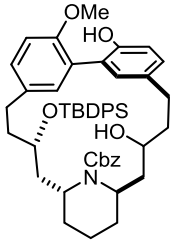
Data of compound **9-*epi*-22:** $[\alpha]_{20}^{D} = 38.7$ (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6, 318 K): $\delta =$ 7.83-7.81 (m, 2H), 7.70 (d, 2H, *J* = 7.2 Hz), 7.37 (d, 2H, *J* = 5.5 Hz), 7.29-7.27 (m, 2H), 7.23-7.20 (m, 1H), 7.17-7.14 (m, 4H), 7.10 (d, 1H, *J* = 2.3 Hz), 7.07-7.03 (m, 3H), 7.00 (d, 1H, *J* = 8.1 Hz), 6.84 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.47 (d, 1H, *J* = 8.3 Hz), 6.42 (d, 1H, *J* = 8.3 Hz), 6.23 (m, 1H), 5.23-5.19 (m, 2H), 5.02 (br s, 1H), 4.83 (br s, 1H), 3.47 (3.50-3.46 m, 1H), 3.16 (s, 3H), 2.82 (ddd, 1H, *J* = 14.4, 11.9, 4.2 Hz), 2.64 (dt, 1H, *J* = 14.4, 4.8), 2.60-2.55 (m, 1H), 2.50 (d, 1H, *J* = 17.5, 10.6 Hz), 2.47 (ddd, 1H, *J* = 13.1 Hz, 13.0 Hz, 4.2 Hz), 2.41-2.37 (br s, 2H), 2.10 (dt, 1H, *J* = 13.6, 4.7 Hz), 1.99 (br s, 1H), 1.91-1.83 (m, 1H), 1.80 (ddd, 1H, *J* = 13.3, 11.3, 3.0 Hz), 1.79-174 (m, 1H), 1.34-1.28 (m, 2H), 1.14 (s, 9H), 1.11-1.06 (m, 2H), 0.78 (d(quint), 1H, *J* = 14.0, 4.0 Hz), 0.49 (q, 1H, *J* = 12.0 Hz); ^{13}C NMR (150 MHz, C_6D_6, 318 K): $\delta =$ 207.9, 155.5, 153.9, 153.5, 138.0, 136.4 (2C), 136.2 (2C), 135.6 (2C), 135.0, 134.8, 134.3, 132.2, 131.1, 130.0, 129.8 (2C), 128.6 (2C), 128.4, 128.3 (6C), 126.4, 118.3, 113.5, 70.0, 67.0, 56.4, 50.9, 48.3, 46.3, 42.2, 38.3, 38.2, 31.1, 30.1, 30.0, 28.2, 27.3 (3C), 26.2, 19.6, 14.2 ppm; IR (film): $\tilde{\nu} =$ 3368, 2932, 2897, 2857, 1711, 1686, 1499, 1454, 1427, 1409, 1359, 1320, 1295, 1271, 1237, 1178, 1108, 1090, 1062, 1022, 1012, 901, 821, 802, 768, 735, 702, 610, 502 cm^{-1}; MS (EI): *m/z* (%): 739 (25), 738 (46), 696 (19), 695 (54), 694 (100), 225 (14), 199 (12), 91 (44), 82 (11); HRMS (ESI): *m/z*: calcd. for $C_{50}H_{57}NO_6SiNa$ $[M+Na]^+$: *m/z*: calcd. for $C_{50}H_{57}NO_6SiNa$ $[M+Na]^+$: 818.38474, found 818.38491.

nOe-analysis:



Compound 23 and 11-*epi*-23. *Procedure A:* $NaBH_4$ (13.3 mg, 0.351 mmol) was added at 0°C to



a solution of ketone **22** (93.1 mg, 0.117 mmol) in MeOH (4.7 mL). The mixture was stirred for 1.5 h at this temperature before the reaction was quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (4 x 25 mL) and the combined extracts were dried ($MgSO_4$) and evaporated. Analysis of the crude material by ^{1}H NMR revealed a ratio of ≈ 1:1 for the two products. Purification of the residue by flash chromatography (hexanes/CH_2Cl_2/acetone, 10:10:1; Merck

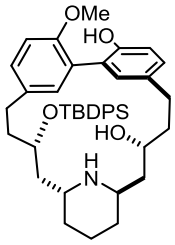
silica gel 60 (15-40 µm)) afforded products **23** (45.7 mg, 49%, 1:0.6 mixture of conformers) and 11-*epi*-**23** (37.4 mg, 40%) as white solids each. *Procedure B*: A Schlenk tube was charged with pre-dried LiCl (39 mg, 0.92 mmol) and was evacuated while being heated (heatgun). After the flask had reached ambient temperature, a solution of compound **22** (73.3 mg, 0.092 mmol) in Et_2O (4.5 mL) was introduced and the mixture was sonicated in an ultrasound bath for 15 min. The suspension was cooled to 0°C before $LiAlH(OtBu)_3$ (1 M in THF, 0.37 mL, 0.37 mmol) was added dropwise at this temperature. Stirring was continued at 0°C for 4 h before the reaction was quenched with aq. sat. NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), the combined extracts were dried (Na_2SO_4) and the solvent was evaporated. ^{1}H NMR analysis of the crude product showed a diastereomeric ratio of 10:1 in favor of **23**. Purification of the crude product by flash chromatography (hexanes/CH_2Cl_2/acetone, 10:10:1; Merck silica gel 60 (15-40 µm)) furnished product **23** as a colorless foam (67.3 mg, 92%, 1:0.6 mixture of conformers). *Data of compound* **23**: $[\alpha]_{20}^{D} = +7.9$ (c = 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.70-7.62 (m, 6.4H), 7.44-7.43 (m, 14.4H), 7.18-7.17 (m, 1.2H), 7.12 (dd, 2H, *J* = 8.4, 2.0 Hz), 7.08-7.07 (m, 2H), 7.06-7.02 (m, 3.2H), 6.97-6.92 (m, 2H), 6.90-6.83 (m, 3H), 6.74 (s, 1H), 5.20 (d, 1H, *J* = 12.2 Hz), 5.02 (d, 1H, *J* = 12.2 Hz), 4.92 (d, 0.6H, *J* = 12.0 Hz), 4.82-4.77 (m, 1H), 4.60 (d, 0.6H, *J* = 12.0 Hz), 4.33 (sext, 0.6H, *J* = 5.1 Hz), 4.09-4.04 (m, 0.6H), 3.91 (s, 1.8H), 3.90 (s, 3H), 3.81-3.75 (m, 1H), 3.73-3.68 (m, 1H), 3.63-3.57 (m, 0.6H), 3.09 (td, 1H, *J* = 9.8, 4.5 Hz), 2.94-2.87 (m, 1H), 2.74-2.61 (5.2H), 2.53-2.36 (m, 3H), 2.02-1.93 (m, 3.2H), 1.88-1.65 (m, 8.2H), 1.63-1.43 (m, 7.6H), 1.28-1.24 (m, 1.2H), 1.05 (s, 5.4H), 1.01 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 157.4, 157.2, 153.3, 153.2, 152.1 (2C), 137.0, 136.6, 136.3, 136.2, 136.1 (2C), 134.5, 134.4 (2C), 134.3, 134.2, 134.1, 133.9, 133.2, 132.2, 131.5, 129.9, 129.8, 129.7, 129.6, 129.0, 128.9, 128.6, 128.4 (2C), 128.1, 128.0 (2C), 127.8, 117.7, 127.6, 126.4, 126.1, 118.0, 117.6, 111.8, 111.6, 71.1, 70.4, 69.2, 68.7, 67.1, 66.9, 56.7, 56.6, 53.8, 51.4, 48.7, 42.2, 39.8, 39.7, 38.7, 38.0, 37.7, 37.3, 36.4, 31.1, 30.3, 29.9, 29.6, 28.2, 27.7, 27.3 (3C), 27.1 (3C), 20.3, 19.5, 19.4 ppm; IR (film): $\tilde{\nu} =$ 3419, 2930, 2897, 2859, 1694, 1499, 1456, 1444, 1427, 1269, 1238, 1111, 1075, 1027, 823, 744, 702, 571, 491, 427 cm^{-1}; MS (EI): *m/z* (%): 742 (22), 741 (56), 740 (97), 723 (18), 722 (30), 697 (23), 696 (45), 679 (11), 678 (23), 663 (20), 662 (46), 634 (14), 633 (48), 632 (100), 619 (19), 618 (40), 589 (14), 588 (33), 554 (15), 528 (15), 524 (17), 510 (16), 480 (22), 450 (25), 406 (14), 316 (10), 225 (21), 211 (13), 199 (28), 183 (11), 135 (12), 96 (14), 91 (73), 84 (11), 83 (14), 82 (13); HRMS (ESI): *m/z*: calcd. for $C_{50}H_{59}NO_6SiNa$ $[M+Na]^+$: 820.40038, found 820.40048.

Data of compound 11-*epi*-**23:** $[\alpha]_{20}^{D} = 15.5$ (c = 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.84-7.82 (m, 2H), 7.67-7.62 (m, 3.5H), 7.59-7.57 (m, 2H), 7.45-7.34 (m, 9.5H), 7.24 (s, 1H), 7.22 (s, 0.7H), 7.18-7.16 (m, 4.4H), 7.14-7.10 (m, 3.4H), 7.05 (dd, 1H, *J* = 8.4, 2.2 Hz), 7.02-7.00 (m, 4.1H), 6.98-6.95 (m, 1.7H), 6.89-6.87 (m, 2.4H), 6.53 (s, 0.7H), 6.45 (s, 1H), 4.96-4.88 (m, 1.4H), 4.59-4.56 (m, 2H), 4.43 (d, 1H, *J* = 12.0 Hz), 4.30-4.23 (m, 1.7H), 4.00-3.97 (m, 1H), 3.93 (s, 3H), 3.86 (s, 2.1H), 3.72-3.66 (m, 0.7H), 3.56-3.48 (m, 1.7H), 3.18-3.08 (m, 2H), 2.97-2.90 (m, 1H), 2.76 (ddd, 1H, *J* = 16.6, 11.3, 4.2 Hz), 2.61-2.27 (m, 6.5H), 2.17-2.10 (m, 1.7H), 1.95-1.78 (m, 5.1H), 1.58-1.11 (m, 13H), 1.06 (s, 15.3H), 0.58 ppm (d, 1H, *J* = 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 156.3, 153.4, 153.3, 152.0 (2C), 136.9, 136.8, 136.5 (2C), 136.3, 136.2, 136.1, 136.0, 135.3, 134.3 (2C), 133.9, 132.6, 131.0, 130.3, 130.0, 129.9, 129.8, 129.7, 129.5, 128.9, 128.6, 128.3, 137.9 (2C), 127.8, 127.7, 127.6, 127.3, 126.2, 126.1, 118.3, 118.0, 111.6, 111.5, 70.4, 40.0, 67.4, 66.5, 65.2, 65.0, 56.6 (2C), 52.8, 51.7, 49.9, 47.8, 42.3, 42.0, 39.4, 38.4, 36.8, 35.4, 31.6, 30.5, 30.2, 30.0, 29.6, 28.4, 27.4 /3C), 27.3 (3C), 26.2, 20.5, 19.4 (2C) ppm; IR (film): $\tilde{\nu} =$ 3406, 2930, 2857, 1699, 1675, 1499, 1427, 1282, 1236, 1212, 1143, 1109, 1076, 1064, 1027, 939, 822, 740, 702, 608, 505, 491 cm^{-1}; MS (pos. ESI): *m/z* (%): 820.5 (100); HRMS (ESI): *m/z*: calcd. for $C_{50}H_{59}NO_6SiNa$ $[M+Na]^+$: 820.40038, found 820.40048.

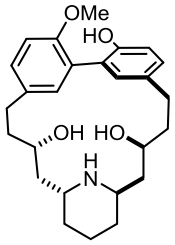
Compound S3. Compound **23** (45.7 mg, 0.057 mmol) was dissolved in HCl/EtOH (0.05 M, 5.73 mL, 0.287 mmol) and palladium black (0.61 mg, 5.7 µmol) was added. The flask was evacuated and backfilled with hydrogen four times. After stirring for 23 h, the suspension was filtered and the filtrate treated with sat. aq. $NaHCO_3$ (25 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL), the combined extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 1:1 + 1 vol.-% NEt_3) to give amine **S3** (35.2 mg, 93%) as a white solid. $[\alpha]_{20}^{D} = -48.3$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.69-7.66 (m, 3H), 7.55-7.54 (m, 2H), 7.43-7.29 (m, 5H), 7.15 (t, 2H, *J* = 7.5 Hz), 7.11 (dd, 1H, *J* = 8.2, 2.2 Hz), 7.08 (dd, 1H, *J* = 8.5, 2.2 Hz), 6.98 (d, 1H, *J* = 8.2 Hz), 6.94 (d, 1H, *J* = 8.4 Hz), 5.66 (br s, 1H), 4.06 (tt, 1H, *J* = 8.7, 4.5 Hz), 3.93 (s, 3H), 3.54 (tt, 1H, *J* = 10.2, 2.0 Hz), 3.21 (dq, 1H, *J* = 8.7, 4.1 Hz), 2.96-2.88 (m, 1H), 2.85-2.80 (m, 2H), 2.65 (dt, 1H, *J* = 14.0, 4.4 Hz), 2.17-2.08 (m, 2H), 1.98-1.89 (m, 1H), 1.84-1.68 (m, 2H), 1.53-1.24 (m, 8H), 1.16-1.00 (m, 2H), 0.88 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 153.0, 152.1, 136.6, 136.2 (2C), 136.1 (2C), 134.8, 134.3, 134.1, 133.7, 132.4, 129.4 (2C), 129.2, 129.1, 128.2, 127.6 (2C), 127.5 (2C), 125.9, 117.5, 112.1, 70.6, 70.0, 56.9, 51.3, 46.8, 42.7, 40.7, 38.1, 35.2, 34.3, 32.9, 30.6, 30.4, 26.9 (3C), 19.5,

19.4 ppm; IR (film): $\tilde{\nu}$ = 3342, 2966, 2923, 2853, 1500, 1427, 1259, 1112, 1016, 747, 704, 506 cm^{-1}; MS (pos. ESI): *m/z* (%): 664.5 (100); HRMS (ESI): *m/z*: calcd. for $C_{42}H_{54}NO_4Si$ $[M+H]^+$: 664.38166, found 664.38166.

Compound 11-*epi*-S3. This epimer was prepared analogously in 65% yield. $[\alpha]_{20}^{D}$ = –6.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ =7.70-7.68 (m, 2H), 7.62-7.60 (m, 2H), 7.41-7.32 (m, 4H), 7.30-7.28 (m, 2H), 7.09-7.02 (m, 4H), 6.94 (d, 1H, *J* = 8.0 Hz), 6.90 (d, 1H, *J* = 8.9 Hz), 6.52 (br s, 1H), 4.13-4.07 (m, 1H), 3.91 (s, 3H), 3.90-3.85 (m, 1H), 3.12 (dt, 1H, *J* = 8.9, 4.5 Hz), 2.82-2.73 (m, 3H), 2.69-2.61 (m, 2H), 2.02-1.81 (m, 4H), 1.74 (dddd, 1H, *J* = 13.2, 9.7, 6.2 4.0 Hz), 1.61-1.52 (m, 1H), 1.46-1.38 (m, 3H), 1.34-1.32 (m, 3H), 1.29-1.24 (m, 1H), 1.19-1.16 (m, 1H), 1.03 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 152.0, 136.3, 136.2 (2C), 136.1 (2C), 134.7, 134.5, 134.3, 132.5, 131.8, 129.7 (2C), 129.6 (2C), 127.7 (2C), 127.6 (2C), 127.4, 126.3, 117.7, 111.6, 70.8, 65.5, 56.6, 47.8, 46.4, 42.9, 40.9, 39.1, 36.5, 33.5, 32.5, 30.3, 29.5, 27.2 (3C), 19.8, 19.5 ppm; IR (film): $\tilde{\nu}$ = 3378, 2929, 2856, 1498, 1427, 1361, 1265, 1237, 1108, 1081, 1022, 821, 736, 702, 612, 507 cm^{-1}; MS (pos. ESI): *m/z* (%): 664.4 (100); HRMS (ESI): *m/z*: calcd. for $C_{42}H_{54}NO_4Si$ $[M+H]^+$: 664.38166, found 664.38183.



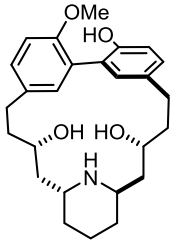
Lythranidine (1). HOAc (6.4 µL, 0.11 mmol) and TBAF (1 M in THF, 0.11 mL, 0.11 mmol) were succesively added to a solution of **S3** (15 mg, 23 µmol) in THF (2 mL). The mixture was stirred for 3 d at 45°C before the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and the aqueous layer was extracted with toluene (4 x 2 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (EtOAc/MeOH/H_2O, 6:1:0.5; neutral Alox) to give the title compound as a white solid (7.9 mg, 82%). ^{1}H NMR (600 MHz, C_6D_6, 318 K): δ = 8.02 (s, 1H), 7.90 (d, 1H, *J* = 1.8 Hz), 7.29 (d, 1H, 8.1 Hz), 7.10 (dd, 1H, *J* = 8.1, 2.2 Hz), 7.05 (dd, 1H, *J* = 8.2, 2.2 Hz), 6.59 (d, 1H, *J* = 8.3 Hz), 3.86-3.83 (m, 2H), 3.18 (m, 3H), 3.01-2.93 (m, 2H), 2.87-2.85 (m, 1H), 2.76 (ddd, 1H, *J* = 14.4, 5.5, 3.5 Hz), 2.60 (br s, 1H), 2.50 (br s, 1H), 1.83-1.76 (m, 2H), 1.70-1.65 (m, 1H), 1.61-1.57 (m, 1H), 1.51-1.45 (m, 1H), 1.40-1.34 (m, 1H), 1.27-1.23 (m, 2H), 1.13-1.05 (m, 2H), 0.95 (ddd, 1H, *J* = 14.3, 4.6, 2.3 Hz), 0.87 (ddd, 2H, *J* = 14.1, 5.6, 3.2 Hz), 0.80-0.75 ppm (m, 1H); ^{13}C NMR (125 MHz, C_6D_6, 318 K): δ = 153.9, 153.4, 137.9, 135.7, 135.3, 134.1, 129.9, 129.2, 128.9, 127.3, 118.2, 112.1, 71.7, 70.8, 56.3, 51.4, 51.0, 41.5, 39.7, 39.3, 38.7, 33.3, 33.0, 31.0 (2C), 20.1 ppm; IR (film): $\tilde{\nu}$ =



3346, 3151, 2933, 2859, 2838, 1499, 1437, 1411, 1276, 1236, 1163, 1101, 1070, 1020, 824, 733, 700, 488 cm^{-1}; MS (ESI): *m/z* (%): 426.0 (100); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{36}NO_4$ $[M+H]^+$: 426.26388 found 426.26367.

Lythranidine•HOAc (1•HOAc). Lythranidine (4.8 mg, 11 µmol) was dissolved in toluene (2 mL) and 3 drops of acetic acid were added. The solution was stirred for 1 h at room temperature and the solvent was evaporated to afford the corresponding hyrdoacetate (5.4 mg, quant.). $[\alpha]_{20}^{D} = -79.0$ (c = 0.88, 1,4-dioxane) [lit.: -71° (c = 1.7, 1,4-dioxane)]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.71 (s, 1H), 7.55 (s, 1H), 7.08 (dd, 1H, *J* = 8.3, 2.0 Hz), 7.03 (dd, 1H, *J* = 8.3, 2.0 Hz), 6.87 (d, 1H, *J* = 8.2 Hz), 6.85 (d, 1H, *J* = 8.4 Hz), 4.11-4.04 (m, 2H), 3.84 (s, 3H), 3.66-3.52 (m, 2H), 2.94-2.71 (m, 4H), 2.30-2.20 (m, 2H), 1.83-1.56 (m, 10H), 1.43 (s, 3H), 1.34-1.22 ppm (m, 2H).

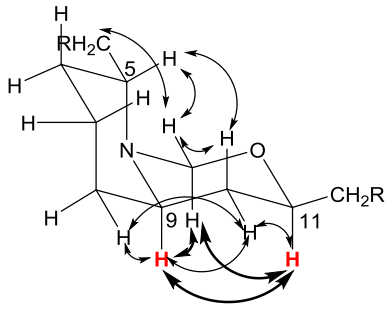
11-*epi*-Lythranidine (11-*epi*-1). The epimer was prepared analogously in 79% yield. The



purification was performed on deactivated silica gel, eluting with EtOAc/MeOH/MeCN/H_2O (6:1:1:0.5). $[\alpha]_{20}^{D} = -38.9$ (c = 1.0, 1,4-dioxane); ^{1}H NMR (600 MHz, C_6D_6, 318 K): $\delta =$ 7.94 (d, 1H, *J* = 1.9 Hz), 7.30 (d, 1H, *J* = 1.9 Hz), 7.26 (d, 1H, *J* = 8.2 Hz), 7.06 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.01 (dd, 1H, *J* = 8.2, 2.0 Hz), 6.59 (d, 1H, *J* = 8.2 Hz), 4.07-4.03 (m, 1H), 3.63 (t, 1H, *J* = 10.4 Hz), 3.40-3.35 (m, 1H), 3.25 (td, 1H, *J* = 13.3, 3.3 Hz), 3.18 (s, 3H), 3.06-3.02 (m, 1H), 2.56-2.52 (m, 2H), 2.16-2.13 (m, 1H), 1.82-1.77 (m, 4H), 1.41-1.19 (m, 5H), 1.13-1.08 (m, 2H), 0.94-0.87 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6, 318 K): $\delta =$ 154.0, 153.3, 136.2, 136.1, 135.6, 130.8, 130.4, 129.0, 128.1, 127.2, 118.4, 111.9, 69.5, 65.8, 55.9, 51.8, 47.4, 42.8, 39.8, 39.1, 38.5, 33.6, 30.7, 30.3, 29.5, 19.9 ppm; IR (film): $\tilde{\nu} =$ 3260, 2928, 2858, 1559, 1499, 1412, 1278, 1239, 1091, 1075, 1020, 816, 734 cm^{-1}; MS (EI): *m/z* (%): 426 (38), 425 (87), 424 (21), 409 (13), 408 (15), 407 (10), 381 (12), 380 (23), 368 (11), 367 (13), 212 (12), 211 (30), 210 (10), 209 (13), 207 (14), 205 (14), 198 (11), 195 (25), 194 (24), 184 (15), 183 (21), 182 (12), 181 (21), 178 (12), 174 (11), 167 (11), 166 (11), 165 (15), 155 (22), 153 (16), 152 (13), 142 (16), 141 (11), 140 (25), 128 (20), 127 (21), 126 (27), 124 (13), 122 (22), 115 (13), 113 (11), 108 (11), 98 (21), 97 (16), 96 (78), 84 (55), 83 (100), 82 (90), 81 (17), 80 (11), 79 (16), 70 (18), 69 (14), 68 (20), 67 (14), 57 (15), 56 (50), 55 (71), 45 (13), 44 (57), 43 (34), 42 (15), 41 (37), 40 (11), 39 (12), 30 (22), 29 (21); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{34}NO_4$ $[M-H]^-$: 424.24933, found 424.24946.

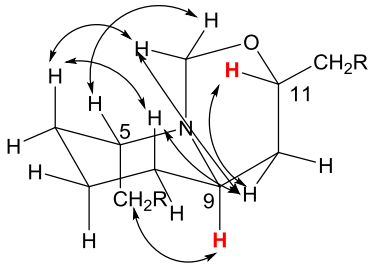
Compound 24. A solution of compound **S3** (16.5 mg, 24.9 µmol) and formaldehyde (37 w-% in H_2O, 2.3 µL, 31 µmol) in MeOH (3 mL) was stirred for 20 h at room temperature before the reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated. Flash chromatography (pentane/Et_2O, 1:2 + 1 vol.-% NEt_3) afforded the product as a colorless oil (12.8 mg, 76 %). $[\alpha]_{20}^{D} = -4.3$ (c = 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $C_6D_5CD_3$, 363 K): $\delta =$ 7.59-7.76 (m, 4H), 7.48 (d, 1H, *J* = 2.2 Hz), 7.18 (d, 1H, *J* = 2.3 Hz), 7.16-7.10 (m, 6H), 7.03 (d, 1H, *J* = 8.1 Hz), 6.94 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.77 (ddt, 1H, *J* = 8.3, 2.3, 0.7 Hz), 6.60 (s, 1H), 6.52 (d, 1H, *J* = 8.3 Hz), 4.09 (dddd, 1H, *J* = 9.1, 8.2, 5.1, 3.3 Hz), 4.04 (d, 1H, 10.3 Hz), 3.77 (d, 1H, *J* = 10.3 Hz), 3.31 (s, 3H), 3.14 (dddd, 1H, *J* = 10.9, 6.4, 4.6, 2.4 Hz), 3.02 (dq, 1H, *J* = 9.1, 3.9 Hz), 2.86 (ddd, 1H, *J* = 14.9, 9.5, 6.8 Hz), 2.75-2.63 (m, 3H), 2.52 (ddd, 1H, *J* = 15.0, 6.4, 5.5 Hz), 2.11-2.04 (m, 1H), 1.91 (ddd, 1H, *J* = 14.8, 4.1, 3.4 Hz), 1.77-1.72 (m, 1H), 1.72-1.67 (m, 1H), 1.62-1.58 (m, 2H), 1.56-1.43 (m, 3H), 1.35-1.21 (m, 3H), 1.20-1.15 (m, 1H), 1.10 (s, 9H), 0.68 ppm (ddd, 1H, *J* = 12.9, 3.3, 2.5 Hz); ^{13}C NMR (125 MHz, $C_6D_5CD_3$, 363 K): $\delta =$ 154.4, 153.4, 136.6 (2C), 136.5 (2C), 136.0, 135.8, 135.3, 135.0, 133.7, 132.9, 130.2, 130.0, 129.9 (2C), 129.6, 128.0 (4C), 127.5, 117.6, 113.0, 83.5, 78.3, 71.8, 56.8, 55.1, 48.6, 44.5, 38.2, 36.8, 36.4, 33.8, 31.7, 31.2, 30.8, 27.8 (3C), 20.1, 19.8 ppm; IR (film): $\tilde{\nu} =$ 2931, 2856, 1497, 1463, 1428, 1377, 1235, 1175, 1111, 1077, 1059, 1020, 983, 821, 802, 741, 703, 612, 544, 508 cm^{-1}; MS (ESI): *m/z* (%): 676.0 (100), 698 (20); HRMS (ESI): *m/z*: calcd. for $C_{43}H_{54}NO_4Si$ $[M+H]^+$: 676.38166, found 676.38195.

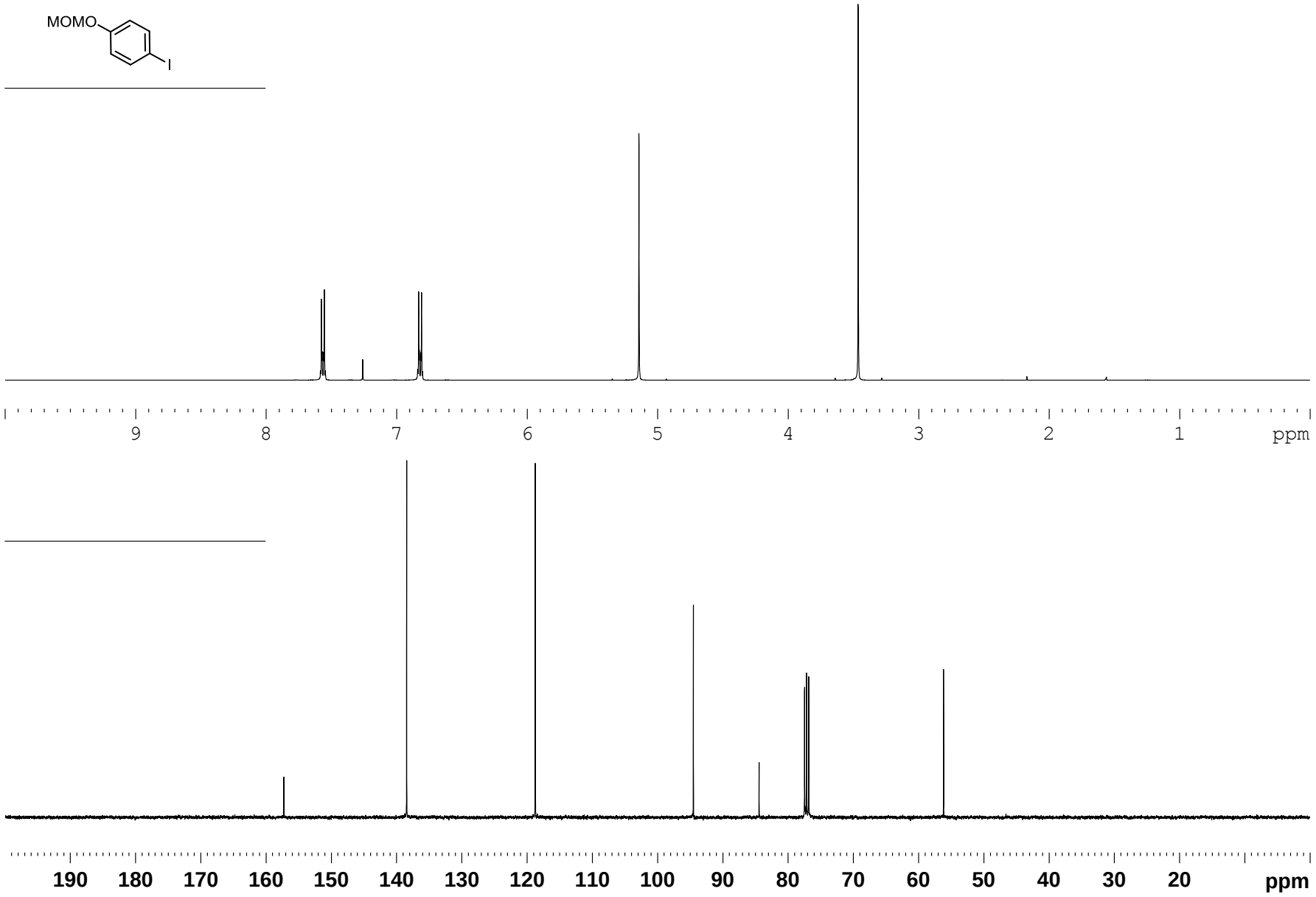
nOe-analysis:



Compound 11-*epi*-24. This compound was prepared analogously in 61 % yield. $[\alpha]_{20}^{D} = -1.4$ (c = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $C_6D_5CD_3$, 363 K): $\delta =$ 7.68-7.66 (m, 2H), 7.54-7.52 (m, 2H), 7.42 (d, 1H, *J* = 2.2 Hz), 7.39 (d, 1H, *J* = 2.2 Hz), 7.19-7.17 (m, 3H), 7.12-7.10 (m, 3H), 7.08 (d, 1H, *J* = 8.2 Hz), 6.97-6.94 (m, 2H), 6.72 (s, 1H), 6.63 (d, 1H, *J* = 8.3 Hz), 4.20 (tt, 1H, *J* = 9.7, 3.9 Hz), 4.13 (d, 1H, *J* = 8.4 Hz), 3.89 (d, 1H, *J* = 8.4 Hz), 3.53 (ddt, 1H, *J* = 9.3, 5.3, 3.9 Hz), 3.32 (s, 3H), 3.24 (ddd, 1H, *J* = 16.3, 11.1, 4.7 Hz), 2.80-2.74 (m, 2H), 2.71-2.67 (m, 1H), 2.63-2.57 (m, 1H), 2.28-2.20 (m, 2H), 2.10-2.04 (m, 1H), 1.83-1.69 (m, 2H), 1.67-1.61 (m, 1H), 1.47-1.38 (m, 2H), 1.30-1.19 (m, 2H), 1.17-1.12 (m, 1H), 1.03 (s, 9H), 1.01-0.99 (m, 1H), 0.88-0.92 (m, 2H), 0.78-0.74 ppm (m, 1H); ^{13}C NMR (125 MHz, $C_6D_5CD_3$, 363 K): $\delta =$ 154.2, 153.4, 136.6 (2C), 136.5 (2C), 135.9, 135.7, 135.2, 134.8, 134.7, 132.2, 130.4, 129.8 (2C), 129.5, 129.2, 128.0 (2C), 127.9 (2C), 126.8, 118.1, 113.5, 79.5, 71.0, 69.9, 56.9, 50.7, 48.8, 41.9, 35.0, 33.9, 32.7, 30.2, 29.6, 27.9, 27.7 (3C), 24.6, 20.8, 19.9 ppm; IR (film): $\tilde{\nu} =$ 2930, 2855, 1499, 1462, 1428, 1387, 1363, 1236, 1152, 1110, 1069, 1022, 981, 821, 799, 740, 704, 612, 543, 510, 493 cm^{-1}; MS (ESI): *m/z* (%): 676.0 (100), 698 (25); HRMS (ESI): *m/z*: calcd. for $C_{43}H_{54}NO_4Si$ $[M+H]^+$: 676.38166, found 676.38216.

nOe-analysis:

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I
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8
7
6
5
4
3
2
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ppm
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160
150
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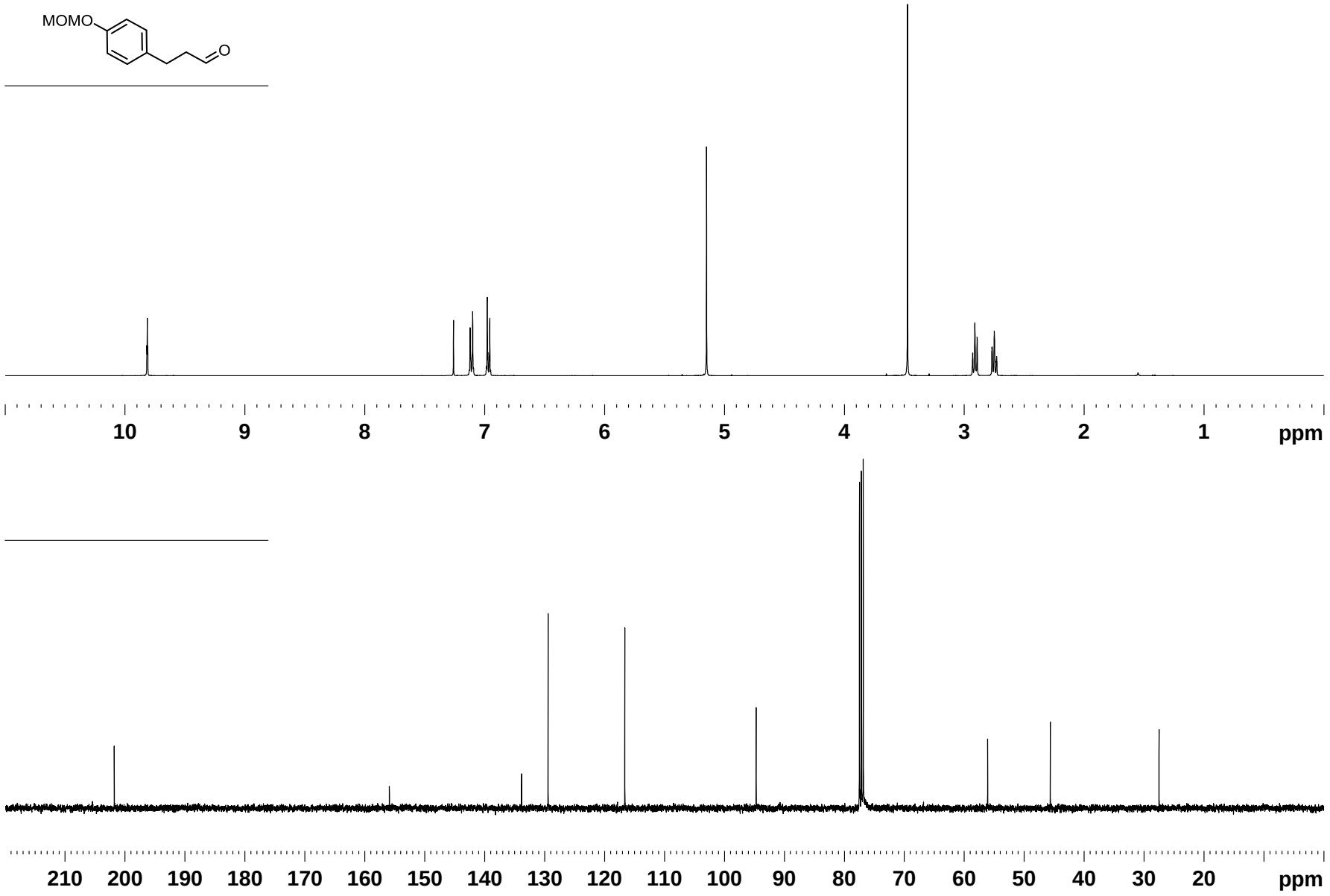
130
120
110
100
90
80
70
60
50
40
30
20
ppm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O
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3
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1
ppm
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80
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40
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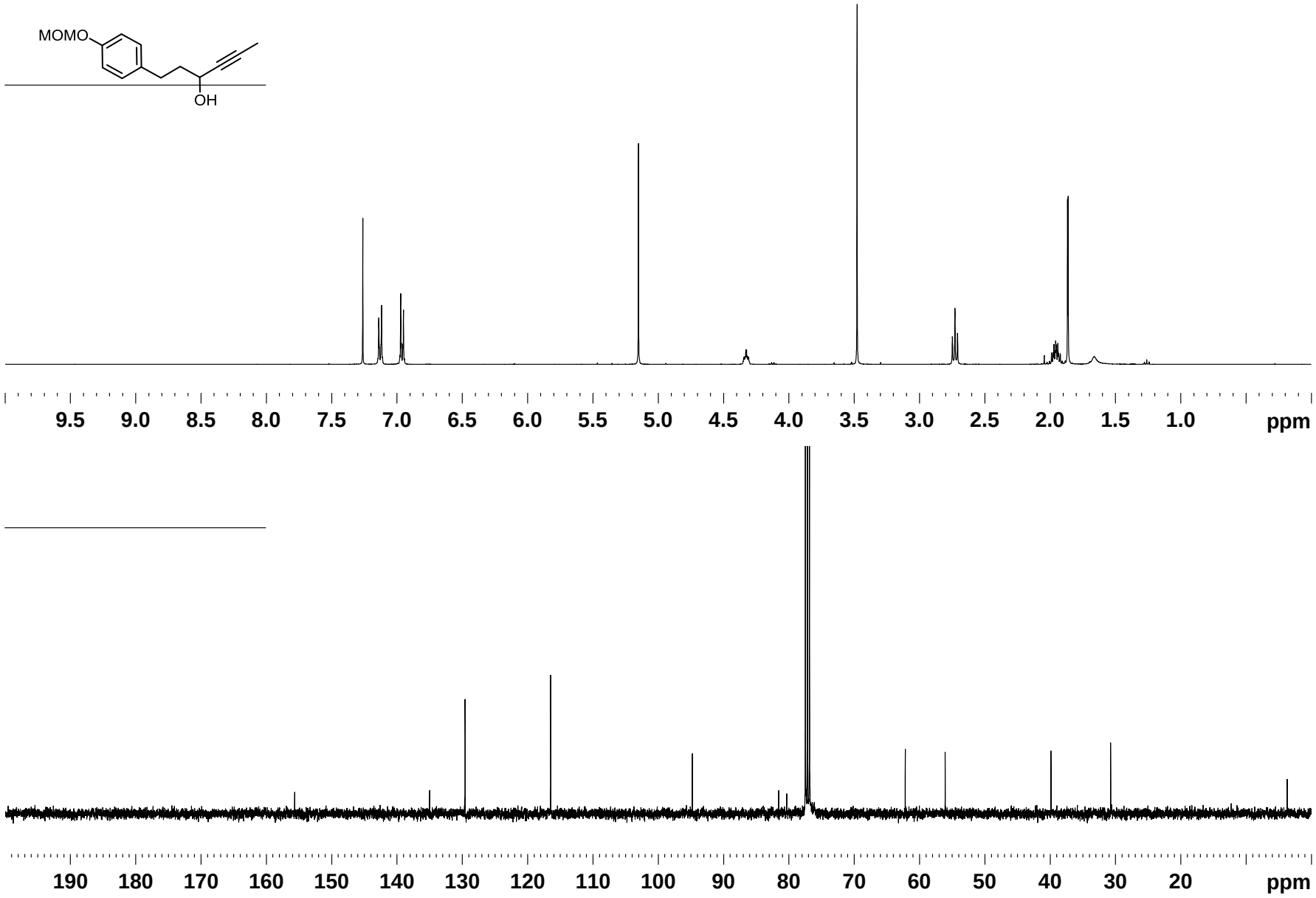
20
ppm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OH
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ppm
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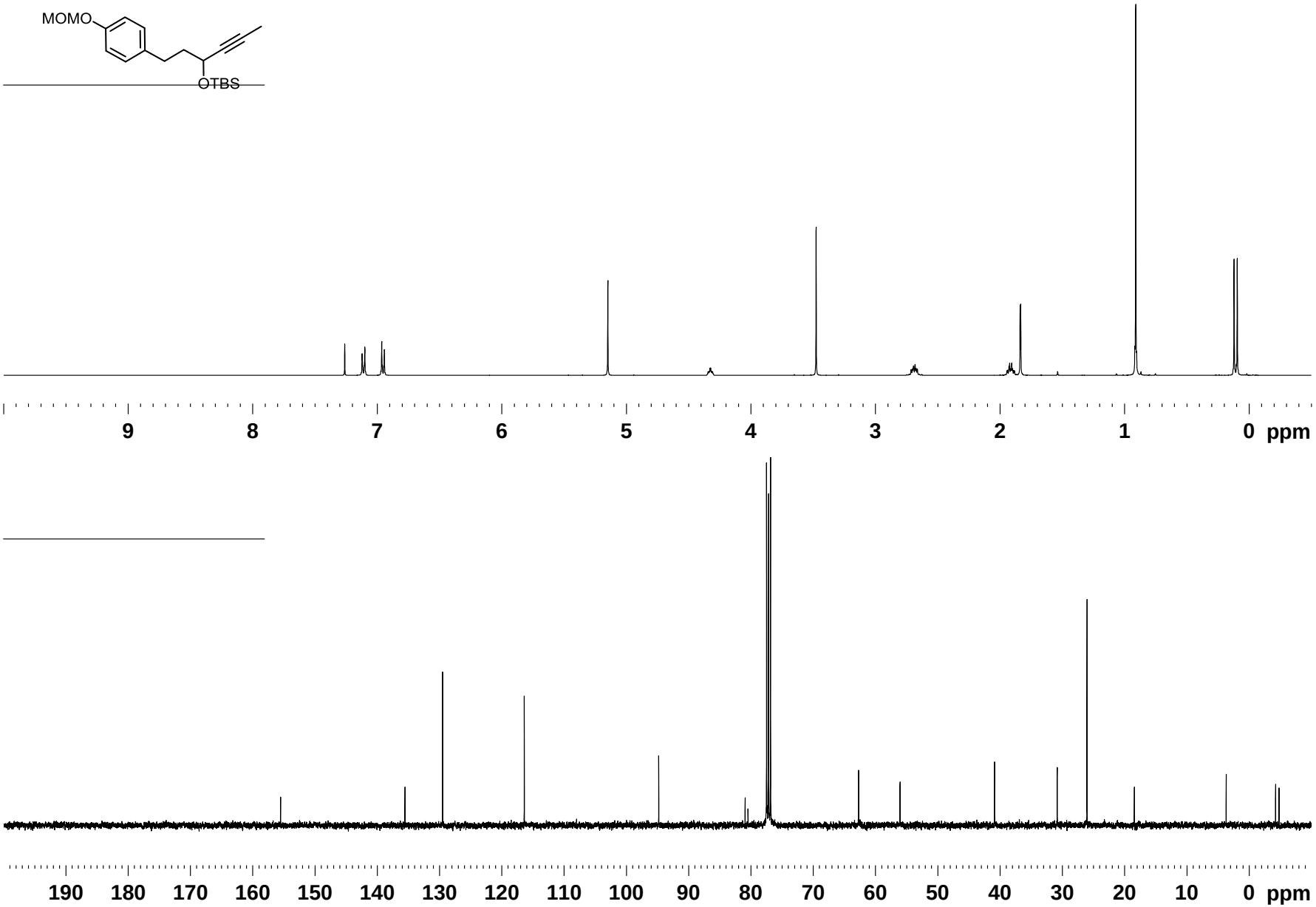
ppm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OTBS
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8
7
6
5
4
3
2
1
0 ppm
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180
170
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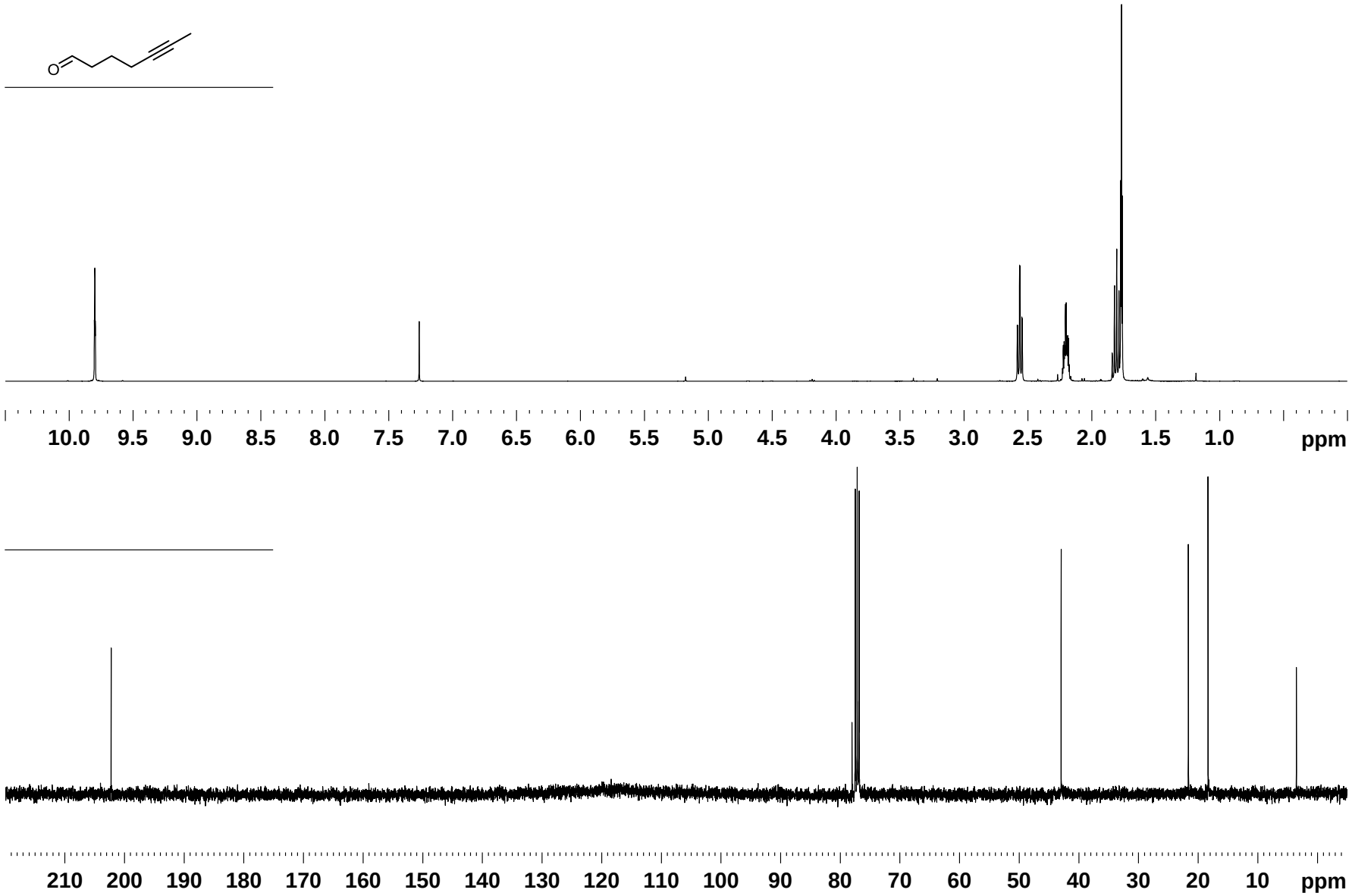
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm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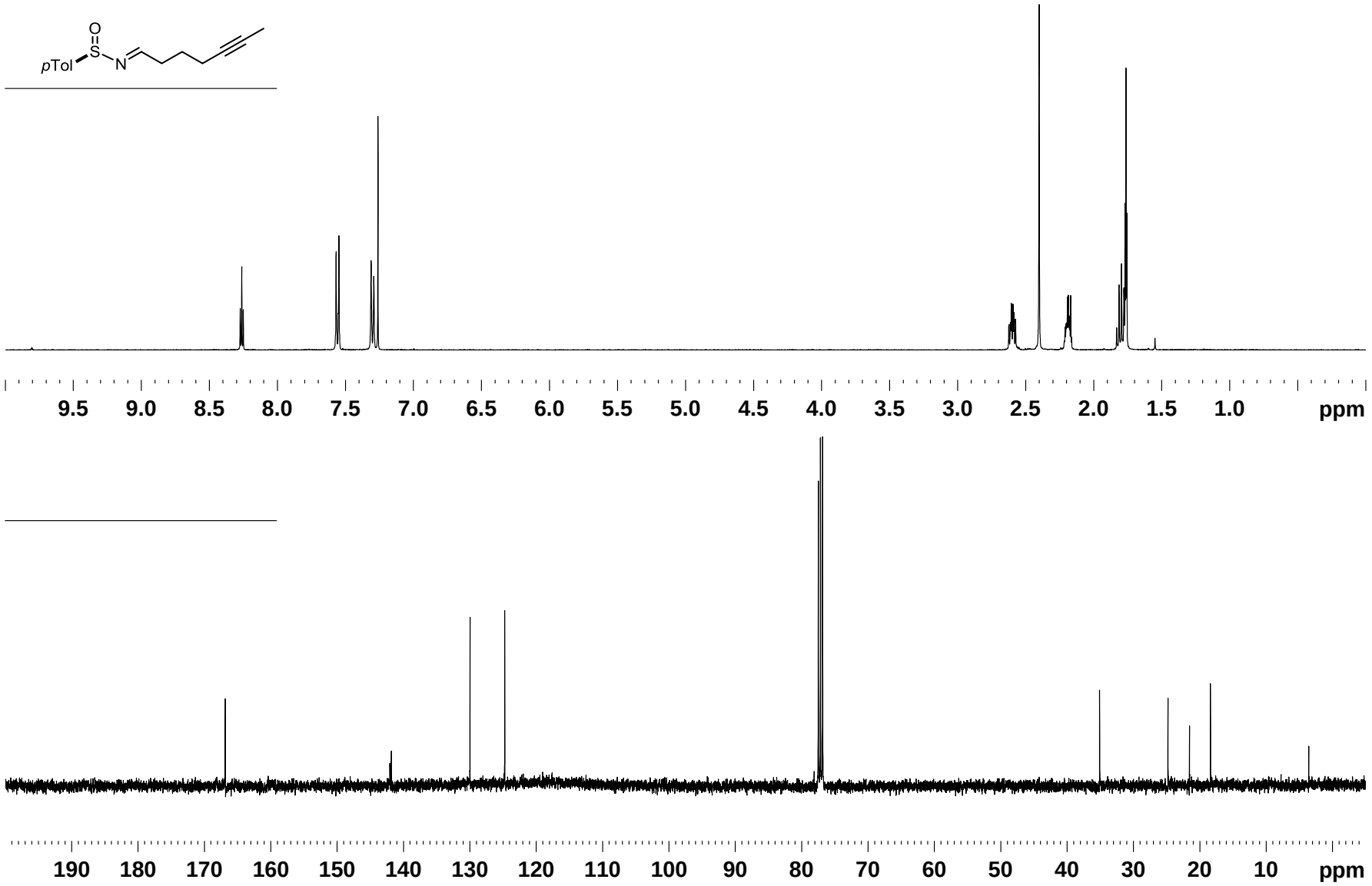
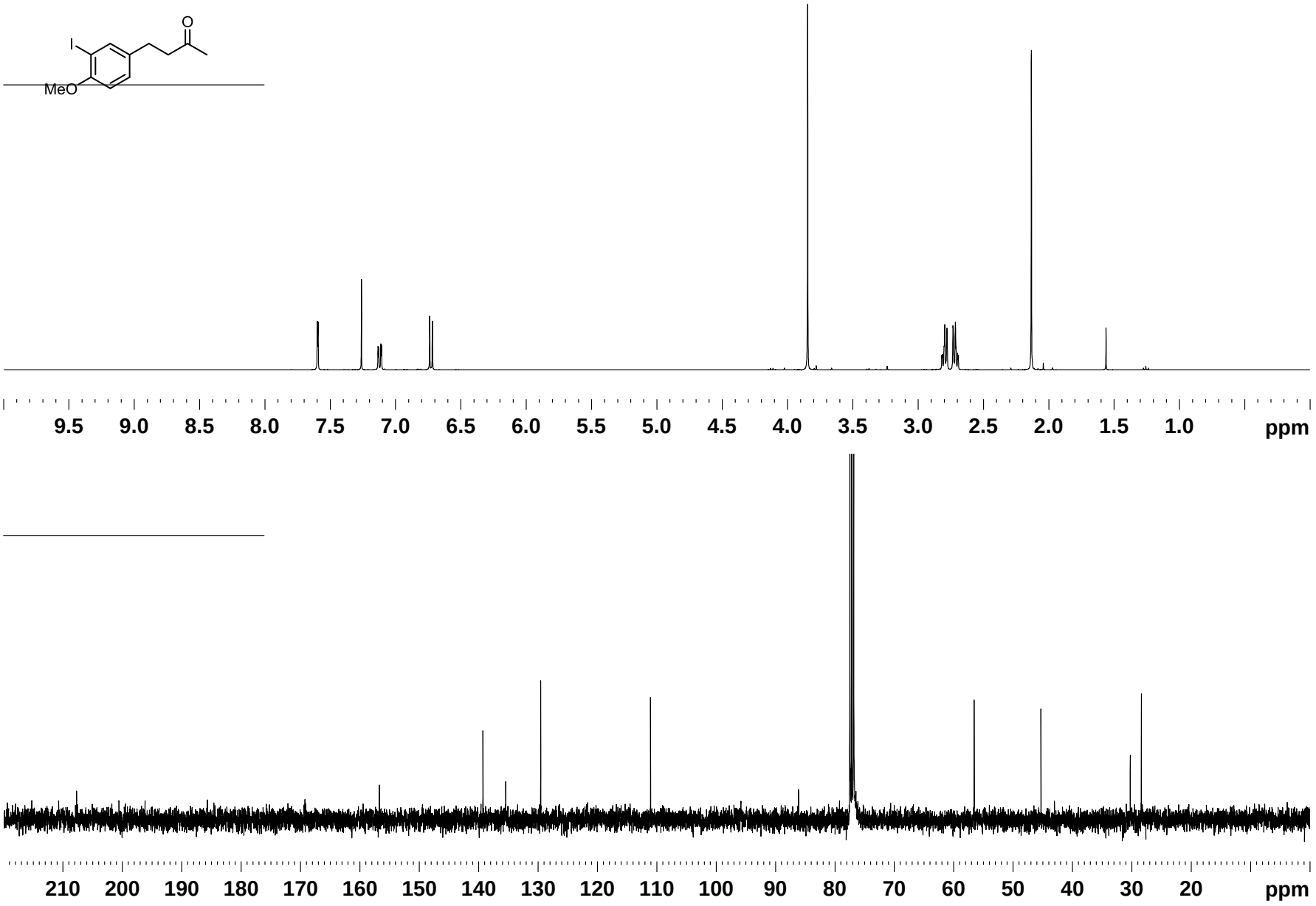

pTol
O
S
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
I
MeO
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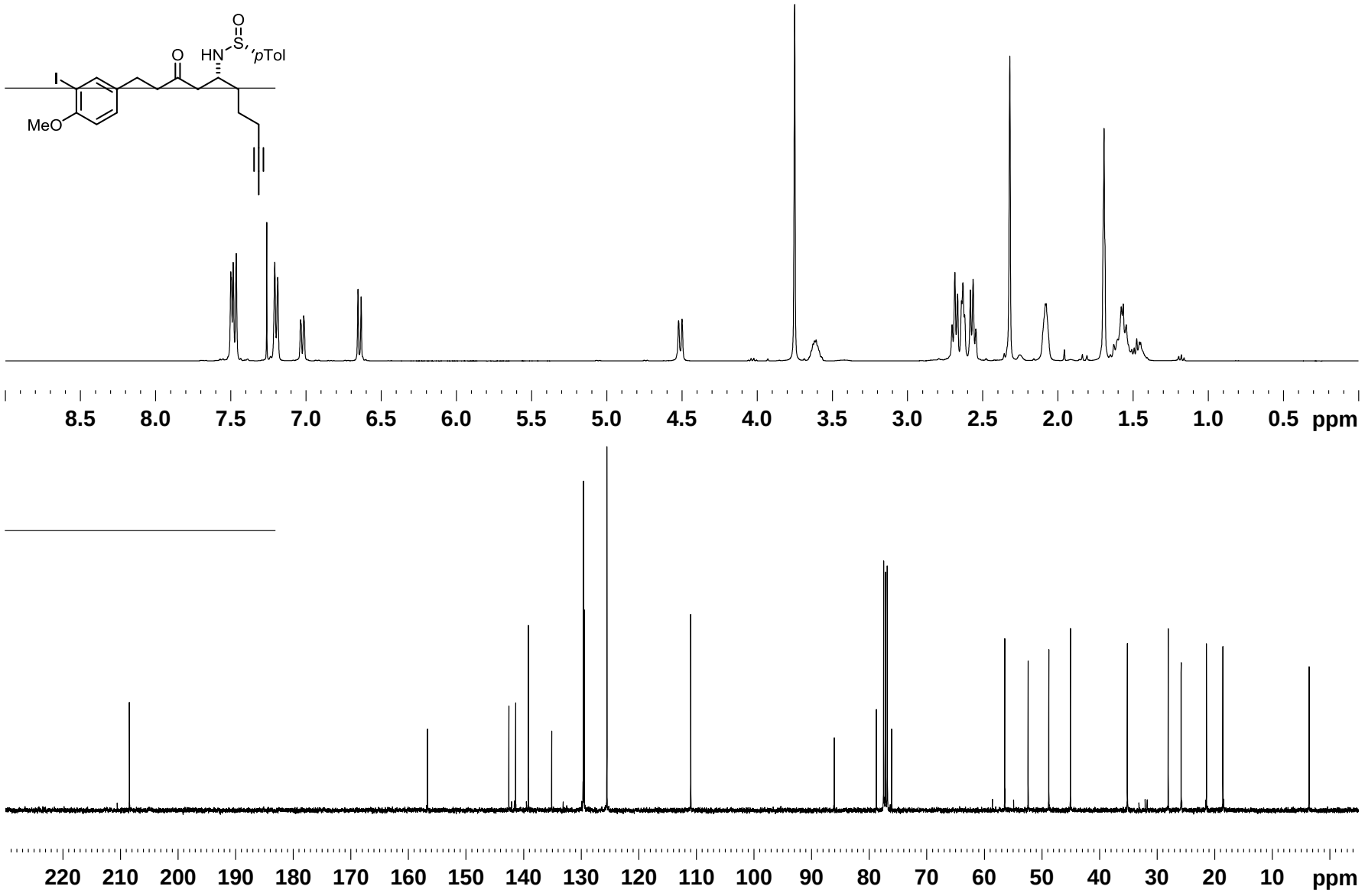
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


O
HN
S
pTol
I
MeO
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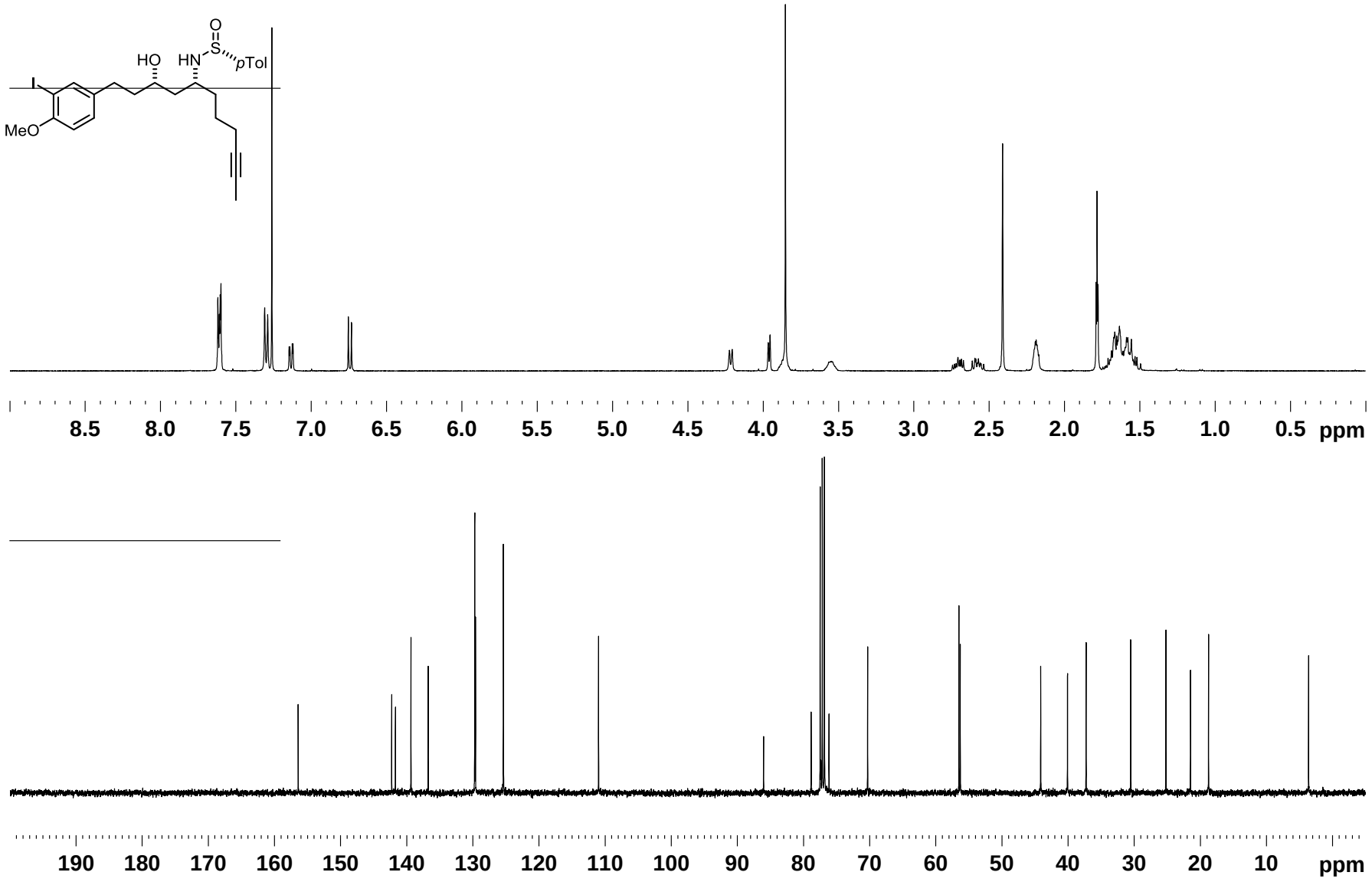
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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S
pTol
I
MeO
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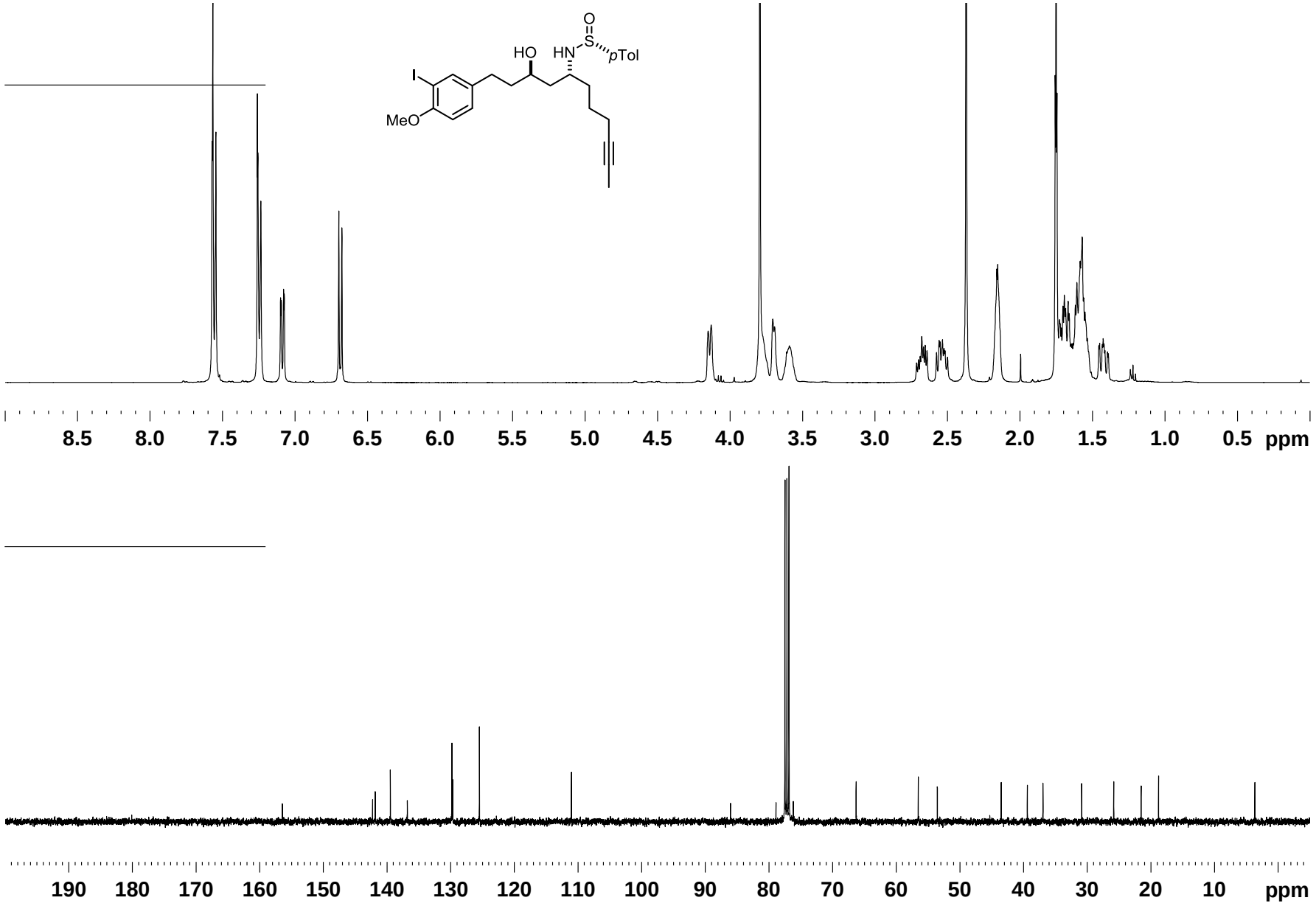
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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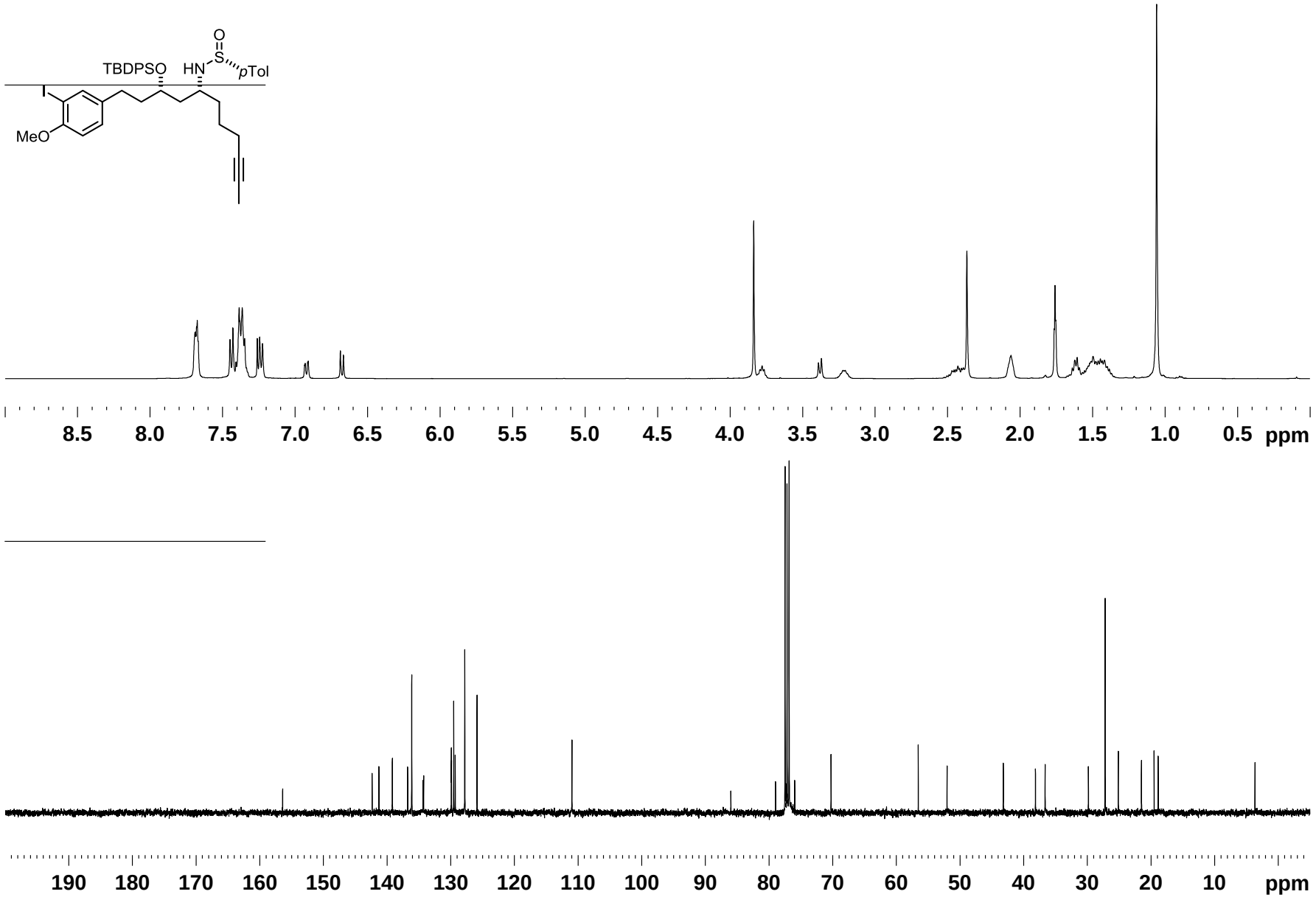
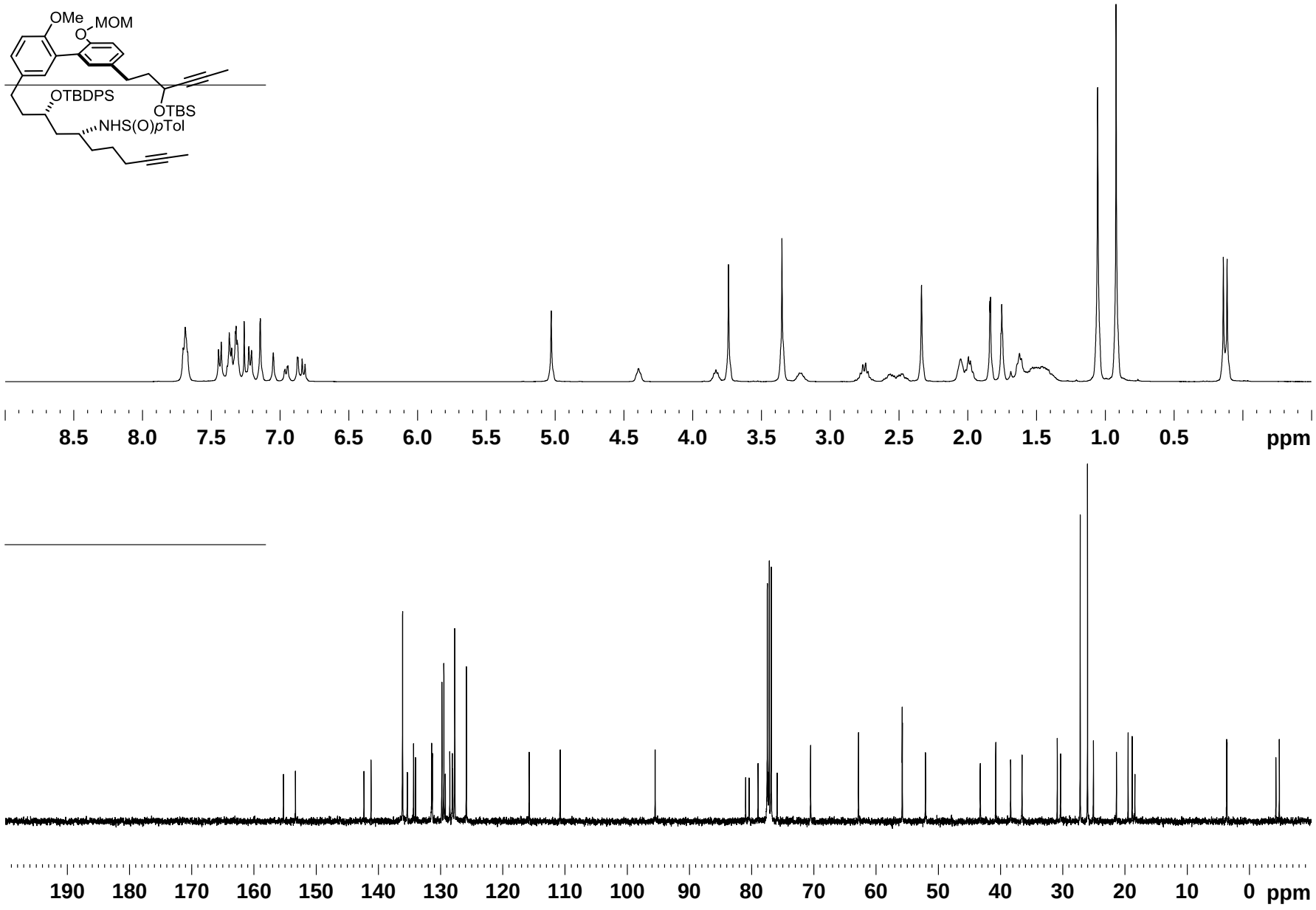
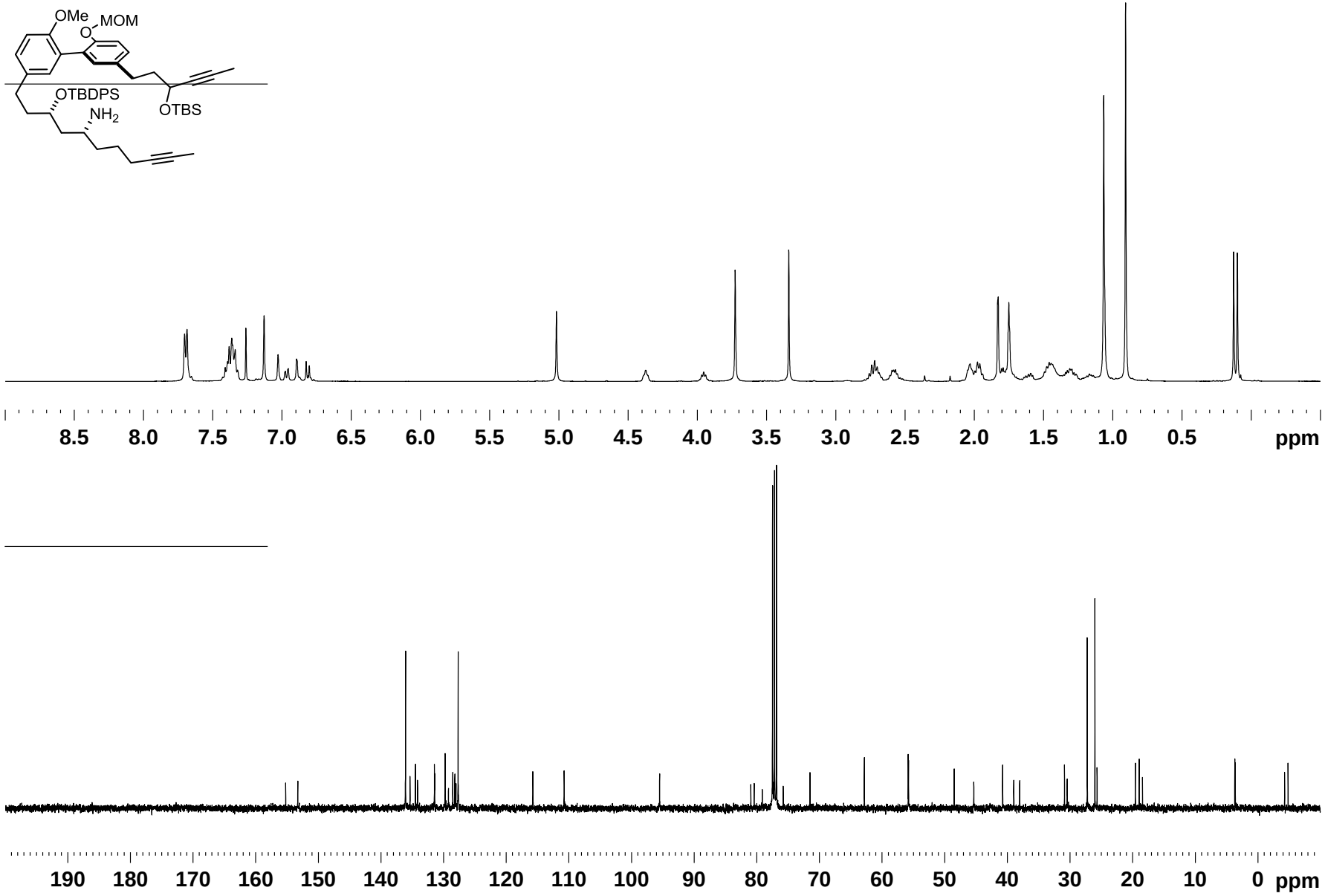
HN
O
S
pTol
I
MeO
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


TBDPSO
HN
O
S
pTol
MeO
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
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OMe
MOM
O
OTBDPS
OTBS
NHS(O)pTol
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
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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MOM
O
OTBDPS
NH2
OTBS
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
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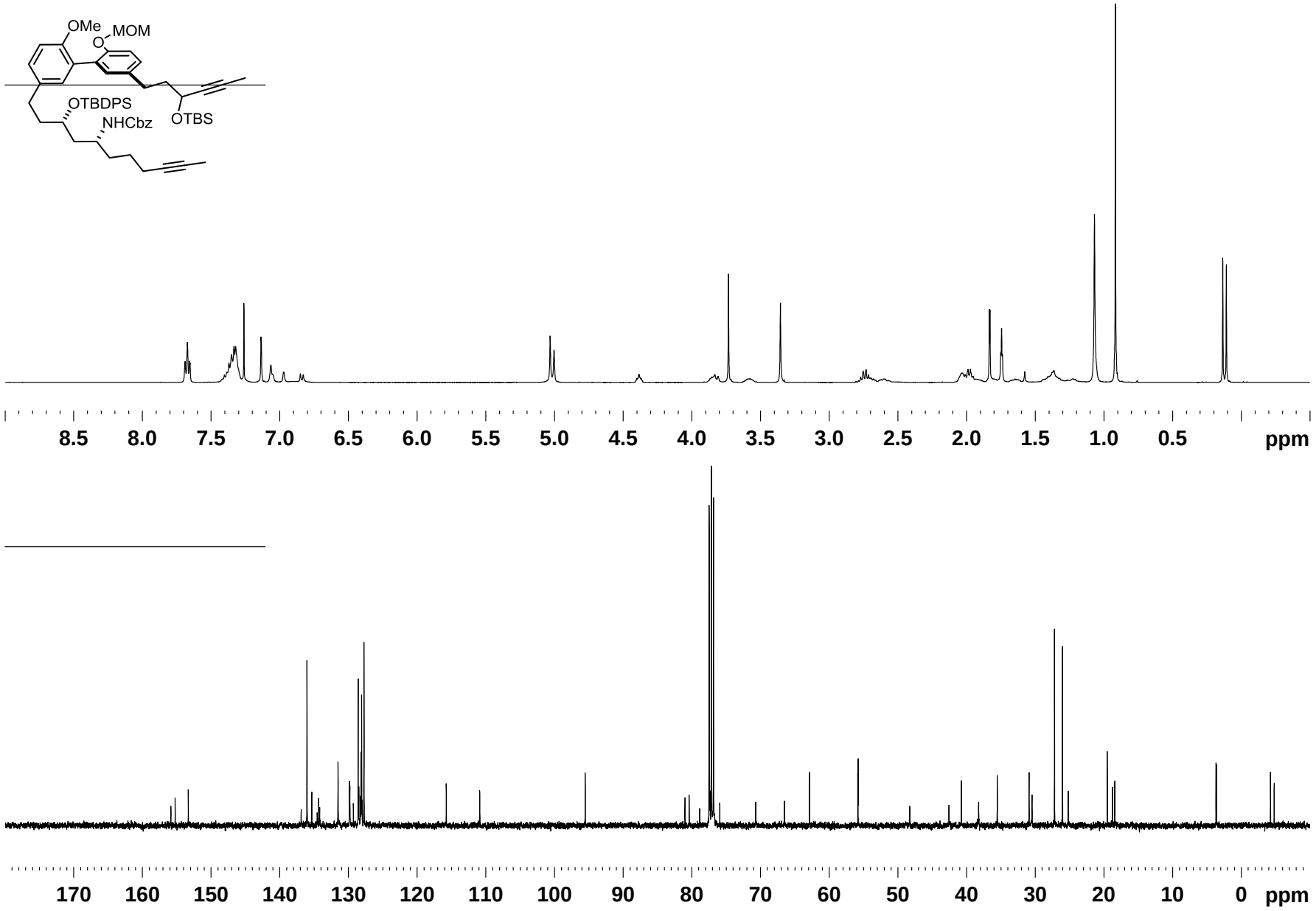
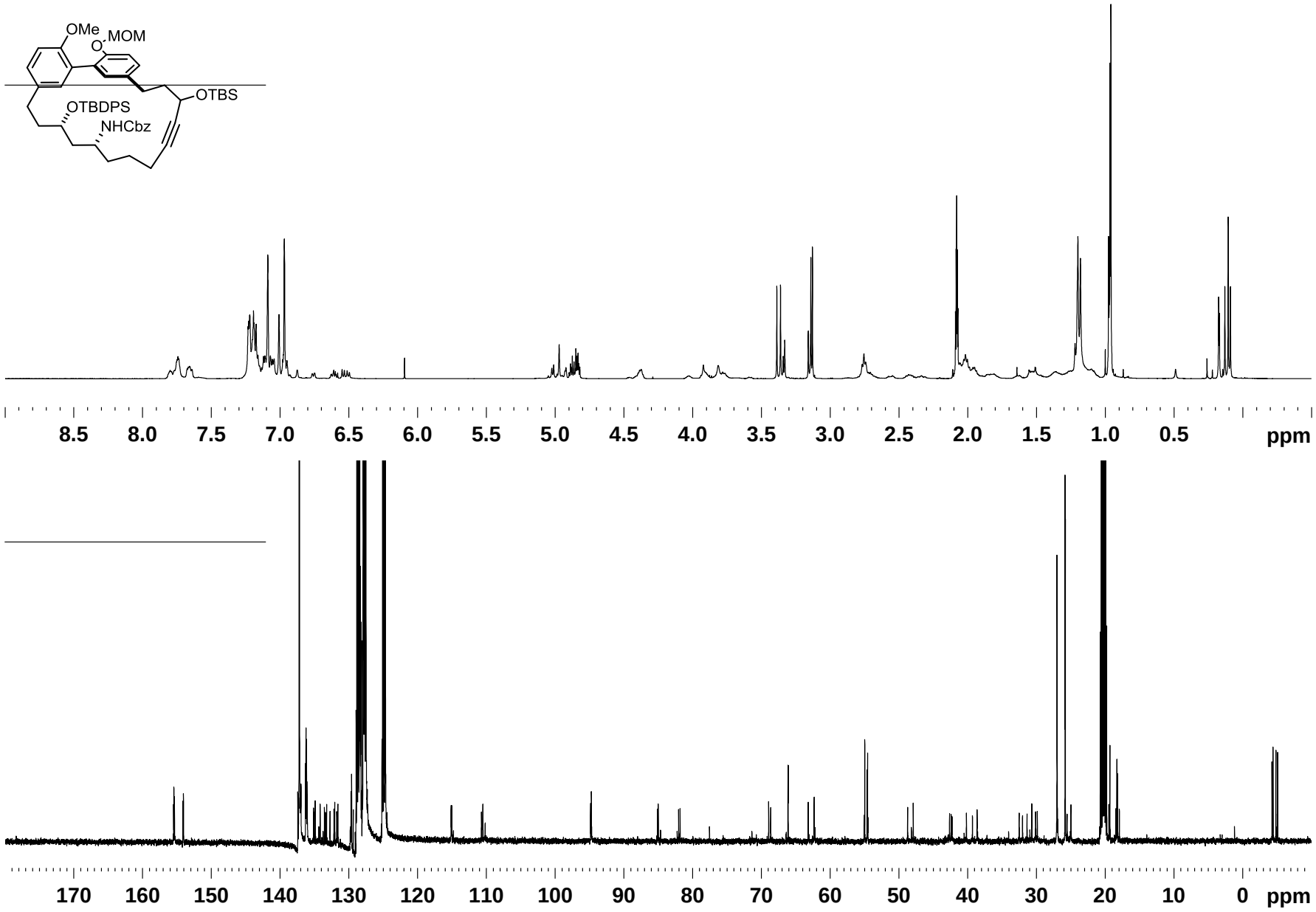
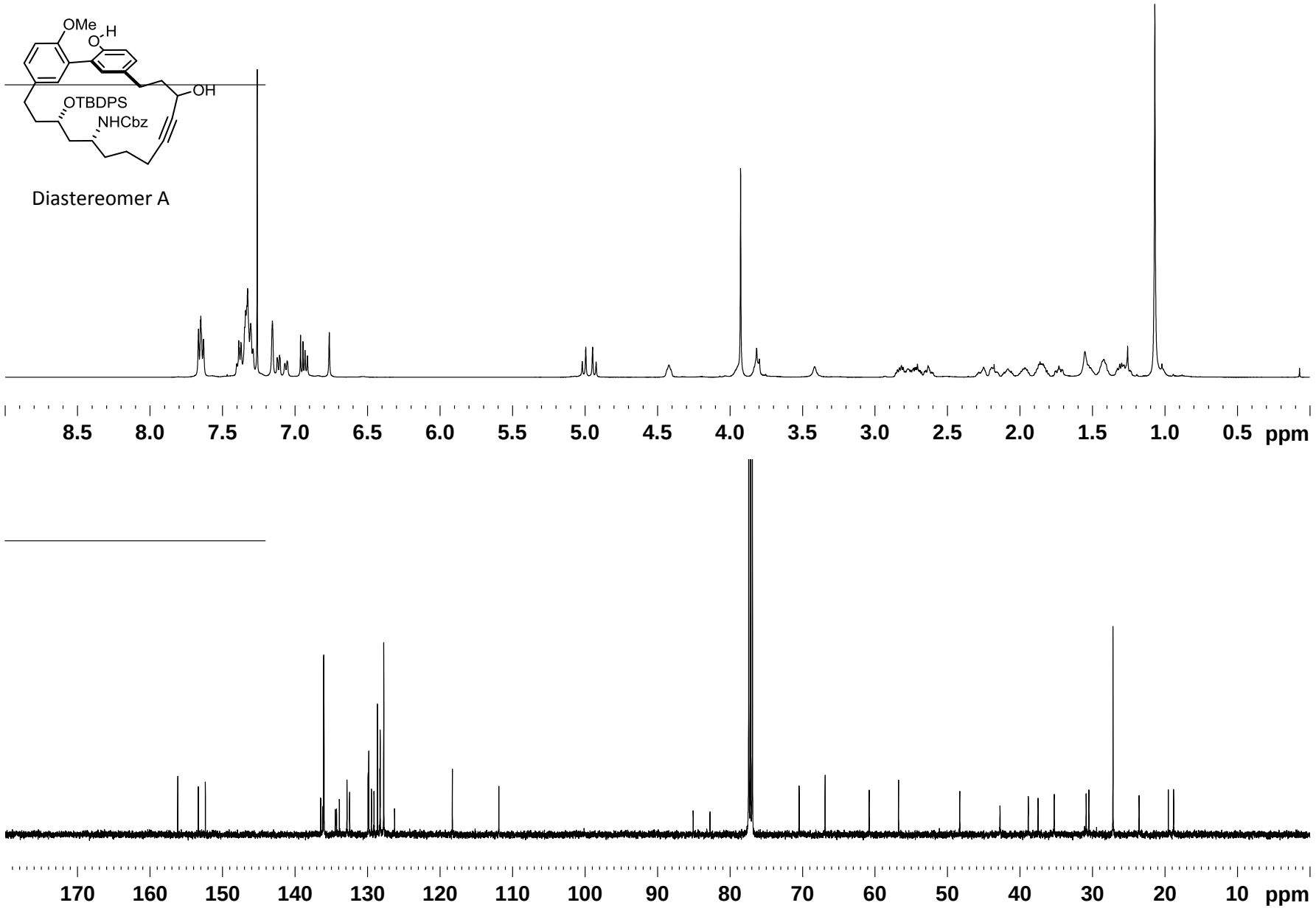

OMe
MOM
O
OTBDPS
NHCbz
OTBS
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OMe
MOM
O
OTBS
OTBDPS
NHCbz
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
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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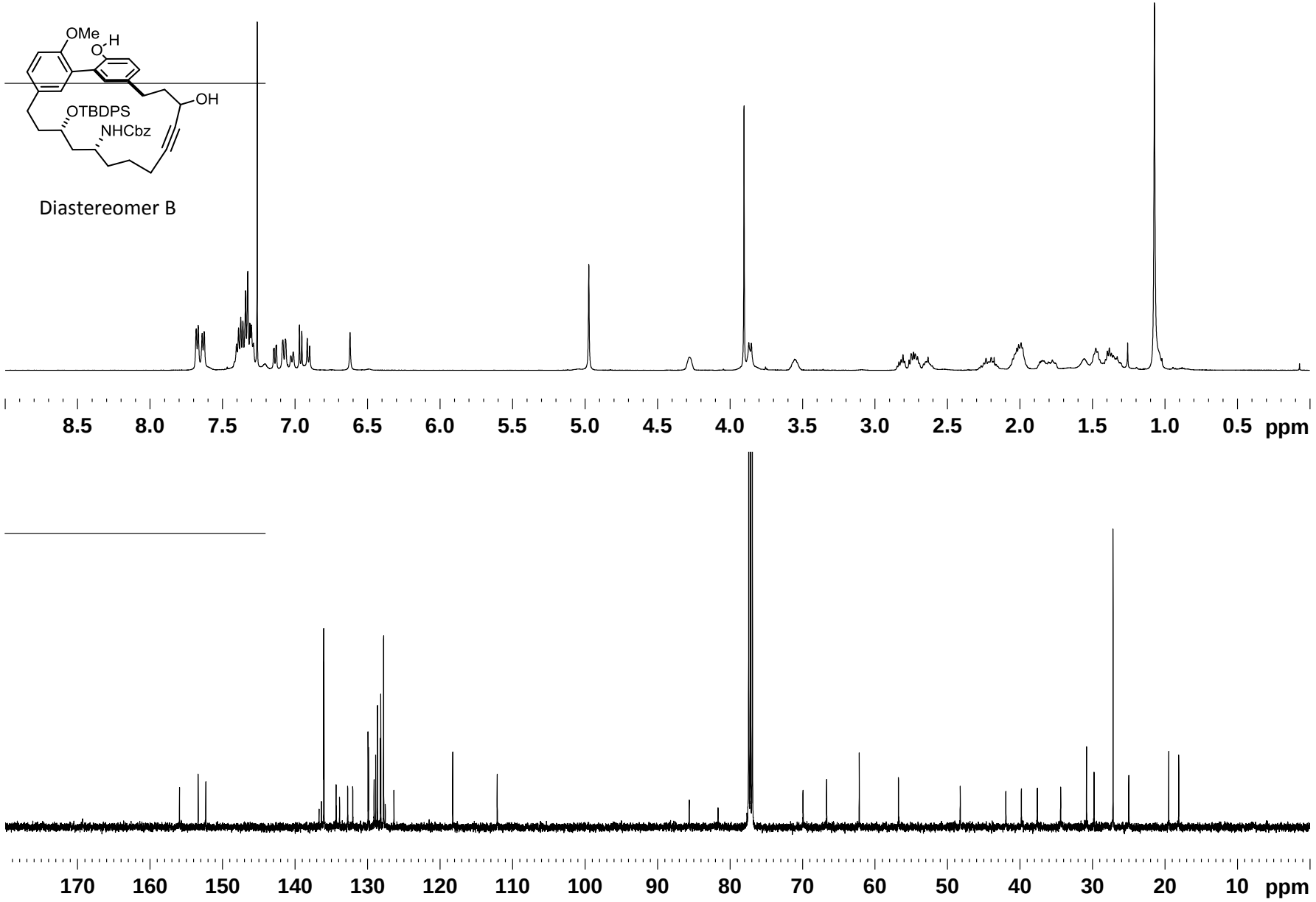
O
H
OH
OTBDPS
NHCbz
Diastereomer A
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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H
O
OH
OTBDPS
NHCbz
Diastereomer B
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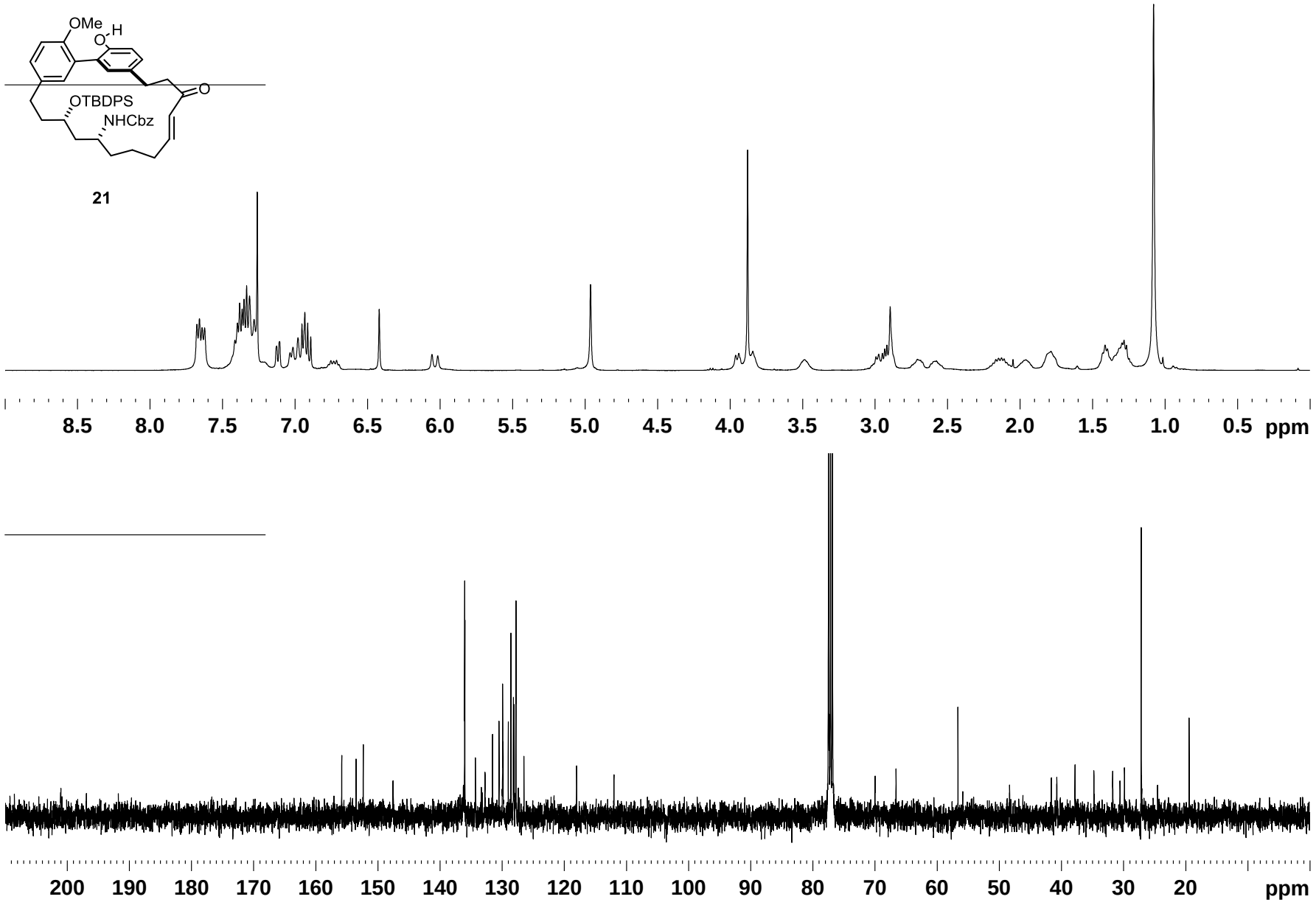
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H
O
O
OTBDPS
NHCbz
21
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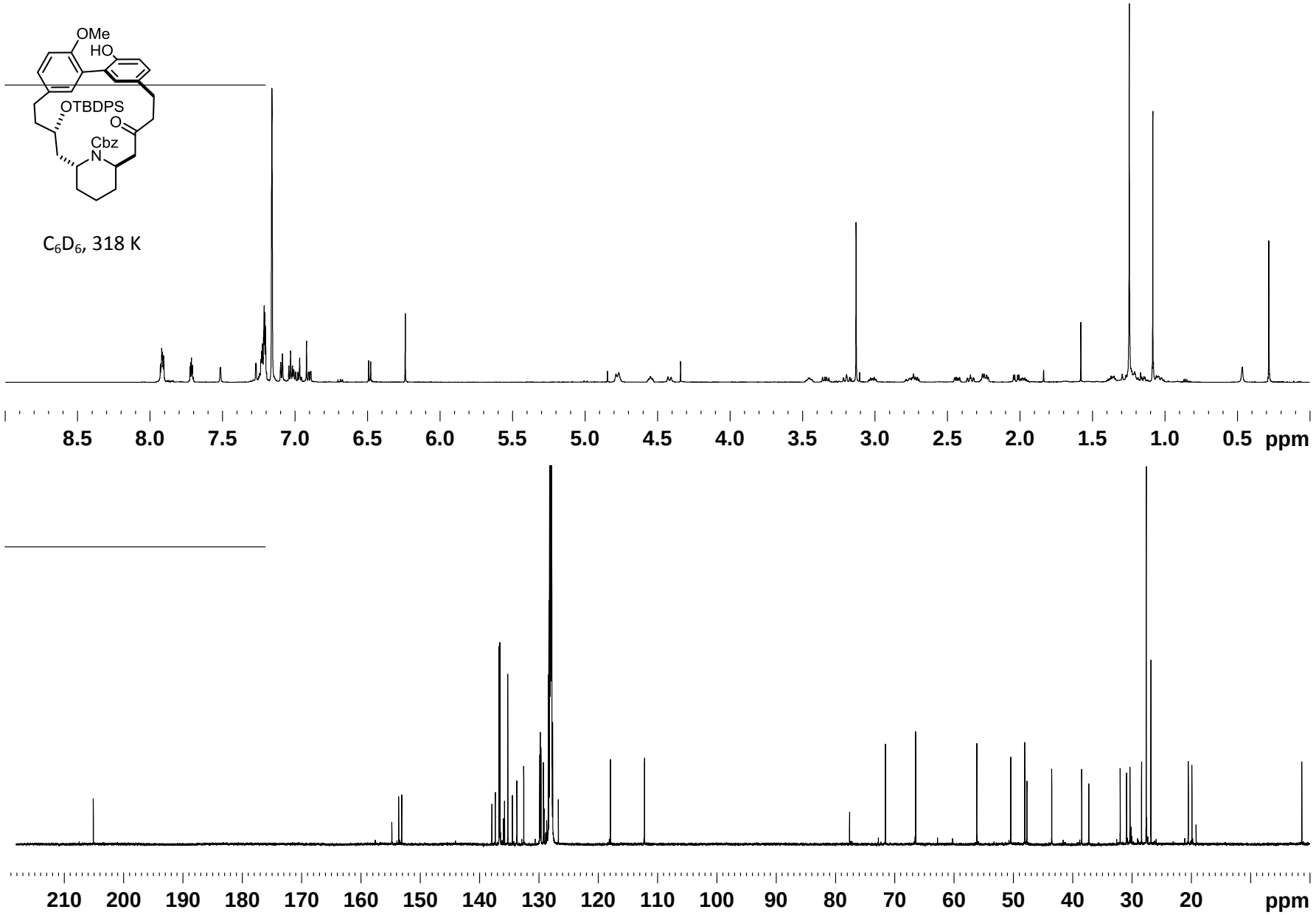
OMe
HO
OTBDPS
O
Cbz
N
C6D6, 318 K
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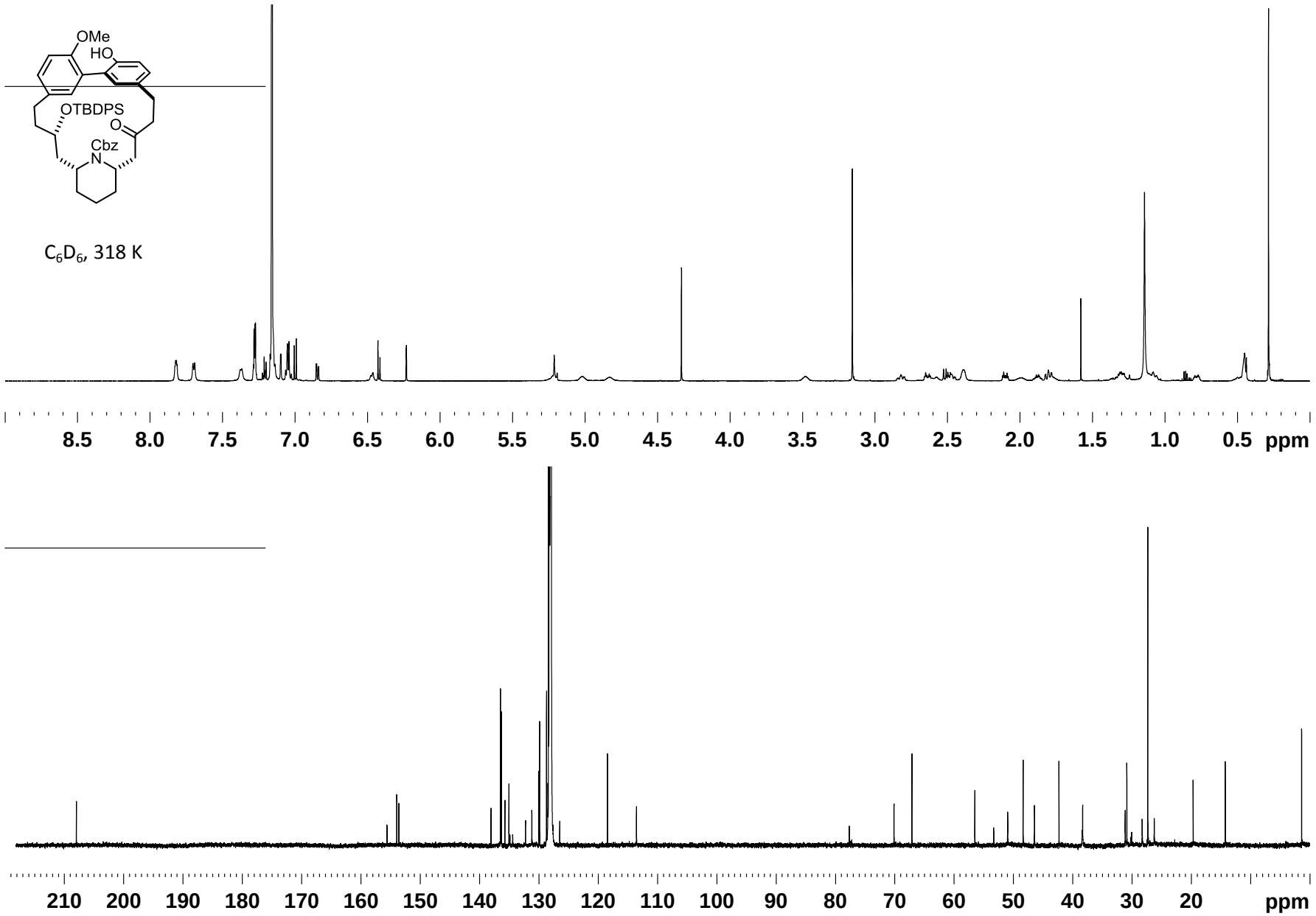
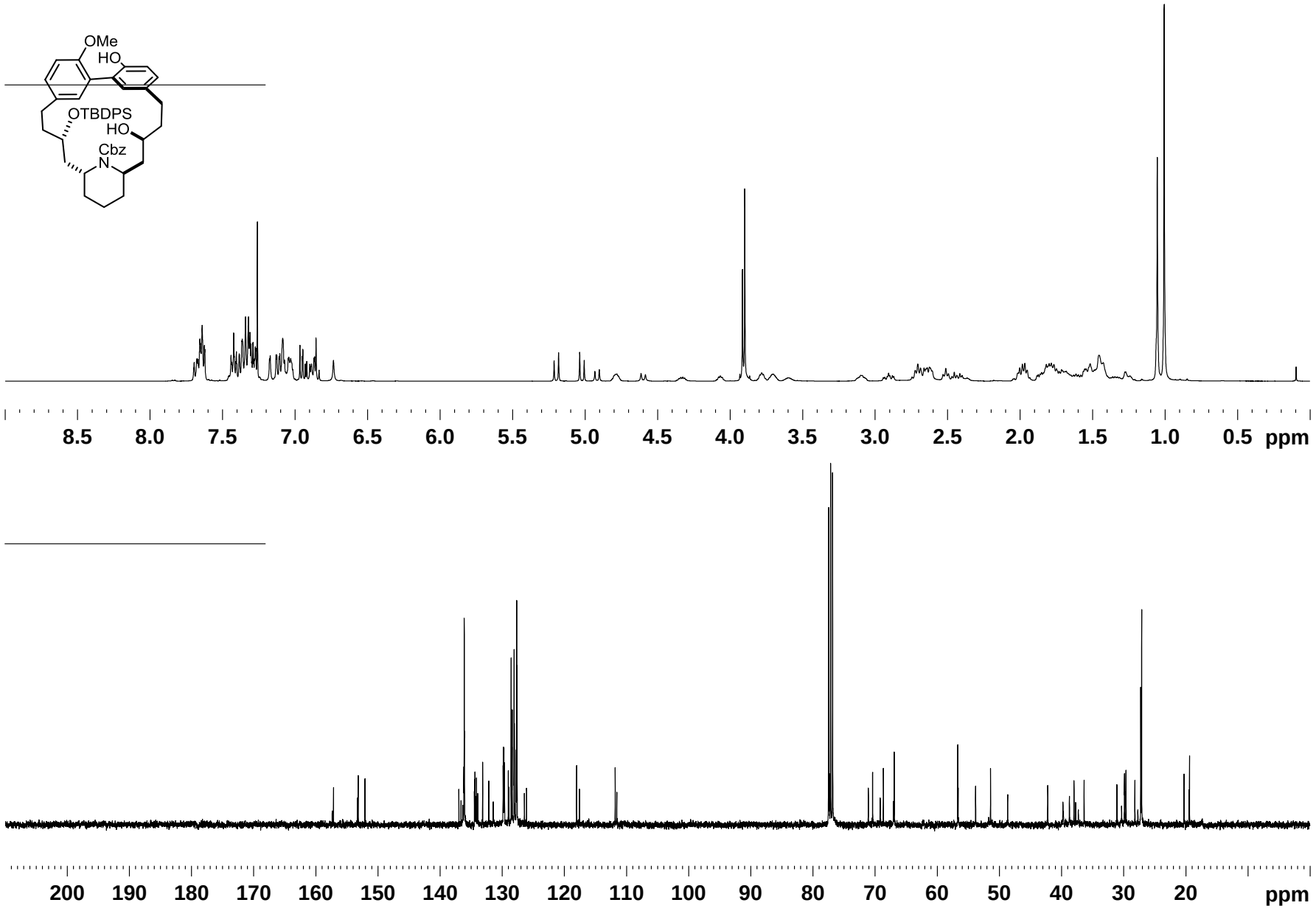
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


OMe
HO
OTBDPS
O
Cbz
N
C6D6, 318 K
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
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


OMe
HO
OTBDPS
HO
Cbz
N
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
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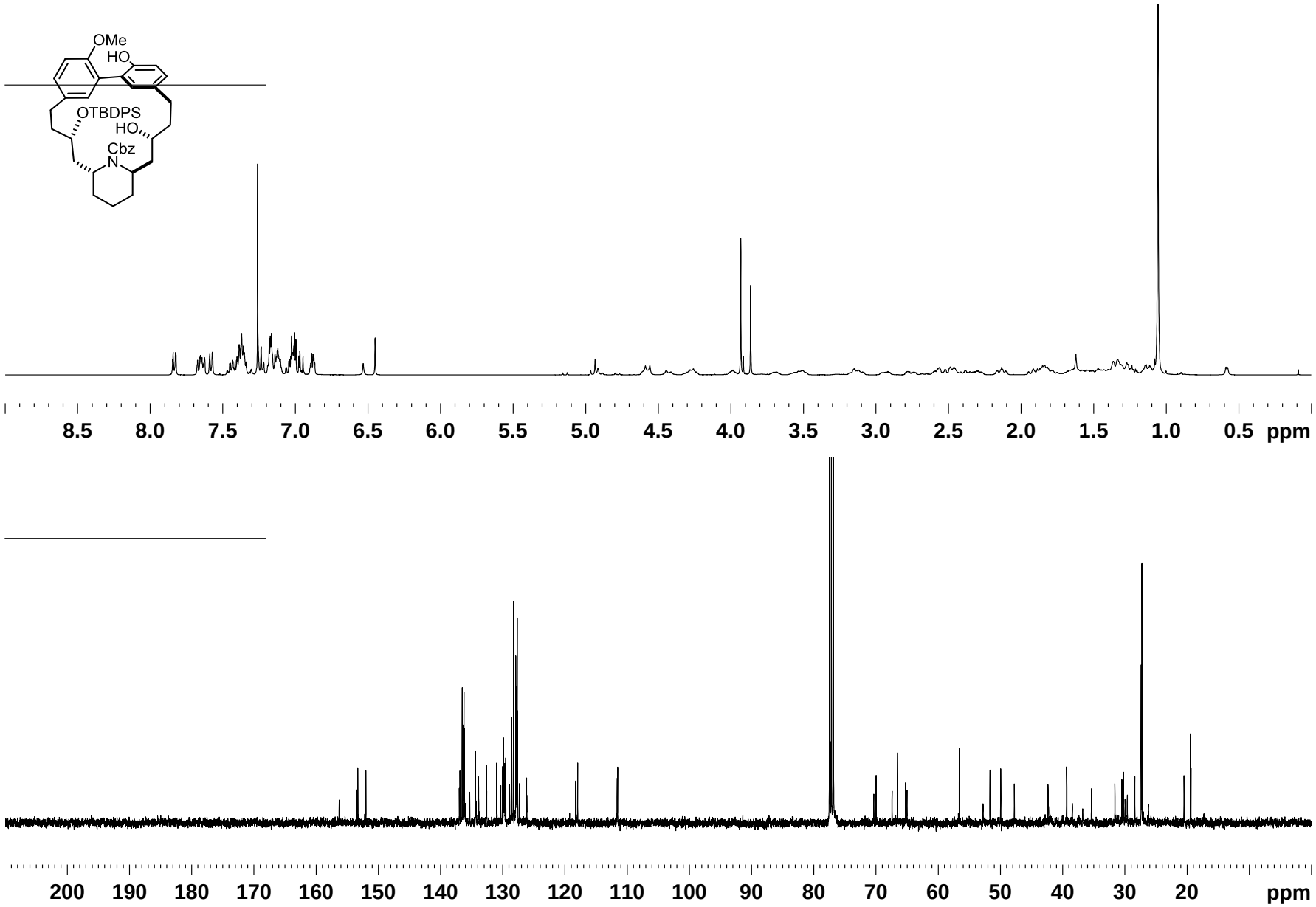
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OTBDPS
HO
Cbz
N
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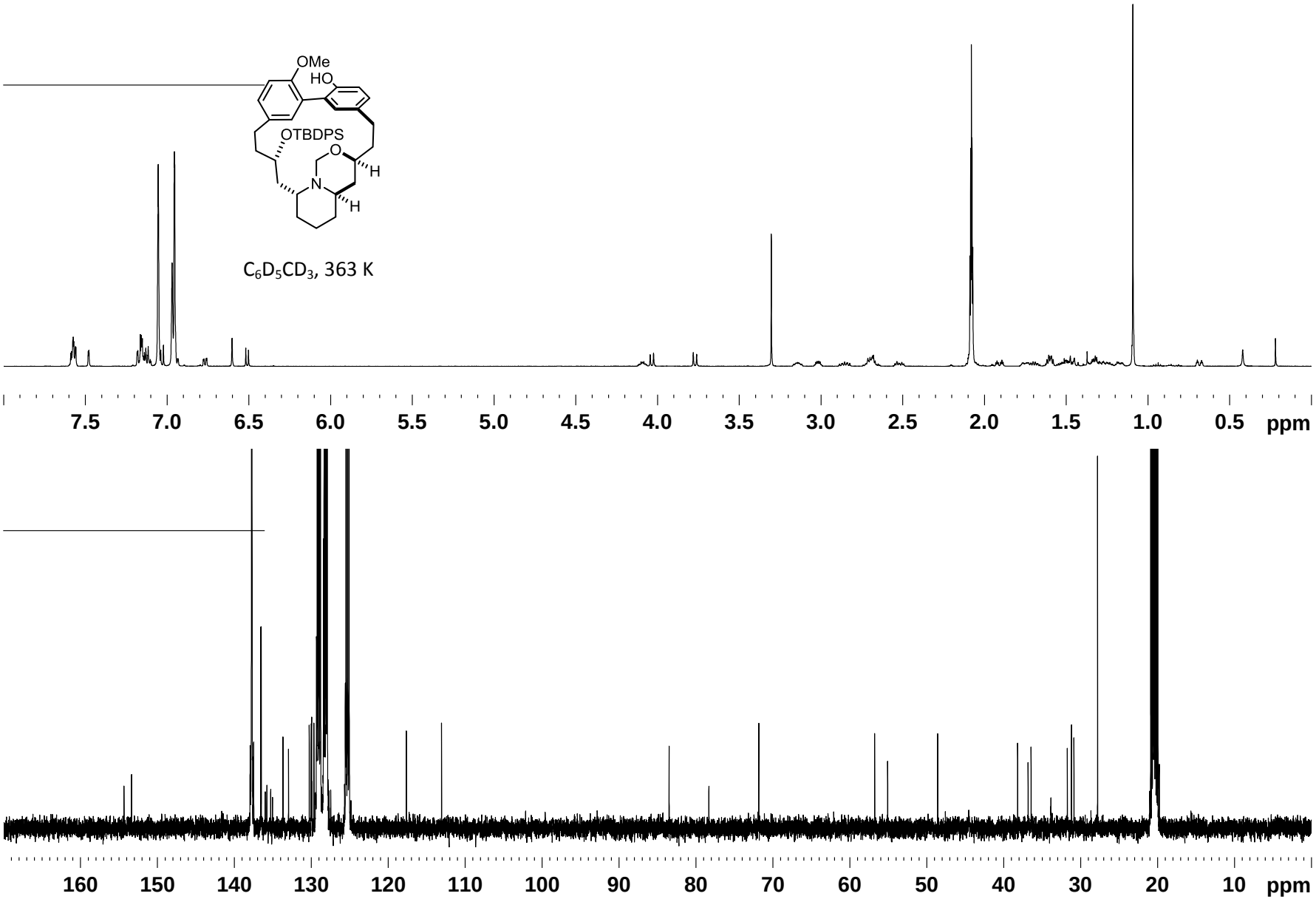
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H
C6D5CD3, 363 K
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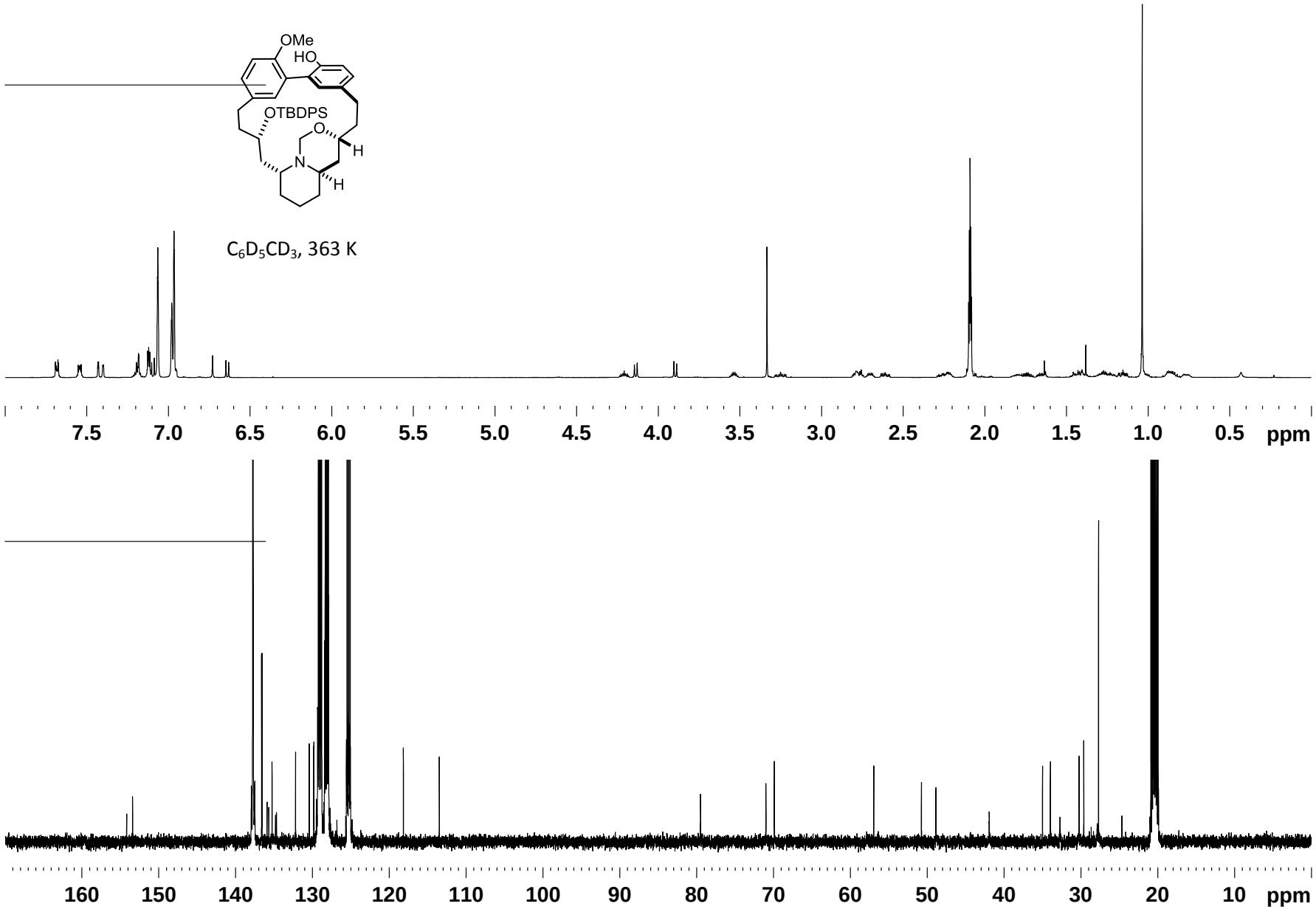
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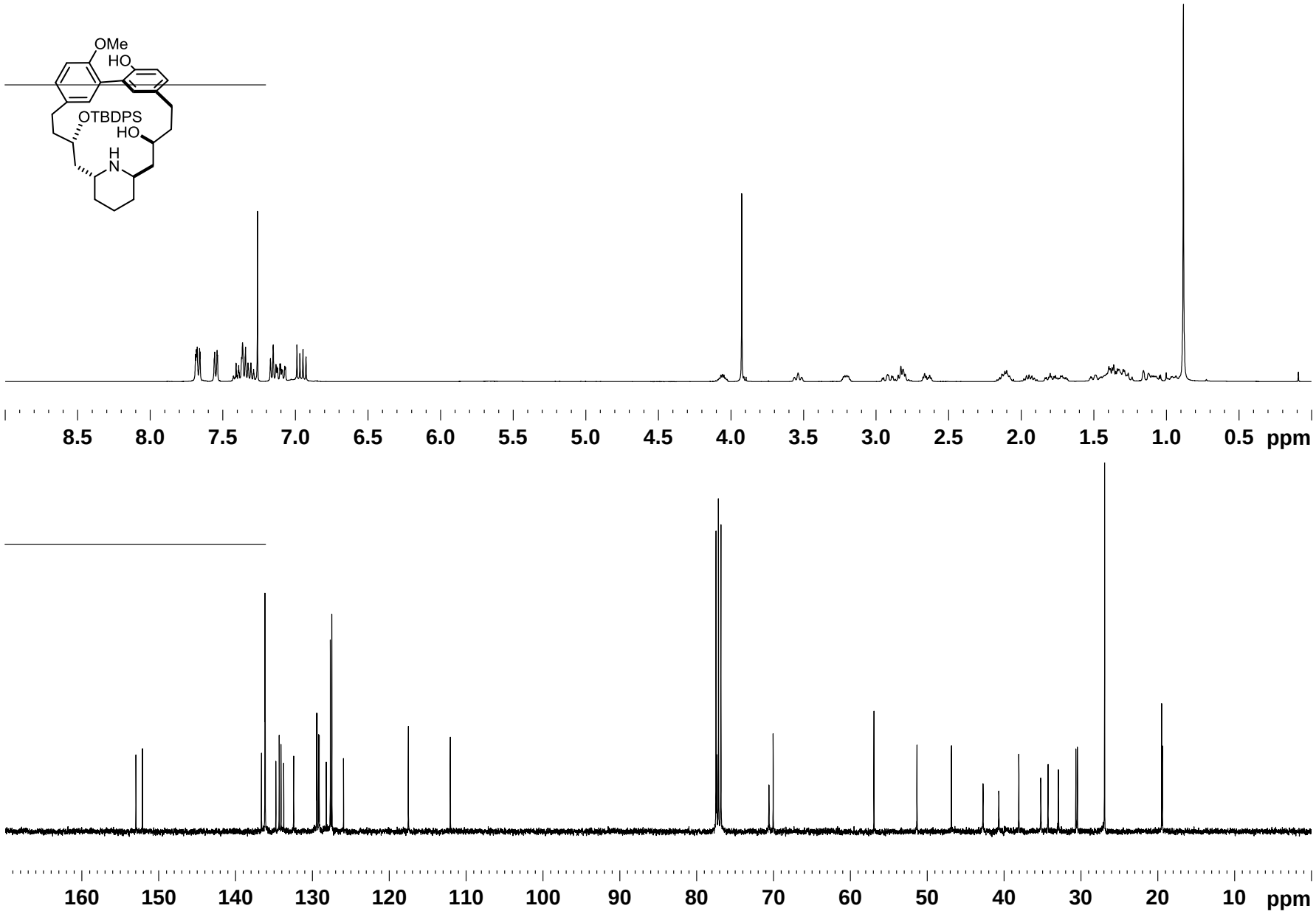
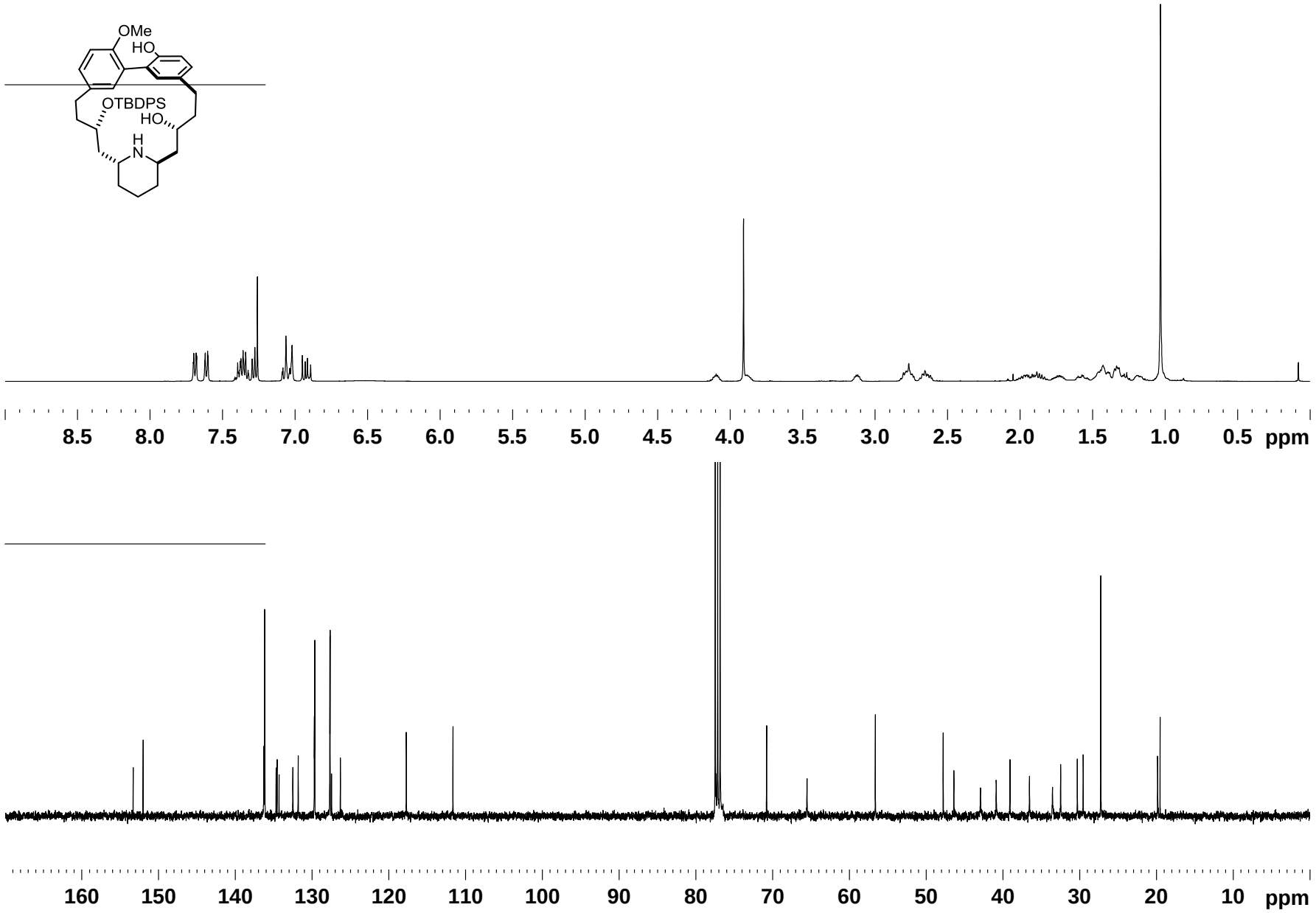
HO
OTBDPS
O
H
N
H
C6D5CD3, 363 K
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OMe
HO
OTBDPS
HO
H
N
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
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OMe
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OTBDPS
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7.0
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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
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150
140
130
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70
60
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40
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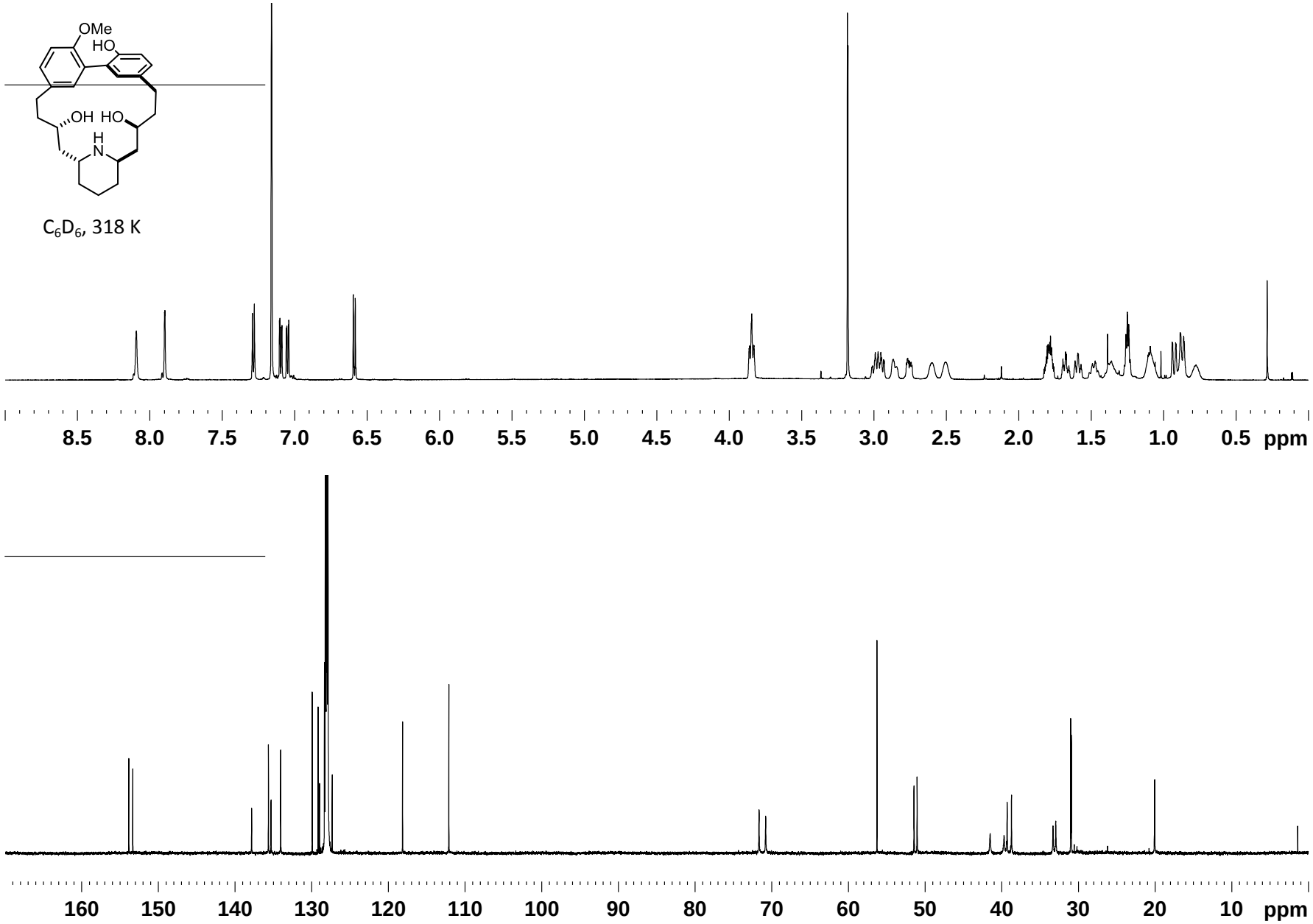
10
ppm


OMe
HO
OH
HO
H
N
C6D6, 318 K
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6.5
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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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70
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40
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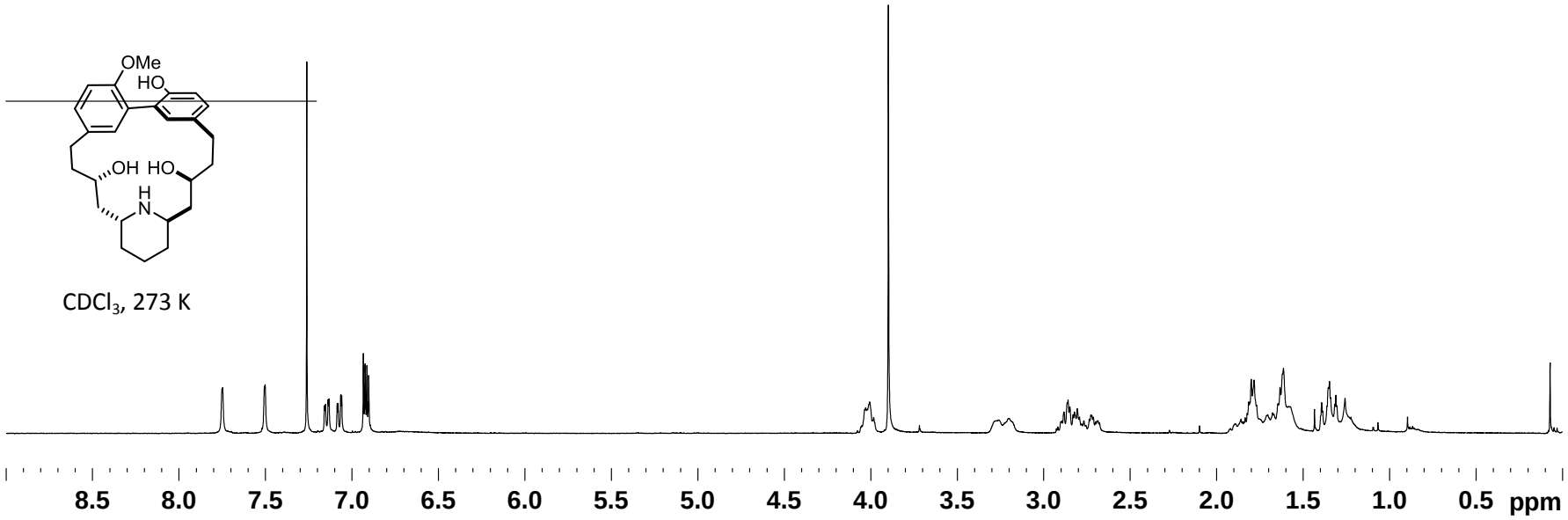
20
10
ppm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HO
H
N
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3.5
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2.0
1.5
1.0
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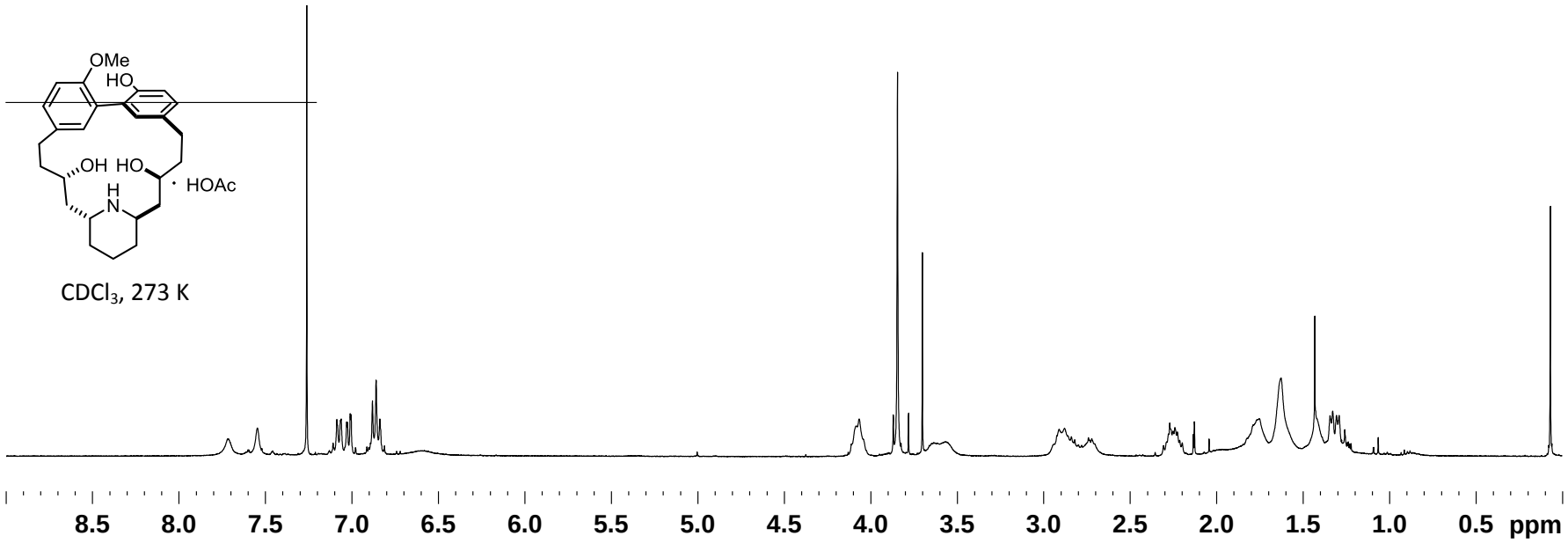
ppm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OH
HO
H
N
· HOAc
CDCl3, 273 K
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5.5
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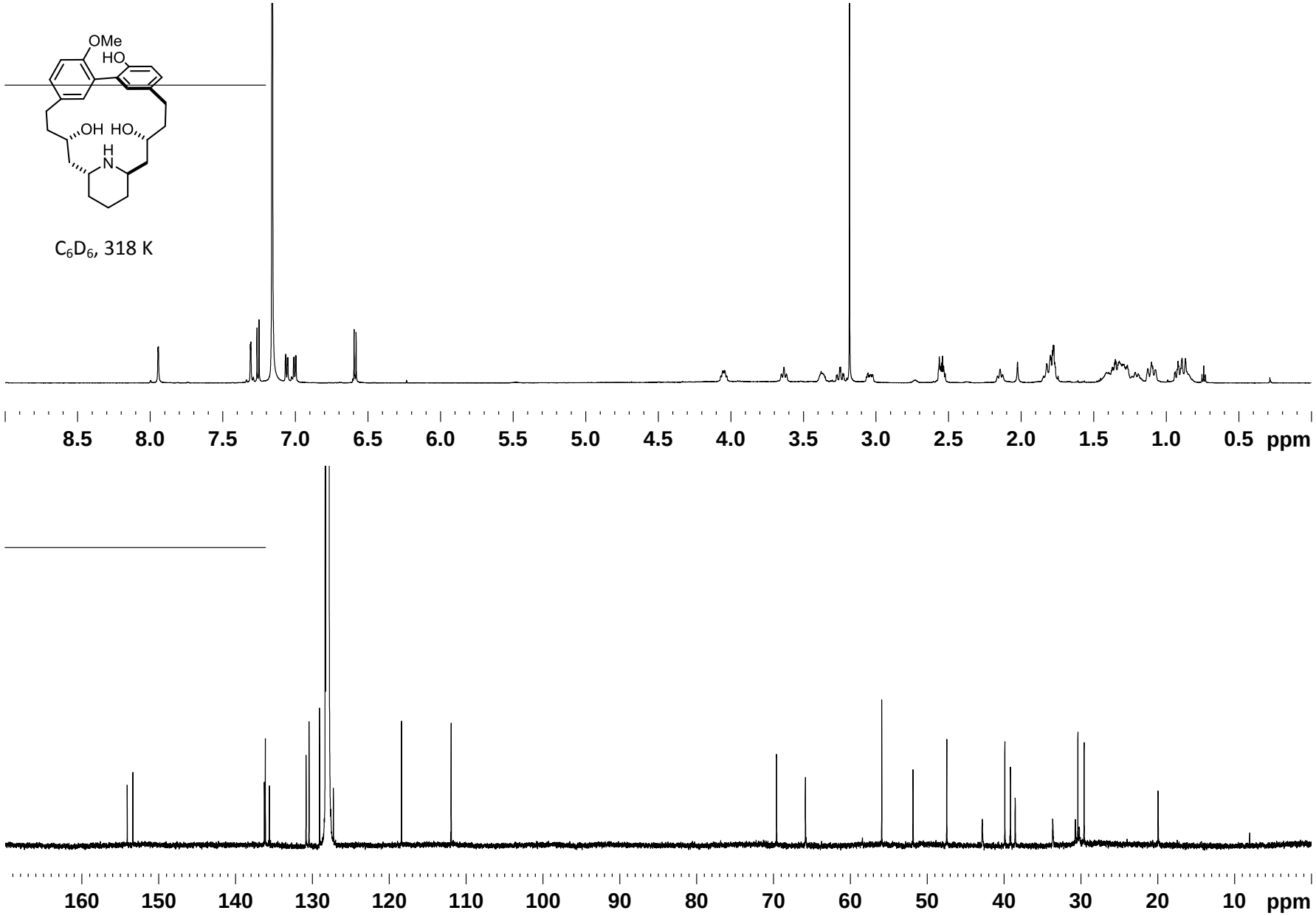
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


OMe
HO
OH
HO
H
N
C6D6, 318 K
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
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm