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Supporting Information

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The Catalytic Enantioselective Total Synthesis of (+)-Liphagal**

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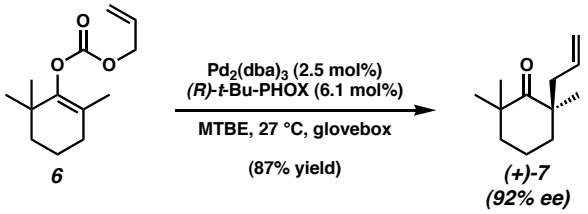
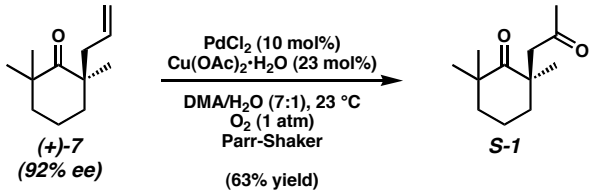
Materials and Methods. Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF was distilled over sodium/benzophenone or dried by passage through an activated alumina column under argon prior to use. Methanol was distilled over $Mg(OMe)_2$ prior to use. Other solvents were dried by passage through an activated alumina column under argon. Diisopropylamine and triethylamine were distilled over CaH_2 prior to use. Iodomethane was distilled prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Phosphinooxazoline (PHOX) ligands were prepared by methods described in our previous work.[1] All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Analytical LC/MS was performed on an Agilent 6140 single quadrupole LC/MS with an Agilent 1290 Infinity UHPLC system. Glove box manipulations were performed under a N_2 atmospere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silica Flash P60 Academic Silica Gel (particle size 0.040–0.063 mm) was used for flash column chromatography. Automated flash column chromatography was performed on a Teledyne Isco CombiFlash R_f system. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, Varian Inova 500 MHz, or Varian Inova 600 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or C_6D_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer (at 75 MHz and 125 Mhz, respectively) and are reported relative to

$CDCl_3$ (δ 77.2 ppm) or C_6D_6 (δ 128.4 ppm). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm) using a 100 mm path-length cell and are reported as: $[\alpha]^T_D$ (concentration in g/100 mL, solvent), ee. Melting points were measured using a Thomas-Hoover capillary melting point apparatus and the reported values are uncorrected. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Ltd. with visualization at 254 nm. Analytical chiral SFC was performed with a Mettler Toledo SFC supercritical CO_2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm) with visualization at 244 nm/235 nm. High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (EI+ or FAB+) or on a Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed (MM: ESI-APCI+) ionization mode.

Experimental Procedures and Spectroscopic Data.

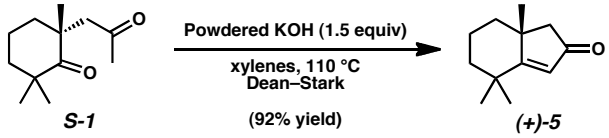


Allyl Ketone (+)-7. In the glovebox, an oven dried recovery flask was charged with $Pd_2(dba)_3$ (25.8 mg, 0.0281 mmol), followed by *(R)-t*-Bu-PHOX (26.8 mg, 0.0691 mmol). Anhydrous *t*-butyl methyl ether (37 mL) was added and the solution stirred for 30 min. After this time, enol carbonate **6** (254.1 mg, 1.13 mmol) was added via pipette as a solution in *t*-butyl methyl ether (~2 mL). The flask was sealed with a yellow WW series Caplugs® and stirred at 27 °C for 15 h. The reaction was removed from the glovebox and vacuum filtered through silica gel. The majority of *t*-butyl methyl ether was removed by distillation under nitrogen and the remaining material purified by flash column chromatography on silica gel (2% Et_2O in pentane) providing allyl ketone **(+)-7** (177.8 mg, 87% yield) as a colorless oil in 92% ee as determined by chiral HPLC of enone **(+)-5** (*vide infra*). $[\alpha]^{25}_{D}$ = +42.7° (*c* 1.005, $CHCl_3$), 92% ee. Other characterization data for this compound matched what has been previously reported.[2]

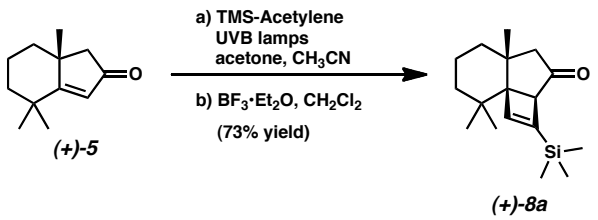


Diketone (+)-S-1. A Parr flask was charged with $PdCl_2$ (7.0 mg, 0.0394 mmol) and $Cu(OAc)_2 \bullet H_2O$ (38.6 mg, 0.229 mmol), followed by H_2O (0.25 mL). A solution of allyl ketone **(+)-7** (152.1 mg, 0.843 mmol) in DMA (1.75 mL) was introduced. The reaction was cooled to –78 °C, then evacuated/backfilled (vacuum/O_2) (3 x). The reaction was warmed to 22 °C and

placed on a Parr Shaker under 1 atm of O_2 for 25 h. At this time additional $PdCl_2$ (10.3 mg, 0.058 mmol) was added and the reaction restarted on the Parr Shaker under 1 atm of O_2. After 60 h the reaction was directly loaded onto a column of silica gel and purified by flash column chromatography (20:80 Et_2O:pentane eluent) giving diketone **(–)-S-1** (105.5 mg, 63% yield) in 92% ee as determined by chiral HPLC of enone **(+)-5** (*vide infra*). $[\alpha]^{25}_D$ = –72.9° (*c* 1.05, $CHCl_3$), 92% ee. Other characterization data for this compound matched what has been previously reported.[2]



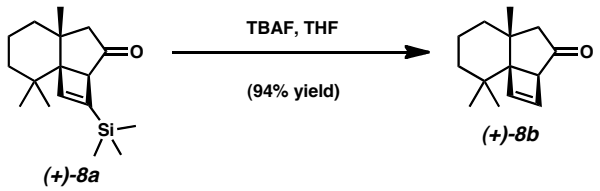
Enone (+)-5. Diketone **(–)-S-1** (105.5 mg, 0.537 mmol) was dissolved in xylenes (2.5 mL) under N_2 and and charged to a round-bottom flask with an attached reflux condenser. Freshly powdered KOH (47.2 mg, 0.841 mmol) was added quickly all at once and the colorless solution was placed in a pre-heated oil bath and stirred at 110 °C for 11 h. After cooling, the reaction was directly loaded onto silica gel and purified by flash column chromatography (20:80 → 50:50 Et_2O:pentane eluent) yielding enone **(+)-5** (87.8 mg, 92% yield) in 92% ee as determined by chiral HPLC. $[\alpha]^{25}_D$ = +99.9° (*c* 1.035, $CHCl_3$), 92% ee. Other characterization data for this compound matched what has been previously reported.[2]



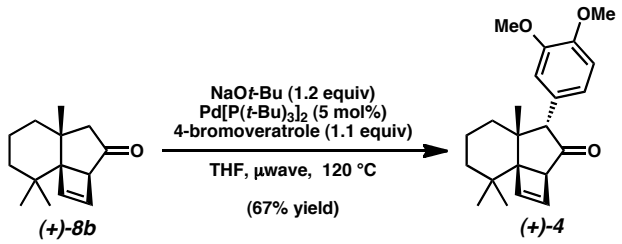
Silylcyclobutene (+)-8a. Enone **(+)-5** (506.7 mg, 2.84 mmol) was distributed into five quartz test tubes and dissolved in anhydrous acetonitrile (5 mL each) and spectrophotometric grade acetone (1 mL each). To each test tube was added trimethylsilyl acetylene (2.5 mL, 17.56 mmol; 0.5 mL each) and then capped with a yellow WW series Caplugs®. The test tubes were inverted (3x) to ensure adequate mixing of the reagents. At this time the reactions were placed in a Luzchem photoreactor and irratdiated with ten UVB lamps (~313 nm) for a total of 22.5 h. The test tubes were removed from the photoreactor and the contents concentrated in vacuo. Due to the instability of one isomeric product the crude reaction mixture was immediately advanced to the next step.

The crude reaction mixture was dissolved in anhydrous CH_2Cl_2 and stirred while BF_3•OEt_2 (0.050 mL, 0.405 mmol) was added dropwise. The contents of the reaction were aged for 30 min and then treated with Celite® (5g). The reaction was vacuum filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (2:98 EtOAc:hexane) providing silylcyclobutene **(+)-8a** (577.4 mg, 73% yield; two stages) as a white waxy solid. R_f = 0.68 (20% EtOAc in hexanes), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.81 (d, *J* = 1.4 Hz, 1H), 3.05 (m, 1H), 2.96 (d, *J* = 16.2 Hz, 1H), 1.65–1.52 (m, 2H), 1.43–1.35, (m, 3H), 1.32–1.10 (m, 5H), 1.02 (s, 3H), 0.89 (s, 3H), 0.046 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.6, 157.1, 153.3, 64.7, 59.2, 52.1, 38.7, 36.7, 36.3, 33.4, 28.1, 24.9, 22.0, 18.4, –2.1; IR (NaCl): ν 2996, 2956, 2927, 2871, 2845, 1732, 1561, 1456, 1413, 1388, 1378, 1249, 1225, 1213, 1161, 962, 907, 840, 753

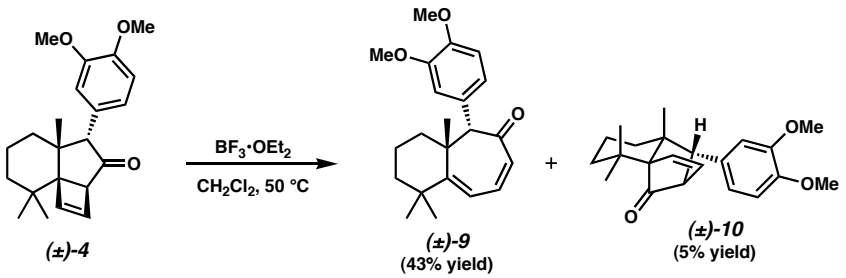
cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* for $C_{17}H_{29}OSi$ $[M+H]^+$: calc'd 277.1982, found 277.1989; $[\alpha]^{25}_D$ = +477.687 (c 3.39, $CHCl_3$), 91% ee.



Cyclobutene (+)-8b. To a solution of silylcyclobutene **(+)-8a** (253.0 mg, 0.915 mmol) in anhydrous THF was added 1.0 M TBAF in THF (2 mL, 2.0 mmol) under a N_2 atmosphere. The colorless solution immediately turned reddish-brown. The reaction was stirred and heated to 40 °C in an oil bath. Following completion of the reaction, as monitored by TLC, it was concentrated in vacuo and loaded directly onto silica gel with CH_2Cl_2 for flash column chromatography (5:95 EtOAc:hexanes) to afford cyclobutene **(+)-8b** (176.6 mg, 94% yield) as a white waxy volatile solid. R_f = 0.39 (10% EtOAc in Hex), sublimation point, sp: <23 °C (3 mmHg); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.37 (m, 1H), 6.32 (m, 1H), 3.06–3.02 (m, 2H), 1.69–1.55 (m, 2H), 1.47–1.36 (m, 3H), 1.30 (m, 1H), 1.21–1.12 (m, 4H), 1.05 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.2, 143.0, 137.8, 65.2, 58.4, 51.9, 38.8, 37.1, 36.1, 33.5, 28.2, 25.1, 22.1, 18.4; IR (NaCl): ν 3046, 2957, 2924, 2870, 2844, 1733, 1456, 1414, 1388, 1378, 1364, 1212, 1161, 725 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* for $C_{14}H_{21}O$ $[M+H]^+$: calc'd 205.1587, found 205.1591; $[\alpha]^{25}_D$ = +642.438° (c 1.065, $CHCl_3$), 91% ee.



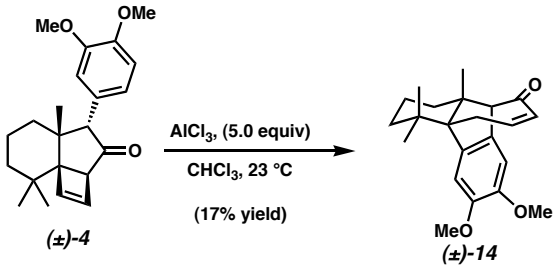
Arylcyclobutene (+)-4. In the glovebox, a 5 mL oven-dried microwave vial was charged with Pd[P(*t*-Bu)$_3$]$_2$ (14.3 mg, 0.02798 mmol, 5 mol%) and NaO*t*-Bu (65.6 mg, 0.6826 mmol). A stir bar was added to the vial before it was sealed and removed from the glovebox. A solution of cyclobutene **(+)-8b** (110.0 mg, 0.5388 mmol) in anhydrous THF was added to the vial under N_2, followed by 4-bromoveratrole (0.085 mL, 0.5908 mmol). The reaction was placed in the microwave reactor and heated to 120 °C for a total of 7.5 h. The reaction was quenched with sat. aq NH_4Cl (0.50 mL) and treated with activated charcoal (0.022 mg) and Celite® (0.310 mg). The heterogeneous mixture was stirred overnight and then vacuum filtered. The residue was purified by flash column chromatography on silica gel (5:95 → 10:90 EtOAc:hexanes) to provide aryl cyclobutene **(+)-4** (124.0 mg, 67% yield) as a white amorphous solid. R_f = 0.28 (20:80 EtOAc:hexane); ^{1}H NMR (500 MHz, C_6D_6): δ 6.80 (d, *J* = 2.2 Hz, 1H), 6.74 (dd, *J* = 8.3 Hz, 2.2 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.15 (app. dd, *J* = 2.9 Hz, 0.9 Hz, 1H), 6.05 (app. dd, *J* = 2.9 Hz, 1.5 Hz, 1H), 4.35 (s, 1H), 3.54 (s, 3H), 3.46 (s, 3H), 3.12 (app. dd, *J* = 1.5 Hz, 0.9 Hz, 1H), 1.37–1.18 (m, 3H), 1.09 (app. ddd, *J* = 13.7 Hz, 3.7 Hz, 3.4 Hz, 1H), 1.08–1.02, (m, 1H), 1.07 (app. ddd, *J* = 12.9 Hz, 3.7 Hz, 3.2 Hz, 1H), 1.02 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 212.8, 149.93, 149.92, 142.6, 140.4, 126.9, 125.1, 117.1, 112.3, 63.1, 60.7, 57.1, 56.3, 56.0, 40.5, 39.3, 34.0, 33.6, 28.7, 25.9, 20.7, 18.6; IR (NaCl): ν 2930, 2871, 2842, 1732, 1608, 1588, 1517, 1464, 1253, 1146, 1030, 739 cm^{-1}; HRMS (EI$^+$) *m/z* for $C_{22}H_{28}O_3$ [M]$^{+\bullet}$: calc'd 340.2039, found 340.2040; $[\alpha]^{25}_D$ = +512.59° (*c* 1.015, $CHCl_3$), 91% ee.



(±)-4 *(±)-9* (43% yield) *(±)-10* (5% yield)

Aryl Cycloheptadienone (±)-9 and **Cargill Rearrangement Adduct (±)-10**. A Schlenk flask was charged with a solution of aryl cyclobutene **(±)-4** (563 mg, 1.65 mmol) and CH_2Cl_2 (52 mL). BF_3•OEt_2 (1.05 mL, 8.27 mmol) was then introduced. The vessel was sealed and heated with stirring to 50 °C behind a blast shield for 20 h. The reaction was cooled to 23 °C and added slowly to a suspension of brine (25 mL), sat. aq $NaHCO_3$ (25 mL), and CH_2Cl_2 (25 mL). After addition was complete, the reaction was stirred vigorously for 5 min. The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (0:100 → 40:60 EtOAc:hexane eluent), affording aryl cycloheptadienone **(±)-9** (242 mg, 43% yield) as a yellow oil. R_f = 0.61 (50:50 EtOAc:hexane); ^{1}H NMR (500 MHz, C_6D_6): δ 7.01 (app. d, J = 2.0 Hz, 1H), 6.95 (app. dd, J = 8.3 Hz, 2.0 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 6.17 (d, J = 6.8 Hz, 1H), 6.16 (d, J = 2.0 Hz, 1H), 5.91 (dd, J = 6.8 Hz, 2.0 Hz, 1H), 3.55 (s, 1H), 3.48 (s, 3H), 3.38 (s, 3H), 1.82 (app. td, J_t = 13.2 Hz, J_d = 5.1 Hz, 1H), 1.53–1.43 (m, 1H), 1.29–1.16 (m, 2H), 1.24 (s, 3H), 1.13–1.00 (m, 2H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 198.5, 166.8, 150.1, 150.0, 137.0, 129.8, 129.5, 123.1, 121.0, 114.8, 112.3, 70.6, 56.1, 55.9, 41.0, 38.6, 38.3, 36.8, 33.6, 31.7, 25.2, 17.9; IR (NaCl): ν 2924, 1645, 1573, 1516, 1463, 1419, 1264, 1236, 1148, 1028 cm^{-1}; HRMS (EI$^+$) *m/z* for $C_{22}H_{28}O_3$ $[M]^{+\bullet}$: calc'd 340.2039, found 340.2038.

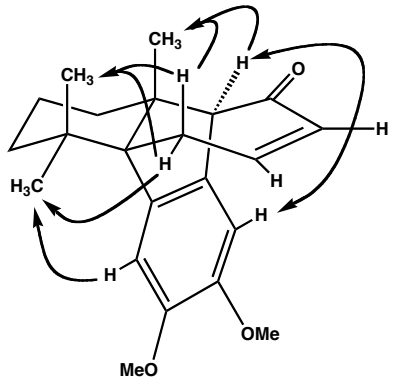
In addition to **(±)-9**, several fractions containing a second compound in semipure form were collected from the flash column above. These fractions were combined and concentrated. The residue was purified by flash column chromatography on silica gel (50:50 CH_2Cl_2:PhH → 10:50:50 EtOAc:CH_2Cl_2:PhH), affording pure Cargill rearrangement adduct **(±)-10** (28.1 mg, 5.0% yield) as colorless crystals. One of these crystals was suitable for X-Ray analysis, allowing for determination of the relative stereochemistry of the compound. R_f = 0.74 (50:50 EtOAc:hexane); mp 116–118 °C (C_6D_6); ^{1}H NMR (500 MHz, C_6D_6); δ 6.79 (app. d, *J* = 8.3 Hz, 1H), 6.78 (app. s, 1H), 6.57 (app. d, *J* = 8.3 Hz, 1H), 6.32 (app. dd, *J* = 7.1 Hz, 3.9 Hz, 1H), 6.20 (app. dd, *J* = 7.1 Hz, 1.2 Hz, 1H), 3.54 (s, 3H), 3.44 (s, 3H), 2.83 (app. dd, *J* = 3.9 Hz, 0.7 Hz, 1H), 2.23 (s, 1H), 2.04 (app. td, J_t = 13.4 Hz, J_d = 3.9 Hz, 1H), 1.47 (app. qt, J_q = 13.7 Hz, J_t = 3.2 Hz, 1H), 1.35 (app. d, *J* = 14.2 Hz, 1H), 1.32–1.13 (m, 2H), 1.29 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.74 (app. d, *J* = 13.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6): δ 206.5, 150.2, 149.4, 134.6, 134.4, 134.1, 121.0, 113.2, 112.5, 64.0, 56.1, 56.0, 53.4, 40.2, 37.1, 34.3, 32.5, 32.4, 28.1, 26.9, 26.6, 19.6; IR (NaCl): ν 2995, 2934, 2867, 2834, 1772, 1518, 1464, 1267, 1254, 1241, 1147, 1030, 750 cm^{-1}; HRMS (EI$^+$) *m/z* for $C_{22}H_{28}O_3$ $[M]^{+\bullet}$: calc'd 340.2039, found 340.2034.



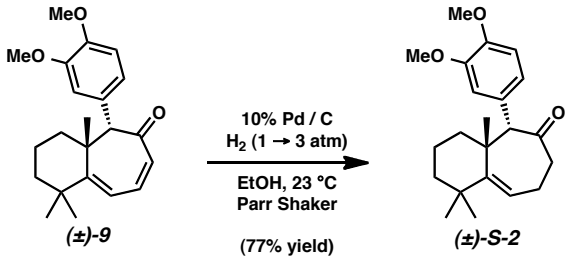
(±)-4 *(±)-14*

Friedel–Crafts Adduct (±)-14. A solution of aryl cyclobutene **(±)-4** (50 mg, 0.147 mmol, 1.0 equiv) in $CHCl_3$ (15.0 mL) was treated with $AlCl_3$ (98.0 mg, 0.735 mmol, 5.0 equiv, weighed in the glovebox). As the reaction stirred for 48 h, it went from peach-colored to maroon. After the

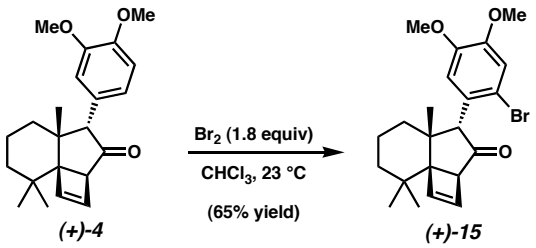
reaction was complete, it was added dropwise to a solution of brine (20 mL) and sat. aq $NaHCO_3$ (20 mL) at 23 °C. The suspension was then extracted with $CHCl_3$ (2 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated to ~500 μL total volume. The brown oil was purified by preparative TLC (20:80 EtOAc:hexane eluent), affording the Friedel–Crafts adduct **(±)-14** (8.3 mg, 17% yield) as a yellow powder. R_f = 0.24 (20:80 EtOAc:hexane); mp 152–155 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.64 (s, 1H), 6.04 (app. ddd, *J* = 12.6 Hz, 5.5 Hz, 3.6 Hz, 1H), 5.66 (app. dd, broad, *J* = 12.6 Hz, 1.9 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.33 (app. d, broad, *J* = 1.6 Hz, 1H), 2.84 (app. d, broad, *J* = 1.9 Hz, 1H), 2.84 (app. dd, *J* = 9.0 Hz, 1.6 Hz, 1H), 1.72–1.58 (m, 1H), 1.54–1.26 (m, 4H), 1.43 (s, 3H), 1.26 (s, 3H), 1.24–1.00 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 148.4, 142.9, 139.5 135.5, 128.7, 110.2, 107.6, 73.1, 57.5, 56.3, 55.9, 46.4, 40.8, 39.9, 38.9, 37.5, 29.6, 26.9, 20.7, 18.4; IR (NaCl): ν 2932, 1659, 1605, 1504, 1464, 1402, 1295, 1206, 1096, 1036, 914, 857, 755 cm^{-1}; HRMS (EI$^+$) *m*/*z* for $C_{22}H_{28}O_3$ [M]$^{+\bullet}$: calc'd 340.2039, found 340.2039. ^{1}H-nOesy-1D spectra were obtained for **(±)-14** (300 MHz, $CDCl_3$); the results are shown below:



nOe's detected for *(±)-14*

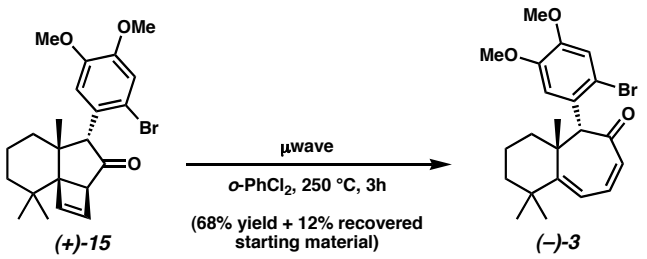


γ,δ-Unsaturated Aryl Cycloheptanone (±)-S-2. A Parr flask was charged with 10% w/w Pd/C (38 mg, 35.3 μmol, 5 mol%), followed by a solution of aryl cycloheptadienone **(±)-9** (240 mg, 0.705 mmol) in absolute EtOH (40 mL). The reaction was placed under H_2 (1 atm) at 23 °C on a Parr shaker for 40 h. At this time, more 10% w/w Pd/C (114 mg, 0.106 mmol, 15 mol%) was carefully added. The reaction was continued under H_2 (now 3 atm) for 20 h. Once the reaction was complete, it was filtered through celite over glass frits with the aid of EtOAc. The filtrate was concentrated and purified by flash chromatography on silica gel (hexane → 20:80 EtOAc:hexane eluent), giving γ,δ-unsaturated aryl cycloheptanone **(±)-S-2** (188 mg, 77% yield) as a colorless oil. R_f = 0.31 (20:80 EtOAc:hexane); ^{1}H NMR (300 MHz, C_6D_6): δ 7.17 (app. d, *J* = 2.1 Hz, 1H), 7.09 (app. dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 6.59 (app. d, *J* = 8.2 Hz, 1H), 5.77 (dd, *J* = 8.2 Hz, 5.2 Hz, 1H), 3.85 (s, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.60 (app. td, J_t = 13.8 Hz, J_d = 4.7 Hz, 1H), 2.30–1.86 (m, 5H), 1.60–1.42 (m, 1H), 1.36–1.20 (m, 1H), 1.27 (s, 3H), 1.16 (s, 3H0, 1.01 (s, 3H), 0.98–0.68 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6): δ 210.0, 153.5, 150.1, 149.7, 130.5, 123.6, 123.5, 115.3, 112.3, 71.8, 56.2, 55.9, 42.0, 41.0, 40.2, 37.8 (2C), 33.8, 33.7, 28.4, 23.7, 18.6; IR (NaCl): ν 2933, 1695, 1603, 1588, 1515, 1464, 1379, 1252, 1146, 1029, 756 cm^{-1}; HRMS (EI$^+$) *m/z* for $C_{22}H_{30}O_3$ [M]$^{+\bullet}$: calc'd 342.2195, found 342.2183.



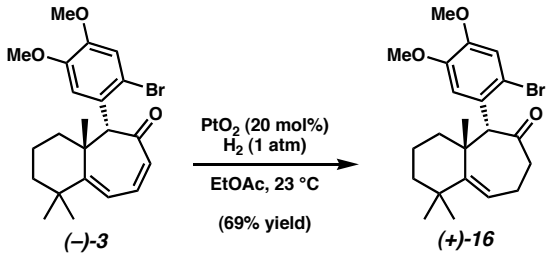
(+)-4 *(+)-15*

Bromoaryl cyclobutene (+)-15. To a solution of aryl cyclobutene **(+)-4** (268.0 mg, 0.787 mmol) in $CHCl_3$ was added a 0.1 g/mL $CHCl_3$ solution of Br_2 (1.2 mL, 0.795 mmol). After 5 min additional Br_2 (0.990 mL, 0.655 mmol) was added portion-wise. The reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and 5% aq $Na_2S_2O_3$ (10 mL). This mixture was extracted with CH_2Cl_2 (3 x 25 mL), washed with brine, dried ($MgSO_4$), vacuum filtered, and concentrated in vacuo. The crude product was recrystallized from EtOAc yielding bromoaryl cyclobutene **(+)-15** (214.5 mg, 65% yield) as colorless crystals in >99% ee as determined by chiral SFC. R_f = 0.39 (20:80 EtOAc:hexane); mp 215–217 °C (EtOAc:hexane, racemate), mp 240–242 °C (95% ee)[3]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.65 (s, 1H), 6.57 (app. dd, *J* = 2.7 Hz, 0.8 Hz, 1H), 6.52 (app. dd, *J* = 2.7 Hz, 1.6 Hz, 1H), 5.21 (s, 1H), 3.84 (app. s, 6H), 3.13 (app. s, 1H), 1.60–1.40 (m, 3H), 1.34 (app. dd, *J* = 12.9 Hz, 3.8 Hz, 1H), 1.28–1.04 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.8, 148.7, 147.5, 142.7, 140.2, 125.0, 118.2, 115.9, 115.4, 62.9, 58.6, 56.3, 56.21, 56.18, 42.0, 39.0, 33.8, 33.5, 28.4, 25.6, 20.7, 17.9; IR (NaCl): ν 2931, 2870, 2844, 1732, 1603, 1571, 1508, 1464, 1379, 1258, 1211, 1166, 1032, 914, 845, 735 cm^{-1}; HRMS (FAB$^+$) *m/z* for $C_{22}H_{27}O_3{}^{81}Br$ $[M+H]^+$: calc'd 420.1123, found 420.1119; $[\alpha]^{25}_D$ = +519.57° (*c* 2.16, $CHCl_3$), >99% ee.

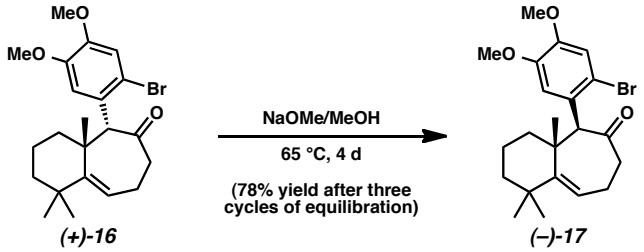


Bromoaryl dienone (–)-3. A round bottom flask was charged with bromoaryl cyclobutene **(+)-15** (214.5 mg, 0.512 mmol) and dissolved in *o*-dichlorobenzene (*o*-$PhCl_2$) (15 mL) with the aid of mild heating from a heat gun. The clear and colorless solution was distributed between three 20 mL microwave vials. The round bottom flask was rinsed with *o*-$PhCl_2$ (15 mL x 2, 9 mL x 1) and again distributed between the three microwave vials (total = 18 mL each). The solutions were sealed, placed under Ar, and degassed by the method of freeze-pump-thaw (3x). At this time, the microwave vials were individually irradiated (3 h) in a microwave reactor at 250 °C. Following irradiation the clear yellow-orange solutions were combined and loaded directly onto silica gel for purification by flash column chromatography (10:90 → 20:80 → 30:70 EtOAc:hexanes eluent) yielding bromoaryl dienone **(–)-3** (147.0 mg, 68% yield) as a yellow solid, in addition to recovered bromoaryl cyclobutene **(+)-15** (26.0 mg, 12% yield) as a white solid. R_f = 0.28 (20:80 EtOAc:hexane); mp 146–147 °C (EtOAc:hexane, racemate), mp 144–147 °C (EtOAc:hexane, 95% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.03 (s, 1H), 6.70 (dd, *J* = 12.4 Hz, 8.8 Hz, 1H), 6.30 (d, *J* = 8.8 Hz, 1H), 6.08 (d, *J* = 12.4 Hz, 1H), 4.16 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 1.75–1.33 (m, 5H), 1.37 (s, 3H), 1.21 (s, 3H), 1.22-1.04 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 168.4, 148.4, 148.0, 137.6, 129.5, 128.1, 120.4, 118.0, 115.8, 112.4, 66.3, 56.1, 55.8, 42.8, 38.4, 37.9, 35.4, 33.5, 31.5, 25.3, 17.0; IR (NaCl): ν 2934, 1644, 1572, 1509, 1463, 1440, 1377, 1267, 1248, 1230, 1205, 1159, 1030, 837 cm^{-1}; HRMS

(EI$^+$) *m/z* for $C_{22}H_{27}BrO_3$ $[M]^{+\bullet}$: calc'd 418.1144, found 418.1158; $[\alpha]^{24}_D$ = –437.31° (*c* 0.985, $CHCl_3$), 95% ee.

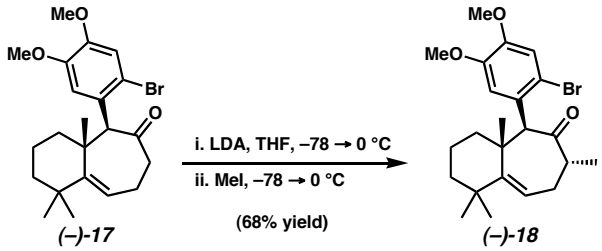


Bromoaryl–γ,δ–Unsaturated Cycloheptanone (+)-16. A round-bottom flask containing bromoaryl dienone **(–)-3** (400 mg, 0.952 mmol) in EtOAc (ACS grade, 50 mL) was degassed with argon for 5 min. Then, PtO_2 (43.2 mg, 0.190 mmol, 20 mol%) was carefully added. The reaction was cooled to –78 °C, then evacuated/backfilled (vacuum/H_2 (1 atm)) (3 x). With vigorous stirring, the reaction was warmed to 23 °C under H_2 (1 atm). After 30 min, the reaction was concentrated, and the residue was taken up in PhH. It was purified by flash chromatography on silica gel (10:90 EtOAc:hexane eluent), giving bromoaryl–γ,δ–unsaturated cycloheptanone **(+)-16** (277 mg, 69% yield) as a white solid. R_f = 0.41 (20:80 EtOAc:hexane); mp 114–116 °C (EtOAc:hexane, racemate), mp 121–123 °C (EtOAc:hexane, 95% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.02 (s, 1H), 6.00 (dd, *J* = 9.9 Hz, 4.4 Hz, 1H), 4.68 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.71–2.49 (m, 2H), 2.43–2.32 (m, 2H), 1.79–1.57 (m, 2H), 1.51–1.39 (m, 2H), 1.36–1.24 (m, 2H), 1.28 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 153.8, 148.6, 147.8, 128.2, 122.7, 118.4, 115.6, 115.0, 66.0, 56.7, 56.2, 43.9, 41.5, 39.7, 37.8, 36.4, 33.7, 33.3, 27.5, 23.4, 17.9; IR (NaCl): ν 2936, 2845, 1716, 1699, 1600, 1567, 1506, 1463, 1440, 1374, 1254, 1212, 1159, 1030, 732 cm^{-1}; HRMS (FAB$^+$) *m/z* for $C_{22}H_{29}BrO_3$ $[M]^{+\bullet}$: calc'd 420.1300, found 420.1303; $[\alpha]^{25}_D$ = +162.47° (*c* 1.250, $CHCl_3$), 95% ee.



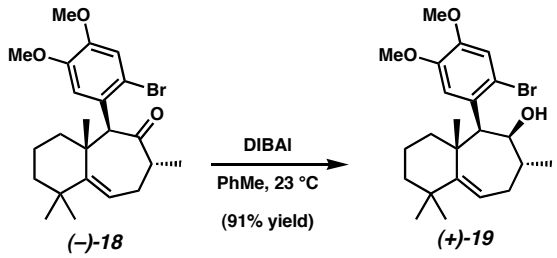
β-Bromoaryl Ketone (–)-17. In a glovebox[4], a 20 mL oven-dried scintillation vial was charged with a solution of bromoaryl–γ,δ–unsaturated cycloheptanone **(+)-16** (138.1 mg, 0.327 mmol) in MeOH (1 mL) and 1M NaOMe (5 mL, 5 mmol) in MeOH. The reaction mixture was heated to 65 °C in the glovebox with stirring for 86 h. The reaction was removed from the glovebox and quenched with AcOH (0.30 mL) under vigorous stirring. The mixture was diluted with H_2O (3.0 mL) and the volatiles concentrated in vacuo. Brine (3.0 mL) was added and the aqueous phase extracted with EtOAc (4 x 3 mL). The organic layers were combined, dried ($MgSO_4$), vacuum filtered, and concentrated in vacuo. The residue was purified by HPLC (Zorbax Rx-Sil, 5 μm, 9.4 x 250 mm, 8:92 EtOAc:hexanes, 7 mL/min, monitored at 254 nm) affording bromoaryl–γ,δ–unsaturated cycloheptanone **(+)-16** (73.4 mg, 53% yield) as a white solid and β-bromoaryl ketone **(–)-17** (61.6 mg, 44% yield) as a colorless oil. Retention times: bromoaryl–γ,δ–unsaturated cycloheptanone **(+)-16** 7.5 min, β-bromoaryl ketone **(–)-17** 8.8 min. This procedure was repeated twice more with the recovered bromoaryl–γ,δ–unsaturated cycloheptanone **(+)-16** to yield β-bromoaryl ketone **(–)-17** (109.0 mg, 78% yield after three cycles of equilibration) as a colorless oil. R_f = 0.33 (20:80 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (s, 1H), 6.99 (s, 1H), 5.97 (dd, J_1 = 3.4 Hz, J_2 = 8.5 Hz, 1H), 5.28 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.77 (m, 1H), 2.66–2.51 (m, 2H), 2.33 (m, 1H), 1.67–1.19 (m, 11H), 1.15 (s, 3H), 0.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 211.1, 155.7, 148.4, 147.5, 128.8, 121.9,

117.4, 115.3, 114.9, 62.3, 56.2, 56.1, 43.5, 43.1, 39.7, 38.2, 37.7, 33.9, 32.2, 24.8, 24.6, 18.2; IR (NaCl): ν 2933, 1706, 1602, 1570, 1506, 1466, 1439, 1375, 1308, 1266, 1209, 1160, 1029 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* for $C_{22}H_{30}O_3Br$ $[M+H]^+$: calc'd 421.1373, found 421.1356; $[\alpha]^{25}_D$ = –212.15° (c 0.74, $CHCl_3$), >99% ee.



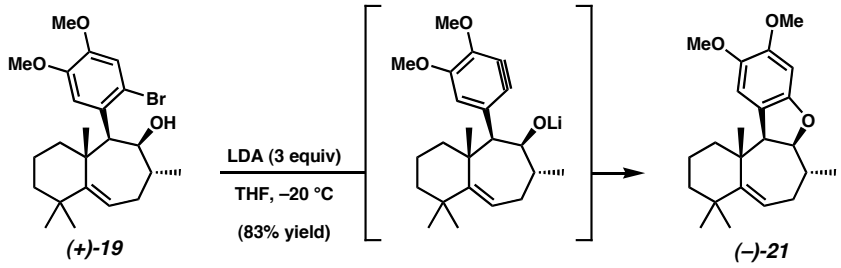
Bromoaryl Methyl Ketone (–)-18. To a solution of freshly distilled *i*-Pr_2NH (0.025 mL, 0.1768 mmol) in anhydrous THF (0.20 mL) cooled to –78 °C was added 2.3 M *n*-BuLi (0.062 mL, 0.1439 mmol) dropwise via syringe. The contents were stirred for 30 min at –78 °C before addition of β-bromoaryl ketone **(–)-17** (57.8 mg, 0.1371 mmol) as a solution in anhydrous THF (1 mL). The pear-shaped flask containing β-bromoaryl ketone **(–)-17** was rinsed with THF (0.20 mL) and added to the reaction mixture at –78 °C. The stirred solution was aged for 30 min at –78 °C followed by 30 min in an ice-water bath. The reaction mixture was cooled to –78 °C and MeI (0.025 mL, 0.4015 mmol) was added dropwise. The reaction stirred for 15 min at –78 °C, followed by 15 min in an ice-water bath. The reaction was allowed to warm to 23 °C and additional MeI (0.050 mL, 0.8030 mmol) was added. Stirring continued for 30 min before quenching with H_2O (5 drops). The volatiles were removed in vacuo and the residue dissolved in EtOAc and diluted with brine. The organic layer was collected and the aqueous layer extracted with EtOAc (3 x 2 mL). All organic layers were combined, dried (Na_2SO_4), vacuum filtered, and concentrated in vacuo. The residue was purified by HPLC (Zorbax Rx-Sil, 5 μm, 9.4 x 250 mm,

8:92 EtOAc:hexanes, 7 mL/min, monitored at 254 nm) affording bromoaryl methyl ketone **(–)-18** (40.6 mg, 68% yield) as a colorless oil and β-bromoaryl ketone **(–)-17** (10.6 mg, 18% yield) as a colorless oil. Retention times: bromoaryl methyl ketone **(–)-18** 5.4 min, β-bromoaryl ketone **(–)-17** 7.7 min. R_f = 0.45 (20:80 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22 (s, 1H), 6.99 (s, 1H), 5.93, (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz, 1H), 5.35, (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 2.79–2.48 (m, 2H), 2.29 (m, 1H), 1.72–1.35 (m, 4H), 1.33 (s, 3H), 1.26 (m, 1H), 1.19 (s, 3H), 1.17–1.10 (m, 6H), 0.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.3, 155.6, 148.5, 147.7, 129.2, 121.4, 117.5, 115.5, 115.0, 61.3, 56.3, 56.2, 47.2, 43.4, 40.0, 38.2, 38.1, 34.0, 33.5, 32.0, 24.7, 18.4, 17.7; IR (NaCl): ν 2932, 2868, 2843, 1706, 1602, 1503, 1462, 1441, 1377, 1308, 1262, 1207, 1162, 1032, 845, 795, 734 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* for $C_{23}H_{32}O_3Br$ $[M+H]^+$: calc'd 435.1529, found 435.1526; $[\alpha]^{25}_D$ = –190.14° (c 0.815, $CHCl_3$), >99% ee.



Aryl alcohol (+)-19. To a solution of bromoaryl methyl ketone **(–)-18** (40.6 mg, 0.0932 mmol) in anhydrous PhMe was added a freshly prepared 1 M solution of DIBAL (0.380 mL, 0.380 mmol) in PhMe at 21 °C dropwise. The reaction aged for 20 min before it was quenched with sat. Na_2SO_4:Celite® (2:1) and stirred for an additional 30 min. The heterogeneous mixture was filtered and concentrated in vacuo. The residue was purified by HPLC (Zorbax Rx-Sil, 5 μm, 9.4 x 250 mm, 25:75 EtOAc:hexanes, 7 mL/min, monitored at 254 nm) providing aryl alcohol **(+)-19** (37.3 mg, 91% yield) as a colorless oil. R_f = 0.28 (20:80 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500

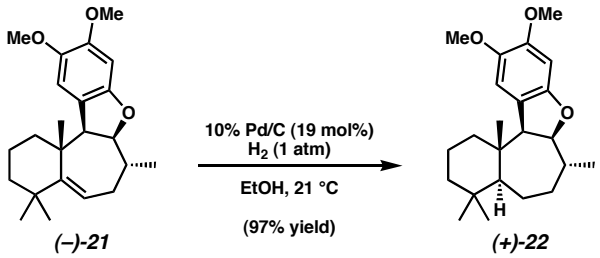
MHz): δ 7.36 (s, 1H), 7.03 (s, 1H), 5.76 (dd, J_1 = 2.9 Hz, J_2 = 8.7 Hz, 1H), 3.95 (d, J = 3.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.41 (ddd, J_1 = 3.9 Hz, J_2 = 4.6 Hz, J_3 = 8.7 Hz, 1H), 2.32–2.06 (m, 3H), 1.72 (d, J = 4.9 Hz, 1H), 1.69 (s, 3H), 1.68–1.60 (m, 1H), 1.44 (m, 1H), 1.37–1.19 (m, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.05 (d, J = 6.4 Hz, 3H), 0.92 (ddd, J_1 = 4.5 Hz, J_2 = 13.0 Hz, J_3 = 13.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.1, 147.9, 147.6, 134.5, 122.2, 116.9, 115.5, 114.5, 81.6, 56.2, 56.2, 54.6, 42.9, 40.0, 39.9, 39.8, 37.9, 34.0, 33.8, 32.4, 24.6, 20.7, 18.0; IR (NaCl): ν 3543, 2953, 2928, 2868, 2839, 1602, 1570, 1503, 1464, 1439, 1385, 1357, 1293, 1261, 1246, 1207, 1157, 1034, 757 cm^{-1}; HRMS (EI+) *m/z* for $C_{23}H_{33}O_3Br$ $[M]^{+\bullet}$: calc'd 436.1613, found 436.1600; $[\alpha]^{25}_D$ = +82.61° (c = 0.145, $CHCl_3$), >99% ee.



Dimethoxy dihydrobenzofuran (–)-21. *Preparation of LDA*: To a solution of freshly distilled *i*-Pr_2NH (0.550 mL, 3.89 mmol) in anhydrous THF (5.4 mL) cooled to –78 °C was added ~2.2 M *n*-BuLi (1.60 mL, 3.52 mmol) dropwise via syringe. The contents were stirred for 30 min at –78 °C before use. This solution was titrated according to the method of Chong[5] and found to be 0.52 M.

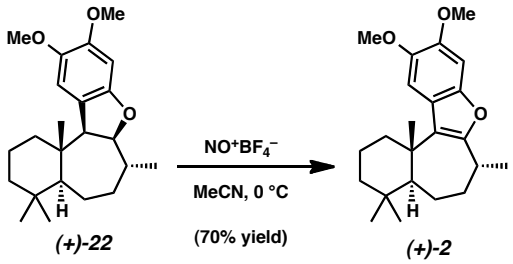
A solution of aryl alcohol **(+)-19** (36.7 mg, 0.0839 mmol) in anhydrous THF (2.8 mL) was stirred and cooled to –20 °C. To this colorless solution was added freshly prepared LDA dropwise via syringe. Following completion of the reaction (20 min, monitored by TLC) it was quenched with H_2O (one drop) at –20 °C and allowed to warm to 22 °C. The crude reaction was

filtered through Celite®, concentrated in vacuo, and purified by flash column chromatography on silica gel (10:90 → 20:80 EtOAc:hexanes eluent) yielding dimethoxy dihydrobenzofuran **(–)-21** (25.0 mg, 83% yield) as a white solid. R_f = 0.56 (20:80 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.79 (s, 1H), 6.48 (s, 1H), 5.76 (dd, J_1 = 2.2 Hz, J_2 = 8.5 Hz, 1H), 4.18 (dd, J_1 = 7.1 Hz, J_2 = 10.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.09 (d, J = 7.1 Hz, 1H), 2.61 (m, 1H), 2.20–1.99 (m, 2H), 1.74–1.56 (m, 2H), 1.53–1.43 (m, 2H), 1.32 (m, 2H), 1.12 (d, J = 6.5 Hz, 3H), 1.11 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.7, 152.8, 150.0, 142.4, 121.9, 120.0, 113.7, 95.7, 95.0, 57.5, 56.2, 56.1, 41.5, 40.6, 39.2, 38.0, 34.6, 34.2, 33.6, 32.3, 22.9, 21.2, 17.9; IR (NaCl): ν 3056, 2953, 2929, 2868, 2846, 1618, 1496, 1454, 1396, 1376, 1349, 1340, 1298, 1224, 1191, 1166, 1103, 989, 822 cm^{-1}; HRMS (FAB+) *m/z* for $C_{23}H_{32}O_3$ $[M]^{+\bullet}$: calc'd 356.2352, found 356.2359; $[\alpha]^{25}_D$ = –99.55° (c 1.25, $CHCl_3$), >99% ee.



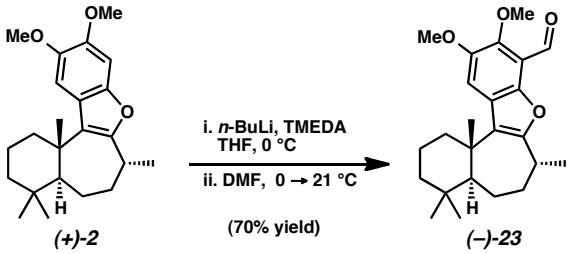
***trans*-Fused Dihydrobenzofuran (+)-22.** To an oven-dried 25 mL Schlenk flask was added dimethoxy dihydrobenzofuran **(–)-21** (24.9 mg, 0.06984 mmol) as a solution in EtOH (7 mL). The flask was evacuated and backfilled with N_2 (3x) before addition of Pd/C (14.4 mg, 0.01353 mmol, 10 wt. %, 19 mol%). The rubber septum was replaced under a positive N_2 flow by a three-way Teflon stopcock connected to a H_2 balloon. The heterogeneous mixture was cooled to –78 °C before it was evacuated and backfilled with H_2 (3x). The –78 °C cold bath was removed and the reaction was allowed to warm to 21 °C. After stirring for 12 h the contents of the flask

were filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (10:90 EtOAc:hexanes eluent) affording *trans*-fused dihydrobenzofuran **(+)-22** (24.3 mg, 97% yield) as a white solid. R_f = 0.53 (10:90 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.82 (s, 1H), 6.44 (s, 1H), 4.15 (dd, J_1 = 7.7 Hz, J_2 = 10.0 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.79 (d, J = 7.6 Hz, 1H), 2.25 (m, 1H), 2.02 (m, 1H), 1.66 (m, 2H), 1.55 (m, 1H), 1.39 (m, 3H), 1.29–1.16 (m, 3H), 1.14 (d, J = 6.5 Hz, 3H), 1.00 (dd, J_1 = 2.4 Hz, J_2 = 12.1 Hz, 1H), 0.94 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.2, 149.9, 142.2, 119.5, 114.1, 95.7, 94.7, 59.9, 57.7, 57.5, 56.1, 43.2, 40.9, 40.7, 37.7, 35.0, 34.1, 34.1, 28.1, 23.1, 22.2, 18.3, 16.3; IR (NaCl): ν 2949, 2928, 2868, 2845, 1618, 1496, 1464, 1453, 1389, 1340, 1224, 1193, 1167, 1121, 1099, 987 cm^{-1}; HRMS (FAB+) *m/z* for $C_{23}H_{34}O_3$ $[M]^{+\bullet}$: calc'd 358.2508, found 358.2509; $[\alpha]^{25}_D$ = +40.47° (c 1.03, $CHCl_3$), >99% ee.



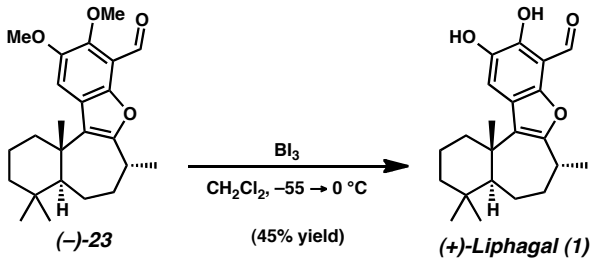
Dimethoxybenzofuran (+)-2. To a solution of *trans*-fused dihydrobenzofuran **(+)-22** (5.4 mg, 0.0150 mmol) in anhydrous MeCN at 0 °C was added dropwise a freshly prepared 0.128 mg/μl solution of $NO^+BF_4^-$ (20 μl, 0.0219 mmol) in anhydrous MeCN. The reaction solution turned brown following addition of the $NO^+BF_4^-$ solution, however this color slowly faded. Analysis of the mixture by LC/MS indicated that *trans*-fused dihydrobenzofuran **(+)-22** remained. Additional $NO^+BF_4^-$ (150 μl, 0.164 mmol) was added at 0 °C, however analysis of the mixture by LC/MS again indicated that *trans*-fused dihydrobenzofuran **(+)-22** remained. A final aliquot

of $NO^+BF_4^-$ (75 μl, 0.083 mmol) was added at 0 °C before the reaction was quenched by the addition of urea (40 mg, 0.67 mmol) and H_2O (100 μl). The reaction solution was diluted with EtOAc, filtered through Celite®, and concentrated in vacuo. The residue was purified by flash pipette chromatography on silica gel (5:95 EtOAc:hexanes eluent) providing dimethoxybenzofuran **(+)-2** (3.7 mg, 70% yield) as a white solid. R_f = 0.53 (20:80 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.16 (s, 1H), 6.93 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.18 (sext, *J* = 7.0 Hz, 1H), 2.60 (m, 1H), 2.16 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.66–1.44 (m, 6H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.38 (s, 3H), 1.26 (m, 1H), 0.98 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.0, 148.6, 147.0, 145.0, 125.5, 120.5, 105.7, 95.1, 57.2, 56.3, 53.8, 42.2, 40.5, 39.7, 35.4, 35.0, 33.9, 33.5, 24.5, 22.2, 22.1, 20.4, 19.1; IR (NaCl): ν 2930, 2867, 1623, 1488, 1466, 1439, 1389, 1316, 1281, 1211, 1197, 1166, 1136, 1115 cm^{-1}; HRMS (EI+) *m/z* for $C_{23}H_{32}O_3$ $[M]^{+\bullet}$: calc'd 356.2352, found 356.2353; $[\alpha]^{25}_D$ = +16.85° (c 0.16, $CHCl_3$), >99% ee.



***O,O'*-Dimethyliphagal (–)-23.** *Preparation of n-BuLi•TMEDA*: To a stirred solution of TMEDA (380 μl, 2.5 mmol) in anhydrous THF (5 mL) was added a ~2.0 M solution of *n*-BuLi (1.20 mL, 2.4 mmol) at 21 °C. The contents stirred for 30 min prior to use. This solution was titrated according to the method of Chong[5] and found to be 0.33 M.

A two dram vial containing dimethoxybenzofuran **(+)-2** (3.7 mg, 0.01037 mmol) in anhydrous THF (500 μl) was cooled to 0 °C before dropwise addition of *n*-BuLi•TMEDA (80 μl, 0.0264 mmol). After stirring for 30 min at 0 °C, DMF (7.5 μl, 0.0972 mmol) was introduced and the reaction was allowed to warm to 21 °C. After 20 min the reaction was quenched by the addition of sat. aq NH_4Cl (25 mL) and filtered through $MgSO_4$ prior to HPLC purification (Zorbax Rx-Sil, 5 μm, 9.4 x 250 mm, 5:95 EtOAc:hexanes, 6 mL/min, monitored at 254 nm) providing *O,O*'-dimethyliphagal **(–)-23** (2.8 mg, 70% yield) as a faint yellow solid. R_f = 0.50 (20:80 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.56 (s, 1H), 7.47 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.31 (sext, J = 7.0 Hz, 1H), 2.55 (m, 1H), 2.18 (dddd, J_1 = 3.3 Hz, J_2 = 7.2 Hz, J_3 = 7.2 Hz, J_4 = 12.8 Hz, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1.64–1.48 (m, 6H), 1.46 (d, J = 7.2 Hz, 3H), 1.37 (s, 3H), 1.26 (ddd, J_1 = 2.8 Hz, J_2 = 13.5 Hz, J_3 = 13.5 Hz, 1H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 188.6, 159.1, 149.7, 148.1, 146.5, 125.5, 124.8, 115.0, 113.3, 63.0, 57.5, 53.7, 42.1, 40.5, 39.7, 35.0, 35.0, 33.7, 33.5, 24.2, 22.3, 22.2, 20.4, 19.1; IR (NaCl): ν 2933, 2866, 1690, 1606, 1584, 1464, 1435, 1388, 1330, 1240, 1124, 1054, 979 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* for $C_{24}H_{33}O_4$ $[M+H]^+$: calc'd 385.2373, found 385.2371; $[\alpha]^{25}_D$ = –16.36° (c 0.280, $CHCl_3$), >99% ee.[6]



Liphagal (+)-1. In the glovebox[4], a two dram vial containing *O,O*'-dimethyliphagal **(–)-23** (1.7 mg, 0.00442 mmol) dissolved in anhydrous CH_2Cl_2 (680 μl) was cooled to –55 °C before

addition of a freshly prepared 0.01 M solution of BI_3 (885 μl, 0.00885 mmol) in anhydrous CH_2Cl_2. After 5 min at –55 °C the vial was warmed to 0 °C over 45 min. After 20 min at 0 °C the vial was removed from the glovebox and immediately quenched with H_2O:MeCN (50 μL:300 μL) resulting in a cloudy mixture. The volatiles were removed under a stream of Ar. The yellow residue was dissolved in MeCN, filtered through a Kimwipe® plug, and purified by reversed-phase HPLC (Eclipse XDB-C18, 5 μm, 9.4 x 250 mm, 80:20 MeCN:0.1% AcOH/H_2O, 5 mL/min, monitored at 254 nm) yielding liphagal **(+)-1** (0.7 mg, 45% yield) as a yellow oil/film. Retention time: liphagal **(+)-1** 21 min. R_f = 0.58 (20:80 EtOAc:hexanes + 1% AcOH); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.24 (s, 1H), 10.45 (s, 1H), 7.55 (s, 1H), 5.30 (s, 1H), 3.22 (sext, J = 7.0 Hz, 1H), 2.54 (m, 1H), 2.18 (dddd, J_1 = 3.5 Hz, J_2 = 6.4 Hz, J_3 = 6.4 Hz, J_4 = 13.1 Hz, 1H), 1.87 (m, 1H), 1.71 (m, 1H), 1.65–1.45 (m, 6H), 1.43 (d, J = 7.1 Hz, 3H), 1.35 (s, 3H), 1.25 (ddd, J_1 = 3.1 Hz, J_2 = 13.3 Hz, J_3 = 13.3 Hz, 1H), 0.98 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.7, 156.7, 148.2, 145.5, 139.6, 125.7, 120.5, 116.2, 106.5, 54.0, 42.1, 40.5, 39.7, 35.4, 35.1, 33.9, 33.5, 24.4, 22.2, 21.9, 20.5, 19.0; IR (NaCl): ν 3558, 3436, 2931, 2868, 1654, 1607, 1455, 1391, 1379, 1328, 1297, 1193 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* for $C_{22}H_{27}O_4$ $[M–H]^-$: calc'd 355.1915, found 355.1914; $[\alpha]^{25}_D$ = +25.99° (c 0.072, $CHCl_3$), >99% ee, lit. value $[\alpha]^{25}_D$ = +33.6° (c 0.9, $CHCl_3$).[7]

Comparison of Synthetic Liphagal prepared by Andersen and Stoltz.

^{1}H NMR of (+)-Liphagal, $CDCl_3$[1]

Synthetic, 400 MHz Andersen		Synthetic (+), 600 MHz Stoltz	
Shift (ppm)	Multiplicity/Coupling (Hz)	Shift (ppm)	Multiplicity/Coupling (Hz)
11.24	s	11.24	s
10.45	s	10.45	s
7.55	s	7.55	s
5.32	br s	5.30	s
3.20	m	3.22	sext, 7.0
2.54	m	2.54	m
2.17	m	2.18	dddd, 3.5, 6.4, 6.4, 13.1
1.86	m	1.87	m
-	-	1.71	m
1.8–1.5	m	1.65–1.45	m
1.43	d, 7.0	1.43	d, 7.1
1.34	s	1.35	s
1.25	m	1.25	ddd, 3.1, 13.3, 13.3
0.98	s	0.98	s
0.95	s	0.95	s

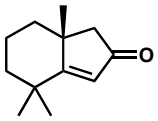
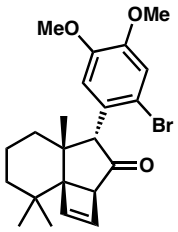
1. The values for Andersen's Synthetic Liphagal have been referenced to residual $CHCl_3$ in $CDCl_3$ at $\delta = 7.26$

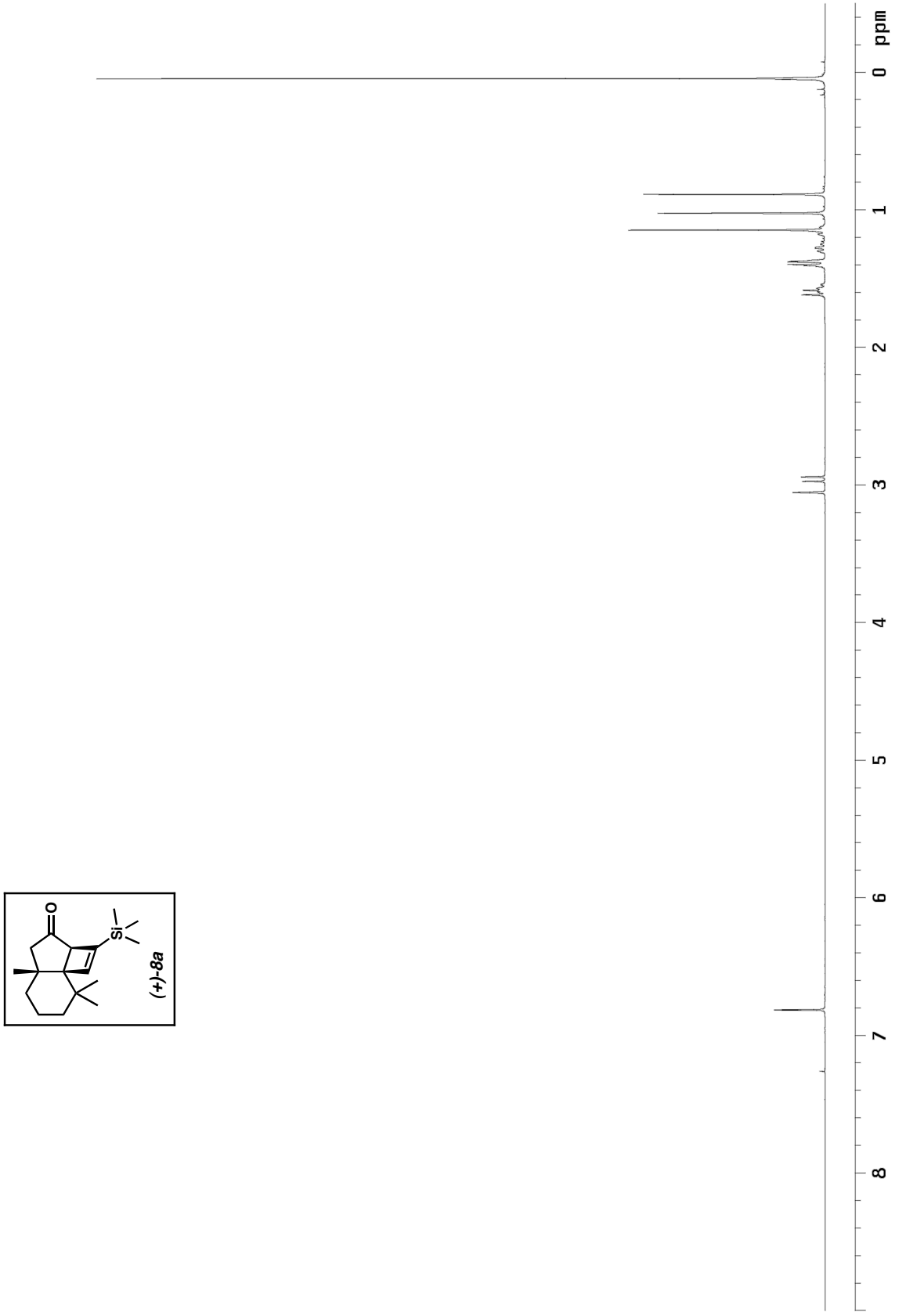
^{13}C NMR of (+)-Liphagal, $CDCl_3$[1]

Synthetic, 400 MHz Andersen	Synthetic (+), 500 MHz Stoltz
Shift (ppm)	Shift (ppm)
192.6	192.7
156.7	156.7
148.1	148.2
145.5	145.5
139.6	139.6
125.7	125.7
120.5	120.5
116.1	116.2
106.4	106.5
53.9	54.0
42.1	42.1
40.4	40.5
39.6	39.7
35.3	35.4
35.0	35.1
33.8	33.9
33.5	33.5
24.3	24.4
22.1	22.2
21.8	21.9
20.4	20.5
18.9	19.0

1. The values for Andersen's Synthetic Liphagal have been referenced to $CDCl_3$ at $\delta = 77.2$

Methods for the Determination of Enantiomeric Excess.

Entry	Substrate	Assay	Column	Method	Retention Time (min)	
1.	 (*R*)-(+)-5	*Enantiomeric Excess*	Chiral HPLC	3%EtOH/Hex monitor@254nm	Major (*R*)	9.1
			Chiralcel AD Column	20 min	Minor (*S*)	10.2
2.	 (*R*)-(+)-15	*Enantiomeric Excess*	Chiral SFC	30%IPA/scCO$_2$ monitor@235/244nm	Major (*R*)	4.6
			Chiralcel AD-H Column	10 min	Minor (*S*)	7.3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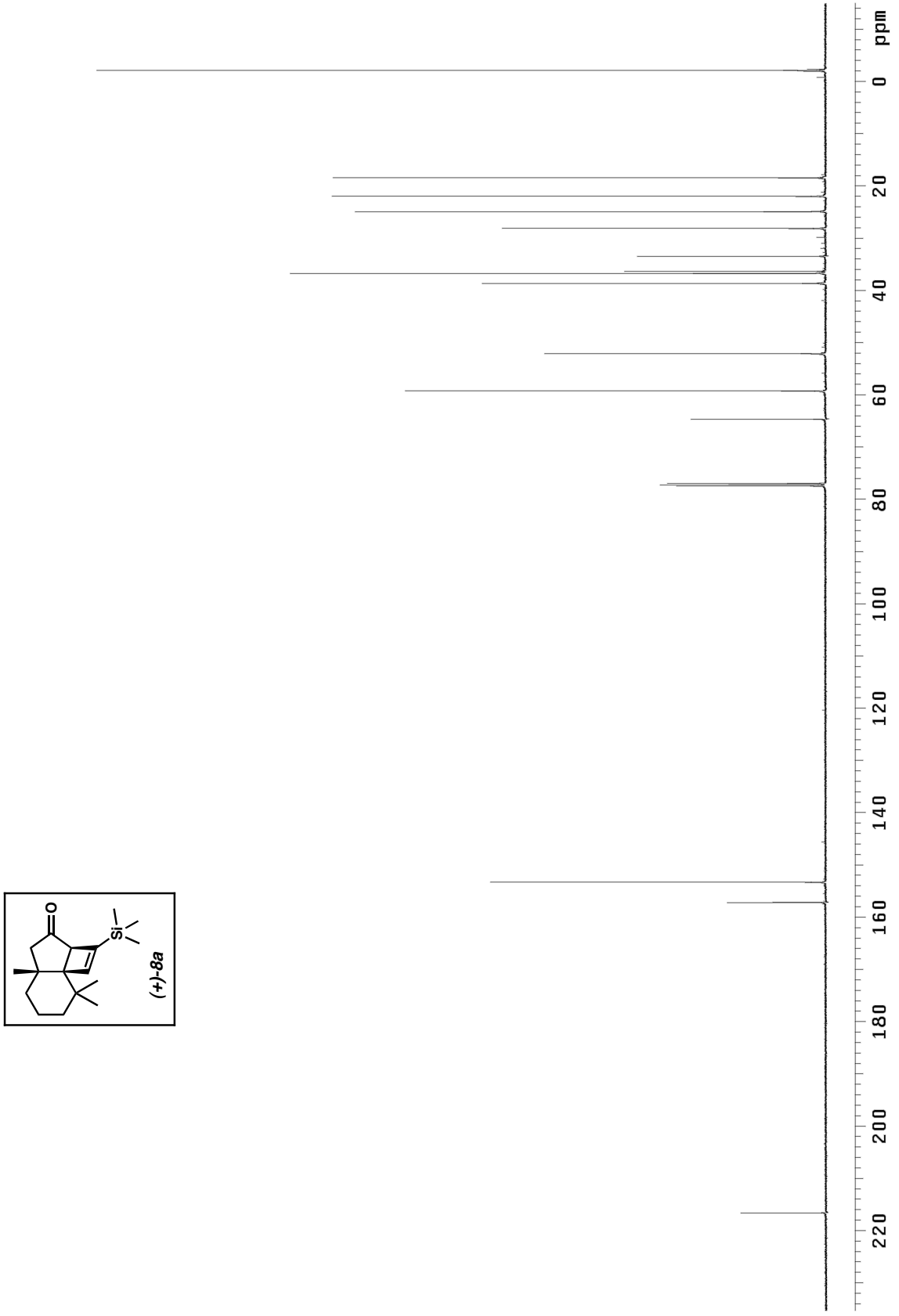
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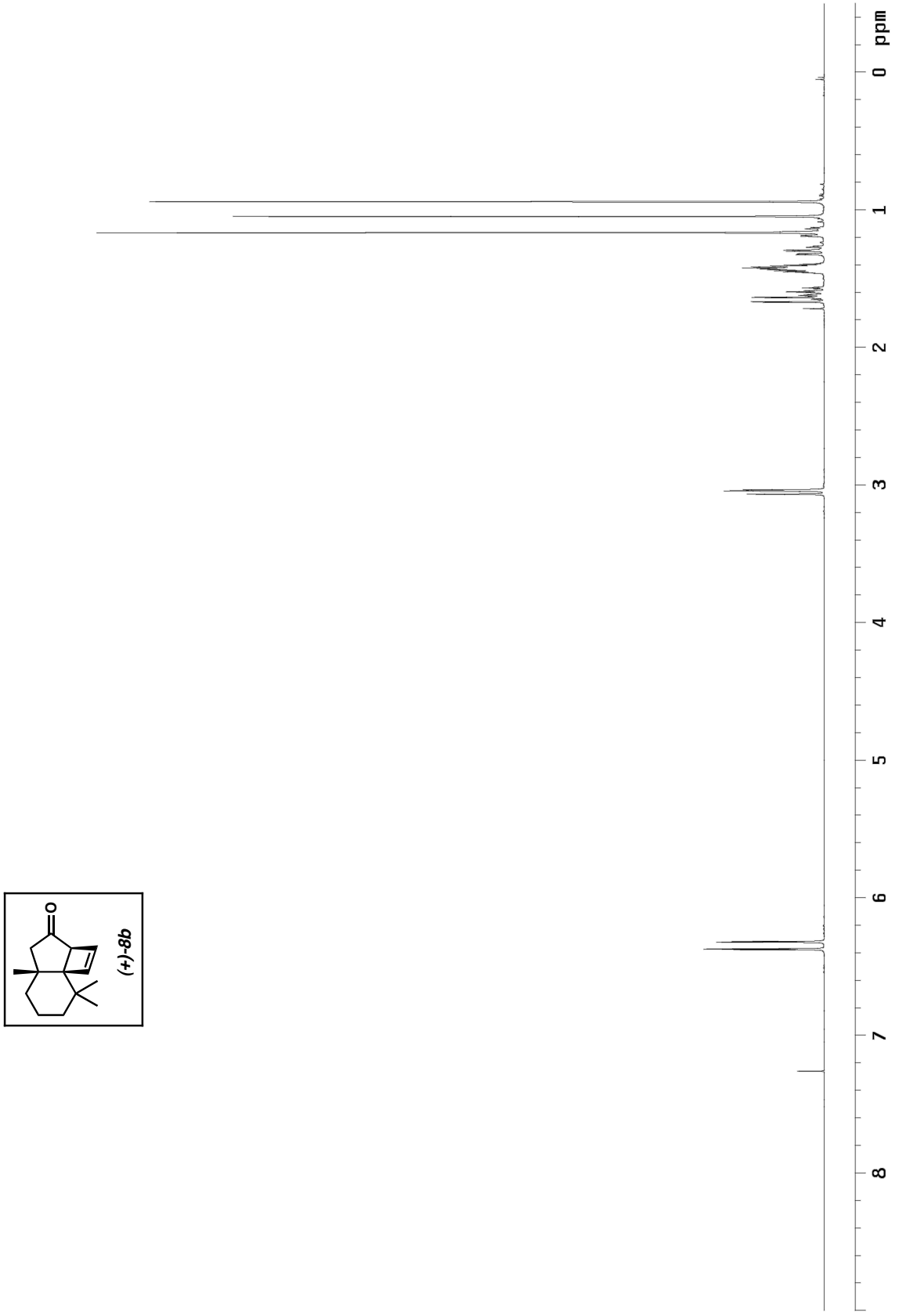
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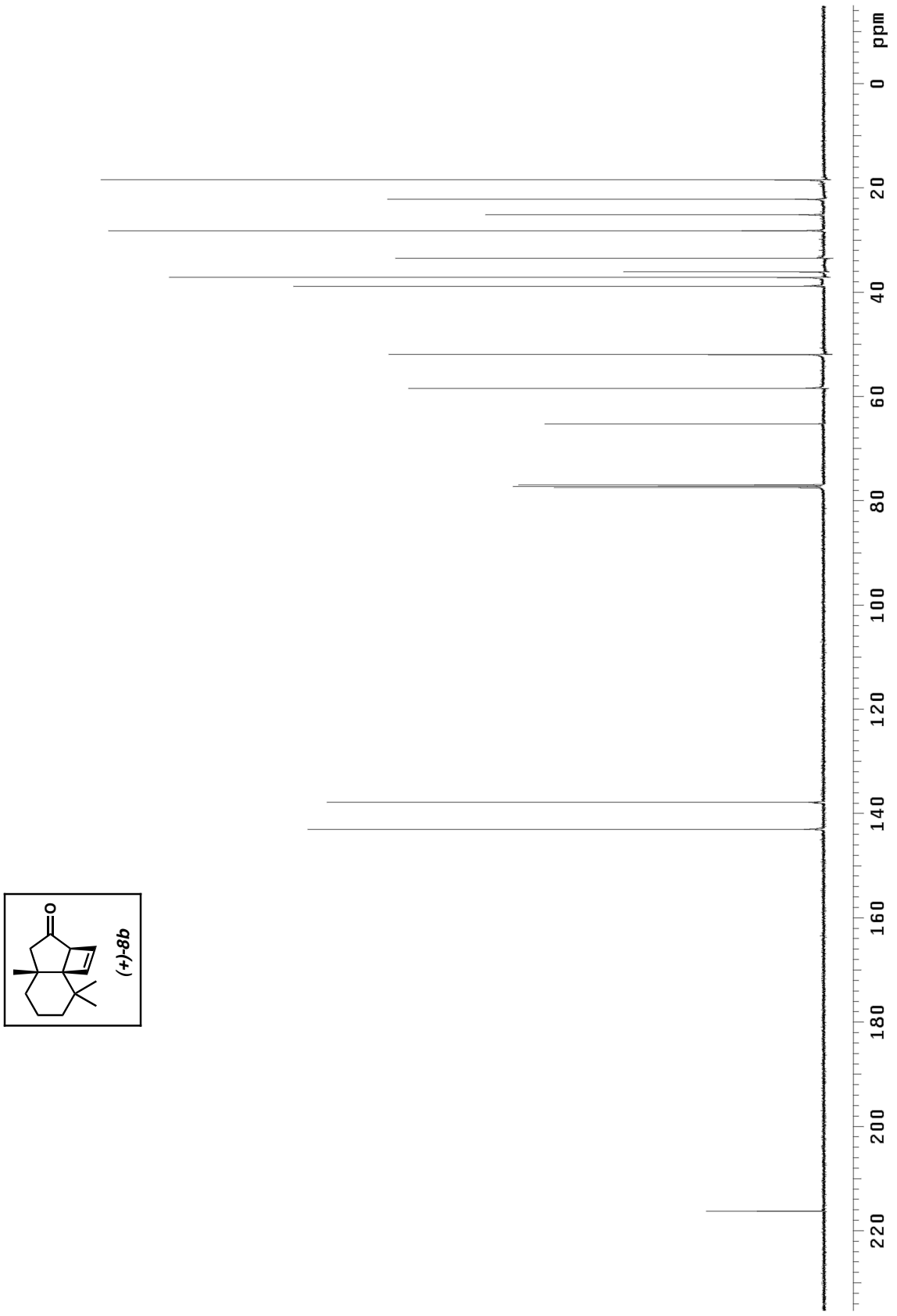
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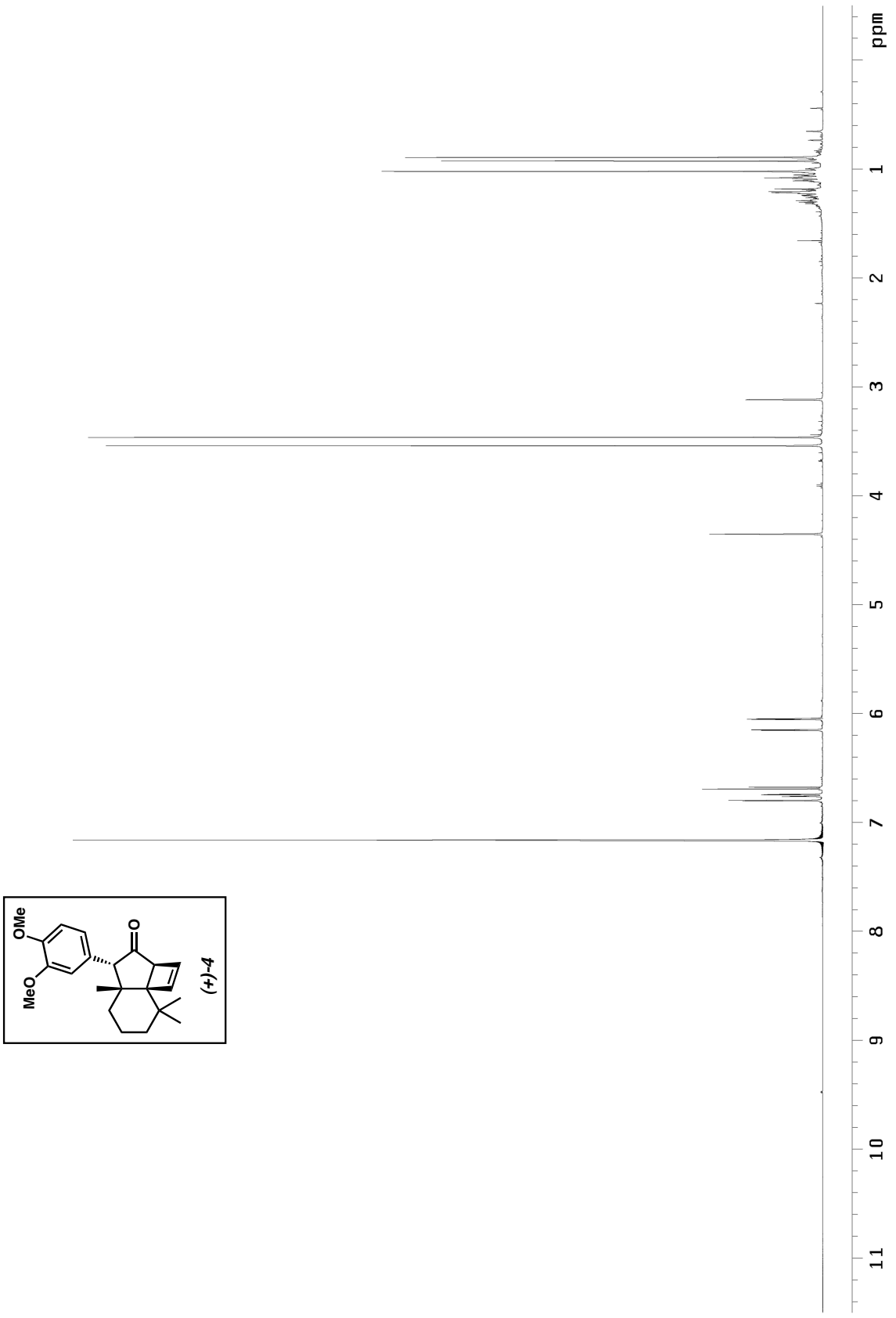
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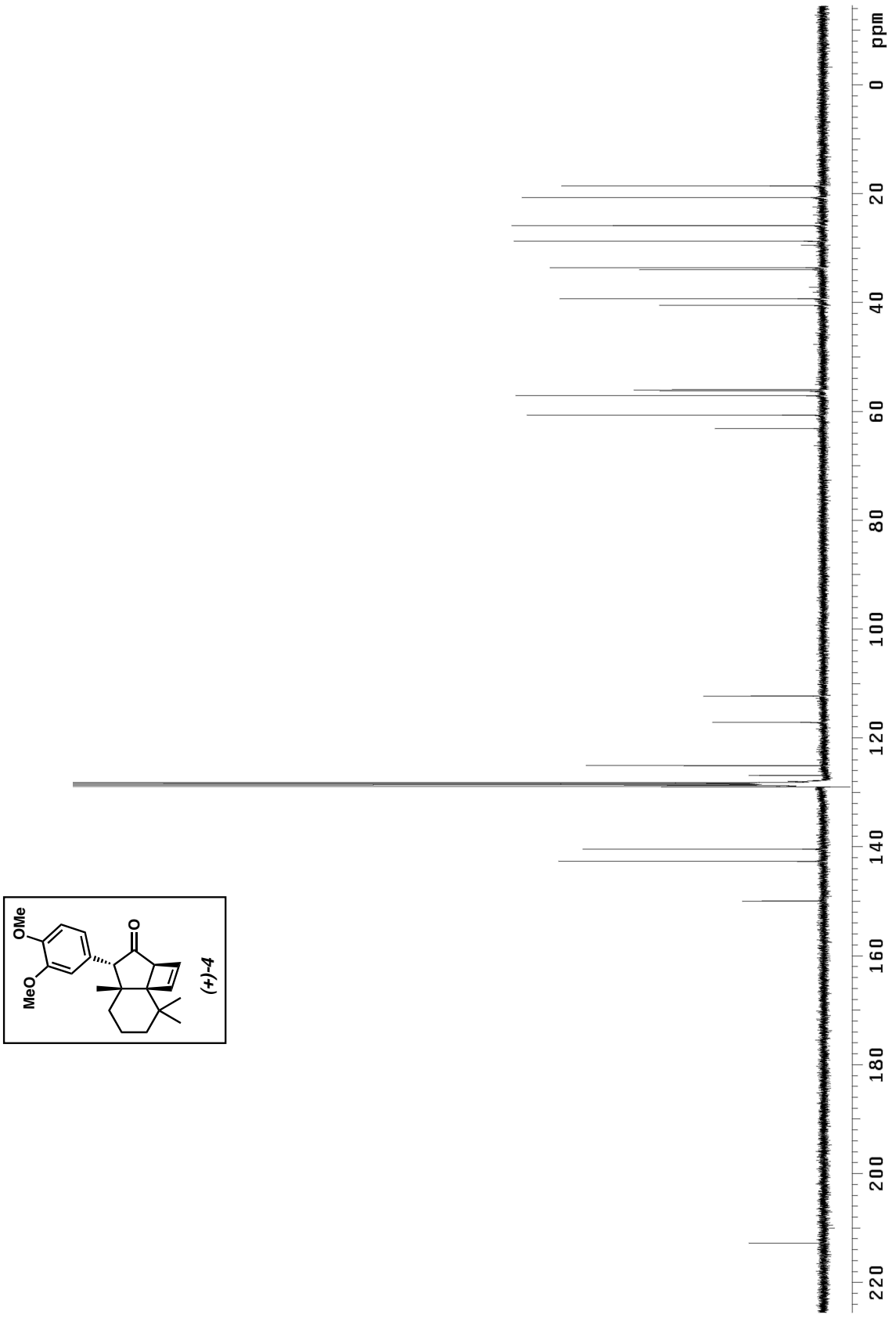
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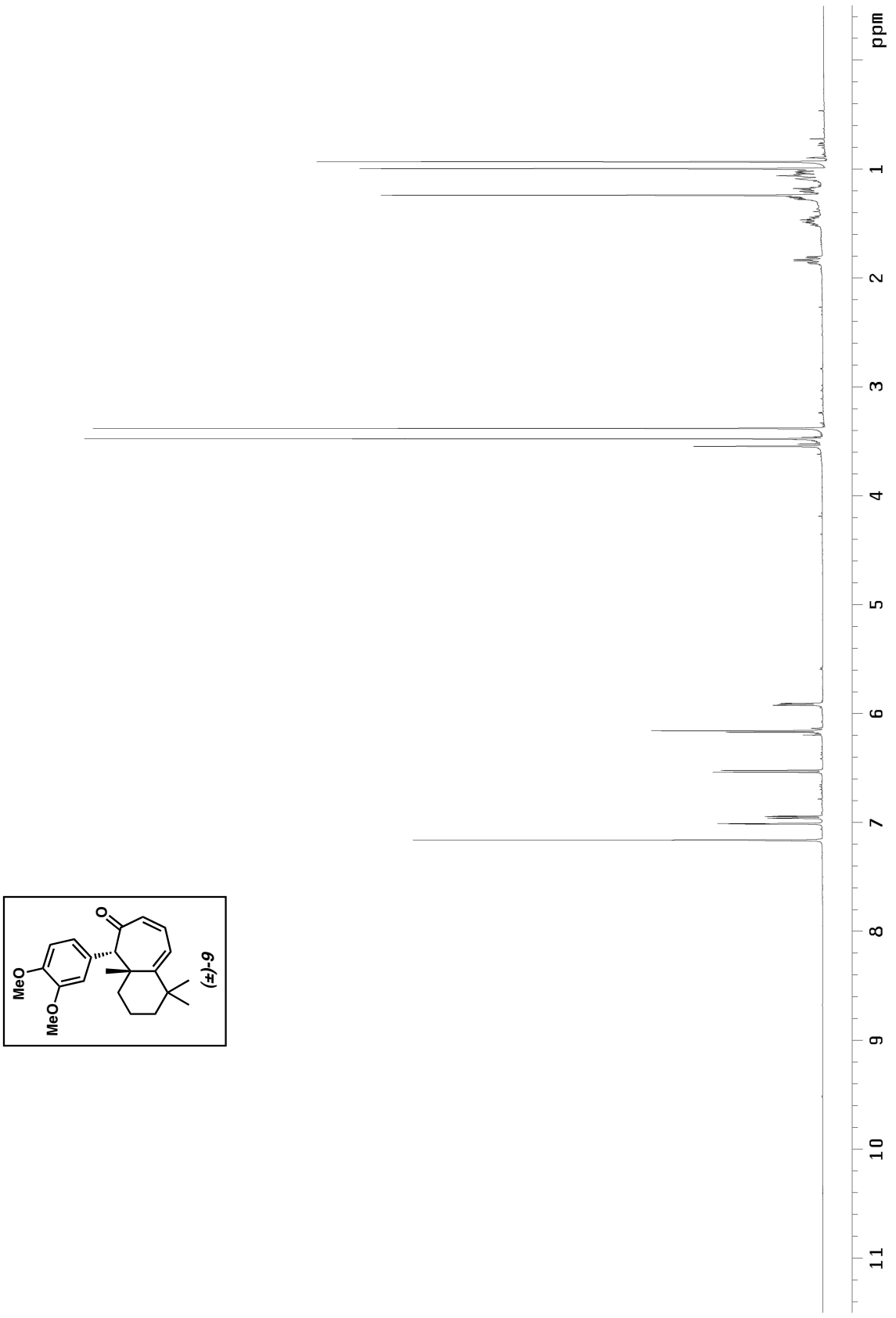
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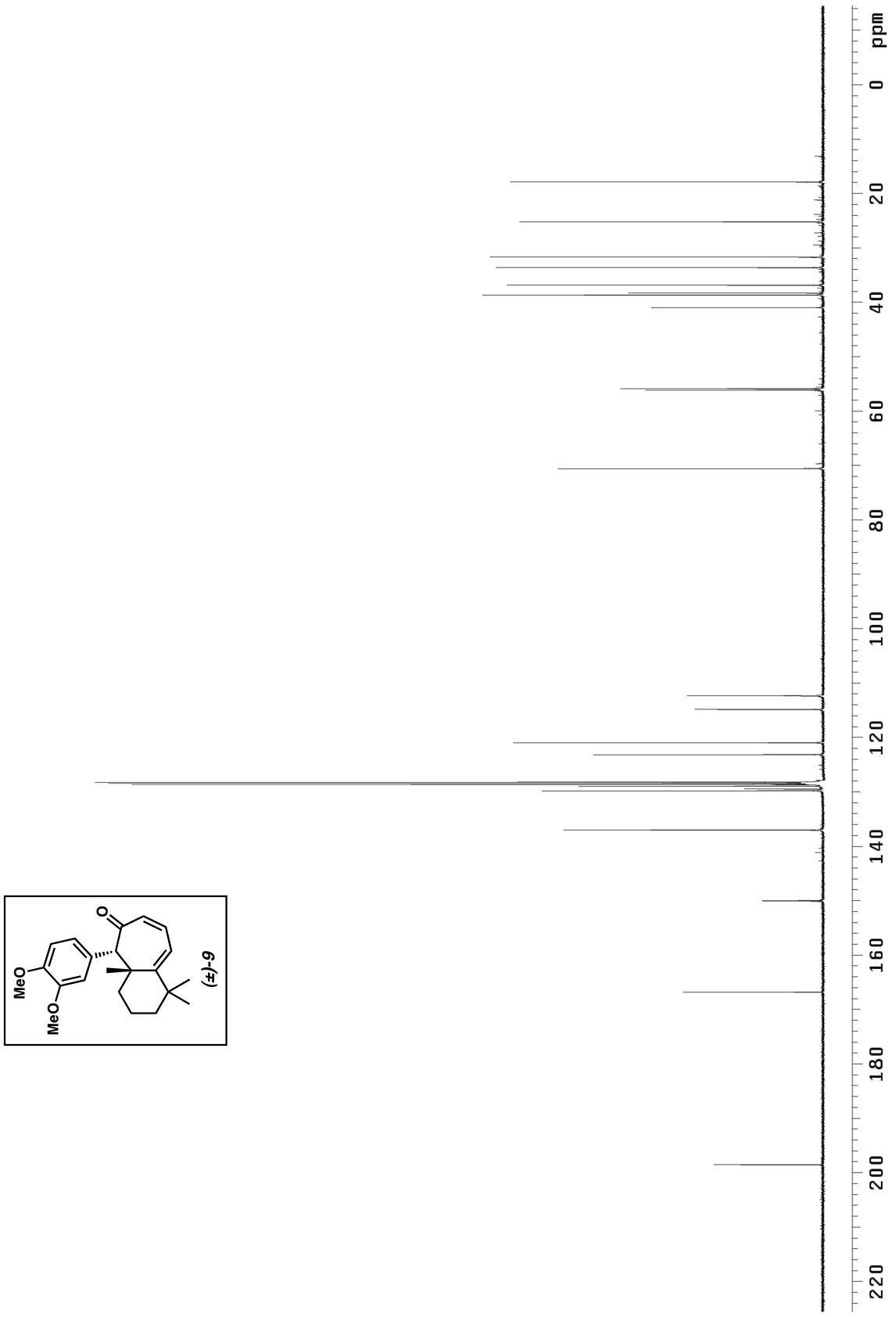
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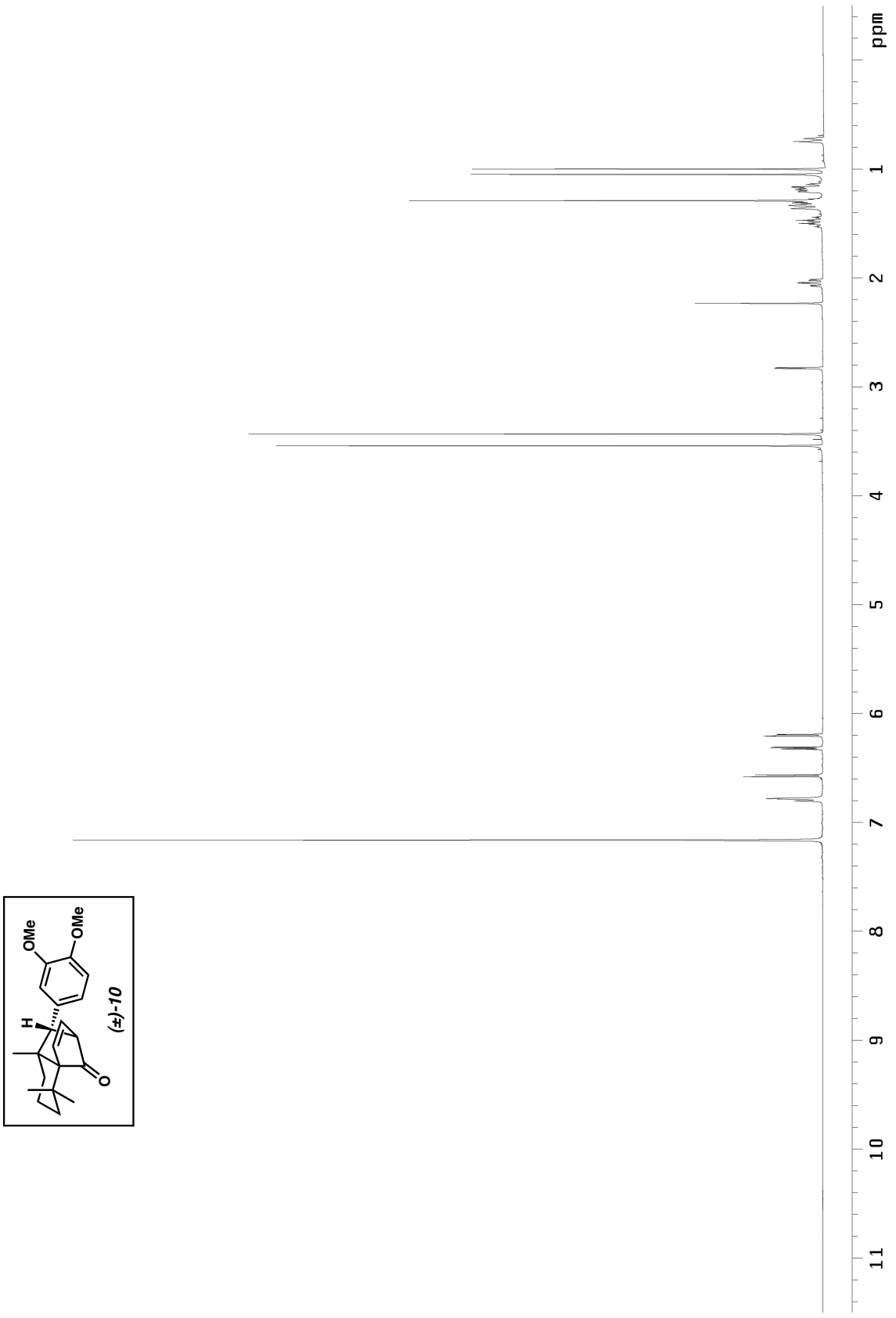
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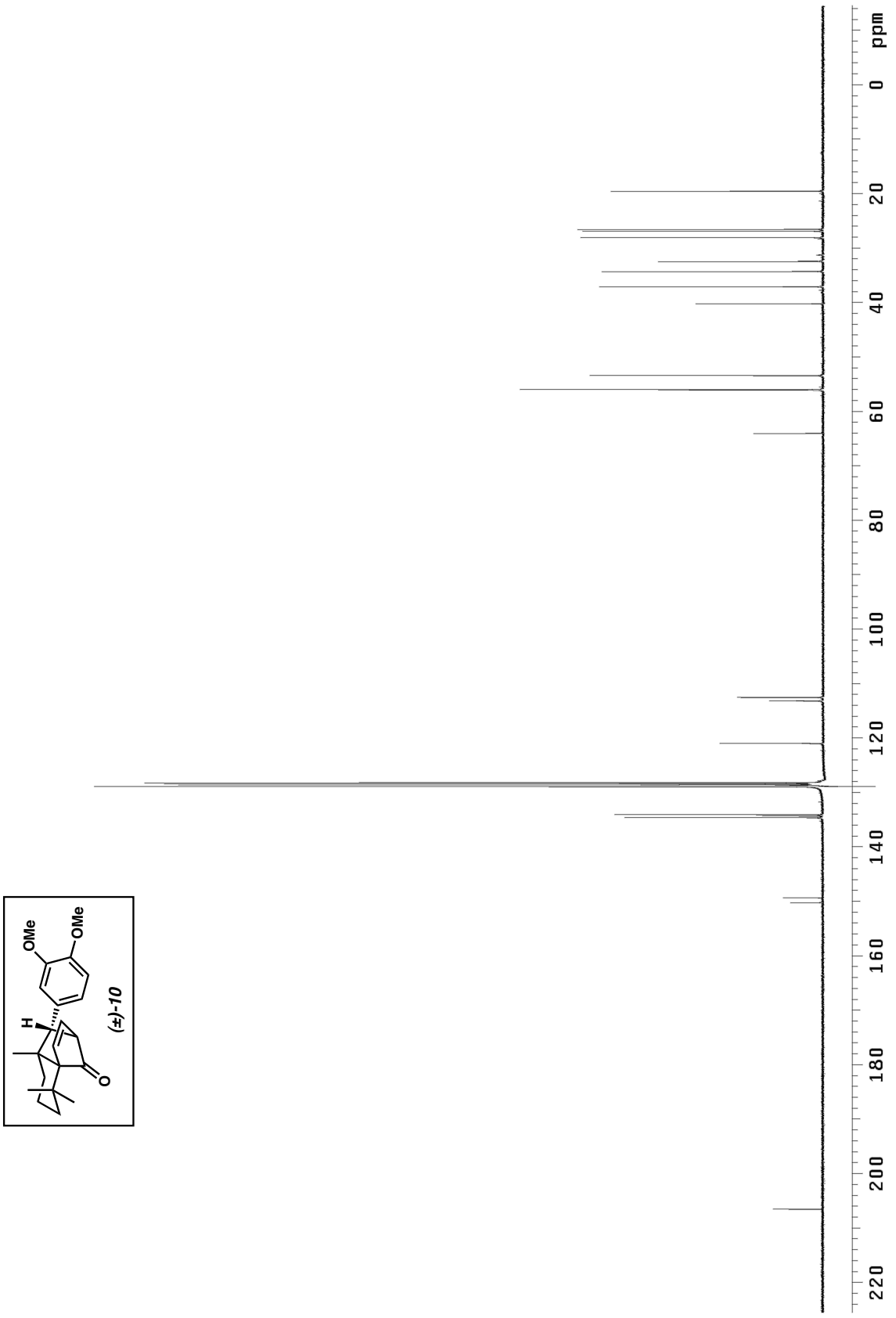
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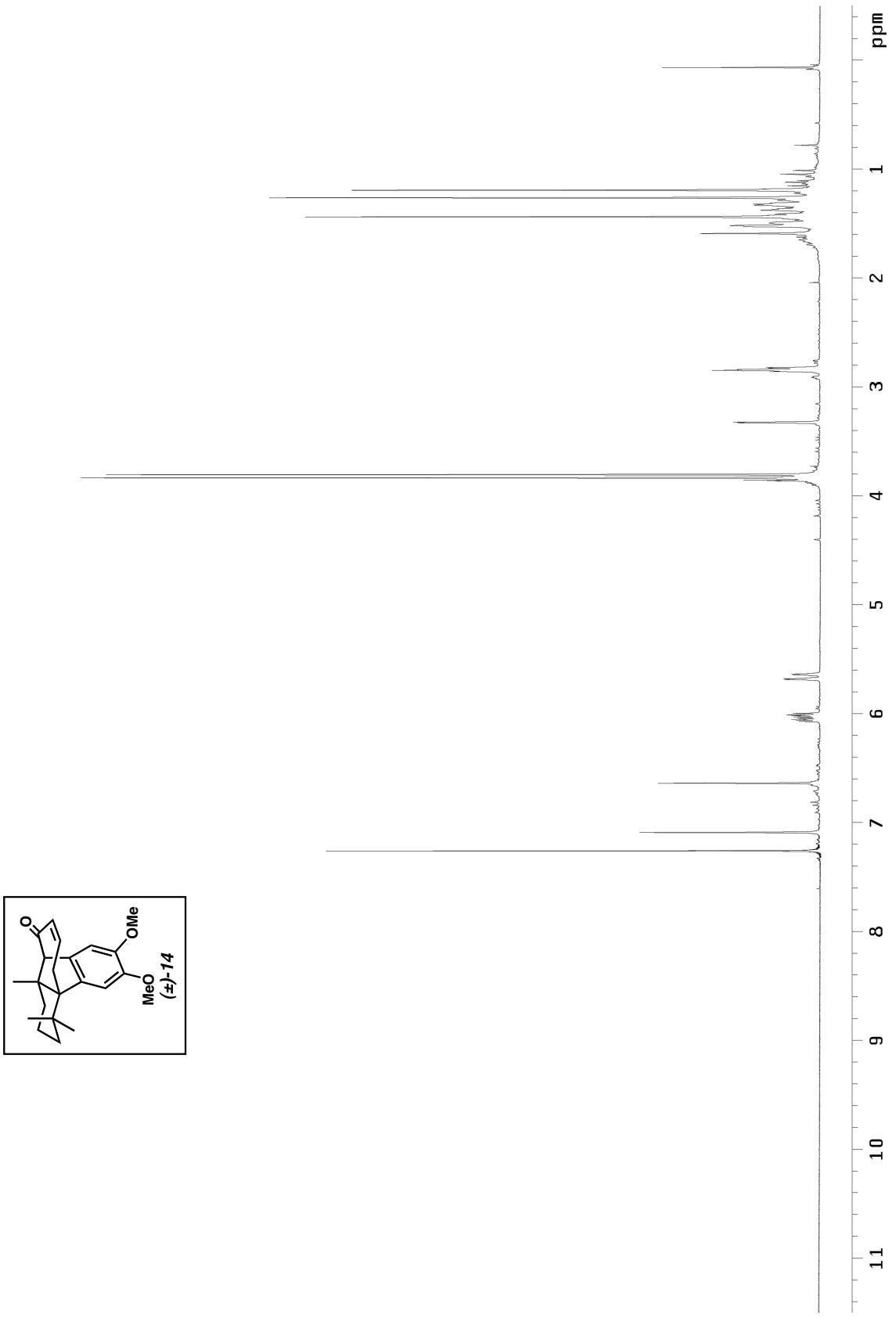
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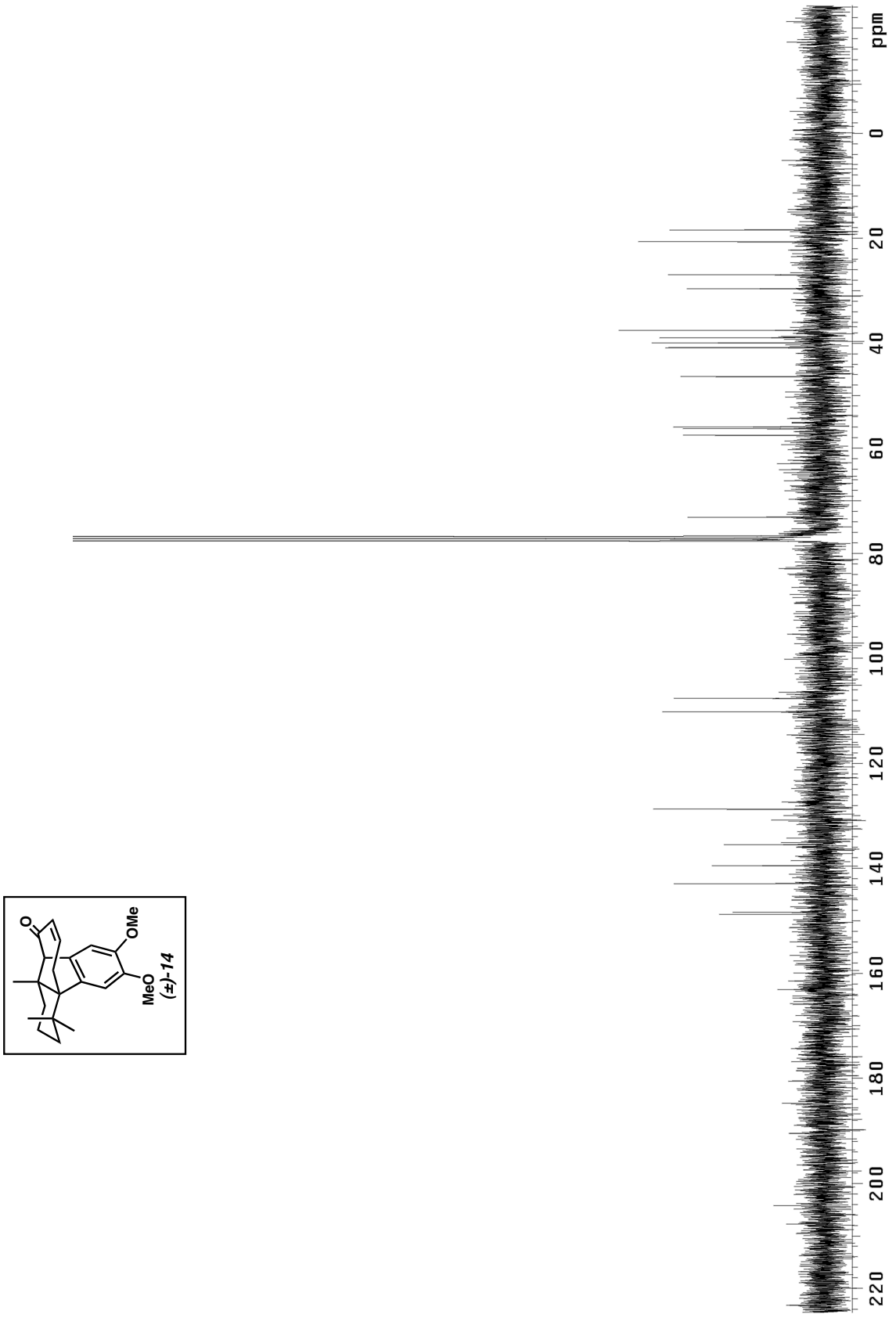
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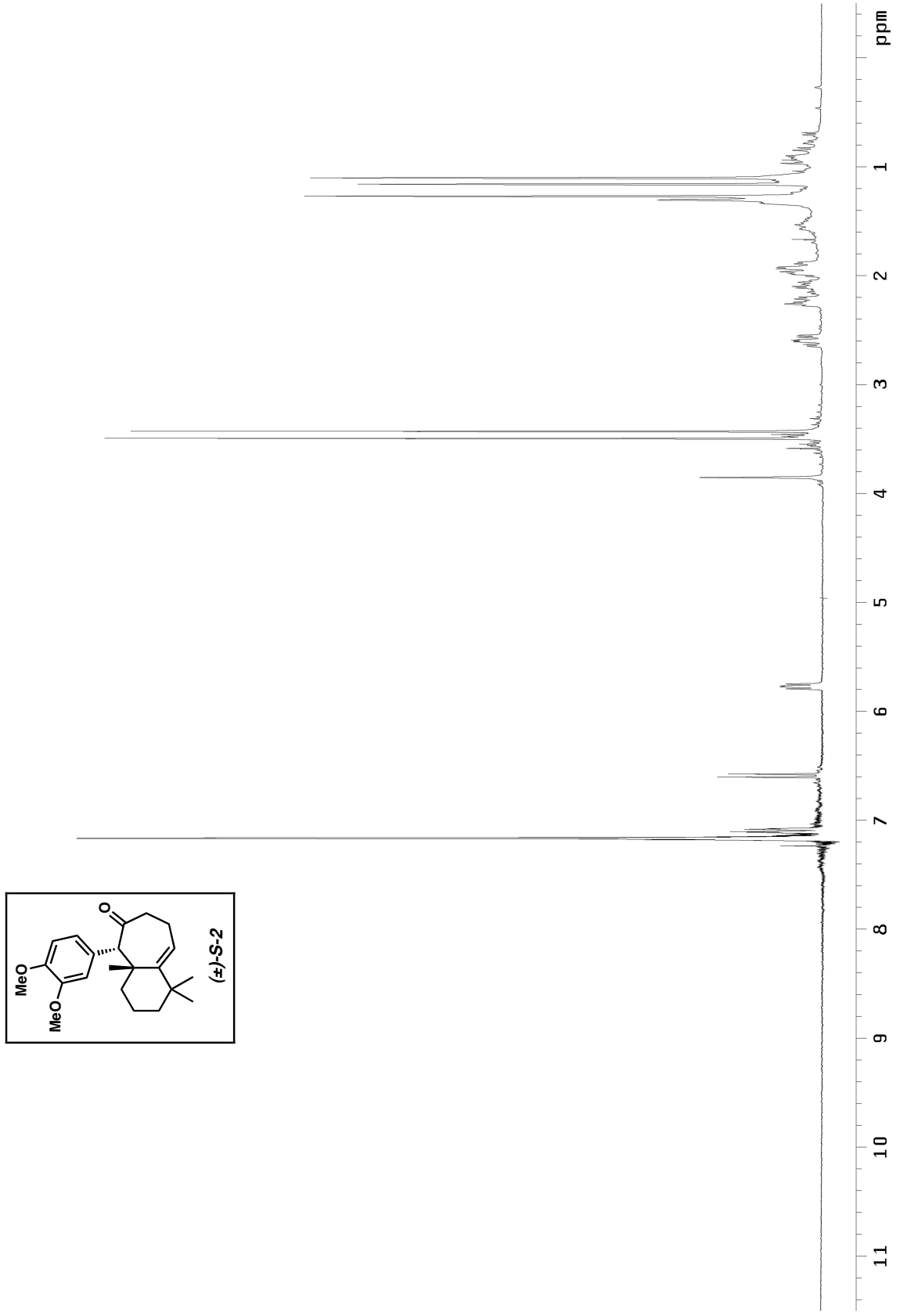
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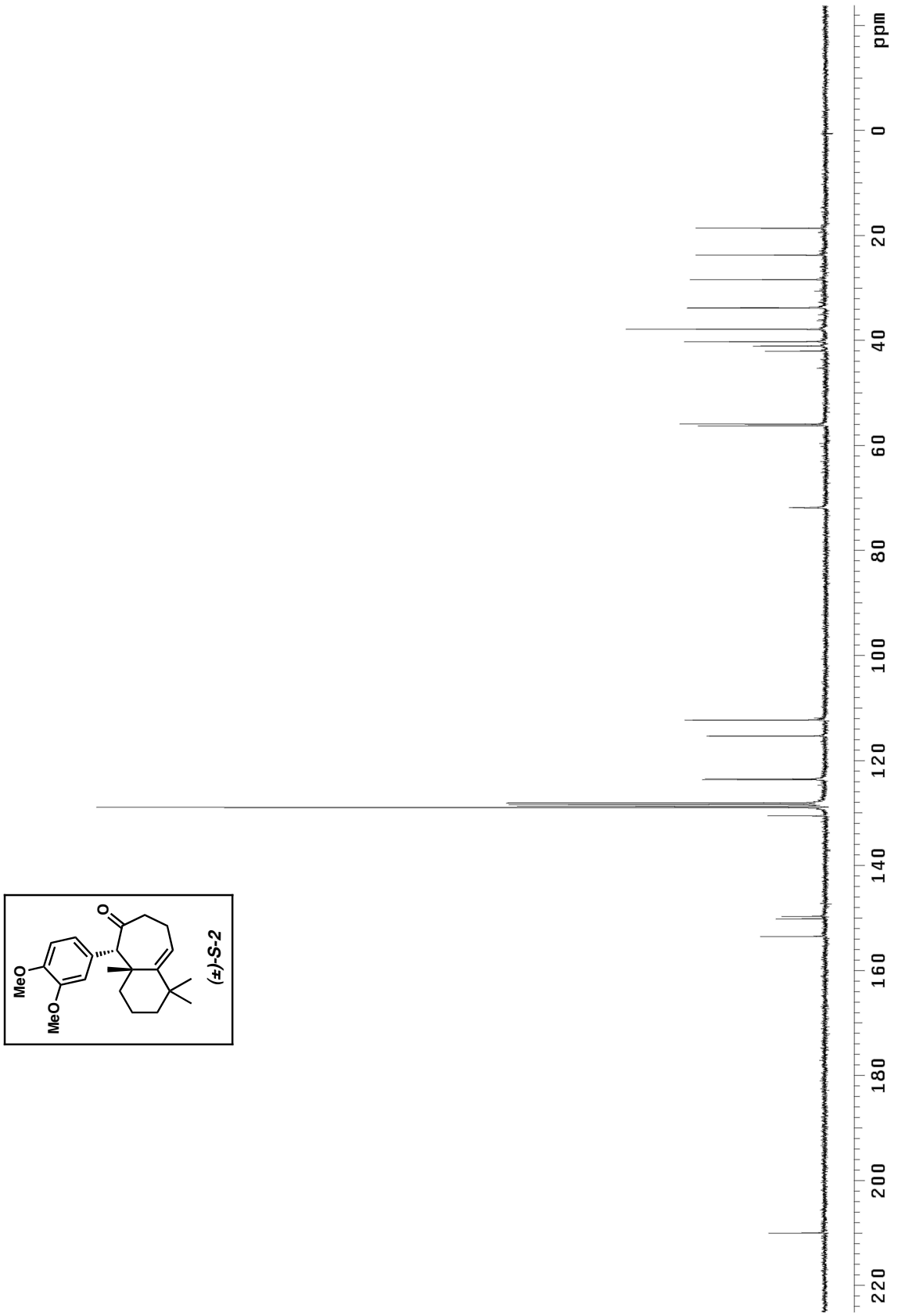
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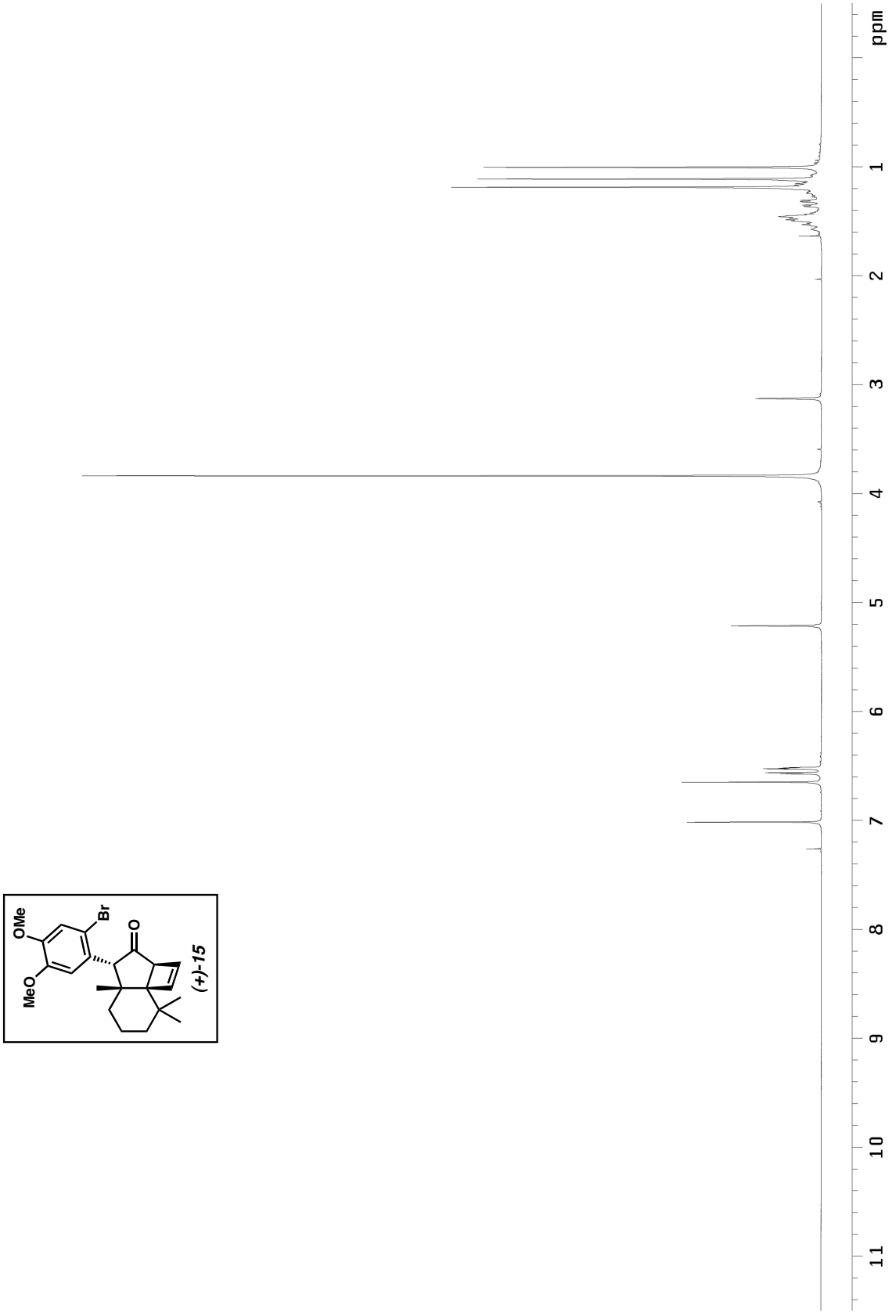
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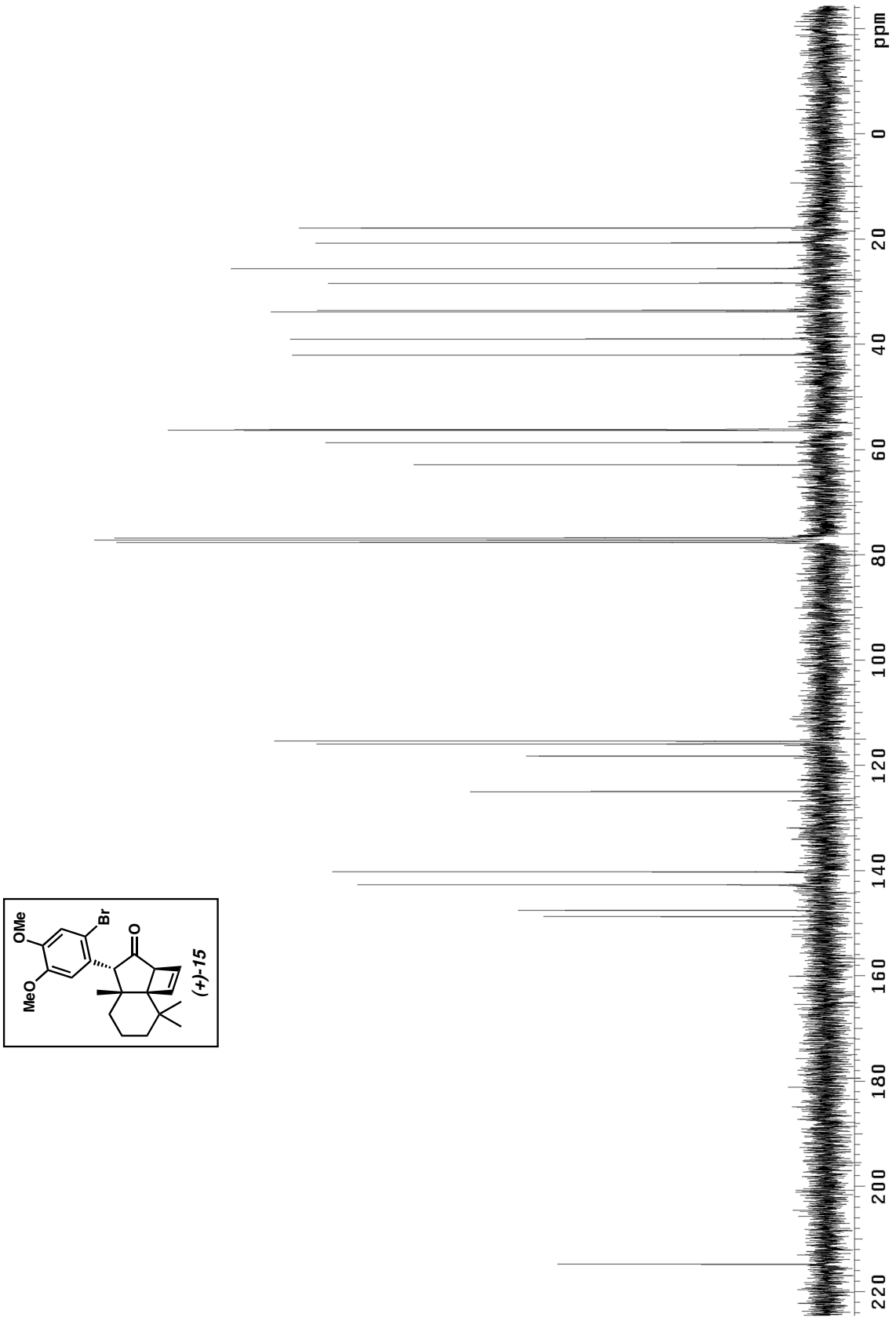
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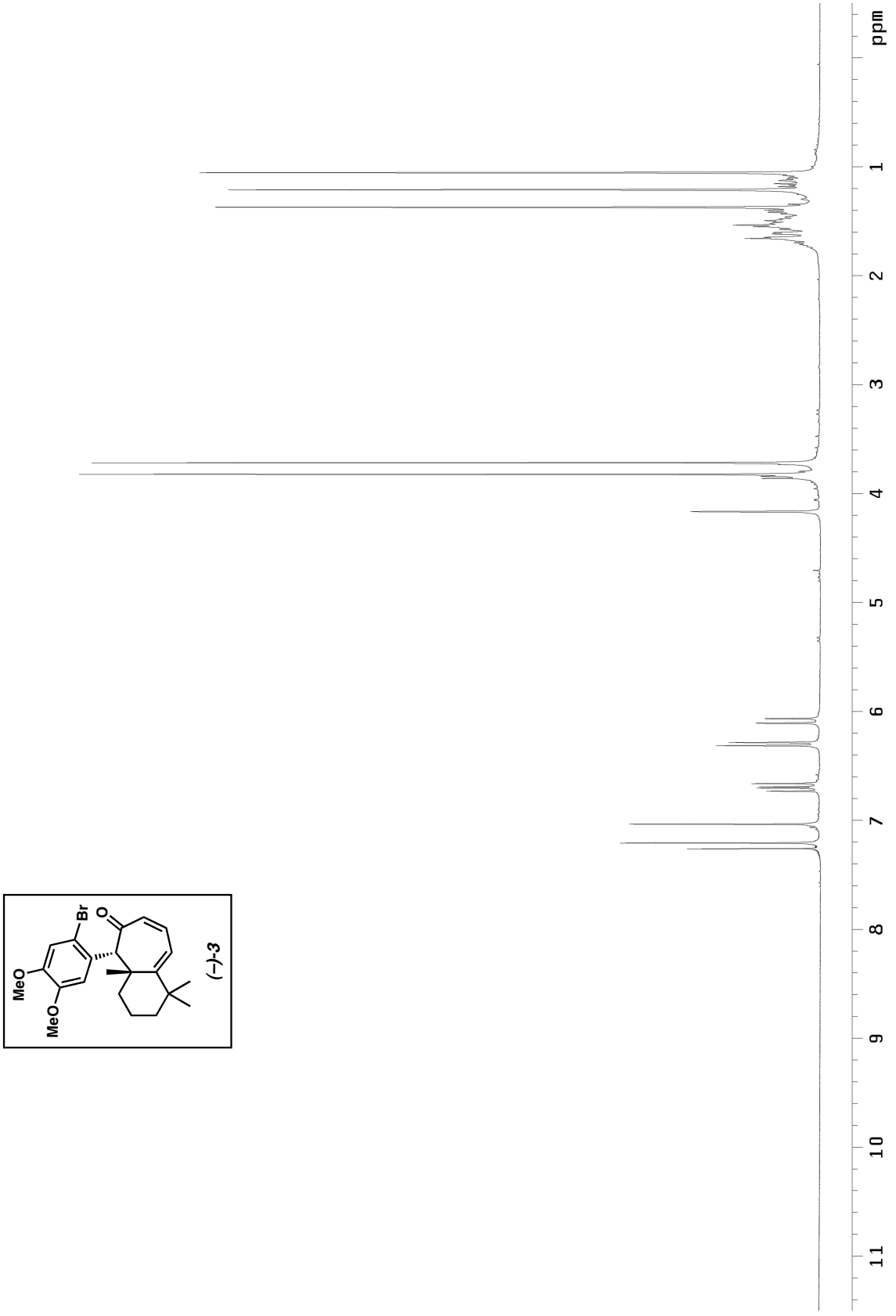
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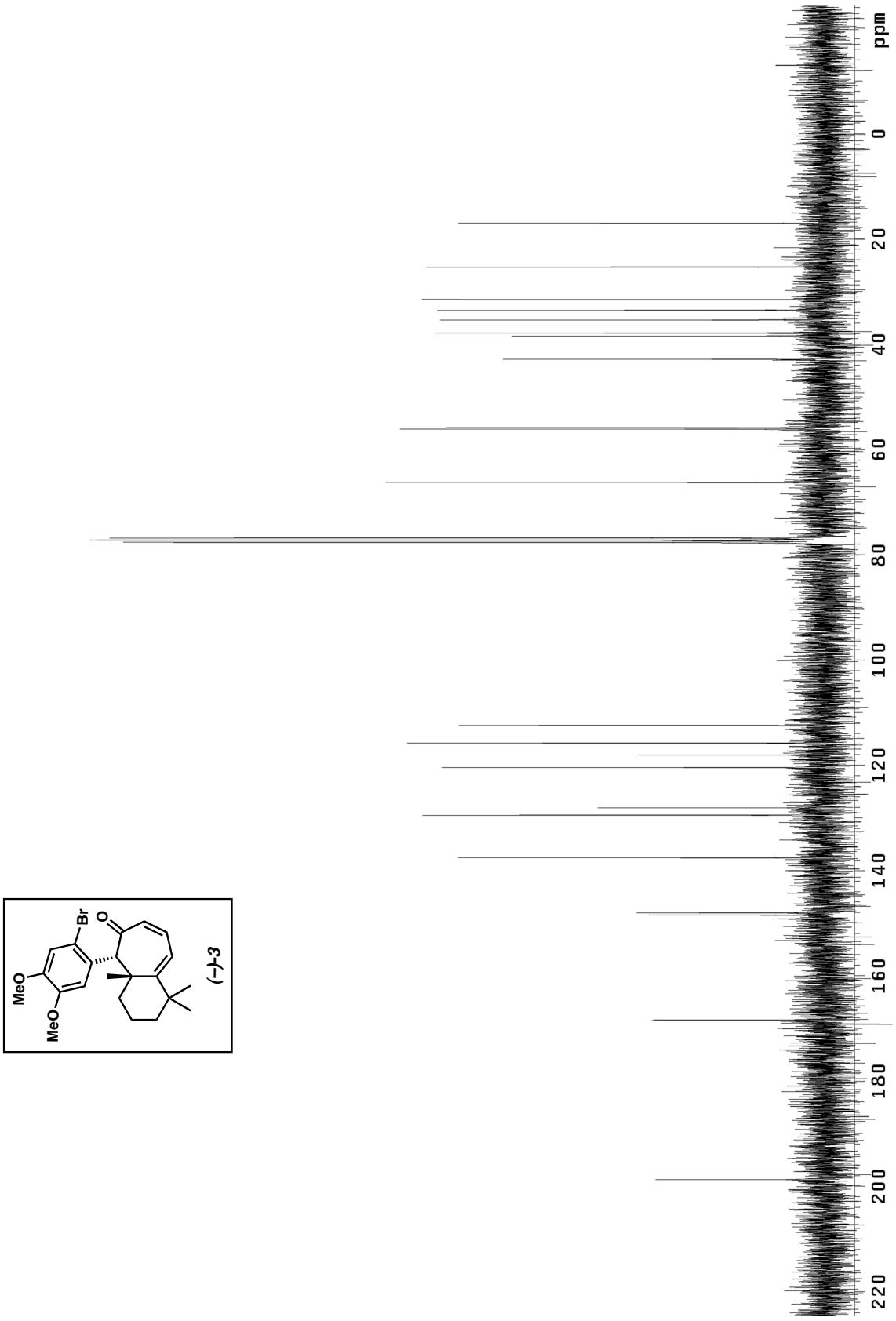
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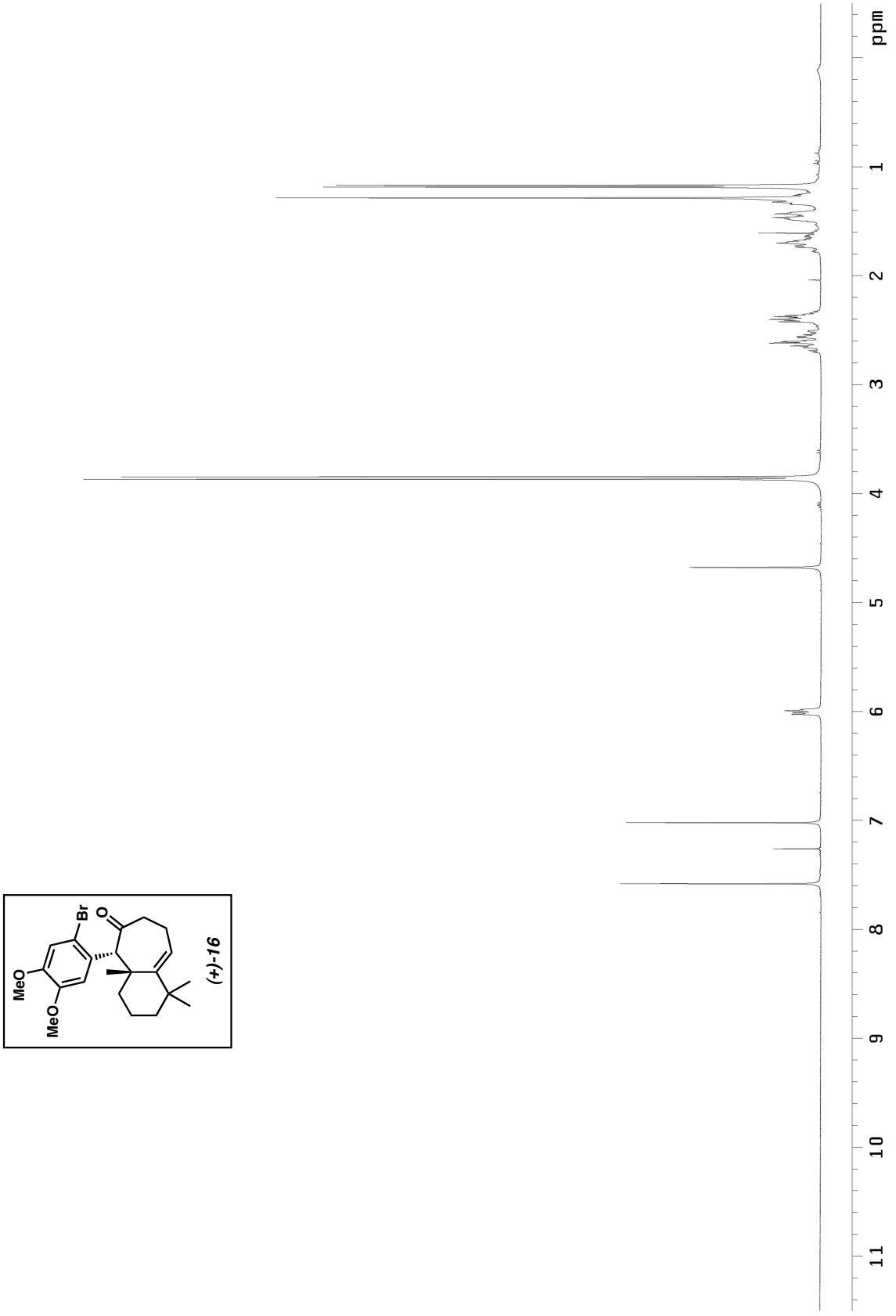
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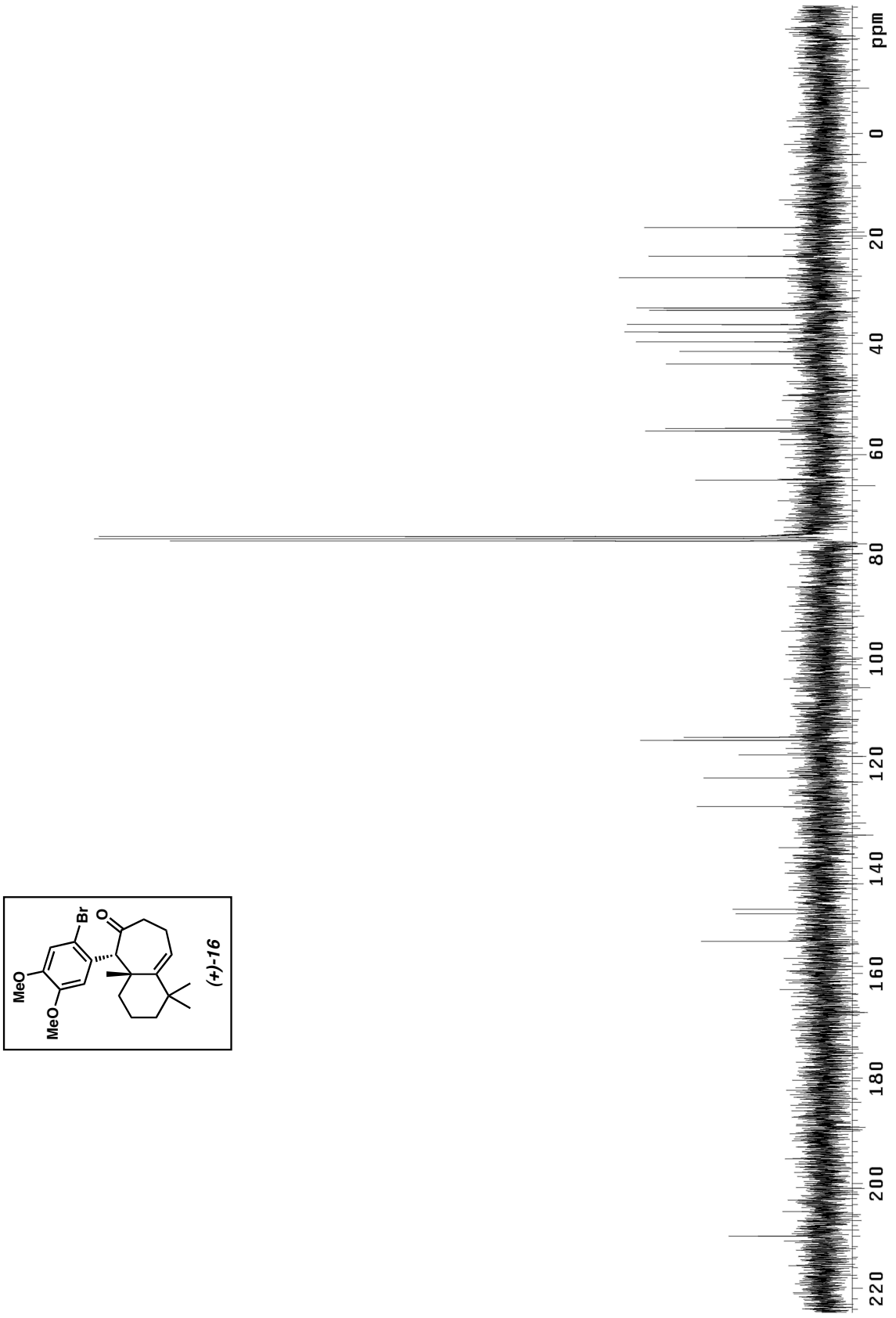
(+)-16


Br
O
MeO
MeO
(+)-16
ppm
0
20
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60
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100
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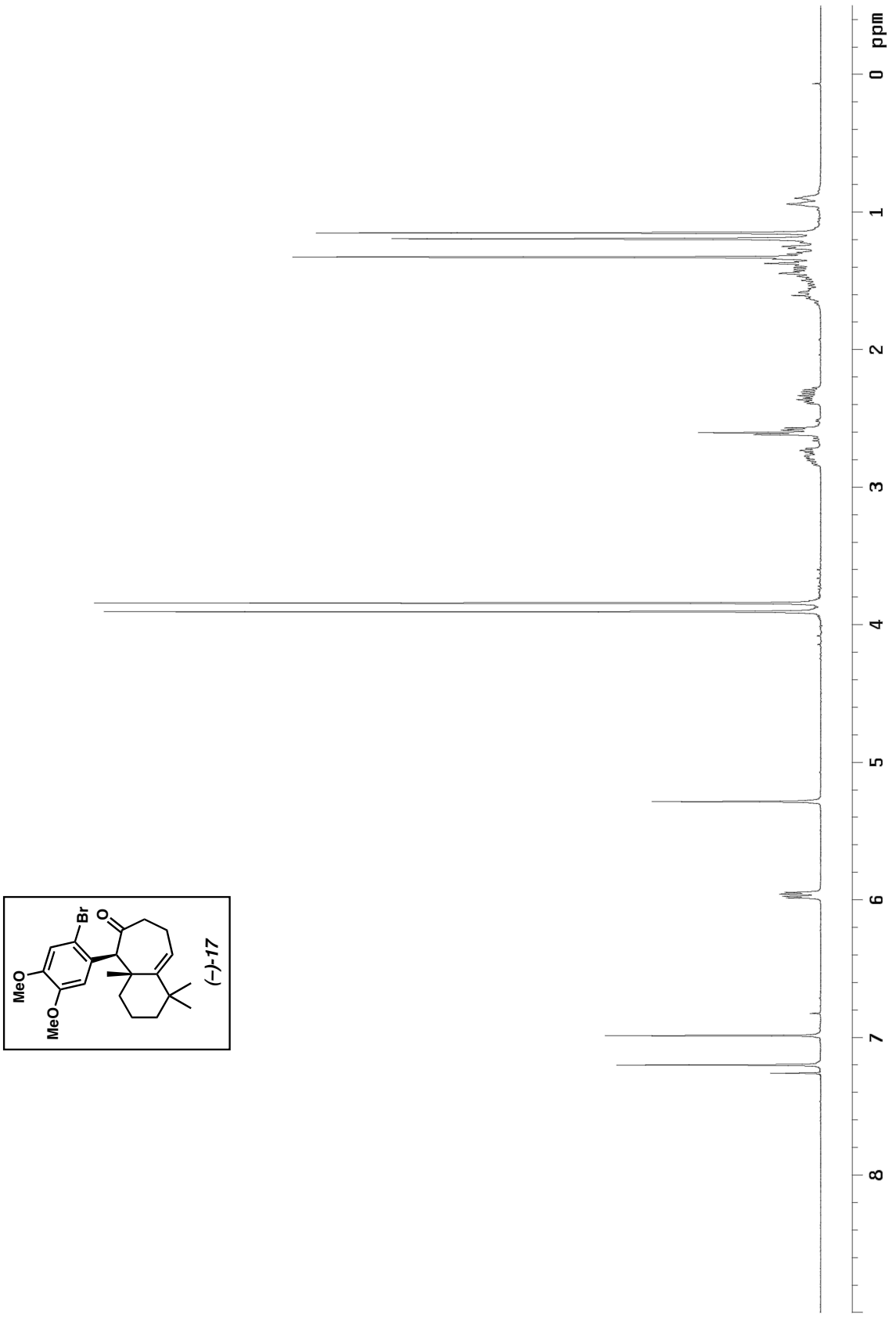
180
200
220


Br
O
MeO
MeO
(–)-17
ppm
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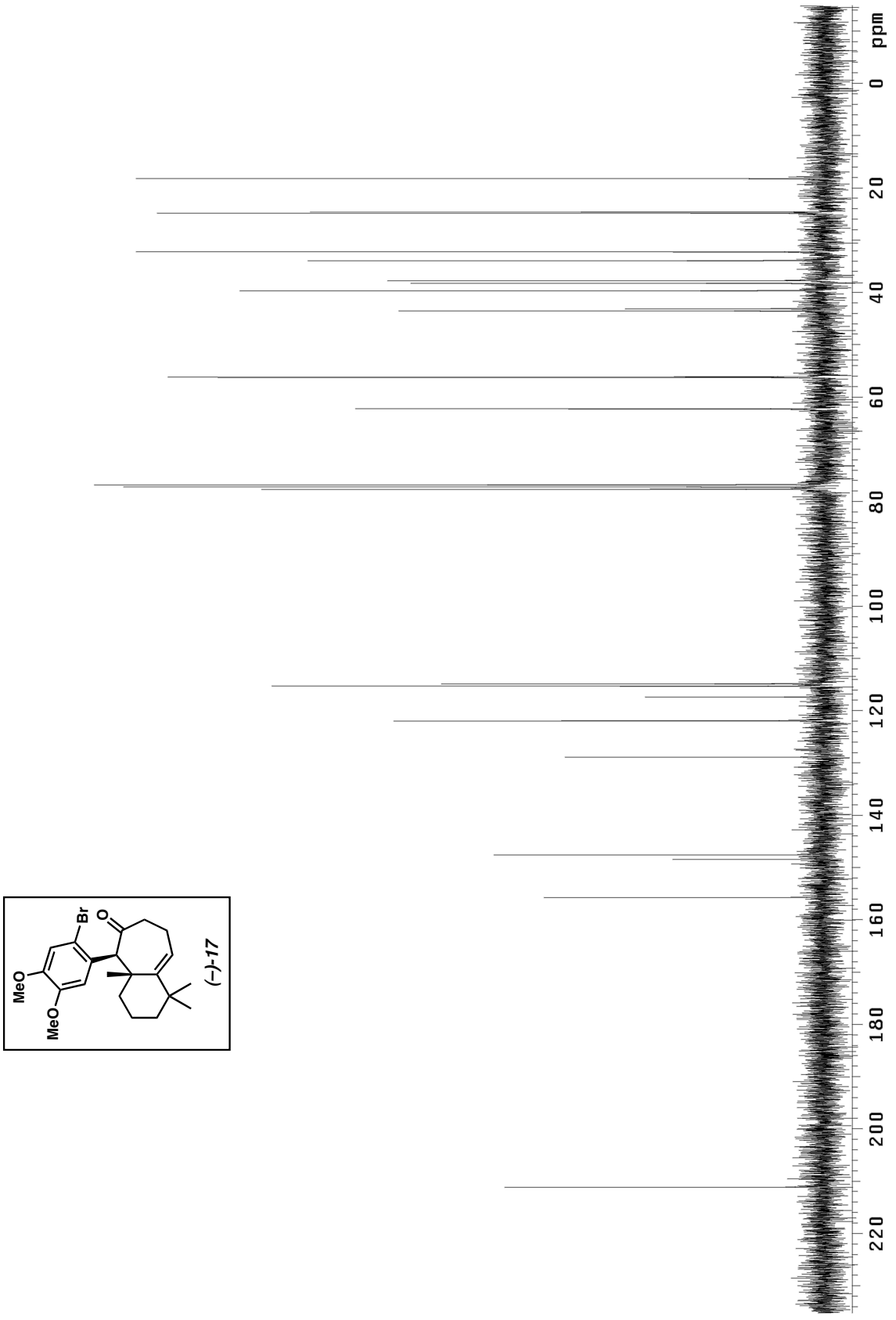
6
7
8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O
MeO
MeO
(–)-17
ppm
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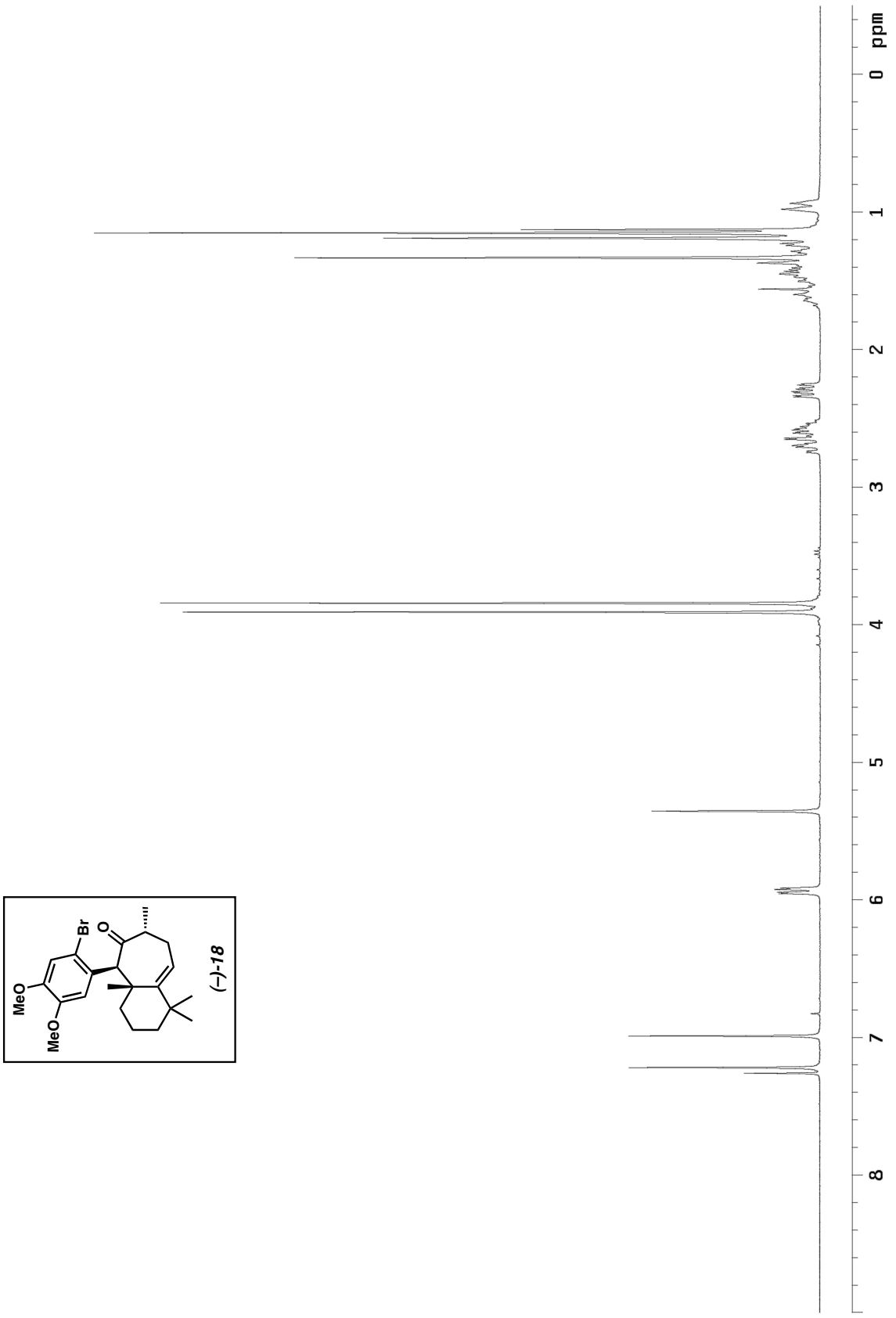
Br
O
MeO
MeO
(–)-18
ppm
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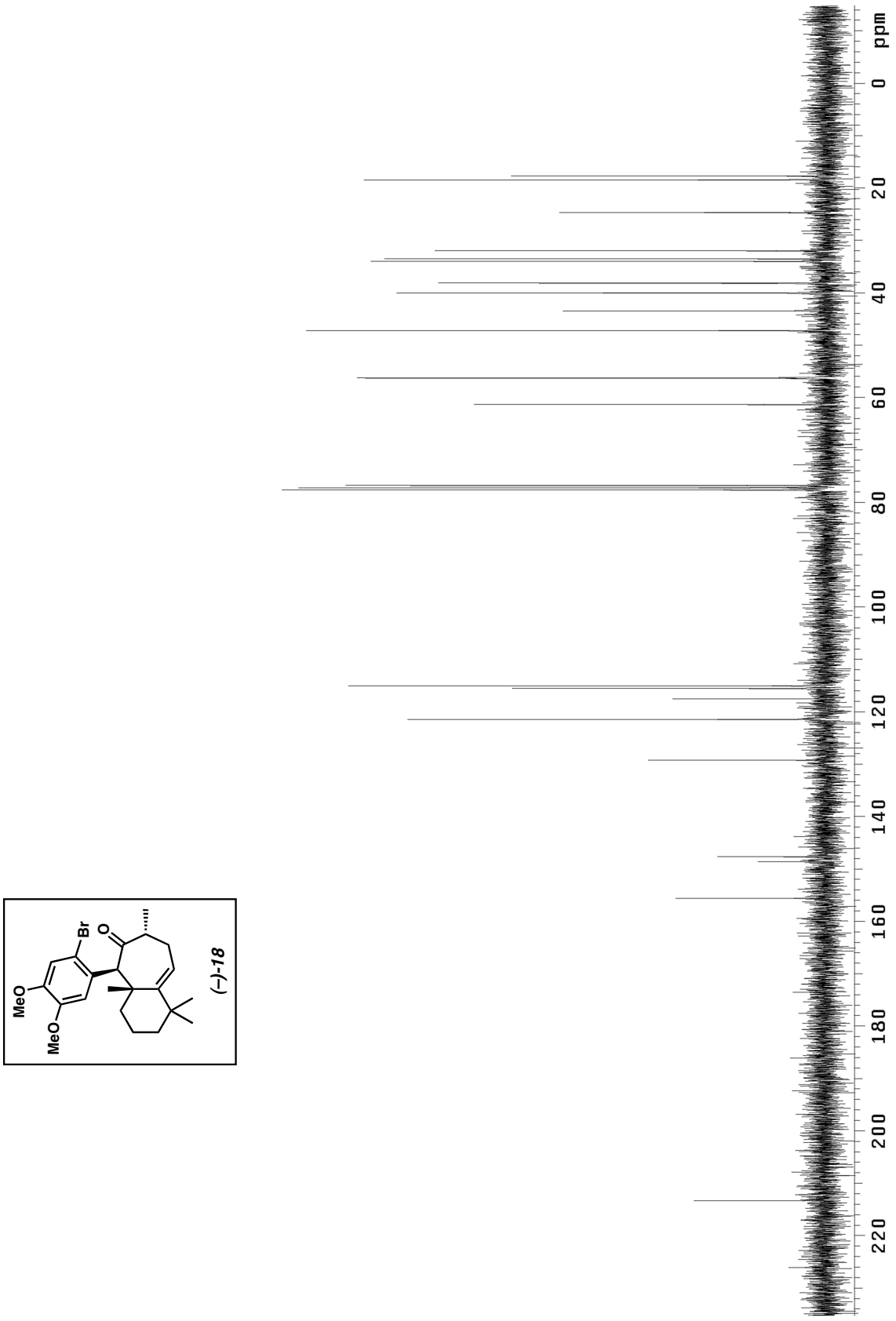
2
3
4
5
6
7
8


Br
O
MeO
MeO
(–)-18
ppm
0
20
40
60
80
100
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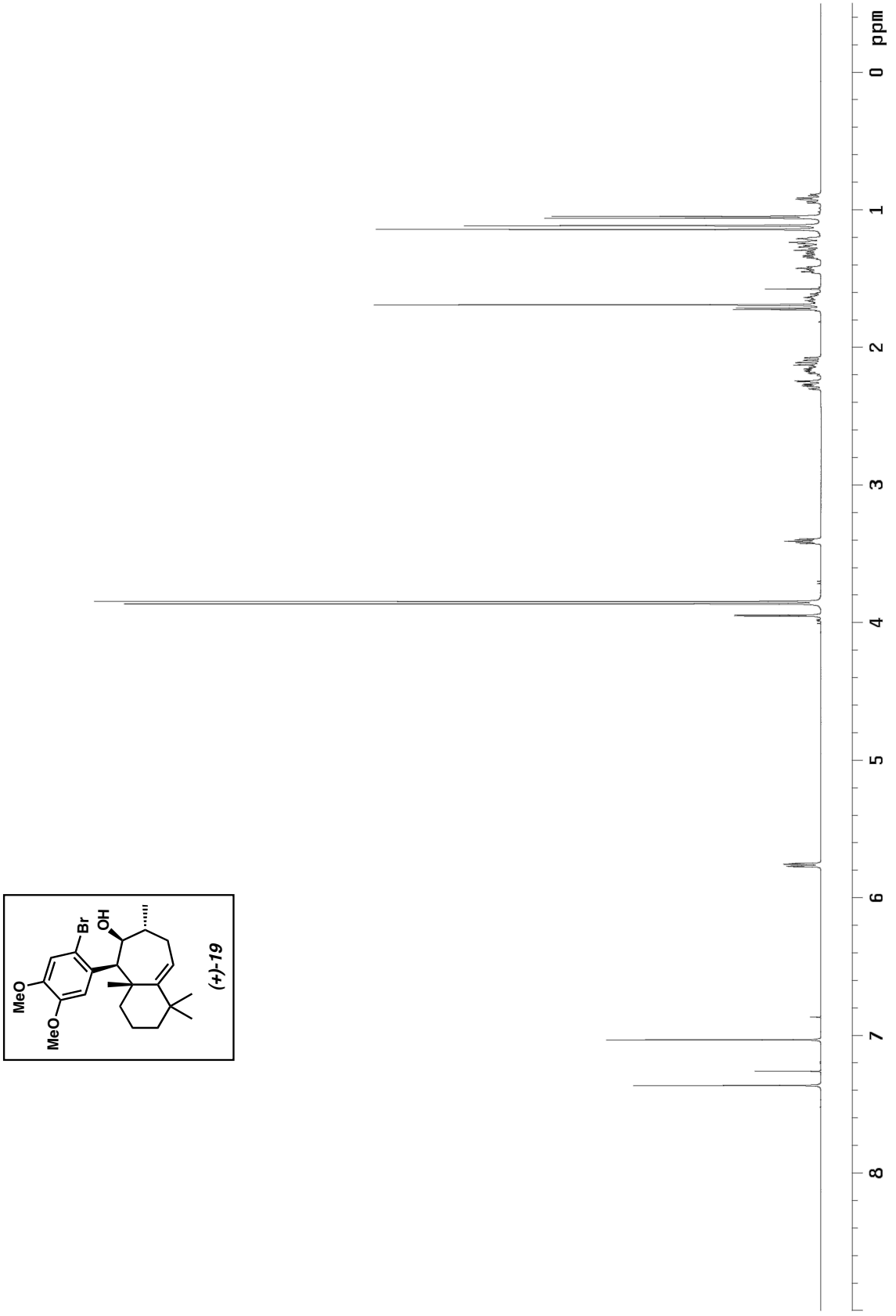
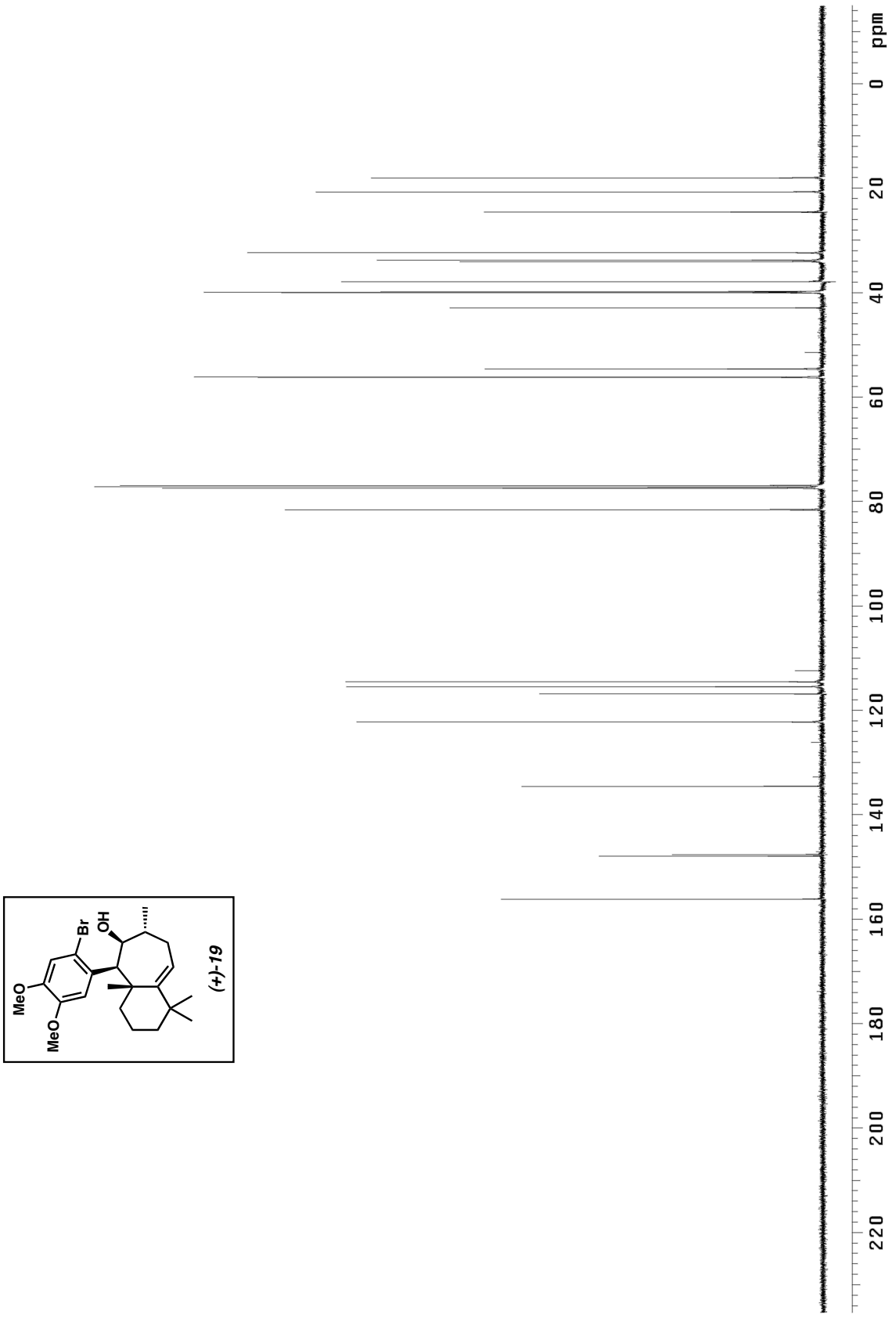
160
180
200
220


Br
OH
MeO
MeO
(+)-19
ppm
0
1
2
3
4
5
6
7
8


ppm
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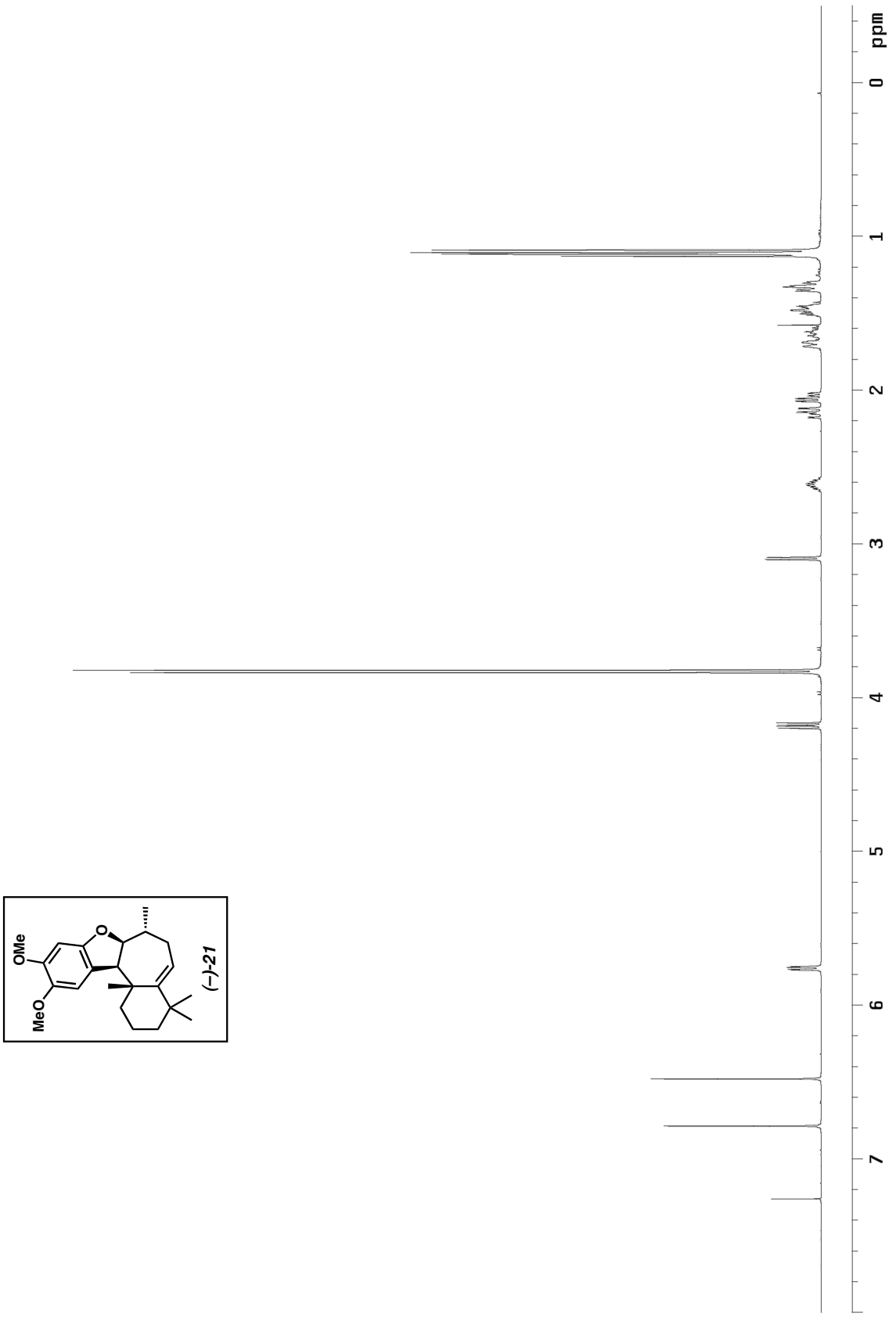
60
80
100
120
140
160
180
200
220
Br
OH
MeO
MeO
(+)-19


OMe
MeO
(–)-21
ppm
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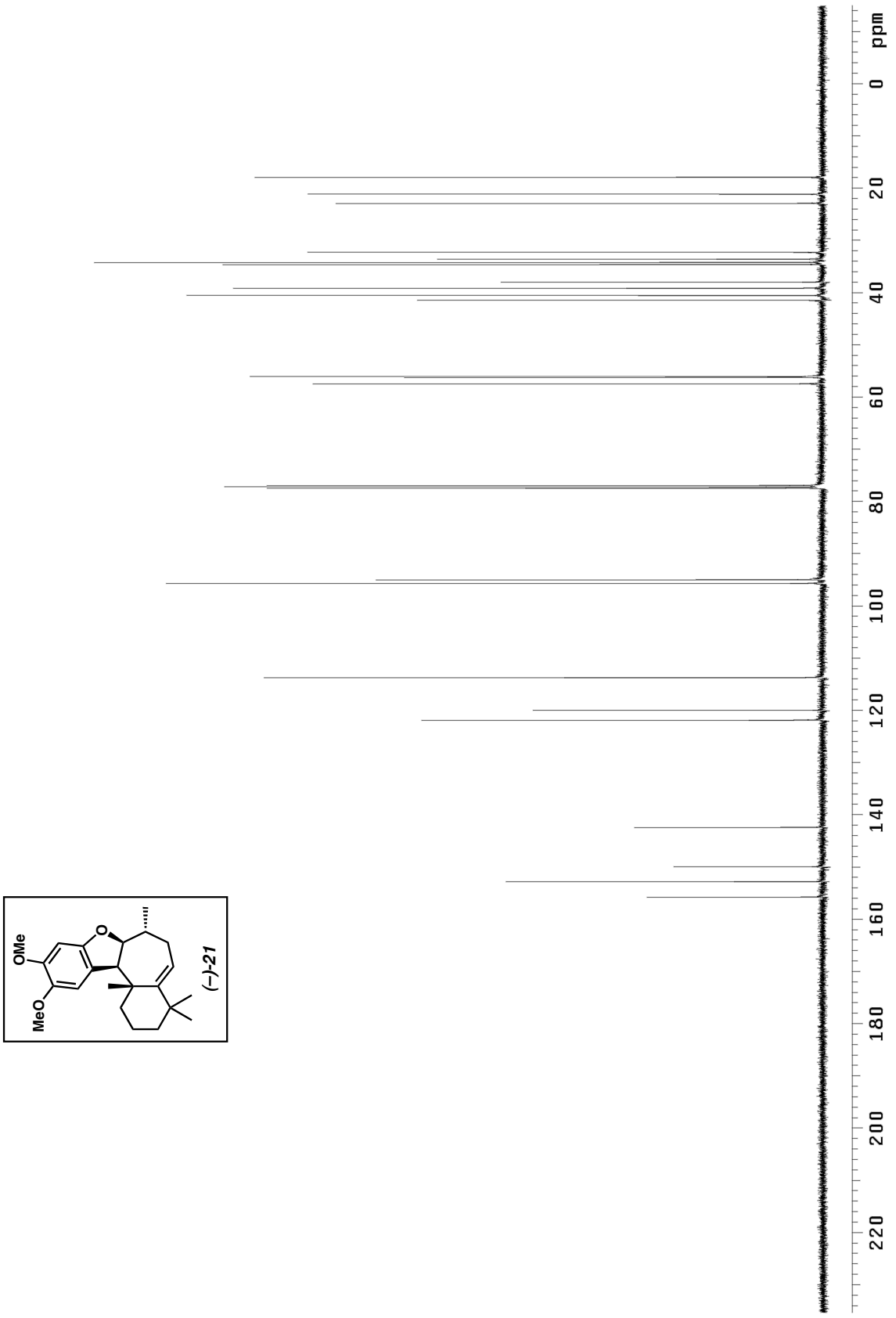
3
4
5
6
7


OMe
MeO
O
(–)-21
ppm
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20
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60
80
100
120
140
160
180
200
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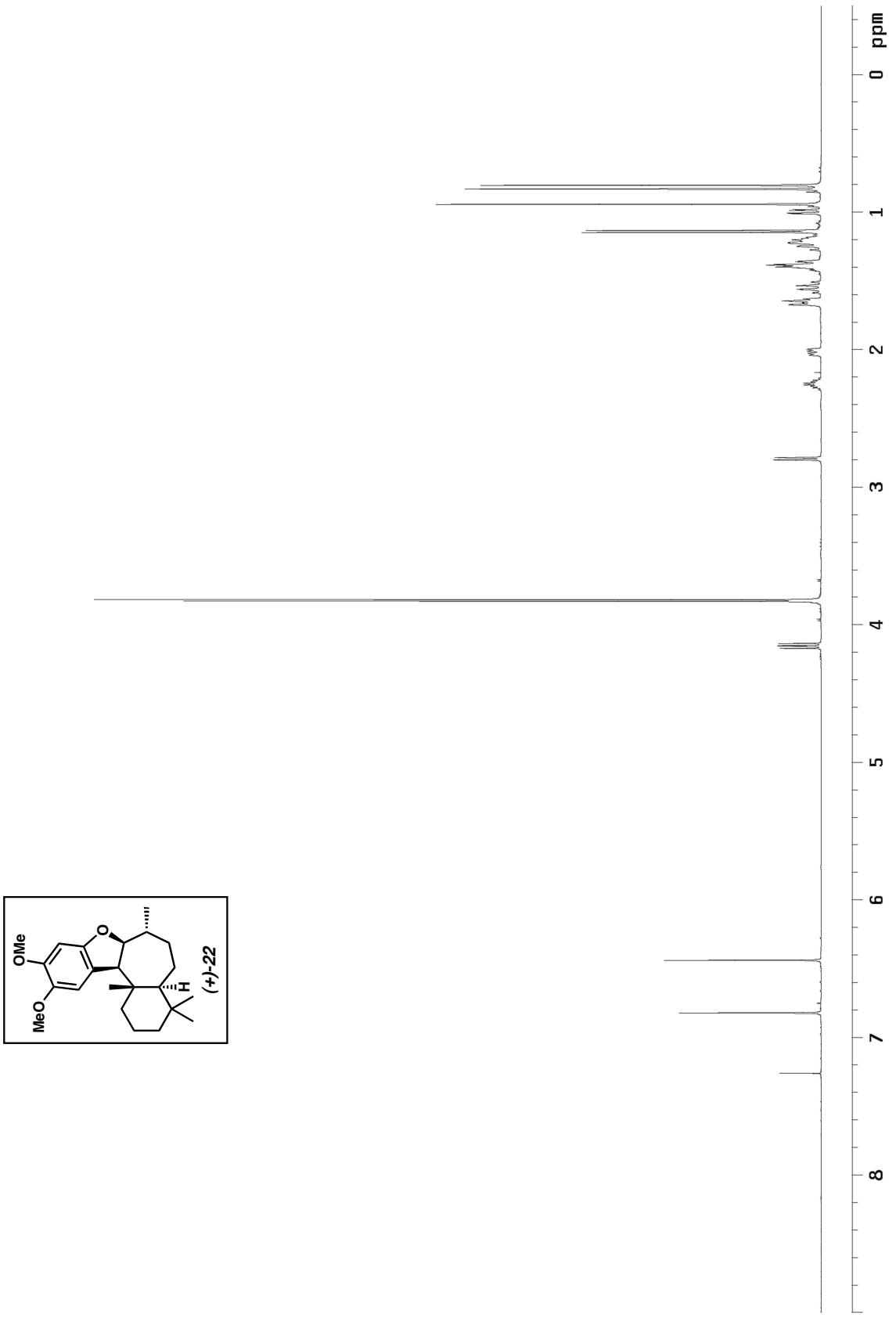
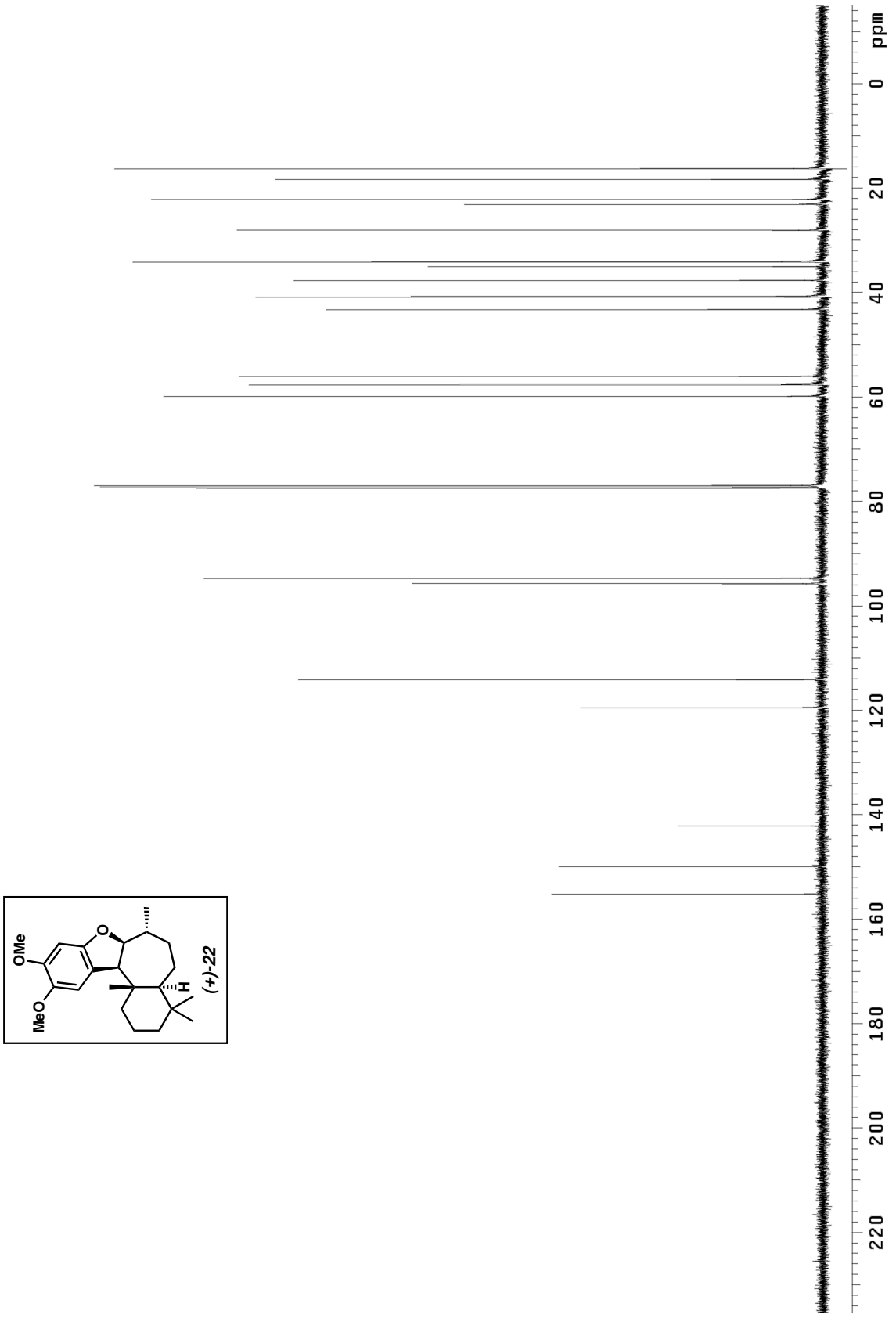

OMe
MeO
H
(+)-22
0
1
2
3
4
5
6
7
8
ppm


ppm
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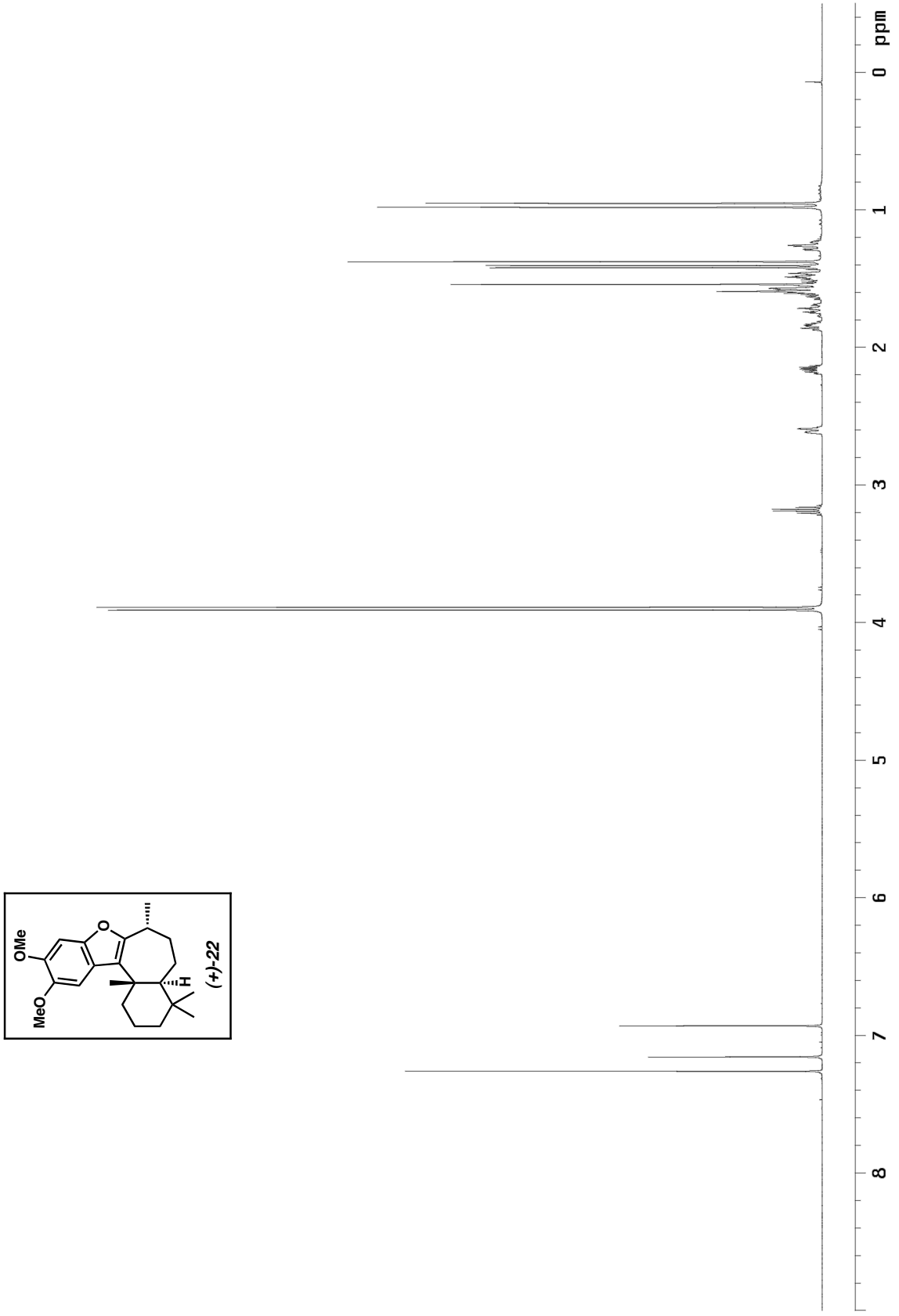
100
120
140
160
180
200
220
OMe
MeO
O
H
(+)-22


OMe
MeO
O
H
(+)-22
ppm
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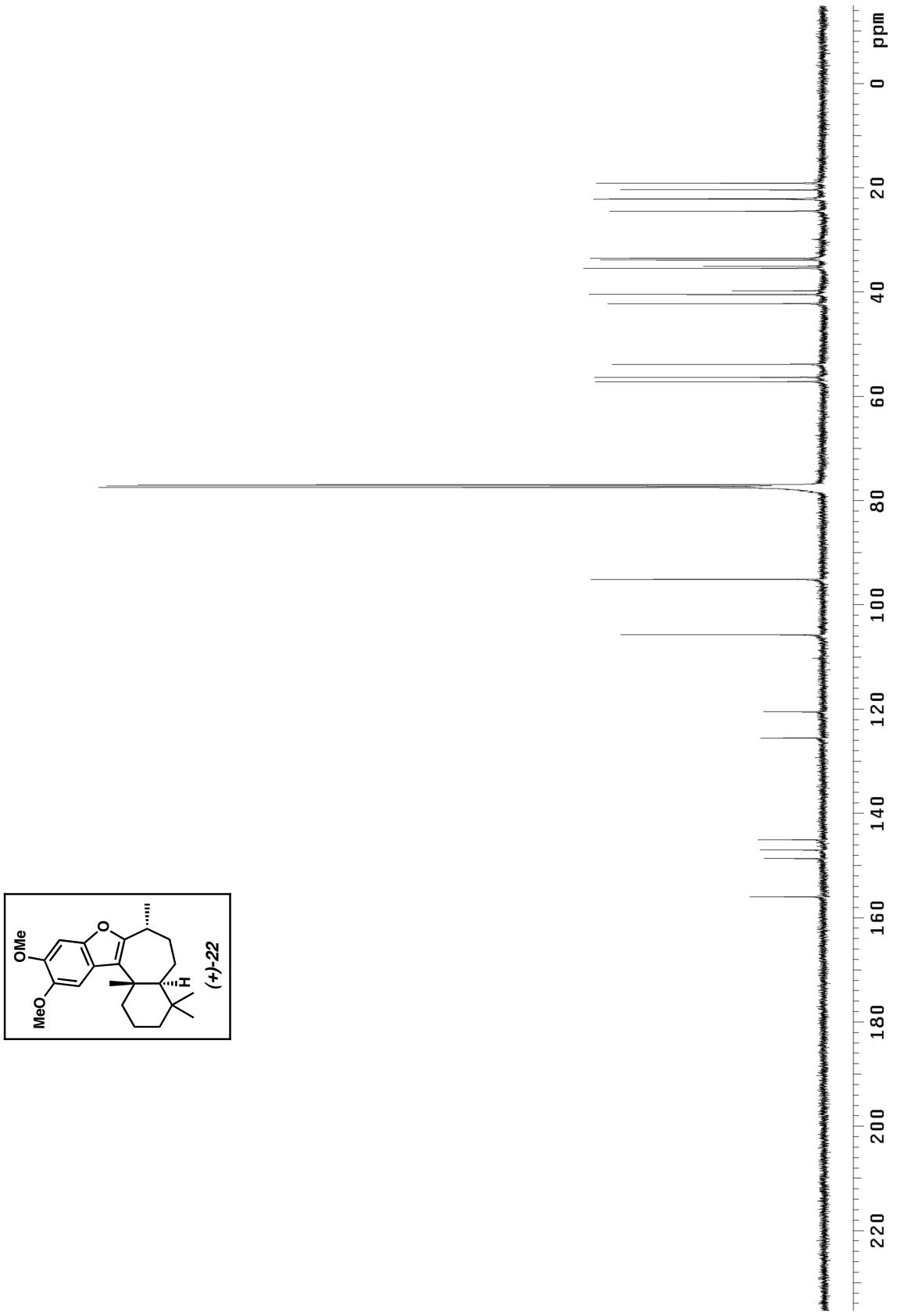
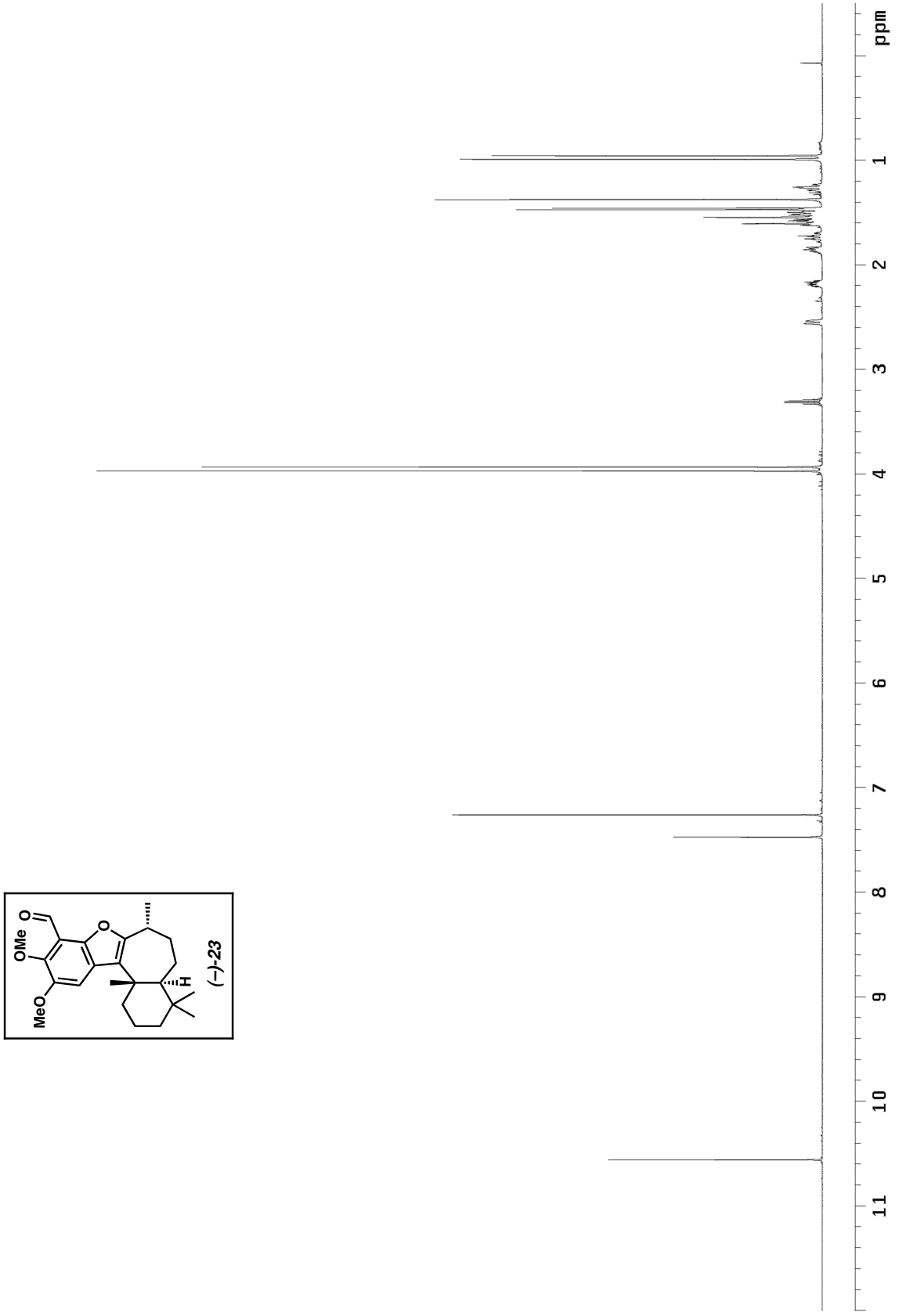
2
3
4
5
6
7
8


OMe
MeO
O
H
(+)-22
ppm
0
20
40
60
80
100
120
140
160
180
200
220


ppm
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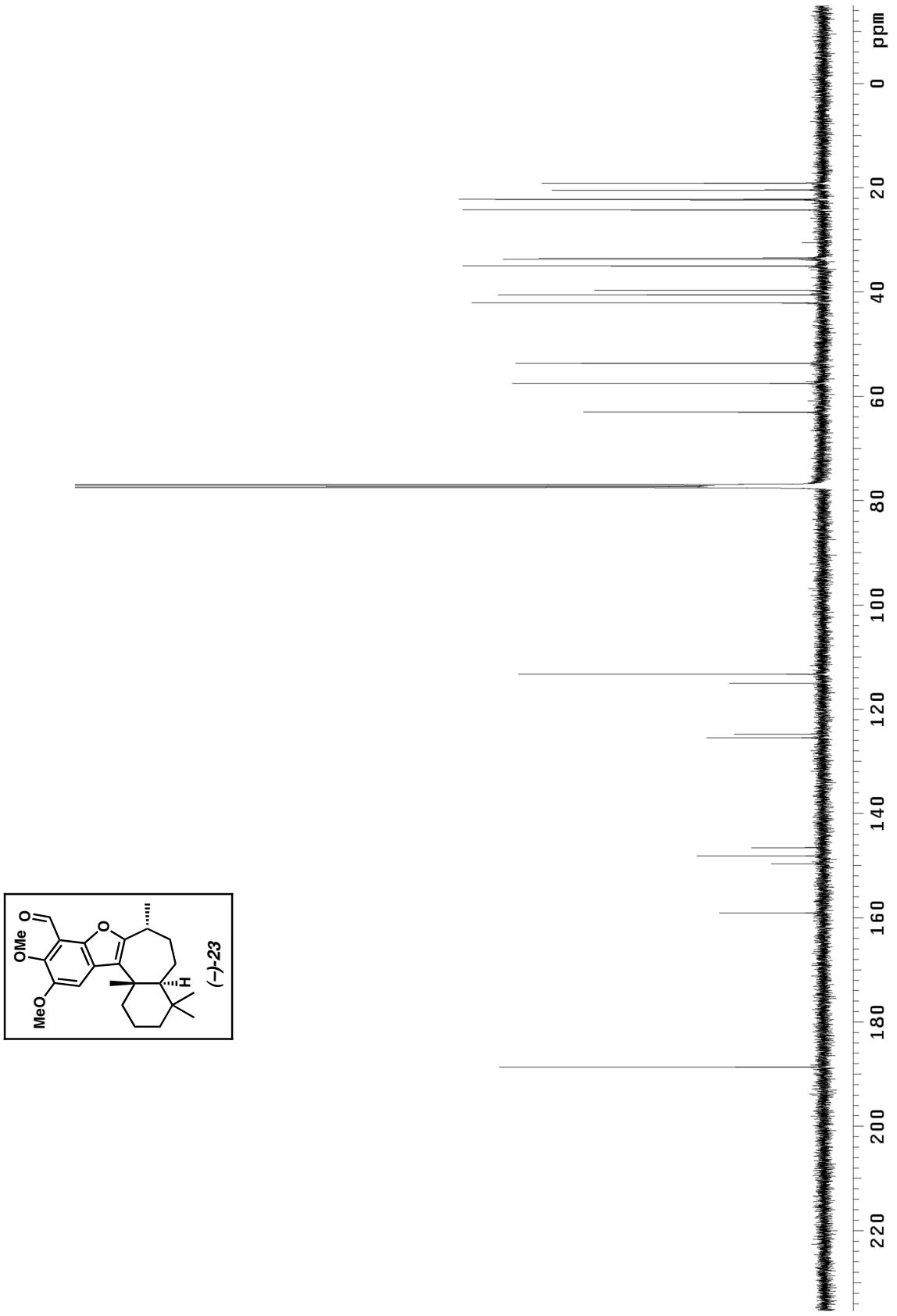
2
3
4
5
6
7
8
9
10
11
OMe
O
MeO
H
(−)-23


OMe
O
MeO
H
(−)-23
ppm
0
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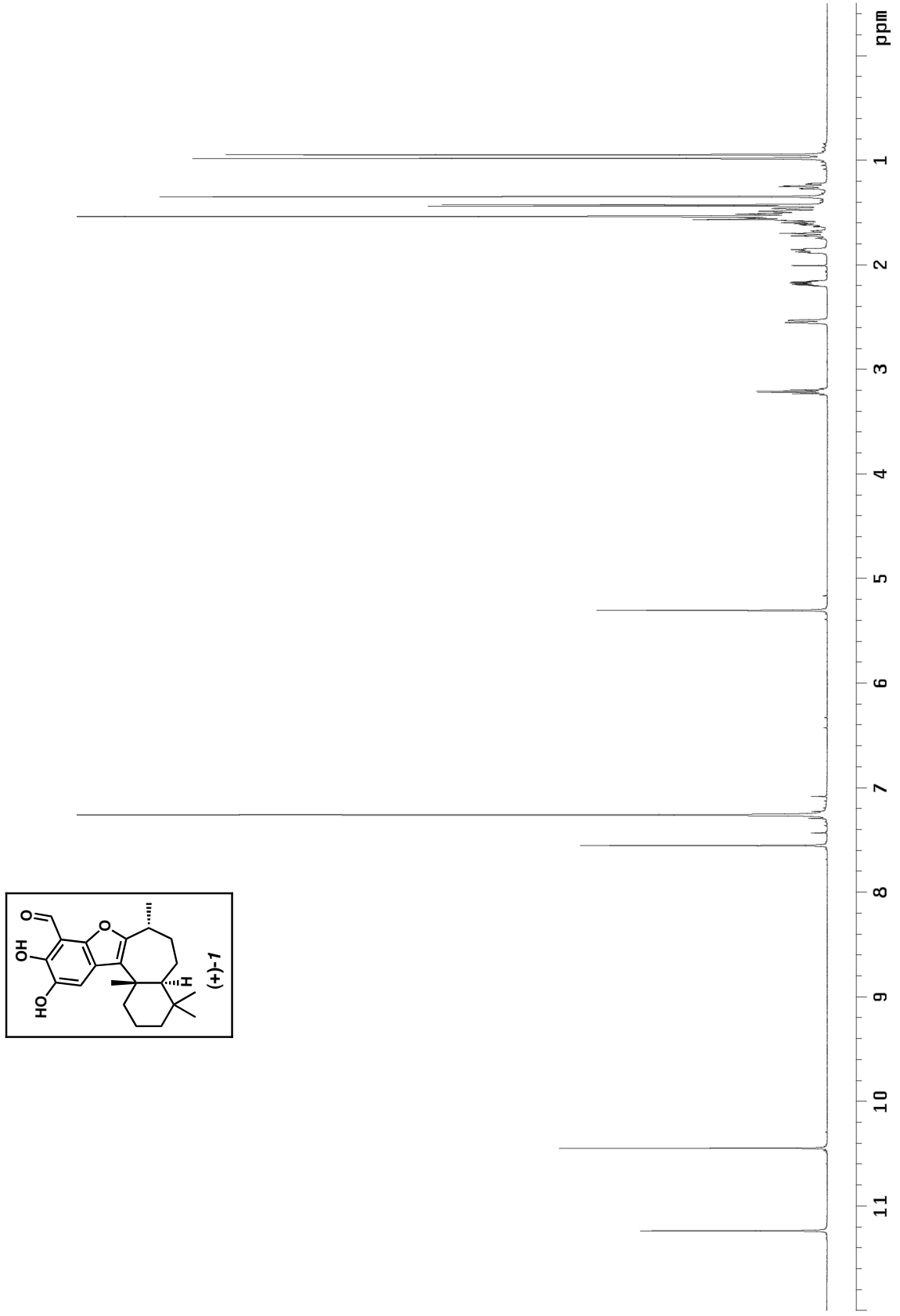
40
60
80
100
120
140
160
180
200
220


ppm
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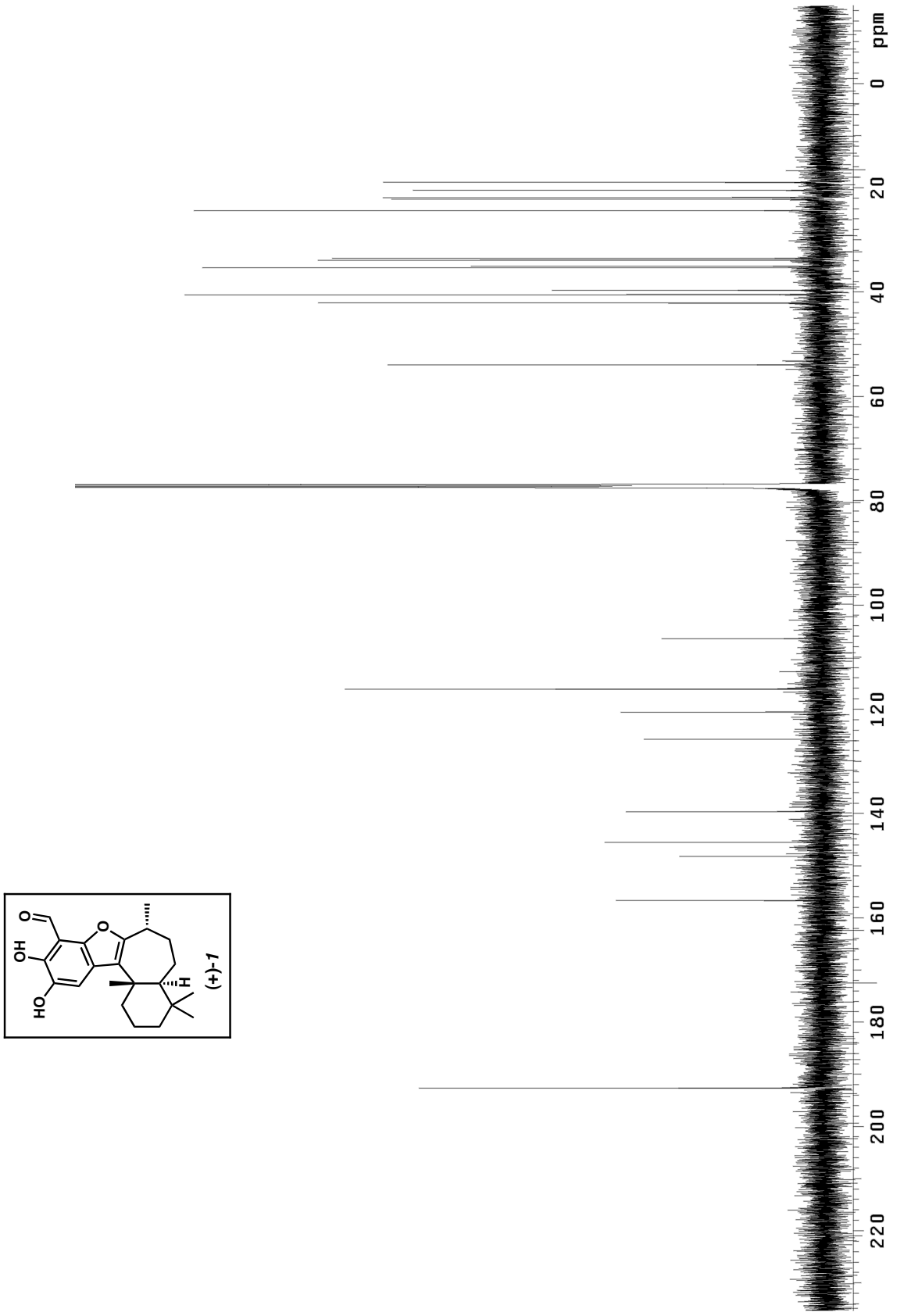
2
3
4
5
6
7
8
9
10
11
O
OH
HO
H
(+)-1


ppm
0
20
40
60
80
100
120
140
160
180
200
220
O
OH
HO
H
(+)-1

References.

(1) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

(2) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.

(3) Due to a limited supply of material of 99% ee, a melting point was not obtained. The reported melting point with material of 95% ee was obtained from enantioenrichment of enone **(+)-5** according to the procedure found in reference 2.

(4) Equipped with a SYMYX core module.

(5) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281–283.

(6) It is unclear why we have obtained the opposite sign as that reported by Baldwin: George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394–2397.

(7) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Cano, M. J.; Haidour, A.; Alvarez-Manzaneda, R. *Org. Lett.* **2010**, *12*, 4450–4453.