Enantioselective Total Synthesis of (+)-Cassiol

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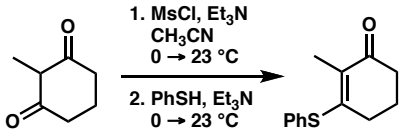
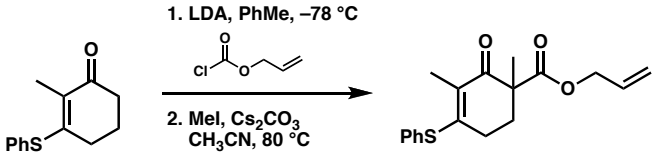
Materials and Methods. Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. Liquids and solutions were transferred via syringe or cannula. All the starting materials were purchased from Sigma-Aldrich or Alfa Aersar, and used as received, unless otherwise stated. Previously reported methods were used to prepare (*R*)-*t*-BuPHOX (**8**),[1] $Pd_2(pmdba)_3$,[2] and $PdCl_2(CH_3CN)_2$.[3] Osmium tetroxide and $Pb(OAc)_4$ were purchased from Sigma-Aldrich, and the $Pb(OAc)_4$ was stored under a glovebox atmosphere prior to use. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or $KMnO_4$ staining. SiliCycle® SiliaFlash® P60 Academic Silica Gel (particle size 40-63 μm; pore diameter 60 Å), or Florisil® (100–200 mesh) were used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to Me_4Si (δ 0.0 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Melting points are uncorrected. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.



SI1 (82% yield) *4*

Vinylogous Thioester 4.[4] To a solution of diketone **SI1** (5.00 g, 39.82 mmol, 1.00 equiv) in CH_3CN (44 mL) was added Et_3N (6.2 mL, 44.40 mmol, 1.12 equiv), and the solution was allowed to stir for 5 min, then cooled to 0 °C. Methanesulfonyl chloride (3.26 mL, 42.00 mmol, 1.06 equiv) was added, and the reaction was warmed to 23 °C over 2 h. Stirring was continued for 5 h, and the reaction was cooled to 0 °C. Triethylamine (6.2 mL, 44.40 mmol, 1.12 equiv) was added, followed by benzenethiol (4.2 mL, 40.80 mmol, 1.03 equiv). The reaction was allowed to warm to 23 °C over 2 h and stirring was continued for 9 h. Saturated aq Na_2CO_3 (70 mL) was added, the phases were separated, and the aq phase was extracted with Et_2O (3 x 120 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded vinylogous thioester **4** (7.15 g, 82% yield) as a white crystalline solid. R_f = 0.33 (20% EtOAc in hexanes); mp 85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.44-7.37 (comp m, 3H), 2.38 (t, J = 6.5 Hz, 2H), 2.18 (tq, J = 6.5, 2.0 Hz, 2H), 1.97 (t, J = 2.0 Hz, 3H), 1.87 (app pentuplet, J = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 157.9, 130.3(2C), 129.6, 129.5, 37.3, 30.5, 22.9, 12.4; IR (Neat Film NaCl) 2944, 1655, 1578, 1339, 1296 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{13}H_{14}OS$ [M + H]$^+$: 219.0844, found 219.0843.

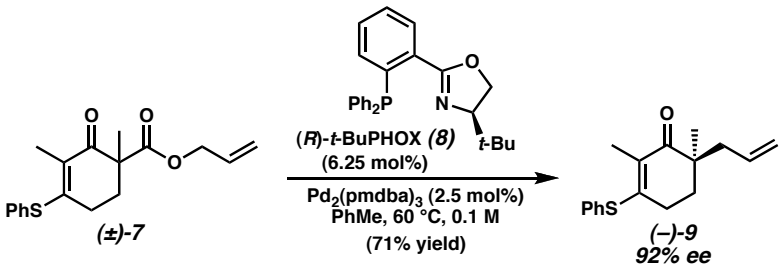


4 (78% yield, two steps) *(±)-7*

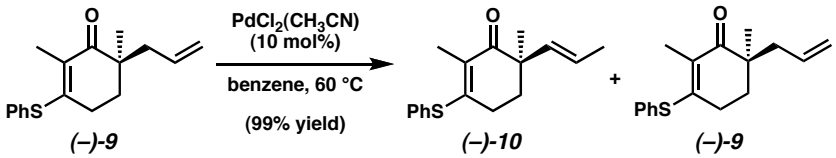
β-Ketoester 7.[5] To a –78 °C solution of diisopropylamine (2.63 mL, 18.78 mmol, 2.00 equiv) in toluene (70 mL) was added dropwise *n*-BuLi (2.53 M in hexanes, 7.24 mL, 2.00 equiv). The reaction vessel was warmed to 0 °C, allowed to stir for 10 min, and cooled to –78 °C. A solution of thioester **4** (2.00 g, 9.16 mmol, 1.00 equiv) in toluene (15 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (1.02 mL, 9.62 mmol, 1.05 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. Stirring was continued for 4 h, then aq $KHSO_4$ (1 N, 70 ml) was added, and the resulting solution was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

To a solution of the crude yellow oil (3.32 g) in CH_3CN (40 mL) was added cesium carbonate (4.48 g, 13.74 mmol, 1.50 equiv), and iodomethane (1.71 mL, 27.48 mmol, 3.00 equiv). The resulting suspension was refluxed at 80 °C for 5 h, and then MeI (1.00 mL, 16.06 mmol, 1.75 equiv) was added. The reaction was refluxed at 80 °C for 2 h, cooled to room temperature, filtered through Celite (EtOAc eluent), dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded β-ketoester (±)-**7** (2.26 g, 78% yield over two steps) as white solid. R_f = 0.35 (30% EtOAc in hexanes); mp 34 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.35 (comp m, 5H), 5.87 (app ddt, J = 10.5, 17.1, 5.4 Hz, 1H), 5.27 (app ddt, J = 17.1, 1.7, 1.8 Hz, 1H), 5.22 (app ddt, J = 9.9, 1.7, 1.2 Hz, 1H), 4.65 (dddd, J = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 4.55 (dddd, J = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 2.41-

2.32 (m, 1H), 2.30-2.21 (m, 1H), 2.16-2.06 (1H), 2.00 (t, J = 1.8 Hz, 3H), 1.78 (ddd, J = 4.5, 8.1, 13.2 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 172.6, 156.7, 135.6, 131.9, 129.7, 129.5, 128.9, 118.1, 65.7, 52.3, 33.1, 27.4, 20.7, 12.9; IR (Neat Film NaCl) 2936, 1733, 1656, 1580, 1314, 1254, 1238, 1174, 985, 752, 693 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{18}H_{20}O_3S$ [M + H]$^+$: 317.1211, found 317.1211.

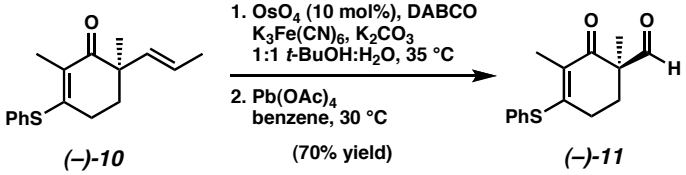


Allyl Ketone (–)-9. A solution of $Pd_2(pmdba)_3$ (0.1306 g, 0.1185 mmol, 0.025 equiv) and (*R*)-*t*-BuPHOX (**8**) (0.1148 g, 0.2964 mmol, 0.0625 equiv) in toluene (30 mL) was prepared in a glovebox under N_2 atmosphere, and allowed to stir at 23 °C for 30 min. A solution of β-ketoester (±)-**7** (1.50 g, 4.741 mmol, 1.00 equiv) in toluene (10 mL) was transferred to the reaction vessel dropwise via glass pipette, washing with toluene (7.5 mL) for quantitative transfer. The reaction vessel was sealed with a rubber septum, removed from the glove box, heated in a 60 °C oil bath, and the solution was allowed to stir for 24 h. The reaction vessel was cooled to room temperature, and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford allyl ketone (–)-**9** (0.92 g, 71% yield, 92% ee as determined by chiral HPLC using a Chiralpak AD column with 4% EtOH in hexanes as the eluent, see graphical HPLC data on page SI 9) as a colorless oil. R_f = 0.45 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.43-7.35 (comp m, 3H), 5.68 (app ddt, J = 10.8, 16.8, 7.5 Hz, 1H), 5.03 (dddd, J = 9.9, 2.4, 0.9, 0.6 Hz, 1H), 5.01 (dddd, J = 17.4, 2.4, 1.5, 1.2 Hz, 1H), 2.32 (app ddt, J = 13.8, 7.2, 1.2 Hz), 2.19-2.10 (comp m, 3H), 1.96 (t, J = 1.8 Hz, 3H), 1.86-1.75 (m, 1H), 1.66-1.56 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 155.6, 135.6, 134.4 130.3, 129.6, 129.5, 128.8, 118.2, 43.1, 41.7, 33.1, 26.9, 22.3, 12.9; IR (Neat Film NaCl) 3074, 2964, 2929, 1652, 1582, 1440, 1339, 1287, 1228 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{17}H_{20}OS$ [M + H]$^+$: 273.1313, found 273.1317; $[\alpha]_D^{25.4}$ –57.4 (*c* 1.00, CH_2Cl_2).



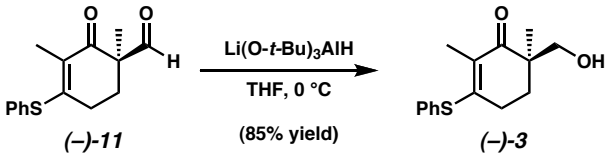
Isomerized alkene (–)-10. A solution of allyl ketone (–)-**9** (0.80 g, 2.94 mmol, 1.00 equiv) and $PdCl_2(CH_3CN)_2$ (76.3 mg, 0.29 mmol, 0.10 equiv) in benzene (5.8 mL) was sparged with Ar for 10 min. The flask was sealed, and heated to 60 °C for 12 h. The reaction was cooled to room temperature, the solvent was evaporated in vacuo, and the resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford an inseparable mixtures of isomerized alkene (–)-**10** and starting material (–)-**9** (0.7951 g, 99% overall yield, ratio of 13:1 of **10**:**9** by NMR). R_f = 0.45 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ (additional peaks correspond to compound **9**) 7.52-7.47 (m, 2H), 7.36-7.42 (comp m, 3H), 5.45 (dq, J = 1.5, 15.5 Hz, 1H), 5.33 (dq, J = 6.0, 15.5 Hz, 1H), 2.26-2.04 (m, 2H), 1.98 (t, J = 1.5 Hz, 3H), 1.83-1.72 (m, 2H), 1.66 (dd, J = 2.0, 6.5 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 155.9, 135.5, 133.7, 130.4, 129.5, 129.4, 129.3, 124.9, 46.2, 35.3, 27.4, 24.3, 18.5, 12.9;

IR (Neat Film NaCl) 2923, 1651, 1588, 1440, 1372, 1339 1287, 1230 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{17}H_{20}OS$ $[M + H]^+$: 273.1313, found 273.1314; $[\alpha]_D^{26.0}$ –34.8 (*c* 1.00, CH_2Cl_2).

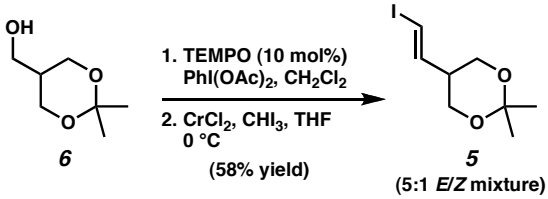


Aldehyde (–)-11. To a solution of $K_3Fe(CN)_6$ (2.18 g, 6.61 mmol, 3.00 equiv), K_2CO_3 (0.91 g, 6.61 mmol, 3.00 equiv), 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.124 g, 1.01 mmol, 0.50 equiv), and 13:1 isomeric mixture of allyl ketone (–)-**10** and allyl ketone (–)-**9** (0.60 g, 2.20 mmol, 1.00 equiv) was added solid OsO_4 (56.0 mg, 0.22 mmol, 0.10 equiv), and the solution was allowed to stir at 35 °C for 12 h. Saturated aq Na_2SO_3 (20 mL) was added, and the solution was allowed to stir for 1 h. The phases were separated, and the aq phase was extracted with Et_2O (3 x 30 mL), dried over Na_2SO_3, filtered, and concentrated. e isolated white solid was used in the next step without further purification.

To a solution of the crude white solid (0.64 g) in benzene (17 mL) was added $Pb(OAc)_4$ (1.02 g, 2.31 mmol, 1.10 equiv), and the solution was allowed to stir at 30 °C for 1 h. The solution was concentrated in vacuo, and the resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford aldehyde (–)-**11** (0.40 g, 70% yield over two steps) as a white solid. R_f = 0.60 (30% EtOAc in hexanes); *mp* 41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.52-7.36 (comp m, 5H), 2.35-2.10 (m, 3H), 1.98 (t, *J* = 1.5 Hz, 3H), 1.76-1.67 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 193.7, 159.2, 135.9, 130.0, 129.7, 129.4, 128.9, 56.4, 29.0, 26.7, 18.9, 12.5; IR (Neat Film NaCl) 2931, 1725, 1642, 1578, 1440, 1339, 1312, 1239, 1025 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{15}H_{16}O_2S$ $[M + H]^+$: 261.0949, found 261.0944; $[\alpha]_D^{25.6}$ –30.4 (*c* 1.00, CH_2Cl_2).

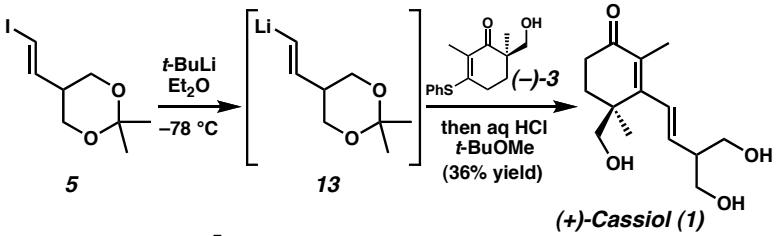


Alcohol (–)-3. A solution of lithium tri-*tert*-butoxy aluminium hydride (1.34 mL, 1.00 M solution in THF, 1.41 mmol, 1.05 equiv) in THF (7 mL) was cooled to 0 °C. This solution was then added to a 0 °C solution of aldehyde (–)-**11** (0.35 g, 1.35 mmol, 1.00 equiv) in THF (20 mL) in seven equal portions over 2 h. The reaction was allowed to stir for an additional 30 min, then H_2O (0.3 mL) was added, followed by 15% aq NaOH (0.3 mL), and then H_2O (0.9 mL). The reaction was warmed to 23 °C, and allowed to stir for 30 min. The solution was filtered through Celite (washing with EtOAc), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford alcohol (–)-**3** (0.30 g, 85% yield) as a white solid (90.3% ee as determined by chiral HPLC using a Chiralpak AD column with 80% EtOH in hexanes as the eluent, see graphical HPLC data on page SI 11). R_f = 0.22 (30% EtOAc in hexanes); mp 49 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H), 7.46-7.40 (comp m, 3H), 3.51 (dd, *J* =11.1, 8.1 Hz, 2H), 2.88 (dd, *J* = 5.1, 7.8 Hz, 1H), 2.38-2.10 (comp m, 2H), 1.98-1.88 (comp m, 4H), 1.46 (ddd, *J* = 3.3, 4.8, 13.2 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 157.8, 135.8, 129.8, 129.6, 128.4, 69.5, 44.5, 31.1, 26.7, 18.8, 12.5; IR (Neat Film NaCl) 3433 (br), 2927, 1642, 1578, 1440, 1339, 1025, 750 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{15}H_{18}O_2S$ $[M + H]^+$: 263.1106, found 263.1115; $[\alpha]_D^{26.1}$ –13.3 (*c* 1.00, CH_2Cl_2).



Vinyl iodide 5. 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 0.0424 g, 0.27 mmol, 0.10 equiv) was added to a solution of alcohol **6**[6] (0.40 g, 2.74 mmol, 1.00 equiv) in CH_2Cl_2 (8 mL), and the reaction was allowed to stir for 5 min. To the reaction vessel was added solid bis(acetoxy)iodobenzene (0.97 g, 3.01 mmol, 1.10 equiv) was added, and the reaction was allowed to stir for 12 h at 23 °C. The reaction was diluted with CH_2Cl_2 (8 mL), washed with saturated aq $Na_2S_2O_3$ (1 x 15 mL), and the aq phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, filtered through Celite, and concentrated in vacuo to yield a white oil. The crude product was used without further purification in the following step.

The crude oil was added to a solution of iodoform (2.15 g, 5.47 mmol, 2.00 equiv) in THF (7 mL), and then cooled to 0 °C. The resulting solution was transferred via cannula to a 0 °C suspension of chromium(II) chloride (2.00 g, 16.27 mmol, 5.95 equiv) in THF (30 mL), washing with THF (2 mL) to effect quantitative transfer. The reaction was allowed to stir for 4 h, and then H_2O (40 mL) was added, the phases were separated, and the aq phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (gradient elution of 3% to 10% EtOAc in hexanes) yielded vinyl iodide **5** (0.42 g, 58% yield, 5:1 *E*/*Z* by ^{1}H NMR) as a thick yellow oil. R_f = 0.29 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ (trans isomer) 6.02 (dd, *J* = 8.5, 15.0 Hz, 1H), 5.62 (d, *J* = 15.0 Hz, 1H), 3.45 (dd, *J* = 5.0, 12.0 Hz, 2H), 3.25 (dd, *J* = 9.0, 12.0 Hz, 2H), 2.04 (dtt, *J* = 9.0, 8.5, 5.0 Hz, 1H), 1.38 (s, 3H), 1.20 (s, 3H); (cis isomer): 5.89 (d, *J* = 7.5 Hz, 1H), 5.79 (dd, *J* = 7.5, 8.5 Hz, 1H), 3.67 (dd, *J* = 4.0, 11.5 Hz, 2H), 3.41 (dd, *J* = 7.0, 11.5 Hz, 2H), 3.25 (dd, *J* = 9.0, 11.5 Hz, 2H), 2.66 (dtt, *J* = 7.0, 8.5, 4.0 Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ (trans isomer) 143.6, 98.0, 78.5, 63.2, 42.2, 27.6, 21.2; IR (Neat Film NaCl) 2992, 2940, 2863, 1604, 1478, 1453, 1386, 1371, 1262, 1205, 1153, 1131, 1076, 1036, 949, 830 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_8H_{13}O_2I$ [M + H]$^+$: 269.0039, found 269.0040.



(+)-Cassiol (1).[7] To a solution of vinyl iodide **5** (0.204 g, 0.76 mmol, 2.00 equiv) in diethyl ether (5 mL) at –78 °C was added dropwise *t*-BuLi (1.37 M soln in pentane, 1.18 mL, 1.62 mmol, 4.25 equiv). The solution was allowed to stir for 1 h, and then warmed to 0 °C. A solution of alcohol (–)-**3** (0.10 g, 0.38 mmol, 1 equiv) in diethyl ether (2.5 mL) was cooled to 0 °C, and added to the reaction vessel dropwise via cannula, washing with ether (2.5 mL) for quantitative transfer. The resulting solution was warmed to 24 °C, and allowed to stir for 72 h. To the reaction vessel was added saturated aq $NaHCO_3$ buffered to pH 8 with saturated aq NH_4Cl (7 mL). The phases were separated, the aq phase was extracted with

EtOAc (3 x 10 mL), and the combined organic extracts were concentrated in vacuo. The residue was dissolved in *t*-butyl methyl ether (8 mL), and 10% aq HCl solution (10 mL) was added to the reaction vessel. The solution was allowed to stir for 2 h, and solid $NaHCO_3$ (4.0 g) was added in small portions. The phases were separated, and the aq phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% MeOH in EtOAc), followed by purification by column chromatography on Florisil (100% EtOAc) afforded (+)-cassiol (**1**, 35.0 mg, 36%) as a thick colorless oil. R_f = 0.10 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, D_2O) δ 6.27 (d, *J* = 16.5 Hz, 1H), 5.66 (dd, *J* = 8.5, 16.5 Hz, 1 H), 3.77 (d, *J* = 11.5 Hz, 1H), 3.74 (ddd, *J* = 3.0, 6.0, 11.0 Hz, 2H), 3.66 (ddd, *J* = 2.0, 7.0, 11.0 Hz, 2H), 3.43 (d, *J* =11.5, 1H), 2.68-2.52 (comp m, 3H), 2.17 (ddd, *J* = 5.5, 11.0, 14.0 Hz, 1H), 1.80 (s, 3H), 1.75 (app dt, *J* = 13.5, 6.0 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, D_2O, uncorrected) δ 204.8, 162.4, 136.7, 132.0, 129.0, 68.0, 62.1, 48.0, 40.8, 33.5, 30.8, 20.5, 13.2; IR (Neat Film NaCl) 3369, 2930, 2868, 1643, 1591, 1455, 1358, 1038 cm^{-1}; HRMS (FAB+) *m/z*: calc'd for $C_{14}H_{22}O_4$ $[M + H]^+$: 255.1596, found 255.1604; $[\alpha]_D^{26.8}$ +8.2 (*c* 1.00, MeOH).

NMR data for (+)-cassiol was also collected in $CDCl_3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (d, *J* = 16.5 Hz, 1H), 5.59 (dd, *J* = 8.0, 16.5 Hz, 1H), 3.73-3.86 (comp m, 4H), 3.67 (d, *J* = 11.5 Hz, 1H), 3.38 (d, *J* = 11.5 Hz, 1H), 2.78-2.58 (comp. m, 3H), 2.58-2.51 (comp m, 2H), 2.41 (br. s, 1H), 2.21 (ddd, *J* = 6.5, 10.5, 14.0 Hz, 1H), 1.82 (s, 3H), 1.64 (dt, *J* = 13.5, 5.5 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 158.4, 135.2, 132.1, 129.6, 69.7, 64.139, 64.131, 47.7, 41.0, 34.0, 32.1, 21.1, 13.7.

Comparison Tables for Properties of Synthetic and Natural Cassiol:

Table SI1. Comparison of ^{1}H NMR data for synthetic, literature, and natural (+)-cassiol.

Synthetic[a] (ppm)	Multiplicity	Literature[b] (ppm)	Multiplicity	Natural sample[c] (ppm)	Multiplicity
6.27	d (1H)	6.28	d (1H)	6.28	dt (1H)
5.66	dd (1H)	5.67	dd (1H)	5.67	dd (1H)
3.76	d (1H)	3.76	d (1H)	3.76	d (1H)
3.75	ddd (2H)	3.75	dd (2H)	3.75	dd (2H)
3.66	ddd (2H)	3.66	dd (2H)	3.66	dd (2H)
3.43	d (1H)	3.43	d (1H)	3.43	d (1H)
2.68–2.52	comp m (3H)	2.71–2.55	m (3H)	2.69–2.51	ddd (3H)
2.17	ddd	2.17	ddd (1H)	2.17	ddd (1H)
1.80	br s	1.81	d (3H)	1.81	d (3H)
1.75	app dt	1.74	dt (1H)	1.75	ddd (1H)
1.11	s (3H)	1.12	s (3H)	1.12	s (3H)

[a] ^{1}H NMR data measured at 500 MHz in D_2O (this work).
[b] ^{1}H NMR data measured at 250 MHz in D_2O.[8]
[c] ^{1}H NMR data measured at 250 MHz in D_2O.[9]

Table SI2. Comparison of ^{13}C NMR data for synthetic, literature, and natural (+)-cassiol.

Synthetic[a]	Literature[b]	Natural sample[c]
204.8	207.12	207.1
162.4	164.87	164.7
136.7	139.17	139.0
132.0	134.35	134.2
129.0	131.37	131.3
68.0	70.44	70.4
62.1	64.55	64.5
48.0	50.30	50.1
40.8	43.18	43.1
33.5	35.89	35.8
30.8	33.28	33.2
20.5	23.02	22.9
13.2	15.63	15.5

[a] ^{13}C NMR data measure at 125 MHz in D_2O (this work).
[b] ^{13}C NMR data measure at 50 MHz in D_2O.[8]
[c] ^{13}C NMR data measure at 50.3 MHz in 1:1 $CDCl_3$/methanol-d_4.[9]

Table SI3. Comparison of IR data for synthetic, literature, and natural (+)-cassiol.

Synthetic[a]	Literature[b]	Natural sample[c]
3369	3368	3400
2930	2930	
2868	2876	
1643	1644	1650
1591	1594	1600
1455	1456	
1358		1340
1038	1044	1040
975		980

[a] Thin film (this work).
[b] Neat.[8]
[c] Thin film.[9]

Table SI4. Comparison of HRMS data for synthetic, literature, and natural (+)-cassiol.

Synthetic calculated	Synthetic found[a]	Literature calculated	Literature found[b]	Natural sample found[c]
255.1596	255.1604	254.1518	254.1519	254

[a] FAB+, measured $[M + H]^+$ (this work).
[b] EI-MS, measured $[M]^+$.[10]
[c] EI-MS, measured $[M]^+$.[9]

Table SI5. Comparison of optical rotation data for synthetic, literature, and natural (+)-cassiol.

Synthetic[a]	Literature[b]	Natural sample[c]
$[\alpha]_D^{26.8}$ +8.2	$[\alpha]_D^{30}$ +8.3	$[\alpha]_D^{28.5}$ +8.6

[a] c = 1.00 in MeOH (this work).
[b] c = 0.35 in MeOH.[8]
[c] c = 0.25 in MeOH.[9]

Graphical HPLC Data for Compounds 9 and 3:

Data File C:\HPCHEM\3\DATA\KVP\AYHI79W.D Sample Name: AYH-I-79W

KVP-199, racemic, inst. 3, pos. 2

```
======================================================================
Injection Date  : 7/14/2008 5:03:50 AM          Seq. Line :   3
Sample Name     : AYH-I-79W                      Location : Vial 11
Acq. Operator   : KVP                               Inj :   1
                                                Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\3\METHODS\4-EOH20.M
Last changed    : 8/22/2002 11:44:36 PM by jeff
Analysis Method : C:\HPCHEM\3\METHODS\POS2.M
Last changed    : 7/14/2008 7:24:53 AM by KVP
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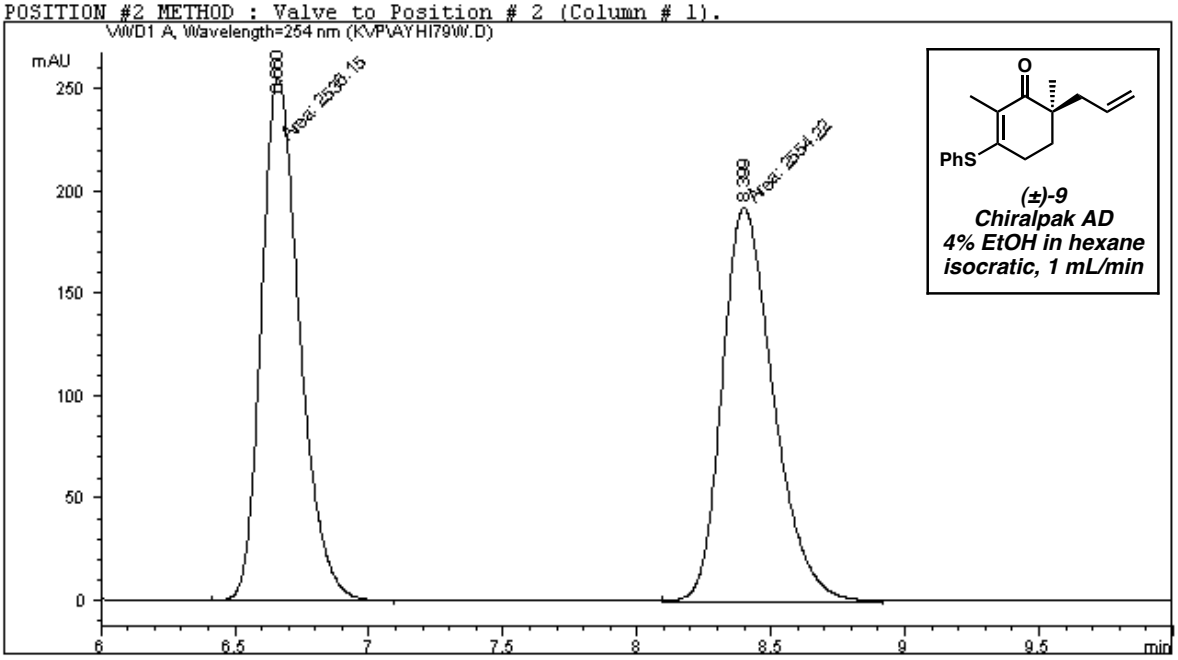


```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   6.660 MM    0.1653 2536.14502  255.71037  49.8225
   2   8.399 MM    0.2213 2554.21875  192.35776  50.1775

Totals :                  5090.36377  448.06813

 Results obtained with standard integrator!
======================================================================
                        *** End of Report ***
```

Data File C:\HPCHEM\3\DATA\KVP\KVP265E.D Sample Name: KVP265E

kvp265e, inst. 3, pos 2, 4%EtOH, enantioenriched (R-tBu -PHOX)

```
==========================================================================
Injection Date  : 4/10/2008 10:04:27 PM          Seq. Line :   3
Sample Name     : KVP265E                         Location : Vial 11
Acq. Operator   : kvp                                Inj :   1
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\3\METHODS\4-EOH20.M
Last changed    : 8/22/2002 11:44:36 PM by jeff
Analysis Method : C:\HPCHEM\3\METHODS\POS2.M
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POSITION #2 METHOD : Valve to Position # 2 (Column # 1).
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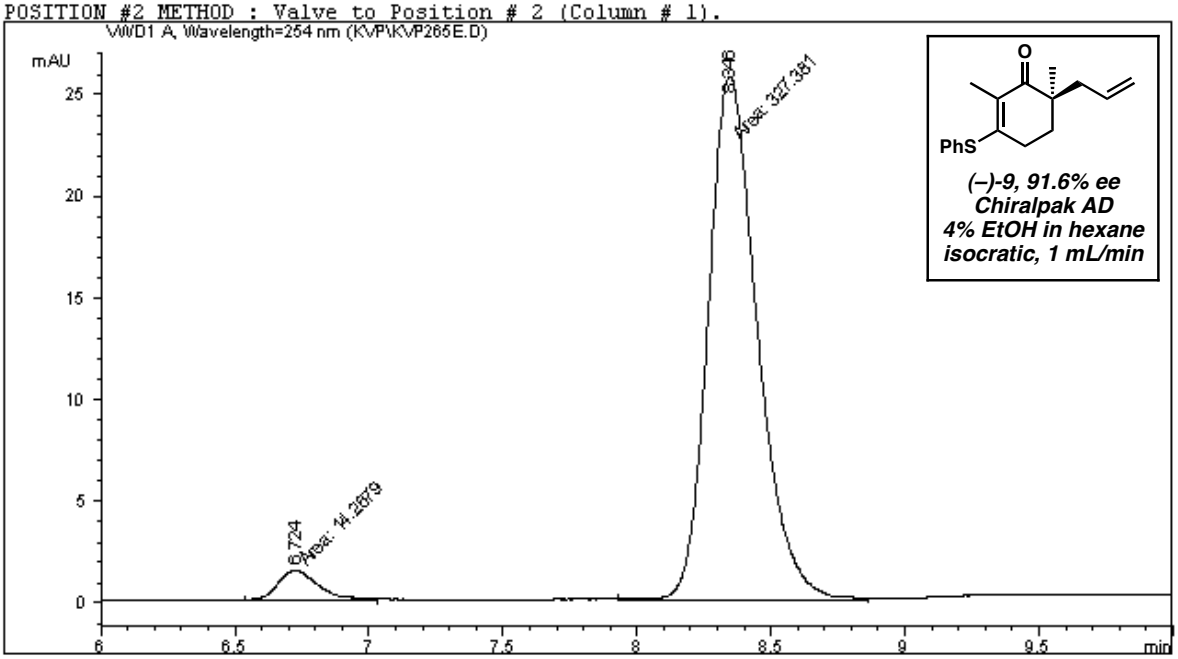


```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   6.724 MM    0.1650   14.26786    1.44141   4.1762
   2   8.346 MM    0.2123  327.38068   25.70616  95.8238

Totals :                   341.64854   27.14757

 Results obtained with standard integrator!
==========================================================================
                        *** End of Report ***
```

Data File C:\HPCHEM\3\DATA\KVP\KVPRAL3.D Sample Name: KVP-racl3

racemic alcohol, inst. 3, pos. 2, 80%EtOH

```
==================================================================
Injection Date  : 7/14/2008 6:11:42 AM          Seq. Line :   3
Sample Name     : KVP-racl3                      Location : Vial 12
Acq. Operator   : KVP                               Inj :   1
                                                Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\3\METHODS\80-EOH30.M
Last changed    : 9/20/2005 10:52:31 AM by dave
Analysis Method : C:\HPCHEM\3\METHODS\POS2.M
Last changed    : 7/14/2008 7:22:15 AM by KVP
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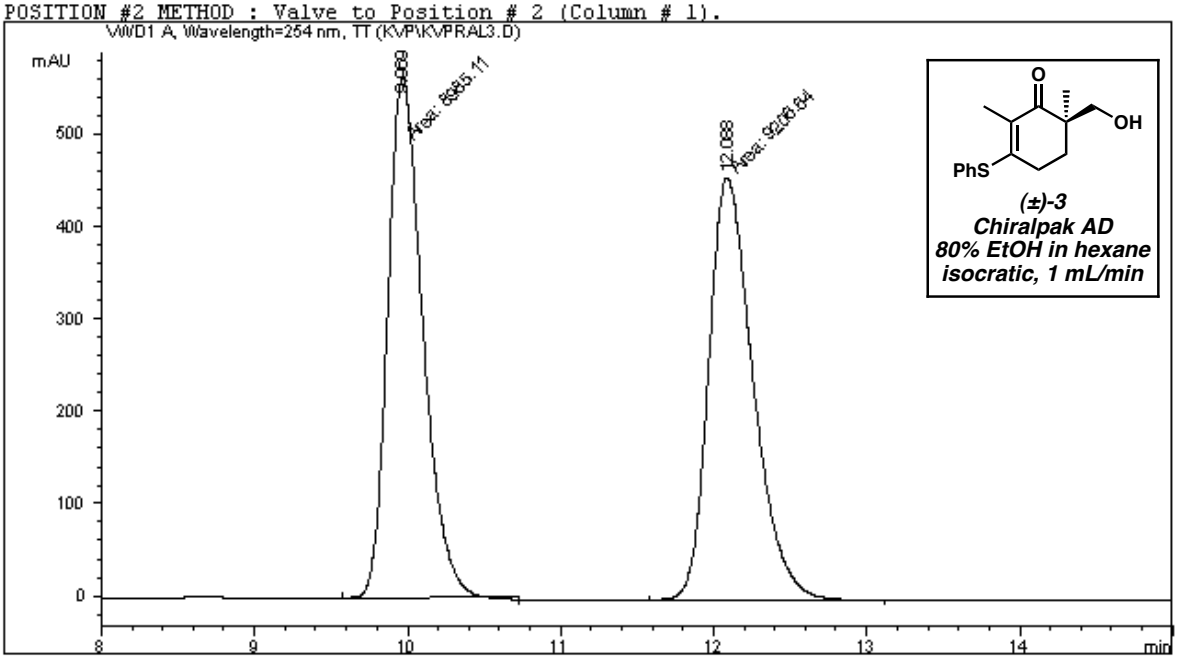


```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: VWD1 A, Wavelength=254 nm, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   9.969 MM    0.2657 8985.10547  563.55981  49.3911
   2  12.088 MM    0.3360 9206.64258  456.72882  50.6089

Totals :                  1.81917e4  1020.28864

 Results obtained with standard integrator!
==================================================================
                        *** End of Report ***
```

Data File C:\HPCHEM\3\DATA\KVP\KVP-EALC.D Sample Name: KVP-ealc

KVP alcohols, inst 3, pos 2, 80% EOH30

```
==========================================================================
Injection Date  : 7/7/2008 6:21:00 PM          Seq. Line :   5
Sample Name     : KVP-ealc                      Location : Vial 12
Acq. Operator   : KVP                             Inj :   1
                                               Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\3\METHODS\80-EOH30.M
Last changed    : 9/20/2005 10:52:31 AM by dave
Analysis Method : C:\HPCHEM\3\METHODS\POS2.M
Last changed    : 7/14/2008 7:18:38 AM by KVP
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POSITION #2 METHOD : Valve to Position # 2 (Column # 1).
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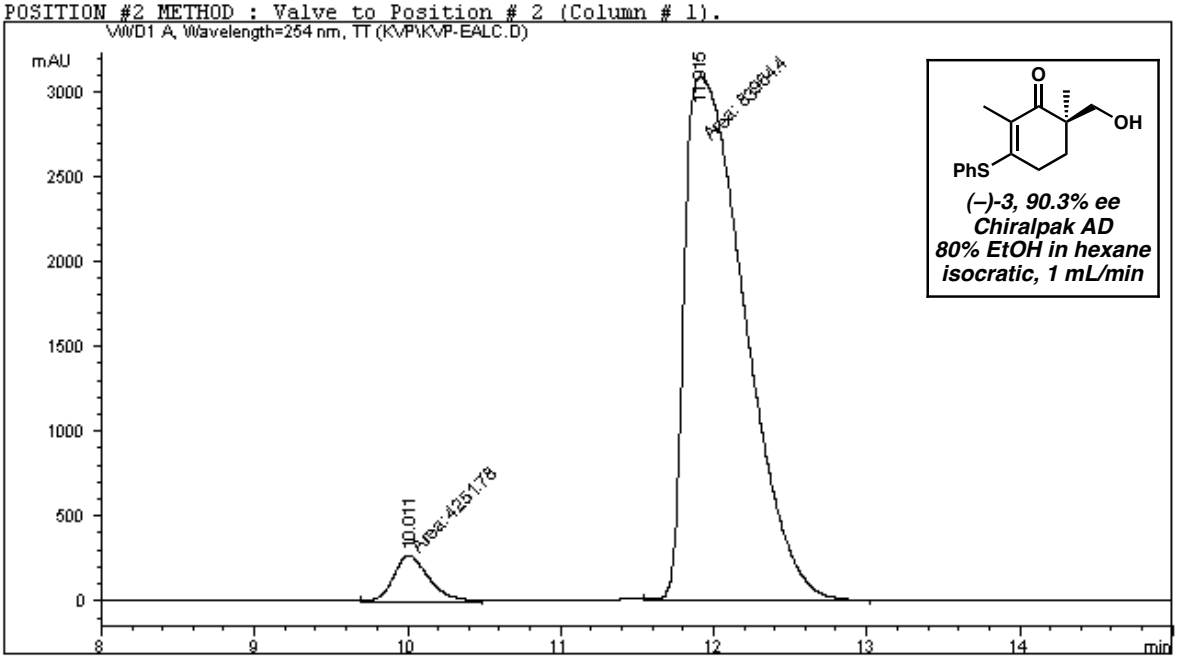
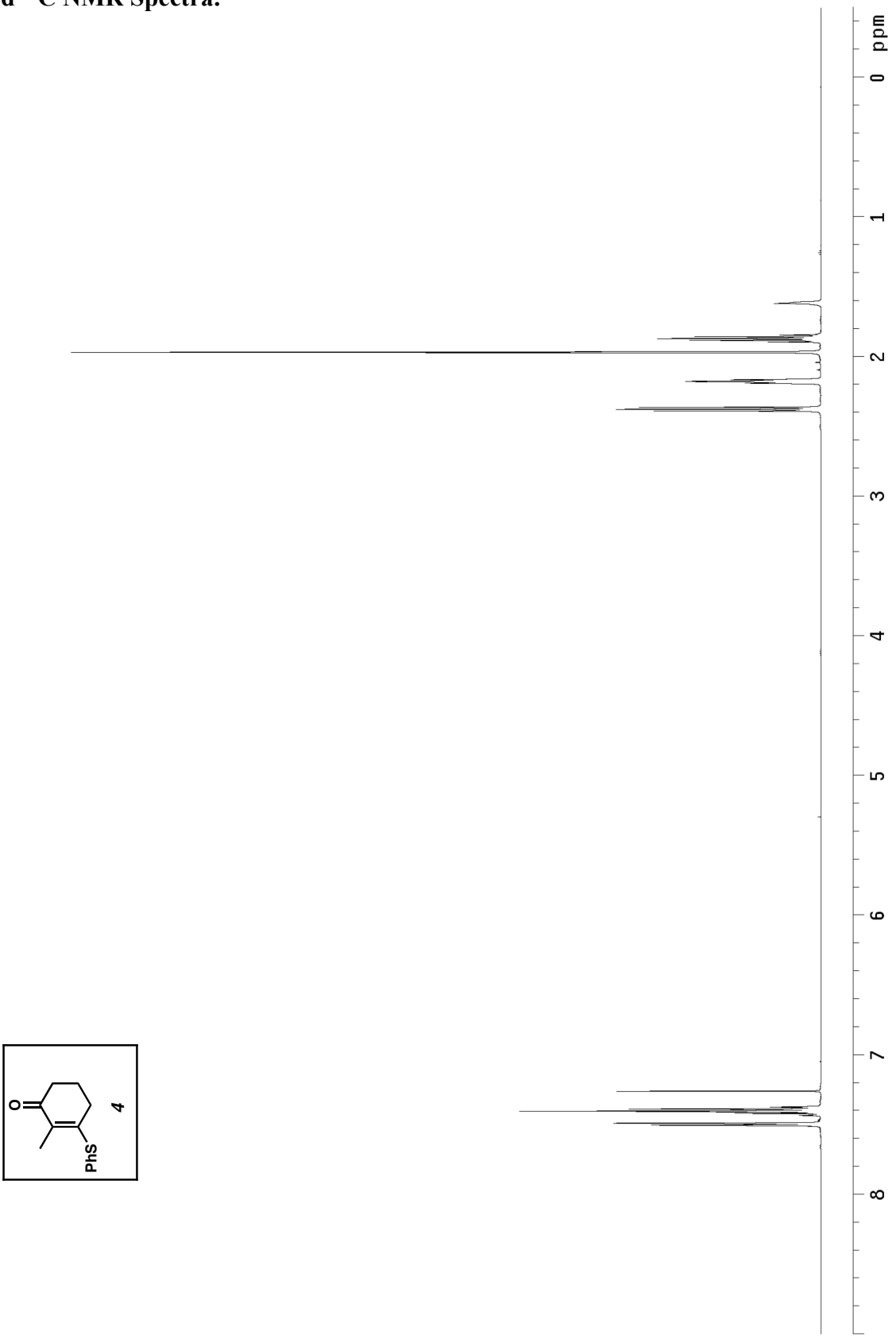
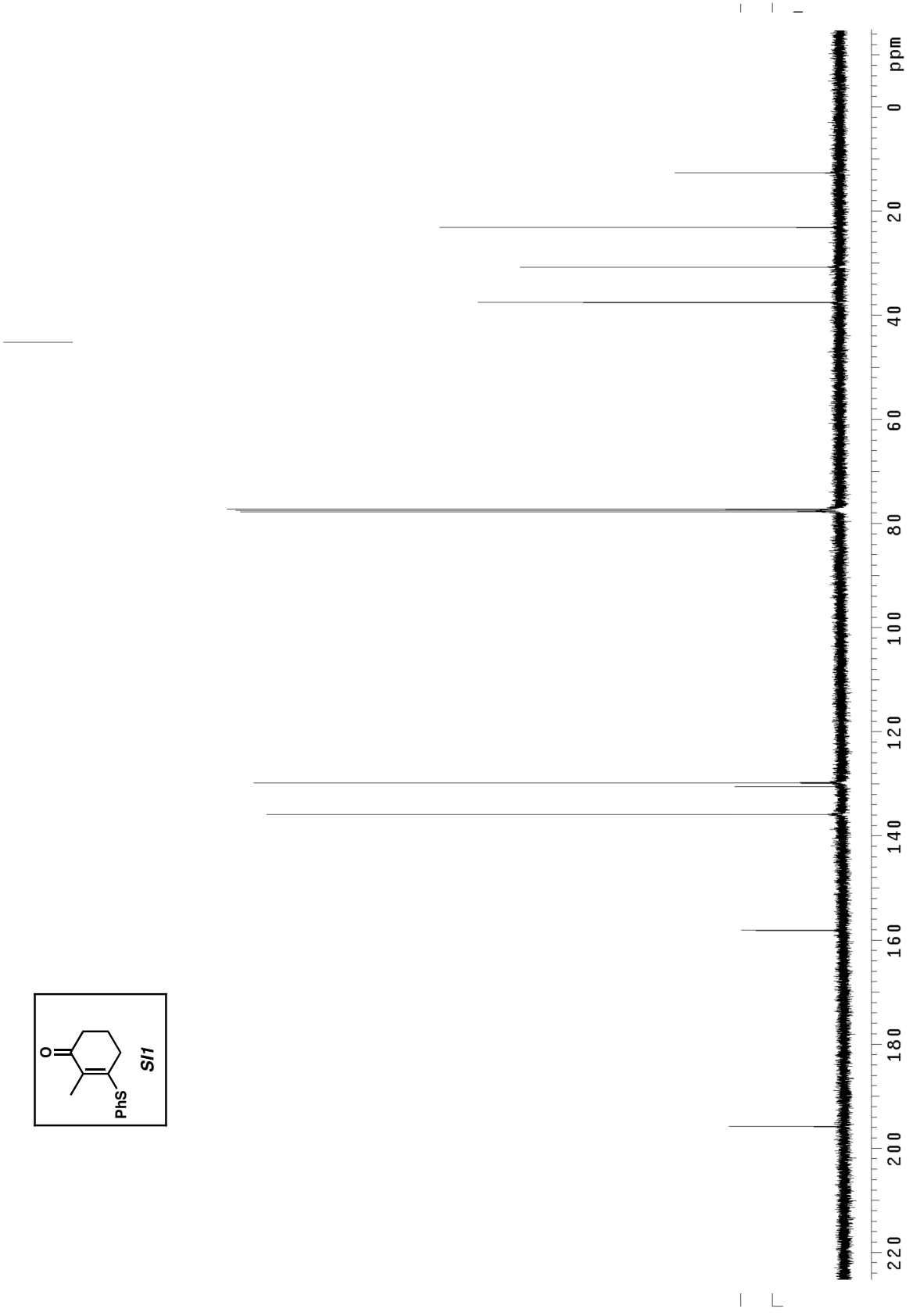



```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: VWD1 A, Wavelength=254 nm, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  10.011 MM    0.2656 4251.78027  266.76822   4.8197
   2  11.915 MM    0.4543 8.39644e4  3080.27637  95.1803

Totals :                  8.82162e4  3347.04459

 Results obtained with standard integrator!
==========================================================================
                          *** End of Report ***
```

^{1}H and ^{13}C NMR Spectra:

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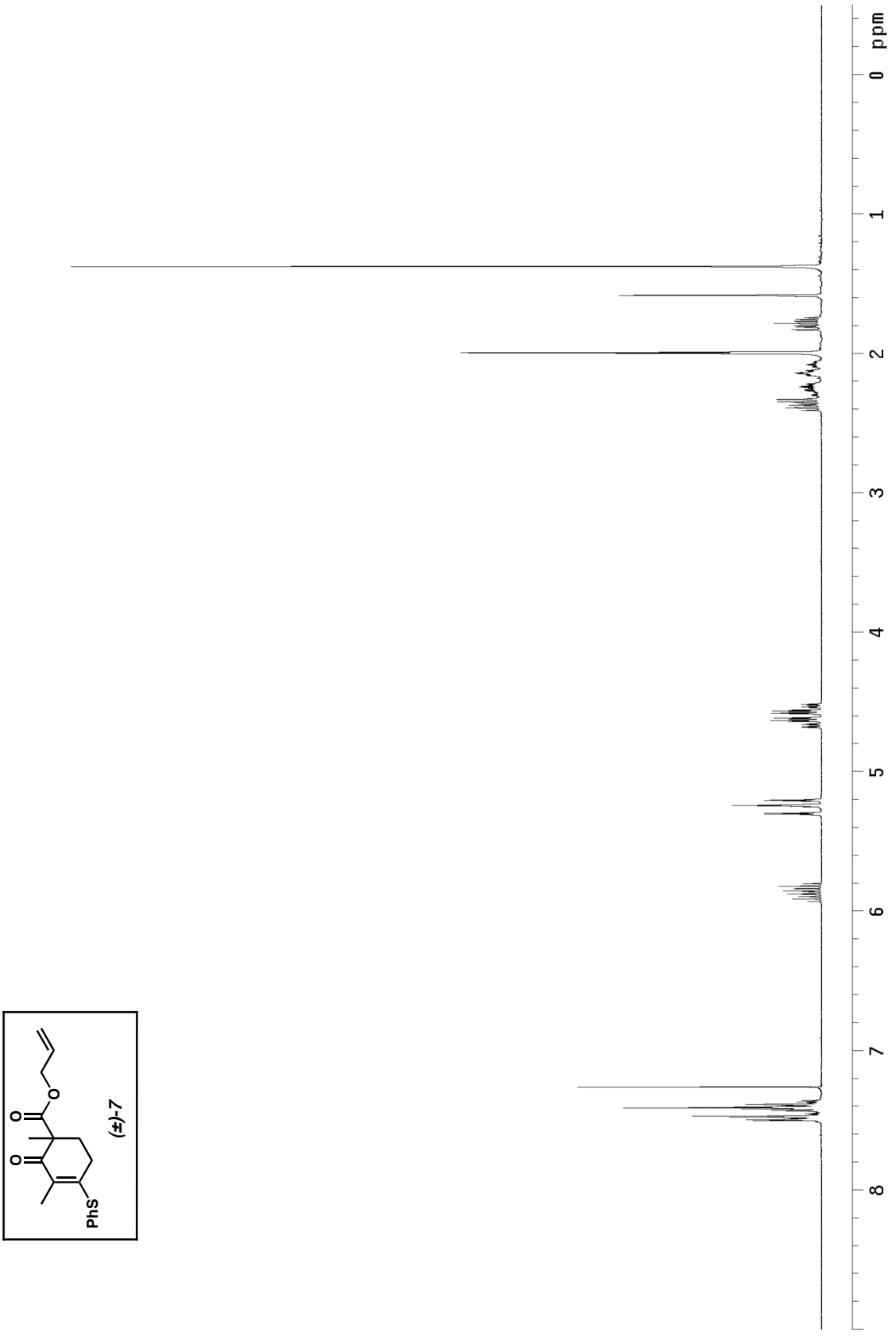
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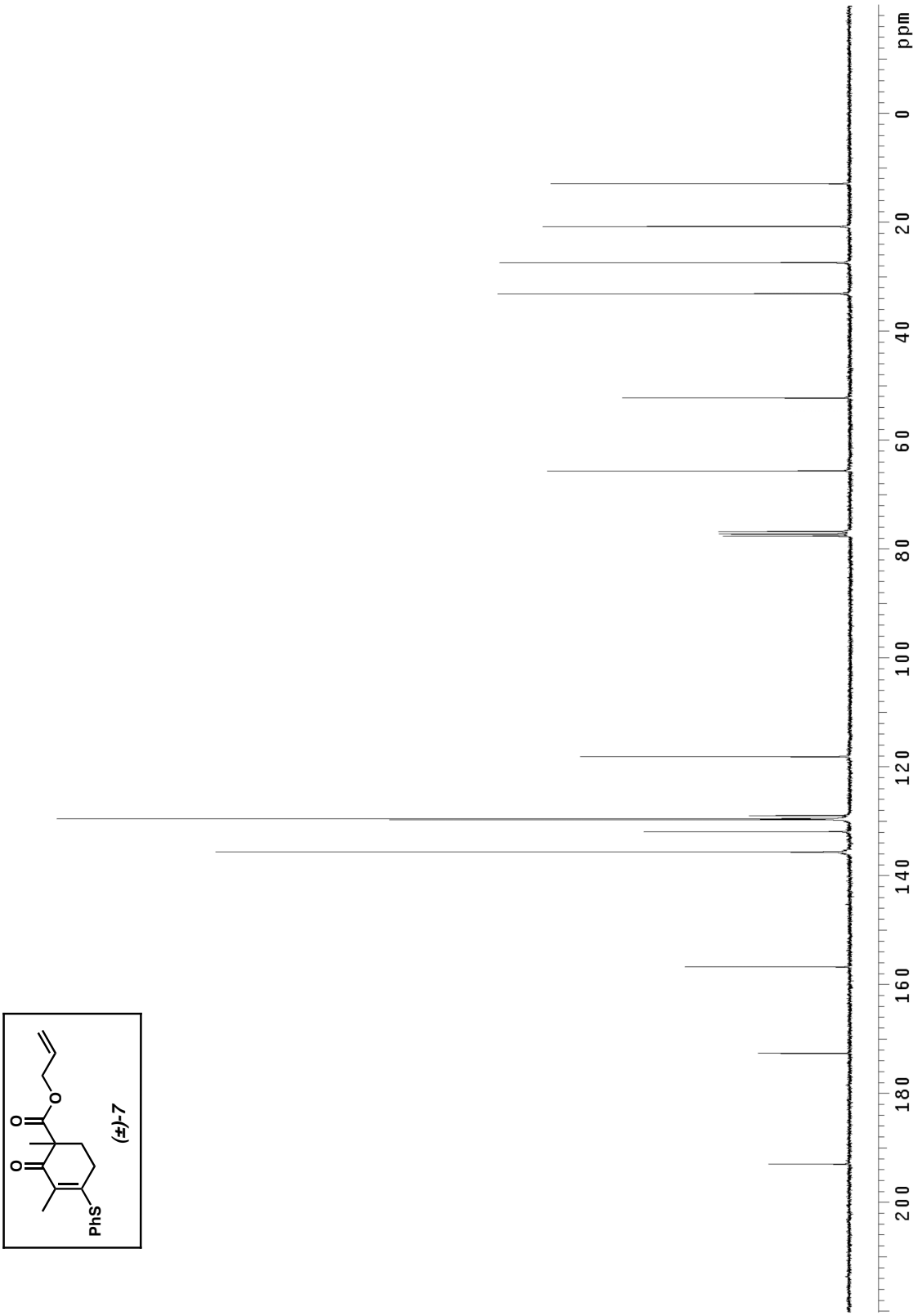
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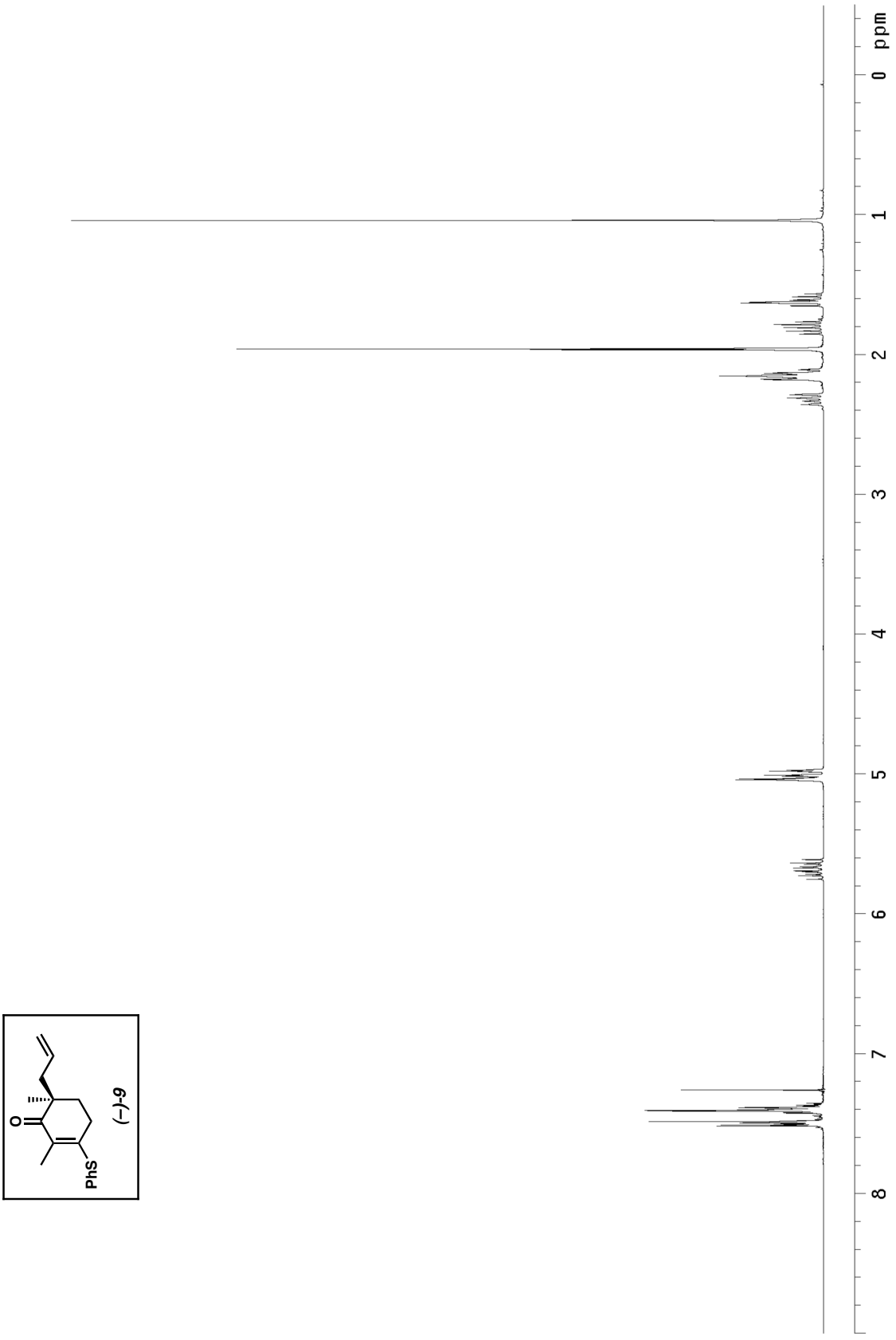
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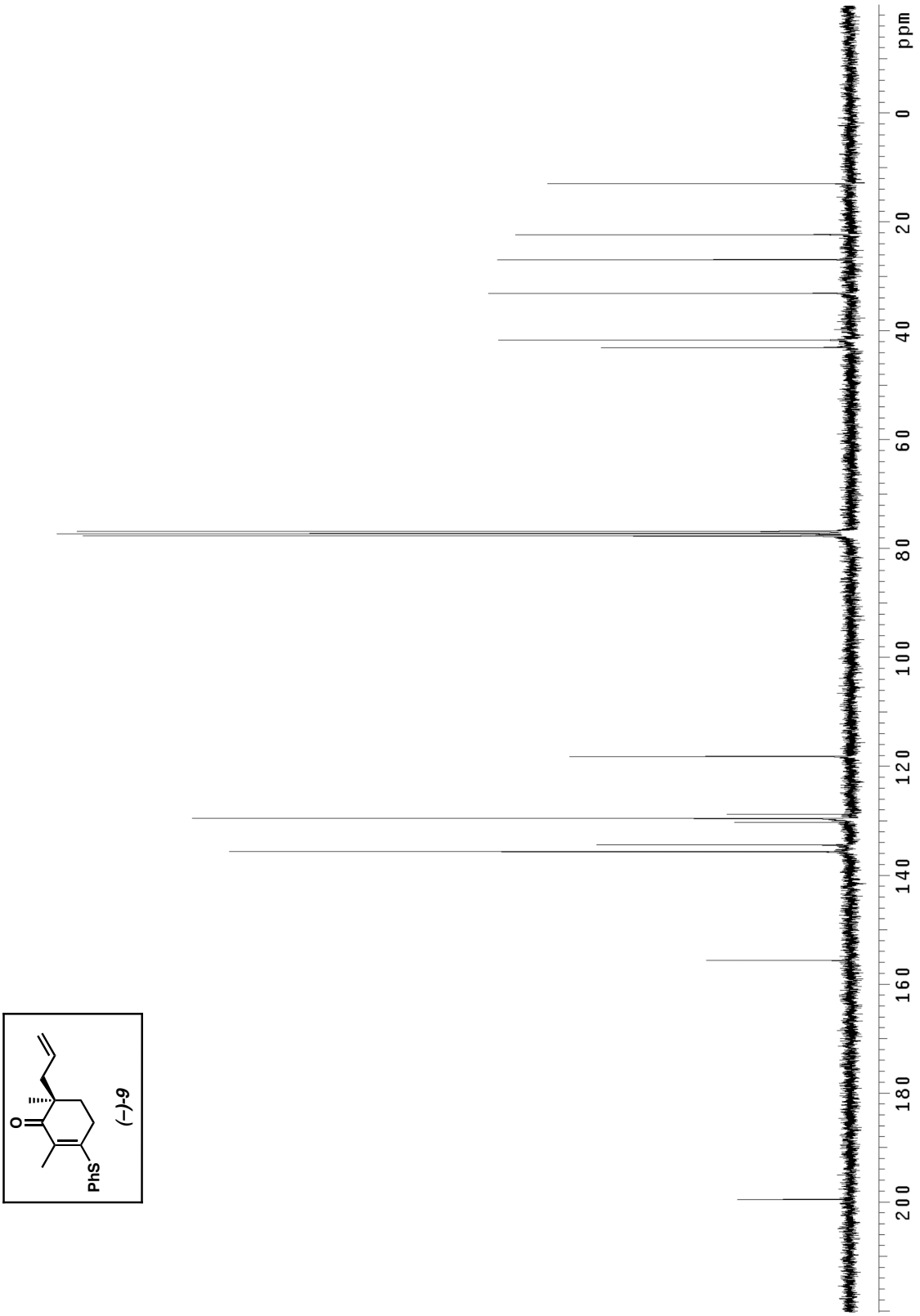
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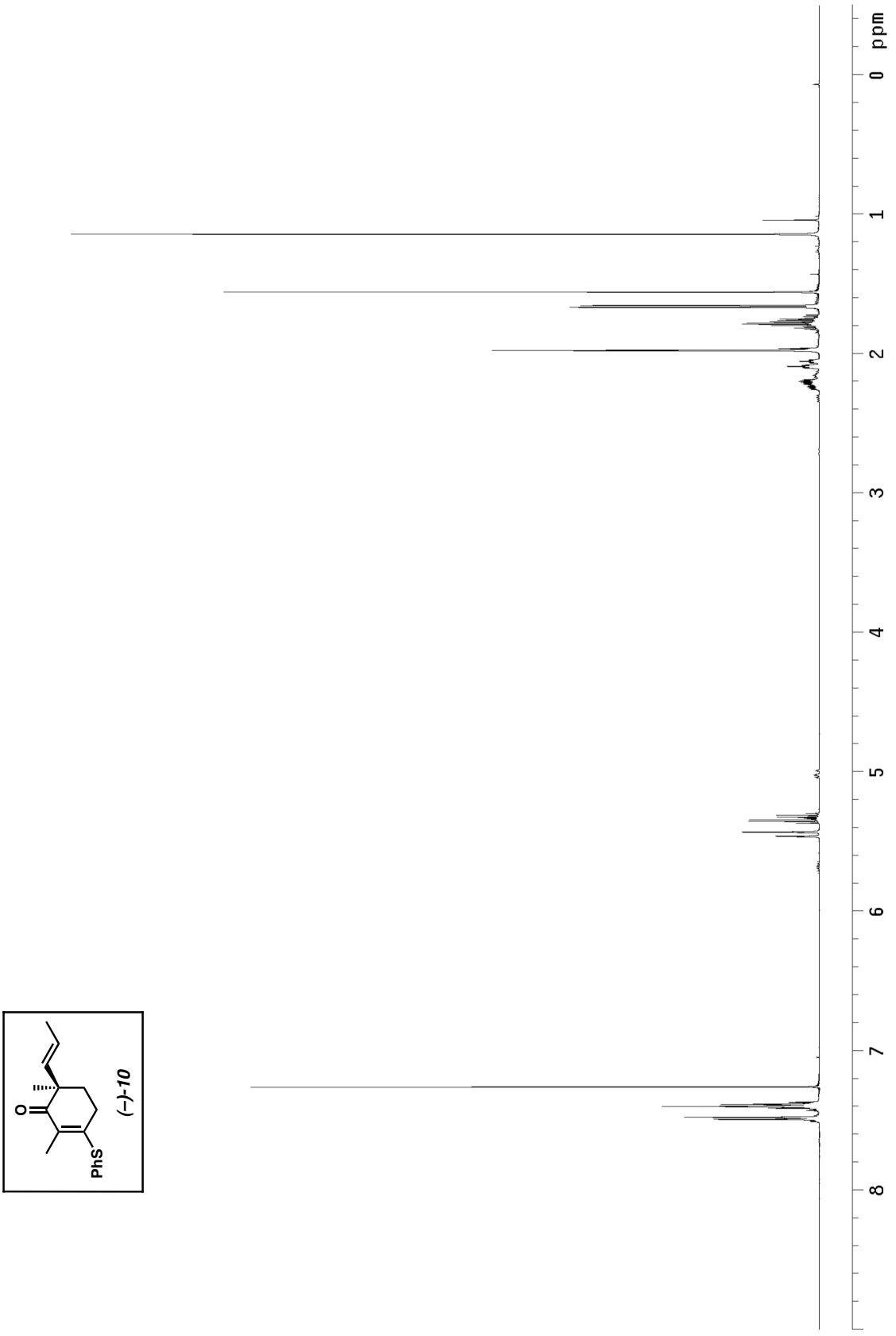
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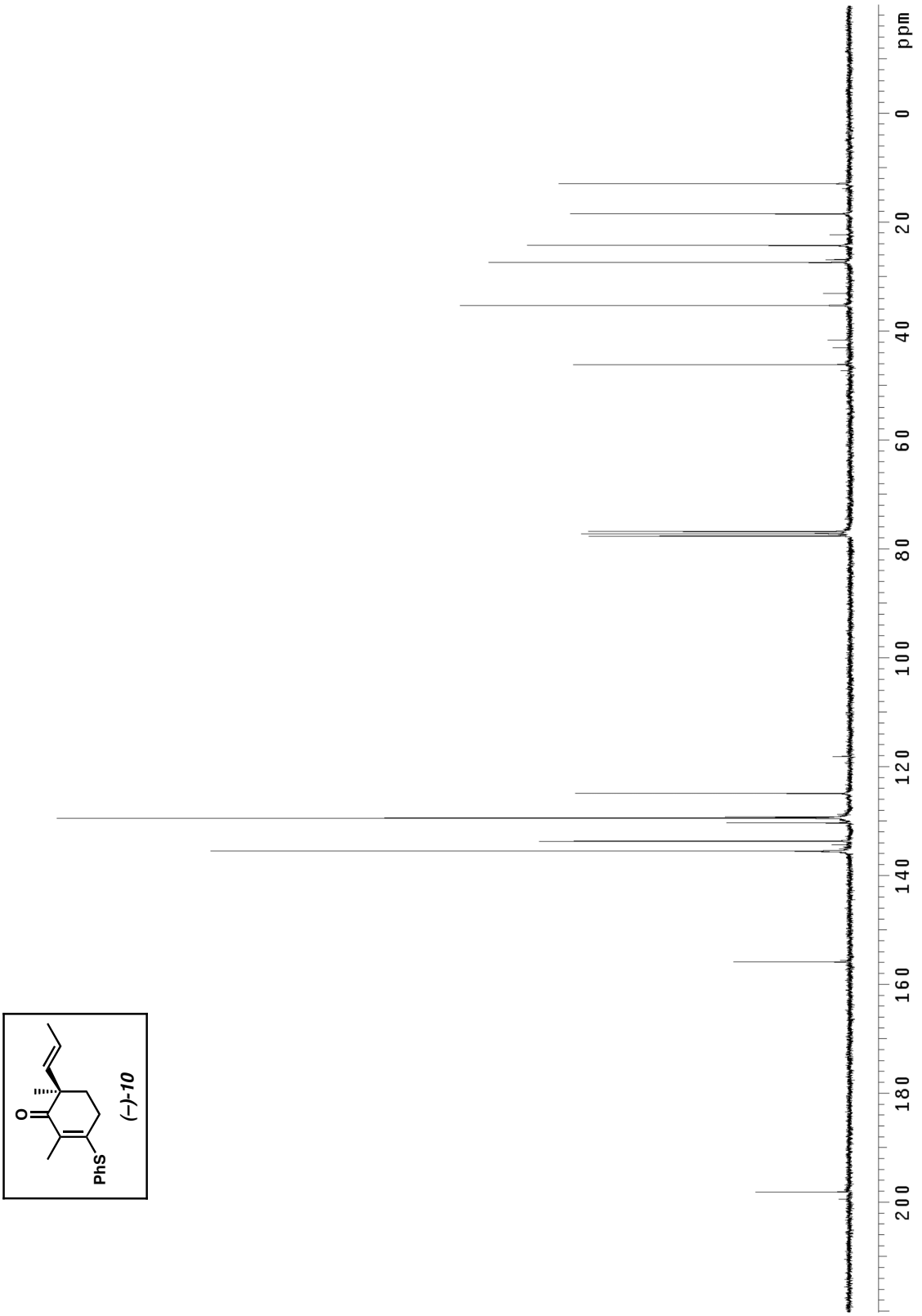
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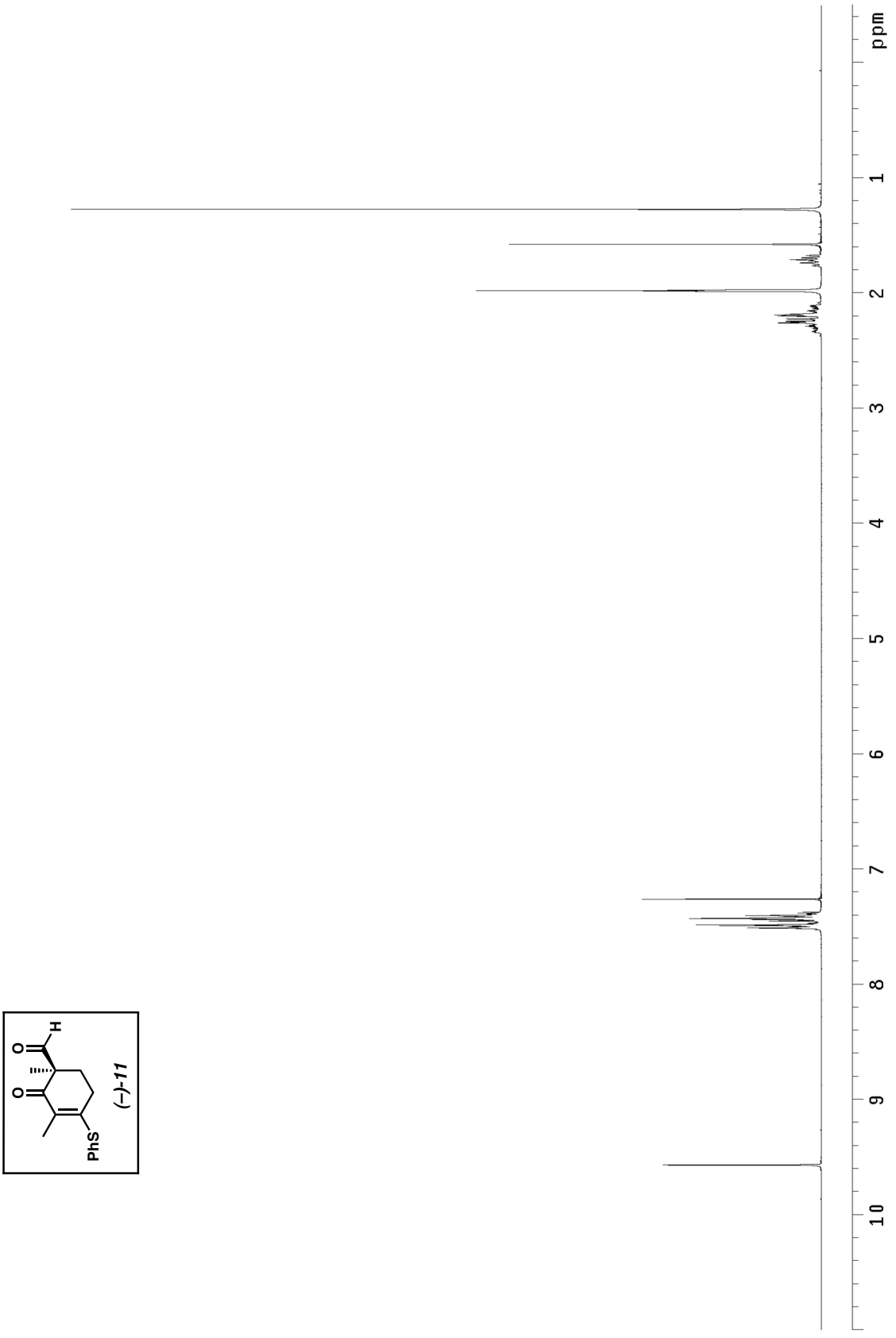
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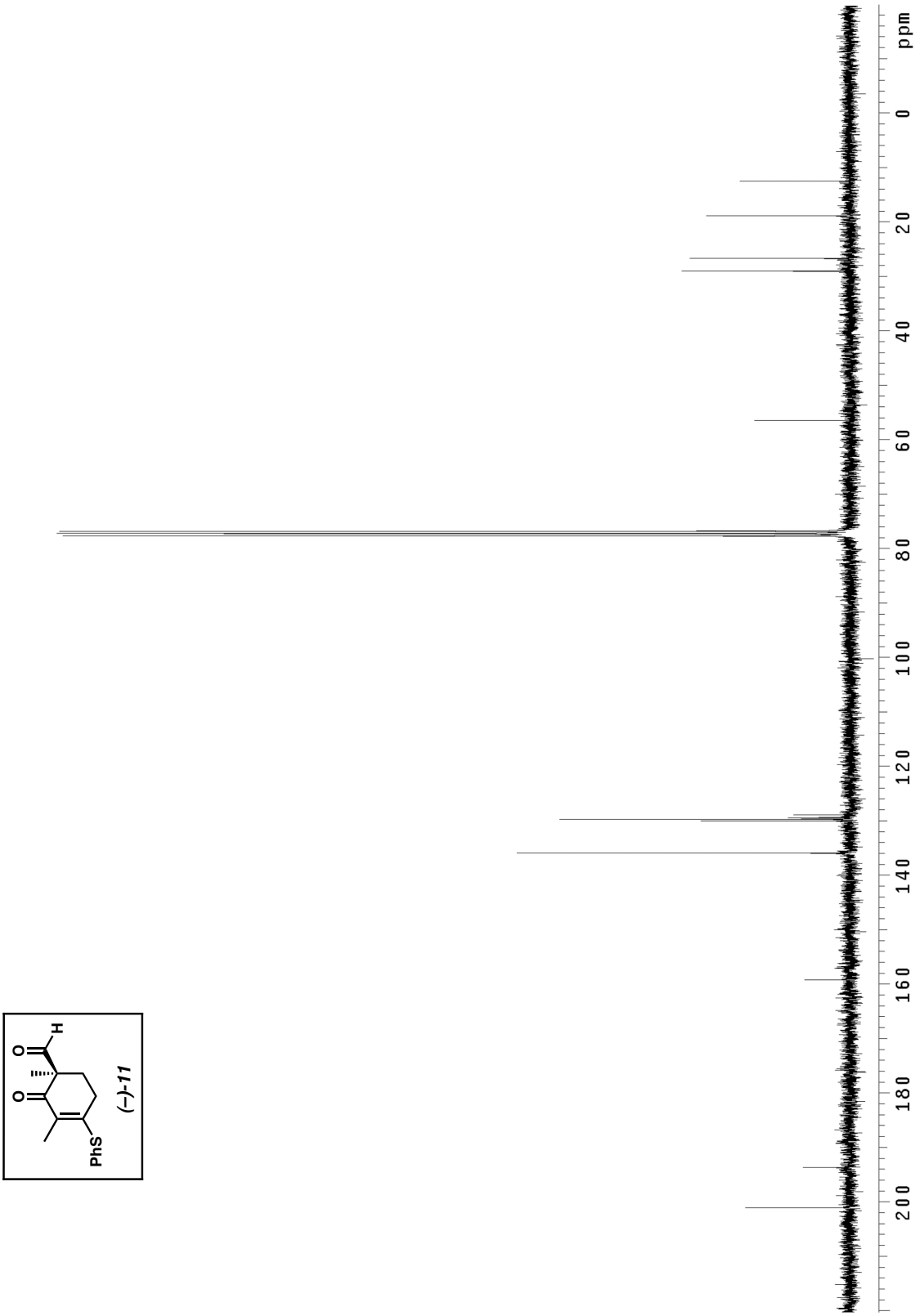
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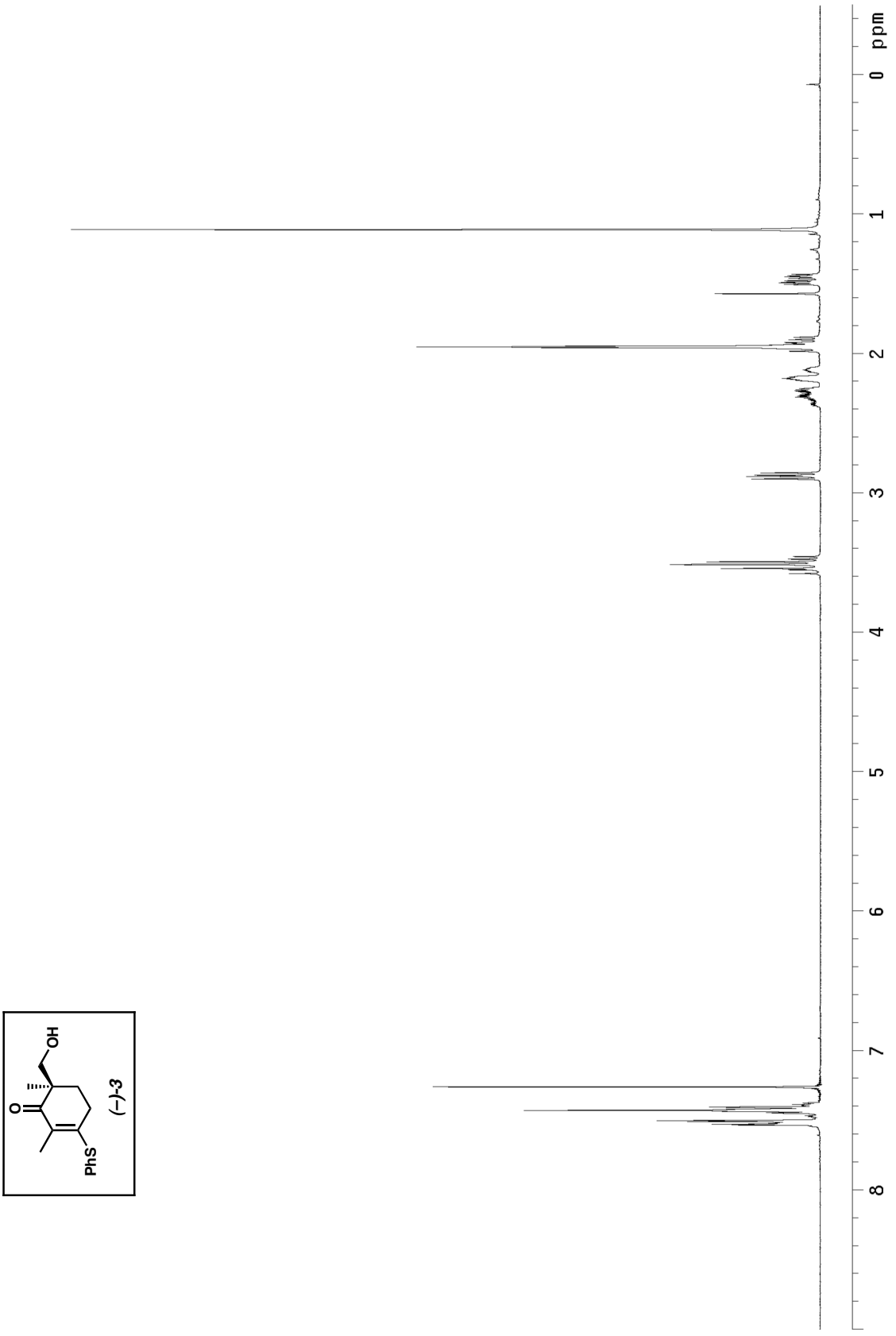
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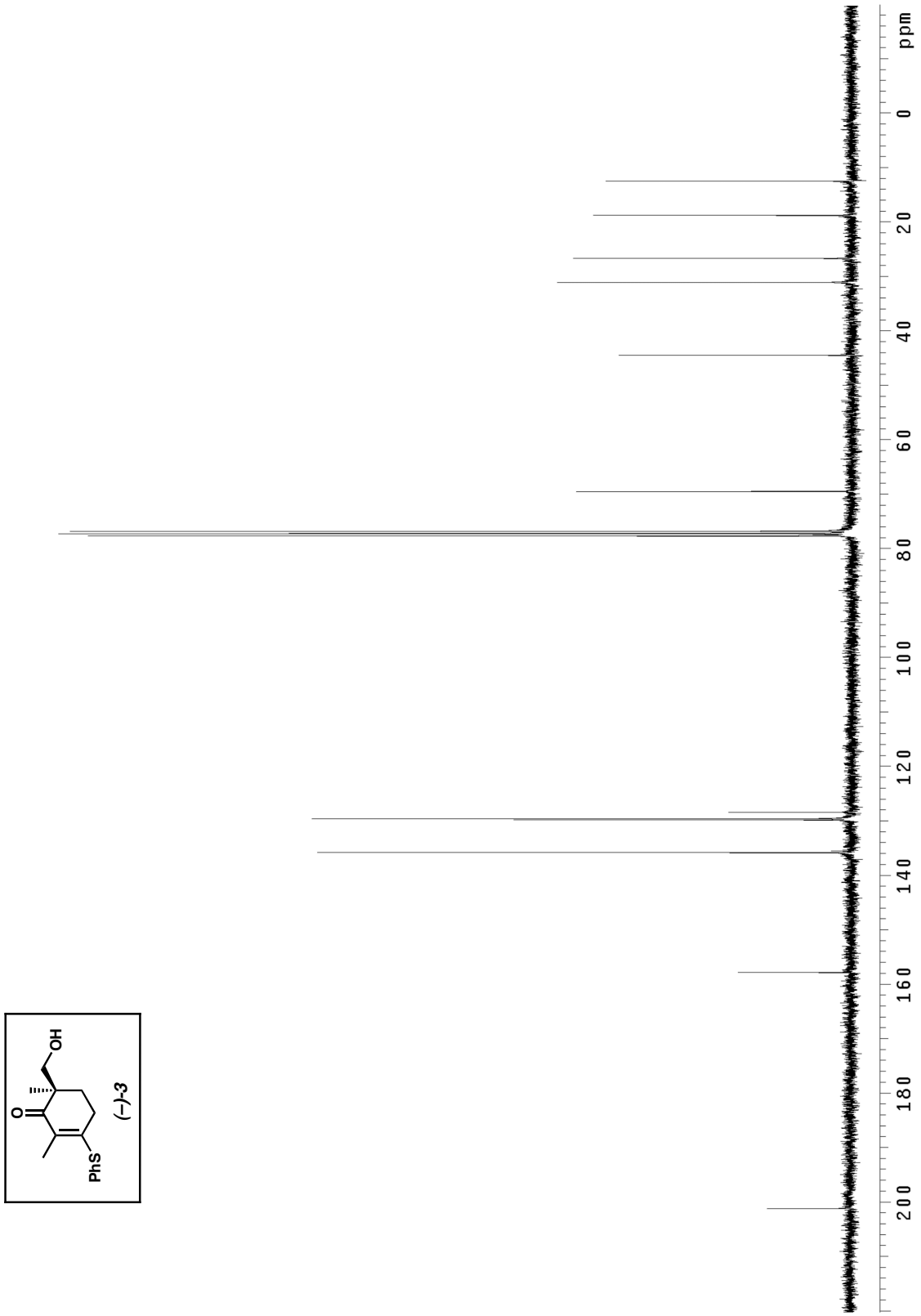
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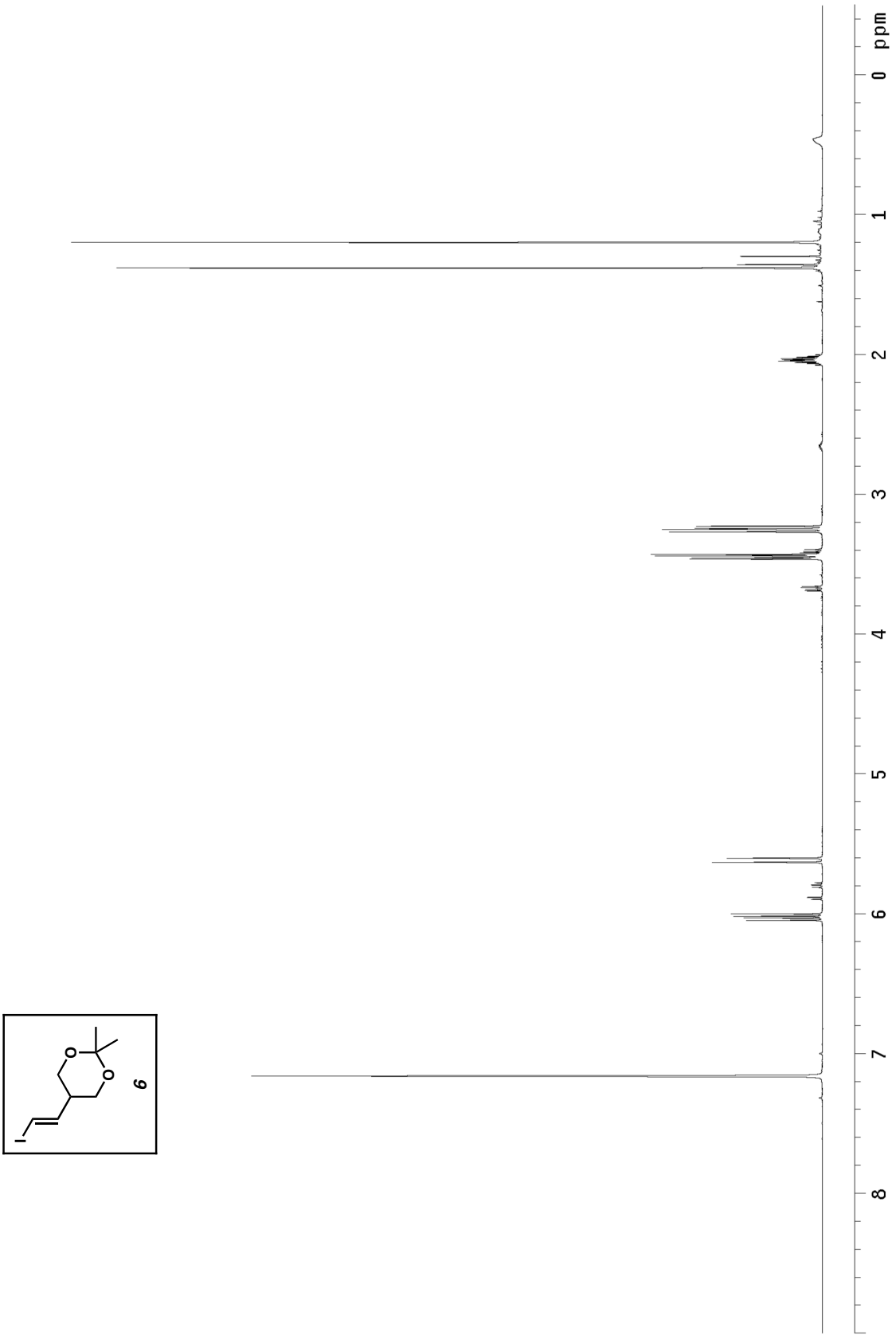
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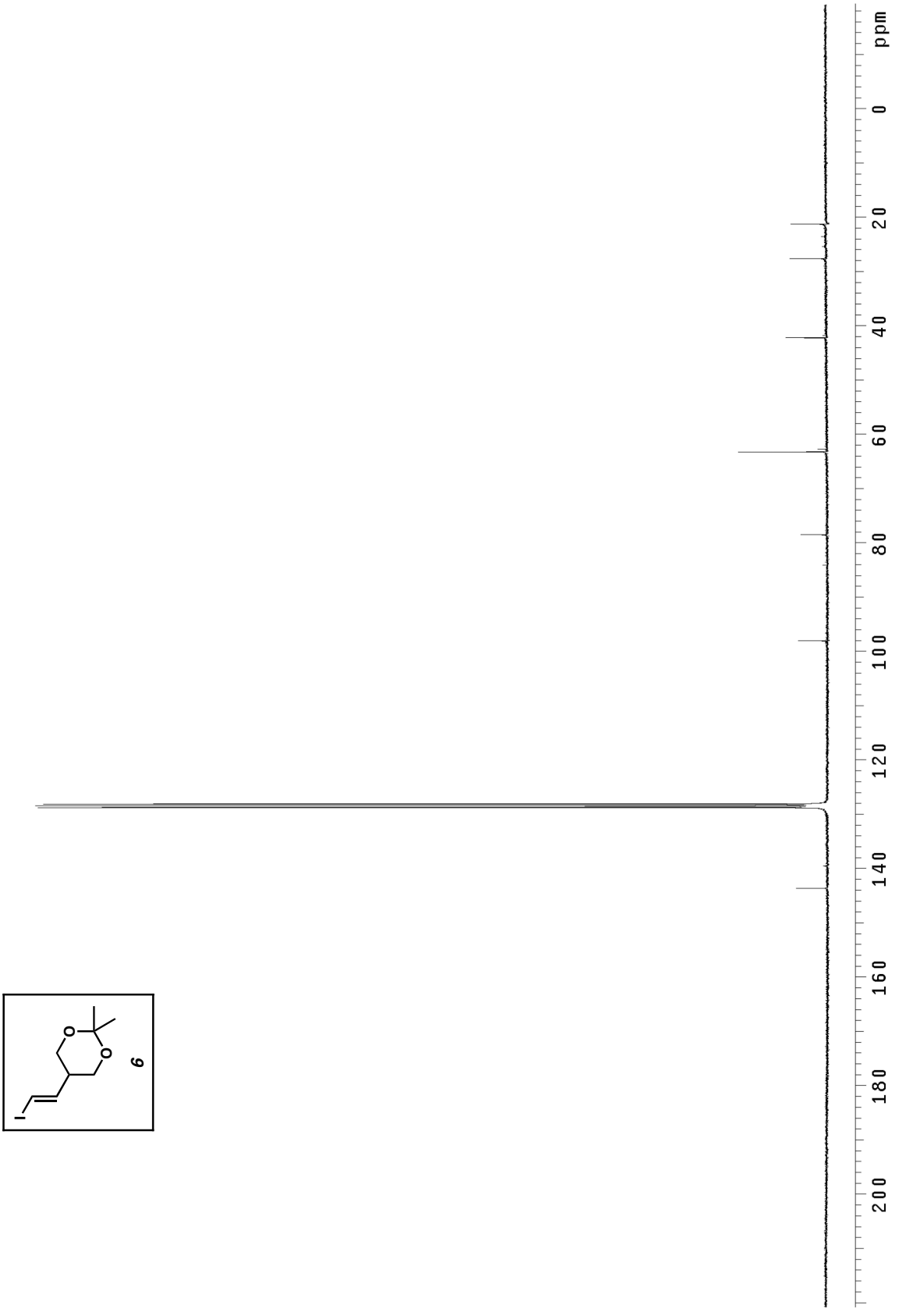
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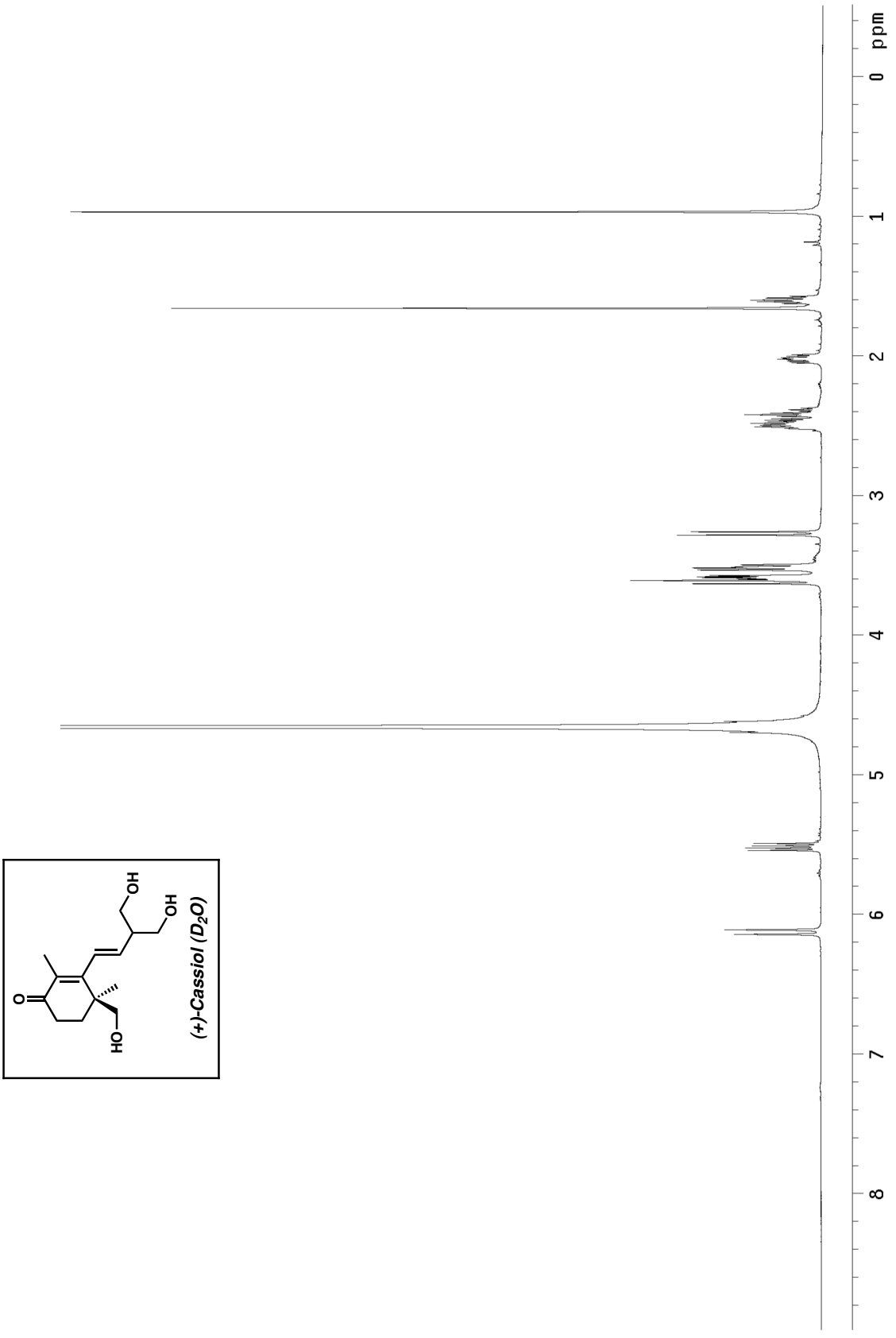
O
9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O
HO
(+)-Cassiol (D_2O)
ppm
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7
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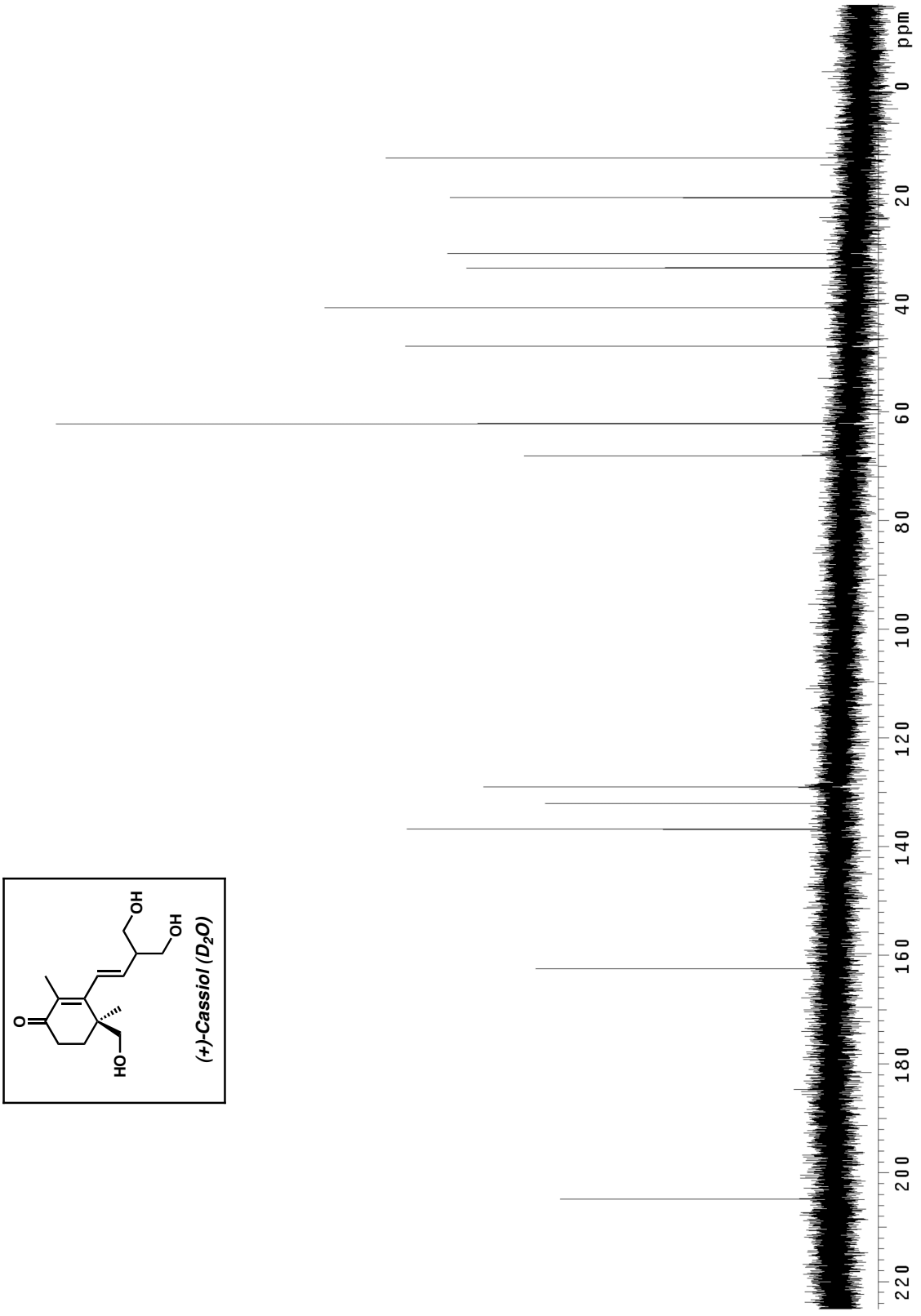
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HO
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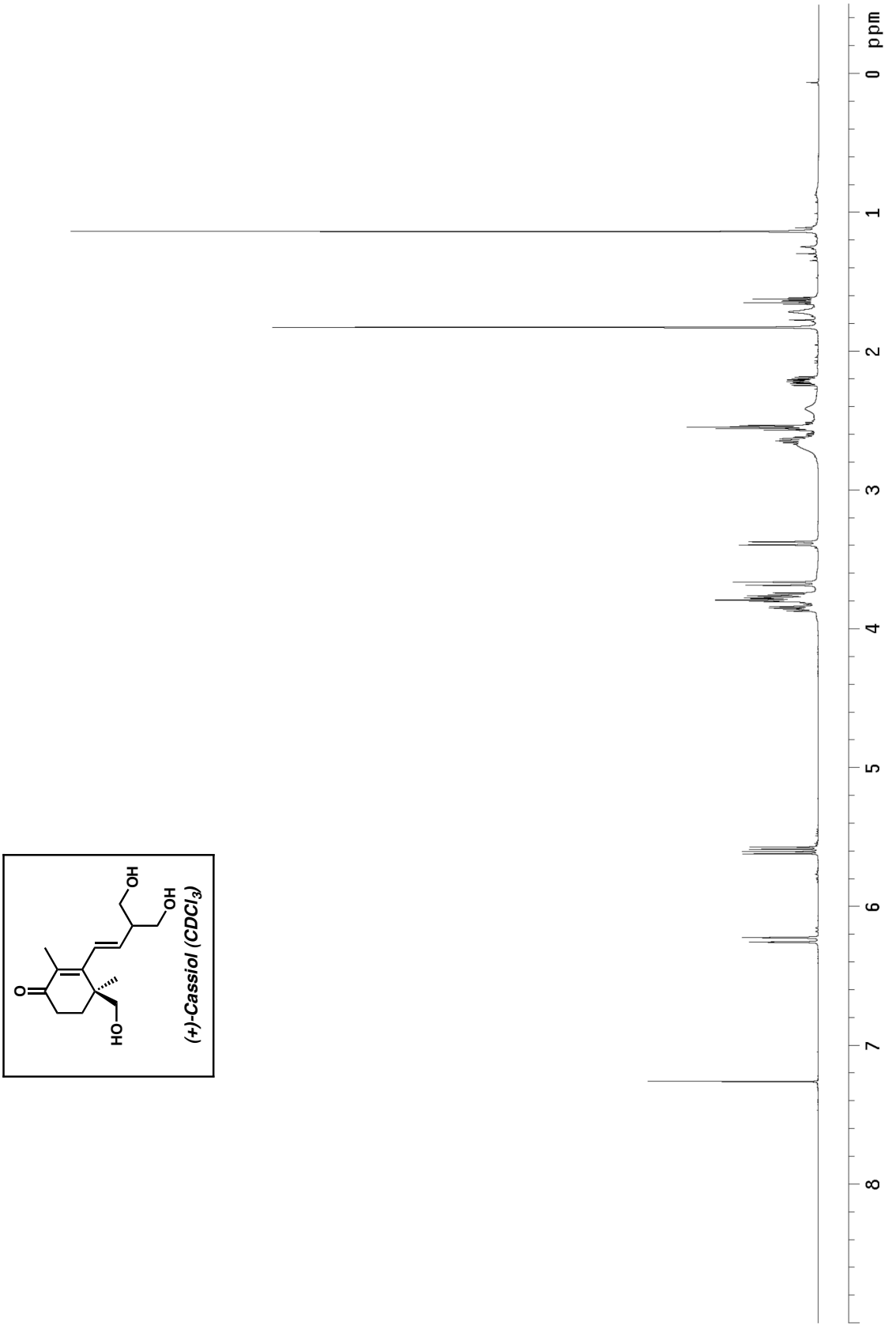
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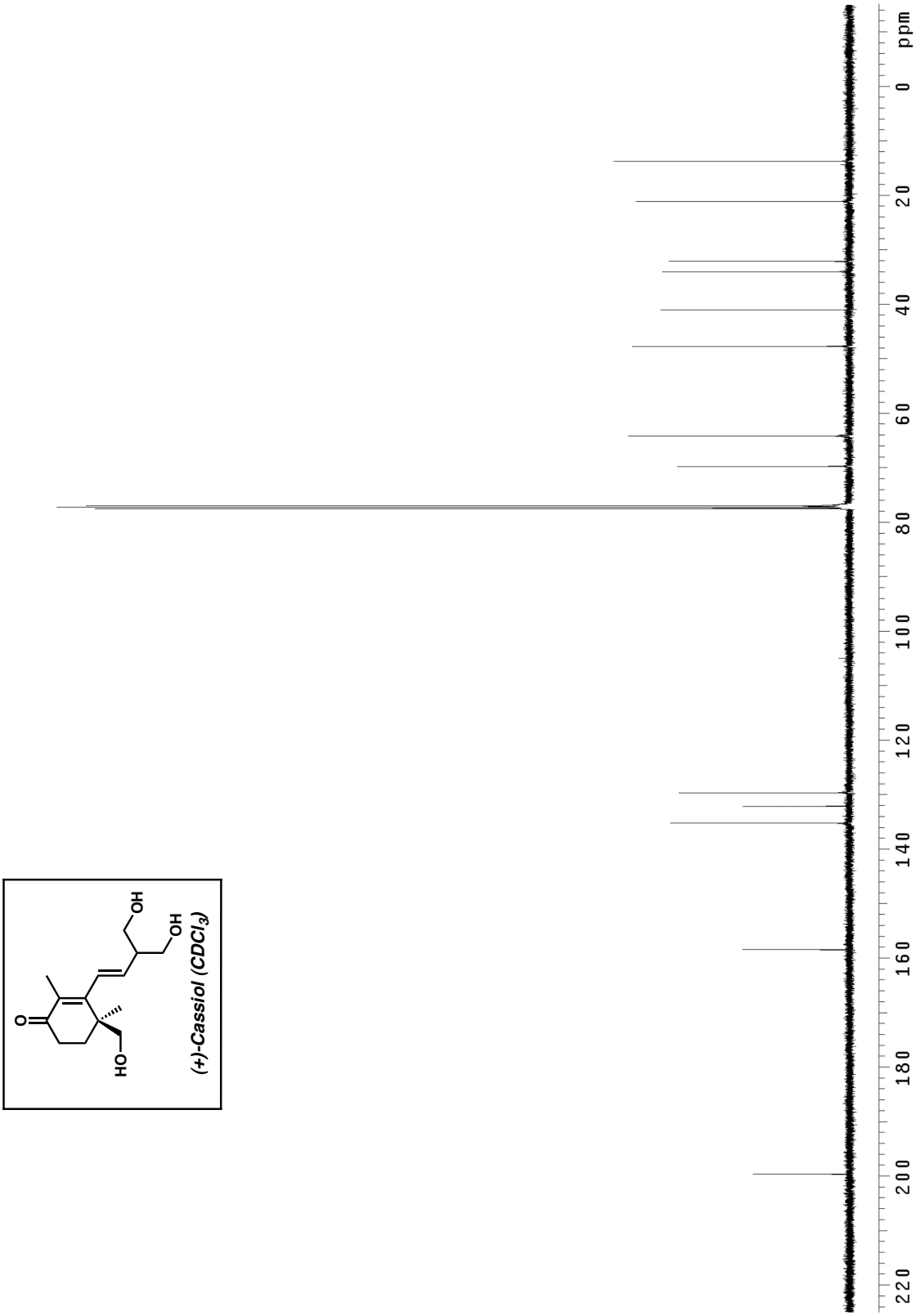
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OH
O
HO
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180
200
220

References:

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