

## Catalytic Enantioselective Approach to the Eudesmane Sesquiterpenoids: Total Synthesis of (+)-Carissone

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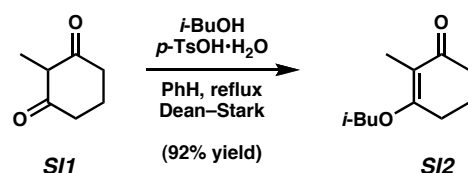
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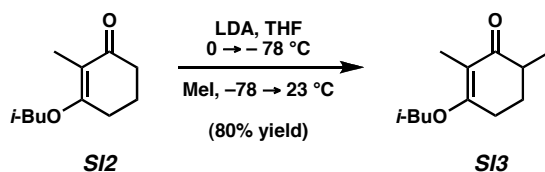
**Materials and Methods.** Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. All the starting materials were purchased from commercial sources and used as received, unless otherwise stated. Liquids and solutions were transferred via syringe or positive-pressure cannula. Brine solutions refer to saturated aqueous sodium chloride solutions. TMEDA was distilled from sodium under nitrogen prior to use. Benzenethiol was distilled under nitrogen prior to use. Previously reported methods were used to prepare (*S*)-*t*-BuPHOX ((*S*)-**12**) and (*R*)-*t*-BuPHOX ((*R*)-**12**),<sup>1</sup> as well as Pd<sub>2</sub>(pmdba)<sub>3</sub>.<sup>2</sup> Grubbs' catalyst **18** was a generous gift from Materia, Inc. Rhodium was purchased from Strem as a 1 wt % loading on alumina powder in reduced form. Diazomethane was freshly prepared from Diazald<sup>®</sup> as a solution in Et<sub>2</sub>O. Manganese dioxide was purchased from Aldrich in activated form, ~85%, <5 μm, and used as received. Reaction temperatures were controlled by an IKA<sup>®</sup> Mag 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<sub>4</sub> staining. SiliCycle<sup>®</sup> SiliaFlash<sup>®</sup> P60 Academic Silica Gel (particle size 40-63 μm; pore diameter 60 Å) was 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 1 mL/min flow rate and visualization at 254 nm. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 2 mL/min flow rate at 30 °C and visualization at 244 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm in spectrophotometric grade solvents. <sup>1</sup>H and <sup>13</sup>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 126 MHz, respectively), and are reported relative to Me<sub>4</sub>Si (δ 0.0 ppm).<sup>3</sup> Data for <sup>1</sup>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. On occasion, an artifact appears in

the  $^{13}\text{C}$  NMR spectra (126 MHz) with negative phasing at  $\delta$  44.9 ppm ( $\text{CDCl}_3$ ) or  $\delta$  45.2 ppm ( $\text{C}_6\text{D}_6$ ). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption ( $\text{cm}^{-1}$ ). Melting points are uncorrected. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

## Experimental Procedures and Tabulated Spectroscopic Data

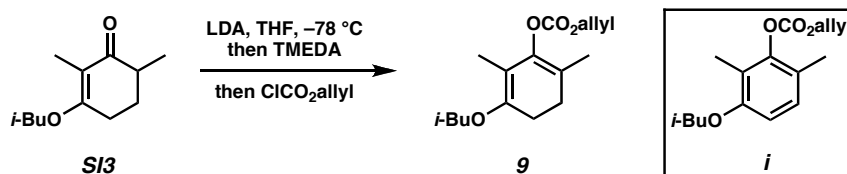


**Vinylogous Ester SI2.**<sup>4</sup> Diketone **SI1** (3.000 g, 23.78 mmol, 1.0 equiv) was partially dissolved in PhH (42.5 mL, 0.56 M), and *i*-BuOH (12.75 mL, 137.9 mmol, 5.8 equiv) and *p*-TsOH $\cdot$ H<sub>2</sub>O (226 mg, 1.19 mmol, 0.05 equiv) were added with vigorous stirring. The flask was affixed with a Dean–Stark adapter and a water-cooled condenser and warmed to reflux in a 104 °C oil bath. Upon consumption of **SI1** by TLC analysis (ca. 3.5 h), the reaction was cooled to ambient temperature, diluted with Et<sub>2</sub>O (50 mL), and poured into saturated aq NaHCO<sub>3</sub> (20 mL). The layers were separated and the aqueous was extracted with Et<sub>2</sub>O (3 x 15 mL). The organics were combined, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to afford a pale brown oil. To this oil was added PhMe (ca. 10 mL) followed by further concentration *in vacuo*. Purification by bulb-to-bulb distillation yielded vinylogous ester **SI2** (3.988 g, 21.88 mmol, 92% yield) as a clear, colorless oil.  $R_f$  = 0.48 (2:1 EtOAc-hexanes); bp = 135–140 °C at 0.8 torr;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.76 (d,  $J$  = 6.5 Hz, 2H), 2.54 (ddd,  $J$  = 6.1, 1.5, 1.5 Hz, 2H), 2.34 (t,  $J$  = 7.1 Hz, 2H), 2.08–1.90 (comp m, 3H), 1.72 (app t,  $J$  = 1.5 Hz, 3H), 0.99 (d,  $J$  = 6.7 Hz, 6H). All other data were consistent with reported values.



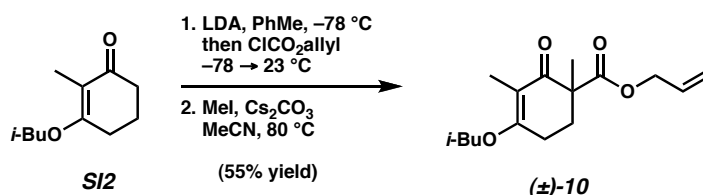
**Methyl Vinylogous Ester SI3.**<sup>4</sup> To a solution of *i*-Pr<sub>2</sub>NH (1.12 mL, 7.99 mmol, 1.9 equiv) in THF (26 mL, 0.15 M) at 0 °C was added dropwise a solution of *n*-BuLi (2.55 M in hexanes, 3.06 mL, 7.80 mmol, 1.85 equiv). After 15 min, a solution of vinylogous ester **SI2** (765.2 mg, 4.198 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise via cannula transfer. The resulting solution was cooled to –78 °C and stirred for 45 min, to which a solution of MeI (485  $\mu\text{L}$ , 7.80 mmol, 1.85 equiv) in THF (5.0 mL) was added over 30 min via positive-pressure cannula transfer. The cooling bath was allowed to expire over ca. 4 h and the reaction was quenched with brine (15 mL). The phases were separated and the aqueous phase was extracted with hexanes (3 x 25 mL). The combined organics were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to a yellow oil. Purification by flash chromatography (4:1  $\rightarrow$  2:1 hexanes-Et<sub>2</sub>O) afforded methyl vinylogous ester **SI3** (659 mg, 3.36 mmol, 80% yield) as a

pale yellow oil.  $R_f = 0.48$  (2:1 hexanes-EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.73 (ddd,  $J = 15.6, 9.2, 6.5$  Hz, 2H), 2.61 (ddd,  $J = 17.3, 5.3, 1.2$  Hz, 1H), 2.55-2.44 (m, 1H), 2.35-2.19 (m, 1H), 2.06 (app dq,  $J = 8.3, 4.8$  Hz, 1H), 1.98 (app septet,  $J = 6.6$  Hz, 1H), 1.71 (dd,  $J = 1.6, 1.6$  Hz, 3H), 1.73-1.60 (m, 1H), 1.14 (d,  $J = 6.9$  Hz, 3H), 0.99 (d,  $J = 6.7$  Hz, 6H). All other data are consistent with reported values.



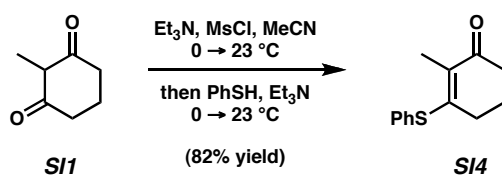
**Enol Carbonate 9.** To a solution of *i*-Pr<sub>2</sub>NH (1.56 mL, 11.15 mmol, 1.2 equiv) in THF (85 mL, 0.11 M) at 0 °C was added a solution of *n*-BuLi (2.55 M in hexanes, 4.0 mL, 10.22 mmol, 1.1 equiv) dropwise. The reaction mixture was allowed to stir for 30 min and then cooled to  $-78^\circ\text{C}$ . A solution of ketone **SI3** (1.824 g, 9.29 mmol, 1.0 equiv) in THF (10 mL) was added dropwise via cannula and stirred for 1 h. TMEDA (1.67 mL, 11.15 mmol, 1.2 equiv) was then added via syringe and the resulting solution stirred for 75 min. To this solution allyl chloroformate (1.08 mL, 10.13 mmol, 1.09 equiv) was added via syringe and the reaction mixture was stirred at  $-78^\circ\text{C}$  for an additional hour. The reaction was quenched with saturated aq NaHCO<sub>3</sub> (40 mL) and H<sub>2</sub>O (40 mL), and the flask was transferred to a 23 °C water bath and allowed to equilibrate. The phases were separated and the aqueous was extracted with Et<sub>2</sub>O (2 x 200 mL). The combined organics were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to afford enol carbonate **9** as a yellow oil (2.472 g);  $^1\text{H}$  NMR analysis shows **9** is the major product with other impurities present.  $R_f = \text{unstable to SiO}_2$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.97 (dddd,  $J = 16.4, 10.8, 5.8, 5.8$  Hz, 1H), 5.42 (app d,  $J = 17.2$  Hz, 1H), 5.33 (app d,  $J = 10.4$  Hz, 1H), 4.72 (dd,  $J = 5.7, 0.8$  Hz, 2H), 3.86 (d,  $J = 6.7$  Hz, 2H), 2.85 (app t,  $J = 7.9$  Hz, 2H), 2.52 (app t,  $J = 7.9$  Hz, 2H), 2.19 (s, 3H), 1.92 (app septuplet,  $J = 6.7$  Hz, 1H), 1.82 (s, 3H), 0.93 (d,  $J = 6.7$  Hz, 6H); IR (Neat Film NaCl) 2963, 1760, 1736, 1699, 1361, 1248, 1170, 990  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$ : calc'd for C<sub>13</sub>H<sub>19</sub>O<sub>4</sub> [M – C<sub>3</sub>H<sub>5</sub>]<sup>+</sup>: 239.1283, found 239.1273.

This material was unstable to various purification attempts (distillation or flash chromatography using silica gel or Florisil) and storage. Aromatic carbonate **i** was identified as a colorless oil from this complex mixture.  $R_f = 0.51$  (4:1 hexanes-EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.97 (d,  $J = 8.4$  Hz, 1H), 6.65 (d,  $J = 8.4$  Hz, 1H), 6.00 (dddd,  $J = 17.1, 10.5, 5.7, 5.7$  Hz, 1H), 5.43 (dddd,  $J = 17.2, 1.4, 1.4, 1.4$  Hz, 1H), 5.33 (dddd,  $J = 10.5, 1.2, 1.2, 1.2$  Hz, 1H), 4.75 (app dt,  $J = 5.8, 1.3$  Hz, 2H), 3.70 (d,  $J = 6.4$  Hz, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 2.09 (app septuplet,  $J = 6.6$  Hz, 1H), 1.03 (d,  $J = 6.7$  Hz, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.3, 153.0, 148.7, 131.4, 127.7, 121.8, 119.5, 119.4, 109.1, 74.9, 69.2, 28.6, 19.5, 15.7, 9.2; IR (Neat Film NaCl) 2960, 2874, 1762, 1620, 1494, 1470, 1365, 1244, 1202, 1172, 1115, 1048, 799  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$ : calc'd for C<sub>16</sub>H<sub>22</sub>O<sub>4</sub> [M]<sup>+</sup>: 278.1518, found 278.1517.

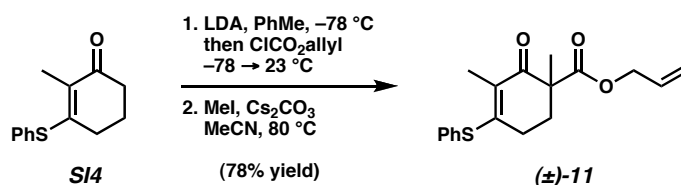


**(±)-β-Ketoester 10.** To a  $-78\text{ }^{\circ}\text{C}$  solution of  $i\text{-Pr}_2\text{NH}$  (425  $\mu\text{L}$ , 3.03 mmol, 1.9 equiv) in PhMe (10 mL) was added dropwise  $n\text{-BuLi}$  (2.55 M in hexanes, 1.16 mL, 2.96 mmol, 1.85 equiv). The reaction vessel was placed in an ice/water bath and allowed to stir for 10 min, and then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of vinylogous ester **SI2** (291 mg, 1.60 mmol, 1.0 equiv) in PhMe (1.4 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (173  $\mu\text{L}$ , 1.63 mmol, 1.02 equiv) was added dropwise, and the reaction vessel was allowed to warm to  $23\text{ }^{\circ}\text{C}$  over 1 h. After stirring for 4 h, the reaction was slowly quenched with aq  $\text{KHSO}_4$  (1 N, 4 mL) and the resulting biphasic mixture was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with  $\text{Et}_2\text{O}$  (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The isolated crude yellow oil was used in the next step without further purification.

The resulting crude yellow oil was dissolved in MeCN (5.9 mL, 0.27 M), and  $\text{Cs}_2\text{CO}_3$  (603 mg, 1.85 mmol, 1.16 equiv), and MeI (276  $\mu\text{L}$ , 4.44 mmol, 2.8 equiv) were added. The flask was affixed a water-cooled condenser and resulting suspension was warmed to reflux in an  $80\text{ }^{\circ}\text{C}$  oil bath with vigorous stirring. After 10 h, the reaction was cooled to room temperature, diluted with EtOAc (25 mL). The organics were dried with  $\text{MgSO}_4$ , filtered, and the solvent was evaporated *in vacuo*. Purification by flash chromatography (15:1  $\rightarrow$  9:1  $\rightarrow$  4:1 hexanes-EtOAc) afforded  $\beta$ -ketoester (±)-**10** as pale yellow oil (246 mg, 55% yield over two steps).  $R_f = 0.27$  (2:1 hexanes-EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.82 (dddd,  $J = 17.2, 10.7, 5.4, 5.4\text{ Hz}$ , 1H), 5.22 (dddd,  $J = 17.2, 1.6, 1.6, 1.6\text{ Hz}$ , 1H), 5.15 (dddd,  $J = 10.5, 1.2, 1.2, 1.2\text{ Hz}$ , 1H), 4.56 (dddd,  $J = 13.5, 5.4, 1.5, 1.5\text{ Hz}$ , 2H), 3.72 (ddd,  $J = 9.2, 6.6, 3.2\text{ Hz}$ , 2H), 2.69-2.62 (m, 1H), 2.53-2.44 (comp m, 2H), 1.95 (app septuplet,  $J = 6.6\text{ Hz}$ , 1H), 1.85-1.80 (m, 1H), 1.70 (dd,  $J = 1.5, 1.5\text{ Hz}$ , 3H), 1.36 (s, 3H), 0.95 (dd,  $J = 6.7, 0.8\text{ Hz}$ , 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.8, 172.6, 170.3, 131.9, 117.8, 113.8, 73.9, 65.5, 51.6, 31.2, 28.8, 23.0, 20.8, 19.1, 19.0, 8.0; IR (Neat Film NaCl) 2961, 2935, 2875, 1733, 1649, 1618, 1460, 1382, 1354, 1237, 1176, 1103, 983  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$ : calc'd for  $\text{C}_{16}\text{H}_{25}\text{O}_4$   $[\text{M} + \text{H}]^+$ : 281.1753, found 281.1740.

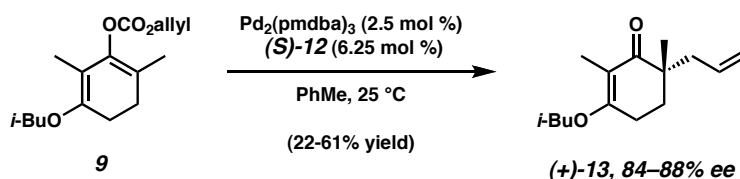


**Vinylogous Thioester SI4.**<sup>5</sup> To a solution of diketone **SI1** (2.500 g, 19.82 mmol, 1.0 equiv) in MeCN (22.0 mL, 0.9 M) was added  $\text{Et}_3\text{N}$  (3.1 mL, 22.2 mmol, 1.12 equiv), and the solution was allowed to stir for 5 min, then cooled to  $0\text{ }^{\circ}\text{C}$ . Methanesulfonyl chloride (1.63 mL, 21.0 mmol, 1.06 equiv) was added, and the reaction was warmed to  $23\text{ }^{\circ}\text{C}$  over 2 h. Stirring was continued for 5 h, and the reaction was cooled to  $0\text{ }^{\circ}\text{C}$ . Triethylamine (3.1 mL, 22.2 mmol, 1.12 equiv) was added, followed by benzenethiol (2.1 mL, 20.4 mmol, 1.03 equiv). The reaction was allowed to warm to  $23\text{ }^{\circ}\text{C}$  over 2 h and stirring was continued for 9 h. Saturated aq  $\text{Na}_2\text{CO}_3$  (35 mL) was added, the phases were separated, and the aq phase was extracted with  $\text{Et}_2\text{O}$  (3 x 60 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was evaporated *in vacuo*. Purification by flash chromatography (4:1 to 2:1 hexanes- $\text{Et}_2\text{O}$ ) afforded vinylogous thioester **SI4** as a white crystalline solid (3.565 g, 16.33 mmol, 82% yield).  $R_f = 0.34$  (1:1 hexanes- $\text{Et}_2\text{O}$ ); mp  $85\text{ }^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51-7.49 (m, 2H), 7.44-7.37 (comp m, 3H), 2.38 (t,  $J = 6.5\text{ Hz}$ , 2H), 2.18 (tq,  $J = 6.5, 2.0\text{ Hz}$ , 2H), 1.97 (t,  $J = 2.0\text{ Hz}$ , 3H), 1.87 (app pentuplet,  $J = 6.0\text{ Hz}$ , 2H). All other data are consistent with reported values.



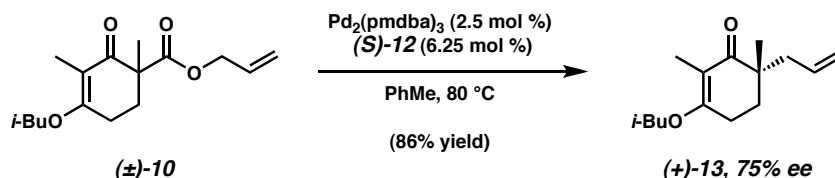
**β-Ketoester (±)-11.** To a  $-78^\circ\text{C}$  solution of *i*-Pr<sub>2</sub>NH (2.63 mL, 18.78 mmol, 2.00 equiv) in PhMe (70 mL) was added dropwise *n*-BuLi (2.53 M in hexanes, 7.24 mL, 2.00 equiv). The reaction vessel was warmed to  $0^\circ\text{C}$ , allowed to stir for 10 min, and cooled to  $-78^\circ\text{C}$ . A solution of vinylogous thioester **SI4** (2.00 g, 9.16 mmol, 1.00 equiv) in PhMe (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  $23^\circ\text{C}$  over 1 h. Stirring was continued for 4 h, then aq KHSO<sub>4</sub> (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<sub>2</sub>O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, 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<sub>3</sub>CN (40 mL) was added cesium carbonate (4.48 g, 13.74 mmol, 1.50 equiv), and MeI (1.71 mL, 27.48 mmol, 3.00 equiv). The resulting suspension was refluxed at  $80^\circ\text{C}$  for 5 h, and then MeI (1.00 mL, 16.06 mmol, 1.75 equiv) was added. The reaction was refluxed at  $80^\circ\text{C}$  for 2 h, cooled to room temperature, filtered through Celite (EtOAc eluent), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was evaporated *in vacuo*. Purification by flash chromatography (18% EtOAc in hexanes) afforded β-ketoester (±)-**11** as a colorless oil that solidifies to a white solid over time or in a  $-20^\circ\text{C}$  freezer (2.26 g, 78% yield over two steps).  $R_f = 0.35$  (30% EtOAc in hexanes); mp  $34^\circ\text{C}$ ; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>; HRMS (FAB+)  $m/z$ : calc'd for C<sub>18</sub>H<sub>20</sub>O<sub>3</sub>S [M + H]<sup>+</sup>: 317.1211, found 317.1211.

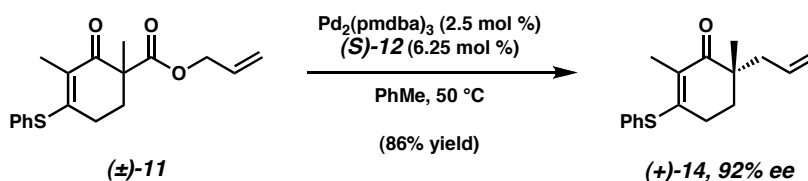


**Ketone (+)-13 from enol carbonate 9.** A 1-dram vial containing a stirbar was charged with Pd<sub>2</sub>(pmdba)<sub>3</sub> (4.9 mg, 0.0045 mmol, 0.025 equiv) and (S)-**12** (4.4 mg, 0.0112 mmol, 0.0625 equiv), sealed with a septum, and the atmosphere was purged by three evacuate/purge cycles. To this was added PhMe (0.9 mL) and the complexation was stirred for 30 min in a  $25^\circ\text{C}$  oil bath, upon which time a solution of enol carbonate **9** (50.2 mg, 0.179 mmol, 1.0 equiv) in PhMe (0.9 mL, 0.1 M total) was added via cannula. After 21.5 h at  $25^\circ\text{C}$ , the reaction was diluted with Et<sub>2</sub>O (2 mL), filtered through a

SiO<sub>2</sub> plug, and concentrated in vacuo. The filtrate was purified by flash chromatography on SiO<sub>2</sub> (15:1 → 4:1 hexanes-EtOAc) to afford ketone (+)-**13** as a pale yellow oil (22–61% yield, 84–88% ee). *R*<sub>f</sub> = 0.49 (4:1 hexanes-EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.73 (dddd, *J* = 16.6, 10.6, 7.4, 7.4 Hz, 1H), 5.06–5.04 (m, 1H), 5.04–5.01 (m, 1H), 3.74 (dd, *J* = 9.7, 6.7 Hz, 2H), 2.59–2.47 (comp m, 2H), 2.33 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.16 (dddd, *J* = 13.7, 7.6, 1.0, 1.0 Hz, 1H), 1.98 (app septuplet, *J* = 6.6 Hz, 1H), 1.90 (ddd, *J* = 13.3, 7.2, 5.7 Hz, 1H), 1.72–1.67 (m, 1H), 1.70 (dd, *J* = 1.6, 1.6 Hz, 3H), 1.06 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 6H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 202.7, 169.5, 134.8, 117.8, 113.3, 73.8, 42.5, 41.9, 31.5, 29.0, 22.5, 22.4, 19.2, 8.0; IR (Neat Film NaCl) 3076, 2962, 2931, 1622, 1463, 1381, 1355, 1229, 1113, 1002, 915 cm<sup>-1</sup>; HRMS (EI+) *m/z*: calc'd for C<sub>15</sub>H<sub>24</sub>O<sub>2</sub> [M]<sup>+</sup>: 236.1776, found 236.1771; [α]<sub>D</sub><sup>21.2</sup> +13.2° (*c* 0.20, CH<sub>2</sub>Cl<sub>2</sub>, 88% ee). SFC conditions: 5% IPA, AD column, *t*<sub>R</sub> (min): major = 5.18, minor = 6.02; see graphical HPLC data on page SI 13 and SI 14.

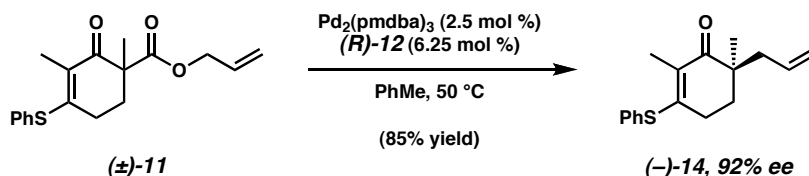


**Ketone (+)-13 from β-ketoester (±)-10.** A 2-dram vial containing a stir bar was charged with Pd<sub>2</sub>(pmdba)<sub>3</sub> (10.6 mg, 0.00968 mmol, 0.025 equiv) and (S)-**12** (9.4 mg, 0.0242 mmol, 0.0625 equiv). This was connected to a 1-dram vial containing a stirbar and β-ketoester (±)-**10** (108.6 mg, 0.387 mmol, 1.0 equiv) via a cannula, and PhMe (3.9 mL, 0.1 M) was added to the vial containing the Pd/L and immediately immersed in liquid N<sub>2</sub>. The vials were rigorously degassed by three freeze-pump-thaw cycles and warmed to 23 °C. After complexation for 30 min (purple → orange color change), the catalyst solution was transferred to the substrate via cannula and immersed in an 80 °C oil bath. The reaction immediately turned yellow in color. After 23 h the reaction was cooled to ambient temperature, diluted with Et<sub>2</sub>O (4 mL), and filtered through a small SiO<sub>2</sub> plug. The filtrate was concentrated and purified by flash chromatography as above to afford ketone (+)-**13** as a colorless oil (78.5 mg, 0.332 mmol, 86% yield, 75% ee).

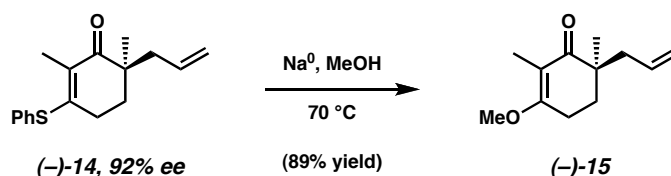


**Ketone (+)-14 from β-ketoester (±)-11.** The reaction was performed exactly as described for enol carbonate **9** using β-ketoester (±)-**11** (41.8 mg, 0.132 mmol, 1.0 equiv). After complexation of the metal for 30 min at 25 °C, a solution of the substrate was added and the reaction was warmed to 50 °C in an oil bath. After 23 h, the reaction was cooled to room temperature, diluted with Et<sub>2</sub>O, and filtered through a SiO<sub>2</sub> plug. The filtrate was concentrated and purified by flash chromatography (15:1 → 9:1 hexanes-EtOAc) to afford ketone (+)-**14** as a colorless oil (31.0 mg, 0.114 mmol, 86% yield, 92% ee). *R*<sub>f</sub> = 0.35 (9:1 hexanes-EtOAc); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.52–7.48 (m, 2H), 7.43–7.35 (comp m, 3H), 5.68 (dddd, *J* = 16.6, 10.4, 7.6, 7.6 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 (app t, *J* = 1.8 Hz, 3H), 1.81 (ddd, 13.5, 6.4, 6.4 Hz, 1H), 1.66–1.56 (m, 1H), 1.04 (s, 3H); <sup>13</sup>C NMR (75 MHz,

CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>; HRMS (FAB+)  $m/z$ : calc'd for C<sub>17</sub>H<sub>20</sub>OS [M + H]<sup>+</sup>: 273.1313, found 273.1317; [ $\alpha$ ]<sub>D</sub><sup>19.0</sup> +56.7° (*c* 1.36, CH<sub>2</sub>Cl<sub>2</sub>, 92% ee). HPLC conditions: 4% EtOH in hexanes, AD column, *t*<sub>R</sub> (min): major = 7.24, minor = 9.48; see graphical HPLC data on page SI 15 and SI 16.

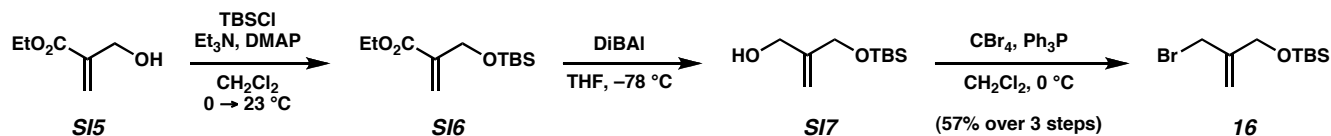


**Scale up of ketone (–)-14 from  $\beta$ -ketoester (±)-11.** In a glove box, a flask containing a stirbar was charged with Pd<sub>2</sub>(pmdba)<sub>3</sub> (493.1 mg, 0.45 mmol, 0.025 equiv) and ligand (*R*)-12 (435.9 mg, 1.125 mmol, 0.0625 equiv). The solids were dissolved in PhMe (150 mL) and stirred for 45 min (purple → orange color change). To this was added a solution of  $\beta$ -ketoester (±)-11 (5.6956 g, 18.00 mmol, 1.0 equiv) in PhMe (30 mL, 0.1 M total). The flask was transferred out of the glove box, placed under an argon atmosphere, and warmed in a 50 °C oil bath (orange → yellow color change). After 66 h, the reaction was cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (as above, dry load onto SiO<sub>2</sub>) afforded ketone (–)-14 as a pale yellow oil (4.184 g, 15.36 mmol, 85% yield, 92% ee) and recovered  $\beta$ -ketoester (±)-11 (500.5 mg, 1.582 mmol, 9% yield). [ $\alpha$ ]<sub>D</sub><sup>25.4</sup> –57.4 (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); see graphical HPLC data on pages SI 15 and SI 17.



**Methoxy vinyllogous ester (–)-15.** A 3-neck flask equipped with water-cooled reflux condenser was charged with dry MeOH (33.7 mL, 0.26 M), cooled in an ice/water bath, hexanes-washed Na<sup>0</sup> (1.047 g, 45.5 mmol, 5.2 equiv) was added and the bath was removed. The contents were stirred at 23 °C until all Na<sup>0</sup> was dissolved. A solution of ketone (–)-14 (2.3991 g, 8.81 mmol, 1.0 equiv) in MeOH (10 mL) was added dropwise via cannula to the generated NaOMe and the resulting solution was heated in an oil bath at 70 °C. Upon consumption of (–)-14 by TLC analysis (4:1 hexanes-EtOAc), the reaction mixture was cooled to ambient temperature and transferred to a separate flask with Et<sub>2</sub>O and concentrated *in vacuo* to a viscous yellow slurry. This was dissolved in saturated aq NaHCO<sub>3</sub> (150 mL), stirred for ca. 20 min, and extracted with Et<sub>2</sub>O (3 x 100 mL). The organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to a yellow oil. Purification by flash chromatography (15:1 → 6:1 hexanes-EtOAc) afforded ketone (–)-15 as a colorless oil that solidifies in a –20 °C freezer to an off-white semi-solid (1.5241 g, 7.845 mmol, 89% yield). *R*<sub>f</sub> = 0.40 (4:1 hexanes-EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  5.74 (dddd, *J* = 16.8, 10.5, 7.5, 7.5 Hz, 1H), 5.07–5.05 (m, 1H), 5.05–5.02 (m, 1H), 3.80 (s, 3H), 2.62–2.49 (comp m, 2H), 2.33 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.17 (dddd, *J* = 13.8, 7.6, 1.0, 1.0 Hz, 1H), 1.92 (ddd, *J* = 13.4, 7.2, 5.8 Hz, 1H), 1.72 (ddd, *J* = 13.4, 6.7, 5.6 Hz, 1H), 1.68 (dd, *J* = 1.6, 1.6 Hz, 3H), 1.06 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  202.6, 169.6, 134.8, 117.9, 113.2, 55.0, 42.5, 41.9, 31.4, 22.4, 21.8, 7.9; IR (Neat

Film NaCl) 2929, 1620, 1461, 1375, 1356, 1234, 1154, 1116, 999, 916  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$ : calc'd for  $\text{C}_{12}\text{H}_{18}\text{O}_2$   $[\text{M}]^+$ : 194.1307, found 194.1310;  $[\alpha]_{\text{D}}^{22.9} -10.6^\circ$  ( $c$  1.26,  $\text{CH}_2\text{Cl}_2$ , 92% ee).

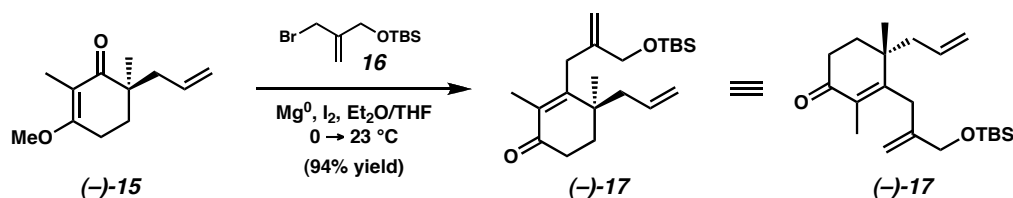


**Acrylate SI6.**<sup>6</sup> To a solution of acrylate **SI5**<sup>7</sup> (4.7012 g, 36.19 mmol, 1.0 equiv) and TBSCl (6.00 g, 39.8 mmol, 1.1 equiv) in  $\text{CH}_2\text{Cl}_2$  (72 mL, 0.5 M) at  $0^\circ\text{C}$  was added  $\text{Et}_3\text{N}$  (15.1 mL, 108.6 mmol, 3.0 equiv) and DMAP (442 mg, 3.62 mmol, 0.1 equiv). The reaction was allowed to stir for 30 min, at which point the cooling bath was removed and the contents warmed to  $23^\circ\text{C}$  and stirred overnight. The reaction mixture was filtered into a separatory funnel and washed with 1N HCl (70 mL), saturated aq  $\text{NaHCO}_3$  (100 mL), and brine (100 mL). The organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to afford ester **SI6** as a colorless oil (8.806 g). The material was used in the next step without purification.  $R_f$  = 0.63 (6:1 hexanes-EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.25 (dd,  $J$  = 2.0, 2.0 Hz, 1H), 5.90 (dd,  $J$  = 2.0, 2.0 Hz, 1H), 4.37 (dd,  $J$  = 2.1, 2.1 Hz, 2H), 4.21 (q,  $J$  = 7.1 Hz, 2H), 1.30 (t,  $J$  = 7.1 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H).

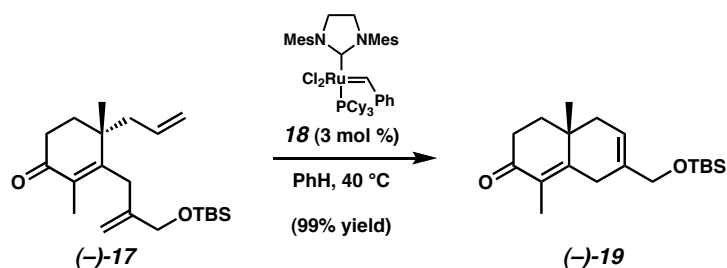
**Allylic Alcohol SI7.**<sup>6</sup> To a solution of crude ester alcohol **SI6** (8.806 g, 36.03 mmol, 1.0 equiv) in THF (144 mL, 0.25 M) cooled to  $-78^\circ\text{C}$  was added dropwise DiBAL (neat, 14.1 mL, 79.3 mmol, 2.2 equiv) over 15 min. The resulting solution was stirred at  $-78^\circ\text{C}$  until complete consumption by TLC analysis (4:1 hexanes-EtOAc), at which point the excess DiBAL was quenched with dry EtOAc (4 mL). The resulting solution was stirred for 10 min at  $-78^\circ\text{C}$ , then warmed to  $0^\circ\text{C}$  and aged for 30 min. A solution of Rochelle's salt (75 mL, 1 M) was then added slowly with vigorous stirring. The cooling bath was removed and the contents were vigorously stirred until two homogeneous layers appeared (several hours). The phases were separated and the aqueous was extracted with  $\text{Et}_2\text{O}$  (3 x 75 mL), the combined organics were washed with brine (2 x 100 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to afford **SI7** as a cloudy colorless oil (7.29 g). The crude material was used in the next reaction without purification.  $R_f$  = 0.19 (4:1 hexanes-EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.10 (s, 1H), 5.08 (s, 1H), 4.24 (s, 2H), 4.17 (d,  $J$  = 5.5 Hz, 2H), 1.95 (t,  $J$  = 6.0 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H).

**Allylic Bromide 16.**<sup>8</sup> To a solution of crude allylic alcohol **SI7** (7.29 g, 36.04 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (120 mL, 0.3 M) cooled to  $0^\circ\text{C}$  was added  $\text{CBr}_4$  (17.942 g, 54.1 mmol, 1.5 equiv) and  $\text{PPh}_3$  (11.331 g, 43.2 mmol, 1.2 equiv). The reaction mixture was stirred at  $0^\circ\text{C}$  until consumption by TLC analysis (4:1 hexanes-EtOAc; required ca. 30 min). The reaction was then quenched slowly with saturated aq  $\text{NaHCO}_3$  (40 mL) and warmed to ambient temperature while stirring. The phases were separated and the aqueous was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to a yellow oil containing a  $\text{Ph}_3\text{PO}$  precipitate. This material was dry loaded on  $\text{SiO}_2$  and purified by flash chromatography (24:1  $\rightarrow$  15:1  $\rightarrow$  3:1 hexanes- $\text{Et}_2\text{O}$ ). Fractions containing the desired product were repurified by flash chromatography on  $\text{SiO}_2$  (49:1  $\rightarrow$  24:1 hexanes-acetone) to afford allylic bromide **16** as a pale yellow oil (5.4251 g, 20.45 mmol, 57% yield over 3 steps).  $R_f$  = 0.48 (24:1 hexanes- $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.26-5.25 (m, 1H), 5.23 (ddd,  $J$  = 1.4, 1.4, 1.4 Hz, 1H), 4.27 (dd,  $J$  = 1.4, 1.4 Hz, 2H), 4.01 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H). All other data are consistent with reported values.



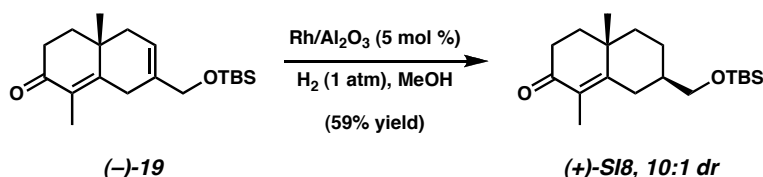


**Triolefin (–)-17.** To a flask containing  $\text{Mg}^0$  turnings (125.4 mg, 5.16 mmol, 3.0 equiv) was added  $\text{Et}_2\text{O}$  (30 mL) and a chip of  $\text{I}_2$ . The contents were stirred for 25 min at 23 °C and then cooled to 0 °C. Allylic bromide **16** (1.141 g, 4.30 mmol, 2.5 equiv) was dissolved in  $\text{Et}_2\text{O}$  (5 mL) and transferred via cannula to the  $\text{Mg}/\text{Et}_2\text{O}$  and stirred for 30 min at 0 °C, then warmed to 23 °C over 30 min. A solution of ketone (–)-**15** (333.5 mg, 1.72 mmol, 1.0 equiv) in THF (5 mL) and transferred dropwise to the allylmagnesium bromide via cannula, followed by washings to total 35 mL of THF. Upon consumption of ketone (–)-**15** by TLC analysis (4:1 hexanes- $\text{EtOAc}$ ), the reaction was quenched slowly with aq ammonium chloride (50 mL) and stirred until complete dissolution of  $\text{Mg}^0$ . The phases were separated and the aqueous phase was extracted with  $\text{EtOAc}$  (3 x 50 mL). The combined organics were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated to a pale yellow oil. Purification by flash chromatography (9:1  $\rightarrow$  4:1 hexanes- $\text{Et}_2\text{O}$ , dry load onto  $\text{SiO}_2$ ) afforded the desired triolefin (–)-**17** as a colorless oil (563.4 mg, 1.616 mmol, 94% yield).  $R_f$  = 0.62 (4:1 hexanes- $\text{EtOAc}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  5.54 (dddd,  $J$  = 17.6, 10.3, 7.3, 7.3 Hz, 1H), 5.06 (dd,  $J$  = 3.2, 1.7 Hz, 1H), 4.97 (ddd,  $J$  = 10.3, 2.2, 1.2 Hz, 1H), 4.92 (dddd,  $J$  = 16.9, 2.4, 1.2, 1.2 Hz, 1H), 4.56 (d,  $J$  = 1.2 Hz, 2H), 3.95 (s, 2H), 2.75 (dd,  $J$  = 17.1, 17.1 Hz, 2H), 2.36 (dddd,  $J$  = 17.1, 17.1, 10.3, 5.1 Hz, 1H), 2.33 (dddd,  $J$  = 17.1, 17.1, 7.1, 5.4 Hz, 1H), 2.01 (dddd,  $J$  = 13.9, 13.9, 13.9, 7.6 Hz, 2H), 1.89 (s, 3H), 1.60 (ddd, 13.4, 6.8, 5.1 Hz, 1H), 1.41 (ddd, 13.4, 10.0, 5.1 Hz, 1H), 0.98 (s, 9H), 0.87 (s, 3H), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  196.6, 158.9, 144.4, 134.5, 134.3, 118.0, 110.3, 67.1, 43.2, 39.2, 34.2, 33.9, 33.2, 26.1, 23.9, 18.5, 12.5, –5.2; IR (Neat Film NaCl) 3078, 2930, 2857, 1668, 1610, 1463, 1337, 1081, 1005, 912, 836, 776  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$ : calc'd for  $\text{C}_{21}\text{H}_{36}\text{O}_2\text{Si}$   $[\text{M}]^+$ : 348.2485, found 348.2499;  $[\alpha]_{\text{D}}^{21.0}$  –37.3° ( $c$  1.11,  $\text{CH}_2\text{Cl}_2$ , 92% ee).

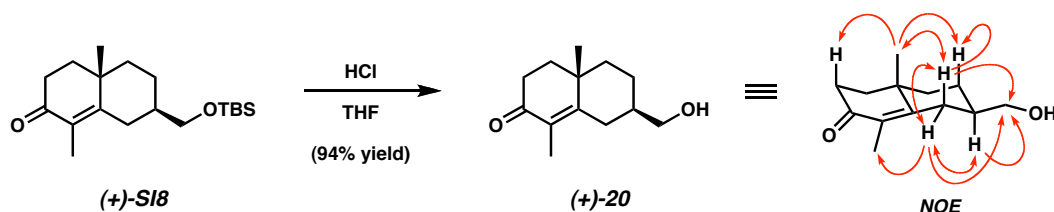


**Cyclohexene (–)-19.** Triolefin (–)-**17** (280.1 mg, 0.804 mmol, 1.0 equiv) was dissolved in PhH (16 mL, 0.05 M) and sparged with  $\text{N}_2$  for 15 min. Grubbs' catalyst **18** (20.5 mg, 0.0241 mmol, 0.03 equiv) was added to the solution, and the flask was placed in a 40 °C oil bath. Upon consumption by TLC analysis (3:1 hexanes- $\text{Et}_2\text{O}$ ), the reaction was cooled to ambient temperature and ethyl vinyl ether (8 mL) was added to the solution. After stirring for ca. 30 min, the solution was concentrated *in vacuo*. Purification via flash chromatography (9:1  $\rightarrow$  4:1 hexanes- $\text{Et}_2\text{O}$ ) afforded cyclohexene (–)-**19** as a colorless oil (256.3 mg, 0.800 mmol, 99% yield).  $R_f$  = 0.30 (3:1 hexanes- $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  5.58 (dddd,  $J$  = 5.4, 1.5, 1.5, 1.5 Hz, 1H), 3.93 (d,  $J$  = 1.2 Hz, 1H), 2.86 (d,  $J$  = 22.0 Hz, 1H), 2.60 (d,  $J$  = 21.7 Hz, 1H), 2.32–2.29 (comp m, 2H), 1.87 (d,  $J$  = 1.2 Hz, 3H), 1.83 (dd,  $J$  = 16.9, 2.0 Hz, 1H), 1.61 (dd,  $J$  = 16.9, 6.1 Hz, 1H), 1.45–1.35 (comp m, 2H), 0.99 (s, 9H), 0.85 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  196.4, 157.4, 135.1, 129.5, 119.5, 66.7, 39.6, 36.4, 35.1, 34.3, 29.7, 26.1,

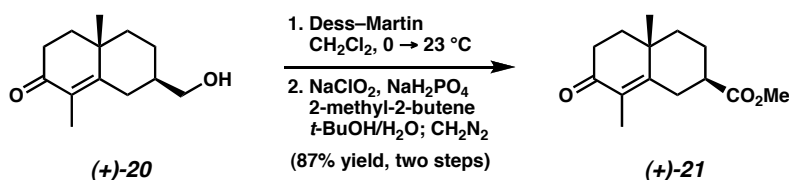
24.0, 18.6, 11.2, -5.1, -5.2; IR (Neat Film NaCl) 2929, 2857, 1668, 1615, 1463, 1305, 1257, 1158, 1086, 1048, 837, 776  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$ : calc'd for  $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$   $[\text{M} + \text{H} - \text{H}_2]^+$ : 319.2093, found 319.2096;  $[\alpha]_{\text{D}}^{21.2}$  -9.4° ( $c$  0.60,  $\text{CH}_2\text{Cl}_2$ , 92% ee).



**Enone (+)-SI8.** Cyclohexene  $(-)\text{-19}$  (25.0 mg, 78.0  $\mu\text{mol}$ , 1.0 equiv) was dissolved in MeOH (3.1 mL, 25 mM), and Rh/ $\text{Al}_2\text{O}_3$  catalyst (40.1 mg, 3.90  $\mu\text{mol}$ , 0.05 equiv) was added with vigorous stirring. The vial was placed under an atmosphere of hydrogen via a balloon and stirred at 26 °C. Upon consumption by TLC (3:1 hexanes- $\text{Et}_2\text{O}$ , developed thrice), the solids were filtered over Celite washing with EtOAc and concentrated *in vacuo*. Purification via flash chromatography (9:1 hexanes- $\text{Et}_2\text{O}$ ) afforded the desired enone  $(+)\text{-SI8}$  as a colorless oil (14.8 mg, 45.9  $\mu\text{mol}$ , 59% yield, 10:1 dr).  $R_f$  = 0.36 (3:1 hexanes- $\text{Et}_2\text{O}$ , developed twice);  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ , major diastereomer):  $\delta$  3.33 (ddd,  $J$  = 14.0, 9.8, 5.1 Hz, 2H), 2.63 (ddd,  $J$  = 14.7, 1.7, 1.7 Hz, 1H), 2.38-2.26 (comp m, 2H), 1.96 (s, 3H), 1.68 (dd,  $J$  = 13.7, 13.7 Hz, 1H), 1.44 (ddd,  $J$  = 13.4, 13.4, 3.7 Hz, 1H), 1.42-1.39 (m, 1H), 1.31-1.23 (comp m, 2H), 1.08 (ddd,  $J$  = 14.2, 14.2, 3.6 Hz, 1H), 0.99 (s, 9H), 0.84 (s, 3H), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  197.0, 160.0, 129.2, 68.1, 41.6, 41.5, 37.7, 36.0, 34.1, 30.9, 26.1, 24.7, 22.2, 18.5, 11.2, -5.2 (2C); IR (Neat Film NaCl) 2928, 2857, 1668, 1612, 1472, 1256, 1098, 838, 776  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$ : calc'd for  $\text{C}_{19}\text{H}_{35}\text{O}_2\text{Si}$   $[\text{M} + \text{H}]^+$ : 323.2406, found 323.2402;  $[\alpha]_{\text{D}}^{21.4}$  +73.0° ( $c$  0.53,  $\text{CH}_2\text{Cl}_2$ , 92% ee).

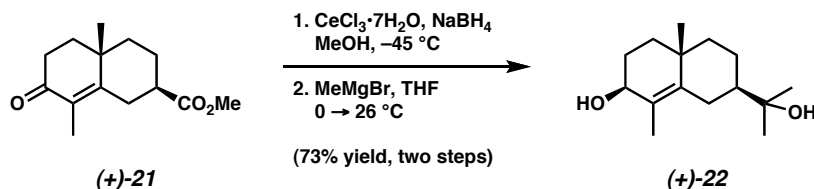


**Alcohol (+)-20.** Enone  $(+)\text{-SI8}$  (40.3 mg, 0.125 mmol, 1.0 equiv) was dissolved in THF (2.5 mL, 50 mM) and aq HCl (1N, 1.0 mL) was added with vigorous stirring. Upon consumption by TLC (2:1 hexanes-EtOAc), brine was added, the layers were separated, and the aqueous was extracted with  $\text{Et}_2\text{O}$  (3 x 4 mL). The combined organics were washed with saturated aq  $\text{NaHCO}_3$ , this aq was back extracted with  $\text{Et}_2\text{O}$  (2 x 5 mL), and the organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification via flash chromatography (2:1  $\rightarrow$  1:1 hexanes-EtOAc) afforded alcohol  $(+)\text{-20}$  as a colorless oil (24.5 mg, 0.118 mmol, 94% yield, 10:1 d.r.).  $R_f$  = 0.37 (1:1 hexanes-EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ , major diastereomer):  $\delta$  3.12 (d,  $J$  = 5.5 Hz, 2H), 2.52 (ddd,  $J$  = 14.6, 1.9, 1.9 Hz, 1H), 2.37-2.24 (comp m, 2H), 1.92 (dd,  $J$  = 1.3, 1.3 Hz, 3H), 1.52 (ddd,  $J$  = 13.1, 13.1, 3.1 Hz, 1H), 1.43 (ddd,  $J$  = 13.4, 13.4, 5.3 Hz, 1H), 1.36-1.33 (m, 1H), 1.29-1.21 (comp m, 3H), 1.17-1.09 (m, 1H), 1.03 (ddd,  $J$  = 12.9, 12.9, 3.3 Hz, 1H), 0.79 (s, 3H), 0.74 (br s, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  197.2, 160.1, 129.1, 67.7, 41.5, 41.4, 37.7, 35.9, 34.1, 30.8, 24.6, 22.2, 11.3; IR (Neat Film NaCl) 3418 (br), 2924, 1660, 1652, 1608, 1453, 1352, 1150, 1083, 1013  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$ : calc'd for  $\text{C}_{13}\text{H}_{20}\text{O}_2$   $[\text{M}]^+$ : 208.1463, found 208.1463;  $[\alpha]_{\text{D}}^{23}$  +120.9° ( $c$  0.35,  $\text{CH}_2\text{Cl}_2$ , 92% ee).



**Ester (+)-21.** Alcohol (+)-20 (24.5 mg, 0.118 mmol, 1.0 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2.4 mL, 50 mM) and cooled in an ice/water bath. To this solution was added Dess–Martin periodinane (69.8 mg, 0.165 mmol, 1.4 equiv), and after 5 min the bath was removed and the reaction was stirred at room temperature. Upon completion by TLC analysis (2:1 hexanes-EtOAc), the reaction was diluted with 1:1 hexanes-Et<sub>2</sub>O (4 mL) and filtered through a small silica gel plug. Heptanes (5 mL) were added and the filtrate was concentrated *in vacuo* to a white solid. Purification by filtration through a silica gel plug (3:1  $\rightarrow$  1:1 hexanes-Et<sub>2</sub>O) afforded a colorless oil (22.3 mg) that was used in the next step.

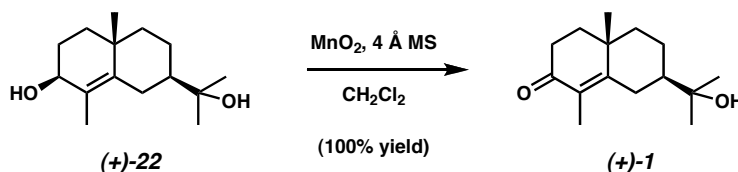
The resulting material was dissolved in *t*-BuOH (1.7 mL), to which 2-methyl-2-butene (85  $\mu\text{L}$ , 0.80 mmol, 7.4 equiv) was added with stirring. To this was added a solution of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$  (103 mg, 0.746 mmol, 6.9 equiv) and  $\text{NaClO}_2$  (89.9 mg, 0.995 mmol, 9.2 equiv) in water (850  $\mu\text{L}$ ) over ca. 5 min. Upon consumption by TLC analysis (1:1 hexanes-EtOAc), the *t*-BuOH was removed on a rotovap, water (2 mL) was added to this slurry, and 1 N HCl was added dropwise until pH < 3. The resulting aq was extracted with Et<sub>2</sub>O (4 x 4 mL), a stir bar was added and the extract was cooled in an ice/water bath. A fresh solution of  $\text{CH}_2\text{N}_2$  in Et<sub>2</sub>O (5 mL) was added and the bath was allowed to expire. After the solution was colorless it was dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification via flash chromatography (3:1  $\rightarrow$  2:1 hexanes-Et<sub>2</sub>O) afforded ester (+)-21 as a colorless oil that solidifies to a white solid over time or in a  $-20\text{ }^\circ\text{C}$  freezer (24.4 mg, 0.103 mmol, 87% yield over two steps). The diastereomers are separable by flash chromatography with 3:1 hexanes-Et<sub>2</sub>O.  $R_f$  = 0.59 (1:1 hexanes-EtOAc); mp = 46–48  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ , major diastereomer):  $\delta$  3.38 (s, 3H), 2.83–2.76 (m, 1H), 2.30–2.09 (comp m, 4H), 1.82 (m, 3H), 1.66–1.62 (comp m, 2H), 1.32 (ddd,  $J$  = 13.6, 13.6, 4.9 Hz, 1H), 1.17 (ddd,  $J$  = 13.2, 3.9, 3.9 Hz, 1H), 1.12 (ddd,  $J$  = 13.5, 2.8, 2.8 Hz, 1H), 0.91–0.85 (m, 1H), 0.72 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  196.8, 174.7, 157.7, 129.9, 51.3, 43.5, 40.9, 37.4, 35.4, 34.0, 29.9, 24.7, 21.9, 11.2; IR (Neat Film NaCl) 2949, 1733, 1668, 1613, 1435, 1350, 1301, 1256, 1190, 1173, 1024, 914  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$ : calc'd for  $\text{C}_{14}\text{H}_{21}\text{O}_3$   $[\text{M} + \text{H}]^+$ : 237.1491, found 237.1493;  $[\alpha]_{\text{D}}^{20.4} +64.0^\circ$  ( $c$  0.56,  $\text{CH}_2\text{Cl}_2$ , 92% ee).



**Diol (+)-22.**<sup>9</sup> To a solution of ester (+)-21 (10.1 mg, 42.7  $\mu\text{mol}$ , 1.0 equiv) in MeOH (1.7 mL, 25 mM) was added  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (47.8 mg, 128  $\mu\text{mol}$ , 3.0 equiv), followed by cooling to ca.  $-45\text{ }^\circ\text{C}$  in a MeCN/ $\text{CO}_2(\text{s})$  bath. Solid  $\text{NaBH}_4$  (3.2 mg, 85.5  $\mu\text{mol}$ , 2.0 equiv) was added, and upon consumption by TLC analysis (1:1 hexanes-EtOAc), acetone (5 drops) was added, followed by brine (1 mL) and EtOAc (1 mL). The suspension was warmed to room temperature, the aq was extracted with EtOAc (2 x 4 mL),

dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to a colorless film (9.1 mg). This material was used directly in the subsequent reaction.

The resulting material was dissolved in THF (1.5 mL, 25 mM) and cooled in an ice/water bath. A solution of  $\text{MeMgBr}$  (71  $\mu\text{L}$ , 2.7 M in THF, 191  $\mu\text{mol}$ , 5 equiv) was added and the bath was removed after 5 min. Upon consumption by TLC analysis (1:1 hexanes-EtOAc), the reaction was cooled in an ice/water bath, and MeOH (200  $\mu\text{L}$ ), brine (1 mL), saturated aq  $\text{NH}_4\text{Cl}$  (1 mL), and EtOAc (2 mL) were added. The aq layer was extracted with EtOAc (2 x 4 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification via flash chromatography (2:1 hexanes-EtOAc) afforded diol (+)-**22** as a colorless film that solidifies over time to an off-white solid (7.4 mg, 31.0  $\mu\text{mol}$ , 73% yield over two steps, > 20:1 dr).  $R_f$  = 0.30 (1:1 hexanes-EtOAc); mp = 123-126  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.03 (app t,  $J$  = 6.6 Hz, 1H), 2.60 (app dt,  $J$  = 13.5, 2.8 Hz, 1H), 1.94-1.88 (m, 1H), 1.73 (s, 3H), 1.71-1.23 (comp m, 11H), 1.21 (s, 6H), 1.08 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.7, 126.9, 72.9, 71.7, 50.7, 41.7, 36.2, 35.3, 29.0, 27.4, 27.0, 26.9, 24.8, 23.2, 15.2; IR (Neat Film NaCl) 3366 (br), 2934, 2863, 1455, 1374, 1277, 1138, 1076, 1014, 922, 734  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$ : calc'd for  $\text{C}_{15}\text{H}_{26}\text{O}_2$   $[\text{M}]^+$ : 238.1933, found 238.1921;  $[\alpha]_{\text{D}}^{21.6} +21.6^\circ$  ( $c$  0.34, MeOH, 92% ee).



**(+)-Carissone (1).**<sup>9b</sup> To a solution of diol (+)-**22** (3.1 mg, 13.0  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (520  $\mu\text{L}$ , 25 mM) was added oven-dried 4ÅMS (15 mg), followed by  $\text{MnO}_2$  (13.3 mg, 130  $\mu\text{mol}$ , 10 equiv). Upon consumption by TLC (1:1 hexanes-EtOAc), the reaction was diluted with  $\text{Et}_2\text{O}$  (2 mL) and filtered through a small plug of silica gel, washing with  $\text{Et}_2\text{O}$ . This was concentrated *in vacuo* to afford (+)-carissone (**1**) as a colorless film (3.1 mg, 131  $\mu\text{mol}$ , 100% yield).  $R_f$  = 0.34 (1:1 hexanes-EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.86 (app dt,  $J$  = 14.4, 2.6 Hz, 1H), 2.51 (ddd,  $J$  = 16.9, 13.3, 6.4 Hz, 1H), 2.39 (app dt,  $J$  = 16.8, 3.8 Hz, 1H), 1.90 (app t,  $J$  = 13.9 Hz, 1H), 1.82-1.69 (comp m, 4H), 1.78 (s, 3H), 1.55-1.36 (comp m, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.1, 162.6, 128.8, 72.4, 49.6, 41.9, 37.3, 35.8, 33.7, 28.7, 27.5, 26.7, 22.5, 22.4, 10.9; IR (Neat Film NaCl) 3448 (br), 2970, 2935, 1652, 1608, 1452, 1353, 1300, 1212, 1189, 1149, 1014, 918, 817  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$ : calc'd for  $\text{C}_{15}\text{H}_{25}\text{O}_2$   $[\text{M} + \text{H}]^+$ : 237.1855, found 237.1844;  $[\alpha]_{\text{D}}^{23.1} +119.6^\circ$  ( $c$  0.31,  $\text{CHCl}_3$ , 92% ee); lit.  $[\alpha]_{\text{D}}^{22} +138.7^\circ$  ( $c$  0.163,  $\text{CHCl}_3$ ).

## Chiral SFC and HPLC Data

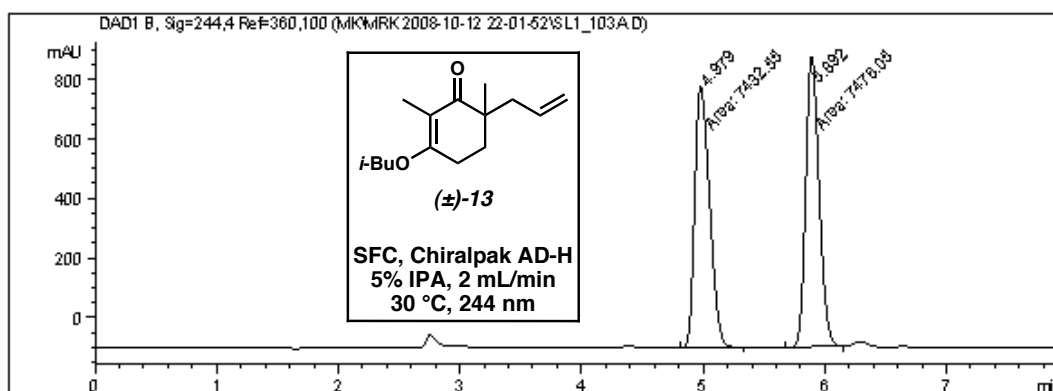
Data File C:\CHEM32\1\DATA\MK\MRK 2008-10-12 22-01-52\SL1\_103A.D

Sample Name: srlI-103-1

```

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Acq. Operator   : mike krout                      Seq. Line :    1
Acq. Instrument : Instrument 1                    Location  : Pl-B-06
Injection Date  : 10/12/2008 10:02:12 PM          Inj       :    1
                                           Inj Volume: 5 µl
Acq. Method     : C:\Chem32\1\DATA\MK\MRK 2008-10-12 22-01-52\MK1.M
Last changed    : 10/7/2008 10:30:51 PM by M. Krout
Analysis Method : C:\CHEM32\1\METHODS\ACHIRAL S6C1 IS015.M
Last changed    : 10/12/2008 10:49:24 PM by SKEDROWSKI
                  (modified after loading)
Sample Info     : srlI-103-1
                  AD column, 5% IPA, 2 ml/min, 30 degC
=====

```



## Area Percent Report

```

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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
=====

```

Signal 1: DAD1 B, Sig=244,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.979	MM	0.1413	7432.54736	876.57025	49.8541
2	5.892	MM	0.1275	7476.04688	976.92639	50.1459

Totals : 1.49086e4 1853.49664

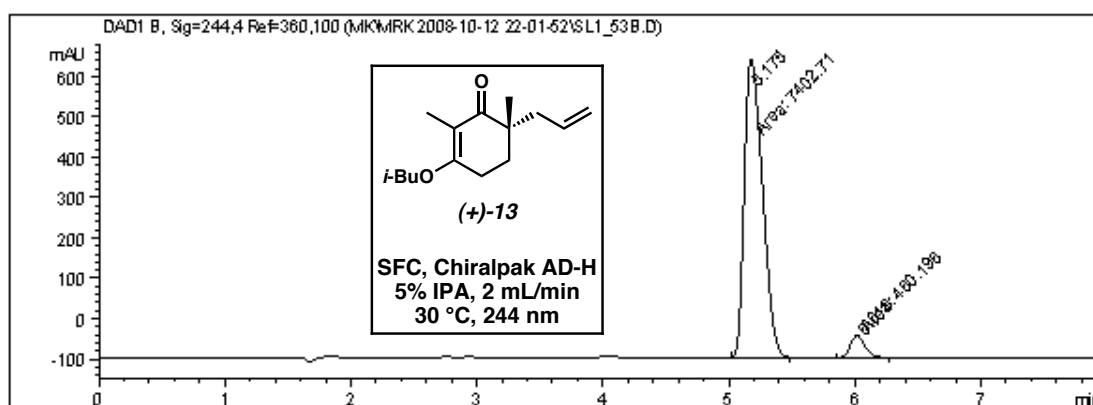
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*** End of Report ***
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Data File C:\CHEM32\1\DATA\MK\MRK 2008-10-12 22-01-52\SL1\_53B.D  
 Sample Name: srlI-53-3

```
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Acq. Operator   : mike krout                      Seq. Line :    7
Acq. Instrument : Instrument 1                     Location  : P1-B-07
Injection Date  : 10/12/2008 10:54:37 PM          Inj       :    1
                                                Inj Volume: 5 µl
Different Inj Volume from Sequence ! Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\MK\MRK 2008-10-12 22-01-52\MK1.M
Last changed    : 10/7/2008 10:30:51 PM by M. Krout
Analysis Method : C:\CHEM32\1\METHODS\ACHIRAL S6C1 IS015.M
Last changed    : 10/12/2008 10:49:24 PM by SKEDROWSKI
                  (modified after loading)
Sample Info     : srlI-53-3
                  AD column, 5% IPA, 2 ml/min, 30 degC
=====
```



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

```
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
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Signal 1: DAD1 B, Sig=244,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.175	MM	0.1666	7402.71484	740.43445	94.1473
2	6.016	MM	0.1373	460.19623	55.86982	5.8527

Totals : 7862.91107 796.30427

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=====
*** End of Report ***
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Data File C:\HPCHEM\3\DATA\SRL1\SL1\_105A.D

Sample Name: srlI-105-1

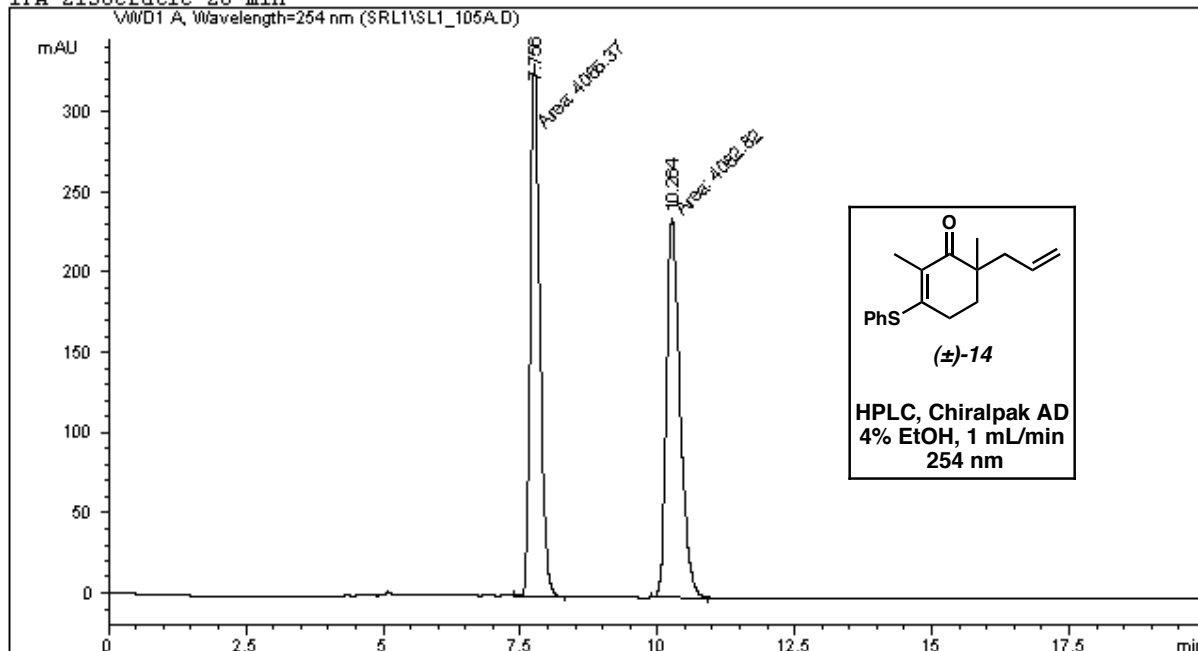
AD column, 4% EtOH  
racemic assay

```

=====
Injection Date : 10/12/2008 11:54:20 PM      Seq. Line :    3
Sample Name    : srlI-105-1                  Location  : Vial 1
Acq. Operator  : mike k                      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\2 EOH30.M
Last changed   : 10/12/2008 11:29:34 PM by ACJ
                (modified after loading)
  
```

IPA-2isocratic 20 min



```

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

```

Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
  
```

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area %	Height [mAU]
1	7.756	MM	0.2041	4065.37305	49.8929	331.89786
2	10.264	MM	0.2889	4082.82129	50.1071	235.55995

Totals :                      8148.19434   567.45781

Results obtained with enhanced integrator!

```

=====
*** End of Report ***
  
```

Data File C:\HPCHEM\3\DATA\MRK12\M12\_39A.D

Sample Name: mrkXII-39a

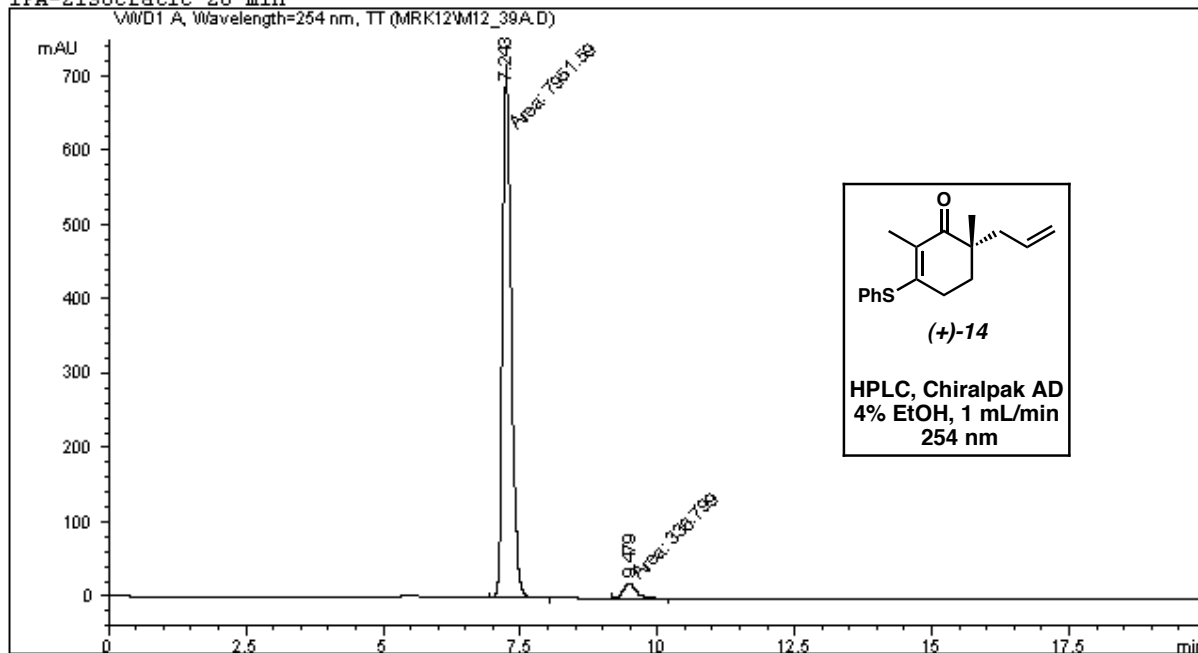
4% EtOH, AD column

```

=====
Injection Date   : 10/2/2008 12:22:13 AM      Seq. Line :    3
Sample Name     : mrkXII-39a                 Location  : Vial 1
Acq. Operator   : mike k                     Inj      :    1
                                           Inj Volume: 5 µl

Acq. Method     : C:\HPCHEM\3\METHODS\4-EOH30.M
Last changed    : 5/4/2008 9:16:49 AM by dave e
Analysis Method : C:\HPCHEM\3\METHODS\2 EOH30.M
Last changed    : 10/12/2008 11:29:26 PM by ACJ
                  (modified after loading)
  
```

IPA-2isocratic 20 min



```

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

```

Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
  
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Signal 1: WVD1 A, Wavelength=254 nm, TT

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.243	MM	0.1847	7951.59326	717.50653	95.9365
2	9.479	MM	0.2664	336.79871	21.07184	4.0635

Totals :                      8288.39197   738.57837

Results obtained with enhanced integrator!

```

=====
*** End of Report ***
  
```



Data File C:\HPCHEM\3\DATA\MRK12\SL1\_243H.D

Sample Name: srlI-243 mixA

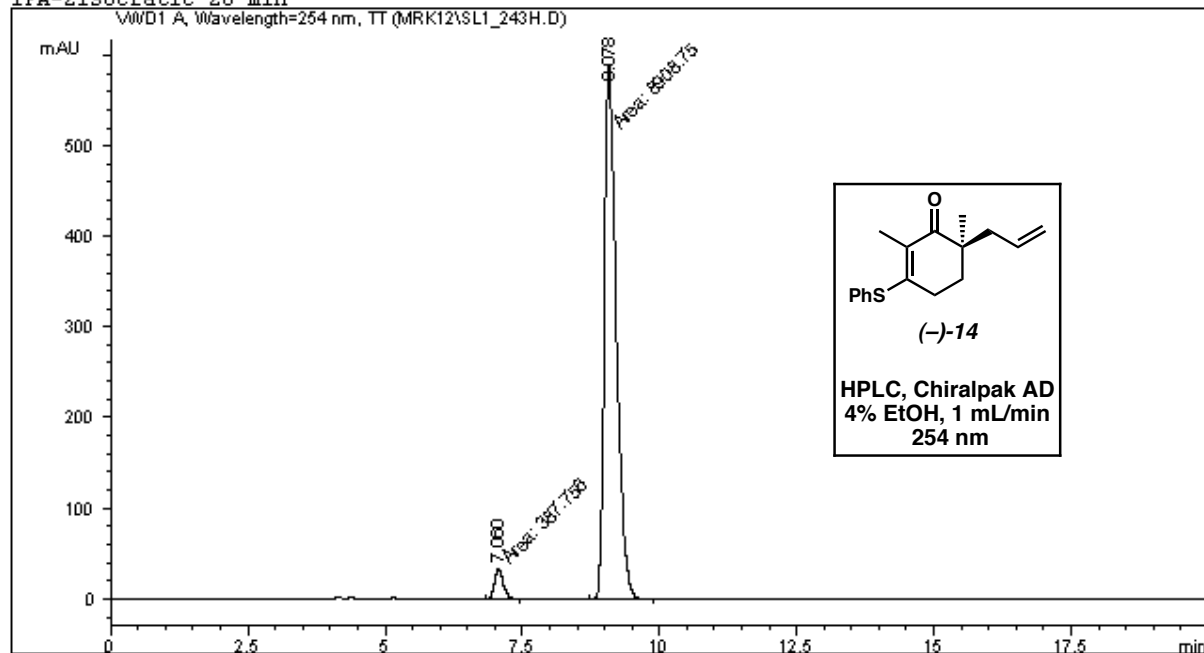
4% EtOH, AD column

```

=====
Injection Date   : 10/2/2008 10:39:58 AM      Seq. Line :    4
Sample Name     : srlI-243 mixA              Location  : Vial 2
Acq. Operator   : mike k                     Inj       :    1
                                           Inj Volume: 5 µl

Acq. Method     : C:\HPCHEM\3\METHODS\4-EOH30.M
Last changed    : 5/4/2008 9:16:49 AM by dave e
Analysis Method : C:\HPCHEM\3\METHODS\2 EOH30.M
Last changed    : 10/12/2008 11:12:47 PM by ACJ
                  (modified after loading)
  
```

IPA-2isocratic 20 min



```

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

```

Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
  
```

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

Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
1	7.060	MM	0.1893	387.75558	34.13660	4.1710
2	9.078	MM	0.2518	8908.74707	589.68390	95.8290

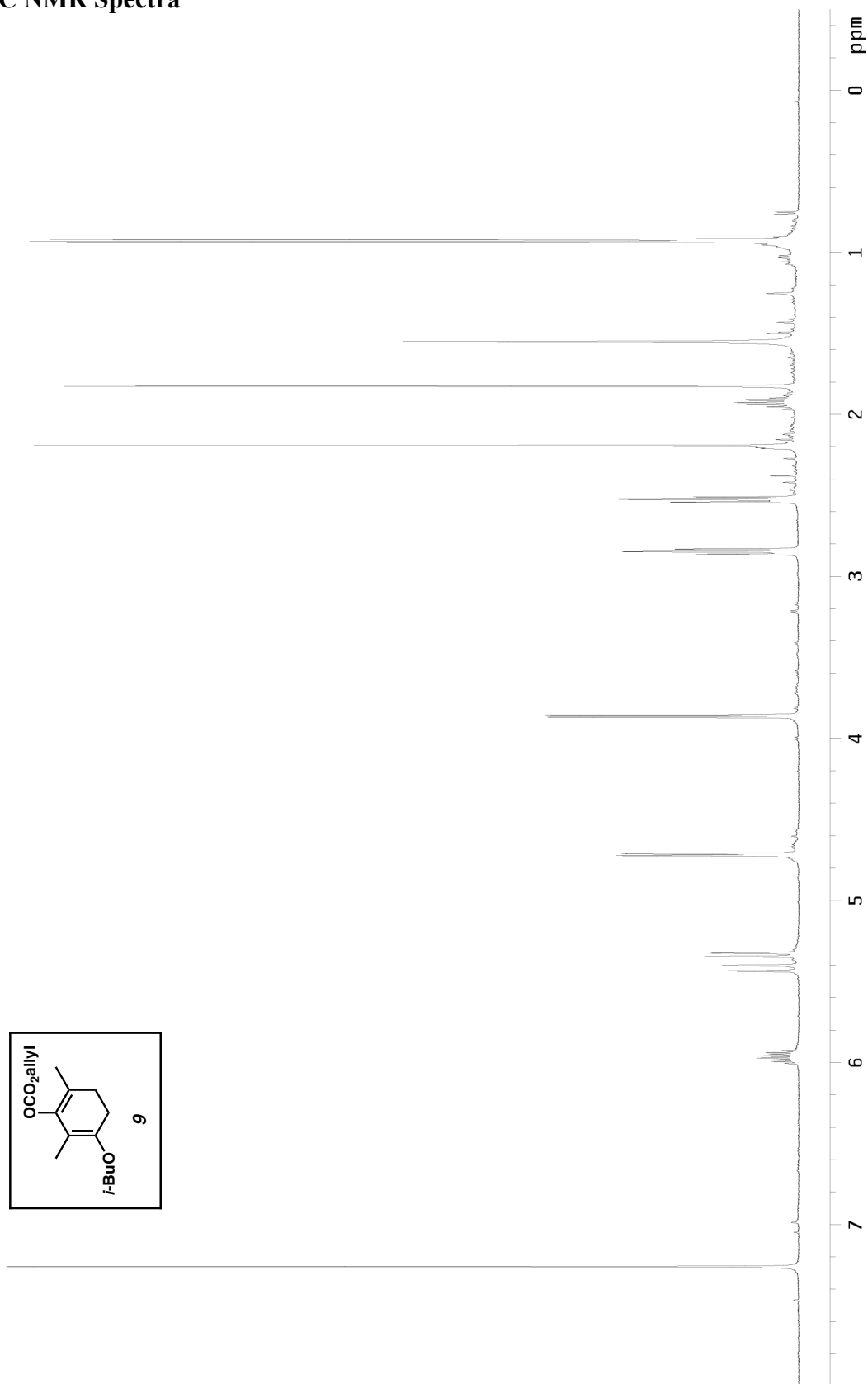
Totals :                      9296.50266   623.82050

Results obtained with enhanced integrator!

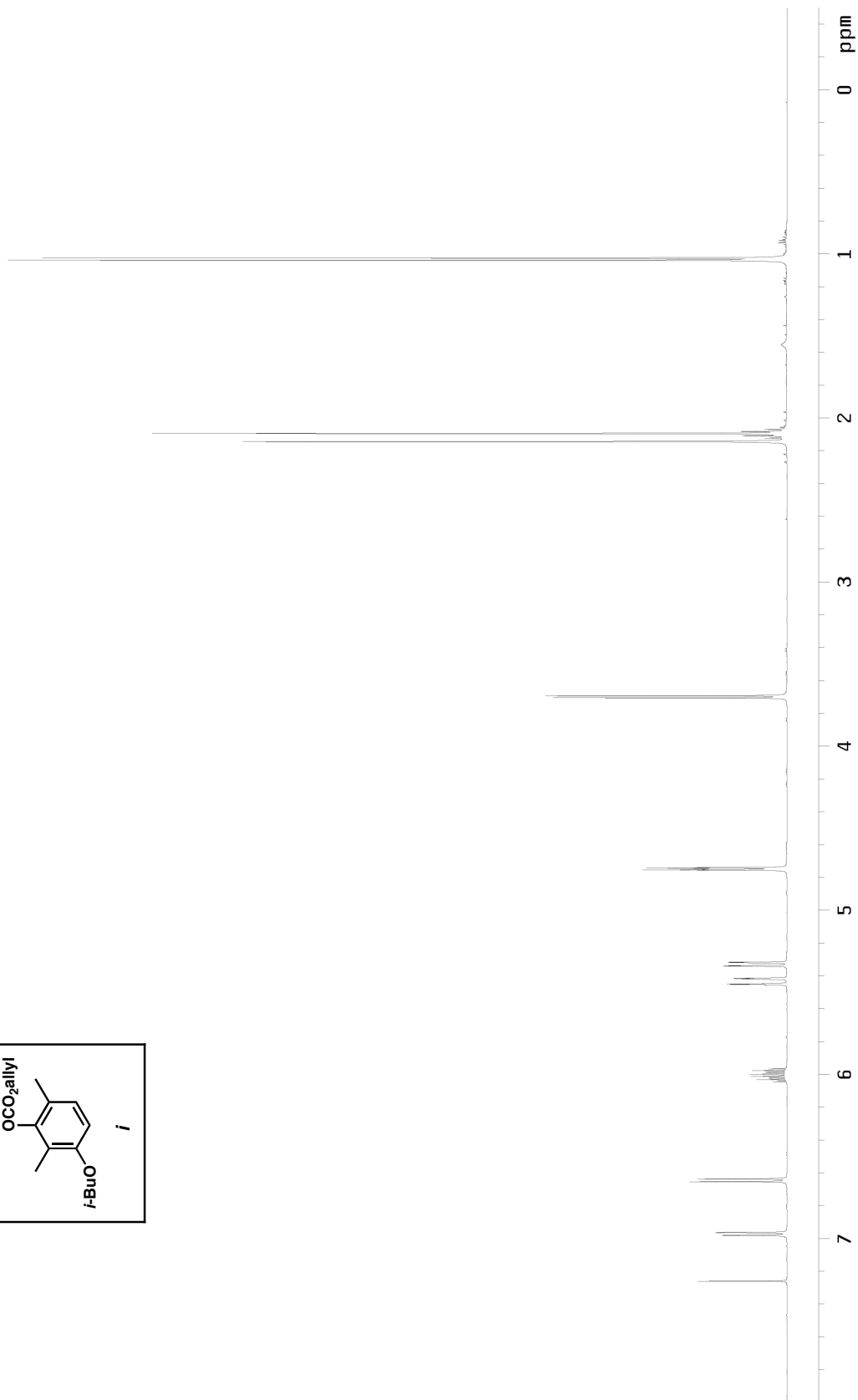
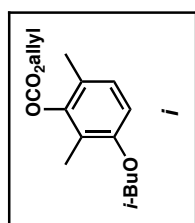
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*** End of Report ***
  
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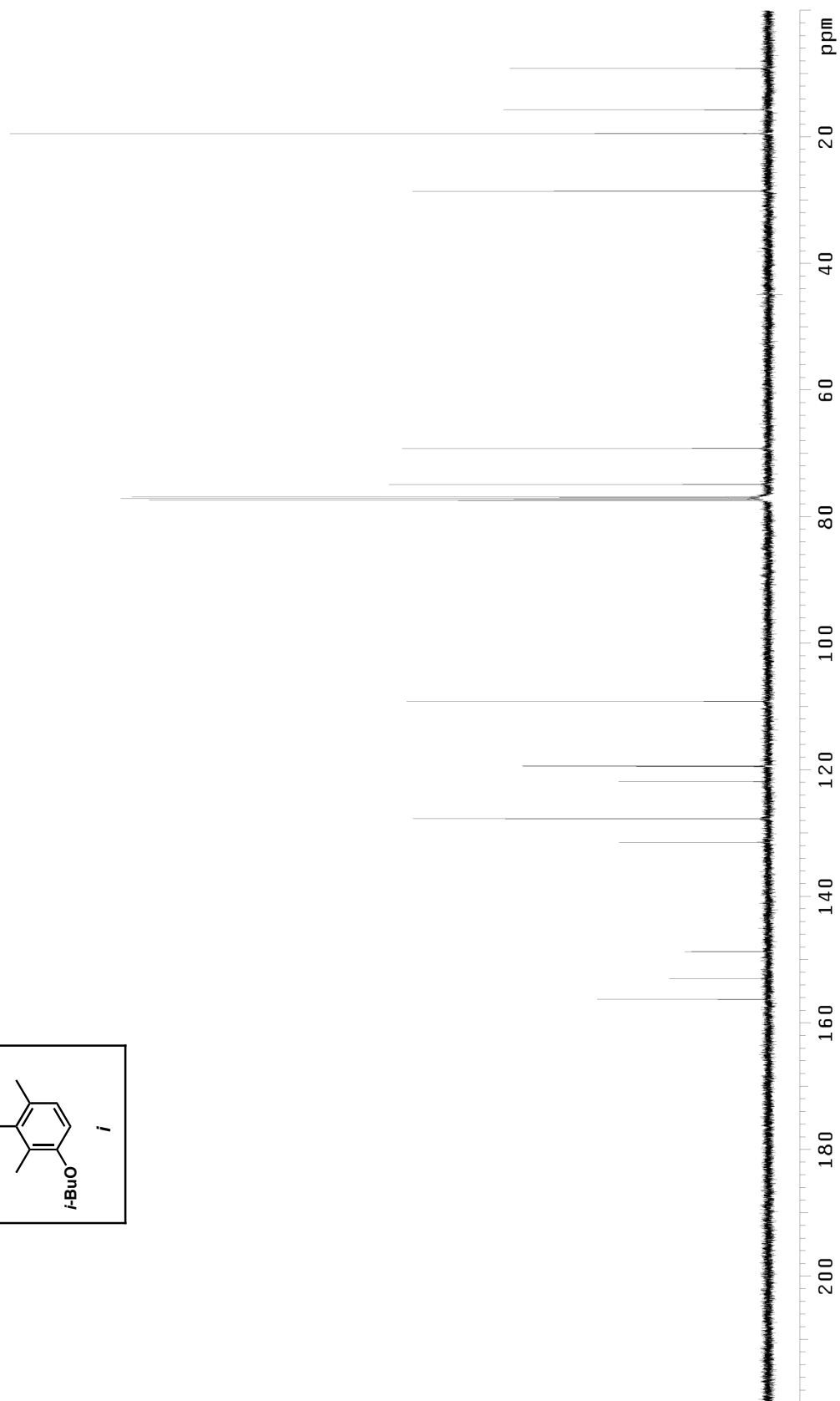
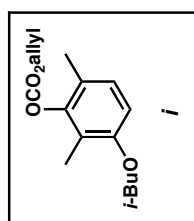
**$^1\text{H}$  and  $^{13}\text{C}$  NMR Spectra**



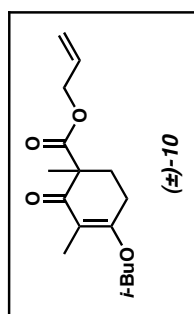
$^1\text{H}$  NMR spectrum of enol carbonate **9** (500 MHz,  $\text{CDCl}_3$ )



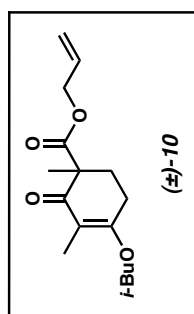
<sup>1</sup>H NMR spectrum of aromatic carbonate **i** (500 MHz, CDCl<sub>3</sub>)



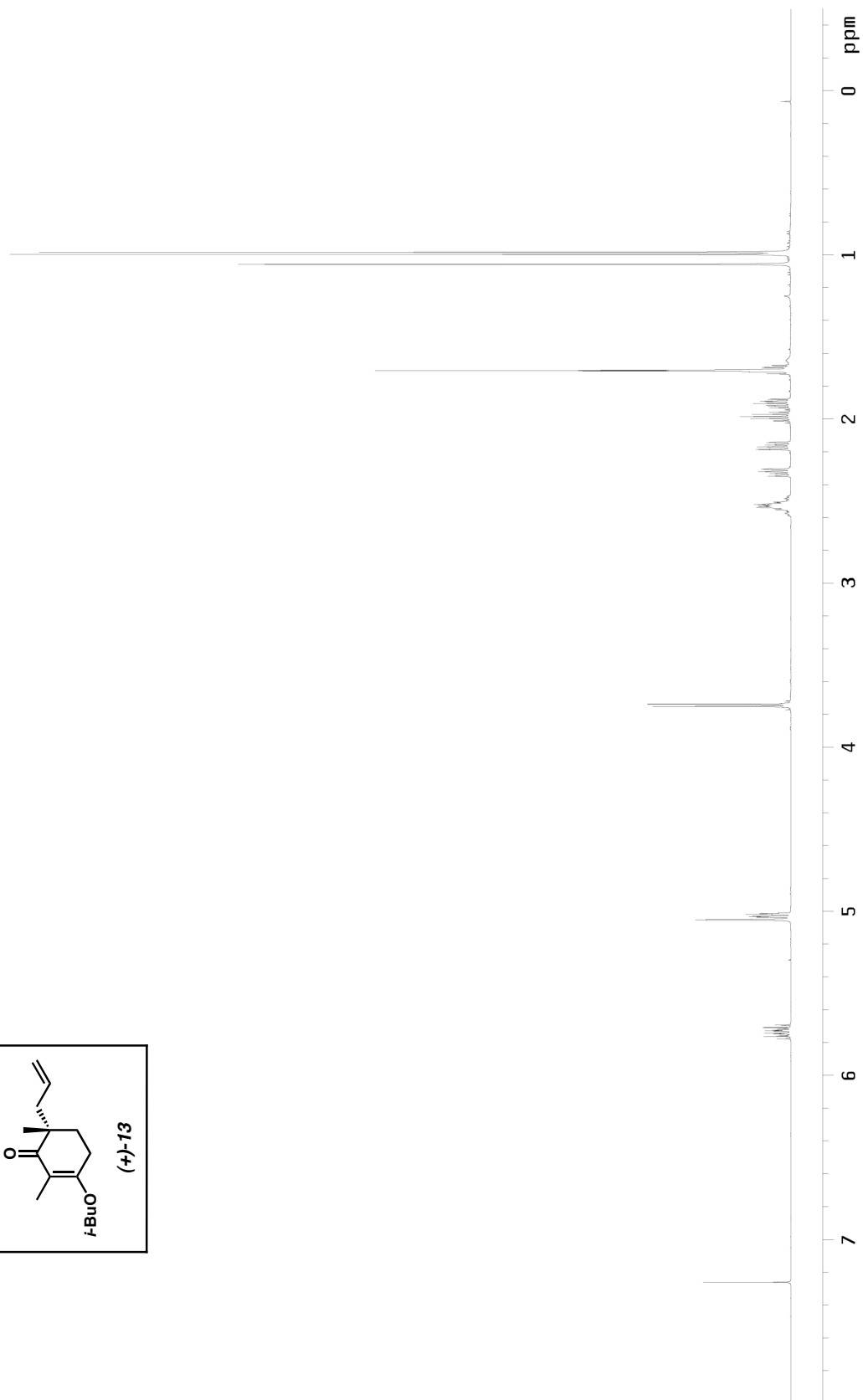
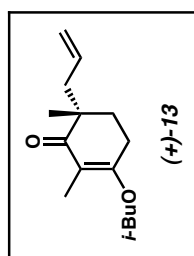
<sup>13</sup>C NMR spectrum of aromatic carbonate **i** (126 MHz, CDCl<sub>3</sub>)



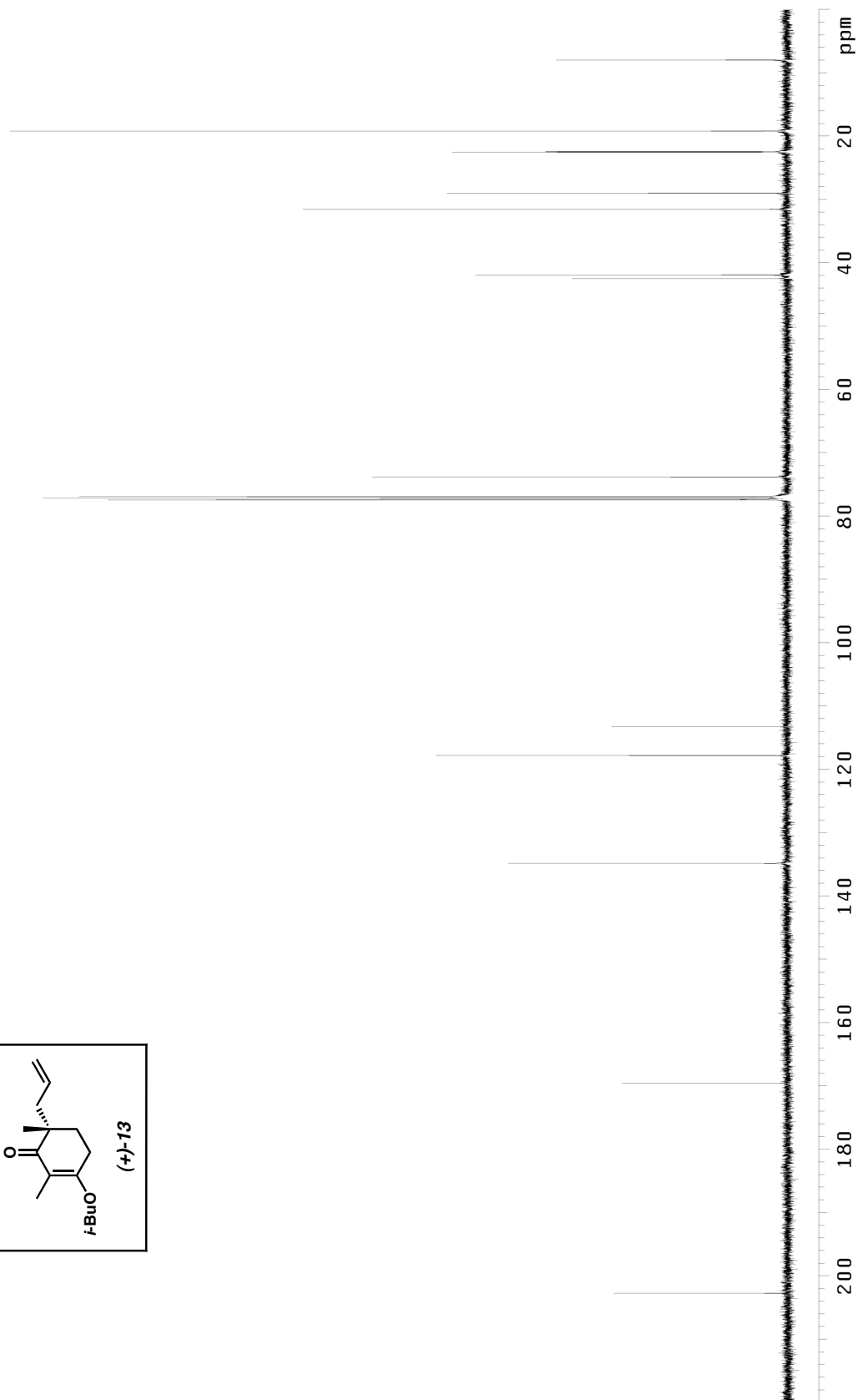
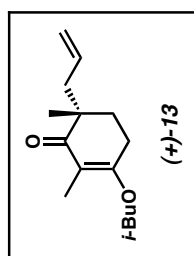
$^1\text{H}$  NMR spectrum of  $\beta$ -ketoester ( $\pm$ )-**10** (500 MHz,  $\text{CDCl}_3$ )



<sup>13</sup>C NMR spectrum of β-ketoester (±)-**10** (126 MHz, CDCl<sub>3</sub>)

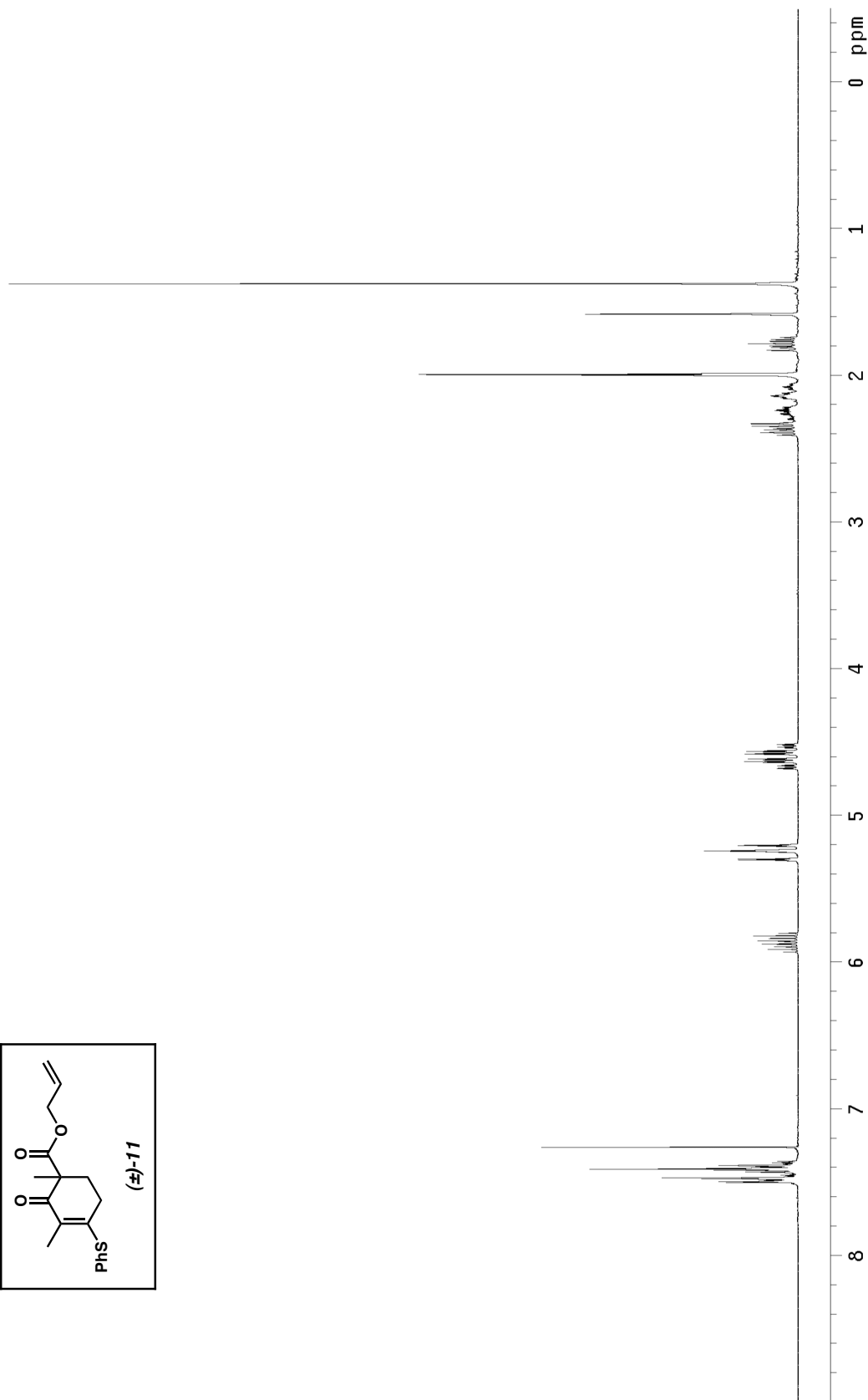
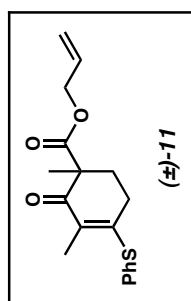


$^1\text{H}$  NMR spectrum of vinyllogous ester (+)-**13** (500 MHz,  $\text{CDCl}_3$ )

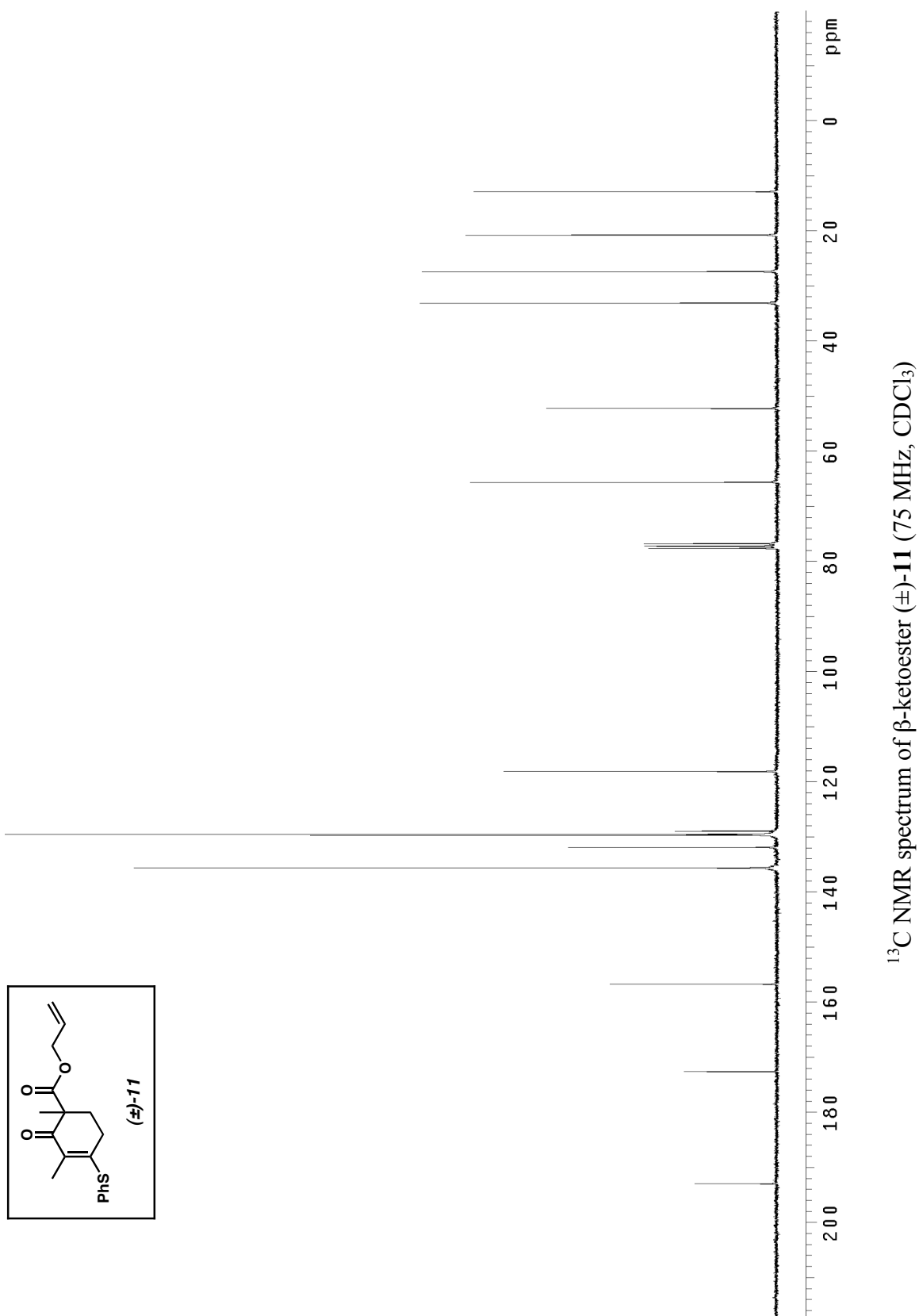


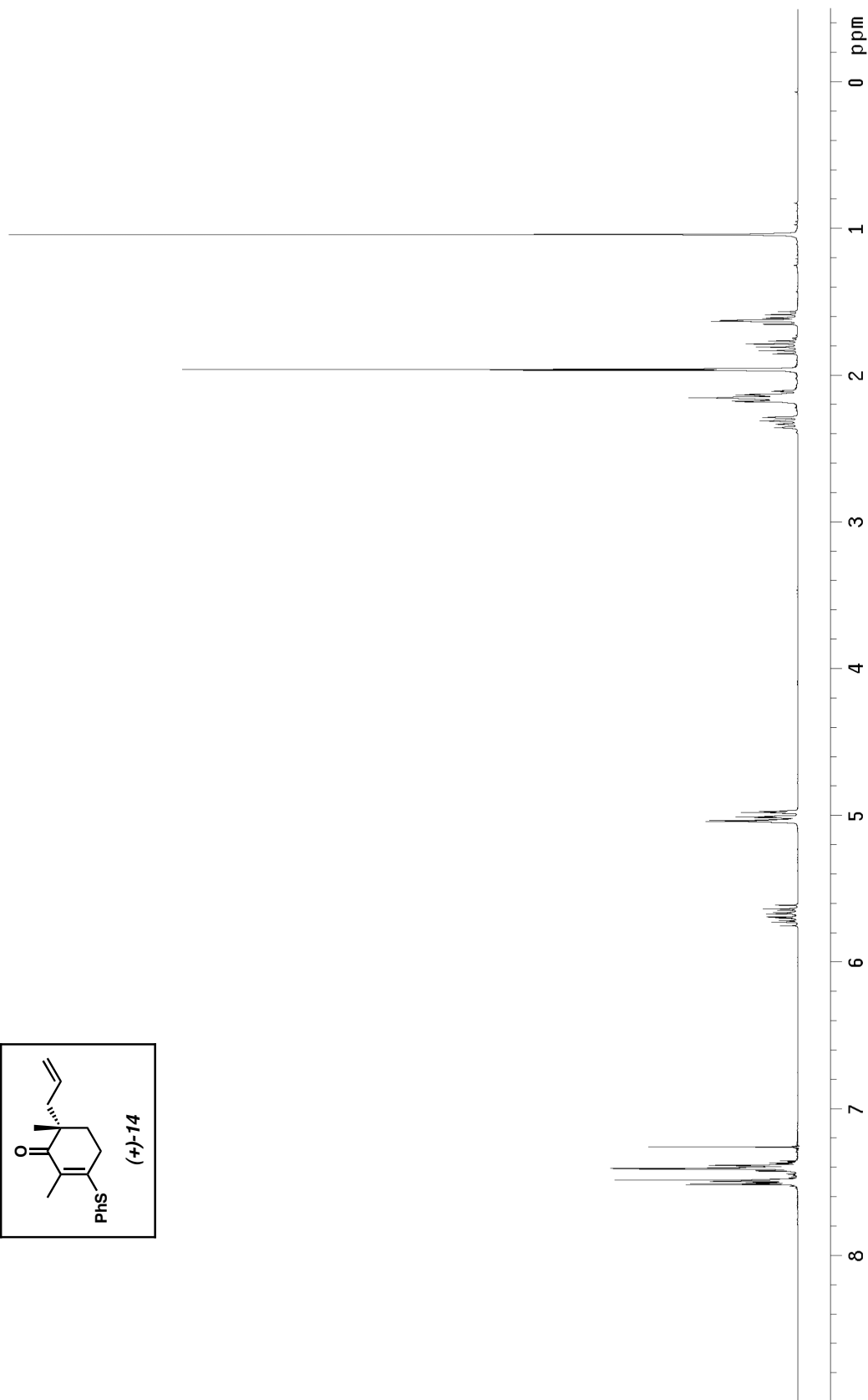
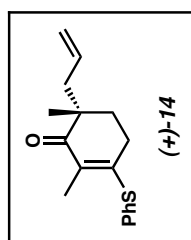
<sup>13</sup>C NMR spectrum of vinylogous ester (+)-13 (126 MHz, CDCl<sub>3</sub>)



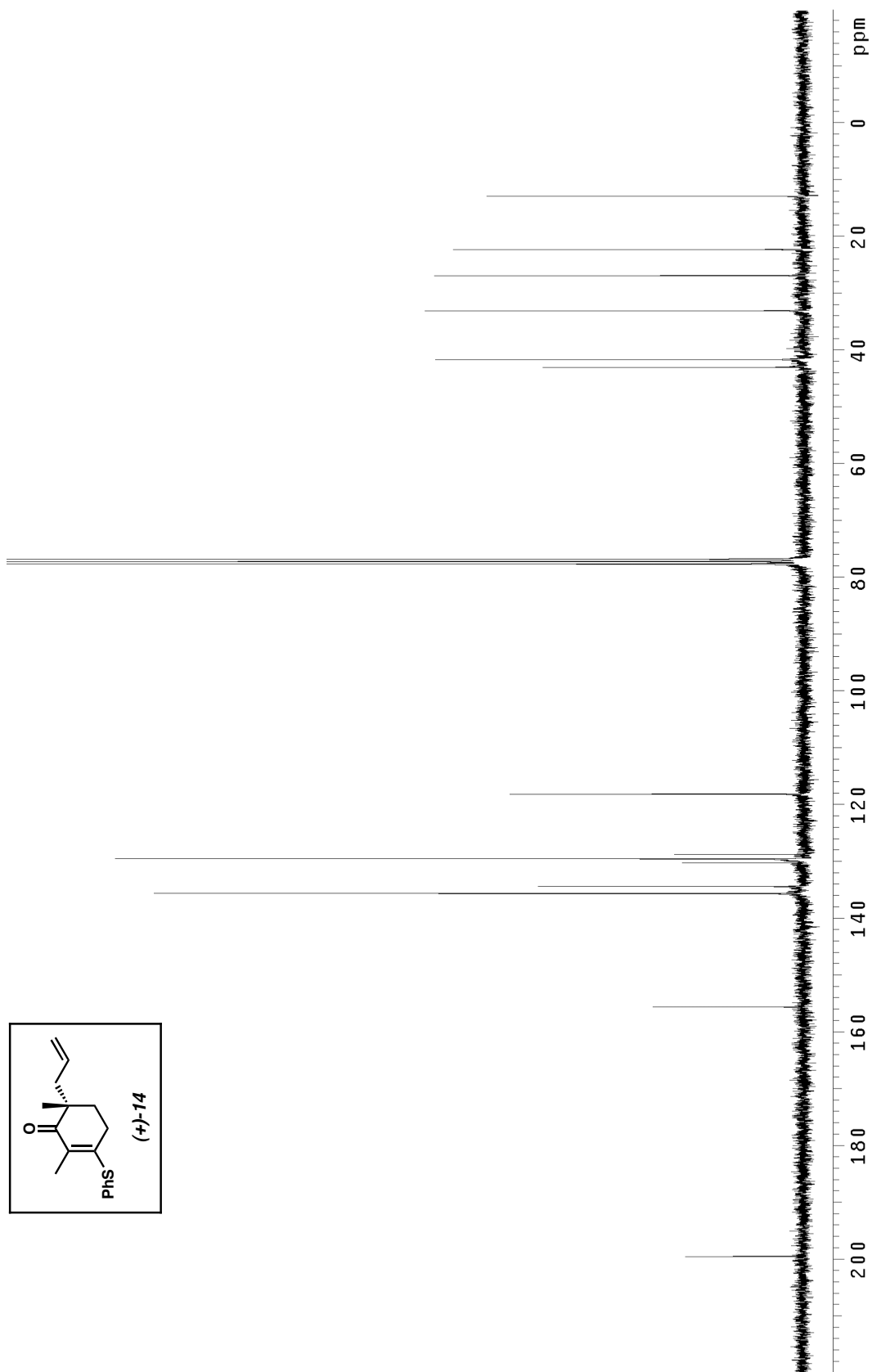


$^1\text{H}$  NMR spectrum of  $\beta$ -ketoester (±)-11 (300 MHz,  $\text{CDCl}_3$ )

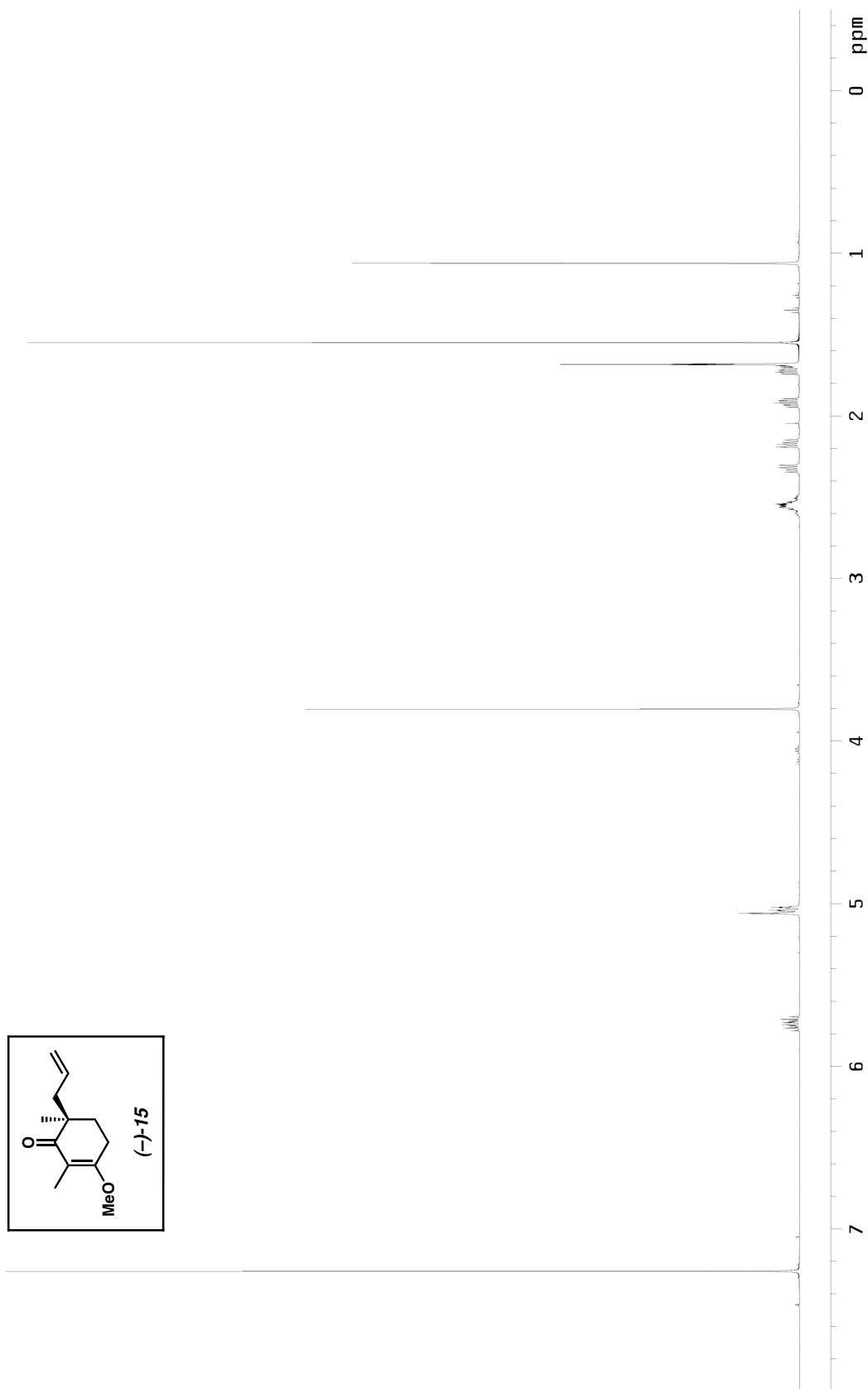




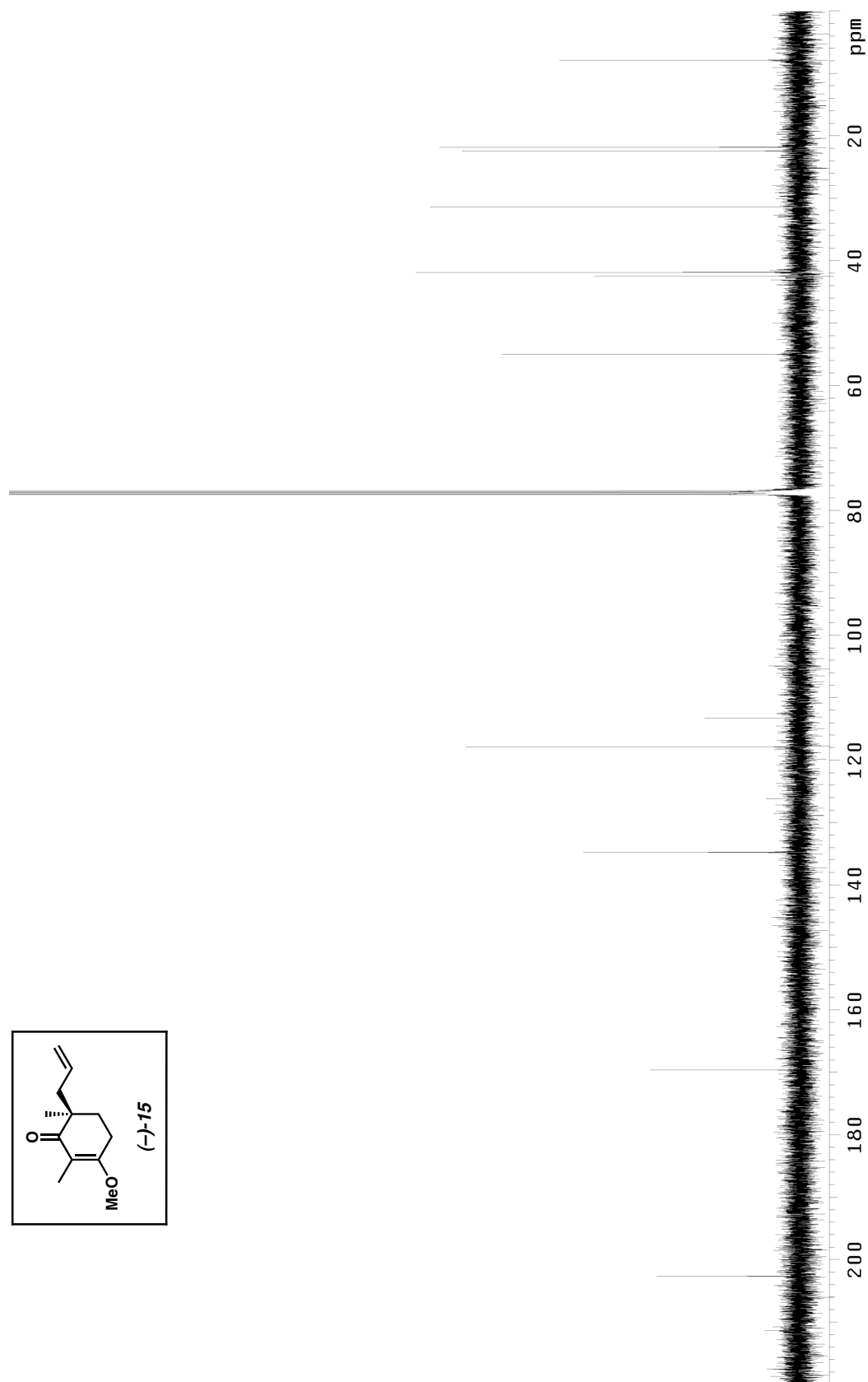
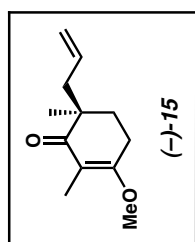
$^1\text{H}$  NMR spectrum of vinyllogous thioester (+)-14 (300 MHz,  $\text{CDCl}_3$ )



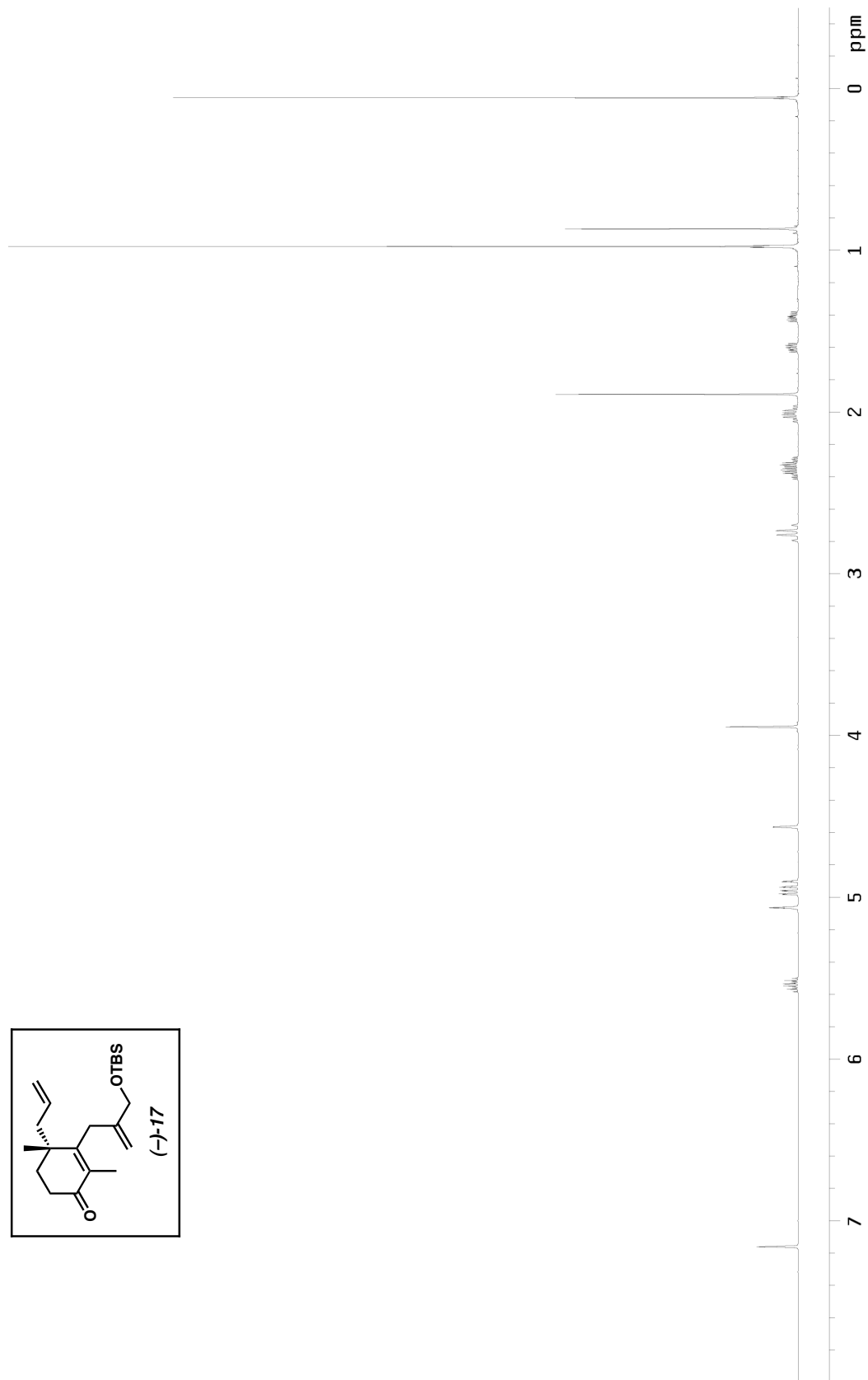
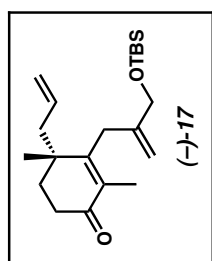
$^{13}\text{C}$  NMR spectrum of vinyllogous thioester (+)-14 (75 MHz,  $\text{CDCl}_3$ )

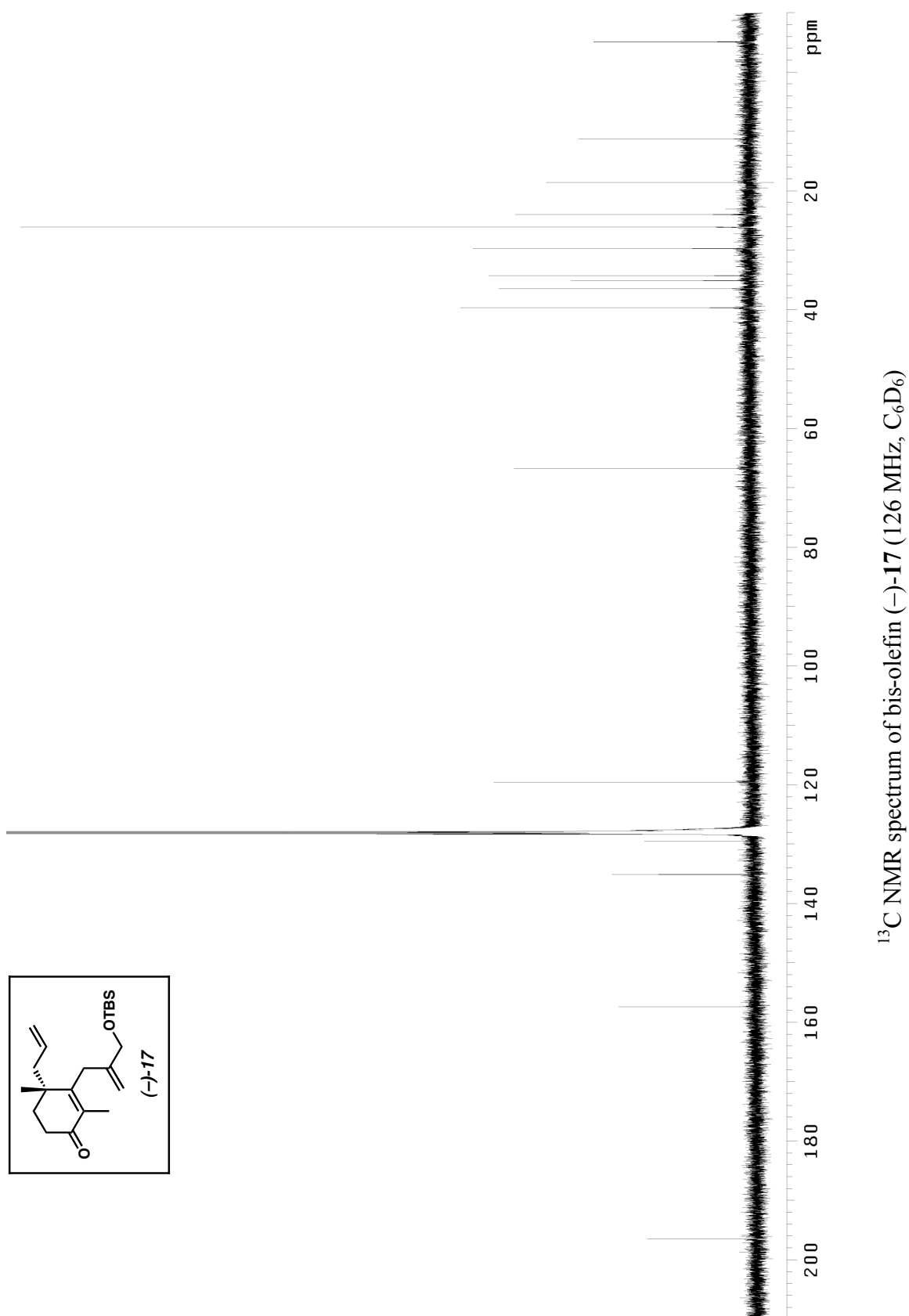


$^1\text{H}$  NMR spectrum of vinyllogous ester **(-)-15** (500 MHz,  $\text{CDCl}_3$ )

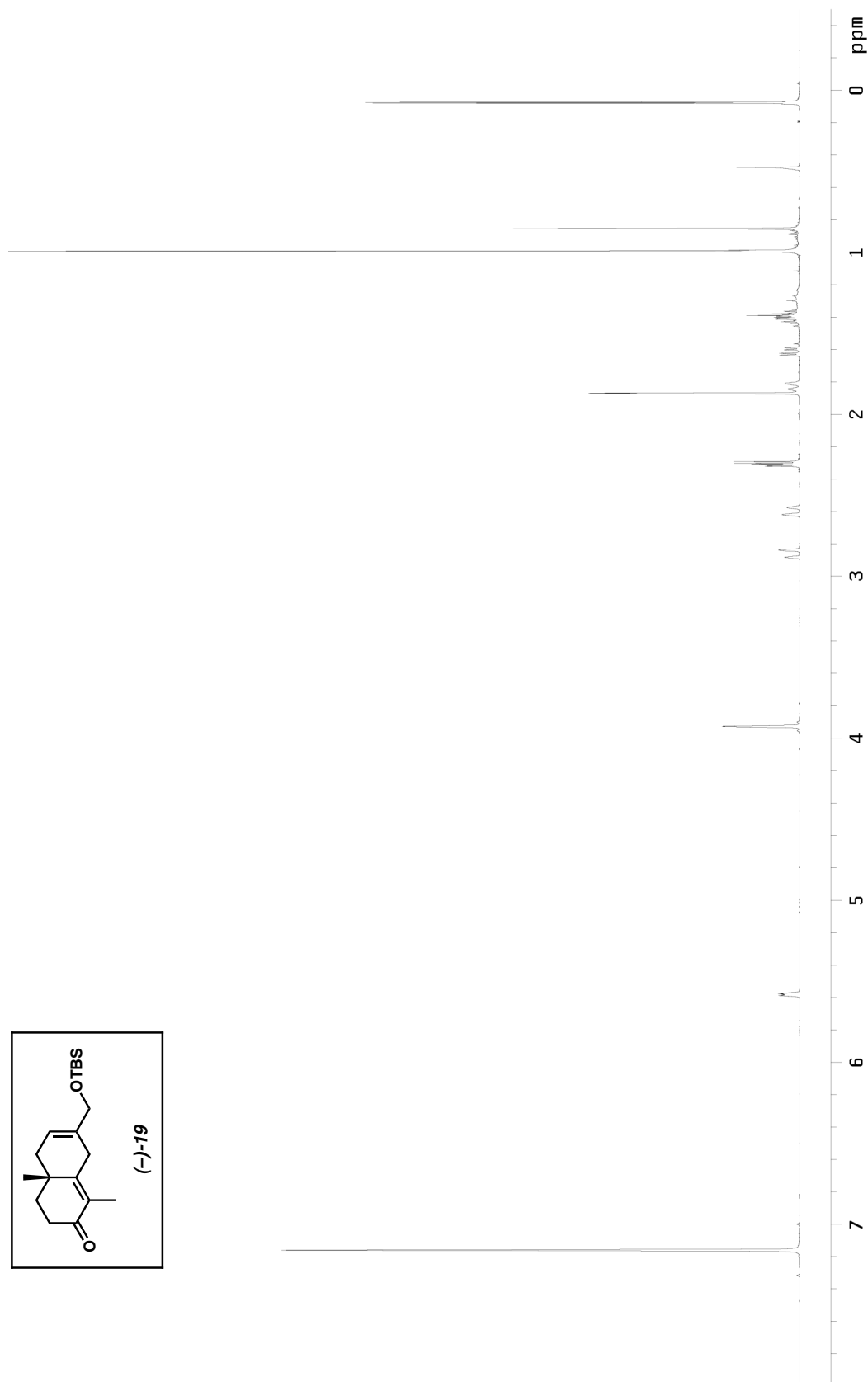
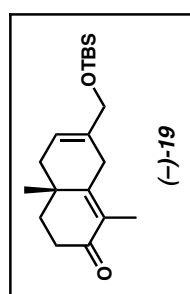


<sup>13</sup>C NMR spectrum of vinyllogous ester (-)-15 (126 MHz, CDCl<sub>3</sub>)

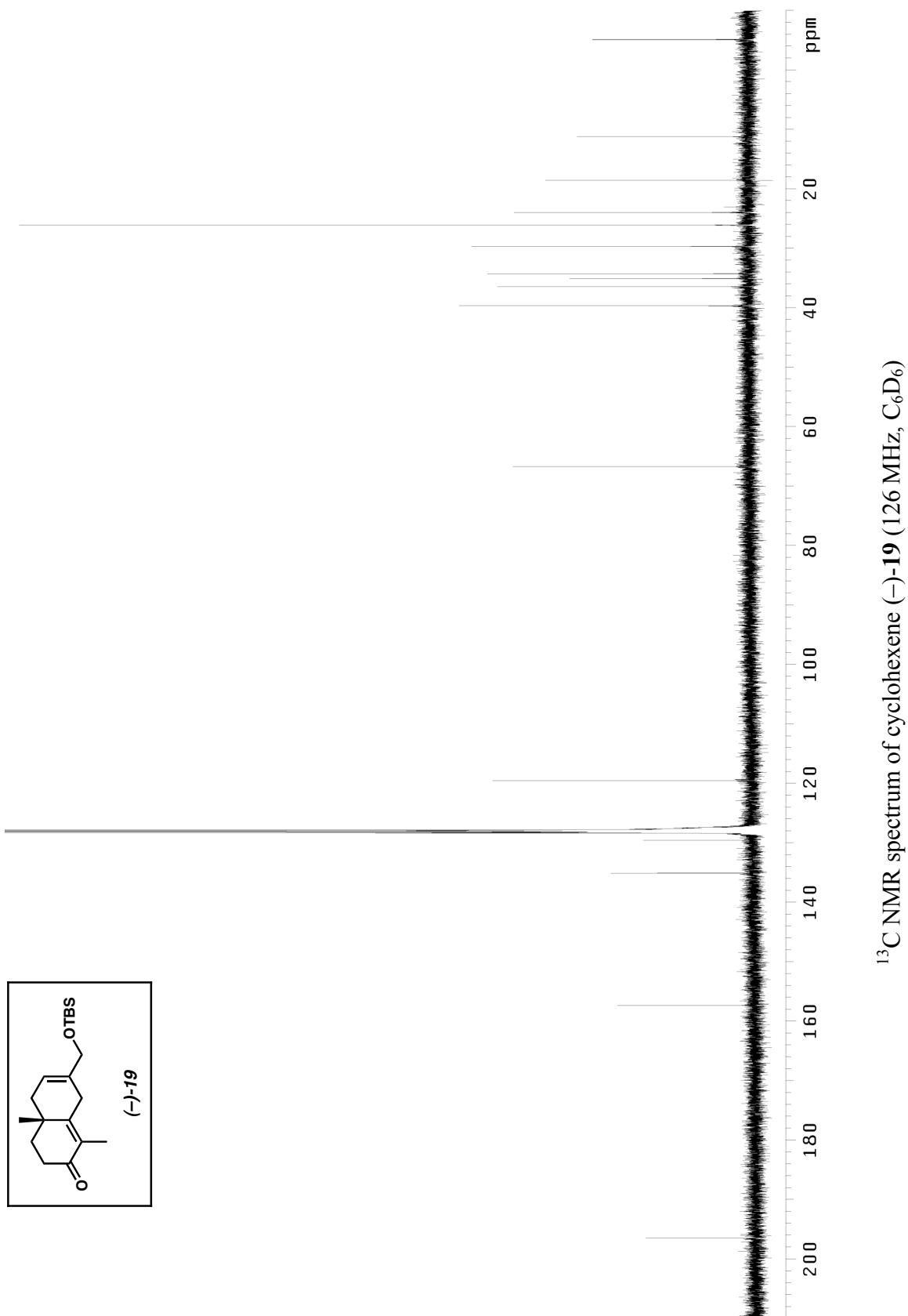


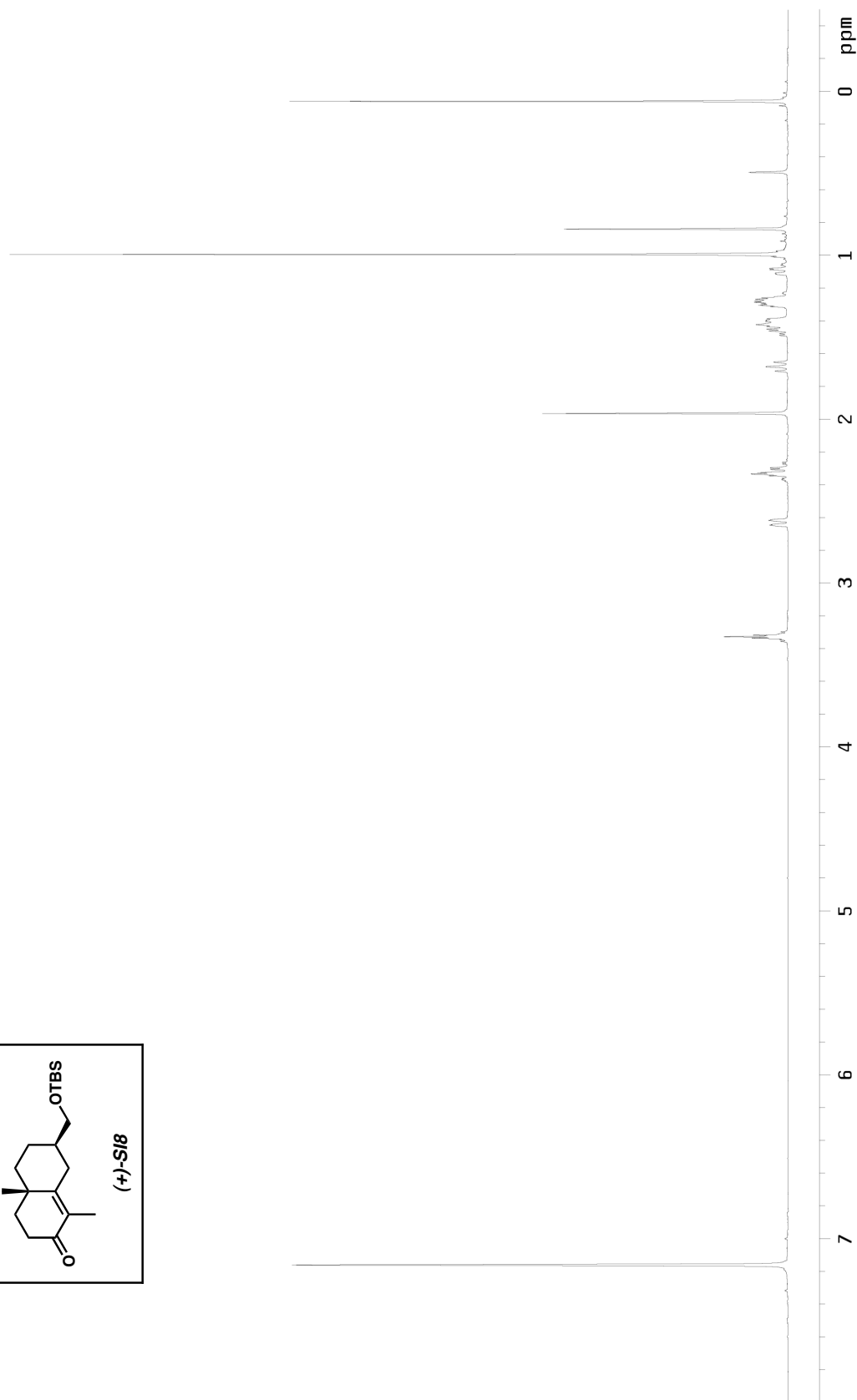
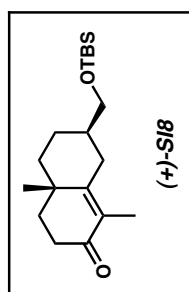




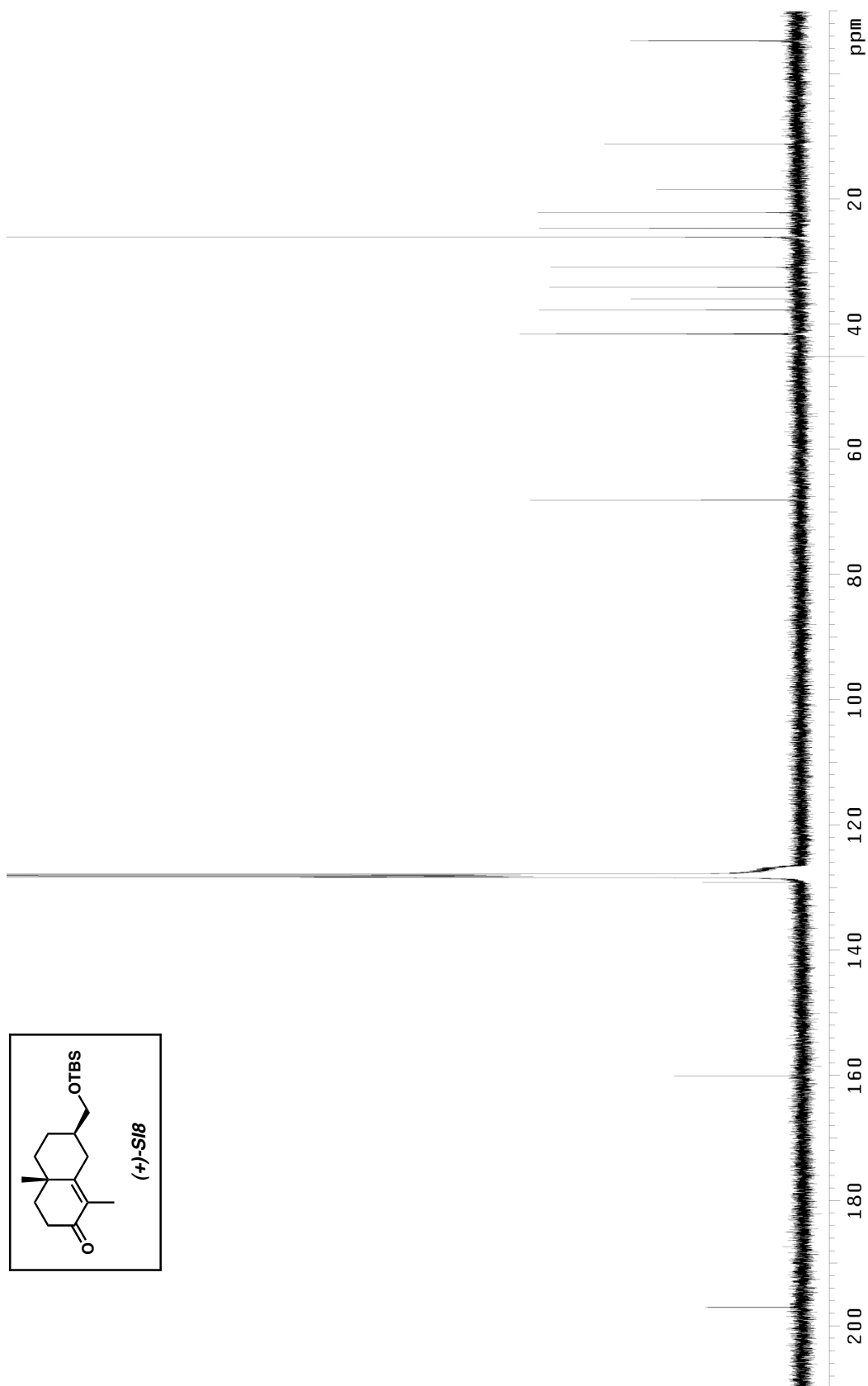


$^1\text{H}$  NMR spectrum of cyclohexene (-)-**19** (500 MHz,  $\text{C}_6\text{D}_6$ )

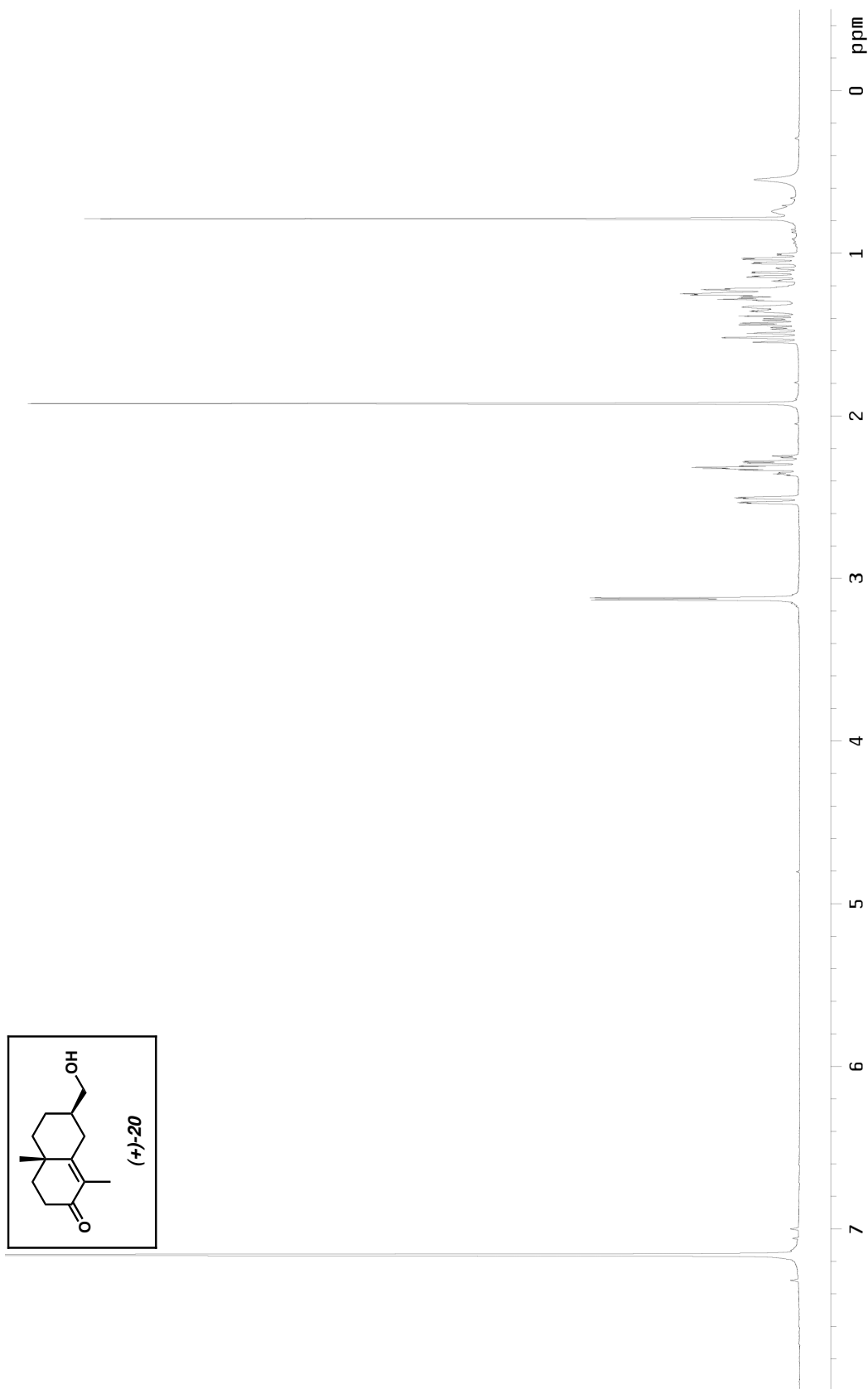


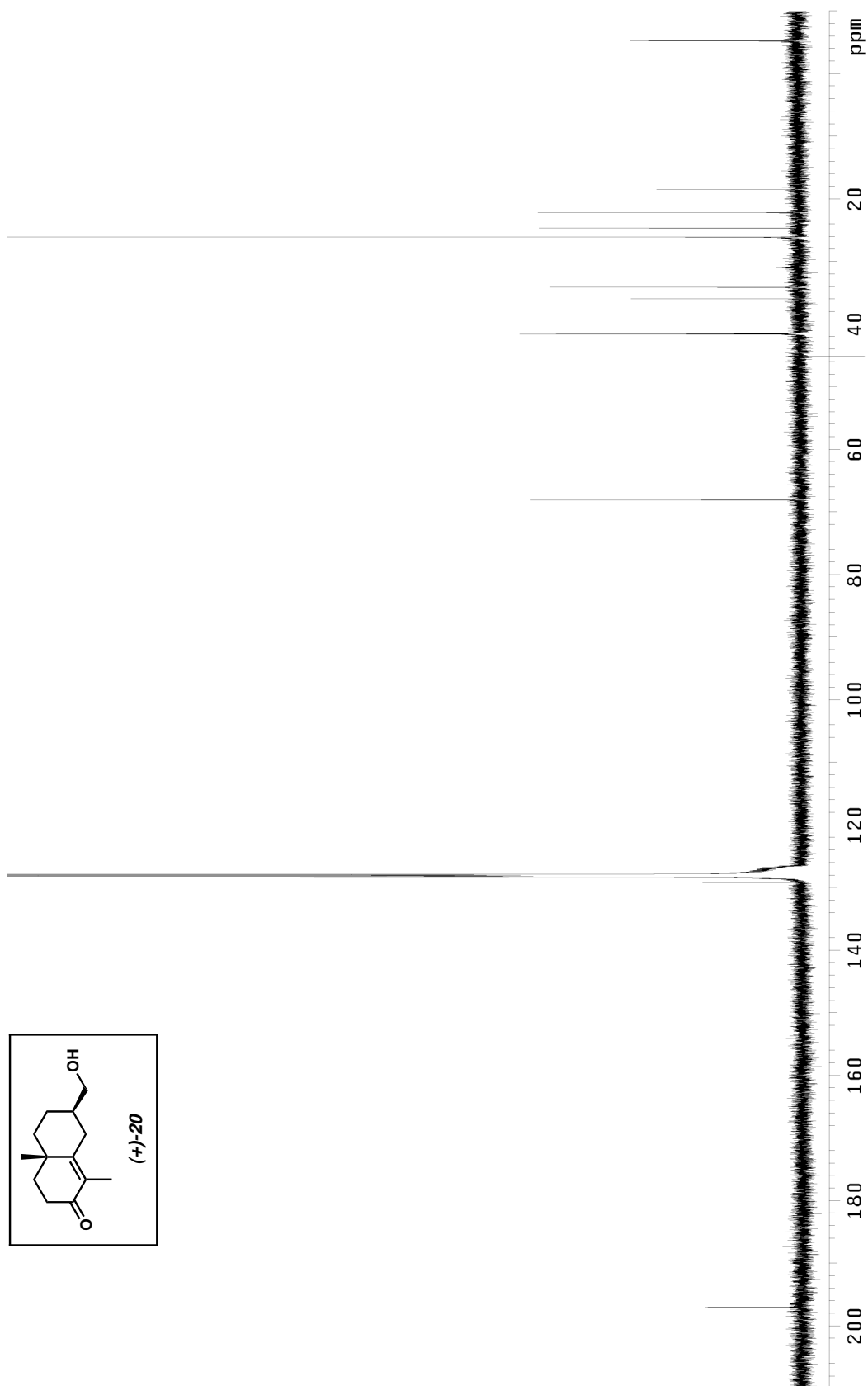


<sup>1</sup>H NMR spectrum of enone (+)-**SI8** (500 MHz, C<sub>6</sub>D<sub>6</sub>)

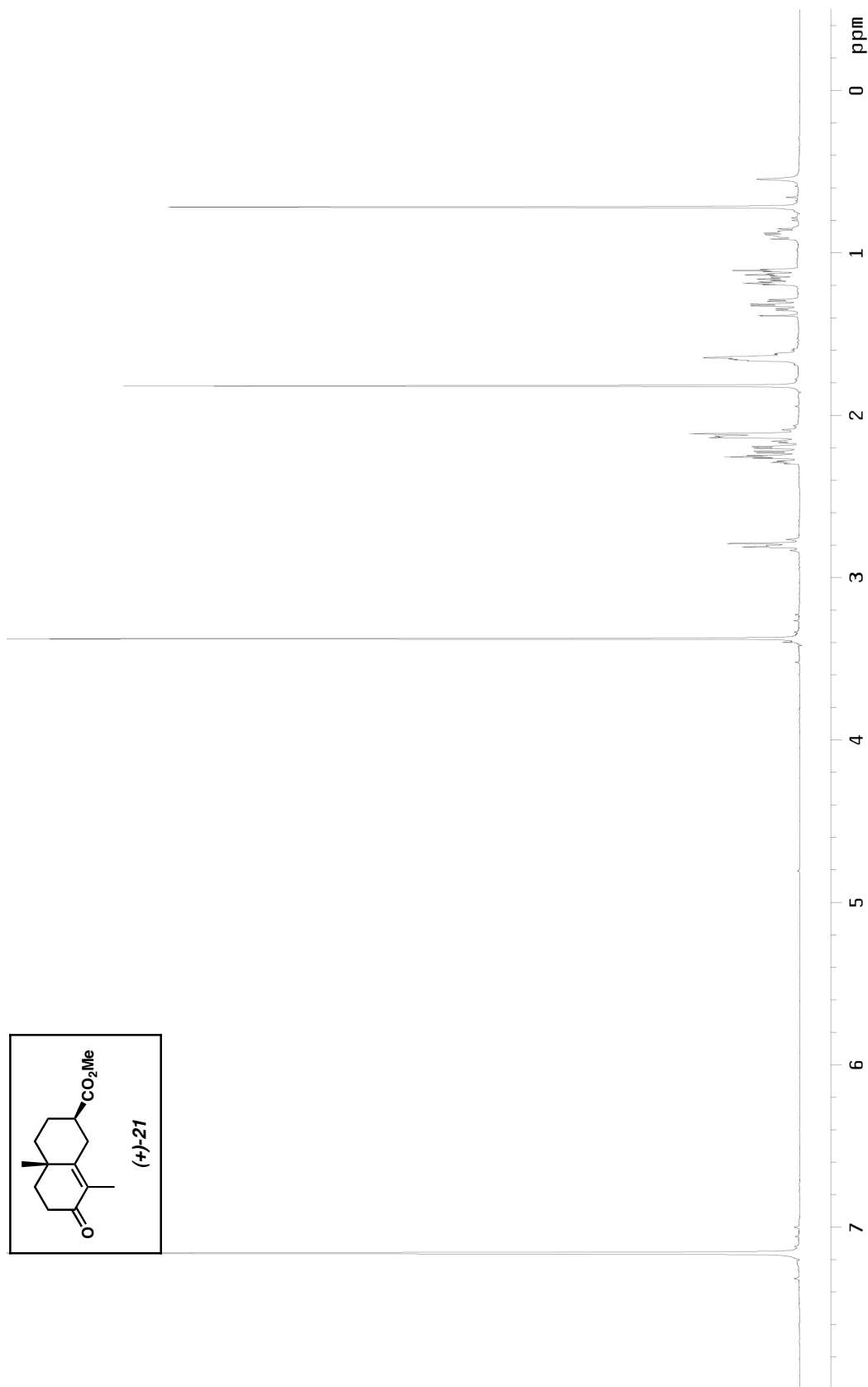


$^{13}\text{C}$  NMR spectrum of enone (+)-SI8 (126 MHz,  $\text{C}_6\text{D}_6$ )

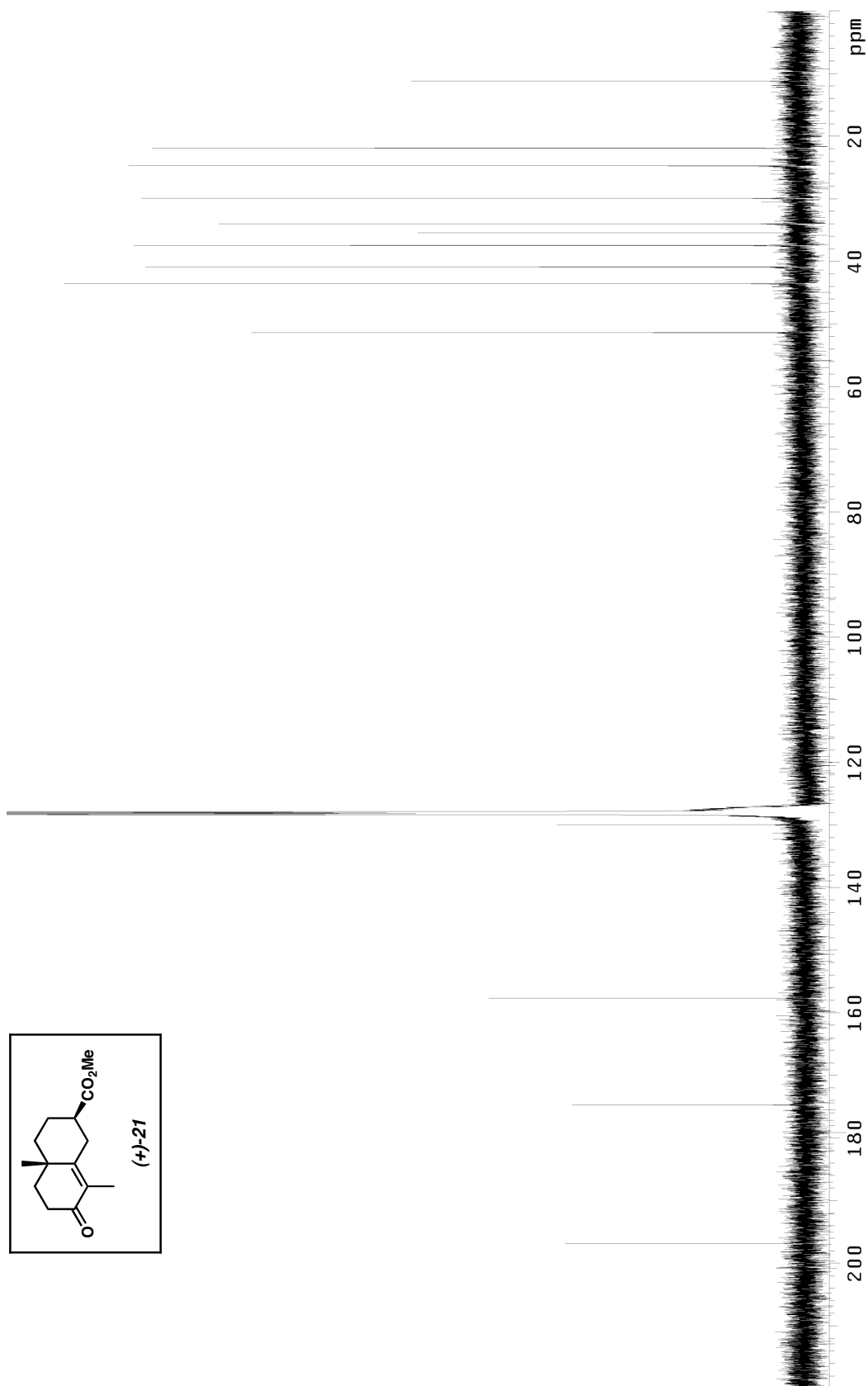




$^{13}\text{C}$  NMR spectrum of alcohol (+)-20 (126 MHz,  $\text{C}_6\text{D}_6$ )

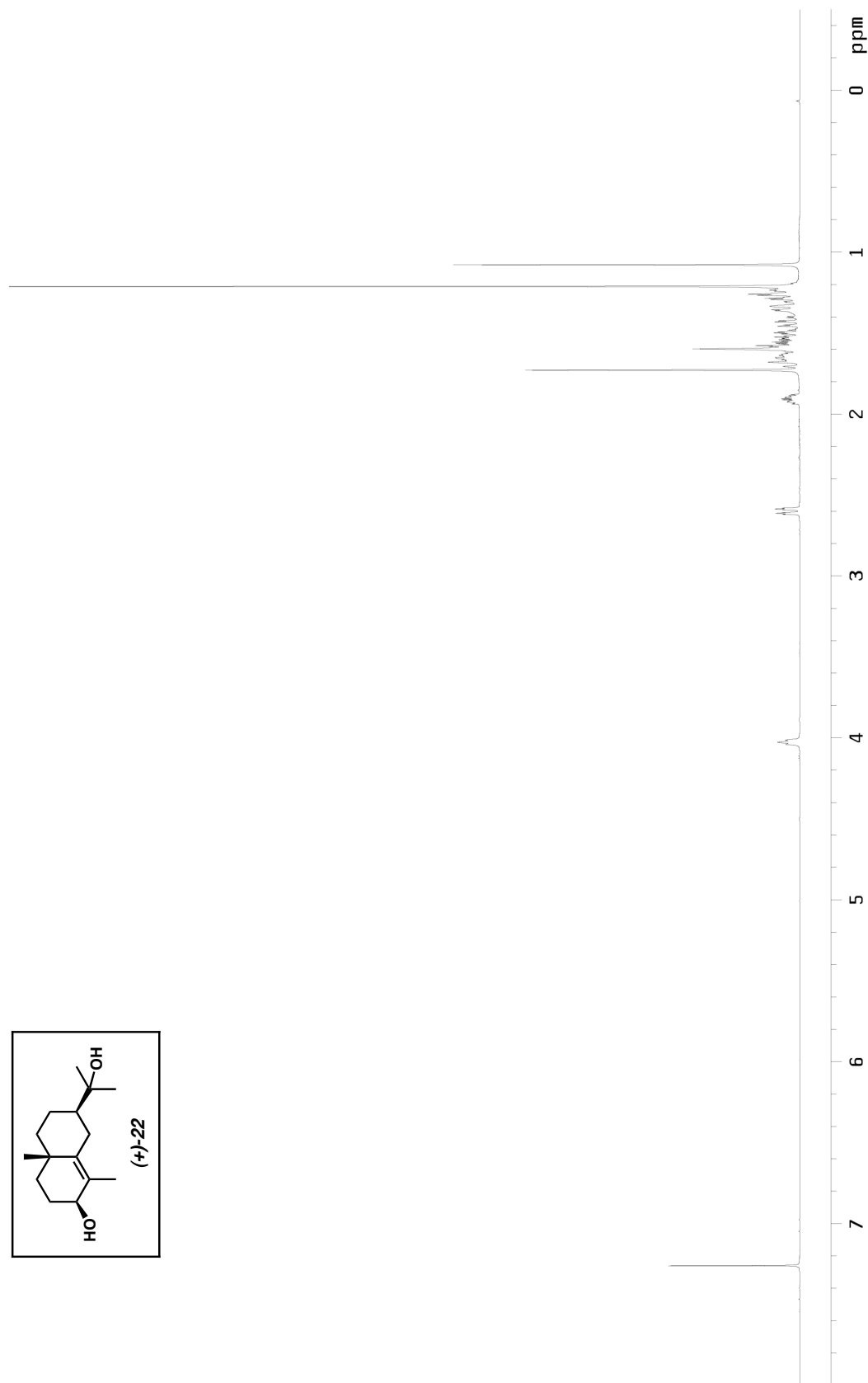
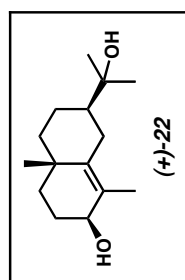


$^1\text{H}$  NMR spectrum of ester (+)-**21** (500 MHz,  $\text{C}_6\text{D}_6$ )

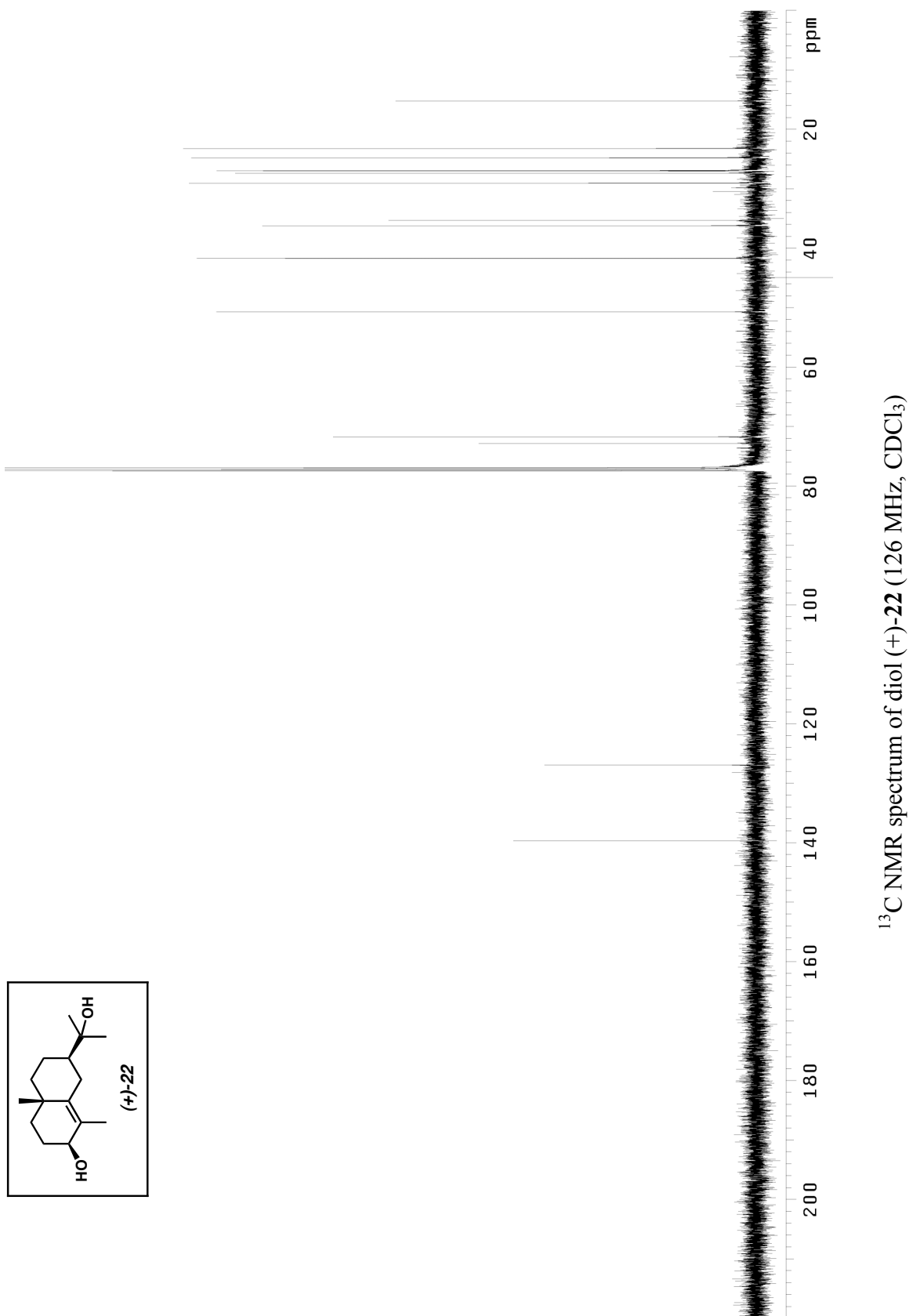


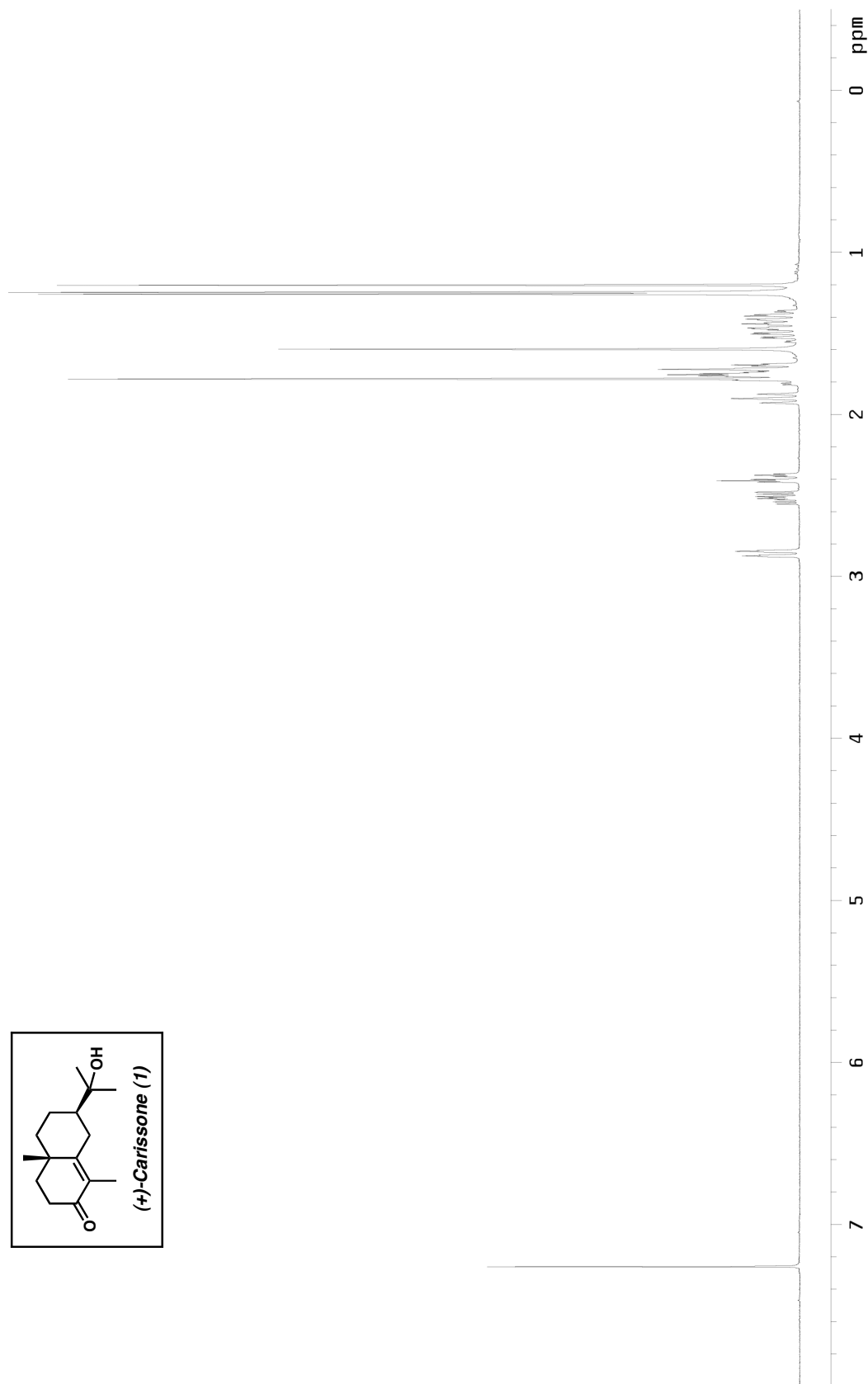
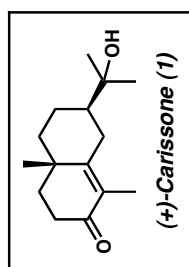
$^{13}\text{C}$  NMR spectrum of ester (+)-21 (126 MHz,  $\text{C}_6\text{D}_6$ )



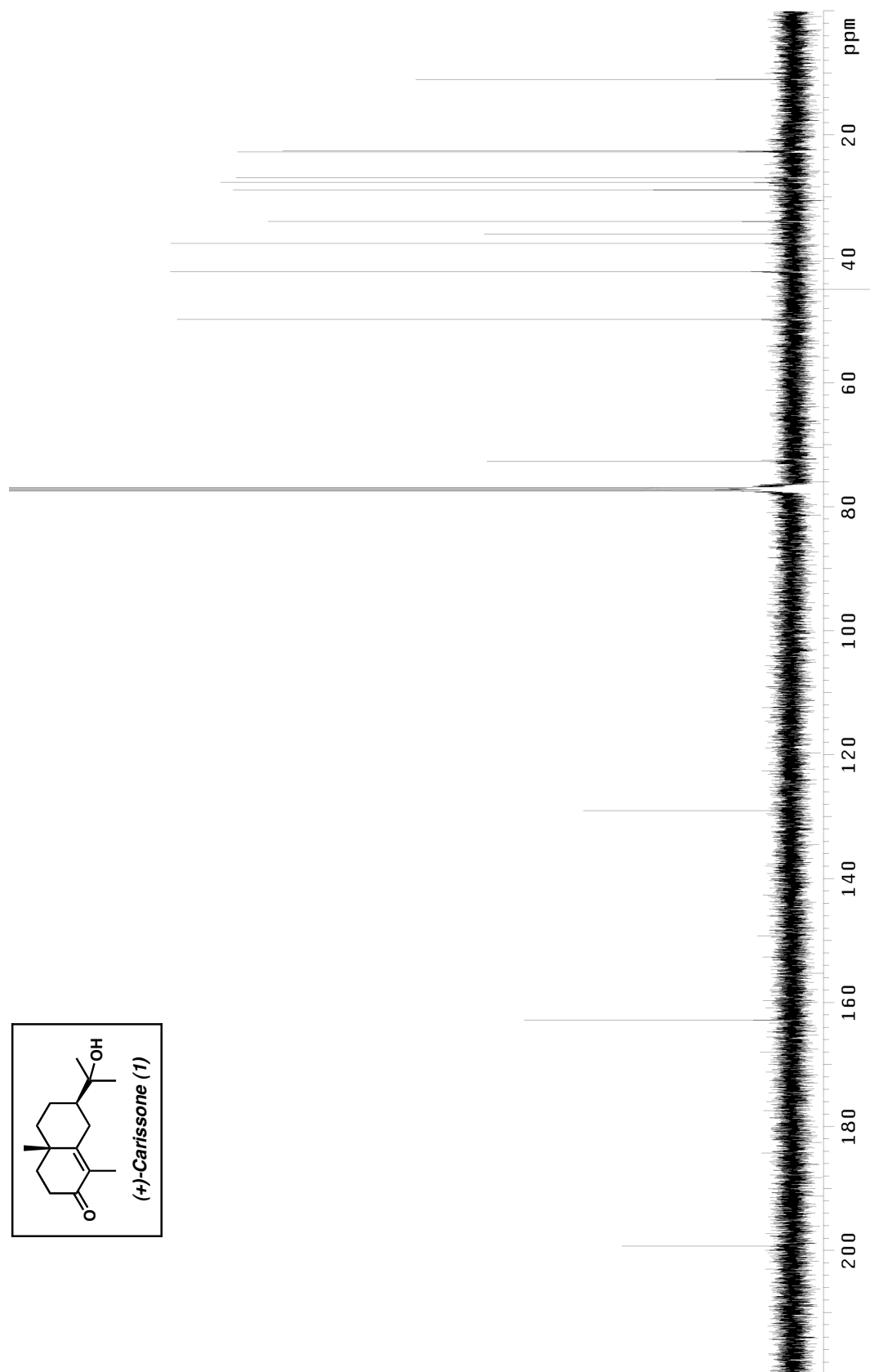
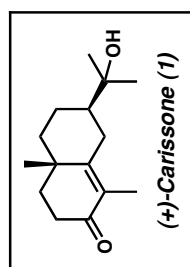


$^1\text{H}$  NMR spectrum of diol (+)-22 (500 MHz,  $\text{CDCl}_3$ )





<sup>1</sup>H NMR spectrum of (+)-carissone (**1**) (500 MHz, CDCl<sub>3</sub>)



$^{13}\text{C}$  NMR spectrum of (+)-carissone (**1**) (126 MHz,  $\text{CDCl}_3$ )

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