

SUPPORTING INFORMATION FOR  
**Concise Total Synthesis of (+)-Crocacin C**

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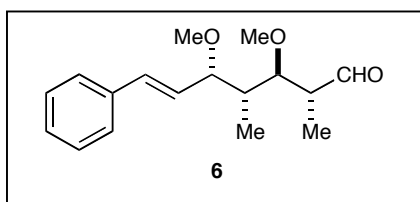
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CONTENTS:

<b>Experimental Procedures.....</b>	<b>S2-S4</b>
General methods.....	S2
Experimental procedures.....	S2-S4
<b>Copies of <sup>1</sup>H NMR Spectra.....</b>	<b>S5-S13</b>
<sup>1</sup> H NMR (400 MHz) Spectrum of Compound <b>11</b> .....	S5
<sup>1</sup> H NMR (400 MHz) Spectrum of Compound <b>12</b> .....	S7
<sup>1</sup> H NMR (400 MHz) Spectrum of Compound <b>13</b> .....	S9
<sup>1</sup> H NMR (300 MHz) Spectrum of Compound <b>14</b> .....	S11
<sup>1</sup> H NMR (400 MHz) Spectrum of Compound <b>(+)-Crocacin C (1)</b> .....	S13
<b>Copies of <sup>13</sup>C NMR Spectra.....</b>	<b>S6-S14</b>
<sup>13</sup> C NMR (100 MHz) Spectrum of Compound <b>11</b> .....	S6
<sup>13</sup> C NMR (100 MHz) Spectrum of Compound <b>12</b> .....	S8
<sup>13</sup> C NMR (100 MHz) Spectrum of Compound <b>13</b> .....	S10
<sup>13</sup> C NMR (100 MHz) Spectrum of Compound <b>14</b> .....	S12
<sup>13</sup> C NMR (100 MHz) Spectrum of Compound <b>(+)-Crocacin C (1)</b> .....	S14
<b>Figure S1. LC component of LCMS trace of synthetic Crocacin C (1).....</b>	<b>S15</b>
<b>Figure S2. MS component of LCMS trace of synthetic Crocacin C (1).....</b>	<b>S16</b>

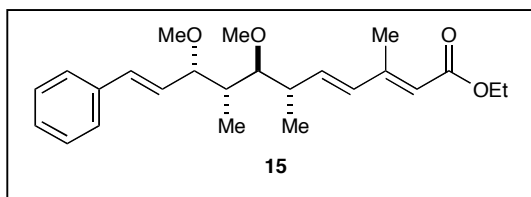
**General Methods.** All reactions containing water or air sensitive reagents were performed in oven-dried glassware under nitrogen or argon. Propionimide **7** was prepared according to the procedure of Evans (Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127). Phosphonate **5** was prepared according to the procedure of Thomas (Mata, E. G.; Thomas, E. J. *J. Chem. Soc., Perkin Trans 1*, **1995**, 785). Tetrahydrofuran and dichloromethane were passed through two columns of neutral alumina. Acetonitrile, chloroform, DMPU, DMSO, diisopropylamine, diisopropylethyl-amine, and triethylamine were distilled from calcium hydride. Propionaldehyde and *trans*-cinnamaldehyde (**8**) were both distilled prior to use. Methanol was distilled from magnesium. All other reagents were purchased from commercial sources and used without further purification. All solvents for work-up procedures were used as received. Flash column chromatography was performed according to the procedure of Still (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923) using ICN Silitech 32-63 D 60Å silica gel with the indicated solvents. Thin layer chromatography was performed on Analtech 60F<sub>254</sub> silica gel plates. Detection was performed using either UV light, KMnO<sub>4</sub> stain, *p*-anisaldehyde (PAA) or phosphomolybdic acid (PMA) stain and subsequent heating. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at the indicated field strength in the indicated solvent at rt. Chemical shifts are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS, δ = 0.00) and referenced to either CDCl<sub>3</sub> or acetone-*d*<sub>6</sub>. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).



**Aldehyde 6.** To a stirred solution of **14** (40.0 mg, 0.09 mmol) in THF (2.0 mL) were added MeOH (1.26 mg, 0.20 mmol) and LiBH<sub>4</sub> (5.0 mg, 0.20 mmol) at 0 °C. After stirring for 1.5 h at this temperature, the

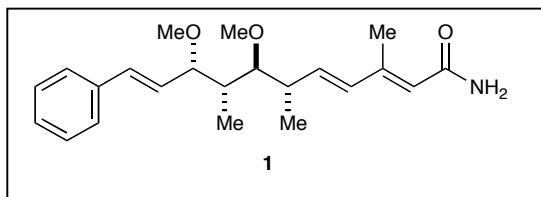
reaction mixture was quenched with 1 M NaOH solution (0.5 mL) and stirred for additional 5 min. The reaction mixture was extracted with (3 x 5 mL) of CH<sub>2</sub>Cl<sub>2</sub>, washed with brine solution (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to afford 15.9 mg (64%) of alcohol as a yellow oil. Spectral data for the alcohol matched those reported in the literature (Dias, L. C.; de Oliveira, L.

G. *Org. Lett.* **2001**, 3, 3951-3954). To a stirred solution of the alcohol (15.9 mg, 0.057 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) at rt was added the Dess Martin periodinane (48.4 mg, 0.11 mmol). The reaction mixture was stirred for 20 min. Saturated aqueous NaHCO<sub>3</sub> (1.0 mL), aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (1.5 M, 1.0 mL) and Et<sub>2</sub>O (3 mL) were added sequentially and stirring was continued for 15 min. The aqueous layer was back-extracted with Et<sub>2</sub>O (3x2 mL). The combined organic layers were washed with brine solution (4 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to afford 14.5 mg (59% from **14**) of aldehyde **6** as a yellow oil. Spectral data for aldehyde **6** matched those reported in the literature (Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2001**, 3, 3951-3954).



**Dienoate 15.** To a solution of diisopropylamine (38.5 mg, 0.38 mmol) in THF (1.0 mL) at -78 °C was added *n*-BuLi (2.04 M in hexane, 1.78 mL, 0.36 mmol).

The reaction mixture was stirred at this temperature for 30 min. DMPU (286 mg, 1.03 mmol) was added, and the reaction mixture and stirred an additional 5 min. Phosphonate **5** (96.0 mg, 0.36 mmol) in THF (0.2 mL) was added to the reaction mixture followed immediately by aldehyde **6** (50.0 mg, 0.18 mmol) in THF (0.2 mL). The reaction mixture was stirred at -78 °C for 8 h and quenched by the addition of saturated aqueous NH<sub>4</sub>Cl solution (1.5 mL) and warmed to rt. The reaction mixture was diluted with EtOAc (25 mL), washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:19) to afford 40.0 mg (57%) of dienoate **15** as a colorless oil. Spectral data for **15** matched those reported in the literature (Chakraborty, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, 57, 9461-9467).

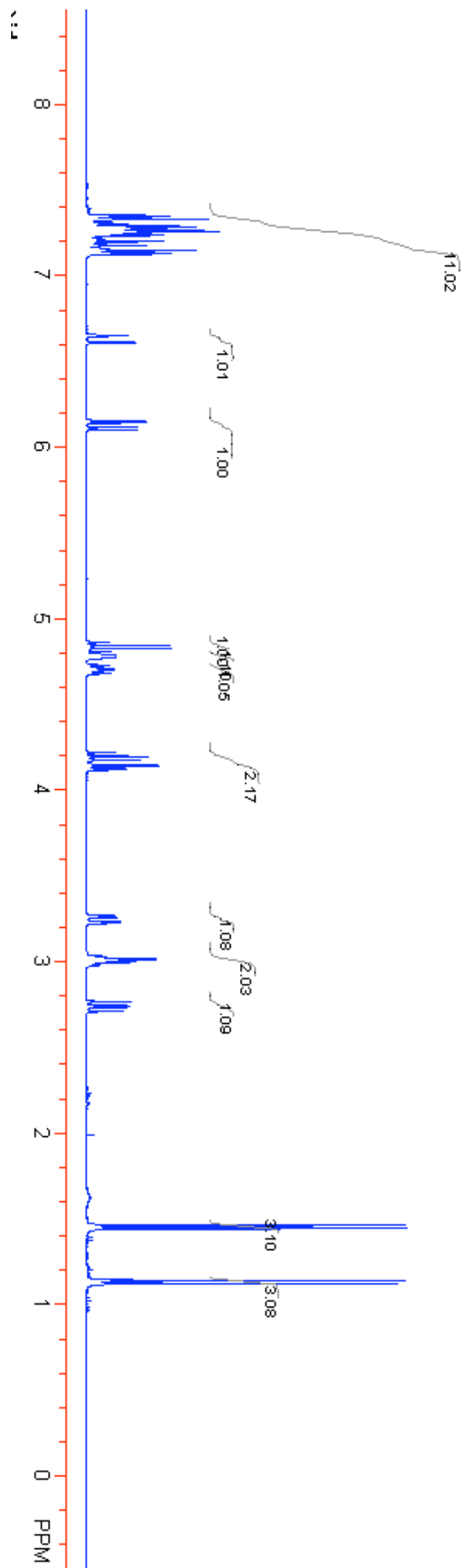
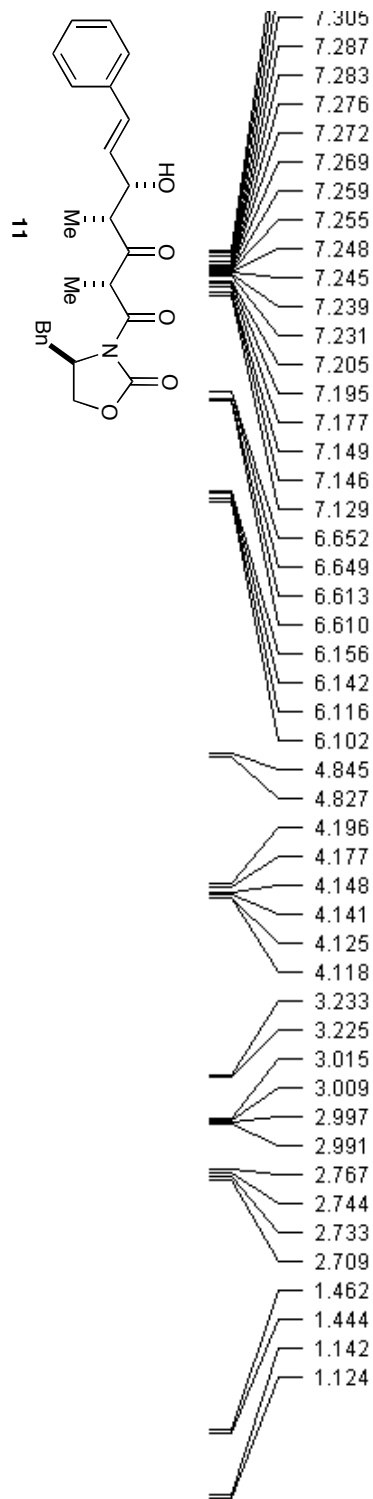


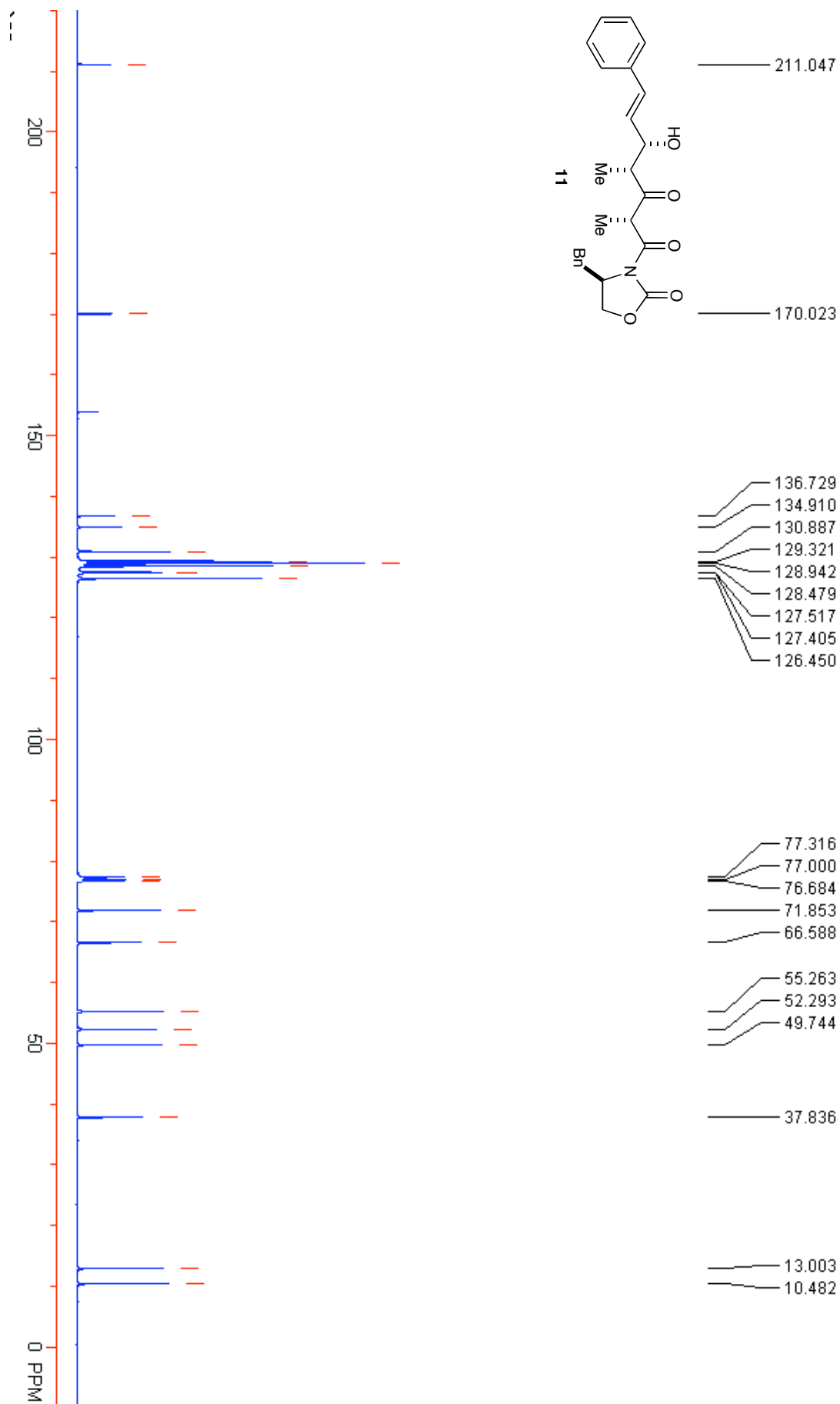
**Crocacin C (1).** To a solution of dienoate **15** (32.0 mg, 0.09 mmol) in THF/MeOH/H<sub>2</sub>O (3:1:1, 1.0 mL) at 0 °C was added LiOH·H<sub>2</sub>O (67 mg, 1.59 mmol) in one portion. The

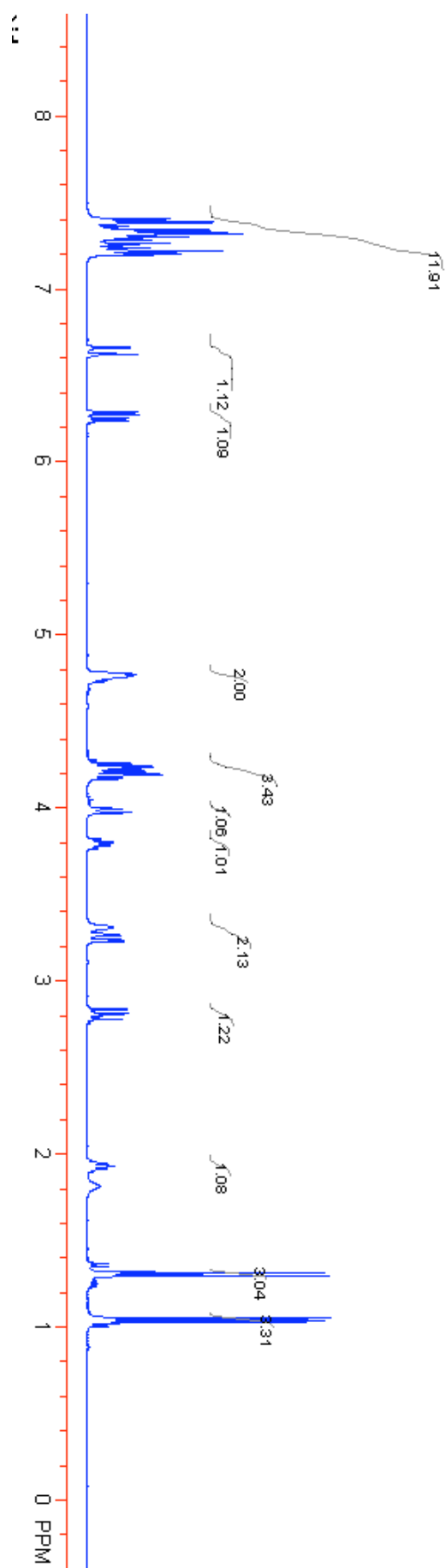
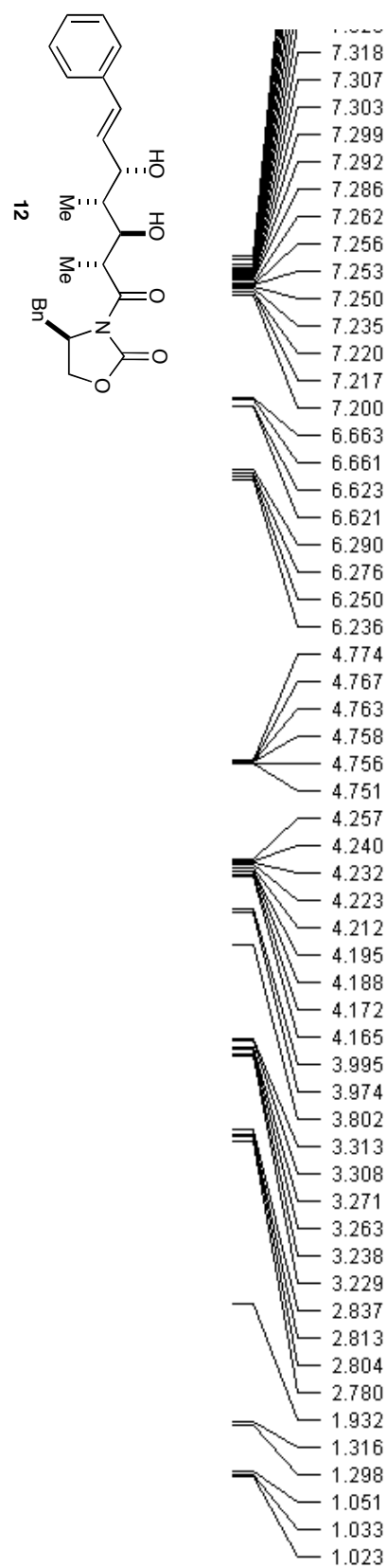
reaction mixture was stirred at rt for 15 h, cooled to 0 °C and acidified to pH 2 with 1 M

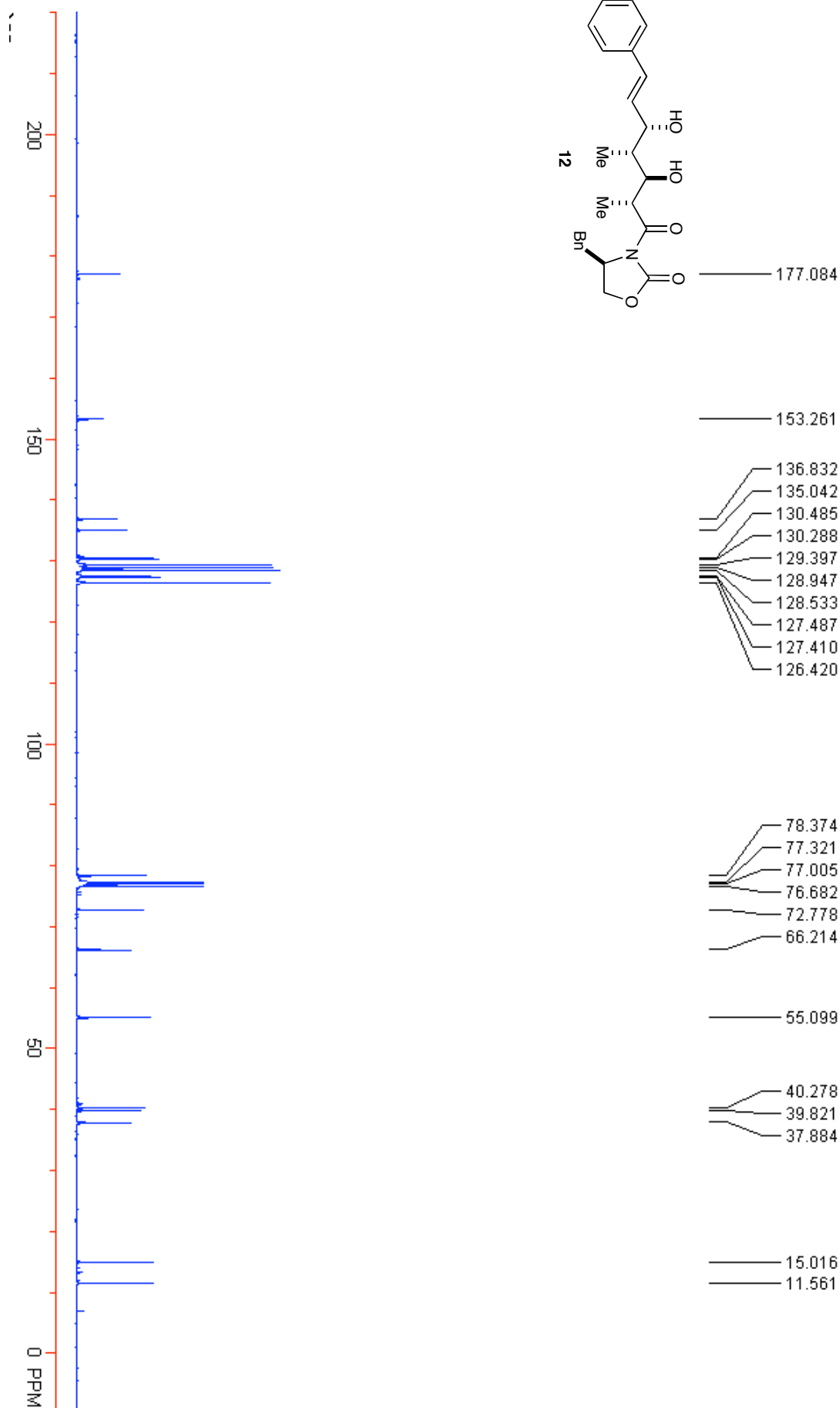
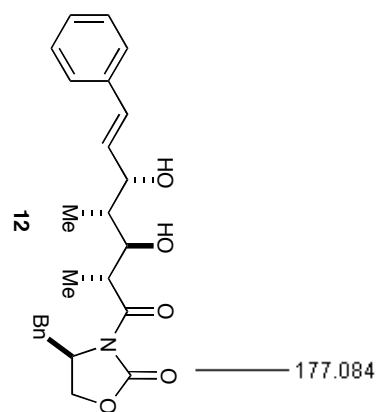
HCl. The reaction mixture was diluted with EtOAc (10 mL) and washed with brine (5 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and filtered. The solvent was concentrated under reduced pressure, and the crude acid was dissolved in THF (0.7 mL) and cooled to  $-20\text{ }^\circ\text{C}$ . Triethylamine (8.8 mg, 0.09 mmol) was added. After stirring for 5 min, ethyl chloroformate (10 mg, 0.09 mmol) was added, and the reaction mixture was stirred at  $-20\text{ }^\circ\text{C}$  for an additional 30 min at which point  $\text{NH}_4\text{OH}$  solution (25% aq., 0.035 mL, 0.5 mmol) was added. The reaction mixture was warmed to  $0\text{ }^\circ\text{C}$  and stirred for 20 min. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  solution (5 mL), extracted with EtOAc (10 mL), washed with brine (5 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and filtered. The solvent was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:1) to afford 18.7 mg (63%) of Crocacin C (**1**) as a colorless semi-solid.

$[\alpha]_{\text{D}}^{20} +59.8^\circ$  ( $c$  0.31, MeOH), lit.  $[\alpha]_{\text{D}}^{20} +52.2$  ( $c$  0.3, MeOH);  $^1\text{H}$  NMR (400 MHz, acetone- $d_6$ )  $\delta$  7.52-7.50 (m, 2H), 7.38-7.34 (m, 2H), 7.29-7.27 (m, 1H), 6.72 (br s, 1H), 6.57 (d,  $J = 16.0$  Hz, 1H), 6.29 (dd,  $J = 16.4, 7.6$  Hz, 1H), 6.14-6.11 (m, 3H), 5.84 (s, 1H), 4.14-4.11 (m, 1H), 3.56 (s, 3H), 3.33 (s, 3H), 3.21 (dd,  $J = 9.6, 2.0$  Hz, 1H), 2.58-2.67 (m, 1H), 2.26 (d,  $J = 1.6$  Hz, 3H), 1.62-1.57 (m, 1H), 1.21 (d,  $J = 6.8$  Hz, 3H), 0.89 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz, acetone- $d_6$ )  $\delta$  169.4, 148.5, 138.3, 137.5, 135.5, 133.0, 130.9, 129.8, 129.7, 128.7, 127.7, 122.4, 87.6, 82.2, 61.9, 56.9, 43.9, 41.2, 19.7, 13.9, 10.5.

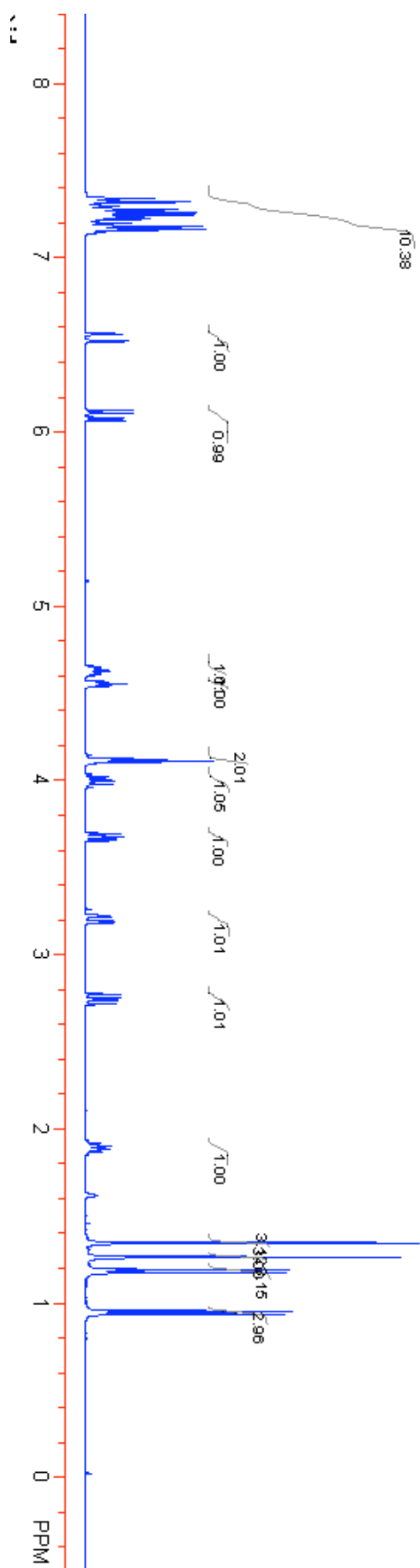
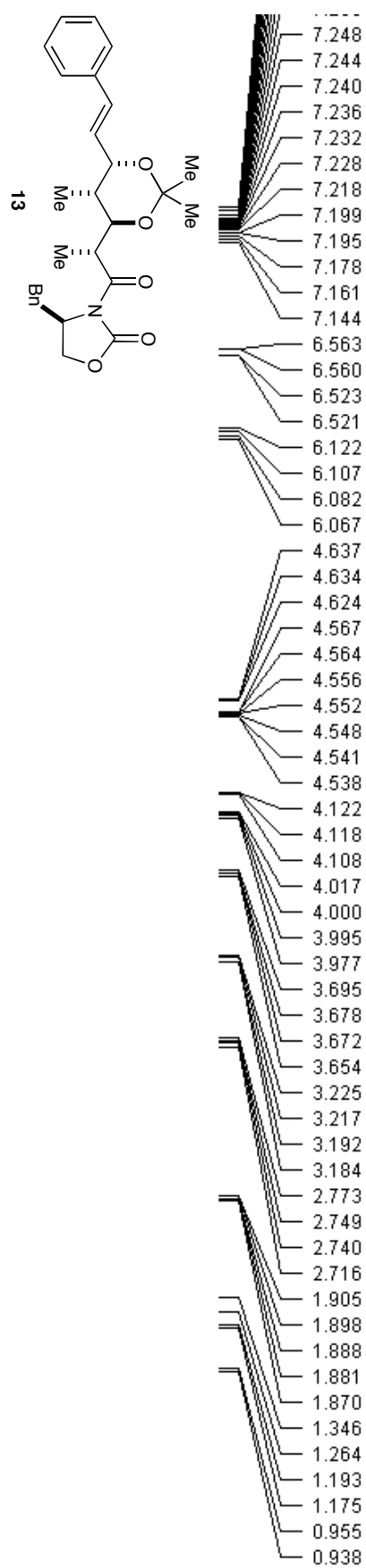


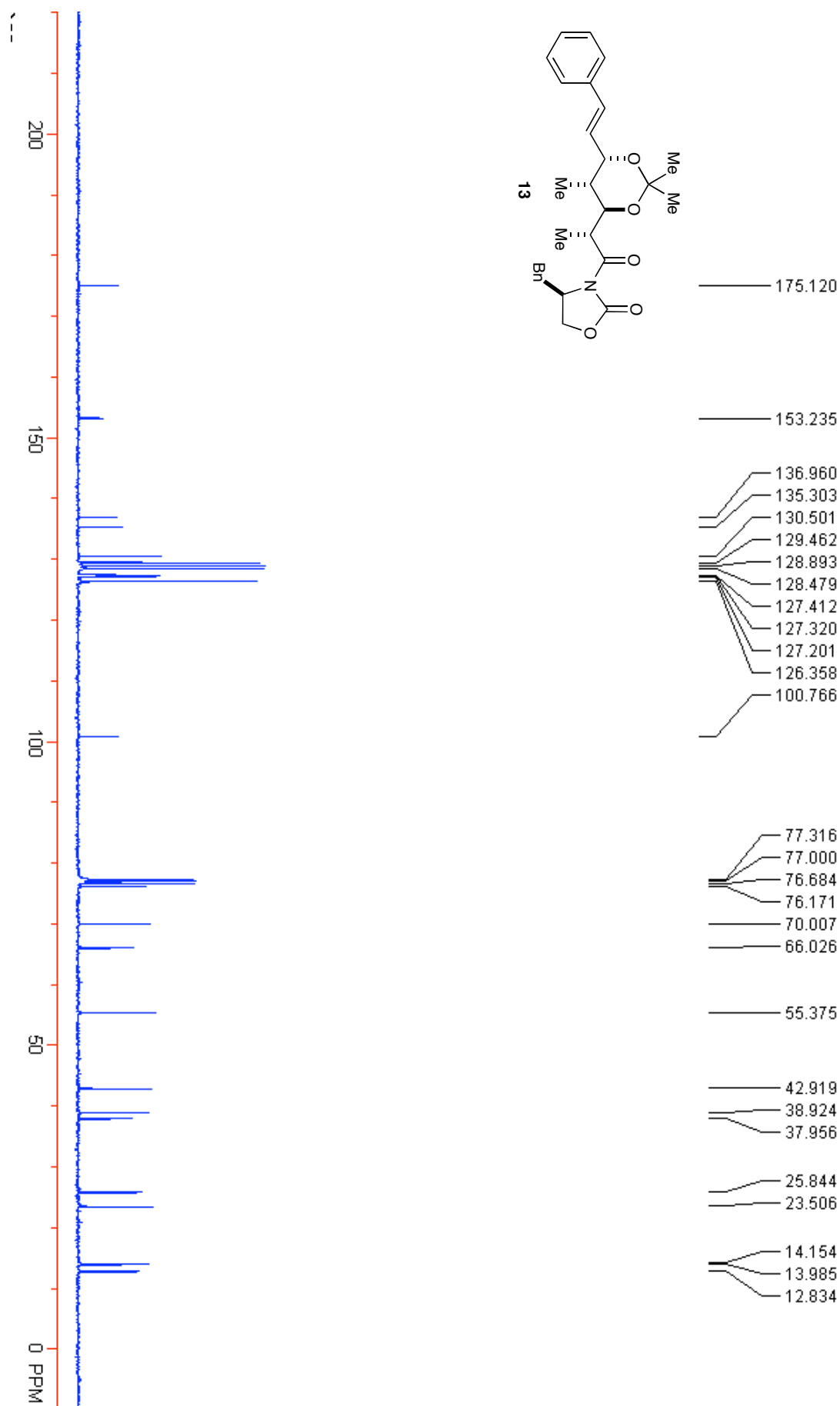


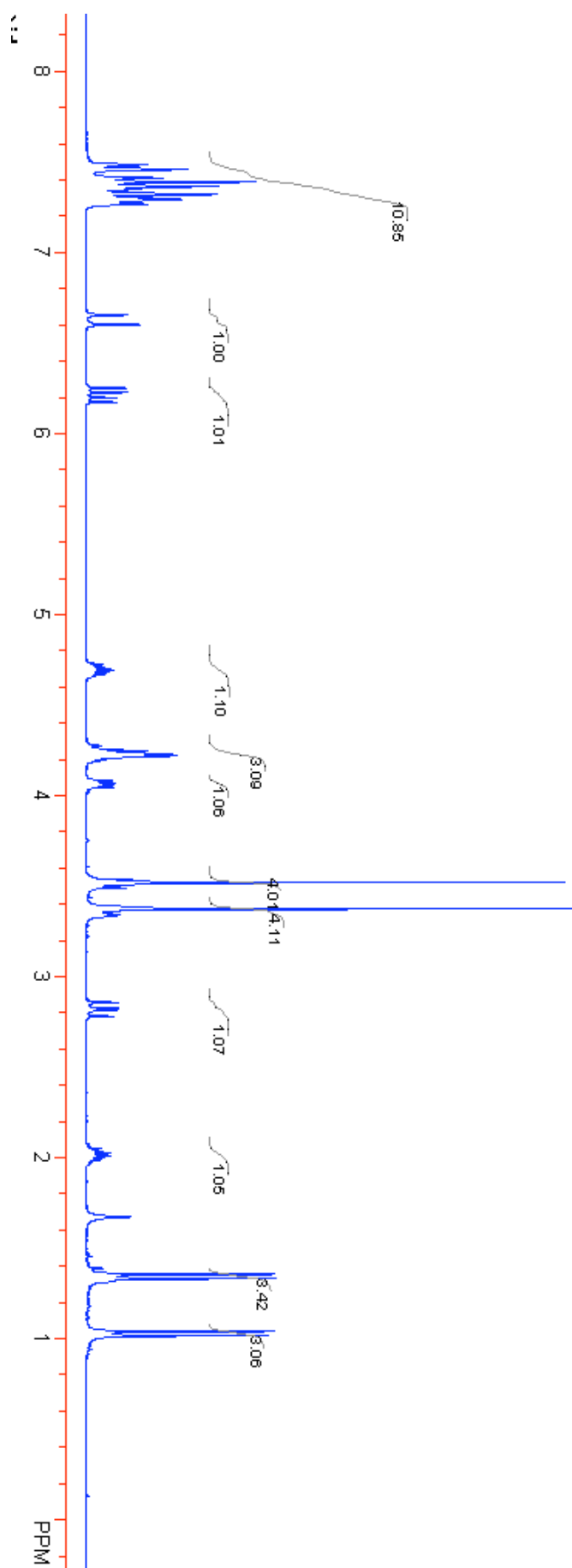
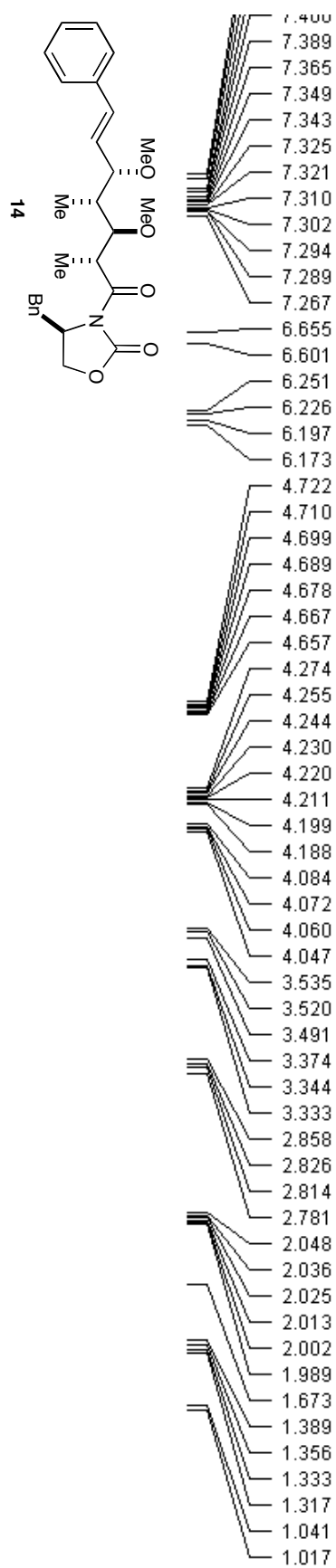


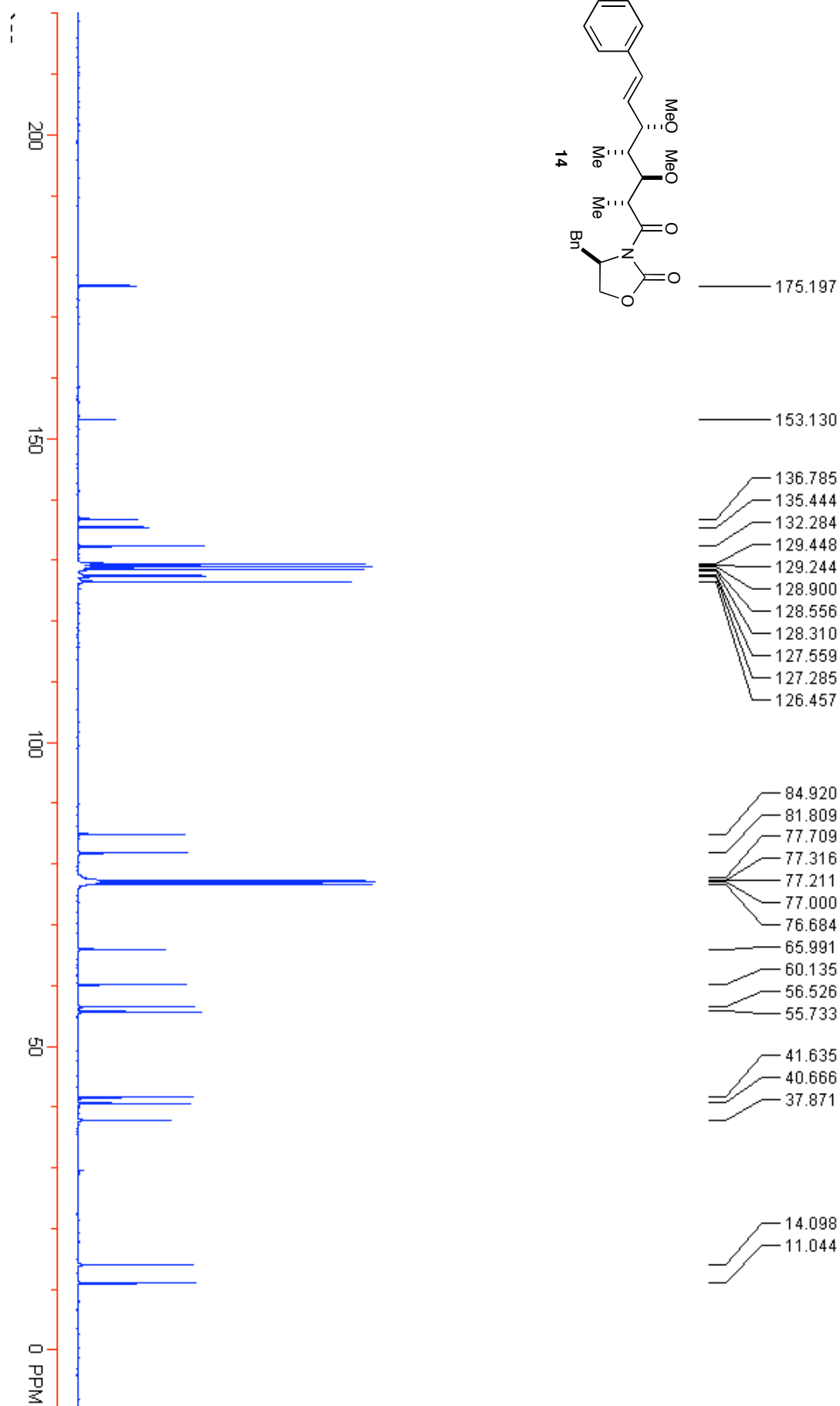
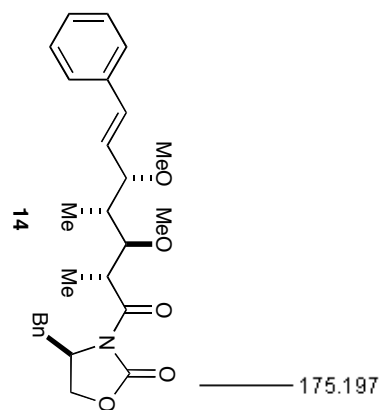


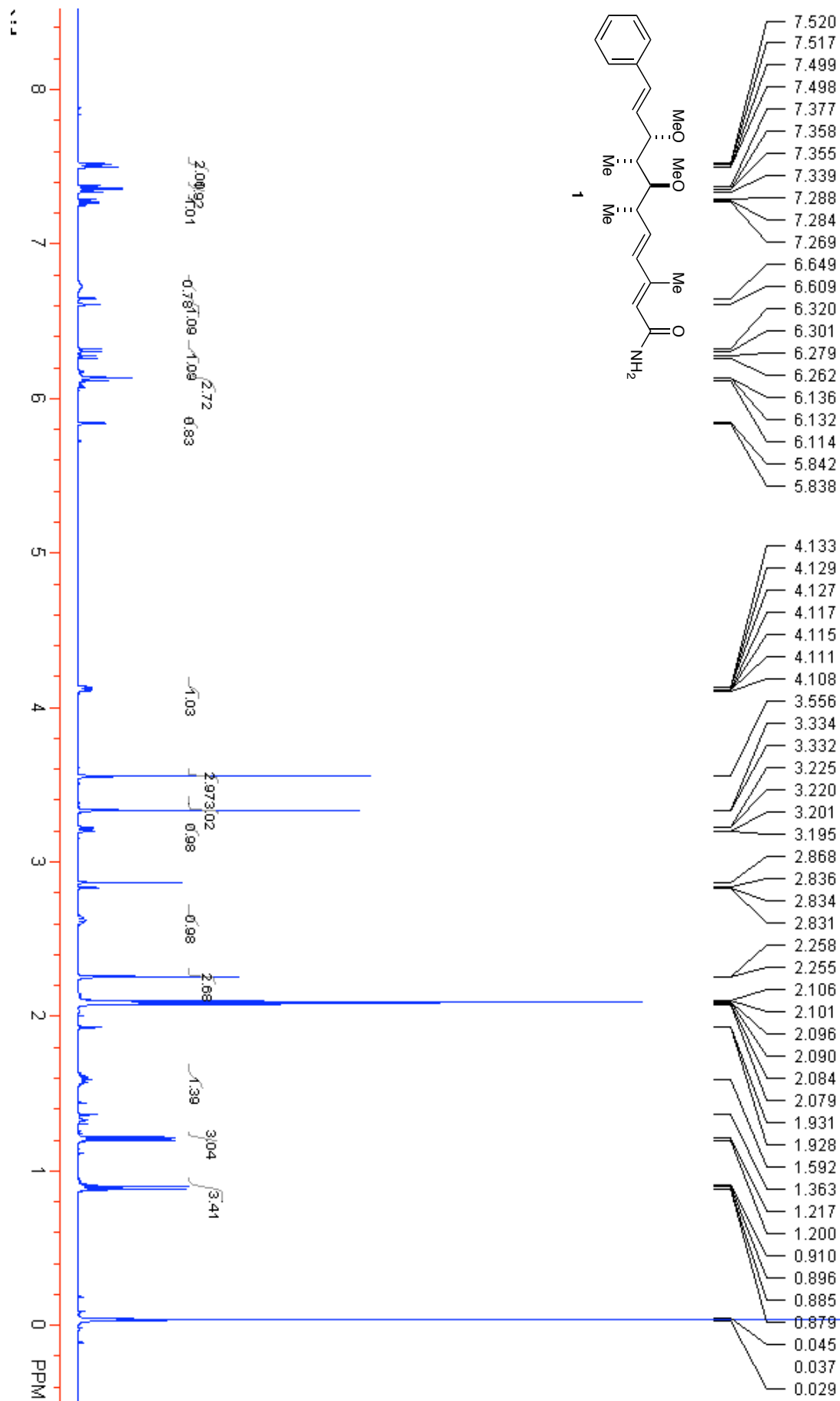


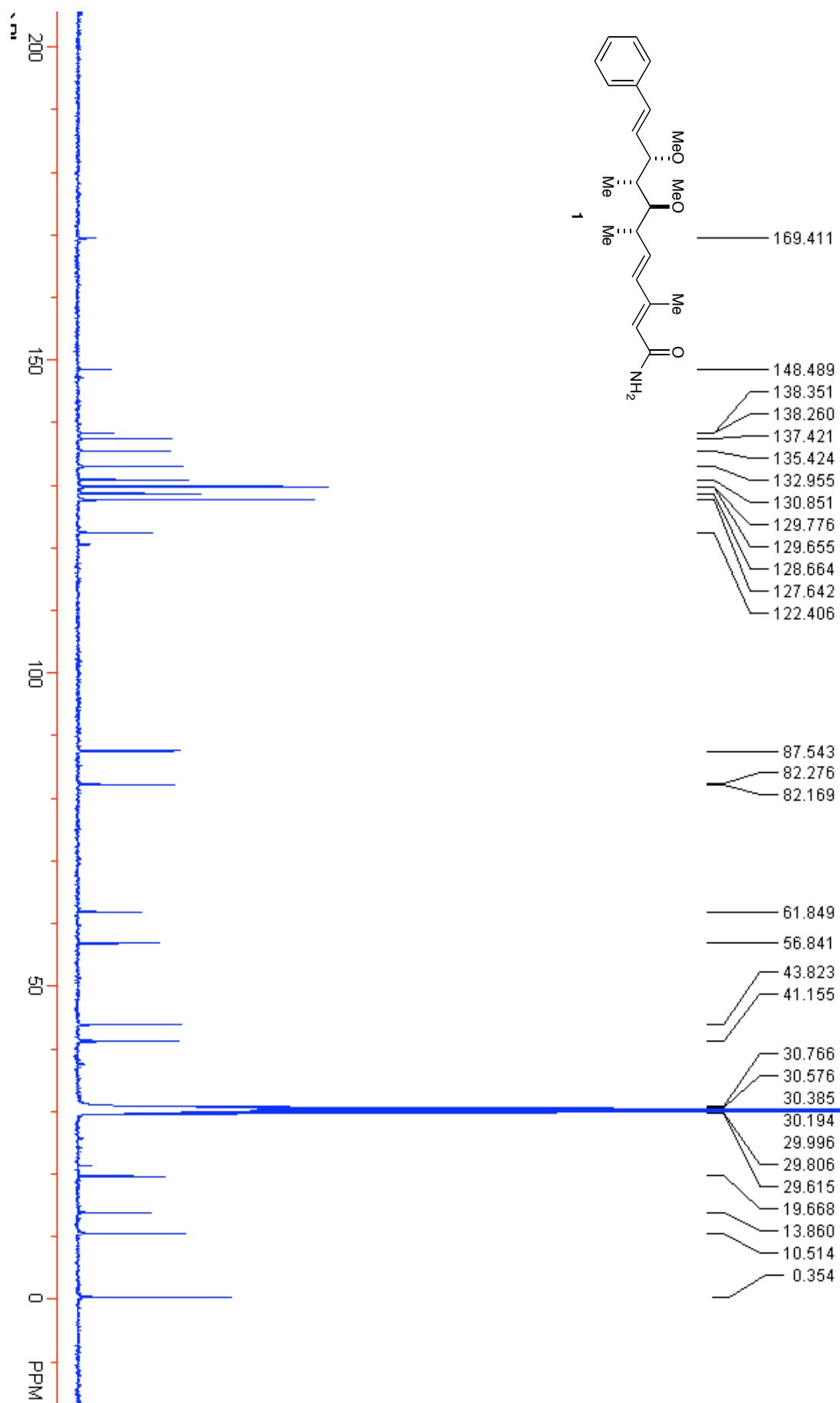




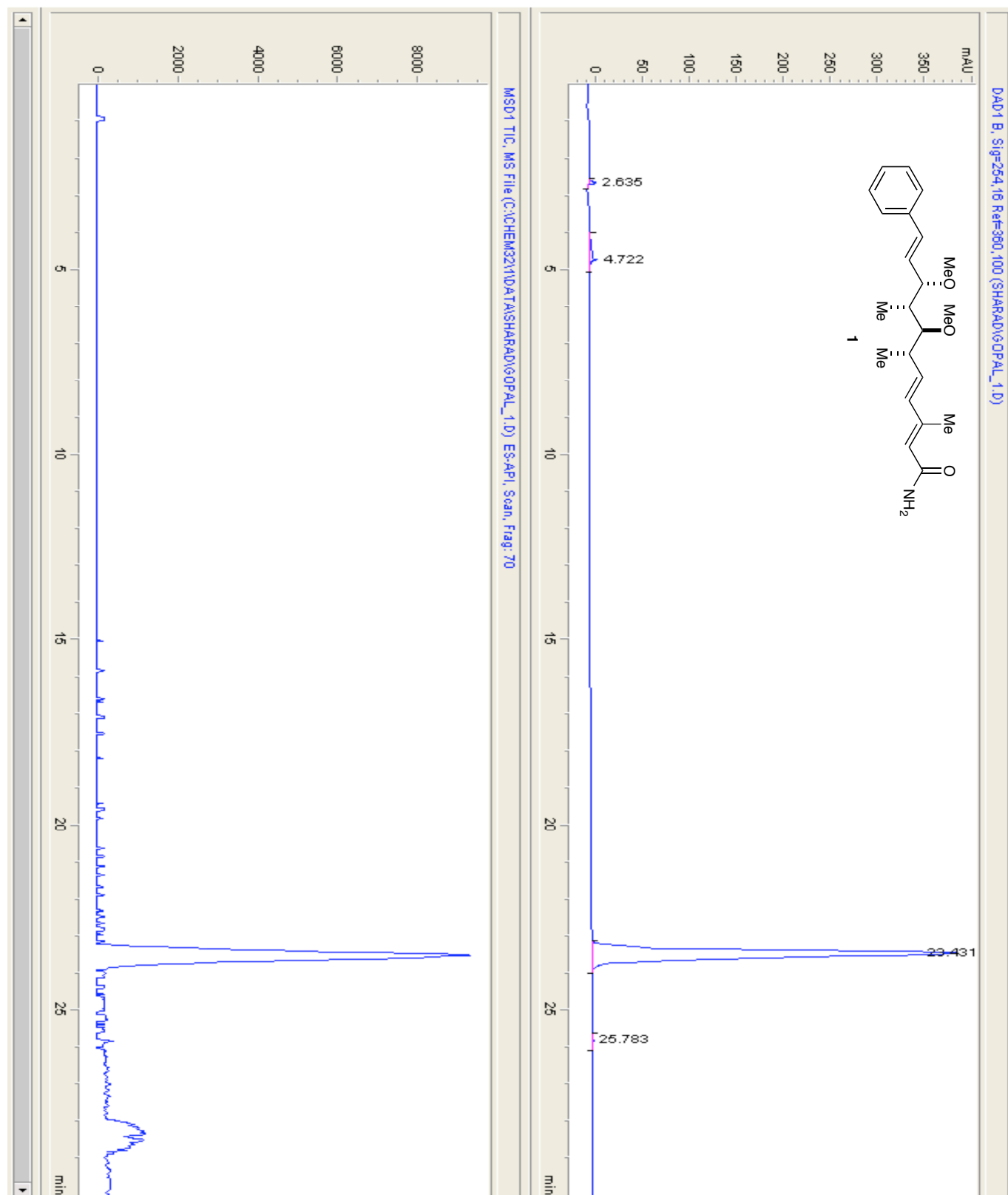








**Figure S1.** LC component of LCMS trace of synthetic Crocacin C (**1**).



**Figure S2.** MS component of LCMS trace of synthetic Crocacin C (1).

Print of window 80: MS Spectrum

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