

# Formal Synthesis of (+)-Brefeldin A: Application of a Zinc-mediated Ring Expansion Reaction

*Weimin Lin and Charles K. Zercher\**

Department of Chemistry, University of New Hampshire, Durham, NH 03824

\*[ckz@cisunix.unh.edu](mailto:ckz@cisunix.unh.edu)

## Supporting Information

1) General Experimental	S-2
2) Experimental procedures	
( <i>S,E</i> )-Ethyl 6-bromo-5-hydroxyhex-2-enoate ( <b>11</b> )	S-3
( <i>S,E</i> )-Ethyl 6-bromo-5-(methoxymethoxy)hex-2-enoate ( <b>6</b> );	
Procedure 1:	S-4
( <i>R,E</i> )-Ethyl 5-(hydroxy)-6-(tosyloxy)hex-2-enoate ( <b>9</b> )	S-5
( <i>R,E</i> )-Ethyl 5-(methoxymethoxy)-6-(tosyloxy)hex-2-enoate ( <b>10</b> )	S-6
( <i>S,E</i> )-Ethyl 6-bromo-5-(methoxymethoxy)hex-2-enoate ( <b>6</b> );	
Procedure 2:	S-6
3) NMR Spectra	
<sup>1</sup> H NMR Spectrum of <b>2</b>	S-8
<sup>13</sup> C NMR Spectrum of <b>2</b>	S-9

<sup>1</sup> H NMR Spectrum of <b>3A</b>	S-10
<sup>13</sup> C NMR Spectrum of <b>3A</b>	S-11
<sup>1</sup> H NMR Spectrum of <b>3B</b>	S-12
<sup>13</sup> C NMR Spectrum of <b>3B</b>	S-13
<sup>1</sup> H NMR Spectrum of <b>4</b>	S-14
<sup>13</sup> C NMR Spectrum of <b>4</b>	S-15
<sup>1</sup> H NMR Spectrum of <b>5</b>	S-16
<sup>13</sup> C NMR Spectrum of <b>5</b>	S-17
<sup>1</sup> H NMR Spectrum of <b>6</b>	S-18
<sup>13</sup> C NMR Spectrum of <b>7</b>	S-19
<sup>1</sup> H NMR Spectrum of <b>9</b>	S-20
<sup>1</sup> H NMR Spectrum of <b>10</b>	S-21
<sup>13</sup> C NMR Spectrum of <b>10</b>	S-22
<sup>1</sup> H NMR Spectrum of <b>11</b>	S-23
<sup>13</sup> C NMR Spectrum of <b>11</b>	S-24
<sup>1</sup> H NMR Spectrum of <b>13</b>	S-25
<sup>13</sup> C NMR Spectrum of <b>13</b>	S-26
<sup>1</sup> H NMR Spectrum of <b>14</b>	S-27
<sup>13</sup> C NMR Spectrum of <b>14</b>	S-28
<sup>1</sup> H NMR Spectrum of <b>15</b>	S-29
<sup>13</sup> C NMR Spectrum of <b>15</b>	S-30
<sup>1</sup> H NMR Spectrum of <b>17</b>	S-31
<sup>13</sup> C NMR Spectrum of <b>17</b>	S-32
<sup>1</sup> H NMR Spectrum of <b>18</b>	S-33
<sup>13</sup> C NMR Spectrum of <b>18</b>	S-34

## General Experimental

All reactions were run in oven-dried glassware and stirred with teflon-coated magnetic stir-bars. The terms concentrated *in vacuo* or under reduced pressure refer to the use of a

rotary-evaporator or vacuum pump. Methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), tetrahydrofuran (THF), acetonitrile ( $\text{CH}_3\text{CN}$ ), toluene, diethylether ( $\text{Et}_2\text{O}$ ), *N,N*-dimethylformamide (DMF) and methanol were dried by pressure filtration of HPLC quality solvents through an alumina column. Methylene iodide was purchased and copper was added as a stabilizer. Ethyl acetate ( $\text{EtOAc}$ ) and hexanes were distilled prior to use. Thin Layer Chromatography (TLC) was carried out on F254 glass plates and visualized by UV and anisaldehyde or  $\text{KMnO}_4$  stains. Column chromatography was performed with flash silica gel (32-63 $\mu\text{m}$ ). Mobile phases were used as noted. Melting points are uncorrected. Optical rotations were conducted in the specified solution, with the concentrations given in g/mL. Nuclear Magnetic Resonance (NMR) spectroscopy was performed at 399.768 MHz for  $^1\text{H}$  nuclei and 100.522 MHz for  $^{13}\text{C}$  nuclei or at 499.766 MHz for  $^1\text{H}$  nuclei and 125.679 MHz for  $^{13}\text{C}$  nuclei. All  $^{13}\text{C}$  are  $^1\text{H}$ -decoupled. Unless otherwise noted, all NMR experiments were carried out in deuteriochloroform ( $\text{CDCl}_3$ ) solvent. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (TMS) internal standard. Iodine was sublimed prior to use. Bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (Grubbs' 1<sup>st</sup> catalyst) was used without further purification. Compound **8** was prepared by the method of Labelle.<sup>13</sup> Compound **12** was prepared by the methods described in the literature.<sup>18,19</sup>

### **(*S,E*)-Ethyl 6-bromo-5-hydroxyhex-2-enoate (11)**

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (30 mL), compound **8** (0.87 g, 5.0 mmol, in 5 mL of dichloromethane), and carbon tetrabromide

(2.0 g, 6.0 mmol) in the indicated order. After the solution was cooled to 0 °C in the ice bath, triphenylphosphine (1.6 g, 6.0 mmol, in 5 mL of dichloromethane) was added in 30 minutes using syringe pump. After TLC analysis (hexanes:ethyl acetate = 1:1;  $R_f$  = 0.15) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (15 mL). The mixture was extracted with diethyl ether (2 x 15 mL). The combined organic layers was washed with brine (10 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 3:1,  $R_f$  = 0.30) to offer 0.83 g (70%) of **11** as a colorless liquid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.95 (m, 1H), 5.94 (d, 1H,  $J$  = 16.6 Hz), 4.20 (q, 2H,  $J$  = 7.2 Hz), 3.98 (m, 1H), 3.64 (dd, 1H,  $J$  = 3.9, 11.3 Hz), 3.52 (dd, 1H,  $J$  = 6.5, 11.2 Hz), 2.53-2.48 (m, 2H), 2.36 (m, 1H, OH), 1.29 (t, 3H,  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.2, 143.3, 124.5, 69.7, 60.5, 39.0, 37.8, 14.2. IR (neat,  $\text{cm}^{-1}$ ): 3500, 2956, 1725, 1630.  $[\alpha]_D^{25} = +13.0$  ( $c$  = 0.002 g/mL,  $\text{CHCl}_3$ ). HRMS (FAB $^+$ )  $m/z$  Calcd for  $\text{C}_8\text{H}_{14}\text{O}_3\text{Br}$  ( $M+1$ ): 237.0107. Found 237.0104.

**(*S,E*)-Ethyl 6-bromo-5-(methoxymethoxy)hex-2-enoate (**6**); Procedure 1:**

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (40 mL), compound **11** (2.12 g, 9.0 mmol, in 4.5 mL of dichloromethane), and MOM-Cl (1.0 mL, 13.5 mmol) in the indicated order. After the solution was cooled to 0 °C in the ice bath, diisopropylethylamine (2.4 mL, 13.5 mmol) was added in one portion. After overnight reaction at room temperature, diethyl ether (25 mL) was added to the mixture and the

solution was washed with 1M HCl (3 x 10 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1,  $R_f$  = 0.25) to offer 2.0 g (79%) of **6** as a colorless liquid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.93 (m, 1H), 5.95 (d, 1H,  $J$  = 15.6 Hz), 4.75-4.68 (m, 2H), 4.22-4.17 (m, 2H), 3.89 (m, 1H), 3.46 (d, 2H,  $J$  = 5.5 Hz), 3.41 (s, 3H), 2.63-2.58 (m, 2H), 1.29 (t, 3H,  $J$  = 7.1 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.1, 143.3, 124.6, 96.1, 75.4, 60.3, 56.0, 36.0, 34.6, 14.2. IR (neat,  $\text{cm}^{-1}$ ): 2978, 1732, 1625.  $[\alpha]_D^{25}$  = +34.6 ( $c$  = 0.005 g/mL,  $\text{CHCl}_3$ ). HRMS (FAB $^+$ )  $m/z$  Calcd for  $\text{C}_{10}\text{H}_{18}\text{O}_4\text{Br}$  ( $M+1$ ): 281.0388. Found 281.0392.

**(*R,E*)-Ethyl 5-(methoxymethoxy)-6-(tosyloxy)hex-2-enoate (**10**)**

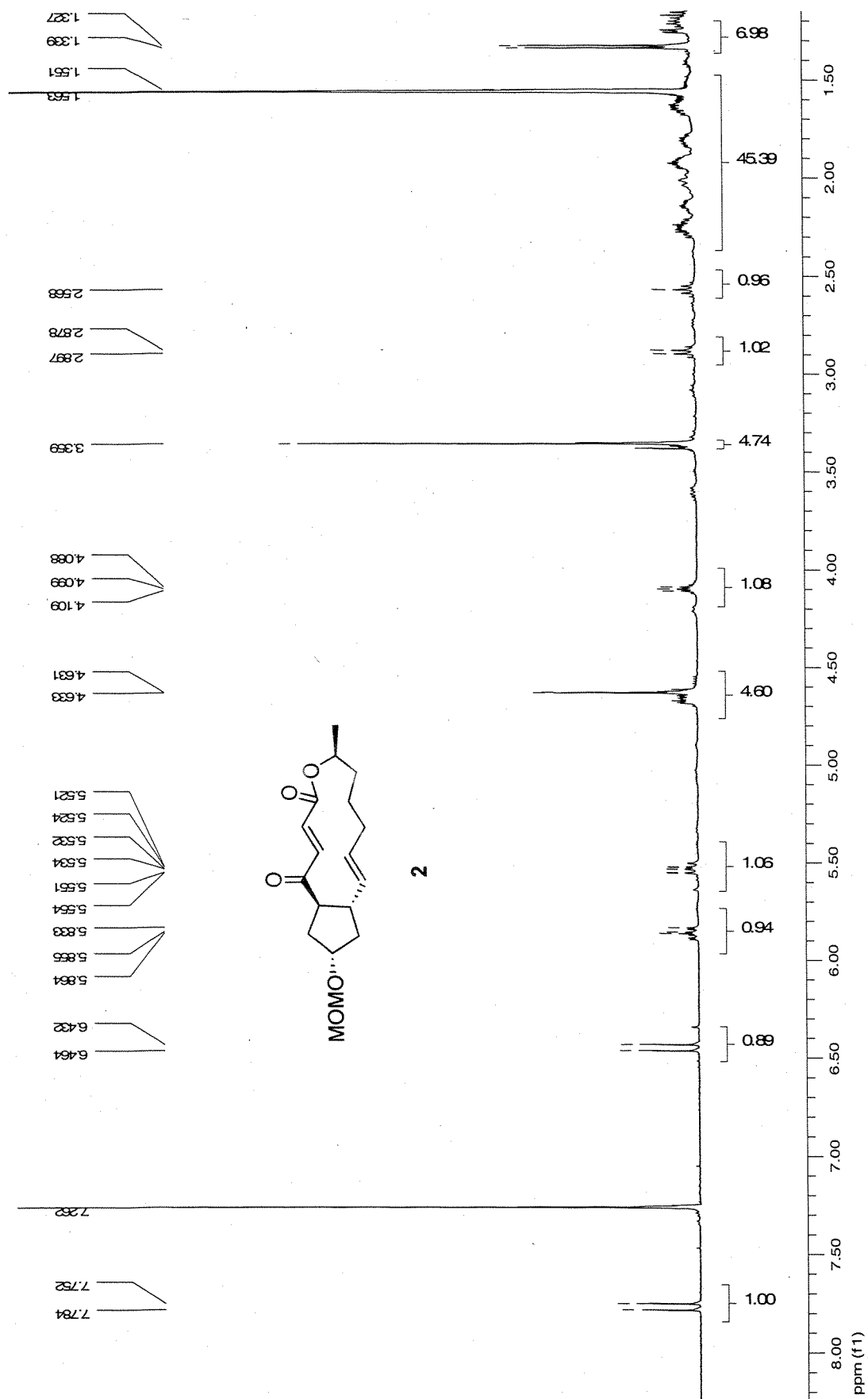
A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with pyridine (3 mL), compound **8** (57 mg, 0.33 mmol, in 0.5 mL of dichloromethane), and *p*-toluenesulfonyl chloride (63 mg, 0.33 mmol) in the indicated order. The reaction was stirred at room temperature overnight. The reaction mixture was diluted with 20 mL of ether and extracted with 1N HCl (3 x 10 mL). The organic layer was washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration, the solvent was removed under reduced pressure to provide approximately 100 mg of the crude reaction mixture that contained (*R,E*)-Ethyl 5-(hydroxy)-6-(tosyloxy)hex-2-enoate (**9**) as its primary component. The material was typically used in the next step without purification. Spectroscopic data of the crude material:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d, 2H,  $J$  = 8.0 Hz), 7.36 (d, 2H,  $J$  = 8.0 Hz), 6.84 (m, 1H), 5.84 (d, 1H,  $J$  = 16.3 Hz), 4.16 (m, 2H), 4.02-3.99 (m, 2H), 3.91 (m,

1H), 2.43 (s, 3H), 2.42-2.38 (m, 2H), 1.28 (t, 3H,  $J = 7.1$  Hz); A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (3 mL), compound **9** (82 mg, 0.25 mmol, in 0.5 mL of dichloromethane), and MOM-Cl (0.05 mL, 0.68 mmol) in the indicated order. After the solution was cooled to 0 °C in the ice bath, Diisopropylethylamine (0.18 mL, 1.0 mmol,) was added in one portion. After overnight reaction at room temperature, diethyl ether (25 mL) was added to the mixture and the solution was washed with 1M HCl (3 x 5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1,  $R_f = 0.30$ ) to offer 60 mg (65%) of **10** as a colorless liquid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d, 2H,  $J = 8.1$  Hz), 7.36 (d, 2H,  $J = 8.1$  Hz), 6.83 (m, 1H), 5.84 (d, 1H,  $J = 16.8$  Hz), 4.62 (d, 1H,  $J = 7.1$  Hz), 4.57 (d, 1H,  $J = 7.1$  Hz), 4.17 (q, 2H,  $J = 7.1$  Hz), 4.02-4.01 (m, 2H), 3.87 (m, 1H), 3.31 (s, 3H), 2.46 (s, 3H), 2.46-2.42 (m, 2H), 1.28 (q, 3H,  $J = 7.2$  Hz);  $^{13}\text{C}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.0, 145.1, 142.9, 132.7, 129.9, 128.0, 124.6, 96.1, 73.5, 70.5, 60.4, 55.8, 34.4, 21.7, 14.3. HRMS (FAB $^+$ )  $m/z$  Calcd for  $\text{C}_{17}\text{H}_{25}\text{O}_7\text{S}$  (M+1): 373.1321. Found 373.1317.

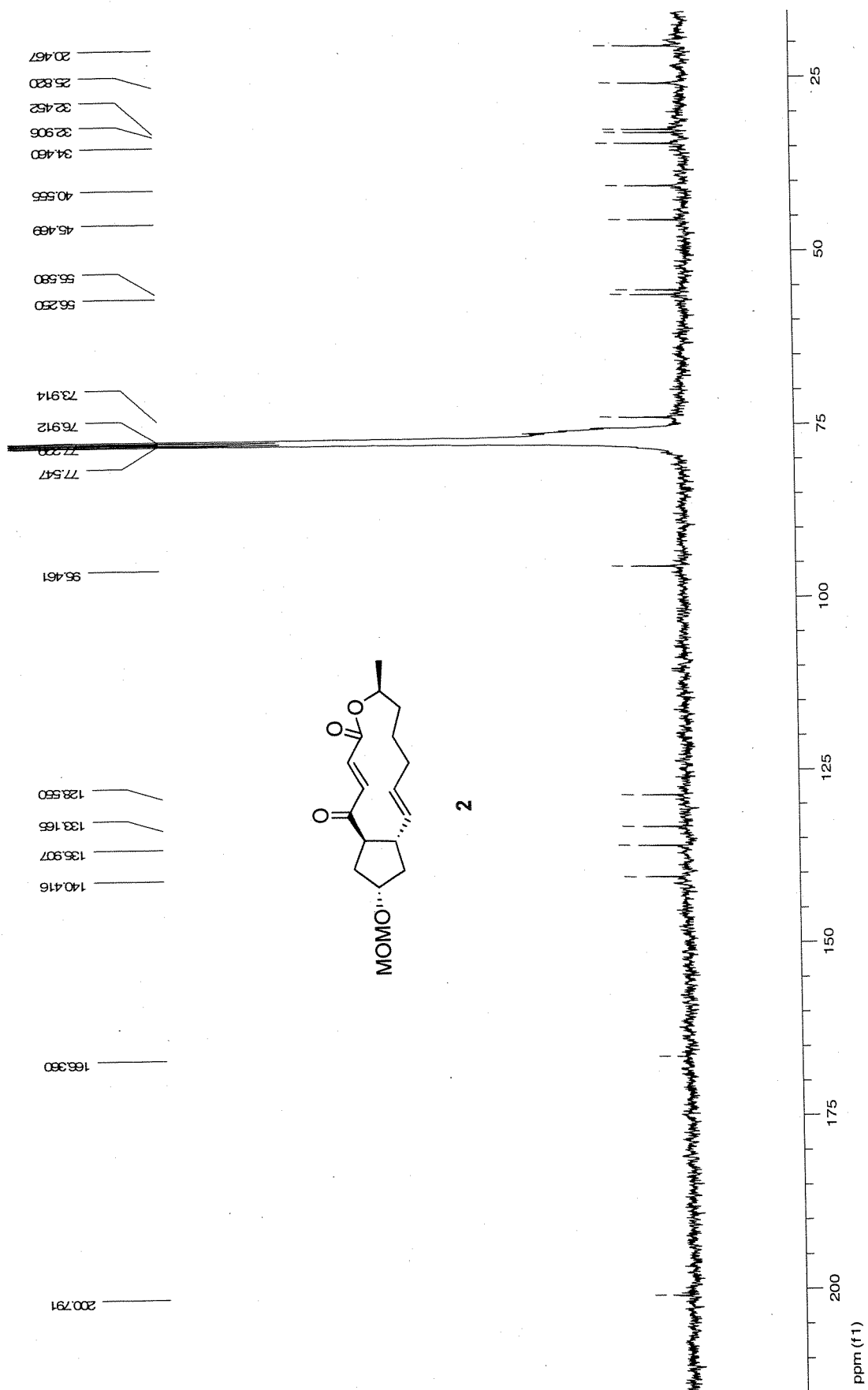
**(*S,E*)-Ethyl 6-bromo-5-(methoxymethoxy)hex-2-enoate (**6**); Procedure 2:**

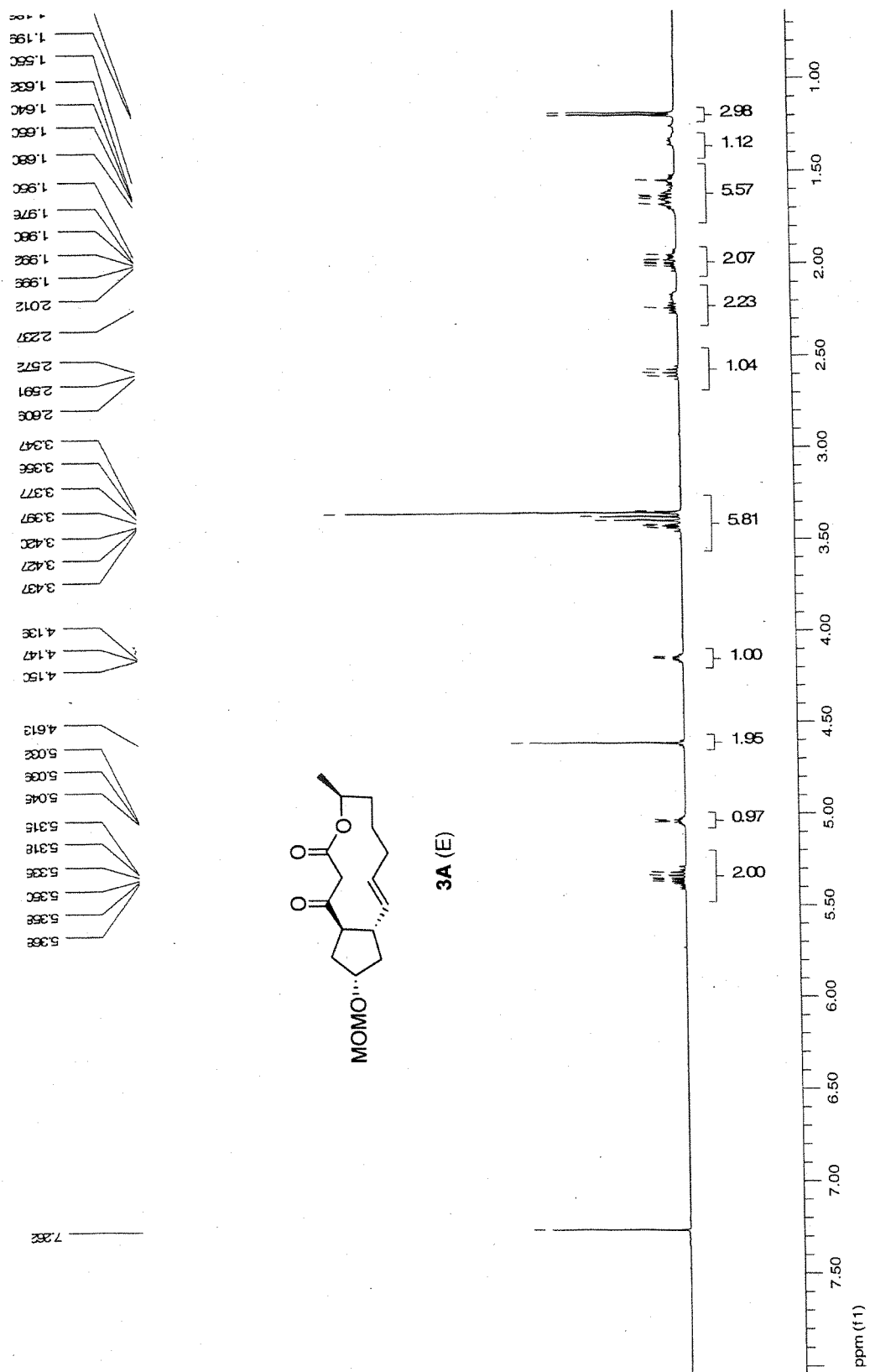
Compound **10** (74 mg, 0.2 mmol) was dissolved in a 5-mL round-bottomed flask with 2 mL of THF. Sodium bromide (0.1 g, 1.0 mmol) was added to the solution and the mixture was allowed to stir for overnight under room temperature and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried carefully over anhydrous sodium

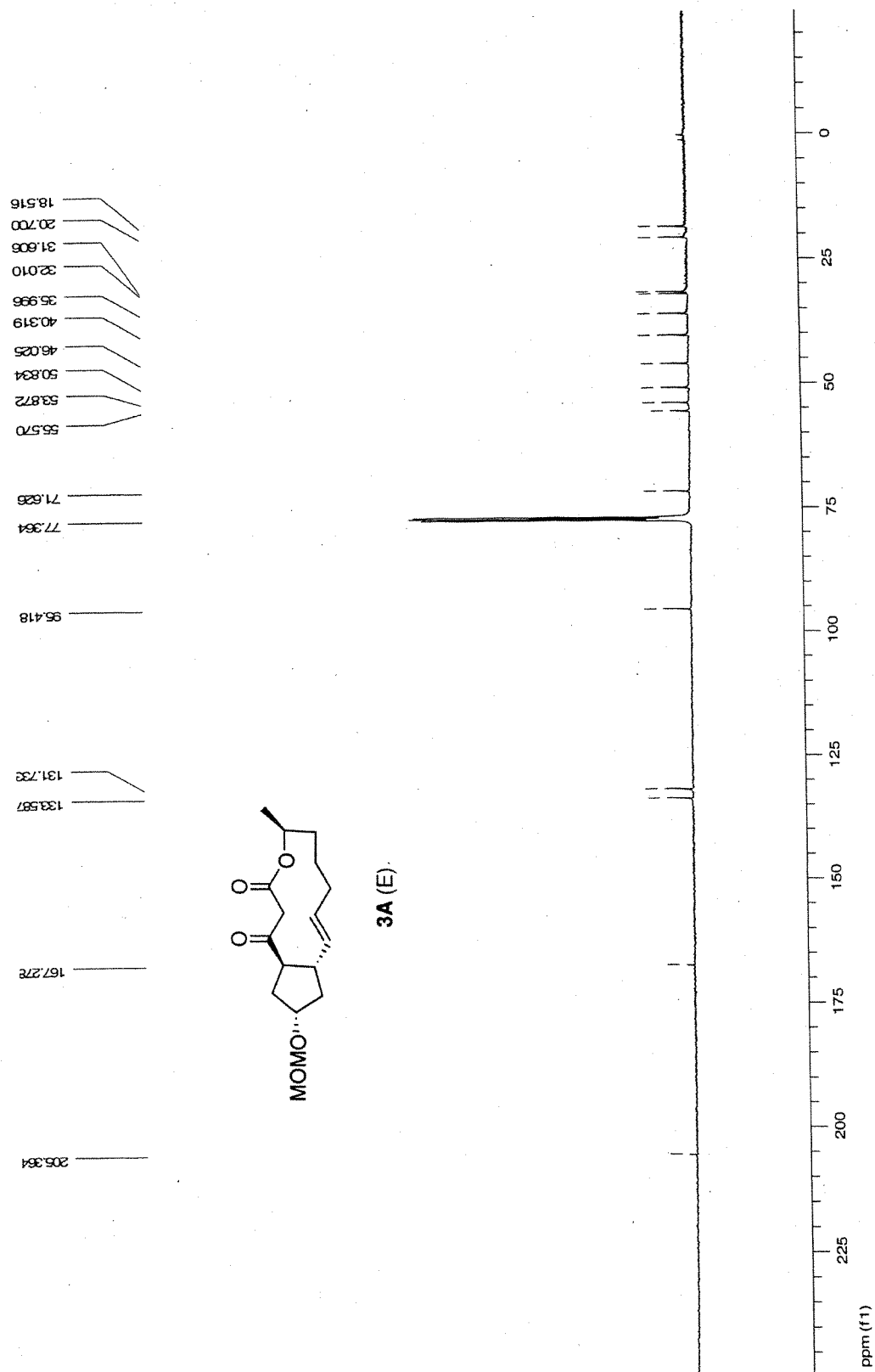
sulfate and concentrated *in vacuo* to yield 44 mg (79%) **6** of as a colorless liquid. The product was identical to that prepared above.

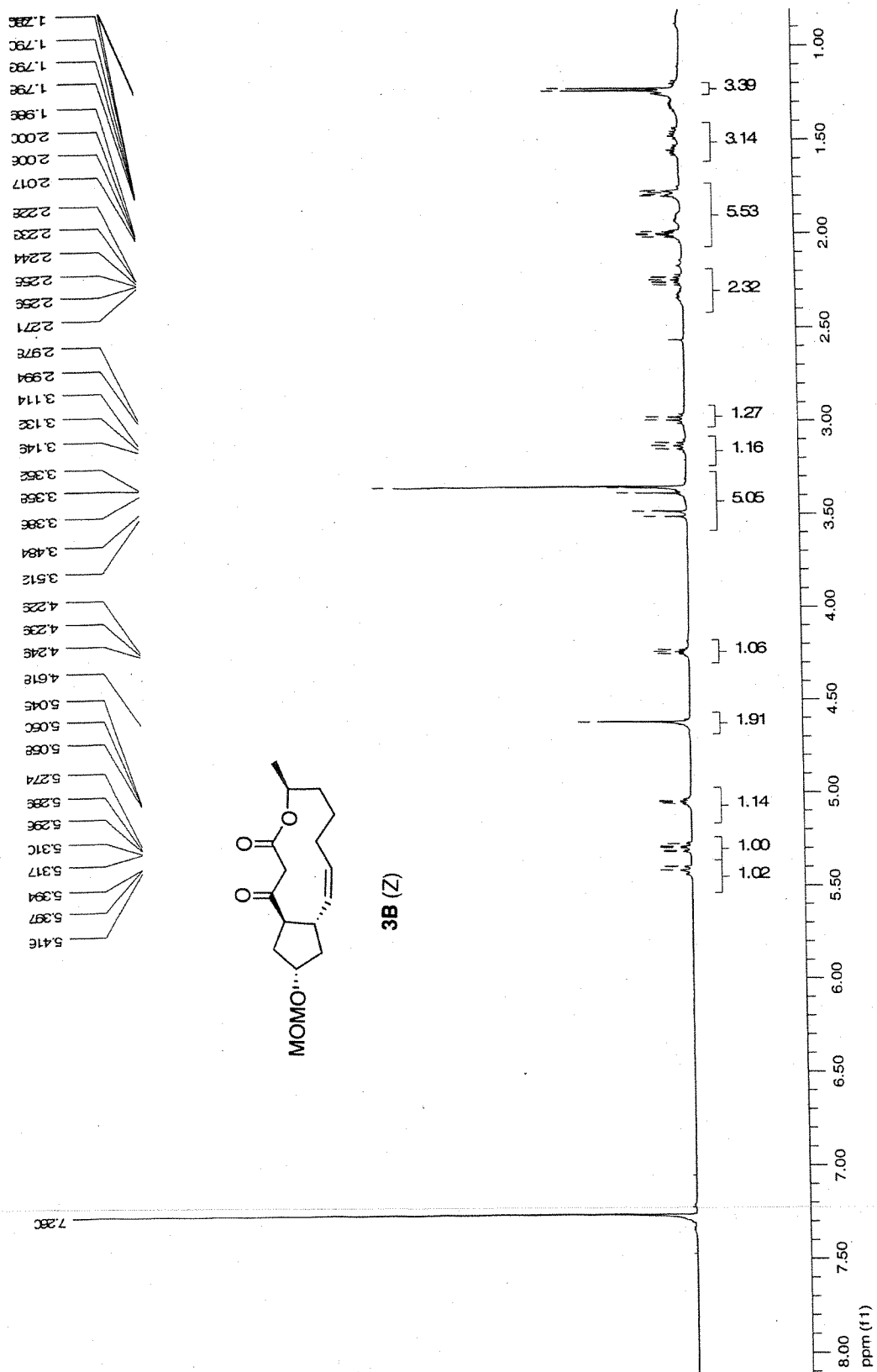


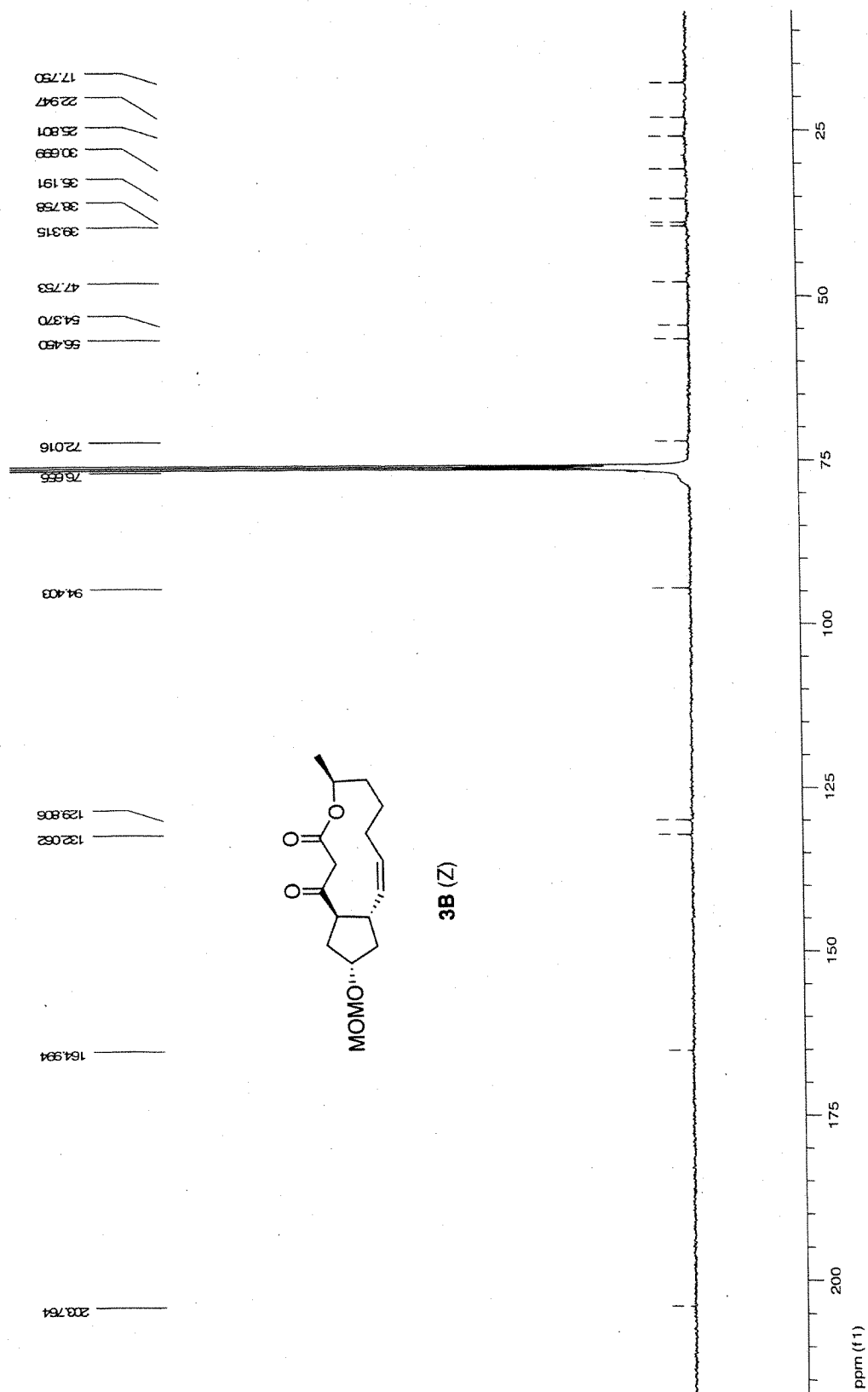


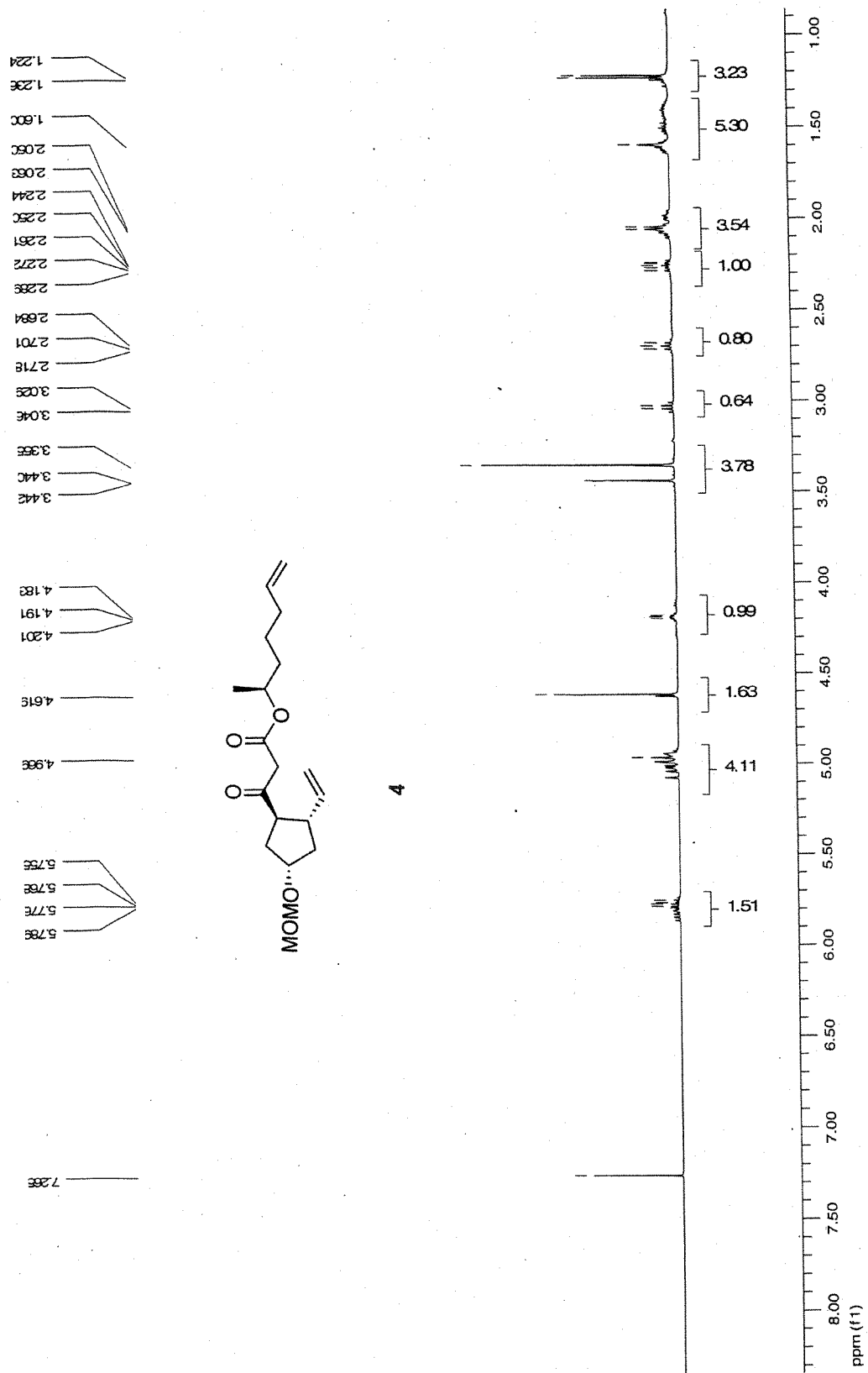


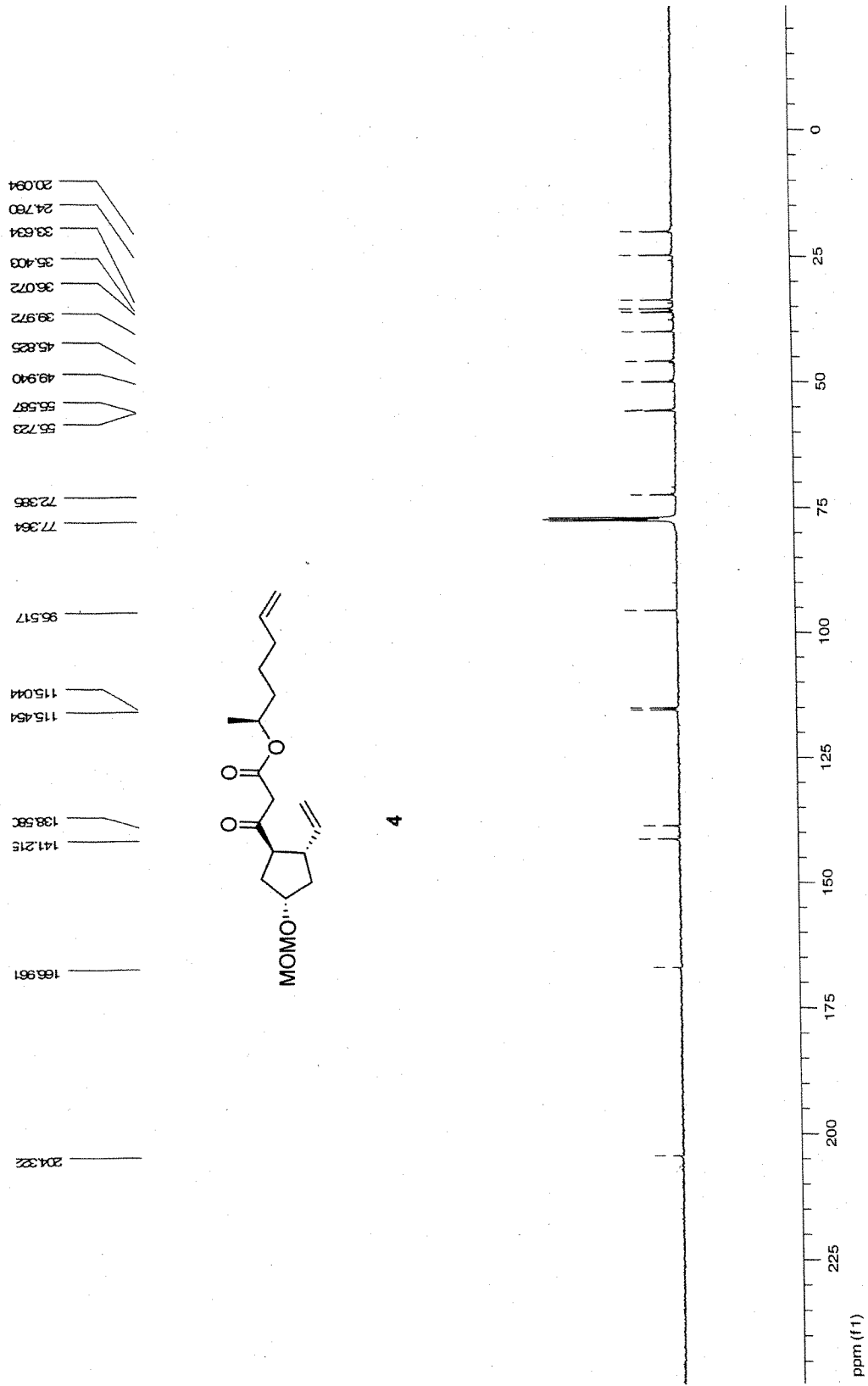


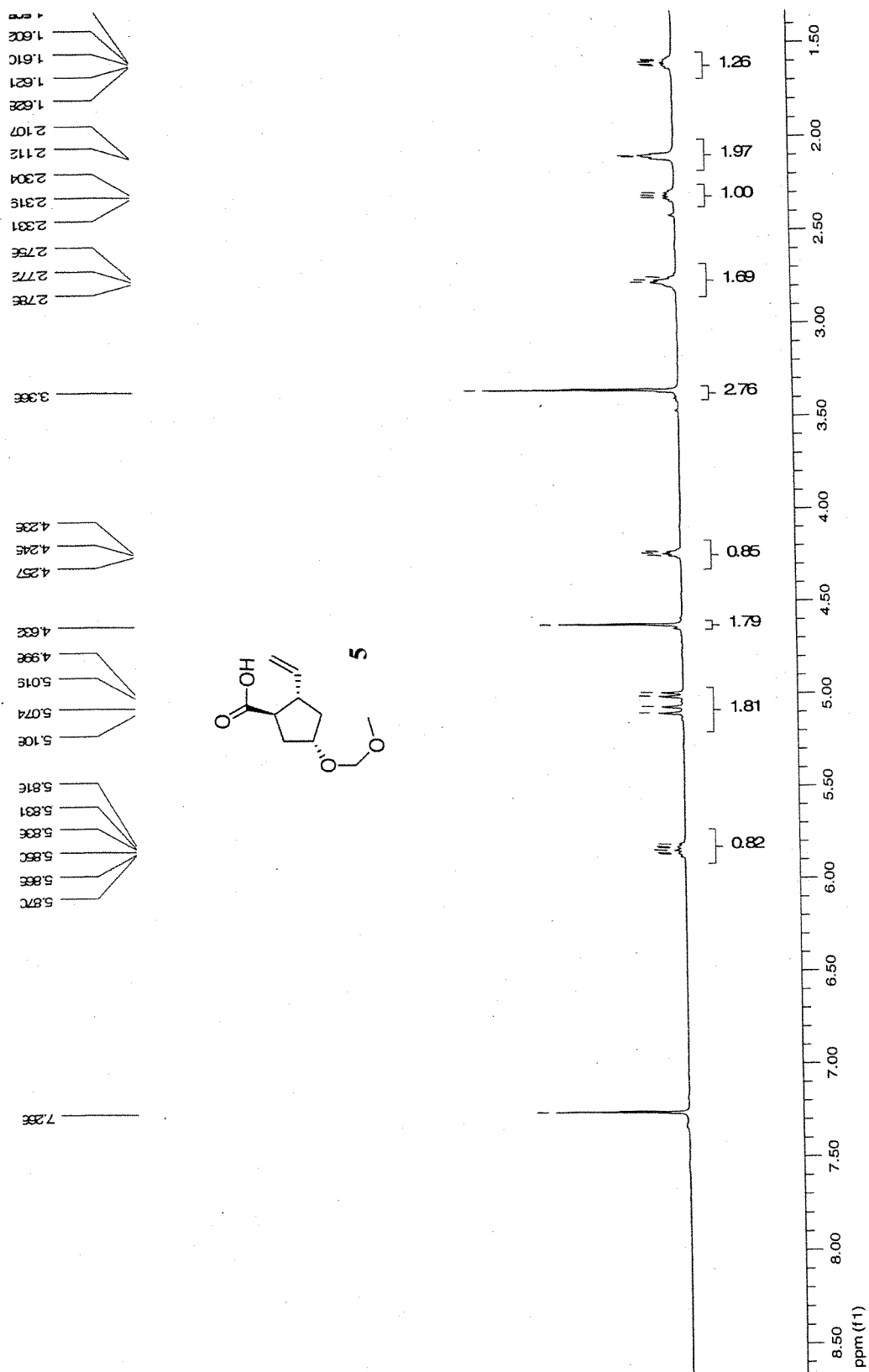




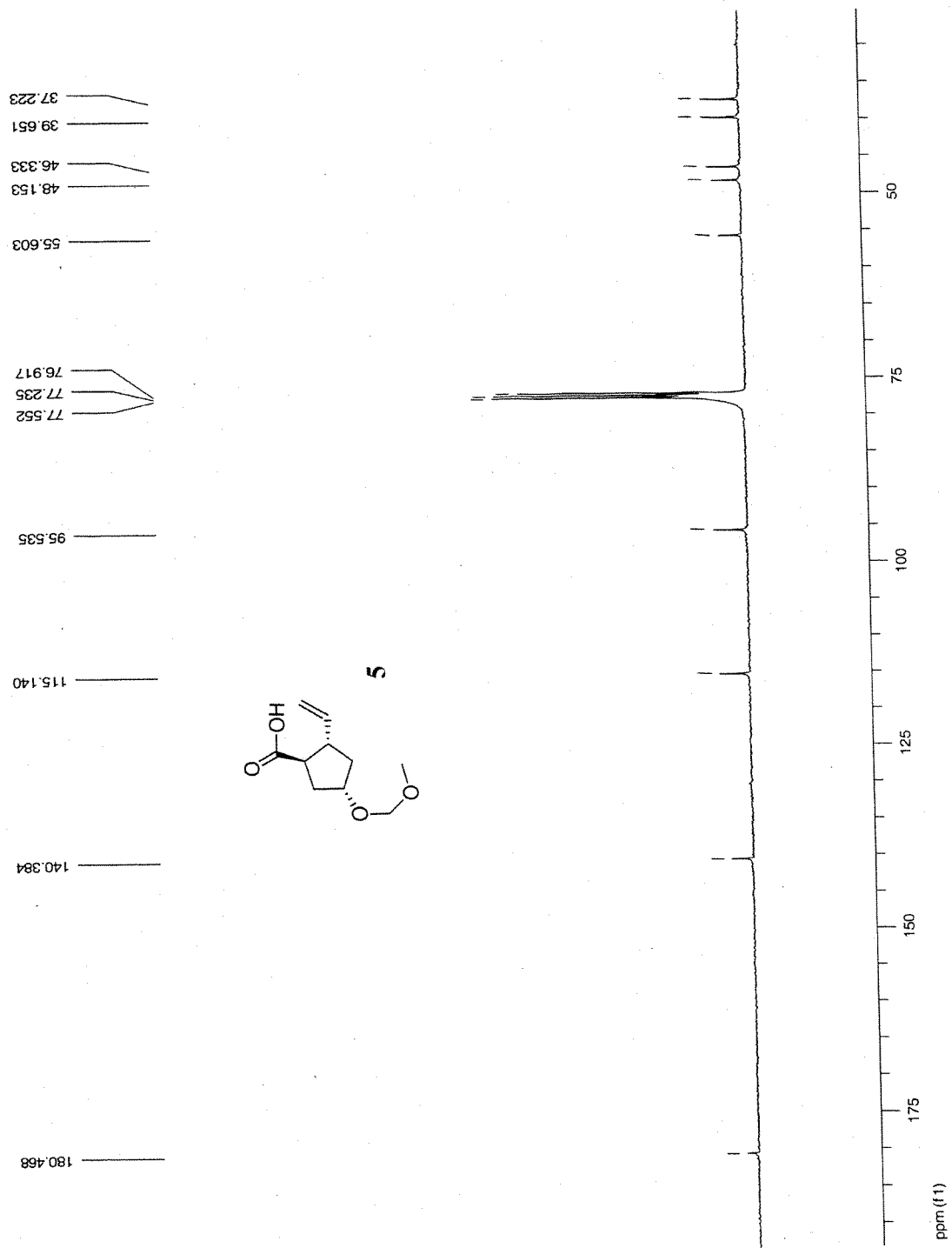


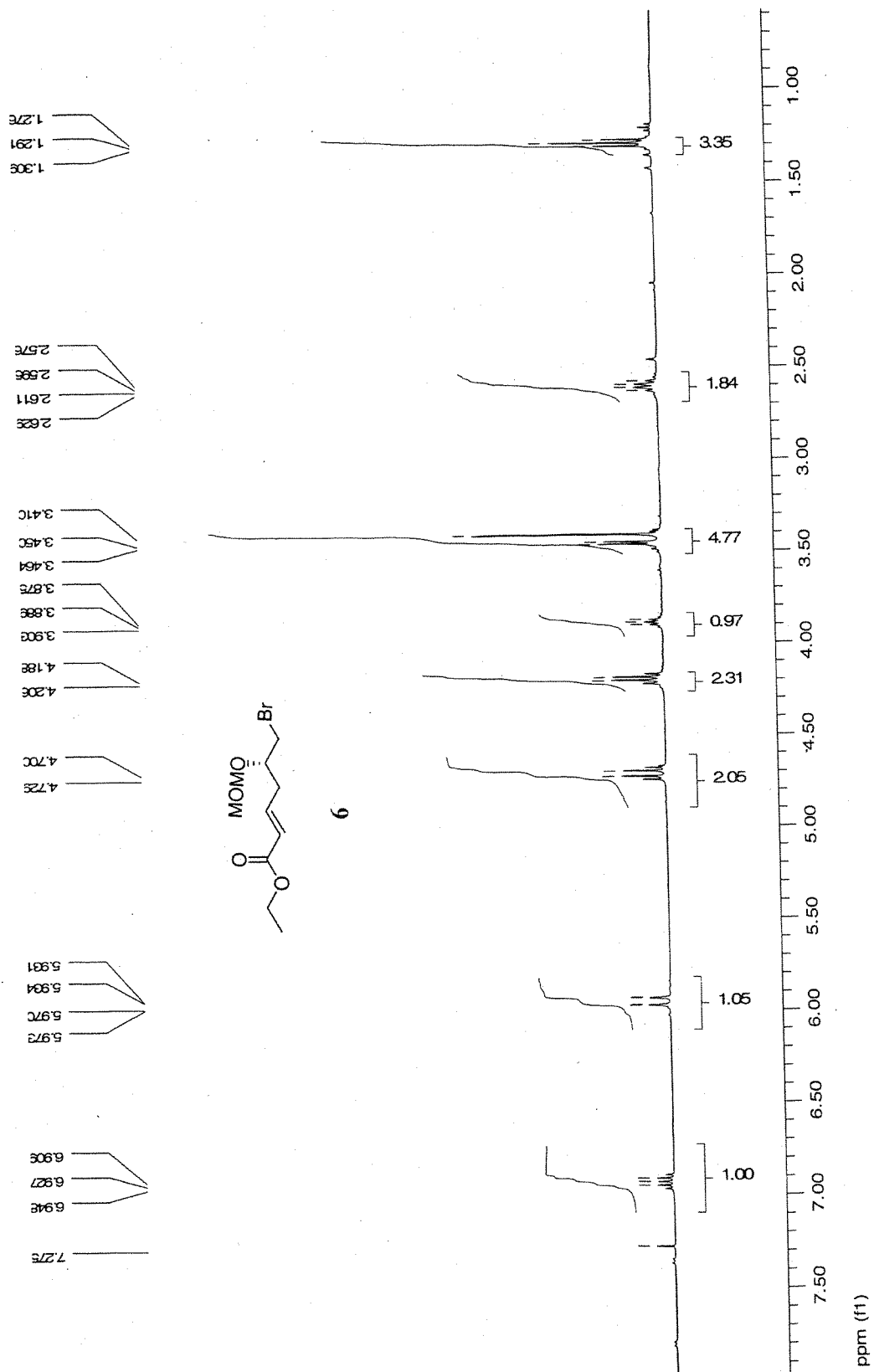


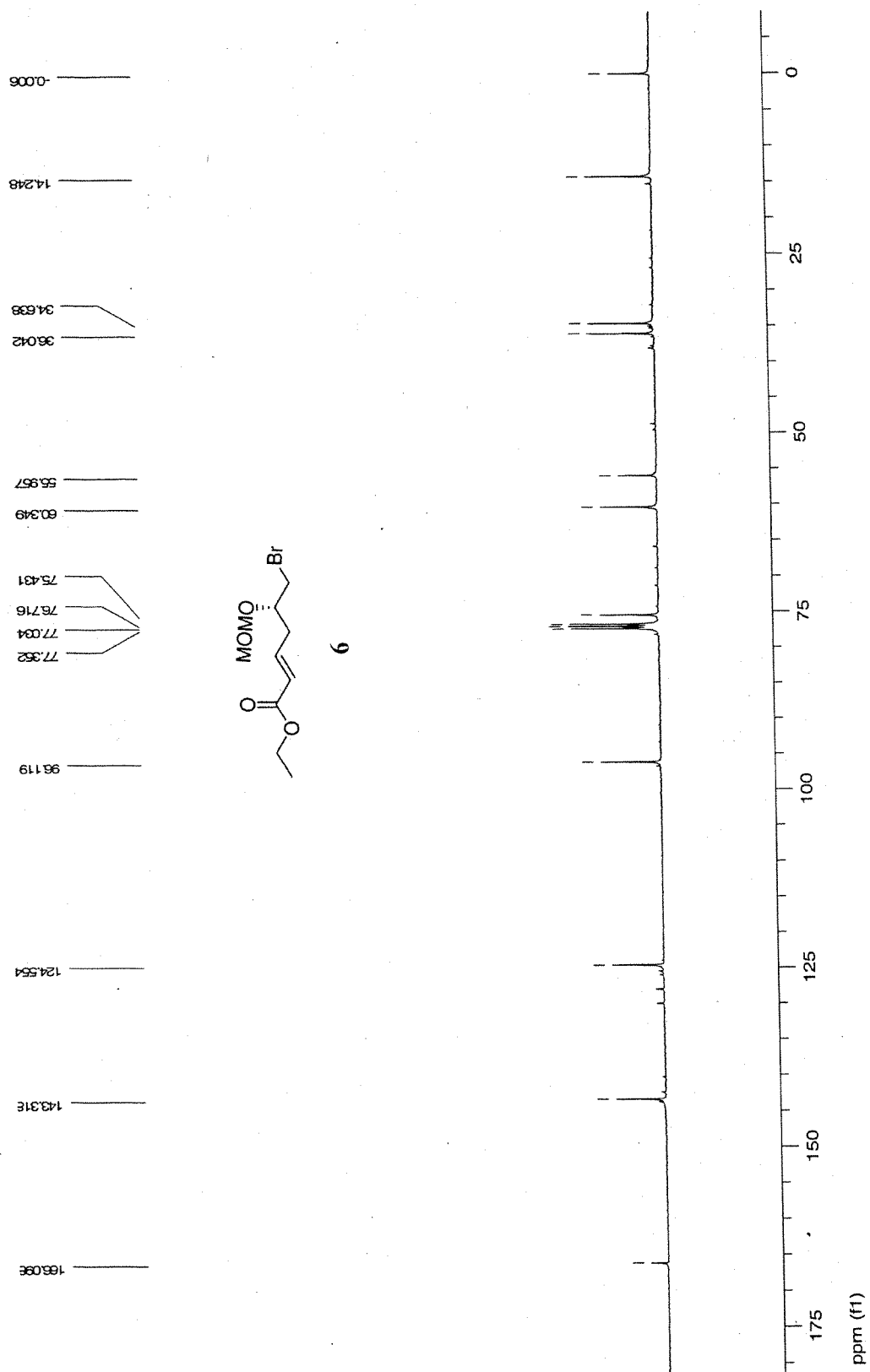












with pyridine for 18 hours

Archive directory: /export/home/uml/vnmrSYS/data  
Sample directory: wml1425\_22Jan2005-17:31:15  
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3  
Ambient temperature  
Mercury-400BB "lyle4.unh.edu"

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 3.008 sec

Width 6385.7 Hz

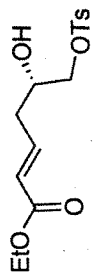
8 repetitions

OBSERVE H1 399.7490257 MHz

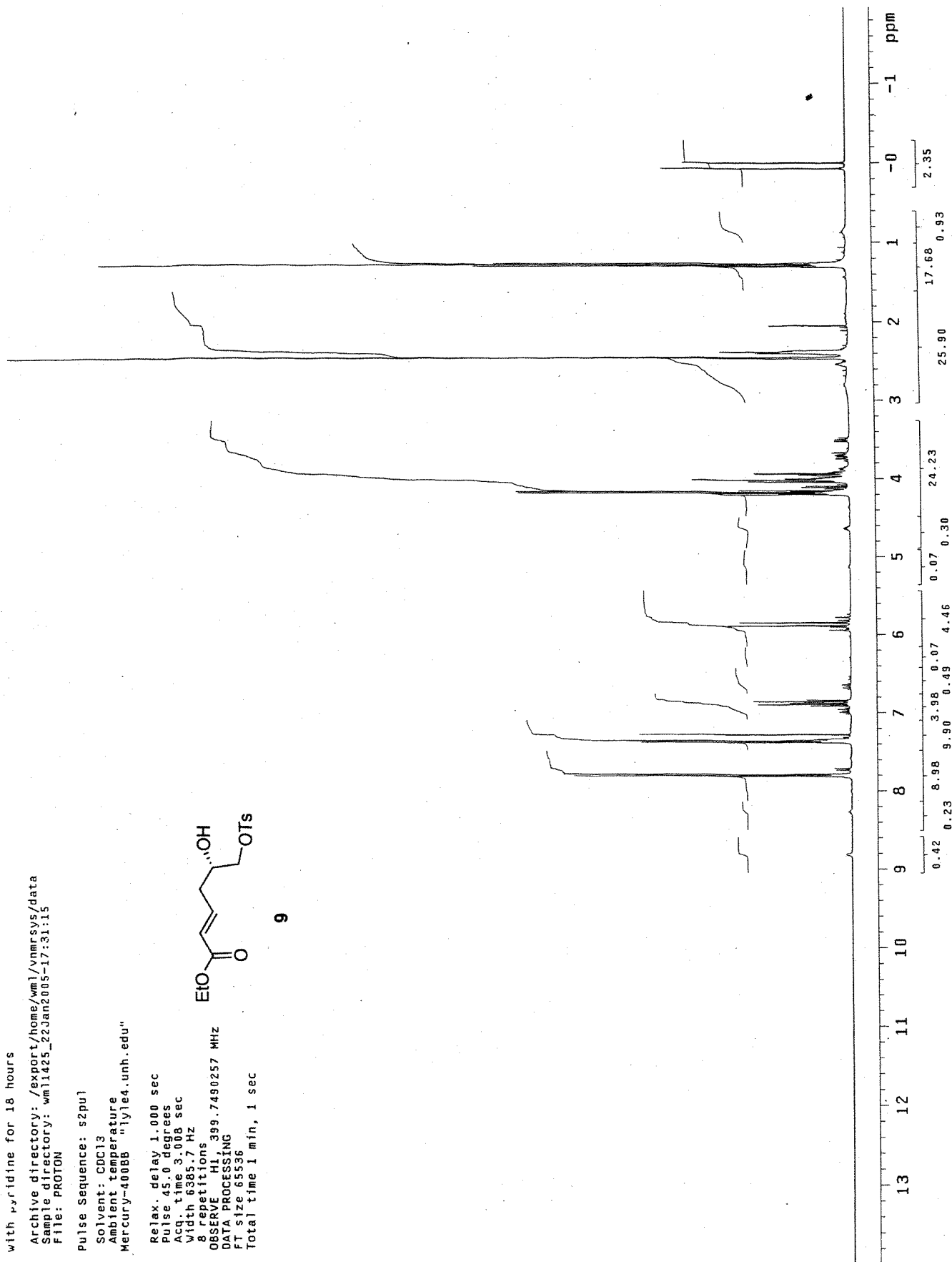
DATA PROCESSING

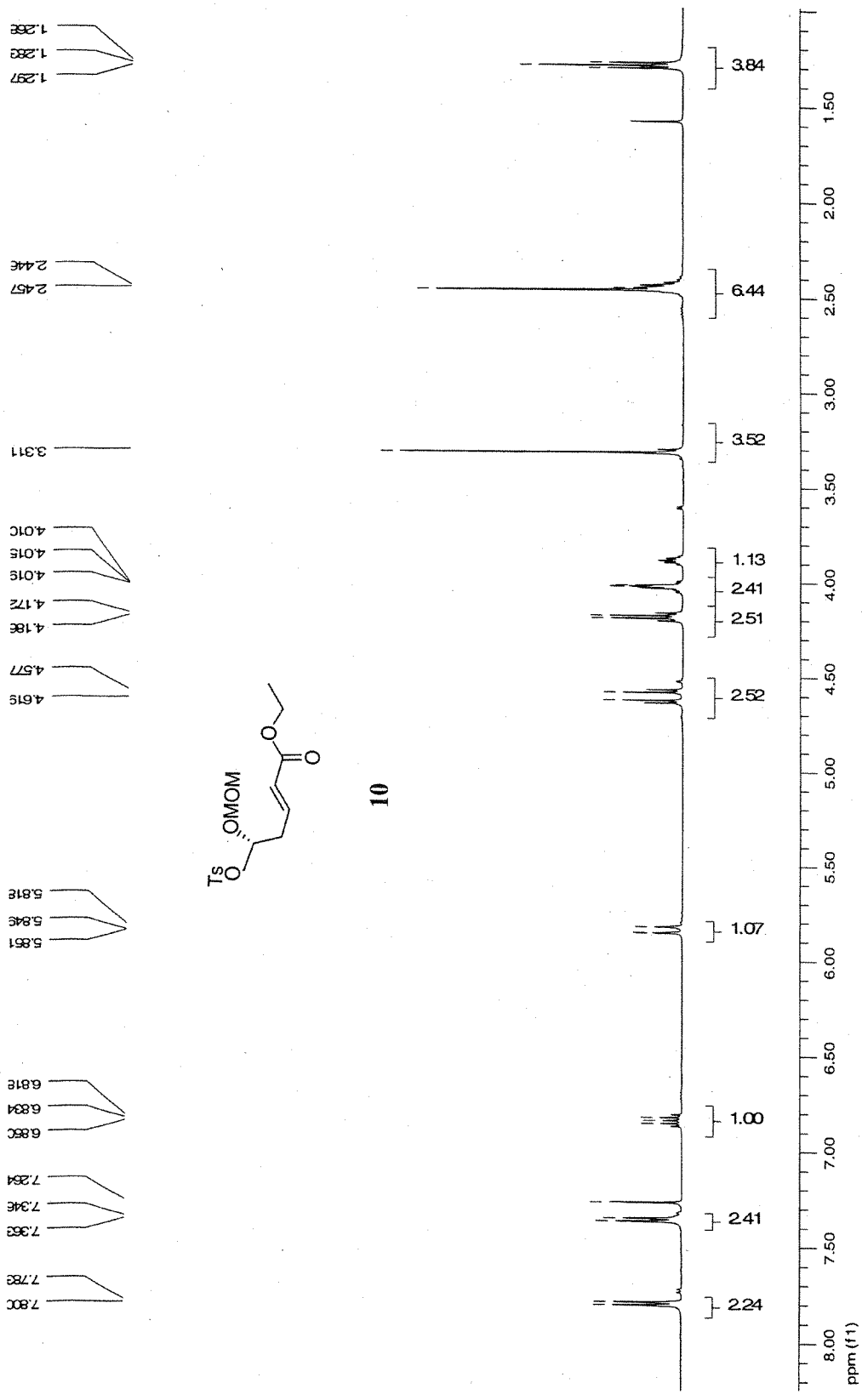
FT size 65536

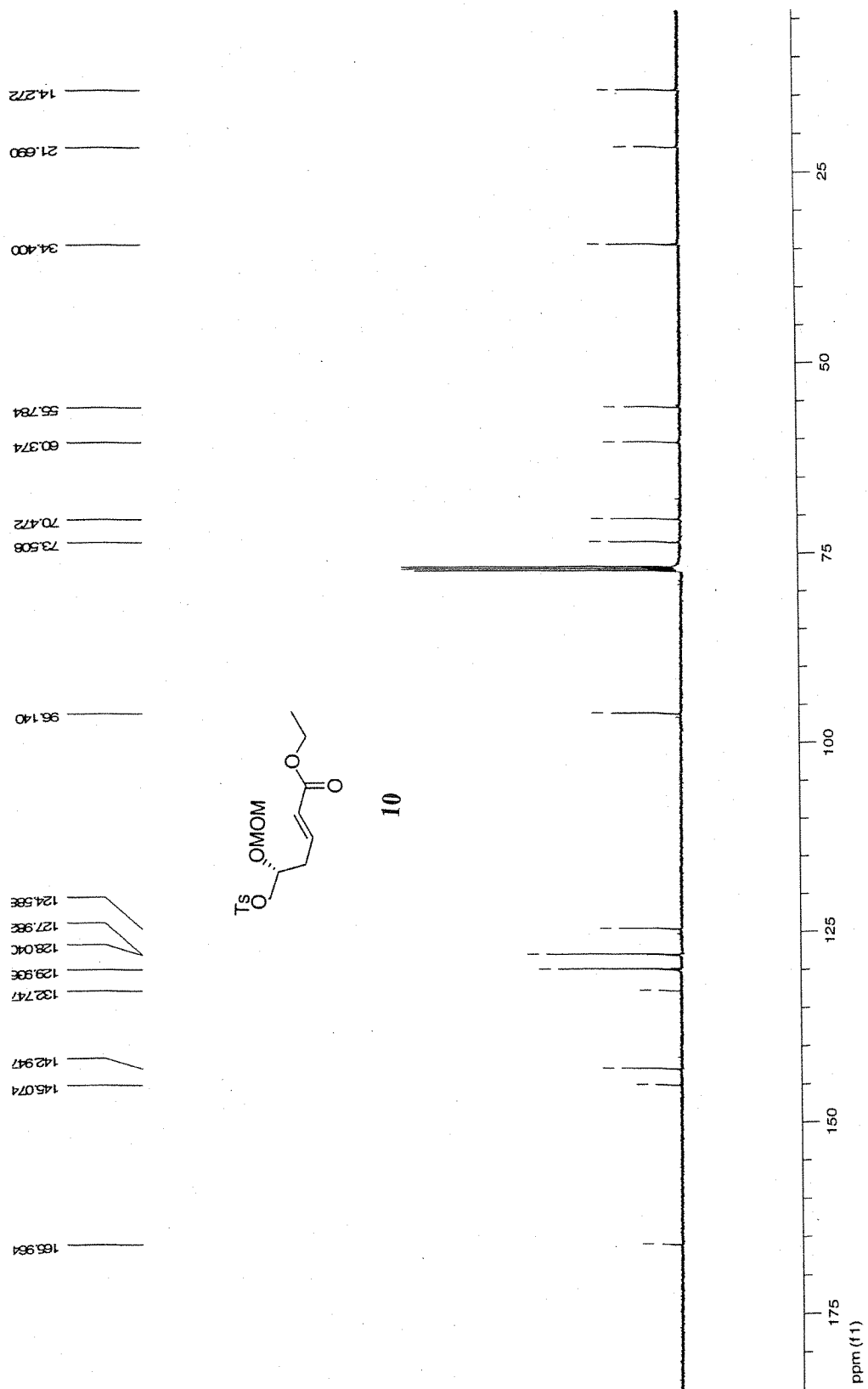
Total time 1 min, 1 sec

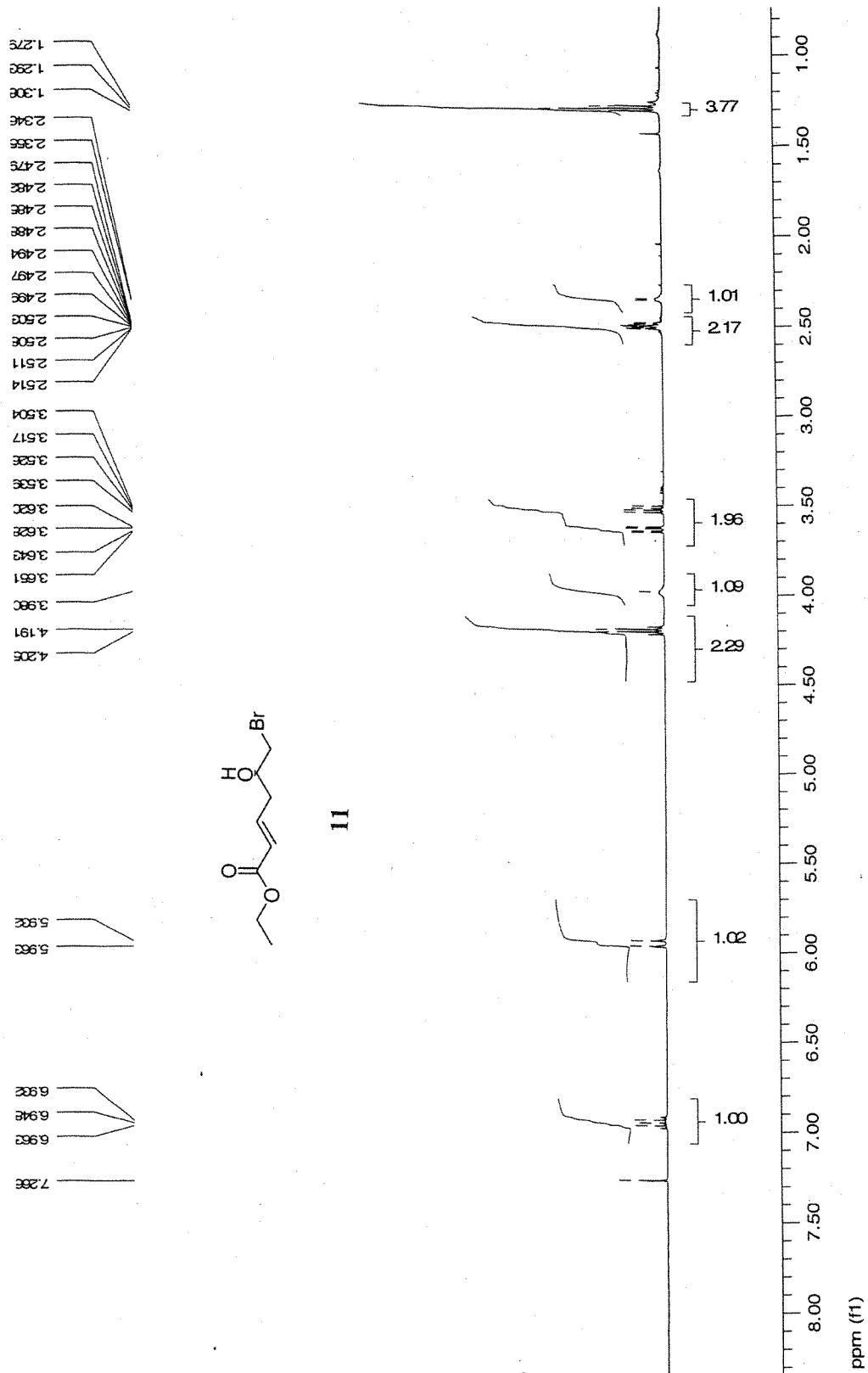


9



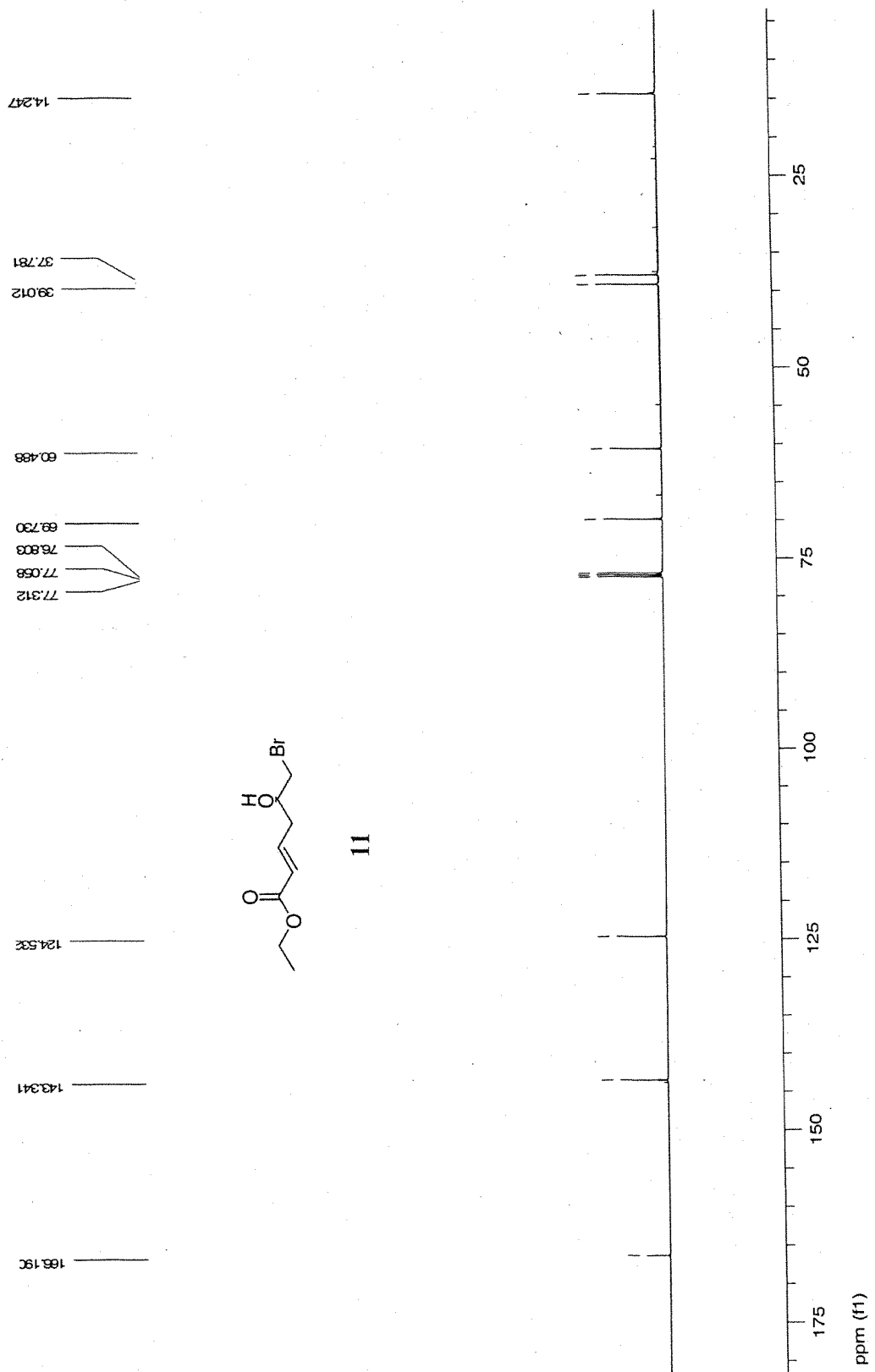




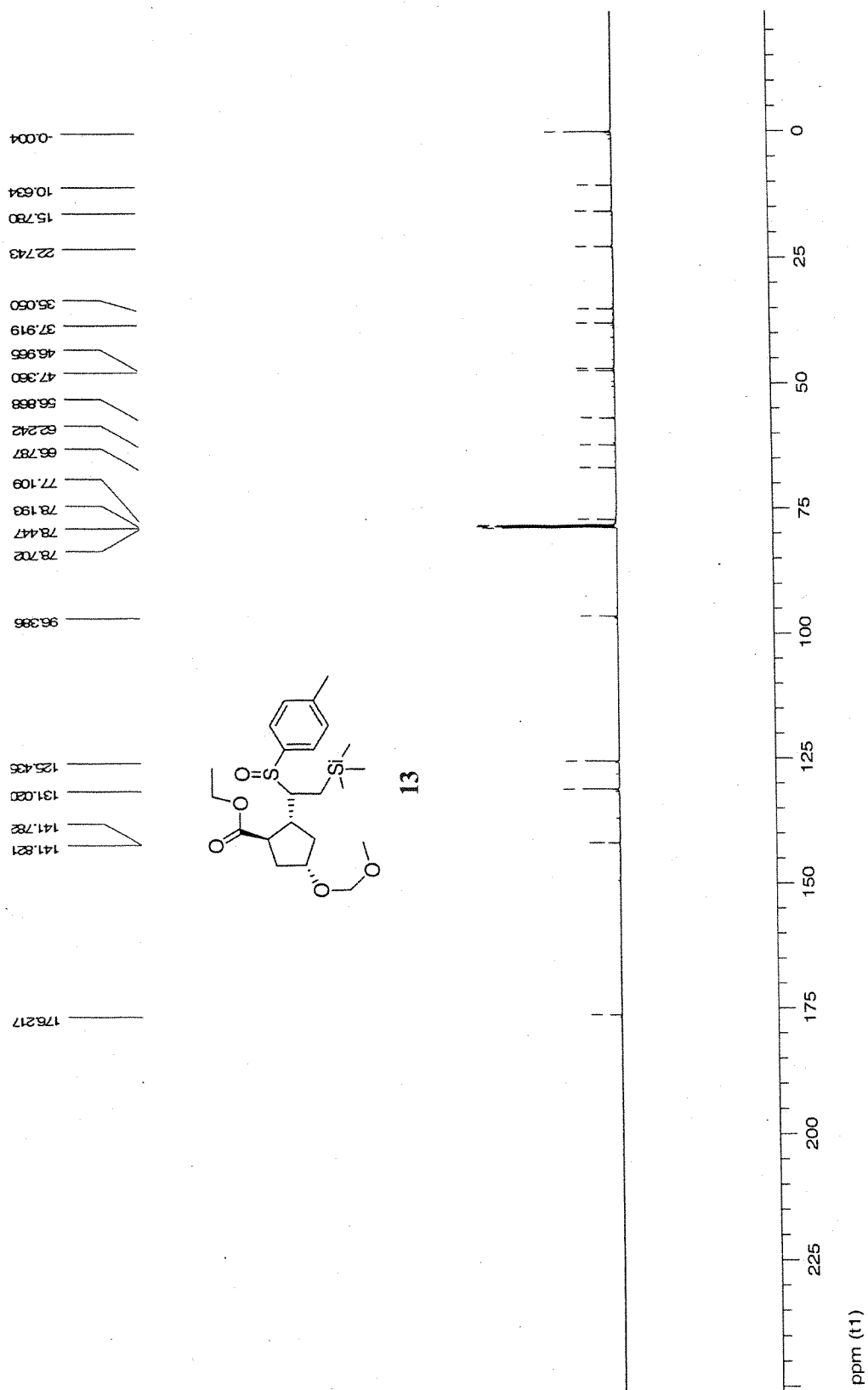


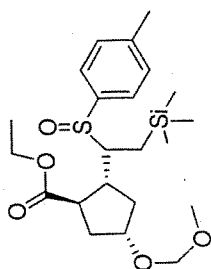
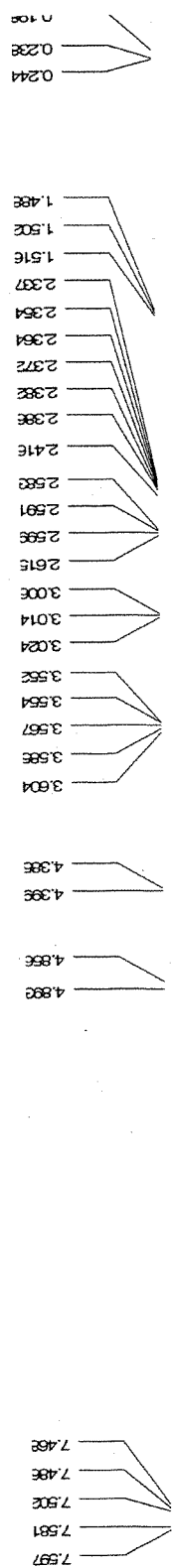


11









13

