

## A Total Synthesis of *trans*-Kumausyne

Carley L. Chandler and Andrew J. Phillips\*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215

### SUPPORTING INFORMATION

#### General Experimental Procedures.

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 25 °C on Varian Inova spectrometers at 500 or 400, and 125 or 100 MHz, respectively, using CDCl<sub>3</sub> as the solvent and internal reference. All non-aqueous reactions were run in flame-dried glassware under a dry N<sub>2</sub> atmosphere. Toluene, THF, CH<sub>2</sub>Cl<sub>2</sub>, and Et<sub>2</sub>O were obtained from Aldrich (Pure-Pac) and further dried by passage through activated alumina as described by Bergman and Grubbs.<sup>1</sup> All flash chromatography was performed with normal phase silica gel (Sorbent Technologies, 32-63 μm particle size, 60 Å pore size), following the general protocol of Still.<sup>2</sup>

#### (±)-1-((1*R*,2*R*,4*R*)-7-Oxa-bicyclo[2.2.1]hept-5-en-2-yl)prop-2-en-1-one, (2)



To a stirred solution of methyl ester **1** (8.00 g, 52.00 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (400 mL) at -95 °C was added DIBAL-H (10.20 mL, 57.20 mmol, 1.1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (55 mL) via an addition funnel. The reaction mixture was stirred for 30 min after the addition was complete. The reaction was quenched with a saturated Na<sub>2</sub>SO<sub>4</sub> solution and allowed to warm to room temp. The phases were separated and the organic phase was filtered through Celite, dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo*.

The crude residue obtained above was taken up in CH<sub>2</sub>Cl<sub>2</sub> (285 mL) and the solution was cooled to 0 °C. A 1 M solution of vinyl magnesium bromide (74.00 mL, 74.00 mmol, 1.3 eq) was added and the reaction was allowed to warm to room temp. The mixture was stirred for 45 min and was then carefully quenched with saturated NH<sub>4</sub>Cl (150 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic washed with saturated NaCl. The organic phase was dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo*.

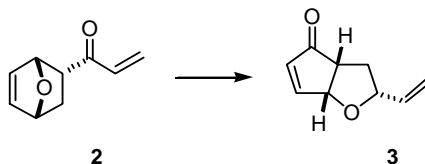
The crude material from the previous reaction was taken up in CH<sub>2</sub>Cl<sub>2</sub> (190 mL) and Dess-Martin periodinane (36.00 g, 85.50 mmol, 1.5 eq) was added in two equal portions separated by 15 min of stirring. The mixture was allowed to stir for 1 h and was then quenched with Na<sub>2</sub>SO<sub>3</sub> doped saturated NaHCO<sub>3</sub> solution. The mixture was stirred vigorously for 30 min (until the organic layer was clear) and then the two layers were separated. The organic phase was washed

<sup>1</sup> a) Alaimo, P. J.; Peters, D.W.; Arnold, J.; Bergman, R.G. *J. Chem. Educ.* **2001** 78 64. b) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R.K.; Timmers, F. J. *Organometallics* **1996**, 15, 151.

<sup>2</sup> Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923.

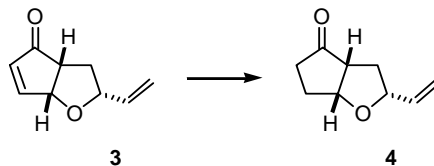
with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo* to yield **2** (4.6 g, 59% yield) as a pale yellow oil, which could be used without purification. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.26-6.43 (m, 3H), 6.15 (dd, J = 1.6, 6.0 Hz, 1H), 5.86 (dd, J = 1.6, 10.4, 1H), 5.18-5.20 (m, 1H), 5.03-5.05 (m, 1H), 3.44-3.49 (m, 1H), 2.04-2.10 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 198.09, 136.54, 135.98, 131.83, 128.67, 79.25, 79.20, 48.72, 27.77; IR(neat, cm<sup>-1</sup>) 1697 (CO); HRMS (ESI) calc for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub><sup>+</sup> 150.0675, found 150.0676.

**(±)-(2*R*,3*aR*,6*aR*)-3,3*a*-Dihydro-2-vinyl-2H-cyclopenta[*b*]furan-4(6*aH*)-one, (3)**

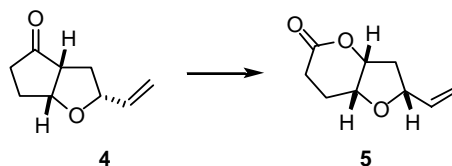


To a stirred solution of vinyl ketone **2** (0.15g, 1 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added catalyst **9** (0.021 g, 0.025 mmol, 0.025 eq). The reaction was stirred for 8 h at room temperature and a further portion of **9** (0.021 g, 0.025 mmol, 0.025 eq) was added. After stirring for a further 12 h at rt, the reaction was concentrated and purified by flash chromatography (25% EtOAc/hexanes) to yield **3** (0.124 g, 83% yield) as an oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.60 (dd, J = 2.0, 3.5 Hz, 1H), 6.19 (d, J = 6.0 Hz, 1H), 5.76-5.082(m, 1H), 5.25 (dt, J = 1.5, 14.5 Hz, 1H), 5.19 (dd, J = 2.0, 4.0 Hz, 1H), 5.15 (dt, J = 1.0, 8.0 Hz, 1H), 4.55-4.57 (m, 1H), 3.06-3.11 (m, 1H), 2.37-2.43 (m, 1H), 1.64-1.70 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 208.04, 160.85, 137.51, 133.91, 117.15, 84.60, 82.46, 49.11, 34.28; IR(neat, cm<sup>-1</sup>) 1720 (CO); HRMS (ESI) calc for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub><sup>+</sup> 150.0675, found 150.0673.

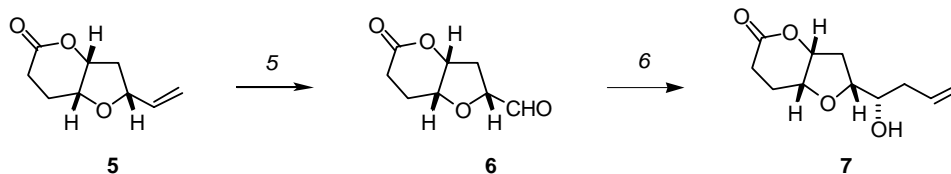
**(±)-(2*R*,3*aR*,6*aR*)-Tetrahydro-2-vinyl-2H-cyclopenta[*b*]furan-4(5*H*)-one, (4)**



To a stirred solution of Stryker's reagent (0.65 g, 0.17 mmol, 1eq) in PhCH<sub>3</sub> (0.4 mL) was added phenylsilane (0.03 mL, 0.25 mmol, 1.5 eq) followed by enone **3** (0.025 g, 0.17 mmol, 1 eq). After stirring at room temperature for 6 h, the reaction was diluted with EtOAc (100 mL), washed with saturated NH<sub>4</sub>Cl (100 mL), saturated NaHCO<sub>3</sub> (100 mL), and saturated NaCl (100 mL). The organic phase was dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% *i*-PrOH/hexanes) to yield **4** (0.016 g, 63% yield) as a yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.74-5.81 (m, 1H), 5.26 (dt, J = 1.0, 14.5 Hz, 1H), 5.13 (dt, J = 1.5, 8.0 Hz, 1H), 4.61 (t, J = 5.0 Hz), 4.28-4.33 (m, 1H), 2.71-2.74 (m, 1H), 2.42-2.55 (m, 2H), 2.26-2.34 (m, 2H), 2.03-2.11 (m, 1H), 1.83-1.88 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 183.51, 137.86, 117.03, 82.49, 81.52, 52.80, 36.59, 35.17, 26.17; IR(neat, cm<sup>-1</sup>) 1731 (CO); HRMS (ESI) calc for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub><sup>+</sup> 152.0832, found 152.0849.

**(±)-(2R,3aR,7aR)-Tetrahydro-2-vinyl-2H-furo[3,2-b]pyran-5(6H)-one, (5)**

To a stirred solution of ketone **4** (0.2 g, 1.31 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at rt was added scandium triflate (0.032 g, 0.066 mmol, 0.05 eq). After stirring for 10 min *m*-chloroperoxybenzoic acid (0.45 g, 2.63 mmol, 2 eq) was added. The reaction was stirred for 3 h and quenched with Na<sub>2</sub>SO<sub>3</sub>-doped saturated NaHCO<sub>3</sub> solution. After stirring for 10 min, the layers were separated and the combined organics were washed with saturated NaCl, dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to yield **5** (0.158 g, 71% yield) as a clear oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.85-5.92 (m, 1H), 5.30 (dt, *J* = 1.0, 15.0 Hz, 1H), 5.18 (dt, 1.0, 8.0 Hz, 1H), 4.92-4.95 (m, 1H), 4.34-4.39 (m, 1H), 4.12-4.15 (m, 1H), 2.59-2.68 (m, 2H), 2.40-2.46 (m, 1H), 2.12-2.17 (m, 2H), 1.94-1.99 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.91, 137.19, 117.16, 81.82, 78.90, 73.95, 40.61, 25.75, 23.19; IR (neat, cm<sup>-1</sup>) 1752 (CO); HRMS (ESI) calc for C<sub>9</sub>H<sub>12</sub>O<sub>3</sub><sup>+</sup> 168.0781, found 168.0772.

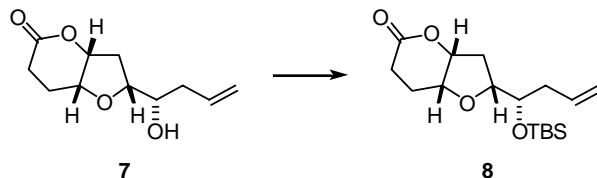
**(±)-(2R,3aR,7aR)-Tetrahydro-2-((S)-1-hydroxybut-3-enyl)-2H-furo[3,2-b]pyran-5(6H)-one, (7)**

Ozone gas was bubbled through a stirred solution of alkene **5** (0.03 g, 0.18 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at -78 °C for 10 min. Nitrogen gas was then bubbled through the solution for 10 min and then dimethylsulfide (0.053 mL, 0.72 mmol, 4 eq) was added. The reaction was stirred for 15 min at -78 °C and was warmed to rt for 1 h. After concentration, the residue was purified by flash chromatography (80% MeOH, EtOAc) to yield **6** (0.018 g, 88% yield) as a clear oil. This sensitive aldehyde was used immediately in the next reaction. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.67 (s, 1H), 4.89 (m, 2H), 4.44 (m, 1H), 4.34 (m, 1H), 2.73 (m, 1H), 2.60 (m, 1H), 2.45 (m, 2H), 2.26 (m, 1H).

To a stirred solution of aldehyde **6** (0.04 g, 0.24 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) at -78 °C was added BF<sub>3</sub>•Et<sub>2</sub>O (0.06 mL, 0.24 mmol, 1 eq). After stirring for 15 min, allyltrimethylsilane (0.06 mL, 0.36 mmol, 1.5 eq) was added, and the reaction was stirred for 10 min at -78 °C and then warmed to rt for 3 h. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo*. The crude mixture of diastereomers was separated by flash chromatography (50% *i*-PrOH/hexanes) to yield **7** (0.0303 g, 64% yield) as a clear oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.79-5.87 (m, 1H), 5.14-5.18 (m, 2H), 4.90-4.93 (m, 1H), 4.11-4.13 (m,

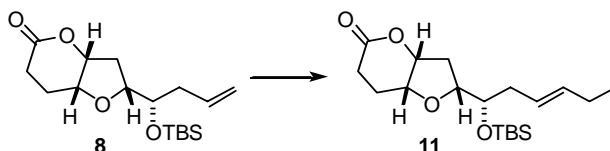
1H), 3.85-3.89 (m, 1H), 3.78-3.82 (m, 1H), 2.58-2.64 (m, 1H), 2.32-2.46 (m, 3H), 2.10-2.22 (m, 4H), 1.99 (br, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.09, 133.92, 118.51, 81.34, 80.25, 74.13, 71.01, 37.88, 34.87, 25.89, 23.28; IR(neat,  $\text{cm}^{-1}$ ) 1734 (CO), 3457 (OH); HRMS (ESI) calc for  $\text{C}_{11}\text{H}_{16}\text{O}_4\text{Na}^+$  235.0941, found 235.0932.

**( $\pm$ )-(2*R*,3*aR*,7*aR*)-Tetrahydro-2-((*S*)-1-(*tert*-butyldimethylsiloxy)but-3-enyl)-2H-furo[3,2-*b*]pyran-5(6*H*)-one, (**8**)**



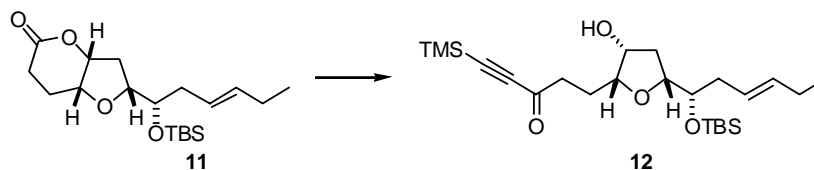
To a stirred solution of alcohol **7** (0.012 g, 0.057 mmol, 1 eq) in DMF (0.5 mL) was added TBSCl (0.026 g, 0.17 mmol, 3 eq) and imidazole (0.23 g, 0.34 mmol, 6 eq). The reaction was heated to 50 °C for 6 h. After cooling to rt, the reaction was diluted with EtOAc (100 mL) and washed with  $\text{H}_2\text{O}$  (2 x 100 mL). Separated the layers and dried the organics over  $\text{MgSO}_4$ , vacuum filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (25% EtOAc/hexanes) to yield **8** (0.026 g, 93% yield) as a clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.78-5.87 (m, 1H); 5.05-5.10 (m, 2H), 4.86-4.89 (m, 1H), 4.03-4.06 (m, 1H), 3.76-3.85 (m, 2H), 2.56-2.62 (m, 1H), 2.24-2.41 (m, 4H), 2.07-2.14 (m, 3H), 0.88 (s, 9H), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.25, 134.06, 117.45, 81.39, 79.81, 73.96, 72.24, 39.23, 35.46, 26.13, 25.78 (3C), 23.40, 18.04, -4.30, -4.47; IR(neat,  $\text{cm}^{-1}$ ) 1754 (CO); HRMS (ESI) calc for  $\text{C}_{17}\text{H}_{30}\text{O}_4\text{SiNa}^+$  349.1806, found 349.1807.

**( $\pm$ )-(2*R*,3*aR*,7*aR*)-Tetrahydro-2-((*S,E*)-1-(*tert*-butyldimethylsiloxy)hex-3-enyl)-2H-furo[3,2-*b*]pyran-5(6*H*)-one, (**11**)**



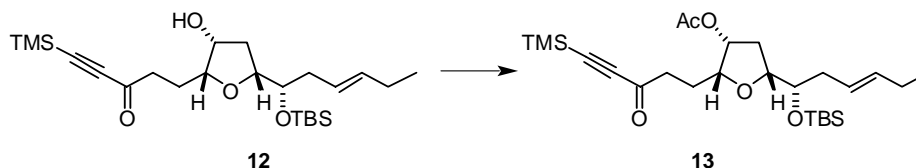
To a stirred solution of alkene **8** (0.062 g, 0.19 mmol, 1 eq)  $\text{CH}_2\text{Cl}_2$  (2 mL) was added *trans*-3-hexene (0.47 mL, 3.8 mmol, 20 eq) followed by catalyst **10** (0.016 g, 0.019 mmol, 0.1 eq). The reaction was stirred for 10 h and was concentrated *in vacuo*. The crude product was purified by flash chromatography (25% EtOAc/hexanes) to yield **11** (0.065 g, 97% yield) as a yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.47-5.53 (m, 1H), 5.39 (m, 1H), 4.87-4.90 (m, 1H), 4.03-4.06 (m, 1H), 3.75-3.82 (m, 2H), 2.56-2.62 (m, 1H), 2.34-2.40 (m, 2H), 1.98-2.24 (m, 7H), 0.97 (t,  $J = 7.0$  Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.30, 134.96, 124.23, 81.41, 79.96, 73.85, 72.45, 37.99, 35.16, 26.16, 25.79 (3C), 25.61, 23.45, 18.05, 13.61, -4.35, -4.43; IR(neat,  $\text{cm}^{-1}$ ) 1748 (CO); HRMS (ESI) calc for  $\text{C}_{19}\text{H}_{34}\text{O}_4\text{SiNa}^+$  377.2119, found 377.2103.

**(±)-5-((2*R*,3*R*,5*R*)-Tetrahydro-3-hydroxy-5-((*S*,*E*)-1-(*tert*-butyldimethylsiloxy)hex-3-enyl)furan-2-yl)-1-(trimethylsilyl)pent-1-yn-3-one, (**12**)**



To a stirred solution of trimethylsilylacetylene (0.23 mL, 0.45 mmol, 1.5 eq) in THF (1 mL) at -78 °C was added *n*-BuLi (1.6 M in THF, 0.3 mL, 0.45 mmol, 1.5 eq) dropwise. The reaction was stirred for 2 min and was warmed to 0 °C for 10 min. This solution was then transferred via cannula to a stirred solution of lactone **11** (0.105 g, 0.3 mmol, 1 eq) in THF (1.5 mL) at -78 °C. The reaction was stirred for 1 h and was then quenched with anhydrous ethereal HCl (1 M, 0.5 mL, 0.5 mmol, 1.6 eq). The mixture was stirred for 15 min and was poured into saturated NaCl solution (150 mL). The solution was extracted with EtOAc, dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo*. The crude product **12** could be used without further purification. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.46-5.52 (m, 1H), 5.26-5.32 (m, 1H), 4.05-4.08 (m, 1H), 3.93-3.96 (m, 1H), 3.87-3.91 (m, 1H), 3.55-3.58 (m, 1H), 3.37-3.40 (m, 1H), 2.68-2.72 (m, 2H), 2.23-2.26 (m, 1H), 2.12-2.18 (m, 1H), 1.95-2.07 (m, 6H), 0.97 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.25 (s, 9H), 0.06 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 187.31, 135.28, 123.67, 101.87, 97.68, 82.29, 78.63, 78.63, 73.43, 71.07, 41.97, 38.54, 34.08, 25.88 (3C), 25.53, 23.16, 18.13, 13.54, -0.79 (3C), -4.08, -4.83; IR(neat, cm<sup>-1</sup>) 1681 (CO), 3448 (OH); HRMS (ESI) calc for C<sub>24</sub>H<sub>44</sub>O<sub>4</sub>Si<sub>2</sub>Na<sup>+</sup> 475.2670, found 475.2673.

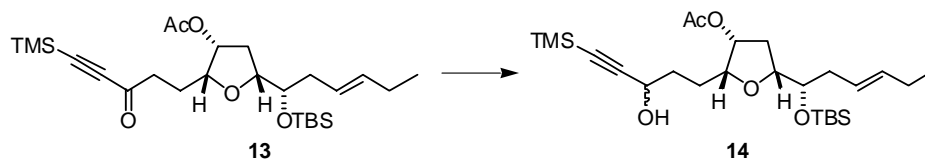
**(±)-((2*R*,3*R*,5*R*)-Tetrahydro-5-((*S*,*E*)-1-(*tert*-butyldimethylsiloxy)hex-3-enyl)-2-(5-(trimethylsilyl)-3-oxopent-4-ynyl)furan-3-yl acetate, (**13**)**



The crude alcohol **12** was dissolved in dry pyridine (7.5 mL) and cooled to 0 °C. To the stirred solution was added *N,N*-dimethylaminopyridine (0.004 g, 0.03 mmol, 0.1 eq) followed by acetic anhydride (0.1 mL, 1.05 mmol, 3.5 eq). After stirring for 10 min the reaction was allowed to warm to rt for 2 h. The reaction was diluted with EtOAc and washed with 1N HCl (150 mL) followed by saturated NaHCO<sub>3</sub> solution (200 mL). The organic layer was separated and dried with MgSO<sub>4</sub>, vacuum filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to yield **13** (0.126 g, 85% yield) in two steps as a clear oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.44-5.51 (m, 1H), 5.35-5.41 (m, 1H), 5.21-5.24 (m, 1H), 3.83-3.88 (m, 1H), 3.65-3.71 (m, 2H), 2.73-2.79 (m, 1H), 2.62-2.69 (m, 1H), 2.07-2.39 (m, 3H), 2.06 (s, 3H), 1.84-2.04 (m, 5H), 0.97 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.25 (s, 9H), 0.06 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 186.99, 170.66, 134.75, 124.67, 101.86, 97.84, 79.99, 79.96, 74.80, 72.35, 42.18, 38.25, 33.56, 25.86 (3C), 25.62, 23.03, 21.05, 18.19, 13.64, -0.79 (3C), -4.33, -4.40; IR(neat, cm<sup>-1</sup>) 1747 (CO), 1675 (CO); HRMS (ESI) calc for

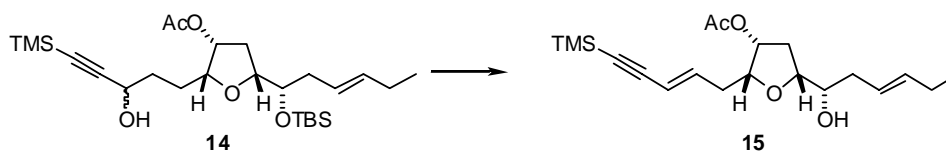
$C_{26}H_{46}O_5Si_2Na^+$  517.2776, found 517.2798.

**(±)-(2R,3R,5R)-Tetrahydro-2-(3-hydroxy-5-(trimethylsilyl)pent-4-ynyl)-5-((S,E)-1-(tert-butyl)dimethylsiloxy)hex-3-enylfuran-3-yl acetate, (14)**



To a stirring solution of ketone **13** (0.054 g, 0.11 mmol, 1.0 eq) in THF (1 mL) at  $-78^\circ\text{C}$  was added lithium borohydride (2 M in THF, 0.055 mL, 0.11 mmol, 1 eq). After stirring for 2 min the reaction was warmed to  $0^\circ\text{C}$  for 30 min. The reaction was poured into  $\text{H}_2\text{O}$  (100 mL), extracted with EtOAc, dried over  $\text{MgSO}_4$ , vacuum filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to yield **14** (0.054 g, 99% yield) as a clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.46-5.53 (m, 1H), 5.34-5.43 (m, 1H), 5.23-5.26 (m, 1H), 4.39-4.47 (m, 1H), 3.88 (m, 1H), 3.67-3.78 (m, 2H), 2.78-2.89 (m, 1H), 2.11-2.30 (m, 3H), 2.06 (s, 3H), 1.68-2.04 (m, 7H), 0.98 (t,  $J = 7.0$  Hz, 3H), 0.09 (s, 9H), 0.17 (s, 9H), 0.08 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.71, 134.94, 134.88, 124.53, 124.40, 122.65, 106.44, 81.71, 81.39, 80.17, 80.13, 74.98, 74.92, 72.38, 72.20, 62.88, 62.34, 38.25, 38.10, 35.30, 34.88, 33.56, 33.36, 25.88 (3C), 25.62, 25.09, 24.22, 21.05, 18.17, 13.63, -0.12 (3C), -4.32, -4.41; IR (neat,  $\text{cm}^{-1}$ ) 1738 (CO), 3425 (OH); HRMS (ESI) calc for  $C_{26}H_{48}O_5Si_2Na^+$  519.2932, found 519.2922.

**(±)-(2R,3R,5R)-Tetrahydro-5-((S,E)-1-hydroxy)-2-((E)-5-(trimethylsilyl)pent-2-en-4-ynyl)furan-3-yl acetate, (15)**



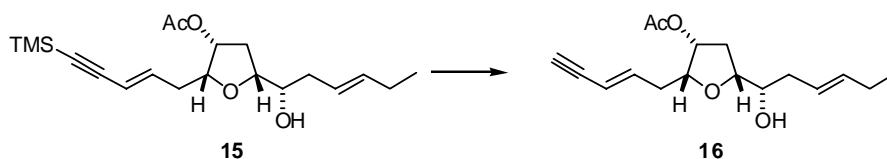
To a stirred solution of propargylic alcohol **14** (0.04 g, 0.08 mmol, 1 eq) in benzene (1.3 mL) was added cobalt carbonyl (0.055 g, 0.16 mmol, 2 eq). After stirring 2.5 h the reaction was concentrated *in vacuo*.

The crude complexed residue was taken up in  $\text{CH}_2\text{Cl}_2$  (1.1 mL) and cooled to  $-78^\circ\text{C}$ . Trifluoromethanesulfonic anhydride (0.04 mL, 0.24 mmol, 3 eq) was added dropwise and the mixture was warmed to  $-10^\circ\text{C}$ . The reaction was stirred for 2.5 h, poured into saturated  $\text{NaHCO}_3$  solution, and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried over  $\text{MgSO}_4$ , vacuum filtered, and concentrated *in vacuo*.

The crude residue was taken up in acetone (0.5 mL) and ceric ammonium nitrate (0.1 g, 0.32 mmol, 4 eq) was added. The reaction was stirred at rt for 45 min and was then poured into 5%  $\text{Na}_2\text{CO}_3$  aqueous solution. The mixture was extracted with EtOAc and the organic phase was dried over  $\text{MgSO}_4$ , vacuum filtered, and concentrated *in vacuo*. The crude product was purified

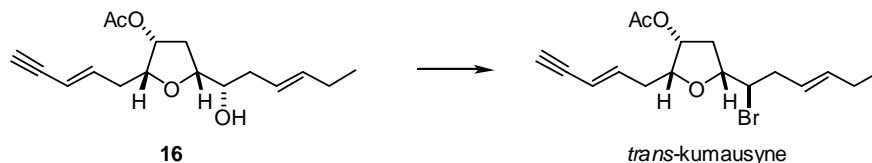
by flash chromatography (20% EtOAc/hexanes) to yield **15** (0.014 g, 46% over 3 steps) as a pale yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.18 (dt,  $J$  = 7.0, 16.0 Hz, 1H), 5.56-5.62 (m, 2H), 5.37-5.43 (m, 1H), 5.21-5.24 (m, 1H), 3.82-3.88 (m, 2H), 3.75-3.78 (m, 1H), 2.39-2.48 (m, 2H), 2.26-2.32 (m, 2H), 2.14-2.17 (m, 2H), 2.08 (s, 3H), 1.98-2.07 (m, 3H), 0.98 (t,  $J$  = 7.0 Hz, 3H), 0.18 (s, 9H)  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.44, 140.88, 135.81, 124.00, 112.21, 103.39, 80.26, 70.99, 74.40, 71.04, 36.29, 32.74, 32.65, 30.95, 25.60, 21.06, 13.69, -0.11 (3C); IR(neat,  $\text{cm}^{-1}$ ) 1741 (CO), 3473 (OH); HRMS (ESI) calc for  $\text{C}_{20}\text{H}_{32}\text{O}_4\text{SiNa}^+$  387.1962, found 387.1948.

**(±)-(2R,3R,5R)-Tetrahydro-5-((S,E)-1-hydroxyhex-3-enyl)-2-((E)-pent-2-en-4-ynyl)furan-3-yl acetate, (16)**



To a stirred solution of alkynyl silane **15** (0.009 g, 0.025 mmol, 1 eq) in THF (0.13 mL) at  $-10\text{ }^\circ\text{C}$  was added 1M tetrabutylammonium fluoride (0.03 mL, 0.03 mmol, 1.2 eq). The reaction was stirred for 5 min and was then poured into  $\text{NH}_4\text{Cl}$  saturated solution (100 mL). The solution was extracted with EtOAc, and the organic phase was dried over  $\text{MgSO}_4$ , vacuum filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (25% EtOAc/hexanes) to yield **16** (0.0073 g, 100% yield) as a clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.23 (dt,  $J$  = 7.5, 16.0 Hz, 1H), 5.54-5.62 (m, 2H), 5.37-5.44 (m, 1H), 5.23-5.25 (m, 1H), 3.84-3.87 (m, 2H), 3.77-3.83 (m, 1H), 2.83 (d,  $J$  = 2.5 Hz, 1H), 2.42-2.48 (m, 2H), 2.30 (m, 2H), 2.16 (m, 2H), 2.08 (s, 3H), 1.98-2.07 (m, 2H), 0.98 (t,  $J$  = 7.0 Hz, 3H)  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.42, 141.68, 135.84, 123.97, 111.08, 81.91, 80.12, 76.63, 74.41, 71.04, 36.30, 32.72, 32.64, 25.60, 21.04, 13.69; IR(neat,  $\text{cm}^{-1}$ ) 1732 (CO), 3468 (OH); HRMS (ESI) calc for  $\text{C}_{17}\text{H}_{24}\text{O}_4\text{Na}^+$  315.1567, found 315.1562.

**trans-Kumausyne**



To a stirred solution of alcohol **16** (0.0079 g, 0.027 mmol, 1 eq) in PhH (1.35 mL) was added 2,6-di-*tert*-butylpyridine (0.015 mL, 0.066 mmol, 2.4 eq) followed by carbon tetrabromide (0.022 g, 0.066 mmol, 2.4 eq) and triphenylphosphine (0.017 g, 0.066 mmol, 2.4 eq). Once the reaction reached  $40\text{ }^\circ\text{C}$ , another 2.4 eq each of carbon tetrabromide and triphenylphosphine were added. The reaction was stirred for 30 min at  $40\text{ }^\circ\text{C}$ . After cooling to rt, the mixture was diluted with EtOAc (50 mL) and filtered through a silica gel plug and concentrated *in vacuo*. Purification by preparative TLC (25% EtOAc/hexanes) yielded *trans*-kumausyne (0.0028 g, 30% yield) as a yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.24 (dt,  $J$  = 7.0, 16.0, 1H), 5.54-5.62 (m, 2H), 5.46-5.50 (m, 1H), 5.23-5.26 (m, 1H), 3.99-4.07 (m, 2H), 3.83-3.86 (m, 1H), 2.83 (d,  $J$  = 2.0 Hz, 1H),

2.67-2.71 (m, 1H), 2.41-2.56 (m, 4H), 2.09 (s, 3H), 2.02-2.08 (m, 2H), 1.88-1.93 (m, 1H), 0.99 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.42, 141.65, 135.78, 124.71, 111.11, 82.70, 80.24, 79.49, 77.23, 74.16, 56.60, 37.49, 36.52, 32.82, 25.58, 21.01, 13.67; IR(neat,  $\text{cm}^{-1}$ ) 1734 (CO); HRMS (ESI) calc for  $\text{C}_{17}\text{H}_{24}^{81}\text{BrO}_3^+$  357.0889, found 357.1447.

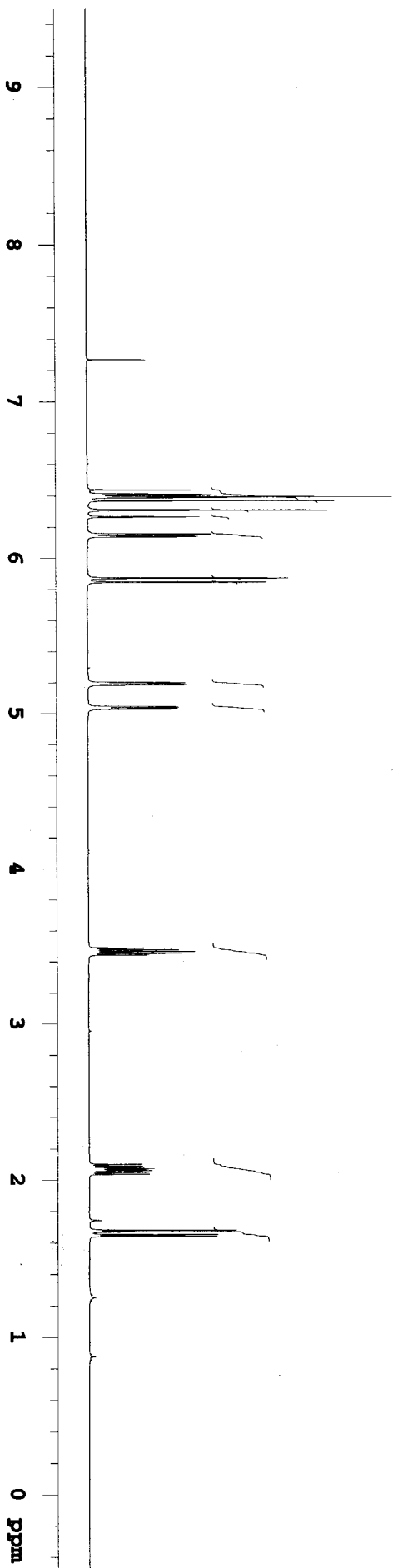
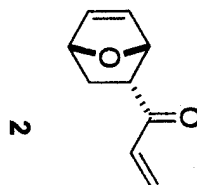
Comparison of data for synthetic and natural *trans*-Kumausyne

	Synthetic		Natural	
	$^1\text{H}$ $\delta$ (mult, $J$ )	$^{13}\text{C}$ $\delta^3$	$^1\text{H}$ $\delta$ (mult, $J$ )	$^{13}\text{C}$ $\delta$
1	2.83 (d, 2.1)	82.7	2.82 (d, 2.0)	82.7
2	-	77.2	-	77.6
3	5.54-5.58 (m)	135.8	5.55 (dd, 16.0, 2.0)	136.0
4	6.24 (dt, 7.0, 16.0)	141.7	6.26 (dt, 16.0, 7.5)	141.6
5a	2.42-2.53 (m)	32.8	2.41-2.56 (m)	33.3
5b	2.42-2.53 (m)		2.41-2.56 (m)	
6	3.83-3.86 (m)	80.3	3.85 (ddd, 7.2, 6.1, 4.4)	80.8
7	5.23-5.26 (m)	74.2	5.24 (ddd, 7.5, 4.5, 2.5)	74.5
8a	2.41-2.48 (m)	36.5	2.41-2.56 (m)	37.0
8b	1.88-1.93 (m)		1.91 (ddd, 14.5, 7.1, 2.6)	
9	4.03-4.07 (m)	79.5	4.00 (m)	79.8
10	3.99-4.03 (m)	56.6	4.00 (m)	57.1
11a	2.50-2.56 (m)	37.5	2.41-2.56 (m)	38.2
11b	2.67-2.71 (m)		2.67-2.72 (m)	
12	5.46-5.50 (m)	124.7	5.46 (ddd, 15.0, 6.5, 6.5)	125.9
13	5.59-5.62 (m)	111.1	5.61 (dt, 15.0, 6.5)	111.8
14a	2.02-2.08 (m)	25.6	2.04 (dq, 6.5, 7.5)	26.3
14b	2.02-2.08 (m)		2.04 (dq, 6.5, 7.5)	
15	0.98 (t, 7.0)	13.7	0.99 (t, 7.5)	14.2
16	2.08 (s)	21.0	2.08 (s)	20.7
17	-	170.4	-	169.8

<sup>3</sup> Due to limited sample, this data was obtained by HSQC and HMBC experiments.



00

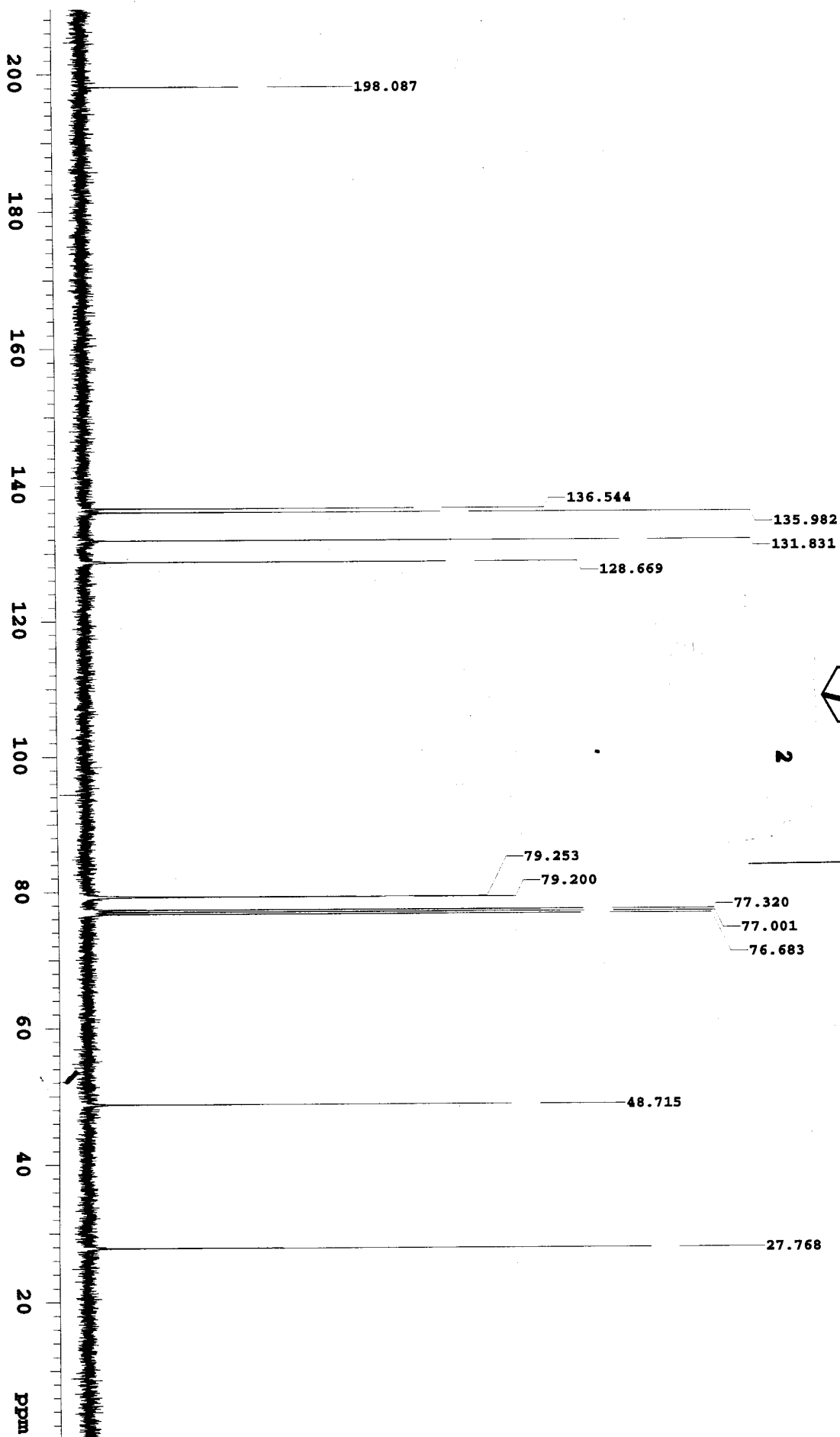


Relax. delay 1.500 sec  
Pulse 30.0 degrees  
Acq. time 3.000 sec  
Width 6000.6 Hz  
24 repetitions

OBSERVE H1, 400.1547236

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 131072  
Total time 1 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-08-121-01

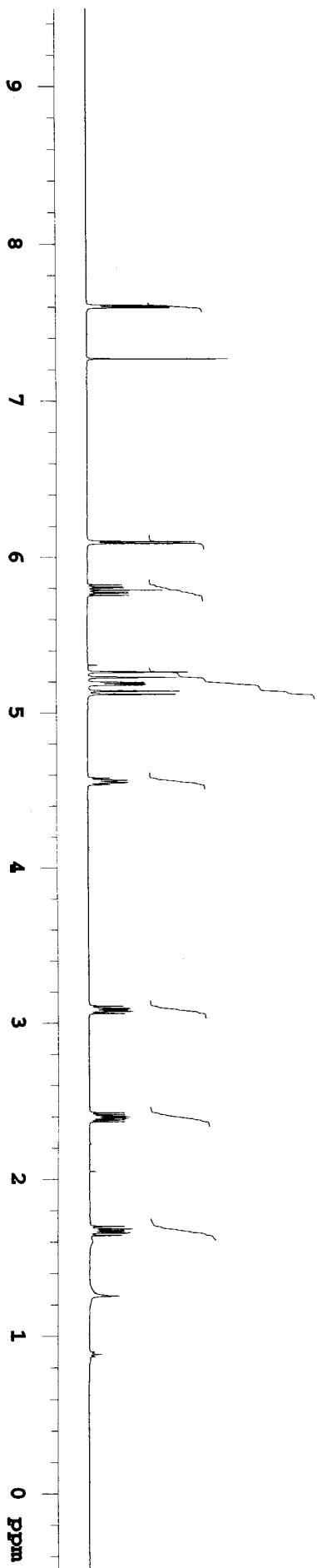
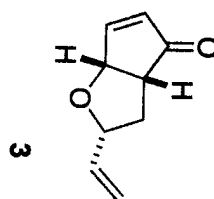
S  
10

Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 25000.0 Hz  
208 repetitions

OBSERVE C13, 100.6189920  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on  
WALTZ-16 modulated

DATA PROCESSING  
Line broadening 1.2 Hz  
FT size 131072  
Total time 9 minutes

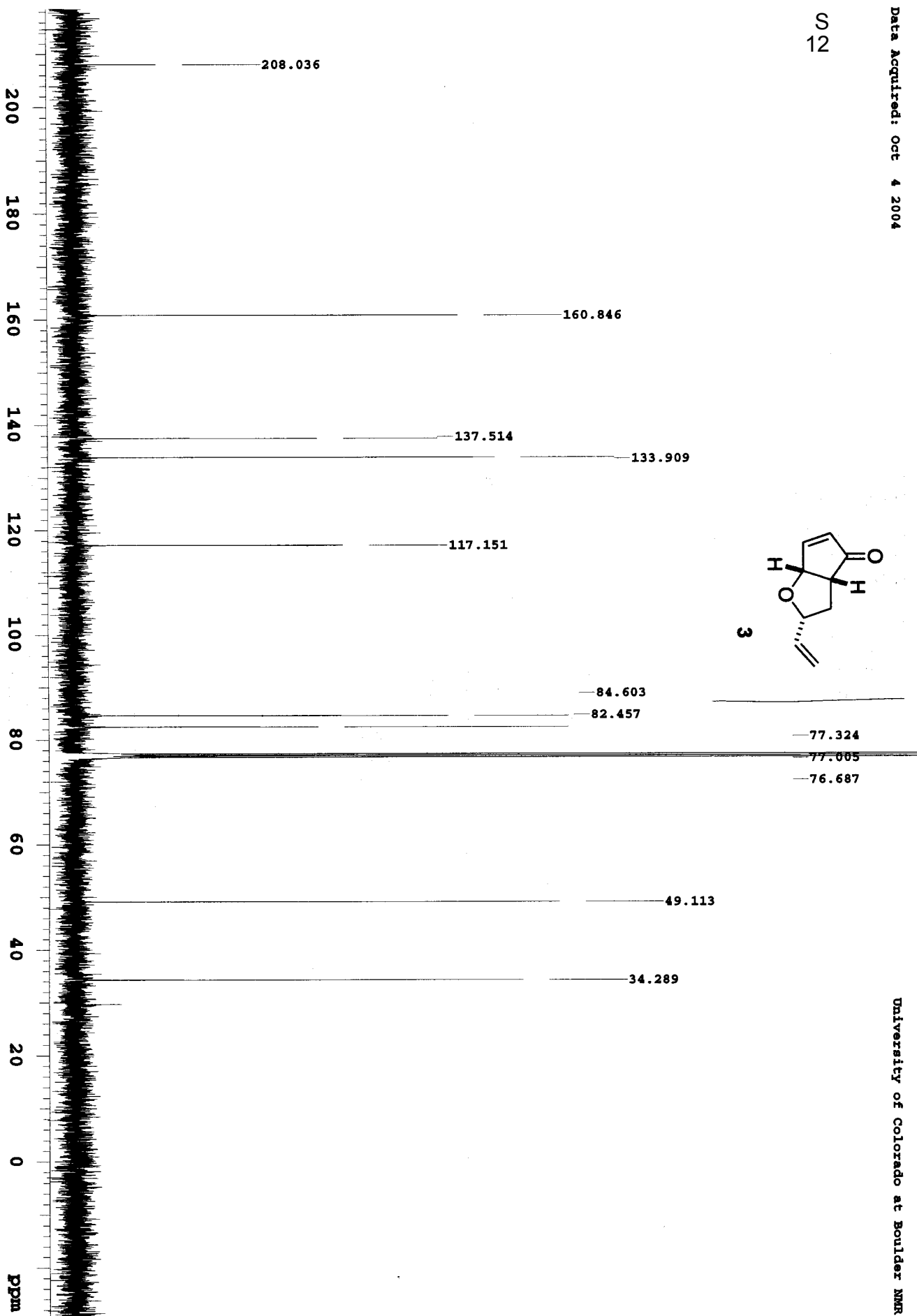
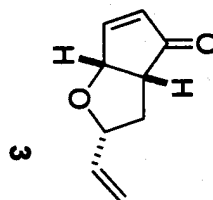
Solvent: CDCl3  
Ambient temperature  
File: cc-08-121-C13

S  
11

Relax. delay 1.000 sec  
Pulse 26.5 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
32 repetitions

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 65536  
Total time 2 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-08-082-fp

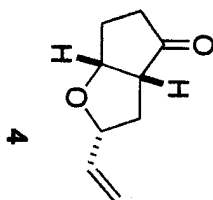
S  
12

Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 25000.0 Hz  
768 repetitions

OBSERVE C13, 100.6189878  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on  
WALTZ-16 modulated

DATA PROCESSING  
Line broadening 1.2 Hz  
Ft size 131072  
Total time 36 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-08-082-C13

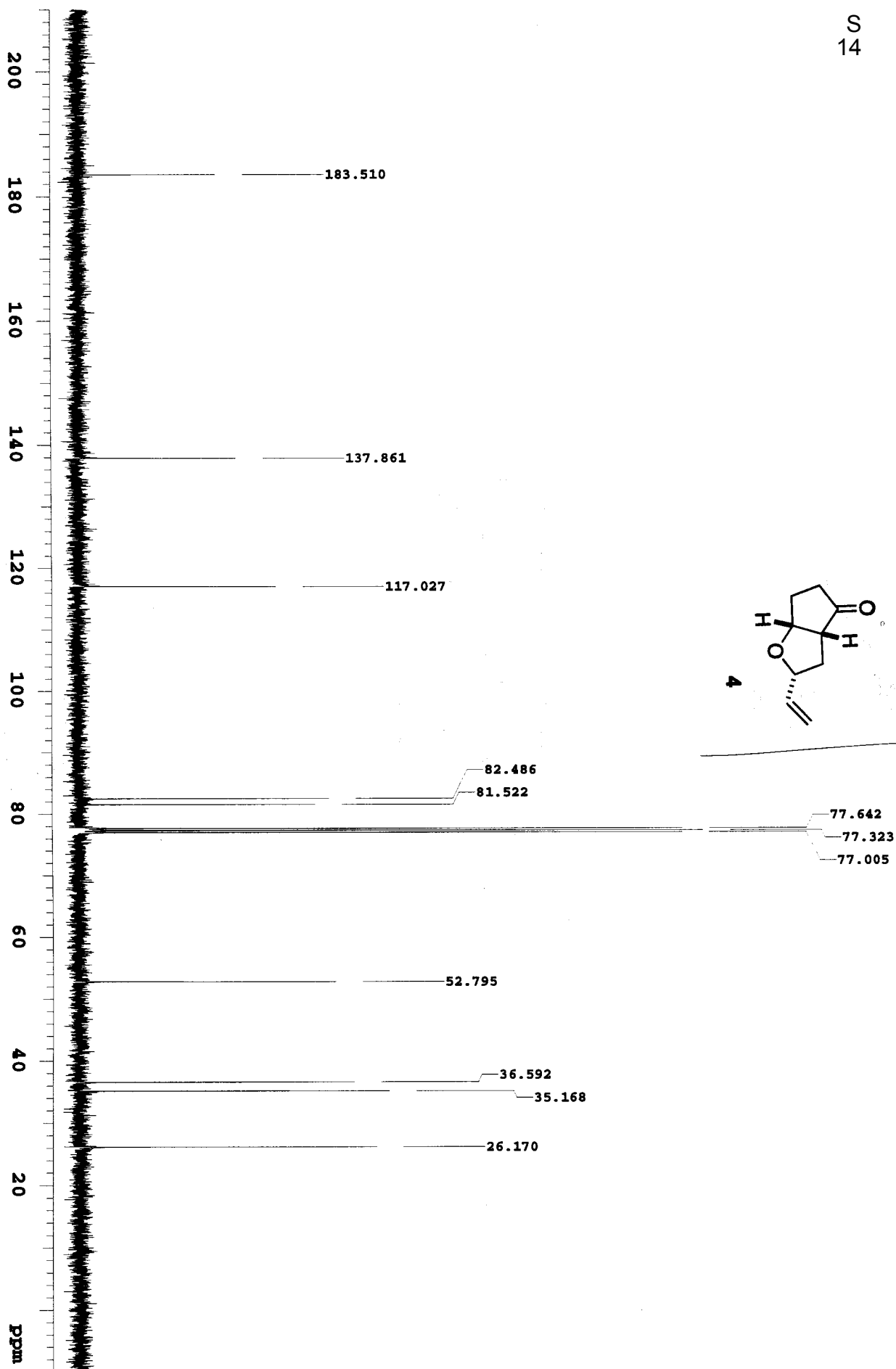
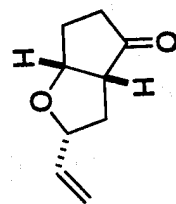
S  
13

Relax. delay 1.000 sec  
Pulse 26.5 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
30 repetitions

OBSERVE H1, 500.3674340

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 65536  
Total time 2 minutes

Solvent: CDCl3  
Ambient temperature  
File: cc-08-084-fp01

S  
14

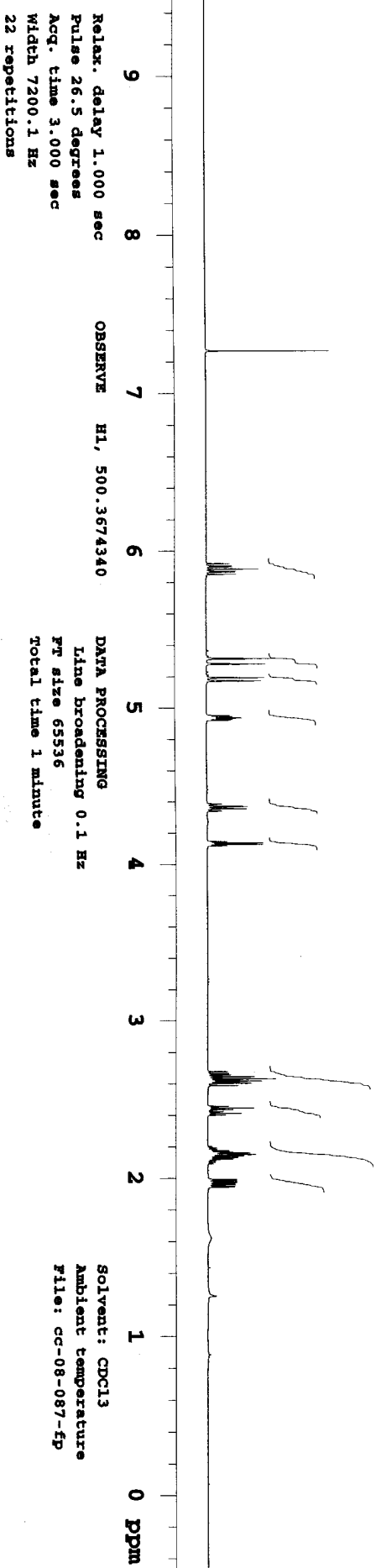
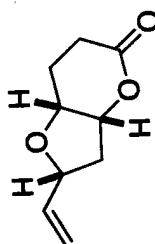
Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 29996.3 Hz  
256 repetitions

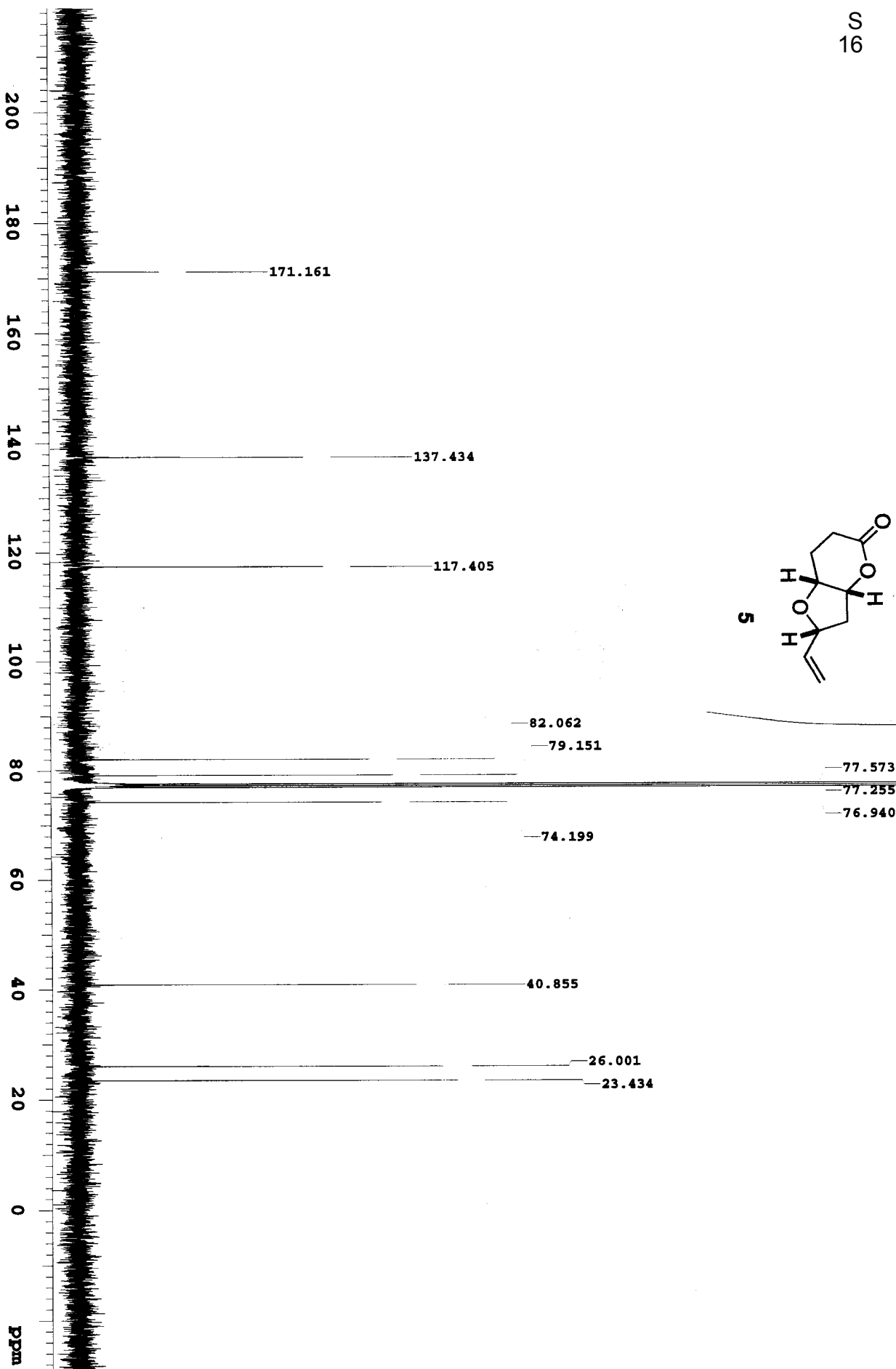
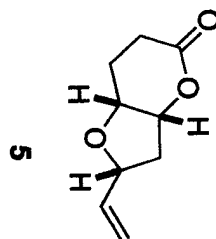
OBSERVE C13, 100.6189557  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on

WALTZ-16 modulated

DATA PROCESSING  
line broadening 1.2 Hz  
FT size 131072  
Total time 12 minutes

Solvent: CDCl3  
Ambient temperature  
File: cc-08-084-tpc13

S  
15

S  
16

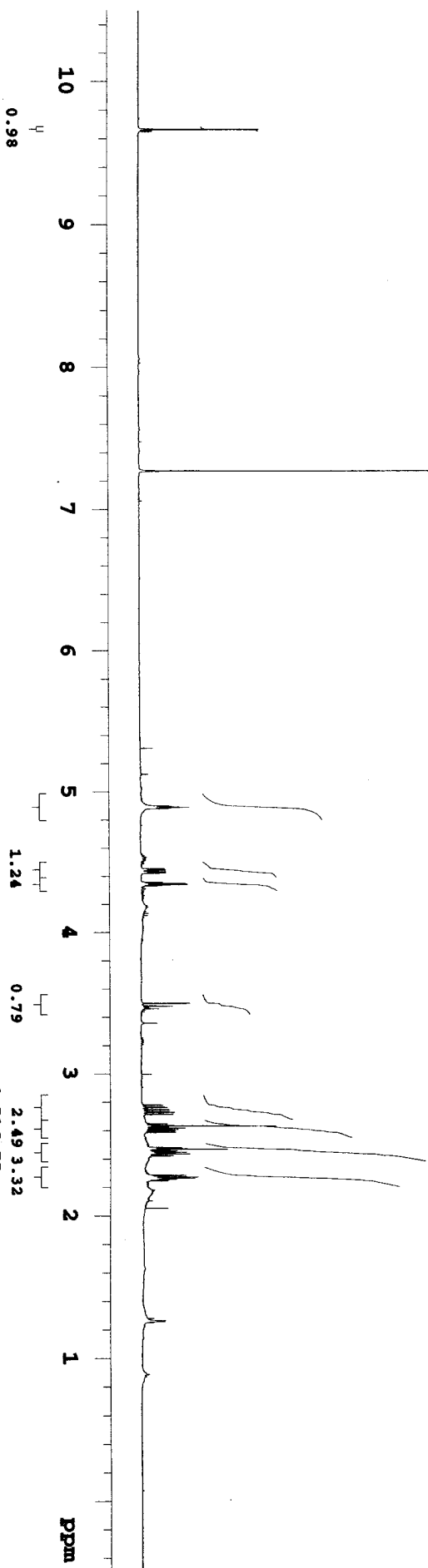
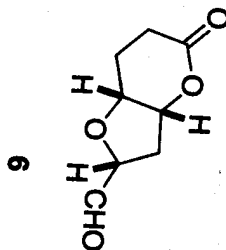
Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 25000.0 Hz  
624 repetitions

OBSERVE C13, 100.6189623  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on  
WALTZ-16 modulated

DATA PROCESSING  
Line broadening 1.2 Hz  
FT size 131072  
Total time 29 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: GC-08-087-fpC13



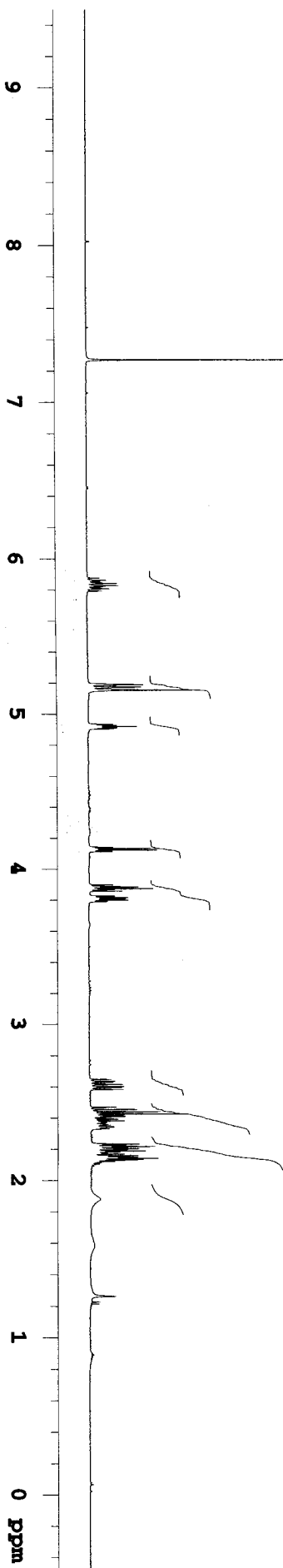
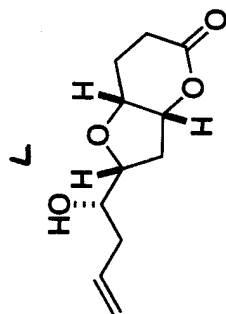
S  
17

Relax. delay 1.500 sec  
Pulse 26.5 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
48 repetitions

OBSERVE H1, 500.3674331

DATA PROCESSING  
Line broadening 0.1 Hz  
F2 size 131072  
Total time 3 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: GC-09-110-4p

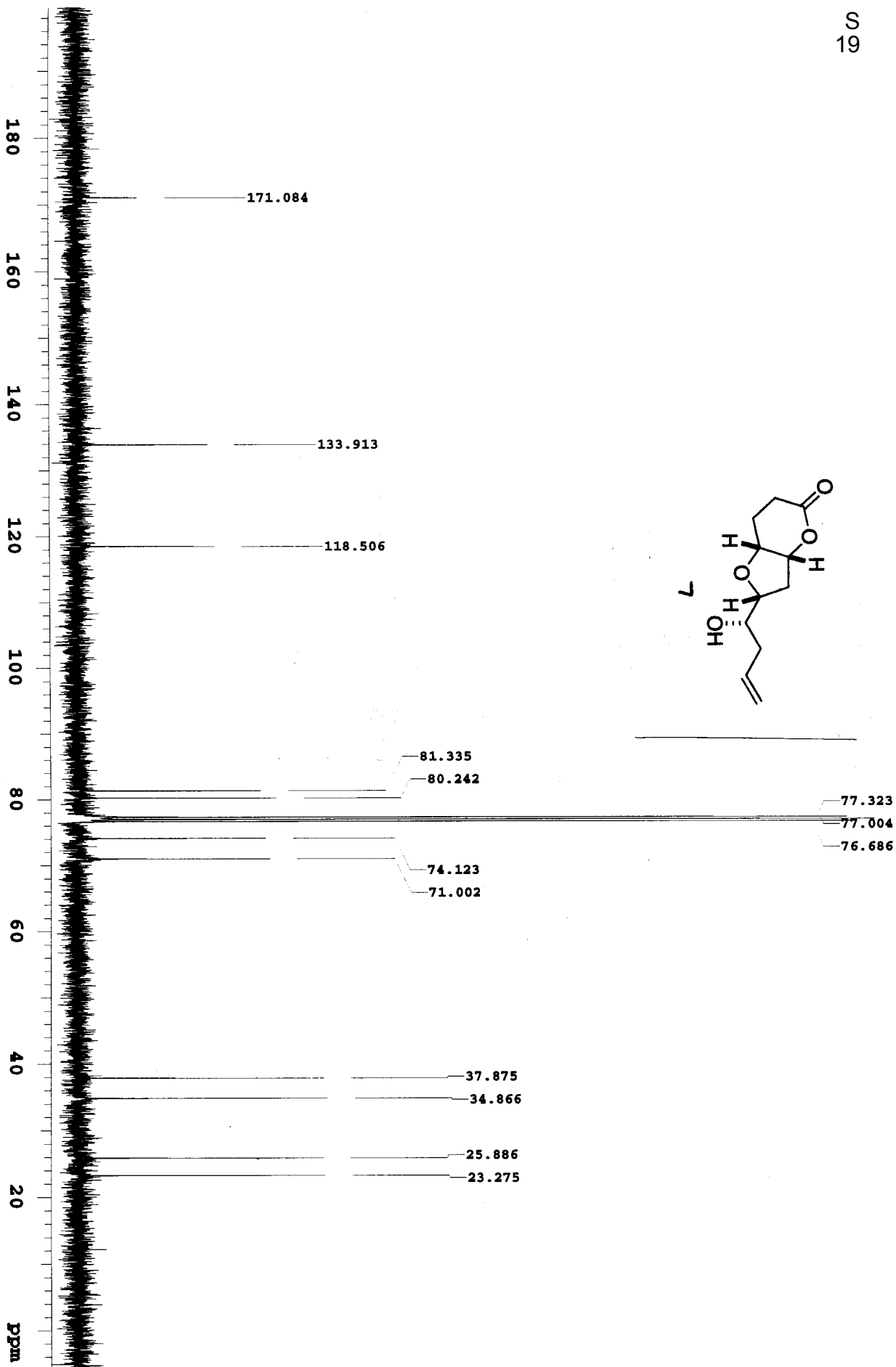
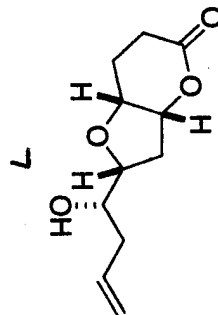
S  
18

Relax. delay 1.500 sec  
Pulse 19.7 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
32 repetitions

OBSERVE H1, 500.3674333

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 131072  
Total time 2 minutes

Solvent: CDCl<sub>3</sub>  
Temp. 20.0 C / 293.1 K  
File: CC-10-018-ft

S  
19

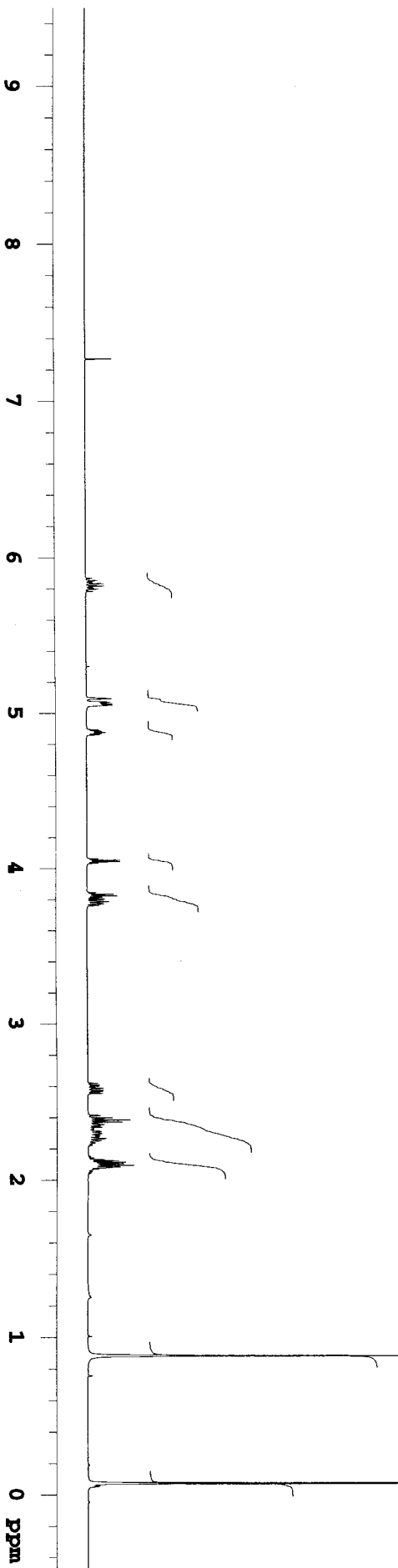
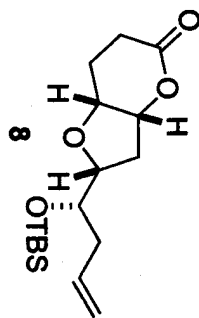
Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 34995.6 Hz  
224 repetitions

OBSERVE C13, 100.6189886  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on  
WALTZ-16 modulated

DATA PROCESSING  
line broadening 1.2 Hz  
FT size 131072  
Total time 10 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-09-110-C13

S  
20

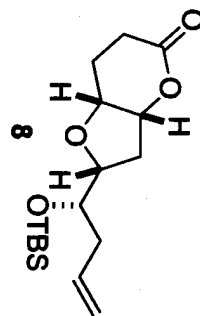


Relax. delay 1.500 sec  
Pulse 26.5 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
32 repetitions

OBSERVE H1, 500.3674331

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 131072  
Total time 2 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-09-111-fp

S  
21

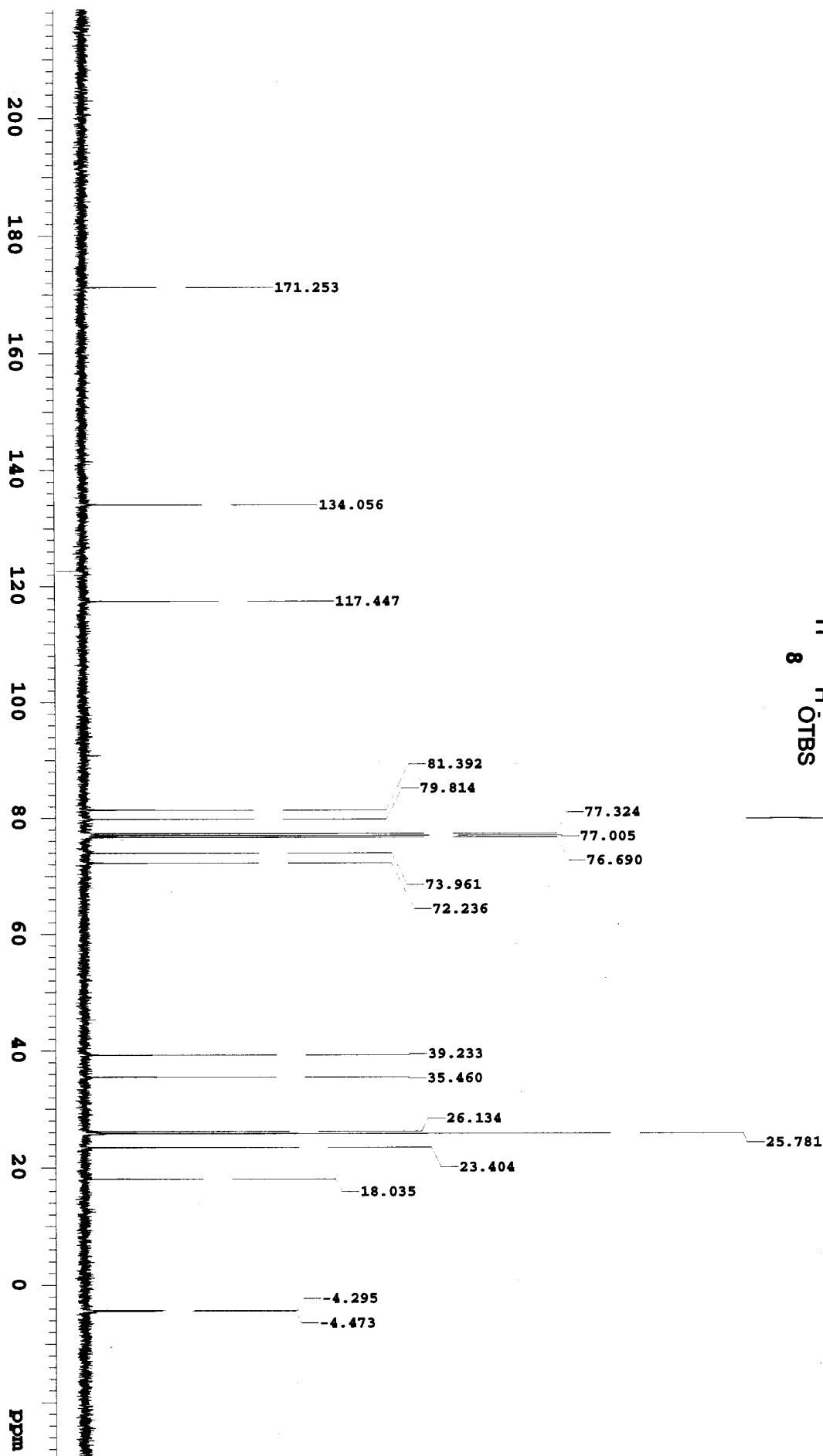
Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 25000.0 Hz  
320 repetitions

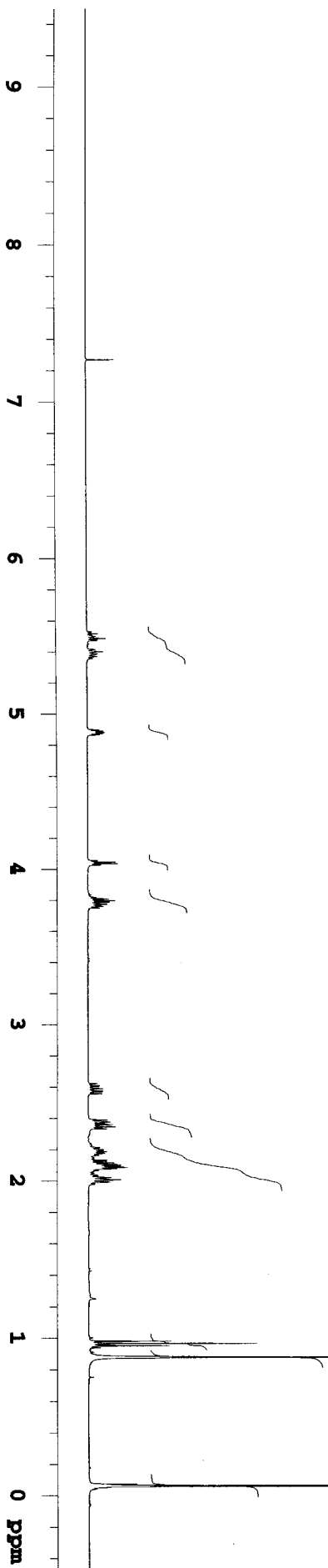
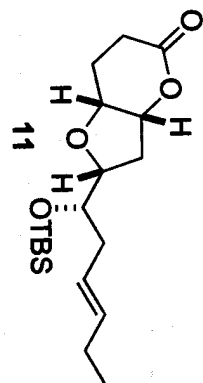
OBSERVE C13, 100.6189886  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on

WALTZ-16 modulated

DATA PROCESSING  
Line broadening 1.2 Hz  
FT size 131072  
Total time 15 minutes

Solvent: CDCl3  
Ambient temperature  
File: cc-09-111-C13

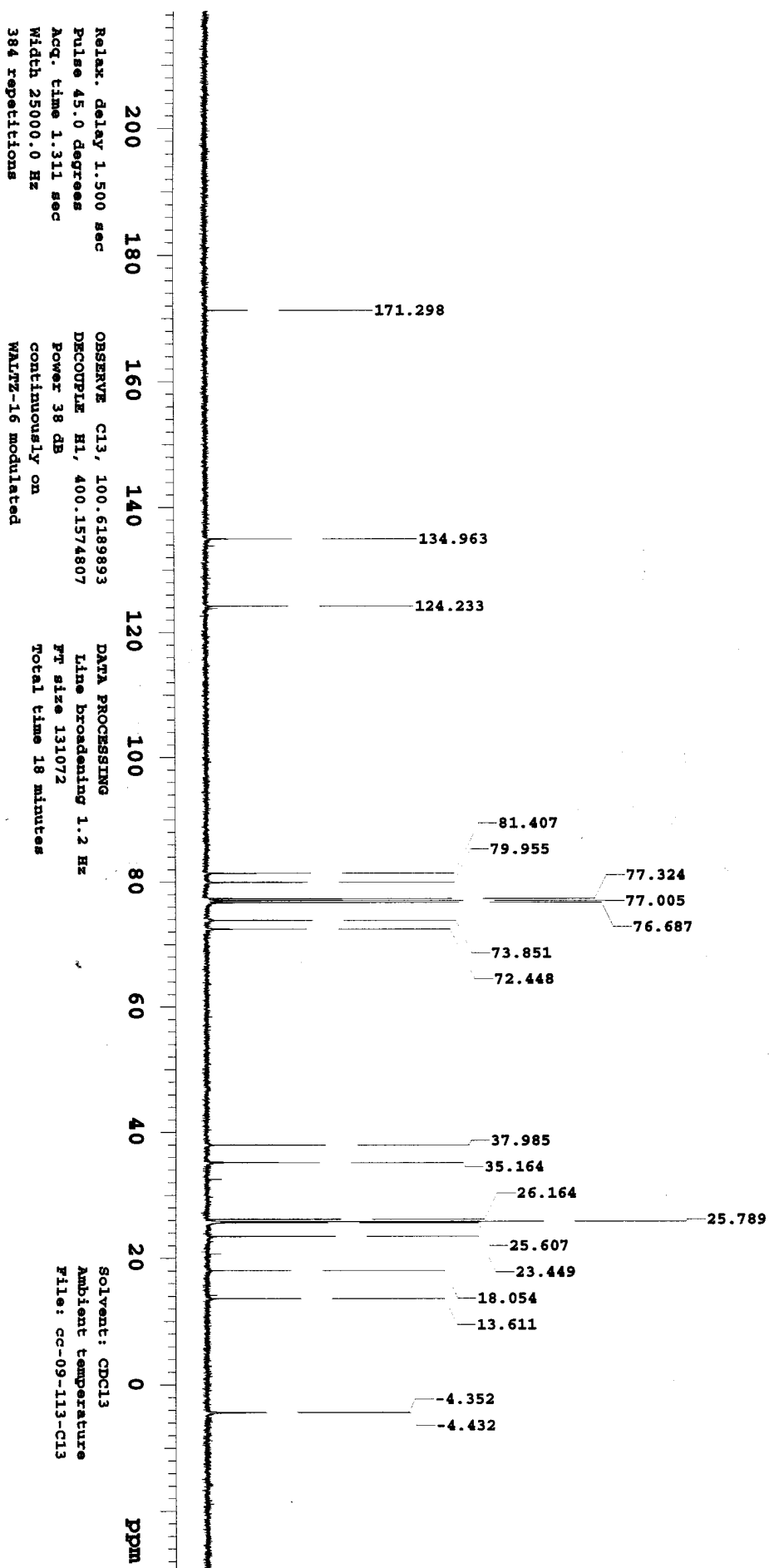
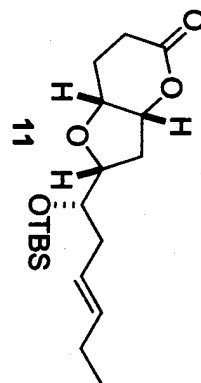


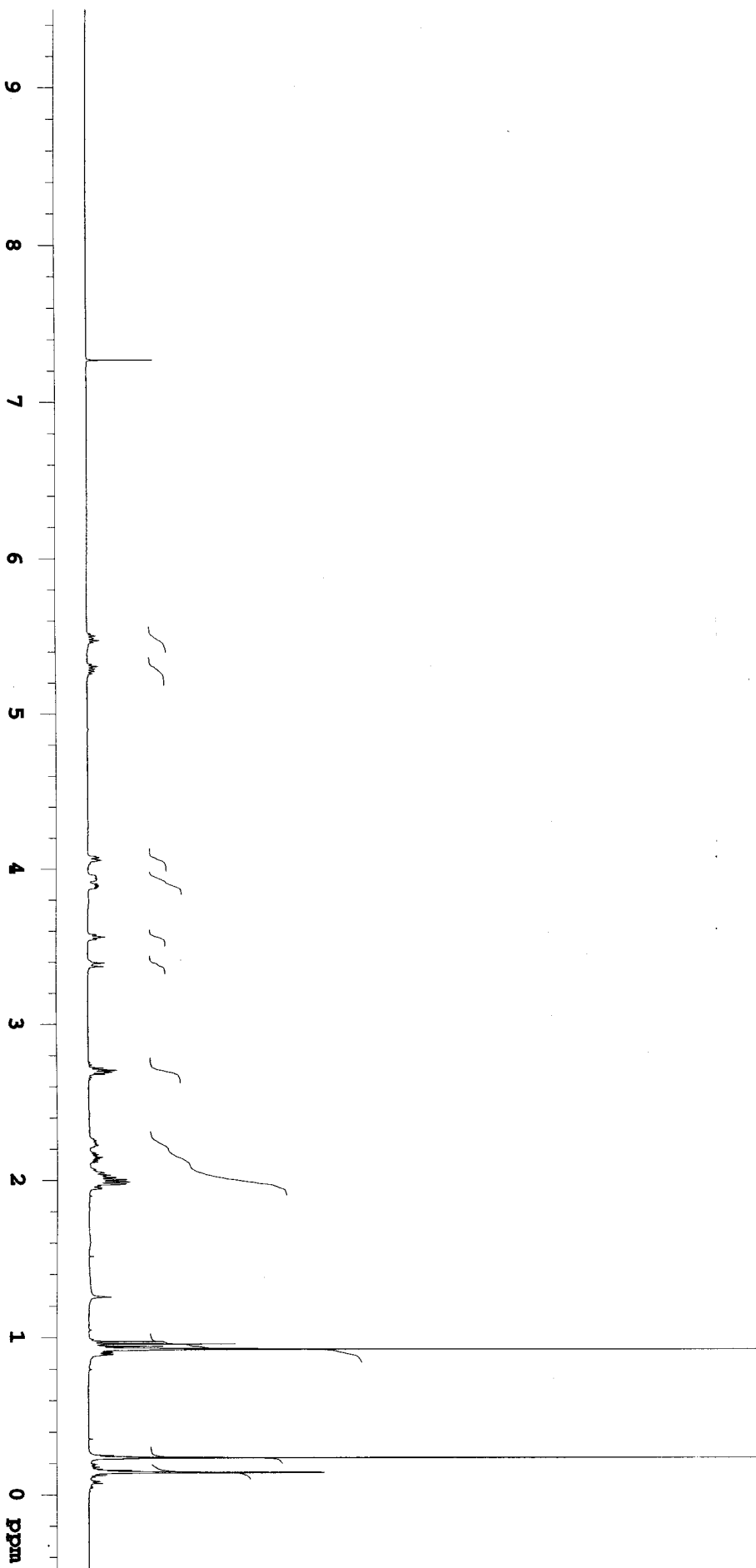
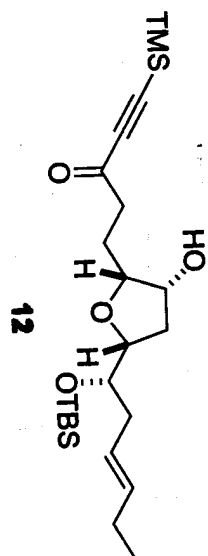
S  
22

Relax. delay 1.500 sec  
Pulse 26.5 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
32 repetitions

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 131072  
Total time 2 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-09-115-tp

S  
23

S  
24

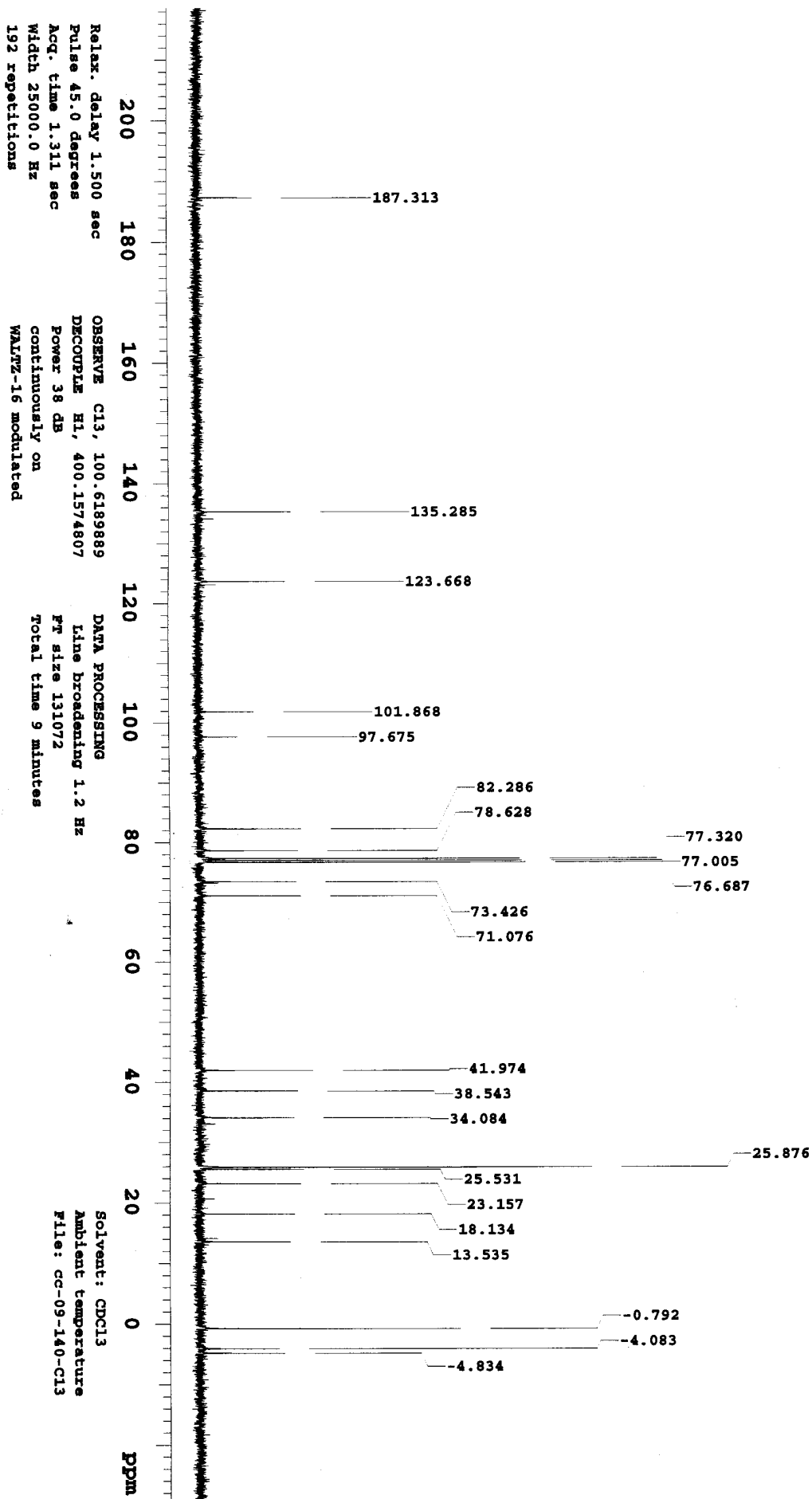
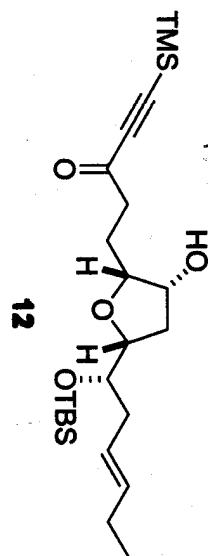
Relax. delay 1.000 sec  
Pulse 26.5 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
24 repetitions

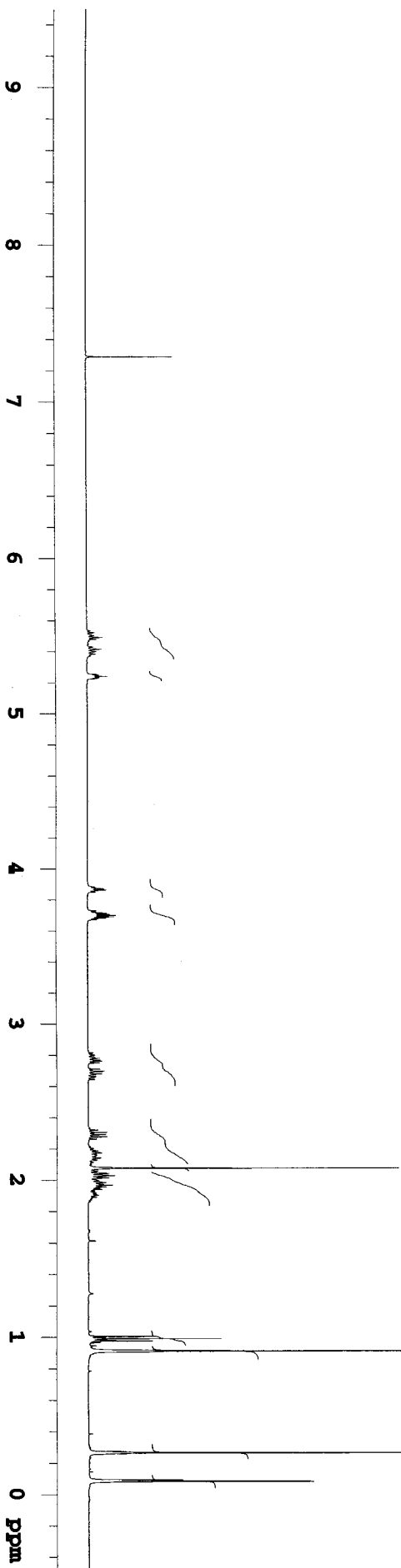
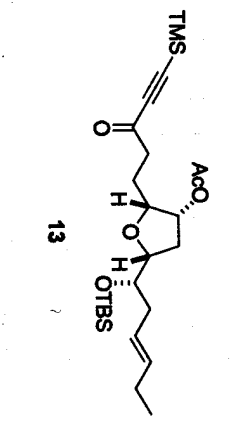
OBSERVE H1, 500.3674331

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 131072  
Total time 1 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-09-062-01



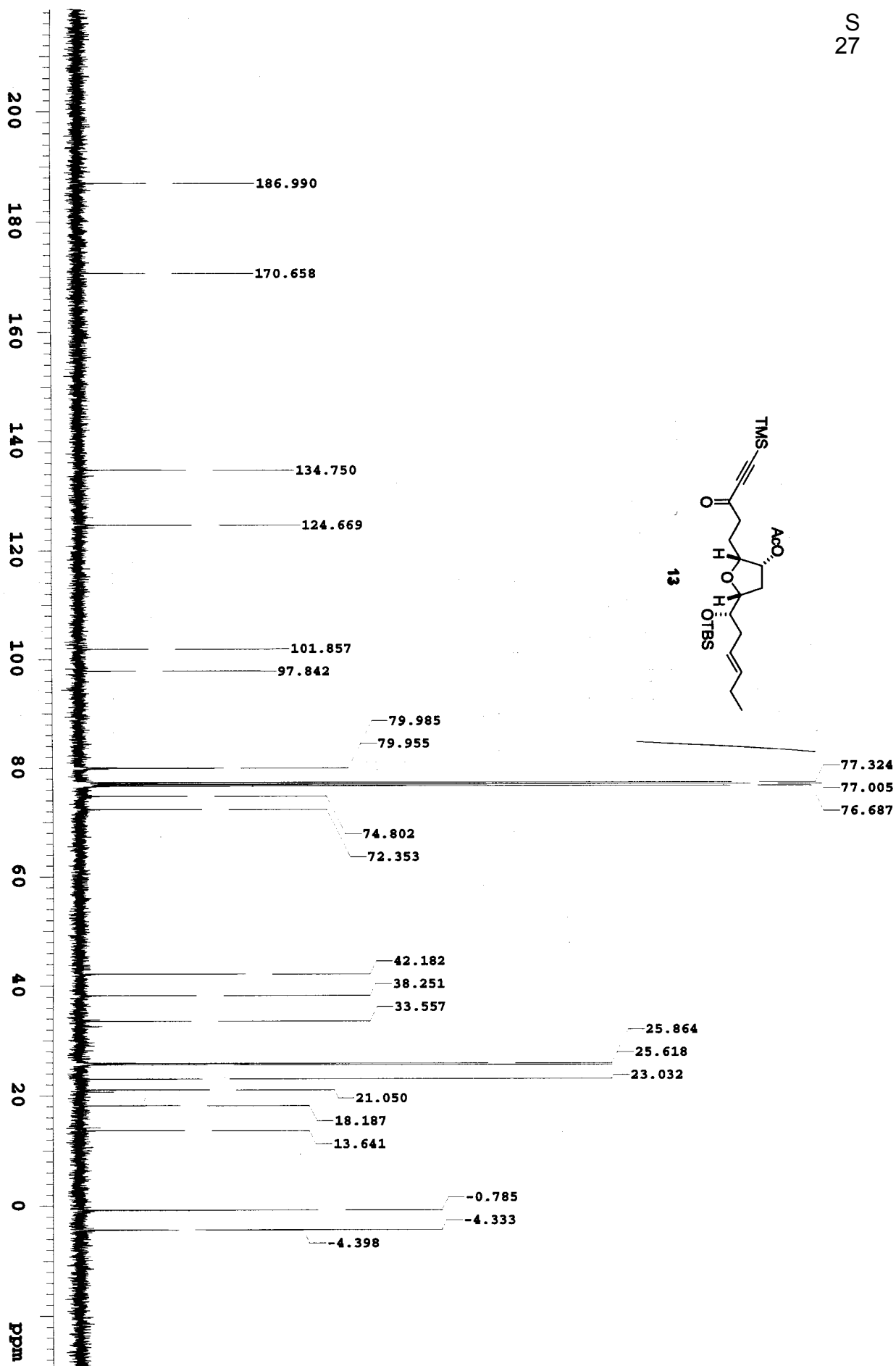
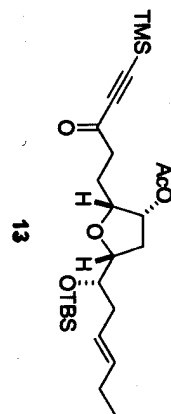
S  
25

S  
26

Relax. delay 0.100 sec  
Pulse 17.7 degrees  
Acq. time 3.000 sec  
Width 6505.1 Hz  
16 repetitions

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 65536  
Total time 1 minute

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-10-048-fp

S  
27

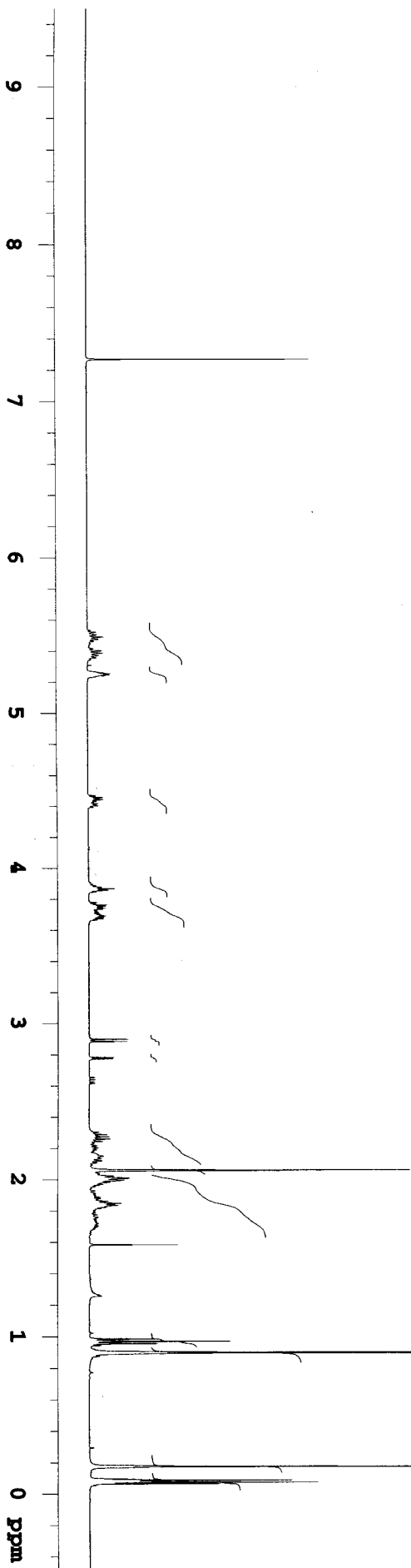
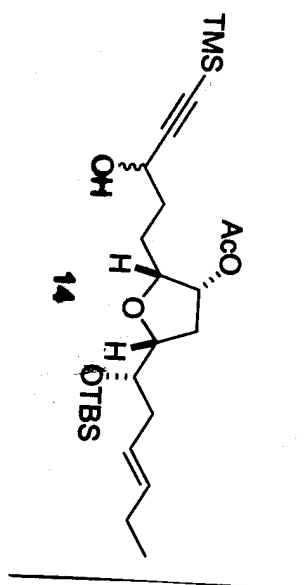
Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 25000.0 Hz  
448 repetitions

OBSERVE C13, 100.6189870  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on

WALTZ-16 modulated

DATA PROCESSING  
Line broadening 1.2 Hz  
FT size 131072  
Total time 21 minutes

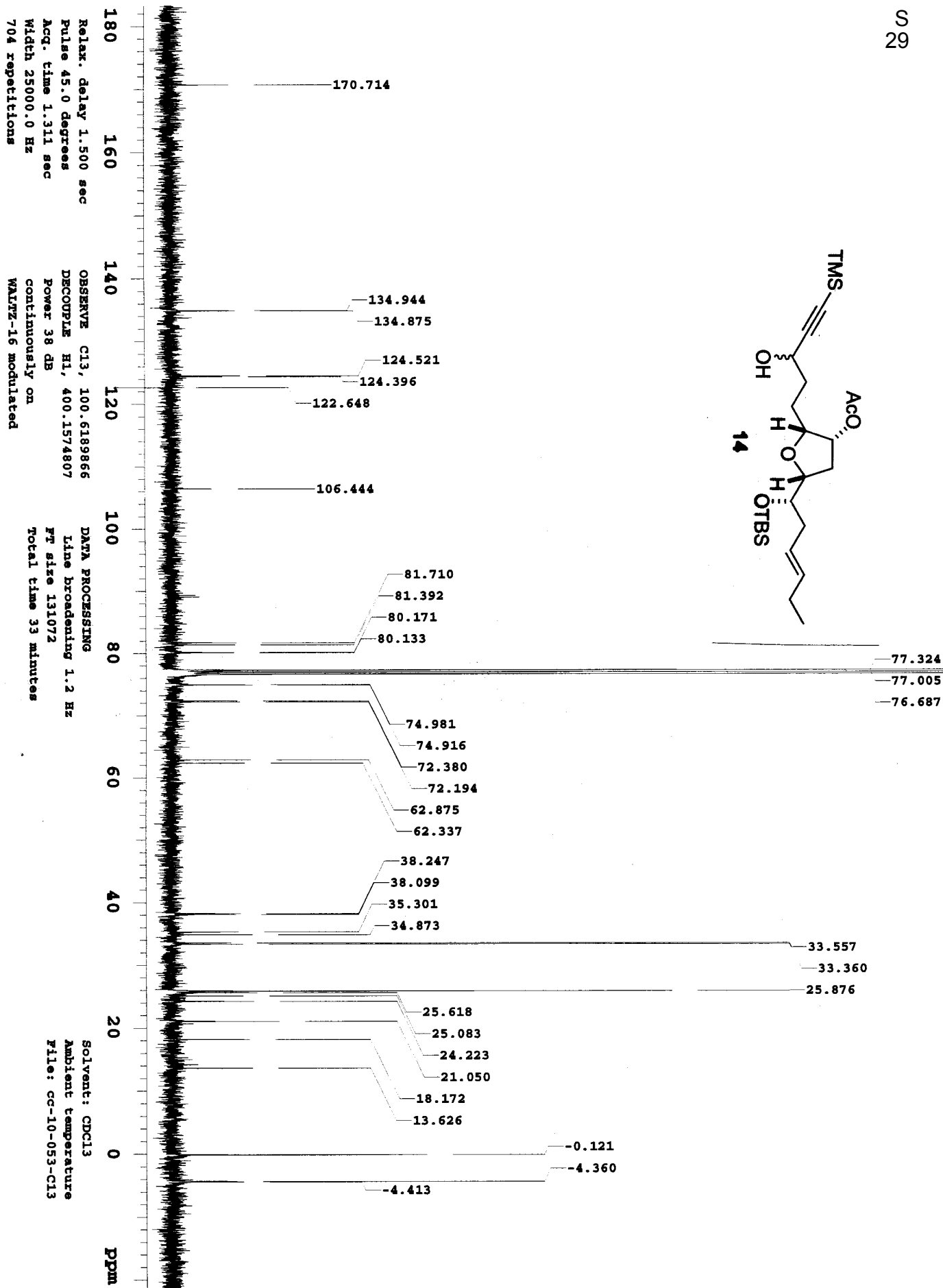
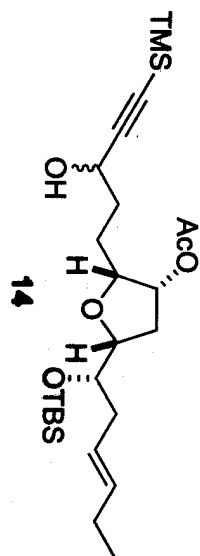
Solvent: CDCl3  
Ambient temperature  
File: cc-09-115-C13

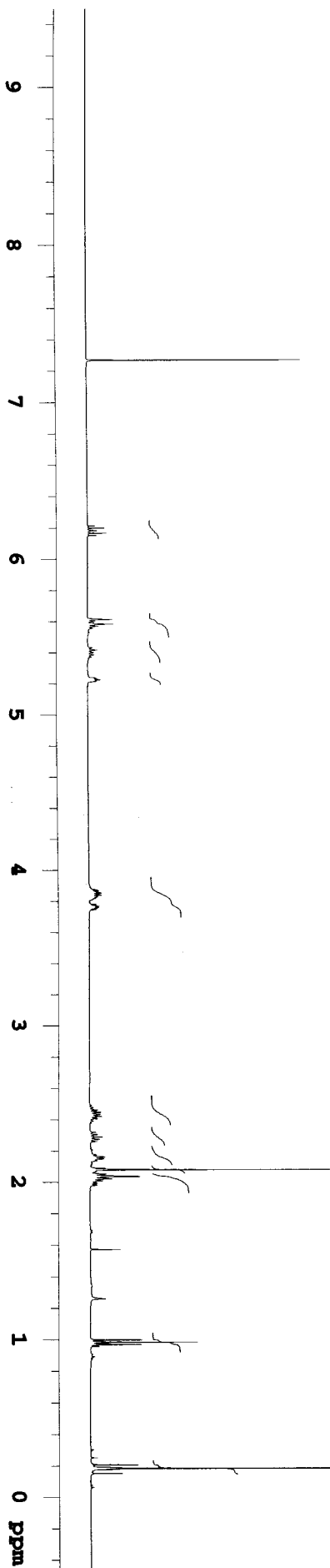
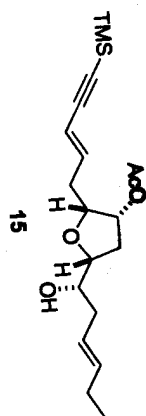
S  
28

Relax. delay 0.100 sec  
Pulse 19.7 degrees  
Acq. time 3.000 sec  
Width 6505.1 Hz  
40 repetitions

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 65536  
Total time 2 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-10-053-fp

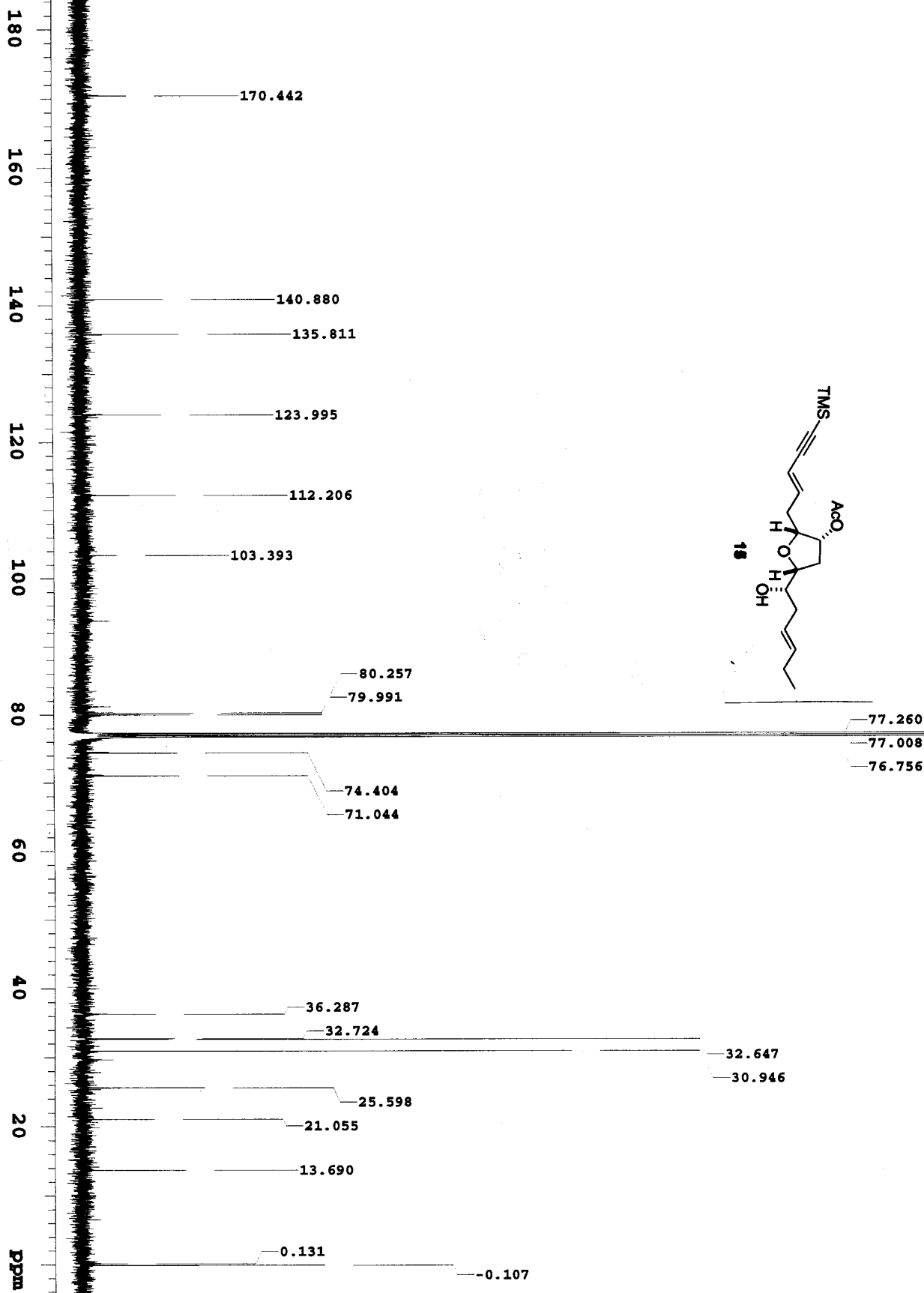
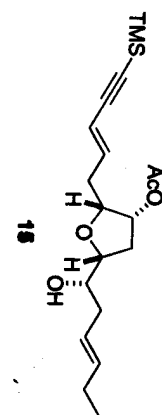
S  
29

S  
30

Relax. delay 1.500 sec  
Pulse 19.7 degrees  
Acq. time 3.000 sec  
Width 7199.4 Hz  
36 repetitions

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 131072  
Total time 2 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-10-065-ft

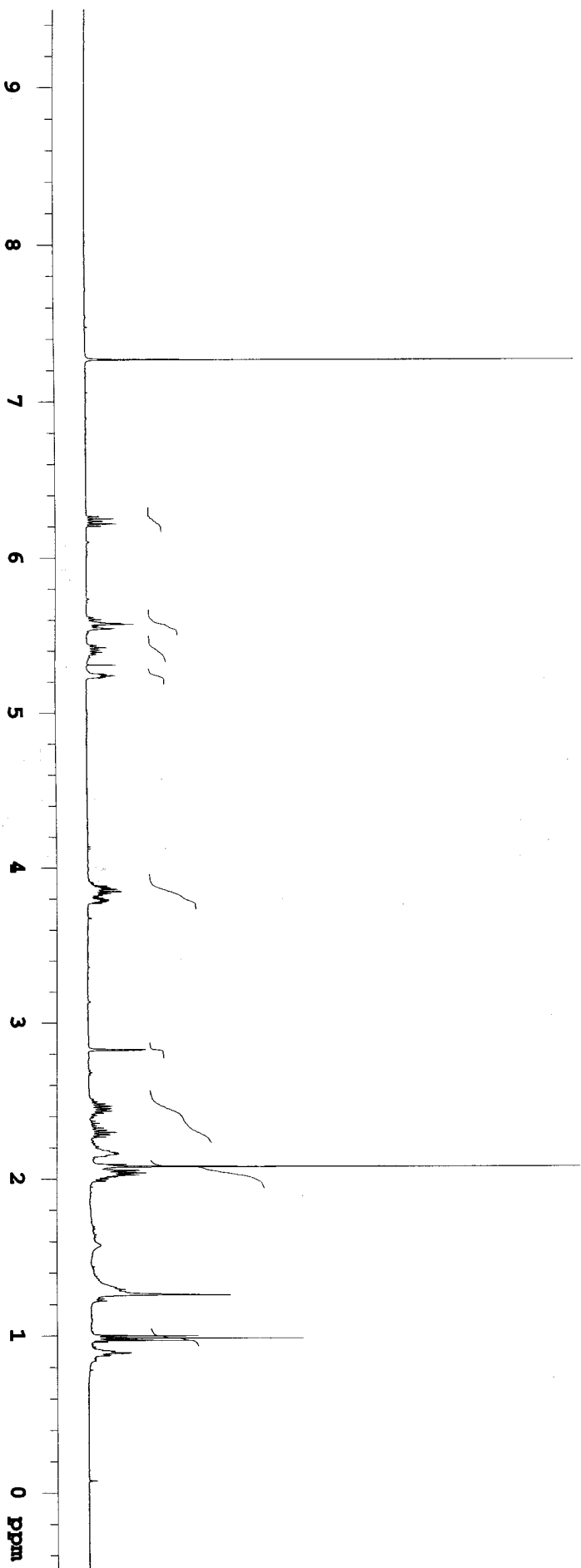
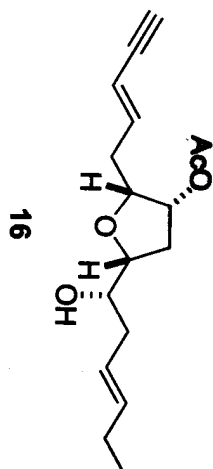
S  
31

Relax. delay 1.000 sec  
Pulse 32.6 degrees  
Acq. time 1.135 sec  
Width 28860.0 Hz  
1024 repetitions

OBSERVE C13, 125.8174931  
DECOUPLE H1, 500.3697761  
Power 44 dB  
continuously on  
WALTZ-16 modulated

DATA PROCESSING  
Line broadening 0.8 Hz  
FT size 65536  
Total time 36 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-10-057-C13

S  
32

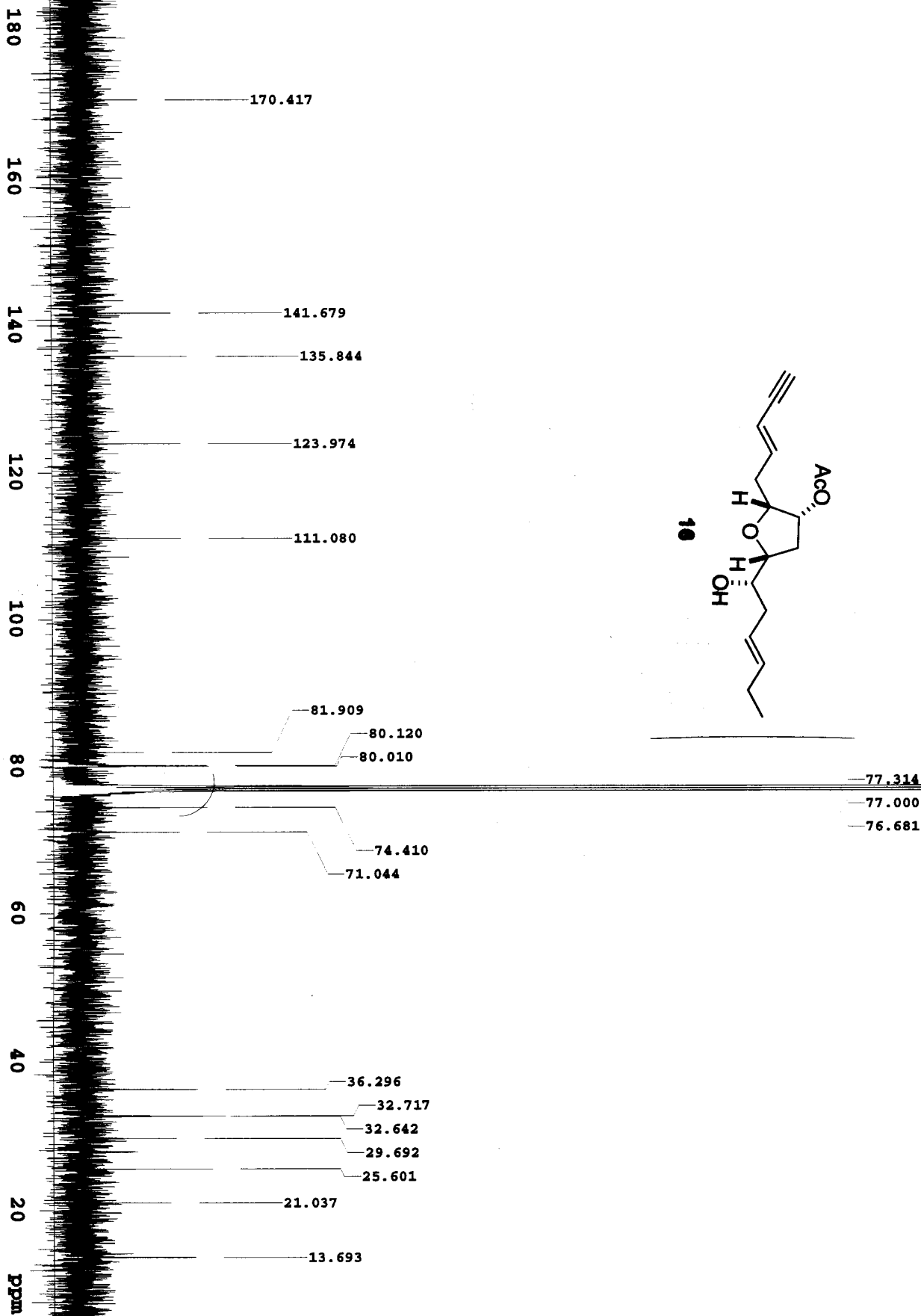
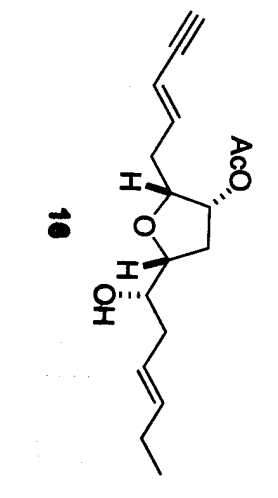
Relax. delay 1.500 sec  
Pulse 26.5 degrees  
Acq. time 3.000 sec  
Width 7200.1 Hz  
23 repetitions

OBSERVE F1, 500.3674330

DATA PROCESSING  
Line broadening 0.1 Hz  
FT size 131072  
Total time 1 minutes

Solvent: CDCl<sub>3</sub>  
Ambient temperature  
File: cc-09-108-4p



S  
33

Relax. delay 1.500 sec  
Pulse 45.0 degrees  
Acq. time 1.311 sec  
Width 25000.0 Hz  
1024 repetitions

OBSERVE C13, 100.6189872  
DECOUPLE H1, 400.1574807  
Power 38 dB  
continuously on  
WALTZ-16 modulated

DATA PROCESSING  
Line broadening 1.2 Hz  
FT size 131072  
Total time 48 minutes

Solvent: CDCl3  
Ambient temperature  
File: cc-10-066-C13

