

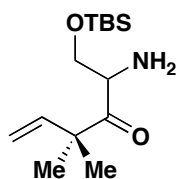
## A Remarkable Ring Contraction En Route to the Chartelline Alkaloids

Phil S. Baran\*, Ryan A. Shenvi, Christos Mitsos

*Contribution from the Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037*

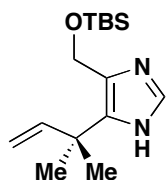
### SUPPORTING INFORMATION

**General procedures.** All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), toluene, benzene, dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), methanol (MeOH), *N,N*-dimethylformamide (DMF), and triethylamine ( $\text{Et}_3\text{N}$ ) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Copper(I) iodide was freshly purified from refluxing saturated aqueous NaI solution (aqueous). Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde or phosphomolybdic acid or basic aqueous potassium permanganate ( $\text{KMnO}_4$ ) and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.



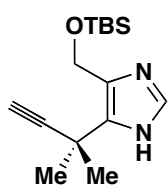
**Aminoketone 13:** A solution of prenylmagnesium bromide was prepared by dropwise addition of 1-bromo-3-methylbut-2-ene (11 g, 74 mmol) to magnesium turnings (10 g, 0.41 mol, 5.6 equiv) in THF (150 mL). This solution was added dropwise to a solution of *O*-tert-

butyldimethylsilyl-DL-serine methyl ester (1.52 g, 6.5 mmol) in THF (30 mL), cooled to -78 °C, until TLC (silica gel, 1:1 EtOAc:hexanes) showed consumption of the aminoester. The mixture was poured into 1:1 sodium potassium tartrate:brine, stirred for 15 min, and extracted with EtOAc (2 × 30 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, hexanes → 2:5 EtOAc:hexanes) to give compound **13** as yellowish syrup (1.64 g, 93%).

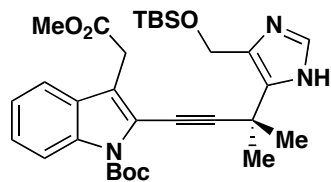


**Imidazole 14:** Potassium thiocyanate (17.5 g, 0.18 mol, 20 equiv) and NH<sub>4</sub>Cl (9.6 g, 0.18 mol, 20 equiv) were added to a solution of aminoketone **13** (2.4 g, 8.8 mmol) in toluene (90 mL) and the mixture was heated at 105-110 °C (oil bath temperature) with vigorous stirring. When TLC (silica gel, 4:1 EtOAc:hexanes) indicated consumption of the aminoketone (4 h), the mixture was allowed to cool to rt and filtered through a sintered glass frit. The filtrate was treated with 6M HCl (1 mL) and stirred vigorously until TLC (silica gel, 1:1 EtOAc: hexanes) showed complete conversion of the intermediate thiourea (20 min). The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extracts were washed successively with water, saturated aqueous NaHCO<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give an orange solid (2.7 g). The crude imidazoline-2-thione was dissolved in THF (85 mL) and H<sub>2</sub>O<sub>2</sub> (35% in water; 8.5 mL, 99 mmol, 11 equiv) was added. The mixture was stirred at ambient temperature for 6 h, then a 4:1 mixture of 2M NaOH and saturated aqueous NaHCO<sub>3</sub> (30 mL) was added and stirring was continued until gas evolution ceased (1 h). The mixture was extracted with EtOAc (3 × 30 mL), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give a yellow syrup. Flash column chromatography (silica gel, 1:1 EtOAc:hexanes → 9:1 EtOAc:hexanes) gave compound **14** as colorless crystals (1.5 g, 60% from aminoketone **13**); mp 75-80 °C (EtOAc/Hexanes); *R*<sub>f</sub> = 0.20 (silica gel, 1:3 hexanes:EtOAc); IR (neat)  $\nu_{\max}$  2929, 2857, 1472, 1361, 1256, 1092, 1053, 1005, 912, 836, 774, 733, 665 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.36 (bs, 1 H), 7.44 (s, 1 H), 6.05 (dd, *J* = 17.5, 10.5 Hz, 1 H), 5.01 (dd, *J* = 17.5, 1.2 Hz, 1 H), 4.99 (dd, *J* = 10.5, 1.2 Hz, 1 H), 4.69 (s, 2 H), 1.41 (s, 6 H), 0.87 (s, 9 H), 0.03 (s, 6 H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  146.6, 138.4, 132.1, 127.9, 110.7, 57.9, 38.0, 27.6 (2 C), 25.9 (3 C), 18.2, -5.4 (2 C); HRMS (ESI-TOF) calcd for C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>Si [M + H<sup>+</sup>]: 281.2044; found: 281.2047. Elution of the column with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> gave the crude unprotected alcohol, as yellow solid (0.5 g), which was suspended in CH<sub>2</sub>Cl<sub>2</sub> (6 mL). Triethylamine (0.43 mL, 3.1 mmol) and *t*-butyldimethylsilyl chloride (0.47 g, 3.1 mmol) were added and the mixture was stirred for 24 h. The mixture was partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>,

the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give yellow syrup. Flash column chromatography (silica gel, 1:1 EtOAc:hexanes → 9:1 EtOAc:hexanes) gave 0.60 g of imidazole **14** (84% totally from the aminoketone **13**).

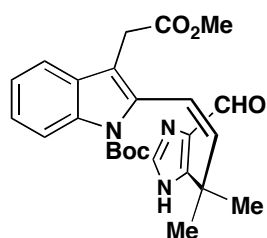


**Alkyne 16:** Sodium periodate (2.2 g, 10.3 mmol, 3 equiv) and osmium tetroxide (2.5% in *t*-BuOH; 1.3 mL, 0.10 mmol, 0.03 equiv) were added to a solution of imidazole **14** (0.96 g, 3.4 mmol) in 2:1 THF:H<sub>2</sub>O (34 mL) and the mixture was vigorously stirred for 18 h. The reaction was quenched with 1:1 saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>:saturated aqueous NaHCO<sub>3</sub> (40 mL), the mixture was stirred for 30 min and then extracted with EtOAc (3 × 30 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and the brown foam obtained was dissolved in methanol (35 mL). Diazophosphonate **15** (0.68 g, 3.5 mmol, 1 equiv) and K<sub>2</sub>CO<sub>3</sub> (0.73 g, 5.3 mmol, 1.5 equiv) were added and the mixture was stirred at rt for 6 h. After partitioning between EtOAc (30 mL) and brine, the aqueous layer was re-extracted with EtOAc (30 mL), and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 50-60% EtOAc in hexanes) to give compound **16** as white solid (0.61 g, 63%); mp 97-99 °C (EtOAc/Hexanes); *R*<sub>f</sub> = 0.25 (silica gel, 1:3 hexanes-EtOAc); IR (neat)  $\nu_{\max}$  3310, 2930, 2857, 2361, 1464, 1256, 1092, 1051, 1005, 938, 836, 776, 732, 632 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.43 (bs, 1 H), 7.48 (s, 1 H), 4.95 (s, 2 H), 2.26 (s, 1 H), 1.61 (s, 6 H), 0.90 (s, 9 H), 0.08 (s, 6 H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  137.1, 131.9, 126.0, 90.4, 68.8, 57.5, 31.1, 30.4 (2 C), 25.9 (3 C), 18.3, -5.4 (2 C); HRMS (ESI-TOF) calcd for C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>OSi [M + H<sup>+</sup>]: 279.1887; found: 279.1880.



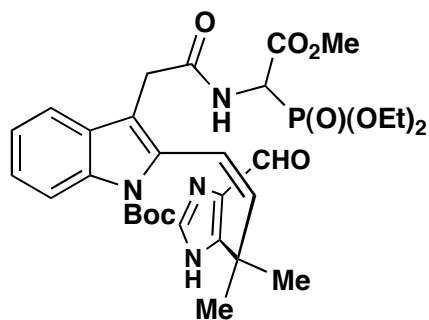
**Coupling product 18:** A solution of alkyne **16** (11 mg, 0.35 mmol) and bromoindole **17** (195 mg, 0.53 mmol, 1.5 equiv) in DME (2 mL) was frozen with liquid nitrogen and thoroughly degassed under high vacuum. Pd(PPh<sub>3</sub>)<sub>4</sub> (120 mg, 0.10 mmol, 0.3 equiv) was added and the resulting suspension was degassed in the same way. Freshly purified copper(I) iodide (48 mg, 0.25 mmol, 0.7 equiv) was added and degassing was repeated. Previously degassed isopropylamine (0.30 mL, 3.5 mmol, 10 equiv) was added and the mixture was heated at 70 °C for 30 min. The reaction was allowed to cool to ambient temperature, saturated aqueous NaHCO<sub>3</sub> (3 mL) was added and the mixture was extracted with EtOAc (2 × 5 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give brown foam. Flash column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub> → 1:5 acetone:CH<sub>2</sub>Cl<sub>2</sub>) gave compound **18** as pale yellow foam (145 mg,

71%);  $R_f = 0.27$  (silica gel, 1:3 hexanes:EtOAc); IR (neat)  $\nu_{\max}$  2929, 1734, 1452, 1362, 1329, 1257, 1158, 1138, 1121, 1052, 908, 838, 776, 731, 648  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (d,  $J = 8.4$  Hz, 1 H), 7.57 (s, 1 H), 7.53 (d,  $J = 7.8$  Hz, 1 H), 7.36 (t,  $J = 7.2$  Hz, 1 H), 7.28 (t,  $J = 7.3$  Hz, 1 H), 4.83 (s, 2 H), 3.84 (s, 1 H), 3.69 (s, 3 H), 1.80 (s, 6 H), 1.72 (s, 9 H), 0.89 (s, 9 H), 0.09 (s, 6 H);  $^{13}\text{C NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 150.0, 135.1, 133.8, 130.9, 128.7, 125.8, 123.4, 120.8, 119.4, 119.2, 115.7, 104.7, 85.3, 73.3, 58.8, 52.2, 32.7, 30.9, 29.8, 28.3 (2 C), 25.9 (3 C), 18.3, -5.2 (2 C); HRMS (ESI-TOF) calcd for  $\text{C}_{31}\text{H}_{43}\text{N}_3\text{O}_5\text{Si}$  [ $\text{M} + \text{H}^+$ ]: 566.3045; found: 566.3050.

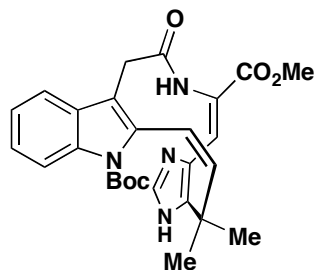


**Aldehyde 19:** To a solution of alkyne **18** (240 mg, 0.42 mmol) in EtOH (5 mL) was added anhydrous  $\text{MgSO}_4$  (100 mg, 0.83 mmol, 2 equiv) and 10% Pd/C (45 mg, 0.042 mmol, 0.1 equiv). Hydrogen gas was bubbled through the solution for 1 h. The reaction was filtered through Celite, concentrated *in vacuo*, and resubmitted to the reaction conditions. This procedure was repeated 3 times or until alkyne **18** did not

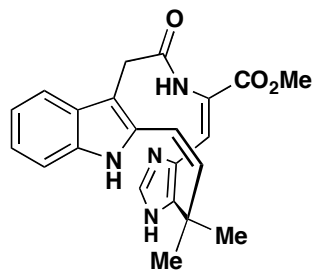
appear by TLC (silica gel, 3:1 EtOAc:hexanes). After filtration and concentration, the crude material was dissolved in THF (4.3 mL), cooled to 0 °C, and a solution of tetrabutylammonium fluoride (0.47 mL from a 1 M solution in THF, 0.47 mmol, 1.1 equiv) was added dropwise. The reaction mixture was warmed to ambient temperature and stirred vigorously for 3 h. The reaction was poured onto brine (5 mL), extracted with EtOAc (3 × 15 mL), dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. This crude mixture was dissolved in  $\text{CH}_2\text{Cl}_2$ , filtered through silica gel with 1:19 MeOH- $\text{CH}_2\text{Cl}_2$ , concentrated, and redissolved in 5 mL dry dichloromethane.  $\text{MnO}_2$  (730 mg, 8.4 mmol, 20 equiv) was added and the suspension was stirred vigorously for 8 h, at which time the reaction was filtered through anhydrous  $\text{MgSO}_4$ /Celite and concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica gel, 3:1 EtOAc:hexanes) to give compound **19** (190 mg, 98% over 3 steps): colorless crystals; mp 50-55 °C;  $R_f = 0.31$  (silica gel, 3:1 EtOAc:hexanes); IR (neat)  $\nu_{\max} = 2928, 2251, 1728, 1156, 914, 733, 649, 566$   $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.00 (s, 1H), 7.94 (d,  $J = 8$  Hz, 1 H), 7.71 (s, 1 H), 7.37 (d,  $J = 7.2$  Hz, 1 H), 7.25 (t,  $J = 8$  Hz, 1 H), 7.19 (t,  $J = 6.8$  Hz, 1 H), 6.54 (d,  $J = 12.4$  Hz, 1 H), 6.12 (d,  $J = 12.4$  Hz, 1 H), 3.68 (s, 3 H), 3.59 (s, 2 H), 1.67 (s, 9 H), 1.62 (s, 3 H), 1.51 (s, 3 H); HRMS (ESI-TOF) calcd for  $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_5$  [ $\text{M} + \text{H}^+$ ]: 452.2180; found: 452.2186.



**Amidophosphonate 21:** To a solution of aldehyde **19** (207 mg, 0.46 mmol) in 4:1 THF:water (4.6 mL total volume) was added LiOH·H<sub>2</sub>O (58 mg, 1.38 mmol, 3 equiv) and the reaction was stirred vigorously. After 5 h, EtOAc (5 mL) and water (5 mL) were added and the aqueous layer was titrated to pH 1 with 1 M HCl. The organic layer was removed and the aqueous layer extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated to a glassy yellow solid, to which was added amine **20** (270 mg, 1.2 mmol, 2.6 equiv). This mixture was azeotropically dried with benzene, dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL), and cooled to 0 °C. *N,N*-diisopropylethylamine (167 μL, 0.96 mmol, 2 equiv) was added, followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (183 mg, 0.72 mmol, 1.5 equiv). After 2 h, 1 M HCl (5 mL) was added, and the reaction was stirred for an additional 1 h. The reaction was diluted with EtOAc (20 mL) and the aqueous layer was removed. The organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica gel, 1:2 acetone:CH<sub>2</sub>Cl<sub>2</sub> → 1:19 MeOH:CH<sub>2</sub>Cl<sub>2</sub>) to yield compound **21** (253 mg, 86%).

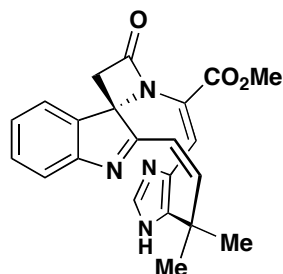


**Macrocycle 22:** Compound **21** (220 mg, 0.341 mmol) was azeotropically dried with benzene and dissolved in freshly distilled acetonitrile (600 mL). To this solution was added anhydrous LiCl (130 mg, 3.07 mmol, 9 equiv) and *N,N*-diisopropylethylamine (1.2 mL, 6.82 mmol, 20 equiv) and the reaction was heated at 70 °C for four hours. The solvent was evaporated and the crude material was purified by flash column chromatography (silica gel, 1:2 acetone:CH<sub>2</sub>Cl<sub>2</sub>, → 1:19 MeOH:CH<sub>2</sub>Cl<sub>2</sub>) to yield compound **22** (126 mg, 75%).



**Indole 11:** Macrolactam **22** (68 mg, 0.14 mmol) was heated as a thin film to 180 °C for 8 min. The crude material was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, filtered through a column of silica gel in 1:9 MeOH: CH<sub>2</sub>Cl<sub>2</sub>, and concentrated *in vacuo* to give indole **11** (53 mg, 98%, purified for characterization, but otherwise used directly for subsequent chemistry): glassy yellow solid; m.p. 220 °C dec.; *R*<sub>f</sub> = 0.23 (silica gel, 1:9 *i*PrOH:CH<sub>2</sub>Cl<sub>2</sub>); IR (neat):  $\nu_{\max}$  = 3222, 1706, 1654, 1257, 1436, 1364, 1244, 1129, 997, 907, 734, 644, 610, 546 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.78 – 7.72 (m, 2 H), 7.70 (s, 1 H), 7.29 (s, 1 H), 7.19 (d, *J*

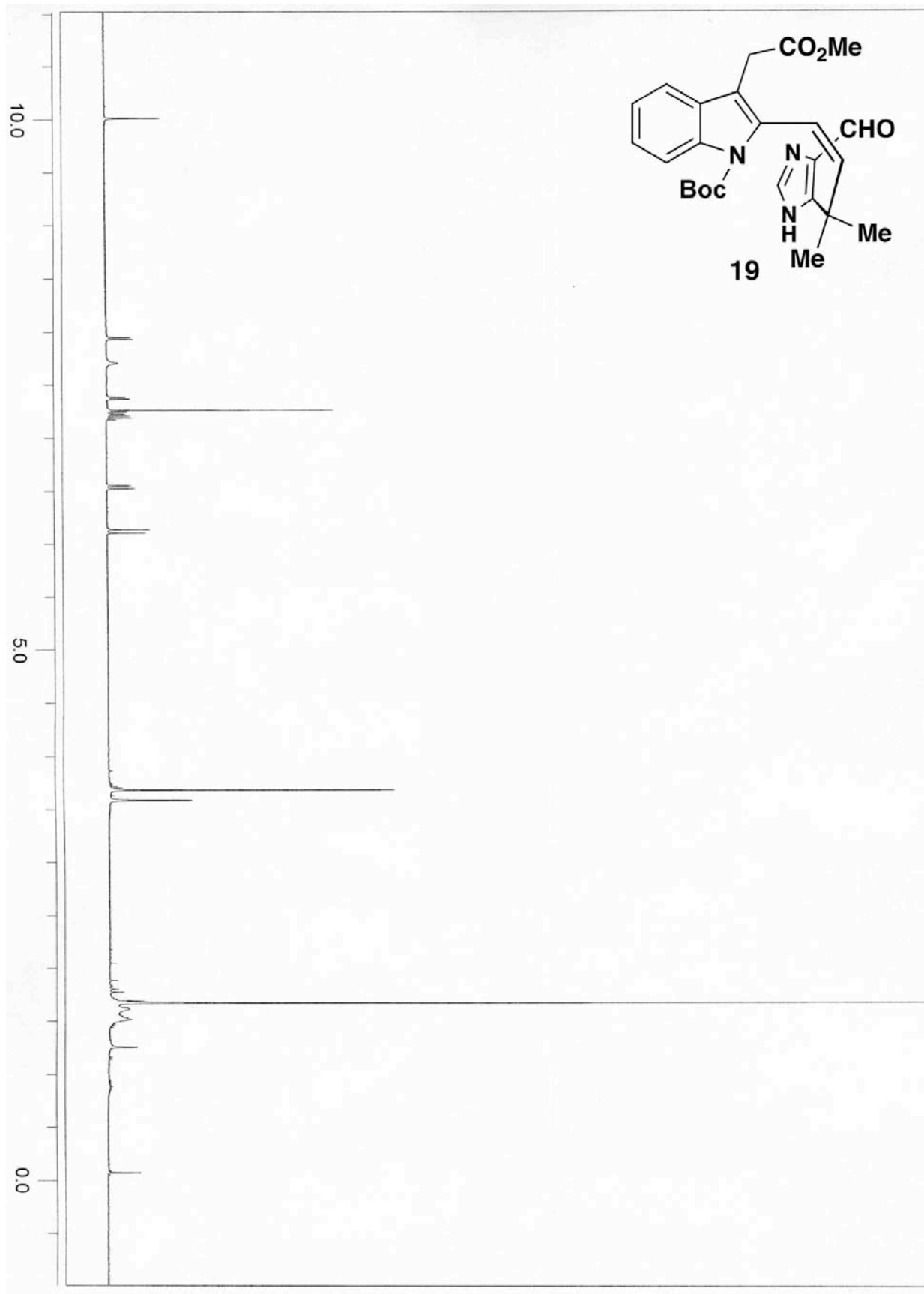
= 8.0 Hz, 1 H), 6.96 (t,  $J = 7.4$  Hz, 1 H), 6.80 (t,  $J = 7.4$  Hz, 1 H), 6.39 (s, 1 H), 6.29 (d,  $J = 11.6$  Hz, 1 H), 6.20 (d,  $J = 11.6$ , 1 H), 3.86 (s, 3 H), 3.39 (d,  $J = 12.8$  Hz, 1 H), 3.35 (d,  $J = 12.8$  Hz, 1 H), 1.80 (s, 3 H), 1.64 (s, 3 H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  175.1, 165.8, 151.6, 149.3, 135.5, 135.4, 131.6, 131.5, 128.9, 127.5, 121.7, 120.0, 119.8, 119.6, 118.9, 110.7, 102.6, 52.8, 37.7, 31.0, 30.6, 29.6; HRMS (ESI-TOFF) calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_3$  [ $\text{M} + \text{H}^+$ ]: 391.1765; found 391.1769.



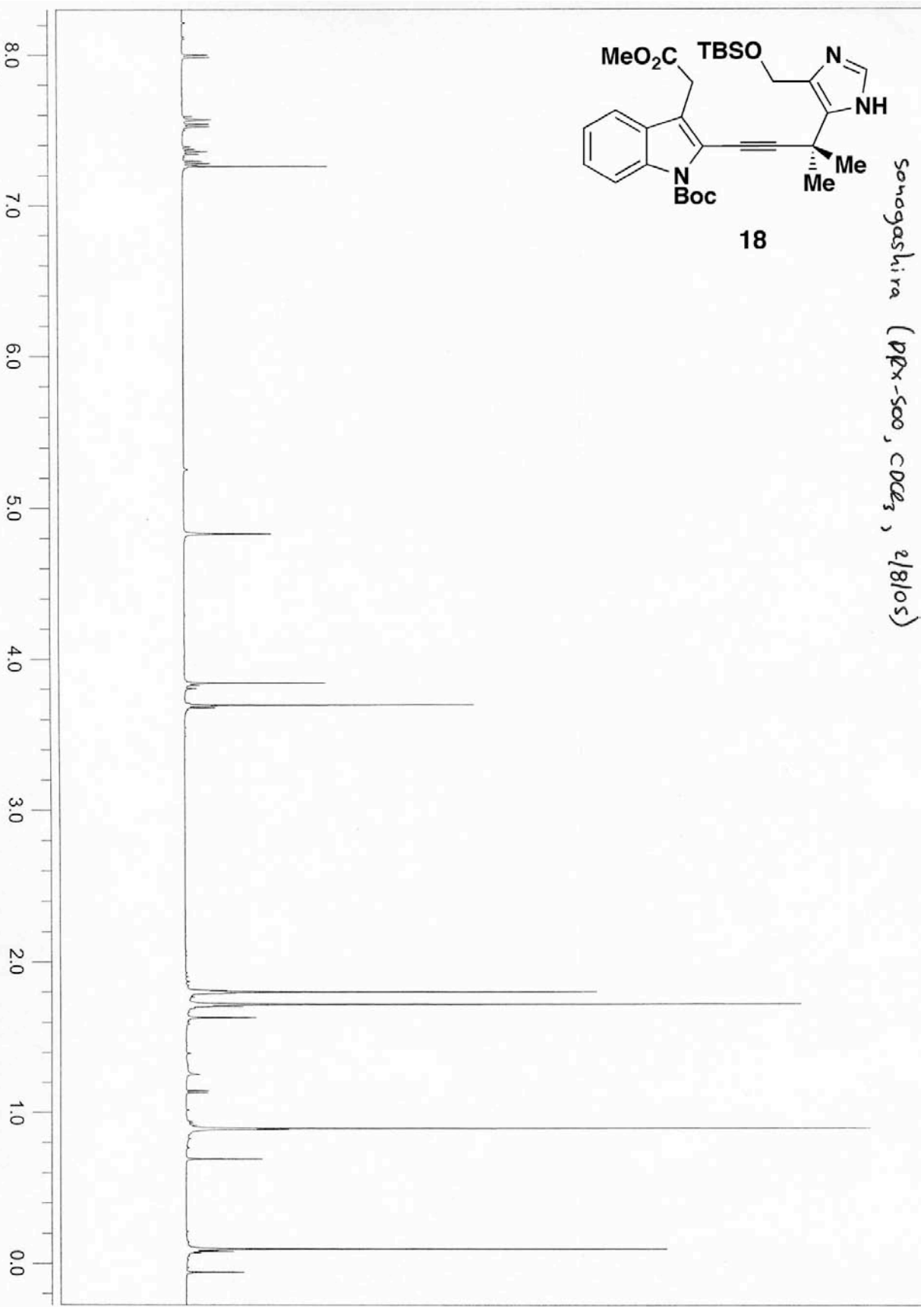
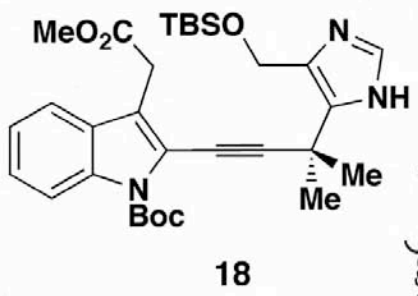
**Spiro- $\beta$ -lactam 10:** To a solution of macrolactam **11** (6.6 mg, 0.017 mmol) in THF

(2 mL) was added potassium hydrogen carbonate (135  $\mu\text{L}$  from a 2.5 M solution in water, 0.338 mmol, 20 equiv) and water (200  $\mu\text{L}$ ). NBS (600  $\mu\text{L}$  from a 0.028 M solution in THF, 0.017 mmol, 1.0 equiv) was added over a period of 30 min. The reaction was stirred for an additional 5 min, diluted with 10 mL  $\text{CH}_2\text{Cl}_2$  and 1 mL

brine, extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL), dried over anhydrous  $\text{MgSO}_4$ , and purified by flash column chromatography (silica gel, 1:25 *i*PrOH:  $\text{CH}_2\text{Cl}_2$ ) to yield compound **10** (5.8 mg, 88%): colorless cubes; m.p. 190  $^\circ\text{C}$  dec.;  $R_f = 0.13$  (silica gel, 1:9 *i*PrOH: $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\nu_{\text{max}}$  3236, 1786, 1730, 1546, 1460, 1388, 1281, 1257, 1218, 1147, 1030, 944, 768, 717, 623, 589, 500  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.45 (s, 1H), 7.42 (d,  $J = 7.2$  Hz, 1 H), 7.34 (t,  $J = 7.6$ , Hz, 1 H), 7.26 (d,  $J = 8$  Hz, 1 H), 7.20 (t,  $J = 7.4$  Hz, 1 H), 6.78 (s, 1 H), 6.27 (d,  $J = 11.6$  Hz, 1 H), 6.13 (d,  $J = 11.6$  Hz, 1 H), 3.90 (s, 3 H), 3.46 (d,  $J = 15.6$  Hz, 1 H), 3.29 (d,  $J = 15.6$  Hz, 1 H), 1.51 (s, 6 H);  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  180.2, 166.7, 164.7, 155.0, 149.8, 137.2, 133.7, 131.7, 130.0, 127.5, 124.0 (2 C), 121.4, 118.4, 72.6, 53.7, 48.1, 39.1, 31.0, 27.4; HRMS (ESI-TOF) calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_3$  [ $\text{M} + \text{H}^+$ ]: 389.1608; found: 389.1606.



Sonogashira (DPE-500, CDCl<sub>3</sub>, 2/8/05)



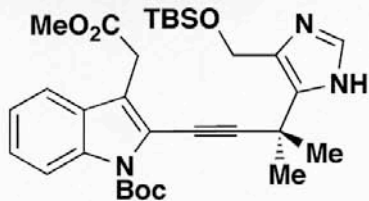
ppm (f1)

150

100

50

0



18

sonogashira (Dlx-500, CDCl<sub>3</sub>, 2/8/05)

170.861

150.054

135.113

133.773

130.918

128.696

125.817

123.431

123.050

120.826

119.440

119.240

118.954

115.708

104.687

85.323

73.341

58.794

52.222

32.694

30.864

29.839

28.325

28.239

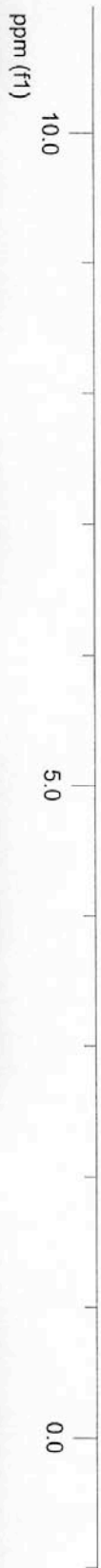
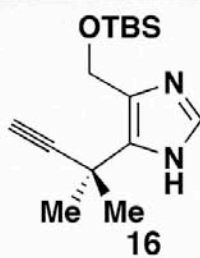
25.953

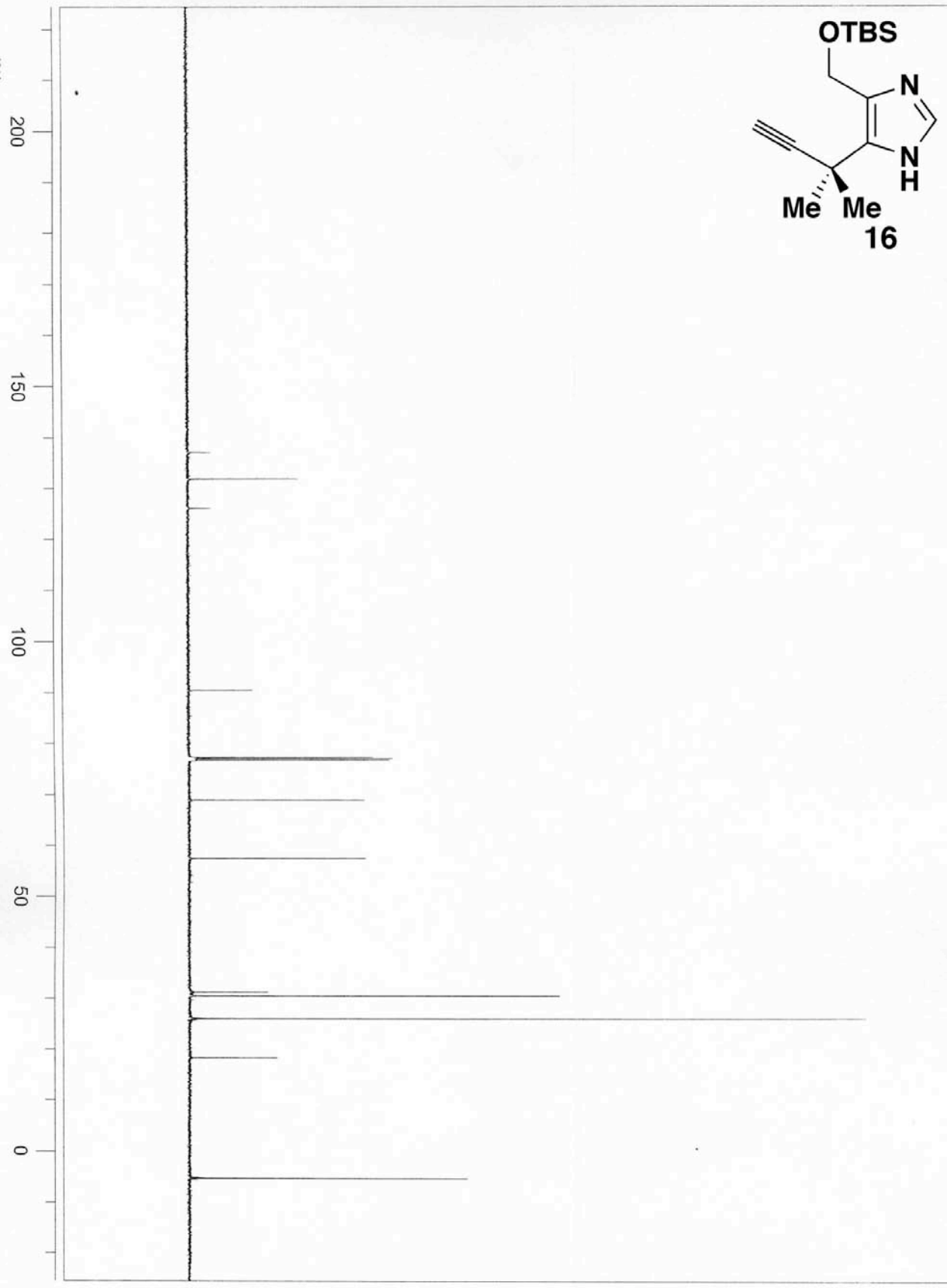
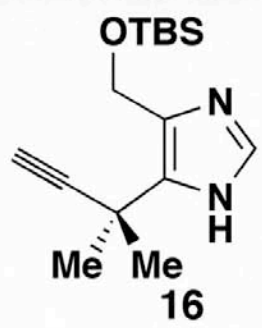
25.541

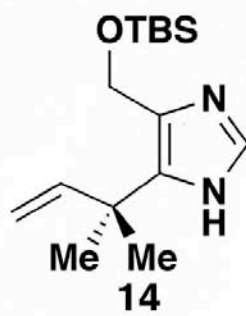
18.281

-5.227

alkyne ( DRX-500, CDCl<sub>3</sub>, 2/9/05)





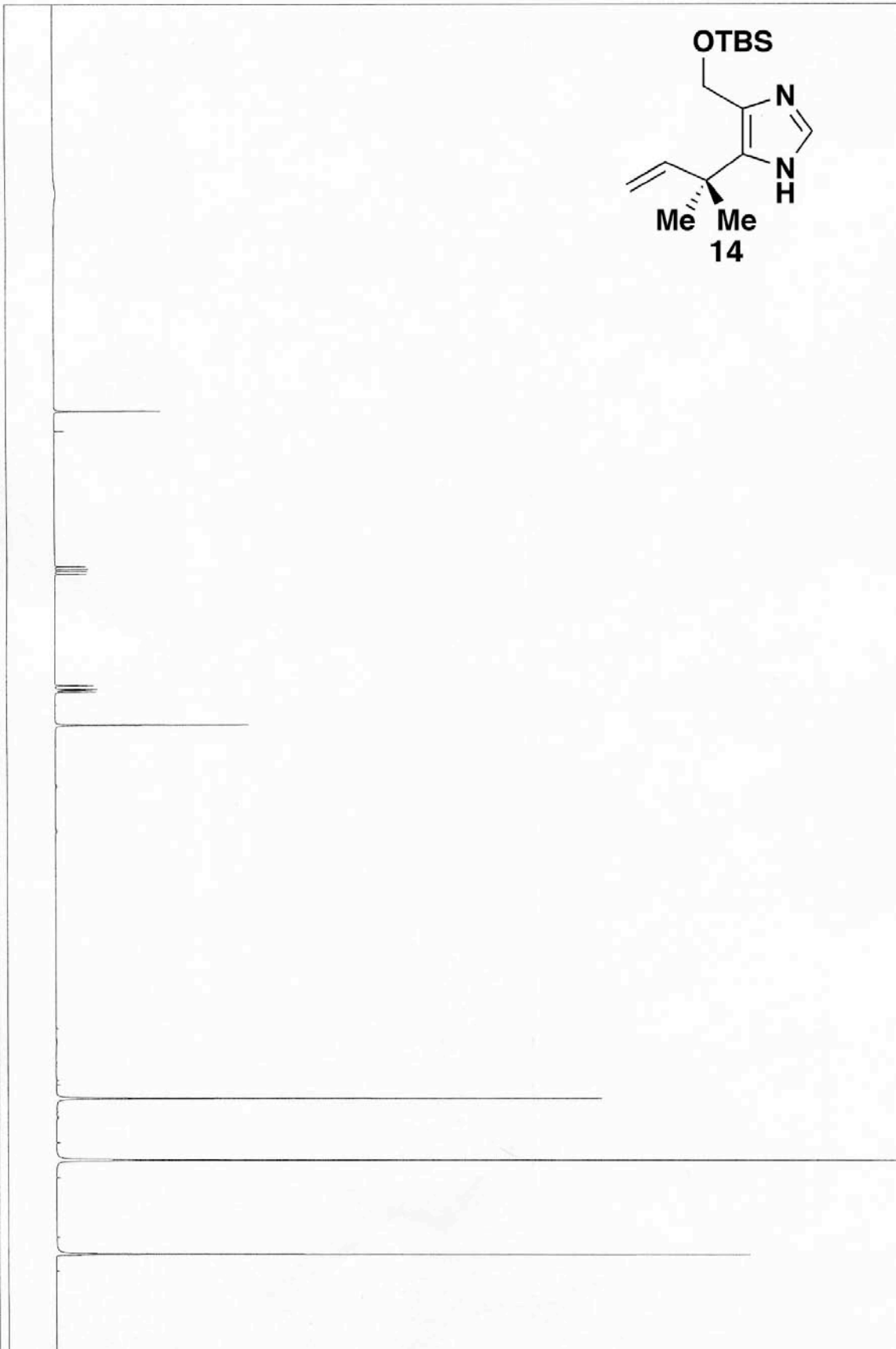


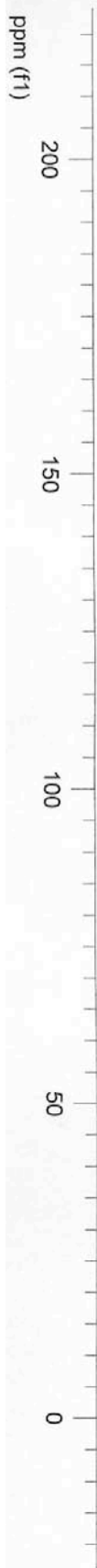
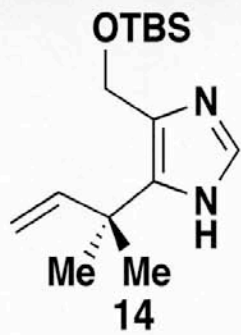
ppm (f1)

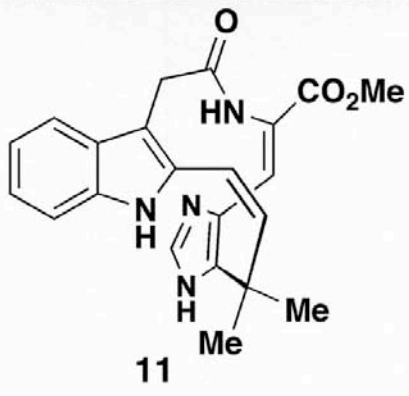
10.0

5.0

0.0





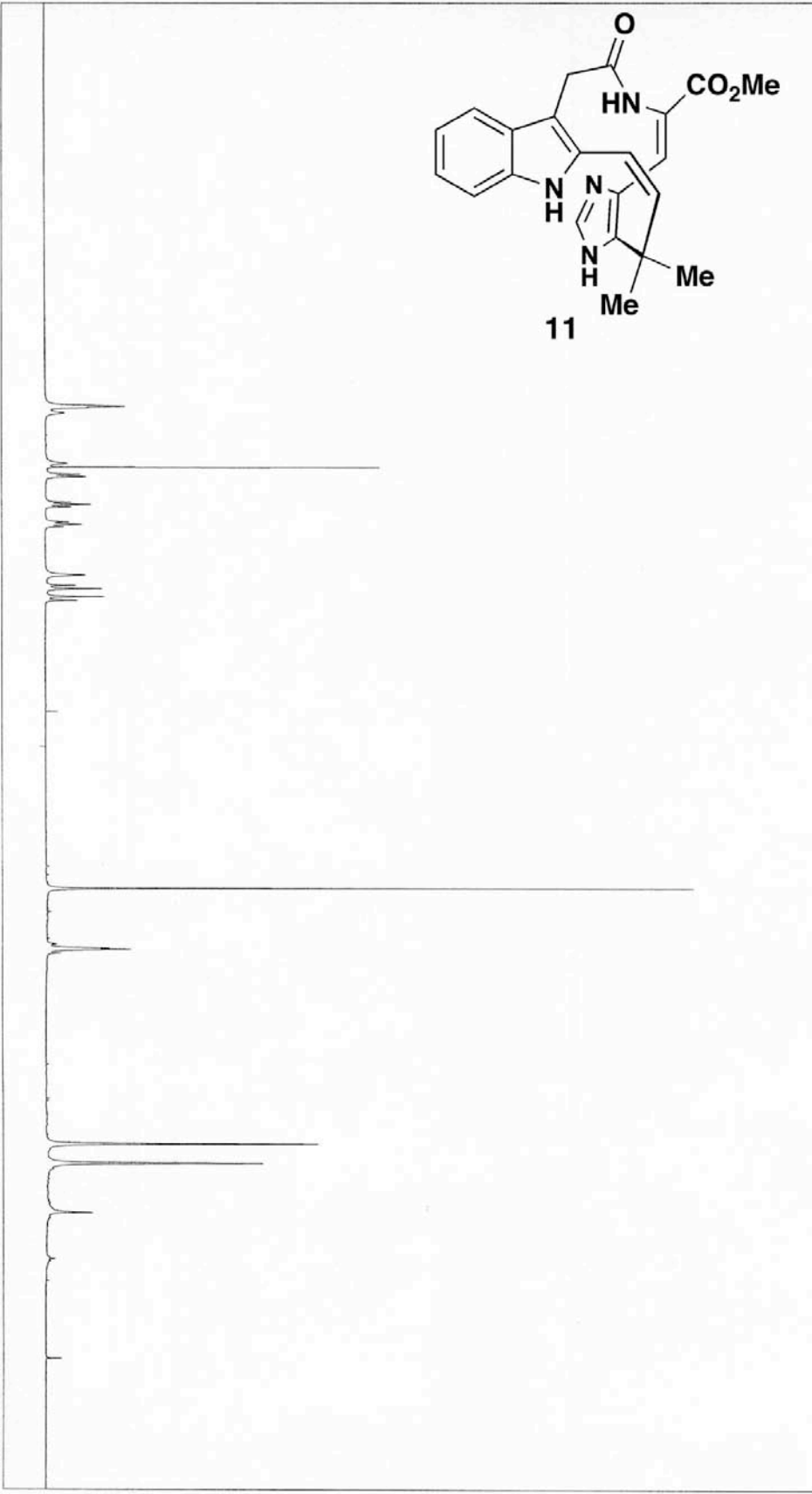


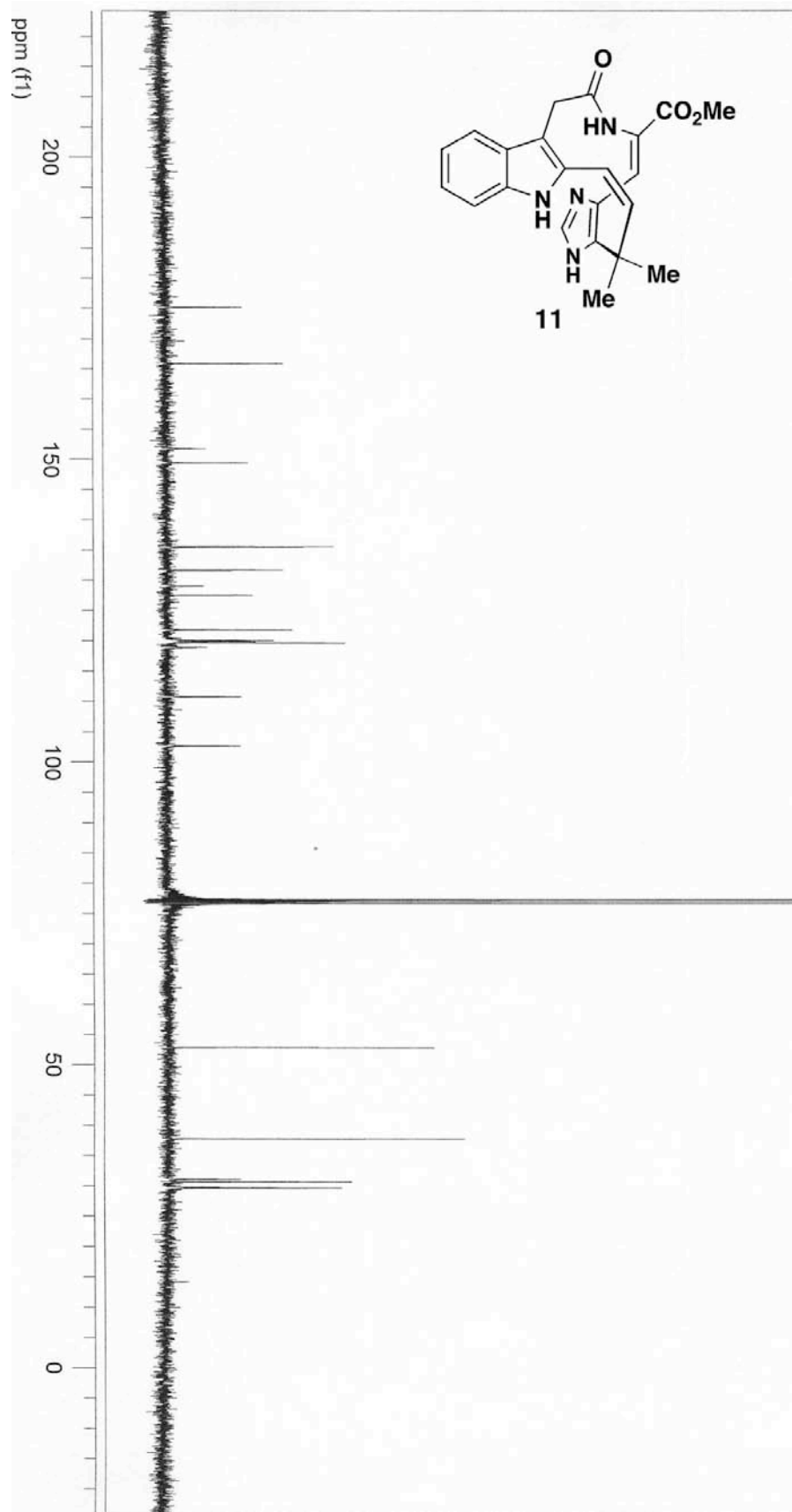
10.0

5.0

0.0

ppm (f1)



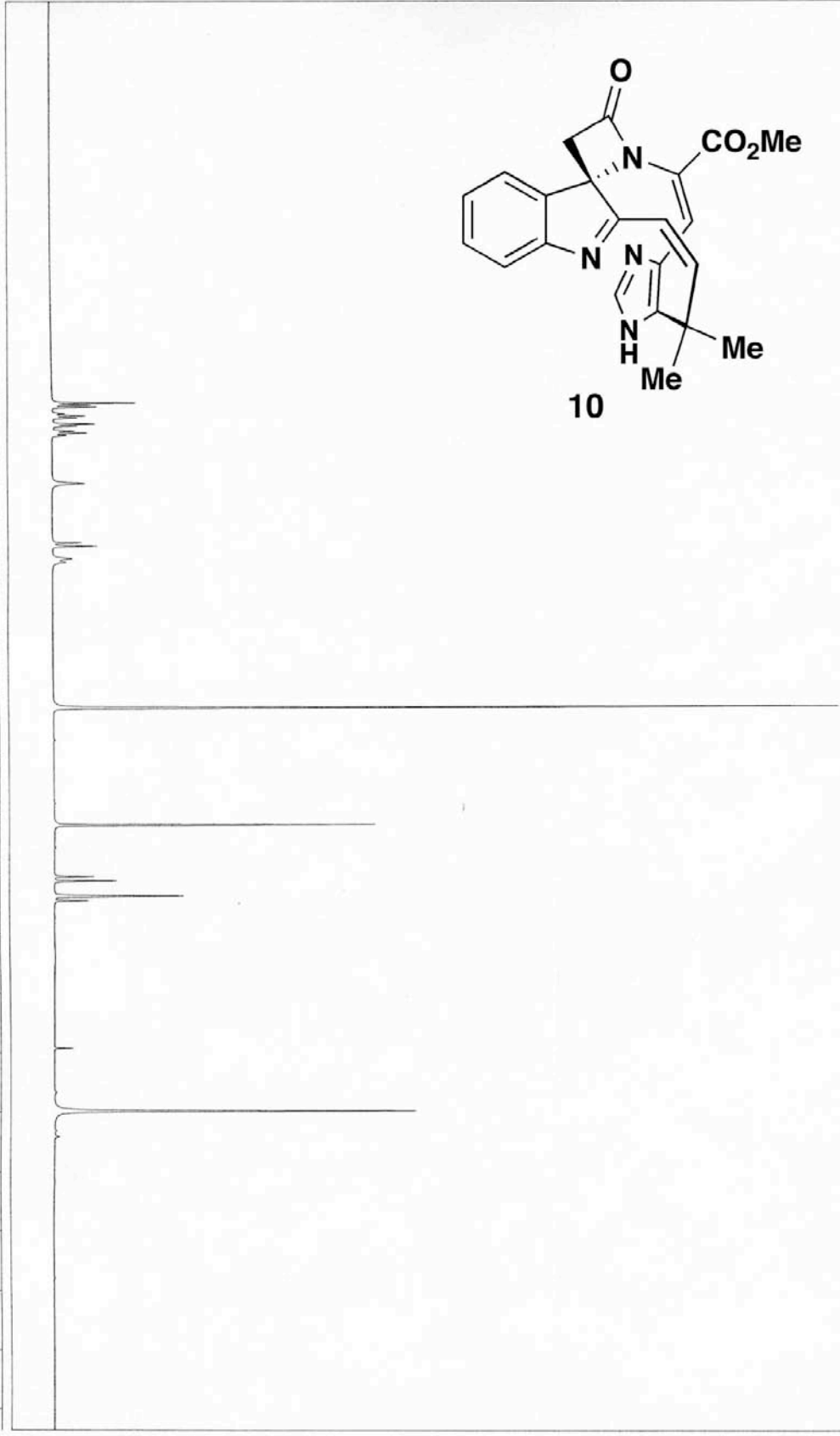
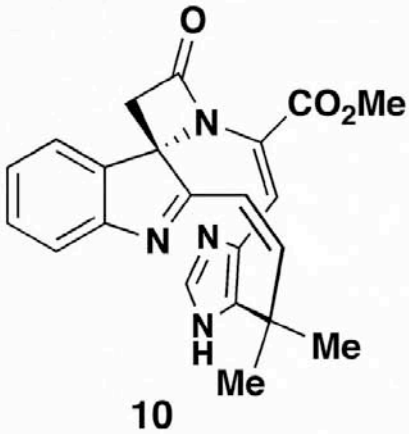


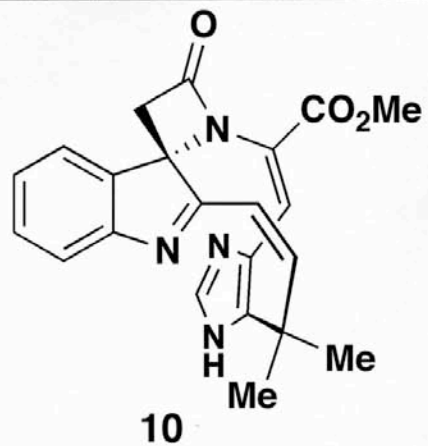
ppm (11)

10.0

5.0

0.0





ppm (t1)

200

150

100

50

0

