



Supporting Information

© Wiley-VCH 2008

69451 Weinheim, Germany

Supporting Information

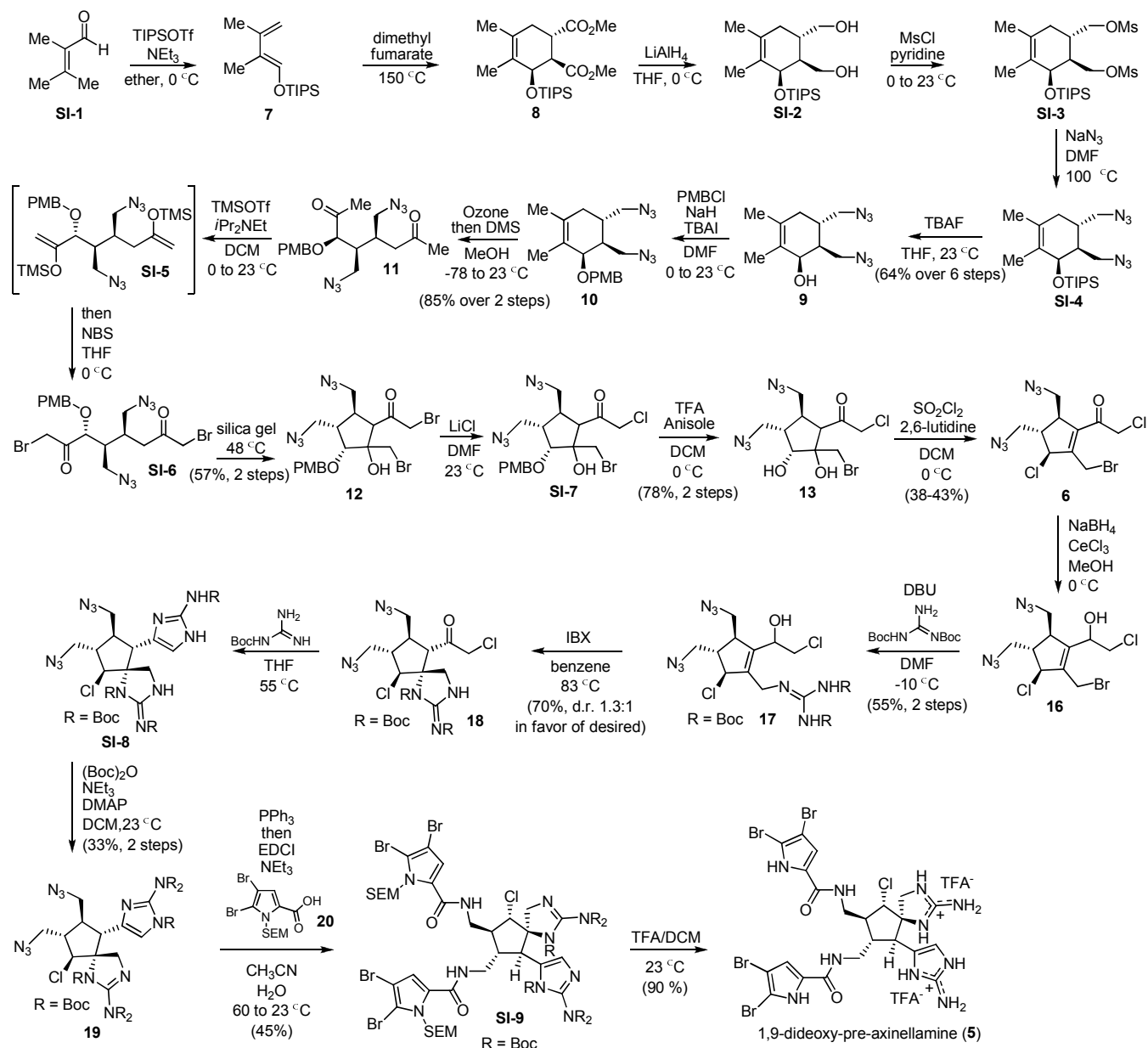
Synthesis of 1,9-dideoxy-pre-axinellamine.

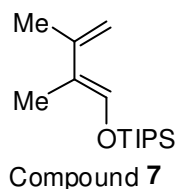
Junichiro Yamaguchi,⁺ Ian B. Seiple,⁺ Ian S. Young, Daniel P. O'Malley, Michael Maue
and Phil S. Baran*

*Contribution from the Department of Chemistry, The Scripps Research Institute, 10650 North
Torrey Pines Road, La Jolla, California 92037*

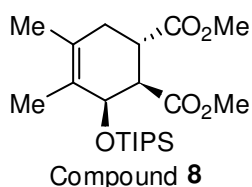
General Procedures. All reactions were carried out under an inert atmosphere of nitrogen or argon with dry solvents, using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), toluene, acetonitrile (CH₃CN), dichloromethane (CH₂Cl₂), methanol (MeOH), *N,N*-dimethylformamide (DMF), triethylamine (NEt₃), diethyl ether and benzene were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Trimethylsilyl trifluoromethanesulfonate was purified by reduced pressure distillation. *N*-bromosuccinimide (NBS) was purified by recrystallization from water. Yields refer to chromatographically and spectroscopically (¹H-NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde or phosphomolybdic acid or basic aqueous potassium permanganate and heat as the developing agents. E. Merck silica (60, particle size 0.043-0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out using 0.25 or 0.5 mm E. Merck silica plates (60F-254). Analytically pure **5** was obtained by reversed phase PTLC on 0.25 mm E. Merck silica plates (RP-8 F-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 multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, AB = second order AB systems. High resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. IR experiments were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

Chart 1. Synthetic Scheme for 1,9-dideoxy-pre-axinellamine (**5**).





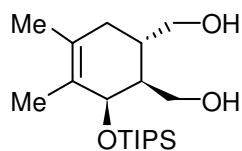
2,3-dimethylbut-2-enal **S-1** (25.10 g, 255.8 mmol, 1.0 eq) was dissolved in diethyl ether (400 mL) and the solution cooled to 0 °C. Triethylamine (51.76 g, 71.0 mL, 511.5 mmol, 2.0 eq) was slowly added over 10 min, followed by dropwise addition of triisopropylsilyl triflate (82.27 g, 72.2 mL, 268.5 mmol, 1.05 eq) over 30 minutes, and the reaction allowed to stir at 0 °C for 30 min. Saturated aqueous sodium bicarbonate (400 mL) was then added and the layers separated. The aqueous layer was extracted with ether (2 x 200 mL), and the combined organics washed with water (2 x 100 mL), then brine (100 mL) and dried with anhydrous magnesium sulfate. The solution was then passed through a small plug of silica and the solvent removed under reduced pressure to yield crude diene **7** (67.68 g, 255.8 mmol (contains 4% triethylamine by mass)) as a pale yellow oil, which was of sufficient purity to be used directly in the subsequent step. Purification of a sample by flash column chromatography on silica gel (hexanes as eluent) yielded a colorless oil for characterization purposes. R_f = 0.50 (silica gel, hexanes); IR (neat) ν = 2944, 2868, 1465, 1383, 1088, 997, 883, 830, 682 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.64 (s, 1 H), 4.85 (s, 1 H), 4.72 (s, 1 H), 1.86 (s, 3 H), 1.79 (s, 3 H), 1.23 – 1.14 (m, 3 H), 1.09 (d, J = 7.2 Hz, 18 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 142.2, 139.0, 118.6, 108.7, 20.2, 17.1, 11.9, 10.2; HRMS (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{31}\text{OSi}$ $[\text{M}+\text{H}^+]$ 255.2144; found 255.2139.



To crude diene **7** (67.68 g, 255.8 mmol, 1.0 eq (4% by mass triethylamine)) was added dimethyl fumarate (33.08 g, 229.5 mmol, 0.9 eq) and the mixture heated to 150 °C. After 40 min a small amount of diene was visible by TLC, so additional dimethyl fumarate (1.70 g, 11.80 mmol, 0.05 eq) was added, and heating continued for 20 min. Cooling to room temperature yielded compound **8** as a yellow oil (102.7 g, contains dimethyl fumarate (3%) and triethylamine (4%) by mass) which was of high purity (>90%) and could be used directly in the following step.

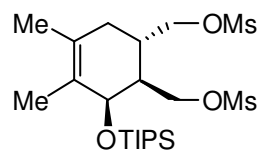
Small Scale Procedure with Purification of Compound 8: A procedure similar to above was used with the following amounts: diene **7** (1.03 g, 4.05 mmol, 1.0 eq), dimethyl fumarate (0.555 g, 3.85 mmol, 0.95 eq) with the mixture being heated to 150 °C for 25 min. Purification by column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) produced compound **8** (1.45 g, 3.64 mmol, 95%) as a colorless oil, that upon standing at 2 °C yielded colorless blocks suitable for x-ray crystallographic analysis.

$R_f = 0.80$ (silica gel, 10% ethyl acetate in hexanes); IR (neat) $\nu = 2946, 2866, 1739, 1460, 1436, 1385, 1320, 1258, 1162, 1120, 1088, 1014, 882, 740, 680 \text{ cm}^{-1}$; $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 4.54 (d, $J = 2.5$ Hz, 1 H), 3.69 (s, 3 H), 3.65 (s, 3 H), 3.32 (ddd, $J = 12.0, 12.0, 7.0$ Hz, 1 H), 2.78 (dd, $J = 12.0, 2.5$ Hz, 1 H), 2.40 (dd, $J = 18.0, 7.0$ Hz, 1 H) 2.03 (dd, $J = 18.0, 12.0$ Hz, 1 H), 1.04 – 1.00 (m, 21 H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 176.5, 172.5, 128.7, 127.0, 71.6, 51.8, 51.5, 49.2, 36.4, 35.0, 18.6, 18.4, 18.3, 18.2, 13.6; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{38}\text{O}_5\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 421.2381; found 421.2384. The relative stereochemistry of compound **8** was confirmed by X-Ray analysis.¹²



Compound **SI-2**

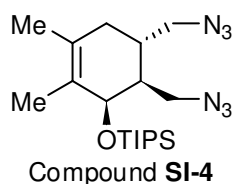
To a slurry of lithium aluminum hydride (21.17 g, 557.7 mmol, 2.2 eq) in THF (600 mL) at 0 °C was added a solution of the crude **8** (102.7 g, ~ 255.8 mmol, 1.0 eq) in THF (400 mL) over 30 min. After an additional 30 min at 0 °C, water (21 mL, initially added dropwise, caution), 2M aqueous sodium hydroxide (42 mL) and water (63 mL) were sequentially added with vigorous stirring. The reaction mixture was then filtered through Celite, and the resulting filter cake washed thoroughly with ethyl acetate. The filtrate was dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure to yield diol **SI-2** (76.81 g, 224.2 mmol) as a white solid. The material was of high purity (>90%) and could be used directly in the next step without further purification. Purification of a sample by flash column chromatography on silica gel (30% ethyl acetate in hexanes as eluent) yielded a colorless oil that formed colorless needles upon standing at 2 °C. m.p. = 78-81 °C; $R_f = 0.30$ (silica gel, 30% ethyl acetate in hexanes); IR (neat) $\nu = 3306$ (broad), 2942, 2866, 1464, 1382, 1242, 1034, 1012, 882, 676 cm^{-1} ; $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 4.25 (d, $J = 2.5$ Hz, 1 H), 3.89 – 3.81 (m, 2 H), 3.73 (dd, $J = 11.0, 4.0$ Hz, 1 H), 3.58 (dd, $J = 11.0, 5.5$ Hz, 1 H), 2.91 (br s, 2 H), 2.27 – 2.19 (m, 1 H), 2.06 (dd, $J = 17.5, 6.0$ Hz, 1 H), 1.87 (dd, $J = 17.5, 10.0$ Hz, 1 H), 1.73 (s, 3 H), 1.66 – 1.62 (m, 1 H), 1.60 (s, 3 H), 1.13 – 1.04 (m, 21 H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 130.5, 127.3, 75.6, 65.5, 65.3, 45.4, 35.3, 34.2, 19.0, 18.4, 18.3, 17.8, 13.7; HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{38}\text{O}_3\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 365.2488; found 365.2492.



Compound **SI-3**

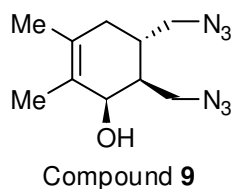
Crude diol **SI-2** (76.78 g, 224.1 mmol, 1.0 eq) was dissolved in pyridine (200 mL) and the solution cooled to 0 °C. Methanesulfonyl chloride (102.5 g, 71 mL, 896.7 mmol, 4.0 eq) was added dropwise over 30 min. The reaction temperature was

maintained at 0 °C for 30 min, and then warmed to room temperature and stirred for 30 min. The reaction mixture was cooled to 0 °C, diluted with 200 mL of dichloromethane that was previously cooled to 0 °C, and poured into ice water (500 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), dried with anhydrous magnesium sulfate, passed through a silica plug, and the solvent removed under reduced pressure to produce bis-mesylate **SI-3** (110.8 g, ~ 210 mmol, (4% by mass pyridine)) as a white, low melting solid. This material was of sufficient purity to be used directly in the next step without further purification. Purification of a sample by flash column chromatography on silica gel (30% ethyl acetate in hexanes as eluent) yielded material for characterization purposes. Material should be used immediately in the subsequent step, as decomposition is apparent after less than one week at room temperature, or in less than one month at 2 °C. $R_f = 0.30$ (silica gel, 30% ethyl acetate in hexanes); IR (neat) $\nu = 2944, 2864, 1464, 1354, 1174, 953, 882, 815, 669\text{ cm}^{-1}$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 4.45 (dd, $J = 10.0, 5.6\text{ Hz}$, 1 H), 4.36 (d, $J = 1.2\text{ Hz}$, 1 H), 4.32 (dd, $J = 10.0, 7.6\text{ Hz}$, 1 H), 4.23 – 4.16 (m, 2 H), 3.04 (s, 3 H), 3.02 (s, 3 H), 2.50 – 2.42 (m, 1 H), 2.26 (dd, $J = 18.0, 5.6\text{ Hz}$, 1 H), 2.17 – 2.11 (m, 1 H), 1.92 (dd, $J = 18.0, 6.8\text{ Hz}$, 1 H), 1.74 (s, 3 H), 1.63 (s, 3 H), 1.14 – 1.05 (m, 21 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 128.4, 127.5, 70.6, 70.3, 69.2, 41.8, 37.3, 37.2, 32.7, 31.2, 18.9, 18.3, 18.2, 17.0, 13.2; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{43}\text{O}_7\text{S}_2\text{Si}$ [$\text{M} + \text{H}^+$] 499.2214; found 499.2224.

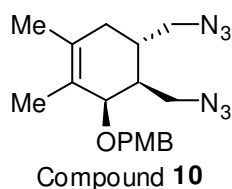


Crude bis-mesylate **SI-3** (110.8 g, ~210 mmol, 1.0 eq (4% by mass pyridine)) was dissolved in DMF (400 mL) and sodium azide (82.11 g, 1263 mmol, 6.0 eq) was added. The reaction mixture was heated to 100 °C (blast shield) for 11 h, and then cooled to room temperature. Water (2000 mL) and diethyl ether (600 mL) was added, and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 500 mL) and the combined organics washed with water (4 x 500 mL), brine (300 mL), dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure to yield bis-azide **SI-4** (82.8 g, ~206 mmol (2% by mass pyridine) as a brown oil, which was of sufficient purity to be used directly in the next step. Purification of a sample by PTLC (5% ethyl acetate in hexanes as eluent, eluted 2x) yielded a colorless oil for characterization purposes. $R_f = 0.10$ (silica gel, 2% ethyl acetate in hexanes); IR (neat) $\nu = 2944, 2866, 2097, 1459, 1383, 1274, 1113, 1083, 1062, 1014, 918, 883, 676, 610\text{ cm}^{-1}$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 4.29 (d, $J = 2.4\text{ Hz}$, 1 H), 3.59 (dd, $J = 12.0, 7.2\text{ Hz}$, 1 H), 3.36 – 3.31 (m, 3

H), 2.26 – 2.15 (m, 2 H), 1.86 – 1.80 (m, 2 H), 1.72 (s, 3 H), 1.61 (s, 3 H), 1.09 – 1.06 (m, 21H); ^{13}C -NMR (100 MHz, CDCl_3) δ 128.2, 127.8, 70.7, 54.6, 50.8, 42.5, 34.1, 32.1, 19.1, 18.4, 18.3, 16.9, 13.3; HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{36}\text{N}_6\text{OSiNa}^+$ [$\text{M} + \text{Na}^+$] 415.2612; found 415.2615.

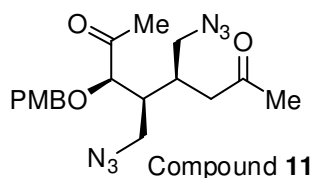


Crude compound **SI-4** (82.00 g, 206 mmol, 1.0 eq) was dissolved in THF (500 mL) and *n*-tetrabutylammonium fluoride (TBAF) (230 mL of a 1M solution in THF, 230 mmol, 1.1 eq) was added. After 25 min TLC indicated that starting material remained, and additional TBAF (10 mL, 10 mmol, 0.05 eq) was added. After 30 min, water (100 mL) was added, and approximately 600 mL of THF was removed under reduced pressure. Water (300 mL) and ether (200 mL) were added, and the layers separated. The aqueous layer was extracted with ether (2 x 100 mL) and the combined organics were washed with water (100 mL), brine (100 mL), dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes to 20% ethyl acetate in hexanes) to yield alcohol **9** (39.21 g, 164.5 mmol, 64% over 6 steps) as a pale yellow oil. R_f = 0.30 (silica gel, 20% ethyl acetate in hexanes); IR (neat) ν = 3386 (broad), 2912, 2096, 1448, 1350, 1280, 1110, 1060, 1030, 942, 892 cm^{-1} ; ^1H -NMR (500 MHz, CDCl_3) δ 4.00 (d, J = 2.0 Hz, 1 H), 3.53 (dd, J = 12.0, 5.5 Hz, 1 H), 3.48 (dd, J = 12.0, 9.0 Hz, 1 H), 3.41 (dd, J = 12.5, 3.5 Hz, 1 H), 3.30 (dd, J = 12.5, 5.5 Hz, 1 H), 2.10 – 2.02 (m, 1 H), 1.98 – 1.90 (m, 2 H), 1.77 (s, 3 H), 1.72 – 1.66 (m, 1 H), 1.65 (s, 3 H), 1.62 (br. s, 1 H); ^{13}C -NMR (125 MHz, CDCl_3) δ 130.0, 127.0, 70.1, 54.0, 51.2, 41.4, 36.5, 32.0, 18.9, 17.9; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_{16}\text{N}_6\text{ONa}^+$ [$\text{M} + \text{Na}^+$] 259.1278; found 259.1277.

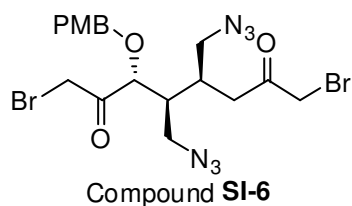


A solution of alcohol **9** (39.10 g, 164.0 mmol, 1.0 eq) and *n*-tetrabutylammonium iodide (1.00 g, 2.71 mmol, 0.017 eq) in DMF (400 mL) was cooled to 0 °C. Sodium hydride (5.94 g, 9.84 g of 60% suspension in mineral oil, 246.0 mmol, 1.5 eq) was added cautiously, and the slurry stirred at 0 °C for 30 min, warmed to 23 °C for 30 min and then cooled to 0 °C. *p*-Methoxybenzyl chloride (26.50 g, 23.25 mL, 164 mmol, 1.0 eq) was added dropwise, and the reaction was allowed to warm to 23 °C. After 2 h the reaction was cooled to 0 °C, water (5 mL) was added cautiously, and then the reaction mixture was added to water (1500 mL)

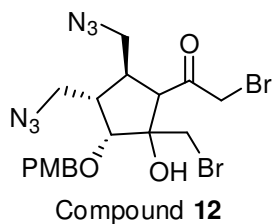
and ether (800 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 500 mL). The combined organics were washed with water (4 x 500 mL), brine (400 mL), dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure to yield compound **10** as a yellow oil (63.78 g, 164.0 mmol (contains ~4 g of mineral oil from sodium hydride) which was of sufficient purity to be used directly in the next step. Purification of a sample by flash column chromatography on silica gel (10% ethyl acetate in hexanes as eluent) yielded a colorless oil for characterization purposes. $R_f = 0.40$ (silica gel, 10% ethyl acetate in hexanes); IR (neat) $\nu = 2909, 2095, 1612, 1513, 1458, 1248, 1173, 1035, 934, 822\text{ cm}^{-1}$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.28 (d, $J = 8.8\text{ Hz}$, 2 H), 6.90 (d, $J = 8.8\text{ Hz}$, 2 H), 4.63 (AB d, $J = 11.2\text{ Hz}$, 1 H), 4.60 (AB d, $J = 11.2\text{ Hz}$, 1 H), 3.88 (d, $J = 3.2\text{ Hz}$, 1 H), 3.82 (s, 3 H), 3.50 – 3.48 (m, 2 H), 3.38 – 3.32 (m, 2 H), 2.14 – 2.10 (m, 2 H), 1.94 – 1.86 (m, 2 H), 1.76 (s, 3 H), 1.66 (s, 3 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 159.2, 130.9, 129.5, 129.4, 126.3, 113.8, 77.2, 73.5, 55.3, 54.1, 50.8, 41.1, 35.5, 32.4, 19.0, 17.6; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_6\text{O}_2\text{Na}^+ [\text{M} + \text{Na}^+]$ 379.1853; found 379.1841.



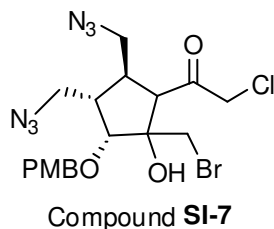
Crude **10** (20.00 g, 56.27 mmol, 1.0 eq) was dissolved in methanol (560 mL) and the reaction cooled to $-78\text{ }^\circ\text{C}$. Ozone was bubbled through the solution until a blue/grey color persisted (~30 min), and dimethyl sulfide (40 mL) was added. The solution was allowed to warm to room temperature and stirred vigorously for 5 h (starch-iodine paper indicated the absence of peroxide), after which the solvent was removed under reduced pressure. Purification of the resulting oil by flash column chromatography on silica (20% ethyl acetate in hexanes as eluent) yielded compound **11** (19.18 g, 50.46 mmol, 85% over two steps) as a yellow oil. $R_f = 0.20$ (silica gel, 20% ethyl acetate in hexanes); IR (neat) $\nu = 2937, 2100, 1715, 1612, 1514, 1458, 1356, 1249, 1175, 1112, 1033, 824\text{ cm}^{-1}$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.25 (d, $J = 8.8\text{ Hz}$, 2 H), 6.90 (d, $J = 8.8\text{ Hz}$, 2 H), 4.62 (d, $J = 11.4\text{ Hz}$, 1 H), 4.23 (d, $J = 11.4\text{ Hz}$, 1 H), 3.95 (d, $J = 5.2\text{ Hz}$, 1 H), 3.81 (s, 3 H), 3.49 (dd, $J = 12.4, 5.2\text{ Hz}$, 1 H), 3.40 (dd, $J = 12.4, 4.8\text{ Hz}$, 1 H), 3.32 (dd, $J = 12.4, 8.8\text{ Hz}$, 1 H), 3.26 (dd, $J = 12.4, 6.8\text{ Hz}$, 1 H), 2.56 – 2.46 (m, 2 H), 2.39 – 2.31 (m, 1 H), 2.23 (s, 3 H), 2.18 – 2.12 (m, 1 H), 2.10 (s, 3 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 209.3, 206.7, 159.6, 129.9, 128.8, 113.9, 83.5, 72.5, 55.2, 52.6, 49.6, 43.6, 41.4, 33.1, 30.2, 26.5; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_6\text{O}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 411.1751; found 411.1737.



A solution of compound **11** (10.00 g, 25.74 mmol, 1.0 eq) in dichloromethane (250 mL) was cooled to 0 °C, and diisopropylethylamine (20.07 g, 25.4 mL, 154.4 mmol, 6.0 eq) added. Trimethylsilyl triflate (22.86, 18.6 mL, 103.0 mmol, 4.0 eq) was added dropwise over 15 min, and the reaction mixture stirred for 1.5 h. The reaction mixture was warmed to 23 °C and stirred at this temperature for 1.5 h (R_f of product (0.8, 20% ethyl acetate in hexanes), after which it was azeotroped at 30 °C under reduced pressure with toluene (6 x 100 mL). The resulting slurry was filtered through Celite using hexanes, and the solvent was removed under reduced pressure to yield a red oil (**SI-5**). The oil was then dissolved in THF (120 mL) and cooled to 0 °C. A solution of *N*-bromosuccinimide (NBS) (9.15 g, 51.48 mmol, 2.0 eq) in THF (100 mL) was prepared, and this solution was added dropwise until the reaction was deemed complete by TLC (~90 mL, 8.23 g, 46.8 mmol, 1.8 eq of NBS) (syringe for addition and vessel containing NBS solution were wrapped in aluminum foil). The reaction mixture was then poured into water (500 mL) and dichloromethane (300 mL) that had been previously cooled to 0 °C, and the layers separated. The aqueous layer was washed with dichloromethane (3 x 100 mL) and the combined organics washed with water (3 x 100 mL), dried with magnesium sulfate and the solvent removed under reduced pressure. The resulting orange oil was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes to 25% ethyl acetate in hexanes as eluent) to yield compound **SI-6** (8.60 g, 15.74 mmol, 61%) as a pale yellow oil, which contained a minor impurity (~5%) which likely corresponds to the product resulting from silica induced aldol cyclization (compound **12**). R_f = 0.25 (silica gel, 20% ethyl acetate in hexanes); IR (neat) ν = 2939, 2100, 1718, 1612, 1514, 1458, 1356, 1302, 1248, 1175, 1032, 821 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 7.28 – 7.26 (m, 2 H), 6.92 – 6.90 (m, 2 H), 4.62 (d, J = 11.2 Hz, 1 H), 4.34 (d, J = 4.8 Hz, 1 H), 4.30 (d, J = 11.2 Hz, 1 H), 4.14 (d, J = 12.8 Hz, 1 H), 4.08 (d, J = 12.8 Hz, 1 H), 3.82 (d, J = 1.2 Hz, 2 H) 3.81 (s, 3 H), 3.54 – 3.46 (m, 2 H), 3.34 (dd, J = 12.4, 8.8 Hz, 1 H), 3.26 (dd, J = 12.4, 7.2 Hz, 1 H), 2.84 – 2.72 (m, 2 H), 2.36 – 2.30 (m, 1 H), 2.18 – 2.12 (m, 1 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 202.1, 200.7, 159.7, 130.1, 128.3, 114.0, 81.1, 72.7, 55.3, 52.2, 49.2, 41.6, 40.1, 34.0, 33.2, 31.7; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{21}\text{Br}_2\text{N}_6\text{O}_4$ [$\text{M} - \text{H}^+$] 542.9996; found 542.9997.

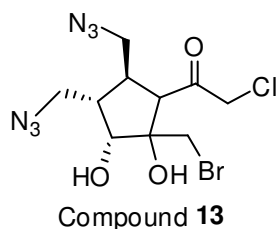


Dibromo compound **SI-6** (8.60 g, 15.74 mmol) was dissolved in dichloromethane (600 mL) and silica gel (103.2 g, 12x by weight) was added. The solvent was removed under reduce pressure to produce free flowing silica, which was heated to 47 °C with vigorous stirring for 12 h (reaction progress monitored by $^1\text{H-NMR}$ after removing a small sample of silica gel, filtering with ethyl acetate, and solvent removal under reduce pressure). Once the reaction was complete, the silica was filtered and washed with ethyl acetate. Removal of the solvent under reduced pressure yielded aldol product **12** (8.10 g, 14.82 mmol, 94%, (57% over 2 steps)) as a pale yellow oil. This material was of sufficient purity to be used directly in the subsequent step. R_f = 0.25 (silica gel, 20% ethyl acetate in hexanes); IR (neat) ν = 3465 (broad), 2934, 2100, 1718, 1611, 1513, 1458, 1302, 1248, 1175, 1093, 1032, 831 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.26 (d, J = 8.8 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 4.64 (d, J = 11.6 Hz, 1 H), 4.56 (d, J = 11.6 Hz, 1 H), 4.13 (d, J = 12.6 Hz, 1 H), 4.01 (d, J = 12.6 Hz, 1 H), 3.99 (d, J = 6.0 Hz, 1 H), 3.81 (s, 3 H), 3.55 – 3.39 (m, 8 H), 2.77 – 2.70 (m, 1 H), 2.12 – 2.04 (m, 1 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 198.8, 159.9, 130.1, 128.6, 114.1, 81.8, 80.4, 74.7, 55.5, 55.3, 52.3, 50.5, 42.4, 41.9, 37.7, 35.4; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{21}\text{Br}_2\text{N}_6\text{O}_4$ [$\text{M} - \text{H}^+$] 542.9996; found 542.9992.



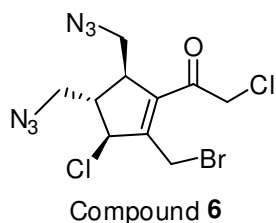
To a solution of compound **12** (8.46 g, 15.49 mmol, 1.0 eq) in DMF (80 mL) was added lithium chloride (2.19 g, 51.68 mmol, 3.25 eq) and the reaction mixture stirred at 23 °C for 1.5 h. Water (100 mL) and diethyl ether (150 mL) were added and the layers separated. The aqueous layer was washed with ether (3 x 150 mL) and the combined organics washed with water (3 x 150 mL), brine (1 x 150 mL) and dried with anhydrous magnesium sulfate. Removal of the solvent under reduced pressure produced compound **SI-7** as a yellow oil (7.75 g, 15.49 mmol) that was of sufficient purity to be used directly in the next step. Purification of a sample by flash column chromatography on silica gel (15% ethyl acetate in hexanes as eluent) yielded a colorless oil for characterization purposes. R_f = 0.25 (silica gel, 20% ethyl acetate in hexanes); IR (neat) ν = 3471 (broad), 2934, 2100, 1733, 1612, 1514, 1454, 1302, 1248, 1176, 1092, 1031, 824 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.25 (d, J = 8.4 Hz, 2 H), 6.90 (d, J = 8.4 Hz, 2 H), 4.64 (d, J = 11.2 Hz, 1 H), 4.55 (d, J = 11.2 Hz, 1 H), 4.22 (s, 2 H), 3.99 (d, J = 5.6 Hz, 1 H), 3.81 (s, 3 H), 3.53 – 3.40 (m, 6 H), 3.35 (dd, J = 12.6, 6.0 Hz, 1 H), 3.26 (d, J = 9.6 Hz, 1 H), 2.78 – 2.70 (m, 1 H), 2.10 – 2.02 (m, 1 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 199.5, 159.9, 130.1, 128.6,

114.1, 81.6, 80.3, 74.4, 55.7, 55.3, 52.6, 50.5, 49.1, 42.5, 42.0, 37.6; HRMS (ESI-TOF) calcd for $C_{18}H_{22}BrClN_6O_4Na^+$ [$M + Na^+$] 523.0467; found 523.0477.



To a solution of crude compound **SI-7** (7.75 g, 15.49 mmol, 1.0 eq) and anisole (3.30 g, 3.30 mL, 30.98 mmol, 2.0 eq) in dichloromethane (270 mL) at 0 °C was added trifluoroacetic acid (27 mL) dropwise. After stirring at this temperature for 25 min, the solution was azeotroped with toluene (5 x 50 mL, bath temperature <30 °C) to produce a red oil, which was purified by flash column

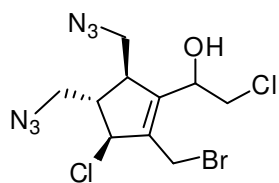
chromatography on silica gel (16% ethyl acetate in hexanes to 20% ethyl acetate in hexanes as eluent) to yield diol **13** (4.26 g, 11.15 mmol, 72% for two steps) as a pale yellow oil. Performing this chlorination/deprotection sequence on a smaller scale (1.739 g, 3.47 mmol of compound **12**) using similar reaction conditions led to a higher yield of compound **13** (78% for 2 steps). R_f = 0.30 (silica gel, 25% ethyl acetate in hexanes); IR (neat) ν = 3448 (broad), 2929, 1718, 1092 cm^{-1} ; 1H -NMR (500 MHz, $CDCl_3$) δ 4.36 (AB d, J = 16.0 Hz, 1 H), 4.32 (AB d, J = 16.0, 1 H), 4.13 (dd, J = 7.0, 6.5 Hz, 1 H), 3.81 (s, 1 H), 3.68 (dd, J = 12.0, 7.5 Hz, 1 H), 3.63 (d, J = 11.0 Hz, 1 H), 3.52 (d, J = 11.0 Hz, 1 H), 3.52 – 3.47 (m, 2 H), 3.38 (dd, J = 12.5, 6.0 Hz, 1 H), 3.31 (d, J = 9.0 Hz, 1 H), 2.90 (d, J = 7.5 Hz, 1 H), 2.76 – 2.70 (m, 1 H), 2.14 – 2.08 (m, 1 H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 202.3, 80.6, 76.1, 55.7, 52.7, 50.4, 49.6, 43.3, 43.1, 38.6; HRMS (ESI-TOF) calcd for $C_{10}H_{15}BrClN_6O_3$ [$M + H^+$] 381.0072; found 381.0083.



To a solution of diol **13** (2.90 g, 7.63 mmol, 1.0 eq) in dichloromethane (150 mL) containing 3 Å MS beads (15 g) at 0 °C was added freshly distilled sulfuryl chloride (9.24 g, 5.5 mL, 68.4 mmol, 9.0 eq) dropwise over 5 min (solution turns green to purple to pink), followed by freshly distilled 2,6-lutidine (4.06 g, 4.4 mL, 37.9 mmol, 5.0 eq) dropwise over 5 min and the reaction stirred for 30 min

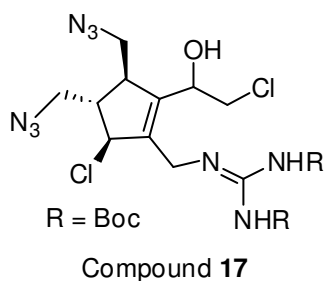
at this temperature. Ice (50 g) and water (100 mL) previously cooled to 0 °C were added, the mixture added to a separatory funnel and shaken vigorously for 10 min. The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 100 mL), the combined organics dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The resulting oil was purified by

flash column chromatography on silica gel (33% dichloromethane in hexanes as eluent) to yield compound **6** (1.07 g, 2.82 mmol, 37%) as a yellow oil. The bis- α -chloroketone **21** and the epichloroketone 17-*epi*-**6** were each also isolated in ca. 15% yield. R_f = 0.71 (silica gel, 33% ethyl acetate in hexanes); IR (neat) ν = 2931, 2105, 1670, 1388, 1094 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 4.93 (d, J = 2.8 Hz, 1 H), 4.48 (d, J = 11.2 Hz, 1 H), 4.41 (d, J = 14.4 Hz, 1 H), 4.24 (d, J = 14.4 Hz, 1 H), 4.11 (d, J = 11.2 Hz, 1 H), 3.69 (dd, J = 12.0, 6.4 Hz, 1 H), 3.58 (dd, J = 11.6, 8.0 Hz, 1 H), 3.52 (dd, J = 6.8, 2.4 Hz, 2 H), 3.19 – 3.14 (m, 1 H), 2.51 – 2.46 (m, 1 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 192.2, 147.4, 140.2, 64.2, 53.9, 52.2, 49.7, 49.2, 47.5, 23.0; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_{10}\text{BrCl}_2\text{N}_6\text{O}$ [$\text{M} - \text{H}^+$] 378.9482; found 378.9474.



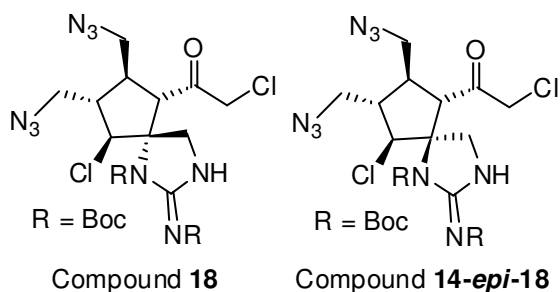
Compound **16**

To a solution of enone **6** (1.96 g, 5.10 mmol, 1.0 eq) and cerium(III) chloride heptahydrate (1.00 g, 2.69 mmol, 0.52 eq) in methanol (60 mL) at 0 °C was added sodium borohydride (0.20 g, 5.28 mmol, 1.03 eq, added as 2 x 100 mg portions, 5 min apart) and the mixture stirred for 20 min. Diethyl ether (50 mL), water (50 mL) and saturated aqueous sodium potassium tartrate (50 mL) were added, and the mixture vigorously stirred for 20 min. The layers were separated, and the aqueous layer was extracted with ether (3 x 50 mL) and the combined organics washed with brine, dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. The resulting oil was contaminated with water, and was dissolved in methylene chloride, dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield alcohol **16** (1.96 g, 5.10 mmol, as a 9:1 mixture of diastereomers) as a yellow oil that turned brown on standing at room temperature. The material was of sufficient purity to be used directly in the next step without further purification. Proton and carbon data is given for the major diastereomer only. R_f = 0.55 (silica gel, 33% ethyl acetate in hexanes); IR (neat) ν = 3300 (broad), 2930, 2872, 2102, 1450, 1286, 1270, 1074, 911 cm^{-1} ; ^1H -NMR (600 MHz, CDCl_3) δ 4.85 (d, J = 3.0 Hz, 1 H), 4.71 – 4.68 (m, 1 H), 4.46 (d, J = 10.8 Hz, 1 H), 4.06 (d, J = 10.8 Hz, 1 H), 3.69 (dd, J = 10.8, 9.0 Hz, 1 H), 3.64 (d, J = 6.0 Hz, 2 H), 3.61 (dd, J = 11.4, 3.6 Hz, 1 H), 3.54 – 3.46 (m, 2 H), 2.84 – 2.81 (m, 1 H), 2.67 (d, J = 3.6 Hz, 1 H), 2.56 – 2.52 (m, 1 H); ^{13}C -NMR (150 MHz, CDCl_3) δ 142.7, 138.7, 70.0, 65.2, 53.2, 52.4, 49.9, 49.2, 47.9, 24.0; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_{12}\text{BrCl}_2\text{N}_6\text{O}$ [$\text{M} - \text{H}^+$] 380.9638; found 380.9644.



To a solution of crude compound **16** (2.00 g, 5.20 mmol, 1.0 eq) and *N,N'*-bis-Bocguanidine (2.69 g, 10.40 mmol, 2.0 eq) in DMF (100 mL) at -10 °C was added DBU (1.18g, 1.18 mL, 1.5 eq) dropwise. Over the course of 2.75 h the reaction gradually warmed to 0 °C. The reaction mixture was poured into water (500 mL) and ethyl acetate (300 mL) and the layers separated.

The aqueous layer was extracted once with ethyl acetate (100 mL) and 50 mL of brine was added to the aqueous layer. The aqueous layer was then extracted with ethyl acetate (2 x 100 mL) and the combined organics washed with water (3 x 200 mL), brine (200 mL), dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. The resulting brown foam was purified by flash column chromatography on silica (10% ethyl acetate in hexanes to 20% ethyl acetate in hexanes) to yield compound **17** (1.62 g, 2.88 mmol, 55% for two steps) as a yellow oil. R_f = 0.5 (silica gel, 25% ethyl acetate in hexanes); IR (neat) ν = 3388, 2977, 2101, 1719, 1648, 1610, 1508, 1451, 1367, 1289, 1246, 1145, 1115, 984, 887, 850, 810 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 9.40 (br. s, 1 H), 9.26 (br. s, 1 H), 5.03 (d, J = 15.2 Hz, 1 H), 4.93 (dd, J = 5.6, 5.2 Hz, 1 H), 4.61 (d, J = 15.2 Hz, 1 H), 4.51 (s, 1 H), 3.74 (dd, J = 11.6, 6.0 Hz, 1 H), 3.67 – 3.63 (m, 2 H), 3.56 (dd, J = 12.0, 8.8 Hz, 1 H), 3.32 (dd, J = 12.0, 6.4 Hz, 1H), 3.17 (dd, J = 12.0, 8.0 Hz, 1 H), 2.68 – 2.64 (m, 1 H), 2.59 (dd, J = 8.0, 7.2 Hz, 1 H), 1.59 (s, 9 H), 1.47 (s, 9 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 162.5, 160.3, 154.5, 144.1, 137.2, 85.5, 79.7, 69.3, 65.6, 53.8, 53.4, 50.3, 49.0, 47.4, 41.6, 28.8, 28.0; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{34}\text{Cl}_2\text{N}_9\text{O}_5$ [$\text{M} + \text{H}^+$] 562.2054; found 562.2057.



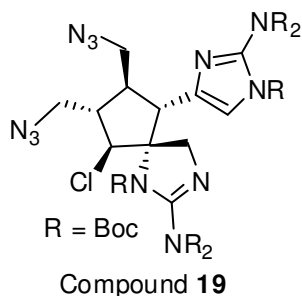
To a solution of compound **17** (200 mg, 0.425 mmol, 1.0 eq) in benzene (20 mL) was added 2-iodoxybenzoic acid (IBX) (200 mg, 0.85 mmol, 2.0 eq) and the reaction heated to 83 °C in a sealed pressure tube for 10 h. Ethyl acetate (50 mL), saturated aqueous sodium bicarbonate (50 mL) and saturated aqueous sodium thiosulfate (50 mL) were

added, and the biphasic mixture stirred vigorously for 1 hr. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with water (50 mL), brine (50 mL), dried with anhydrous magnesium sulfate and the solvent removed under reduced

pressure to yield an orange foam, which was approximately a 1:1 ratio of epimers at the spirocenter. Compounds **18** and 14-*epi*-**18** were separated by preparative thin layer chromatography (25% hexanes in dichloromethane as eluent, elute 4x) to yield compound **18** (82 mg, 0.146 mmol, 41% bottom band on PTLC) and compound 14-*epi*-**18** (58 mg, 0.103 mmol, 29%) as white foams. When the reaction was performed on larger scales, flash column chromatography (10% ethyl acetate in hexanes as eluent) was used to separate the mixture of spirocenter diastereomers from the IBX derived impurities, and this ca. 1:1 mixture of diastereomers was used directly in the subsequent step.

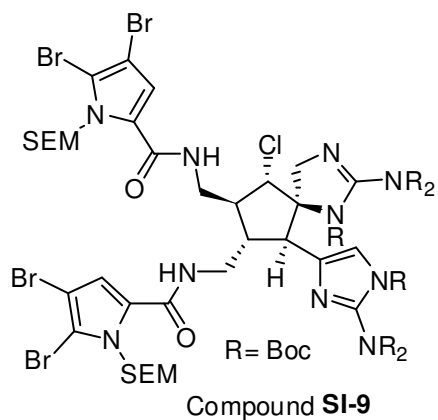
Data for Compound **18** (desired spirocenter) R_f = 0.25 (silica gel, 20% ethyl acetate in hexanes); IR ν = 3294, 2926, 2103, 1762, 1706, 1648, 1535, 1458, 1370, 1341, 1260, 1146, 848, 767, 749 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 9.55 (br. s, 1 H), 4.56 (d, J = 14.2 Hz, 1 H), 4.17 (d, J = 12.4 Hz, 1 H), 4.07 (d, J = 11.2 Hz, 1 H), 4.01 (d, J = 10.4 Hz, 1H) 3.79 – 3.72 (m, 2 H), 3.56 (dd, J = 10.0, 6.0 Hz, 1 H), 3.51 – 3.50 (m, 2 H), 3.44 (d, J = 6.0 Hz, 1 H), 2.80 – 2.75 (m, 1 H), 2.05 – 1.99 (m, 1 H), 1.49 (s, 9 H), 1.47 (s, 9 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 201.9, 151.6, 149.3, 148.1, 84.2, 81.9, 76.4, 66.4, 58.7, 53.4, 52.6, 51.9, 49.9, 46.4, 39.5, 28.1, 28.0; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{32}\text{Cl}_2\text{N}_9\text{O}_5$ $[\text{M} + \text{H}^+]$ 560.1898; found 560.1903.

Data for Compound 14-*epi*-**18** (undesired spirocenter) R_f = 0.22 (silica gel, 20% ethyl acetate in hexanes); IR (neat) ν = 3295, 3922, 2104, 1764, 1706, 1535, 1370, 1341, 1148 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 9.57 (br. s, 1H), 4.33 (d, J = 15.4 Hz, 1 H), 4.22 (d, J = 15.4 Hz, 1 H), 4.21 (d, J = 10.8 Hz, 1 H), 3.84 – 3.74 (m, 3 H), 3.62 (dd, J = 12.4, 3.6 Hz, 1 H), 3.50 (dd, J = 12.8, 5.6 Hz, 1 H), 3.43 (d, J = 12.0 Hz, 1 H), 3.27 (d, J = 3.6 Hz 1 H), 2.48 – 2.41 (m, 1 H), 2.05 – 1.99 (m, 1H), 1.50 (s, 9 H), 1.49 (s, 9 H); ^{13}C -NMR (150 MHz, CDCl_3) δ 202.3, 151.9, 149.4, 147.2 84.0, 81.7, 75.6, 66.2, 59.1, 55.7, 50.9, 49.8, 47.9, 47.1, 43.3, 28.2, 28.1; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{32}\text{Cl}_2\text{N}_9\text{O}_5$ $[\text{M} + \text{H}^+]$ 560.1898; found 560.1906.

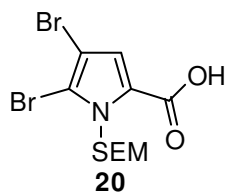


To a solution of spirocenter **18** (54 mg, 0.096 mmol, 1.0 eq) in THF (1.05 mL) was added *N*-Bocguanidine (60 mg, 0.484 mmol, 4.0 eq) and the solution was heated to 55 °C for 24 h. The solvent was removed under reduced pressure to produce a residue that was subjected to flash column chromatography on silica gel (20 to 30% ethyl acetate in hexanes gradient as eluent) to yield crude **SI-8** (R_f = 0.3-0.05, 33% ethyl acetate in hexanes) which was contaminated with

tricycle **22** and residual *N*-Bocguanidine. Compound **SI-8** streaked badly on silica gel, resulting in the inability to completely remove the byproducts. To a solution of the crude aminoimidazole **SI-8** (34 mg, from the previous reaction) in dichloromethane (1.0 mL) was added Di-*tert*-butyl dicarbonate ((Boc)₂O) (169 mg, 0.772 mmol, 15 eq), triethylamine (105 mg, 145 μ L, 1.03 mmol, 20.1 eq) and *N,N*-dimethylaminopyridine (one crystal, 2.2 mg, catalytic) and the reaction stirred for 3 h. The solvent was removed under reduced pressure and the resulting residue purified by PTLC (eluent 16% ethyl acetate in hexanes, eluted 5x) to yield compound **19** (34 mg, 0.0351 mmol, 33% for 2 steps) as a colorless oil. R_f = 0.5 (silica gel, 33% ethyl acetate in hexanes); IR (neat) ν = 2982, 2100, 1805, 1756, 1734, 1647, 1397, 1369, 1320, 1277, 1255, 1152, 1101, 849, 769 cm^{-1} ; ¹H-NMR (400 MHz, CDCl₃) δ 7.34 (s, 1 H), 4.33 (d, J = 11.6 Hz, 1 H), 4.00 (d, J = 2.0 Hz, 1 H), 3.63 (dd, J = 12.0, 6.0 Hz, 1 H), 3.58 – 3.52 (m, 3H), 3.38 (dd, J = 12.4, 7.2 Hz, 1 H), 3.35 (d, J = 10.8 Hz, 1 H), 2.49 – 2.42 (m, 1 H), 2.31 – 2.24 (m, 1 H), 1.54 – 1.38 (m, 54 H); ¹³C-NMR (150 MHz, CDCl₃) δ 149.1, 149.0, 148.6, 148.2, 146.1, 137.0, 135.2, 117.4, 84.0, 83.6, 83.3, 83.2, 82.7, 77.9, 66.3, 54.7, 53.8, 51.6, 50.8, 47.8, 47.7, 28.04, 27.98, 27.90, 27.86, 27.81 (4 carbon signals are absent, either due to overlap or decreased intensity due to broadening (rotamers)); HRMS (ESI-TOF) calcd for C₄₂H₆₆ClN₁₂O₁₂ [M + H⁺] 965.4606; found 965.4591

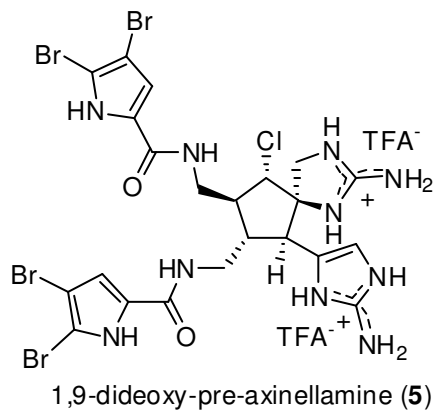


To a solution of hexaBoc compound **19** (40.2 mg, 0.041 mmol, 1.0 eq) in CH₃CN (2.6 mL) was added triphenylphosphine (44 mg, 0.1677 mmol, 4.1 eq) and the reaction heated to 60 °C for 40 min, then water (0.2 mL) was added and heating continued for 1.5 h (reaction was monitored by LCMS, under prolonged heating intermolecular Boc transfer occurs to the newly formed amines). The reaction was cooled to 23 °C and sodium sulfate (500 mg) was added and the mixture stirred for 10 min. Pyrrole acid **20** (100 mg, 0.251 mmol, 6.1 eq), dichloromethane (1.5 mL), EDCI (80 mg, 0.417 mmol, 10.2 eq), and triethylamine (0.2 mL, 1.42 mmol, 34.6 eq) were added sequentially and the reaction proceeded for 1.5 h after which the crude reaction mixture was filtered through a short silica plug using ethyl acetate as eluent. The reaction was then purified by PTLC (33% ethyl acetate in hexanes as eluent, eluted 1x) to yield acylation compound **SI-9** (31 mg, 0.0185 mmol, 45%) as a colorless oil. *R*_f = 0.65 (silica gel, 33% ethyl acetate in hexanes); IR (neat) ν = 2978, 1806, 1736, 1648, 1542, 1459, 1370, 1319, 1250, 1150, 1100, 836, 769 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ 7.78 (br. t, 1 H), 7.34 (s, 1 H), 7.33 (br. t, 1 H), 7.14 (s, 1 H), 6.95 (s, 1 H), 5.90 (s, 1 H), 5.88 (d, *J* = 7.2 Hz, 1 H), 5.83 (d, *J* = 7.2 Hz, 1 H), 4.40 (d, *J* = 7.6 Hz, 1 H), 3.94 (d, *J* = 2.0 Hz, 1 H), 3.82 – 3.78 (m, 1 H), 3.70 – 3.66 (m, 1 H), 3.62 – 3.56 (m, 6 H), 3.28 – 3.24 (m, 2 H), 2.43 – 2.37 (m, 2 H), 2.13 – 2.05 (m, 1 H), 1.54 (s, 9 H), 1.45 (s, 18 H), 1.44 (s, 9 H), 1.40 (s, 18 H), 0.93 – 0.85 (m, 4 H), -0.05 (s, 9 H), -0.07 (s, 9 H); ¹³C-NMR (150 MHz, CDCl₃) δ 161.1, 160.7, 148.6, 146.0, 137.2, 135.6, 128.2, 127.7, 117.4, 115.9, 111.4, 111.1, 99.9, 86.1, 84.2, 84.0, 83.8, 83.55, 83.54, 83.52, 75.2, 75.0, 70.7, 68.0, 66.1, 66.0, 60.4, 51.2, 50.6, 48.7, 48.3, 48.2, 42.4, 41.1, 36.7, 30.0, 28.1, 28.0, 27.9, 27.8, 21.0, 17.81, 17.67, 14.2, -1.24 (4 carbon signals are absent, either due to overlap or decreased intensity due to broadening (rotamers)); HRMS (ESI-TOF) calcd for C₆₄H₁₀₀Br₄ClN₁₀O₁₆Si₂ [M + H⁺] 1671.3273; found 1671.3368.



To a solution of 5-trichloroacetyl-2,3-dibromopyrrole (3.00 g, 8.10 mmol, 1.0 eq) in THF/DMF (50 mL/5 mL) was added sodium hydride (428 mg, 73 mg, of 60% suspension in mineral oil, 17.82 mmol, 2.2 eq), and the mixture stirred for 30 min, after which 2-(trimethylsilyl)ethoxymethyl chloride (2.66 g, 2.82 mL, 16.2 mmol, 2.0 eq) was added dropwise and the reaction stirred for 3 h. 2M aqueous sodium hydroxide (40 mL) was

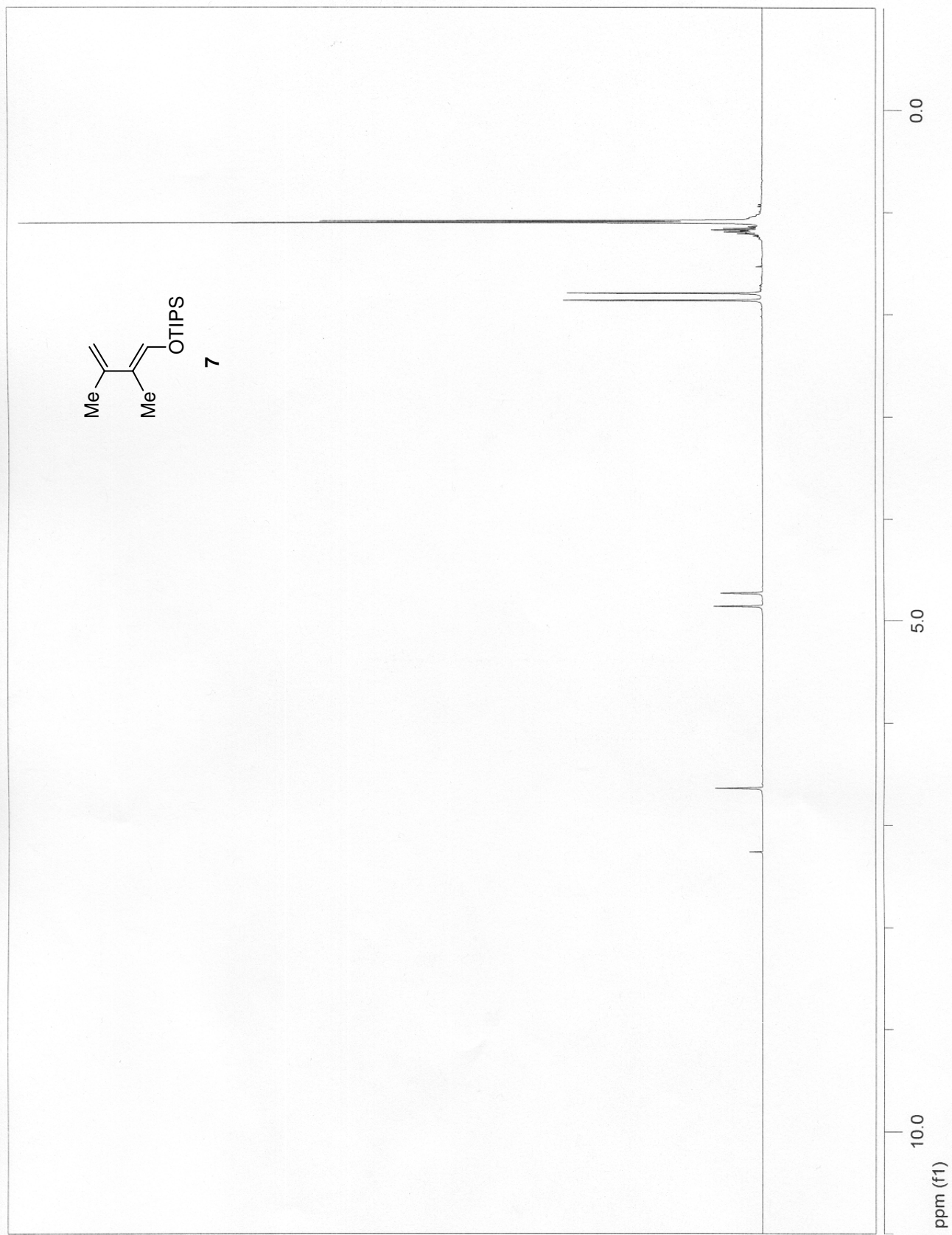
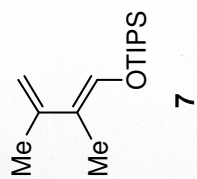
then added, and the reaction heated to 60 °C for 12 h. The mixture was cooled to room temperature and diluted with diethyl ether (40 mL) and the layers separated. The aqueous layer was extracted with ether (3 x 40 mL), and the combined organics washed with 1M HCl (40 mL), brine (40 mL), dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield a yellow solid. This solid was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes as eluent) to yield a pale yellow solid that was further purified by trituration with hexanes. Pyrrole acid **20** (1.46 g, 3.66 mmol, 45%) was isolated as a beige solid. This procedure has not been optimized. m.p. = 99-101 °C; R_f = 0.3 (silica gel, 33% ethyl acetate in hexanes); IR (neat) ν = 3100 (broad), 2951, 1676, 1527, 1424, 1318, 1235, 1140, 1093, 955, 914, 858, 834, 758, 725, 694 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.21 (s, 1 H), 5.82 (s, 2 H), 3.60 (t, J = 6.8 Hz, 2 H), 0.91 (t, J = 6.8 Hz, 2 H), -0.03 (s, 9 H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 164.1, 123.2, 122.7, 115.3, 101.1, 75.7, 66.4, 17.8, 1.5; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_{17}\text{Br}_2\text{NO}_3\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 419.9237; found 419.9239

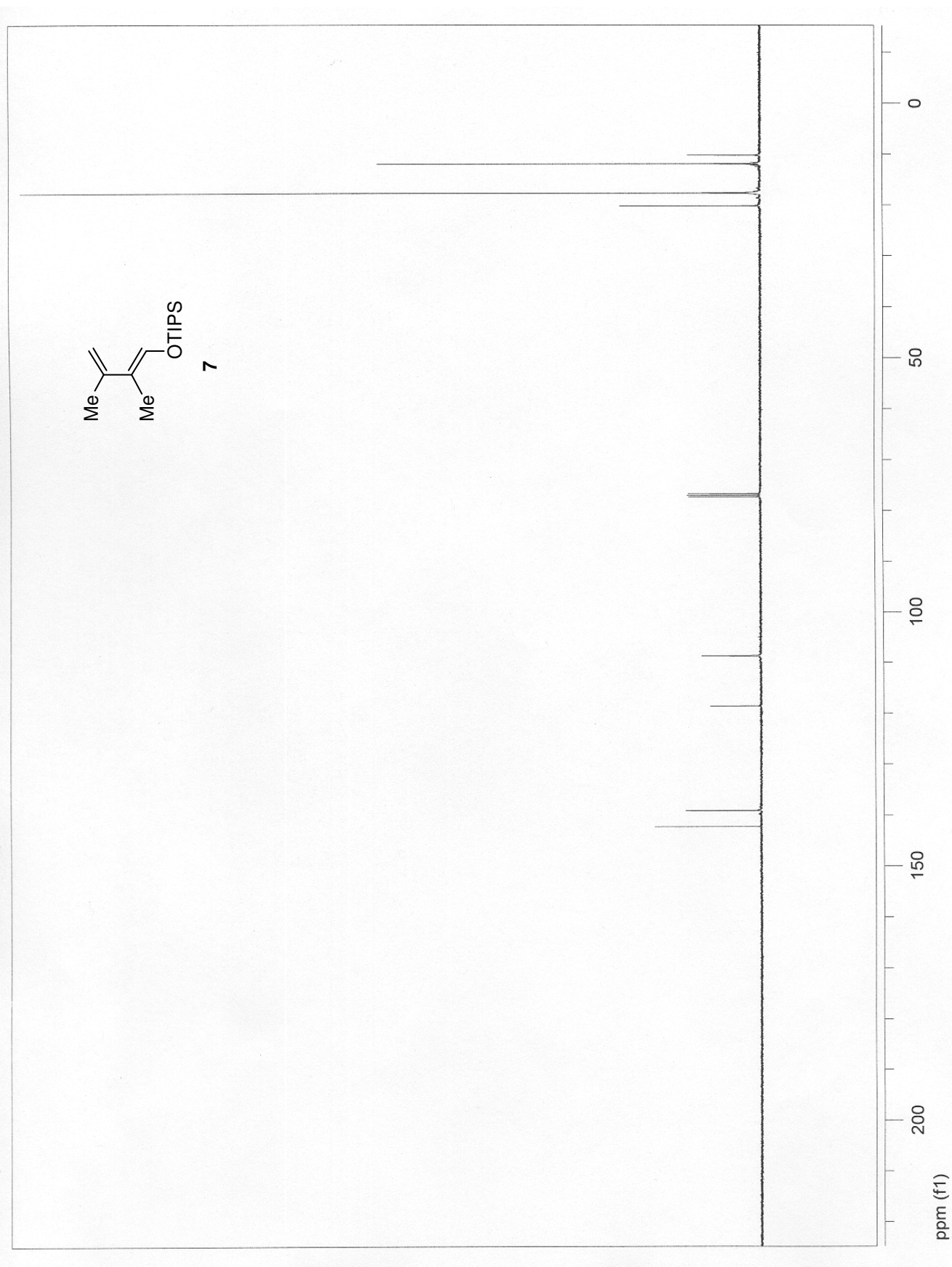
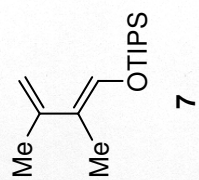


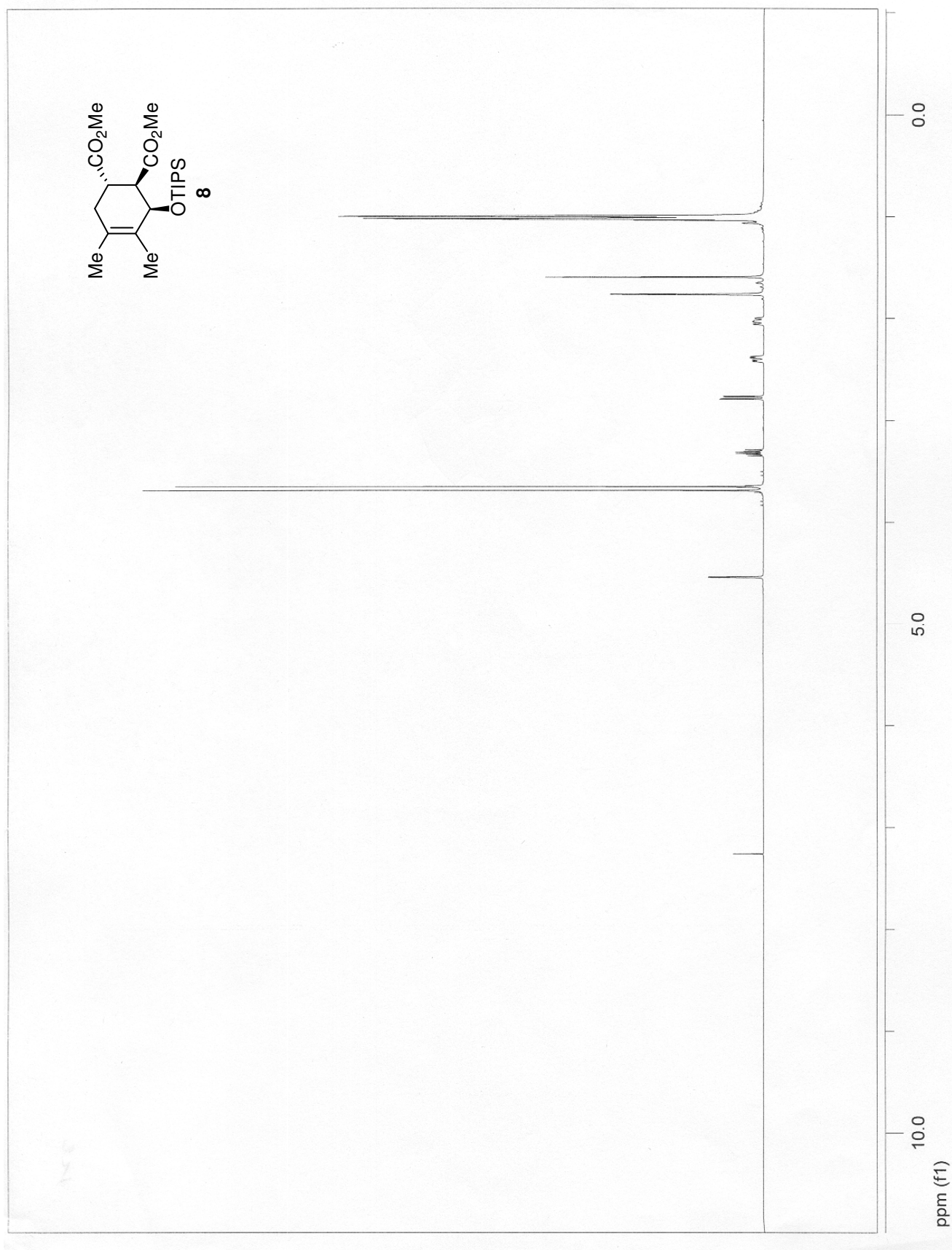
To a solution of acylation compound **SI-9** (21 mg, 0.0125 mmol, 1.0 eq) in dichloromethane (0.8 mL) was added trifluoroacetic acid (1.6 mL) and the reaction was stirred for 3 h at 23 °C, after which the solvent was removed under reduced pressure. $^1\text{H-NMR}$ analysis of the crude product (12.8 mg, 0.0125 mmol, quantitative) indicated that hydroxymethylene groups were still present on both pyrrole units. The hydroxymethylene units were removed using the following general procedure on the material prepared above. To a solution of the bis-hydroxymethylene compound (9.0 mg, 0.0084 mmol, 1.0 eq) in CH_3CN (3.6 mL) was added an aqueous 0.266 M sodium acetate solution (0.47 mL) and after initial mixing, the reaction stood at 23 °C for 30 min. Trifluoroacetic acid (1.8 mL) was added, and the solvent removed under reduced pressure to yield a white solid (contained sodium acetate) that was >90% pure based on LCMS. The mixture was then purified by reversed phase PTLC (30% water in acetonitrile +1% TFA as eluent, eluted 1x) to give 1,9-dideoxy-pre-axinellamine **5** (8.5 mg, 0.0076 mmol, 90%) as a white film.

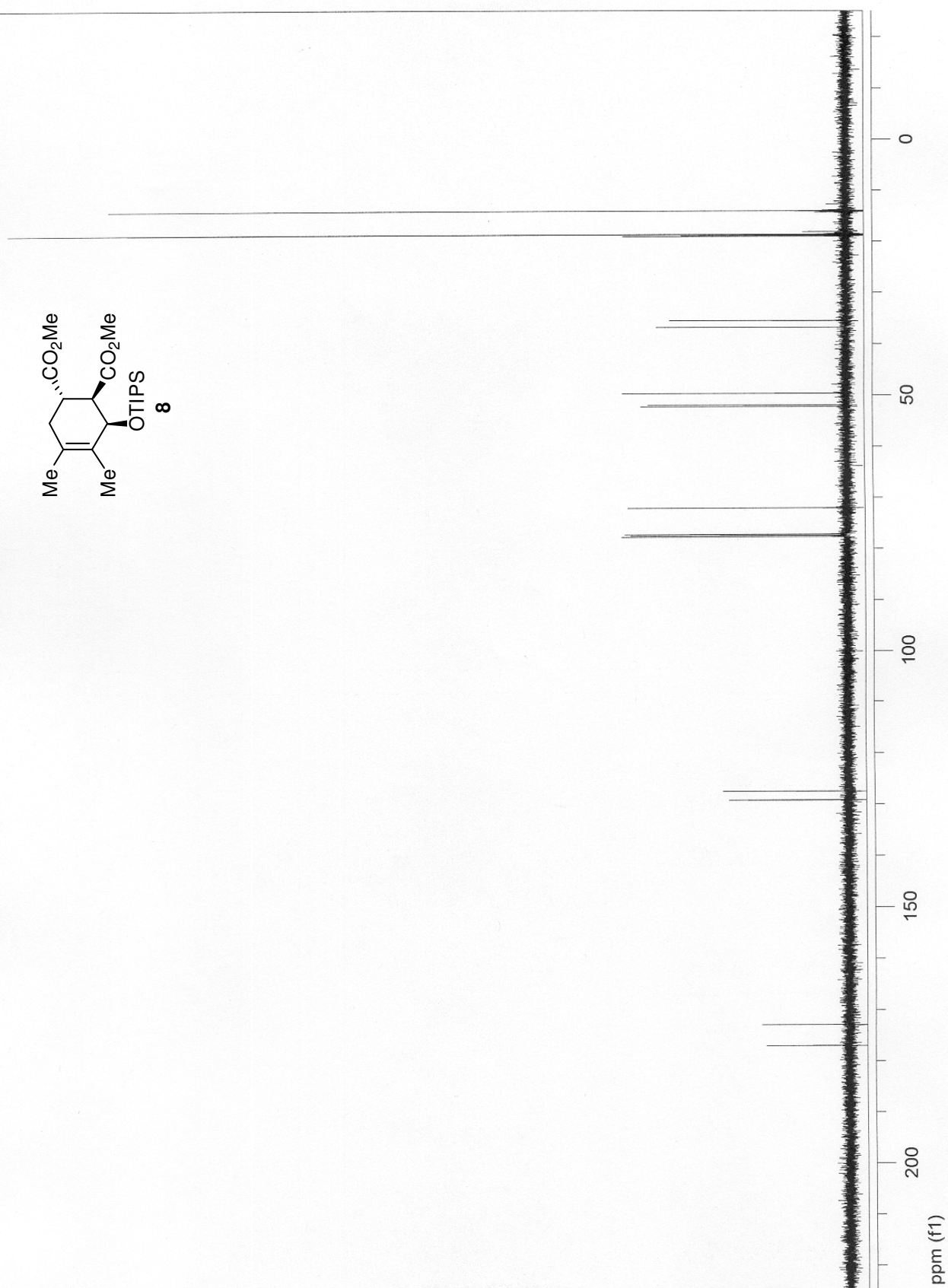
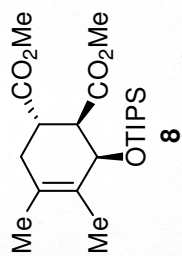
R_f = 0.8 (reversed phase silica gel, 30% water in acetonitrile +1% TFA); IR (neat) ν = 3325 (broad), 1679, 1445, 1205, 1139, 800, 725, 620 cm^{-1} ; $^1\text{H-NMR}$ (600 MHz, CD_3OD) δ 6.93 (s, 1 H), 6.80 (s, 1 H), 6.58 (s, 1 H), 4.21 (d, J = 9.6 Hz, 1 H), 4.08 (d, J = 9.6 Hz, 1 H), 3.72 (dd, J = 8.4, 5.4 Hz, 1 H), 3.59

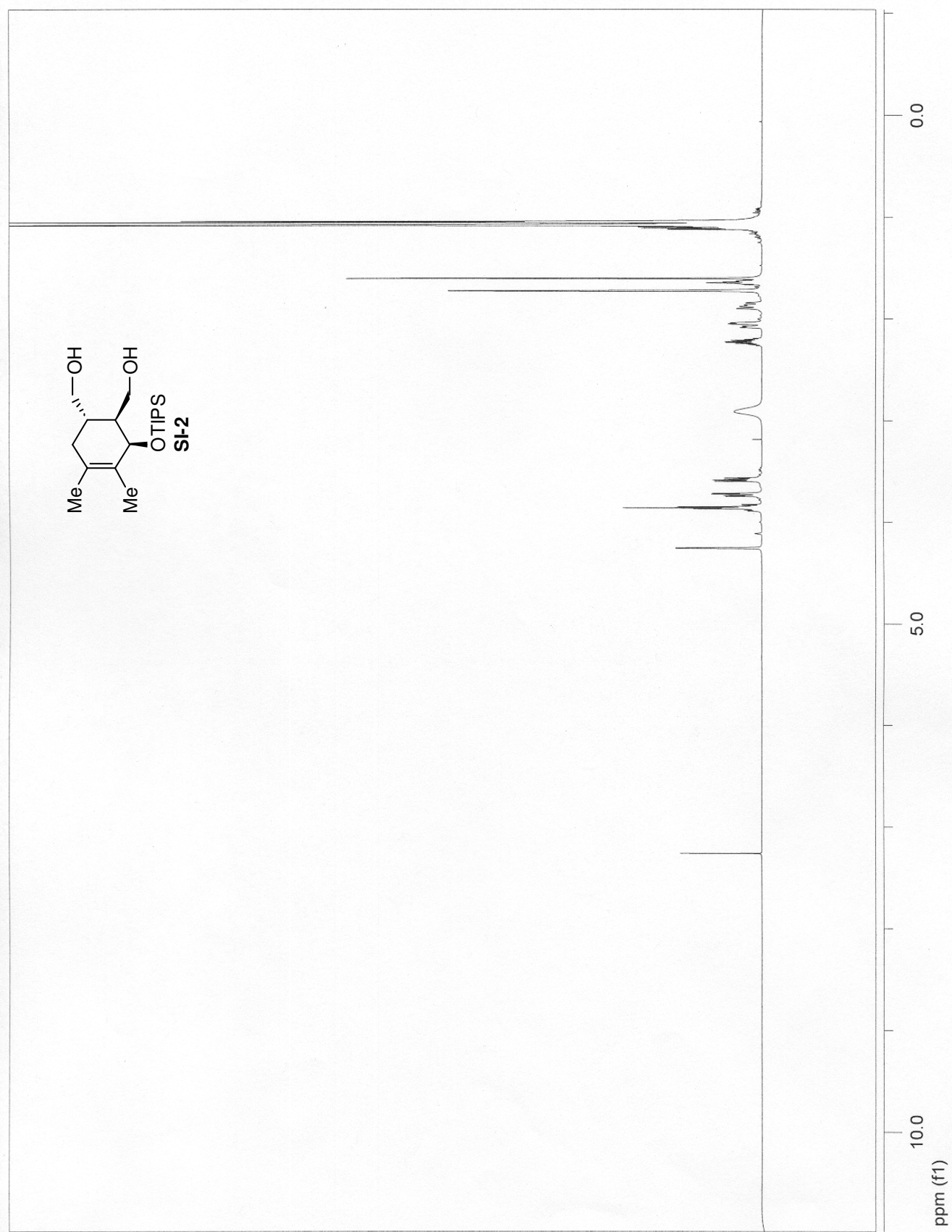
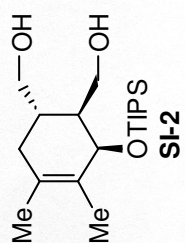
(dd, $J = 13.8, 5.4$ Hz, 1 H), 3.51 (d, $J = 5.4$ Hz, 2 H), 3.27 (d, $J = 7.8$ Hz, 1 H), 2.36 – 2.26 (m, 1 H), 2.25 – 2.18 (m, 1 H); ^{13}C -NMR (150 MHz, CD_3OD) δ 162.4, 162.2, 160.6, 149.2, 128.4, 128.3, 125.9, 114.9, 114.6, 112.2, 106.7, 106.6, 100.3, 100.2, 73.5, 67.4, 52.4, 47.6, 44.8, 42.1, 40.5 (one sp^3 carbon signal is absent, possibly due to overlap with solvent); HRMS (ESI-TOF) calcd for $\text{C}_{22}\text{H}_{24}\text{Br}_4\text{ClN}_{10}\text{O}_2$ $[\text{M} + \text{H}^+]$ 810.8505; found 810.8494.

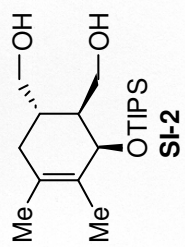


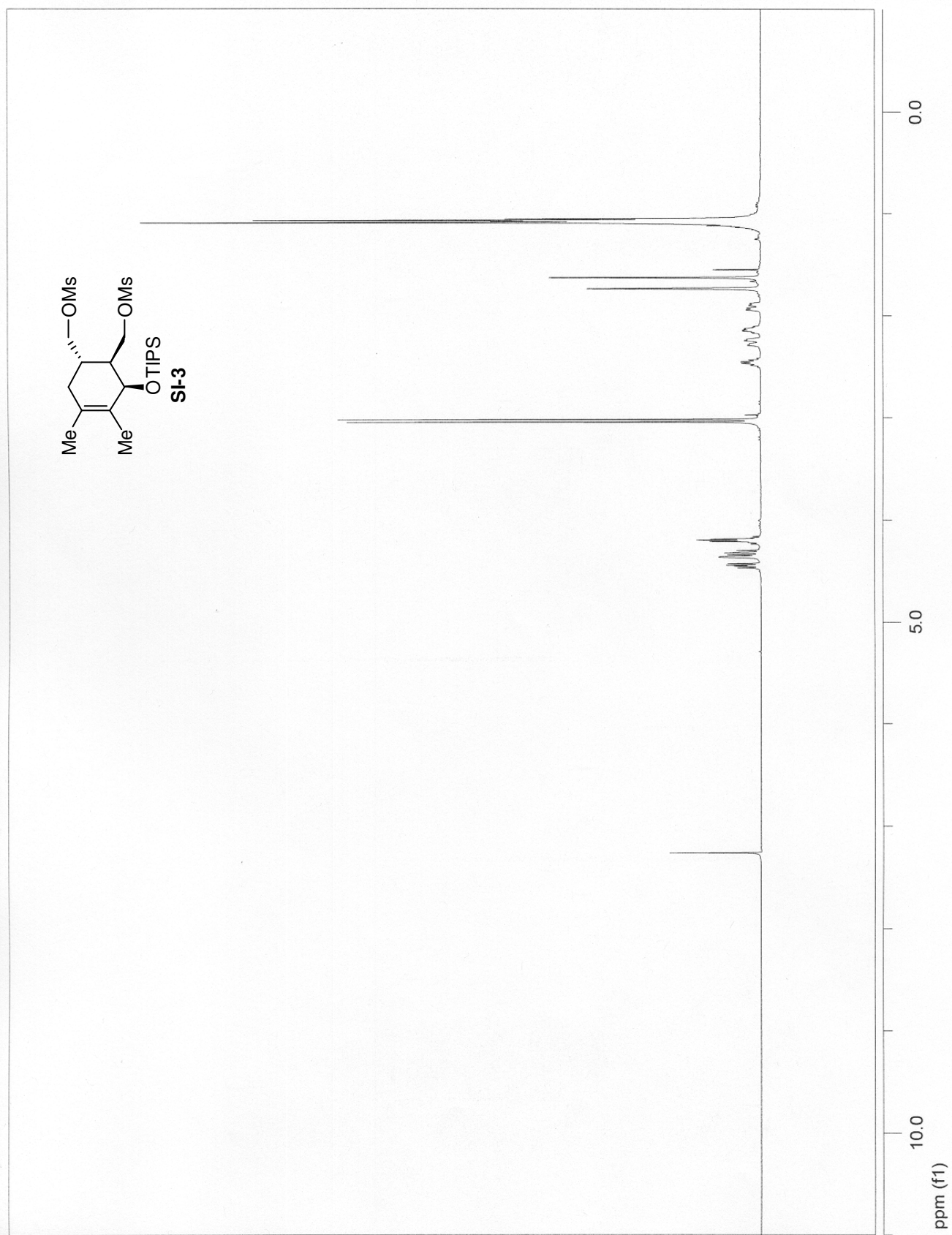


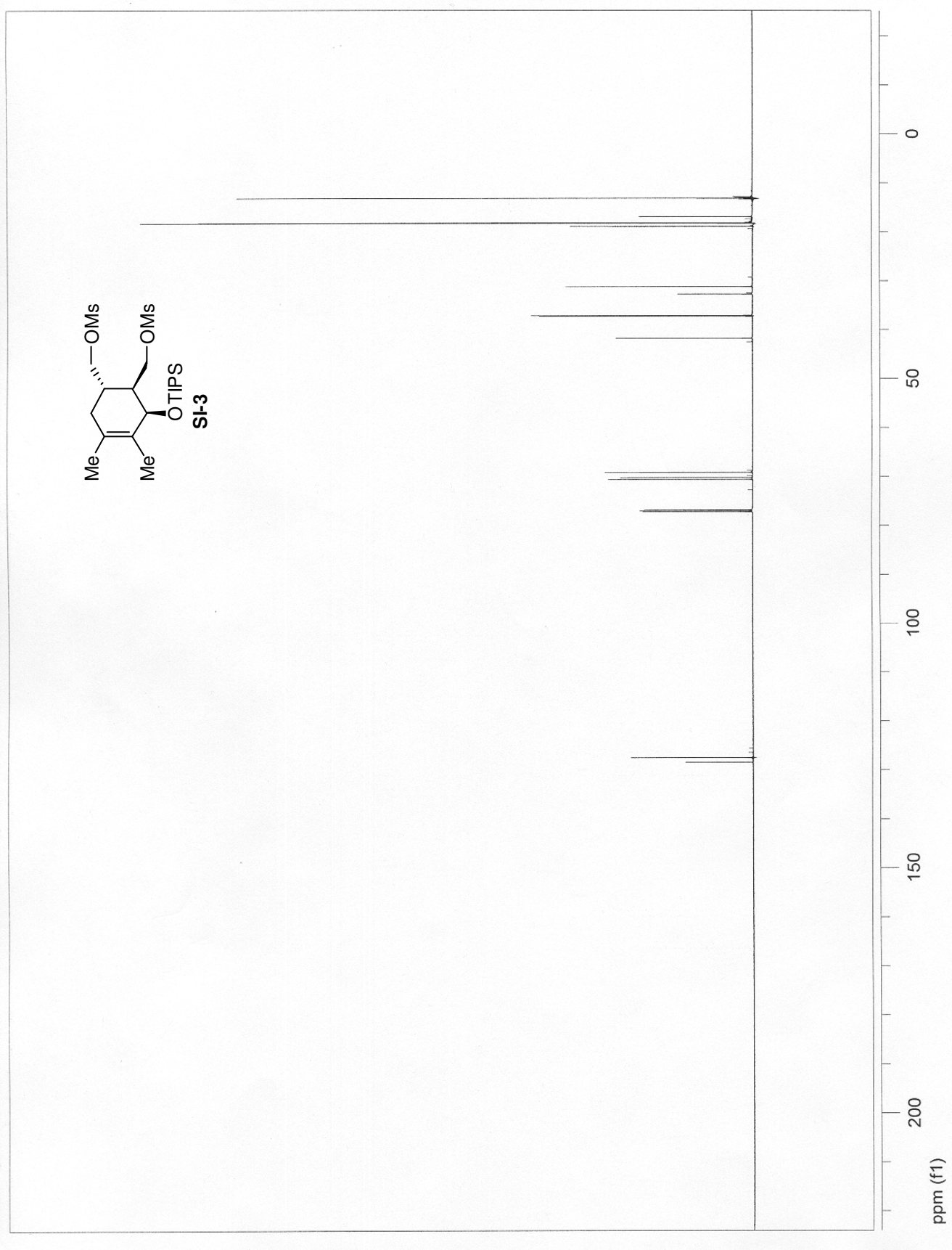


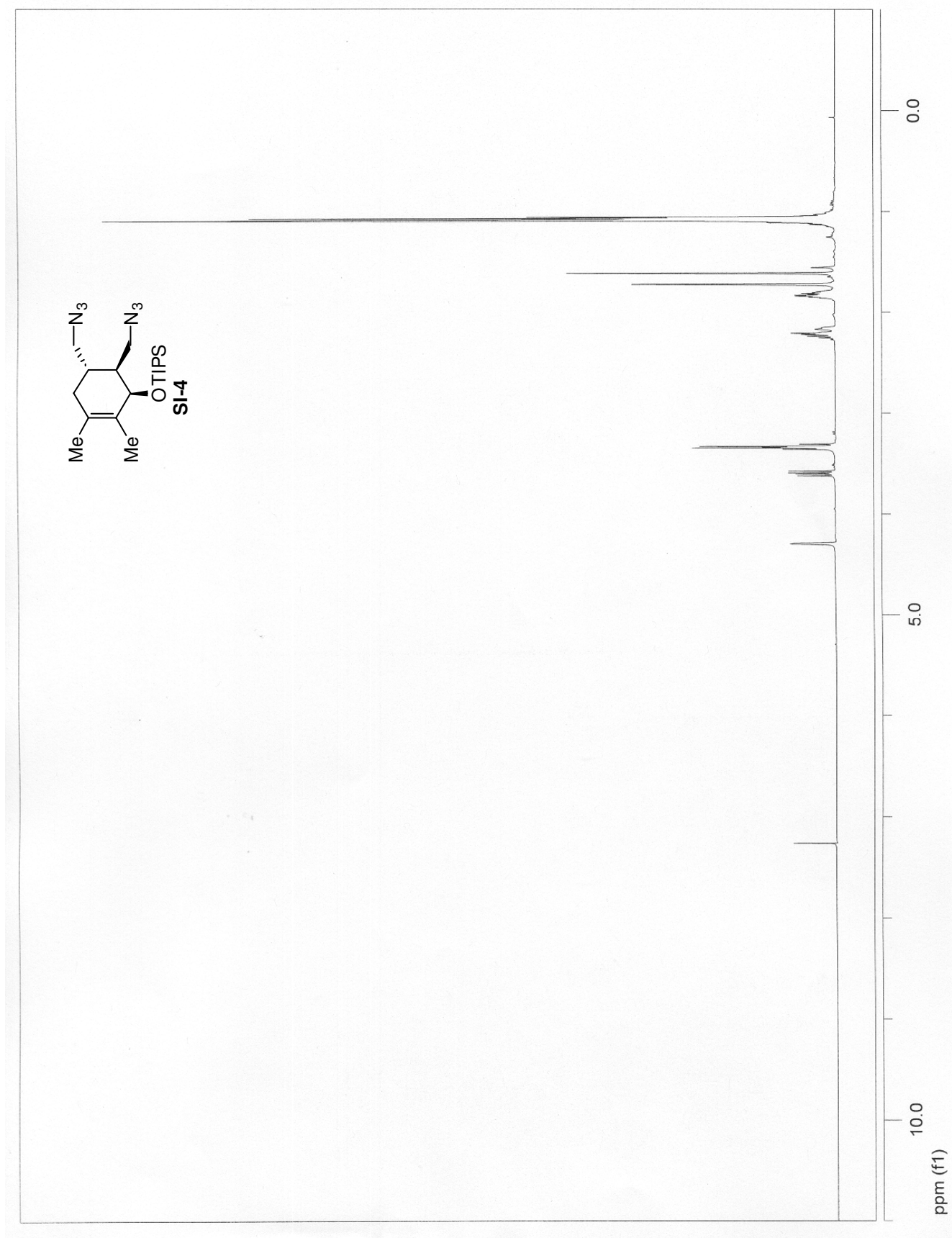


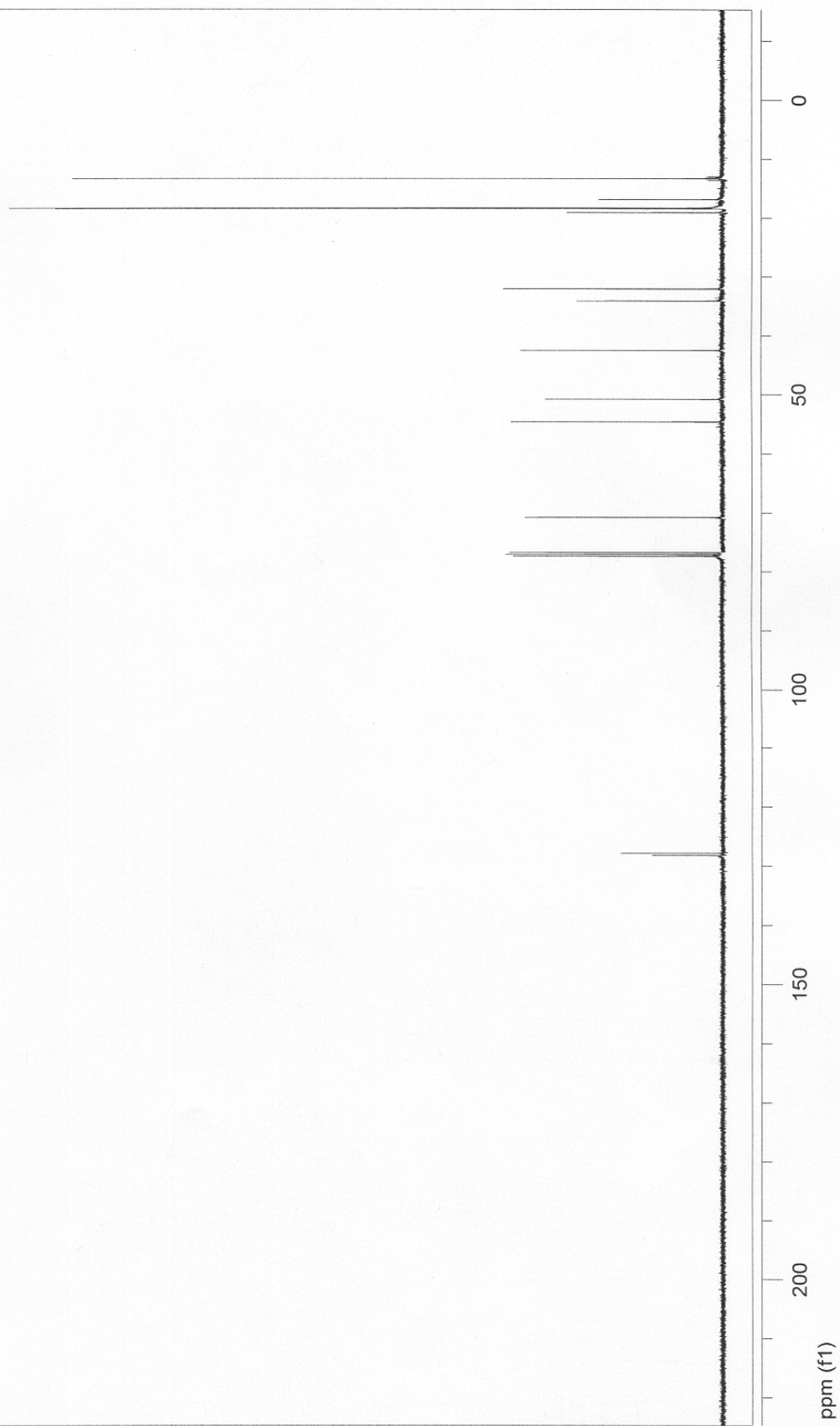
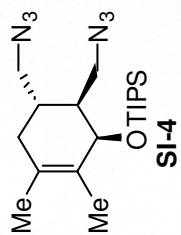


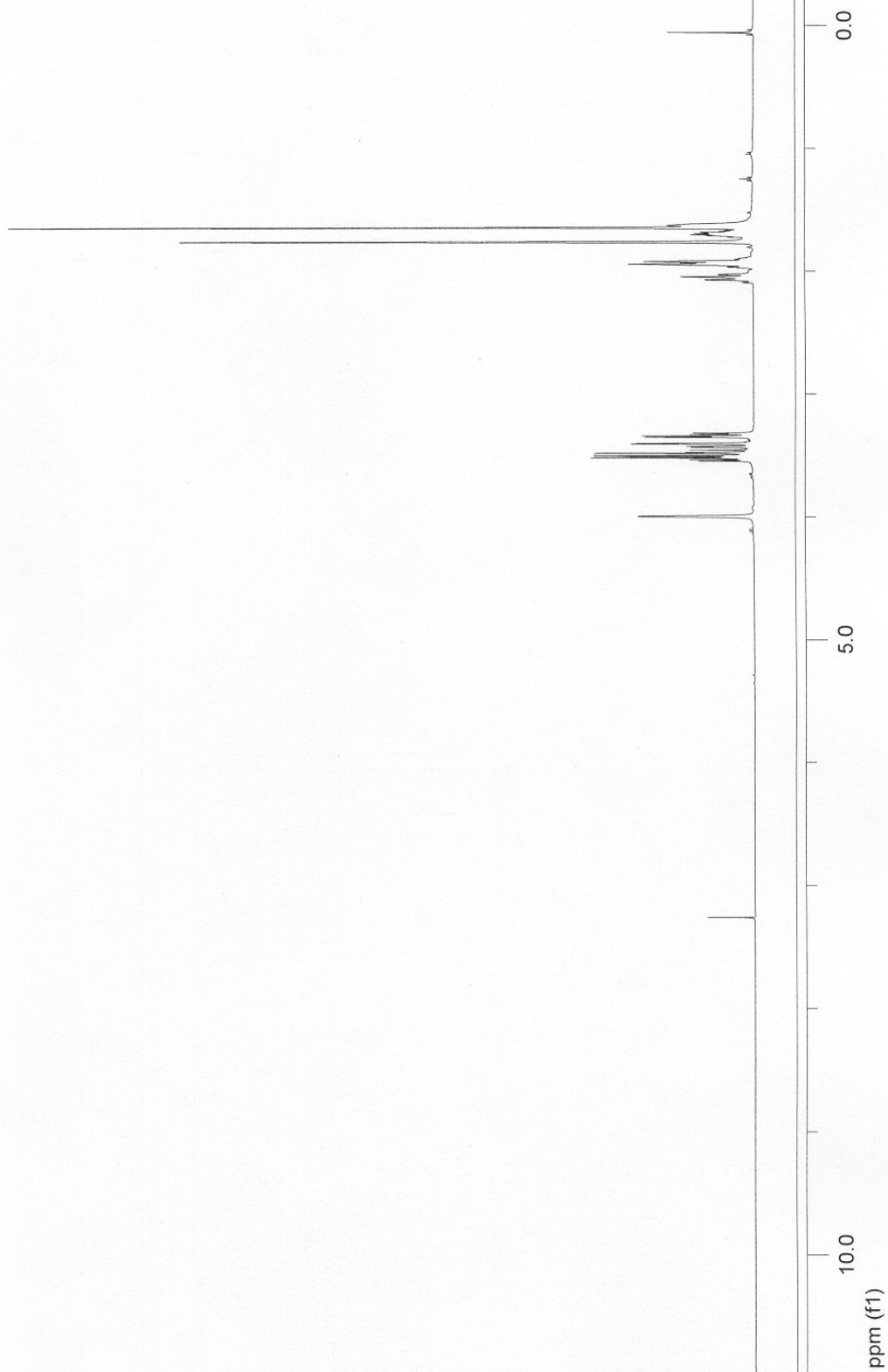
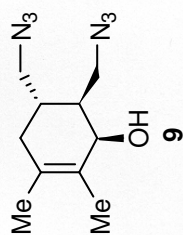


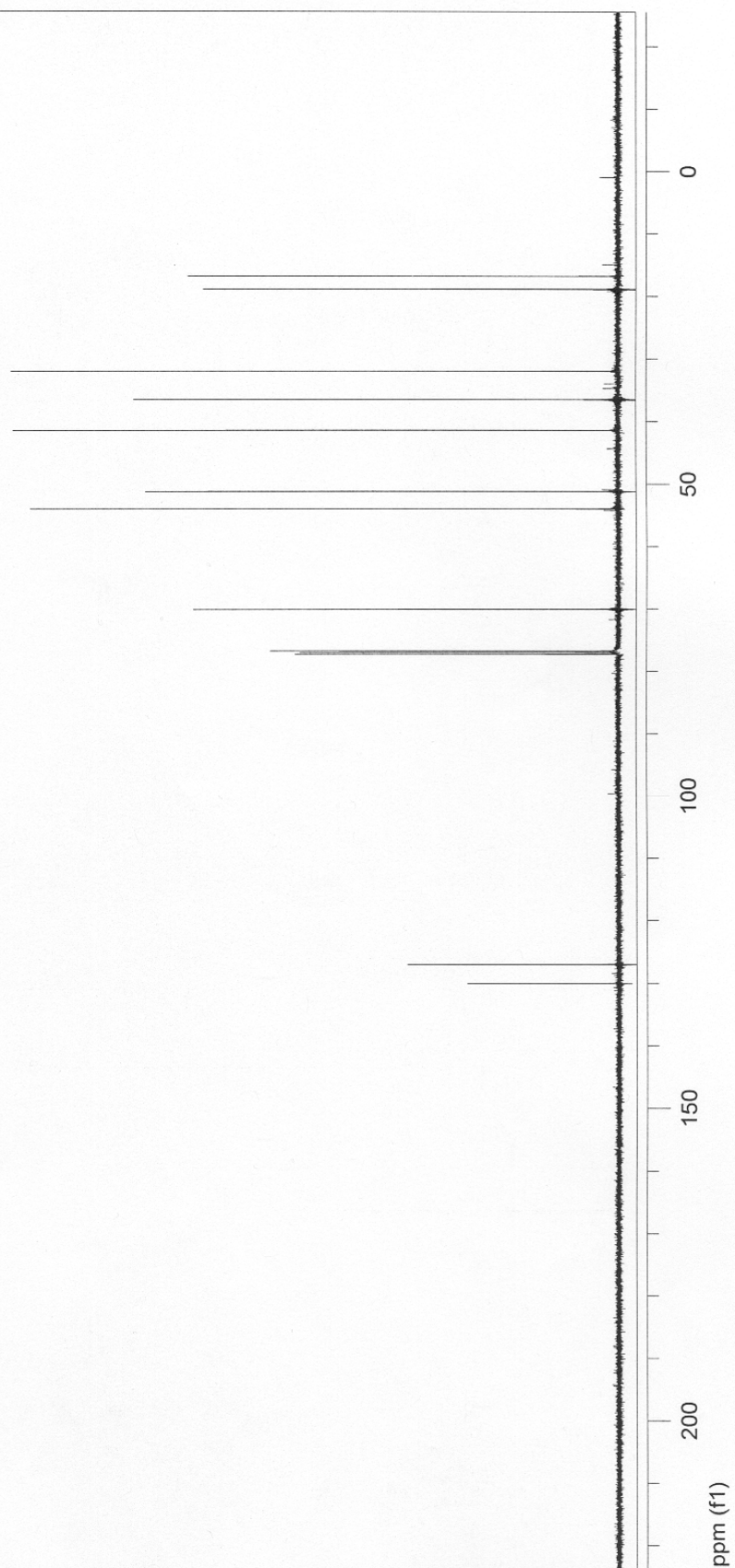
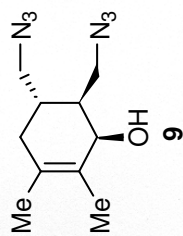


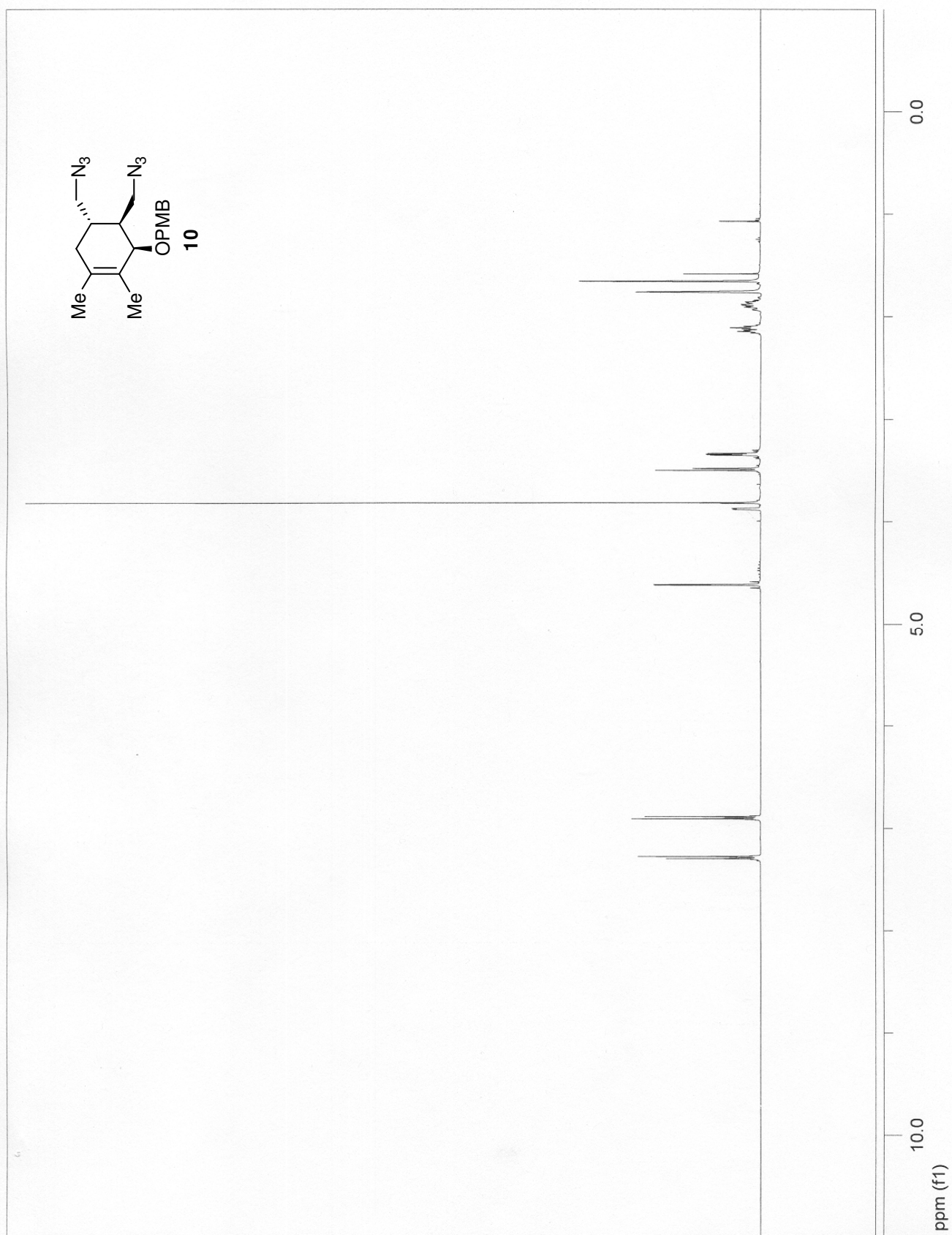


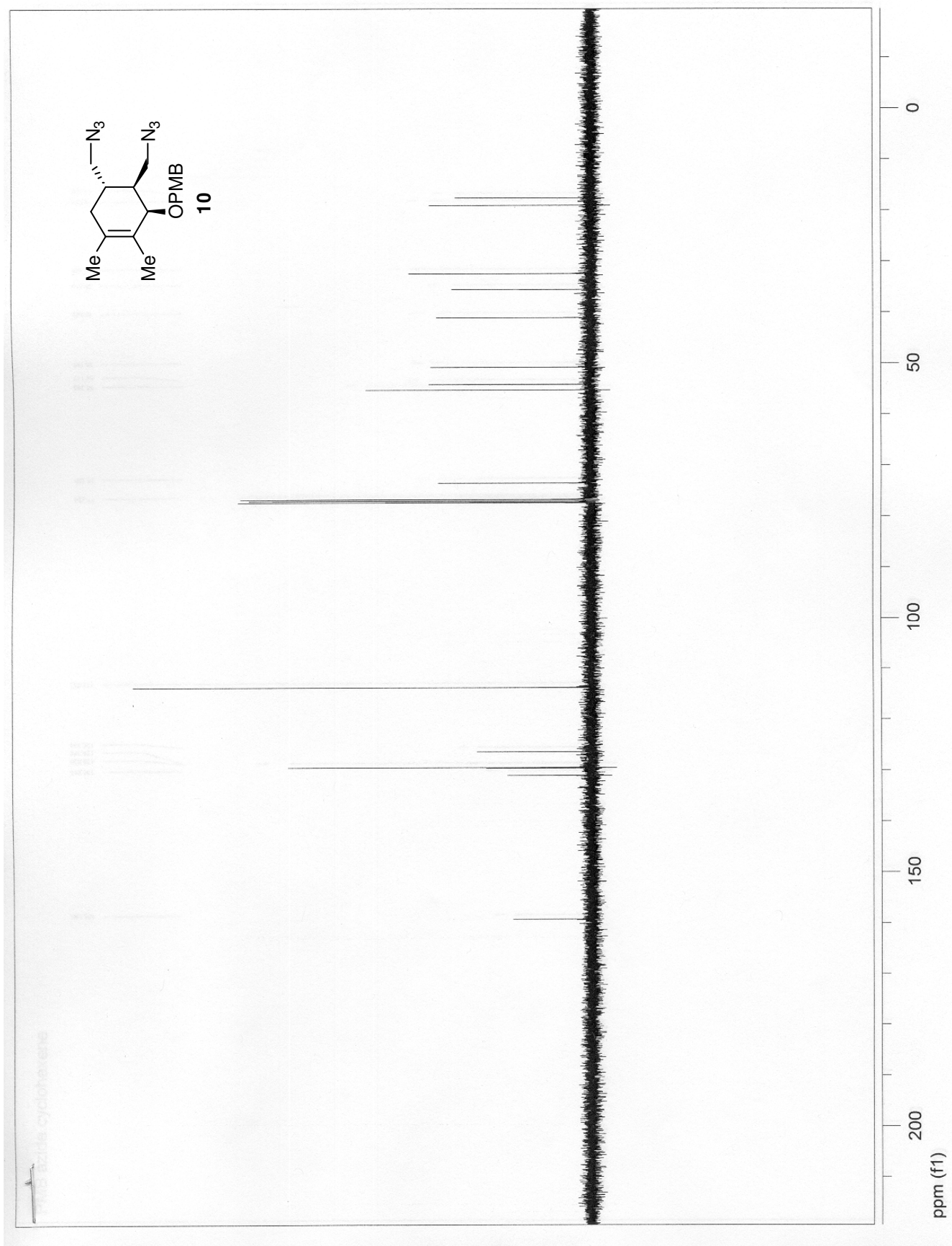




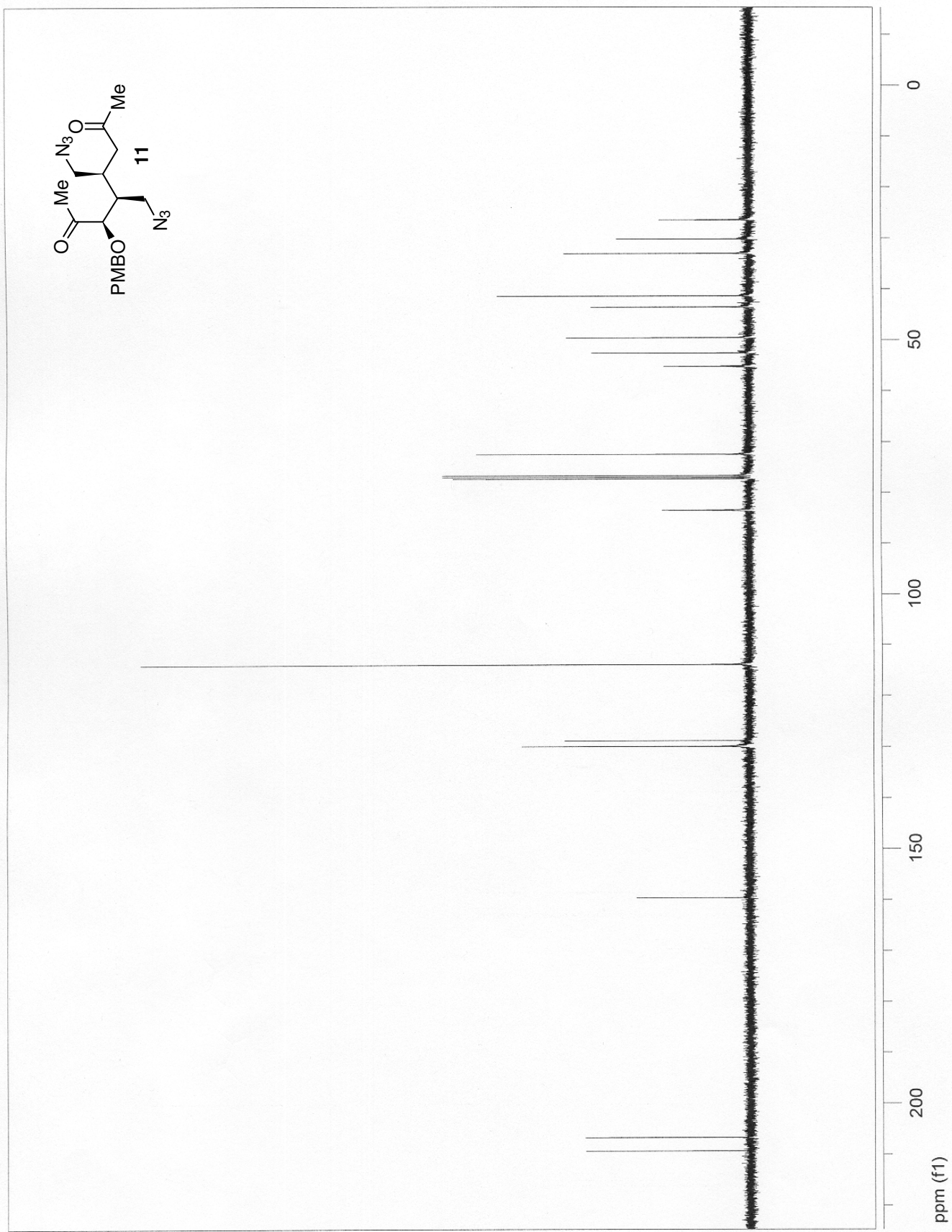


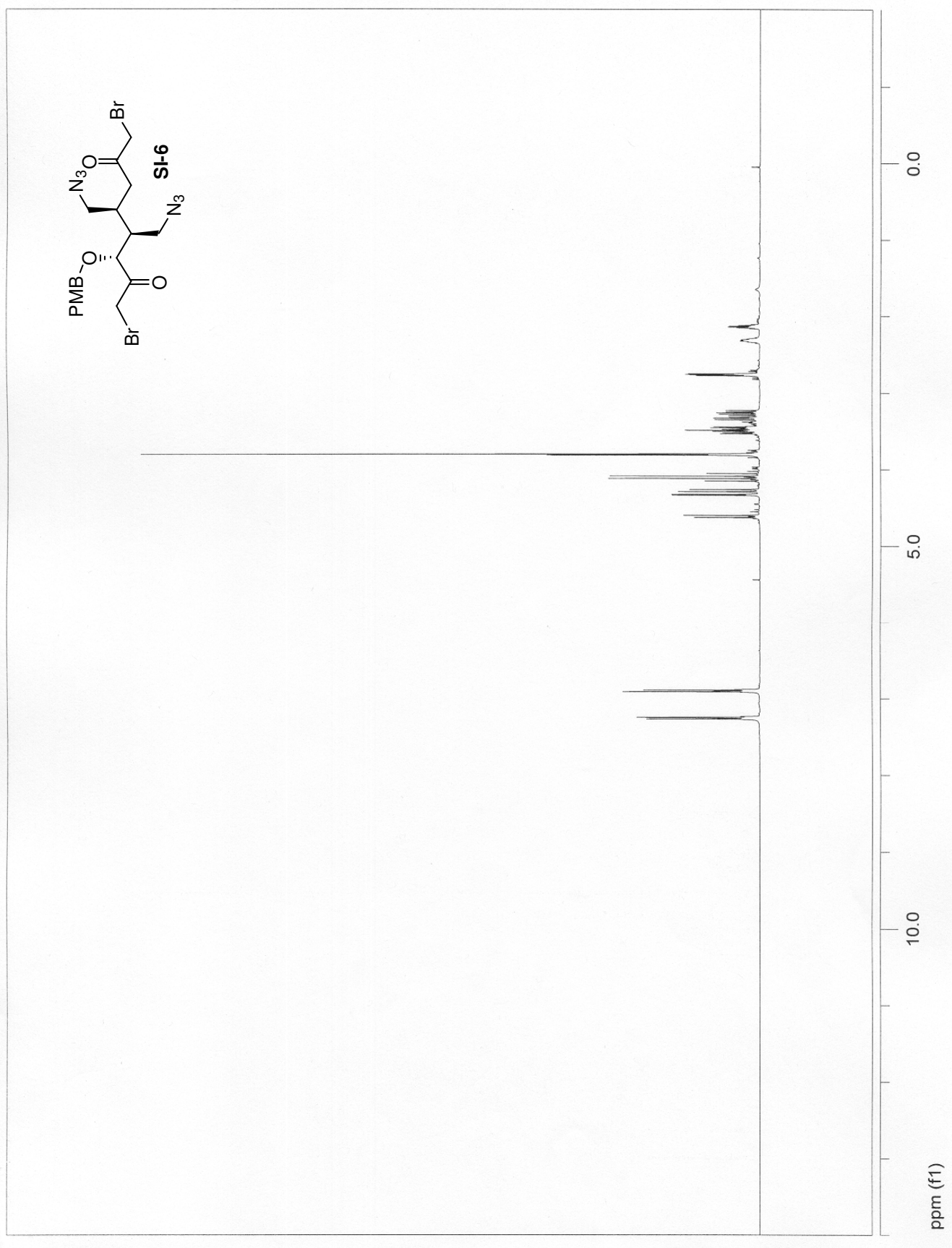




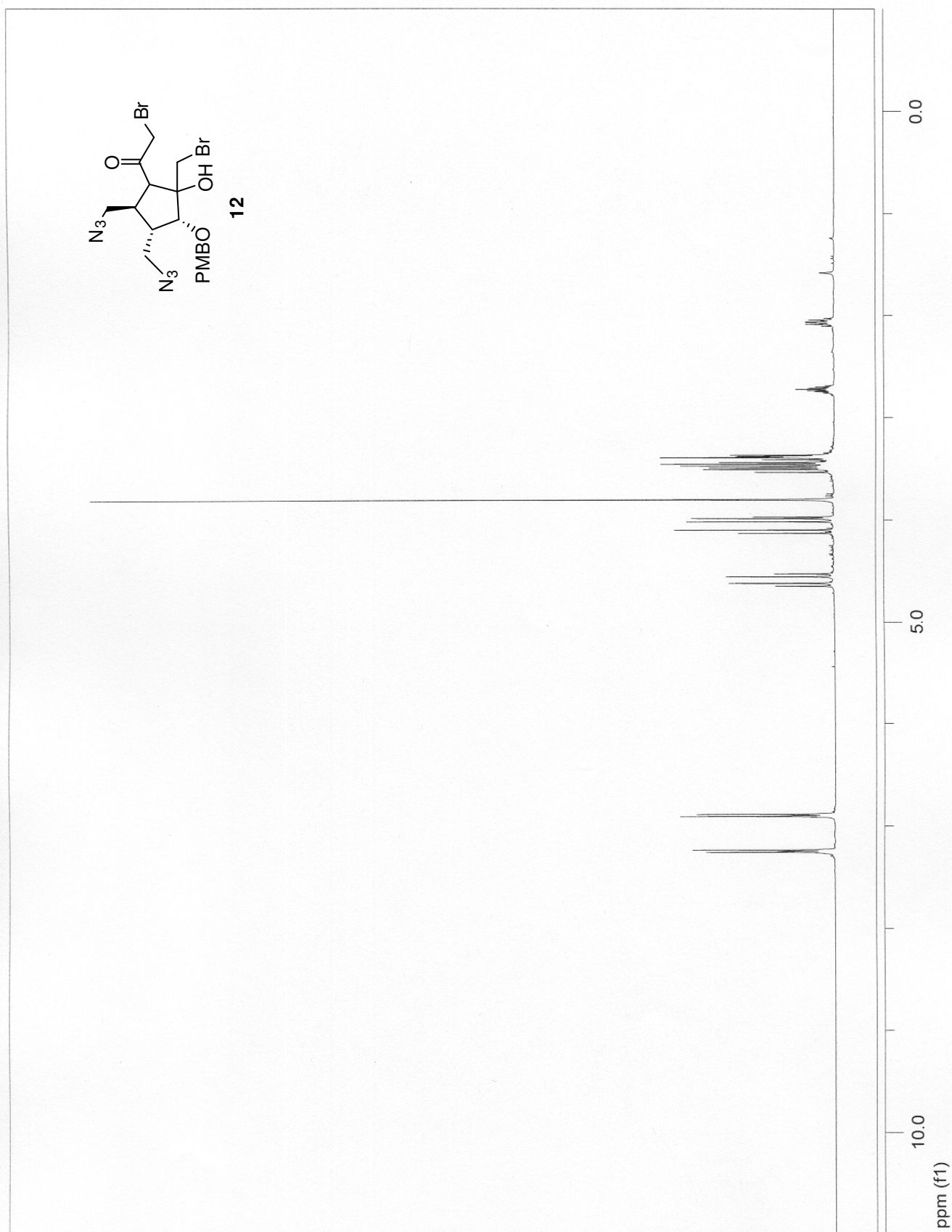
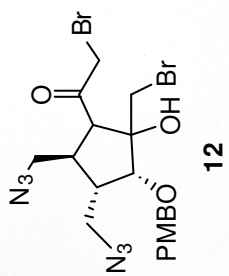


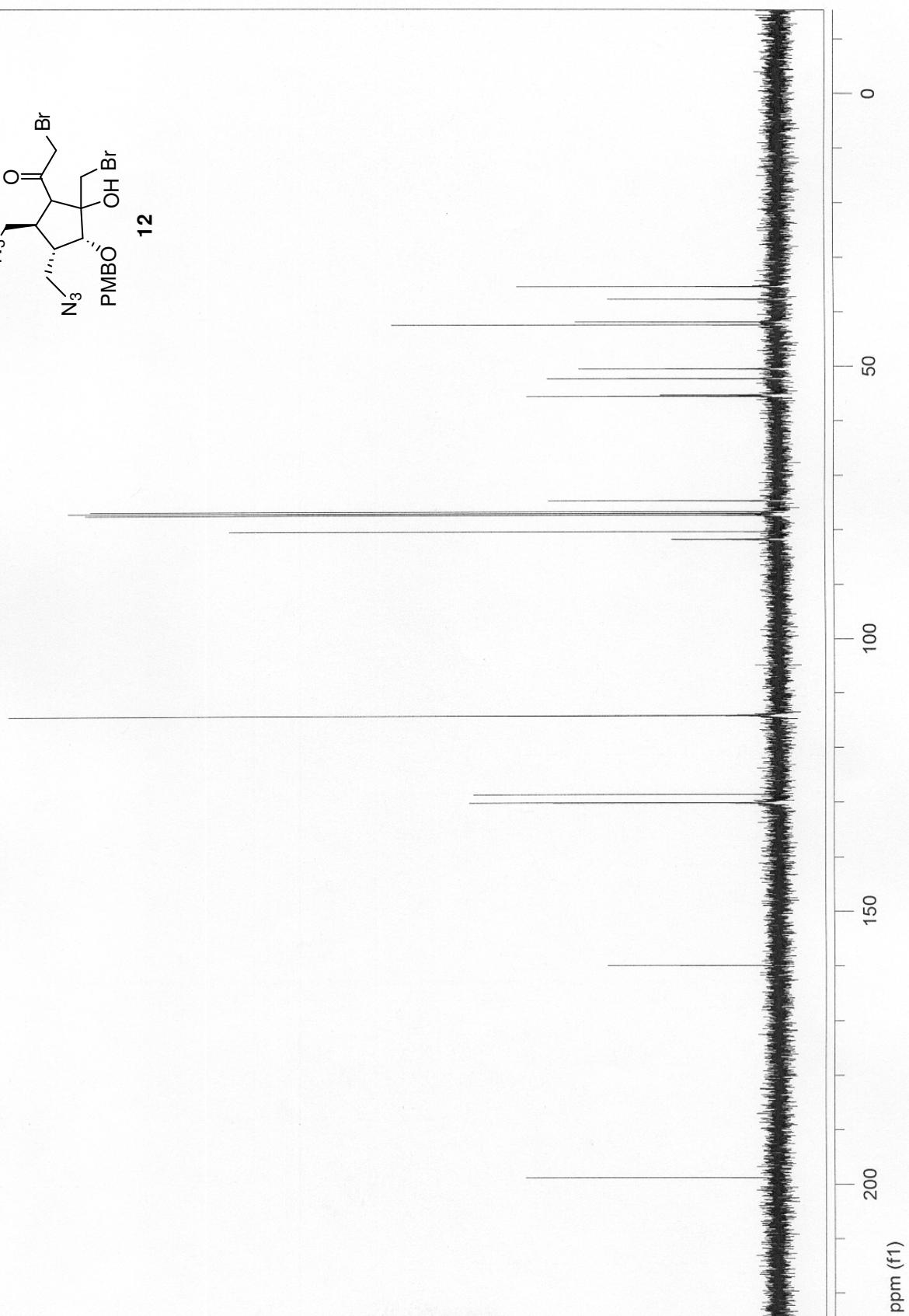
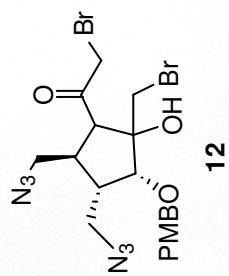


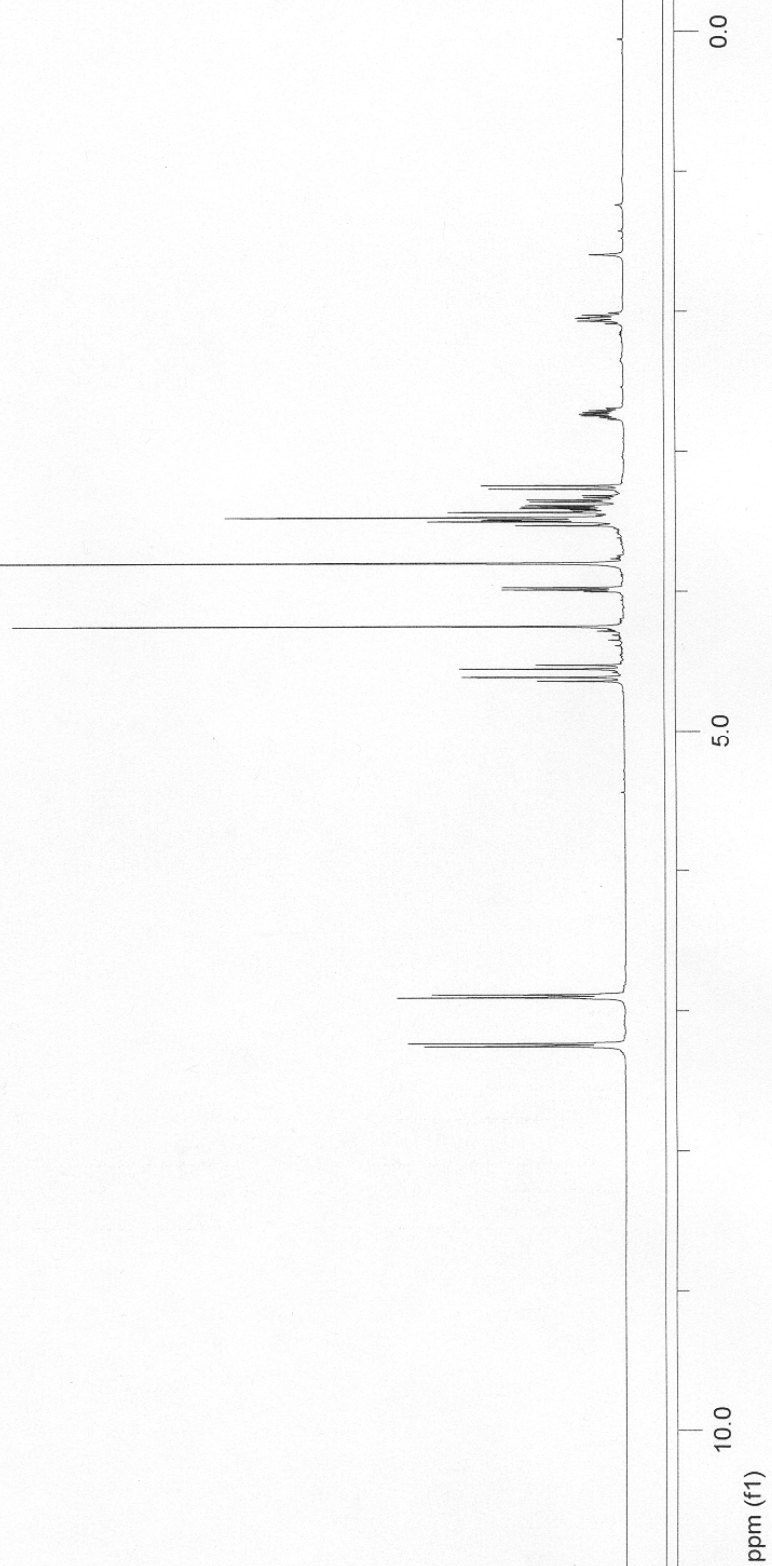
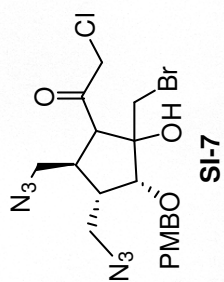


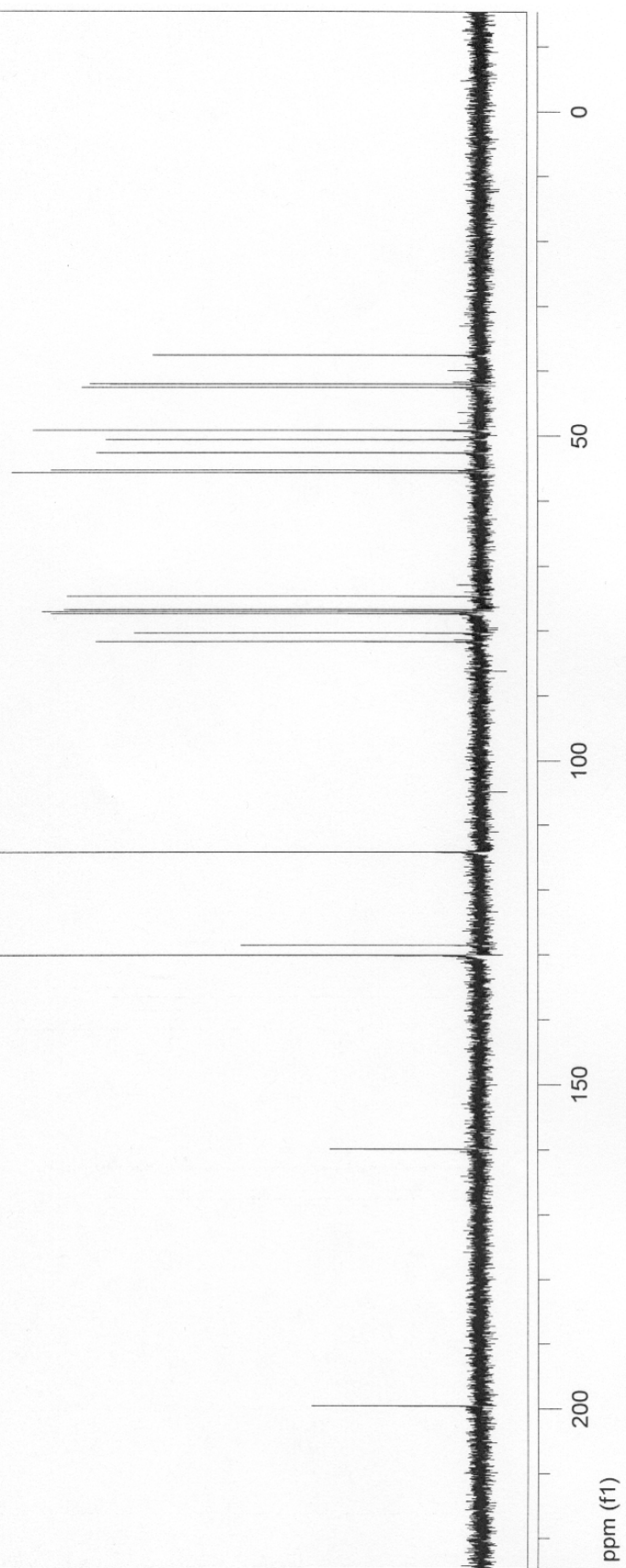
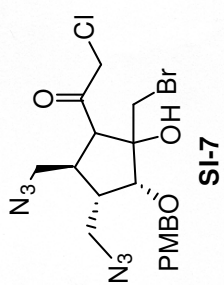


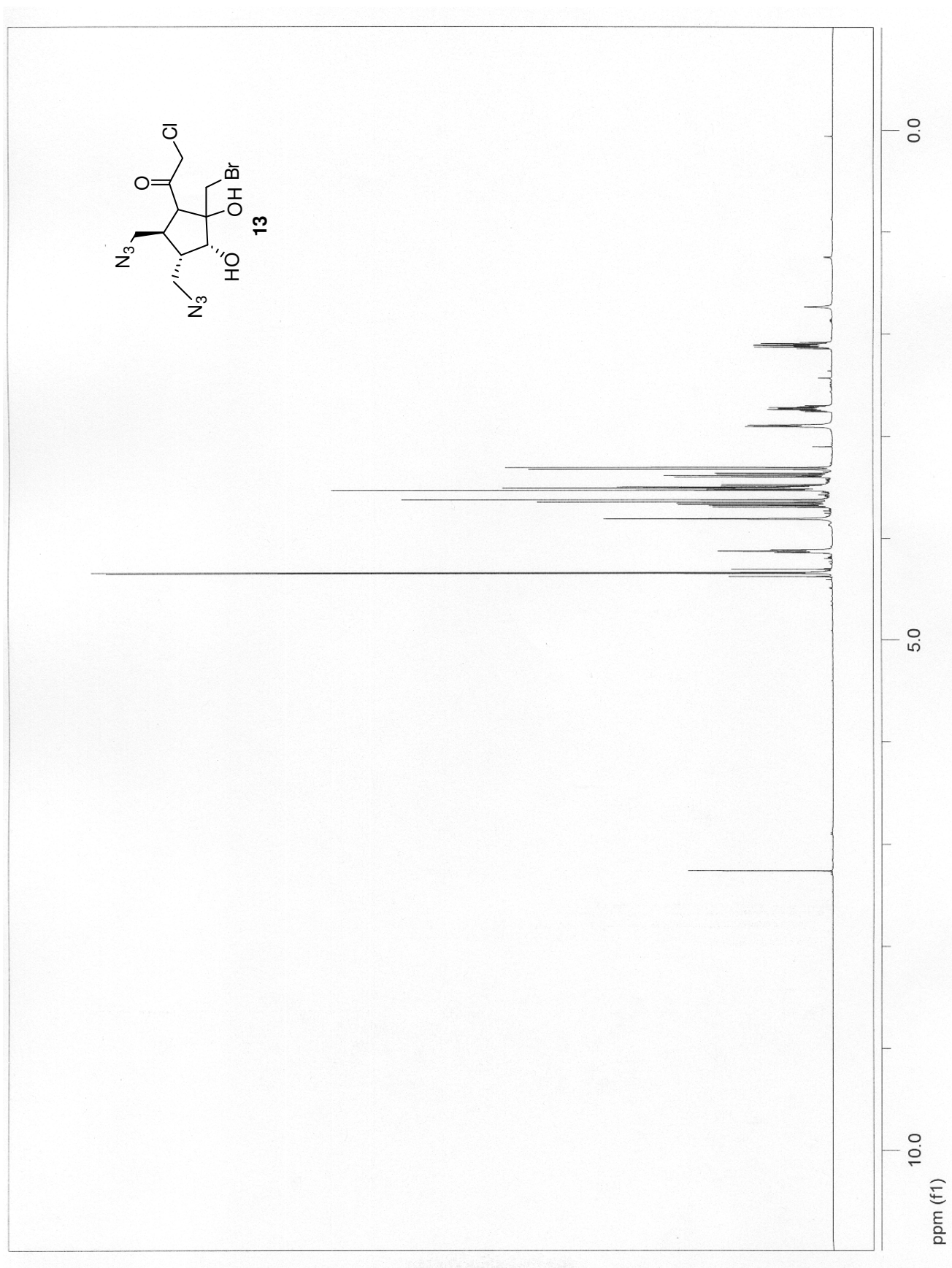


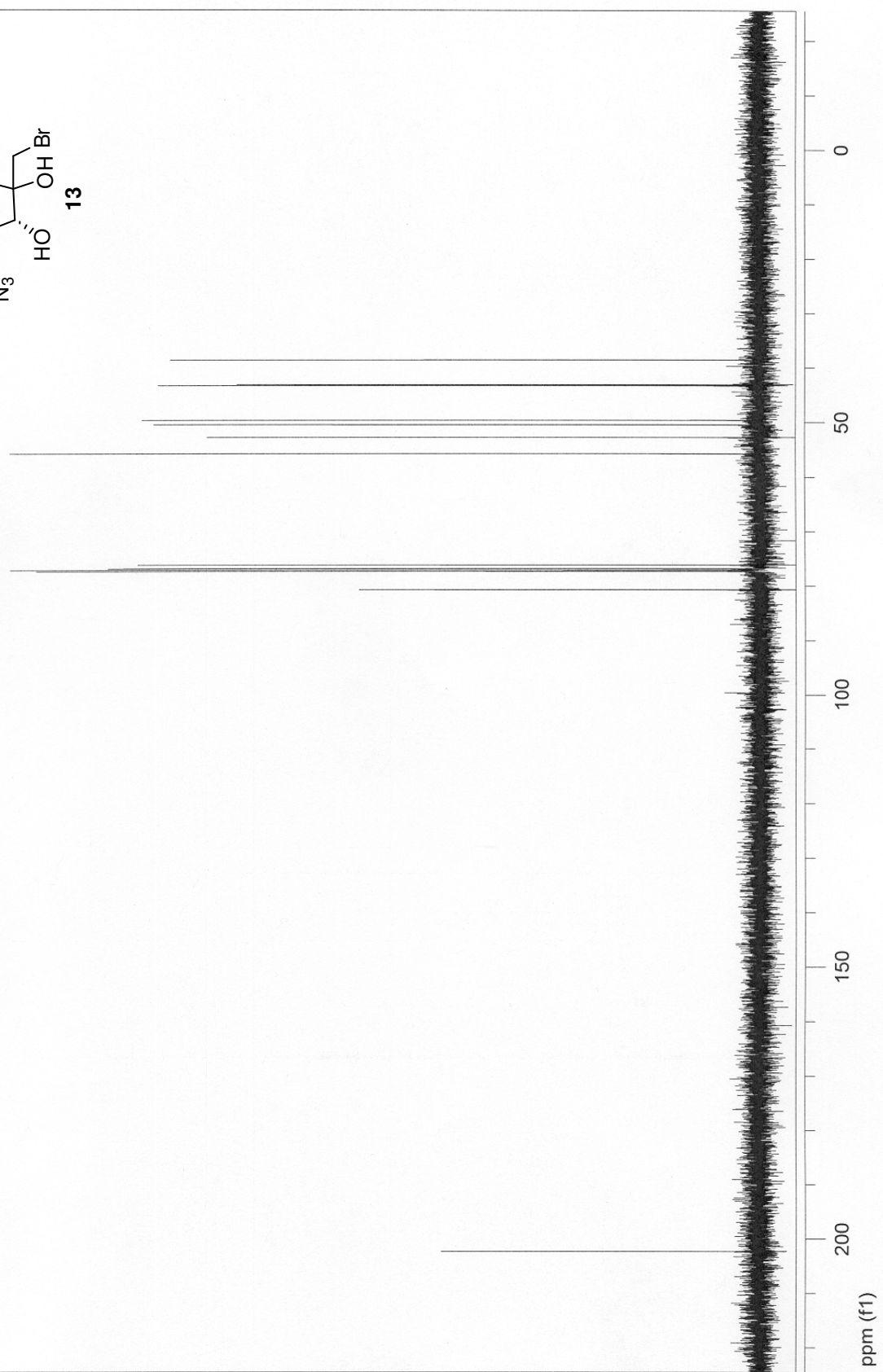
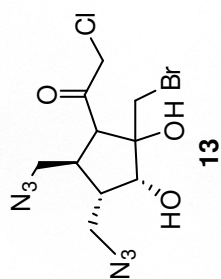




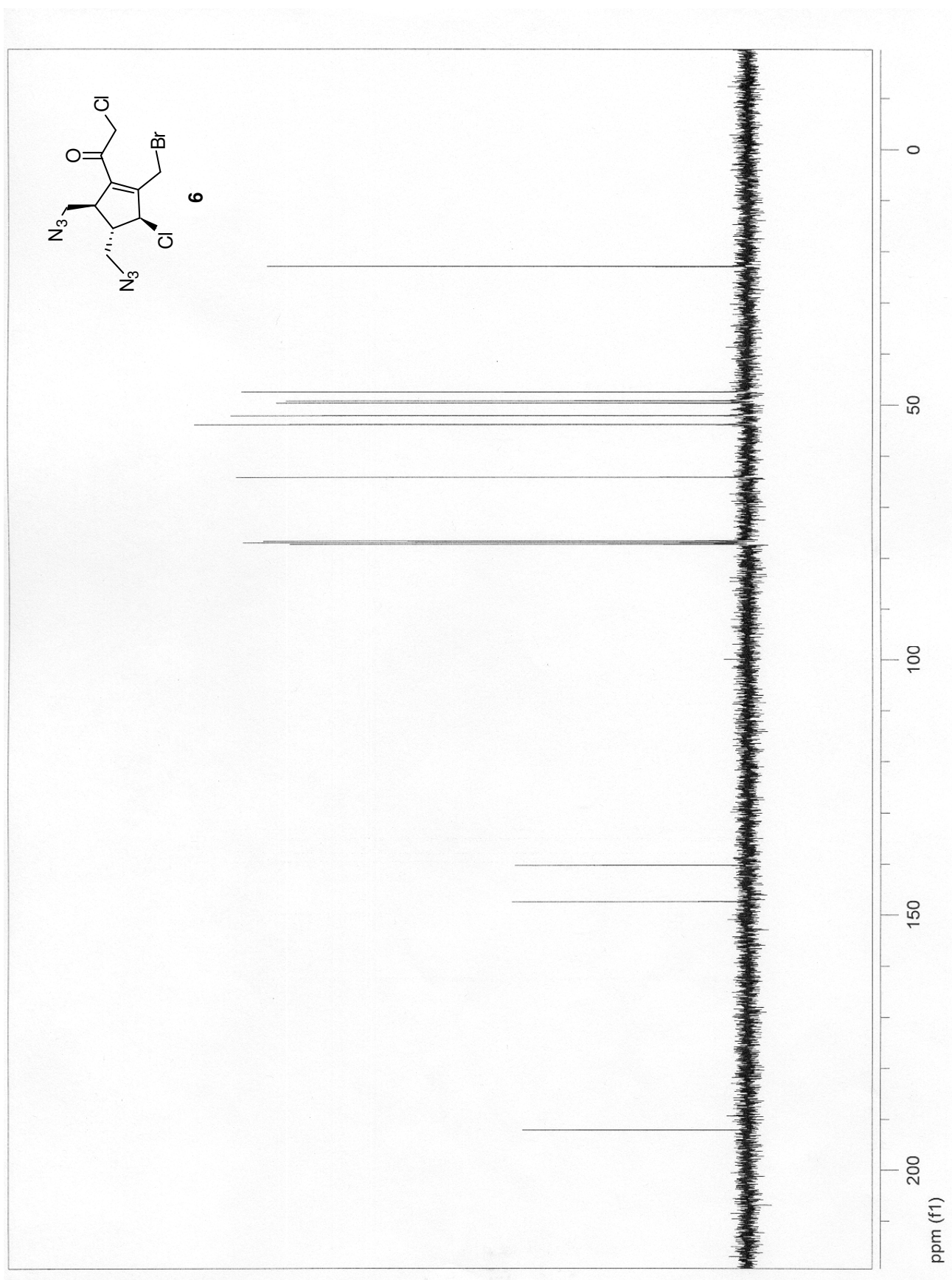


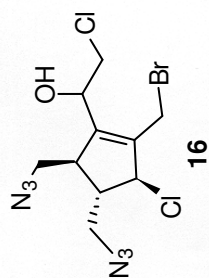




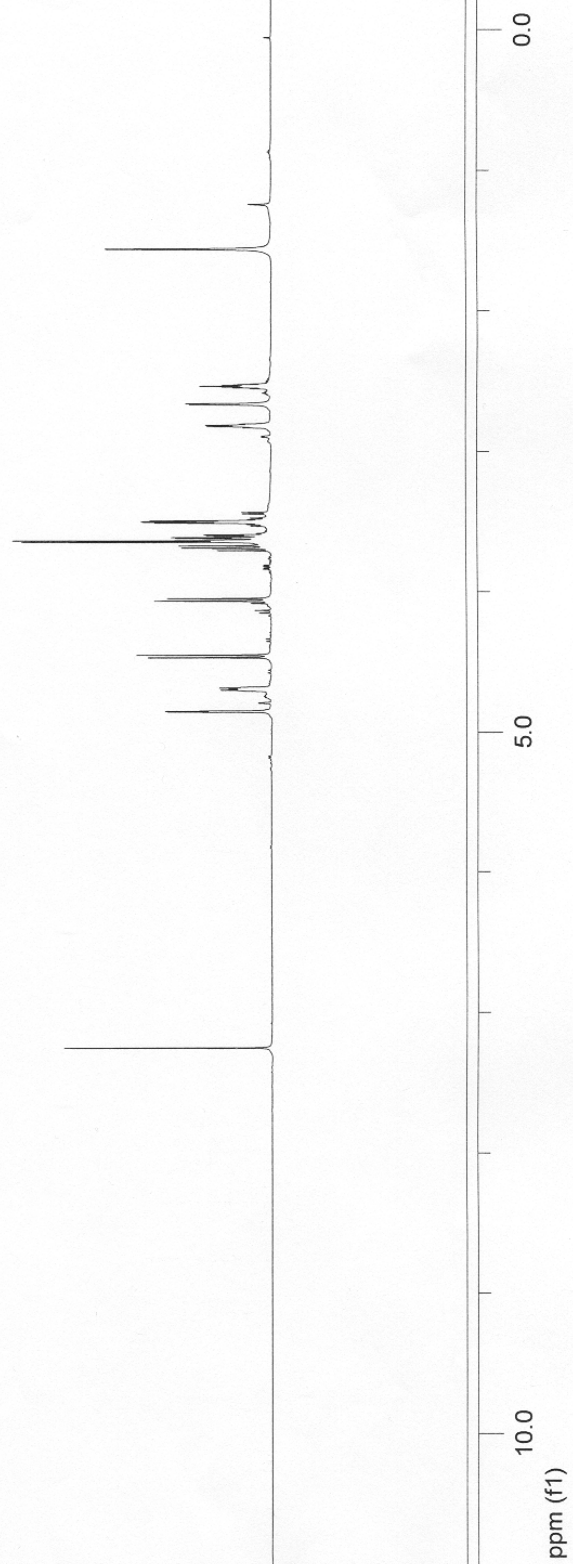


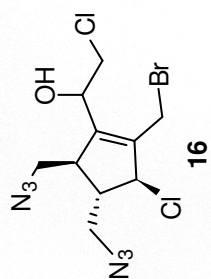




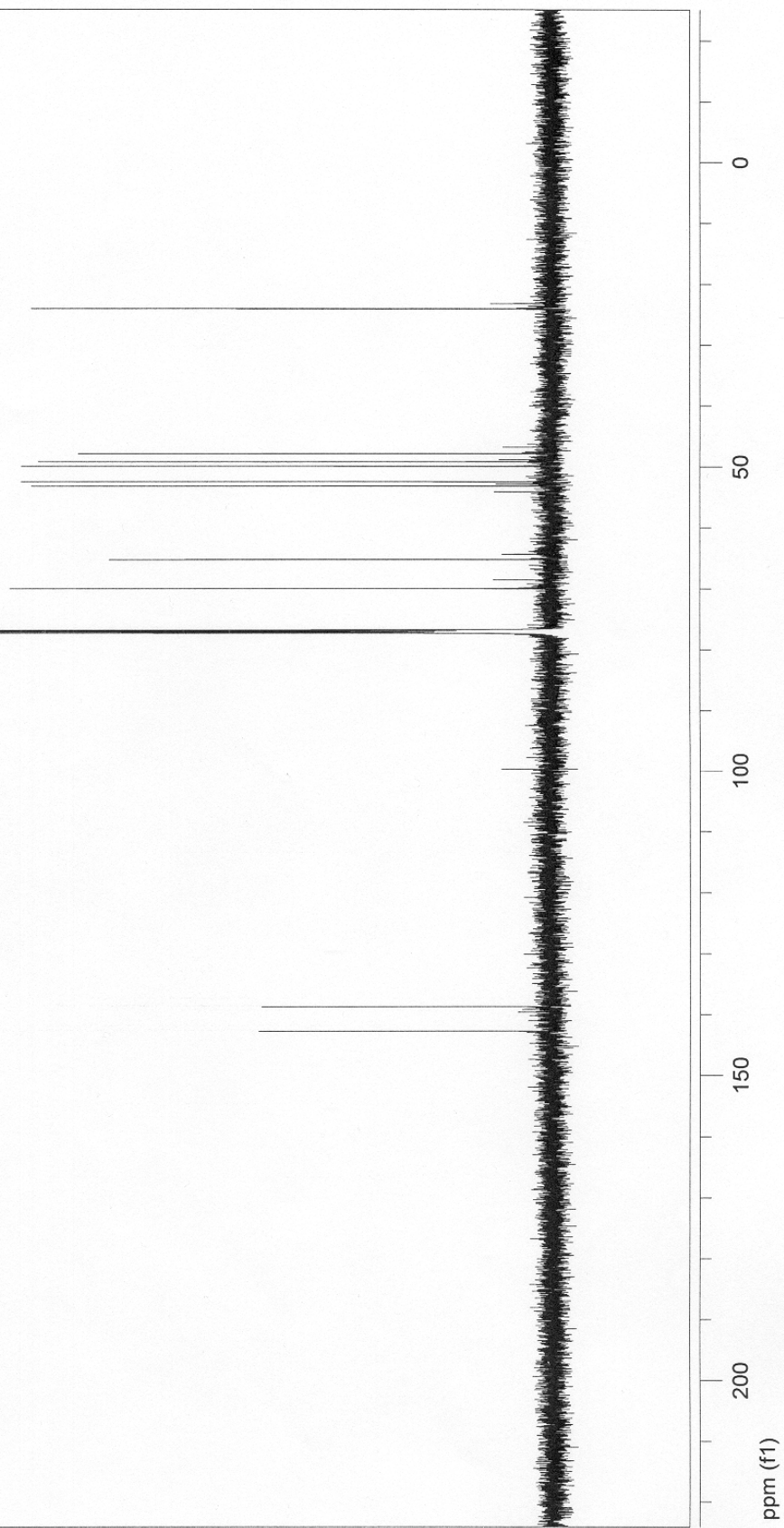


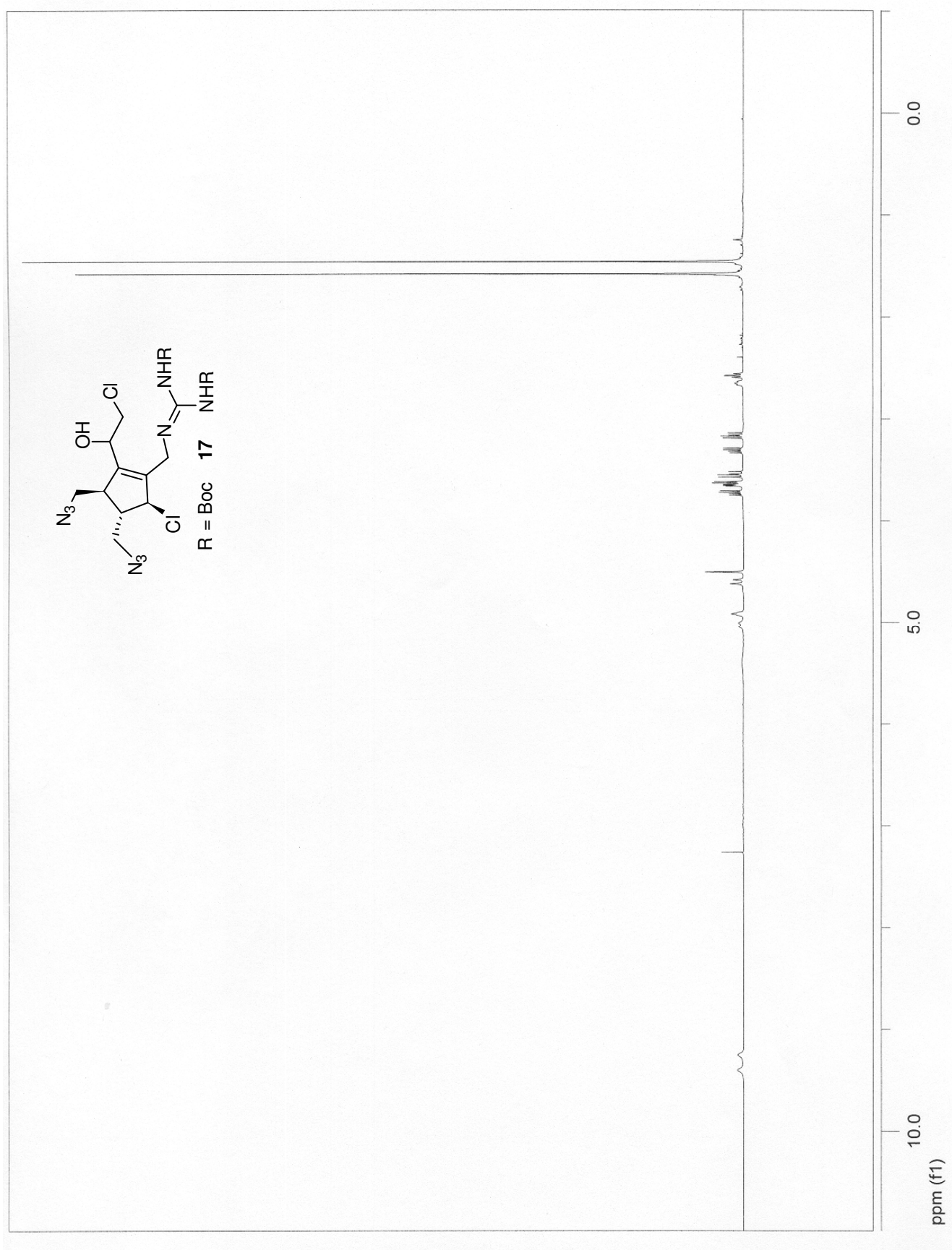
9:1 diastereomers

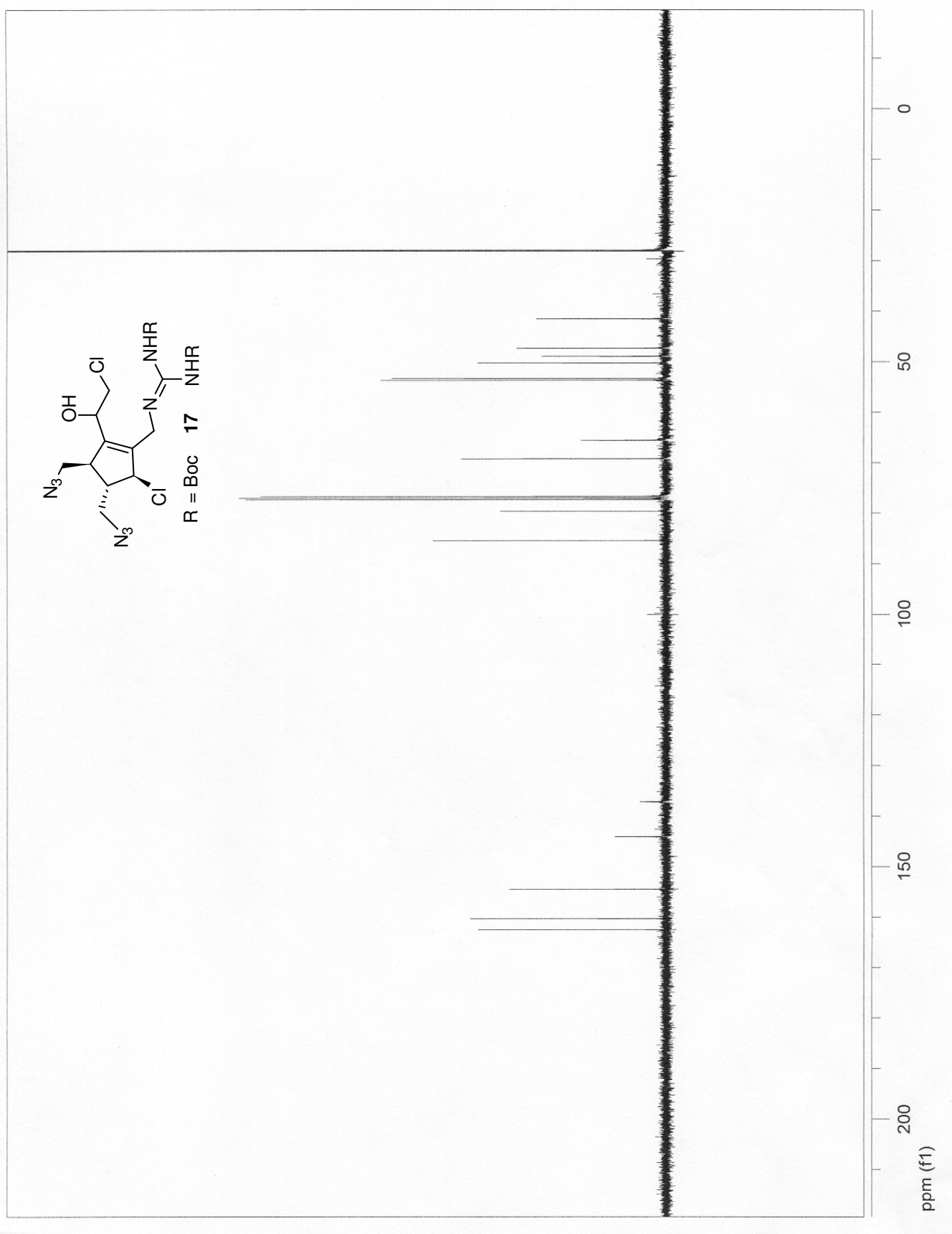


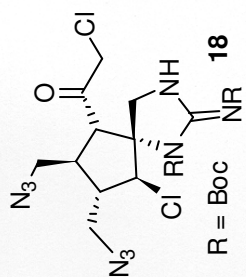


9:1 diastereomers









0.0

5.0

10.0

ppm (f1)

