Supporting Information

Total Synthesis of Pumiliotoxins 209F and 251D via Late-Stage, Nickel-Catalyzed Epoxide-Alkyne Reductive Cyclization

Katrina S. Woodin and Timothy F. Jamison

Department of Chemistry, Massachusetts Institute of Technology,

Cambridge, Massachusetts 02139

Table of Contents

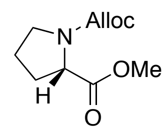
General Methods:

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. All commercially available materials were used as is, unless otherwise noted. Pyridine was distilled from CaH_2, and stored over 4Å molecular sieves. Acetone was distilled from K_2CO_3 and stored over 4Å molecular sieves. Na_2CO_3 was stored in an oven to keep dry prior to use. Tetrahydrofuran and diethyl ether were freshly distilled over blue solutions of sodium/benzophenone ketyl, and dichloromethane was distilled over calcium hydride.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates precoated with a fluorescent indicator or EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and ethanolic phosphomolybdic acid (PMA), cerium molybdate (CAM), or aqueous potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography)[1] of the indicated solvent system on Silicycle silica gel 60 (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$) on a 500MHz instrument. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded as a thin film between NaCl plates on a FT-IR transform spectrometer. High resolution mass spectra (HRMS) were obtained on a Fourier Transform Mass Spectrometer. Gas

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

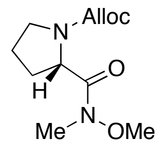
chromatography was performed on a chromatograph equipped with a Chiraldex B-OA column. Optical rotations were measured on a polarimeter.



6b

(*S*)-1-Allyl 2-methyl pyrrolidine-1,2-dicarboxylate (6b).[2] L-proline methyl ester hydrochloride (0.664 g, 4 mmol) was dissolved in CH_2Cl_2 (16 mL) and cooled to 0 ºC. To the stirring solution was added pyridine (0.808 mL, 10 mmol) and allyl chloroformate (0.638 mL, 6 mmol), and the solution was allowed to stir for 20 min as a white precipitate formed. The solution was allowed to warm to rt and was diluted with $CHCl_3$ (10 mL) which dissolved the precipitate. The solution was washed with sat. $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give alloc-protected ester **6b** as a colorless oil (848 mg, 99% yield). R_f 0.53 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 5.98-5.82 (m, 2H), 5.30 (t, *J* = 15.9 Hz, 2H), 5.27-5.16 (m, 2H), 4.64-4.56 (m, 2H), 4.53 (d, *J* = 5.3, Hz, 1H), 4.51 (d, *J* = 5.3, Hz, 1H), 4.38 (dd, *J* = 8.7, 3.8 Hz, 1H), 4.35 (dd, *J* = 8.7, 3.8 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.64-3.57 (m, 2H), 3.55-3.45 (m, 2H), 2.28-2.18 (m, 2H), 2.06-1.88 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 173.5, 173.3, 154.9, 154.3, 133.1, 133.0, 117.5, 117.1, 66.1, 66.0, 59.3, 59.0, 52.4, 52.3, 47.0, 46.5, 31.1, 30.1, 24.5, 23.7. IR (thin film NaCl) 2955, 2883, 1750, 1708, 1408, 1350, 1202, 1174, 1129, 1089 cm^{-1}. HRMS (ESI) *m/z* 236.0897 [M+Na; calcd for $C_{10}H_{15}NO_4$: 236.0893]. $[\alpha]_D$ = –51.0 (23 ºC, 589 nm, 75.76 g/100 mL, $CHCl_3$).

[2] Yamada, Y.; Takahashi, W.; Asada, Y.; Holiuchi, J.; Takeda, K.; Harigaya, Y. *Chem. Pharm. Bull.* **2004**, *52*, 1082-1085.

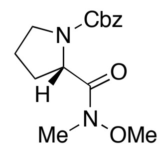


7b

(*S*)-Allyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (7b). *N-O*-dimethylhydroxylamine hydrochloride (9.95 g, 102 mmol) was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 ºC. Trimethylaluminium (51 mL, 102 mmol) was added and the reaction was allowed to stir 10 min at 0 ºC, then warmed to rt and stirred for 20 min. The ester **6b** was added (7.26 g, 34 mmol), and the reaction stirred for an additional 5 h at rt. The reaction was quenched with ether (200 mL) and Rochelle's salt (300 mL) and stirred for 2 h. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organics were washed with brine (500 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (1:19 MeOH:EtOAc) to give alloc-protected Weinreb amide **7b** as a colorless oil (7.84 g, 95% yield). R_f 0.41 (1:9 MeOH:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as 1:0.6 mixture of rotamers, asterisk denotes minor rotamer peaks[3]) δ 5.97-5.82 (m, 1H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.25* (dd, *J* = 17.2, 1.4 Hz, 0.6H), 5.19 (dd, *J* = 10.5, 1.4, 1H), 5.15* (dd, *J* = 10.5, 1.4, 0.6H), 4.76-4.65 (m, 1H), 4.63-4.53 (m, 2H), 3.78 (s, 3H), 3.71* (s, 1.8H), 3.66-3.61 (m, 1H), 3.57-3.46 (m, 1H), 3.20 (s, 3H), 3.19* (s, 1.8H), 2.27-2.15 (m, 1H), 2.08-1.97 (m, 1H), 1.96-1.82 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) (1.6:1 mixture of rotamers) δ 173.3, 172.8, 154.7, 154.1, 133.1, 133.0, 117.1, 117.0, 65.7, 65.6, 61.3, 56.9, 56.5, 47.1, 46.6, 32.3, 32.1, 30.6, 26.6, 24.2, 23.3. IR (thin film NaCl) 2979, 2882, 1737, 1707, 1676, 1409, 1354, 1243, 1175, 1122, 997 cm$^-$

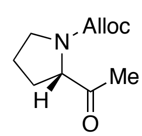
[3] When minor rotamer overlaps with major, no asterisk is indicated.

[1]. HRMS (ESI) *m/z* 243.1335 [M+H; calcd for $C_{11}H_{18}N_2O_4$: 243.1339]. $[\alpha]_D = -13.7$ (23 ºC, 589 nm, 39.59 g/100 mL, $CHCl_3$).



7a

(*S*)-benzyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (7a). Followed same procedure as **7b**, to produce **7a** in 75% yield. Spectral data were consistent with those previously reported.[4] ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 7.37-7.28 (m, 10H), 5.12-5.03 (m, 4H), 4.78 (d, *J* = 7.7 Hz, 1H), 4.65 (d, *J* = 7.7 Hz, 1H), 3.80 (s, 3H), 3.70-3.64 (m, 2H), 3.60-3.44 (m, 2H), 3.34 (s, 3H), 3.22 (s, 3H), 3.09 (s, 3H), 2.24-2.16 (m, 2H), 2.14-1.95 (m, 2H), 1.93-1.85 (m, 4H). HRMS (ESI) *m/z* 315.1314 [M+Na; calcd for $C_{15}H_{20}N_2O_4$: 315.1315].

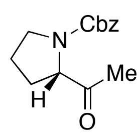


4b

(*S*)-Allyl 2-ethanoylpyrrolidine-1-carboxylate (4b). The Weinreb amide **7b** (5.33 g, 22 mmol) was dissolved in ether (280 mL) and cooled to 0 ºC. Methylmagnesium bromide (18 mL, 54 mmol) in ether (50 mL) was added to the flask with vigorous stirring, and was allowed to warm to rt over 2 h. The reaction was quenched with sat. NH_4Cl (200 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organics were washed with brine (500 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7

[4] De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem*. **2001**, *66*, 2534-2537.

EtOAc:hexanes) to give alloc-protected ketone **4b** as a pale yellow oil (4.07 g, 94% yield).[5] R_f 0.26 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 5.95-5.81 (m, 2H), 5.30 (dd, J = 17.2, 1.4 Hz, 1H), 5.23 (dd, J = 17.2, 1.4 Hz, 1H), 5.19 (dd, J = 10.4, 1.1 Hz, 1H), 5.16 (dd, J = 10.4, 1.1 Hz, 1H), 4.59-4.49 (m, 4H), 4.38 (dd, J = 8.5, 4.5 Hz, 1H), 4.29 (dd, J = 8.5, 4.5 Hz, 1H), 3.61-3.46 (m, 4H), 2.25-2.11 (m, 2H), 2.17 (s, 3H), 2.12 (s, 3H), 1.91-1.82 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 208.1, 207.7, 155.1, 154.5, 133.1, 132.8, 117.9, 117.6, 66.2, 65.7, 47.4, 46.8, 30.0, 28.9, 27.0, 26.1, 24.6, 23.8. IR (thin film NaCl) 2980, 2956, 2883, 1703, 1649, 1409, 1354, 1190, 1165, 1125, 1092, 988, 769 cm^{-1}. HRMS (ESI) m/z 220.0949 [M+Na; calcd for $C_{10}H_{15}NO_3$: 220.0944]. $[\alpha]_D$ = –72.3 (23 ºC, 589 nm, 0.65 g/100 mL, $CHCl_3$).

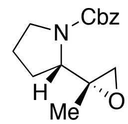


4a

(*S*)-benzyl 2-ethanoylpyrrolidine-1-carboxylate (4a). Followed same procedure as **4b**, to produce **4a** in 47% yield. Spectral data were consistent with those previously reported.[6] ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 7.34-7.26 (m, 10H), 5.19-5.07 (m, 4H), 4.44-4.41 (m, 1H), 4.34-4.31 (m, 1H), 3.63-3.52 (m, 4H), 2.20-2.16 (m, 2H), 2.21 (s, 3H), 2.04 (s, 3H), 1.92-1.79 (m, 6H). HRMS (ESI) m/z 270.1098 [M+Na; calcd for $C_{14}H_{17}NO_3$: 270.1101].

[5] >98% ee of ketone determined by chiral GC (cyclodex column): 50-180 ºC, at 0.2 ºC/min, at 1 mL/min. Retention time of desired ketone is 294 min (undesired retention time is 292 min).

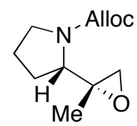
[6] Barrett, A. G. M.; Damiani, F. *J. Org. Chem.* **1999**, *64*, 1410-1411.



8a

(*S*)-benzyl 2-((*R*)-2-methyloxiran-2-yl)pyrrolidine-1-carboxylate (8a). NaH (0.012 g, 0.3 mmol) and Me_3SOCl (0.040 g, 0.3 mmol) were dissolved in THF (0.9 mL) and refluxed for 4.5 h. The reaction was cooled to 0 ºC and the slurry was then added to the ketone **4a** (0.025 g, 0.1 mmol), which was dissolved in THF (0.1 mL), dropwise via cannula over 20 min. The reaction was allowed to stir to rt for 16 h and was quenched 0.1 M $NaHSO_4$ (1 mL).[7] The aqueous layer was extracted with ethyl acetate (3 × 2 mL), and the organic extracts were washed with brine (10 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give Cbz-protected epoxide **8a** as a light yellow oil (0.020 g, 75% yield, 91:9 dr favoring desired diastereomer). R_f 0.43 (1:1 EtOAc:hexanes). Spectral data were consistent with those previously reported.[8] ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers)[9] δ 7.40-7.28 (m, 10H), 5.07-5.22 (m, 4H), 4.07 (d, *J* = 6.4 Hz, 1H), 3.96 (app. s, 1H), 3.53-3.30 (m, 4H), 2.64-2.42 (m, 4H), 2.10-1.72 (m, 8H), 1.35 (s, 3H), 1.28 (s, 3H).

[7] Added enough acid until the pH of the aqueous layer was neutral.
[8] Overman, L. E.; Bell, K. L.; Fumitaka, I. *J. Am. Chem. Soc.* **1984**, *106*, 4192-4201.
[9] Minor diastereomer not reported as it overlaps with the rotamers of the major diastereomer. Minor ^{1}H NMR peaks do not overlap at: δ 2.94, 2.72, 1.25, 1.18. Determined dr from integration of methyl groups for each diastereomer.



8b

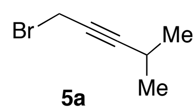
(*S*)-Allyl 2-((*R*)-2-methyloxiran-2-yl)pyrrolidine-1-carboxylate (8b).

Using NaH as base: NaH (0.030 g, 0.75 mmol) and Me_3SOCl (0.129 g, 1 mmol) were dissolved in THF (7 mL) and refluxed for 4.5 h. The reaction was cooled to –20 ºC and the slurry was then added to the ketone **4b** (0.099 g, 0.5 mmol), which was dissolved in THF (2 mL), dropwise via cannula over 20 min. The reaction was allowed to stir at –20 ºC for 40 h and was quenched 0.1 M $NaHSO_4$ (10 mL).[7] The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the organic extracts were washed with brine (50 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give alloc-protected epoxide **8b** as a light yellow oil (0.040 g, 38% yield, 11:1 dr favoring desired diastereomer, >98% ee, as determined by chiral GC[10]).

Using *n*BuLi as base: Me_3SOCl (0.096 g, 0.75 mmol) was dissolved in THF (7 mL) and *n*BuLi (0.22 mL, 0.55 mmol, 2.5M in hexanes) was added dropwise at rt. The reaction was stirred at rt for 4.5 h, then cooled to –20 ºC and the slurry was added to the ketone **4b** (0.099 g, 0.5 mmol), dissolved in THF (2 mL), dropwise via cannula over 20 min. The reaction was stirred at –20 ºC for 32 h and quenched with 0.1 M $NaHSO_4$ (10 mL).[7] The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the organic extracts were washed with brine (50 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, and was purified by flash column chromatography (3:7 EtOAc:hexanes) to give alloc-protected epoxide **8b** (0.076 g, 72% yield, 91:9 dr favoring desired diastereomer, >98% ee, as determined by chiral GC[10]).

[10] Determined by chiral GC, using a Chiraldex B-OA column; ran from 60-170 ºC, at 0.2 ºC/min, at 1 mL/min. Retention time of desired epoxide is 220 min (undesired retention time is 222 min).

R_f 0.41 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers)[11] δ 5.97-5.90 (m, 2H), 5.31 (dd, J = 10.4, 1.1 Hz, 2H), 5.20 (dd, J = 10.4, 1.1 Hz, 2H), 4.68-4.52 (m, 4H), 4.06 (d, J = 6.4 Hz, 1H), 3.94 (d, J = 6.4 Hz, 1H), 3.62-3.28 (m, 4H), 2.63 (d, J = 4.6 Hz, 2H), 2.53 (d, J = 4.6 Hz, 2H), 2.10-1.67 (m, 8H), 1.35 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 155.6, 155.3, 133.3, 117.5, 117.4, 65.9, 59.5, 59.0, 52.6, 52.4, 47.7, 47.2, 29.0, 27.8, 24.6, 23.9, 19.9, 19.6. IR (thin film NaCl) 3057, 2980, 2882, 1702, 1648, 1405, 1350, 1335, 1277, 1186, 1121, 1098, 919, 774 cm^{-1}. HRMS (ESI) *m/z* 234.1105 [M+Na; calcd for $C_{11}H_{17}NO_3$: 234.1101]. $[\alpha]_D$ = –80.8 (23 ºC, 589 nm, 0.45 g/100 mL, $CHCl_3$).



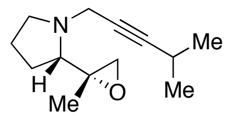
5a

1-Bromo-4-methylpent-2-yne (5a). 4-Methylpent-2-yn-1-ol[12] (1.96 g, 20 mmol) was dissolved in dichloromethane (60 mL) and cooled to 0 ºC. Carbon tetrabromide (7.96 g, 24 mmol) and triphenylphosphine (6.29 g, 24 mmol) were added and the reaction was stirred at 0 ºC for 1 h. The reaction was quenched with sat. $NaHCO_3$ solution (60 mL) and was further diluted with ether (120 mL) and water (60 mL). Separated the organic layer and washed with water (3 × 120 mL), brine (120 mL), dried over $MgSO_4$, filtered and concentrated. The residue was then purified by flash column chromatography (hexanes to 1:49 EtOAc:hexanes) to give propargyl bromide **5a** as a colorless liquid (3.03 g. 94% yield). R_f 0.58 (1:9 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (d, J = 2.1 Hz, 2H), 2.62 (m, 1H), 1.17 (d, J = 6.9 Hz, 6H). ^{13}C NMR

[11] Minor diastereomer not reported as it overlaps with the rotamers of the major diastereomer. Minor ^{1}H NMR peaks do not overlap at: δ 2.92, 2.81, 2.76, 2.71, 2.46, 2.36, 1.25. Determined dr from integration of methyl groups for each diastereomer. Confirmed dr in subsequent step, when the two diastereomers are more distinguished due to lack of rotamers.

[12] Formation of alcohol from 3-methylbut-1-yne and paraformaldehyde: Hatch, L. F.; Li, T. P. *J. Org. Chem.* **1963**, *28*, 2400-2403.

(125 MHz, $CDCl_3$) δ 93.6, 74.8, 22.8, 20.9, 16.0. IR (thin film NaCl) 2972, 2935, 2872, 2228, 1466, 1320, 1210 cm^{-1}. LR GCMS *m/z* 159, 161 [M^+; calcd for C_6H_9Br: 159, 161].

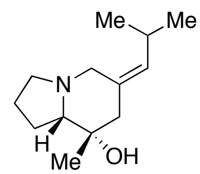


3a

(*S*)-2-((*R*)-2-methyloxiran-2-yl)-1-(4-methylpent-2-ynyl)pyrrolidine (3a). $Pd(dba)_2$ (0.086 g, 0.15 mmol) and dppb (0.064 g, 0.15 mmol) were combined in a glove box. Alloc-protected epoxide **8b** (0.317 g, 1.5 mmol) in THF (4 mL) was added followed by addition of diethylamine (2.3 mL, 22.5 mmol). The reaction was stirred at rt for 2 h, then filtered through a plug of celite with ether (10 mL) to removed the palladium catalyst and was concentrated in vacuo[13] to form free amine. The amine was dissolved in acetone (15 mL) and Na_2CO_3 (0.398 g, 3.75 mmol) and propargyl bromide **5a** (0.290 g, 1.8 mmol) were added, and the reaction was allowed to stir at rt for 16 h. The solvent was removed in vacuo, and the compound was purified by flash column chromatography using a solvent gradient (1:19 to 3:7 EtOAc:hexanes) to give amine **3a** as a pale yellow oil (0.17 g, 55% yield over the two steps, 91:9 dr retained). R_f 0.51 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) (reported as a 10:1 mixture of diastereomers, asterisk denotes minor diastereomer)[14]: δ 3.60 (dd, *J* = 16.7, 1.9 Hz, 1H), 3.49* (dd, *J* = 16.7, 1.9 Hz, 0.1H), 3.41* (dd, *J* = 16.7, 1.9 Hz, 0.1H), 3.31 (dd, *J* = 16.7, 1.9 Hz, 1H), 3.08 (t, *J* = 7.3 Hz, 1H), 2.96* (t, *J* = 7.3 Hz, 0.1H), 2.77* (d, *J* = 5.3 Hz, 0.1H), 2.62-2.48 (m, 4H), 2.27 (t, *J* = 7.33 Hz, 1H), 1.89-1.70 (m, 4H), 1.33 (s, 3H), 1.29* (s, 0.3H), 1.60 (d, *J* = 6.9 Hz, 6H) 1.15* (d, *J* = 6.9 Hz, 0.6H). ^{13}C NMR (125 MHz, $CDCl_3$) (major and minor peaks reported) δ 91.2, 90.4, 74.7, 73.9, 66.8, 65.4, 58.1, 57.4, 54.0, 53.5, 53.2, 51.0, 42.6, 41.8, 28.4, 27.8, 23.6, 23.5, 23.3, 23.1, 20.8, 20.7, 16.8,

[13] Free amine may be volatile, and precaution was used when concentrating solvent.
[14] When minor overlaps with major diastereomer, no asterisk is indicated.

16.7. IR (thin film NaCl) 3035, 2969, 2873, 2813, 2242, 1462, 1444, 1400, 1368, 1319, 1180, 1123, 1095, 1067, 909 cm^{-1}. HRMS (ESI) *m/z* 208.1695 [M+H; calcd for $C_{13}H_{21}NO$: 208.1696]. $[\alpha]_D$ = –40.4 (23 ºC, 589 nm, 0.2 g/100 mL, $CHCl_3$).



2, pumiliotoxin 209 F

Pumiliotoxin 209F (2). In a glovebox, $Ni(cod)_2$ (5.6 mg, 0.02 mmol) and PMe_2Ph (5.7 μL, 0.04 mmol) were placed into an oven-dried, sealed tube, which was sealed with a rubber septum and teflon cap. The tube was removed from the glovebox, placed under argon, and triethylborane (22 μL, 0.15 mmol) was added via syringe. The resulting solution was stirred 5 min, and the epoxy-alkyne **3a** (21 mg, 0.10 mmol) was added dropwise via microsyringe.[15] The reaction was heated to 65 ºC and allowed to stir 16 h. The solution was then cooled to rt, and ether (2 mL) was added to dilute the solution at which point the septum was removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (1:49 to 1:19 MeOH:$CHCl_3$) to give pumiliotoxin 209F (**2**) as a colorless oil (14.6 mg, 70% yield, 1 diastereomer).[16] R_f 0.33 (1:9 MeOH:$CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (d, *J* = 9.2 Hz, 1H), 3.80 (d, *J* = 11.9 Hz, 1H), 3.07 (t, *J* = 8.3 Hz, 1H), 2.67 (s, 1H), 2.60-2.55 (m, 1H), 2.36 (d, *J* = 11.9 Hz, 1H), 2.24-2.20 (m, 1H), 2.12 (d, *J* = 13.8 Hz, 1H), 2.09 (d, *J* = 13.8 Hz, 1H), 1.98 (t, *J* = 5.0 Hz, 1H), 1.79-1.65 (m, 4H), 1.14 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125

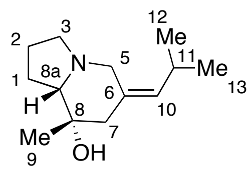
[15] Order of addition of substrate or Et_3B did not affect chemical yield.

[16] Spectral data is in accord with literature values: (a) Tokuyama, T.; Tsujita, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **1991**, *47*, 5415-5424. (b) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167-4170. See Tables E1 and E2 for comparison.

MHz, $CDCl_3$) δ 135.8, 129.4, 71.9, 68.6, 54.6, 53.1, 48.9, 26.96, 24.5, 23.7, 23.6, 23.4, 21.3. IR (thin film NaCl) 3512, 2959, 2874, 2785, 2743, 1464, 1445, 1424, 1396, 1376, 1321, 1309, 1297, 1275, 1216, 1175, 1150, 1098, 967 cm^{-1}. HRMS (ESI) *m/z* 210.1852 [M+H; calcd for $C_{13}H_{23}NO$: 210.1849]. $[\alpha]_D$ = –12.8 (23 ºC, 589 nm, 0.3 g/100 mL, $CHCl_3$).[17]

Table E1. ^{1}H NMR data for pumiliotoxin 209F.

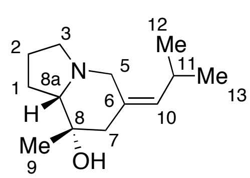
[17] $[\alpha]_D$ reported to be –11.6 (589 nm, 0.1 g/100 mL, $CHCl_3$), see ref 12a.



2, pumiliotoxin 209F

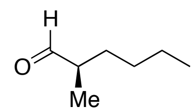
Carbon #	Natural Product 209F	Synthetic 209F	Overman's Synthetic 209F
1	not reported	1.79-1.65 (m, 2H)	not reported
2	"	1.79-1.65 (m, 2H)	"
3	"	3.07 (t, *J* = 8.3 Hz, 1H)	"
3'	"	2.24-2.20 (m, 1H)	"
5	"	3.80 (d, *J* = 11.9 Hz, 1H)	3.79 (d, *J* = 12 Hz, 1H)
5'	"	2.36 (d, *J* = 11.9 Hz, 1H)	2.32 (d, *J* = 11.9 Hz, 1H)
7	"	2.12 (d, *J* = 13.8 Hz, 1H)	not reported
7'	"	2.09 (d, *J* = 13.8 Hz, 1H)	"
8a	"	1.98 (t, *J* = 5.0 Hz, 1H)	"
9	"	1.14 (s, 3H)	"
10	"	5.11 (d, *J* = 9.2 Hz, 1H)	5.10 (d, *J* = 9.8 Hz, 1H)
11	"	2.60-2.55 (m, 1H	not reported
12	0.99	0.99 (d, *J* = 6.7 Hz, 3H)	"
13	0.91	0.92 (d, *J* = 6.7 Hz, 3H)	"
OH	not reported	2.67	"

Table E2. ^{13}C NMR data for pumiliotoxin 209F.



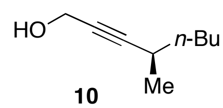
2, pumiliotoxin 209F

Carbon #	Natural Product 209F	Synthetic 209F
1	23.3	23.4
2	21.2	21.3
3	54.6	54.6
5	53.0	53.1
6	129.4	129.4
7	48.8	48.9
8	68.4	68.6
8a	71.8	71.9
9	24.3	24.5
10	135.7	135.8
11	26.8	26.9
12	23.4	23.4
13	23.5	23.7



9

(R)-2-Methylhexanal (9). Followed previously reported procedure to synthesize aldehyde **9** in 56% yield over 4 steps from commercially available materials.[18] Spectral data, including optical rotation to confirm ee (>98%), were consistent with those previously reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, *J* = 2.3 Hz, 1H), 2.35-2.30 (m, 1H), 1.79-1.68 (m, 1H), 1.42-1.21 (m, 5H), 1.09 (d, 7.0 Hz, 3H), 0.93-0.86 (m, 1H).



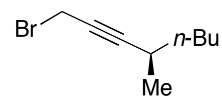
10

(R)-4-Methyl-2-octyn-1-ol (10). The dibromide was prepared according to Overman's procedure[19] in 90% yield. Spectral data were consistent with those previously reported. Then the dibromide (0.184 g, 0.68 mmol) was dissolved in THF (2.1 mL) and cooled to –78 ºC. *n*BuLi (0.54 mL, 1.4 mmol; 2.5 M solution in hexanes) was then added and the reaction was stirred at –78 ºC for 30 min. To this cooled solution was added a suspension of paraformaldehyde (0.245 g, 2.7 mmol) in THF (1.4 mL) and the mixture was allowed to warm to rt over 1 h. The mixture was filtered through celite, brine was added (2 mL) and the organic layer was separated. The aqueous layer was extracted with ether (3 × 2 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (1:9 EtOAc:hexanes) to give **10** as a colorless liquid (86 mg, 90% yield). Spectral data were consistent with those previously reported.[20] ^{1}H NMR (500 MHz,

---

[18] Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179-1190.
[19] Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073-9082.
[20] Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393-11409.

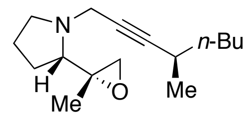
$CDCl_3$) δ 4.26 (d, J = 2.0 Hz, 2H), 2.48-2.41 (m, 1H), 1.50-1.30 (m, 6H), 1.16 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H).



5b

(*R*)-1-Bromo-4-methyloct-2-yne (5b).[21] This procedure is similar to that for propargyl bromide **5a**. Propargyl alcohol **10** (42 mg, 0.3 mmol,) was dissolved in dichloromethane (0.9 mL) and cooled to 0 ºC. Carbon tetrabromide (0.119 g, 0.36 mmol) and triphenylphosphine (0.094 g, 0.36 mmol) were added and the reaction was stirred at 0 ºC for 1 h. The reaction was quenched with sat. $NaHCO_3$ solution (1 mL) and was further diluted with ether (2 mL) and water (1 mL). Separated the organic layer and washed with water (3 × 2 mL), brine (2 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography using a solvent gradient (hexanes to 1:49 EtOAc:hexanes) to give propargyl bromide **5b** as a colorless liquid (59 mg, 96% yield). R_f 0.47 (1:9 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (d, J = 2.2 Hz, 2H), 2.49-2.41 (m, 1H), 1.44-1.22 (m, 6H), 1.13 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 92.9, 75.6, 36.6, 29.7, 29.3, 22.7, 20.9, 16.1, 14.3. IR (thin film NaCl) 2959, 2931, 2872, 2858, 2231, 1458, 1376, 1333, 1208, 7660 cm^{-1}. HRMS (ESI) *m/z* 202.0353 [M+H; calcd for $C_9H_{15}Br$: 202.0357]. $[\alpha]_D$ = -19.8 (23 ºC, 589 nm, 0.45 g/100 mL, $CHCl_3$).

[21] Spectral data for **5b** is in accord with literature values: Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984-6990.

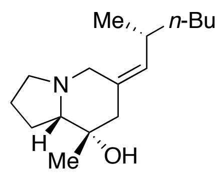


3b

(*S*)-1-((*R*)-4-methyloct-2-ynyl)-2-((*R*)-2-methyloxiran-2-yl)pyrrolidine (3b). $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) was weighed into a vial and to this was added a solution of the alloc-protected epoxide **8b** (0.026 g, 0.12 mmol) in THF (0.28 mL) followed by diethylamine (0.20 mL, 1.8 mmol). The reaction was stirred at rt for 2 h, then filtered through a plug of celite with ether (5 mL) to remove the palladium catalyst, and was subsequently concentrated in vacuo to form the free amine.[22] The amine was dissolved in acetone (1 mL) and Na_2CO_3 (0.064 g, 0.6 mmol) and propargyl bromide **5b** (0.024 g, 0.12 mmol) were added, and the reaction was allowed to stir at rt for 16 h. The solvent was removed in vacuo, and the compound was purified by flash column chromatography using a solvent gradient (1:19 to 3:7 EtOAc:hexanes) to give amine **3b** as a colorless oil (0.14 g, 48% yield over the two steps, 91:9 dr retained). R_f 0.58 (1:1 EtOAc:hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) (reported as a 10:1 mixture of diastereomers, asterisk denotes minor diastereomer)[23]: δ 3.61 (dd, J = 16.7, 1.9 Hz, 1H), 3.50* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.44* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.36 (dd, J = 16.7, 1.9 Hz, 1H), 3.06 (t, J = 7.3 Hz, 1H), 2.95* (t, J = 7.3 Hz, 0.1H), 2.77* (d, J = 5.3 Hz, 0.1H), 2.62* (d, J = 5.3 Hz, 0.1H), 2.56 (d, J = 5.0 Hz, 1H), 2.54 (d, J = 5.0 Hz, 1H), 2.42 (br. dd, J = 13.4, 6.8 Hz, 1H), 2.32 (t, J = 7.3 Hz, 1H), 1.89-1.70 (m, 4H), 1.45-1.26 (m, 7H), 1.31 (s, 3H), 1.14 (d, J = 6.9 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) (major and minor peaks reported[24]) δ 89.5, 75.6, 66.5, 65.2, 58.1, 53.9, 53.4, 53.0, 51.1, 42.5, 41.7, 29.9, 28.4, 27.8, 26.1, 23.4, 23.1, 22.8, 22.4,

[22] $Pd(PPh_3)_4$ was utilized due to ease of purification (relative to $Pd(dba)_2$).
[23] Not all protons for minor diastereomer are reported, as they overlap with major diastereomers or are not well resolved.
[24] Not all minor diastereomer carbon peaks are resolved, or overlap with major diastereomer.

21.6, 18.9, 16.9, 16.7, 14.3, 12.1. IR (thin film NaCl) 3034, 2963, 2930, 2873, 2860, 2814, 2243, 1460, 1401, 1373, 1327, 1280, 1123, 1096, 1068, 908 cm^{-1}. HRMS (ESI) *m/z* 250.2169 [M+H; calcd for $C_{16}H_{27}NO$: 250.2165]. $[\alpha]_D = –66.1$ (23 ºC, 589 nm, 0.22 g/100 mL, $CHCl_3$).



1, pumiliotoxin 251D

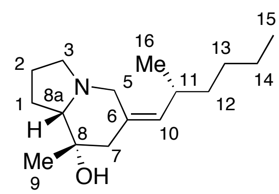
Pumiliotoxin 251 D (1). Epoxy-alkyne **3b** (15 mg, 0.06 mmol) was added to a sealed tube which was brought into a glovebox.[25] In the glove box, Ni(cod)$_2$ (3.3 mg, 0.012 mmol) and 1.2 (3.4 µL, 0.024 mmol) were added to the sealed tube, which was sealed with a rubber septum and teflon cap. The tube was removed from the glovebox, placed under argon, and triethylborane (13 µL, 0.09 mmol) was added via syringe. The reaction was heated to 65 ºC and allowed to stir 16 h. The solution was cooled to rt, and ether (2 mL) was added to dilute the solution at which point the septum was removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (1:49 to 1:19 MeOH:$CHCl_3$) to give pumiliotoxin 251D (**1**) as a colorless solid (12.4 mg, 82% yield, 1 diastereomer).[26] R_f 0.30 (1:9 MeOH:$CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (d, *J* = 9.5 Hz, 1H), 3.78 (d, *J* = 12.0 Hz, 1H), 3.07-3.03 (m, 1H), 2.67 (s, 1H), 2.42-2.30 (m, 1H), 2.34 (d, *J* = 12.0 Hz, 1H), 2.25-2.15 (m, 1H), 2.15-2.12 (m, 2H),

[25] Due to small scale, the substrate was dissolved in ether, place in sealed tube, and solvent was removed via vacuum pump.

[26] Spectral data is in accord with literature values: (a) see Ref. 12a. (b) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830-836. (b) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192-4201. (c) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3315-3325. See Tables E3 and E4 for a comparison. Also see Figure E1 for comparison of the ^{1}H NMR spectra.

2.00-1.90 (m, 1H), 1.78-1.60 (m, 4H), 1.32-1.10 (m, 6H), 1.14 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 130.0, 71.8, 68.4, 54.7, 53.3, 48.9, 37.6, 32.2, 29.8, 24.4, 23.3, 22.9, 21.8, 21.2, 14.2. IR (thin film NaCl) 3418, 2982, 2909, 2872, 1660, 1465, 1420, 1324, 1305, 1291, 1176, 1121, 1072, 939, 913, 871 cm^{-1}. HRMS (ESI) *m/z* 252.2321 [M+H; calcd for $C_{16}H_{29}NO$: 252.2322]. $[\alpha]_D$ = –9.3 (23 ºC, 589 nm, 0.05 g/100 mL, $CHCl_3$).

Table E3. ^1H NMR data for pumiliotoxin 251D.

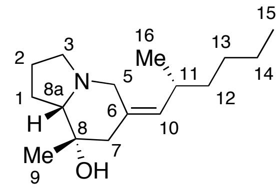


1, pumiliotoxin 251D

Carbon #	Natural Product 251D	Synthetic 251D	Overman's Synthetic 251D	Nubbemeyers's Synthetic 251D
1	1.73	1.78-1.60 (m, 1H)	not reported	1.78-1.60 (m, 1H)
1'[a]	2.36	1.78-1.60 (m, 1H)	not reported	1.78-1.60 (m, 1H)
2	1.73	1.78-1.60 (m, 2H)	not reported	1.78-1.60 (m, 2H)
3	3.09	3.07-3.03 (m, 1H)	3.07 (m, 1H)	3.07-3.00 (m, 1H)
3'	2.24	2.25-2.15 (m, 1H)	2.1-2.3 (m, 1H)	2.25-2.15 (m, 1H)
5	not reported	3.78 (d, J = 12.0 Hz, 1H)	3.78 (d, J = 12.1Hz, 1H)	3.78-3.73 (d, J = 12.0Hz, 1H)
5'	not reported	2.34 (d, J = 12.0 Hz, 1H)	2.34 (d, J = 12.1Hz, 1H)	2.35-2.29 (d, J = 12.0 Hz, 1H)
7	2.16	2.15-2.12 (m, 2H)	2.17 (br app. s, 2H)	2.15-2.12 (s, 2H)
8a[a]	3.82	2.00-1.90	2.0-1.9 (m, 1H)	1.99-1.92 (m, 1H)
9	1.16	1.14 (s, 3H)	1.16 (s, 3H)	1.11 (s, 3H)
10	5.07	5.04 (d, J = 9.5 Hz, 1H)	5.05 (d, J = 9.5 Hz, 1H)	5.04-4.97 (d, J = 9.5 Hz, 1H)
11	2.37	2.42-2.30 (m, 1H)	2.3-2.5 (m, 1H)	2.43-2.40 (m, 1H)
12	not reported	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
13	1.16	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
14	1.16	1.32-1.10 (m, 2H)	1.4-1.1 (m, 2H)	1.30-1.10 (m, 2H)
15	0.89	0.87 (t, J = 6.9 Hz, 3H)	0.87 (app. t, J = 6.8 Hz, 3H)	0.87-0.80 (t, J = 6.5 Hz, 3H)
16	0.98	0.97 (d, J = 6.5 Hz, 3H)	0.98 (d, J = 6.2 Hz, 3H)	0.96-0.93 (d, J = 6.5 Hz, 3H)
OH	not reported	2.67 (s, 1H)	2.6 (br s, 1H)	2.65 (s, 1H)

(a) The assignments of the C5 and C5' protons are consistent with those reported by Overman and by Nubbeymeyer but are inconsistent with Daly's nomenclature. Similar discrepancies exist for C1 and C8a.

Table E4. ^{13}C NMR data for pumiliotoxin 251D.

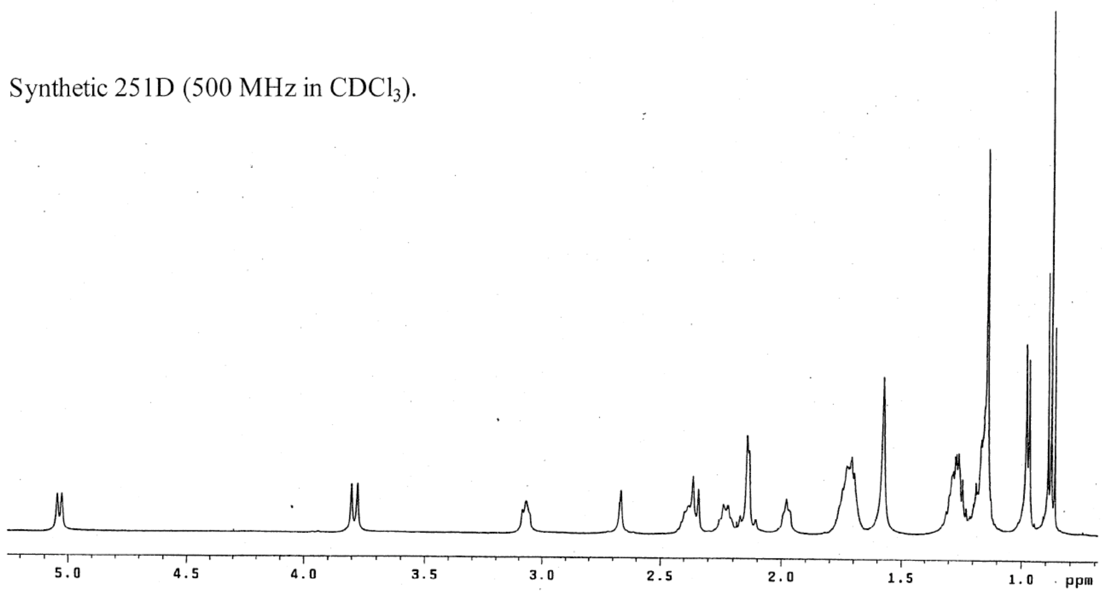


1, pumiliotoxin 251D

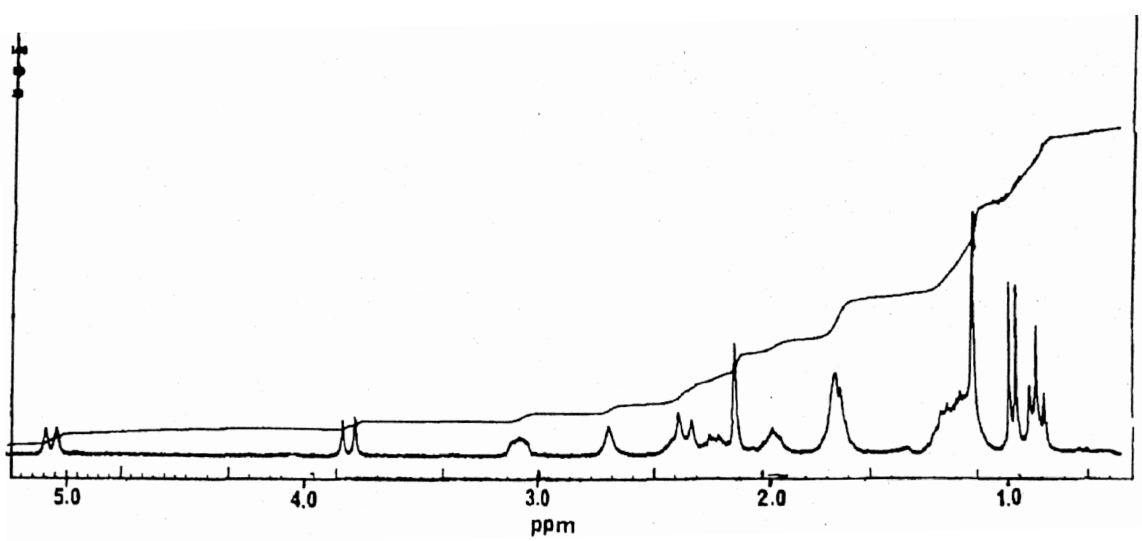
Carbon #	Natural Product 251D	Synthetic 251D
1	23.4	23.3
2	21.2	21.2
3	54.7	54.7
5	53.0	53.3
6	130.0	130.0
7	49.0	48.9
8	68.4	68.4
8a	71.8	71.8
9	24.3	24.4
10	134.7	134.7
11	32.1	32.2
12	37.6	37.6
13	29.8	29.8
14	22.9	22.9
15	14.2	14.2
16	21.8	21.8

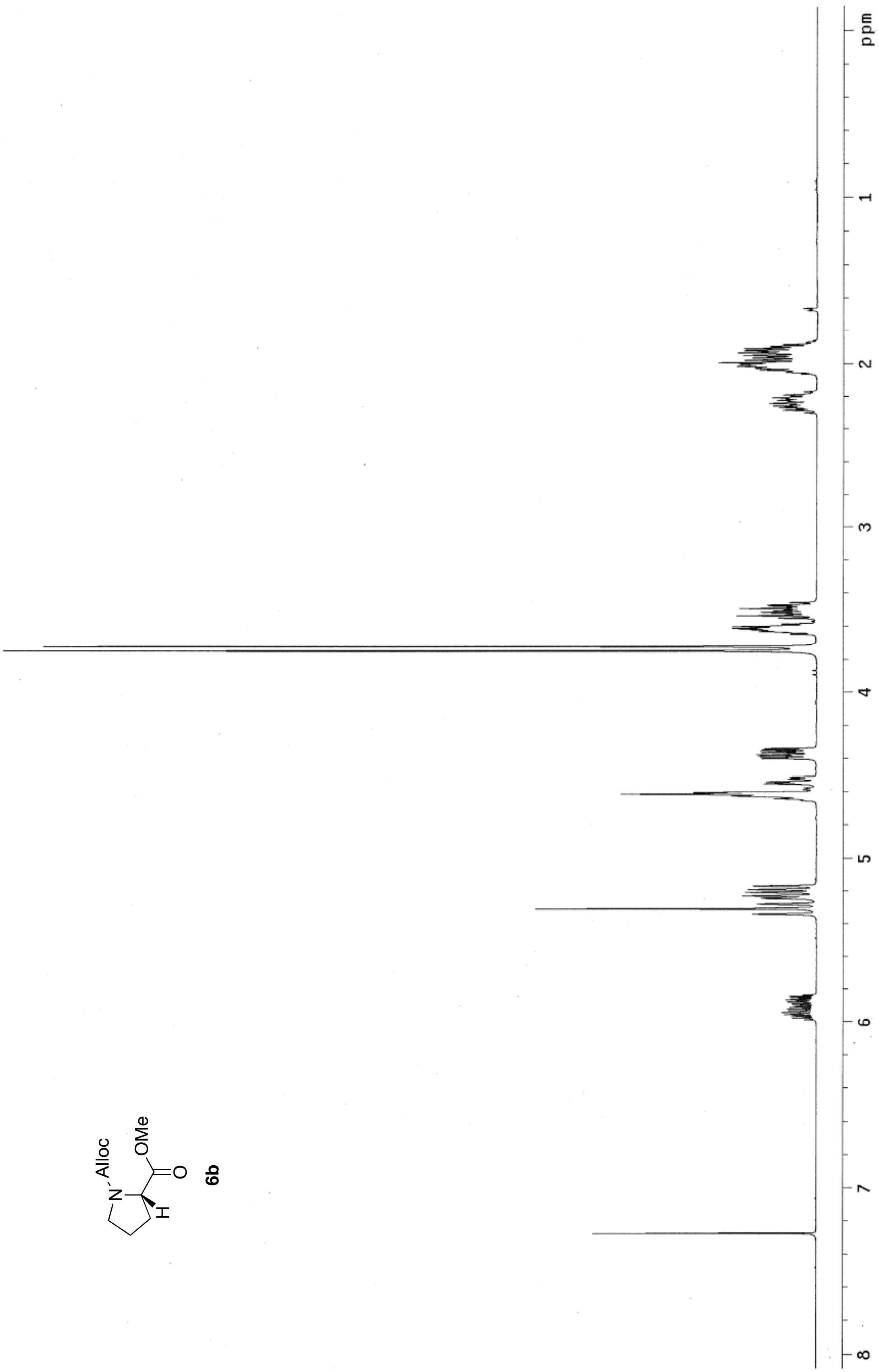
Figure E1. Pumiliotoxin 251D.

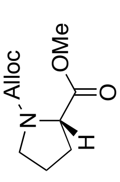
Synthetic 251D (500 MHz in $CDCl_3$).



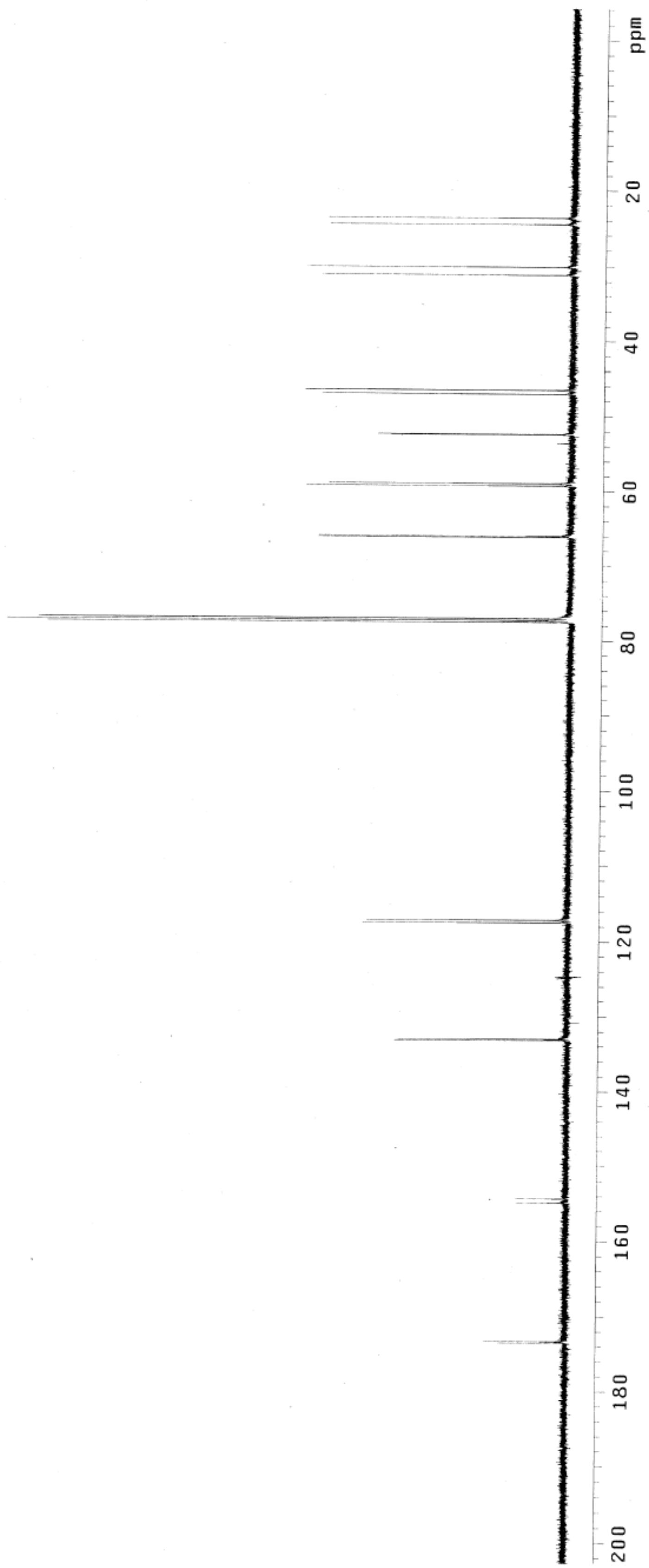
Natural 251D (220 MHz in $CDCl_3$).



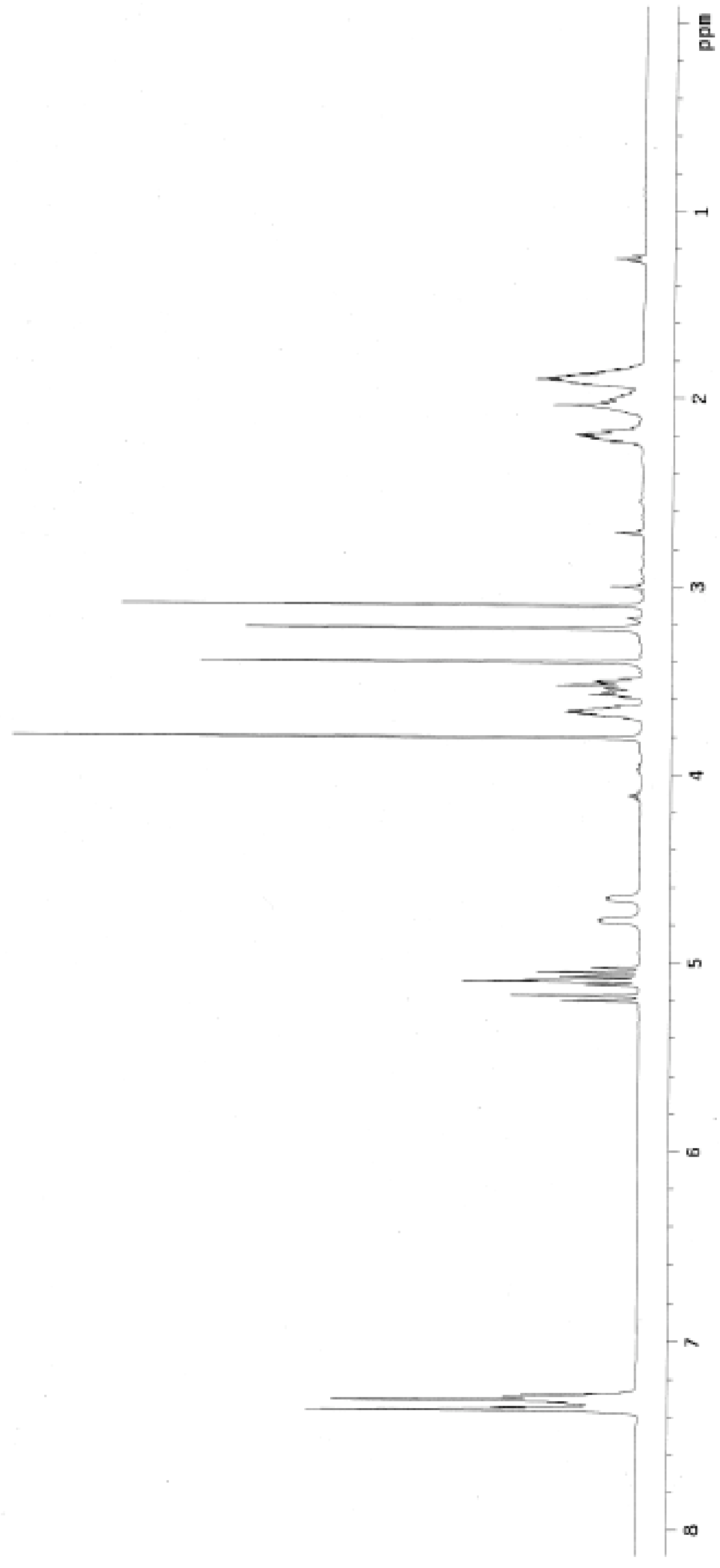

Alloc
N
OMe
O
H
6b
ppm
1
2
3
4
5
6
7
8

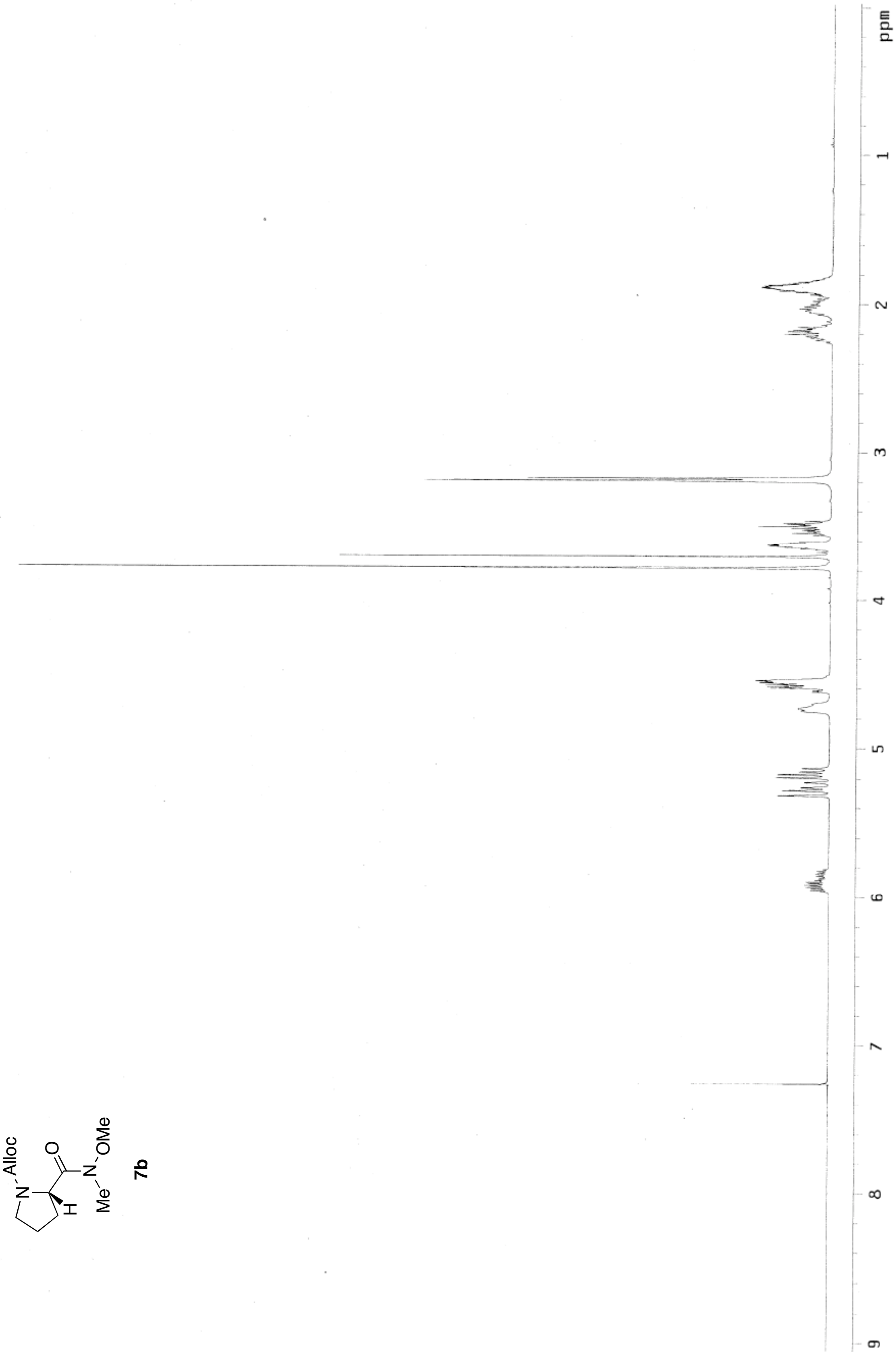


6b

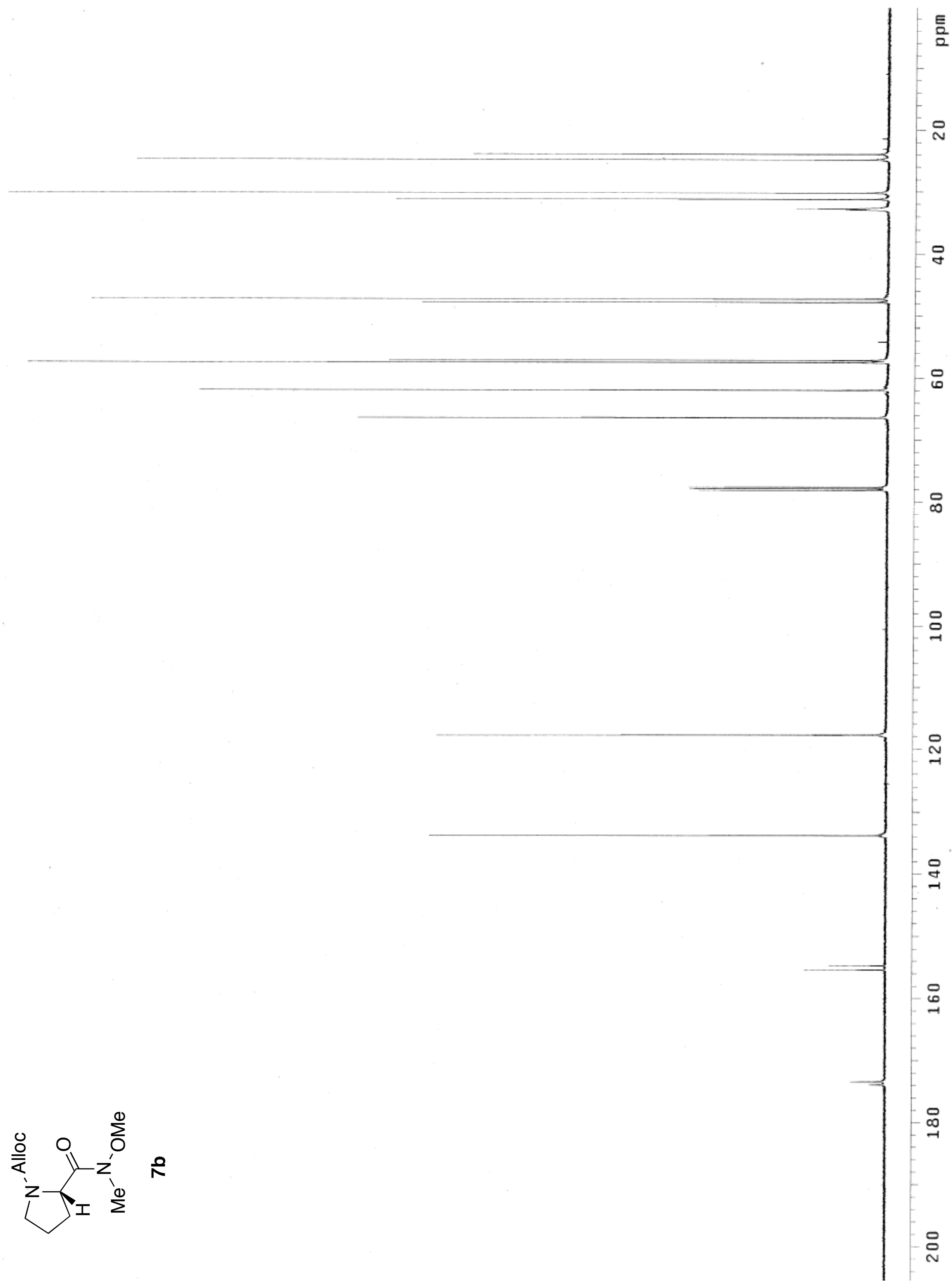


7a

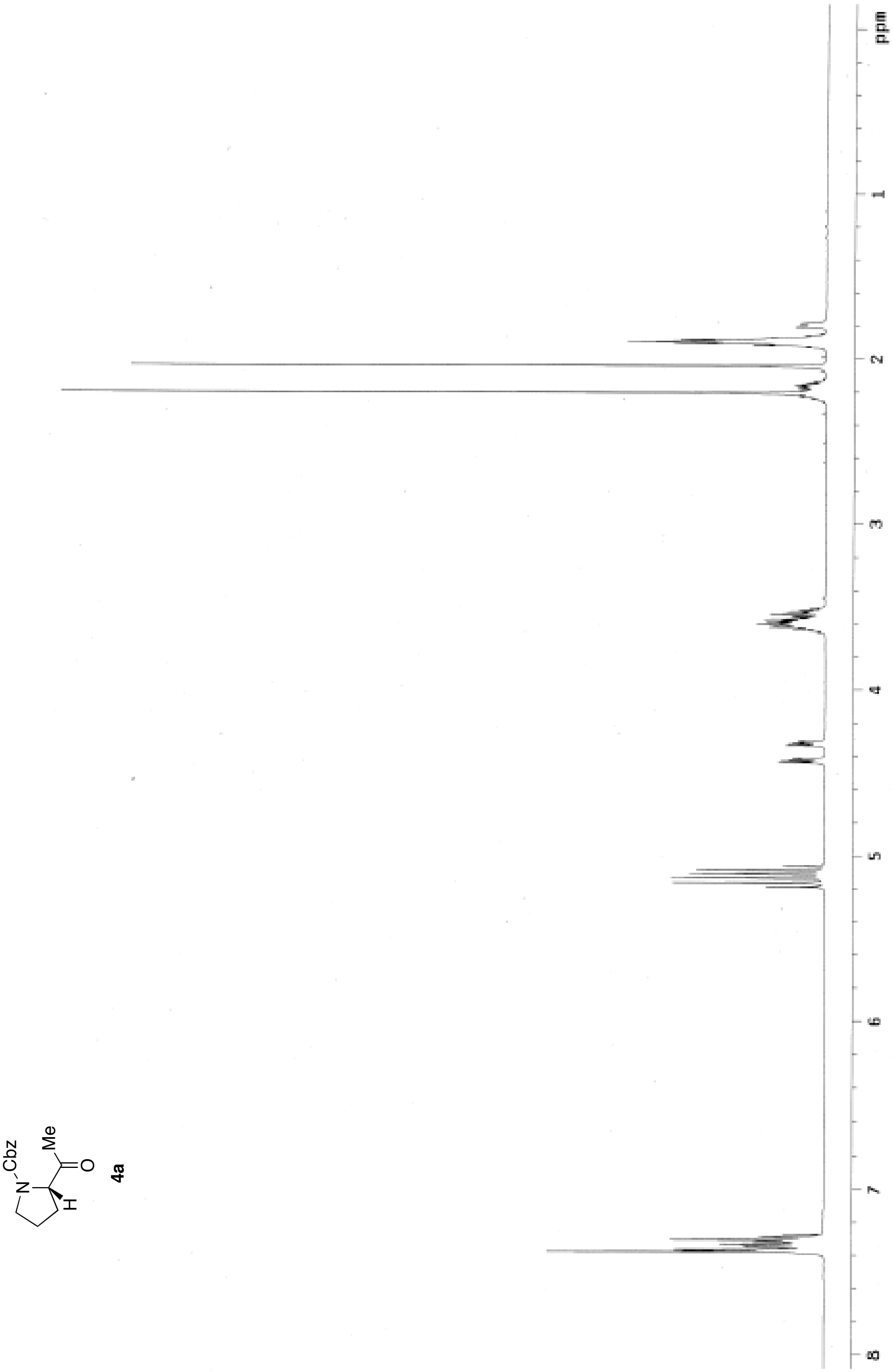




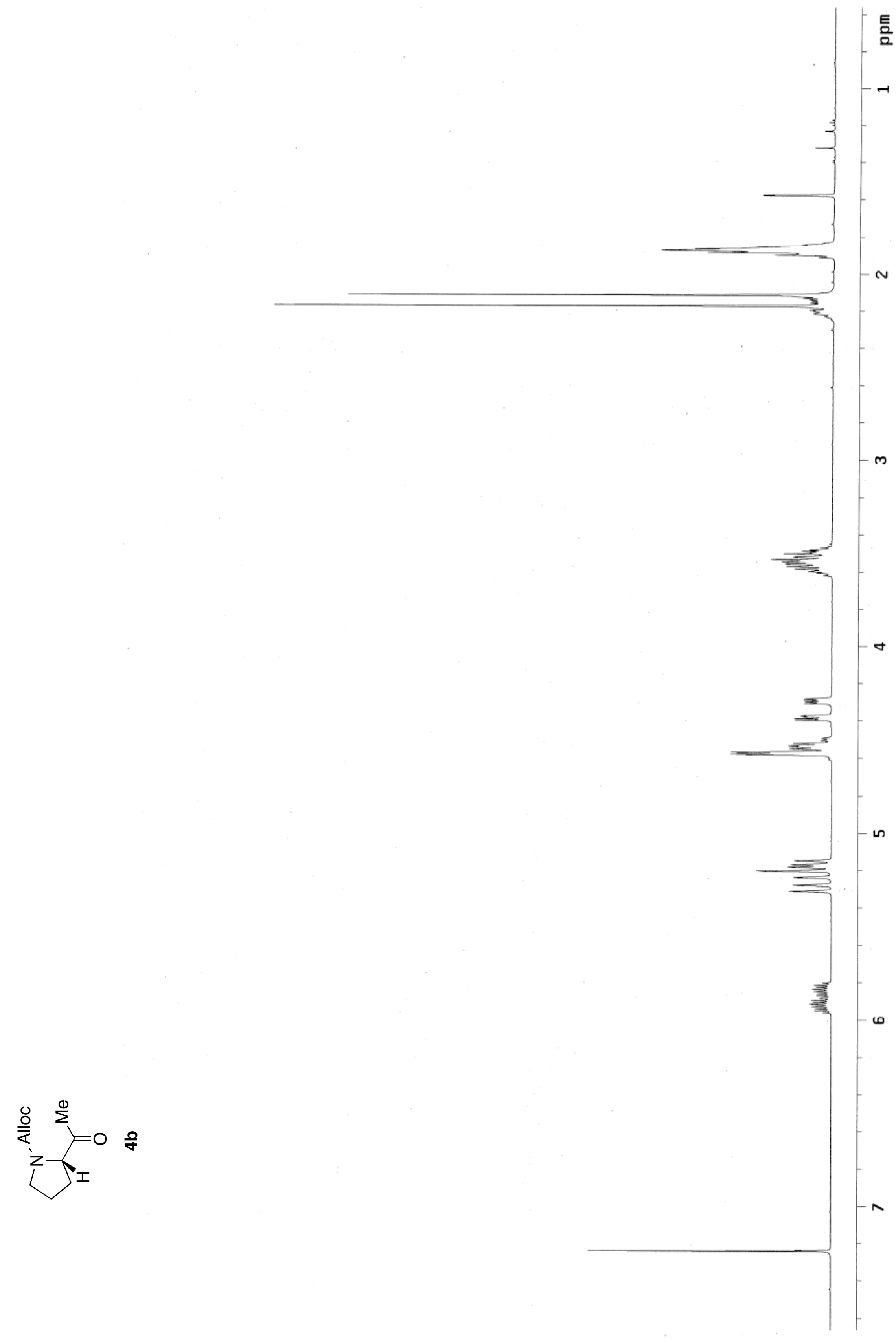
Alloc
O
N
OMe
Me
H
7b
ppm
1
2
3
4
5
6
7
8
9



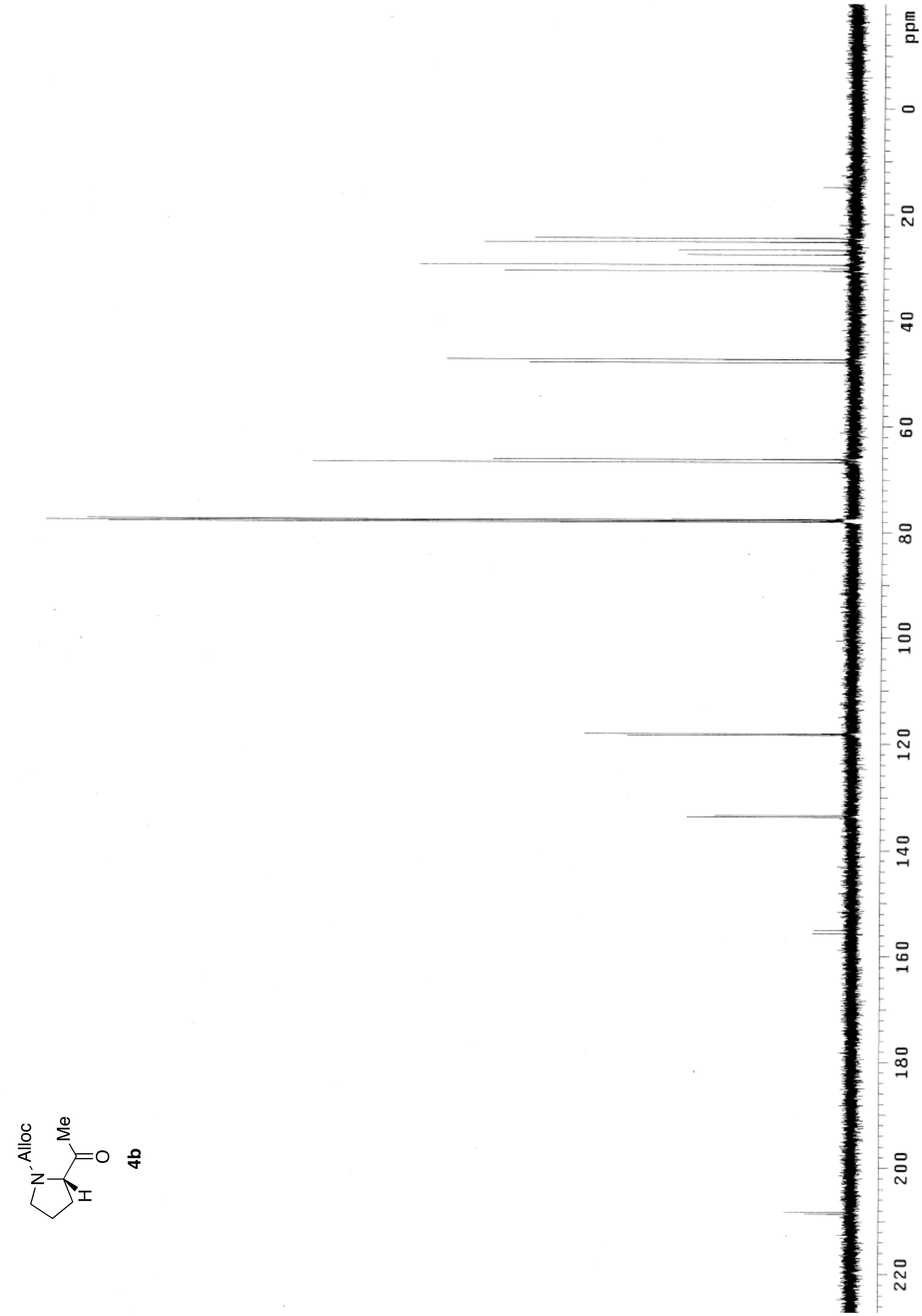
7b



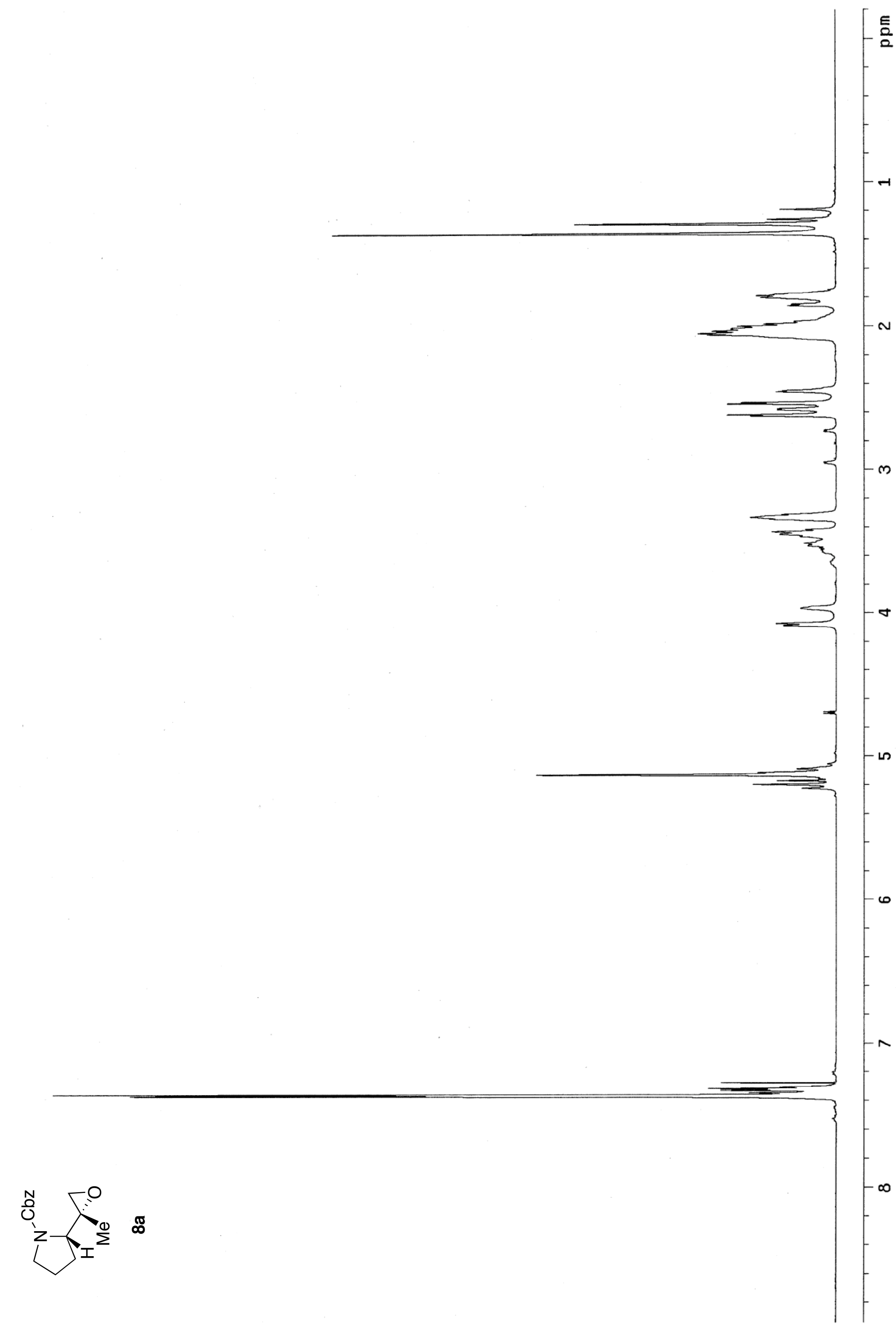
4a

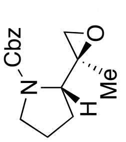


Alloc
N
Me
O
H
4b
ppm
1
2
3
4
5
6
7

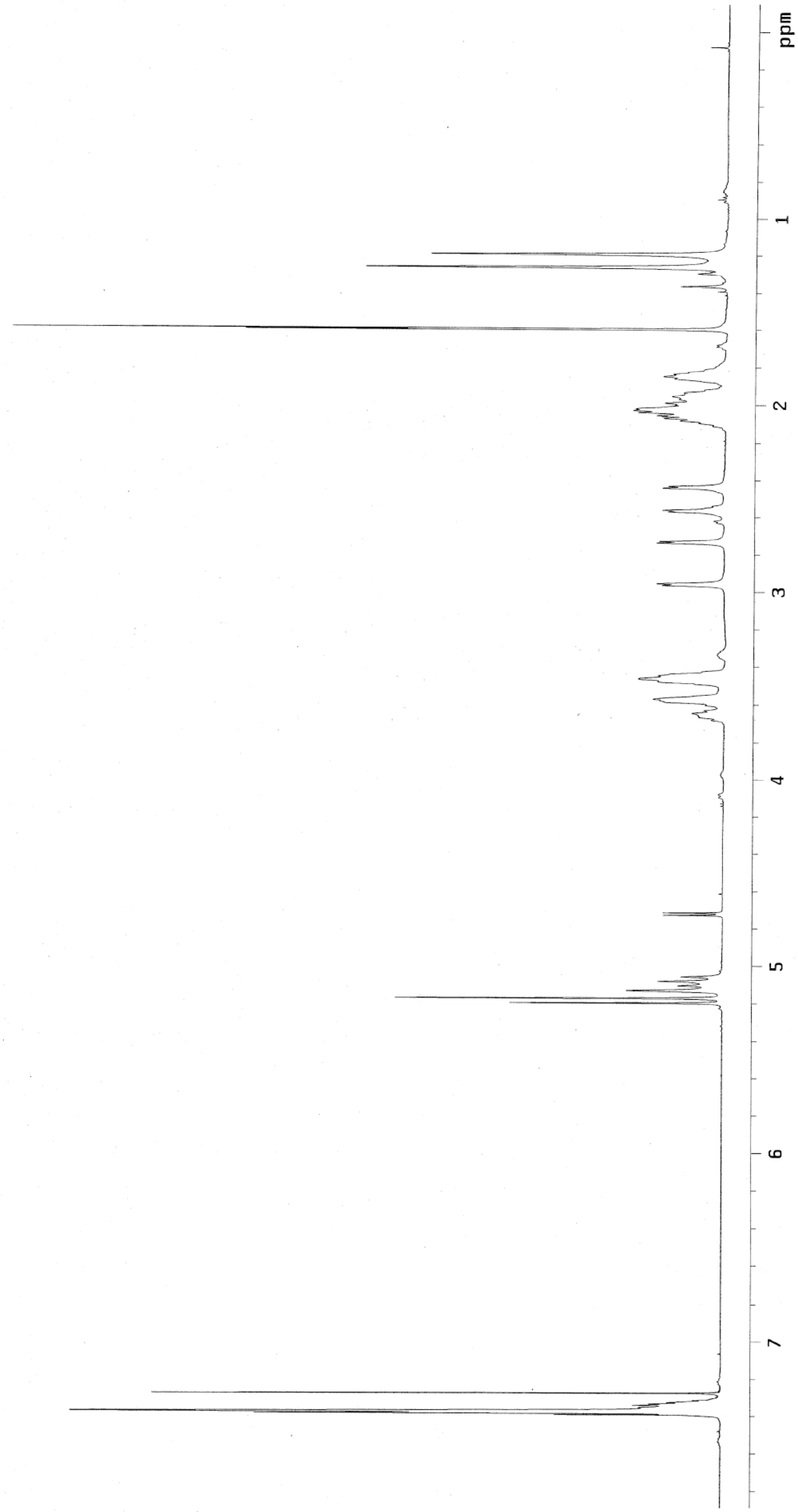


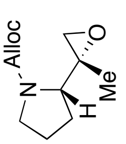
N
Alloc
Me
O
H
4b
ppm


N
Cbz
O
H
Me
8a
ppm
1
2
3
4
5
6
7
8

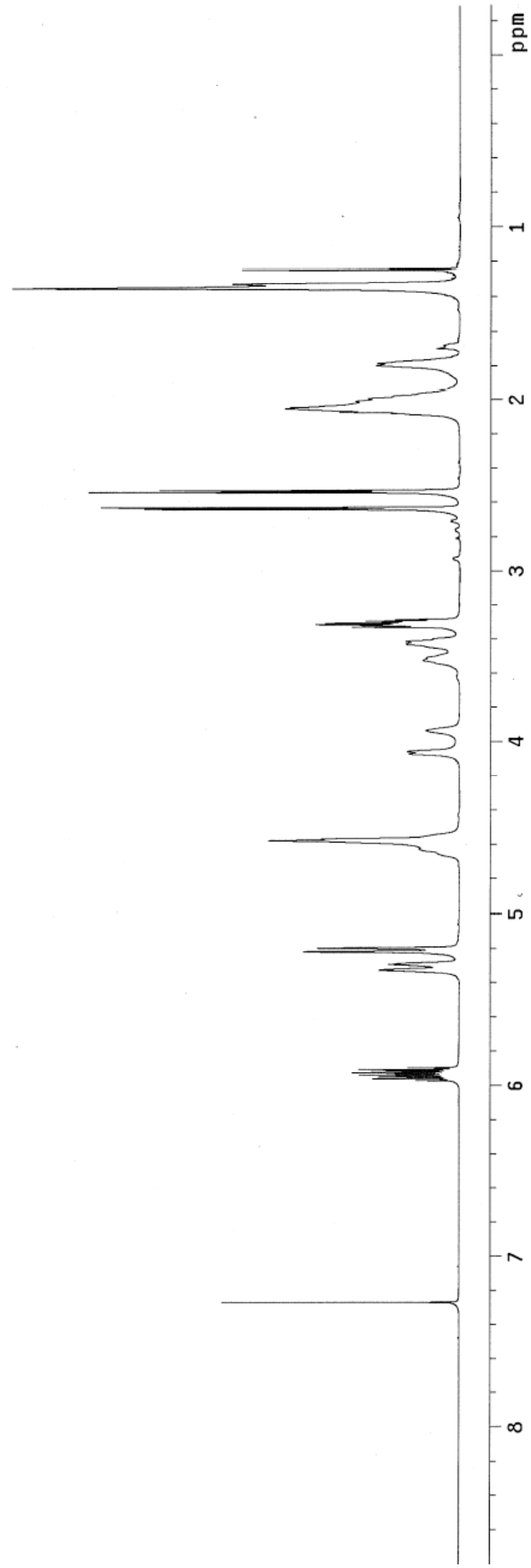


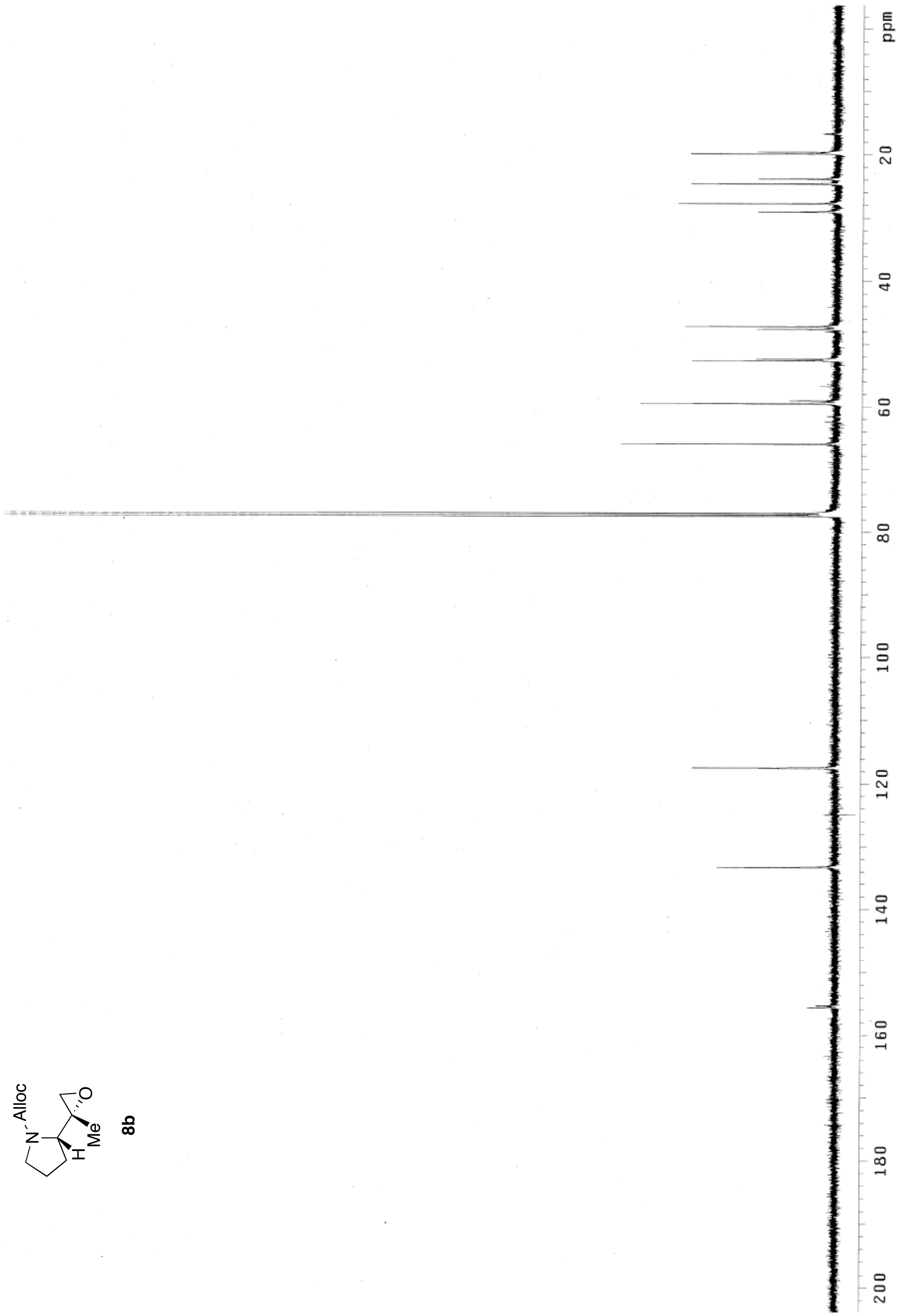
8a'



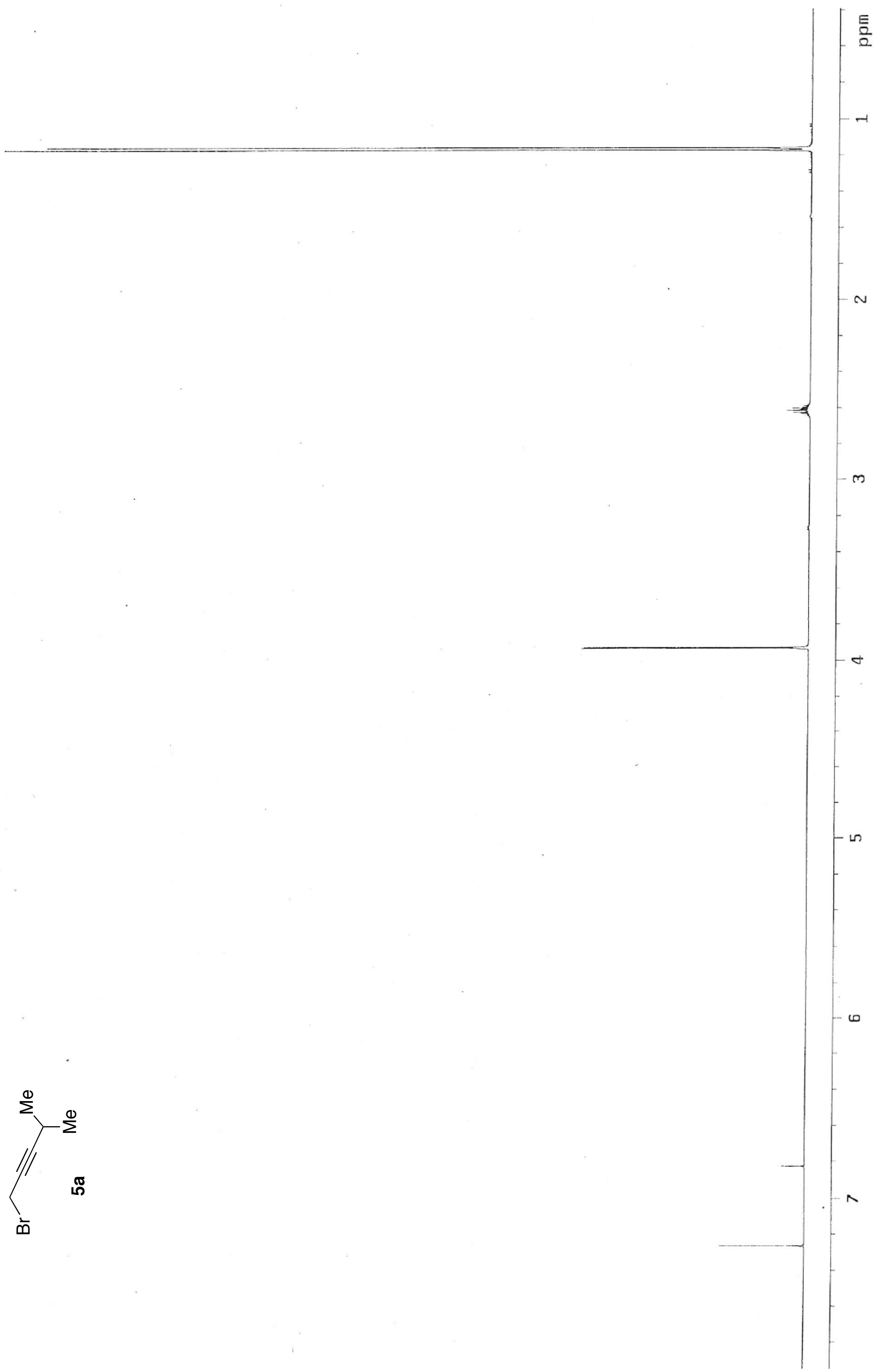


8b

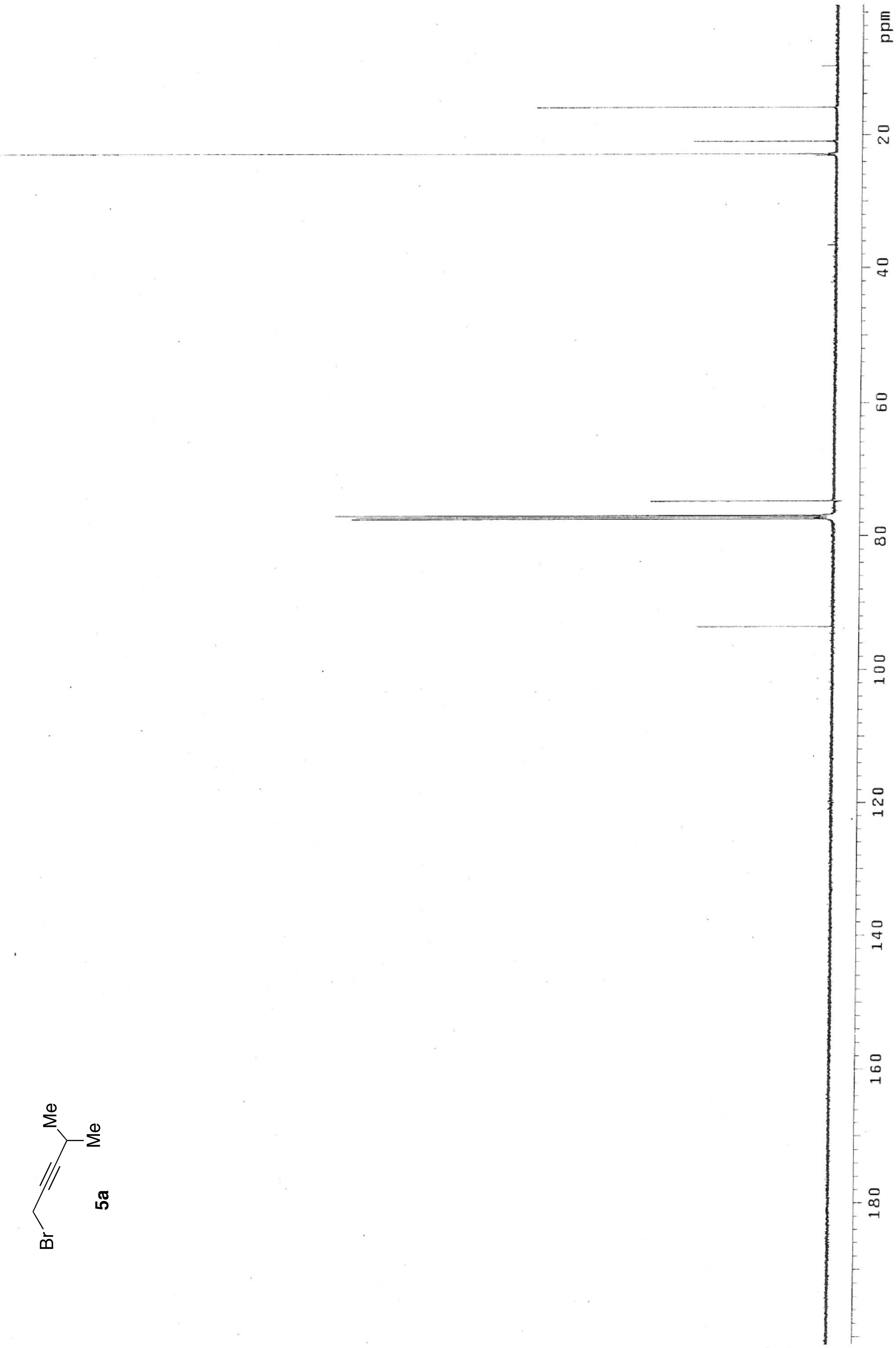




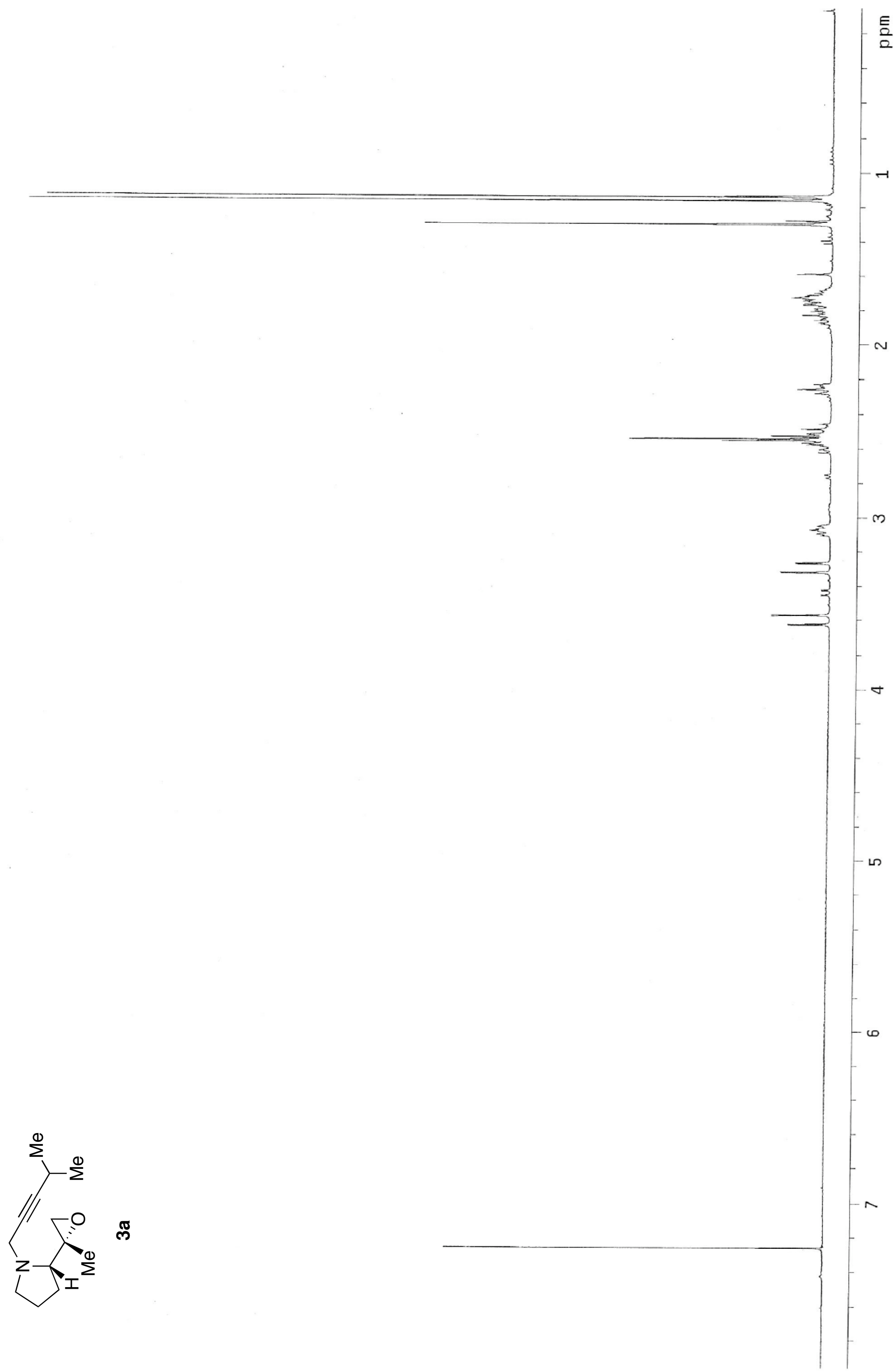
8b



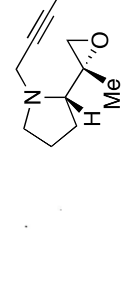
Me
Me
Br
5a
ppm
1
2
3
4
5
6
7



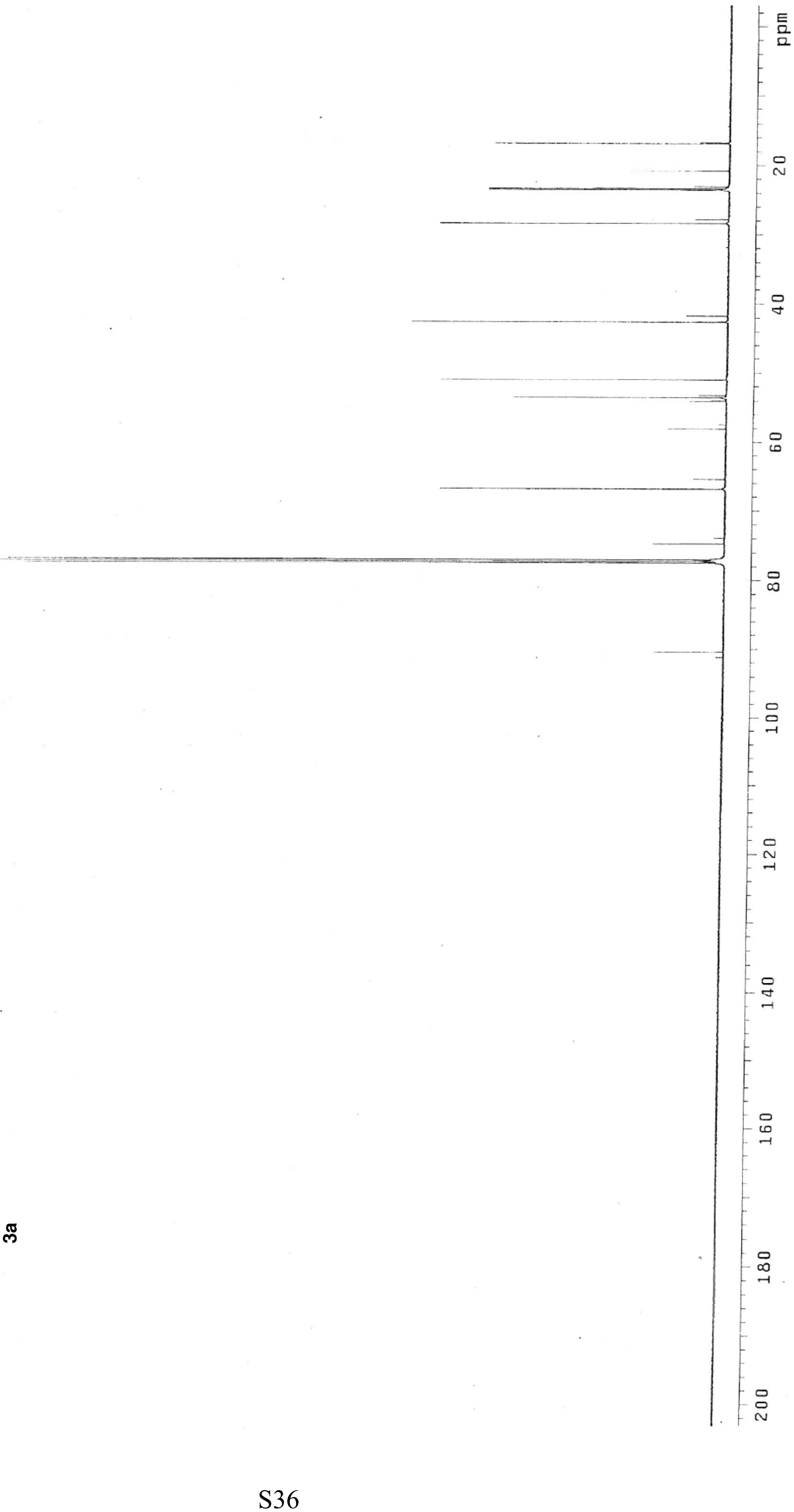
ppm
20
40
60
80
100
120
140
160
180
Br
Me
Me
5a

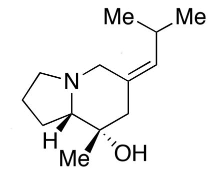


3a

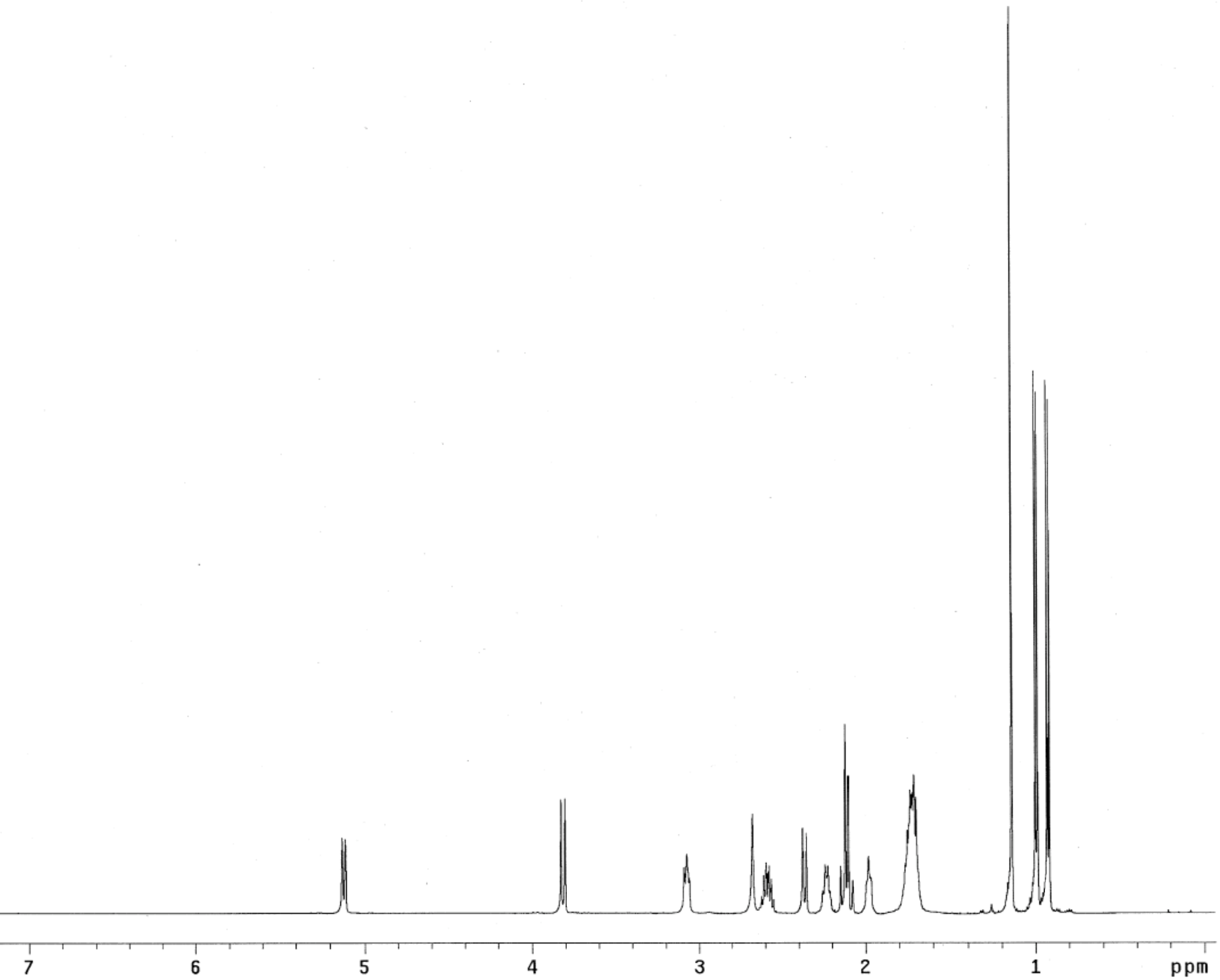


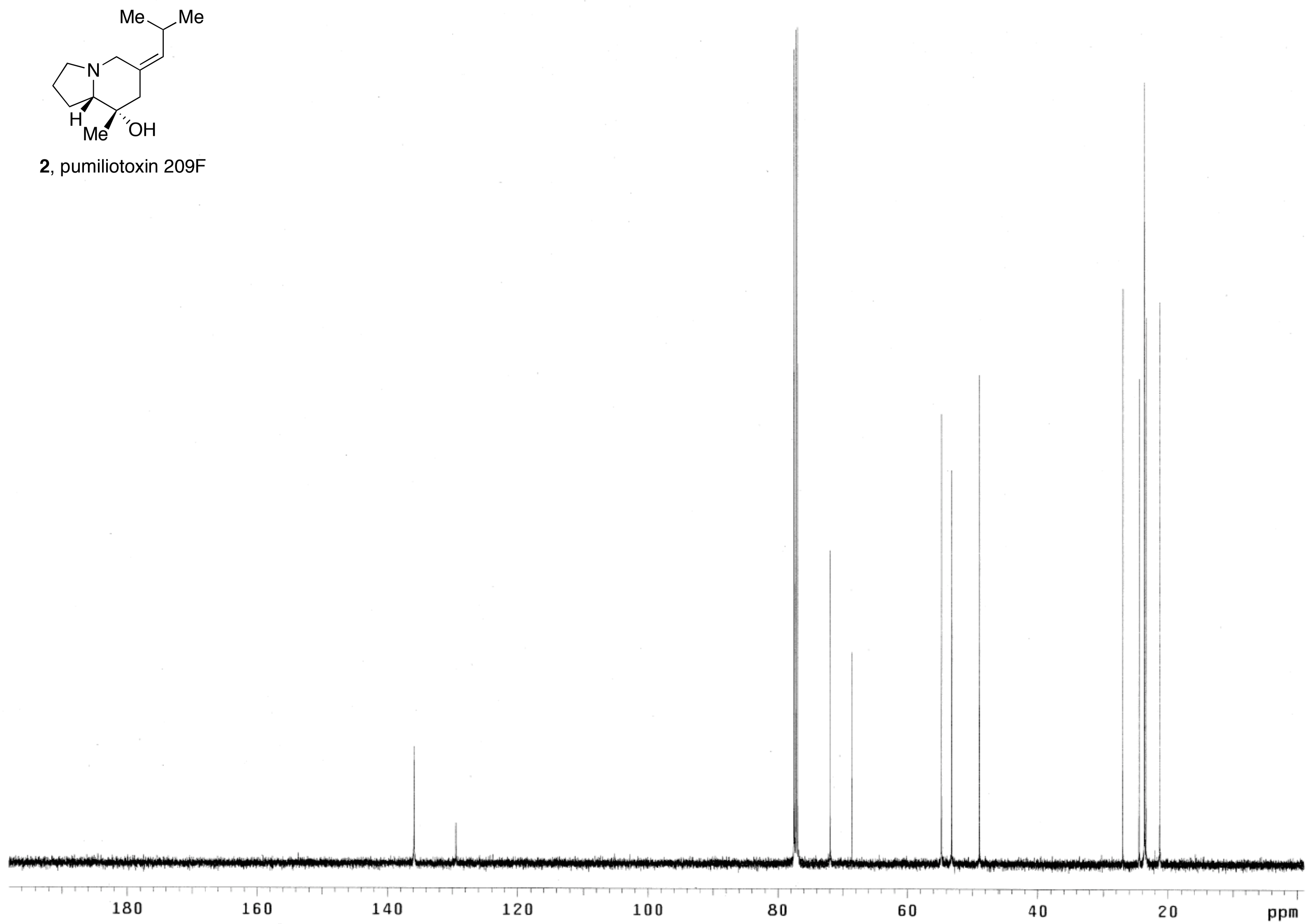
3a



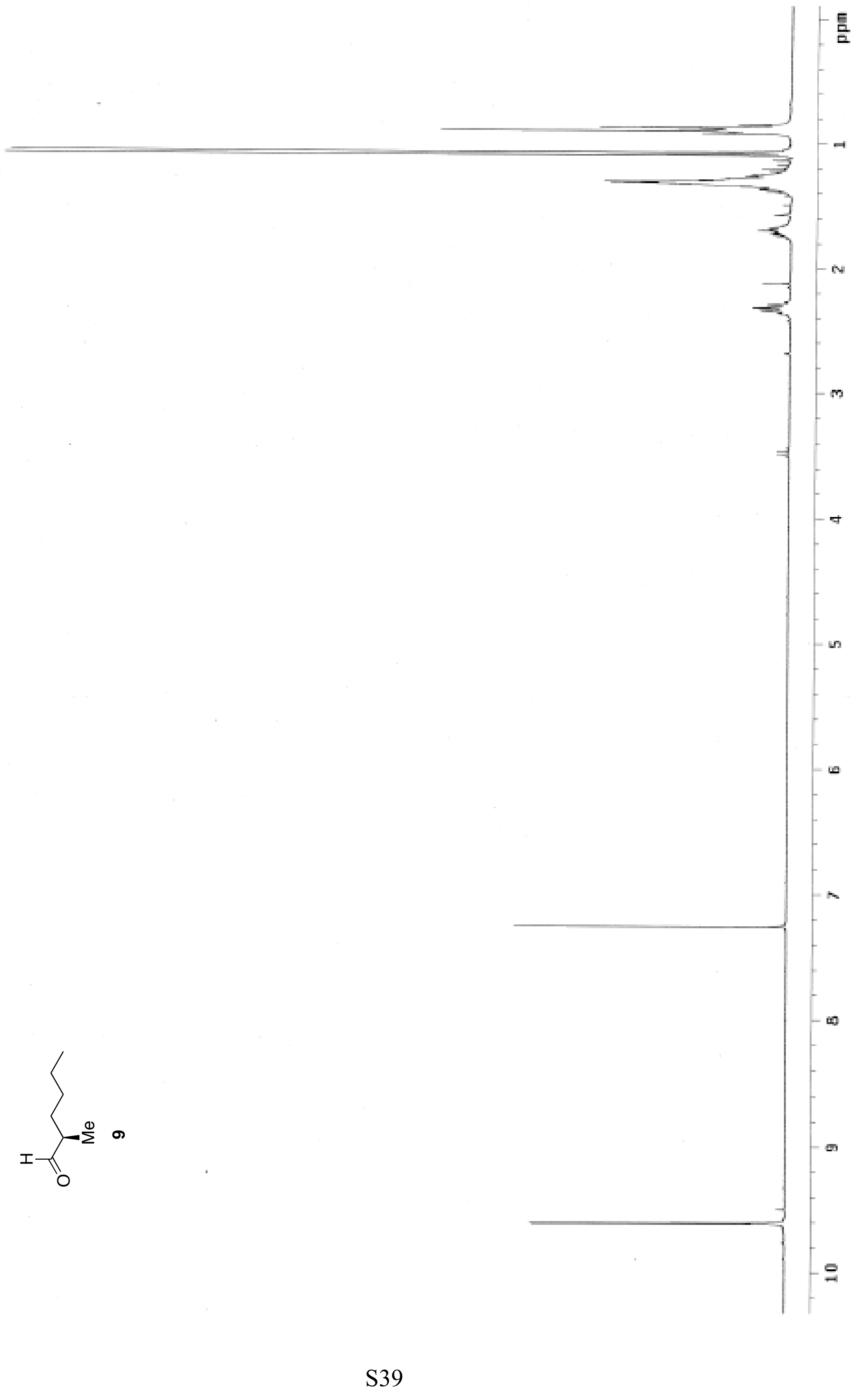


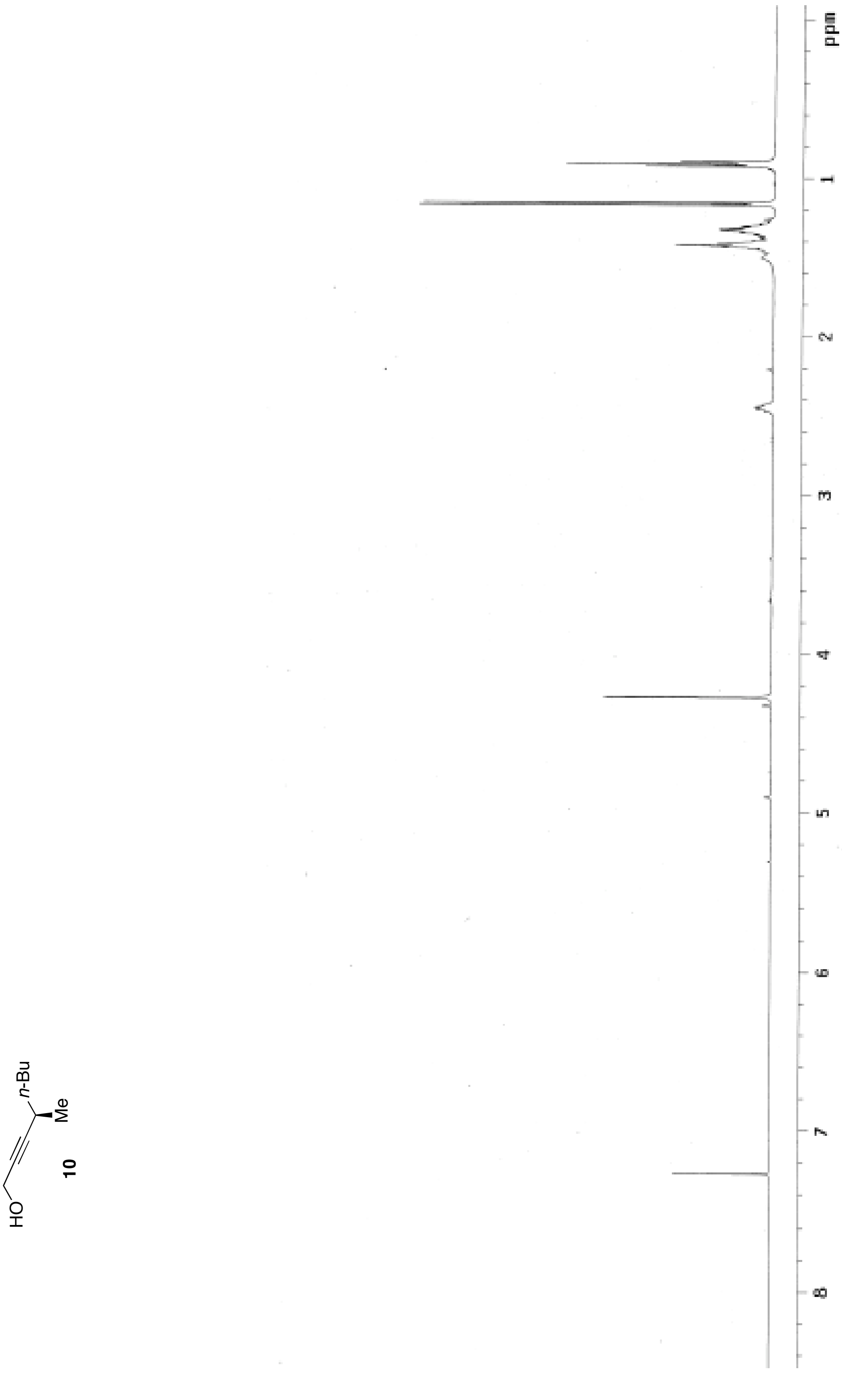
2, pumiliotoxin 209F



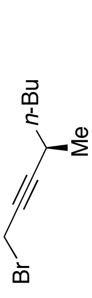


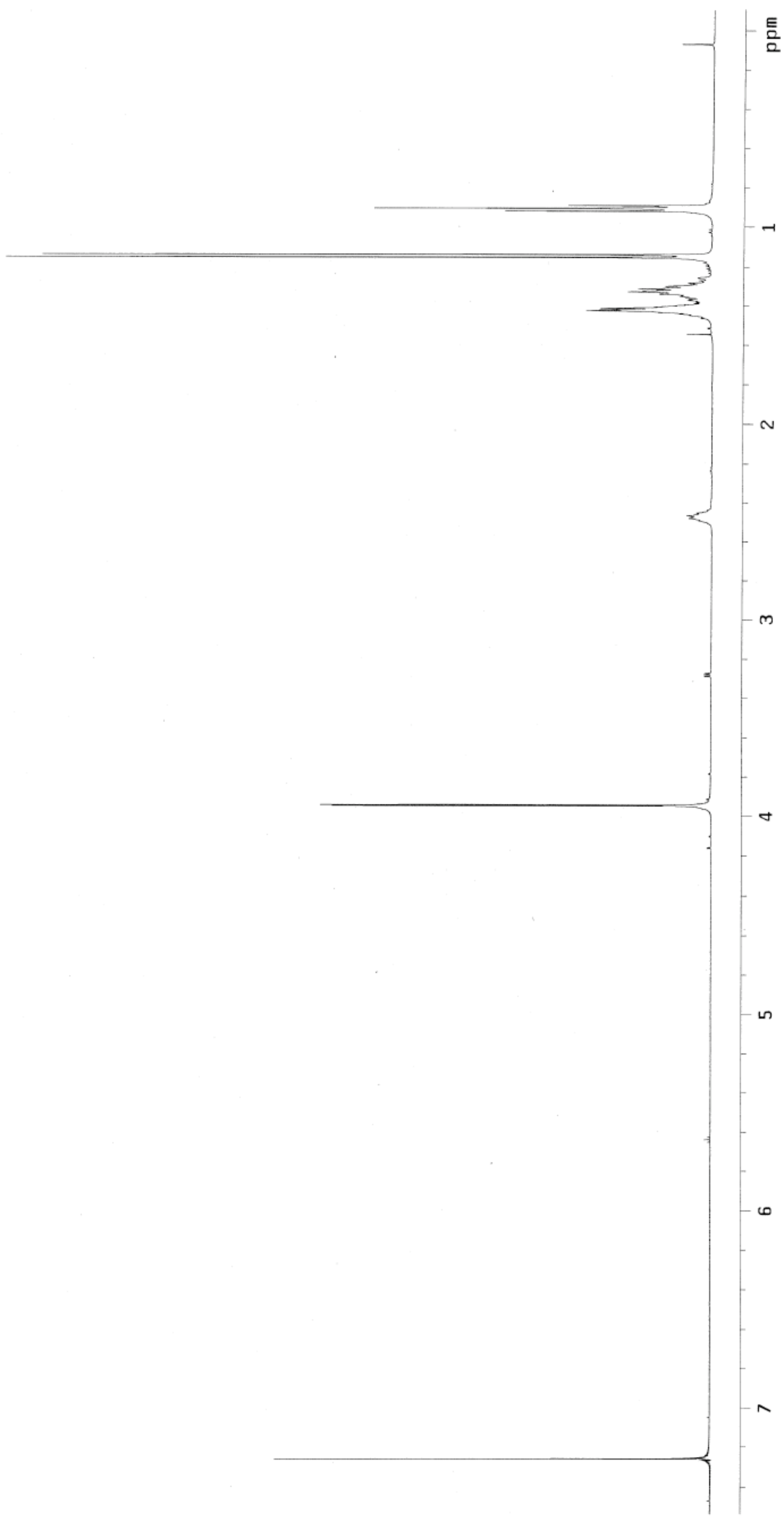
2, pumiliotoxin 209F

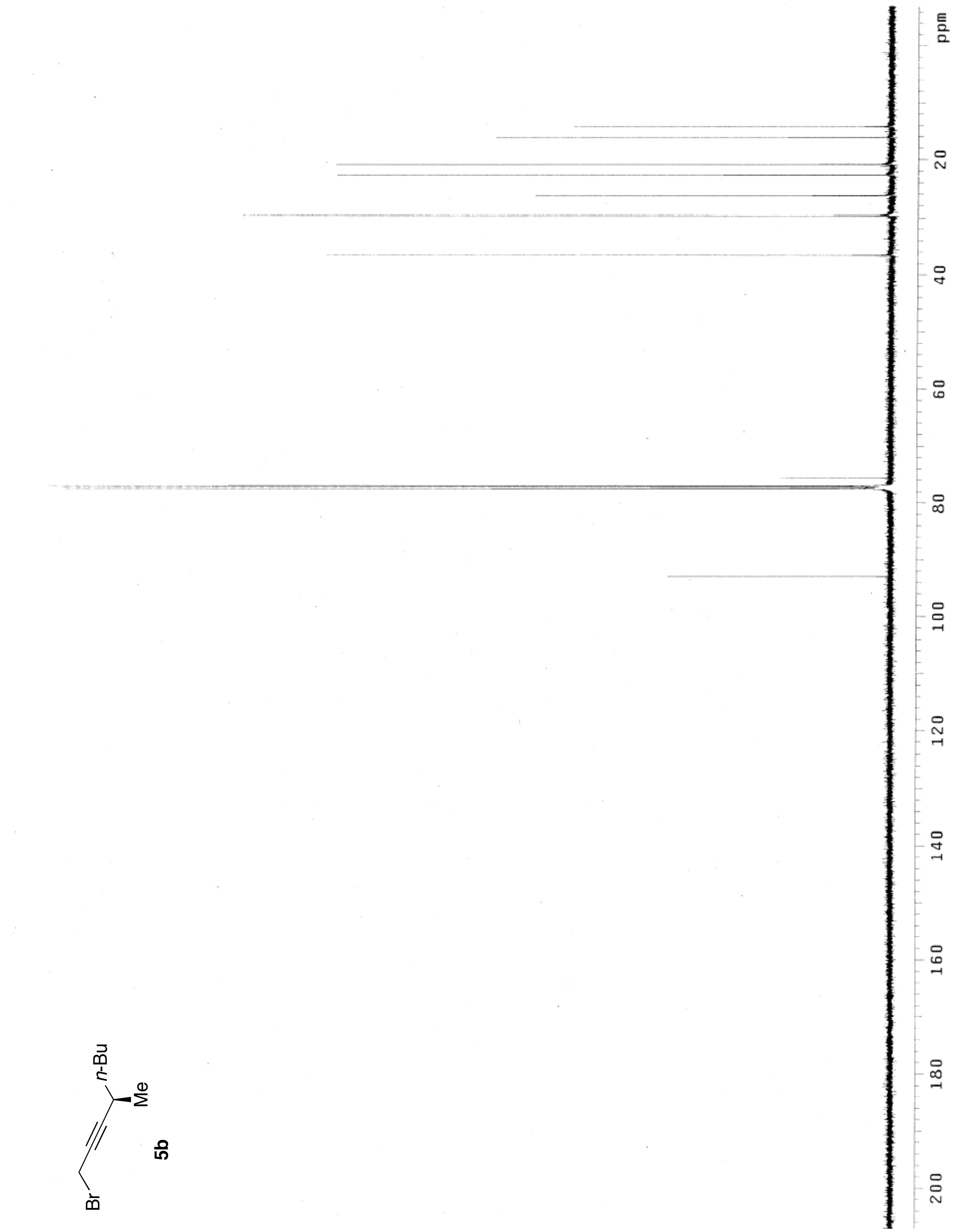

H
O
Me
9
ppm
1
2
3
4
5
6
7
8
9
10



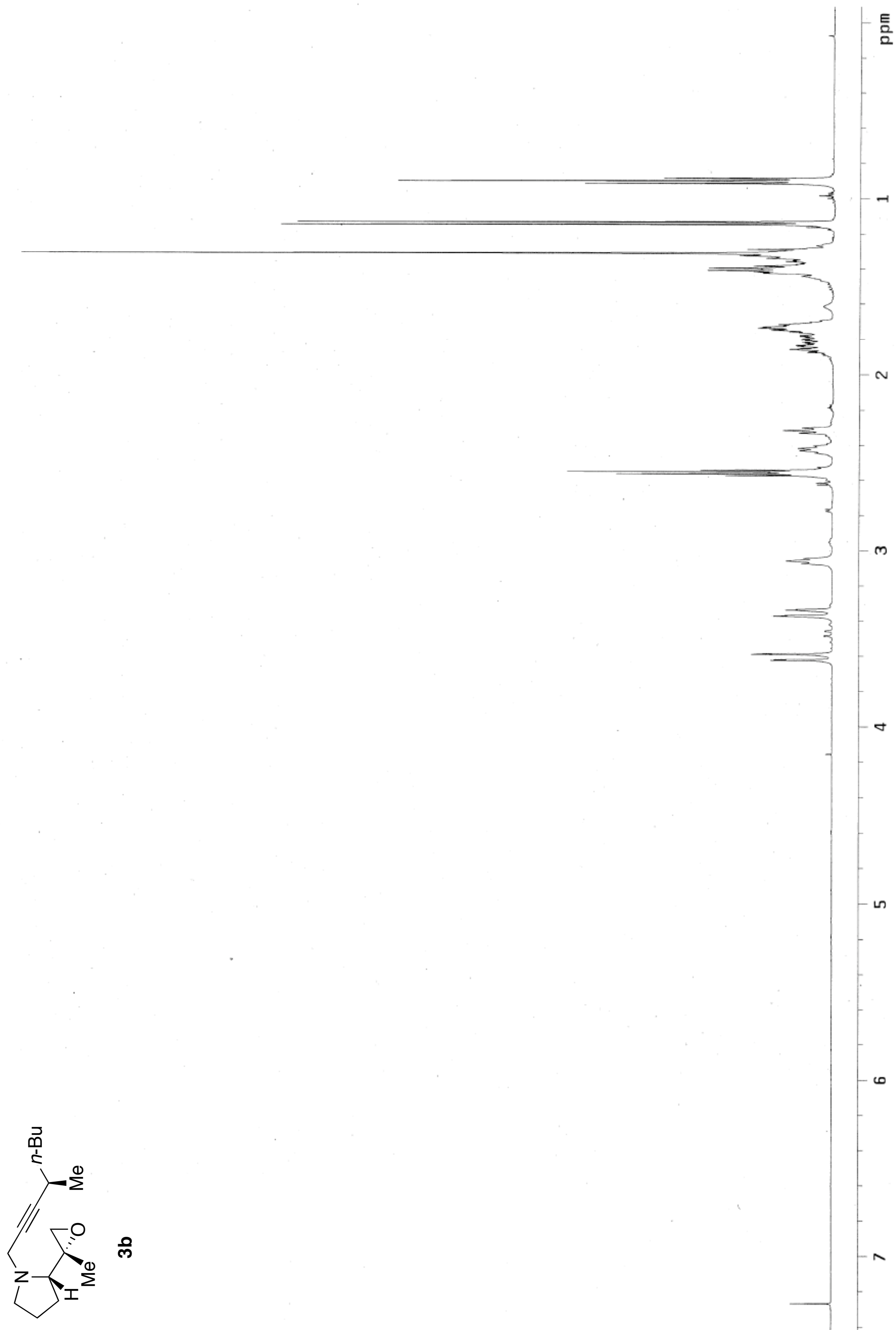
10

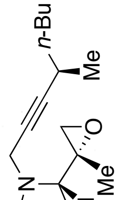

5b



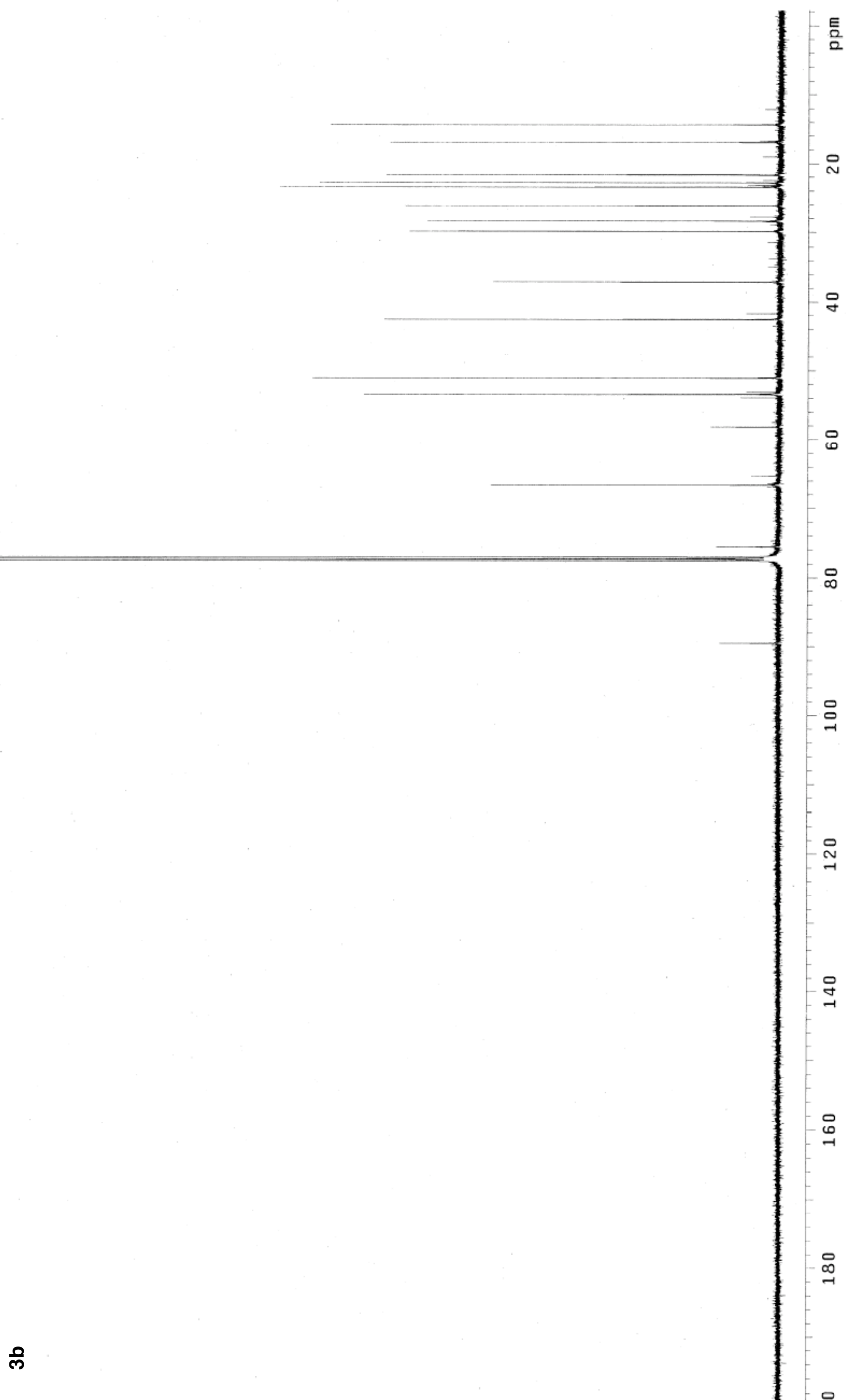


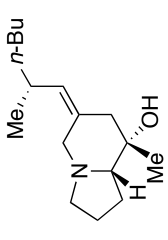
5b


ppm
1
2
3
4
5
6
7
n-Bu
Me
N
O
H
Me
3b

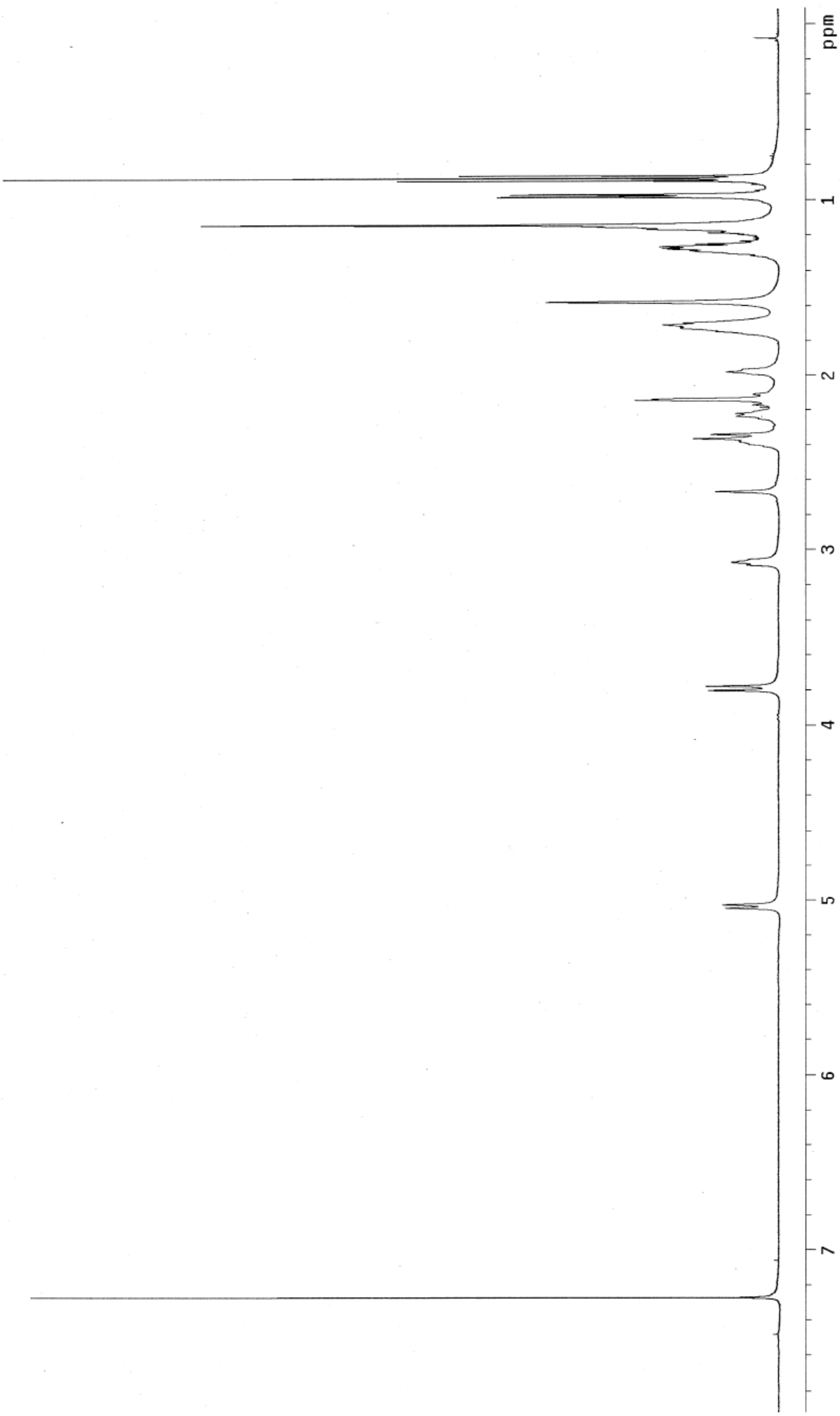


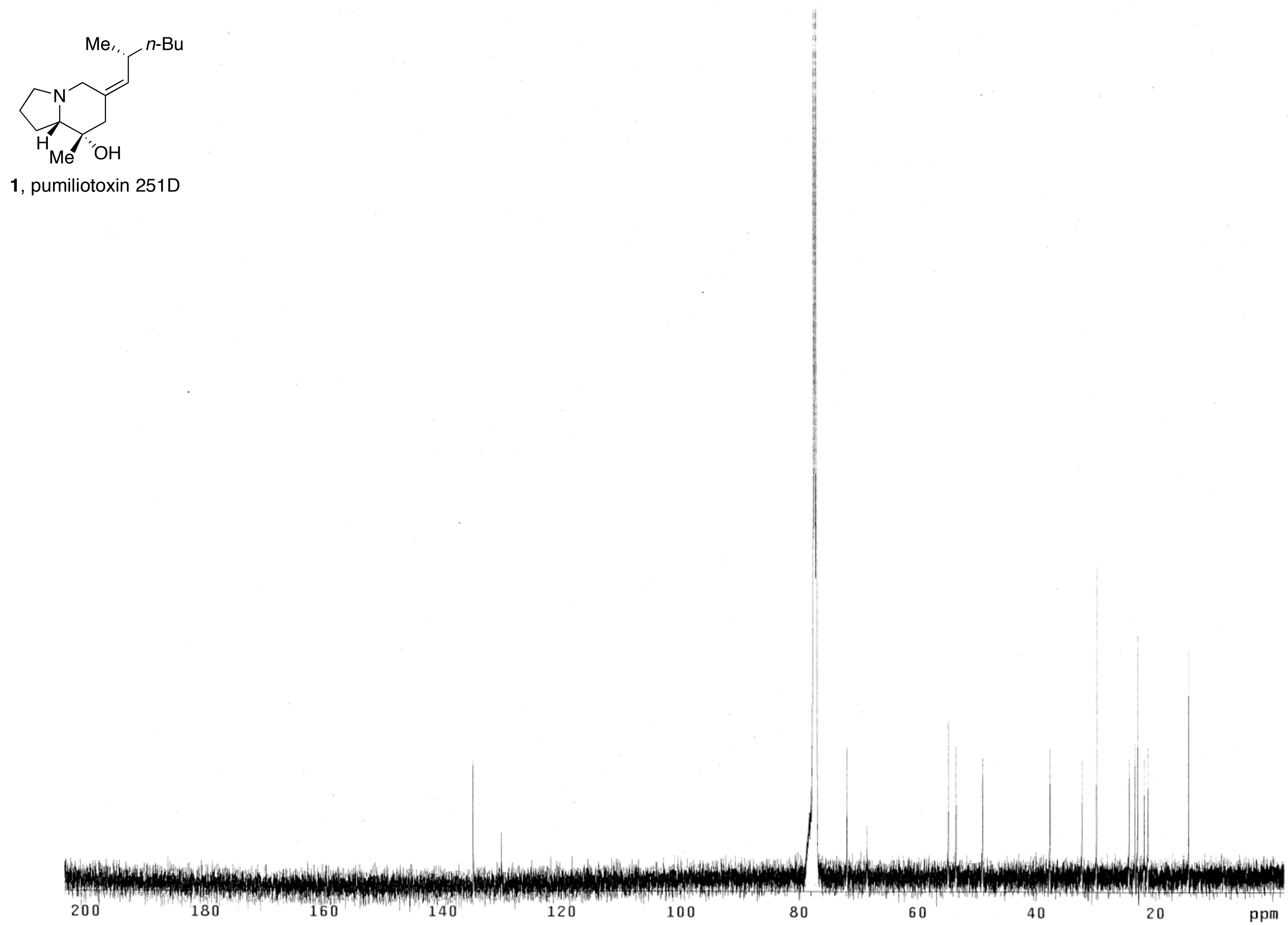
3b





1, pumiliotoxin 251D





1, pumiliotoxin 251D