FACULTAT DE FARMÀCIA
DEPARTAMENT DE FARMACOLOGIA i QUÍMICA TERAPÈUTICA

REACCIONS D'ALQUENILACIÓ INTRAMOLECULAR D'ENOLATS i NUCLEÒFILS RELACIONATS CATALITZADES PER PAL·LADI. APROXIMACIONS SINTÈTIQUES A L'ESTRICNOPIVOTINA i LA CALICIFILINA A

XAVIER URBANEJA i BIOSCA

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EXPERIMENTAL DEL CAPÍTOL 4

Strychnopivotine Synthesis Studies.
Preparation of the Bridged Azatricyclic Fragment

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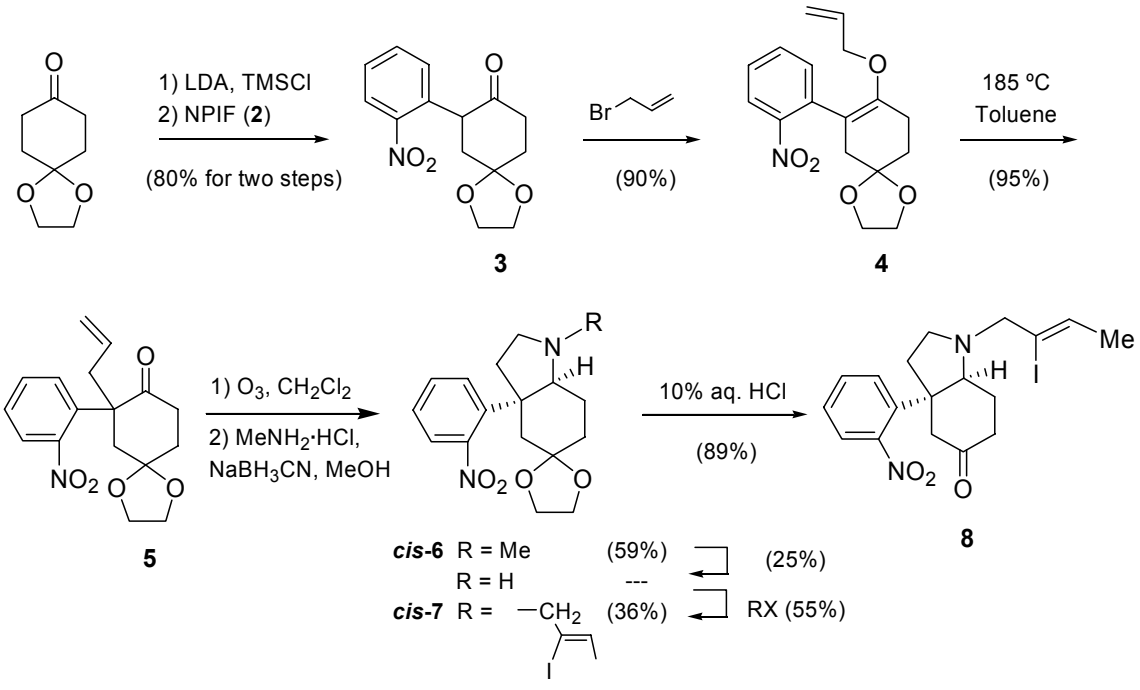
Experimental

General. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) and the spots were located with iodoplatinate reagent or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-240 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.



Scheme 1

2-(2-Nitrophenyl)-1,4-cyclohexane dione monoethylene acetal (3). A solution of 1,4-cyclohexanedione monoethylene acetal (5.06 g, 31.4 mmol) in THF (20 mL) was added to a cooled solution (-78 ºC) of LDA (26 mL, 1.5 M in cyclohexane) in THF (80 mL) over 10 min. After stirring for 1 h, TMSCl (7.2 mL, 55.60 mmol) was slowly added over 5 min. The solution was allowed to warm-up to room temperature and, after stirring for 1 h, the solvent was evaporated. Dry pentane (100 mL) was added and the LiCl removed by filtration. Concentration of the filtrate gave the corresponding silyl enol ether **1** (6.82 g, 95%), which was used without purification in the next step.

To a stirred solution of NPIF, **2**, (6.06 g, 17.56 mmol) in dry DMSO-CH_2Cl_2 (25/37 mL) was added the above silyl enol ether **1** (4.15 g, 18.17 mmol) dropwise at -40 ºC. The mixture was stirred for 2 h at this temperature and allowed to warm to room temperature gradually over 2-3 h. The reaction mixture was poured into H_2O (50 mL), and the whole was extracted with ether. The extracts were washed with brine, dried, and concentrated. The residue was purified by chromatography (hexane to hexane/EtOAc 1:1) to give **3** (4.03 g, 83%): IR 1716, 1523, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 2.12 (dm, *J* = 13. 2 Hz), 2.22 (td, *J* = 13.8, 5.1 Hz, 1H), 2.30 (ddd. *J* = 13, 6, 3.6 Hz, 1H), 2.48 (t, *J* = 13 Hz, 1H), 2.53 (ddd, *J* = 15, 4.8, 2.7 Hz, 1H), 2.85 (tdd, *J* = 14.5, 7.2, 0.8 Hz, 1H), 4.02-4.13 (m, 4H), 4.54 (dd, *J* = 10.5, 6 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.2 Hz), 7.44 (td, *J* = 8, 1.5 Hz), 7.60 (td, *J* = 8, 1.2 Hz,1H), 8.03 (dd, *J* = 8.1, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) 33.9 (CH_2), 38.1 (CH_2), 40.3 (CH_2), 50.3 (CH), 64.7 (CH_2), 64.8 (CH_2), 107.1 (C), 125.1 (CH), 128.0 (CH), 130.6 (CH), 133.0 (C), 133.3 (CH), 148.9 (C), 206.3 (CO). Anal. calcd for $C_{12}H_{15}NO_5$: C 60.65, H 5.45, H 5.05. Found C 60.02, H 5.50, N 4.92.

4-Allyloxy-3-(2-nitrophenyl)-3-cyclohexenone ethylene acetal (4). A mixture of ketone **3** (6.3 g, 22.8 mmol), allyl bromide (5.2 ml, 60.2 mmol), and anhydrous Cs_2CO_3 (23.5 g, 70.6 mmol) in acetone (125 ml) was stirred at reflux temperature for 18 h. The solvent was removed, and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated to give enol ether **4** (6.50 g, 90%) as an oil, which was used in the next step without further purification: ^1H NMR (200 MHz) 1.95 (m, 2H), 2.40 (m, 2H), 2.65 (m, 2H), 2.59 (s, 2H), 4.03 (s, 2H), 4.06 (m, 4H), 5.00 (ddt, *J* = 10.5, 2.5, and 1.5 Hz, 1H), 5.05 (ddt, *J* = 17.2, 2.5, and 1.5 Hz, 1H), 5.65 (ddt, *J* = 17.2, 10.5, and 5.4 Hz, 1H), 7.35 (ddd, *J* = 8.2, 7.3, and 1.5 Hz, 1H, H-4'), 7.40 (dd, *J* = 7.8 and 1.5 Hz, 1H, H-6'), 7.55

(ddd, *J* = 7.8, 7.3, and 1.2 Hz, 1H, H-5'), 7.85 (dd, *J* = 8.2 and 1.2 Hz, 1H, H-3'). ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) 24.1 (CH_2), 31.1 (CH_2), 39.0 (CH_2), 64.5 (OCH_2), 68.6 (CH_2), 107.2 (C), 116.5 (CH_2), 123.8 (CH), 127.1 (CH), 128.0 (C), 131.0 (CH), 132.4 (CH), 133.8 (CH), 148.0 (C).

2-Allyl-2-(2-nitrophenyl)-1,4-cyclohexanedione monoethylene acetal (5). A solution of enol ether **4** (6.50 g, 20.5 mmol) in toluene (60 mL) was stirred at 180-190 °C in a sealed tube for 12 h. After the solvent was evaporated, the residue was crystallized (1% EtOAc in hexane) affording **5** (6.17 g, 95%) as pale brown crystals. IR ($CDCl_3$) 1701, 1519, 1359 cm^{-1}. ^{1}H NMR (200 MHz) 2.03 (d, *J* = 13 Hz, 1H), 2.41-2.60 (m, 3H), 2.79 (m, 1H), 2.84 (d, *J* = 13.5 Hz, 1H), 2.97 (dd, *J* =16.5, 6 Hz, 1H), 3.39 (dd, *J* = 16.5, 7.2 Hz, 1H), 3.95 and 4.12 (AA'BB' system, 4H), 4.93 (dd, *J* = 10 and 1.5 Hz, 1H), 5.06 (dd, *J* = 17 and 1.5 Hz, 1H), 5.36 (dddd, *J* = 17, 10, 7 and 6 Hz, 1H), 7.39 (td, *J* = 8 and 1.5 Hz, 1H), 7.44-7.62 (m, 2H), 7.87 (dd, *J* = 8 and 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) 32.4 (CH_2), 36.1 (CH_2), 40.3 (CH_2), 47.4 (CH_2), 56.1 (C), 64.1 (CH_2), 64.8 (CH_2), 107.1 (C), 117.9 (CH_2), 125.7 (CH), 127.6 (CH), 129.3 (CH), 132.6 (C), 132.8 (CH), 136.4 (C), 149.0 (C), 206.2 (CO). Anal. Calcd for $C_{17}H_{19}NO_5$ (317.34): C 64.34, H 6.03, N 4.28. Found: C 64.19, H 6.09, N 4.31.

2-Methyl-3a-(2-nitrophenyl)octahydroindol-5-one ethylene acetal (6). A stirred solution of ketone **5** (520 mg, 1.64 mmol) in CH_2Cl_2 (30 mL) at -78 °C was treated with a constant stream of ozone. After 15 min, the solution turned a characteristic pale blue and was purged with oxygen. The solvent was removed without warming, and the residue was dissolved in MeOH (15 mL). To this solution were added methylamine hydrochloride (1.72 g, 25.0 mmol) and then sodium cyanoborohydride (74 mg, 1.12 mmol). After stirring for 30 min, an additional portion of sodium cyanoborohydride (88 mg, 1.33 mmol) was added and stirring was continued for 1 h. A third portion of sodium cyanoborohydride (203 mg, 3.1 mmol) was then added, and stirring was continued overnight. After removal of the methanol, CH_2Cl_2 was added and the resulting organic solution was washed with saturated aqueous $NaHCO_3$ solution, dried and concentrated. The resulting oil was purified by chromatography (CH_2Cl_2) to give 371 mg (71%) of ***cis*-6** and 63 mg (12%) of ***trans*-6**.

Compound ***cis*-6**: ^{1}H (400 MHz, $CDCl_3$, gCOSY) 1.38 (ddd, *J* = 12, 6, 3.2 Hz, H-6eq), 1.89 (td, *J* = 12, 6 Hz, H-6ax), 1.97 (m, H-3), 1.99-2.05 (m, 2H, H-7), 2.02 (d, *J* = 14.4

Hz, H-4), 2.10 (dd, *J* = 14,4, 1.6 Hz, H-4), 2.24 (m, H-2), 2.30 (s, NCH_3), 2.69 (br s, H-7a), 3.18 (ddd, *J* = 10.5, 7, 7 Hz, H-2), 3.57 and 3.82 (2m, 2H each, OCH_2), 7.30 (ddd, *J* = 7, 6.8, 2 Hz, 1H, ArH) 7.42-7.50 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC), see Table 1.

Compound ***trans*-6**: ^1H (300 MHz, $CDCl_3$) 1.56-1.67 (m, 4H), 1.80-2.05 (m, 3H), 2.27-2.42 (m, 2H), 2.38 (s, NCH_3), 2.52 (ddd, *J* = 12.5, 8.1, 3 Hz, 1H), 3.16 (dt, *J* = 10, 8, Hz, H-2), 3.56 (m, 1H), 3.77 (m, 4H, OCH_2), 7.25 (td, *J* = 8, 1.5 Hz, 1H, ArH), 7.43 (td, *J* = 8, 1.5 Hz, 1H, ArH), 7.49 (dd, *J* = 8, 1.5 Hz, 1H, ArH), 8.58 (dd, *J* = 8, 1.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-(2-nitrophenyl)octahydroindol-5-one ethylene acetal (7)**. Operating as above, from ketone **5** (940 mg, 2.97 mmol) and 2-iodobut-2-enamine hydrochloride (1.18 g, 5.04 mmol), ***cis*-7** (744 mg, 43%) and ***trans*-7** (129 mg, 9%) were obtained after chromatography (hexane to 1:1 hexane/EtOAc).

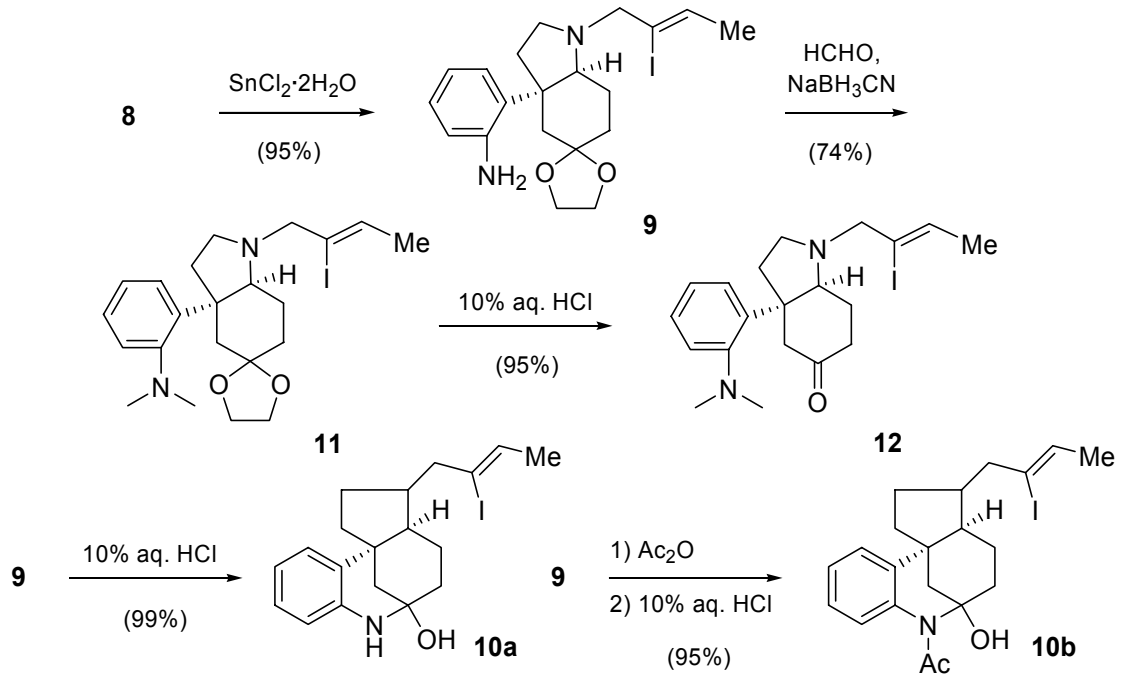
Data for ***cis*-7**: ^1H NMR (200 MHz, $CDCl_3$) 1.38 (dm, *J* = 11.4 Hz, 1H), 1.79 (dd, *J* = 6.4, 1.8 Hz, CH_3), 1.90-2.29 (m, 7H), 2.90 (d, *J* = 14 Hz, 1H), 3.13 (m, 1H), 3.56-3.70 (m, 3H), 3.76-3.89 (m, 4H), 5.88 (q, *J* = 6.6 Hz, 1H), 7.26-7.48 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

Compound ***trans*-7**: ^1H (300 MHz, $CDCl_3$) 0.95 (m, 1H), 1.58 (m, 2H), 1.80 (dd, *J* = 6.5, 1.5 Hz, CH_3), 1.88 (m, 1H), 2.05 (qd, *J* = 12.6, 4.5 Hz, H-7ax), 2.17 (m, 1H), 2.28-2.41 (m, 2H), 2.57 (ddd, *J* = 12.5, 8, 2.1 Hz, H-7a), 2.71 (dd, *J* = 13.5, 1.5 Hz, 1H, NCH_2), 3.01 (q, *J* = 8.5 Hz, H-2), 3.05 (d, *J* = 13.5 Hz, 1H, NCH_2), 3.58 (m, 1H), 3.77 (m, 4H, OCH_2), 5.86 (q, *J* = 6.5 Hz, =CH), 7.26 (td, *J* = 8, 1.5 Hz, 1H, ArH), 7.47 (m, 2H, ArH), 8.91 (d, *J* = 8 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-(2-nitrophenyl)octahydroindol-5-one (8)**. To a solution of ***cis*-7** (531 mg, 1.10 mmol) in THF (10 mL) was added 10% aqueous HCl (15 mL). After being stirred overnight, the mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give ketone **8** (444 mg, 92%), which was used without purification in the next step. An analytical sample was obtained by chromatography (CH_2Cl_2): ^1H NMR (300 MHz, $CDCl_3$) 1.79 (dd, *J* = 6.3, 1.2 Hz, CH_3), 1.91-2.06 (m, 2H), 2.11-2.31 (m, 4H), 2.79 (d, *J* = 15 Hz, 1H, H-4ax), 2.82 (ddd, *J* = 17, 12, 6 Hz, 1H, H-6ax), 2.96 (dd, *J* = 15, 0.6 Hz, 1H, H-

4eq), 3.02 (d, J = 13.5 Hz, 1H, NCH_2), 3.11 (m, 1H), 3.27 (t, J = 3 Hz, 1H, H-7a), 3.65 (dt, J = 13.5, 1.8 Hz, 1H, NCH_2), 5.85 (qd, J = 6.3, 1.8 Hz, =CH), 7.37 (m, 1H, ArH), 7.49-7.52 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1. Anal. Calcd for $C_{18}H_{21}IN_2O_3$: C 49.10, H 4.81, N 6.36. Found: C 49.19, H 4.79, N 6.32.

Attempts at cyclization of 8. To a stirred solution of ketone **8** (77 mg, 0.175 mmol) in THF (5 mL) were added *t*-BuOK (0.180 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (47 mg, 0.041 mmol). The solution was heated at reflux for 45 min. After being cooled to room temperature, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was dried and concentrated to give a residue resulting from decomposition of the starting material.



Scheme 2

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-(2-aminophenyl)octahydroindol-5-one ethylene acetal (9)**. To a solution of ***cis*-7** (877 mg, 1.81 mmol) in DMF (20mL) was added $SnCl_2·2H_2O$ (4.30 g, 18.68 mmol). After stirring at room temperature for 24 h, the reaction mixture was basified with 50% aqueous NaOH, extracted with CH_2Cl_2 and washed with brine. The organic layer was dried and concentrated to give **9** (782 mg, 95%), which was used without purification in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (dm, J = 9 Hz, 1H), 1.80 (dd, J = 6.3, 1.2 Hz, CH_3), 1.95 (m, 3H), 2.07-

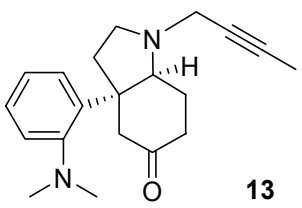
2.27 (m, 4H), 2.72 (dd, *J* = 13.8, 1.5 Hz, 1H), 2.92 (d, *J* = 13.5 Hz, 1H), 3.08-3.16 (m, 2H), 3.57 (q, *J* = 8 Hz, 1H), 3.68-3.90 (m, 5H), 5.88 (q, *J* = 6.6 Hz, =CH), 6.64 (dd, *J* = 7.5, 1.5 Hz, 1H, ArH), 6.73 (td, *J* = 7.5, 1.5 Hz, 1H, ArH), 7.02 (td, *J* = 7.5, 1.5 Hz, 1H, ArH), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

Hydrolysis of acetal 9. To a solution of **9** (47 mg, 0.103 mmol) in THF (2 mL) was added 10% aqueous HCl (2 mL). After stirring overnight at room temperature, the reaction mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give quantitatively **10a**: ^{1}H NMR (200 MHz, $CDCl_3$) 1.80 (d, *J* = 6.6 Hz, CH_3), 5.87 (q, *J* = 6.2 Hz, 1H, =CH), 6.51 (d, *J* = 8 Hz, 1H, ArH), 6.65 (t, *J* = 8 Hz, 1H, ArH), 7.02 (t, *J* = 8 Hz, 1H, ArH), 7.11 (d, *J* = 8 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) 21.6 (CH_3), 21.7 (CH_2), 30.8 (CH2), 35.1 (CH_2), 40.3 (CH_2), 47.0 (C), 50.3 (CH_2), 65.4 (CH_2), 68.5 (CH), 81.5 (C), 110.9 (C), 113.4 (CH), 117.1 (CH), 123.9 (CH), 124.6 (C), 127.6 (CH), 130.2 (CH), 144.5 (C).
Acetylation of aniline **9** (Ac_2O) followed by acid treatment of the resulting amido acetal gave tetracyclic hemiaminal **10b**: ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) 21.7 (CH_3), 23.9 (CH_2), 25.6 (NAc), 30.7 (CH_2), 32.2 (CH_2), 41.4 (CH_2), 46.1 (C), 49.6 (CH_2), 65.3 (CH_2), 66.2 (CH), 89.7 (C), 110.3 (C), 123.6 (CH), 124.1 (CH), 124.3 (CH), 126.3 (CH), 130.4 (CH), 135.1 (C), 138.7 (C), 175.6 (C).

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-[2-(*N*,*N*-dimethylamino)phenyl]octahydroindol-5-one ethylene acetal (11)**. To a stirred solution of **9** (782 mg, 1.72 mmol) and 37% aqueous formaldehyde (1.6 mL) in acetonitrile (7 mL) was added $NaBH_3CN$ (0.41 g, 6.20 mmol). Glacial acetic acid (0.180 mL) was added over 10 min, and the reaction was stirred at room temperature for 2 h. An additional amount of glacial acetic acid (0.180 mL) was added, and stirring was continued for an additional 30 min. The reaction mixture was poured into CH_2Cl_2, basified with 1 N NaOH and washed with brine. The organic layer was dried and concentrated, and the residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give **11** (613 mg, 74%): ^{1}H NMR (200 MHz, $CDCl_3$) 1.44 (dm, *J* = 8 Hz, 1H), 1.68 (m, 1H), 1.79 (dd, *J* = 6.3, 1.2 Hz, CH_3), 1.97-2.27 (m, 4H), 2.56 and 2.58 (2s, 6H, NMe), 2.77 (dd, *J* = 14, 2 Hz, 1H), 2.94 (d, *J* = 14 Hz, 1H), 3.07 (br, 1H), 3.15 (ddd, *J* = 9.2, 9.2, 6.4, 1H), 3.50 (m, 1H), 3.60

(m, 1H), 3.75-3.90 (m, 4H), 5.88 (q, J = 6.2 Hz, =CH), 7.07-7.35 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-[2-(*N*,*N*-dimethylamino)phenyl]octahydroindol-5-one (12)**. To a solution of **11** (1.16 g, 2.41 mmol) in THF (10 mL) was added 10% aqueous HCl (30 mL). After stirring overnight at room temperature, the reaction mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give **12** (1.00 g, 95%), which was used without purification in the next step; ^{1}H NMR (300 MHz, $CDCl_3$) 1.58 (m, 1H), 1.79 (dd, J = 6.3, 1.8 Hz, CH_3), 1.95-2.06 (m, 2H), 2.10-2.19 (m, 2H), 2.28-2.39 (m, 2H), 2.55 and 2.58 (2s, 3H each, NMe), 2.72-2.82 (m, 2H), 3.02-3.18 (m, 3H), 3.64 (d, J = 13.5 Hz, 1H, NCH_2), 5.84 (q, J = 6.3 Hz, =CH), 7.24 (td, J = 8, 1.5 Hz, 1H, ArH), 7.23-7.30 (m, 2H, ArH), 7.39 (dd, J = 8, 1.5 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.



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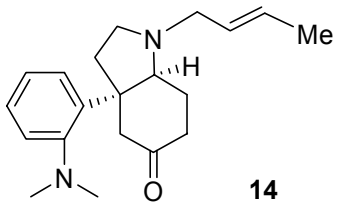
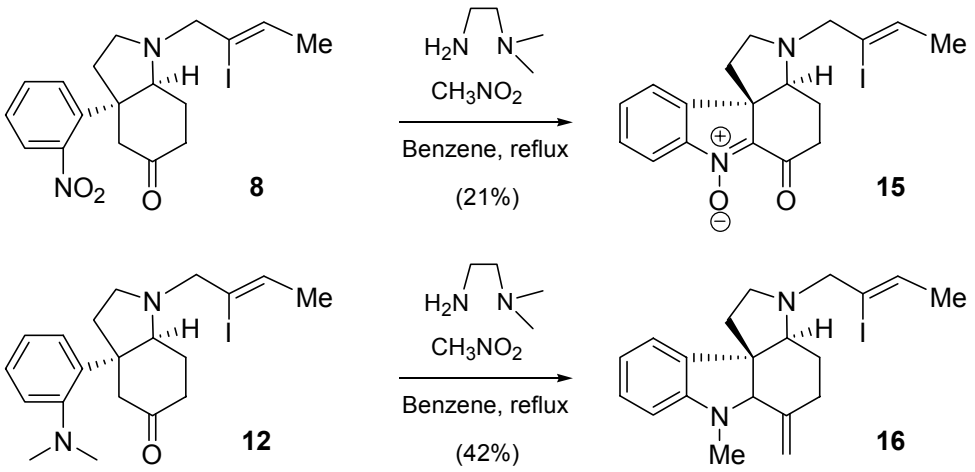


14

Attempts of cyclization of 12. a) To a stirred solution of ketone **12** (65 mg, 0.148 mmols) in THF (5 mL) were added *t*-BuOK (0.230 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmols). The solution was heated at reflux for 45 min. After being cooled to room temperature, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 92:8) to give alkyne **13** (40 mg, 87%): ^{1}H NMR (200 MHz, $CDCl_3$) 1.71 (s, CH3), 2.0-2.5 (m, 6H), 2.58 (s, 6H, NMe), 2.65-3.15 (m, 4H), 3.30-3.55 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

b) To a stirred solution of ketone **12** (300 mg, 0.685 mmol) and phenol (194 mg, 2.05 mmol) in THF (5 mL) were added *t*-BuOK (1.70 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (81 mg, 0.069 mmol). The solution was heated at reflux for 2 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and 1 N aqueous NaOH. The organic layer

was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 84:16) to give **14** (41 mg, 19%): ^{1}H NMR (400 MHz, $CDCl_3$, *g*COSY) 1.68 (d, *J* = 6 Hz, CH_3), 2.05 (m, 2H, H-6 and H-7), 2.10 (m, 2H, H-3 and H-7), 2.20 (m, 1H, H-6), 2.30 (m, 1H, H-2), 2.45 (masked, 1H, H-3), 2.50 (br s, 6H, NMe), 2.82 (d, *J* = 15 Hz, H-4), 2.83 (masked, 1H, NCH_2), 2.99 (d, *J* = 15 Hz, H-4), 3.15 (br, 1H, H-7a), 3.20 (m, 1H, H-2), 3.39 (dd, *J* = 13.2, 4.8 Hz, 1H, NCH_2), 5.55 (m, =CH), 5.60 (m, =CH), 7.14 (td, *J* = 8, 1.5 Hz, 1H, ArH), 7.25 (m, 2H, ArH), 7.38 (dd, *J* = 8, 1.5 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC), see Table 1.



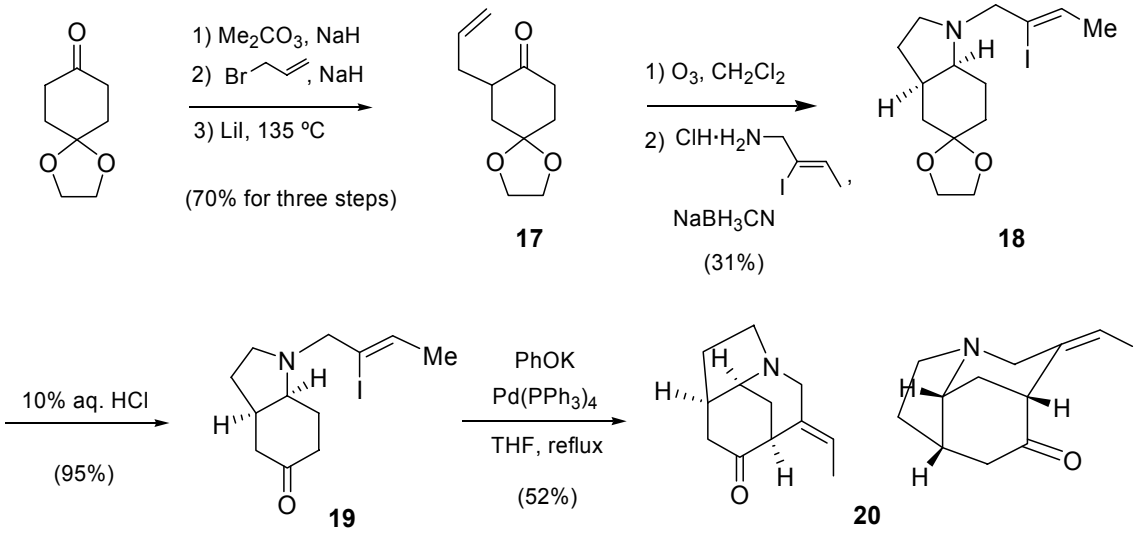
Scheme 3

Treatment of ketone 8 with nitromethane in basic medium. In a round-bottomed flask fitted with a Dean-Stark trap were placed **8** (444 mg, 1.01 mmol), nitromethane (1.0 mL, 17.54 mmol), *N*,*N*-dimethylethylendiamine (40 μL, 0.346 mmol), and benzene (10 mL), and the solution was refluxed for 8 h. The benzene solution was cooled, washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give tetracyclic keto nitrone **15**[1] (89 mg, 21%): ^{1}H NMR (300 MHz, $CDCl_3$) 1.56 (tt, *J* = 14,1, 3.5 Hz H-5) 1.81 (dd, *J* = 6.3, 1.2 Hz, CH_3), 1.82 (masked, 1H), 2.05 (dm, J = 14.5 Hz, 1H), 2.41 (td, *J* = 12.3, 3.6 Hz, H-4), 2.51 (dm, *J* = 16 Hz, 1H), 2.79 (ddd, *J* = 12, 9.3, 5.1 Hz, 1H), 3.11 (ddd, *J* = 16, 14.5, 3.6 Hz, 1H), 3.26 (dd, *J* = 9, 6.6 Hz, 1H), 3.37 (br s, 1H, H-3a), 3.40 (d, *J* = 12, 1H, NCH_2), 3.66 (dt, *J* = 12, 1.5 Hz, 1H, NCH_2), 5.95 (q, *J* = 6.3 Hz, 1H, =CH), 7.47-7.59 (m, 3H, ArH), 7.86 (d, *J* = 8 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), 21.8 (CH_3), 27.0 (CH_2), 36.9 (CH_2), 37.0 (CH_2), 51.7

[1] IUPAC name: 3-[(*Z*)-2-iodo-2-butenyl]-7-oxide-1,2,3,3a,4,5-hexahydropyrrolo[2,3-*d*]carbazol-6-one.

(CH_2), 55.9 (C), 65.2 (CH), 65.5 (CH_2), 109.0 (C), 116.9 (CH), 122.2 (CH), 128.8 (CH), 132.1 (CH), 131.6 (CH), 141.6 (C), 142.4 (C), 145.9 (C), 190.3 (C).

Treatment of ketone 11 with nitromethane in basic medium. In a round-bottomed flask fitted with a Dean and Stark trap were placed **11** (444 mg, 1.01 mmol), nitromethane (1.3 mL, 22.80 mmol), N,N-dimethylethylendiamine (54 μL, 0.467 mmol), and benzene (5 mL), and the solution was refluxed for 8 h. The benzene solution was cooled, washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The residue was purified by chromatography (CH_2Cl_2) to give **16**[2] (180 mg, 42%): ^{1}H NMR (200 MHz, $CDCl_3$) 1.37 (m, 1H), 1.71 (m, 1H), 1.75 (d, J = 6.6 Hz, CH_3), 1.85 (m, 1H), 2.11-2.30 (m, 2H), 2.37 (m, 1H), 2.52 (m, 1H), 2.60 (s, 3H, NMe), 2.70 (m, 1H), 2.80 (m, 1H), 3.17 and 3.39 (2d, J = 14 Hz, 1H each, NCH_2), 3.23 (s, H-6a), 4.99 and 5.08 (2s, 1H each, $=CH_2$), 5.82 (q, J = 6.6 Hz, =CH), 6.49 (d, J = 8 Hz, 1H, ArH), 6.74 (t, J = 8 Hz, 1H, ArH), 7.12 (t, J = 8 Hz, 1H, ArH), 7.24 (d, J = 8 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) 21.7 (CH_3), 26.1 (CH_2), 30.3 (CH_3), 33.5 (CH), 34.8 (CH_2), 50.4 (CH_2), 54.4 (C), 63.6 (CH_2), 67.3 (CH), 79.1 (CH), 107.5 (CH), 109.9 (C),114.6 (CH2), 118.3 (CH), 123.5 (CH), 127.6 (CH), 130.3 (CH), 137.7 (C), 143.8 (C), 151.7 (C).



Scheme 4

[2] IUPAC name: 3-[(*Z*)-2-iodo-2-butenyl]-7-methyl-6-methylene-1,2,3,3a,4,5,6a,7-octahydropyrrolo[2,3-*d*]carbazole.

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]octahydroindol-5-one ethylene acetal (18)**. A stirred solution of 2-allyl-1,4-cyclohexanedione monoethyelene acetal[3] (**17**, 1.50 g, 7.64 mmol) in CH_2Cl_2 (120 mL) at -78 ºC was charged with a constant stream of ozone. After 25 min, the solution turned a characteristic pale blue and was purged with oxygen. The solvent was evaporated without warning, and the residue was dissolved in MeOH (26 mL). To this solution were added 2-Iodobut-2-enylamine hydrochloride (3.77 g, 16.16 mmol) and then $NaBH_3CN$ (350 mg, 5.29 mmols). After stirring for 30 min, an additional portion of $NaBH_3CN$ (370 mg, 5.59 mmol) was added and stirring was continued for 1 h. An additional portion of $NaBH_3CN$ (960 mg, 14.51 mmol) was then added. The reaction mixture was stirred overnight, and the MeOH was then evaporated. The crude was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2) to give **18** (862 mg, 31%); ^{1}H NMR (200 MHz, $CDCl_3$) 1.32-1.75 (m, 5H), 1.77 (dd, J = 6.6, 1.5 Hz, CH_3), 1.80-2.30 (m, 5H), 2.54 (q, J = 3 Hz, H-7a), 2.88 (d, J = 14 Hz, 1H, NCH_2), 3.12 (td, J = 9.2, 6 Hz, 1H, H-2), 3.58 (dt, J = 14, 1.8 Hz, 1H, NCH_2), 3.94 (s, 4H), 5.82 (q, J = 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]octahydroindol-5-one (19)**. To a solution of **18** (0.55 g, 1.51 mmol) in THF (60 mL) was added 10% aqueous HCl (60 mL). After stirring at room temperature for 17 h, the mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give **19** (468 mg, 95%), which was used without purification in the next step: ^{1}H NMR ($CDCl_3$, 300 MHz) 1.40 (m, 1H), 1.78 (dd, J = 6.6, 1.5 Hz, CH_3), 1.80-2.0 (m, 3H), 2.1-2.2 (m, 2H), 2.32 (dd, J = 15, 6,6 Hz, H-4), 2.42 (dd, J = 15, 6,6 Hz, H-4), 2.60 (m, 1H), 2.72 (m, 1H), 2.78 (ddd, J = 8.5, 8.1, 3.6 Hz, H-2), 3.03 (td, J = 8.5, 2.1 Hz, H-2), 3.06 (d, J = 13.8 Hz, 1H, NCH_2), 3.58 (dt, J = 13.8, 1.8 Hz, 1H, NCH_2), 5.84 (q, J = 6.4 Hz, =CH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

(1*RS*,7*RS*,8*RS*)-2-(*E*)-ethylidene-4-azatricyclo[5.2.2.0^{4,8}]undecan-10-one (20). To a stirred solution of ketone **19** (75 mg, 0.232 mmol) and phenol (69 mg, 0.729 mmol) in THF (30 mL) were added *t*-BuOK (0.58 mL of 1 M solution in *tert*-butyl alcohol) and

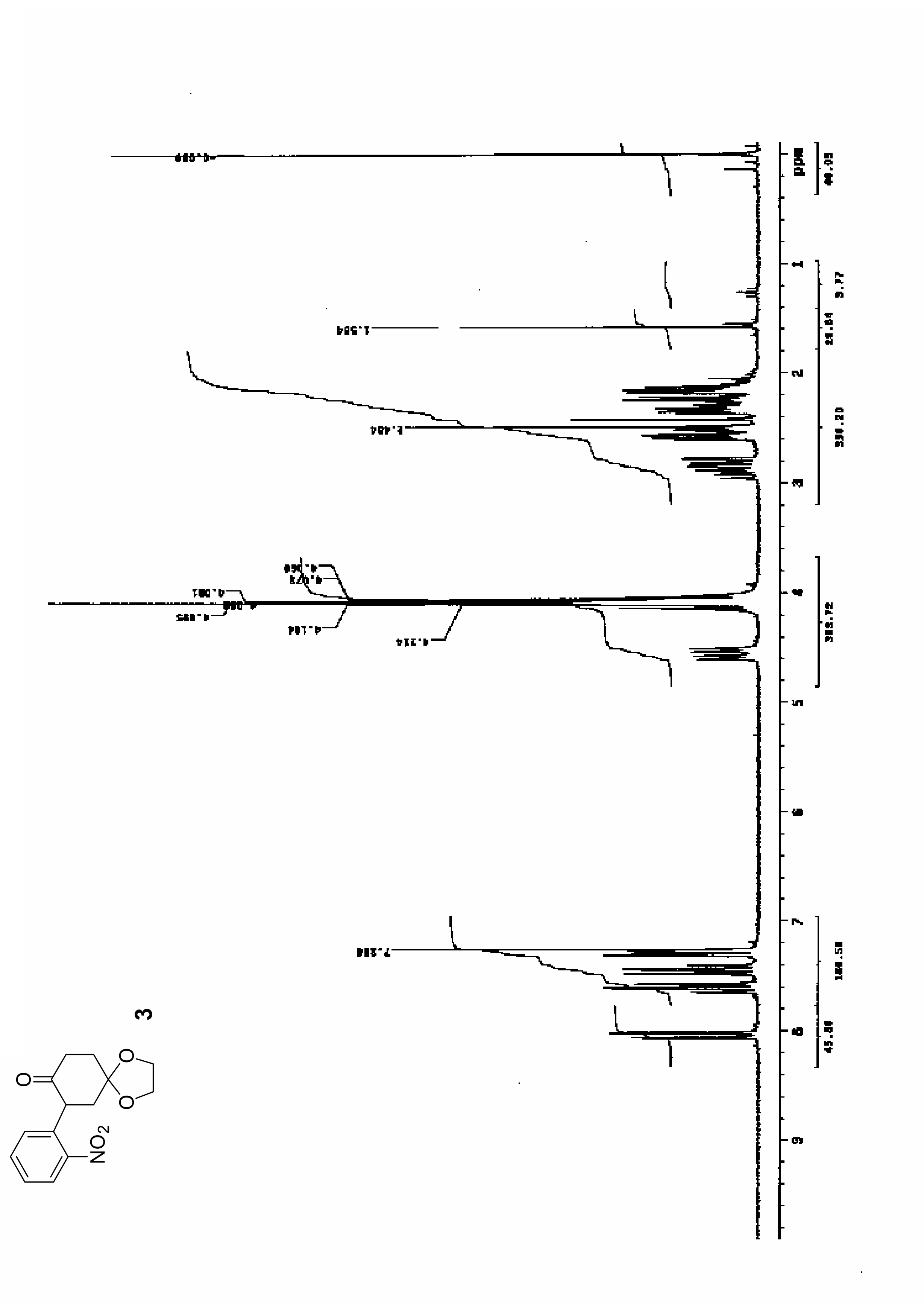
[3] Solé,D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461-5464 and references therein.

$Pd(PPh_3)_4$ (17 mg, 0.015 mmol). The solution was heated at reflux for 16 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and 1 M aqueous NaOH. The organic layer was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2/MeOH 98:2 to CH_2Cl_2/DEA 90:10) to give ketone **20** (23 mg, 52%); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.63 (d, *J* = 7 Hz, 3H, CH_3), 1.65 (m, 2H, H-6), 2.00 (br d, *J* = 14 Hz, H-9), 2.14 (m, 1H, H-11), 2.42 (m, 1H, H-9), 2.55 (m, H-7), 2.60 (m, 1H, H-11), 2.79 (td, *J* = 11.2, 6 Hz, 1H, H-5), 2.95 (d, *J* = 15.5 Hz, 1H, H-3), 3.15 (m,1H, H-5), 3.38 (m, 1H, H-1), 3.63 (br s, 1H, H-8), 3.78 (d, *J* = 15.5 Hz, 1H, H-3), 5.49 (q, *J* = 7 Hz 1H, =CH); ^{13}C NMR (100MHz, $CDCl_3$, DEPT, *g*HSQC) 13.1 (CH_3), 25.9 (C-9), 32.4 (C-6), 38.8 (C-7), 41.4 (C-11), 45.5 (C-1), 51.2 (C-5), 52.6 (C-3), 55.8 (C-8), 125.0(=CH), 211.2 (C-10).

Table 1. ^{13}C NMR Data for Octahydroindol-5-ones

	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	NCH_2	CHI	=CH	CH_3
***cis*-6**[a]	54.1	39.2	48.5	40.9	108.2	29.1	21.4	66.5	40.0			
***trans*-6**[b]	54.1	39.0	48.4	44.3	108.3	35.0	20.4	77.3	41.6			
***cis*-7**[c]	50.1	38.6	48.8	39.8	108.3	29.4	21.7	63.1	65.1	110.0	131.0	21.8
***trans*-7**[c]	50.9	39.0	48.6	44.2	108.5	35.0	20.7	74.3	66.8	110.0	132.1	21.8
8[b]	51.2	37.1	51.6	50.2	210.5	34.7	23.1	64.5	64.7	108.3	131.6	21.6
9[b]	50.4	29.4	48.0	38.1	108.9	37.4	22.1	64.7	64.7	109.4	131.1	21.7
11[c]	50.1	29.3	48.9	40.7	109.6	38.5	22.4	63.1	65.7	110.7	130.1	21.7
12[c]	50.6	34.9	50.9	50.4	212.7	37.9	23.1	65.6	65.5	109.6	130.8	21.8
13[c]	51.1	34.6	50.8	49.7	212.4	38.4	33.8	62.9	40.5	73.9	80.3	3.3
14[a]	50.6	34-0	51.1	50.9	212.2	38.4	23.1	65.6	55.3	143.9	128.0	17.8
18[b]	51.1	31.1	37.6	29.1	109.5	28.6	23.6	60.5	65.4	111.1	129.8	21.6
19[b]	51.7	31.1	36.6	43.4	213.6	35.7	24.6	59.7	65.7	109.9	130.9	21.7

All spectra were recorded in $CDCl_3$ (at [a]100 MHz, [b]75 MHz or [c]50 MHz) and the assignments were aided by HSQC experiments for compounds ***cis*-6** and **14**, and DEPT in all cases.



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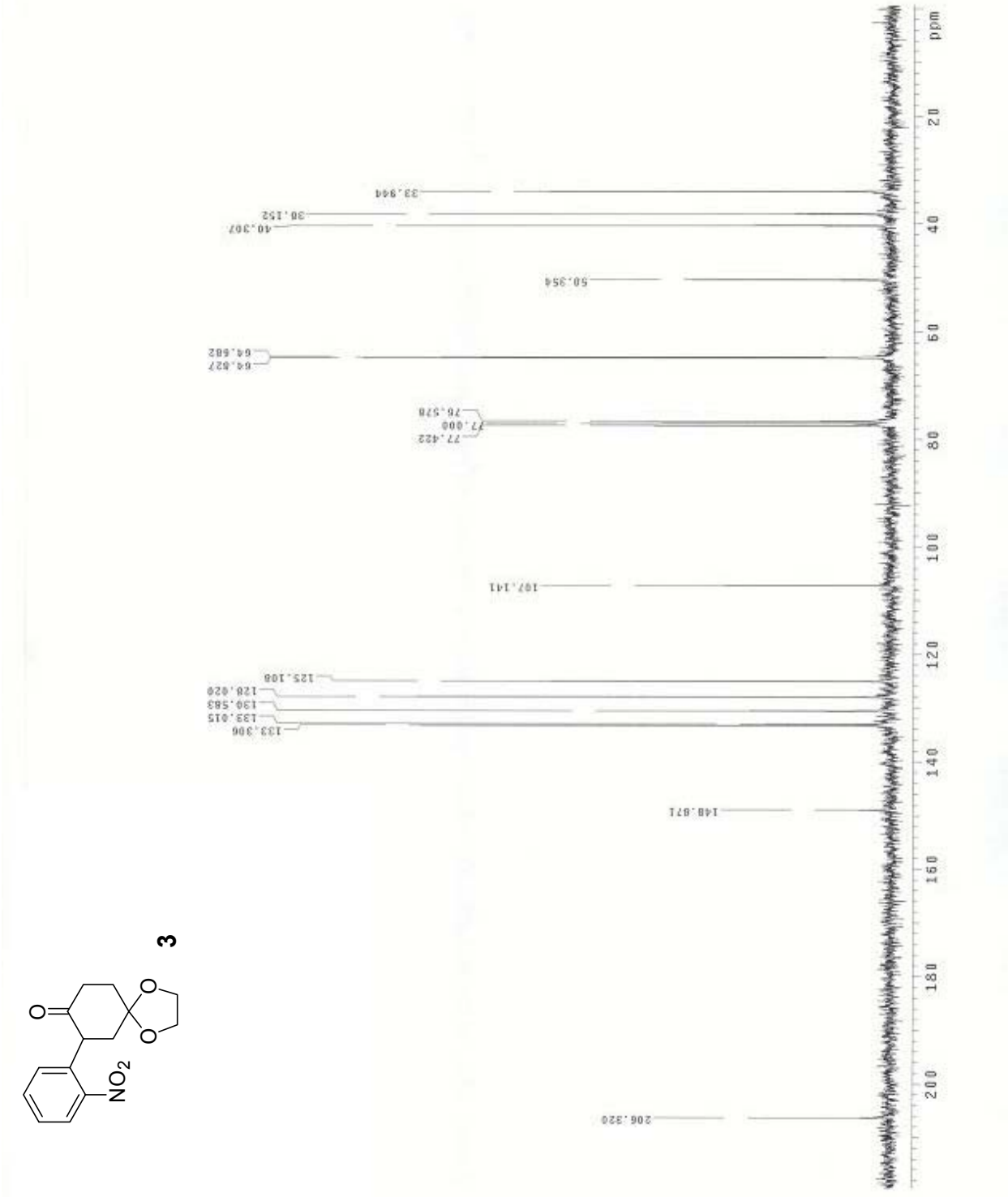
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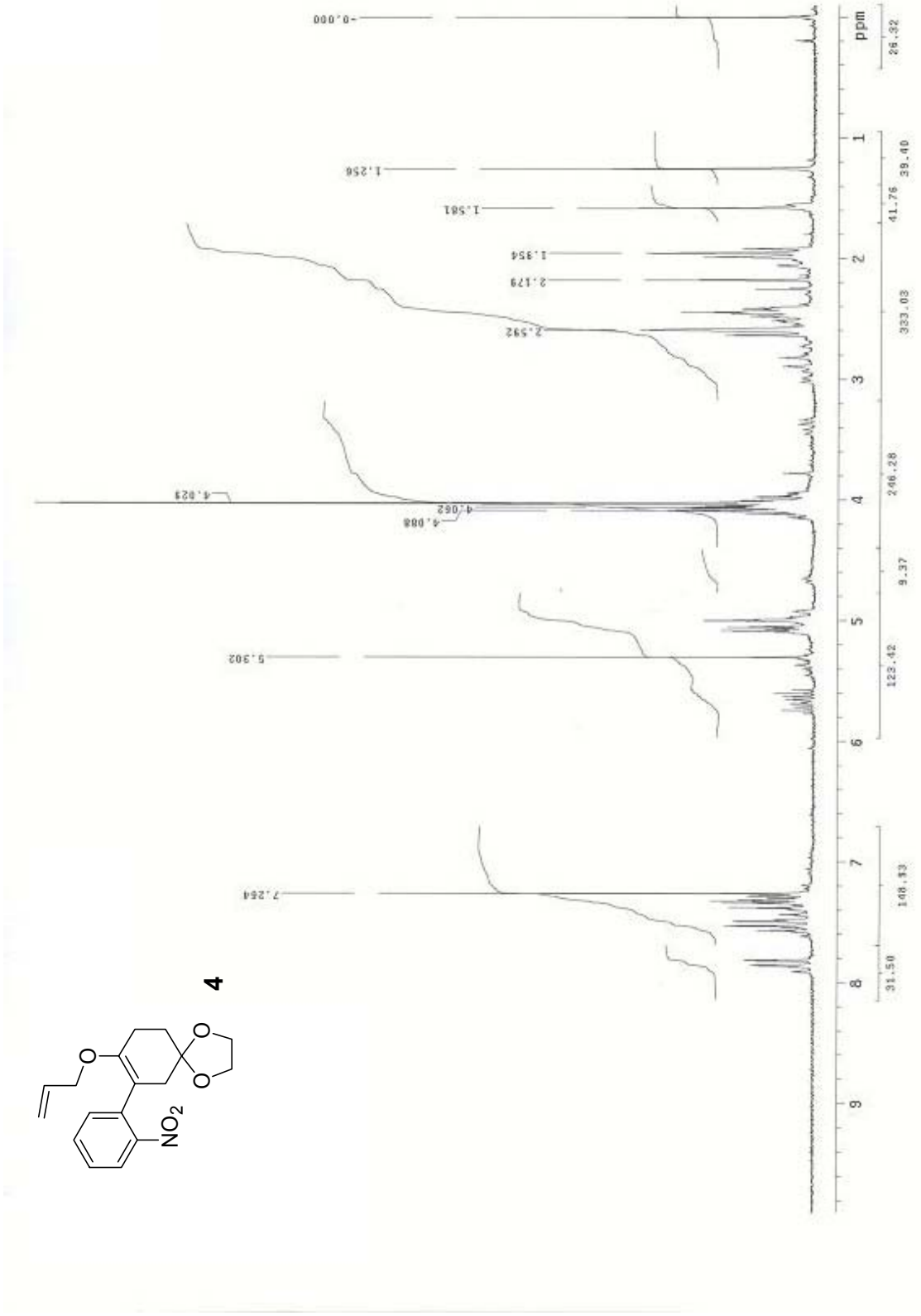
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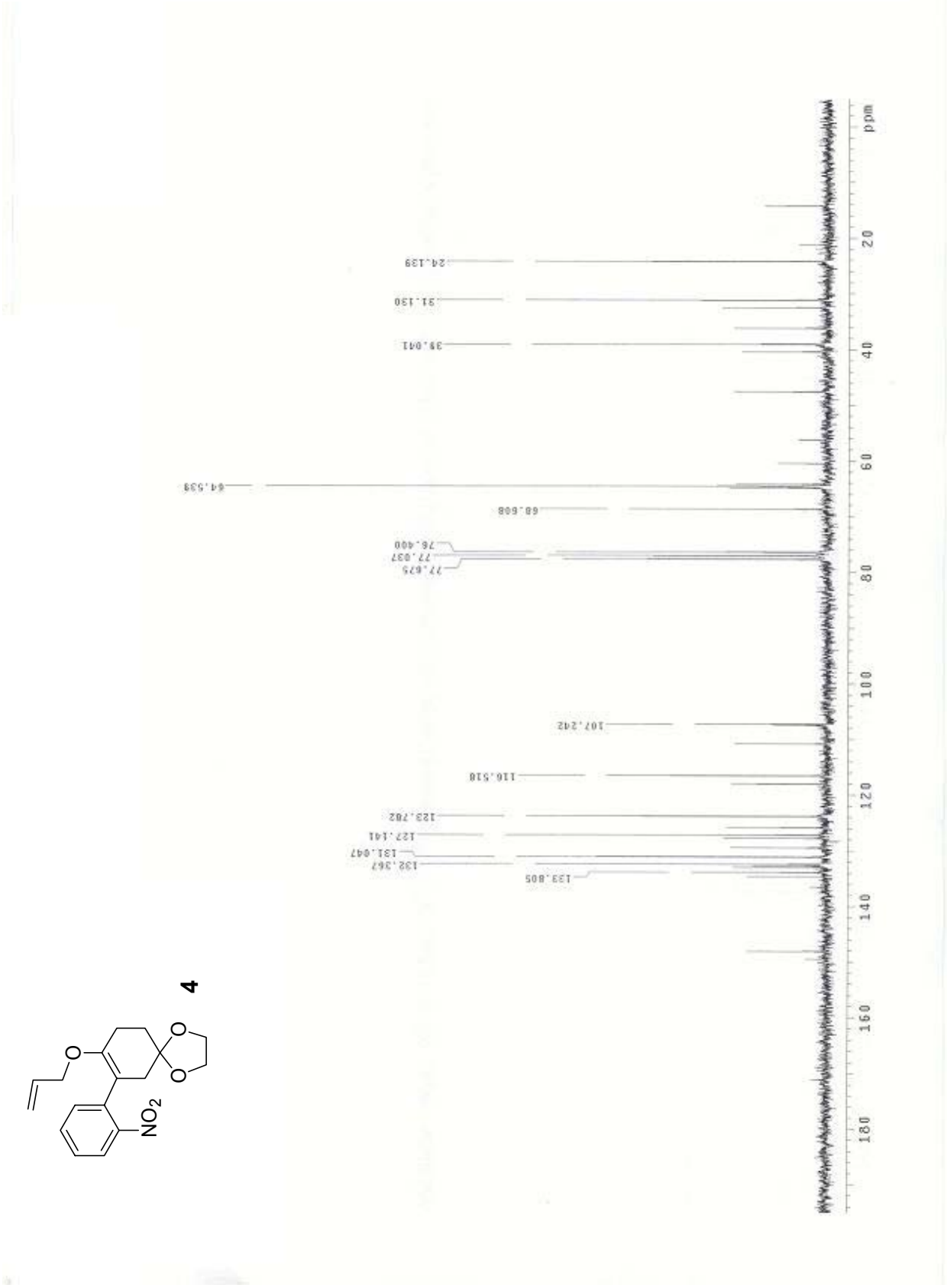
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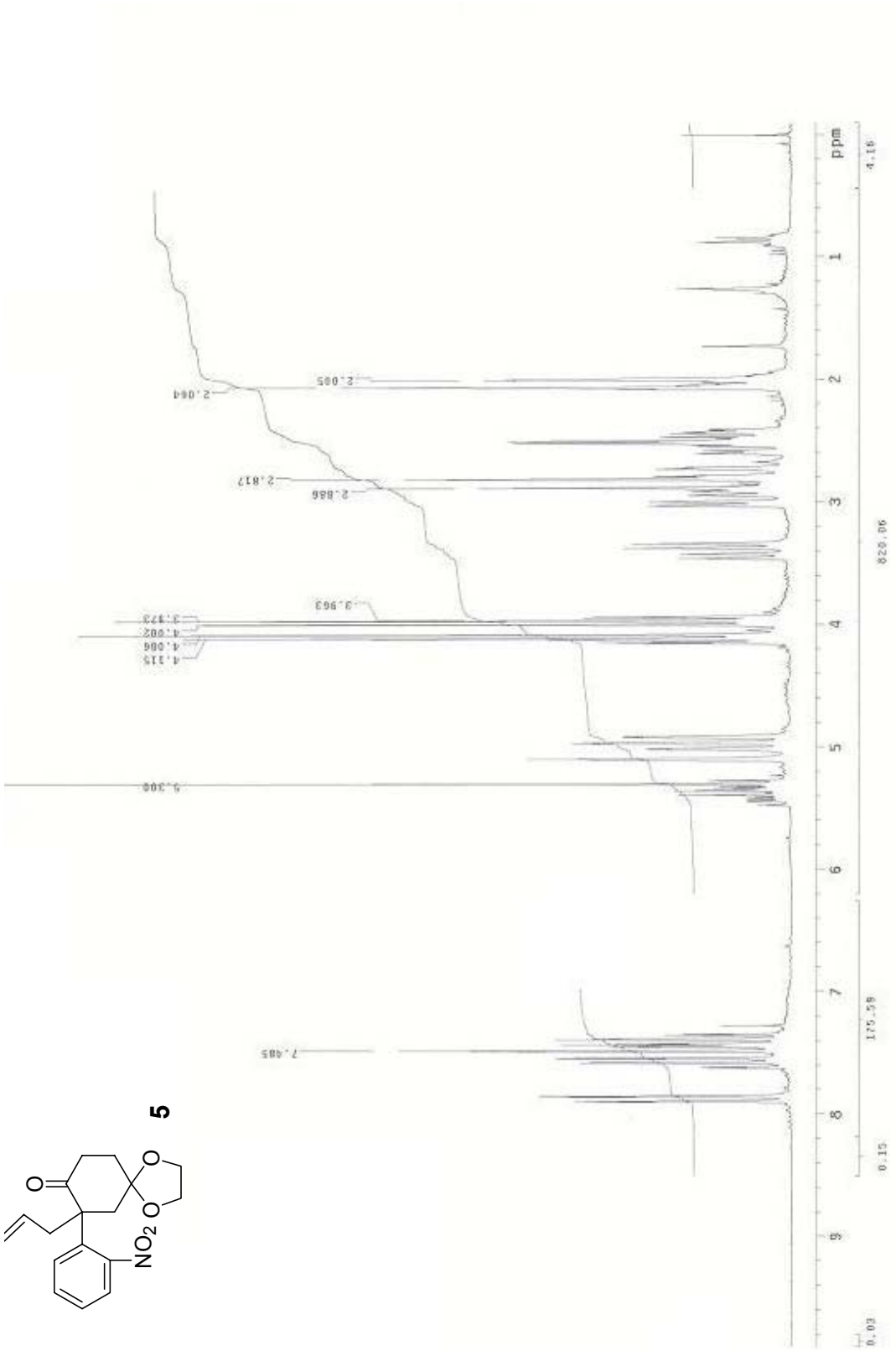
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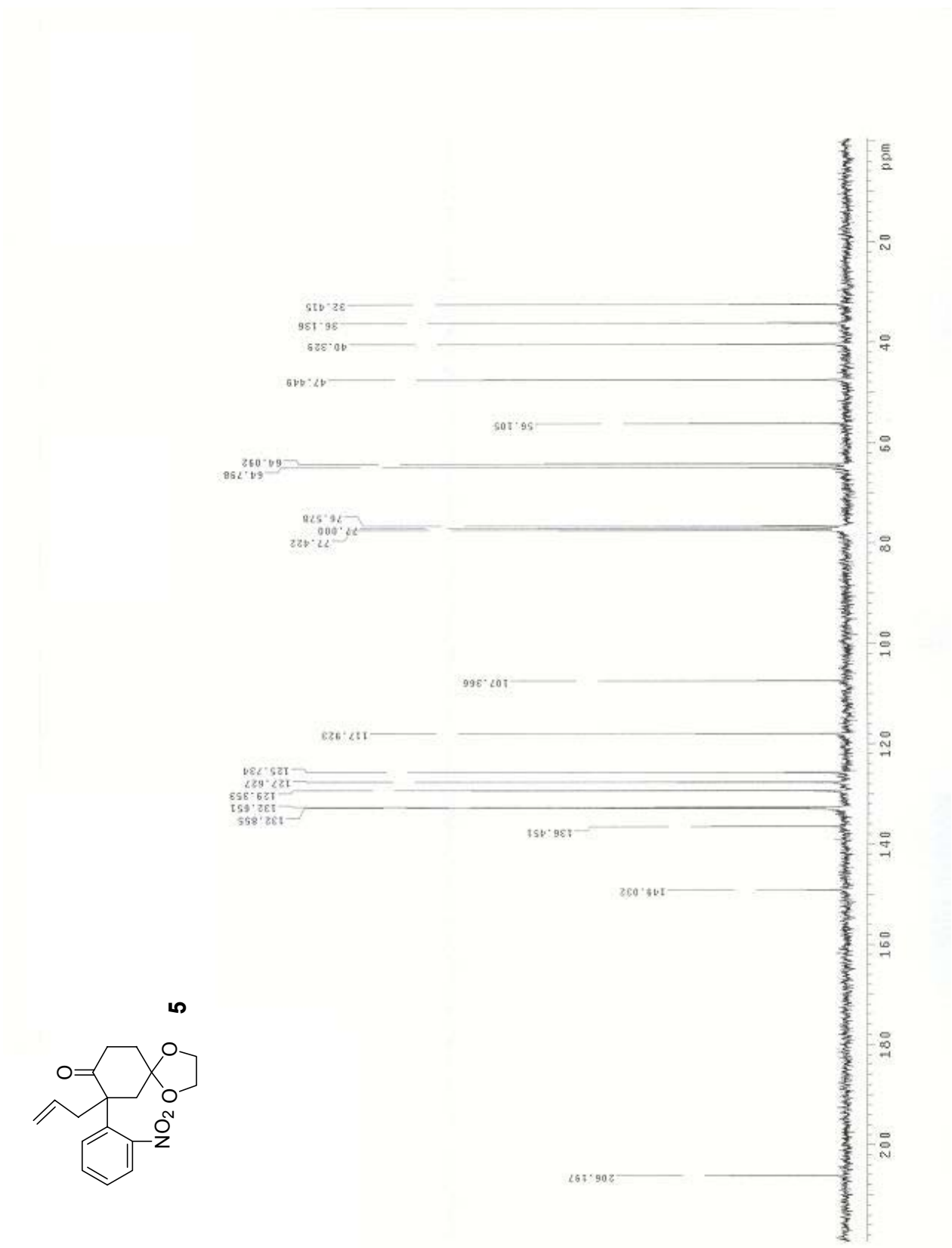
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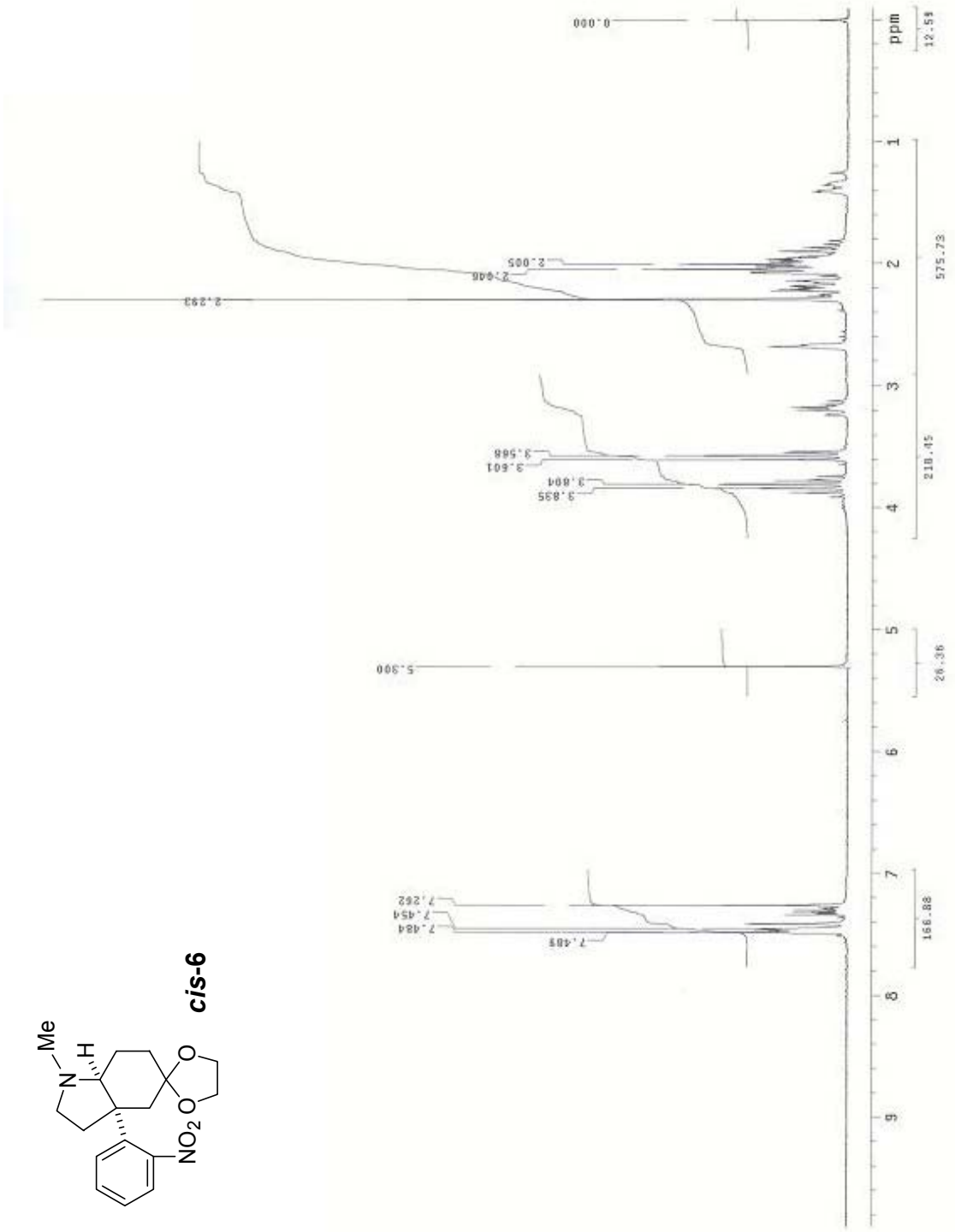
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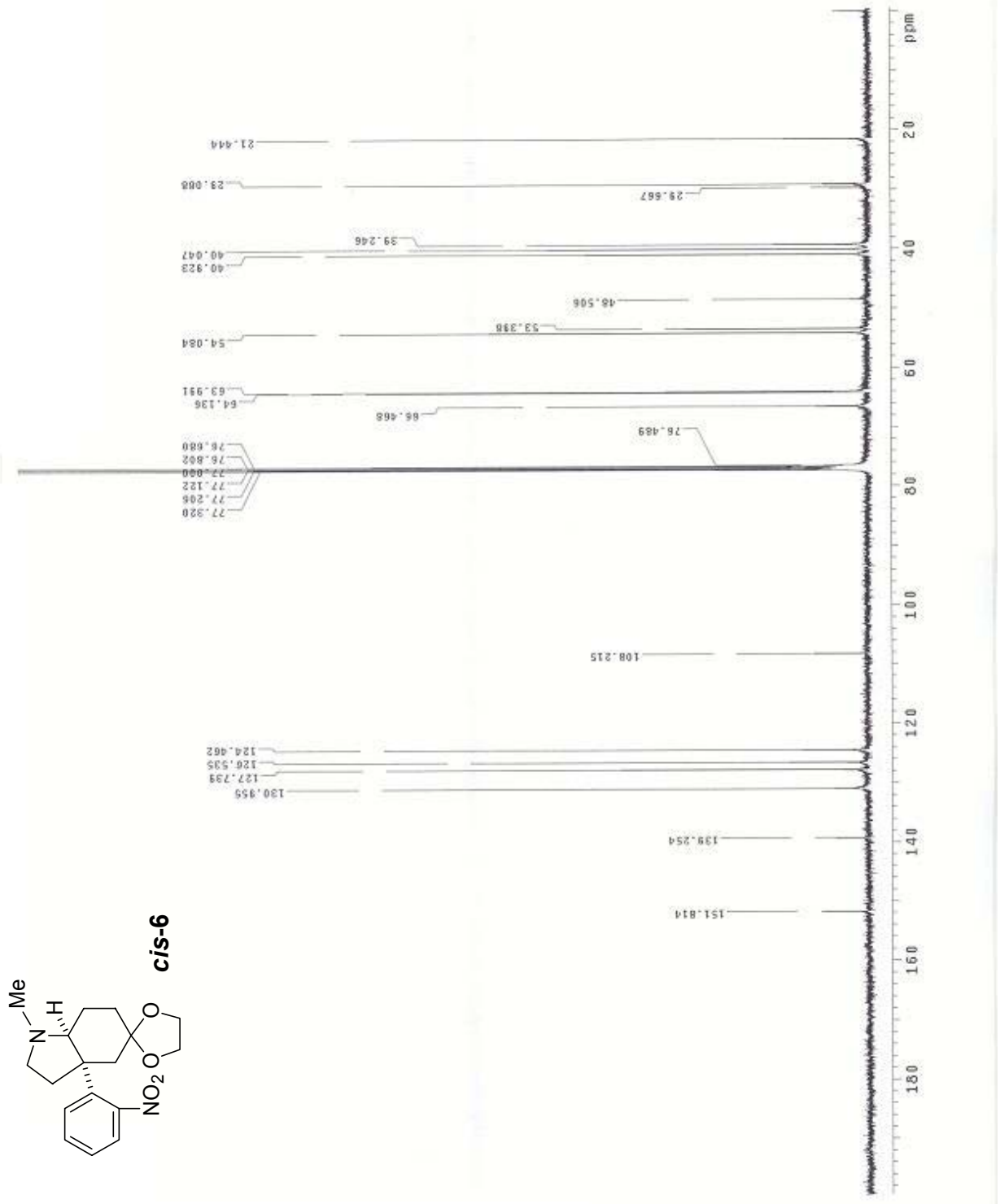
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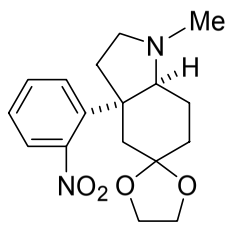
***cis*-6**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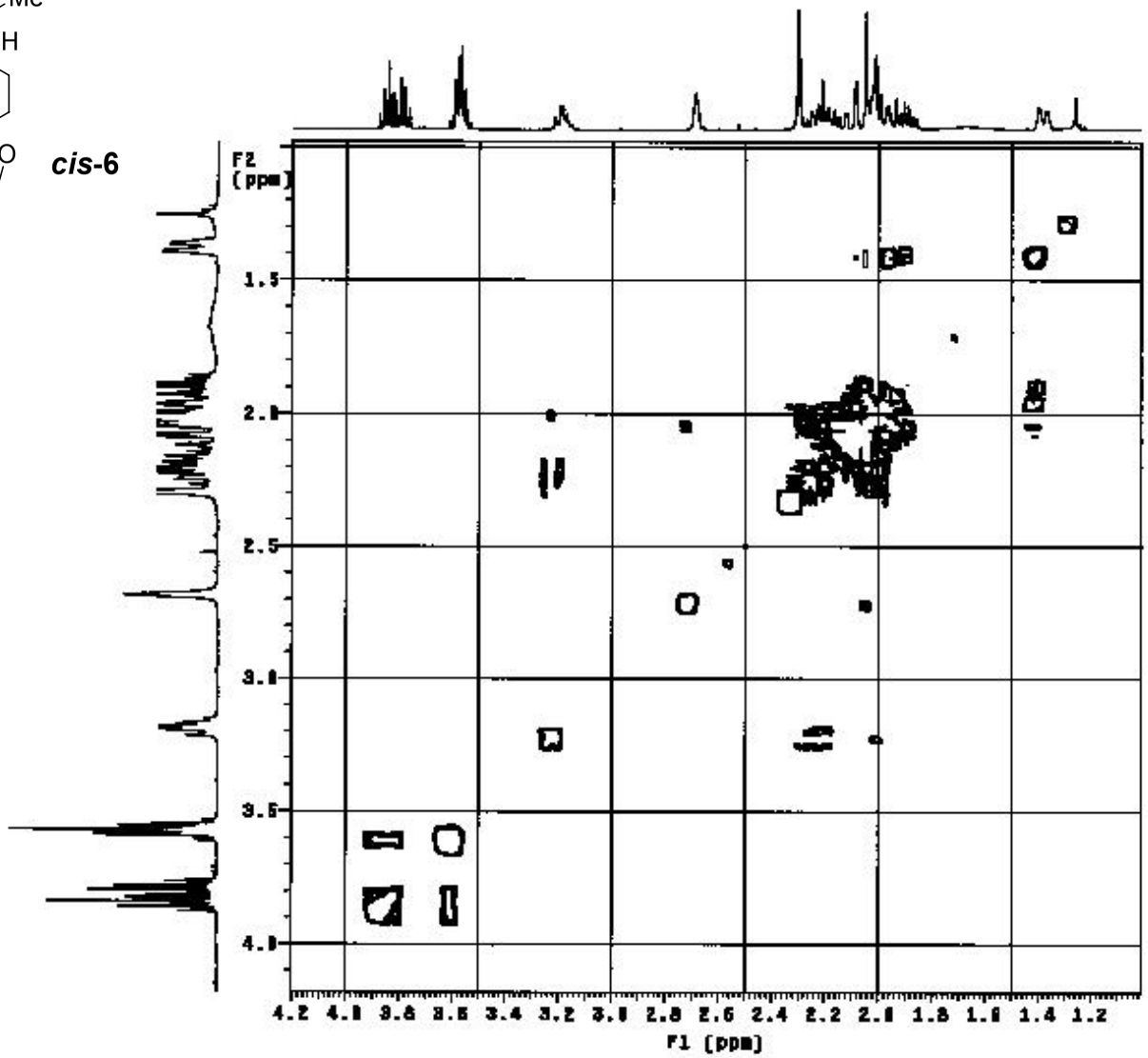
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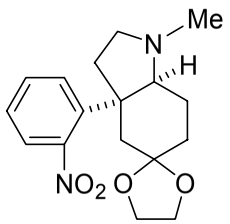
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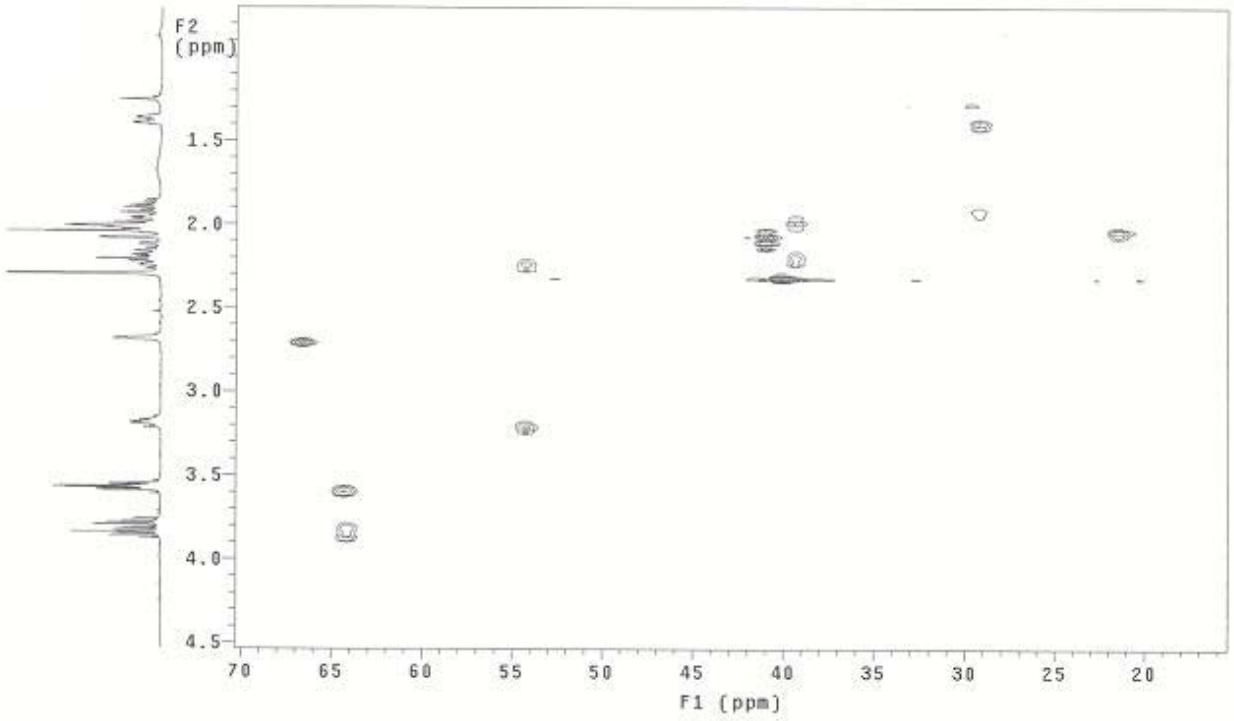
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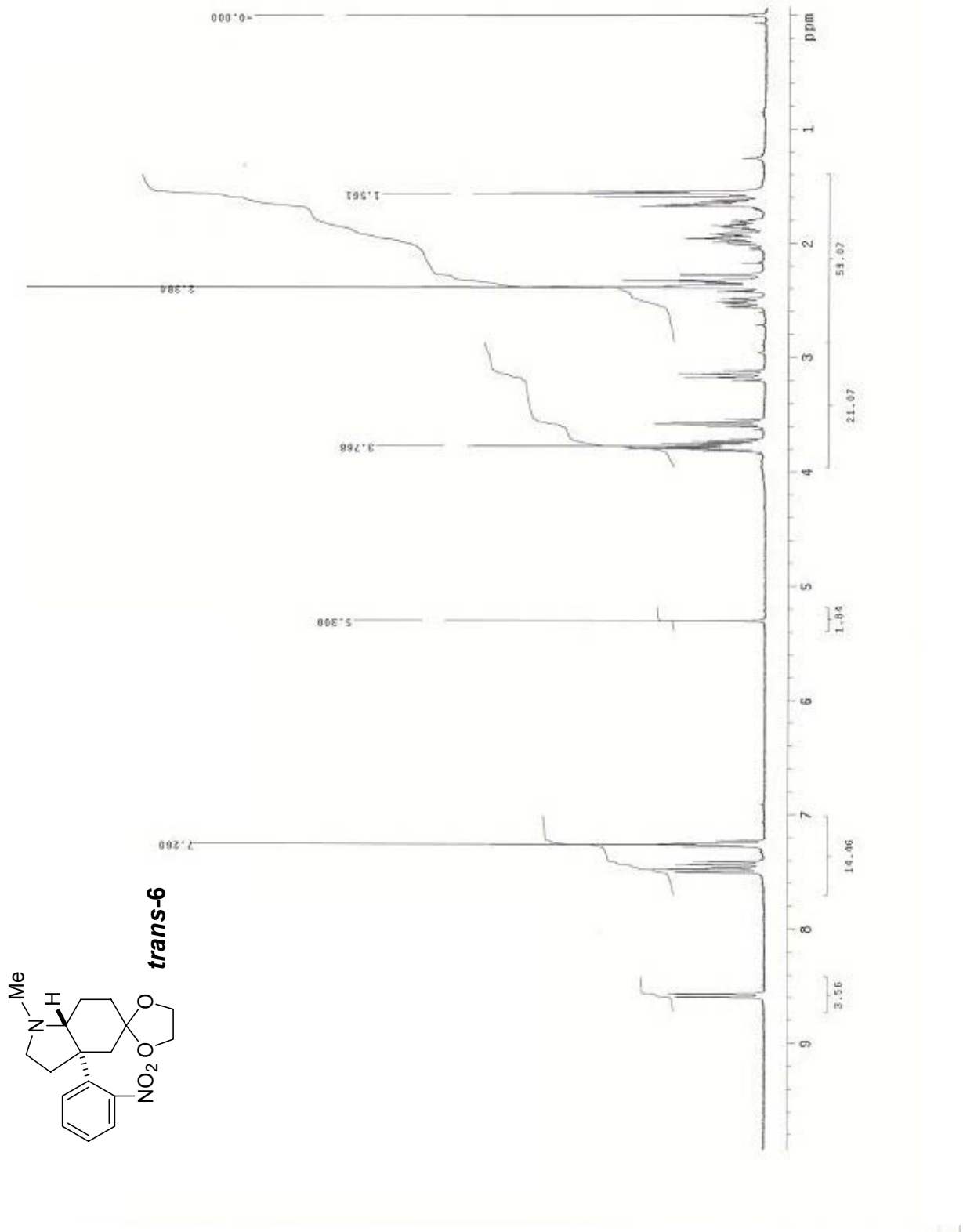
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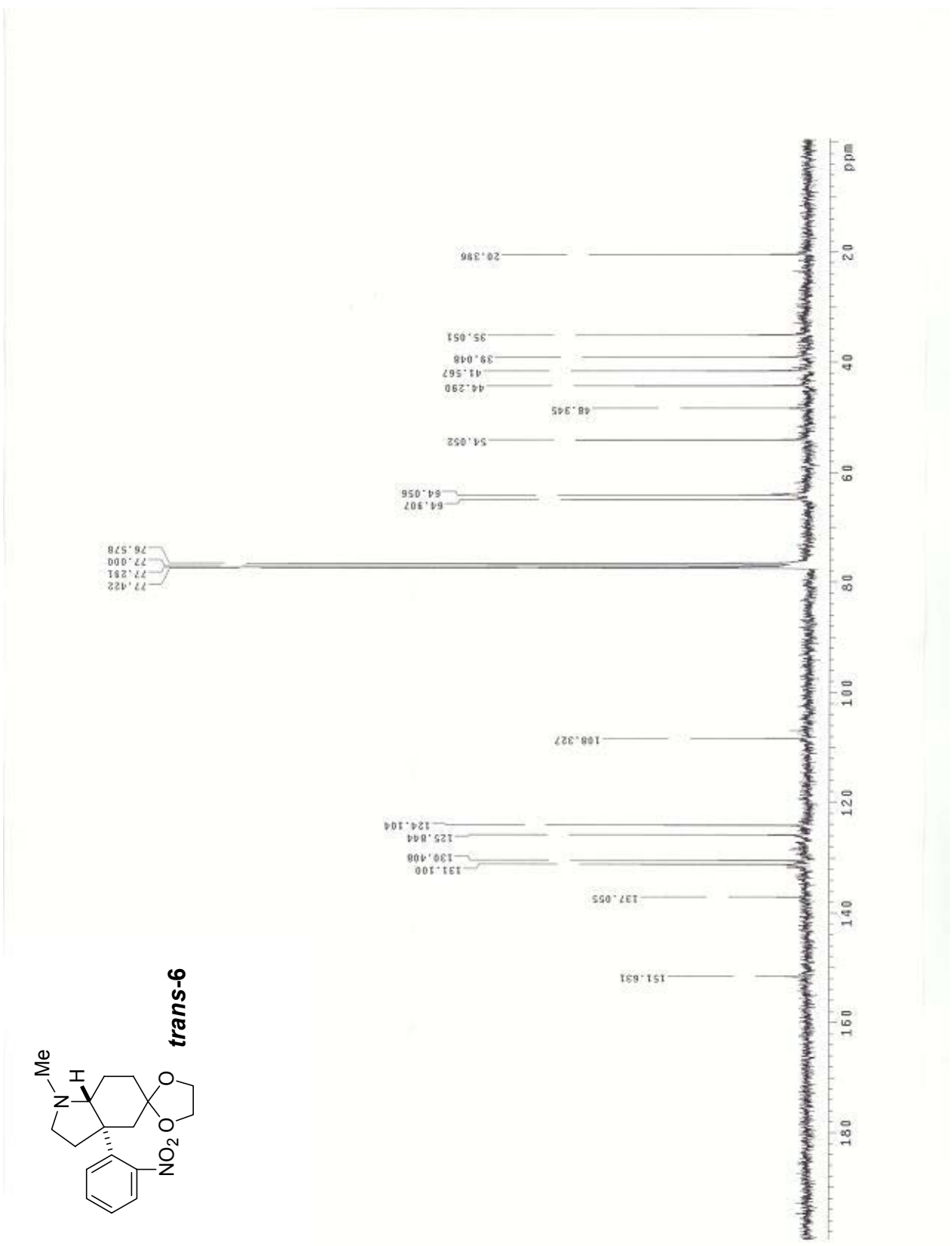
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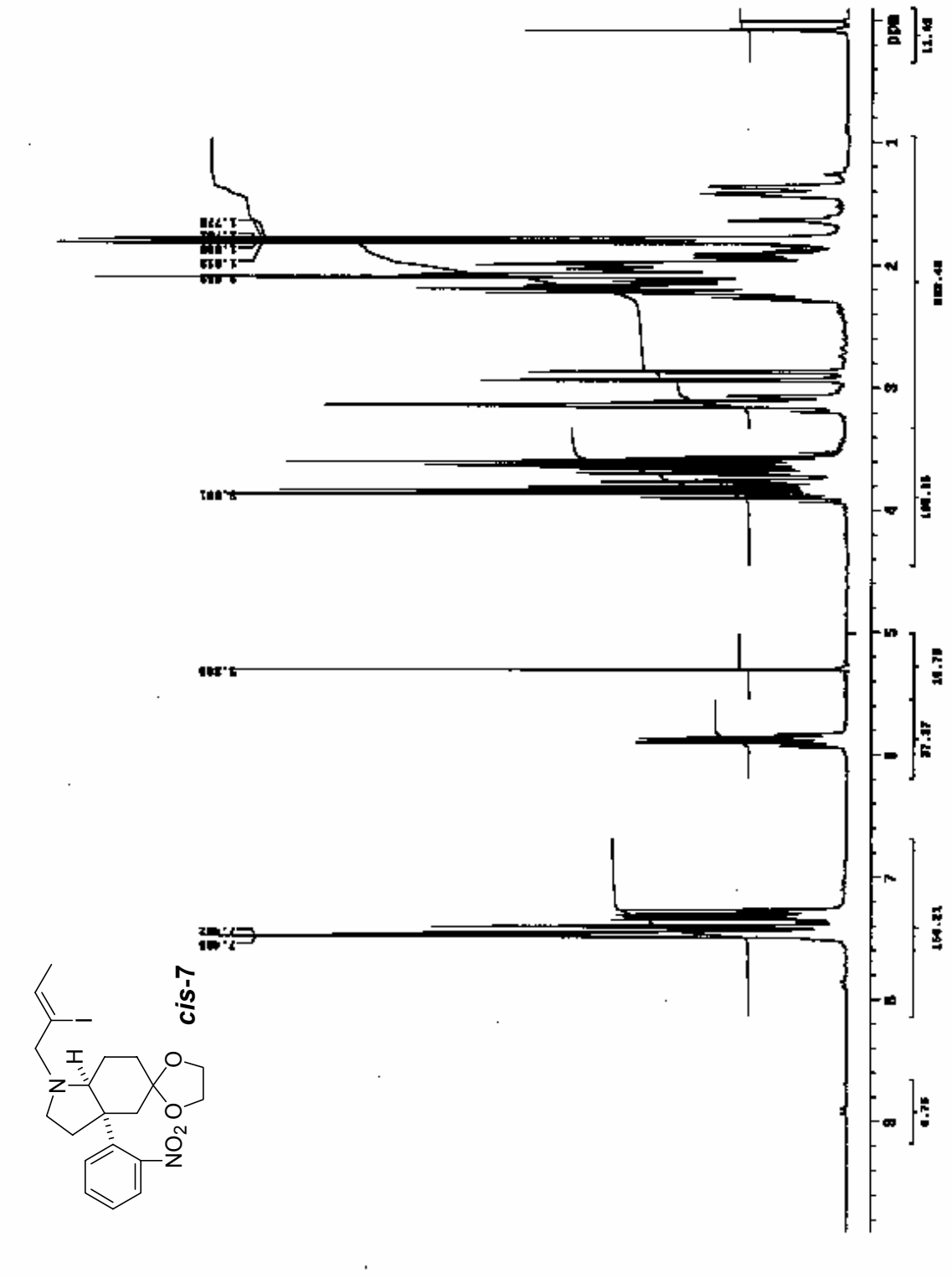
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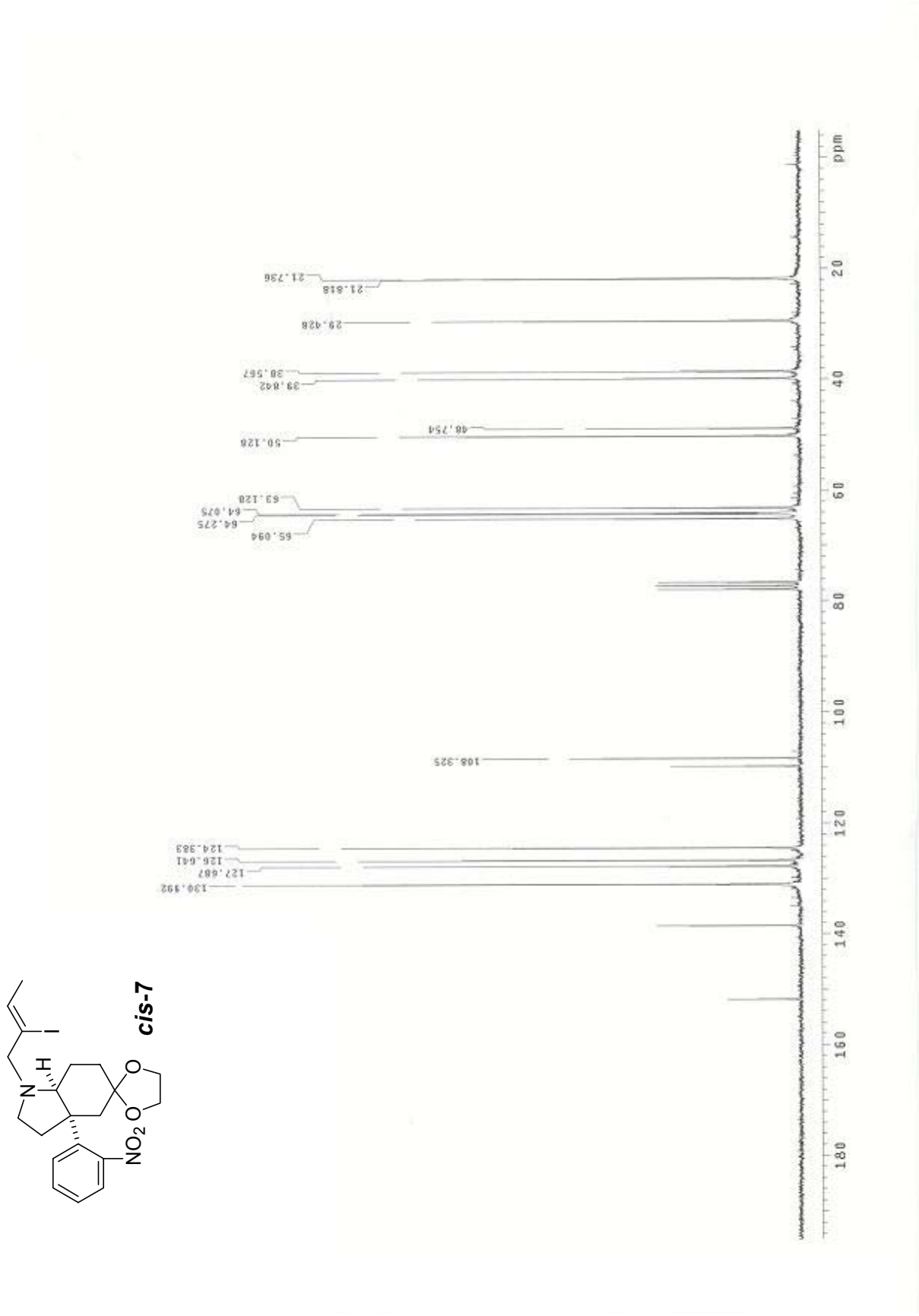
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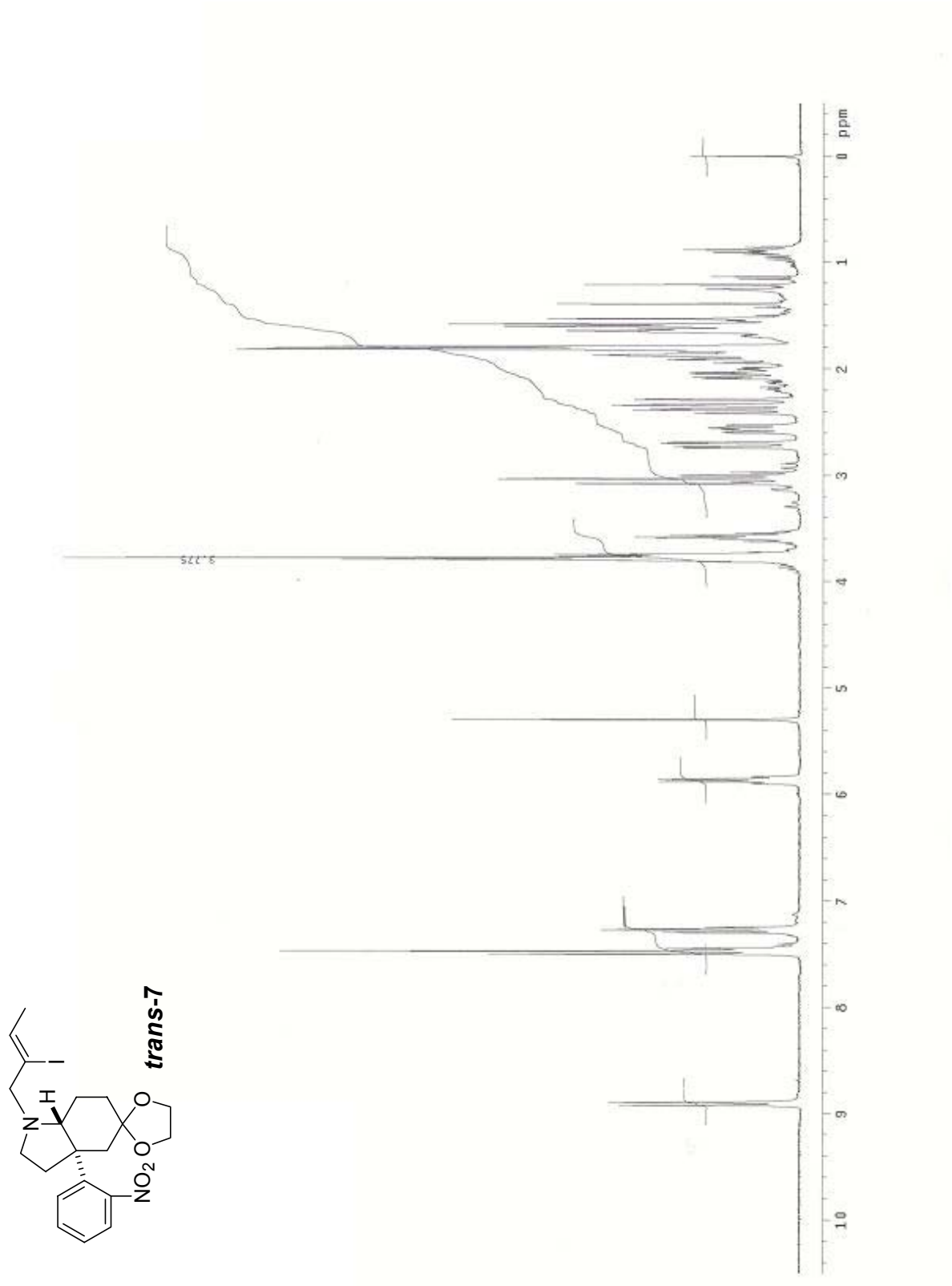
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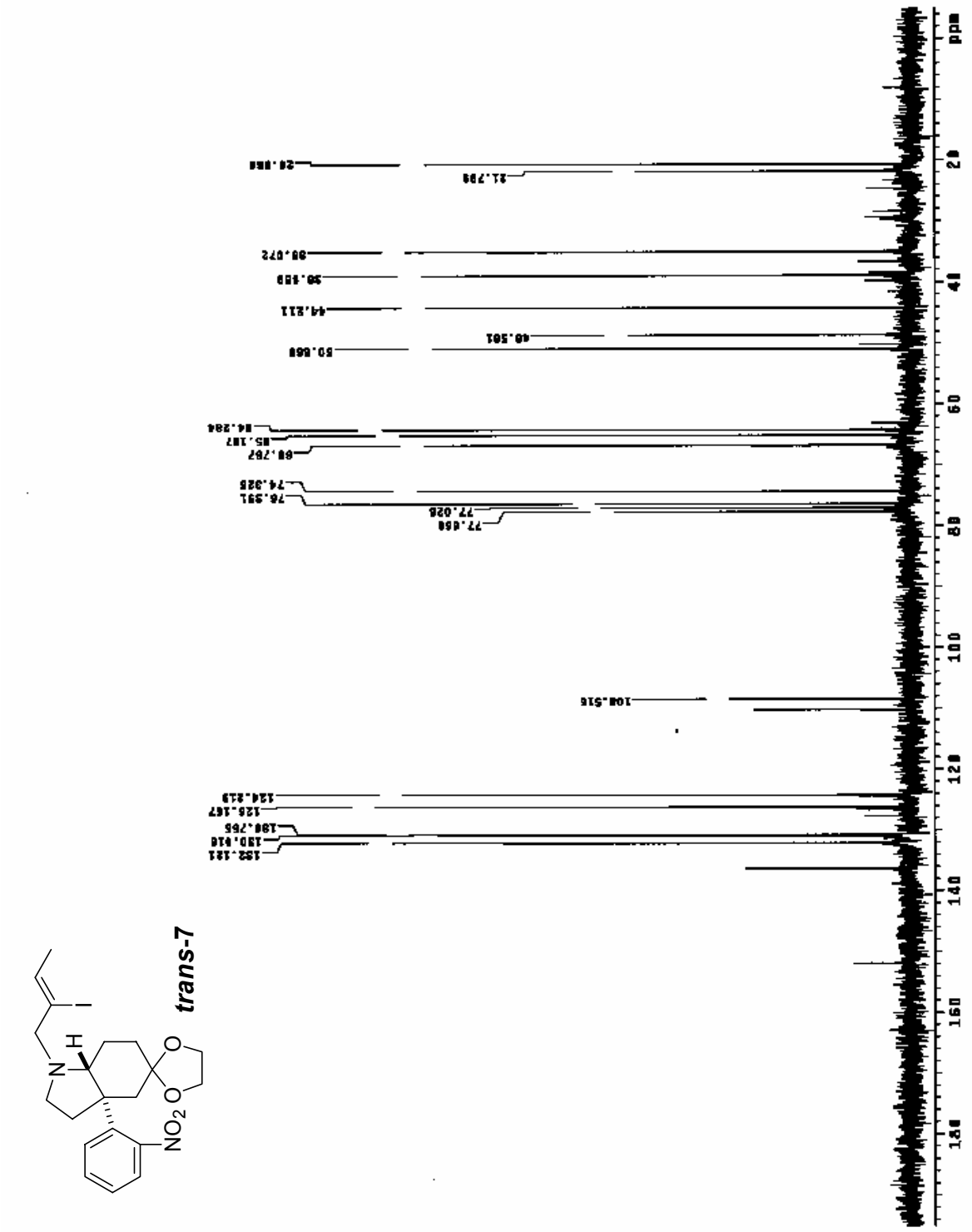
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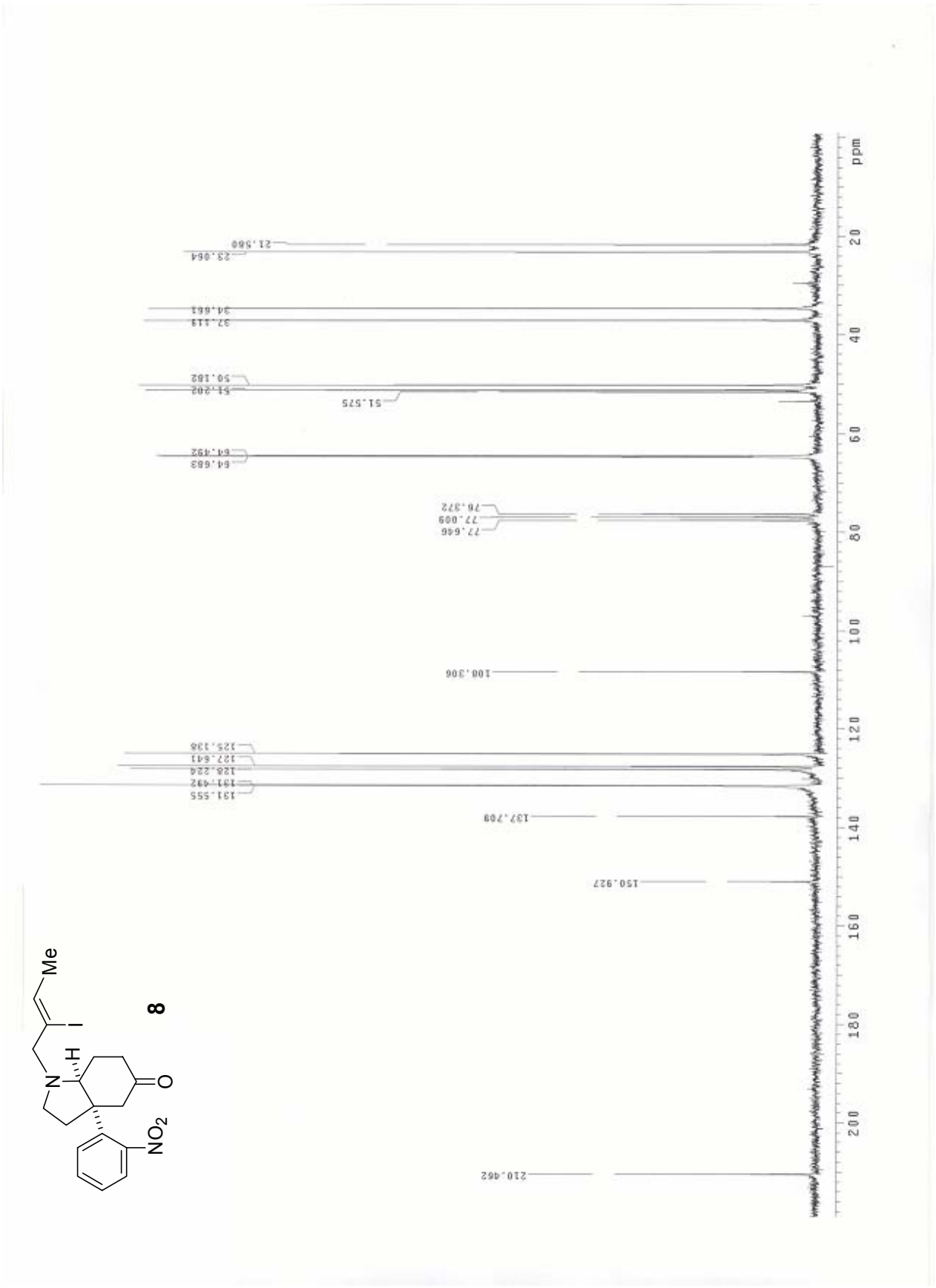
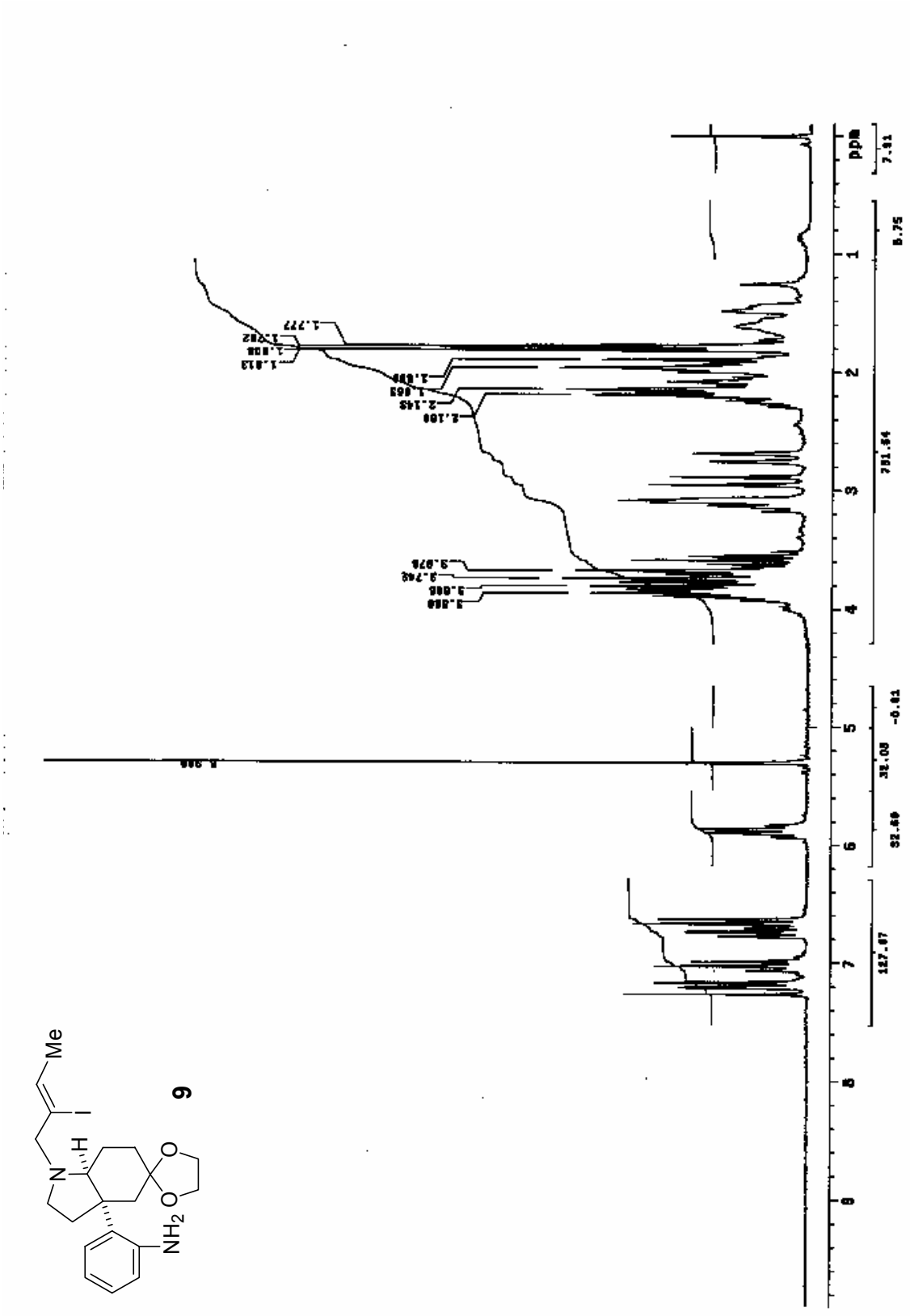
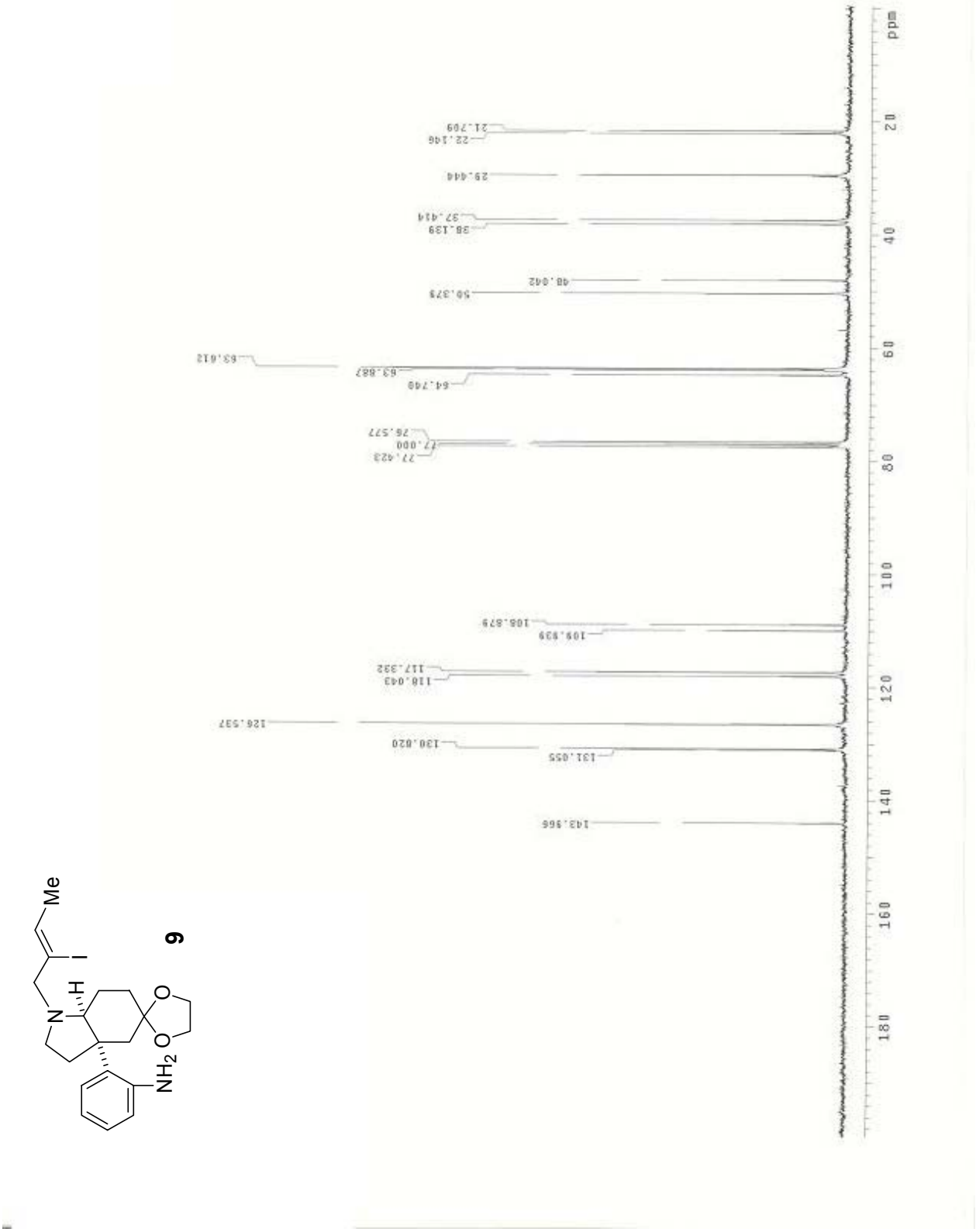
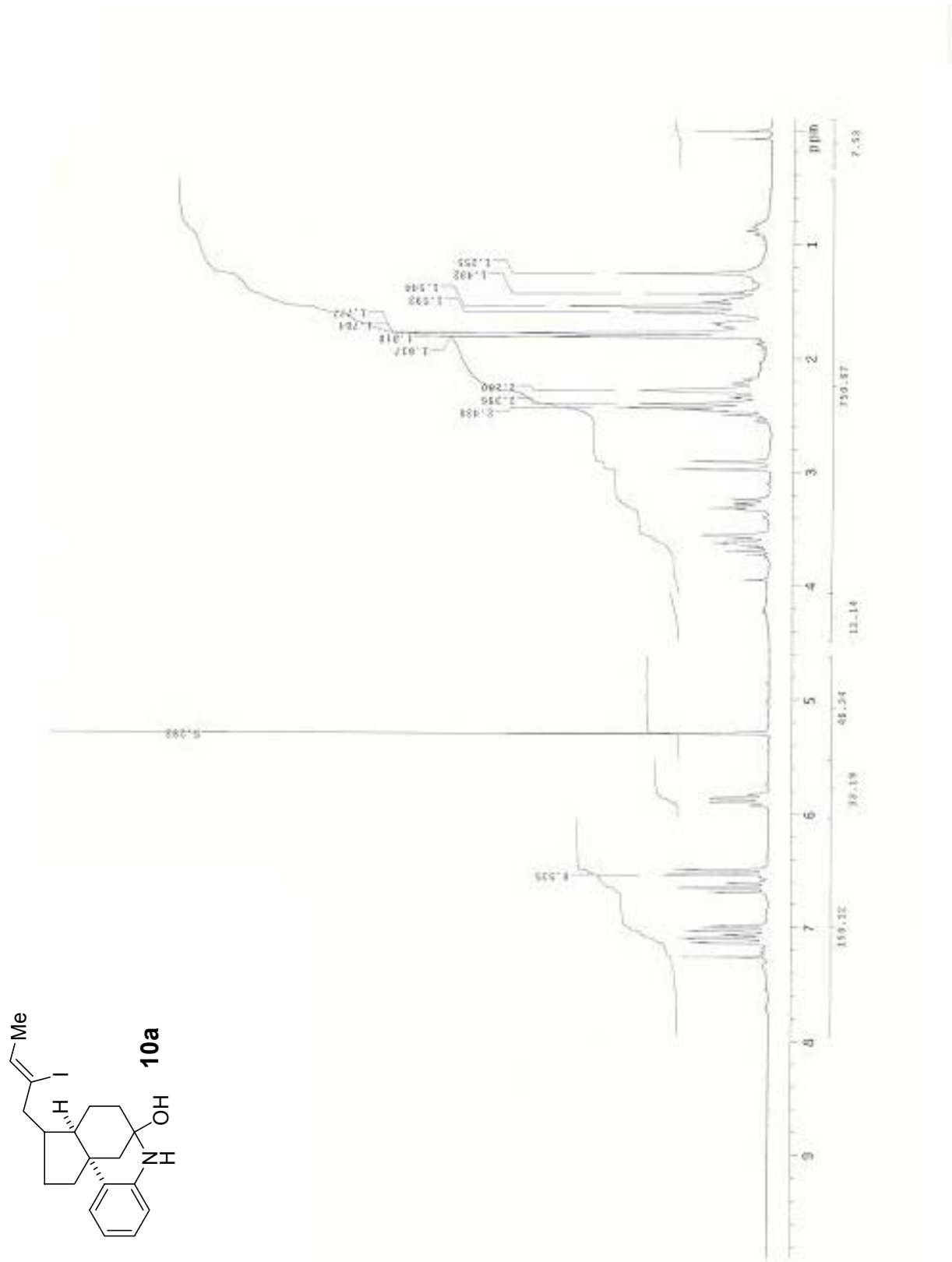
NO2
8

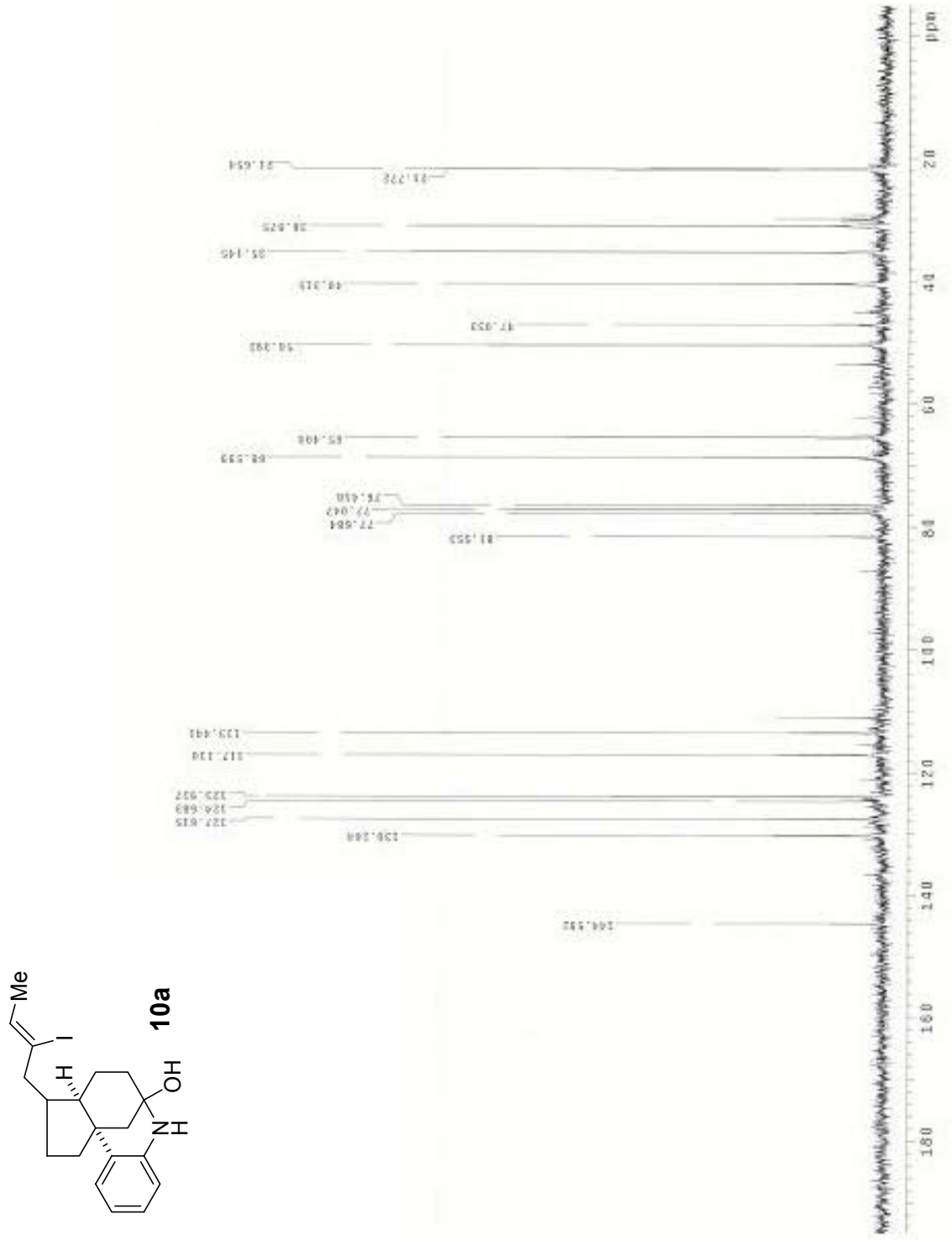

ppm
20
40
60
80
100
120
140
160
180
200
21.560
23.064
34.661
37.119
50.182
51.202
51.575
64.483
64.492
76.372
77.009
77.646
100.306
125.136
127.641
128.224
131.492
131.555
137.709
150.927
210.462
Me
I
H
N
O
NO2
8

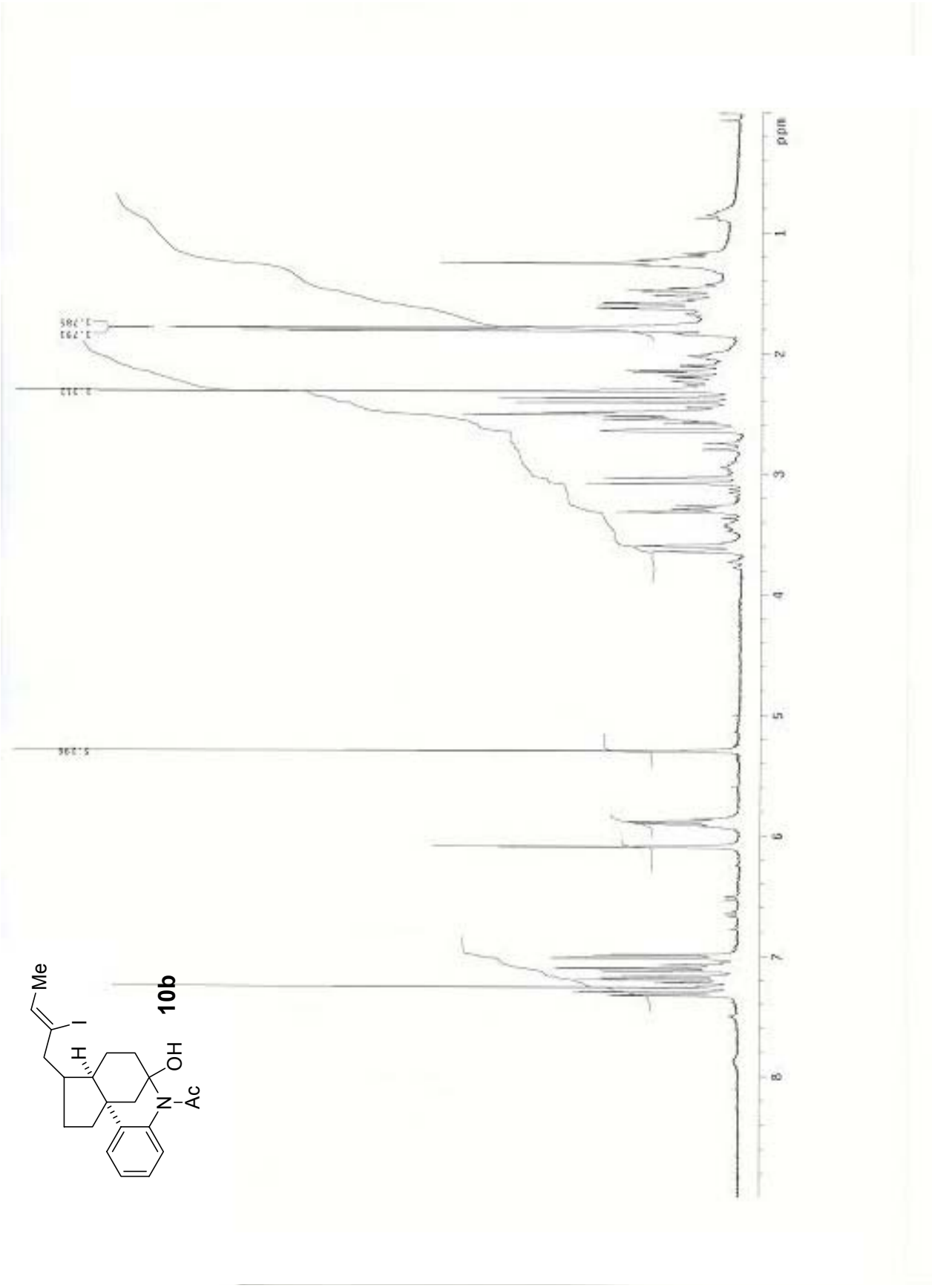

Me
I
H
N
O
O
NH2
9
ppm

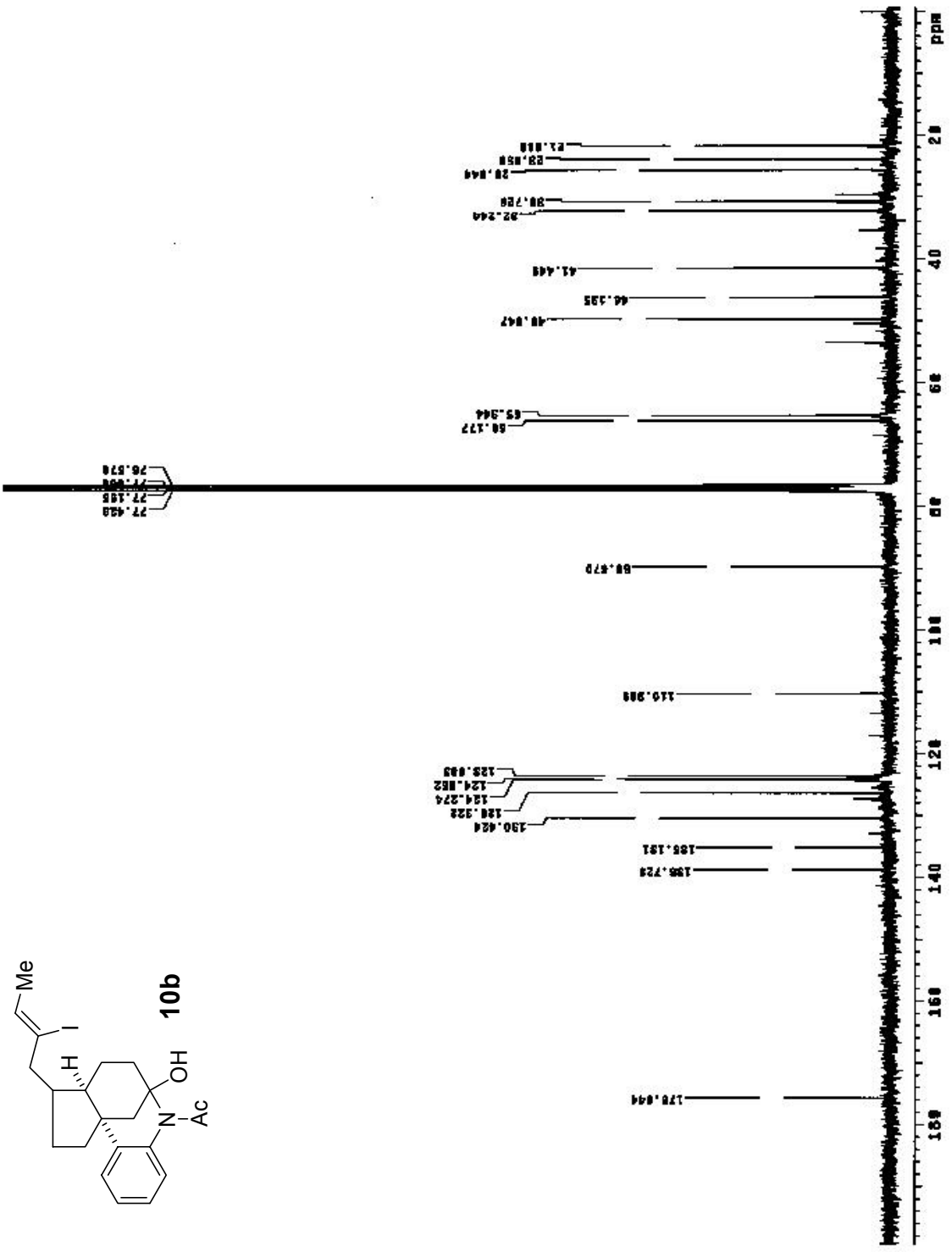

21.709
22.146
28.444
37.414
38.139
48.042
50.379
63.612
63.887
64.748
76.527
77.000
77.423
106.879
109.939
117.332
118.043
126.537
130.020
131.055
143.966
ppm
20
40
60
80
100
120
140
160
180
Me
I
H
N
O
O
NH2

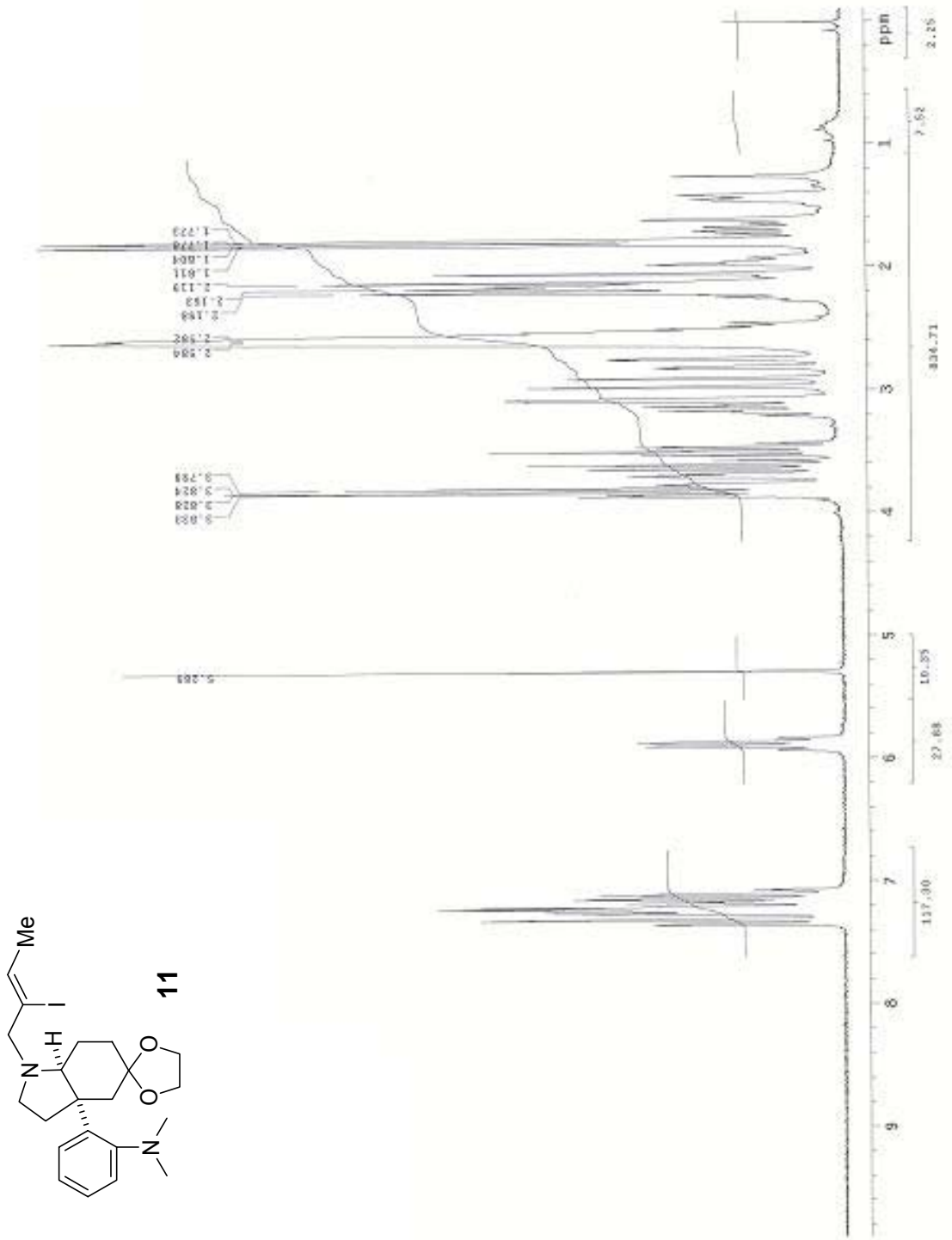
9

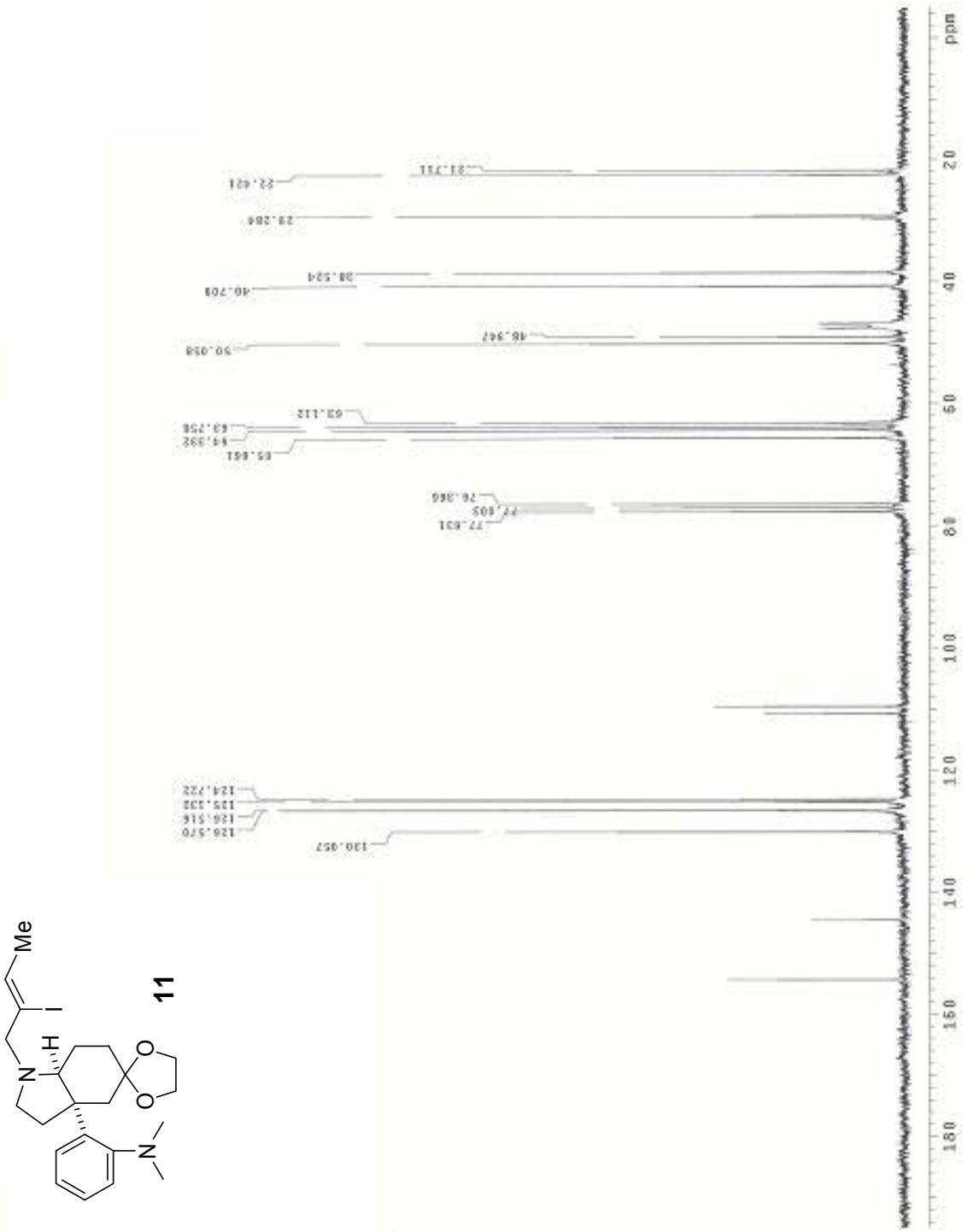

Me
I
H
OH
N
H
10a

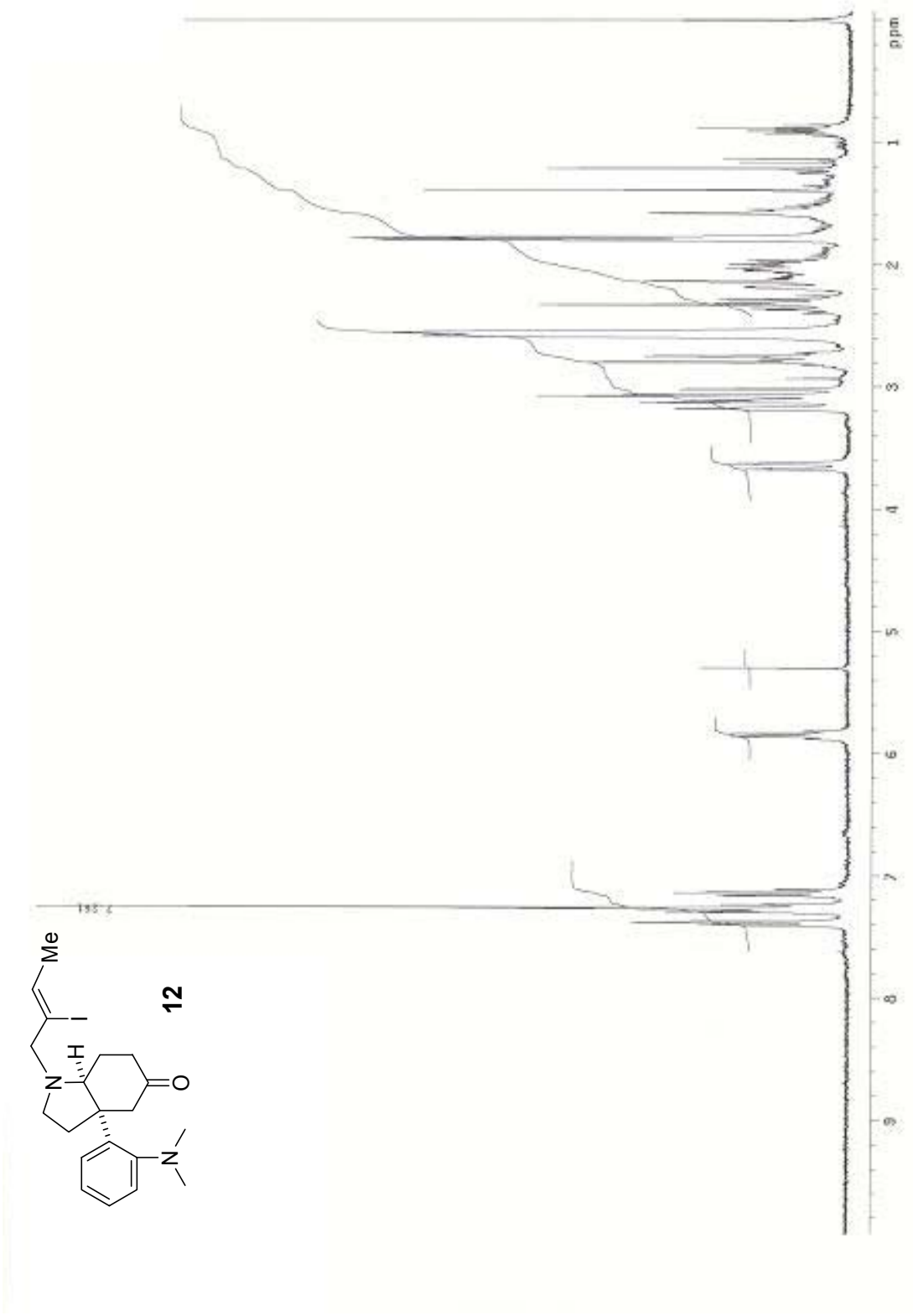

ppm
20
40
60
80
100
120
140
160
180
Me
I
H
OH
N
H
10a

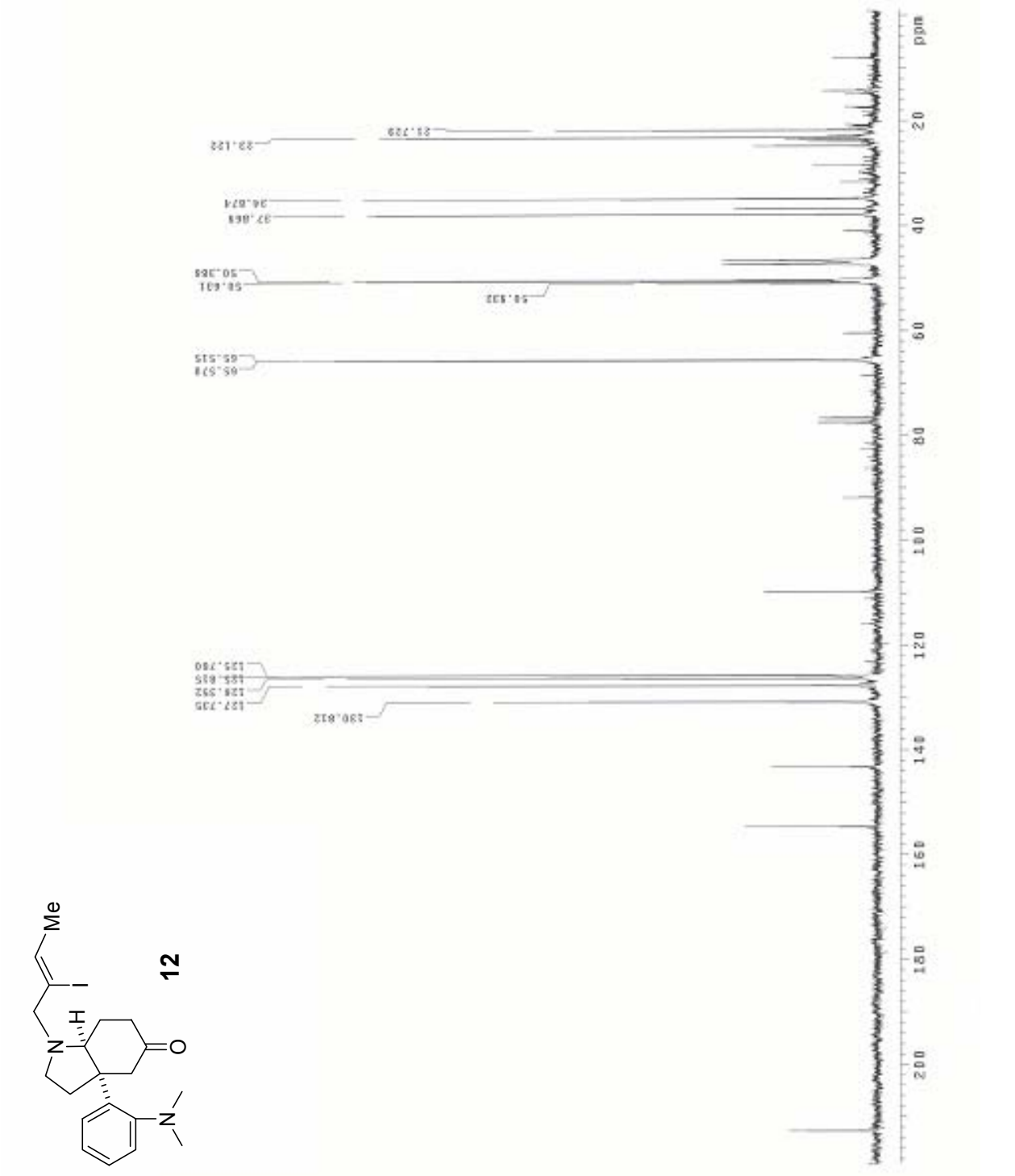

Me
I
H
OH
N
Ac
10b
ppm

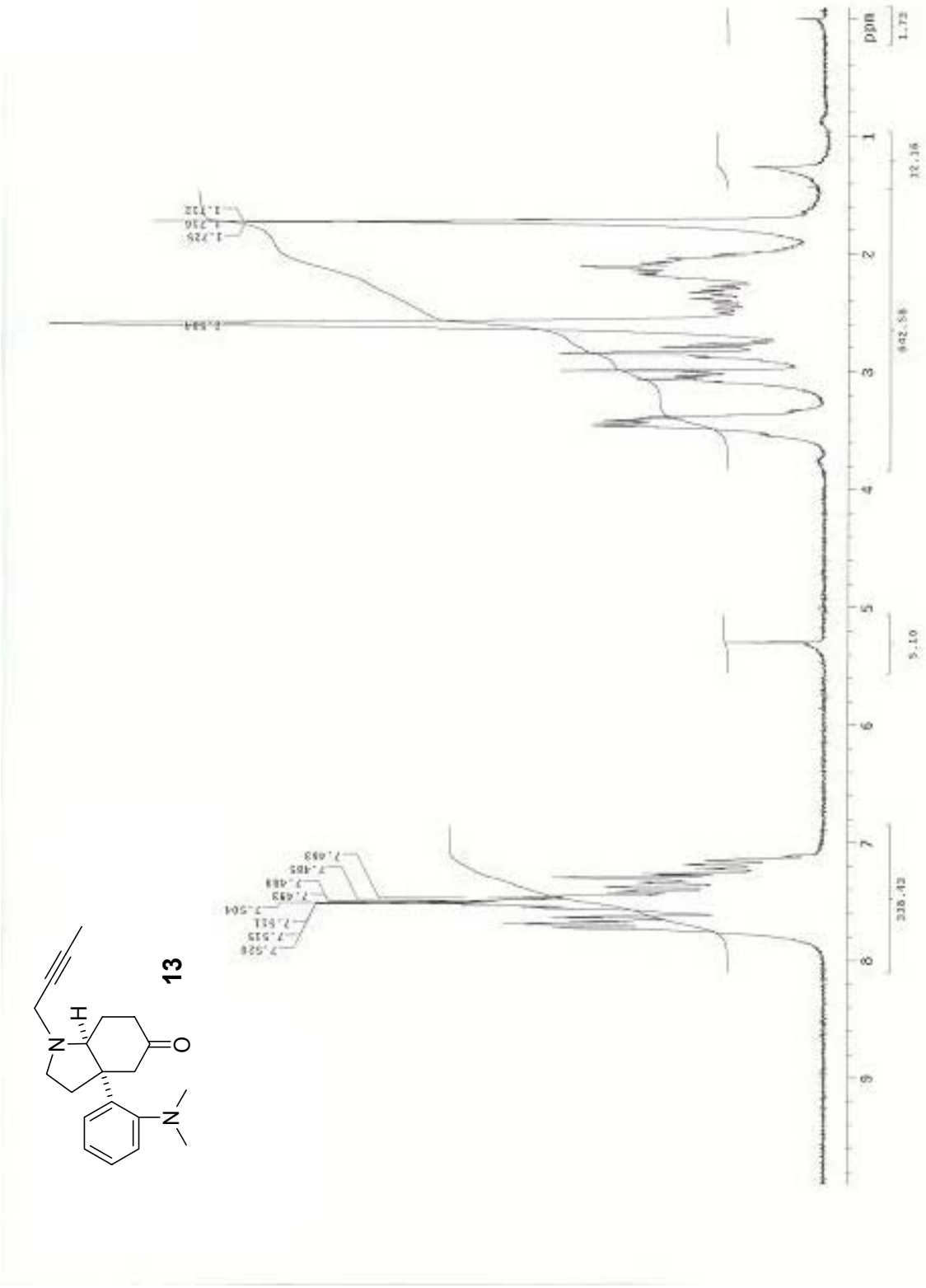

Me
I
H
OH
N
Ac
10b
ppm

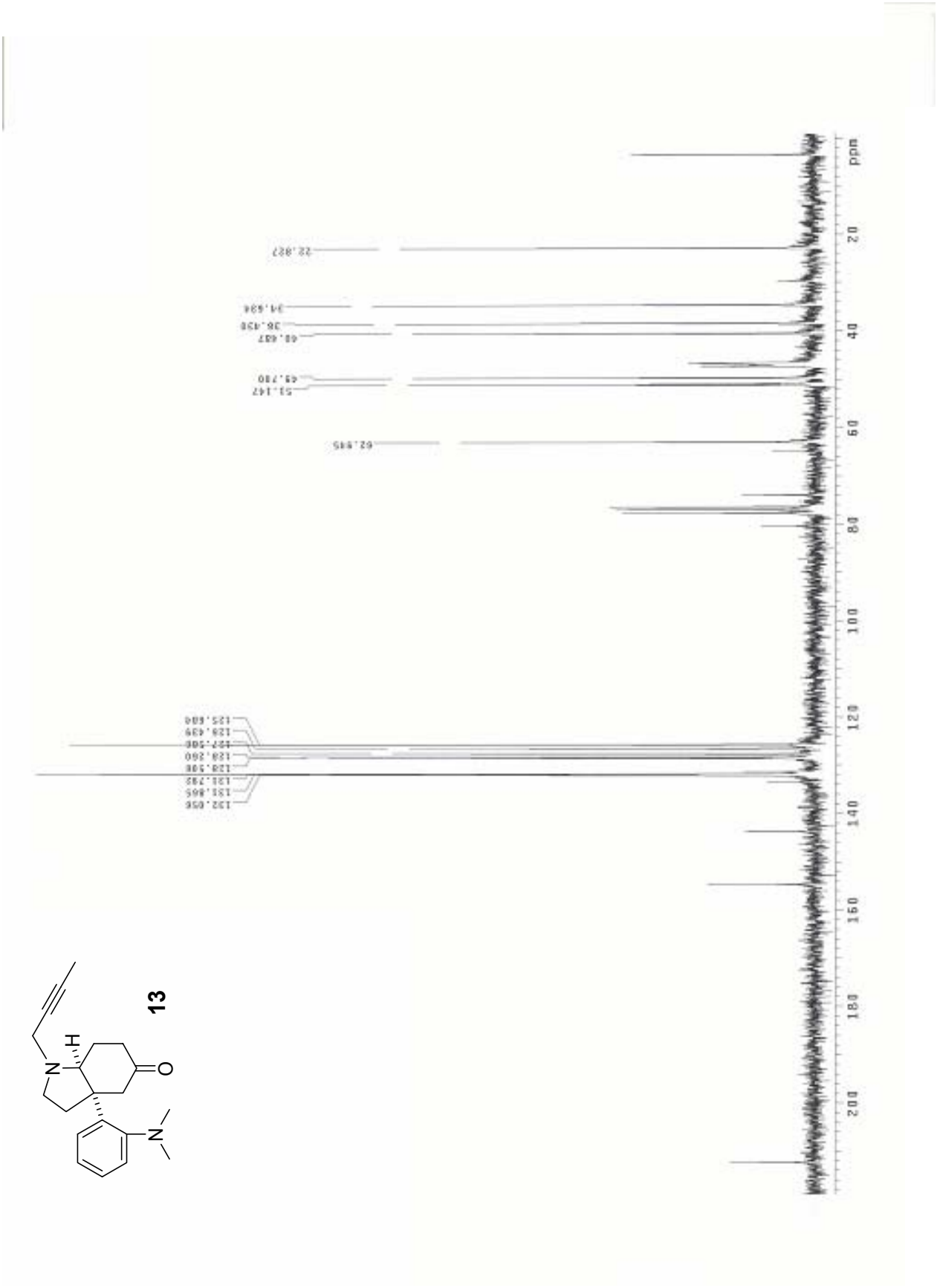

Me
I
H
N
O
O
N
11
ppm


ppm
20
40
60
80
100
120
140
160
180
31.711
22.621
29.284
38.524
40.709
46.967
50.058
63.112
63.758
69.392
65.661
76.866
77.805
77.631
124.722
125.332
126.516
126.570
130.057
Me
I
H
N
O
O
N
11

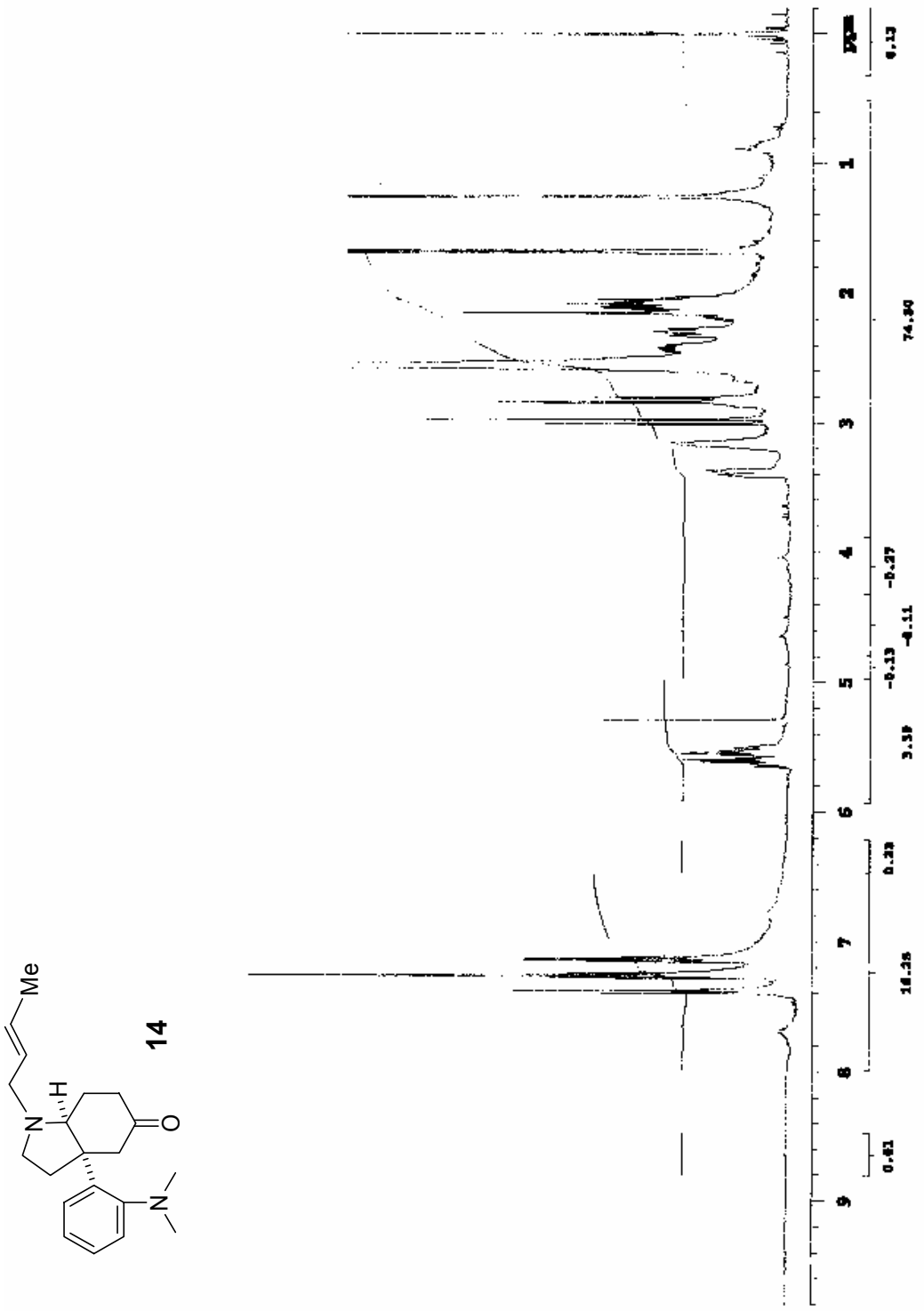

Me
I
H
N
O
N
12
ppm
1
2
3
4
5
6
7
8
9

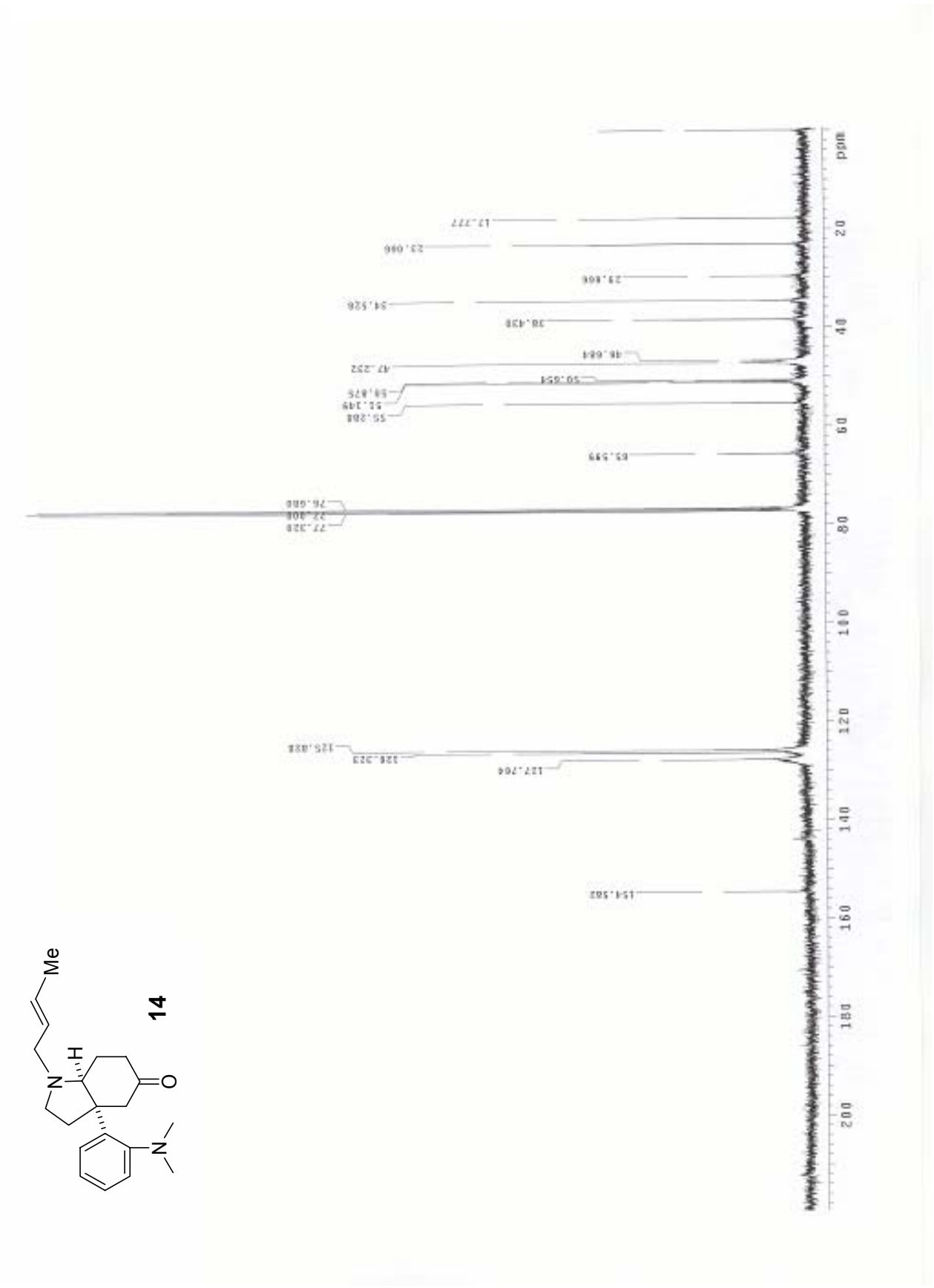

Me
I
H
N
O
N
12
ppm
20
40
60
80
100
120
140
160
180
200
21.729
33.122
36.874
37.069
50.385
58.631
58.933
65.515
65.578
125.780
125.815
128.092
127.735
130.812


13
ppm
1.72
12.36
642.58
5.10
338.43
1.725
1.716
1.722
7.484
7.529
7.519
7.511
7.504
7.493
7.488
7.485
7.483


22.827
34.494
36.458
48.687
49.780
51.147
62.915
125.606
126.439
127.508
128.260
128.588
131.785
131.865
132.056
ppm
20
40
60
80
100
120
140
160
180
200

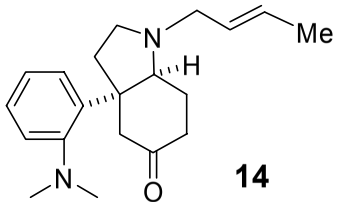
13
H
N
O
N


Me
H
N
O
N
14

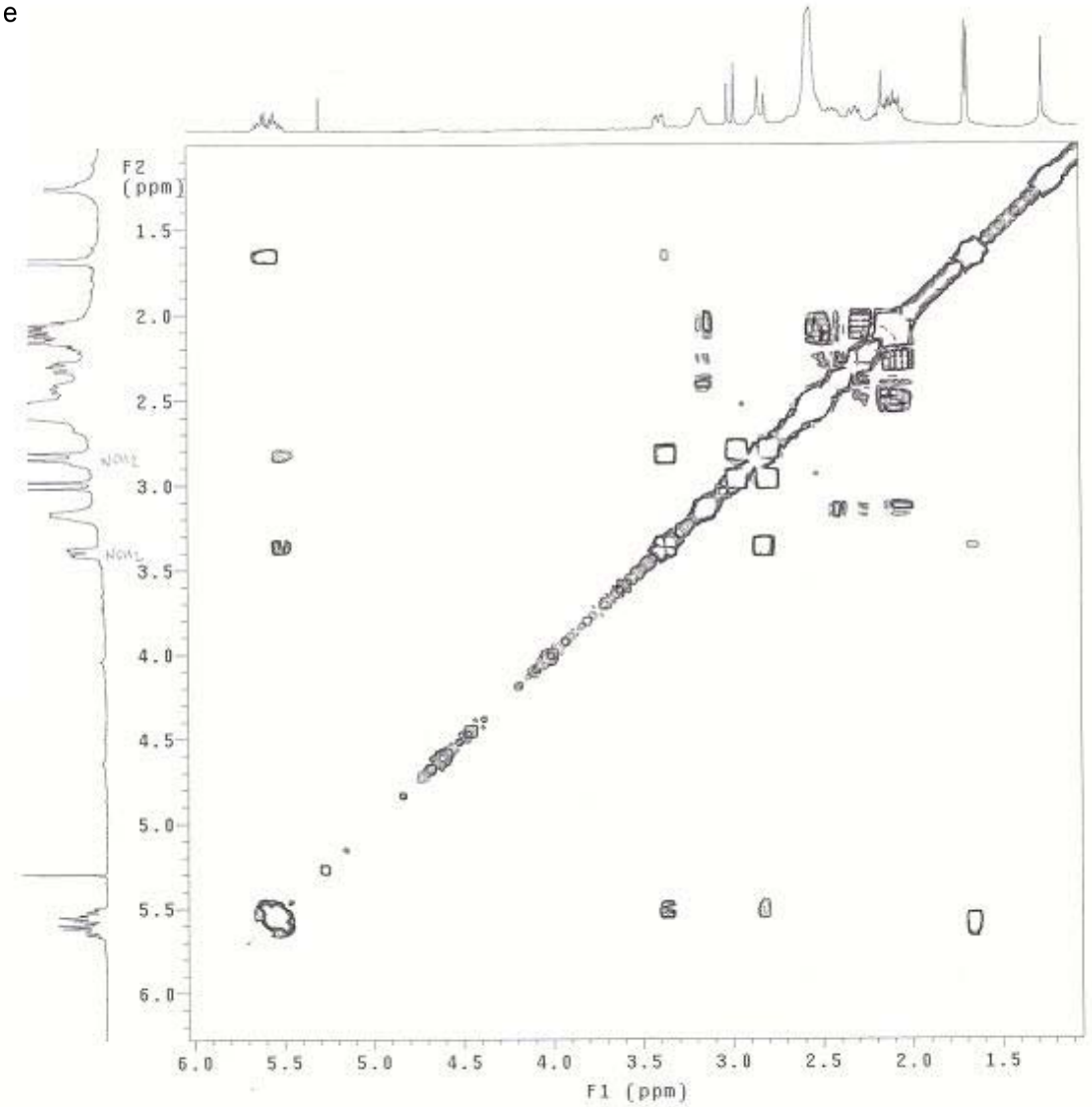

17.727
23.086
29.806
34.526
38.438
46.684
47.252
50.654
53.875
55.288
63.599
77.328
125.088
128.023
137.764
154.582
ppm
20
40
60
80
100
120
140
160
180
200

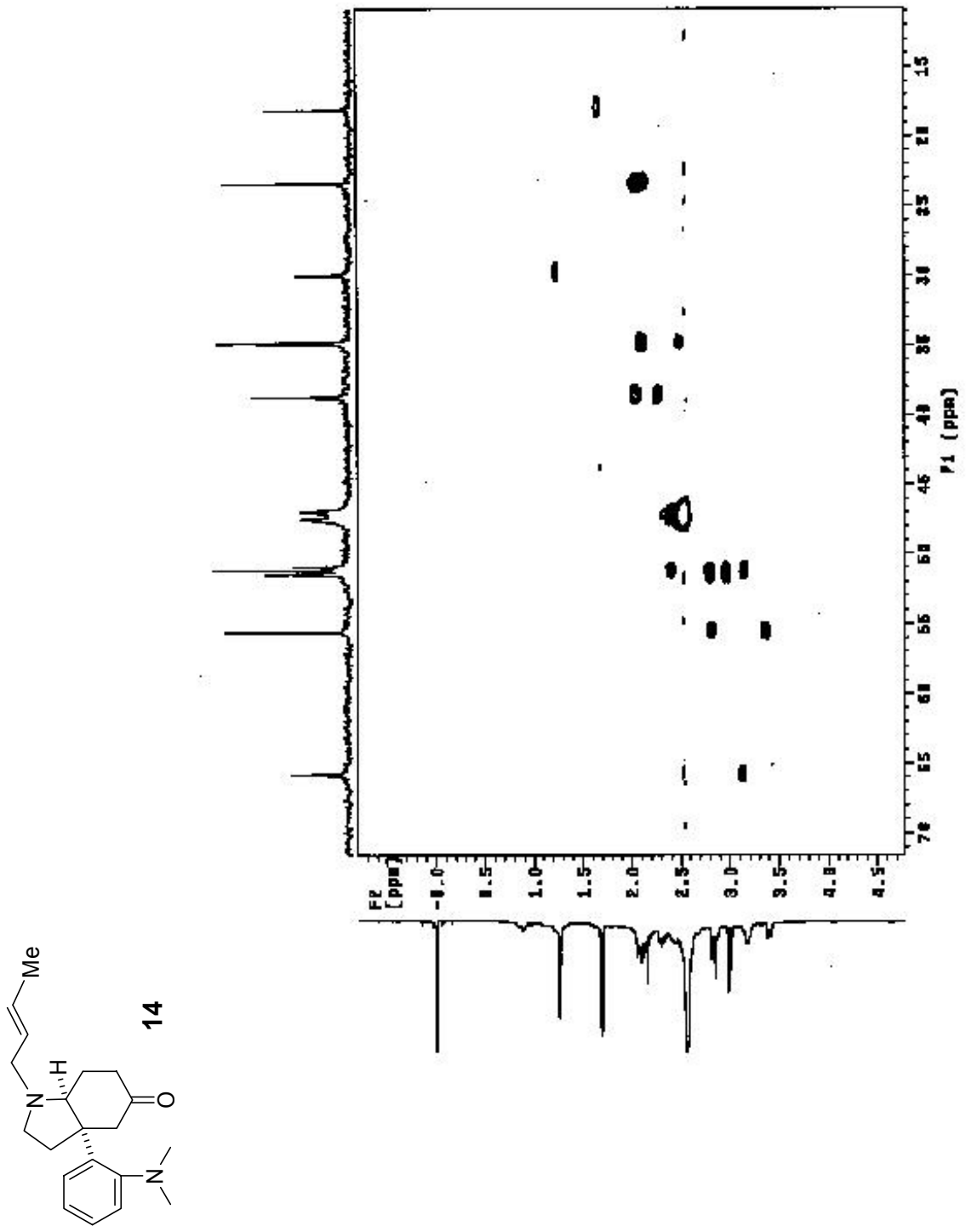
Me
H
N
O
N

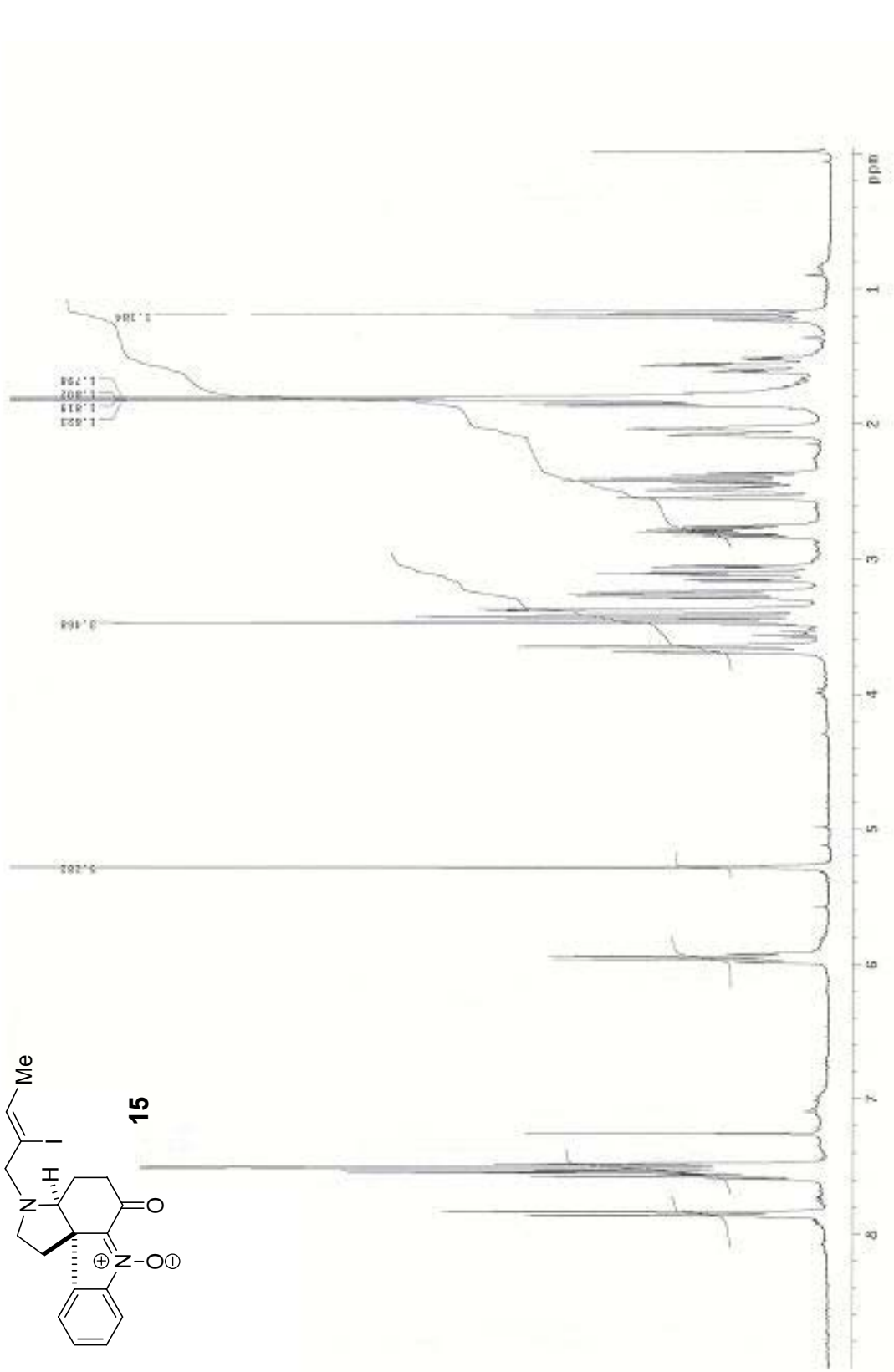
14

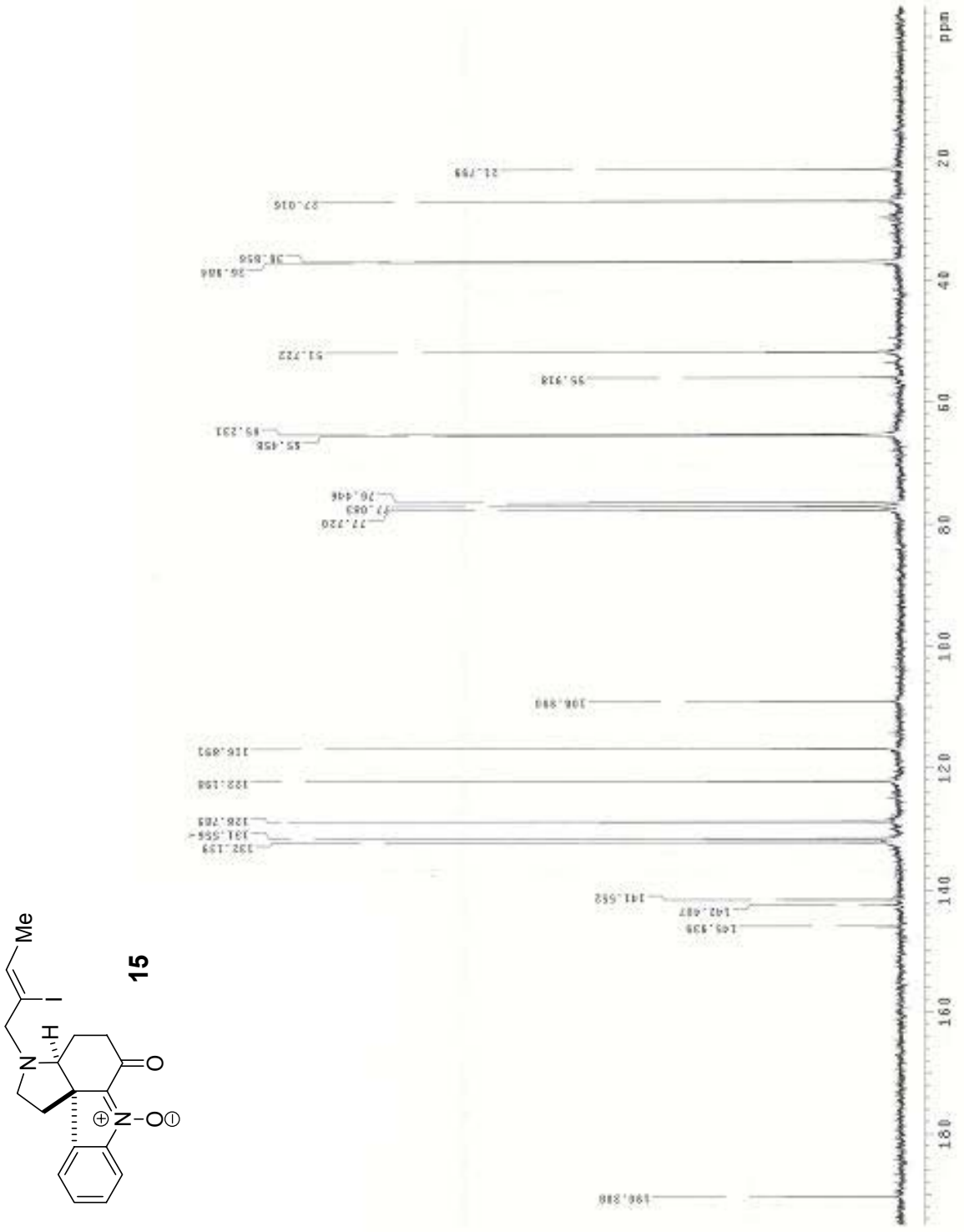

N
H
Me
N
O

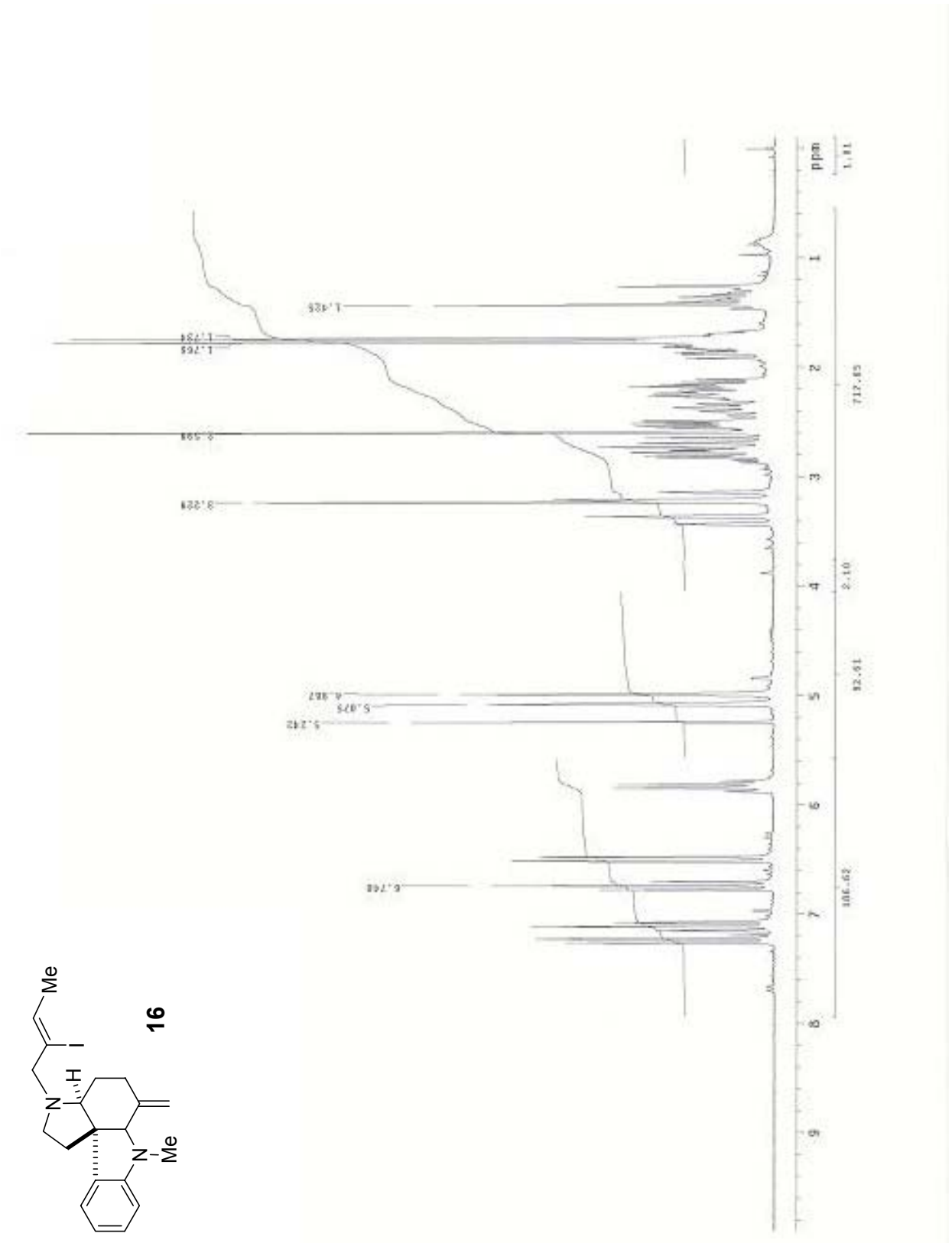
14

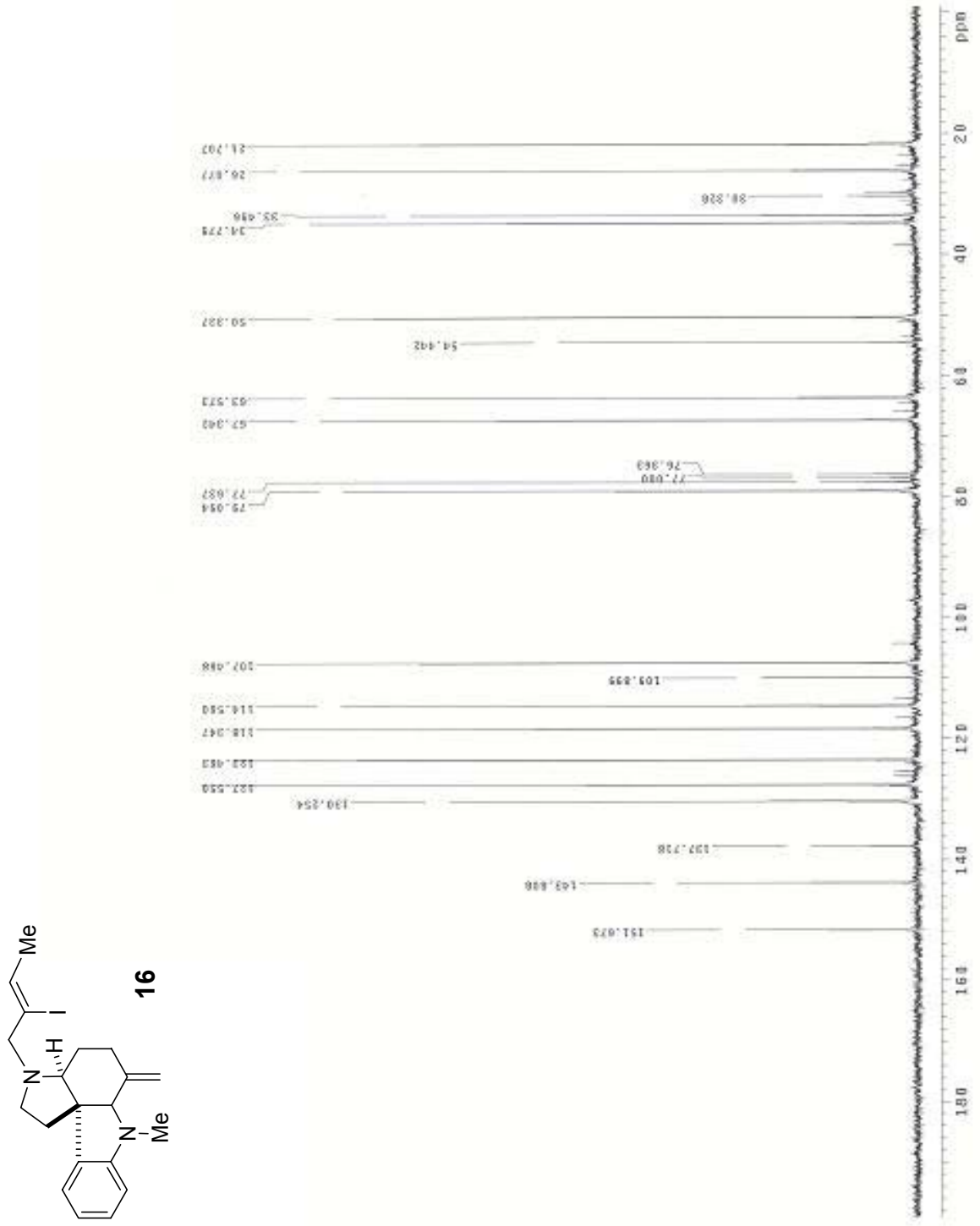

F2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F1 (ppm)

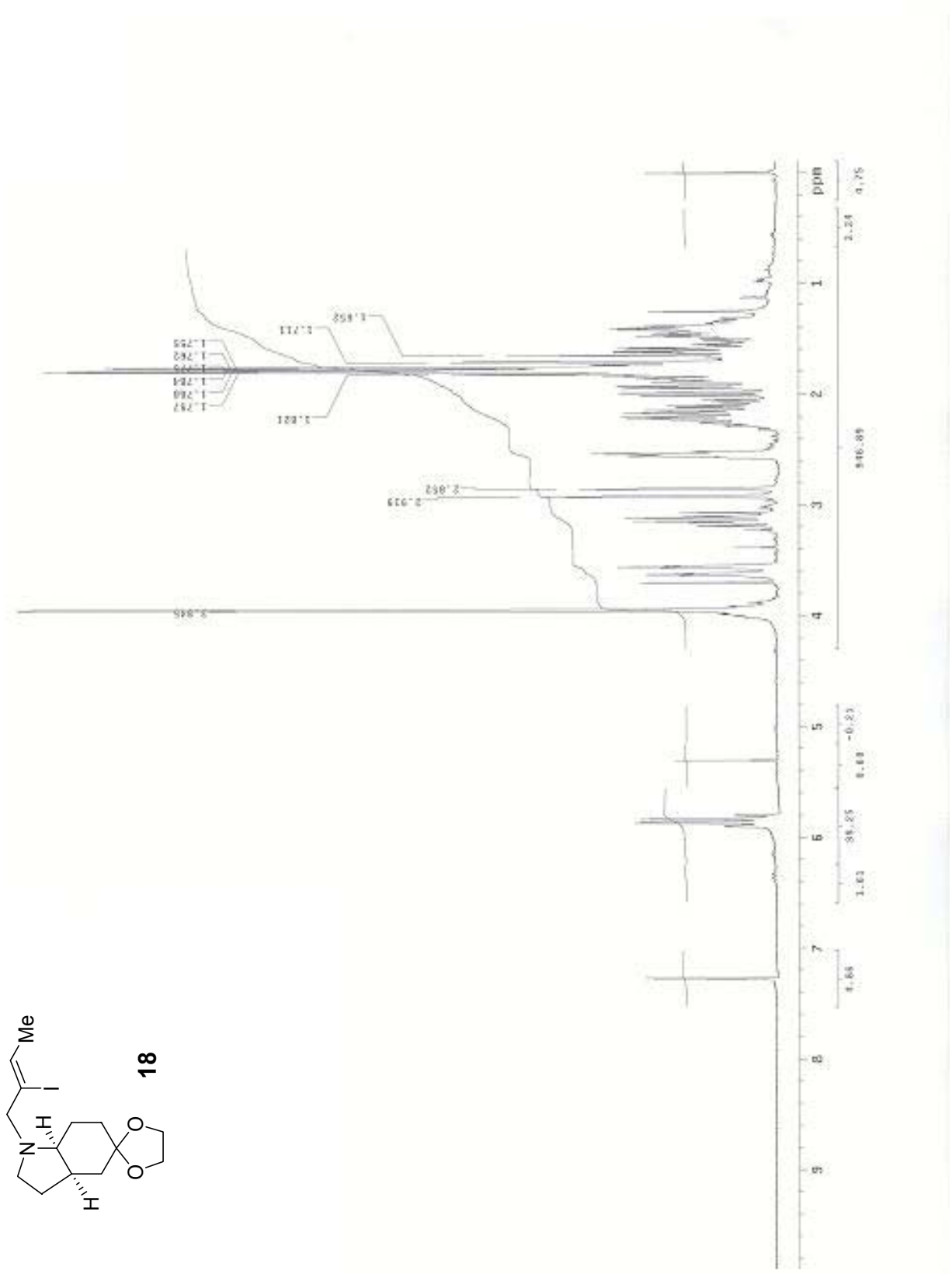

Me
H
N
O
N
14
F2 (ppm)
F1 (ppm)

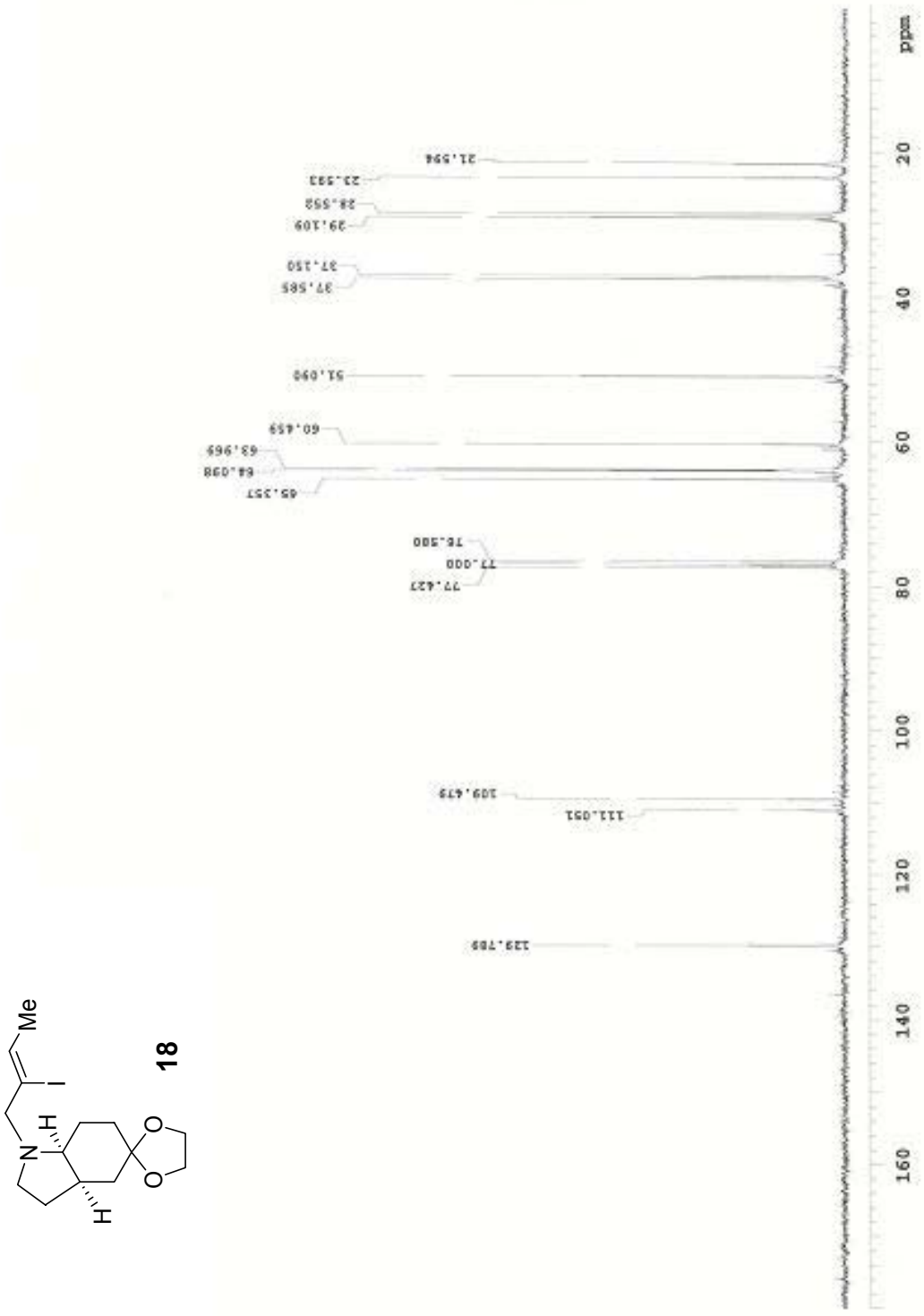

Me
I
H
N
O
⊕N–O⊖
15
ppm
1
2
3
4
5
6
7
8


Me
I
H
N
O
⊕N–O⊖
15
ppm
20
40
60
80
100
120
140
160
180

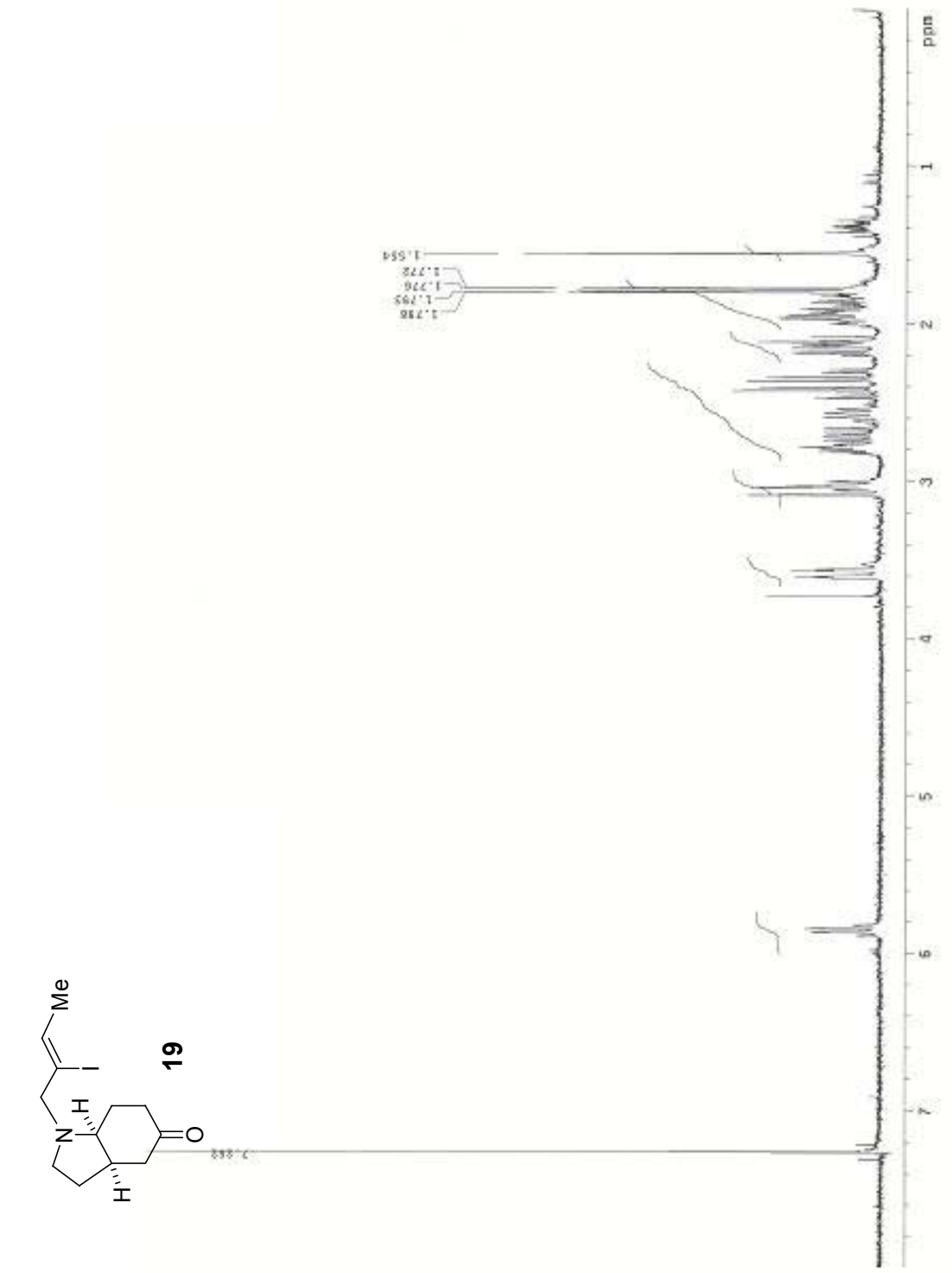

Me
I
H
N
N
Me
16
ppm

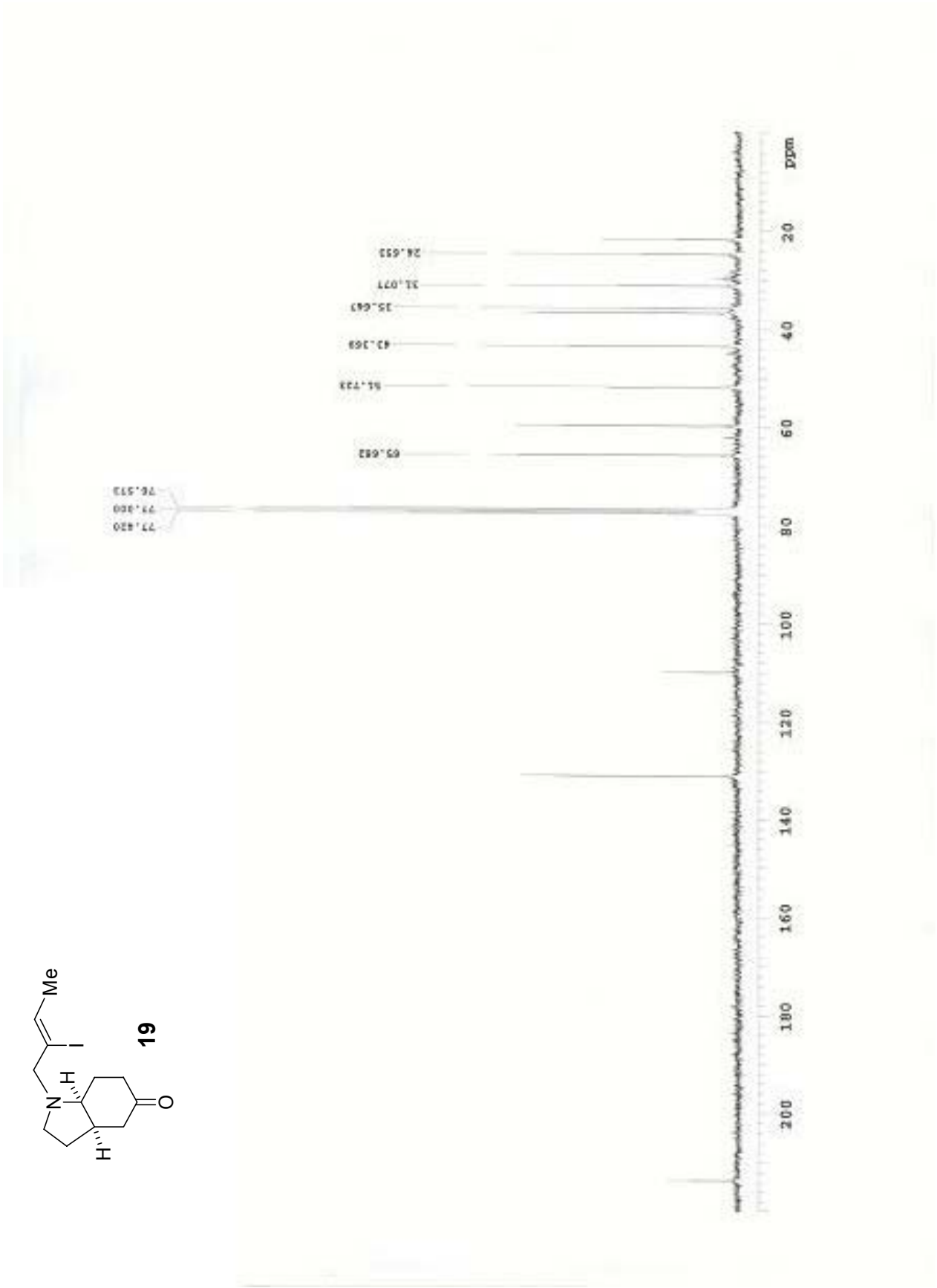

Me
I
H
N
N
Me
16
21.707
26.077
33.496
34.778
50.337
54.442
63.573
67.040
76.863
77.080
77.657
79.054
107.488
109.899
116.560
118.047
123.483
127.550
130.254
137.738
143.888
151.673
ppm
20
40
60
80
100
120
140
160
180


Me
I
H
N
O
O
H
18
ppm


ppm
20
40
60
80
100
120
140
160
21.594
23.383
28.552
29.109
37.150
37.585
51.099
60.459
63.969
64.098
65.357
76.580
77.000
77.427
109.479
111.051
139.789
Me
I
H
N
O
O
H

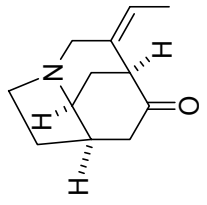
18

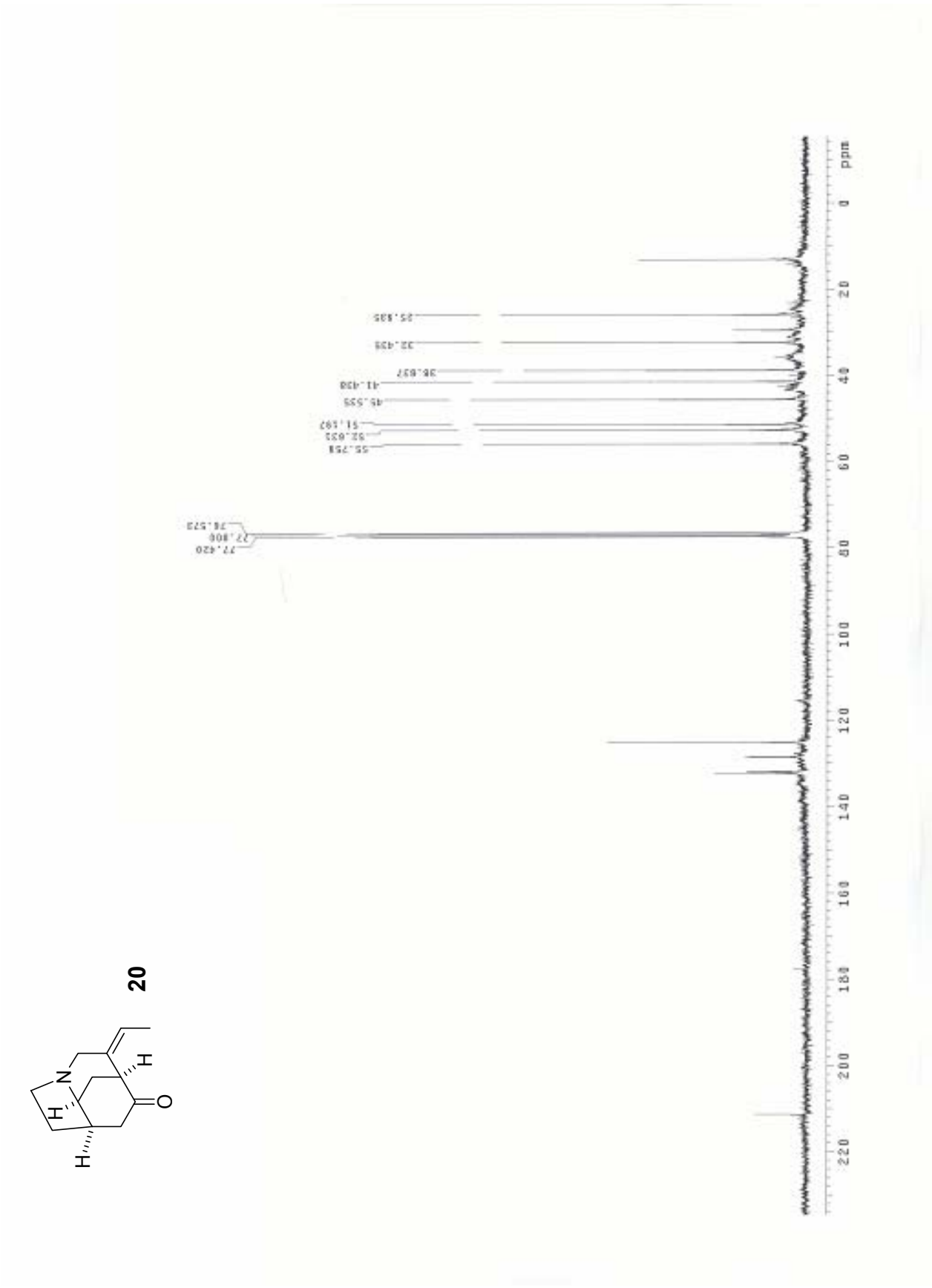

Me
I
19
H
N
O
H
7.869
1.554
1.778
1.776
1.793
1.798
ppm
1
2
3
4
5
6
7



19

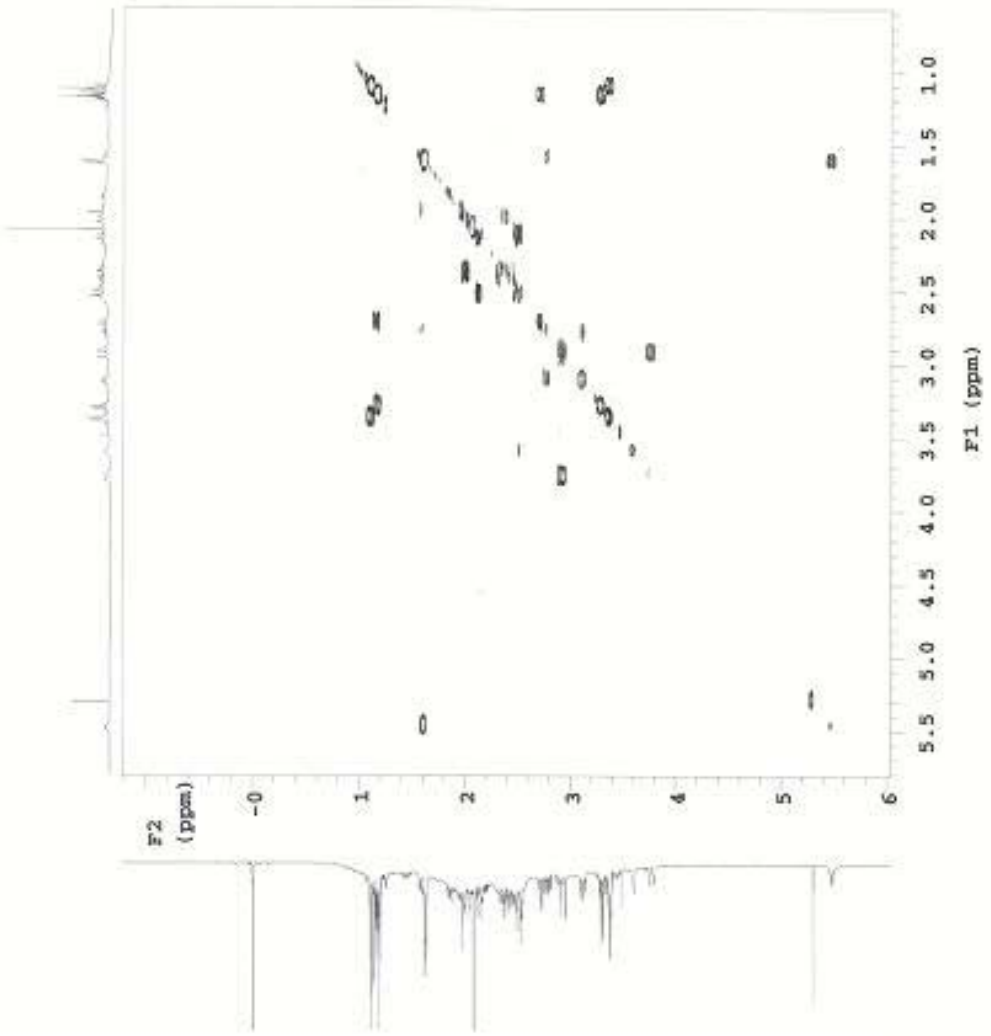
20



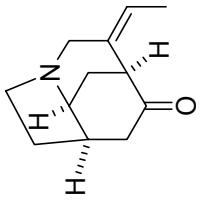

ppm
0
20
40
60
80
100
120
140
160
180
200
220
55.838
53.435
36.857
41.438
45.535
51.197
52.033
55.758
77.420
77.806
78.573

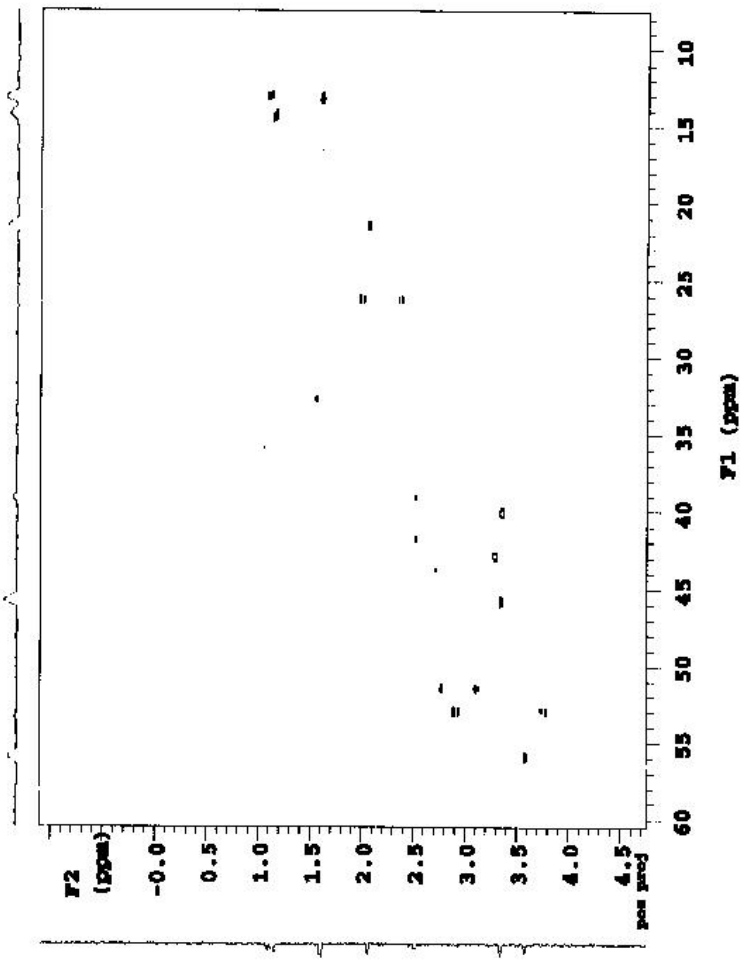
20

N
H
H
O

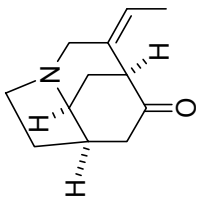


20




F2 (ppm)
-0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
F1 (ppm)
10
15
20
25
30
35
40
45
50
55
60

20


H
N
H
O
H