Supporting Information to Accompany:

The Practical Synthesis of a Renin Inhibitor via Diastereoselective Dieckmann Cyclization

Danny Gauvreau,* Greg J. Hughes, Stephen Y. W. Lau, Daniel J. McKay, Paul D. O'Shea, Rick R. Sidler, Bing Yu and Ian W. Davies

Department of Process Research, Merck Frosst Centre for Therapeutic Research

16711 route Transcanadienne, Kirkland, Québec, Canada H9H 3L1

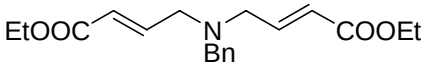
Table of Contents

General

Reactions were carried out under an atmosphere of dry nitrogen. Reagents and solvents were used as received from commercial sources. ^{1}H NMR spectra were recorded on 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (acetone-d_6: δ 2.04, dmso-d_6: δ 2.49, chloroform-*d:* δ 7.24). Data are reported as follows: chemical shift, multiplicity (s =

singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (acetone-d_6: δ 206.0, dmso-d_6: δ 39.5, chloroform-*d:* δ 77.0). ^{19}F NMR spectra were recorded on 375 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with α,α,α-trifluorotoluene added as an internal reference (δ – 67). All compounds were characterized using the same HPLC conditions: gradient elution: (0.1% H_3PO_4/CH_3CN 60:40 to 5:95 over 8 min, hold 2 min), flow rate = 1.0 mL/min, T = 35 °C, UV detection at 210 nm.

Experimental Procedures:

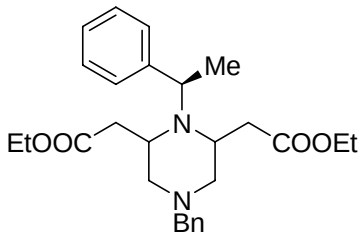


Diethyl (2E)-4,4'-(benzylimino)bisbut-2-enoate (**8**): Ethyl 4-bromocrotonate (100 g, 90wt%, 0.466 mol) was added to a 5°C suspension of K_2CO_3 (64.4 g, 0.466 mol) and benzyl amine (25 g, 0.233 mol) in CH_3CN (200 mL) over 30 min with the internal temperature rising to 30 °C. The mixture was allowed to cool to 20 °C and aged for 4hr. The mixture was partitioned between toluene (500 mL) and water (300 mL). The organic layer was washed with 3N HCl (240+50 mL). The aqueous layers were combined, mixed with toluene (500 mL) and treated with NaOH (1N, 95 mL). The organic layer was washed with water (3x250 mL) and concentrated. The residue assayed at 65.6 g (85%) and was used directly in the next step. HPLC: (ACE5-C18 250x4.6 mm, 70:30 to 5: 95 0.1% H_3PO_4 : CH_3CN over 10 min, hold 5 min, 220 nm, 35 °C, 2.0 ml/min) Product retention time: 4.1 min (*E*,*E* isomer), 3.8 min, (*Z*,*E* isomer). A sample was purified using column chromatography EtOAc/Hexane, 90/10 to 50/50, for characterization.

^{1}H NMR (400 MHz, acetone-d_6): δ 7.41-7.28 (m, 4 H); 7.24 (t, J = 7.1 Hz, 1 H); 6.93 (dt, J = 15.7, 5.7 Hz, 2 H); 6.06 (d, J = 15.7 Hz, 2 H); 4.13 (q, J = 7.1 Hz, 4 H); 3.64 (s, 2 H); 3.27 (d, J = 5.7 Hz, 4 H); 1.23 (t, J = 7.1 Hz, 6 H). **^{13}C NMR (101 MHz, acetone-d_6):** δ 166.2, 146.6, 139.7, 129.4, 129.2, 127.9, 123.6, 60.6, 59.0, 55.1, 14.5. **IR (neat):** 2980, 2802, 1715, 1656, 1262, 1172, 1036. **HRMS:** (ESI) m/z calcd for $C_{19}H_{26}NO_4$ (M + H) 332.1856, found 332.1857.

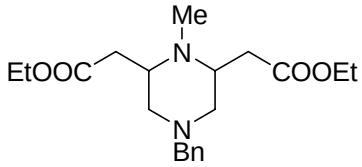
General Procedure for the Preparation of the Piperazines :

(R)-α-Methylbenzylamine (72 g, 0.594 mol) was added to a solution of dienolate (65.6 g, 0.198 mol) in trifluoroethanol (230 mL) which was then warmed to 80 ° for 12hrs. The mixture was cooled to ambient temperature and washed with 2N HCl (500 mL). The aqueous layer was extracted with toluene (100 mL). The organic layers were combined and concentrated. The residue was diluted with toluene (500 mL) and washed with 2N NaOH (300 mL) and water (3x200 mL) and concentrated. The residue assayed at 80.7 g (90% yield as a 20:1 mixture of *cis* and *trans* mixture) and was used directly in the Dieckmann cyclization. HPLC: (ACE5-C18 250x4.6 mm, 70:30 to 5: 95 0.1% H_3PO_4 : CH_3CN over 10 min, hold 5 min, 220 nm, 35 °C, 2.0 ml/min) Product retention time: 6.3 min. A sample was purified using column chromatography (Hexane/EtOAc 100/0 to 80/20) for characterization.



Diethyl 2,2'-{4-benzyl-1-[(1R)-1-phenylethyl]piperazine -2,6-diyl}diacetate (6c)

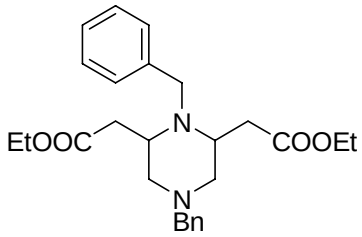
^{1}H NMR (500 MHz, acetone-d_6): δ 7.41-7.34 (m, 4 H); 7.35-7.29 (m, 4 H); 7.27-7.20 (m, 2 H); 4.11-4.01 (m, 2 H); 4.02-3.94 (m, 1 H); 3.94-3.83 (m, 2 H); 3.72 (d, J = 10.0 Hz, 1 H); 3.49 (s, 2 H); 3.04 (d, J = 10.0 Hz, 1 H); 2.82-2.85 (m, 6 H); 2.27 (dd, J = 3.3 and 10.3 Hz, 1 H); 2.08 (dd, J = 3.0 and 11.0 Hz, 1 H); 1.36 (d, J = 6.6 Hz, 3 H); 1.18 (t, J = 7.1 Hz, 3 H); 1.08 (t, J = 7.1 Hz, 3 H). **^{13}C NMR (126 MHz, acetone-d_6):** δ 172.2, 171.9, 145.6, 138.7, 128.7, 128.4, 128.1, 127.2, 126.9, 126.8, 62.4, 59.7, 59.4, 57.8, 56.7, 56.6, 51.2, 50.7, 34.3, 33.5, 21.4, 13.8, 13.7. **IR (neat):** 297, 2936, 2810, 1725, 1453, 1301, 1287, 1145, 1026. **HRMS:** (ESI) m/z calcd for $C_{27}H_{37}N_2O_4$ (M + H) 453.2748, found 453.2741. **$[\alpha]_D^{20}$** +26.0° (c = 0.01, Acetone)



Diethyl 2,2'-(4-benzyl-1-methylpiperazine-2,6-diyl) diacetate (**6a**)

Reaction time = 15hrs, yield = 50% as a 1.5:1 mixture of cis:trans isomer

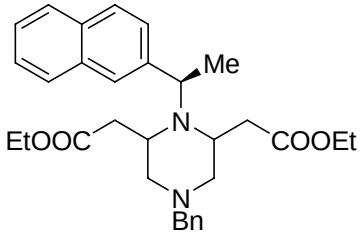
Major diastereomer : ^{1}H NMR (400 MHz, acetone-d_6): δ 7.34-7.26 (m, 4 H); 7.21 (t, J = 6.51 Hz, 1 H); 4.06-3.97 (m, 4 H); 3.57-3.38 (m, 1 H); 3.35 (d, J = 13.2 Hz, 1 H); 3.07 (m, 1 H); 2.77-2.64 (m, 2 H); 2.58-2.44 (m, 5 H); 2.29-2.18 (m, 4 H); 2.08-1.98 (m, 1 H); 1.14 (t, J = 7.1 Hz, 6 H). **^{13}C NMR (101 MHz, acetone-d_6):** δ 172.2, 139.5, 129.5, 128.9, 127.7, 63.2, 60.5, 59.8, 58.5, 39.0, 38.2, 14.4. **IR (neat):** 2979, 2806, 1727, 1452, 1368, 1150, 1025. **HRMS:** (ESI) m/z calcd for $C_{20}H_{31}N_2O_4$ (M + H) 364.2310, found 364.2313



Diethyl 2,2'-(1,4-dibenzylpiperazine-2,6-diyl)diacetate (6b)

Reaction time = 15hrs, yield = 55%

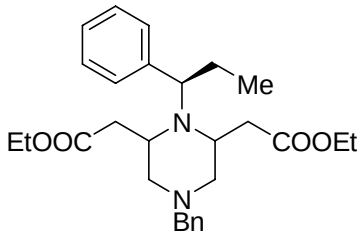
^{1}H NMR (400 MHz, Acetone-d_6): δ 7.35 (t, J = 6.75 Hz, 4 H); 7.33-7.24 (m, 4 H); 7.21 (q, J = 6.44 Hz, 2 H); 3.96 (q, J = 7.12 Hz, 4 H); 3.81 (s, 2 H); 3.48 (s, 2 H); 3.18 (dd, J = 9.30, 4.23 Hz, 2 H); 2.69-2.59 (m, 2 H); 2.56-2.45 (m, 4 H); 2.41 (dd, J = 10.93, 3.59 Hz, 2 H); 1.09 (t, J = 7.08 Hz, 6 H). **^{13}C NMR** (101 MHz, Acetone-d_6): δ 171.7, 140.0, 138.7, 128.7, 128.2, 128.1, 128.1, 126.9, 126.8, 62.4, 59.7, 56.6, 55.6, 55.2, 35.5, 13.6. **IR (neat):** 2980, 2810, 1727, 1453, 1368, 1301, 1134, 1027, 697. **HRMS:** (ESI) m/z calcd for $C_{26}H_{35}N_2O_4$ (M + H) 439.2591, found 439.2596.



Diethyl 2,2'-{4-benzyl-1-[(1R)-1-(2-naphthyl)ethyl] piperazine-2,6-diyl}diacetate (6d)

Reaction time = 72hrs at 80 °C, yield = 45%

^{1}H NMR (400 MHz, acetone-d_6): δ 7.90-7.78 (m, 4 H); 7.59 (dd, J = 8.5, 1.7 Hz, 1 H); 7.49-7.41 (m, 2 H); 7.37-7.25 (m, 4 H); 7.21 (t, J = 7.2 Hz, 1 H); 4.17-4.08 (m, 1 H); 4.10-4.00 (m, 2 H); 3.83-3.73 (m, 3 H); 3.47 (s, 2 H); 3.03 (d, J = 9.9 Hz, 1 H); 2.85-2.56 (m, 6 H); 2.29 (dd, J = 11.2, 3.7 Hz, 1 H); 2.08 (dd, J = 11.3, 3.5 Hz, 1 H); 1.42 (d, J = 6.5 Hz, 3 H); 1.16 (t, J = 7.1 Hz, 3 H); 0.94 (t, J = 7.1 Hz, 3 H). **^{13}C NMR (101 MHz, Acetone-d_6):** δ 172.5, 172.0, 143.3, 141.2, 139.0, 133.9, 133.3, 128.9, 128.4, 128.3, 128.0, 127.1, 126.2, 126.1, 125.7, 125.5, 62.6, 60.0, 59.6, 58.2, 57.1, 56.9, 51.5, 51.1, 34.6, 33.9, 21.3, 13.9, 13.5. **IR (neat):** 3061, 3017, 2974, 2926, 2809, 1726, 1600, 1456, 1370,1300, 1174,1148,1021,743. **HRMS:** (ESI) m/z calcd for $C_{31}H_{39}N_2O_4$ (M + H) 503.29043, found 503.28998. **$[\alpha]_D^{20}$** +7.5° (c = 0.023, $CHCl_3$)

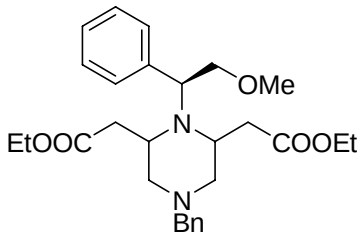


Diethyl 2,2'-{4-benzyl-1-[(1R)-1-phenylpropyl] piperazine-2,6-diyl}diacetate (6e)

Reaction time = 96hrs at 80 °C, yield = 60%

^{1}H NMR (400 MHz, acetone-d_6): δ 7.34-7.24 (m, 8 H); 7.25-7.17 (m, 2 H); 4.05-3.96 (m, 2 H); 3.92-3.82 (m, 2 H); 3.70 (dd, J = 9.7, 4.1 Hz, 2 H); 3.42 (s, 2 H); 3.04-2.99 (m, 1 H); 2.79-2.48 (m, 7 H); 2.13 (ddd, J = 11.1, 3.8, 1.8 Hz, 1 H); 2.03-1.92 (m, 2 H); 1.15 (t, J = 7.1 Hz, 3 H); 1.06 (t, J = 7.1 Hz, 3 H); 0.60 (t, J = 7.3 Hz, 3 H). **^{13}C NMR (101 MHz, acetone-d_6):** δ 172.2, 171.9, 142.8, 138.8, 128.6, 128.4, 128.1, 128.0, 127.0, 126.8, 64.8, 62.4, 59.7, 59.4, 56.6, 56.6, 51.7, 50.5, 34.5, 33.8, 26.1, 13.7, 13.6, 10.2. **IR (neat):**

3026, 2978, 2804, 1730, 1448, 1361, 1283, 1143, 1022, 861. **HRMS:** (ESI) m/z calcd for $C_{28}H_{39}N_2O_4$ (M + H) 467.2904, found 467.2904. **$[\alpha]_D^{20}$** +12.6° (c = 0.010, $CHCl_3$).



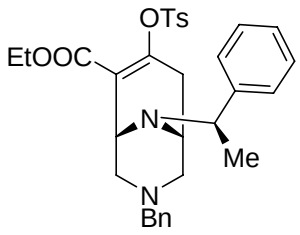
Diethyl 2,2'-{4-benzyl-1-[(1S)-2-methoxy-1-phenylethyl] piperazine-2,6-diyl}diacetate (6f)

Reaction time = 72hrs at 80 °C, yield = 52%

^{1}H NMR (400 MHz, acetone-d_6): δ 7.43-7.20 (m, 10 H); 4.11-4.01 (m, 3 H); 3.96-3.86 (m, 2 H); 3.68 (dd, J = 18.7, 9.4 Hz, 2 H); 3.53 (dd, J = 10.0, 4.1 Hz, 1 H); 3.48 (d, J = 7.2 Hz, 2 H); 3.23 (s, 3 H); 3.08 (s, 1 H); 2.77 (d, J = 7.9 Hz, 3 H); 2.68-2.58 (m, 3 H); 2.27 (dd, J = 11.0, 3.6 Hz, 1 H); 2.12-2.05 (m, 2 H); 1.20 (t, J = 7.1 Hz, 3 H); 1.09 (t, J = 7.1 Hz, 3 H). **^{13}C NMR (101 MHz, acetone-d_6):** δ 172.3, 171.9, 141.8, 138.8, 128.6, 128.2, 128.1 ,128.0 ,127.2 ,126.8, 75.6, 63.5, 62.5, 59.5, 59.4, 57.8, 56.9, 56.5, 51.5, 51.4, 35.5, 34.5, 13.7 ,13.6. **IR (neat):** 3030, 2982, 2926, 2809, 2757, 2361, 1735, 1491, 1452, 1370, 1187, 1139, 1113, 1030, 974, 696. **HRMS:** (ESI) m/z calcd for $C_{28}H_{39}N_2O_5$ (M + H) 483.2854, found 483.2852. **$[\alpha]_D^{20}$** -11.4° (c = 0.018, $CHCl_3$).

General Procedure for the Dieckmann Condensation/Tosylation :

A solution of the piperazine (80.7 g, 0.178 mol) in DMF (200 mL) was added to a -25 °C solution of ^{t}AmOK (180 g, 25 wt% solution in toluene, 0.356 mol) in DMF (600 mL) over 45 min with the internal temperature not rising above -20 °C. The mixture was allowed to warm to -5 °C over 2hrs. HPLC showed >98% conversion. (HPLC: (ACE5-C18 250x4.6 mm, 70:30 to 5: 95 0.1% H_3PO_4 : CH_3CN over 10 min, hold 5 min, 220 nm, 35 °C, 2.0 ml/min) Piperizine retention time: 6.3 min, diazabicyclo retention time: 5.5 min (major isomer), 5.9 min (minor isomer). BHT (45.8 g, 0.208 mol) was added and the mixture was aged for 10 min. Toluenesulfonic andydride (77.1 g, 0.236 mol) was added and the mixture was aged for 1hr at 0 to 10 °C. HPLC showed >95% conversion (HPLC: (ACE5-C18 250x4.6 mm, 70:30 to 5: 95 0.1% H_3PO_4 : CH_3CN over 10 min, hold 5 min, 220 nm, 35 °C, 2.0 ml/min). Product retention time: 7.0 min (major isomer), 7.5 min (minor isomer). Directly used in the purification step (MsOH salt formation)



Ethyl 3-benzyl-7-{[(4-methylphenyl)sulfonyl]oxy}-9-[(1R)-1-phenylethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylate (4c)

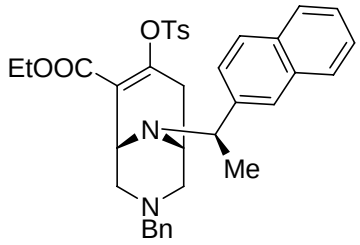
The crude tosylate was purified by bis MsOH salt formation: The product was dissolved into iPAc (1000 mL) and MsOH (25.4 mL, 0.378 mol) was added and the mixture was seeded. After 20hrs, the mixture was filtered to afford 89.8 g of a beige solid containing <1 % of the minor diastereomer (67% yield over cyclization/salt formation). A sample of the salt

was salt-broken for characterization purpose. To this end, a sample of the bis MsOH salt was suspended into MTBE/EtOAc (1/1) and a solution of 1N NaOH was added. The mixture was stirred for 10 minutes at 20 °C, then the layers were separated. The organic layer was washed with brine, then dried using $MgSO_4$, filtered and concentrated.

Reaction yield = 90%, reaction diastereoselectivity = 8.5:1, upgraded to 160:1 with MsOH salt formation. Note that salt formation was only applied on **4c**. Diastereomeric ratio of other substrates refers to the ratio observed by HPLC at the end of the reaction (before work-up and purification).

All Dieckmann products were characterized as their free base.

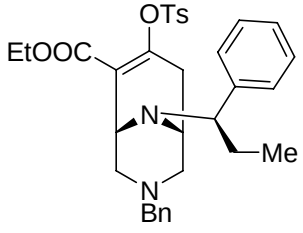
^{1}H NMR (500 MHz, Acetone-d$_6$): δ 7.98 (d, J = 8.1 Hz, 2 H); 7.50 (d, J = 8.1 Hz, 2 H); 7.34-7.31 (m, 2 H); 7.30-7.16 (m, 8 H); 3.83 (q, J = 7.1 Hz, 2 H); 3.58-3.54 (m, 1 H); 3.53-3.46 (m, 3 H); 3.34-3.32 (m, 1 H); 2.79 (dt, J = 10.7, 2.2 Hz, 1 H); 2.67-2.59 (m, 2 H); 2.46 (s, 3 H); 2.39 (dd, J = 10.7, 2.8 Hz, 1 H); 2.19 (d, J = 19.1 Hz, 1 H); 2.08 (dd, J = 10.7, 2.9 Hz, 1 H); 1.26 (d, J = 6.5 Hz, 3 H); 1.05 (t, J = 7.1 Hz, 3 H). **^{13}C NMR (126 MHz, Acetone-d$_6$)**: δ 164.7, 153.3, 146.4, 145.9, 139.2, 134.6, 130.7, 129.4, 129.4, 129.2, 129.1, 129.0, 128.1, 127.8, 127.6, 120.6, 62.4, 60.7, 59.1, 56.0, 54.2, 49.5, 29.6, 21.6, 21.5, 14.3. **IR (neat):** 2974, 2805, 1703, 1453, 1369, 1193, 1176, 1084, 1051, 899. **HRMS:** (ESI) m/z calcd for $C_{32}H_{37}N_2O_5S$ (M + H) 561.2418, found 561.2414. **$[\alpha]_D^{20}$** +16.6° (c = 0.035, CH_2Cl_2).



Ethyl 3-benzyl-7-{[(4-methylphenyl)sulfonyl]oxy}-9-[(1*R*)1 (2-naphthyl)ethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylate (4d)

Yield = 59%, diastereoselectivity = 17:1

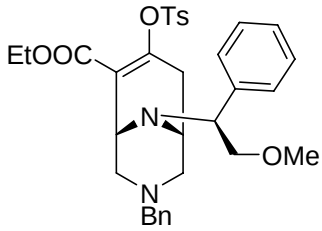
^{1}H NMR (400 MHz, acetone-*d*$_6$): δ 8.01 (d, J = 8.2 Hz, 2 H); 7.87-7.77 (m, 3 H); 7.63-7.33 (m, 6 H); 7.35-7.16 (m, 5 H); 3.75 (t, J = 7.1 Hz, 2 H); 3.70-3.60 (m, 2 H); 3.53 (d, J = 2.6 Hz, 2 H); 3.33 (m, 1 H); 2.87-2.75 (m, 1 H); 2.71 (dd, J = 19.2, 7.3 Hz, 1 H); 2.59 (dt, J = 10.6 Hz, 2.2 Hz, 1 H); 2.47 (s, 3 H); 2.43 (dd, J = 10.7, 2.8 Hz, 1 H); 2.23 (d, J = 19.2 Hz, 1 H); 2.11 (dd, J = 10.7, 2.9 Hz, 1 H); 1.36 (d, J = 6.5 Hz, 3 H); 0.93 (t, J = 7.1 Hz, 3 H). **^{13}C NMR (101 MHz, acetone-*d*$_6$):** δ 163.8, 152.6, 145.6, 142.5, 138.4, 133.8, 133.6, 133.1, 129.9, 128.6, 128.4, 128.2, 128.1, 127.6, 127.5, 126.8, 126.3, 126.0, 125.9, 125.5, 125.1, 119.8, 61.6, 59.9, 59.8, 58.4, 55.3, 53.5, 48.8, 20.7, 20.5, 13.3. **IR (neat):** 2978, 2800, 1730, 1465, 1374, 1296, 1278, 1170, 1143, 1030, 743. **HRMS:** (ESI) m/z calcd for $C_{36}H_{39}N_2O_5S$ (M + H) 611.2574, found 611.2568. **$[\alpha]_D^{20}$** +7.9° (c = 0.0043, $CHCl_3$).



Ethyl 3-benzyl-7-{[(4-methylphenyl)sulfonyl]oxy}-9-[(1*R*)-1-phenylpropyl]-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylate (4e)

Yield = 50%, diastereoselectivity = 4:1

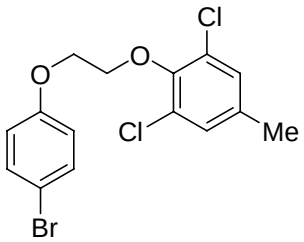
^{1}H NMR (400 MHz, Acetone-d$_6$): δ 7.96 (d, J = 8.0 Hz, 2 H); 7.50 (d, J = 8.0 Hz, 2 H); 7.36-7.30 (m, 2 H); 7.31-7.23 (m, 4 H); 7.20 (dd, J = 11.1, 7.2 Hz, 4 H); 3.80 (q, J = 7.1 Hz, 2 H); 3.63-3.56 (m, 1 H); 3.52 (q, J = 7.1 Hz, 2 H); 3.32-3.26 (m, 2 H); 2.80 (s, 1 H); 2.70-2.58 (m, 2 H); 2.46 (s, 3 H); 2.37 (dd, J = 10.8, 2.8 Hz, 1 H); 2.20 (d, J = 19.1 Hz, 1 H); 2.11-2.05 (m, 1 H); 1.96-1.87 (m, 1 H); 1.60-1.45 (m, 1 H); 1.03 (t, J = 7.1 Hz, 3 H); 0.57 (t, J = 7.3 Hz, 3 H). **^{13}C NMR (101 MHz, acetone-*d*$_6$):** δ 164.6, 153.3, 146.4, 143.2, 139.2, 134.7, 130.7, 129.5, 129.2, 129.2, 129.1, 129.0, 129.0, 127.9, 127.6, 120.6, 65.6, 62.4, 60.7, 56.2, 54.4, 49.6, 29.7, 26.6, 21.5, 14.3, 10.5. **IR (neat):** 2906, 2926, 1701, 1453, 1369, 1192, 1176, 1085, 1071, 825. **HRMS:** (ESI) m/z calcd for $C_{33}H_{39}N_2O_5S$ (M + H) 576.2606, found 576.2595. **$[\alpha]_D^{20}$** -8.0° (c = 0.01, $CHCl_3$).



Ethyl 3-benzyl-9-[(1*S*)-2-methoxy-1-phenylethyl]-7-{[(4-methylphenyl)sulfonyl]oxy}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylate (4f)

Yield = 67%, diastereoselectivity = 11:1

^{1}H NMR (400 MHz, acetone-*d*$_6$): δ 7.97 (d, J = 8.2 Hz, 2 H); 7.50 (d, J = 8.2 Hz, 2 H); 7.35-7.16 (m, 10 H); 3.83 (q, J = 7.1 Hz, 2 H); 3.73-3.61 (m, 3 H); 3.55-3.43 (m, 2 H); 3.43-3.33 (m, 1 H); 3.27 (d, J = 3.3 Hz, 1 H); 3.24 (s, 3 H); 2.85 (d, J = 7.4 Hz, 1 H); 2.76 (s, 1 H); 2.66-2.53 (m, 1 H); 2.47 (s, 3 H); 2.41 (dd, J = 10.6, 2.7 Hz, 1 H); 2.13 (d, J = 19.1 Hz, 2 H); 1.05 (t, J = 7.1 Hz, 3 H). **^{13}C NMR (101 MHz, acetone-*d*$_6$):** δ 163.9, 153.1, 145.6, 141.5, 138.4, 134.1, 129.9, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.4, 126.8, 119.5, 77.2, 63.7, 61.6, 60.0, 59.8, 58.0, 55.4, 53.6, 50.2, 20.7, 13.4. **IR (neat):** 3056, 3026, 2974, 2878, 2804, 2356, 1700, 1596, 1496, 1370, 1283, 1191, 1091, 804. **HRMS:** (ESI) m/z calcd for $C_{33}H_{39}N_2O_6S$ (M + H) 591.2523, found 591.2527. **$[\alpha]_D^{20}$** -7.5° (c = 0.0017, $CHCl_3$)



2-[2-(4-Bromophenoxy)ethoxy]-1,3-dichloro-5-methylbenzene (9)

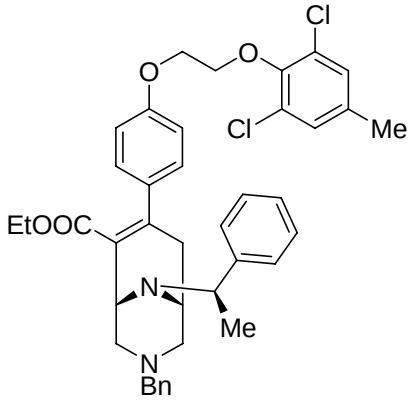
Two-step sequence :

A visually clean 3 L 3-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple, one nitrogen inlets and a heating mantle was charged with bromo phenol (80.0 g) and DCE (1.12 L, 14 mL/g). $Bu_4N^+Br^-$ (2.98 g, 0.02 eq) were added to the solution, followed by 5N NaOH (0.480 L, 6 mL/g). The biphasic mixture was warmed to 85 ºC using the heating mantle. The solution was aged with stirring at 85 ºC for a period of 15 hrs. The mixture was cooled to 22 ºC and transferred to a separation funnel. The layers were

separated. The organic layer was concentrated and flushed with heptane (2 x 3 mL/g, 2 x 240 mL). The chloride was obtained as a 95%wt white solid in 104.8 g (96.3% yield).

A visually clean 1 L 3-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple, one nitrogen inlets and a heating mantle was charged with the chloride (30.2 g as 95%wt solid) and DMF (160 mL, 8 mL/g of cresol). K_2CO_3 (17.2 g, 1.10 eq) was added to the solution. The heterogeneous mixture was warmed to 100 ºC using the heating mantel. A DMF (40 mL, 2 mL/g) solution of the cresol (21.4 g, 1.05 eq) was added to the chloride solution at 100 ºC over a period of 2.5hrs. The mixture was aged with stirring at 100 ºC for a period of 2 hrs. The mixture was cooled to 22 ºC and water (200 mL, 10 mL/g) was added to the DMF solution over a period of 30 minutes during which, the biaryl crystallized out. The solution was aged 30 minutes at room temperature and then filtered. The cake was washed 2 x 10 mL/g (2 x 200 mL) with a 1/1 mixture of DMF/H_2O, then washed with water (2 x 200 mL, 2 x 10 mL/g). The bromo diaryl was dried on the frit, then in the vacuum oven at 40ºC for 15 hrs. The diaryl was obtained as a 95%wt off-white solid in 41.52 g (93% yield).

^{1}H NMR (500 MHz, acetone-d_6): δ 7.42 (d, J = 8.9 Hz, 2 H); 7.2 (s, 2 H); 6.92 (d, J = 8.9 Hz, 2 H); 4.37 (s, 4 H); 2.29 (s, 3 H). **^{13}C NMR (126 MHz, acetone-d_6):** δ 158.2, 149.0, 136.1, 132.2, 129.5, 128.5, 116.7, 112.4, 71.8, 67.5, 19.5. **IR (neat):** 2926, 1486, 1451, 1266, 1243, 1065, 822 . **HRMS:** (ESI) m/z calcd for $C_{15}H_{14}O_2Cl_2Br$ (M + H) 374.95489, found 374.95488. **Melting point** = 81.5 – 83.7 °C.



Ethyl 3-benzyl-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-[(1R)-1-phenylethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylate (10)

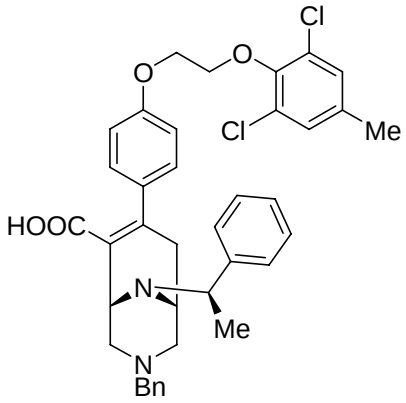
In a 10 mL vial, $PdCl_2$ (42 mg, 0.24 mmol) and dppb (102 mg, 0.24 mmol) were suspended in 4 mL DMF, degassed and stirred under N_2 for 24 hrs.

In a 250 mL round bottom flask, 25 mL THF was cooled to 0 ºC. BuLi (5.46 mL, 2.1M in hex, 11.47 mmol) was added dropwise over 30 min. *n*BuMgCl (3.19 mL, 1.8M in THF, 5.74 mmol) was added dropwise over 30 min and the whole solution brought to -45 ºC in a dry ice/acetonitrile bath. Aryl bromide (5.39 g, 14.34 mmol) in 25 mL THF was added to the *n*Bu_3MgLi solution dropwise over 30 min and aged at -45 ºC for 15 min. $B(OMe)_3$ (4.0 mL, 35.85 mmol) was added dropwise neat over 30 min and the reaction mixture was allowed to warm to 20 ºC over 30 min.

The reaction was diluted with 20 mL DMF and tosylate bis methanesulfonic acid salt (9.0 g, 11.95 mmol) was added, followed by $PdCl_2$-dppb solution formed above and degassed. K_3PO_4 (21.5 mL, 2M, 43 mmol) was added and the reaction mixture was heated to 60 ºC for 2 hrs with vigorous stirring.

Reaction was cooled to 20 ºC and quenched with 180 mL H_2O and extracted 3 x 60 mL toluene. Combined organic layers were washed with 1 x 90 mL 1N NaOH, 3 x 60 mL H_2O, treated with $MgSO_4$ and 10 g Darco KB, filtered and concentrated to give a light yellow thick oil. Oil dissolved in 100 mL Et_2O. HCl (25 mL, 1M, 25 mmol) added dropwise over 30 min, aged 30 min to form a light yellow solid and filtered to give bis HCl salt as a light yellow powder 7.54g, 92% yield, 90 LCAP.

^{1}H NMR (400 MHz, Acetone-d$_6$): δ 7.38-7.27 (m, 6 H); 7.28-7.13 (m, 8 H); 7.01-6.96 (m, 2 H); 4.42 (s, 4 H); 3.80 (q, J = 6.5 Hz, 1 H); 3.78-3.65 (m, 2 H); 3.57 (dd, J = 6.5, 2.6 Hz, 1 H); 3.55-3.45 (m, 2 H); 3.35 (m, 1 H); 2.86 (d, J = 10.6 Hz, 1 H); 2.83-2.70 (m, 4 H); 2.54 (dd, J = 10.5, 2.8 Hz, 1 H); 2.31 (s, 3 H); 2.23-2.13 (m, 2 H); 1.34 (d, J = 6.5 Hz, 3 H); 0.80 (t, J = 7.1 Hz, 3 H). **^{13}C NMR (101 MHz, acetone-*d*$_6$):** δ 168.3, 158.2, 149.1, 148.3, 145.9, 139.4, 136.1, 135.4, 129.5, 128.5, 128.3, 128.2, 128.2, 128.0, 127.4, 126.8, 126.6, 126.2, 114.1, 72.0, 67.2, 61.5, 60.6, 59.0, 58.7, 55.5, 53.3, 48.6, 31.9, 21.2, 19.4, 13.3. **IR (neat):** 3300 (broad), 2930, 2424, 1710, 1513, 1474, 1289, 1250, 1224, 1054, 899. **HRMS:** (ESI) m/z calcd for $C_{40}H_{43}N_2O_4Cl_2$ (M + H) 685.25846, found 685.25944. **$[\alpha]_D^{20}$** -7.1° (c = 0.011, $CHCl_3$).

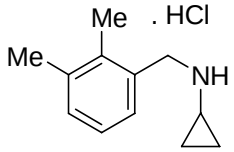


3-Benzyl-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-[(1R)-1-phenylethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid (3a)

A visually clean 25 mL round-bottom flask equipped with a magnetic stirrer, a thermocouple, one nitrogen inlets and an oil bath was charged with ethyl ester HCl salt (2.00 g) and *t*-BuOH (6.0 mL, 3 mL/g) at 35 ºC. *t*-BuOK (2.071 g, 7.0 eq) was added to the solution, then the mixture was warmed to 50 ºC using an oil bath. The solution was aged with stirring at 50 ºC for a period of 6 hrs. The mixture was cooled to 35 ºC and the reaction was quenched by the addition of 2M AcOH (6.3 mL, 9.5 eq). The mixture was diluted with toluene (30 mL, 15 mL/g) and water (20 mL, 10 mL/g), then cooled to 22 ºC and the layers were separated. The organic layer was washed 2 x 10 mL/g Na_2CO_3 and 1 x 10 mL/g brine. The organic layer was dried using $MgSO_4$, filtered and concentrated under reduced pressure. The acid was obtained as a 77%wt oil in 93.4% yield (1.334 g), as a 4.8:1 ratio of conjugated / non-conjugated isomers.

^{1}H NMR (400 MHz, Acetone-d$_6$): δ 7.41-7.23 (m, 12 H); 7.19 (m, 2 H); 6.98 (d, J = 8.1 Hz, 2 H); 4.40 (s, 4 H); 3.83 (m, 1 H); 3.51 (m, 4 H); 2.87-2.73 (m, 2 H); 2.53 (d, J = 10.3 Hz, 1 H); 2.31 (s, 3 H); 2.22 (m, 3 H); 2.15 (m, 1 H); 1.34 (d, J = 6.4 Hz, 3 H). **^{13}C NMR** (101 MHz, Acetone-d$_6$): δ 169.4, 159.0, 149.9, 149.6, 146.8, 140.1, 136.9, 136.2, 130.3, 129.3, 129.2, 129.1, 128.9, 128.2, 127.6, 127.5, 126.5, 114.8, 72.8, 67.9, 62.4, 61.3, 59.5, 56.9, 54.1, 49.3, 33.2, 30.5, 22.1, 20.3. **IR (neat):** 3200 (broad), 2930, 2802, 1710, 1606, 1509, 1475, 1455, 1363, 1243, 1224, 1050. **HRMS:** (ESI) m/z calcd for

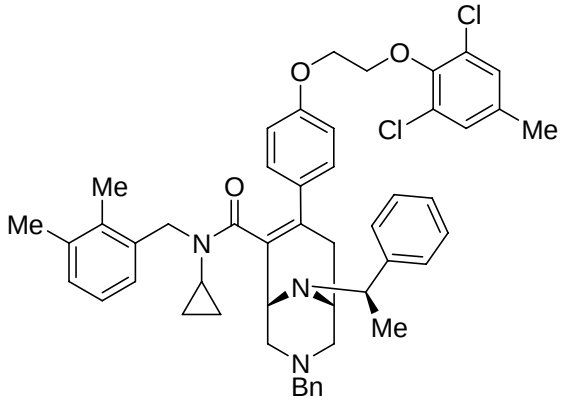
$C_{38}H_{39}N_2O_4Cl_2$ (M + H) 657.22712, found 657.22814. $[\alpha]_D^{20}$ +50.0° (c = 0.01, Acetone). **Melting point** = 98.1 – 100.6 °C.



***N*-(2,3-Dimethylbenzyl)cyclopropanamine . HCl salt (7)**

2,3-Dimethylbenzaldehyde (16.14 g, 120 mmol) was added to a mixture of $NaHCO_3$ (15.2 g, 180 mmol) and cyclopropylamine (8.24 g, 144 mmol) in MeOH (32 mL) and the resulting suspension was heated to 45 °C for 4hrs, then cooled to 0 °C. $NaBH_4$ (5.46 g, 144 mmol) was added portion-wise and the mixture was aged 18hrs at 20 °C. The mixture was concentrated, partitioned between CH_2Cl_2 (100 mL) and water (200 mL). The organic layer was washed with brine (100 mL), filtered through cotton and concentrated. The residue assayed at 20 g (95% yield).

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.53 (s, 2 H); 7.36 (d, J = 7.6 Hz, 1 H); 7.19 (m, 1 H); 7.14-7.07 (m, 1 H); 4.19 (s, 2 H); 2.66 (m, 1 H); 2.26 (s, 6 H); 0.95 (s, 2 H); 0.75-0.69 (m, 2 H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 136.9, 136.0, 130.4, 130.1, 128.8, 125.4, 48.5, 29.7, 20.3, 15.2, 3.2. **IR (neat):** 2917, 2810, 2711, 2444, 1586, 1446, 1400, 1361, 1008, 782. **HRMS:** (ESI) m/z calcd for $C_{12}H_{18}N$ (M + H) 176.1434, found 176.1431. **Melting point** = 185.2 – 186.1 °C.

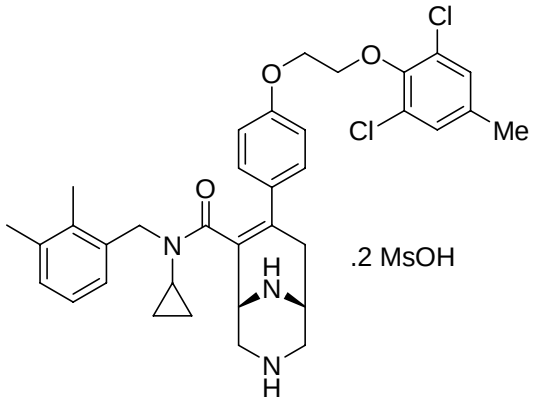


3-Benzyl-*N*-cyclopropyl-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy] phenyl}-*N*-(2,3-dimethylbenzyl)-9-[(1*R*)-1-phenylethyl]-3,9-diazabicyclo[3.3.1] non-6-ene-6-carboxamide (11)

Oxalyl chloride (1.81 g, 14.2 mmol) and DMF (2 drops) were added to a 23 °C solution of acid (6.01 g, 11.2 mmol) in toluene, 60 mL. The mixture was aged for 1hr at 20 °C, then concentrated and solvent switched to CH_2Cl_2 (35 mL). The mixture was cooled to 0 °C and $^iPr_2NEt$ (3.4 mL, 19.0 mmol) and the cyclopropylamine (2.00 g, 11.4 mmol) were added. The mixture was aged for 2hrs at 20 °C. The mixture was washed with water (2x50mL). The organic layer was concentrated and stripped from toluene (2x10mL). The amide was obtained at 5.67 g (73% yield).

^{1}H NMR (400 MHz, Acetone-d_6): δ 7.50 (m, 2 H); 7.42-7.17 (m, 11 H); 7.11-7.00 (m, 2 H); 7.02-6.85 (m, 3 H); 6.74 (d, J = 7.8 Hz, 1 H); 4.95 (d, J = 16.9 Hz, 1 H); 4.43 (m, 5 H); 3.81 (q, J = 6.6 Hz, 1 H); 3.72-3.42 (m, 3 H); 2.81 (m, 2 H); 2.51-2.32 (m, 3 H); 2.34-2.24 (m, 4 H); 2.24-2.09 (m, 2 H); 1.95 (s, 3 H); 1.84 (s, 3 H); 1.28-1.22 (d, J = 6.6 Hz, 3 H); 0.68-0.57 (m, 1 H); 0.50-0.41 (m, 1 H); 0.21-0.11 (m, 1 H); -0.15--0.23 (m, 1 H). **^{13}C NMR** (101 MHz, Acetone-d_6): δ 174.6, 159.5, 153.2, 147.3, 139.5, 137.4,

137.3, 137.1, 134.5, 133.7, 132.4, 132.2, 131.3, 129.5, 129.3, 129.1, 128.8, 128.7, 127.5, 125.9, 125.8, 124.4, 123.0, 115.2, 115.2, 68.9, 67.7, 61.7, 60.0, 59.3, 57.1, 55.4, 50.2, 49.3, 31.1, 28.7, 22.1, 20.2, 14.5, 8.4, 6.1. **IR (neat):** 2941, 2876, 2802, 1610, 1509, 1455, 1405, 1370, 1251, 1177, 1050, 853, 834. **HRMS:** (ESI) m/z calcd for $C_{50}H_{54}N_3O_3Cl_2$ (M + H) 814.35260, found 814.35367. $[\alpha]_D^{20}$ +31.4° (c = 0.01, Acetone). **Melting point** = 79.4 – 81.7 °C.



_N_-Cyclopropyl-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-_N_-(2,3-dimethylbenzyl)-3,9-diazabicyclo [3.3.1]non-6-ene-6-carboxamide . 2MsOH (1)

MsOH (3.34 g, 34.8 mmol) was added to a solution of the protected amine (5.67 g, 6.96 mmol) and $ZnBr_2$ (0.94 g, 4.2 mmol) in IPA (35 mL). The mixture was charged with $Pd(OH)_2$ (0.86 g, 20wt%, 1.4 mmol) and was placed under 200 psi H_2. The mixture was heated to 75 °C for 36hrs. The mixture was treated with water and extracted with toluene. The aqueous layer was treated with 1N NaOH and extracted with toluene (65 mL). The organic layer was washed with water (3x30 mL) and concentrated. The residue was solvent switched to CH_3CN (100 mL) and a solution of MsOH (2 equiv) in THF (10 mL) was added. The mixture was seeded with authentic MK-8141 bis-mesylate salt and aged 4hrs at 20 °C. The mixture was filtered to afford the desired product 4.0 g (71% yield).

^{1}H NMR (400 MHz,CD_3OD): rotamer in a 3/1 ratio, major rotamer : 7.26 (d, *J* = 8.8 Hz, 2 H), 7.19 (s, 2 H), 7.04-6.99 (m, 2 H), 6.92 (t, *J* = 7.6 Hz, 1 H), 6.73 (d, *J* = 8.8 Hz, 2 H), 4.75 (d, *J* = 15.2 Hz, 1 H), 4.66 (br s, 1 H), 4.40 (br s, 1 H), 4.37-4.21 (m, 4 H), 4.16 (d, *J* = 15.1 Hz, 1 H), 4.13 (d, *J* = 13.2 Hz, 1 H), 3.75-3.63 (m, 4 H), 2.67 (s, 6 H), 2.66 (d, *J* = 19.0 Hz, 1 H), 2.28 (s, 3 H), 2.25 (s, 3 H), 2.16 (s, 3 H), 1.78-1.74 (m, 1 H), 0.84-0.76 (m, 1 H), 0.74-0.67 (m, 1 H), 0.52-0.47 (m, 2 H). **IR (neat):** 2959, 1605, 1509, 1244, 797. **HRMS :** (ESI) m/z calcd for $C_{35}H_{39}Cl_2N_3O_3Na$ (M + Na) : 642.2261, found: 642.2292. CHN Anal Calcd for $C_{37}H_{50}Cl_2N_3O_{10.5}S_2$: C 52.91, H 6.00, N 5.00. Found: C 52.75, H 5.94, N 4.97

X-Ray and Computational Data of 6c

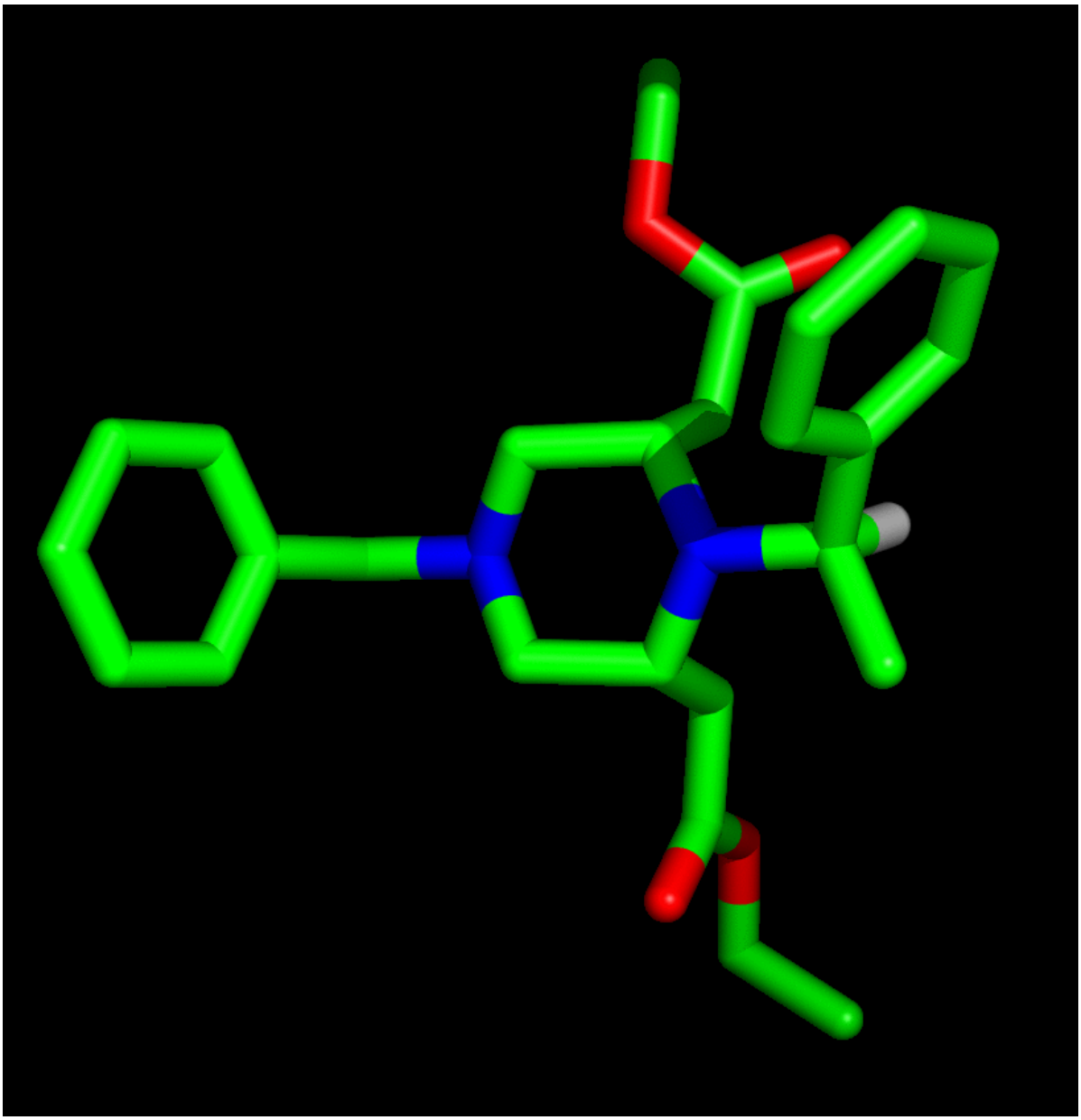


Figure 1. Compound **6c**.

This image is of the fully optimized lowest energy conformation examined at the RHF/6-31G(d) level of theory and basis set in gas phase. All calculations were performed using the G03 suite (reference is: Gaussian 03, Revision C.01 M.J. Frisch et al. Gaussian, Inc., Pittsburgh PA, 2003).

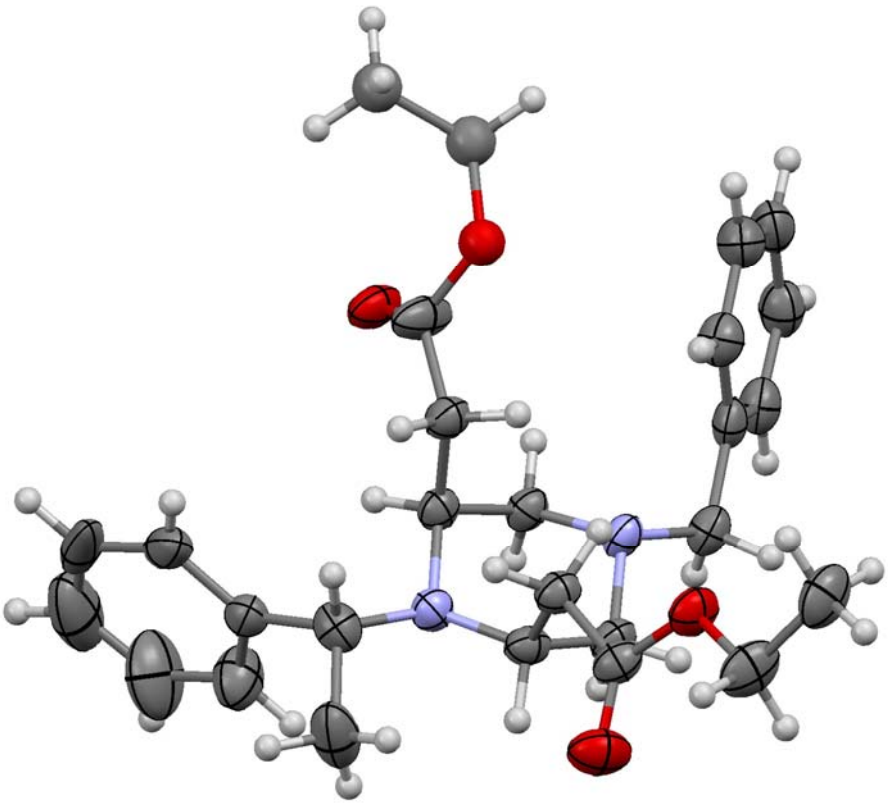
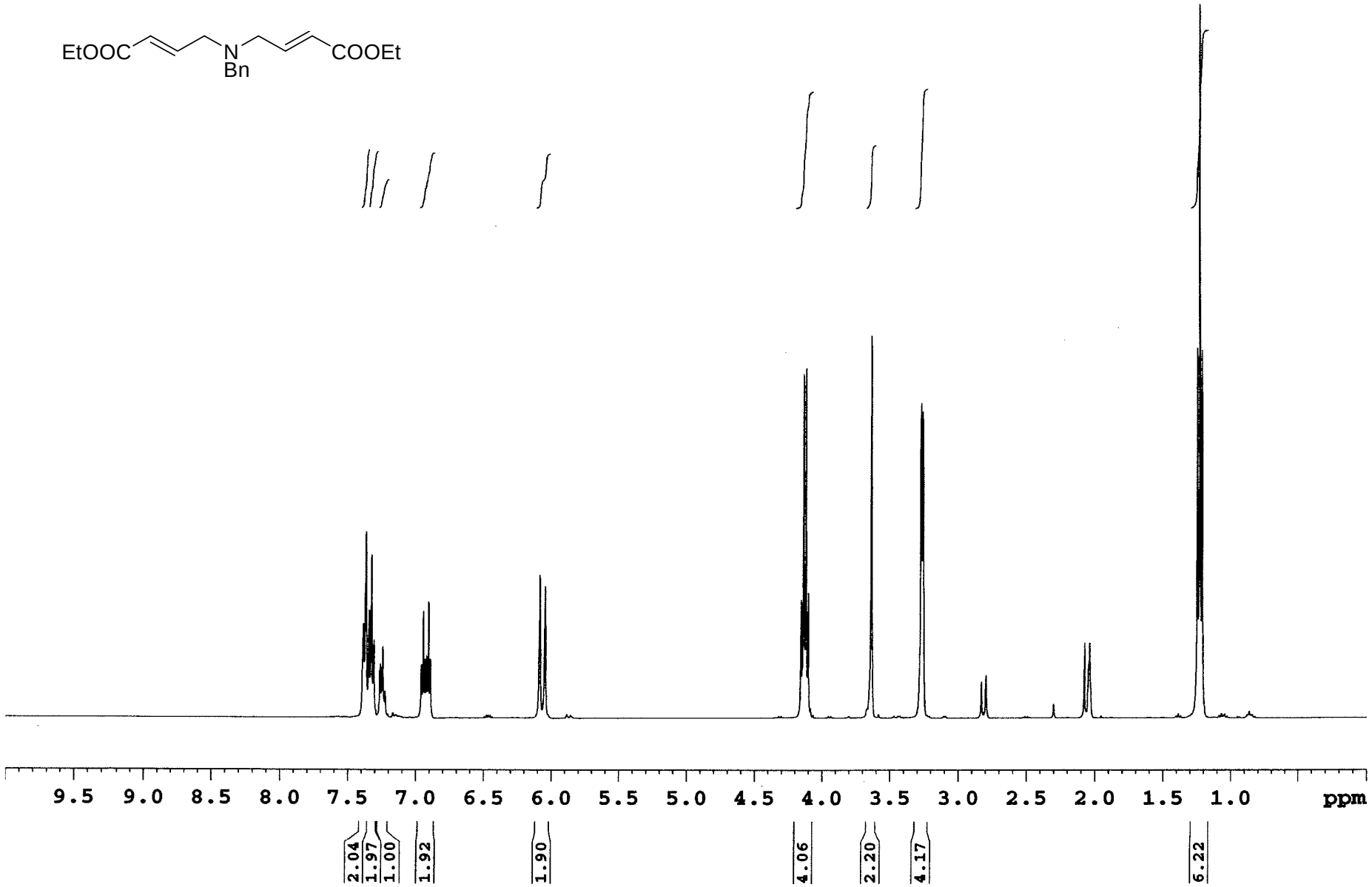
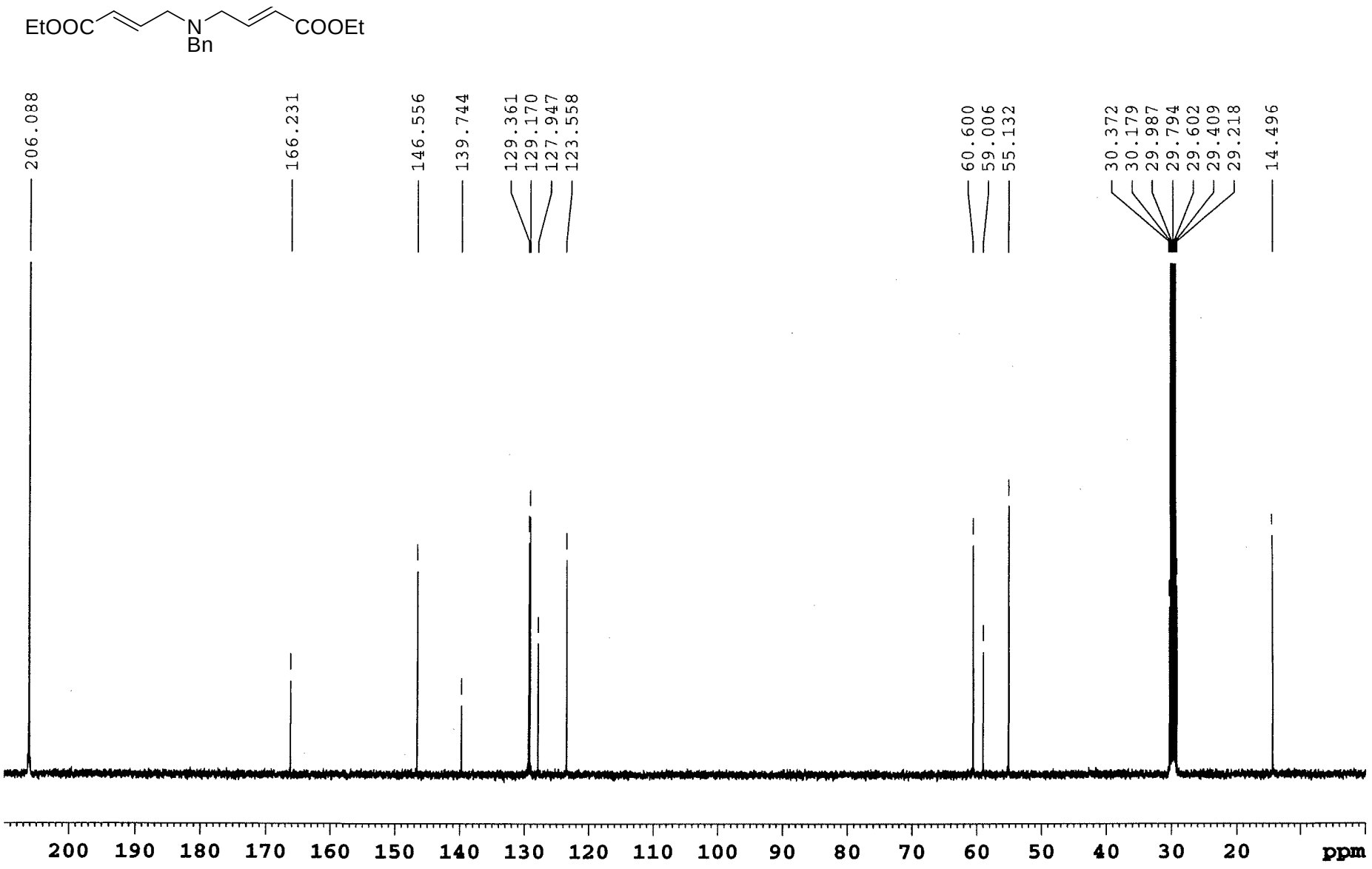
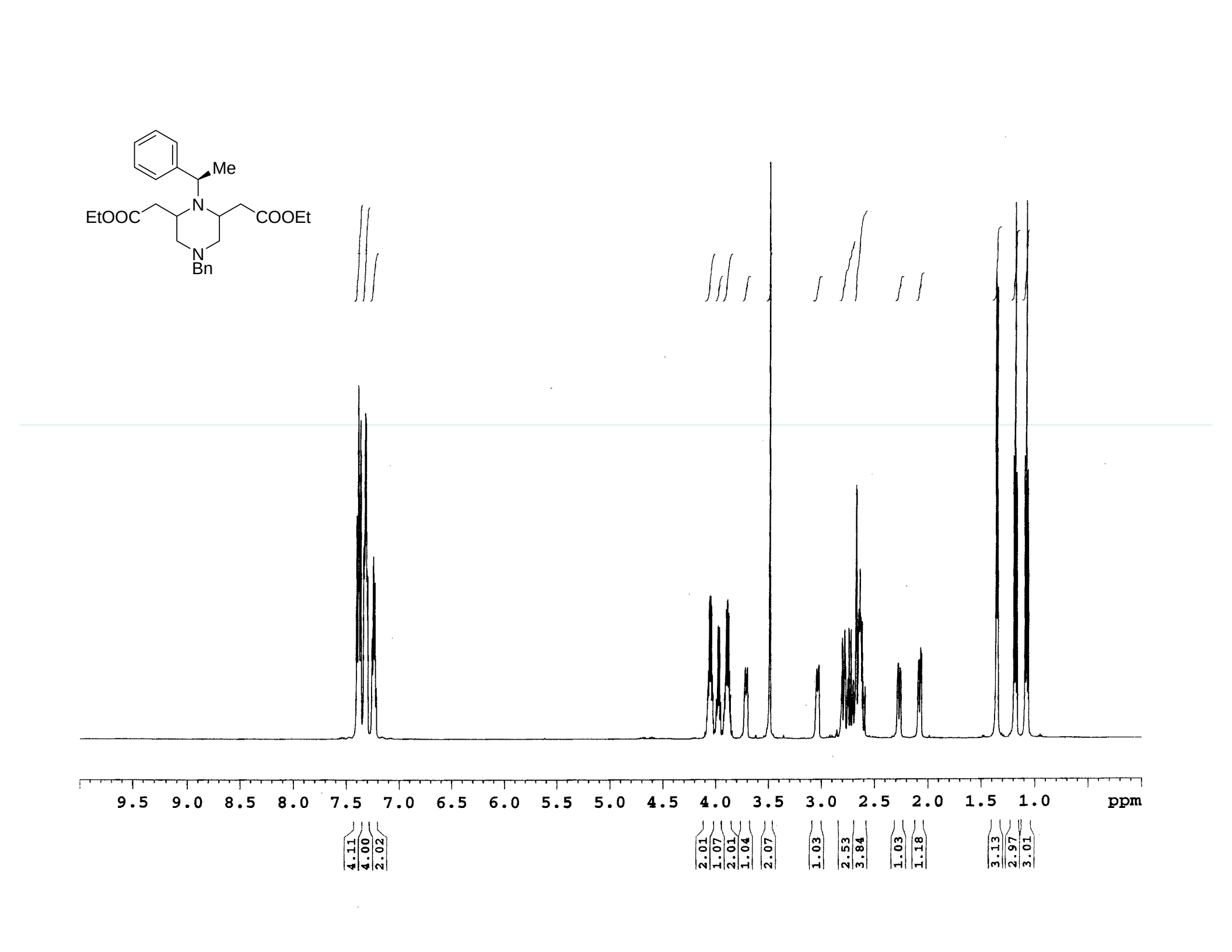


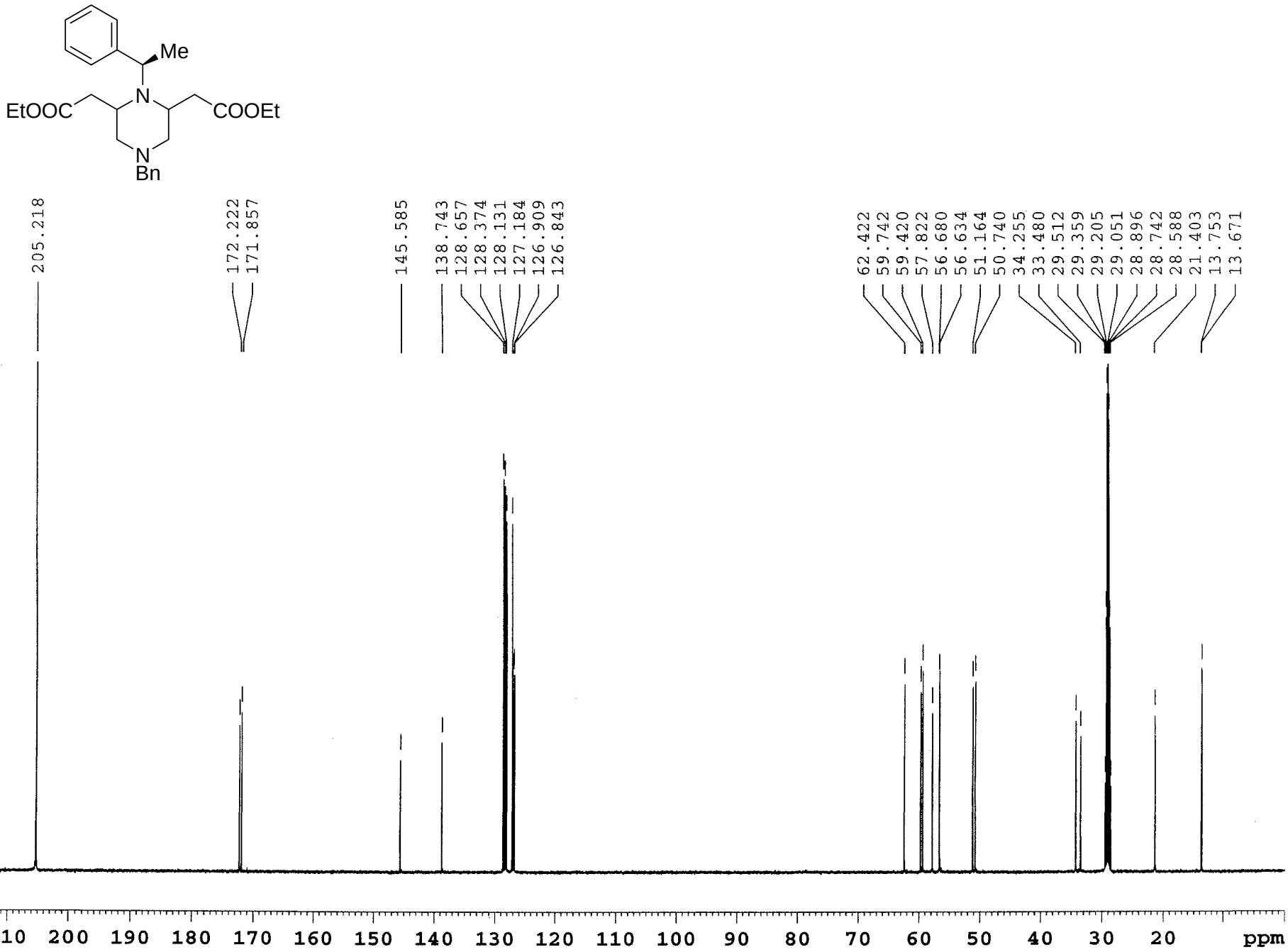
Figure 2. Molecule plot of compound **6c**.

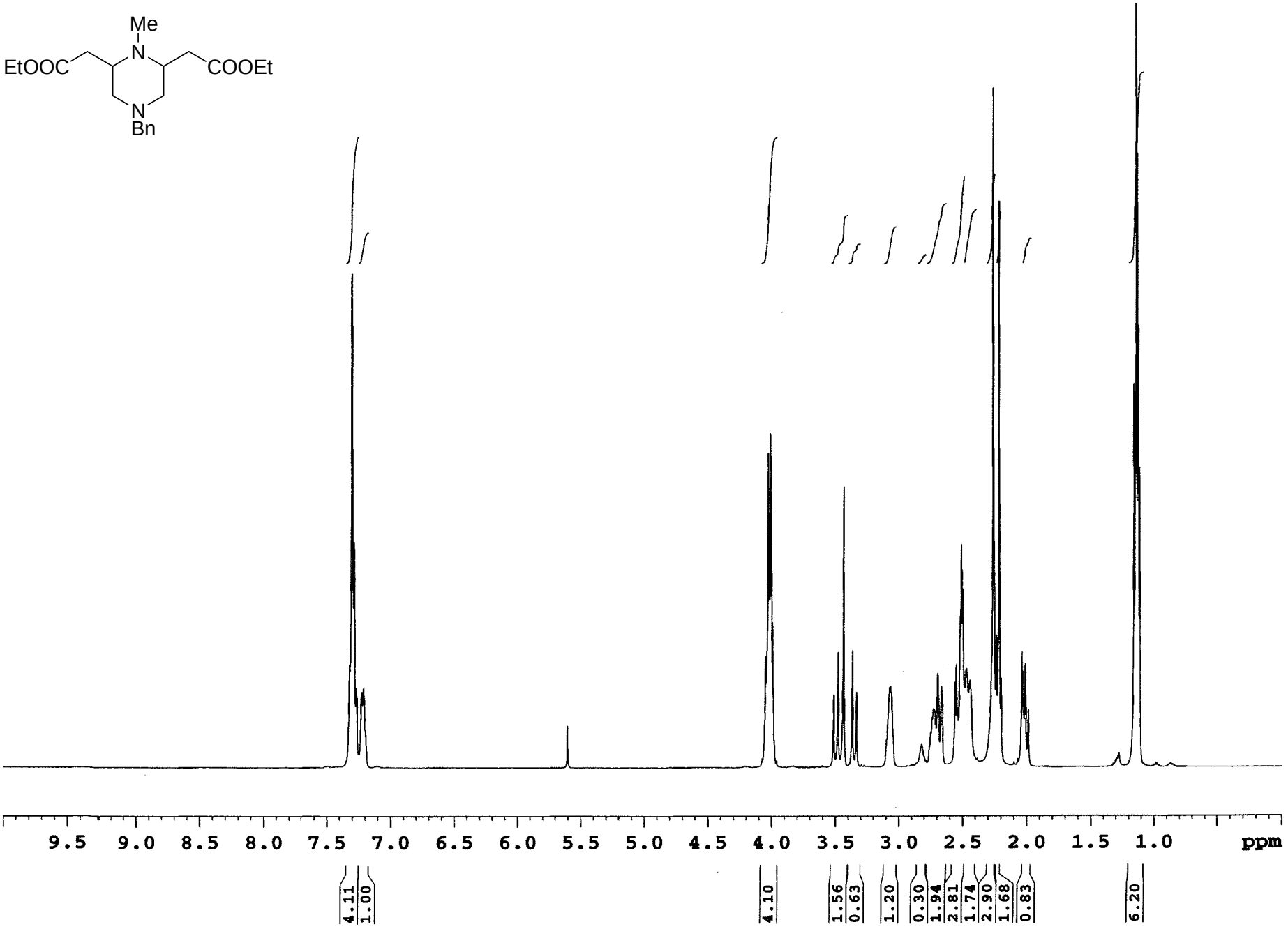
Compound **6c**, $C_{27}H_{36}N_2O_4$, M_r = 452.586, monoclinic, $P2_1$, a = 8.4185(5), b = 12.2201(7), c = 12.7854(7) Å, β=105.671(4)°, V = 1266.41(13) Å^3, Z = 2, D_x = 1.187 gcm^{-3}, monochromatized radiation λ(Cu) = 1.54184 Å, μ = 0.63 mm^{-1}, F(000) = 488, T = 100 K. Data were collected on a Bruker CCD diffractometer to a θ limit of 68.26° which yielded 20009 reflections. There are 4534 unique reflections with 4206 observed at the 2σ level. The structure was solved by direct methods (SHELXS-97, Sheldrick, G.M. *Acta Crystallogr.*, 1990, A46, 467-473) and refined using full-matrix least-squares on F^2 (SHELXL-97, Sheldrick, G.M. *SHELXL-97. Program for the Refinement of Crystal Structures.* Univ. of Göttingen, Germany). The final model was refined using 298 parameters and all 4534 data. In the final model one of the -OEt groups is disordered over two positions. All non-hydrogen atoms, excepting those atoms of the disordered group, were refined with anisotropic thermal displacements. The final agreement statistics are: R = 0.038 (based on 4206 reflections with $I > 2\sigma(I)$), wR = 0.098, S = 1.03 with $(\Delta/\sigma)_{max}$ = 0.01. The maximum peak height in a final difference Fourier map is 0.198 eÅ^{-3} and this peak is without chemical significance. An ORETP-like plot of the molecule, without the disorder model, is included in Figure 2. CCDC contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

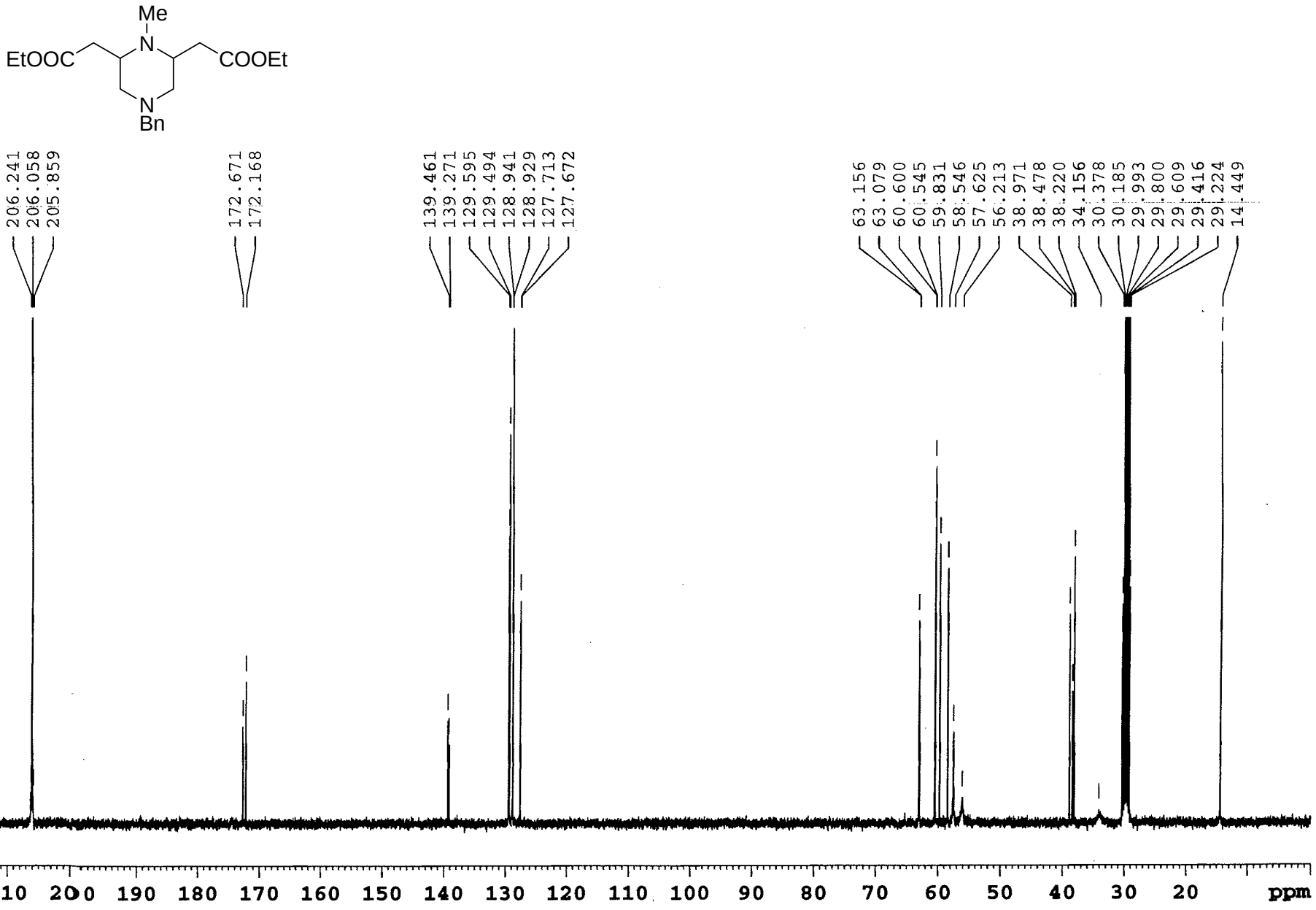

EtOOC
N
Bn
COOEt
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
2.04
1.97
1.00
1.92
1.90
4.06
2.20
4.17
6.22

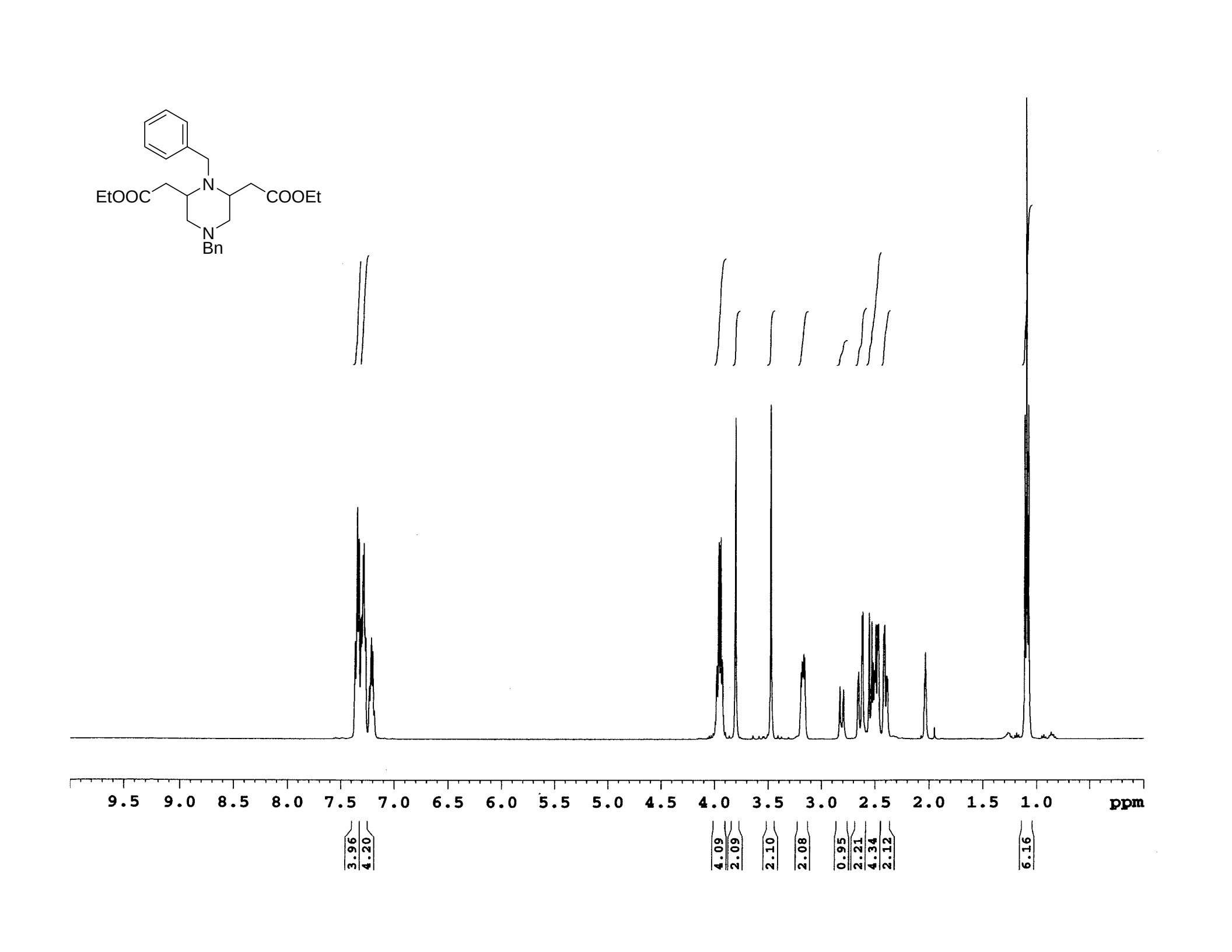

EtOOC
N
Bn
COOEt
206.088
166.231
146.556
139.744
129.361
129.170
127.947
123.558
60.600
59.006
55.132
30.372
30.179
29.987
29.794
29.602
29.409
29.218
14.496
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

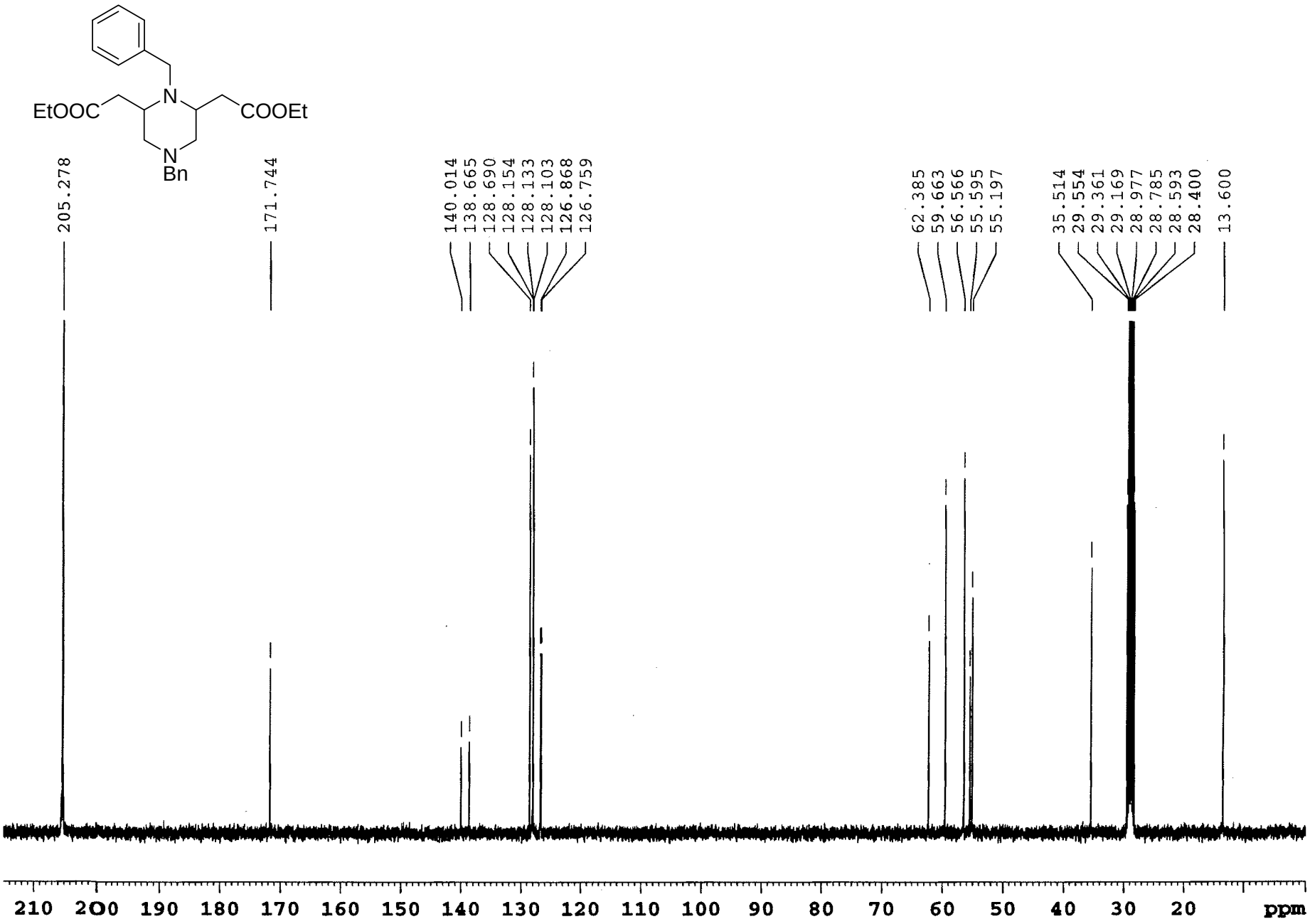

Me
N
EtOOC
COOEt
N
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
4.11
4.00
2.02
2.01
1.07
2.01
1.04
2.07
1.03
2.53
3.84
1.03
1.18
3.13
2.97
3.01

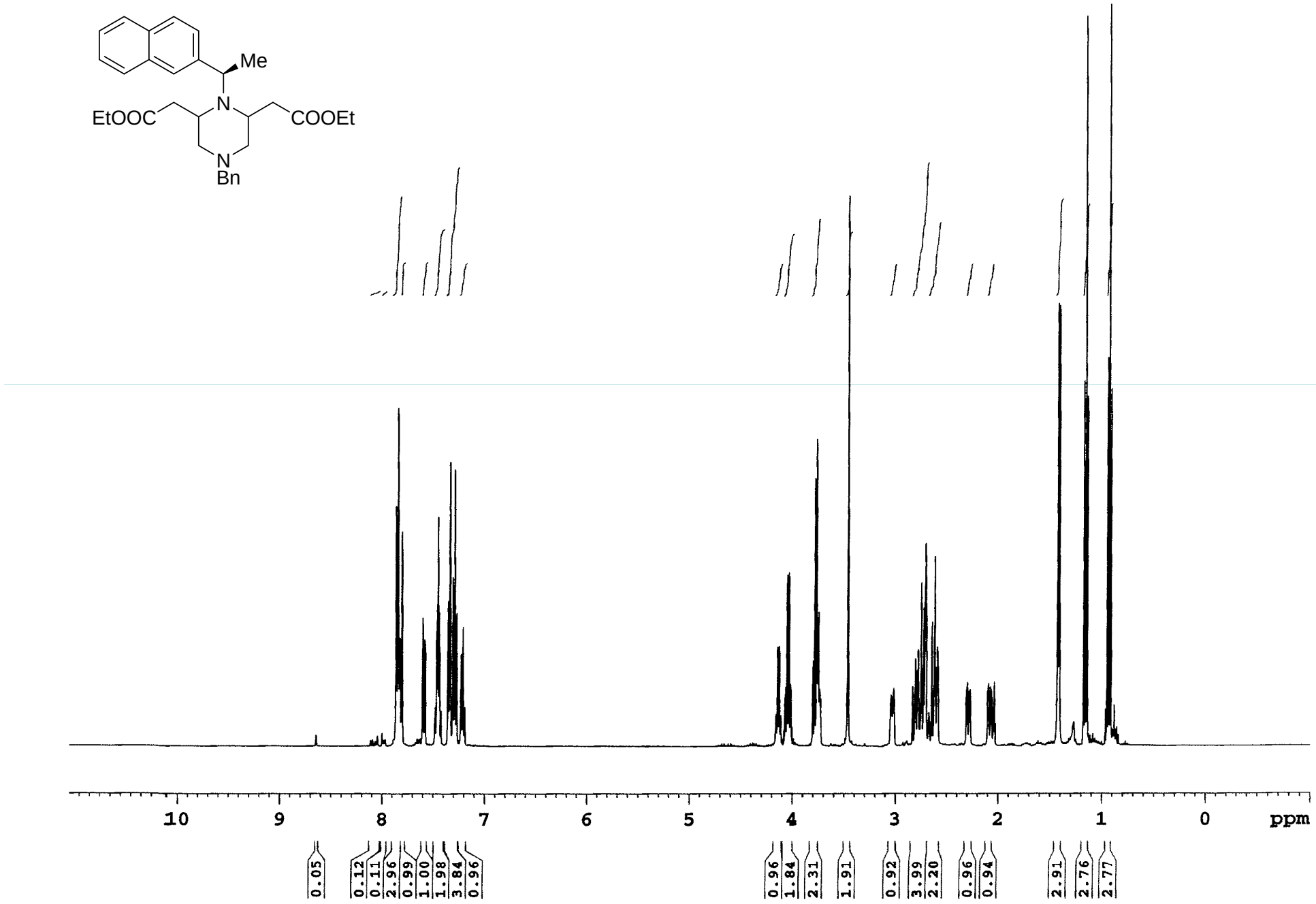

Me
N
EtOOC
COOEt
N
Bn
205.218
172.222
171.857
145.585
138.743
128.657
128.374
128.131
127.184
126.909
126.843
62.422
59.742
59.420
57.822
56.680
56.634
51.164
50.740
34.255
33.480
29.512
29.359
29.205
29.051
28.896
28.742
28.588
21.403
13.753
13.671
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

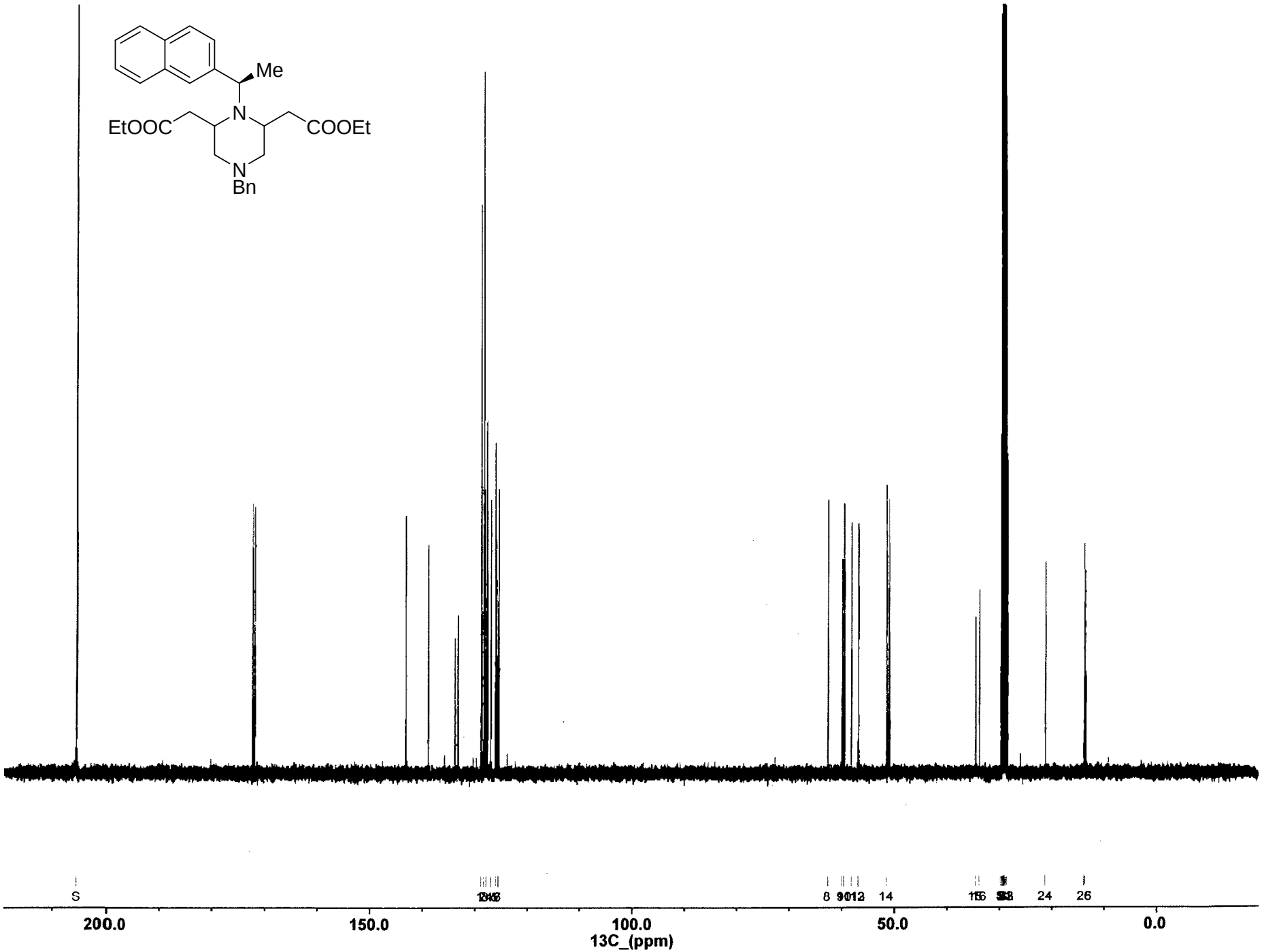

Me
N
EtOOC
COOEt
N
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
4.11
1.00
4.10
1.56
0.63
1.20
0.30
1.94
2.81
1.74
2.90
1.68
0.83
6.20

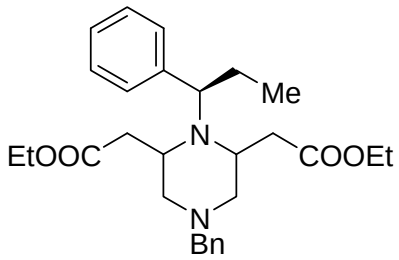

Me
N
EtOOC
COOEt
N
Bn
206.241
206.058
205.859
172.671
172.168
139.461
139.271
129.595
129.494
128.941
128.929
127.713
127.672
63.156
63.079
60.600
60.545
59.831
58.546
57.625
56.213
38.971
38.478
38.220
34.156
30.378
30.185
29.993
29.800
29.609
29.416
29.224
14.449
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


EtOOC
COOEt
N
N
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
3.96
4.20
4.09
2.09
2.10
2.08
0.95
2.21
4.34
2.12
6.16

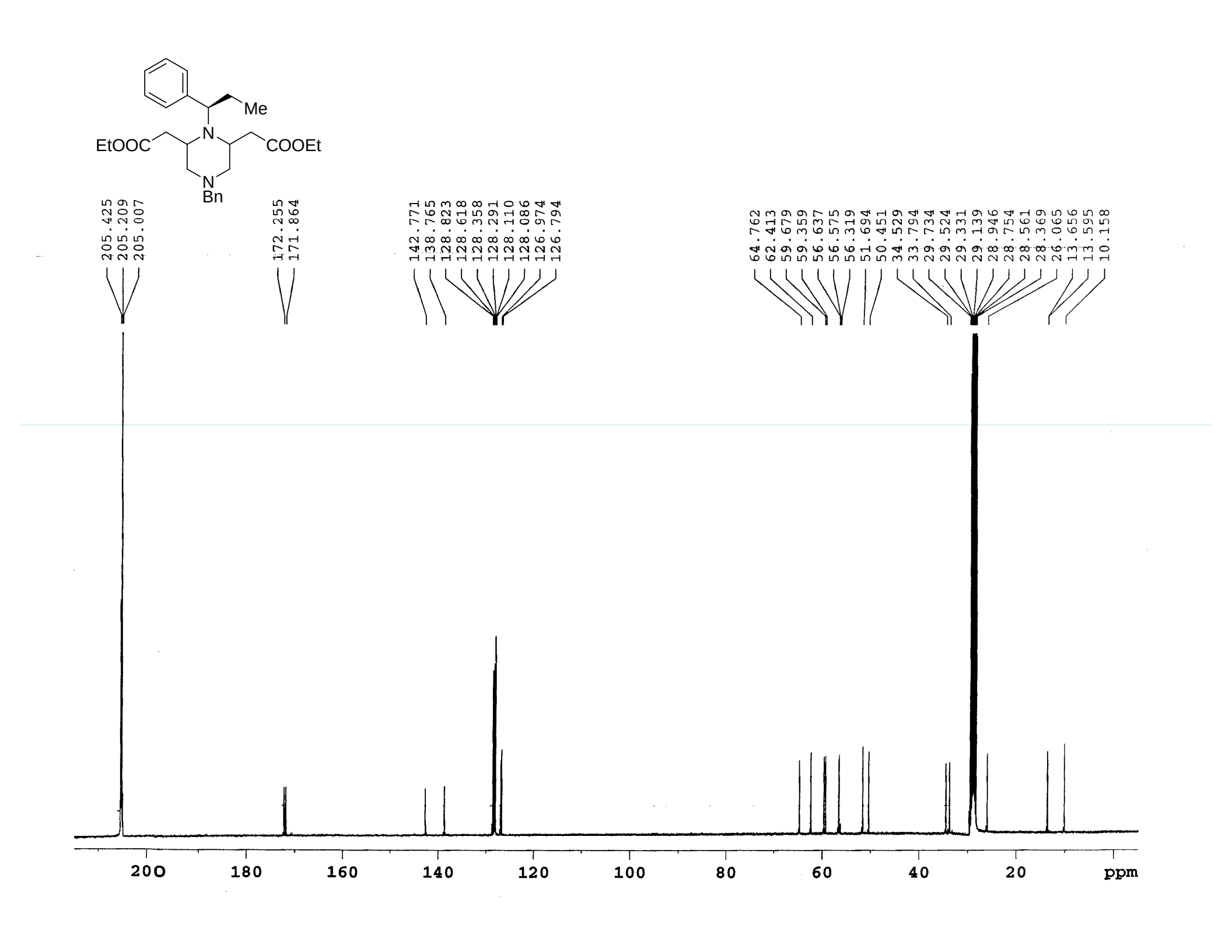

EtOOC
COOEt
N
N
Bn
205.278
171.744
140.014
138.665
128.690
128.154
128.133
128.103
126.868
126.759
62.385
59.663
56.566
55.595
55.197
35.514
29.554
29.361
29.169
28.977
28.785
28.593
28.400
13.600
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

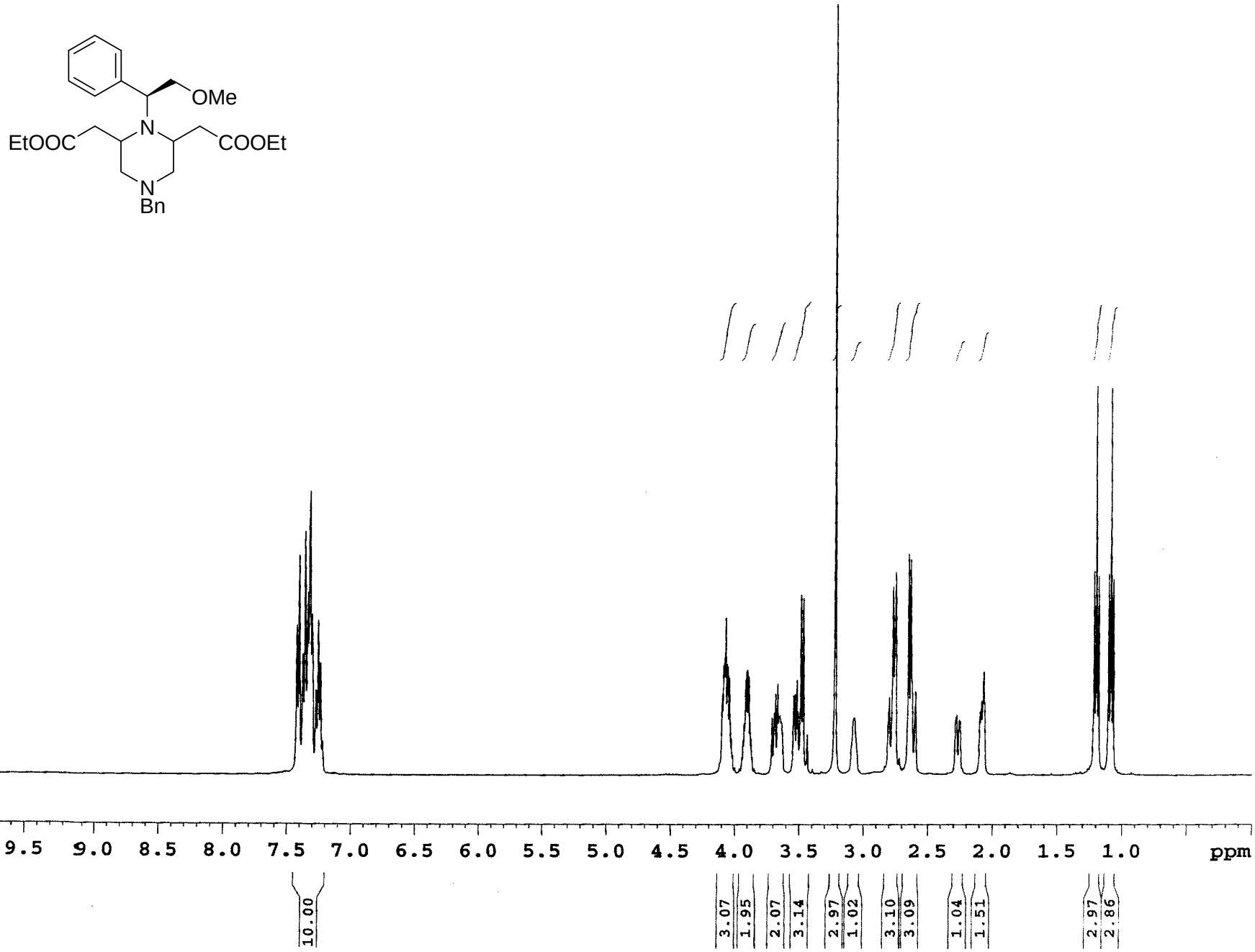

Me
N
EtOOC
COOEt
N
Bn
10
9
8
7
6
5
4
3
2
1
0
ppm
0.05
0.12
0.11
2.96
0.99
1.00
1.98
3.84
0.96
0.96
1.84
2.31
1.91
0.92
3.99
2.20
0.96
0.94
2.91
2.76
2.77

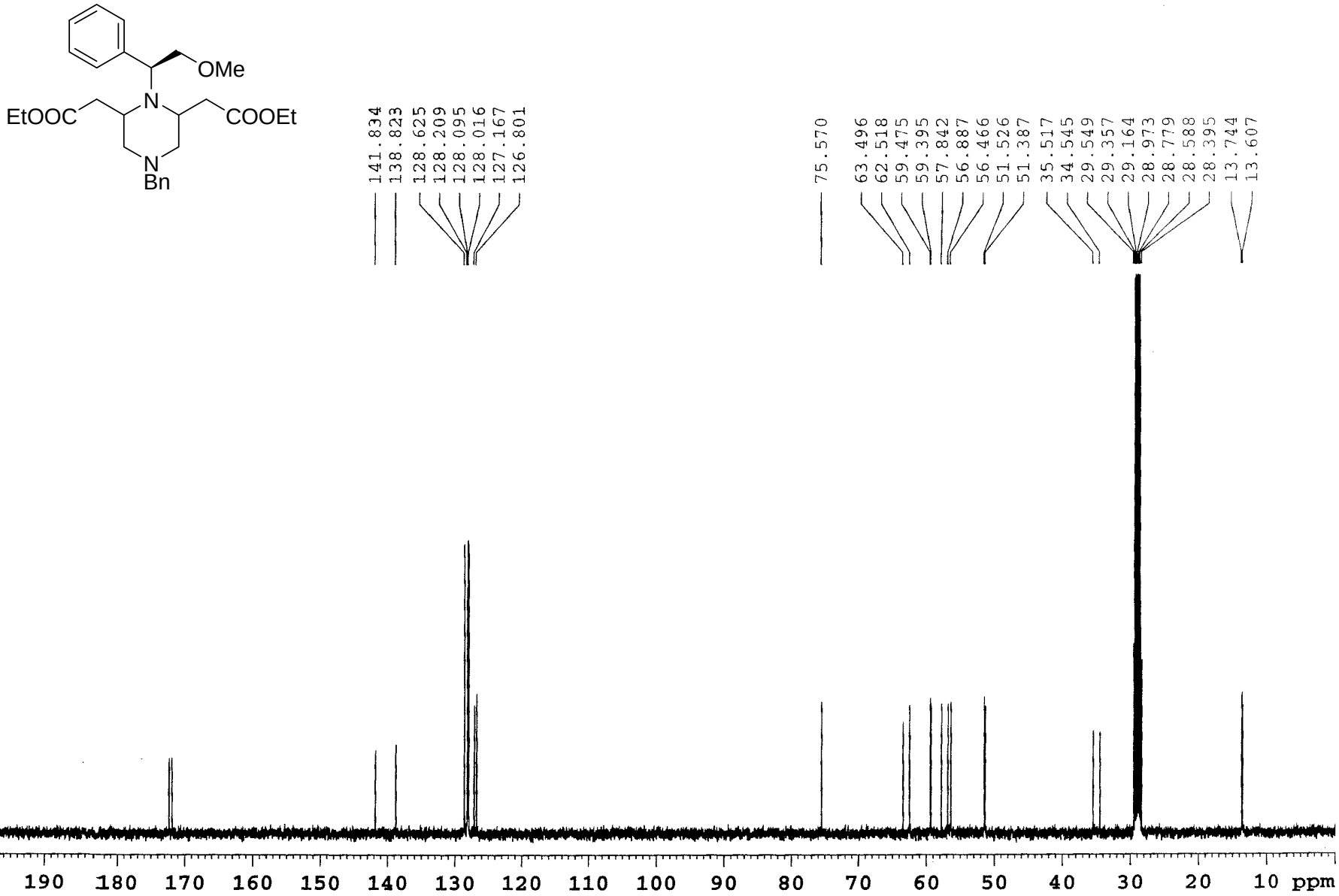

Me
N
EtOOC
COOEt
N
Bn
S
8
14
24
26
200.0
150.0
100.0
50.0
0.0
13C_(ppm)

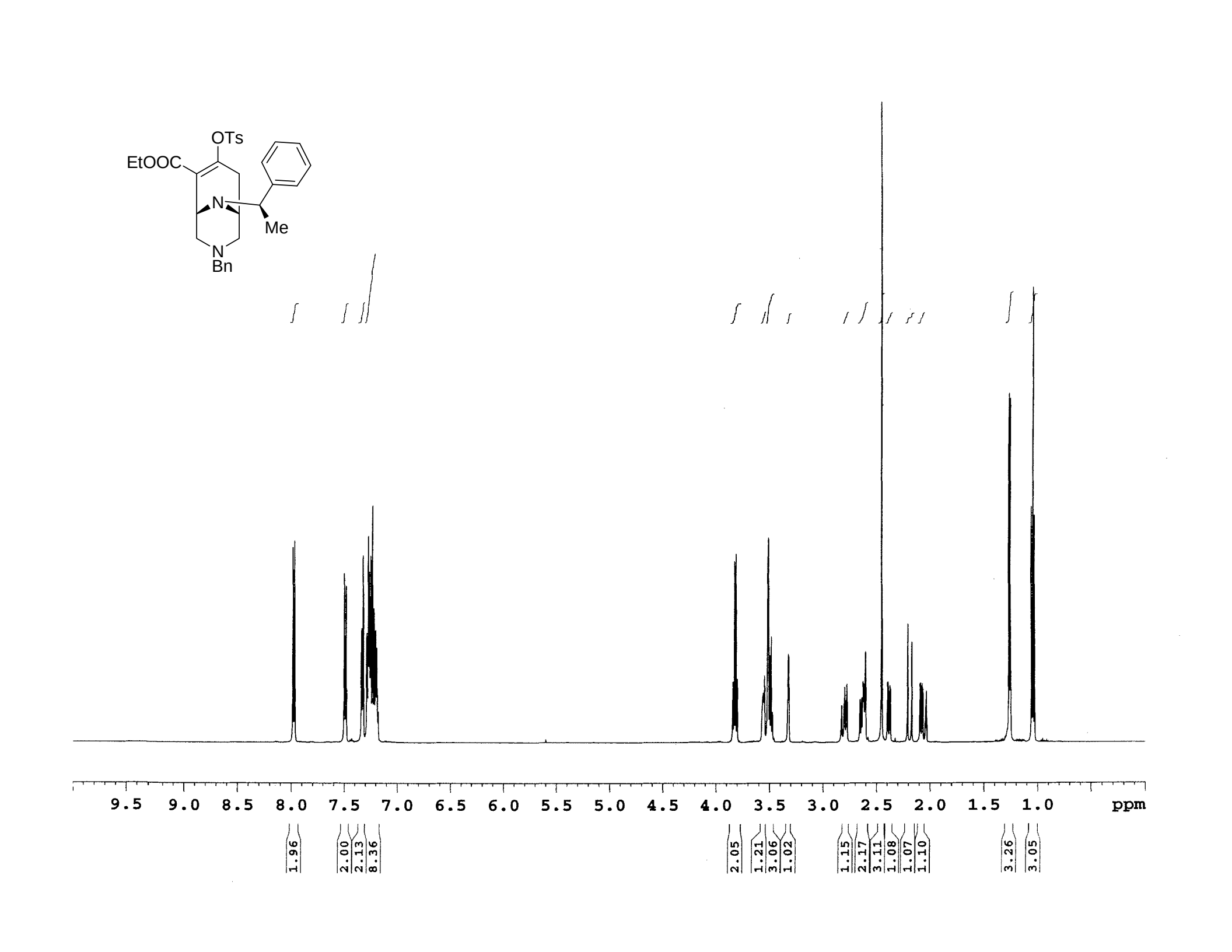

Me
N
EtOOC
COOEt
N
Bn

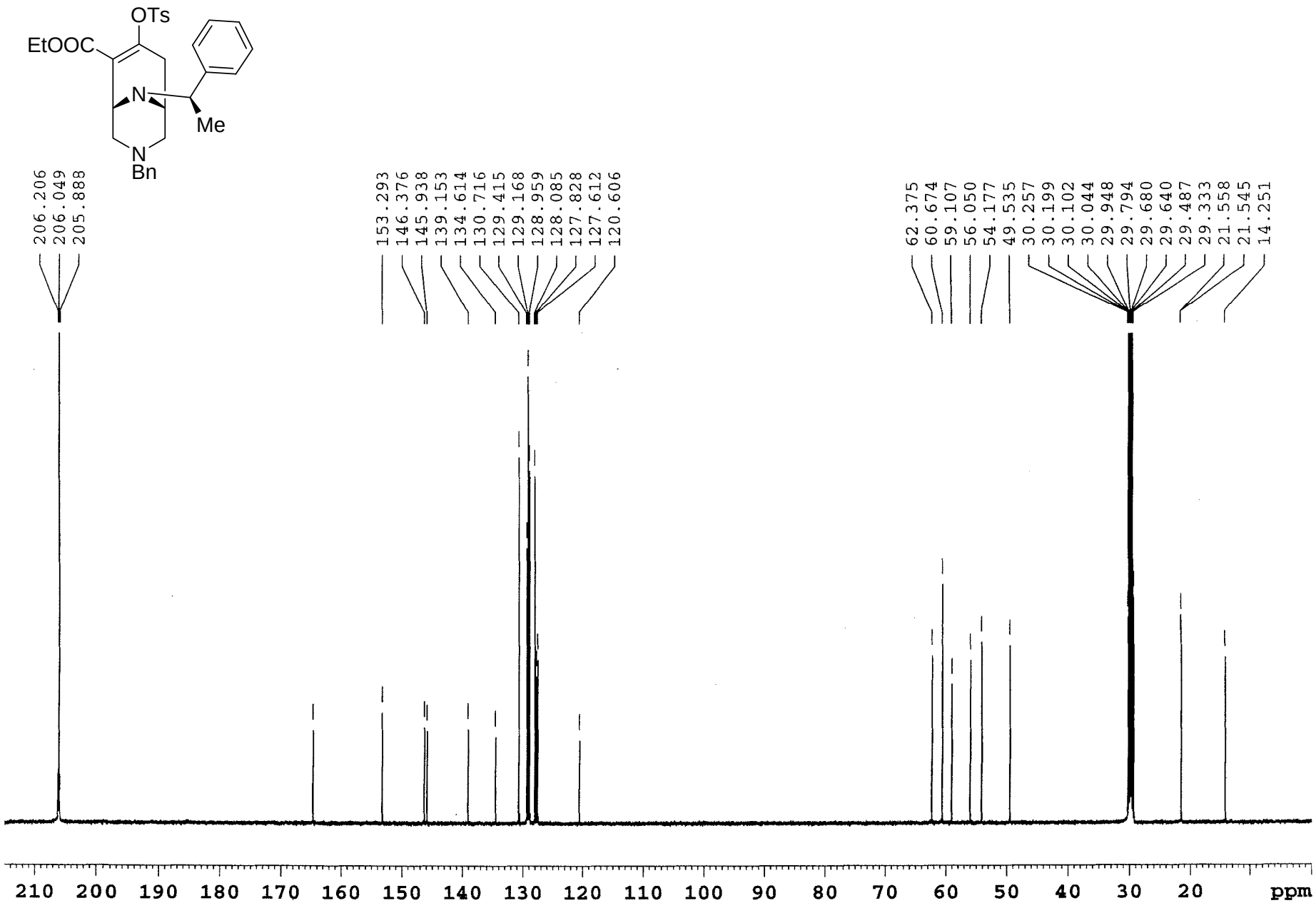
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
10.00
1.96
1.89
2.00
1.80
0.97
2.28
1.23
1.86
4.15
0.99
2.29
1.02
2.85
2.85
3.10

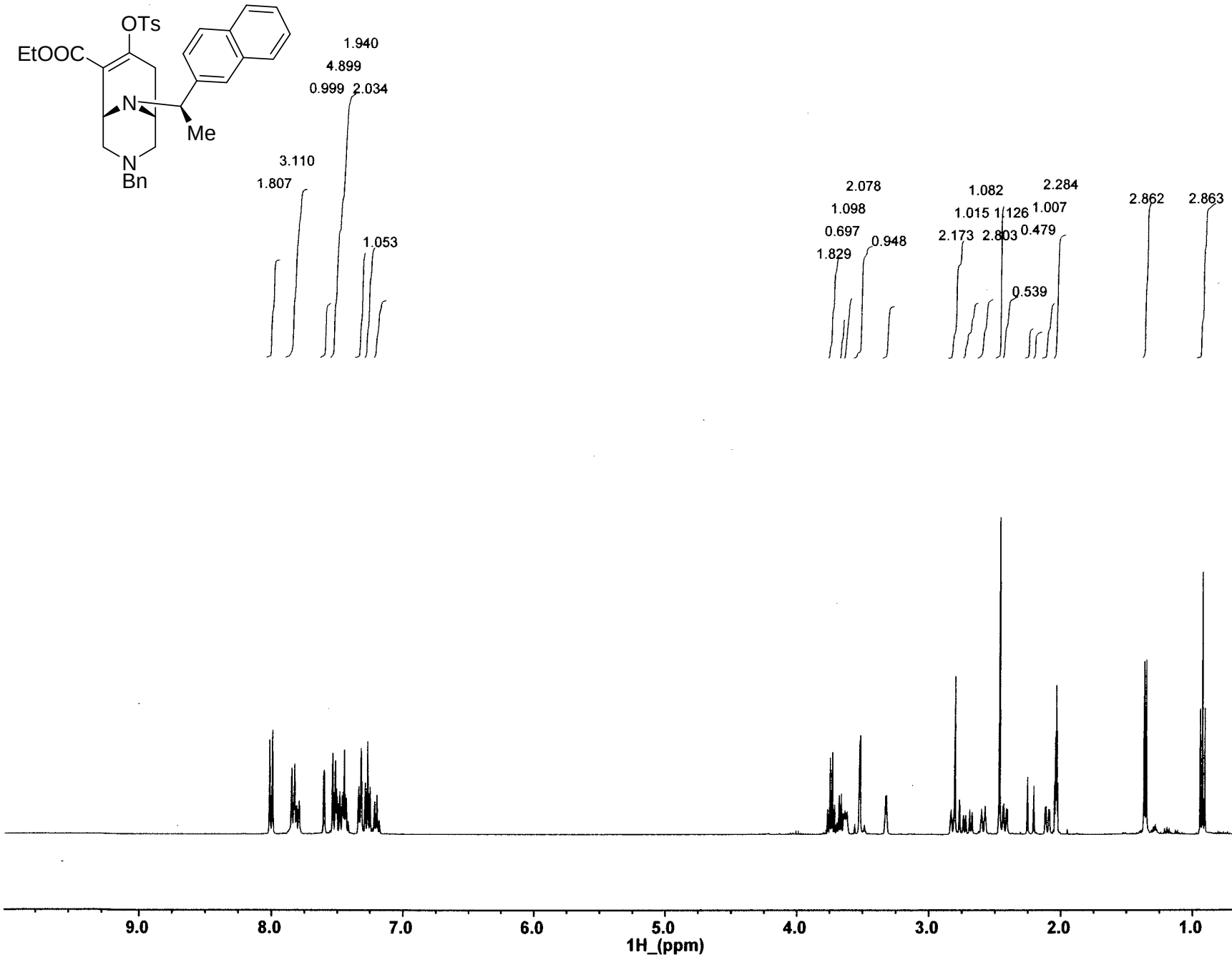

Me
N
EtOOC
COOEt
N
Bn
205.425
205.209
205.007
172.255
171.864
142.771
138.765
128.823
128.618
128.358
128.291
128.110
128.086
126.974
126.794
64.762
62.413
59.679
59.359
56.637
56.575
56.319
51.694
50.451
34.529
33.794
29.734
29.524
29.331
29.139
28.946
28.754
28.561
28.369
26.065
13.656
13.595
10.158
200
180
160
140
120
100
80
60
40
20
ppm

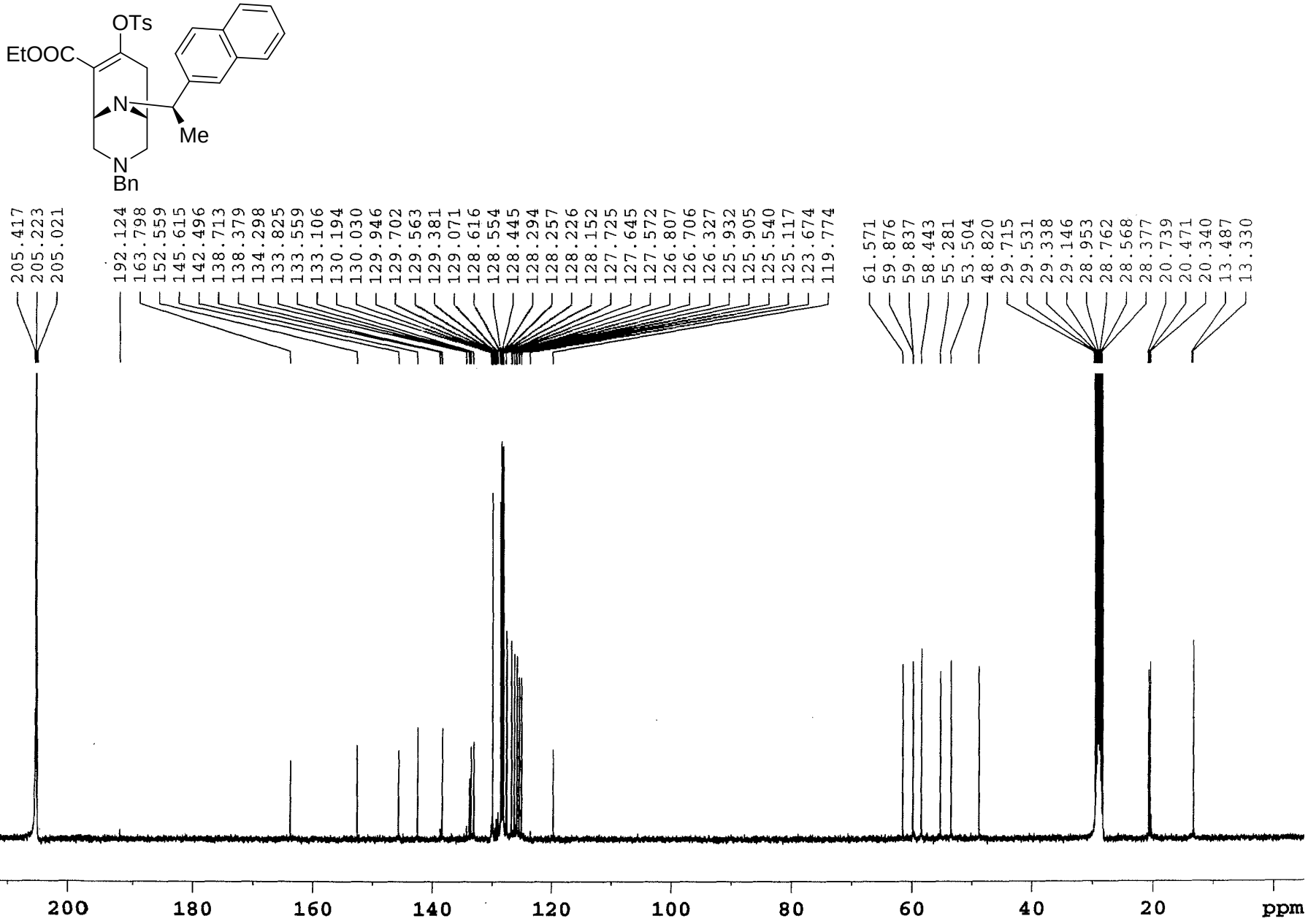

OMe
EtOOC
COOEt
N
N
Bn
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
10.00
3.07
1.95
2.07
3.14
2.97
1.02
3.10
3.09
1.04
1.51
2.97
2.86

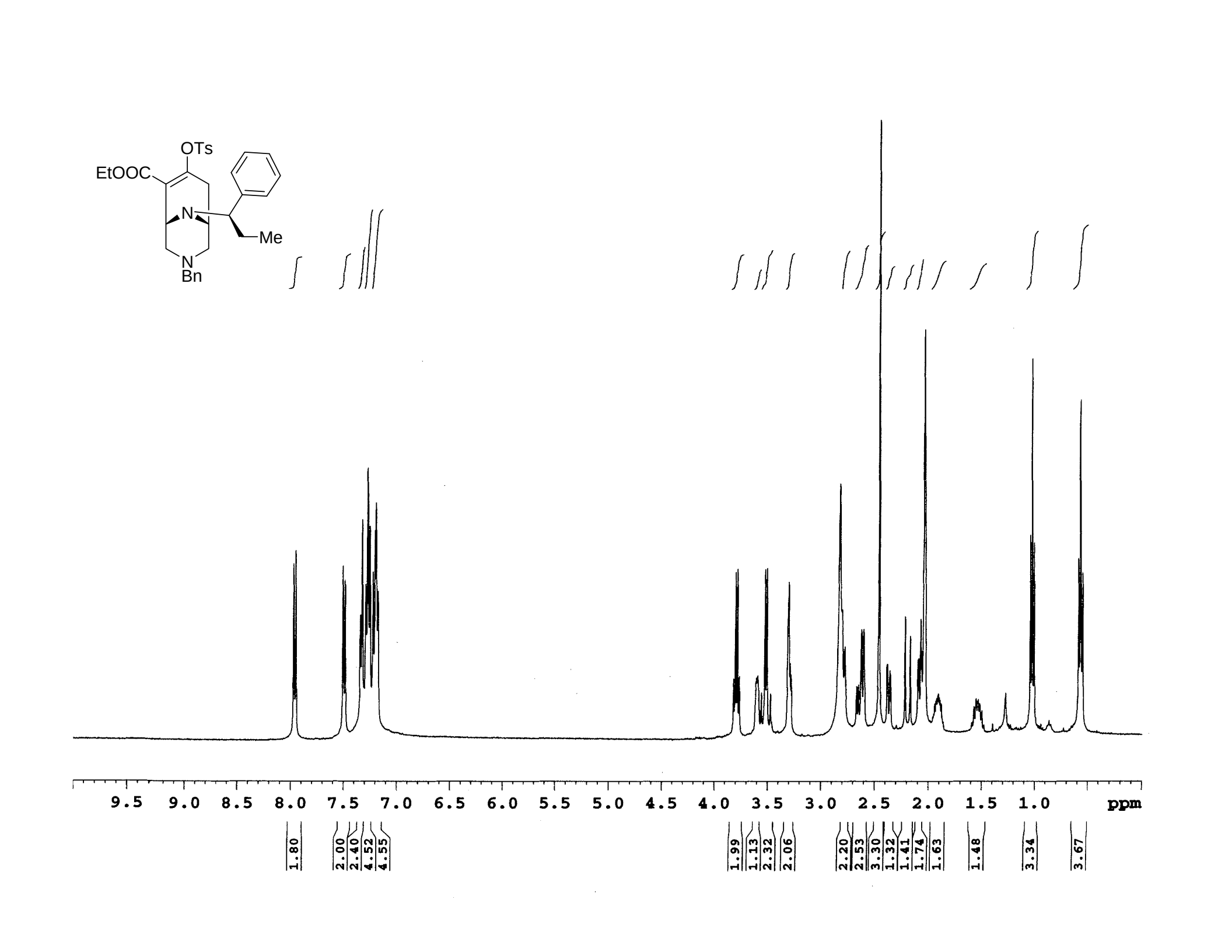

OMe
N
EtOOC
COOEt
N
Bn
141.834
138.823
128.625
128.209
128.095
128.016
127.167
126.801
75.570
63.496
62.518
59.475
59.395
57.842
56.887
56.466
51.526
51.387
35.517
34.545
29.549
29.357
29.164
28.973
28.779
28.588
28.395
13.744
13.607
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

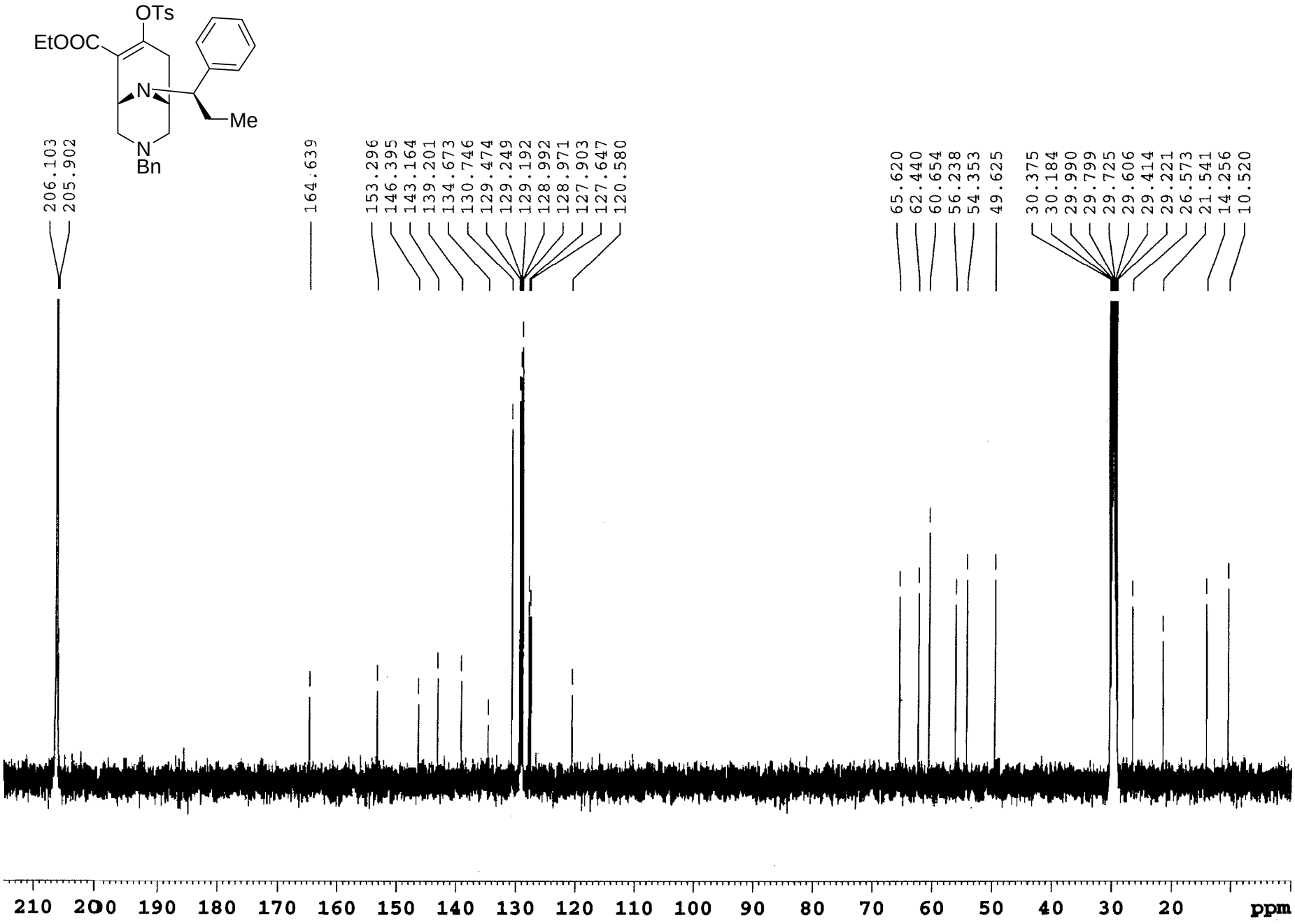

OTs
EtOOC
N
Me
N
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.96
2.00
2.13
8.36
2.05
1.21
3.06
1.02
1.15
2.17
3.11
1.08
1.07
1.10
3.26
3.05

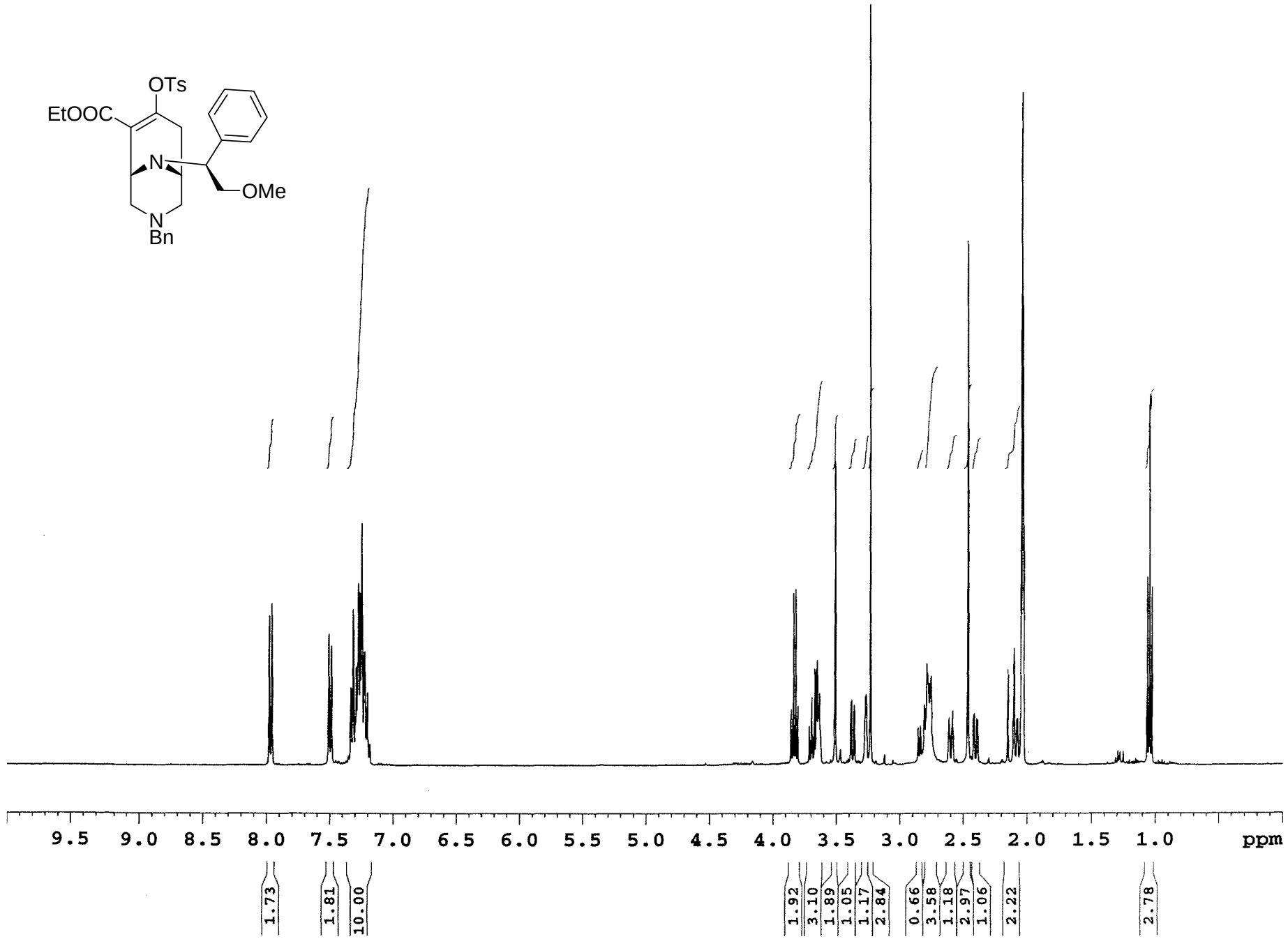

OTs
EtOOC
N
Me
N
Bn
206.206
206.049
205.888
153.293
146.376
145.938
139.153
134.614
130.716
129.415
129.168
128.959
128.085
127.828
127.612
120.606
62.375
60.674
59.107
56.050
54.177
49.535
30.257
30.199
30.102
30.044
29.948
29.794
29.680
29.640
29.487
29.333
21.558
21.545
14.251
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

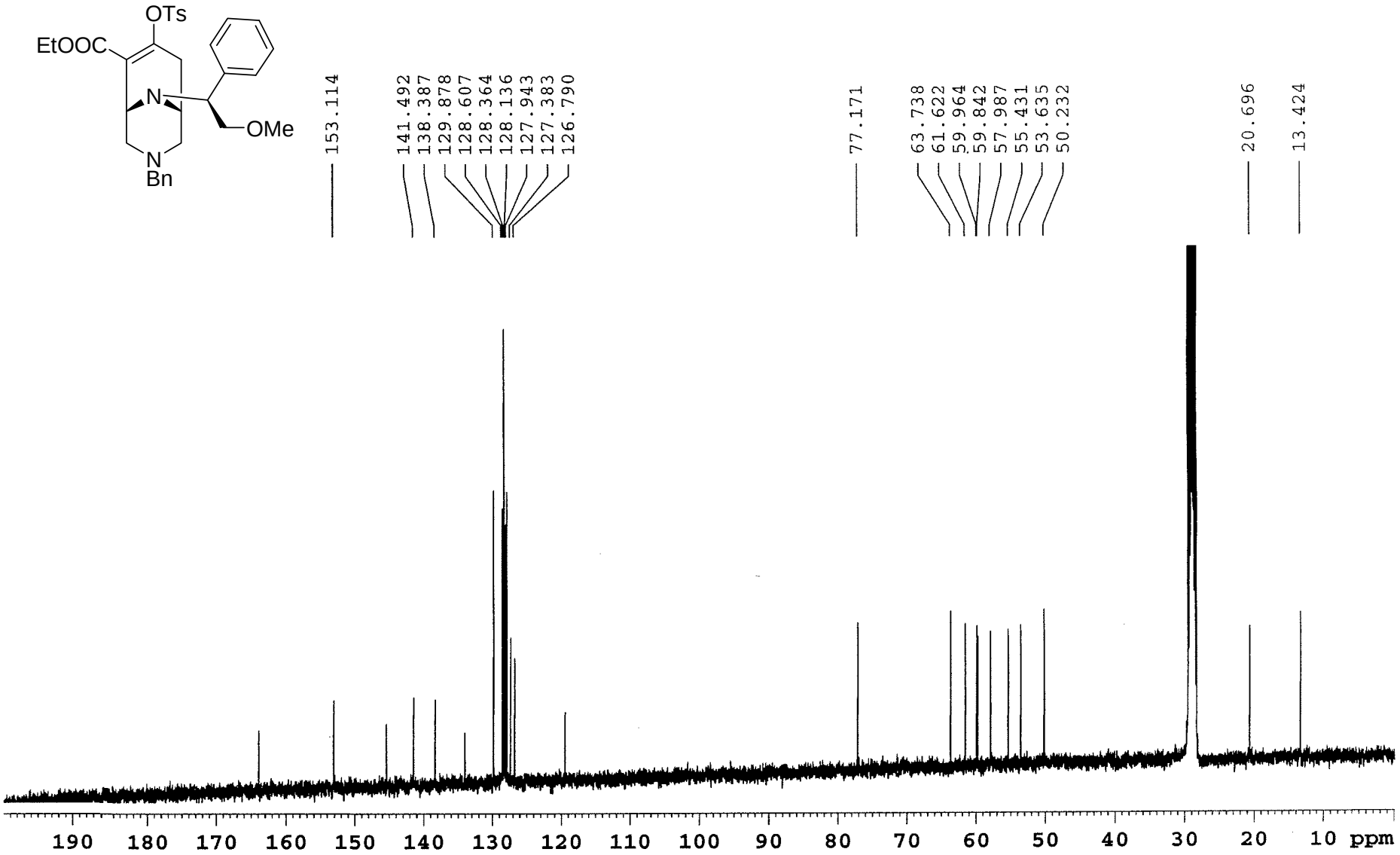

OTs
EtOOC
N
Me
N
Bn
1.940
4.899
0.999
2.034
3.110
1.807
1.053
2.078
1.098
0.697
1.829
0.948
1.082
1.015
1.126
2.173
2.803
0.479
2.284
1.007
0.539
2.862
2.863
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
1H_(ppm)

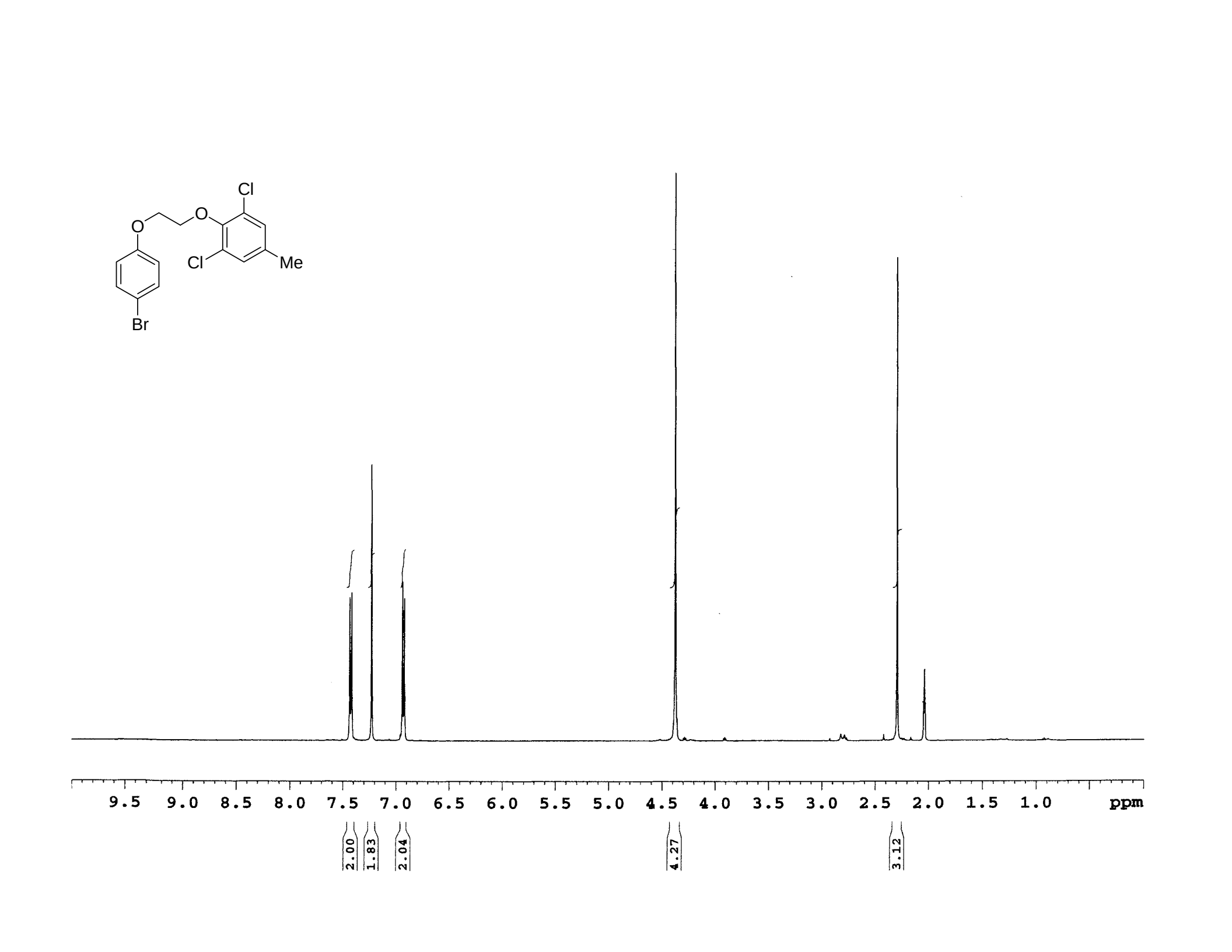

OTs
EtOOC
N
Me
N
Bn
205.417
205.223
205.021
192.124
163.798
152.559
145.615
142.496
138.713
138.379
134.298
133.825
133.559
133.106
130.194
130.030
129.946
129.702
129.563
129.381
129.071
128.616
128.554
128.445
128.294
128.257
128.226
128.152
127.725
127.645
127.572
126.807
126.706
126.327
125.932
125.905
125.540
125.117
123.674
119.774
61.571
59.876
59.837
58.443
55.281
53.504
48.820
29.715
29.531
29.338
29.146
28.953
28.762
28.568
28.377
20.739
20.471
20.340
13.487
13.330
200
180
160
140
120
100
80
60
40
20
ppm

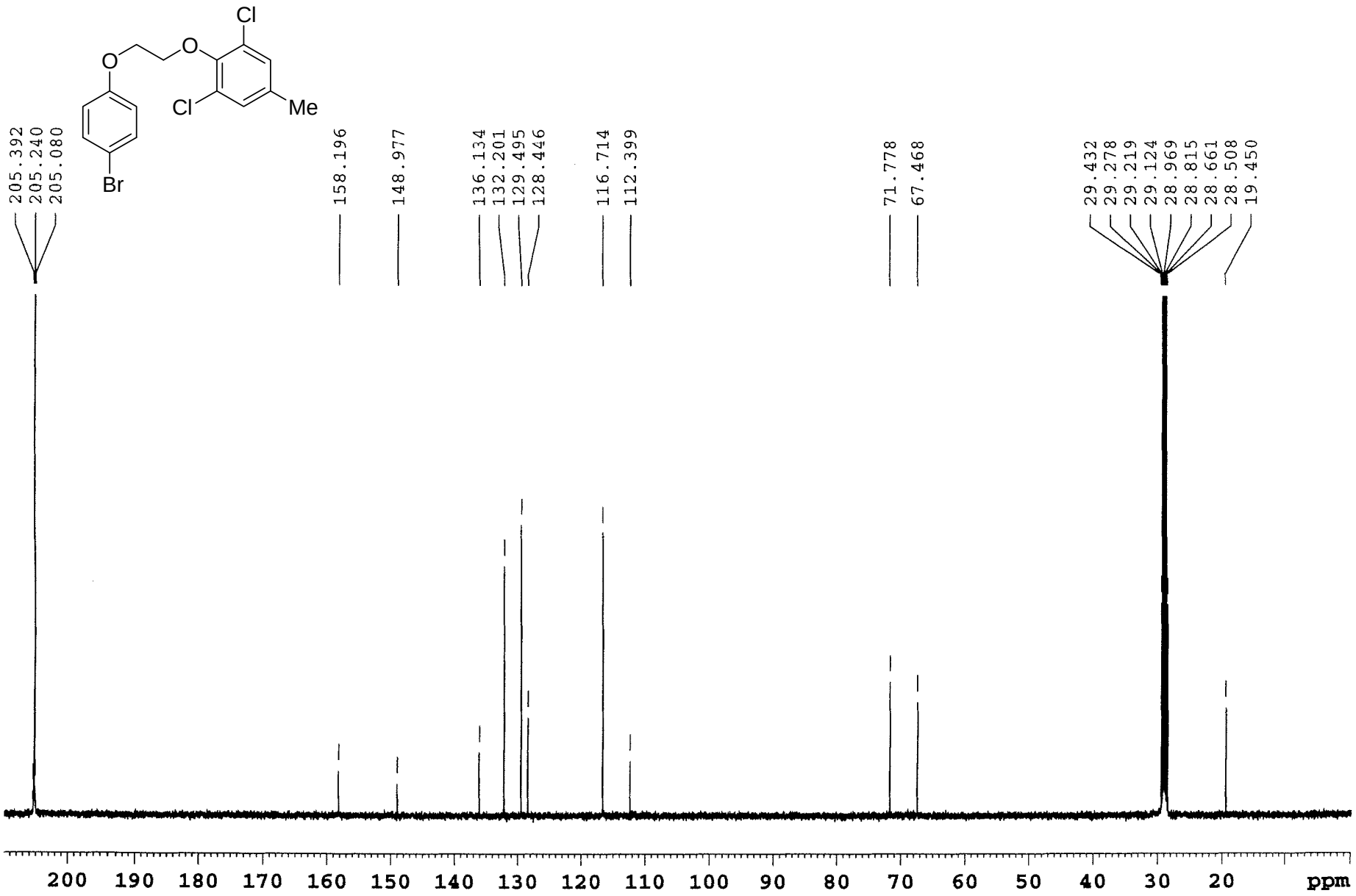

OTs
EtOOC
N
Me
N
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
1.80
2.00
2.40
4.52
4.55
1.99
1.13
2.32
2.06
2.20
2.53
3.30
1.32
1.41
1.74
1.63
1.48
3.34
3.67

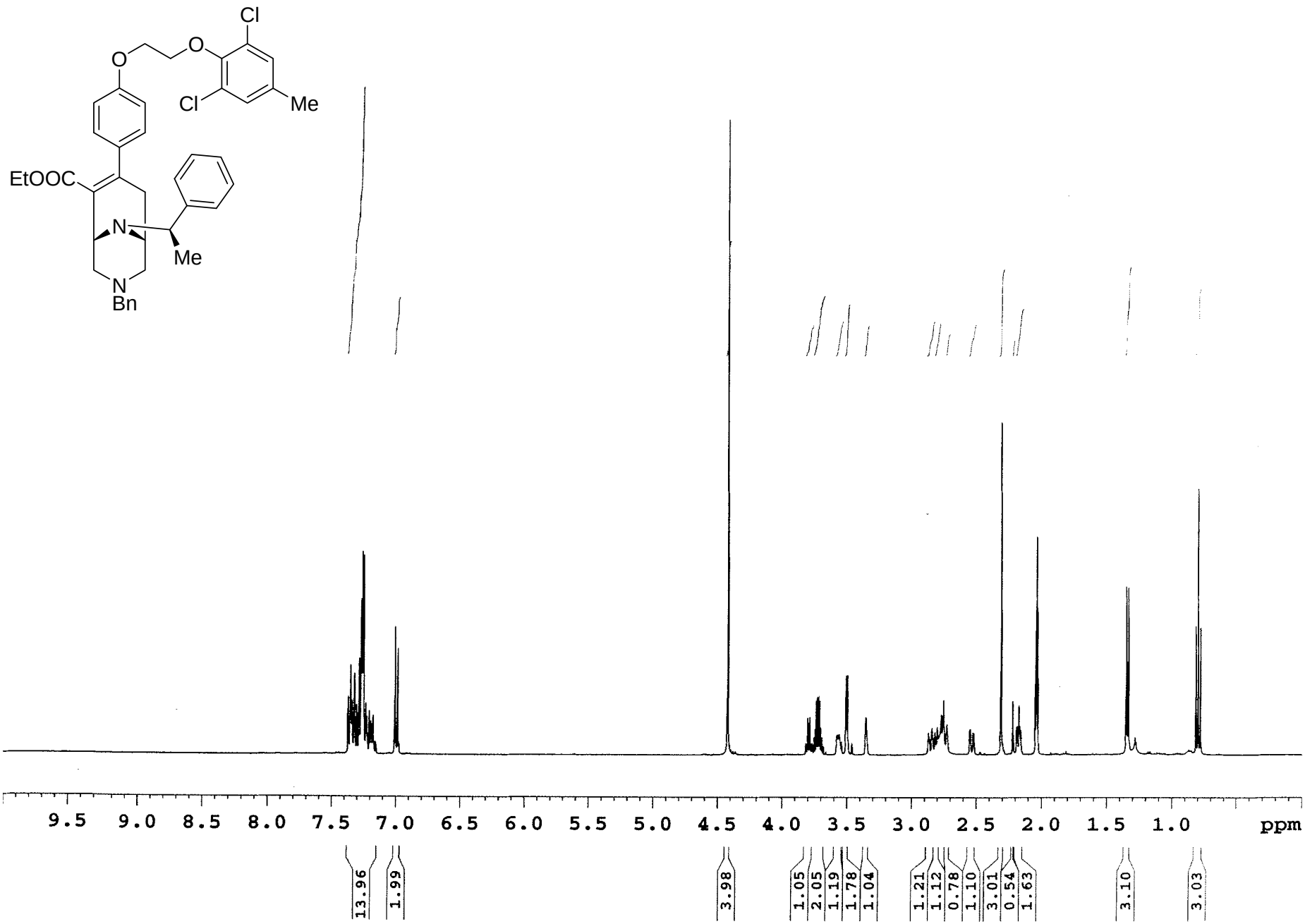

OTs
EtOOC
N
Me
N
Bn
206.103
205.902
164.639
153.296
146.395
143.164
139.201
134.673
130.746
129.474
129.249
129.192
128.992
128.971
127.903
127.647
120.580
65.620
62.440
60.654
56.238
54.353
49.625
30.375
30.184
29.990
29.799
29.725
29.606
29.414
29.221
26.573
21.541
14.256
10.520
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

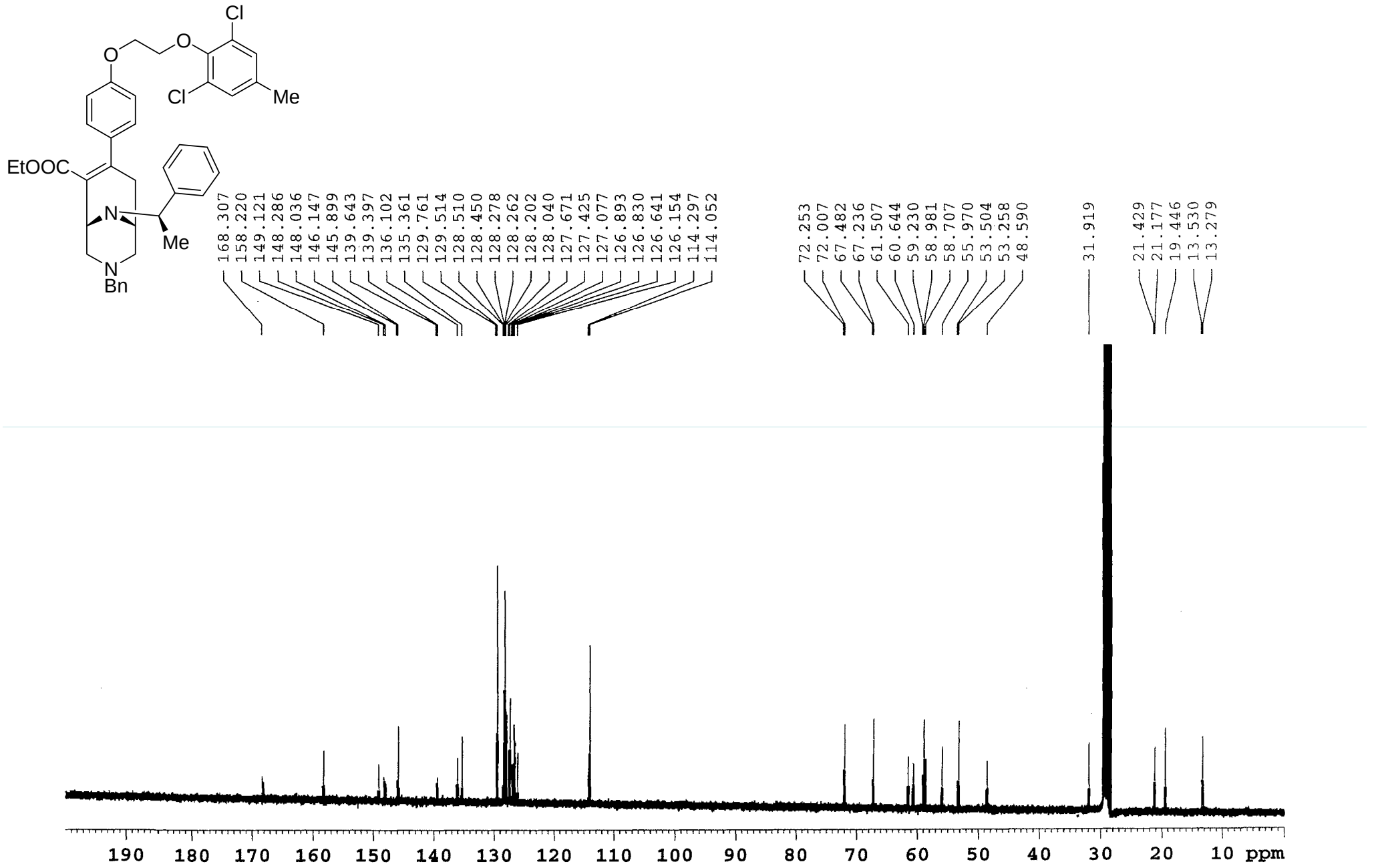

OTs
EtOOC
N
OMe
N
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
1.73
1.81
10.00
1.92
3.10
1.89
1.05
1.17
2.84
0.66
3.58
1.18
2.97
1.06
2.22
2.78

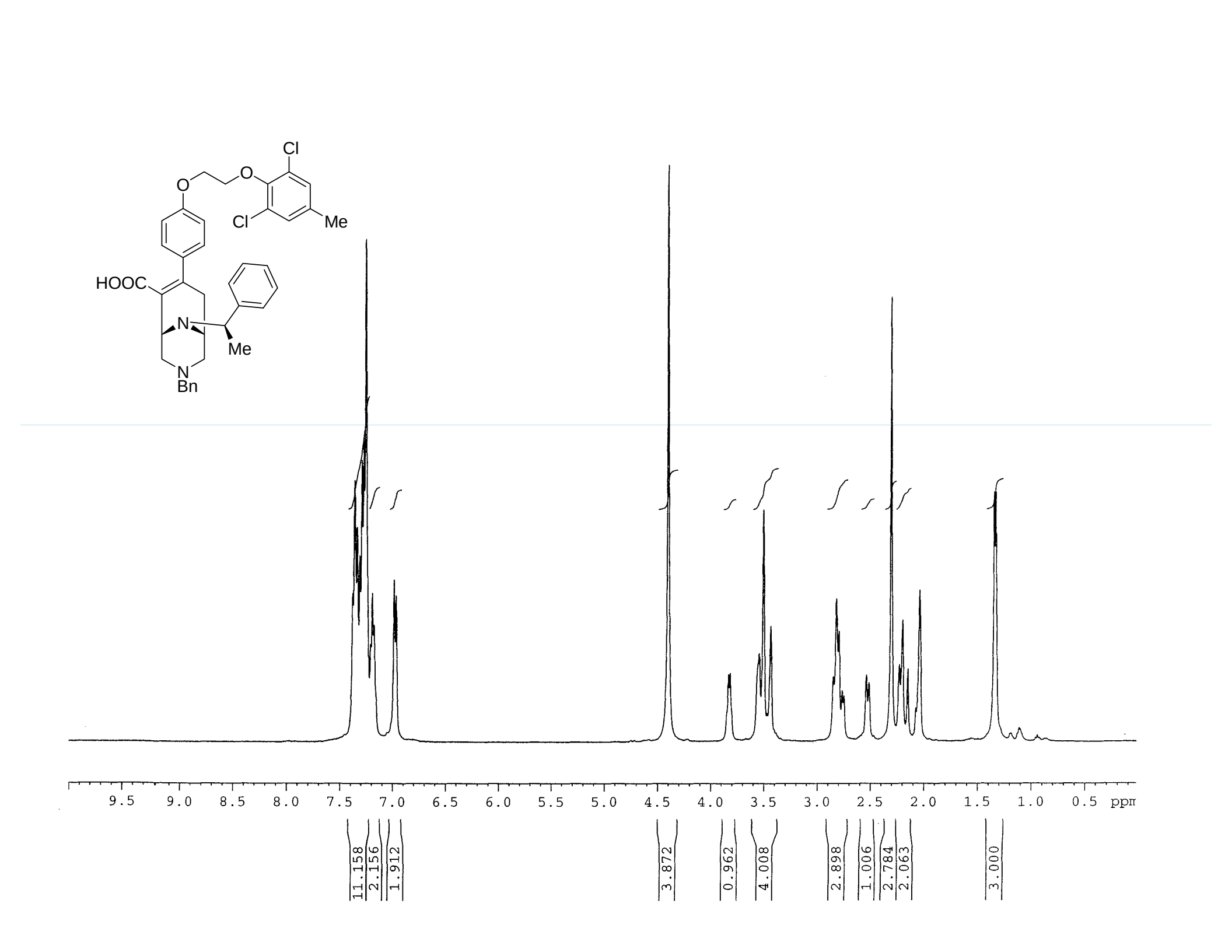

OTs
EtOOC
N
OMe
N
Bn
153.114
141.492
138.387
129.878
128.607
128.364
128.136
127.943
127.383
126.790
77.171
63.738
61.622
59.964
59.842
57.987
55.431
53.635
50.232
20.696
13.424
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

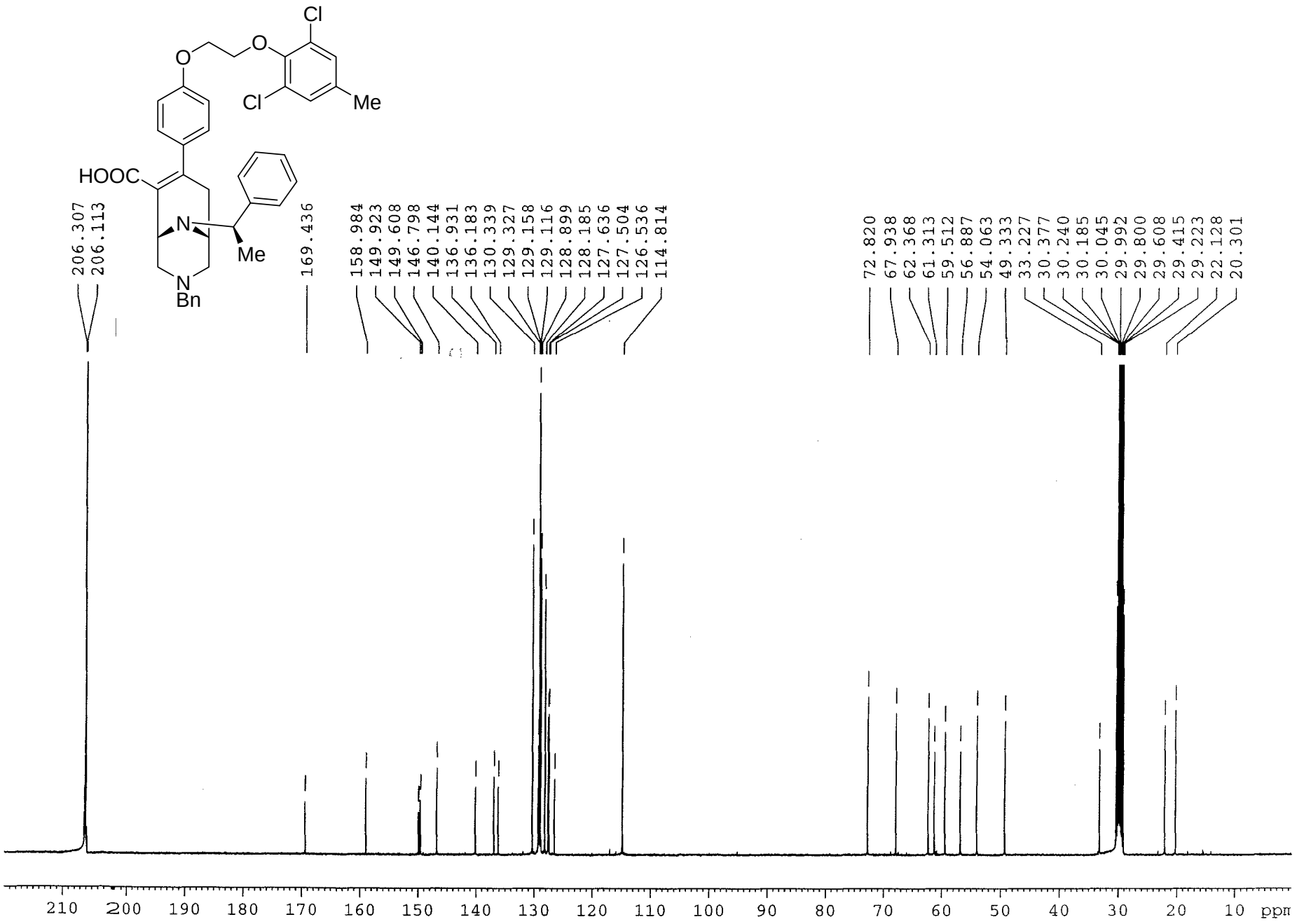

Cl
O
O
Cl
Me
Br
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
1.83
2.04
4.27
3.12

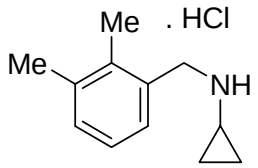

Cl
O
O
Cl
Me
Br
205.392
205.240
205.080
158.196
148.977
136.134
132.201
129.495
128.446
116.714
112.399
71.778
67.468
29.432
29.278
29.219
29.124
28.969
28.815
28.661
28.508
19.450
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Cl
O
O
Cl
Me
EtOOC
N
Me
N
Bn
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
13.96
1.99
3.98
1.05
2.05
1.19
1.78
1.04
1.21
1.12
0.78
1.10
3.01
0.54
1.63
3.10
3.03

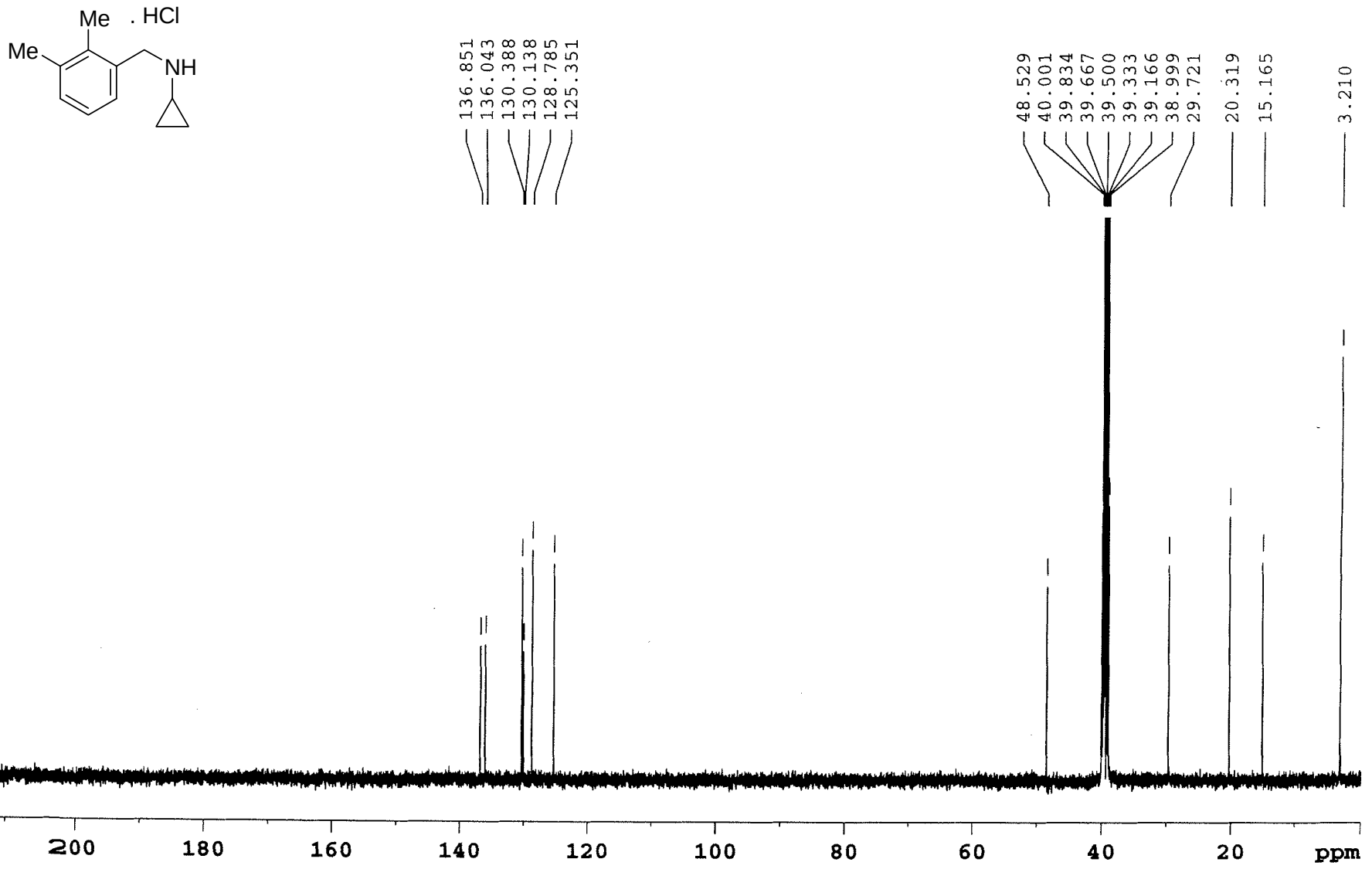

Cl
O
O
Cl
Me
EtOOC
N
Me
N
Bn
168.307
158.220
149.121
148.286
148.036
146.147
145.899
139.643
139.397
136.102
135.361
129.761
129.514
128.510
128.450
128.278
128.262
128.202
128.040
127.671
127.425
127.077
126.893
126.830
126.641
126.154
114.297
114.052
72.253
72.007
67.482
67.236
61.507
60.644
59.230
58.981
58.707
55.970
53.504
53.258
48.590
31.919
21.429
21.177
19.446
13.530
13.279
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

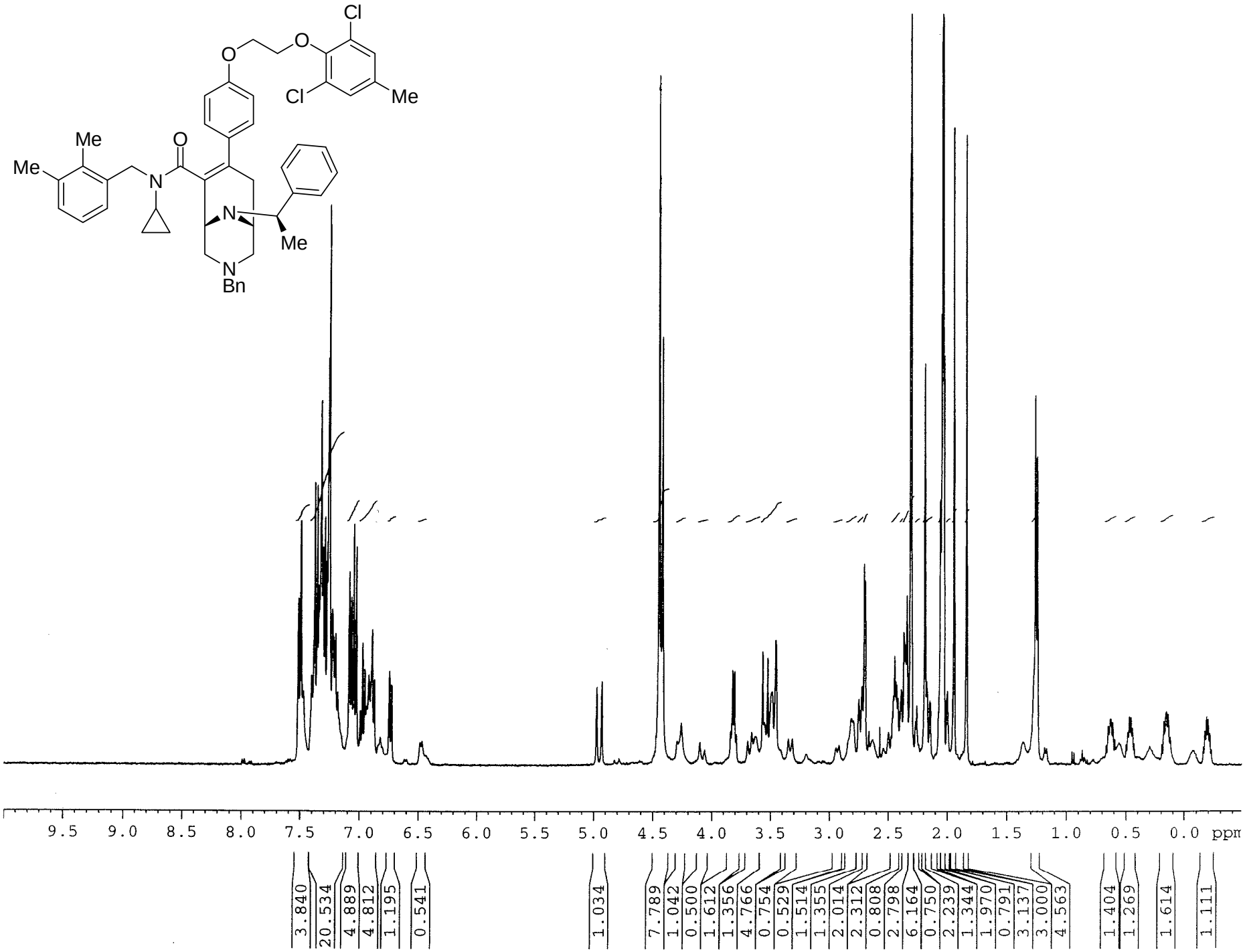

Cl
O
O
Cl
Me
HOOC
N
Me
N
Bn
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
11.158
2.156
1.912
3.872
0.962
4.008
2.898
1.006
2.784
2.063
3.000

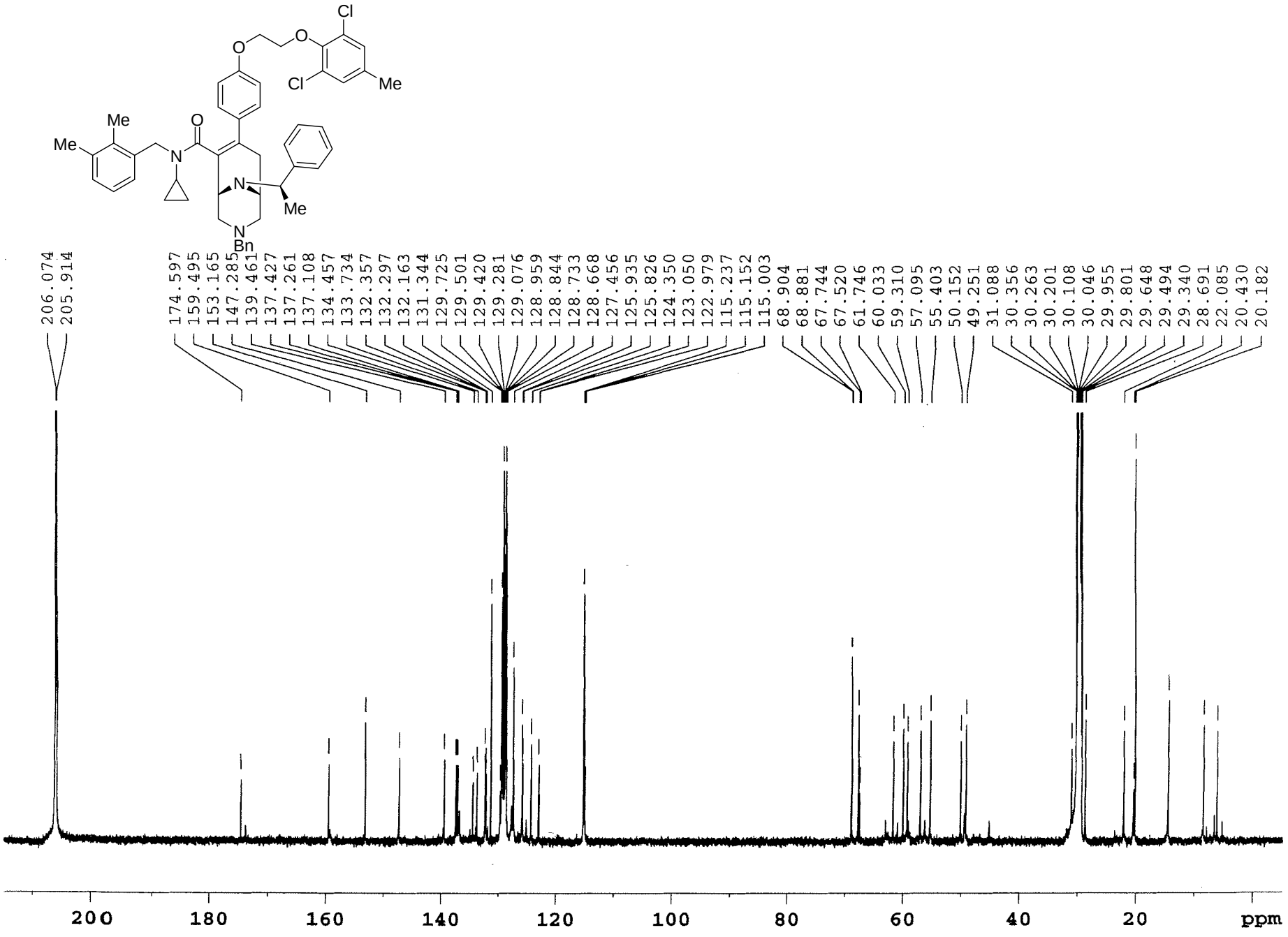

Cl
O
O
Cl
Me
HOOC
N
Me
N
Bn
206.307
206.113
169.436
158.984
149.923
149.608
146.798
140.144
136.931
136.183
130.339
129.327
129.158
129.116
128.899
128.185
127.636
127.504
126.536
114.814
72.820
67.938
62.368
61.313
59.512
56.887
54.063
49.333
33.227
30.377
30.240
30.185
30.045
29.992
29.800
29.608
29.415
29.223
22.128
20.301
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Me
. HCl
Me
NH

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.99
1.00
0.98
1.00
2.05
0.35
1.02
6.15
2.00
2.01


Me
. HCl
Me
NH
136.851
136.043
130.388
130.138
128.785
125.351
48.529
40.001
39.834
39.667
39.500
39.333
39.166
38.999
29.721
20.319
15.165
3.210
200
180
160
140
120
100
80
60
40
20
ppm


Cl
O
O
Cl
Me
Me
Me
O
N
N
Me
N
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
3.840 20.534 4.889 4.812 1.195 0.541 1.034 7.789 1.042 0.500 1.612 1.356 4.766 0.754 0.529 1.514 1.355 2.014 2.312 0.808 2.798 6.164 0.750 2.239 1.344 1.970 0.791 3.137 3.000 4.563 1.404 1.269 1.614 1.111


Cl
O
O
Cl
Me
Me
Me
O
N
N
Me
N
Bn
206.074
205.914
174.597
159.495
153.165
147.285
139.461
137.427
137.261
137.108
134.457
133.734
132.357
132.297
132.163
131.344
129.725
129.501
129.420
129.281
129.076
128.959
128.844
128.733
128.668
127.456
125.935
125.826
124.350
123.050
122.979
115.237
115.152
115.003
68.904
68.881
67.744
67.520
61.746
60.033
59.310
57.095
55.403
50.152
49.251
31.088
30.356
30.263
30.201
30.108
30.046
29.955
29.801
29.648
29.494
29.340
28.691
22.085
20.430
20.182
200
180
160
140
120
100
80
60
40
20
ppm