Supporting Information

Oxazaborolidine-catalyzed reductive parallel kinetic resolution of ketones from β-nitro-azabicycles for the synthesis of chiral hypoestestatins 1, 2

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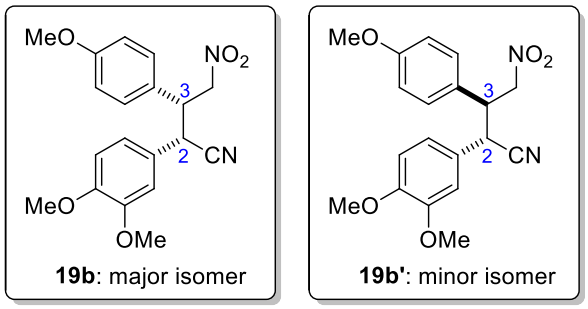
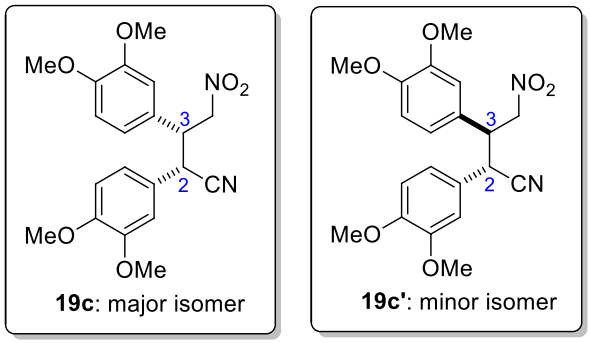
1. Experimental procedures

1.1. Synthesis of compounds 19b and 19c

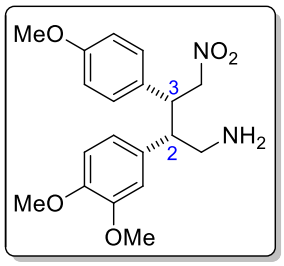


(2*S,3*R**)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-4-nitrobutanenitrile (19b) and (2*S**,3*S**)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-4-nitrobutanenitrile (19b').** Following the general procedure for the synthesis of **19** and purification of the crude products (*dr* = 97:3) by recrystallization with EtOAc, the product **19b** (3.01 g, 89%) was obtained as a white solid, M. p. 132.3–133.6 °C (from EtOAc). *Rf* = 0.40 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 2939, 2839, 2245, 1611, 1555, 1516, 1465, 1422, 1380, 1345, 1255, 1182, 1145, 1026, 835, 813, 765; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.3 Hz, 1H), 6.70 (dd, J = 8.3, 2.1 Hz, 1H), 6.50 (d, J = 2.1 Hz, 1H), 4.79 (dd, J = 13.4, 7.3 Hz, 1H), 4.71 (dd, J = 13.4, 7.6 Hz, 1H), 4.19 (d, J = 6.8 Hz, 1H), 3.86 (s, 3H), 3.86–3.78 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.82, 149.29, 149.19, 129.31, 125.91, 124.57, 120.47, 118.45, 114.26, 111.24, 110.81, 77.03, 55.84, 55.81, 55.17, 47.53, 41.01; HRMS (ESI$^+$) calcd for $C_{19}H_{20}N_2Na_1O_5$ $(M+Na)^+$ 379.1264, found 379.1259. The remaining oil was further purified by column chromatography on silica gel (hexane/EtOAc = 3:1 to 2:1) to afford **19b'** (93.1 mg, 3%) as a yellow oil. *Rf* = 0.33 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 2938, 2839, 2241, 1611, 1553, 1515, 1464, 1423, 1370, 1301, 1252, 1182, 1145, 1024, 833, 812, 765, 734, 702, 663; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.3 Hz, 1H), 6.74 (dd, J = 8.3, 2.0 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 4.84 (dd, J = 13.2, 9.0 Hz, 1H), 4.78 (dd, J = 13.2, 6.3 Hz, 1H), 4.09 (d, J = 6.5 Hz, 1H), 4.02–3.89 (m, 1H), 3.86 (s, 3H), 3.77 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.74, 149.32, 149.11, 129.15, 126.32, 123.81, 120.61, 118.63, 114.29, 111.22, 111.10, 76.17, 55.84, 55.18, 47.27, 41.18; HRMS (ESI$^+$) calcd for $C_{19}H_{20}N_2Na_1O_5$ $(M+Na)^+$ 379.1264, found 379.1259.

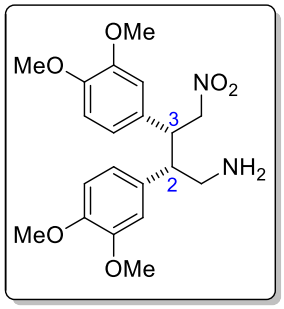


(2*S,3*R**)-2,3-Bis(3,4-dimethoxyphenyl)-4-nitrobutanenitrile (19c) and (2*S**,3*S**)-2,3-Bis(3,4-dimethoxyphenyl)-4-nitrobutanenitrile (19c').** Following the general procedure for the synthesis of **19** and purification of the crude products (*dr* = 95:5) by recrystallization with EtOAc, the product **19c** (3.34 g, 91%) was obtained as a white solid, M.p. 158.7–159.9 °C (from EtOAc). *Rf* = 0.28 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 2939, 2839, 2243, 1594, 1555, 1518, 1465, 1422, 1380, 1263, 1243, 1145, 1024, 861, 815, 767, 734, 664; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, J = 8.2, 0.8 Hz, 2H), 6.70 (dd, J = 8.2, 2.1 Hz, 1H), 6.66 (dd, J = 8.2, 2.1 Hz, 1H), 6.55 (d, J = 2.1 Hz, 1H), 6.53 (d, J = 2.1 Hz, 1H), 4.83 (dd, J = 13.4, 7.5 Hz, 1H), 4.74 (dd, J = 13.4, 7.3 Hz, 1H), 4.21 (d, J = 6.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.86–3.77 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.41, 149.31, 149.04, 126.25, 124.62, 120.57, 120.50, 118.46, 111.49, 111.30, 110.86, 77.01, 55.94, 55.91, 55.85, 47.95, 41.09; HRMS (ESI$^+$) calcd for $C_{20}H_{22}N_2Na_1O_6$ $(M+Na)^+$ 409.1370, found 409.1371. The remaining solid was further purified by column chromatography on silica gel (hexane/EtOAc = 3:1 to 1:1) to afford **19c'** (175.8 mg, 5%) as a white solid, M.p. 102.5–104.1 °C. *Rf* = 0.20 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 2938, 2839, 2241, 1594, 1554, 1516, 1464, 1422, 1379, 1261, 1240, 1187, 1143, 1023, 903, 859, 812, 766, 734, 701, 663; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.74 (dd, J = 8.3, 2.0 Hz, 1H), 6.67 (dd, J = 8.2, 2.1 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.57 (d, J = 2.1 Hz, 1H), 4.85 (dd, J = 13.2, 9.0 Hz, 1H), 4.76 (dd, J = 13.2, 6.4 Hz, 1H), 4.12 (d, J = 6.1 Hz, 1H), 4.00–3.85 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.46, 149.35, 149.23, 149.12, 126.79, 123.76, 120.74, 120.30, 118.67, 111.32, 111.29, 111.26, 111.12, 76.06, 55.94, 55.86, 47.59, 41.26; HRMS (ESI$^+$) calcd for $C_{20}H_{22}N_2Na_1O_6$ $(M+Na)^+$ 409.1370, found 409.1367.

1.2 Preparation of 2,3-diaryl 4-nitrobutan-1-amines from 19b and 19c

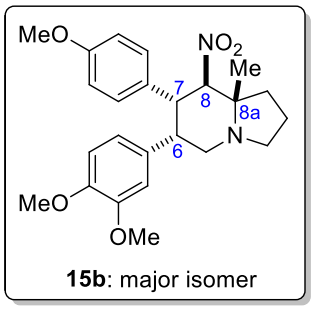


(2*S,3*R**)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-4-nitrobutan-1-amine.** Following the general procedure for the preparation of 2,3-diaryl 4-nitrobutan-1-amine, using **19b** as a starting material, and purification of the crude product by flash column chromatography on silica gel (DCM/MeOH = 19:1) to afford (1.60 g, 94%) as a white solid, M.p. 80.3–81.6 °C. *Rf* = 0.31 (DCM/MeOH = 10:1); IR (UATR) ν_{max}/cm^{-1} 3374, 2937, 2837, 1586, 1548, 1513, 1464, 1380, 1251, 1181, 1142, 1027, 834, 813, 766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.94–6.84 (m, 4H), 6.80 (s, 1H), 4.41 (dd, J = 12.4, 11.0 Hz, 1H), 4.27 (dd, J = 12.4, 4.3 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.61 (td, J = 11.0, 4.3 Hz, 1H), 2.87–2.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.12, 149.60, 148.48, 132.32, 130.11, 128.78, 120.28, 114.39, 111.80, 110.72, 80.13, 55.96, 55.89, 55.18, 52.22, 47.66, 45.67; HRMS (ESI$^+$) calcd for $C_{19}H_{24}N_2Na_1O_5$ $(M+Na)^+$ 383.1577, found 383.1578.



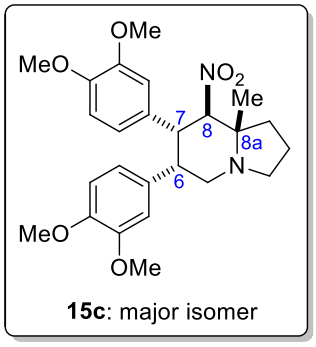
(2*S,3*R**)-2,3-Bis(3,4-dimethoxyphenyl)-4-nitrobutan-1-amine.** Following the general procedure for the preparation of 2,3-diaryl 4-nitrobutan-1-amine, using **19c** as a starting material, and purification of the crude product by flash column chromatography on silica gel (DCM/MeOH = 9:1) to afford amine (1.79 g, 97%) as a white solid, M.p. 130.9–131.8 °C. *Rf* = 0.25 (DCM/MeOH = 10:1); IR (UATR) ν_{max}/cm^{-1} 3369, 3175, 2936, 2837, 1591, 1548, 1514, 1463, 1420, 1379, 1260, 1238, 1193, 1141, 1023, 900, 863, 810, 766, 733, 701, 660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.70 (m, 6H), 4.44 (dd, J = 12.2, 11.2 Hz, 1H), 4.28 (dd, J = 12.4, 4.2 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.69–3.49 (m, 1H), 2.90–2.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.51, 149.16, 148.52, 148.40, 132.12, 130.54, 120.18, 119.90, 111.71, 111.42, 110.74, 110.63, 79.98, 55.87, 55.81, 55.74, 51.97, 48.03, 45.56; HRMS (ESI$^+$) calcd for $C_{20}H_{26}N_2Na_1O_6$ $(M+Na)^+$ 413.1683, found 413.1678.

1.3 Synthesis of β-nitro-azabicycles 15b-f



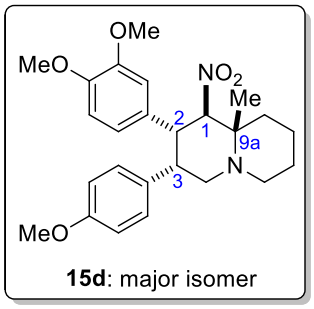
(6*S,7*R**,8*R**,8a*S**)-6-(3,4-Dimethoxyphenyl)-7-(4-methoxyphenyl)-8a-methyl-8-nitrooctahydroindolizine (15b).**

Following the general procedure for the synthesis of β-nitro-azabicycles **15**, using amine prepared from **19b** and 5-chloropentan-2-one, and purification of the crude products (*dr* = 95:5) by column chromatography on silica gel (hexane/EtOAc = 5:1 to 3:1) to afford **15b** (1.04 g, 88%) as a white solid, M.p. 133.6–134.4 °C. *Rf* = 0.40 (hexane/EtOAc = 3:1); IR (UATR) ν_{max}/cm^{-1} 2939, 2835, 1611, 1586, 1545, 1514, 1464, 1420, 1373, 1251, 1182, 1141, 1031, 827, 763, 663; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dd, J = 8.3, 1.9 Hz, 1H), 6.67–6.60 (m, 5H), 6.51 (d, J = 1.9 Hz, 1H), 4.97 (d, J = 12.5 Hz, 1H), 3.86 (dd, J = 12.5, 5.8 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.55 (s, 3H), 3.18–3.08 (m, 3H), 3.03–2.97 (m, 1H), 2.66 (td, J = 9.2, 6.7 Hz, 1H), 2.18–1.92 (m, 2H), 1.92–1.80 (m, 2H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.34, 147.46, 147.39, 134.04, 130.61, 128.78, 121.59, 113.68, 113.47, 110.24, 92.59, 62.24, 55.68, 55.32, 55.08, 49.13, 48.79, 46.11, 44.92, 38.81, 20.15, 7.25; HRMS (ESI^+) calcd for $C_{24}H_{31}N_2O_5$ $(M+H)^+$ 427.2228, found 427.2225.

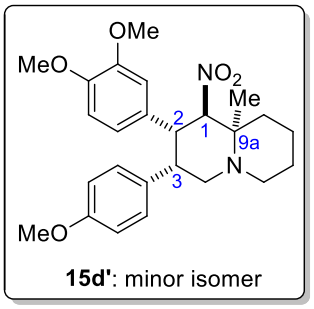


(6*S,7*R**,8*R**,8a*S**)-6,7-Bis(3,4-dimethoxyphenyl)-8a-methyl-8-nitrooctahydroindolizine (15c).** Following the general procedure for the synthesis of β-nitro-azabicycles **15**, using amine prepared from **19c** and 5-chloropentan-2-one, and purification of the crude products (*dr* = 89:11) by column chromatography on silica gel (hexane/EtOAc = 3:1 to 1:1) to afford **15c** (1.16 g, 92%) as a white solid, M.p. 80.5–82.2 °C. *Rf* = 0.33 (hexane/EtOAc = 3:1); IR (UATR) ν_{max}/cm^{-1} 2938, 2834, 1590, 1545, 1515, 1464, 1421, 1370, 1331, 1264, 1234, 1143, 1028, 888, 858, 820, 762, 733, 671; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 6.80 (dd, J = 8.3, 1.7 Hz, 1H), 6.72 (s, 1H), 6.62 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 6.31 (d, J = 6.6 Hz, 1H), 6.15 (s, 1H), 4.97 (d, J = 12.5 Hz, 1H), 3.84 (dd, J = 12.5, 5.8 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.60 (s, 6H), 3.19–3.10 (m, 3H), 3.05–3.00 (m, 1H), 2.67 (td, J = 8.8, 6.6 Hz, 1H), 2.20–1.94 (m, 2H), 1.94–1.80 (m, 2H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.37, 147.78, 147.71, 147.53, 134.20, 130.98, 121.89, 120.21, 113.54, 111.12, 110.75, 110.32, 92.70, 62.26, 55.75, 55.72, 55.58, 55.49, 49.14, 48.81, 46.10, 45.32, 38.79, 20.16, 7.28; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_6$ $(M+H)^+$ 457.2333, found 457.2332.



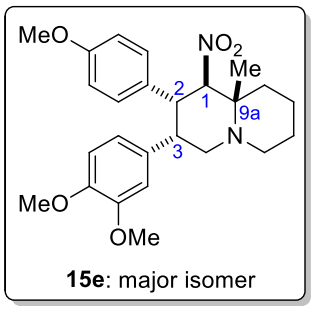
15d: major isomer



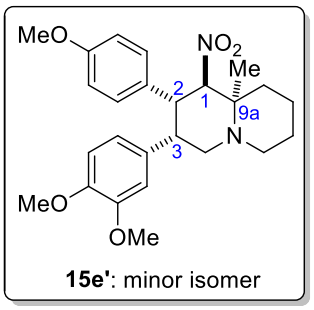
15d': minor isomer

(1*R,2*R**,3*S**,9a*S**)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-9a-methyl-1-nitrooctahydroquinolizine (15d) and (1*R**,2*R**,3*S**,9a*R**)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-9a-methyl-1-nitrooctahydroquinolizine (15d').** Following the general procedure for the synthesis of β-nitro-azabicycles **15**, using amine prepared from **19d** and 6-chlorohexan-2-one, and purification of the crude products (*dr* = 73:27) by column chromatography on silica gel (hexane/EtOAc = 5:1 to 3:1) to afford **15d** (970.5 mg, 80%) as a white solid, M.p. 115.7–116.9 °C. *Rf* = 0.42 (hexane/EtOAc = 3:1); IR (UATR) ν_{max}/cm^{-1} 2935, 2835, 1610, 1545, 1509, 1465, 1363, 1301, 1266, 1251, 1180, 1145, 1117, 1030, 838, 806, 759, 728; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 8.2 Hz, 1H), 6.37 (d, J = 7.7 Hz, 1H), 5.99 (br s, 1H), 5.01 (d, J = 12.8 Hz, 1H), 3.86 (dd, J = 12.8, 5.7 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.52 (s, 3H), 3.16 (dd, J = 12.4, 4.3 Hz, 1H), 3.01 (dd, J = 4.7, 4.5 Hz, 1H), 2.78 (d, J = 12.4 Hz, 1H), 2.63–2.50 (m, 2H), 1.90–1.45 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.23, 148.08, 147.78, 133.55, 131.18, 130.61, 120.58, 112.87, 110.96, 110.61, 94.36, 57.35, 55.64, 55.36, 55.12, 54.24, 49.36, 45.47, 44.97, 37.54, 26.08, 19.96, 5.49; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_5$ $(M+H)^+$ 441.2384, found 441.2391. The minor diastereomer **15d'** (122.3 mg, 10%) was obtained as a yellow oil. *Rf* = 0.29 (hexane/EtOAc = 3:1); IR (UATR) ν_{max}/cm^{-1} 2936, 2835, 1611, 1544, 1509, 1465, 1363, 1302, 1266, 1251, 1181, 1145, 1117, 1030, 838, 806, 760, 728; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 8.4 Hz, 1H), 6.37 (dd, J = 8.4, 1.8 Hz, 1H), 6.06 (d, J = 1.8 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 3.91 (dd, J = 12.6, 5.7 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.56 (s, 3H), 3.23 (d, J = 12.3, 1H), 3.17–2.95 (m, 2H), 1.98–1.55 (m, 8H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.35,

148.18, 147.88, 131.43, 131.28, 130.94, 120.55, 113.06, 111.08, 110.65, 90.02, 55.64, 55.47, 55.13, 52.02, 45.50, 45.27, 44.71, 41.02, 32.71, 19.84, 18.75; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_5$ $(M+H)^+$ 441.2384, found 441.2389.

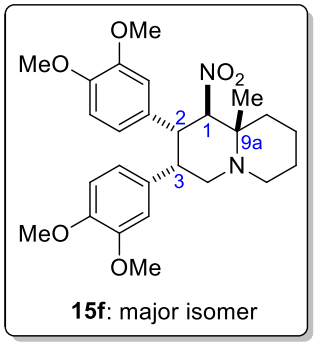


15e: major isomer

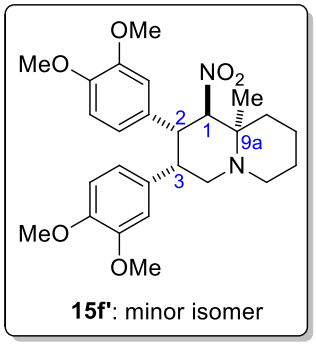


15e': minor isomer

(1*R,2*R**,3*S**,9a*S**)-3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-9a-methyl-1-nitrooctahy-droquinolizine (15e) and (1*R**,2*R**,3*S**,9a*R**)-3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-9a-methyl-1-nitrooctahydroquinolizine (15e').** Following the general procedure for the synthesis of β-nitro-azabicycles **15**, using amine prepared from **19e** and 6-chlorohexan-2-one, and purification of the crude products (*dr* = 69:31) by column chromatography on silica gel (hexane/EtOAc = 5:1 to 3:1) to afford **15e** (951.2 mg, 78%) as a white solid, M.p. 125.7–128.0 °C. *Rf* = 0.42 (hexane/EtOAc = 3:1); IR (UATR) ν_{max}/cm^{-1} 2934, 2834, 1611, 1585, 1544, 1512, 1463, 1420, 1365, 1291, 1249, 1183, 1168, 1143, 1111, 1029, 964, 893, 844, 824, 765, 733, 662; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.82 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.65–6.58 (m, 5H), 5.02 (d, *J* = 12.8 Hz, 1H), 3.88 (dd, *J* = 12.8, 5.7 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 3.18 (dd, *J* = 12.5, 4.2 Hz, 1H), 3.12 (dd, *J* = 4.5, 4.4 Hz, 1H), 2.82 (dd, *J* = 12.5, 1.0 Hz, 1H), 2.65–2.52 (m, 2H), 1.85–1.45 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.48, 147.59, 147.43, 133.66, 130.32, 128.94, 122.28, 113.71, 113.42, 110.17, 94.27, 57.33, 55.73, 55.44, 55.10, 54.24, 49.35, 45.15, 45.12, 37.83, 26.34, 20.00, 5.55; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_5$ $(M+H)^+$ 441.2384, found 441.2385. The minor diastereomer **15e'** (125.7 mg, 10%) was obtained as a yellow oil. *Rf* = 0.25 (hexane/EtOAc = 3:1); IR (UATR) ν_{max}/cm^{-1} 2936, 2834, 1610, 1585, 1544, 1512, 1463, 1421, 1365, 1291, 1249, 1184, 1168, 1143, 1111, 1029, 965, 893, 844, 824, 765, 733, 662; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.3, Hz, 1H), 6.73–6.58 (m, 6H), 5.18 (d, *J* = 12.6 Hz, 1H), 3.94 (dd, *J* = 12.7, 5.6 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.62 (s, 3H), 3.65–3.53 (m, 1H), 3.27 (d, *J* = 12.5 Hz, 1H), 3.03 (dd, *J* = 4.5, 3.3 Hz, 1H), 1.95–1.50 (m, 6H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.50, 147.73, 147.55, 133.27, 130.35, 128.97, 127.97, 113.63, 113.48, 110.18, 89.13, 56.05, 55.74, 55.61, 55.13, 45.85, 45.33, 45.21, 44.86, 41.30, 32.72, 19.87, 19.16; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_5$ $(M+H)^+$ 441.2384, found 441.2387.



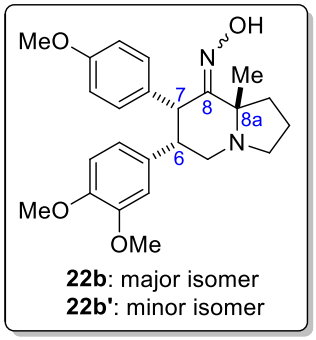
15f: major isomer



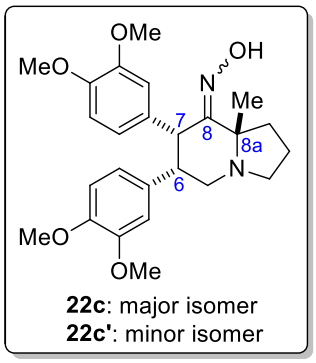
15f': minor isomer

(1*R,2*R**,3*S**,9a*S**)-2,3-Bis(3,4-dimethoxyphenyl)-9a-methyl-1-nitrooctahydroquinolizine (15f) and (1*R**,2*R**,3*S**,9a*R**)-2,3-Bis(3,4-dimethoxyphenyl)-9a-methyl-1-nitrooctahydroquinolizine (15f').** Following the general procedure for the synthesis of β-nitro azabicycles **15**, using amine prepared from **19f** and 6-chlorohexan-2-one, and purification of the crude products (*dr* = 75:25) by column chromatography on silica gel (hexane/EtOAc = 3:1 to 2:1) to afford **15f** (1.19 g, 91%) as a white solid, M.p. 143.6–144.8 °C. *Rf* = 0.39 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 2935, 2834, 1590, 1607, 1544, 1514, 1464, 1422, 1366, 1266, 1250, 1230, 1184, 1143, 1113, 1027, 960, 892, 853, 819, 766, 732, 701, 669; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 8.3 Hz, 2H), 6.33 (d, J = 7.0 Hz, 1H), 6.10 (s, 1H), 5.02 (d, J = 12.8 Hz, 1H), 3.87 (dd, J = 12.8, 5.6 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 3.57 (s, 3H), 3.18 (dd, J = 12.5, 4.1 Hz, 1H), 3.00 (dd, J = 4.6, 4.4 Hz, 1H), 2.82 (d, J = 12.5 Hz, 1H), 2.70–2.50 (m, 2H), 1.88–1.42 (m, 6H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.18, 147.82, 147.72, 147.46, 133.72, 130.62, 122.47, 120.34, 113.51, 111.07, 110.64, 110.17, 94.28, 57.28, 55.71, 55.65, 55.51, 55.47, 54.16, 49.26, 45.42, 45.02, 37.75, 26.29, 19.91, 5.50; HRMS (ESI$^+$) calcd for $C_{26}H_{35}N_2O_6$ $(M+H)^+$ 471.2490, found 471.2504. The minor diastereomer **15f'** (65.7 mg, 5%) was obtained as a yellow solid, M.p. 95.7–98.0 °C. *Rf* = 0.32 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 2936, 2834, 1591, 1607, 1544, 1514, 1466, 1422, 1366, 1266, 1250, 1230, 1184, 1145, 1113, 1028, 960, 892, 853, 819, 766, 732, 701, 670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 1.9 Hz, 1H), 6.74 (dd, J = 8.3, 1.9 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 6.32 (dd, J = 8.3, 1.9 Hz, 1H), 6.17 (d, J = 1.9 Hz, 1H), 5.18 (d, J = 12.6 Hz, 1H), 3.92 (dd, J = 12.6, 5.6 Hz, 1H), 3.89 (d, J = 4.8 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.61 (s, 3H), 3.67–3.56 (m, 2H), 3.27 (d, J = 11.9 Hz, 1H), 3.03 (t, J = 4.5 Hz, 1H), 2.00–1.45 (m, 6H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.38, 147.99, 147.71, 133.46, 130.73, 122.28, 120.39, 113.57, 111.35, 110.75, 110.33, 89.42, 55.80, 55.75, 55.66, 45.88, 45.64, 45.37, 44.80, 41.31, 32.70, 19.85, 19.03; HRMS (ESI$^+$) calcd for $C_{26}H_{35}N_2O_6$ $(M+H)^+$ 471.2490, found 471.2494.

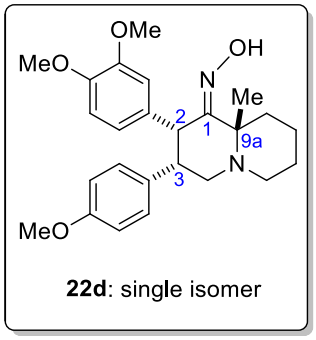
1.4 Preparation of oximes 22b-f.



(6*S,7*R**,8a*S**)-6-(3,4-Dimethoxyphenyl)-7-(4-methoxyphenyl)-8a-methylhexahydroindolizin-8(5H)-one oxime (22b/b').** Following the general procedure for the preparation of oximes **22** and purfication of the crude products (isomer ratio of **22b:22b'** = 2:1) by column chromatography on silica gel (hexane/EtOAc = 2:1 to 1:1) to afford **22b** (632.2 mg, 66%) as a yellow solid, M.p. 128.5–130.1 °C. *Rf* = 0.35 (hexane/EtOAc = 1:1); IR (UATR) ν_{max}/cm^{-1} 3456, 3211, 2963, 2835, 1609, 1510, 1464, 1250, 1178, 1162, 1144, 1029, 947, 838, 817, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.66 (d, J = 8.5 Hz, 3H), 6.43 (dd, J = 8.3, 1.4 Hz, 1H), 6.07 (d, J = 1.4 Hz, 1H), 4.28 (d, J = 5.1 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.62–3.47 (m, 1H), 3.54 (s, 3H), 3.10–2.93 (m, 3H), 2.87–2.75 (m, 1H), 2.10–1.84 (m, 4H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.94, 157.87, 147.95, 147.51, 132.95, 131.57, 130.42, 120.89, 112.90, 111.84, 110.30, 61.41, 55.65, 55.36, 55.02, 50.89, 48.74, 46.08, 41.96, 38.50, 24.10, 21.91; HRMS (ESI$^+$) calcd for $C_{24}H_{31}N_2O_4$ $(M+H)^+$ 411.2278, found 411.2271. The oxime **22b'** (310.9 mg, 32%) was obtained as a white solid, M.p. 83.2–84.5 °C. *Rf* = 0.44 (hexane/EtOAc = 1:1); IR (UATR) ν_{max}/cm^{-1}3456, 3227, 2935, 2837, 1608, 1509, 1464, 1422, 1364, 1301, 1249, 1178, 1158, 1143, 1028, 958, 839, 815, 766, 734, 702; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 8.7 Hz, 2H), 6.53 (dd, J = 8.2, 1.9 Hz, 1H), 6.31 (d, J = 1.9 Hz, 1H), 3.88–3.76 (m, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.58 (s, 3H), 3.54 (td, J = 9.0, 5.1 Hz, 1H), 3.06–2.95 (m, 3H), 2.77–2.62 (m, 1H), 2.42–2.30 (m, 1H), 2.17–1.83 (m, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.38, 158.00, 148.08, 147.56, 133.69, 131.67, 121.02, 113.04, 112.11, 110.40, 62.11, 55.71, 55.44, 55.08, 51.71, 48.64, 48.23, 43.73, 36.06, 21.08, 15.97; HRMS (ESI$^+$) calcd for $C_{24}H_{31}N_2O_4$ $(M+H)^+$ 411.2278, found 411.2273.

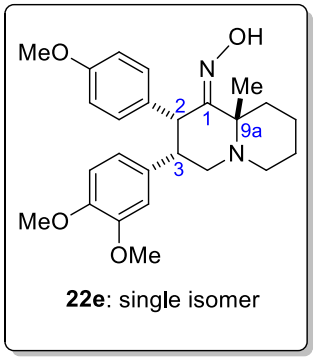


(6*S,7*R**,8a*S**)-6,7-Bis(3,4-dimethoxyphenyl)-8a-methylhexahydroindolizin-8(5H)-one oxime (22c/c').** Following the general procedure for the preparation of oximes **22** and purification of the crude products (isomer ratio of **22c**:**22c'** = 2:1) by column chromatography on silica gel (hexane/EtOAc = 1:1 to 1:2) to afford **22c** (678.0 mg, 66%) as a white solid, M.p. 155.0–156.6 °C. *Rf* = 0.17 (hexane/EtOAc = 1:2); IR (UATR) ν_{max}/cm^{-1} 3451, 3198, 2934, 2835, 1590, 1513, 1464, 1421, 1367, 1260, 1236, 1142, 1071, 1027, 949, 855, 811, 732, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 6.84 (d, J = 1.8 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 6.49 (dd, J = 8.3, 1.9 Hz, 1H), 6.40 (dd, J = 8.3, 1.9 Hz, 1H), 6.18 (d, J = 1.9 Hz, 1H), 4.29 (d, J = 5.2 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 3.59 (s, 3H), 3.65–3.53 (m, 1H), 3.13–2.95 (m, 3H), 2.88–2.75 (m, 1H), 2.18–1.90 (m, 4H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.67, 148.01, 147.86, 147.54, 147.13, 132.88, 130.66, 122.84, 120.81, 113.84, 111.90, 110.34, 110.12, 61.27, 55.66, 55.58, 55.43, 55.29, 50.48, 48.46, 46.37, 41.96, 38.44, 23.34, 21.77; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_5$ $(M+H)^+$ 441.2384, found 441.2373. The oxime **22c'** (340.1 mg, 33%) was obtained as a white solid, M.p. 93.5–94.8 °C. *Rf* = 0.33 (hexane/EtOAc = 1:2); IR (UATR) ν_{max}/cm^{-1} 3451, 3237, 2935, 2835, 1590, 1513, 1464, 1422, 1363, 1263, 1230, 1199, 1143, 1027, 960, 860, 811, 732, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 6.95 (s, 1H), 6.68 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.51 (dd, J = 8.3, 1.8 Hz, 1H), 6.46 (dd, J = 8.3, 1.8 Hz, 1H), 6.37 (d, J = 1.8 Hz, 1H), 3.88–3.75 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 3.58–3.46 (m, 1H), 3.09–2.95 (m, 3H), 2.79–2.66 (m, 1H), 2.46–2.34 (m, 1H), 2.20–2.05 (m, 1H), 2.00–1.87 (m, 2H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.00, 148.11, 147.97, 147.59, 147.28, 133.67, 131.97, 122.97, 121.07, 113.61, 112.11, 110.41, 110.27, 62.08, 55.71, 55.65, 55.46, 55.22, 52.08, 48.60, 48.04, 43.86, 35.94, 21.00, 15.56; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_5$ $(M+H)^+$ 441.2384, found 441.2373.



22d: single isomer

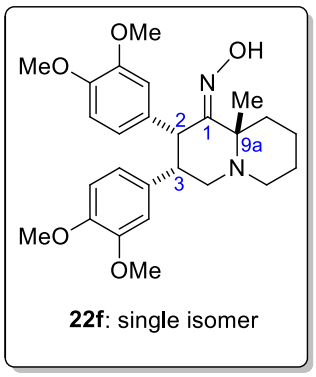
(2*R,3*S**,9a*S**)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-9a-methyloctahydroquinolizin-1-one oxime (22d).** Following the general procedure for the preparation of oximes **22** and purification of the crude products (a single isomer) by column chromatography on silica gel (hexane/EtOAc = 3:1 to 2:1) to afford **22d** (965.3 mg, 97%) as a white solid, M.p. 150.8–152.0 °C. *Rf* = 0.43 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 3464, 3265, 2931, 2834, 1609, 1588, 1509, 1463, 1359, 1249, 1179, 1143, 1114, 1030, 952, 924, 835, 804, 763, 734, 701, 675; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 7.41 (s, 1H), 6.74–6.58 (m, 6H), 4.38 (d, J = 5.3 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.54–3.38 (m, 1H), 2.98 (t, J = 11.3 Hz, 1H), 2.71 (d, J = 8.7 Hz, 1H), 2.68 (d, J = 9.6 Hz, 1H), 2.54 (br dd, J = 11.3, 8.7 Hz, 1H), 2.03 (d, J = 12.7 Hz, 1H), 1.70–1.40 (m, 5H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.23, 158.15, 147.97, 147.08, 132.44, 130.50, 129.75, 123.74, 114.22, 113.07, 110.13, 56.01, 55.54, 55.48, 55.03, 52.28, 48.82, 45.25, 40.50, 37.71, 26.05, 20.38, 16.64; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_4$ $(M+H)^+$ 425.2435, found 425.2432.



22e: single isomer

(2*R,3*S**,9a*S**)-3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-9a-methyloctahydroquinolizin-1-one oxime (22e).** Following the general procedure for the preparation of oximes **22** and purification of the crude products (a single isomer) by column chromatography on silica gel (hexane/EtOAc = 3:1 to 2:1) to afford **22e** (975.1 g, 98%) as a white solid, M.p. 135.1–136.9 °C. *Rf* = 0.39 (hexane/EtOAc = 2:1); IR (UATR) ν_{max}/cm^{-1} 3461, 3273, 2933, 2834, 1608, 1509, 1464, 1441, 1371, 1301, 1261, 1244, 1180, 1143, 1115, 1029, 958, 934, 872, 830, 802, 760, 734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 2H), 7.29 (s, 1H), 6.72 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.49 (dd, J = 8.2, 1.9 Hz, 1H), 6.11 (d, J = 1.9 Hz, 1H), 4.39 (d, J = 5.5 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.52 (s, 3H),

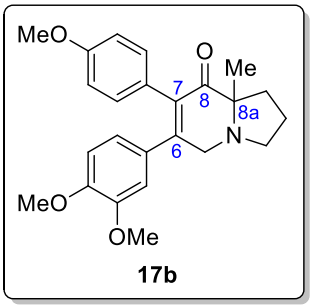
3.50–3.39 (m, 1H), 2.96 (t, J = 11.4 Hz, 1H), 2.78–2.65 (m, 2H), 2.62–2.48 (m, 1H), 2.06 (d, J = 13.4 Hz, 1H), 1.80–1.60 (m, 5H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.54, 158.02, 147.98, 147.58, 133.23, 132.45, 130.53, 121.15, 113.12, 112.02, 110.34, 56.06, 55.69, 55.34, 55.08, 52.69, 48.96, 44.92, 41.01, 37.65, 25.90, 20.49, 16.60; HRMS (ESI$^+$) calcd for $C_{25}H_{33}N_2O_4$ $(M+H)^+$ 425.2435, found 425.2447.



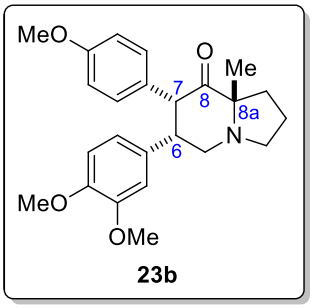
22f: single isomer

(2*R,3*S**,9a*S**)-2,3-Bis(3,4-dimethoxyphenyl)-9a-methyloctahydroquinolizin-1-one oxime (22f).** Following the general procedure for the preparation of oximes **22** and purification of the crude products (a single isomer) by column chromatography on silica gel (hexane/EtOAc = 1:1 to 1:2) to afford **22f** (1.01 g, 95%) as a white solid, M.p. 160.7–162.1 °C. *Rf* = 0.19 (hexane/EtOAc = 1:2); IR (UATR) ν_{max}/cm^{-1} 3461, 3273, 2932, 2834, 1605, 1590, 1512, 1463, 1422, 1371, 1264, 1251, 1230, 1143, 1113, 1027, 986, 959, 933, 860, 803, 760, 733, 702, 678; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.63 (s, 2H), 6.45 (dd, J = 8.2, 1.5 Hz, 1H), 6.15 (d, J = 1.2 Hz, 1H), 4.37 (d, J = 5.4 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.55 (s, 3H), 3.52–3.40 (m, 1H), 2.96 (t, J = 11.3 Hz, 1H), 2.75 (d, J = 9.1 Hz, 1H), 2.71 (d, J = 11.3 Hz, 1H), 2.59 (br dd, J = 11.3, 9.1 Hz, 1H), 2.06 (d, J = 12.2 Hz, 1H), 1.85–1.48 (m, 6H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.36, 148.27, 148.01, 147.63, 147.27, 133.07, 130.75, 124.02, 121.10, 114.28, 111.99, 110.35, 110.29, 56.07, 55.71, 55.67, 55.66, 55.42, 52.69, 48.89, 45.29, 41.06, 37.79, 26.14, 20.44, 16.69; HRMS (ESI$^+$) calcd for $C_{26}H_{35}N_2O_5$ $(M+H)^+$ 455.2541, found 455.2552.

1.5 Synthesis of α,β-unsaturated ketones 17b-f and 23b-f



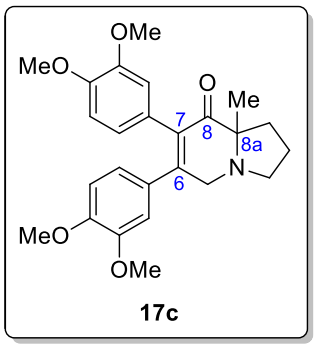
17b



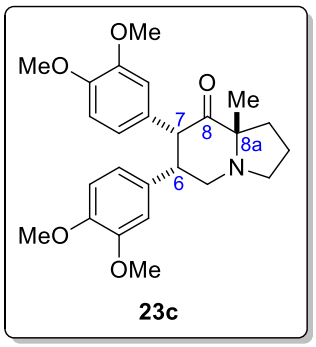
23b

(±)-6-(3,4-Dimethoxyphenyl)-7-(4-methoxyphenyl)-8a-methyl-1,2,3,8a-tetrahydroindolizin-8(5H)-one (17b) and (6*S,7*R**,8a*S**)-6-(3,4-Dimethoxyphenyl)-7-(4-**

methoxyphenyl)-8a-methylhexahydroindolizin-8(5H)-one (23b). Following the general procedure for the synthesis of α,β-unsaturated ketones **17** and purification of the crude products by column chromatography on silica gel (hexane/EtOAc = 2:1 to 1:1) to afford **17b** (377.0 mg, 80%) as a yellow oil. *Rf* = 0.33 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2960, 2836, 1662, 1601, 1574, 1508, 1463, 1416, 1363, 1242, 1168, 1143, 1025, 864, 830, 806, 761, 733, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, J = 8.8 Hz, 2H), 6.81 (dd, J = 8.3, 1.9 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 1.9 Hz, 1H), 4.15 (d, J = 19.5 Hz, 1H), 3.98 (d, J = 19.5 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.50 (s, 3H), 3.16 (dd, J = 7.7, 6.8 Hz, 2H), 2.62–2.49 (m, 1H), 1.92–1.66 (m, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.21, 158.48, 150.00, 149.09, 148.17, 132.87, 132.02, 130.41, 127.54, 120.90, 113.39, 112.82, 110.46, 66.84, 55.73, 55.54, 55.14, 51.28, 49.71, 34.52, 20.49, 19.10; HRMS (ESI$^+$) calcd for $C_{24}H_{28}N_1O_4$ $(M+H)^+$ 394.2013, found 394.2013. The ketone **23b** (24.0 mg, 5%) was obtained as a yellow oil. *Rf* = 0.17 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2936, 2835, 1706, 1610, 1512, 1463, 1420, 1367, 1247, 1178, 1142, 1068, 1027, 825, 807, 764, 733, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.68 (s, 1H), 6.66 (d, J = 1.8 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.80–3.70 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.60 (td, J = 11.0, 4.5 Hz, 1H), 3.27 (dd, J = 11.6, 4.3 Hz, 1H), 3.27–3.17 (m, 1H), 2.93 (t, J = 11.0 Hz, 1H), 2.95–2.83 (m, 1H), 2.14 (dd, J = 11.5, 9.0 Hz, 1H), 2.04–1.75 (m, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.75, 158.16, 148.67, 147.56, 134.07, 129.94, 129.60, 119.34, 113.65, 111.04, 111.01, 70.77, 58.48, 56.86, 55.76, 55.68, 55.00, 54.61, 46.13, 34.83, 24.32, 21.77; HRMS (ESI$^+$) calcd for $C_{24}H_{30}N_1O_4$ $(M+H)^+$ 396.2169, found 396.2171.



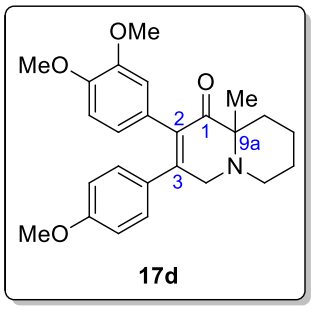
17c



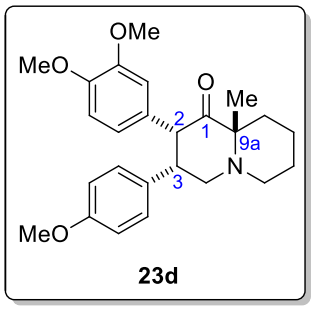
23c

(±)-6,7-Bis(3,4-dimethoxyphenyl)-8a-methyl-1,2,3,8a-tetrahydroindolizin-8(5H)-one (17c) and (6*S,7*R**,8a*S**)-6,7-Bis(3,4-dimethoxyphenyl)-8a-methylhexahydroindolizin-8(5H)-one (23c).** Following the general procedure for the synthesis of α,β-unsaturated ketones **17** and purification of the crude products by column chromatography on silica gel (hexane/EtOAc = 2:1 to 1:2) to afford **17c** (406.0 mg, 80%) as a white solid, M.p. 110.7–112.3 °C. *Rf* = 0.31 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2961, 2835, 1663, 1600, 1582, 1510,

1463, 1411, 1362, 1308, 1253, 1140, 1025, 859, 808, 761, 733, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, J = 8.3, 1.8 Hz, 1H), 6.75 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 8.3, 1.8 Hz, 1H), 6.51 (d, J = 1.8 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 4.13 (d, J = 19.5 Hz, 1H), 3.98 (d, J = 19.5 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.53 (s, 3H), 3.21–3.13 (m, 2H), 2.62–2.50 (m, 1H), 1.93–1.67 (m, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.12, 150.42, 149.15, 148.36, 148.27, 148.02, 132.95, 130.42, 127.77, 123.57, 120.91, 114.41, 112.53, 110.72, 110.48, 66.85, 55.79, 55.61, 51.24, 49.79, 34.46, 20.47, 18.93; HRMS (ESI$^+$) calcd for $C_{25}H_{30}N_1O_5$ $(M+H)^+$ 424.2118, found 424.2114. The ketone **23c** (35.2 mg, 7%) was obtained as a yellow oil. *Rf* = 0.31 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2935, 2836, 1705, 1592, 1515, 1463, 1419, 1259, 1141, 1069, 1025, 860, 806, 764, 732, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72–6.65 (m, 3H), 6.65–6.58 (m, 2H) 6.58–6.53 (m, 1H), 3.80–3.70 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.62 (td, J = 12.0, 3.9 Hz, 1H), 3.27 (dd, J = 11.7, 4.2 Hz, 1H), 3.28–3.17 (m, 1H), 2.92 (t, J = 11.1 Hz, 1H), 2.90–2.82 (m, 1H), 2.15 (dd, J = 11.7, 9.0 Hz, 1H), 2.05–1.75 (m, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.69, 148.77, 148.53, 147.72, 134.06, 130.04, 121.13, 119.45, 112.44, 111.10, 110.93, 70.91, 58.84, 56.91, 55.83, 55.74, 55.71, 55.67, 54.74, 46.16, 34.81, 24.60, 21.81; HRMS (ESI$^+$) calcd for $C_{25}H_{32}N_1O_5$ $(M+H)^+$ 426.2275, found 426.2271.



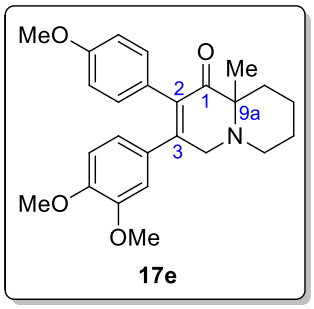
17d



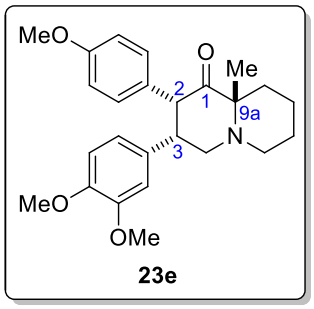
23d

(±)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-9a-methyl-4,6,7,8,9,9a-hexahydroquinolizin-1-one (17d) and (2*R,3*S**,9a*S**)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-9a-methyloctahydroquinolizin-1-one (23d).** Following the general procedure for the synthesis of α,β-unsaturated ketones **17** and purification of the crude products by column chromatography on silica gel (hexane/EtOAc = 2:1 to 1:1) to afford **17d** (401.4 mg, 82%) as a yellow oil. *Rf* = 0.45 (EtOAc); IR (UATR) ν_{max} /cm^{-1} 2934, 2837, 1669, 1604, 1509, 1464, 1293, 1250, 1175, 1140, 1027, 832, 808, 784, 761, 733, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 8.8 Hz, 2H), 6.60 (dd, J = 8.3, 1.9 Hz, 1H), 6.49 (d, J = 1.9 Hz, 1H), 3.82 (s, 3H), 3.81–3.67 (m, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 2.91–2.70 (m, 2H), 1.98–1.50 (m, 6H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.22, 159.50, 151.98, 148.13, 147.90, 132.66, 130.08, 129.93, 127.57, 123.75, 114.58, 113.55, 110.57, 60.98, 55.72, 55.69, 55.17, 55.12, 49.70, 32.88, 25.52, 20.37, 12.72;

HRMS (ESI$^+$) calcd for $C_{25}H_{30}N_1O_4$ $(M+H)^+$ 408.2169, found 408.2174. The ketone **23d** (20.0 mg, 4%) was obtained as a yellow oil. *Rf* = 0.40 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2936, 2836, 1717, 1610, 1513, 1464, 1420, 1251, 1178, 1142, 1069, 1029, 830, 806, 761, 734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 8.6 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 6.67 (d, J = 8.2 Hz, 1H), 6.48 (dd, J = 8.2, 1.8 Hz, 1H), 6.42 (d, J = 1.8 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.22–3.07 (m, 2H), 3.06–2.94 (m, 1H), 2.75–2.58 (m, 2H), 1.90–1.56 (m, 6H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.35, 157.88, 148.23, 147.42, 136.22, 129.18, 128.28, 121.91, 113.62, 112.90, 110.69, 64.53, 56.27, 56.04, 55.66, 55.59, 55.02, 48.27, 45.16, 33.35, 24.89, 19.64, 10.99; HRMS (ESI$^+$) calcd for $C_{25}H_{32}N_1O_4$ $(M+H)^+$ 410.2326, found 410.2324.



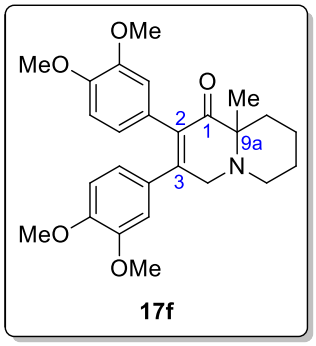
17e



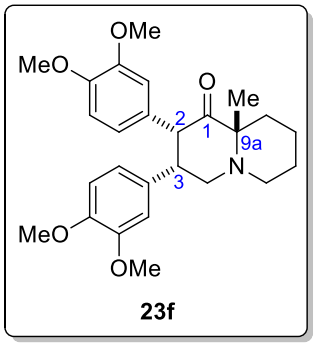
23e

(±)-3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-9a-methyl-4,6,7,8,9,9a-hexahydroquinoli-zin-1-one (17e) and (2*R,3*S**,9a*S**)-3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-9a-methyloctahydroquinolizin-1-one (23e).** Following the general procedure for the synthesis of α,β-unsaturated ketones **17** and purification of the crude products by column chromatography on silica gel (hexane/EtOAc = 2:1 to 1:1) to afford **17e** (397.0 mg, 81%) as a yellow oil. *Rf* = 0.36 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2935, 2837, 1669, 1603, 1509, 1464, 1443, 1414, 1320, 1247, 1173, 1142, 1025, 970, 860, 830, 809, 764, 734, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 8.6 Hz, 2H), 6.82 (dd, J = 8.3, 1.8 Hz, 1H), 6.77–6.69 (m, 3H), 6.46 (d, J = 1.7 Hz, 1H), 3.87–3.70 (m, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.50 (s, 3H), 2.91–2.70 (m, 2H), 1.97–1.50 (m, 6H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.32, 158.47, 151.54, 149.04, 148.12, 132.56, 132.06, 130.15, 127.57, 120.85, 113.36, 112.83, 110.43, 60.93, 55.72, 55.53, 55.15, 54.83, 49.68, 32.84, 25.51, 20.36, 12.74; HRMS (ESI$^+$) calcd for $C_{25}H_{30}N_1O_4$ $(M+H)^+$ 408.2169, found 408.2167. The ketone **23e** (29.9 mg, 6%) was obtained as a yellow oil. *Rf* = 0.46 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2927, 2852, 1717, 1612, 1514, 1464, 1421, 1363, 1247, 1178, 1162, 1140, 1069, 1029, 813, 762, 736, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 6.68–6.63 (m, 3H), 4.37 (d, J = 11.5 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.22–3.08 (m, 2H), 3.07–2.97 (m, 1H), 2.75–2.58 (m, 2H), 1.74–1.58 (m, 6H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.42, 158.06, 148.64, 147.32, 136.79, 130.51, 128.74, 119.51, 113.40, 110.83,

110.60, 64.55, 55.98, 55.92, 55.74, 55.67, 55.01, 48.33, 45.51, 33.51, 25.09, 19.65, 10.86; HRMS (ESI$^+$) calcd for $C_{25}H_{32}N_1O_4$ $(M+H)^+$ 410.2326, found 410.2327.



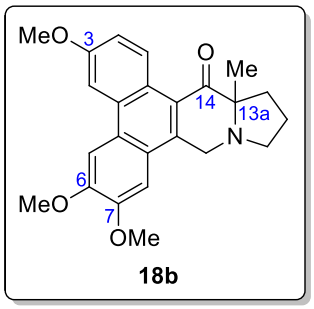
17f



23f

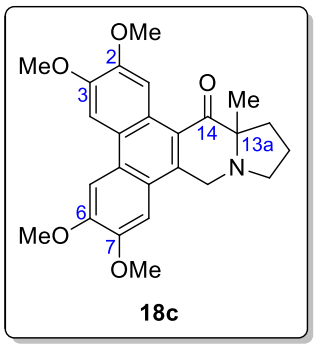
(±)-2,3-Bis(3,4-dimethoxyphenyl)-9a-methyl-4,6,7,8,9,9a-hexahydroquinolizin-1-one (17f) and (2*R,3*S**,9a*S**)-2,3-Bis(3,4-dimethoxyphenyl)-9a-methyloctahydroquinolizin-1-one (23f).** Following the general procedure for the synthesis of α,β-unsaturated ketones **17** and purification of the crude products by column chromatography on silica gel (hexane/EtOAc = 2:1 to 1:2) to afford **17f** (447.1 mg, 85%) as a yellow solid, M.p. 125.7–126.6 °C. *Rf* = 0.28 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2931, 2854, 1669, 1600, 1512, 1464, 1412, 1322, 1256, 1174, 1140, 1024, 860, 809, 764, 733, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (dd, J = 8.3, 2.0 Hz, 1H), 6.72 (d, J = 9.6 Hz, 2H), 6.59 (dd, J = 8.3, 1.9 Hz, 1H), 6.52 (dd, J = 9.6, 2.0 Hz, 1H), 3.87–3.73 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 3.52 (s, 3H), 2.91–2.70 (m, 2H), 2.00–1.50 (m, 6H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.22, 151.95, 149.20, 148.41, 148.31, 148.08, 132.72, 130.24, 127.88, 123.65, 120.90, 114.56, 112.66, 110.81, 110.55, 61.03, 55.83, 55.82, 55.80, 55.65, 54.87, 49.70, 32.88, 25.51, 20.36, 12.59; HRMS (ESI$^+$) calcd for $C_{26}H_{32}N_1O_5$ $(M+H)^+$ 438.2275, found 438.2265. The ketone **23f** (16.1 mg, 3%) was obtained as a yellow oil. *Rf* = 0.27 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2933, 2834, 1717, 1592, 1515, 1464, 1419, 1363, 1257, 1236, 1140, 1069, 1027, 903, 850, 805, 764, 733, 657; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73–6.61 (m, 3H), 6.67 (d, J = 8.1 Hz, 1H), 6.48 (dd J = 10.2, 1.8 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 3.773 (s, 6H), 3.765 (s, 3H), 3.75 (s, 3H), 3.23–3.07 (m, 2H), 3.07–2.97 (m, 1H), 2.77–2.59 (m, 2H), 1.70–1.50 (m, 6H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.12, 148.53, 148.16, 147.38, 147.23, 136.62, 129.06, 121.84, 119.45, 112.78, 110.70, 110.60, 110.37, 64.45, 56.11, 55.76, 55.61, 55.58, 55.53, 55.48, 48.12, 45.44, 33.36, 24.95, 19.48, 10.66; HRMS (ESI$^+$) calcd for $C_{26}H_{34}N_1O_5$ $(M+H)^+$ 440.2432, found 440.2444.

1.6 Oxidative coupling reaction of ketones 17b-f to 18b-f



18b

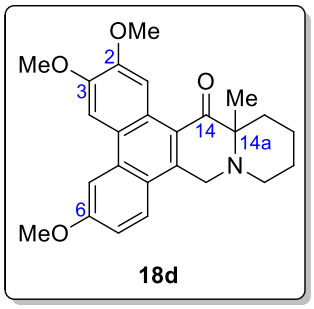
(±)-3,6,7-Trimethoxy-13a-methyl-11,12,13,13a-tetrahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinolin-14(9H)-one (18b). Following the general procedure for the oxidative coupling reaction of ketones **17** to **18** and purification of the crude product by column chromatography on silica gel (EtOAc/MeOH = 100:1 to 20:1) to afford **18b** (370.5 mg, 79%) as a white solid, M.p. 145.9–146.0 °C. *Rf* = 0.22 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2958, 2935, 2833, 1663, 1615, 1522, 1509, 1468, 1419, 1394, 1365, 1319, 1263, 1234, 1204, 1168, 1141, 1106, 1039, 904, 839, 766, 733, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (d, J = 9.4 Hz, 1H), 7.92 (s, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.30 (s, 1H), 7.28 (dd, J = 9.4, 2.6 Hz, 1H), 4.68 (d, J = 17.8 Hz, 1H), 4.59 (d, J = 17.8 Hz, 1H), 4.14 (s, 3H), 4.08 (s, 3H), 4.02 (s, 3H), 3.25–3.14 (m, 1H), 3.10–2.98 (m, 1H), 2.74–2.61 (m, 1H), 1.98–1.70 (m, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.05, 157.78, 151.02, 149.60, 136.07, 131.05, 129.25, 127.59, 123.64, 122.68, 122.32, 115.55, 104.50, 104.45, 103.71, 67.90, 55.95, 55.92, 55.41, 51.85, 45.76, 35.05, 20.76, 19.29; HRMS (ESI$^+$) calcd for $C_{24}H_{26}N_1O_4$ $(M+H)^+$ 392.1856, found 392.1854.



18c

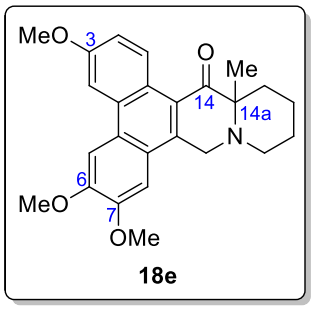
(±)-2,3,6,7-Tetramethoxy-13a-methyl-11,12,13,13a-tetrahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinolin-14(9H)-one (18c). Following the general procedure for the oxidative coupling reaction of ketones **17** to **18** and purification of the crude product by column chromatography on silica gel (EtOAc/MeOH = 20:1) to afford **18c** (420.5 mg, 83%) as a yellow solid, 171.70–172.6 °C *Rf* = 0.15 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2961, 2937, 2833, 1660, 1617, 1509, 1465, 1420, 1316, 1249, 1213, 1197, 1150, 1109, 1042, 1027, 874, 837, 777, 732, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.83 (s, 1H), 7.80 (s, H), 7.30 (s, 1H), 4.71 (d, J = 17.9 Hz, 1H), 4.63 (d, J = 17.9 Hz, 1H), 4.16 (s, 3H), 4.12 (s, 3H), 4.10 (s, 3H), 4.08 (s, 3H), 3.25–3.14

(m, 1H), 3.01–3.13 (m, 1H), 2.76–2.63 (m, 1H), 1.99–1.74 (m, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.69, 151.28, 149.65, 148.94, 148.65, 136.75, 128.00, 124.47, 123.64, 122.47, 121.08, 107.82, 104.38, 103.02, 102.49, 67.90, 55.94, 55.90, 55.82, 51.71, 45.97, 34.99, 20.63, 19.08; HRMS (ESI$^+$) calcd for $C_{25}H_{28}N_1O_5$ $(M+H)^+$ 422.1962, found 422.1965.



18d

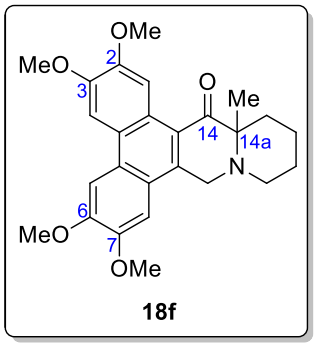
(±)-2,3,6-Trimethoxy-14a-methyl-12,13,14,14a-tetrahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-15(11H)-one (18d). Following the general procedure for the oxidative coupling reaction of ketones **17** to **18** and purification of the crude product by column chromatography on silica gel (EtOAc/MeOH = 100:1 to 20:1) to afford **18d** (415.0 mg, 85%) as a white solid, M.p. 160.3–162.6 °C. *Rf* = 0.27 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2935, 2834, 1661, 1612, 1509, 1466, 1449, 1410, 1386, 1307, 1256, 1231, 1203, 1128, 1113, 1066, 1037, 979, 874, 833, 805, 785, 733, 702, 671; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.85 (s, 2H), 7.21 (dd, J = 9.1, 2.5 Hz, 1H), 4.48 (d, J = 17.8 Hz, 1H), 4.38 (d, J = 17.8 Hz, 1H), 4.10 (s, 3H), 4.09 (s, 3H), 4.03 (s, 3H), 2.98–2.80 (m, 2H), 2.10–1.85 (m, 2H), 1.80–1.60 (m, 4H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.62, 160.07, 149.97, 148.29, 138.83, 133.84, 126.22, 124.82, 124.25, 121.69, 119.87, 115.55, 108.03, 104.23, 102.87, 62.15, 55.74, 55.61, 55.26, 50.95, 50.17, 33.44, 25.49, 20.53, 14.00; HRMS (ESI$^+$) calcd for $C_{25}H_{28}N_1O_4$ $(M+H)^+$ 406.2013, found 406.2016.



18e

(±)-3,6,7-Trimethoxy-14a-methyl-12,13,14,14a-tetrahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-15(11H)-one (18e). Following the general procedure for the oxidative coupling reaction of ketones **17** to **18** and purification of the crude product by column chromatography on silica gel (EtOAc/MeOH = 100:1 to 20:1) to afford **18e** (414.8 mg, 85%) as a white solid, M.p. 155.0–156.8 °C. *Rf* = 0.21 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2937, 2832, 1663, 1615, 1523, 1509, 1470, 1416, 1327, 1296, 1260, 1233, 1204, 1169, 1135, 1112, 1066, 1040, 946, 893,

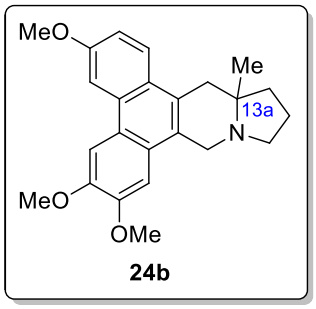
840, 785, 733, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (d, J = 9.4 Hz, 1H), 7.84 (s, 1H), 7.82 (d, J = 2.6 Hz, 1H), 7.25 (dd, J = 9.4, 2.6 Hz, 1H), 7.22 (s, 1H), 4.40 (d, J = 17.5 Hz, 1H), 4.27 (d, J = 17.5 Hz, 1H), 4.10 (s, 3H), 4.05 (s, 3H), 3.98 (s, 3H), 3.00–2.80 (m, 2H), 2.08–1.88 (m, 2H), 1.80–1.57 (m, 4H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.18, 157.67, 150.97, 149.50, 137.18, 131.04, 129.38, 127.40, 123.16, 123.06, 121.57, 115.41, 104.45, 104.17, 103.65, 62.15, 55.91, 55.89, 55.33, 51.11, 50.25, 33.42, 25.57, 20.53, 13.76; HRMS (ESI$^+$) calcd for $C_{25}H_{28}N_1O_4$ $(M+H)^+$ 406.2013, found 406.2011.



18f

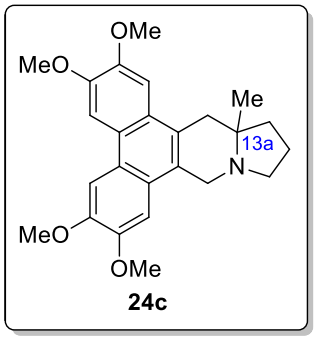
(±)-2,3,6,7-Tetramethoxy-14a-methyl-12,13,14,14a-tetrahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-15(11H)-one (18f). Following the general procedure for the oxidative coupling reaction of ketones **17** to **18** and purification of the crude product by column chromatography on silica gel (EtOAc/MeOH = 100:1 to 20:1) to afford **18f** (471.3 mg, 90%) as a white solid, M.p. 168.1–170.5 °C. *Rf* = 0.22 (EtOAc); IR (UATR) ν_{max}/cm^{-1} 2935, 2833, 1660, 1617, 1509, 1465, 1421, 1378, 1329, 1296, 1254, 1213, 1198, 1137, 1114, 1066, 1042, 872, 837, 809, 770, 732, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.25 (s, 1H), 4.48 (d, J = 17.6 Hz, 1H), 4.33 (d, J = 17.6 Hz, 1H), 4.14 (s, 3H), 4.11 (s, 3H), 4.10 (s, 3H), 4.06 (s, 3H), 3.03–2.80 (m, 2H), 2.10–1.87 (m, 2H), 1.83–1.58 (m, 4H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.88, 151.35, 149.69, 148.98, 148.66, 137.69, 127.91, 124.55, 124.11, 122.13, 120.59, 108.12, 104.27, 103.14, 102.61, 62.32, 55.98, 55.89, 55.86, 51.38, 50.48, 33.62, 25.69, 20.70, 14.40; HRMS (ESI$^+$) calcd for $C_{26}H_{30}N_1O_5$ $(M+H)^+$ 436.2118, found 436.2118.

1.7 Synthesis of (±)-13a-methyl tylophora alkaloids (24b-f)



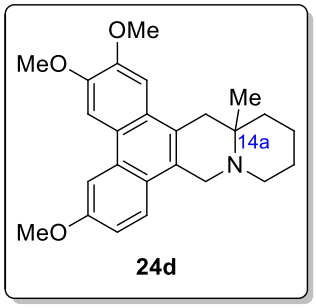
24b

(±)-3,6,7-Trimethoxy-13a-methyl-9,11,12,13,13a,14-hexahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinoline (24b). Following the general procedure for the synthesis of (±)-13a-methyl tylophora alkaloids and purification of the crude product by column chromatography on silica gel (DCM/MeOH = 100:1 to 100:3) to afford **24b** (409.0 mg, 90%) as a yellow solid, M.p. 185.7–188.0 °C. *Rf* = 0.30 (CH_2Cl_2/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 2960, 2935, 2833, 1616, 1511, 1467, 1415, 1369, 1256, 1233, 1203, 1168, 1144, 1133, 1037, 907, 840, 812, 785, 732, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 9.1 Hz, 1H), 7.91 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.21 (dd, J = 9.1, 2.5 Hz, 1H), 7.18 (s, 1H), 4.38 (d, J = 16.1 Hz, 1H), 4.13–3.97 (m, 1H), 4.09 (s, 3H), 4.05 (s, 3H), 4.04 (s, 3H), 3.20–3.10 (m, 1H), 3.13 (d, J = 16.5 Hz, 1H), 3.02 (d, J = 16.5 Hz, 1H), 3.02–2.88 (m, 1H), 2.05–1.90 (m, 4H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.47, 149.33, 148.17, 130.43, 125.91, 125.66, 125.51, 124.86, 123.20, 123.10, 114.65, 104.56, 103.84, 103.02, 57.75, 55.92, 55.81, 55.44, 50.79, 47.20, 39.20, 35.90, 20.12, 17.27; HRMS (ESI$^+$) calcd for $C_{24}H_{28}N_1O_3$ $(M+H)^+$ 378.2064, found 378.2071.



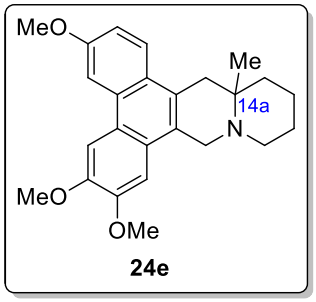
24c

(±)-2,3,6,7-Tetramethoxy-13a-methyl-9,11,12,13,13a,14-hexahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinoline (24c). Following the general procedure for the synthesis of (±)-13a-methyl tylophora alkaloids and purification of the crude product by column chromatography on silica gel (DCM/MeOH = 100:1 to 20:1) to afford **24c** (437.2 mg, 89%) as a yellow solid, M.p. 198.7–200.6 °C. *Rf* = 0.25 (CH_2Cl_2/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 2925, 2853, 1618, 1513, 1468, 1425, 1250, 1213, 1197, 1150, 1040, 1018, 842, 778, 731, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.32 (s, 1H), 7.19 (s, 1H), 4.41 (d, J = 16.1 Hz, 1H), 4.12–4.05 (m, 1H), 4.12 (s, 6H), 4.07 (s, 3H), 4.06 (s, 3H), 3.20–3.08 (m, 1H), 3.04 (s, 2H), 3.02–2.88 (m, 1H), 1.99 (br s, 4H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.66, 148.62, 148.41, 148.35, 125.99, 125.20, 124.28, 123.96, 123.67, 123.22, 103.73, 103.36, 103.32, 103.04, 57.82, 56.00, 55.99, 55.82, 55.80, 50.79, 47.25, 39.26, 36.09, 20.14, 17.40; HRMS (ESI$^+$) calcd for $C_{25}H_{30}N_1O_4$ $(M+H)^+$ 408.2169, found 408.2160.



24d

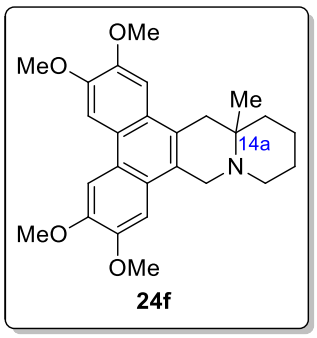
(±)-2,3,6-Trimethoxy-14a-methyl-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinoline (24d). Following the general procedure for the synthesis of (±)-13a-methyl tylophora alkaloids and purification of the crude product by column chromatography on silica gel (DCM/MeOH = 100:1 to 100:3) to afford **24d** (414.4 mg, 88%) as a yellow solid, M.p. 195.7–197.3 °C. *Rf* = 0.31 (CH_2Cl_2/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 2933, 2862, 1614, 1511, 1467, 1416, 1304, 1257, 1232, 1204, 1168, 1123, 1039, 892, 840, 812, 783, 732, 702; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.28 (s, 1H), 7.18 (dd, J = 9.0, 2.5 Hz, 1H), 4.20 (d, J = 16.4 Hz, 1H), 4.08 (s, 3H), 4.06 (s, 3H), 3.98 (s, 3H), 4.00–3.88 (m, 1H), 3.06 (d, J = 16.4 Hz, 1H), 2.93–2.84 (m, 1H), 2.85 (d, J = 16.4 Hz, 1H), 2.68–2.56 (m, 1H), 1.90–1.60 (m, 6H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.28, 149.23, 148.15, 129.88, 126.85, 124.56, 124.01, 123.82, 123.61, 123.42, 114.69, 104.56, 103.78, 103.69, 55.88, 55.78, 55.37, 51.92, 51.47, 49.93, 39.87, 39.12, 26.11, 20.54, 14.26; HRMS (ESI^+) calcd for $C_{25}H_{30}N_1O_3$ $(M+H)^+$ 392.2220, found 392.2218.



24e

(±)-3,6,7-Trimethoxy-14a-methyl-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinoline (24e). Following the general procedure for the synthesis of (±)-13a-methyl tylophora alkaloids and purification of the crude product by column chromatography on silica gel (DCM/MeOH = 100:1 to 100:3) to afford **24e** (428.0 mg, 91%) as a yellow solid, M.p. 178.0–181.3 °C. *Rf* = 0.32 (CH_2Cl_2/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 2932, 2859, 1611, 1511, 1467, 1415, 1369, 1292, 1257, 1234, 1203, 1168, 1137, 1037, 840, 810, 781, 733, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1H), 7.91 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 9.0, 2.5 Hz, 1H), 7.14 (s, 1H), 4.14 (d, J = 16.2 Hz, 1H), 4.09 (s, 3H), 4.05 (s, 3H), 4.00 (s, 3H), 3.91 (d, J = 16.2 Hz, 1H), 3.10 (d, J

= 16.6 Hz, 1H), 2.95 (d, *J* = 16.6 Hz, 1H), 2.95–2.86 (m, 1H), 2.70–2.58 (m, 1H), 1.90–1.60 (m, 6H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.46, 149.31, 148.11, 130.35, 125.36, 125.15, 124.87, 123.20, 123.08, 114.62, 104.58, 103.90, 102.96, 55.92, 55.85, 55.44, 51.90, 51.63, 50.08, 39.88, 39.37, 26.18, 20.56, 14.06; HRMS (ESI$^+$) calcd for $C_{25}H_{30}N_1O_3$ $(M+H)^+$ 392.2220, found 392.2230.

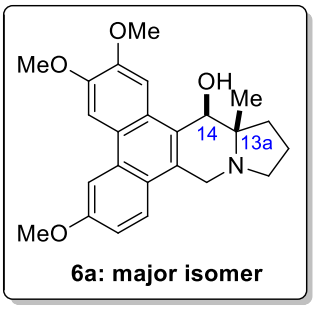


24f

(±)-2,3,6,7-Tetramethoxy-14a-methyl-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinoline (24f). Following the general procedure for the synthesis of (±)-13a-methyl tylophora alkaloids and purification of the crude product by column chromatography on silica gel (DCM/MeOH = 100:51 to 20:1) to afford **24f** (471.2 mg, 93%) as a yellow solid, M.p. 188.7–190.6 °C. *Rf* = 0.22 (CH_2Cl_2/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 2932, 2833, 1619, 1512, 1466, 1440, 1423, 1368, 1246, 1211, 1196, 1149, 1044, 1019, 860, 838, 807, 769, 731, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.28 (s, 1H), 7.14 (s, 1H), 4.15 (d, *J* = 16.1 Hz, 1H), 4.10 (s, 6H), 4.06 (s, 3H), 4.04 (s, 3H), 3.91 (d, *J* = 16.1 Hz, 1H), 3.07 (d, *J* = 16.3 Hz, 1H), 2.97–2.88 (m, 1H), 2.88 (d, *J* = 16.3 Hz, 1H), 2.70–2.57 (m, 1H), 1.91–1.60 (m, 6H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.48, 148.24, 148.14, 125.56, 124.57, 123.93, 123.79, 123.46, 123.07, 103.64, 103.29, 103.23, 102.86, 55.86, 55.85, 55.74, 51.81, 51.63, 49.99, 39.89, 39.42, 26.13, 20.52, 13.98; HRMS (ESI$^+$) calcd for $C_{26}H_{32}N_1O_4$ $(M+H)^+$ 422.2326, found 422.2329.

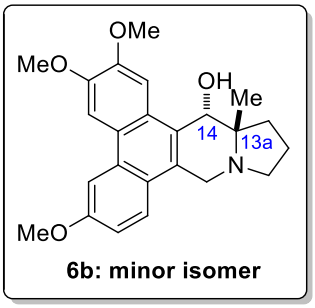
1.8 Preparation of (±)-hypoestestatin 2 (6a) and its diastereomer (6b)

A solution of ketone **18a** (100 mg, 0.26 mmol, 1.0 equiv.) in MeOH (4 mL) at 0 °C was added $NaBH_4$ (100.0 mg, 97% purity, 2.6 mmol, 10 equiv.) in a small portion over 1 h. The mixture was warmed to room temperature and stirred for the additional 11 h. The reaction was cooled down under ice-bath, quenched with sat. NH_4Cl (3 mL), and extracted with DCM (2 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude products (*dr* = 5:1) were purified by column chromatography on silica gel (DCM/MeOH = 50:1 to 9:1) to afford compound **6a** (82.0 mg, 82%) as a white solid, and **6b** (16.2 mg, 16%) as a yellow solid.



6a: major isomer

(13a*S,14*R**)-2,3,6-Trimethoxy-13a-methyl-9,11,12,13,13a,14-hexahydrodibenzo[f,h]pyrrolo-[1,2-b] isoquinolin-14-ol (6a).** M.p. 125.0–126.6 °C. *Rf* = 0.22 (CH_2Cl_2/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 3517, 2961, 2932, 2832, 1615, 1510, 1467, 1369, 1304, 1254, 1232, 1202, 1140, 1127, 1041, 919, 856, 834, 813, 788, 732, 701; ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.96 (s, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.78 (d, J = 9.1 Hz, 1H), 7.16 (dd, J = 9.1, 2.5 Hz, 1H), 5.19 (s, 1H), 4.24 (d, J = 15.8 Hz, 1H), 4.06 (d, J = 15.8 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.10–3.00 (m, 1H), 2.98–2.80 (m, 1H), 2.13–1.85 (m, 4H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.73, 150.09, 149.80, 132.29, 129.12, 128.44, 127.86, 126.15, 125.87, 124.62, 116.82, 108.68, 105.15, 105.09, 74.74, 65.07, 56.39, 56.24, 55.90, 52.08, 48.68, 39.31, 21.54, 12.64; HRMS (ESI$^+$) calcd for $C_{24}H_{28}N_1O_4$ $(M+H)^+$ 394.2018, found 394.2020.

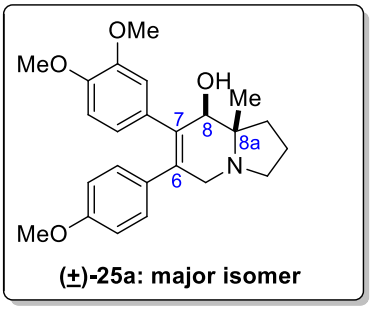


6b: minor isomer

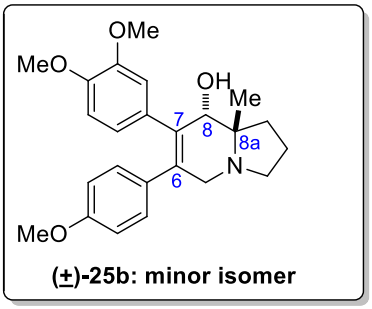
(13a*S,14*S**)-2,3,6-Trimethoxy-13a-methyl-9,11,12,13,13a,14-hexahydrodibenzo[f,h]pyrrolo-[1,2-b] isoquinolin-14-ol (6b).** M.p. 128.2–130.0 °C. *Rf* = 0.44 (CH_2Cl_2/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 3389, 2956, 2928, 2831, 1616, 1511, 1468, 1305, 1255, 1234, 1203, 1169, 1129, 1041, 903, 853, 833, 809, 787, 734, 702; ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.31 (d, J = 9.0 Hz, 1H), 6.95 (dd, J = 9.0, 2.5 Hz, 1H), 4.78 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 3.76 (d, J = 16.0 Hz, 1H), 3.50 (d, J =16.0 Hz, 1H), 3.20–3.06 (m, 1H), 2.68–2.48 (m, 2H), 2.05–1.85 (m, 2H), 1.68–1.58 (m, 1H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.63, 150.82, 149.90, 132.15, 128.50, 127.84, 127.46, 125.70, 125.50, 124.12, 116.52, 106.43, 105.14, 105.06, 70.42, 63.94, 56.47, 56.29, 55.82, 51.83, 48.79, 32.75, 21.03, 13.64; HRMS (ESI$^+$) calcd for $C_{24}H_{28}N_1O_4$ $(M+H)^+$ 394.2018, found 394.2019.

1.9 Preparation of (±)-seco-hypoestestatin 2 ((±)-25a) and its diastereomer ((±)-25b)

A solution of ketone **17a** (100.0 mg, 0.25 mmol, 1.0 equiv.) and anhydrous $CeCl_3$ (67.9 mg, 0.28 mmol, 1.1 equiv.) in anhydrous MeOH (6 mL) was slowly added $NaBH_4$ (20.0 mg, 0.51 mmol, 2.0 equiv.) in a small portion at 0 °C over 1 h, and the mixture was warmed to room temperature and stirred for the additional 11 h. The reaction was quenched with sat. NH_4Cl (2 mL), and extracted with DCM (2 x 20 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude product (*dr* = 5:1) was purified by column chromatography on silica gel using (DCM/MeOH = 50:1 to 50:4) to afford compound **(±)-25a** (78.0 mg, 79%) as a yellow oil, and **(±)-25b** (16.0 mg, 16%) as a yellow oil.



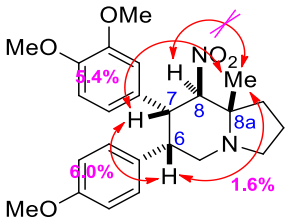
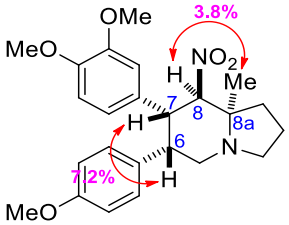
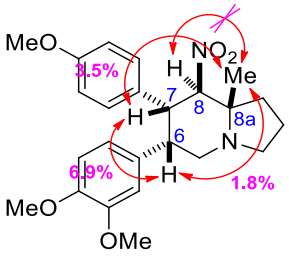
(8*R,8a*S**)-7-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-8a-methyl-1,2,3,5,8,8a-hexahydroindolizin-8-ol ((±)-25a).** *Rf* = 0.30 (DCM/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 3530, 2958, 2930, 1607, 1579, 1510, 1464, 1408, 1246, 1172, 1139, 1029, 914, 831, 766, 732; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.67 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.52 (d, *J* =1.7 Hz, 1H), 4.55 (br t, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.55 (dd, *J* = 17.0, 3.1 Hz, 1H), 3.46 (dd, *J* = 17.0, 2.0 Hz, 1H), 3.20–3.10 (m, 1H), 2.83–2.70 (m, 1H), 2.07–1.87 (m, 4H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.06, 148.48, 147.73, 135.84, 133.80, 132.67, 129.96, 129.40, 121.81, 113.65, 113.30, 110.82, 75.78, 61.82, 55.69, 55.63, 55.08, 52.14, 50.27, 37.66, 20.50, 9.62; HRMS (ESI^+) calcd for $C_{24}H_{30}N_1O_4$ $(M+H)^+$ 396.2169, found 396.2165.

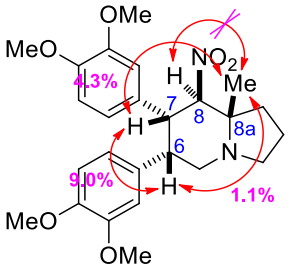
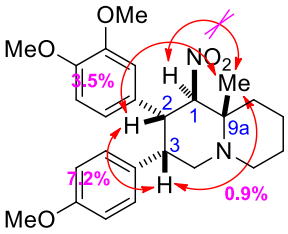
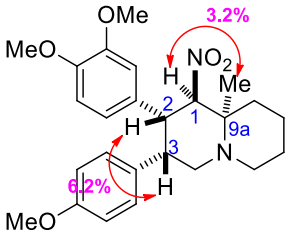
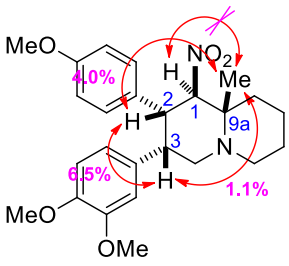
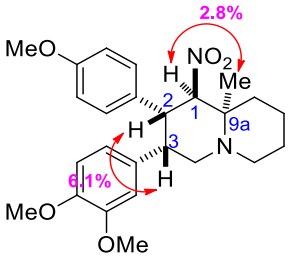


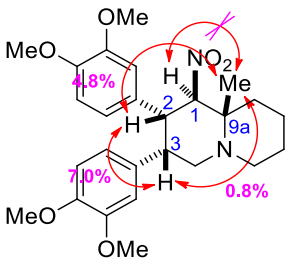
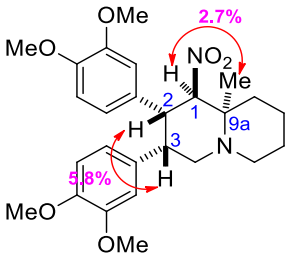
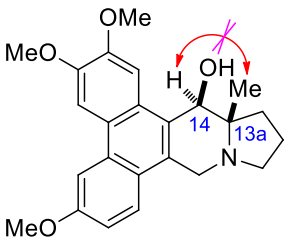
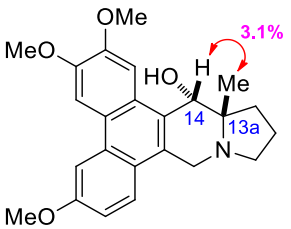
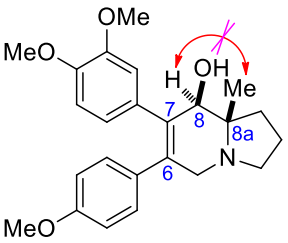
(8*S,8a*S**)-7-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-8a-methyl-1,2,3,5,8,8a-hexahydroindolizin-8-ol ((±)-25b).** *Rf* = 0.33 (DCM/MeOH = 20:1); IR (UATR) ν_{max}/cm^{-1} 3421, 2957, 2835, 1607, 1579, 1509, 1464, 1408, 1245, 1169, 1140, 1028, 914, 831, 766, 730;

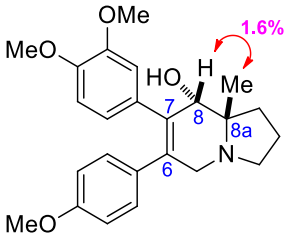
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 8.3, 1.9 Hz, 1H), 6.70 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 1.9 Hz, 1H), 4.03 (br s, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.65 (d, J = 17.4 Hz, 1H), 3.59 (s, 3H), 3.26 (d, J = 17.4 Hz, 1H), 3.21–3.10 (m, 1H), 2.61 (q, J = 8.6 Hz, 1H), 2.51 (br s, 1H), 2.45–2.30 (m, 1H), 1.95–1.80 (m, 2H), 1.60–1.45 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.30, 148.06, 147.42, 135.33, 134.46, 134.22, 132.66, 129.81, 121.19, 113.48, 113.26, 110.61, 74.02, 62.30, 55.70, 55.53, 55.15, 52.52, 50.19, 31.73, 20.69, 13.25; HRMS (ESI$^+$) calcd for $C_{24}H_{30}N_1O_4$ $(M+H)^+$ 396.2169, found 396.2167.

2. Summary of relative configuration of 15a-f, 6a/b, (±)-25a/b using $^{3}J_{H,H}$ coupling constants and/or NOE techniques comparing with reported values

Compound No.	Relative structure, Experiment ^{3}J and/or NOE values of Major isomer		Reference
15a	 **15a**: major isomer	$^{3}J_{H7/8}$ = 12.5 Hz $^{3}J_{H6/7}$ = 5.7 Hz	New compound
15a'	 **15a'**: minor isomer	$^{3}J_{H7/8}$ = 12.5 Hz $^{3}J_{H6/7}$ = 5.7 Hz *analyzed from the crude products (low purity)*	New compound
15b	 **15b**: major isomer	$^{3}J_{H7/8}$ = 12.5 Hz $^{3}J_{H6/7}$ = 5.8 Hz	New compound

Compound No.	Relative structure, Experiment ^3J and/or NOE values of Major isomer		Reference
15c	 **15c**: major isomer	$^3J_{H7/8}$ = 12.5 Hz $^3J_{H6/7}$ = 5.8 Hz	New compound
15d	 **15d**: major isomer	$^3J_{H1/2}$ = 12.8 Hz $^3J_{H2/3}$ = 5.7 Hz	New compound
15d'	 **15d'**: minor isomer	$^3J_{H1/2}$ = 12.6 Hz $^3J_{H2/3}$ = 5.7 Hz	New compound
15e	 **15e**: major isomer	$^3J_{H1/2}$ = 12.8 Hz $^3J_{H2/3}$ = 5.7 Hz	New compound
15e'	 **15e'**: minor isomer	$^3J_{H1/2}$ = 12.6 Hz $^3J_{H2/3}$ = 5.6 Hz	New compound

Compound No.	Relative structure, Experiment ^3J and/or NOE values of Major isomer		Reference
15f	 **15f**: major isomer	$^3J_{H1/2}$ = 12.8 Hz $^3J_{H2/3}$ = 5.6 Hz	New compound
15f'	 **15f'**: minor isomer	$^3J_{H1/2}$ = 12.6 Hz $^3J_{H2/3}$ = 5.6 Hz	New compound
6a	 **6a: major isomer**		1)
6b	 **6b: minor isomer**		1)
(±)-25a	 **(±)-25a: major isomer**		New compound

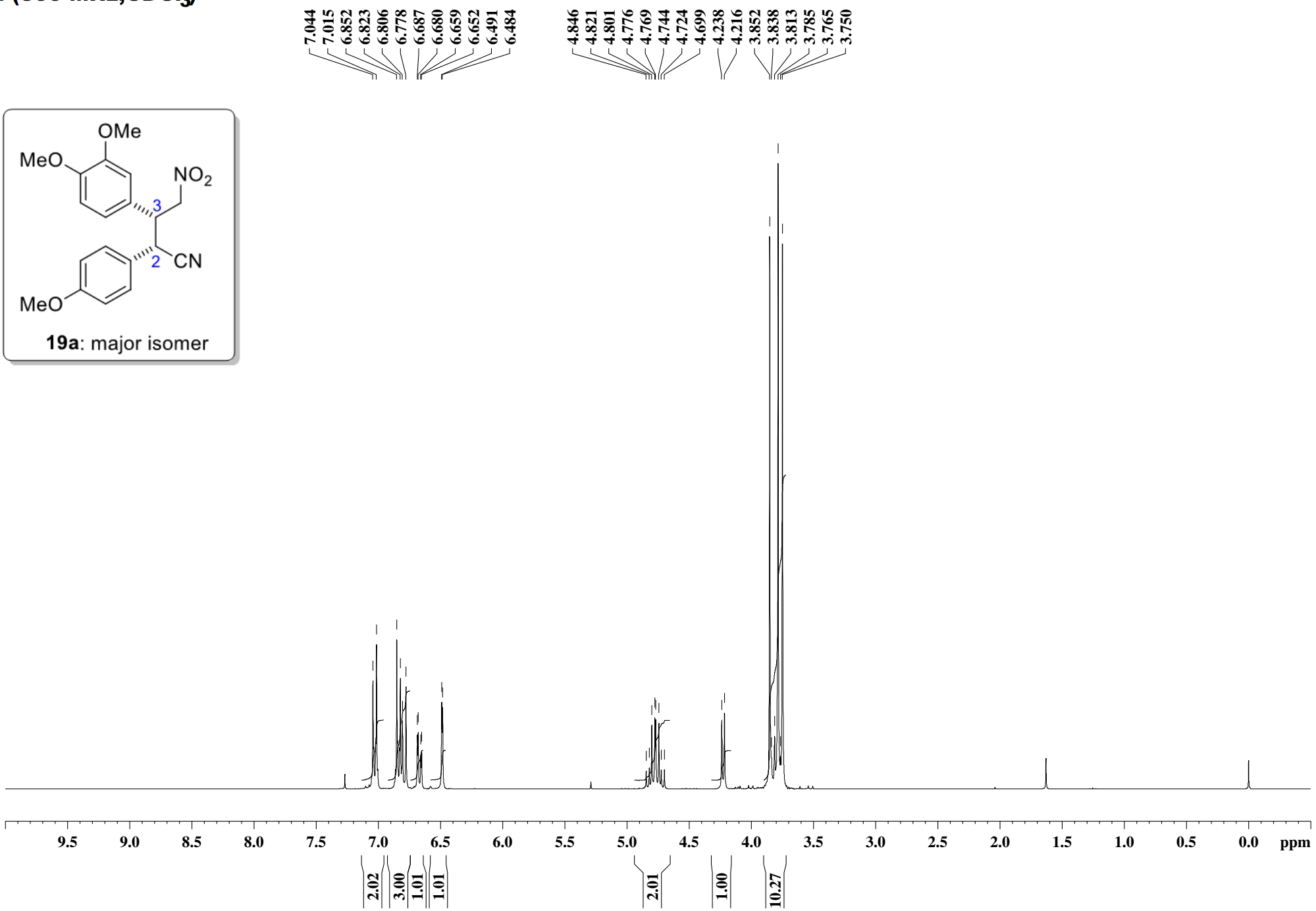
Compound No.	Relative structure, Experiment ^{3}J and/or NOE values of Major isomer	Reference
(±)-25b	 **(±)-25b: minor isomer**	New compound

3. Reference

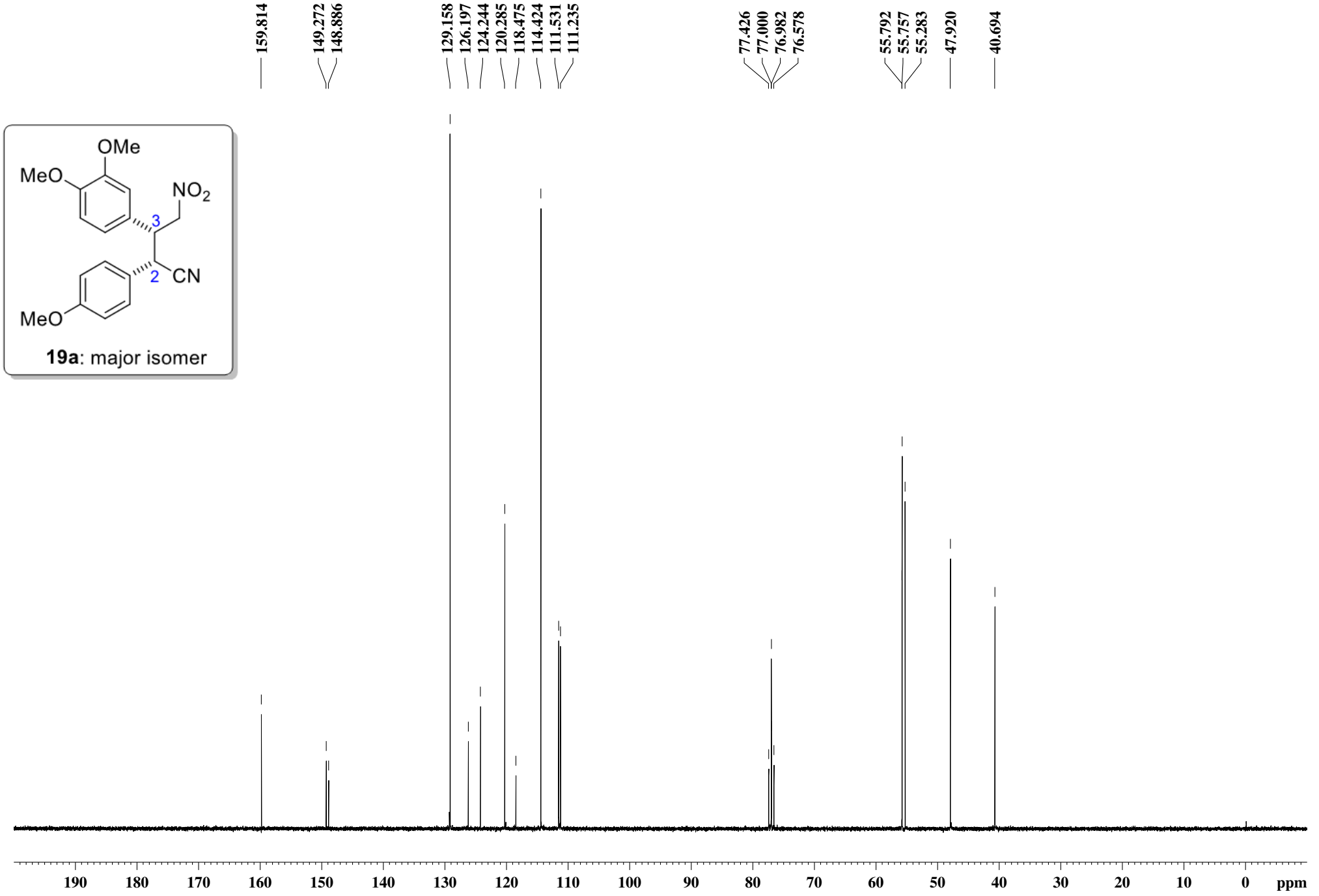
1) B. Su, M. Deng and Q. Wang, *Eur. Org. Chem.*, 2013, 1979.

4. NMR spectra of all compounds and HPLC analysis

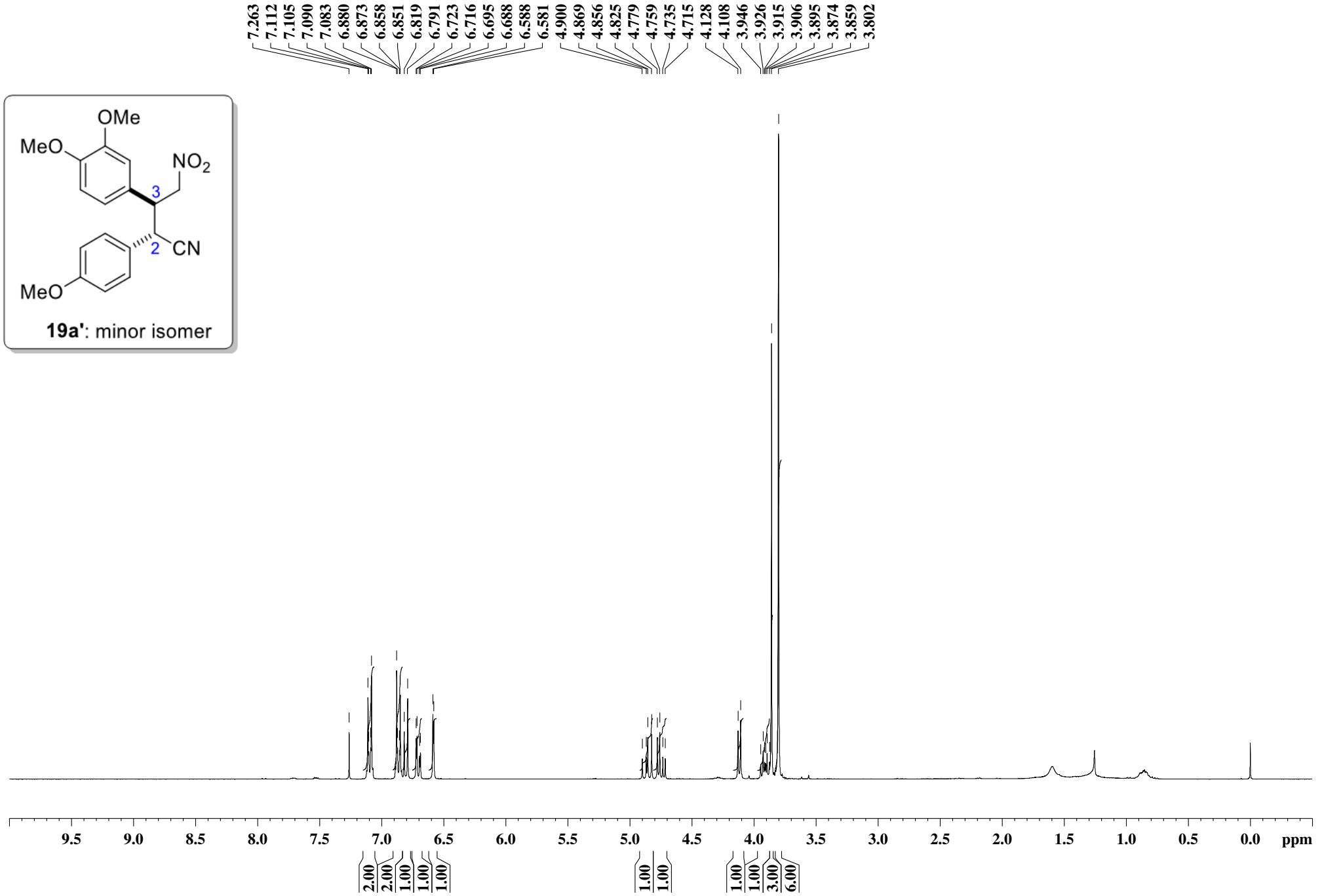
^{1}H (300 MHz,$CDCl_3$)



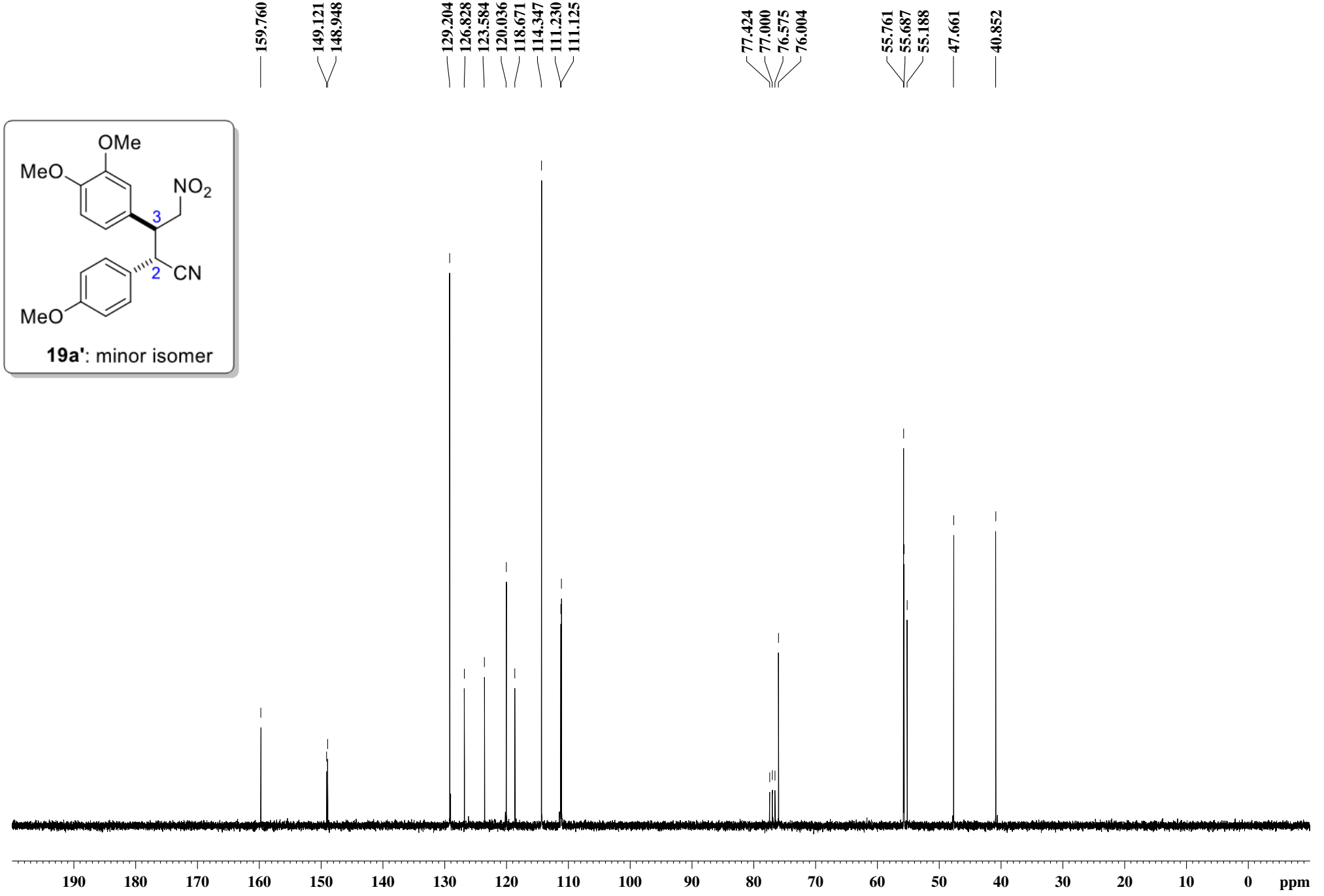
^{13}C (75 MHz, $CDCl_3$)



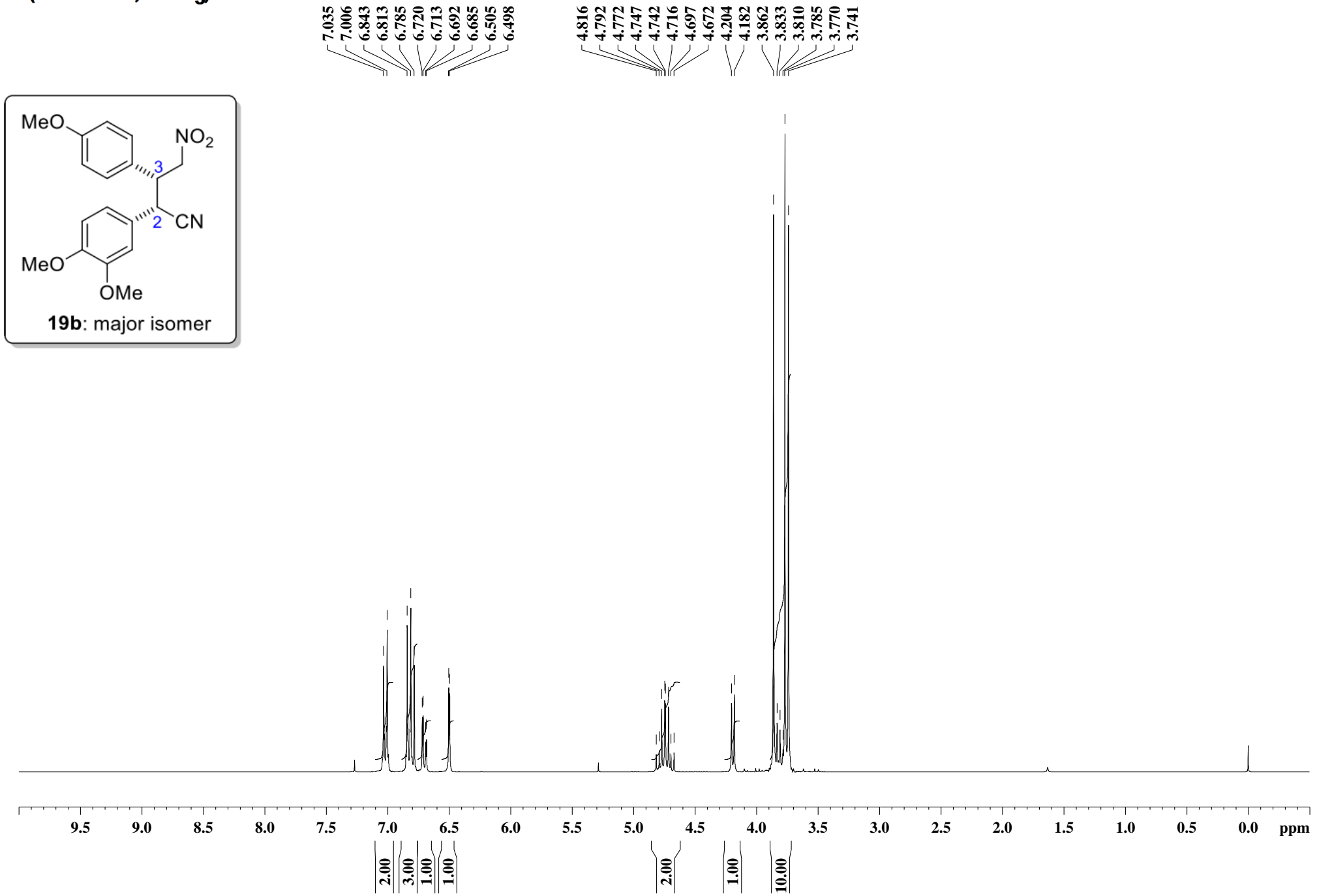
^{1}H (300 MHz,$CDCl_3$)



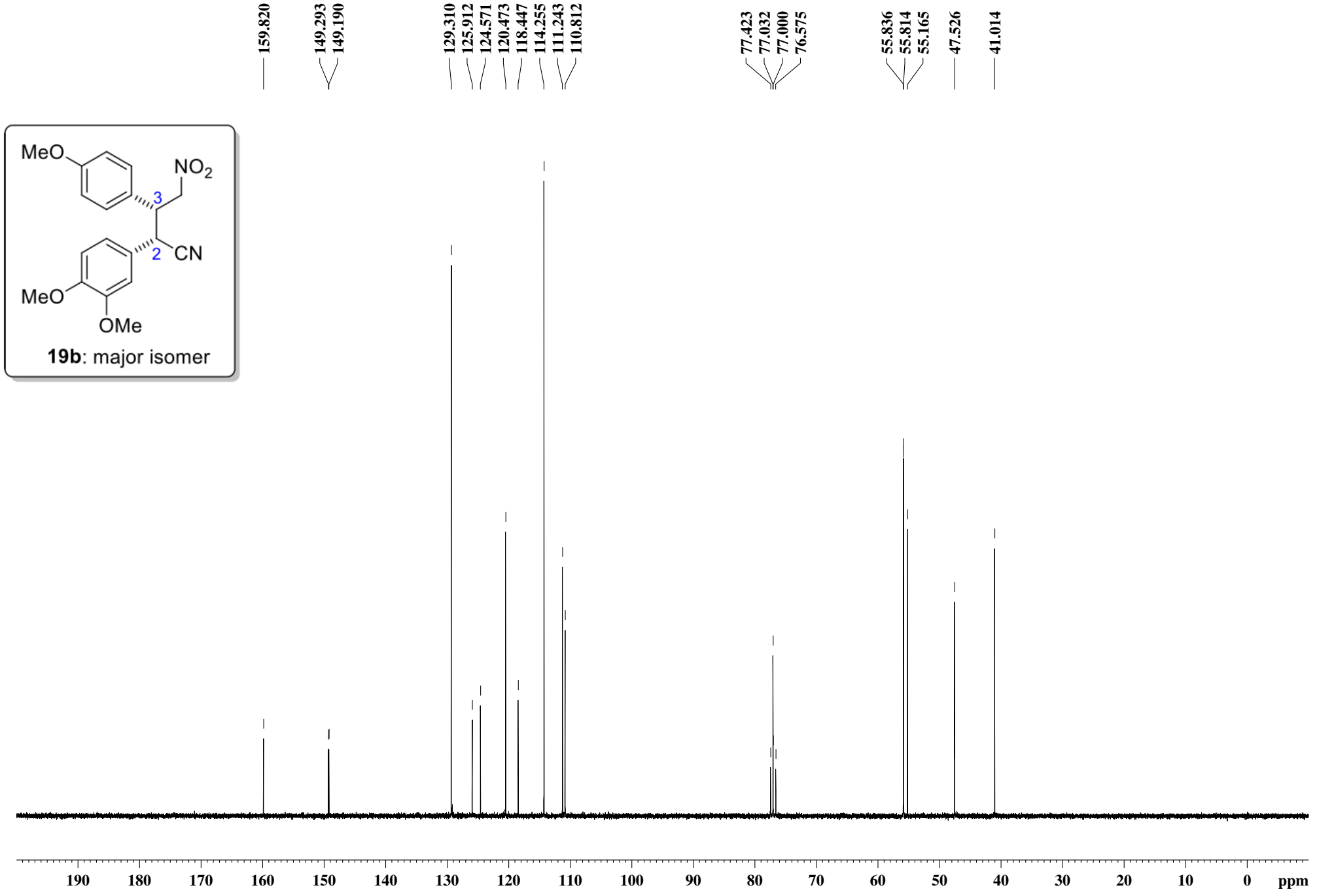
^{13}C (75 MHz, $CDCl_3$)



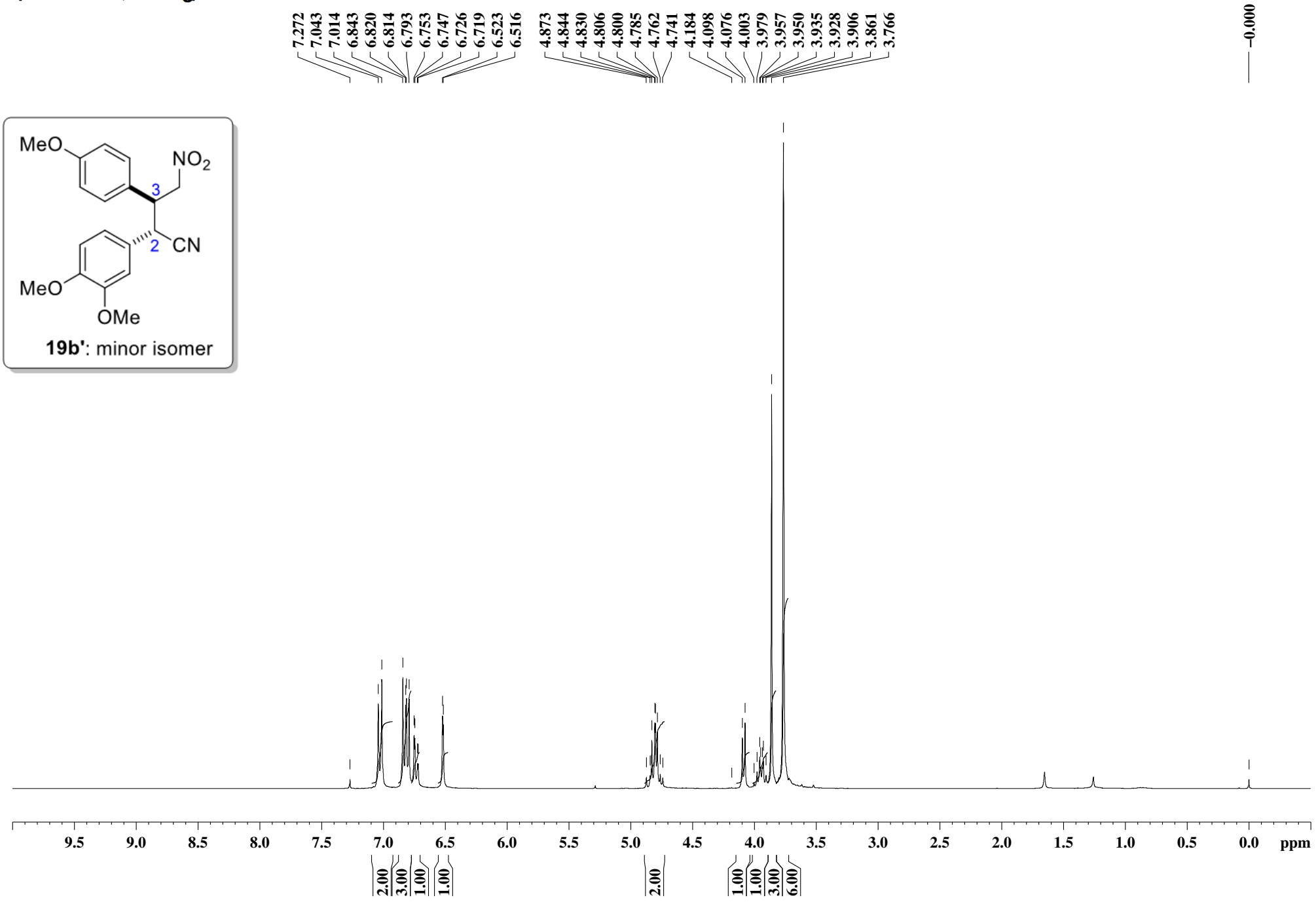
^{1}H (300 MHz,$CDCl_3$)



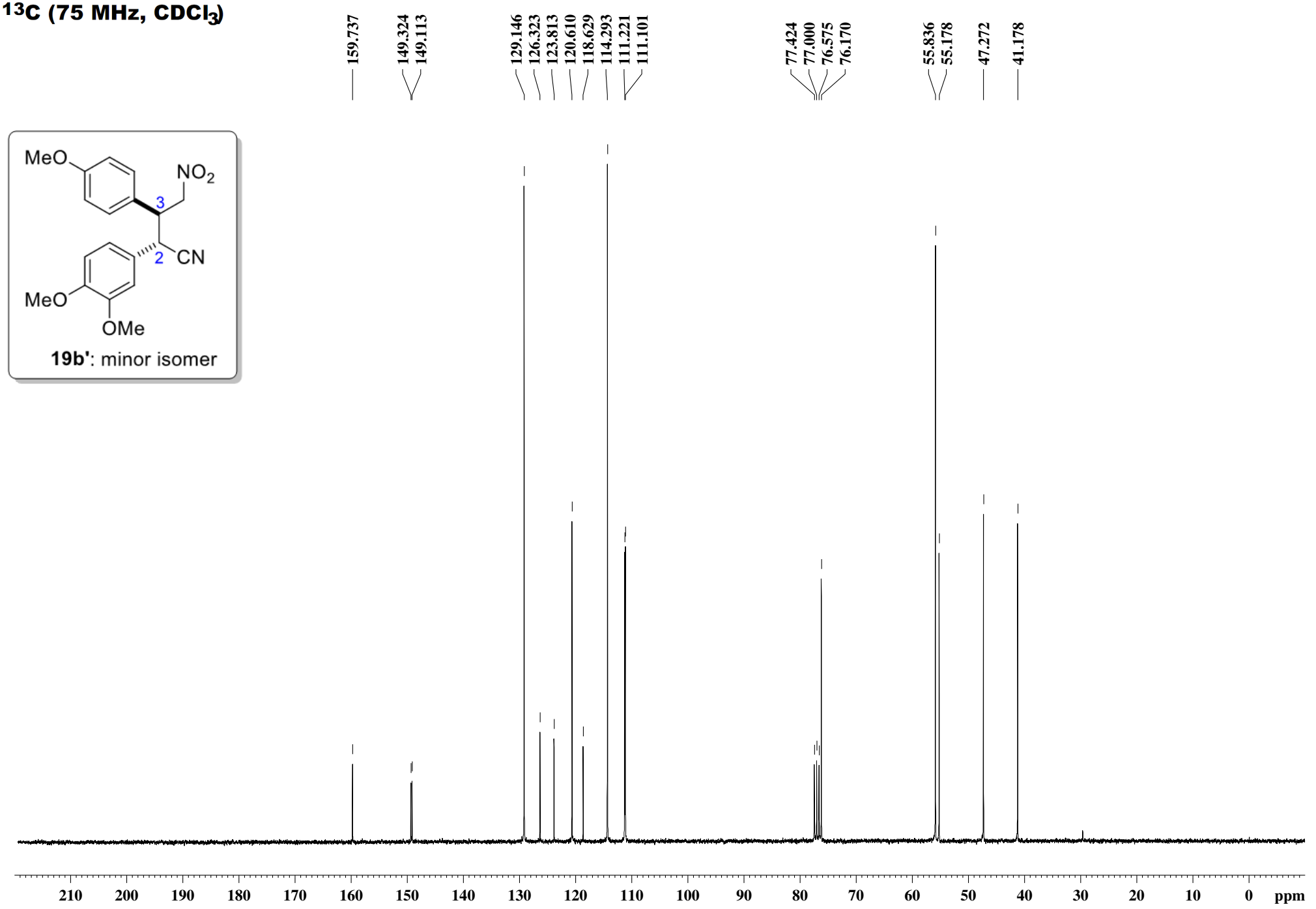
^{13}C (75 MHz, $CDCl_3$)



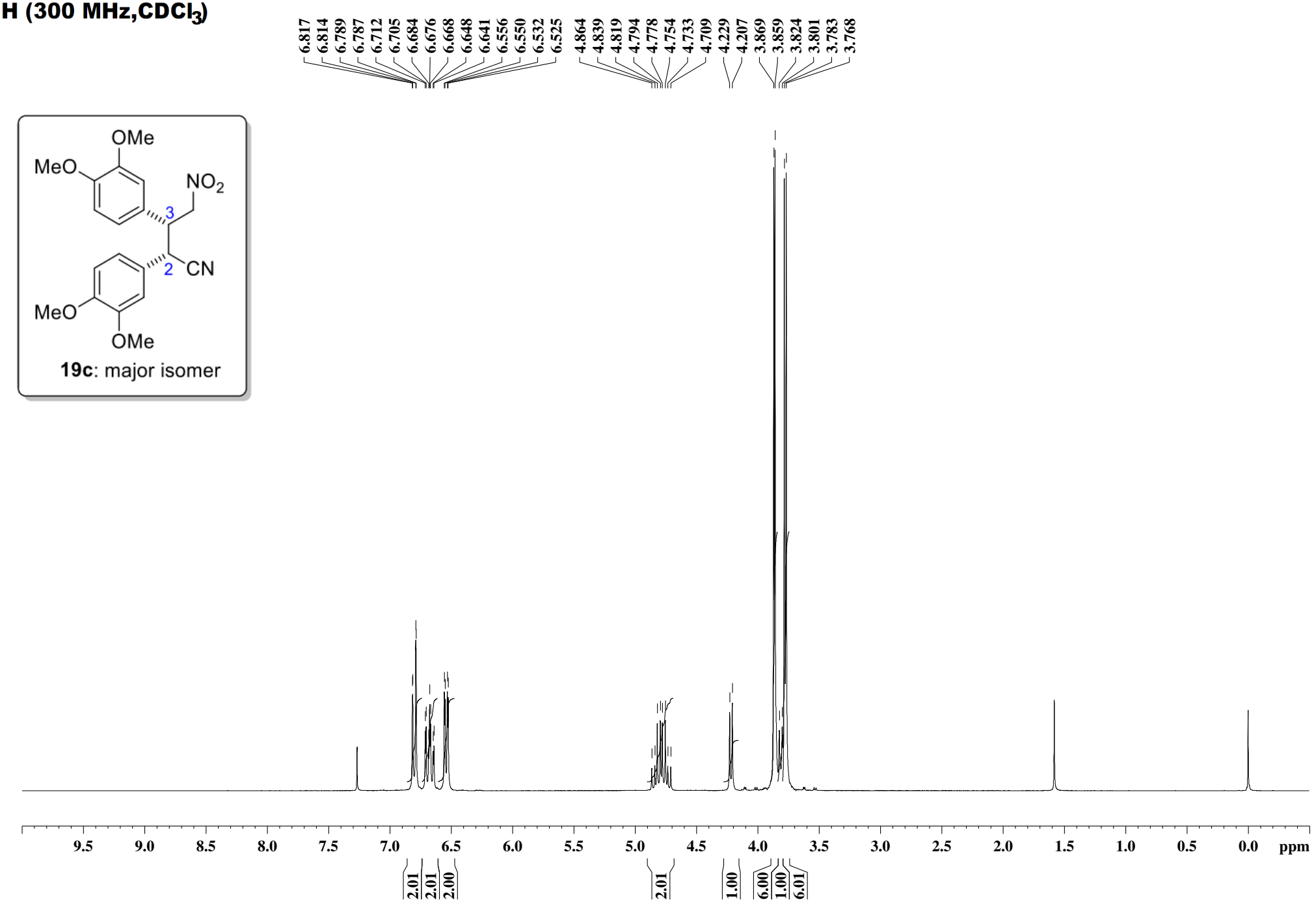
^{1}H (300 MHz,$CDCl_3$)



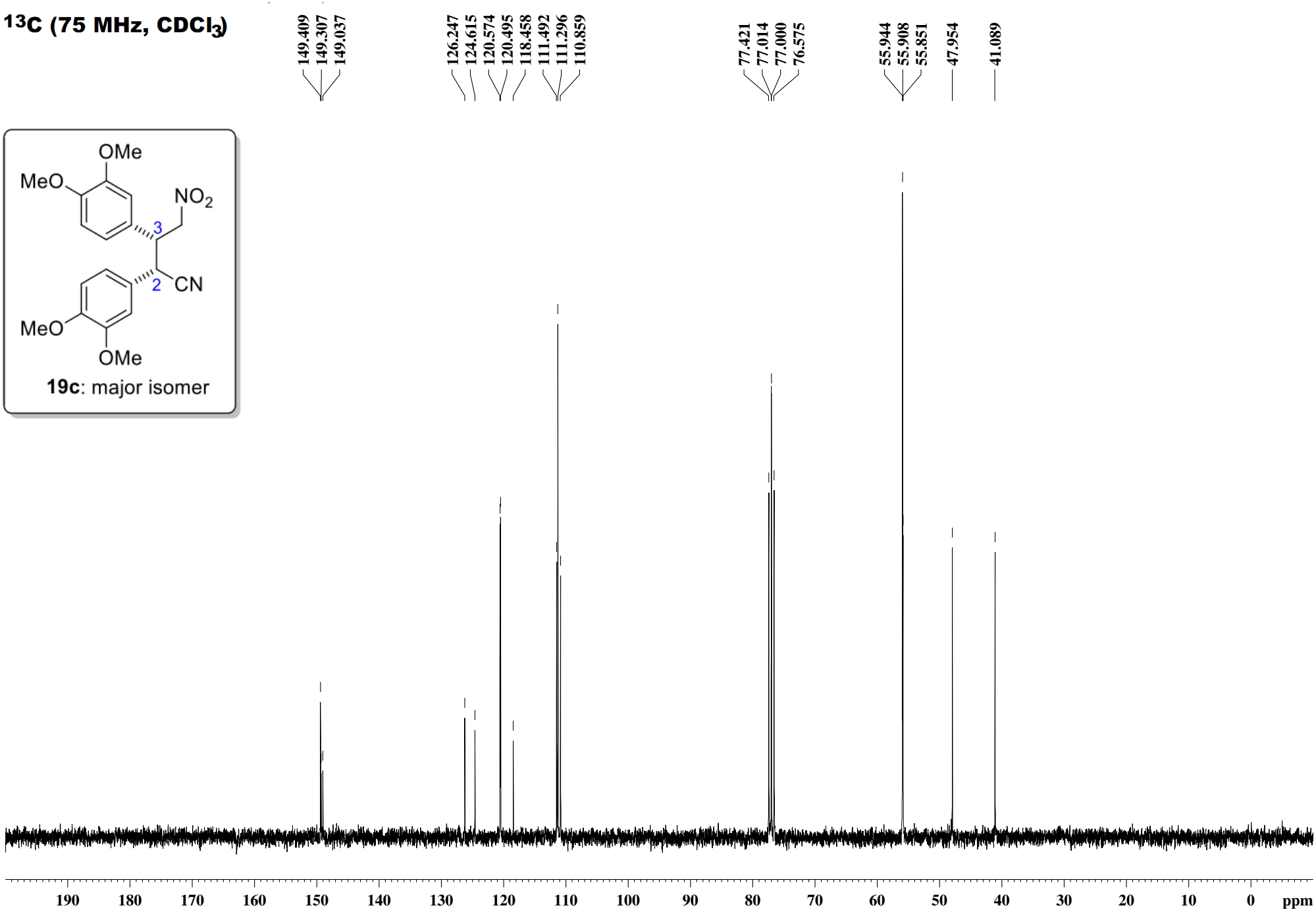
^{13}C (75 MHz, $CDCl_3$)



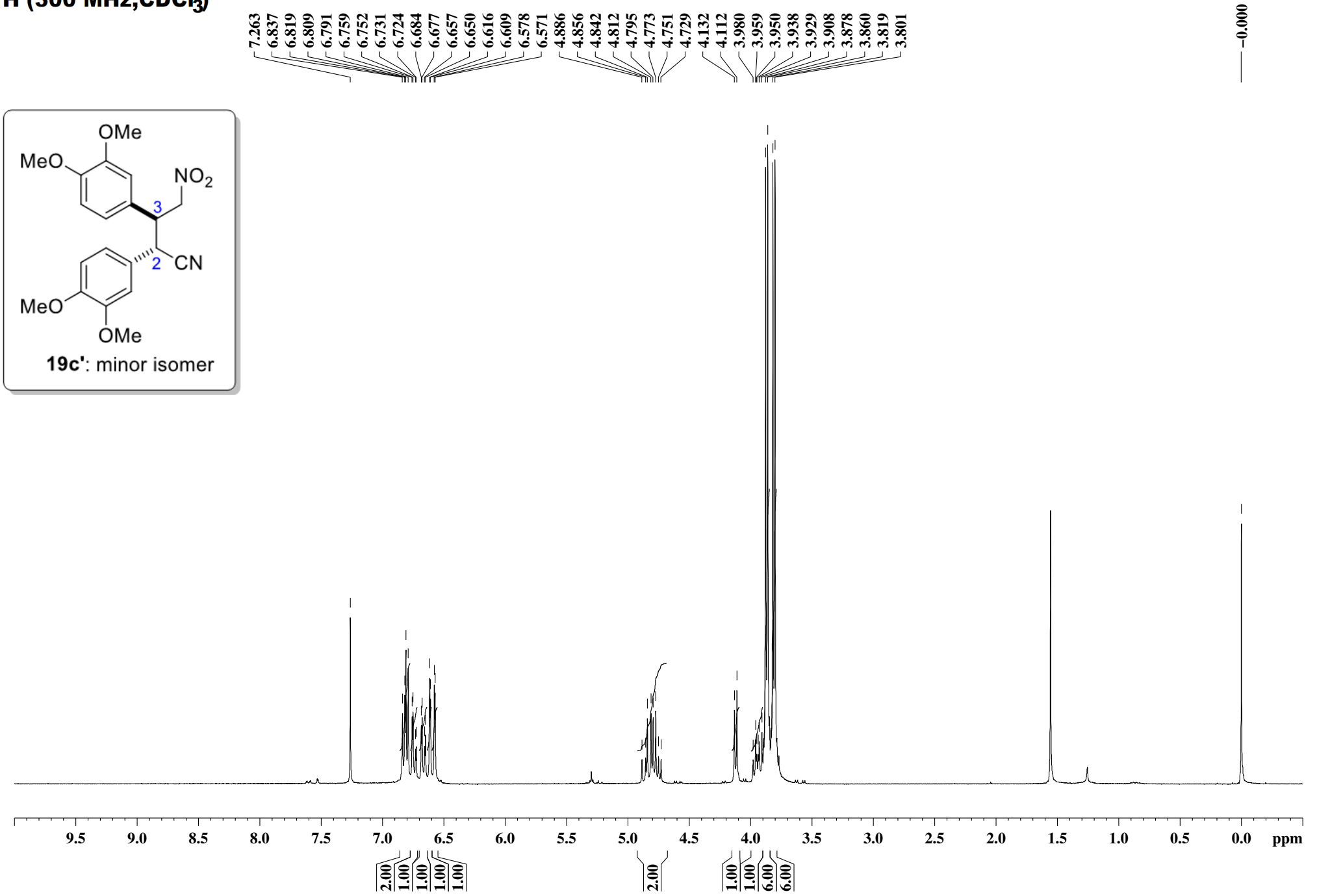
^{1}H (300 MHz,$CDCl_3$)



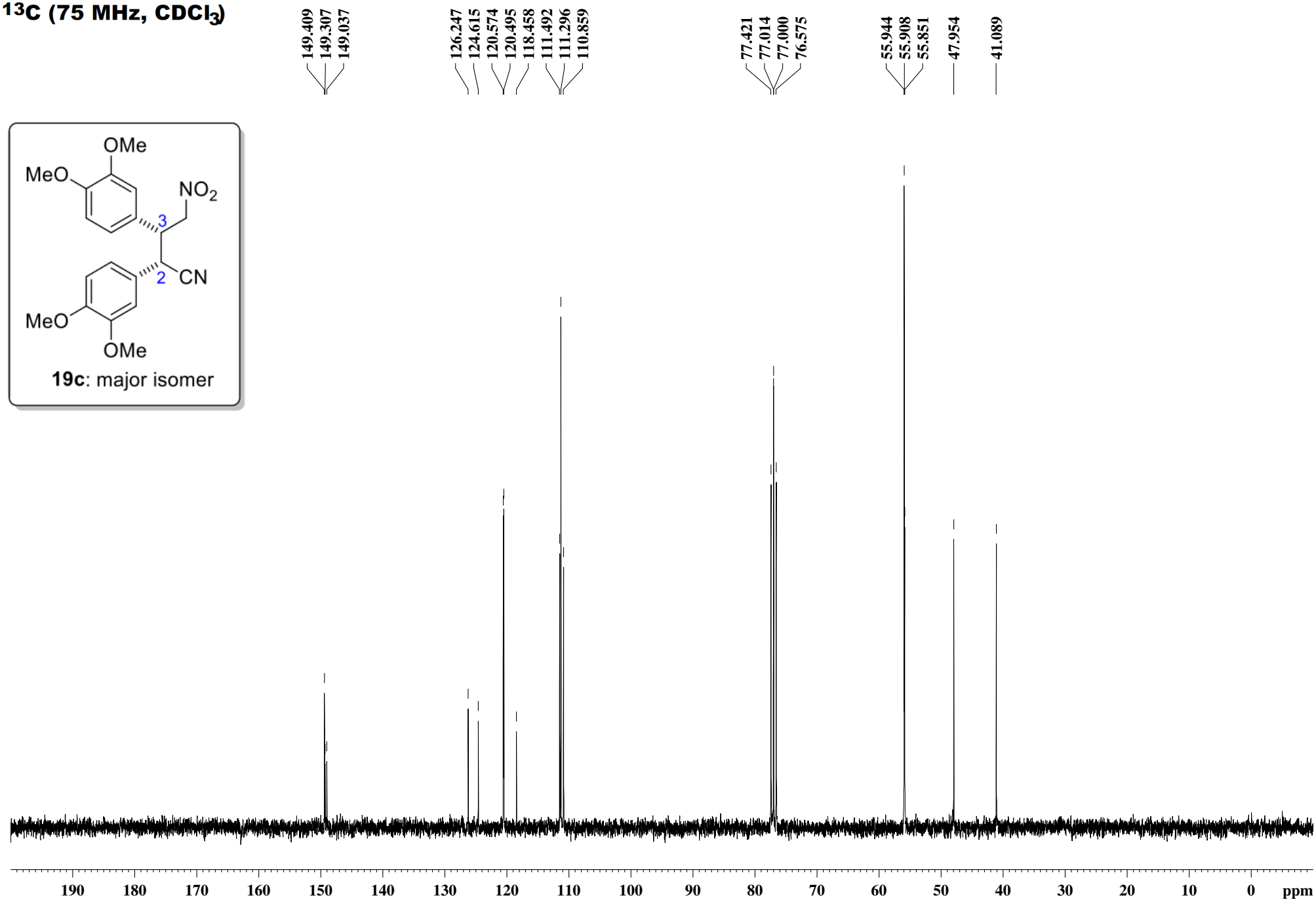
^{13}C (75 MHz, $CDCl_3$)



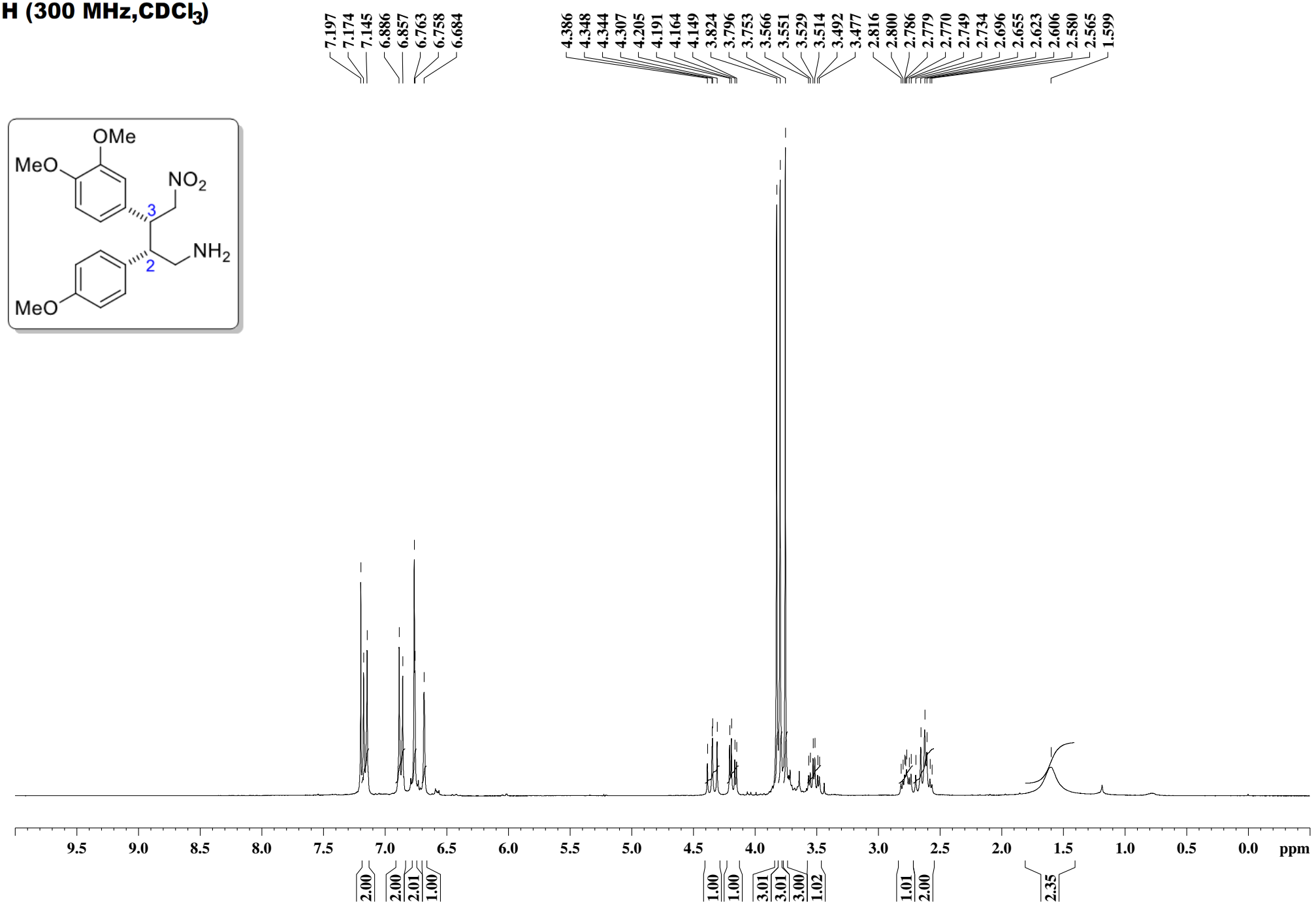
^{1}H (300 MHz,$CDCl_3$)



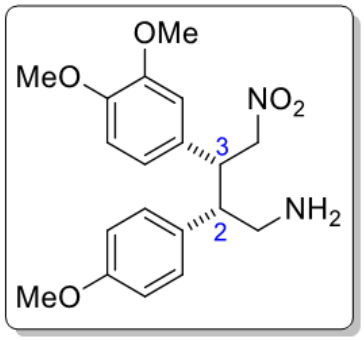
^{13}C (75 MHz, $CDCl_3$)



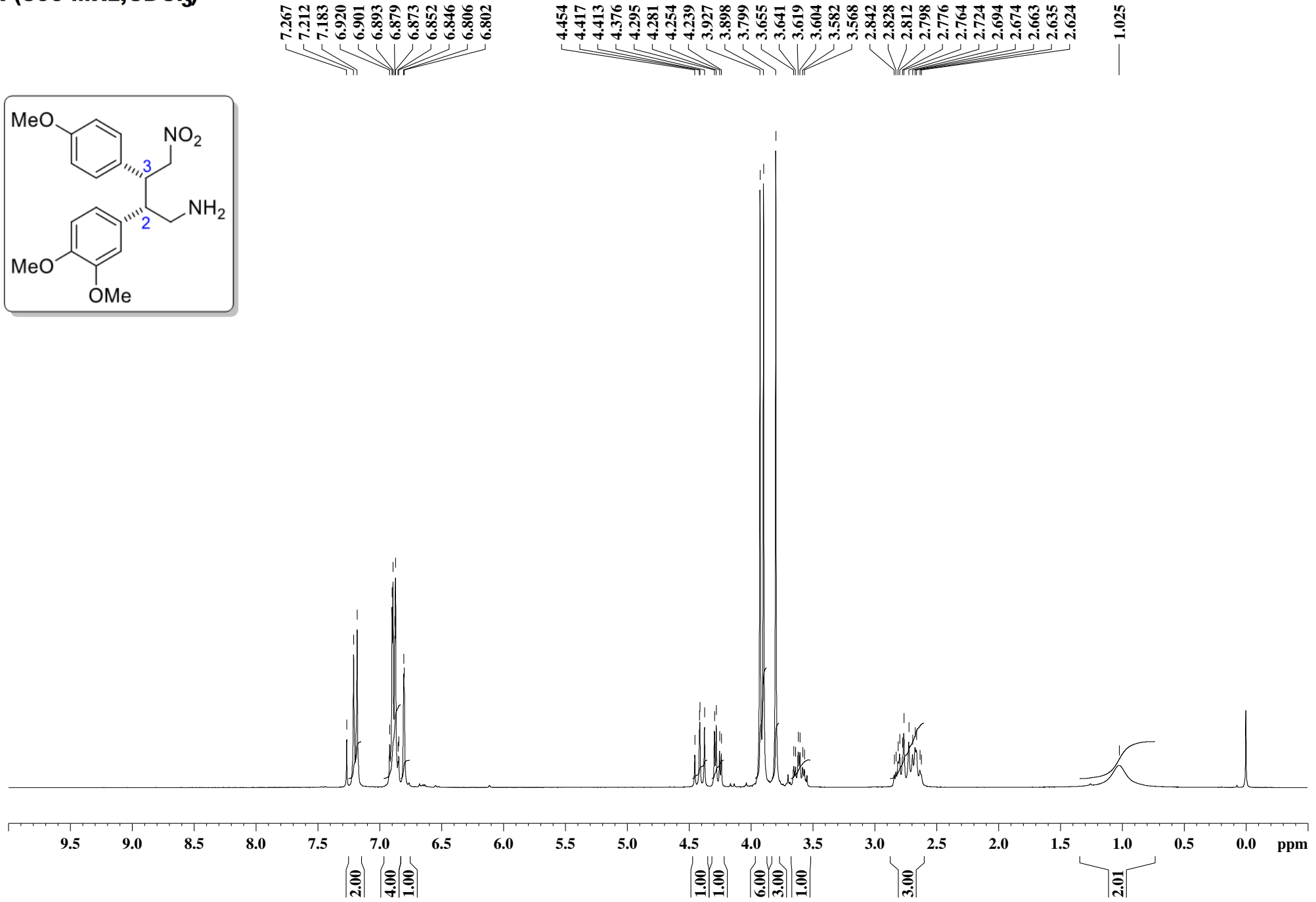
^{1}H (300 MHz,$CDCl_3$)



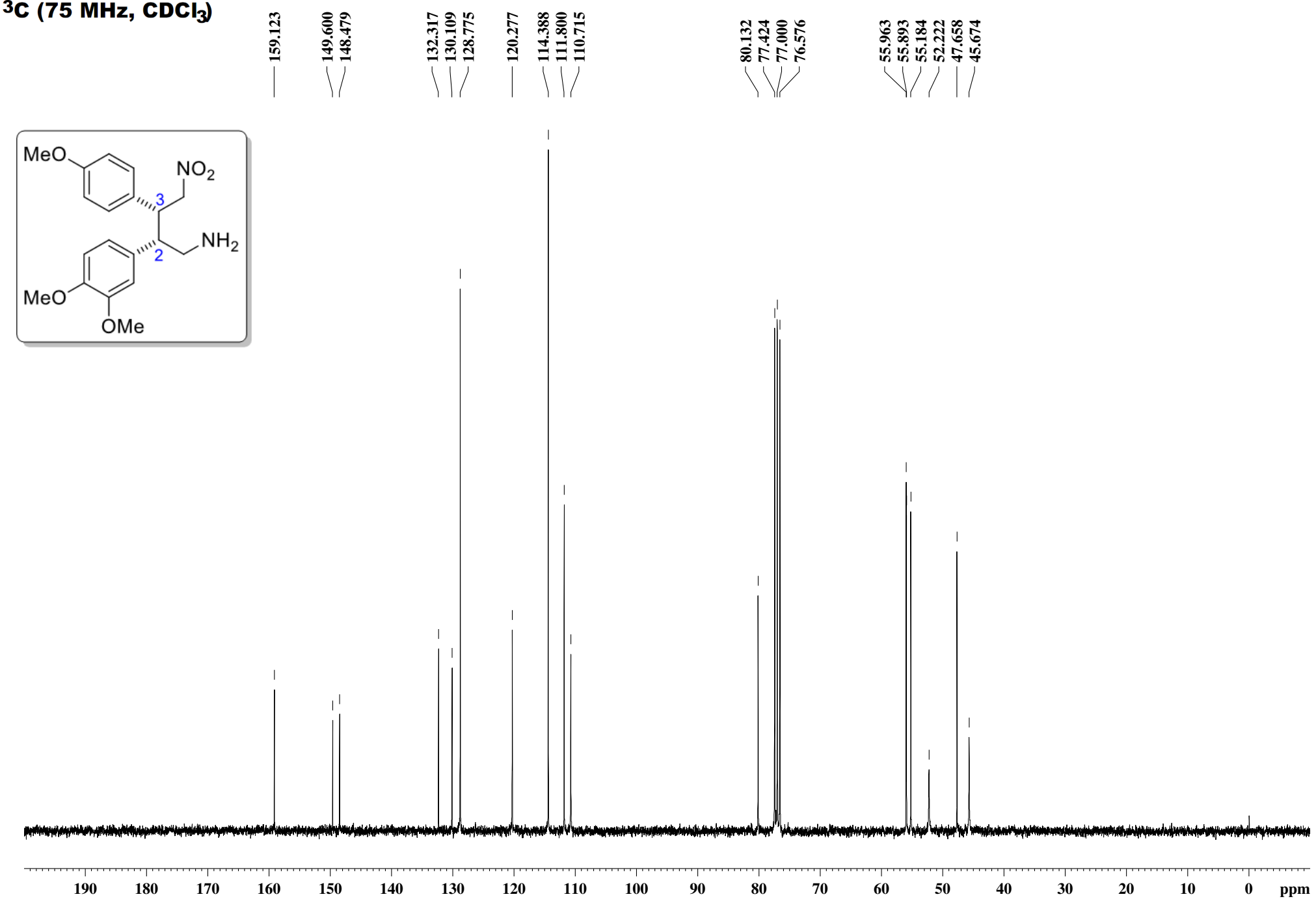
^{13}C (75 MHz, $CDCl_3$)



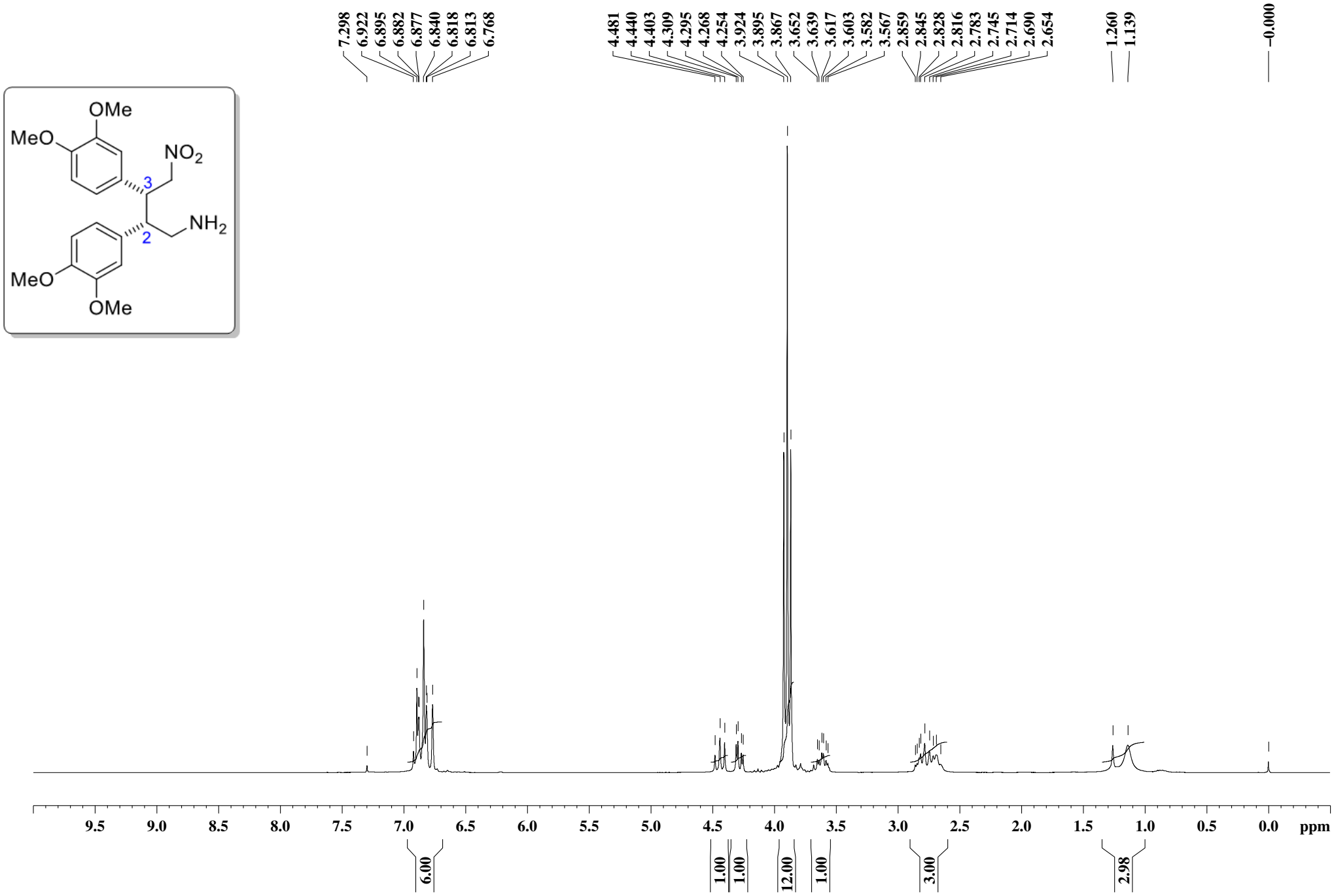
^{1}H (300 MHz,$CDCl_3$)



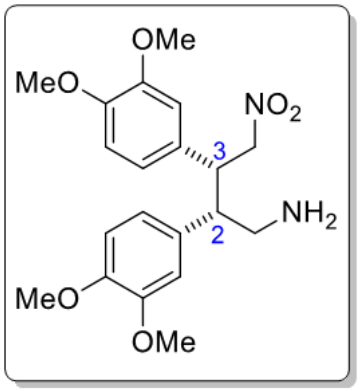
^{13}C (75 MHz, $CDCl_3$)



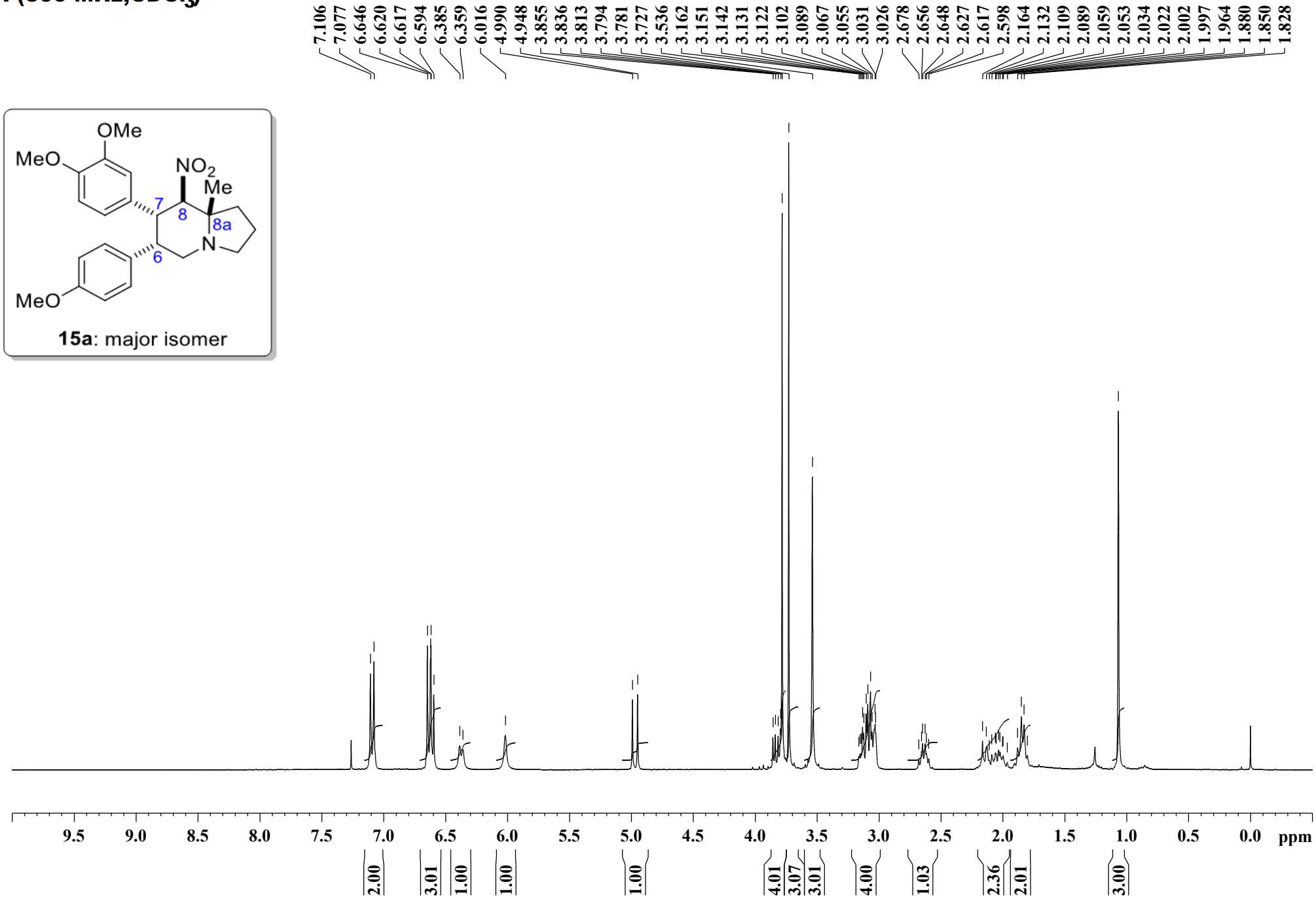
^{1}H (300 MHz,$CDCl_3$)



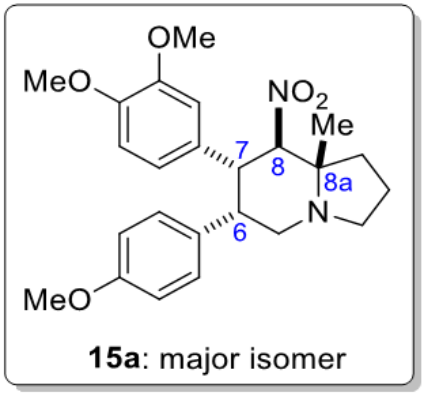
^{13}C (75 MHz, $CDCl_3$)



^{1}H (300 MHz,$CDCl_3$)

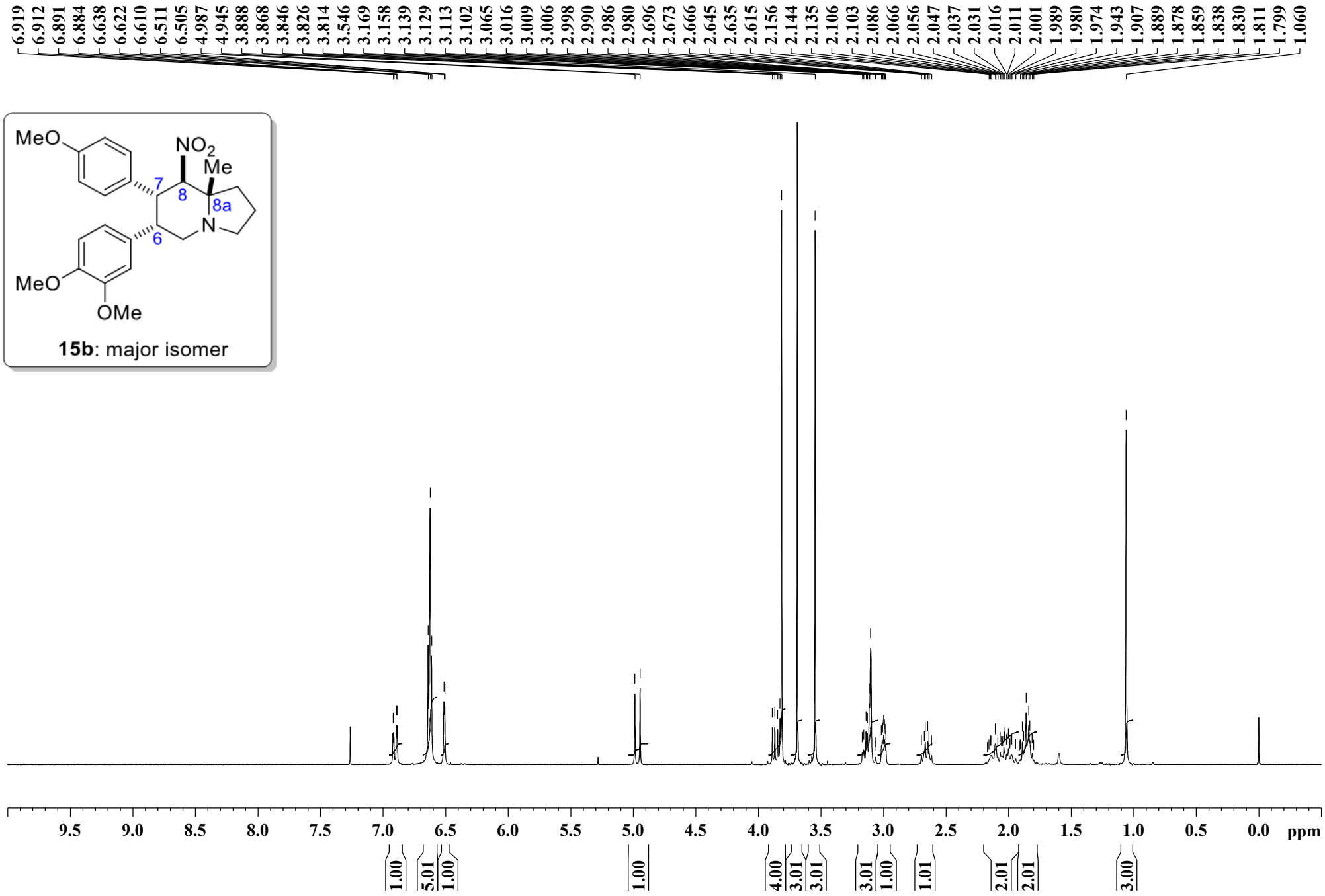


^{13}C (75 MHz, $CDCl_3$)

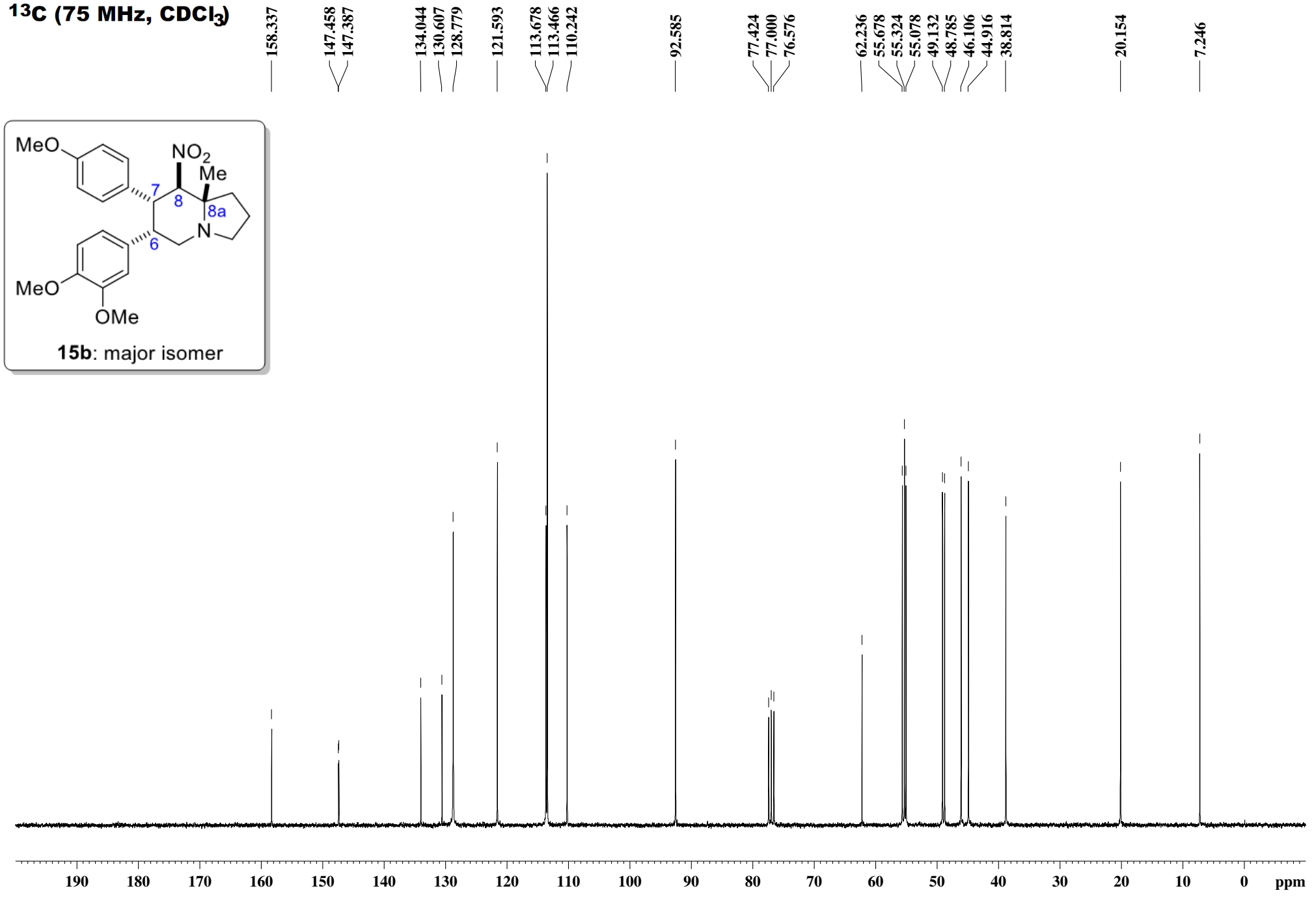


15a: major isomer

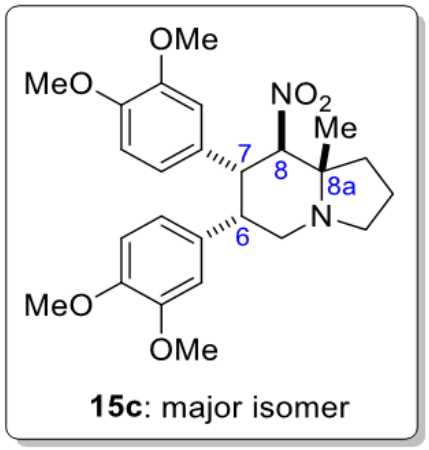
^{1}H (300 MHz,$CDCl_3$)



^{13}C (75 MHz, $CDCl_3$)



^{1}H (300 MHz,$CDCl_3$)



15c: major isomer

^{13}C (75 MHz, $CDCl_3$)

148.374
147.784
147.708
147.528
134.203
130.980
121.888
120.212
113.539
111.122
110.754
110.322
92.696
77.423
77.000
76.575
62.264
55.749
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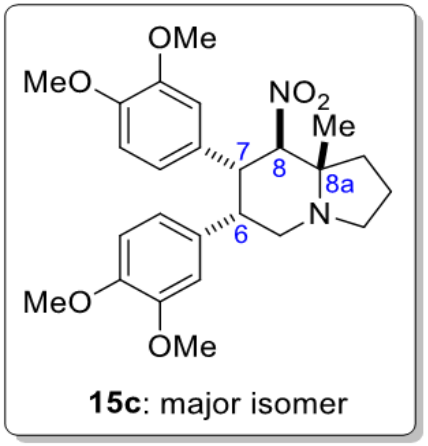
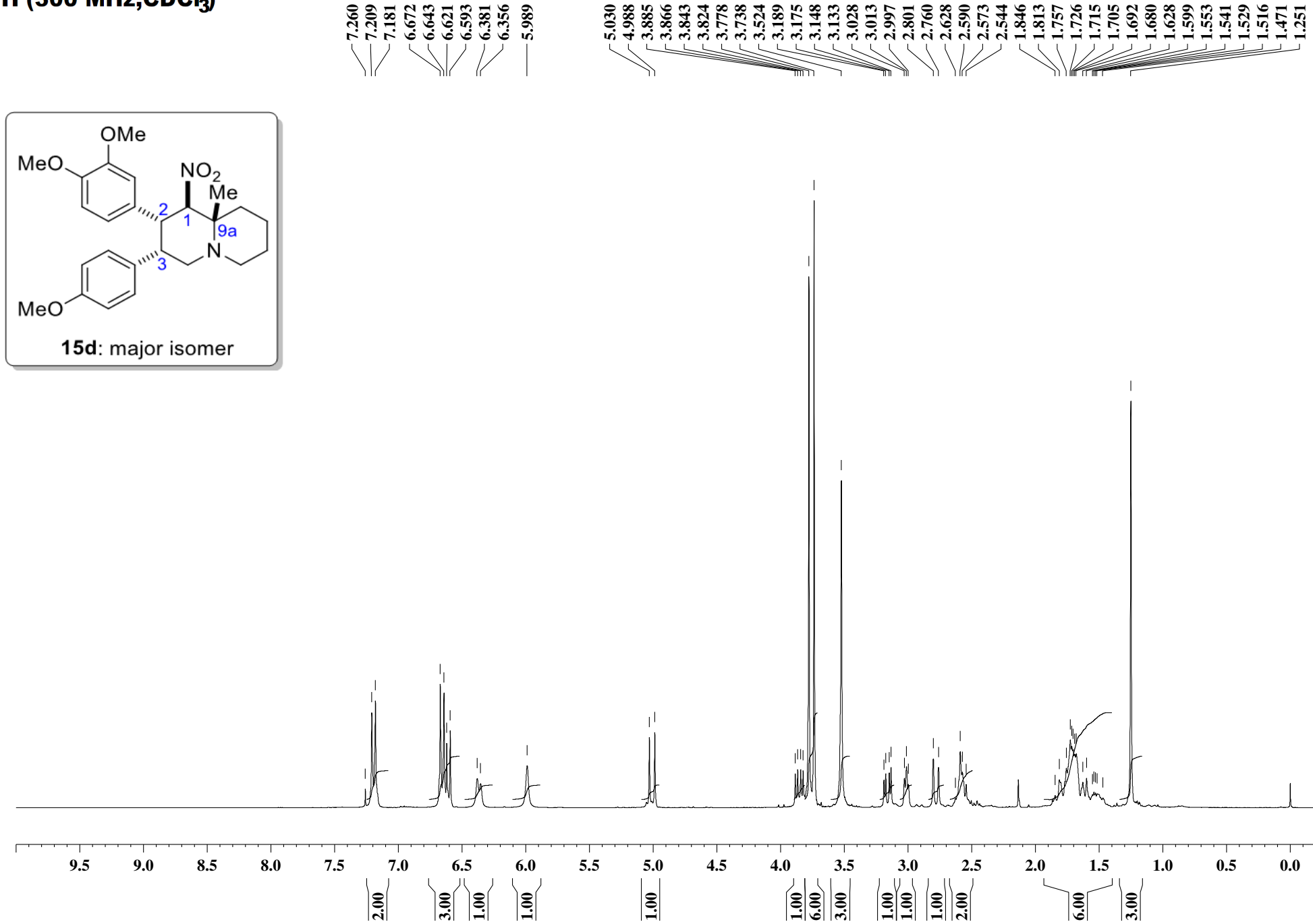
48.811
46.097
45.316
38.787
20.162
7.282

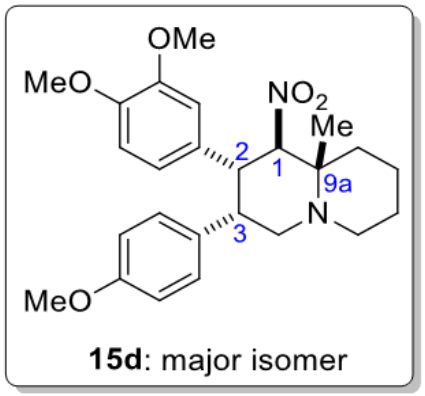


15c: major isomer

^{1}H (300 MHz,$CDCl_3$)

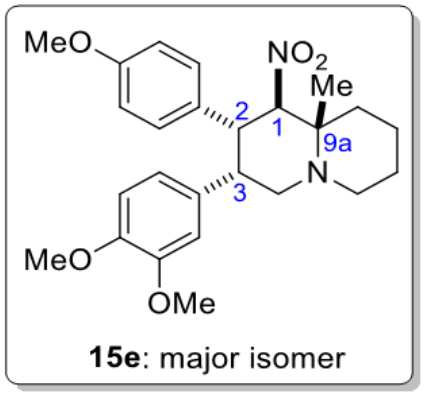


^{13}C (75 MHz, $CDCl_3$)



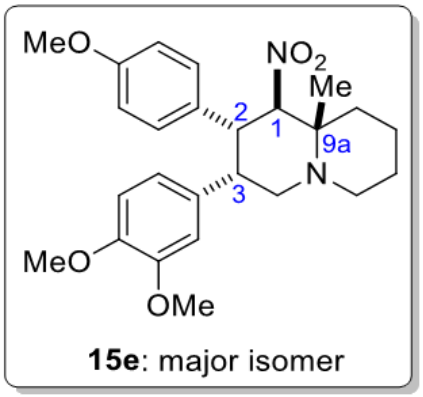
15d: major isomer

^{1}H (300 MHz,$CDCl_3$)



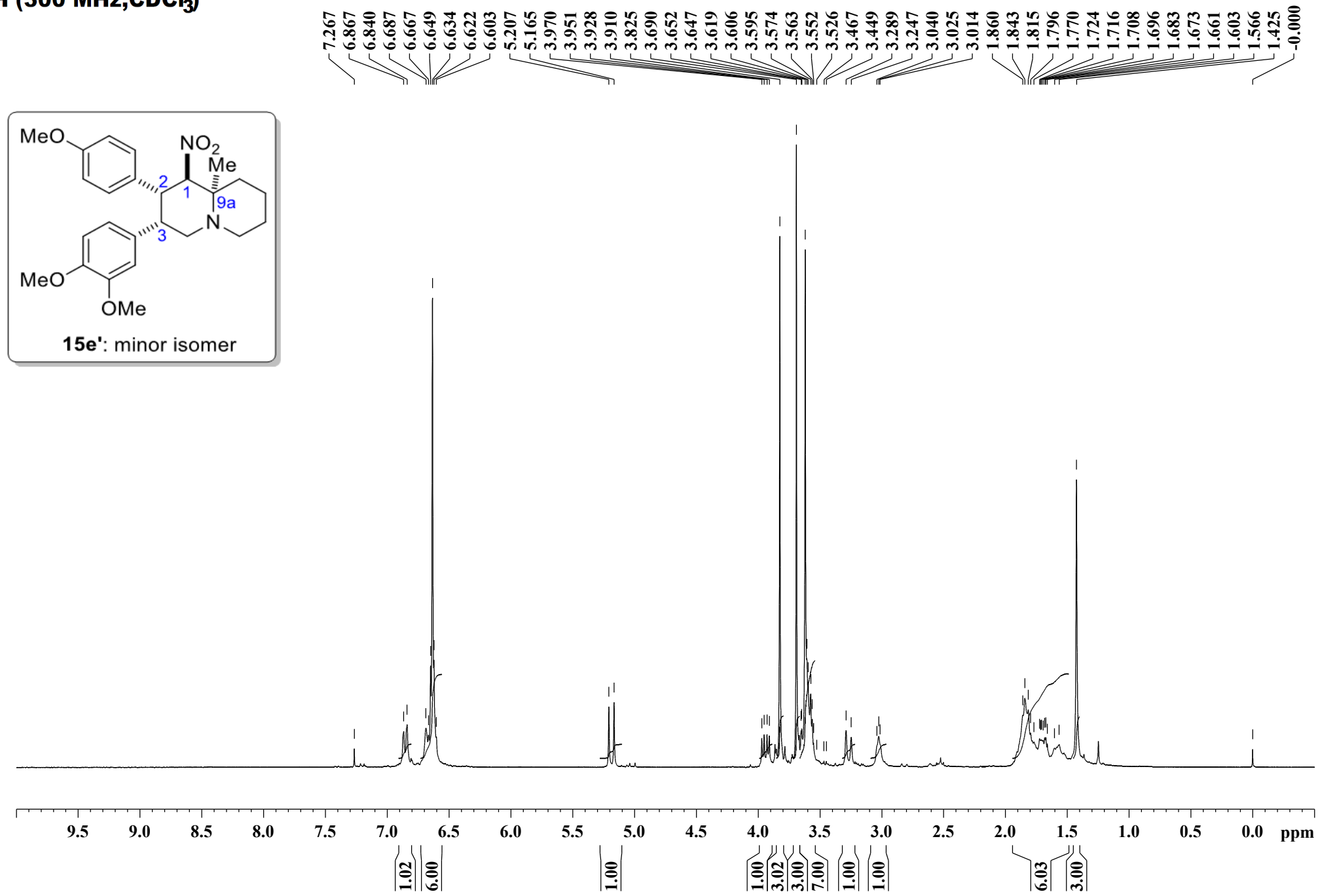
15e: major isomer

^{13}C (75 MHz, $CDCl_3$)

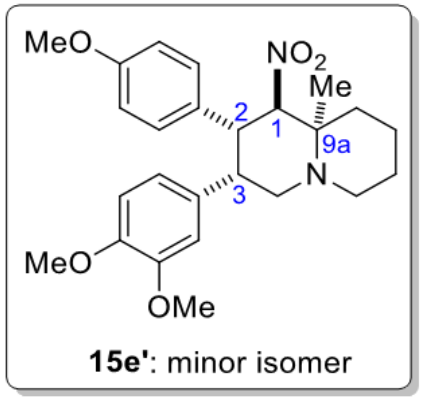


15e: major isomer

^{1}H (300 MHz,$CDCl_3$)

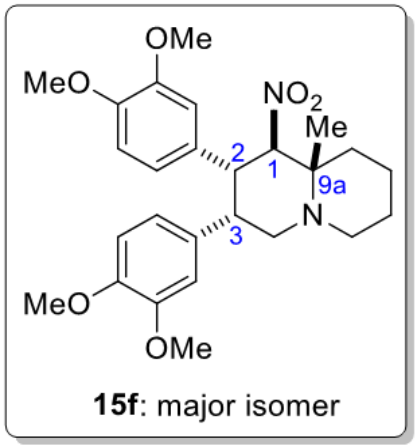


^{13}C (75 MHz, $CDCl_3$)



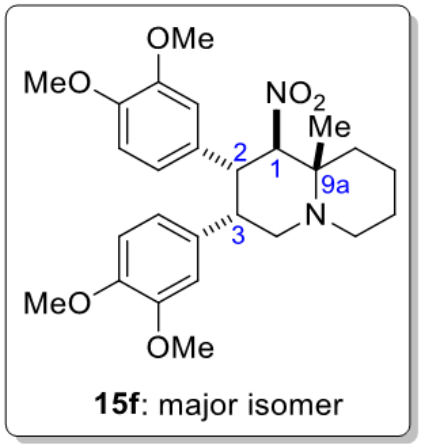
15e': minor isomer

^{1}H (300 MHz,$CDCl_3$)



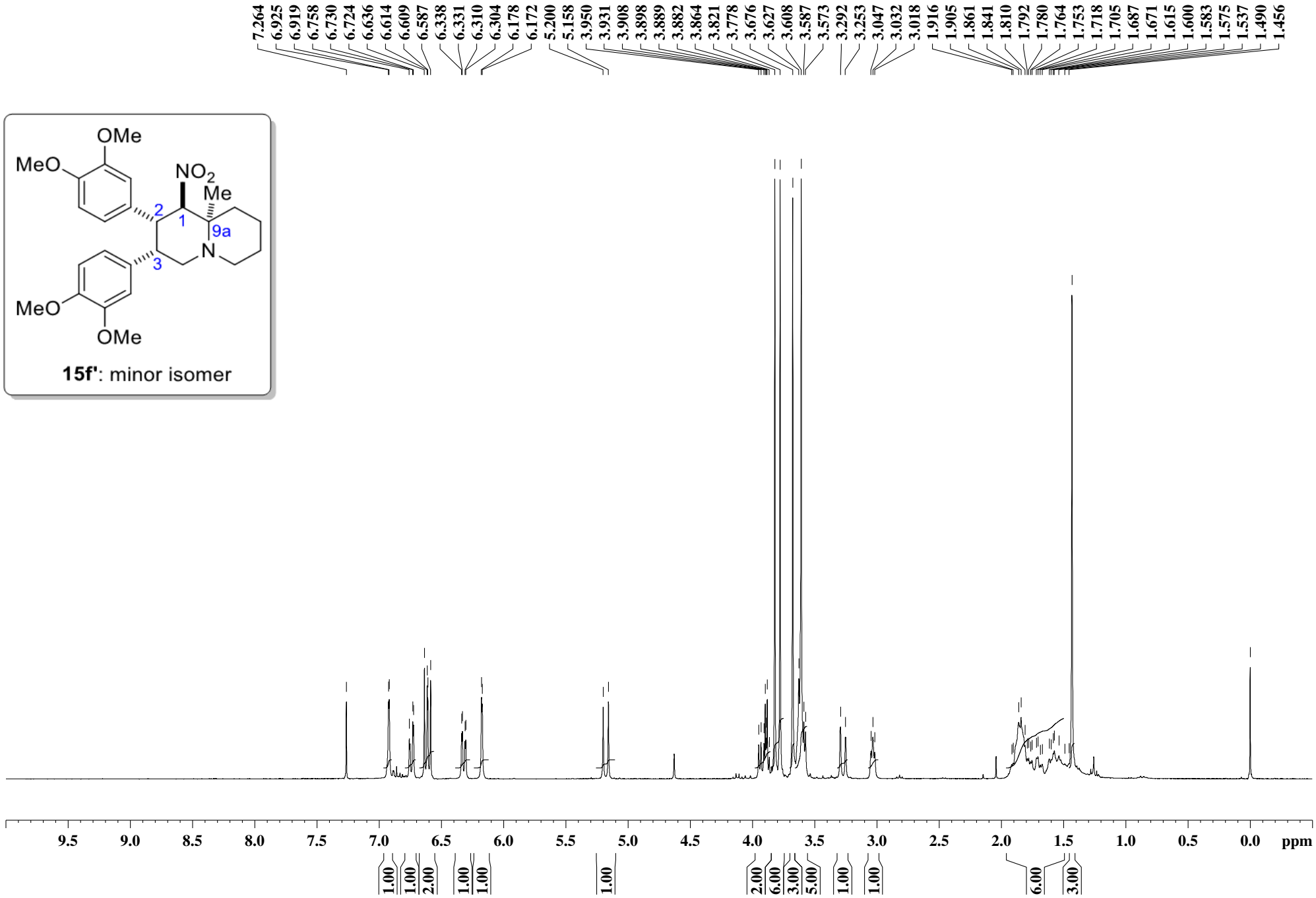
15f: major isomer

^{13}C (75 MHz, $CDCl_3$)

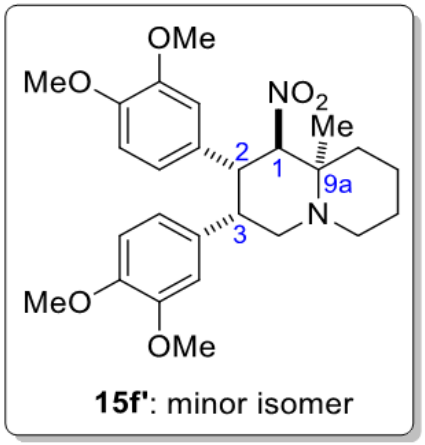


15f: major isomer

^{1}H (300 MHz,$CDCl_3$)

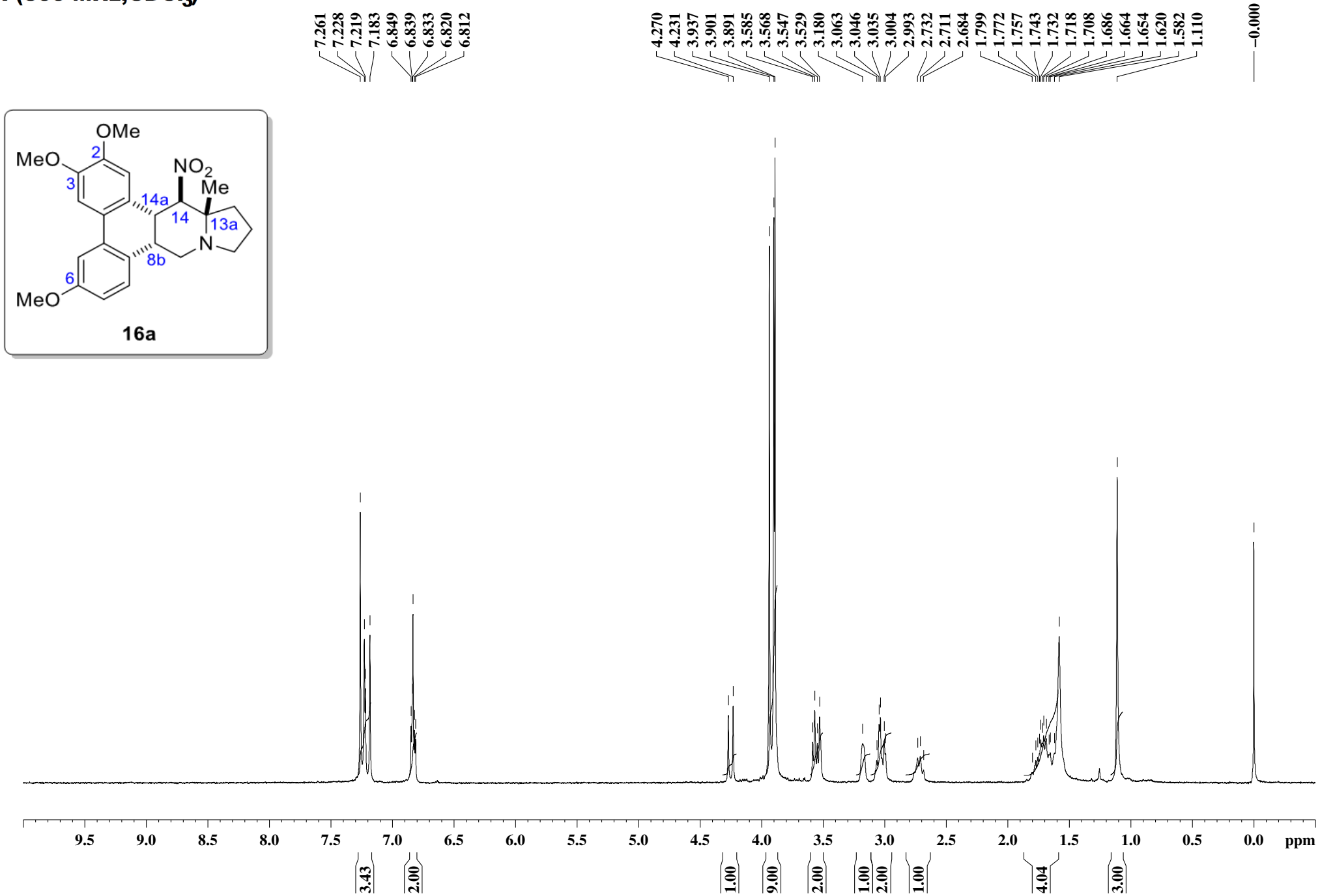


^{13}C (75 MHz, $CDCl_3$)

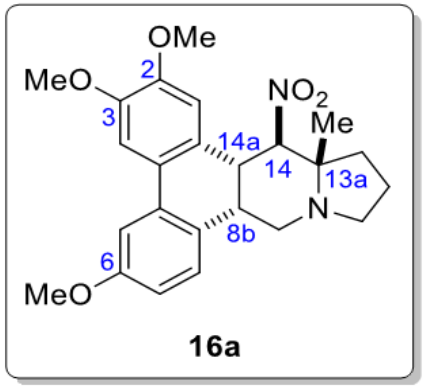


15f': minor isomer

^{1}H (300 MHz,$CDCl_3$)

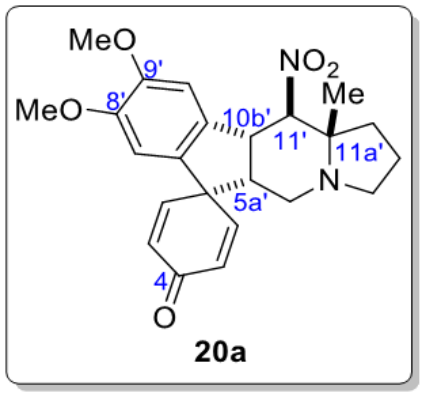


^{13}C (75 MHz, $CDCl_3$)



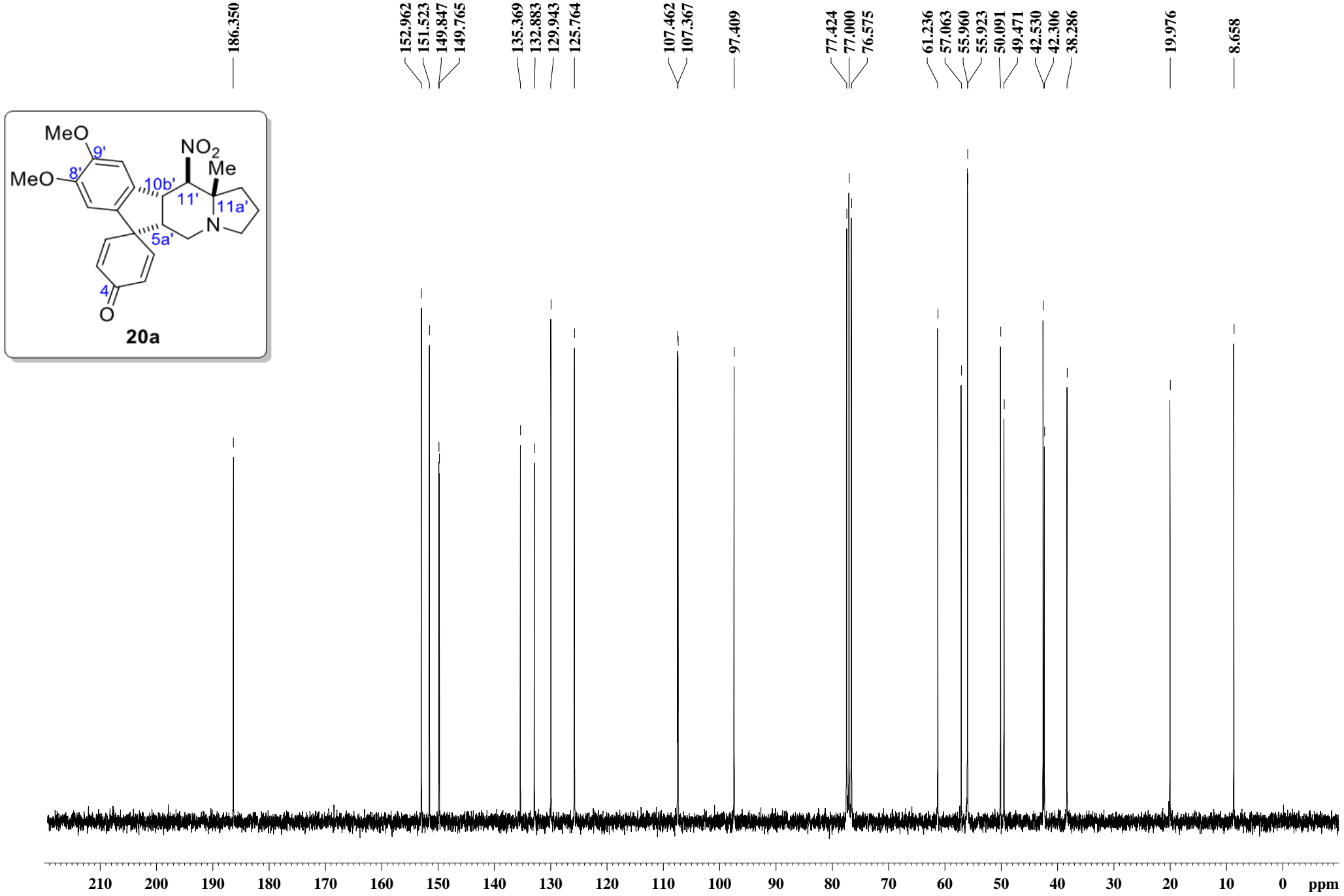
16a

^{1}H (300 MHz,$CDCl_3$)

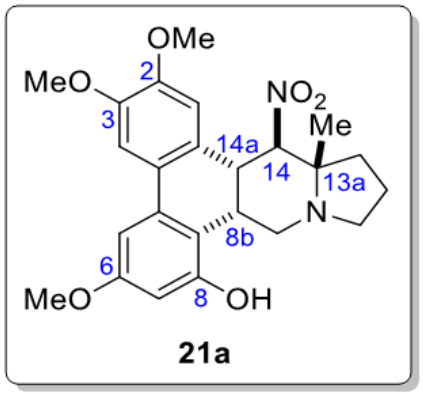


20a

^{13}C (75 MHz, $CDCl_3$)

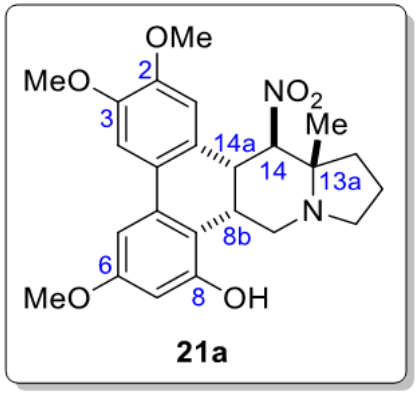


^{1}H (300 MHz,$CDCl_3$)



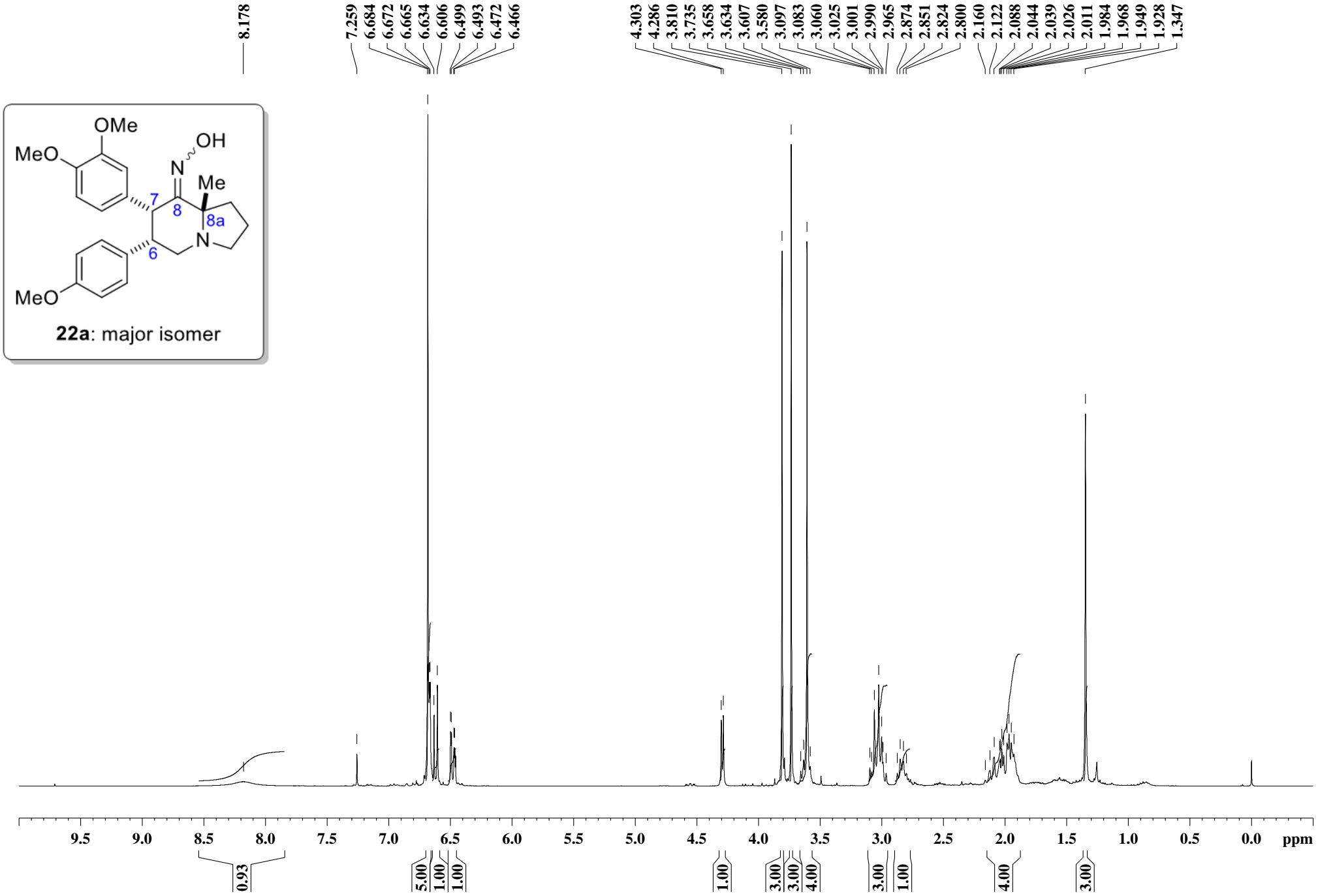
21a

^{13}C (75 MHz, $CDCl_3$)



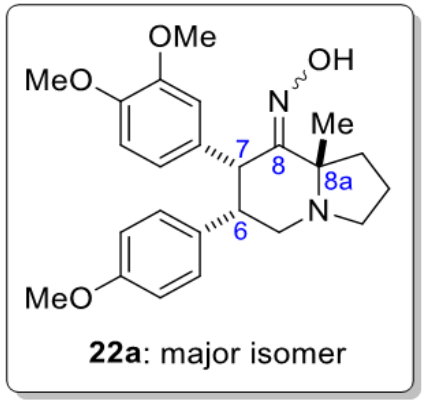
21a

^{1}H (300 MHz,$CDCl_3$)



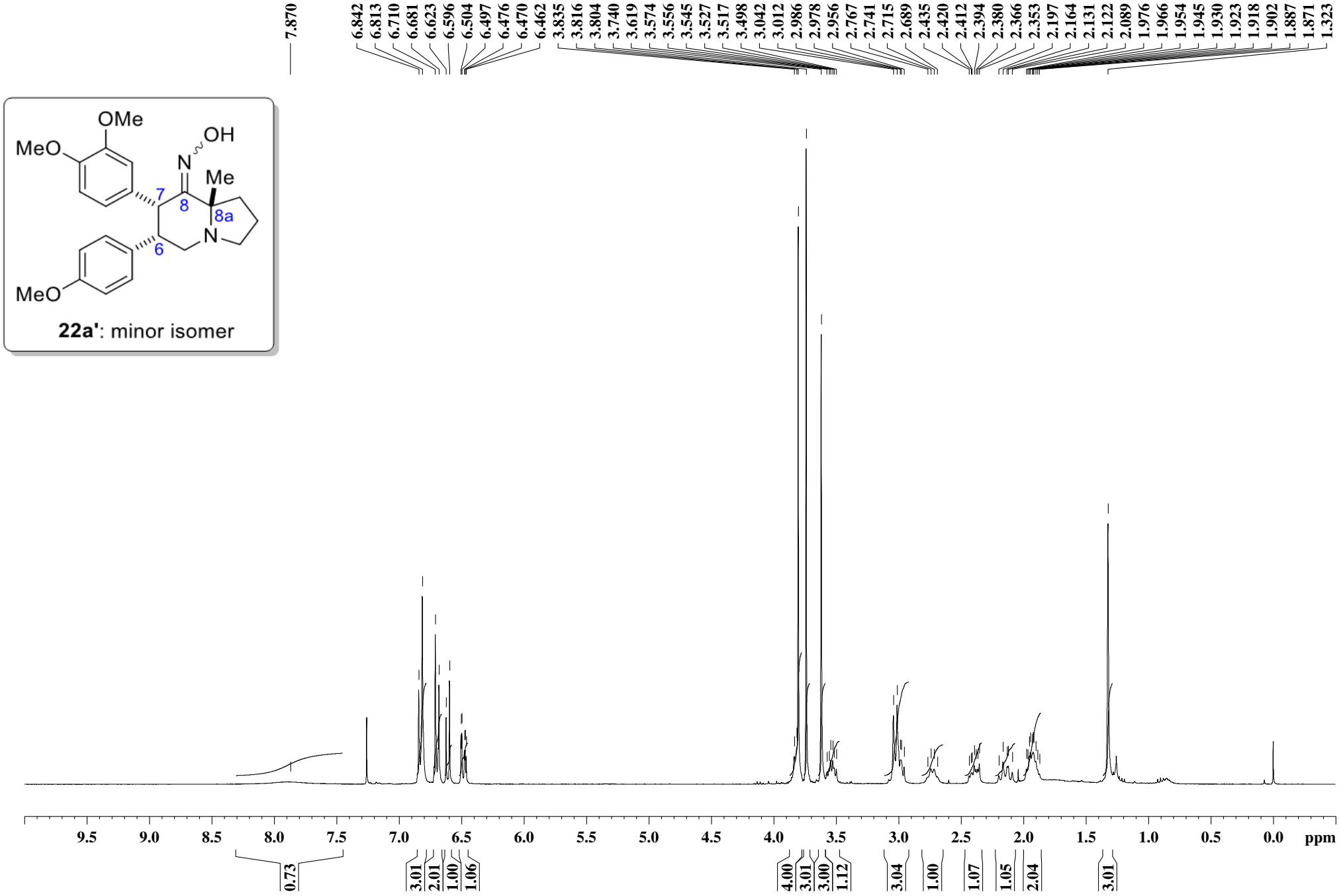
^{13}C (75 MHz, $CDCl_3$)

167.093
158.237
147.750
147.143
132.405
130.530
129.644
122.503
113.884
113.183
110.098
77.424
77.000
76.577
61.427
55.598
55.276
55.144
50.949
48.319
46.400
41.539
38.709
24.311
22.009

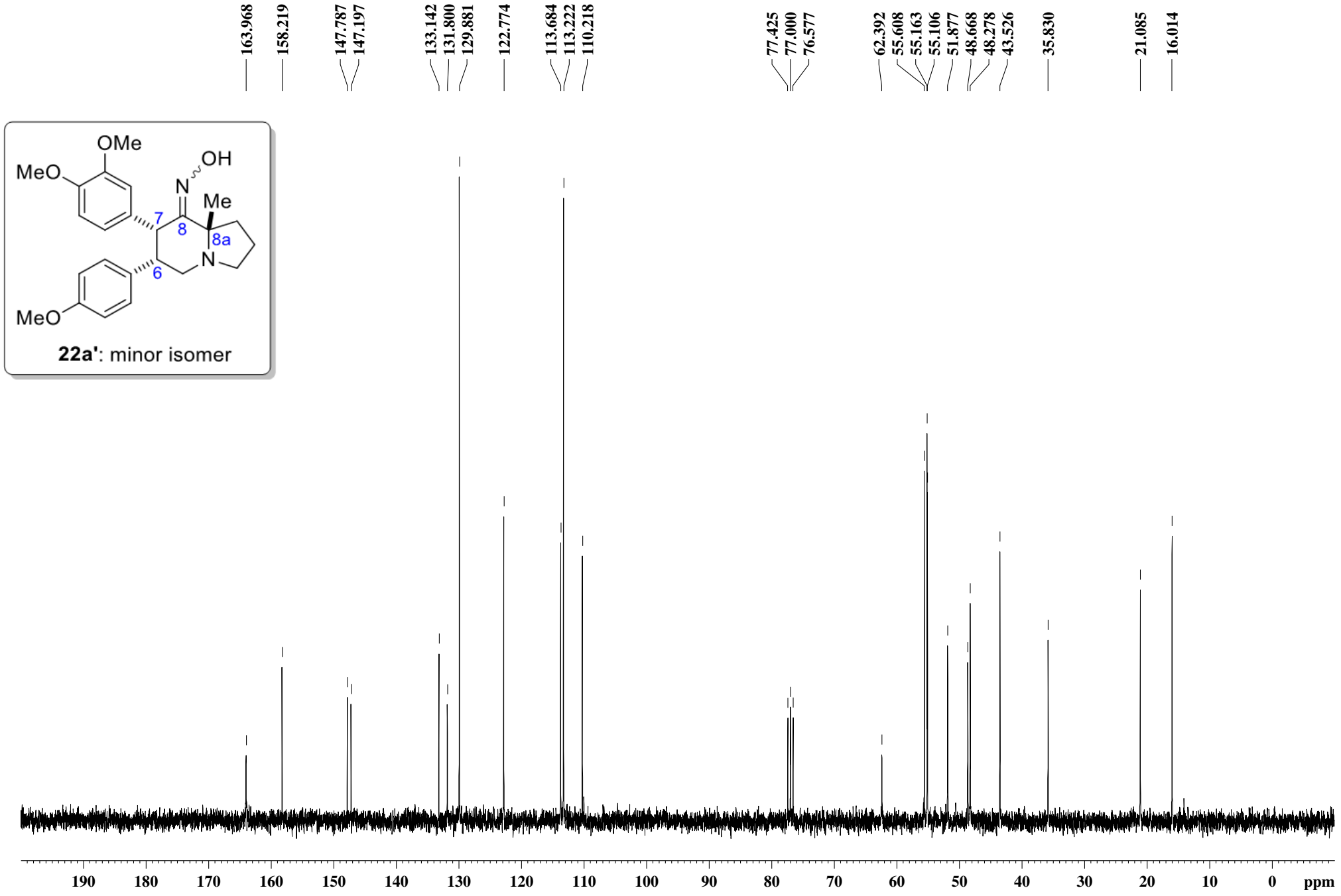


22a: major isomer

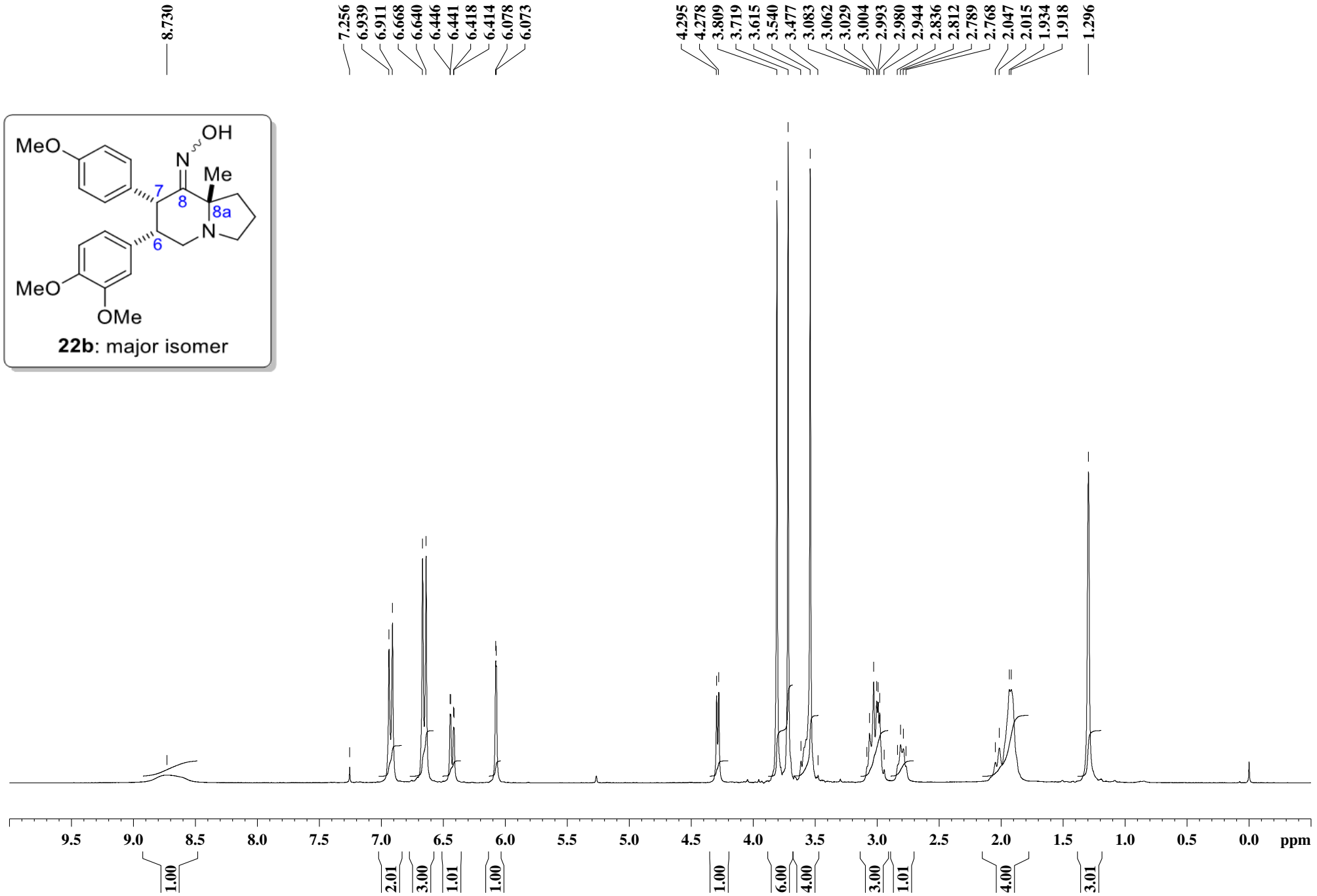
^{1}H (300 MHz,$CDCl_3$)



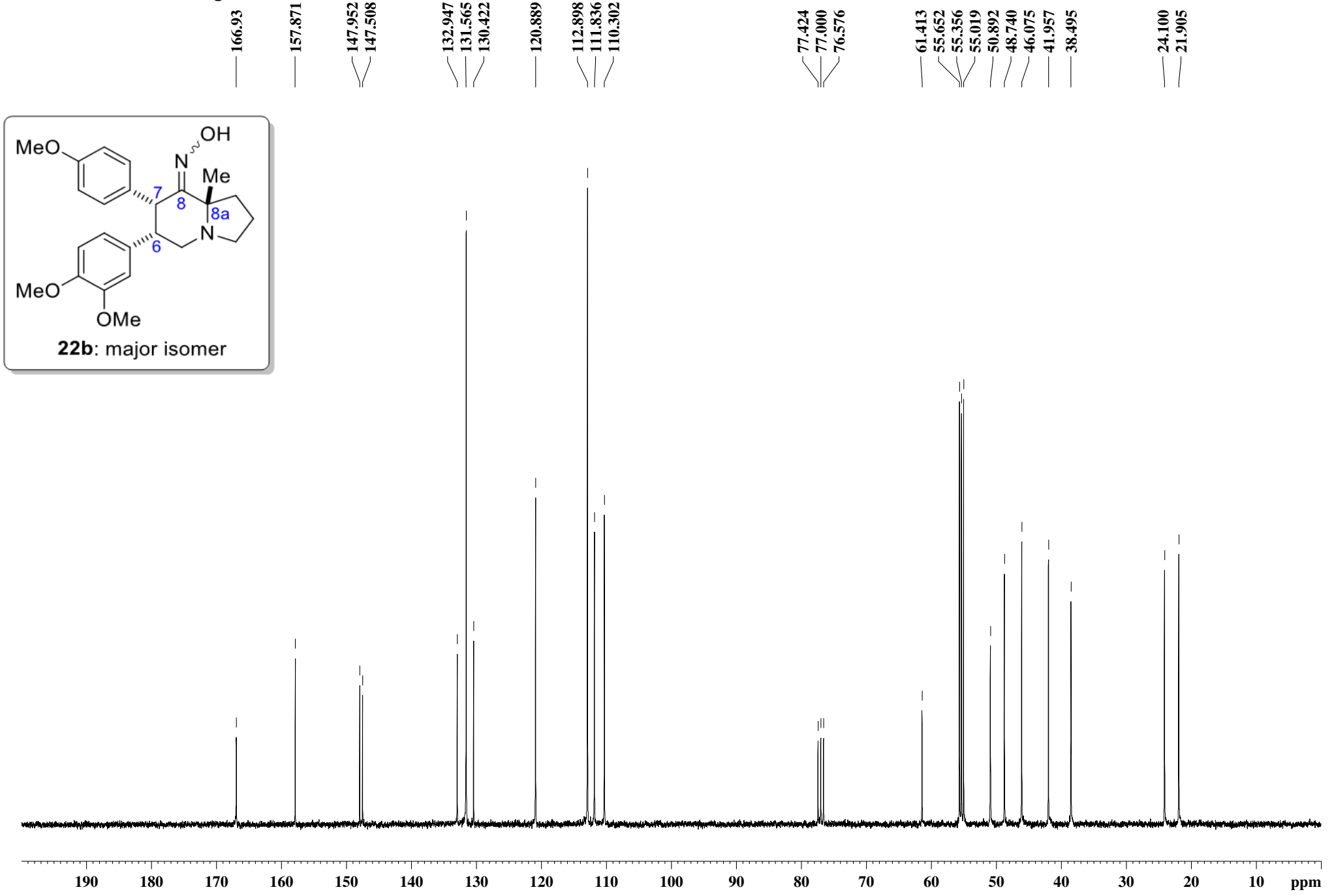
^{13}C (75 MHz, $CDCl_3$)



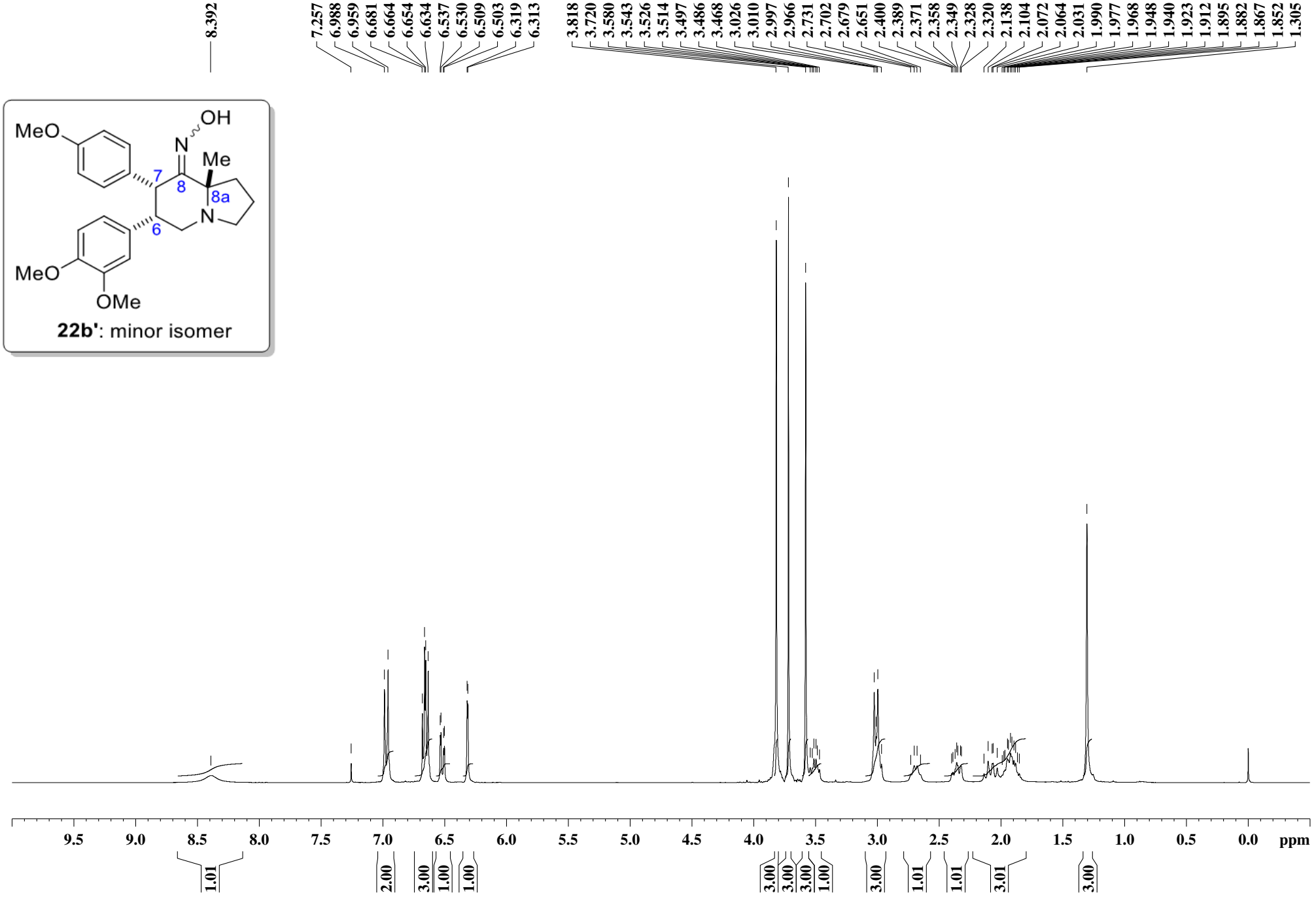
^{1}H (300 MHz,$CDCl_3$)



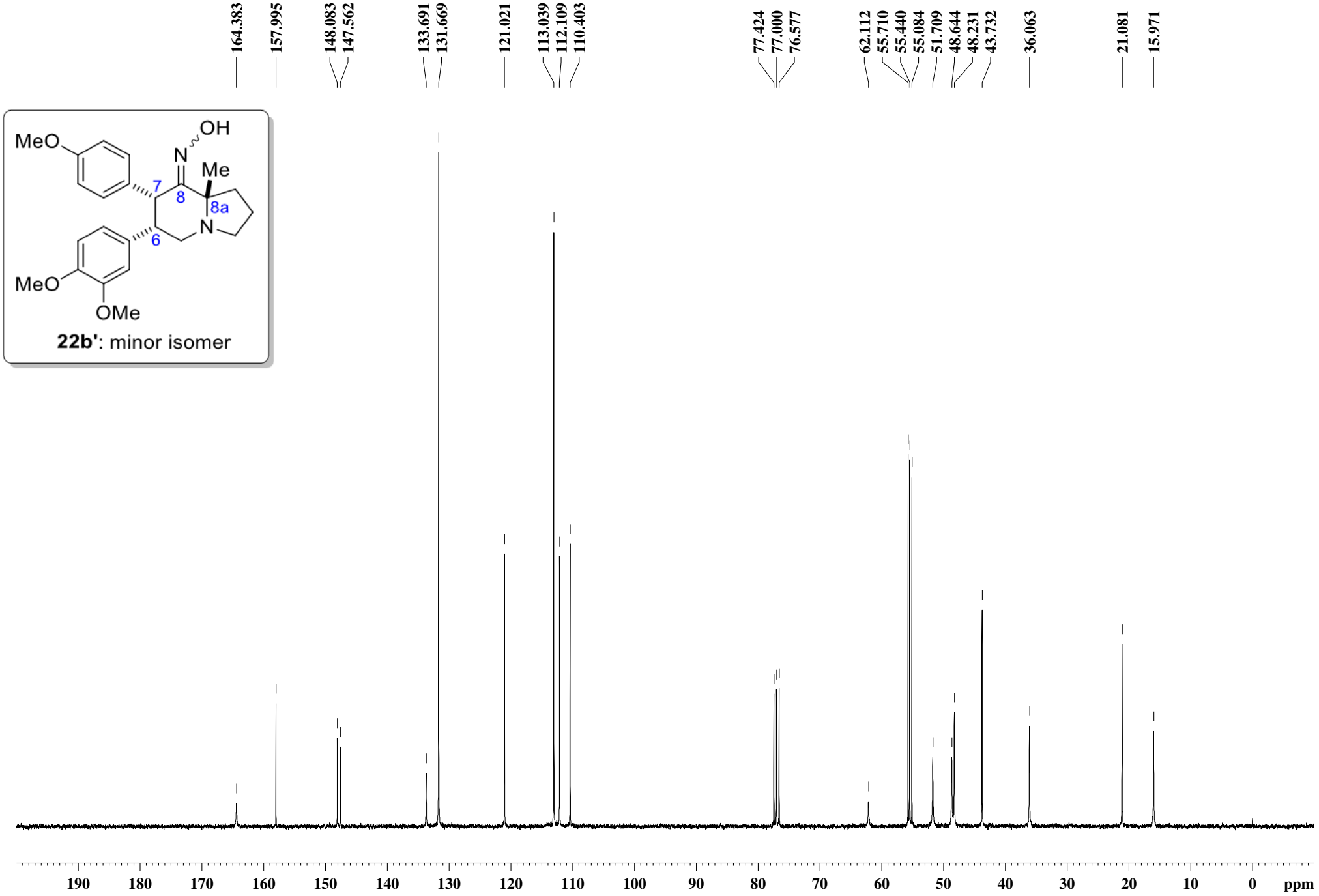
^{13}C (75 MHz, $CDCl_3$)



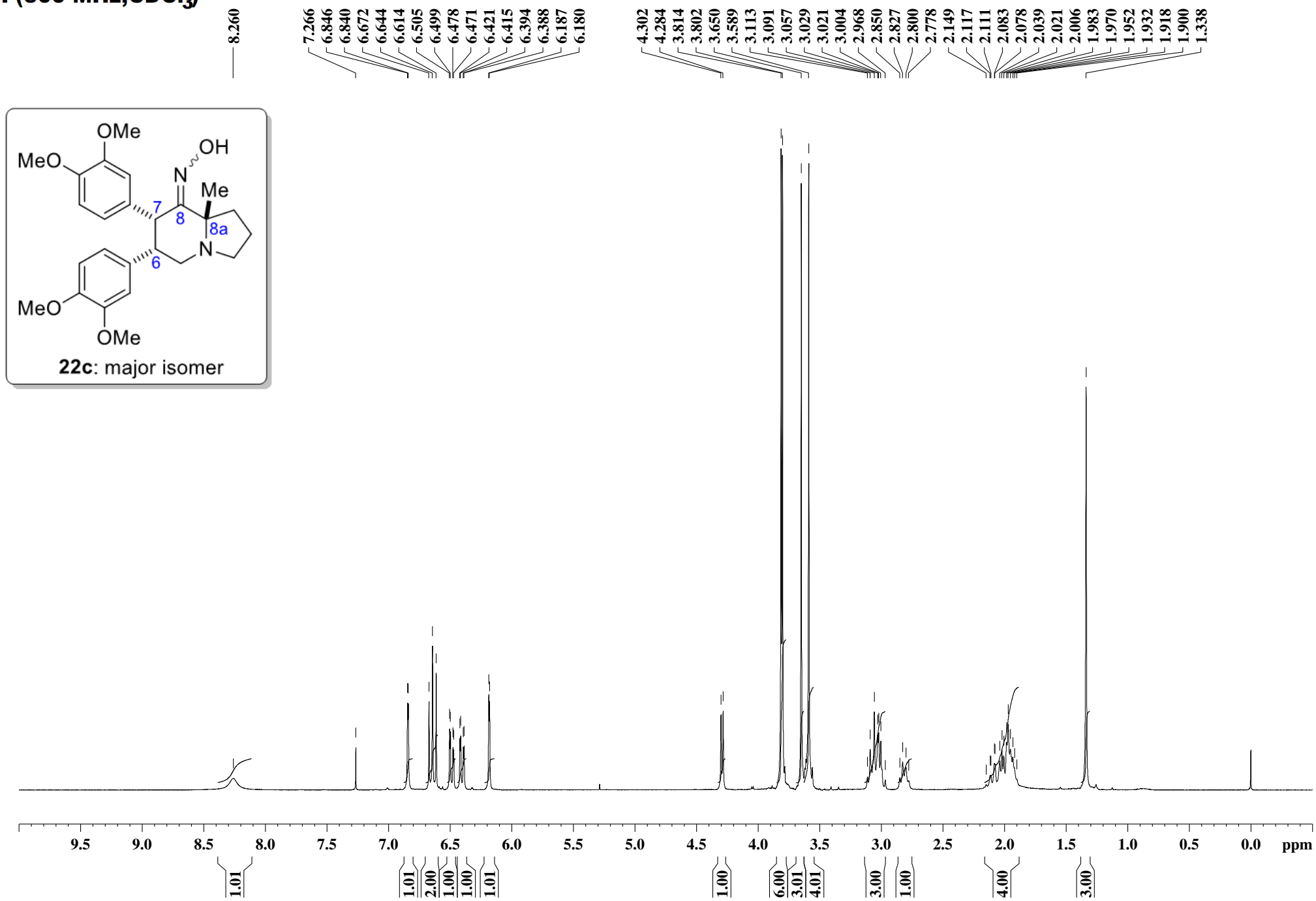
^{1}H (300 MHz,$CDCl_3$)



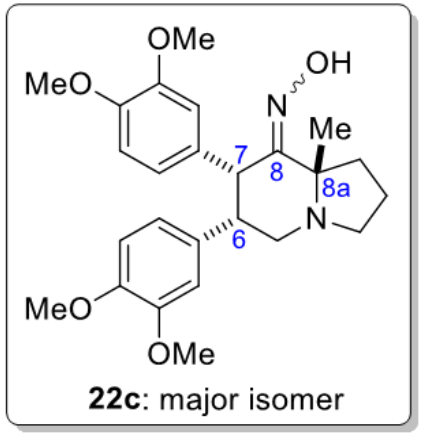
^{13}C (75 MHz, $CDCl_3$)



^{1}H (300 MHz,$CDCl_3$)

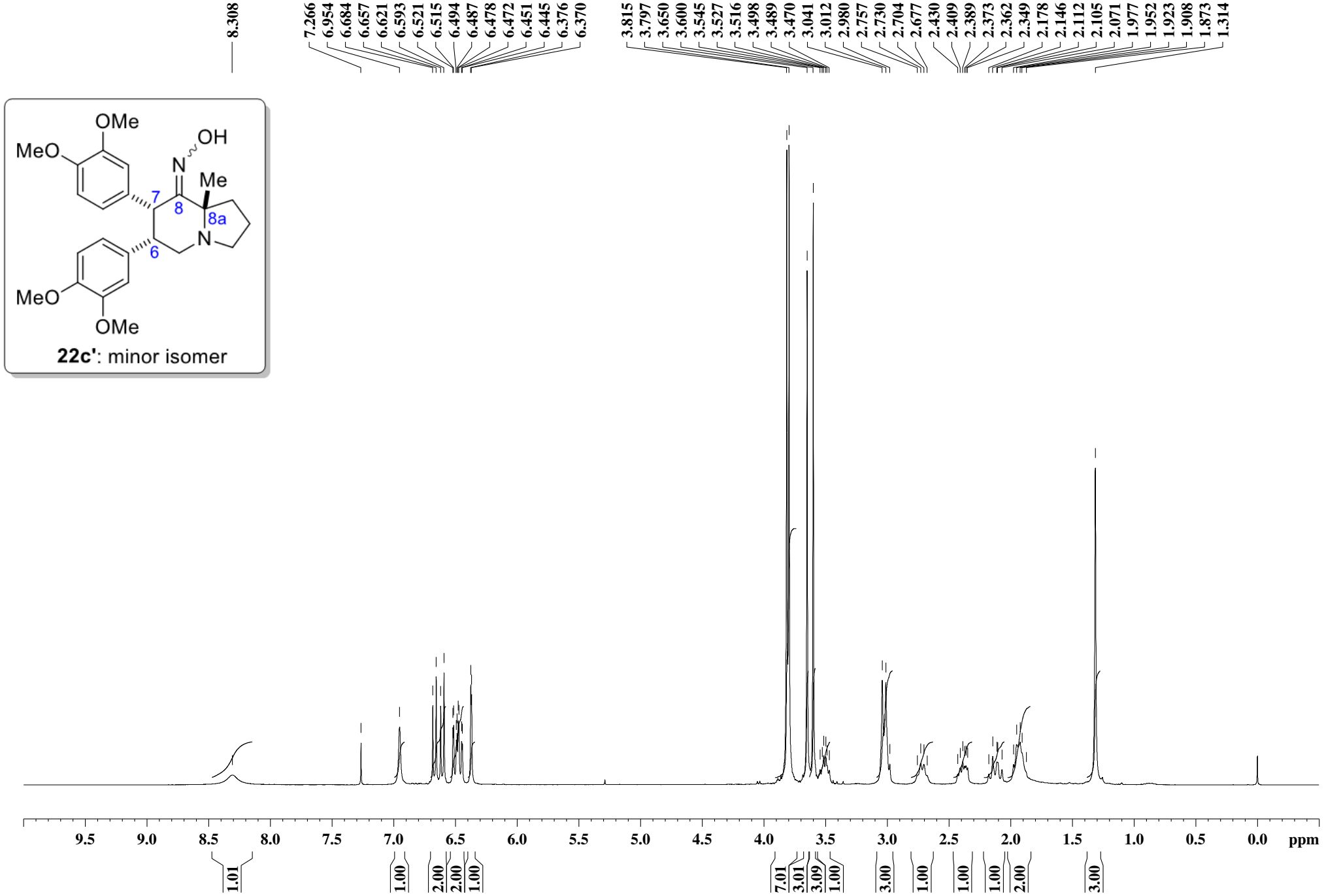


^{13}C (75 MHz, $CDCl_3$)

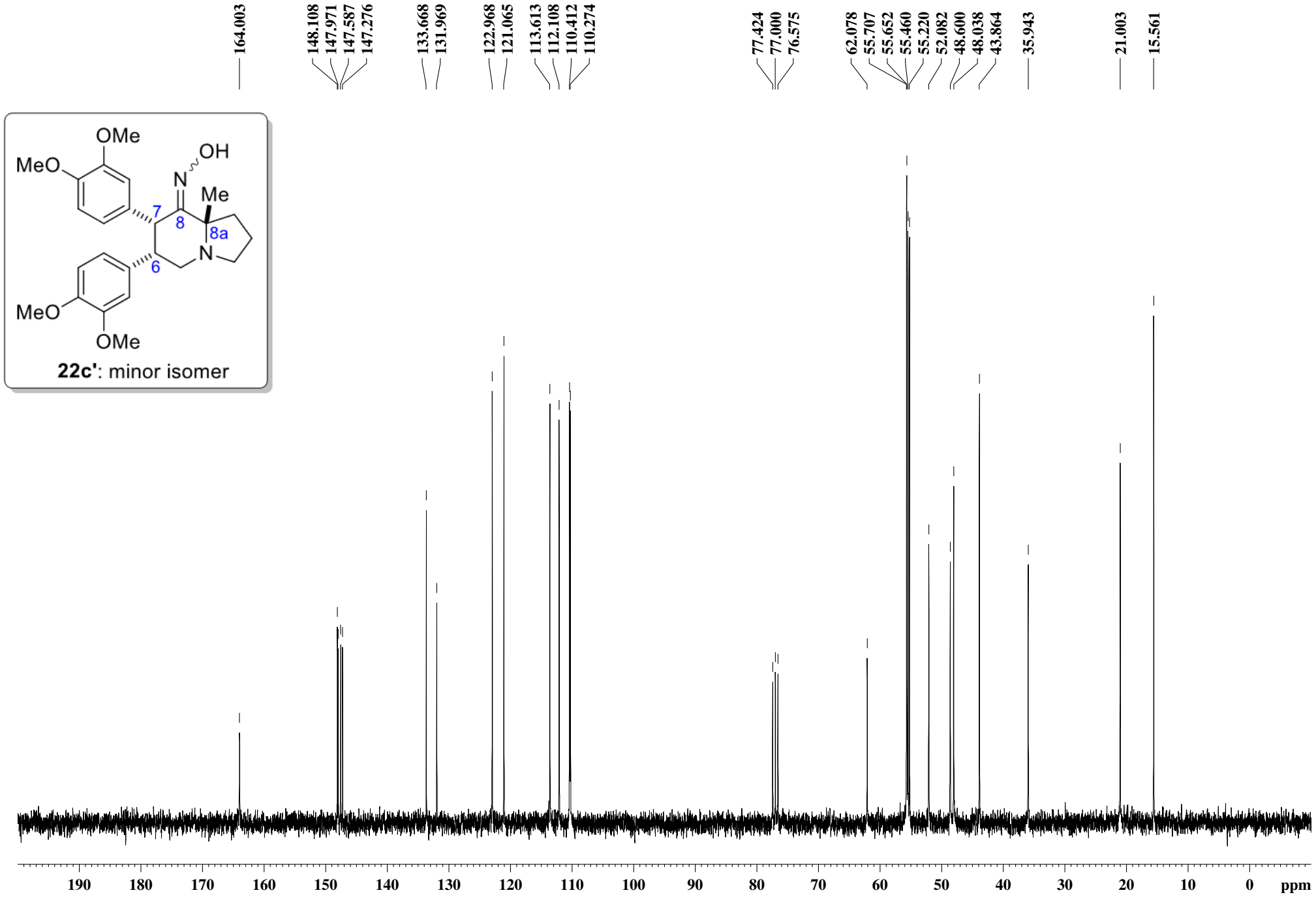


22c: major isomer

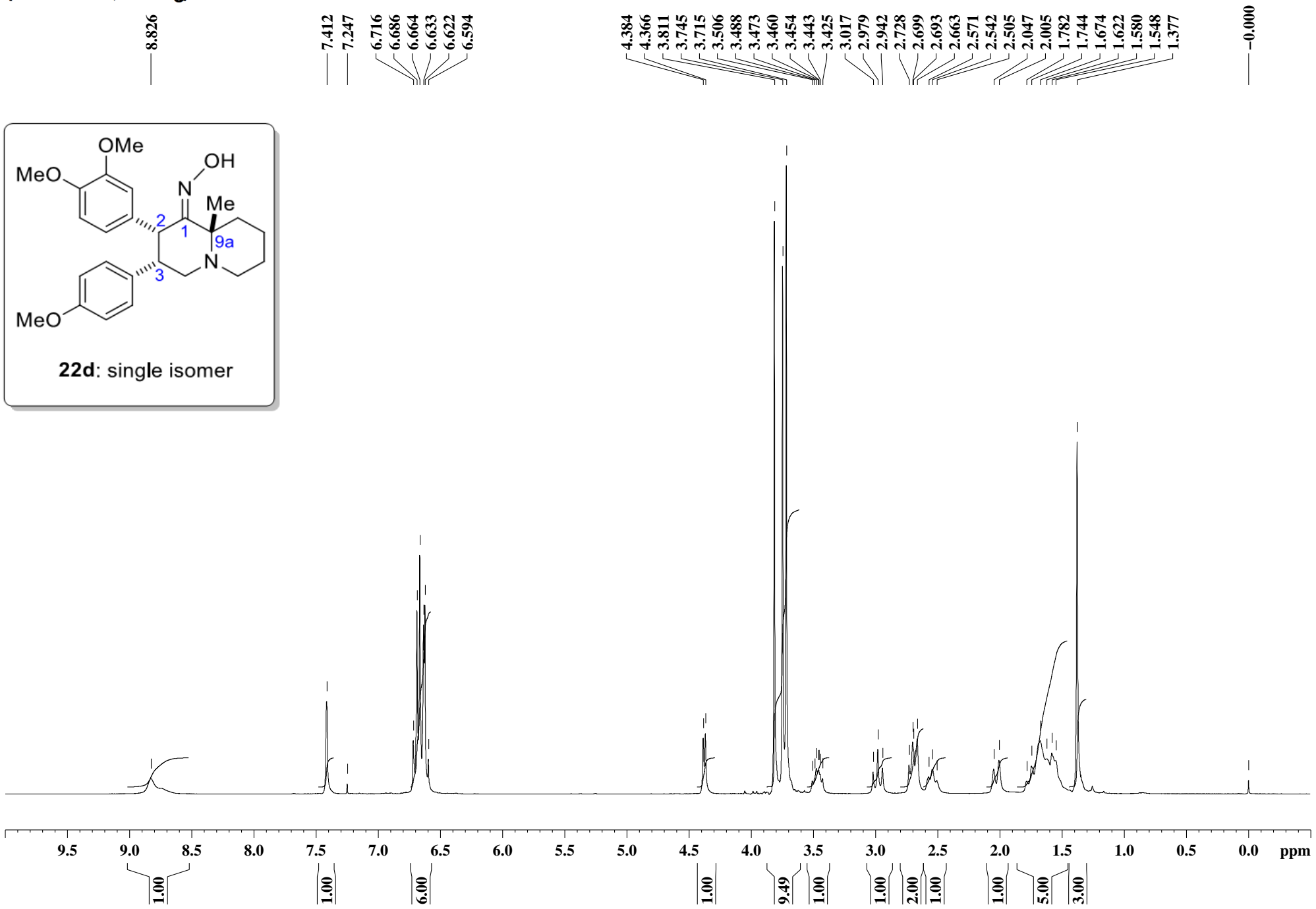
^{1}H (300 MHz,$CDCl_3$)



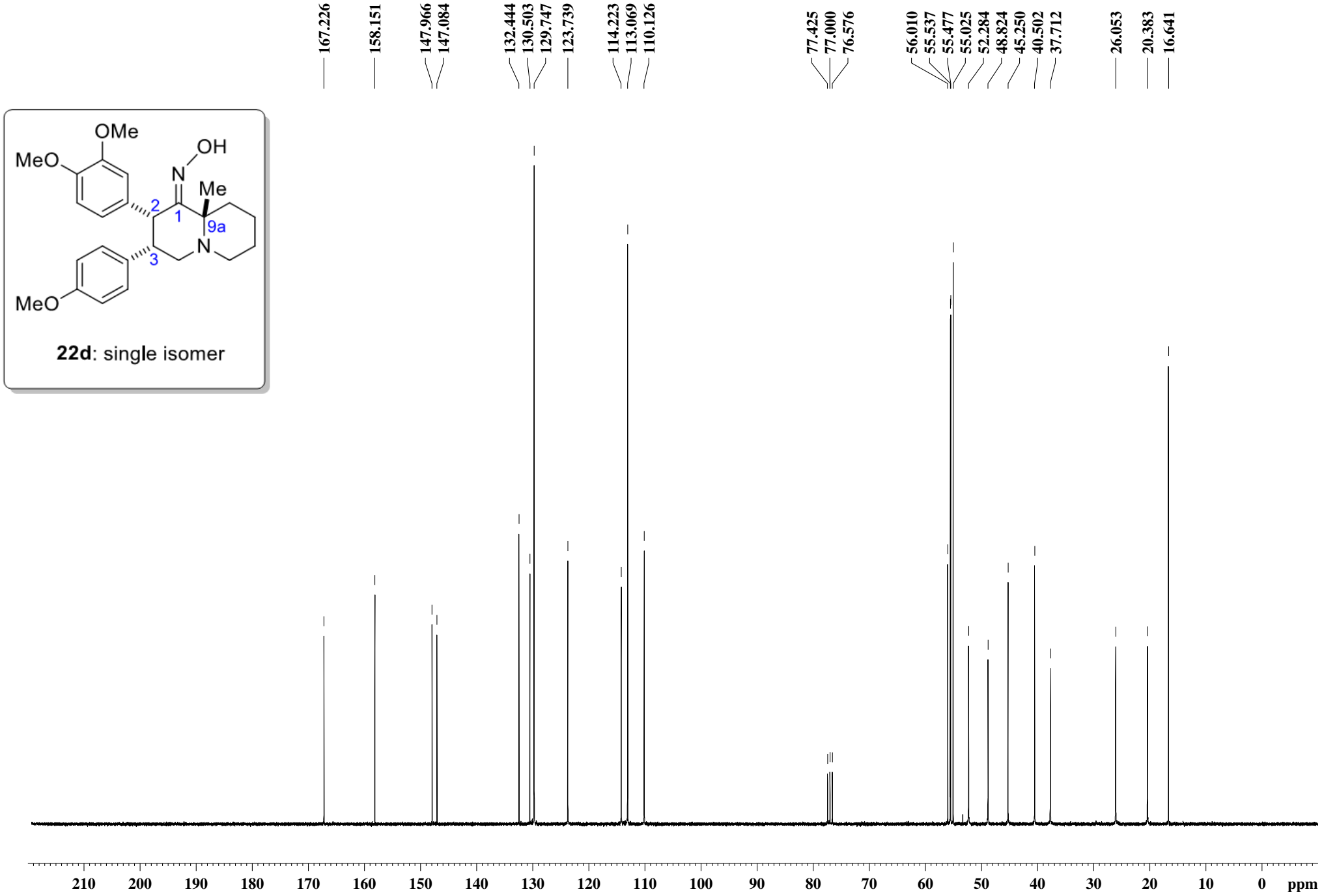
^{13}C (75 MHz, $CDCl_3$)



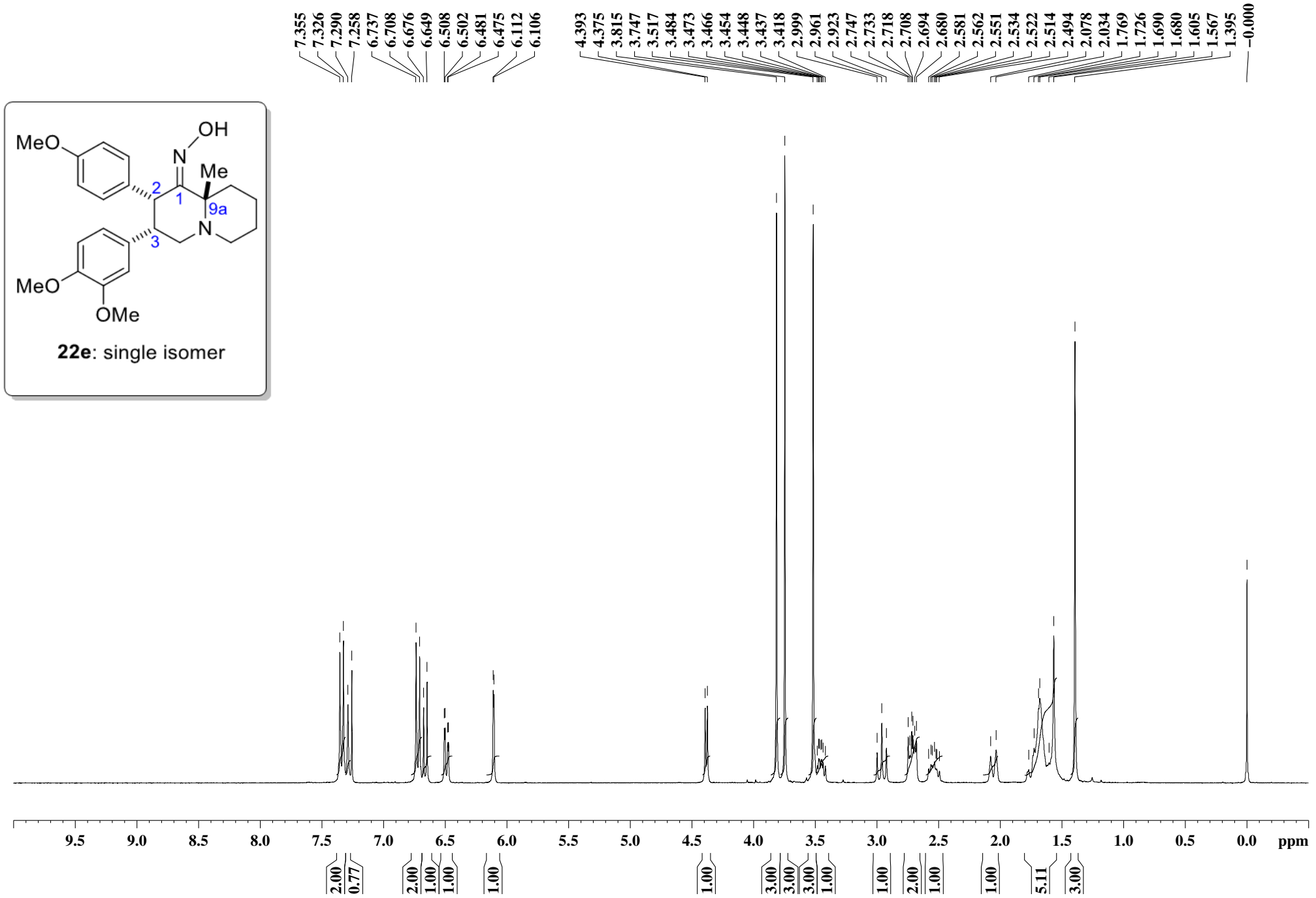
^{1}H (300 MHz,$CDCl_3$)



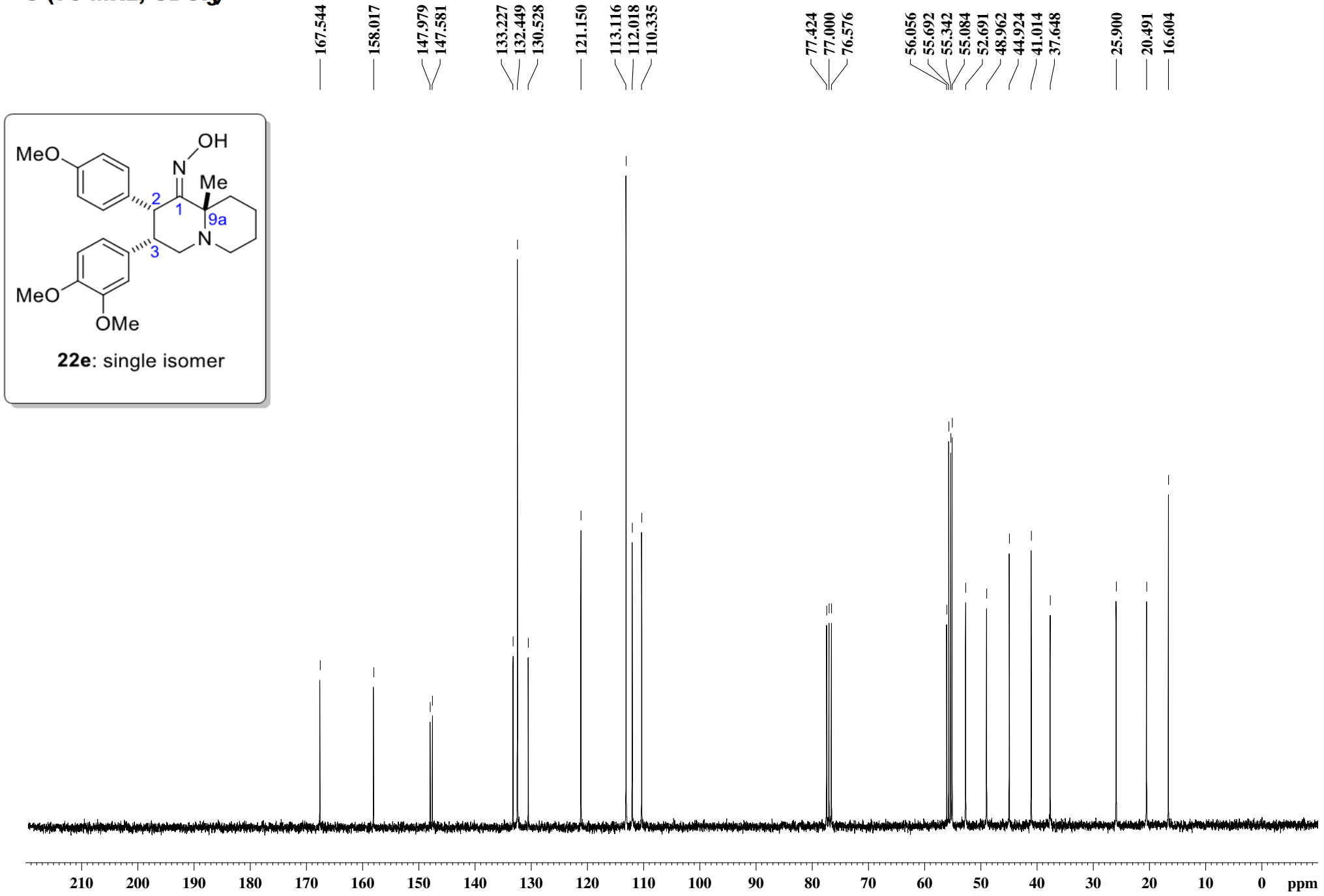
^{13}C (75 MHz, $CDCl_3$)



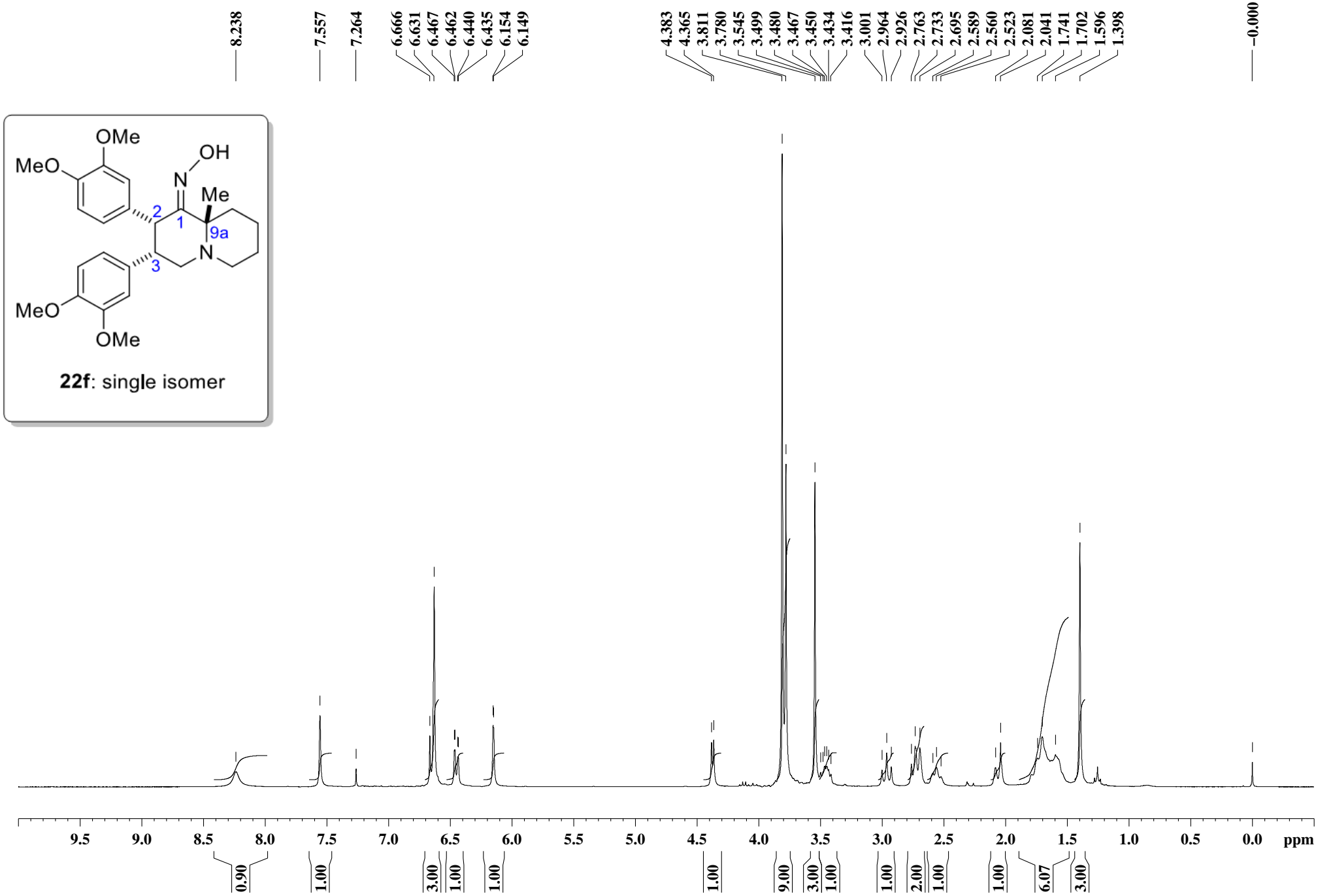
^{1}H (300 MHz,$CDCl_3$)



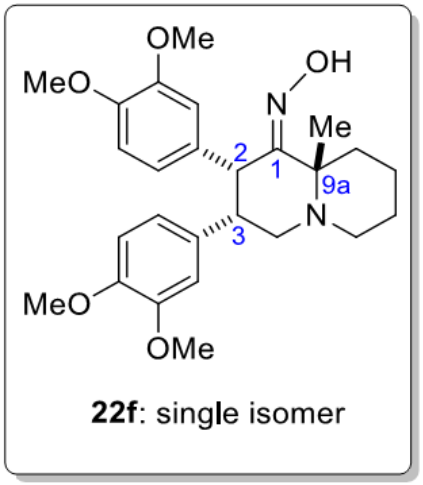
^{13}C (75 MHz, $CDCl_3$)



^{1}H (300 MHz,$CDCl_3$)

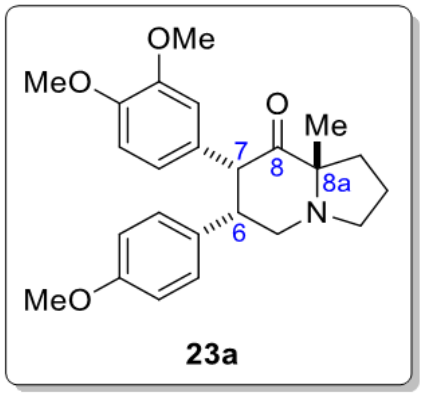


^{13}C (75 MHz, $CDCl_3$)



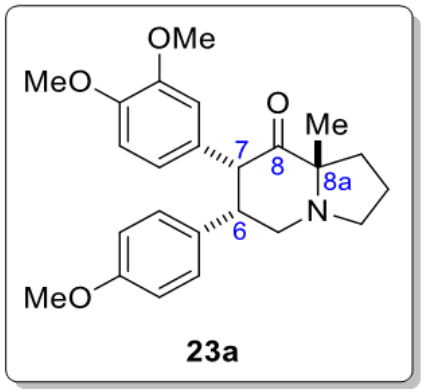
22f: single isomer

^{1}H (300 MHz,$CDCl_3$)



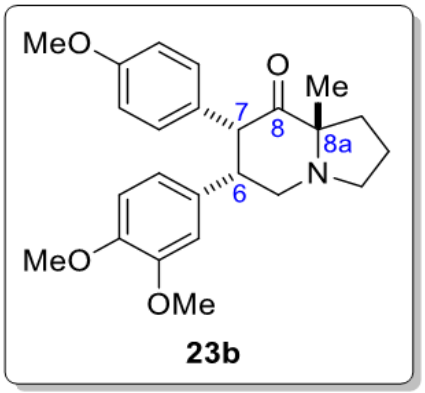
23a

^{13}C (75 MHz, $CDCl_3$)



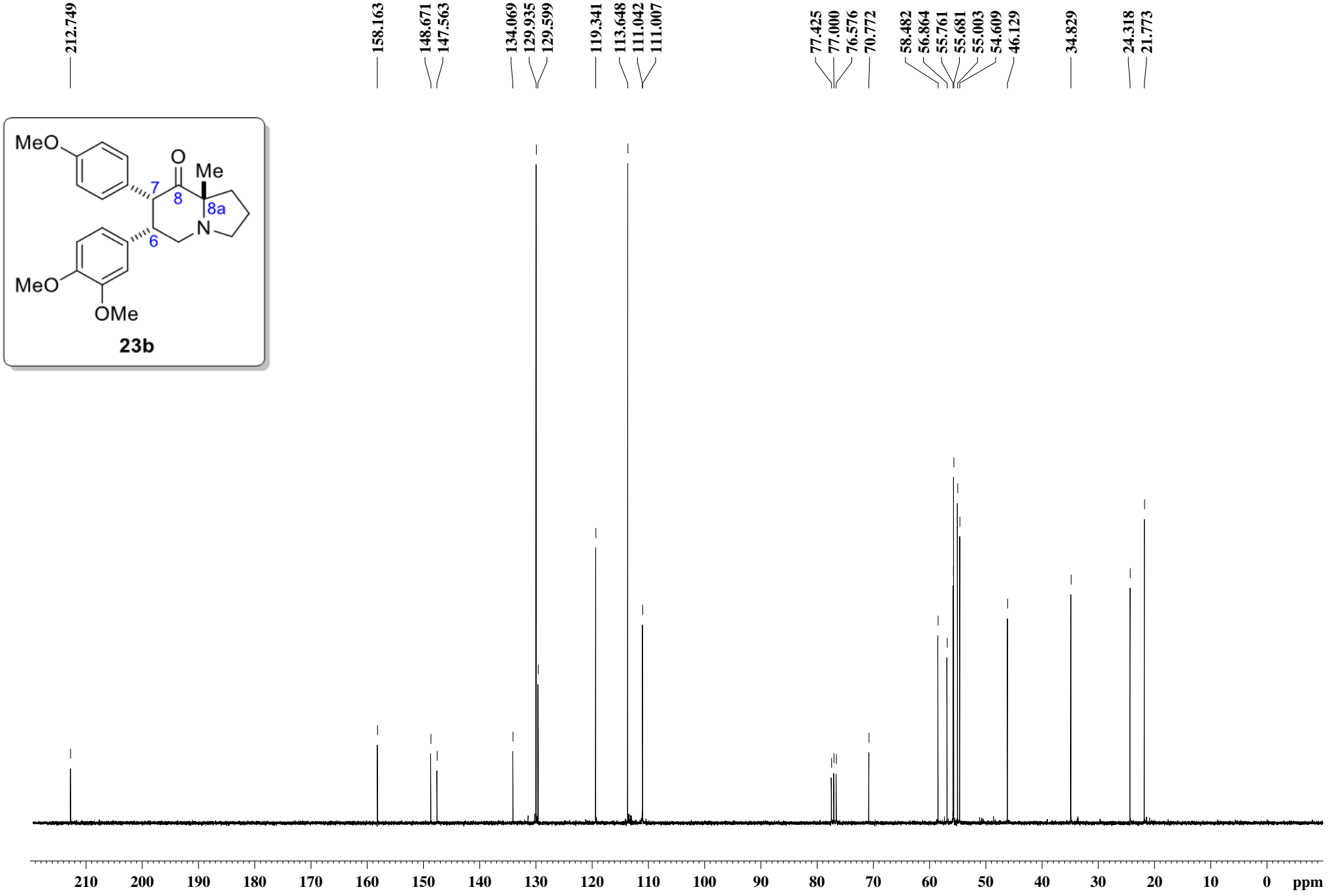
23a

^{1}H (300 MHz,$CDCl_3$)

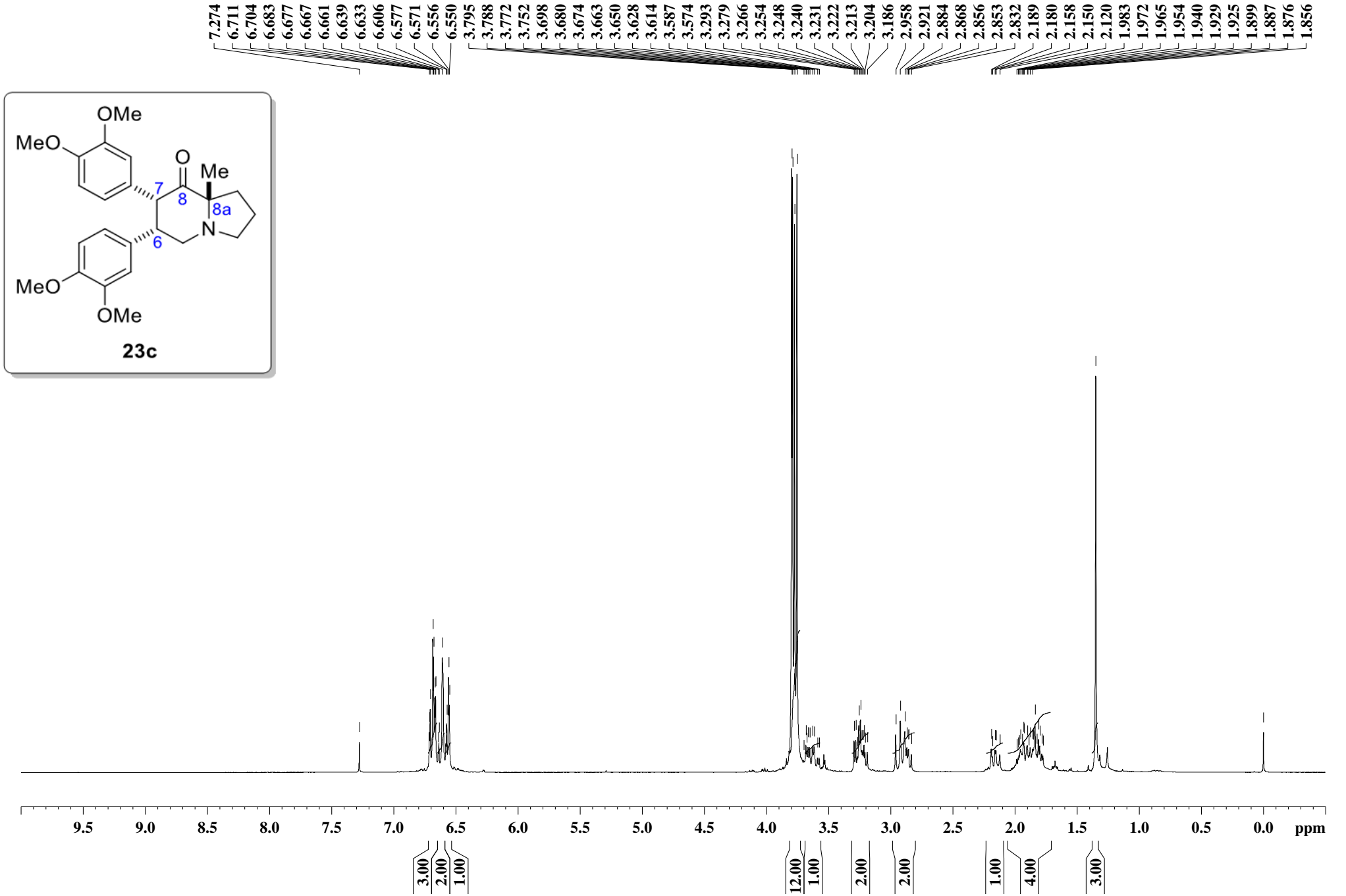


23b

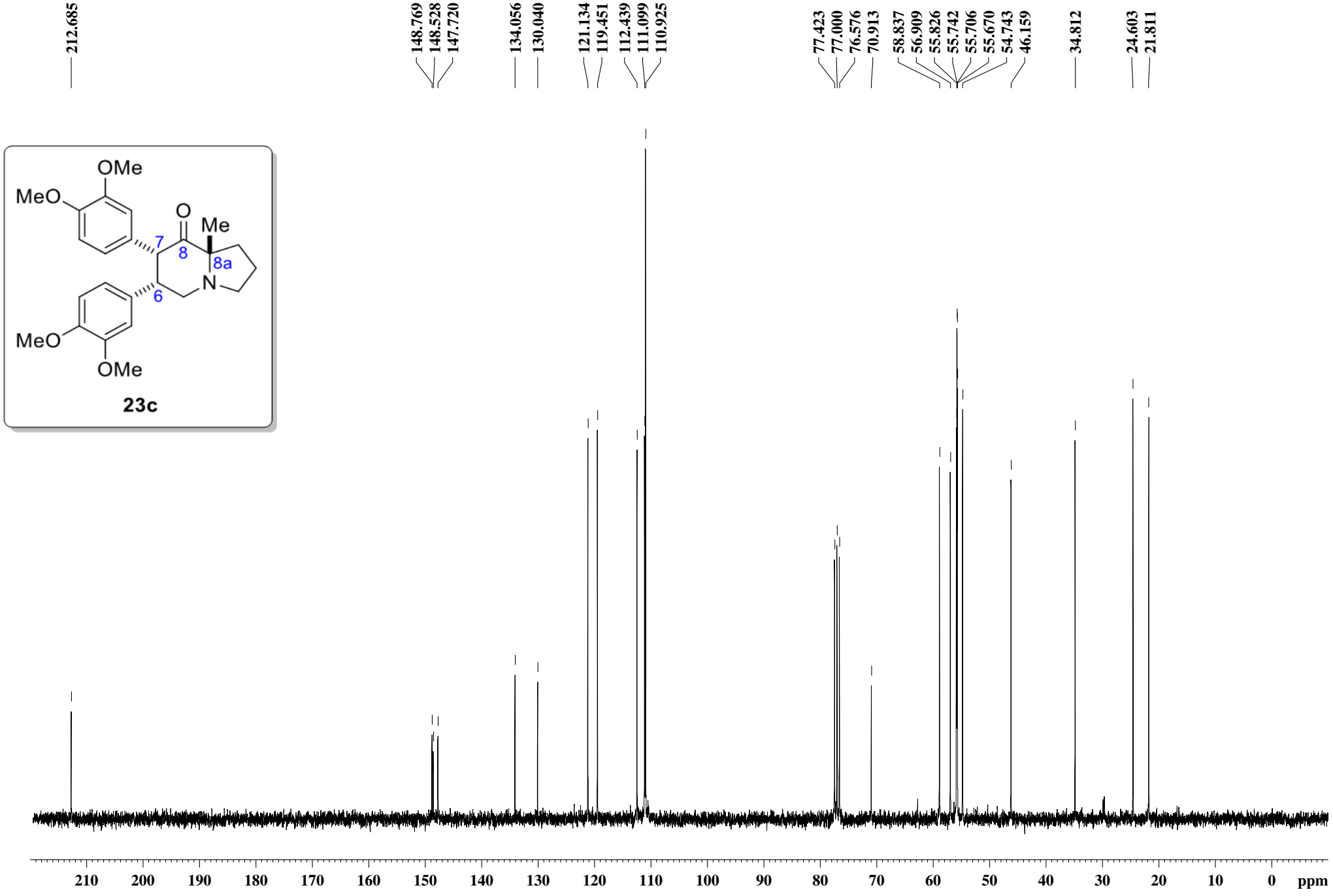
^{13}C (75 MHz, $CDCl_3$)



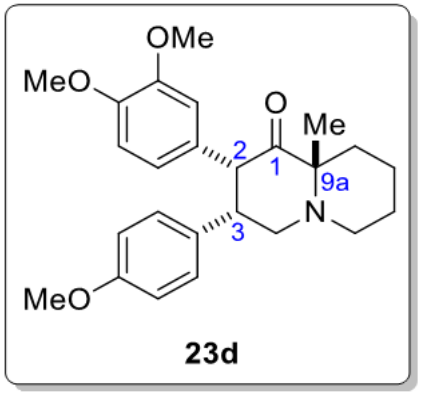
^{1}H (300 MHz,$CDCl_3$)



^{13}C (75 MHz, $CDCl_3$)

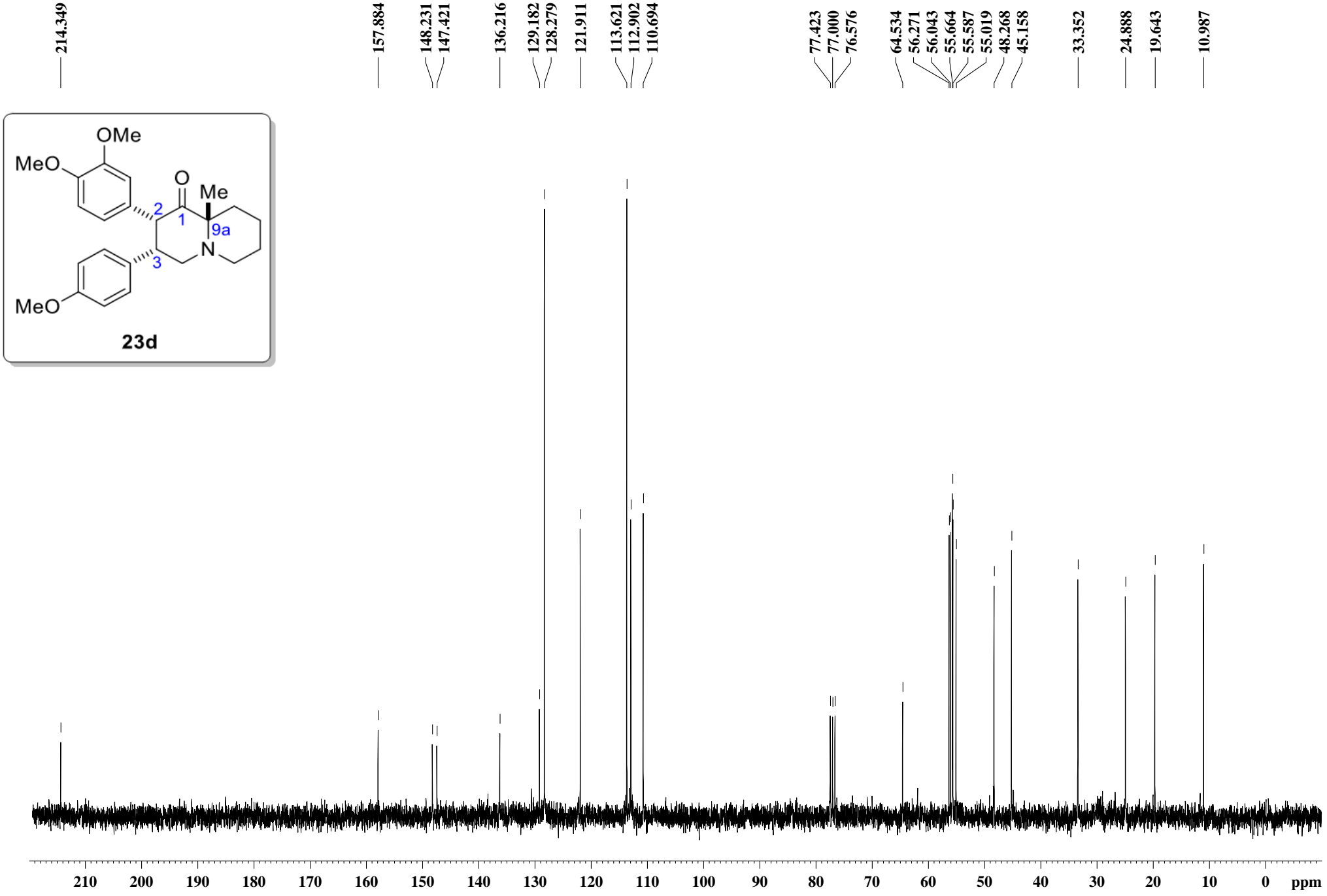


^{1}H (300 MHz,$CDCl_3$)

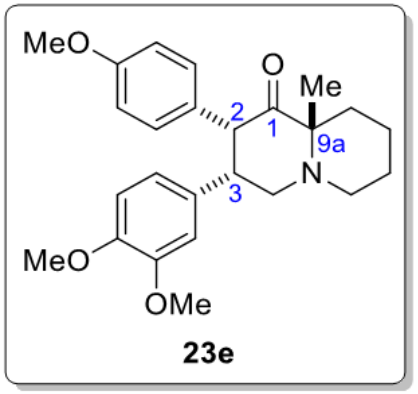


23d

^{13}C (75 MHz, $CDCl_3$)

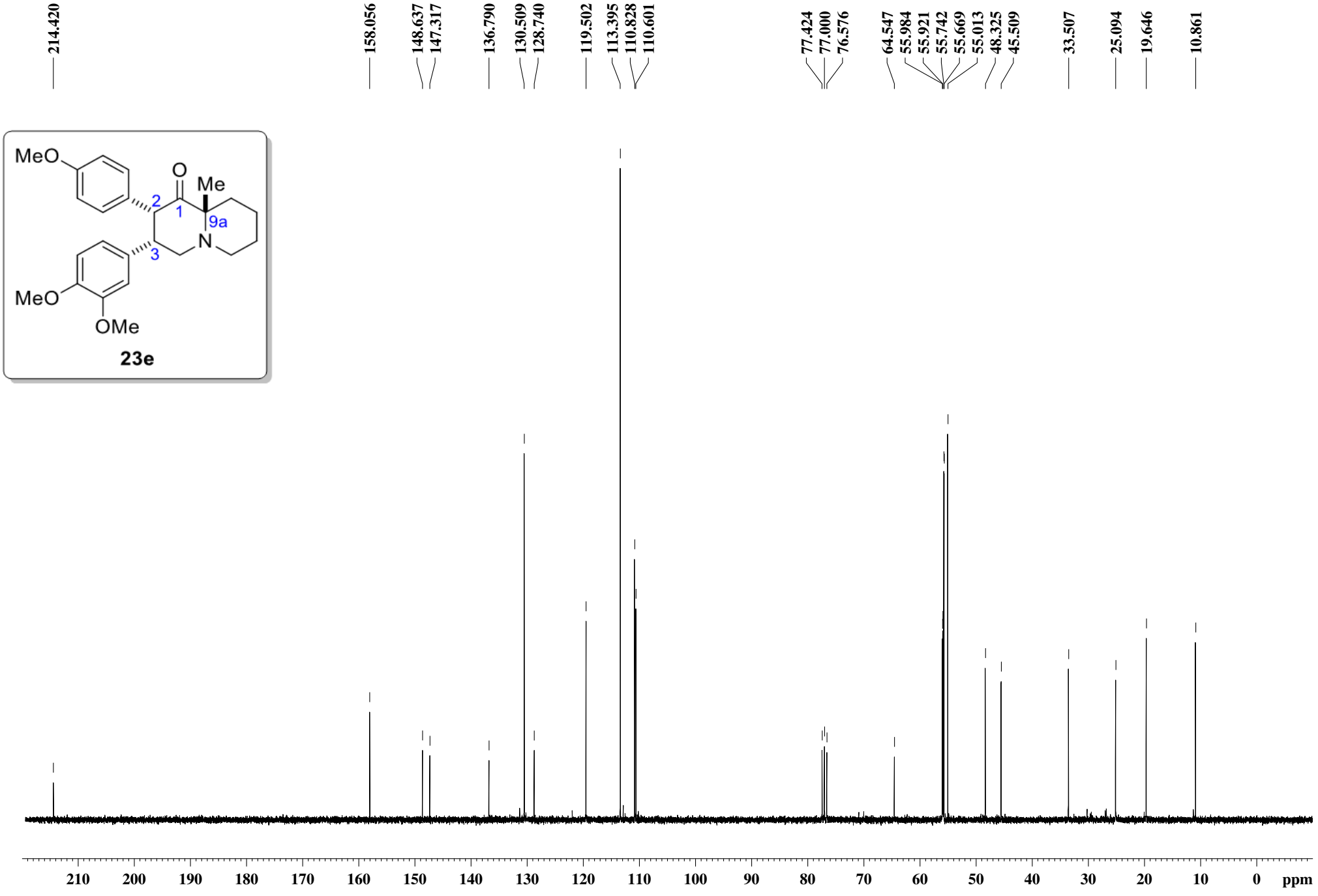


^{1}H (300 MHz,$CDCl_3$)

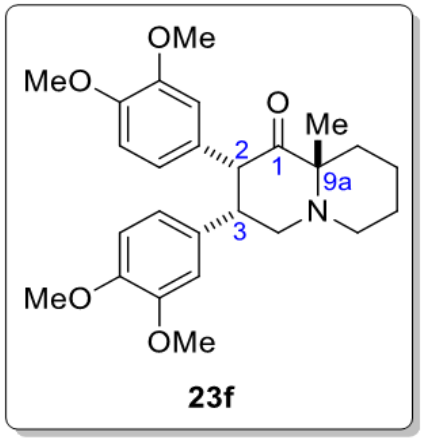


23e

^{13}C (75 MHz, $CDCl_3$)

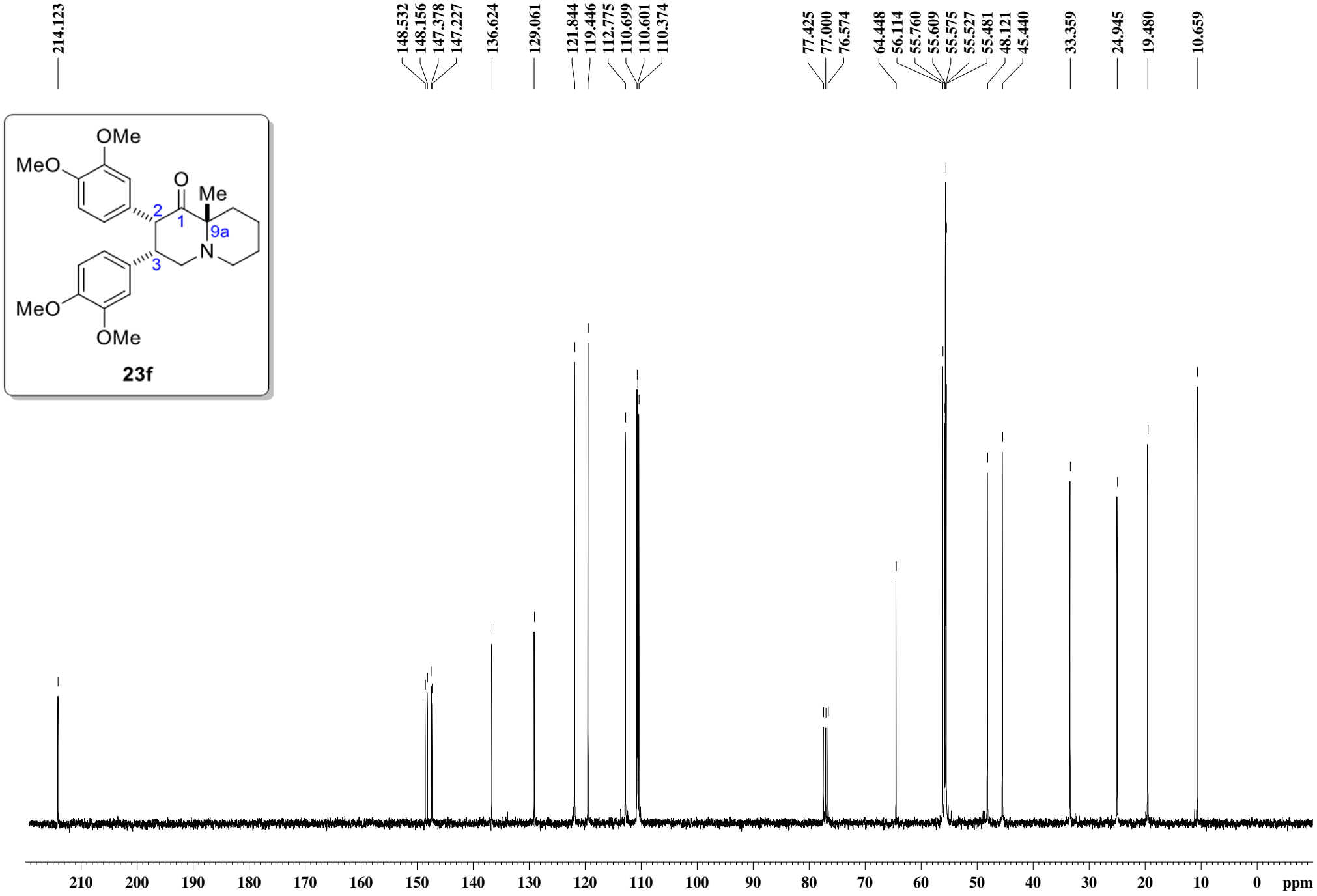


^{1}H (300 MHz,$CDCl_3$)

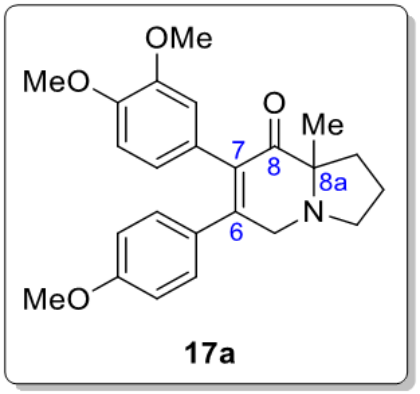


23f

^{13}C (75 MHz, $CDCl_3$)

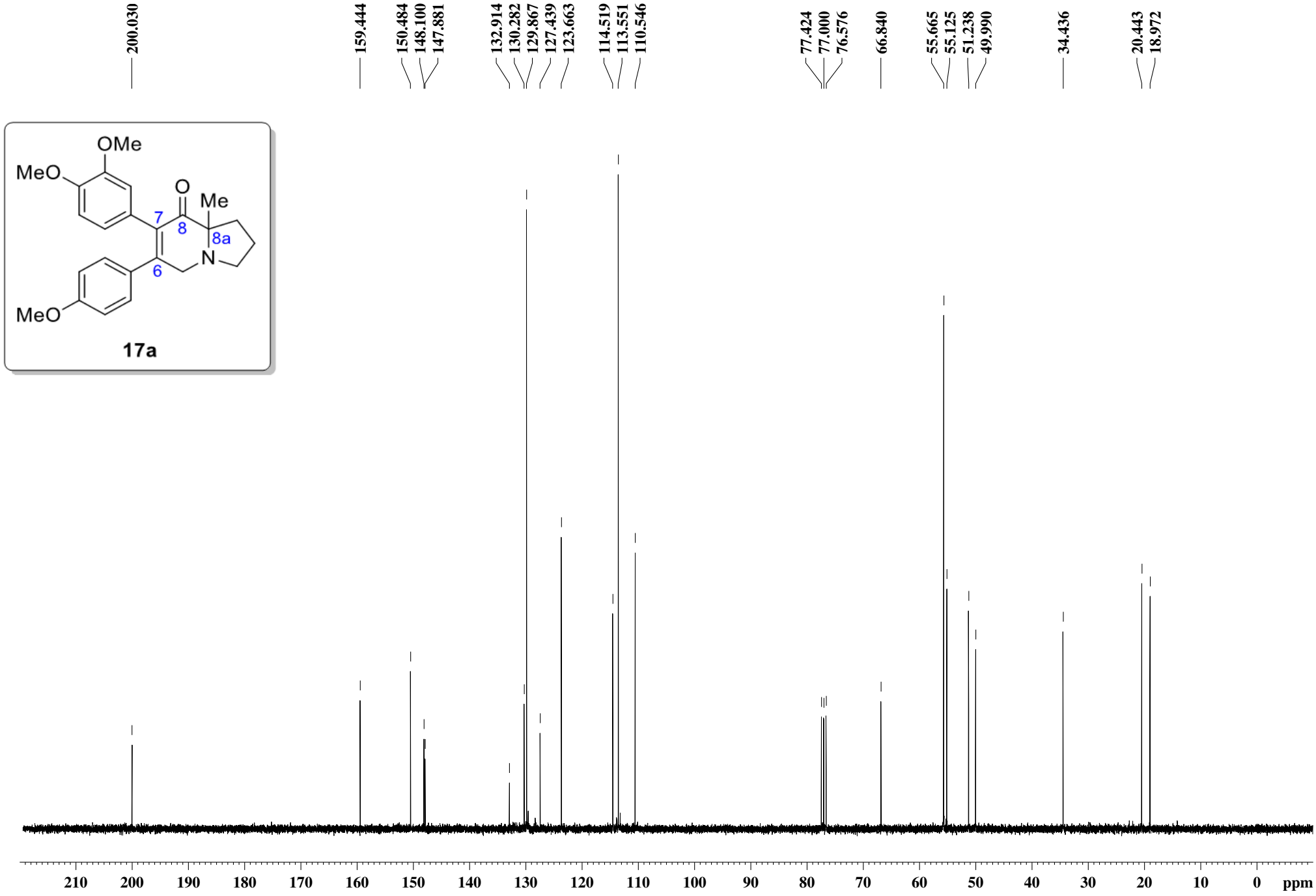


^{1}H (300 MHz,$CDCl_3$)

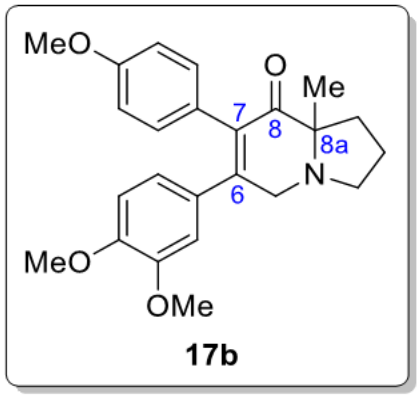


17a

^{13}C (75 MHz, $CDCl_3$)

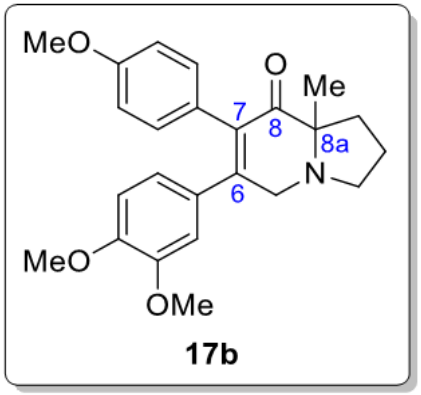


^{1}H (300 MHz,$CDCl_3$)



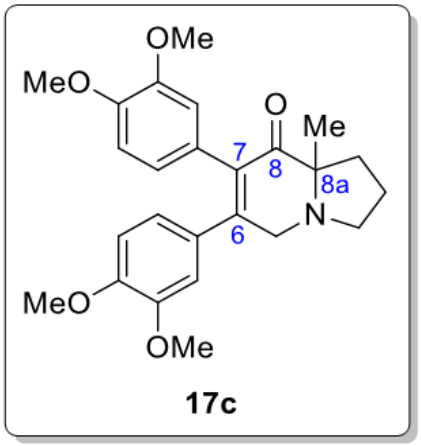
17b

^{13}C (75 MHz, $CDCl_3$)



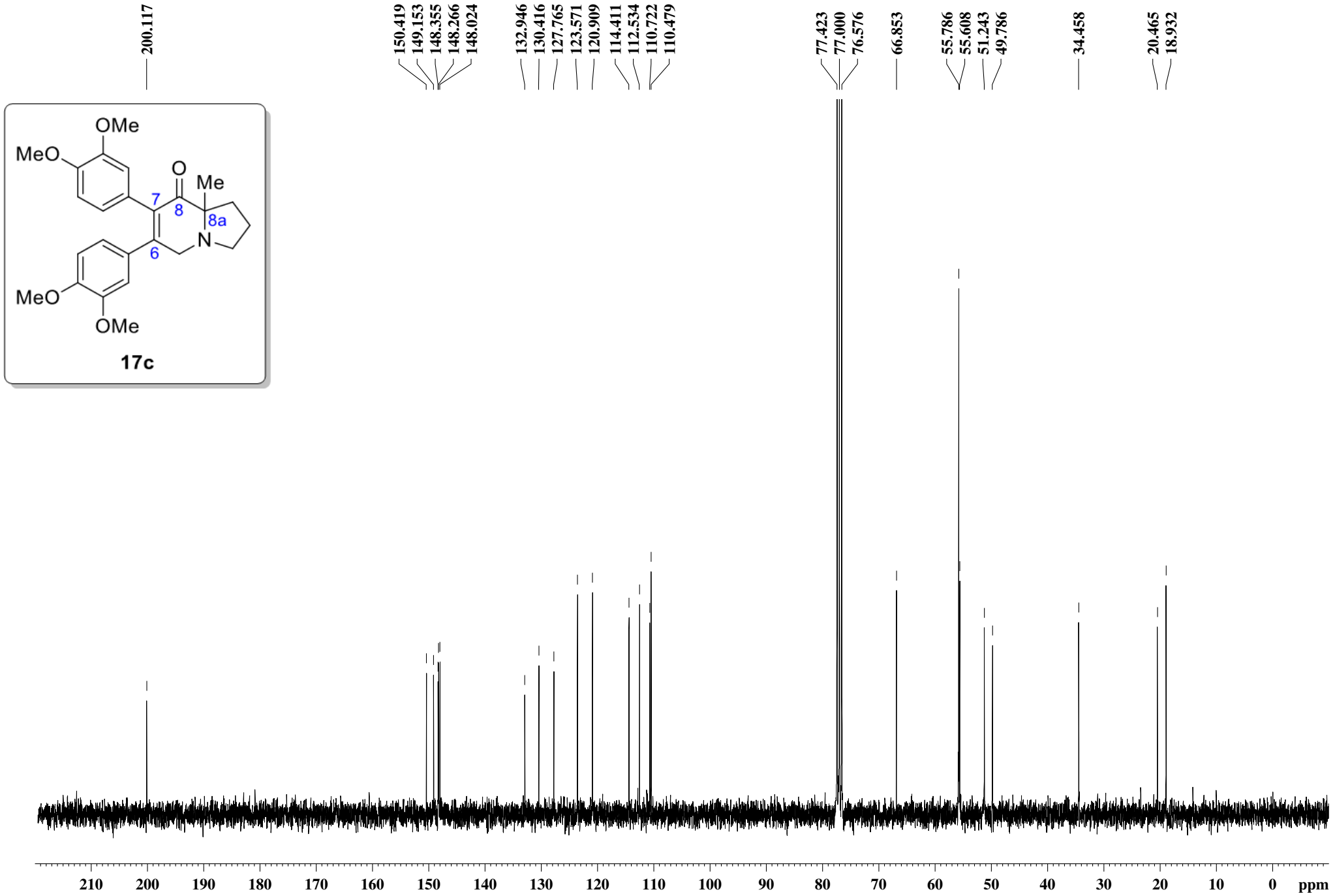
17b

^{1}H (300 MHz,$CDCl_3$)

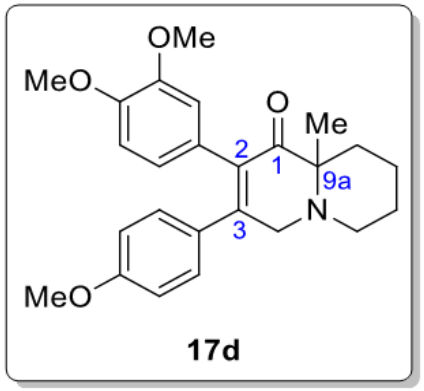


17c

^{13}C (75 MHz, $CDCl_3$)

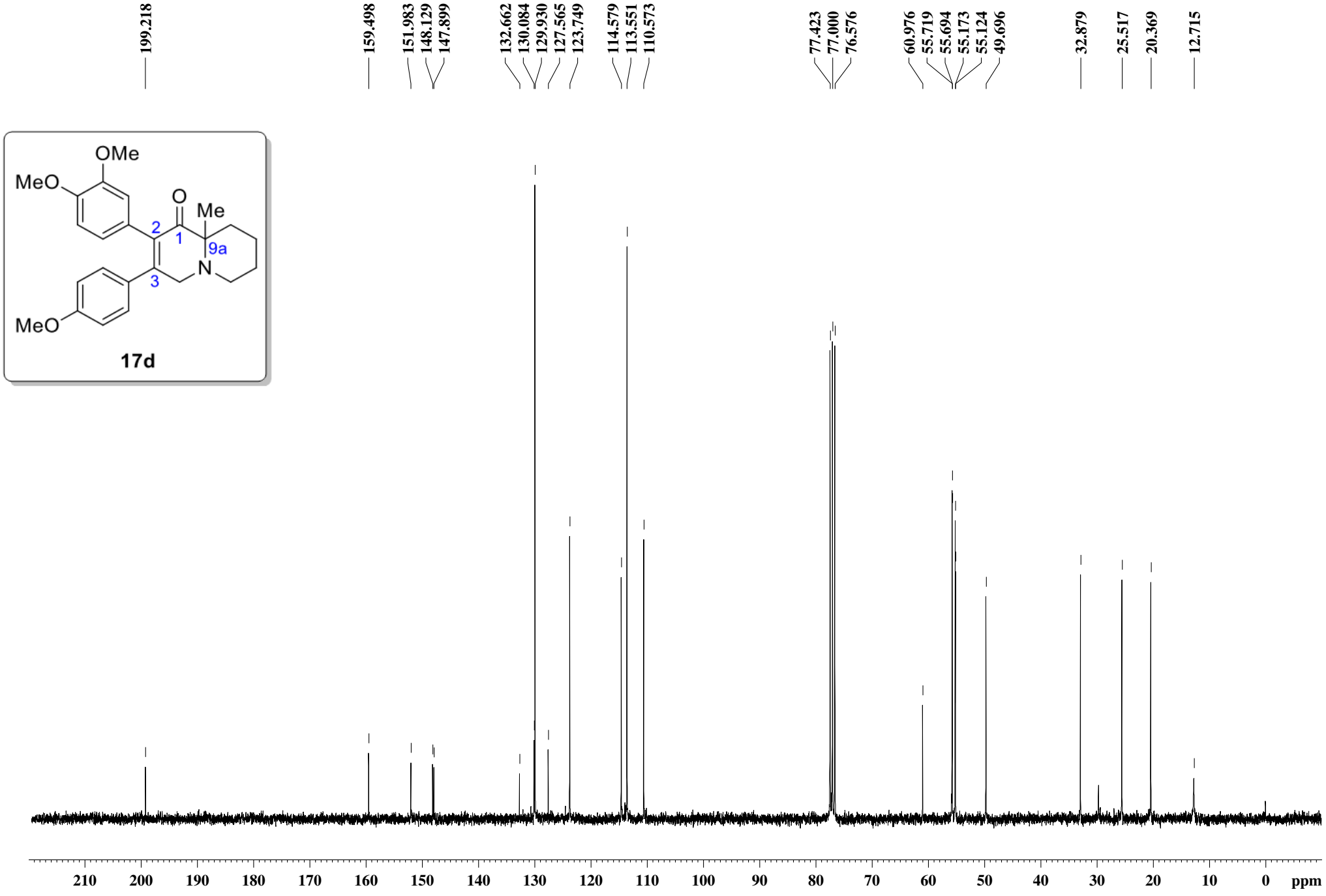


^{1}H (300 MHz,$CDCl_3$)

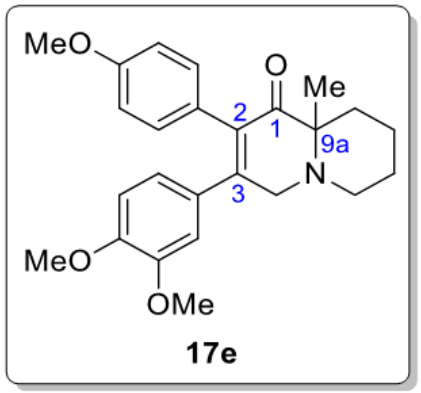


17d

^{13}C (75 MHz, $CDCl_3$)

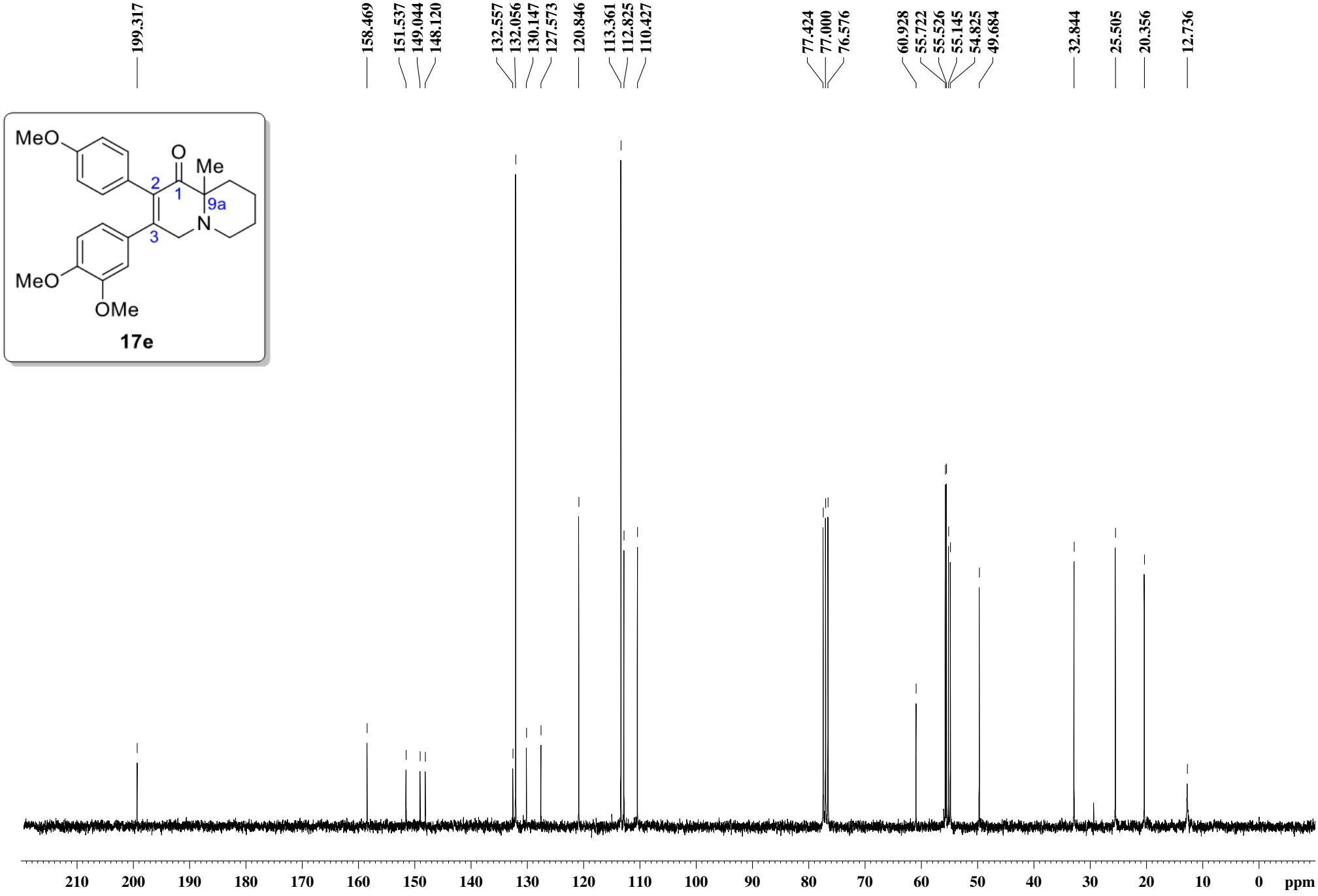


^{1}H (300 MHz,$CDCl_3$)

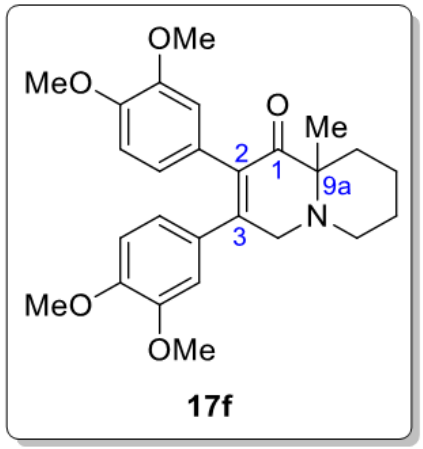


17e

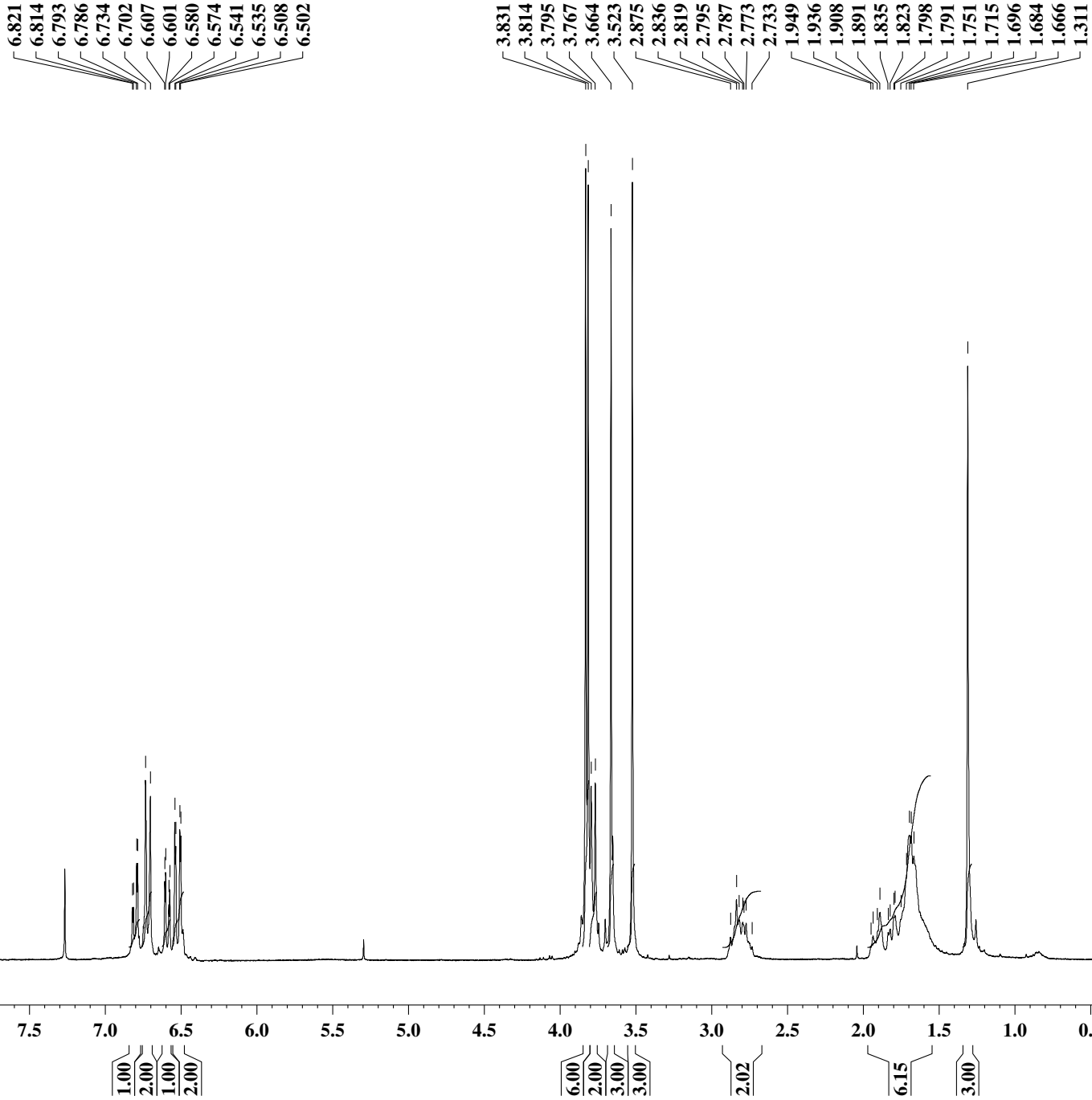
^{13}C (75 MHz, $CDCl_3$)



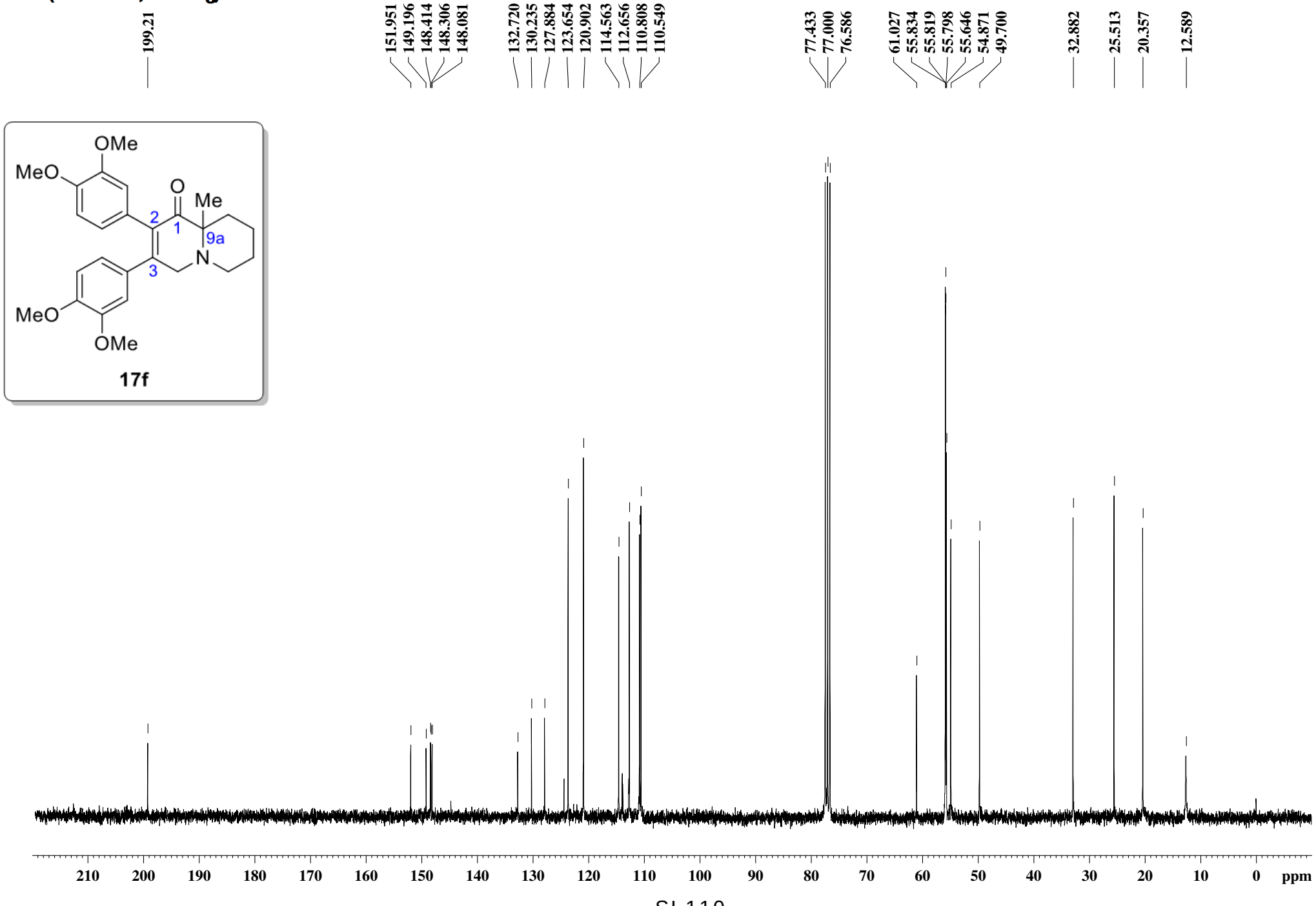
^{1}H (300 MHz,$CDCl_3$)



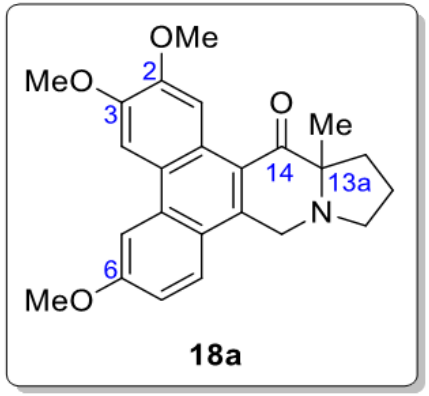
17f



^{13}C (75 MHz, $CDCl_3$)

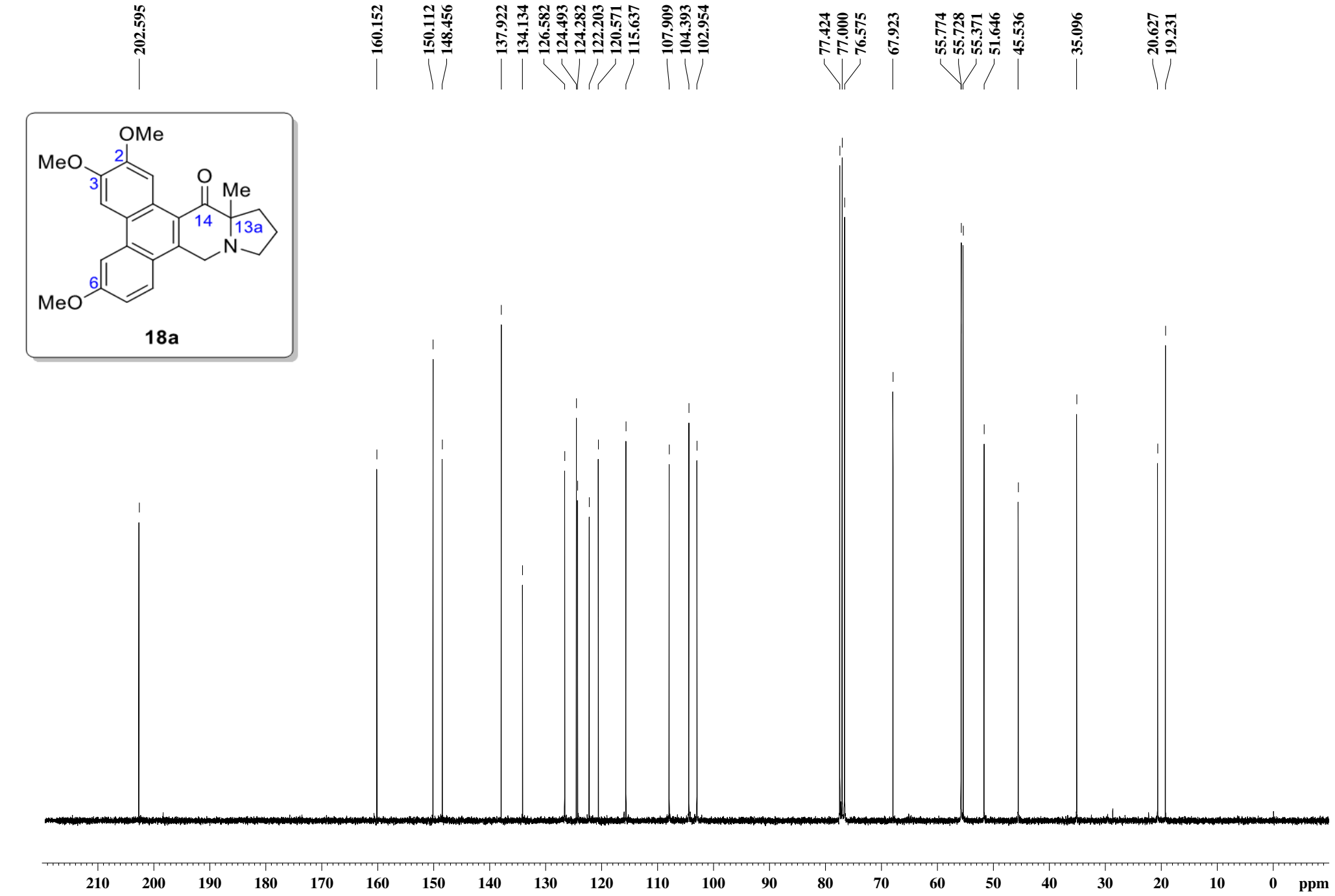


^{1}H (300 MHz,$CDCl_3$)

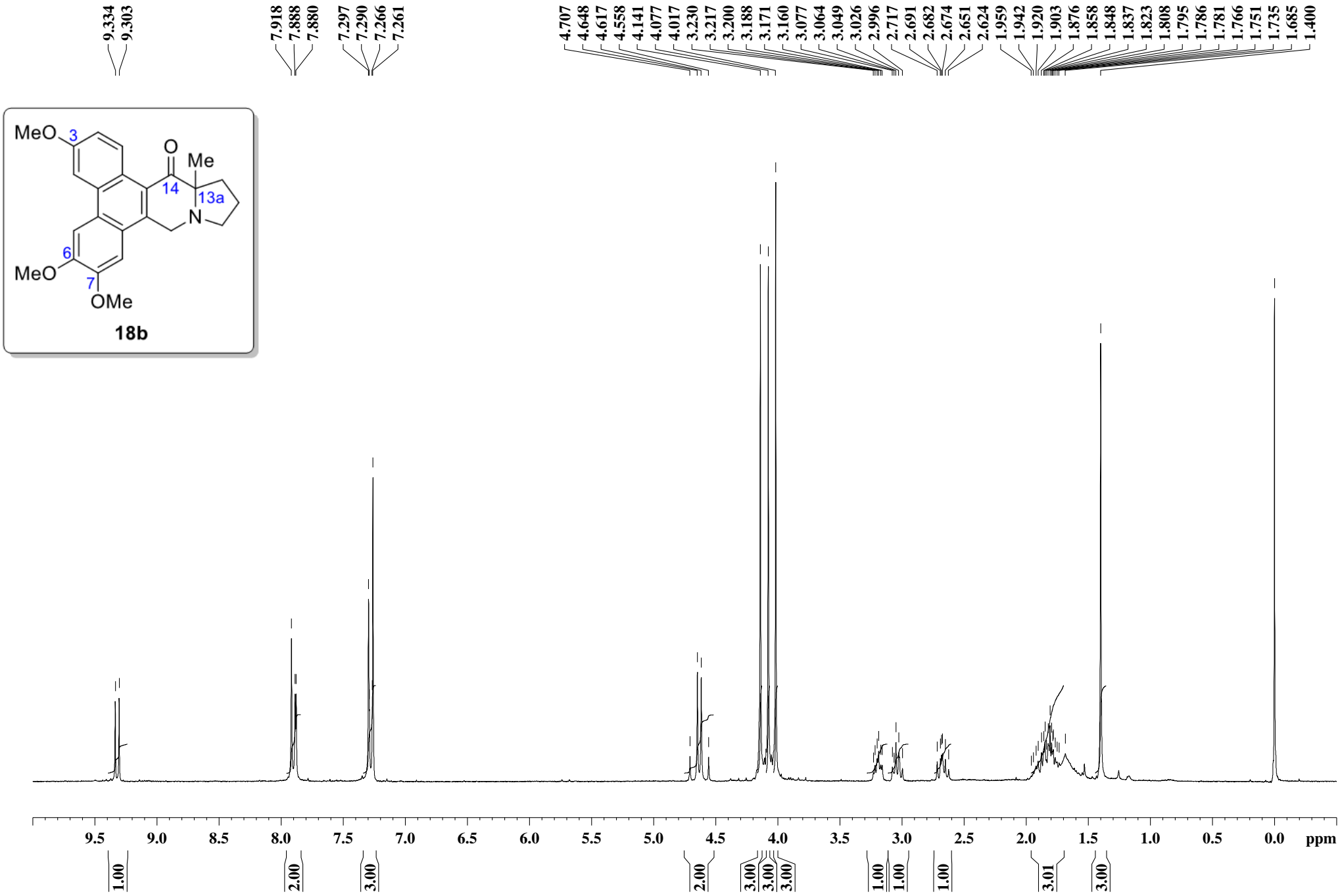


18a

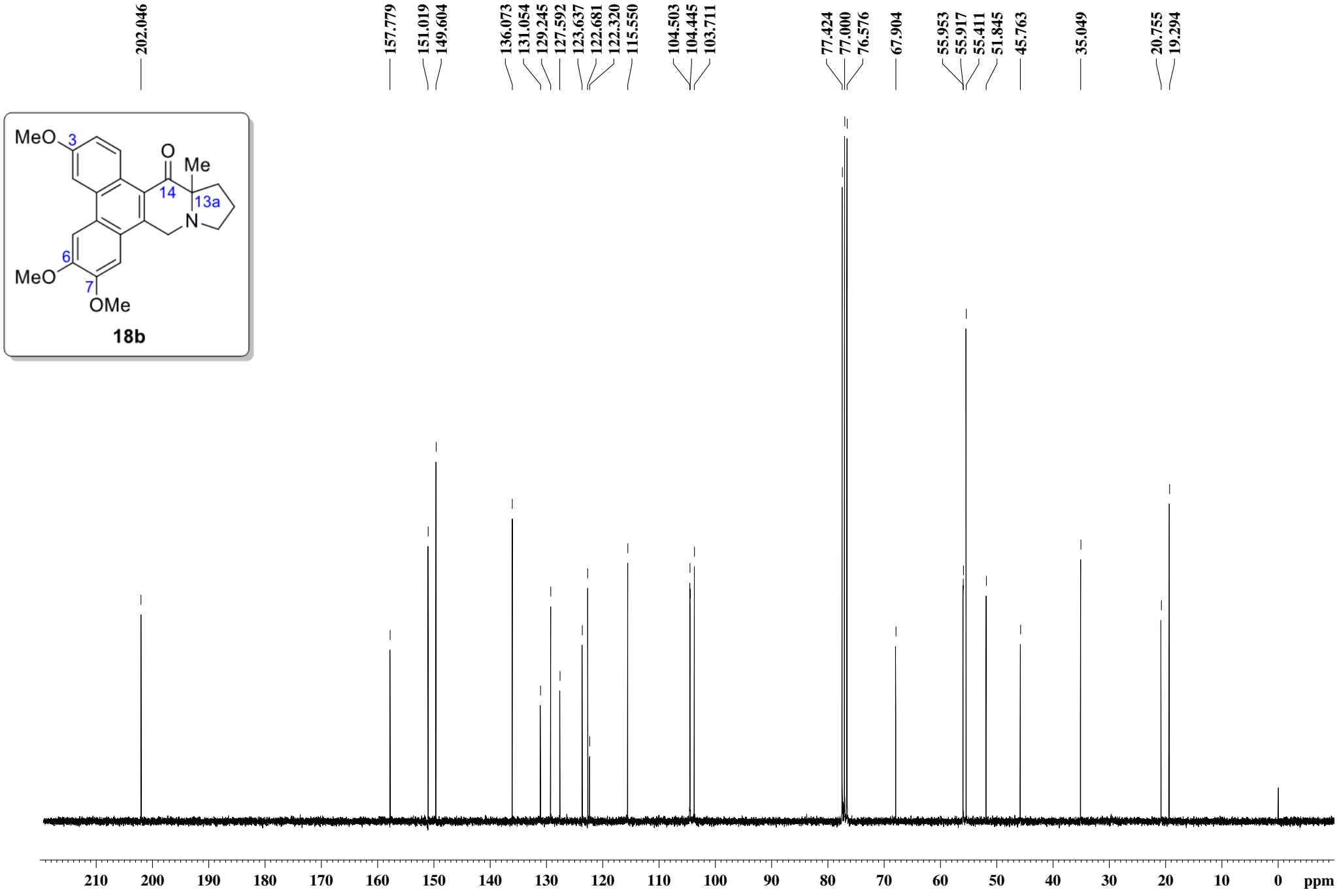
^{13}C (75 MHz, $CDCl_3$)



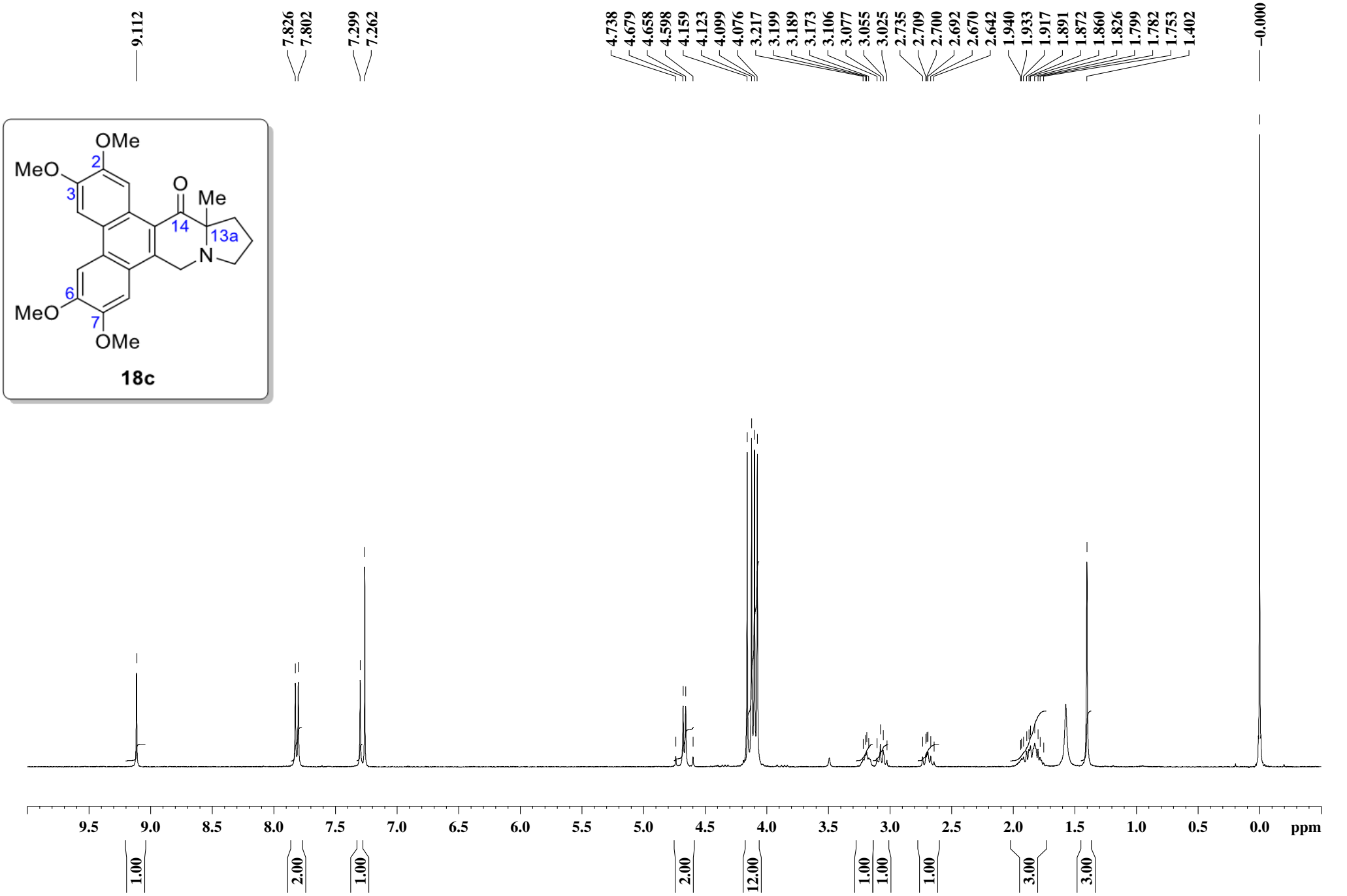
^{1}H (300 MHz,$CDCl_3$)



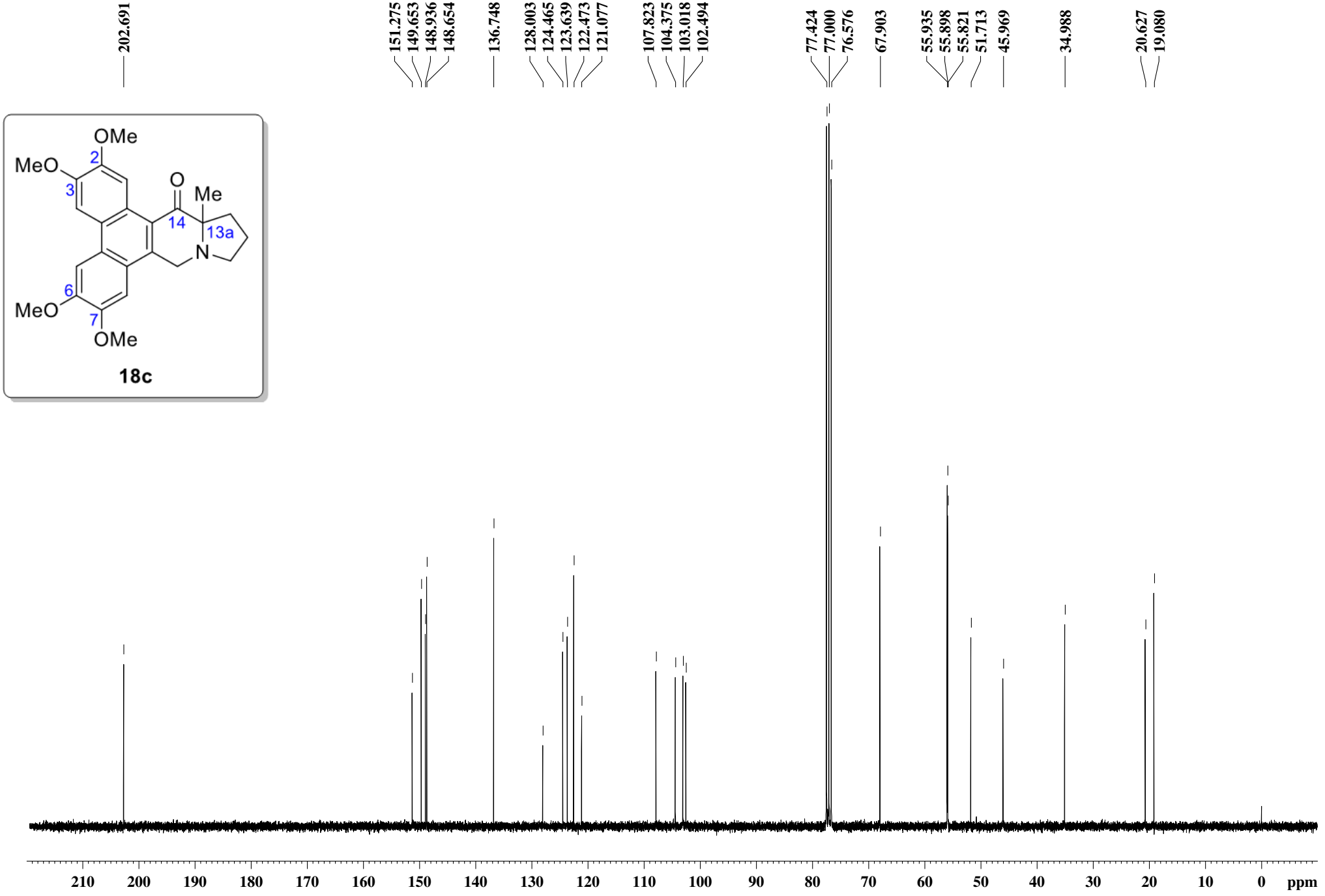
^{13}C (75 MHz, $CDCl_3$)



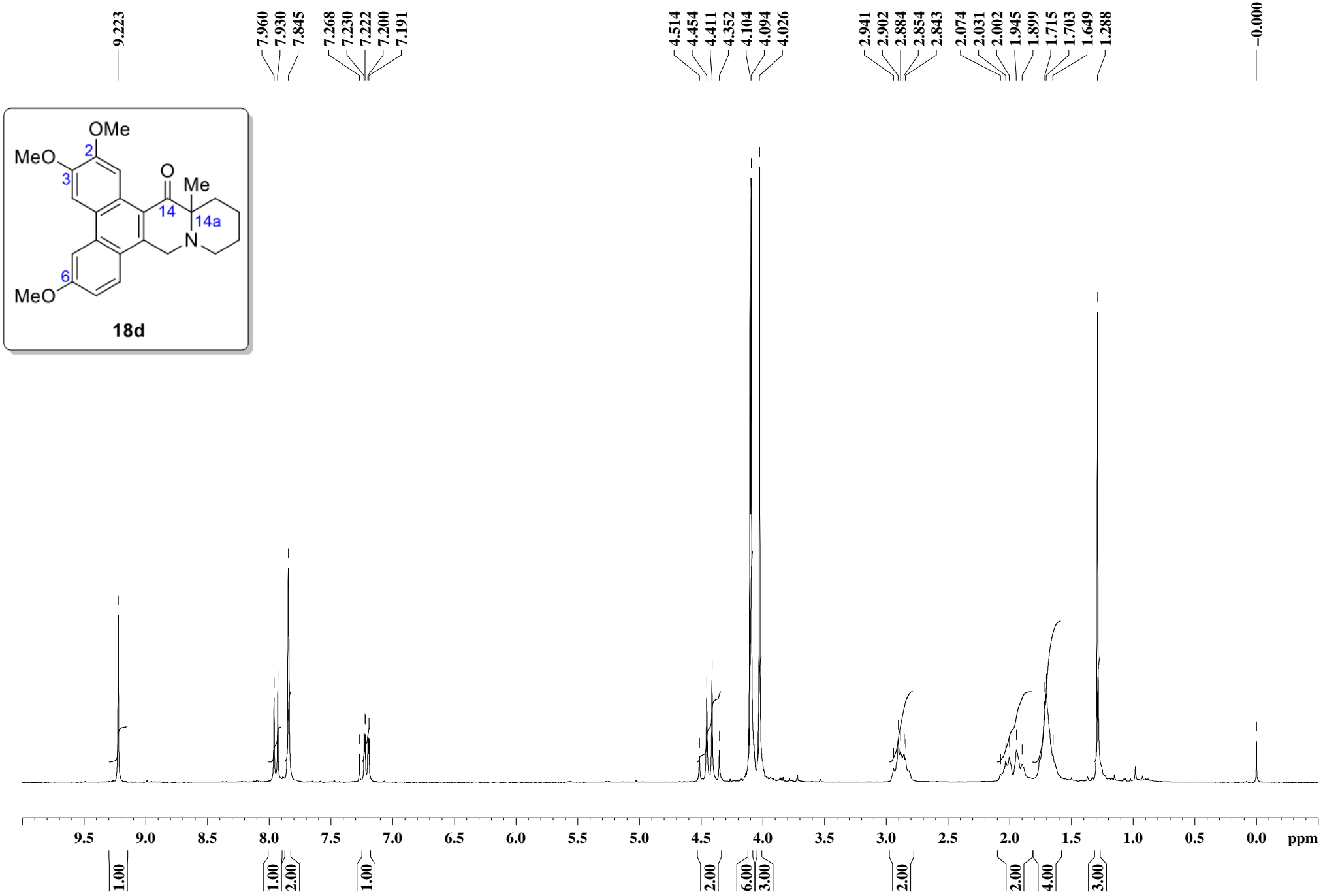
^{1}H (300 MHz,$CDCl_3$)



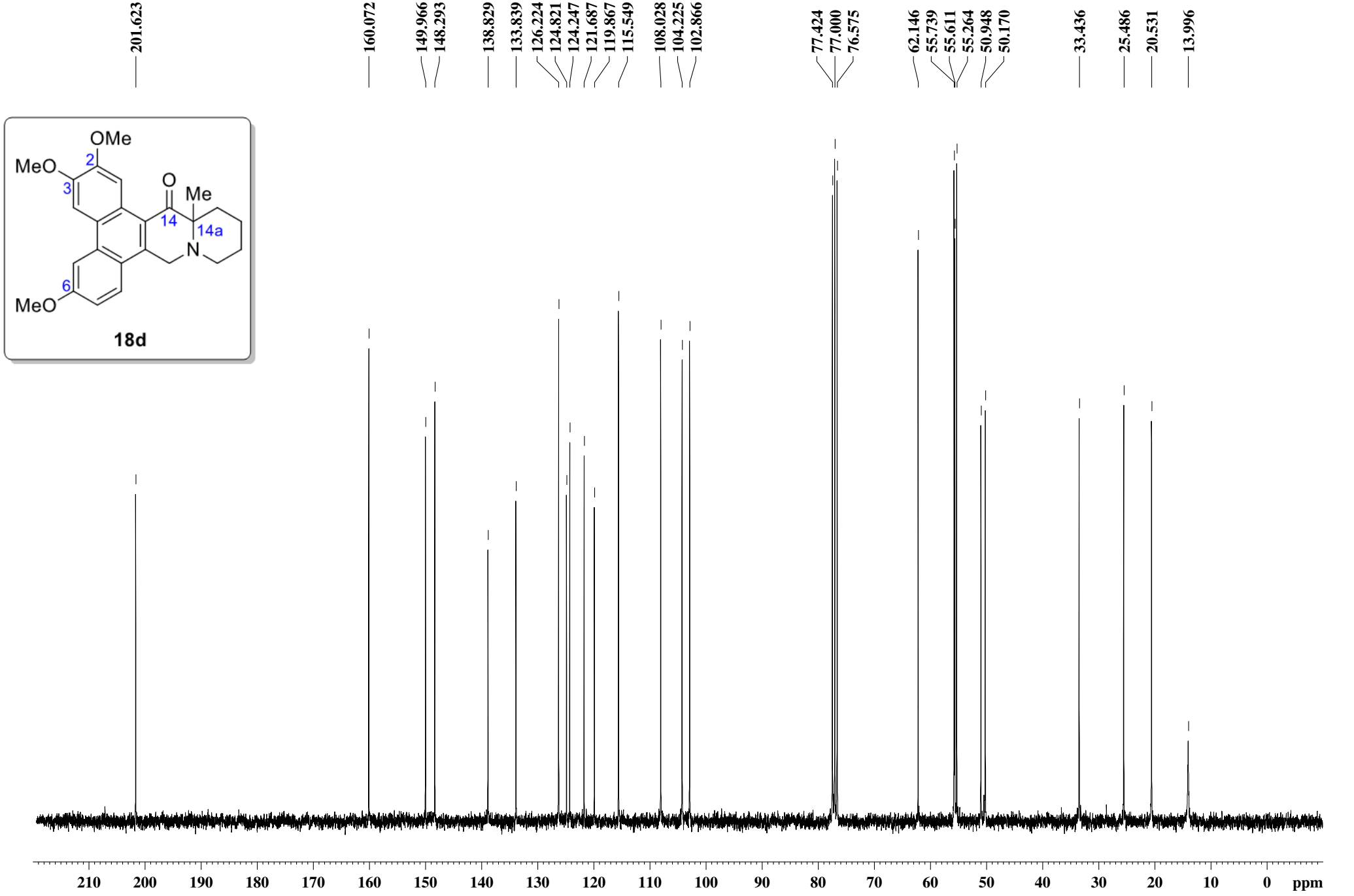
^{13}C (75 MHz, $CDCl_3$)



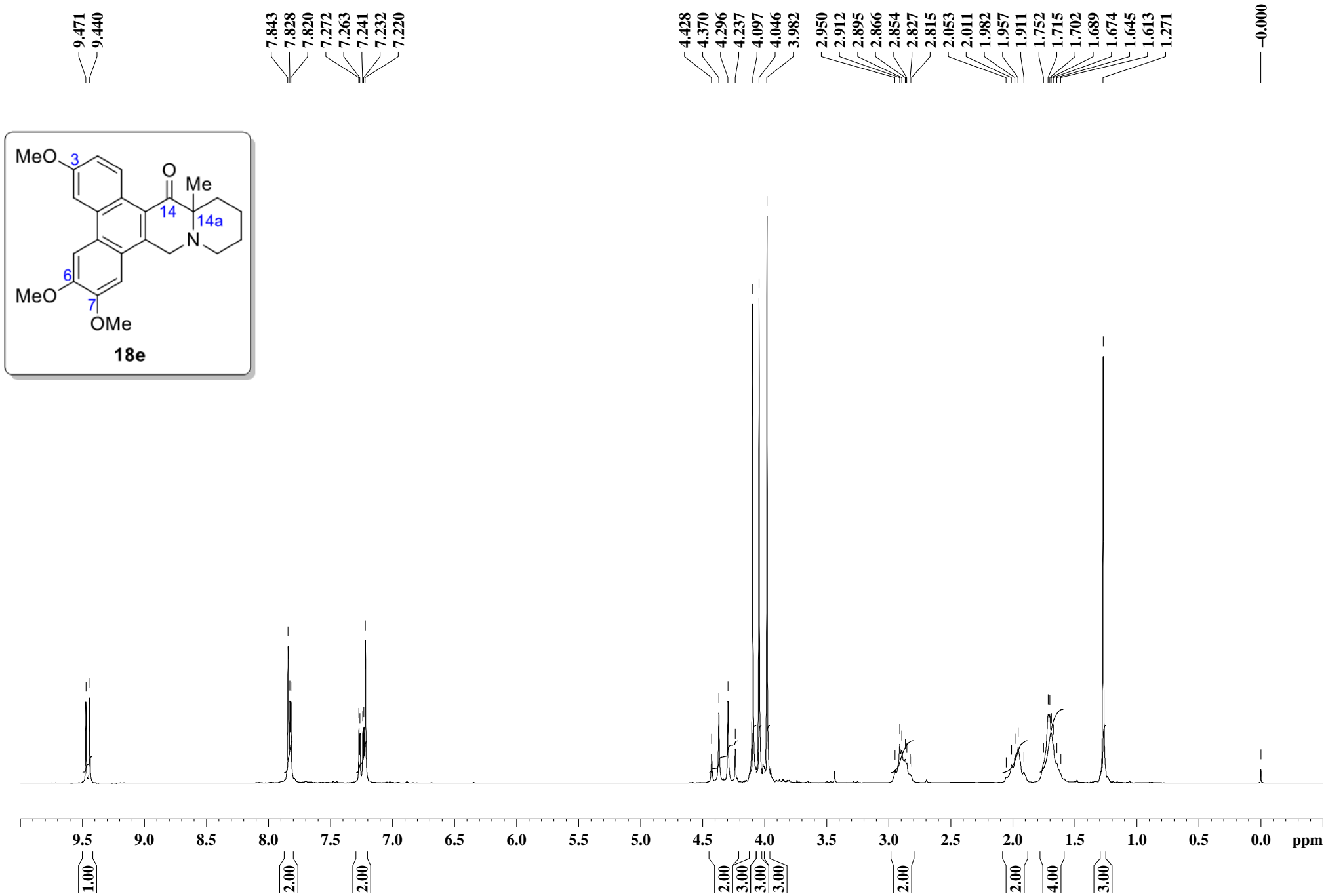
^{1}H (300 MHz,$CDCl_3$)



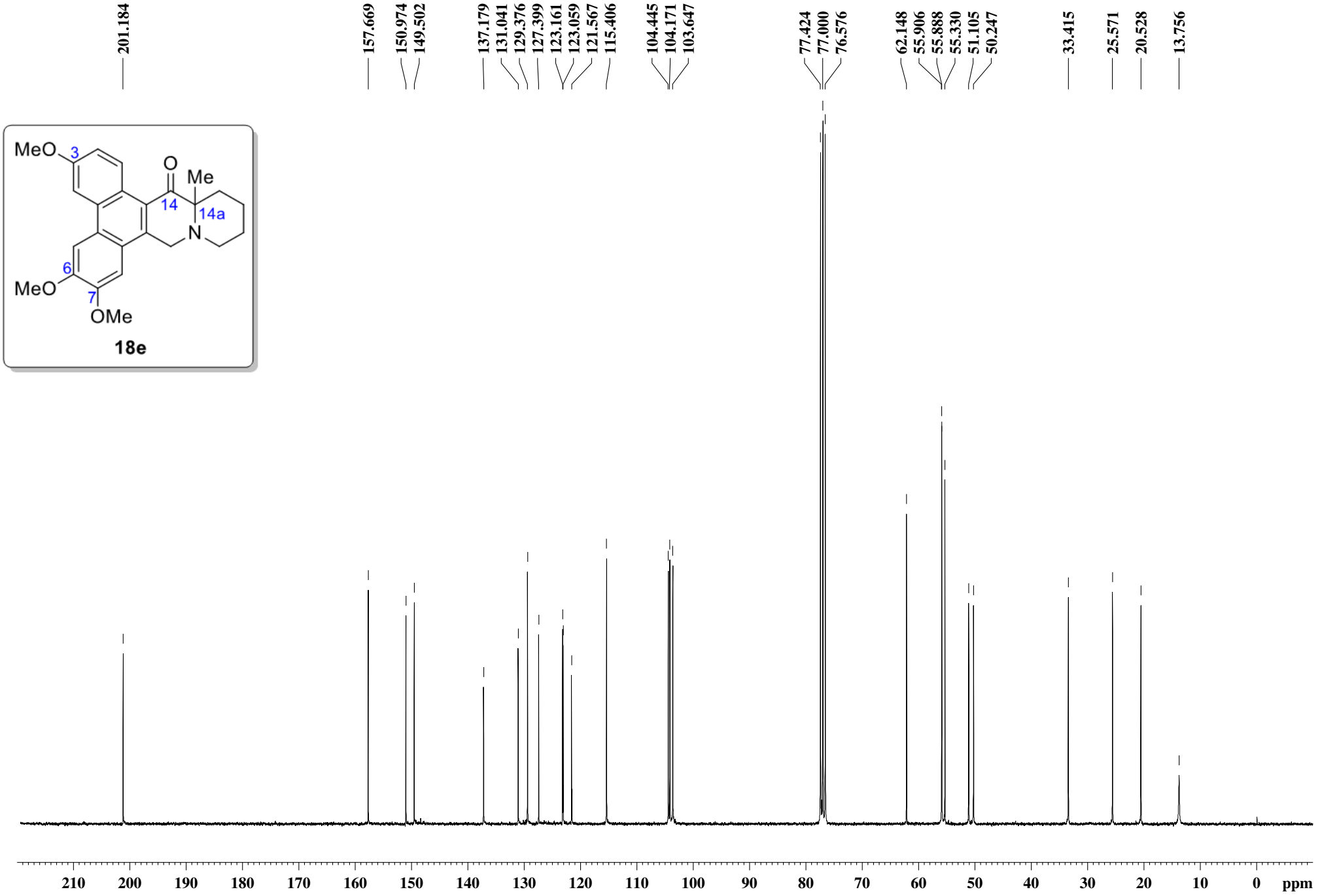
^{13}C (75 MHz, $CDCl_3$)



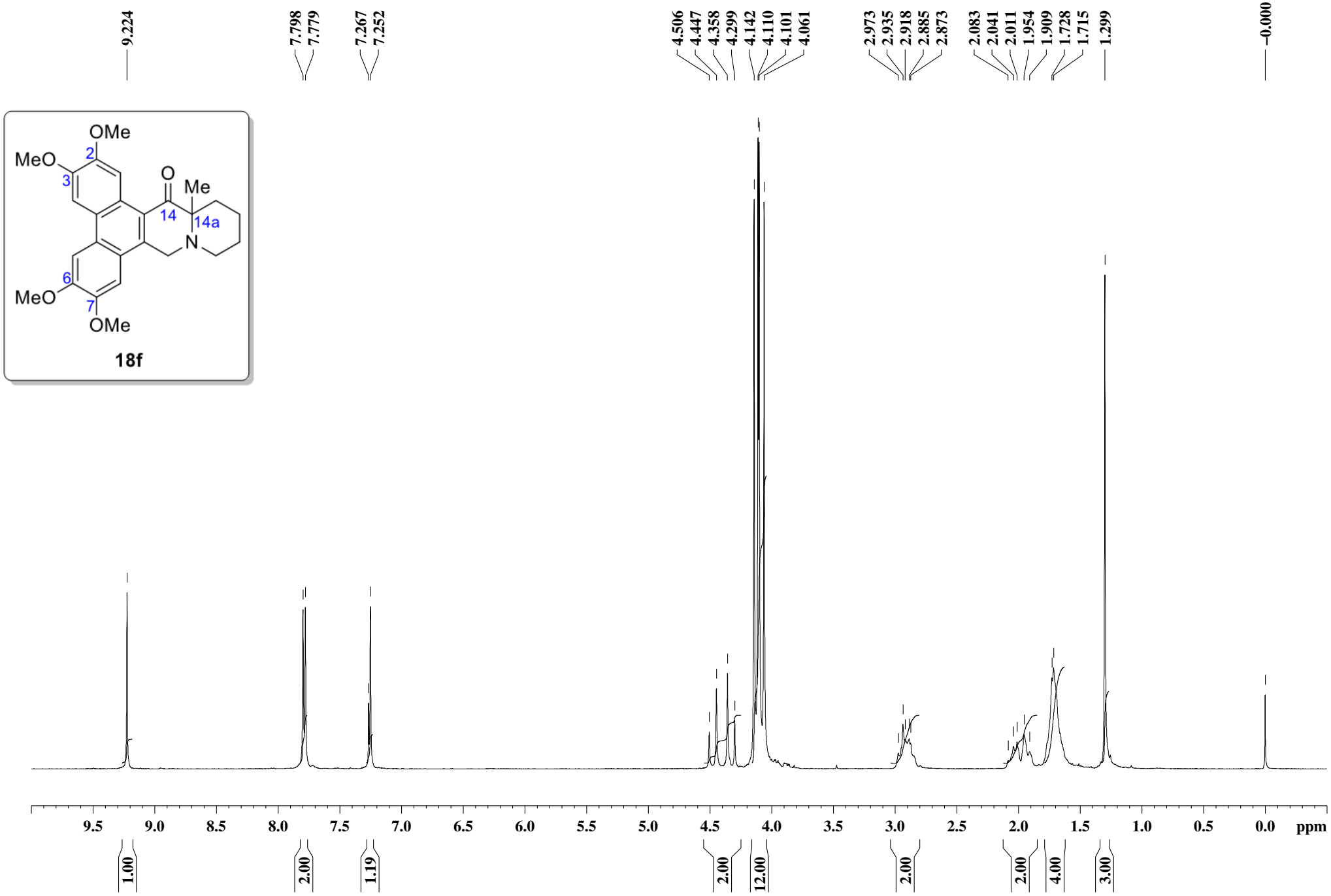
^{1}H (300 MHz,$CDCl_3$)



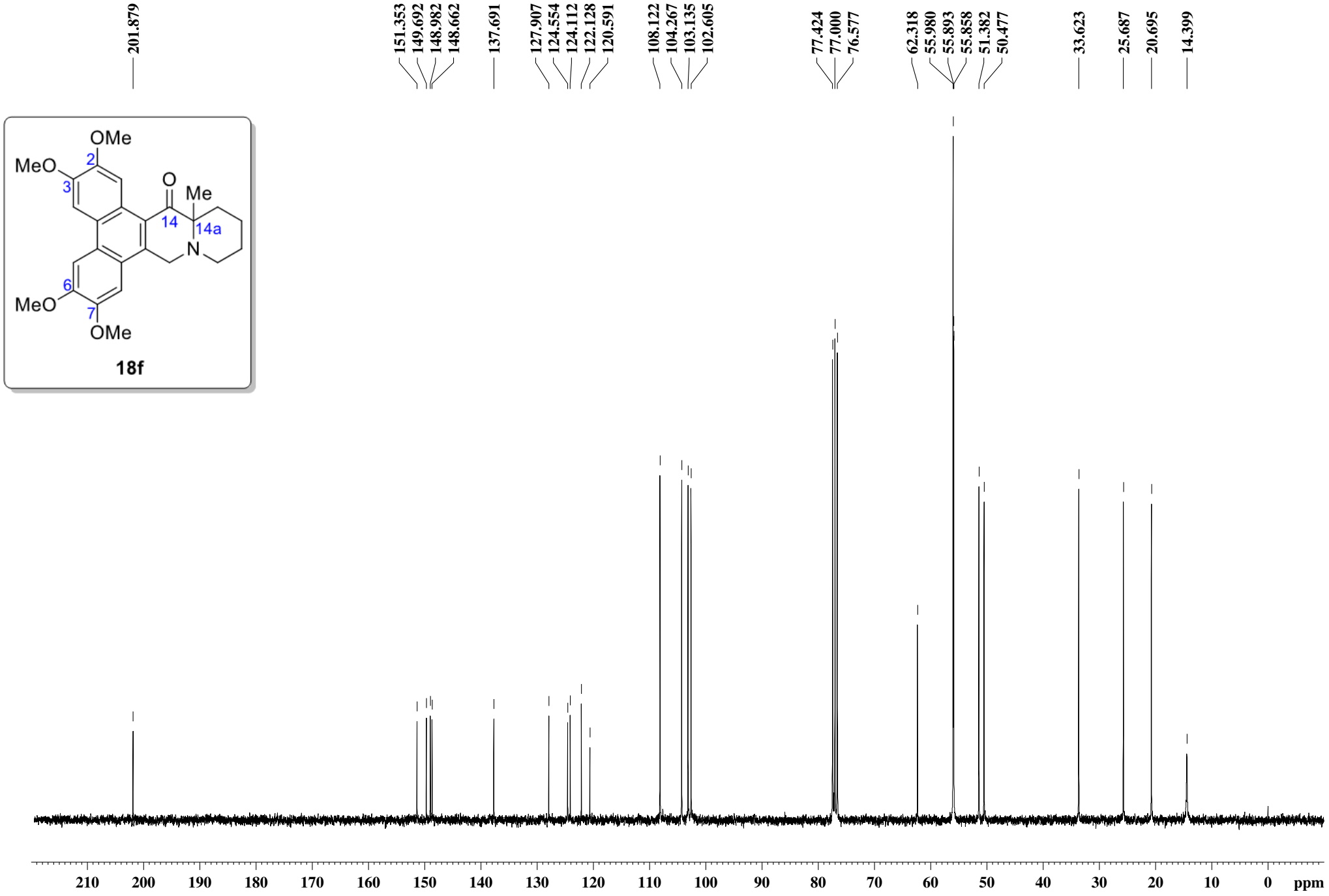
^{13}C (75 MHz, $CDCl_3$)



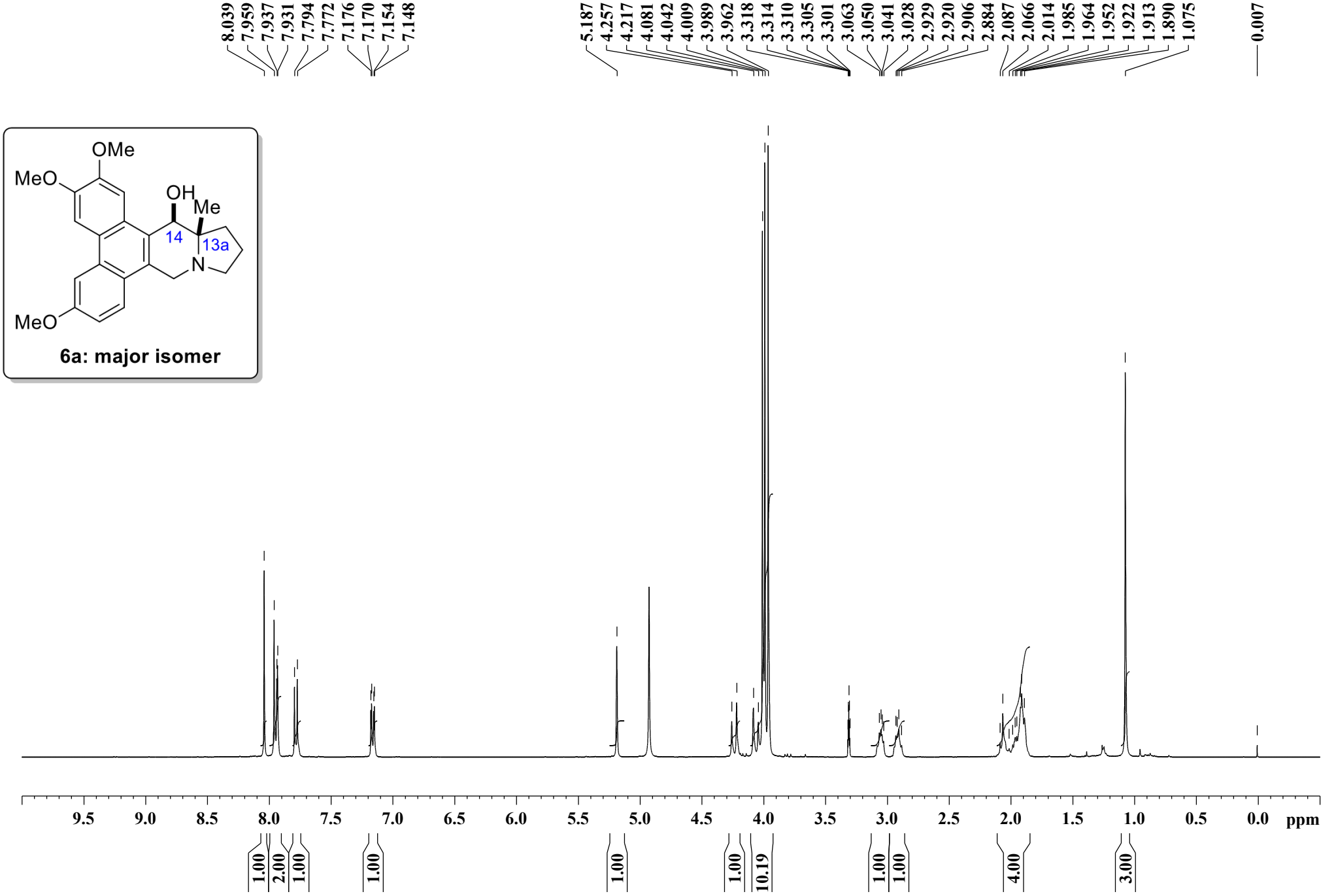
^{1}H (300 MHz,$CDCl_3$)



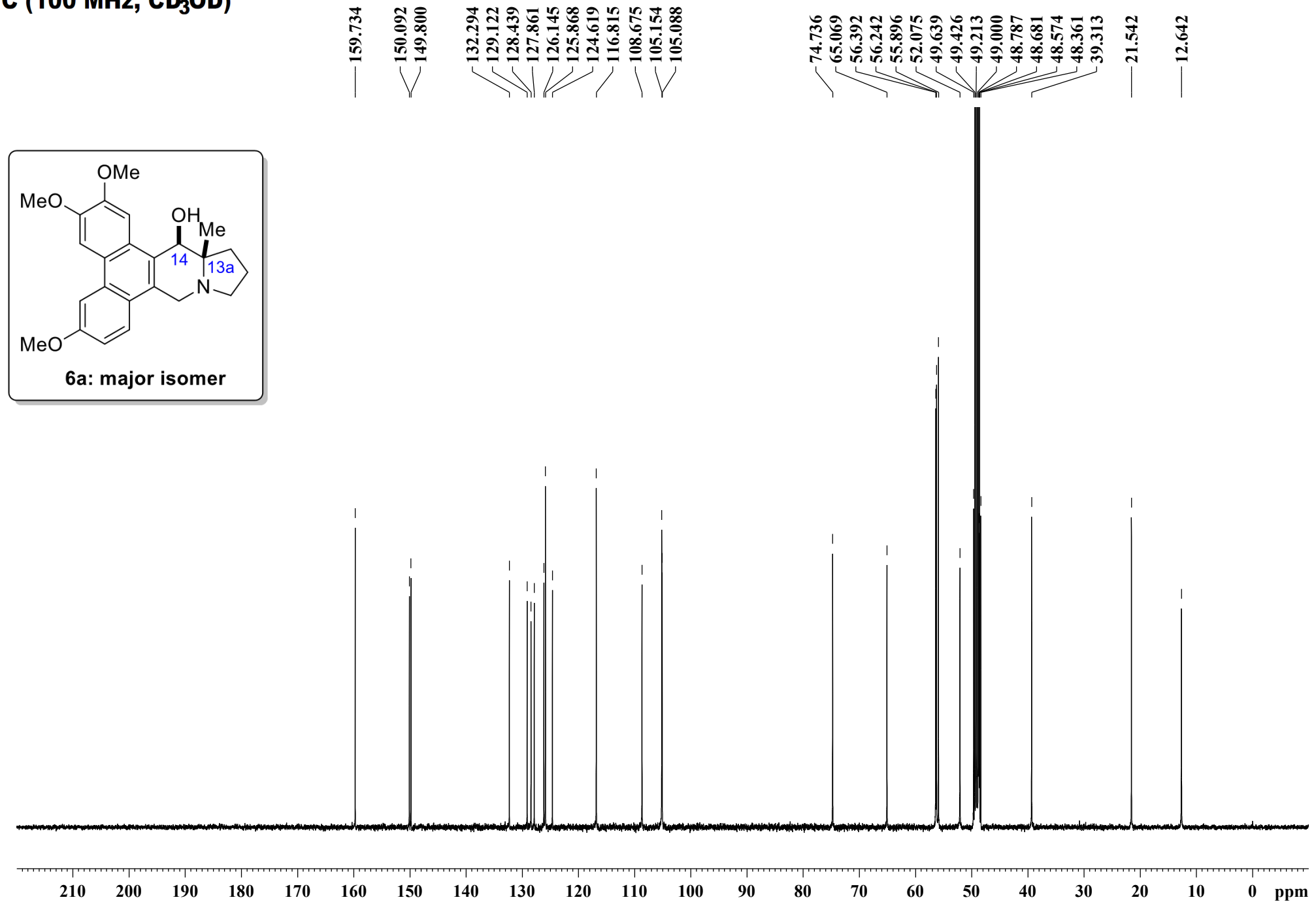
^{13}C (75 MHz, $CDCl_3$)



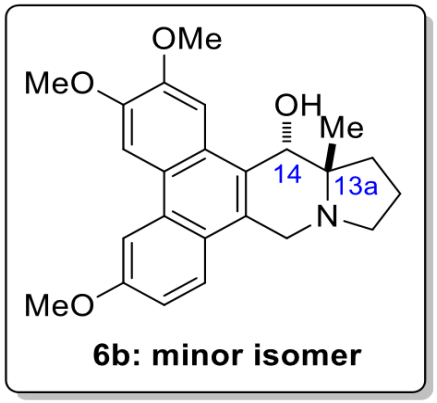
^{1}H (400 MHz, CD_3OD)



^{13}C (100 MHz, CD_3OD)

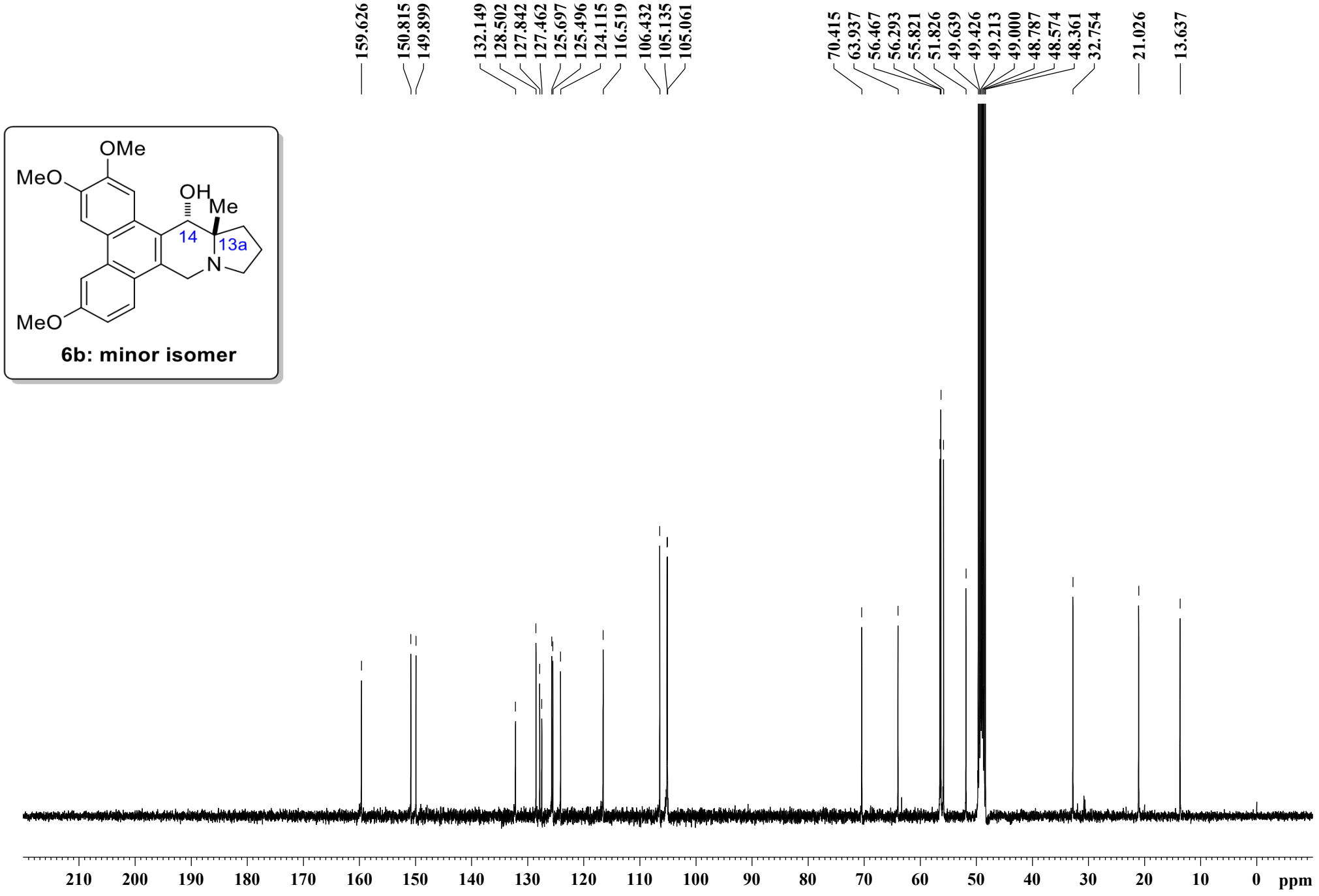


^{1}H (400 MHz, CD_3OD)

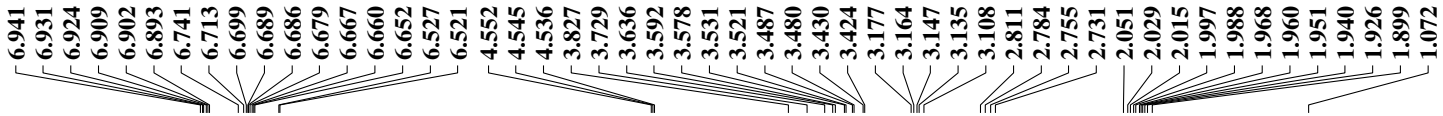


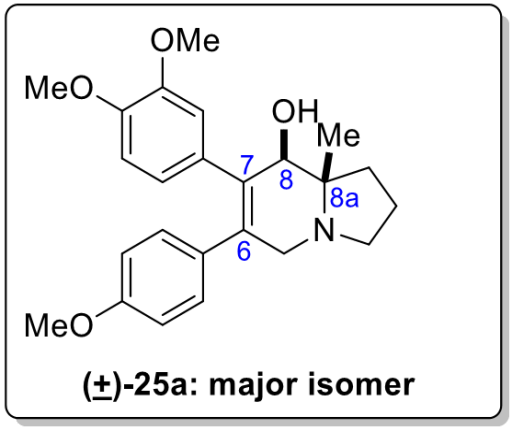
6b: minor isomer

^{13}C (100 MHz, CD_3OD)



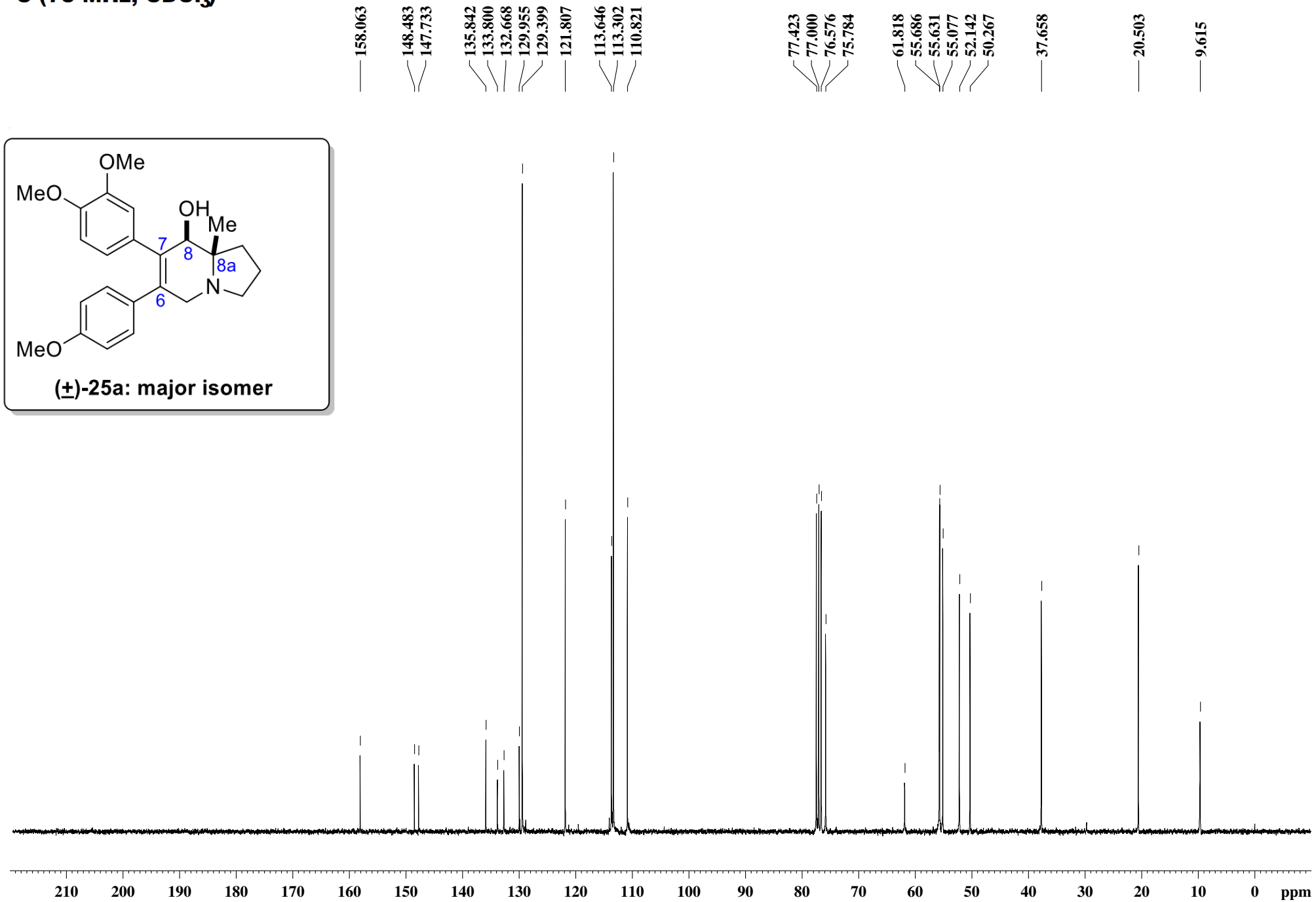
^{1}H (300 MHz,$CDCl_3$)



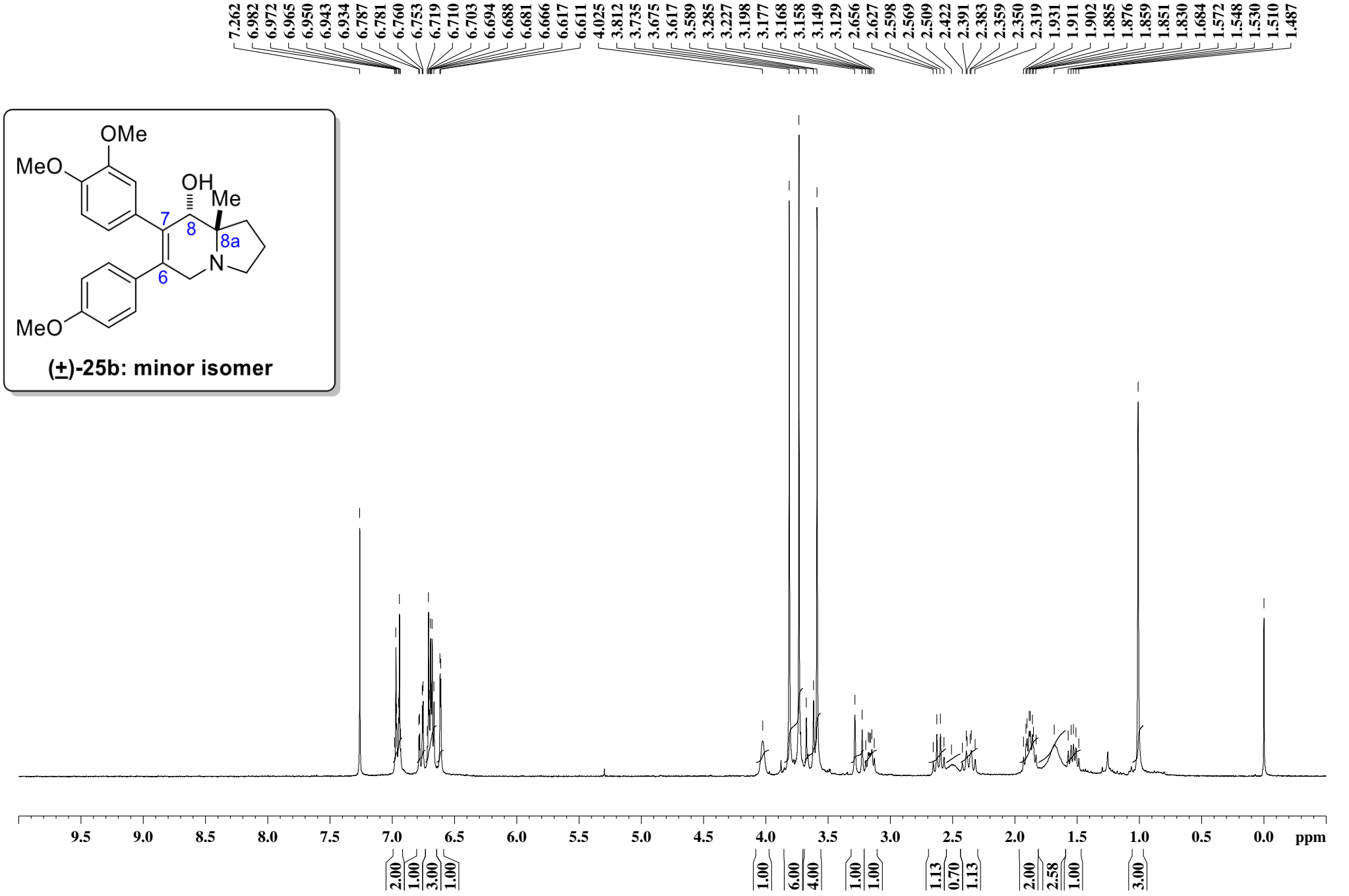


(±)-25a: major isomer

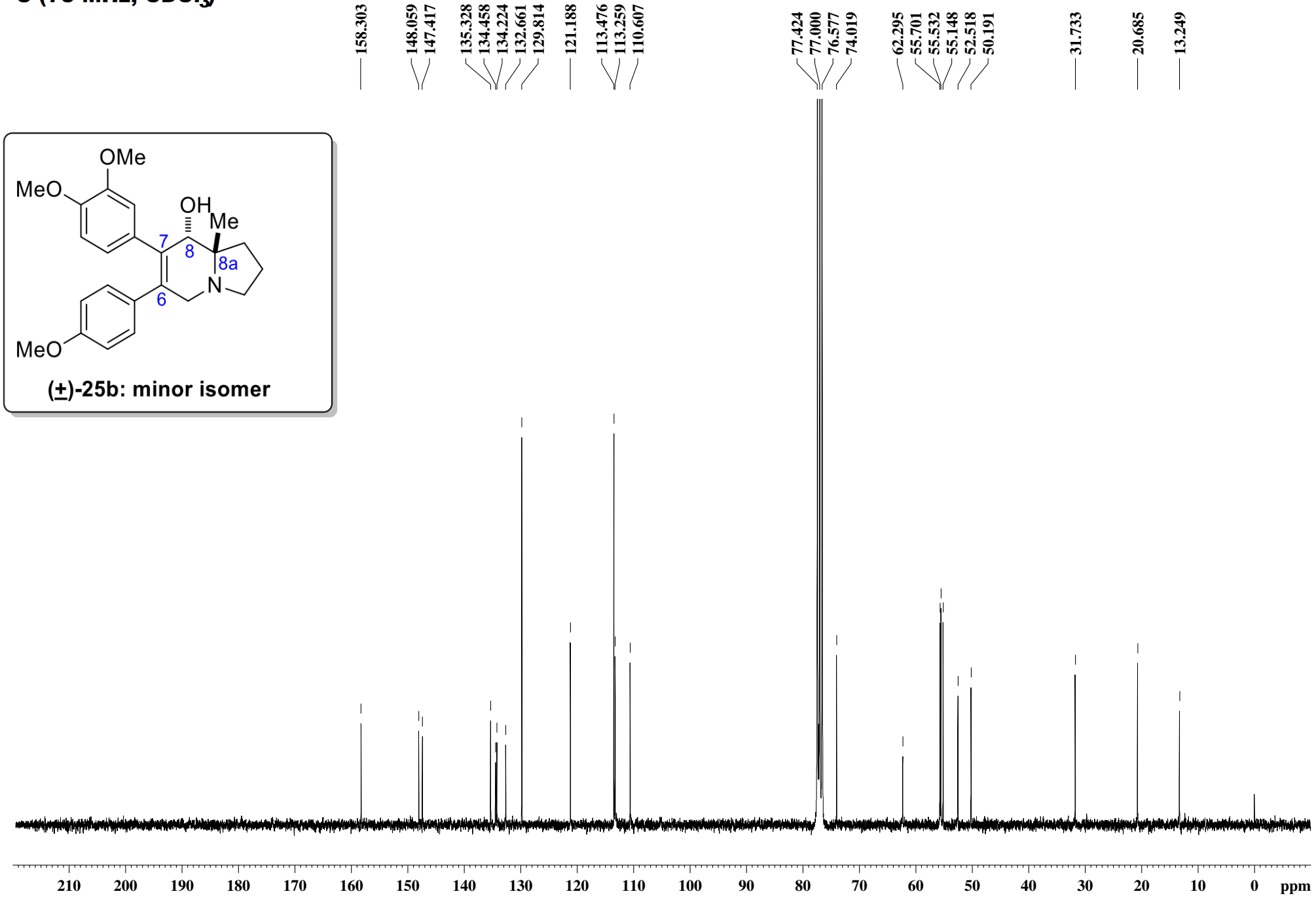
^{13}C (75 MHz, $CDCl_3$)



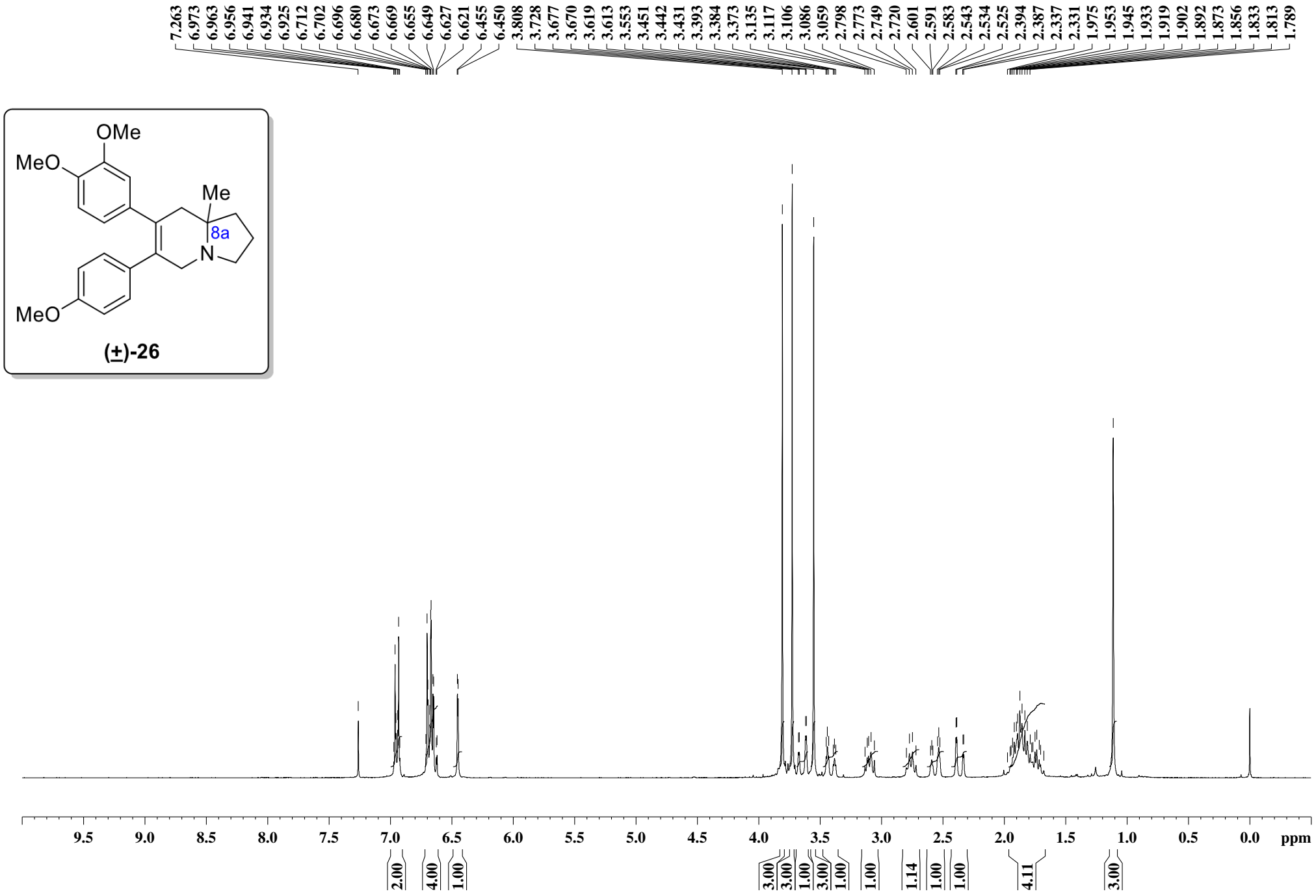
^{1}H (300 MHz,$CDCl_3$)



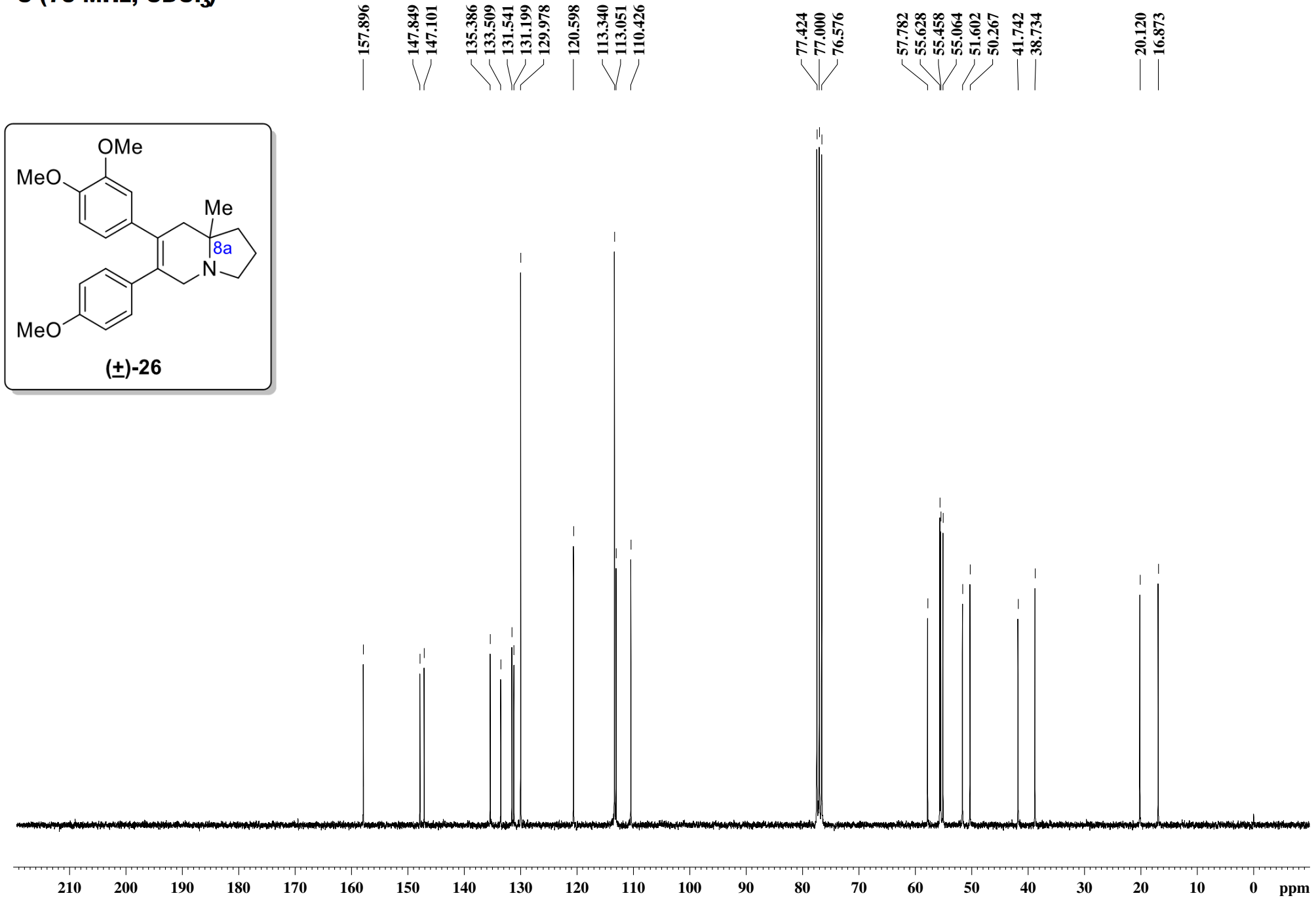
^{13}C (75 MHz, $CDCl_3$)



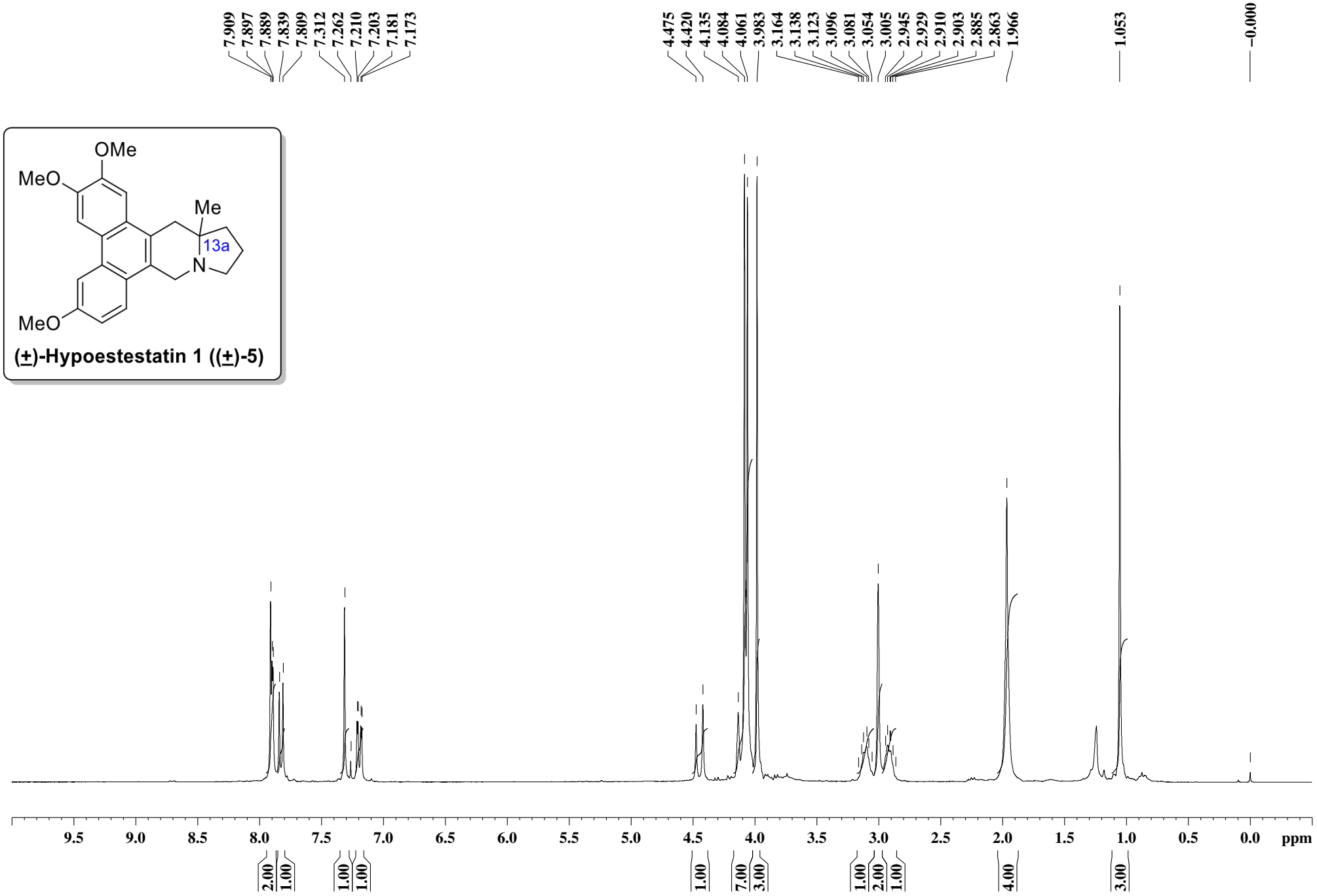
^{1}H (300 MHz,$CDCl_3$)



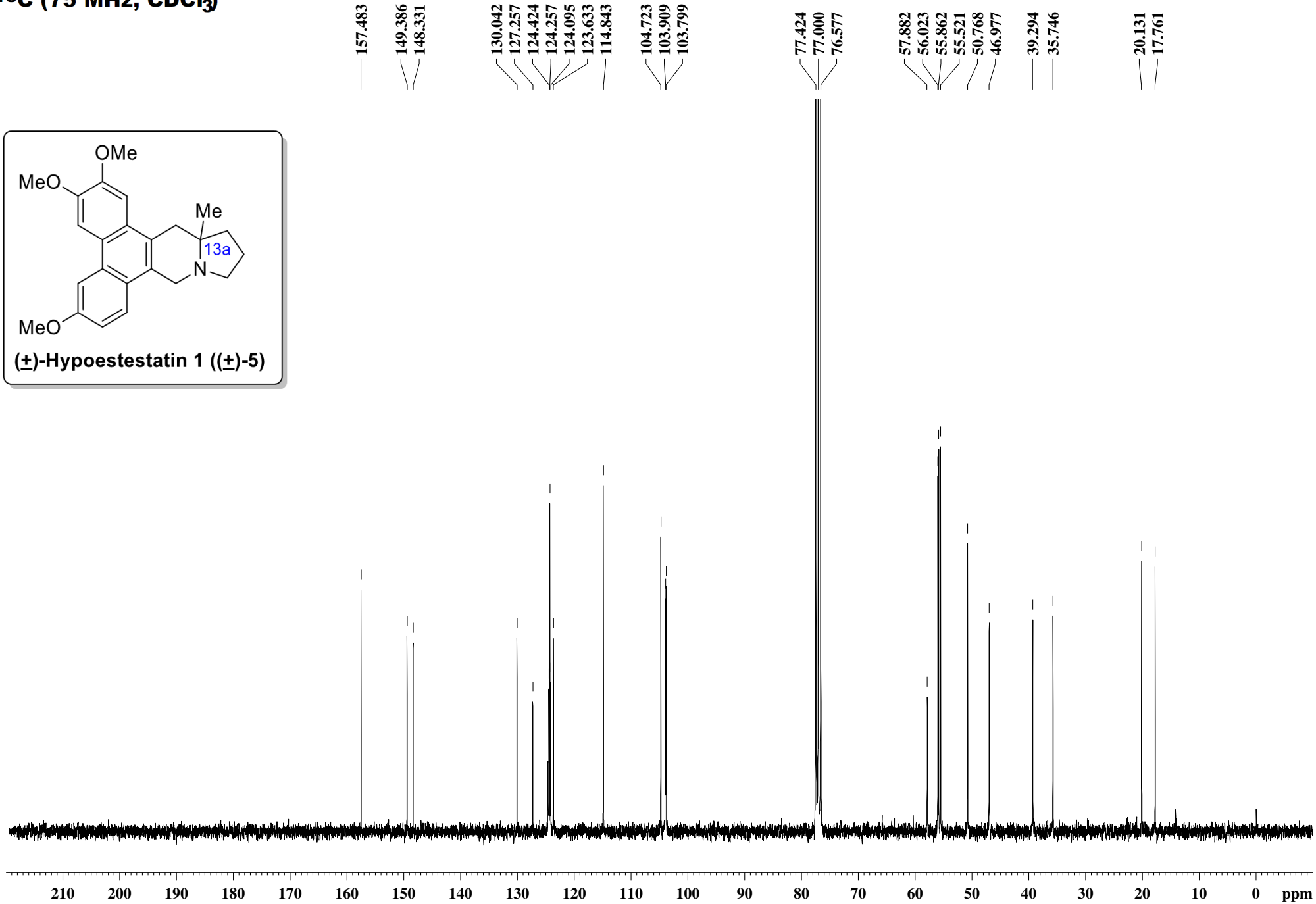
^{13}C (75 MHz, $CDCl_3$)



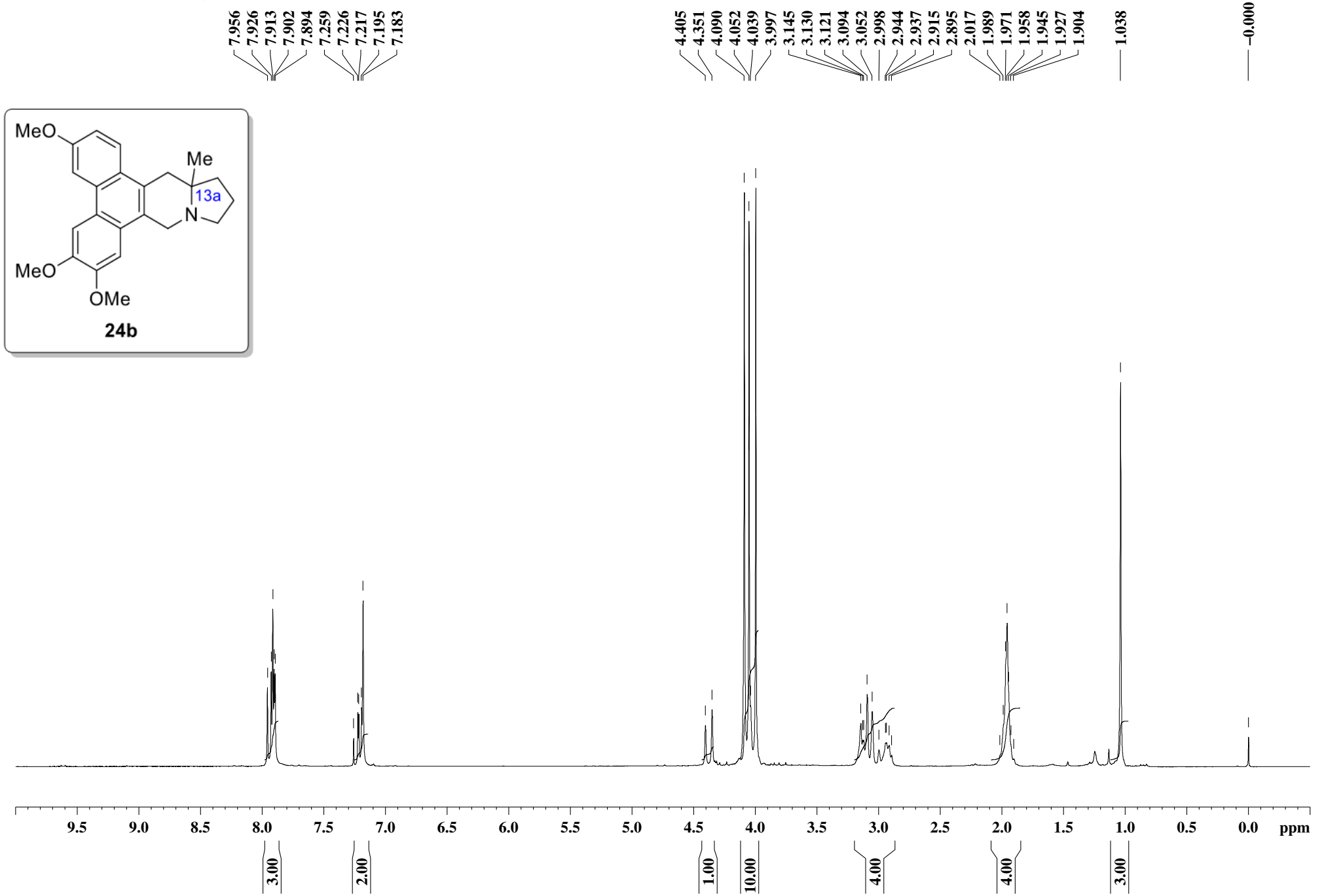
^{1}H (300 MHz,$CDCl_3$)



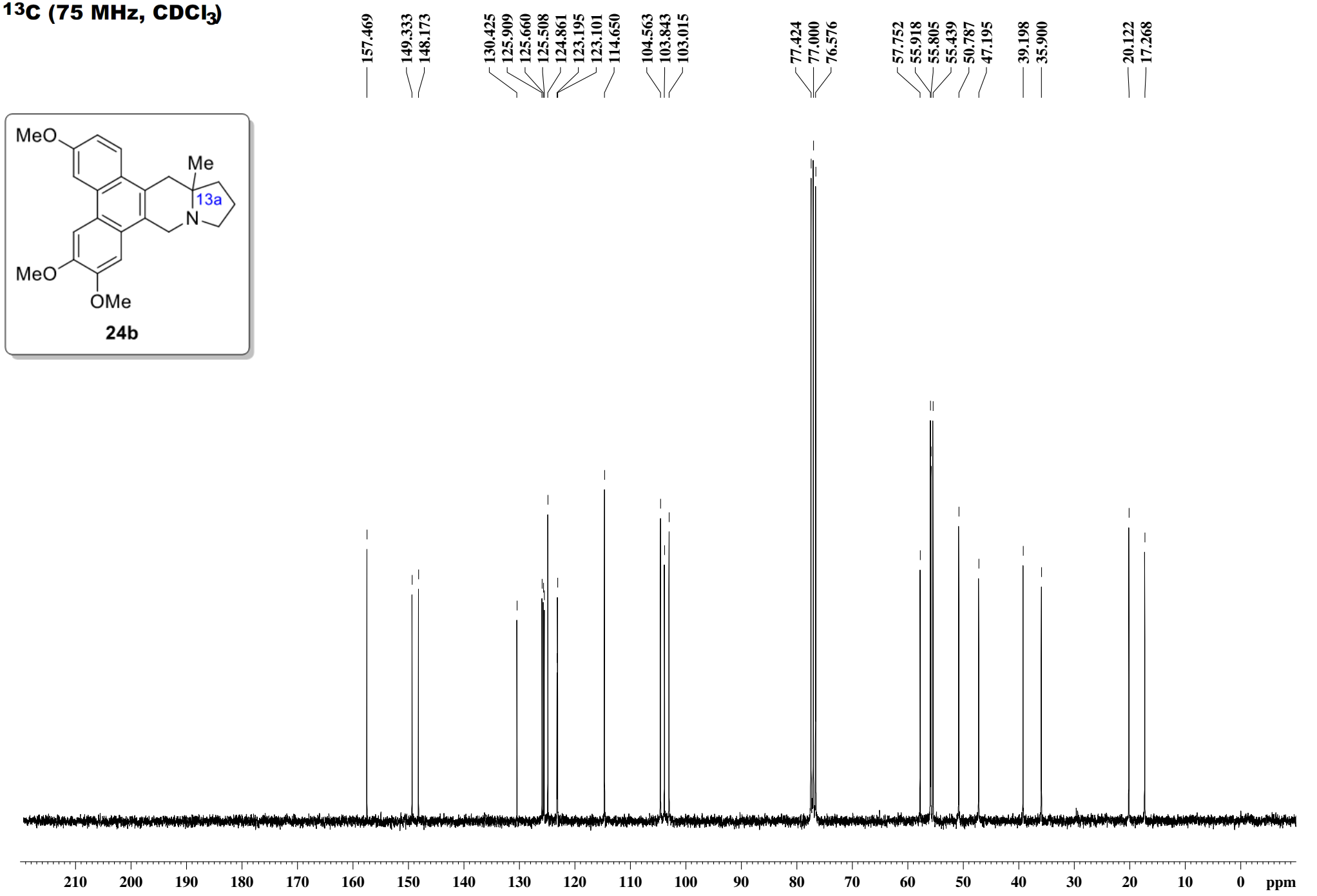
^{13}C (75 MHz, $CDCl_3$)



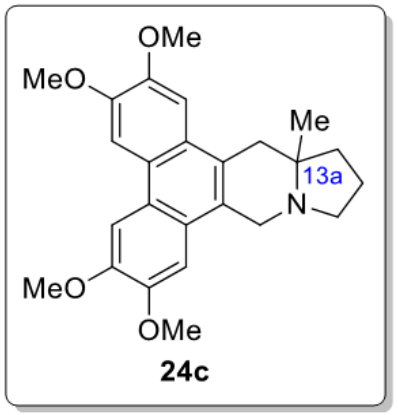
^{1}H (300 MHz,$CDCl_3$)



^{13}C (75 MHz, $CDCl_3$)

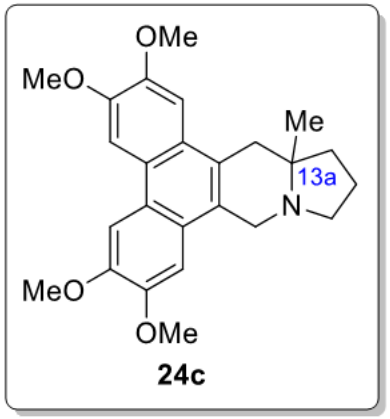


^{1}H (300 MHz,$CDCl_3$)



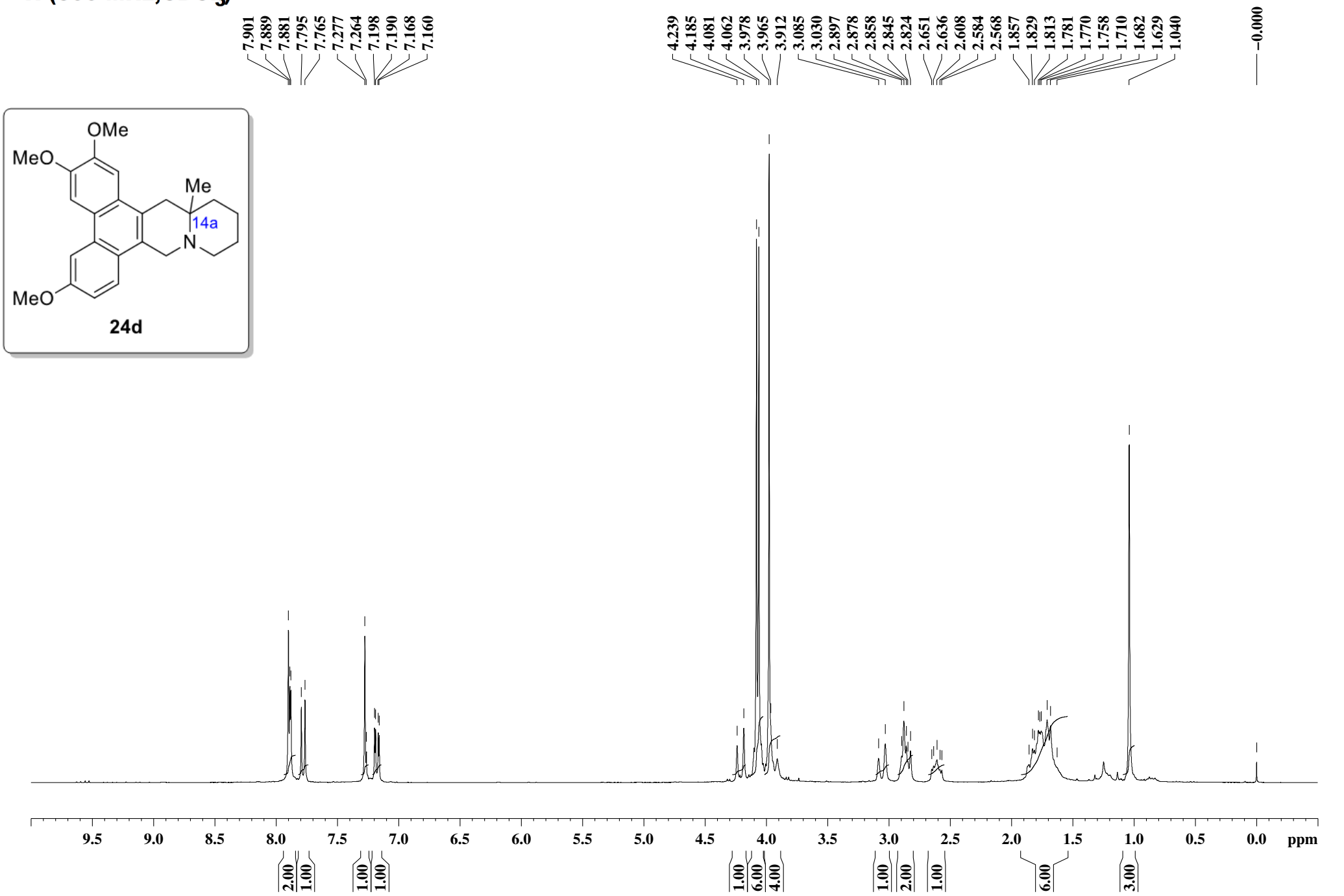
24c

^{13}C (75 MHz, $CDCl_3$)

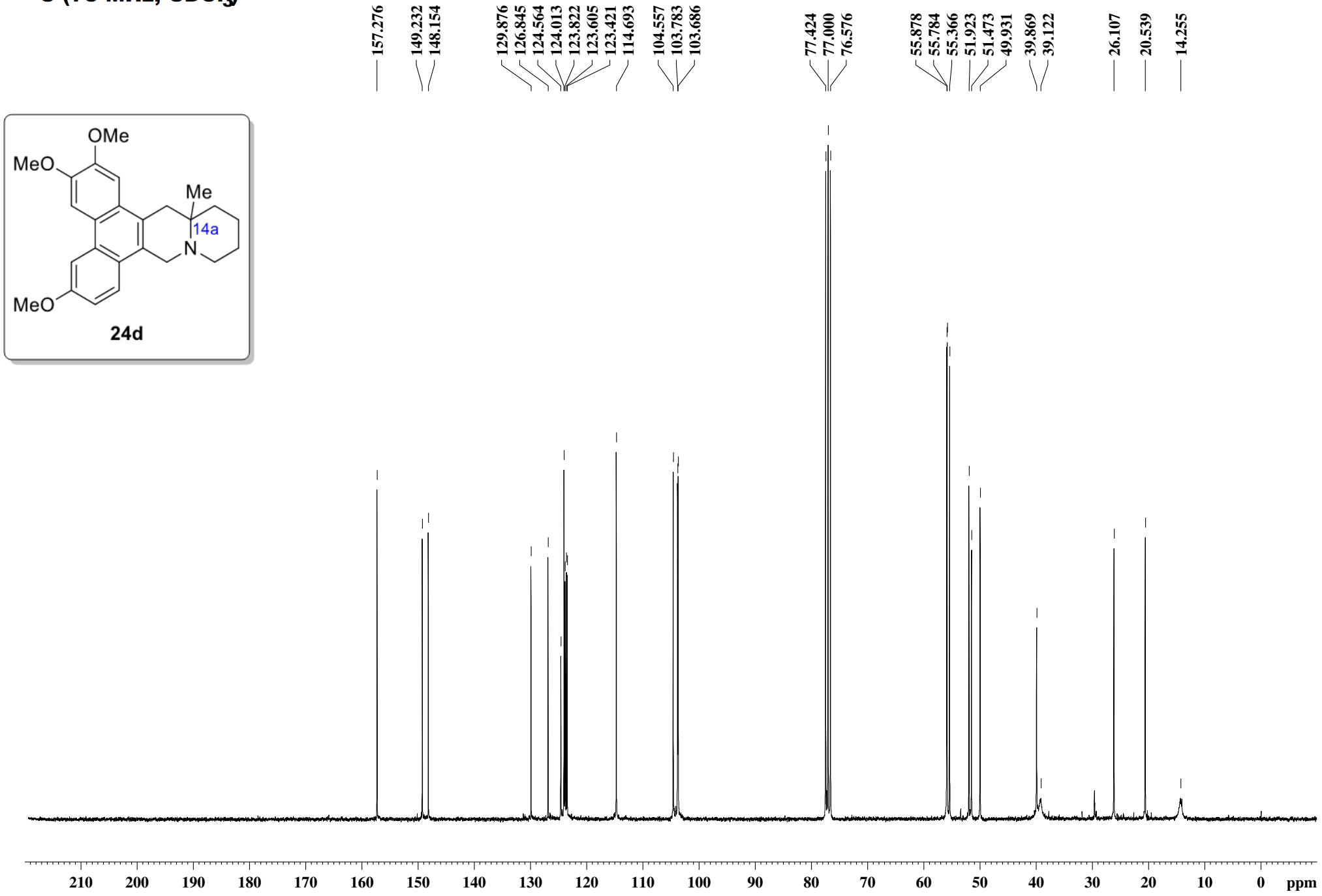


24c

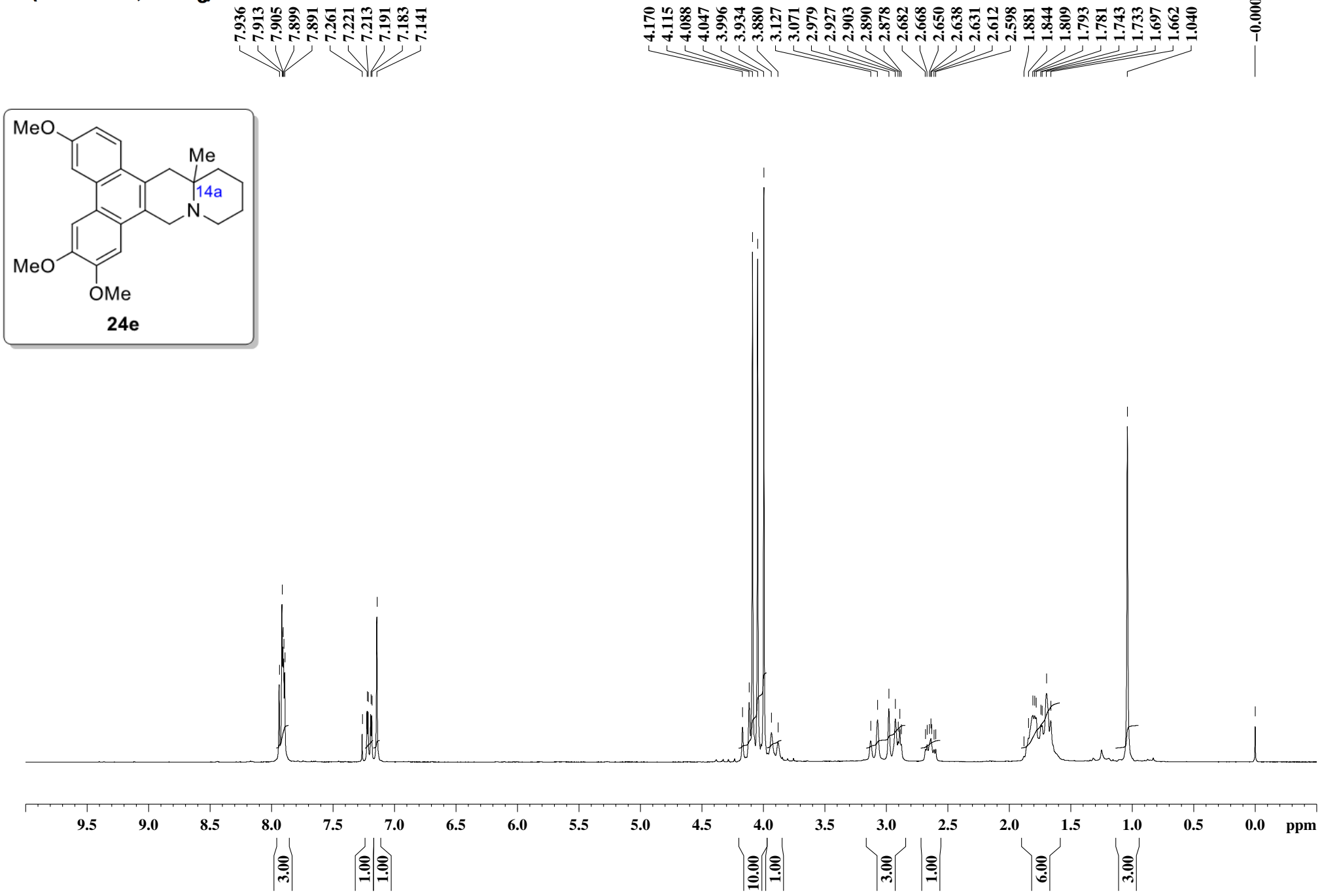
^{1}H (300 MHz,$CDCl_3$)



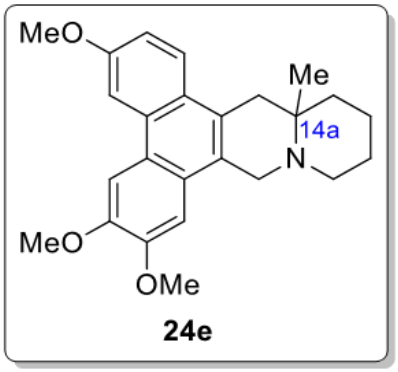
^{13}C (75 MHz, $CDCl_3$)



^{1}H (300 MHz,$CDCl_3$)

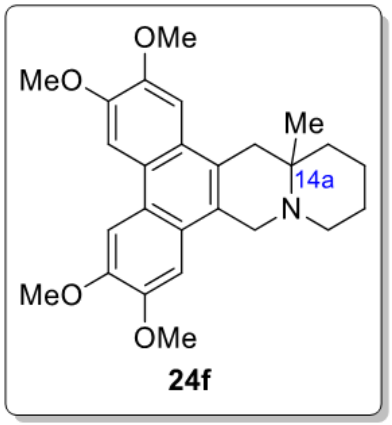


^{13}C (75 MHz, $CDCl_3$)



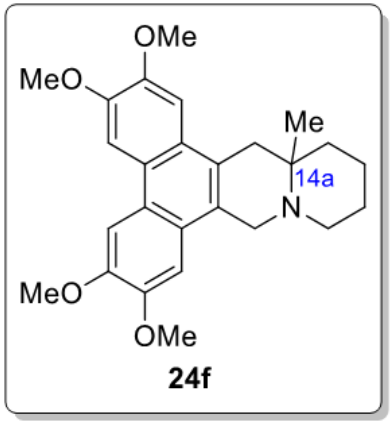
24e

^{1}H (300 MHz,$CDCl_3$)



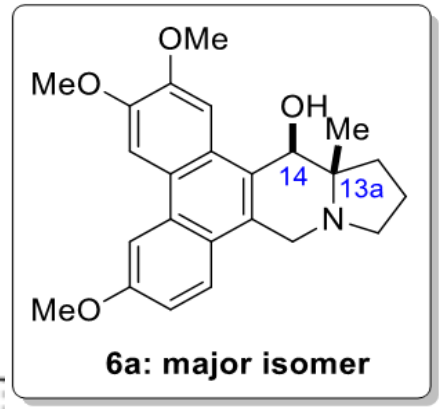
24f

^{13}C (75 MHz, $CDCl_3$)



24f

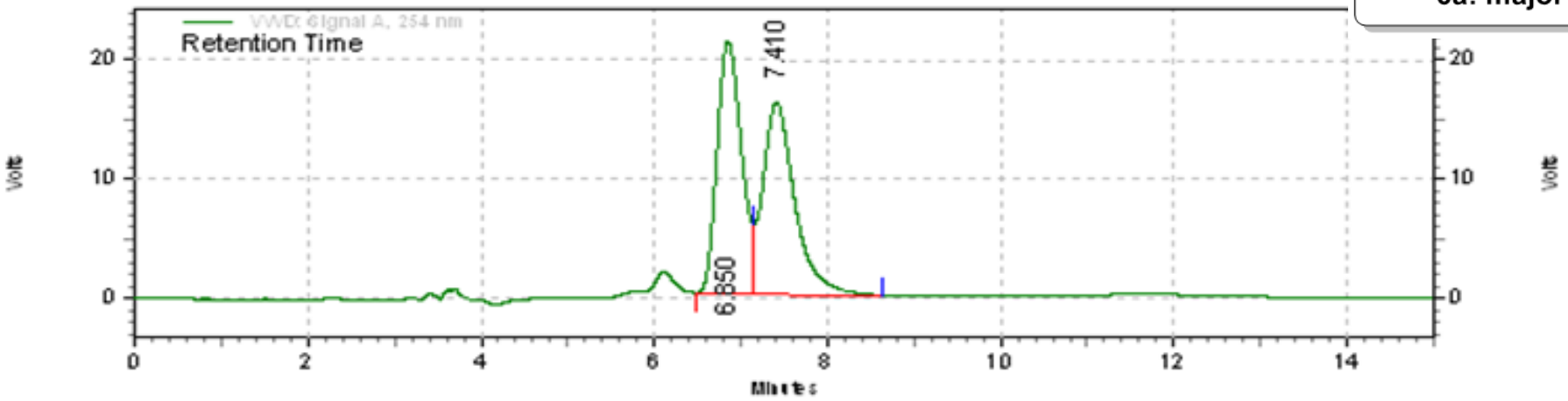
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



6a: major isomer

(±)-Hypoestestatin 2, 6a (major isomer)

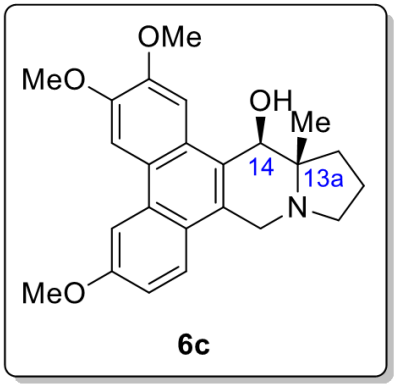
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

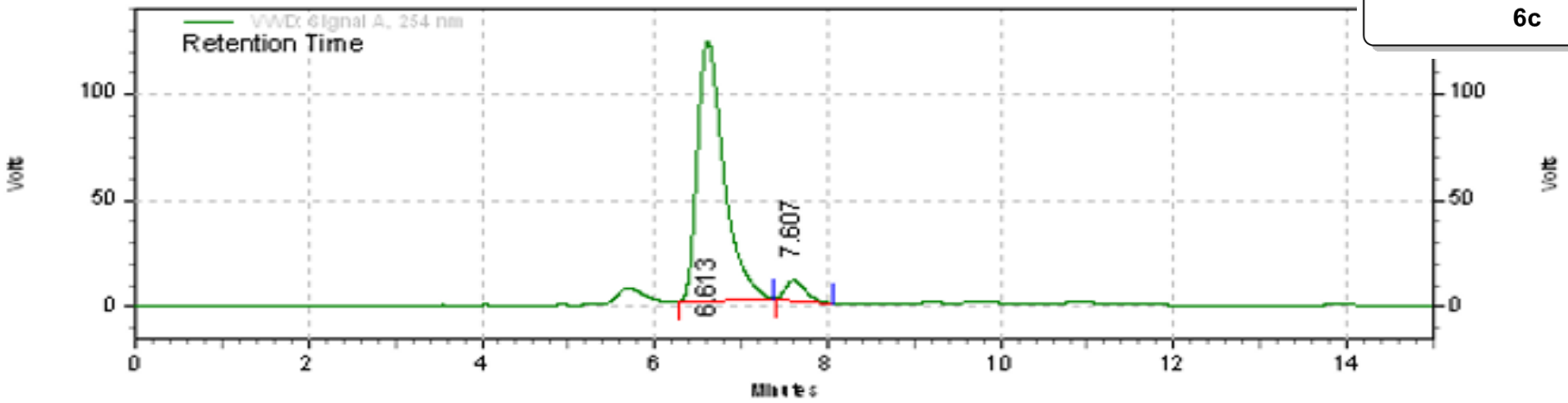
Retention Time	Area	Area %	Height	Height %
6.850	6941273	50.10	354340	56.74
7.410	6913158	49.90	270136	43.26
Totals	13854431	100.00	624476	100.00

Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(+)-Hypoestestatin 2, (14*R*,13a*S*)-6c

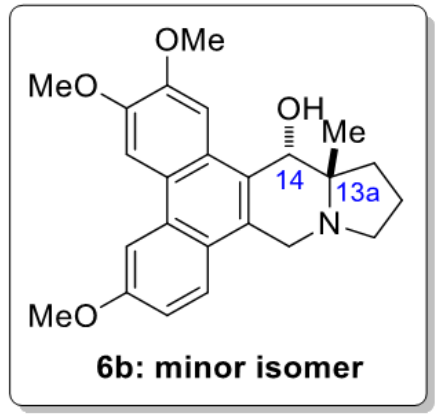
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

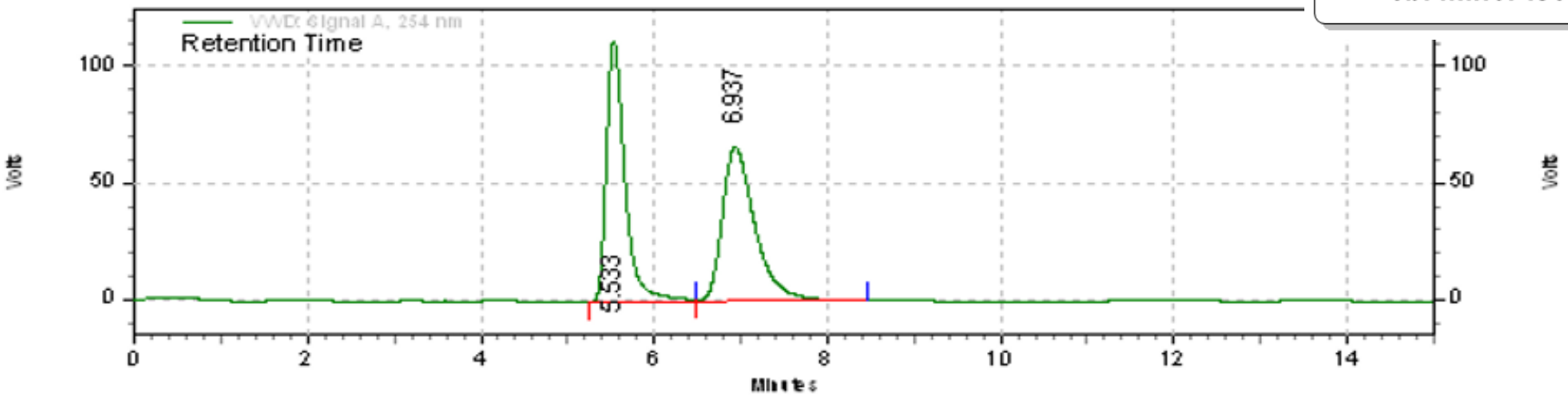
Retention Time	Area	Area %	Height	Height %
6.613	43435181	94.65	2047580	92.92
7.607	2454247	5.35	156047	7.08
Totals	45889428	100.00	2203627	100.00

Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



6b (minor isomer)

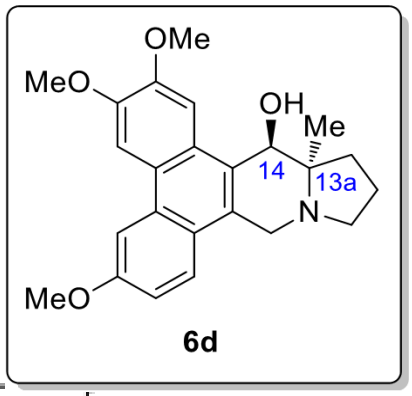
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

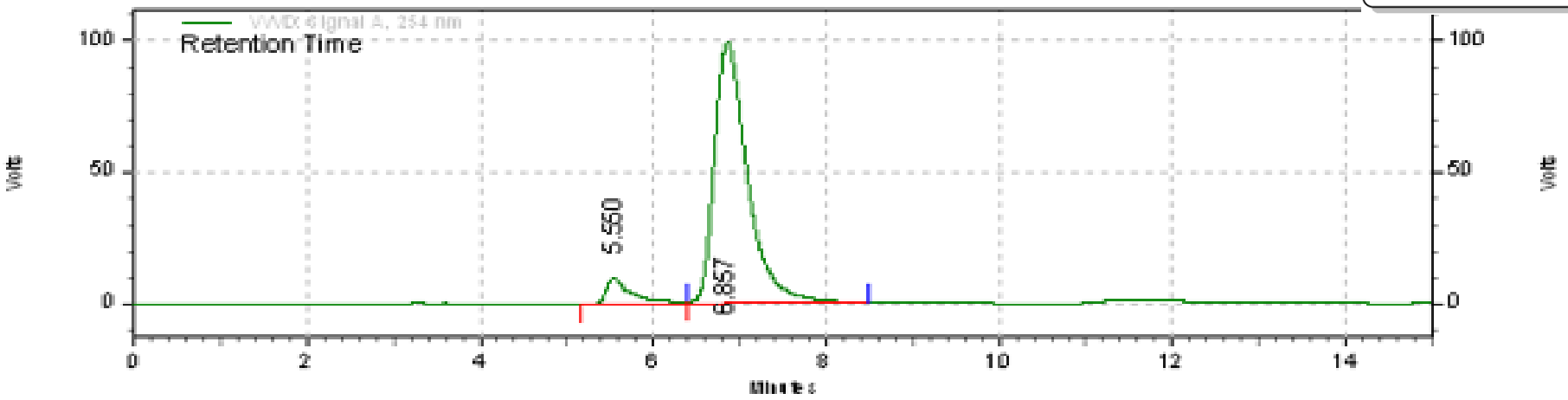
Retention Time	Area	Area %	Height	Height %
5.533	28003162	49.08	1870447	62.87
6.937	29058178	50.92	1104726	37.13
Totals	57061340	100.00	2975173	100.00

Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(14*R*,13a*R*)-6d

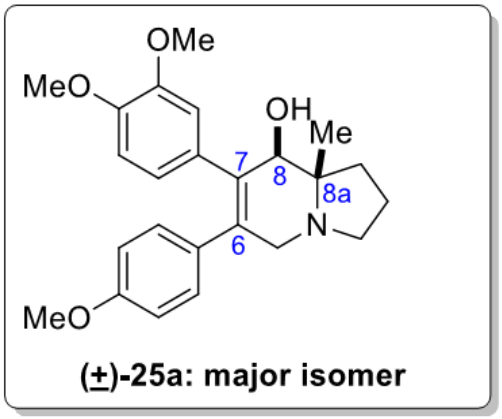
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.550	3422796	7.21	164639	9.01
6.857	44043633	92.79	1663640	90.99
Totals	47466429	100.00	1828279	100.00

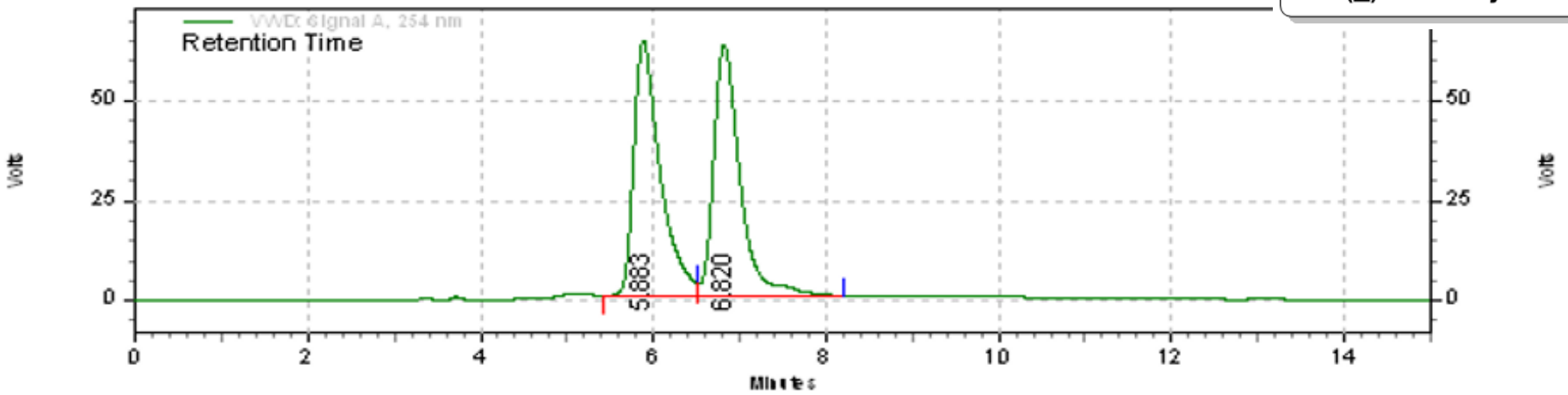
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(±)-25a: major isomer

(±)-*seco*-Hypoestestatin 2, (±)-25a (major isomer)

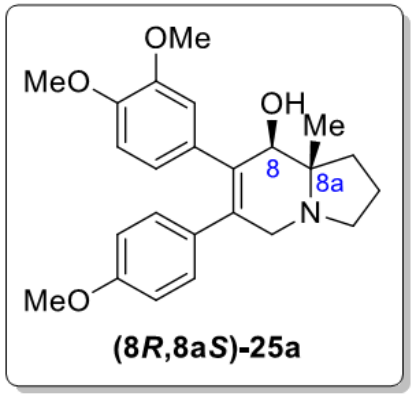
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.883	22958744	50.37	1075740	50.35
6.820	22618973	49.63	1060606	49.65
Totals	45577717	100.00	2136346	100.00

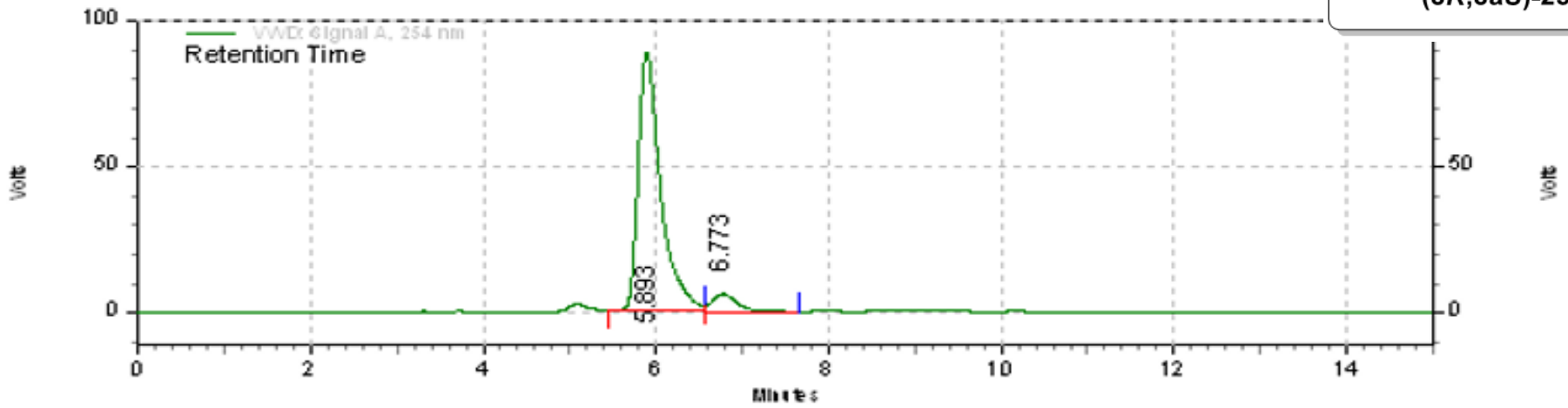
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(8*R*,8a*S*)-25a

(+)-*seco*-Hypoestestatin 2, (8*R*,8a*S*)-25a

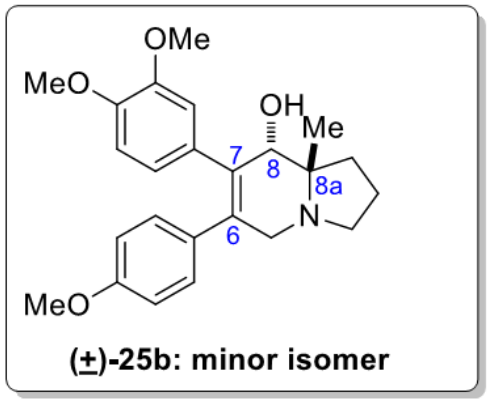
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.893	26858447	93.27	1485056	93.77
6.773	1939178	6.73	98630	6.23
Totals	28797625	100.00	1583686	100.00

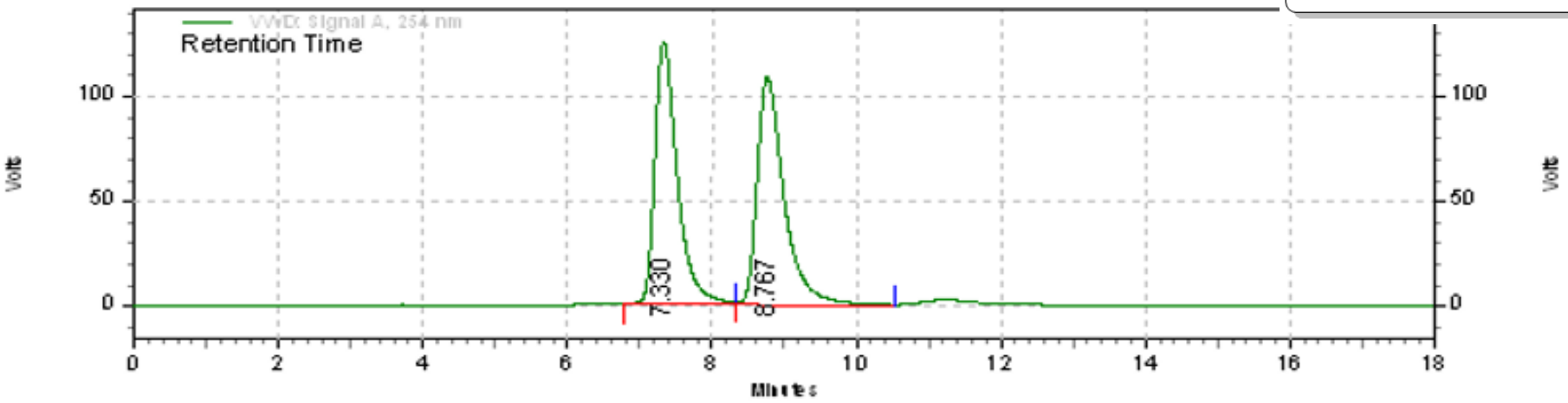
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(±)-25b: minor isomer

(±)-25b (minor isomer)

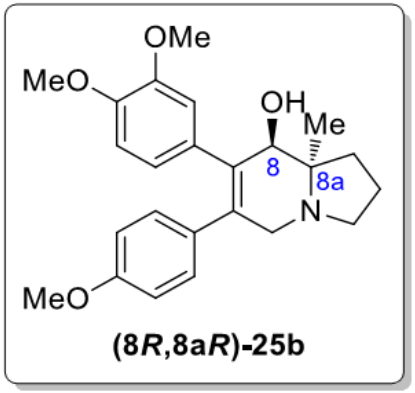
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

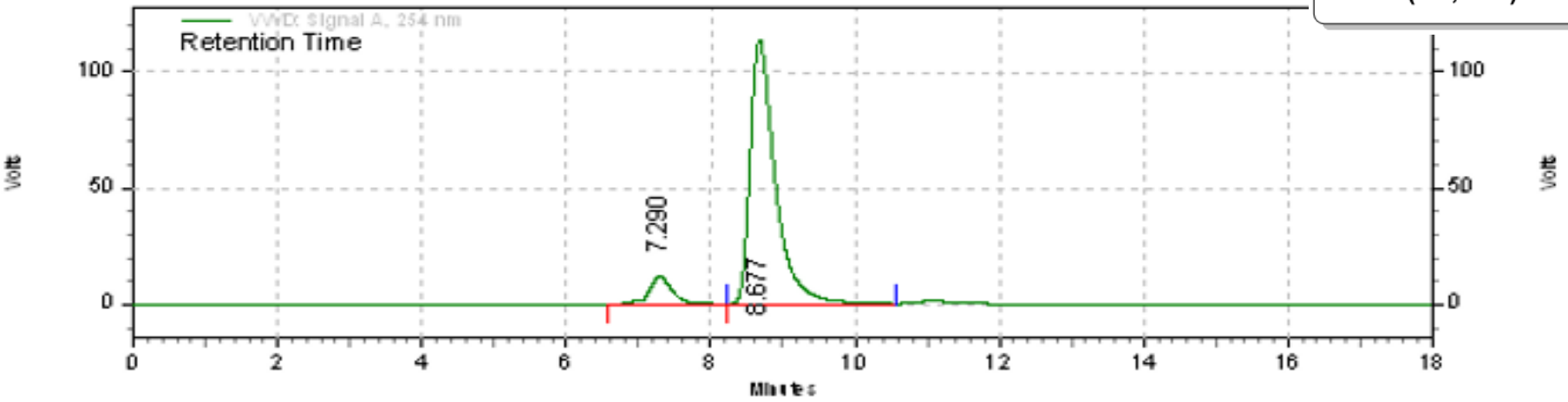
Retention Time	Area	Area %	Height	Height %
7.330	45791214	49.34	2104111	53.60
8.767	47023827	50.66	1821398	46.40
Totals	92815041	100.00	3925509	100.00

Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(8*R*,8a*R*)-25b

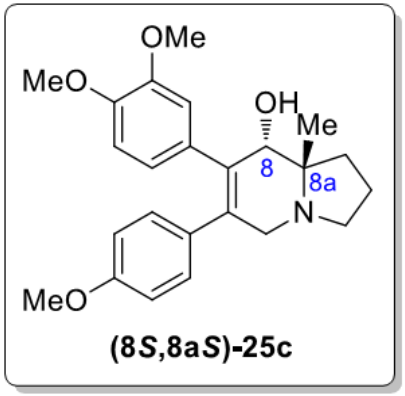
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

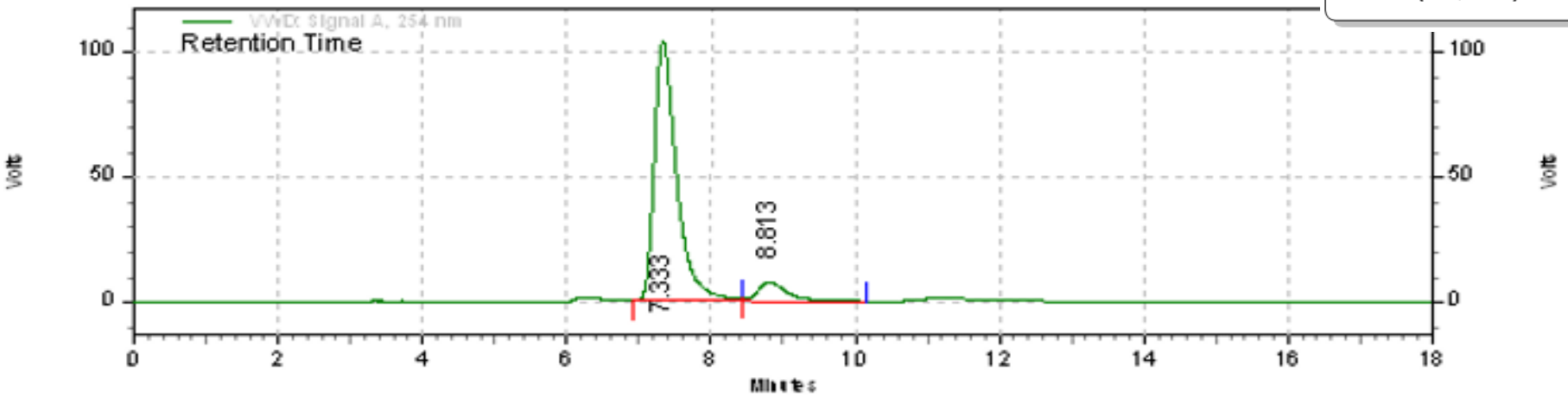
Retention Time	Area	Area %	Height	Height %
7.290	4632127	9.14	200722	9.55
8.677	46025734	90.86	1902019	90.45
Totals	50657861	100.00	2102741	100.00

Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(8*S*,8a*S*)-25c

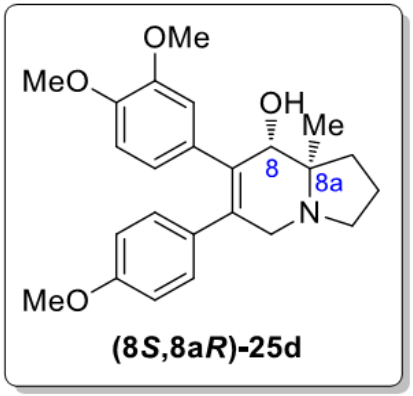
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
7.333	37473878	91.36	1744130	93.31
8.813	3544440	8.64	124976	6.69
Totals	41018318	100.00	1869106	100.00

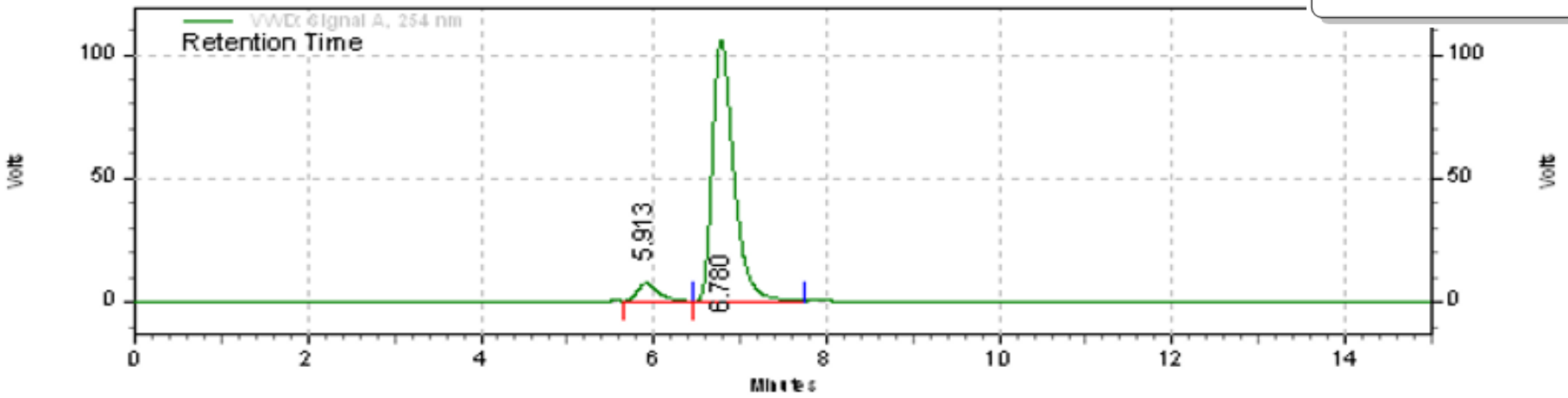
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 50% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(8*S*,8a*R*)-25d

(-)-*seco*-Hypoestestatin 2, (8*S*,8a*R*)-25d

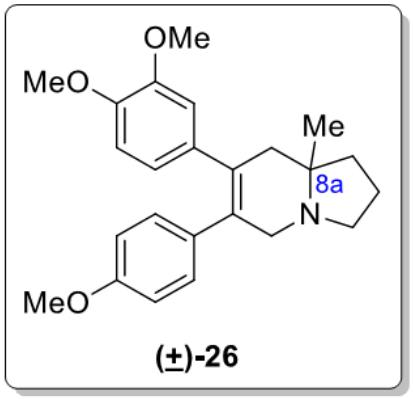
Method: D:\Wannaporn\50%EtOH50%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.913	2025535	6.26	121240	6.41
6.780	30308732	93.74	1770242	93.59
Totals	32334267	100.00	1891482	100.00

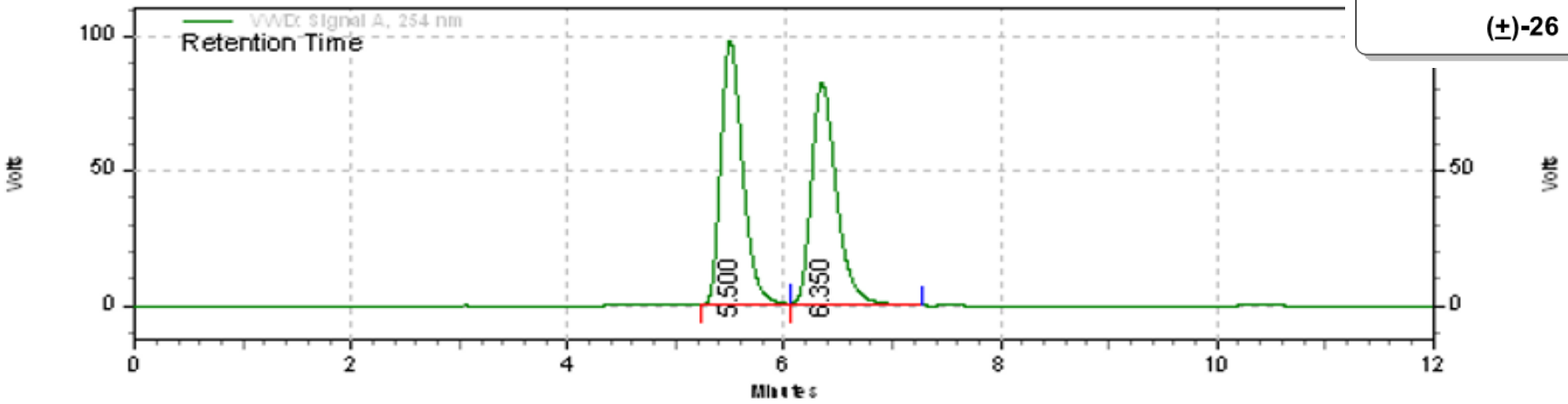
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(±)-26

(±)-*seco*-Hypoestestatin 1, (±)-26

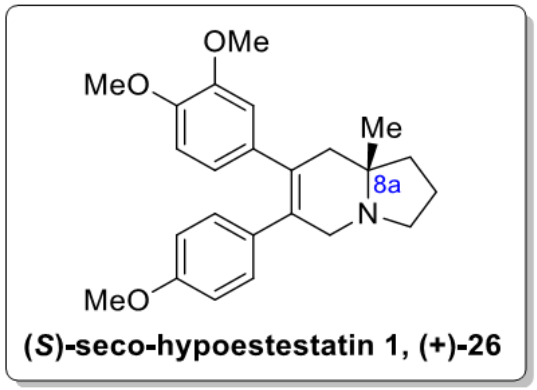
Method: D:\Wannaporn\40%EtOH60%Hexane_F1_254nm_11min.met



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
5.500	23076943	50.85	1644137	54.33
6.350	22306556	49.15	1382282	45.67
Totals	45383499	100.00	3026419	100.00

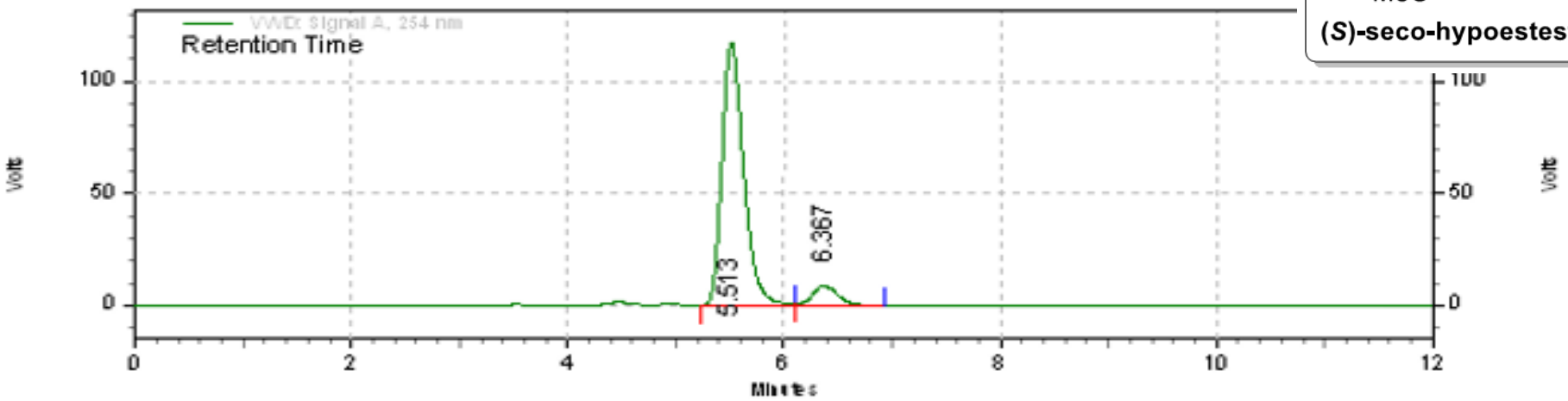
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(*S*)-seco-hypoestestatin 1, (+)-26

(+)-*seco*-Hypoestestatin 1, (*S*)-26, *using (8S,8aS)-25c as a starting material*

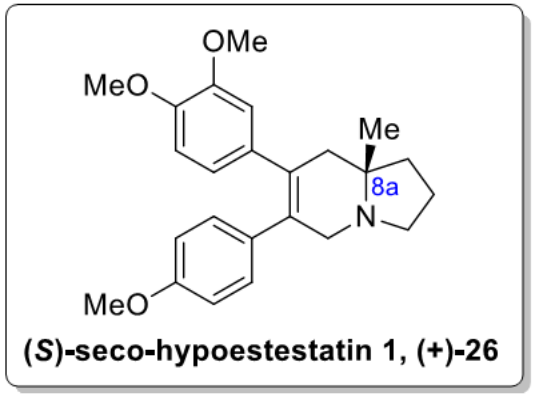
Method: D:\Wannaporn\40%EtOH60%Hexane_F1_254nm_11min.met



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
5.513	27490355	91.68	1970088	92.85
6.367	2493789	8.32	151696	7.15
Totals	29984144	100.00	2121784	100.00

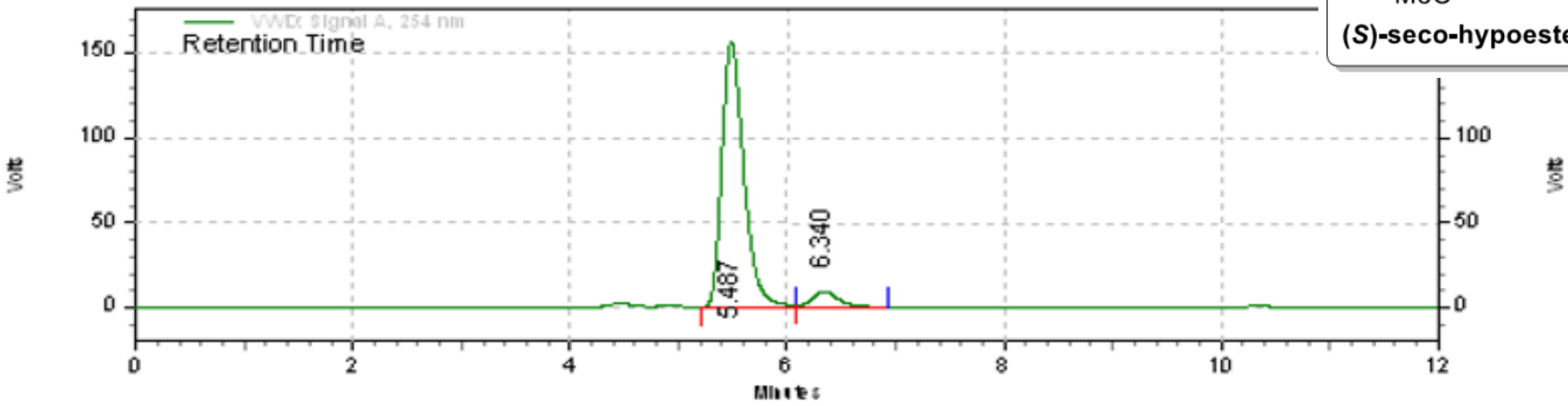
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(*S*)-seco-hypoestestatin 1, (+)-26

(+)-*seco*-Hypoestestatin 1, (*S*)-26, *using (8R,8aS)-25a as a starting material*

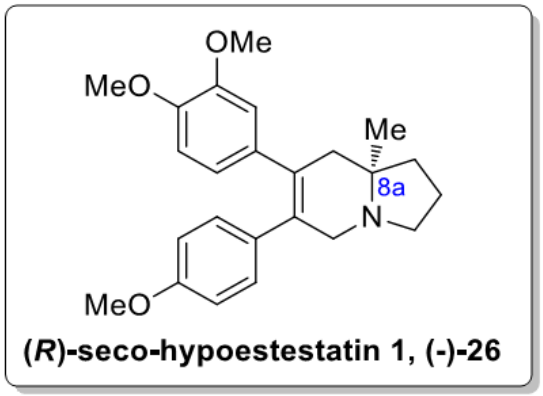
Method: D:\Wannaporn\40%EtOH60%Hexane_F1_254nm_11min.met



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
5.487	36927372	93.42	2626042	94.45
6.340	2600430	6.58	154176	5.55
Totals	39527802	100.00	2780218	100.00

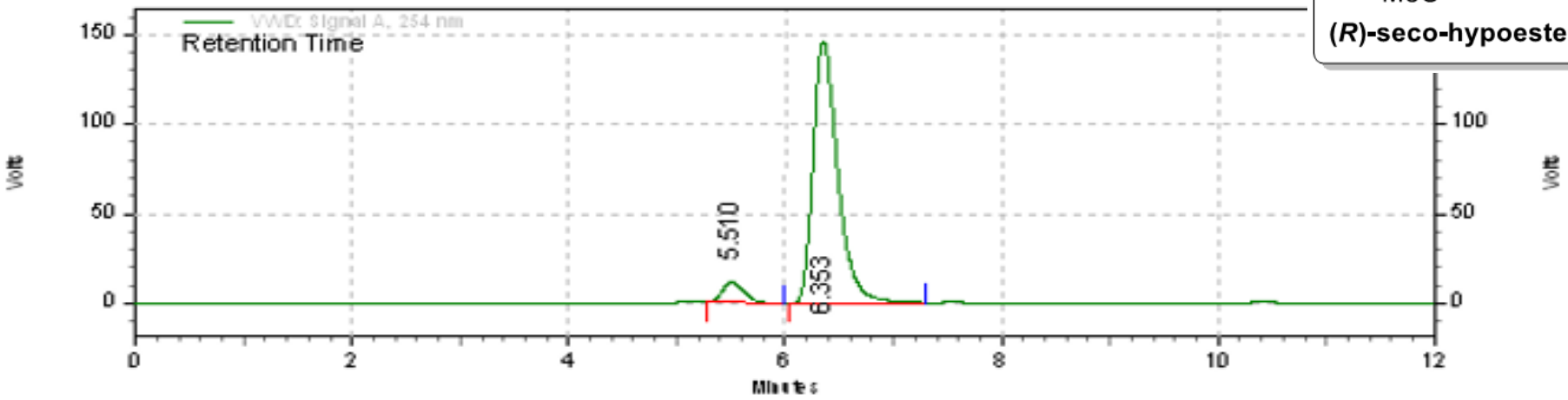
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(*R*)-seco-hypoestestatin 1, (-)-26

(-)-*seco*-Hypoestestatin 1, (*R*)-26, *using (8S,8aR)-25d as a starting material*

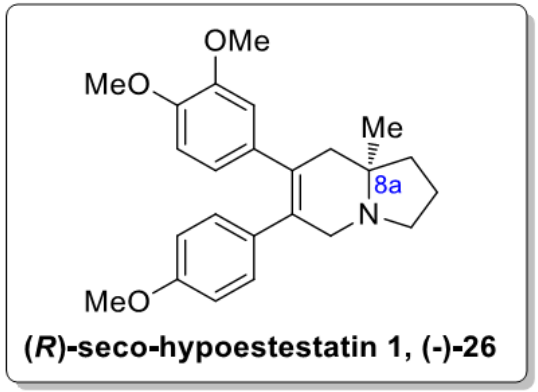
Method: D:\Wannaporn\40%EtOH60%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.510	2585256	6.26	191052	7.23
6.353	38708071	93.74	2452431	92.77
Totals	41293327	100.00	2643483	100.00

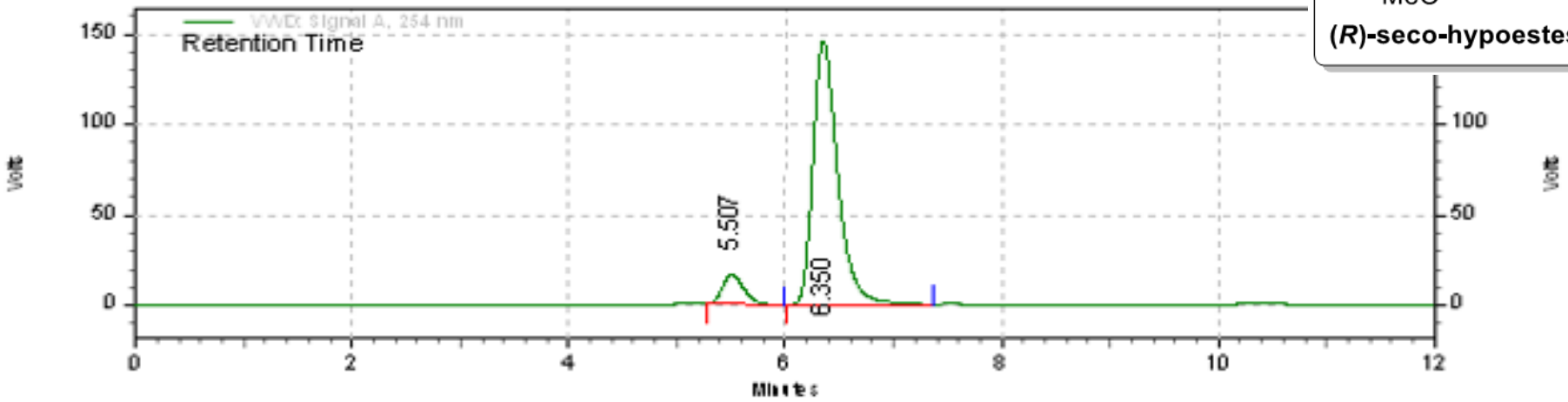
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 1.0 ml/min
Detector : 254 nm



(*R*)-seco-hypoestestatin 1, (-)-26

(-)-*seco*-Hypoestestatin 1, (*R*)-26, *using (8R,8aR)-25b as a starting material*

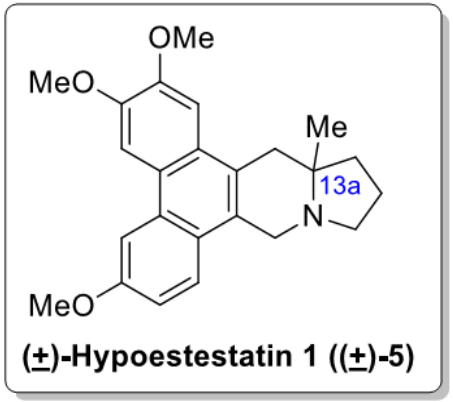
Method: D:\Wannaporn\40%EtOH60%Hexane_F1_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.507	3741925	8.84	274913	10.12
6.350	38598912	91.16	2442527	89.88
Totals	42340837	100.00	2717440	100.00

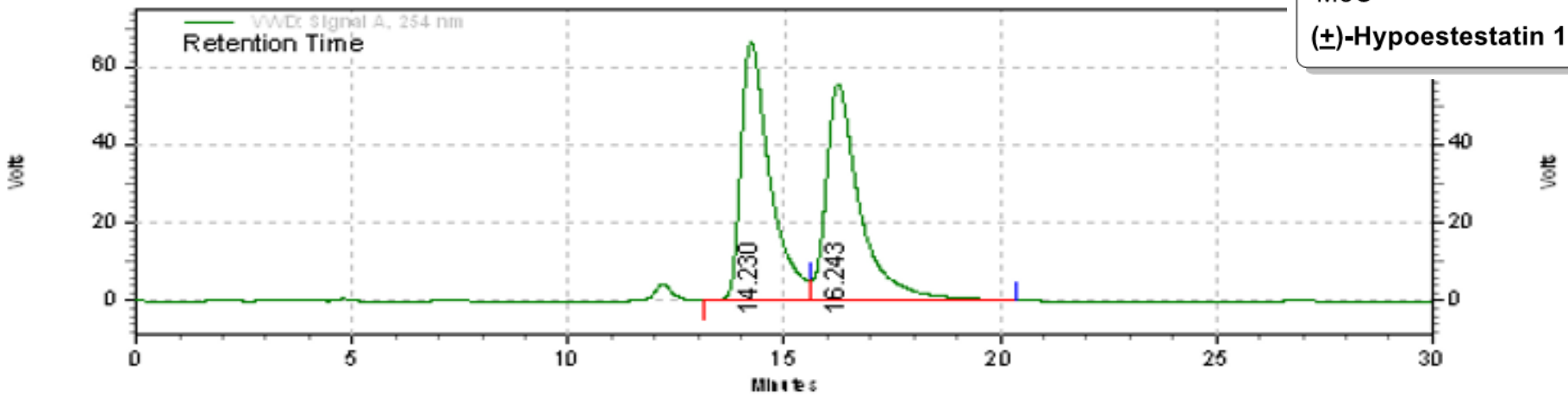
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 0.8 ml/min
Detector : 254 nm



(±)-Hypoestestatin 1 ((±)-5)

(±)-Hypoestestatin 1, (±)-5

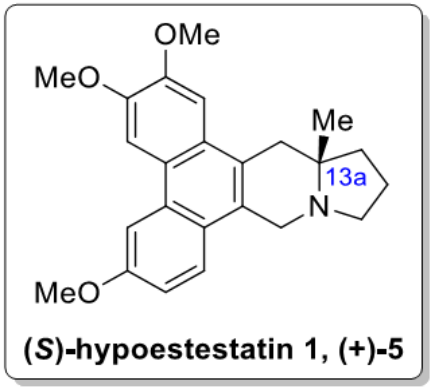
Method: D:\Wannaporn\40%EtOH60%Hexane_F08_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
14.230	52008744	50.48	1119627	54.45
16.243	51017555	49.52	936463	45.55
Totals	103026299	100.00	2056090	100.00

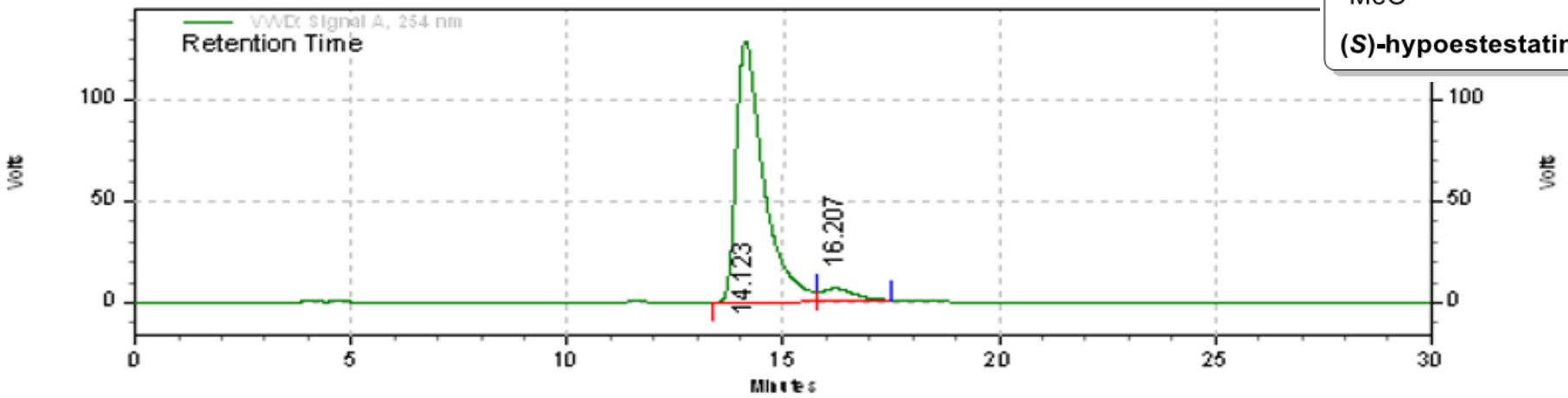
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 0.8 ml/min
Detector : 254 nm



(*S*)-hypoestestatin 1, (+)-5

(+)-Hypoestestatin 1, (+)-5, *using (14R,13aS)-6c as a starting material*

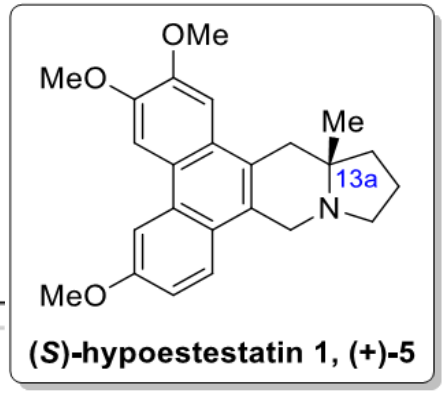
Method: D:\Wannaporn\40%EtOH60%Hexane_F08_254nm_11min.met



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
14.123	96225415	94.58	2163087	95.40
16.207	5516038	5.42	104306	4.60
Totals	101741453	100.00	2267393	100.00

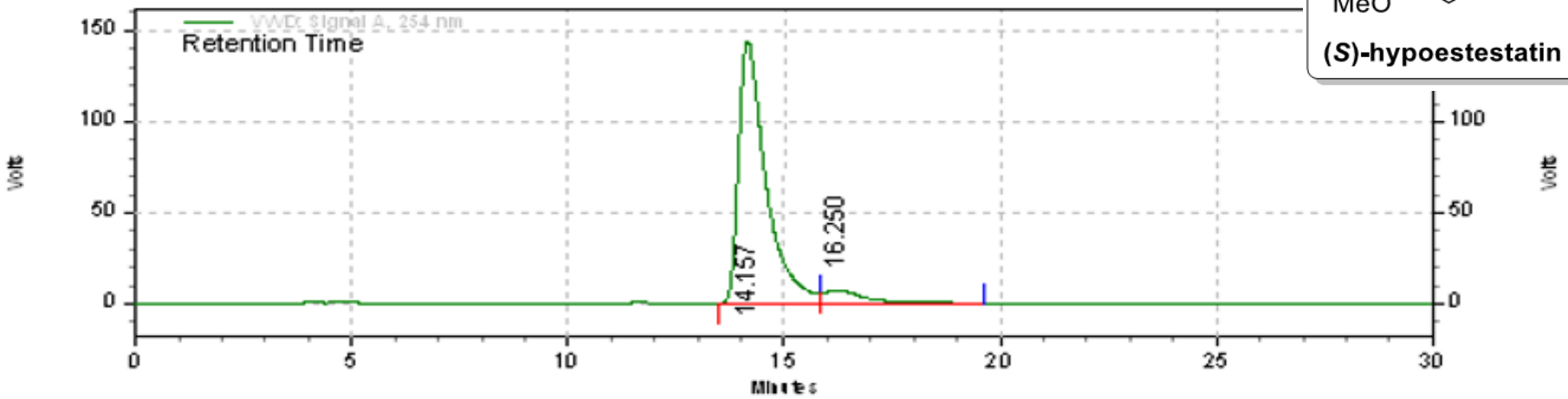
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 0.8 ml/min
Detector : 254 nm



(*S*)-hypoestestatin 1, (+)-5

(+)-Hypoestestatin 1, *using (S)-26 as a starting material*

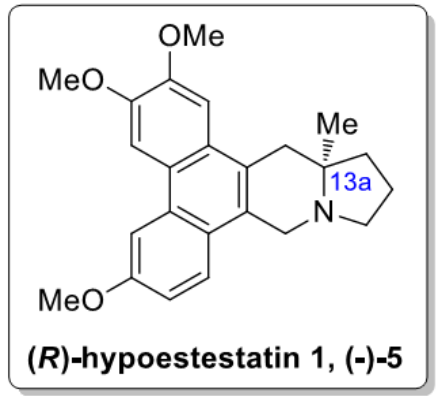
Method: D:\Wannaporn\40%EtOH60%Hexane_F08_254nm_11min.met



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
14.157	107245496	92.51	2421348	94.97
16.250	8686492	7.49	128187	5.03
Totals	115931988	100.00	2549535	100.00

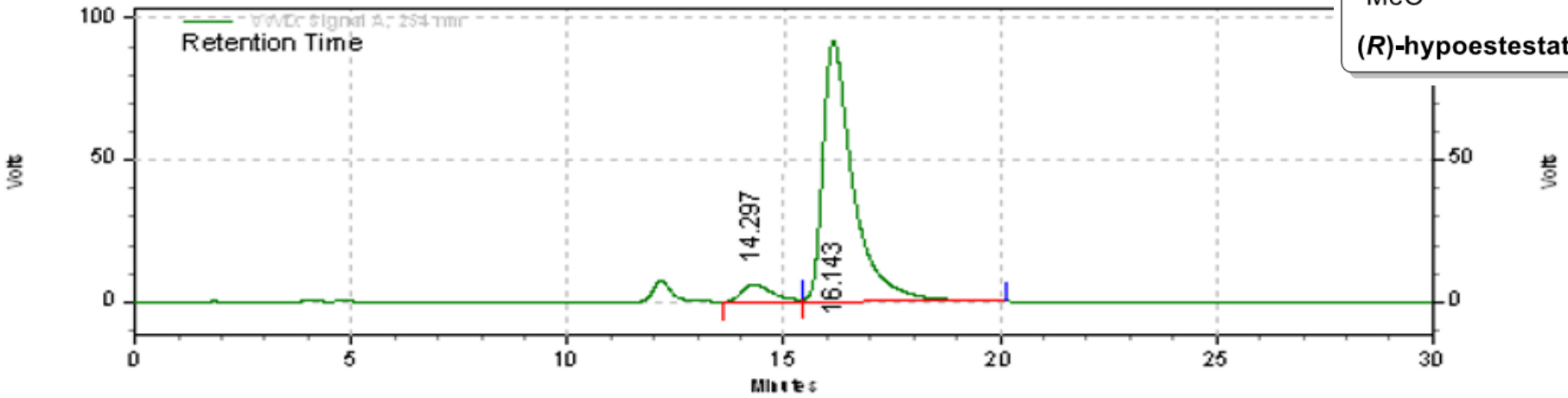
Column : CHIRALPACK-IF (250 mm x 5 um)
System: 40% EtOH in Hexane
Flow rate : 0.8 ml/min
Detector : 254 nm



(*R*)-hypoestestatin 1, (-)-5

(-)-Hypoestestatin 1, *using (R)-seco-hypoestestatin 1 as a starting material*

Method: D:\Wannaporn\40%EtOH60%Hexane_F08_254nm_11min.met



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
14.297	4902188	6.13	102124	6.21
16.143	75013716	93.87	1541556	93.79
Totals	79915904	100.00	1643680	100.00