Supporting Information

Synthesis of substituted hydantoin in low melting mixtures

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General Information

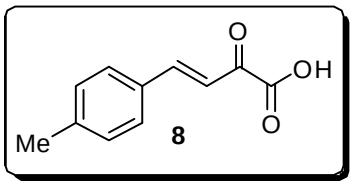
^{1}H NMR spectra were recorded on Bruker ADVANCE 400 MHz and 500 MHz spectrometers. ^{13}C NMR spectra were recorded on 100 MHz and 125 MHz spectrometers. The NOESY spectrums were recorded on Bruker ADVANCE 500 MHz spectrometer. Chemical shifts are expressed in δ units relative to tetramethylsilane (TMS) signal as internal reference in $CDCl_3$. FTIR spectra were recorded in $CHCl_3$ or neat.

Synthesis of the 1,3,5-trisubstituted hydantoins from β,γ-unsaturated ketoacids

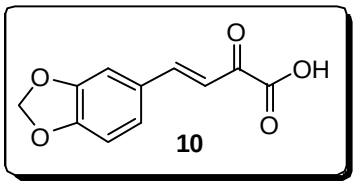
General procedure for the synthesis of synthesis of 1,3,5-trisusbstituted hydantoin derivatives from β,γ-unsaturated ketoacids in low melting mixture

In a typical experiment, 1.5 g of L-(+)-tartaric acid-DMU (30:70) mixture was heated to 70 ^{o}C to obtain a clear melt. To the melt, 1 mmol of *β,γ*-unsaturated ketoacid was added at 70 ^{o}C. The reaction was monitored by thin layer chromatography. After the completion of reaction, the reaction mixture was quenched by adding water while still hot. The reaction mixture was cooled to room temperature and aqueous layer was extracted with DCM (3 x 5 mL) and washed with water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by flash coloumn chromatography and then recrystallized from EtOAc-DCM mixture to afford pure *anti*-isomer of hydantoin derivative.

Synthesis of (E)-2-oxo-4-p-tolylbut-3-enoic acid (8): Yellow solid; Yield 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.48 (bs, 1H), 7.28 (d, 2H, J = 10.0 Hz), 7.54–7.66 (m, 3H), 8.12 (d, 1H, J = 20.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 116.6, 129.7, 130.1, 131.1, 143.6, 151.5, 160.7, 182.2; HRMS calcd. for $C_{11}H_{10}O_3Na$ (M^++Na) 213.0528, found 213.0532.



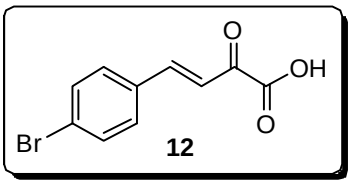
Synthesis of (E)-4-(benzo[d][1,3]dioxol-5-yl)-2-oxobut-3-enoic acid (10):



10

Yellow solid; Yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 2H), 6.87 (d, 1H, J = 8.4 Hz), 7.10–7.22 (m, 2H), 7.42 (d, 1H, J = 16.0 Hz), 8.01 (d, 1H, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.2, 107.3, 109.1, 115.5, 127.9, 128.6, 148.9, 151.4, 151.9, 160.6, 182.0; HRMS calcd. for $C_{11}H_8O_5K$ (M^++K) 259.0009, found 259.0003.

Synthesis of (E)-4-(4-bromophenyl)-2-oxobut-3-enoic acid (12): Yellow solid; Yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (bs, 1H), 7.50–7.61 (m, 5H), 8.03 (d, 1H, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.5, 127.3, 130.8, 132.7, 132.8, 149.8, 160.6, 182.4; HRMS calcd. for $C_{10}H_7O_3NaBr$ (M^++Na) 276.9476, found 276.9475.



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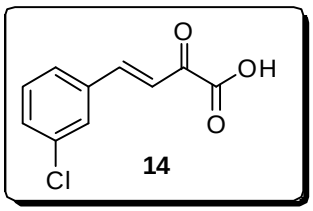
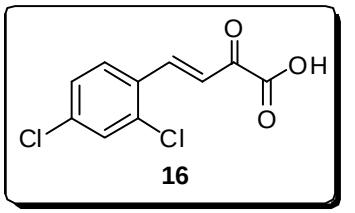
Synthesis of (E)-4-(3-chlorophenyl)-2-oxobut-3-enoic acid (14): Yellow solid; Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (bs, 1H), 7.39 (t, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.51–7.62 (m, 2H), 7.66 (s, 1H), 8.02 (d, 1H, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.3, 127.7, 129.1, 130.6, 132.2, 135.5, 135.6, 149.3, 160.6, 182.4; HRMS calcd. for $C_{10}H_7O_3NaCl$ (M^++Na) 232.9981, found 232.9993.



14

Synthesis of (E)-4-(2,4-dichlorophenyl)-2-oxobut-3-enoic acid (16): Yellow solid; Yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, 1H, J = 8.4, 2.0 Hz), 7.51 (d, 1H, J = 2.0 Hz), 7.58 (d, 1H, J = 16.0 Hz), 7.77 (d, 1H, J = 8.4 Hz), 8.44 (d, 1H, J = 16.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.1, 127.9, 128.9, 130.5, 137.3, 138.5, 144.9, 160.6, 182.1; HRMS calcd. for $C_{10}H_6O_3NaCl_2$ (M^++Na) 266.9592, found 266.9597.



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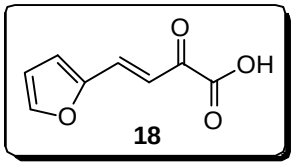
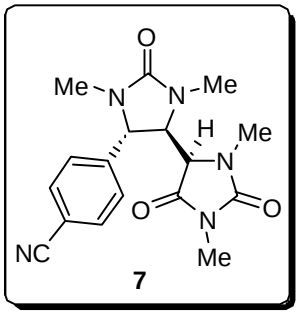
Synthesis of (E)-4-(furan-2-yl)-2-oxobut-3-enoic acid (18): Yellow solid; Yield



18

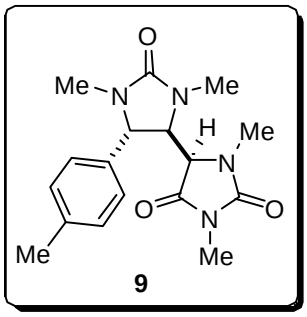
93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (bs, 1H), 6.59 (dd, 1H, *J* = 3.2, 1.6 Hz), 6.94 (d, 1H, *J* = 3.6 Hz), 7.38 (d, 1H, *J* = 15.6 Hz), 7.63 (s, 1H), 7.89 (d, 1H, *J* = 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.7, 115.5, 120.5, 136.2, 147.5, 151.2, 160.5, 182.0; HRMS calcd. for $C_8H_7O_4$ (M^++H) 167.0344, found 167.0346.

Synthesis of 4-((4R,4'R,5S)-1,1',3,3'-tetramethyl-2,2',5'-trioxo-4,4'-biimidazolidin-5-yl)benzonitrile (7): Colorless solid; Yield 84%; M.p. 249–250 °C; IR (neat): 1706, 1653, 1478 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.85 (s, 3H), 2.95 (s, 6H), 3.71 (dd, 1H, *J* = 7.2, 2.0 Hz), 4.09 (d, 1H, *J* = 1.6 Hz), 4.24 (d, 1H, *J* = 6.8 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.63 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.5, 29.6, 30.2, 59.9, 60.1, 64.8, 113.2, 118.2, 127.7, 133.1, 143.6, 157.1, 159.8, 169.3; HRMS calcd. for $C_{17}H_{20}N_5O_3$ (M^++H) 342.1566, found 342.1581.



7

Synthesis of (4R,4'R,5'S)-1,1',3,3'-tetramethyl-5'-p-tolyl-4,4'-biimidazolidine-2,2',5-trione (9): Colorless solid; Yield 86%; M.p. 191–194 °C; IR (neat): 1774, 1712, 1639, 1267 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.59 (s, 3H), 2.88 (s, 3H), 2.94 (s, 3H), 3.00 (s, 3H), 3.74 (dd, 1H, *J* = 7.6, 2.0 Hz), 4.08 (d, 1H, *J* = 1.6 Hz), 4.20 (d, 1H, *J* = 7.6 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 25.1, 29.2, 29.4, 30.5, 60.0, 60.2, 65.6, 127.0, 129.9, 134.8, 139.1, 157.2, 160.3, 169.4; HRMS calcd. for $C_{17}H_{22}N_4O_3Na$ (M^++Na) 353.1590, found 353.1595.



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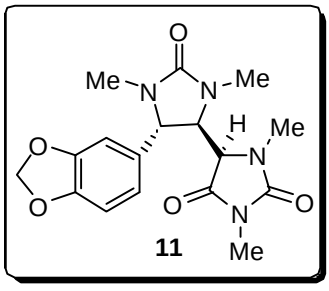
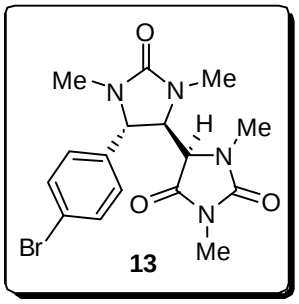
Synthesis of (4R,4'R,5'S)-5'-(benzo[d][1,3]dioxol-5-yl)-1,1',3,3'-tetramethyl-4,4'-biimidazolidine-2,2',5-trione (11): Colorless solid; Yield 85%; M.p. 208–210 °C; IR (neat): 1713, 1707, 1485, 1245 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 2.88 (s, 3H), 2.96 (s, 3H), 3.00 (s, 3H), 3.72 (d, 1H, *J* = 7.6 Hz), 4.08 (s, 1H, *J* = 8.0 Hz), 4.16 (d, 1H, *J* = 8.0 Hz), 5.97 (s, 2H), 6.55 (d, 1H, *J* = 7.6



11

Hz), 6.64 (s, 1H), 6.74 (s, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.3, 29.5, 30.5, 60.0, 60.3, 65.6, 101.6, 106.8, 108.5, 121.1, 131.7, 148.4, 148.8, 157.2, 160.2, 169.4; HRMS calcd. for $C_{17}H_{20}N_4O_5$ (M^++H) 361.1512, found 361.1507.

Synthesis of (4R,4'R,5'S)-5'-(4-bromophenyl)-1,1',3,3'-tetramethyl-4,4'-bi-imidazolidine-2,2',5-trione (13): Colorless solid; Yield 87%; M.p. 210–213 °C; IR (neat): 1712, 1704, 1397, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 2.89 (s, 3H), 2.97 (s, 3H), 2.99 (s, 3H), 3.73 (dd, 1H, J = 7.6, 2.0 Hz), 4.09 (d, 1H, J = 2.0 Hz), 4.21 (d, 1H, J = 7.2 Hz), 7.02 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.4, 29.5, 30.4, 59.9, 60.1, 65.2, 123.3, 128.7, 132.5, 137.2, 157.2, 160.0, 169.3; HRMS calcd. for $C_{16}H_{20}N_4O_3Br$ (M^++H) 395.0719, found 395.0734.



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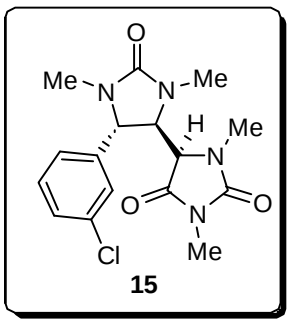
Synthesis of (4R,4'R,5'S)-5'-(3-chlorophenyl)-1,1',3,3'-tetramethyl-4,4'-bi-imidazolidine-2,2',5-trione (15): Colorless solid; Yield 92%; M.p. 174–176 °C; IR (neat): 1714, 1708, 1474, 1269 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 2.89 (s, 3H), 2.98 (s, 3H), 3.00 (s, 3H), 3.74 (dd, 1H, J = 7.6, 2.0 Hz), 4.09 (d, 1H, J = 2.0 Hz), 4.21 (d, 1H, J = 7.6 Hz), 7.02–7.06 (m, 1H), 7.12 (bs, 1H), 7.27–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.4, 29.5, 30.4, 60.0, 60.1, 65.3, 125.2, 127.4, 129.5, 130.7, 135.2, 140.3, 157.2, 160.1, 169.3; HRMS calcd. for $C_{16}H_{20}N_4O_3Cl$ (M^++H) 351.1224, found 351.1214.



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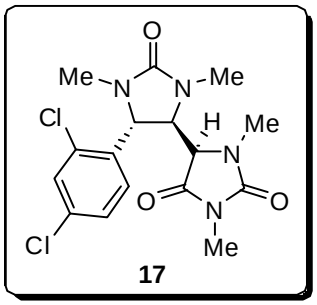
Synthesis of (4R,4'R,5'S)-5'-(2,4-dichlorophenyl)-1,1',3,3'-tetramethyl-4,4'-biimidazolidine-2,2',5-trione (17): Colorless solid; Yield 85%; M.p. 222–224 °C; IR (neat): 1715, 1655, 1421, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 2.71 (s, 3H), 3.02 (s, 6H), 3.81 (d, 1H, J = 4.0 Hz), 4.11 (d, 1H, J = 0.8 Hz), 4.82 (bs, 1H), 7.16 (d, 1H, J = 8.4 Hz), 7.33 (dd, 1H, J = 8.4, 2.0 Hz), 7.45 (d, 1H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 29.2, 29.5, 30.4, 61.0, 62.6, 63.6, 128.6,



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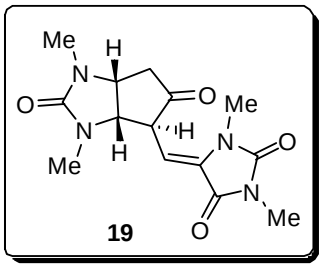
130.3, 133.6, 134.7, 135.5, 157.0, 159.7, 170.4; HRMS calcd. for $C_{16}H_{19}N_4O_3Cl_2$ (M^++H) 385.0834, found 385.0817.

Synthesis of (3aS,4S,6aR)-4-((Z)-(1,3-dimethyl-2,5-dioxoimidazolidin-4-ylidene)methyl)-1,3-dimethyltetrahydrocyclopenta[d]imidazole-2,5(1H,3H)-dione (19): Colorless solid; Yield 88%; M.p. 198–200 ^oC; IR (neat): 1769, 1718, 1656, 1448, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 1H), 2.78 (s, 3H), 2.80 (s, 1H), 2.82 (s, 3H), 3.03 (s, 3H), 3.11 (s, 3H), 3.80 (dd, 1H, J = 10.4, 6.8 Hz), 4.04 (t, 1H, J = 6.8 Hz), 4.14 (dt, 1H, J = 8.8, 2.8 Hz), 5.34 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.4, 29.8, 29.9, 42.5, 52.6, 55.9, 65.0, 108.9, 132.4, 153.7, 160.0, 162.4, 211.0; HRMS calcd. for $C_{14}H_{19}N_4O_4$ (M^++H) 307.1406, found 307.1396.



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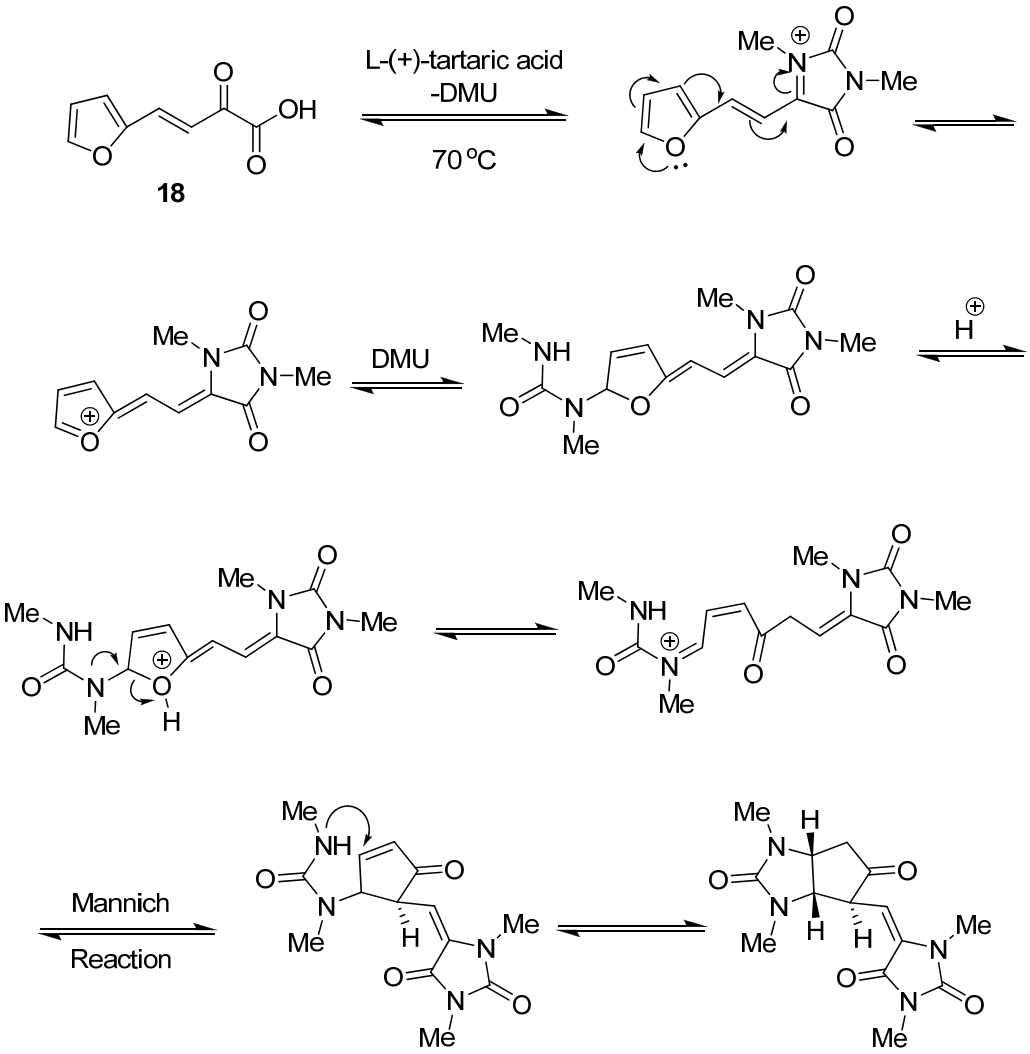
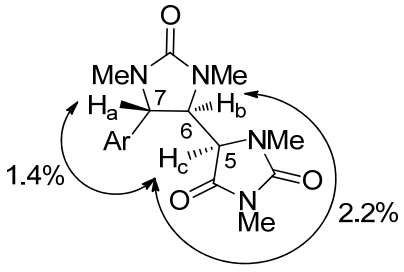
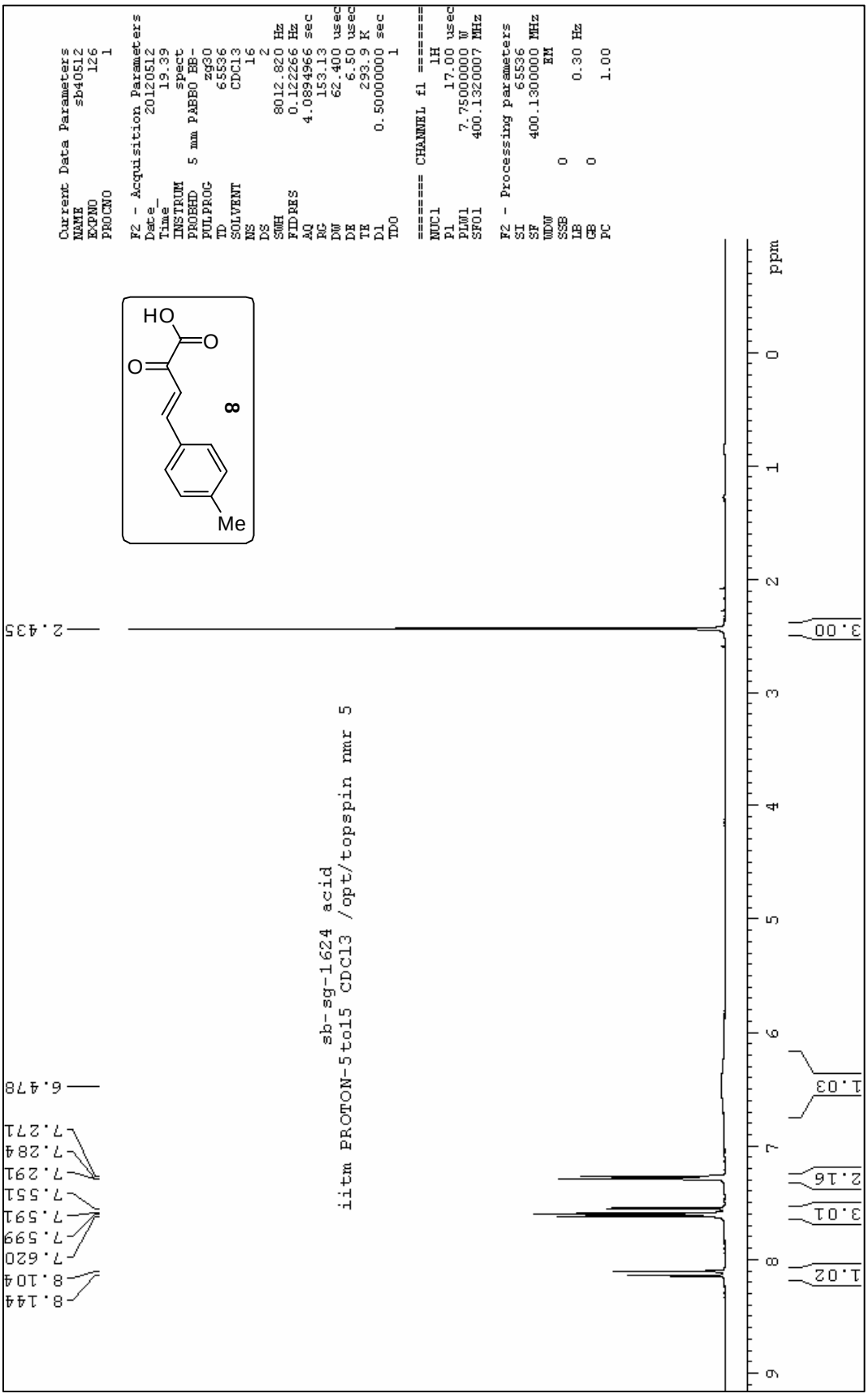
Proposed reaction mechanism



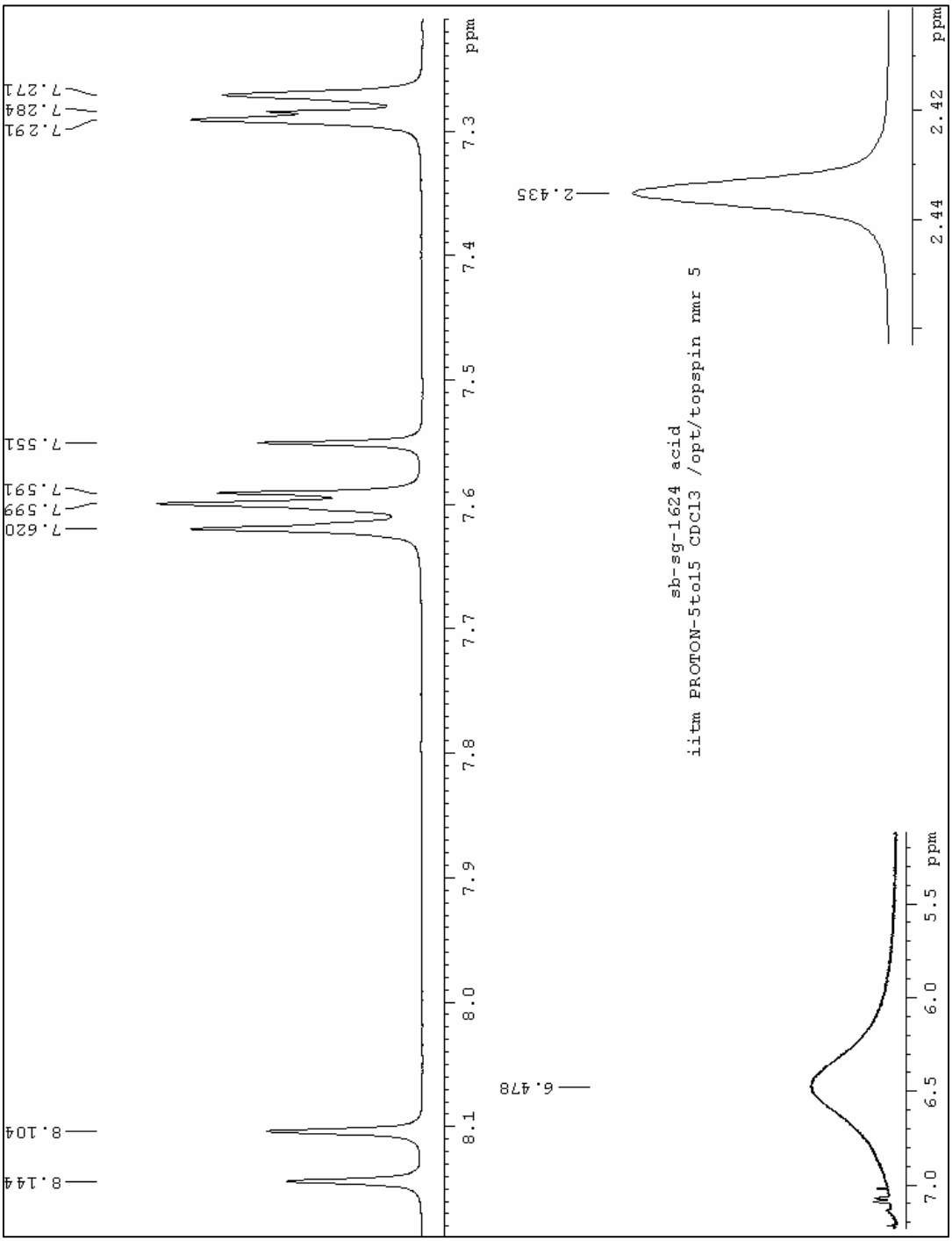
NOEs observed for 6,7-*anti*- hydantoin derivative 13



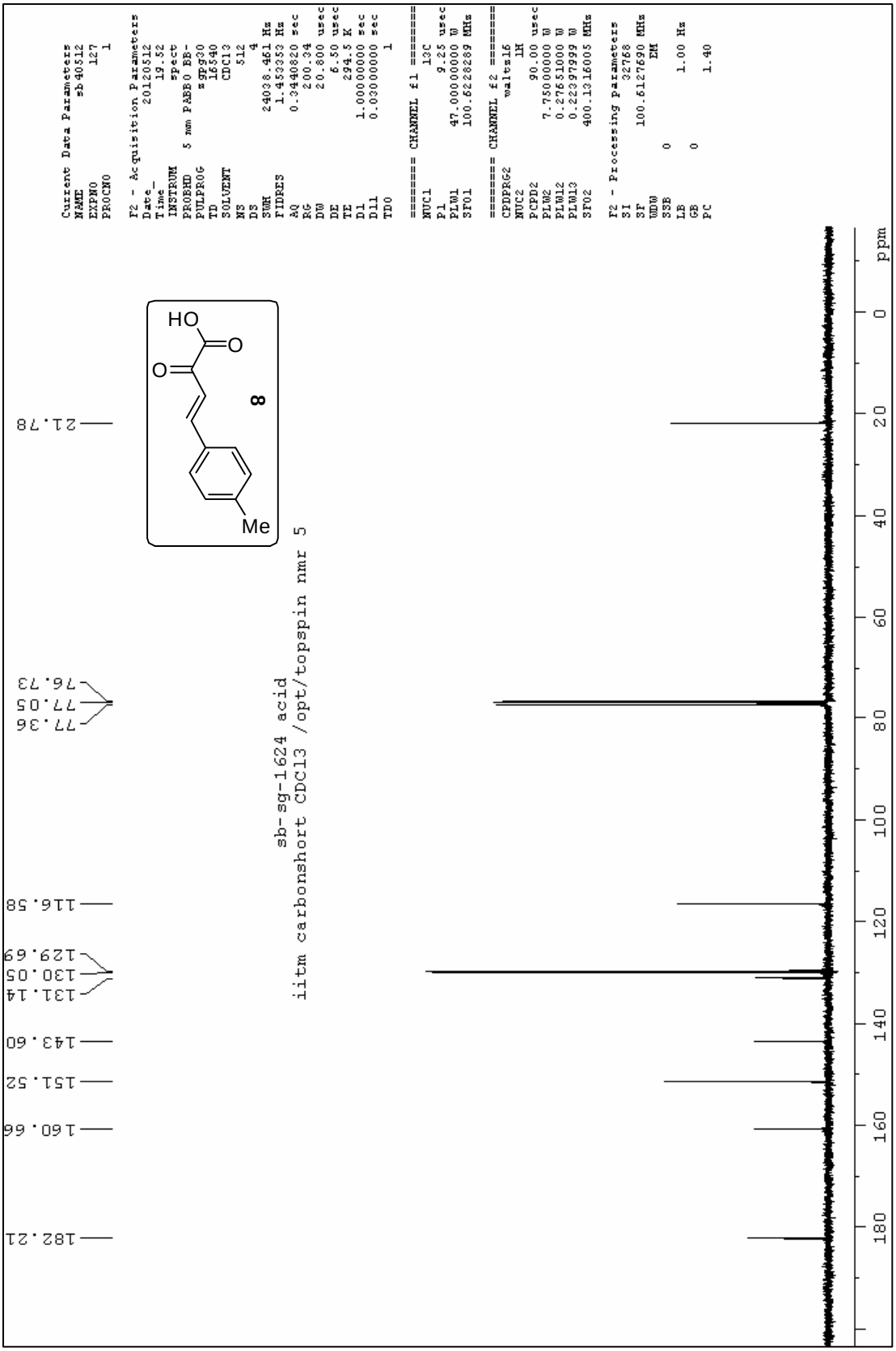
Ar = 4-bromophenyl



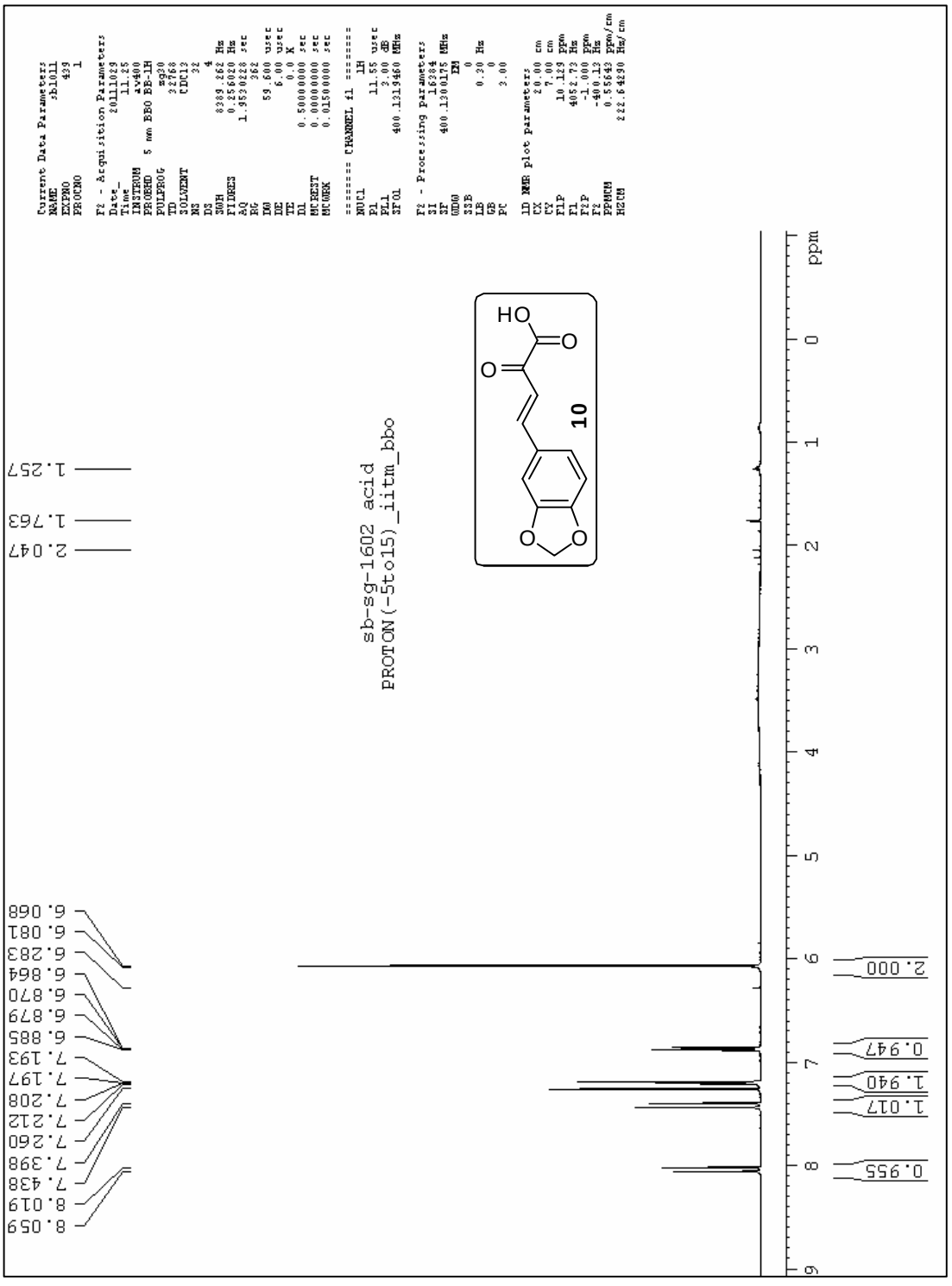
^{1}H NMR spectrum of compound **8**



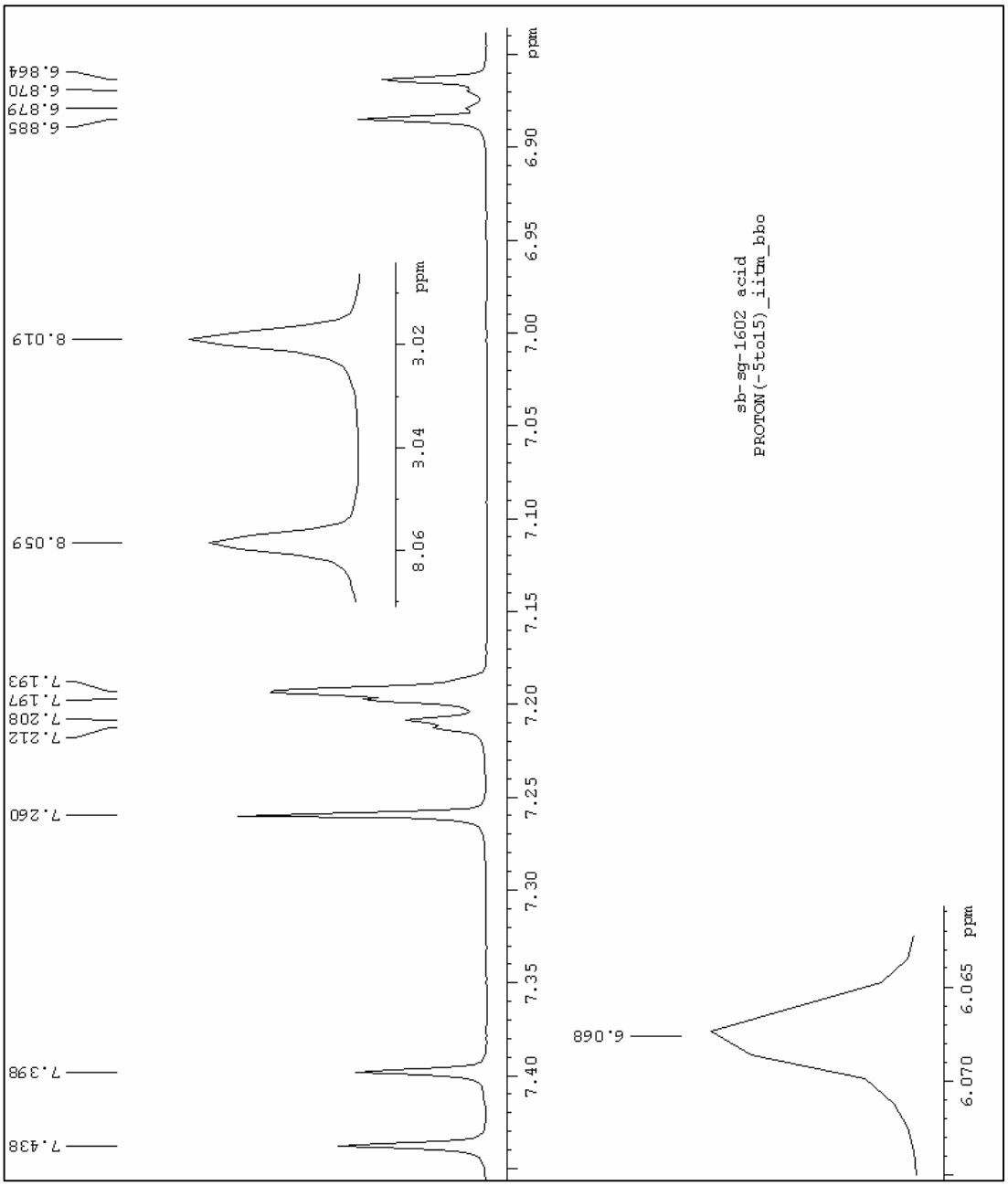
Expanded ^{1}H NMR spectrum of compound **8**



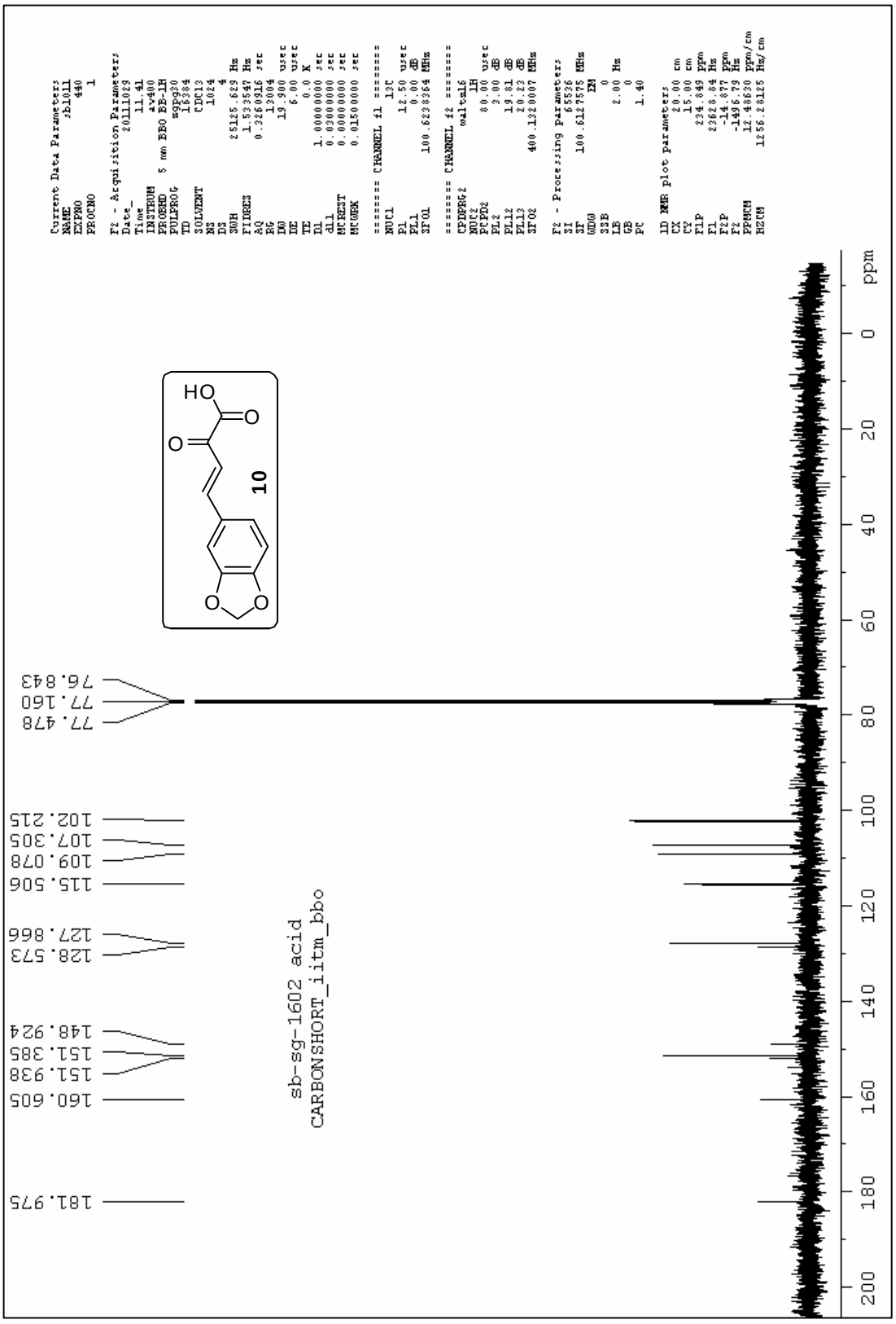
^{13}C NMR spectrum of compound **8**



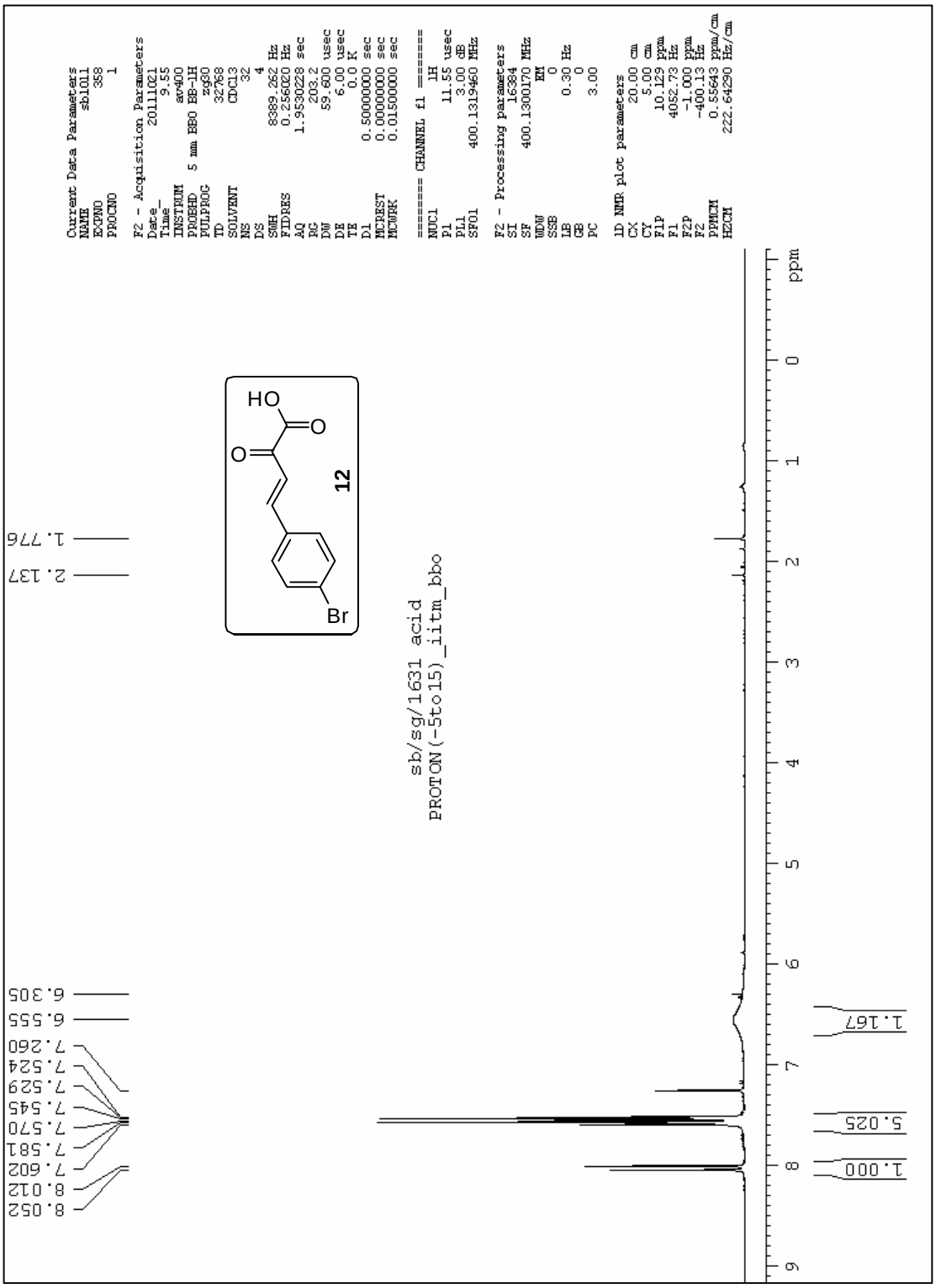
^{1}H NMR spectrum of compound **10**



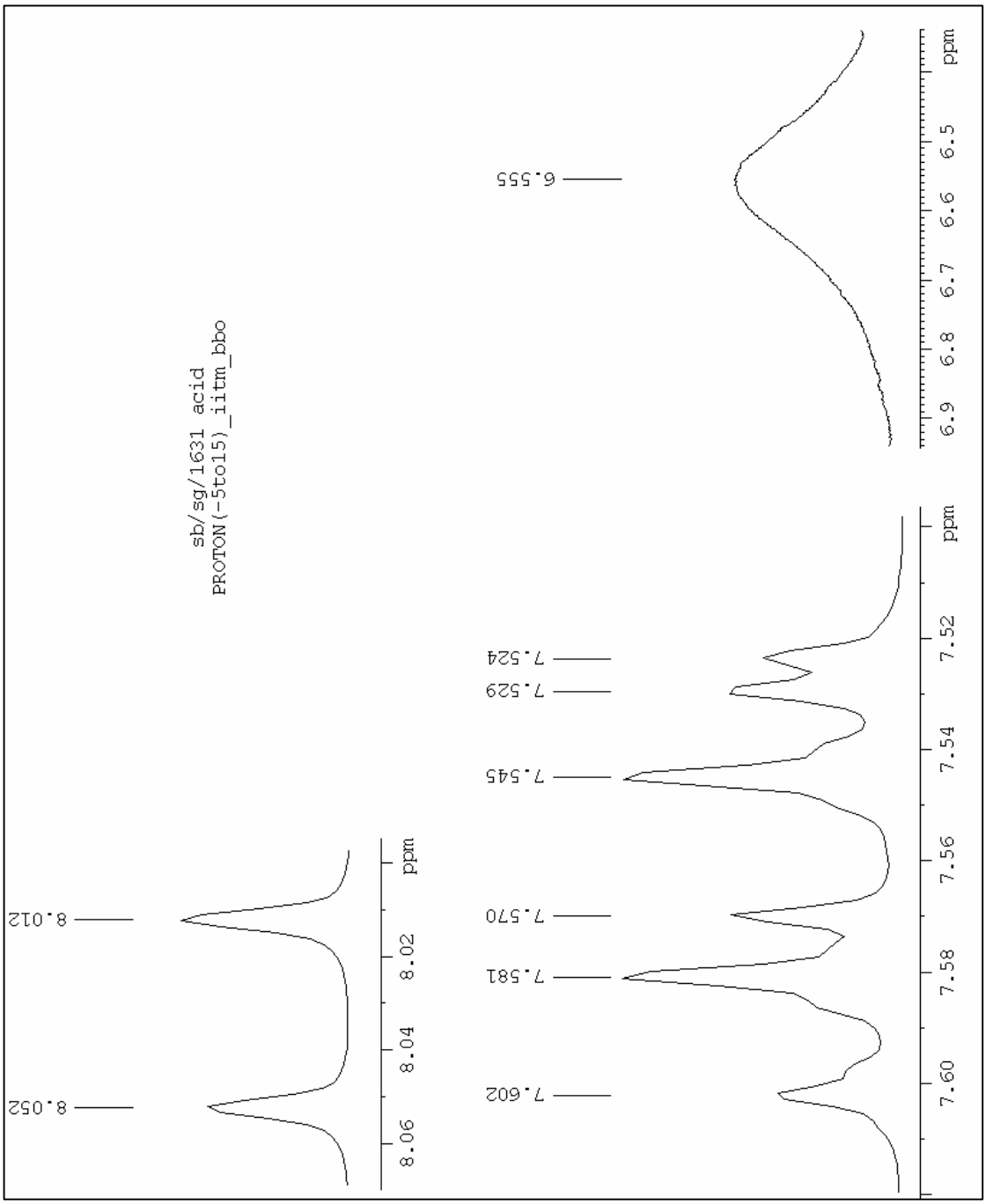
Expanded ^{1}H NMR spectrum of compound **10**



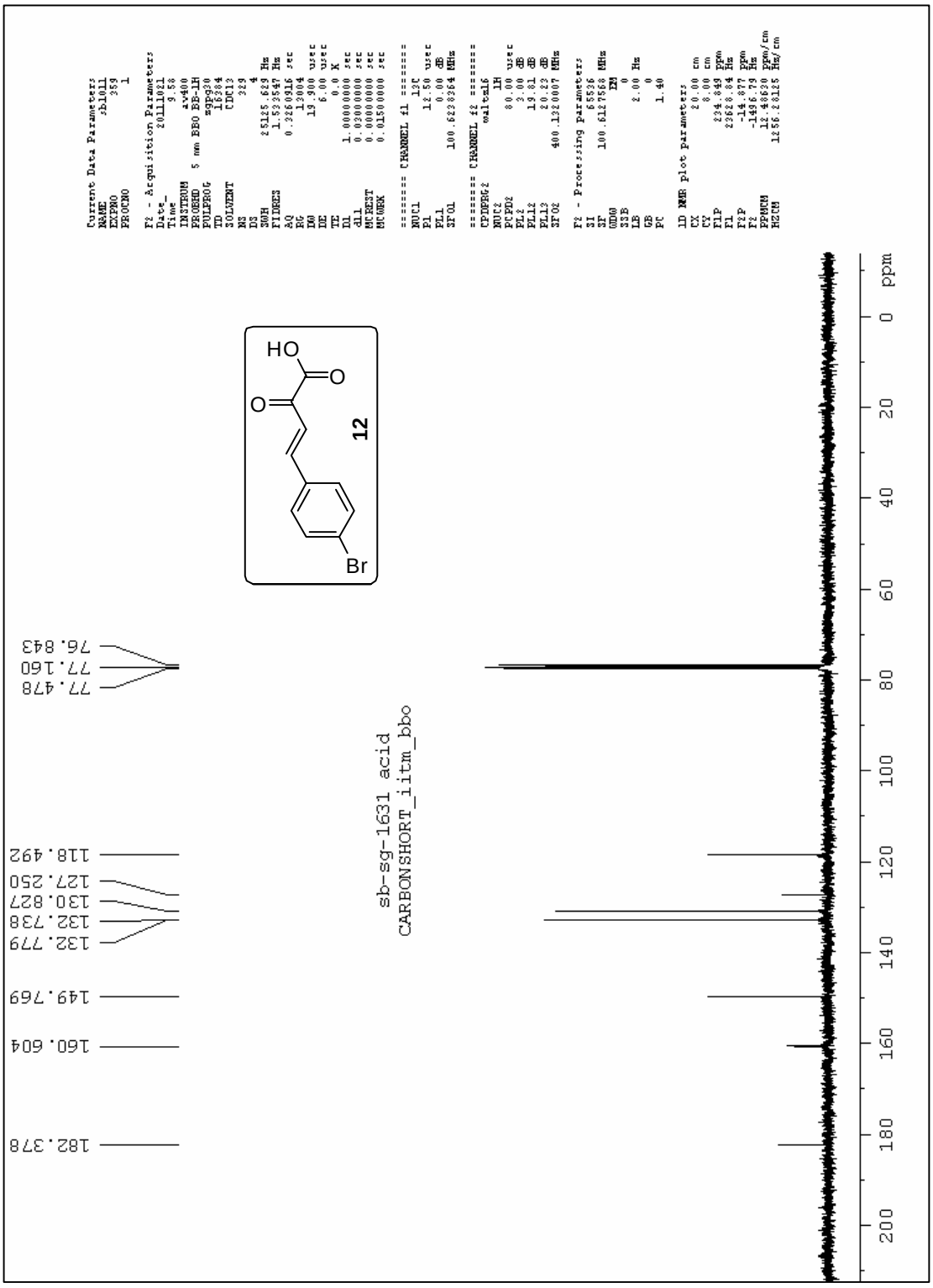
^{13}C NMR spectrum of compound **10**



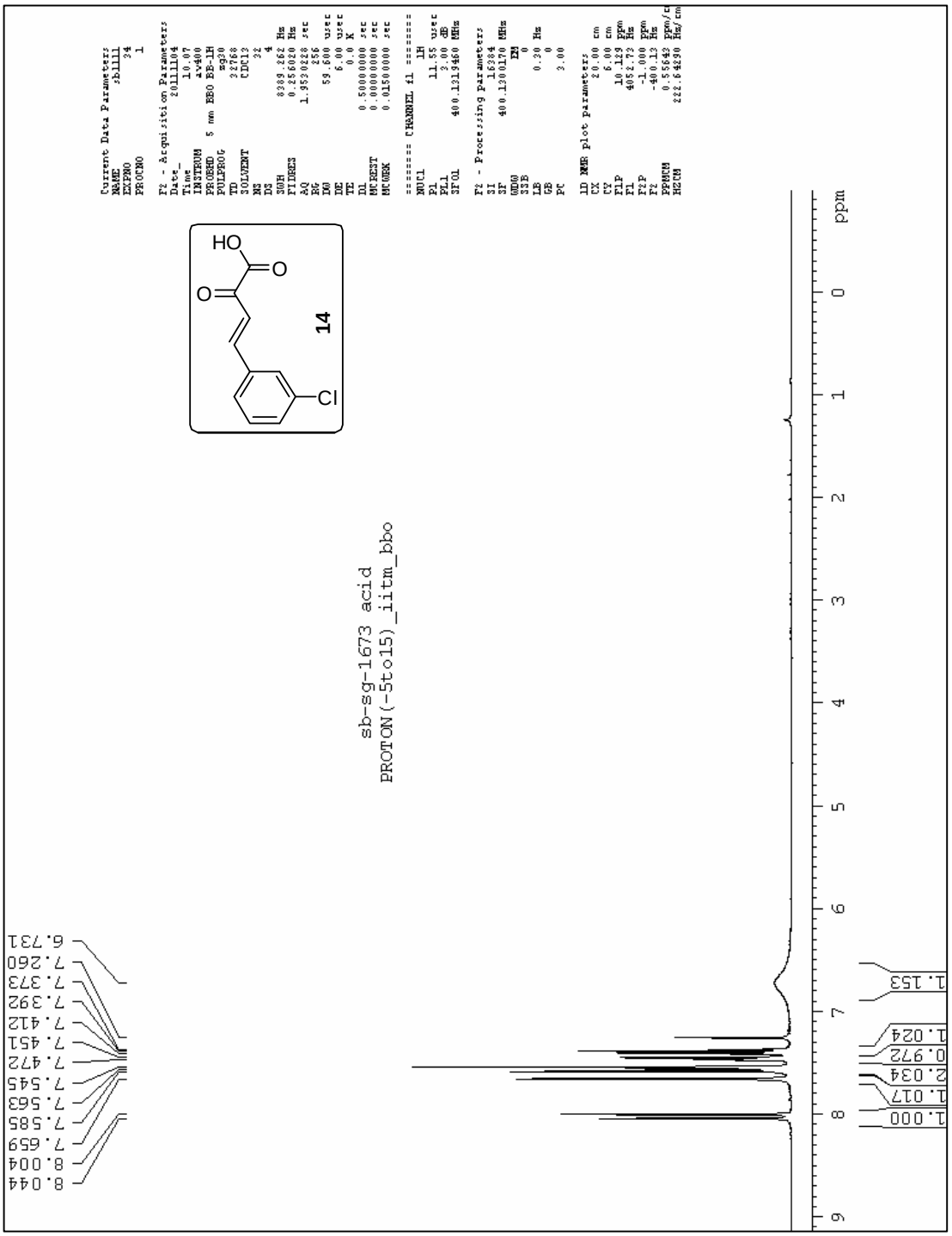
^{1}H NMR spectrum of compound **12**



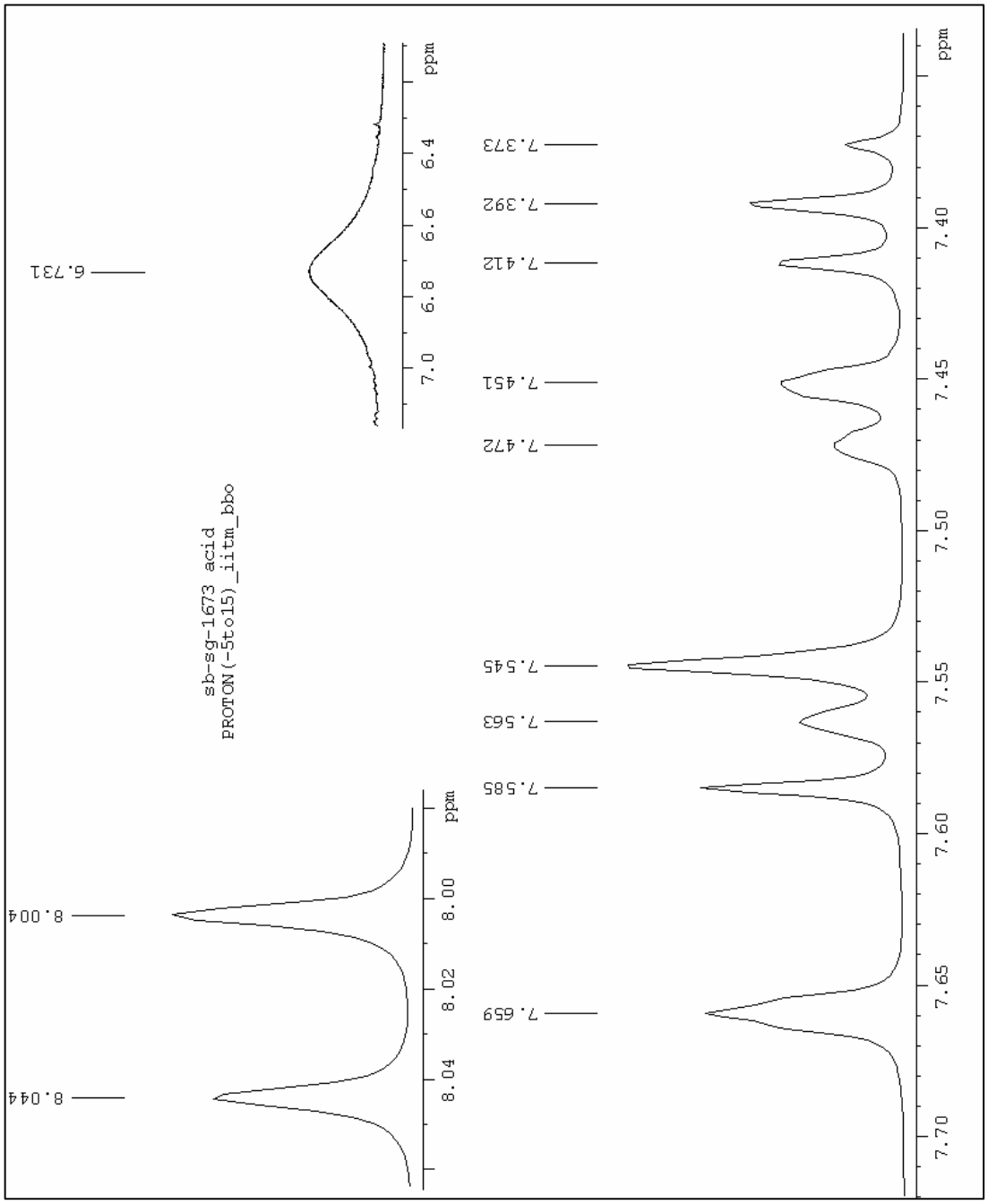
Expanded ^{1}H NMR spectrum of compound **12**



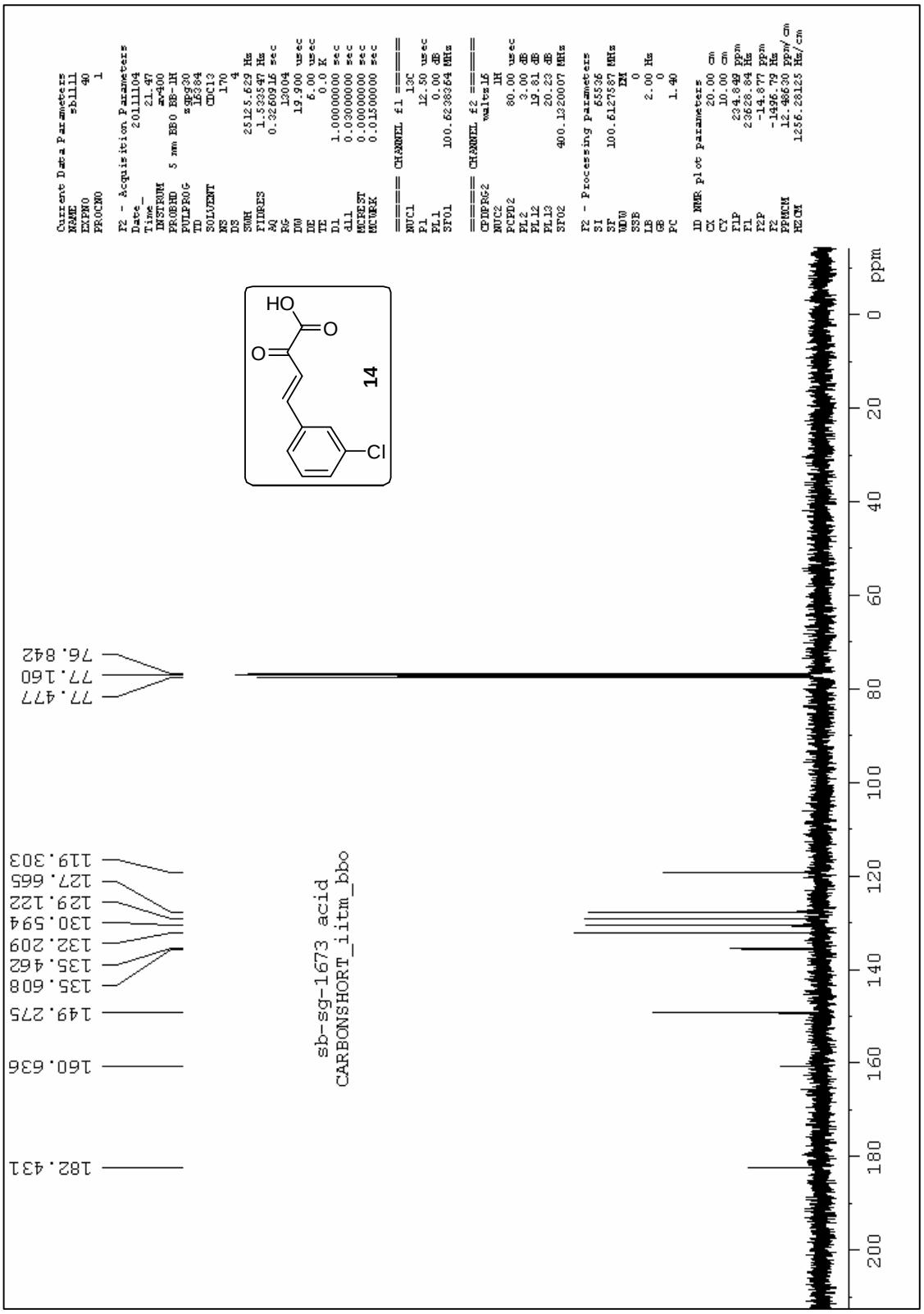
^{13}C NMR spectrum of compound **12**



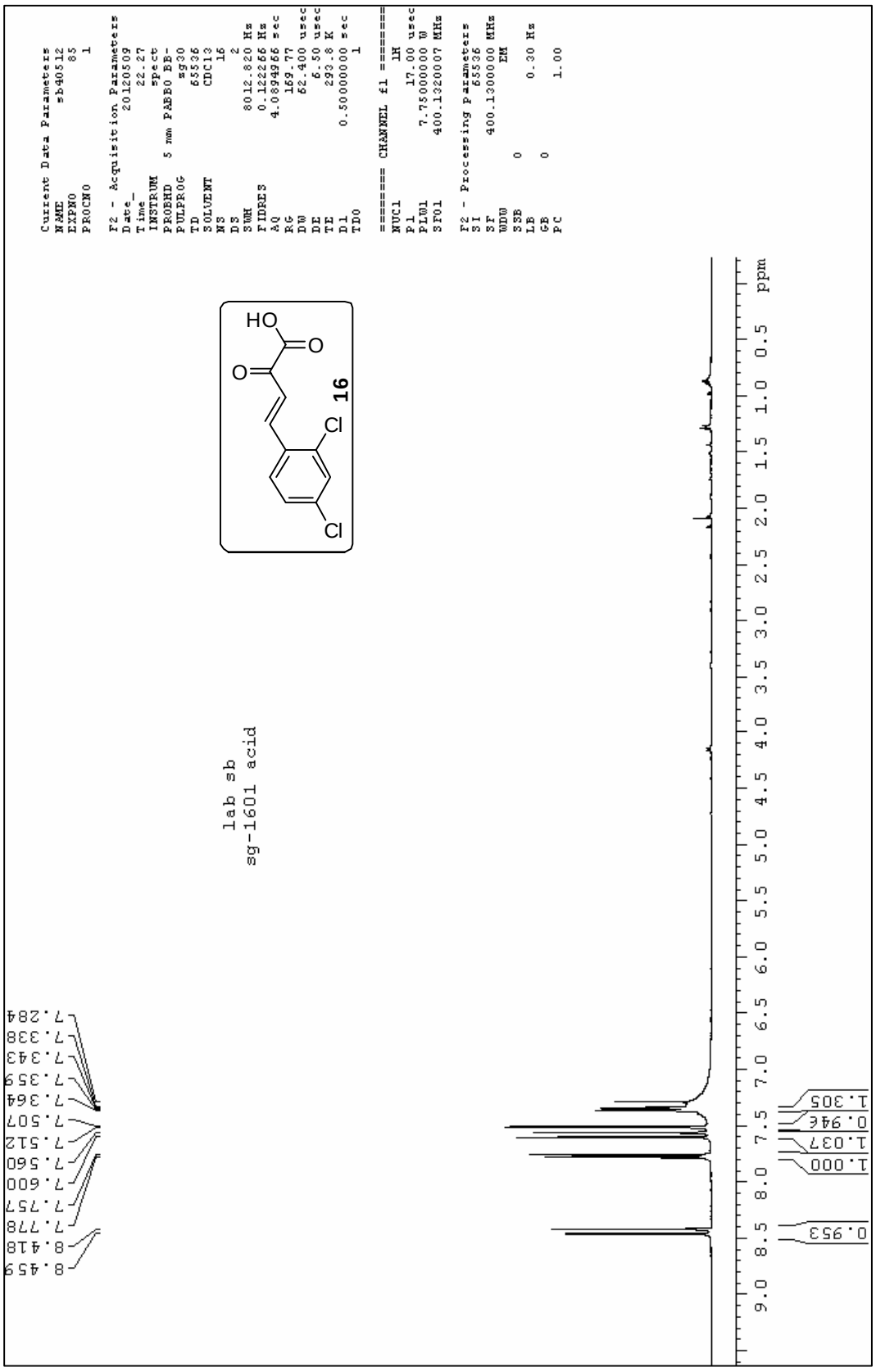
^{1}H NMR spectrum of compound **14**



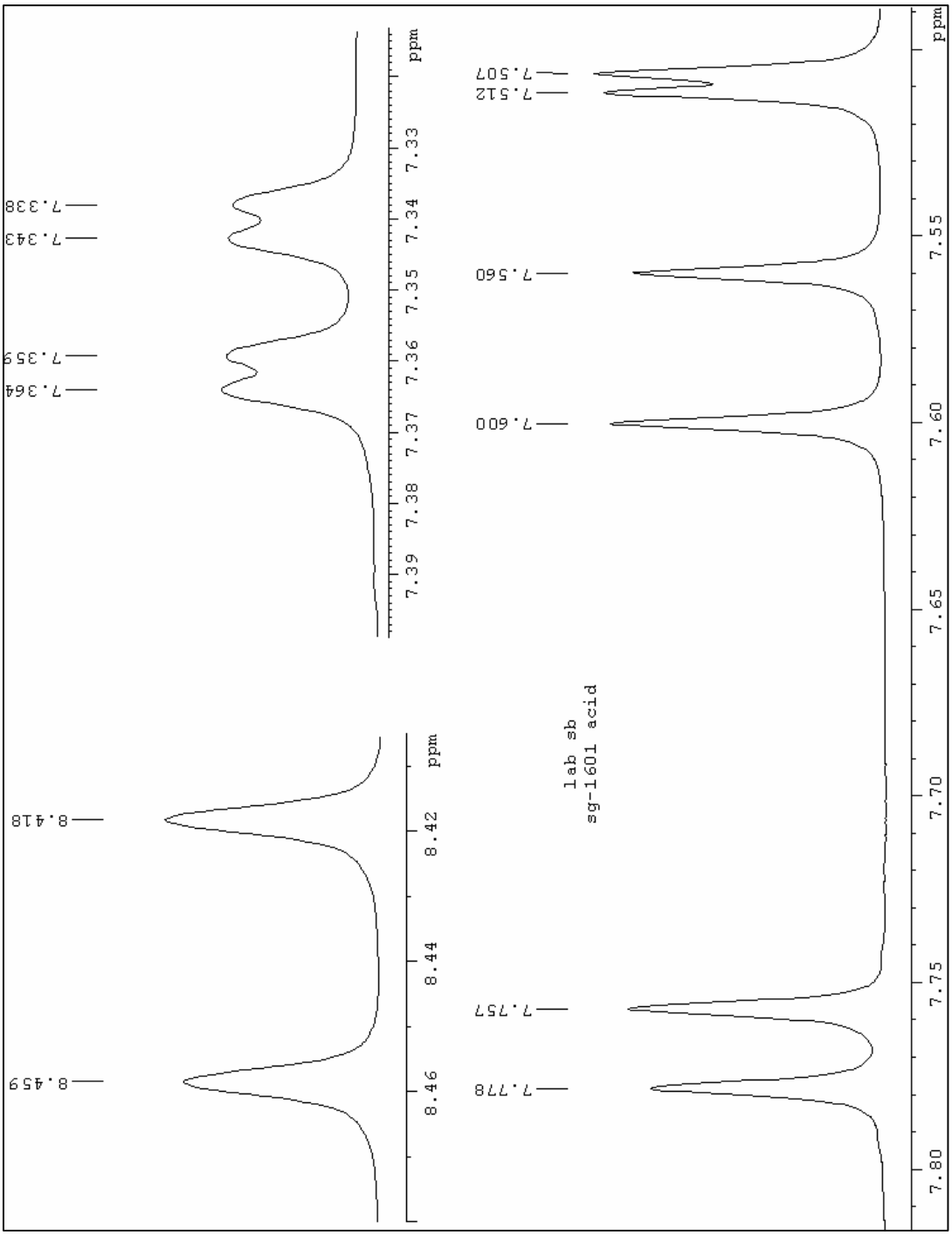
Expanded ^{1}H NMR spectrum of compound **14**



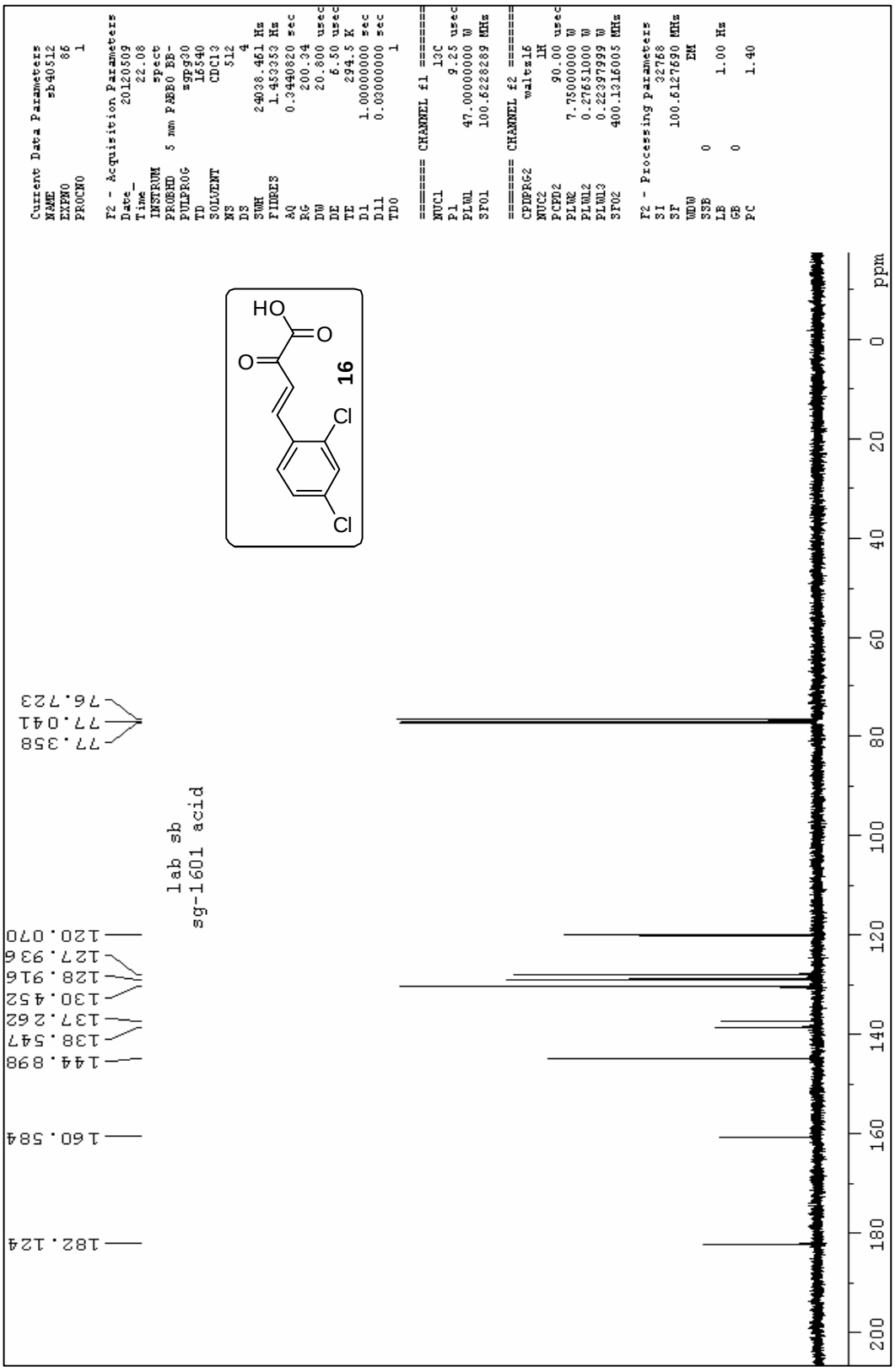
^{13}C NMR spectrum of compound **14**



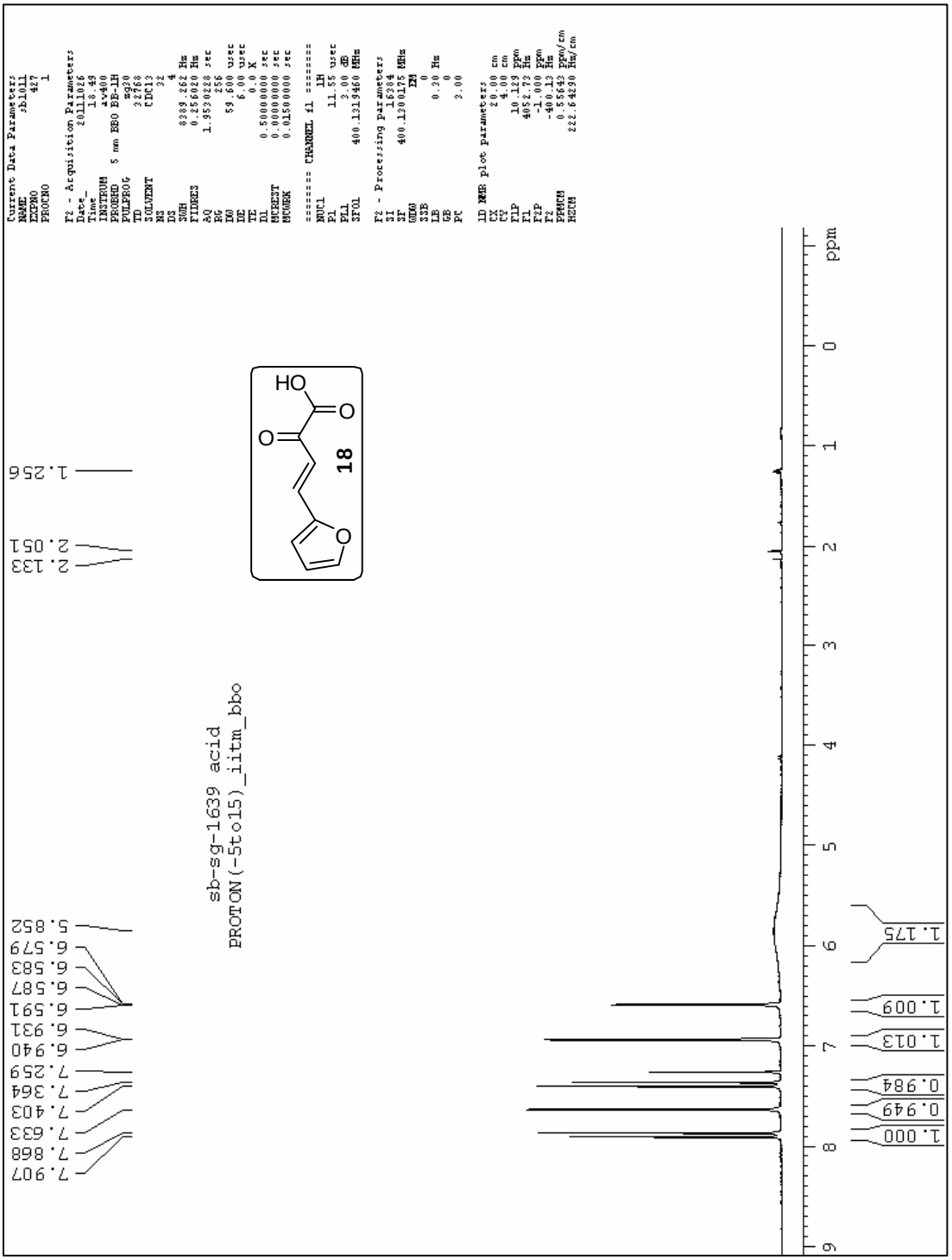
^{1}H NMR spectrum of compound **16**



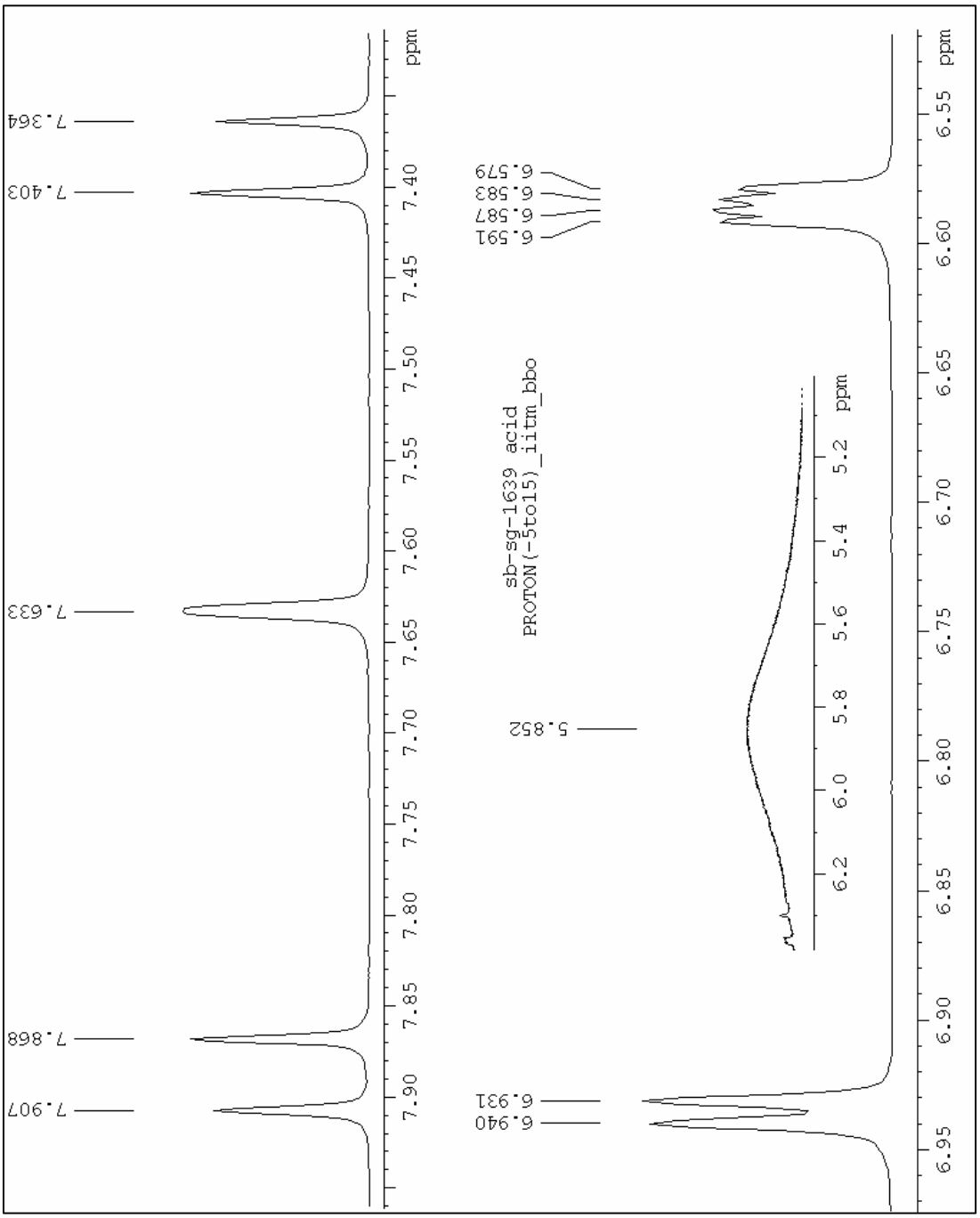
Expanded ^{1}H NMR spectrum of compound **16**



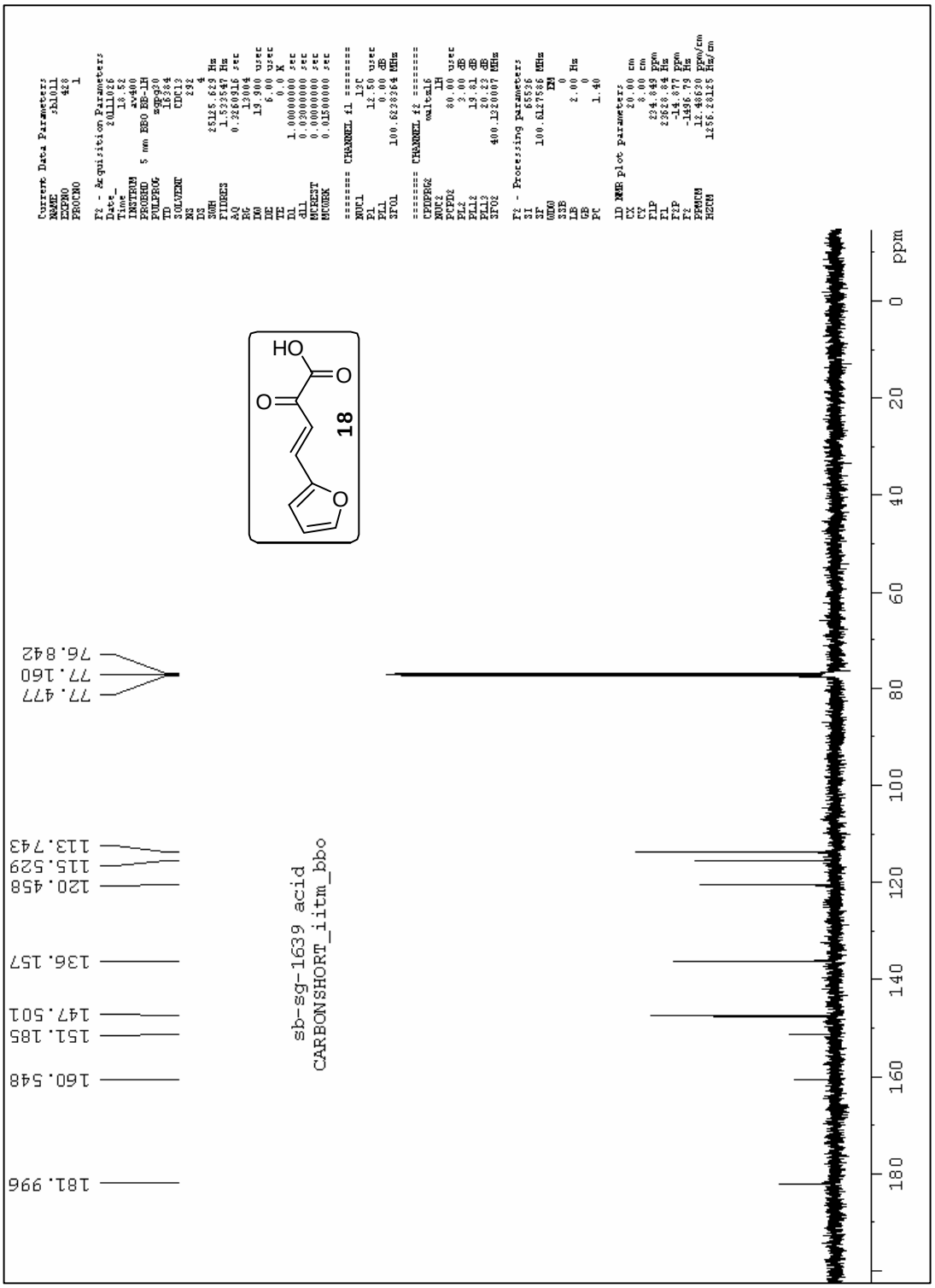
^{13}C NMR spectrum of compound **16**



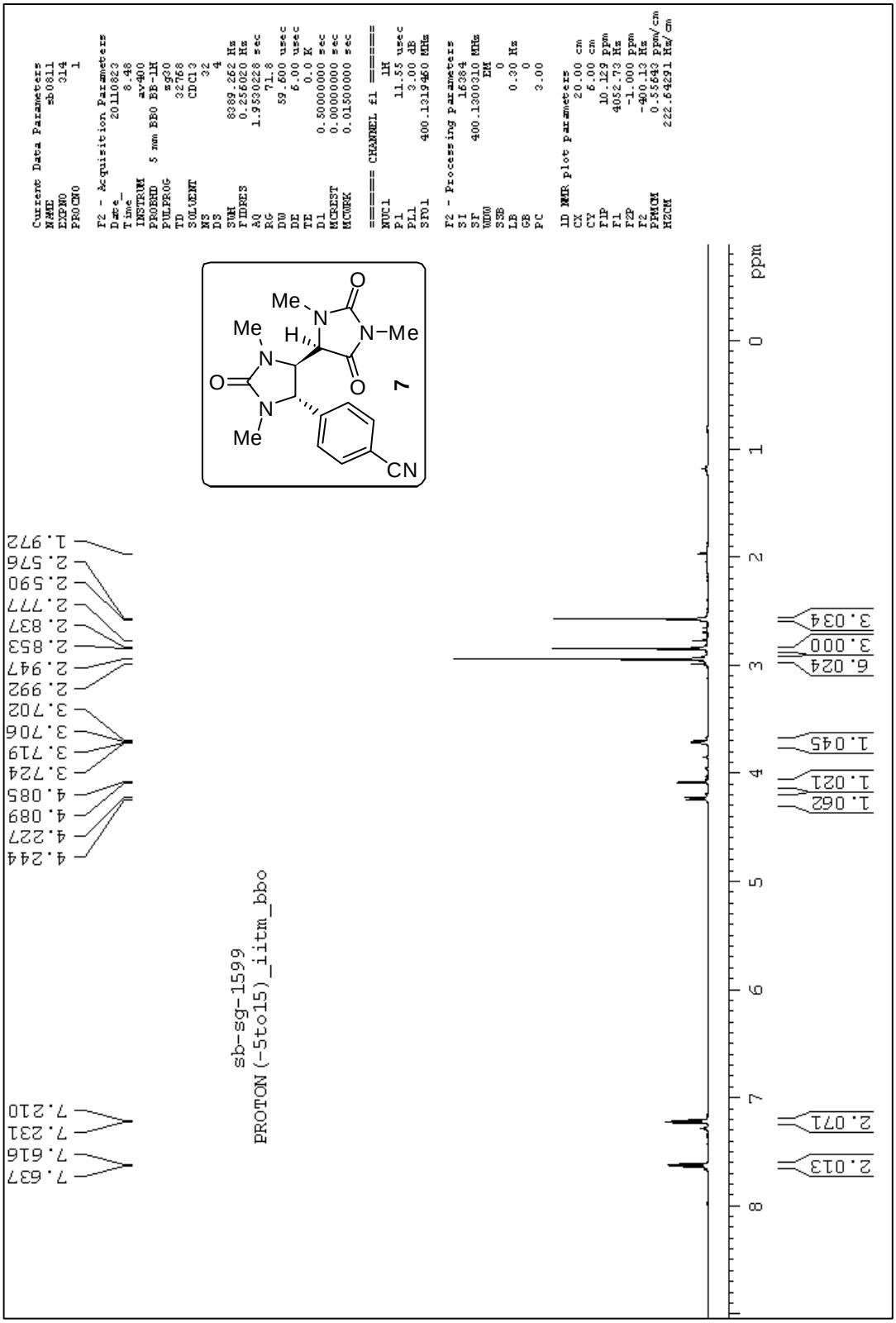
^{1}H NMR spectrum of compound **18**



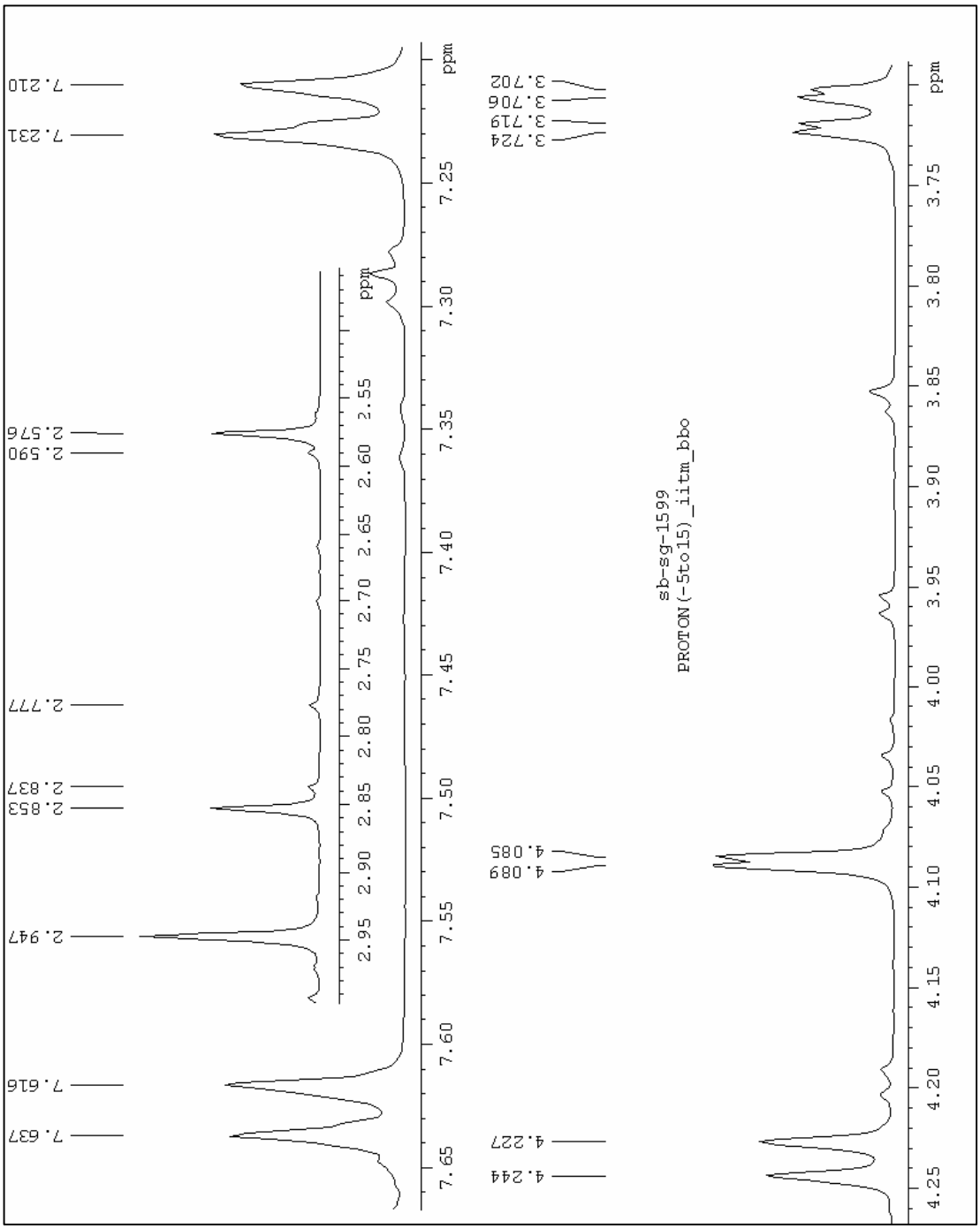
Expanded ^{1}H NMR spectrum of compound **18**



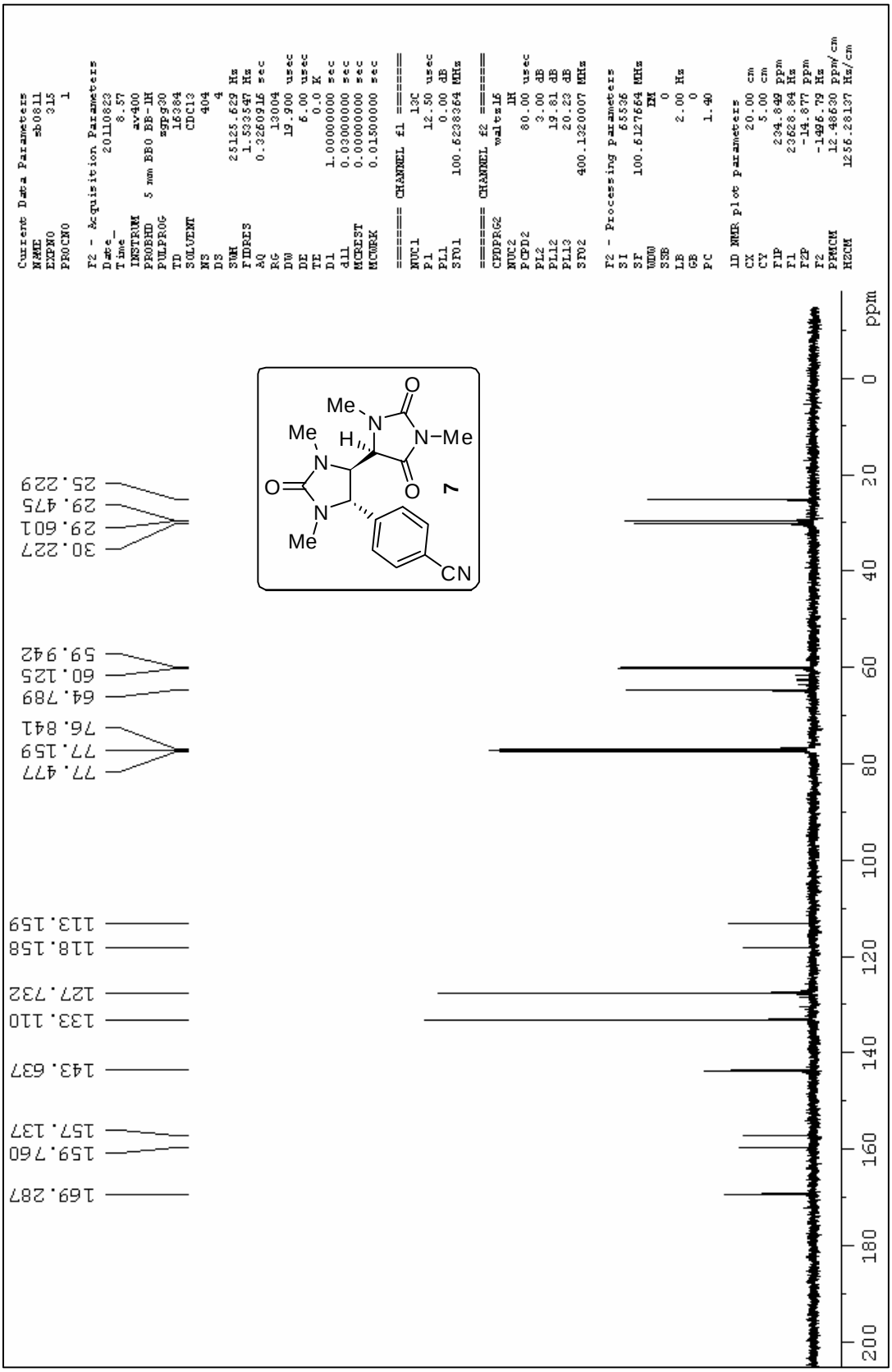
^{13}C NMR spectrum of compound **18**



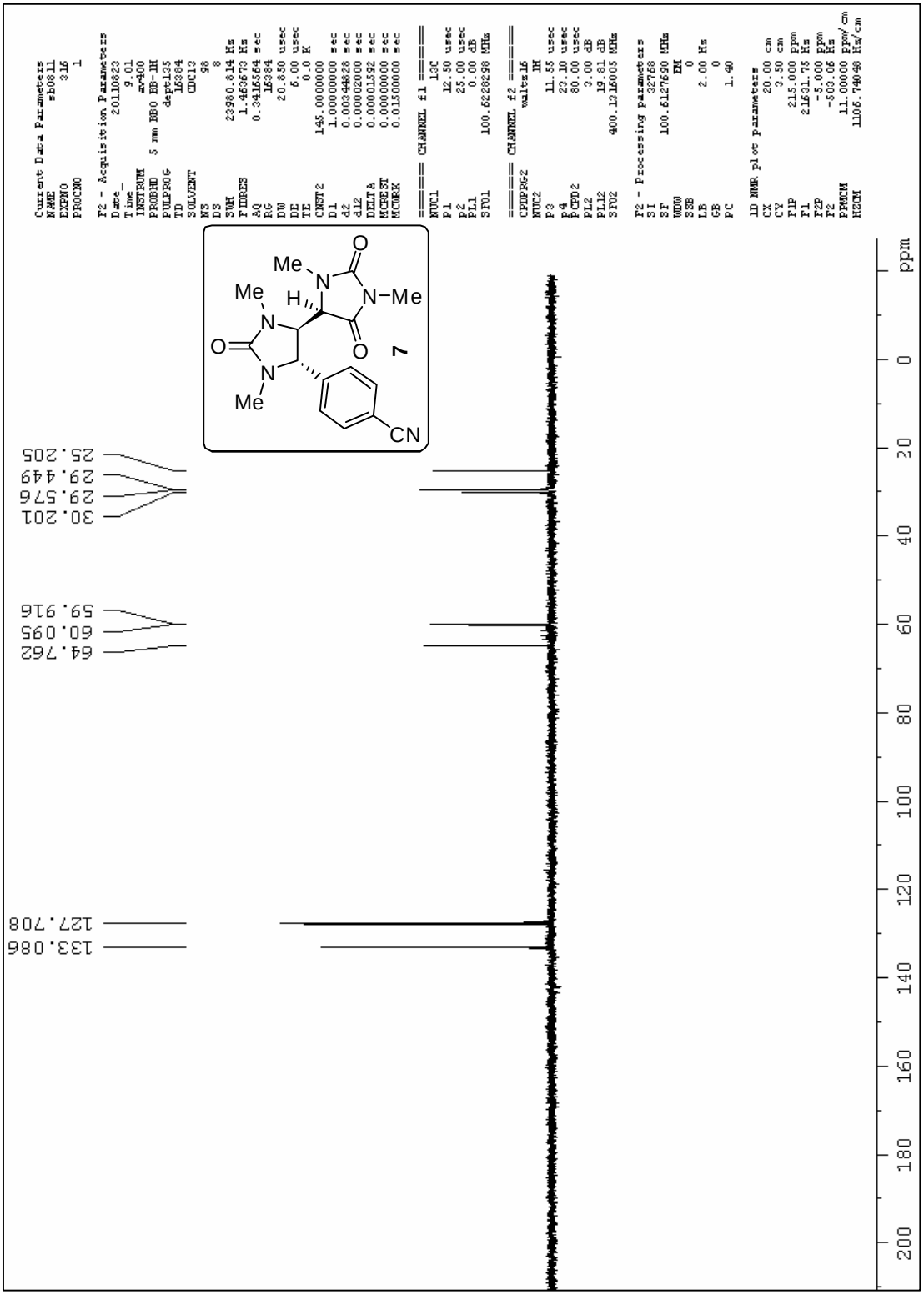
^{1}H NMR spectrum of compound **7**



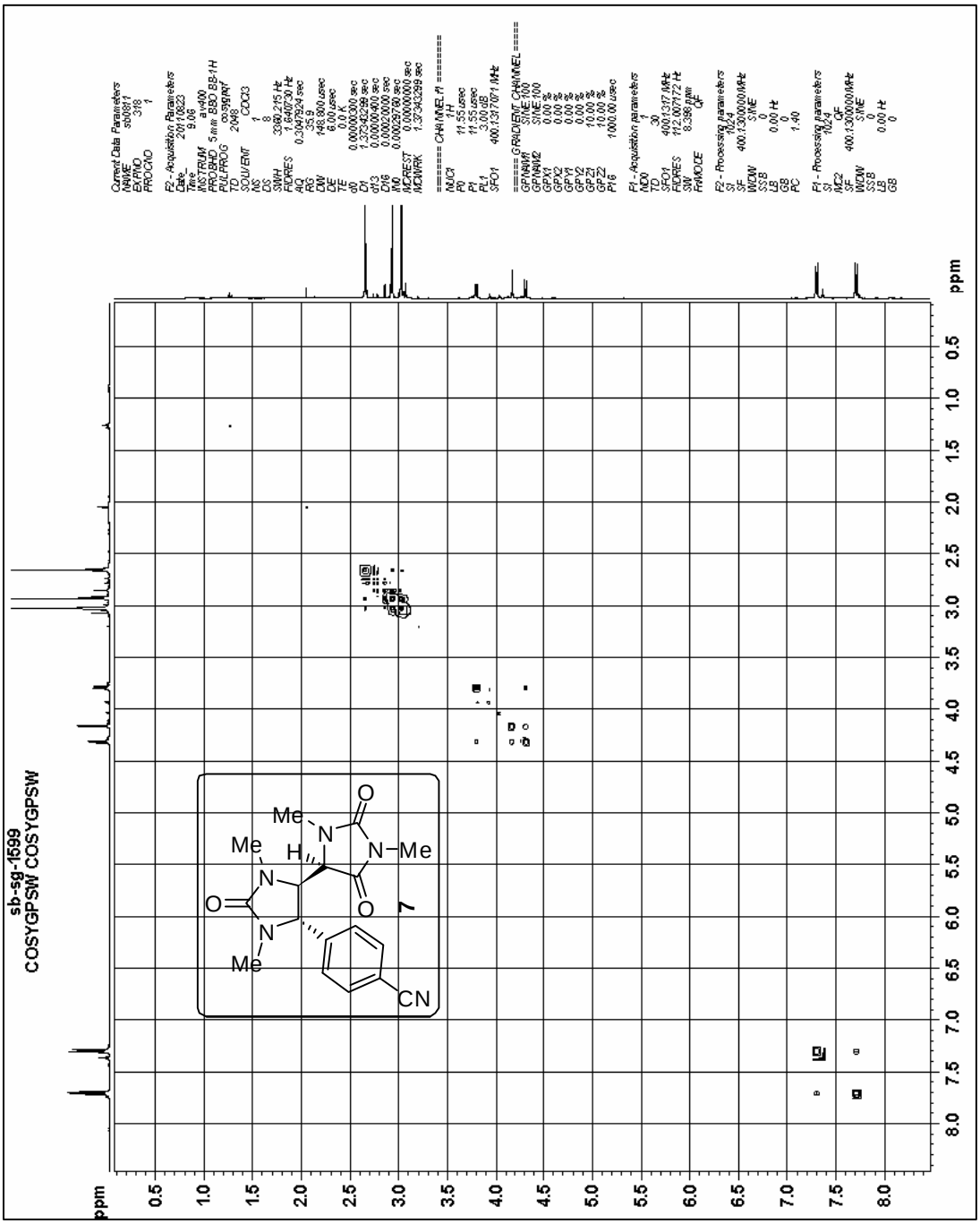
Expanded ^{1}H NMR spectrum of compound **7**



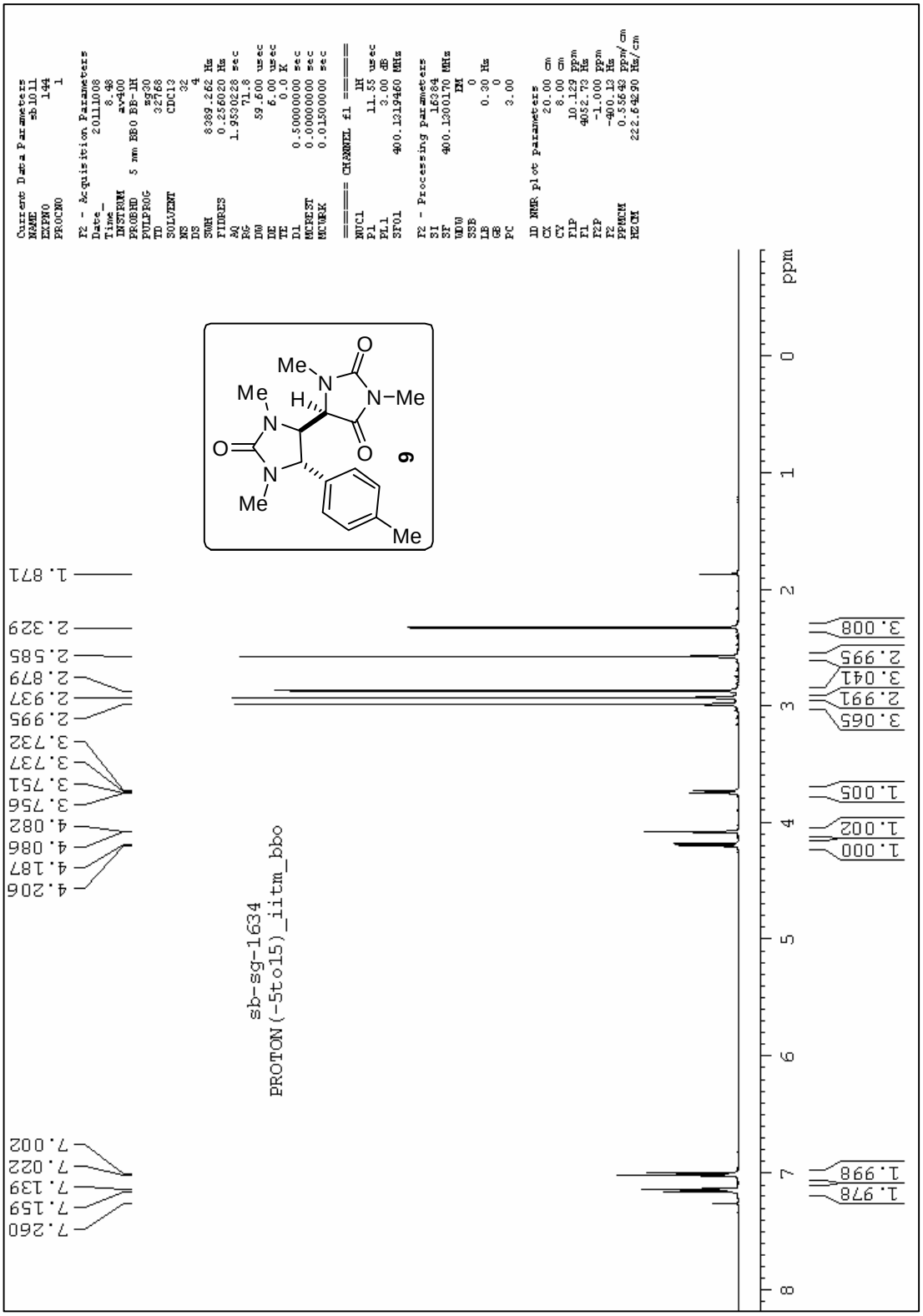
^{13}C NMR spectrum of compound **7**



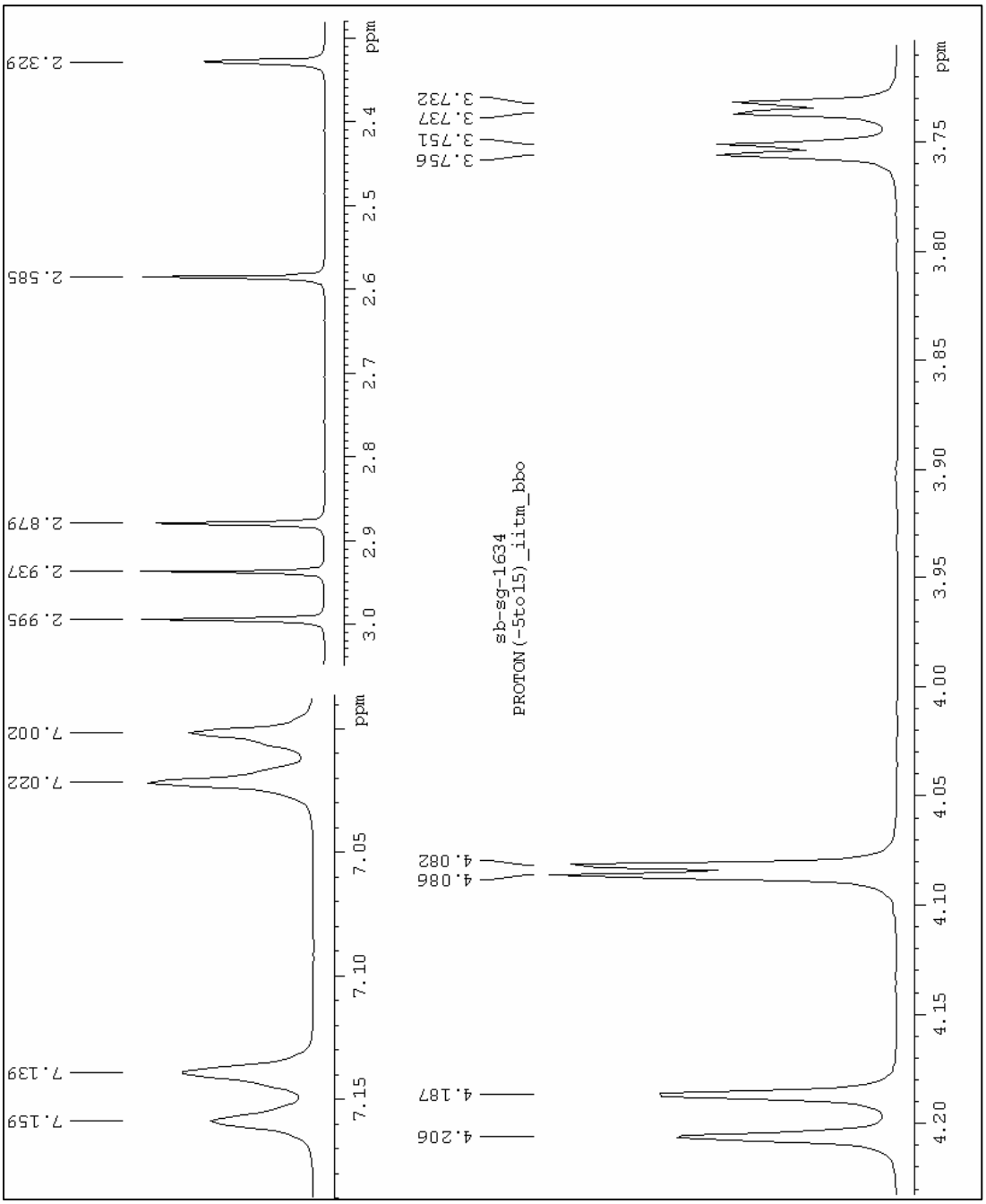
^{13}C DEPT NMR spectrum of compound **7**



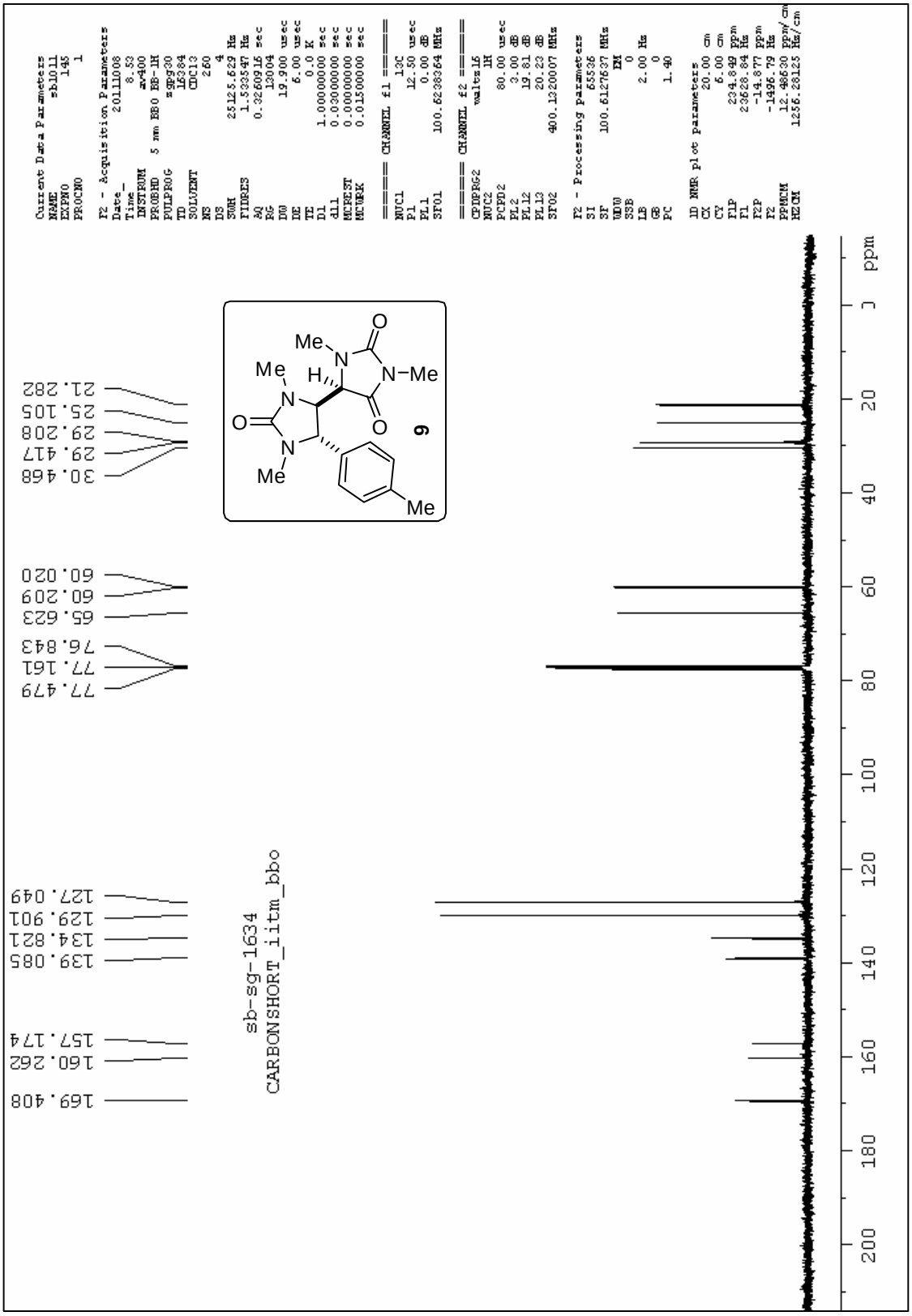
^{1}H ^{1}H COSY NMR spectrum of compound **7**



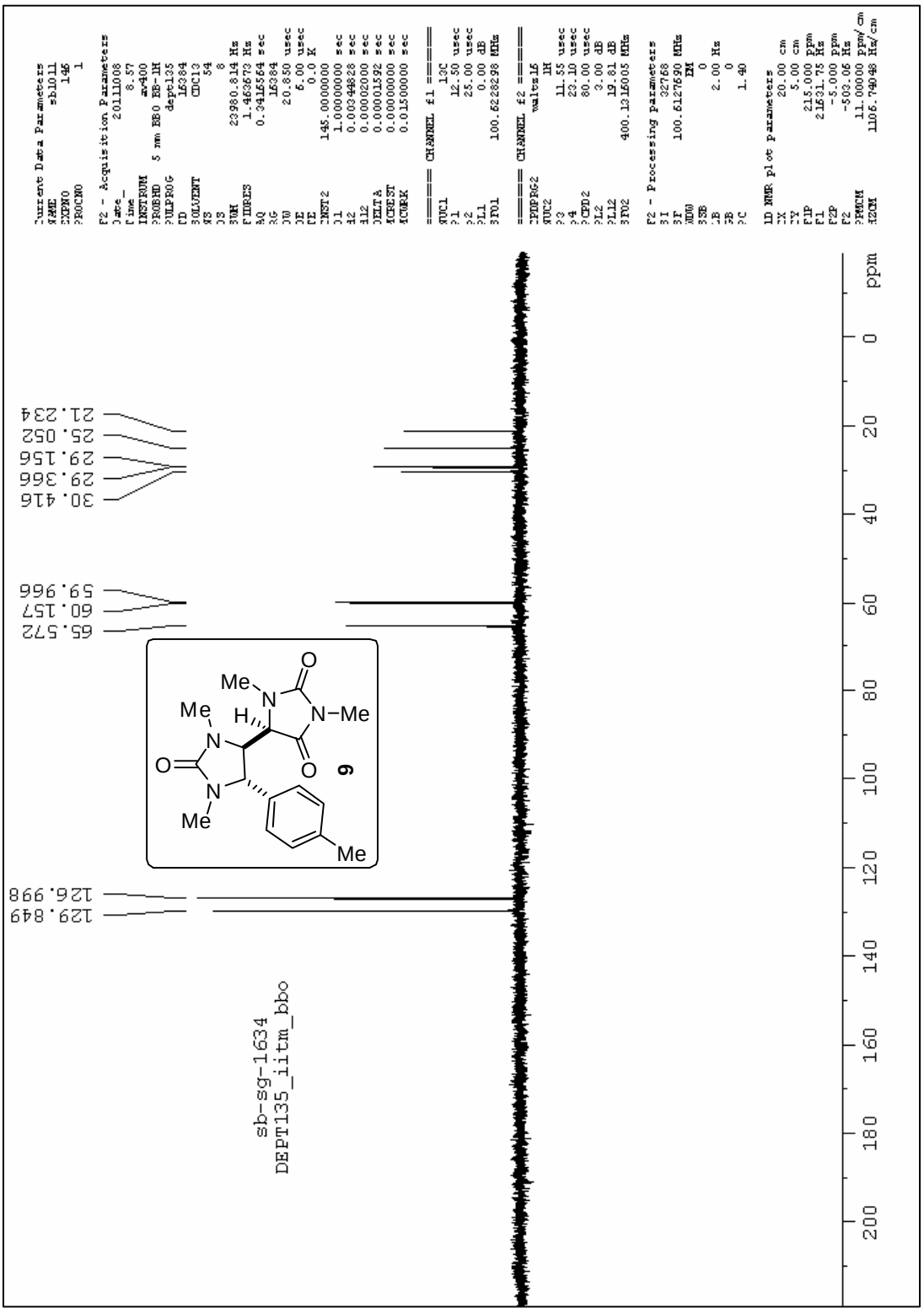
^{1}H NMR spectrum of compound **9**



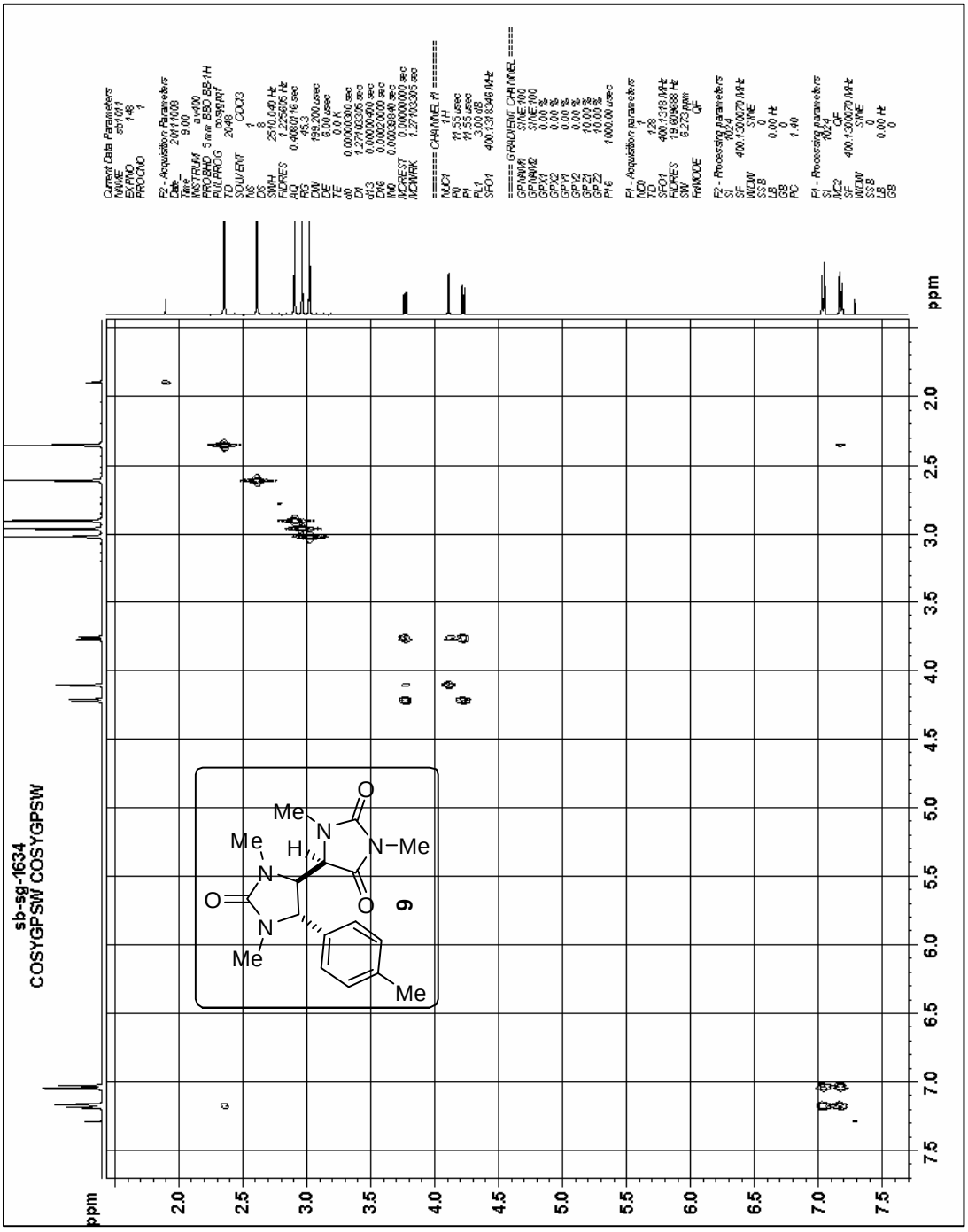
Expanded ^{1}H NMR spectrum of compound **9**



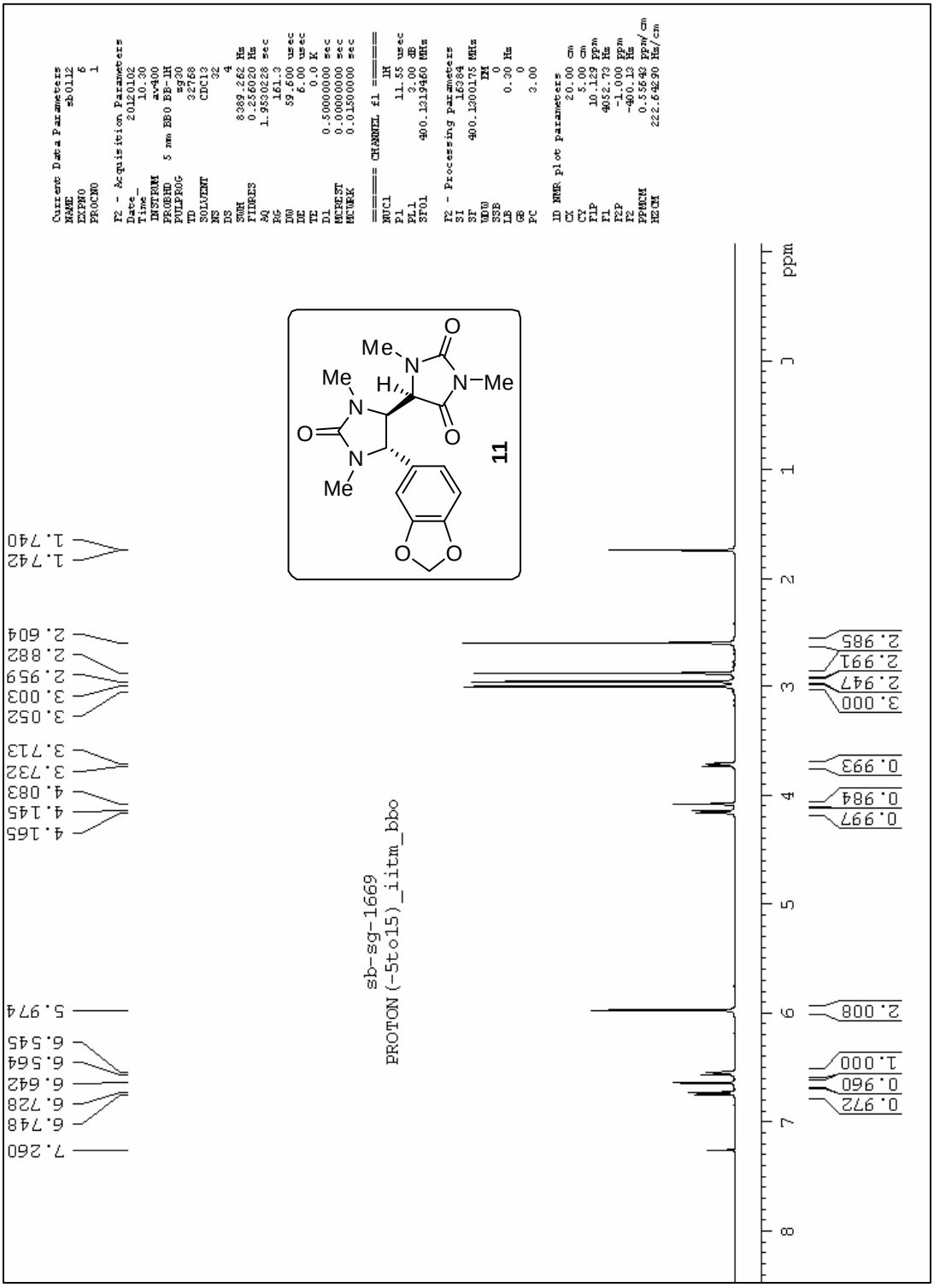
^{13}C NMR spectrum of compound **9**



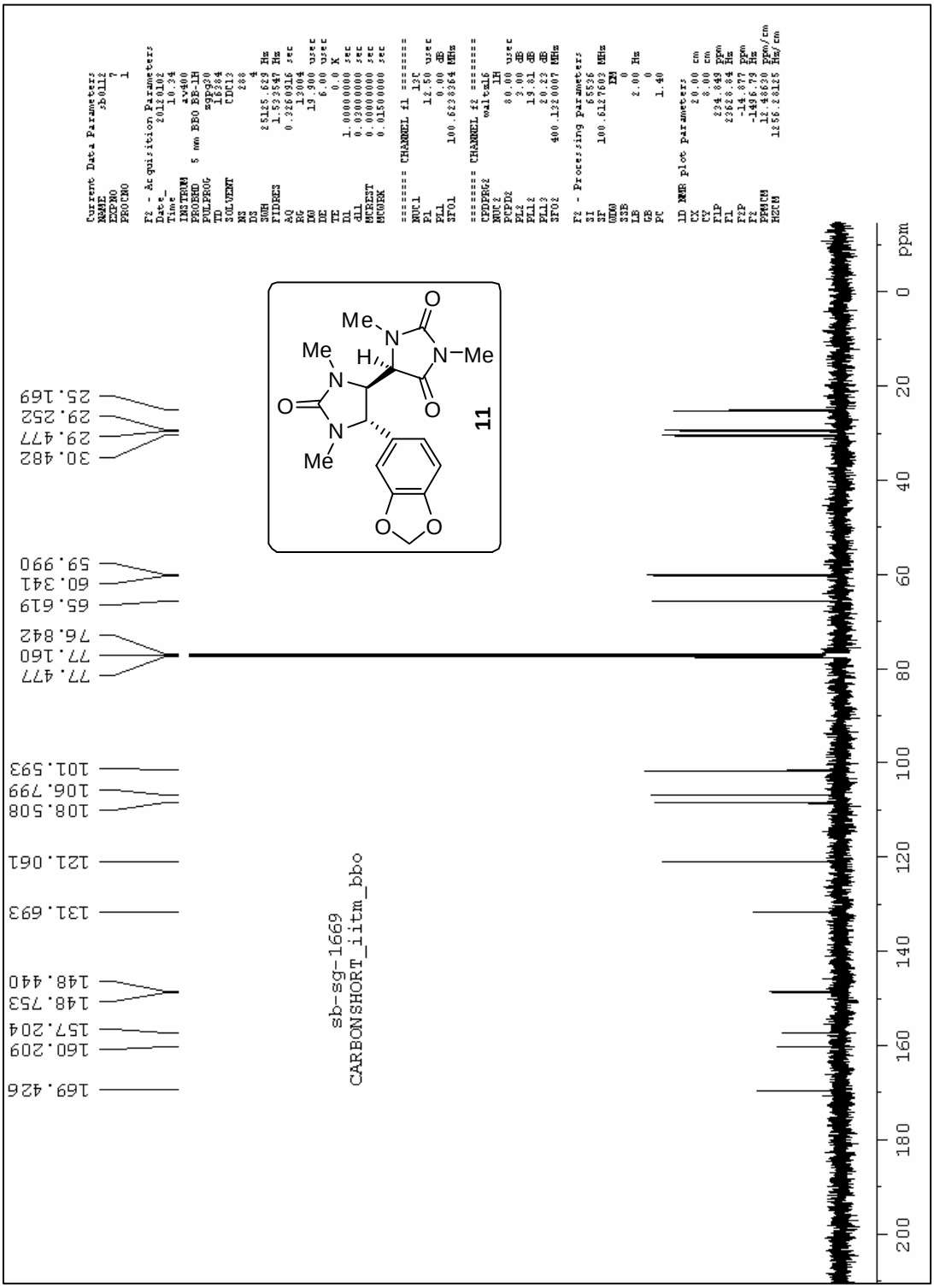
^{13}C DEPT NMR spectrum of compound **9**



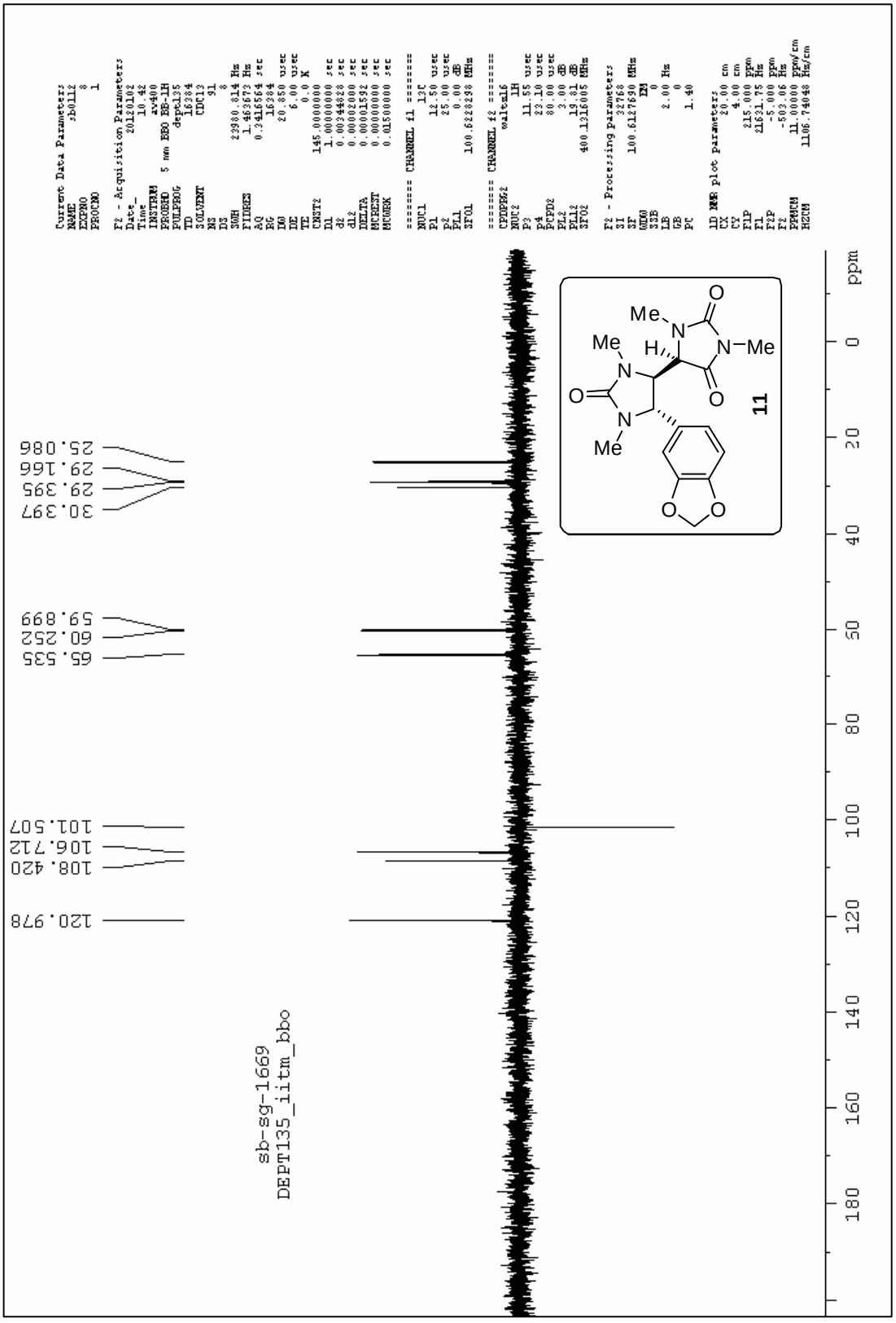
^{1}H ^{1}H COSY NMR spectrum of compound **9**



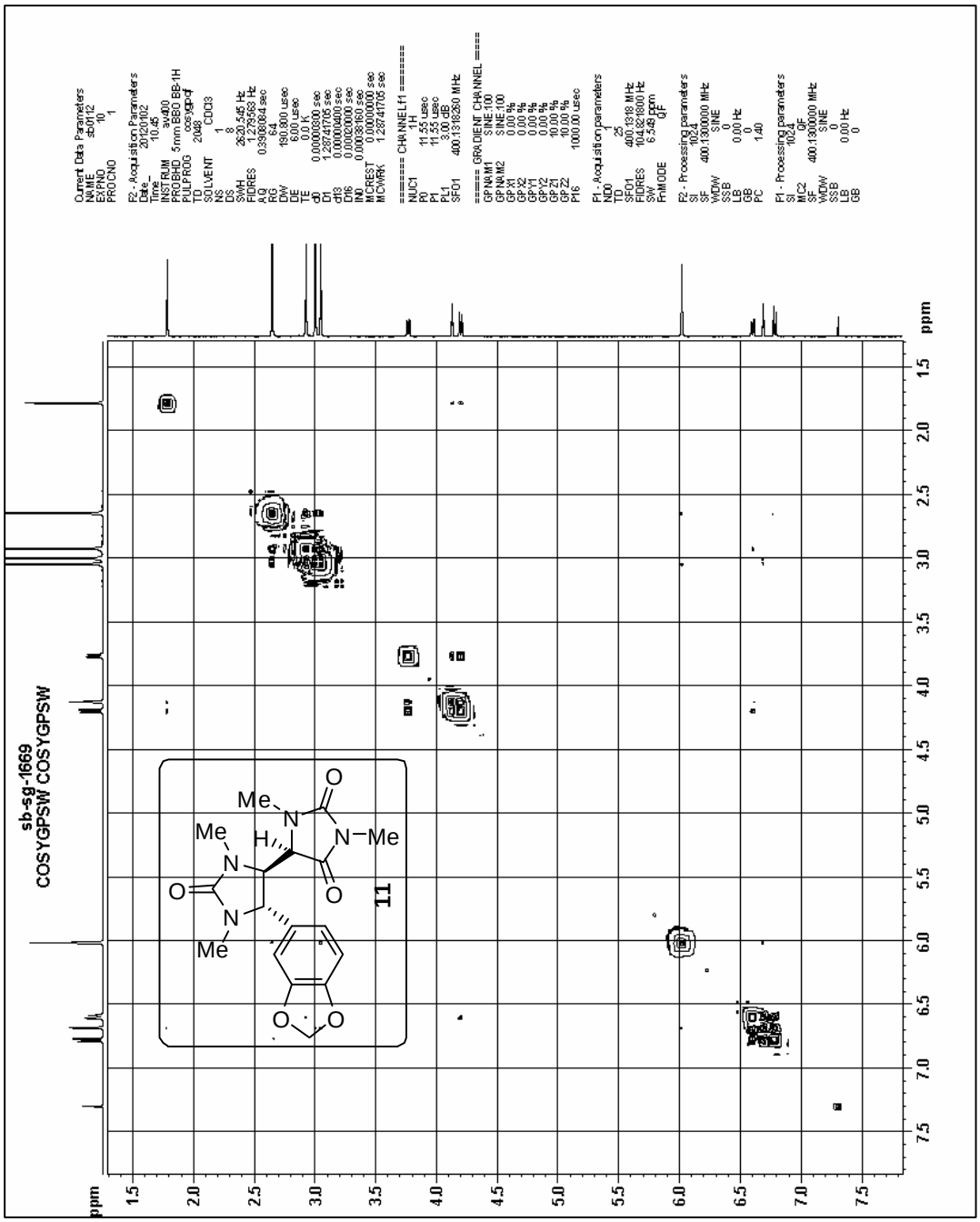
^{1}H NMR spectrum of compound **11**



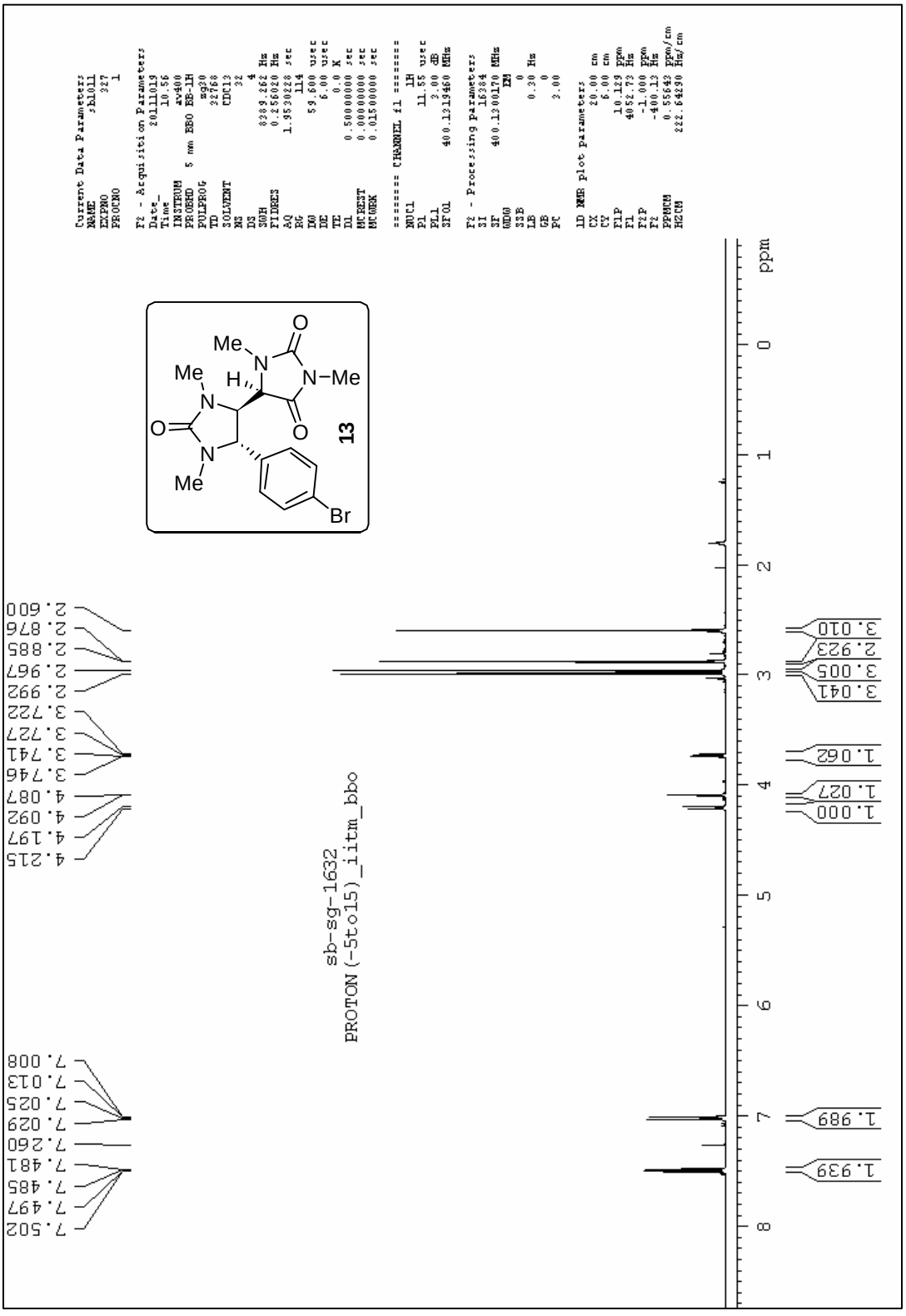
^{13}C NMR spectrum of compound **11**



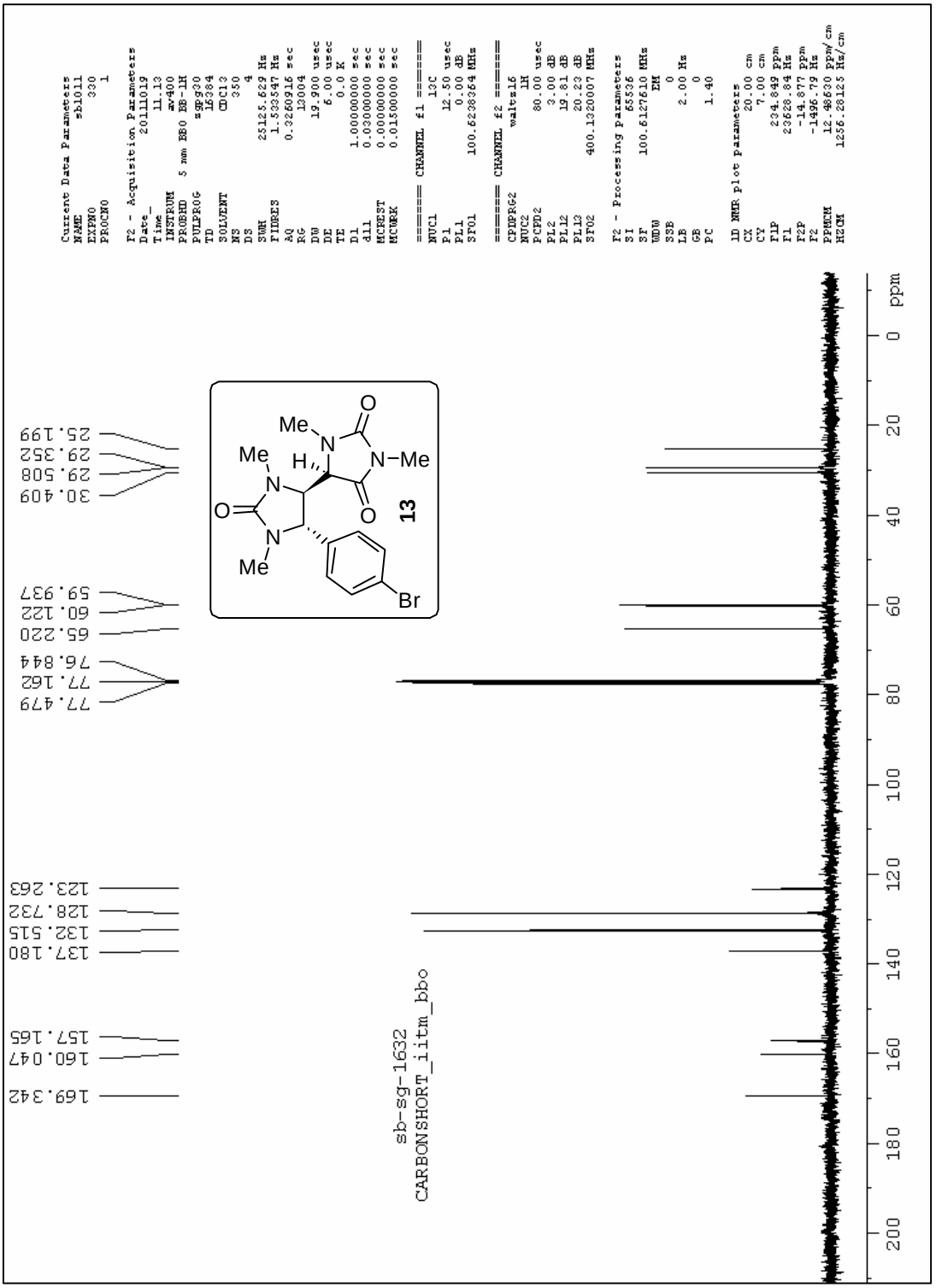
^{13}C DEPT NMR spectrum of compound **11**



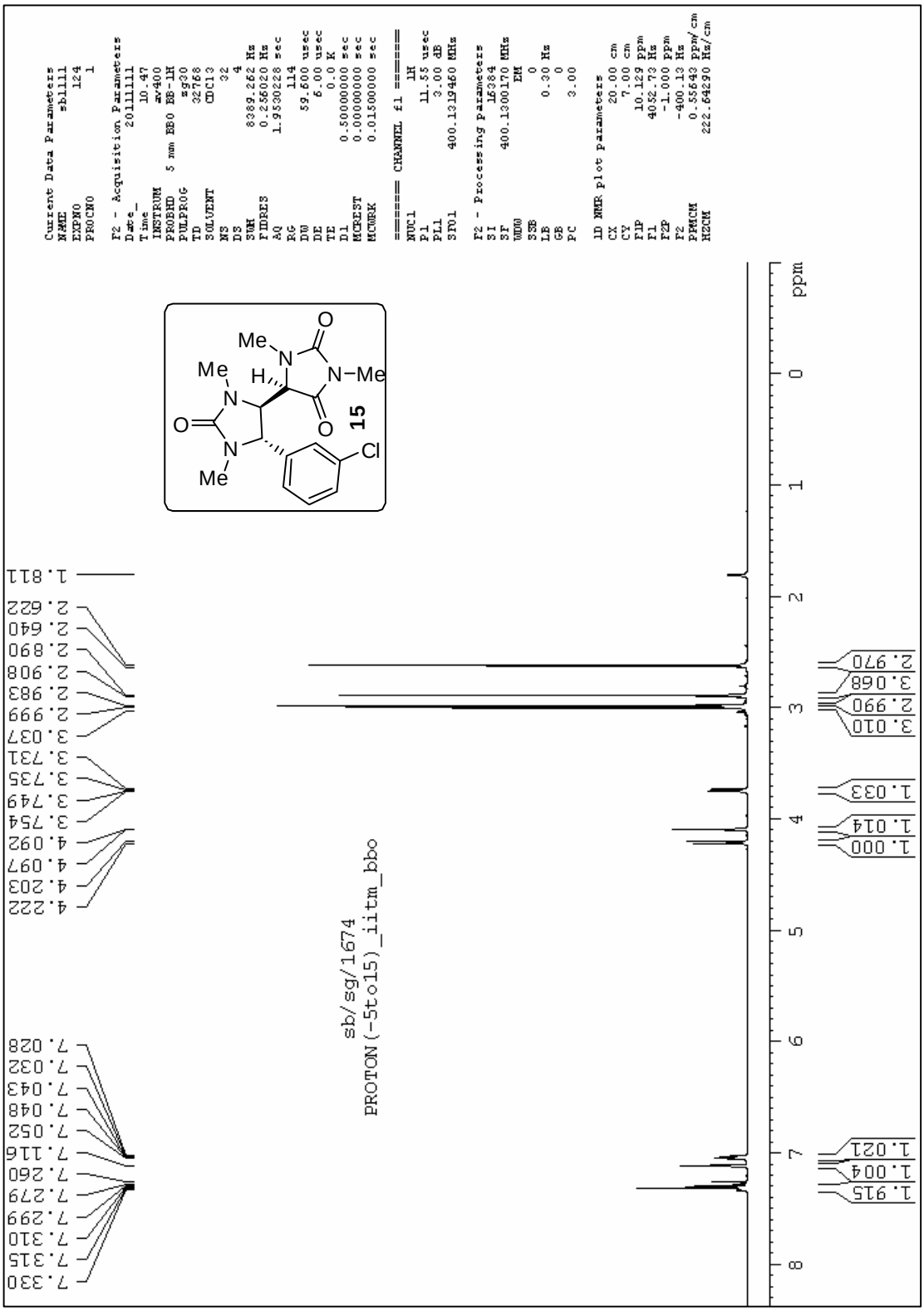
^{1}H ^{1}H COSY NMR spectrum of compound **11**



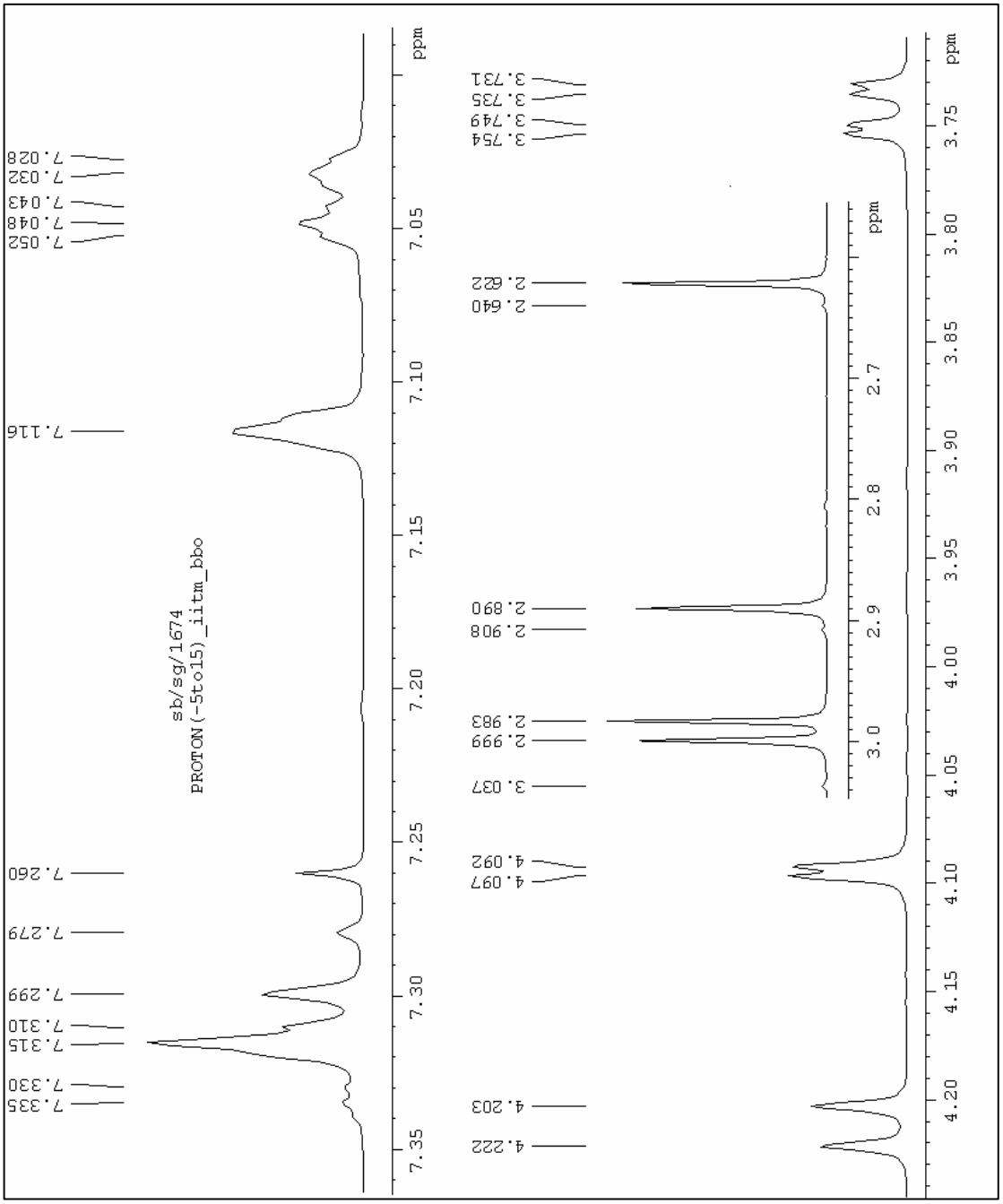
^{1}H NMR spectrum of compound **13**



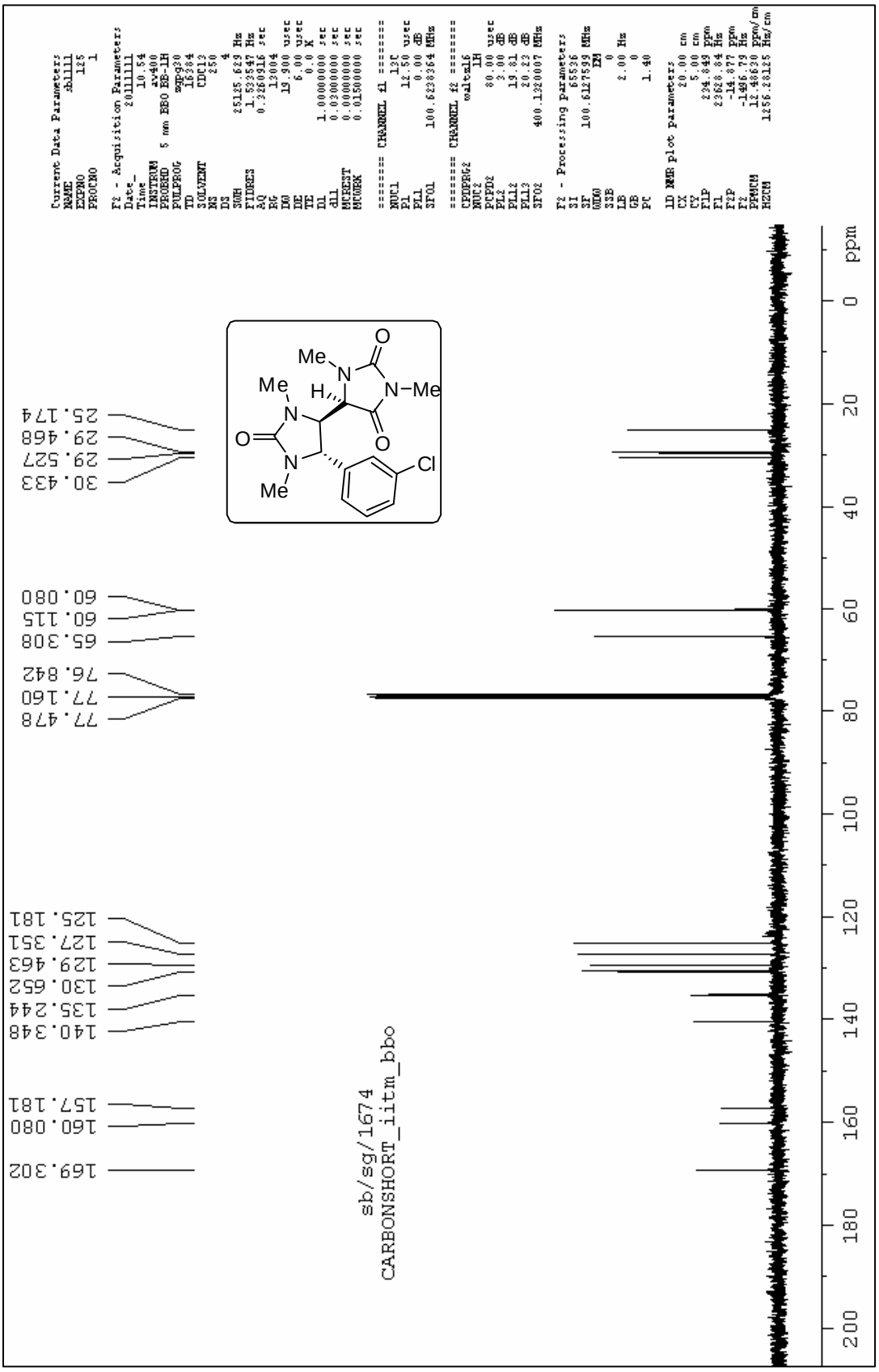
^{13}C NMR spectrum of compound **13**



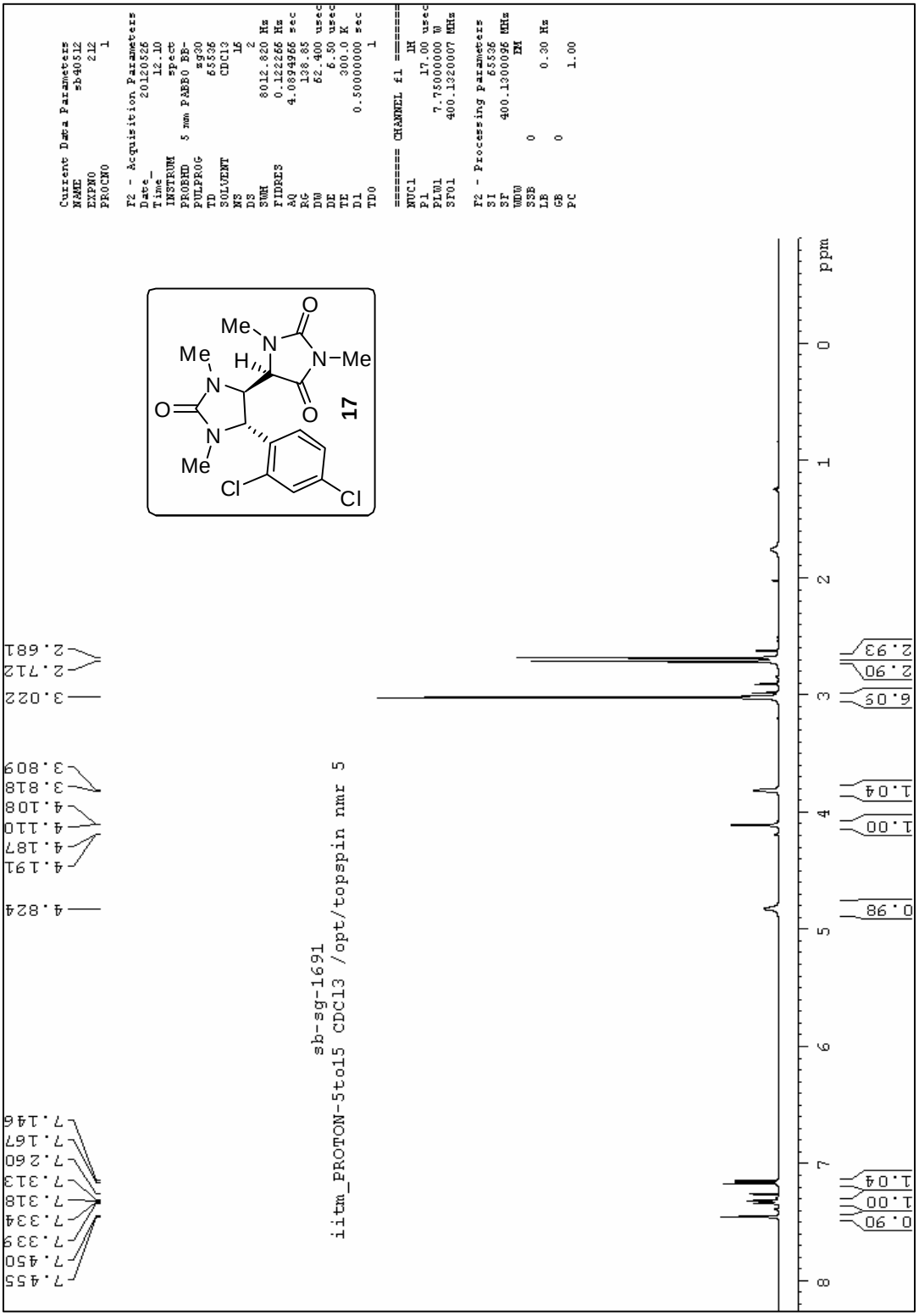
^{1}H NMR spectrum of compound **15**



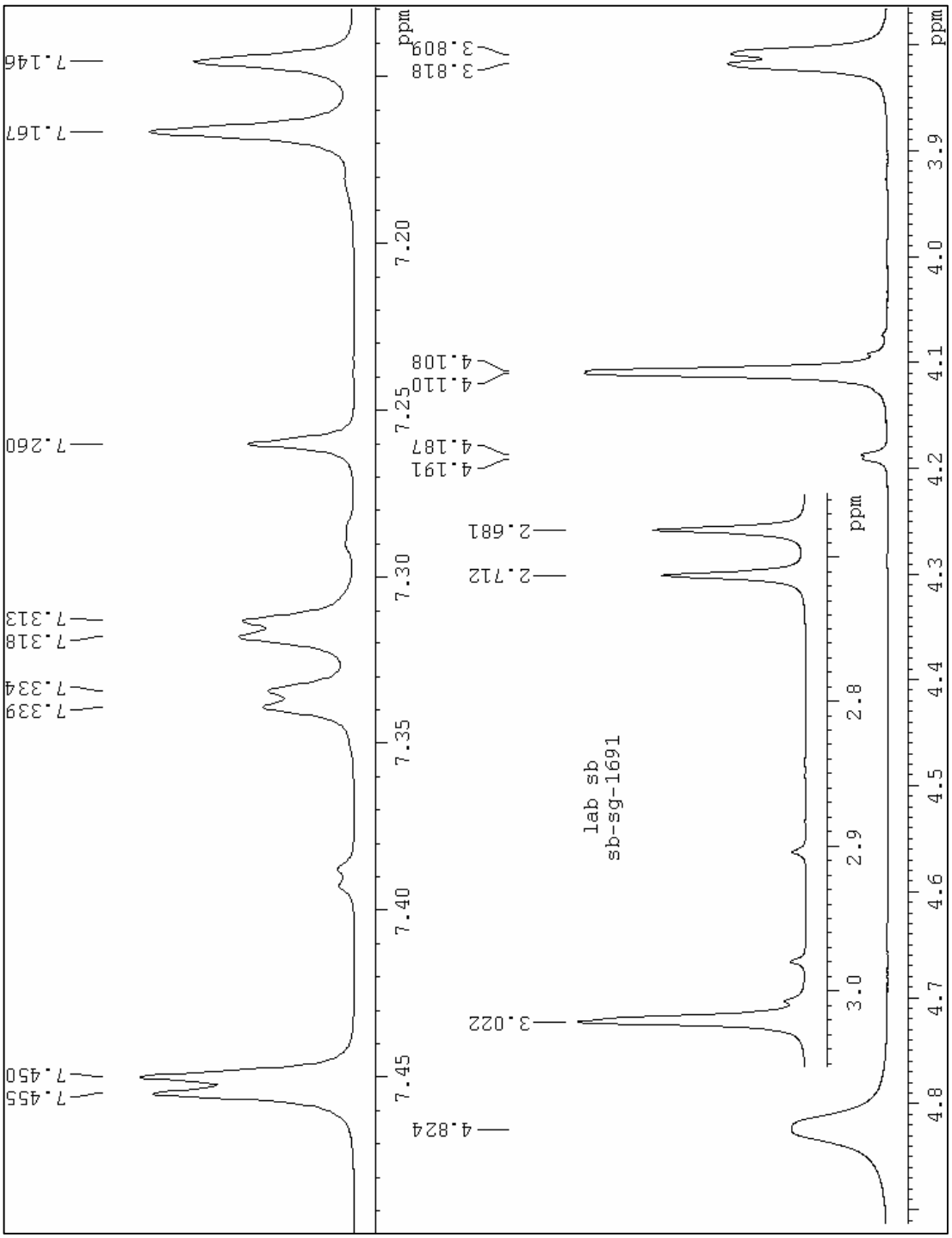
Expanded ^{1}H NMR spectrum of compound **15**



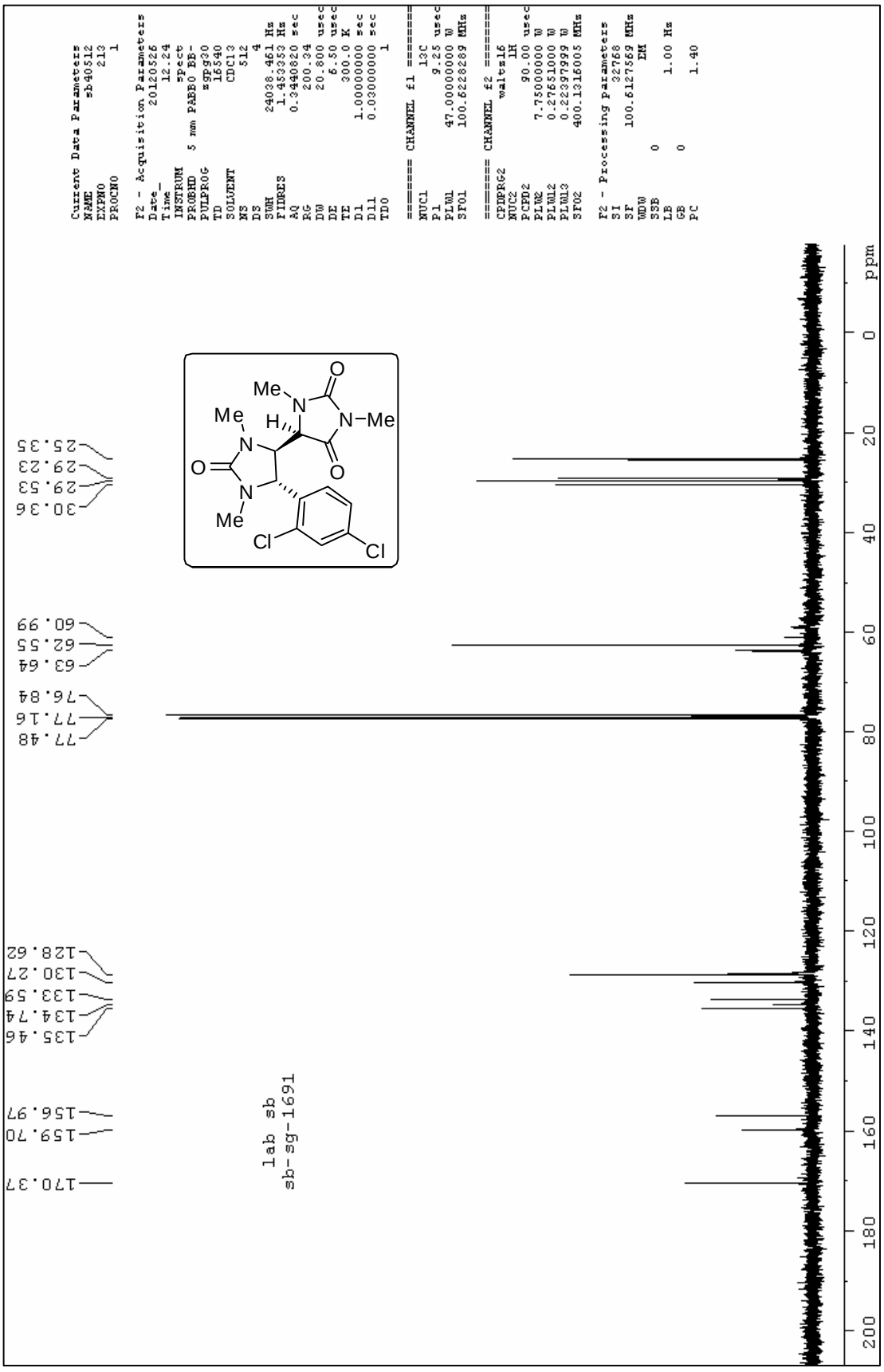
^{13}C NMR spectrum of compound **15**



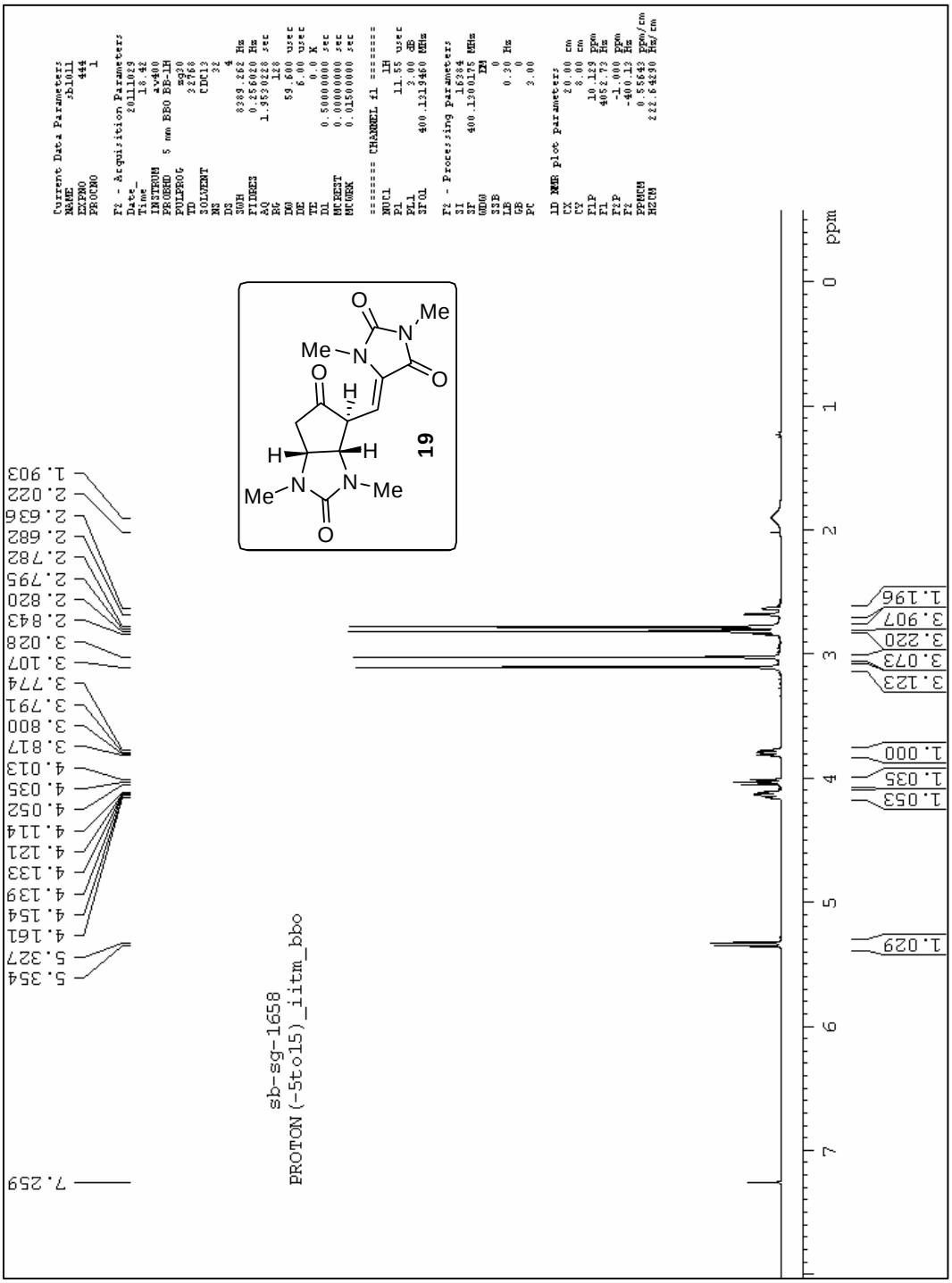
^{1}H NMR spectrum of compound **17**



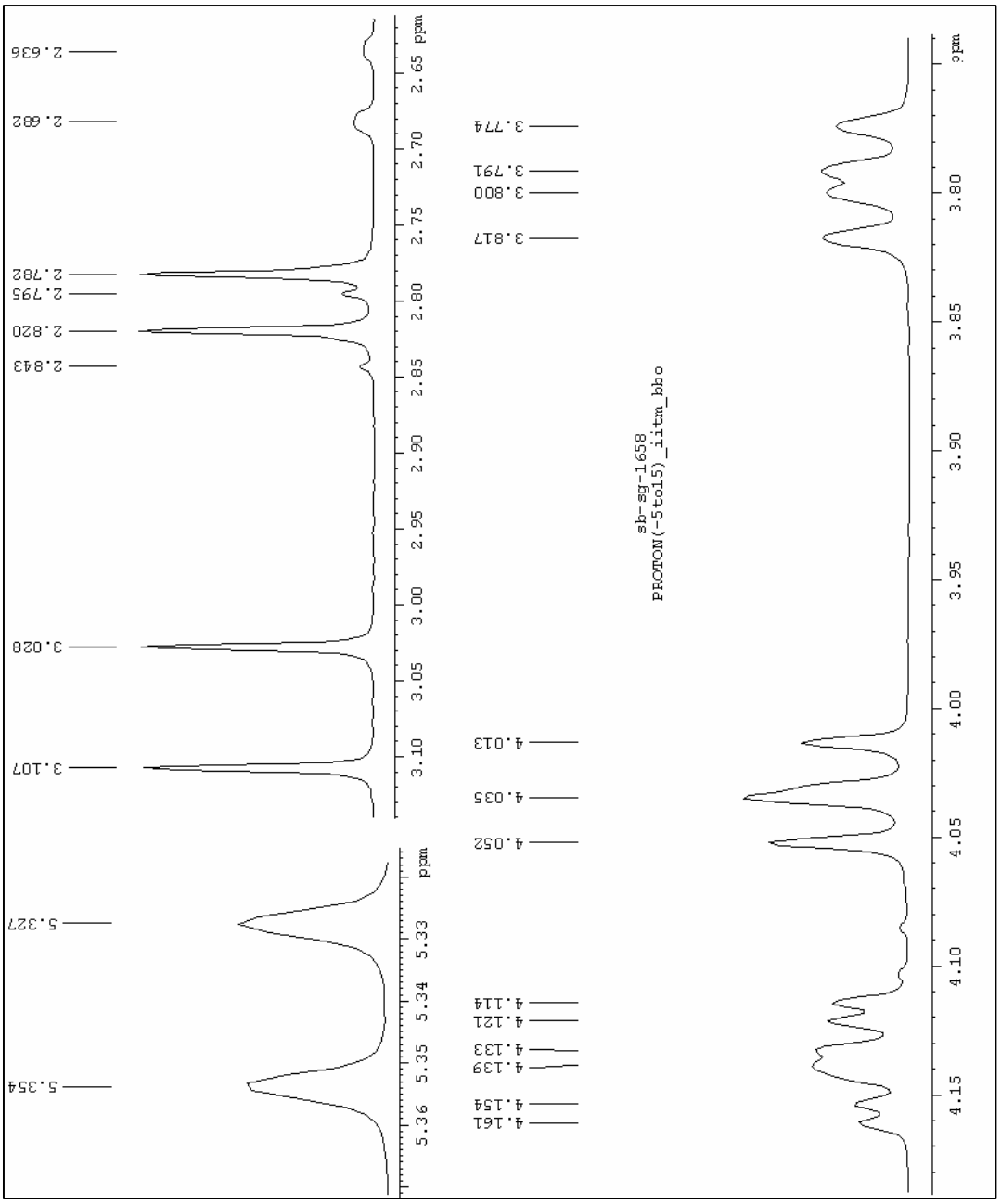
Expanded ^{1}H NMR spectrum of compound **17**



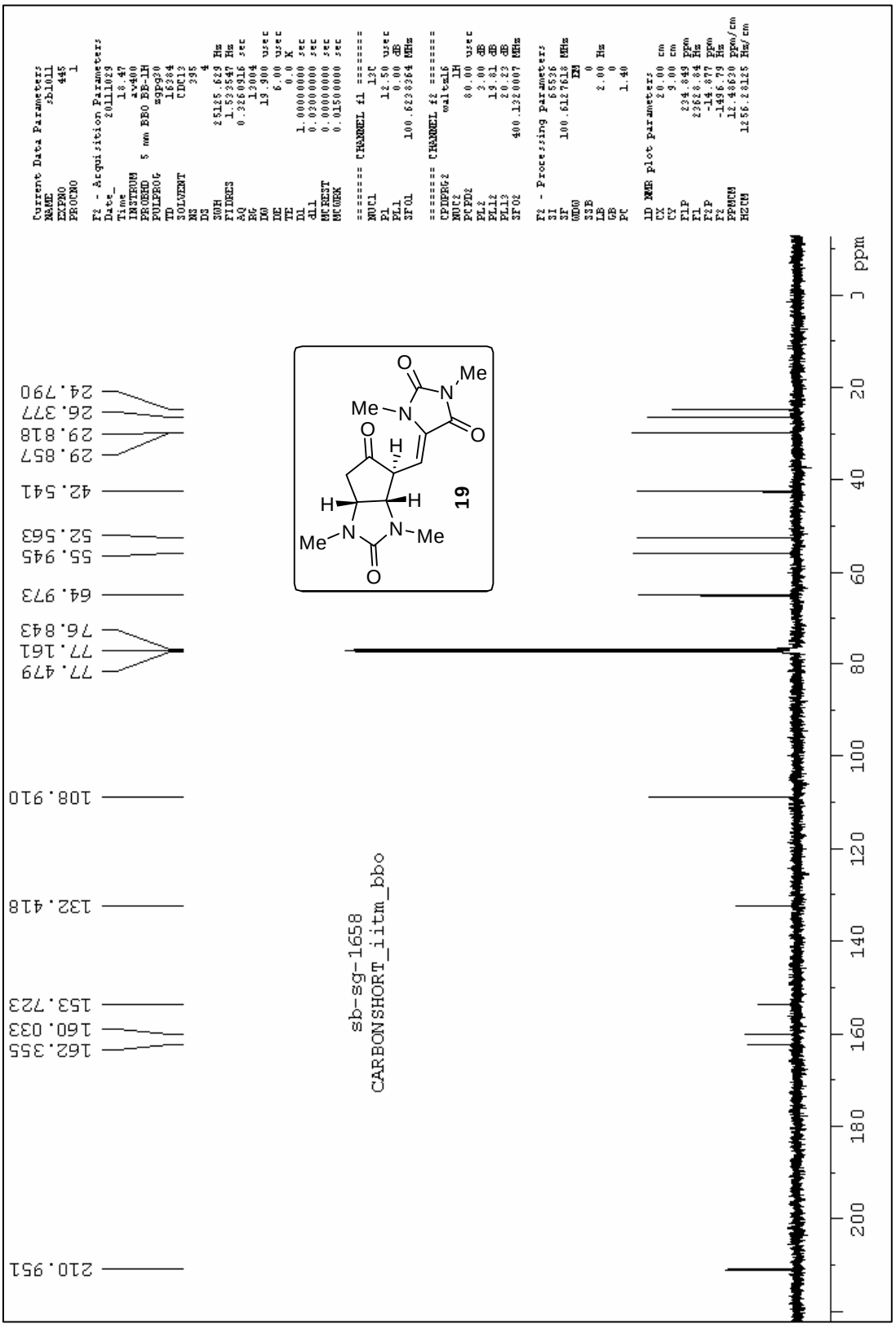
^{13}C NMR spectrum of compound **17**



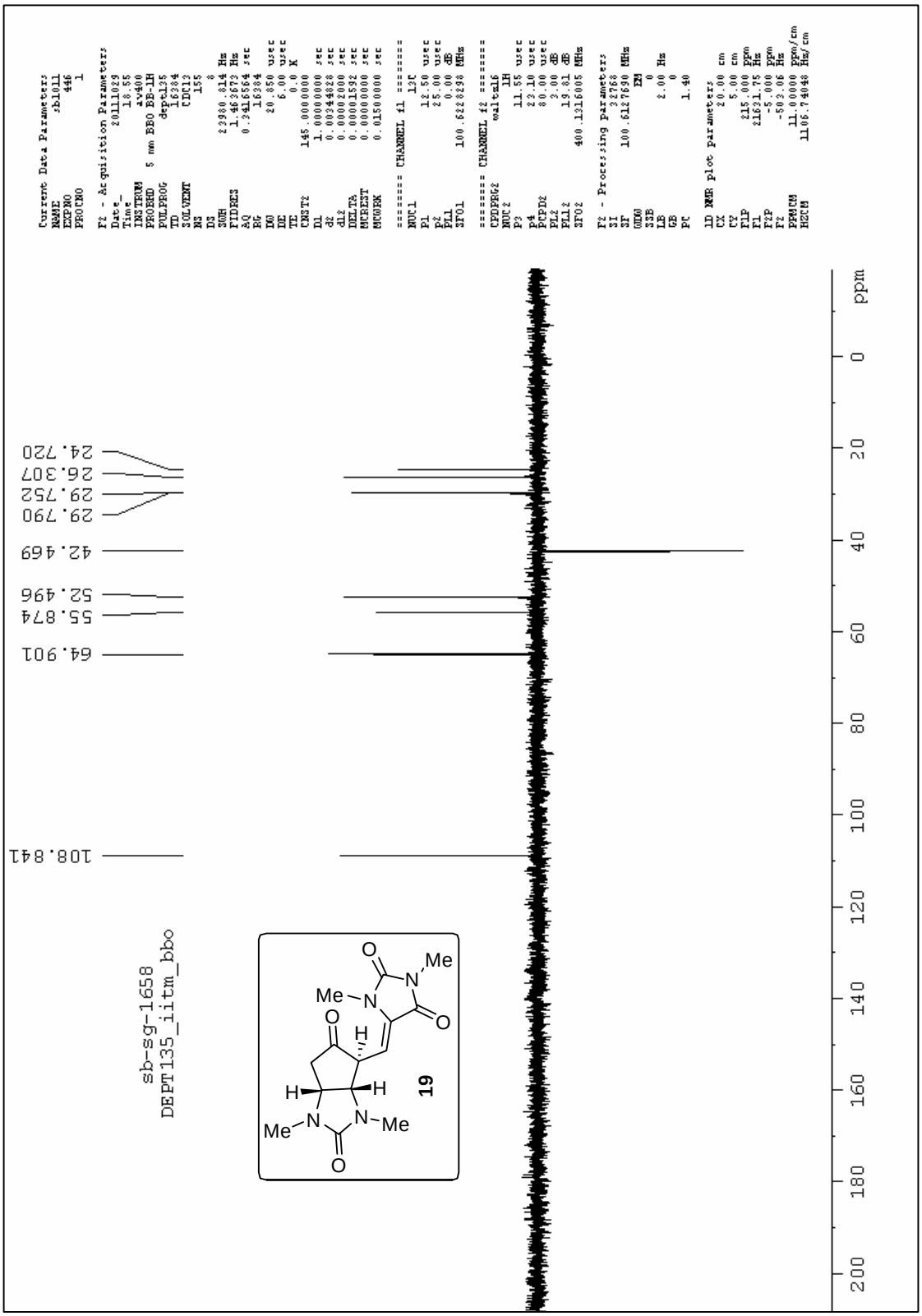
^{1}H NMR spectrum of compound **19**



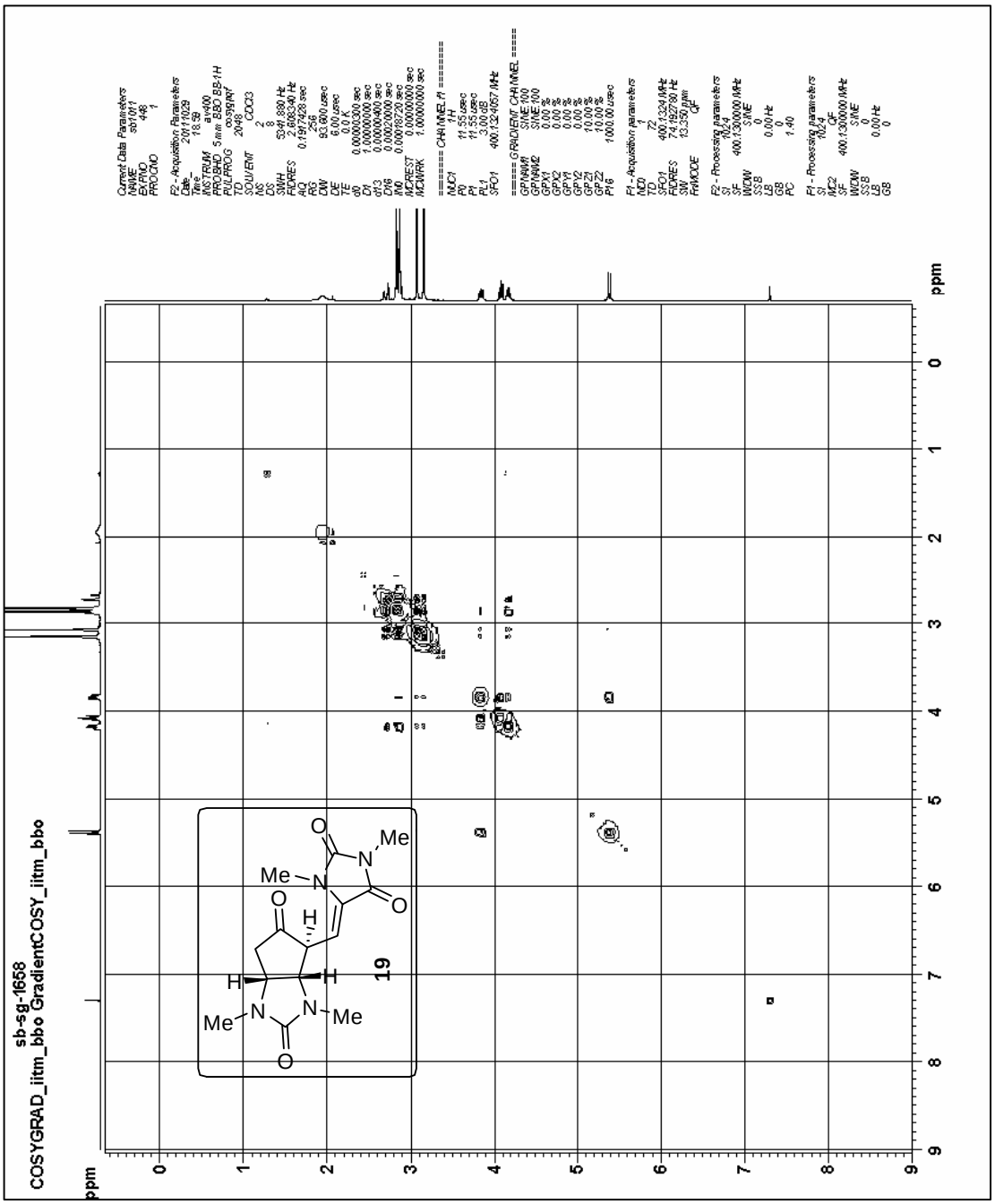
Expanded ^{1}H NMR spectrum of compound **19**



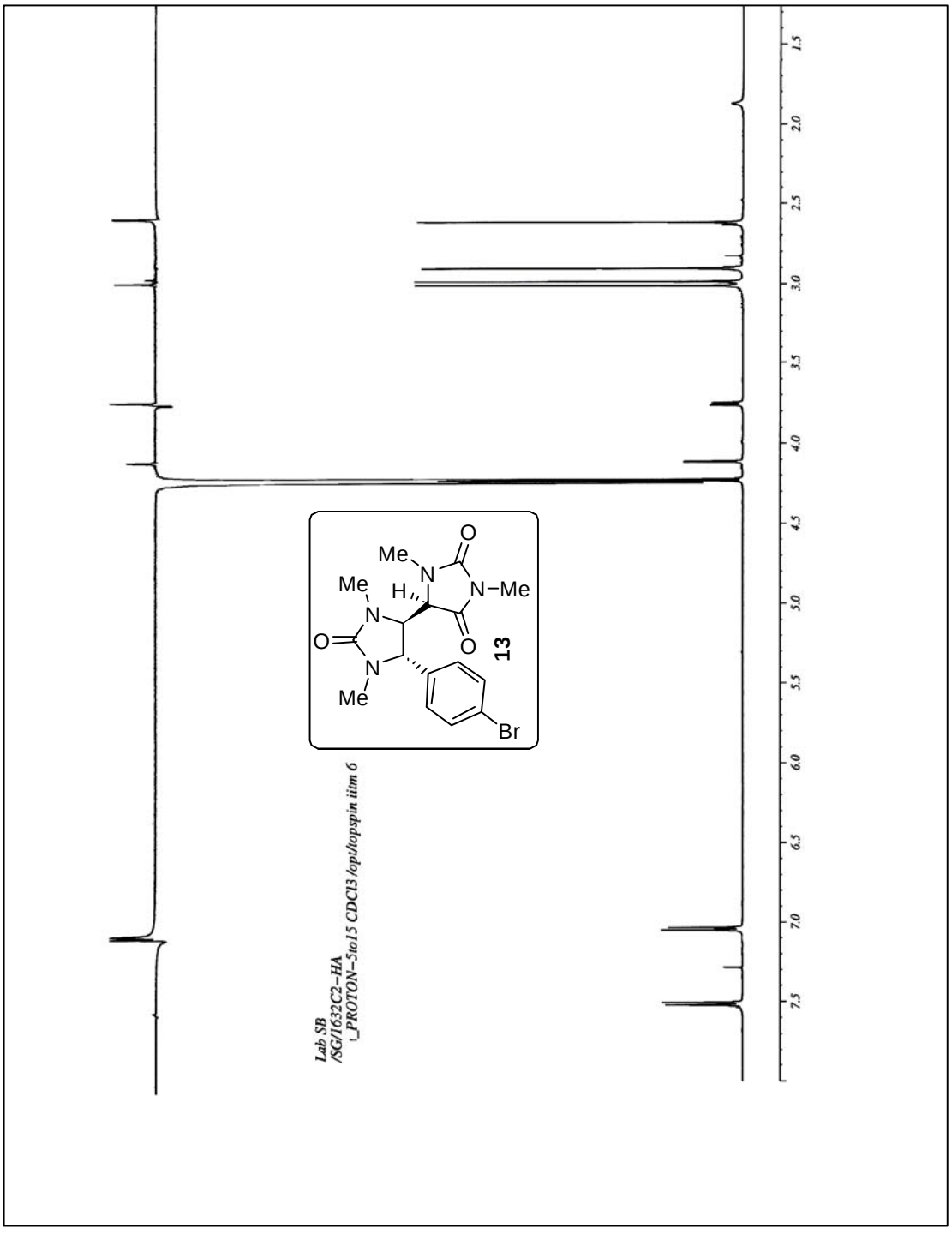
^{13}C NMR spectrum of compound **19**



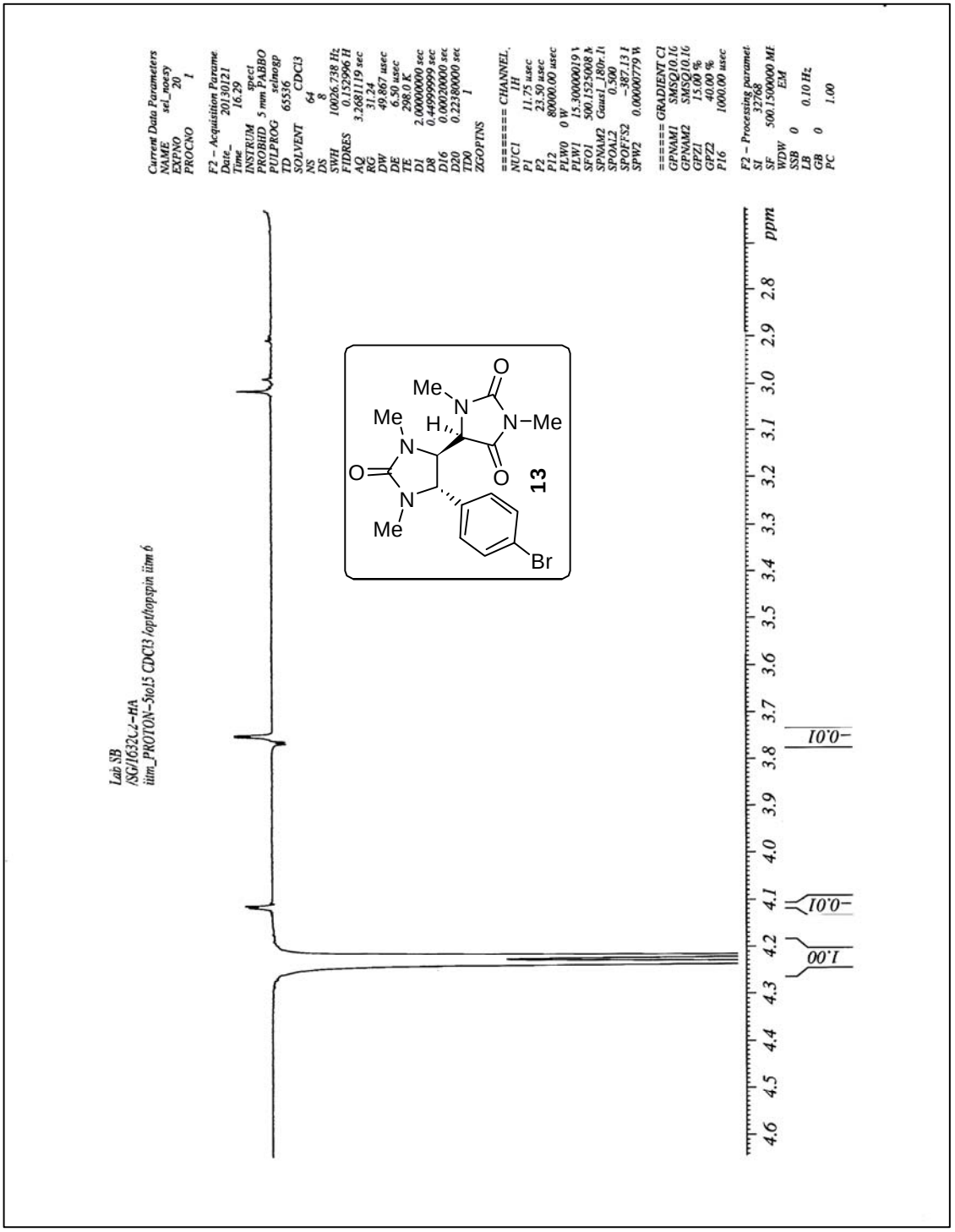
^{13}C DEPT NMR spectrum of compound **19**



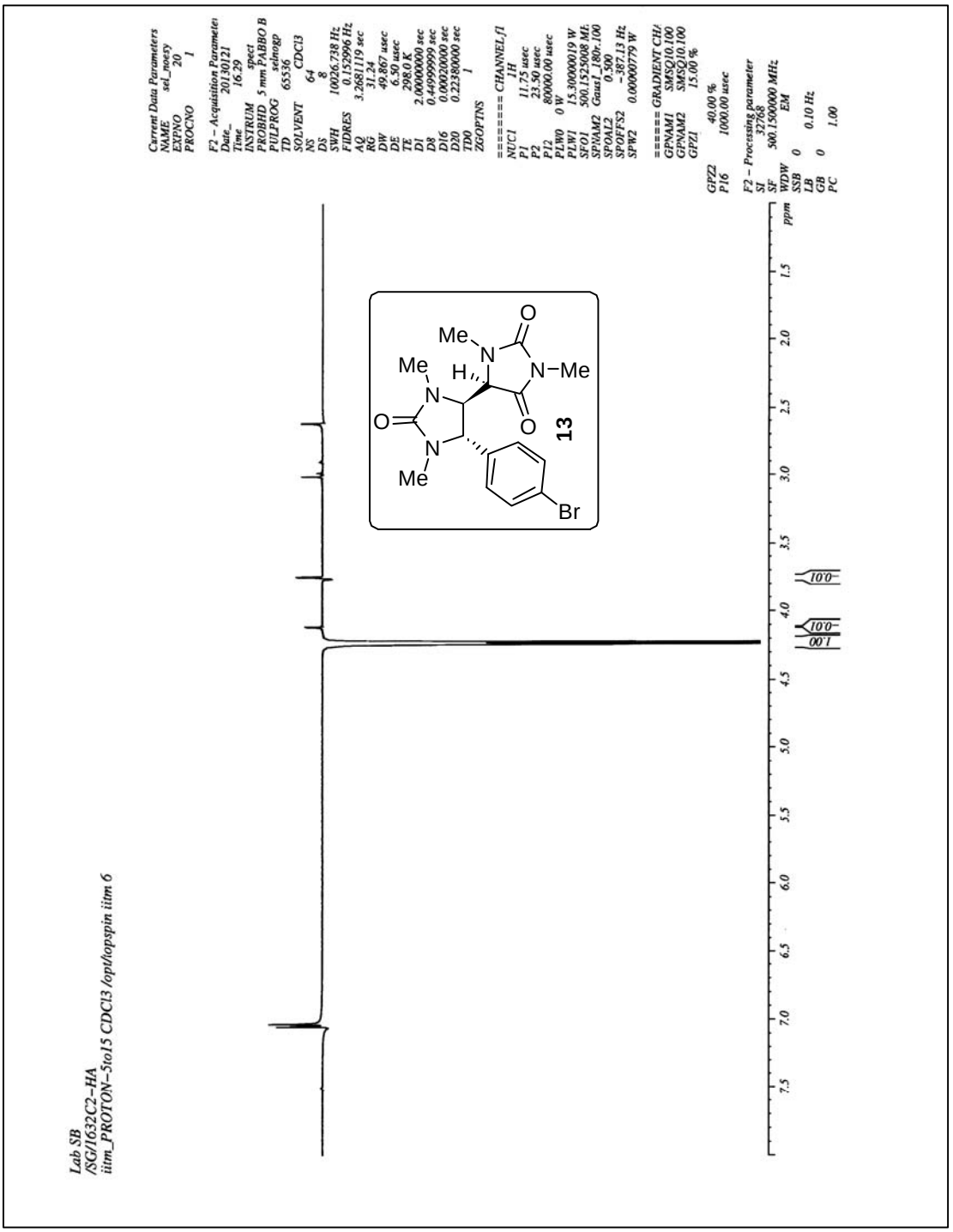
^{1}H ^{1}H COSY NMR spectrum of compound **19**



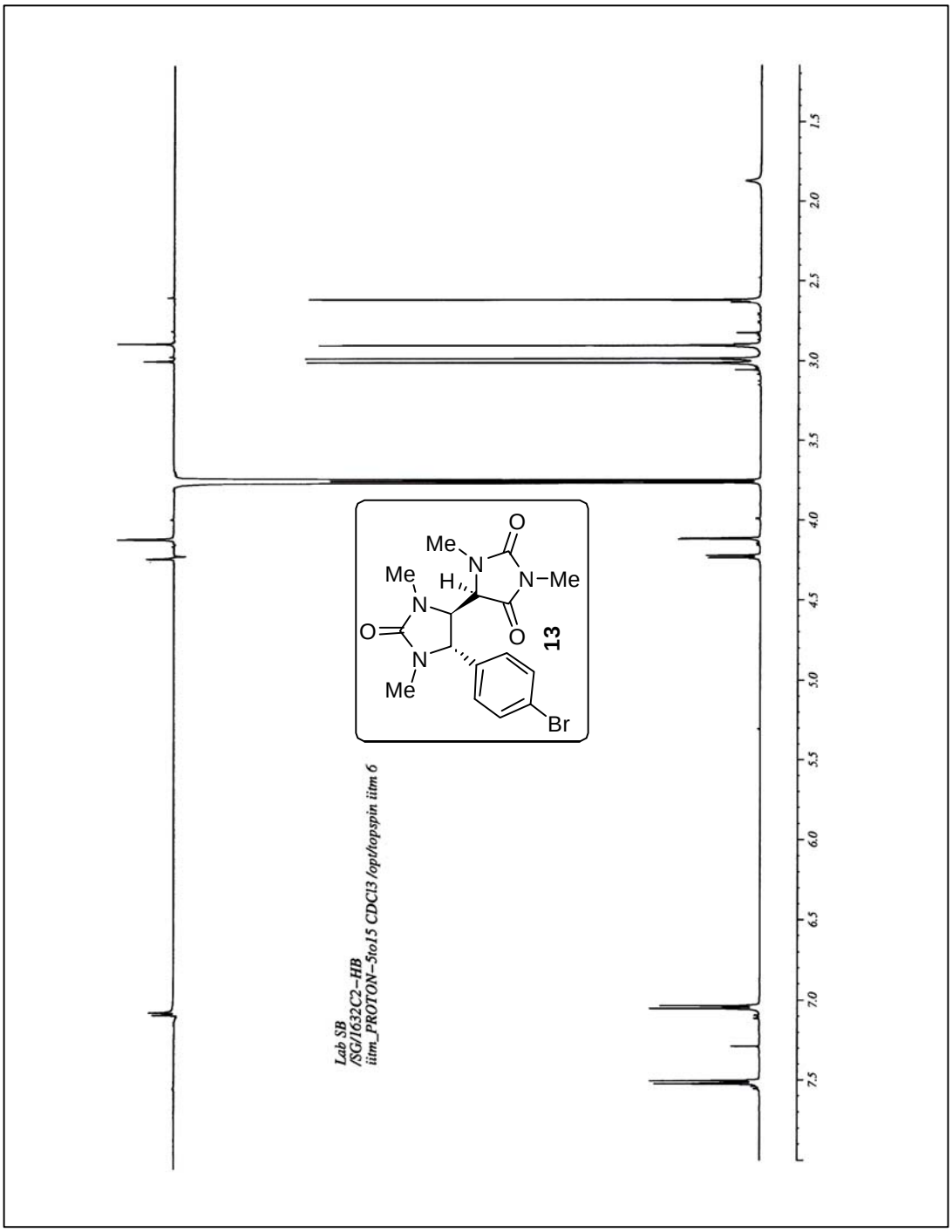
NOE spectrum of hydantoin derivative **13**



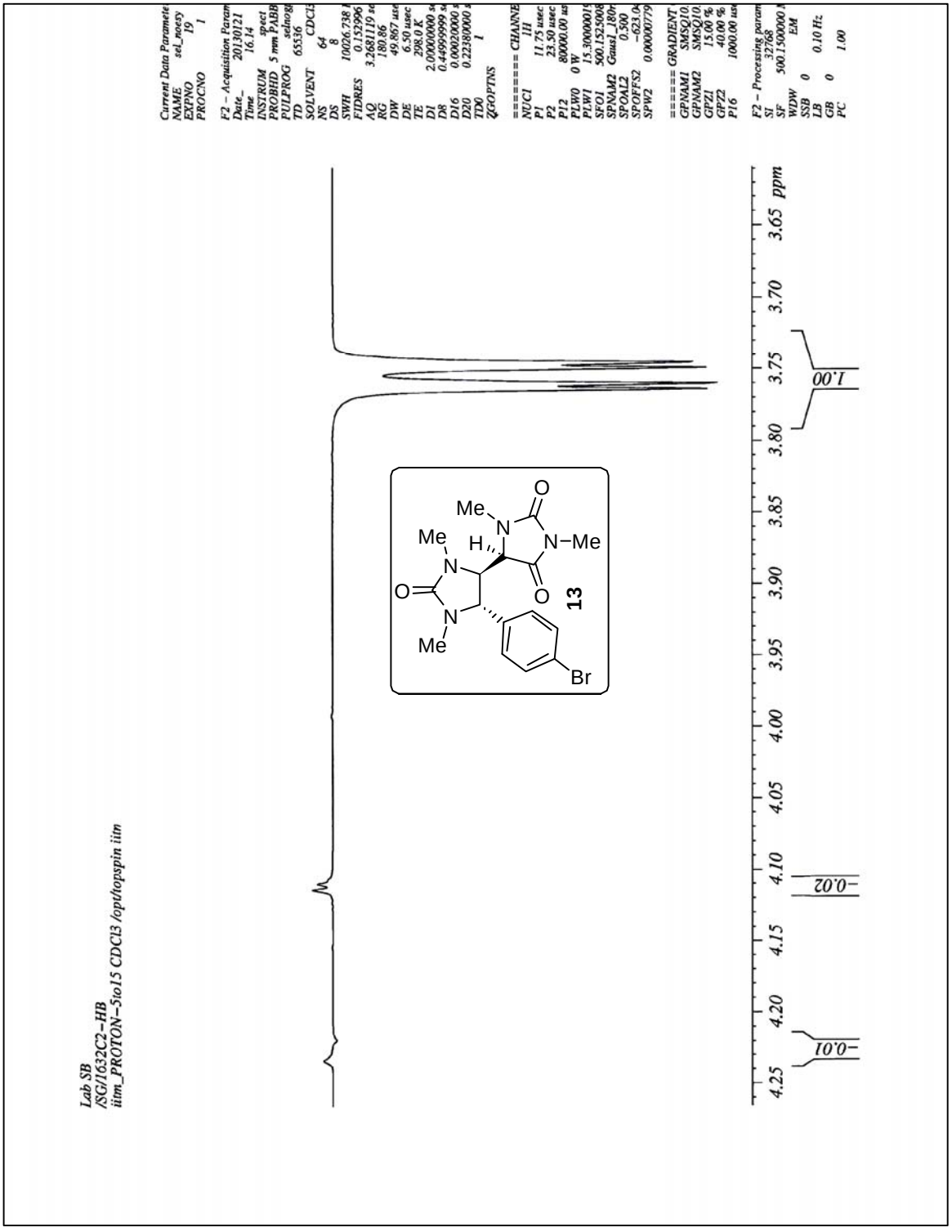
NOE spectrum of hydantoin derivative **13**



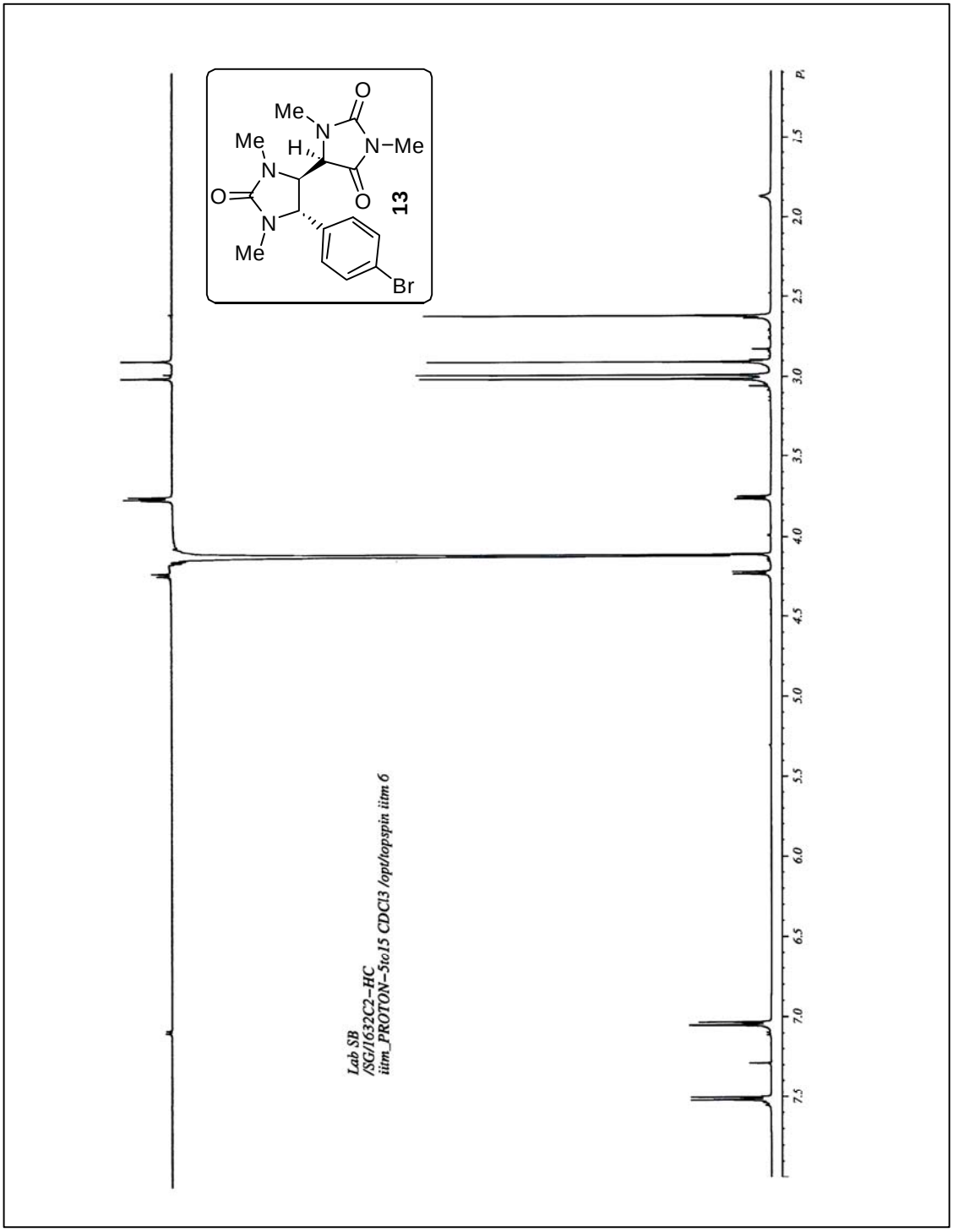
NOE spectrum of hydantoin derivative **13**



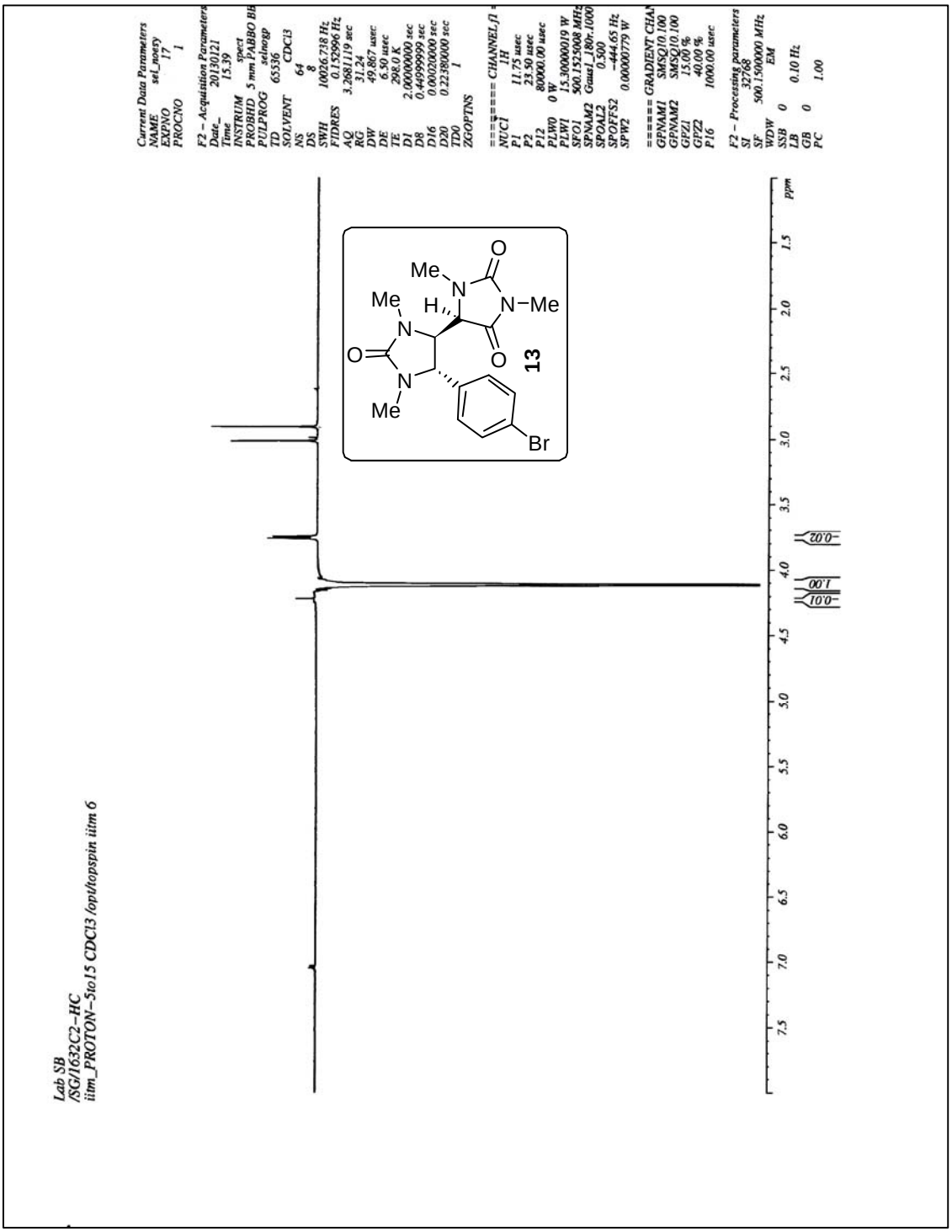
NOE spectrum of hydantoin derivative **13**



NOE spectrum of hydantoin derivative **13**



NOE spectrum of hydantoin derivative **13**



NOE spectrum of hydantoin derivative **13**