SYNTHETIC STUDIES ON KERAMAPHIDIN B: FORMATION OF A MACROCYCLIC RING BY INTRAMOLECULAR DIELS-ALDER REACTION

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Supporting Information

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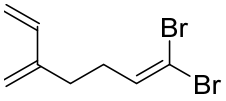
General Information

^{1}H and ^{13}C-NMR spectra were recorded on JEOL ECZ500R and Bruker AVANCE 600 spectrometers. Chemical shifts are reported in ppm with the residual solvent resonance as internal standard ($CDCl_3$ ^{1}H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm). The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet: br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Mass spectra analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and phosphomolybdic acid, basic potassium permanganate, *p*-anisaldehyde and heat as developing agents. Kanto Chemical Silica Gel 60N (spherical, neutral, 63-210 μm or 40-50 μm partial size) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). TLC R_fs of purified compounds were included.

Materials.

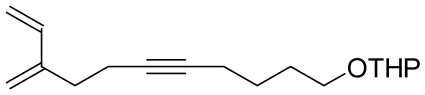
THF and Et_2O were distilled from sodium/benzophenone ketyl, and CH_2Cl_2, benzene, and MeCN from calcium hydride. Toluene was distilled from sodium. MeOH was distilled from magnesium and I_2. All reagents were purchased from Aldrich, TCI, Merck, or Kanto Chemical Co. Ltd.

1,1-dibromo-5-methylenehepta-1,6-diene (11)



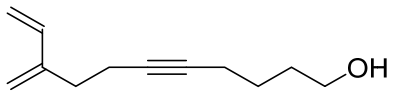
To a stirred solution of CBr_4 (13.2 g, 39.9 mmol, 2.0 equiv.) and PPh_3 (20.9 g, 79.8 mmol, 4.0 equiv) dissolved in CH_2Cl_2 (200 mL) at 0 °C was added **10** (2.20 g, 20.0 mmol) in CH_2Cl_2 (20 mL) via a cannula (5 mL×2) and the reaction mixture was stirred at 0 °C for 10 min before quenching with sat. $NaHCO_3$ aq. (40mL) and H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was dried over Na_2SO_4. After filtration, the solution was filtered through a celite pad. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (hexane) to afford the product **24** (3.96 g, 75%) as a colorless oil: R_f = 0.71 (hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (t, *J* = 6.4 Hz, 1H), 6.38 (dd, *J* = 10.9, 17.8 Hz, 1H), 5.24 (d, *J* = 17.8 Hz, 1H), 5.10 (d, *J* = 10.9, 1H), 5.08 (s, 1H), 5.02 (s, 1H), 2.38-2.27 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 138.5, 138.2, 116.7, 113.7, 89.3, 31.7, 29.4; IR (ATR) ν_{max} 3087, 2932, 1630, 1594, 1439, 1270, 990, 896, 793, 753 cm^{-1}; HRMS (DART) $[M+NH_4]^+$ calculated for $C_8H_{14}Br_2N$: 281.9488, found: 281.9482.

2-((9-methyleneundec-10-en-5-yn-1-yl)oxy)tetrahydro-2H-pyran (**13**)



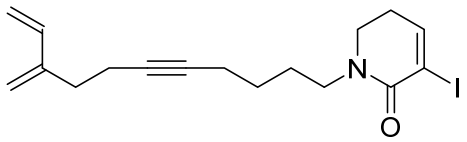
To a stirred solution of **11** (3.94 g, 14.8 mmol) in THF (150 mL) was added *n*-BuLi (1.60 M in hexane, 18.5 mL, 29.6 mmol, 2.0 equiv) at –78 °C. After stirring for 1 h, HMPA (38 mL) and TMEDA (4.4 mL, 29.6 mmol, 2.0 equiv) were added at –78 °C and stirred for 40 min. To the reaction mixture was added **12** (4.20 g, 14.8 mmol, 1.0 equiv) in THF (20 mL) at –78 °C via a cannula (5 mL×2). The mixture was warmed to room temperature and stirred for 4 h, then warmed to 50 °C and stirred for additional 1.5 h before quenching with sat. NH_4Cl aq. (20 mL) and water (40 mL). The resulting mixture was evaporated and then, the aqueous layer was extracted with hexane (30 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane→hexane/AcOEt = 30/1→hexane/AcOEt = 20/1) to afford a mixture of the product **13** and **12** (3.44 g). The mixture was used in the next step without further purification: R_f = 0.69 (hexane/ethyl acetate = 4/1).

9-methyleneundec-10-en-5-yn-1-ol (**14**)



To a stirred solution of the mixture of **13** and **12** (3.44 g) in MeOH (130 mL) was added TsOH·H_2O (49.9 mg, 0.26 mmol, 2 mol%) at room temperature. After stirring at room temperature for 3 h, additional TsOH·H_2O (49.5 mg, 0.26 mmol, 2 mol%) was added. After stirring at room temperature for 2.5 h, the reaction mixture was quenched with sat. $NaHCO_3$ aq. (20 mL) and water (10 mL). The mixture was evaporated and the aqueous layer was then extracted by diethyl ether (30 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 6/1) to afford **14** (1.23 g, 48%, 2 steps) as a pale yellow oil: R_f = 0.23 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 10.9, 17.8 Hz, 1H), 5.22 (d, *J* = 17.8 Hz, 1H), 5.09-5.02 (m, 3H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.44-2.38 (m, 2H), 2.37-2.30 (m, 2H), 2.19 (tt, *J* = 2.3, 6.9 Hz, 2H), 1.71-1.62 (m, 2H), 1.60-1.52 (m, 2H); 1.46 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 138.6, 116.4, 113.4, 80.5, 80.2, 62.6, 32.0, 31.2, 25.4, 18.6, 18.0; IR (ATR) ν_{max} 3333, 3088, 2937, 2864, 1595, 1434, 1335, 1056, 990, 896 cm^{-1}; HRMS (DART) $[M+NH_4]^+$ calculated for $C_{12}H_{22}NO$: 196.1696, found: 196.1694.

5,6-dihydro-3-iodo-1-(9-methyleneundec-10-en-5-ynyl)pyridin-2(1H)-one (**15**)

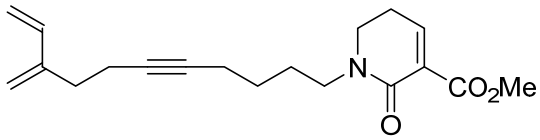


To a stirred solution of **6** (422.4 mg, 2.37 mmol) in CH_2Cl_2 (24 mL) were added 2,6-lutidine (0.55 mL, 4.74 mmol, 2.0 equiv.) and Tf_2O (0.58 mL, 3.56 mmol, 1.5 equiv.) at −78 °C. The reaction mixture was stirred at −78 °C for 45 min before quenching with 10 mL of 0.5 N H_2SO_4 aq. at −78 °C. The solution was diluted with hexane (20 mL) and the organic layer was washed by water (5 mL×3). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude product **7c** (741.9 mg) was dried under vacuum and diluted with dry diethyl ether (1.5 mL) and used for the next step.

To a stirred solution of **8** (535.2 mg, 2.40 mmol, 1.0 equiv) in THF (24mL) was added KHMDS in toluene (4,7 mL, 2.40 mmol, 1.0 equiv) at −78 °C. After the reaction mixture was stirred at −78 °C for 1 h, the crude triflate **7c** (741.9 mg) in diethyl ether (1.5 mL) was added at −78 °C via cannula (1.5 mL×2). The reaction mixture was stirred at −78 °C for 2 h before quenching with sat. NH_4Cl aq. (10 mL) and water (10 mL). The aqueous layer was extracted

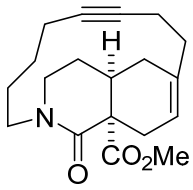
with diethyl ether (20 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (benzene/ethyl acetate = 50/1→40/1) to afford **15** (795.0 mg, 88%) as a yellow oil: R_f = 0.50 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.28 (m,1 H), 6.36 (dd, *J* = 10.9, 17.2 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.10-5.02 (m, 3H), 3.49-3.44 (m, 4H,), 2.44-2.31 (m, 6H), 2.19 (tt, *J* = 2.3, 6.9 Hz, 2H), 1.70-1.62 (m, 2H), 1.53-1.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 148.2, 144.9, 138.6, 116.5, 113.5, 97.8, 80.31, 80.28, 48.3, 45.8, 31.2, 28.2, 26.9, 26.3, 18.6, 18.0; IR (ATR) ν_{max} 3086, 2931, 2860, 1722, 1647, 1596, 1477, 1205, 1136, 901 cm^{-1}; HRMS (DART) $[M+NH_4]^+$ calculated for $C_{17}H_{26}IN_2O$: 401.1084, found: 401.1077.

methyl 1,2,5,6-tetrahydro-1-(9-methyleneundec-10-en-5-ynyl)-2-oxopyridine-3-carboxylate (**5**)

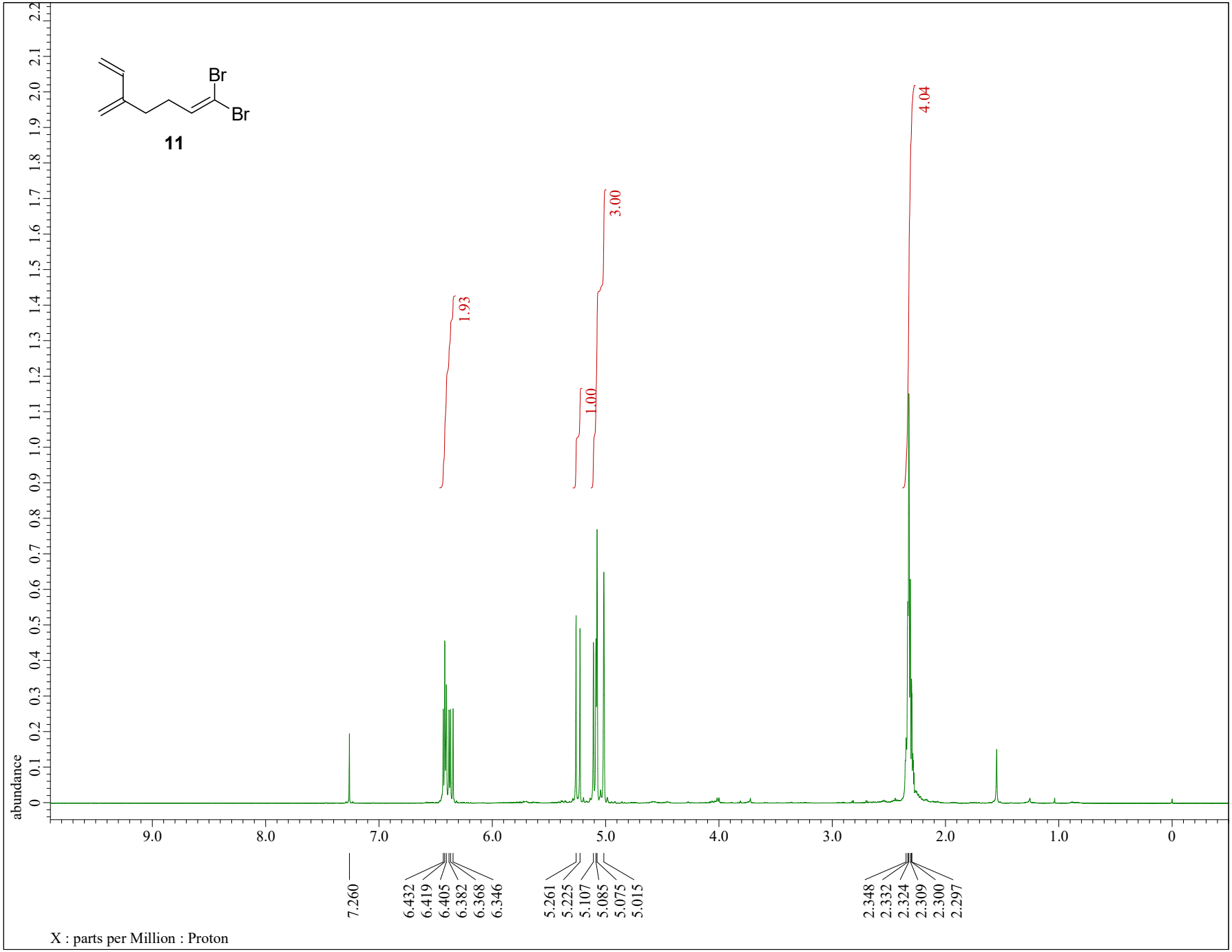


To a stirred solution of **15** (263.0 mg, 0.686 mmol) in MeCN (14 mL) and MeOH (2.7 mL) were added triethylamine (0.58 mL, 4.12 mmol, 6.0 equiv) and $PdCl_2$(dppf)· CH_2Cl_2 (43.0 mg, 0.055 mmol, 0.08 equiv). The reaction mixture was stirred at room temperature for 2 h before quenching with sat. NH_4Cl aq. (5 mL) and water (5 mL). The solution was evaporated and then the aqueous layer was extracted with ethyl acetate (10 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford **5** (128.5 mg, 59%) as an orange oil: R_f = 0.41 (hexane/ethyl acetate = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 4.6 Hz, 1H), 6.37 (dd, *J* = 10.9, 17.8 Hz, 1H), 5.23 (d, *J* = 17.8 Hz, 1H), 5.10-5.02 (m, 3H), 3.82 (s, 3H), 3.49-3.40 (m, 4H), 2.48 (dt, *J* = 4.6, 6.9 Hz, 2H), 2.44-2.38 (m, 2H), 2.37-2.30 (m, 2H), 2.24-2.15 (m, 2H), 1.74-1.62 (m, 2H), 1.55-1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 160.9, 145.7, 144.9, 138.6, 130.0, 116.5, 113.5, 80.30, 80.28, 52.5, 46.4, 44.9, 31.2, 27.0, 26.4, 24.5, 18.6, 18.0; IR (ATR) ν_{max} 3468, 2929, 2859, 1737, 1656, 1621, 1595, 1483, 1434, 1276, 1209, 1123, 899 cm^{-1}; HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{26}NO_3$: 316.1907, found: 316.1909.

methyl (4a*R*,8a*S*)-6,2-oct[3]ynyl-1-oxo-2,3,4,4a,5,8-hexahydroisoquinoline-8a(1*H*)-carboxylate (19)



To a stirred solution of **5** (77.8 mg, 0.247 mmol) in degassed $(CH_2Cl)_2$ (250 mL, 0.001 M) was added $SnCl_4$ (0.085 mL, 0.074 mmol, 0.3 equiv). The reaction mixture was stirred at 80 °C for 17 h before quenching with 0.5 N HCl aq. (2 mL), sat. NH_4Cl aq. (5 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (30 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 1.5/1→1/1.5) to afford **19** (24.7 mg, 32%) as a colorless glassy oil: R_f = 0.41 (hexane/ethyl acetate = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (d, *J* = 5.2 Hz, 1H), 4.29 (dd, *J* = 5.7, 13.8 Hz, 1H), 3.72 (s, 3H), 3.62 (ddd, *J* = 8.3, 9.7, 12.6 Hz, 1H), 3.29 (ddd, *J* = 1.7, 8.0, 12.6 Hz, 1H), 3.19 (dd, *J* = 5.2, 16.3 Hz, 1H), 2.62-2.54 (m, 1H), 2.50-2.32 (m, 4H), 2.31-2.10 (m, 3H), 2.07-1.90 (m, 4H), 1.89-1.66 (m, 3H), 1.63-1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 167.6, 134.2, 120.5, 81.6, 79.5, 53.4, 52.8, 48.0, 45.5, 35.5, 32.7, 31.2, 30.1, 28.1, 27.5, 24.2, 18.7, 17.8; IR (ATR) ν_{max} 2932, 2239, 1727, 1636, 1496, 1430, 1356, 1263, 1232, 1218, 911, 724 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{25}NO_3Na$: 338.1727, found: 338.1724.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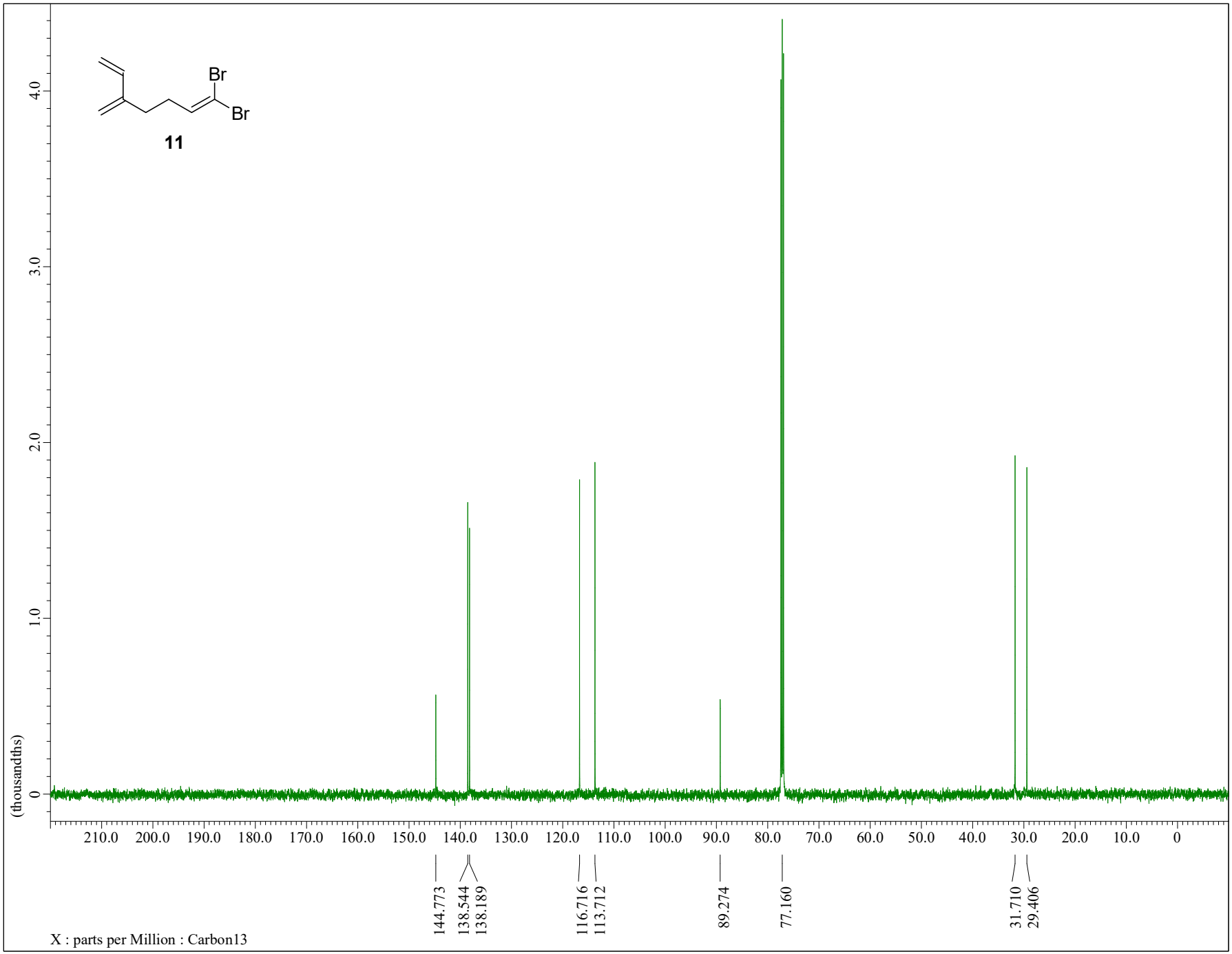
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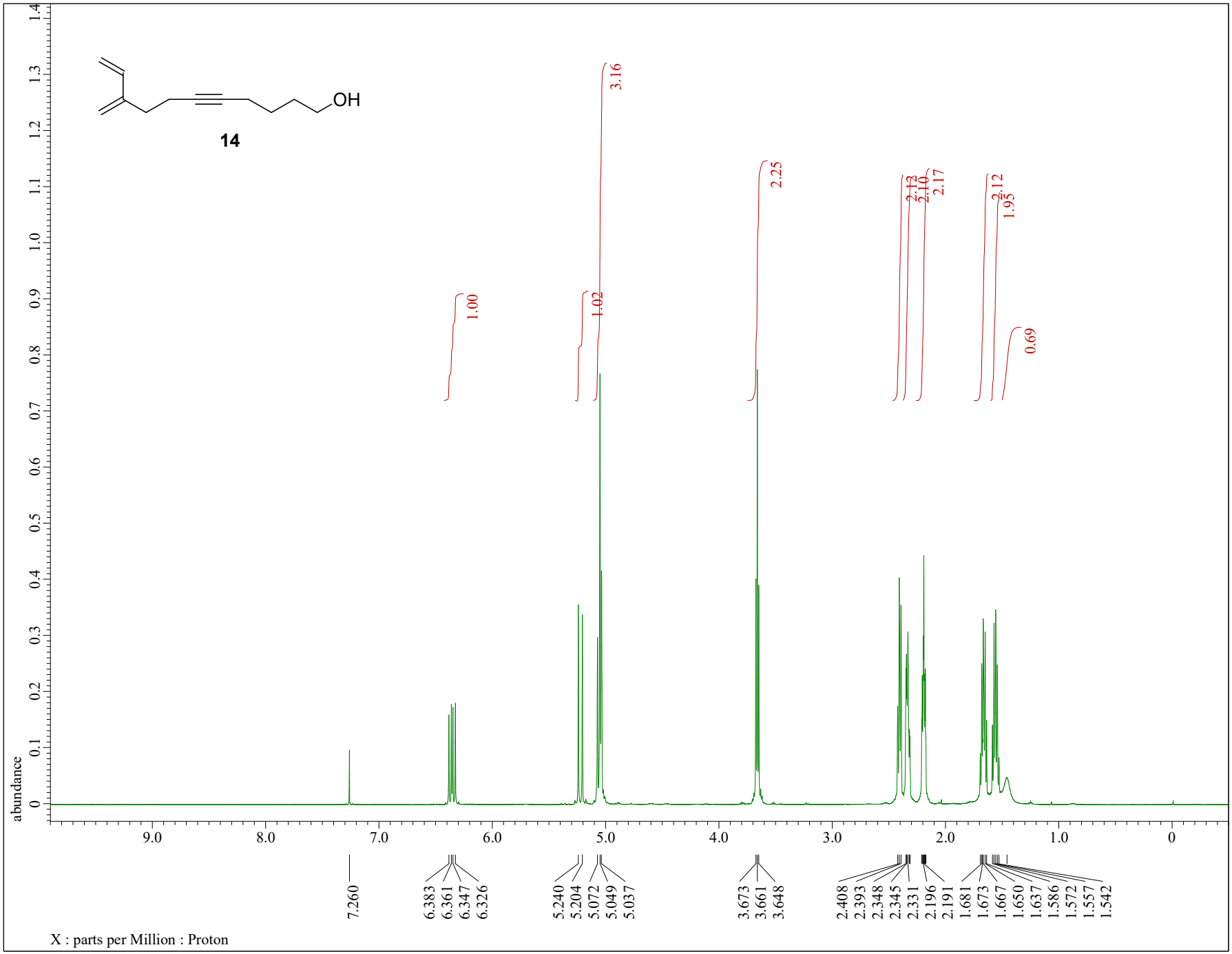
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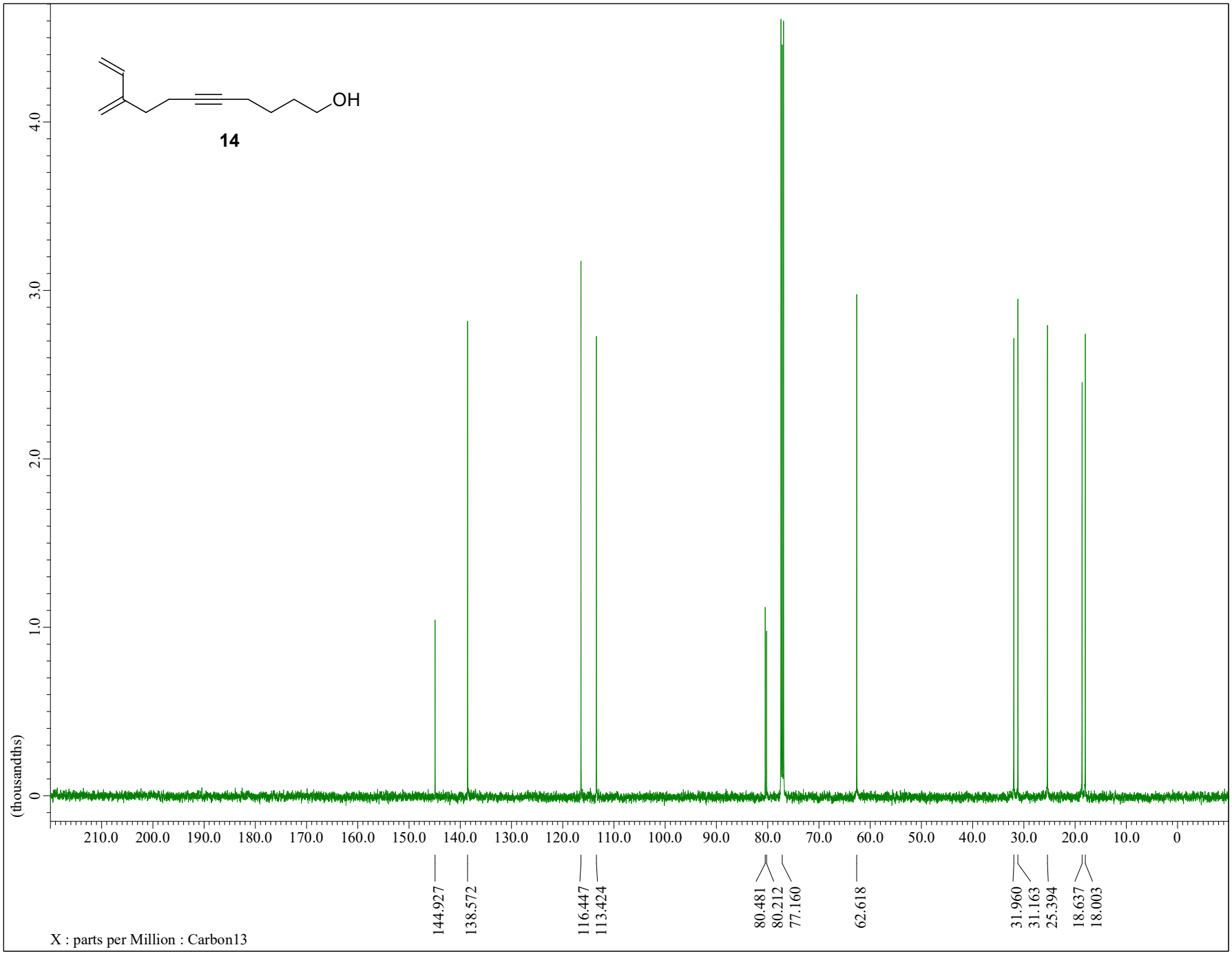
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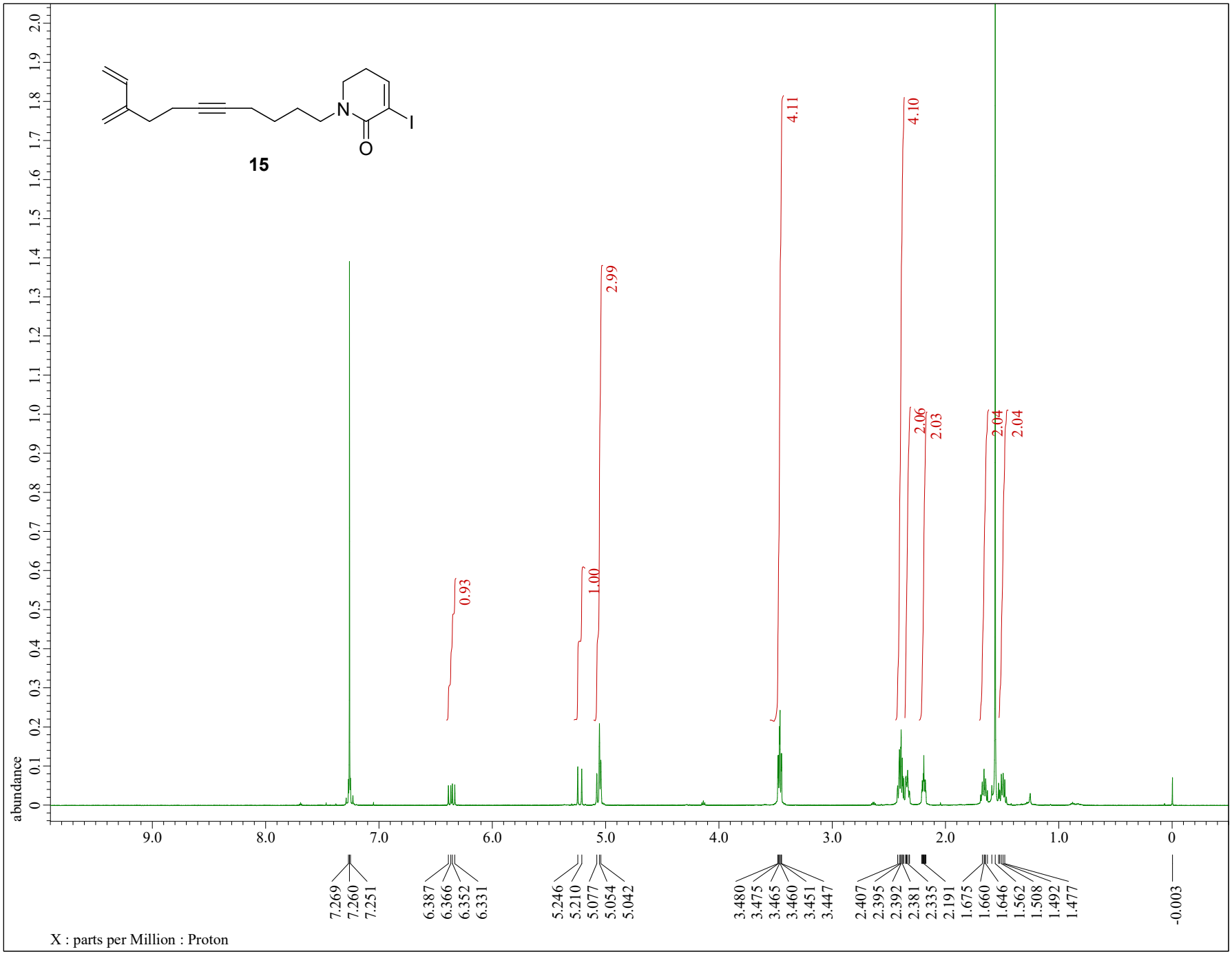
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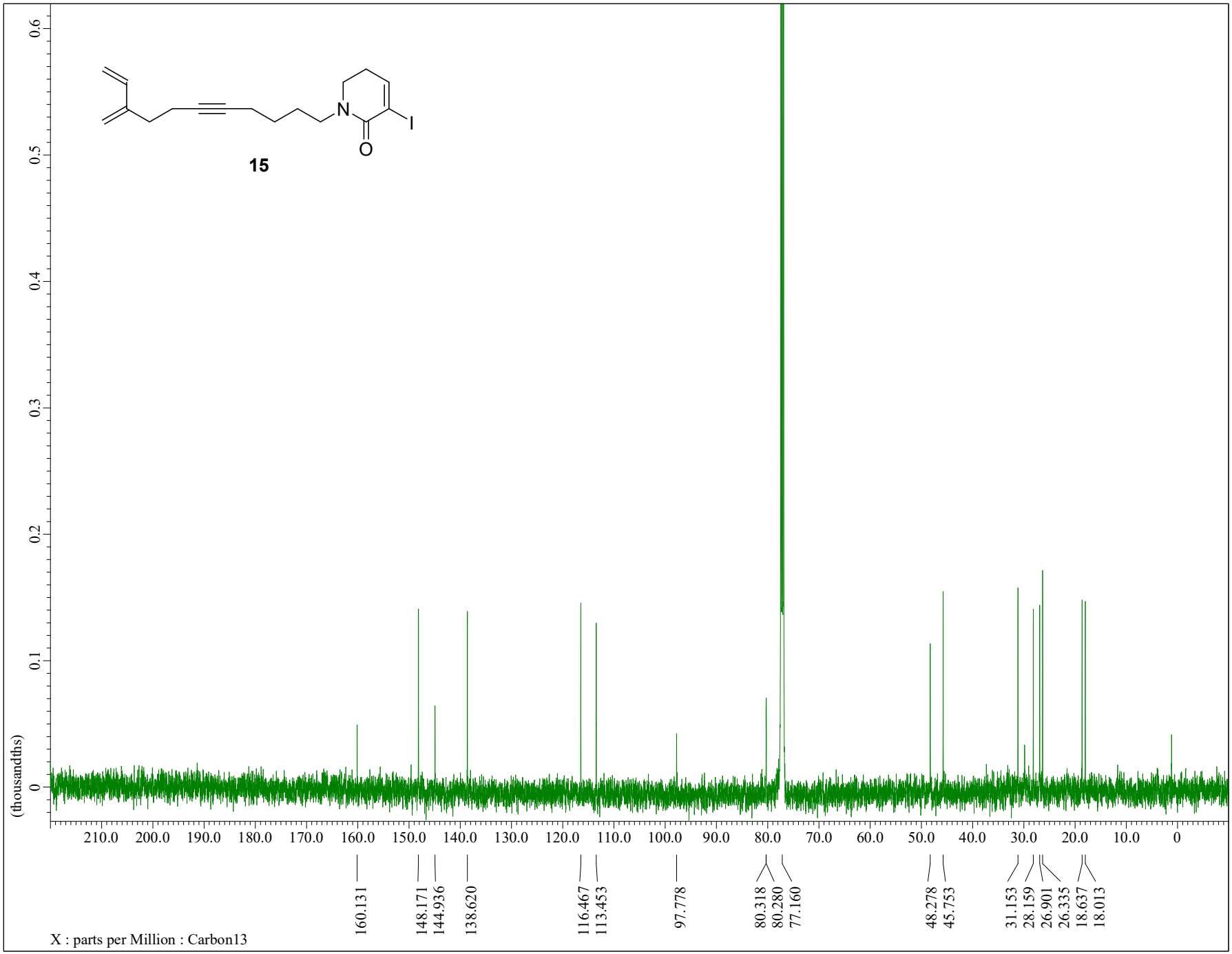
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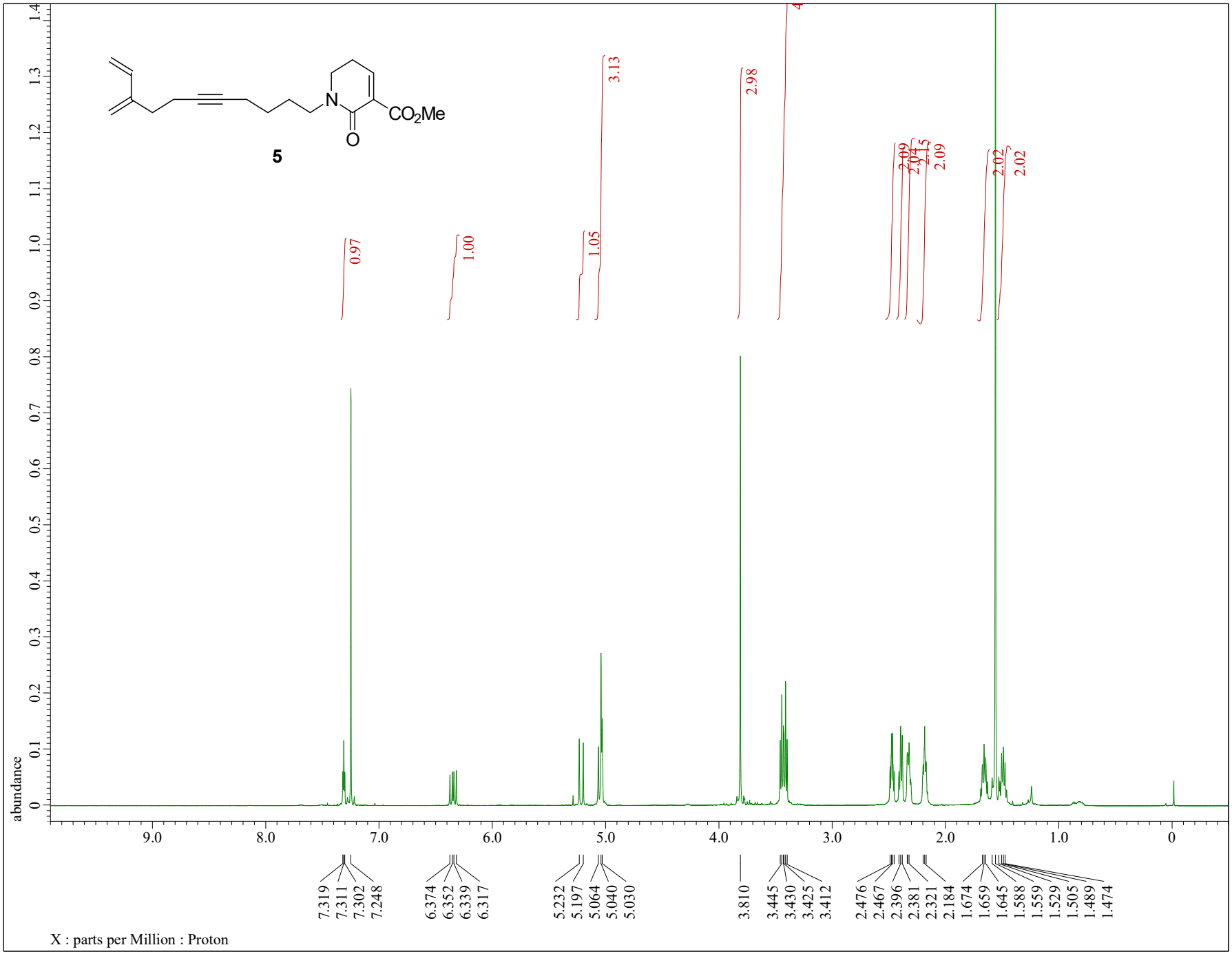
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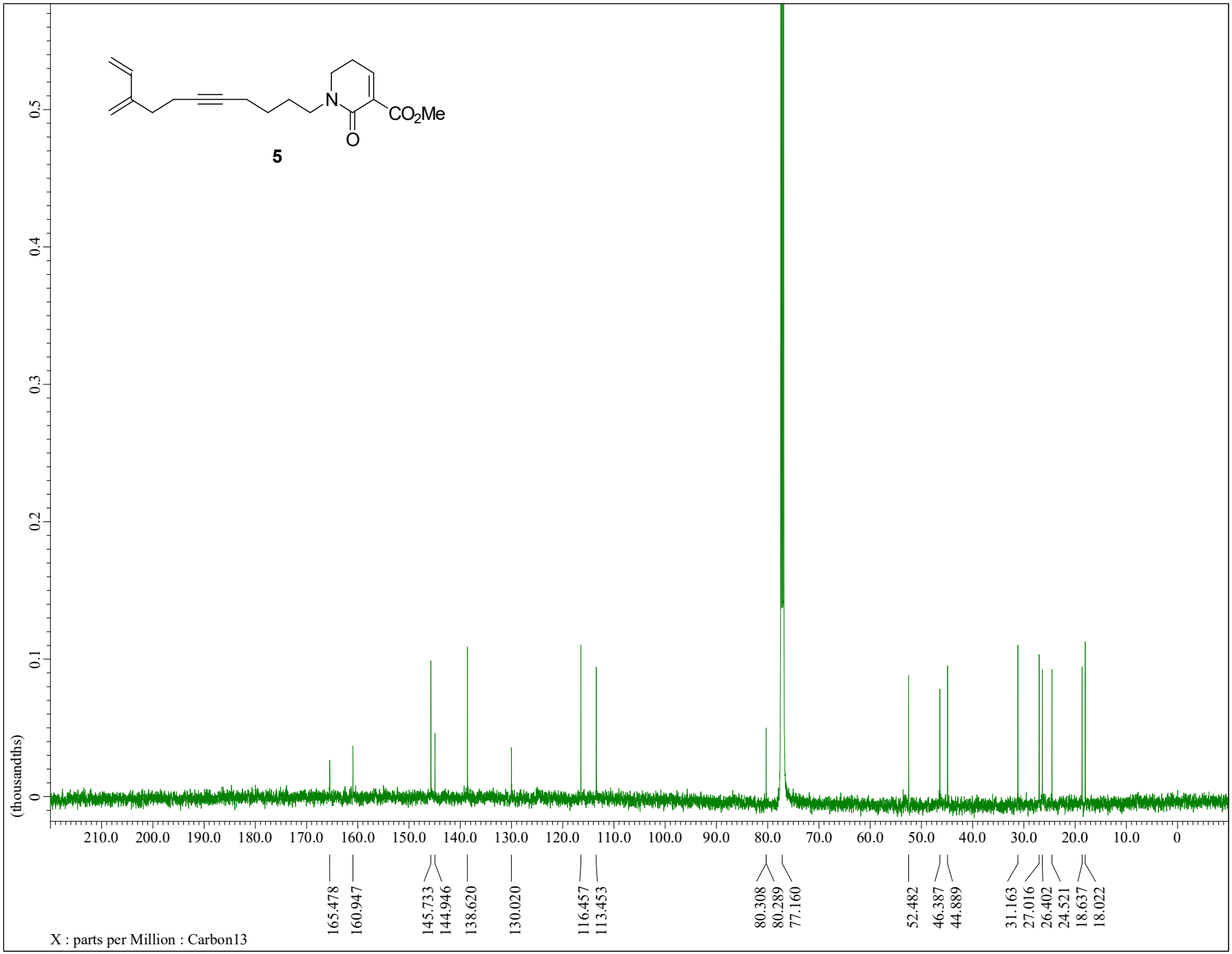
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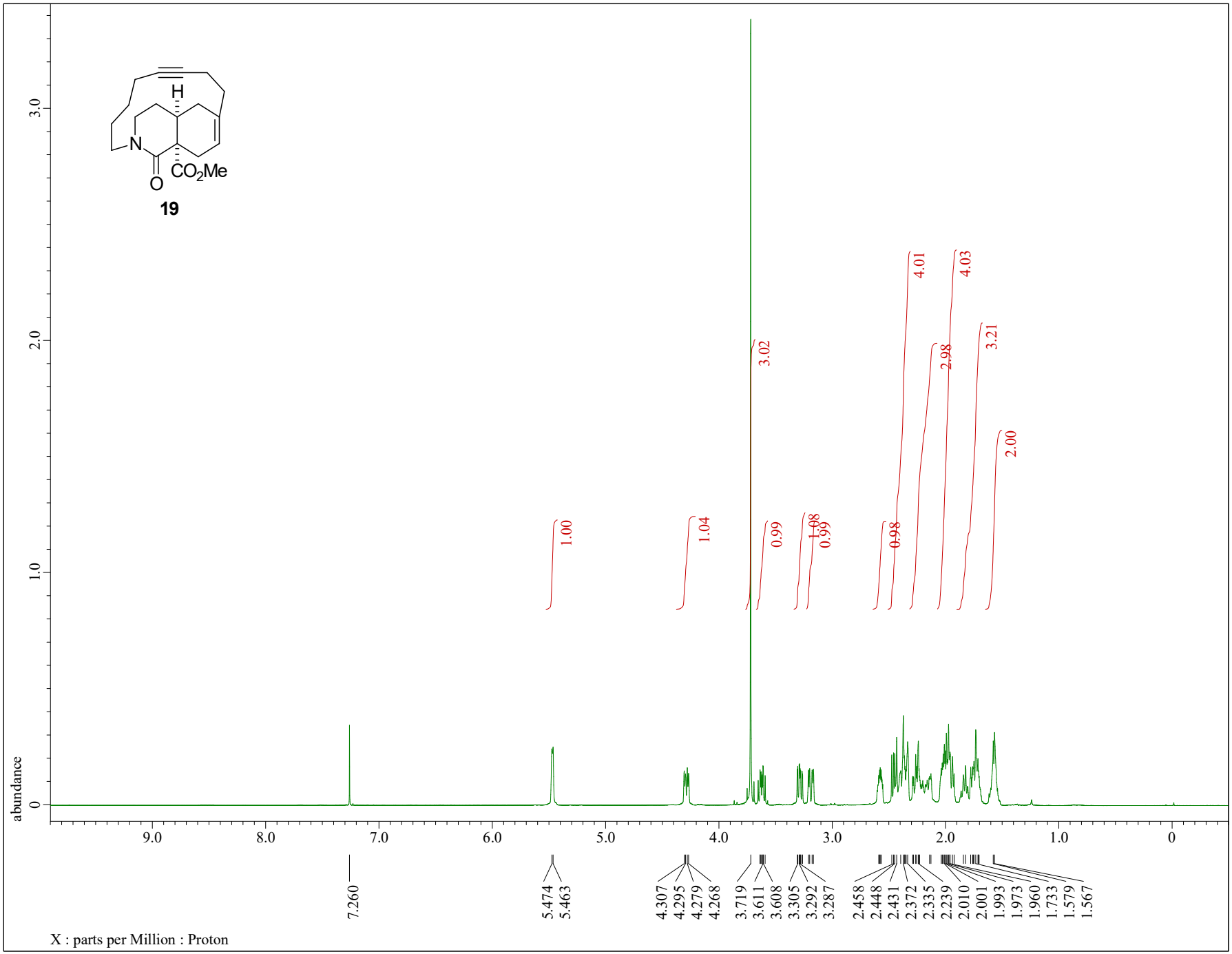
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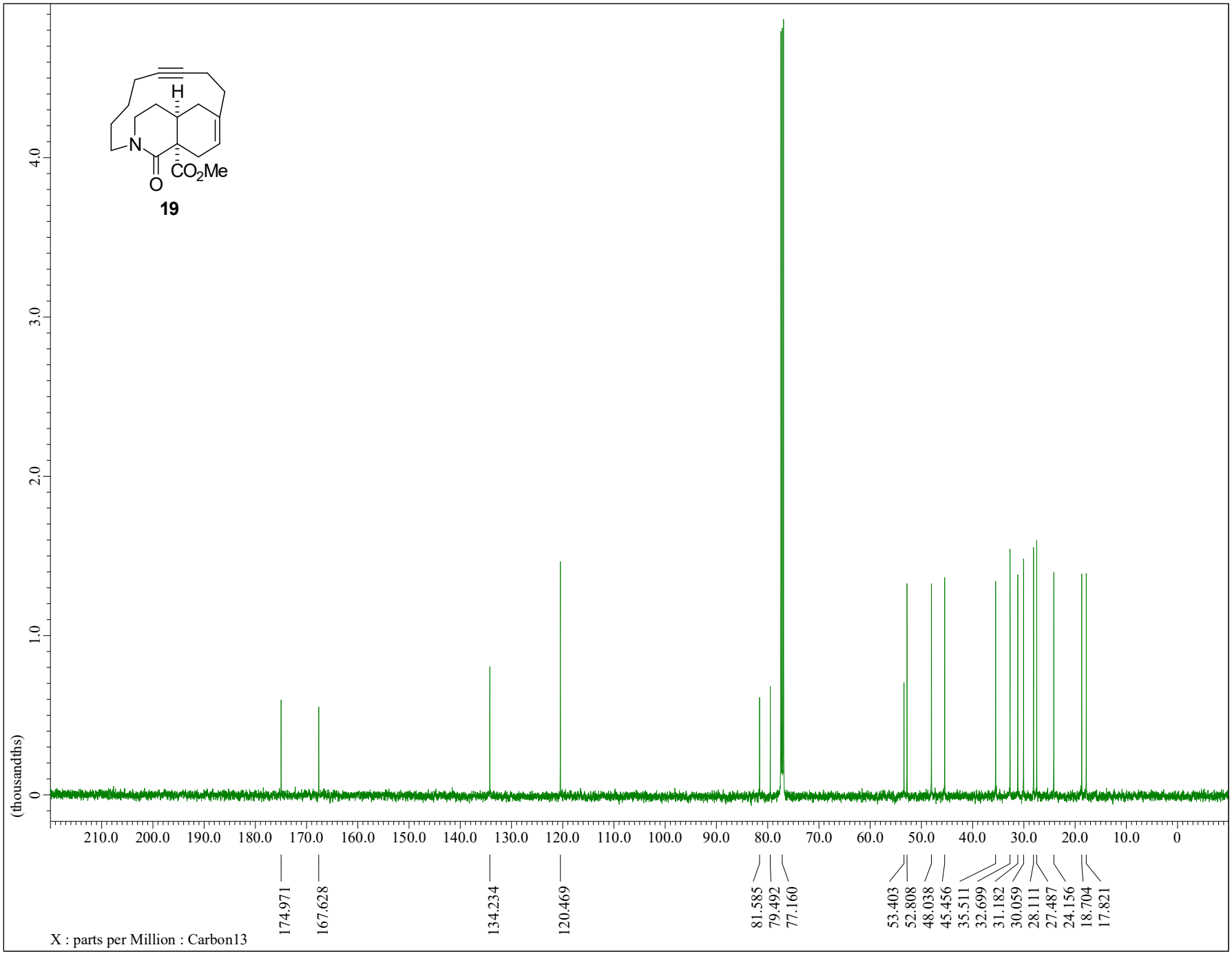
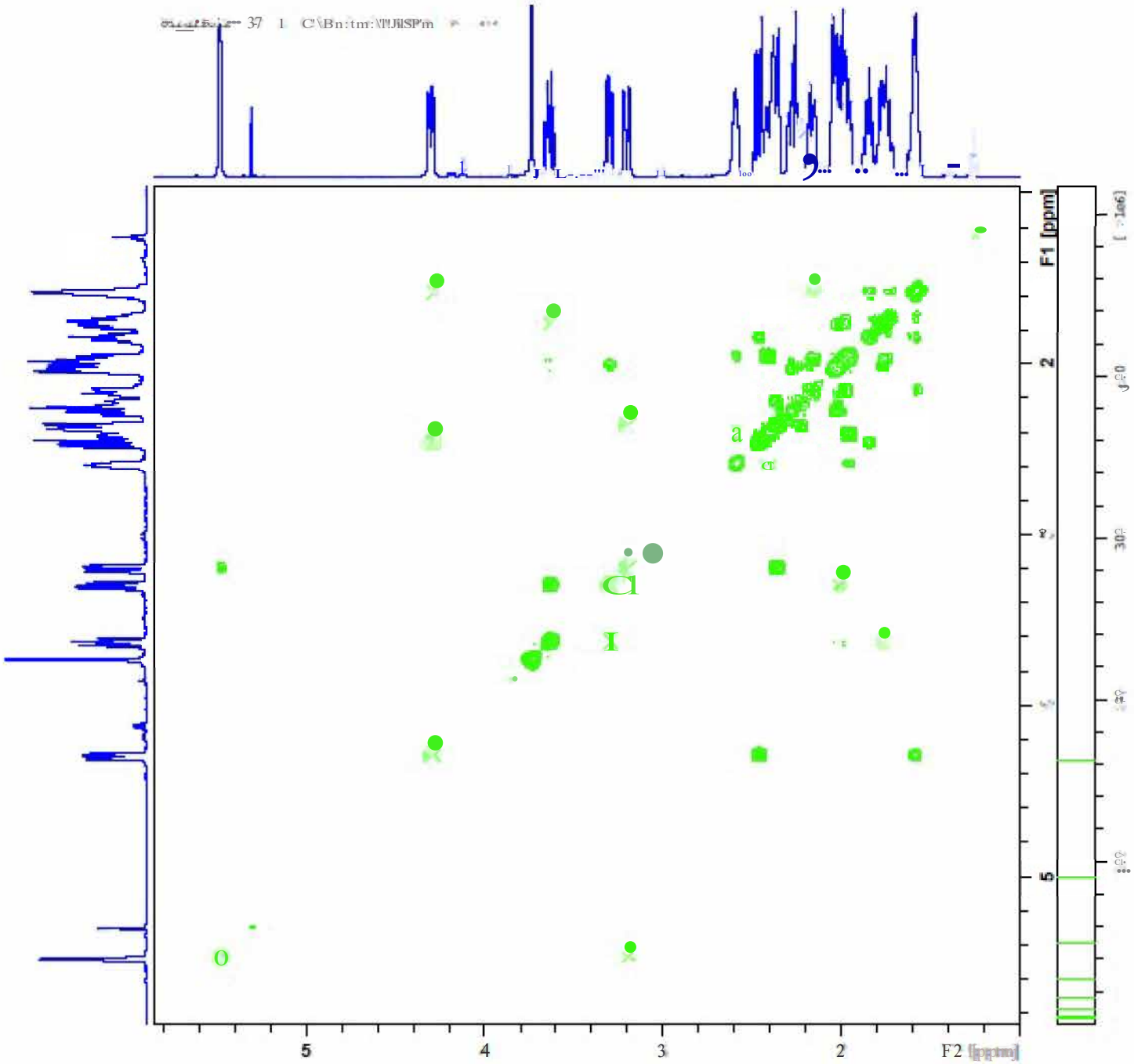
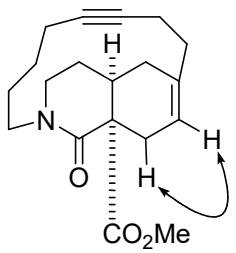
1.567
X : parts per Million : Proton


H
N
O
CO2Me
19
(thousandths)
4.0
3.0
2.0
1.0
0
210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
174.971
167.628
134.234
120.469
81.585
79.492
77.160
53.403
52.808
48.038
45.456
35.511
32.699
31.182
30.059
28.111
27.487
24.156
18.704
17.821
X : parts per Million : Carbon13

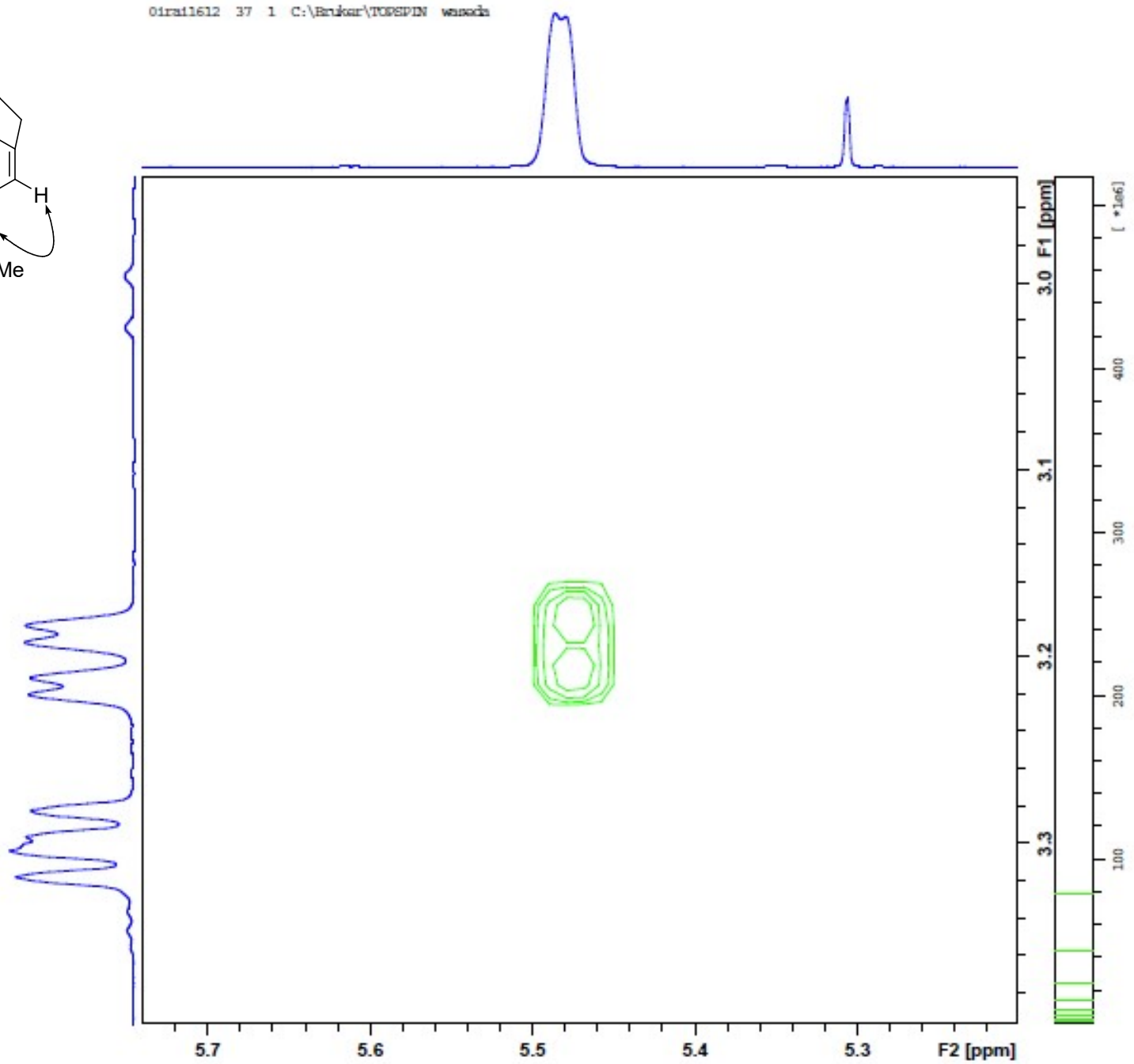
H-H COSY of 19



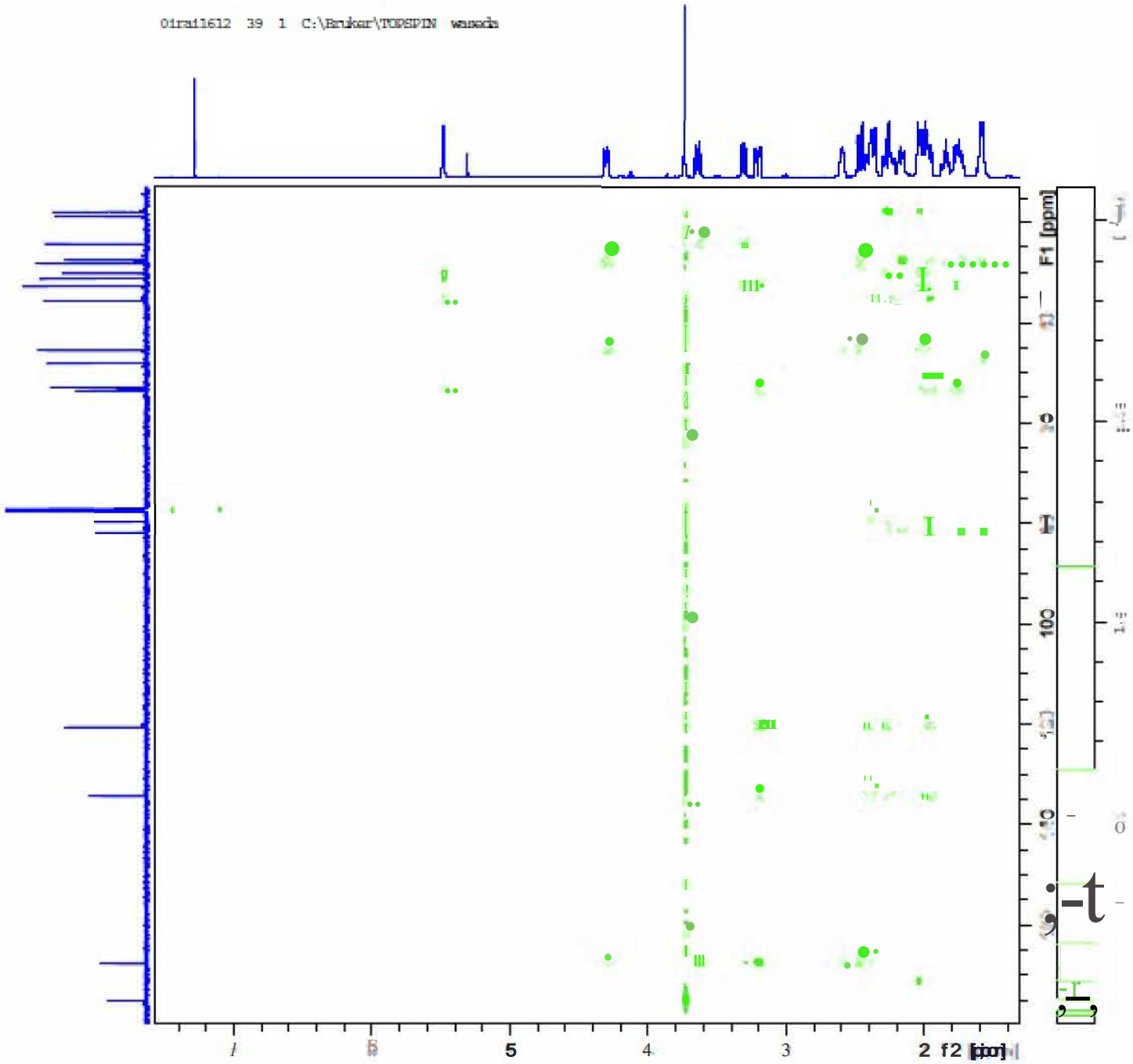
H-H COSY of 19



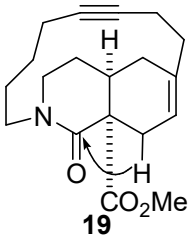
19



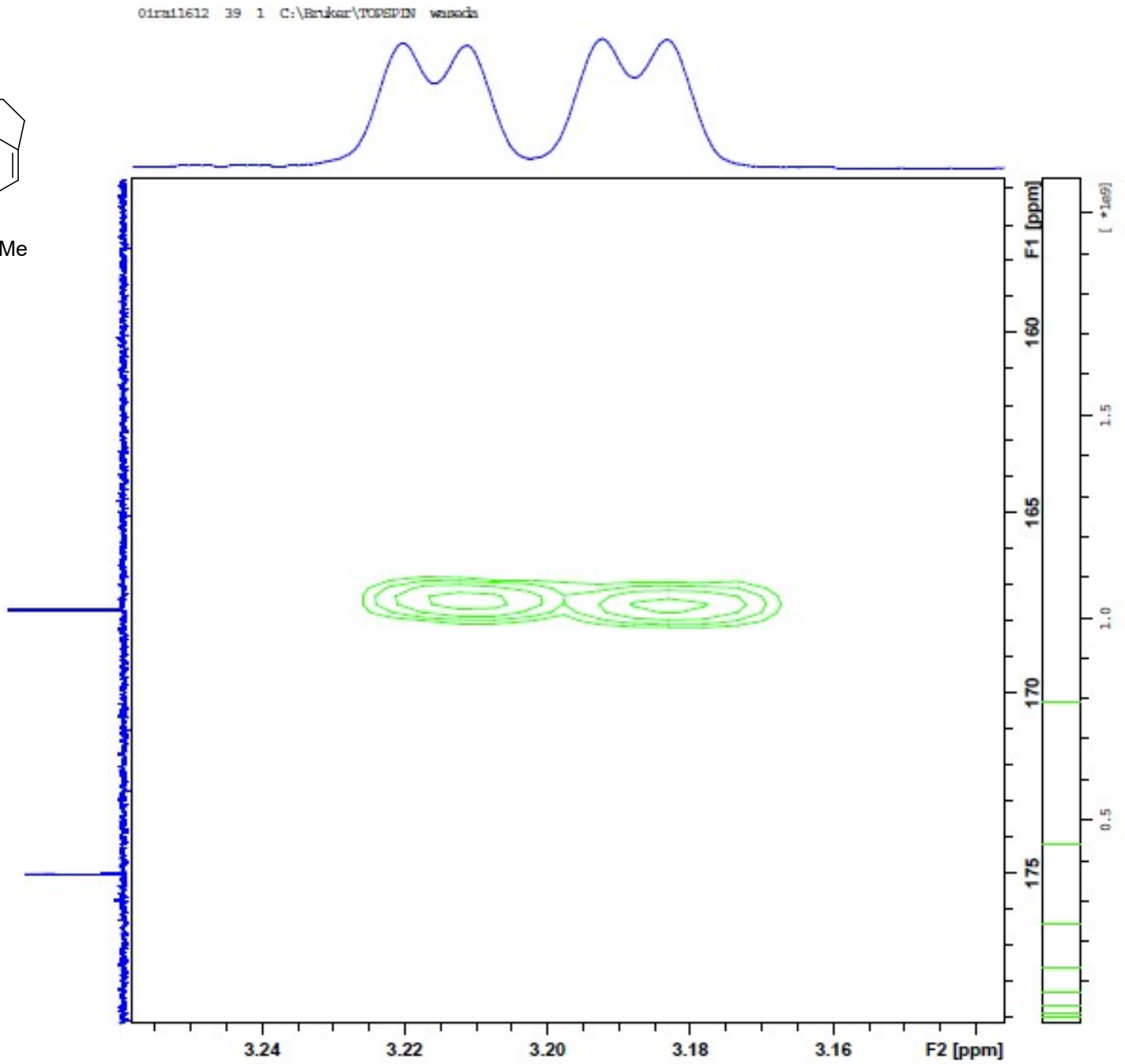
HMBC of 19



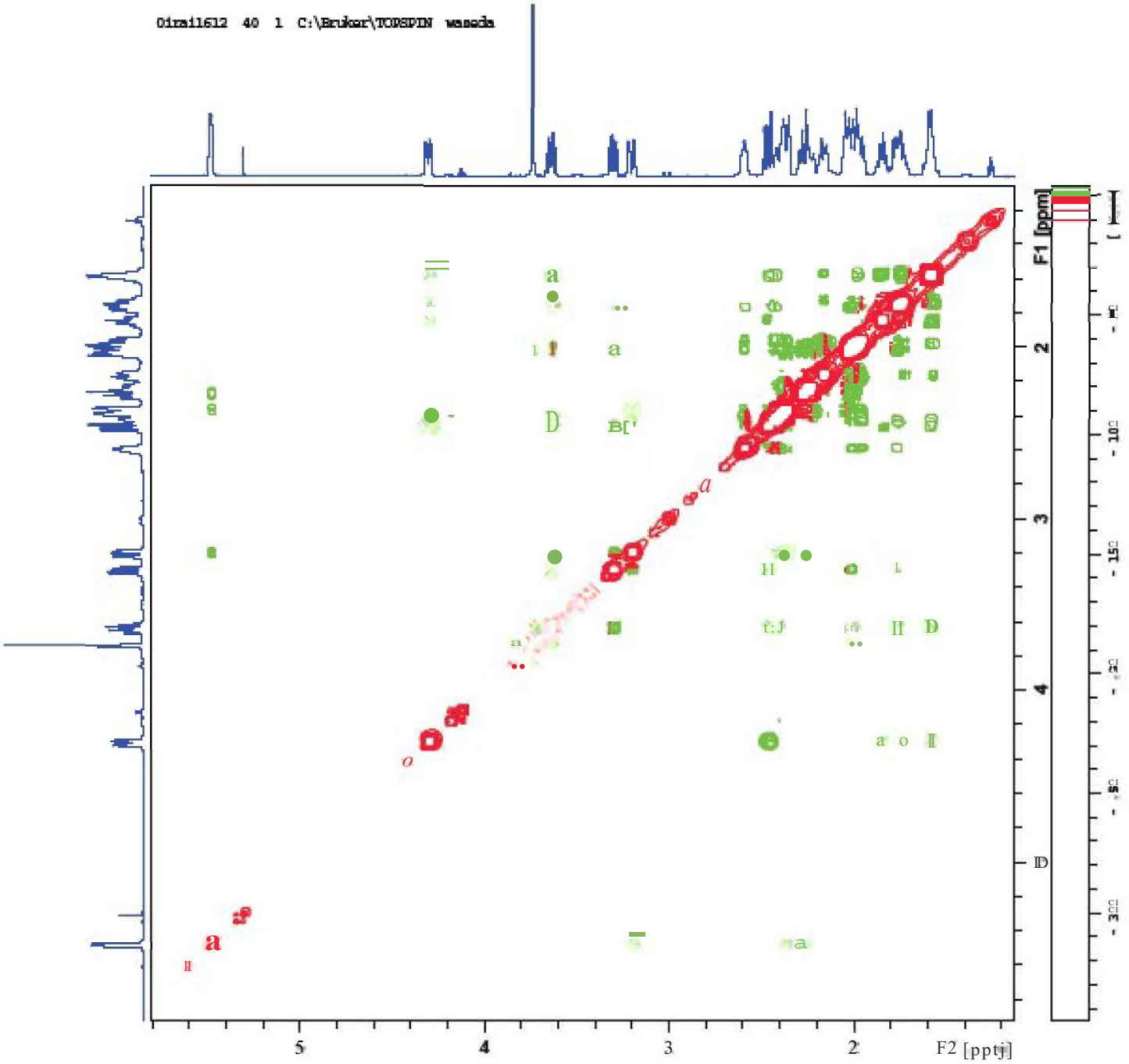
HMBC of 19


H
N
O
H
CO_2Me

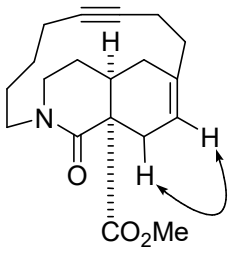
19


01ra11612 39 1 C:\Bruker\TOPSPIN wasada
F1 [ppm]
160
165
170
175
3.24
3.22
3.20
3.18
3.16
F2 [ppm]
1.5
1.0
0.5

NOESY of 19



NOESY of 19



19