Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

for

A Concise Formal Total Synthesis of Lactimidomycin

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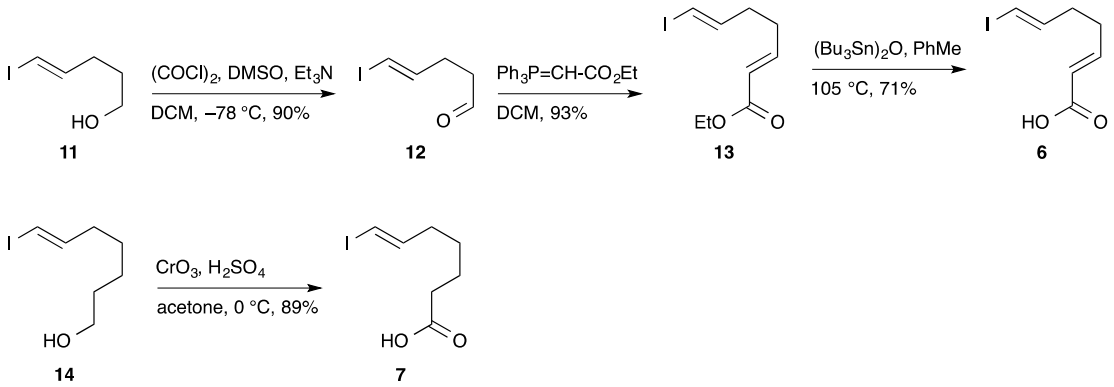
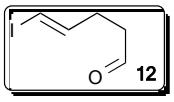
1. General Information

THF, CH_2Cl_2, and toluene were dried and deoxygenated by passing the nitrogen-purged solvents through activated alumina columns on a solvent purification system. DMF was similarly dried by passing through a column of activated 4Å molecular sieves. All other commercially available reagents and solvents were used as received without further purification. All reactions were conducted under a nitrogen atmosphere unless otherwise noted. Flash column chromatography was carried out on silica gel. TLC was conducted on 250 micron, F_{254} silica gel plates. ^{1}H NMR analyses were performed on a 400 MHz spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts were reported as ppm relative to the solvent residual peak ($CHCl_3$: 7.26 ppm for ^{1}H, 77.2 ppm for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad), coupling constant (Hz), and integration. IR spectra were obtained on a FT-IR instrument from thin films on a NaCl plate. High-resolution mass spectra were acquired on an ESI-TOF instrument using PEG or PPG as an internal calibrant.

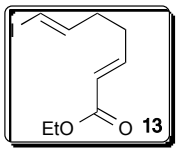
2. Experimental Procedures and Compound Characterizations

2.1 Synthesis of acids 6 and 7

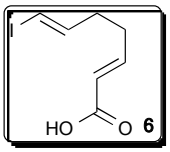




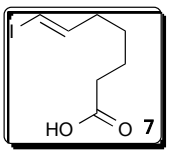
(*E*)-5-Iodopent-4-enal (12). At –78°C, to a solution of oxalyl chloride (0.93 mL, 1.4 g, 11 mmol) in DCM (73 mL) was added DMSO (1.5 mL, 1.7 g, 22 mmol) dropwise. The solution was stirred for 10 min, after which (*E*)-5-iodopent-4-en-1-ol (**11**, 1.54 g, 7.25 mmol) was added over 5 min. The solution was further stirred for 30 min. Triethylamine (6.6 mL, 4.8 g, 47 mmol) was added over 5 min and the solution was further stirred for 1 h at –78 °C. The reaction was allowed to warm to room temperature and stirred for another 1 h before it was quenched with saturated aqueous NH_4Cl solution. The organic compounds were extracted by DCM, washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **12** (1.38 g, 90%) was isolated as a nearly colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, J = 1.2 Hz, 1H), 6.52 (dt, J = 14.4, 7.2 Hz, 1H), 6.12 (dt, J = 14.4, 1.5 Hz, 1H), 2.59—2.55 (m, 2H), 2.41—2.35 (m, 2H).



Ethyl (2*E*,6*E*)-7-Iodohepta-2,6-dienoate (13). To a solution of aldehyde **12** (1.06 g, 5.04 mmol) in DCM (50 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (2.64 g, 7.56 mmol) in one portion and the solution was stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution and extracted with DCM. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **13** (1.32 g, 93%) was isolated as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, *J* = 15.7, 6.6 Hz, 1H), 6.50 (dt, *J* = 14.4, 6.9 Hz, 1H), 6.08 (dt, *J* = 14.4, 1.4 Hz, 1H), 5.83 (dt, *J* = 15.7, 1.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.33—2.28 (m, 2H), 2.24—2.19 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 147.1, 144.6, 122.4, 76.1, 60.4, 34.4, 30.9, 14.4; IR (film, cm^{-1}) 3058, 2980, 2935, 2905, 2848, 1717, 1655, 1606, 1367, 1269, 1182, 976, 948.



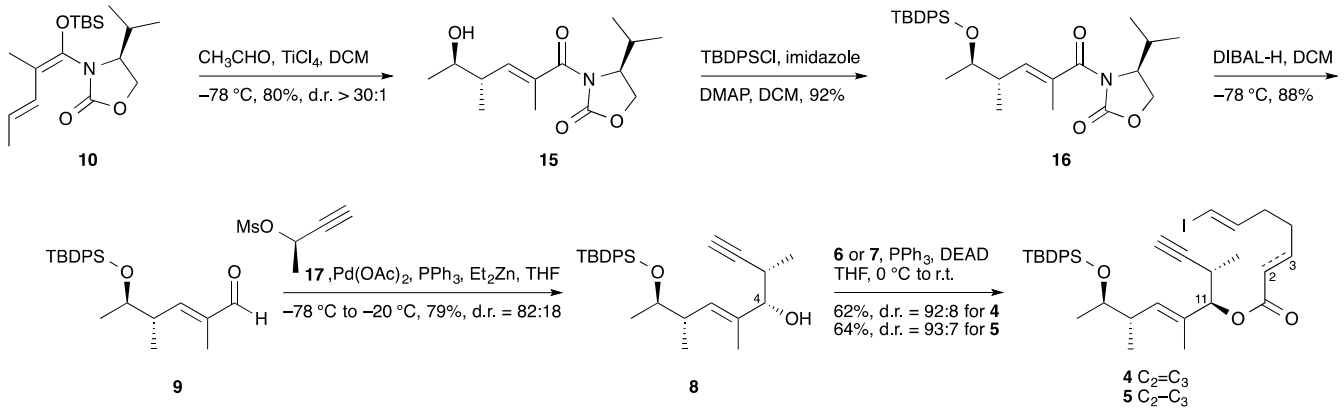
(2*E*,6*E*)-7-Iodohepta-2,6-dienoic Acid (6). Ester **13** (572 mg, 2.04 mmol) and bis(tributyltin) oxide (2.1 mL, 2.4 g, 4.1 mmol) were dissolved in toluene. The solution was heated at 105 °C with stirring for 48 h. The mixture was cooled to room temperature and partitioned between aqueous HCl solution (1 M) and EtOAc. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 70:30 hexanes/EtOAc). Compound **6** (364 mg, 71%) was isolated as white crystals (mp 155 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (br, 1H), 7.03 (dt, *J* = 15.6, 6.6 Hz, 1H), 6.50 (dt, *J* = 14.4, 7.1 Hz, 1H), 6.10 (d, *J* = 14.4 Hz, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 2.38—2.32 (m, 2H), 2.27—2.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 150.3, 144.5, 121.8, 76.4, 34.4, 31.1; IR (film, cm^{-1}) 3054, 2986, 1697, 1654, 1421, 1262, 896, 750; HRMS (ESI+) *m/z* calc'd for $[M–H+2Na]^+$ $C_7H_8IO_2Na_2$: 296.9359, found 296.9372.

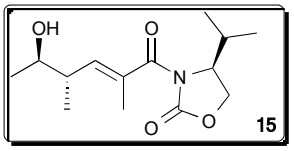


(*E*)-7-Iodohept-6-enoic Acid (7). At 0 °C, to a solution of alcohol **14** (631 mg, 2.63 mmol) in acetone (26 mL) was added Jones reagent (2.76 M CrO_3 in H_2SO_4, 3.8 mL, 10.5 mmol) and the mixture was stirred at 0 °C for 3 h before it was diluted with water. Organic materials were extracted with DCM, washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 80:20 hexanes/EtOAc). Compound **7** (601 mg, 89%) was isolated as white crystals (mp 64—65 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (br, 1H), 6.50 (dt, *J* = 14.4, 7.1 Hz, 1H), 6.02 (d, *J* = 14.4 Hz, 1H), 2.36 (t, *J* =

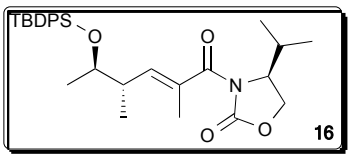
7.3 Hz, 2H), 2.09 (q, J = 7.2 Hz, 2H), 1.69—1.61 (m, 2H), 1.50—1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 146.0, 75.2, 35.8, 33.9, 27.9, 24.1; IR (film, cm^{-1}) 3047, 2937, 1699, 1412, 1291, 1210, 950; HRMS (ESI+) *m/z* calc'd for $[M–H+2Na]^+$ $C_7H_{10}IO_2Na_2$: 298.9515, found 298.9521.

2.2 Synthesis of ester 4 and 5



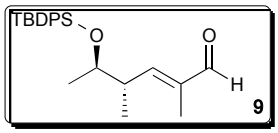


(*S*)-3-((4*S*,5*R*,*E*)-5-Hydroxy-2,4-dimethylhex-2-enoyl)-4-isopropyloxazolidin-2-one (15). At –78°C, to a solution of acetaldehyde (0.898 g, 20.4 mmol) in DCM (25 mL) were sequentially added $TiCl_4$ solution (1 M in DCM, 5.1 mL, 5.1 mmol) and a solution of vinylketene silyl *N*,*O*-acetal **10** (1.73 g, 5.09 mmol) in DCM (25 mL). The resultant dark orange solution was stirred at –78 °C for 24 h, after which the color turned bright yellow. The reaction was quenched with aqueous saturated Rochelle salt solution and stirred at room temperature for several hours until precipitates disappeared. The mixture was extracted with DCM. The combine organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (90:10 — 60:40 hexanes/EtOAc). Compound **15** (1.10 g, 80%) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +11 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dq, J = 10.4, 1.5 Hz, 1H), 4.58 (ddd, J = 8.9, 5.8, 4.6Hz, 1H), 4.34 (t, J = 9.0 Hz, 1H), 4.19 (dd, J = 9.0, 5.8 Hz, 1H), 3.51 (quint, J = 6.6 Hz, 1H), 3.24 (s, 1H), 2.49 (ddq, J = 10.4, 8.3, 6.6 Hz, 1H), 2.34 (septd, J = 7.0, 4.5 Hz, 1H), 1.95 (d, J = 1.4 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 154.6, 142.0, 131.3, 71.6, 63.6, 58.1, 41.9, 28.5, 20.1, 17.8, 16.2, 15.2, 14.0; IR (film, cm^{-1}) 3517, 2968, 2931, 2876, 1773, 1685, 1390, 1366, 1301, 1210; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{23}NO_4Na$: 292.1519, found 292.1514.

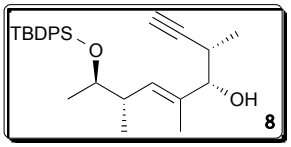


(*S*)-3-((4*S*,5*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethylhex-2-enoyl)-4-isopropyloxazolidin-2-one (16).

A solution of alcohol **15** (1.02 g, 3.79 mmol), imidazole (774 mg, 11.4 mmol) and DMAP (92.5 mg, 0.757 mmol) in DCM (19 mL) was cooled to 0 °C and *tert*-butylchlorodiphenylsilane (1.9 mL, 2.1 g, 7.6 mmol) was added. The solution was stirred at room temperature overnight and then water was added. The mixture was extracted with DCM. The combine organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 85:15 hexanes/EtOAc). Compound **16** (1.78 g, 92%) was isolated as a colorless syrup. $[\alpha]_D^{21}$ = +16 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72—7.68 (m, 4H), 7.45—7.36 (m, 6H), 6.08—6.05 (m, 1H), 4.52 (ddd, *J* = 8.8, 5.5, 4.3 Hz, 1H), 4.32 (t, *J* = 8.9 Hz, 1H), 4.18 (dd, *J* = 9.0, 5.6 Hz, 1H), 3.89 (qd, *J* = 6.4, 3.4 Hz, 1H), 2.54 (dqd, *J* = 10.2, 6.8, 3.4 Hz, 1H), 2.37 (septd, *J* = 6.9, 4.2 Hz, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.07 (s, 9H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 153.7, 141.2, 136.1, 134.7, 134.2, 131.1, 129.8, 129.6, 127.7, 127.6, 72.2, 63.5, 58.3, 40.1, 28.3, 27.2, 20.5, 19.6, 18.0, 15.3, 15.2, 13.6; IR (film, cm^{-1}) 3072, 3049, 2964, 2931, 1789, 1683, 1428, 1300, 1111, 703; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{30}H_{41}NO_4SiNa$: 530.2697, found 530.2703.

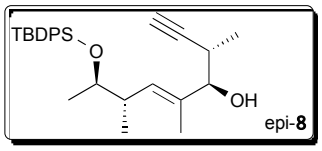


(4*S*,5*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethylhex-2-enal (9). A solution of compound **16** (1.16 g, 2.28 mmol) in DCM (50 mL) was cool to –78 °C and DIBAL-H solution (1.49 M in toluene, 3.3 mL, 4.9 mmol) was added dropwise. The reaction was stirred at –78 °C for 20 min before it was quenched by MeOH and then aqueous saturated Rochelle salt solution. The mixture was stirred at room temperature until precipitates disappeared and then extracted with DCM. The combine organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **9** (761 mg, 88%) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +1.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.70—7.65 (m, 4H), 7.46—7.35 (m, 6H), 6.40 (dq, *J* = 9.8, 1.3 Hz, 1H), 3.85 (qd, *J* = 6.2, 4.4 Hz, 1H), 2.71 (dqd, *J* = 9.8, 6.8, 4.4 Hz, 1H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H), 1.04 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 157.1, 139.3, 136.1 134.6, 133.9, 130.0, 129.8, 127.8, 127.7, 72.4, 41.2, 27.2, 21.0, 19.6, 15.6, 9.5; IR (film, cm^{-1}) 3071, 3050, 2964, 2931, 2858, 2820, 2708, 1690, 1641, 1428, 1377, 1111, 1025, 703; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{24}H_{32}O_2SiNa$: 403.2064, found 403.2064.

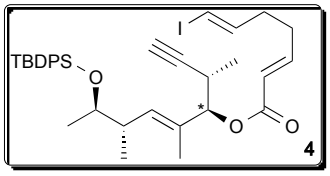


(3*S*,4*S*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethylnon-5-en-1-yn-4-ol (8). Anhydrous THF was pretreated with 3Å molecular sieves (20% M/V) overnight. A solution of palladium acetate (11.2 mg, 0.0500 mmol) and triphenylphosphine (13.1 mg, 0.0500 mmol) in THF (18 mL) was cooled to –78 °C. To this solution were sequentially added mesylate **17** (0.15 mL, 178 mg, 1.20 mmol), a solution of aldehyde **9** (382 mg, 1.00

mmol) in THF (2mL), and diethylzinc (1.0 M in hexanes, 3.0 mL, 3.0 mmol). The resultant mixture was stirred at –78 °C for 10 min, warmed up to –20 °C, stirred at –20 °C for 20 h, left in 0 °C fridge for another 16 h, and then quenched with saturated aqueous NH_4Cl solution. The organic compounds were extracted by EtOAc, washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). An inseparable mixture of compound **8** and its C_4-epimer (342 mg, 79%, d.r. = 82:18) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +2.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71—7.66 (m, 4H), 7.44—7.34 (m, 6H), 5.32—5.29 (m, 1H), 3.80 (qd, *J* = 6.3, 4.0 Hz, 1H), 3.76 (d, *J* = 8.0 Hz, 1H), 2.65—2.55 (m, 1H), 2.47 (dqd, *J* = 9.6, 6.8, 4.1 Hz, 1H), 2.12 (d, *J* = 2.4 Hz, 1H), 1.86 (br, 1H), 1.39 (d, *J* = 1.3 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.06 (s, 9H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 134.9, 134.5, 134.1, 132.0, 129.7, 129.6, 127.7, 127.6, 86.3, 81.2, 72.5, 70.7, 39.3, 31.3, 27.3, 19.9, 19.6, 17.7, 15.6, 11.3; IR (film, cm^{-1}) 3308, 3071, 2964, 2932, 2858, 1428, 1376, 1111, 702; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{28}H_{38}O_2SiNa$: 457.2533, found 457.2528.

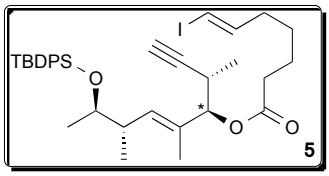


(3*S*,4*R*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethylnon-5-en-1-yn-4-ol (epi-8). Featured ^{1}H NMR (400 MHz, $CDCl_3$) peaks: δ 5.39—5.36 (m, 1H), 3.91 (d, *J* = 7.0 Hz, 1H), 1.96 (d, *J* = 2.5 Hz, 1H), 1.42 (d, *J* = 1.4 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H). The minor isomer is in an inseparable mixture and therefore not all signals are visible in the spectrum.

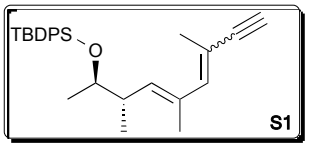


(3*S*,4*R*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethylnon-5-en-1-yn-4-yl (2*E*,6*E*)-7-Iodohepta-2,6-dienoate (4). A solution of alcohol **8** (56.8 mg, 0.131 mmol), acid **6** (98.8 mg, 0.392 mmol), and triphenylphosphine (103 mg, 0.392 mmol) in toluene (1.3 mL) was cooled to 0 °C and DEAD (40% in toluene, 0.18 mL, 69 mg, 0.39 mmol) was added. The mixture was stirred at room temperature for 22 h before the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (100:0 — 50:50 hexanes/DCM). Compound **4** along with its inseparable epimer (54.2 mg, 62%, d.r. = 92:8) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70—7.65 (m, 4H), 7.43—7.34 (m, 6H), 6.92 (dt, *J* = 15.6, 6.5 Hz, 1H), 6.49 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.07 (dt, *J* = 14.4, 1.5 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.42 (d, *J* = 9.4 Hz, 1H), 5.12 (d, *J* = 7.9 Hz, 1H), 3.78 (qd, *J* = 6.2, 3.2 Hz, 1H), 2.78 (quintd, *J* = 7.0, 2.5 Hz, 1H), 2.43 (dqd, *J* = 9.8, 6.7, 3.2 Hz, 1H), 2.31—2.26 (m, 2H), 2.23—2.19 (m, 2H), 1.93 (d, *J* = 2.4 Hz, 1H), 1.42 (d, *J* = 1.5 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.02 (d, *J* = 6.8, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 147.6, 144.7, 136.1, 135.0, 134.4, 132.9, 131.4, 129.7, 129.6, 127.7, 127.6, 122.4, 85.1, 81.1, 76.2, 72.4,

70.5, 39.1, 34.5, 31.0, 29.3, 27.3, 19.8, 19.6, 17.2, 15.4, 12.5; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{35}H_{45}IO_3Si$: 691.2075, found 691.2096.

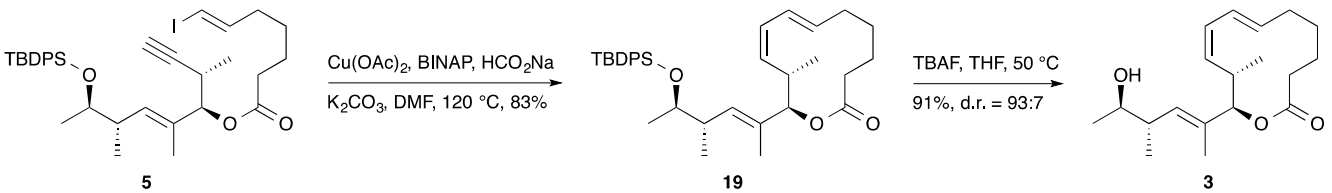


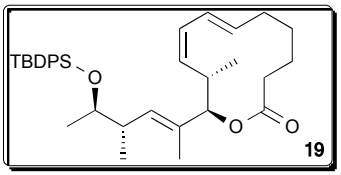
(3*S*,4*R*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethylnon-5-en-1-yn-4-yl (*E*)-7-Iodohept-6-enoate (5). A solution of alcohol **8** (78.8 mg, 0.181 mmol), acid **7** (139 mg, 0.543 mmol), and triphenylphosphine (142 mg, 0.543 mmol) in toluene (1.8 mL) was cooled to 0 °C and DEAD (40% in toluene, 0.25 mL, 95 mg, 0.54 mmol) was added. The mixture was stirred at room temperature for 20 h before the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (100:0 — 50:50 hexanes/DCM). Compound **5** along with its inseparable epimer (77.8 mg, 64%, d.r. = 93:7) was isolated as a colorless oil. $[\alpha]_D^{22}$ = +7.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70—7.66 (m, 4H), 7.44—7.34 (m, 6H), 6.48 (dt, *J* = 14.2, 7.1 Hz, 1H), 6.02 (dt, *J* = 14.3, 1.5 Hz, 1H), 5.40 (d, *J* = 9.6 Hz, 1H), 5.06 (d, *J* = 7.8 Hz, 1H), 3.78 (qd, *J* = 6.3, 3.3 Hz, 1H), 2.75 (quintd, *J* = 6.9, 2.4 Hz, 1H), 2.43 (dqd, *J* = 9.9, 6.8, 3.4 Hz, 1H), 2.31 (td, *J* = 7.5, 1.8 Hz, 2H), 2.06 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.92 (d, *J* = 2.4 Hz, 1H), 1.66—1.58 (m, 2H), 1.45—1.37 (m, 5H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 146.0, 136.1, 134.9, 134.4, 132.7, 131.4, 129.7, 129.6, 127.9, 127.5, 85.1, 80.9, 75.1, 72.3, 70.4, 39.0, 35.8, 34.3, 29.1, 27.9, 27.2, 24.4, 19.8, 19.6, 17.1, 15.4, 12.5; IR (film, cm^{-1}) 3308, 3070, 2931, 2857, 1736, 1427, 1110, 702, HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{35}H_{47}IO_3SiNa$: 693.2231, found 693.2236.



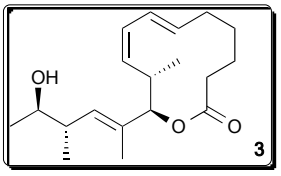
***tert*-Butyldiphenyl(((2*R*,3*S*,4*E*)-3,5,7-trimethylnona-4,6-dien-8-yn-2-yl)oxy)silane (S1).** Elimination product **S1** (15.9 mg, 21%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73—7.68 (m, 4H), 7.52—7.30 (m, 6H), 6.12 (br, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 3.80 (qd, *J* = 6.2, 4.1 Hz, 1H), 3.15 (s, 1H), 2.55 (dqd, *J* = 9.5, 6.8, 4.2, 1H), 1.95 (d, *J* = 1.4 Hz, 3H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.08 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 127.2, 136.2, 135.1, 134.5, 133.8, 129.7, 129.6, 127.7, 127.6, 112.9, 85.0, 82.5, 72.6, 39.8, 27.3, 25.9, 20.0, 19.6, 15.6, 15.1.

2.3 Macrocyclization and completion



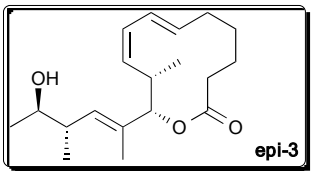


(7*E*,9*Z*,11*S*,12*R*)-12-((4*S*,5*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylhex-2-en-2-yl)-11-methyloxacyclododeca-7,9-dien-2-one (19). A suspension of copper acetate (13.4 mg, 0.0738 mmol), BINAP (69.7 mg, 0.112 mmol), sodium formate (60.9 mg, 0.896 mmol) and potassium carbonate (46.4 mg, 0.336 mmol) in DMF (22 mL) was stirred at 120 °C for 30 min, after which a solution of ester **5** (150 mg, 0.224 mmol) in DMF (23 mL) was added dropwise in one portion. The resultant mixture was stirred at 120 °C for an additional 4 h before it was cooled and quenched with saturated aqueous NH_4Cl solution. After stirring at room temperature for 15 min, the mixture was diluted with water and extracted with EtOAc/hexanes (1:1). The combine organic layer was sequentially washed with NH_4Cl/NH_3 buffer (made from 3:1 saturated NH_4Cl/28% aqueous ammonium hydroxide), water and brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 50:50 hexanes/DCM). Compound **19** (102 mg, 83%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = –25 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72—7.66 (m, 4H), 7.44—7.35 (m, 6H), 6.21 (dd, *J* = 15.8, 10.5 Hz, 1H), 6.10 (t, *J* = 10.4 Hz, 1H), 5.74 (dt, *J* = 15.8, 5.3 Hz, 1H), 5.30 (d, *J* = 9.6 Hz, 1H), 5.10 (d, *J* = 5.0 Hz, 1H), 4.99 (t, *J* = 10.0 Hz, 1H), 3.78 (qd, *J* = 6.2, 3.1 Hz, 1H), 3.38—3.29 (m, 1H), 2.44—2.23 (m, 4H), 2.04—1.93 (m, 2H), 1.90—1.84 (m, 1H), 1.59—1.50 (m, 2H), 1.35 (d, *J* = 1.3 Hz, 3H), 1.07 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 136.2, 136.1, 135.0, 134.4, 133.6, 131.6, 131.3, 131.1, 130.1, 129.7, 129.6, 127.7, 127.6, 126.7, 83.5, 72.5, 39.2, 33.6, 33.4, 30.5, 27.2, 24.1, 23.2, 20.1, 19.6, 17.8, 15.6, 14.3; IR (film, cm^{-1}) 3071, 2962, 2930, 2857, 1728, 1427, 1376, 1200, 1111, 739, 702; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{35}H_{48}O_3SiNa$: 567.3265, found 567.3267.



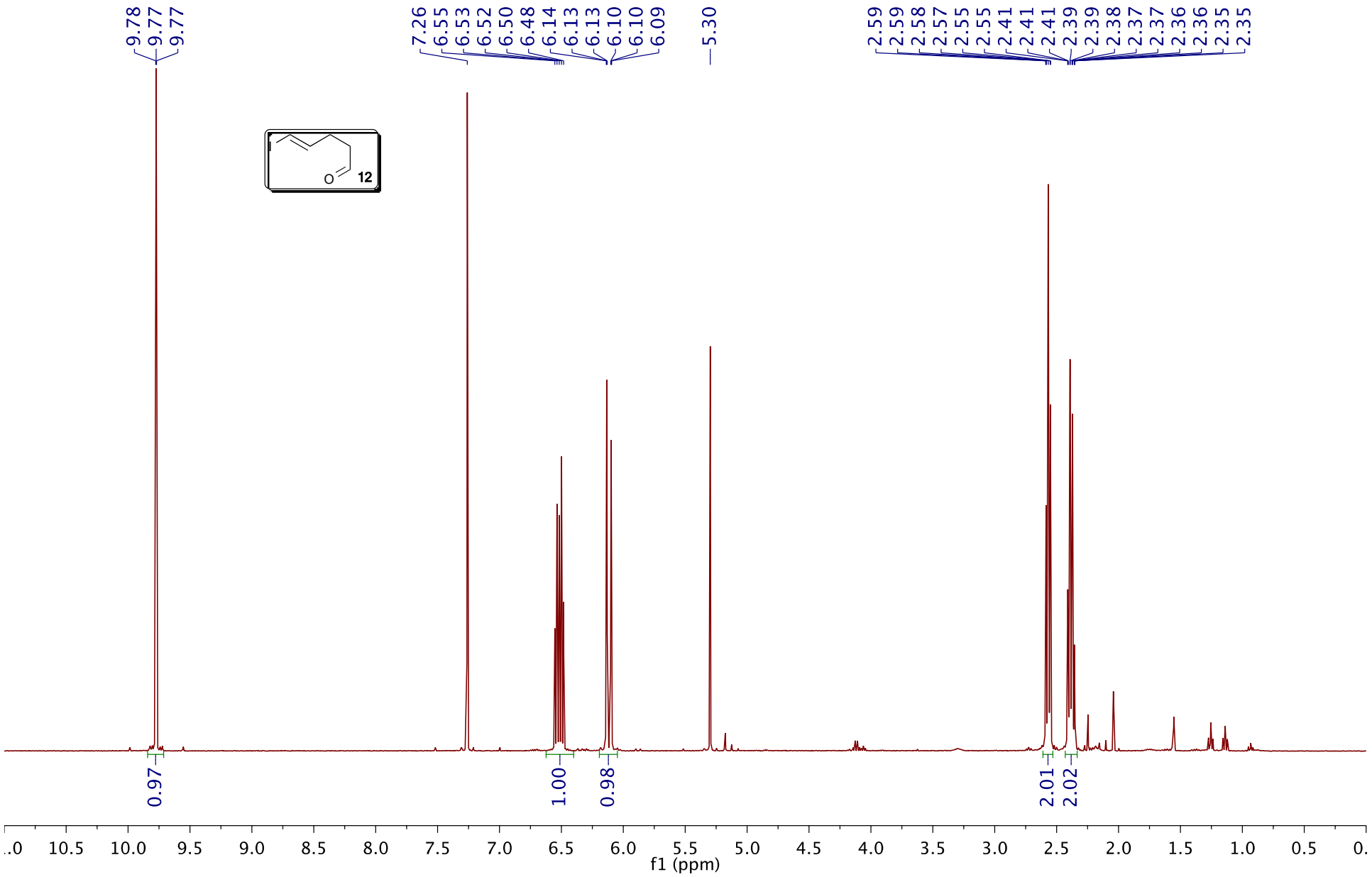
(7*E*,9*Z*,11*S*,12*R*)-12-((4*S*,5*R*,*E*)-5-Hydroxy-4-methylhex-2-en-2-yl)-11-methyloxacyclododeca-7,9-dien-2-one (3). To a vial containing lactone **19** (71.5 mg, 0.131 mmol) was added TBAF solution (1.0 M in THF, 3.4 mL, 3.4 mmol) and the solution was heated to 50 °C and heated for 4 h. The mixture was cooled, diluted with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 85:15 hexanes/EtOAc). Compound **3** (34 mg, 85%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = –85 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.12 (t, *J* = 10.4 Hz, 1H), 5.74 (dt, *J* = 15.6, 5.2 Hz, 1H), 5.24 (d, *J* = 9.8 Hz, 1H), 5.13 (d, *J* = 5.0 Hz, 1H), 5.05 (t, *J* = 9.9 Hz, 1H), 3.58 (quint, *J* = 6.2 Hz, 1H), 3.40—3.32 (m, 1H), 2.41 (dquint, *J* = 9.9, 6.7 Hz, 1H), 2.34—2.24 (m, 3H), 2.04—1.96 (m, 2H), 1.93—1.83 (m, 1H), 1.64 (d, *J* = 1.1 Hz, 3H), 1.59—1.48 (m, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.8, 3H), 0.95 (d, *J* = 6.8,

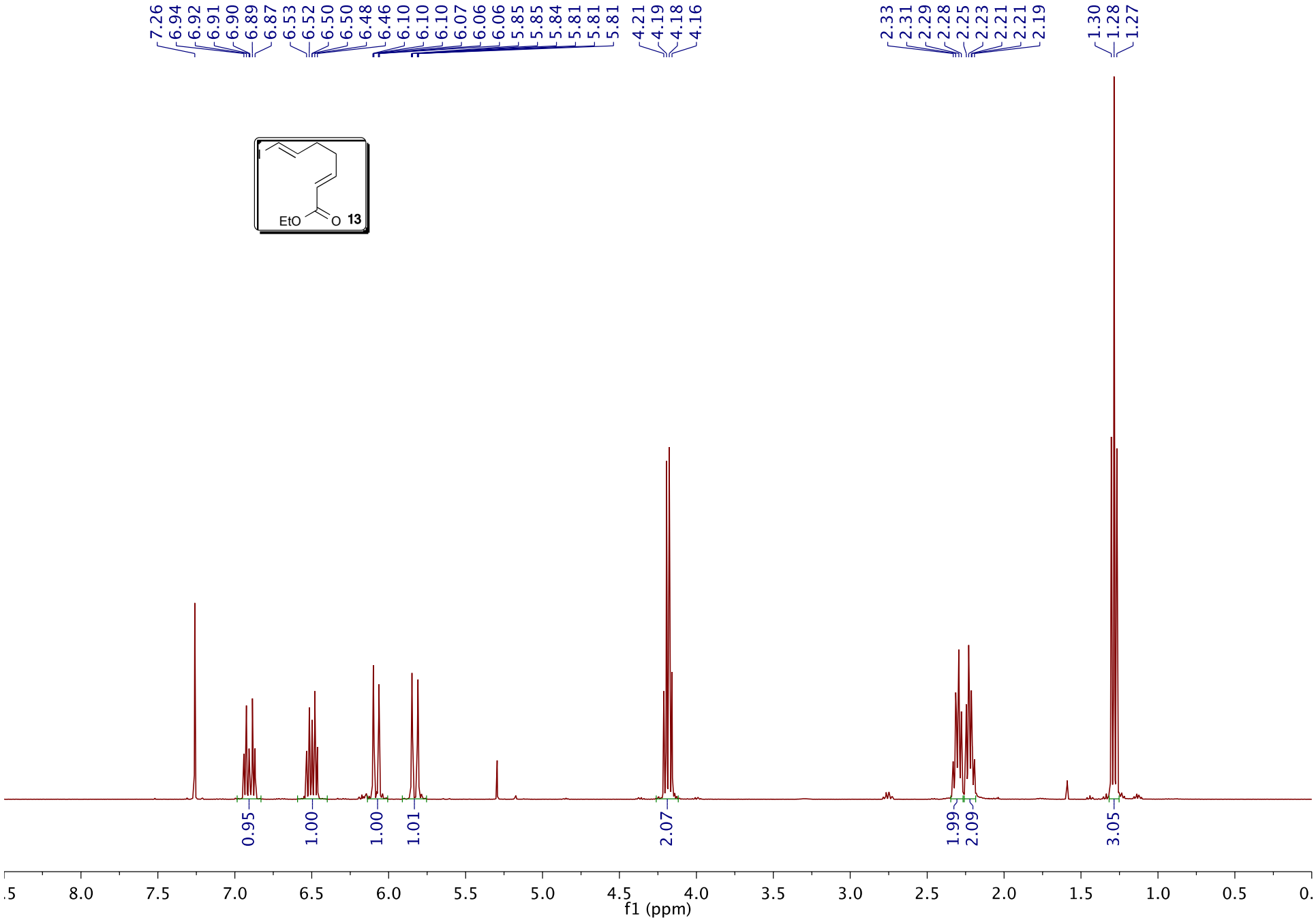
3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 133.3, 133.0, 131.6, 131.3, 130.3, 126.7, 83.3, 71.7, 40.2, 33.5, 33.4, 30.5, 24.1, 23.2, 20.4, 17.9, 16.6, 14.8; IR (film, cm^{-1}) 3449, 3008, 2966, 2929, 2876, 1726, 1453, 1376, 1201, 1146, 1093, 994, 955; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{19}H_{30}O_3Na$: 329.2087, found 329.2085.



(7*E*,9*Z*,11*S*,12*S*)-12-((4*S*,5*R*,*E*)-5-Hydroxy-4-methylhex-2-en-2-yl)-11-methyloxacyclododeca-7,9-dien-2-one (epi-3). The epimer (2.5 mg, 6%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = +16 (*c* 0.050, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.13 (t, *J* = 10.4 Hz, 1H), 5.75 (dt, *J* = 15.6, 5.2 Hz, 1H), 5.24 (d, *J* = 9.8 Hz, 1H), 5.15 (d, *J* = 4.9 Hz, 1H), 5.05 (t, *J* = 9.9 Hz, 1H), 3.55 (quint, *J* = 6.3 Hz, 1H), 3.41—3.33 (m, 1H), 2.41 (dquint, *J* = 9.8, 6.8 Hz, 1H), 2.38—2.25 (m, 3H), 2.05—1.95 (m, 2H), 1.93—1.81 (m, 1H), 1.66 (s, 3H, overlapping with water signal), 1.60—1.52 (m, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 6H).

3. NMR spectra

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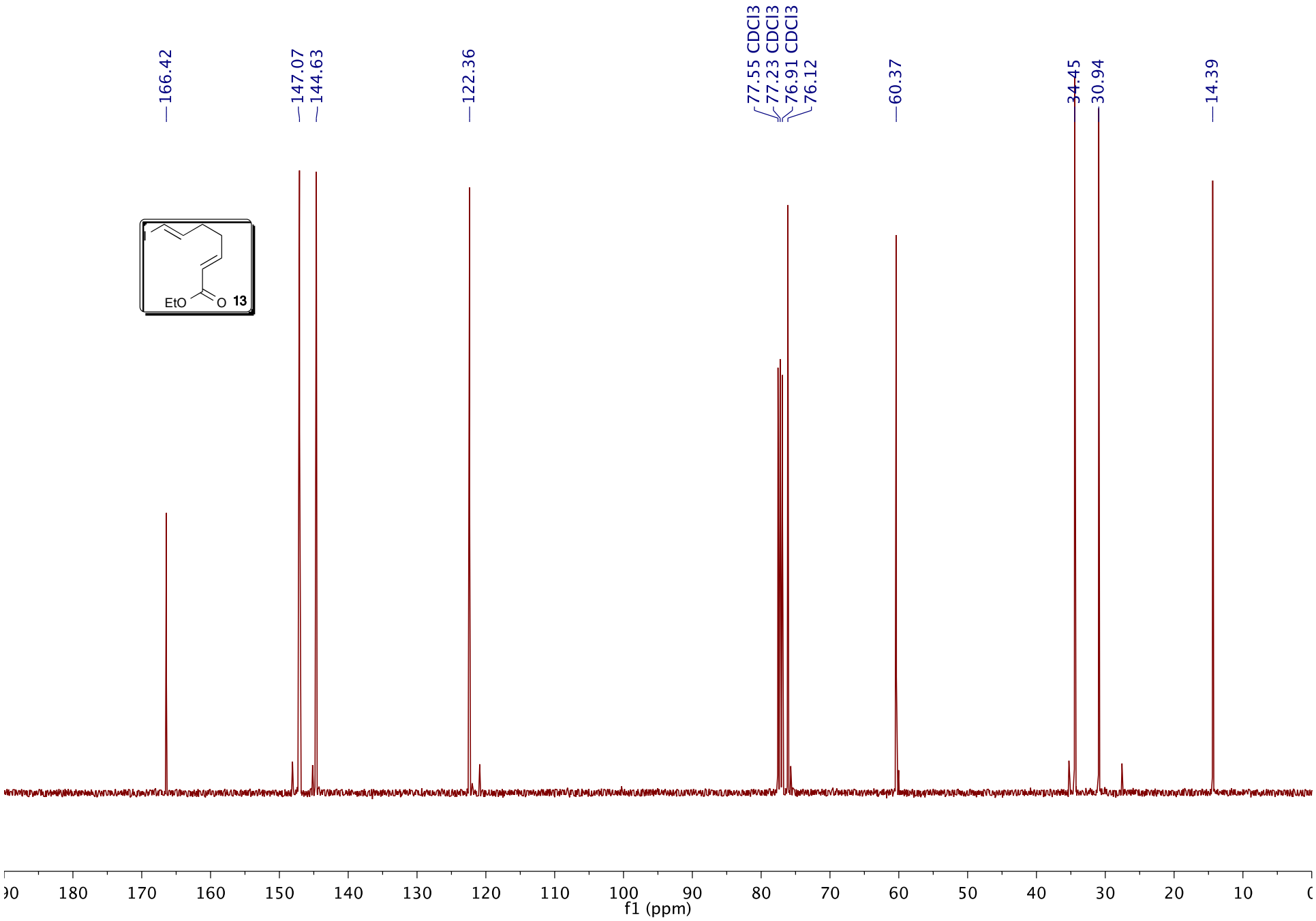
6.92
6.91
6.90
6.89
6.87
6.53
6.52
6.50
6.50
6.48
6.46
6.10
6.10
6.10
6.07
6.06
6.06
5.85
5.85
5.84
5.81
5.81
5.81
4.21
4.19
4.18
4.16
2.33
2.31
2.29
2.28
2.25
2.23
2.21
2.21
2.19
1.30
1.28
1.27
EtO
O
13
0.95
1.00
1.00
1.01
2.07
1.99
2.09
3.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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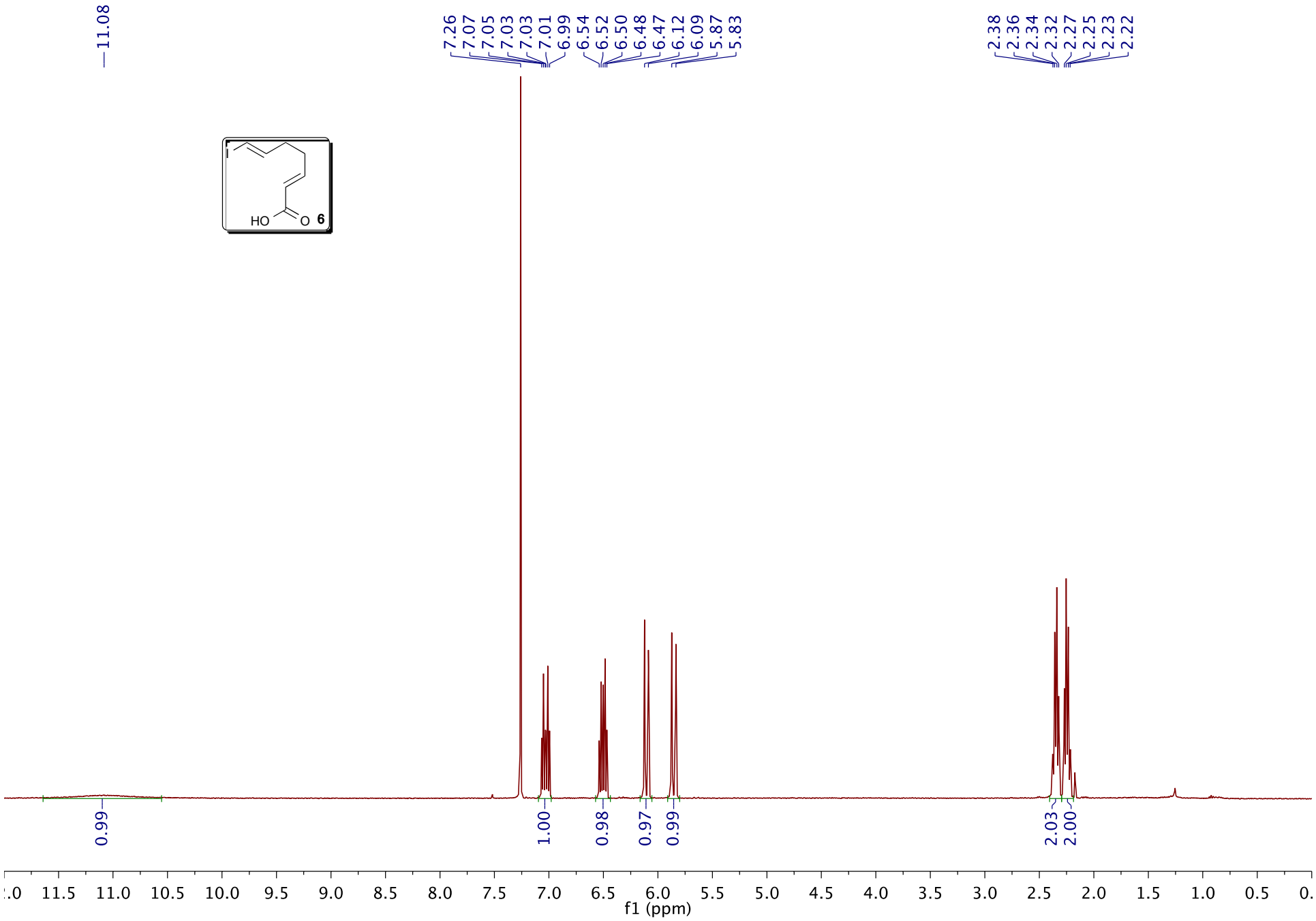
147.07
144.63
122.36
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
76.12
60.37
34.45
30.94
14.39
EtO
O
13
f1 (ppm)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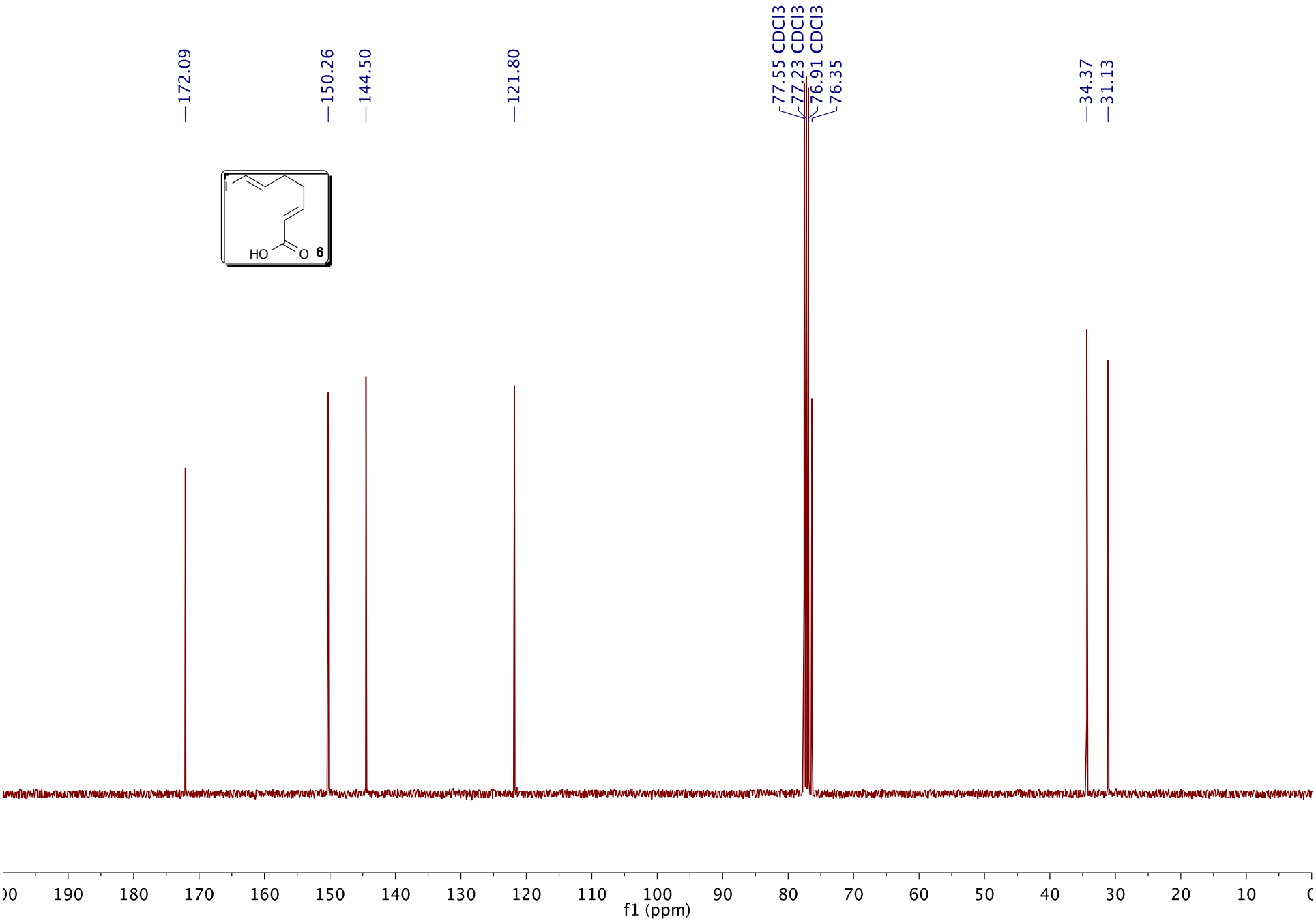
7.07
7.05
7.03
7.03
7.01
6.99
6.54
6.52
6.50
6.48
6.47
6.12
6.09
5.87
5.83
2.38
2.36
2.34
2.32
2.27
2.25
2.23
2.22
HO
O
6
0.99
1.00
0.98
0.97
0.99
2.03
2.00
f1 (ppm)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144.50
121.80
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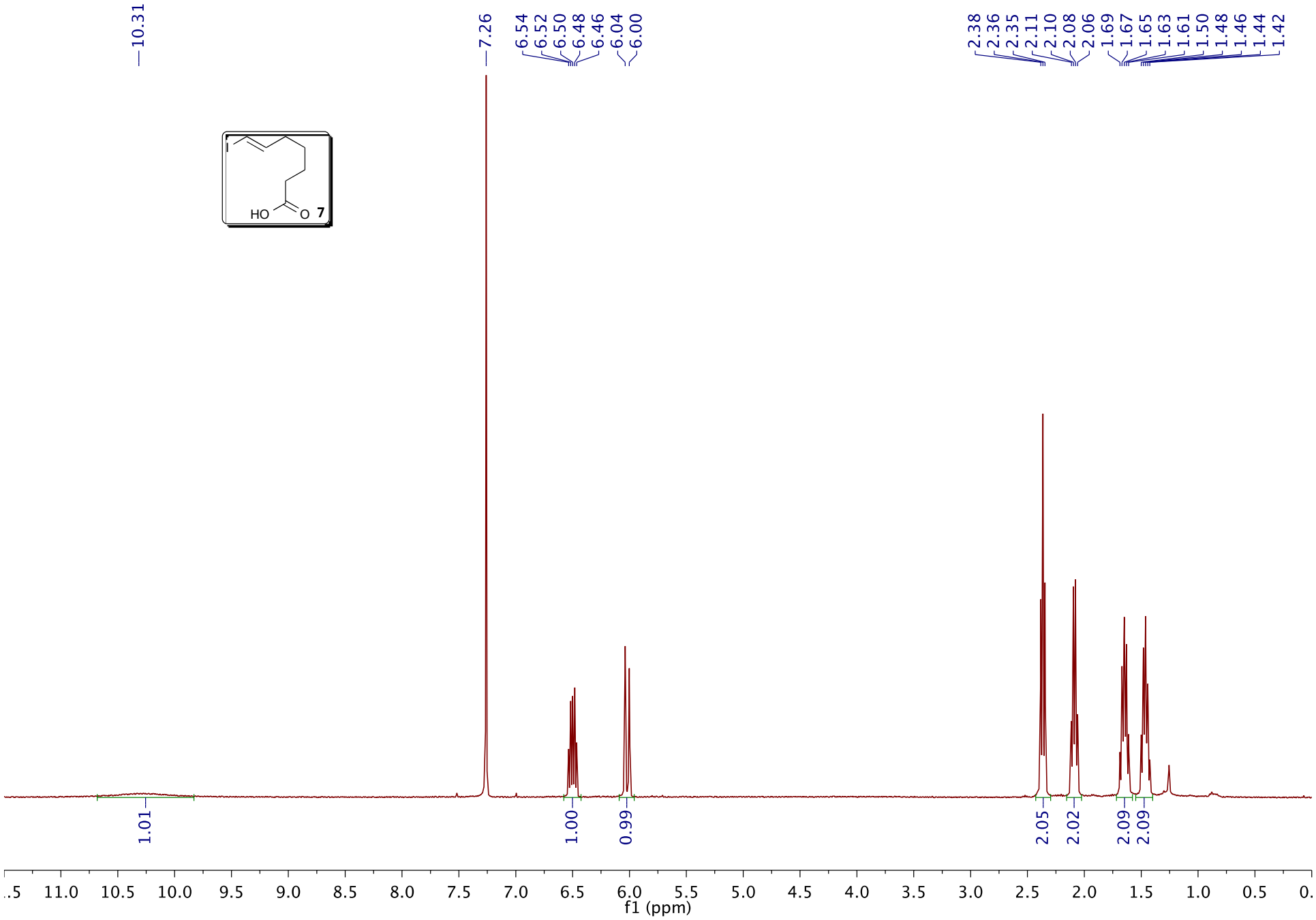
77.23 CDCl3
76.91 CDCl3
76.35
34.37
31.13
HO
O
6
f1 (ppm)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7.26
6.54
6.52
6.50
6.48
6.46
6.04
6.00
2.38
2.36
2.35
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2.08
2.06
1.69
1.67
1.65
1.63
1.61
1.50
1.48
1.46
1.44
1.42
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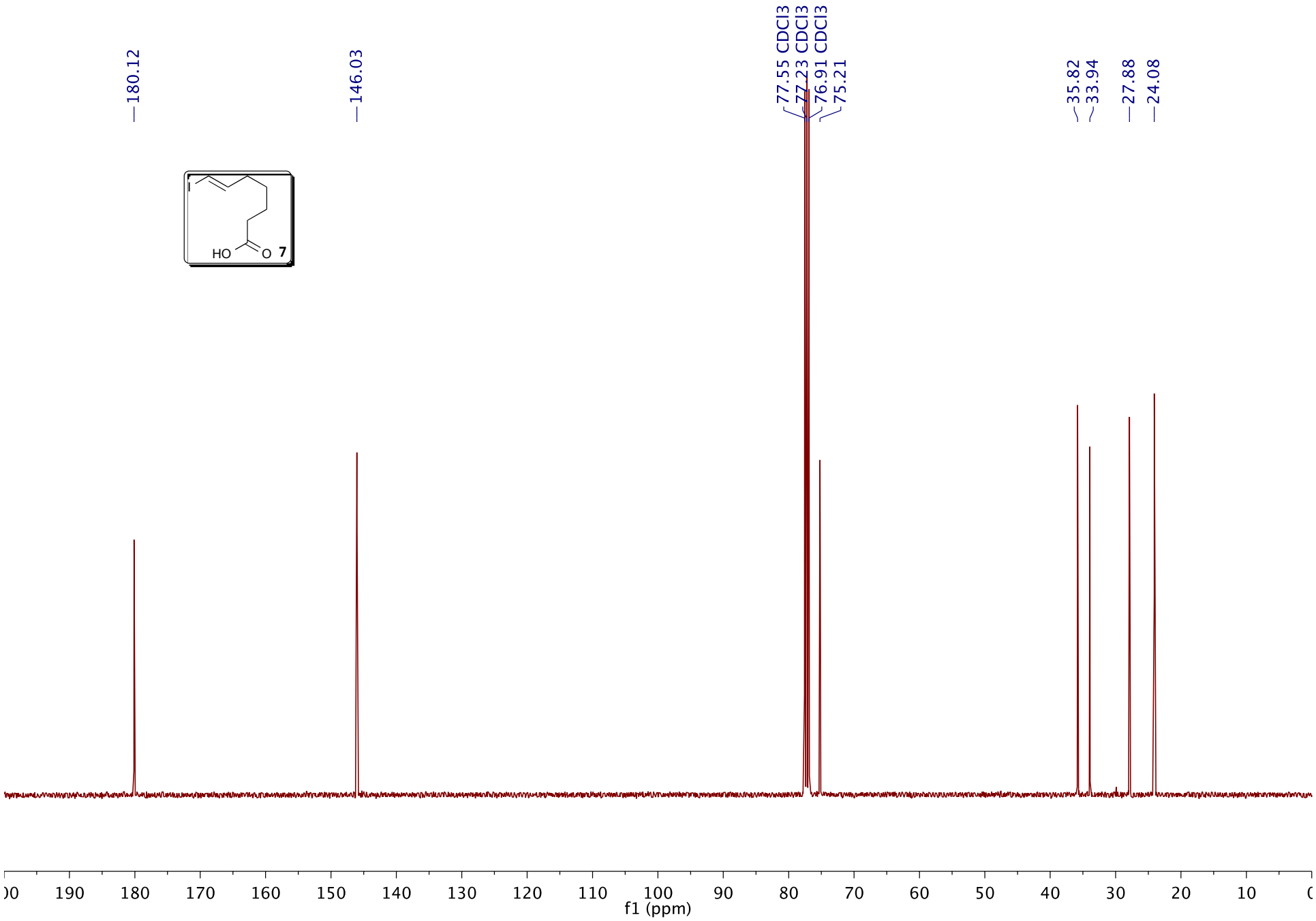
O
7
1.01
1.00
0.99
2.05
2.02
2.09
2.09
f1 (ppm)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27.88
24.08
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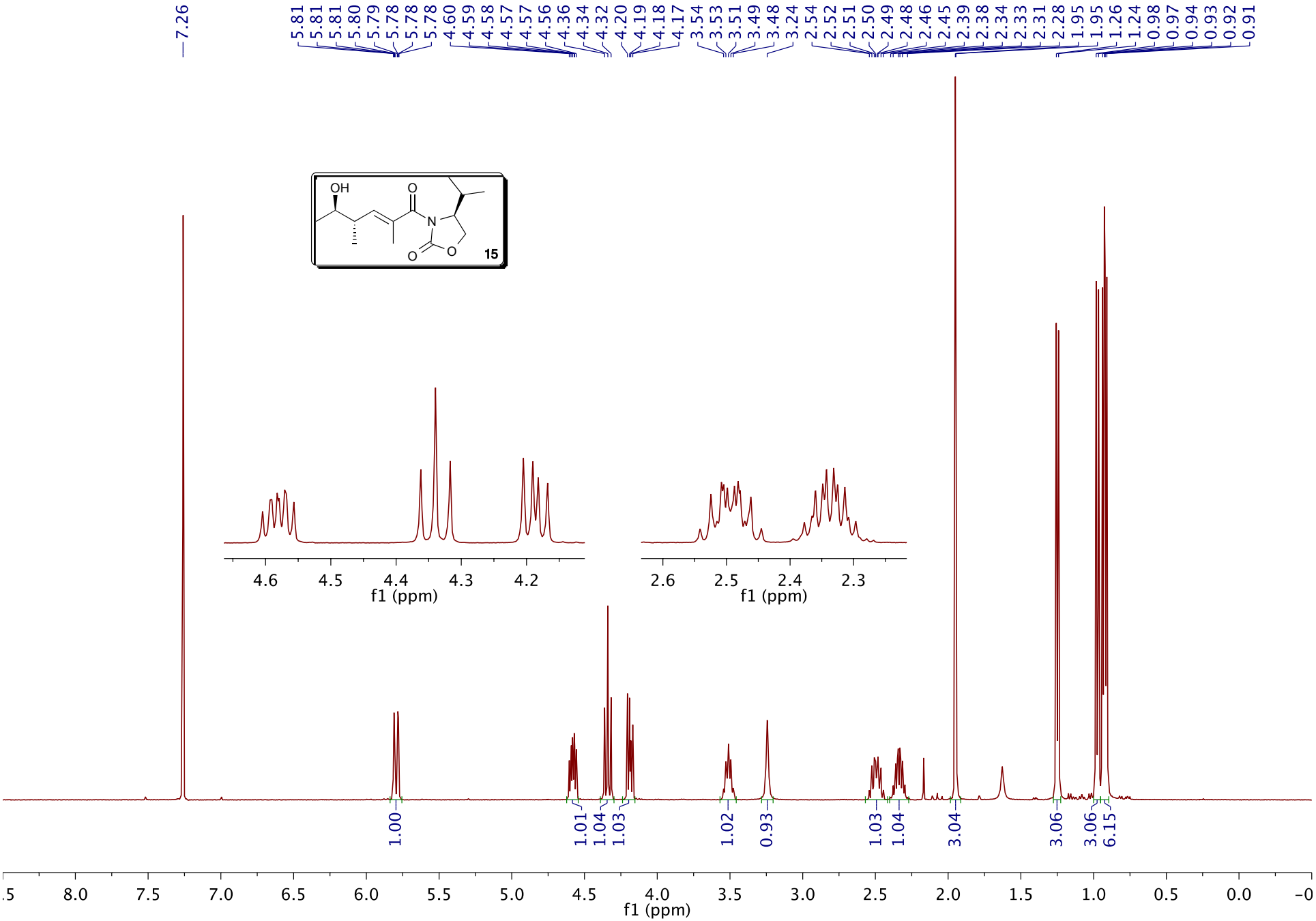
O
7
f1 (ppm)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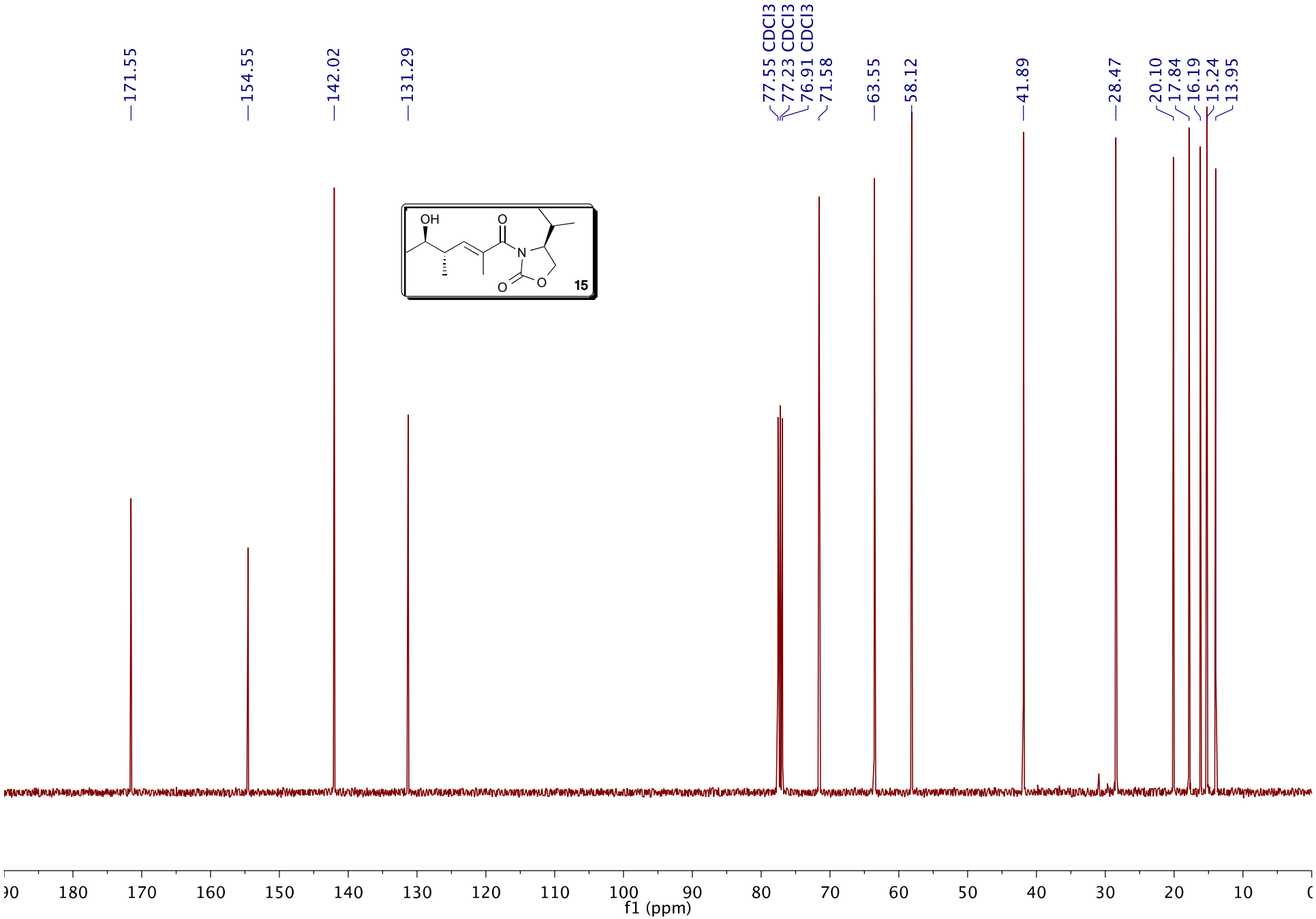
3.54 3.53 3.51 3.49 3.48 3.24
2.54 2.52 2.51 2.50 2.49 2.48 2.46 2.45 2.39 2.38 2.34 2.33 2.31 2.28 1.95 1.95 1.26 1.24 0.98 0.97 0.94 0.93 0.92 0.91
OH
O
N
O
O
15
4.6 4.5 4.4 4.3 4.2
f1 (ppm)
2.6 2.5 2.4 2.3
f1 (ppm)
1.00 1.01 1.04 1.03 1.02 0.93 1.03 1.04 3.04 3.06 3.06 6.15
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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154.55
142.02
131.29
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
71.58
63.55
58.12
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28.47
20.10
17.84
16.19
15.24
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N
O
O
15
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140
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120
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100
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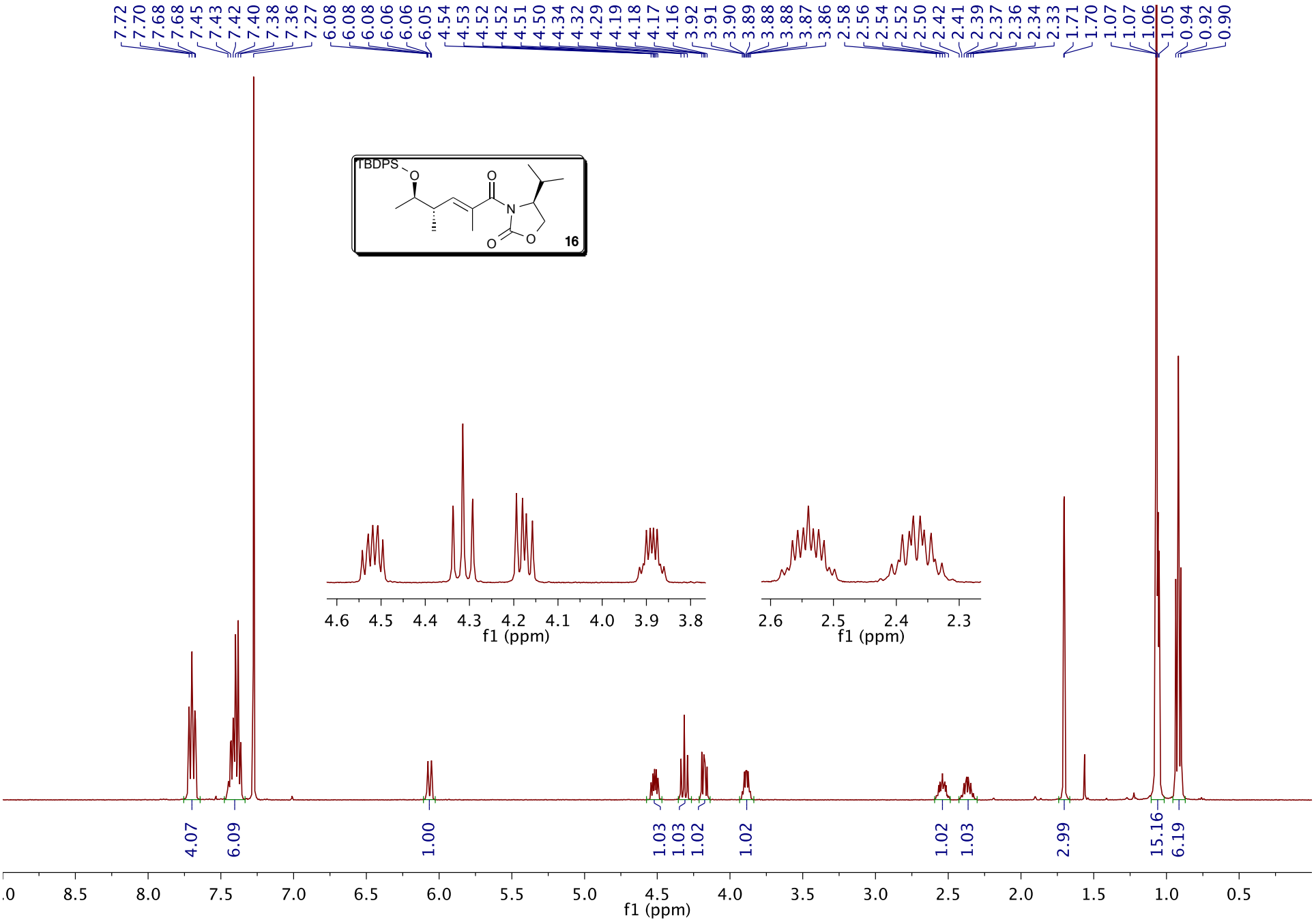
80
70
60
50
40
30
20
10
f1 (ppm)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4.54 4.53 4.52 4.52 4.51 4.50 4.34 4.32 4.29 4.19 4.18 4.17 4.16 3.92 3.91 3.90 3.89 3.88 3.88 3.87 3.86
2.58 2.56 2.54 2.52 2.50 2.42 2.41 2.39 2.37 2.36 2.34 2.33
1.71 1.70
1.07 1.07 1.06 1.05
0.94 0.92 0.90
TBDPS
O
O
N
O
O
16
4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8
f1 (ppm)
2.6 2.5 2.4 2.3
f1 (ppm)
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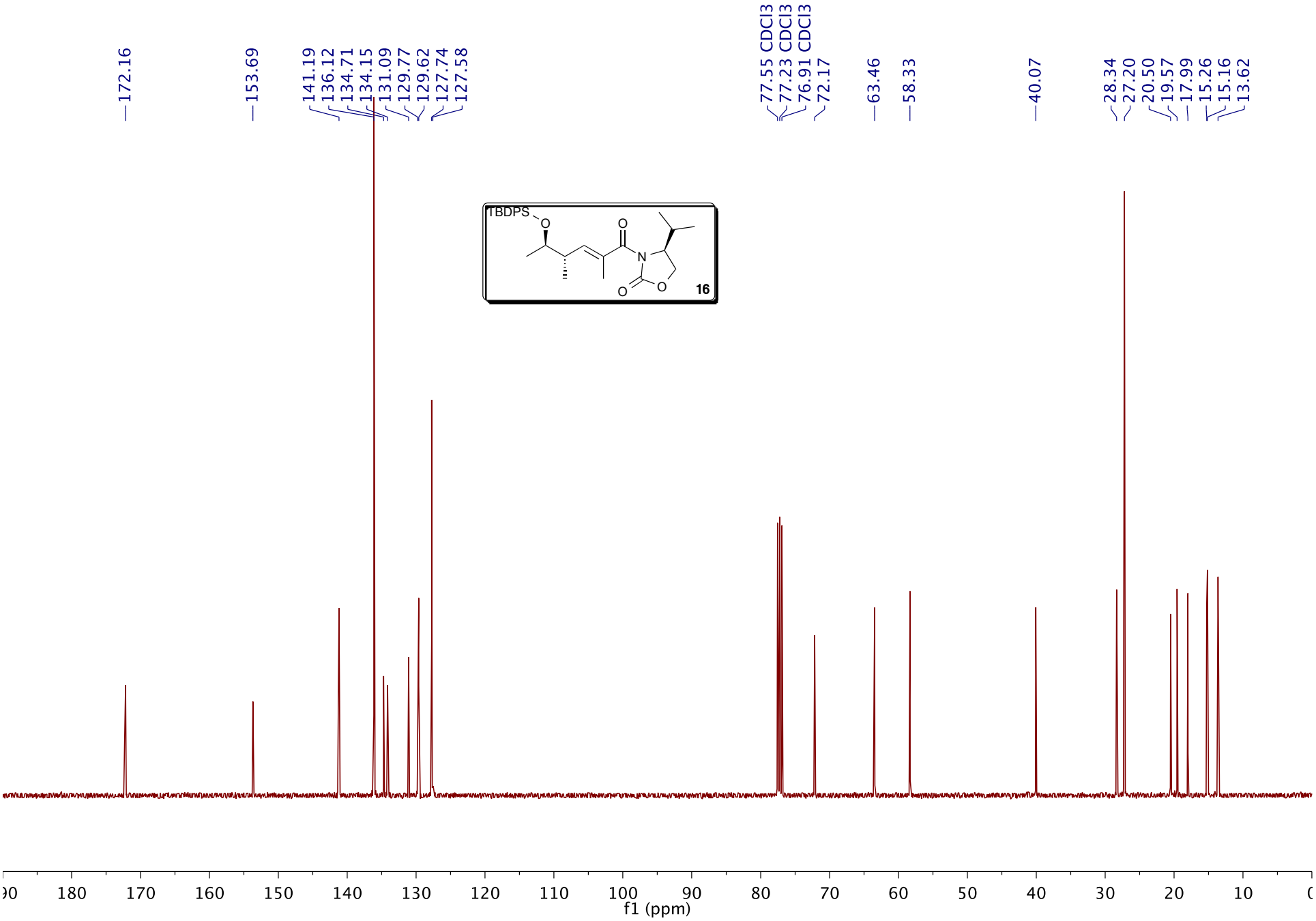
f1 (ppm)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127.58
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77.23 CDCl3
76.91 CDCl3
72.17
63.46
58.33
40.07
28.34
27.20
20.50
19.57
17.99
15.26
15.16
13.62
TBDPS
O
O
N
O
O
16
180
170
160
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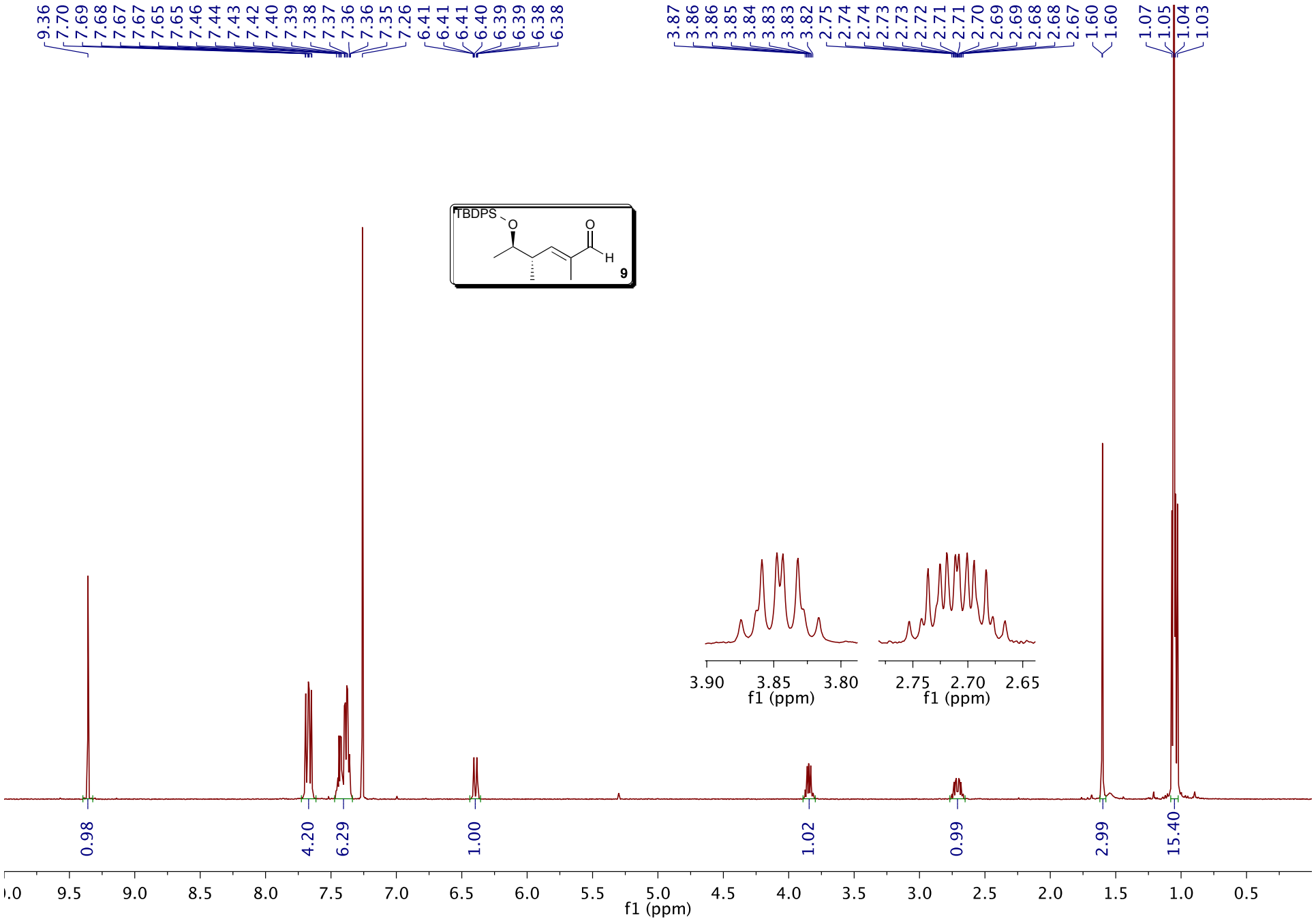
80
70
60
50
40
30
20
10
f1 (ppm)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3.87 3.86 3.86 3.85 3.84 3.83 3.83 3.82 2.75 2.74 2.74 2.73 2.73 2.72 2.71 2.71 2.70 2.69 2.69 2.68 2.68 2.67 1.60 1.60
1.07 1.05 1.04 1.03
TBDPS
O
O
H
9
3.90 3.85 3.80
f1 (ppm)
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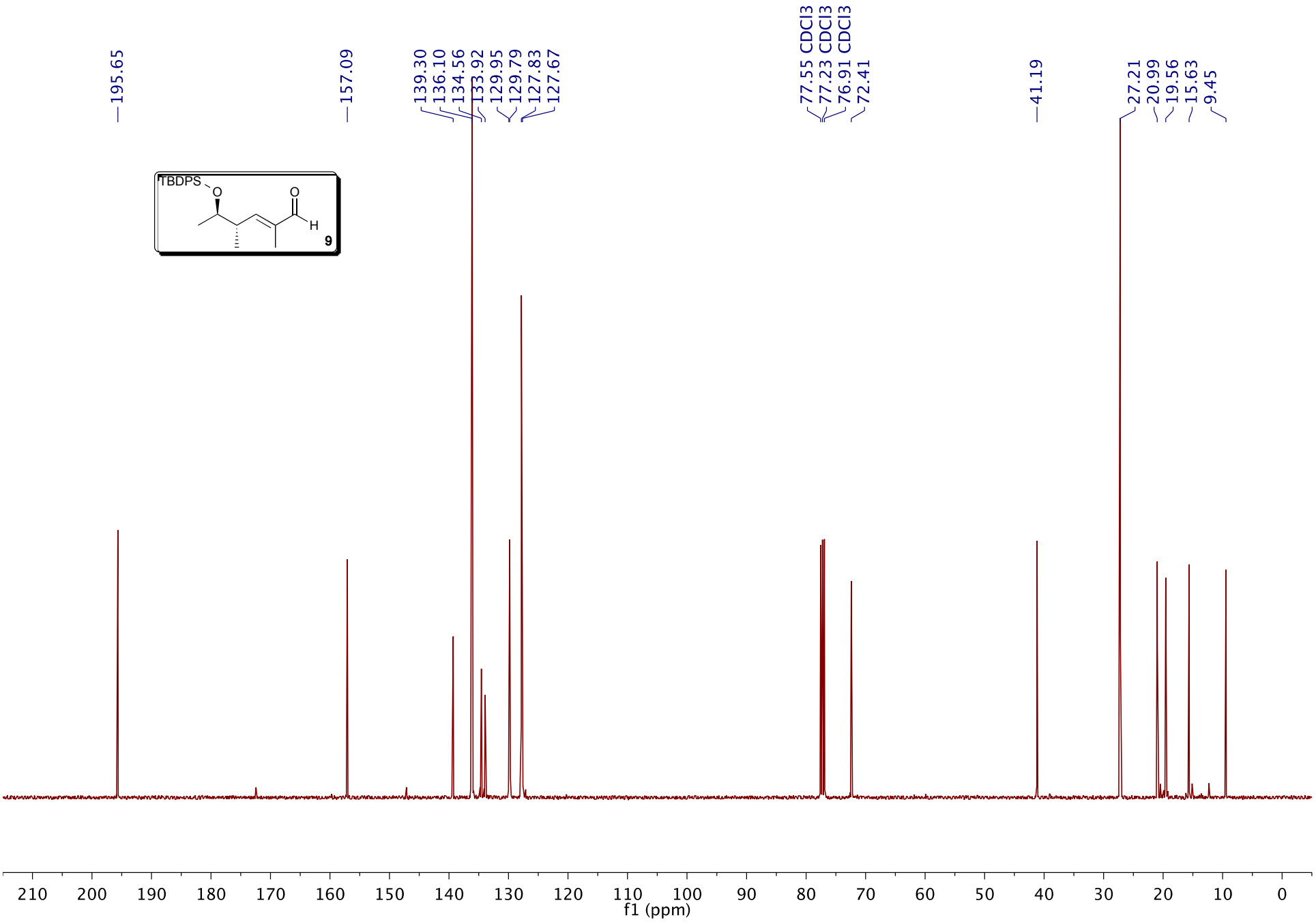
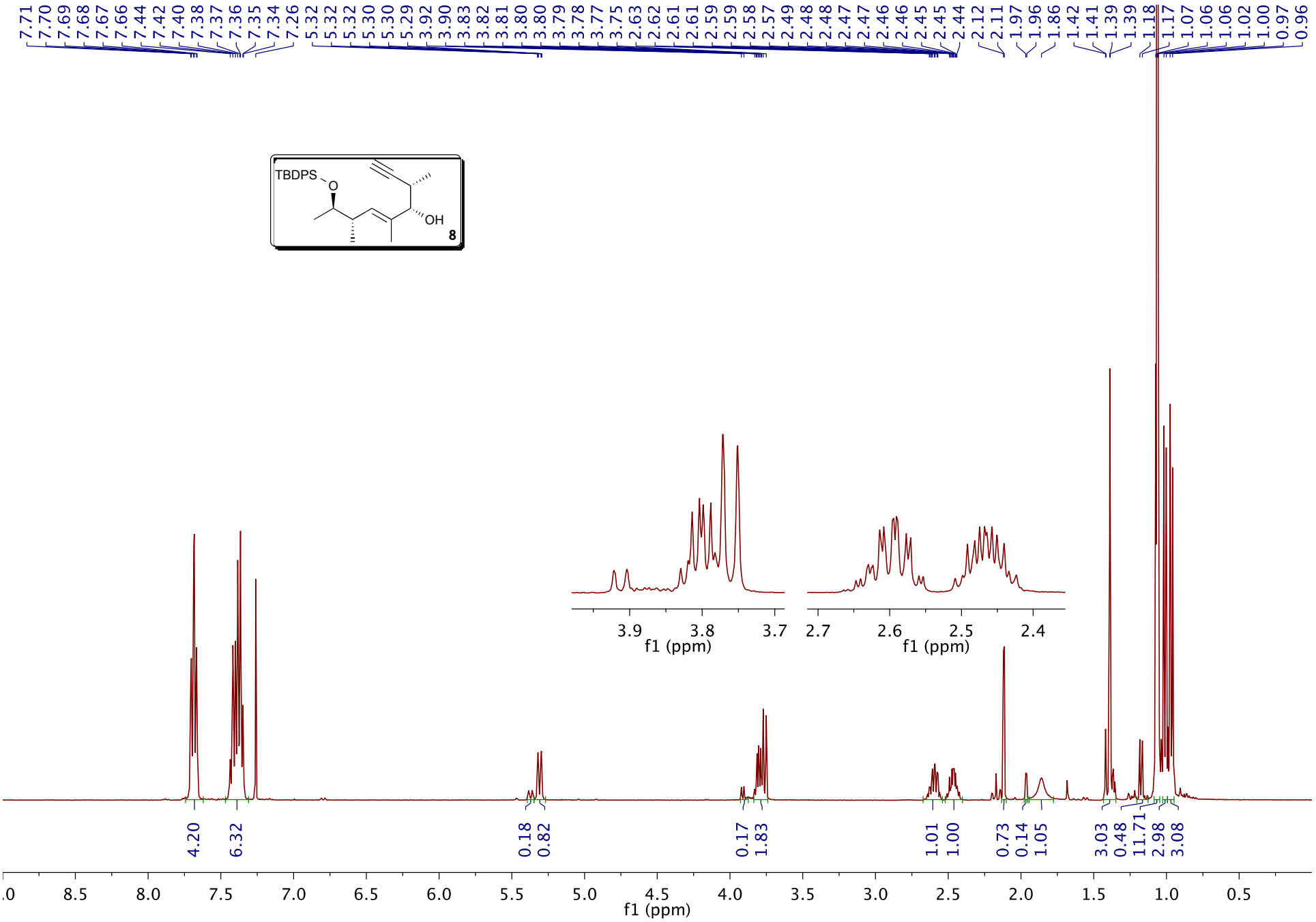
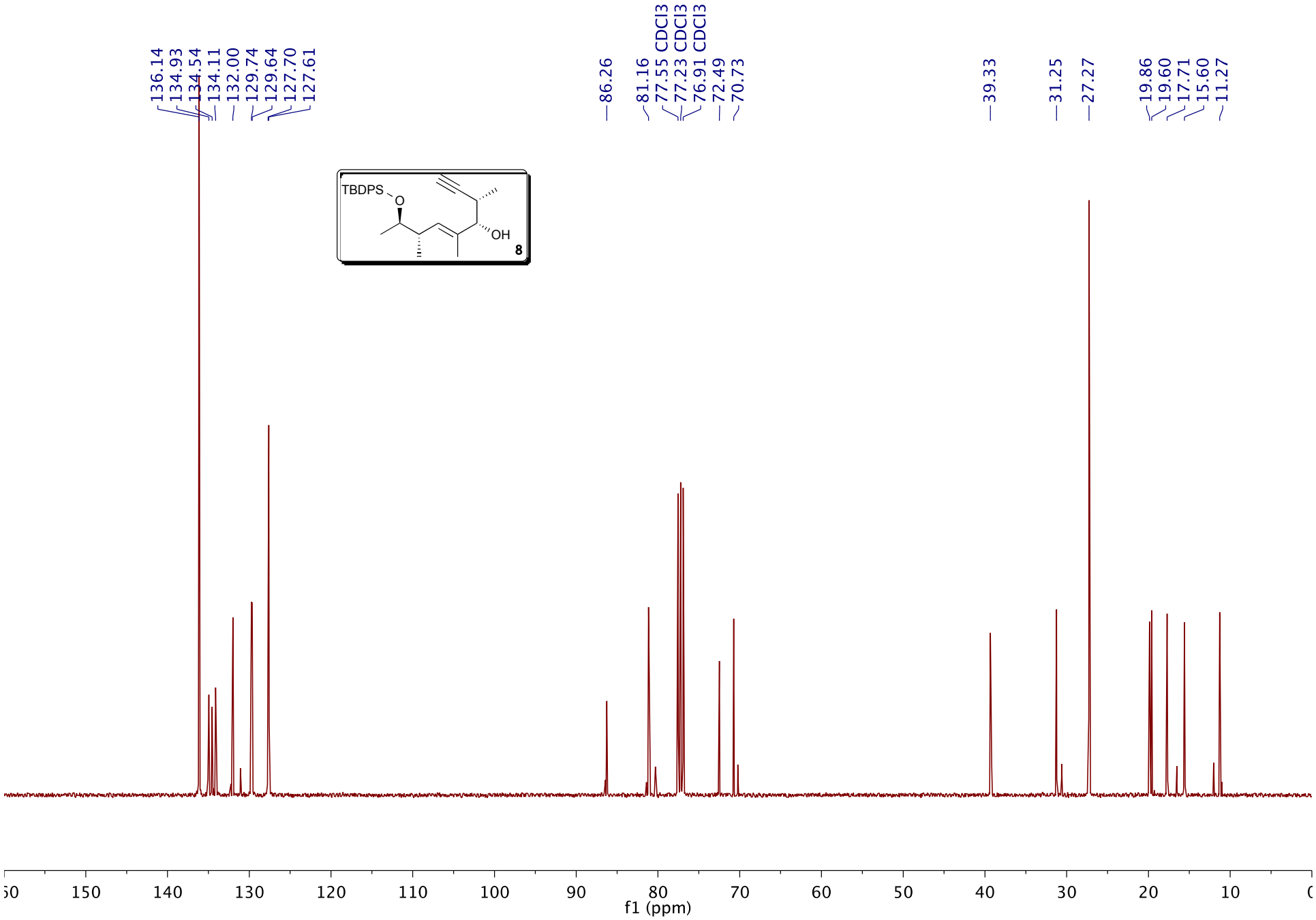
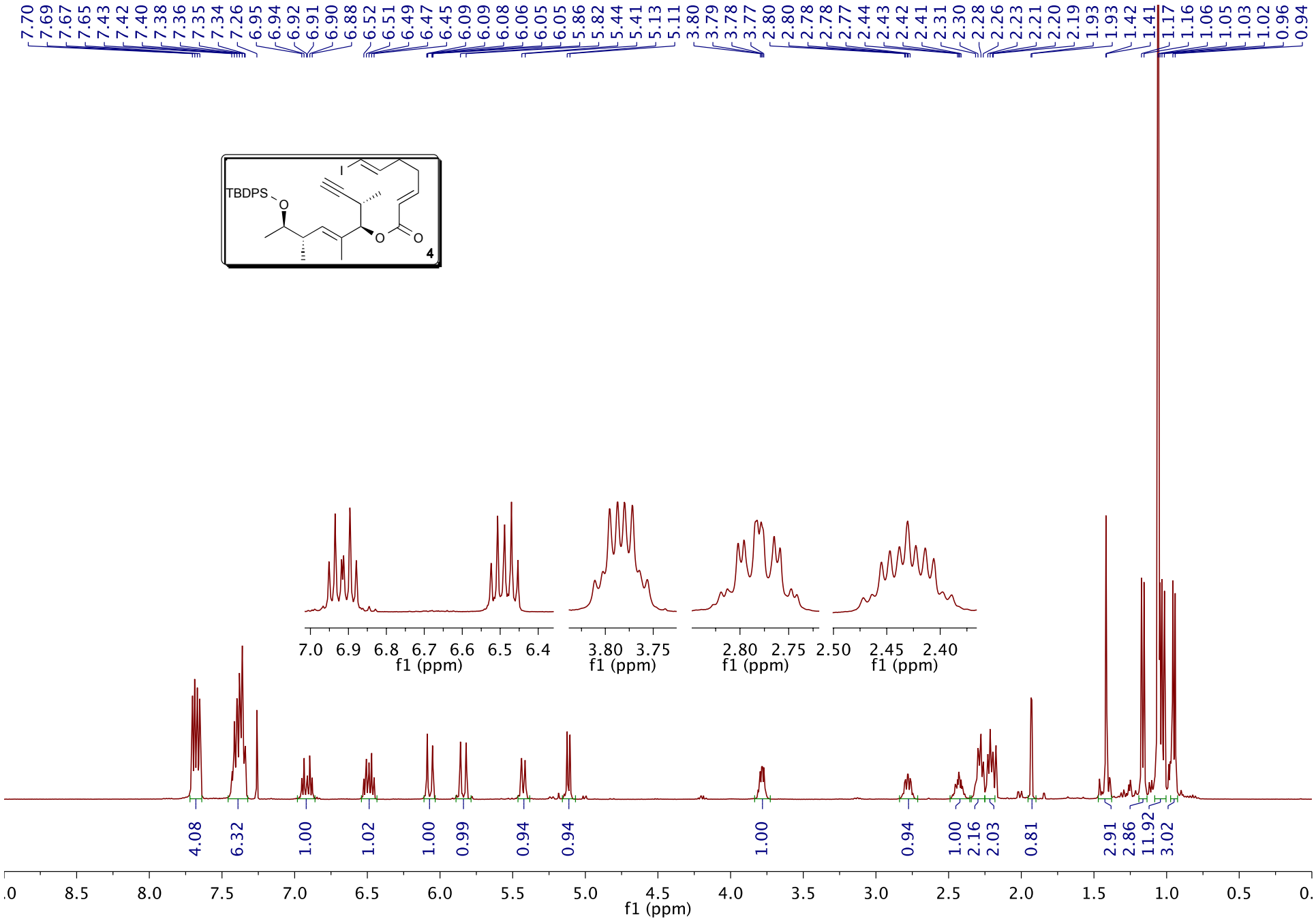
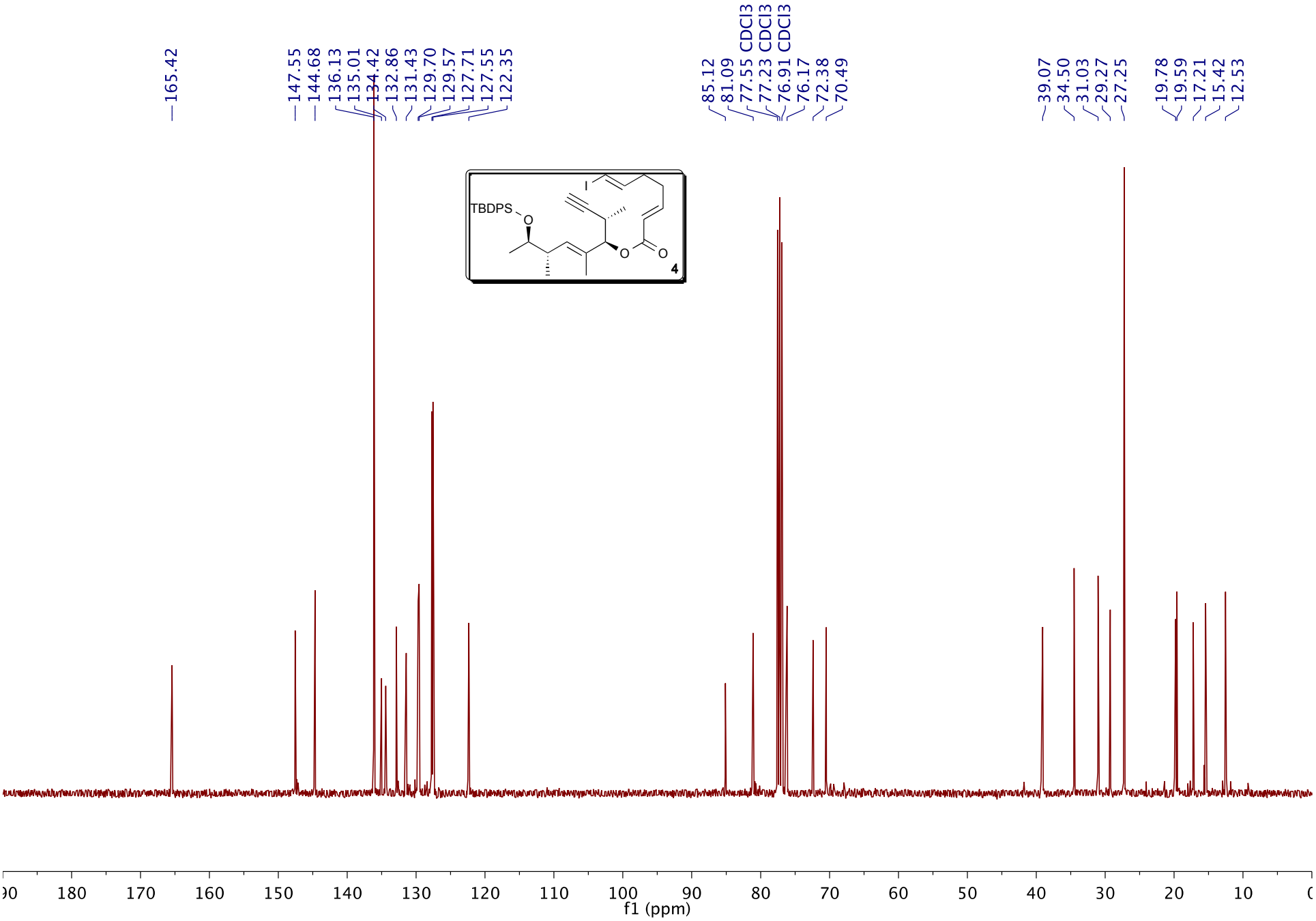
f1 (ppm)
0.98 4.20 6.29 1.00 1.02 0.99 2.99 15.40
f1 (ppm)

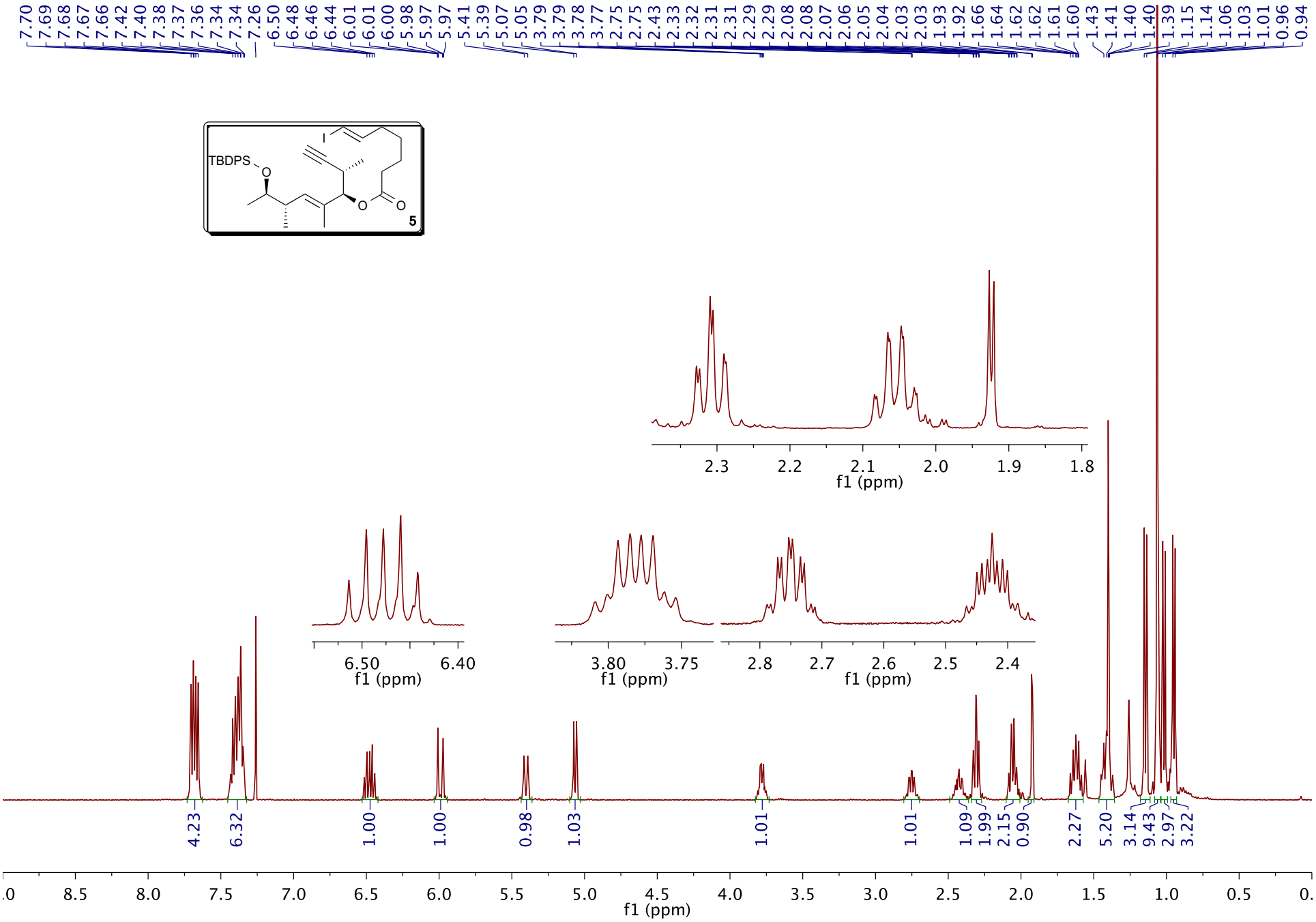

195.65
157.09
139.30
136.10
134.56
133.92
129.95
129.79
127.83
127.67
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
72.41
41.19
27.21
20.99
19.56
15.63
9.45
TBDPS
O
O
H
9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

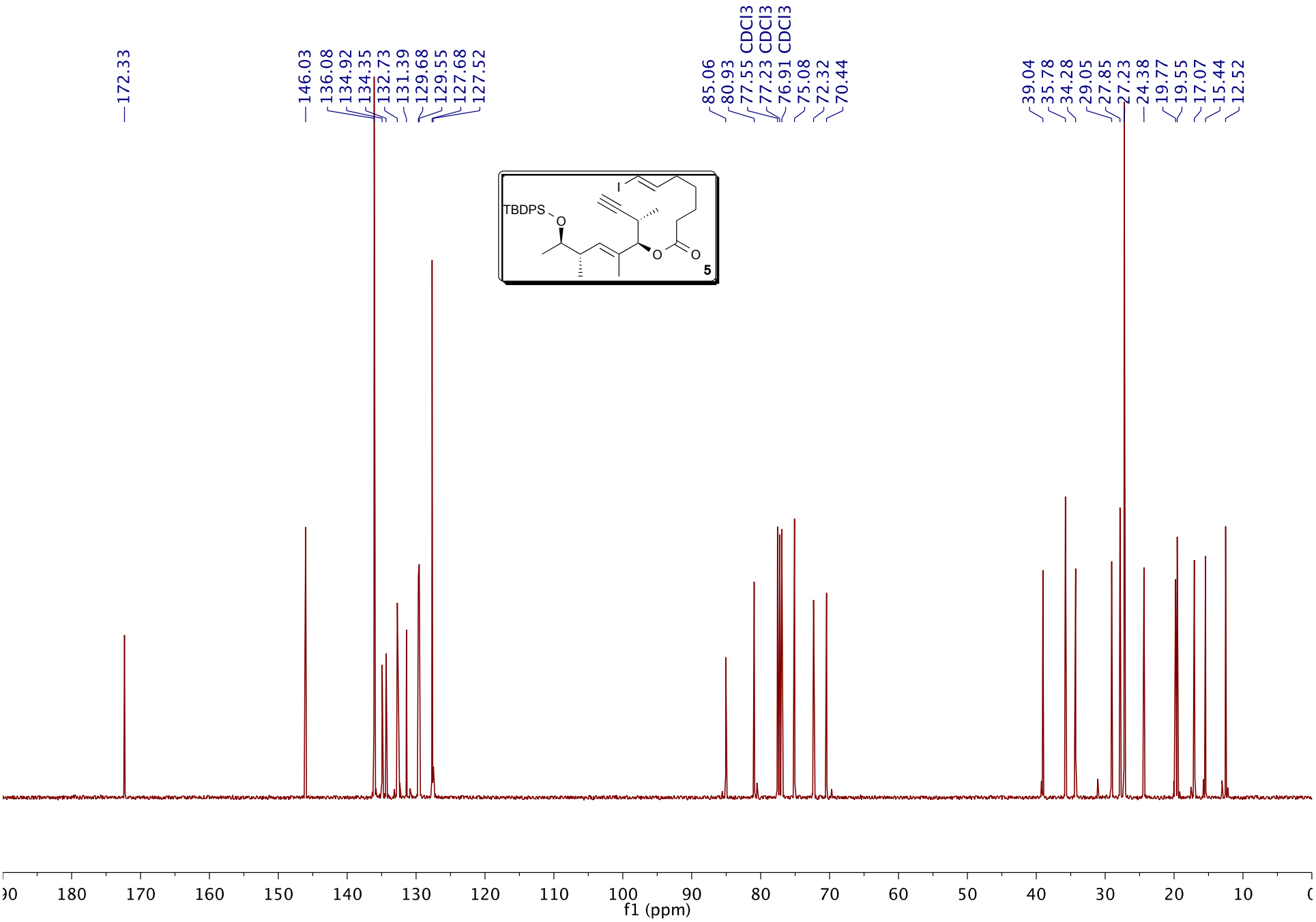

7.71 7.70 7.69 7.68 7.67 7.66 7.44 7.42 7.40 7.38 7.37 7.36 7.35 7.34 7.26
5.32 5.32 5.32 5.30 5.30 5.29 3.92 3.90 3.83 3.82 3.81 3.80 3.80 3.79 3.78 3.77 3.75 2.63 2.62 2.61 2.61 2.59 2.59 2.58 2.57 2.49 2.48 2.48 2.47 2.47 2.46 2.46 2.45 2.45 2.44 2.12 2.11 1.97 1.96 1.86 1.42 1.41 1.39 1.39 1.18 1.17 1.07 1.06 1.06 1.02 1.00 0.97 0.96
TBDPS
O
OH
8
3.9 3.8 3.7
f1 (ppm)
2.7 2.6 2.5 2.4
f1 (ppm)
4.20 6.32 0.18 0.82 0.17 1.83 1.01 1.00 0.73 0.14 1.05 3.03 0.48 11.71 2.98 3.08
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

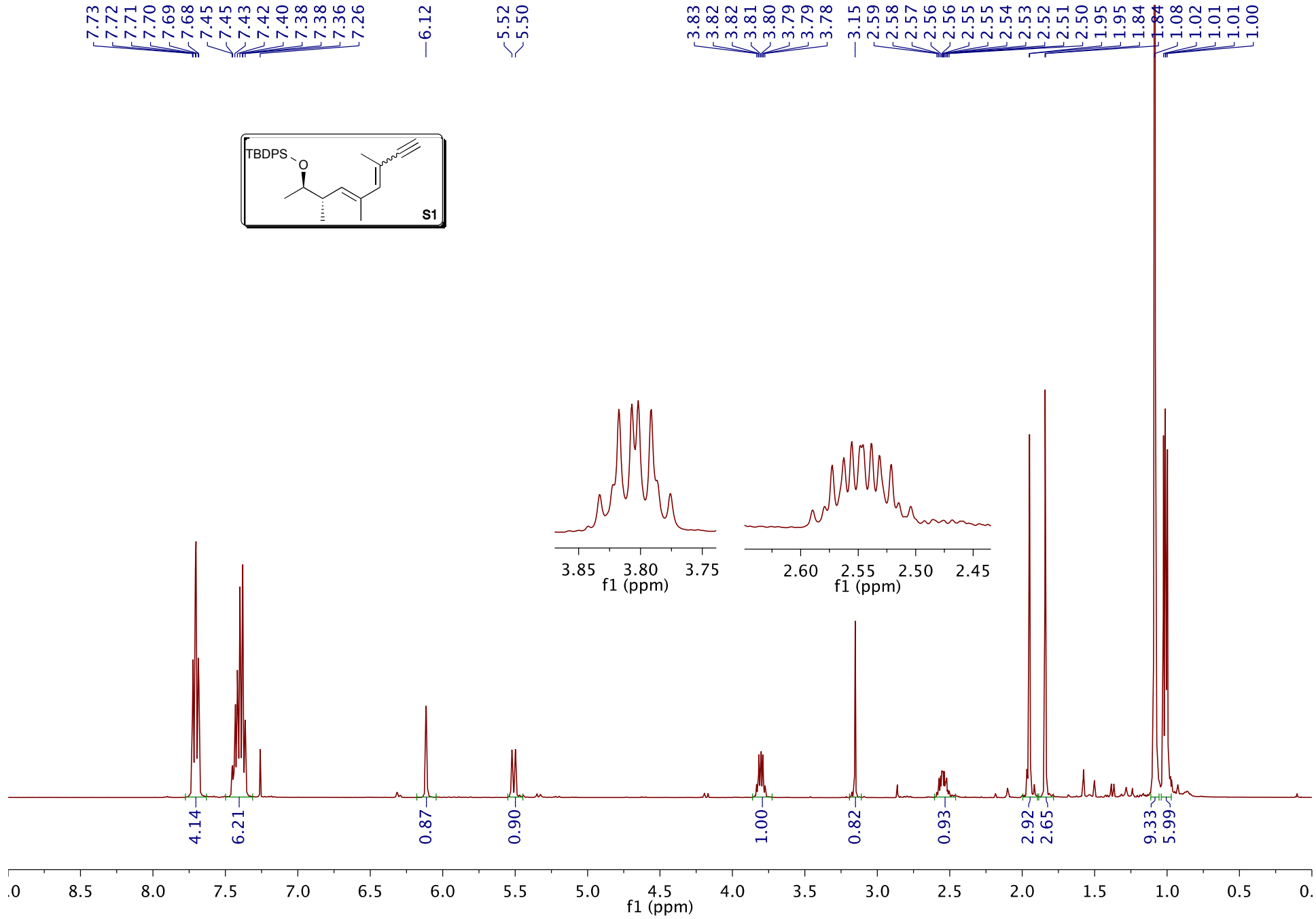

136.14
134.93
134.54
134.11
132.00
129.74
129.64
127.70
127.61
86.26
81.16
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
72.49
70.73
39.33
31.25
27.27
19.86
19.60
17.71
15.60
11.27
TBDPS
O
OH
8
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

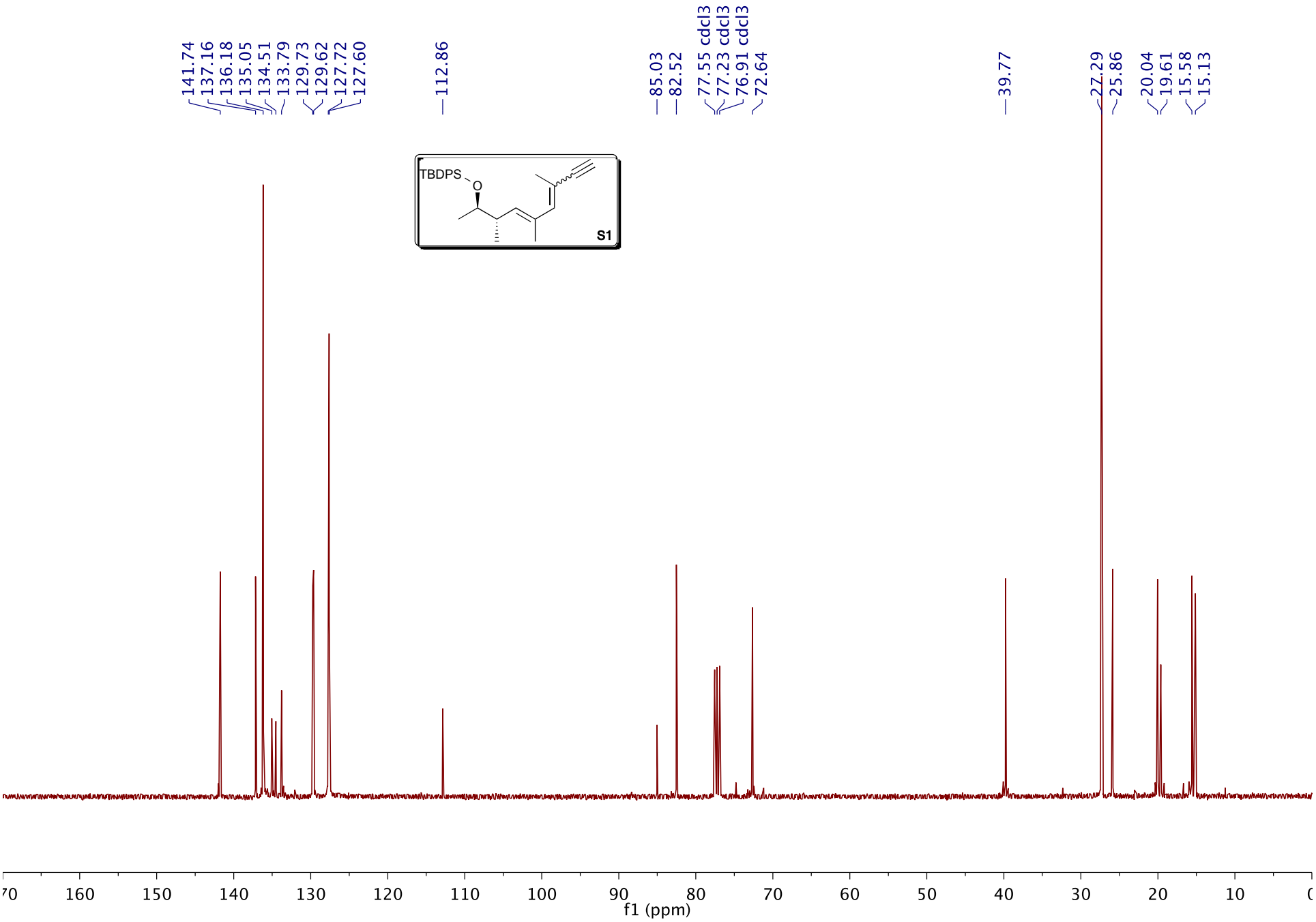

7.70 7.69 7.67 7.65 7.43 7.42 7.40 7.38 7.36 7.35 7.34 7.26 6.95 6.94 6.92 6.91 6.90 6.88 6.52 6.51 6.49 6.47 6.45 6.09 6.09 6.08 6.06 6.05 6.05 5.86 5.82 5.44 5.41 5.13 5.11 3.80 3.79 3.78 3.77 2.80 2.80 2.78 2.78 2.77 2.44 2.43 2.42 2.41 2.31 2.30 2.28 2.26 2.23 2.21 2.20 2.19 1.93 1.93 1.42 1.41 1.17 1.16 1.06 1.05 1.03 1.02 0.96 0.94
TBDPS
O
I
O
O
4
7.0 6.9 6.8 6.7 6.6 6.5 6.4
f1 (ppm)
3.80 3.75
f1 (ppm)
2.80 2.75 2.50 2.45 2.40
f1 (ppm)
4.08 6.32 1.00 1.02 1.00 0.99 0.94 0.94 1.00 0.94 1.00 2.16 2.03 0.81 2.91 2.86 11.92 3.02
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

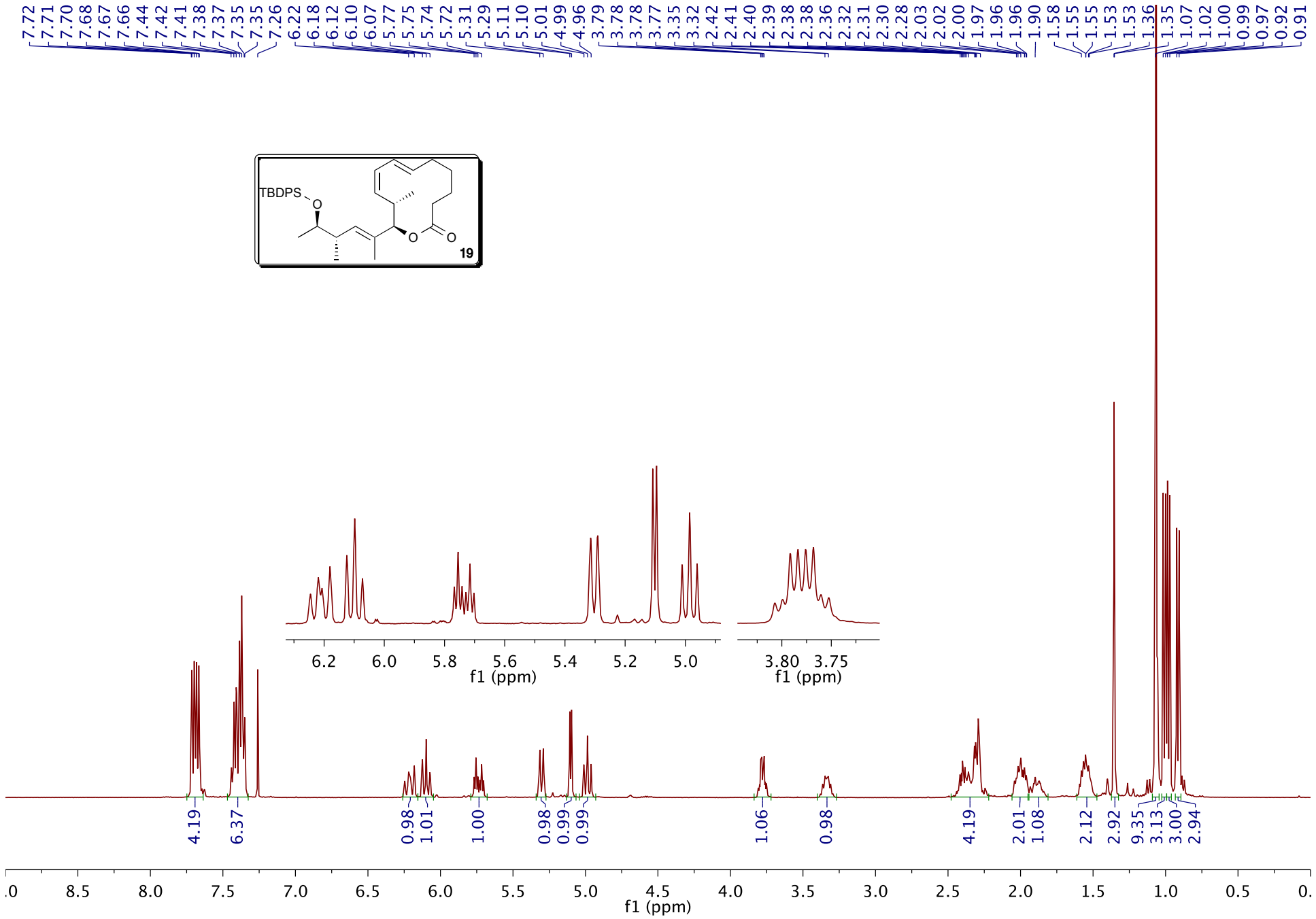

165.42
147.55
144.68
136.13
135.01
134.42
132.86
131.43
129.70
129.57
127.71
127.55
122.35
85.12
81.09
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
76.17
72.38
70.49
39.07
34.50
31.03
29.27
27.25
19.78
19.59
17.21
15.42
12.53
TBDPS
O
I
O
O
4
f1 (ppm)

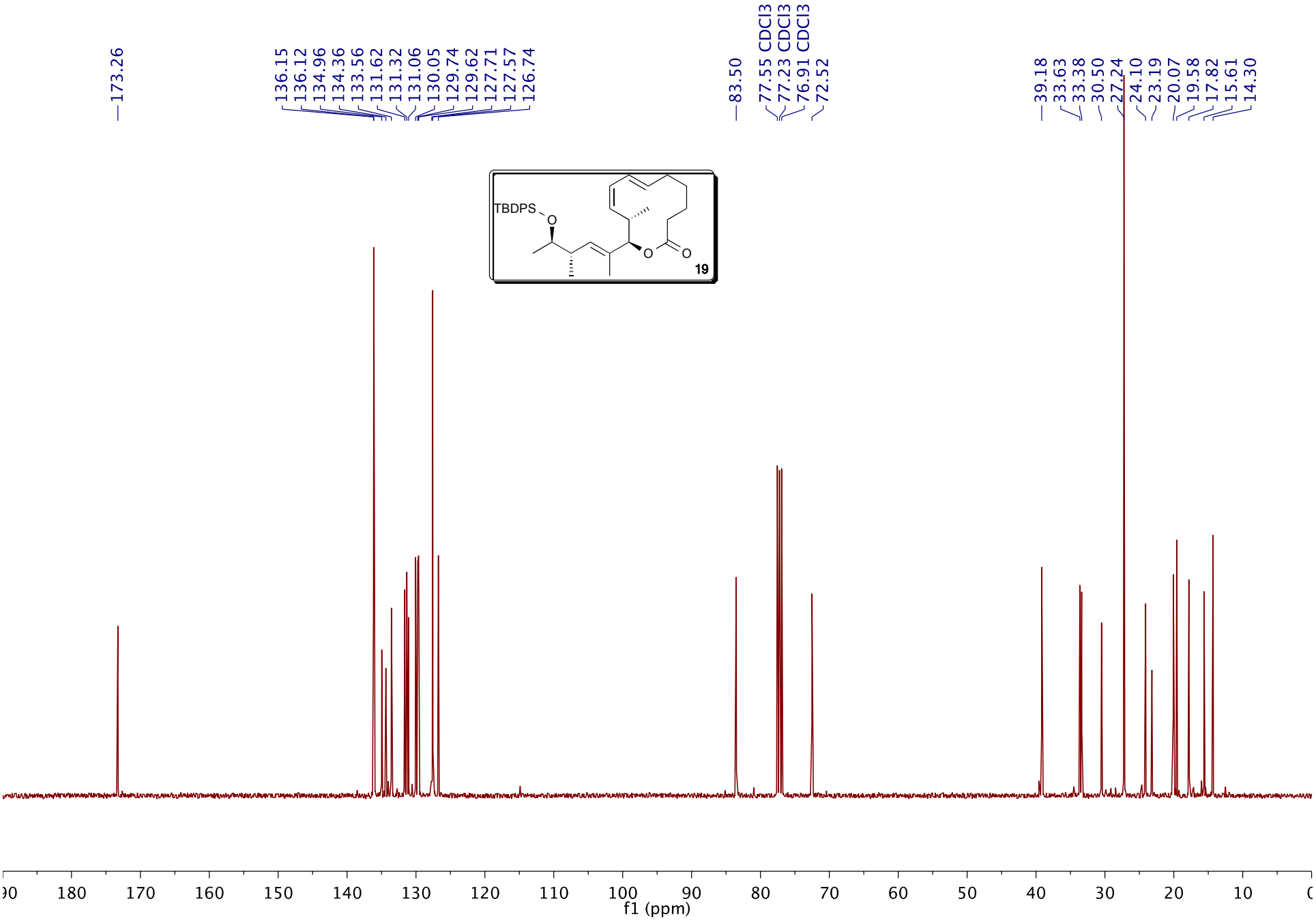

7.70 7.69 7.68 7.67 7.66 7.42 7.40 7.38 7.37 7.36 7.34 7.34 7.26 6.50 6.48 6.46 6.44 6.01 6.01 6.00 5.98 5.97 5.97 5.41 5.39 5.07 5.05 3.79 3.79 3.78 3.77 2.75 2.75 2.43 2.33 2.32 2.31 2.31 2.29 2.29 2.08 2.08 2.07 2.06 2.05 2.04 2.03 2.03 1.93 1.92 1.66 1.64 1.62 1.62 1.61 1.60 1.43 1.41 1.40 1.40 1.39 1.15 1.14 1.06 1.03 1.01 0.96 0.94
TBDPS
O
I
O
O
5
2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
6.50 6.40
f1 (ppm)
3.80 3.75
f1 (ppm)
2.8 2.7 2.6 2.5 2.4
f1 (ppm)
4.23 6.32 1.00 1.00 0.98 1.03 1.01 1.01 1.09 1.99 2.15 0.90 2.27 5.20 3.14 9.43 2.97 3.22
.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

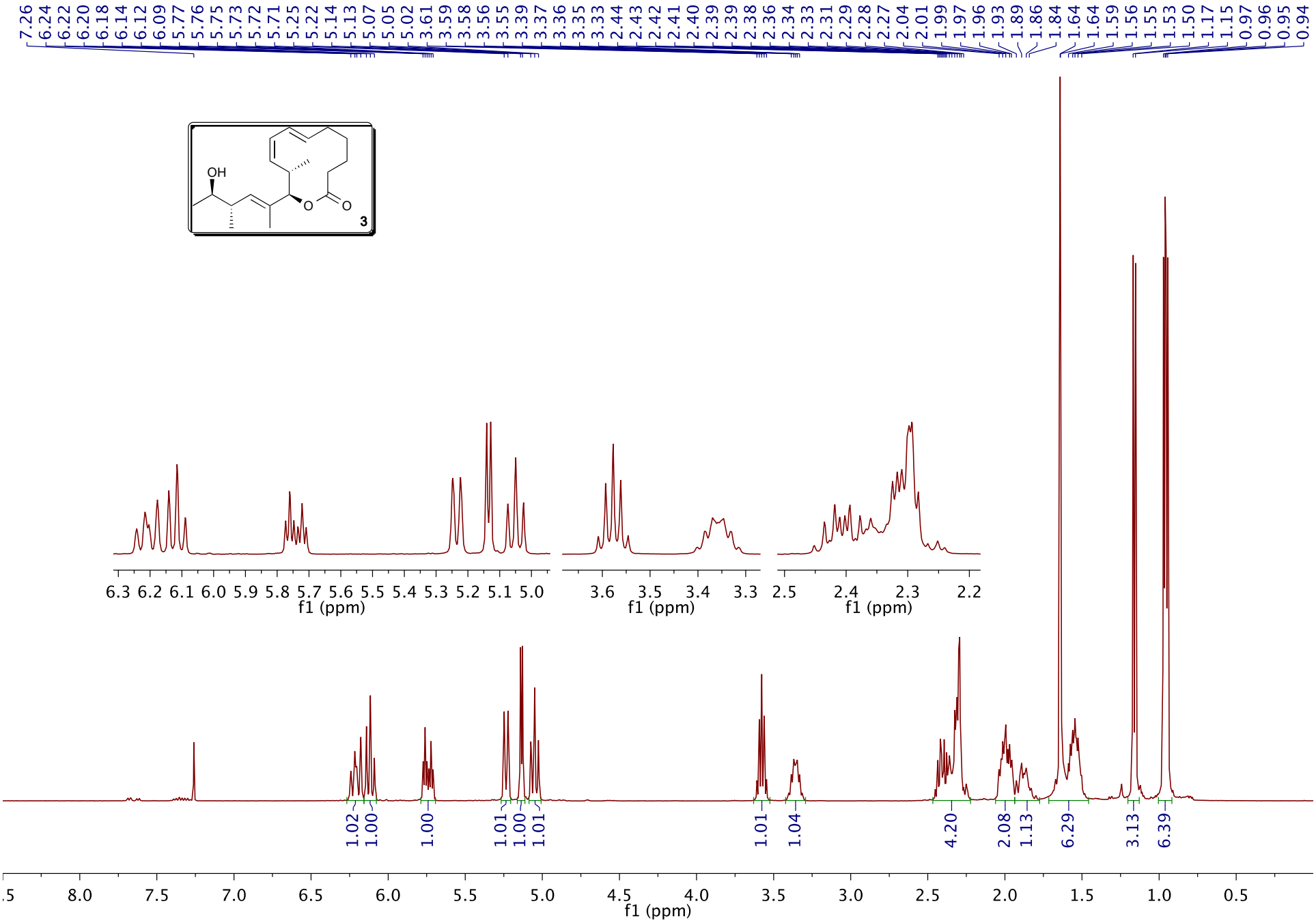

172.33
146.03
136.08
134.92
134.35
132.73
131.39
129.68
129.55
127.68
127.52
85.06
80.93
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
75.08
72.32
70.44
39.04
35.78
34.28
29.05
27.85
27.23
24.38
19.77
19.55
17.07
15.44
12.52
TBDPS
O
I
O
O
5
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

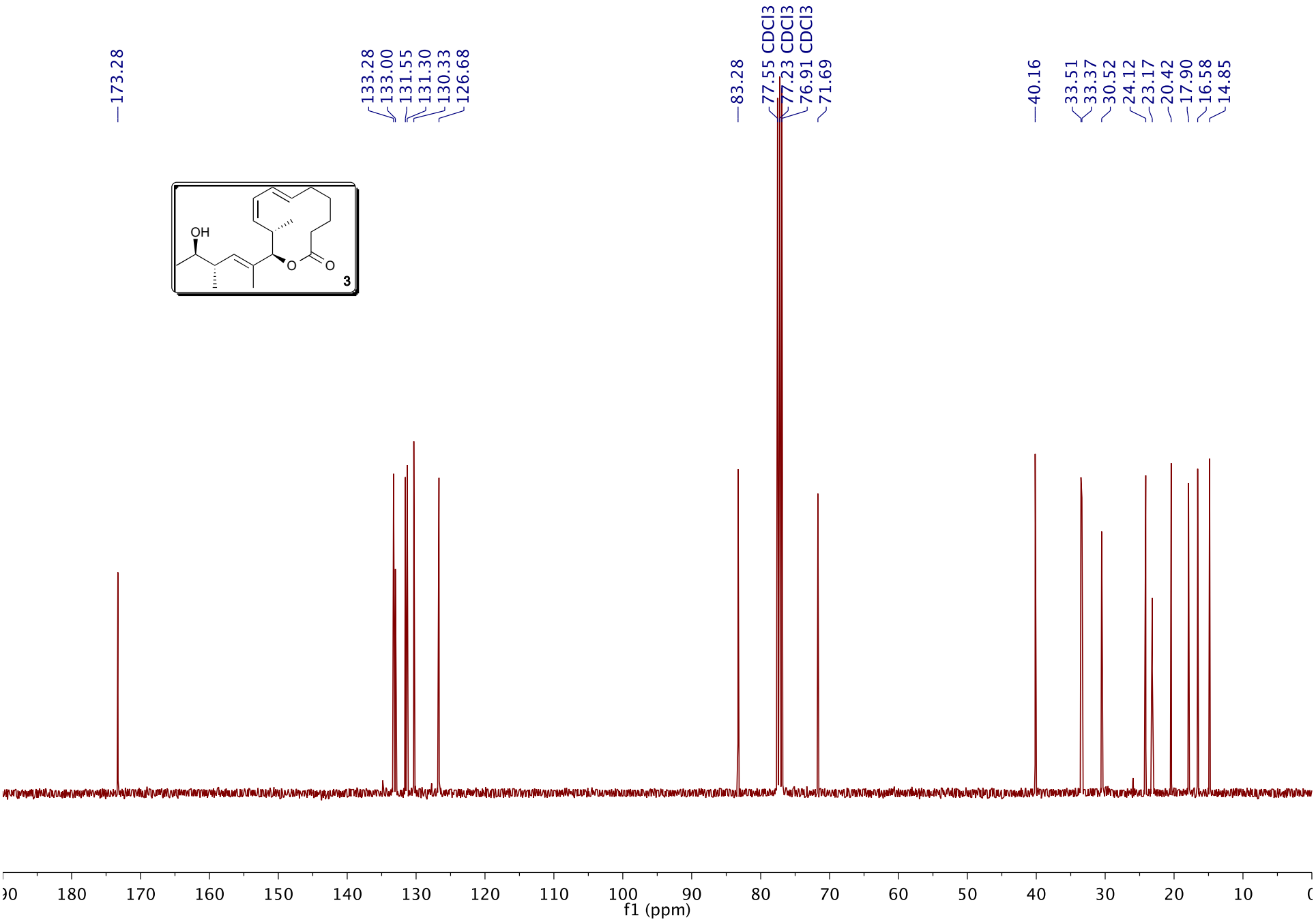

7.73 7.72 7.71 7.70 7.69 7.68 7.45 7.45 7.43 7.42 7.40 7.38 7.38 7.36 7.26
6.12
5.52 5.50
3.83 3.82 3.82 3.81 3.80 3.79 3.79 3.78
3.15
2.59 2.58 2.57 2.56 2.56 2.55 2.55 2.54 2.53 2.52 2.51 2.50
1.95 1.95 1.84 1.84
1.08 1.02 1.01 1.01 1.00
TBDPS
O
S1
3.85 3.80 3.75
f1 (ppm)
2.60 2.55 2.50 2.45
f1 (ppm)
4.14 6.21 0.87 0.90 1.00 0.82 0.93 2.92 2.65 9.33 5.99
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

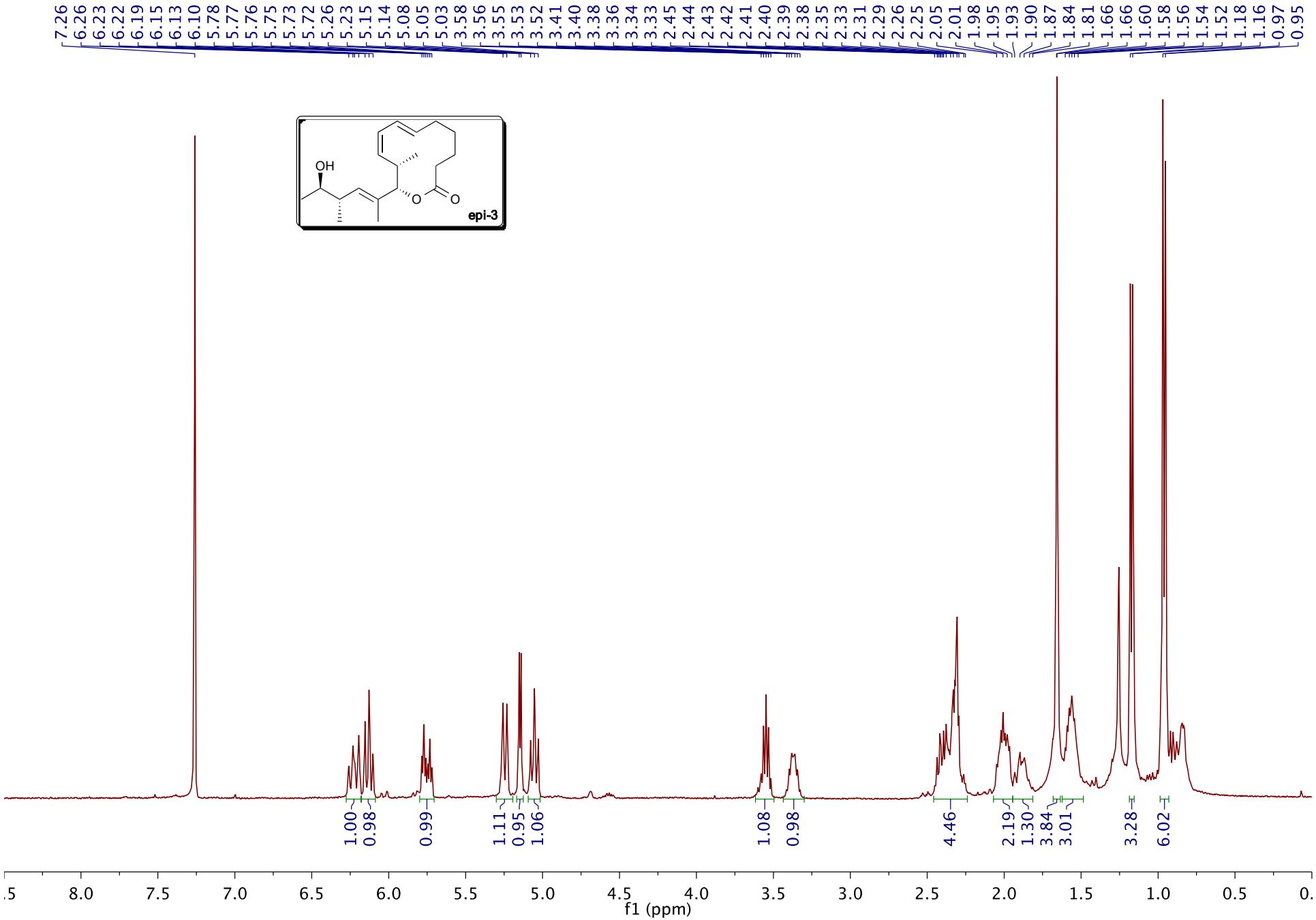

141.74
137.16
136.18
135.05
134.51
133.79
129.73
129.62
127.72
127.60
112.86
85.03
82.52
77.55 cdcl3
77.23 cdcl3
76.91 cdcl3
72.64
39.77
27.29
25.86
20.04
19.61
15.58
15.13
TBDPS
O
S1
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.72 7.71 7.70 7.68 7.67 7.66 7.44 7.42 7.41 7.38 7.37 7.35 7.35 7.26
6.22 6.18 6.12 6.10 6.07 5.77 5.75 5.74 5.72 5.31 5.29 5.11 5.10 5.01 4.99 4.96
3.79 3.78 3.78 3.77 3.35 3.32 2.42 2.41 2.40 2.39 2.38 2.38 2.36 2.32 2.31 2.30 2.28 2.03 2.02 2.00 1.97 1.96 1.96 1.90
1.58 1.55 1.55 1.53 1.53 1.36 1.35 1.07 1.02 1.00 0.99 0.97 0.92 0.91
TBDPS
O
O
O
19
6.2 6.0 5.8 5.6 5.4 5.2 5.0
f1 (ppm)
3.80 3.75
f1 (ppm)
4.19 6.37 0.98 1.01 1.00 0.98 0.99 0.99 1.06 0.98 4.19 2.01 1.08 2.12 2.92 9.35 3.13 3.00 2.94
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


173.26
136.15
136.12
134.96
134.36
133.56
131.62
131.32
131.06
130.05
129.74
129.62
127.71
127.57
126.74
83.50
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
72.52
39.18
33.63
33.38
30.50
27.24
24.10
23.19
20.07
19.58
17.82
15.61
14.30
TBDPS
O
O
O
19
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.26 6.24 6.22 6.20 6.18 6.14 6.12 6.09 5.77 5.76 5.75 5.73 5.72 5.71 5.25 5.22 5.14 5.13 5.07 5.05 5.02 3.61 3.59 3.58 3.56 3.55 3.39 3.37 3.36 3.35 3.33 2.44 2.43 2.42 2.41 2.40 2.39 2.39 2.38 2.36 2.34 2.33 2.31 2.29 2.28 2.27 2.04 2.01 1.99 1.97 1.96 1.93 1.89 1.86 1.84 1.64 1.64 1.59 1.56 1.55 1.53 1.50 1.17 1.15 0.97 0.96 0.95 0.94
OH
O
O
3
6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0
f1 (ppm)
3.6 3.5 3.4 3.3
f1 (ppm)
2.5 2.4 2.3 2.2
f1 (ppm)
1.02 1.00 1.00 1.01 1.00 1.01 1.01 1.04 4.20 2.08 1.13 6.29 3.13 6.39
.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


173.28
133.28
133.00
131.55
131.30
130.33
126.68
83.28
77.55 CDCl3
77.23 CDCl3
76.91 CDCl3
71.69
40.16
33.51
33.37
30.52
24.12
23.17
20.42
17.90
16.58
14.85
OH
O
O
3
f1 (ppm)


7.26 6.26 6.23 6.22 6.19 6.15 6.13 6.10 5.78 5.77 5.76 5.75 5.73 5.72 5.26 5.23 5.15 5.14 5.08 5.05 5.03 3.58 3.56 3.55 3.53 3.52 3.41 3.40 3.38 3.36 3.34 3.33 2.45 2.44 2.43 2.42 2.41 2.40 2.39 2.38 2.35 2.33 2.31 2.29 2.26 2.25 2.05 2.01 1.98 1.95 1.93 1.90 1.87 1.84 1.81 1.66 1.60 1.58 1.56 1.54 1.52 1.18 1.16 0.97 0.95
OH
O
O
epi-3
1.00 0.98 0.99 1.11 0.95 1.06 1.08 0.98 4.46 2.19 1.30 3.84 3.01 3.28 6.02
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)