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Synthesis of an isomer of lycoplanine A via cascade cyclization to construct the spiro-N,O-acetal moiety

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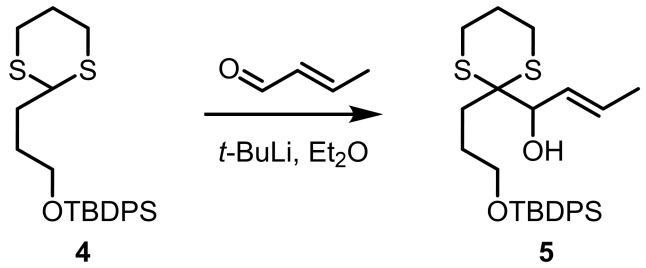
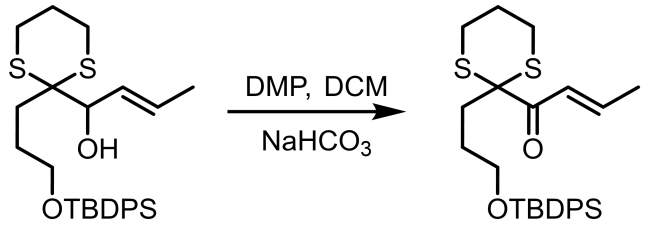
I General Information

All reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Methylene chloride (CH_2Cl_2), acetonitrile and toluene were taken directly from the solvent treatment system and used immediately without further purification. Diethyl ether and tetrahydrofuran (THF) were distilled immediately before use from sodium-benzophenone ketyl. External bath temperatures were used to record all reaction temperatures. Silica gel (300~400 mesh) and petroleum ether, EtOAc, CH_2Cl_2 and MeOH are used for product purification by flash column chromatography. NMR spectra were recorded on Bruker 300 MHz, 400 MHz and 600 MHz (400 MHz and 600 MHz for ^1H NMR, 76MHz, 101 MHz and 151 MHz for ^{13}C NMR) spectrometers. Proton chemical shifts are reported relative to a residual solvent peak ($CDCl_3$ at 7.26 ppm, MeOD at 3.31 ppm) and carbon chemical shifts are reported relative to a residual solvent peak ($CDCl_3$ at 77.0 ppm). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. IR (KBr ν/cm^{-1}) is recorded on Agilent Cary 630 FTIP. High-resolution mass spectra (HRMS) were measured on a BruckerDaltonics Apex II 47e Specification (for HRMS).

II Experimental Procedures and Spectroscopic Data of Compounds

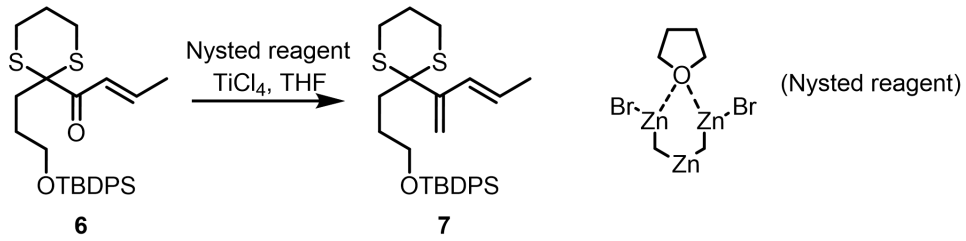


(*E*)-1-(2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-1,3-dithian-2-yl)but-2-en-1-ol (5). *t*-BuLi (29.5 mL, 38.4 mmol, 1.3 M in hexanes, 4.0 equiv) was added dropwise to a solution of **4** (4 g, 9.6 mmol, 1.0 equiv) in Et_2O (30 mL) at –78 ºC and the mixture was stirred for 10 min at this temperature before stirring at –20 ºC for 1 h. Then *E*-2-butenal(E/Z>98%) (3.2 mL, 2.7 g, 38.4 mmol, 4.0 equiv) was added dropwise via a syringe. After completion of the reaction monitored by TLC, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (5 mL) and warmed to ambient temperature, diluted with water (20 mL). Then the aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic phase was washed with water (20 mL) and brine (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude product was purified by flash column chromatography with petroleum ether/EtOAc (10:1) to afford alcohol **5** (4.1 g, 88%) as a yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (dd, *J* = 7.7, 1.5 Hz, 4H), 7.46 – 7.33 (m, 6H), 5.92 – 5.81 (m, 1H), 5.75 – 5.66 (m, 1H), 4.48 (d, *J* = 6.1 Hz, 1H), 3.64 (t, *J* = 5.8 Hz, 2H), 3.05 – 2.92 (m, 2H), 2.77 (d, *J* = 2.0 Hz, 1H), 2.67 (ddd, *J* = 14.3, 5.2, 3.5 Hz, 2H), 2.11 – 2.00 (m, 1H), 2.00 – 1.77 (m, 5H), 1.75 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)**. δ 135.6, 133.9, 129.7, 129.5, 127.6, 127.2, 73.1, 63.8, 58.5, 31.5, 27.5, 26.8 (-C($\underline{C}H_3)_3$), 26.0, 25.3, 24.5, 19.2, 18.0. **IR (KBr ν/cm^{-1})):** 3073, 2933,2858, 1472, 1427, 1381, 1112, 972, 824, 741, 702. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{27}H_{39}O_2S_2Si$ 487.2155; found 487.2158.

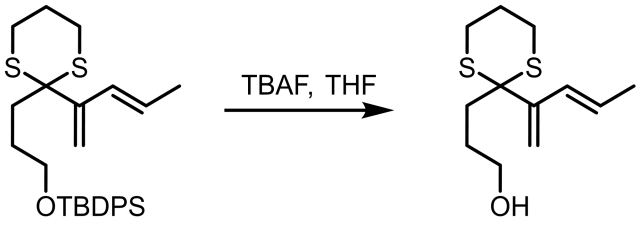


5 **6**

(E)-1-(2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-1,3-dithian-2-yl)but-2-en-1-one 6. The freshly prepared Dess–Martin periodinane (8.4 g, 19.8 mmol, 1.2 equiv) was added to a stirred solution of compound **5** (8.0 g, 16.4 mmol, 1.0 equiv) and $NaHCO_3$ (3.3 g, 39.3 mmol, 2.4 equiv) in CH_2Cl_2 (80 mL) at room temperature. After 1 h, the mixture was quenched with saturated aqueous solution of sodium thiosulfate (50 mL), and the organic layer was separated. Then the aqueous layer was extracted with DCM (3 × 50 mL) and the combined organic phase was washed with water (20 mL) and brine (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc=20:1) to give compound **6** (6.4 g, 80%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 – 7.60 (m, 4H), 7.45 – 7.34 (m, 6H), 7.15 – 7.03 (m, 1H), 6.73 (dd, *J* = 15.2, 1.6 Hz, 1H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.05 – 2.93 (m, 2H), 2.63 (dt, *J* = 14.4, 4.0 Hz, 2H), 2.14 – 2.08 (m, 2H), 2.08 – 2.02 (m, 1H), 1.89 (dd, *J* = 6.9, 1.6 Hz, 3H), 1.87 – 1.77 (m, 1H), 1.66 – 1.58 (m, 2H), 1.04 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 192.4, 144.3, 135.5, 133.6, 129.6, 127.6, 125.1, 63.1, 60.6, 34.8, 27.6 (-S$\underline{\underline{C}}H_2CH_2$$\underline{\underline{C}}H_2$S-), 27.1, 26.8 (-C($\underline{\underline{C}}H_3$)$_3$), 24.8, 19.2, 18.4. **IR (KBr ν/cm^{-1}):** 3073, 2933, 2875, 1688, 1627, 1429, 1472, 1287, 1112, 965,823, 734, 702. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{27}H_{37}O_2S_2Si$ 485.1999; found 485.1994.

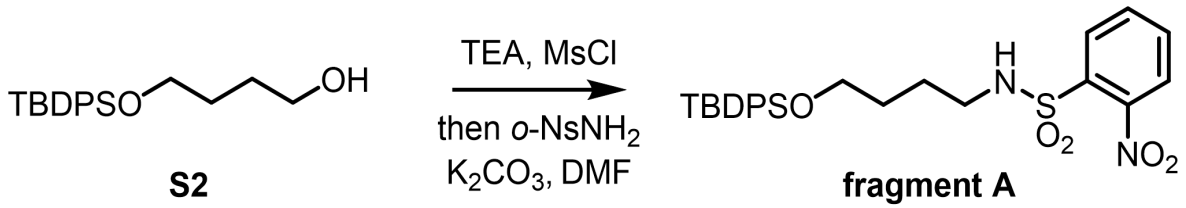


(E)-tert-butyl(3-(2-(penta-1,3-dien-2-yl)-1,3-dithian-2-yl)propoxy)diphenylsilane 7. Under argon atmosphere, Nysted reagent (20 wt. % suspension in THF, 8.4 g, 3.72 mmol, 1.2 equiv) and 13 mL of THF was added in a dried flask. The suspension was cooled to -20 °C and titanium(IV) chloride (410 μL, 3.74 mmol, 1.2 equiv) was added dropwise. When the emission of fume stopped, a solution of compound **6** (1.5 g, 3.1 mmol, 1.0 equiv) in 5 mL THF was added via canula. The mixture was then allowed to warm to room temperature, and the temperature was increased to 50 °C. After completion of the reaction monitored by TLC, the mixture was cooled and quenched with saturated aqueous solution of $NaHCO_3$ (150 mL). The suspension was then filtered over a pad of celite/silica gel, diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic phase was washed with water (20 mL) and brine (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (petroleum ether/EtOAc=50:1) gave alkene **7** (940 mg, 63%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.67 – 7.62 (m, 4H), 7.44 – 7.35 (m, 6H), 6.25 – 6.17 (m, 1H), 5.97 (dq, *J* = 15.2, 6.6 Hz, 1H), 5.53 (s, 1H), 5.39 (d, *J* = 1.3 Hz, 1H), 3.62 (t, *J* = 6.1 Hz, 2H), 2.85 (ddd, *J* = 14.4, 11.4, 2.9 Hz, 2H), 2.64 (ddd, *J* = 14.4, 5.0, 3.3 Hz, 2H), 2.06 – 1.82 (m, 4H), 1.74 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.65 – 1.56 (m, 2H), 1.04 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.5, 135.6, 133.9, 129.5, 129.0, 127.6, 127.0, 115.4, 63.6, 57.7, 45.0, 36.8, 27.3 (-S$\underline{\underline{C}}H_2CH_2$$\underline{\underline{C}}H_2$S-), 26.8 (-C($\underline{\underline{C}}H_3$)$_3$), 25.3, 19.2, 18.4. **IR (KBr ν/cm^{-1}):** 2955, 2931, 2860, 1647, 1608, 1472, 1429, 1112, 998, 967, 823, 702. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{28}H_{39}OS_2Si$ 483.2206; found 483.2210.

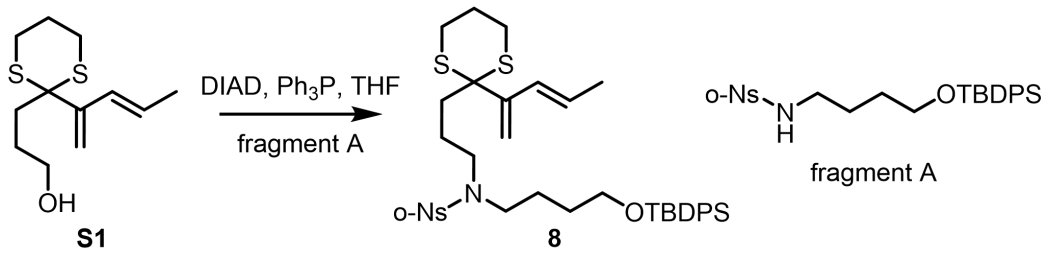


7 **S1**

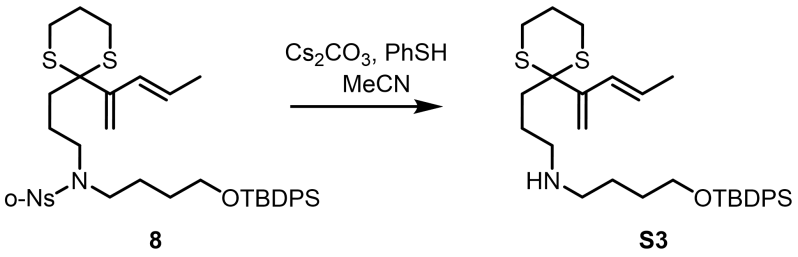
(E)-3-(2-(penta-1,3-dien-2-yl)-1,3-dithian-2-yl)propan-1-ol S1. To a solution of compound **7** (1.5 g, 3.1 mmol, 1.0 equiv) in 15 mL THF was added slowly 4.7 mL of tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF, 1.5 equiv) at room temperature. After 1 h, the reaction mixture was quenched with water. The aqueous layer was extracted with EtOAc （3 × 50 mL） and the combined organic phase was washed with water (10 mL) and brine (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (petroleum ether/EtOAc=6:1) gave compound **S1** (690 mg, 91%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.20 (d, *J* = 15.2 Hz, 1H), 6.02 – 5.91 (m, 1H), 5.52 (s, 1H), 5.39 (s, 1H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.89 – 2.77 (m, 2H), 2.67 – 2.56 (m, 2H), 2.05 – 1.94 (m, 1H), 1.94 – 1.83 (m, 3H), 1.74 (dd, *J* = 6.6, 1.4 Hz, 3H), 1.65 – 1.52 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.6, 129.0, 127.2, 115.6, 62.8, 57.6, 36.8, 27.3 (-S$\underline{\underline{C}}H_2CH_2$$\underline{\underline{C}}H_2$S-), 27.1, 25.3, 18.3. **IR (KBr ν/cm^{-1}):** 3399, 3373, 2950, 2935, 2912, 1608, 1448, 1423, 1276, 1049, 956, 907, 795. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{12}H_{21}OS_2$ 245.1028; found 245.1031.



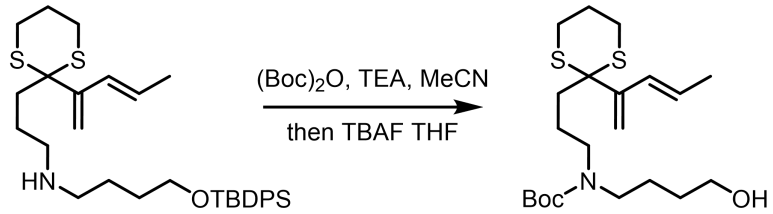
N-(4-((tert-butyldiphenylsilyl)oxy)butyl)-2-nitrobenzenesulfonamide. To a solution of compound **S2** (20 g, 61 mmol, 1.0 equiv) in DCM (120 mL) were added TEA (16.8 mL, 122 mmol, 2.0 equiv) and MsCl (9.4 mL, 122 mmol, 2.0 equiv) at 0 °C under Ar. After being stirred for 10 minutes at 0 ºC, the solution was warmed to room temperature and stirred for 30 minutes. The reaction was quenched with H_2O (200 mL), and extracted with DCM (3 × 150 mL). DCM was removed under reduced pressure and the residue was dissolved in DMF (200 mL), then K_2CO_3 (16 g, 116 mmol, 1.9 equiv) and *o*-$NsNH_2$ (15 g, 74mmol, 1.2 equiv) was added to the resulting mixture at room temperature. After stirring for 5 h at 80 °C, the reaction mixture was diluted with EtOAc (120 mL) and saturated aqueous solution of NaCl (600 mL), then the organic layer was separated. The reaction mixture was extracted and the combined organic phase was washed with brine (3 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (petroleum ether/EtOAc=10:1) gave **fragment A**. (26 g, 83 %). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 – 8.08 (m, 1H), 7.87 – 7.80 (m, 1H), 7.73 – 7.66 (m, 2H), 7.66 – 7.60 (m, 4H), 7.46 – 7.35 (m, 6H), 5.29 (t, *J* = 6.0 Hz, 1H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.13 (q, *J* = 6.7 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.59 – 1.51 (m, 2H), 1.02 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 148.0, 135.5, 133.8, 133.7, 133.5, 132.7, 131.0, 129.6, 127.6, 125.3, 63.1, 43.7, 29.3, 26.8 (-C(**C**H_3)$_3$), 26.3, 19.1. **IR (KBr ν/cm^{-1}):** 3354, 3073, 3052, 2935, 2860, 1591, 1541, 1442, 1427, 1362, 1168, 1112, 823, 782, 702. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{26}H_{33}N_2O_5SSi$ 513.1874; found 513.1872.



(E)-N-(4-((tert-butyldiphenylsilyl)oxy)butyl)-2-nitro-N-(3-(2-(penta-1,3-dien-2-yl)-1,3-dithian-2-yl) propyl)benzenesulfonamide 8. A solution of DIAD (1.16g, 5.74mmol, 2.0 equiv) in THF (28 mL) was added dropwise via syringe to a stirred solution of **S1** (700 mg, 2.87 mmol, 1.0 equiv), PPh_3 (1.5 g, 5.74 mmol, 2.0 equiv) and **fragment A** (1.9 g, 3.7 mmol, 1.3 equiv) in THF (13 mL) at -20 °C at such a rate as to maintain the temperature at -20 °C (approx. 10 min of addition time). The resultant solution was then allowed to warm to rt and stirred at rt for 5 h, then concentrated in vacuo. Direct purification by flash chromatography (petroleum ether/EtOAc=10:1) gave compound **8** (1.82 g, 86 %). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 – 7.95 (m, 1H), 7.66 – 7.56 (m, 7H), 7.45 – 7.35 (m, 6H), 6.15 (d, *J* = 15.3 Hz, 1H), 5.99 – 5.87 (m, 1H), 5.48 (s, 1H), 5.34 (s, 1H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.29 (q, *J* = 7.2 Hz, 4H), 2.80 (ddd, *J* = 14.1, 11.3, 2.7 Hz, 2H), 2.65 – 2.56 (m, 2H), 2.03 – 1.93 (m, 1H), 1.93 – 1.79 (m, 1H), 1.77 – 1.68 (m, 5H), 1.65 – 1.54 (m, 4H), 1.53 – 1.45 (m, 2H), 1.03 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.8, 145.4, 135.5, 133.7, 133.2, 131.5 130.6, 129.5, 128.8, 127.6, 127.3, 124.0, 115.4, 63.2, 57.2, 46.3, 46.2, 36.9, 29.5, 27.2 **(-S$\underline{\underline{C}}H_2CH_2$$\underline{\underline{C}}H_2$S-)**, 26.8 **(-C($\underline{\underline{C}}H_3$)$_3$)**, 25.1, 24.1, 21.9, 19.1, 18.3. IR (KBr ν/cm-1): 3073, 3050, 2935, 2860, 1545,1472, 1429, 1373, 1162, 1110, 909, 823, 736, 704. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{38}H_{51}N_2O_5S_3Si$ 739.2724; found 739.2726.

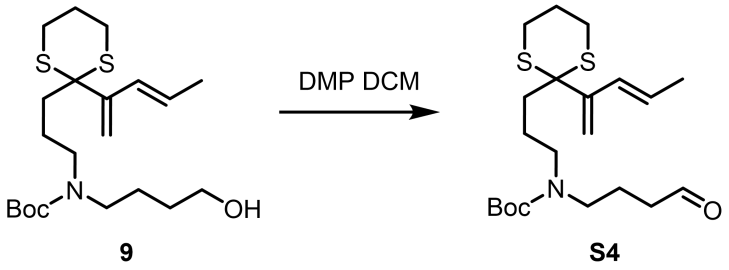


(E)-4-((tert-butyldiphenylsilyl)oxy)-N-(3-(2-(penta-1,3-dien-2-yl)-1,3-dithian-2-yl)propyl)butan-1-amine S3. To a solution of **8** (2.5 g, 3.4 mmol, 1.0 equiv) in MeCN (17 mL) were added anhydrous Cs_2CO_3 (2.2 g, 6.7 mmol, 2.0 equiv) and PhSH (690 μL, 6.8 mmol, 2.0 equiv) at room temperature. After stirring for 10 h, the reaction was quenched with H_2O (10 mL), and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/CH_3OH=40:1) gave amide **S3** (1.62 g, 86 %). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.67 – 7.62 (m, 4H), 7.42 – 7.34 (m, 6H), 6.21 (d, *J* = 15.3 Hz, 1H), 5.98 (dq, *J* = 15.3, 6.6 Hz, 1H), 5.52 (s, 1H), 5.40 (s, 1H), 3.65 (t, *J* = 6.1 Hz, 2H), 2.83 (ddd, *J* = 14.3, 11.3, 2.9 Hz, 2H), 2.69 – 2.58 (m, 6H), 2.05 – 1.94 (m, 1H), 1.93 – 1.80 (m, 3H), 1.75 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.70 – 1.53 (m, 6H), 1.04 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.4, 135.5, 133.9, 129.5, 129.0, 127.6, 127.1, 115.6, 63.7, 57.6, 49.5, 49.3, 38.1, 30.3, 27.2 **(-S$\underline{\underline{C}}H_2CH_2$$\underline{\underline{C}}H_2$S-)**, 26.8 **(-C($\underline{\underline{C}}H_3$)$_3$)**, 26.1, 25.3, 23.7, 19.1, 18.3. **IR (KBr *ν*/cm^{-1}):** 2933, 2858, 1654, 1608, 1472, 1429, 1276, 1112, 907,823, 743, 702. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{32}H_{48}NOS_2Si$ 554.2941; found 554.2942.



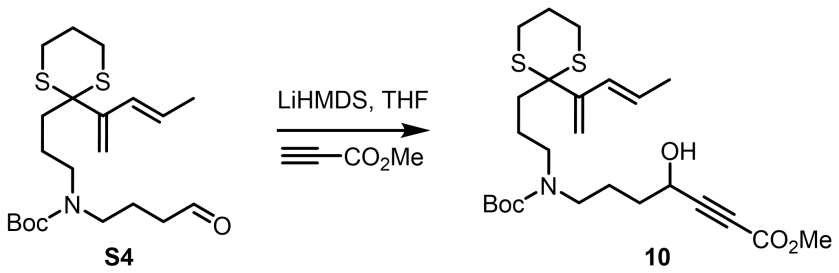
S3 **9**

tert-butyl (E)-(4-hydroxybutyl)(3-(2-(penta-1,3-dien-2-yl)-1,3-dithian-2-yl)propyl)carbamate 9. To a solution of **S3** (2.7 g, 4.9 mmol, 1.0 equiv) in MeCN (16 mL) were added TEA (880 μL, 6.3 mmol, 1.3 equiv) and $(Boc)_2O$ (1.45 mL, 6.3 mmol, 1.3 equiv) at room temperature. After stirring for 1 h, the reaction was quenched with H_2O (20 mL), and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were removed under reduced pressure and the residue was dissolved in THF (10 mL), then to the resulting mixture was added TBAF (7.3 mL, 7.3 mmol, 1.0 M in THF, 1.5 equiv) at room temperature. The resulting mixture was stirred for 5 h, then quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (4 × 40 mL). The combined organic phases were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: PE/EtOAc=1/6 to 1/2) to give compound **9** (1.61g, 79%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.18 (d, *J* = 15.2 Hz, 1H), 5.96 (dq, *J* = 13.2, 6.5 Hz, 1H), 5.52 (s, 1H), 5.38 (s, 1H), 3.64 (t, *J* = 5.8 Hz, 2H), 3.22 – 3.05 (m, 4H), 2.87 – 2.78 (m, 2H), 2.61 (dt, *J* = 14.1, 4.0 Hz, 2H), 2.00 (d, *J* = 13.5 Hz, 1H), 1.88 – 1.76 (m, 3H), 1.74 (dd, *J* = 6.6, 1.4 Hz, 3H), 1.62 – 1.48 (m, 6H), 1.42 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 155.5, 145.5, 128.9, 126.9, 115.3, 79.1, 62.1, 57.5, 46.8, 46.4, 37.6, 29.6, 28.3 **(-C(CH_3)$_3$)**, 27.1 **(-SCH_2CH_2CH_2S-)**, 25.1, 24.5, 22.8, 18.2. **IR (KBr v/cm-1):**3440, 2737, 1690, 1479, 1443, 1420,1366, 1278, 1250, 1135, 1067, 965, 907, 874, 732. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{37}NO_3S_2Na$ 438.2107; found 438.2105.



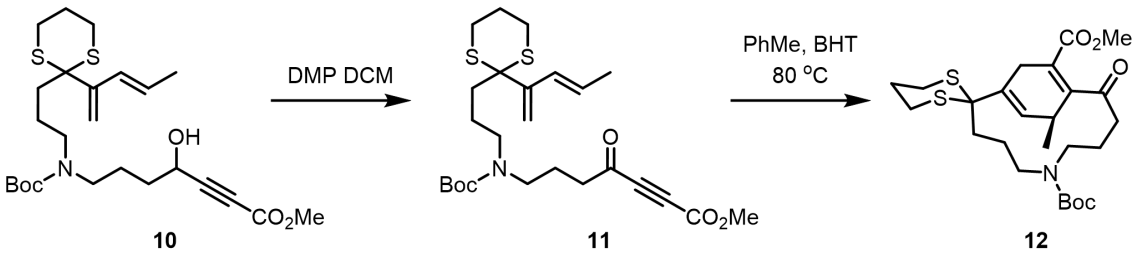
9 **S4**

tert-butyl (E)-(4-oxobutyl)(3-(2-(penta-1,3-dien-2-yl)-1,3-dithian-2-yl)propyl)carbamate S4. Freshly prepared Dess–Martin periodinane (1.5 g, 3.5 mmol, 1.2 equiv) was added to a stirred solution of compound **9** (1.2 g，2.9 mmol, 1.0 equiv) and $NaHCO_3$ (0.6 g, 7.1 mmol, 2.4 equiv) in CH_2Cl_2 (15 mL) at room temperature. After 30 minutes，the mixture was quenched with saturated aqueous sodium thiosulfate (20 mL), and the organic layer was separated. Then the aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic phases were washed with water (20 mL) and brine (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc=15:1) to give compound **S4** (710 mg, 60%) as a pale yellow oil. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.76 (s, 1H), 6.19 (d, *J* = 15.1 Hz, 1H), 6.06 – 5.90 (m, 1H), 5.53 (s, 1H), 5.39 (s, 1H), 3.24 – 3.05 (m, 4H), 2.84 (t, *J* = 12.5 Hz, 2H), 2.66 – 2.58 (m, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.05 – 1.98 (m, 1H), 1.92 – 1.77 (m, 5H), 1.76 (d, *J* = 6.6 Hz, 3H), 1.60 – 1.53 (m, 2H), 1.44 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 201.5, 155.5, 145.5, 128.9, 127.0, 115.4, 79.4, 57.6, 46.9, 45.9, 41.0, 37.7, 28.3 **(-C(<u>C</u>H$_3$)$_3$)**, 27.2 **(-S<u>C</u>H$_2$CH$_2$<u>C</u>H$_2$S-)**, 25.2, 22.8, 20.8, 18.2. IR (KBr ν/cm-1):2933, 1725, 1692, 1477, 1418, 1289, 1248, 1168, 1135, 963, 907, 775. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{21}H_{35}NO_3S_2Na$ 436.1951; found 436.1954.

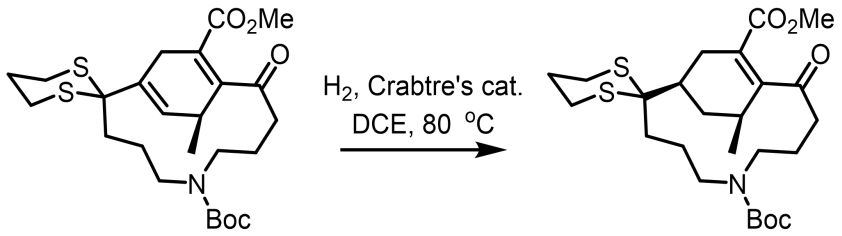


S4 10

Methyl (E)-7-((tert-butoxycarbonyl)(3-(2-(penta-1,3-dien-2-yl)-1,3-dithian-2-yl)propyl)amino)-4-hydroxy hept-2-ynoate 10. To a solution of methyl propiolate (200 μL, 2.2 mmol, 3.0 equiv) in THF (5 mL) was added LiHMDS (2.2 mL, 2.9 mmol, 1.3M in THF, 4.0 equiv) at -78 ℃ under argon. After stirring for 1.5 h at this temperature, compound **S4** (300 mg, 0.73 mmol, 1.0 equiv) in THF (2.0 mL) was introduced and the reaction was stirred continuously for 15 minutes before being quenched with sat. aq. NH_4Cl. The organic phase was separated and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE=1/6 to 1/4) to give compound **10** (300 mg, 83%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.20 (d, *J* = 15.3 Hz, 1H), 6.03 – 5.92 (m, 1H), 5.54 (s, 1H), 5.40 (s, 1H), 4.59 – 4.49 (m, 1H), 3.77 (s, 3H), 3.24 – 3.04 (m, 4H), 2.90 – 2.78 (m, 2H), 2.68 – 2.56 (m, 2H), 2.06 – 1.96 (m, 1H), 1.93 – 1.78 (m, 3H), 1.76 (dd, *J* = 6.6, 1.6 Hz, 3H), 1.74 – 1.66 (m, 3H), 1.66 – 1.60 (m, 2H), 1.59 – 1.52 (m, 2H), 1.44 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 155.8, 153.7, 145.5, 129.0, 127.1, 115.5, 88.4, 79.6, 75.9, 61.7, 57.6, 52.6, 46.8, 46.1, 37.7, 33.5, 28.4 **(-C(CH_3)$_3$)**, 27.3 **(-SCH_2CH_2CH_2S-)**, 25.2, 23.9, 22.8, 18.3. **IR (KBr ν/cm^{-1}):** 3421, 3315, 2916, 2234, 1718,1686, 1666, 1422,1366, 1252, 1164, 1090, 956, 907, 767, 751. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{39}NO_5S_2Na$ 520.2162; found 520.2159.

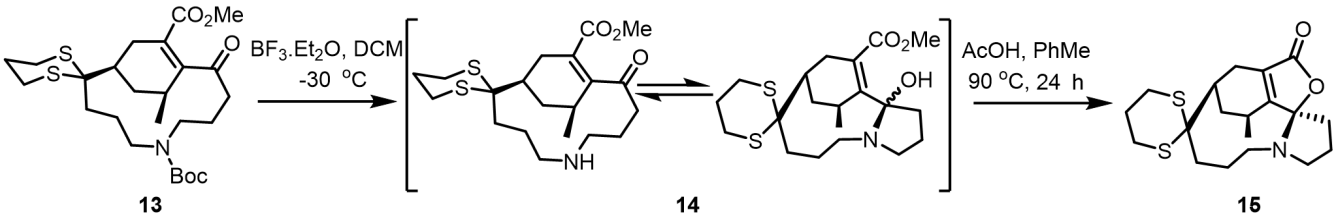


Compound 12. To a solution of freshly prepared Dess–Martin periodinane (584 mg, 1.4 mmol, 1.5 equiv) in DCM (5 mL) were added compound **10** (450 mg, 0.91 mmol, 1.0 equiv) in DCM (2.0 mL) at room temperature. After 15 minutes, the mixture was quenched with saturated aqueous sodium thiosulfate (4 mL) and sat. aq. $NaHCO_3$（4 mL）The organic layer was separated. Then the aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic phases were washed with water (10 mL) and brine (2 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The resulting residue was dissolved in PhMe (90 mL), then were added BHT (20 mg, 0.1 mmol, 0.1 equiv) under argon. After stirring for 3 h at 80 ℃, toluene was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE=1/6 to 1/4) to give compound **12** (216 mg, 48%) as a pale yellow oil.

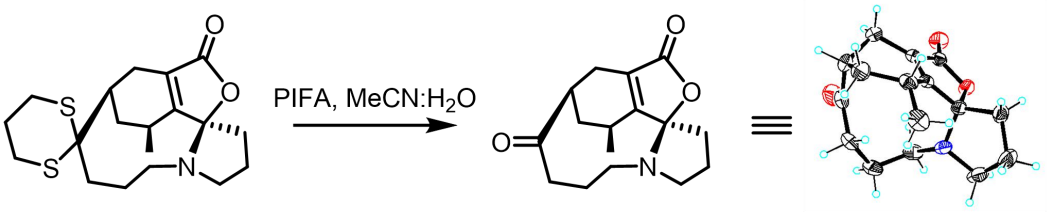


12 **13**

Compound 13. In order to prevent aromatization of compound **12**, the next reaction needed to be conducted immediately. In a glovebox, a sealed reaction glass vial containing a stirring bar was charged with Crabtree's catalyst (58 mg, 0.07 mmol, 0.3 equiv) and then flushed with argon. Then a solution of compound **12** (119 mg, 0.24 mmol, 1.0 equiv) in dry DCE (1.2 mL) was added. Hydrogen was bubbled through the solution for 30 minutes, then the flask was placed at an oil bath of 80 °C under an atmosphere of H_2 (non-bubbling) for 12 hours. After completion of the reaction, DCE was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE=1/6 to 1/4) to give compound **13** (56 mg, 47%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.71 (s, 3H), 3.61 – 3.37 (m, 3H), 3.19 – 3.09 (m, 1H), 3.06 – 2.90 (m, 2H), 2.86 – 2.78 (m, 1H), 2.66 (d, *J* = 11.1 Hz, 3H), 2.63 – 2.51 (m, 2H), 2.48 – 2.38 (m, 2H), 2.24 – 2.11 (m, 1H), 2.10 – 1.97 (m, 3H), 1.86 – 1.72 (m, 4H), 1.63 – 1.54 (m, 2H), 1.45 (s, 9H), 1.24 (s, 1H), 1.10 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 207.8, 166.2, 156.5, 156.1, 129.2, 79.8, 58.4, 52.1, 50.0, 49.1, 42.7, 36.5, 35.0, 33.0, 32.6, 28.4 **(-C($\underline{C}H_3)_3$)**, 25.9, 25.7, 25.2, 24.6, 24.2, 24.1, 16.9. **IR (KBr ν/cm^{-1}):** 2933, 1690, 1418, 1366, 1293, 1258, 1166, 1146, 771, 756. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{25}H_{39}NO_5S_2Na$ 520.2162; found 520.2166.



Compound 15. To a solution of compound **13** (45 mg, 0.09 mmol, 1.0 equiv) in dry DCM (1.0 mL) was added a solution of $BF_3 \cdot Et_2O$ (98%, 17 μL, 0.13 mmol, 1.4 equiv) at -30 ℃ under argon. After stirring for 15 minutes at this temperature, the mixture was quenched with sat. aq. $NaHCO_3$ (4 mL). The organic layer was separated. Then the aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic phases were washed with water (10 mL) and brine (2 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was dissolved in PhMe (2 mL), then AcOH (10 μL, 0.17 mmol, 1.9 equiv) was added to the resulting mixture under argon. After stirring for 7 h at 90 ℃, toluene was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE=1/6 to 1/4) to give compound **15** (12 mg, 35%) as a pale yellow oil. **^{1}H NMR (600 MHz,$CDCl_3$)** δ 3.21 (d, *J* = 16.1 Hz, 1H), 3.05 (td, *J* = 8.5, 2.6 Hz, 1H), 2.90 (q, *J* = 8.6 Hz, 1H), 2.83 – 2.71 (m, 6H), 2.70 – 2.67 (m, 2H), 2.44 (ddd, *J* = 14.0, 11.1, 5.7 Hz, 1H), 2.37 – 2.29 (m, 3H), 2.26 – 2.19 (m, 2H), 2.05 – 1.98 (m, 2H), 1.97 – 1.91 (m, 2H), 1.91 – 1.85 (m, 1H), 1.83 – 1.75 (m, 1H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.17 (dd, *J* = 15.4, 8.6 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 171.2, 163.4, 131.2, 107.0, 58.0, 53.7, 46.5, 41.0, 37.8, 34.5, 33.4, 28.7, 26.9, 25.1, 25.0, 22.9, 21.4, 21.2, 16.2. **IR (KBr ν/cm^{-1}):** 2935, 2797, 1736, 1654, 1606, 1248, 1101, 952, 844. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{28}NO_2S_2$ 366.1556; found 366.1552.



15 **16** ORTEP of **16**

Compound 16. To a solution of compound **15** (15 mg, 0.04 mmol, 1.0 equiv) in MeCN:H_2O=9:1 (2 mL) was added PIFA (22 mg, 0.05 mmol, 1.25 equiv) at 0 ℃. After stirring for 15 minutes at this temperature, the mixture was quenched with saturated aqueous solution of sodium thiosulfate (4 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE=1/6 to 1/4) to give compound **16** (9.1 mg, 83%) as a colorless solid (m.p. 116-118℃). **^{1}H NMR (600 MHz, CD_3OD)** δ 3.27 (td, J = 8.2, 2.3 Hz, 1H), 3.04 – 2.97 (m, 1H), 2.96 – 2.90 (m, 2H), 2.74 – 2.71 (m, 1H), 2.66 – 2.59 (m, 1H), 2.59 – 2.52 (m, 2H), 2.45 – 2.39 (m, 1H), 2.38 – 2.32 (m, 2H), 2.18 – 2.10 (m, 2H), 2.03 (ddd, *J* = 15.0, 5.5, 3.7 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.91 – 1.83 (m, 1H), 1.59 – 1.51 (m, 1H), 1.42 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 217.3, 171.2, 166.6, 130.7, 106.5, 55.3, 46.4, 46.1, 38.7, 35.7, 32.9, 28.3, 26.2, 25.1, 21.7, 18.3. **IR (KBr ν/cm^{-1}):** 2965, 2920, 2853, 1749, 1692, 1459, 1328, 1261, 1125, 1099, 799. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_3$ 276.1594; found 276.1595.

III Cif Check Report

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 2

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: 2

```
Bond precision:  C-C = 0.0030 A          Wavelength=0.71073

Cell:           a=13.1376(12)    b=14.5412(13)      c=15.0949(14)
                alpha=90         beta=102.733(2)    gamma=90
Temperature:    296 K

                Calculated                Reported
Volume          2812.8(4)                 2812.8(4)
Space group     P 21/c                    P 21/c
Hall group      -P 2ybc                   -P 2ybc
Moiety formula  C16 H21 N O3              ?
Sum formula     C16 H21 N O3              C16 H21 N O3
Mr              275.34                    275.34
Dx,g cm-3       1.300                     1.300
Z               8                         8
Mu (mm-1)       0.089                     0.089
F000            1184.0                    1184.0
F000'           1184.56
h,k,lmax        15,17,18                  15,17,18
Nref            5050                      5025
Tmin,Tmax       0.979,0.982               0.673,0.745
Tmin'           0.974

Correction method= # Reported T Limits: Tmin=0.673 Tmax=0.745
AbsCorr = MULTI-SCAN

Data completeness= 0.995          Theta(max)= 25.169

R(reflections)= 0.0448( 3391)     wR2(reflections)= 0.1553( 5025)

S = 1.001                  Npar= 363
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The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

PLAT230_ALERT_2_C	Hirshfeld Test Diff for C9 --C10 .	6.5 s.u.
PLAT241_ALERT_2_C	High 'MainMol' Ueq as Compared to Neighbors of	C2 Check
PLAT911_ALERT_3_C	Missing FCF Refl Between Thmin & STh/L= 0.598	25 Report

Alert level G

PLAT398_ALERT_2_G	Deviating C-O-C Angle From 120 for O1	109.3 Degree
PLAT398_ALERT_2_G	Deviating C-O-C Angle From 120 for O4	109.4 Degree
PLAT793_ALERT_4_G	Model has Chirality at C4 (Centro SPGR)	R Verify
PLAT793_ALERT_4_G	Model has Chirality at C9 (Centro SPGR)	R Verify
PLAT793_ALERT_4_G	Model has Chirality at C11 (Centro SPGR)	S Verify
PLAT793_ALERT_4_G	Model has Chirality at C20 (Centro SPGR)	R Verify
PLAT793_ALERT_4_G	Model has Chirality at C25 (Centro SPGR)	R Verify
PLAT793_ALERT_4_G	Model has Chirality at C27 (Centro SPGR)	S Verify
PLAT909_ALERT_3_G	Percentage of I>2sig(I) Data at Theta(Max) Still	37% Note
PLAT910_ALERT_3_G	Missing # of FCF Reflection(s) Below Theta(Min).	1 Note
PLAT978_ALERT_2_G	Number C-C Bonds with Positive Residual Density.	1 Info
PLAT992_ALERT_5_G	Repd & Actual _reflns_number_gt Values Differ by	1 Check

0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
3 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
12 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
5 ALERT type 2 Indicator that the structure model may be wrong or deficient
3 ALERT type 3 Indicator that the structure quality may be low
6 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

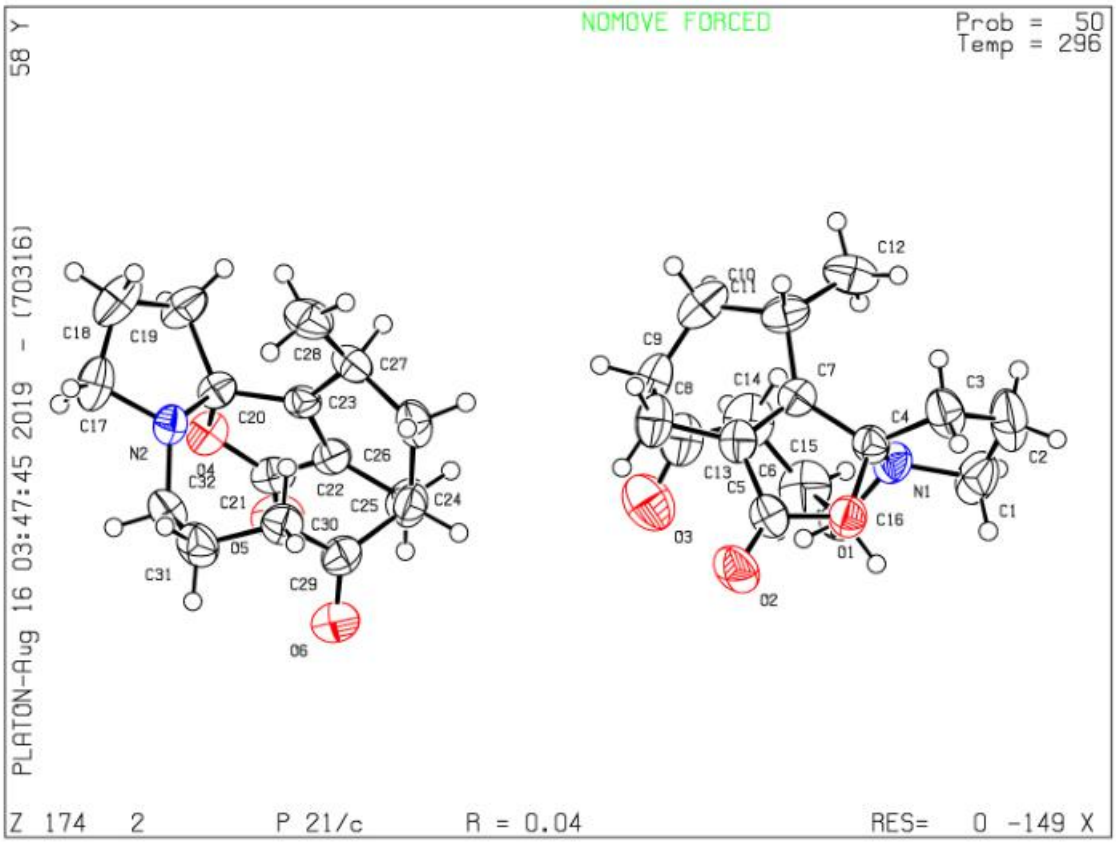
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 07/08/2019; check.def file version of 30/07/2019

Datablock 2 - ellipsoid plot



IV Biological Studies

Evaluation of the inhibitory activity against EeAChE and eqBuChE. Kinetic assays of eqBuChE were performed by the spectrometric method of Ellman. Acetylthiocholine iodide , butyrylthiocholine iodide and 5,5-dithiobis-(2-nitrobenzoic) acid (DTNB) were purchased from Sigma Aldrich. EeAChE (E.C. 3.1.1.7, type V-S, purified from E. electricus) and eqBuChE (E.C. 3.1.1.8, purified from equine serum) were diluted in 20 mM HEPES buffer pH 7.2-7.4, phosphate buffer pH 7.4 such as to have enzyme solution with 0.25 units/mL enzyme activity.

In the procedure, 50 µL of compound solution (5×final concentration) or 50 µL of sodium phosphate buffer (pH 7.2-7.4) were added to plate wells containing 50 µL of enzyme (0.01-0.05 IU/mL final). After 10 min of preincubation, 100 µL of 0.3 mM DTNB dissolved in phosphate buffer (pH 7.2-7.4) and 50 µL of substrate (acetylthiocholine or butyrylthiocholine iodide, 1 mM final) were added and the plate was read at 405 nm for 10 min. All experiments were run in triplicate and performed at least twice. Tested compounds were dissolved at 0.1 M in DMSO and diluted in phosphate buffer to the required concentrations just before use. Donepezil was used as reference standard. The final concentrations of DMSO (<0.4% v.v.) did not affect enzyme activity.

The percentage of inhibition was calculated as follows: % inhibition = (E-S)/E × 100 (E is the activity of the enzyme without test compound and S is the activity of enzyme with test compounds). IC_{50} (the concentration of test compounds required to inhibit enzyme activity by 50%) values were determined with Origin 8.0.

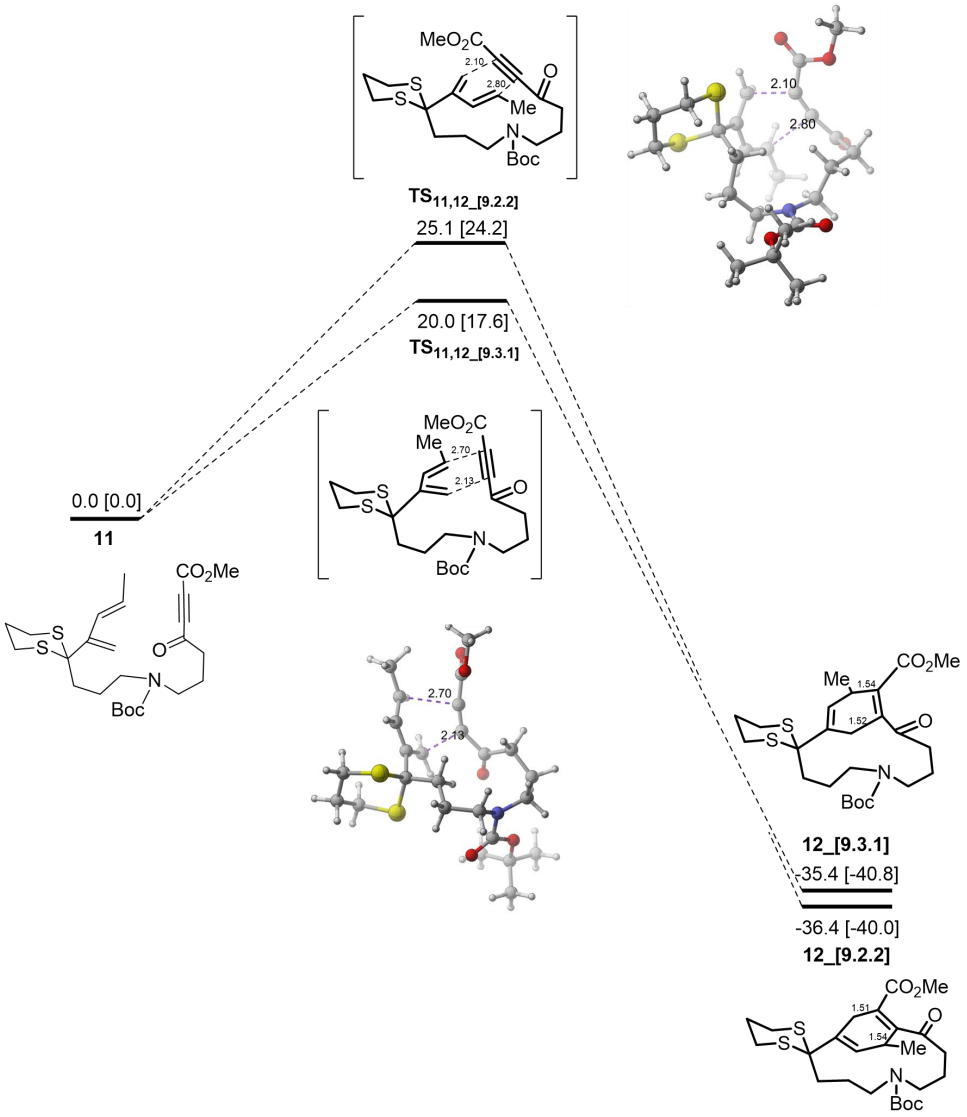
Table S1. Results of the in Vitro Evaluation of the Inhibitory Effect of AChE/BChE

Compd.	IC_{50} [a] (µM)	
	eqBuChE	EeAChE
16	130.25±25.10	>200
Donepezil	-	1.73±0.26

[a] The values are expressed as Mean±SD of at least 2 independent experiments.

V Calculation Details

DFT calculations were conducted in Gaussian 09.[1] Optimizations were carried out with B3LYP, along with basis set 6-31G(d) for all atoms in gas phase. Vibrational frequencies were computed for all stationary points to confirm them as either minima or transition structures (TSs), possessing zero or a single imaginary frequency, respectively. TSs were confirmed with the use of intrinsic reaction coordinate (IRC) calculations, which connected each TS to appropriate species on either side of the reaction barrier on the potential energy surface (PES). Single point energies of all optimized structures were further estimated in solvated phase using SMD[2] (Toluene)-B3LYP/6-311++G(d,p) level of DFT theory. Schemes and figures were prepared using ChemDraw and CYLview.[3]



Scheme S1. Computed free energy profiles for the D-A precursor **11** that protected by 1,3-dithiane protecting group. Gibbs free energies (Grel, 298K) are quoted in kcal·mol^{-1}. SMD (toluene)-B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) free energies in toluene solvated phase are quoted outsides brackets. B3LYP/6-31G(d) free energies in gas phase (without solvents) are quoted in brackets.

Cartesian Coordinate

11

C	1.773483	-0.21589	2.557819	H	-2.81713	0.790915	2.376793
C	2.826513	0.610474	2.607935	H	-1.18288	1.444777	2.280564
C	2.463989	2.629353	-0.69897	H	-0.76625	2.958749	0.946576
C	3.2821	1.757449	-0.89831	H	-2.12993	3.60804	0.034557
C	2.677649	-2.47822	2.247865	H	-1.39097	2.56121	-2.01817
C	1.785317	-1.54194	1.892897	H	-0.13539	1.63893	-1.19358
H	0.840624	0.103542	3.023113	H	0.705053	3.703536	-2.4357
C	4.283588	0.715606	-1.03671	H	-0.17504	4.71964	-1.26753
C	0.806943	-1.78779	0.727808	S	1.905344	-1.86348	-0.78721
C	1.477974	3.675249	-0.43967	S	-0.02428	-3.42351	1.008773
O	1.593317	4.399152	0.53654	C	0.714937	-2.35975	-2.09524
O	4.91378	0.257255	-0.10708	C	-0.91524	-3.63921	-0.58278
O	4.423012	0.343332	-2.31889	C	-0.00751	-3.67891	-1.8143
C	5.369482	-0.72165	-2.53546	H	1.331211	-2.44737	-2.9962
H	5.045162	-1.62055	-2.00556	H	-0.00549	-1.55446	-2.27942
H	5.375237	-0.88483	-3.6129	H	-1.68171	-2.86169	-0.68815
H	6.360999	-0.42906	-2.18156	H	-1.43944	-4.59353	-0.46836
H	3.370332	-2.2965	3.063229	H	0.727472	-4.48318	-1.69942
C	2.816832	1.95467	3.275157	H	-0.62849	-3.92073	-2.68938
H	2.921656	2.759302	2.534875	C	-3.37608	1.326203	-0.20898
H	1.887142	2.126147	3.82932	O	-3.71558	1.990465	-1.18052
H	3.655518	2.055742	3.976313	O	-4.05609	0.266473	0.297126
C	-0.20723	-0.63855	0.548276	C	-5.30394	-0.19533	-0.32716
C	-1.36231	-0.5814	1.56161	C	-6.36693	0.904996	-0.26014
C	-1.92135	0.836987	1.748981	H	-6.08545	1.759603	-0.87631
N	-2.236	1.566032	0.510063	H	-7.32604	0.510998	-0.61451
C	-1.45637	2.747875	0.12556	H	-6.49899	1.240356	0.774422
C	-0.67888	2.589995	-1.1898	C	-5.69852	-1.38178	0.554853
C	0.316739	3.751815	-1.41142	H	-6.63287	-1.82362	0.193525
H	2.7407	-3.43462	1.738604	H	-4.92135	-2.1529	0.538316
H	3.742704	0.325603	2.093324	H	-5.84419	-1.06135	1.591395
H	-0.63748	-0.68008	-0.45532	C	-5.03143	-0.65479	-1.76248
H	0.376036	0.287564	0.582061	H	-4.24107	-1.41421	-1.77292
H	-1.03986	-0.94092	2.545642	H	-5.93793	-1.10336	-2.18377
H	-2.16632	-1.25222	1.248637	H	-4.72674	0.183897	-2.38959

$TS_{11,12\_[9.3.1]}$

C	3.448092	-2.9127	-0.39166	C	4.757127	-3.69443	1.403787
O	4.159452	-3.51819	-1.1767	H	4.757295	-3.59818	2.490034
O	3.643207	-2.90787	0.953763	H	4.63625	-4.7407	1.110524

H	5.694892	-3.31674	0.987599	H	5.677416	-0.07309	0.183821
C	2.312721	-2.1199	-0.74322	H	5.632535	-1.45546	-0.94756
C	1.188748	-1.64829	-1.0098	H	6.120024	0.129506	-1.52553
C	-0.25269	-1.9834	-0.92197	H	-2.45819	0.444144	3.355553
O	-1.09716	-1.54339	-1.67956	N	-2.41378	-0.74592	1.602468
C	-0.57551	-2.97034	0.201511	S	1.911456	2.774023	1.514966
H	-0.20306	-3.94213	-0.1539	S	-0.28593	2.863466	-0.58185
H	0.048061	-2.72556	1.069001	C	0.850201	4.069688	-1.36282
C	-2.06319	-3.06862	0.563516	C	2.672912	4.043682	0.427505
H	-2.29106	-4.10671	0.837893	C	1.669197	4.885314	-0.36122
H	-2.66595	-2.83176	-0.31446	H	0.195989	4.723944	-1.94741
C	-2.51848	-2.20918	1.754898	H	1.505921	3.543265	-2.06675
H	-1.9165	-2.47333	2.630226	H	3.383689	3.557493	-0.25081
H	-3.55572	-2.47817	1.988346	H	3.24927	4.673909	1.1122
C	-1.72233	0.033485	2.650785	H	0.995737	5.404787	0.328925
H	-1.10341	-0.68149	3.201402	H	2.23171	5.650873	-0.91555
C	-0.83476	1.187234	2.148493	C	-3.36111	-0.06243	0.868553
H	-1.47056	1.98068	1.756347	O	-3.49576	1.152043	0.900596
H	-0.30393	1.591157	3.018776	O	-4.10796	-0.91129	0.127592
C	0.1487	0.711473	1.078343	C	-5.01432	-0.4012	-0.91488
H	0.876992	0.012952	1.512281	C	-6.15983	0.386107	-0.27327
H	-0.42255	0.14905	0.338042	H	-5.78747	1.290291	0.209209
C	0.951845	1.773665	0.284173	H	-6.88815	0.666106	-1.04292
C	1.833802	1.017319	-0.73779	H	-6.67374	-0.23021	0.472955
C	1.210566	0.343318	-1.77693	C	-5.53433	-1.68813	-1.5587
H	0.158303	0.495049	-1.98231	H	-6.25611	-1.44706	-2.34601
H	1.791247	-0.00246	-2.62401	H	-4.71198	-2.25631	-2.00487
C	3.212193	0.764644	-0.463	H	-6.03159	-2.31904	-0.81441
H	3.615471	1.174012	0.459433	C	-4.22264	0.428148	-1.92994
C	4.011871	-0.07091	-1.19148	H	-3.35901	-0.14253	-2.28589
H	3.688693	-0.43103	-2.16424	H	-4.86355	0.663359	-2.78729
C	5.432364	-0.3827	-0.83703	H	-3.87007	1.361555	-1.48838

12_[9.3.1]

C	2.929541	-3.1032	-0.04201	H	0.274551	-3.15637	1.690122
O	2.240508	-3.90487	0.563207	H	0.061768	-1.43358	1.806062
O	4.110302	-3.44779	-0.60373	C	-1.82632	-2.53799	1.576417
C	4.494246	-4.82152	-0.42606	H	-1.96128	-3.43083	2.199768
H	5.449261	-4.92467	-0.94169	H	-2.33676	-2.74242	0.635635
H	4.601214	-5.05594	0.636171	C	-2.54009	-1.40016	2.329439
H	3.744856	-5.48625	-0.86273	H	-2.05905	-1.26947	3.303557
C	2.557327	-1.69002	-0.32751	H	-3.57147	-1.72259	2.524443
C	1.253465	-1.40209	-0.49538	C	-2.26313	1.124358	2.540612
C	0.050477	-2.25998	-0.17704	H	-1.81151	0.745314	3.462343
O	-0.62277	-2.75266	-1.06389	C	-1.32363	2.163911	1.89482
C	-0.32656	-2.32561	1.302843	H	-1.8503	2.621064	1.057403

H	-1.13228	2.955045	2.629299	C	1.881382	4.805017	-1.28269
C	-0.0239	1.499954	1.434793	H	0.512627	4.157516	-2.83939
H	0.632236	1.295444	2.291671	H	1.731236	2.951333	-2.40926
H	-0.31375	0.525685	1.04352	H	3.495785	3.531461	-0.60089
C	0.868362	2.166754	0.345657	H	3.350643	5.047221	0.296553
C	1.67245	1.02627	-0.26971	H	1.20438	5.560149	-0.86891
C	0.878681	-0.02837	-1.01974	H	2.525767	5.305569	-2.02021
H	-0.19649	0.142545	-0.96859	C	-3.34015	0.182177	0.592496
H	1.125111	0.004365	-2.0919	O	-3.59863	1.304277	0.180801
C	2.965336	0.756367	-0.06822	O	-3.76984	-0.97178	0.037127
H	3.593322	1.435016	0.501266	C	-4.39415	-0.98708	-1.29776
C	3.589967	-0.56254	-0.50881	C	-5.73694	-0.25407	-1.25562
H	3.836872	-0.49924	-1.58256	H	-5.59572	0.8081	-1.0533
C	4.906958	-0.77174	0.262233	H	-6.24809	-0.37012	-2.21811
H	4.712447	-0.90601	1.333043	H	-6.37774	-0.68235	-0.47683
H	5.460253	-1.63721	-0.10021	C	-4.59201	-2.48265	-1.55276
H	5.538802	0.115862	0.149123	H	-5.07402	-2.6348	-2.52423
H	-3.20201	1.623284	2.811918	H	-3.62842	-3.00161	-1.55639
N	-2.5537	-0.06083	1.701344	H	-5.22776	-2.92561	-0.77883
S	1.883435	3.446402	1.212064	C	-3.42702	-0.39212	-2.3248
S	-0.2158	2.951583	-0.95147	H	-2.47223	-0.92801	-2.29194
C	1.070876	3.726723	-2.00239	H	-3.84714	-0.50644	-3.33041
C	2.778964	4.24432	-0.17979	H	-3.25295	0.668788	-2.13672

$TS_{11,12\_[9.2.2]}$

C	-1.44255	0.254184	2.249489	H	-2.12084	-1.68272	4.749284
C	-2.06821	-0.83625	2.781728	C	0.39561	1.218317	0.053771
C	-2.50548	-2.00906	0.273311	C	1.588117	1.167612	1.041488
C	-3.08324	-1.07112	-0.31821	C	1.98897	-0.21237	1.598336
C	-3.21486	0.774506	0.664856	N	2.091742	-1.30468	0.621581
C	-1.93999	1.019594	1.148665	C	1.192771	-2.46303	0.725063
H	-0.45893	0.50645	2.630513	C	0.324721	-2.71457	-0.51386
C	-3.84805	-0.83466	-1.56013	C	-0.77631	-3.7483	-0.23096
C	-0.94424	1.949077	0.442296	H	-3.63557	1.358691	-0.14203
C	-1.91617	-3.25721	0.664336	H	-3.08322	-1.08205	2.48932
O	-2.33881	-3.92095	1.610765	H	0.760417	1.683176	-0.863
O	-4.58284	0.100597	-1.7969	H	0.110363	0.206467	-0.24604
O	-3.62437	-1.84467	-2.43092	H	1.403275	1.823565	1.899795
C	-4.33925	-1.73487	-3.67385	H	2.466944	1.572942	0.53177
H	-4.06108	-0.81538	-4.19542	H	2.947861	-0.09817	2.115519
H	-4.04614	-2.61109	-4.25253	H	1.265803	-0.54552	2.343802
H	-5.41802	-1.73201	-3.49736	H	0.550518	-2.28658	1.591613
H	-3.95418	0.368332	1.346387	H	1.785664	-3.3627	0.929988
C	-1.49171	-1.70644	3.848846	H	0.965116	-3.06583	-1.32669
H	-1.48416	-2.75152	3.508885	H	-0.13521	-1.77903	-0.85006
H	-0.47647	-1.40677	4.129777	H	-1.23481	-4.05005	-1.18244

H	-0.37141	-4.65076	0.240481	O	4.011429	-0.37777	-0.0925
S	-1.72143	2.563544	-1.14037	C	5.245332	-0.30407	-0.88782
S	-0.7439	3.360083	1.645263	C	6.193514	-1.44234	-0.49948
C	-0.53662	3.867409	-1.64315	H	5.775205	-2.41072	-0.77601
C	0.305917	4.513965	0.677741	H	7.153831	-1.31058	-1.01053
C	-0.33892	4.989254	-0.6236	H	6.378696	-1.42964	0.580294
H	-0.97305	4.26228	-2.56618	C	5.827975	1.048312	-0.47208
H	0.428127	3.42003	-1.91171	H	6.773197	1.227948	-0.99481
H	1.281399	4.050708	0.486986	H	5.136792	1.860906	-0.71943
H	0.472032	5.356883	1.356187	H	6.018322	1.071948	0.60578
H	-1.29998	5.467197	-0.40577	C	4.906749	-0.31285	-2.38115
H	0.314903	5.749202	-1.07564	H	4.196317	0.488423	-2.61332
C	3.189649	-1.45514	-0.18445	H	5.816972	-0.14043	-2.96632
O	3.384603	-2.43724	-0.88807	H	4.471757	-1.26829	-2.67668

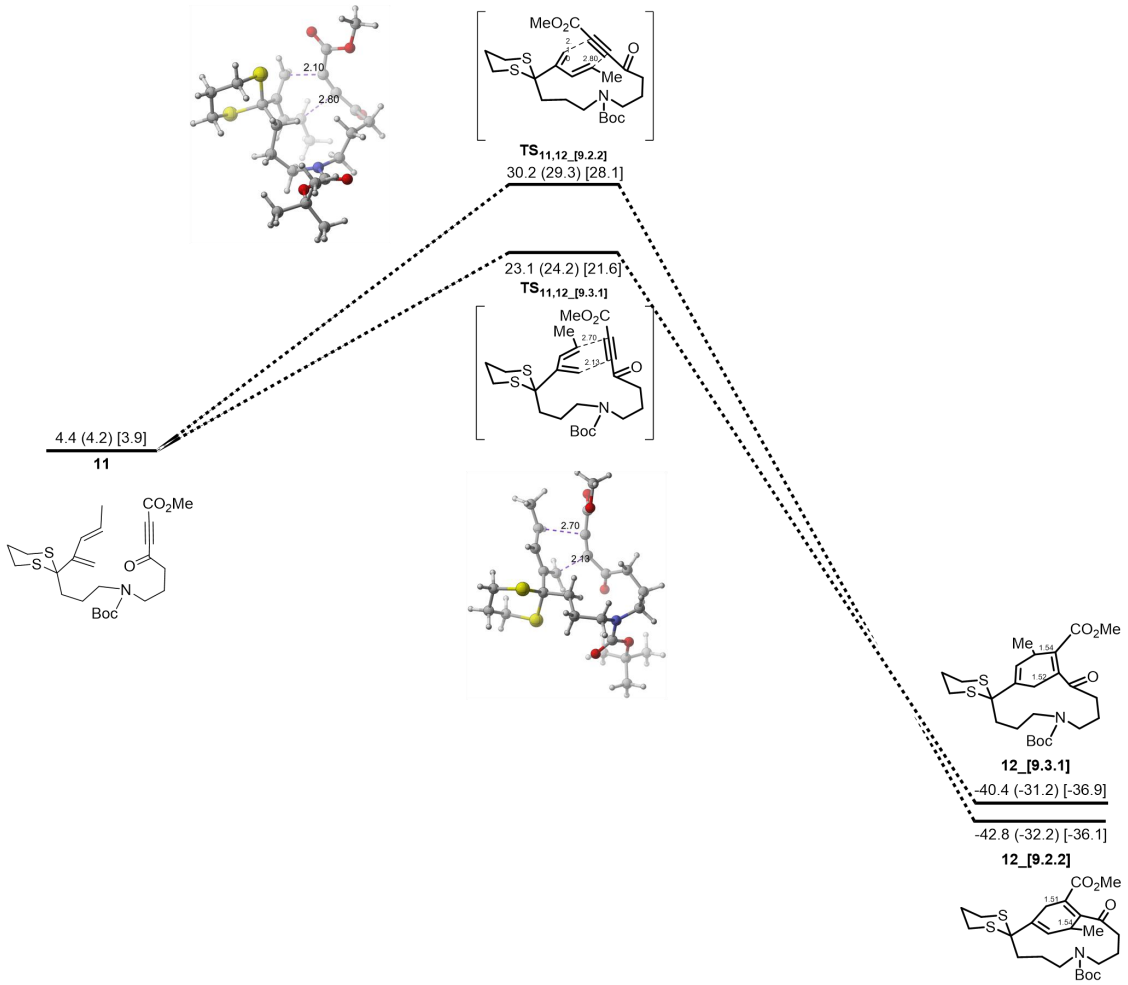
12_[9.2.2]

C	-2.16773	0.273676	1.526991	H	-3.76947	-1.12589	1.708837
C	-2.66864	-1.13631	1.789796	H	0.020846	2.635582	-1.60156
C	-2.19052	-2.06049	0.658104	H	-0.166	0.920621	-1.37384
C	-2.2346	-1.57796	-0.5985	H	1.312017	2.879446	0.461127
C	-2.57867	-0.12763	-0.84502	H	2.03805	1.813595	-0.71965
C	-2.07889	0.758842	0.285075	H	2.230187	1.261652	1.762024
H	-1.86287	0.849793	2.39616	H	0.54451	0.774044	1.720637
C	-1.92156	-2.36197	-1.82284	H	0.145942	-1.22738	1.625391
C	-1.46519	2.10013	-0.10224	H	1.627345	-2.08628	2.063893
C	-1.68633	-3.43134	1.030811	H	1.676645	-3.23067	-0.08017
O	-2.41538	-4.21218	1.616597	H	0.34037	-2.27813	-0.69642
O	-1.6481	-1.86842	-2.90081	H	-0.23331	-4.67745	0.122954
O	-1.99784	-3.69699	-1.62468	H	0.159145	-4.16646	1.742013
C	-1.66107	-4.51001	-2.76052	S	-2.699	2.858148	-1.29736
H	-0.62965	-4.32539	-3.07272	S	-1.33398	3.171582	1.410711
H	-1.78607	-5.54016	-2.42678	C	-2.00044	4.529373	-1.56869
H	-2.3307	-4.29005	-3.59544	C	-0.84312	4.782621	0.684468
H	-3.6716	-0.01204	-0.92689	C	-1.85551	5.366794	-0.2996
C	-2.33325	-1.59639	3.21637	H	-2.70692	4.996183	-2.26259
H	-2.75747	-2.5798	3.425002	H	-1.03989	4.451695	-2.09229
H	-1.25099	-1.64747	3.384203	H	0.144101	4.696639	0.215956
H	-2.74515	-0.87988	3.93497	H	-0.73317	5.435909	1.55585
C	-0.09287	1.868452	-0.82873	H	-2.82972	5.472814	0.18958
C	1.210775	1.895383	-0.0085	H	-1.51542	6.372661	-0.58582
C	1.442164	0.866555	1.110897	C	3.128706	-0.76285	0.332676
N	1.823903	-0.49599	0.681452	O	3.600666	-1.88992	0.268993
C	1.072663	-1.64036	1.22556	O	3.811762	0.380483	0.075082
C	0.744769	-2.7407	0.208341	C	5.221199	0.341018	-0.34178
C	-0.21452	-3.79839	0.776241	C	6.081354	-0.2693	0.768679
H	-2.17943	0.164161	-1.81717	H	5.83616	-1.321	0.920505

H	7.140441	-0.18634	0.499931	H	5.397433	2.372755	0.407177
H	5.926218	0.271914	1.708649	C	5.357113	-0.41438	-1.66661
C	5.553066	1.823299	-0.52688	H	4.694176	0.022505	-2.42159
H	6.599411	1.939466	-0.82769	H	6.387461	-0.33383	-2.03098
H	4.919107	2.269171	-1.30025	H	5.10636	-1.46845	-1.54287

Three GMMX conformer searching methods, *i.e.* MMFF94, MMX and MM3, have been employed to search the conformers of reactant, TS and product structures. Optimizations were carried out with B3LYP-D3(BJ), which includes the D3 version of Grimme's dispersion with Becke-Johnson damping [4] directly into the B3LYP functional, and with the 6-31G(d) basis set for all atoms in gas phase. Vibrational frequencies were computed for all stationary points to confirm them as either minima or transition structures (TSs), possessing zero or a single imaginary frequency, respectively. TSs were confirmed with the use of intrinsic reaction coordinate (IRC) calculations, which connected each TS to appropriate species on either side of the reaction barrier on the potential energy surface (PES). Using the same B3LYP-D3(BJ) method, the single point energies of all optimized structures were further estimated using SMD[2], with the 6-311++G(d,p) basis set for all atoms in toluene-solvated phase. Furthermore, the M06-2X method were used to estimate the single point energies as well, with the same 6-311++G(d,p) basis set. Schemes and figures were prepared using ChemDraw and CYLview.[3]

As a result, the new calculations have shown similar patterns, in which energy of $TS_{11,12\_[9,3,1]}$ leading to the desired product is lower (by 7.1 kcal/mol using the SMD(toluene)-M06-2X/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) level of DFT theory) than the $TS_{11,12\_[9,2,2]}$ leading to the actually observed product (**Scheme S2**). Moreover, the undesired, but experimentally observed product is thermodynamically more favorable by 2.4 kcal/mol, undergoing a similar crossing over of the reaction paths in the energy diagram.



Scheme S2. **Computed free energy profiles for the D-A precursor 11 that protected by 1,3-dithiane protecting group.** The relative free energies (RFEs) are compared with the D-A precursor **11** (zero point). Gibbs free energies (Grel, 298K) are quoted in kcal·mol^{-1}. SMD (toluene)-M06-2X/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) free energies in solvated phase are quoted outside parentheses and brackets. SMD (toluene)-B3LYP-D3(BJ)/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) free energies in solvated phase are quoted in parentheses. B3LYP-D3(BJ)/6-31G(d) free energies in gas phase (without solvents) are quoted in brackets.

In addition, the MM conformational searching methods, *i.e.* the GMMX conformer searching methods, have been used to search the conformers of both the desired product (12_[9,3,1]) and the observed product (12_[9,2,2]). Three GMMX conformer searching methods, *i.e.* MMFF94, MMX and MM3, have been employed, leading to different conformers with the lowest energies (**Figure S1**). All these conformers of both 12_[9,3,1] and 12_[9,2,2] were further optimized using B3LYP-D3(BJ)/6-31G(d) level of DFT theory, and have been estimated in solvated phase using both B3LYP-D3(BJ) and M06-2X methods, with the same 6-311++G(d,p) basis set (**Figures S1-S3**; **Table S2**). Eventually, 12_[9,3,1]_MMFF94 and 12_[9,2,2]_MMX are the two conformers that have been determined with the lowest relative free energies (RFEs).

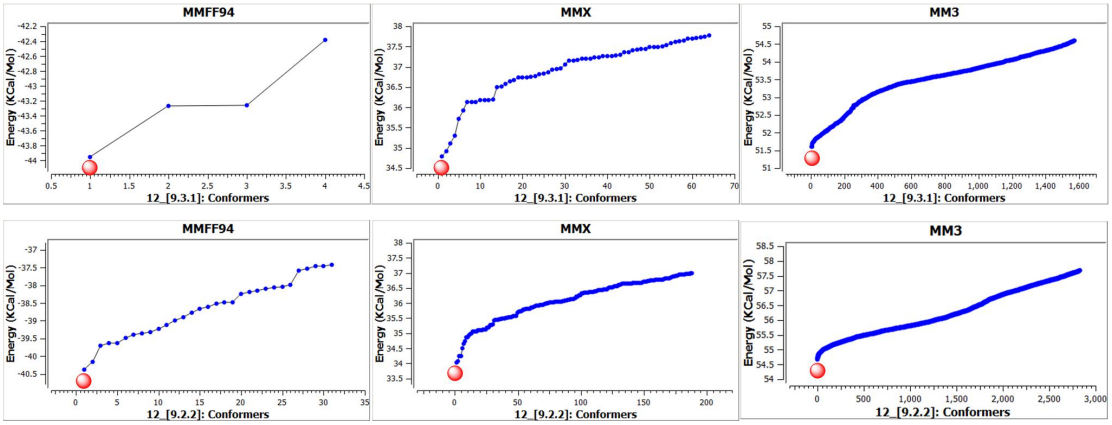


Figure S1. The conformer searching results for both 12_[9,3,1] and 12_[9,2,2] using three GMMX conformer searching methods, *i.e.* MMFF94, MMX and MM3.

Table S2. Computed free energy data for both 12_[9,3,1] and 12_[9,2,2], along with their conformers determined by the GMMX conformer searching methods. The relative free energies (RFEs) are compared with the D-A precursor **11** (zero point). Gibbs free energies (Grel, 298K) are quoted in kcal·mol^{-1}. SMD (toluene)-M06-2X/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) free energies in solvated phase are quoted outside parentheses and brackets. SMD (toluene)-B3LYP-D3(BJ)/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) free energies in solvated phase are quoted in parentheses. B3LYP-D3(BJ)/6-31G(d) free energies in gas phase (without solvents) are quoted in brackets.

	12_[9,3,1]	**12_[9,3,1]_MMFF94**	**12_[9,3,1]_MMX**	**12_[9,3,1]_MM3**
RFEs	-40.4 (-31.2) [-36.9]	-52.8 (-43.3) [-47.5]	-51.3 (-42.3) [-46.9]	-47.5 (-37.2) [-42.1]
	12_[9,2,2]	**12_[9,2,2]_MMFF94**	**12_[9,2,2]_MMX**	**12_[9,2,2]_MM3**
RFEs	-42.8 (-32.2) [-36.1]	-51.9 (-41.6) [-45.9]	-55.2 (-43.9) [-48.2]	-48.0 (-37.3) [-41.5]

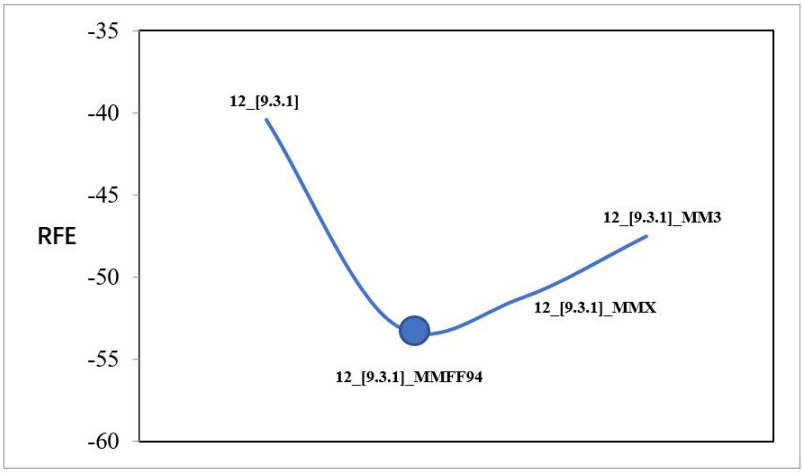


Figure S2. The relative free energies (RFEs) of 12_[9.3.1] and its conformers determined by the GMMX conformer searching methods. The relative free energies (RFEs) are compared with the D-A precursor **11** (zero point). Gibbs free energies (Grel, 298K) are quoted in kcal·mol^{-1}, using the SMD (toluene)-M06-2X/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) level of DFT theory.

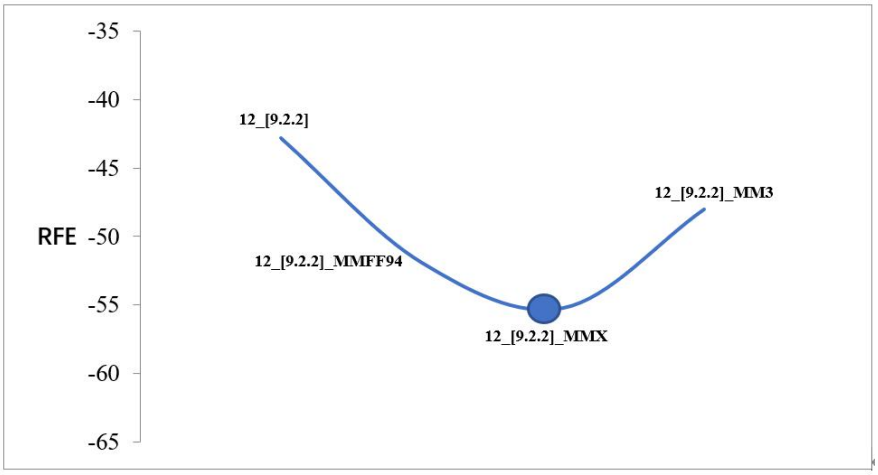
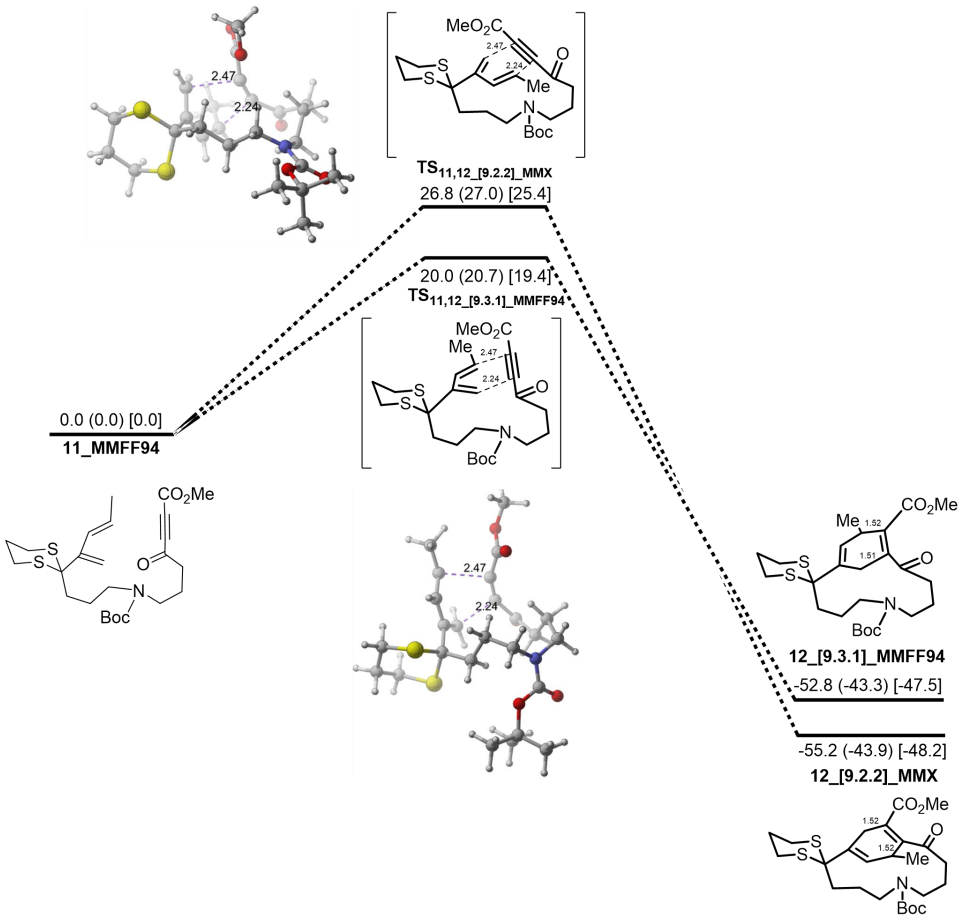


Figure S3. The relative free energies (RFEs) of 12_[9.2.2] and its conformers determined by the GMMX conformer searching methods. The relative free energies (RFEs) are compared with the D-A precursor **11** (zero point). Gibbs free energies (Grel, 298K) are quoted in kcal·mol^{-1}, using the SMD (toluene)-M06-2X/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) level of DFT theory.

As both the 12_[9,3,1]_MMFF94 and 12_[9,2,2]_MMX being determined, the corresponding TS structures (*i.e.* $TS_{11,12\_[9,3,1]\_MMFF94}$ and $TS_{11,12\_[9,2,2]\_MMX}$) have been found subsequently, which give a new energy diagram (**Scheme S3**). The new energy diagram has once again shown a similar pattern, in which energy of $TS_{11,12\_[9,3,1]\_MMFF94}$ leading to the desired product is lower (by 6.8 kcal/mol using the SMD(toluene)-M06-2X/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) level of DFT theory) than the $TS_{11,12\_[9,2,2]\_MMX}$ leading to the actually observed product. Moreover, the undesired, but experimentally observed product is thermodynamically more favorable by 2.4 kcal/mol, undergoing the same crossing over of the reaction paths in the new energy diagram.



Scheme S3. **Computed free energy profiles (assisted by GMMX conformer searching methods) for the D-A precursor 11 that protected by 1,3-dithiane protecting group.** The relative free energies (RFEs) are compared with the D-A precursor **11** (zero point). Gibbs free energies (Grel, 298K) are quoted in kcal·mol^{-1}. SMD (toluene)-M06-2X/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) free energies in solvated phase are quoted outsides parentheses and brackets. SMD (toluene)-B3LYP-D3(BJ)/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d) free energies in solvated phase are quoted in parentheses. B3LYP-D3(BJ)/6-31G(d) free energies in gas phase (without solvents) are quoted in brackets.

Cartesian Coordinate

11_MMFF94

C	-5.40716	-0.9404	-0.5582	C	-1.12157	-2.9271	0.007597
O	-5.47133	0.036705	-1.27584	H	-1.57277	-2.26109	-0.73731
O	-6.3371	-1.90722	-0.48644	H	-1.83154	-3.75377	0.142353
C	-7.4798	-1.71621	-1.3435	C	0.179238	-3.5273	-0.54195
H	-7.99231	-0.78473	-1.09115	H	0.586797	-4.2481	0.167594
H	-7.16895	-1.68328	-2.39063	H	-0.04792	-4.06336	-1.47484
H	-8.12356	-2.57524	-1.15734	C	1.080004	-1.64534	-1.94835
C	-4.29939	-1.2114	0.331932	H	2.036068	-1.55607	-2.46891
C	-3.3294	-1.36828	1.044292	C	0.543024	-0.24577	-1.59206
C	-2.18369	-1.56441	1.929516	H	0.259478	0.249533	-2.52911
O	-2.25837	-1.21331	3.094843	H	-0.37459	-0.35294	-1.00612
C	-0.93115	-2.17828	1.329819	C	1.563168	0.612784	-0.83379
H	-0.2268	-1.34551	1.19469	H	2.418139	0.814823	-1.48904
H	-0.48774	-2.82123	2.098867	H	1.944114	0.046682	0.020544

C	1.044357	1.958794	-0.26591	H	1.128552	4.205393	1.735361
C	-0.0563	1.722535	0.791825	H	-0.67621	4.460124	-0.16431
C	0.260527	1.333746	2.04036	H	-0.20526	5.24213	-1.67745
H	-0.51274	1.043335	2.744809	H	2.167096	5.367878	-0.91912
H	1.289235	1.284045	2.380622	H	1.077113	6.188717	0.208695
C	-1.47311	1.851591	0.386964	C	2.440613	-2.73786	-0.15032
H	-1.73363	1.557802	-0.62719	O	2.602465	-3.54092	0.758159
C	-2.437	2.338225	1.184776	O	3.394103	-1.91081	-0.63891
H	-2.15883	2.701036	2.174982	C	4.750353	-1.89306	-0.06259
C	-3.88899	2.43027	0.82606	C	5.416436	-3.2583	-0.25437
H	-4.09744	2.01553	-0.16415	H	5.399543	-3.54358	-1.3121
H	-4.50031	1.881004	1.555004	H	6.462905	-3.20264	0.065548
H	-4.23771	3.472089	0.849911	H	4.908259	-4.02721	0.328589
H	0.377054	-2.12602	-2.63932	C	4.692278	-1.47357	1.408732
N	1.243237	-2.55763	-0.80957	H	5.71141	-1.36032	1.79506
S	0.469293	2.984039	-1.70062	H	4.183695	-0.50863	1.510712
S	2.569574	2.735478	0.46949	H	4.169305	-2.21922	2.008802
C	1.903284	4.365304	0.976891	C	5.452566	-0.82401	-0.90204
C	0.149283	4.590492	-0.87253	H	4.960467	0.14696	-0.78734
C	1.369872	5.204438	-0.18563	H	6.49453	-0.72306	-0.58121
H	2.744768	4.869656	1.462334	H	5.442346	-1.09656	-1.9625

12_[9.3.1]_MMFF94

C	-4.10561	-1.60499	0.094787	H	2.828382	-0.57923	-2.48357
O	-3.82537	-2.74918	-0.20257	C	0.904577	0.300023	-2.00174
O	-5.3708	-1.19338	0.336479	H	0.902612	0.959722	-2.87876
C	-6.37455	-2.21859	0.241021	H	-0.12832	-0.03561	-1.86946
H	-6.39703	-2.64141	-0.76688	C	1.36758	1.075527	-0.76125
H	-6.16955	-3.0174	0.95781	H	2.299323	1.609704	-0.97404
H	-7.31818	-1.7243	0.472977	H	1.605605	0.361352	0.031773
C	-3.12124	-0.49445	0.265733	C	0.343298	2.095922	-0.18943
C	-1.97228	-0.76033	0.906745	C	-0.9856	1.417277	0.127325
C	-1.61198	-2.13137	1.445504	C	-0.95244	0.32211	1.175518
O	-2.18391	-2.5924	2.414462	H	-1.14742	0.745041	2.172907
C	-0.43423	-2.82269	0.770849	H	0.045613	-0.11348	1.258167
H	0.480525	-2.29913	1.07893	C	-2.14013	1.674334	-0.49694
H	-0.36296	-3.83072	1.189025	H	-2.17473	2.443593	-1.26249
C	-0.51025	-2.85262	-0.76706	C	-3.42125	0.89196	-0.29344
H	-0.94514	-1.91964	-1.13829	H	-4.06075	1.424052	0.430876
H	-1.20311	-3.64348	-1.07567	C	-4.19139	0.843565	-1.63064
C	0.843599	-3.08668	-1.45387	H	-3.61757	0.295795	-2.38703
H	1.320769	-3.98118	-1.04841	H	-5.16515	0.364423	-1.51451
H	0.675421	-3.24954	-2.52556	H	-4.35481	1.859841	-2.00508
C	1.799875	-0.90956	-2.33027	H	1.454544	-1.35229	-3.27218

N	1.805933	-1.98186	-1.32507	O	3.706891	-1.11193	-0.47885
S	0.23969	3.467973	-1.42965	C	4.862957	-1.04758	0.431185
S	1.151276	2.700979	1.381088	C	5.775972	-2.25528	0.203896
C	0.037458	4.080135	1.843143	H	6.0616	-2.32122	-0.85181
C	-0.65656	4.782011	-0.5085	H	6.690373	-2.13961	0.796519
C	-0.00481	5.204042	0.807448	H	5.279972	-3.18162	0.495831
H	0.434084	4.445134	2.795628	C	4.386149	-0.94103	1.882254
H	-0.96852	3.687063	2.032556	H	5.248521	-0.77683	2.538012
H	-1.69039	4.465351	-0.33536	H	3.70659	-0.08942	1.998844
H	-0.68097	5.621196	-1.21108	H	3.874722	-1.85201	2.195373
H	1.009329	5.574243	0.622568	C	5.554906	0.244934	-0.00645
H	-0.59147	6.036361	1.222759	H	4.889129	1.104446	0.121507
C	2.818201	-2.13307	-0.40623	H	6.45339	0.411017	0.596811
O	2.884979	-3.06813	0.381139	H	5.850681	0.187982	-1.05913

12_[9.3.1]_MMX

C	1.807273	2.467642	-1.32153	C	-1.82925	0.414682	-0.25375
O	2.300081	2.264082	-2.41658	C	-1.42181	1.575316	0.639929
O	2.439065	3.165476	-0.35161	H	-2.10737	2.424612	0.498794
C	3.77558	3.591698	-0.66053	H	-1.52699	1.325642	1.696739
H	4.422573	2.726081	-0.82474	C	-1.34668	0.37889	-1.50163
H	3.776742	4.217412	-1.55624	H	-1.60981	-0.44037	-2.16454
H	4.106318	4.159862	0.208808	C	-0.3867	1.414378	-2.03485
C	0.459601	1.994411	-0.91472	H	0.299251	0.924943	-2.73539
C	-0.01082	2.04877	0.344908	C	-1.11212	2.525808	-2.83092
C	0.730895	2.554666	1.564561	H	-1.69108	2.0937	-3.65503
O	0.348955	3.564474	2.127332	H	-0.38516	3.225237	-3.25624
C	1.801908	1.63918	2.132239	H	-1.7989	3.085303	-2.18674
H	2.526802	2.252239	2.676697	H	0.967529	-3.5252	1.575118
H	2.328529	1.127111	1.326923	N	1.627623	-1.56179	1.861943
C	1.172254	0.593418	3.095788	S	-4.05206	0.013418	1.401744
H	0.115919	0.432049	2.857646	S	-3.31856	-1.94507	-0.81062
H	1.189123	0.989252	4.118175	C	-4.53834	-0.94925	-1.75491
C	1.872709	-0.7735	3.076951	C	-5.10462	0.728799	0.082054
H	1.526625	-1.36745	3.930817	C	-5.63687	-0.30798	-0.90746
H	2.953074	-0.64328	3.175436	H	-4.96825	-1.66222	-2.46565
C	0.53541	-2.54982	1.81505	H	-4.00551	-0.18572	-2.33174
H	0.126526	-2.62006	2.828359	H	-4.5468	1.514898	-0.44048
C	-0.58925	-2.23315	0.801671	H	-5.92762	1.210264	0.619246
H	-0.15788	-1.66067	-0.02182	H	-6.19388	-1.08164	-0.36807
H	-0.93993	-3.17648	0.368608	H	-6.34029	0.193478	-1.58805
C	-1.78561	-1.47994	1.408642	C	2.591581	-1.53684	0.883226
H	-1.42885	-0.75786	2.151605	O	3.570295	-0.79897	0.904368
H	-2.436	-2.17833	1.947864	O	2.306512	-2.42686	-0.09528
C	-2.65684	-0.69461	0.387104	C	3.147078	-2.52485	-1.30149

C	2.434703	-3.61207	-2.10837	H	5.066561	-2.20629	-0.32952
H	1.407932	-3.3113	-2.33995	H	5.142645	-3.15805	-1.83089
H	2.401754	-4.55163	-1.54724	C	3.135504	-1.19412	-2.05672
H	2.965521	-3.78856	-3.04953	H	3.622938	-0.40579	-1.48304
C	4.561412	-2.97049	-0.92108	H	2.107676	-0.88532	-2.27368
H	4.524083	-3.9009	-0.34366	H	3.66138	-1.30807	-3.011

12_[9.3.1]_MM3

C	-1.14921	3.067753	-0.87897	C	1.296237	2.368196	-1.42903
O	-1.51928	4.187274	-0.59818	H	2.005282	3.160323	-1.12772
O	-1.83738	2.231567	-1.68715	C	0.916566	2.624289	-2.89238
C	-3.07844	2.756042	-2.19918	H	0.221739	1.865099	-3.26194
H	-3.75869	2.98844	-1.37642	H	0.451038	3.607314	-3.0209
H	-3.49006	1.964986	-2.82463	H	1.817275	2.598409	-3.51466
H	-2.89642	3.661864	-2.78263	H	-0.41615	-1.86327	2.75357
C	0.138327	2.456439	-0.42031	N	-2.07621	-1.1851	1.737029
C	0.378735	2.024642	0.833639	S	3.020943	-1.9369	-1.04217
C	-0.60948	1.874351	1.950328	S	4.201701	-0.67171	1.485248
O	-0.1962	1.713541	3.092714	C	5.460858	-0.09419	0.285969
C	-2.10028	1.817972	1.651505	C	4.539533	-1.2303	-1.79996
H	-2.47079	2.850977	1.599548	C	5.725574	-1.08429	-0.84792
H	-2.26363	1.384	0.661748	H	6.361738	0.057209	0.888649
C	-2.91237	1.041228	2.693331	H	5.160238	0.881869	-0.11279
H	-2.85318	1.55001	3.661933	H	4.30535	-0.2656	-2.26212
H	-3.95534	1.048684	2.371512	H	4.777161	-1.93321	-2.60495
C	-2.46282	-0.41423	2.931895	H	5.996923	-2.06046	-0.43174
H	-3.26708	-0.93802	3.465637	H	6.584242	-0.72222	-1.43211
H	-1.58522	-0.40205	3.578342	C	-3.02121	-1.37343	0.766514
C	-0.83431	-1.97729	1.749858	O	-4.1302	-0.85354	0.779142
H	-1.07546	-3.0378	1.623903	O	-2.55217	-2.19587	-0.20777
C	0.213076	-1.53721	0.700101	C	-3.32862	-2.4332	-1.43023
H	-0.05142	-0.5345	0.357769	C	-4.62357	-3.17805	-1.09409
H	0.156733	-2.18211	-0.18107	H	-5.14884	-3.44116	-2.01926
C	1.639632	-1.52585	1.275098	H	-4.39824	-4.10514	-0.55561
H	1.994509	-2.54398	1.4704	H	-5.27774	-2.56051	-0.47739
H	1.620902	-1.01493	2.245347	C	-2.39085	-3.31781	-2.25453
C	2.697951	-0.80638	0.389297	H	-1.45678	-2.79154	-2.47644
C	2.209434	0.577606	0.002535	H	-2.14899	-4.23563	-1.70897
C	1.784845	1.521661	1.119162	H	-2.86832	-3.5929	-3.2008
H	1.831515	1.076528	2.110225	C	-3.59019	-1.10624	-2.15095
H	2.473227	2.381101	1.140648	H	-2.65117	-0.55678	-2.28132
C	1.977871	1.022966	-1.2372	H	-4.01583	-1.30447	-3.14121
H	2.165479	0.416925	-2.11737	H	-4.28475	-0.48598	-1.58274

TS11,12_[9.3.1]_MMFF94

C	3.79376	-1.84981	0.457524	C	3.745441	1.240146	0.083008
O	3.386908	-2.25849	1.533019	H	4.021416	1.052993	-0.95111
O	5.092015	-1.91997	0.069965	C	4.8825	1.29265	1.056316
C	5.959557	-2.59488	0.997115	H	4.533095	1.410492	2.086598
H	6.947901	-2.56975	0.537617	H	5.49251	0.385143	0.989881
H	5.969264	-2.08309	1.962887	H	5.550709	2.13378	0.821268
H	5.631509	-3.62697	1.146273	H	-0.65388	-2.10047	2.624766
C	2.95322	-1.26315	-0.54329	N	-1.7345	-2.28583	0.863059
C	2.024729	-1.07687	-1.34977	S	-0.03759	3.007452	1.531707
C	1.120561	-1.78604	-2.29048	S	-1.11253	2.667194	-1.27548
O	1.301397	-1.73171	-3.49161	C	-0.18711	4.220635	-1.56888
C	-0.05085	-2.52654	-1.66208	C	0.700208	4.52559	0.809166
H	-0.80865	-1.75607	-1.46231	C	-0.10172	5.131574	-0.34319
H	-0.4736	-3.17734	-2.43325	H	-0.72959	4.715197	-2.38065
C	0.235339	-3.28485	-0.3565	H	0.813134	3.972422	-1.9427
H	0.978545	-2.75346	0.242691	H	1.727898	4.308098	0.496516
H	0.674206	-4.26486	-0.58359	H	0.75301	5.22488	1.649623
C	-1.02495	-3.51357	0.49277	H	-1.11079	5.384545	-0.00012
H	-1.73893	-4.13714	-0.04618	H	0.390178	6.068137	-0.64386
H	-0.74097	-4.03686	1.415192	C	-2.96612	-2.07291	0.28603
C	-1.20233	-1.44226	1.940829	O	-3.4317	-2.77761	-0.59996
H	-2.04796	-1.02793	2.492213	O	-3.57951	-0.98801	0.81826
C	-0.26068	-0.29863	1.505887	C	-4.89255	-0.54354	0.320283
H	-0.00127	0.258128	2.415443	C	-5.94321	-1.62785	0.574887
H	0.676371	-0.7081	1.118447	H	-5.95471	-1.90336	1.635263
C	-0.89825	0.640631	0.474274	H	-6.9356	-1.24423	0.312586
H	-1.8634	0.997496	0.845091	H	-5.73883	-2.5181	-0.02079
H	-1.111	0.074913	-0.4395	C	-4.79414	-0.16201	-1.15946
C	-0.06702	1.880202	0.05415	H	-5.74572	0.271141	-1.48754
C	1.339691	1.524139	-0.47467	H	-4.01148	0.589889	-1.30908
C	1.485653	0.95325	-1.72858	H	-4.57357	-1.03467	-1.7754
H	2.438644	0.99001	-2.24386	C	-5.17247	0.691836	1.178698
H	0.629247	0.872313	-2.38854	H	-4.4088	1.459754	1.018542
C	2.466635	1.600498	0.401424	H	-6.14719	1.115321	0.915165
H	2.268395	1.891337	1.429554	H	-5.18509	0.429637	2.241676

12_[9.2.2]_MMFF94

C	-1.69174	0.417211	1.741182	C	0.650984	3.383534	1.34474
C	-1.09772	1.735216	2.172067	O	0.433334	4.393781	1.990159
C	-0.50226	2.47433	0.987727	O	0.41057	3.95783	-1.24745
C	-1.02892	2.323529	-0.24107	O	-1.20253	2.989035	-2.49418
C	-2.12751	1.317508	-0.51711	C	-0.77031	3.795036	-3.60286
C	-2.15388	0.19214	0.505946	H	-0.85273	4.856599	-3.35692
H	-1.71956	-0.35699	2.502017	H	0.268389	3.568615	-3.85715
C	-0.51751	3.172523	-1.3457	H	-1.43471	3.535716	-4.42712
C	-2.6454	-1.1714	0.028277	H	-3.10563	1.82156	-0.53246

C	-2.13427	2.632612	2.895768	S	-4.25582	-0.86076	-0.87034
H	-1.67506	3.579248	3.191764	C	-3.70686	-3.74007	0.723034
H	-2.98033	2.843935	2.234534	C	-4.8161	-2.56522	-1.25557
H	-2.51393	2.121236	3.787087	C	-5.00751	-3.45534	-0.02838
C	-1.60311	-1.82064	-0.93216	H	-3.8936	-4.40721	1.570619
C	-0.17158	-1.93364	-0.36015	H	-2.98132	-4.24364	0.0741
C	0.778719	-0.88816	-0.96845	H	-4.13137	-3.02906	-1.97424
N	2.017305	-0.70407	-0.21513	H	-5.76958	-2.41322	-1.77148
C	2.05198	0.371403	0.775803	H	-5.73187	-2.99434	0.651729
C	2.361761	1.744075	0.154256	H	-5.42884	-4.41495	-0.36158
C	2.096992	2.941916	1.077247	C	3.08999	-1.48855	-0.53638
H	-2.00744	0.925773	-1.5301	O	3.046213	-2.38228	-1.37232
H	-0.29661	1.530748	2.896426	O	4.185423	-1.1379	0.186427
H	-1.59108	-1.2341	-1.85928	C	5.445083	-1.88012	0.047297
H	-1.97105	-2.80816	-1.2225	C	6.357947	-1.17517	1.05294
H	-0.19604	-1.8191	0.72817	H	5.9498	-1.2527	2.066009
H	0.243543	-2.92717	-0.55742	H	7.352603	-1.6329	1.044069
H	0.284413	0.086335	-1.01099	H	6.462273	-0.11451	0.802274
H	1.036315	-1.17485	-1.99118	C	5.988337	-1.72726	-1.37647
H	1.073183	0.380558	1.265064	H	6.980208	-2.18823	-1.4442
H	2.792878	0.125484	1.538174	H	5.325085	-2.20427	-2.09895
H	3.419448	1.749877	-0.13386	H	6.088458	-0.66635	-1.63134
H	1.794225	1.867676	-0.77175	C	5.241563	-3.34688	0.438093
H	2.53866	2.76472	2.069528	H	4.812367	-3.41479	1.443894
H	2.5967	3.834252	0.687431	H	4.577069	-3.84976	-0.2654
S	-2.94172	-2.26864	1.503099	H	6.208515	-3.86235	0.445161

12_[9.2.2]_MMX

C	-1.97159	-0.1049	-1.33742	C	-3.42158	1.836165	-2.09284
C	-1.99158	1.345464	-1.75188	H	-3.83878	1.237842	-2.91076
C	-1.37623	2.230157	-0.67744	H	-3.40193	2.886963	-2.39297
C	-1.47187	1.877126	0.617633	H	-4.07604	1.733474	-1.22118
C	-2.06962	0.549768	1.036379	C	-0.44482	-2.24747	0.966783
C	-1.99132	-0.49949	-0.05801	C	0.737412	-1.83057	0.060843
H	-1.92051	-0.83966	-2.13541	C	1.421751	-0.54367	0.554649
C	-0.99924	2.724803	1.744042	N	2.286344	0.091405	-0.43855
C	-1.85842	-1.95681	0.377913	C	1.699395	1.128468	-1.28283
C	-0.71449	3.468832	-1.2317	C	1.676697	2.506392	-0.60072
O	-1.39889	4.339417	-1.73975	C	0.81739	3.553907	-1.32216
O	-0.96647	2.362521	2.904517	H	-3.11735	0.689807	1.341674
O	-0.61455	3.961041	1.349543	H	-1.39603	1.447534	-2.66996
C	-0.13211	4.823712	2.392056	H	-0.40567	-3.31737	1.192761
H	-0.90743	4.975975	3.146791	H	-0.36875	-1.73124	1.933093
H	0.115223	5.76391	1.899126	H	1.485154	-2.62896	0.025563
H	0.751305	4.391781	2.869577	H	0.391761	-1.68219	-0.96737
H	-1.57098	0.219347	1.950726	H	0.665233	0.195905	0.830884

H	2.003974	-0.75514	1.454382	H	-5.83537	-3.15845	-0.63768
H	2.278873	1.180581	-2.20688	C	3.607725	-0.22135	-0.60805
H	0.685678	0.804216	-1.53937	O	4.345401	0.34541	-1.40366
H	2.709429	2.869903	-0.55104	O	3.968216	-1.23775	0.217184
H	1.339697	2.398695	0.434801	C	5.352784	-1.7279	0.246406
H	1.072051	4.561163	-0.97511	C	6.29972	-0.60666	0.683732
H	1.045944	3.553634	-2.39812	H	5.971032	-0.1848	1.640047
S	-2.0732	-3.18439	-1.00037	H	6.333338	0.188631	-0.06185
S	-3.03821	-2.3543	1.762155	H	7.309503	-1.01002	0.819198
C	-3.8494	-2.98062	-1.41678	C	5.732529	-2.31061	-1.11798
C	-4.64647	-2.23428	0.889928	H	5.009245	-3.07751	-1.4165
C	-4.8077	-3.23601	-0.25376	H	6.720532	-2.78048	-1.05506
H	-4.01813	-3.70451	-2.22043	H	5.757887	-1.5317	-1.88085
H	-4.00993	-1.97994	-1.83216	C	5.29207	-2.82931	1.306781
H	-5.39329	-2.41377	1.669586	H	4.97904	-2.41983	2.272754
H	-4.78774	-1.20829	0.529014	H	6.278175	-3.28951	1.428265
H	-4.67303	-4.25475	0.125443	H	4.58017	-3.60799	1.014183

12_[9.2.2]_MM3

C	-1.78908	0.624448	-1.80226	C	2.70875	1.339167	-1.27745
C	-1.1959	1.968683	-2.1857	C	2.117773	2.533219	-0.4926
C	-0.45107	2.539825	-0.97118	H	-3.20393	2.222825	0.149956
C	-1.0606	2.435822	0.228778	H	-2.03268	2.667801	-2.35858
C	-2.31986	1.602675	0.370813	H	-2.15155	-2.45509	1.342241
C	-2.30223	0.417703	-0.58518	H	-1.74959	-0.83242	1.831764
H	-1.74672	-0.15836	-2.55369	H	0.073698	-2.66841	0.769685
C	-0.50605	3.137197	1.414713	H	-0.34256	-1.74541	-0.66181
C	-2.78008	-0.93133	-0.0659	H	0.864783	-0.72139	1.957541
C	0.907978	3.168658	-1.17746	H	0.175495	0.378254	0.761524
O	1.042386	4.072371	-1.98458	H	0.913779	0.117151	-1.48955
O	0.370248	3.982513	1.376073	H	2.420041	-0.71105	-1.85715
O	-1.09096	2.744369	2.568859	H	2.790134	1.605556	-2.33965
C	-0.60898	3.400441	3.752984	H	3.730004	1.1709	-0.92159
H	-0.74791	4.481534	3.673974	H	1.881362	2.218287	0.525351
H	-1.20075	2.992602	4.572544	H	2.872248	3.322987	-0.43092
H	0.453125	3.188548	3.900535	S	-4.42906	-0.61606	0.759254
H	-2.43742	1.290446	1.408381	S	-3.00057	-2.09222	-1.50236
C	-0.40889	1.891125	-3.50101	C	-4.97751	-2.31341	1.191172
H	-0.03223	2.872222	-3.79342	C	-3.75942	-3.54665	-0.68544
H	-1.06792	1.518115	-4.29227	C	-5.09702	-3.25958	-0.00287
H	0.441552	1.204409	-3.42931	H	-5.95625	-2.15734	1.656075
C	-1.761	-1.50572	0.965574	H	-4.31955	-2.73365	1.959847
C	-0.32362	-1.70495	0.43211	H	-3.04888	-3.99741	0.016779
C	0.639894	-0.5992	0.896346	H	-3.89396	-4.25864	-1.50592
N	1.912186	-0.5847	0.17329	H	-5.80062	-2.84547	-0.73306
C	1.953347	0.002178	-1.17149	H	-5.51238	-4.21294	0.354802

C	2.938382	-1.339	0.680548	C	4.941313	-3.54697	0.244918
O	2.878388	-1.94933	1.739684	H	5.877388	-4.10298	0.368589
O	4.016496	-1.30063	-0.14478	H	4.279301	-3.77743	1.080385
C	5.240201	-2.0462	0.180052	H	4.468983	-3.87988	-0.68602
C	6.148459	-1.72763	-1.00939	C	5.846814	-1.51711	1.482633
H	5.689278	-2.06041	-1.94593	H	5.190919	-1.72303	2.329235
H	6.332603	-0.65059	-1.07843	H	6.816665	-1.99615	1.658187
H	7.110868	-2.23711	-0.89479	H	6.009372	-0.43583	1.413013

TS11,12_[9.2.2]_MMX

C	-2.31401	0.156678	-1.57677	H	1.257507	0.533958	1.350399
C	-2.55769	1.428189	-2.08387	H	2.240207	-0.91941	1.211185
C	-1.26169	2.544828	-0.64313	H	2.930938	1.947895	-1.69454
C	-1.55702	2.312322	0.548508	H	1.282408	1.336686	-1.62289
C	-3.17209	0.453228	0.673437	H	2.609007	3.353966	0.250647
C	-2.58379	-0.34808	-0.27684	H	1.130184	2.529854	0.715998
H	-1.64272	-0.45267	-2.1752	H	0.628928	4.726655	-0.28557
C	-1.6558	2.511086	1.971491	H	1.459435	4.295239	-1.78361
C	-1.92018	-1.68058	0.166757	S	-1.66418	-2.86694	-1.23602
C	-0.42512	3.370746	-1.5393	S	-2.89644	-2.52884	1.505473
O	-0.76143	3.669591	-2.67208	C	-3.4034	-3.2126	-1.70983
O	-2.50076	3.192783	2.5177	C	-4.44588	-2.91827	0.606301
O	-0.68345	1.833364	2.637914	C	-4.24858	-3.83824	-0.59951
C	-0.7258	1.970013	4.070373	H	-3.32145	-3.89505	-2.56153
H	-0.60979	3.0174	4.359268	H	-3.85993	-2.28507	-2.07327
H	0.107825	1.373458	4.44066	H	-5.08549	-3.39598	1.355047
H	-1.67405	1.593765	4.462607	H	-4.92884	-1.98063	0.307819
H	-3.22781	0.132318	1.707841	H	-3.79513	-4.78116	-0.27541
C	-3.75413	2.3449	-1.9398	H	-5.23856	-4.07367	-1.01667
H	-4.58161	1.93883	-2.53884	C	3.916866	0.108547	-0.45421
H	-3.50052	3.326121	-2.34862	O	4.699507	0.683543	-1.19895
H	-4.11877	2.491083	-0.92429	O	4.205713	-1.0073	0.261175
C	-0.52884	-1.4273	0.811261	C	5.540796	-1.61765	0.194928
C	0.533955	-0.84898	-0.13568	C	6.597108	-0.63562	0.709476
C	1.681048	-0.18259	0.637352	H	6.334571	-0.28956	1.715397
N	2.624753	0.522841	-0.23504	H	6.682165	0.227518	0.048477
C	2.132877	1.662038	-1.00916	H	7.569261	-1.13822	0.765893
C	1.713698	2.861649	-0.1465	C	5.831934	-2.0924	-1.23161
C	0.889373	3.885357	-0.94329	H	5.035682	-2.76045	-1.57801
H	-3.80058	1.287951	0.410823	H	6.775198	-2.64992	-1.24825
H	-2.03443	1.623808	-3.01695	H	5.907933	-1.24681	-1.91598
H	-0.17233	-2.36715	1.248648	C	5.404592	-2.81048	1.143819
H	-0.69113	-0.72596	1.638987	H	5.155332	-2.47349	2.155416
H	0.93858	-1.6277	-0.79212	H	6.346788	-3.36676	1.186619
H	0.065327	-0.10218	-0.77842	H	4.616549	-3.48891	0.80111

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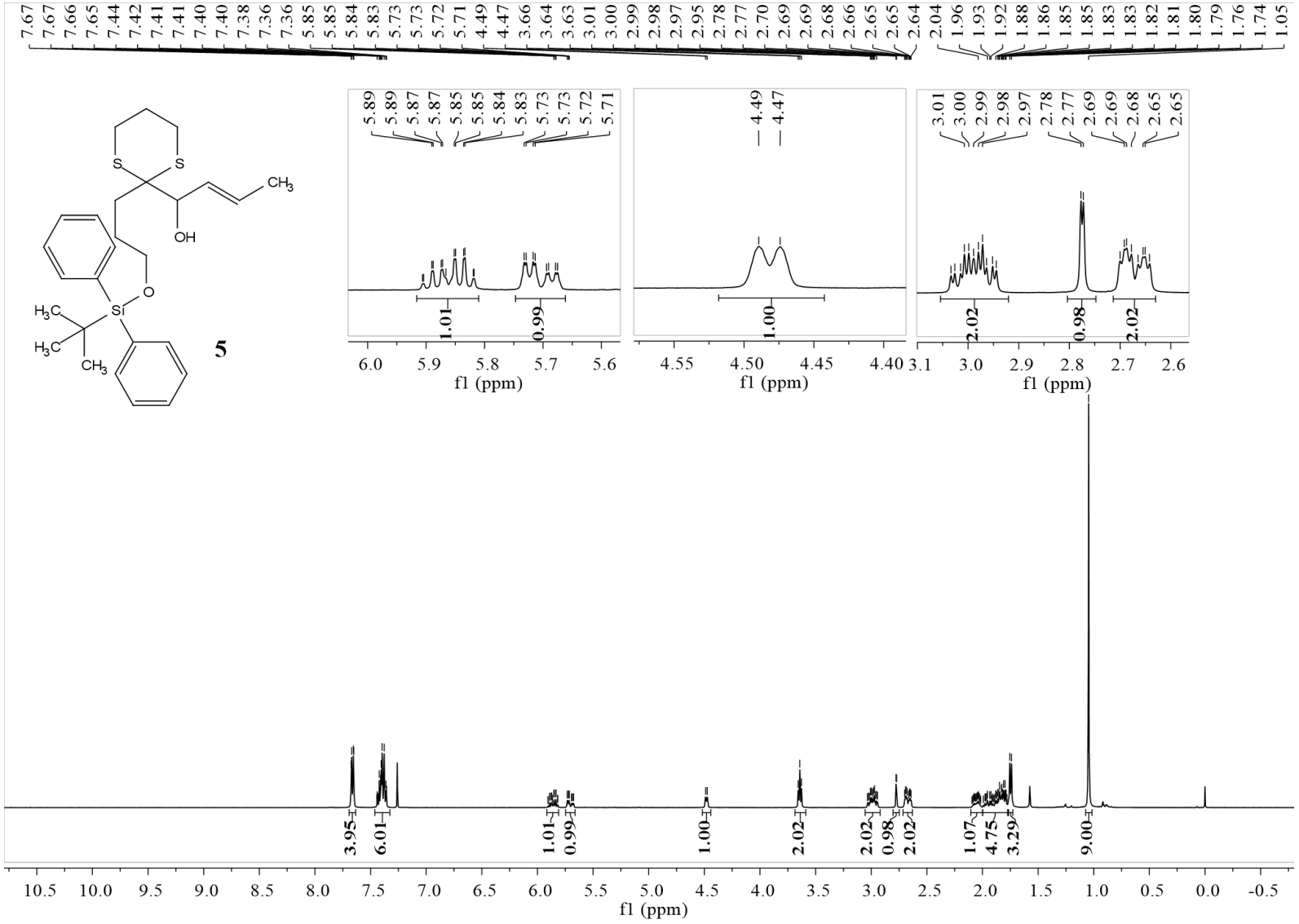
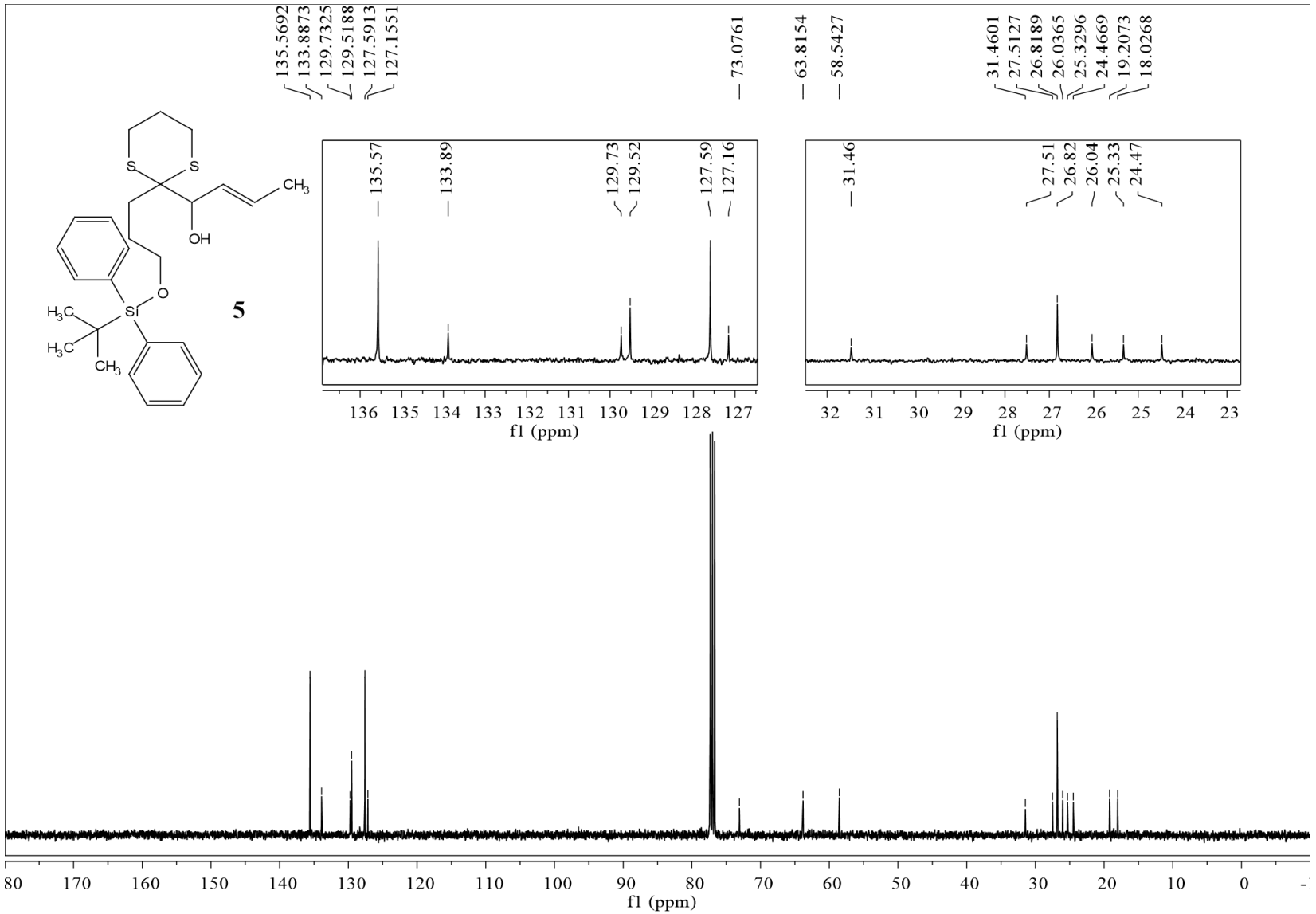
VI. ^{1}H and ^{13}C NMR Spectra of Synthesized Compounds

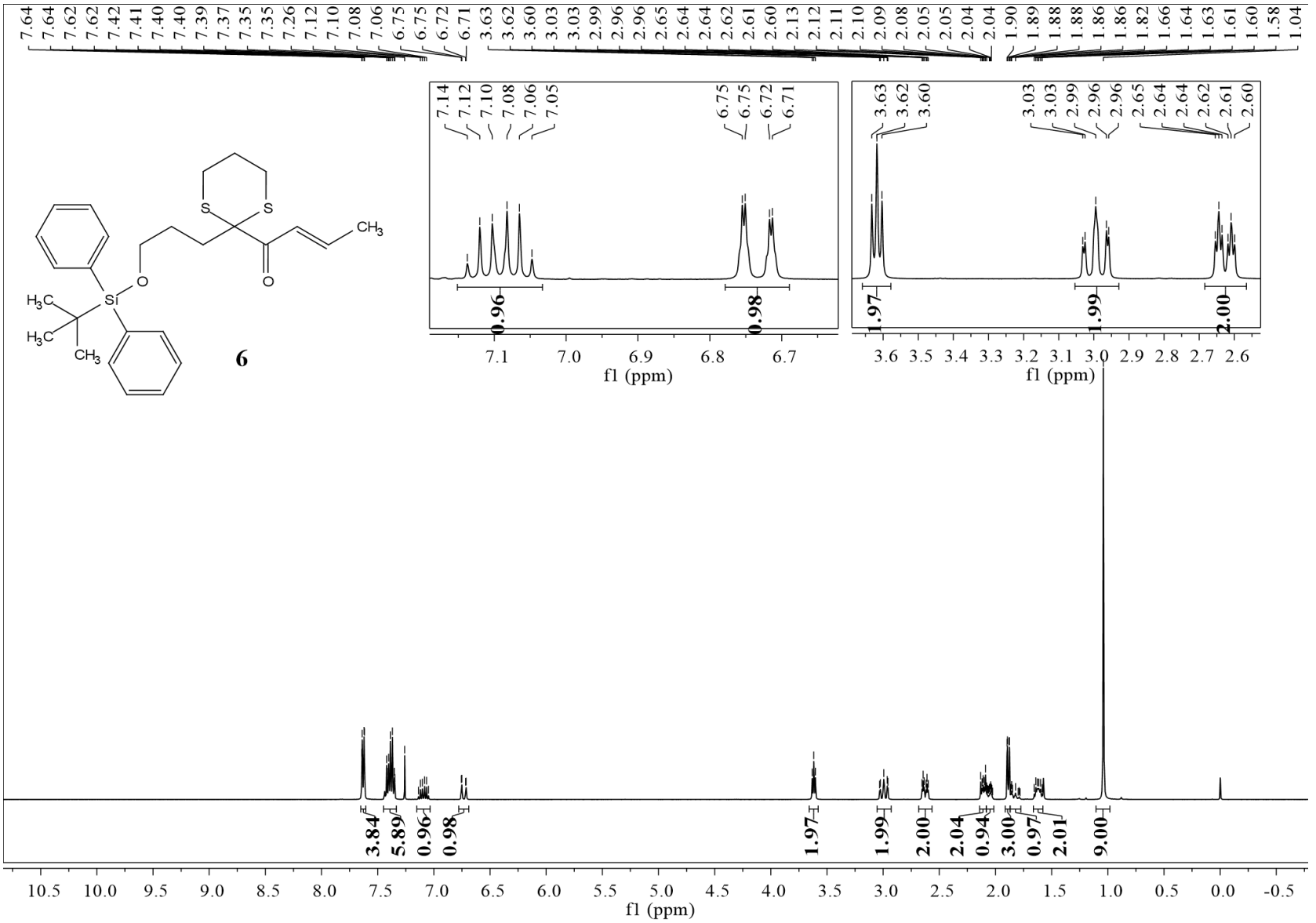
^{1}H NMR Spectrum of compound 5 (400 MHz, $CDCl_3$)



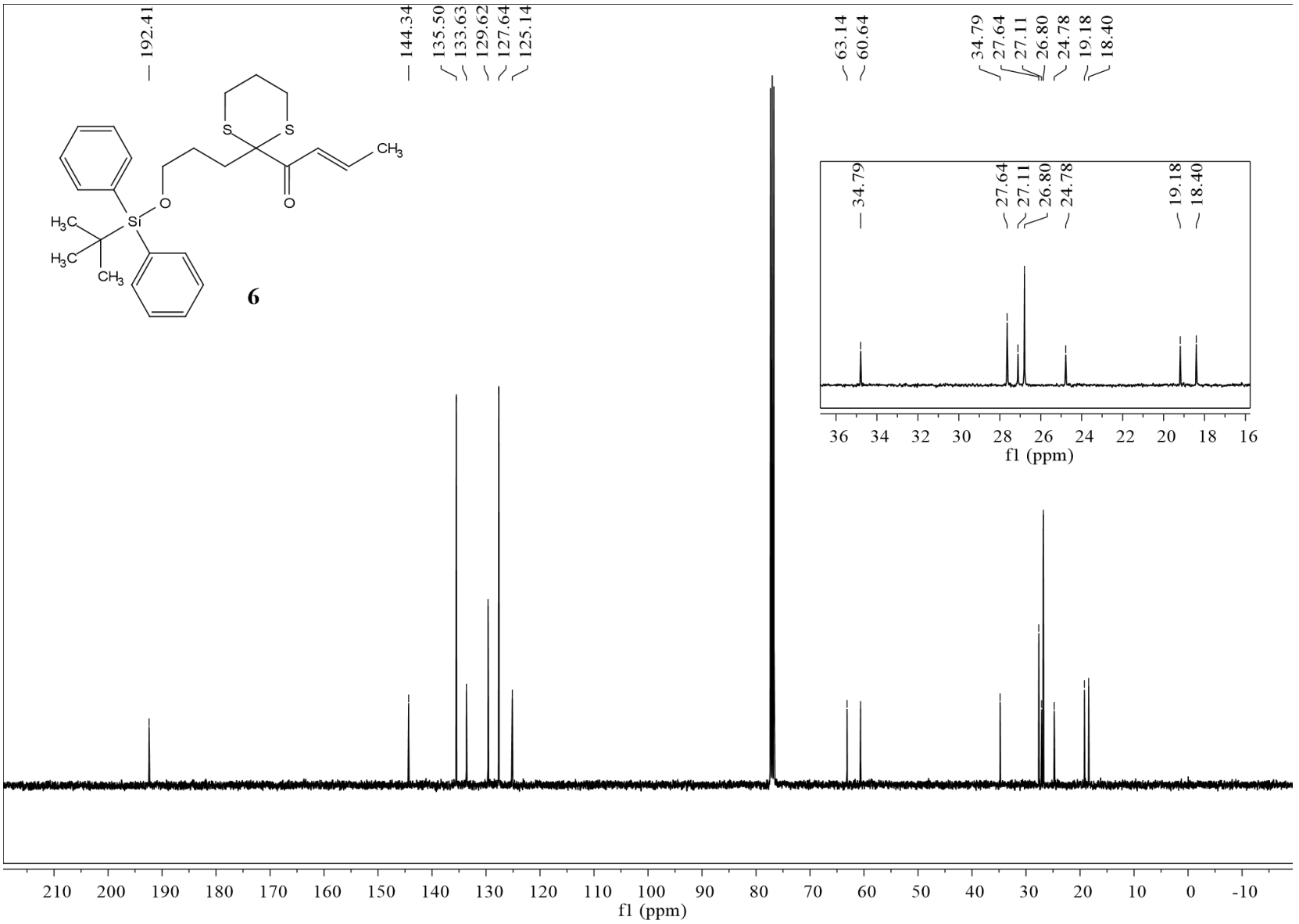
^{13}C NMR Spectrum of compound 5 (101 MHz, $CDCl_3$)



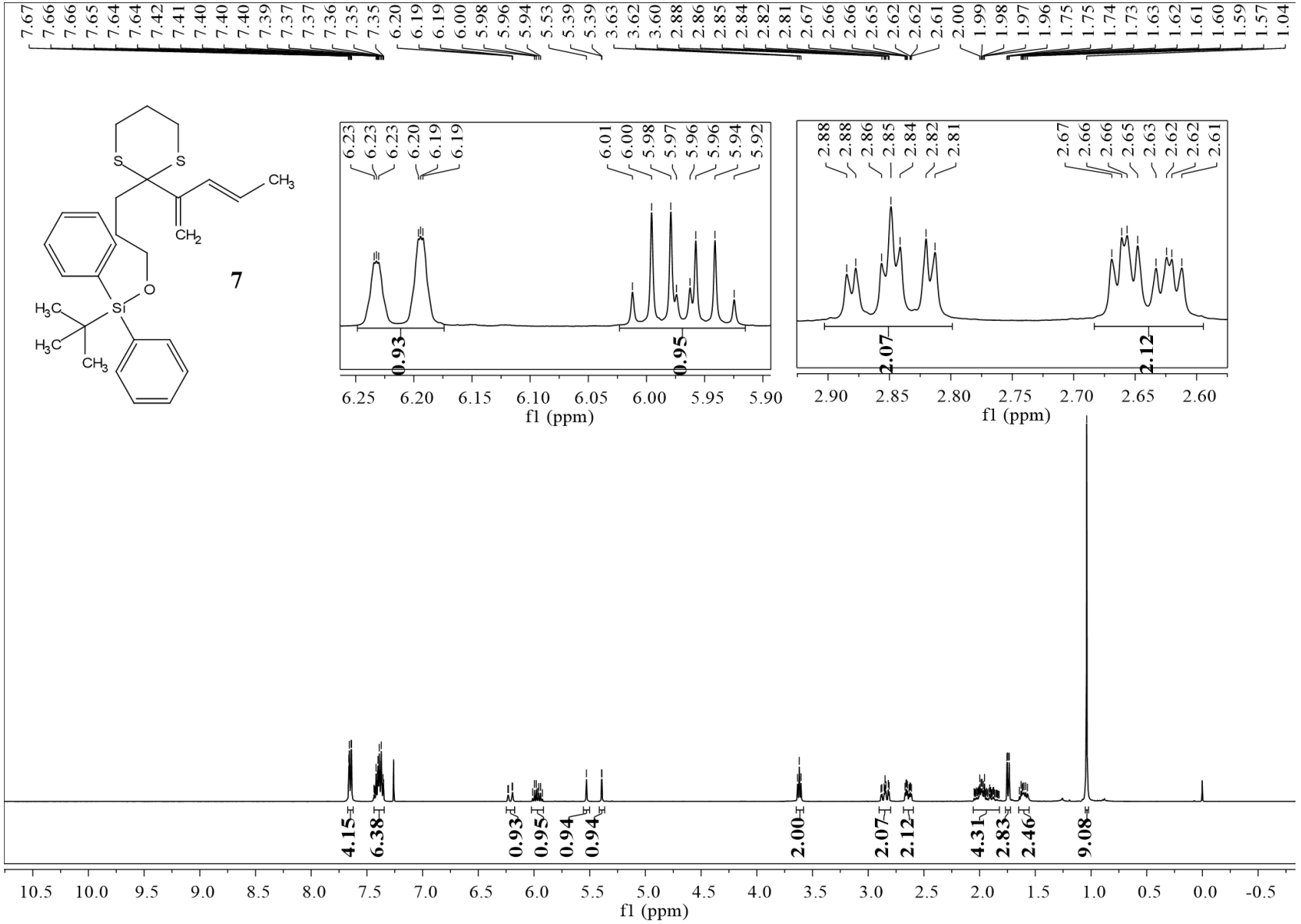
^{1}H NMR Spectrum of compound 6 (400 MHz, $CDCl_3$)



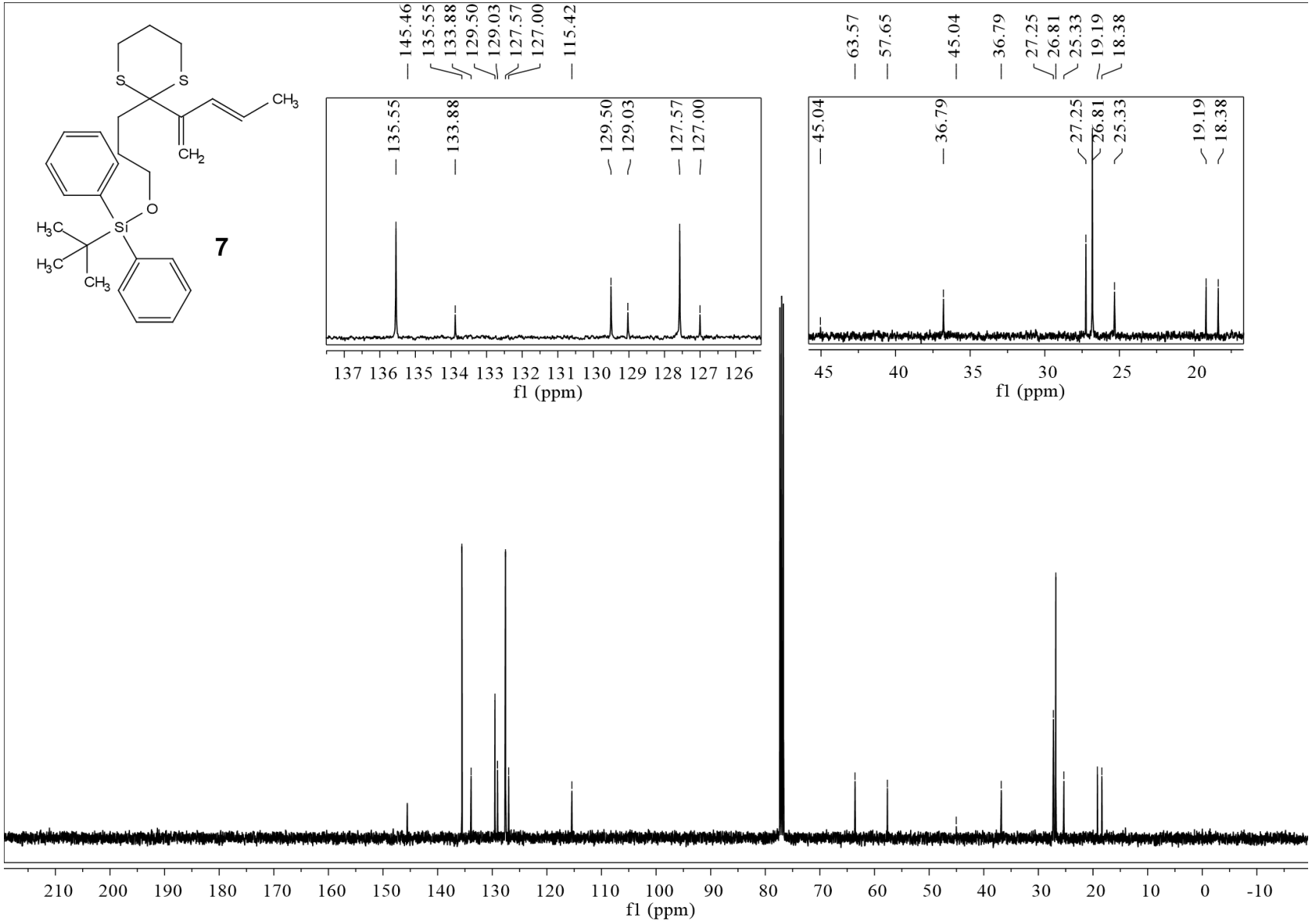
^{13}C NMR Spectrum of compound 6 (101 MHz, $CDCl_3$)



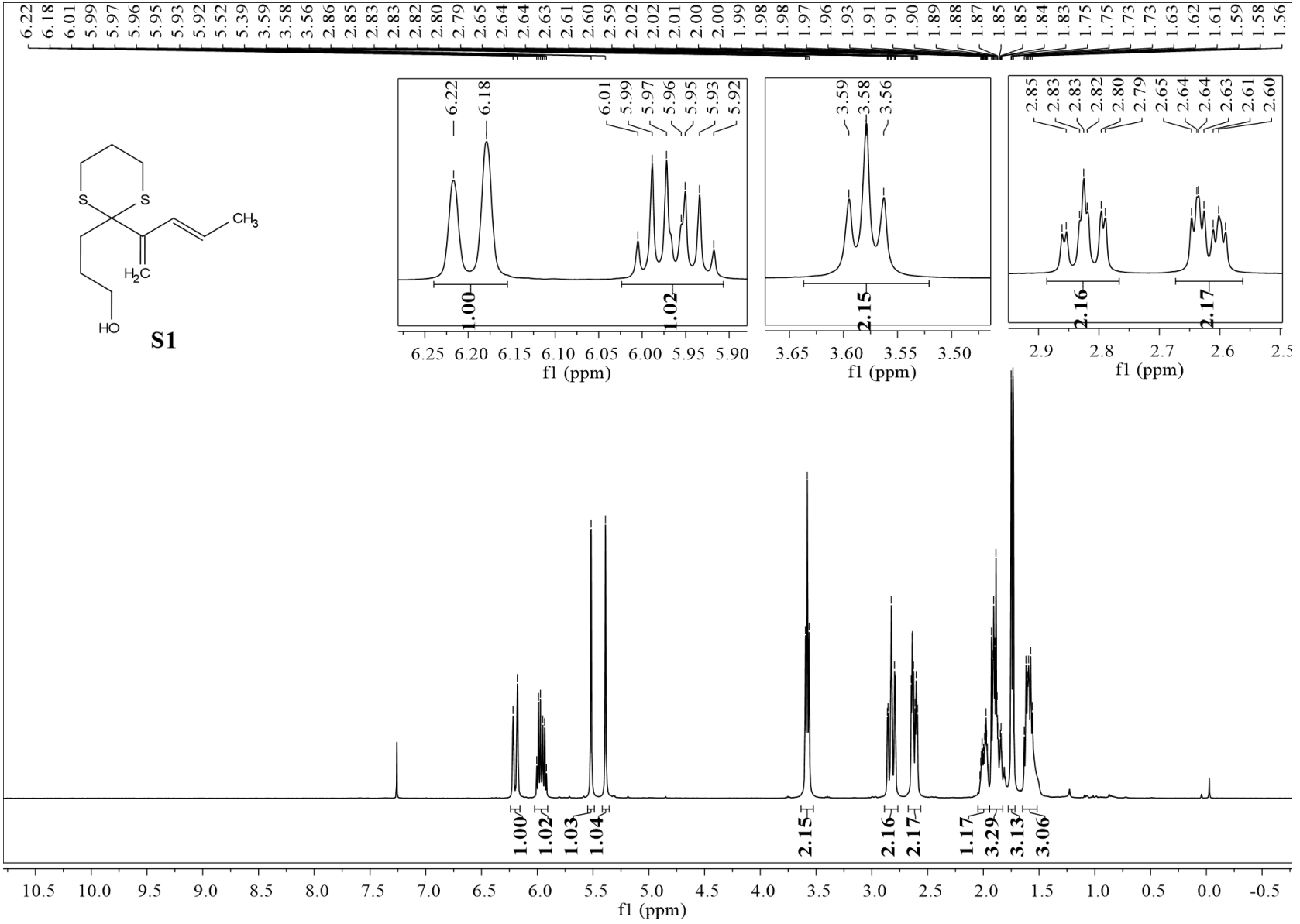
^{1}H NMR Spectrum of compound 7 (400 MHz, $CDCl_3$)



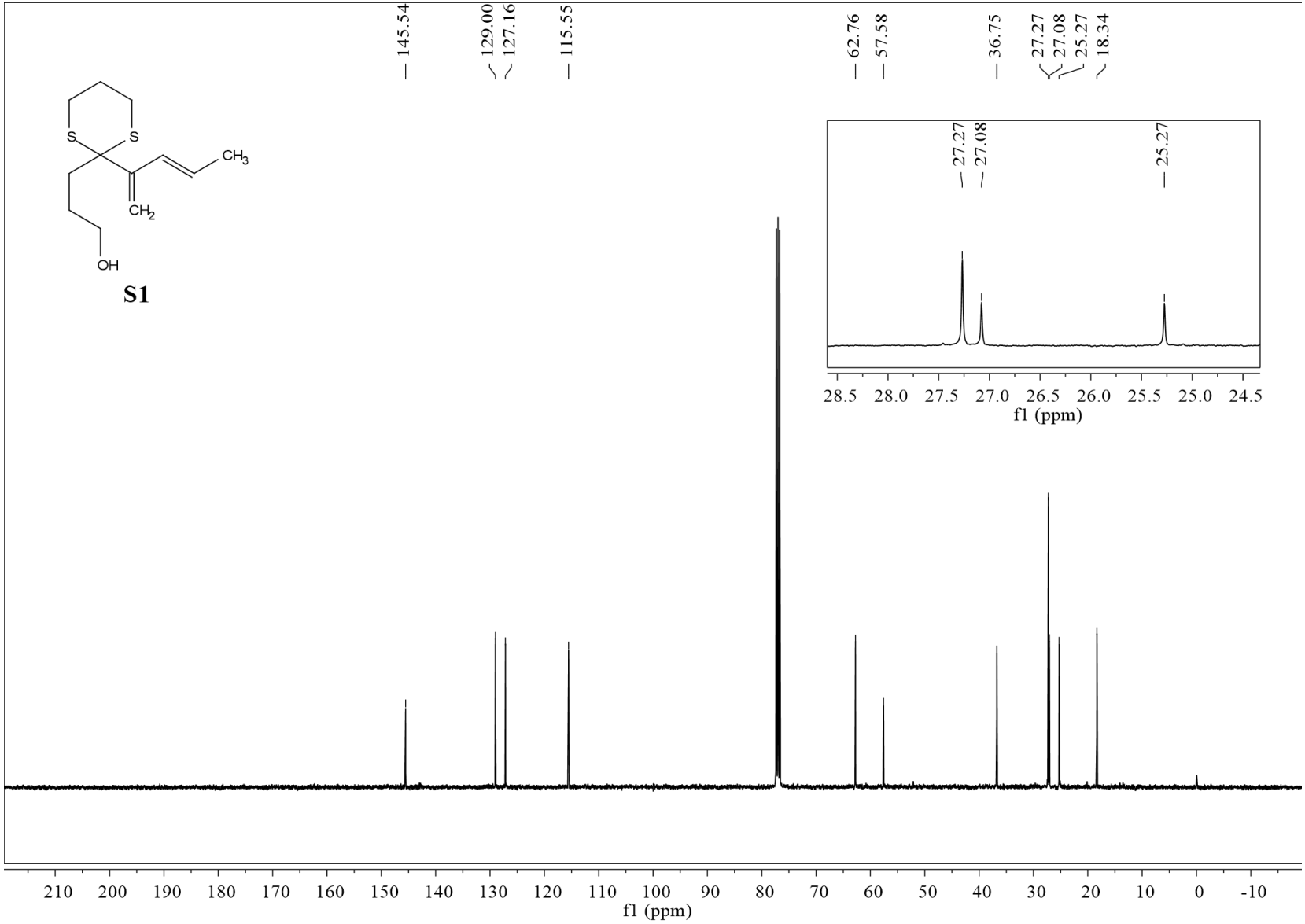
^{13}C NMR Spectrum of compound 7 (101 MHz, $CDCl_3$)



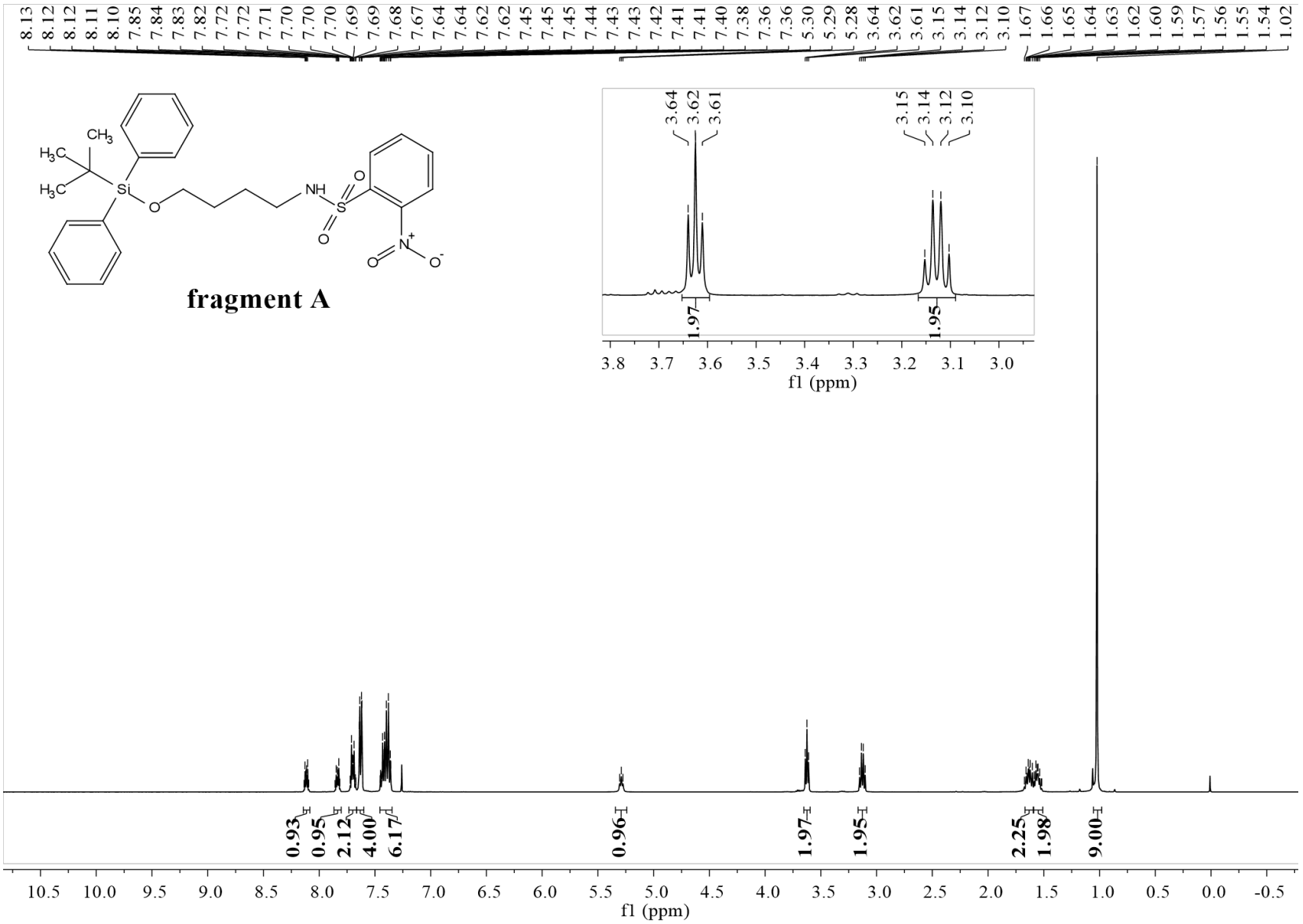
^{1}H NMR Spectrum of compound S1 (400 MHz, $CDCl_3$)



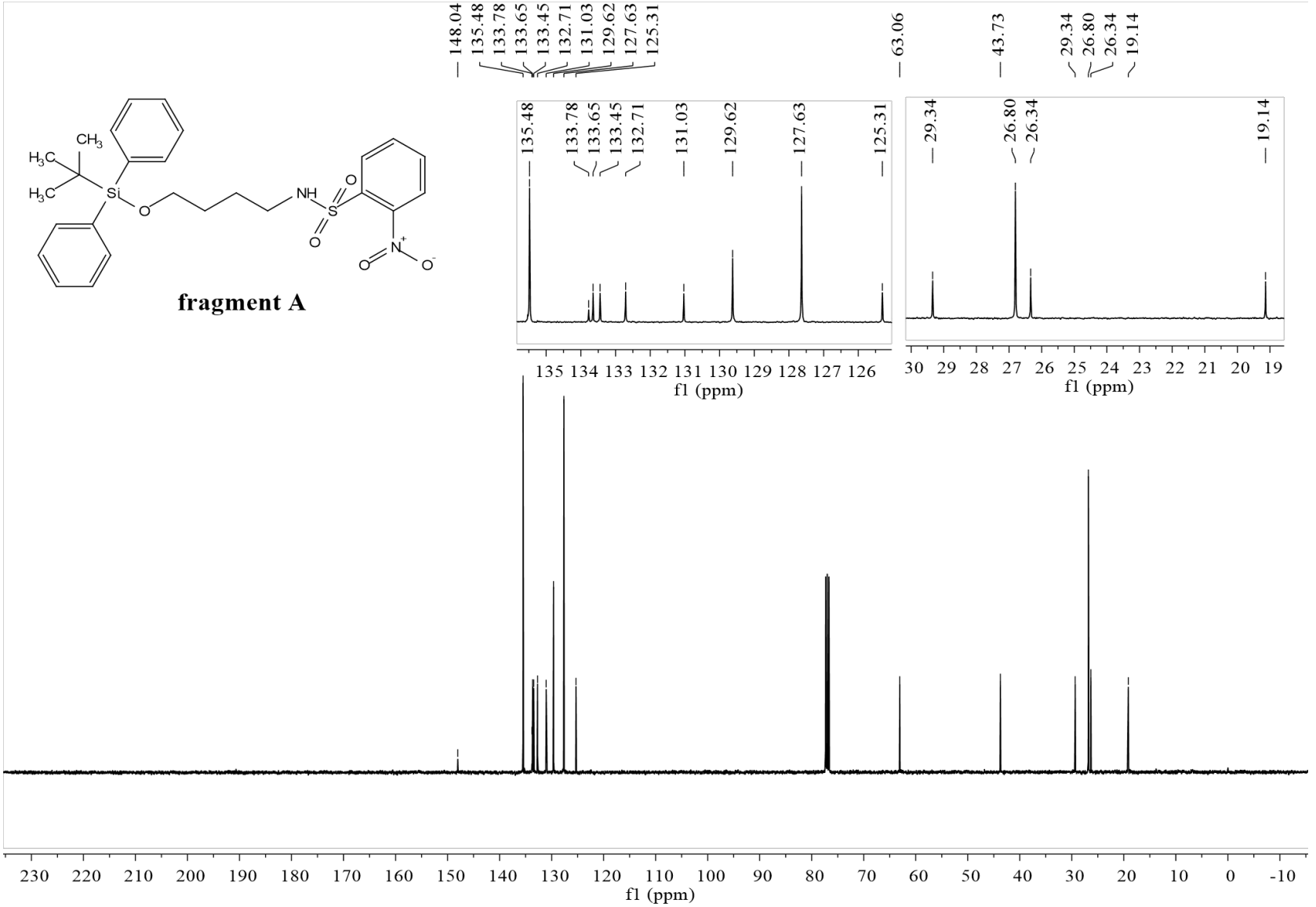
^{13}C NMR Spectrum of compound S1 (101 MHz, $CDCl_3$)



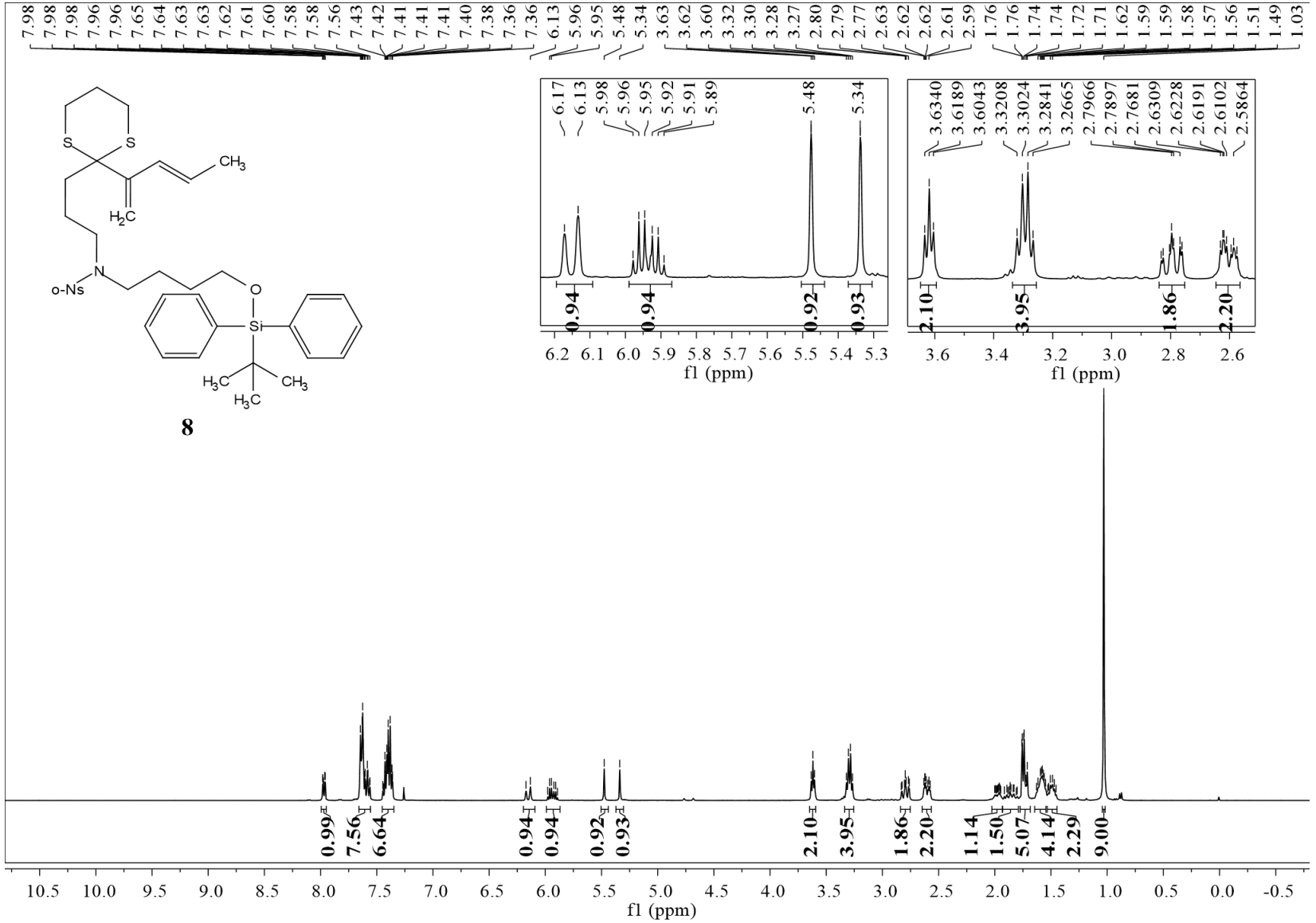
^{1}H NMR Spectrum of fragment A (400 MHz, $CDCl_3$)



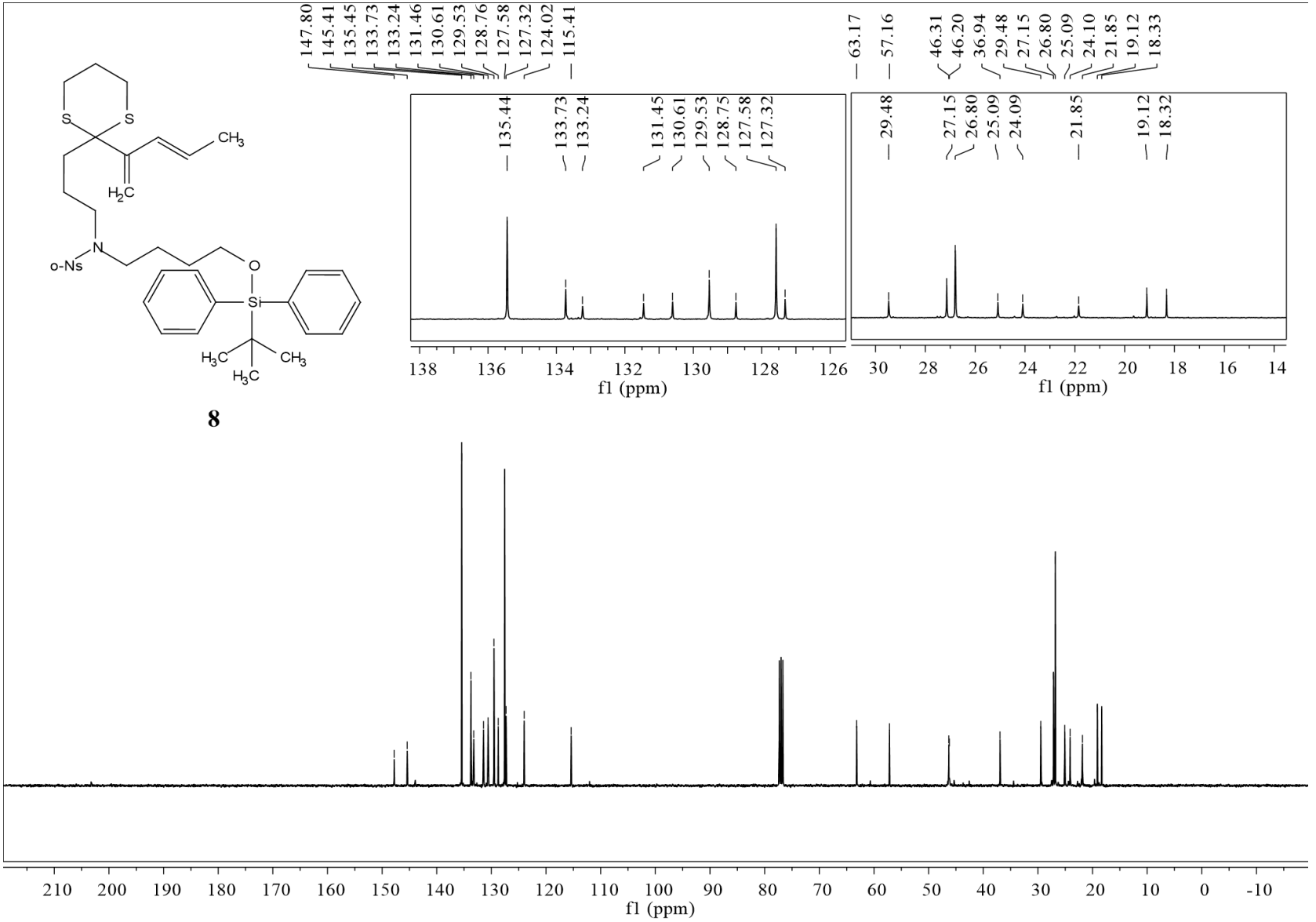
^{13}C NMR Spectrum of fragment A (101 MHz, $CDCl_3$)



^{1}H NMR Spectrum of compound 8 (400 MHz, $CDCl_3$)

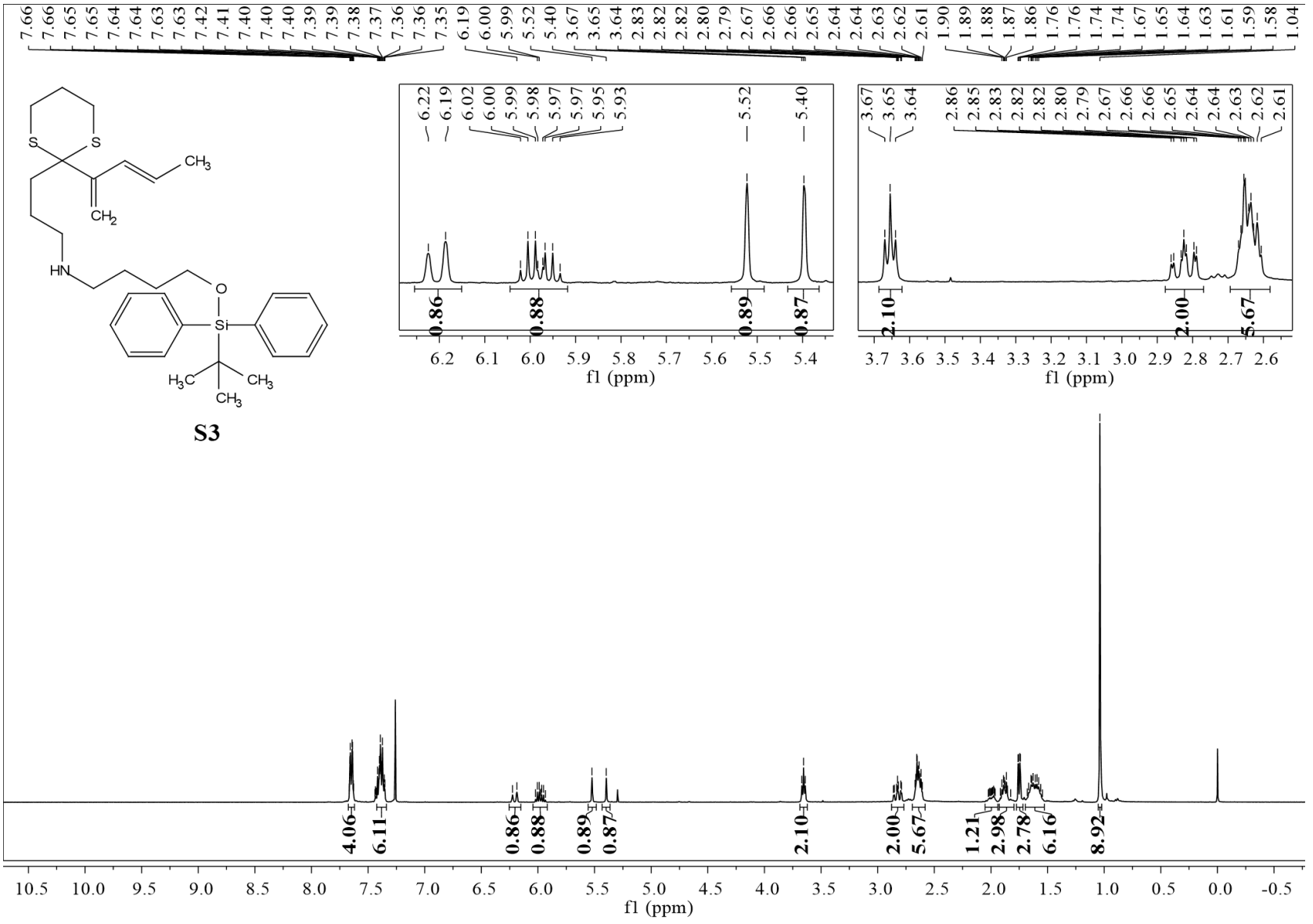


^{13}C NMR Spectrum of compound 8 (101 MHz, $CDCl_3$)



8

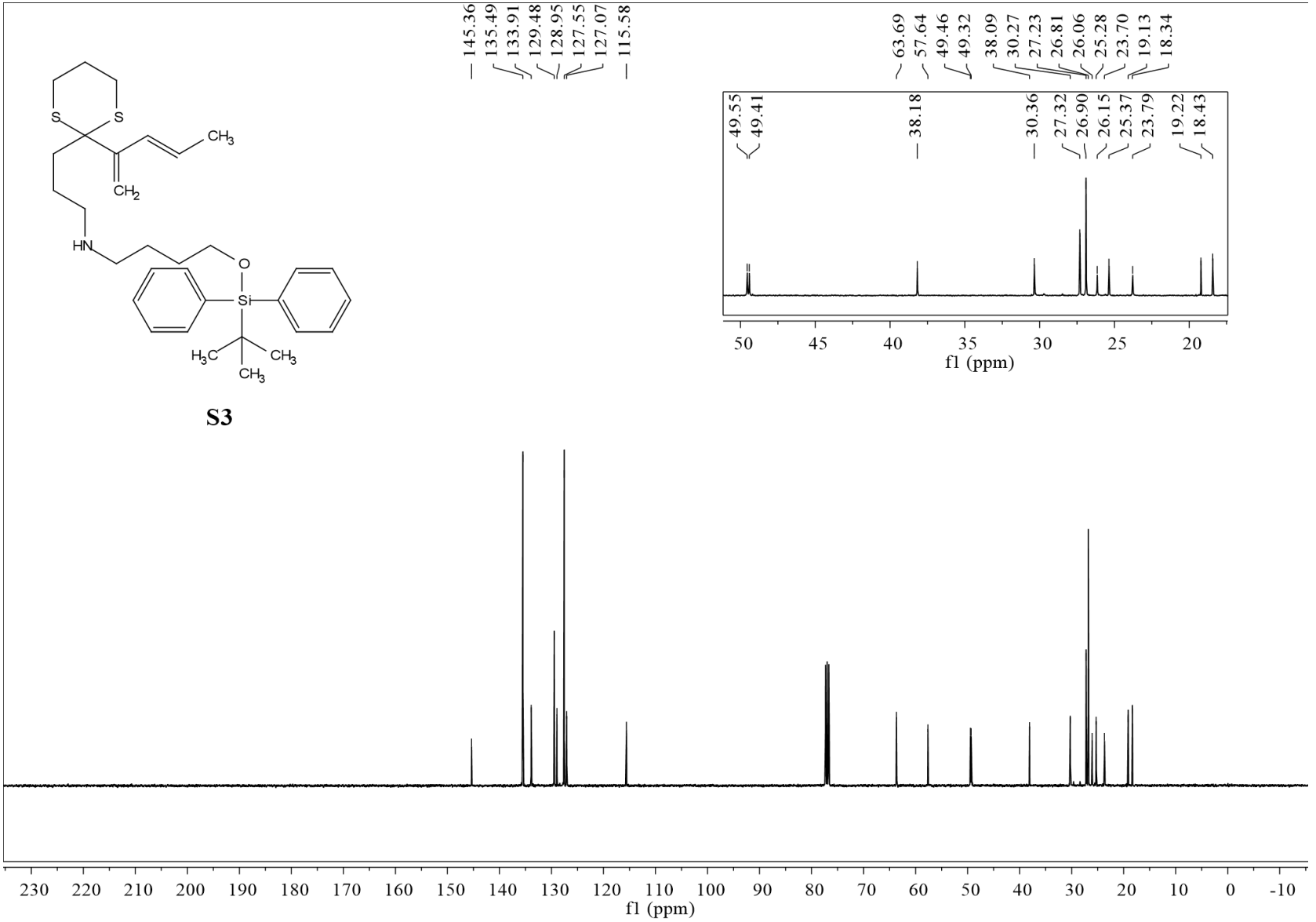
^{1}H NMR Spectrum of compound S3 (400 MHz, $CDCl_3$)



S3

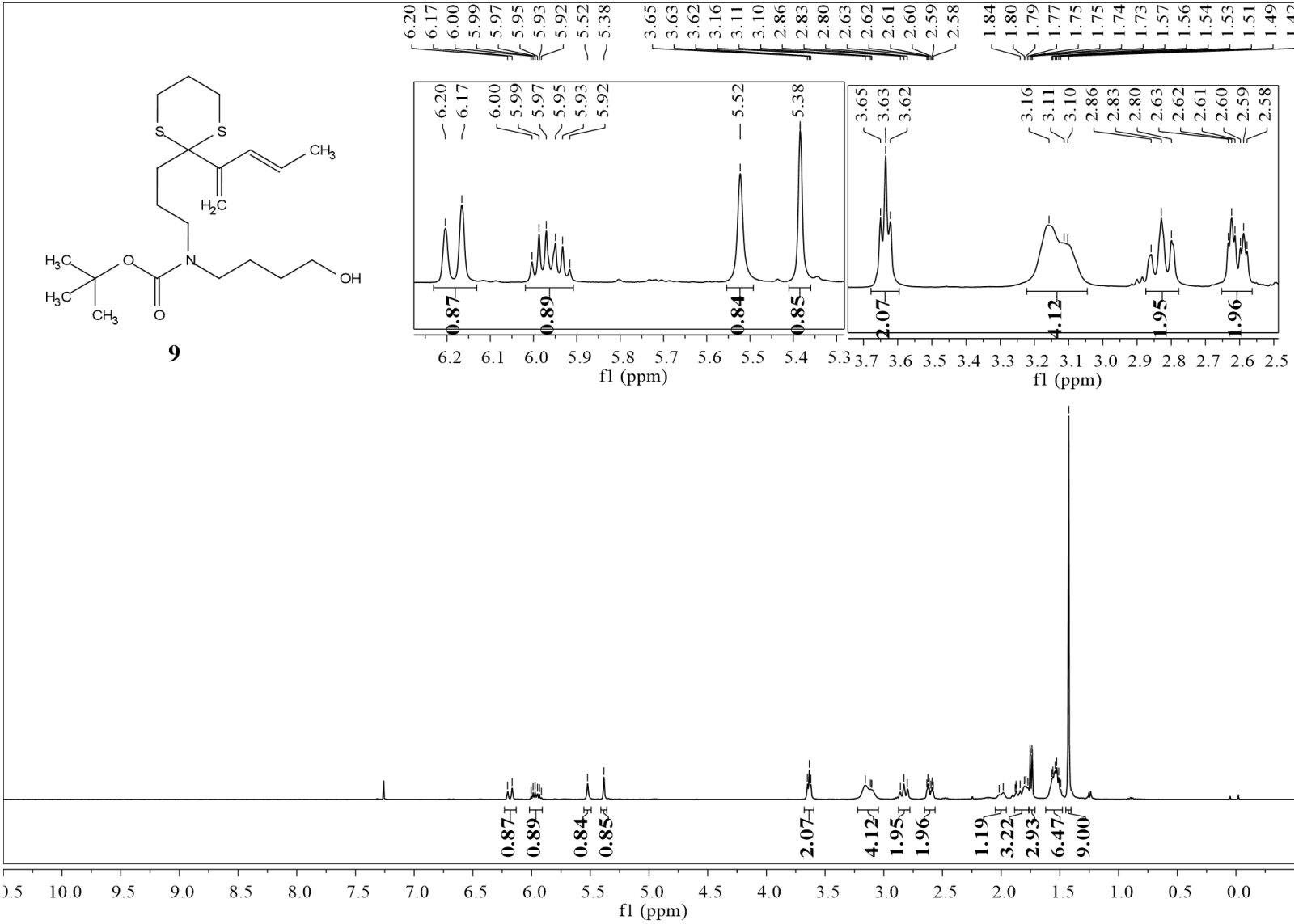
S50/S63

^{13}C NMR Spectrum of compound S3 (101 MHz, $CDCl_3$)

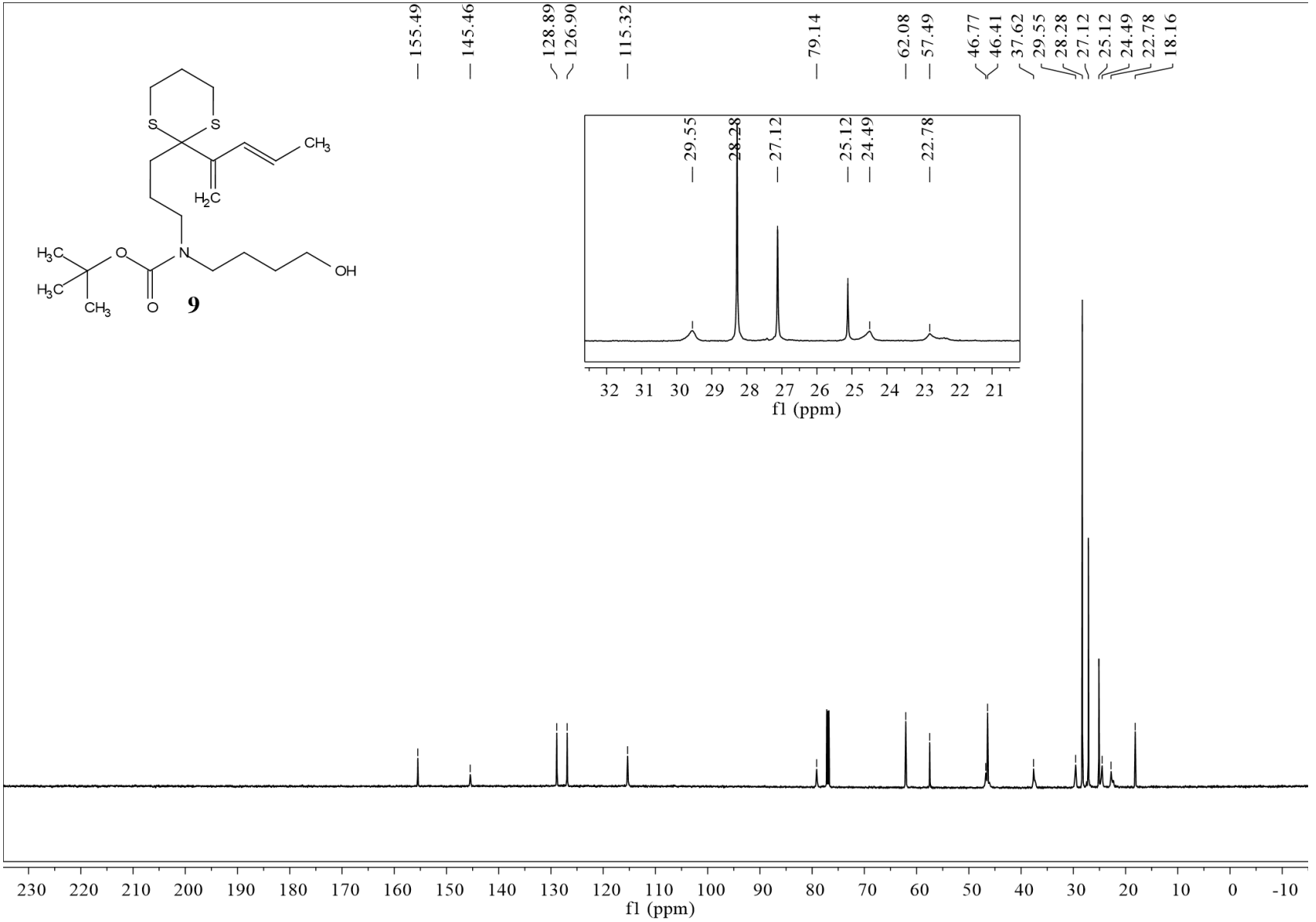


S3

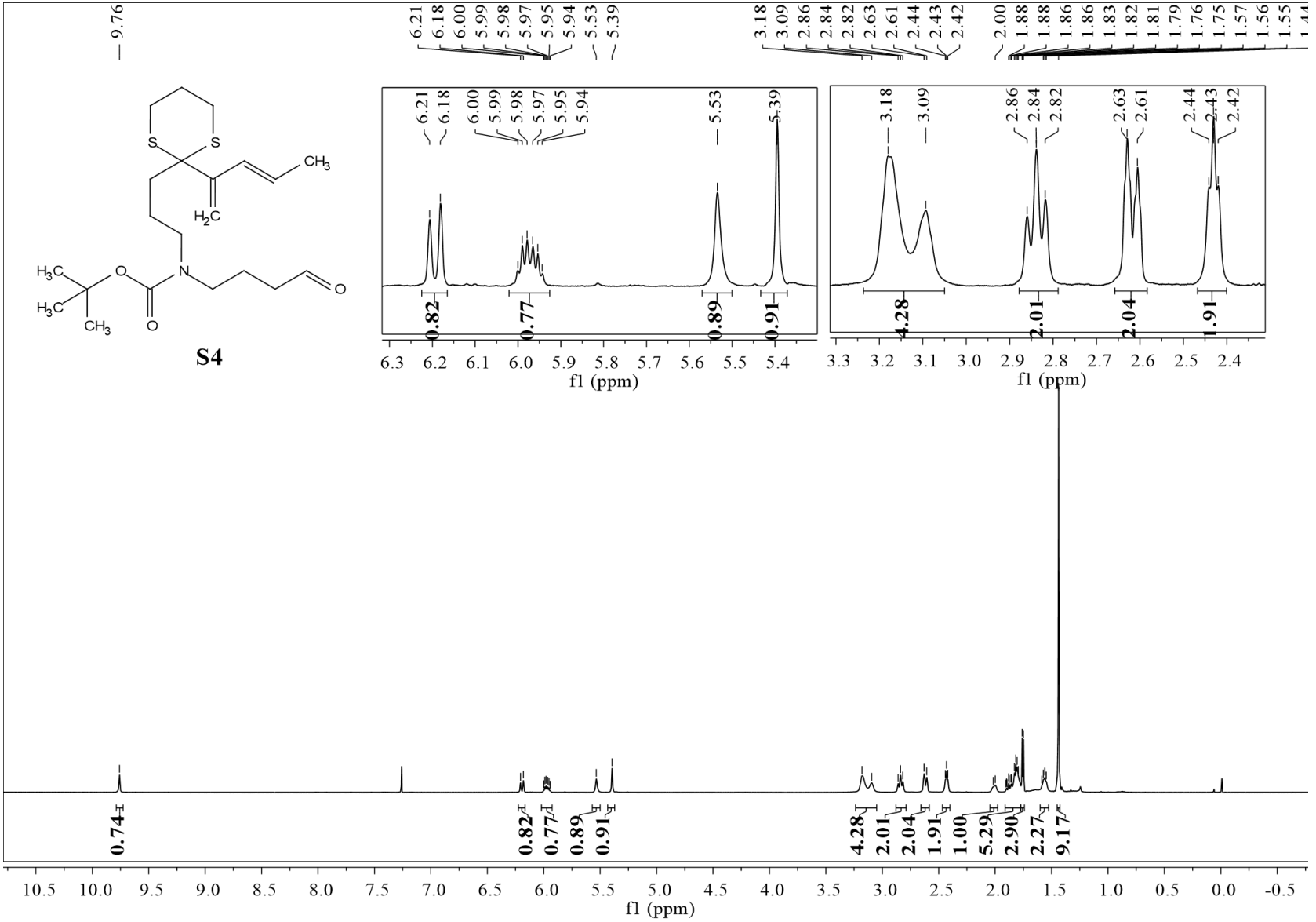
^{1}H NMR Spectrum of compound 9 (400 MHz, $CDCl_3$)



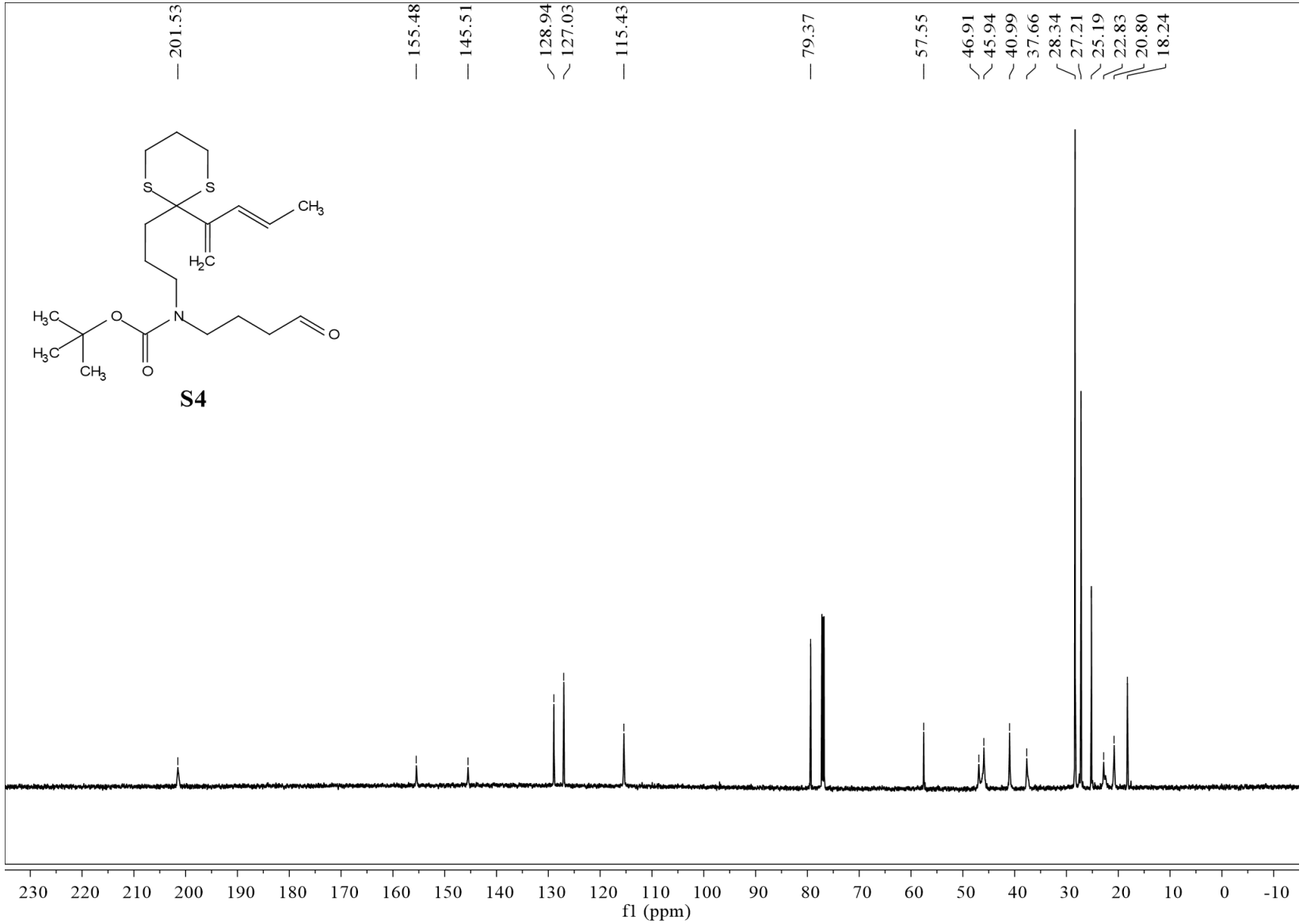
^{13}C NMR Spectrum of compound 9 (151 MHz, $CDCl_3$)



^{1}H NMR Spectrum of compound S4 (600 MHz, $CDCl_3$)

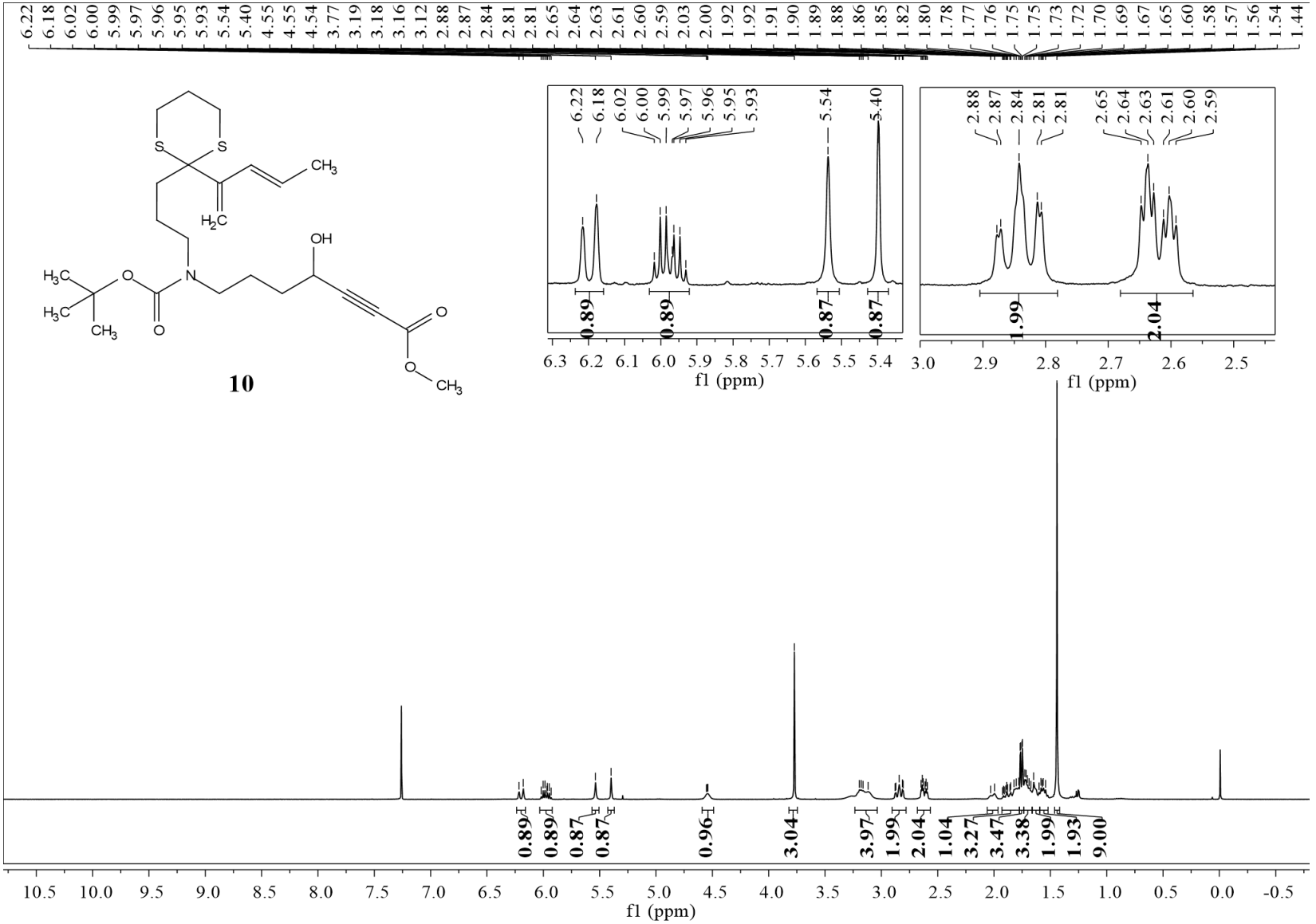


^{13}C NMR Spectrum of compound S4 (151 MHz, $CDCl_3$)

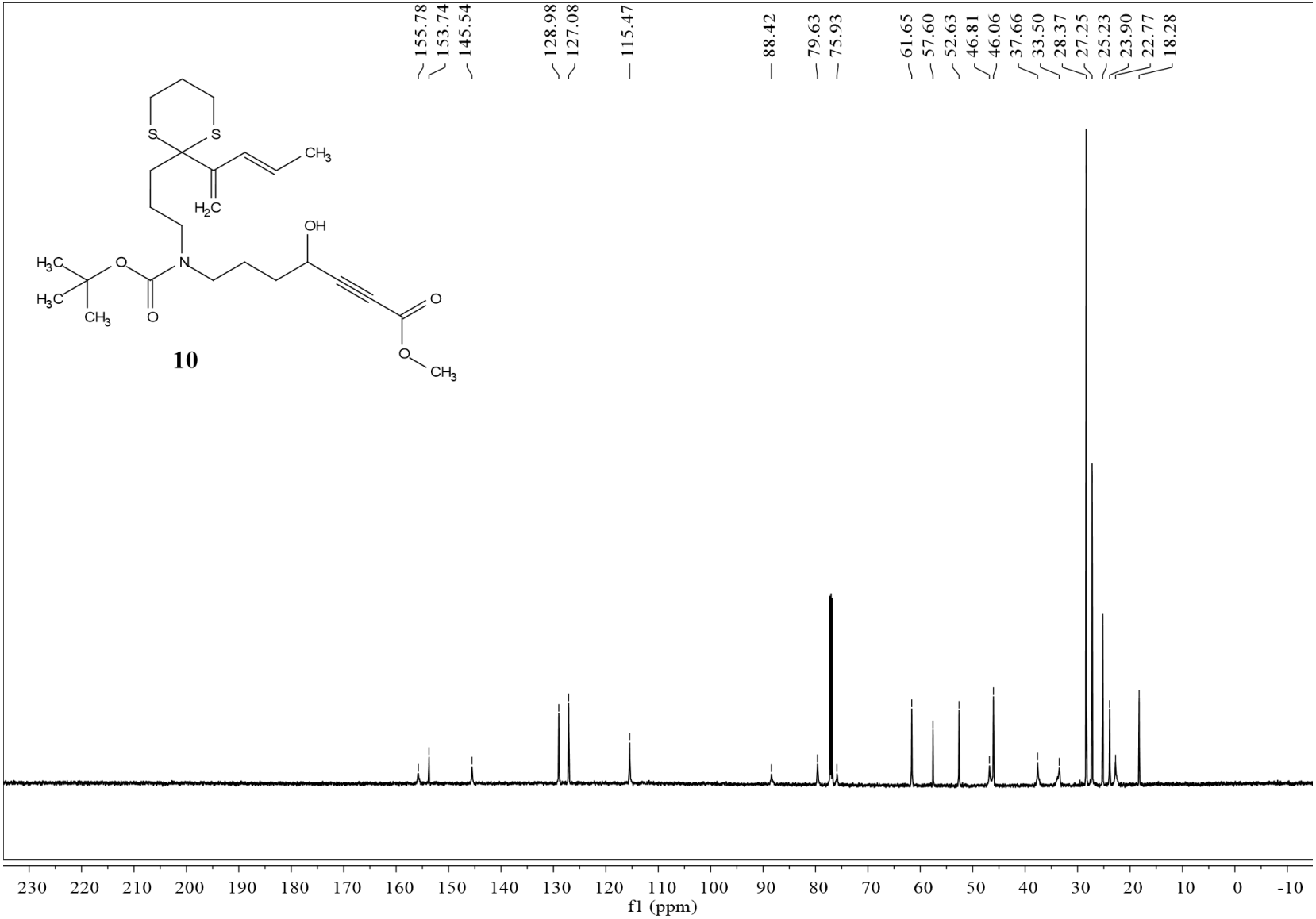


S4

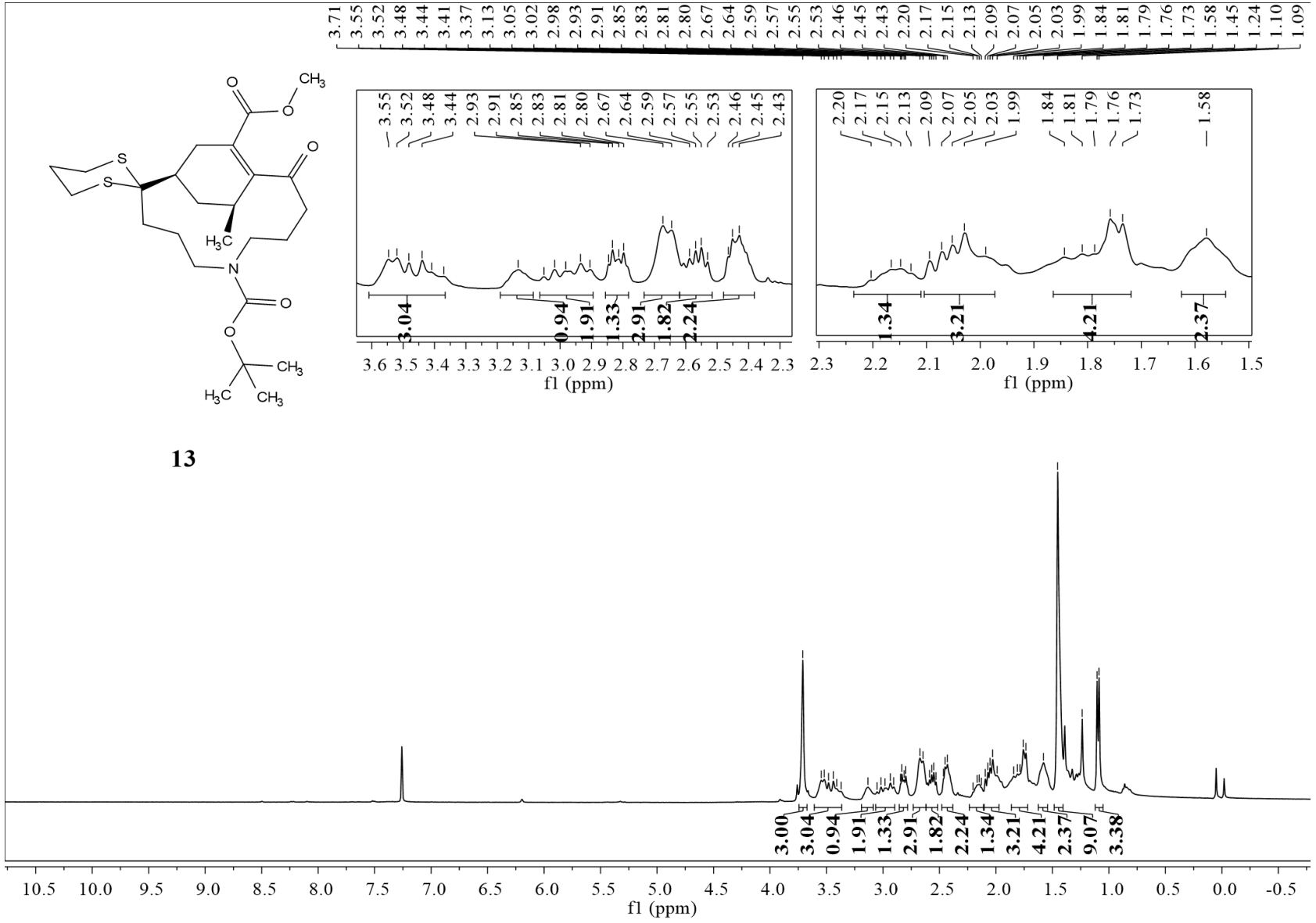
^{1}H NMR Spectrum of compound 10 (400 MHz, $CDCl_3$)



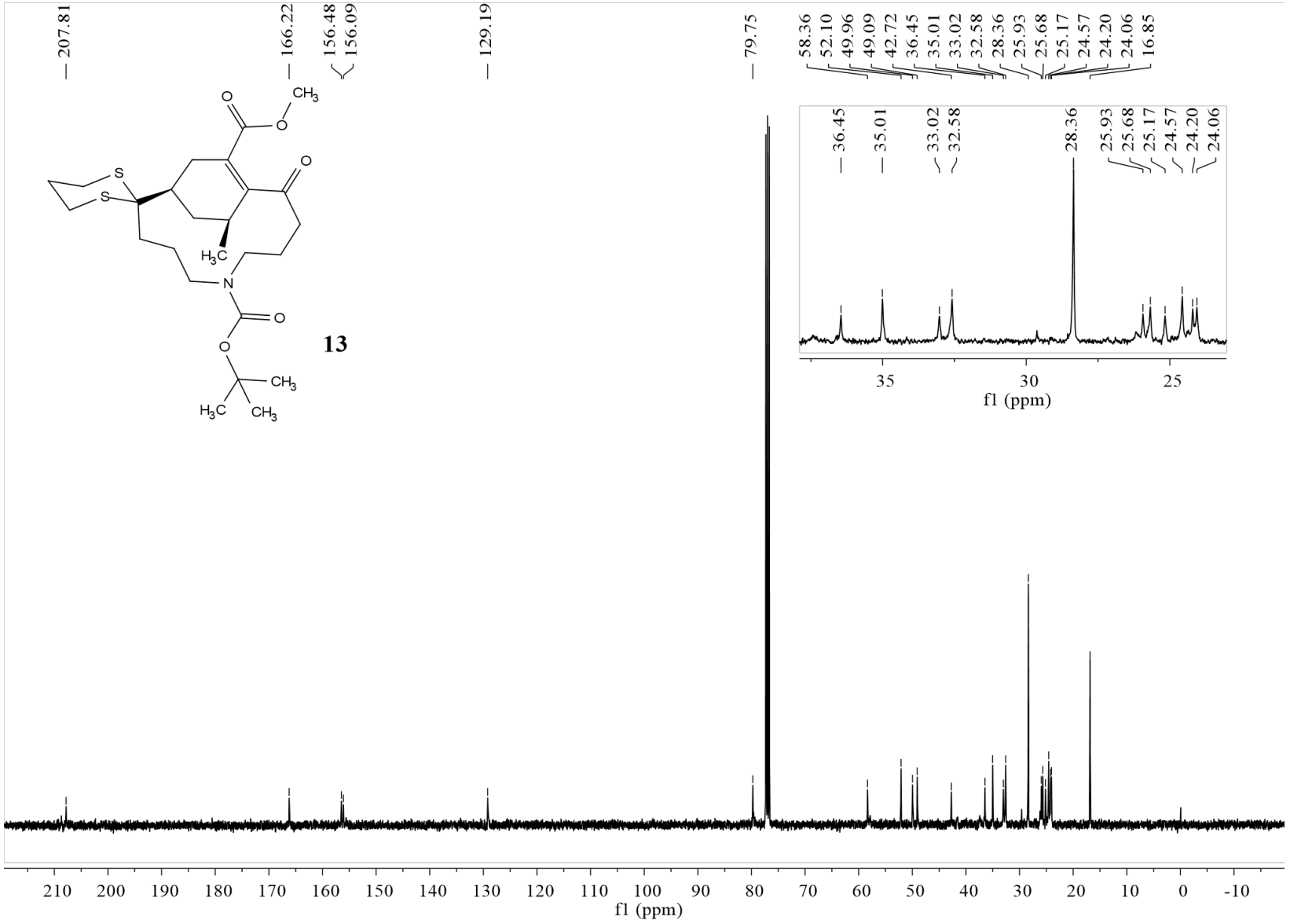
^{13}C NMR Spectrum of compound 10 (151 MHz, $CDCl_3$)



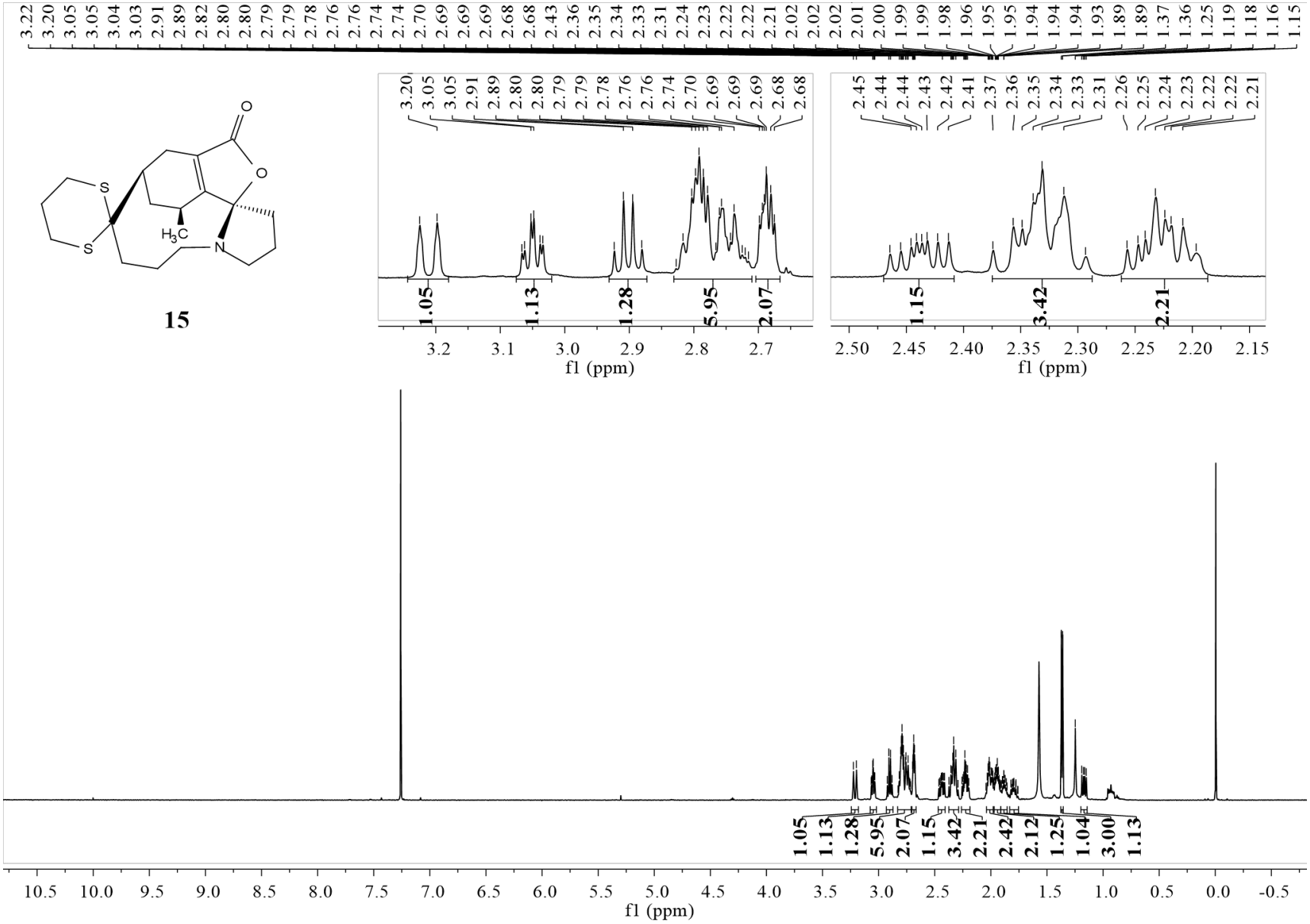
^{1}H NMR Spectrum of compound 13 (400 MHz, $CDCl_3$)



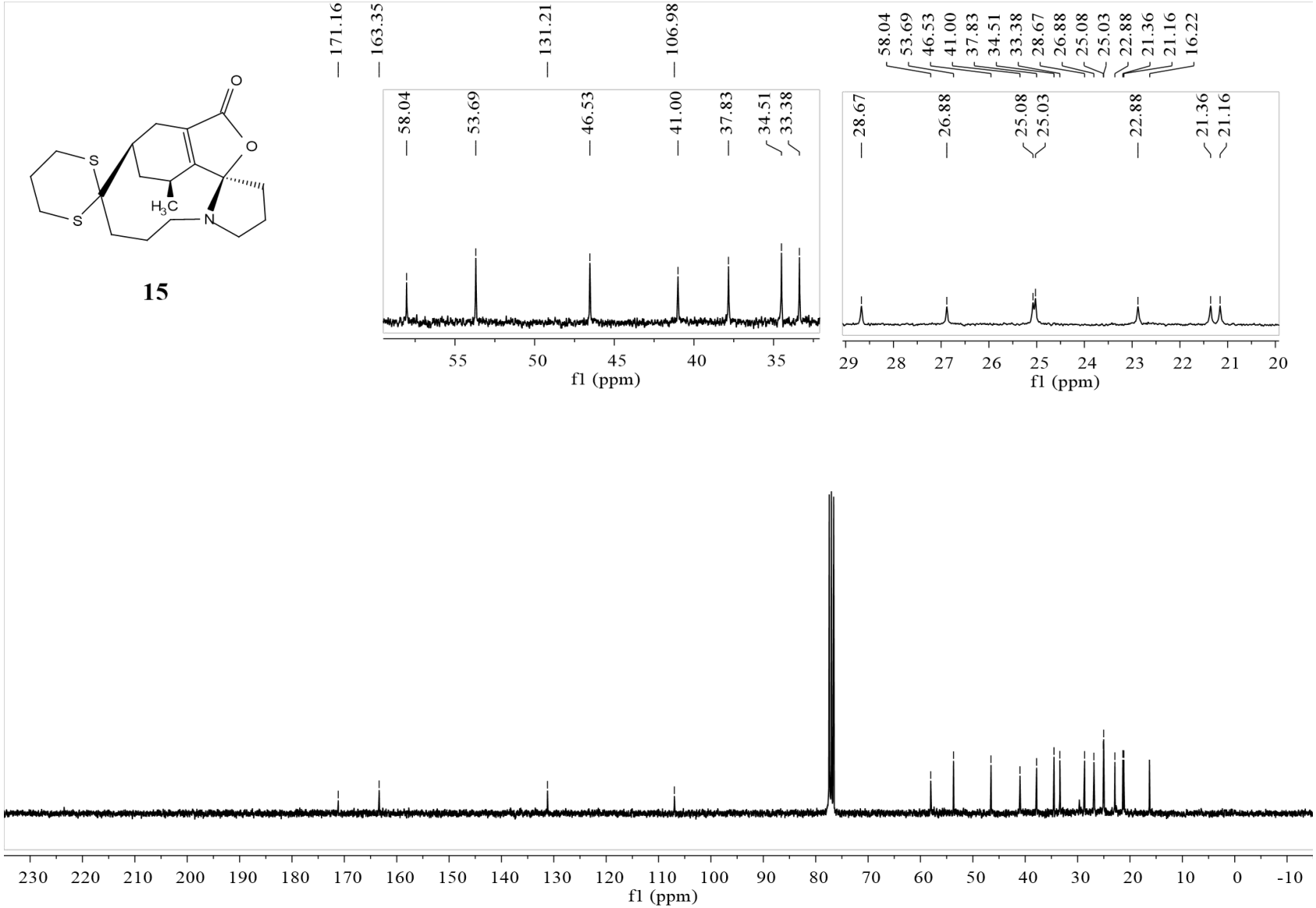
^{13}C NMR Spectrum of compound 13 (101 MHz, $CDCl_3$)



^{1}H NMR Spectrum of compound 15 (600 MHz, $CDCl_3$)

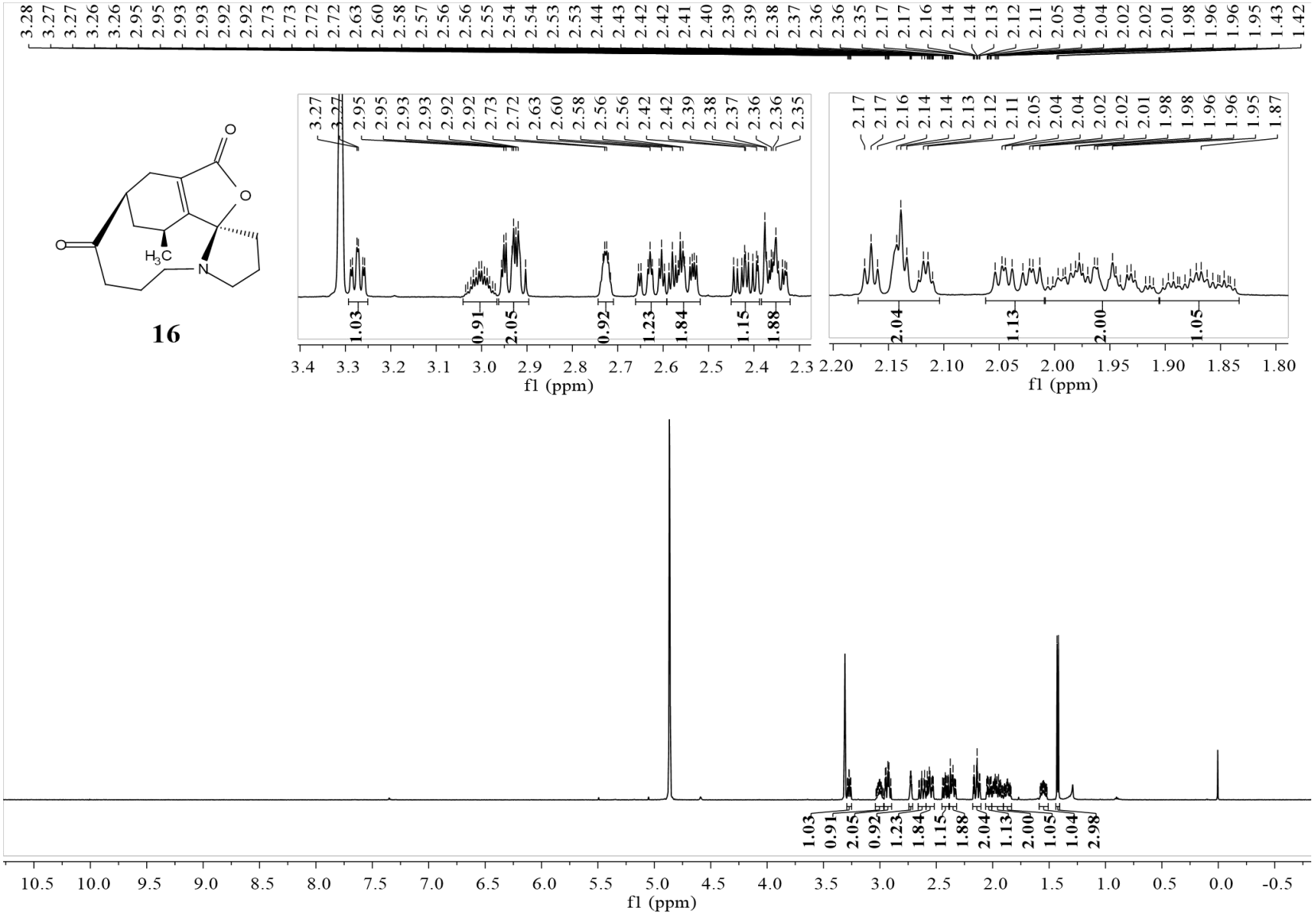


^{13}C NMR Spectrum of compound 15 (75 MHz, $CDCl_3$)



15

^{1}H NMR Spectrum of compound 16 (600 MHz, MeOD)



^{13}C NMR Spectrum of compound 16 (75 MHz, $CDCl_3$)