Supporting Information

A Modular Construction of Epidithiodiketopiperazines

Thomas N. Snaddon, Toya D. Scaggs, Colin M. Pearson and James W. B. Fyfe
Department of Chemistry, Indiana University, 800 E. Kirkwood Ave., Bloomington, IN 47405, USA

Correspondence to: tsnaddon@indiana.edu

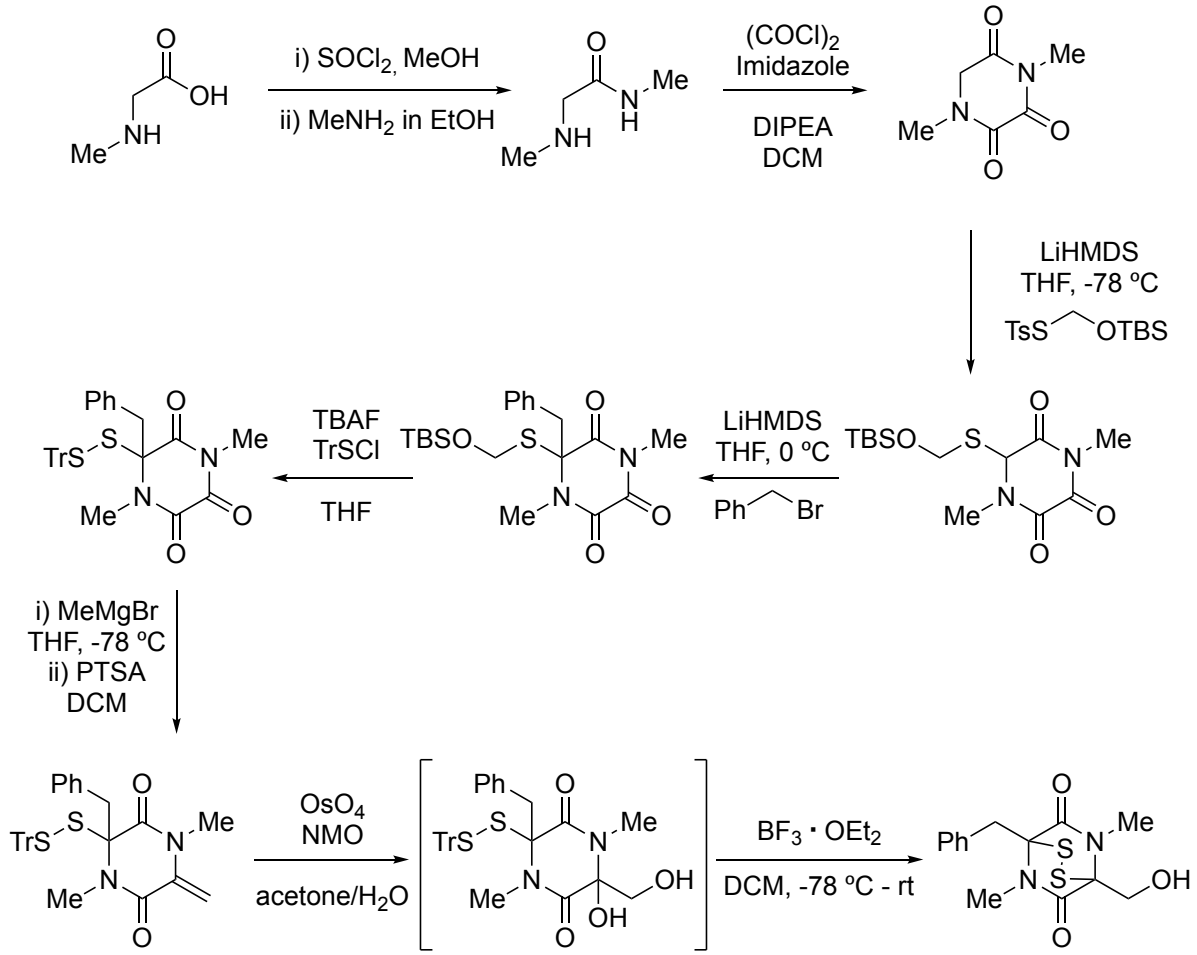
General Information

Commercial reagents were purified prior to use using standard laboratory procedures. Unless otherwise noted, all reactions have been carried out with distilled and degassed solvents under an atmosphere of dry N_2 in flame or oven dried glassware with standard vacuum-line techniques. All reactions were carried out in Teflon screw cap reaction vials with magnetic stirring unless otherwise indicated. Dichloromethane, tetrahydrofuran, dioxane, and acetonitrile were purified under a positive pressure of dry argon by passage through two columns of activated alumina. Toluene was purified under a positive pressure of dry argon by passage through columns of activated alumina and Q5 (Grubbs apparatus). All workup and purification procedures were carried out with reagent grade solvents. TrSCl was freshly prepared prior to use. $Ha(OTf)_4$ was purchased from Alfa Aesar and used as supplied. Standard column chromatography techniques using ZEOprep 60/40-63 μm silica gel were used for purification. Liquids and solutions were transferred via syringe or cannula.

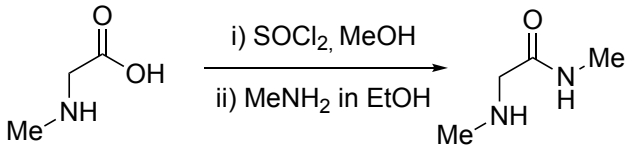
^1H and ^{13}C NMR spectra were recorded at room temperature on Varian Inova-instrumentation: Varian I400 (^1H NMR at 400MHz and ^{13}C NMR at 100 MHz), Varian VXR400 (^1H NMR at 400 MHz and ^{13}C NMR at 100 MHz), Varian I500 (^1H NMR at 500 MHz and ^{13}C NMR at 126 MHz) and Varian I600 (^1H NMR at 600 MHz and ^{13}C NMR at 151 MHz) using deuterium lock. Data for ^1H NMR spectra are quoted relative to chloroform as an internal standard (7.26 ppm) and data for ^{13}C NMR spectra are quoted relative to chloroform or as an internal standard (77.16 ppm) and are reported in terms of chemical shift (δ ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. Infrared spectra (IR) were obtained on the Bruker TENSOR II FTIR Spectrometer and recorded in wavenumbers (cm^{-1}). High Resolution Mass (HRMS) analysis was obtained using Electron Impact Ionization (EI), Chemical Ionization (CI), Electrospray (ESI) and Atmospheric Pressure Chemical Ionization (APCI) and reported as m/z (relative intensity) for the $[M]^+$, $[M+H]^+$ or $[M+Na]^+$ molecular ion. Chiral HPLC analyses were performed on an Agilent 1200 Series system.

Experimental Section

Synthesis of (±)-Hyalodendrin (Scheme 1 in manuscript)



***N*-methyl amide formation**



***N*-methyl-2-(methylamino)acetamide:** Sarcosine (60 g, 0.67 mol, 1 equiv) was added to a round bottom flask equipped with stirred bar and dissolved in MeOH (825 mL, 0.8 M). The reaction mixture was then cooled to 0 °C and thionyl chloride (202 mL, 2.78 mol, 4.14 equiv) was added dropwise over 90 minutes. Upon completion of the addition the reaction mixture was heated to reflux for 2 hours before being cooled to room temperature and concentrated under vacuum. The crude was then triturated with Et_2O (2 x 1 L) to yield methyl methylglycinate (92 g, 99%) as a white solid. This process was repeated and the material was used directly without purification.

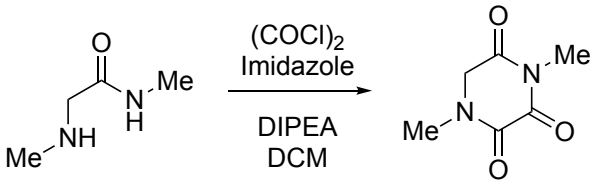
Methyl methylglycinate (92 g, 0.66 mol, 1 equiv) was added to a round bottom flask equipped with stirred bar. Methylamine (33% in EtOH, 420 mL, 3.31 mol, 5 equiv) was then added and

the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was the concentrated under vacuum and the solid obtained was treated with methylamine (40% in H_2O, 150 mL) and extracted with DCM (3 × 500 mL). The organics were then combined, dried with $MgSO_4$ and concentrated under reduced pressure. This process was then repeated and the crude material of both batches combined and purified by vacuum distillation (95 °C at 1 mmHg) to afford the title compound (66 g, 49% over 2 steps) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 (s, 2H), 2.83 (d, J = 5.1 Hz, 3H), 2.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.8, 53.9, 36.0, 25.0.

Triketopiperazine formation



13

1,4-Dimethylpiperazine-2,3,5-trione (13): Imidazole (12.33 g, 180 mmol, 3 equiv.) was added to a round bottom flask equipped with stirred bar and dissolved in DCM (170 mL, 0.35 M) before adding DIPEA (31.5 mL, 180 mmol, 3 equiv). The reaction mixture was then cooled to 0 °C and oxalyl chloride (7.65 mL, 90 mmol, 1.5 equiv) in DCM (85 mL) was added dropwise over 30 minutes. The reaction mixture was then warmed to room temperature and stirred for 1 hour before cooling to 0 °C again and adding of *N*-methyl-2-(methylamino)acetamide (6.12 g, 60 mmol, 1 equiv) in DCM (60 mL) dropwise over 20 minutes. The reaction mixture was then stirred at room temperature for 18 hours before being diluted with 1 M HCl (150 mL) and poured into a separation funnel containing 1 M HCl (150 mL). The layers were separated and the aqueous phase was extracted with DCM (2 × 150 mL). The organics were then combined, dried with $MgSO_4$ and concentrated under reduced pressure. The *title compound* was obtained (3.7 g, 24 mmol, 40%) as a white solid following purification by column chromatography [SiO_2, 50–100% EtOAc/petroleum ether].

IR (neat): 2929, 2888, 1675, 1425, 1330, 1167, 987, 725 cm^{-1}.

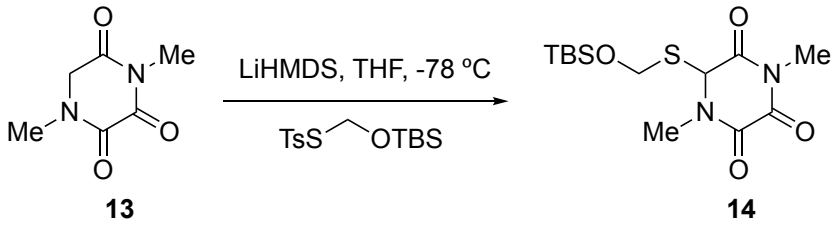
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.35 (s, 2H), 3.19 (s, 3H), 3.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.2, 156.8, 152.4, 52.4, 34.1, 27.1.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$: $C_6H_8O_3N_2Na$: 179.0427 Found: 179.0427.

This process was repeated ten times on 120 mmol scale to afford a total of 72 g (0.46 mol) of the title compound.

Thiolation of triketopiperazine



6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (14): 1,4-Dimethylpiperazine-2,3,5-trione **13** (5.0 g, 32 mmol, 1 equiv) was added to a flame dried 3-neck round bottom flask equipped with stirred bar and nitrogen inlet and purged ×3 with nitrogen gas. The TKP was then dissolved in THF (320 mL, 0.1 M) and cooled to -78 °C before adding lithium hexamethyldisilazane (1 M in THF, 35.2 mL, 35.2 mmol, 1.1 equiv) dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 1 hour before adding *S*-(((tert-butyldimethylsilyl)oxy)methyl) 4-methylbenzenesulfonothioate* (11.7 g, 35.2 mmol, 1.1 equiv) via syringe over 5 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours before being quenched with sat. aqueous NH_4Cl (150 mL) and extracted with EtOAc (2 × 200 mL). The organics were then combined, dried with $MgSO_4$ and concentrated under reduced pressure. The *title compound* was obtained (9.02 g, 27.2 mmol, 85%) as a white solid following purification by column chromatography [SiO_2, 25–50% EtOAc/petroleum ether].

IR (neat): 2929, 2857, 1683, 1318, 1248, 1063, 831 cm^{-1}.

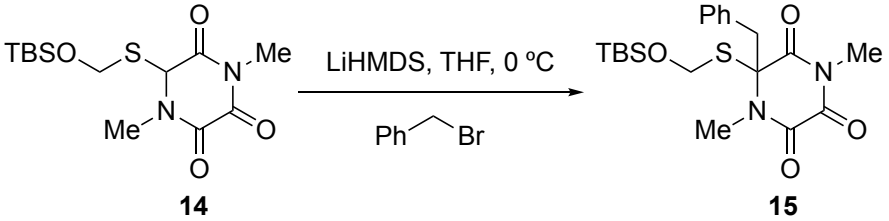
^1H NMR (500 MHz, $CDCl_3$): δ 5.18 (s, 1H), 4.91 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 11.7 Hz, 1H), 3.21 (s, 3H), 3.11 (s, 3H), 0.82 (s, 9H), 0.05 (d, J = 1.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.6, 155.8, 153.0, 64.9, 62.7, 32.7, 27.6, 25.7, 18.3, -5.1, -5.5.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$: $C_{13}H_{24}O_4N_2NaSSi$: 355.1118 Found: 355.1121.

***The sulfenating reagent was prepared according to the procedure of Clive and coworkers: Org. Synth. **2013**, 90, 10–24.*

Benzylation of triketopiperazine



6-Benzyl-6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (15): 6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-

trione **14** (2.98 g, 9 mmol, 1 equiv) was added to a flame dried round bottom flask equipped with stirred bar and purged ×3 with nitrogen gas. THF (45 mL, 0.2 M) and distilled DMPU (22.5 mL, 0.4 M) were then added and the reaction mixture was cooled to 0 °C before adding lithium hexamethyldisilazane (1 M in THF, 9.9 mL, 9.9 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred at 0 °C for 1 hour before adding benzyl bromide (1.62 mL, 13.5 mmol, 1.5 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was then diluted with EtOAc (100 mL) and washed with 10% aqueous LiCl (2 × 100 mL) and brine (100 mL). The organic phase was the dried with $MgSO_4$ and concentrated under reduced pressure. The *title compound* was obtained (3.2 g, 7.6 mmol, 84%) as a yellow oil following purification by column chromatography [SiO_2, 10–30% EtOAc/petroleum ether].

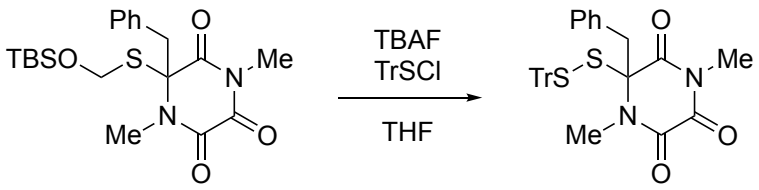
IR (neat): 2855, 1681, 1333, 1257, 1060, 833, 779, 700 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 3H), 7.02 – 6.98 (m, 2H), 4.74 (q, *J* = 12.1 Hz, 2H), 3.64 (d, *J* = 14.2 Hz, 1H), 3.37 (s, 3H), 3.30 (d, *J* = 14.2 Hz, 1H), 3.11 (s, 3H), 0.83 (s, 9H), 0.05 (d, *J* = 4.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 154.9, 153.7, 132.6, 129.4, 129.0, 128.3, 75.4, 65.3, 43.2, 30.6, 27.7, 25.7, 18.4, -5.2, -5.5.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{20}H_{30}O_4N_2NaSSi$: 445.1588 Found: 445.1590.

Deprotection/STr trapping



15 **16**

6-Benzyl-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (16): A round bottom flask equipped with stirrer bar was charged with 6-benzyl-6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione **15** (3.1 g, 7.38 mmol, 1 equiv) and tritylsulfenyl chloride (5.27 g, 17 mmol, 2.3 equiv) in THF (37 mL, 0.2 M). Tetrabutylammonium fluoride (1 M in THF, 8.1 mL, 8.1 mmol, 1.1 equiv) was then added dropwise and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (50 mL). The organic phase was washed with brine (50 mL) before being dried with $MgSO_4$ and concentrated under reduced pressure. The *title compound* was obtained (3.5 g, 6.3 mmol, 85%) as a yellow solid following purification by column chromatography [SiO_2, 10–30% EtOAc/petroleum ether].

IR (neat): 3053, 2359, 2341, 1682, 1335, 1088, 696 cm^{-1}.

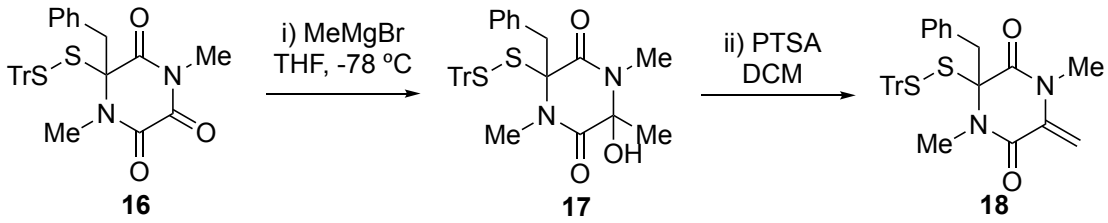
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.23 (m, 15H), 7.21 – 7.14 (m, 3H), 6.86 (dd, *J* = 6.7, 2.9 Hz, 2H), 3.47 (d, *J* = 14.3 Hz, 1H), 3.10 (s, 3H), 2.84 (d, *J* = 14.3 Hz, 1H), 2.78 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 154.9, 153.7, 143.0, 132.8, 130.3, 129.01, 128.99, 128.2, 128.1, 127.7, 79.2, 73.1, 41.6, 31.0, 27.3.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$: $C_{32}H_{28}O_3N_2NaS_2$: 575.1432 Found: 575.1434.

The intermediate thiol resulting from deprotection is unstable. When using standard fluoride sources (see manuscript text) various quantities of desulfenylated material was produced. This corresponds to the N,N-dimethyltriketopiperazine derived from phenylalanine.

Grignard addition/elimination



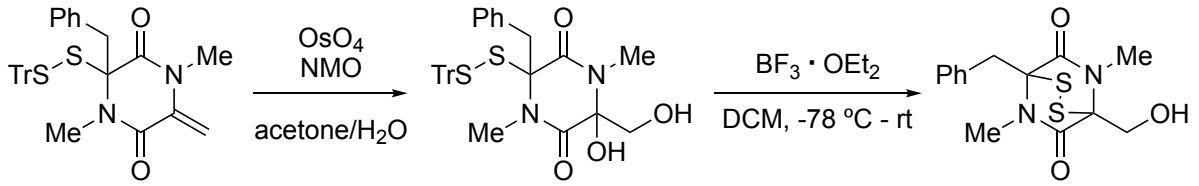
3-Benzyl-1,4-dimethyl-6-methylene-3-(trityldisulfaneyl)piperazine-2,5-dione (18): A flame dried round bottom flask equipped with stirrer bar was charged with 6-benzyl-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione **16** (2.72 g, 4.9 mmol, 1 equiv) in THF (49 mL, 0.1 M) and cooled to -78 °C. Methylmagnesium bromide (3 M in Et_2O, 2.45 mL, 7.35 mmol, 1.5 equiv) was then added dropwise and the reaction mixture was stirred for 30 minutes at -78 °C. The reaction mixture was warmed to room temperature and quenched with sat. aqueous NH_4Cl (50 mL) and extracted with EtOAc (50 mL). The organic phase was washed with brine (10 mL) before being dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude diols **17** (dr 1:1) as a white solid. This material was then dissolved in DCM (49 mL, 0.1 M) before adding *p*-toluenesulfonic acid (84 mg, 0.49 mmol, 10 mol%) and stirring for 2 hours at room temperature. The reaction mixture was then quenched with H_2O (50 mL) and extracted with DCM (50 mL). The combined organics were then washed with brine (50 mL) before being dried with $MgSO_4$ and concentrated under reduced pressure. The title compound was obtained (1.57 g, 2.8 mmol, 58%) as a white solid following purification by column chromatography [SiO_2, 10% EtOAc/petroleum ether].

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.34 (m, 6H), 7.33 – 7.22 (m, 9H), 7.19 – 7.13 (m, 3H), 6.95 – 6.85 (m, 2H), 5.63 (d, *J* = 1.3 Hz, 1H), 4.59 (d, *J* = 1.3 Hz, 1H), 3.50 (d, *J* = 14.3 Hz, 1H), 2.98 (s, 3H), 2.84 (s, 3H), 2.51 (d, *J* = 14.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5, 158.5, 143.2, 135.4, 133.9, 130.1, 129.0, 128.3, 127.7, 127.2, 127.1, 101.7, 78.3, 72.6, 40.5, 30.5, 29.9.

Spectral data are consistent with those reported previously by Fukuyama and coworkers: *Chem. Sci.* **2014**, *5*, 2003–2006.

Dihydroxylation/ring closure



18 **19** **2**

(±)-Hyalodendrin (2): A round bottom flask equipped with stirrer bar was charged with 3-benzyl-1,4-dimethyl-6-methylene-3-(trityldisulfaneyl)piperazine-2,5-dione **18** (1.57 g, 2.8 mmol, 1 equiv) in acetone/H_2O (4:1, 14 mL, 0.2 M). Osmium tetroxide (75 mg, 0.28 mmol, 10 mol%) and *N*-methylmorpholine *N*-oxide (653 mg, 5.6 mmol, 2 equiv) were then added and the reaction mixture was stirred at room temperature for 5 hours, during which time the reaction became homogeneous. The reaction mixture was then poured into a 1:1 mixture of EtOAc and sat. $NaHCO_3$ in a separation funnel. The layers were separated and the aqueous phase was extracted twice more with EtOAc (10 mL). The combined organics were then washed with H_2O (50 mL) and brine (50 mL) before being dried with $MgSO_4$ and concentrated under reduced pressure. The crude diol was passed through a plug of silica gel with 50% EtOAc/petroleum ether to afford the clean diols **19** as a 1:1 mixture of diastereomers in 89% yield.

An aliquot of this sample was then separated and the individual diastereomers compared with previously reported spectra from Fukuyama and coworkers: *Chem. Sci.* **2014**, *5*, 2003–2006.

Less polar diasteromer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.6, 2.1 Hz, 6H), 7.35 – 7.31 (m, 6H), 7.29 (dt, *J* = 7.9, 3.7 Hz, 3H), 7.21 – 7.18 (m, 3H), 6.87 (dt, *J* = 7.3, 2.2 Hz, 2H), 3.67 – 3.53 (m, 2H), 3.46 (dd, *J* = 14.4, 2.1 Hz, 1H), 2.87 (s, 3H), 2.83 (s, 3H), 2.10 (dd, *J* = 14.4, 2.1 Hz, 1H).

More polar diasteromer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.36 (m, 6H), 7.34 – 7.29 (m, 6H), 7.28 (dd, *J* = 7.0, 1.5 Hz, 3H), 7.23 – 7.18 (m, 3H), 6.93 (dd, *J* = 6.3, 2.8 Hz, 2H), 3.50 (d, *J* = 14.1 Hz, 1H), 3.20 (dd, *J* = 11.9, 1.6 Hz, 1H), 2.84 (s, 3H), 2.78 (s, 3H), 2.45 – 2.22 (m, 2H).

A flame dried round bottom flask equipped with stirrer bar was charged with diols **19** (877 mg, 1.5 mmol, 1 equiv) in DCM (7.5 mL, 0.2 M) under nitrogen and cooled to -78 °C. Boron trifluoride diethyl etherate (0.37 mL, 3 mmol, 2 equiv) was then added dropwise. The reaction mixture was stirred at this temperature for 5 minutes, then warmed to room temperature and stirred for 1 hour before being quenched with sat. $NaHCO_3$ (10 mL) and extracted with DCM (10 mL). The combined organics were then washed with brine (20 mL) before being dried with $MgSO_4$ and concentrated under reduced pressure. The title compound was obtained (341 mg, 1.05 mmol, 70%) as a white solid following purification by column chromatography [SiO_2, 10–20% EtOAc/petroleum ether].

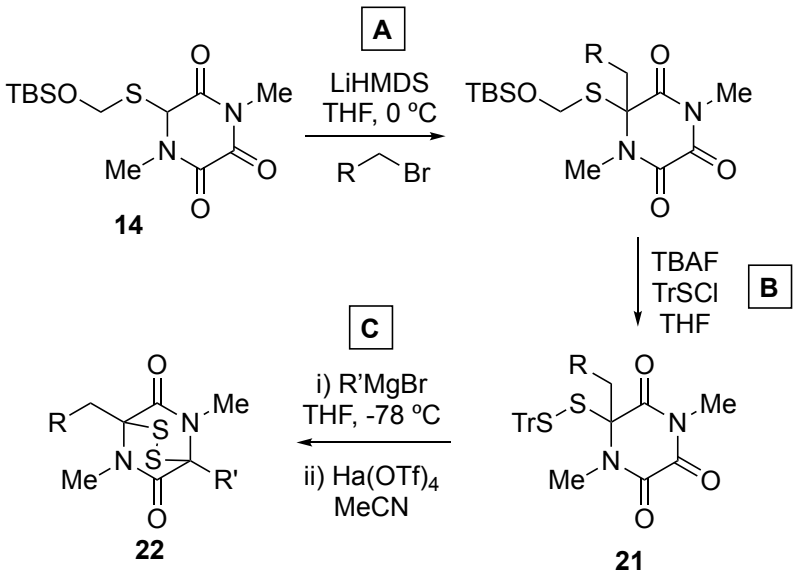
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 – 7.22 (m, 5H), 4.39 (d, *J* = 12.5 Hz, 1H), 4.32 (d, *J* = 10.7 Hz, 1H), 4.09 (d, *J* = 17.7 Hz, 1H), 3.63 (d, *J* = 17.8 Hz, 1H), 3.21 (s, 3H), 2.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.9, 165.6, 134.2, 129.2, 128.8, 127.4, 75.8, 75.4, 61.2, 36.9, 28.7, 27.6.

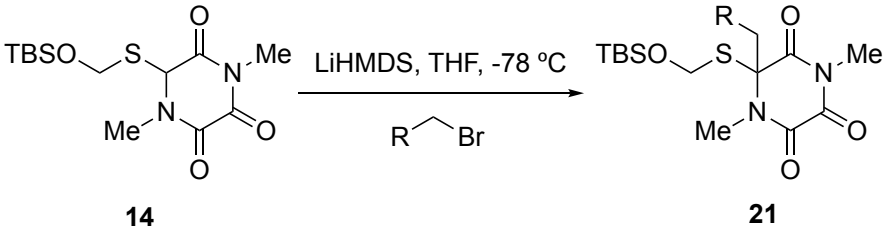
Spectral data are consistent with those reported previously by Fukuyama and co-workers: *Chem. Sci.* **2014**, *5*, 2003–2006.

Note: It was found that the BF_3-mediated ring closure was much less effective on the crude diols, delivering yields of <20%, even over extended time.

Synthesis of ETP derivatives: Scheme 2

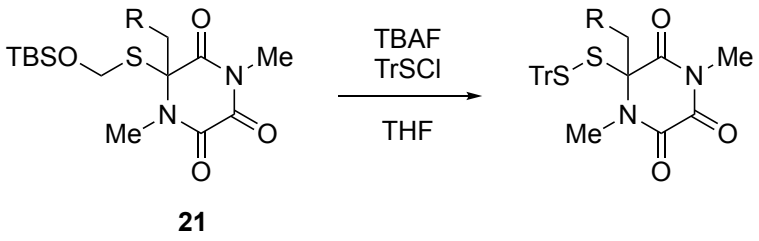


General Procedure A for alkylation of TKP



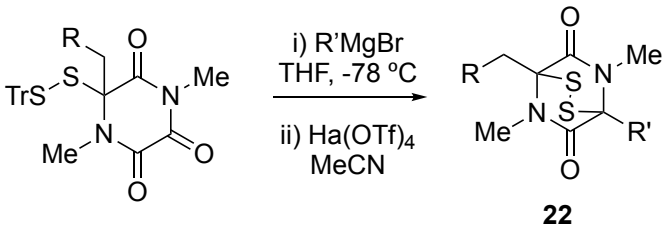
6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione **14** (664 mg, 2 mmol, 1 equiv) was added to a flame dried round bottom flask equipped with stirred bar and purged ×3 with nitrogen gas. THF (10 mL, 0.2 M) and distilled DMPU (5 mL, 0.4 M) were then added and the reaction mixture was cooled to 0 °C before adding lithium hexamethyldisilazane (1 M in THF, 2.2 mL, 2.2 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred at 0 °C for 1 hour before adding the specified alkyl halide (3 mmol, 1.5 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was then diluted with EtOAc (20 mL) and washed with 10% aqueous LiCl (2 × 20 mL) and brine (20 mL). The organic phase was the dried with $MgSO_4$ and concentrated under reduced pressure and the crude material was purified by column chromatography [SiO_2, specified eluent].

General Procedure B for deprotection/STr trapping



A round bottom flask equipped with stirrer bar was charged with the appropriate alkylated TKP (1 mmol, 1 equiv) and tritylsulfenyl chloride (714 mg, 2.3 mmol, 2.3 equiv) in THF (5 mL, 0.2 M). Tetrabutylammonium fluoride (1 M in THF, 1.1 mL, 1.1 mmol, 1.1 equiv) was then added dropwise and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was then diluted with H_2O (10 mL) and extracted with EtOAc (10 mL). The organic phase was washed with brine (10 mL) before being dried with $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography [SiO_2, specified eluent].

General Procedure C for Grignard addition and disulfide bridge formation



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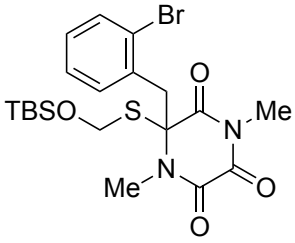
Step i) A flame dried round bottom flask equipped with stirrer bar was charged with the appropriate alkylated/dithiolated TKP (0.5 mmol, 1 equiv) in THF (5 mL, 0.1 M) and cooled to -78 °C. The specified Grignard reagent (0.75 mmol, 1.5 equiv) was then added dropwise and the reaction mixture was stirred for 30 min at -78 °C. The reaction mixture was warmed to room temperature and quenched with sat. aqueous NH_4Cl (10 mL) and extracted with EtOAc (10 mL). The organic phase was washed with brine (10 mL) before being dried with $MgSO_4$ and concentrated under reduced pressure. When necessary the crude material was passed through a silica plug prior to the next step.

Step ii) The diastereomeric mixture of alcohols (assumed quant, 0.5 mmol) was dissolved in MeCN (140 mL), 0.0357 M), charged with a stirrer bar and purged ×3 with nitrogen gas. To this solution was added $Ha(OTf)_4$ (581 mg, 0.75 mmol) in one portion. The solution immediately turns bright yellow. After 30 min, sat. $NaHCO_3$ (50 mL) was added and extracted with EtOAc (2 × 100 mL), washed with sat. brine (50 mL). The organic phase was the dried with $MgSO_4$ and concentrated under reduced pressure and the crude material was purified by column chromatography [SiO_2, specified eluent].

Scope of Electrophile

6-(2-Bromobenzyl)-6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (23A): Prepared according to General Procedure A using 2- bromobenzyl bromide (750 mg, 3 mmol, 1.5 equiv). The *title compound* was obtained as a colourless oil (705 mg, 70%) following purification by column chromatography (SiO_2, 10–20% EtOAc/petroleum ether).



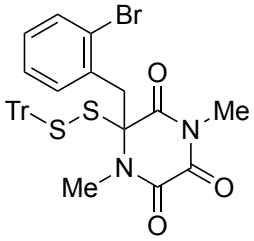
IR (neat): 2933, 2848, 1681, 1396, 1328, 1258, 1065, 829, 786 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.59 – 7.52 (m, 1H), 7.17 (dt, *J* = 7.5, 5.2 Hz, 1H), 7.13 – 7.05 (m, 1H), 6.87 (dd, *J* = 7.9, 2.9 Hz, 1H), 4.79 (qd, *J* = 12.6, 3.0 Hz, 2H), 4.00 (d, *J* = 15.9 Hz, 1H), 3.63 (d, *J* = 15.9 Hz, 1H), 3.27 (s, 3H), 3.19 (s, 3H), 0.85 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.1, 155.2, 153.8, 134.0, 133.3, 129.4, 128.7, 128.1, 125.3, 74.1, 65.7, 41.9, 30.6, 28.2, 25.8, 18.5, -5.0, -5.4.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{20}H_2O_4N_2BrNaSSi$: 523.0693 Found: 523.0693.

6-(2-Bromobenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (23B): Prepared according to General Procedure B. The *title compound* was obtained as a white solid (464 mg, 74%) following purification by column chromatography (SiO_2, 10–40% EtOAc/petroleum ether).



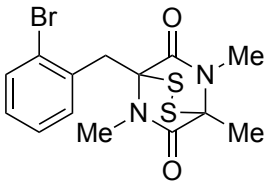
IR (neat): 2927, 1682, 1440, 1328, 734, 699, 666 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.38 – 7.23 (m, 15H), 7.11 (td, *J* = 7.6, 1.5 Hz, 1H), 7.06 (td, *J* = 7.6, 1.7 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 3.86 (d, *J* = 16.1 Hz, 1H), 3.25 (d, *J* = 16.2 Hz, 1H), 2.84 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 155.6, 153.9, 142.9, 133.8, 133.3, 130.4, 129.2, 128.2, 128.0, 125.0, 77.9, 73.6, 39.8, 30.1, 27.7.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{32}H_{27}O_3N_2BrNaS_2$: 653.0539 Found: 653.0540.

1-(2-Bromobenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (23): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (63 mg, 33%) following purification by column chromatography (SiO_2, 10–30% Et_2O/petroleum ether).



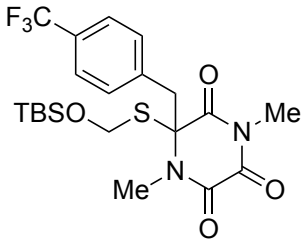
IR (neat): 2940, 1681, 1349, 1244, 907, 726 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 4.02 (d, *J* = 17.0 Hz, 1H), 3.72 (d, *J* = 16.9 Hz, 1H), 3.13 (s, 3H), 2.93 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.5, 165.2, 133.8, 133.2, 128.9, 128.7, 127.8, 124.9, 75.9, 72.9, 37.2, 28.8, 28.0, 19.1.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{14}H_{15}O_2N_2BrNaS_2$: 408.9651 Found: 408.9653.

6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(4-(trifluoromethyl)benzyl)piperazine-2,3,5-trione (24A): Prepared according to General Procedure A using 4-trifluoromethylbenzyl bromide (717 mg, 3 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (652 mg, 66%) following purification by column chromatography (SiO_2, 10–30% EtOAc/petroleum ether).



IR (neat): 2933, 2859, 1685, 1323, 1113, 1065, 831, 786, 664 cm^{-1}.

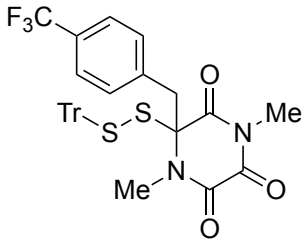
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.76 (dd, *J* = 3.8, 1.7 Hz, 2H), 3.76 (d, *J* = 14.3 Hz, 1H), 3.38 – 3.32 (m, 4H), 3.15 (s, 3H), 0.84 (s, 9H), 0.06 (d, *J* = 4.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 154.8, 153.7, 137.0, 130.6 (d, $^2J_{C\text{-}F}$ = 32.8 Hz), 130.0, 126.0 (q, $^3J_{C\text{-}F}$ = 3.4 Hz), 123.8 (d, $^1J_{C\text{-}F}$ = 272.4 Hz), 75.0, 65.4, 42.7, 30.6, 27.8, 25.8, 18.5, -5.1, -5.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.95 (s, 3F).

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{21}H_{29}O_4N_2F_3NaSSi$: 513.1462 Found: 513.1461.

1,4-dimethyl-6-(4-(trifluoromethyl)benzyl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (24B): Prepared according to General Procedure B. The *title compound* was obtained as a white solid (400 mg, 65%) following purification by column chromatography (SiO_2, 10–30% EtOAc/petroleum ether).



IR (neat): 1683, 1323, 1121, 1067, 699 cm^{-1}.

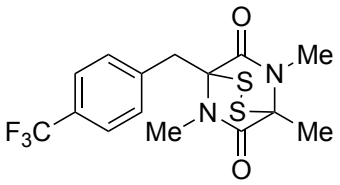
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.24 (m, 15H), 7.00 (d, *J* = 7.9 Hz, 2H), 3.56 (d, *J* = 14.7 Hz, 1H), 3.06 (s, 3H), 2.83 (s, 3H), 2.71 (d, *J* = 14.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.4, 154.9, 153.8, 143.0, 137.3, 130.4, 129.6, 128.2, 127.8, 126.0 (q, $^2J_{C\text{-}F}$ = 3.6 Hz), 123.8 (app. d, $^1J_{C\text{-}F}$ = 272.3 Hz), 78.3, 73.6, 40.3, 30.8, 27.6. Carbon bearing CF_3 not observed.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.88 (s, 3F).

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{33}H_{27}O_3N_2F_3NaS_2$: 643.1307 Found: 643.1306.

1,5,7-trimethyl-4-(4-(trifluoromethyl)benzyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (24): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as an off-white solid (111 mg, 59%) following purification by column chromatography (SiO_2, 10–30% Et_2O/petroleum ether).



IR (neat): 2931, 1678, 1322, 1167, 1105, 1066, 729, 692, 429 cm^{-1}.

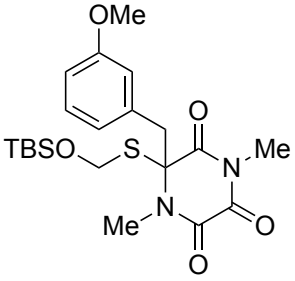
^1H NMR (600 MHz, $CDCl_3$): δ 7.63 – 7.52 (m, 2H), 7.41 (dd, J = 8.4, 3.5 Hz, 2H), 4.12 (d, J = 12.6 Hz, 1H), 3.65 (d, J = 12.7 Hz, 1H), 3.12 (s, 3H), 2.97 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.6, 165.2, 138.6, 129.6 (app. d, $^2J_{C\text{-}F}$ = 32.8 Hz), 129.3, 125.7 (q, $^3J_{C\text{-}F}$ = 3.3 Hz), 124.1 (app. d, $^1J_{C\text{-}F}$ = 272.4 Hz), 75.8, 72.7, 37.1, 28.9, 28.0, 19.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.72 (s, 3F).

HRMS (ESI): *m/z* calcd for $[M+H]^+$ $C_{15}H_{16}O_2N_2F_3S_2$: 377.0600 Found: 377.0600.

6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-6-(3-methoxybenzyl)-1,4-dimethylpiperazine-2,3,5-trione (25A): Prepared according to General Procedure A using 3-methoxybenzyl bromide (0.42 mL, 3 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (660 mg, 73%) following purification by column chromatography (SiO_2, 10–20% EtOAc/petroleum ether).



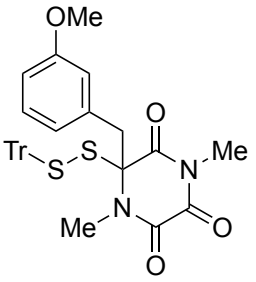
IR (neat): 2924, 2854, 1683, 1355, 1261, 1071, 830, 781, 693 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.15 (t, J = 7.9 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 6.54 (s, 1H), 4.93 – 4.59 (m, 2H), 3.72 (s, 2H), 3.62 (d, J = 14.2 Hz, 1H), 3.35 (s, 3H), 3.25 (d, J = 14.4 Hz, 1H), 3.14 (s, 3H), 0.83 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.6, 160.0, 155.1, 153.8, 134.2, 130.1, 121.6, 115.4, 113.6, 75.5, 65.4, 55.3, 43.3, 30.8, 27.9, 25.8, 18.5, -5.1, -5.4.

HRMS (ESI): *m/z* calcd for $[M+H]^+$ $C_{21}H_{33}O_5N_2SSi$: 453.1874 Found: 453.1876.

6-(3-methoxybenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (25B): Prepared according to General Procedure B. The *title compound* was obtained as a white solid (496 mg, 85%) following purification by column chromatography (SiO_2, 10–30% EtOAc/petroleum ether).



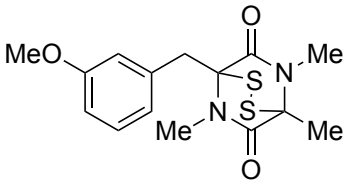
IR (neat): 1685, 1348, 1259, 906, 725, 698, 647 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.40 – 7.23 (m, 15H), 7.09 (t, J = 8.0 Hz, 1H), 6.72 (dd, J = 8.3, 2.6 Hz, 1H), 6.42 (d, J = 7.7 Hz, 1H), 6.38 (s, 1H), 3.69 (s, 3H), 3.43 (d, J = 14.3 Hz, 1H), 3.09 (s, 3H), 2.79 (s, 3H), 2.73 (d, J = 14.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.9, 159.9, 155.1, 153.8, 143.1, 134.4, 130.4, 130.1, 128.2, 127.8, 121.2, 115.1, 113.4, 79.2, 73.2, 55.3, 41.6, 31.1, 27.5.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{33}H_{30}O_4N_2NaS_2$: 605.1539 Found: 605.1542.

1-(3-methoxybenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (25C): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (106 mg, 63%) following purification by column chromatography (SiO_2, 10–30% Et_2O/petroleum ether).



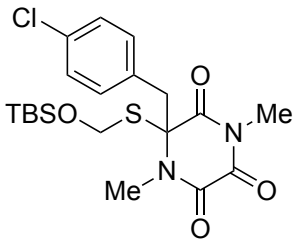
IR (neat): 2929, 1670, 1580, 1352, 1229, 1121, 1052, 777, 699, 631 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (t, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 7.1 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 1H), 4.09 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 3H), 3.56 (d, *J* = 15.8 Hz, 1H), 3.12 (s, 3H), 2.98 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 165.4, 159.8, 136.0, 129.7, 121.3, 115.4, 112.1, 76.2, 72.7, 55.3, 37.2, 29.0, 28.0, 19.1.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{15}H_{18}O_3N_2NaS_2$: 361.0651 Found: 361.0653.

6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-6-(4-chlorobenzyl)-1,4-dimethylpiperazine-2,3,5-trione (26A): Prepared according to General Procedure A using 4-chlorobenzyl bromide (616 mg, 3 mmol, 1.5 equiv). The *title compound* was obtained as a colourless oil (721 mg, 79%) following purification by column chromatography (SiO_2 10–20% EtOAc/petroleum ether).



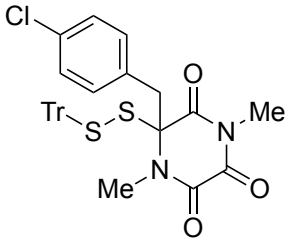
IR (neat): 2929, 2856, 1681, 1332, 1257, 1065, 907, 831, 723 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 4.83 – 4.63 (m, 2H), 3.60 (d, *J* = 14.2 Hz, 1H), 3.33 (s, 3H), 3.26 (d, *J* = 14.3 Hz, 1H), 3.11 (s, 3H), 0.81 (s, 9H), 0.03 (d, *J* = 4.4 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.3, 154.8, 153.7, 134.4, 131.2, 130.8, 129.3, 75.2, 65.4, 42.4, 30.7, 27.8, 25.8, 18.5, -5.1, -5.5.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{20}H_{29}O_4N_2ClNaSSi$: 479.1198 Found: 479.1200.

6-(4-Chlorobenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (26B):



Prepared according to General Procedure B. The *title compound* was obtained as a white solid (502 mg, 86%) following purification by column chromatography (SiO_2, 10–30% EtOAc/petroleum ether).

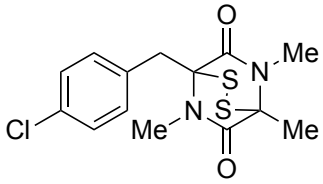
IR (neat): 1683, 1488, 1329, 758, 732, 698, 486 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.24 (m, 15H), 7.17 (d, J = 6.7 Hz, 2H), 6.80 (d, J = 6.8 Hz, 2H), 3.44 (d, J = 13.0 Hz, 1H), 3.07 (s, 3H), 2.79 (s, 3H), 2.70 (d, J = 14.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.6, 154.9, 153.7, 143.0, 131.5, 130.5, 130.4, 129.2, 128.2, 127.8, 78.7, 73.4, 40.5, 30.9, 27.5.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{32}H_{27}O_3N_2ClNaS_2$: 609.1044 Found: 609.1046.

1-(4-chlorobenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (26C):



Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as an off-white solid (93 mg, 54%) following purification by column chromatography (SiO_2, 10–30% Et_2O/petroleum ether).

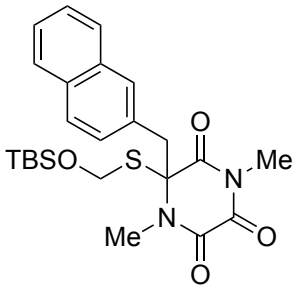
IR (neat): 1682, 1491, 1347, 1095, 1015 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.16 (m, 5H), 4.03 (d, J = 15.8 Hz, 1H), 3.57 (d, J = 15.9 Hz, 1H), 3.12 (s, 3H), 2.98 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 165.3, 133.3, 132.9, 130.5, 128.9, 76.0, 72.6, 36.7, 28.9, 28.0, 19.0.

HRMS (ACPI): *m/z* calcd for $[M+H]^+$ $C_{14}H_{16}O_2N_2ClS_2$: 343.0336 Found: 343.0337.

6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(naphthalen-2-ylmethyl)piperazine-2,3,5-trione (27A):



Prepared according to General Procedure A using 2-(bromomethyl)naphthalene (663 mg, 3 mmol, 1.5 equiv). The *title compound* was obtained as a colourless oil (637 mg, 66%) following purification by column chromatography (SiO_2, 10–30% EtOAc/petroleum ether).

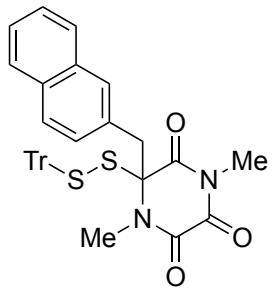
IR (neat): 2929, 2856, 1685, 1392, 1258, 1051, 832, 780 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.76 (dd, J = 6.1, 3.4 Hz, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 1.7 Hz, 1H), 7.46 (dd, J = 6.3, 3.2 Hz, 2H), 7.09 (dd, J = 8.5, 1.8 Hz, 1H), 4.76 (q, J = 12.2 Hz, 2H), 3.82 (d, J = 14.2 Hz, 1H), 3.46 (d, J = 14.2 Hz, 1H), 3.43 (s, 3H), 3.08 (s, 3H), 0.84 (s, 9H), 0.06 (d, J = 6.5 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.6, 154.9, 153.8, 133.3, 132.8, 130.2, 129.0, 128.9, 127.83, 127.76, 126.72, 126.68, 126.63, 75.5, 65.4, 43.4, 30.8, 27.8, 25.8, 18.5, -5.1, -5.4.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{24}H_{32}O_4N_2NaSSi$: 495.1744 Found: 495.1744.

1,4-dimethyl-6-(naphthalen-2-ylmethyl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (27B): Prepared according to General Procedure B. The *title compound* was obtained as a white solid (555 mg, 92%) following purification by column chromatography (SiO_2, 10–30% EtOAc/petroleum ether).



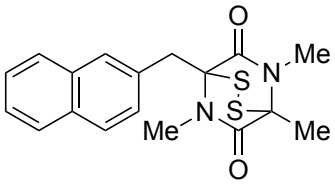
IR (neat): 1679, 1351, 1328, 765, 727, 702, 418 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 6.0, 3.4 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.44 (dd, *J* = 6.3, 3.2 Hz, 2H), 7.36 – 7.27 (m, 16H), 6.95 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.63 (d, *J* = 14.4 Hz, 1H), 3.17 (s, 3H), 2.95 (d, *J* = 14.4 Hz, 1H), 2.73 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.9, 155.0, 153.8, 143.2, 133.3, 132.7, 130.5, 130.4, 128.9, 128.6, 128.2, 127.80, 127.76, 126.7, 126.6, 126.4, 79.2, 73.3, 41.6, 31.1, 27.5.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{36}H_{30}O_3N_2NaS_2$: 625.1590 Found: 625.1596.

1,5,7-trimethyl-4-(naphthalen-2-ylmethyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (27C): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as a colourless oil (91 mg, 51%) following purification by column chromatography (SiO_2, 10–30% Et_2O/petroleum ether).



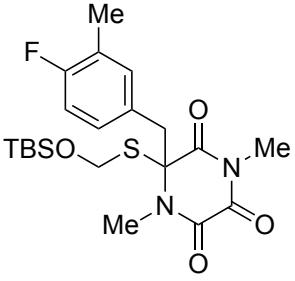
IR (neat): 2927, 1672, 1412, 1368, 1110, 812, 730, 635 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.76 (m, 3H), 7.71 (s, 1H), 7.49 – 7.45 (m, 2H), 7.45 – 7.41 (m, 1H), 4.25 (d, *J* = 15.8 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 1H), 3.15 (s, 3H), 3.02 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.8, 165.5, 133.4, 132.5, 132.0, 128.4, 128.0, 127.8, 127.7, 127.3, 126.4, 126.2, 76.4, 72.7, 37.4, 29.1, 28.0, 19.1.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{18}H_{18}O_2N_2NaS_2$: 381.0702 Found: 381.0704.

6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-6-(4-fluoro-3-methylbenzyl)-1,4-dimethylpiperazine-2,3,5-trione (28A): Prepared according to General Procedure A using 4-(bromomethyl)-1-fluoro-2-methylbenzene (609 mg, 3 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (676 mg, 75%) following purification by column chromatography (SiO_2, 10–20% EtOAc/petroleum ether).



IR (neat): 2955, 2929, 2857, 1683, 1329, 1251, 1211, 1142, 1053 832, 789, 717 cm^{-1}.

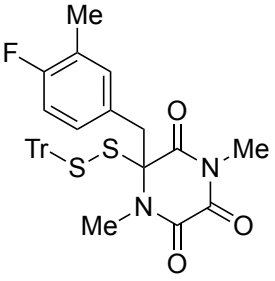
^1H NMR (600 MHz, $CDCl_3$): δ 6.87 (t, J = 8.8 Hz, 1H), 6.83 (dd, J = 7.3, 2.3 Hz, 1H), 6.79 (ddd, J = 7.9, 4.8, 2.4 Hz, 1H), 4.98 – 4.50 (m, 2H), 3.57 (d, J = 14.2 Hz, 1H), 3.35 (s, 3H), 3.23 (d, J = 14.3 Hz, 1H), 3.13 (s, 3H), 2.19 (d, J = 1.9 Hz, 3H), 0.84 (s, 9H), 0.05 (d, J = 4.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.5, 161.1 (d, $^1J_{C\text{-}F}$ = 246.9 Hz), 155.0, 153.8, 132.7 (d, $^3J_{C\text{-}F}$ = 5.2 Hz), 128.4 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 128.2 (d, $J_{C\text{-}F}$ = 3.8 Hz), 125.7 (d, $^2J_{C\text{-}F}$= 17.3 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 75.5, 65.4, 42.4, 30.7, 27.8, 25.8, 18.5, 14.6 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), -5.1, -5.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -117.45 (s, 1F).

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{21}H_{31}O_4N_2FNaSSi$: 477.1650 Found: 477.1651.

6-(4-Fluoro-3-methylbenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (28B): Prepared according to General Procedure B. The *title compound* was obtained as a white solid (534 mg, 91%) following purification by column chromatography (SiO_2, 10–30% EtOAc/petroleum ether).



IR (neat): 1681, 1503, 1442, 1343, 1122, 760, 735, 697 cm^{-1}.

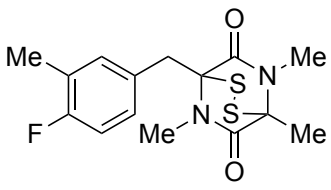
^1H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.11 (m, 15H), 6.77 (td, J = 8.8, 2.9 Hz, 1H), 6.63 (dd, J = 14.8, 5.4 Hz, 2H), 3.42 – 3.24 (m, 1H), 3.07 (s, 3H), 2.81 – 2.55 (m, 4H), 2.11 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.8, 161.0 (d, $^1J_{C\text{-}F}$ = 247.0 Hz), 155.0, 153.8, 143.1, 132.3 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 130.4, 128.2, 128.0 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 127.8, 125.7 (d, $^2J_{C\text{-}F}$ = 17.1 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 22.6 Hz), 79.2, 73.2, 40.8, 31.0, 27.4, 14.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -117.55 (s, 1F).

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{33}H_{29}O_3N_2FNaS_2$: 607.1496 Found: 607.1498.

1-(4-Fluoro-3-methylbenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8- dione (28C): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as an off-white solid (71 mg, 42%) following purification by column chromatography (SiO_2, 10–30% Et_2O/petroleum ether).



IR (neat): 2920, 1674, 1503, 1412, 1355, 1241, 1110, 818, 622 cm^{-1}.

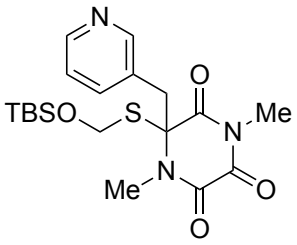
^1H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, J = 7.3 Hz, 1H), 7.06 (td, J = 5.7, 2.7 Hz, 1H), 6.91 (td, J = 8.9, 2.1 Hz, 1H), 3.98 (d, J = 15.8 Hz, 1H), 3.54 (d, J = 15.7 Hz, 1H), 3.10 (s, 3H), 2.98 (s, 3H), 2.23 (s, 3H), 2.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.8, 165.4, 160.5 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 132.3 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 129.8 (d, $J_{C\text{-}F}$ = 3.8 Hz), 128.0 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 125.1 (d, $^2J_{C\text{-}F}$ = 17.4 Hz), 115.1 (d, $^2J_{C\text{-}F}$ = 22.4 Hz), 76.3, 72.5, 36.5, 28.9, 28.0, 19.0, 14.8 (d, $^3J_{C\text{-}F}$ = 3.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -119.46 (s, 1F).

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{15}H_{17}O_2N_2FNaS_2$: 363.0608 Found: 363.0609.

6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(pyridin-3-ylmethyl)piperazine-2,3,5-trione (29A): Prepared according to General Procedure A using 3-(bromomethyl)pyridine hydrobromide (758 mg, 3 mmol, 1.5 equiv) with 3 equiv LiHMDS (6 mL, 1 M in THF, 6 mmol). The *title compound* was obtained as an off-white solid (210 mg, 25%) following purification by column chromatography (SiO_2, 50% EtOAc/petroleum ether with 2% Et_3N).



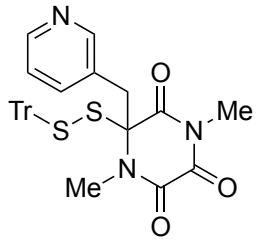
IR (neat): 2926, 2851, 1682, 1398, 1331, 1257, 1061, 830, 788 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.45 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 2.8 Hz, 1H), 7.31 (dt, J = 6.6, 2.3 Hz, 1H), 7.15 (dd, J = 7.9, 4.5 Hz, 1H), 4.71 (d, J = 1.6 Hz, 1H), 3.68 (d, J = 14.4 Hz, 1H), 3.31 (s, 3H), 3.28 (d, J = 15.6 Hz, 1H), 3.11 (s, 3H), 0.79 (s, 9H), 0.01 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.1, 154.7, 153.7, 150.7, 149.6, 136.7, 128.7, 123.7, 74.8, 65.4, 40.3, 30.5, 27.8, 25.7, 18.4, -5.2, -5.5.

HRMS (ESI): *m/z* calcd for $[M+H]^+$ $C_{19}H_{30}O_4N_3SSi$: 424.1721 Found: 424.1722.

1,4-Dimethyl-6-(pyridin-3-ylmethyl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (29B): Prepared according to General Procedure B on 0.5 mmol scale. The *title compound* was obtained as a white solid (135 mg, 49%) following purification by column chromatography (SiO_2, 10–70% EtOAc/petroleum ether).



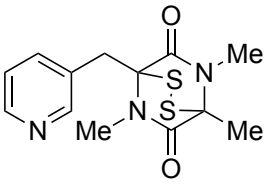
IR (neat): 1681, 1439, 1343, 734, 698, 666, 554 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.47 (s, 1H), 8.21 (s, 1H), 7.41 – 7.28 (m, 15H), 7.21 (s, 1H), 7.16 (dd, J = 8.1, 4.4 Hz, 1H), 3.54 (d, J = 14.9 Hz, 1H), 3.07 (s, 3H), 2.87 (s, 3H), 2.64 (d, J = 14.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3, 154.8, 153.7, 150.4, 149.4, 143.0, 136.4, 130.4, 128.2, 127.8, 123.8, 78.1, 73.6, 37.9, 30.7, 27.6.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{31}H_{27}O_3N_3NaS_2$: 576.1386 Found: 576.1386.

1,5,7-Trimethyl-4-(pyridin-3-ylmethyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (29C): Prepared according to General Procedure C on 0.2 mmol scale using methylmagnesium bromide (3 M in Et_2O, 0.1 mL, 0.3 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (41 mg, 66%) following purification by column chromatography (SiO_2, 10–70% EtOAc/petroleum ether).



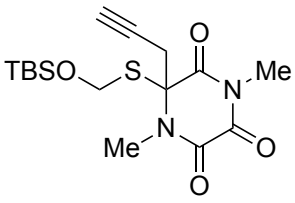
IR (neat): 1677, 1246, 1166, 1033, 637, 518 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.61 – 8.54 (m, 1H), 8.51 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.23 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 4.05 (d, *J* = 14.9 Hz, 1H), 3.59 (d, *J* = 15.8 Hz, 1H), 3.11 (s, 3H), 2.98 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 165.2, 150.6, 148.7, 136.7, 130.5, 123.6, 75.9, 72.5, 35.0, 29.0, 28.0, 19.0.

HRMS (ESI): *m/z* calcd for $[M+H]^+$ $C_{13}H_{16}O_2N_3S_2$: 310.0678 Found: 310.0680.

6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(prop-2-yn-1-yl)piperazine-2,3,5-trione (30A): Prepared according to General Procedure A using propargyl bromide (80% wt. in toluene, 0.71 mL, 3 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (439 mg, 59%) following purification by column chromatography (SiO_2, 10–20% EtOAc/petroleum ether).



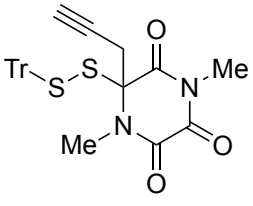
IR (neat): 3242, 2955, 2928, 2850, 1685, 1400, 1334, 1065, 829, 786, 689 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 4.77 (d, *J* = 12.3 Hz, 1H), 4.71 (d, *J* = 12.3 Hz, 1H), 3.44 (dd, *J* = 17.1, 2.5 Hz, 1H), 3.33 (s, 3H), 3.24 (s, 3H), 2.88 (dd, *J* = 17.1, 2.5 Hz, 1H), 2.10 (s, 1H), 0.84 (s, 9H), 0.06 (d, *J* = 0.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.5, 155.4, 153.7, 75.7, 73.8, 72.8, 65.6, 29.2, 28.9, 28.2, 25.8, 18.4, -5.0, -5.4.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{16}H_{26}O_4N_2NaSSi$: 393.1275 Found: 393.1278.

1,4-Dimethyl-6-(prop-2-yn-1-yl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (30B): Prepared according to General Procedure B. The *title compound* was obtained as an off-white solid (425 mg, 85%) following purification by column chromatography (SiO_2, 10–20% EtOAc/petroleum ether).



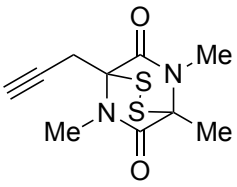
IR (neat): 3284, 1685, 1441, 1346, 1156, 759, 736, 699, 650 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 – 7.21 (m, 15H), 3.16 (dd, *J* = 17.0, 2.7 Hz, 1H), 3.05 (s, 3H), 2.91 (s, 3H), 2.09 – 1.95 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.6, 155.6, 153.7, 142.9, 130.4, 128.3, 127.9, 75.9, 75.8, 73.7, 73.3, 29.0, 27.9, 25.9.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{28}H_{24}O_3N_2NaS_2$: 523.1121 Found: 523.1120.

1,5,7-Trimethyl-4-(prop-2-yn-1-yl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (30C): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as a colourless oil (37 mg, 29%) following purification by column chromatography (SiO_2, 10–20% EtOAc/petroleum ether).



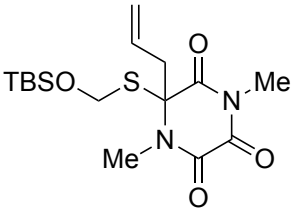
IR (neat): 3245, 1681, 1463, 1356, 1261, 1117, 747, 626 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.35 (dd, *J* = 17.4, 2.8 Hz, 1H), 3.23 – 3.18 (m, 4H), 3.07 (s, 3H), 2.23 (t, *J* = 2.7 Hz, 1H), 2.00 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.1, 164.6, 74.3, 73.1, 72.3, 28.3, 27.7, 23.5, 18.9.

HRMS (ESI): *m/z* calcd for $[M-S_2]^+$ $C_{10}H_{12}N_2O_2$: 192.0899 Found: 192.0893.

6-Allyl-6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (31A): Prepared according to General Procedure A using allyl bromide (0.17 mL, 3 mmol, 1.5 equiv). The *title compound* was obtained as a white solid (600 mg, 81%) following purification by column chromatography (SiO_2, 20% EtOAc/petroleum ether).



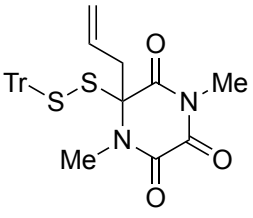
IR (neat): 2928, 2856, 1683, 1337, 1269, 1069, 834, 778, 681 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.54 – 5.39 (m, 1H), 5.28 – 5.14 (m, 2H), 4.84 – 4.59 (m, 2H), 3.29 (s, 3H), 3.25 – 3.21 (m, 4H), 2.76 (dd, *J* = 14.5, 7.3 Hz, 1H), 0.84 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 155.5, 153.9, 128.9, 122.3, 73.6, 65.3, 41.6, 29.2, 28.0, 25.8, 18.5, -5.0, -5.4.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{16}H_{28}O_4N_2NaSSi$: 395.1431 Found: 395.1433.

6-Allyl-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (31B): Prepared according to General Procedure B. The *title compound* was obtained as a colourless oil (251 mg, 50%) following purification by column chromatography (SiO_2, 10–20% EtOAc/petroleum ether).



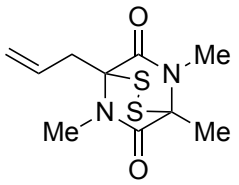
IR (neat): 1683, 1440, 1338, 1283, 756, 730, 697, 542 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 – 7.16 (m, 15H), 5.40 – 5.26 (m, 1H), 5.13 – 5.03 (m, 2H), 3.05 (dd, *J* = 14.7, 6.3 Hz, 1H), 2.92 (s, 3H), 2.86 (s, 3H), 2.16 (dd, *J* = 14.7, 7.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3, 155.9, 154.1, 143.2, 130.6, 129.4, 128.4, 128.0, 122.0, 77.2, 73.6, 39.3, 29.3, 27.8.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{28}H_{26}O_3N_2NaS_2$: 525.1277 Found: 525.1277.

1-Allyl-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (31C): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The *title compound* was obtained as a colourless oil (70 mg, 54%) following purification by column chromatography (SiO_2, 10–30% Et_2O/petroleum ether).



IR (neat): 2922, 1676, 1419, 1358, 1023, 929, 633 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.02 (dddd, *J* = 17.5, 10.3, 7.6, 5.3 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.28 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.31 – 3.23 (m, 1H), 3.11 (s, 3H), 3.08 (s, 3H), 3.07 – 3.01 (m, 1H), 2.01 (s, 3H).

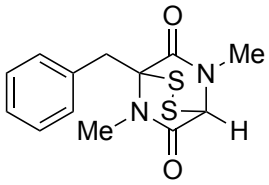
^{13}C NMR (126 MHz, $CDCl_3$): δ 166.8, 165.2, 131.5, 120.4, 74.9, 72.1, 36.9, 28.1, 27.7, 19.0.

HRMS (ESI): *m/z* calcd for $[M-S_2]^+$ $C_{10}H_{14}N_2O_2$: 194.1055 Found: 194.1058.

Scope of Nucleophile

Steps 32A and 32B correspond to compounds 15 and 16. See above for procedures and data.

1-Benzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (32C): Prepared according to General Procedure C using isobutylmagnesium bromide (1.00 mL, 0.75 mmol, 0.75M in Et_2O, 1.5 equiv). The title compound* was obtained as a white solid (60 mg, 41%) following purification by column chromatography (SiO_2, 20-50% Et_2O/petroleum ether).



IR (neat): 2990, 2926, 1688, 1371, 1247, 1121, 730 cm^{-1}.

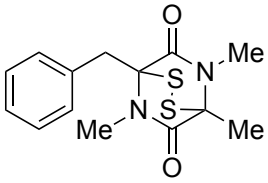
^1H NMR (500 MHz, $CDCl_3$): δ 7.50 – 7.17 (m, 5H), 5.38 (s, 1H), 4.05 (d, *J* = 15.8 Hz, 1H), 3.59 (d, *J* = 15.8 Hz, 1H), 3.17 (s, 3H), 2.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.6, 164.9, 134.2, 129.1, 128.8, 127.4, 76.8, 67.3, 36.8, 32.4, 28.3.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{13}H_{14}O_2N_2NaS_2$: 317.0389 Found: 317.0392.

* This compound has been prepared previously but no spectroscopic data was presented: F Fukuyama, T.; Nakatsuke, S.; Kishi, Y. A New Synthesis of Epidithiapiperazinediones. *Tetrahedron Lett.* **1976**, *38*, 3393-3396.

1-Benzyl-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (33C): Prepared according to General Procedure C using methylmagnesium bromide (3 M in Et_2O, 0.25 mL, 0.75 mmol, 1.5 equiv). The title compound* was obtained as a white solid (96 mg, 62%) following purification by column chromatography (SiO_2, 10–30% EtO_2/petroleum ether).



IR (neat): 2919, 1672, 1415, 1354, 1112, 756, 697, 621, 532 cm^{-1}.

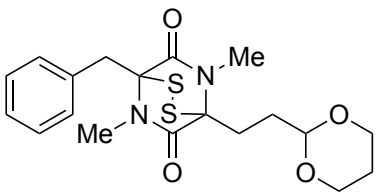
^1H NMR (600 MHz, $CDCl_3$): δ 7.41 – 7.13 (m, 5H), 4.10 (d, *J* = 15.9 Hz, 1H), 3.57 (d, *J* = 15.9 Hz, 1H), 3.10 (s, 3H), 2.95 (s, 3H), 2.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 165.4, 134.4, 128.9, 128.7, 127.2, 76.1, 72.6, 37.1, 28.9, 27.9, 19.0.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{14}H_{16}O_2N_2NaS_2$: 331.0545 Found: 331.0546.

* This compound has been prepared previously: F Fukuyama, T.; Nakatsuke, S.; Kishi, Y. A New Synthesis of Epidithiapiperazinediones. *Tetrahedron Lett.* **1976**, *38*, 3393-3396.

1-(2-(1,3-Dioxan-2-yl)ethyl)-4-benzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (34C): Prepared according to General Procedure C using (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (1.5 mL, 0.75 mmol, 0.5 M in THF, 1.5 equiv). The *title compound* was obtained as a white



solid (63 mg, 32%) following purification by column chromatography (SiO_2, 25-50% EtOAc/petroleum ether).

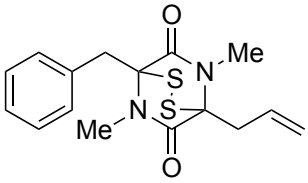
IR (neat): 2958, 2852, 1681, 1336, 1140, 730 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.50 – 7.11 (m, 5H), 4.67 (dd, *J* = 5.7, 3.5 Hz, 1H), 4.19 – 3.97 (m, 3H), 3.76 (td, *J* = 12.4, 2.2 Hz, 2H), 3.56 (d, *J* = 15.9 Hz, 1H), 3.13 (s, 3H), 2.93 (s, 3H), 2.55 (ddd, *J* = 14.2, 11.5, 5.3 Hz, 1H), 2.41 (ddd, *J* = 14.4, 11.3, 3.7 Hz, 1H), 2.25 (dddd, *J* = 13.6, 11.3, 5.3, 3.5 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.74 (dddd, *J* = 13.6, 11.5, 5.7, 3.7 Hz, 1H), 1.34 (dt, *J* = 13.4, 1.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.5, 165.7, 134.5, 128.9, 128.8, 127.3, 101.1, 76.8, 76.7, 67.0, 67.0, 37.1, 30.5, 28.9, 28.8, 26.6, 25.8.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{19}H_{24}O_4N_2NaS_2$: 431.1070 Found: 431.1070.

1-Allyl-4-benzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (35C):



Prepared according to General Procedure C using allylmagnesium bromide (0.75 mL, 0.75 mmol, 1.0 M in THF, 1.5 equiv). The *title compound* was obtained as a colourless oil (78 mg, 47%) following purification by column chromatography (SiO_2, 10-25% Et_2O/petroleum ether).

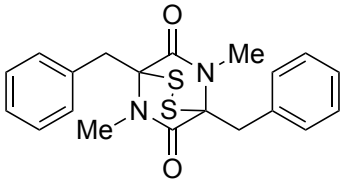
IR (neat): 2925, 1676, 1409, 1339, 1093, 910, 728 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 5H), 6.06 (dddd, *J* = 17.6, 10.3, 7.7, 5.3 Hz, 1H), 5.39 – 5.29 (m, 2H), 4.11 (d, *J* = 15.9 Hz, 1H), 3.59 (d, *J* = 15.9 Hz, 1H), 3.34 – 3.29 (m, 1H), 3.15 (s, 3H), 3.10-3.04 (dd, *J* = 14.9, 7.8 Hz, 1H), 2.97 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.2, 165.8, 134.5, 131.5, 129.0, 128.8, 127.3, 120.5, 76.5, 75.6, 37.1, 36.8, 29.0, 28.4.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{16}H_{18}O_2N_2NaS_2$: 357.0702 Found: 357.0704.

1,4-Dibenzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (36C):



Prepared according to General Procedure C using benzylmagnesium bromide (0.375 mL, 0.75 mmol, 2.0 M in THF, 1.5 equiv). After 30 minutes a further 0.375 mL was added. The title compound* was obtained as a white solid (96 mg, 50%) following purification by column chromatography (SiO_2, 10-25% Et_2O/petroleum ether).

IR (neat): 2924, 1679, 1603, 1337, 1098, 907, 725, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 4.4 Hz, 8H), 7.39 (tt, *J* = 10.5, 4.3 Hz, 2H), 4.26 (d, *J* = 15.8 Hz, 2H), 3.76 (d, *J* = 15.8 Hz, 2H), 3.14 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 134.5, 129.0, 128.8, 127.3, 37.1, 29.2.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{20}H_{20}O_2N_2NaS_2$: 407.0858 Found: 407.0862.

* Spectroscopic data are in accordance with this previous report: Nicolaou, K. C.; Giguère, Totokotsopoulos; Sun, Y.-P. A Practical Sulfenylation of 2,5-Diketopiperazines. *Angew. Chem. Int. Ed.* **2012**, *51*, 728–732,

1-Benzyl-5,7-dimethyl-4-phenyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (37C): Prepared according to General Procedure C using phenylmagnesium bromide (0.25 mL, 0.75 mmol, 3.0 M in Et_2O, 1.5 equiv). After 30 minutes a further 0.25 mL was added. The *title compound* was obtained as a colourless oil (96 mg, 52%) following purification by column chromatography (SiO_2, 10-25% Et_2O/petroleum ether).

IR (neat): 3030, 2927, 2250, 1680, 1327, 908, 694 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 7.0, 2.8 Hz, 2H), 7.55 – 7.49 (m, 3H), 7.41 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 4.19 (d, *J* = 15.8 Hz, 1H), 3.69 (d, *J* = 15.7 Hz, 1H), 3.03 (s, 3H), 2.72 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.2, 165.8, 134.5, 132.3, 130.2, 129.2, 128.9, 128.8, 127.4, 80.9, 76.7, 37.2, 31.4, 29.6.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{19}H_{18}O_2N_2NaS_2$: 393.0702 Found: 393.0703.

1-benzyl-4-(4-chlorophenyl)-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (38C): Prepared according to General Procedure C using 4-chlorophenylmagnesium bromide (0.75 mL, 0.75 mmol, 1.0 M in Et_2O 1.5 equiv). After 30 minutes a further 0.75 mL was added. The *title compound* was obtained as a colourless oil (101 mg, 50%) following purification by column chromatography (SiO_2, 10-25% Et_2O/petroleum ether).

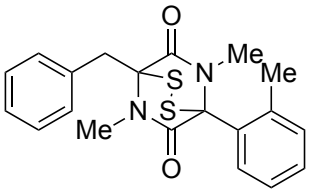
IR (neat): 2929, 1684, 1494, 1336, 1094, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.41 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 4.17 (d, *J* = 15.7 Hz, 1H), 3.69 (d, *J* = 15.8 Hz, 1H), 3.03 (s, 3H), 2.72 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.9, 165.6, 136.5, 134.4, 130.8, 129.2, 128.8, 127.5, 80.2, 76.7, 37.1, 31.4, 29.6.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{19}H_{17}O_2N_2ClNaS_2$: 427.0312 Found: 427.0315.

1-Benzyl-5,7-dimethyl-4-(*o*-tolyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione



(39C): Prepared according to General Procedure C using *o*-tolylmagnesium bromide (0.75 mL, 0.75 mmol, 1.0 M in THF, 1.5 equiv). After 30 minutes a further 0.75 mL was added. The *title compound* was obtained as a colourless oil (102 mg, 53%) following purification by column chromatography (SiO_2, 10-30% Et_2O/petroleum ether).

IR (neat): 3367, 2929, 2249, 1679, 1335, 906 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.43 (td, *J* = 7.5, 1.3 Hz, 1H), 7.40 – 7.28 (m, 7H), 4.21 (d, *J* = 15.8 Hz, 1H), 3.71 (d, *J* = 15.8 Hz, 1H), 3.04 (s, 3H), 2.73 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.3, 164.9, 137.4, 134.6, 132.1, 130.9, 130.3, 129.0, 128.8, 128.3, 127.3, 126.5, 81.6, 77.0, 37.1, 30.5, 29.4, 20.3.

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{20}H_{20}O_2N_2NaS_2$: 407.0858 Found: 407.0865.

1-Benzyl-5,7-dimethyl-4-(4-(trifluoromethoxy)phenyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (40C): Prepared according to General Procedure C using 4-trifluoromethoxyphenylmagnesium bromide (0.75 mL, 0.75 mmol, 1.0 M in THF, 1.5 equiv). The *title compound* was obtained as a white solid (135 mg, 59%) following purification by column chromatography (SiO_2, 10-30% Et_2O/petroleum ether).

IR (neat): 3362, 2920, 2249, 1685, 1330, 906, 730 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.73 – 7.59 (m, 2H), 7.41 – 7.26 (m, 7H), 4.17 (d, *J* = 15.7 Hz, 1H), 3.71 (d, *J* = 15.7 Hz, 1H), 3.04 (s, 3H), 2.72 (s, 3H).

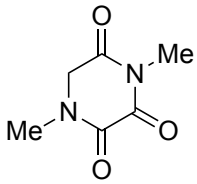
^{13}C NMR (126 MHz, $CDCl_3$): δ 165.8, 165.6, 150.3, 134.3, 130.9, 130.7, 129.2, 128.8, 127.5, 120.9, 120.4 (q, $^1J_{C\text{-}F}$ = 258.5 Hz), 80.0, 76.7, 37.0, 31.4, 29.6.

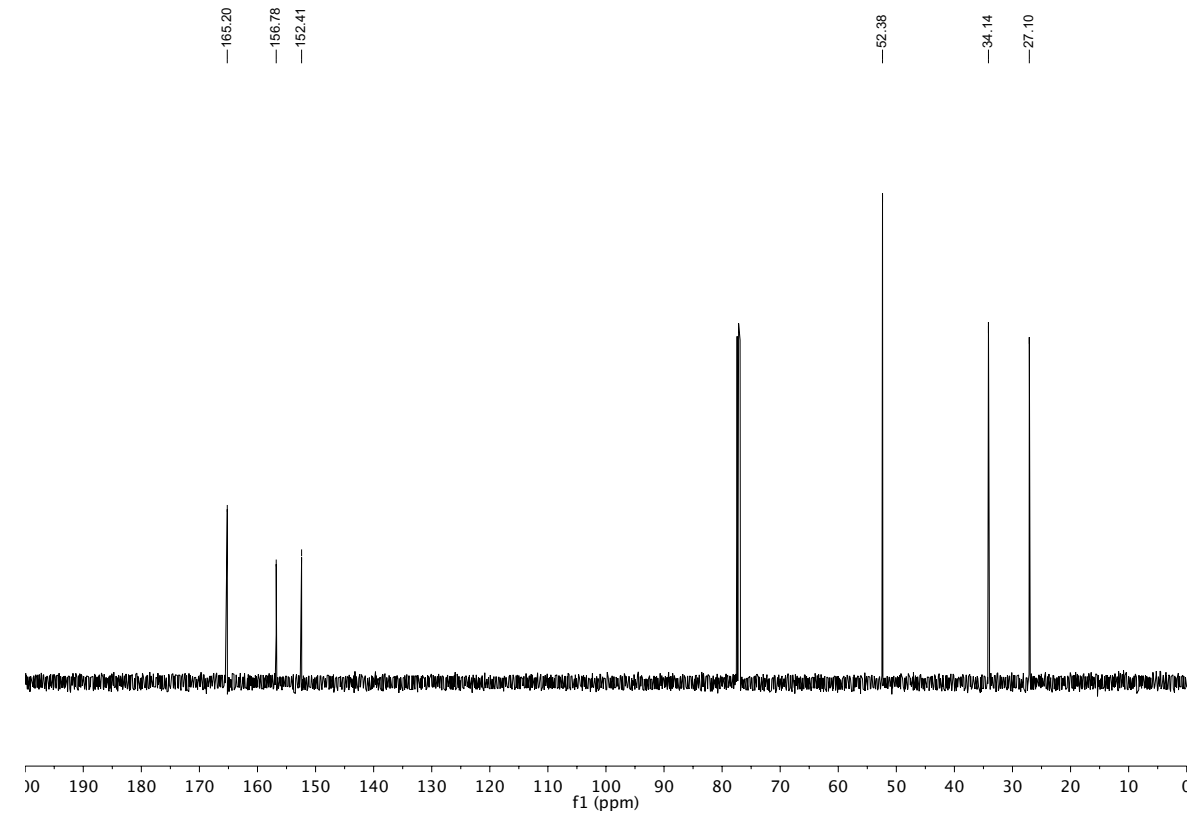
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.75 (s, 3F).

HRMS (ESI): *m/z* calcd for $[M+Na]^+$ $C_{20}H_{17}O_3N_2F_3NaS_2$: 477.0525 Found: 477.0527.

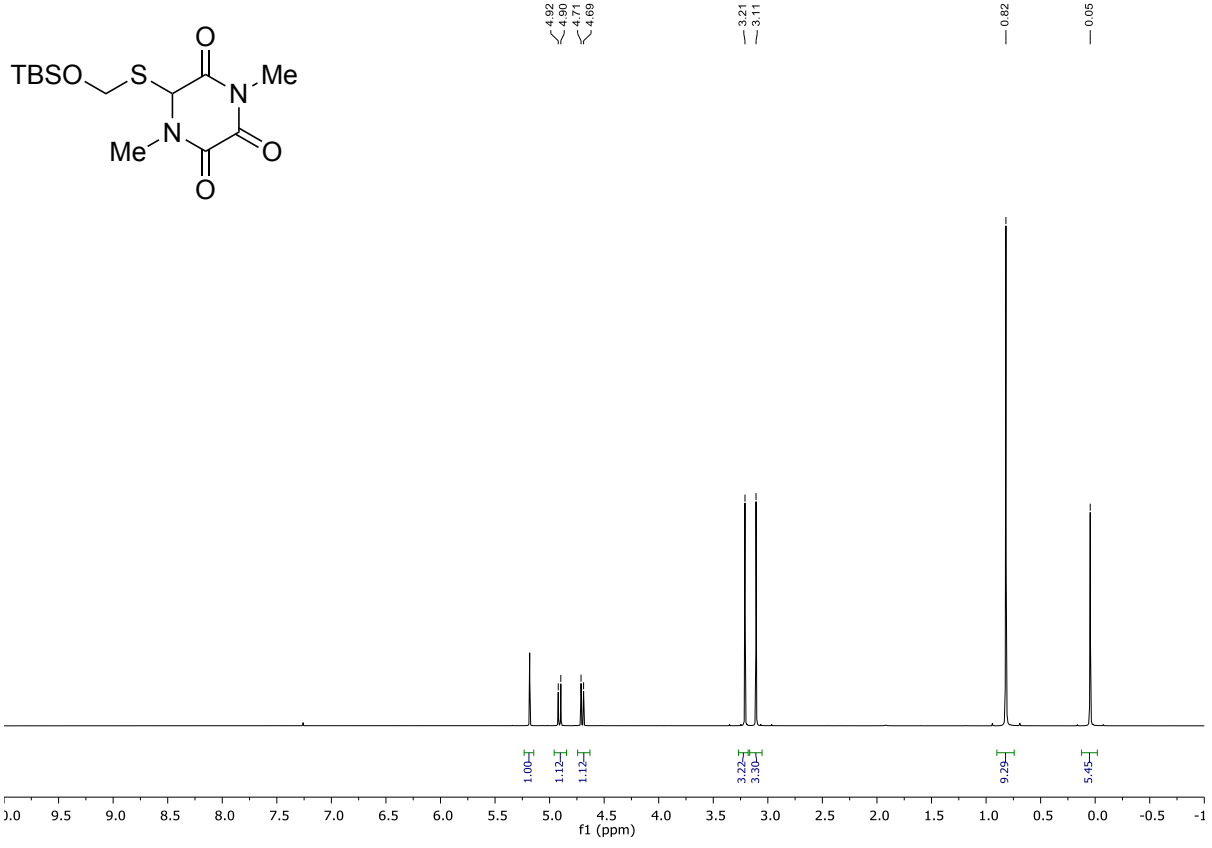
NMR Spectra

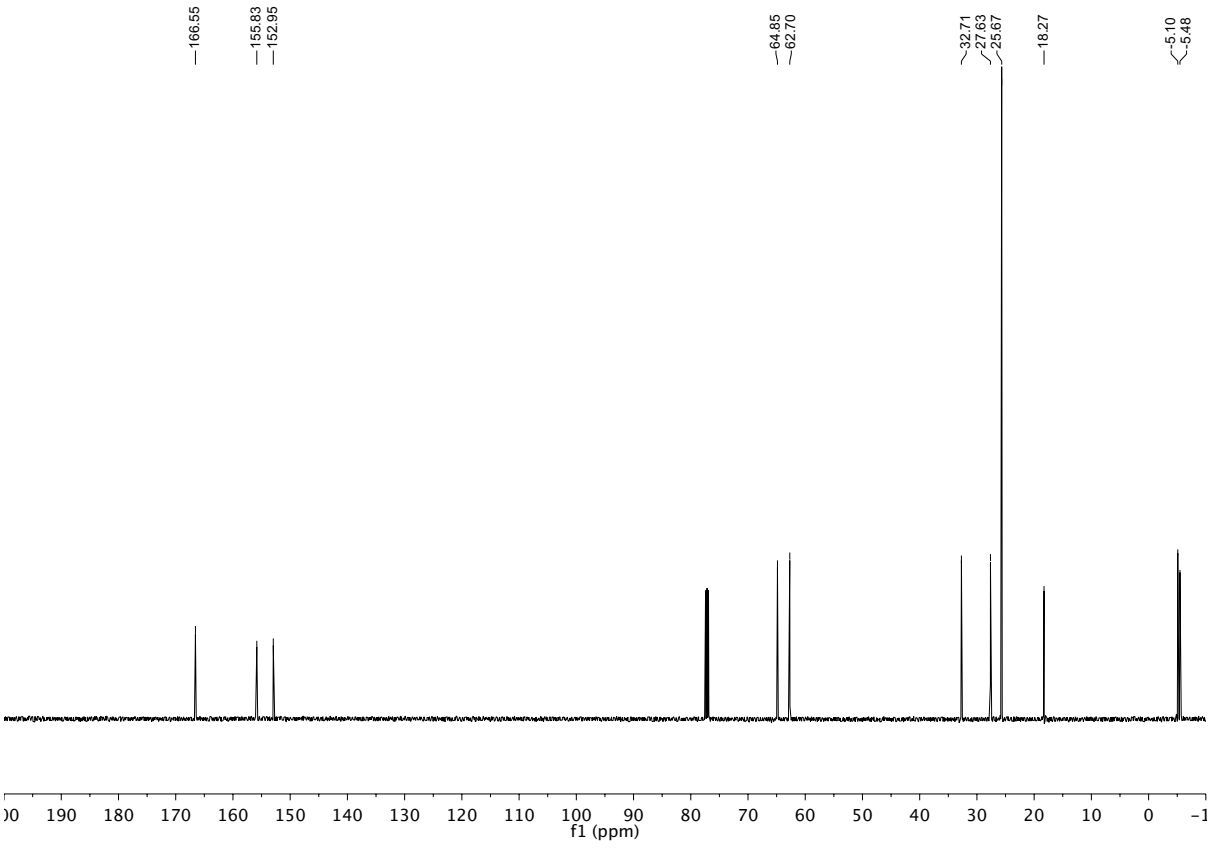
1,4-Dimethylpiperazine-2,3,5-trione (13):



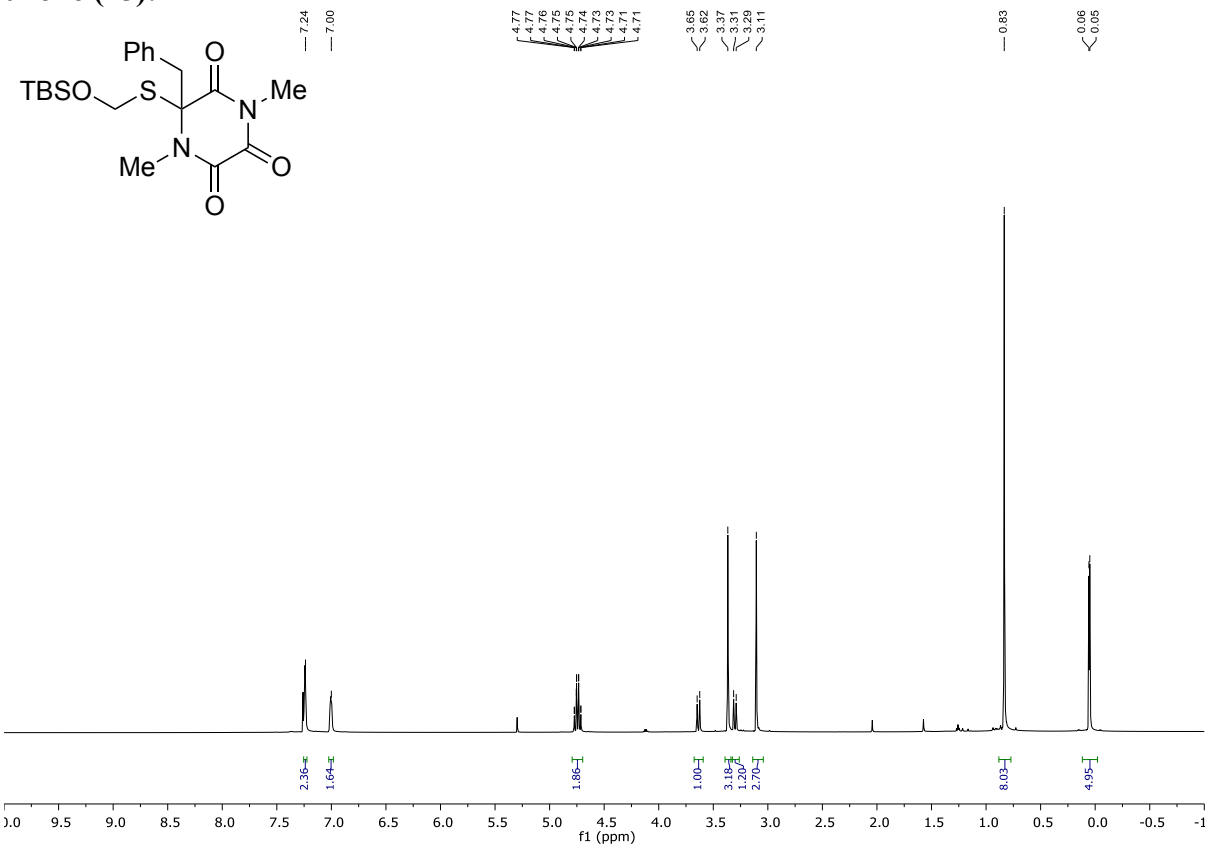


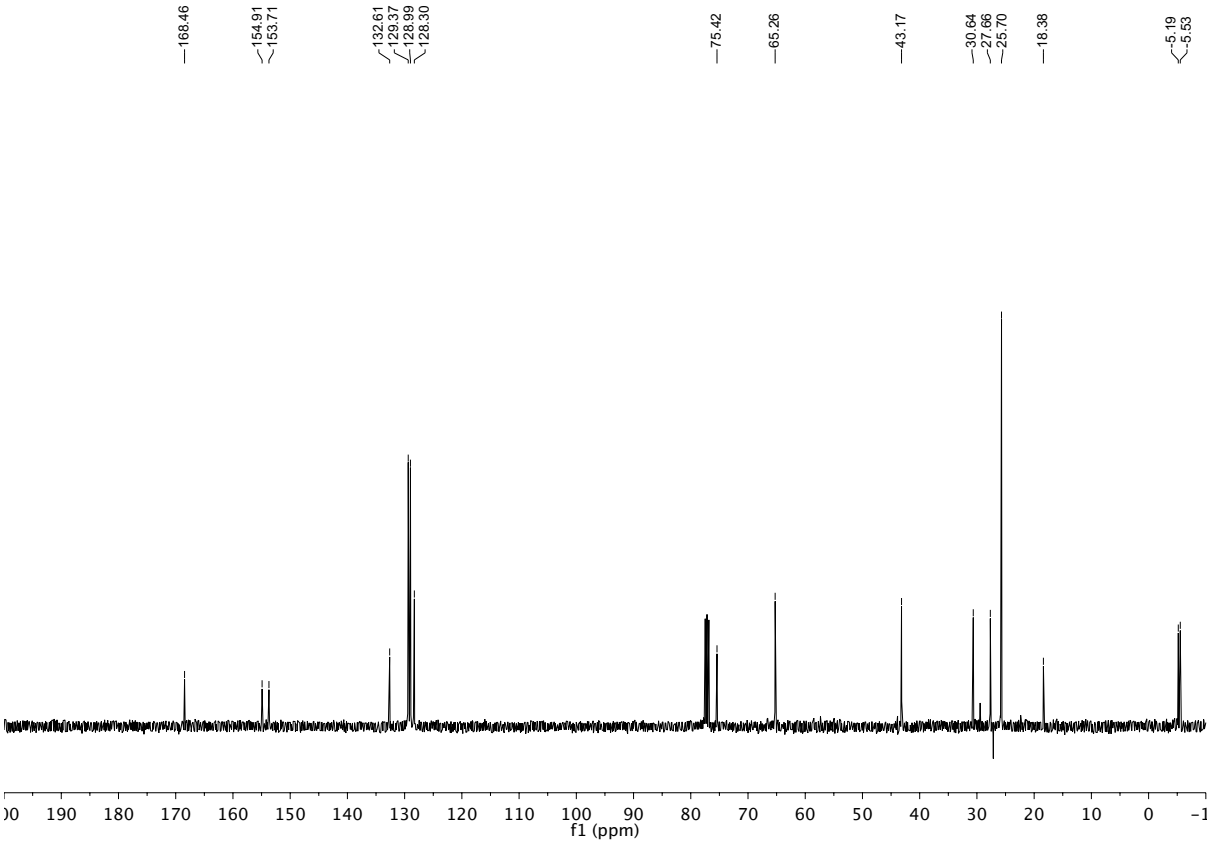
6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (14):



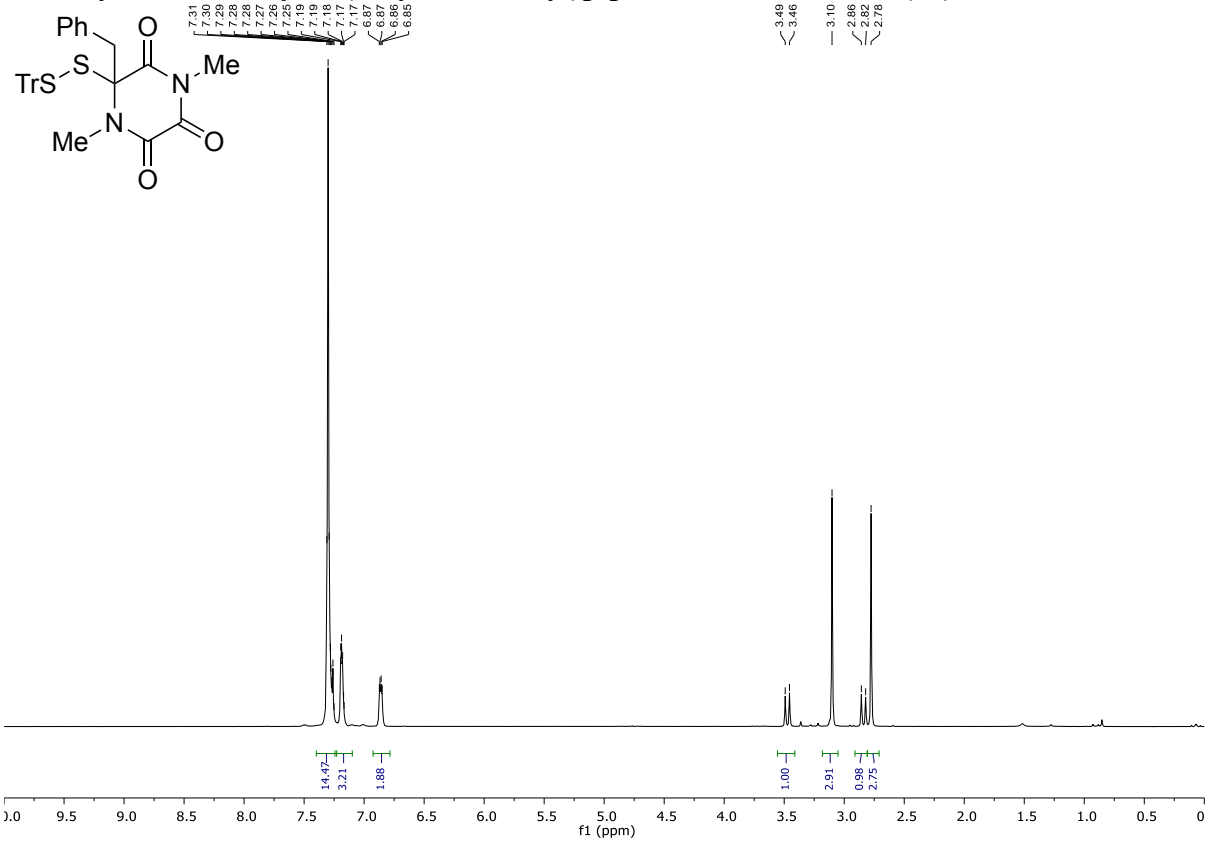


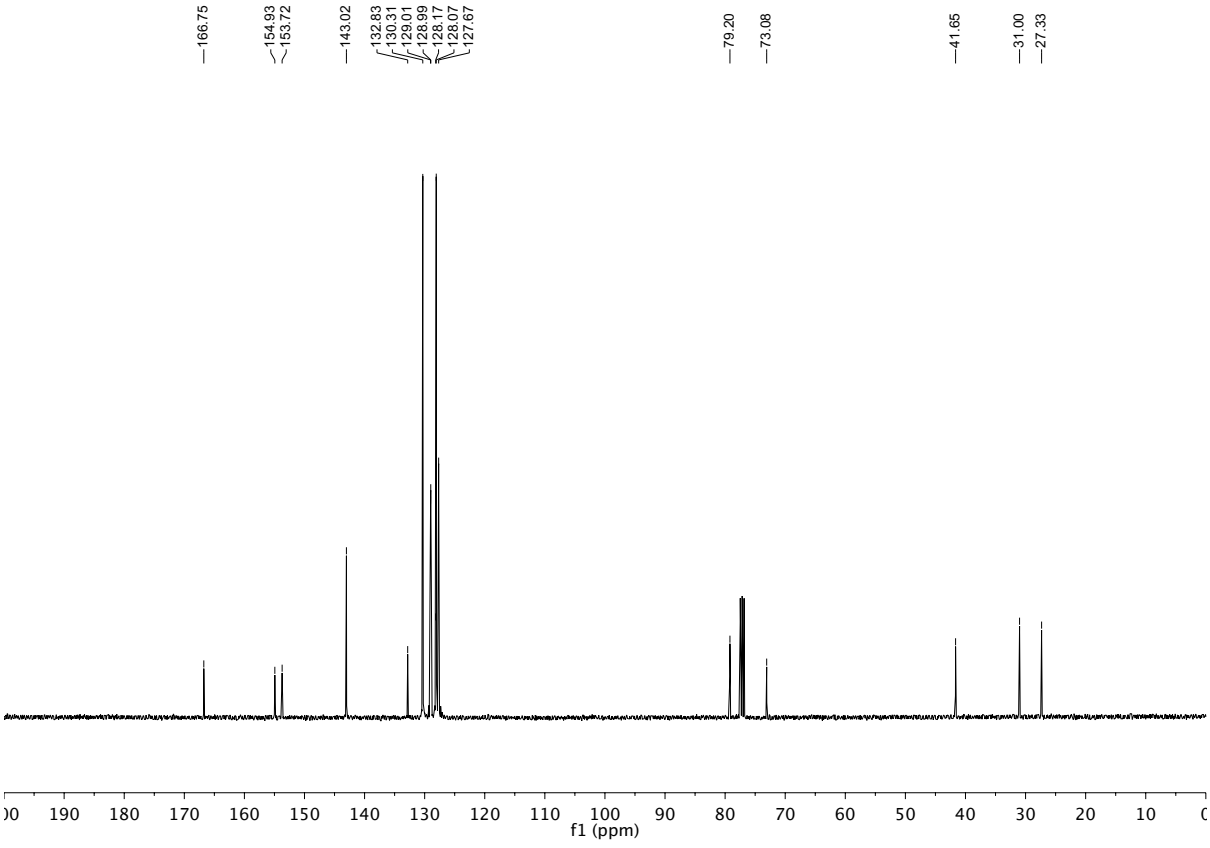
6-Benzyl-6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (15):



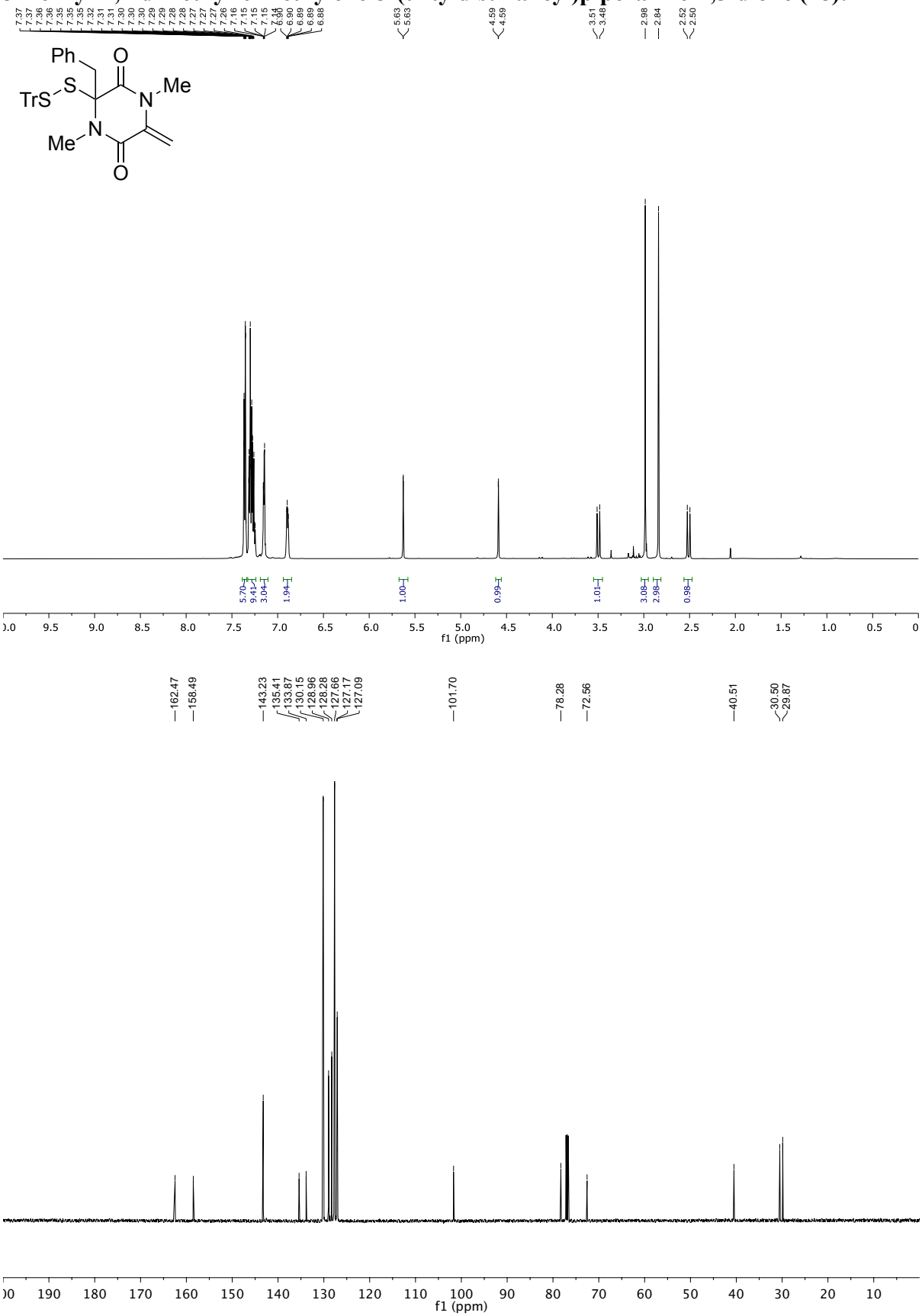


6-Benzyl-1,4-dimethyl-6-(tritylsulfaneyl)piperazine-2,3,5-trione (16):

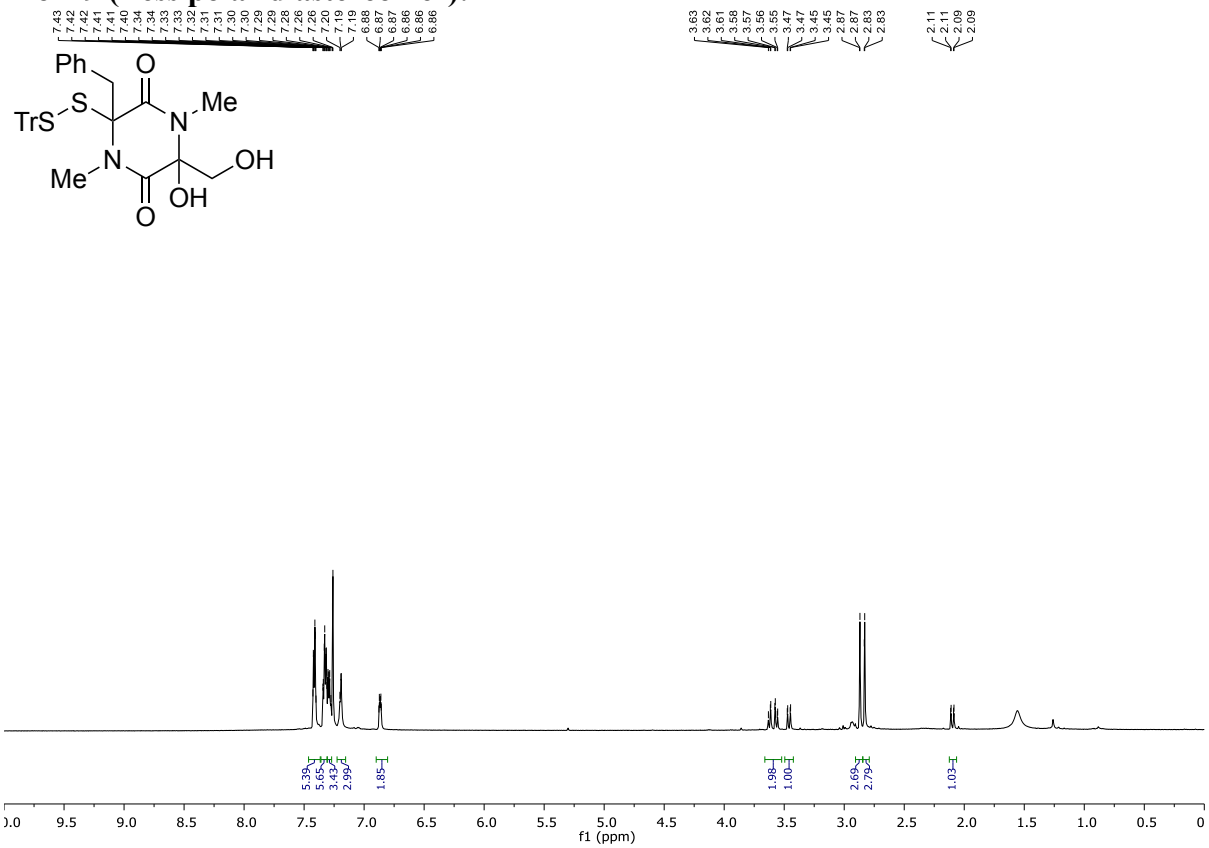




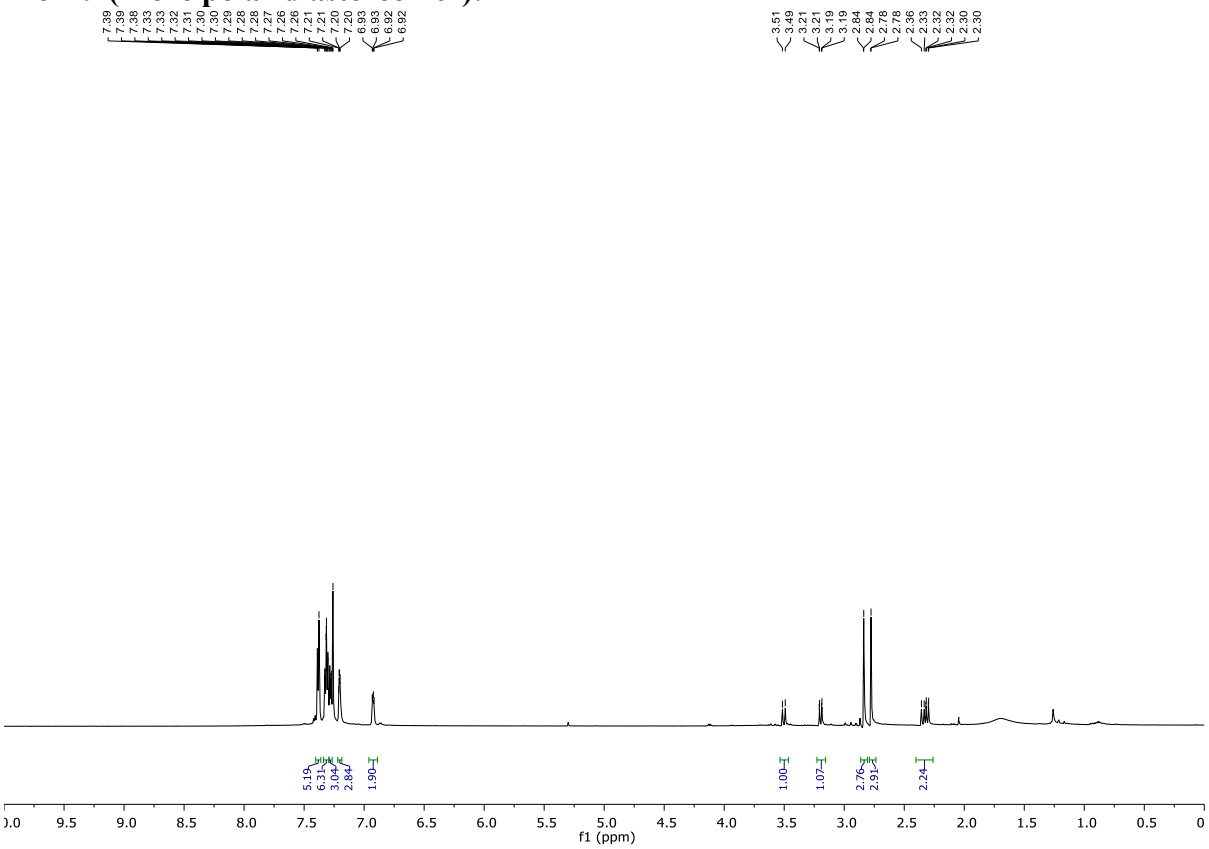
3-Benzyl-1,4-dimethyl-6-methylene-3-(tritylsulfaneyl)piperazine-2,5-dione (18):



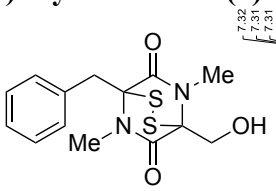
Diol 19 (Less polar diastereomer):

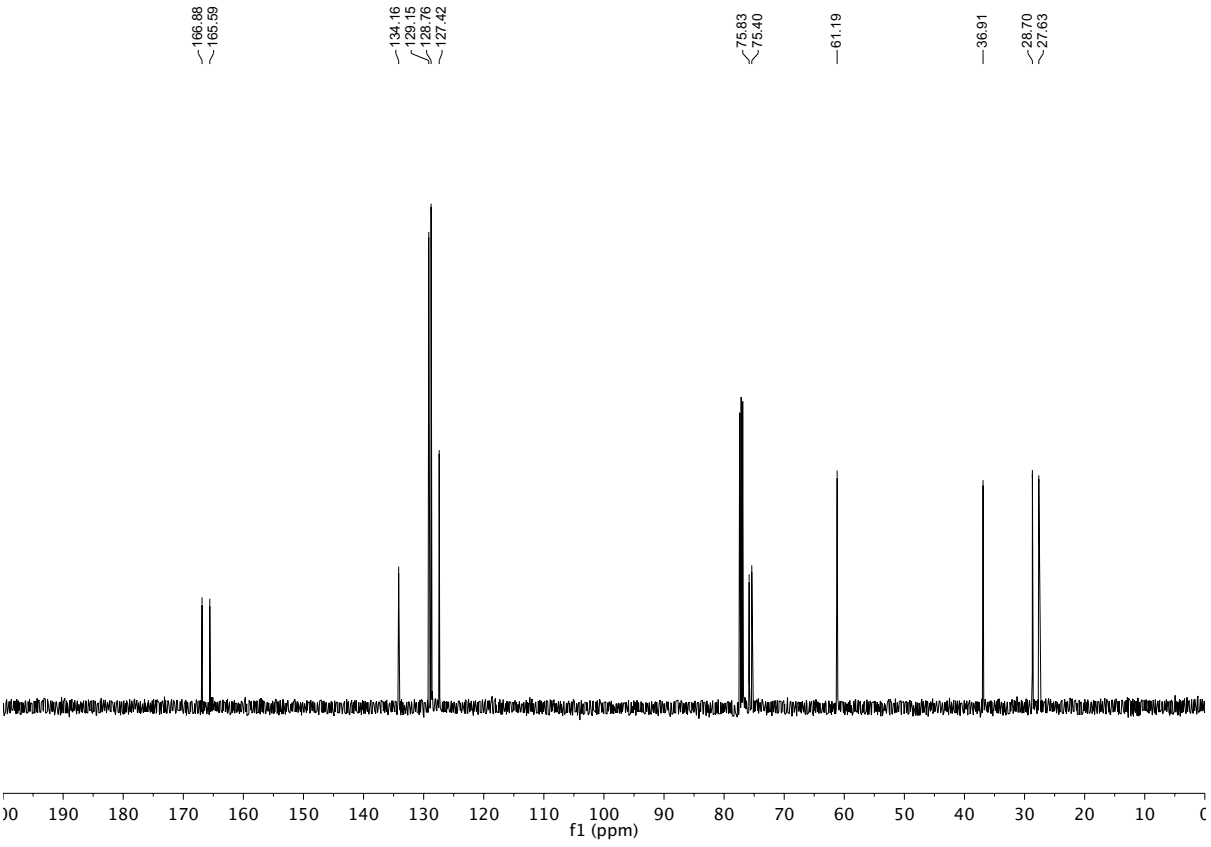


Diol 19 (More polar diastereomer):

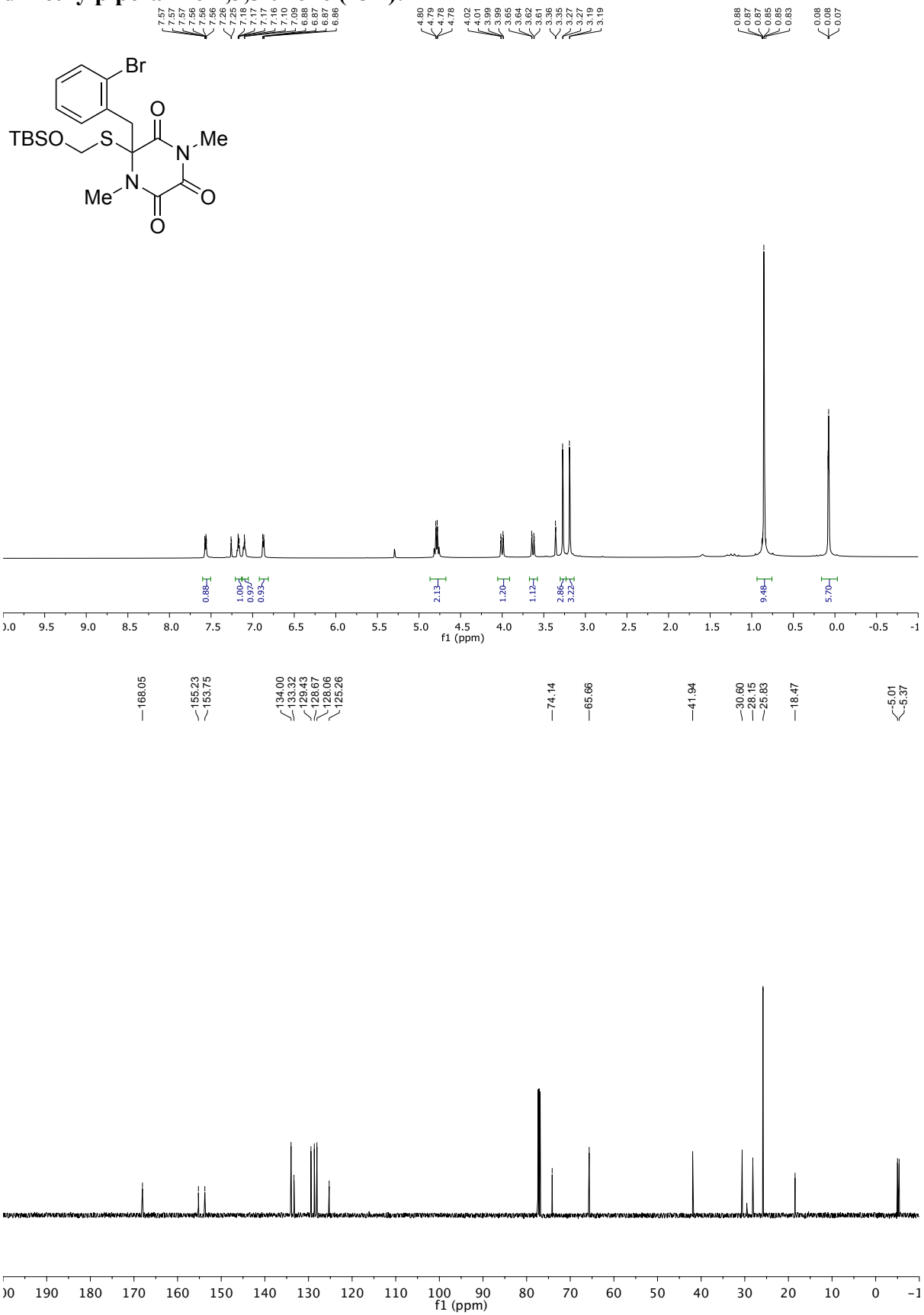


(±)-Hyalodendrin (2):

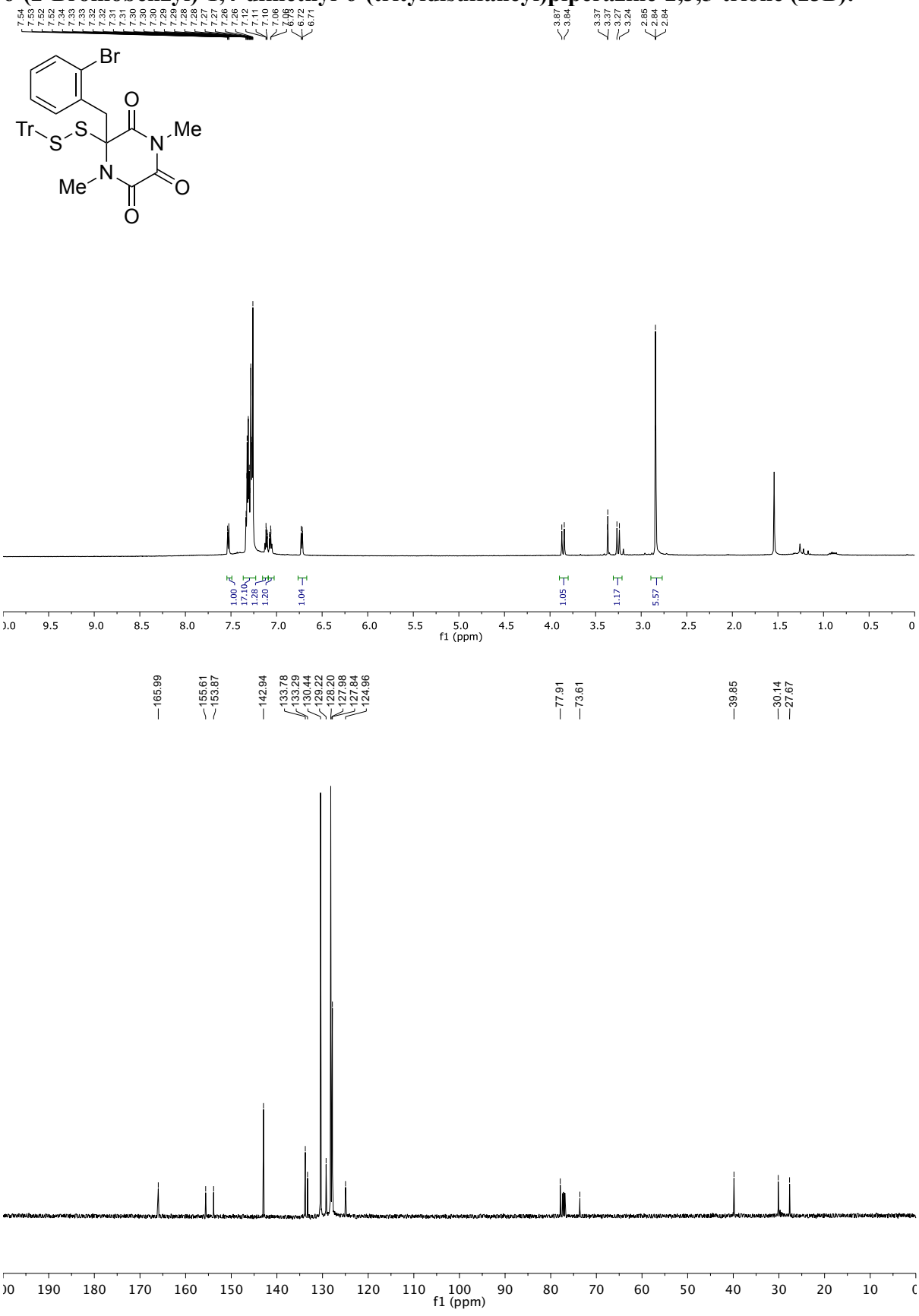




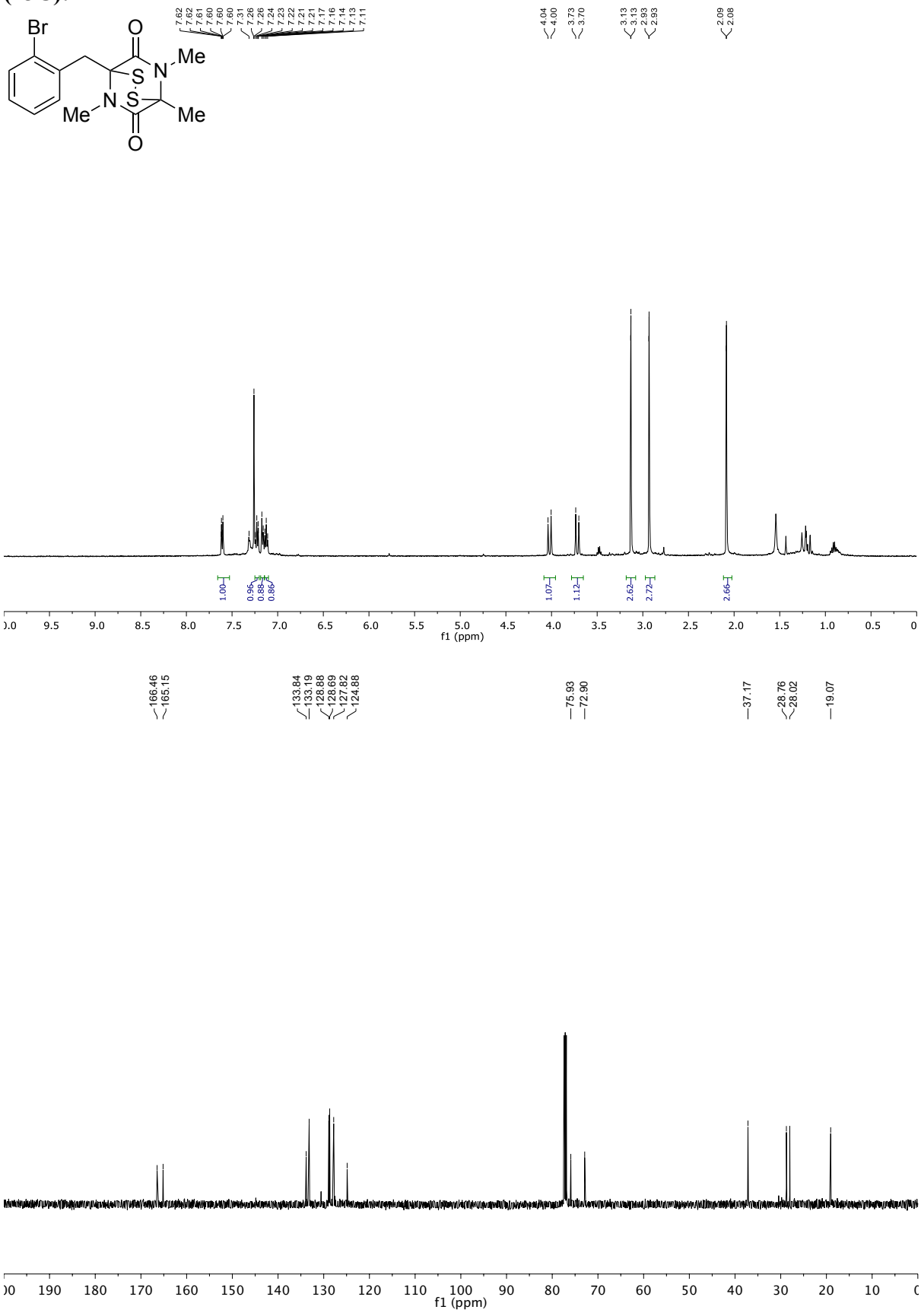
6-(2-Bromobenzyl)-6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (23A):



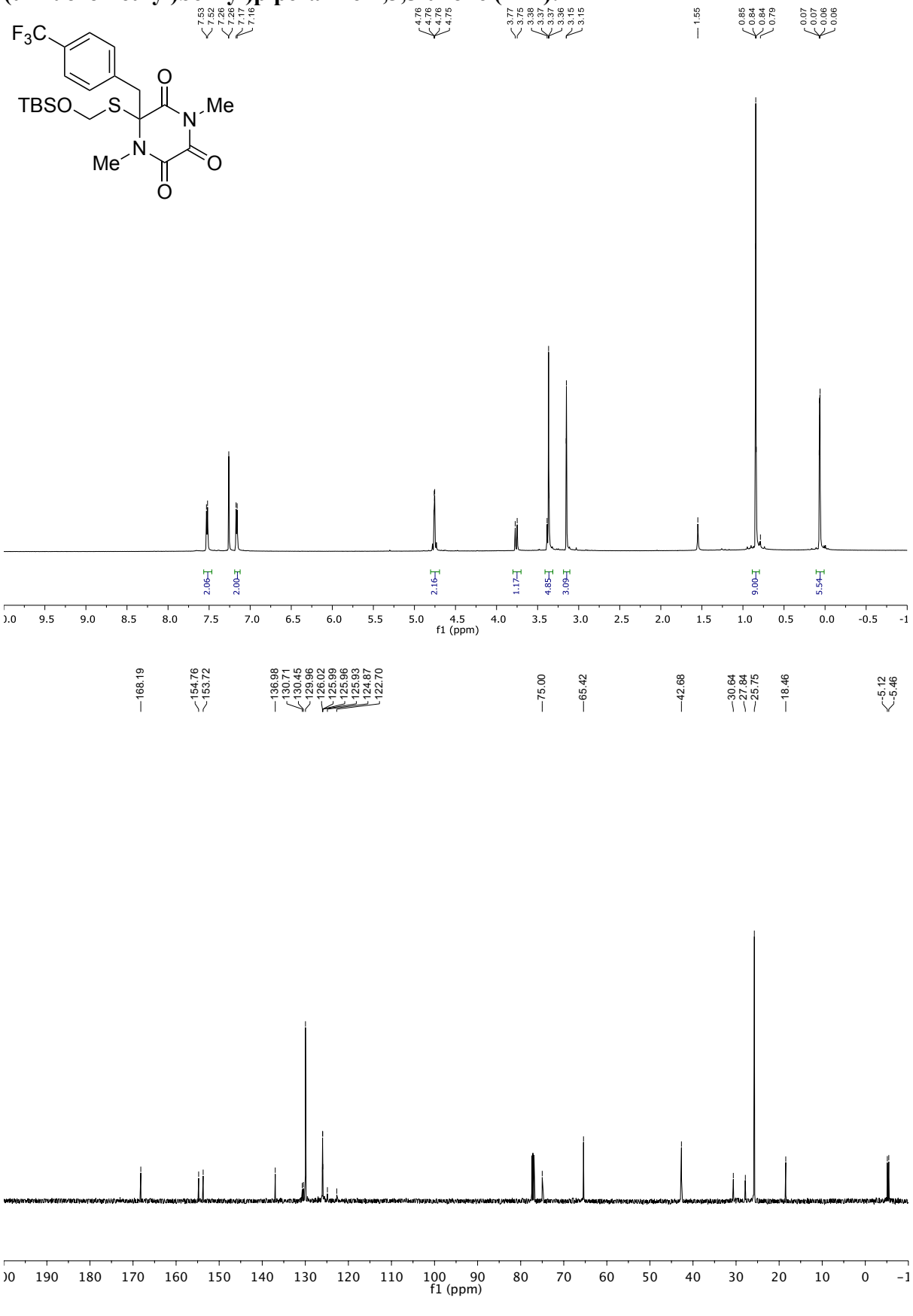
6-(2-Bromobenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (23B):



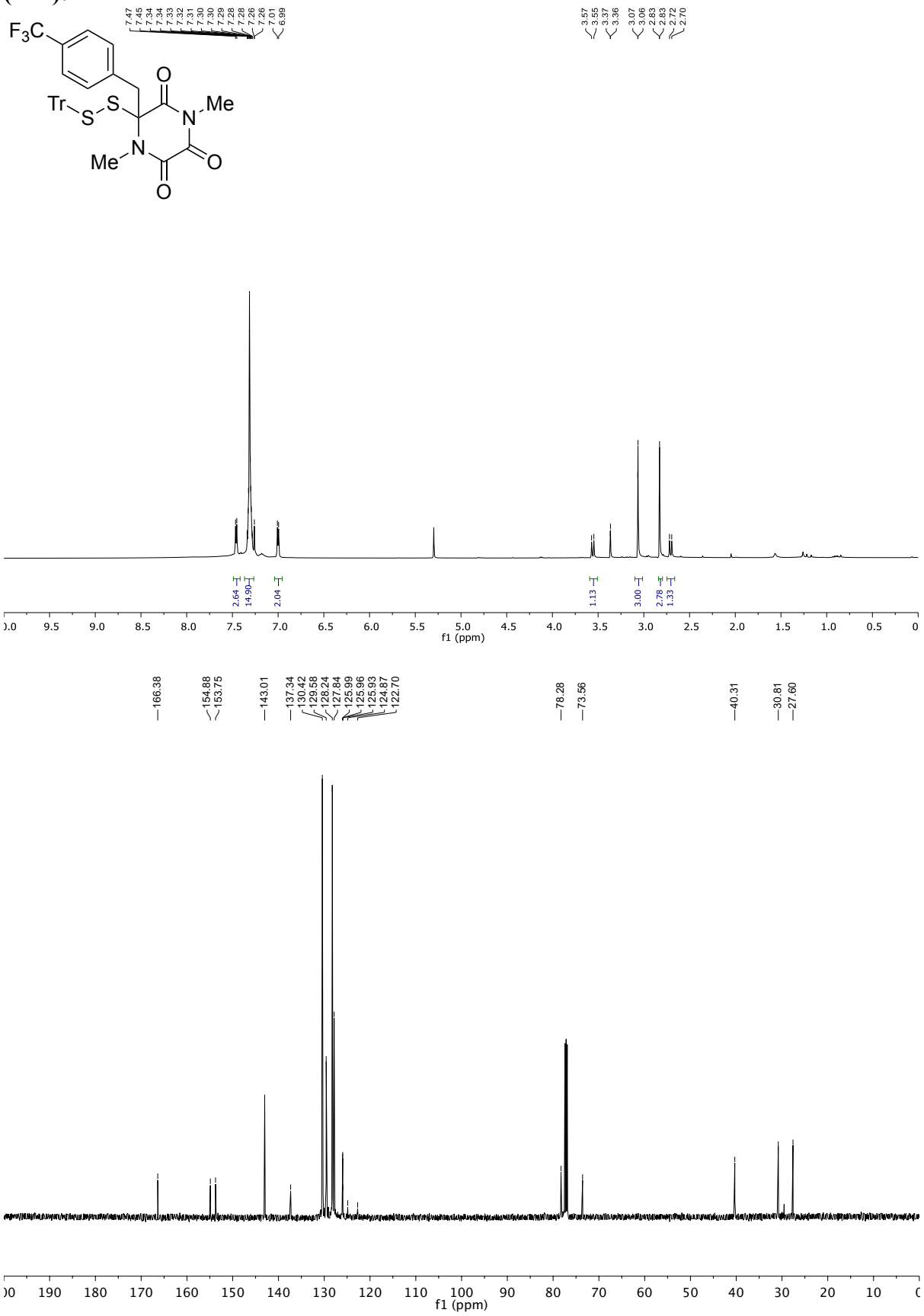
1-(2-Bromobenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (23C):



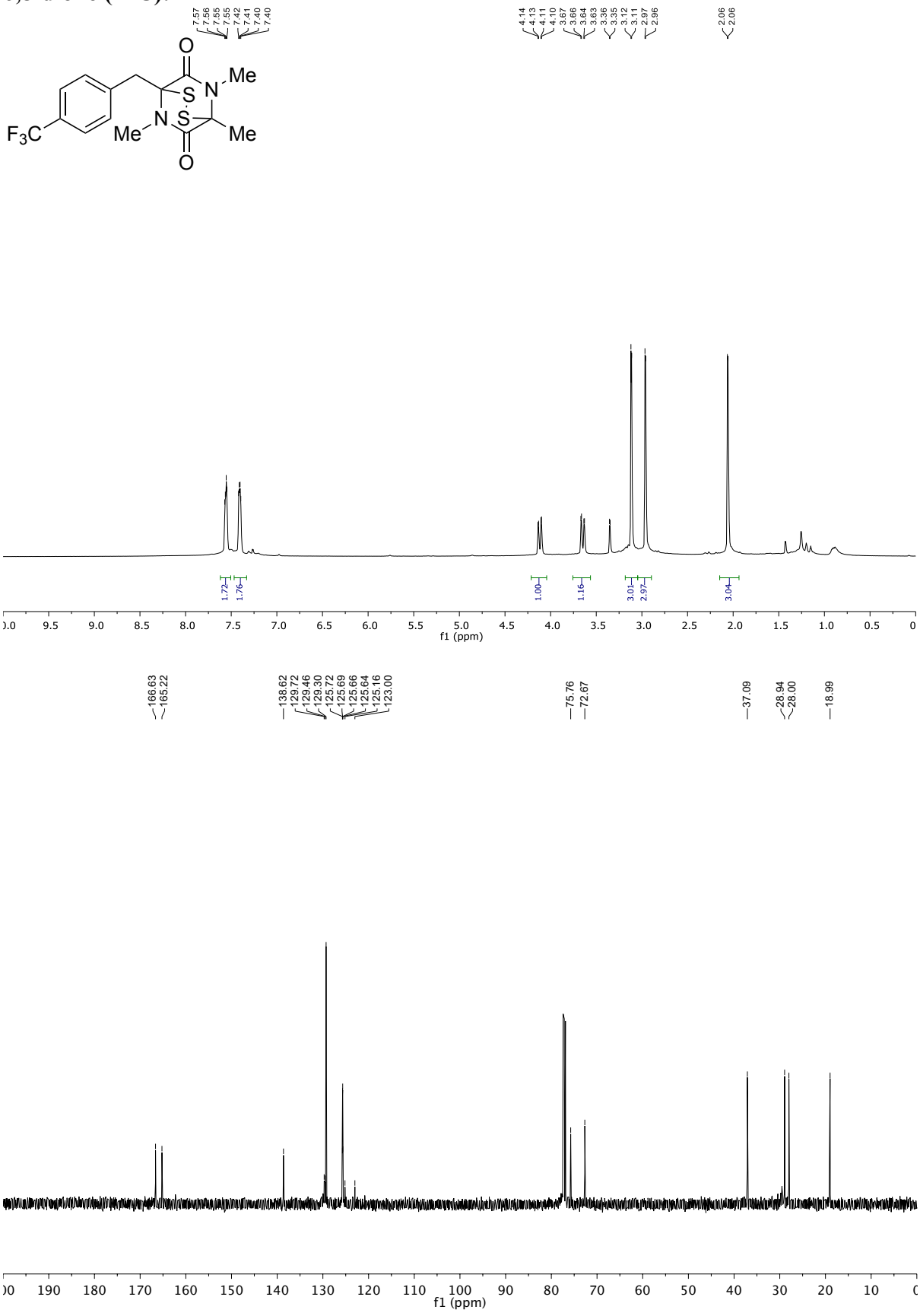
6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(4-(trifluoromethyl)benzyl)piperazine-2,3,5-trione (24A):



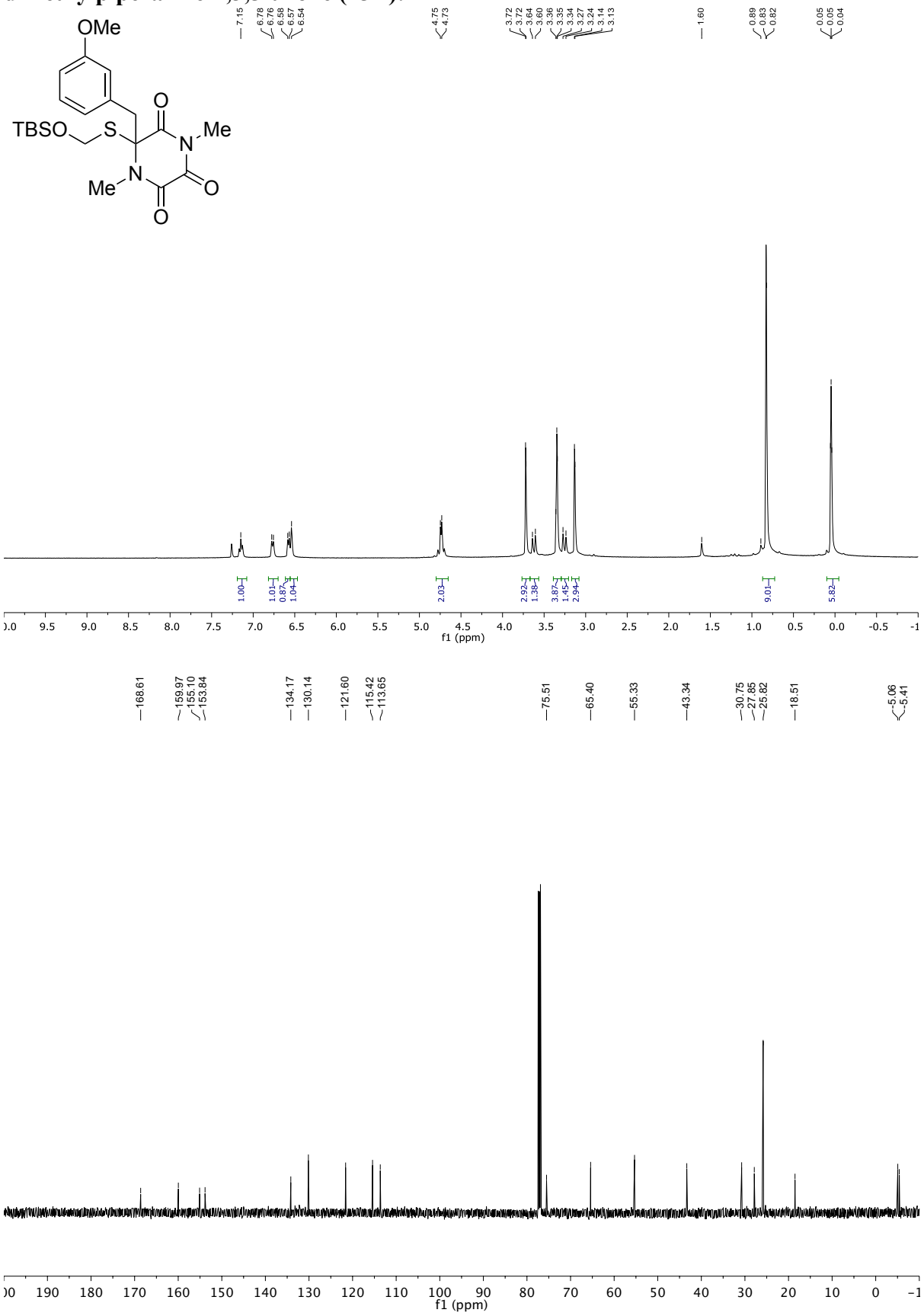
1,4-dimethyl-6-(4-(trifluoromethyl)benzyl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (24B):



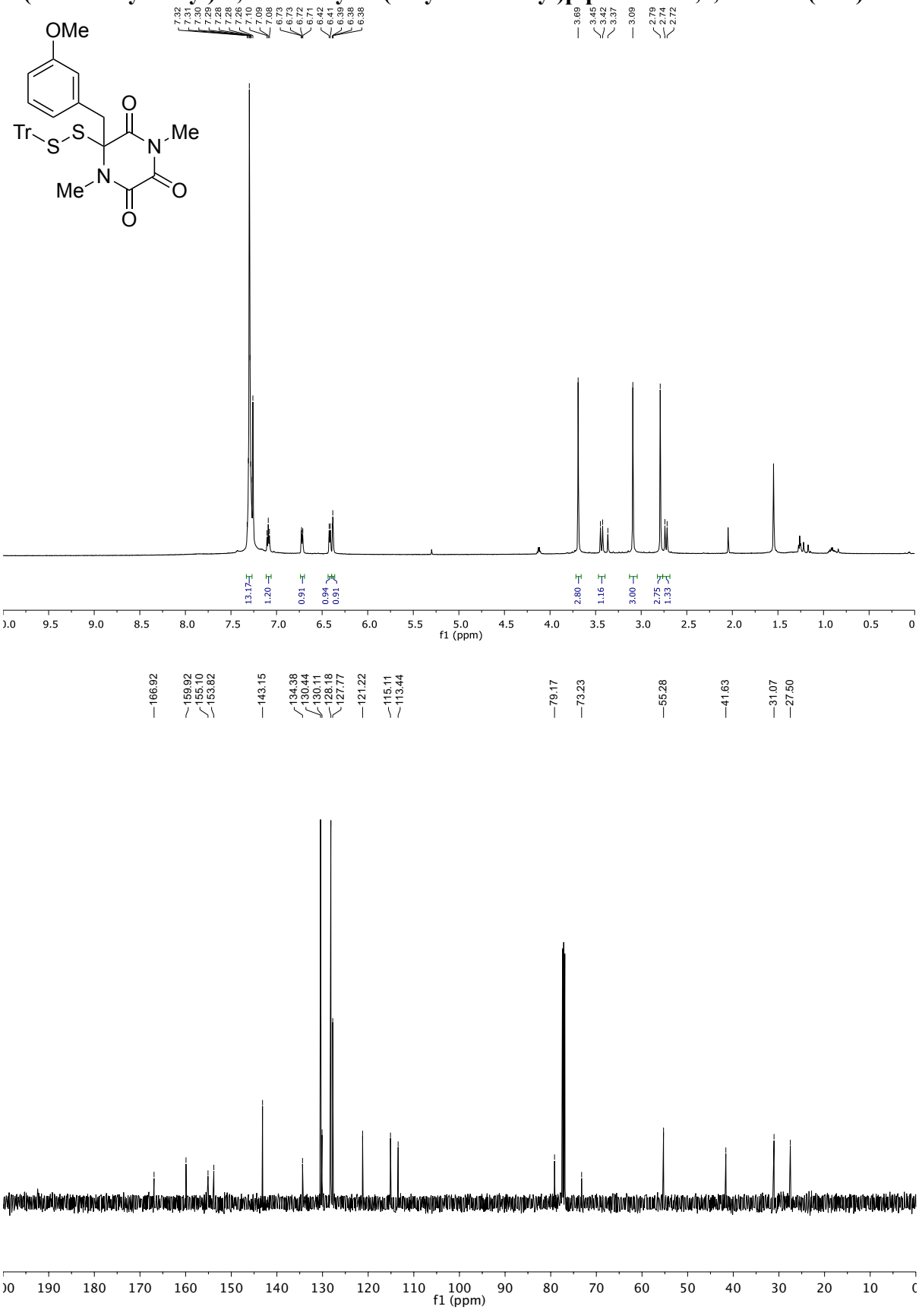
1,5,7-trimethyl-4-(4-(trifluoromethyl)benzyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (24C):



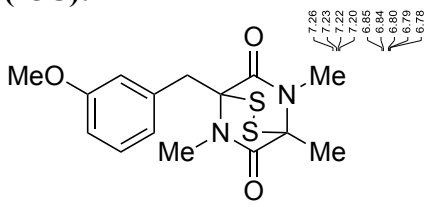
6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-6-(3-methoxybenzyl)-1,4-dimethylpiperazine-2,3,5-trione (25A):

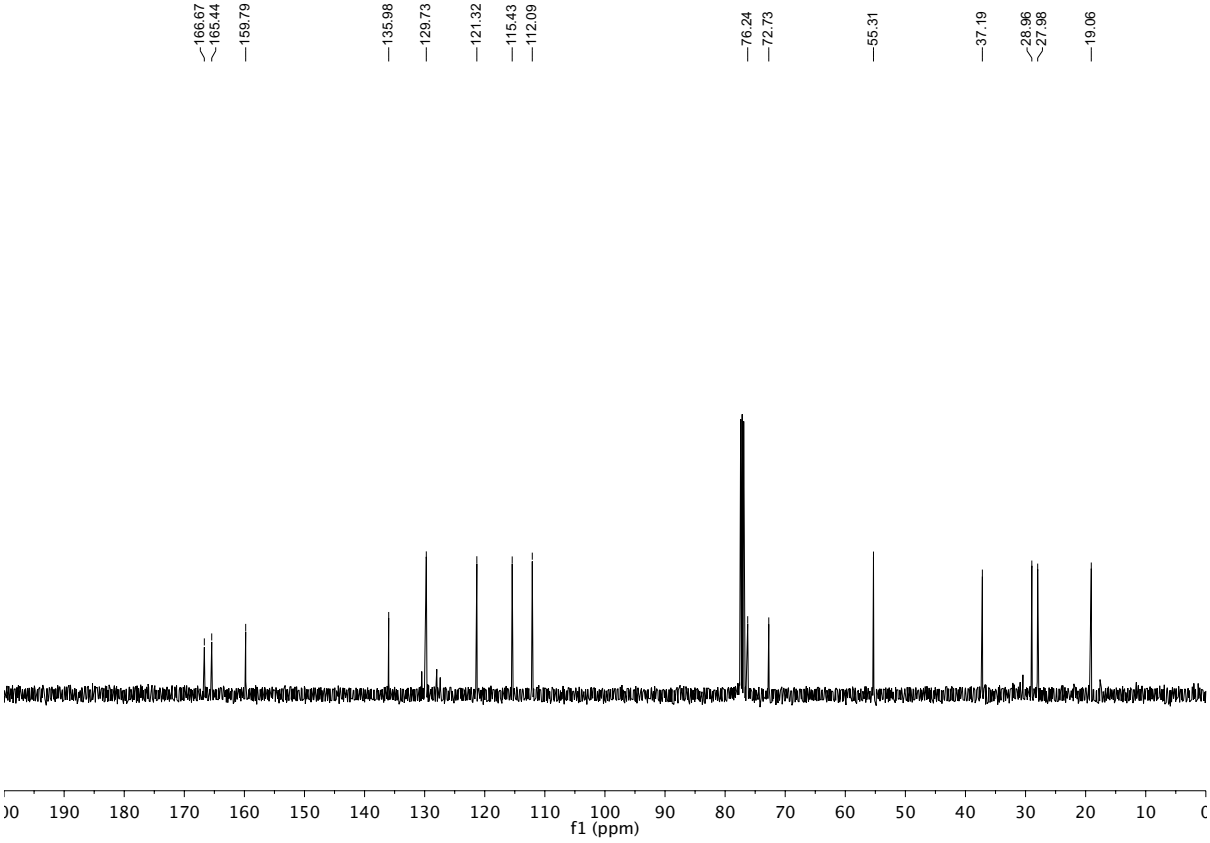


6-(3-methoxybenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (25B):

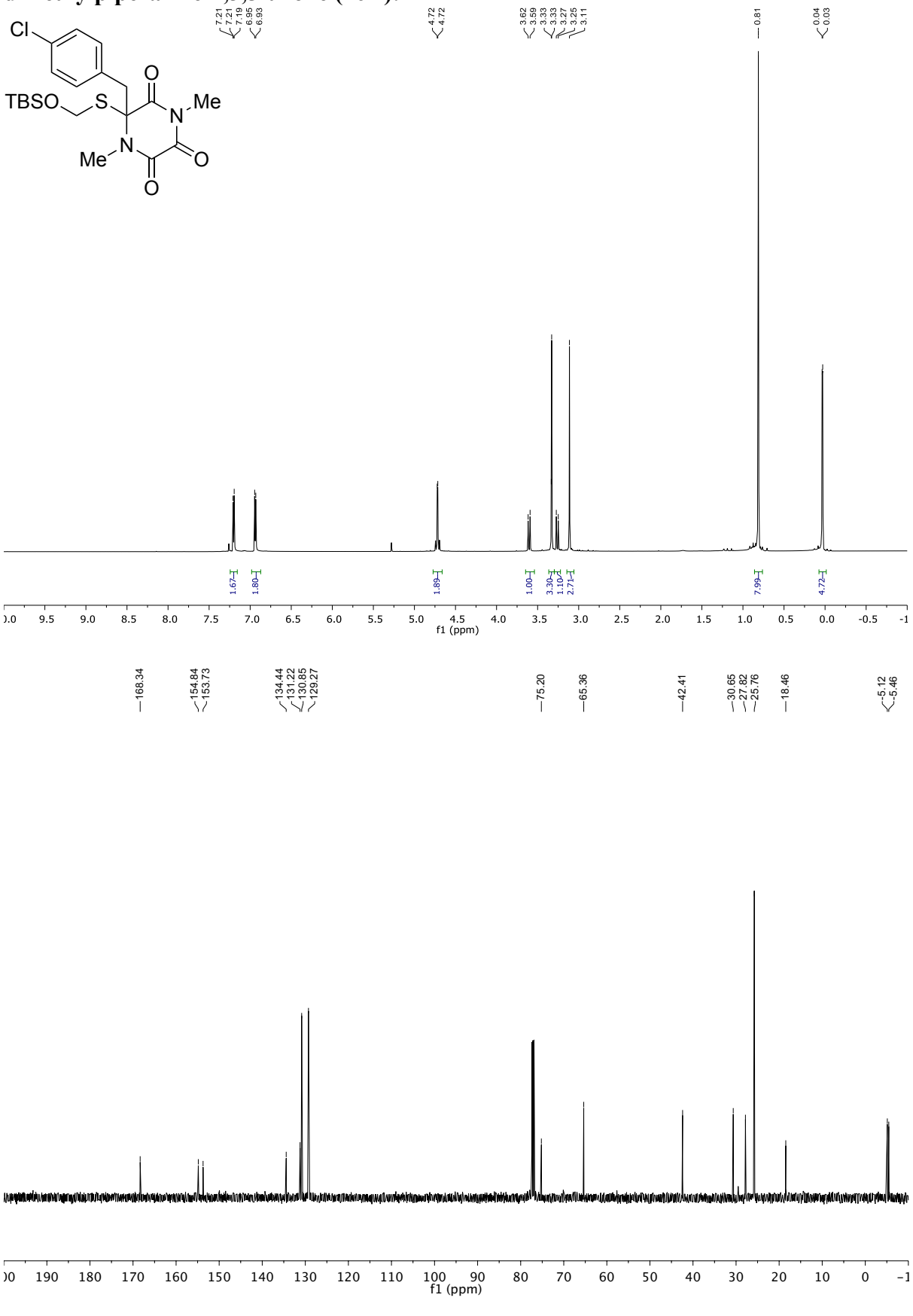


1-(3-methoxybenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (25C):

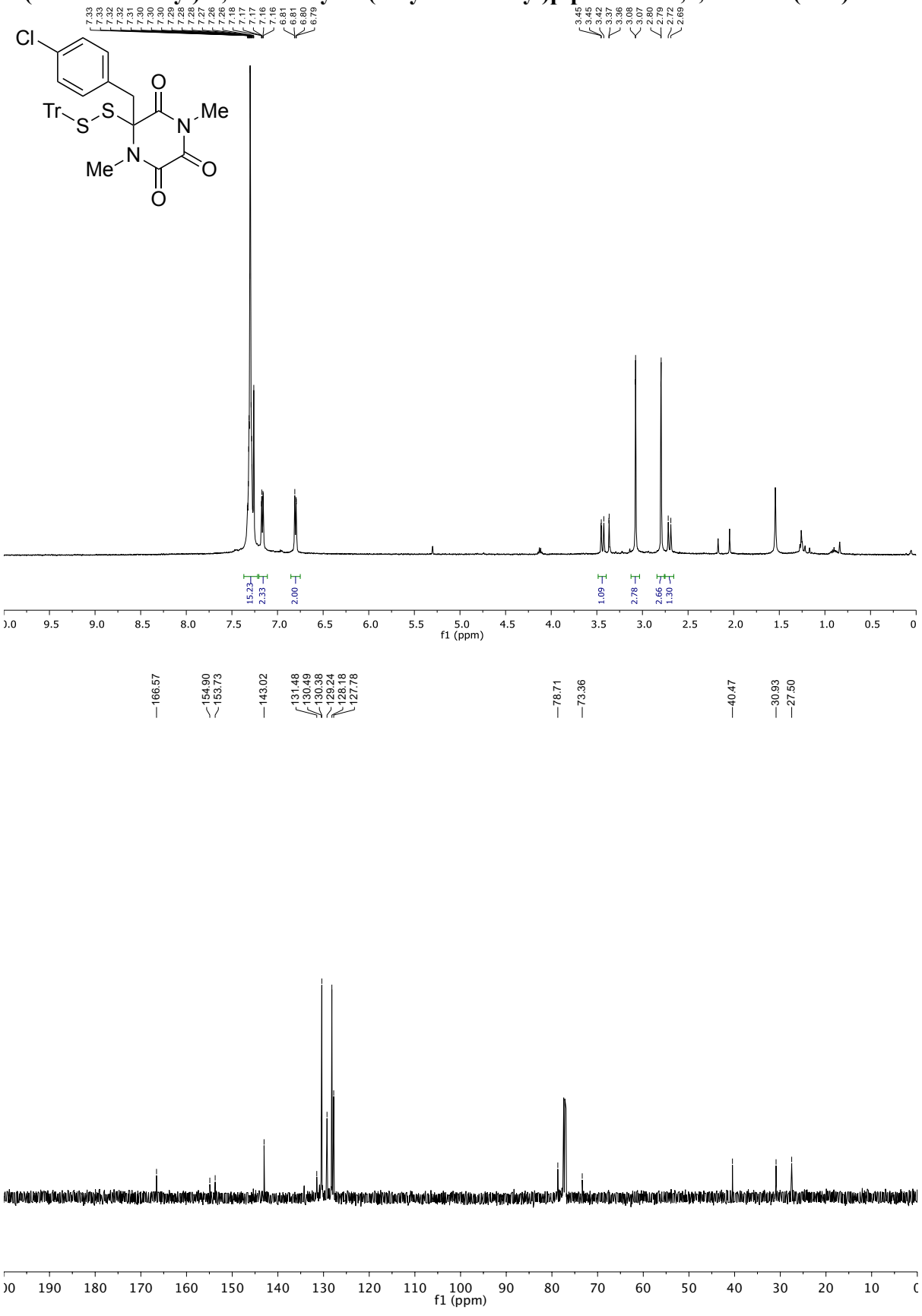




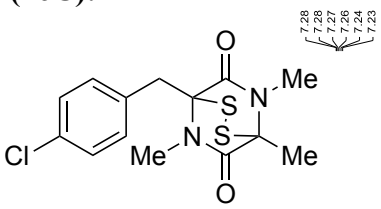
6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-6-(4-chlorobenzyl)-1,4-dimethylpiperazine-2,3,5-trione (26A):

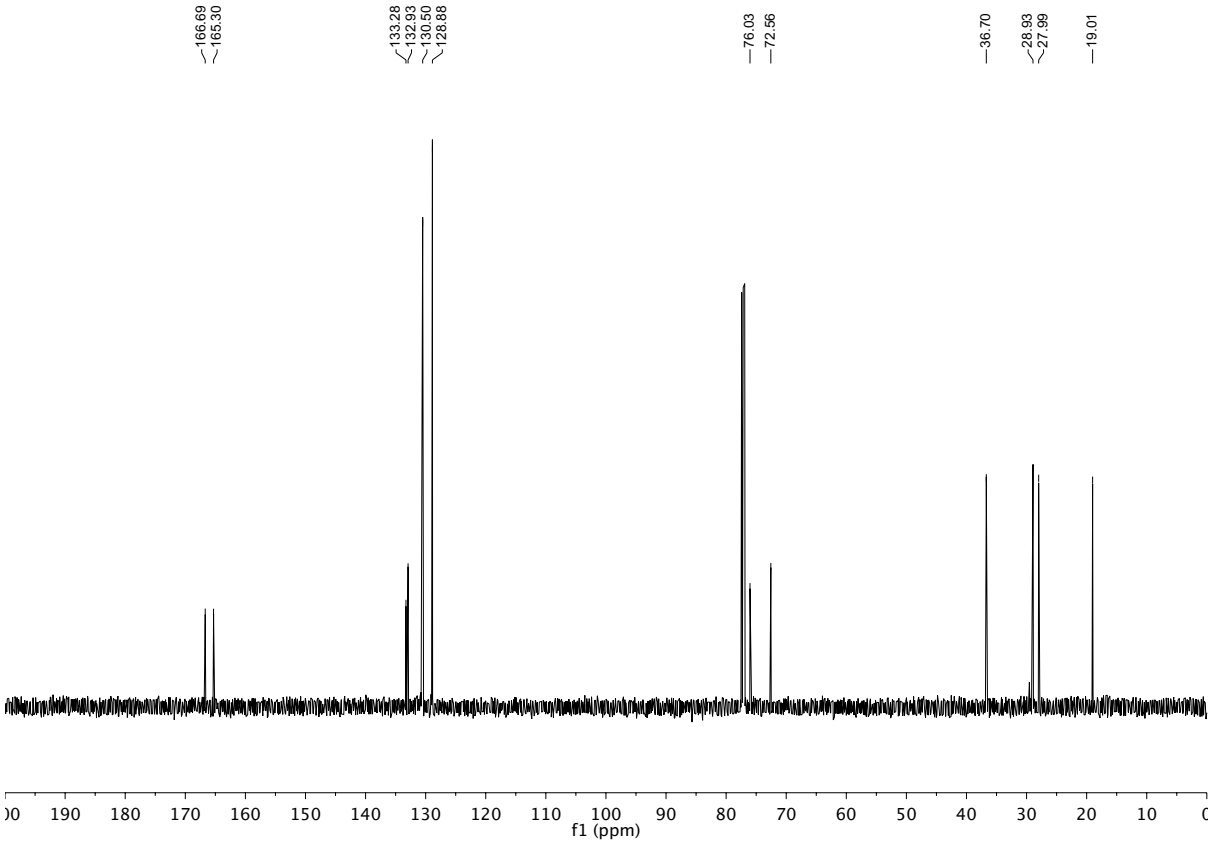


6-(4-Chlorobenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (26B):

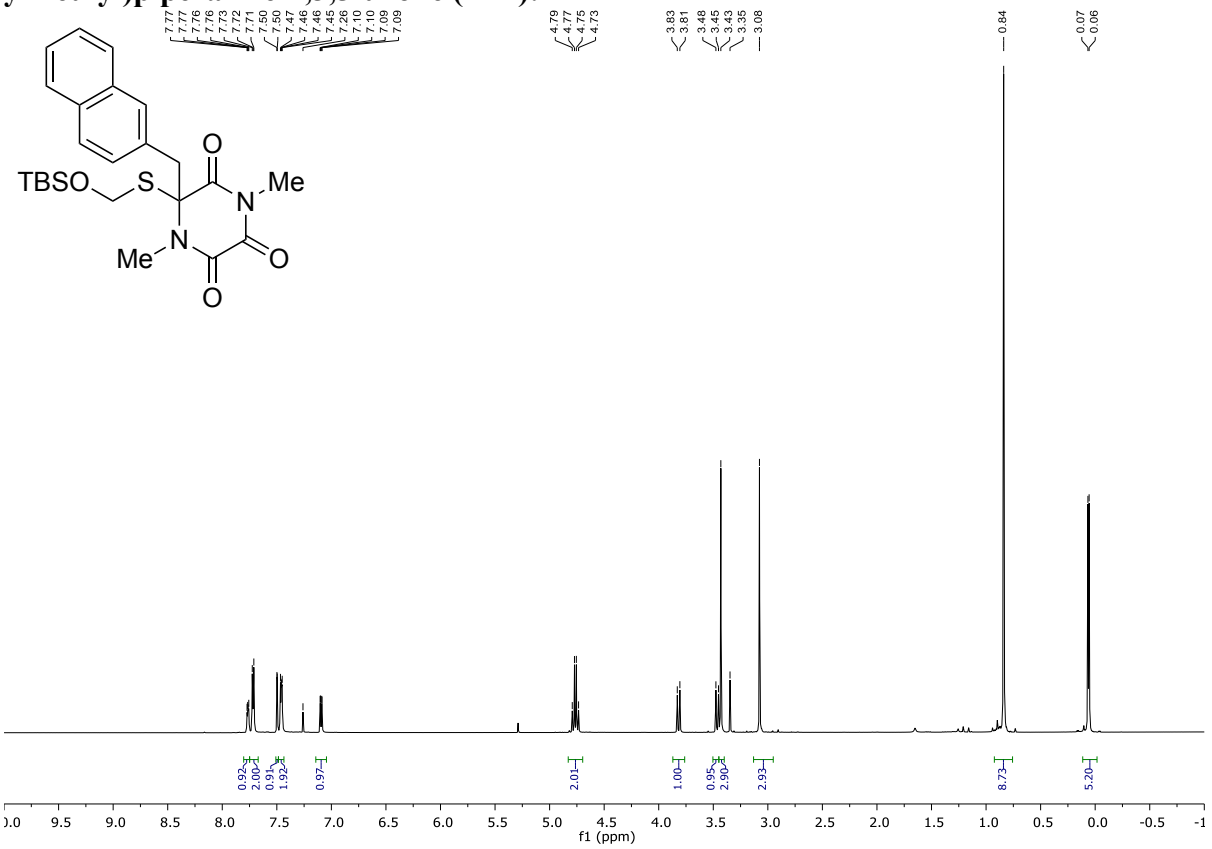


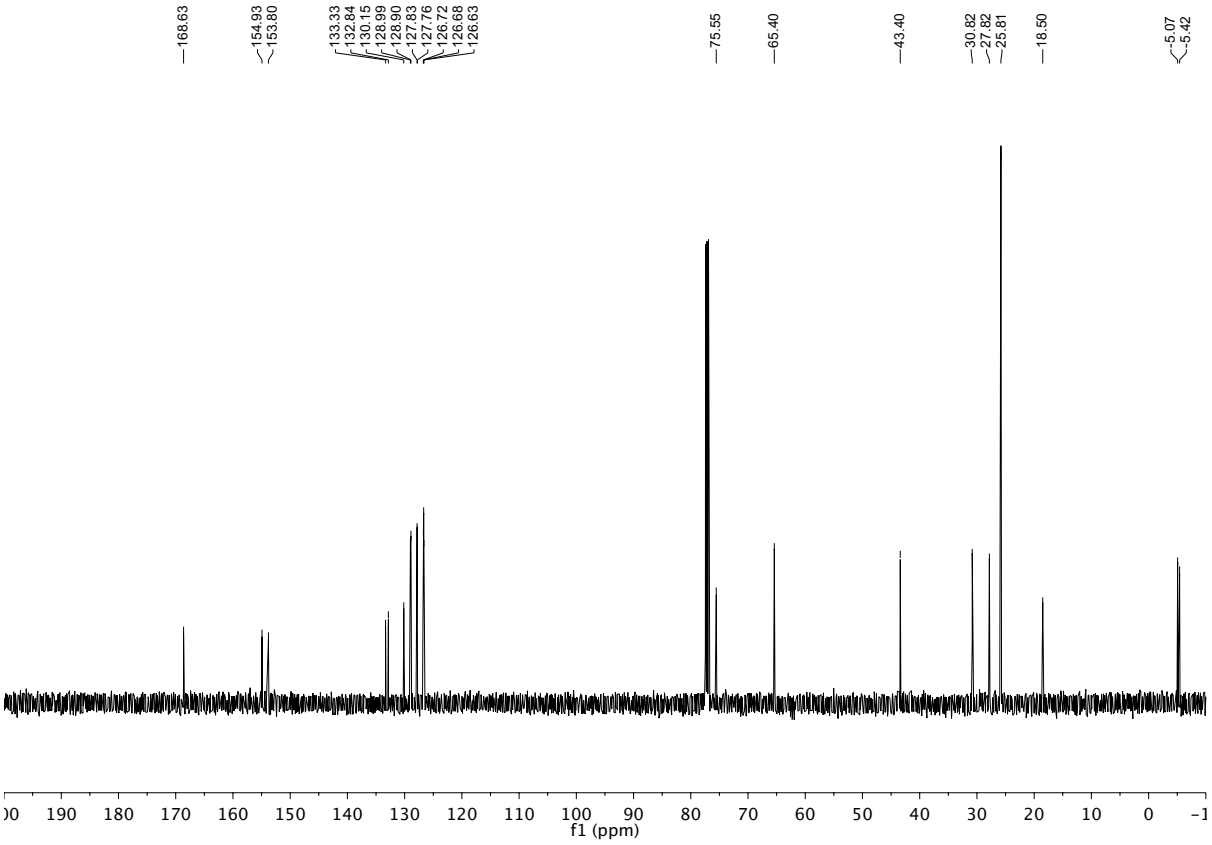
1-(4-chlorobenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (26C):



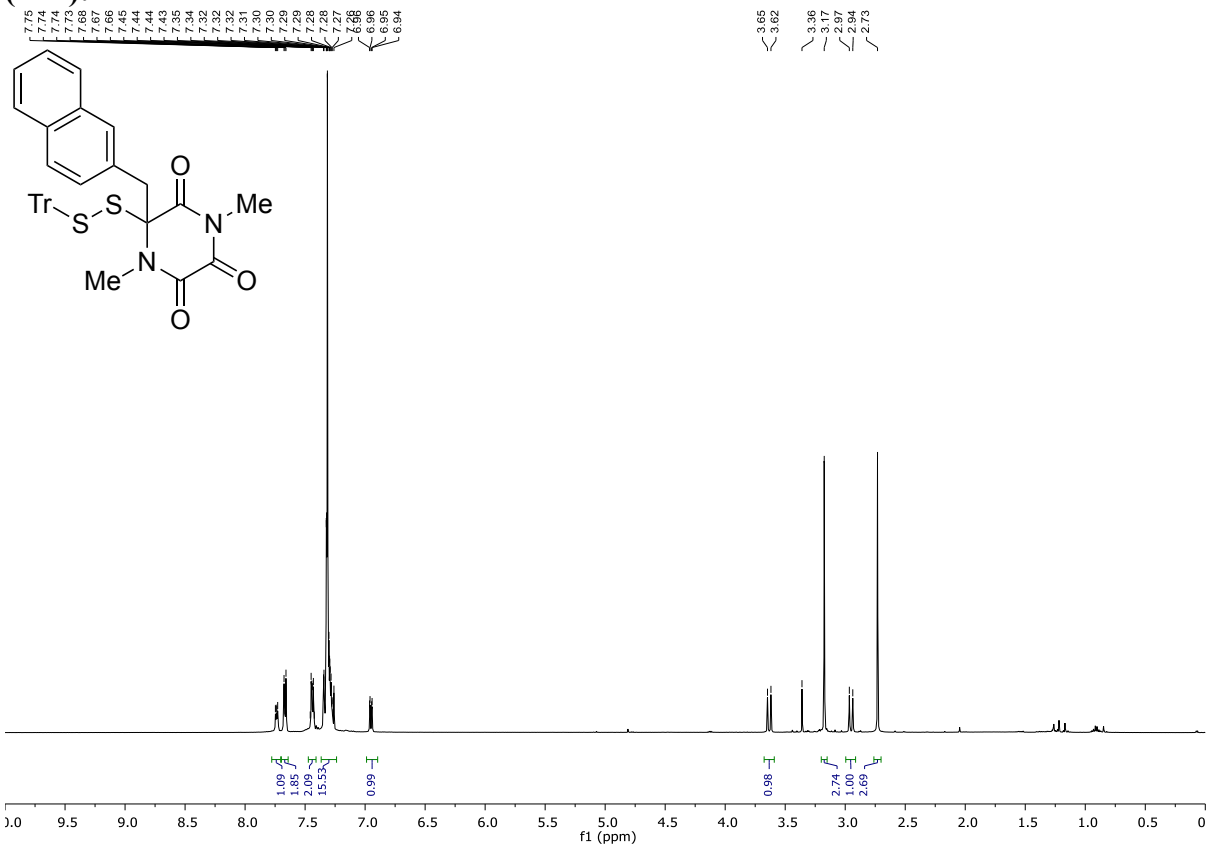


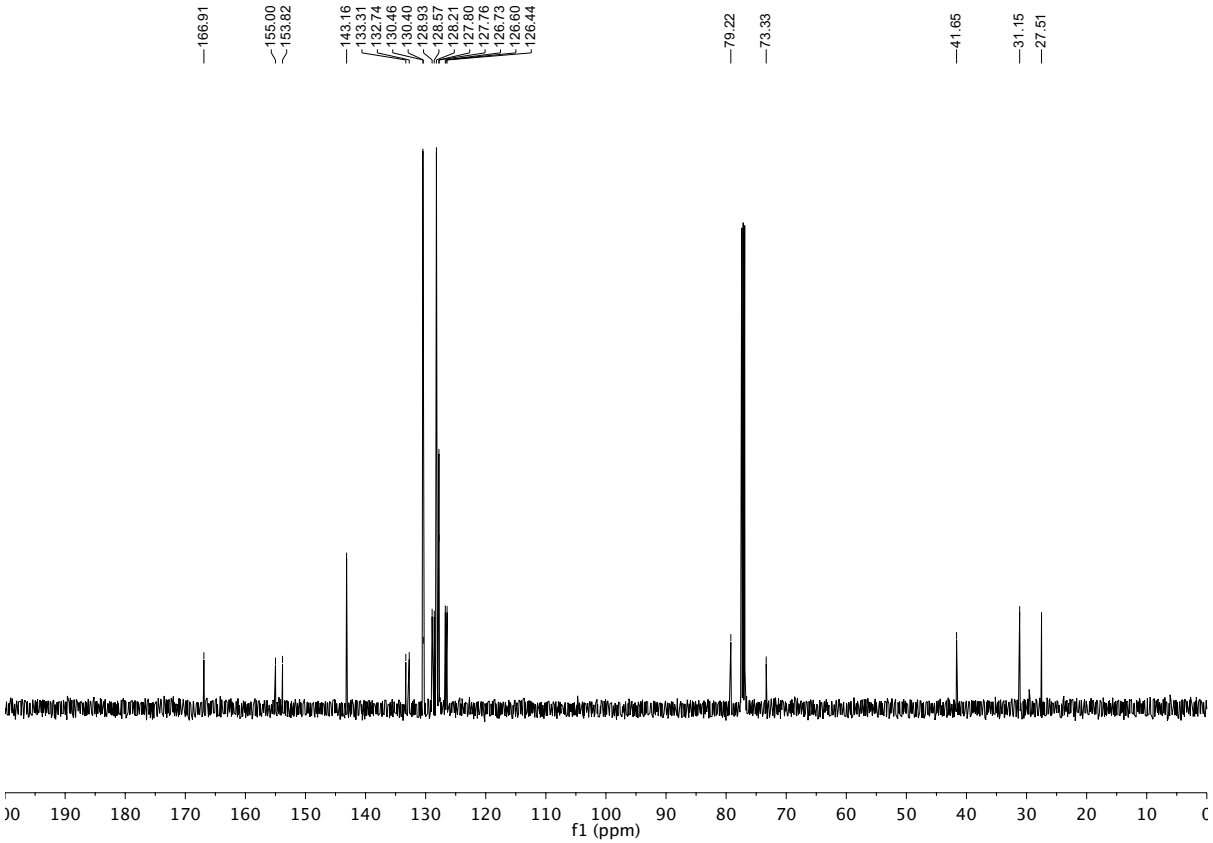
6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(naphthalen-2-ylmethyl)piperazine-2,3,5-trione (27A):



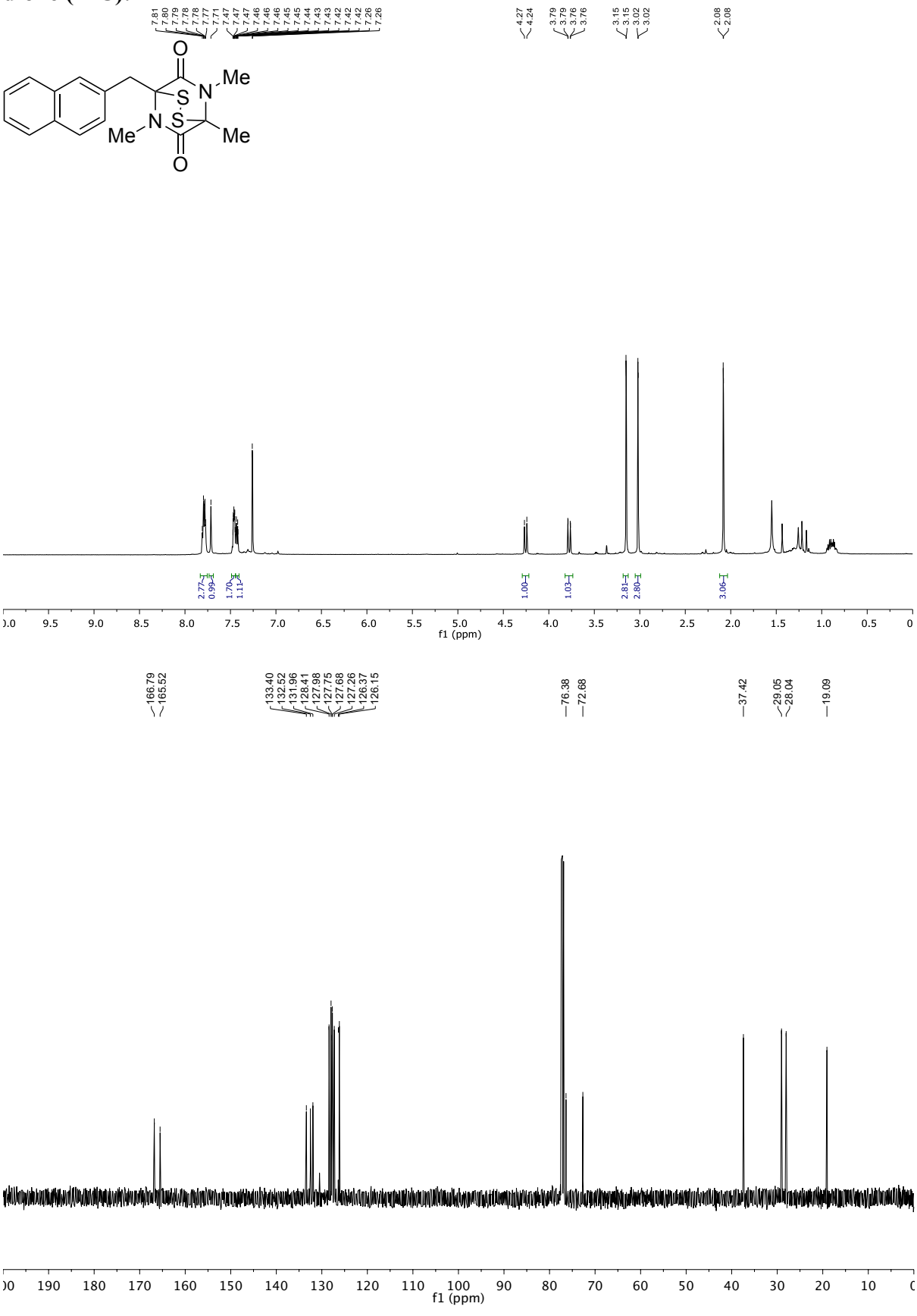


1,4-dimethyl-6-(naphthalen-2-ylmethyl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (27B):

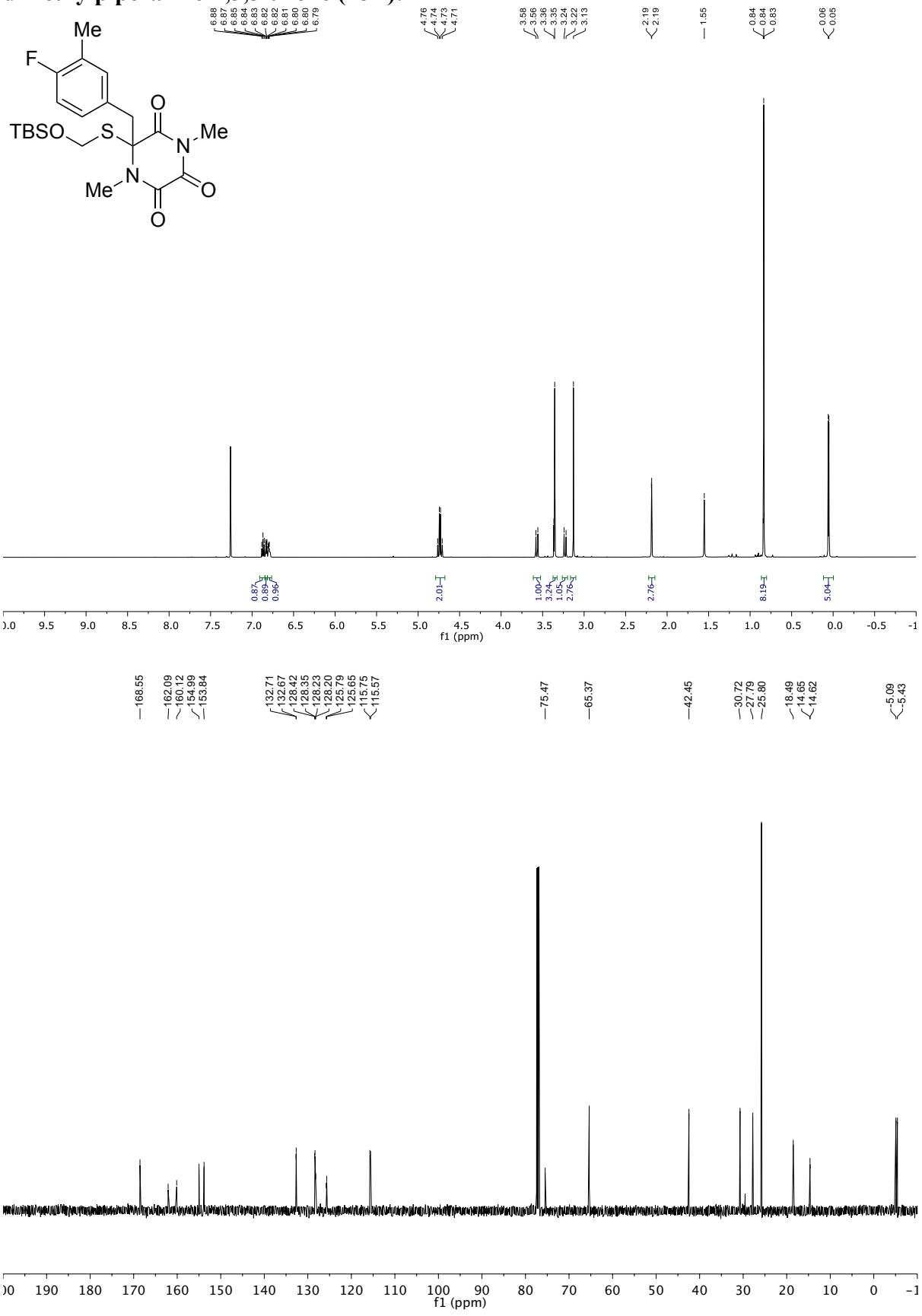




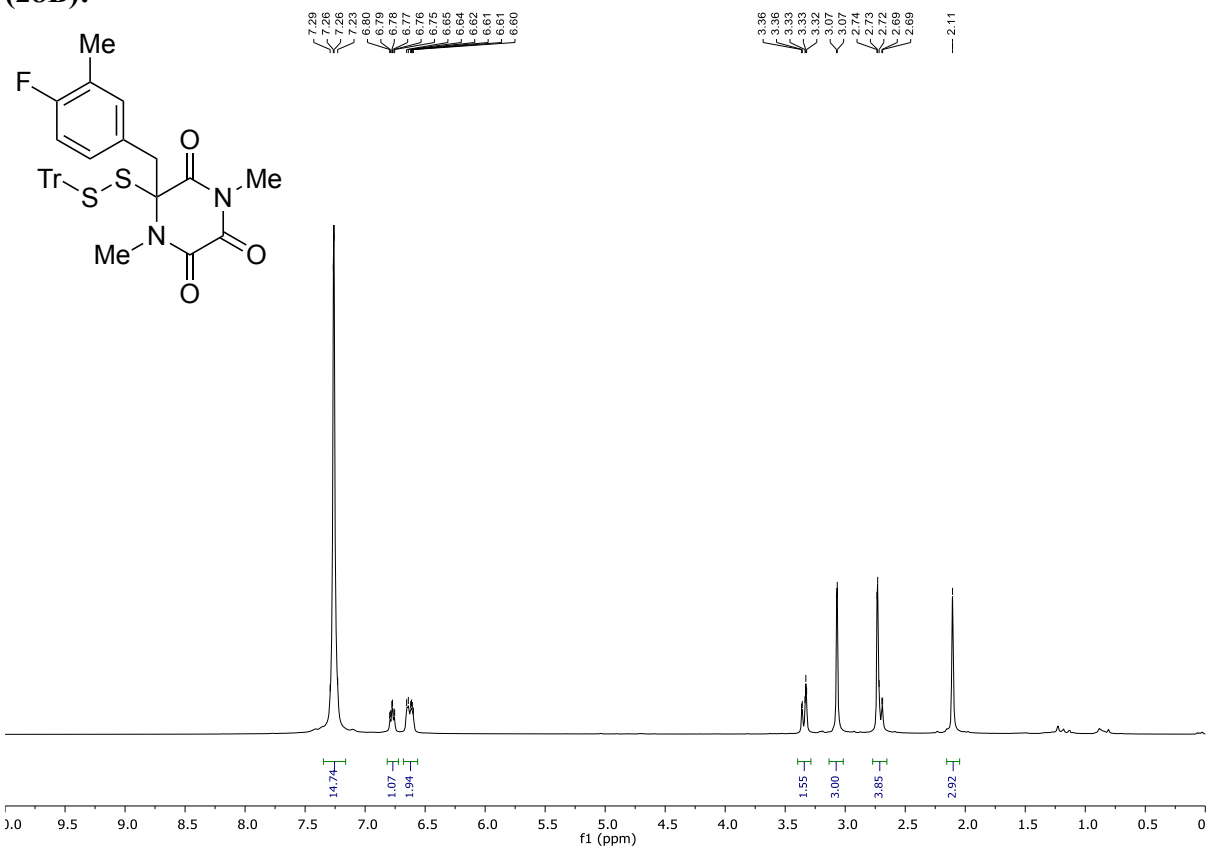
1,5,7-trimethyl-4-(naphthalen-2-ylmethyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (27C):

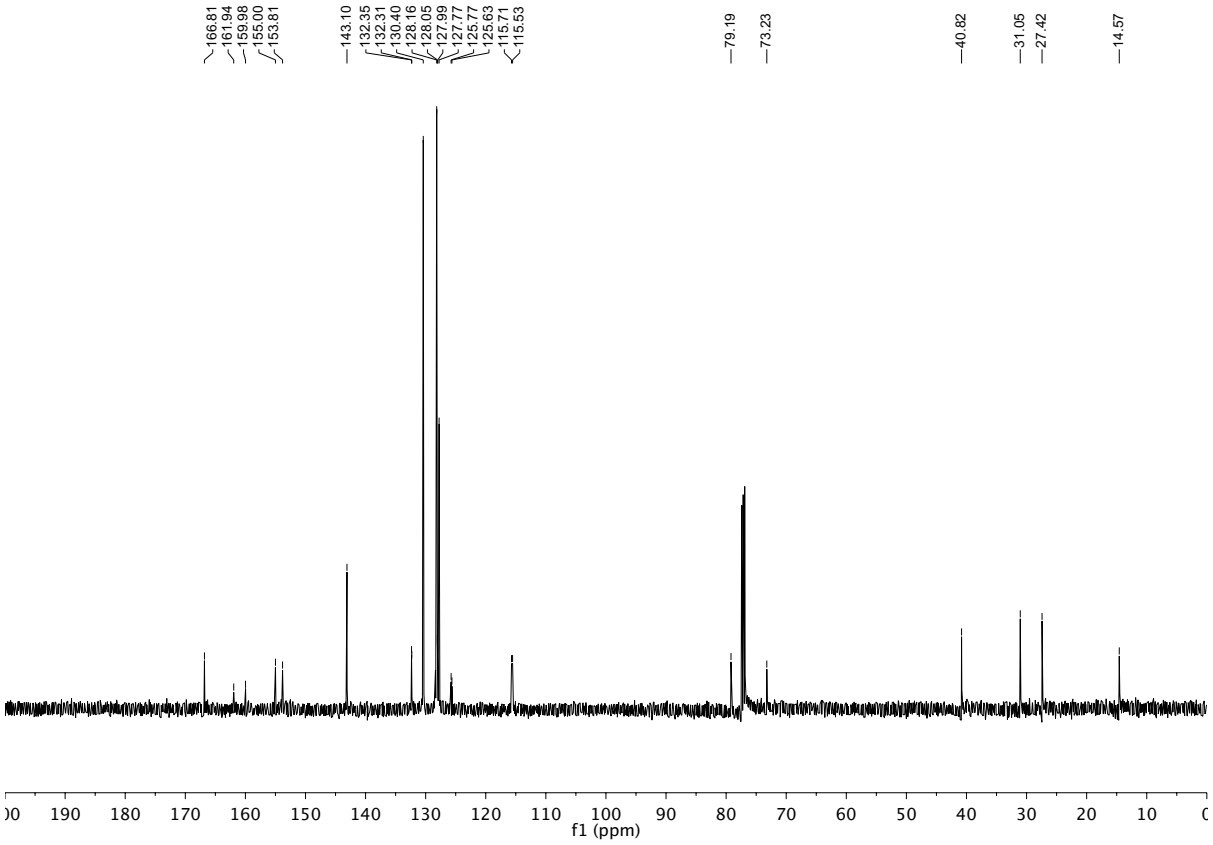


6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-6-(4-fluoro-3-methylbenzyl)-1,4-dimethylpiperazine-2,3,5-trione (28A):

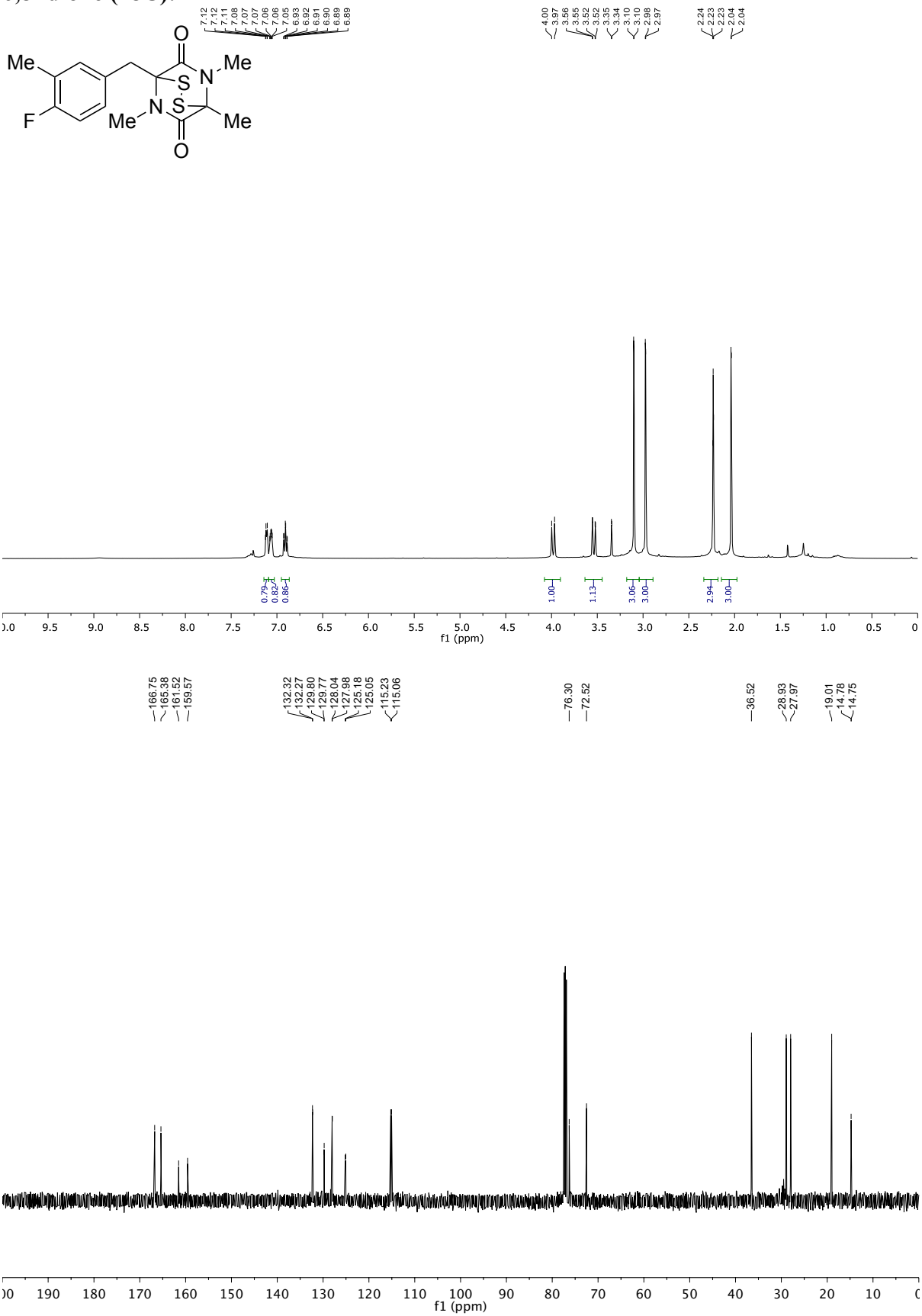


6-(4-Fluoro-3-methylbenzyl)-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (28B):

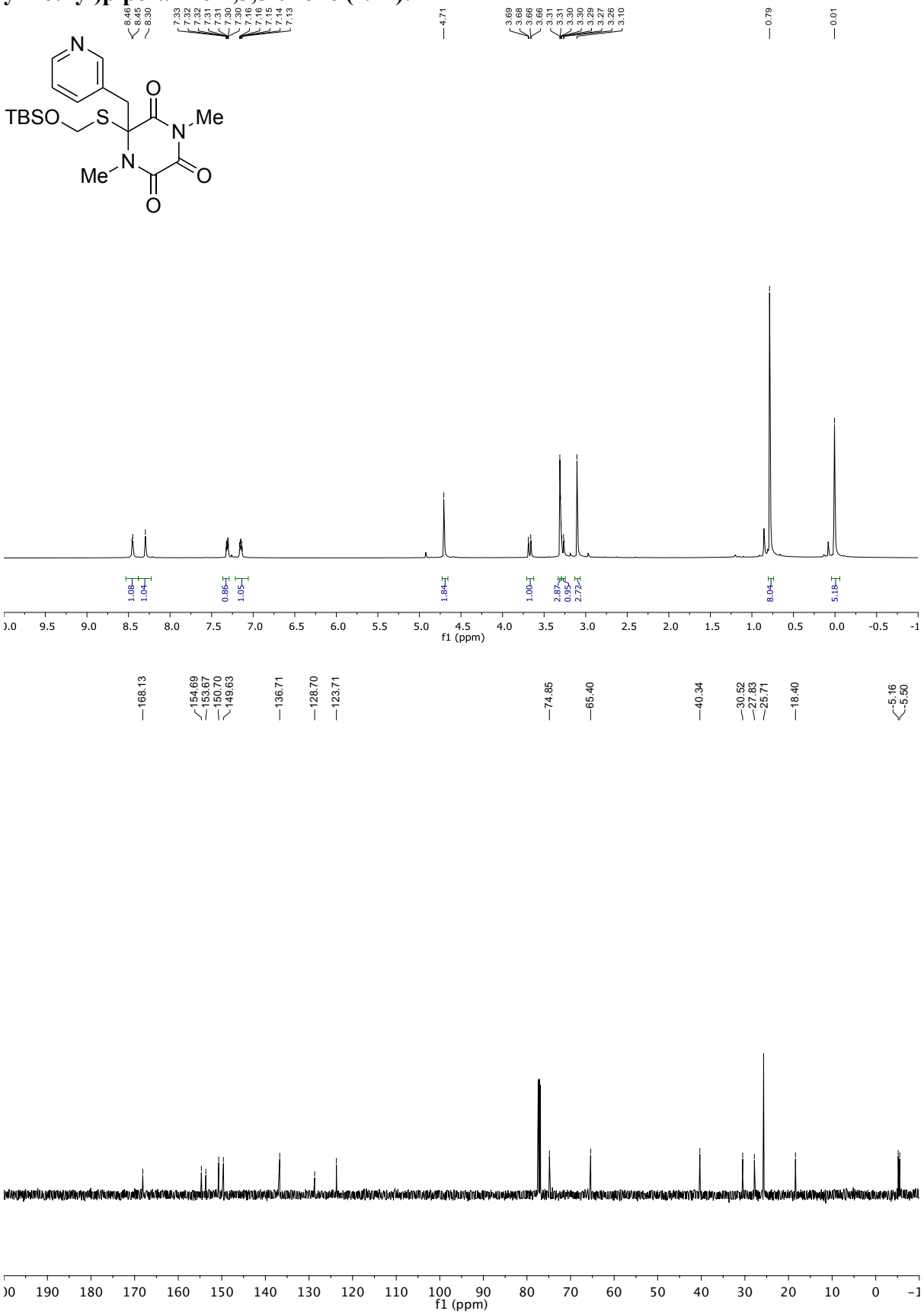




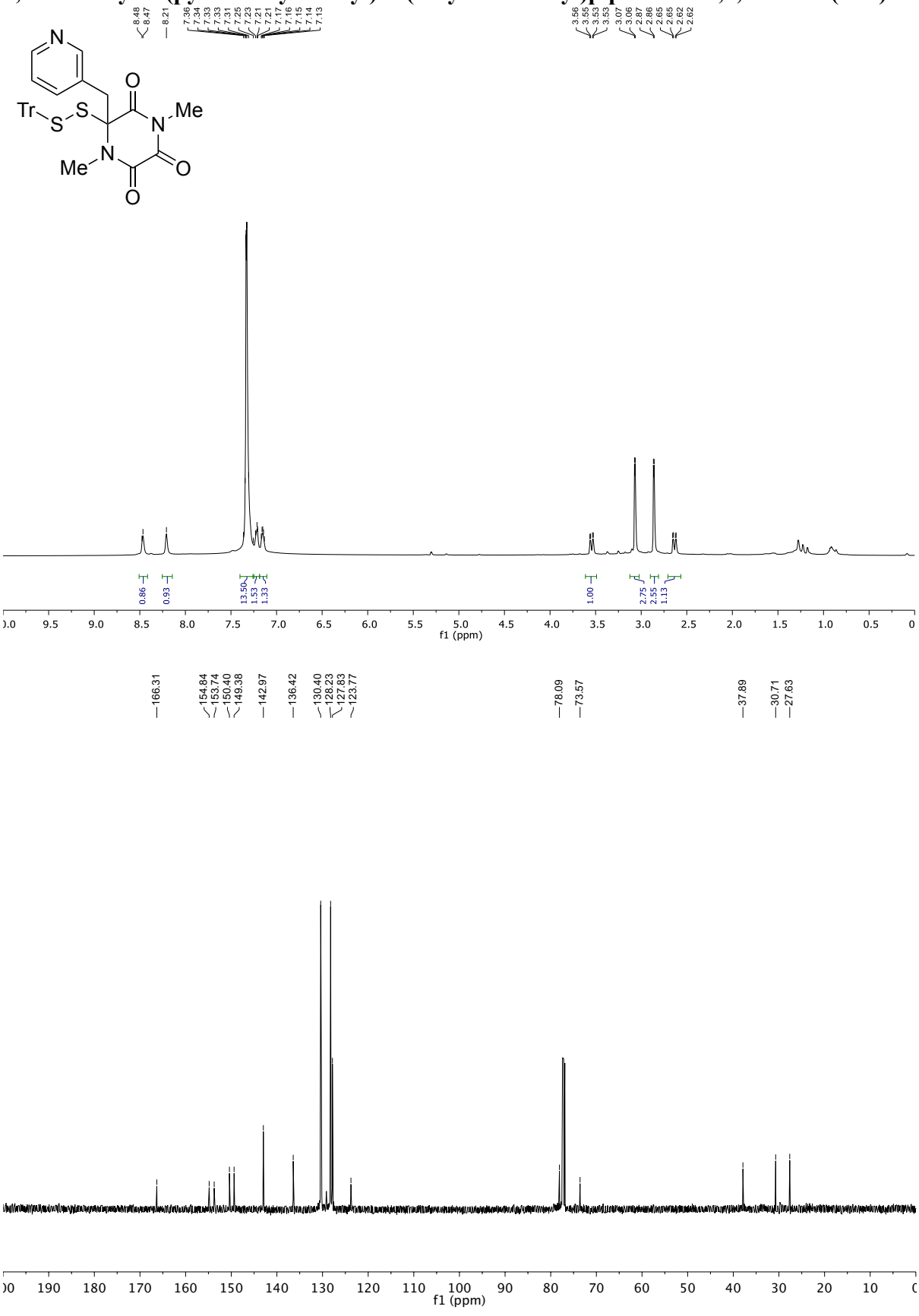
1-(4-Fluoro-3-methylbenzyl)-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8- dione (28C):



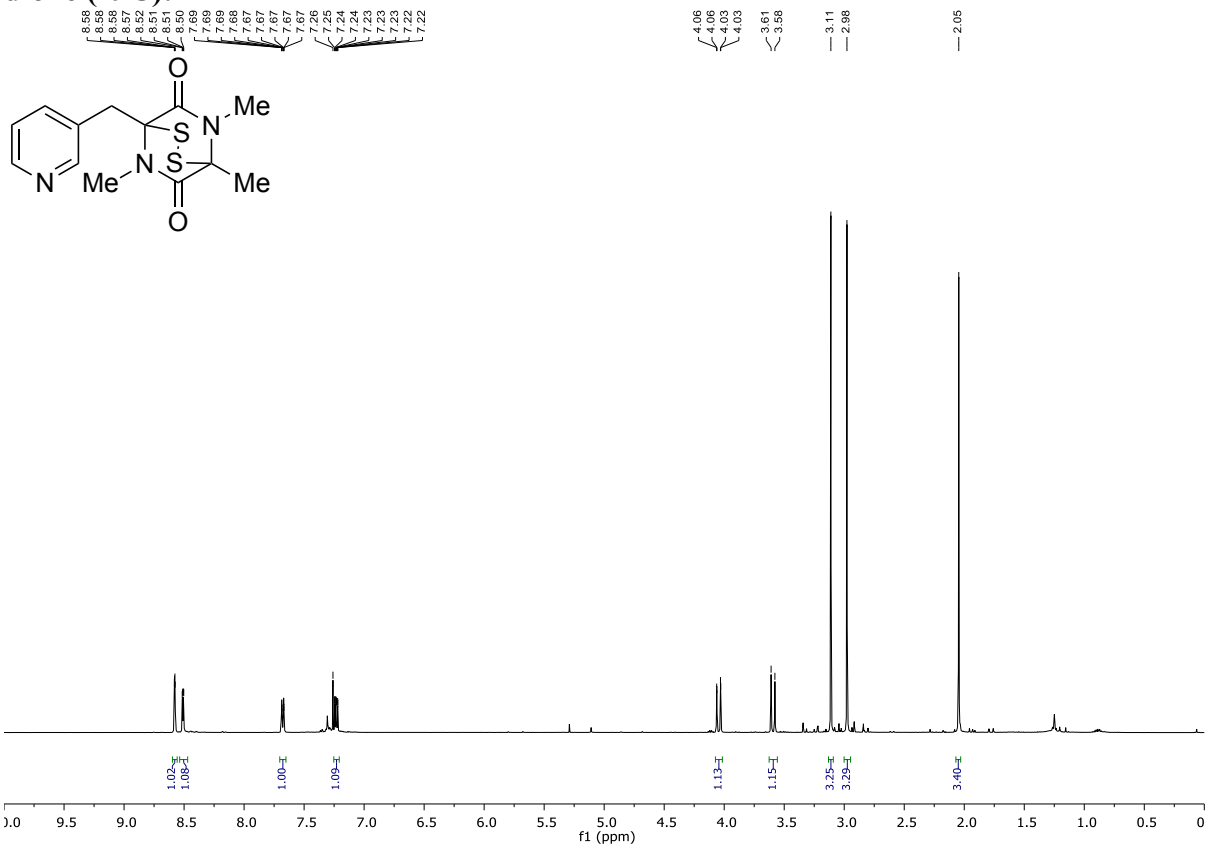
6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(pyridin-3-ylmethyl)piperazine-2,3,5-trione (29A):

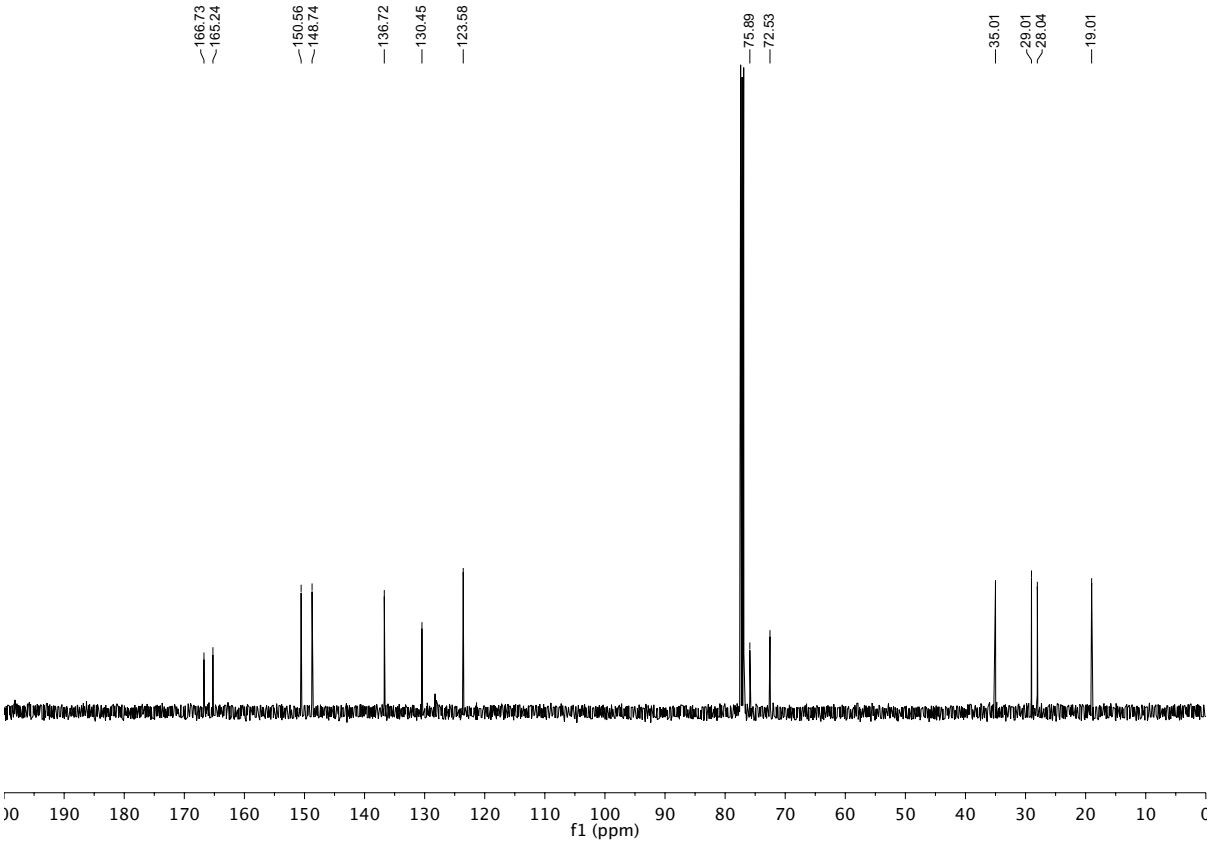


1,4-Dimethyl-6-(pyridin-3-ylmethyl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (29B):

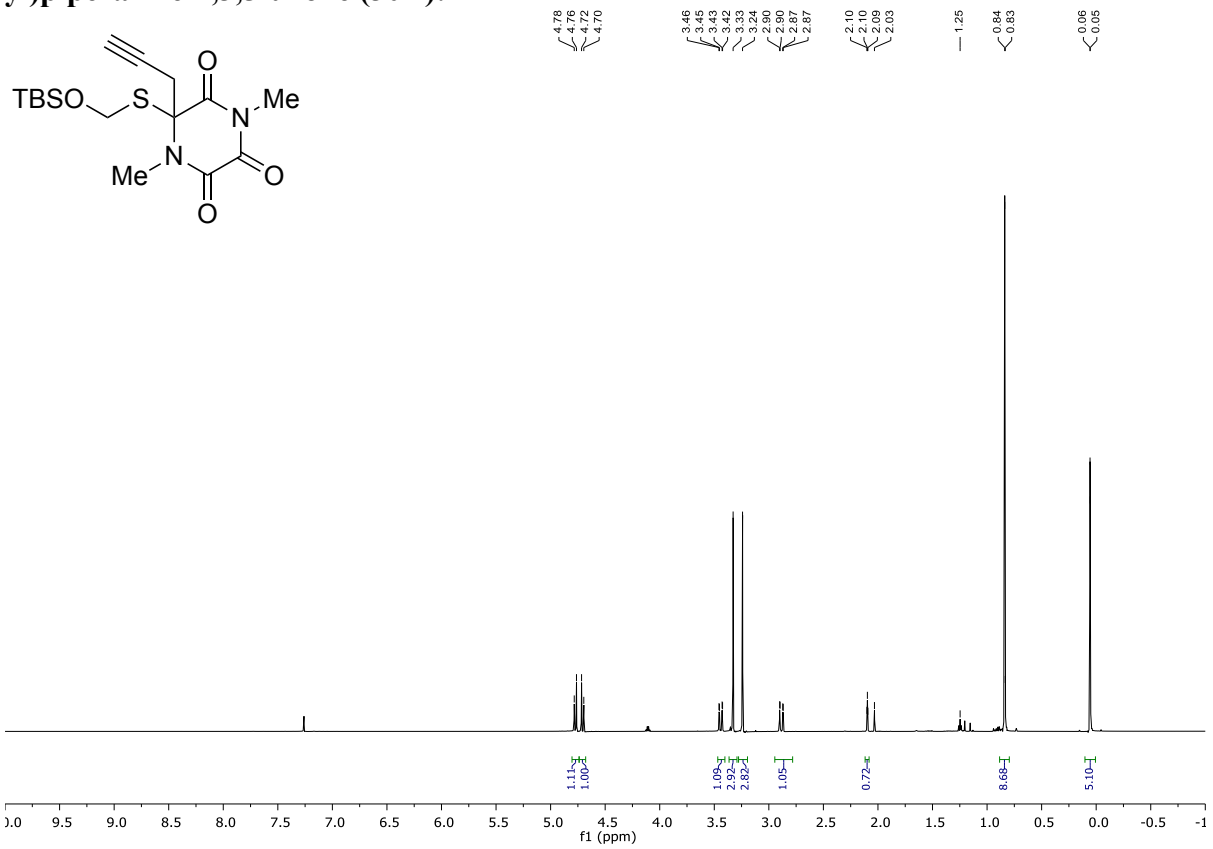


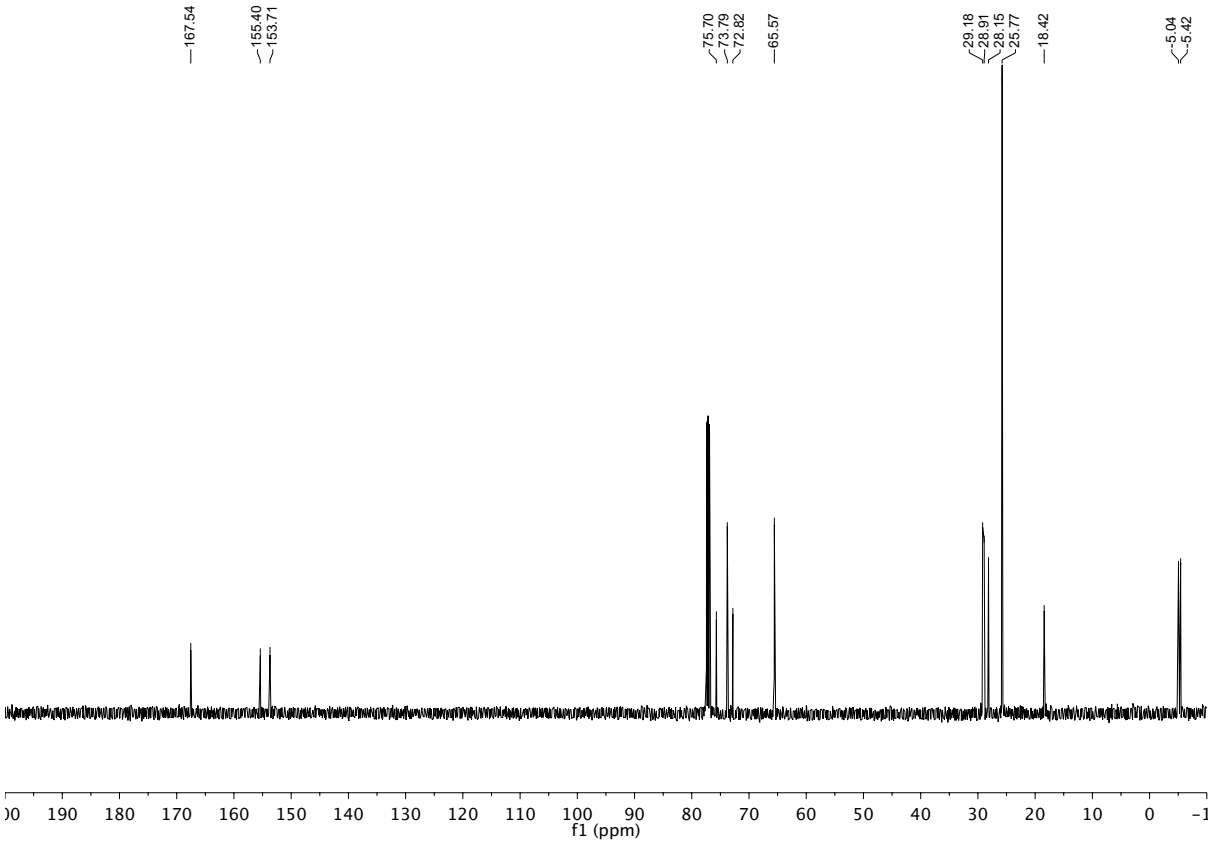
1,5,7-Trimethyl-4-(pyridin-3-ylmethyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (29C):



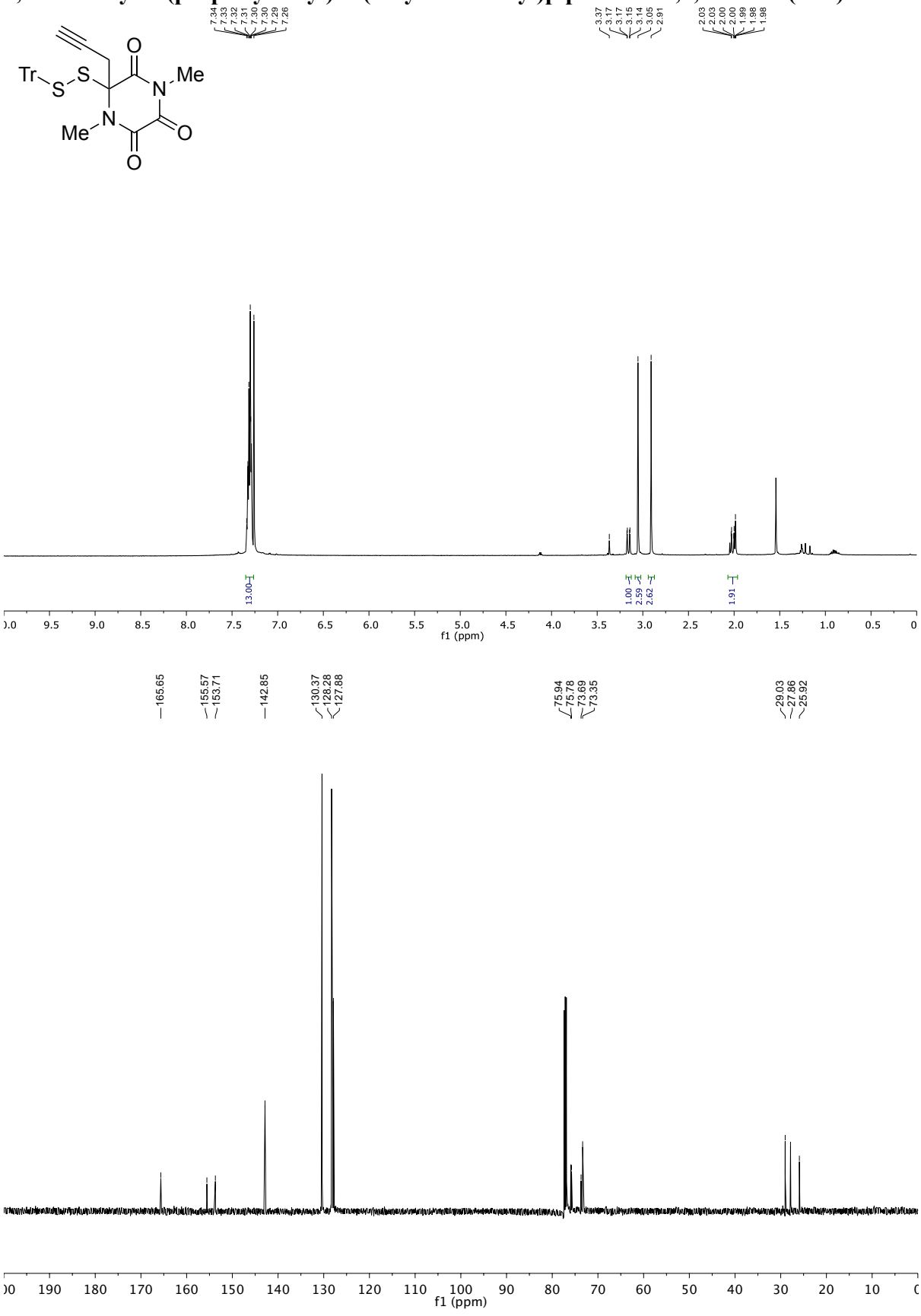


6-((((*Tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethyl-6-(prop-2-yn-1-yl)piperazine-2,3,5-trione (30A):

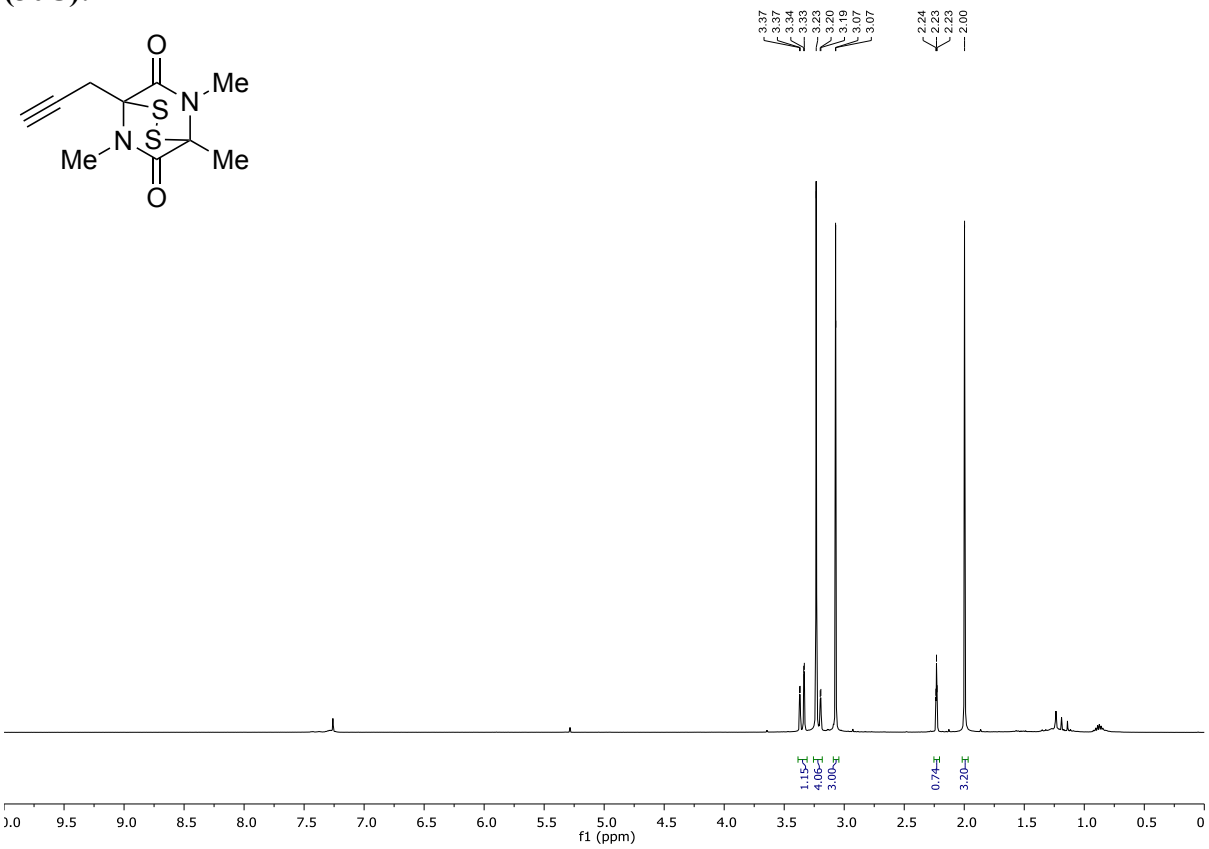


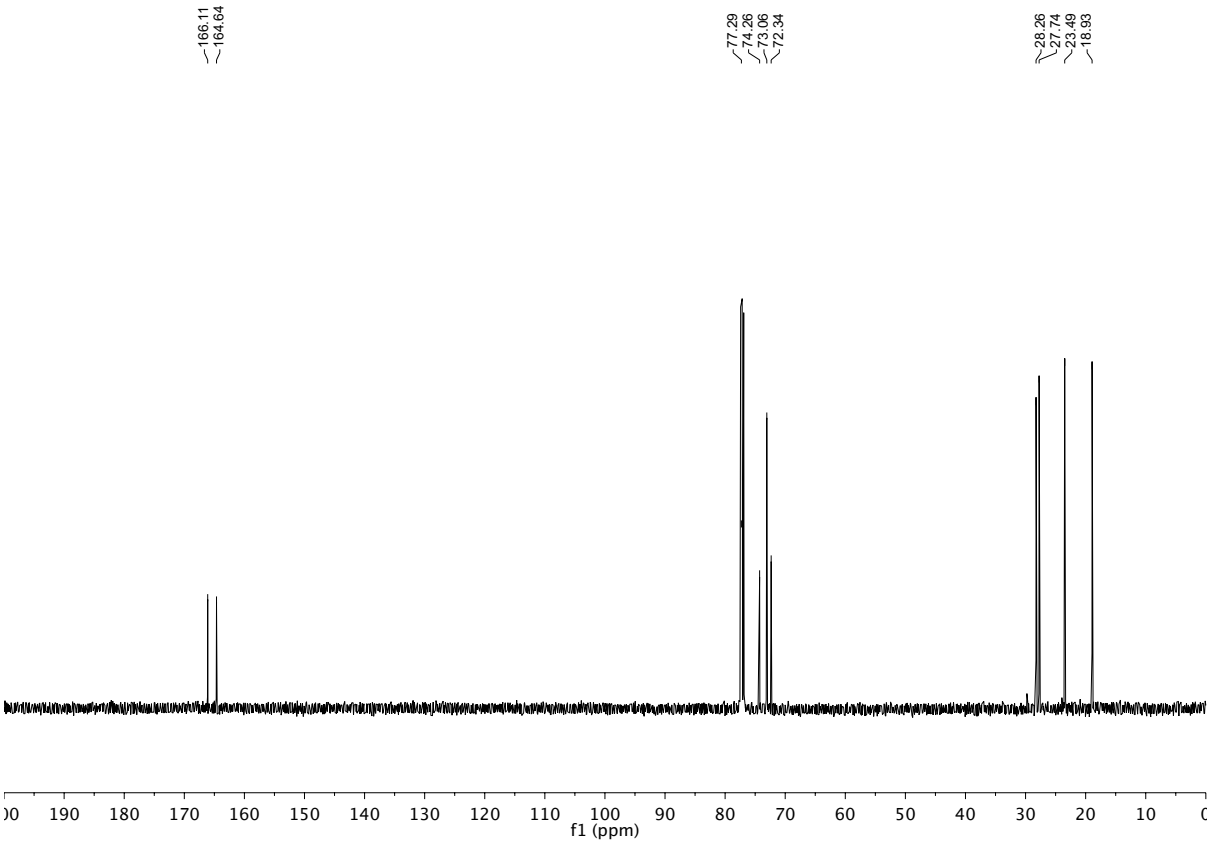


1,4-Dimethyl-6-(prop-2-yn-1-yl)-6-(trityldisulfaneyl)piperazine-2,3,5-trione (30B):

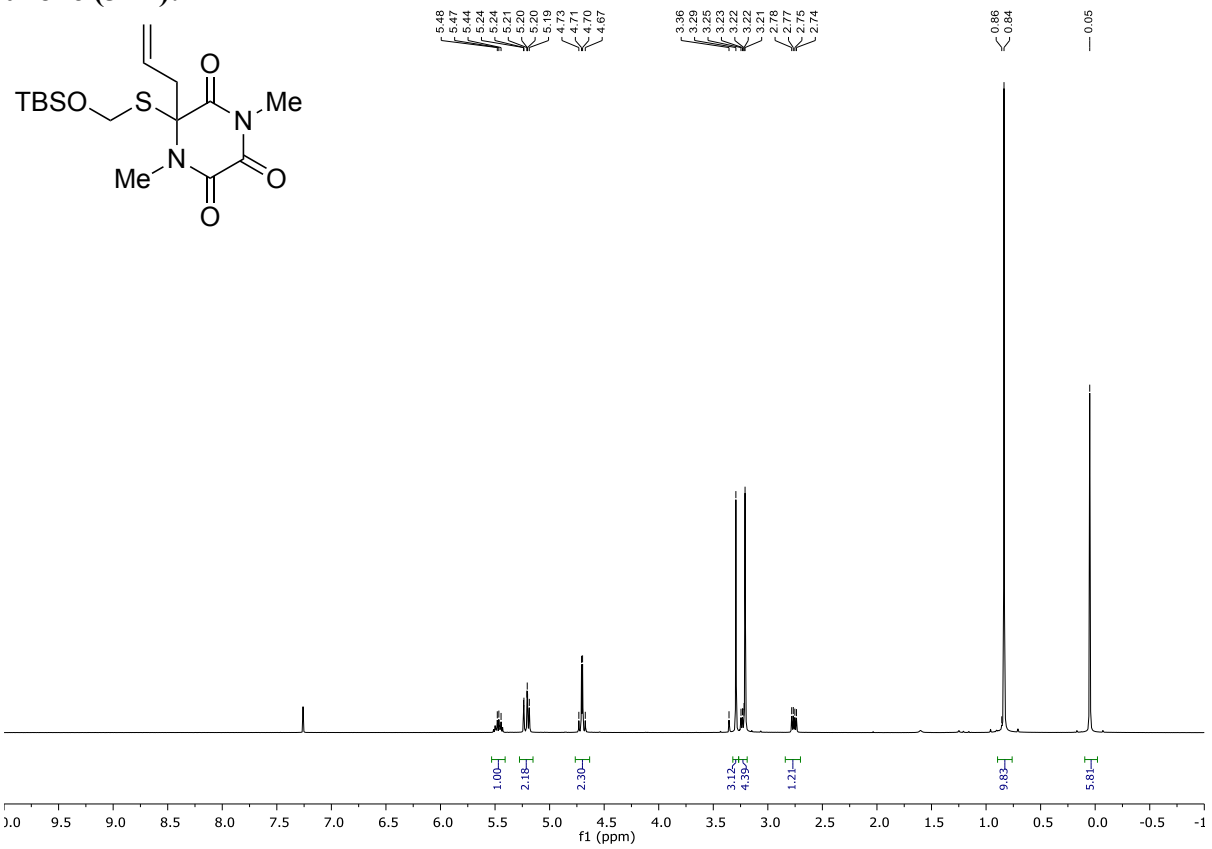


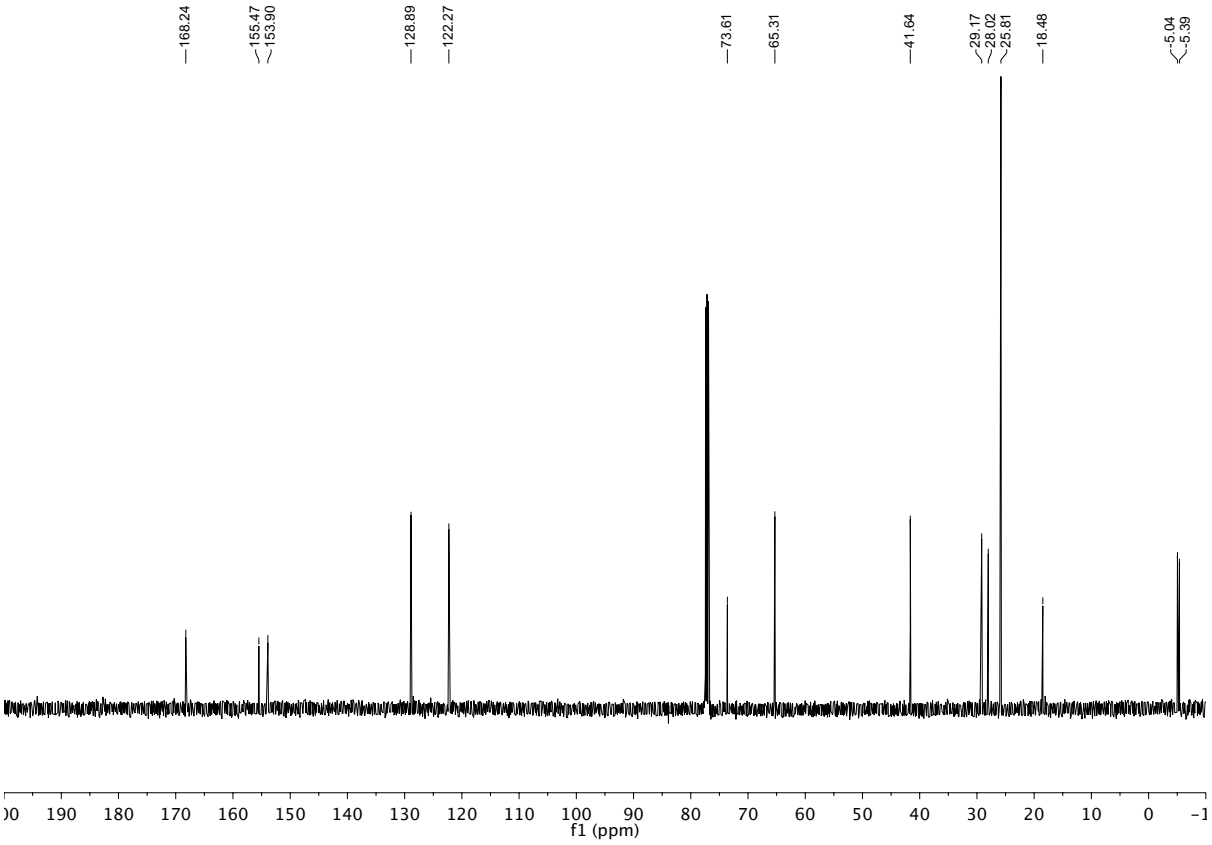
1,5,7-Trimethyl-4-(prop-2-yn-1-yl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (30C):



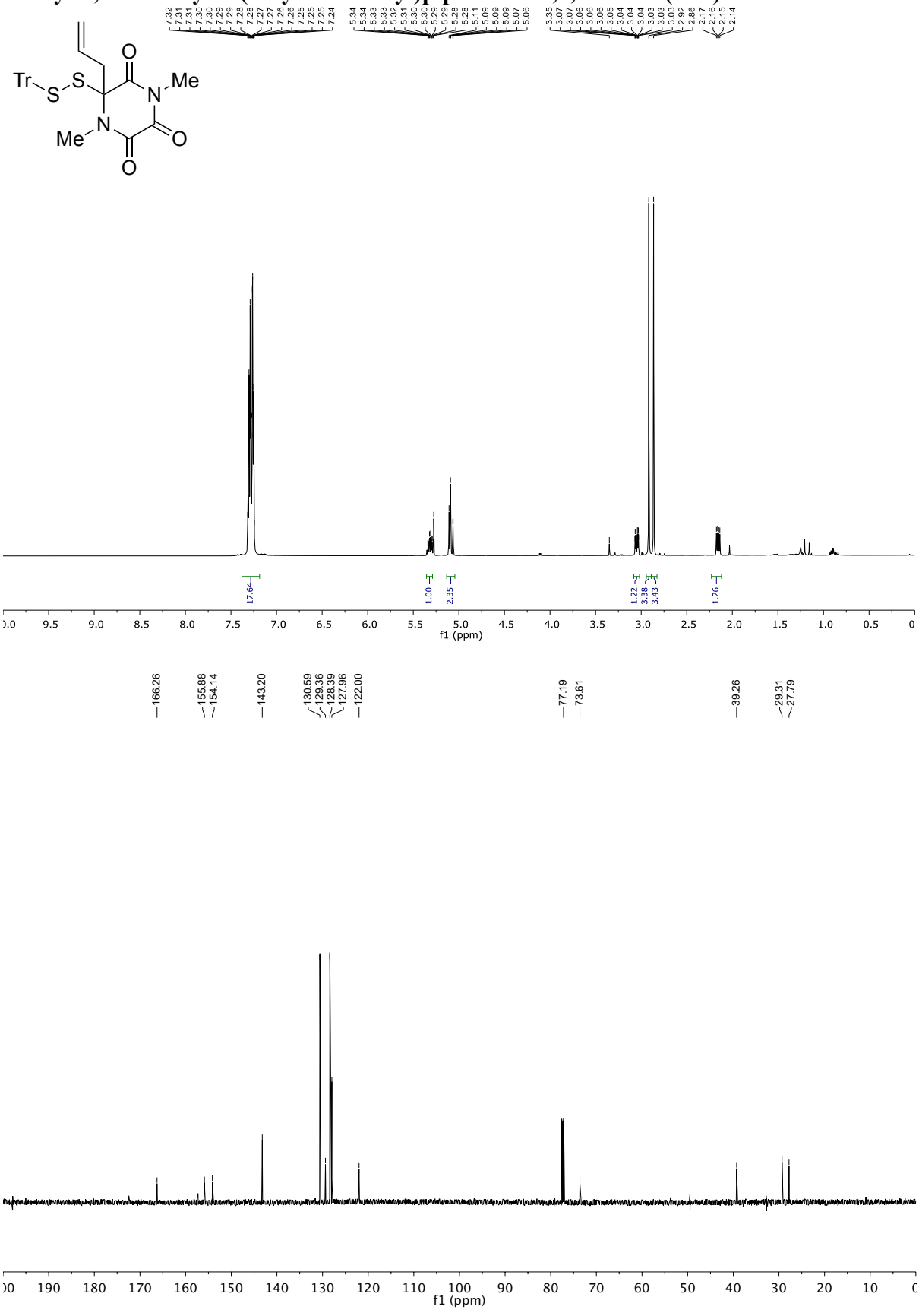


6-Allyl-6-((((*tert*-butyldimethylsilyl)oxy)methyl)thio)-1,4-dimethylpiperazine-2,3,5-trione (31A):

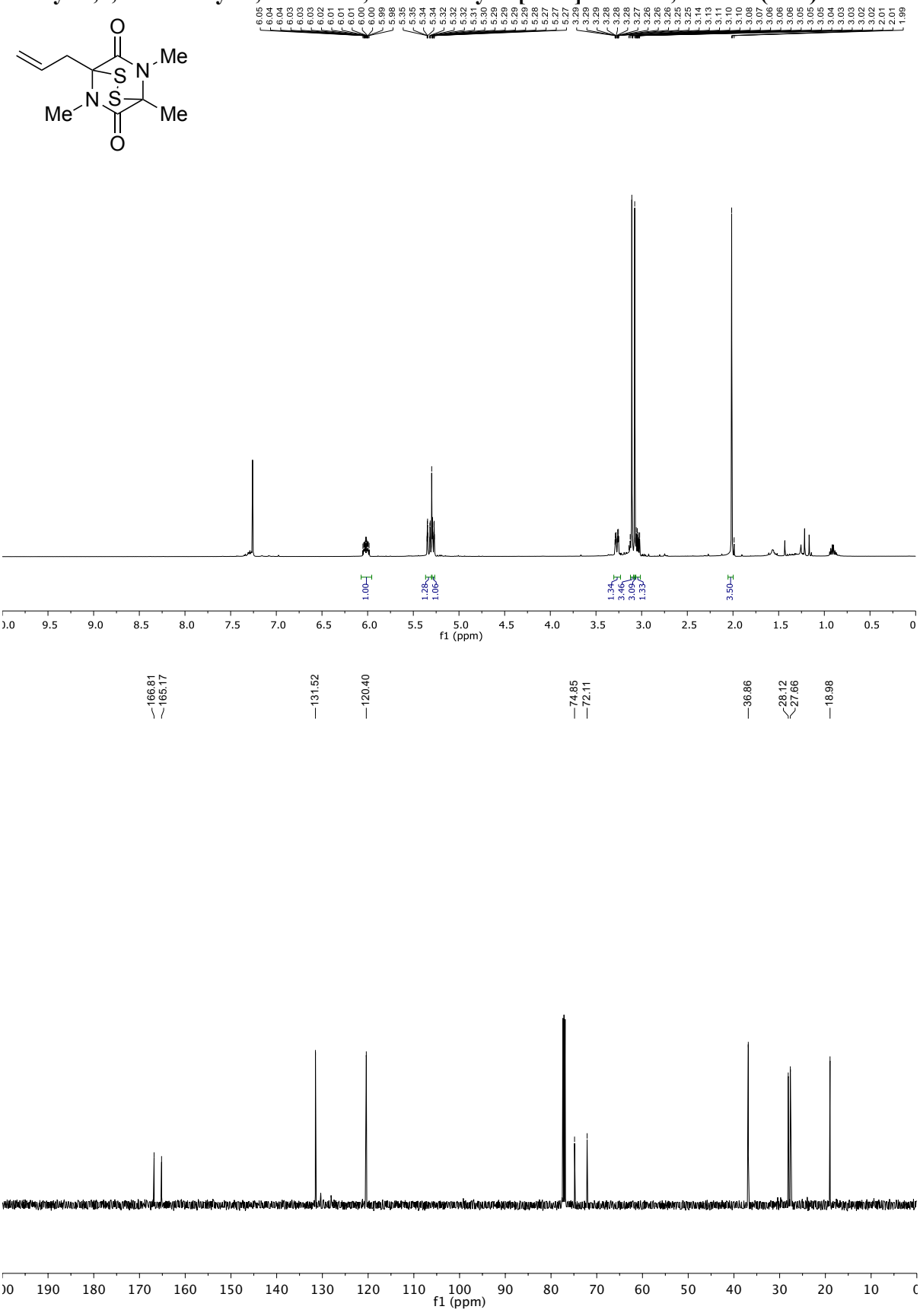




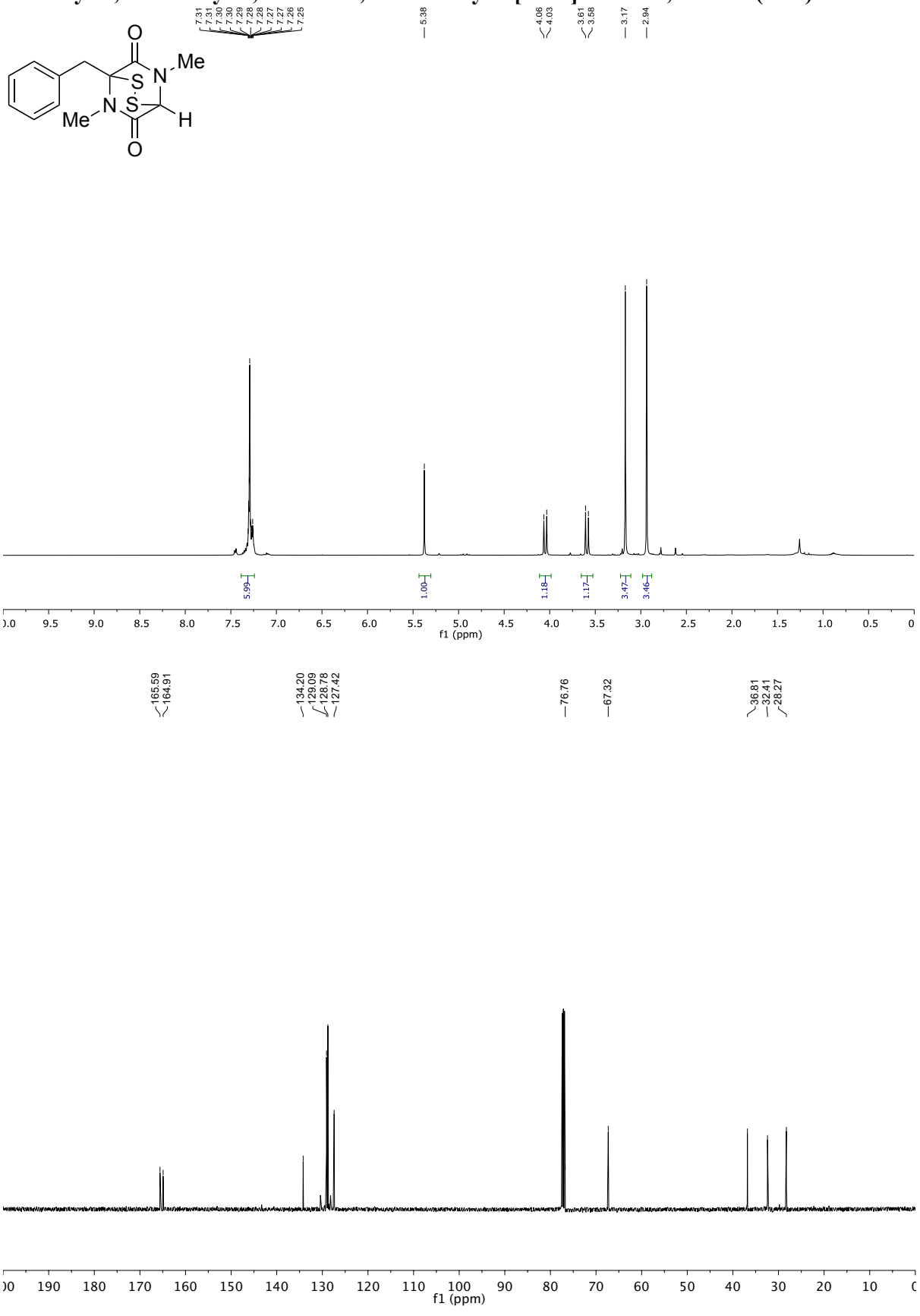
6-Allyl-1,4-dimethyl-6-(trityldisulfaneyl)piperazine-2,3,5-trione (31B):



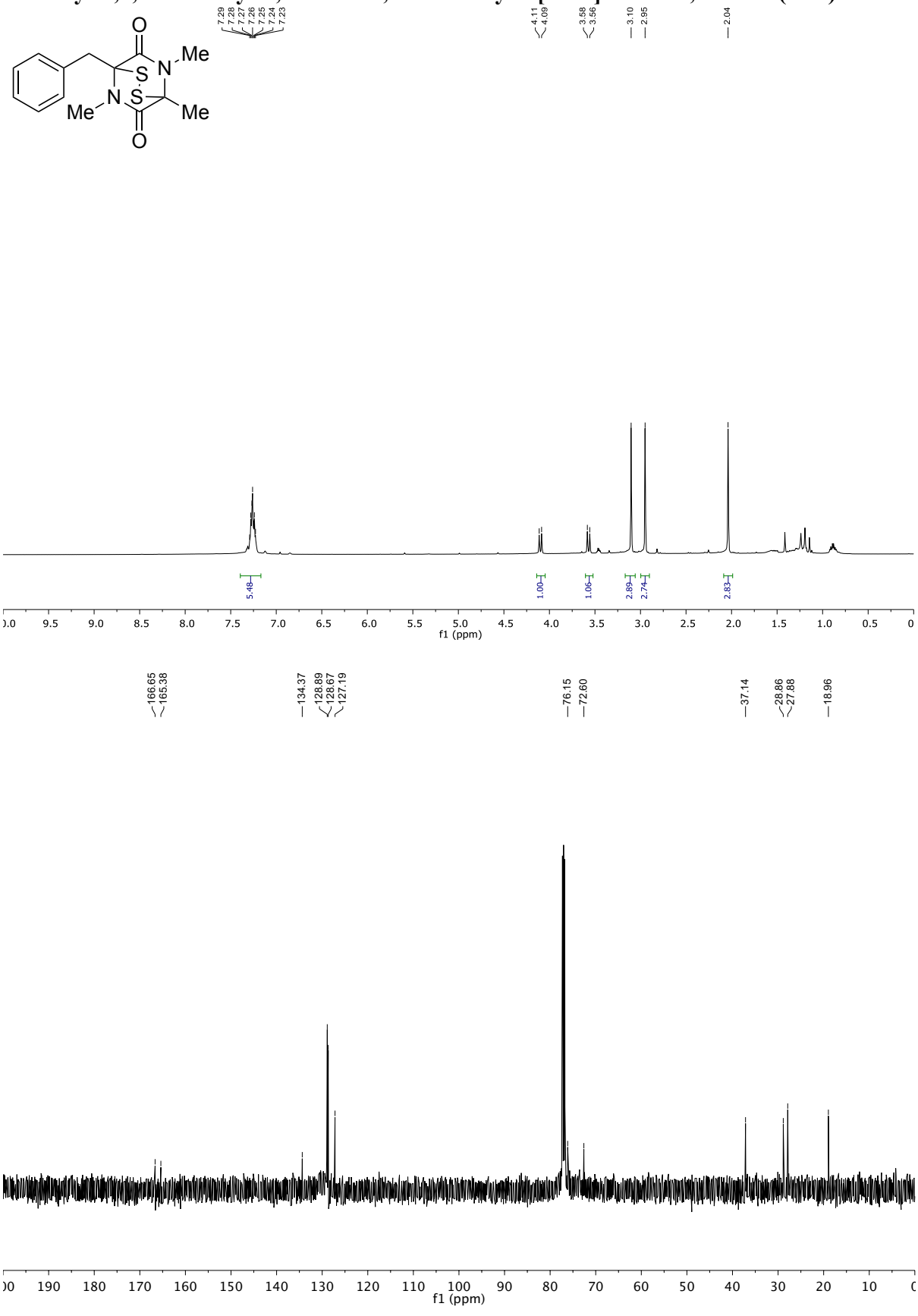
1-Allyl-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (31C):



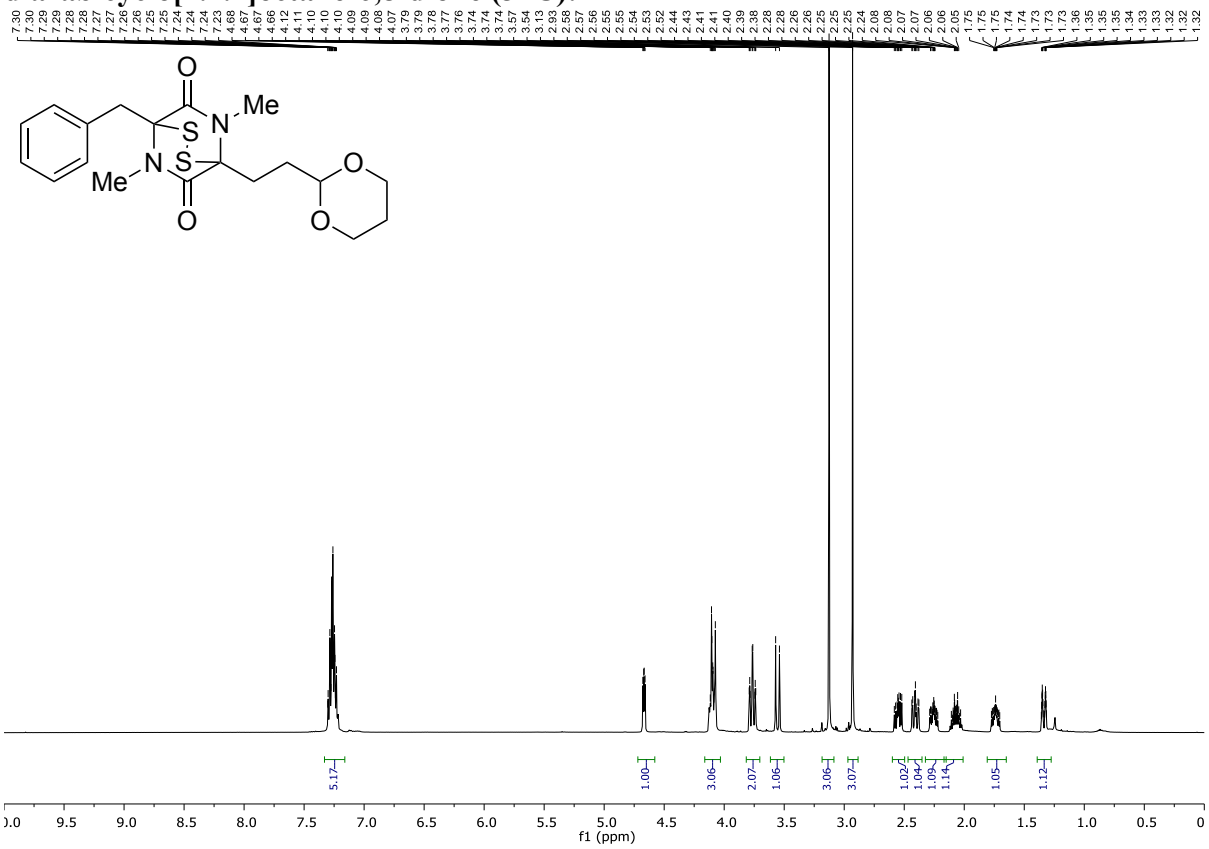
1-Benzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (32C):

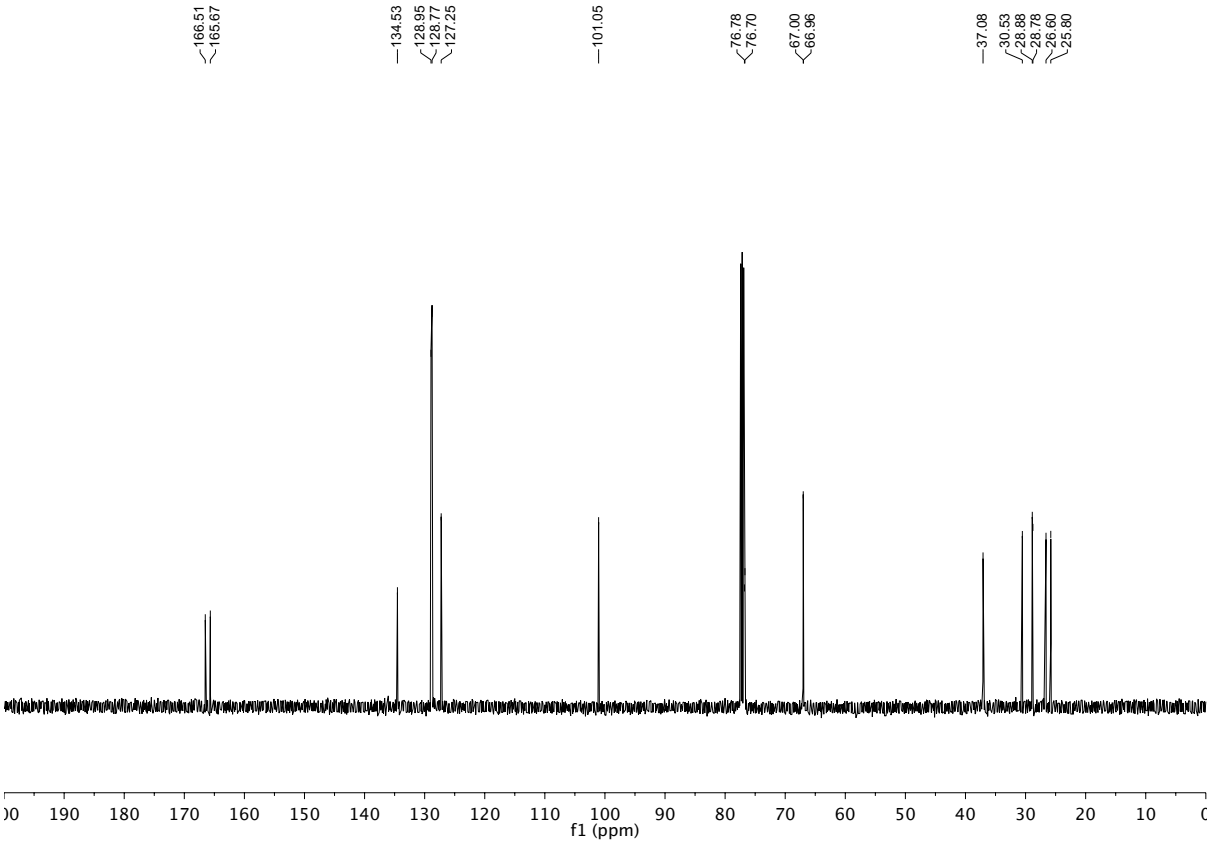


1-Benzyl-4,5,7-trimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (33C):

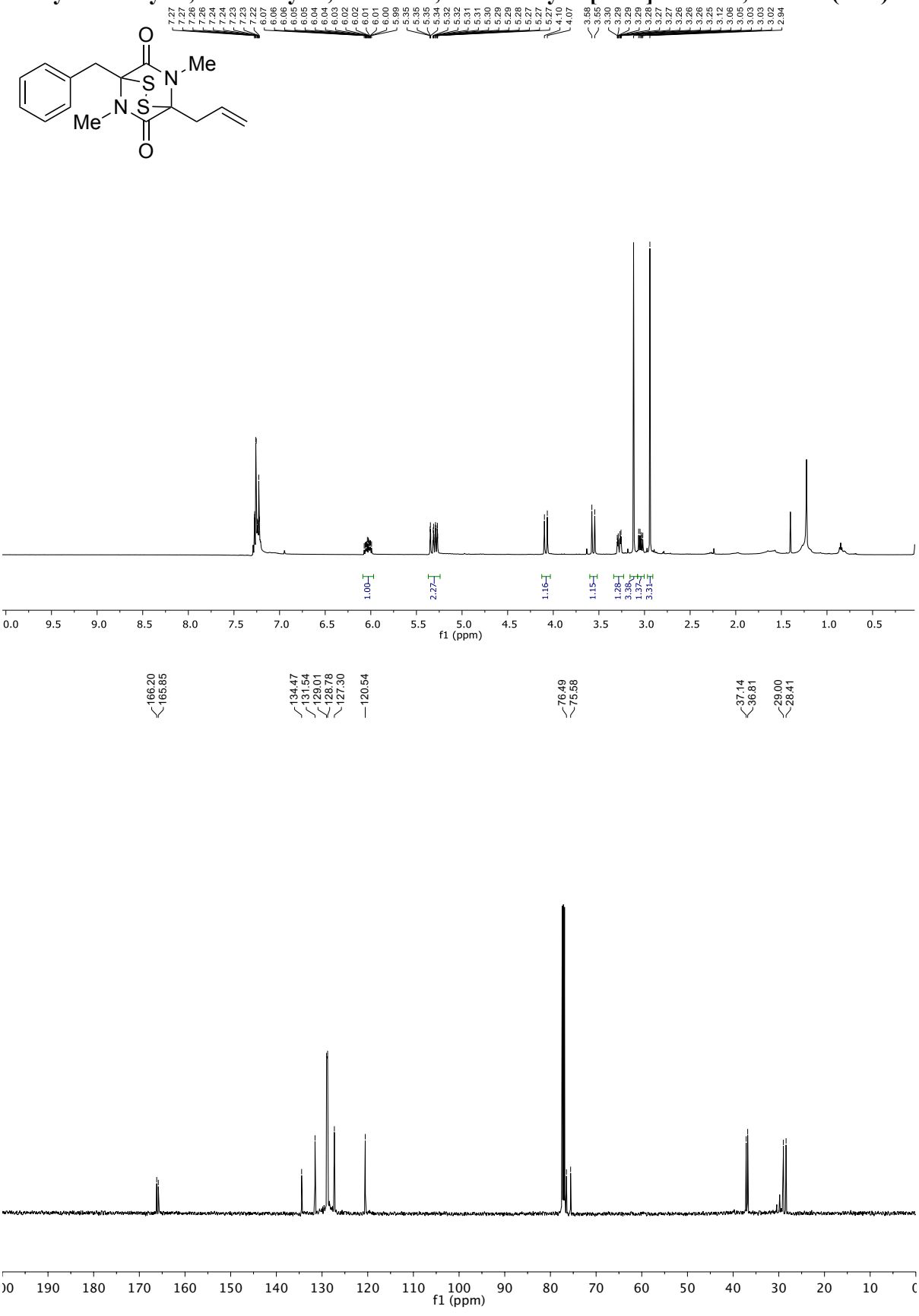


1-(2-(1,3-Dioxan-2-yl)ethyl)-4-benzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (34C):

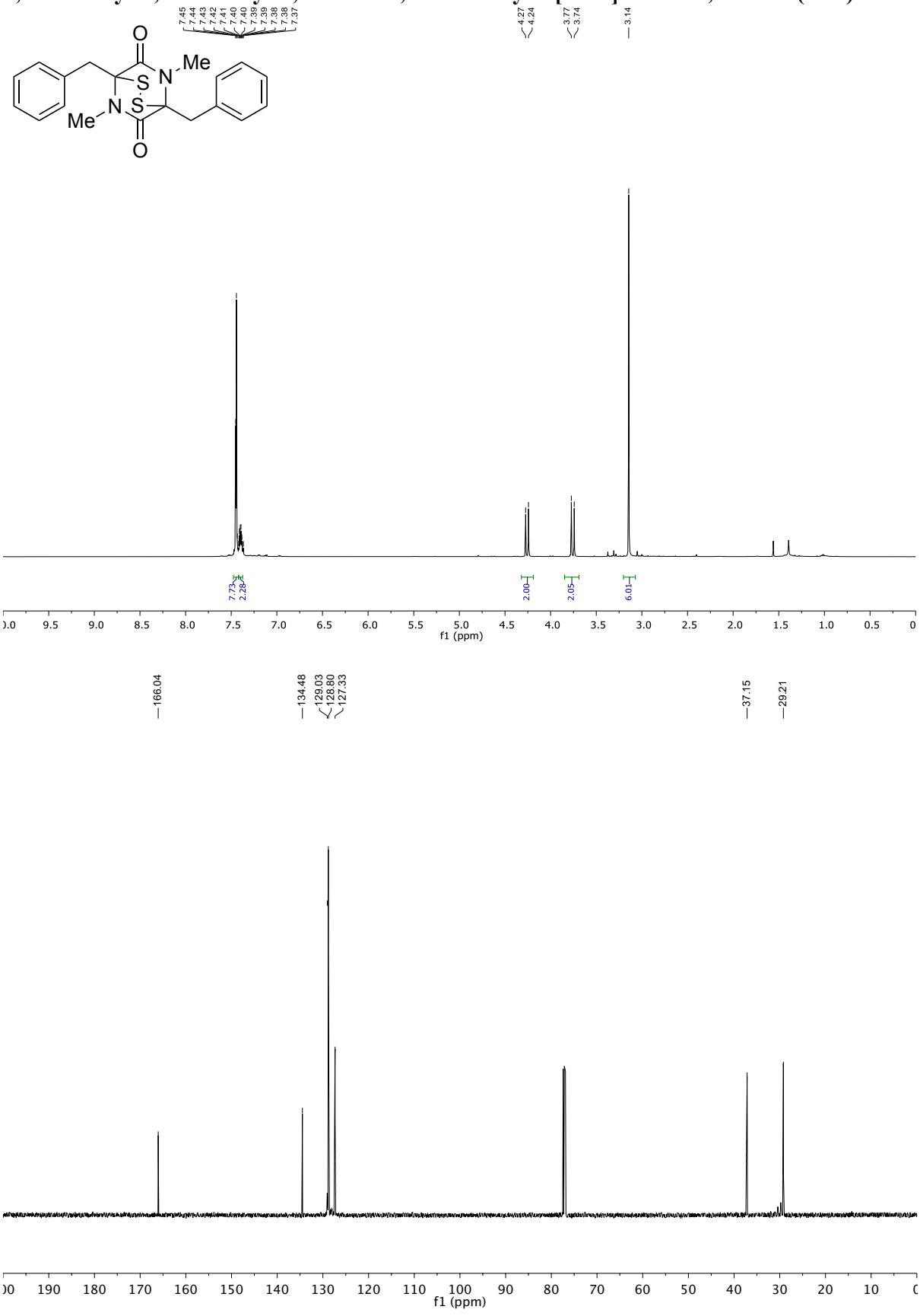




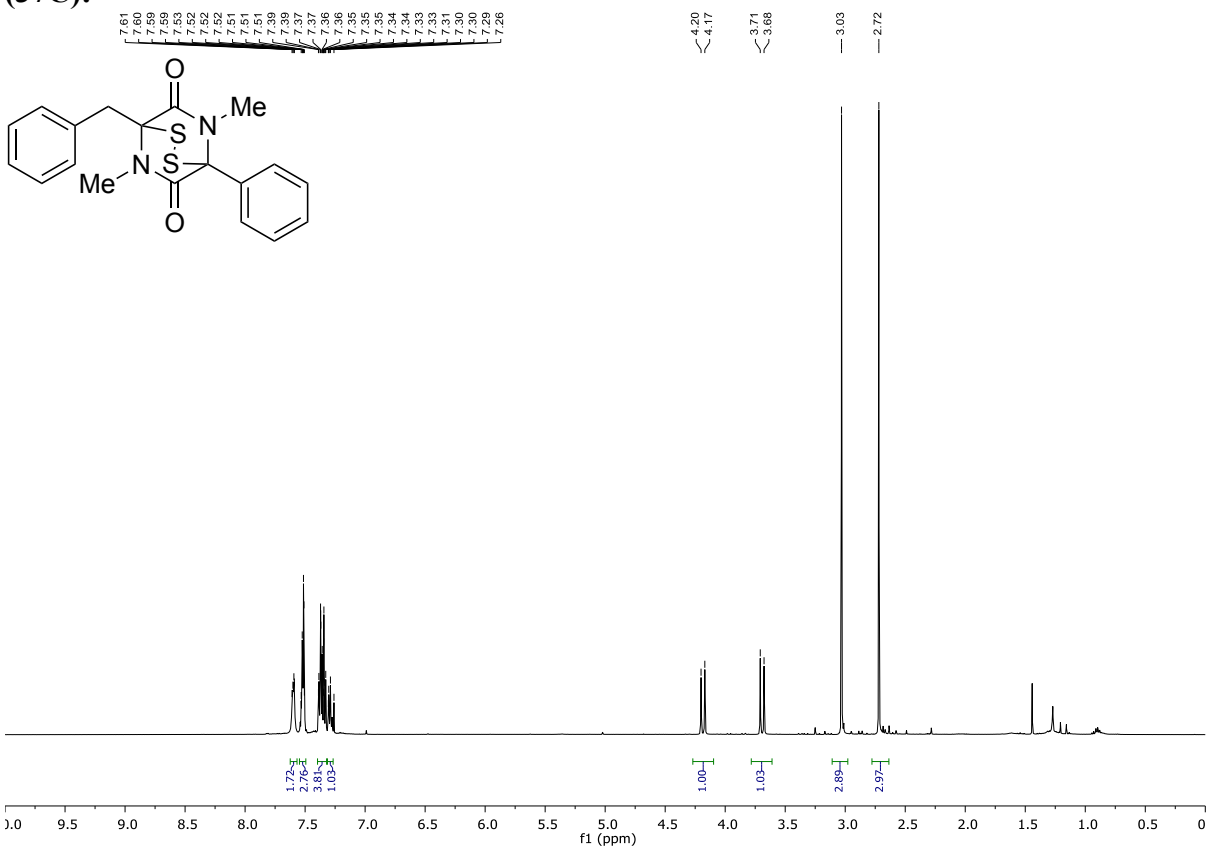
1-Allyl-4-benzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (35C):

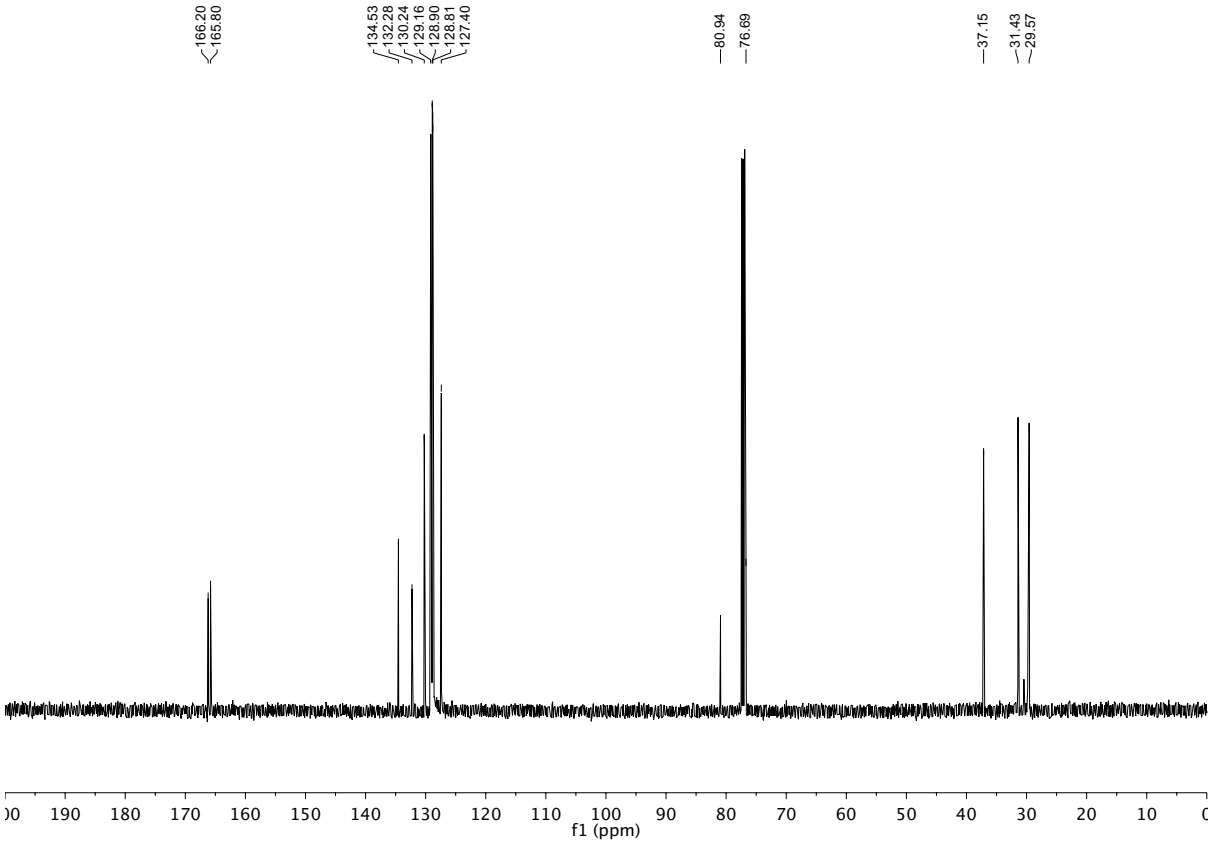


1,4-Dibenzyl-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (36C):

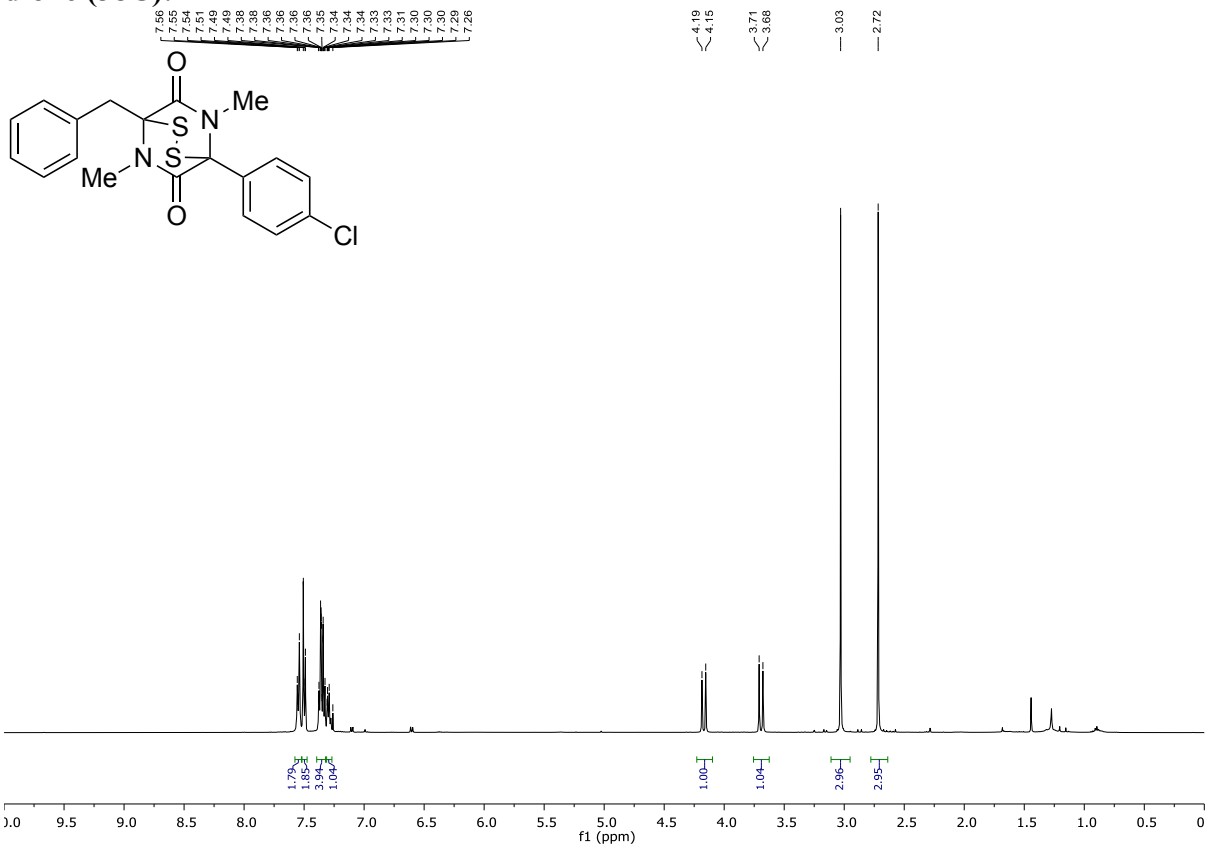


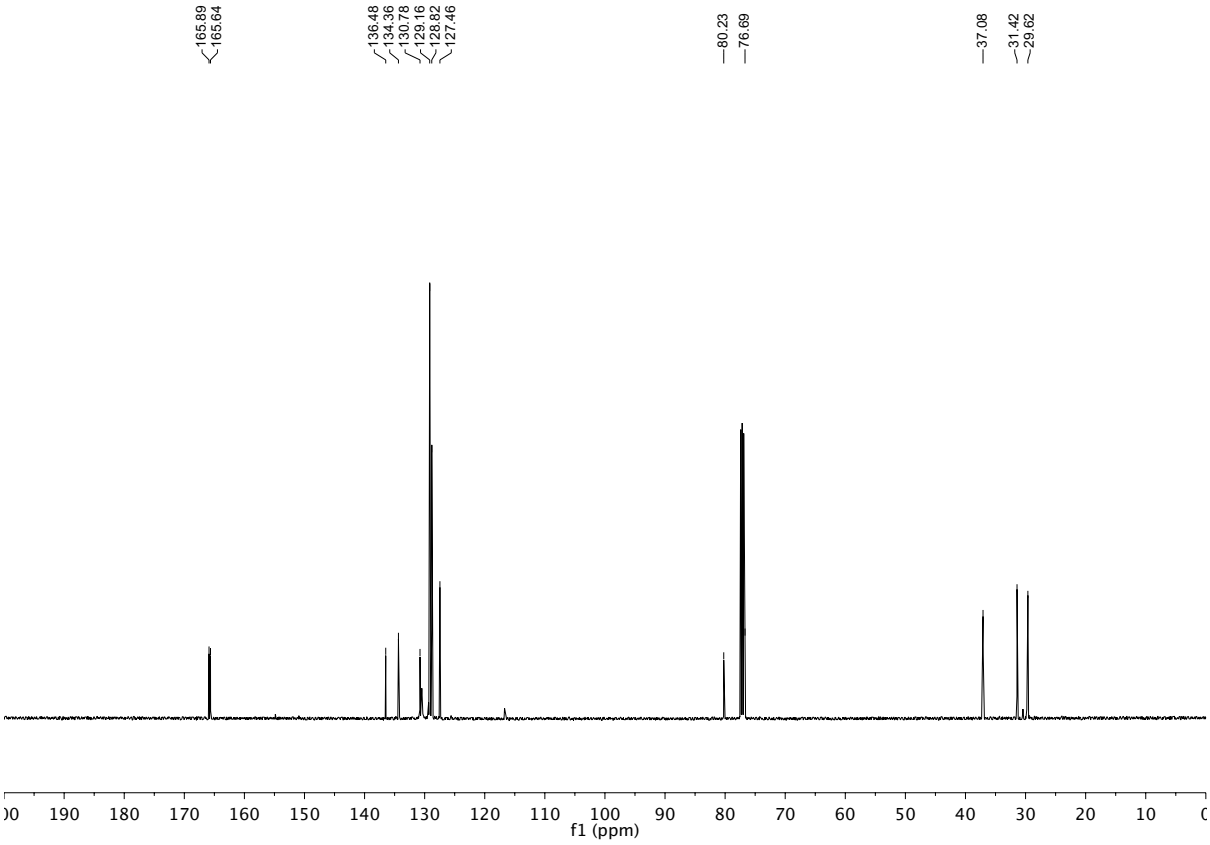
1-Benzyl-5,7-dimethyl-4-phenyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (37C):



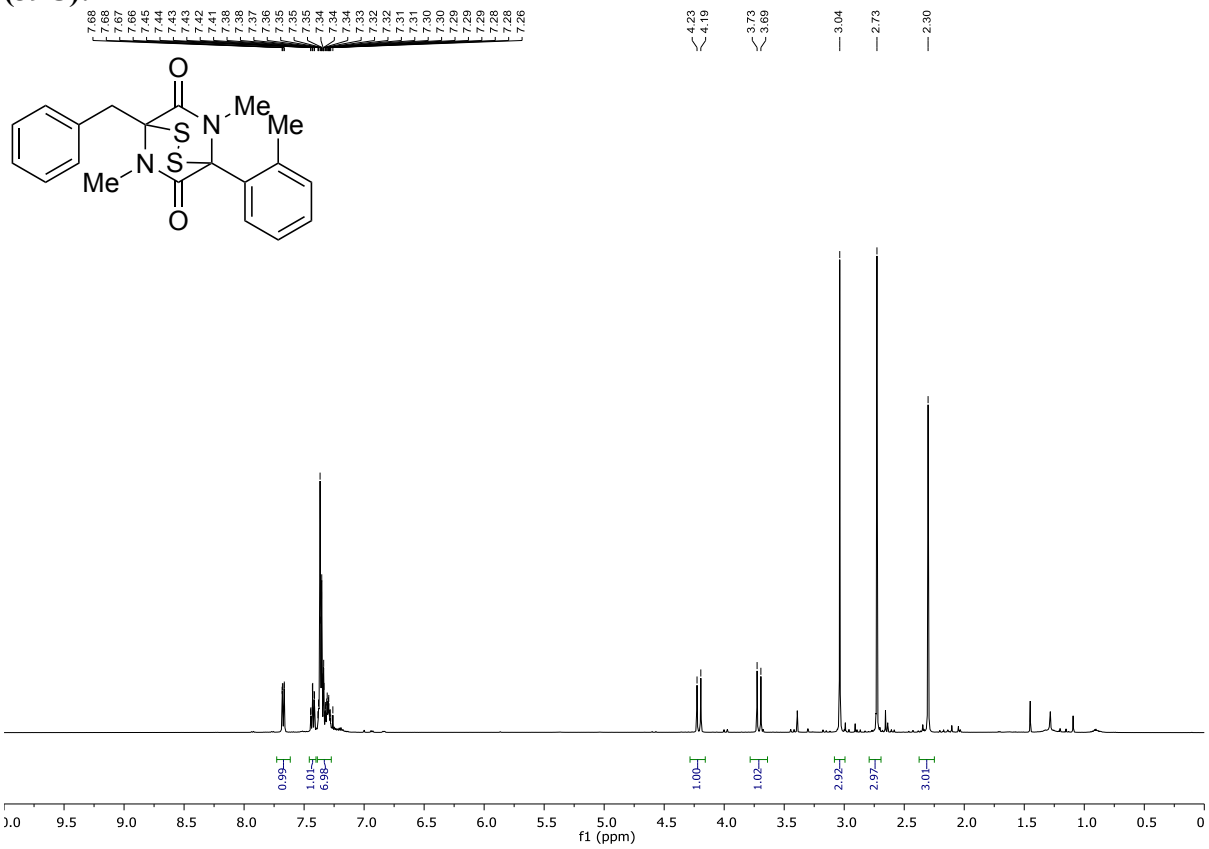


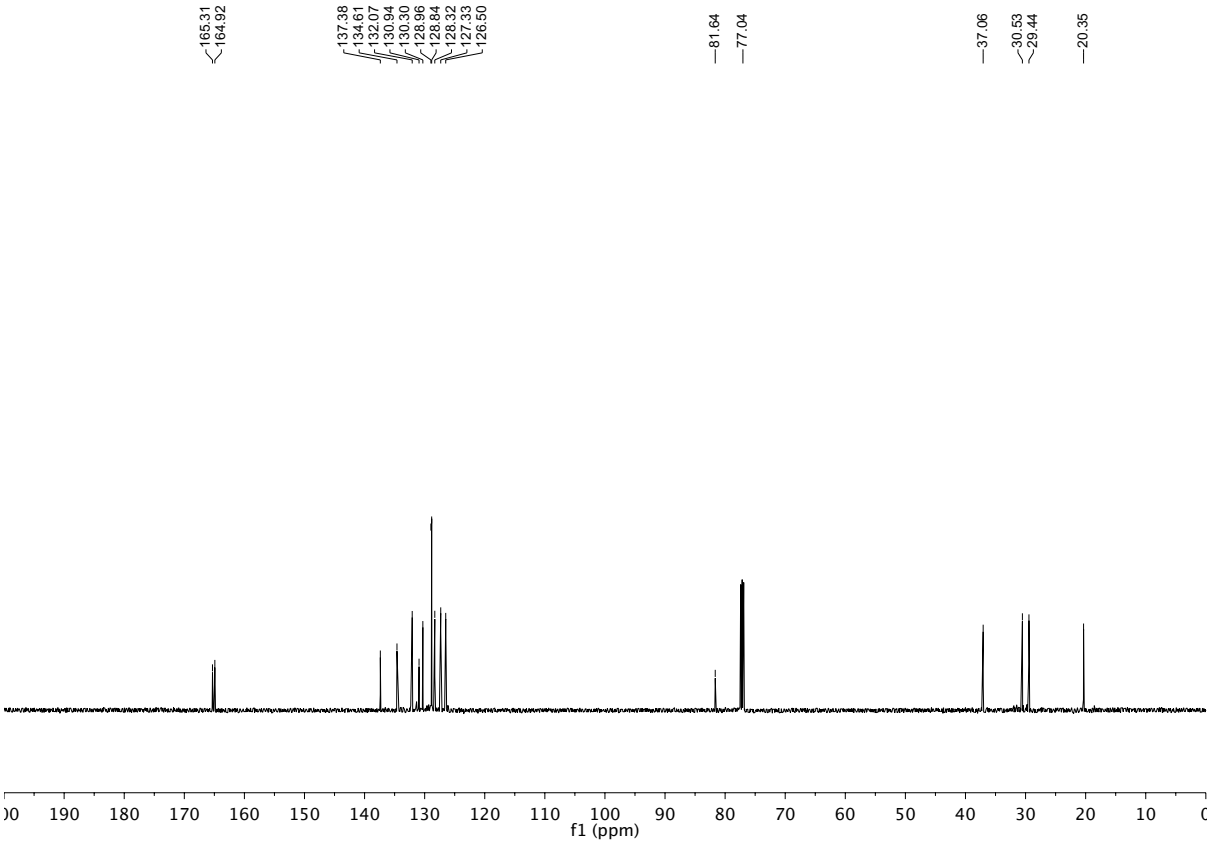
1-benzyl-4-(4-chlorophenyl)-5,7-dimethyl-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (38C):





1-Benzyl-5,7-dimethyl-4-(*o*-tolyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (39C):





1-Benzyl-5,7-dimethyl-4-(4-(trifluoromethoxy)phenyl)-2,3-dithia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (40C):