

## Supporting Information

### Synthesis and Isotopic Labelling of a Naturally-occurring Alkyl-thiadiamondoid

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#### General information

All synthetic manipulations were carried out using standard techniques under a nitrogen atmosphere and in flame-or oven-dried glassware unless otherwise indicated. Dichloromethane and Et<sub>3</sub>N were distilled from calcium hydride under nitrogen. All other solvents were reagent grade. NMR solvents were used as received. Flash chromatography was performed with 40-63 μm particle size silica gel. NMR data were acquired with Bruker Avance 400 MHz or Bruker Avance 500 MHz instruments. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded relative to residual solvent. GC-MS was conducted on an Agilent 5973N MSD interfaced to an Agilent 6890N GC System equipped with an Rtx-35 MS column (30 m × 0.25 mm i.d., 0.10 μm film thickness; Restek, Bellefonte, PA). IR spectra were recorded using a Nicolet Avatar 320 FT-IR spectrometer, and KBr plates. The following chemicals were purchased and used as received: dimethyl malonate (Acros), formaldehyde (37 wt. % solution in water Fisher Scientific), glacial acetic acid (Fisher Scientific), hydrochloric acid (37 wt. % solution in water Fisher Scientific), sodium (Acros), *tert*-butyldimethylsilyl trifluoromethanesulfonate (Gelest), sodium hydroxide (Fisher Scientific), hydrazine monohydrate (Acros).

#### Synthesis and characterization data for the compounds

**Synthesis of Tetramethyl 2,6-Dioxobicyclo[1.3.3]nonane-1,3,5,7-tetracarboxylate, Meerwein's ester (1).**<sup>1</sup> Into a three-necked flask equipped with a mechanical stirrer were placed dimethyl malonate (200 g, 1.5 mol), formaldehyde (100 g, 3.3 mol) and methanol (30 mL), and the mixture was cooled to 0 °C in an ice-water bath. Keeping the mixture under vigorous stirring, diethylamine (10.7 mL, 0.1 mol) was slowly added, and the mixture was kept under stirring for at 0 °C for 12 h. The solution was then stirred at 25 °C for 24 h and at 40 °C for 48 h. The mixture was cooled to 0 °C, washed with a solution of potassium bisulfate (100 mL, 2 M) and heated under vacuum (100 °C, 1 torr) for 12 h. The thick oil was then treated with sodium methoxide (prepared from sodium (26.3 g, 1.14 mol) and anhydrous methanol (375 mL)) and refluxed for 4 h. The methanol was removed under vacuum, and ice-cold water (150 mL) was added to the resulting solid. The solution was washed with ether and the aqueous layer treated with dry ice (CO<sub>2</sub>) until a precipitate formed. Filtration afforded 91.1 g (63% yield) of a light pink solid; mp 150 °C. Data was comparable to that available in the literature<sup>1</sup>: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.31 (s, 2 H), 2.9 (s, 4 H), 3.77 (s, 6 H), 3.78 (s, 6 H), 12.2 (s, 2 H).

**Synthesis of Tetraester 2a.** A solution of sodium methoxide was prepared stirring, under nitrogen atmosphere, sodium metal (4.9 g, 0.2 mol) and dry methanol (163 mL), until complete dissolution of the metal. The mixture was then cooled to -78 °C and Meerwein's ester (1, 20 g, 0.05 mol) was slowly added. The solution was vigorously stirred to completely dissolve the solid. Keeping the solution at -78 °C, methyl iodide (20 mL, 0.32 mol) was slowly added, and the mixture was slowly allowed to warm to rt and stirred for 48 h. The liquid was poured into a stirring saturated solution of ammonium chloride (200 mL), and extracted with dichloromethane (2 × 100 mL). The organic layer was dried over magnesium sulfate and filtered. The solvent was removed under vacuum, affording 16.33 g of product (76% yield). The raw material, which was used in the subsequent synthesis steps without any purification, can be purified via column chromatography (silica, 4:1 hexanes/ethyl acetate) and re-crystallized from methanol to afford white crystals in 50% yield; mp 175-179 °C. The stereochemistry was determined via NOESY NMR (see below). IR (neat): 427, 656, 748, 812, 912, 961, 1073, 1129, 1263, 1332, 1443, 1625, 1666, 1709, 1738, 2953, 3002 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 1.39 (s, 3 H), 2.12 (d, *J* = 14.5 Hz, 1 H), 2.51 (m, 2H), 2.74 (d, *J* = 17.5 Hz, 1 H), 2.88 (dd, *J* = 15.5 Hz, 1 H), 3.29 (dd, *J* = 14.5 Hz, 1 H), 3.51 (s, 3 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 12.05 (s, 1 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 24.7, 29.6, 37.9, 42.2, 48.0, 52.6, 53.0, 53.3, 53.4, 55.5, 56.9, 97.7, 168.1, 171.8, 171.9, 172.1, 172.3, 204.6. **Synthesis of 1-methylbicyclo[3.3.1]nona-2,6-dione (3).** Alkylation product **2a** (14 g, 0.035 mol) was cooled to 0 °C and dissolved in a mixture of glacial acetic acid (42 mL), conc. aq HCl (14.5 mL, 35%) and water (14.5 mL), and subsequently heated to reflux for 18 h. The solution was then neutralized with a sat. aq sodium bicarbonate solution (200 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100

mL). The organic layers were combined and dried with magnesium sulfate. The solvent was removed under vacuum, affording an oil containing a mixture of C2 epimers (5.14 g, 87% yield) that was used without further purification. IR (neat): 412, 1454, 1704, 2223, 2869, 2935, 3392  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.09 (d,  $J$  = 6.4 Hz, 3 H), 1.59-1.65 (m, 1 H), 1.88-1.96 (m, 1 H), 2.07-2.13 (m, 1 H), 2.15-2.23 (m, 1 H), 2.24-2.32 (m, 2 H), 2.41-2.5 (m, 2 H), 2.63-2.73 (m, 2 H), 2.81-2.87 (m, 1 H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.5, 15.0, 24.2, 29.4, 29.7, 30.0, 32.1, 35.0, 36.7, 37.8, 39.1, 40.8, 42.0, 43.4, 43.6, 44.5, 212.0, 213.1, 213.4, 217.0.

**Synthesis of Sulfur dichloride.**<sup>2</sup> In a two-necked round-bottom flask equipped with a reflux condenser, sulfur (50 g) was heated to 100 °C and allowed to liquefy. Chlorine gas was then bubbled in the liquid for 30 min, and the mixture was then cooled to 20 °C with a water bath. A spatula tip of iron powder was added to the solution, and the bubbling of chlorine was kept on for 30 min. The liquid was then allowed to stand for 1 h at rt, a few drops of  $\text{PCl}_3$  were added, and sulfur dichloride was distilled, affording about 70 mL of product (ca. 70% yield, b.p. 56 °C).

### Synthesis of 1-methyl-2-thiaadamantane-4,8-dione (5)

Part 1: Formation of bis-silyl enol ether 4.

1-methylbicyclo[3.3.1]nona-2,6-dione (**3**, 4.7 g, 0.028 mol) was dissolved in dry dichloromethane (30 mL) in a 50-mL round-bottom flask and stirred in a nitrogen atmosphere. In a 250-mL round-bottom flask, *tert*-butyldimethylsilyl trifluoromethanesulfonate (17 mL, 0.074 mol), triethylamine (17.2 mL, 0.12 mol) and dry dichloromethane (120 mL) were stirred under nitrogen and the cooled to -78 °C. The contents of the 50-mL flask were transferred via cannula into the 250-mL flask and the mixture was allowed to slowly warm to rt. The liquid was then washed with sat. aq sodium bicarbonate, and the organic layer dried with magnesium sulfate, filtered, and taken to dryness under vacuum, affording a biphasic thick liquid. The lower red layer was removed by pipette and disposed of. The thick clear layer (11.16 g, 100% yield) was used for the subsequent reaction without any further purification. Selected peaks for  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.12 (s, 6 H), 0.13 (s, 6 H), 0.98 (s, 9 H), 1.00 (s, 9 H), 4.7 (m, 1 H)

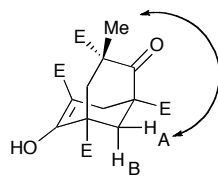
Part 2: Reaction with  $\text{SCl}_2$ .

Silyl enol ether **4** (4.44 g, 0.011 mol) and pyridine (0.88 mL, 0.011 mol) were dissolved in dry dichloromethane (40 mL) and stirred under nitrogen. After warming the mixture to 35 °C, sulfur dichloride (0.7 mL, 0.011 mol) was slowly added to the solution. The mixture was kept under stirring at 35 °C for 1 h and then cooled to rt and stirred for 5 h. The liquid was washed with sat. aq sodium bicarbonate (50 mL) and water (50 mL) and the organic layer was dried over magnesium sulfate. After filtration, the solvent was removed under vacuum and the product was purified by column chromatography (silica, 2:1 hexanes/ethyl acetate), affording 0.56 g of diketone **5** (25% yield). IR (neat): 1000, 1030, 1125, 1189, 1250, 1312, 1450, 1690, 2070, 2248, 2812, 2888  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.072 (s, 3 H), 1.41-1.46 (m, 2 H), 1.723 (dd,  $J$  = 3.2 Hz, 1 H), 1.894 (dt,  $J$  = 4 Hz, 1 H), 2.23-2.27 (m, 1 H), 2.341-2.388 (m, 2 H), 2.437 (dt,  $J$  = 2.8 Hz, 1 H), 2.699 (s, 1 H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 37.7, 37.9, 44.4, 44.6, 45.5, 46.4, 48.9, 53.0, 207.2, 207.3.

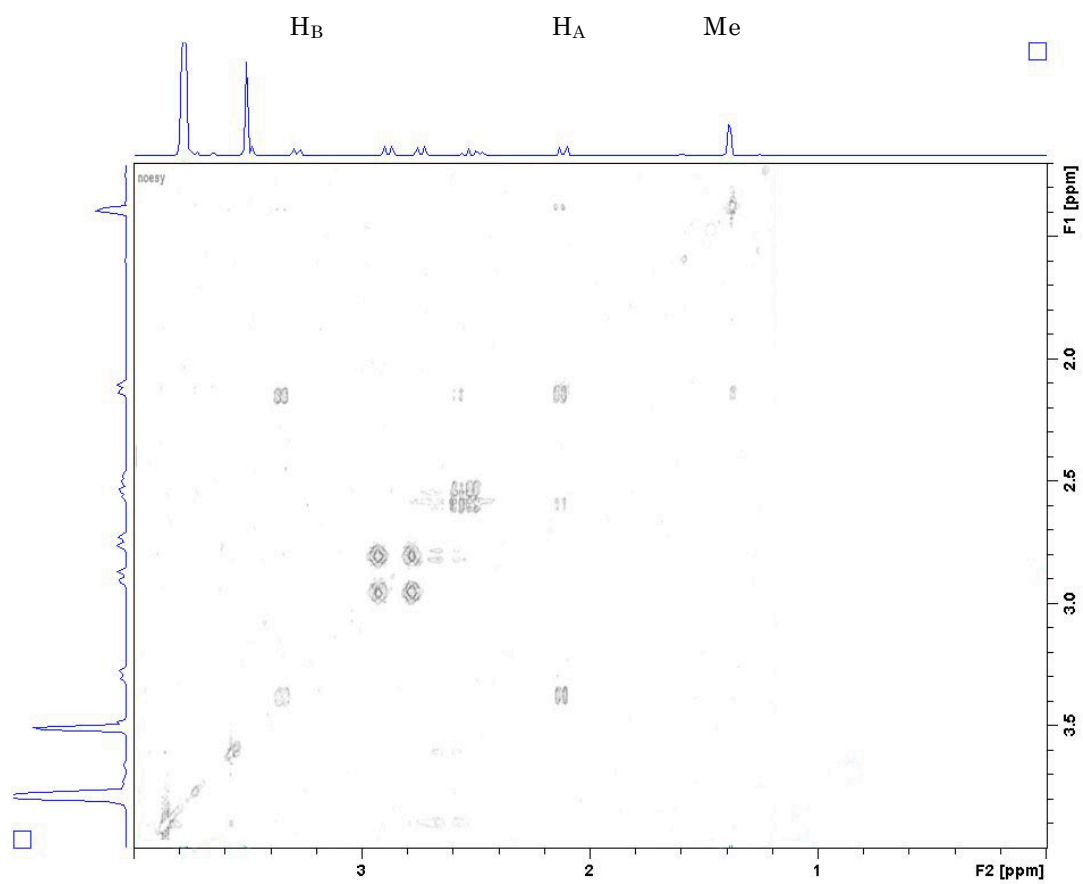
**Synthesis of 1-(methyl-d3)-2-thiaadamantane (6b).** 1-(methyl-d3)-2-thiaadamantane-4,8-dione (**5**, 0.85 g, 4.3 mmol) was stirred in a sealed tube with ground sodium hydroxide (1.9 g, 0.05 mol), hydrazine (1.12g, 0.034 mol) and diethylene glycol (70 mL). The tube was heated to 125 °C for 2 h and to 195 °C for 3 h. The mixture was cooled to rt, diluted with water (200 mL) and extracted with pentane (2 x 50 mL). The organic layer was washed with water and brine and dried over magnesium sulfate. After filtration, the pentane was distilled and the residual green oil was purified via column chromatography. The stationary phase was prepared by mixing silica (100 g), silver nitrate (10 g) and water (200 g) in a round-bottom flask cover with aluminum foil.<sup>3</sup> The water was evaporated under vacuum and the resulting sludge was then dried in an oven overnight at 130 °C. The crude material was eluted with 10:1 pentane/ether to remove byproducts and then with 10:1 ether/dimethyl sulfide, affording the desired product. Collected fractions were best analyzed by GC-MS. Distillation of the solvents gave 75.4 mg of a colorless waxy solid (10.3% yield).  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  = 1.7-1.80 (m, 2 H), 1.80-1.84 (m, 1 H), 1.85-1.86 (m, 1 H), 2.05-2.08 (m, 3 H), 2.08-2.12 (m, 3 H), 2.14-2.21 (m, 2 H), 3.02-3.08 (m, 1 H). GC/MS,  $m/z$  (rel. int.): 171.2 ( $[\text{M}]^+$ , 100%), 138.2 (12.5), 114.1 (50), 96.2 (55), 79.2 (37.5), 59.2 (12.5).

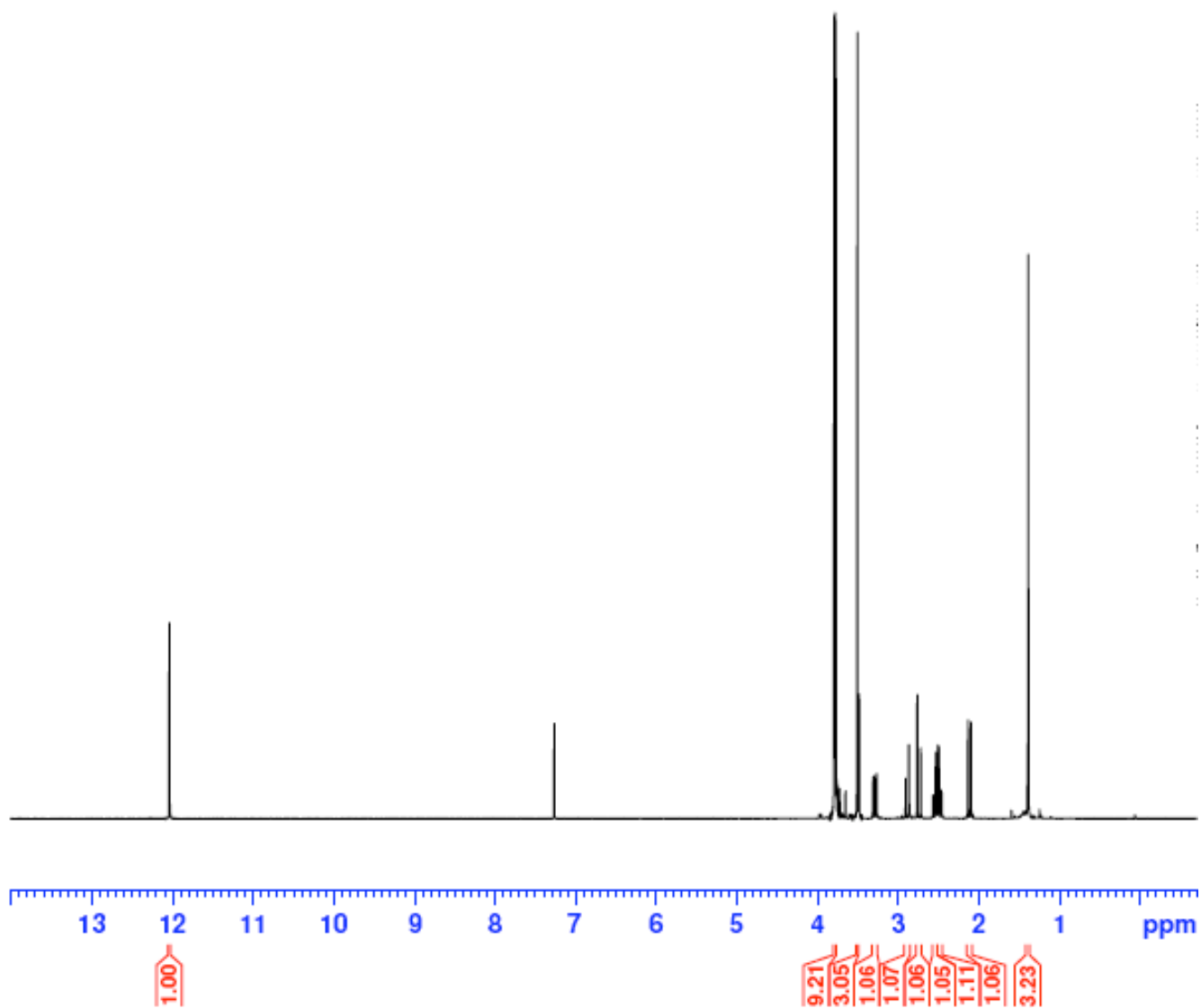
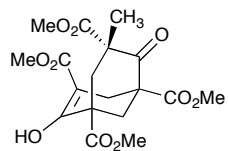
## Selected NMR Spectra

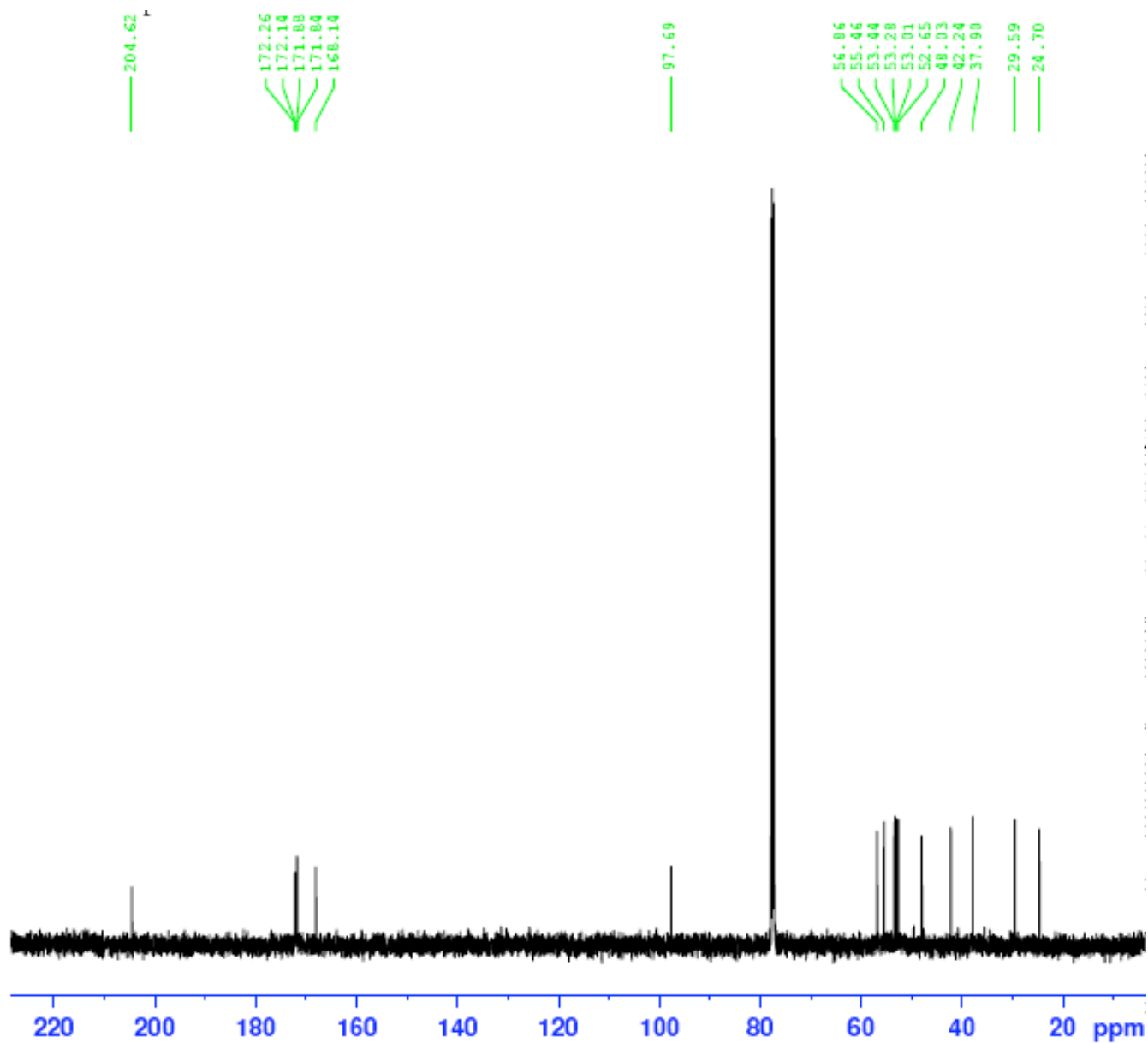
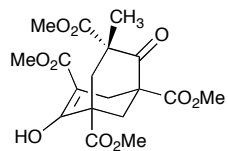
### Tetraester 2a

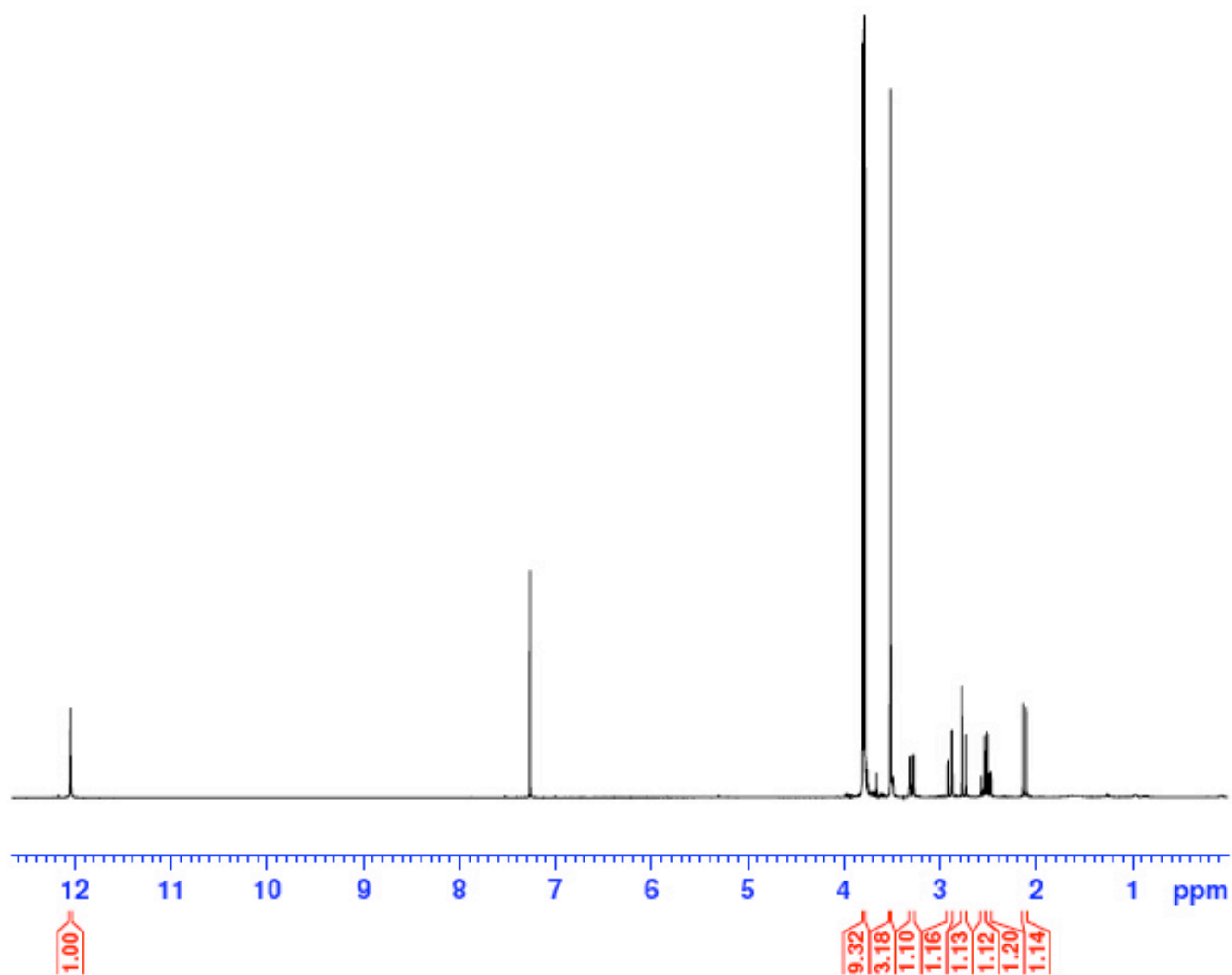
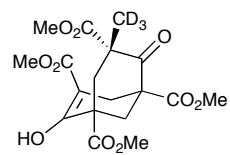


### NOESY NMR

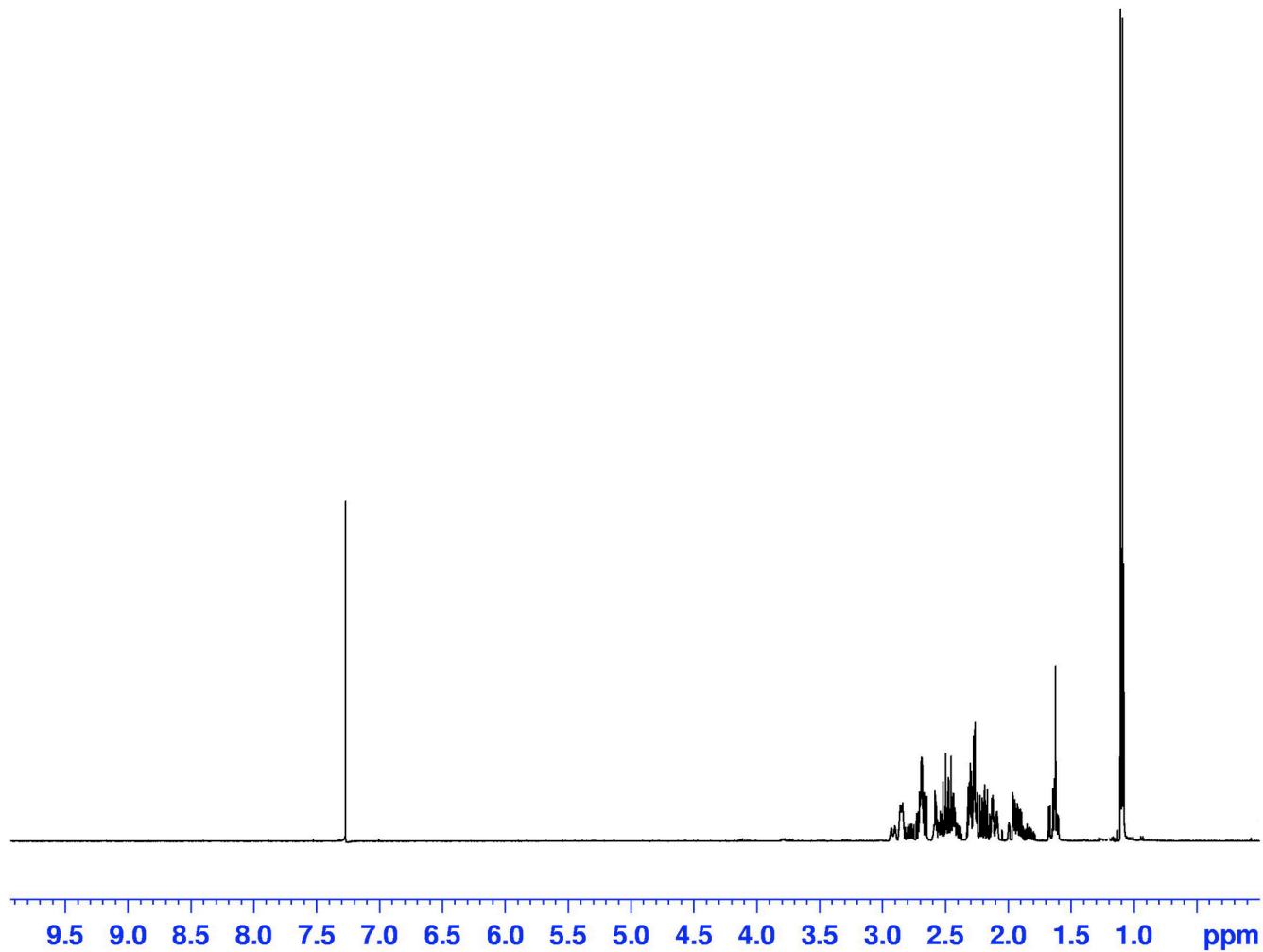
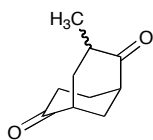


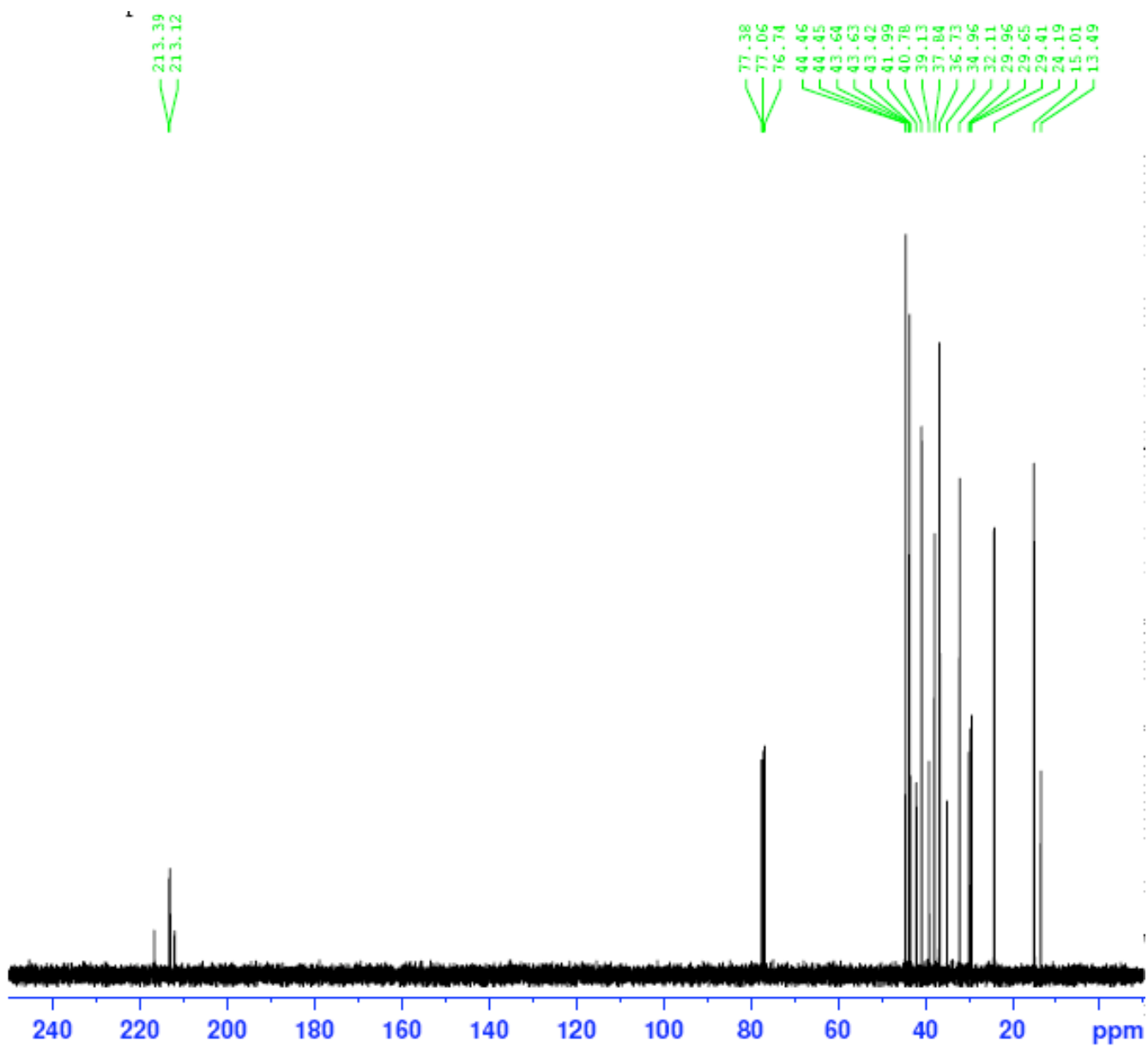
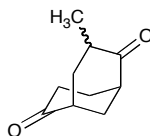






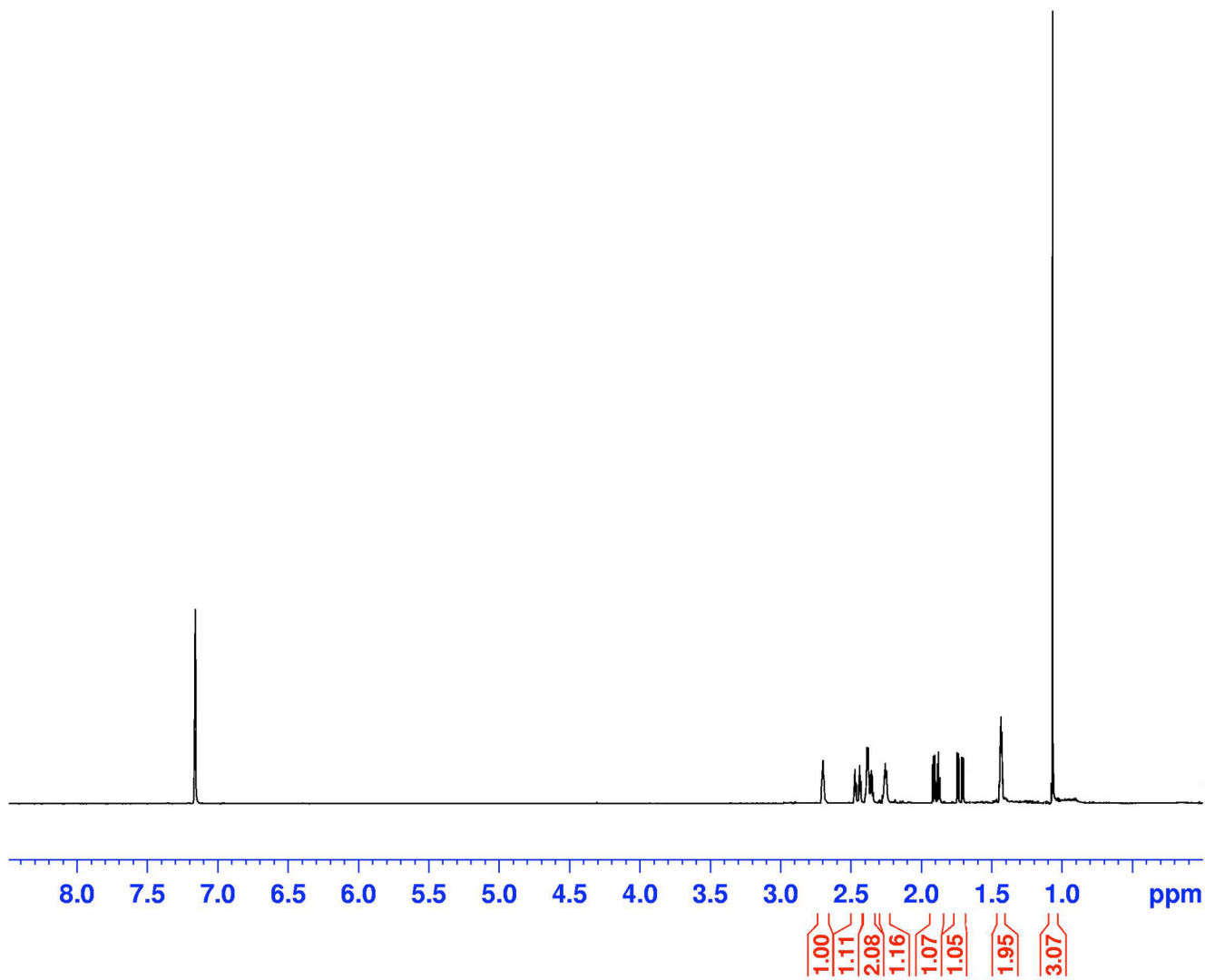
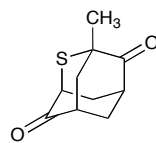
**1-methylbicyclo[3.3.1]nona-2,6-dione (3)**

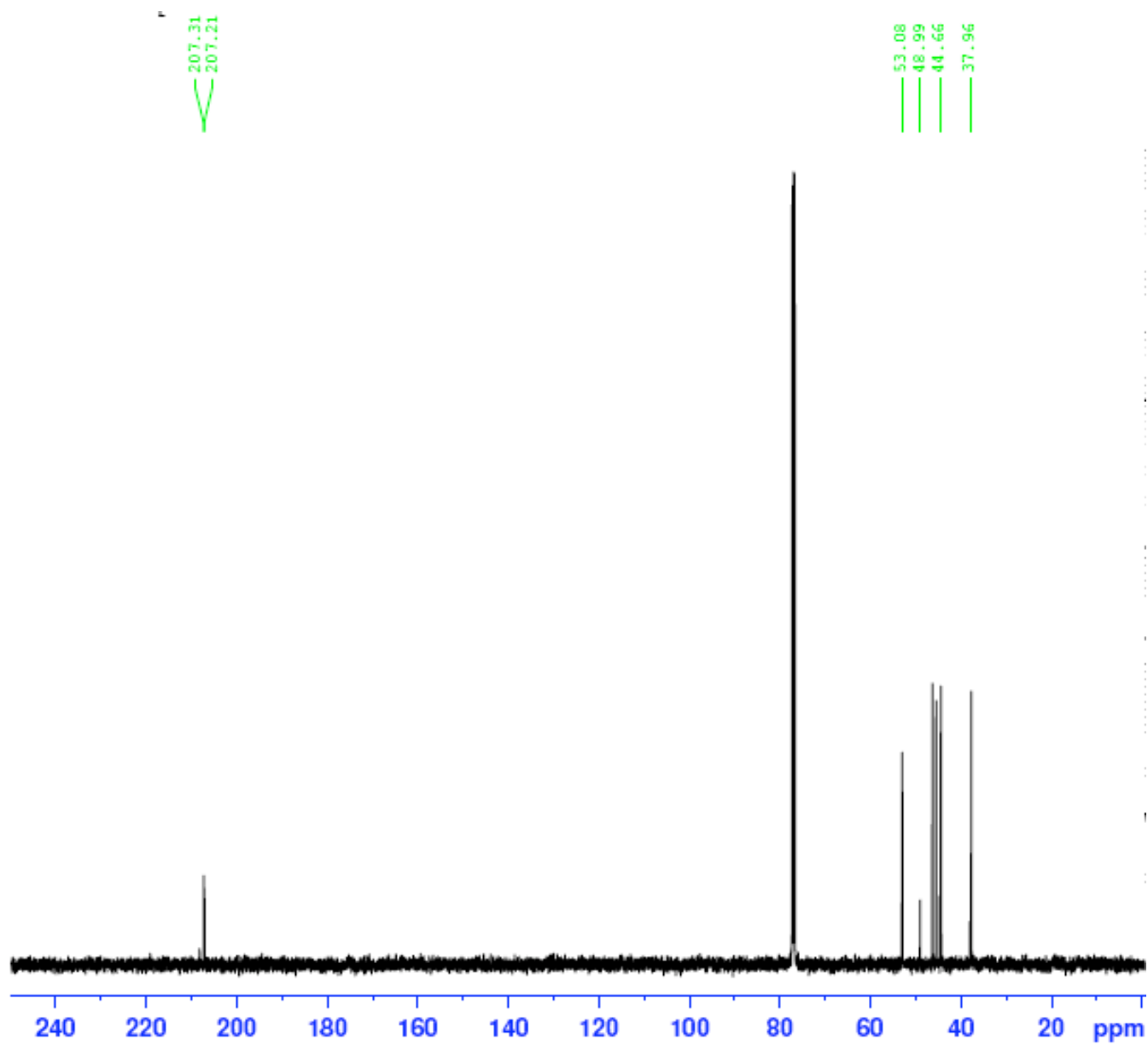
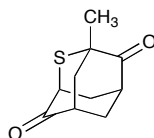




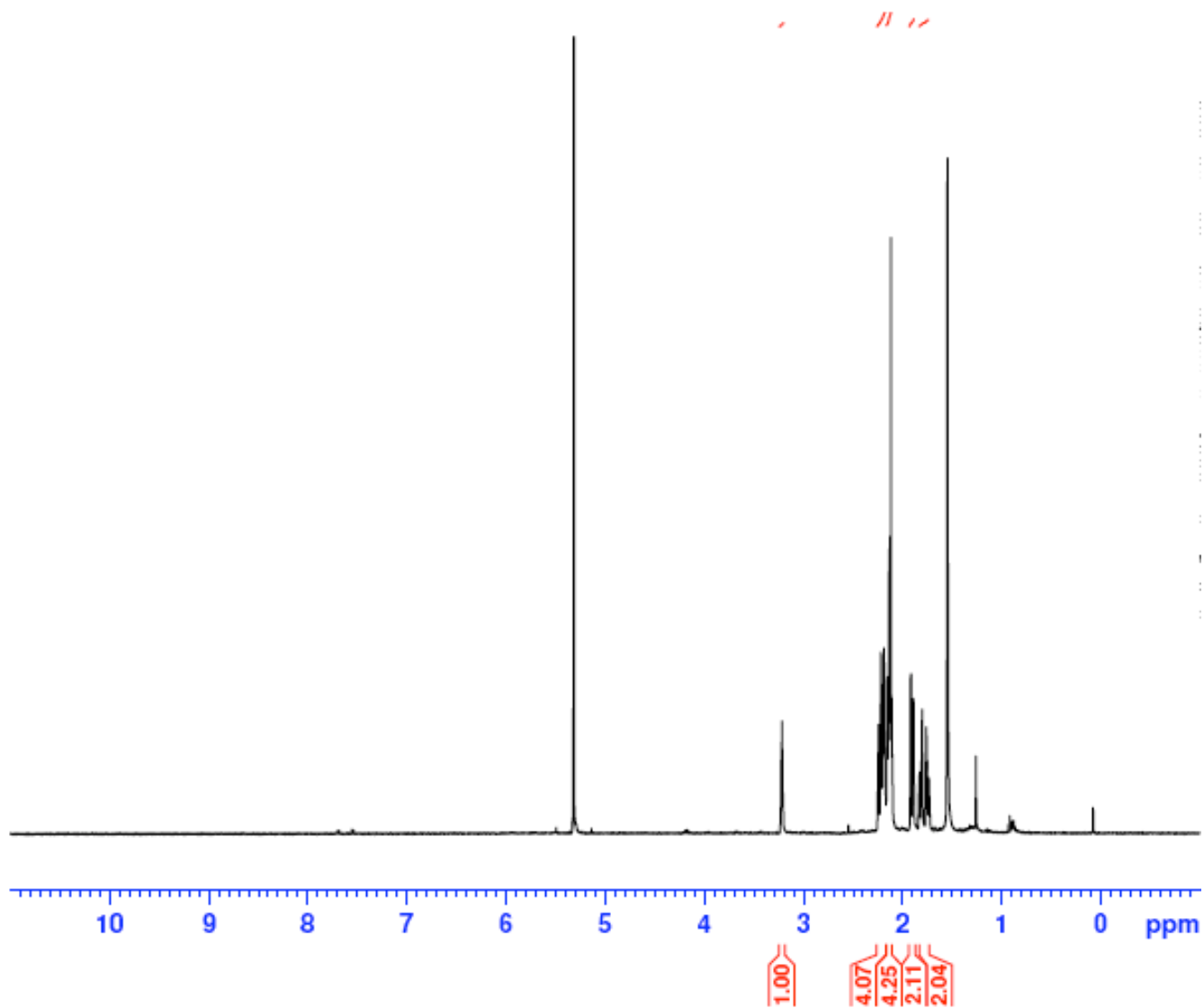
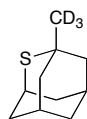


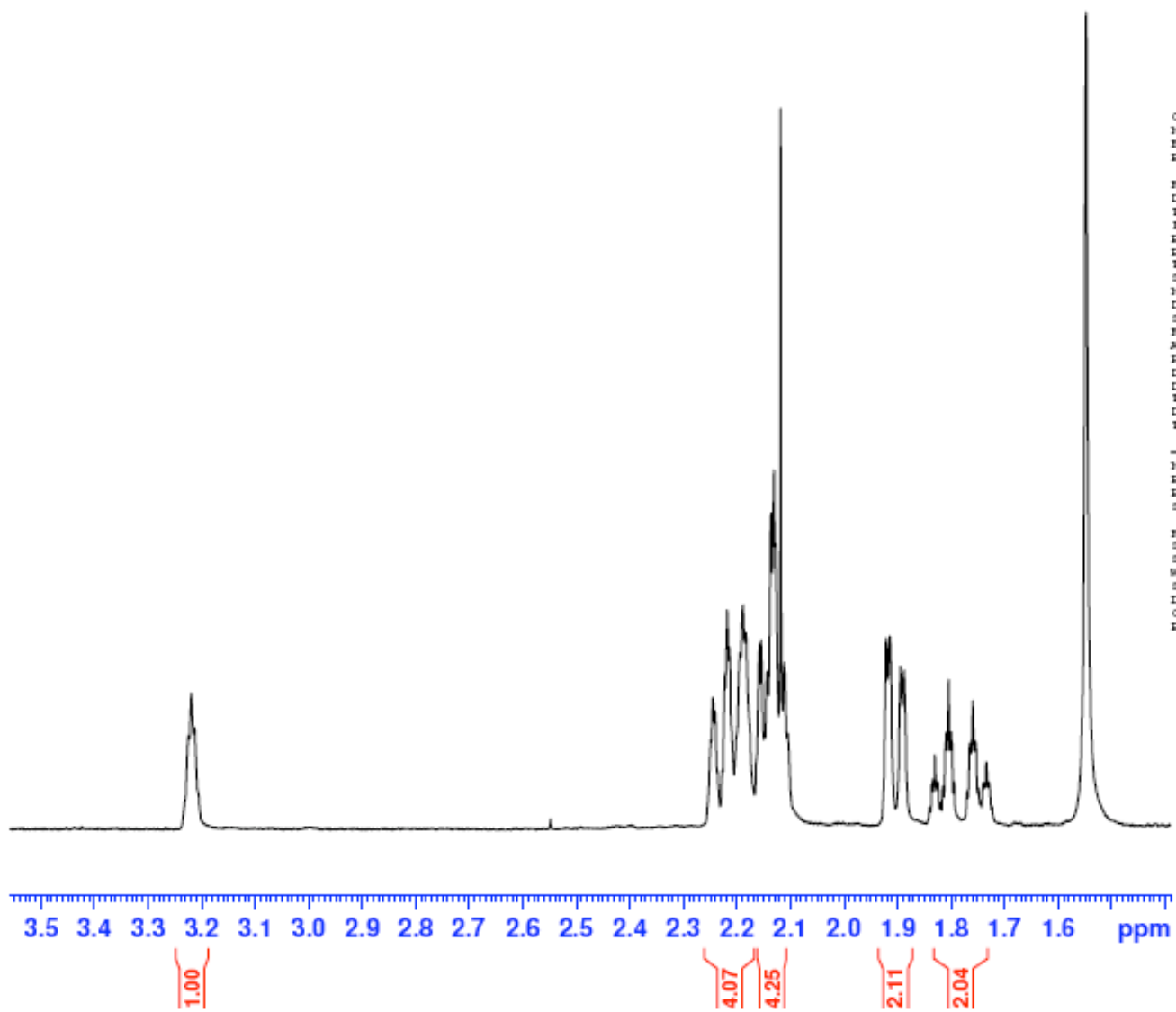
**1-methyl-2-thiaadamantane-4,8-dione (5)**

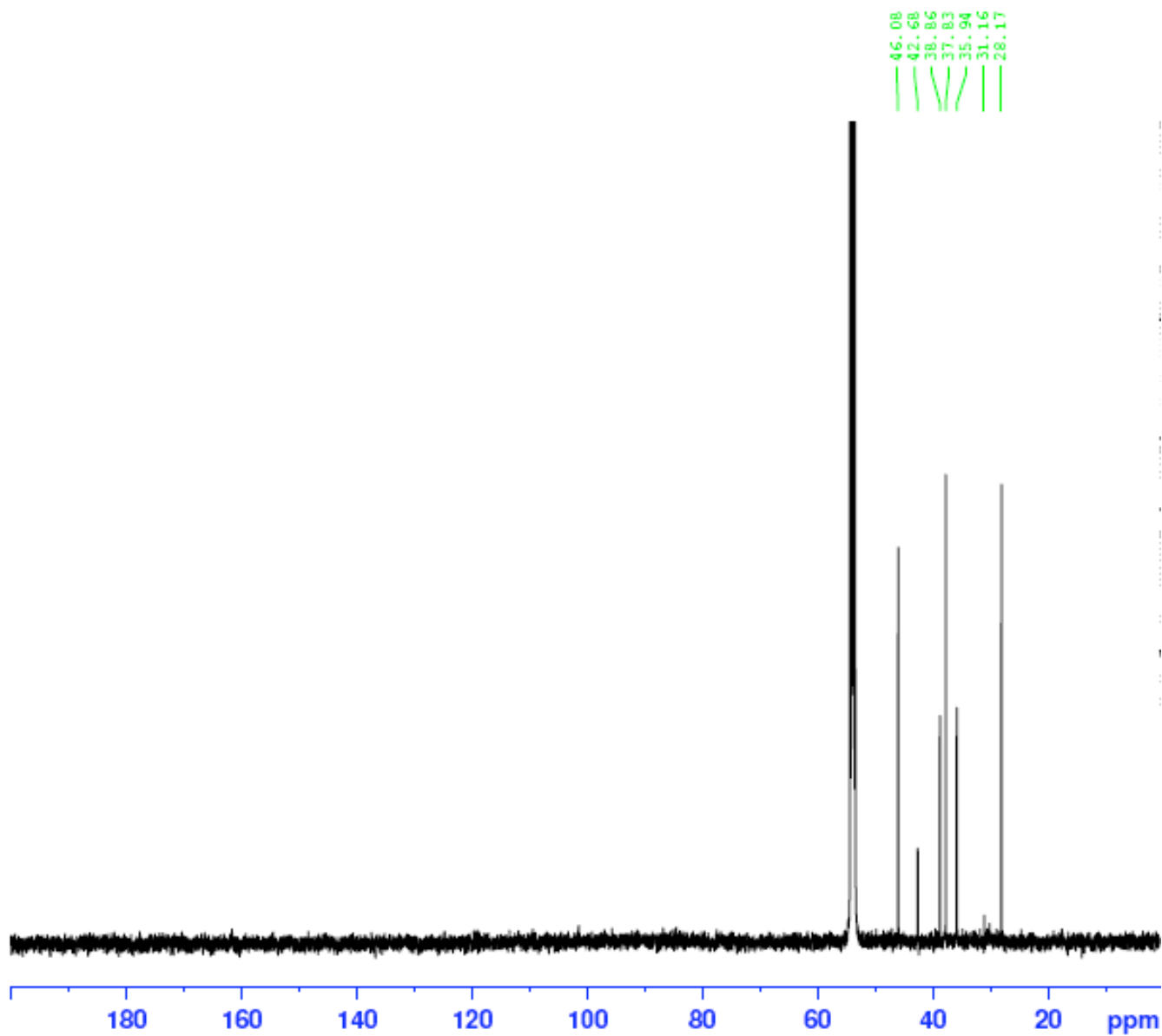
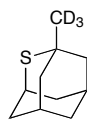




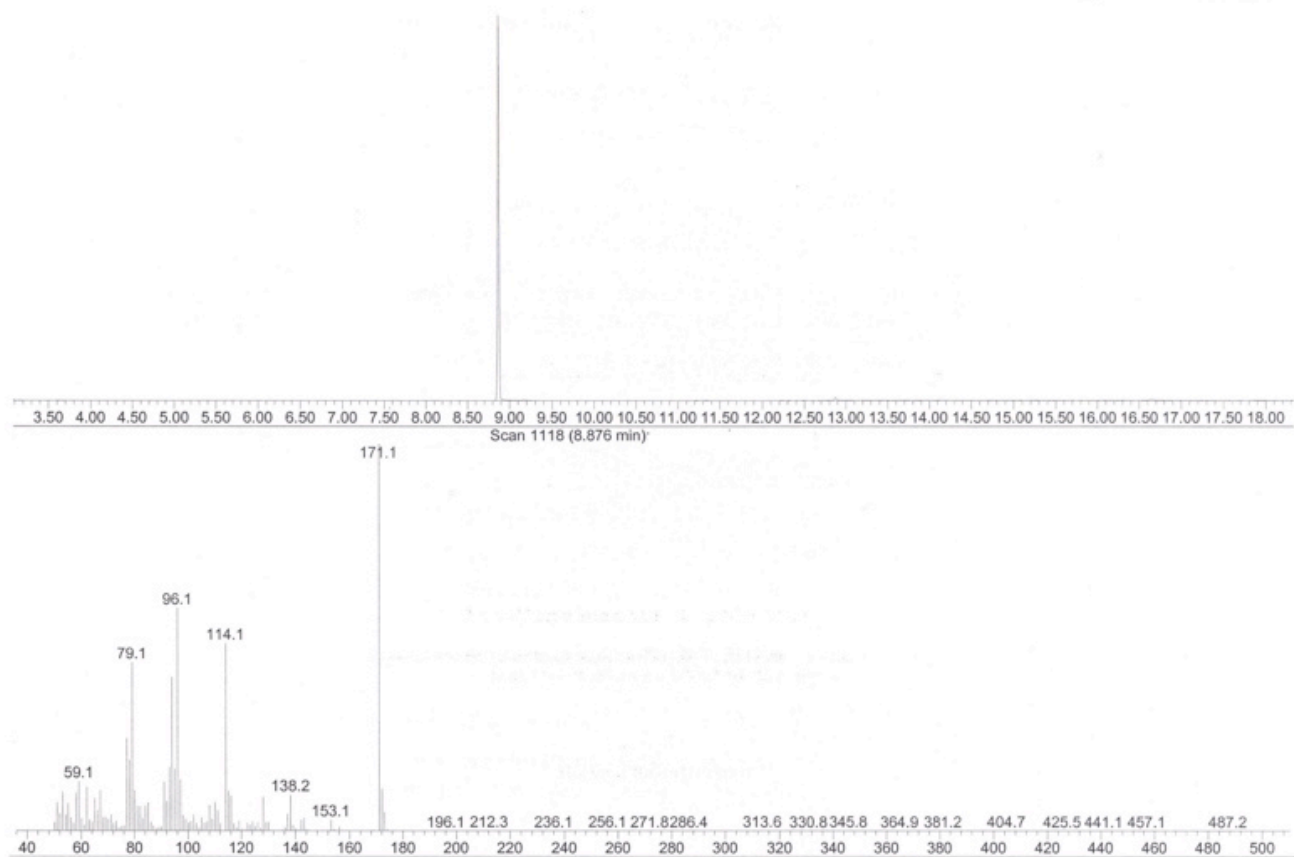
1-(methyl-d3)-2-thiaadamantane (6b)







GC-MS data for 1-(methyl-d3)-2-thiaadamantane (6b)



References

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- (2) W. Ding, C. Xiao, B. Li, R. Zhang, C. Lu, *Fine Chemicals* 1999, **16**, 60.
- (3) (a) B. de Vries, *J. Am. Oil Chem. Soc.* 1963, **40**, 184; (b) T. S. Li, J. T. Li, H. Z. Li, *J. Chrom. A* 1995, **715**, 372; (c) C. M. Williams, L. N. Mander, *Tetrahedron* 2001, **57**, 425.