Electronic Supplementary Material (ESI) for ChemComm.

A Practical Synthesis of 1,3-Disubstituted Cubane Derivatives

Supporting Information

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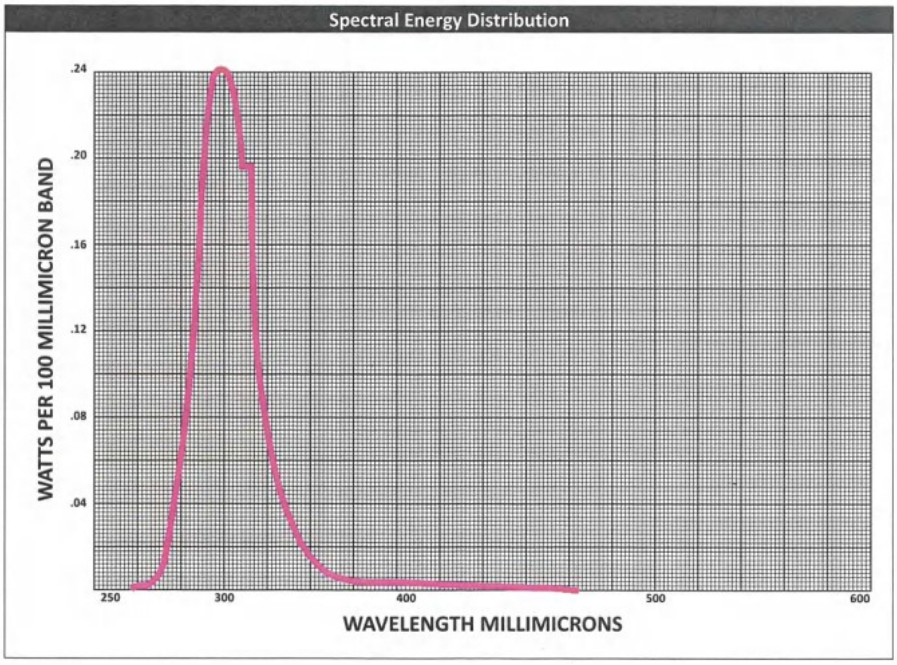
1. Synthetic Procedures and Analytical Data of New Compounds

1.1 General Information

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Merck or Fluorochem. Anhydrous solvents used in reactions were purchased from Acros Organics equipped with AcroSeal™ and all other solvents used were of reagent grade. Brine refers to a saturated aqueous solution of sodium chloride, and water refers to deionised water. Reaction vessels were oven-dried and cooled under an argon atmosphere prior to use and experiments were performed under argon gas.

Photochemical reactions were performed in Duran phototubes (50-mL volume) using a Rayonet RPR-100 photochemical batch reactor equipped with 16 × 8W RPR-3000A lamps, for which the emission is centred at 300 nm – the spectral energy distribution (revised 5/9/2017) is reproduced below as provided by the manufacturer (The Southern New England Ultraviolet Company). When operating, the approximate temperature inside the reactor chamber is 40 °C.



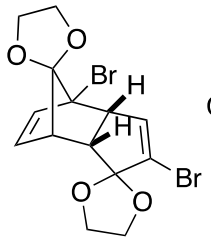
Reactions were monitored by thin-layer chromatography (TLC) and/or ^{1}H NMR spectroscopic analysis (with suppression of solvent signals). Analytical TLC was carried out using Merck pre-coated aluminum-backed TLC silica gel plates (silica gel 60 F_{254}) and the plates were visualised by UV light (254 nm) and by staining with either potassium permanganate, aqueous acidic ammonium

molybdate(IV) or bromocresol green. Normal phase flash column chromatography on silica gel was carried out using silica gel from VWR (40-63 microns).

^{1}H NMR spectroscopic data were obtained on a 400 MHz instruments and ^{13}C{^{1}H} NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemical shifts are reported in parts per million (δ) relative to residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.2 ppm; central line), residual d_5-DMSO (δ_H = 2.50 ppm) and d_6-DMSO (δ_C = 39.52 ppm; central line). The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were performed on a Sanyo Gallenkamp capillary melting point apparatus and are uncorrected. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer.

1.2 Synthetic Procedures

rac-(3a'*S*,4'*S*,7'*S*,7a'*R*)-2',4'-Dibromo-3a',4',7',7a'-tetrahydrodispiro[[1,3]dioxolane-2,1'-[4,7]methanoinden-8',2''-[1,3]dioxolane] S1



$C_{14}H_{14}Br_2O_4$
406.07

Bisketal **S1** was prepared using a modification of the reported procedure.[1] Bromine (256 mL, 5.02 mol) was added dropwise over 2 h to a stirred solution of cyclopentanone ethylene ketal[2] (200 g, 1.56 mol) in 1,4-dioxane (800 mL) in a 5 L 3-neck round-bottomed flask at 10 °C under argon. The resulting solution was stirred at room temperature for 48 h, whilst purging the headspace with nitrogen gas (the output was passed through a scrubber containing a 5% (w/v) aqueous solution of NaOH). The resulting solution was cooled to 0 °C, a solution of NaOH (347 g, 8.68 mol) in MeOH

(1.7 L) was added dropwise over 4 h, and the resulting suspension was heated at reflux for 24 h, then allowed to cool to room temperature. The reaction mixture was poured into an ice-water slurry (4 L) and the resulting precipitate was collected under vacuum, washed with water (5 x 200 mL) dried on the filter and then at 50 °C until constant weight to give **S1** (257 g, 1.26 mol, 81%) as a beige solid, which was used without further purification.

m.p. 171-174 °C

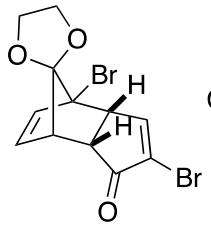
IR (ATR): v (cm^{-1}) = 2980 (w), 2890 (w), 1616 (m), 1473 (m).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.19 (dd, *J* = 6.4, 3.7 Hz, 1H, C*H*=CHCBr), 6.06 (d, *J* = 2.4 Hz, 1H, C*H*=CBr), 5.83 (dd, *J* = 6.4, 1.1 Hz, 1H, CH=C*H*CBr), 4.25-4.12 (m, 4H, CHO), 4.02-3.87 (m, 4H, CHO), 3.50 (dd, *J* = 7.4, 2.4 Hz, 1H, C*H*-CH=CBr), 3.07 (dd, *J* = 7.4, 4.7 Hz, 1H, C*H*CH-CH=CBr), 2.73-2.71 (m, *J* = 1H, C*H*CH=CHCBr).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 134.4 (*C*H=CBr), 132.9 (CH=*C*HCBr), 132.4 (*C*H=CHCBr), 127.9 (OCO), 125.9 (OCO), 115.5 (=CBr), 67.6 (CBr), 66.3 (CH_2O), 66.1 (CH_2O), 65.2 (CH_2O), 65.1 (CH_2O), 55.6 (*C*H-CH=CBr), 49.4 (*C*HCHCH=CBr), 47.1 (*C*HCH=CHCBr).

The spectroscopic data are consistent with those previously reported.[1]

***rac*-(3a'*S*,4'*S*,7'*S*,7a'*R*)-2',4'-Dibromo-3a',4',7',7a'-tetrahydro-1'H-spiro[[1,3]dioxolane-2,8'-[4,7]methanoinden]-1'-one 9a**



$C_{12}H_{10}Br_2O_3$
362.02

Monoketal **9a** was prepared using a modification of the reported procedure.[2] Concentrated HCl (150 mL) was added portionwise over 30 mins to a stirred suspension of **S1** (149.5 g, 368 mmol) in THF (750 mL) at room temperature. The resulting suspension was stirred at room temperature

for 24 h, then poured into a 5% (w/v) aqueous solution of $NaHCO_3$ (4.5 L). After stirring for 1 h at room temperature, the suspension was filtered through a Buchner funnel and the resulting solid was washed with water (3 × 150 mL), dried on the filter under vacuum for 2 h, allowed to stand overnight, the dried over Drierite in a desiccator for 48 h. The solid was recrystallized from PhMe (200 mL), with a hot filtration through a Gooch sintered funnel (porosity 1). The flask was washed with hot toluene (50 mL), and the washings were filtered through the sintered funnel into the original filtrate. The filtrate was allowed to cool to room temperature, then in the refrigerator for 12 h. The resulting crystals were collected on a Buchner funnel and washed with pentane (3 x 100 mL) to give **9a** (110.3 g, 305 mmol, 83%) as an off-white crystalline solid.

m.p. 173-175 °C

TLC: R_f **9a** = 0.35 (CH_2Cl_2), R_f **9b** = 0.35 (CH_2Cl_2); R_f **9a** = 0.41 (2:1 hexanes:TBME), R_f **9b** = 0.20 (2:1 hexanes:TBME); [UV and/or $KMnO_4$].

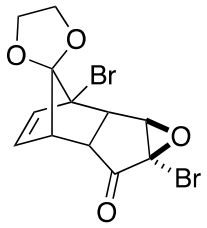
IR (ATR): v (cm^{-1}) = 2952 (w), 1713 (s, C=O), 1583 (s), 1482 (m).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 3.0, 0.5 Hz, 1H, C*H*=CBr), 6.00 (dd, *J* = 6.5, 3.5 Hz, 1H, C*H*=CHCBr), 5.92 (dd, *J* = 6.5, 1.5 Hz, 1H, CH=C*H*CBr), 4.27-4.16 (m, 2H, 2 x CHO), 4.07-4.03 (m, 1H, CHO), 3.98-3.93 (m, 1H, CHO), 3.64 (dd, *J* = 5.5, 3.0 Hz, 1H, C*H*-CH=CBr), 3.19 (t, *J* = 5.5 Hz, 1H, C*H*CHOH), 3.07 (dddd, *J* = 5.5, 3.5, 1.5, 0.5 Hz, 1H, OH).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 199.9 (C=O), 158.3 (*C*H=CBr), 134.9 (CH=*C*HCBr), 131.1 (=CBr or OCO), 130.5 (*C*H=CHCBr), 126.9 (=CBr or OCO), 66.6 (CH_2O), 66.5 (=CH*C*Br), 65.9 (CH_2O), 52.1 (*C*HCH=CBr), 48.2 (*C*HCH=CHCBr), 47.4 (*C*HCHOH).

The spectroscopic data are consistent with those previously reported.[3]

***rac*-(1a'*R*,1b'*S*,2'*S*,5'*S*,5a'*R*,6a'*S*)-2',6a'-Dibromo-1a',1b',2',5',5a',6a'-hexahydro-6'H-spiro[[1,3]dioxolane-2,7'-[2,5]methanoindeno[1,2-b]oxiren]-6'-one 12**



$C_{12}H_{10}Br_2O_4$
378.02

A suspension of enone **9a** (110 g, 304 mmol) in methanol (1.1 L) was cooled to 0 °C. NaOH (66 mL of a 0.5 M aqueous solution) was added, then H_2O_2 (44 mL of a >50% aqueous solution) was added dropwise at 0 °C via Pasteur pipette (CAUTION: concentrated solutions of H_2O_2 are potentially explosive, and metal needles should never be used for the transfer of such solutions). The resulting mixture was allowed to warm slowly to room temperature over 18 hours, then water (2.2 L) was added. The resulting suspension was filtered, and the collected solid was washed with water (3 x 100 mL), then dried on the filter to give epoxy ketone **12** (114 g, 302 mmol, 99%) as a white solid.

m.p. 150-151 °C.

TLC: R_f = 0.40 (CH_2Cl_2); [$KMnO_4$].

IR (ATR): ν (cm^{-1}) = 2991 (w), 2903 (w), 1752 (s, C=O), 1475 (m).

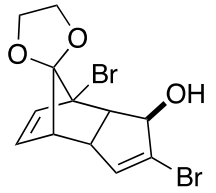
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22 (dd, *J* = 6.5, 1.4 Hz, 1H, CH=C*H*CBr), 6.14 (dd, *J* = 6.5, 3.6 Hz, 1H, C*H*=CHCBr), 4.25-4.16 (m, 2H, CH_2O), 4.04-3.98 (m, 1H, CH_AH_BO), 3.97-3.91 (m, 2H, CH_AH_BO and CHO) 3.46 (d, *J* = 7.0 Hz, 1H, CH), 3.18-3.14 (m, 1H, CH-C=O), 3.02-3.00 (m, 1H, C*H*CH-C=O).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5 (C=O), 136.1 (=CH), 133.0 (=CH), 126.2 (OCH_2O), 69.9 (CBr), 66.7 (CH_2O), 66.0 (CH_2O), 64.5 (OCBr), 64.4 (CHO), 48.6 (CH), 48.2 (CH), 47.4 (CH).

MS (APCI): *m*/*z* (%) = 381 (50) [($^{81}Br_2$-M)$^+$], 379 (100) [($^{81}Br^{79}Br$-M)$^+$], 377 (50) [($^{79}Br_2$-M)$^+$].

HRMS (APCI): calcd for $C_{12}H_{10}Br_2O_4$ [($^{79}Br_2$-M)$^+$], calcd: 376.9005, found: 376.9023.

***rac*-(1'R,3a'S,4'S,7'S,7a'S)-2',7'-dibromo-3a',4',7',7a'-tetrahydro-1'H-spiro[[1,3]dioxolane-2,8'-[4,7]methanoinden]-1'-ol 13**



$C_{12}H_{12}Br_2O_3$
364.03

Hydrazine hydrate (5.9 mL, 120 mmol) was added dropwise to a stirred suspension of epoxy ketone **12** (30.2 g, 79.9 mmol) and Amberlite IRA-402 (Cl form) resin (3.00 g) in ethanol (600 mL). The resulting mixture was stirred at 50 °C for 24 h, then a second portion of hydrazine hydrate (2.0 mL, 40 mmol) was added dropwise. The resulting mixture was stirred at 50 °C for a further 9 h, then a third portion of hydrazine hydrate (2.0 mL, 40 mmol) was added dropwise. After heating at 50 °C for a further 15 h, the reaction mixture was filtered through Celite, washing with ethanol (3 x 20 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (31 × 6 cm) eluting with $CHCl_3$ (500 mL) then CH_2Cl_2 (500 mL) then CH_2Cl_2:Et_2O (98:2) gave **13** (14.8 g, 40.6 mmol, 51%) as a white solid.

m.p. 126-127 °C.

TLC: R_f = 0.16 (CH_2Cl_2); [$KMnO_4$].

IR (ATR): ν (cm^{-1}) = 3423 (m, OH), 2980 (w), 2920 (w), 2889.

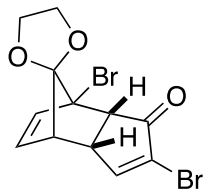
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (dd, *J* = 6.6, 1.2 Hz, 1H, CH=C*H*CBr), 6.05 (dd, *J* = 6.6, 3.7 Hz, 1H, C*H*=CHCBr), 5.82 (dd, *J* = 2.2, 0.9 Hz, 1H, C*H*=CBr), 4.27-4.16 (m, 3H, CH_2O and CHO), 4.04-3.99 (m, 1H, CH_AH_BO), 3.94 – 3.89 (m, 1H, CH_AH_BO), 3.58 (ddd, *J* = 10.2, 5.0, 2.7 Hz, 1H, C*H*-C=O), 3.11 (dd, *J* = 7.7, 2.2 Hz, 1H, C*H*CH-C=O), 2.65 (ddd, *J* = 4.7, 3.7, 1.6 Hz, 1H, C*H*-CHO), 1.97 (s, OH)

^{13}C NMR (101 MHz, $CDCl_3$): δ 134.7 (=CH), 134.2 (=CH), 133.5 (=CH), 126.5 (=CBr), 126.5 (OCH_2O), 79.6 (CHO), 68.1 (CBr), 66.5 (CH_2O), 65.6 (CH_2O), 57.0 (CH), 52.7 (CH), 47.1 (CH).

MS (APCI): *m*/*z* (%) = 367 (50) [($^{81}Br_2$-M + H)$^+$], 365 (100) [($^{81}Br^{79}$Br-M + H)$^+$], 363 (50) [($^{79}Br_2$-M + H)$^+$].

HRMS (APCI): calcd for $C_{12}H_{12}O_3Br_2$ [($^{79}Br_2$-M + H)$^+$], calcd: 362.9226, found: 362.9232.

***rac*-(3a'*S*,4'*S*,7'*S*,7a'*S*)-2',7'-Dibromo-3a',4',7',7a'-tetrahydro-1'H-spiro[[1,3]dioxolane-2,8'-[4,7]methanoinden]-1'-one 9b**



$C_{12}H_{10}Br_2O_3$
362.02

Dess-Martin periodinane (20.7 g, 48.8 mmol) was added portion-wise over 5 minutes to a solution of allylic alcohol **13** (14.8 g, 40.6 mmol) in CH_2Cl_2 (300 mL) at room temperature under argon. The resulting suspension was stirred at room temperature for 3 h, until TLC analysis indicated complete consumption of the starting material (eluent CH_2Cl_2-Et_2O (98:2). A saturated aqueous solution of $NaHCO_3$ (150 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (150 mL) were added sequentially, and the resulting mixture was stirred for 3 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (18 × 6 cm) eluting with $CHCl_3$ then CH_2Cl_2 gave **9b** (13.5 g, 37.4 mmol, 92%) as a white solid.

m.p. 127-128 °C.

TLC: R_f = 0.33 ($CHCl_3$); [UV and/or $KMnO_4$].

IR (ATR): v (cm^{-1}) = 2985 (w), 2896 (w), 1716 (s, C=O), 1580 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 2.9 Hz, 1H, C*H*=CBr), 6.03 (dd, *J* = 6.5, 1.4 Hz, 1H, CH=C*H*CBr), 5.94 (dd, *J* = 6.5, 3.7 Hz, 1H, C*H*=CHCBr), 4.32-4.20 (m, 2H, CH_2O), 4.08-4.03 (m, 1H, CH_AH$_B$O), 3.98 – 3.94 (m, 1H, CH$_A$$H_B$O), 3.66 (ddd, *J* = 5.7, 4.6, 2.9 Hz, 1H, C*H*-C=O), 3.22 (d, *J* = 5.7 Hz, 1H, CH), 2.85 (ddd, *J* = 4.6, 3.7, 1.4 Hz, 1H, CH).

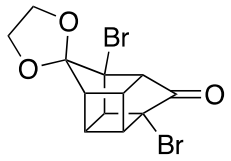
^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1 (C=O), 158.9 (C*H*=CBr), 135.0 (=CH), 130.7 (=CH), 130.3 (=CBr), 127.4 (OCH_2O), 66.8 (CBr), 66.3 (CH_2O), 66.2 (CH_2O), 52.1 (CH), 47.6 (CH), 45.6 (CH).

MS (APCI): *m*/*z* (%) = 365 (50) [($^{81}Br_2$-M + H)$^+$], 363 (100) [($^{81}Br^{79}Br$-M + H)$^+$], 361 (50) [($^{79}Br_2$-M + H)$^+$].

HRMS (ESI): calcd for $C_{12}H_{10}Br_2O_3$ [($^{79}Br_2$-M + H)$^+$], calcd: 360.9069, found: 360.9059.

The spectroscopic data are consistent with those previously reported.[4]

Photocycloadduct 14



$C_{12}H_{10}Br_2O_3$
362.02

A solution of enone **9b** (10.9 g, 30.0 mmol) in acetone (600 mL) was distributed between twelve 50-mL Duran phototubes, and each tube was bubbled with argon for 15 minutes. The tubes were placed in a Rayonet RPR-100 photoreactor and irradiated simultaneously at 300 nm for 16 hours. The contents of the tubes were combined and evaporated under reduced pressure to give the crude product **14** (10.9 g, quantitative) as an off-white solid, which was taken on to the next step without purification.

m.p. 168-170 °C.

TLC: product degrades on silica

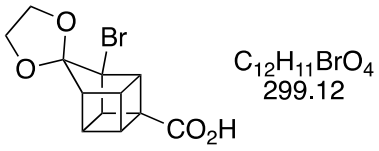
IR (ATR): v (cm^{-1}) = 2991 (w), 1685 (s, C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34-4.26 (m, 2H, CH_2O), 4.04-3.98 (m, 2H, CH_2O), 3.55 (ddd, *J* = 8.9, 7.0, 4.2 Hz, 1H, CH), 3.44 – 3.40 (m, 1H, CH), 3.39 – 3.34 (m, 1H, CH), 3.12 (ddd, *J* = 6.8, 4.8, 4.2 Hz, 1H, CH), 3.00 (dd, *J* = 6.2, 2.3 Hz, 1H, CH), 2.78 – 2.75 (m, 1H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4 (C=O), 121.7 (OCH_2O), 66.7 (CH_2O), 66.3 (CH_2O), 63.6 (CBr), 55.3 (CH), 51.0 (CH), 41.7 (CH), 41.5 (CH), 40.3 (CH), 38.5 (CH).

The spectroscopic data are consistent with those previously reported.[4]

1-Bromospiro[pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-9,2'-[1,3]dioxolane]-5-carboxylic acid 15



$C_{12}H_{11}BrO_4$
299.12

The crude cycloadduct (**14**) obtained in the previous step (10.9 g, 30.0 mmol) was suspended in a 10% (w/v) aqueous solution of KOH (250 mL). The resulting mixture was heated under reflux for 20 hours, then allowed to cool to room temperature. Concentrated HCl (~60 mL) was added until pH 1 was reached, and the mixture was extracted with $CHCl_3$ (5 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography on silica (ϕ 6 × 17 cm) eluting with TBME gave **15** (7.12 g, 23.8 mmol, 81%) as an off-white solid.

m.p. 175-177 °C.

TLC: R_f = 0.65 (TBME); [bromocresol green].

IR (ATR): ν (cm^{-1}) = 2998 (w), 1721 (s, C=O), 1670 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29-4.26 (m, 2H, CH_2O), 4.02-3.98 (m, 2H, CH_2O), 3.89-3.87 (m, 2H, 2 x CH), 3.64-3.56 (m, 3H, 3 x CH), 2.96-2.94 (m, 1H, CH).

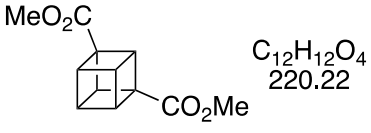
^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8 (C=O), 124.6 (OCH_2O), 66.3 (CH_2O), 62.7 (CH_2O), 52.3 (CBr), 50.9 (*C*-CO_2H), 43.6 (CH), 42.6 (CH), 40.2 (CH).

MS (ESI): *m*/*z* (%) = 299 (100) [(^{81}Br-M – H)$^-$], 297 (100) [(^{79}Br-M – H)$^-$].

HRMS (ESI): calcd for $C_{12}H_{11}BrO_4$ [(^{79}Br-M – H)$^-$], calcd: 296.9768, found: 296.9761.

The spectroscopic data are consistent with those previously reported.[4]

Dimethyl cubane-1,3-dicarboxylate **11**



A solution of acetal **15** (7.12 g, 23.8 mmol) in trifluoroacetic acid (100 mL) was heated at reflux for 72 hours, then evaporated under reduced pressure to give the crude keto acid (**S2**), which was suspended in a 25% (w/v) aqueous solution of NaOH (100 mL), and the resulting mixture was heated under reflux for 3.5 hours, then allowed to cool to room temperature. Concentrated HCl was added dropwise at 0 °C until pH 1 was reached, and the resulting mixture was washed with CH_2Cl_2 (50 mL). The aqueous layer was saturated with NaCl and extracted with EtOAc (5 x 75 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude diacid **5**. (NB **5** is known to be volatile,[5] and it should not be dried under high vacuum). The crude diacid product was suspended in methanol (100 mL), Dowex 50WX8 resin (2.00 g) was added, and the resulting mixture was heated at reflux for 18 hours, then filtered through cotton. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (ϕ 4 × 30 cm) eluting with CH_2Cl_2 then CH_2Cl_2-Et_2O (98:2) gave **11** (2.73 g, 12.4 mmol, 52% across three steps) as a white solid.

NB Diester **11** is difficult to observe by TLC, as it is not UV active and does not stain well with standard visualising reagents. Faint staining can be achieved using *p*-anisaldehyde stain, but often it was more convenient to identify the product-containing fractions through ^{1}H NMR spectroscopy (with solvent suppression).

m.p. 121-123 °C.

TLC: R_f = 0.61 (CH_2Cl_2); [*p*-anisaldehyde].

IR (ATR): ν (cm^{-1}) = 2983 (w), 1714 (C=O).

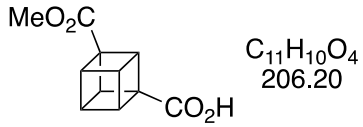
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48-4.44 (m, 2H, CH), 4.20 (tt, 2H, *J* = 5.0, 2.4 Hz, CH), 4.01-3.98 (m, 2H, CH), 3.71 (s, 6H, OMe).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8 (C=O), 53.4 (*C*H-CO_2Me), 51.8 (CH), 51.3 (CH), 50.0 (CH), 43.0 (OMe).

HRMS (ESI): calcd for $C_{12}H_{12}O_4$ [$(M + H)^+$], calcd: 221.0808, found: 221.0797.

The spectroscopic data are consistent with those previously reported.[4,5]

3-(Methoxycarbonyl)cubane-1-carboxylic acid 17



NaOH (2.4 mL of a 2.5 M aqueous solution) was added dropwise at room temperature to a stirred solution of diester **11** (1.31 g, 5.95 mmol) in MeOH (39 mL), and the resulting solution was stirred at room temperature for 24 h. The organic solvent was evaporated under reduced pressure and the residue was diluted with water (20 mL) then washed with CH_2Cl_2 (2 × 10 mL). Concentrated HCl was added dropwise at 0 °C until pH 1 was reached, and the resulting mixture was extracted with EtOAc (6 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (ϕ 2 × 20 cm) eluting with CH_2Cl_2-Et_2O (98:2) then TBME gave **17** (956 mg, 4.64 mmol, 78%) as a white solid.

m.p. 101-104 °C.

TLC: R_f = 0.62 (TBME); [bromocresol green].

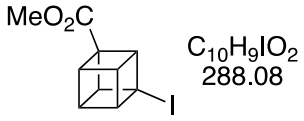
IR (ATR): v (cm^{-1}) = 2992 (w), 1754 (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51-4.49 (m, 2H, CH), 4.28-4.20 (m, 2H, CH), 4.04-4.00 (m, 2H, CH), 3.72 (s, 3H, OMe).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.8 (C=O), 171.7 (C=O), 53.5 (C), 53.2 (C), 51.9 (OMe), 51.2 (CH), 50.1 (CH), 50.0 (CH), 43.0 (CH).

HRMS (ESI): calcd for $C_{11}H_{10}O_4$ [(M – H)$^-$], calcd: 205.0506, found: 205.0503.

Methyl 3-iodocubane-1-carboxylate 18



$C_{10}H_9IO_2$
288.08

Iodobenzene diacetate (469 mg, 1.45 mmol) and I_2 (369 mg, 1.45 mmol) were added to a stirred solution of acid **17** (100 mg, 0.48 mmol) in benzene (8 mL) at room temperature under argon. The resulting solution was heated at reflux for 7 h, then allowed to cool to room temperature. Hexane (8 mL) was added, and the mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 10 mL), water (10 mL), brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (ϕ 2 × 15 cm) eluting with CH_2Cl_2 gave **18** (116 mg, 0.40 mmol, 83%) as a colourless oil.

TLC: R_f = 0.44 (CH_2Cl_2); [phosphomolybdic acid].

IR (ATR): ν (cm^{-1}) = 2996 (m), 2946 (w), 1719 (C=O).

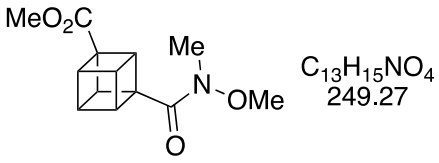
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46-4.41 (m, 2H, CH), 4.36-4.32 (m, 1H, CH), 4.22-4.17 (m, 1H, CH), 4.13-4.07 (m, 2H, CH), 3.65 (s, 3H, OMe).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9 (C=O), 58.7 (CH), 57.8 (CH), 56.8 (*C*-CO_2Me), 51.9 (OMe), 50.0 (CH), 45.8 (CH), 33.1 (C-I).

MS (ESI): *m*/*z* (%) = 289 (15) [(M + H)$^+$], 272 (65), 250 (100).

HRMS (ESI): calcd for $C_{10}H_9IO_2$ [M$^+$], calcd: 287.9647, found: 287.9648.

Methyl 3-(methoxy(methyl)carbamoyl)cubane-1-carboxylate 19



CDI (94 mg, 0.58 mmol) and MeNH(OMe)·HCl (47 mg, 0.48 mmol) were added to a stirred solution of acid **17** (100 mg, 0.48 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 18 h, then evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (ϕ 2 × 20 cm) eluting with CH_2Cl_2 then CH_2Cl_2-Et_2O (4:1) gave **19** (105 mg, 0.42 mmol, 87%) as a colourless oil.

TLC: R_f = 0.33 (4:1 CH_2Cl_2-Et_2O); [phosphomolybdic acid].

IR (ATR): ν (cm^{-1}) = 2994 (w), 1720 (C=O. ester), 1646 (C=O, amide).

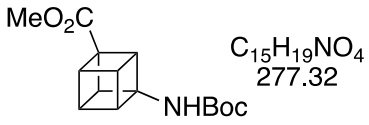
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47-4.43 (m, 2H, CH), 4.23-4.16 (m, 2H, CH), 3.97-3.92 (m, 2H, CH), 3.684 (s, 3H, OMe), 3.678 (s, 3H, OMe), 3.17 (s, 3H, NMe).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5 (C=O, amide), 172.0 (ester), 61.2 (N-OMe), 55.2 (C), 53.4 (C), 51.7 and 51.6 (CH and OMe), 49.5 (CH), 49.4 (CH), 42.8 (CH), 32.6 (NMe).

MS (ESI): *m*/*z* (%) = 272 (90) [$(M + Na)^+$], 250 (100) [$(M + H)^+$].

HRMS (ESI): calcd for $C_{13}H_{15}NO_4$ [M^+], calcd: 249.1001, found: 249.1009.

Methyl 3-((*tert*-butoxycarbonyl)amino)cubane-1-carboxylate 20



Diphenylphosphorylazide (0.1 mL, 0.48 mmol) and Et_3N (70 μL, 0.48 mmol) were added to a suspension of **17** (100 mg, 0.48 mmol) in *tert*-butanol (5 mL) under argon, and the resulting mixture was heated at reflux for 2 h. The mixture was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (ϕ 2 × 20 cm) eluting with hexane-EtOAc (85:15) gave **20** (94 mg, 0.34 mmol, 71%) as a white solid.

m.p. 120-121 °C

TLC: R_f = 0.21 (85:15 hexane-EtOAc); [phosphomolybdic acid].

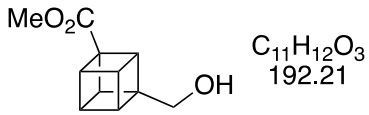
IR (ATR): v (cm^{-1}) = 3343 (NH), 2993 (w), 1720 (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (br s, 1H, NH), 4.28-4.25 (m, 2H, CH), 4.16 (ddd, *J* = 7.1, 4.7, 2.2 Hz, 2H, CH), 3.87-3.83 (m, 2H, CH), 3.69 (s, 3H, OMe), 1.44 (s, 9H, C*Me*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4 (C=O, amide), 172.0, 77.4 (O*C*Me$_3$), 64.0 (C), 54.4 (C), 53.7 (CH), 51.7 (OMe), 50.3 (CH), 40.1 (CH), 28.5 (C*Me*$_3$). NB The signal for the C=O group in the Boc group was not visible.

HRMS (ESI): calcd for $C_{15}H_{19}NO_4$ [(M + Na)$^+$], calcd: 300.1206, found: 300.1197.

Methyl 3-(hydroxymethyl)cubane-1-carboxylate 21



A solution of BH_3-SMe_2 (46 μL in 1 mL THF) was added dropwise to a stirred solution of acid **17** (100 mg, 0.48 mmol) at 0 °C under argon. The reaction was allowed to warm to room temperature and stirred at room temperature for 3 h. Water (1 mL) was cautiously added, and the organic solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica (ϕ 2 × 15 cm) eluting with TBME gave **21** (72 mg, 0.37 mmol, 77%) as a colourless oil.

TLC: R_f = 0.34 (4:1 TBME); [phosphomolybdic acid].

IR (ATR): v (cm^{-1}) = 3405 (OH), 2985 (w), 1720 (C=O).

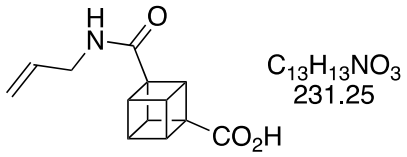
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.26-4.22 (m, 1H, CH), 4.14-4.09 (m, 2H, CH), 3.92-3.84 (m, 3H, CH), 3.76 (s, 2H, CH_2O), 3.68 (s, 3H, OMe), 1.93 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9 (C=O), 63.1 (CH_2O), 56.3 (C), 52.8 (C), 51.7 (CH), 50.5 (CH), 49.0 (CH), 47.3 (CH), 41.9 (CH).

MS (ESI): *m*/*z* (%) = 215 (100) [(M + Na)$^+$], 193 (25) [(M + H)$^+$].

HRMS (ESI): calcd for $C_{11}H_{12}O_3$ [M$^+$], calcd: 192.0786, found: 192.0790.

3-(Allylcarbamoyl)cubane-1-carboxylic acid 22



$C_{13}H_{13}NO_3$
231.25

A solution of ester **17** (100 mg, 0.48 mmol) in allylamine (1 mL) was heated for 8 h in a sealed tube at 50 °C under argon. The resulting solution was evaporated, then diluted with water (5 mL). Concentrated HCl was added dropwise at 0 °C until pH 1 was reached, and the resulting mixture was extracted with EtOAc (6 x 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give **22** (103 mg, 0.45 mmol, 93%) as a white solid.

m.p. 153-155 °C

IR (ATR): v (cm^{-1}) = 3337 (NH), 2983 (w), 2491 (br, CO_2H), 1686 (C=O), 1577 (s), 1546 (s).

^{1}H NMR (400 MHz, d_6-DMSO): δ 12.29 (br s, 1H, OH), 7.96 (t, 1H, *J* = 5.5 Hz, NH), 5.79 (ddt, 1H, *J* = 17.2, 10.2, 5.5 Hz, C*H*=CH_2), 5.09 (dq, 1H, *J* = 17.2, 1.7 Hz, =CH_AH$_B$), 5.04 (dq, 1H, *J* = 10.2, 1.7 Hz, =CH$_A$$H_B$), 4.31-4.27 (m, 2H, CH), 4.12-4.07 (m, 2H, CH), 3.91-3.85 (m, 2H, CH), 3.70 (tt, 2H, *J* = 5.5, 1.7 Hz, CH_2N).

^{13}C NMR (101 MHz, d_6-DMSO): δ 172.3 (C=O, amide), 170.0 (acid), 135.5 (=CH), 115.1 (=CH_2), 54.3 (C), 52.5 (C), 50.8 (CH), 49.1 (CH), 48.9 (CH), 41.4 (CH), 40.7 (CH_2).

MS (ESI): *m*/*z* (%) = 230 (100) [(M – H)$^-$]

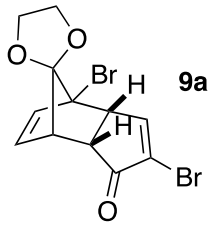
HRMS (ESI): calcd for $C_{13}H_{13}NO_3$ [M$^-$], calcd: 231.0895, found: 231.0894.

2. References

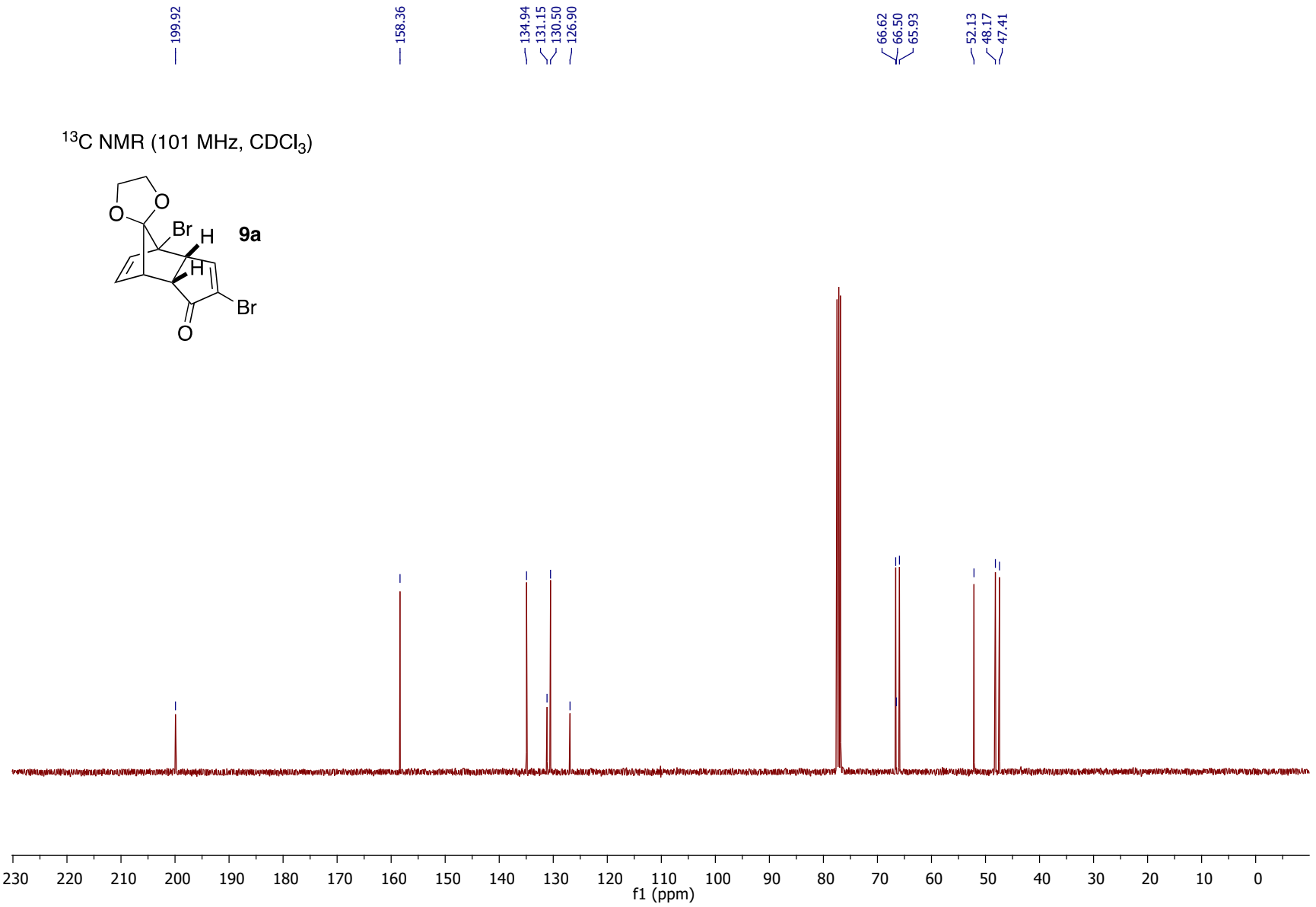
1. M. J. Falkiner, S. W. Littler, K. J. McRae, G. P. Savage and J. Tsanaktsidis, *Org. Process. Res. Dev*. 2013, **17**, 1503-1509.
2. M. Bliese and J. Tsanaktsidis, *Aust. J. Chem*. 1997, **50**, 189-192.
3. N. B. Chapman, J. M. Key, K. J. Toyne, *J. Org. Chem*. 1970, **35**, 3860-3867.
4. T. Nigo, T. Hasegawa, Y. Kuwatani and I. Ueda, *Bull. Chem. Soc. Jpn*. 1993, **66**, 2068-2072.
5. M. P. Wiesenfeldt, J. A. Rossi-Ashton, I. B. Perry, J. Diesel, O. L. Garry, F. Bartels, S. C. Coote, X. Ma, C. S. Yeung, D. J. Bennett and D. W. C. MacMillan, *Nature* 2023, in press.

2. $^{1}H/^{13}C$ NMR Spectra of New/Known Compounds

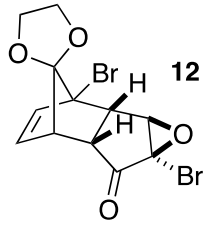
^{1}H NMR (400 MHz, $CDCl_3$)

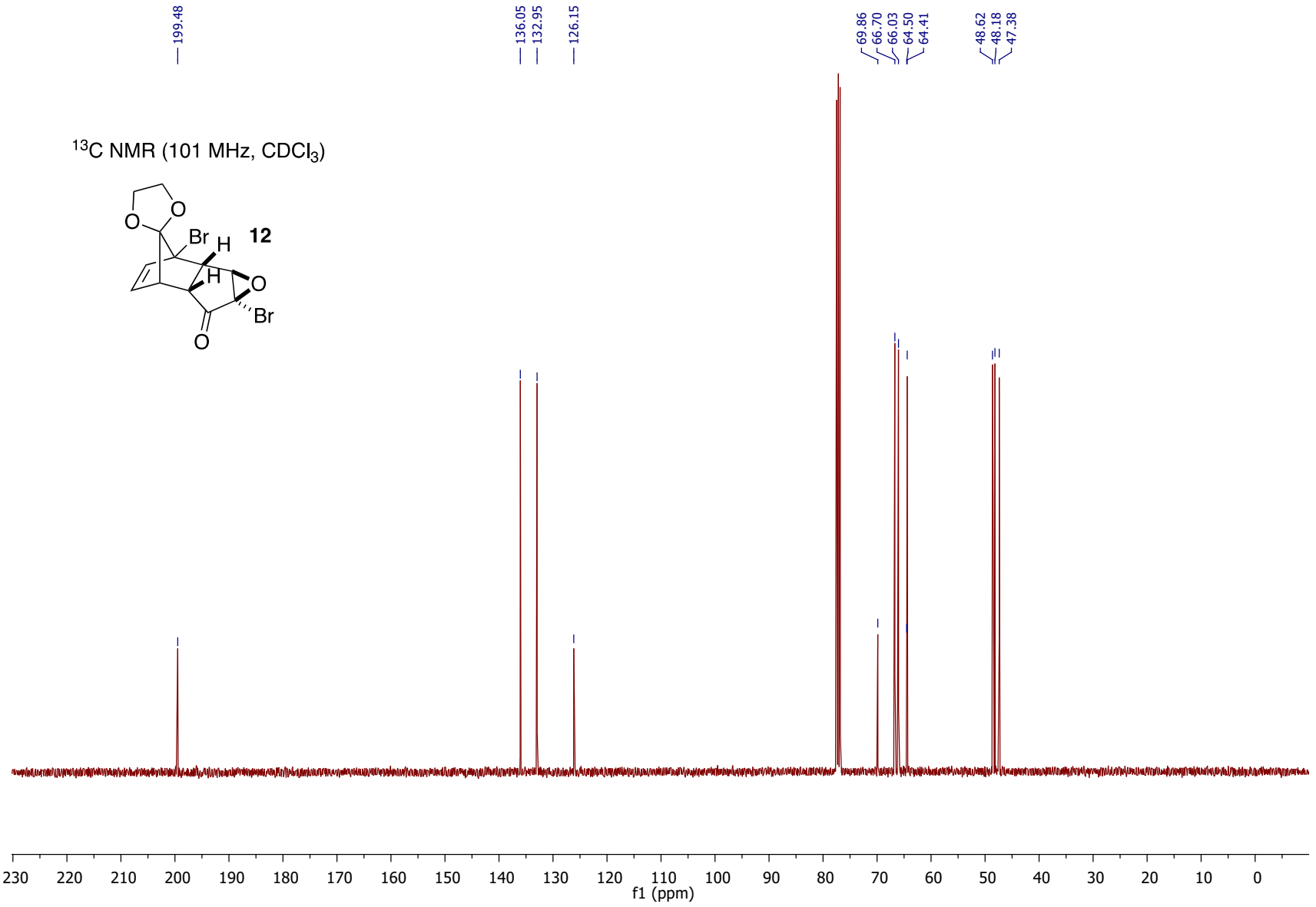


9a

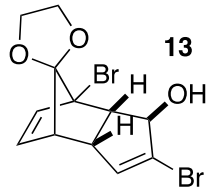

199.92
158.36
134.94
131.15
130.50
126.90
66.62
66.50
65.93
52.13
48.17
47.41
^{13}C NMR (101 MHz, $CDCl_3$)
O
O
Br
H
H
Br
O
9a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



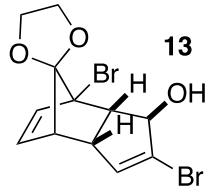

199.48
136.05
132.95
126.15
69.86
66.70
66.03
64.50
64.41
48.62
48.18
47.38
13C NMR (101 MHz, CDCl3)
12
Br
H
H
O
O
O
Br
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



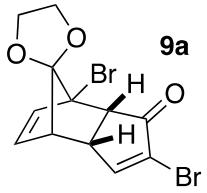
13

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



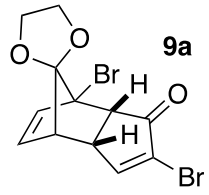
13

^{1}H NMR (400 MHz, $CDCl_3$)



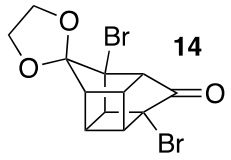
9a

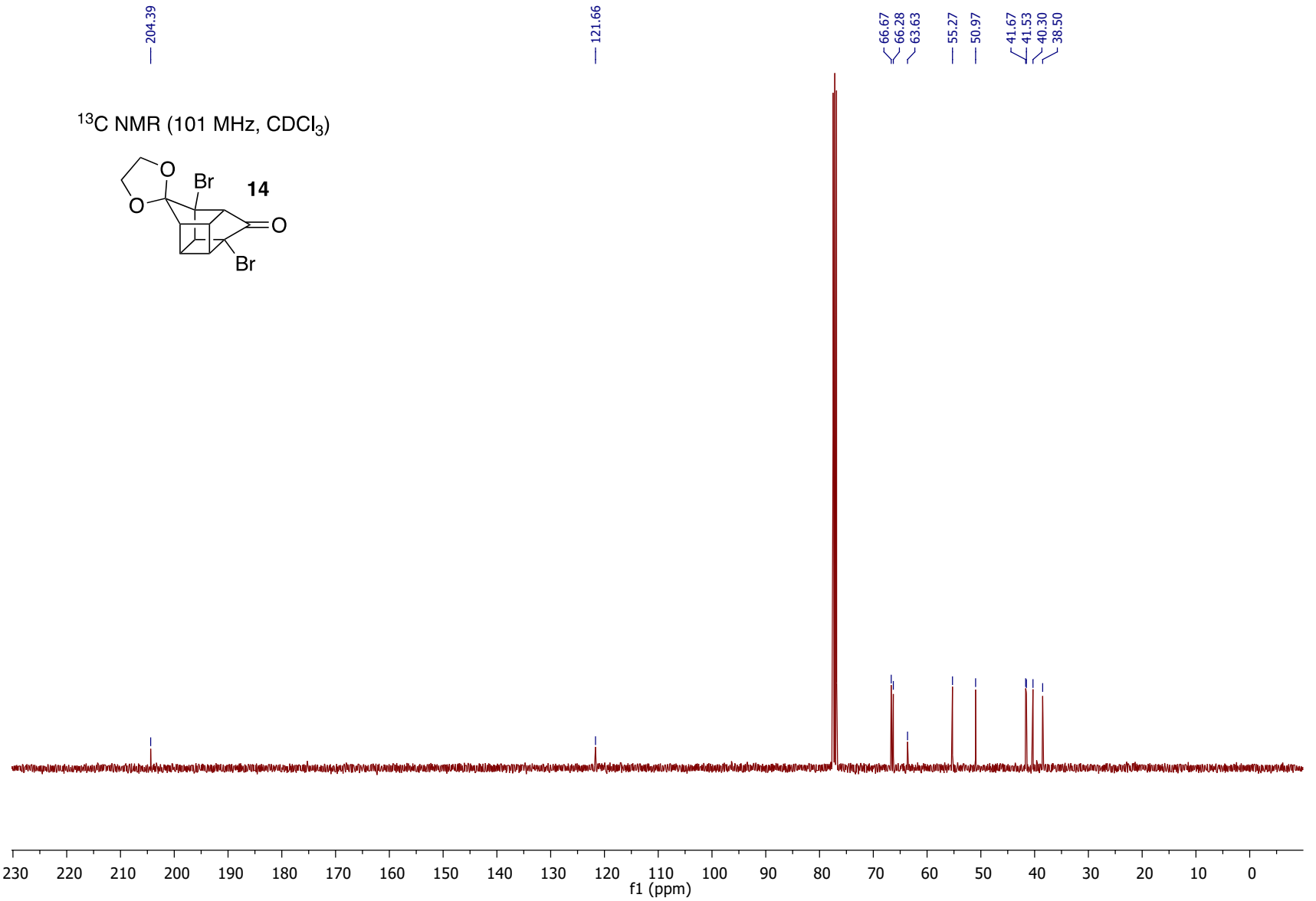
^{13}C NMR (101 MHz, $CDCl_3$)



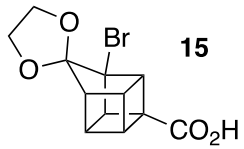
9a

^{1}H NMR (400 MHz, $CDCl_3$)

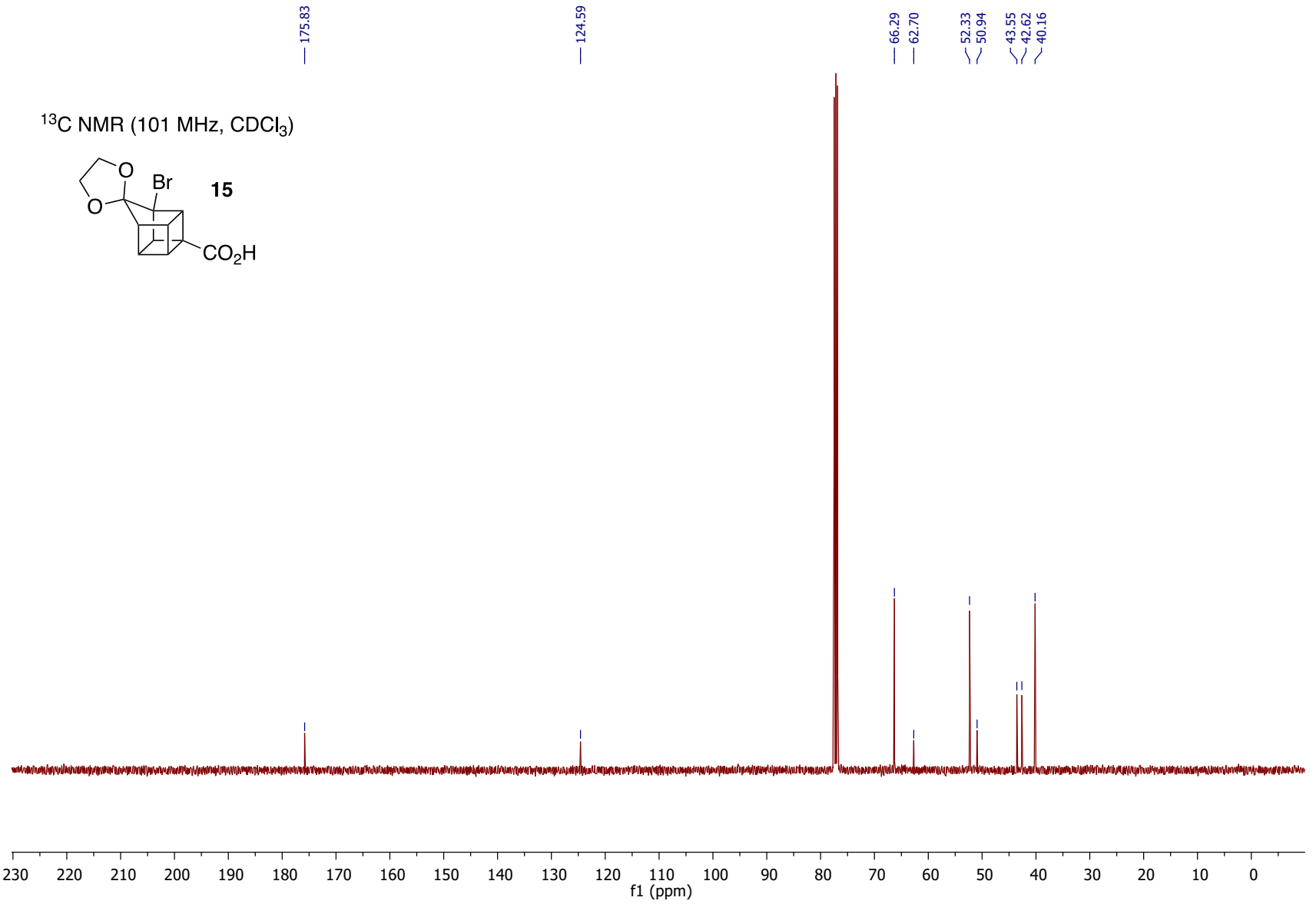


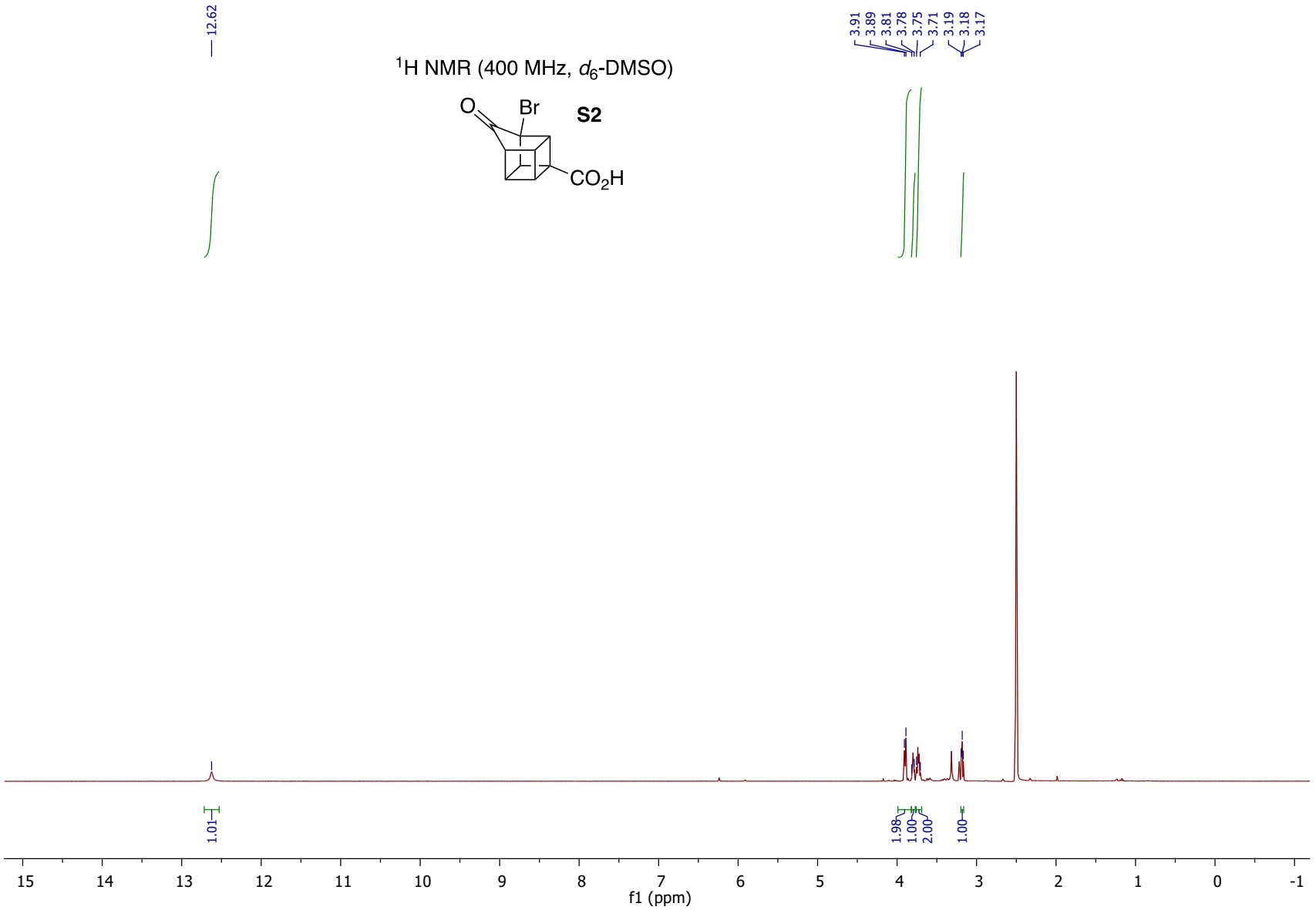

204.39
121.66
66.67
66.28
63.63
55.27
50.97
41.67
41.53
40.30
38.50
^{13}C NMR (101 MHz, $CDCl_3$)
O
Br
14
O
O
Br
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

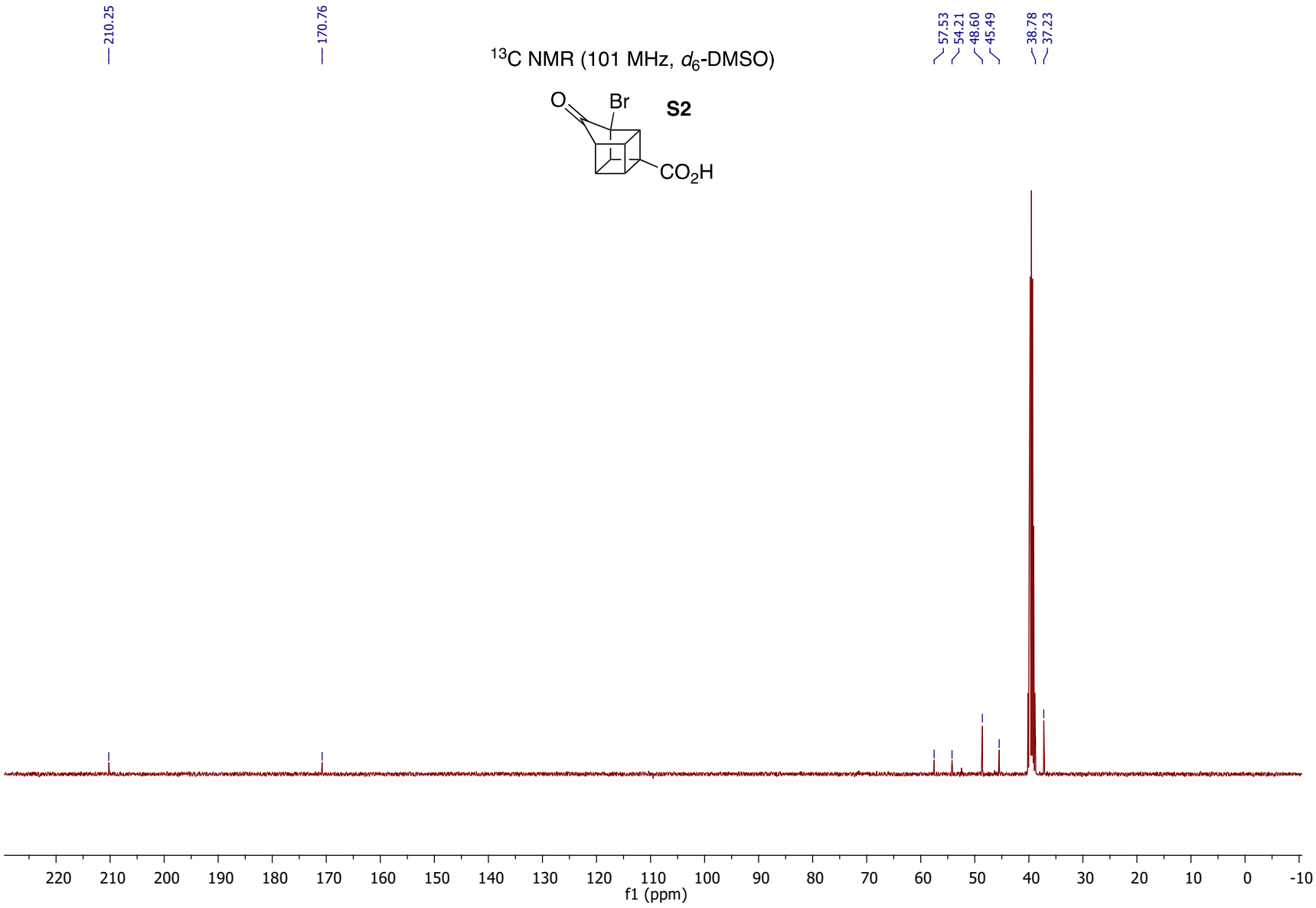
^{1}H NMR (400 MHz, $CDCl_3$)

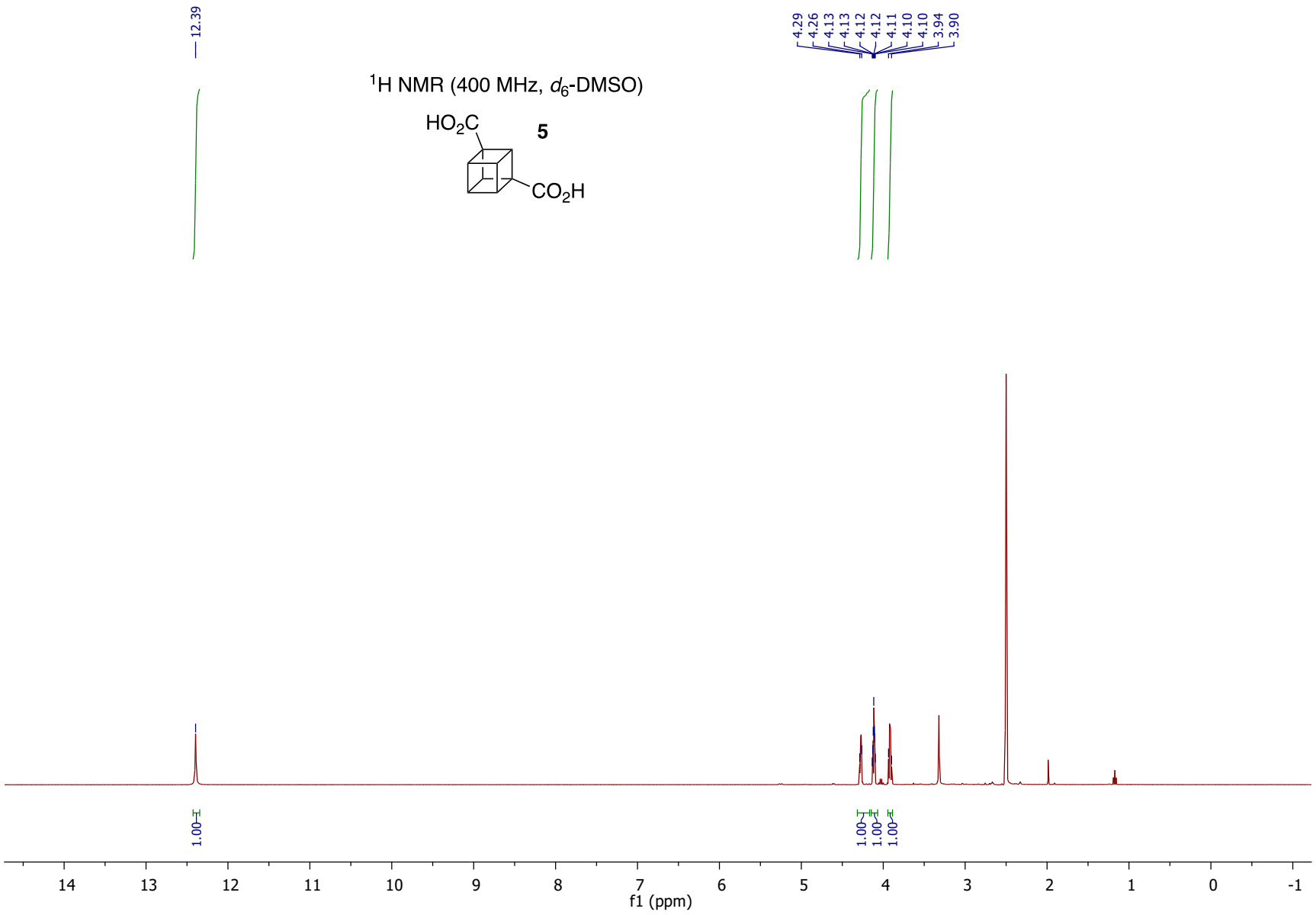


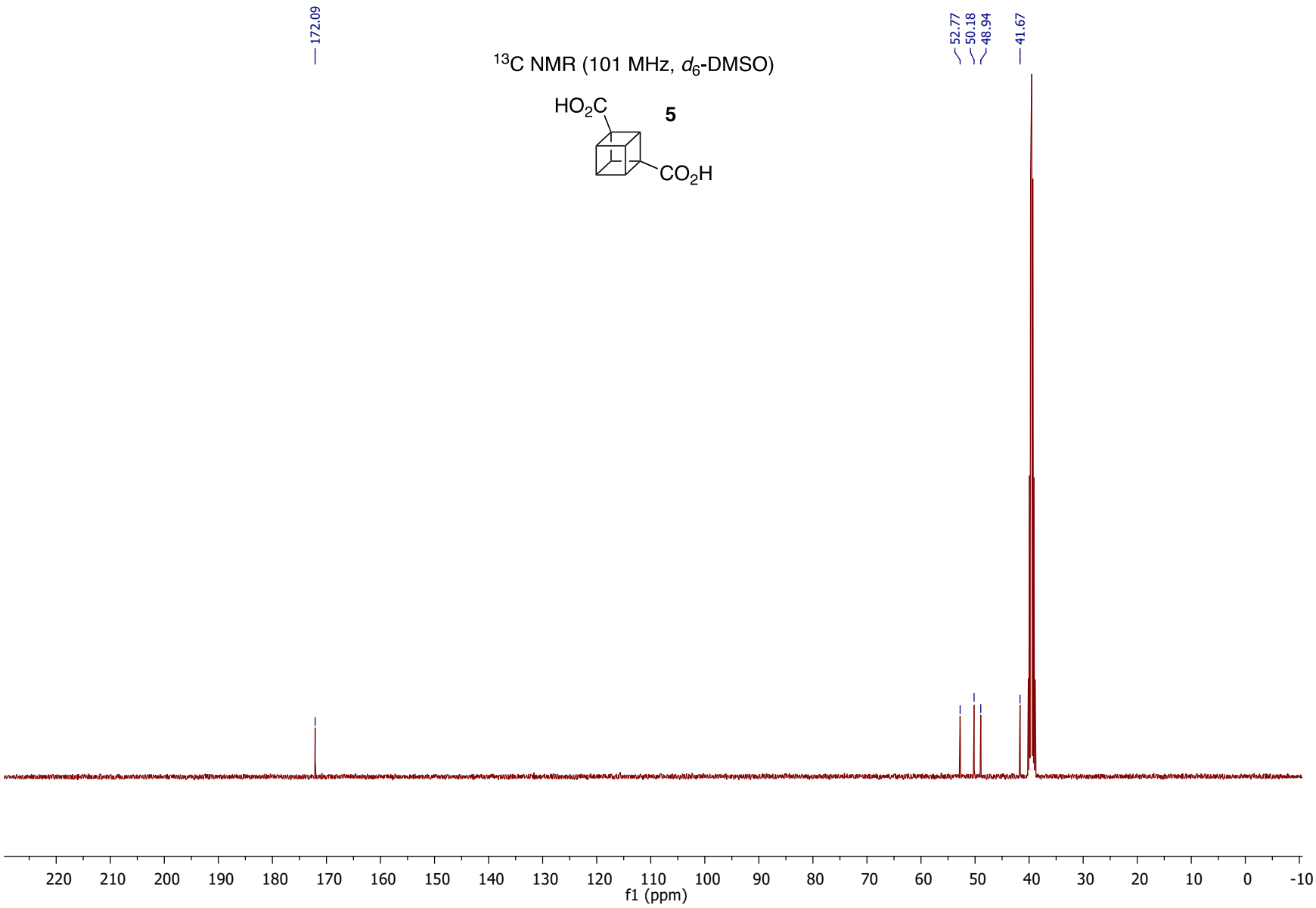
15


175.83
124.59
66.29
62.70
52.33
50.94
43.55
42.62
40.16
^{13}C NMR (101 MHz, $CDCl_3$)
O
O
Br
15
CO_2H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

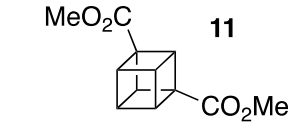

12.62
3.91
3.89
3.81
3.78
3.75
3.71
3.19
3.18
3.17
^{1}H NMR (400 MHz, d_6-DMSO)
O
Br
S2
CO_2H
1.01
1.98
1.00
2.00
1.00
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


210.25
170.76
57.53
54.21
48.60
45.49
38.78
37.23
^{13}C NMR (101 MHz, d_6-DMSO)
O
Br
S2
CO_2H
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

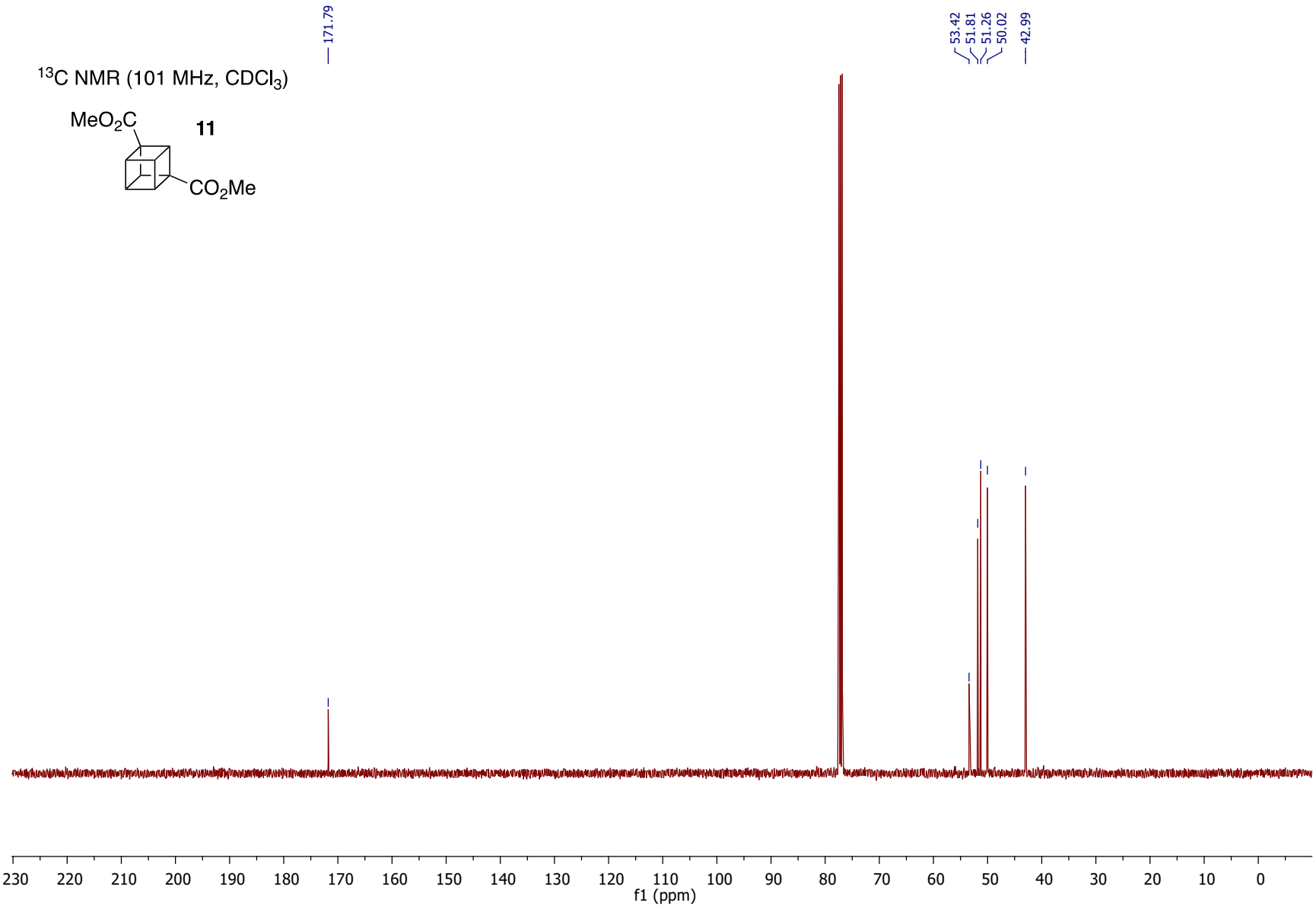

12.39
4.29
4.26
4.13
4.13
4.12
4.12
4.11
4.10
4.10
3.94
3.90
^{1}H NMR (400 MHz, d_6-DMSO)
HO_2C
5
CO_2H
1.00
1.00
1.00
1.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


172.09
52.77
50.18
48.94
41.67
^{13}C NMR (101 MHz, d_6-DMSO)
HO_2C
5
CO_2H
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

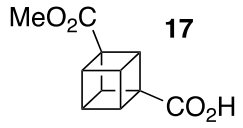
^{1}H NMR (400 MHz, $CDCl_3$)

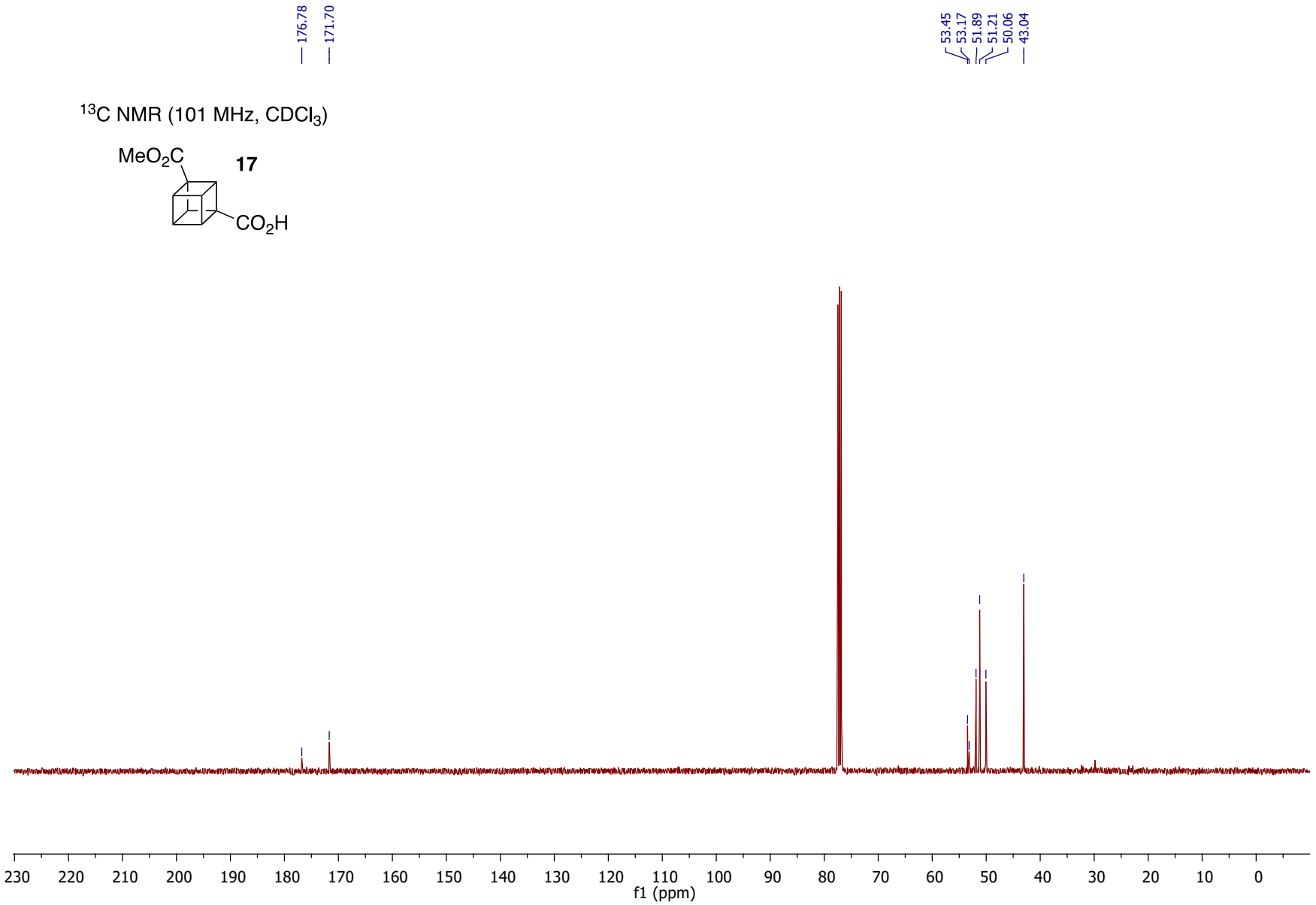


11

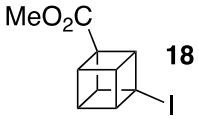

^{13}C NMR (101 MHz, $CDCl_3$)
MeO_2C
11
CO_2Me
171.79
53.42
51.81
51.26
50.02
42.99
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

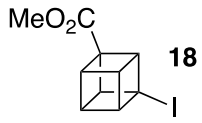



176.78
171.70
53.45
53.17
51.89
51.21
50.06
43.04
^{13}C NMR (101 MHz, $CDCl_3$)
MeO_2C
17
CO_2H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

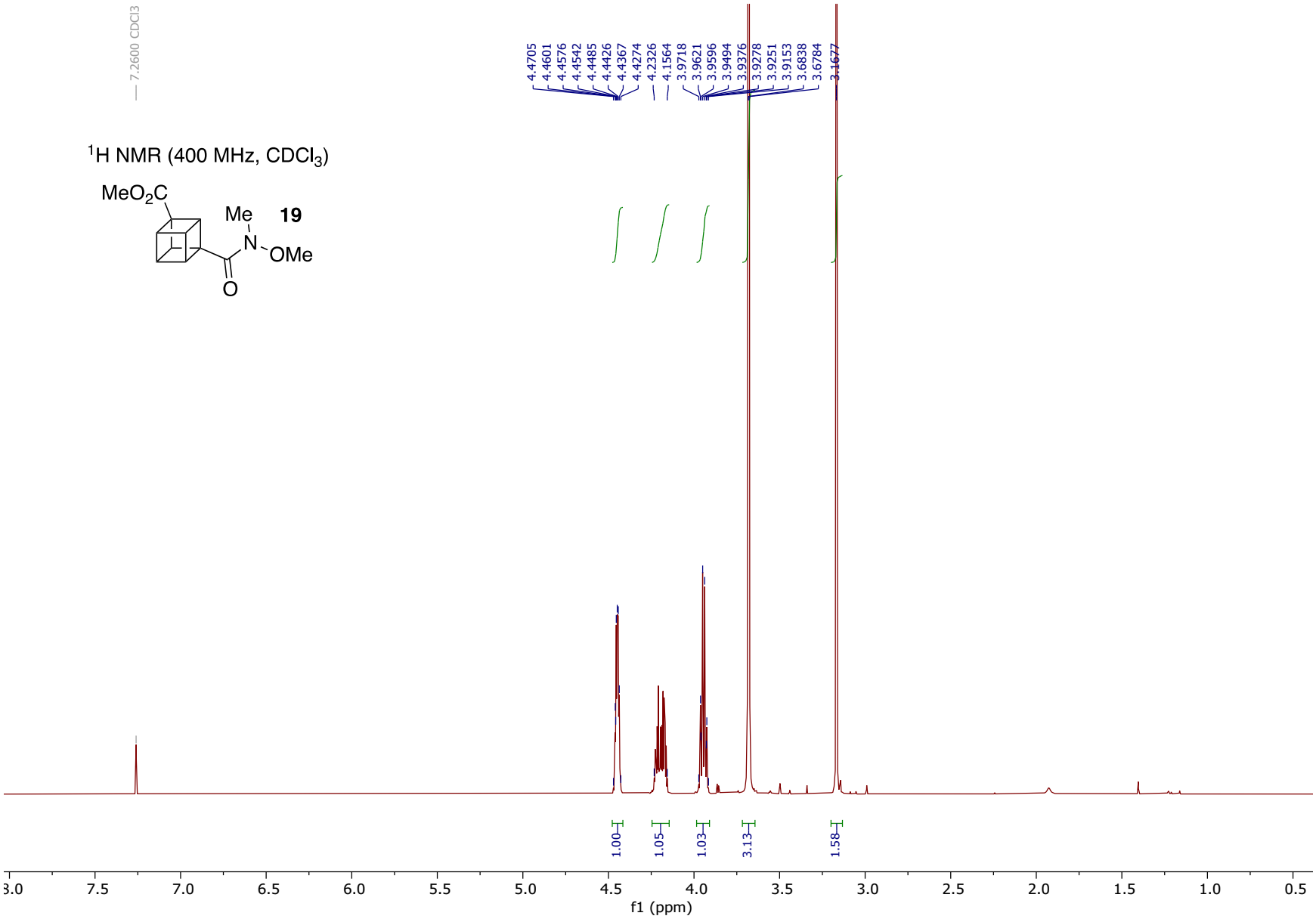
^{1}H NMR (400 MHz, $CDCl_3$)



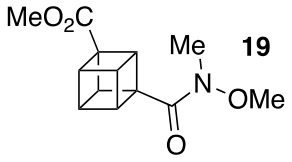
^{13}C NMR (101 MHz, $CDCl_3$)



18

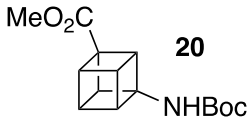

7.2600 CDCl3
4.4705
4.4601
4.4576
4.4542
4.4485
4.4426
4.4367
4.4274
4.2326
4.1564
3.9718
3.9621
3.9596
3.9494
3.9376
3.9278
3.9251
3.9153
3.6838
3.6784
3.1677
1H NMR (400 MHz, CDCl3)
MeO2C
Me
19
N
OMe
O
1.00
1.05
1.03
3.13
1.58
3.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

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

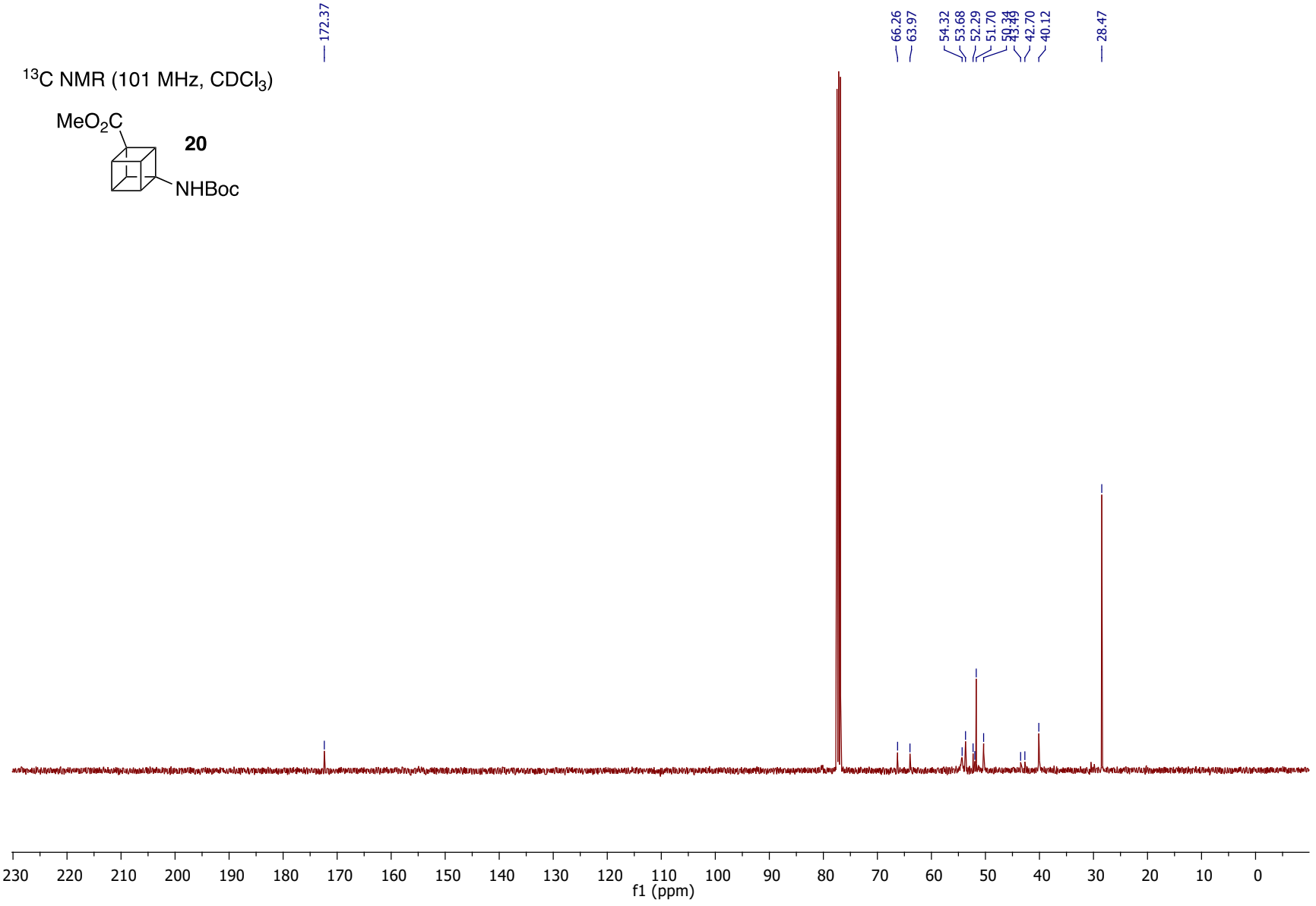


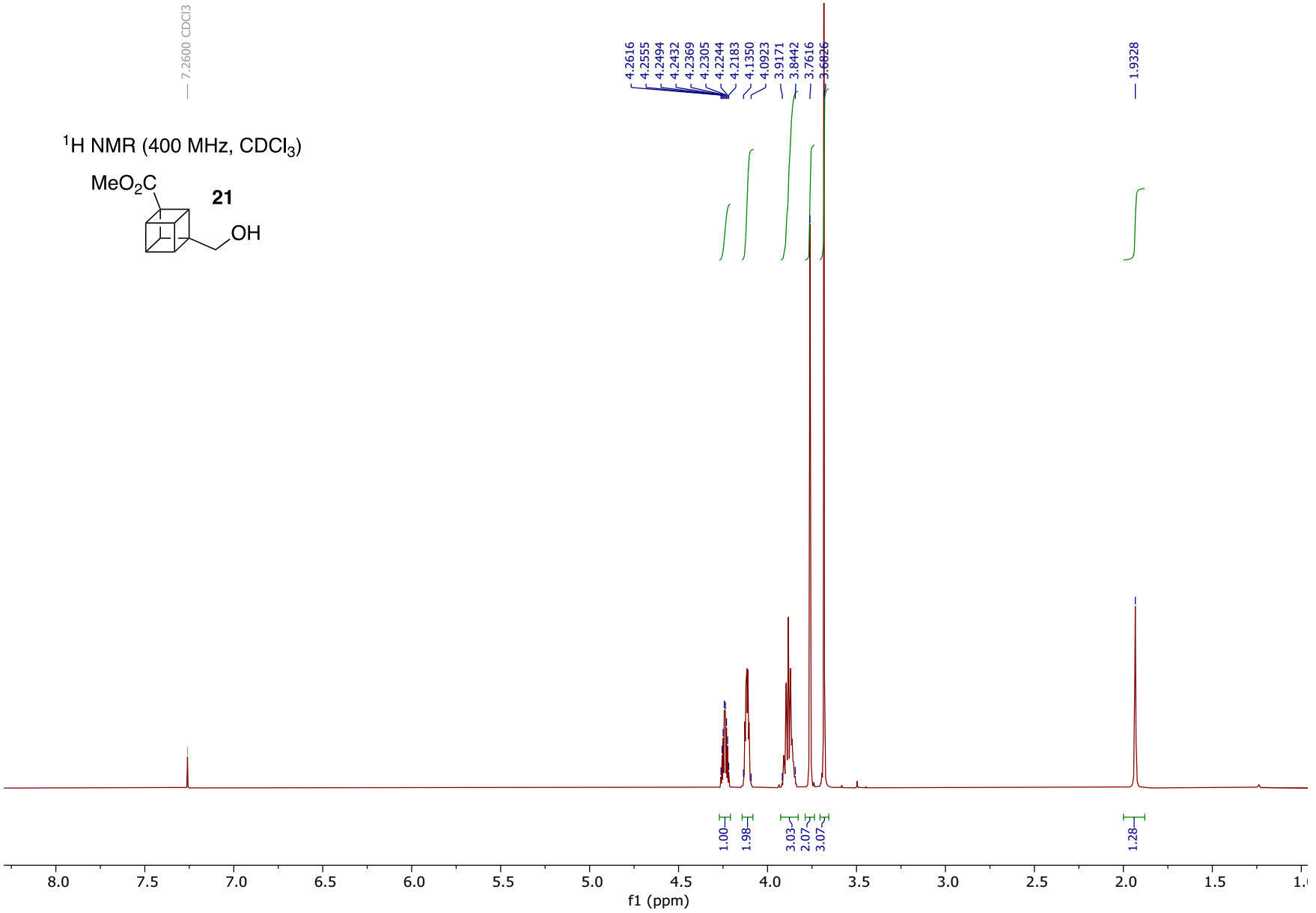
19

^{1}H NMR (400 MHz, $CDCl_3$)

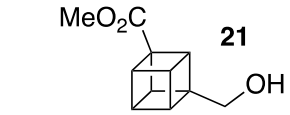


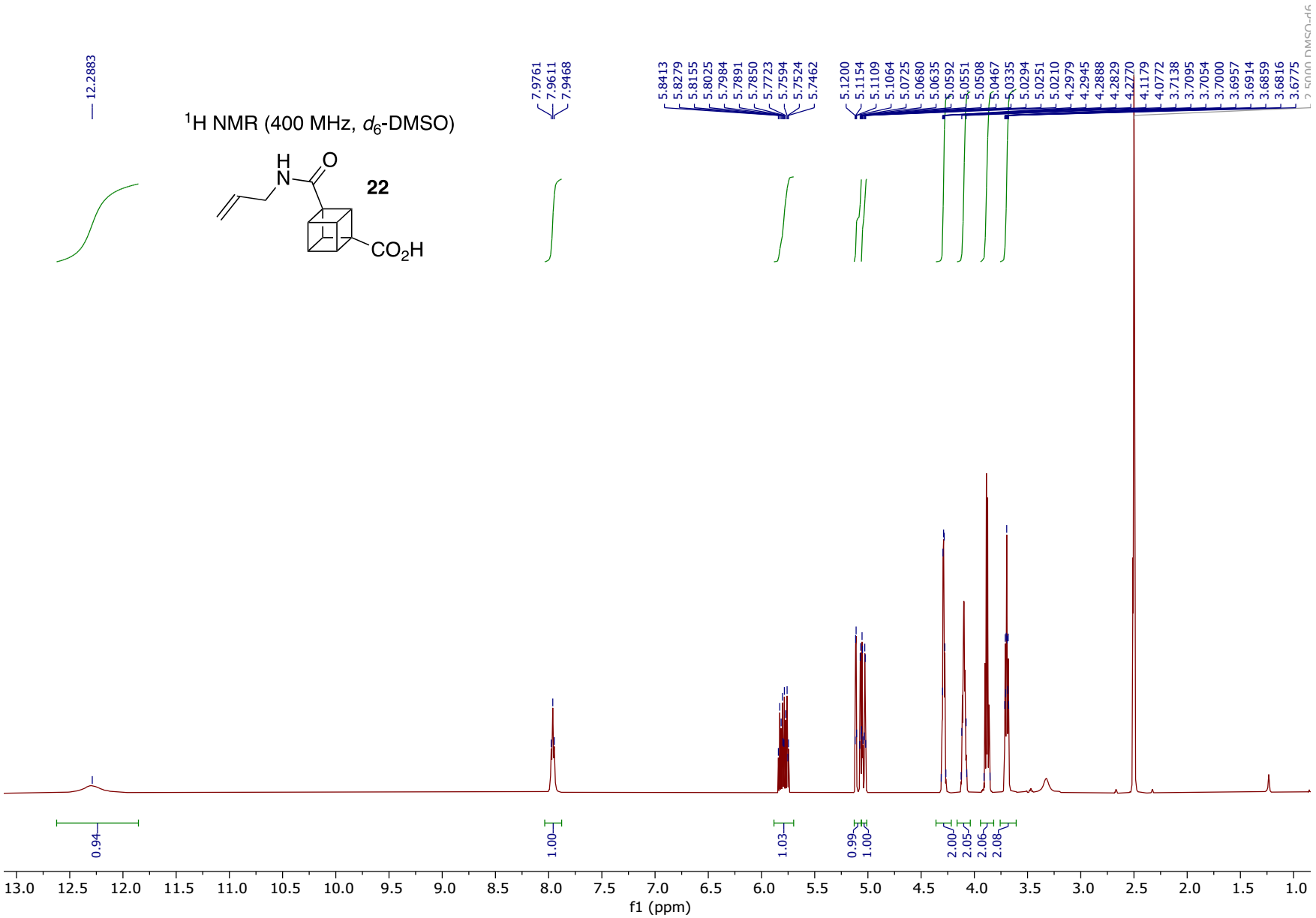
20

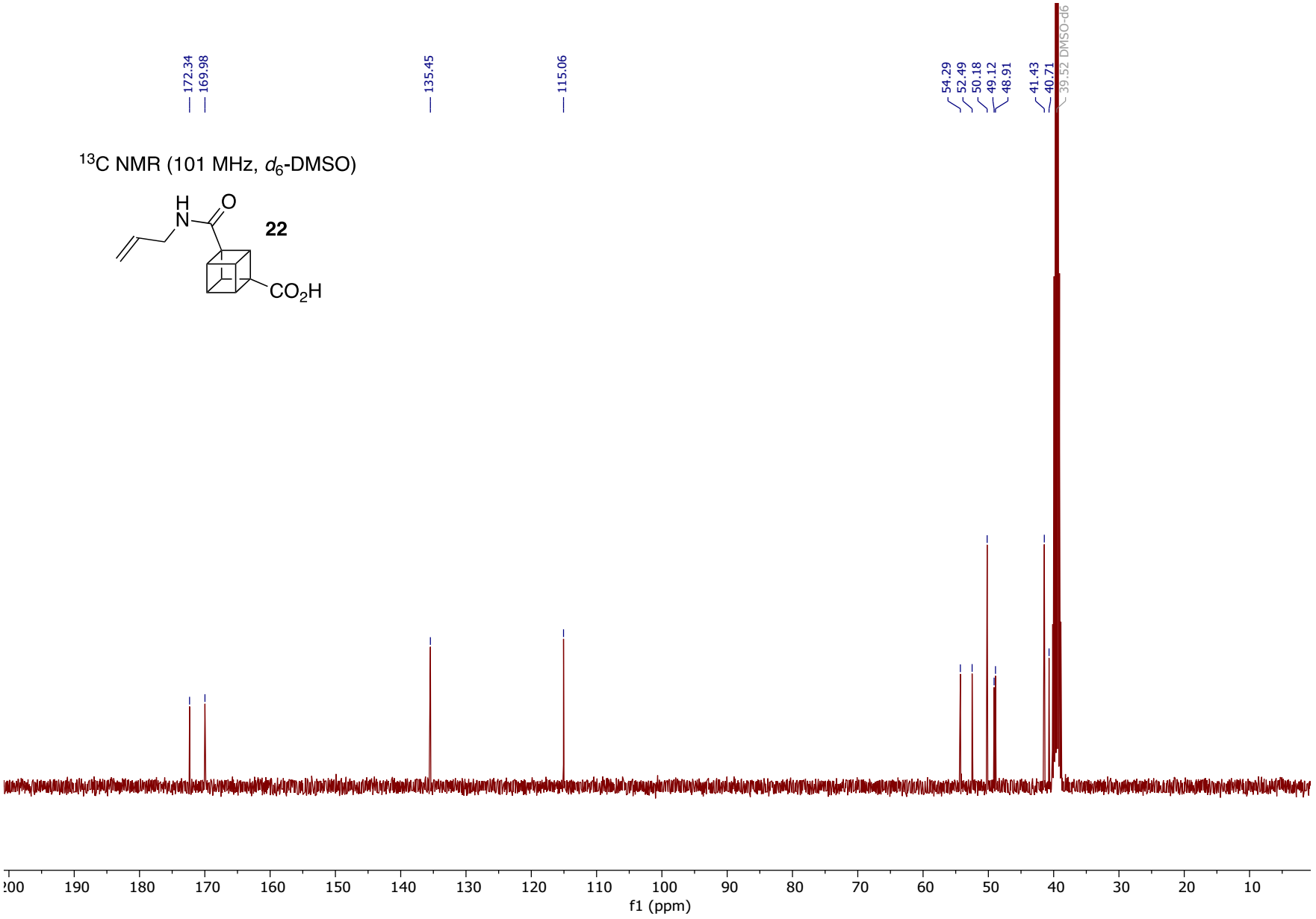

^{13}C NMR (101 MHz, $CDCl_3$)
MeO_2C
20
NHBoc
172.37
66.26
63.97
54.32
53.68
52.29
51.70
42.70
40.12
28.47
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.2600 CDCl3
4.2616
4.2555
4.2494
4.2432
4.2369
4.2305
4.2244
4.2183
4.1350
4.0923
3.9171
3.8442
3.7616
3.6826
1.9328
1H NMR (400 MHz, CDCl3)
MeO2C
21
OH
1.00
1.98
3.03
2.07
3.07
1.28
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

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




12.2883
7.9761
7.9611
7.9468
5.8413
5.8279
5.8155
5.8025
5.7984
5.7891
5.7850
5.7723
5.7594
5.7524
5.7462
5.1200
5.1154
5.1109
5.1064
5.0725
5.0680
5.0635
5.0592
5.0551
5.0508
5.0467
5.0335
5.0294
5.0251
5.0210
4.2979
4.2945
4.2888
4.2829
4.2270
4.1179
4.0772
3.7138
3.7095
3.7054
3.7000
3.6957
3.6914
3.6859
3.6816
3.6775
2.5000 DMSO-d6
1H NMR (400 MHz, d6-DMSO)
22
CO2H
0.94
1.00
1.03
0.99
1.00
2.00
2.05
2.06
2.08
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)


172.34
169.98
135.45
115.06
54.29
52.49
50.18
49.12
48.91
41.43
40.71
39.52 DMSO-d6
^{13}C NMR (101 MHz, d_6-DMSO)
22
H
N
O
CO_2H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)