Supplementary Information (SI) for Organic & Biomolecular Chemistry.

Asymmetric 'Clip-Cycle' Synthesis of 3-spiropiperidines

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ESI

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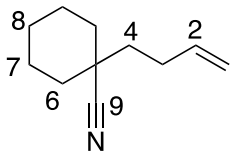
1) General Information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_2 and THF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer (operating at 400 MHz and 100 MHz). All NMR spectra were processed using MNova software. All Spectroscopic data was acquired at 295 K unless stated otherwise. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.26 and δ_c 77.16 for $CDCl_3$ were used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: br s broad singlet, s singlet, d doublet, br d broad doublet, t triplet, br t broad triplet, q quartet, p pentet, dd doublet of doublets, ddd doublet of doublet of doublets, dddd doublet of doublet of doublet of doublets, dt doublet of triplets, ddt doublet of doublet of triplets, td triplet of doublets, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. In cases where products were formed as a mixture of rotamers, their ratio was determined by integration of signals in the ^1H NMR spectrum. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. Mass spectra (high-resolution) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate or ceric ammonium nitrate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 µm, 60 Å, under a light positive pressure of air, eluting with the specified solvent system which is represented as x% of solvent 1/(100-x)% of solvent 2.

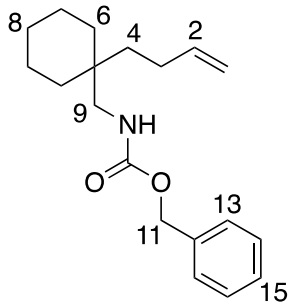
2) Synthetic procedures and characterisation data

1-(But-3-en-1-yl)cyclohexanecarbonitrile (7a)



To a solution of diisopropylamine (2.7 mL, 19.8 mmol, 1.1 eq) in dry THF (10 mL) at –78 °C under N_2 was added *n*-BuLi (1.42 M in hexanes, 15.2 mL, 21.6 mmol, 1.2 eq) and stirred for 50 min. A solution of cyclohexanecarbonitrile **6a** (2.1 mL, 18 mmol, 1 eq) in dry THF (10 mL) was added over 5 min at –78 °C and the reaction stirred for 40 mins. 4-Bromobutene (3.7 mL, 36 mmol, 2 eq) was added dropwise over 5 mins at –78 °C and the reaction warmed to room temperature and stirred overnight. The reaction was quenched with 1 M HCl (20 mL) and partitioned with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL x 2). The combined organics were washed with saturated brine solution (20 mL) and dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography (2% EtOAc/Pet ether) to give the product **7a** as a colourless oil (2.26 g, 13.8 mmol, 77% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.79 (ddt, *J* = 17.0, 10.1, 6.4 Hz, 1H, H-2), 5.05 (dd, *J* = 17.0, 1.5 Hz, 1H, H-1), 4.96 (dd, *J* = 10.1, 1.5 Hz, 1H, H-1'), 2.28 – 2.16 (m, 2H, H-3), 2.04 – 1.88 (m, 2H, H-6), 1.8 – 1.7 (m, 3H, H-7, H-8), 1.70 – 1.50 (m, 4H, H-7', H-4), 1.30 – 1.07 (m, 3H, H-8', H-6') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.3 (C-2), 123.5 (C-9), 115.3 (C-1), 39.7 (C-4), 38.8 (C-5), 35.7 (C-6), 28.7 (C-3), 25.4 (C-8), 23.0 (C-7) ppm; **IR** (ATR): ν_{max} 3079, 2933, 2858, 2230, 1642, 1453, 1361, 1319, 1271, 1113, 998, 964, 912, 849, 766, 691, 646, 615, 557, 520 cm^{-1}; **HRMS** (APCI) 164.1428 ($[MH]^+$ $C_{11}H_{18}N$ requires 164.1433).

1-(But-3-en-1-yl-cyclohexylmethyl) carbamic acid benzyl ester (1a)

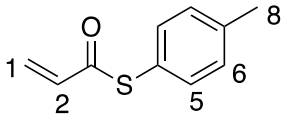


In a flame dried flask, $LiAlH_4$ (697 mg, 18.3 mmol, 1.5 eq) was added and the flask was cooled to 0 °C followed by addition of dry Et_2O (72 mL) under N_2 with continuous stirring. A solution of compound **7a** (2.0 g, 12.2 mmol, 1 eq) in dry Et_2O (12 mL) was added over 5 min and the reaction was stirred at 0 °C under N_2 for 45 min and then warmed to room temperature. After 3.5 hours, the reaction mixture was cooled to 0 °C and quenched with water (0.7 mL), followed by addition of NaOH solution (15% w/w, 0.7 mL), followed by water (2.1 mL). The reaction was then warmed to room temperature and left to stir for 15 min after which $MgSO_4$ was added.

After the reaction mixture was filtered through Celite®, it was concentrated *in vacuo* to give an intermediate amine (1.96 g, 11.7 mmol, 96% yield) which was taken through to the next step without purification.

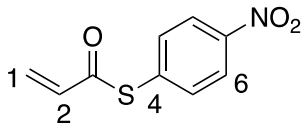
Amine (1.8 g, 10.7 mmol, 1 eq) was dissolved in 1,4-dioxane (50 mL). To this, K_2CO_3 solution (50% w/w aq, 1.2 mL, 12.9 mmol, 1.2 eq) was added followed by benzyl chloroformate (1.8 mL, 12.9 mmol, 1.2 eq) and the reaction was stirred at room temperature. After 4 hours, the reaction was quenched with water (50 mL) and extracted with dichloromethane (50 mL x 3). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was obtained as a pale-yellow oil and purified by flash column chromatography (5% EtOAc/Petroleum ether) to afford **1a** as a light-yellow oil (2.5 g, 15.9 mmol, 78% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.27 (m, 5 H, H-13, H-14, H-15), 5.79 (ddt, *J* = 17.1, 10.4, 6.5 Hz, 1 H, H-2), 5.10 (s, 2 H, H-11), 5.00 (dd, *J* = 17.1, 1.5 Hz, 1 H, H-1), 4.93 (dd, *J*= 10.4, 1.5 Hz, 1 H, H-1'), 4.80 (t, *J* = 6.1 Hz, 1 H, N-H), 3.13 (d, *J* = 6.1 Hz, 2 H, H-9), 2.13 – 1.85 (m, 2 H, H-3), 1.55 – 1.38 (m, 6 H, H-7, H-8), 1.37 – 1.18 (m, 6 H, H-4, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.6 (C-10), 139.2 (C-2), 136.5 (C-12), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 114.2 (C-1), 66.7 (C-11), 47.0 (C-9), 36.2 (C-4), 34.7 (C-5), 33.4 (C-6), 27.3 (C-3), 26.2 (C-8), 21.4 (C-7) ppm; **IR** (ATR): ν_{max} 3341, 3067, 3033, 2923, 2851, 1698 cm^{-1}; **HRMS** (ESI) 302.2115 ($[MH]^+$ $C_{19}H_{28}NO_2$ requires 302.2115).

Thioacrylic acid S-*p*-tolyl ester (2a)



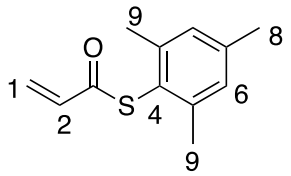
To a solution of NaOH (15% w/w aq. 17 mL, 64 mmol, 2 eq) was added $NaBH_4$ (36 mg, 0.96 mmol, 0.03 eq) and *p*-thiocresol (4 g, 32 mmol, 1 eq) which was then stirred for 1 hour at room temperature. A solution of butylated hydroxytoluene (106 mg, 0.48 mmol, 0.015 eq) and acryloyl chloride (3.90 mL, 48 mmol, 1.5 eq) in cyclohexane (30 mL) was cooled to 0 °C. The aqueous solution of *p*-thiocresol was added dropwise over 5 min to the acryloyl chloride solution and the reaction warmed to room temperature. The reaction was then heated to 55 °C for 5 hours. After this time the reaction was cooled to room temperature and extracted with Et_2O (80 mL). The combined organics were washed with saturated $NaHCO_3$ solution (100 mL) and saturated brine solution (100 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (2% Et_2O/hexane) to afford **2a** as a colourless oil (3 g, 0.016 mmol, 51 % yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.36 (d, J = 8.4 Hz, 2H, H-5), 7.26 (d, *J* = 8.4 Hz, 2H, H-6), 6.48 (dd, *J* = 17.5, 10.0 Hz, 1H, H-2), 6.40 (dd, *J* = 17.5, 1.5 Hz, 1H, H-1 *trans*), 5.78 (dd, *J* = 10.0, 1.5 Hz, 1H, H-1 *cis*), 2.41 (s, 3H, H-8) ppm. The compound was found to have identical ^{1}H NMR and ^{13}C NMR peaks as reported.[1]

Thioacrylic acid-S-*p*-nitrothioester (2b)



Thioester **2b** was synthesised using the same produce used to prepare thioester **2a** (see above) with a solution of NaOH (15% w/w aq. 5.65 mL), $NaBH_4$ (25 mg, 0.661 mmol, 0.05 eq), 4-nitrothiophenol (2 g, 12.8 mmol, 1 eq), butylated hydroxytoluene (42 mg, 0.192 mmol, 0.015 eq), acryloyl chloride (6 mL, 19.58 mmol) dichloromethane (8 mL) and heated at 55 °C for 1.5 hours. Compound **2b** was obtained as a light yellow solid (1.67 g, 7.98 mmol, 63% yield) after column chromatography (15% EtOAc/hexane) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 8.31 – 8.23 (m, 2H, H-6), 7.69 – 7.62 (m, 2H, H-5), 6.52 – 6.41 (m, 2H, H-1, H-2), 5.89 (dd, *J* = 6.7, 4.3 Hz, 1H, H-1') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ ppm 186.3 (C-3), 148.3 (C-7), 135.9 (C-4), 135.0 (C-6), 134.1 (C-2), 129.0 (C-1), 124.1 (C-5) ppm; **IR** (ATR): ν_{max} 3105, 2931, 2856, 1684, 1578, 1598, 1515, 1400, 1478, 1300, 1163, 1111, 1093, 983, 944, 850, 742 cm^{-1}; **HRMS** (APCI) 210.0209 ($[MH]^+$ $C_9H_8NO_3S$ requires 210.0219); m.p. 76 –79.5 °C.

Thioacrylic acid 2,4,6-trimethyl-phenyl ester (2c)

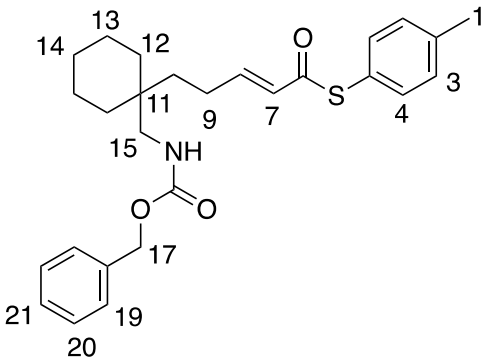


Thioester **2c** was synthesised using the same produce used to prepare thioester **2a** (see above) with a solution of NaOH (15% w/w aq. 5.65 mL), $NaBH_4$ (12 mg, 0.318 mmol), 2,4,6-trimethylthiophenol (1.62 g, 10.6 mmol), butylated hydroxytoluene (35 mg, 0.159 mmol), acryloyl chloride (1.31 mL, 16.2 mmol) cyclohexane (6.6 mL). Compound **2c** was obtained as a pale-yellow oil (1.262 g, 6.12 mmol, 69% yield) after column chromatography (2% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.01 (s, 2 H, H-6), 6.50 (dd, *J* = 17.5, 10.0 Hz, 1 H, H-2), 6.40 (dd, *J* = 17.5, 1.2 Hz, 1 H, H-1 *trans*), 5.76 (dd, *J* = 10.0, 1.2 Hz, 1 H, H-1 *cis*), 2.34 (s, 6 H, H-9), 2.32 (s, 3 H, H-8) ppm. This matched with the reported peaks in the literature.[1]

General Procedure A – Cross metathesis

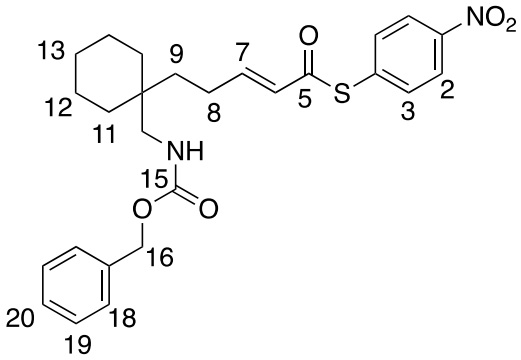
Hoveyda-Grubbs Catalyst™ 2nd generation (0.1 eq), copper iodide (1 eq) and 1,2-dichloroethane (8 mL) were added to a flame dried flask. To this, a solution of thioester (3 eq) in 1,2-dichloroethane (5 mL) was added under a nitrogen atmosphere while stirring, followed by the addition of a solution of Cbz-amine (1 eq) in 1,2 dichloroethane (5 mL). The flask was purged with N_2, and the reaction heated to 50 °C for 24 hours, after which the reaction mixture was cooled to room temperature, exposed to air and concentrated *in vacuo.* The crude residue was purified by flash column chromatography to yield the metathesis product**.**

(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclohexyl)pent-2-enethioate (3a)



Compound **3a** was synthesised by cross metathesis using **general procedure A** with thioester **2a** (193 mg, 1.082 mmol, 3 eq) copper iodide (68.5 mg, 0.36 mmol, 1 eq) and Hoveyda-Grubbs Catalyst™ 2nd generation (22.5 mg, 0.036 mmol, 0.1 eq) and Cbz-amine **1a** (109 mg, 0.36 mmol, 1 eq). The title compound **3a** was onbtained as a pale-yellow oil (123 mg, 0.272 mmol, 76% yield) after column chromatography (20% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.38 – 7.26 (m, 7H, H-19, H-20, H-21, H-4), 7.21 (d, *J* = 8.1 Hz, 2H, H-3) 6.94 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.17 (d, *J* = 15.5 Hz, 1H, H-7), 5.09 (s, 2H, H-17), 4.77 (t, *J* = 6.4 Hz, 1H, N-H), 3.10 (d, *J* = 6.4 Hz, 2H, H-15), 2.35 (s, 3H, H-1), 2.21 – 2.10 (m, 2H, H-9), 1.52 – 1.16 (m, 12H, H-10, H-12, H-13, H-14) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.7 (C-16), 147.0 (C-8), 139.6 (C-2), 136.6 (C-18), 134.7 (C-4), 130.0 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 127.8 (C-7), 124.2 (C-5), 67.0 (C-17) 47.1 (C-15), 36.5 (C-11), 33.4 (C-10 + C-12), 26.2 (C-9 + C-14), 21.4 (C-1), 21.4 (C-13) ppm; **IR** (ATR): ν_{max} 3356, 3033, 2926, 2853, 1710, 1681, 1630, 1518, 1494, 1455, 1237, 1130, 1016, 909, 808, 732, 698 cm^{-1}; **HRMS** (ESI) 452.2257 ([MH]$^+$ $C_{27}H_{34}NO_3S$ requires 452.2254).

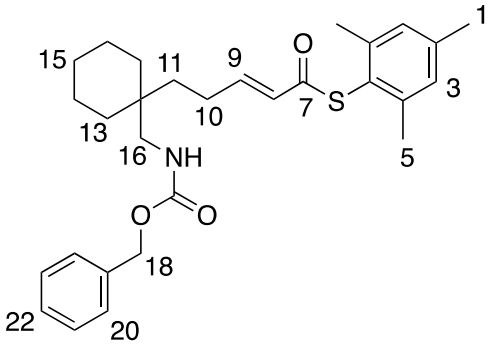
(*E*)-S-(4-Nitrophenyl)-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclohexyl)pent-2-enethioate (3b)



Compound **3b** was synthesised by cross metathesis using **general procedure A** with thioester **2b** (207 mg, 1.0 mmol, 3 eq), copper iodide (64 mg, 0.334 mmol) and Hoveyda-Grubbs^{TM} 2nd generation catalyst (21 mg, 0.033 mmol) and Cbz-amine **1a** (101 mg, 0.334 mmol, 1 eq). The title compound **3b** was obtained as a pale brown oil (136 mg, 0.281 mmol, 84% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR (**400 MHz, Chloroform-*d*): δ 8.30 – 8.18 (m, 2H, H-2), 7.68 – 7.58 (m, 2H, H-3), 7.38 – 7.23 (m, 5H, H-18, H-19, H-20), 7.03 (dt, *J* =

15.2 Hz, 6.8 Hz, 1H, H-7), 6.32 – 6.00 (d, *J* = 15.2 Hz, 1H, H-6), 5.08 (s, 2H, H-16), 4.87 (t, *J* = 6.6 Hz, 1H, N-H), 3.11 (d, *J* = 6.6 Hz, 2H, H-14), 2.32 – 1.99 (m, 2H, H-8), 1.63 – 1.11 (m, 12H, H-9, H-11, H-12, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 185.8 (C-5), 156.8 (C-15), 149.0 (C-7), 148.2 (C-1), 136.6 (C-17 + C-4), 134.9 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 127.4 (C-6), 124.0 (C-2), 67.0 (C-16), 47.1 (C-14), 36.5 (C-10), 33.5 + 33.2 (C-11 + C-9), 26.4 (C-8), 26.2 (C-13), 21.4 (C-12) ppm; **IR (ATR)** 3346, 2925, 2854, 1696, 1628, 1518, 1455, 1342, 1237, 1012, 853, 743, 697 cm^{-1}; **HRMS** (ESI) 505.1767 ([MNa]$^+$ $C_{26}H_{30}N_2NaO_5S$ requires 505.1768).

(*E*)-S-Mesityl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclohexyl)pent-2-enethioate (3c)



Compound **3c** was synthesised by cross metathesis using **general procedure A** with thioester **2c** (303 mg, 1.47 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (31 mg, 0.049 mmol, 0.1 eq) and copper iodide (93.5 mg, 0.491 mmol, 1 eq), Cbz-amine **1a** (115 mg, 0.491 mmol, 1 eq) and reaction stopped after 48 h. The title compound **3c** was obtained as a light brown oil (174 mg, 0.362 mmol, 82% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.28 (m, 5H, H-20, H-21, H-22), 6.98 (s, 2H, H-3), 6.97 – 6.91 (m, 1H, H-9), 6.23 (d, *J* = 15.6 Hz, 1H, H-8), 5.11 (s, 2H, H-18), 4.75 (t, *J* = 6.5 Hz, 1H, N-H), 3.14 (d, *J* = 6.5 Hz, 2H, H-16), 2.32 (s, 6H, H-5), 2.30 (s, 3H, H-1), 2.24 – 2.14 (m, 2H, H-10), 1.54 – 1.12 (m, 12H, H-11, H-13, H-14, H-15) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 187.8 (C-7), 156.8 (C-17), 146.5 (C-9), 142.8 (C-6), 139.9 (C-2), 136.6 (C-19), 129.3 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.0 (C-8), 123.6 (C-4), 66.9 (C-18), 47.1 (C-16), 36.5 (C-12), 33.5 (C-13, C-11), 26.2 (C-10), 26.1 (C-15), 21.7 (C-5), 21.4 (C-14), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 3356, 2923, 2852, 1707, 1673, 1630, 1603, 1529, 1454, 1375, 1237, 1129, 1012, 849, 805, 774, 735, 697, 816, 509, 462 cm^{-1}; **HRMS** (ESI) 480.2574 ([MH]$^+$ $C_{29}H_{38}NO_3S$ requires 480.2567).

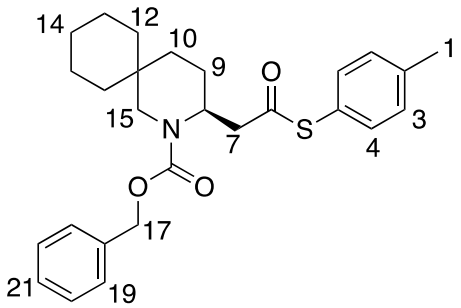
General Procedure B - cyclisation

Racemic (used to make racemic standards for chiral HPLC analysis): To a solution of amino-thioester (1 eq) in 1,2-DCE (0.02 M) was added rac-CSA (3 eq) and the reaction heated to 80 °C for 24 hours under N_2. The reaction was cooled to room temperature and extracted with DCM (2 x 5 mL). The organic fraction was washed with saturated $NaHCO_3$ solution (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography to afford the cyclised product **4**.

Asymmetric: To a solution of amino-thioester (1 eq) in cyclohexane (0.02 M) was added CPA (0.2 eq) and the reaction heated to 80 °C for 24 hours under N_2. The reaction was quenched

with Et_3N (0.2 mL) and cooled to room temperature and concentrated *in vacuo*. The crude material was purified by column chromatography to afford the cyclised product **4**.

(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.5]undecane-2-carboxylate (4a)



Racemic: Compound **4a** was synthesized using the **general procedure B** using the amino-thioester **3a** (29 mg, 0.066 mmol, 1 eq) and rac-CSA (40 mg, 0.18 mmol, 3 eq). Compound **3a** was obtained as a pale-yellow oil (12 mg, 0.027 mmol, 41% yield) after column chromatography (10% EtOAc/hexane).

Asymmetric (*R*)-TRIP, cyclohexane 80 ^oC, 24 h (Table 1, entry 1)

Compound **4a** was synthesized using the **general procedure B** using the amino-thioester **3a** (20 mg, 0.046 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.009 mmol, 0.2 eq). Compound 4a was obtained as a pale-yellow oil (2.0 mg, 0.004 mmol, 10% yield, 96:4 e.r.) after column chromatography (10% EtOAc/hexane).

Asymmetric (*R*)-TRIP, cyclohexane 80 ^oC, 48 h (Table 1, entry 2)

Compound **4a** was synthesized using the **general procedure B** using the amino-thioester **3a** (46 mg, 0.105 mmol, 1 eq) and (*R*)-TRIP (16 mg, 0.021 mmol, 0.2 eq). Compound **4a** was obtained as a pale-yellow oil (9.5 mg, 0.021 mmol, 21% yield, 96:4 e.r.) after column chromatography (10% EtOAc/hexane).

Asymmetric (*R*)-TRIP, octane 100 ^oC, 24 h (Table 1, entry 3)

Compound **4a** was synthesized using the **general procedure B** using the amino-thioester **3a** (18 mg, 0.04 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.008 mmol, 0.2 eq). Compound **4a** was obtained as a pale-yellow oil (6.5 mg, 0.014 mmol, 36% yield, 94:6 e.r.) after column chromatography (20% Et_2O/pentane).

Asymmetric (*R*)-anthra, octane 100 ^oC, 24 h (Table 1, entry 12)

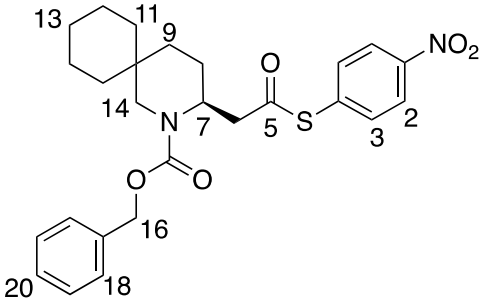
Compound **4a** was synthesized using the **general procedure B** using the amino-thioester **3a** (22 mg, 0.04 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.009 mmol, 0.2 eq). Compound **4a** was obtained as a pale-yellow oil (17 mg, 0.039 mmol, 80% yield, 93:7 e.r.) after column chromatography (20% Et_2O/pentane).

Asymmetric (*R*)-anthra, cyclohexane 80 °C, 24 h (Table 1, entry 13)

Compound **4a** was synthesized using the **general procedure B** using the amino-thioester **216** (29 mg, 0.066 mmol, 1 eq) and (*R*)-anthra (6 mg, 0.009 mmol, 0.2 eq). Compound **4a** was obtained as a pale-yellow oil (16 mg, 0.036 mmol, 78% yield, 96:4 e.r.) after column chromatography (20% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.42 – 7.27 (m, 5H, H-19, H-20, H-21), 7.20 – 7.10 (m, 4H, H-4, H-3), 5.13 (s, 2H, H-17), 4.91 – 4.67 (br. m, 1H, H-8), 4.24 – 3.87 (br. m, 1H, H-15), 3.00 – 2.84 (m, 2H, H-7), 2.67 – 2.44 (br. m, 1H, H-15'), 2.37 (s, 3H, H-1), 1.97 – 1.79 (m, 1H, H-9), 1.58 – 1.12 (m, 13H, H-9', H-10, H-11, H-13, H-14) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.4 (C-16), 139.8 (C-2), 136.9 (C-18), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 124.1 (C-5), 67.2 (C-17), 48.9 (C-8), 47.8 (C-15), 44.0 (C-7), 38.1 (C-13), 33.1 (C-11), 31.2 (C-12), 30.8 (C-12'), 26.6 (C-10), 23.6 (C-9), 21.7 (C-14), 21.5 (C-13'), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2925, 2855, 1694, 1494, 1448, 1421, 1341, 1225, 1147, 1003, 807, 763, 734, 697, 607 cm^{-1}; **HRMS** (ESI) 452.2253 ([MH]$^+$ $C_{27}H_{34}NO_3S$ requires 452.2254); **$[\alpha]_D^{20}$** +37.83 (c= 0.7, $CHCl_3$) for 96:4 er with (*R*)-anthra, cyclohexane at 80 °C.

(*S*)-Benzyl-3-(2-((4-nitrophenyl)thio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (4b)



Racemic: Compound **4b** was synthesized using the **general procedure B** using the amino-thioester **3b** (22 mg, 0.046 mmol, 1 eq) and rac-CSA (32 mg, 0.139 mmol, 3 eq). Compound **4b** was obtained as a light-yellow oil (6.5 mg, 0.013 mmol, 29% yield) after column chromatography (20% Et_2O/hexane).

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 24 h (Table 1, entry 4)

Compound **4b** was synthesized using the **general procedure B** using the amino-thioester **3b** (27 mg, 0.044 mmol, 1 eq) and (*R*)-TRIP (7 mg, 0.008 mmol, 0.2 eq). Compound **4b** was obtained as a light-yellow oil (4 mg, 0.009 mmol, 20% yield, 92:8 e.r.) after column chromatography (20% EtOAc/pentane).

Asymmetric (*R*)-TRIP, cyclohexane 80 °C, 48 h (Table 1, entry 5)

Compound **4b** was synthesized using the **general procedure B** using the amino-thioester **3b** (25.5 mg, 0.052 mmol, 1 eq) and (*R*)-TRIP (8 mg, 0.01 mmol, 0.2 eq). Compound **4b** was

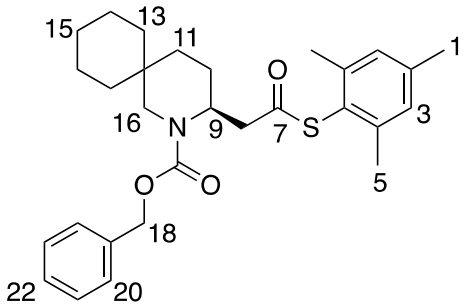
obtained as a light-yellow (5 mg, 0.01 mmol, 21% yield, 84:16 e.r.) after column chromatography (20% Et_2O/hexane).

Asymmetric (*R*)-TRIP, octane, 100 °C, 24 h (Table 1, entry 6)

Compound **221** was synthesized using the **general procedure B** using the amino-thioester **220** (19 mg, 0.038 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.007 mmol, 0.2 eq). Compound **221** was obtained as a light-yellow oil (10 mg, 0.021 mmol, 55% yield, 90:10 e.r.) after column chromatography (20% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 (d, *J* = 8.7 Hz, 2H, H-2), 7.64 – 7.39 (br. m, 2H, H-3), 7.38 – 7.20 (m, 5H, H-18, H-19, H-20), 5.13 (s, 2H, H-16), 4.99 – 4.73 (br. m, 1H, H-7), 4.24 – 3.93 (br. m, 1H, H-14), 3.12 – 2.91 (br. m, 1H, H-6), 2.90 – 2.72 (br. m, 1H, H-6'), 2.70 – 2.45 (br. m, 1H, H-14'), 2.06 – 1.85 (br. m, 1H, H-8), 1.56 – 1.07 (m, 13H, H-8', H-9, H-11, H-12, H-13) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 192.7 (C-5), 156.1 (C-15), 148.1 (C-1), 136.8 (C-17), 136.1 (C-4), 134.7 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.0 (C-2), 67.2 (C-16), 49.0 (C-7), 48.0 (C-14), 44.4 (C-6), 38.0 (C-9), 33.1 (C-10), 31.2 (C-11), 30.9 (C-11'), 26.6 (C-13), 24.0 (C-8), 21.7 (C-12) 21.5 (C-12') ppm; **IR** (ATR): ν_{max} 2927, 2854, 1693, 1599, 1578, 1519, 1497, 1448, 1421, 1341, 1302, 1281, 1258, 1225, 1147, 1093, 852, 742 cm^{-1}; **HRMS** (ESI) 483.1955 ([MH]$^+$ $C_{26}H_{31}N_2O_5S$ requires 483.1948); **$[\alpha]_D^{20}$** +22.5 (c= 0.2955, $CHCl_3$) for e.r. 90:10, (*R*)-TRIP, octane, 100 °C, 24 h.

(*S*)-Benzyl-3-(2-(mesitylthio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (4c)



Racemic: Compound **4c** was synthesized using the **general procedure B** using the amino-thioester **3c** (34 mg, 0.071 mmol, 1 eq) and rac-CSA (49.5 mg, 0.213 mmol, 3 eq). Compound **4c** was obtained as a light-brown oil (28 mg, 0.057 mmol, 81% yield) after column chromatography (20% Et_2O/hexane).

Asymmetric (*R*)-TRIP, octane 100 °C, 24 h (Table 1, entry 7)

Compound **4c** was synthesized using the **general procedure B** using the amino-thioester **3c** (19 mg, 0.039 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.007 mmol, 0.2 eq). Compound **4c** was obtained as a light-brown oil (10 mg, 0.02 mmol, 48% yield, 97:3 e.r.) after column chromatography (20% Et_2O /pentane).

Asymmetric (*R*)-TRIP, octane 110 °C, 24 h (Table 1, entry 8)

Compound **4c** was synthesized using the **general procedure B** using the amino-thioester **3c** (18 mg, 0.038 mmol, 1 eq) and (*R*)-TRIP (6 mg, 0.007 mmol, 0.2 eq). Compound **4c** was

obtained as a light-brown oil (11.5 mg, 0.024 mmol, 63% yield, 95:5 e.r.) after column chromatography (8% EtOAc /hexane).

Asymmetric (*R*)-TiPSY, octane 100 ^{o}C, 24 h (Table 1, entry 9)

Compound **4c** was synthesized using the **general procedure B** using the amino-thioester **3c** (20.5 mg, 0.042 mmol, 1 eq) and (*R*)-TiPSY (6 mg, 0.008 mmol, 0.2 eq). Compound **4c** was obtained as a light-brown oil (3 mg, 0.007 mmol, 17% yield, 37:63 e.r.) after column chromatography (10% EtOAc /hexane).

Asymmetric (*R*)-anthra, octane 100 ^{o}C, 24 h (Table 1, entry 10)

Compound **4c** was synthesized using the **general procedure B** using the amino-thioester **3c** (46.5 mg, 0.096 mmol, 1 eq) and (*R*)- anthra (13.5 mg, 0.019 mmol, 0.2 eq). Compound **4c** was obtained as a light-brown oil (24.5 mg, 0.05 mmol, 67% yield, 92:8 e.r.) after column chromatography (20% Et_2O /pentane).

Asymmetric (*R*)-phenanth, octane 100 ^{o}C, 24 h (Table 1, entry 11)

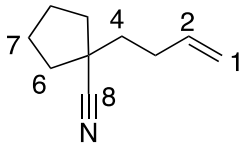
Compound **225** was synthesized using the **general procedure B** using the amino-thioester **224** (19 mg, 0.039 mmol, 1 eq) and (*R*)- phenanth (5.5 mg, 0.007 mmol, 0.2 eq). Compound **225** yielded as a light-brown oil (4 mg, 0.008 mmol, 21% yield, 62:38 e.r.) after column chromatography (20% Et_2O /pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.48 – 7.26 (m, 5H, H-20, H-21, H-22), 6.96 (s, 2H, H-3), 5.23 – 4.97 (br. m, 2H, H-18), 4.96 – 4.71 (br. s, 1H, H-9), 4.22 – 3.78 (br. m, 1H, H-16), 3.01 – 2.79 (m, 2H, H-8), 2.66 – 2.45 (br. m, 1H, H-16'), 2.29 (s, 3H, H-1), 2.27 (s, 6H, H-5), 1.97 – 1.79 (m, 1H, H-10), 1.57 – 1.12 (m, 13H, H-10', H-11, H-13, H-14, H-15) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 194.4 (C-7), 155.6 (C-17), 142.5 (C-6), 140.1 (C-2), 136.9 (C-19), 129.3 (C-3), 128.5 (C-20), 127.9 (C-21, C-22), 123.6 (C-4), 67.2 (C-18), 48.9 (C-9), 47.8 (C-16), 43.8 (C-8), 38.1 (C-14), 33.1 (C-12), 31.2 (C-13) 30.8 (C-13'), 26.6 (C-11). 23.4 (C-10), 21.7 (C-15), 21.6 (C-5), 21.5 (C-14'), 21.2 (C-1) ppm; **IR** (ATR): ν_{max} 2925, 2854, 1696, 1422, 1342, 1225, 1004, 849, 751, 696, 607 cm^{-1}; **HRMS** (ESI) 480.2581 ([MH]$^{+}$ $C_{29}H_{38}NO_3S$ requires 480.2567);**[α]$_D^{20}$** +30.47 (c= 0.3825, $CHCl_3$) for er 97:3, (*R*)-TRIP, octane 100 ^{o}C, 24 h.

General Procedure C – nitrile alkylation

To a solution of diisopropylamine (19.8 mmol1.1 eq) in dry THF (10 mL) at –78 ^{o}C under N_2 was added *n*-BuLi (1.42 M in hexanes, 21.6 mmol 1.2 eq) and stirred for 50 min. A solution of nitrile (18 mmol, 1 eq) in dry THF (10 mL) was added over 5 min at –78 ^{o}C and the reaction stirred for 40 mins. 4-Bromobutene (36 mmol, 2 eq) was added dropwise over 5 mins at –78 ^{o}C and the reaction warmed to room temperature and stirred overnight. The reaction was quenched with 1 M HCl (20 mL) and partitioned with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL x 2). The combined organics were washed with saturated brine solution (20 mL) and dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to give the alkylated product.

1-(But-3-en-1-yl)cyclopentanecarbonitrile (7d)



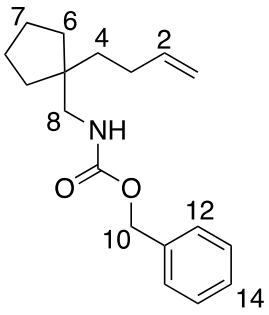
Compound **7d** was synthesised using the **general procedure C** with diisopropylamine (2 mL, 12 mmol, 1.1 eq), *n*-BuLi (2.07 M in hexanes, 6 mL, 12 mmol, 1.1 eq), cyclopentane carbonitrile (1.1 mL, 10.5 mmol, 1 eq) and 4-bromobutene (2 mL, 21.0 mmol, 2 eq). Compound **7b** was obtained as a colourless oil (1 g, 9 mmol, 88% yield) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H, H-2), 5.05 (dd, *J* = 16.9, 1.8 Hz, 1H, H-1), 4.98 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 2.30 – 2.21 (m, 2H, H-3), 2.17 – 2.06 (m, 2H, H-6), 1.88 – 1.78 (m, 2H, H-7), 1.78 – 1.69 (m, 2H, H-7'), 1.69 – 1.63 (m, 2H, H-4), 1.62 – 1.52 (m, 2H, H-6') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.1 (C-2), 125.1 (C-8), 115.4 (C-1), 43.0 (C-5), 38.2 (C-6), 37.8 (C-4), 30.6 (C-3), 24.2 (C-7) ppm; **IR** (ATR): ν_{max} 3083, 2958, 2875, 2231, 1643, 1453, 994, 914 cm^{-1}; **HRMS** (APCI): 150.1280 ([MH]$^{+}$ $C_{10}H_{16}N$ requires 150.1277).

General Procedure D

In a flame dried flask, $LiAlH_4$ (18.3 mmol, 1.5 eq) was added and the flask was cooled to 0 ^{o}C followed by addition of dry Et_2O (72 mL) under N_2 with continuous stirring. A solution of nitrile (12.2 mmol, 1 eq) in dry Et_2O (12 mL) was added over 5 min and the reaction was stirred at 0 ^{o}C under N_2 for 45 min and then warmed to room temperature. After 3.5 hours, the reaction mixture was cooled to 0 ^{o}C and quenched with water (0.7 mL), followed by addition of NaOH solution (15% w/w, 0.7 mL), followed by water (2.1 mL). The reaction was then warmed to room temperature and left to stir for 15 min after which $MgSO_4$ was added. After the reaction mixture was filtered through Celite®, it was concentrated *in vacuo* to give the amine which was taken through to the next step without purification.

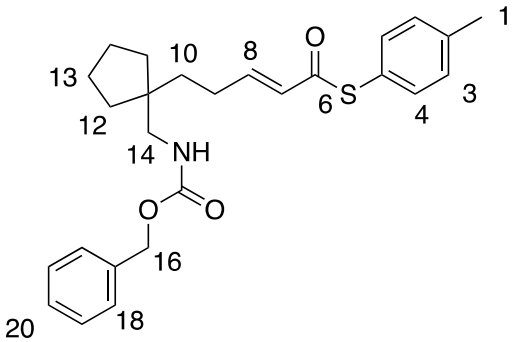
Amine (10.7 mmol, 1 eq) was dissolved in 1,4-dioxane (50 mL). To this, K_2CO_3 solution (50% w/w aq, 12.9 mmol, 1.2 eq) was added followed by benzyl chloroformate (12.9 mmol, 1.2 eq) and the reaction was stirred at room temperature. After 4 hours, the reaction was quenched with water (50 mL) and extracted with dichloromethane (50 mL x 3). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford the Cbz-amine**.**

Benzyl ((1-(but-3-en-1-yl)cyclopentyl)methyl)carbamate (1d)



Compound **1d** was synthesised using the **general procedure D** with $LiAlH_4$ (191 mg, 5.03 mmol, 1.5 eq), nitrile **7d** (500 mg, 3.35 mmol, 1 eq) to give the amine as a colourless oil (521 mg, 3.40 mmol) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 1.2 mL, 8.5 mmol, 2.5 eq) and benzyl chloroformate (0.58 mL, 4.08 mmol, 1.2 eq). Compound **1d** was obtained as a pale-yellow oil (353 mg, 1.22 mmol, 37% yield over two steps) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.28 (m, 5H, H-12, H-13, H-14), 5.80 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, H-2), 5.10 (s, 2H, H-10), 5.00 (dd, *J* = 16.9, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.76 (t, *J* = 6.4 Hz, 1H, N-H), 3.12 (d, *J* = 6.4 Hz, 2H, H-8), 2.09 – 1.95 (m, 2H, H-3), 1.68 – 1.54 (m, 4H, H-7), 1.45 – 1.32 (m, 6H, H-4, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.8 (C-9), 139.1 (C-2), 136.7 (C-11), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 114.3 (C-1), 66.8 (C-10), 47.5 (C-8), 45.9 (C-5), 37.0 (C-4), 35.5 (C-6), 29.1 (C-3), 25.0 (C-7) ppm; **IR (ATR)**: ν_{max} 3340, 3069, 3034, 2946, 2867, 1703, 1640, 1527, 1454, 1410, 1335, 1238, 1136, 1027, 999, 909, 775, 735, 697, 485 cm^{-1}; **HRMS (ESI):** 310.1775 ($[MNa]^+$ $C_{18}H_{25}NNaO_2$ requires 310.1777).

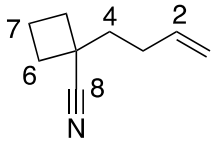
(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclopentyl)pent-2-enethioate (3d)



Compound **3d** was synthesised using the **general procedure A** with thioester **2a** (195 mg, 1.09 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (31 mg, 0.036 mmol, 0.1 eq) and copper iodide (69.5 mg, 0.36 mmol, 1 eq), Cbz-amine **1d** (105 mg, 0.36 mmol, 1 eq). Compound **3d** was obtained as a pale brown oil (139 mg, 0.317 mmol, 87% yield) after column chromatography (15% EtOAc/hexane) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.45 – 7.28 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 8.0 Hz, 2H, H-3), 6.96 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.18 (d, *J* = 15.5 Hz, 1H, H-7), 5.12 (s, 2H, H-16), 4.82 (t, *J* = 6.4 Hz, 1H, N-H), 3.14 (d, *J* = 6.4 Hz, 2H, H-14), 2.38 (s, 3H, H-1), 2.28 – 2.15 (m, 2H, H-9), 1.73 – 1.51 (m, 4H, H-13), 1.52 – 1.43 (m, 2H,

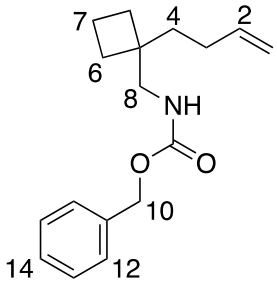
H-10), 1.43 – 1.32 (m, 4H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.7 (C-8), 139.6 (C-2), 136.5 (C-17), 134.7 (C-4), 130.0 (C-3), 128.6 (Ar-CH), 128.2 (Ar-CH), 127.7 (C-7), 124.1 (C-5), 66.8 (C-16), 47.3 (C-14), 46.0 (C-11), 35.6 (C-10), 35.5 (C-12), 27.8 (C-9), 24.9 (C-13), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3353, 3029, 2946, 2866, 1692, 1630, 1523, 1494, 1453, 1402, 1233, 1135, 1010, 806, 751, 696, 665, 535, 474 cm^{-1}; **HRMS** (ESI) 438.2096 ([MH]$^+$ $C_{26}H_{32}NO_3S$ requires 438.2097).

1-(But-3-en-1-yl)cyclobutanecarbonitrile (7e)



Compound **7e** was synthesised using the **general procedure C** with diisopropylamine (4 mL, 27 mmol, 1.1 eq), *n*-BuLi (2.0 M in hexanes, 14 mL, 27 mmol, 1.2 eq), cyclobutane carbonitrile (2 mL, 25 mmol, 1 eq) and 4-bromobutene (5 mL, 49 mmol, 2 eq). Compound **7e** was obtained as a pale-yellow oil (2.01 g, 15 mmol, 61% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.77 (ddt, *J* = 16.8, 10.7, 6.8 Hz, 1H, H-2), 5.04 (dd, *J* = 16.8, 1.5 Hz, 1H, H-1), 4.96 (dd, *J* = 10.7, 1.5 Hz, 1H, H-1'), 2.51 – 2.39 (m, 2H, H-6), 2.19 – 2.12 (m, 2H, H-3), 2.12 – 1.90 (m, 4H, H-6', H-7), 1.81 – 1.72 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.8 (C-2), 124.4 (C-8), 115.5 (C-1), 37.2 (C-4), 35.7 (C-5), 32.1 (C-6), 29.5 (C-3), 16.8 (C-7) ppm; **IR** (ATR): ν_{max} 3080, 2987, 2944, 2861, 2230, 1643, 1452, 996, 914, 616 cm^{-1}; **HRMS** (APCI): 136.1116 ([MH]$^+$ $C_9H_{14}N$ requires 136.1120).

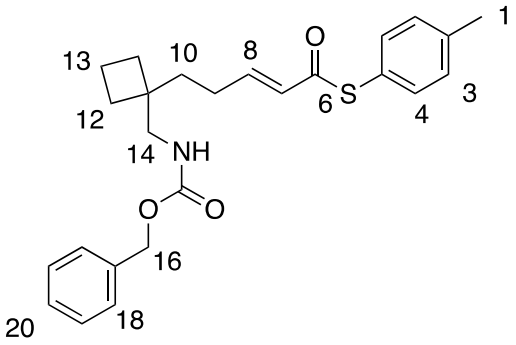
Benzyl ((1-(but-3-en-1-yl)cyclobutyl)methyl)carbamate (1e)



Compound **1e** was synthesised using **general procedure D** with $LiAlH_4$ (421 mg, 11.1 mmol, 1.5 eq), nitrile **7e** (1 g, 7.4 mmol, 1 eq) to give the amine as a colourless oil (1.02 g, 7.35 mmol, 99% yield) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 2.5 mL, 18.37 mmol, 1.2 eq) and benzyl chloroformate (2.6 mL, 18.37 mmol, 1.2 eq). Compound **1e** was obtained as a colourless oil (1.22 g, 4.47 mmol, 61% yield) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.27 (m, 5H, H-12, H-13, H-14), 5.82 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H, H-2), 5.11 (s, 2H, H-10), 5.02 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.94 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.71 (br. S, 1H, N-H), 3.27 (d, *J* = 6.1 Hz, 2H, H-8), 2.07 – 1.95 (m, 2H, H-3), 1.94 – 1.80 (m, 2H, H-7), 1.80 – 1.67 (m, 4H, H-6), 1.57 – 1.46 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.9 (C-9), 139.0 (C-2), 136.7 (C-11), 128.7 (Ar-

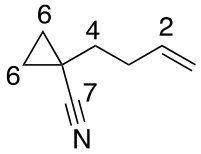
CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 114.4 (C-1), 66.8 (C-10), 47.3 (C-8), 41.8 (C-5), 36.7 (C-4), 29.2 (C-6), 28.4 (C-3), 15.1 (C-7) ppm; **IR (ATR)**: ν_{max} 3339, 3072, 3034, 2931, 2868, 1703, 1640, 1523, 1454, 1344, 1244, 1135, 1004, 910, 853, 775, 739, 697 cm^{-1}; **HRMS (ESI):** 274.1798 ($[MH]^+$ $C_{17}H_{24}NO_2$ requires 274.1802).

(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclobutyl)pent-2-enethioate (3e)



Compound **3e** was synthesised using the **general procedure A** with thioester **2a** (202 mg, 1.133 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (32 mg, 0.037 mmol, 0.1 eq) and copper iodide (72 mg, 0.377 mmol, 1 eq), Cbz-amine **1e** (103 mg, 0.377 mmol, 1 eq). Compound **3e** was obtained as a pale brown oil (127 mg, 0.300 mmol, 80% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.46 – 7.29 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 8.0 Hz, 2H, H-3), 6.98 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.20 (d, *J* = 15.5 Hz, 1H, H-7), 5.12 (s, 2H, H-16), 4.80 (t, *J* = 6.4 Hz, 1H, N-H), 3.28 (d, *J* = 6.4 Hz, 2H, H-14), 2.38 (s, 3H, H-1), 2.26 – 2.14 (m, 2H, H-9), 1.97 – 1.83 (m, 2H, H-13), 1.81 – 1.68 (m, 4H, H-12), 1.65 – 1.53 (m, 2H, H-10) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.5 (C-8), 139.6 (C-2), 136.5 (C-17), 134.7 (C-4), 130.0 (C-3), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 127.8 (C-7), 124.1 (C-5), 66.8 (C-16), 46.9 (C-14), 41.8 (C-11), 35.4 (C-10), 29.2 (C-12), 27.0 (C-9), 21.4 (C-1), 15.0 (C-13) ppm; **IR** (ATR): ν_{max} 3350, 2927, 1689, 1630, 1526, 1494, 1453, 1238, 1132, 1013, 807, 774, 697, 619, 475 cm^{-1}; **HRMS** (ESI) 424.1958 ($[MH]^+$ $C_{25}H_{30}NO_3S$ requires 424.1941).

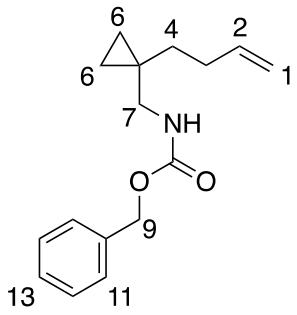
1-(But-3-en-1-yl)cyclopropanecarbonitrile (7f)



Compound **7f** was synthesised using the **general procedure C** with diisopropylamine (2 mL, 16 mmol, 1.1 eq), *n*-BuLi (2.08 M in hexanes, 8.5 mL, 18 mmol, 1.2 eq), cyclopropane cyanide (1 mL, 15 mmol, 1 eq) and 4-bromobutene (3 mL, 30 mmol, 2 eq). Compound **7f** was obtained as a pale-yellow oil (625 mg, 5 mmol, 35% yield) after column chromatography (10% Et_2O/pentane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.5, 6.7 Hz, 1H, H-2), 5.10 (dt, *J* = 16.9, 1.8 Hz, 1H, H-1), 5.00 (dd, *J* = 10.5, 1.8 Hz, 1H, H-1'), 2.40 – 2.30 (m, 2H, H-3), 1.60 – 1.50 (m, 2H, H-4), 1.23 – 1.20 (m, 2H, H-6), 0.81 – 0.78 (m, 2H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.7 (C-2), 123.3 (C-7), 115.9 (C-1), 34.7 (C-4), 31.8 (C-3) , 13.9

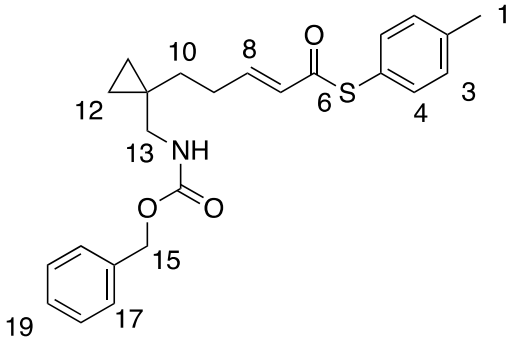
(C-6), 9.5 (C-5) ppm; **IR** (ATR): ν_{max} 3080, 2927, 2237, 1642, 1451, 1430, 1068, 1035, 990, 914, 625, 572 cm^{-1}; **HRMS** (ESI) 122.0962 ($[MH]^+$ $C_8H_{12}N$ requires 122.0964).

Benzyl ((1-(but-3-en-1-yl)cyclopropyl)methyl)carbamate (1f)



Compound **1f** was synthesised using **general procedure D** with $LiAlH_4$ (490 mg, 13 mmol, 1.5 eq), nitrile **7f** (1.05 g, 8.66 mmol, 1 eq) to give the crude amine which was acidified by addition of 2M HCl in ether (4.8 mL, 1.1 eq) and stirred for 20 hours at room temperature to form the corresponding HCl salt which was used without further purification. The HCl salt of the amine was Cbz protected using K_2CO_3 solution (50% w/w aq, 3 mL, 22 mmol, 1.2 eq) and benzyl chloroformate (3 mL, 22 mmol, 1.2 eq). Compound **1f** was obtained as a light-yellow oil (780.5 mg, 3 mmol, 38% yield over two steps) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.28 (m, 5H, H-11, H-12, H-13), 5.81 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H, H-2), 5.13 (s, 2H, H-9), 5.01 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.4, 1.8 Hz, 1H, H-1'), 4.82 (t, *J* = 6.0 Hz, 1H, N-H), 3.10 (d, *J* = 6.0 Hz, 2H, H-7), 2.22 – 2.02 (m, 2H, H-3), 1.46 – 1.30 (m, 2H, H-4), 0.42 – 0.30 (m, 4H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ ppm 156.5 (C-8), 138.7 (C-2), 136.7 (C-10), 128.6 (Ar-CH), 128.2 (Ar-CH), 114.5 (C-1), 66.71 (C-9), 47.1 (C-7), 34.1 (C-4), 31.0 (C-3), 20.0 (C-5), 10.7 (C-6) ppm; **IR** (ATR): ν_{max} 3337, 3072, 2928, 1703, 1640, 1525, 1454, 1240, 1133, 1046, 1015, 995, 910, 775, 735, 697, 627 cm^{-1}; **HRMS** (ESI): 260.1651 ($[MH]^+$ $C_{16}H_{22}NO_2$ requires 260.1645).

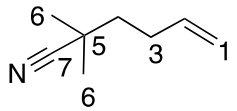
(*E*)-S-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)pent-2-enethioate (3f)



Compound **3f** was synthesised using the **general procedure A** with thioester **2a** (214 mg, 1.210 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (34 mg, 0.040 mmol, 0.1 eq) and copper iodide (76 mg, 0.400 mmol, 1 eq), Cbz-amine **1f** (104 mg, 0.400, 1 eq). Compound **3f** was obtained as a pale brown oil (150 mg, 0.365 mmol, 91% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.29 (m, 7H, H-17, H-18, H-19, H-4), 7.23 (d, *J* = 8.1 Hz, 2H, H-3), 6.97 (dt, *J* = 15.5, 6.9 Hz, 1H, H-8), 6.17

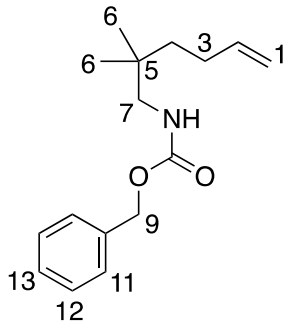
(d, *J* = 15.5 Hz, 1H, H-7), 5.13 (s, 2H, H-15), 4.94 (t, *J* = 5.6 Hz, 1H, N-H), 3.11 (d, *J* = 5.6 Hz, 2H, H-13), 2.38 (s, 3H, H-1), 2.37 – 2.28 (m, 2H, H-9), 1.52 – 1.37 (m, 2H, H-10), 0.48 – 0.29 (m, 4H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.5 (C-14), 146.2 (C-8), 139.7 (C-2), 136.6 (C-16), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 127.9 (C-7), 124.1 (C-5), 66.9 (C-15), 46.8 (C-13), 33.2 (C-10), 29.6 (C-9), 21.4 (C-1), 20.1 (C-11), 10.8 (C-12) ppm; **IR** (ATR): ν_{max} 3346, 2922, 1689, 1630, 1519, 1494, 1453, 1234, 1042, 1016, 988, 806, 751, 697, 515, 475 cm^{-1}; **HRMS** (ESI) 410.1791 ([MH]$^+$ $C_{24}H_{28}NO_3S$ requires 410.1784).

2,2-Dimethylhex-5-enenitrile (7g)



Compound **7g** was synthesised using the **general procedure C** with diisopropylamine (2 mL, 16 mmol, 1.1 eq), *n*-BuLi (1.89 M in hexanes, 9 mL, 17 mmol, 1.2 eq), isobutyronitrile (1 mL, 15 mmol, 1 eq) and 4-bromobutene (3 mL, 29 mmol, 2 eq). Compound **7g** was obtained as a pale-yellow oil (1 g, 10 mmol, 69% yield) after column chromatography (10% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 17.1, 10.1, 6.5 Hz, 1H, H-2), 5.06 (dd, *J* = 17.1, 1.8 Hz, 1H, H-1), 4.99 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 2.28 – 2.15 (m, 2H, H-3), 1.65 – 1.53 (m, 2H, H-4), 1.34 (s, 6H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.0 (C-2), 124.9 (C-7), 115.5 (C-1), 40.2 (C-4), 32.2 (C-5), 29.6 (C-3), 26.7 (C-6) ppm; **IR** (ATR): ν_{max} 3082, 2979, 2939, 2234, 1643, 1455, 1370, 1393, 1249, 1208, 996, 914, 773, 629 cm^{-1}; **HRMS** (APCI) 124.1120 ([MH]$^+$ $C_8H_{14}N$ requires 124.1120).

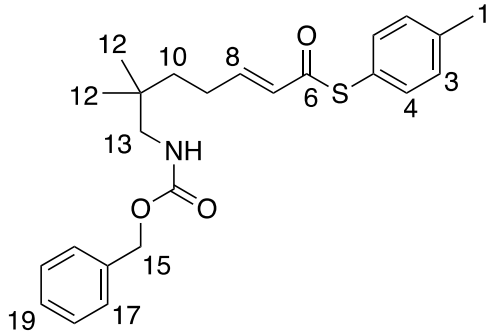
Benzyl (2,2-dimethylhex-5-en-1-yl)carbamate (1g)



Compound **1g** was synthesised using the **general procedure D** with $LiAlH_4$ (693 mg, 18.2 mmol, 1.5 eq), nitrile **7g** (1.5 g, 12.1 mmol, 1 eq) to give the amine as a colourless oil (643 mg, 5.05 mmol, 41% yield) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.83 mL, 6.06 mmol, 1.2 eq) and benzyl chloroformate (1.16 mL, 6.02 mmol, 1.2 eq). Compound **1g** was obtained as a light brown oil (739 mg, 2.82 mmol, 56% yield) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.47 – 7.27 (m, 5H, H-11, H-12, H-13), 5.81 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H, H-2), 5.11 (s, 2H, H-9), 5.02 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.76 (t, *J* = 6.4 Hz, N-H), 3.04 (d, *J* = 6.4 Hz, 2H, H-7), 2.17 – 1.77 (m, 2H, H-3), 1.43 – 1.11 (m, 2H, H-4), 0.89 (s, 6H, H-6) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.7 (C-8), 139.1 (C-2), 136.6 (C-10), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 114.2 (C-1), 66.6 (C-9), 50.9 (C-7), 38.7 (C-4), 34.3 (C-5), 28.3 (C-3), 24.7 (C-6) ppm; **IR**

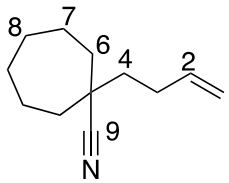
(ATR): ν_{max} 3353, 3071, 3031, 2959, 1701, 1640, 1524, 1454, 1235, 1135, 995, 908, 734, 696 cm^{-1}; **HRMS** (ESI) 284.1617 ($[MNa]^+$ $C_{16}H_{23}NNaO_2$ requires 284.1621).

(*E*)-S-*p*-Tolyl 7-(((benzyloxy)carbonyl)amino)-6,6-dimethylhept-2-enethioate (3g)



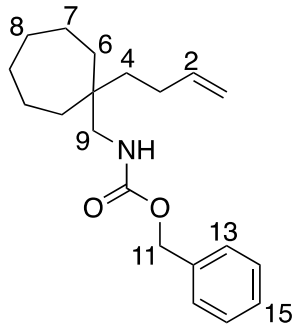
Compound **3g** was synthesised using the **general procedure A** with thioester **2a** (214 mg, 1.210 mmol, 3 eq), Grubbs Catalyst™ 2nd generation (29.5 mg, 0.034 mmol, 0.1 eq) and copper iodide (66 mg, 0.34 mmol, 1 eq), Cbz-amine **1g** (91 mg, 0.348 mmol, 1 eq). Compound **3g** was obtained as a pale-yellow oil (100 mg, 0.242 mmol, 70% yield) after column chromatography (10-12% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.27 (m, 7H, H-17, H-18, H-19, H-4), 7.23 (d, *J* = 7.9 Hz, 2H, H-3), 6.96 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.18 (d, *J* = 15.5 Hz, 1H, H-7), 5.11 (s, 2H, H-15), 4.78 (t, *J* = 6.6 Hz, 1H, N-H), 3.05 (d, *J* = 6.6 Hz, 2H, H-13), 2.38 (s, 3H, H-1), 2.29 – 2.11 (m, 2H, H-9), 1.43 – 1.30 (m, 2H, H-10), 0.90 (s, 6H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.8 (C-14), 146.7 (C-8), 139.7 (C-2), 136.6 (C-16), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 127.8 (C-7), 124.1 (C-5), 66.9 (C-15), 50.8 (C-13), 37.5 (C-10), 34.6 (C-11), 27.1 (C-9), 24.8 (C-12), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3346, 2943, 2864, 1694, 1630, 1523, 1494, 1454, 1233, 1133, 1003, 806, 752, 697, 620, 474 cm^{-1}; **HRMS** (ESI) 412.1933 ($[MH]^+$ $C_{24}H_{30}NO_3S$ requires 412.1941).

1-(But-3-en-1-yl)cycloheptanecarbonitrile (7h)



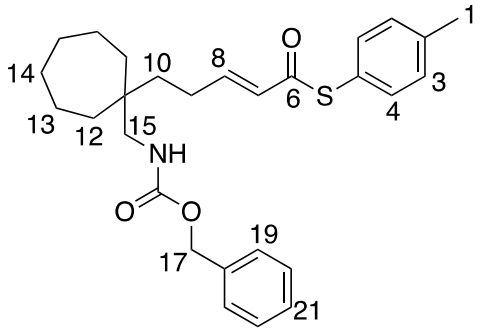
Compound **7h** was synthesised using the **general procedure C** with diisopropylamine (1.25 mL, 9 mmol, 1.1 eq), *n*-BuLi (1.89 M in hexanes, 5 mL, 10 mmol, 1.2 eq), cycloheptane carbonitrile (1 g, 8 mmol, 1 eq) and 4-bromobutene (2 mL, 16 mmol, 2 eq). Compound **7h** was obtained as a pale-yellow oil (1.2 g, 7 mmol, 86% yield) after column chromatography (10% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, H-2), 5.06 (dd, *J* = 16.9, 1.7 Hz, 1H, H-1), 4.99 (dd, *J* = 10.1, 1.7 Hz, 1H, H-1'), 2.31 – 2.17 (m, 2H, H-3), 2.07 – 1.95 (m, 2H, H-6), 1.77 – 1.63 (m, 6H, H-7, H-8, H-8'), 1.63 – 1.58 (m, 2H, H-4), 1.58 – 1.45 (m, 4H, H-6', H-7') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 137.3 (C-2), 124.8 (C-9), 115.4 (C-1), 41.3 (C-5), 40.0 (C-4), 38.0 (C-6), 29.5 (C-3), 28.1 (C-7), 23.5 (C-8) ppm; **IR** (ATR): ν_{max} 3079, 2928, 2858, 2229, 1642, 1462, 1450, 1367, 1150, 995, 912, 851, 683 cm^{-1}; **HRMS** (ESI) 200.1417 ($[MNa]^+$ $C_{12}H_{19}NNa$ requires 200.1410).

Benzyl ((1-(but-3-en-1-yl)cycloheptyl)methyl)carbamate (1h)



Compound **1h** was synthesised using the **general procedure D** with $LiAlH_4$ (278 mg, 7.32 mmol, 1.5 eq), nitrile **7h** (1.13 g, 6.37 mmol, 1 eq) to give the crude product as a colourless oil (1.16 g, 6.39 mmol). The crude amine (908 mg, 5.008 mmol, 1 eq) was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.83 mL, 6.00 mmol, 1.2 eq) and benzyl chloroformate (0.86 mL, 6.00 mmol, 1.2 eq). Compound **1h** was obtained a colourless oil (1.32 g, 4.18 mmol, 66% yield over two steps) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.27 (m, 5H, H-13, H-14, H-15), 5.79 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, H-2), 5.10 (s, 2H, H-11), 5.00 (dd, *J* = 16.9, 1.8 Hz, 1H, H-1), 4.93 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.72 (t, *J* = 6.4 Hz, 1H, N-H), 3.07 (d, *J* = 6.4 Hz, 2H, H-9), 2.07 – 1.88 (m, 2H, H-3), 1.58 – 1.40 (m, 8H, H-7, H-8), 1.41 – 1.32 (m, 4H, H-6), 1.32 – 1.24 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.8 (C-10), 139.3 (C-2), 136.7 (C-12), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 114.3 (C-1), 66.8 (C-11), 48.4 (C-9), 39.5 (C-5), 37.3 (C-4), 36.5 (C-6), 31.0 (C-7), 28.0 (C-3), 22.9 (C-8) ppm; **IR** (ATR): ν_{max} 3342, 2922, 2854, 1707, 1640, 1526, 1460, 1240, 1140, 1002, 908, 735, 697 cm^{-1}; **HRMS** (ESI) 338.2101 ($[MNa]^+$ $C_{20}H_{29}NaO_2$ requires 338.2090).

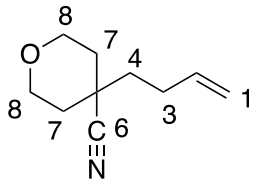
(*E*)-*S*-*p*-Tolyl-5-(1-((((benzyloxy)carbonyl)amino)methyl)cycloheptyl)pent-2-enethioate (3h)



Compound **3h** was synthesised using the **general procedure A** with thioester **2a** (182 mg, 1.01 mmol, 3 eq), Hoveyda-Grubbs Catalyst^{TM} 2nd generation (28 mg, 0.033 mmol, 0.1 eq) and copper iodide (64.5 mg, 0.33 mmol, 1 eq) and Cbz-amine **1h** (107 mg, 0.33 mmol, 1 eq). Compound **3h** was obtained as a light brown oil (101 mg, 0.216 mmol, 64% yield) after column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.27 (m, 7H, H-19, H-20, H-21, H-4), 7.22 (d, *J* = 8.0 Hz, 2H, H-3), 6.96 (dt, *J* = 15.6, 6.8 Hz, 1H, H-8), 6.18 (d, *J* = 15.6 Hz, 1H, H-7), 5.11 (s, 2H, H-17), 4.72 (d, *J* = 6.4 Hz, 1H, N-H), 3.05 (d, *J* = 6.4 Hz, 2H, H-15), 2.38 (s, 3H, H-1), 2.26 – 2.11 (m, 2H, H-9), 1.57 – 1.40 (m, 8H, H-13, H-14), 1.40 – 1.27 (m, 6H, H-10, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.8 (C-16), 146.9

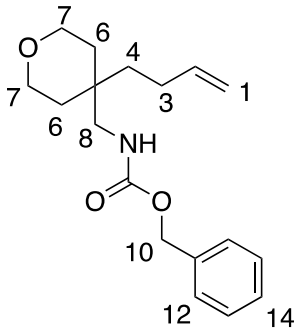
(C-8), 139.7 (C-2), 136.6 (C-18), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.3 (Ar-CH), 127.8 (C-7), 124.2 (C-5), 66.9 (C-17), 48.2 (C-15), 39.6 (C-11), 36.4 (C-12), 36.0 (C-10), 30.9 (C-13), 26.7 (C-9), 22.8 (C-14), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3356, 3032, 2919, 2853, 1694, 1630, 1524, 1494, 1458, 1235, 1136, 1014, 806, 697, 615 cm^{-1}; **HRMS** (ESI) 488.2238 ($[MNa]^+$ $C_{28}H_{35}NNaO_3S$ requires 488.2230).

4-(But-3-en-1-yl)tetrahydro-2H-pyran-4-carbonitrile (7i)



Compound **7i** was synthesised using the **general procedure C** with diisopropylamine (3 mL, 20 mmol, 1.1 eq), *n*-BuLi (2.0 M in hexanes, 11 mL, 21 mmol, 1.2 eq), 4-cyanotetrahydropyran (2 mL, 18 mmol, 1 eq) and 4-bromobutene (4 mL, 36 mmol, 2 eq). Compound **7i** was obtained as a pale-yellow oil (3 g, 16 mmol, 90% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.75 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1H, H-2), 5.02 (dd, *J* = 16.8, 1.8 Hz, 1H, H-1), 4.95 (dd, *J* = 10.3, 1.8 Hz, 1H, H-1'), 3.98 – 3.93 (m, 2H, H-8), 3.62 (td, *J* = 12.3, 2.0 Hz, 2H, H-8'), 2.31 – 2.06 (m, 2H, H-3), 1.81 (dd, *J* = 13.5, 2.1 Hz, 2H, H-7), 1.65 – 1.57 (m, 2H, H-4), 1.60 (td, *J* = 13.0, 4.6 Hz, 2H, H-7') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.9 (C-2), 122.5 (C-6), 115.9 (C-1), 64.8 (C-8), 39.6 (C-4), 36.8 (C-5), 35.5 (C-7), 28.4 (C-3) ppm; **IR** (ATR): ν_{max} 3082, 2954, 2854, 2926, 2230, 1642, 1453, 1242, 1109, 1013, 912, 838, 753, 562 cm^{-1}; **HRMS** (ESI) 188.1048 ($[MNa]^+$ $C_{10}H_{15}NNaO$ requires 188.1046).

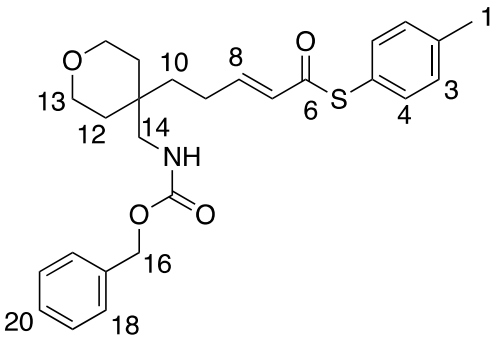
Benzyl ((4-(but-3-en-1-yl)tetrahydro-2H-pyran-4-yl)methyl)carbamate (1i)



Compound **1i** was synthesised using the **general procedure D** with $LiAlH_4$ (73 mg, 1.93 mmol, 1.5 eq), nitrile **7i** (213 mg, 1.28 mmol, 1 eq) to give the crude product as a colourless oil (334 mg, 1.97 mmol) which was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.32 mL, 2.36 mmol, 1.2 eq) and benzyl chloroformate (0.33 mL, 2.36 mmol, 1.2 eq). Compound **1i** was obtained as a colourless oil (283.5 mg, 0.934 mmol, 73% yield over two steps) after column chromatography (20-50% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.45 – 7.28 (m, 5H, H-12, H-13, H-14), 5.79 (ddt, *J* = 17.0, 10.1, 6.4 Hz, 1H, H-2), 5.10 (s, 2H, H-10), 5.03 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.96 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.77 (t, *J* = 6.4 Hz, 1H, N-H), 3.76 – 3.54 (m, 4H, H-7), 3.23 (d, *J* = 6.4 Hz, 2H, H-8), 2.06 – 1.89 (m, 2H, H-3), 1.53 – 1.32 (m, 6H,

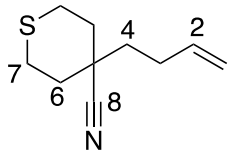
H-6, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.8 (C-9), 138.6 (C-2), 136.5 (C-11), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 114.8 (C-1), 67.0 (C-10), 63.5 (C-7), 46.1 (C-8), 34.8 (C-4), 34.6 (C-5), 33.4 (C-6), 27.2 (C-3) ppm; **IR** (ATR): ν_{max} 3329, 2928, 2854, 1705, 1640, 1536, 1453, 1239, 1137, 1104, 1017, 995, 909, 775, 736, 697, 574 cm^{-1}; **HRMS** (ESI) 304.1905 ([MH]$^+$ $C_{18}H_{26}NO_3$ requires 304.1907).

(*E*)-S-*p*-Tolyl-5-(4-((((benzyloxy)carbonyl)amino)methyl)tetrahydro-2H-pyran-4-yl)pent-2-enethioate (3i)



Compound **3i** was synthesised using the **general procedure A** with thioester **2a** (156 mg, 0.875 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (25 mg, 0.029 mmol, 0.1 eq), copper iodide (55 mg, 0.29 mmol, 1 eq) and Cbz-amine **1i** (88.5 mg, 0.29 mmol, 1 eq). Compound **3i** was obtained as a colourless oil (104.5 mg, 0.230 mmol, 79% yield) after column chromatography (25-40% EtOAc/hexane) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.43 – 7.29 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 8.2 Hz, 2H, H-3), 6.94 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.19 (d, *J* = 15.5 Hz, 1H, H-7), 5.11 (s, 2H, H-16), 4.80 (t, *J* = 6.8 Hz, 1H, N-H), 3.81 – 3.44 (m, 4H, H-13), 3.23 (d, *J* = 6.8 Hz, 2H, H-14), 2.38 (s, 3H, H-1), 2.25 – 2.14 (m, 2H, H-9), 1.54 – 1.47 (m, 2H, H-10), 1.47 – 1.31 (m, 4H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.0 (C-8), 139.8 (C-2), 136.4 (C-17), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.1 (C-7), 124.0 (C-5), 67.1 (C-16), 63.4 (C-13), 46.2 (C-14), 34.7 (C-11), 33.5 (C-10), 33.3 (C-12), 25.9 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3342, 2932, 1700, 1630, 1536, 1494, 1453, 1241, 1139, 1105, 1017, 808, 737, 618, 475 cm^{-1}; **HRMS** (ESI) 454.2053 ([MH]$^+$ $C_{26}H_{32}NO_4S$ requires 454.2047).

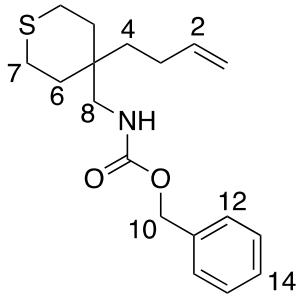
4-(But-3-en-1-yl)tetrahydro-2*H*-thiopyran-4-carbonitrile (7j)



Compound **7j** was synthesised using the **general procedure C** with diisopropylamine (1.21 mL, 8.64 mmol, 1.1 eq), *n*-BuLi (1.89 M in hexanes, 5 mL, 9.43 mmol, 1.2 eq), tetrahydrothiopyran-4-carbonitrile (1 g, 7.86 mmol, 1 eq) and 4-bromobutene (1.6 mL, 15.72 mmol, 2 eq). Compound **7j** was obtained as a colourless oil (1.01 g, 5.57 mmol, 71% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.79 (ddt, *J* = 17.0, 10.5, 6.4 Hz, 1H, H-2), 5.07 (dd, *J* = 17.0, 1.3 Hz, 1H, H-1), 5.01 (dd, *J* = 10.5, 1.3 Hz, 1H, H-1'),

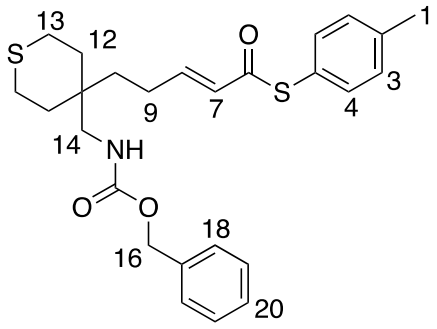
3.00 (td, *J* = 12.5, 2.2 Hz, 2H, H-7), 2.62 – 2.50 (m, 2H, H-7'), 2.30 – 2.17 (m, 4H, H-6, H-3), 1.70 – 1.56 (m, 4H, H-6', H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 136.8 (C-2), 122.1 (C-8), 115.8 (C-1), 39.8 (C-4), 38.6 (C-5), 36.5 (C-6), 28.3 (C-3), 25.3 (C-7) ppm; **IR** (ATR): ν_{max} 3078, 2940, 2912, 2231, 1641, 1452, 1430, 1277, 1141, 996, 939, 916, 616 cm^{-1}; **HRMS** (ESI) 204.0823 ([MNa]$^+$ $C_{10}H_{15}NNaS$ requires 204.0817).

Benzyl ((4-(but-3-en-1-yl)tetrahydro-2*H*-thiopyran-4-yl)methyl)carbamate (1j)



Compound **1j** was synthesised using the **general procedure D** with $LiAlH_4$ (247 mg, 6.24 mmol, 1.5 eq), nitrile **7j** (754 mg, 4.15 mmol, 1 eq) to give the crude product as a pale-yellow oil (874 mg, 4.71 mmol). The crude amine (7034 mg, 3.79 mmol, 1 eq) was Cbz protected with K_2CO_3 solution (50% w/w aq, 0.62 mL, 4.55 mmol, 1.2 eq) and benzyl chloroformate (0.65 mL, 4.55 mmol, 1.2 eq). Compound **1j** was obtained as a colourless oil (883.5 mg, 2.76 mmol, 67% yield over two steps) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.44 – 7.29 (m, 5H, H-12, H-13, H-14), 5.78 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H, H-2), 5.09 (s, 2H, H-10), 5.02 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.96 (dd, *J* = 10.1, 1.8 Hz, 1H, H-1'), 4.72 (t, *J* = 6.9 Hz, 1H, N-H), 3.13 (d, *J* = 6.9 Hz, 2H, H-8), 2.71 – 2.50 (m, 4H, H-7), 2.05 – 1.89 (m, 2H, H-3), 1.73 – 1.56 (m, 4H, H-6), 1.42 – 1.30 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.7 (C-9), 138.6 (C-2), 136.5 (C-11), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 114.8 (C-1), 67.0 (C-10), 47.1 (C-8), 35.7 (C-5), 34.2 (C-4, C-6), 26.9 (C-3), 23.2 (C-7) ppm; **IR** (ATR): ν_{max} 3338, 3068, 2925, 1706, 1639, 1528, 1454, 1240, 1144, 999, 912, 774, 736, 697 cm^{-1}; **HRMS** (ESI) 320.1680 ([MH]$^+$ $C_{18}H_{26}NO_2S$ requires 320.1679).

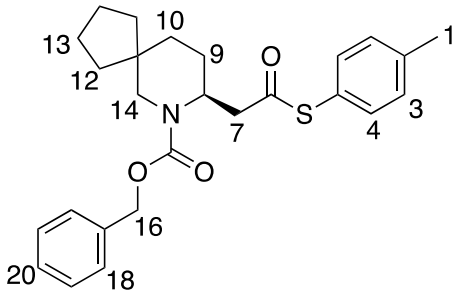
(*E*)-*S*-*p*-Tolyl-5-(4-((((benzyloxy)carbonyl)amino)methyl)tetrahydro-2*H*-thiopyran-4-yl)pent-2-enethioate (3j)



Compound **3j** was synthesised using the **general procedure A** with thioester **2a** (180 mg, 1.01 mmol, 3 eq), Hoveyda-Grubbs Catalyst^{TM} 2nd generation (29 mg, 0.033 mmol, 0.1 eq) and copper iodide (64 mg, 0.33 mmol, 1.1 eq) and Cbz-amine **1j** (108 mg, 0.33 mmol, 1 eq).

Compound **3j** was obtained as a pale-yellow oil (68 mg, 0.144 mmol, 43% yield) after column chromatography (15% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.42 – 7.28 (m, 7H, H-18, H-19, H-20, H-4), 7.23 (d, *J* = 7.7 Hz, 2H, H-3), 6.93 (dt, *J* = 15.5, 6.8 Hz, 1H, H-8), 6.20 (d, *J* = 15.5 Hz, 1H, H-7), 5.10 (s, 2H, H-16), 4.74 (t, *J* = 6.7 Hz, 1H, N-H), 3.15 (d, *J* = 6.7 Hz, 2H, H-14), 2.72 – 2.50 (m, 4H, H-13), 2.38 (s, 3H, H-1), 2.27 – 2.11 (m, 2H, H-9), 1.74 – 1.62 (m, 4H, H-12), 1.48 – 1.39 (m, 2H, H-10) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.5 (C-6), 156.8 (C-15), 146.0 (C-8), 139.8 (C-2), 136.4 (C-17), 134.7 (C-4), 130.1 (C-3), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.1 (C-7), 124.0 (C-5), 67.1 (C-16), 47.0 (C-14), 35.8 (C-11), 34.1 (C-12), 33.0 (C-10), 25.6 (C-9), 23.2 (C-13), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 3356, 2924, 1701, 1630, 1529, 1492, 1453, 1240, 1146, 1016, 985, 808, 735, 698 cm^{-1}; **HRMS** (ESI) 492.1649 ([MNa]$^+$ $C_{26}H_{31}NNaO_3S_2$ requires 492.1638).

(*S*)-Benzyl 8-(2-oxo-2-(*p*-tolylthio)ethyl)-7-azaspiro[4.5]decane-7-carboxylate (4d)

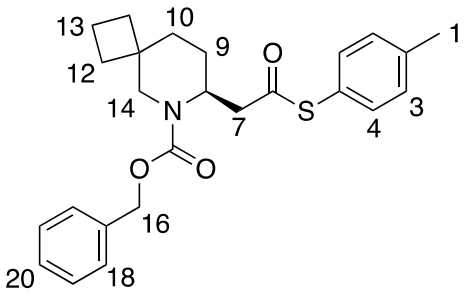


Racemic: Compound **4d** was synthesized using the **general procedure B** using the amino-thioester **3d** (21 mg, 0.047 mmol, 1 eq) and rac-CSA (33 mg, 0.143 mmol, 3 eq). Compound **4d** was obtained as a light brown oil (19.5 mg, 0.044 mmol, 93% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **4d** was synthesized using the **general procedure B** using the amino-thioester **3d** (18.5 mg, 0.042 mmol, 1 eq) and (*R*)-anthra (6 mg, 0.008 mmol, 0.2 eq). Compound **4d** was obtained as a light-brown oil (15 mg, 0.033 mmol, 80% yield, 96:4 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-18, H-19, H-20), 7.30 – 7.20 (br. m, 2H, H-4), 7.20 (d, *J* = 7.8 Hz, 2H, H-3), 5.27 – 5.01 (br. m, 2H, H-16), 4.98 – 4.68 (br. m, 1H, H-8), 4.02 – 3.55 (br. m, 1H, H-14), 2.89 (d, *J* = 7.7 Hz, 2H, H-7), 2.78 – 2.56 (br. m, 1H, H-14'), 2.36 (s, 3H, H-1), 1.91 – 1.72 (m, 1H, H-9), 1.72 – 1.46 (m, 7H, H-9', H-10, H-12, H-12', H-13), 1.48 – 1.28 (br. m, 3H, H-13, H-13'), 1.28 – 1.08 (br. m, 1H, H-12') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.7 (C-15), 139.8 (C-2), 136.9 (C-17), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.2 (C-16), 48.4 (C-14), 48.2 (C-8), 43.5 (C-7), 42.7 (C-11), 38.7 (C-13), 33.8 (C-12), 31.8 (C-13'), 25.7 (C-9), 25.0 (C-12'), 24.3 (C-10), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2924, 2855, 1695, 1420, 1340, 1265, 1150, 1106, 1013, 807, 737, 696, 606, 474 cm^{-1}; **HRMS** (ESI) 438.2101 ([MH]$^+$ $C_{26}H_{32}NO_3S$ requires 438.2097); **$[\alpha]_D^{20}$** +47.5 (c= 0.7285, $CHCl_3$).

(*S*)-Benzyl 7-(2-oxo-2-(p-tolylthio)ethyl)-6-azaspiro[3.5]nonane-6-carboxylate (4e)

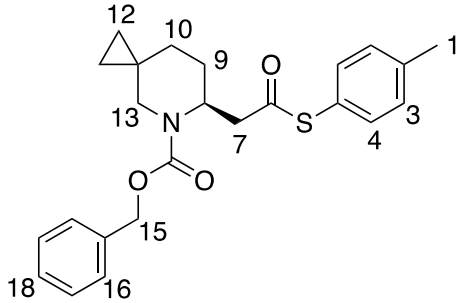


Racemic: Compound **4e** was synthesized using the **general procedure B** using the amino-thioester **3e** (21 mg, 0.049 mmol, 1 eq) and rac-CSA (35 mg, 0.149 mmol, 3 eq). Compound **4e** was obtained as a light-brown oil (18 mg, 0.042 mmol, 84% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **4e** was synthesized using the **general procedure B** using the amino-thioester **3e** (20 mg, 0.047 mmol, 1 eq), (*R*)-anthra (6.5 mg, 0.009 mmol, 0.2 eq). Compound **4e** was obtained as a light-brown oil (12.5 mg, 0.029 mmol, 63% yield, 82:18 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.42 – 7.27 (m, 5H, H-18, H-19, H-20), 7.26 – 7.21 (m, 2H, H-4), 7.19 (d, *J* = 8.0 Hz, 2H, H-3), 5.23 – 4.99 (br. m, 2H, H-16), 4.92 – 4.62 (br. m, 1H, H-8), 4.25 – 3.95 (br. m, 1H, H-14), 2.84 (d, *J* = 7.7 Hz, 2H, H-7), 2.81 – 2.62 (br. m, 1H, H-14'), 2.37 (s, 3H, H-1), 2.09 – 1.77 (m, 3H, H-12, H-12'), 1.77 – 1.58 (m, 5H, H-9, H-10, H-12', H-13), 1.58 – 1.41 (m, 2H, H-10', H-13') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.3 (C-6), 155.7 (C-15), 139.8 (C-2), 136.8 (C-17), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.3 (C-16), 48.6 (C-14), 48.1 (C-8), 43.3 (C-7), 38.3 (C-11), 31.3 (C-13), 30.5 (C-9), 29.7 (C-12), 24.5 (C-10), 21.4 (C-1), 15.0 (C-12') ppm; **IR** (ATR): ν_{max} 2922, 2850, 1694, 1494, 1418, 1334, 1287, 1230, 1195, 1096, 1056, 1027, 989, 918, 807, 746, 697 cm^{-1}; **HRMS** (ESI) 424.1946 ($[MH]^+$ $C_{25}H_{30}NO_3S$ requires 424.1941); **$[\alpha]_D^{20}$** +31.5 (c= 0.59, $CHCl_3$).

(*S*)-Benzyl 6-(2-oxo-2-(p-tolylthio)ethyl)-5-azaspiro[2.5]octane-5-carboxylate (4f)

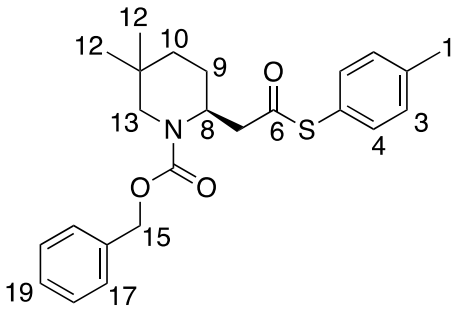


Racemic: Compound **4f** was synthesized using the **general procedure B** using the amino-thioester **3f** (20 mg, 0.047 mmol, 1 eq) and rac-CSA (33 mg, 0.143 mmol, 3 eq). Compound **4f** was obtained as a light-brown oil (16 mg, 0.038 mmol, 80% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **4f** was synthesized using the **general procedure B** using the amino-thioester **3f** (17.5 mg, 0.042 mmol, 1 eq), (*R*)-anthra (6 mg, 0.008 mmol, 0.2 eq). Compound **4f** was obtained as a light-brown oil (15 mg, 0.037 mmol, 87% yield, 89:11 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 – 7.27 (m, 5H, H-16, H-17, H-18), 7.26 – 7.21 (br. m, 2H, H-4), 7.19 (d, *J* = 8.2 Hz, 2H, H-3), 5.20 – 5.03 (m, 2H, H-15), 5.02 – 4.81 (br. m, 1H, H-8), 3.48 – 3.07 (br. m, 2H, H-13), 3.03 – 2.82 (m, 2H, H-7), 2.37 (s, 3H, H-1), 2.10 (ddd, *J* = 13.6, 13.6, 3.7 Hz, 1H, H-10), 1.97 – 1.82 (m, 1H, H-9), 1.79 – 1.61 (m, 1H, H-9'), 0.90 (ddd, *J* = 13.4, 3.7, 3.7 Hz, 1H, H-10'), 0.66 – 0.28 (m, 3H, H-12, H-12'), 0.28 – 0.14 (m, 1H, H-12') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.4 (C-14), 139.8 (C-2), 136.8 (C-16), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 124.1 (C-5), 67.3 (C-15), 48.6 (C-8), 47.6 (C-13), 43.7 (C-7), 28.3 (C-10), 27.6 (C-9), 21.4 (C-1), 18.2 (C-11), 12.4 (C-12), 10.19 (C-12') ppm; **IR** (ATR): ν_{max} 2928, 2856, 1697, 1494, 1418, 1342, 1303, 1211, 1145, 1110, 1011, 975, 743, 697, 605, 473 cm^{-1}; **HRMS** (ESI) 410.1794 ([MH]$^+$ $C_{24}H_{28}NO_3S$ requires 410.1784); **$[\alpha]_D^{20}$** +24.3 (c= 0.715, $CHCl_3$).

(*S*)-Benzyl 5,5-dimethyl-2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (4g)



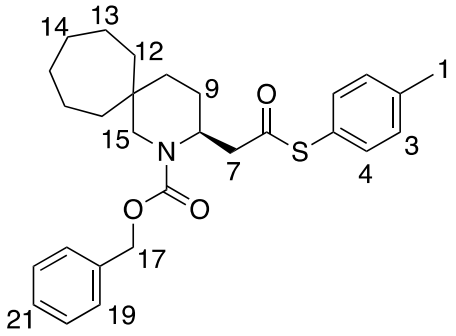
Racemic: Compound **4g** was synthesized using the **general procedure B** using the amino-thioester **3g** (23 mg, 0.055 mmol, 1 eq) and rac-CSA (39 mg, 0.166 mmol, 3 eq). Compound **4g** was obtained as a pale-yellow oil (11.5 mg, 0.028 mmol, 51% yield) after column chromatography (10% EtOAc/hexane).

Asymmetric: Compound **4g** was synthesized using the **general procedure B** using the amino-thioester **3g** (25 mg, 0.058 mmol, 1 eq), (*R*)-anthra (8 mg, 0.012 mmol, 0.2 eq). Compound **4g** was obtained as a pale-yellow oil (7.14 mg, 0.017 mmol, 29% yield (58% brsm), 95:5 e.r.) after column chromatography (15% EtOAc /pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.45 – 7.27 (m, 5H, H-17, H-18, H-19), 7.30 – 7.20 (br. m, 2H, H-4), 7.20 (d, *J* = 8.1 Hz, 2H, H-3), 5.25 – 5.00 (br. m, 2H, H-15), 5.00 – 4.73 (br. m, 1H, H-8), 3.89 – 3.50 (br. m, 1H, H-13), 2.86 (d, *J* = 7.9 Hz, 2H, H-7), 2.77 – 2.55 (br. m, 1H, H-13'), 2.37 (s, 3H, H-1), 2.01 – 1.80 (m, 1H, H-9), 1.55 – 1.37 (m, 2H, H-9', H-10), 1.36 – 1.26 (m, 1H, H-10'), 0.92 (d, *J* = 11.7 Hz, 6H, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.7 (C-14), 139.8 (C-2), 136.9 (C-16), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.2 (C-15), 50.3 (C-13), 48.2 (C-8), 43.5 (C-7), 32.5 (C-10), 30.6 (C-11), 29.0 (C-12), 24.4 (C-9), 23.2 (C-12'), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2922, 1696, 1494, 1454,

1420, 1336, 1285, 1205, 1180, 1098, 1052, 999, 806, 752, 696, 606, 473 cm^{-1}; **HRMS** (ESI) 412.1947 ($[MH]^+$ $C_{24}H_{30}NO_3S$ requires 412.1941); **$[\alpha]_D^{20}$** +34.6 (c= 0.506, $CHCl_3$).

(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.6]dodecane-2-carboxylate (4h)

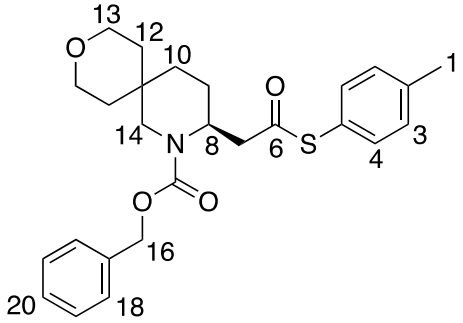


Racemic: Compound **4h** was synthesized using the **general procedure B** using the amino-thioester **3h** (21 mg, 0.045 mmol) and rac-CSA (31 mg, 0.135 mmol, 3 eq). Compound **4h** was obtained as a pale-yellow oil (16 mg, 0.035 mmol, 78% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **4h** was synthesized using the **general procedure B** using the amino-thioester **3h** (24 mg, 0.051 mmol) and (*R*)-anthra (7 mg, 0.01 mmol, 0.2 eq). Compound **4h** was obtained as a pale-yellow oil (3.5 mg, 0.007 mmol, 14% yield, (29% brsm), 95:5 e.r.) after column chromatography (15% EtOAc/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-19, H-20, H-21), 7.30 – 7.20 (m, 2H, H-4), 7.20 (d, *J* = 7.9 Hz, 2H, H-3), 5.30 – 5.00 (br. m, 2H), 4.90 – 4.70 (br. m, 1H, H-8), 4.00 – 3.70 (br. m, 1H, H-15), 2.90 (d, *J* = 7.8 Hz, 2H, H-7), 2.70 – 2.40 (br. m, 1H, H-15), 2.40 (s, 3H, H-1), 2.00 – 1.80 (m, 1H, H-9), 1.80 – 1.10 (m, 15H, H-10, H-12, H-12' H-13, H-13', H-14, H-14') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ ppm 195.4 (C-6), 155.8 (C-2), 139.8 (C-2), 136.9 (C-18), 134.4 (C-4), 130.1 (C-3), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 124.1 (C-5), 67.2 (C-17), 48.9 (C-15), 48.7 (C-8), 43.9 (C-7), 40.6, 36.2 (C-11), 33.6, 32.0, 30.7, 30.6, 23.8 (C-9), 22.7, 22.6, 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2932, 2854, 1694, 1443, 1421, 1341, 1239, 1105, 1032, 1003, 912, 763, 735, 697, 606, 534 cm^{-1}; **HRMS** (ESI) 466.2423 ($[MH]^+$ $C_{28}H_{36}NO_3S$ requires 466.2410); **$[\alpha]_D^{20}$** +11.54 (c= 0.207, $CHCl_3$).

(*S*)-Benzyl-3-(2-oxo-2-(p-tolylthio)ethyl)-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (4i)

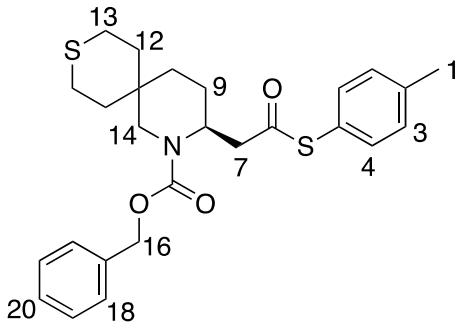


Racemic: Compound **4i** was synthesized using the **general procedure B** using the amino-thioester **3i** (21 mg, 0.047 mmol) and rac-CSA (33 mg, 0.141 mmol, 3 eq). Compound **4i** was obtained as a pale-yellow oil (13 mg, 0.028 mmol, 60% yield) after column chromatography (60% Et_2O/pentane).

Asymmetric: Compound **4i** was synthesized using the **general procedure B** using the amino-thioester **3i** (20 mg, 0.043 mmol), (*R*)-anthra (6 mg, 0.008 mmol, 0.2 eq). Compound **4i** was obtained as a pale-yellow oil (13 mg, 0.027, 65% yield, 94:6 e.r.) after column chromatography (60% Et_2O/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.46 – 7.27 (m, 5H, H-18, H-19, H-20), 7.30 – 7.20 (m, 2H, H-4), 7.20 (d, *J* = 7.8 Hz, 2H, H-3), 5.29 – 4.96 (br. m, 2H, H-16), 5.00 – 4.71 (br. m, 1H, H-8), 4.49 – 3.96 (br. m, 1H, H-14), 3.82 – 3.36 (br. m, 4H, H-13), 3.02 – 2.79 (m, 2H, H-7), 2.74 – 2.46 (br. m, 1H, H-14'), 2.37 (s, 3H, H-1), 1.99 – 1.78 (m, 1H, H-9), 1.71 – 1.29 (m, 7H, H-9', H-10, H-12) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.2 (C-6), 155.6 (C-15), 139.9 (C-2), 136.6 (C-17), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.1 (Ar-CH), 124.0 (C-5), 67.5 (C-16), 64.0 (C-13), 63.3 (C-13'), 48.7 (C-8), 46.8 (C-14), 43.6 (C-7), 37.4 (C-10), 31.5 (C-12), 31.2 (C-11), 30.44 (C-12'), 23.3 (C-9), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2920, 2850, 1694, 1494, 1422, 1342, 1303, 1268, 1234, 1221, 1156, 1105, 1017, 808, 753, 698, 609, 534, 474 cm^{-1}; **HRMS** (ESI) 454.2055 ($[MH]^+$ $C_{26}H_{32}NO_4S$ requires 454.2047); **$[\alpha]_D^{20}$** +33.3 (c= 0.602, $CHCl_3$).

(*S*)-Benzyl-3-(2-oxo-2-(*p*-tolylthio)ethyl)-9-thia-2-azaspiro[5.5]undecane-2-carboxylate (4j)

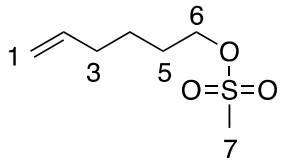


Racemic: Compound **4j** was synthesized using the **general procedure B** using the amino-thioester **3j** (22 mg, 0.046 mmol, 1 eq) and *t*-BuOK (4 mg, 0.036 mmol, 0.8 eq). Compound **4j** was obtained as a colourless oil (14.5 mg, 0.030 mmol, 70% yield) after column chromatography (15% EtOAc/pentane).

Asymmetric: Compound **4j** was synthesized using the **general procedure B** using the amino-thioester **3j** (19 mg, 0.039 mmol, 1 eq) and (*R*)-anthra (5.5 mg, 0.008 mmol, 0.2 eq). Compound **4j** was obtained as a colourless oil (3 mg, 0.005 mmol, 14% yield, (72% brsm) 96:4 e.r.) after column chromatography (15% EtOAc/pentane).

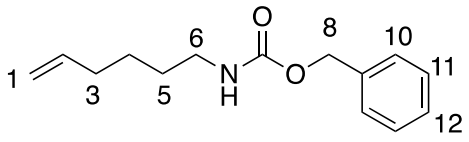
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.38 – 7.27 (m, 5H, H-18, H-19, H-20), 7.26 – 7.21 (m, 2H, H-4), 7.20 (d, *J* = 8.0 Hz, 2H, H-3), 5.24 – 5.04 (br. m, 2H, 16), 4.91 – 4.71 (br. m, 1H, H-8), 4.31 – 3.86 (br. m, 1H, H-14), 2.99 – 2.78 (m, 2H, H-7), 2.80 – 2.41 (br. m, 5H, H-14', H-13, H-13'), 2.37 (s, 3H, H-1), 1.98 – 1.81 (m, 1H, H-9), 1.81 – 1.58 (br. m, 4H, H-12, H-12'), 1.54 – 1.40 (m, 2H, H-9', H-10), 1.34 (td, *J* = 13.3, 3.7 Hz, 2H, H-10') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.2 (C-6), 155.6 (C-15), 139.9 (C-2), 136.7 (C-17), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 124.0 (C-5), 67.4 (C-16), 48.8 (C-8), 47.0 (C-14), 43.8 (C-7), 38.7 (C-12), 32.3 (C-12'), 32.2 (C-11), 30.2 (C-10), 23.7 (C-13), 23.2 (C-13'), 21.4 (C-1) ppm; **IR** (ATR): ν_{max} 2927, 1695, 1494, 1424, 1278, 1215, 1015, 808, 749, 668 cm^{-1}; **HRMS** (ESI) 492.1641 ([MNa]$^+$ $C_{26}H_{31}NNaO_3S_2$ requires 492.1638); **$[\alpha]_D^{20}$** +10.41 (c= 0.1685, $CHCl_3$).

Hex-5-en-1-yl methanesulfonate (S1)



In a flame dried flask, 5-hexene-1-ol (0.5 mL, 4.2 mmol, 1 eq) and Et_3N (2.34 mL, 16.8 mmol, 4 eq) were added to dichloromethane (25 mL) and cooled to 0 °C. Methanesulfonyl chloride (0.4 mL, 6.3 mmol, 1.5 eq) was added at 0 °C and the reaction was warmed to room temperature and stirred for 24 hours. The reaction was concentrated and co-concentrated with toluene *in vacuo* to form the crude residue which was purified with flash column chromatography (20% EtOAc/hexane) to yield compound **S1** as a colourless oil (595 mg, 3.34 mmol, 80% yield) **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.74 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H, H-2), 5.00 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.90 (dd, *J* = 10.2, 1.8 Hz, 1H, H-1'), 4.18 (t, *J* = 6.5 Hz, 2H, H-6), 2.96 (s, 3H, H-7), 2.13 – 1.99 (m, 2H, H-3), 1.81 – 1.64 (m, 2H, H-5), 1.55 – 1.41 (m, 2H, H-4) ppm; **^{13}CNMR** (101 MHz, Chloroform-*d*): δ 137.8 (C-2), 115.1 (C-1), 70.0 (C-6), 37.2 (C-7), 32.9 (C-3), 28.4 (C-5), 24.5 (C-4) ppm. This data obtained match those reported in the literature.[1]

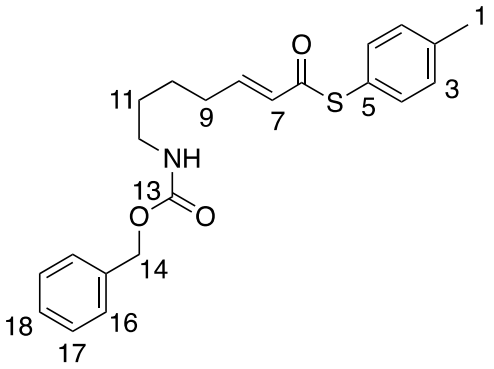
Benzyl hex-5-en-1-ylcarbamate (1k)



To a solution of aq. NH_3 (35%, 20 mL) and methanol (10 mL), mesylate **S1** (252 mg, 1.41 mmol, 1 eq) was added and stirred at room temperature for 24 hours. The reaction mixture was

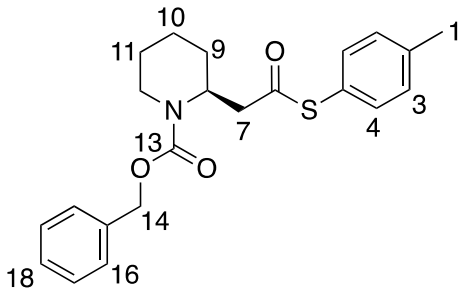
extracted with Et_2O (20 mL x 4) and the combined organics were washed with 2 M HCl (10 mL x 4), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the HCl salt of the amine (688 mg, 5.09 mmol) which was taken through the next step without further purification. The salt was dissolved in water (1 mL) and Cbz-protected using the **general procedure D** method (50% w/w aq, 0.8 mL, 6.11 mmol, 1.2 eq) and benzylchloroformate (0.8 mL, 6.11 mmol, 1.2 eq). Compound **1k** was obtained as a colourless oil (179 mg, 0.77 mmol, 55% yield over two steps) after column chromatography (5% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.46 – 7.26 (m, 5H, H-10, H-11, H-12), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H-2), 5.09 (s, 2H, H-8), 5.03 – 4.92 (m, 2H, H-1), 4.72 (br. s, 1H, N-H), 3.20 (q, *J* = 6.7 Hz, 2H, H-6), 2.07 (m, 2H, H-3), 1.57 – 1.46 (m, 2H, H-5), 1.46 – 1.35 (m, 2H, H-4) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 156.1 (C-7), 138.5 (C-2), 136.7 (C-9), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 114.9 (C-1), 66.7 (C-8), 41.0 (C-6), 33.4 (C-3), 29.5 (C-5), 26.0 (C-4) ppm; **IR** (ATR): ν_{max} 3334, 3066, 3033, 2932, 2859, 1679, 1640, 1530, 1455, 1413, 1248, 1113, 1024, 995, 911,776, 735, 696, 639 cm^{-1}; **HRMS** (ESI) 234.1490 ($[MH]^+$ $C_{14}H_{20}NO_2$ requires 234.1489).

(*E*)-S-*p*-tolyl 7-(((benzyloxy)carbonyl)amino)hept-2-enethioate (3k)



Compound **3k** was synthesised using the **general procedure A** with thioester **2a** (90 mg, 0.506 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (10.5 mg, 0.016 mmol, 0.1 eq), copper iodide (32 mg, 0.168 mmol, 1 eq), Cbz-amine **231k** (39 mg, 0.168 mmol, 1 eq). Compound **3k** yielded as a pale-yellow oil (39 mg, 0.101 mmol, 60% yield) after column chromatography (10-20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.41 – 7.27 (m, 7H, H-16, H-17, H-18, H-4), 7.21 (d, *J* = 8.0 Hz, 2H, H-3), 6.93 (dt, *J* = 15.5, 6.9 Hz, 1H, H-8), 6.16 (d, *J* = 15.5 Hz, 1H, H-7), 5.09 (s, 2H, H-14), 4.80 (t, *J* = 6.4 Hz, 1H, N-H), 3.19 (Q, *J* = 6.4 Hz, 2H, H-12), 2.37 (s, 3H, H-1), 2.28 – 2.13 (m, 2H, H-9), 1.74 – 1.40 (br. m, 4H, H-10, H-11) ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 188.6 (C-6), 156.5 (C-13), 145.8 (C-8), 139.7 (C-2), 136.6 (C-15), 134.7 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.2 (C-7, Ar-CH), 124.0 (C-5), 66.7 (C-14), 40.8 (C-12), 31.9 (C-9), 29.6 (C-11), 25.1 (C-10), 21.4 (C-1) ppm; **IR** (aTR): ν_{max} 3343, 2924, 2854, 1697, 1246, 808 cm^{-1}; **HRMS** (ESI) 406.1445 ($[MNa]^+$ $C_{22}H_{25}NNaO_3S$ requires 406.1447).

(*S*)-Benzyl 2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (4k)

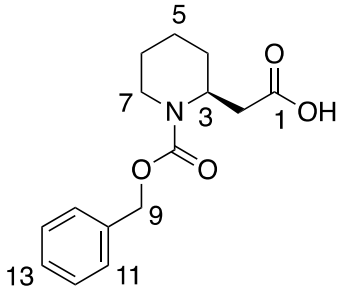


Racemic: Compound **4k** was synthesized using the **general procedure B** using the amino-thioester **3k** (40 mg, 0.104 mmol, 1 eq) and rac-CSA (73 mg, 0.312 mmol, 3 eq). Compound **4k** yielded as a pale-yellow oil (17 mg, 0.044 mmol, 43% yield) after column chromatography (20% EtOAc/hexane).

Asymmetric: Compound **4k** was synthesized using the **general procedure B** using the amino-thioester **3k** (48mg, 0.124 mmol, 1 eq), (*R*)-anthra (17.5 mg, 0.024 mmol, 0.2 eq). Compound **4k** yielded as a pale-yellow oil (10 mg, 0.026 mmol, 21% yield (79% brsm), 84:16 e.r.) after column chromatography (40% Et_2O/pentane).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.39 – 7.29 (m, 5H, H-16, H-17, H-18), 7.25 – 7.21 (br. m, 2H, H-4), 7.19 (d, *J* = 7.8 Hz, 2H, H-3), 5.20 (d, *J* = 12.4 Hz, 1H, H-14), 5.10 (d, *J* = 12.4 Hz, 1H, H-14') 4.92 – 4.77 (br. m, 1H, H-8), 4.21 – 3.95 (br. m, 1H, H-12), 2.99 – 2.80 (m, 3H, H-7, H-12'), 2.36 (s, 3H, H-1), 1.80 – 1.60 (m, 4H, H-9, H-9', H-10, H-11), 1.6 – 1.5 (m, 1H, H-10'), 1.50 – 1.40 (m, 1H, H-11') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 195.4 (C-6), 155.4 (C-13), 139.8 (C-2), 136.8 (C-15), 134.4 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 124.1 (C-5), 67.2 (C-14), 48.8 (C-8), 43.8 (C-7), 39.8 (C-12), 28.2 (C-9), 25.3 (C-11), 21.4 (C-1), 18.9 (C-10) ppm; **IR** (ATR): ν_{max} 2925, 2853, 1704, 1533, 1456, 1260, 1085, 1022, 803, 736, 700 cm^{-1}; **HRMS** (ESI) 384.1633 ($[MH]^+$ $C_{22}H_{26}NO_3S$ requires 384.1628); **$[\alpha]_D^{20}$** +23.7 (c= 0.5345, $CHCl_3$).

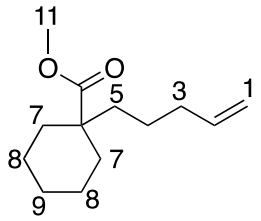
(*S*)-2-(1-((Benzyloxy)carbonyl)piperidin-2-yl)acetic acid (8)



To compound **4k** (10.75 mg, 0.03 mmol, 1 eq) in THF (1.5 mL) was added aq. H_2O_2 (30% w/w, 4 µL, 0.112 mmol, 4 eq) at 0 °C and stirred for 15 min at 0 °C. Aq. NaOH (0.22 M, 0.38 mL, 0.084 mmol, 3 eq) was added at at 0 °C and the reaction warmed to room temperature and stirred for 1 hour. The reaction was quenched with water (15 mL) and the aqueous layer extracted with Et_2O (15 mL x 3). The combined aqueous layers were acidified to pH 2 with 2M HCl and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with

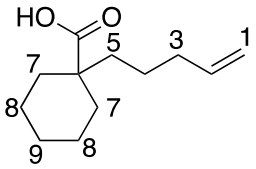
saturated sodium metabisulfite solution (10 mL), followed by saturated brine solution (10 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo.* The crude material was purified by column chromatography (50% EtOAc/hexane) to afford **8** as a colourless oil (7 mg, 0.025 mmol, 92% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-11, H-12, H-13), 5.10 (s, 2H, H-9), 4.90 – 4.70 (m, 1H, H-3), 4.20 – 4.00 (br. m, 1H, H-7), 3.00 – 2.80 (m, 1H, H-7'), 2.70 – 2.50 (m, 2H, H-2), 1.80 – 1.60 (m, 4H, H-4, H-5, H-6), 1.60 – 1.50 (m, 1H, H-5'), 1.50 – 1.40 (m, 1H, H-6') ppm; **^{13}C NMR** (101 MHz, Chloroform-*d*): δ 175.8 (C-1), 155.6 (C-8), 136.8 (C-10), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 67.3 (C-9), 48.1 (C-3), 39.7 (C-7), 35.1 (C-2), 28.3 (C-4), 25.3 (C-6), 18.8 (C-5) ppm; **IR** (ATR): ν_{max} 3035, 2937, 2862, 1731, 1697, 1426, 1319, 1263, 1170, 1138, 1093, 1044, 1015, 766, 697 cm^{-1}; **HRMS** (ESI) 278.1392 ([MH]$^+$ $C_{15}H_{20}NO_4$ requires 278.1387); **$[\alpha]_D^{20}$** +7.14 (c= 0.2055, $CHCl_3$) [lit. $[\alpha]_D$ -18 (c=0.5, $CHCl_3$) for (*R*)-isomer].[2]

Methyl 1-(pent-4-en-1-yl)cyclohexanecarboxylate (S2)



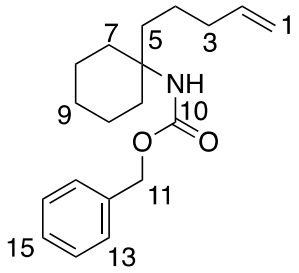
To a solution of diisopropylamine (1.5 0mL, 11 mmol, 1.1 eq) in dry THF (6 mL) at –78 °C under N_2 was added n-BuLi (1.82 M in hexanes, 6.00 mL, 11 mmol, 1.1 eq) and stirred for 50 min. A solution of methyl cyclohexylcarboxylate **9** (1.50 mL, 10 mmol, 1 eq) in dry TFH (6 mL) was then and added over 5 min at –78 °C and the reaction stirred for 40 min. 5-Bromobutene (1.20 mL, 10 mmol, 1 eq) was then added over 5 min at –78 °C and the reaction warmed to RT and attired overnight. The reaction was quenched with 1 M aq. HCl (20 mL) and partitioned with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL x 2). The combined organics were washed with saturated brine solution (20 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography to give compound **S2** as a colourless oil (1.3 g, 6.2 mmol, 62% yield) after column chromatography (5% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H, H-2), 5.00 (dd, *J* = 17.0, 1.7 Hz, 1H, H-1), 5.00 – 4.90 (m, 1H, H-1'), 3.70 (s, 3H, H-11), 2.10 – 2.00 (m, 2H, H-8), 2.00 – 1.90 (m, 2H, H-3), 1.60 – 1.50 (m, 2H, H-7, H-9), 1.50 – 1.40 (m, 2H, H-5), 1.30 – 1.10 (m, 8H, H-4, H-7, H-7', H-8', H-9') ppm; **^{13}C NMR** δ (101 MHz, Chloroform-*d*): δ 177.4 (C-10), 138.6 (C-2), 114.6 (C-1), 51.5 (C-11), 47.0 (C-6), 40.4 (C-5), 34.2 (C-8), 34.1 (C-3), 26.0 (C-9), 23.4 (C-4), 23.3 (C-7) ppm; **IR (ATR)** 2932, 2856, 1727, 1452, 1214, 745, 668 cm^{-1}.

1-(Pent-4-en-1-yl)cyclohexanecarboxylic acid (S3)



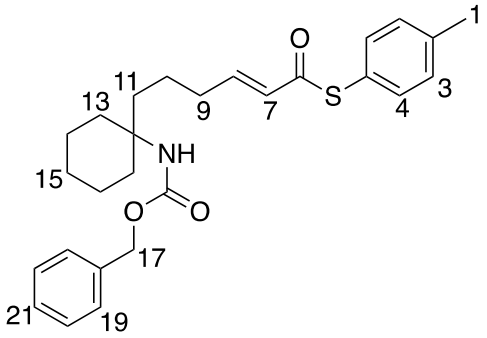
To a solution of alkenyl ester **S2** (898 mg, 4.3 mmol, 1 eq) in MeOH (10 mL) was added aq. NaOH (20% w/w, 2.5 mL) and reaction heated to reflux while stirring overnight. The reaction was cooled to room temperature and diluted with H_2O (10 mL) and extracted with diethyl ether (20 mL). The aqueous layer was acidified to pH 1 with 3M aq. HCl (8 mL), extracted with diethyl ether (3 x 20 mL). Combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*, to yield acid **S3** (275 mg, 1.4 mmol, 33% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 5.80 (ddt, *J* = 16.9, 10.4, 6.7 Hz, 1H, H-2), 5.00 (dd, *J* = 17.0, 1.8 Hz, 1H, H-1), 4.90 (dd, *J* = 10.4, 1.8 Hz, 1H, H-1'), 2.10 – 1.90 (m, 4H, H-3, H-8), 1.70 – 1.50 (m, 5H, H-5, H-7, H-9), 1.50 – 1.30 (m, 4H, H-4, H-7'), 1.30 – 1.20 (m, 3H, H-8', H-9') ppm; **^{13}C NMR** δ (101 MHz, Chloroform-*d*): δ 184.2 (C-10), 138.2 (C-2), 114.7 (C-1), 46.8 (C-6), 39.8 (C-5), 34.1 (C-3), 33.9 (C-8), 26.0 (C-9), 23.3 (C-4), 23.2 (C-7) ppm; **IR (ATR)** 2932, 2856, 1693, 1453, 1242, 908, 752 cm^{-1}; **HRMS** (ESI) 219.1363 (M+ Na^+. $C_{12}H_{20}NaO_2$ requires 219.1356).

Benzyl ((1-(pent-4-en-1-yl)cyclohexyl)methyl)carbamate (1l)



To a solution of carboxylic acid **S3** (0.6 mmol, 1 eq) in dry toluene (6 mL) under N_2 was added Et_3N (0.7 mmol, 1.2 eq, 1.00 mL) and DPPA (0.65 mmol, 1.1 eq, 0.15 mL) and the reaction heated to 90 °C for 2 hours. Benzyl alcohol (0.90 mmol, 1.5 eq, 1 mL) was added and reaction stirred at 90 °C for 64 hours. Reaction was quenched with H_2O (5 mL) and extracted with EtOAc (10 x 30 mL). The combined organics were washed with saturated brine solution (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. Compound **1l** was yielded as a pale brown oil (127 mg, 0.4 mmol, 71% yield), obtained after flash column chromatography (20% EtOAc/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 5H, H-13, H-14, H-15), 5.80 (ddt, *J* = 16.9, 10.6, 6.8 Hz, 1H, H-2), 5.02 (s, 2H, H-11), 5.02 – 4.94 (m, 1H, H-1), 4.91 – 4.89 (m, 1H, H-1'), 4.48 (s, 1H, N-H), 2.04 – 1.99 (m, 2H, H-3), 1.98 – 1.90 (m, 2H, H-7), 1.80 – 1.60 (m, 2H, H-5), 1.60 – 1.30 (m, 10H, H-4, H-7', H-8, H-8', H-9) ppm; **^{13}C NMR** δ 154.5 (C-10), 139.0 (C-2), 137.0 (C-12), 128.6 (Ar-CH), 128.1 (Ar-CH), 114.5 (C-1), 66.0 (C-11), 54.9 (C-6), 38.0 (C-5), 35.0 (C-7), 34.1 (C-3), 25.9 (C-9), 22.6 (C-4), 21.8 (C-8) ppm; **IR (ATR)** 2921, 2853, 1735, 1499, 1455, 1376, 1248, 909 cm^{-1}; **HRMS** (ESI) 302.2115 (M+ H^+. $C_{19}H_{28}NO_2$ requires 302.2115).

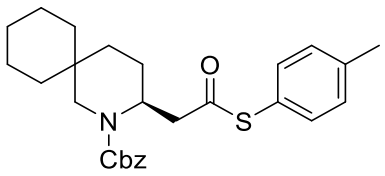
(*E*)-*S*-*p*-tolyl 6-(1-(((benzyloxy)carbonyl)amino)cyclohexyl)hex-2-enethioate (3l)



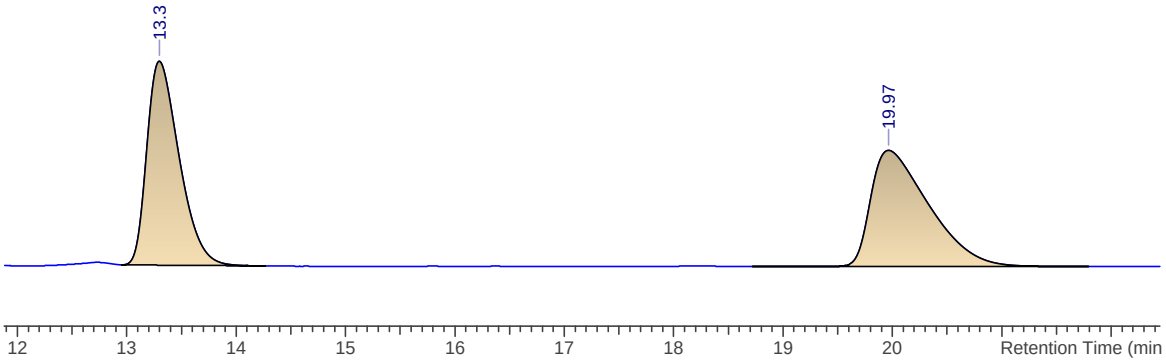
Compound **3l** was synthesised using the **general procedure A** with thioester **2a** (200 mg, 1.1 mmol, 3 eq), Hoveyda-Grubbs Catalyst™ 2nd generation (32 mg, 0.038 mmol, 0.1 eq), Cbz-amine **1l** (115 mg, 0.38 mmol, 1 eq) and copper iodide (72 mg, 0.38 mmol, 1 eq). Compound **3l** was yielded as a pale brown oil (133 mg, 0.3 mmol, 78% yield) after column chromatography (15% Et_2O/hexane). **^{1}H NMR** (400 MHz, Chloroform-*d*): δ 7.40 – 7.30 (m, 7H, H-4, H-19, H-20, H-21), 7.24 – 7.19 (m, 2H, H-3), 6.94 (dt, *J* = 15.2, 7.1 Hz, 1H, H-8), 6.15 (d, *J* = 15.2 Hz, 1H, H-7), 5.05 (s, 2H, H-17), 4.52 (s, 1H, N-H), 2.37 (s, 3H, H-1), 2.30 – 2.10 (m, 2H, H-9), 2.00 – 1.90 (m, 2H, H-13), 1.80 – 1.70 (m, 2H, H-11), 1.60 – 1.10 (m, 10H, H-10, H-13', H-14, H-14' H-15) ppm; **^{13}C NMR** δ 188.7 (C-6), 154.3 (C-16), 146.5 (C-8), 139.7 (C-2), 136.9 (C-18), 134.7 (C-4), 130.1 (C-3), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 128.0 (C-7), 124.2 (C-5), 66.2 (C-17), 54.7 (C-12), 38.1 (C-11), 35.0 (C-13), 32.7 (C-9), 25.8 (C-15), 21.8 (C-10), 21.7 (C-14), 21.4 (C-1) ppm; **IR (ATR)** 3362, 2928, 2856, 1721, 1683, 1631, 1495, 1453, 1245, 1090, 1019, 970, 807, 737, 697 cm^{-1}; **HRMS** (ESI) 452.2262 (M+ H^+. $C_{27}H_{34}NO_3S$ requires 452.2254).

3) HPLC data

(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.5]undecane-2-carboxylate (4a)

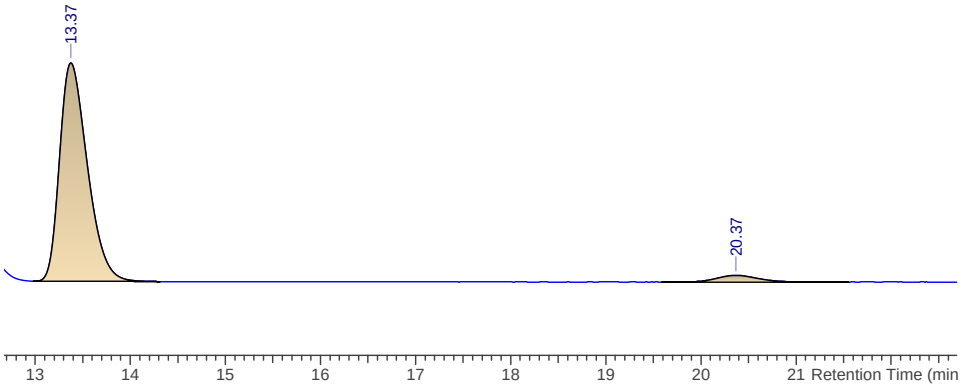


HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 25 °C, λ = 254 nm; tR 13.3 min (major), 20.3 min (minor) (*R*)-TRIP, cyclohexane 80 °C, 24 h, e.r. = 96:4.



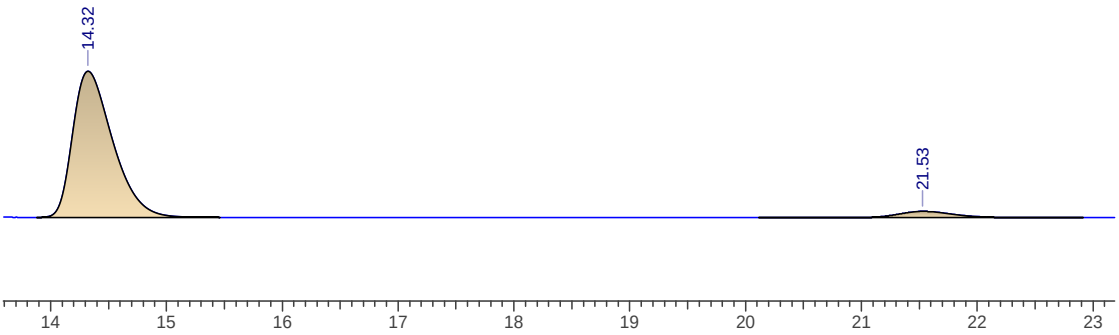
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.30	9500926.000	49.554	0.538
2	19.97	9671766.000	50.446	0.969

(*R*)-TRIP, cyclohexane 80 °C, 24 h, e.r. = 96:4.



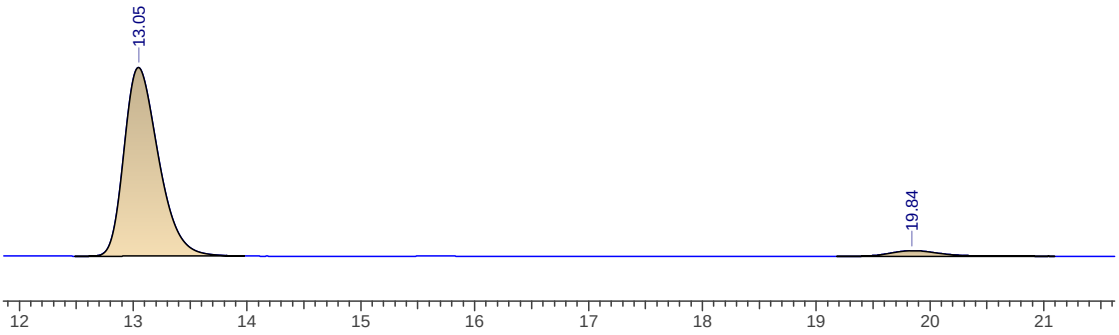
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.37	6660466.000	95.691	0.530
2	20.37	299931.688	4.309	0.782

(*R*)-TRIP, octane, 100 °C, 24 h, e.r. = 94:6



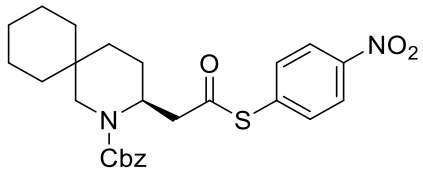
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.32	7307619.500	94.267	0.626
2	21.53	444424.781	5.733	0.860

(*R*)-anthra, cyclohexane, 80 °C, 24 h, e.r. = 96:4

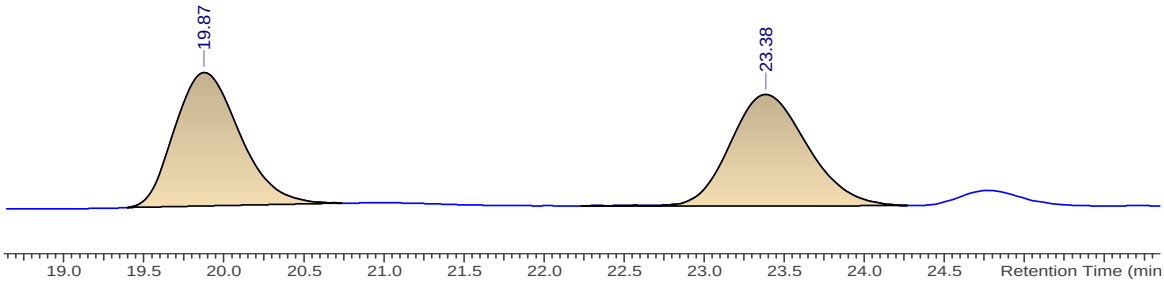


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.05	4184735.500	95.741	0.546
2	19.84	186159.891	4.259	0.781

(*S*)-Benzyl 3-(2-((4-nitrophenyl)thio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (4b)

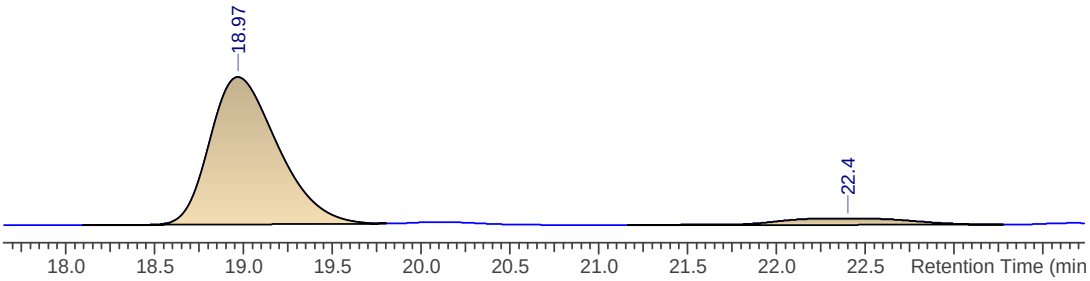


HPLC data: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 19.8 min (major), 23.38 min (minor)



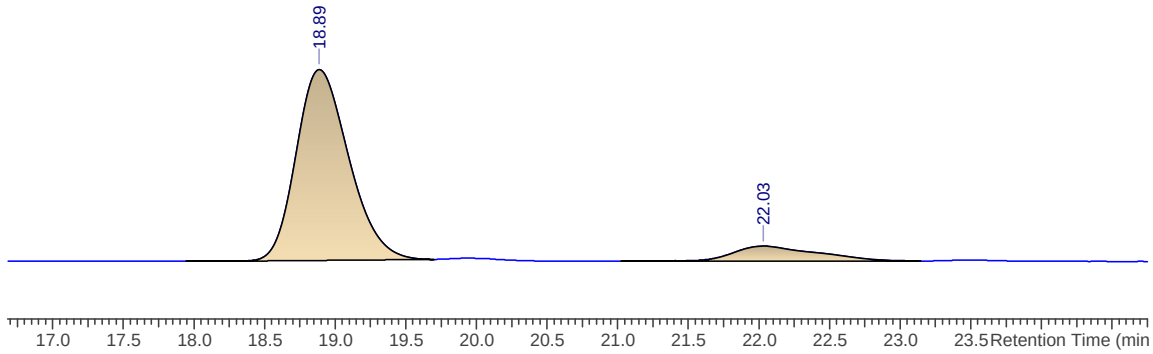
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	19.87	281308.219	50.259	0.755
2	23.38	278406.219	49.741	0.883

(*R*)-TRIP, cyclohexane, 80 °C, 24 h, e.r. = 92:8



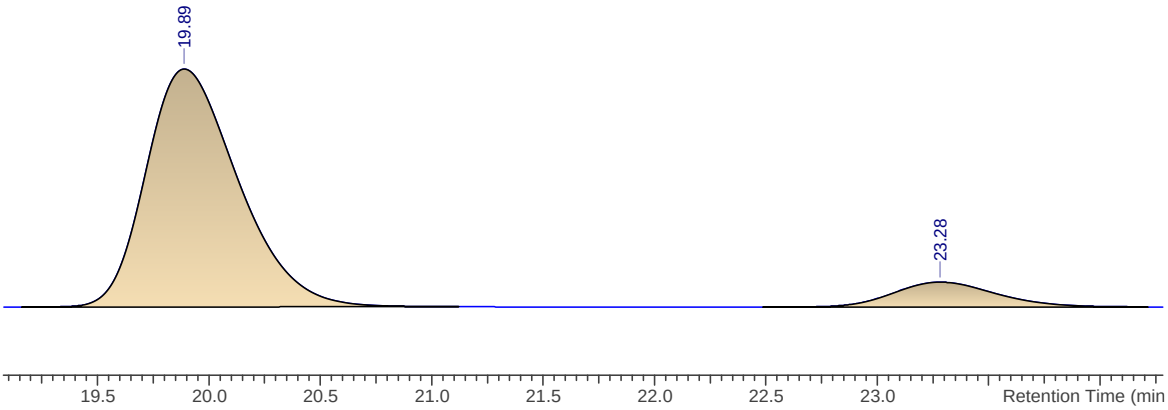
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	18.97	6508034.000	92.470	0.699
2	22.40	529962.938	7.530	1.431

(*R*)-TRIP, octane, 100 °C, 24 h, e.r. = 89:11



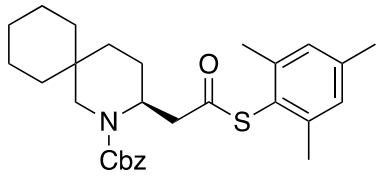
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	18.89	2803674.000	88.835	0.681
2	22.03	352373.969	11.165	1.136

(*R*)-anthra, octane, 100 °C, 24 h, e.r. = 89:11

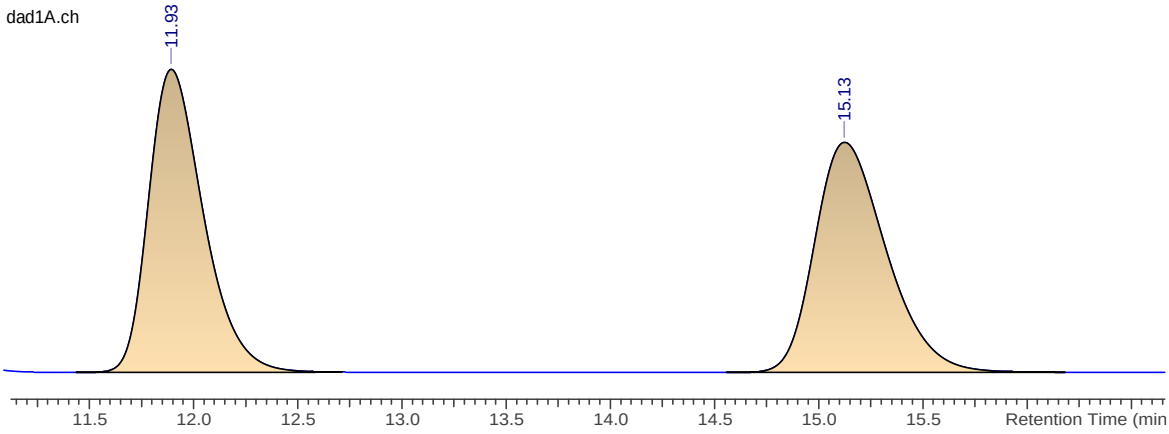


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	19.89	6203331.500	89.470	0.756
2	23.28	730083.438	10.530	0.844

(*S*)-Benzyl 3-(2-(mesitylthio)-2-oxoethyl)-2-azaspiro[5.5]undecane-2-carboxylate (4c)

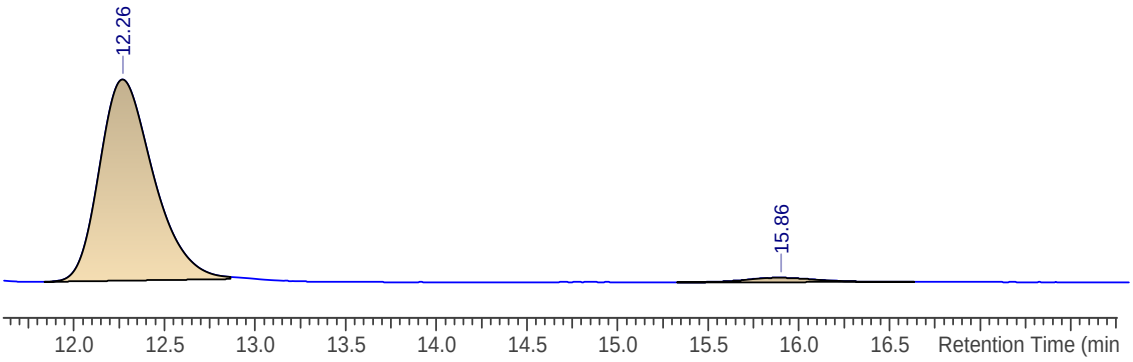


HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 12.0 min (major), 15.3 min (minor)



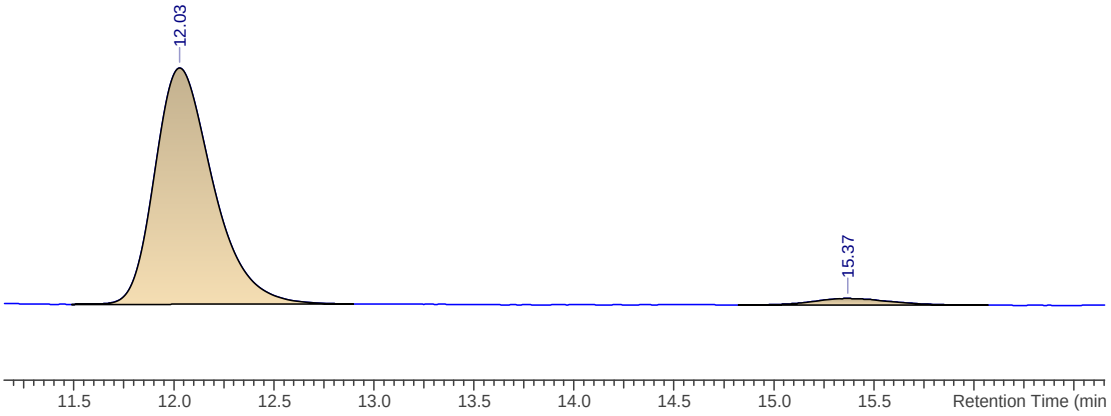
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	11.92	3639067.500	50.289	0.472
2	15.13	3597187.250	49.711	0.620

(*R*)-TRIP, cyclohexane, 80 °C, 24 h, e.r = 97:3



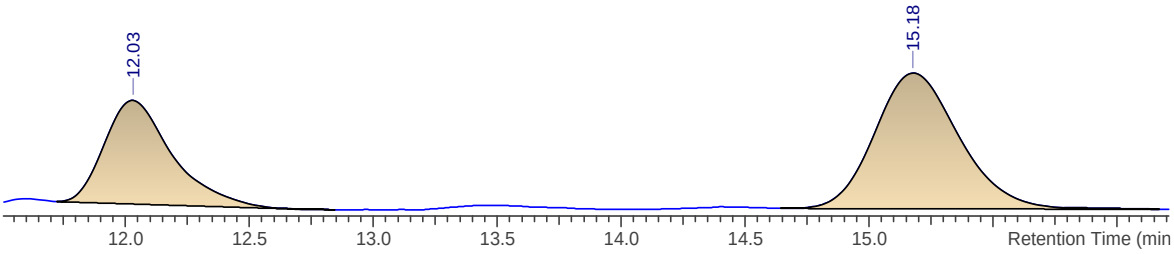
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.26	1063003.625	97.239	0.531
2	15.86	30187.508	2.761	0.689

(*R*)-TRIP, octane, 100 °C, 24 h, e.r. = 96:4



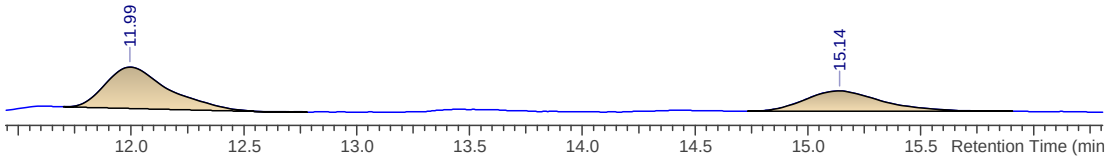
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.03	1472033.250	96.365	0.520
2	15.37	55526.348	3.635	0.711

(*R*)-TiPSY, octane, 100 °C, 24 h, e.r. = 38:62



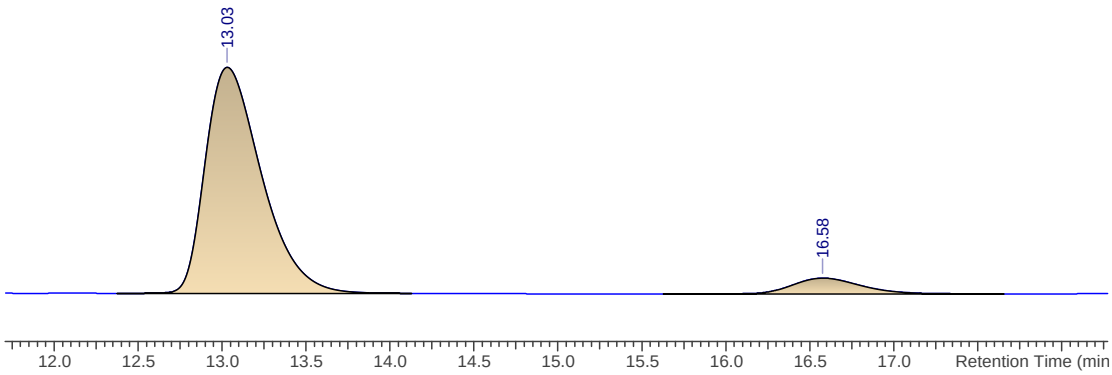
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	12.03	271485.656	37.952	0.477
2	15.18	443862.563	62.048	0.618

(*R*)-phenanth, octane, 100 °C, 24 h, e.r. = 62:38



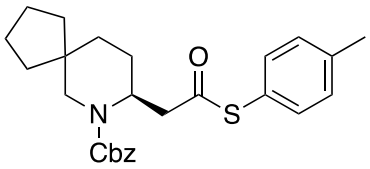
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	11.99	128061.117	62.365	0.480
2	15.14	77281.563	37.635	0.605

(*R*)-anthra, octane, 100 °C, 24 h, e.r. = 92:8

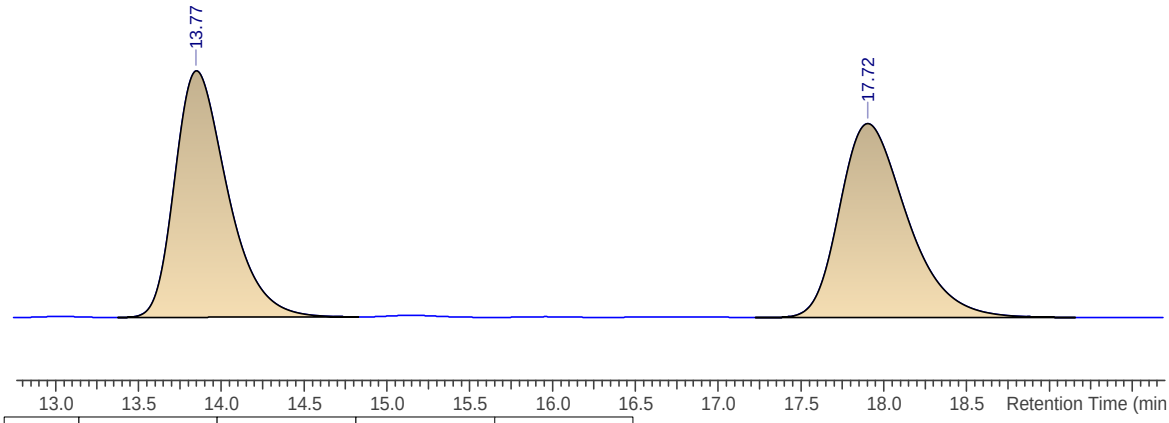


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.03	9609169.000	92.230	0.610
2	16.58	809506.312	7.770	0.739

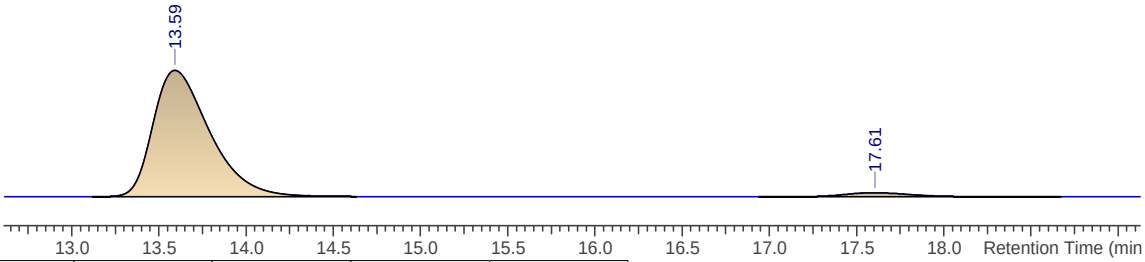
(*S*)-Benzyl 8-(2-oxo-2-(*p*-tolylthio)ethyl)-7-azaspiro[4.5]decane-7-carboxylate (4d)



HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 13.77 min (major), 17.72 min (minor) e.r. = 96:4

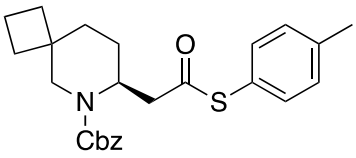


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.77	4339710.500	49.719	0.555
2	17.72	4388849.000	50.281	0.714

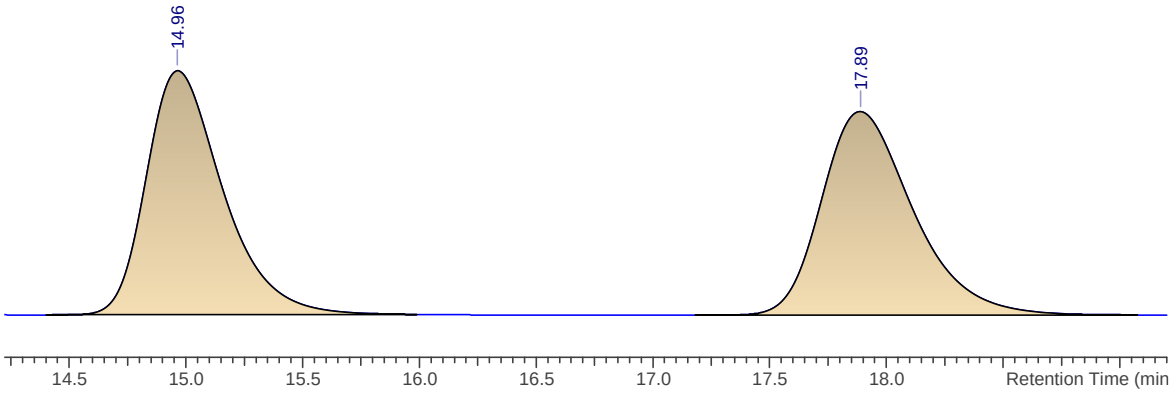


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.59	8679875.000	96.287	0.582
2	17.61	334694.563	3.713	0.689

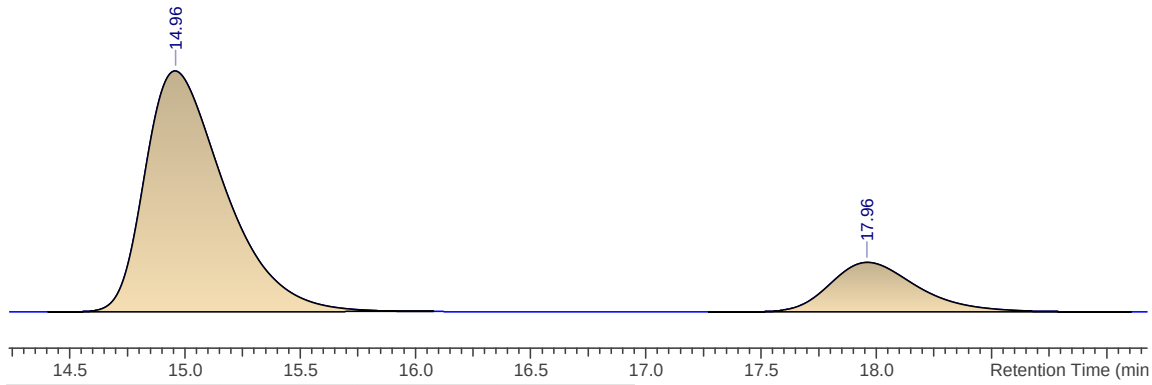
(*S*)-Benzyl 7-(2-oxo-2-(p-tolylthio)ethyl)-6-azaspiro[3.5]nonane-6-carboxylate (4e)



HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 14.96 min (major), 17.96 min (minor) e.r. = 82:18.

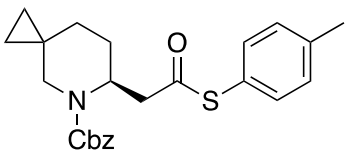


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.96	4267824.500	50.034	0.586
2	17.89	4262097.500	49.966	0.704

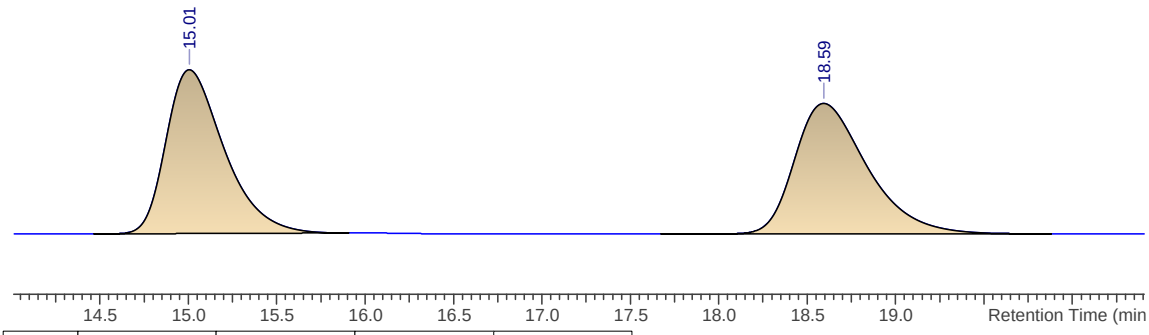


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.96	10361550.000	81.538	0.623
2	17.96	2346110.250	18.462	0.679

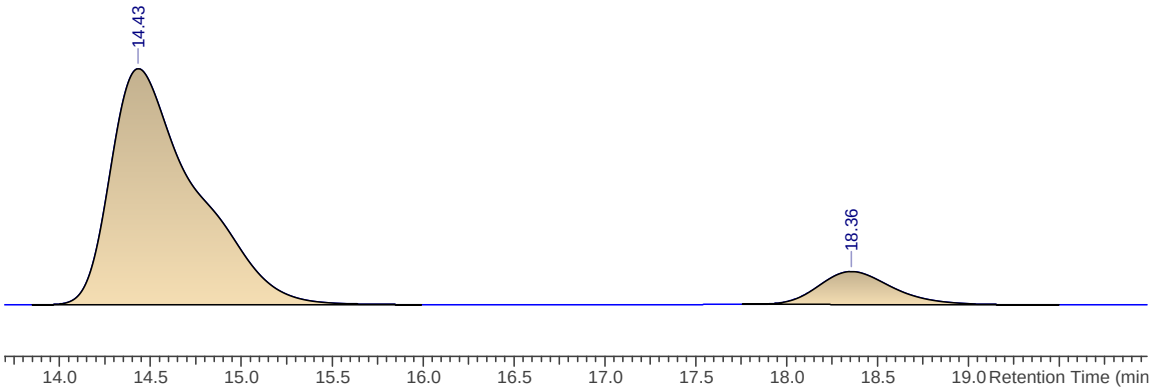
(*S*)-Benzyl 6-(2-oxo-2-(p-tolylthio)ethyl)-5-azaspiro[2.5]octane-5-carboxylate (4f)



HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 ^{o}C, λ = 254 nm; tR 14.43 min (major), 18.36 min (minor) e.r. = 89:11

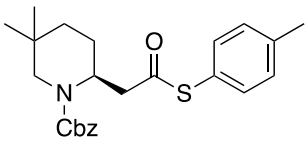


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	15.01	7303541.500	50.069	0.590
2	18.59	7283321.000	49.931	0.736

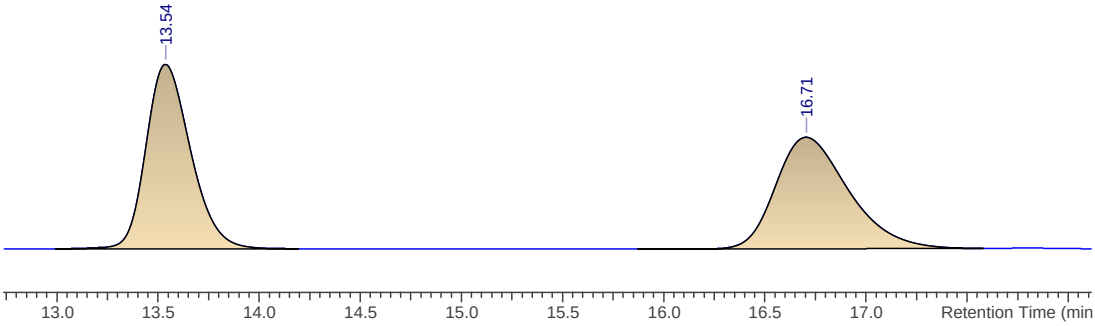


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	14.43	9134949.000	89.087	0.800
2	18.36	1119040.375	10.913	0.733

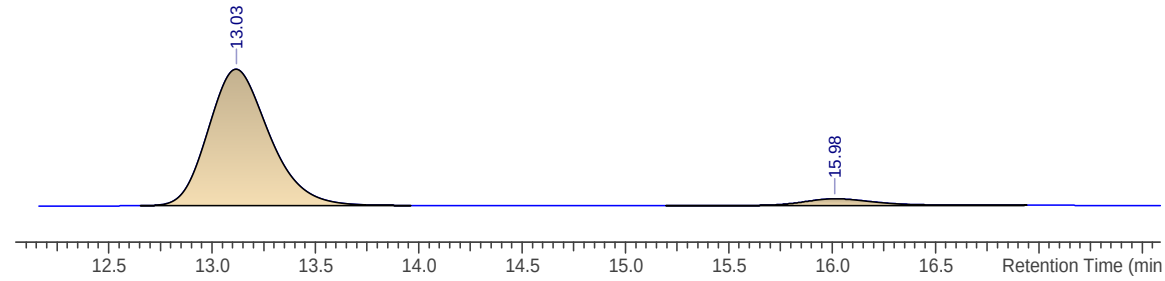
(*S*)-Benzyl 5,5-dimethyl-2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (4g)



HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 ^{o}C, λ = 254 nm; tR 13.54 min (major), 16.71 min (minor) e.r. = 95:5

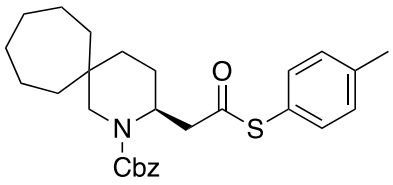


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.54	5282031.000	50.351	0.399
2	16.71	5208444.500	49.649	0.651

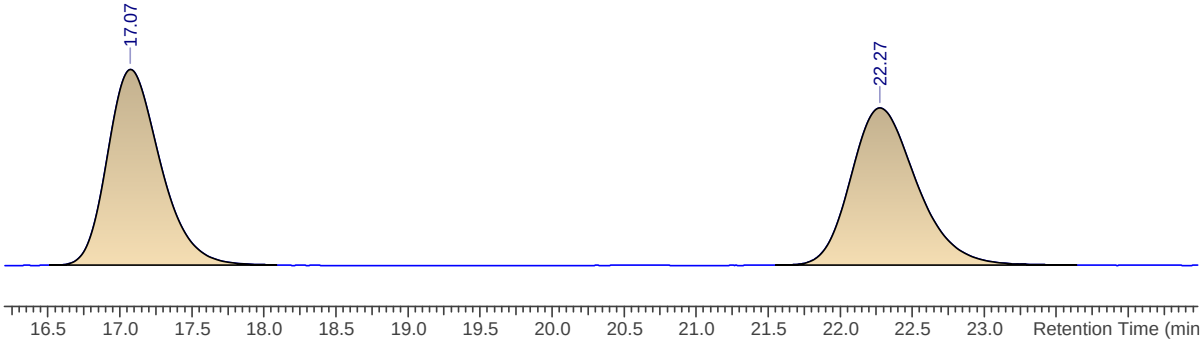


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	13.03	10260320.000	94.670	0.544
2	15.98	577684.375	5.330	0.618

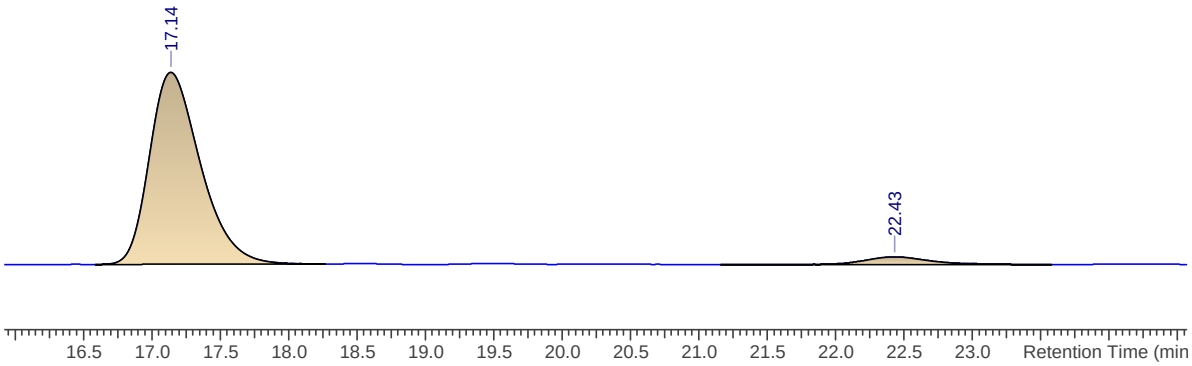
(*S*)-Benzyl 3-(2-oxo-2-(p-tolylthio)ethyl)-2-azaspiro[5.6]dodecane-2-carboxylate (4h)



HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 17.07 min (major), 22.27 min (minor) e.r. = 95:5

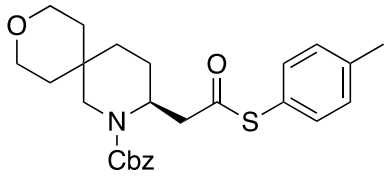


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.07	2093842.875	49.943	0.662
2	22.27	2098596.000	50.057	0.825

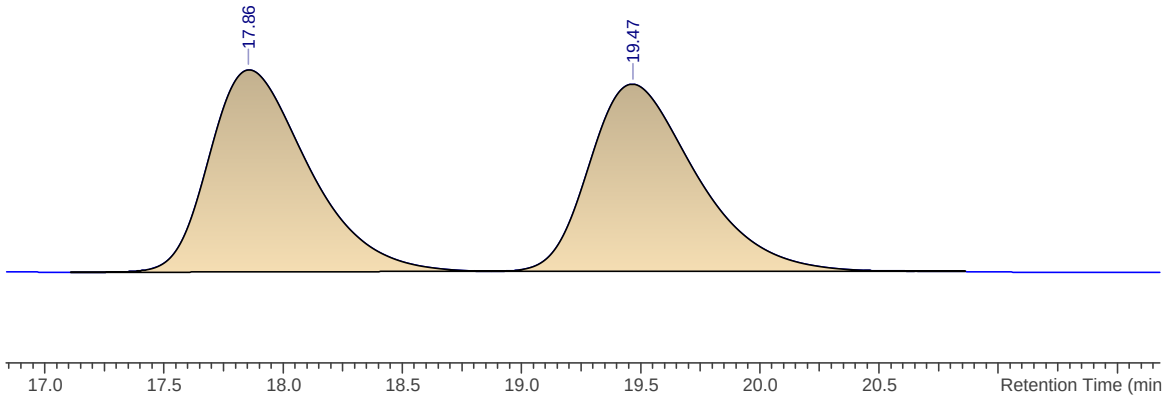


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.14	4523534.000	94.806	0.672
2	22.43	247808.266	5.194	0.836

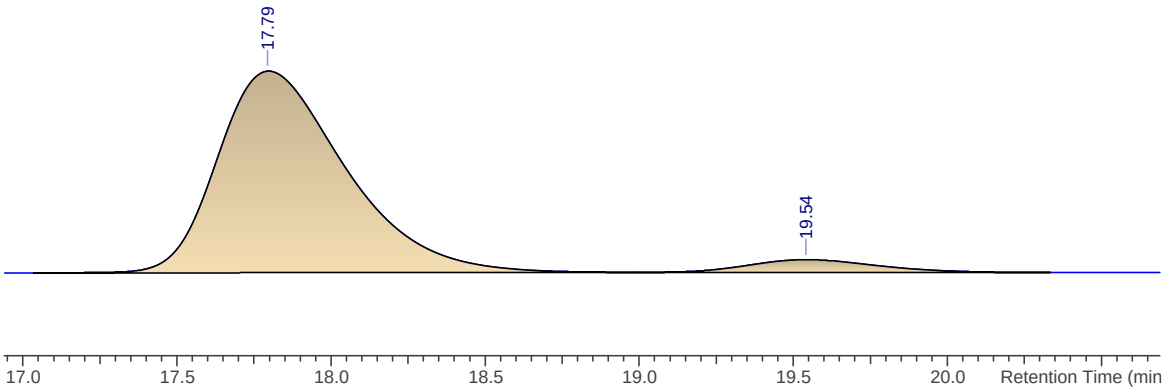
(*S*)-Benzyl-3-(2-oxo-2-(p-tolylthio)ethyl)-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (4i)



HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 17.79 min (major), 19.54 min (minor) e.r. = 94:6.

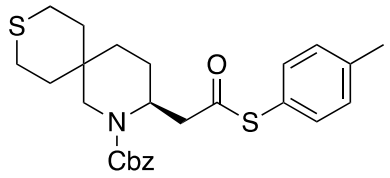


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.86	7152566.500	50.054	0.753
2	19.47	7137064.000	49.946	0.808

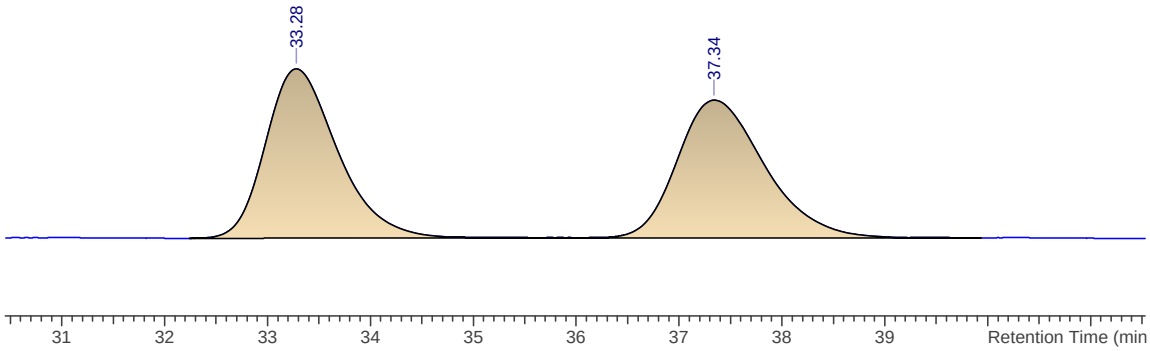


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.79	7691958.000	94.003	0.748
2	19.54	490726.250	5.997	0.768

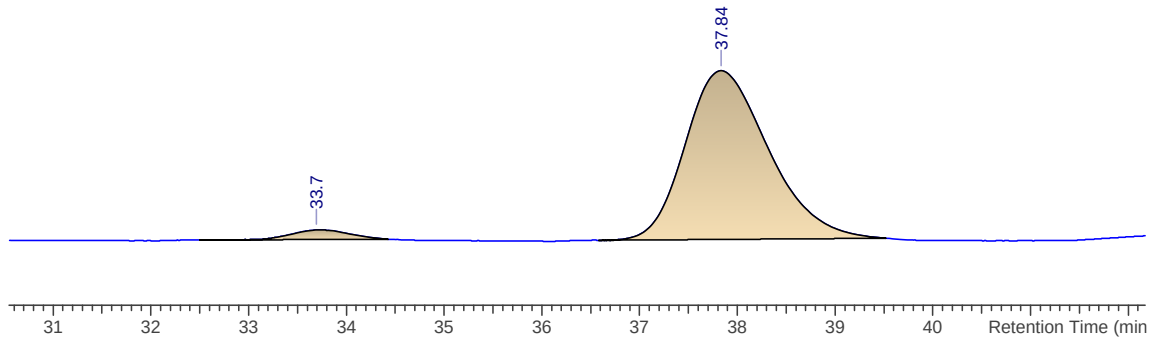
(*S*)-Benzyl-3-(2-oxo-2-(*p*-tolylthio)ethyl)-9-thia-2-azaspiro[5.5]undecane-2-carboxylate (4j)



HPLC conditions: Chiralpak ® IA Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 °C, λ = 254 nm; tR 33.7 min (minor), 37.8 min (major) e.r. = 96:4

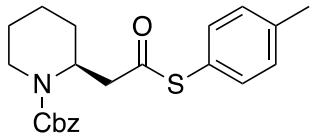


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	33.28	9957055.000	50.324	1.256
2	37.34	9828861.000	49.676	1.535

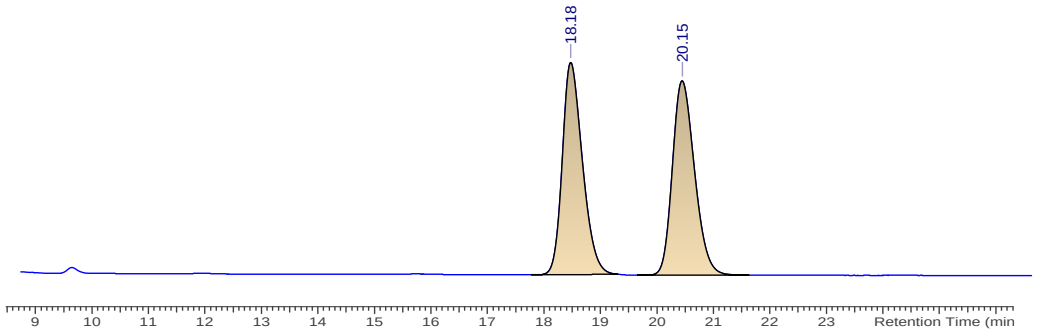


No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	33.69	305050.063	3.797	1.117
2	37.83	7728554.000	96.203	1.551

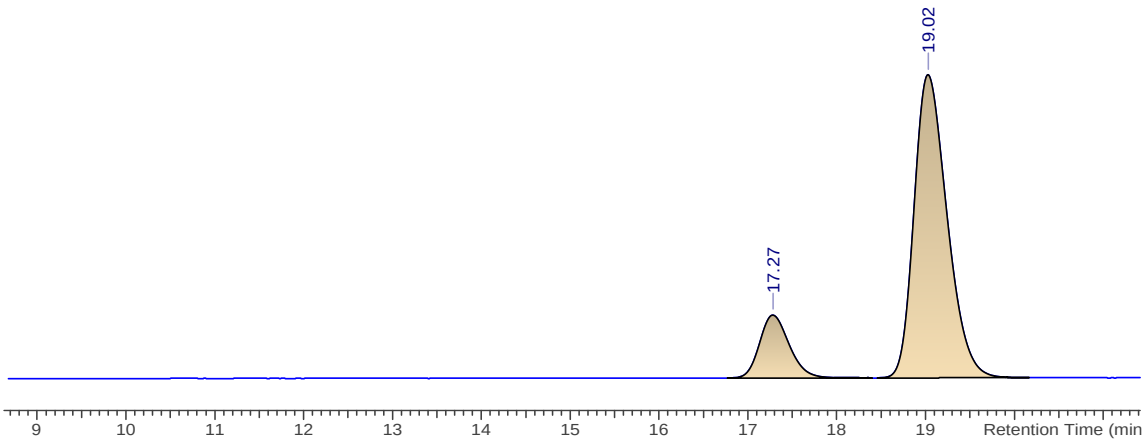
(*S*)-Benzyl 2-(2-oxo-2-(p-tolylthio)ethyl)piperidine-1-carboxylate (4k)



HPLC conditions: Chiralpak ® IB Column, hexane/2-propanol (95:5), flow rate: 1.0 mL/min, 40 ^{o}C, λ = 254 nm; tR 17.27 min (minor), 19.02 min (major) e.r. = 84:16



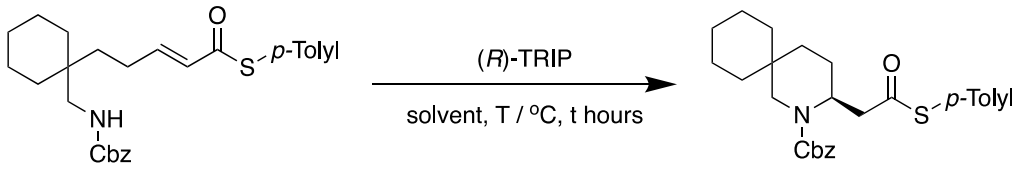
No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	18.18	3614383.750	49.876	0.638
2	20.15	3632293.250	50.124	0.709



No.	tR	Peak Area (Y units*ms)	Area (%)	Width
1	17.27	1043379.250	15.725	0.605
2	19.02	5591787.500	84.275	0.678

4) Additional optimisation tables

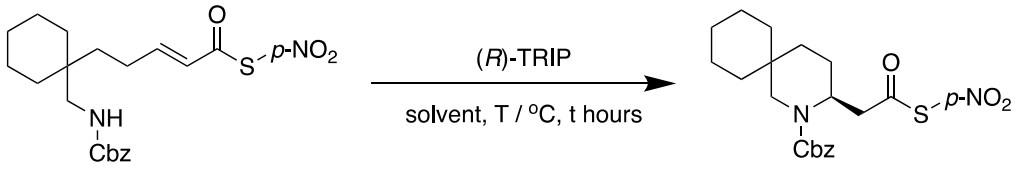
These screening Tables supplement the selected results summarised in the Table 1 of the main manuscript. All experiments were performed and analysed as in Table 1 of the main manuscript.



2a **4a**

Entry	Solvent	T / °C	t / hours	Yield / %	e.r.
1	cyclohexane	80	24	10	96:4
2	cyclohexane	80	48	21	96:4
3	octane	95	24	23	95:5
4	octane	100	24	36	94:6

Table S1 : Screening reaction conditions with p-tolyl thioester

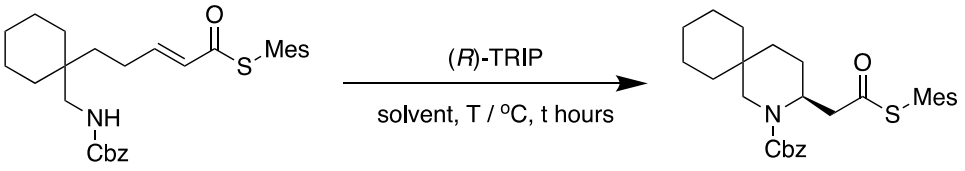


3b **4b**

Entry	Solvent	T / °C	t / hours	Yield / %	e.r.
1	cyclohexane	80	24	20	92:8
2	cyclohexane	80	48	21	84:16
3	toluene	80	48	8	71:29
4	octane	95	24	17	93:7
5	octane	100	24	55	90:10
6	octane	100 [a]	1	9	50:50

[a] *microwave*

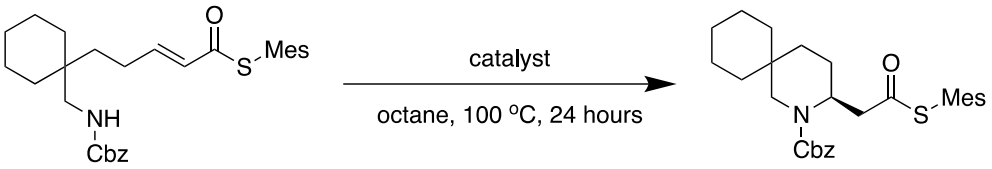
*Table S2 : Reaction conditions to synthesise **4b** asymmetrically*



3c **4c**

Entry	Solvent	T / °C	t / hours	Yield / %	e.r.
1	cyclohexane	80	24	15	97:3
2	cyclohexane	80	48	14	97:3
3	heptane	80	24	24	97:3
4	heptane	95	24	45	96:4
5	octane	95	24	44	96:4
6	octane	100	24	47	96:4
7	octane	110	24	63	95:5
8	octane	120	24	56	93:7

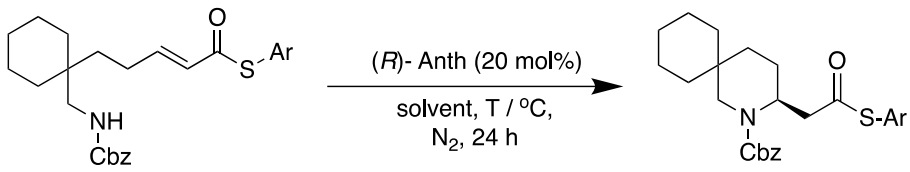
*Table S3 : Screening of reaction conditions with Cbz amine-mesityl thioester **3c***



3c **4c**

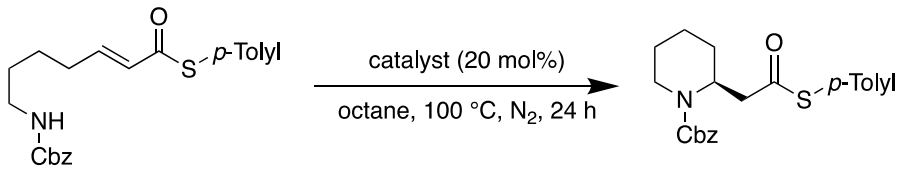
Entry	Catalyst	Yield / %	e.r.
1	(*R*)-TRIP	47	97:3
2	(*R*)-TiPSY	17	38:62
4	(*R*)-Anth	67	92:8
3	(*R*)- Phen	21	62:38

Table S4 : CPA catalyst screen



entry	Ar (Substrate)	Solvent	T / °C	Yield / % [with (*R*)-Anth]	e.r. [with (*R*)-Anth]	Yield / % [with (*R*)-TRIP]	e.r. [with (*R*)-TRIP]
1	*p*-Tol (**3a**)	octane	100	80	93:7	36	94:6
2	*p*-NO_2 (**3b**)	octane	100	65	89:11	55	89:11
3	Mes (**3c**)	octane	100	67	92:8	47	97:3
4	*p*-Tol (**3a**)	cyclohexane	80	78	96:4	10	96:4
5	*p*-NO_2 (**3b**)	cyclohexane	80	72	86:14	20	93:7
6	Mes (**3c**)	cyclohexane	80	36	94:6	15	98:2

Table S5 : Screening of substrates with (R)-Anth as catalyst



3k **4k**

Entry	catalyst	yield (%)	e.r.
1	(*R*)-TRIP	25	31:69
2	(*R*)-TiPSY	2	25:75

Table S5 : Cyclisation of unsubstituted piperidine under different conditions

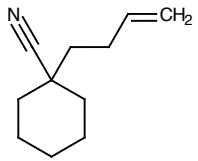
5) References

1) C. J. Maddocks, K. Ermanis and P. A. Clarke, *Org. Lett*. 2020, **22**, 8116–8121

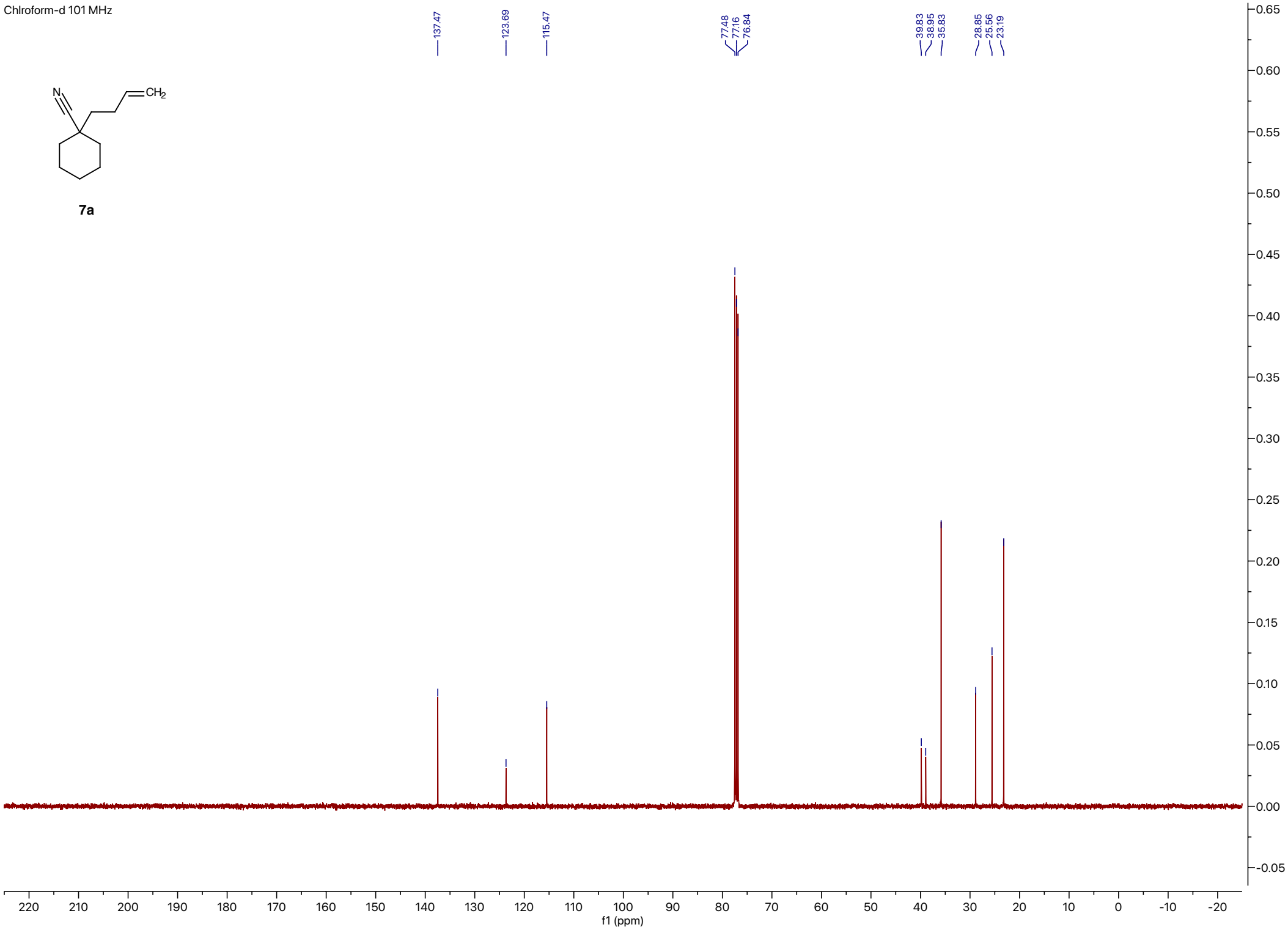
2) T. Aubineau and J. Cossy, *Chem. Commun.*, 2013, **49**, 3303–3305.

3) E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett and R. G. Carter, *J. Org. Chem.*, 2008, **73**, 5155–5158.

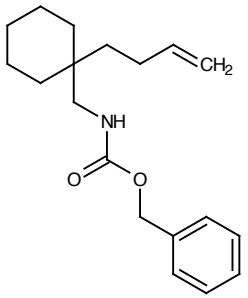
Chloroform-d 400 MHz



7a

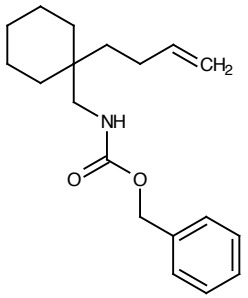

Chlroform-d 101 MHz
137.47
123.69
115.47
77.48
77.16
76.84
39.83
38.95
35.83
28.85
25.56
23.19
N
CH2
7a
f1 (ppm)

Chloroform-d 400 MHz

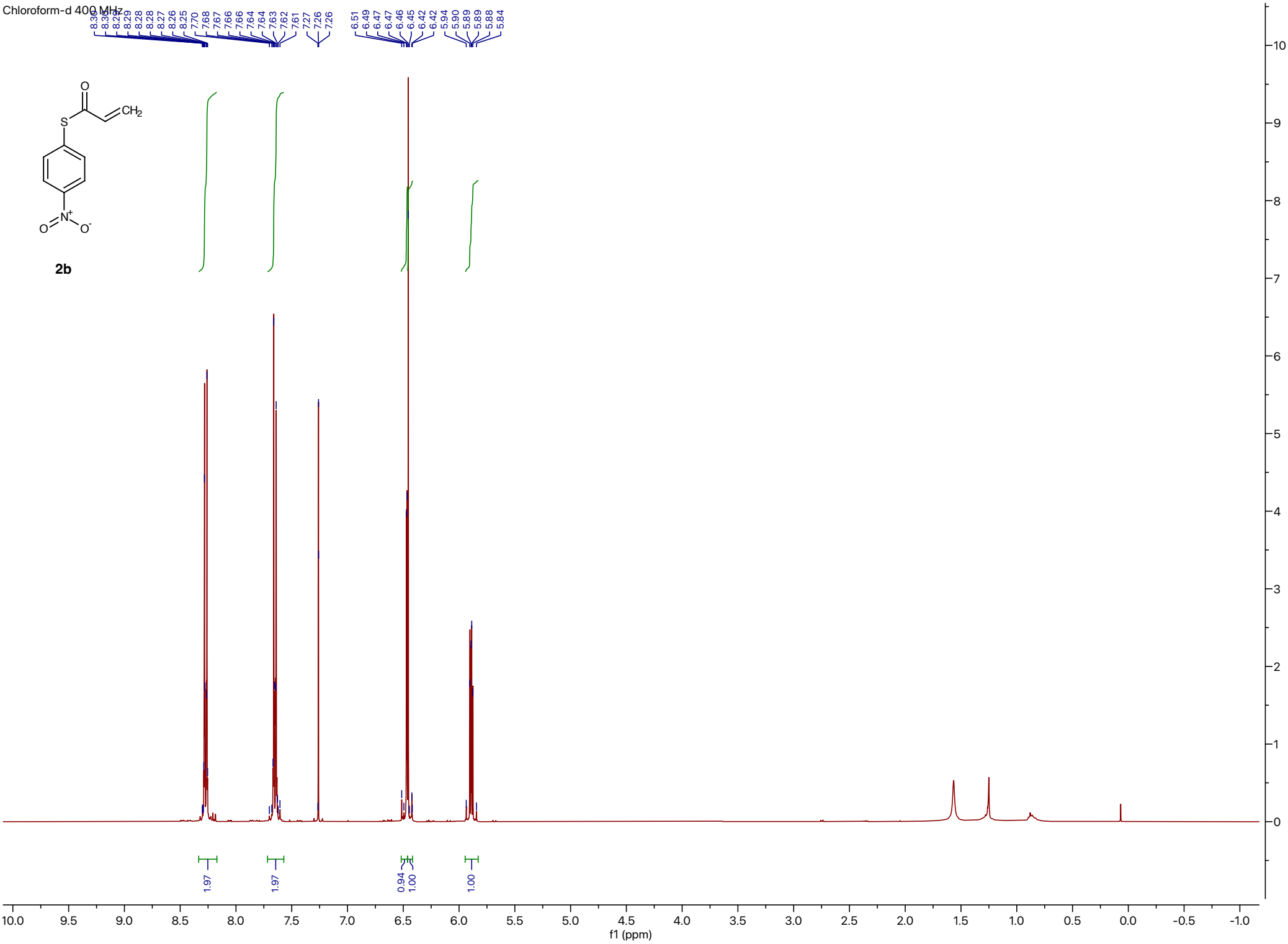


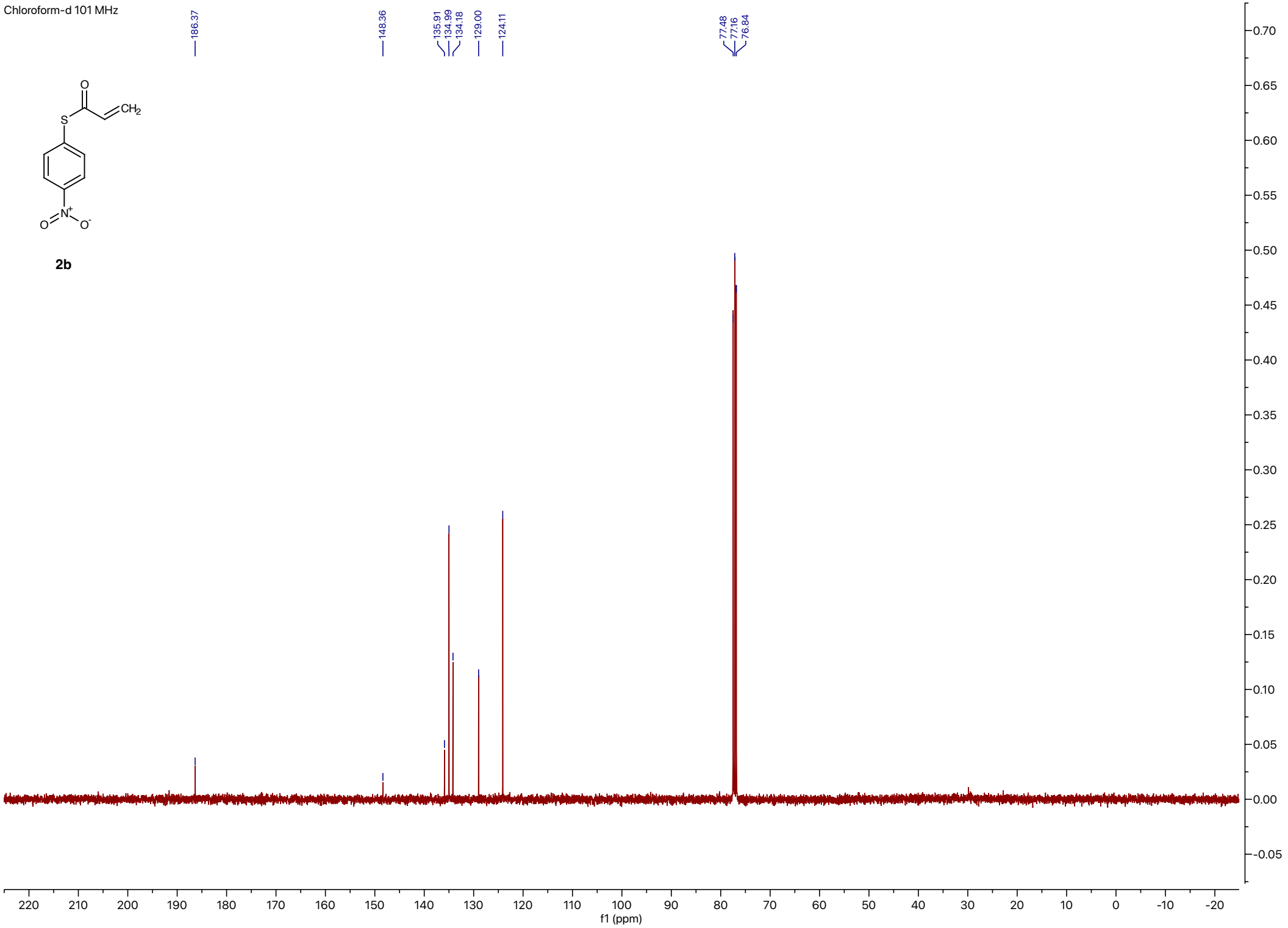
1a

Chloroform-d 101 MHz

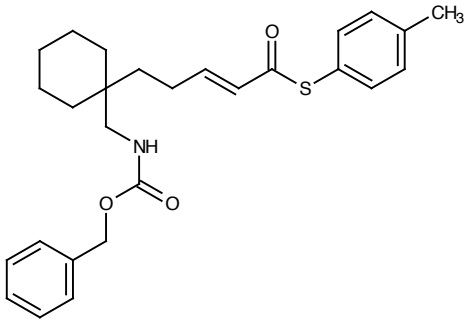


1a

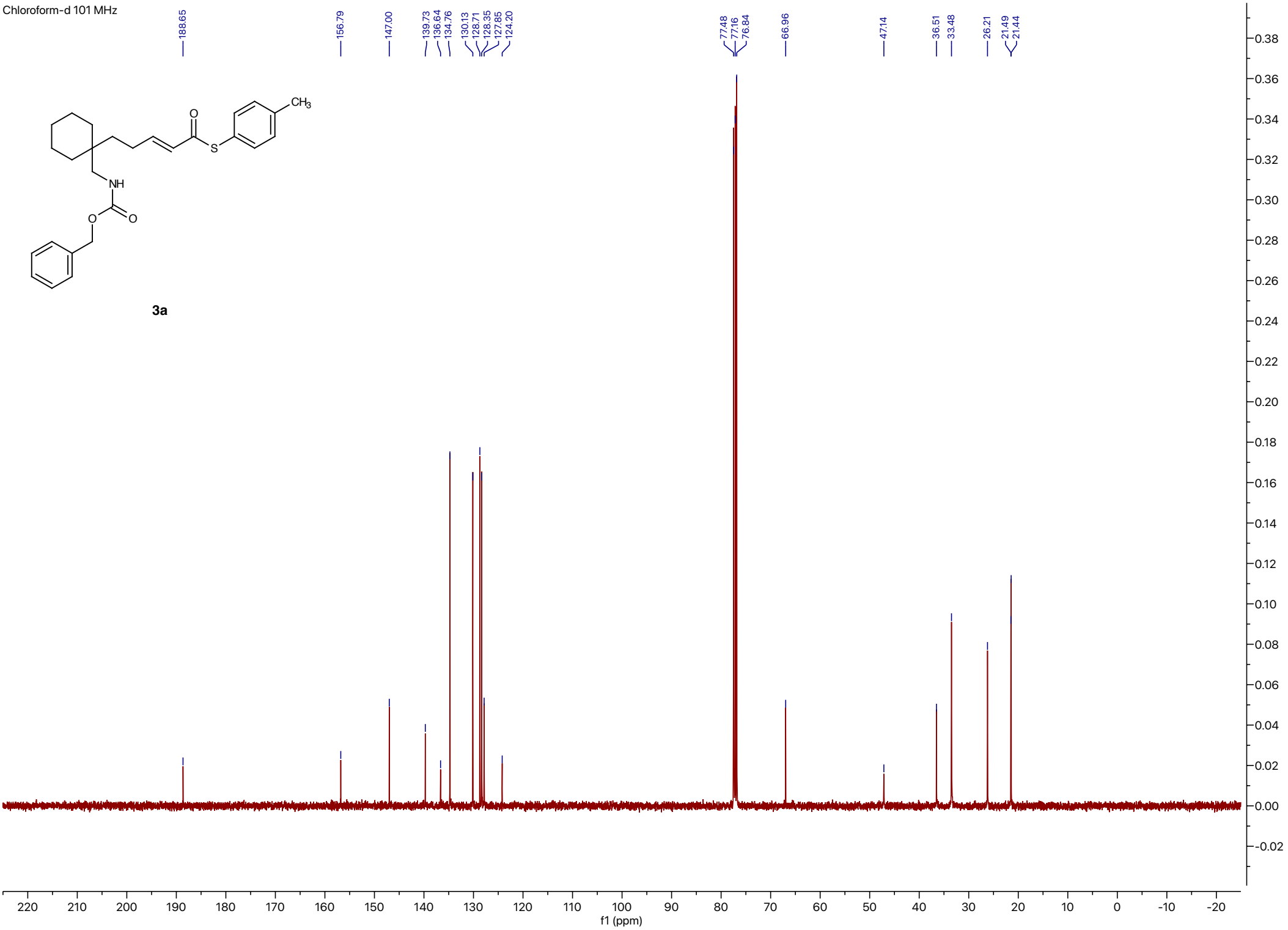

Chloroform-d 400 MHz
8.39 8.39 8.29 8.29 8.28 8.28 8.27 8.26 8.25 7.70 7.68 7.67 7.66 7.66 7.64 7.64 7.63 7.62 7.61 7.27 7.26 7.26
6.51 6.49 6.47 6.47 6.46 6.45 6.42 6.42 5.94 5.90 5.89 5.89 5.88 5.84
O
S
CH2
O
N+
O-
2b
1.97
1.97
0.94
1.00
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
10 9 8 7 6 5 4 3 2 1 0

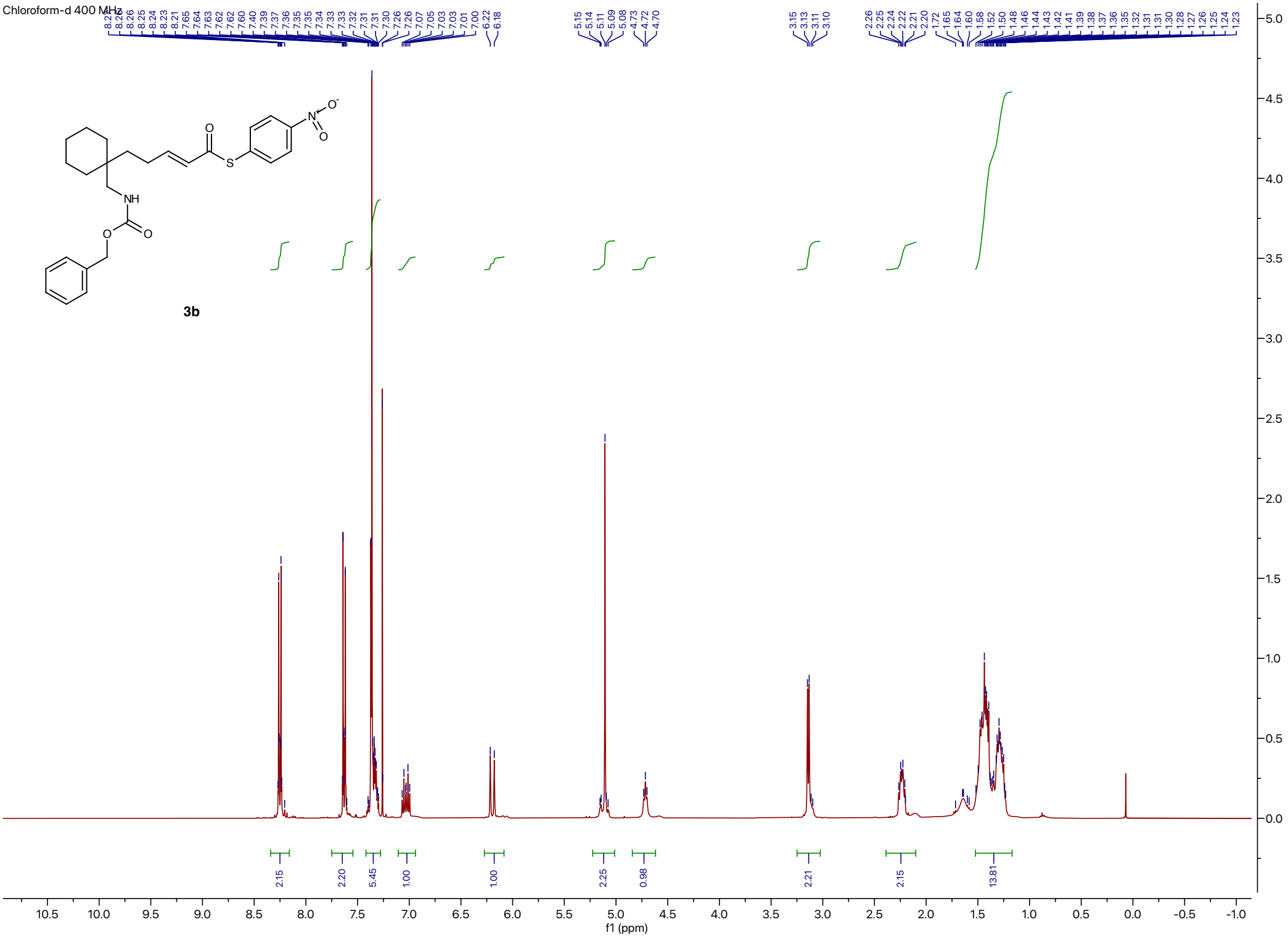

Chloroform-d 101 MHz
186.37
148.36
135.91
134.99
134.18
129.00
124.11
77.48
77.16
76.84
O
S
CH2
O
N+
O-
2b
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

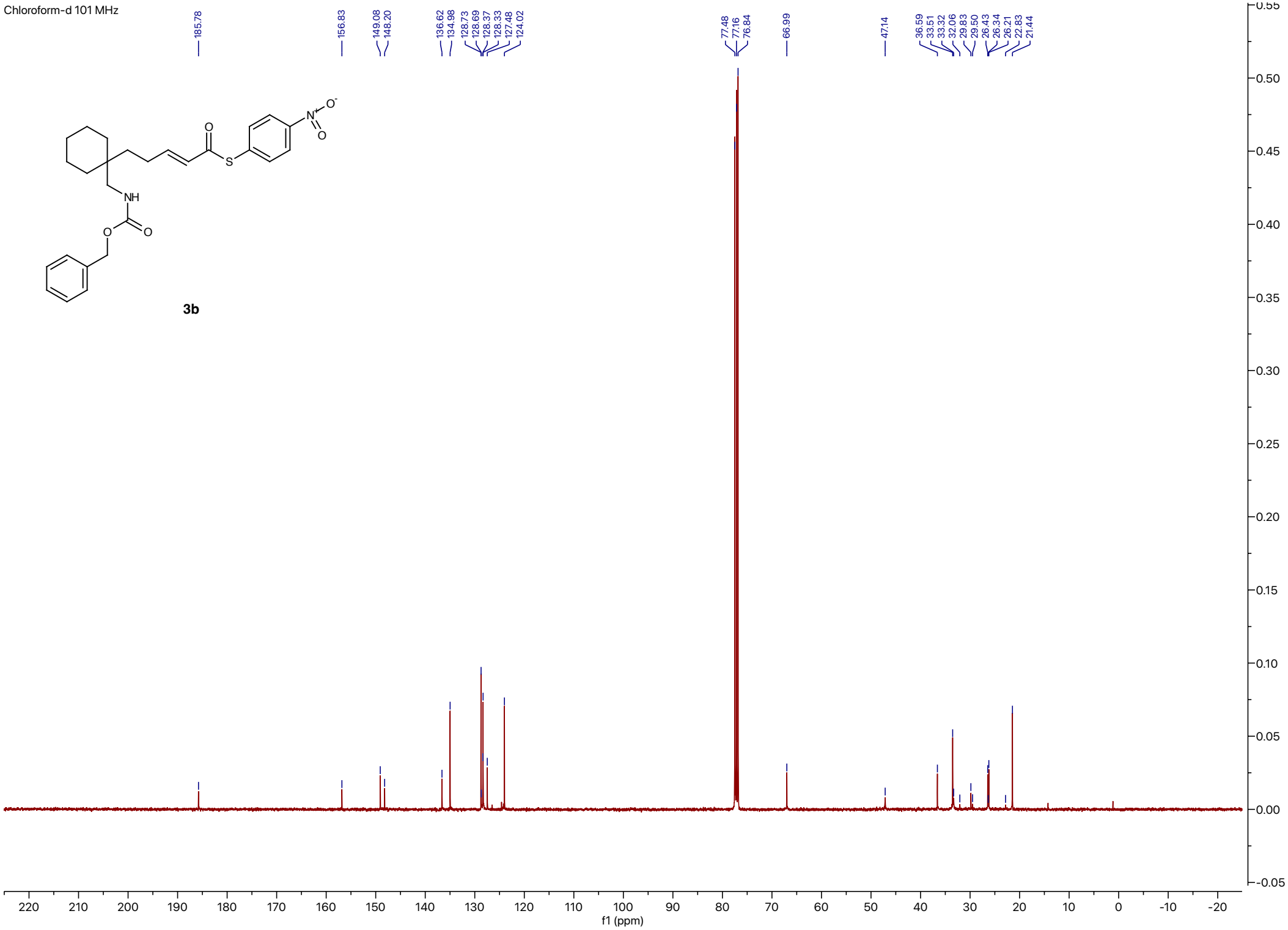
Chloroform-d 400 MHz

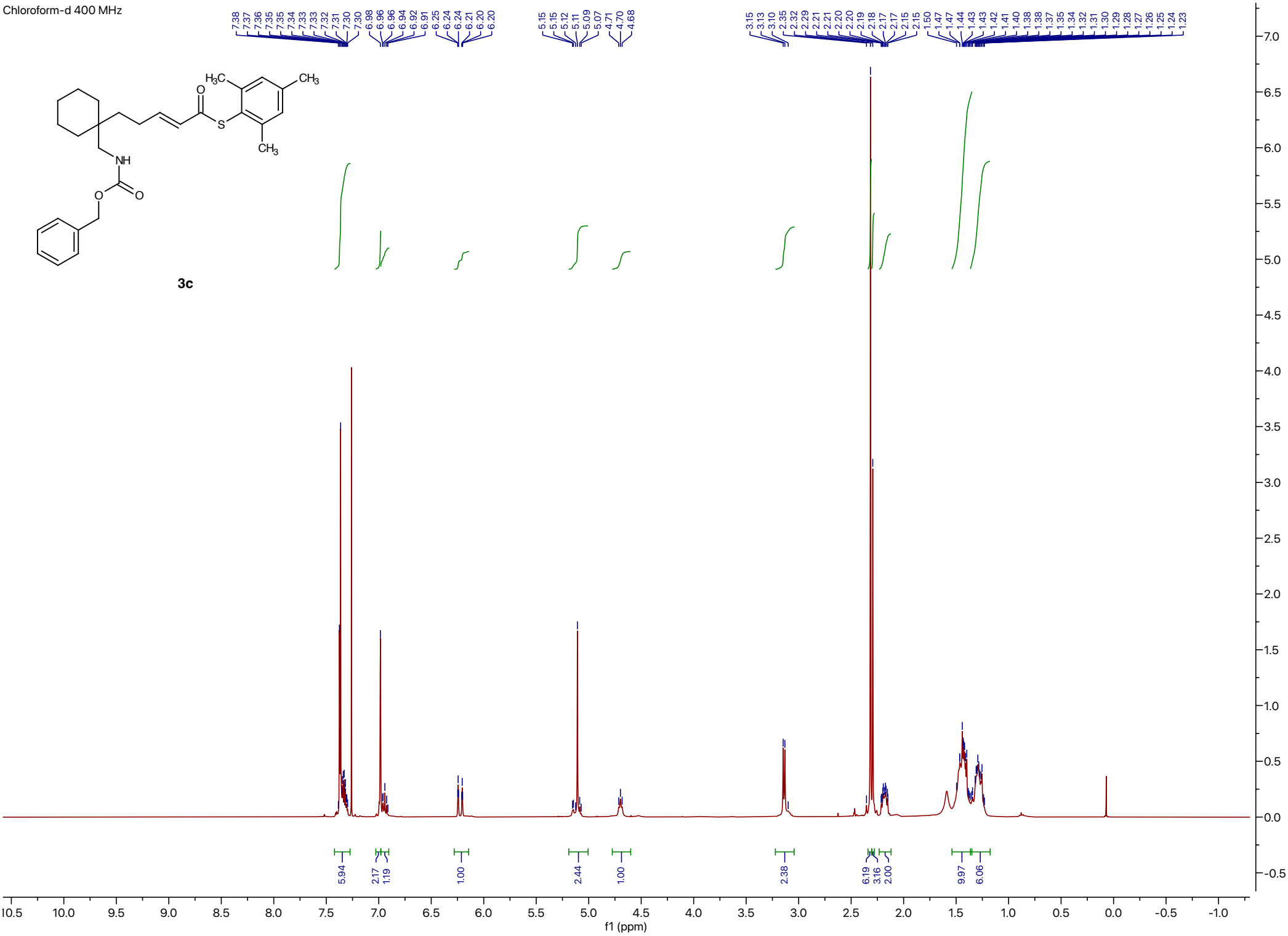


3a

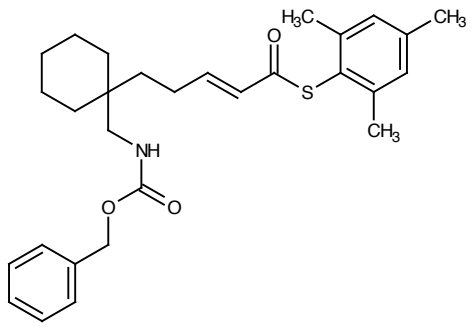

Chloroform-d 101 MHz
188.65
156.79
147.00
139.73
136.64
134.76
130.13
128.71
128.35
127.85
124.20
77.48
77.16
76.84
66.96
47.14
36.51
33.48
26.21
21.49
21.44
CH3
O
S
NH
O
O
3a
f1 (ppm)


Chloroform-d 400 MHz
8.27 8.26 8.26 8.25 8.24 8.23 8.21 7.65 7.64 7.63 7.62 7.62 7.60 7.40 7.39 7.37 7.36 7.35 7.35 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.26 7.26 7.07 7.05 7.03 7.03 7.01 7.00 6.22 6.18
5.15 5.14 5.11 5.09 5.08 4.73 4.72 4.70
3.15 3.13 3.11 3.10
2.26 2.25 2.24 2.22 2.21 2.20 1.72 1.65 1.64 1.60 1.58 1.52 1.50 1.48 1.46 1.44 1.43 1.42 1.41 1.39 1.38 1.37 1.36 1.35 1.32 1.31 1.31 1.30 1.28 1.27 1.26 1.25 1.24 1.23
O
S
N+
O-
O
NH
O
O
3b
2.15
2.20
5.45
1.00
1.00
2.25
0.98
2.21
2.15
13.81
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 0.5 0.0 -0.5 -1.0
f1 (ppm)
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


Chloroform-d 101 MHz
185.78
156.83
149.08
148.20
136.62
134.98
128.73
128.69
128.37
128.33
127.48
124.02
77.48
77.16
76.84
66.99
47.14
36.59
33.51
33.32
32.06
29.83
29.50
26.43
26.34
26.21
22.83
21.44
O
S
N+
O-
O
NH
O
O
3b
f1 (ppm)

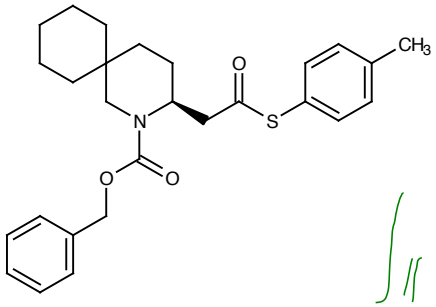

Chloroform-d 400 MHz
3c
f1 (ppm)

Chloroform-d 101 MHz



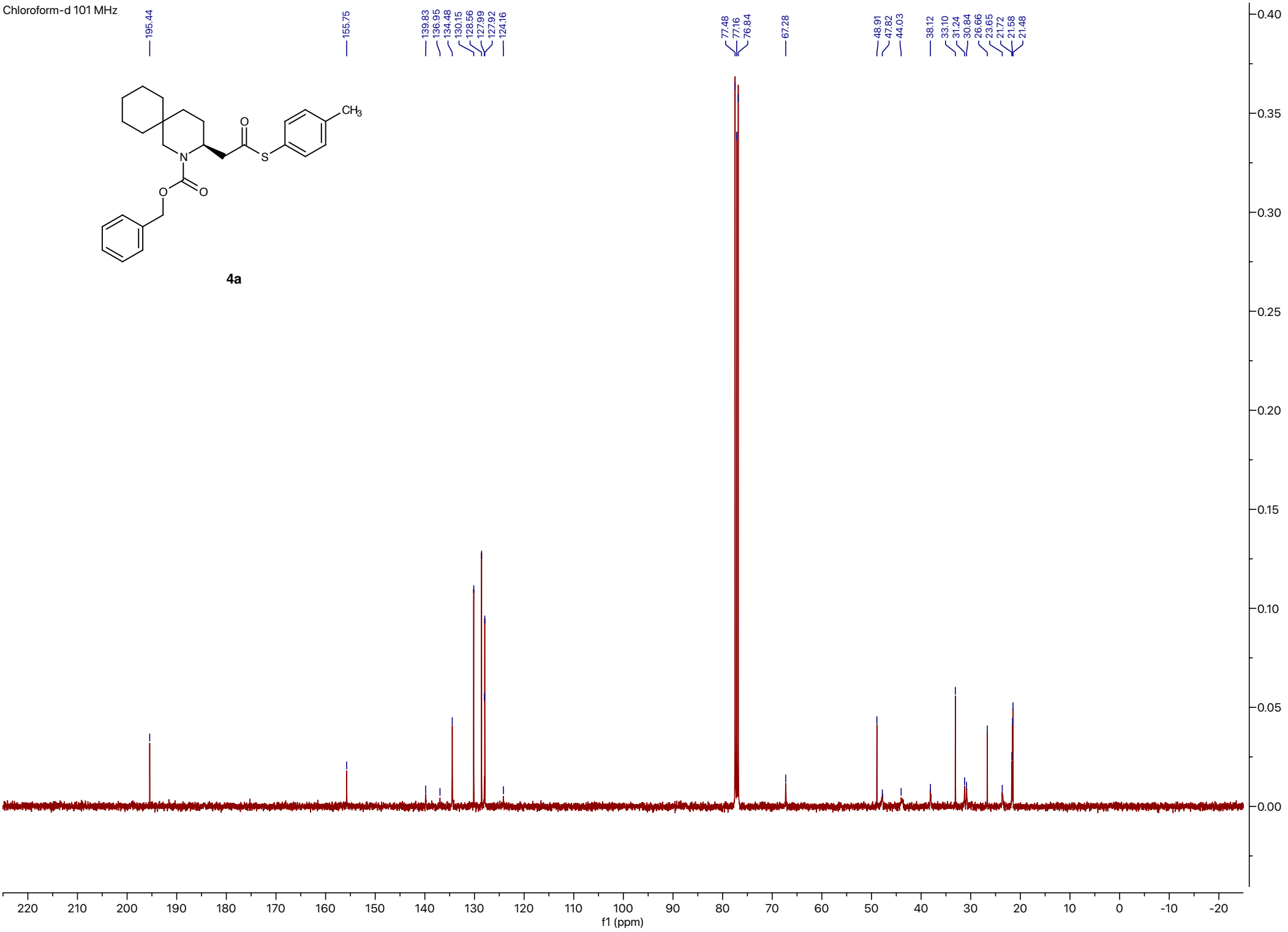
3c

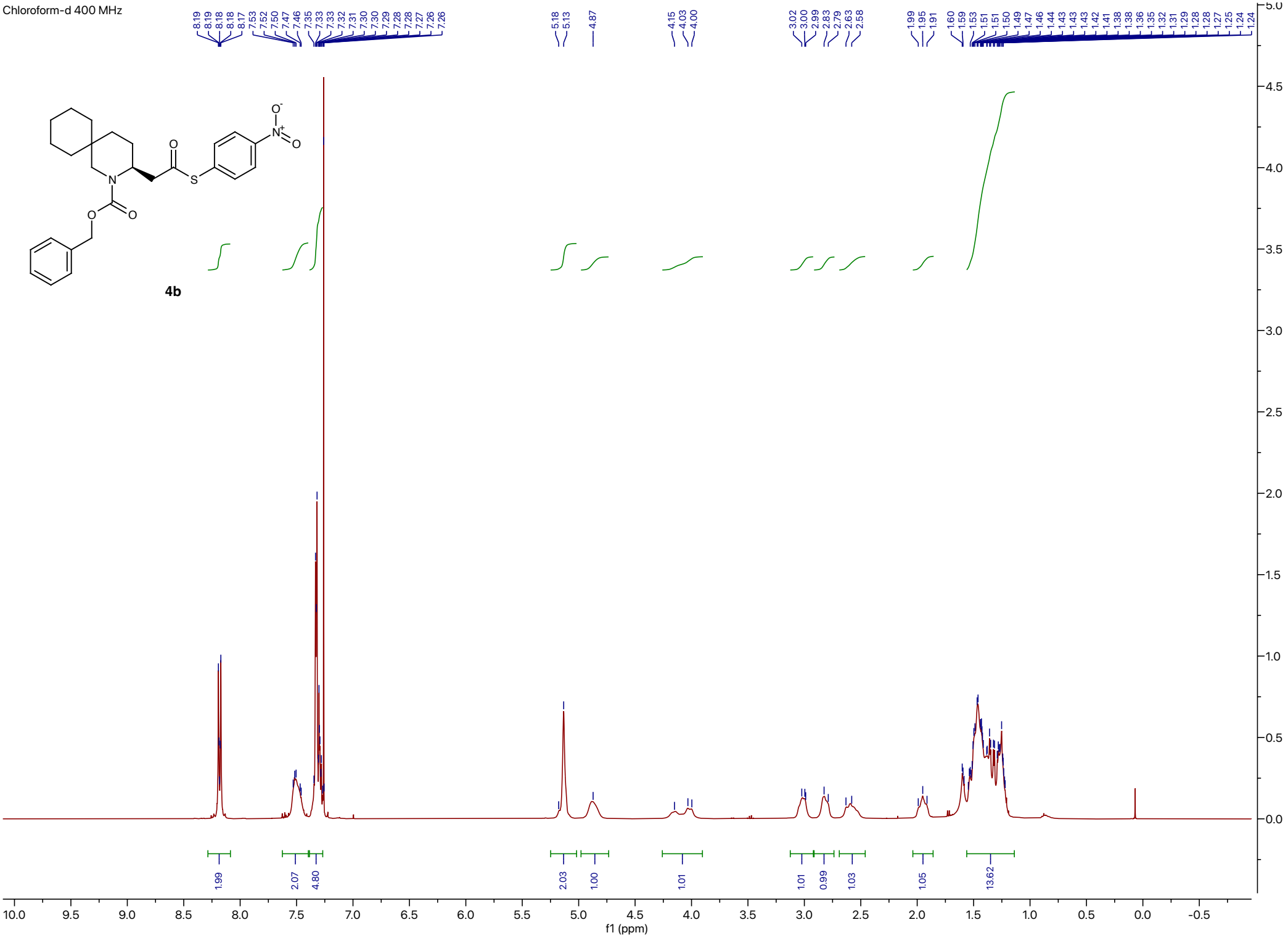
Chloroform-d 400 MHz

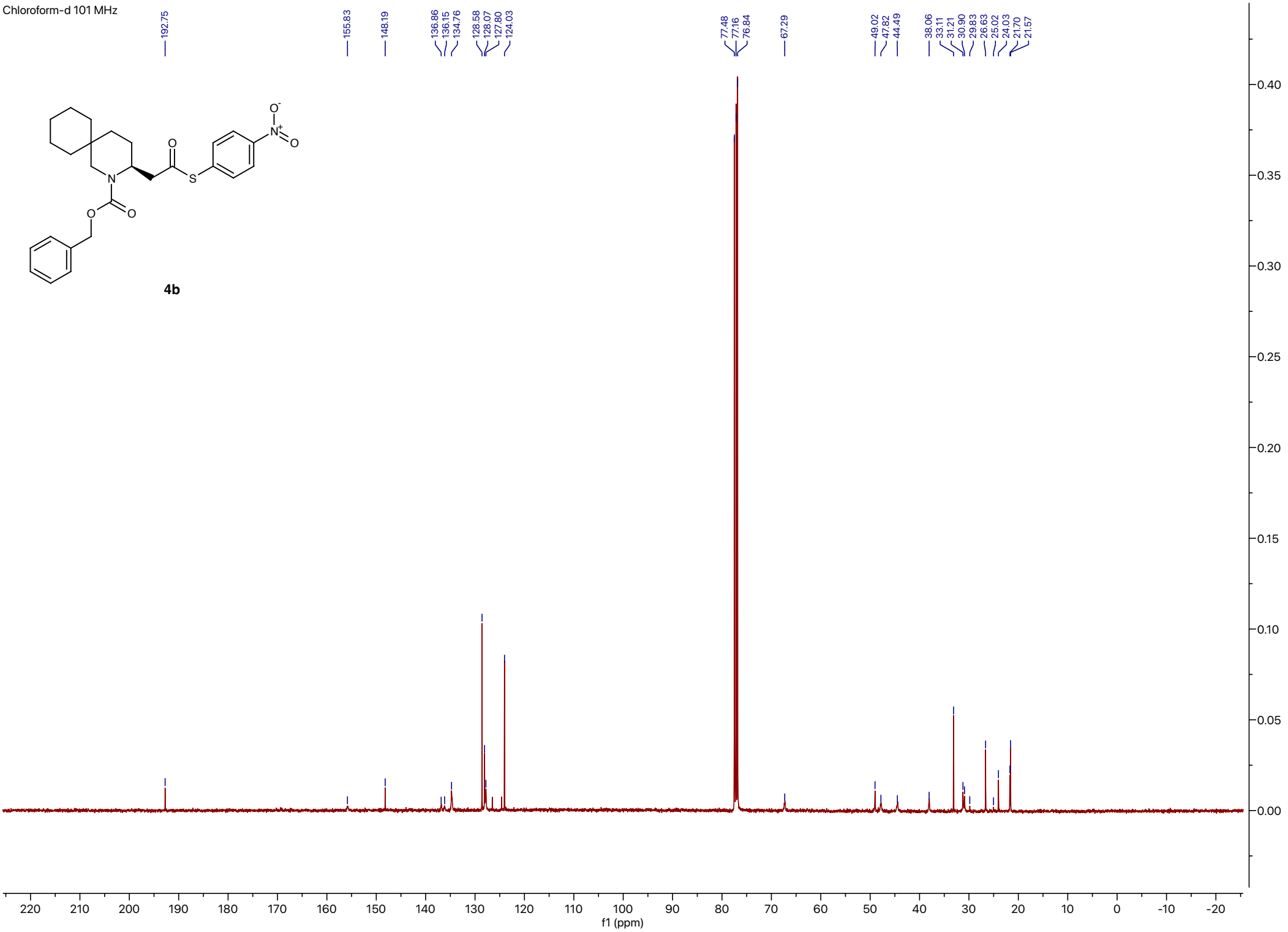


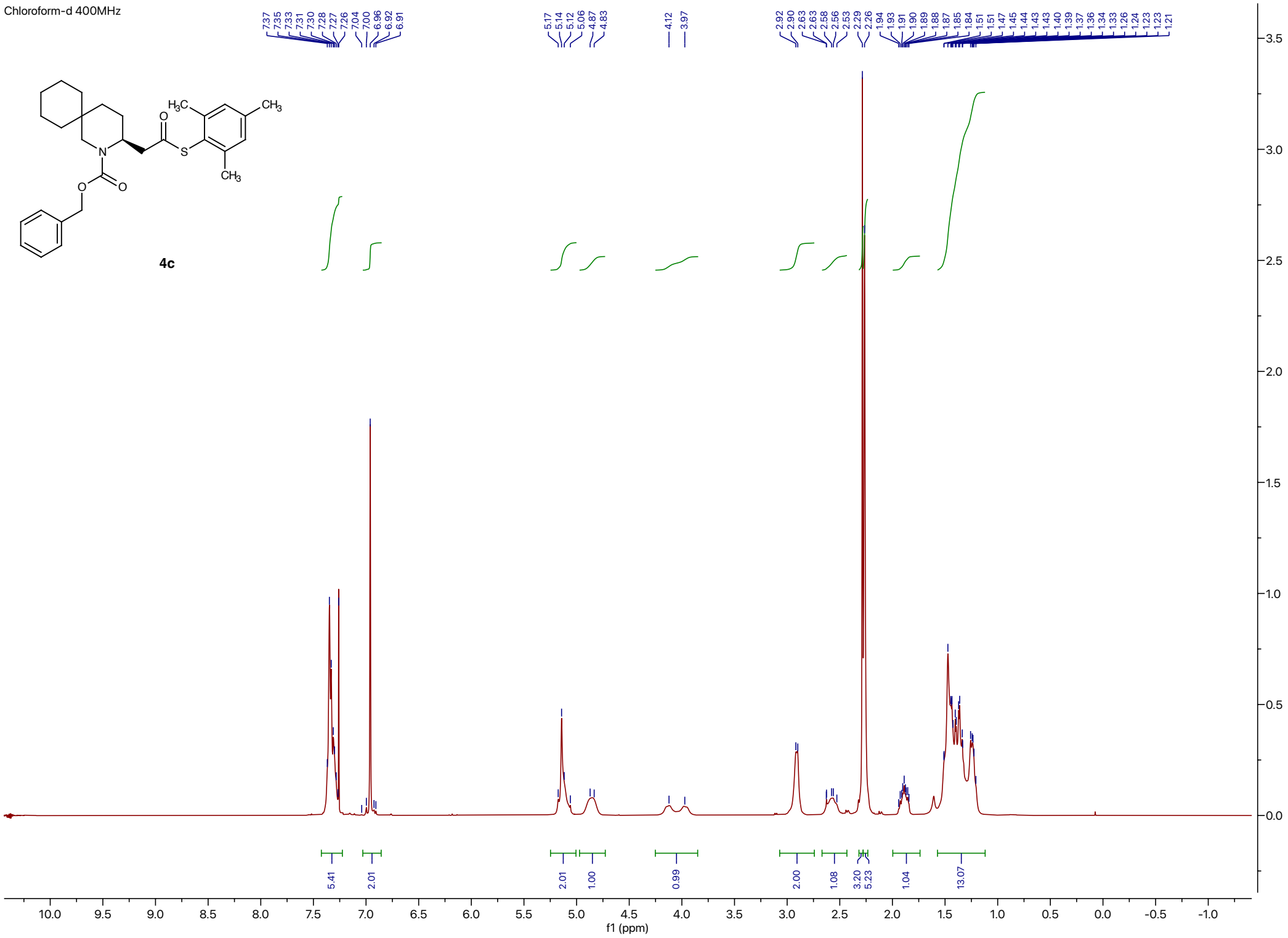
4a

f1 (ppm)

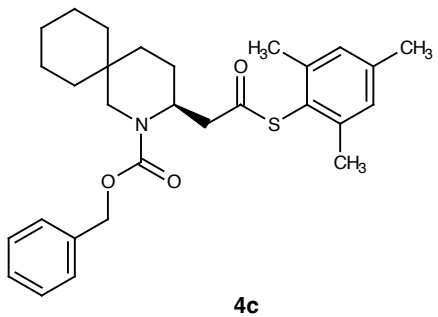

Chloroform-d 101 MHz
195.44
155.75
139.83
136.95
134.48
130.15
128.56
127.99
127.92
124.16
77.48
77.16
76.84
67.28
48.91
47.82
44.03
38.12
33.10
31.24
30.84
26.66
23.65
21.72
21.58
21.48
CH3
O
S
N
O
O
4a
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


Chloroform-d 400 MHz
4b
f1 (ppm)


Chloroform-d 101 MHz
192.75
155.83
148.19
136.86
136.15
134.76
128.58
128.07
127.80
124.03
77.48
77.16
76.84
67.29
49.02
47.82
44.49
38.06
33.11
31.21
30.90
29.83
26.63
25.02
24.03
21.70
21.57
4b
f1 (ppm)

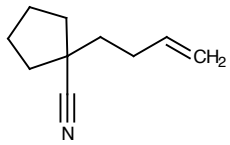

Chloroform-d 400MHz
7.37
7.35
7.33
7.31
7.30
7.28
7.27
7.26
7.04
7.00
6.96
6.92
6.91
5.17
5.14
5.12
5.06
4.87
4.83
4.12
3.97
2.92
2.90
2.63
2.63
2.58
2.56
2.53
2.29
2.26
1.94
1.93
1.91
1.90
1.89
1.88
1.87
1.85
1.84
1.51
1.51
1.47
1.45
1.44
1.43
1.43
1.40
1.39
1.37
1.36
1.34
1.33
1.26
1.24
1.23
1.23
1.21
H3C
CH3
O
S
N
O
O
CH3
4c
5.41
2.01
2.01
1.00
0.99
2.00
1.08
3.20
5.23
1.04
13.07
f1 (ppm)

Chloroform-d 101 MHz



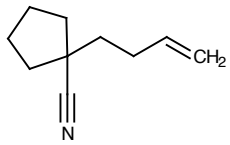
4c

Chloroform-d 400 MHz



7d

Chloroform-d 101 MHz

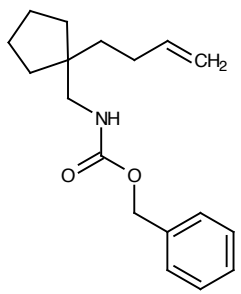


7d

137.19
125.16
115.41
77.48
77.16
76.84
43.02
38.23
37.84
30.69
24.22

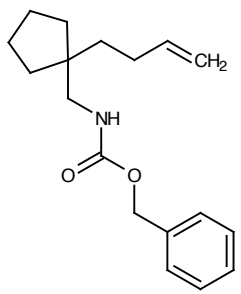
f1 (ppm)

Chloroform-d 400 MHz



1d

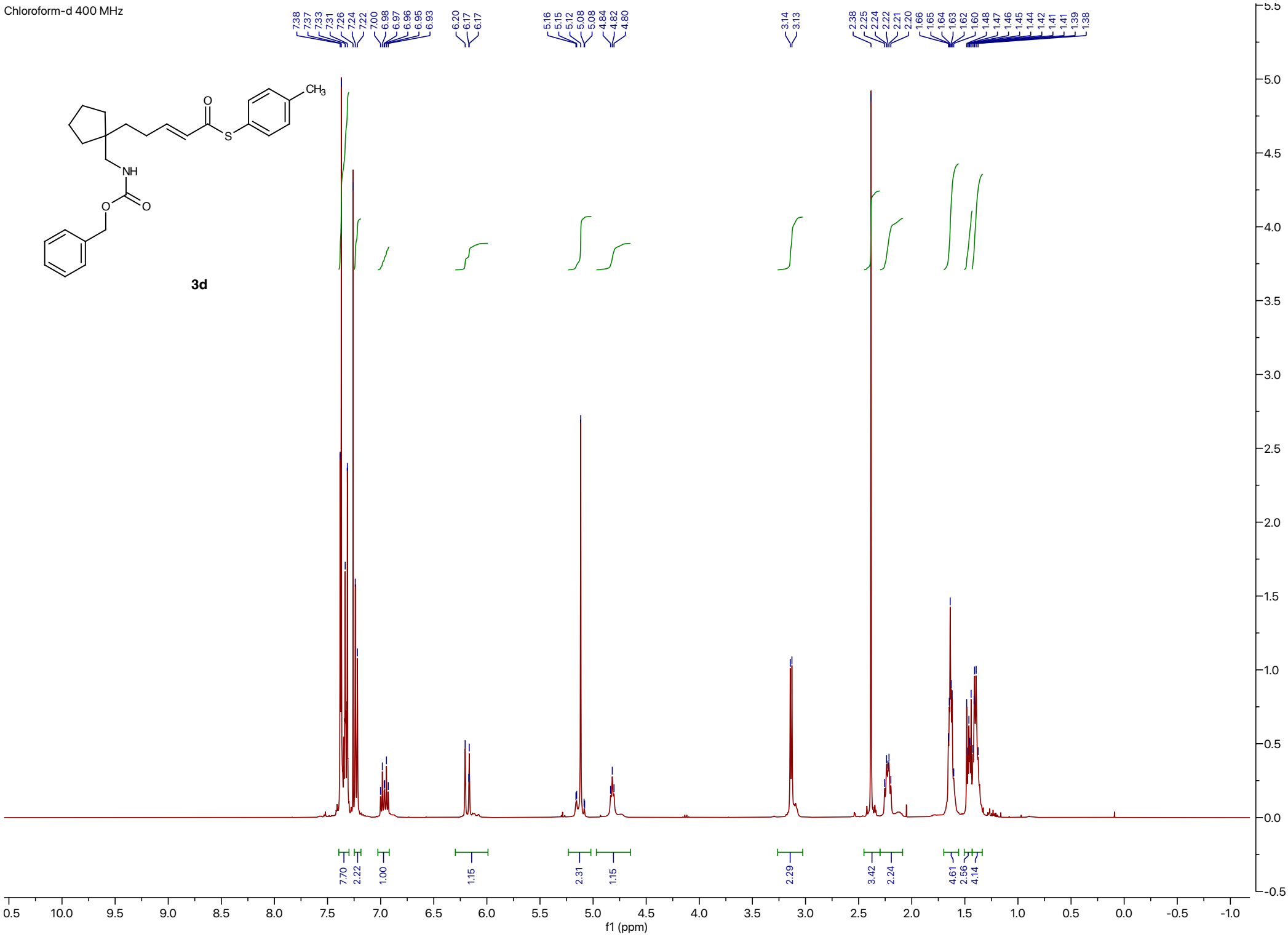
Chloroform-d 101 MHz

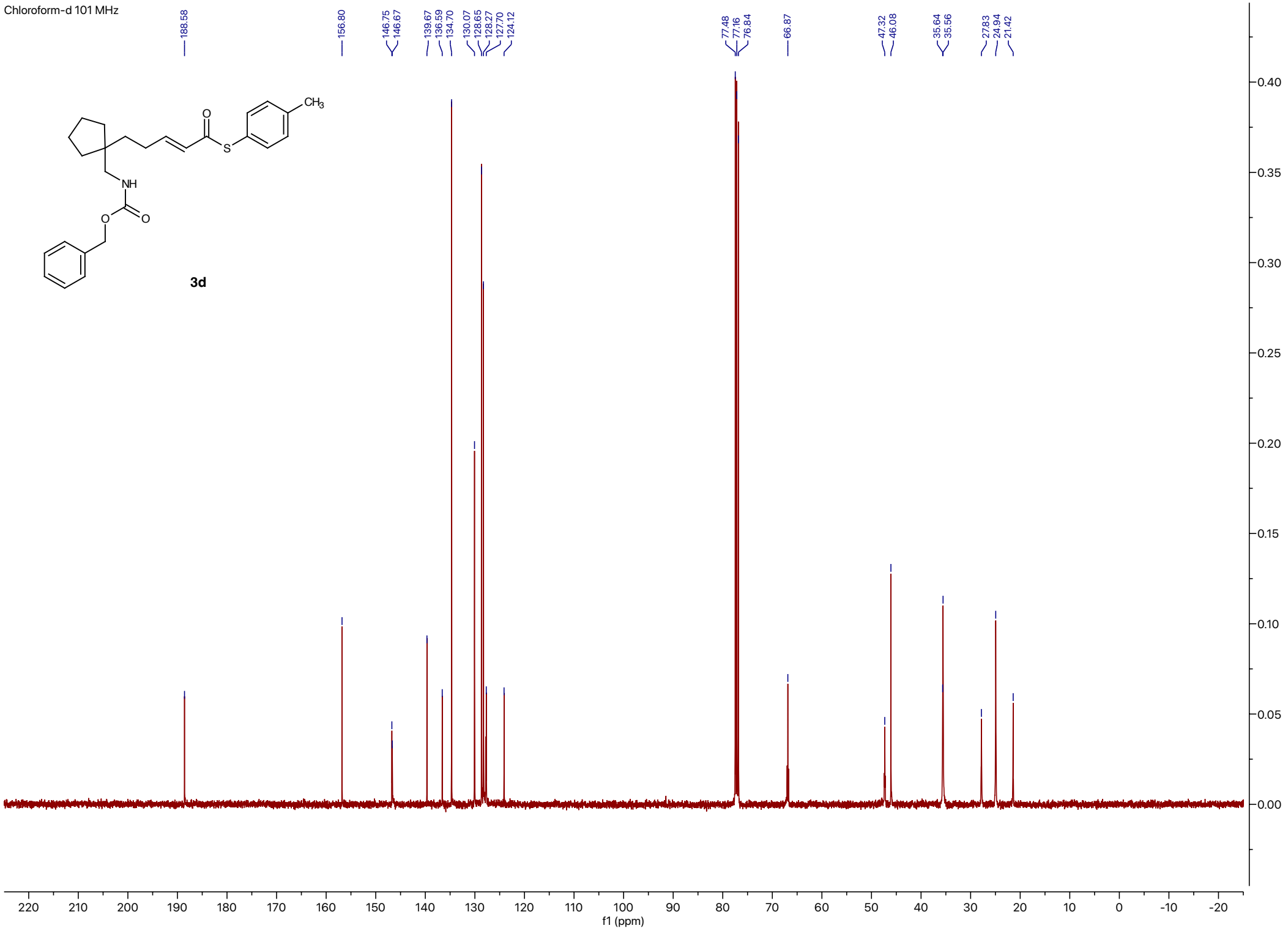


1d

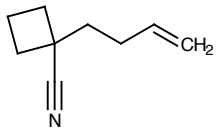
156.86
139.18
136.72
128.67
128.30
128.27
114.34
77.48
77.16
76.84
66.83
47.57
45.99
37.00
35.58
29.18
25.06

f1 (ppm)


Chloroform-d 400 MHz
7.38 7.37 7.33 7.31 7.26 7.24 7.22 7.00 6.98 6.97 6.96 6.95 6.93
6.20 6.17 6.17
5.16 5.15 5.12 5.08 5.08 4.84 4.82 4.80
3.14 3.13
2.38 2.25 2.24 2.22 2.21 2.20
1.66 1.65 1.64 1.63 1.62 1.60 1.48 1.47 1.46 1.45 1.44 1.42 1.41 1.41 1.39 1.38
CH3
O
S
NH
O
O
3d
7.70 2.22 1.00 1.15 2.31 1.15 2.29 3.42 2.24 4.61 2.56 4.14
f1 (ppm)

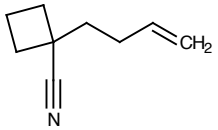

Chloroform-d 101 MHz
188.58
156.80
146.75
146.67
139.67
136.59
134.70
130.07
128.65
128.27
127.70
124.12
77.48
77.16
76.84
66.87
47.32
46.08
35.64
35.56
27.83
24.94
21.42
CH3
O
S
NH
O
O
3d
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

Chloroform-d 400 MHz



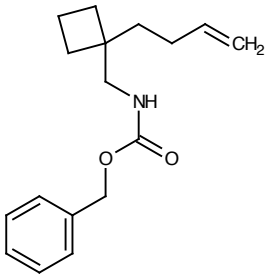
7e

Chloroform-d 101 MHz



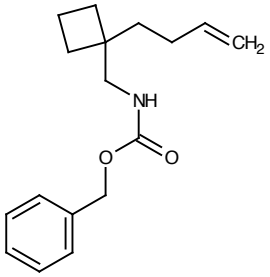
7e

Chloroform-d 400 MHz

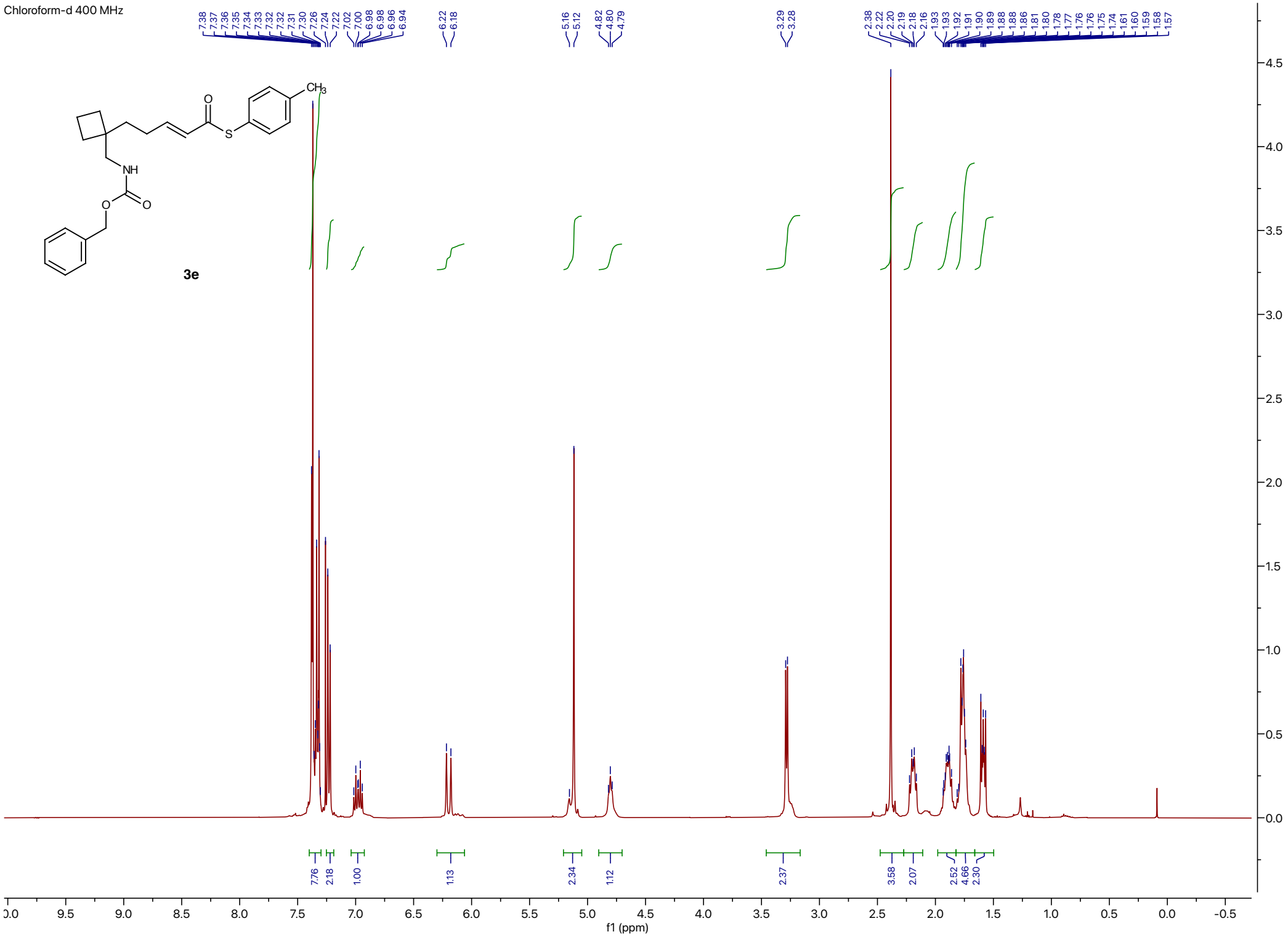


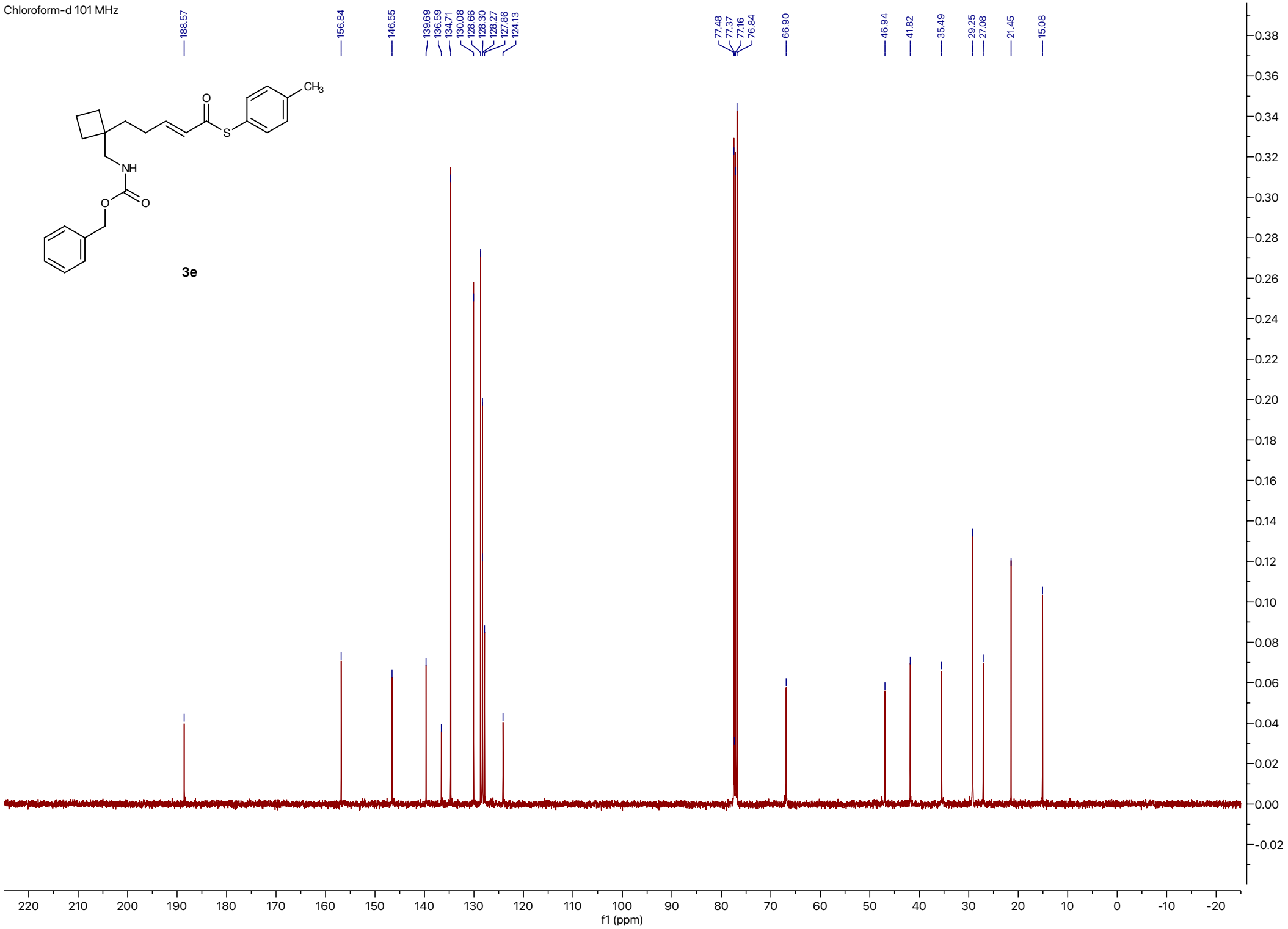
1e

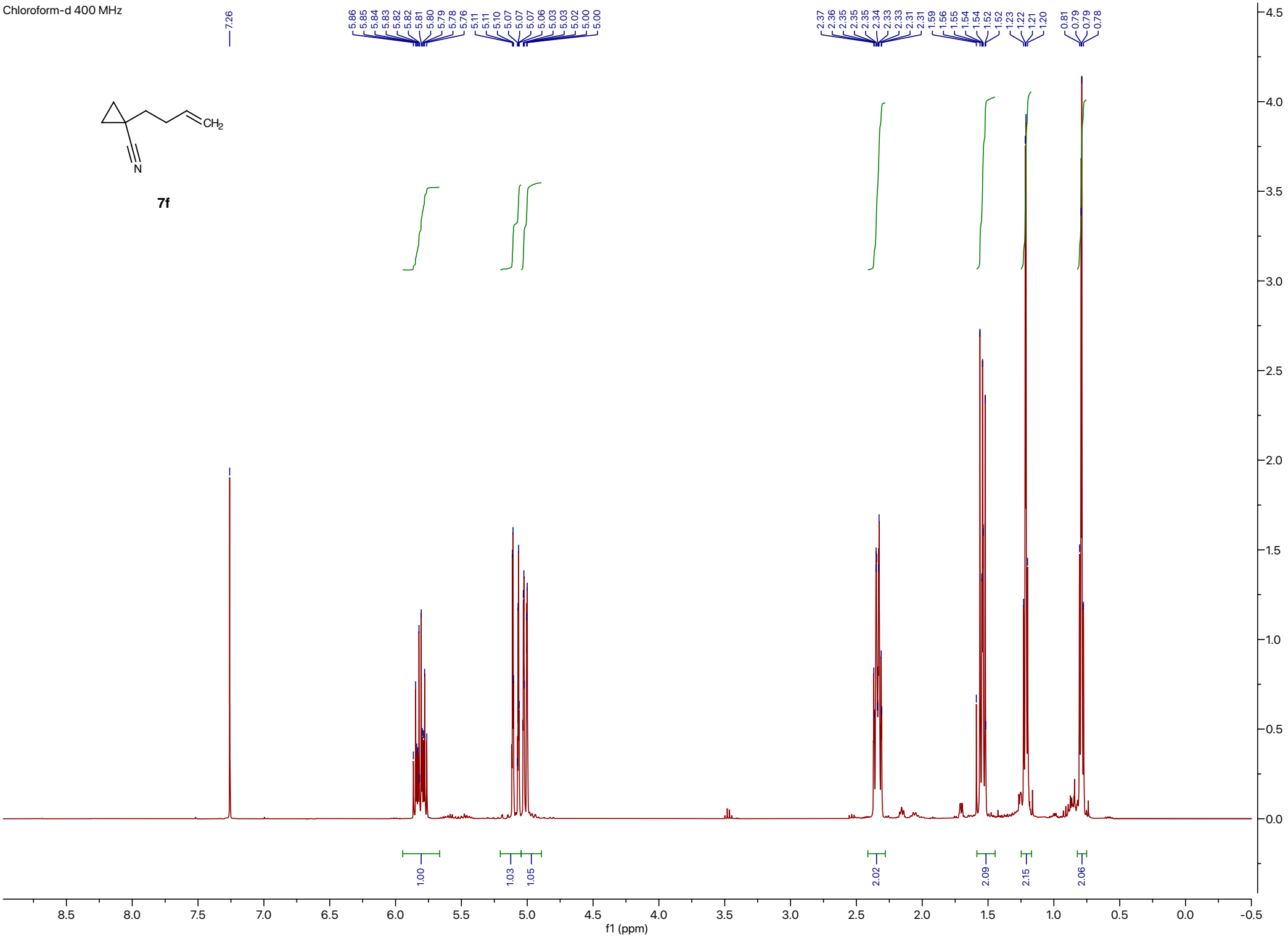
Chloroform-d 101 MHz



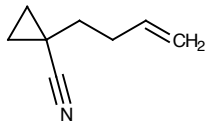
1e


Chloroform-d 400 MHz
7.38 7.37 7.36 7.35 7.34 7.33 7.32 7.32 7.31 7.30 7.26 7.24 7.22 7.02 7.00 6.98 6.98 6.96 6.94
6.22 6.18
5.16 5.12
4.82 4.80 4.79
3.29 3.28
2.38 2.22 2.20 2.19 2.18 2.16 1.93 1.93 1.92 1.91 1.90 1.89 1.88 1.88 1.86 1.81 1.80 1.78 1.77 1.76 1.76 1.75 1.74 1.61 1.60 1.59 1.58 1.57
CH3
O
S
NH
O
O
3e
7.76 2.18 1.00 1.13 2.34 1.12 2.37 3.58 2.07 2.52 4.66 2.30
f1 (ppm)


Chloroform-d 101 MHz
188.57
156.84
146.55
139.69
136.59
134.71
130.08
128.66
128.30
128.27
127.86
124.13
77.48
77.37
77.16
76.84
66.90
46.94
41.82
35.49
29.25
27.08
21.45
15.08
CH3
O
S
NH
O
O
3e
f1 (ppm)

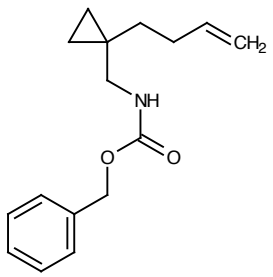

Chloroform-d 400 MHz
7.26
5.86 5.85 5.84 5.83 5.82 5.82 5.81 5.80 5.79 5.78 5.76
5.11 5.11 5.10 5.07 5.07 5.07 5.06 5.03 5.03 5.02 5.00 5.00
2.37 2.36 2.35 2.35 2.35 2.34 2.33 2.33 2.31 2.31
1.59 1.56 1.55 1.54 1.54 1.52 1.52
1.23 1.22 1.21 1.20
0.81 0.79 0.79 0.78
CH2
N
7f
1.00
1.03
1.05
2.02
2.09
2.15
2.06
f1 (ppm)

Chloroform-d 101 MHz



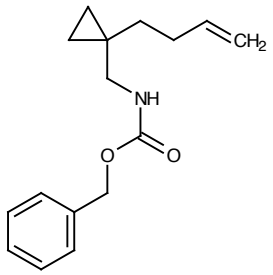
7f

Chloroform-d 400 MHz

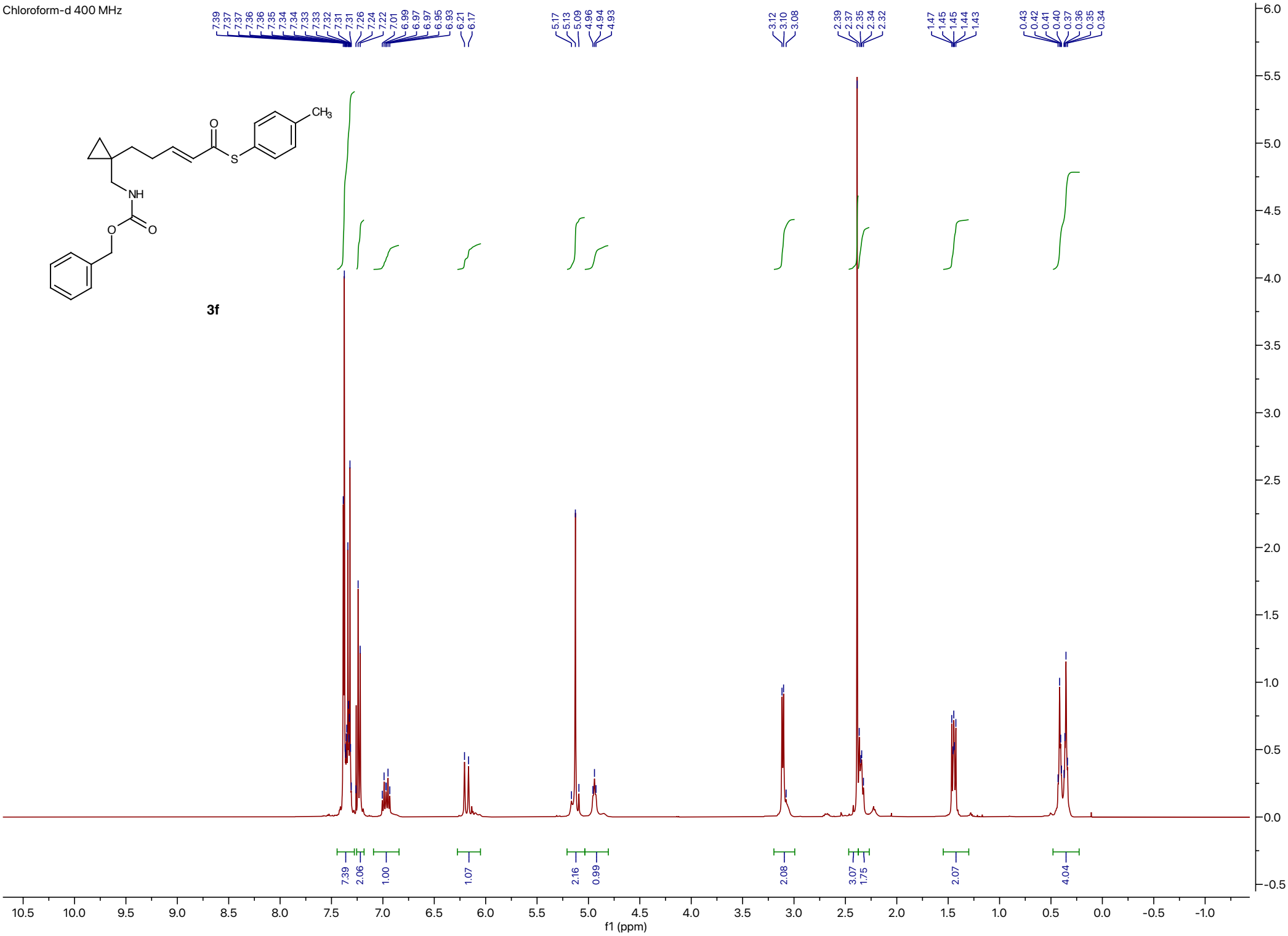


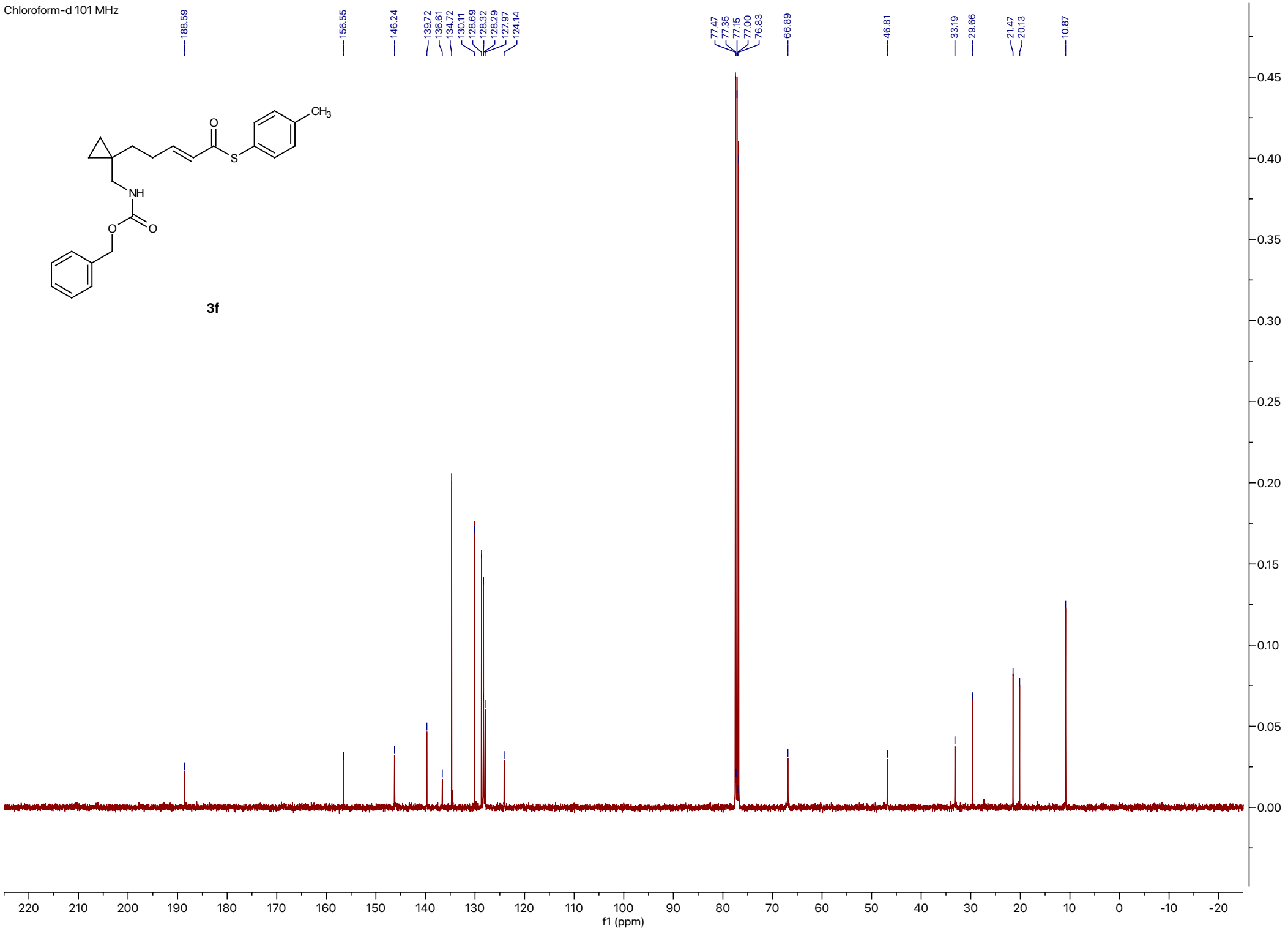
1f

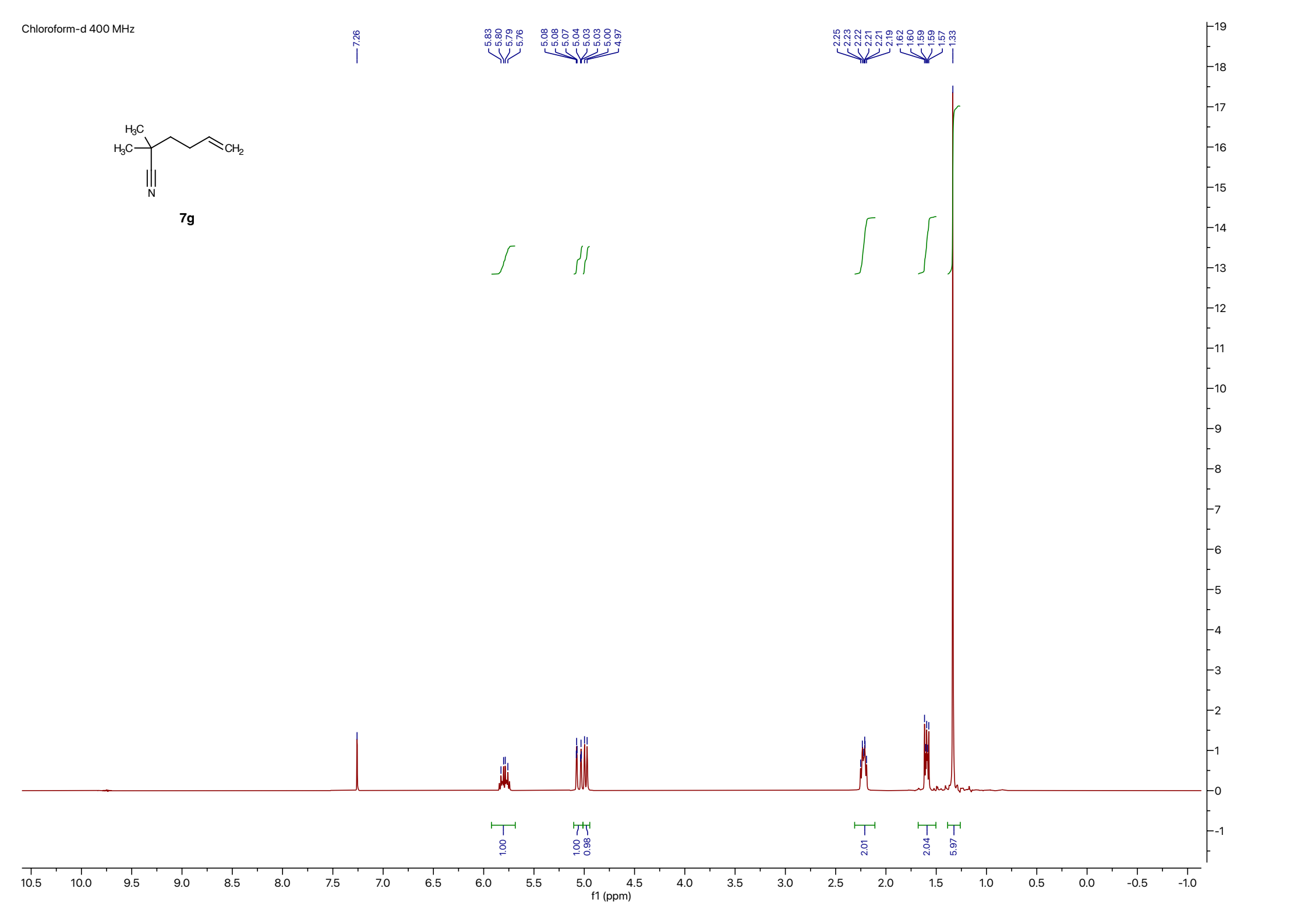
Chloroform-d 101 MHz



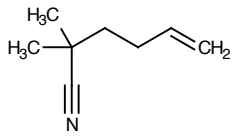
1f


Chloroform-d 400 MHz
7.39 7.37 7.37 7.36 7.36 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.31 7.26 7.24 7.22 7.01 6.99 6.97 6.97 6.95 6.93 6.21 6.17
5.17 5.13 5.09 4.96 4.94 4.93
3.12 3.10 3.08
2.39 2.37 2.35 2.34 2.32
1.47 1.45 1.45 1.44 1.43
0.43 0.42 0.41 0.40 0.37 0.36 0.35 0.34
CH3
O
S
NH
O
O
O
3f
7.39 2.06 1.00 1.07 2.16 0.99 2.08 3.07 1.75 2.07 4.04
f1 (ppm)

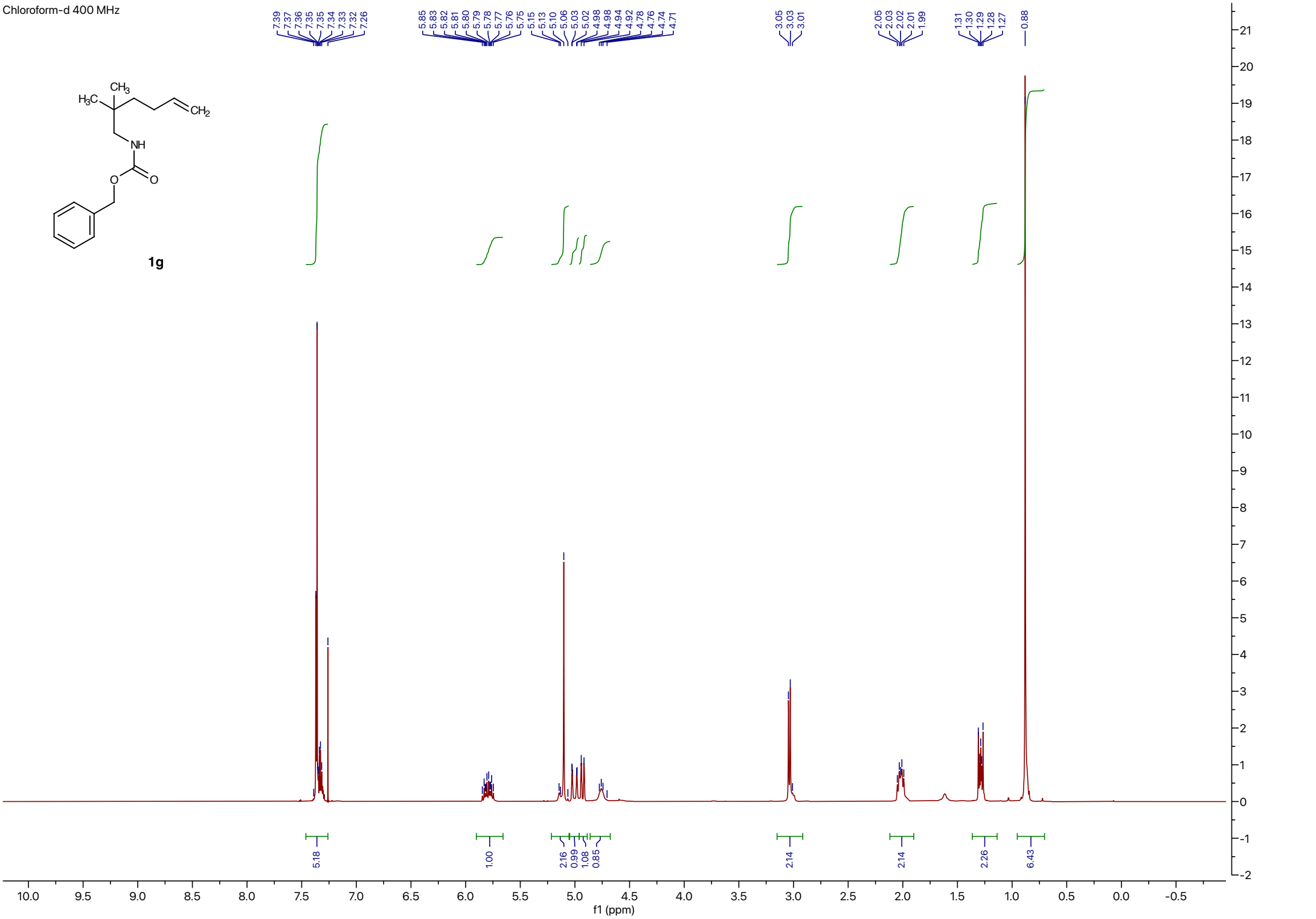

Chloroform-d 101 MHz
188.59
156.55
146.24
139.72
136.61
134.72
130.11
128.69
128.32
128.29
127.97
124.14
77.47
77.35
77.15
77.00
76.83
66.89
46.81
33.19
29.66
21.47
20.13
10.87
CH3
O
S
NH
O
O
O
3f
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


Chloroform-d 400 MHz
7.26
5.83
5.80
5.79
5.76
5.08
5.08
5.07
5.04
5.03
5.03
5.00
4.97
2.25
2.23
2.22
2.21
2.21
2.19
1.62
1.60
1.59
1.59
1.57
1.33
H3C
H3C
CH2
N
7g
1.00
1.00
0.98
2.01
2.04
5.97
f1 (ppm)

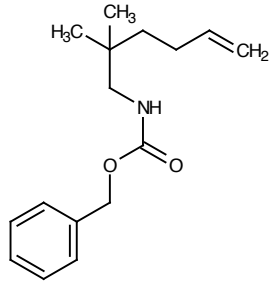
Chloroform-d 101 MHz



7g


Chloroform-d 400 MHz
7.39
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.26
5.85
5.83
5.82
5.81
5.80
5.79
5.78
5.77
5.76
5.75
5.15
5.13
5.10
5.06
5.03
5.02
4.98
4.98
4.94
4.92
4.78
4.76
4.74
4.71
3.05
3.03
3.01
2.05
2.03
2.02
2.01
1.99
1.31
1.30
1.29
1.28
1.27
0.88
CH3
H3C
CH2
NH
O
O
1g
5.18
1.00
2.16
0.99
1.08
0.85
2.14
2.14
2.26
6.43
f1 (ppm)

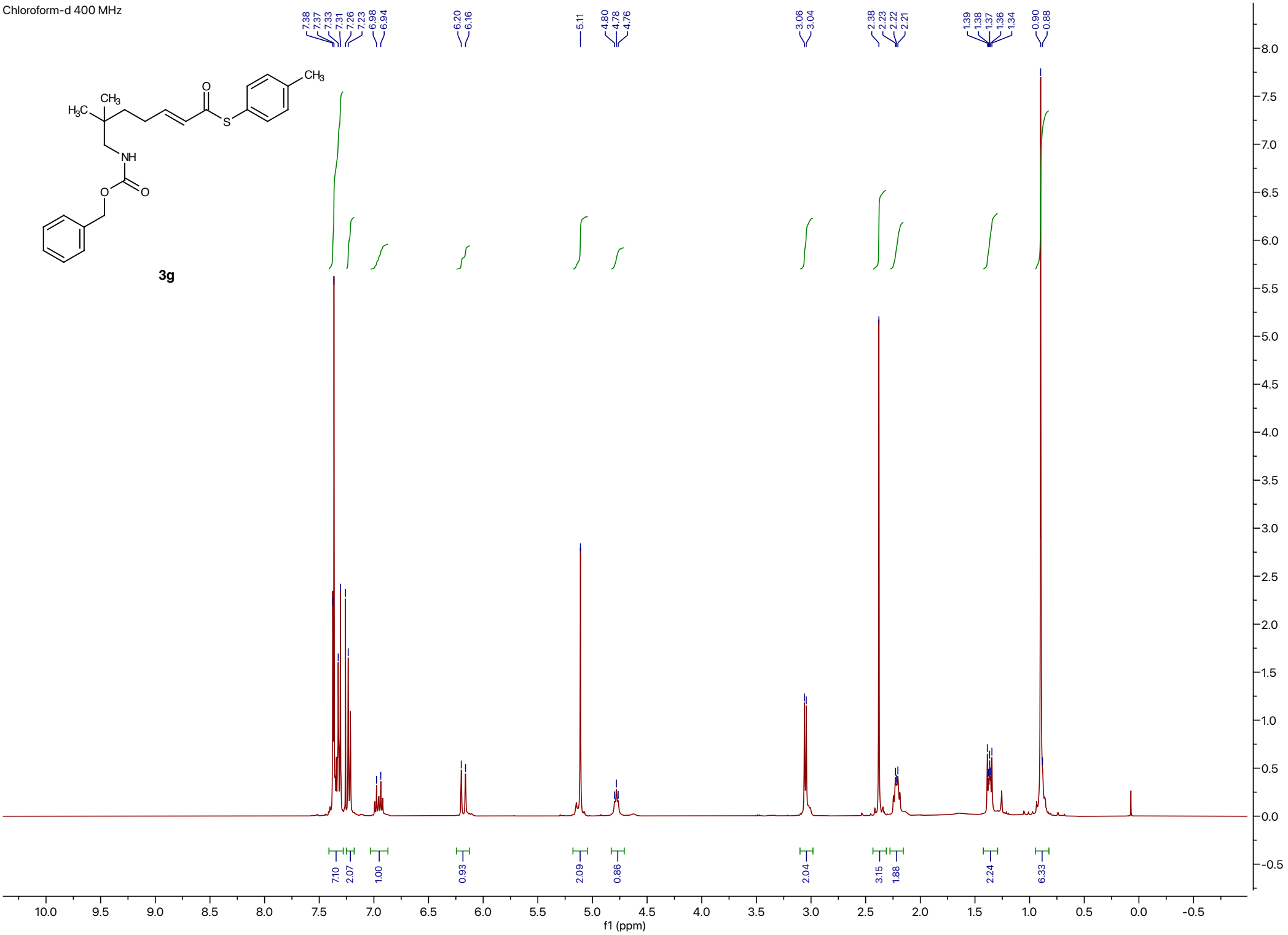
Chloroform-d 101 MHz

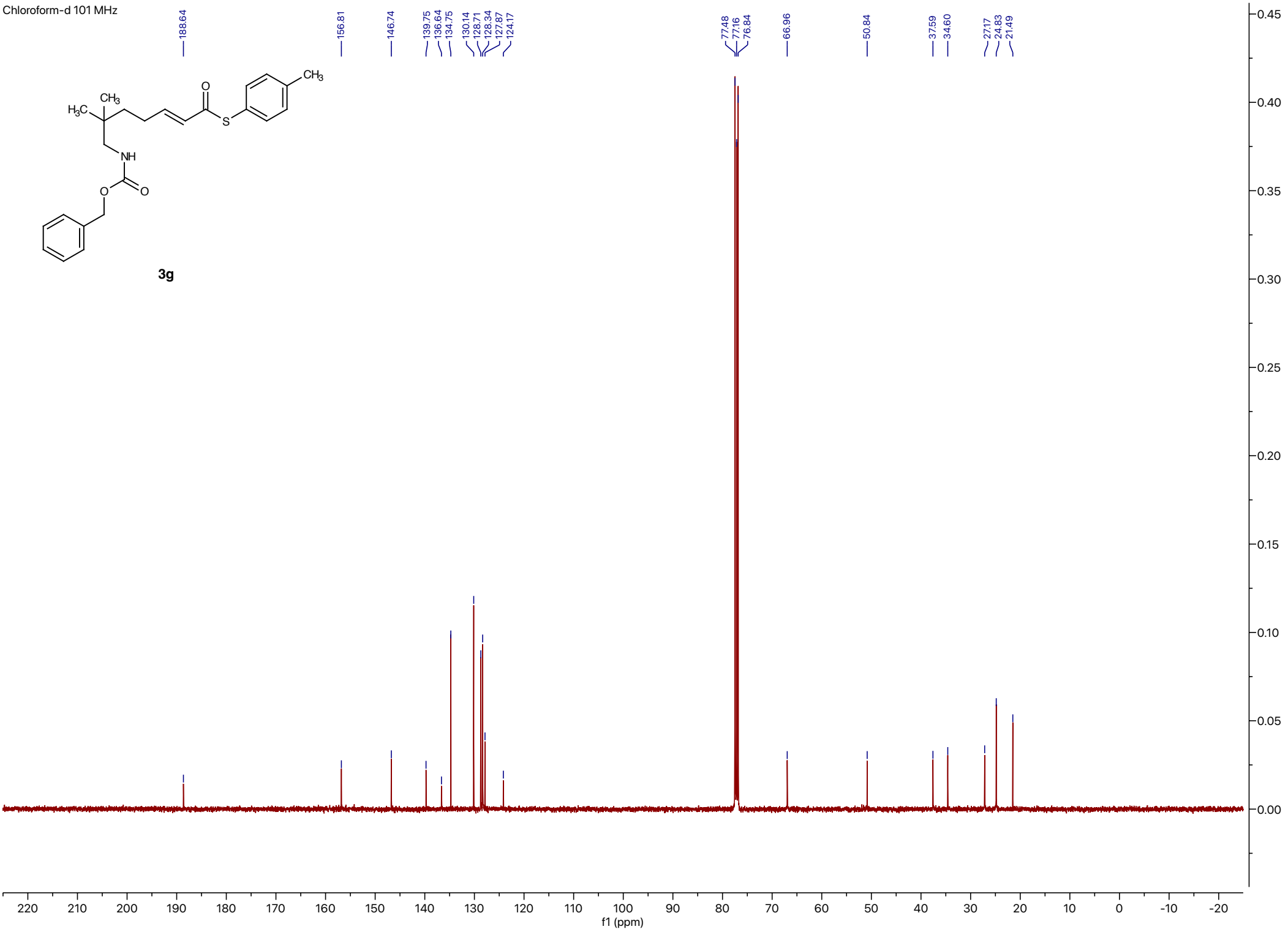


1g

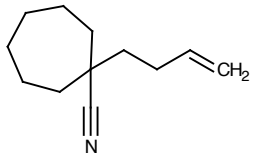
156.77
139.17
136.69
128.55
128.17
128.13
114.23
77.48
77.16
76.84
66.68
50.97
38.78
34.36
28.33
24.74

f1 (ppm)


Chloroform-d 400 MHz
7.38
7.37
7.33
7.31
7.26
7.23
6.98
6.94
6.20
6.16
5.11
4.80
4.78
4.76
3.06
3.04
2.38
2.23
2.22
2.21
1.39
1.38
1.37
1.36
1.34
0.90
0.88
CH3
H3C
CH3
O
S
NH
O
O
3g
7.10
2.07
1.00
0.93
2.09
0.86
2.04
3.15
1.88
2.24
6.33
f1 (ppm)

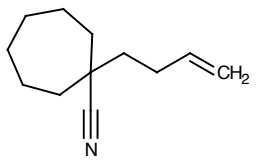

Chloroform-d 101 MHz
188.64
156.81
146.74
139.75
136.64
134.75
130.14
128.71
128.34
127.87
124.17
77.48
77.16
76.84
66.96
50.84
37.59
34.60
27.17
24.83
21.49
3g
f1 (ppm)

Chloroform-d 400 MHz



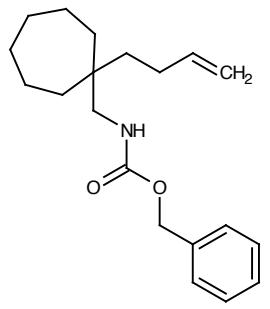
7h

Chloroform-d 101 MHz



7h

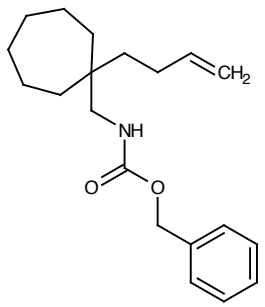
Chloroform-d 400 MHz



1h

f1 (ppm)

Chloroform-d 101 MHz

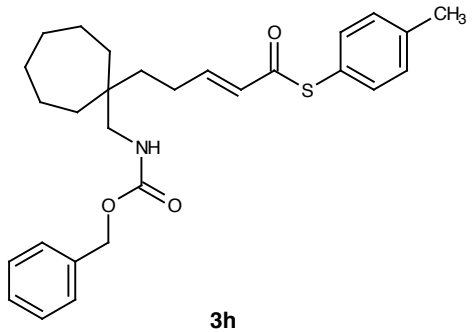


1h

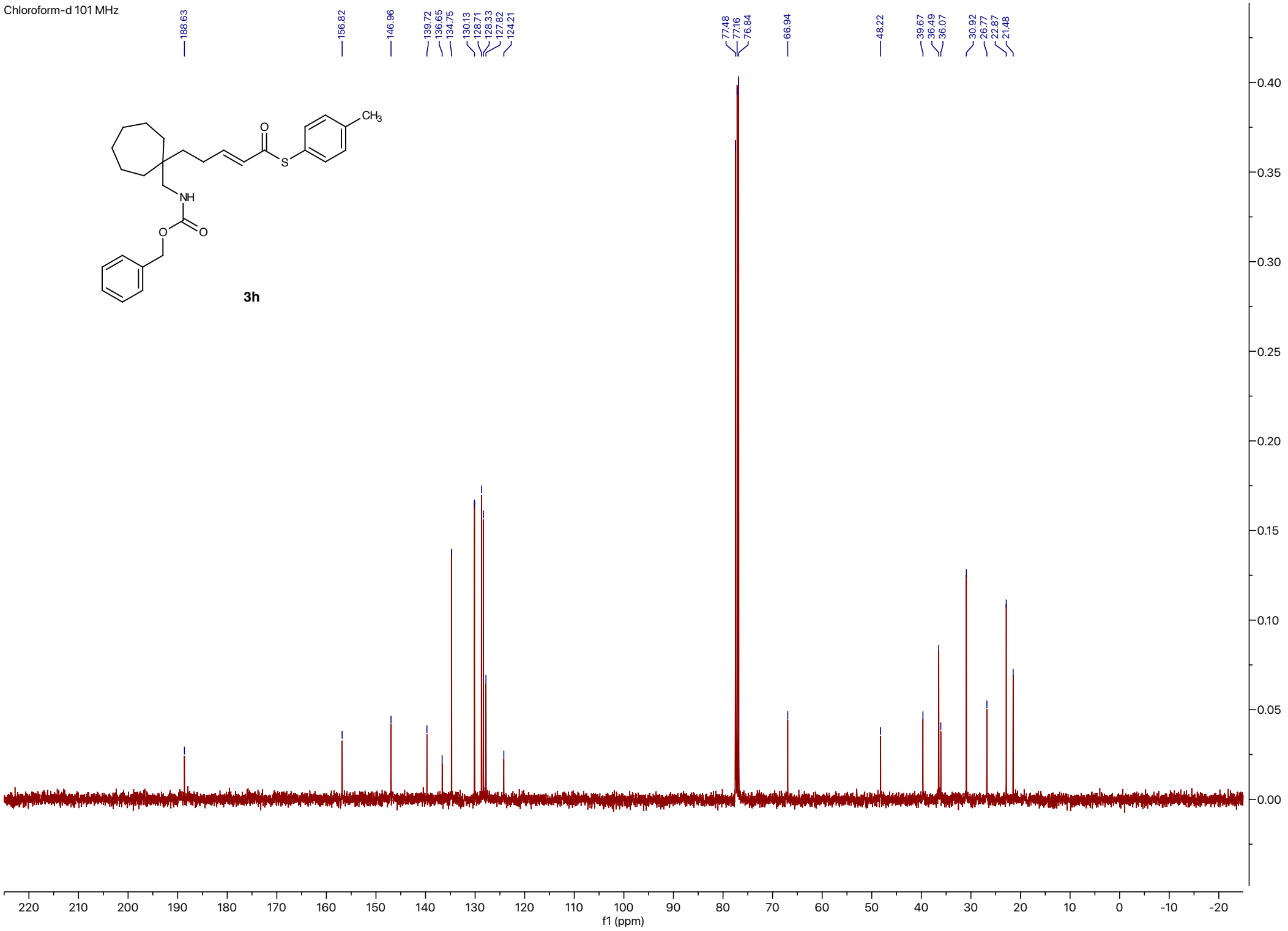
156.85
139.34
136.79
128.70
128.35
128.29
114.35
77.48
77.16
76.84
66.85
48.41
39.52
37.37
36.50
31.02
28.06
22.98

f1 (ppm)

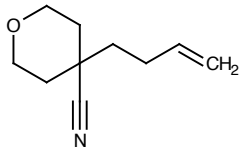
Chloroform-d 400 MHz



3h

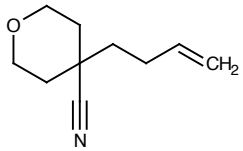

Chloroform-d 101 MHz
188.63
156.82
146.96
139.72
136.65
134.75
130.13
128.71
128.33
127.82
124.21
77.48
77.16
76.84
66.94
48.22
39.67
36.49
36.07
30.92
26.77
22.87
21.48
CH3
O
S
NH
O
O
3h
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

Chloroform-d 400 MHz



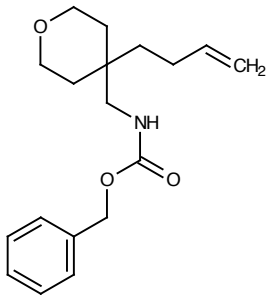
7i

Chloroform-d 101 MHz



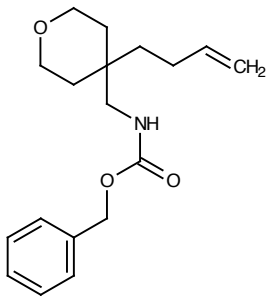
7i

Chloroform-d 400 MHz



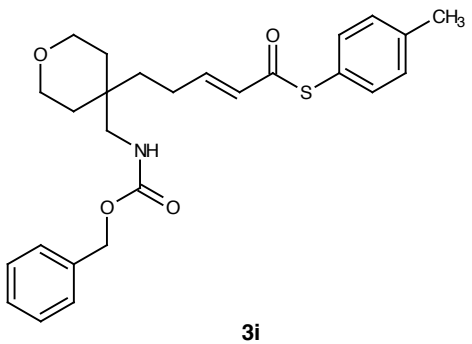
1i

Chloroform-d 101 MHz

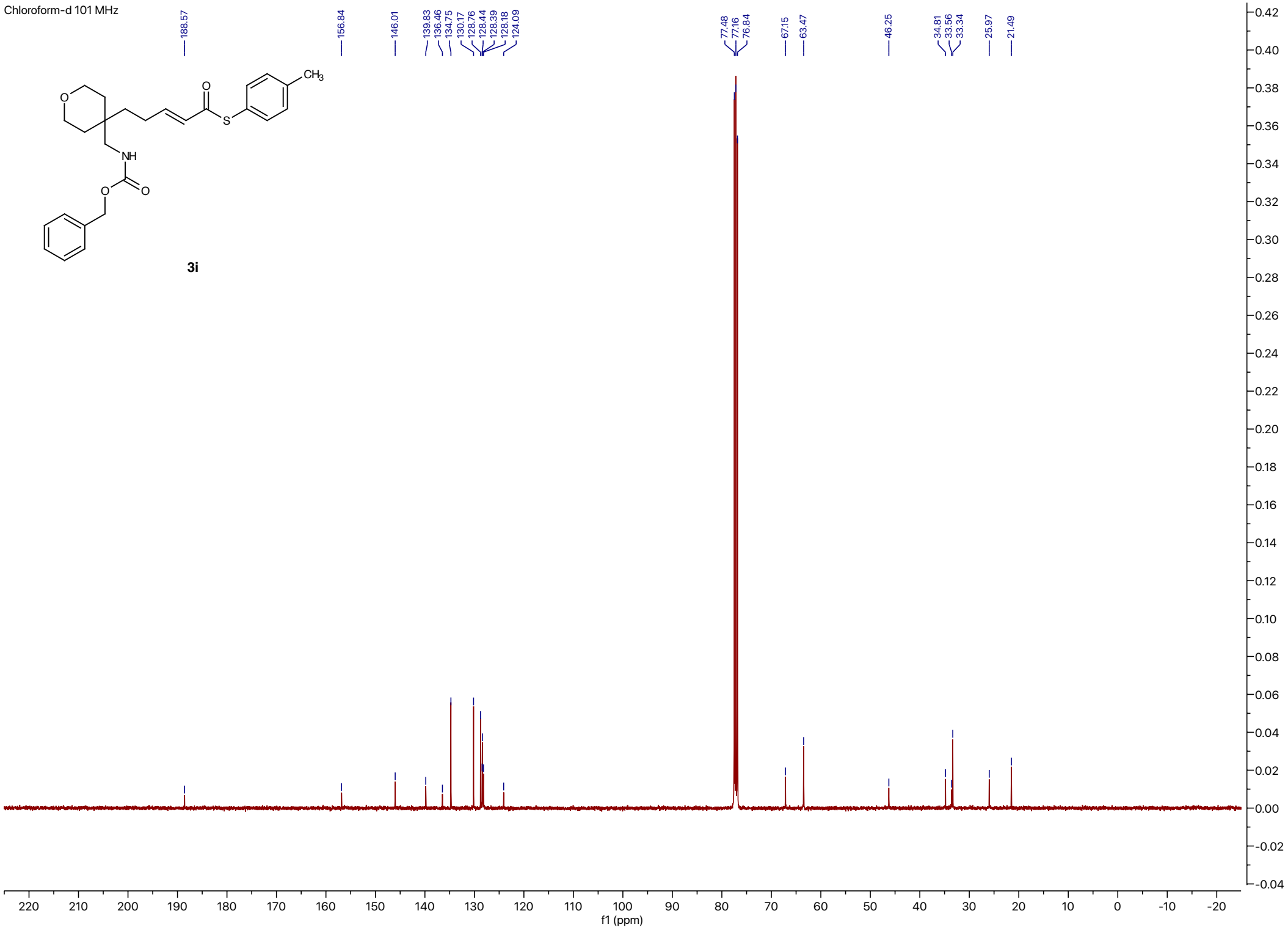


1i

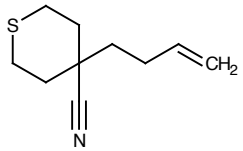
Chloroform-d 500 MHz



3i

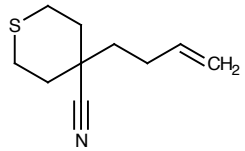

Chloroform-d 101 MHz
188.57
156.84
146.01
139.83
136.46
134.75
130.17
128.76
128.44
128.39
128.18
124.09
77.48
77.16
76.84
67.15
63.47
46.25
34.81
33.56
33.34
25.97
21.49
O
O
S
CH3
NH
O
O
3i
f1 (ppm)

Chloroform-d 400 MHz



7j

Chloroform-d 101 MHz

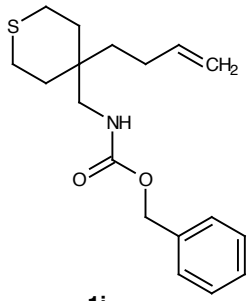


7j

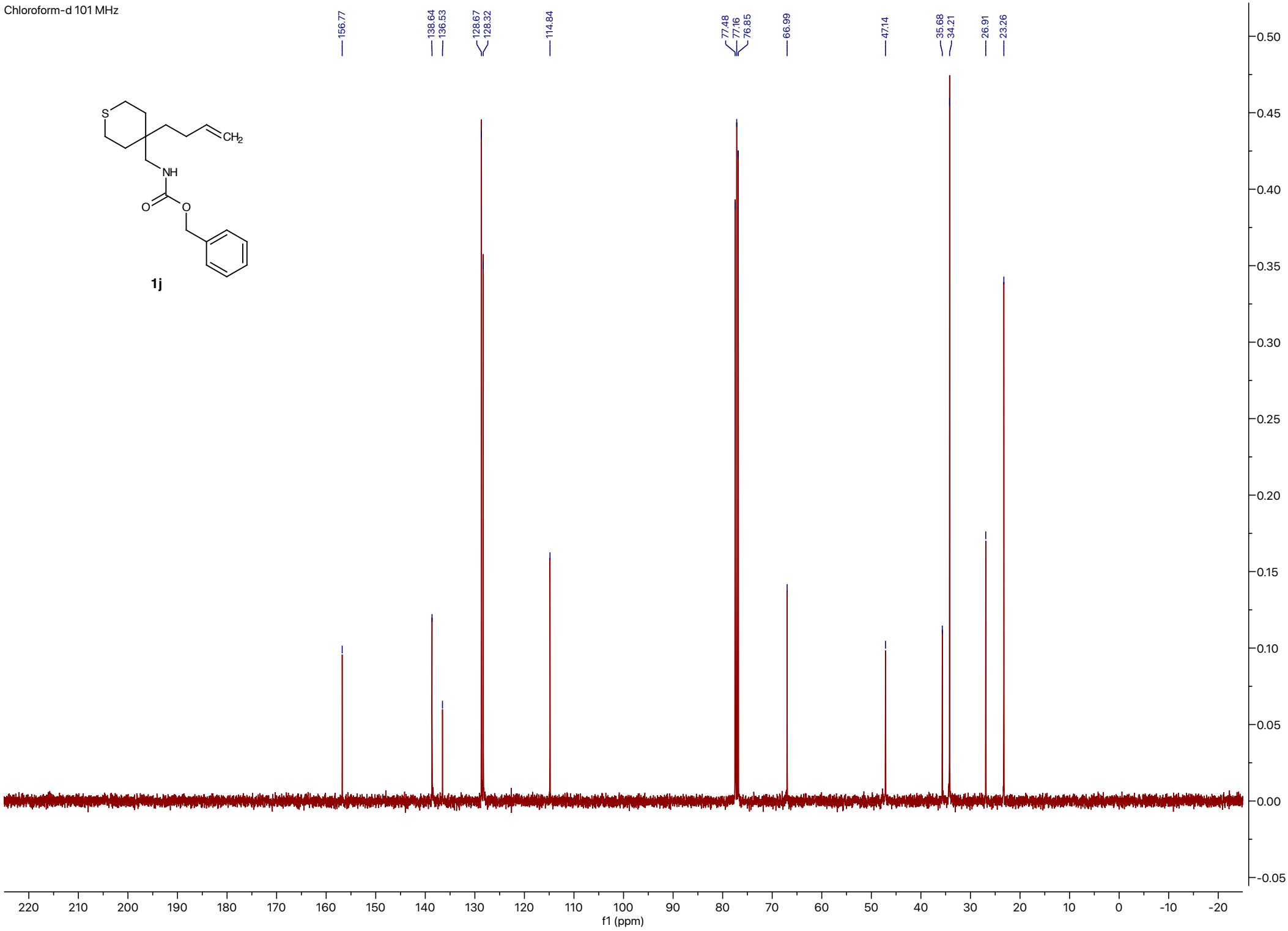
136.80
122.14
115.84
77.48
77.16
76.84
39.88
38.66
36.51
28.31
25.39

f1 (ppm)

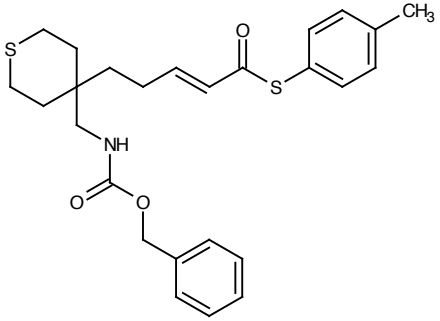
Chloroform-d 400 MHz



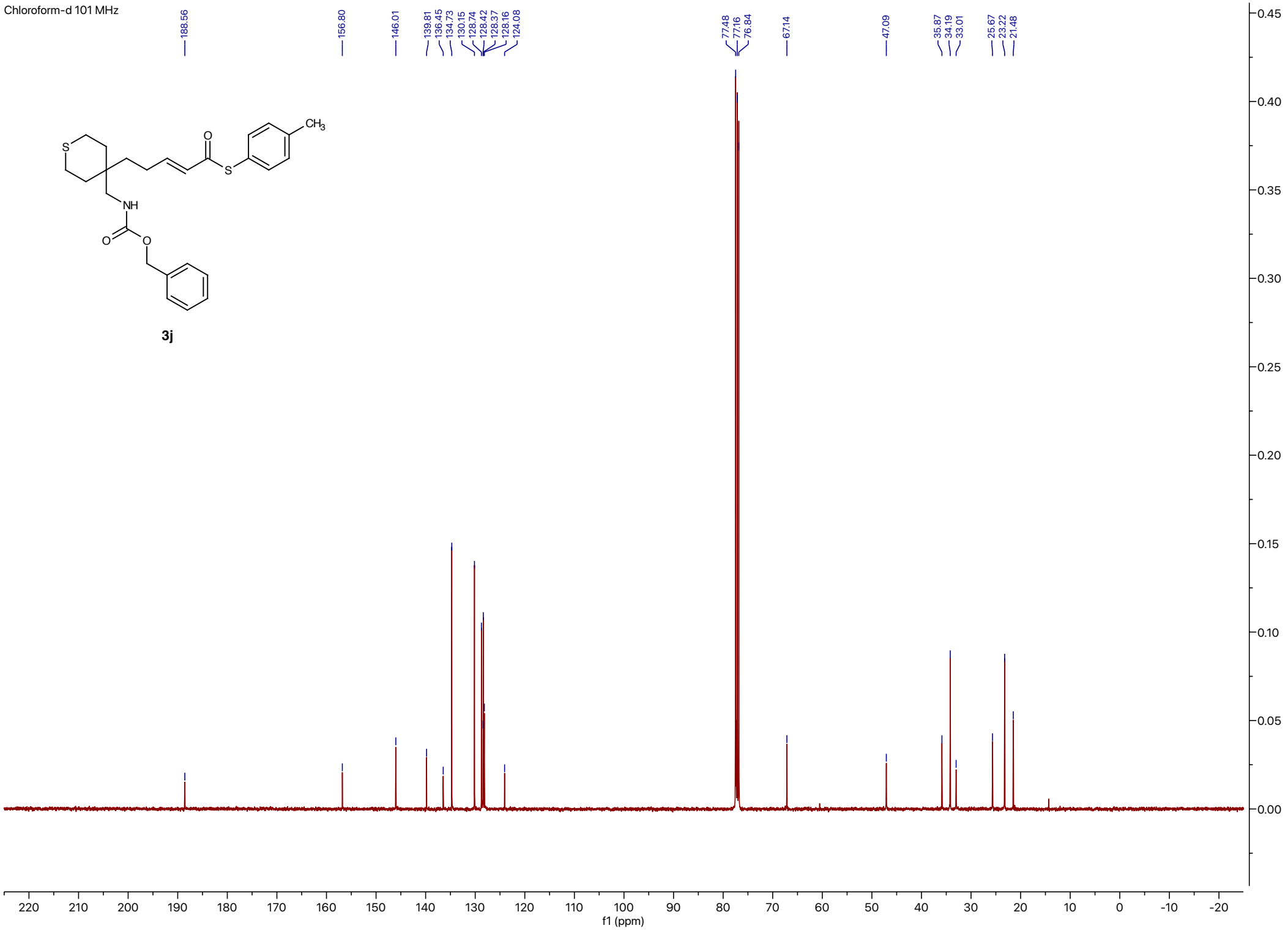
1j

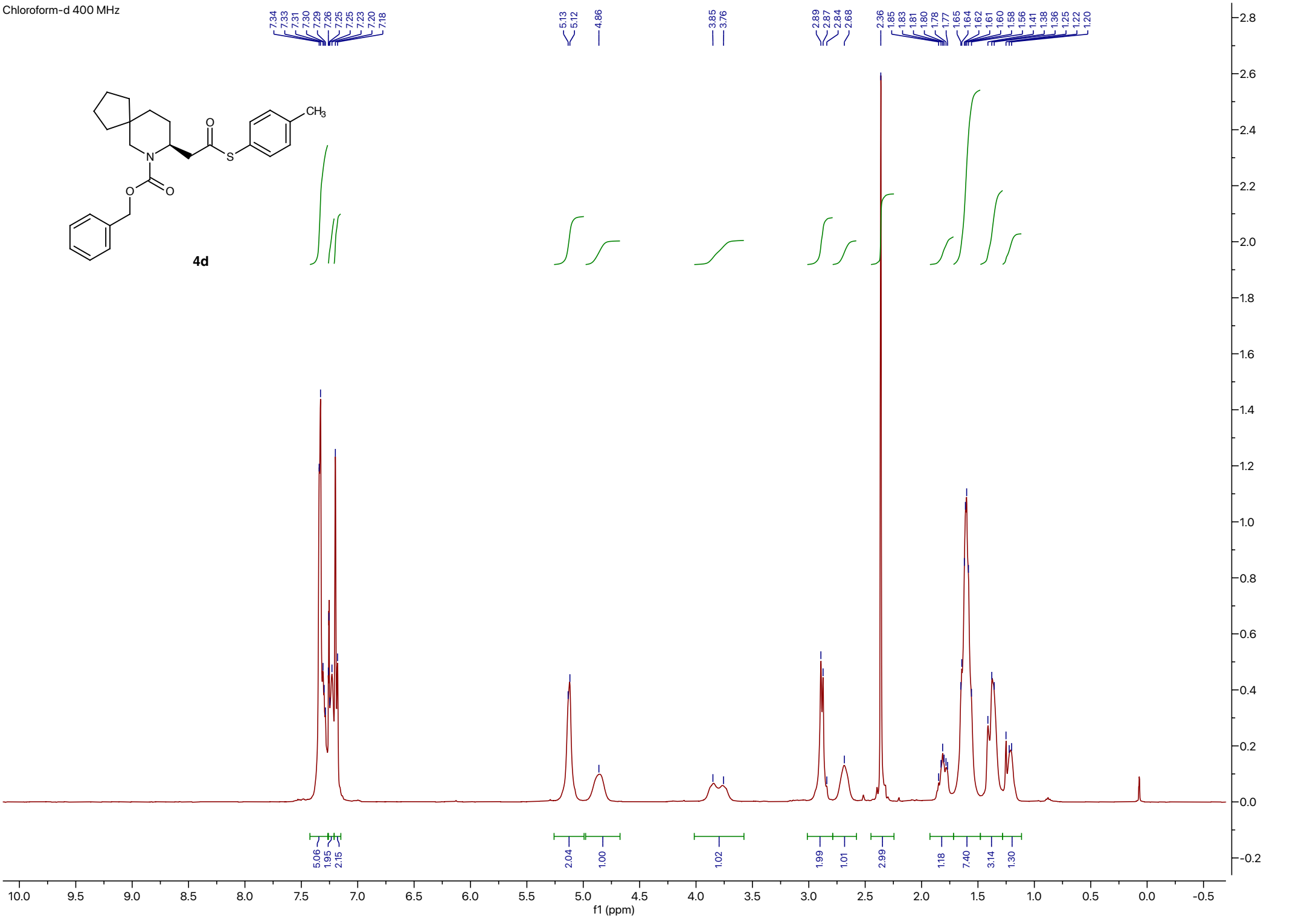

Chloroform-d 101 MHz
156.77
138.64
136.53
128.67
128.32
114.84
77.48
77.16
76.85
66.99
47.14
35.68
34.21
26.91
23.26
S
CH2
NH
O
O
1j
f1 (ppm)

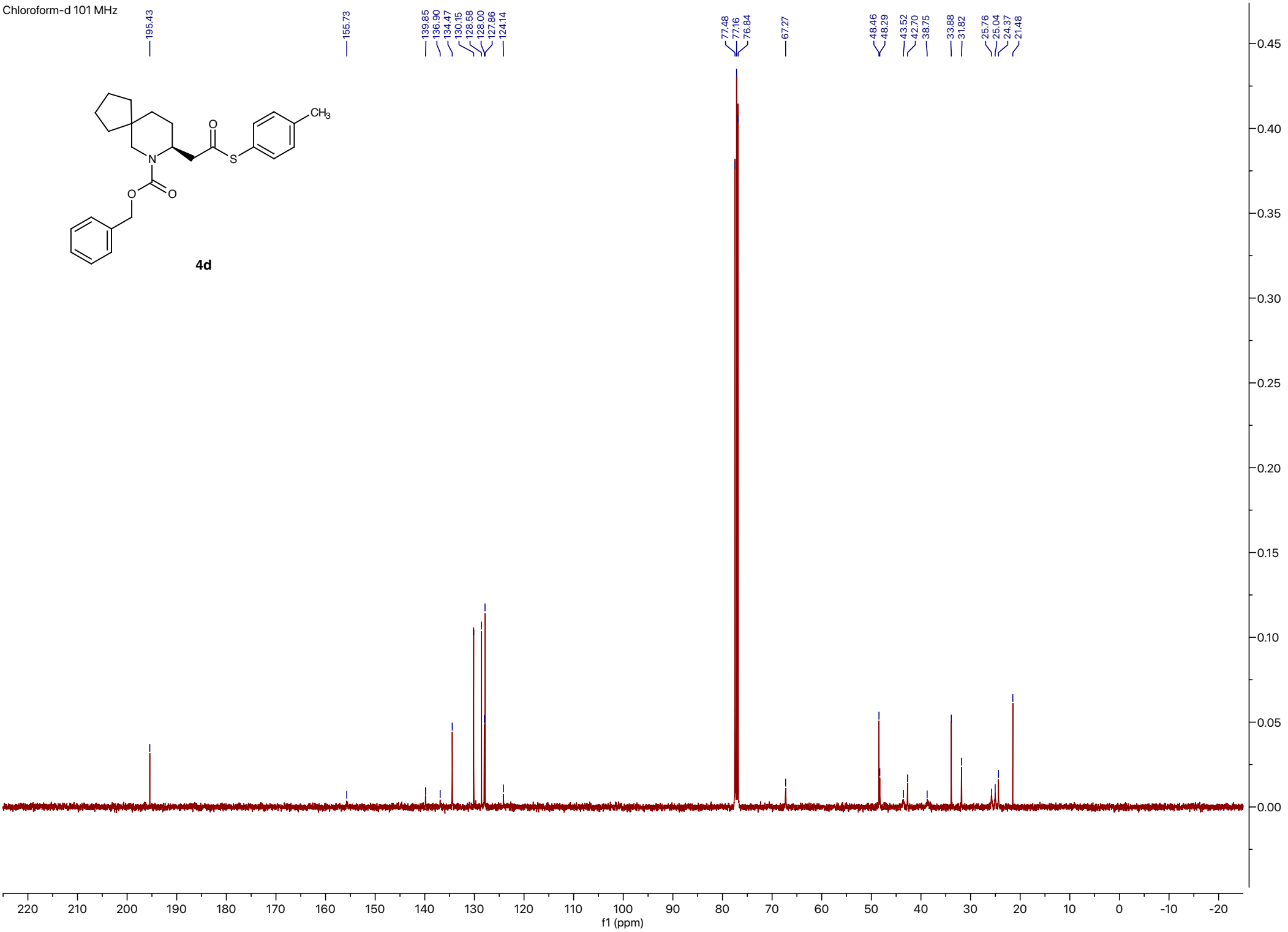
Chloroform-d 400 MHz

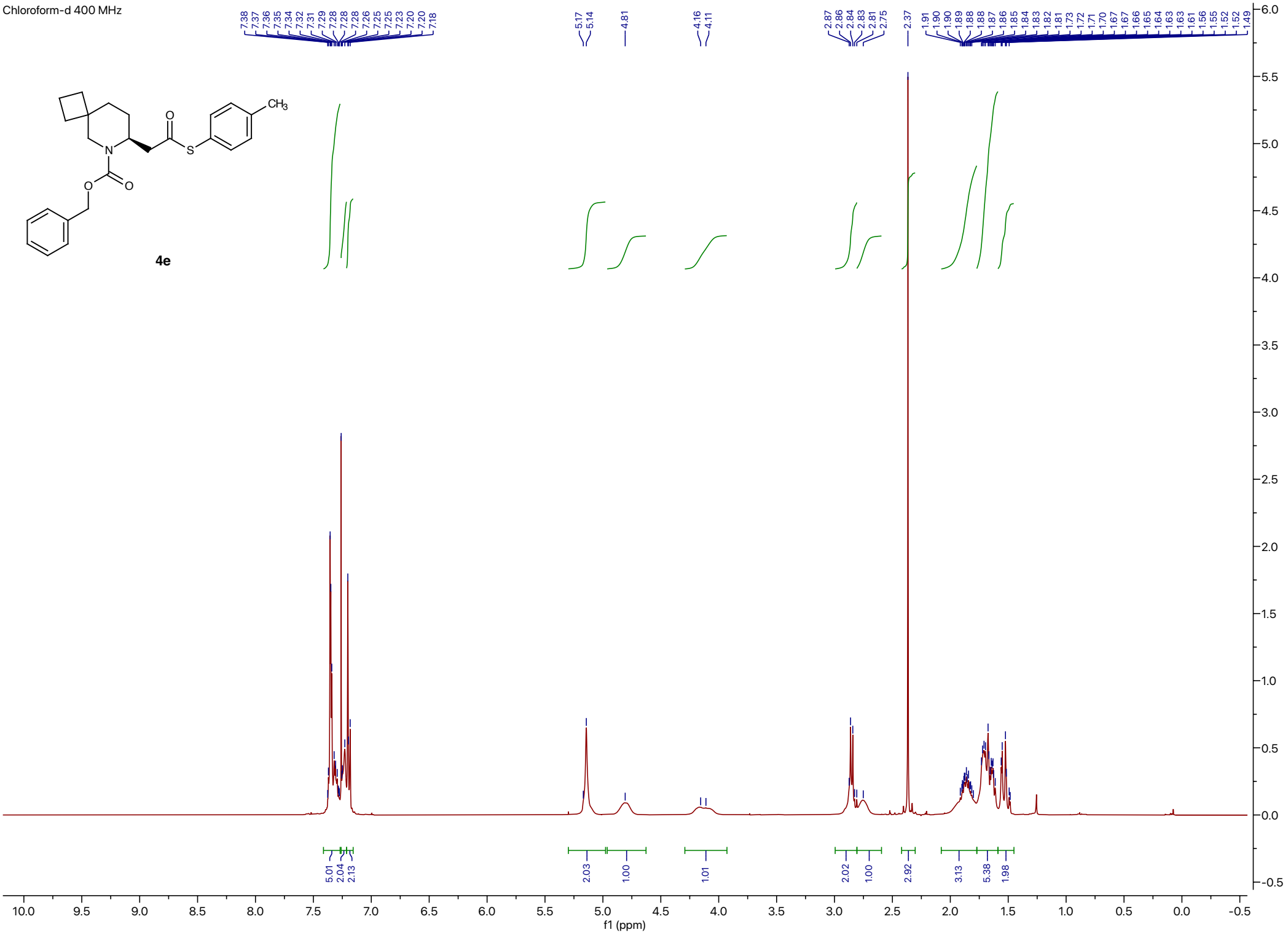


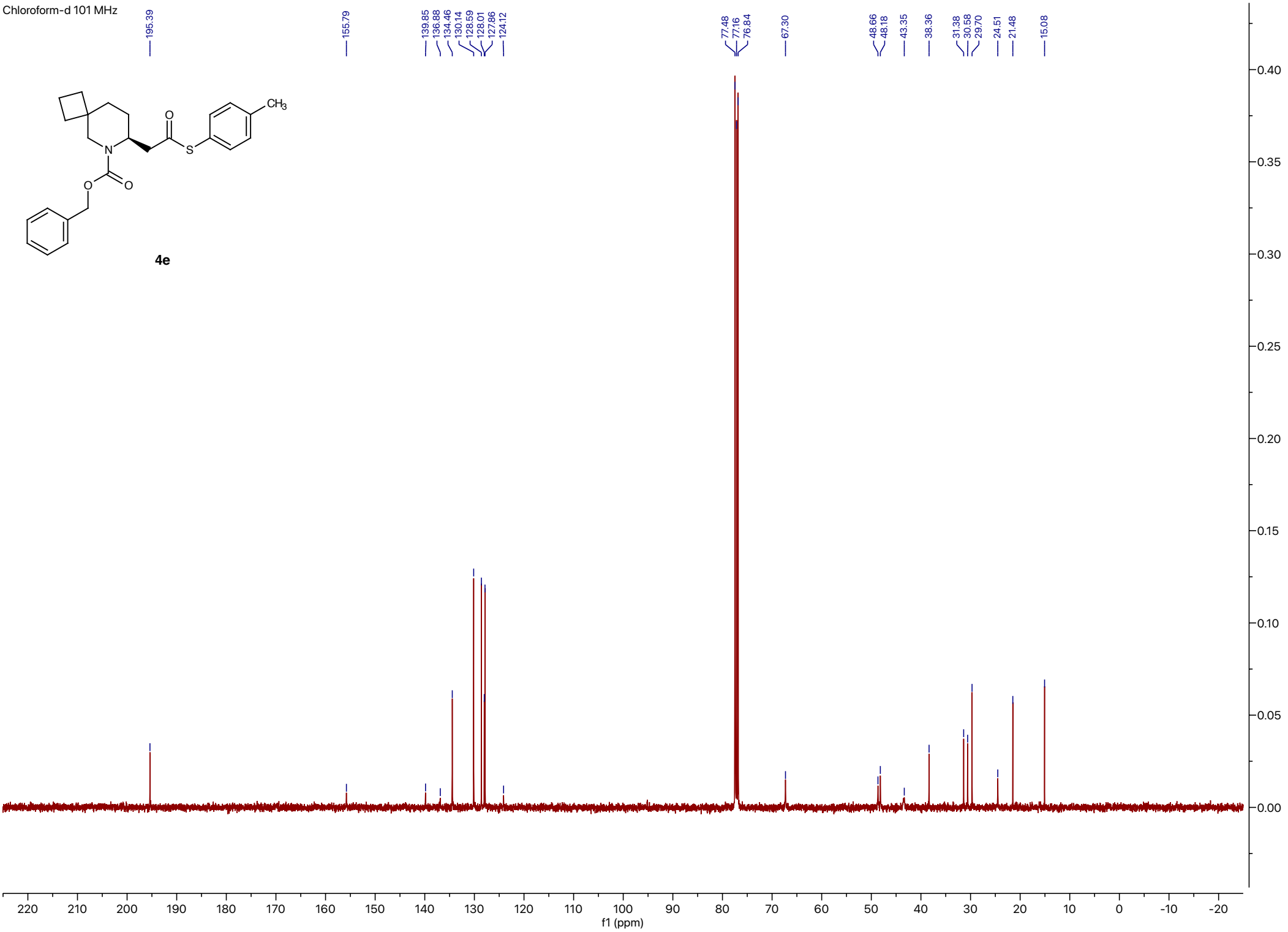
3j


Chloroform-d 101 MHz
188.56
156.80
146.01
139.81
136.45
134.73
130.15
128.74
128.42
128.37
128.16
124.08
77.48
77.16
76.84
67.14
47.09
35.87
34.19
33.01
25.67
23.22
21.48
CH3
S
O
S
NH
O
O
3j
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

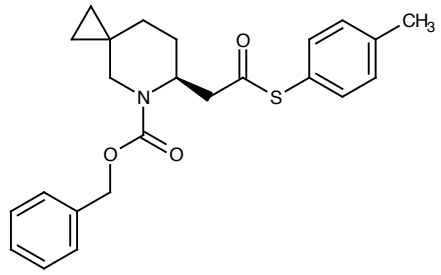

Chloroform-d 400 MHz
7.34
7.33
7.31
7.30
7.29
7.26
7.25
7.25
7.23
7.20
7.18
5.13
5.12
4.86
3.85
3.76
2.89
2.87
2.84
2.68
2.36
1.85
1.83
1.81
1.80
1.78
1.77
1.65
1.64
1.62
1.61
1.60
1.58
1.56
1.41
1.38
1.36
1.25
1.22
1.20
CH3
O
N
S
O
O
4d
5.06
1.95
2.15
2.04
1.00
1.02
1.99
1.01
2.99
1.18
7.40
3.14
1.30
f1 (ppm)


Chloroform-d 101 MHz
195.43
155.73
139.85
136.90
134.47
130.15
128.58
128.00
127.86
124.14
77.48
77.16
76.84
67.27
48.46
48.29
43.52
42.70
38.75
33.88
31.82
25.76
25.04
24.37
21.48
CH3
O
N
S
O
O
4d
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


Chloroform-d 400 MHz
7.38 7.37 7.36 7.35 7.34 7.32 7.31 7.29 7.28 7.28 7.28 7.26 7.25 7.25 7.23 7.20 7.20 7.18
5.17 5.14
4.81
4.16 4.11
2.87 2.86 2.84 2.83 2.81 2.75
2.37
1.91 1.90 1.90 1.89 1.88 1.88 1.87 1.86 1.85 1.84 1.83 1.82 1.81 1.73 1.72 1.71 1.70 1.67 1.67 1.66 1.65 1.64 1.63 1.63 1.61 1.56 1.55 1.52 1.52 1.49
CH3
O
N
S
O
O
4e
5.01 2.04 2.13
2.03 1.00
1.01
2.02 1.00 2.92 3.13 5.38 1.98
f1 (ppm)

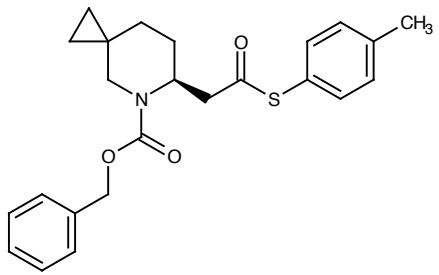

Chloroform-d 101 MHz
195.39
155.79
139.85
136.88
134.46
130.14
128.59
128.01
127.86
124.12
77.48
77.16
76.84
67.30
48.66
48.18
43.35
38.36
31.38
30.58
29.70
24.51
21.48
15.08
CH3
O
N
S
O
O
4e
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

Chloroform-d 400 MHz



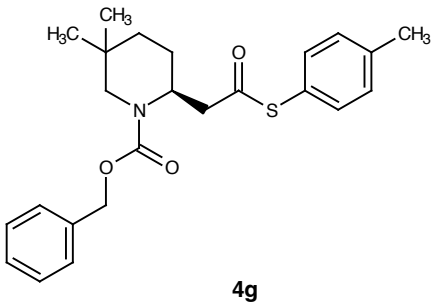
4f

Chloroform-d 101 MHz



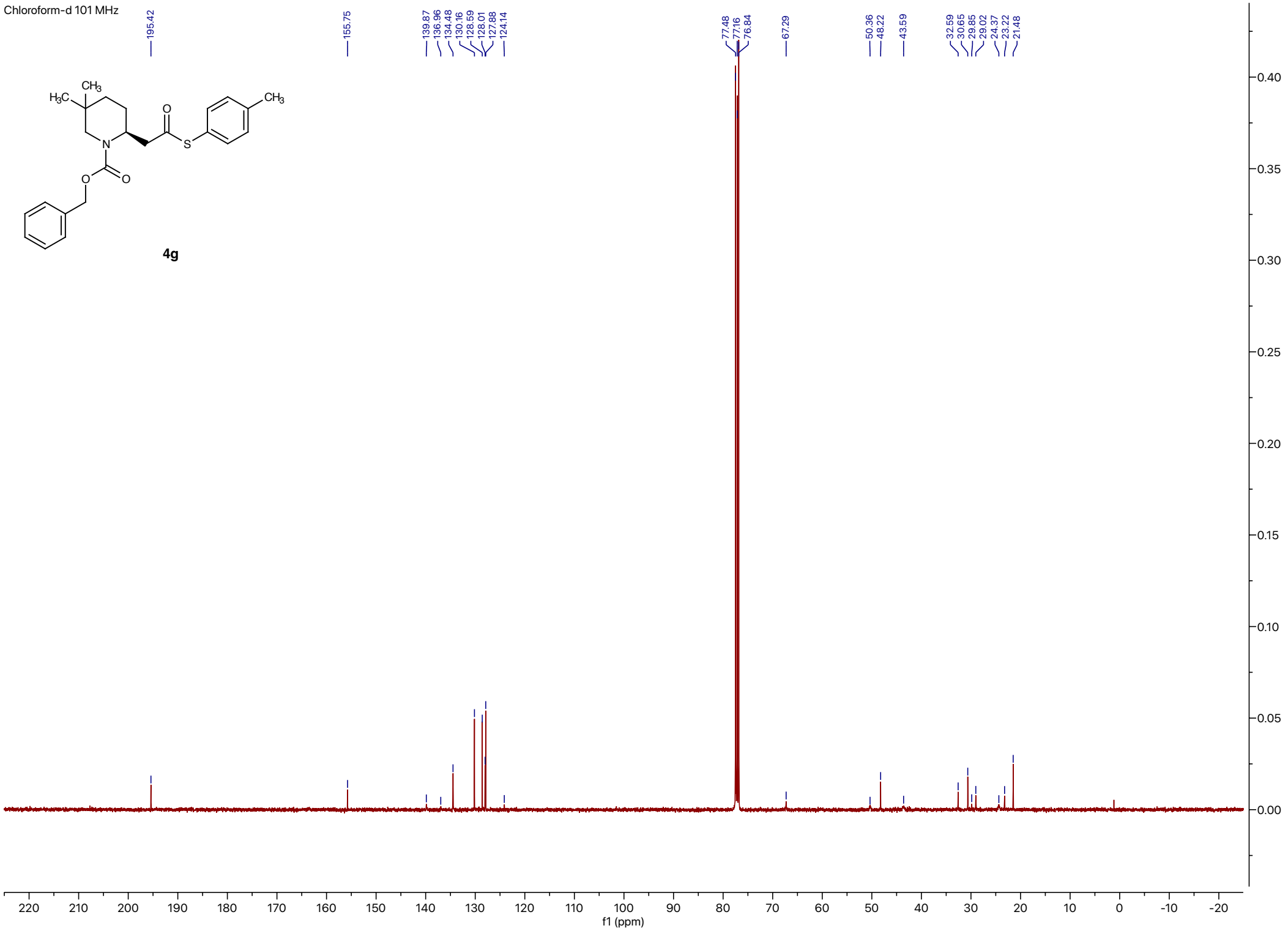
4f

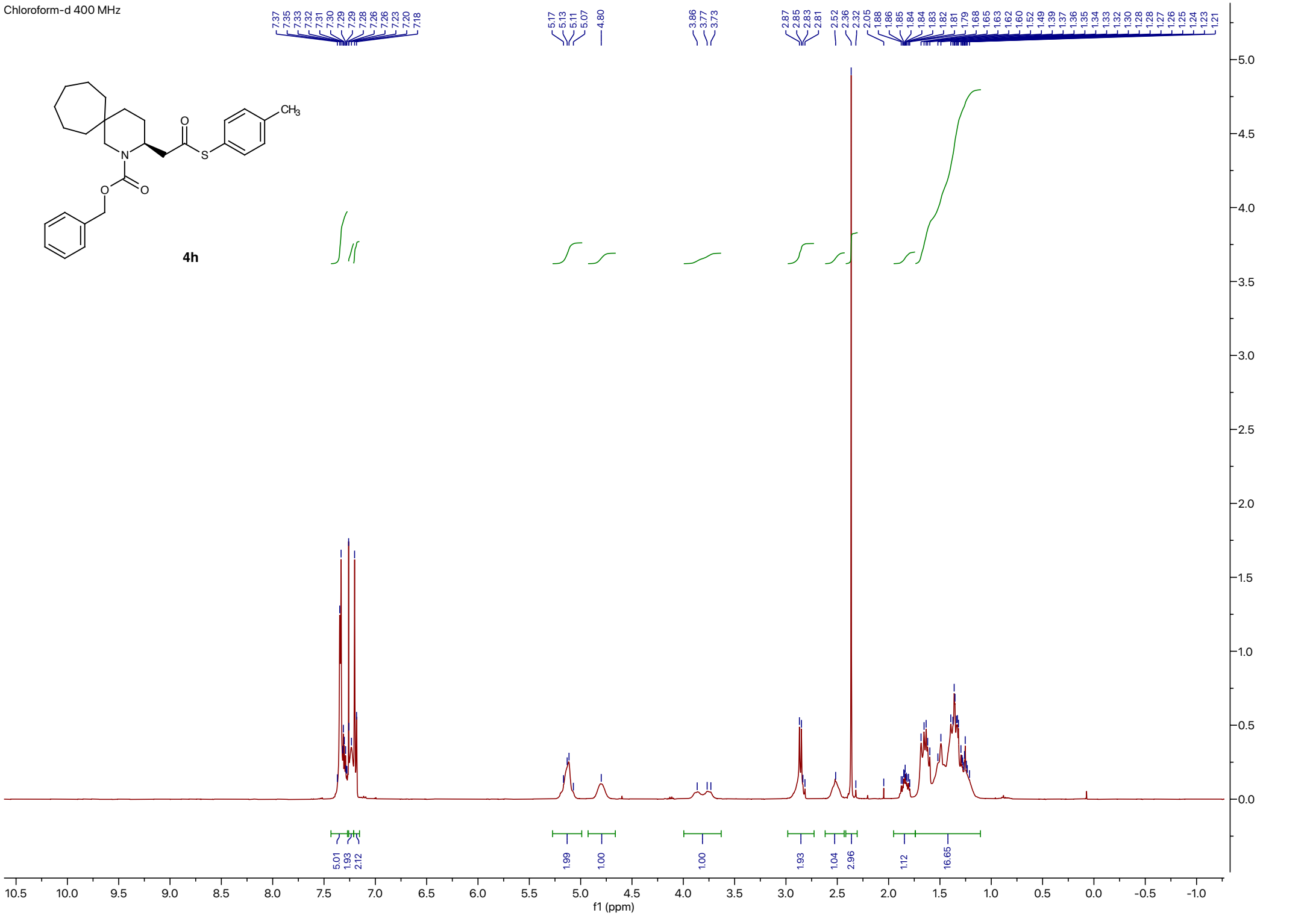
Chloroform-d 400 MHz

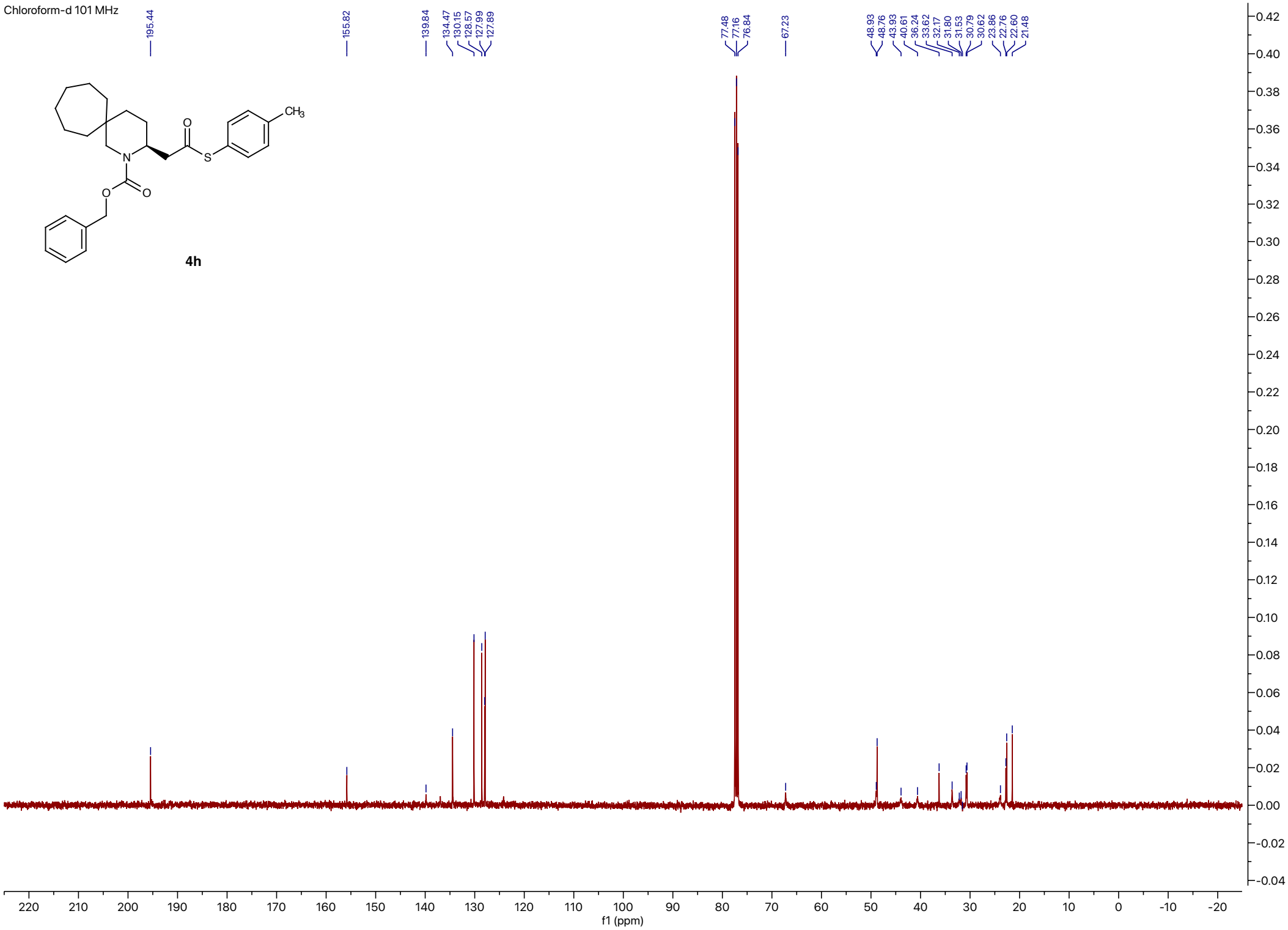


4g

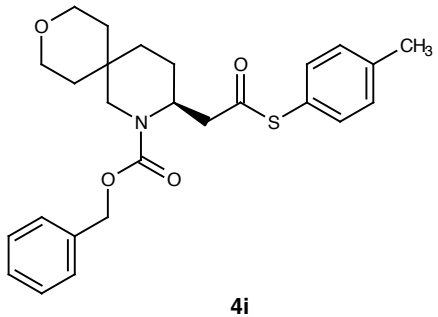
f1 (ppm)


Chloroform-d 101 MHz
195.42
155.75
139.87
136.96
134.48
130.16
128.59
128.01
127.88
124.14
77.48
77.16
76.84
67.29
50.36
48.22
43.59
32.59
30.65
29.85
29.02
24.37
23.22
21.48
4g
f1 (ppm)

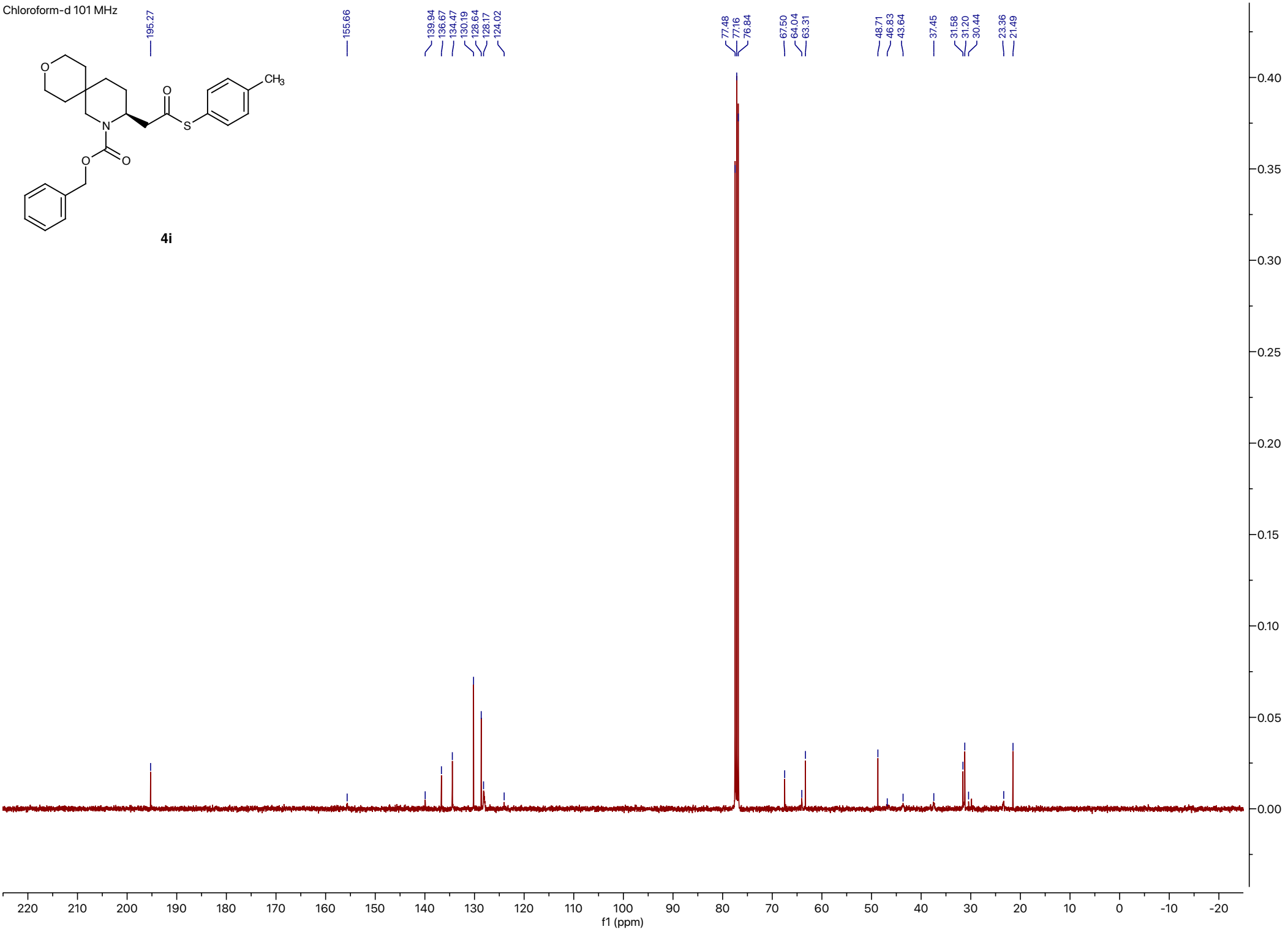

Chloroform-d 400 MHz
7.37 7.35 7.33 7.32 7.31 7.30 7.29 7.29 7.28 7.26 7.26 7.23 7.20 7.18
5.17 5.13 5.11 5.07
4.80
3.86 3.77 3.73
2.87 2.85 2.83 2.81
2.52 2.36 2.32
2.05 1.88 1.86 1.85 1.84 1.84 1.83 1.82 1.81 1.79 1.68 1.65 1.63 1.62 1.60 1.52 1.49 1.39 1.37 1.36 1.35 1.34 1.33 1.32 1.30 1.28 1.27 1.26 1.25 1.24 1.23 1.21
O
S
CH3
N
O
O
4h
5.01
1.93
2.12
1.99
1.00
1.00
1.93
1.04
2.96
1.12
16.65
f1 (ppm)


Chloroform-d 101 MHz
195.44
155.82
139.84
134.47
130.15
128.57
127.99
127.89
77.48
77.16
76.84
67.23
48.93
48.76
43.93
40.61
36.24
33.62
32.17
31.80
31.53
30.79
30.62
23.86
22.76
22.60
21.48
CH3
O
N
S
O
O
O
4h
f1 (ppm)

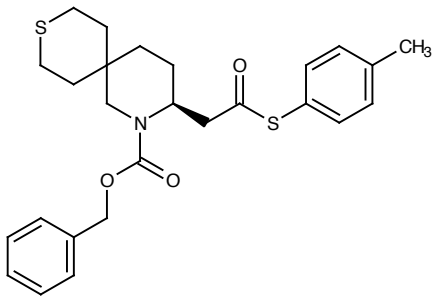
Chloroform-d 400 MHz



4i

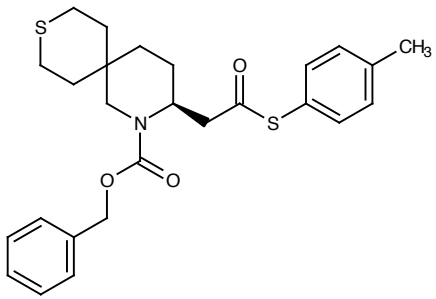

Chloroform-d 101 MHz
195.27
155.66
139.94
136.67
134.47
130.19
128.64
128.17
124.02
77.48
77.16
76.84
67.50
64.04
63.31
48.71
46.83
43.64
37.45
31.58
31.20
30.44
23.36
21.49
O
O
N
O
O
S
CH3
4i
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

Chloroform-d 400 MHz



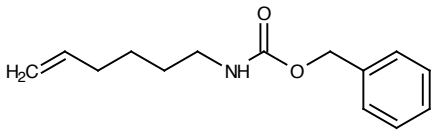
4j

Chloroform-d 101 MHz



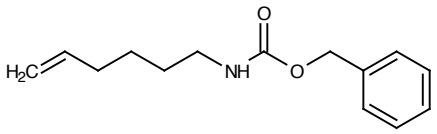
4j

Chloroform-d 400 MHz



1k

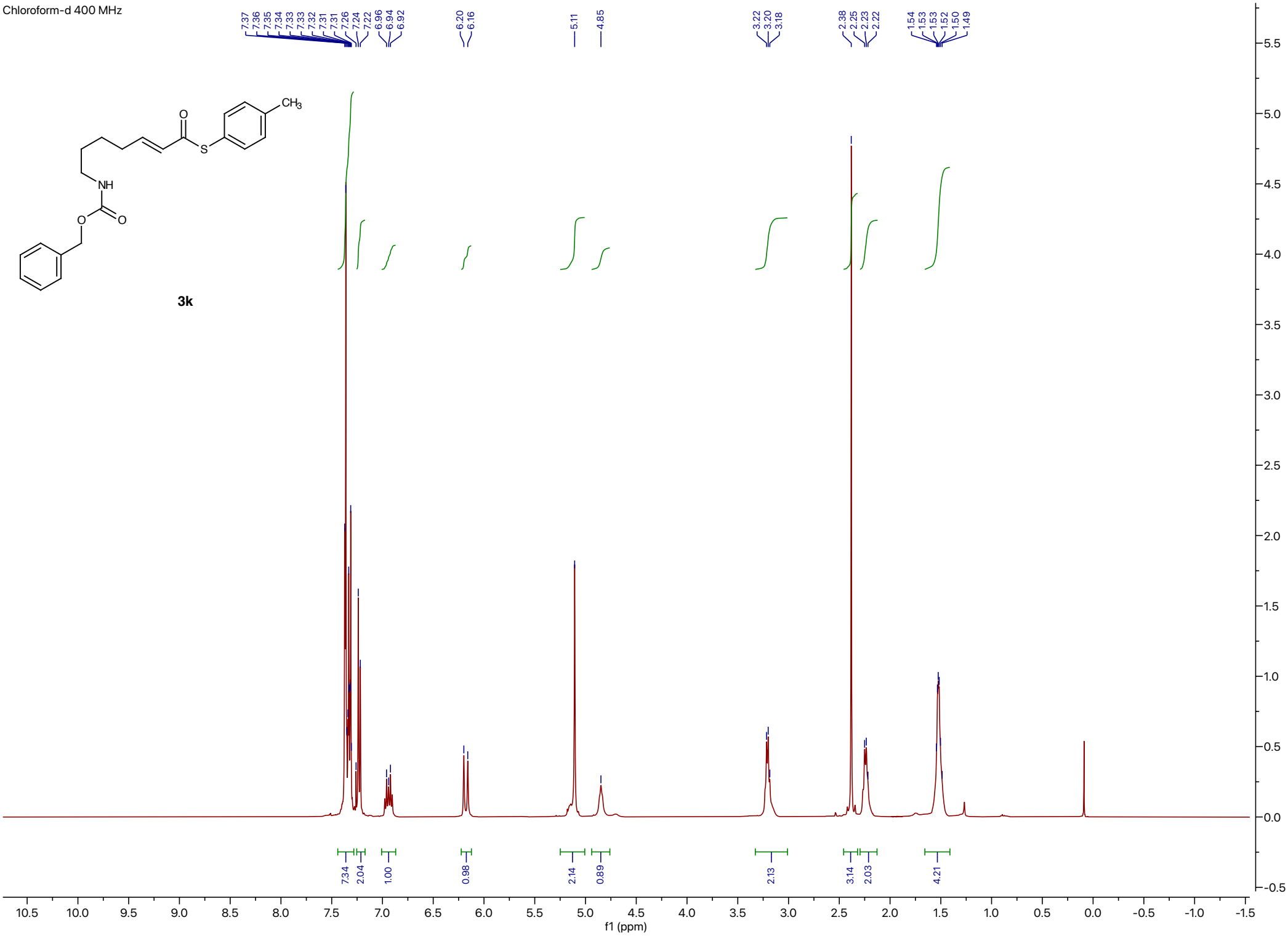
Chloroform-d 101 MHz

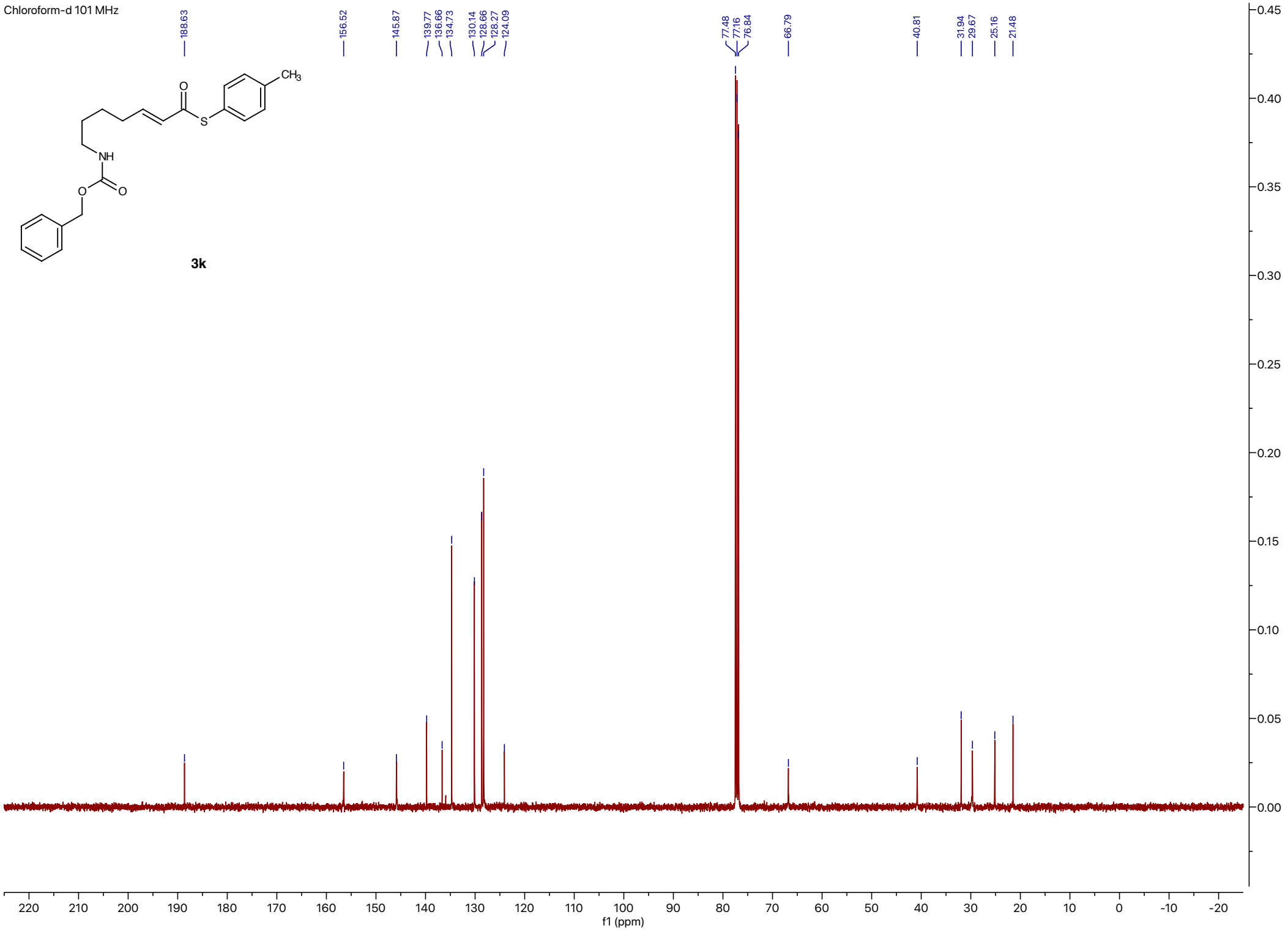


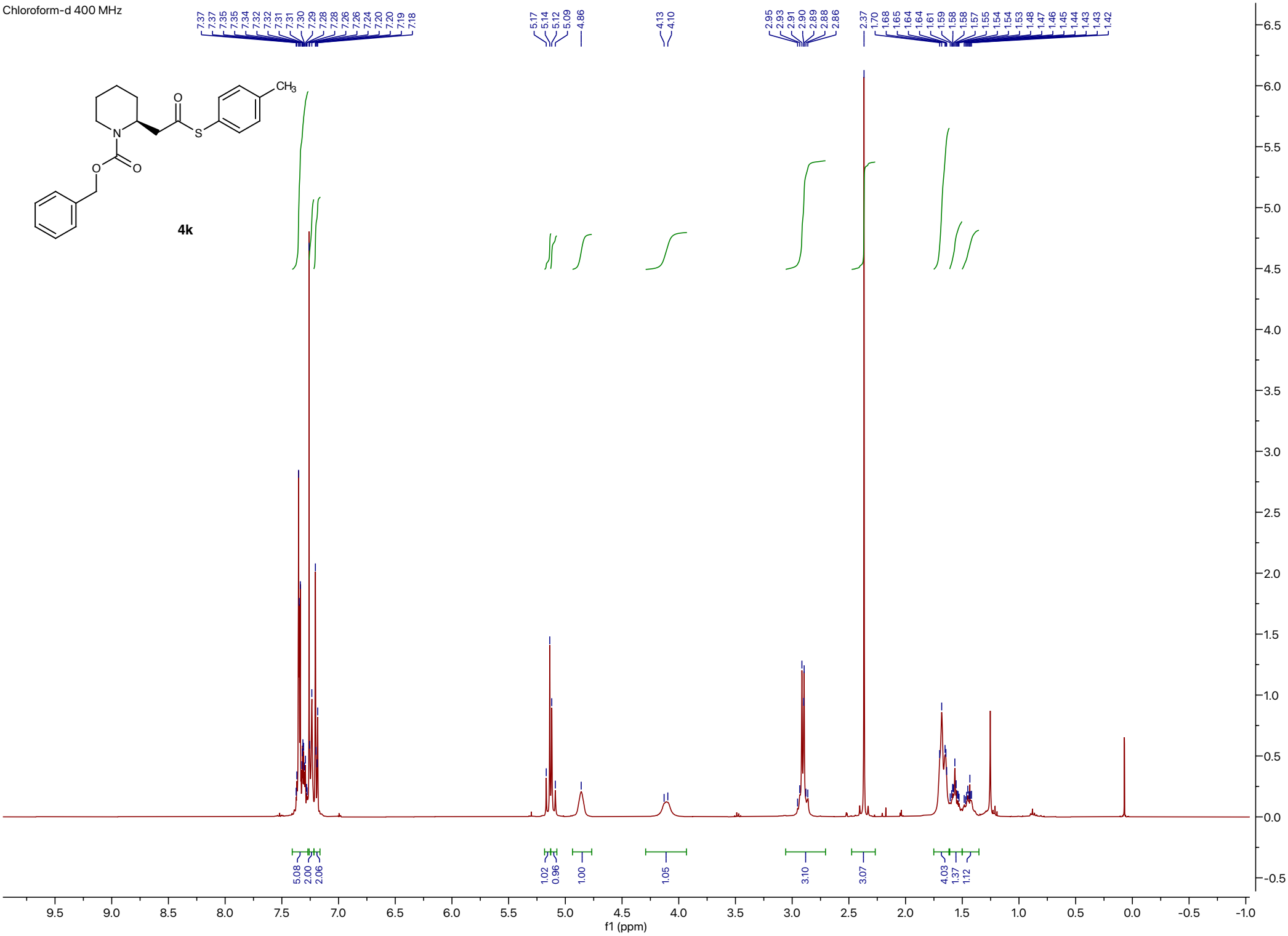
1k

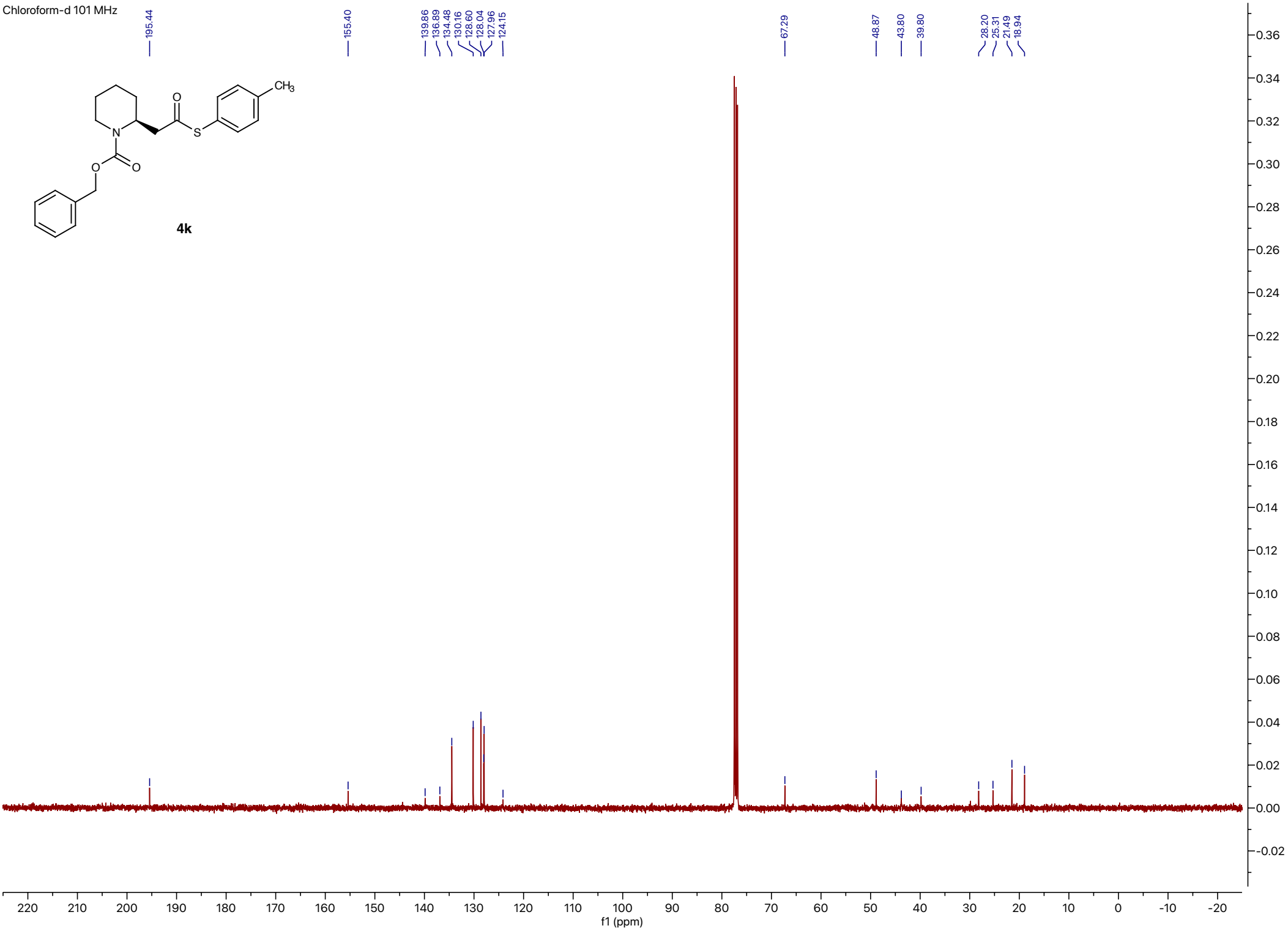
156.51
138.54
136.76
128.67
128.28
128.25
114.94
77.48
77.16
76.84
66.75
41.06
33.44
29.53
26.09

f1 (ppm)

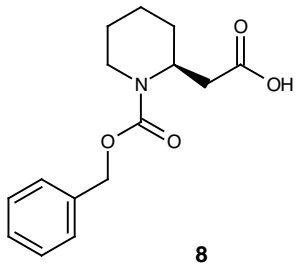

Chloroform-d 400 MHz
7.37
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.26
7.24
7.22
6.96
6.94
6.92
6.20
6.16
5.11
4.85
3.22
3.20
3.18
2.38
2.25
2.23
2.22
1.54
1.53
1.53
1.52
1.50
1.49
CH3
O
S
NH
O
O
O
3k
7.34
2.04
1.00
0.98
2.14
0.89
2.13
3.14
2.03
4.21
f1 (ppm)


Chloroform-d 101 MHz
188.63
156.52
145.87
139.77
136.66
134.73
130.14
128.66
128.27
124.09
77.48
77.16
76.84
66.79
40.81
31.94
29.67
25.16
21.48
CH3
O
S
NH
O
O
3k
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

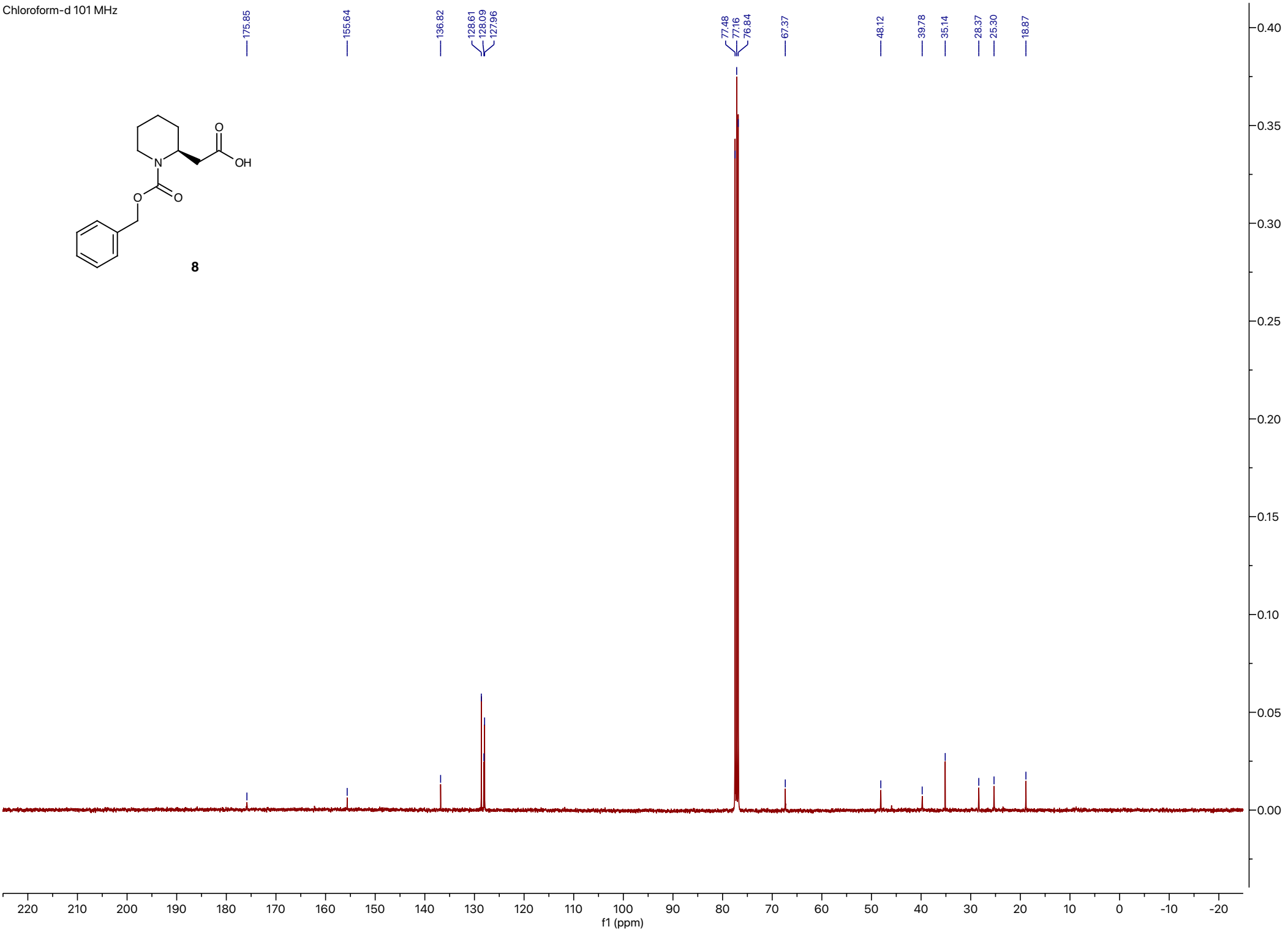

Chloroform-d 400 MHz
7.37 7.37 7.35 7.35 7.34 7.32 7.32 7.31 7.31 7.30 7.29 7.28 7.28 7.26 7.26 7.24 7.20 7.20 7.19 7.18
5.17 5.14 5.12 5.09 4.86
4.13 4.10
2.95 2.93 2.91 2.90 2.89 2.88 2.86
2.37 1.70 1.68 1.65 1.64 1.64 1.61 1.59 1.58 1.58 1.57 1.55 1.54 1.54 1.53 1.48 1.47 1.46 1.45 1.44 1.43 1.43 1.42
CH3
O
N
S
O
O
4k
5.08 2.00 2.06
1.02 0.96 1.00 1.05 3.10 3.07 4.03 1.37 1.12
f1 (ppm)

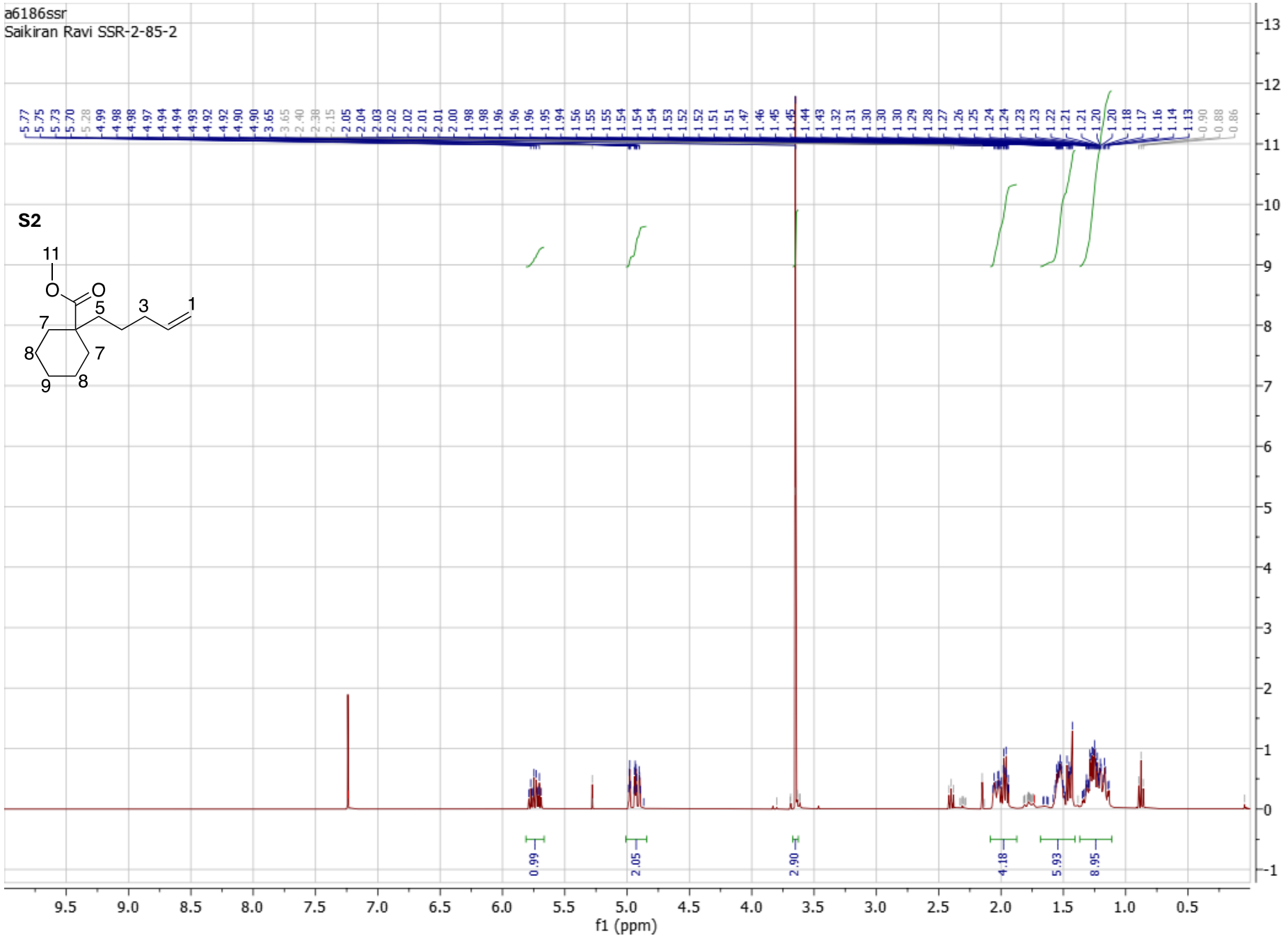

Chloroform-d 101 MHz
195.44
155.40
139.86
136.89
134.48
130.16
128.60
128.04
127.96
124.15
67.29
48.87
43.80
39.80
28.20
25.31
21.49
18.94
CH3
O
N
S
O
O
4k
f1 (ppm)

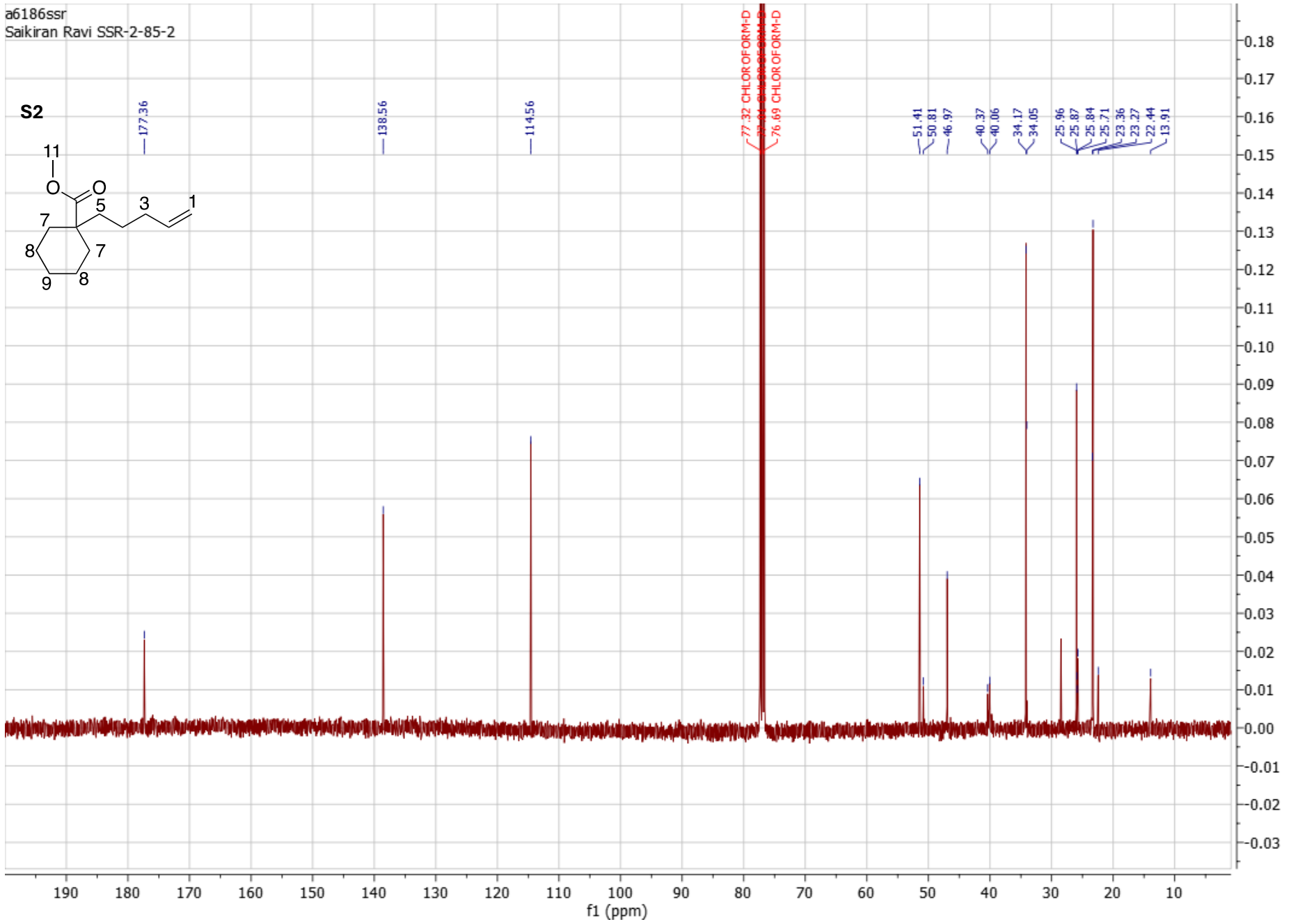
Chloroform-d 400 MHz

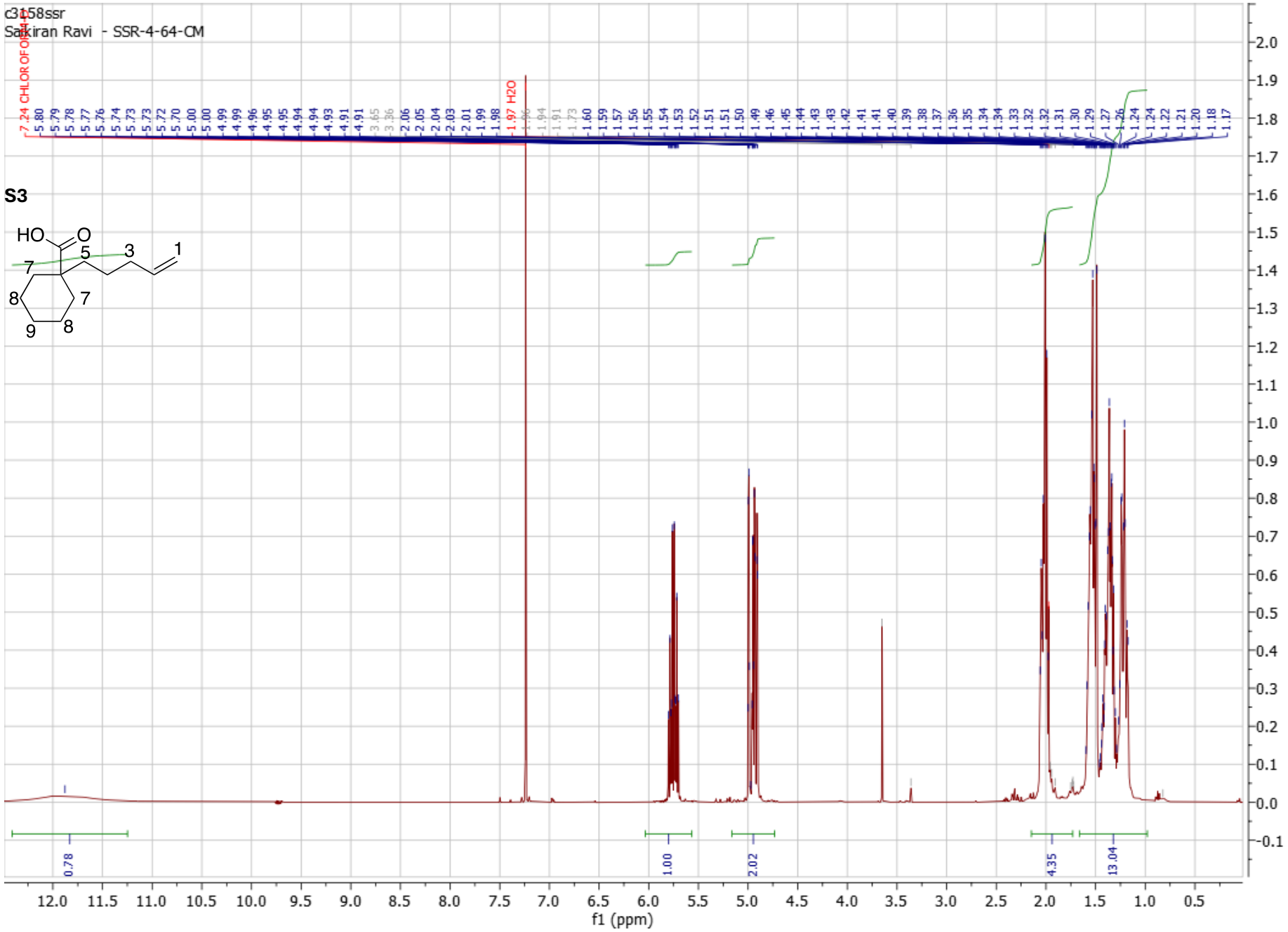


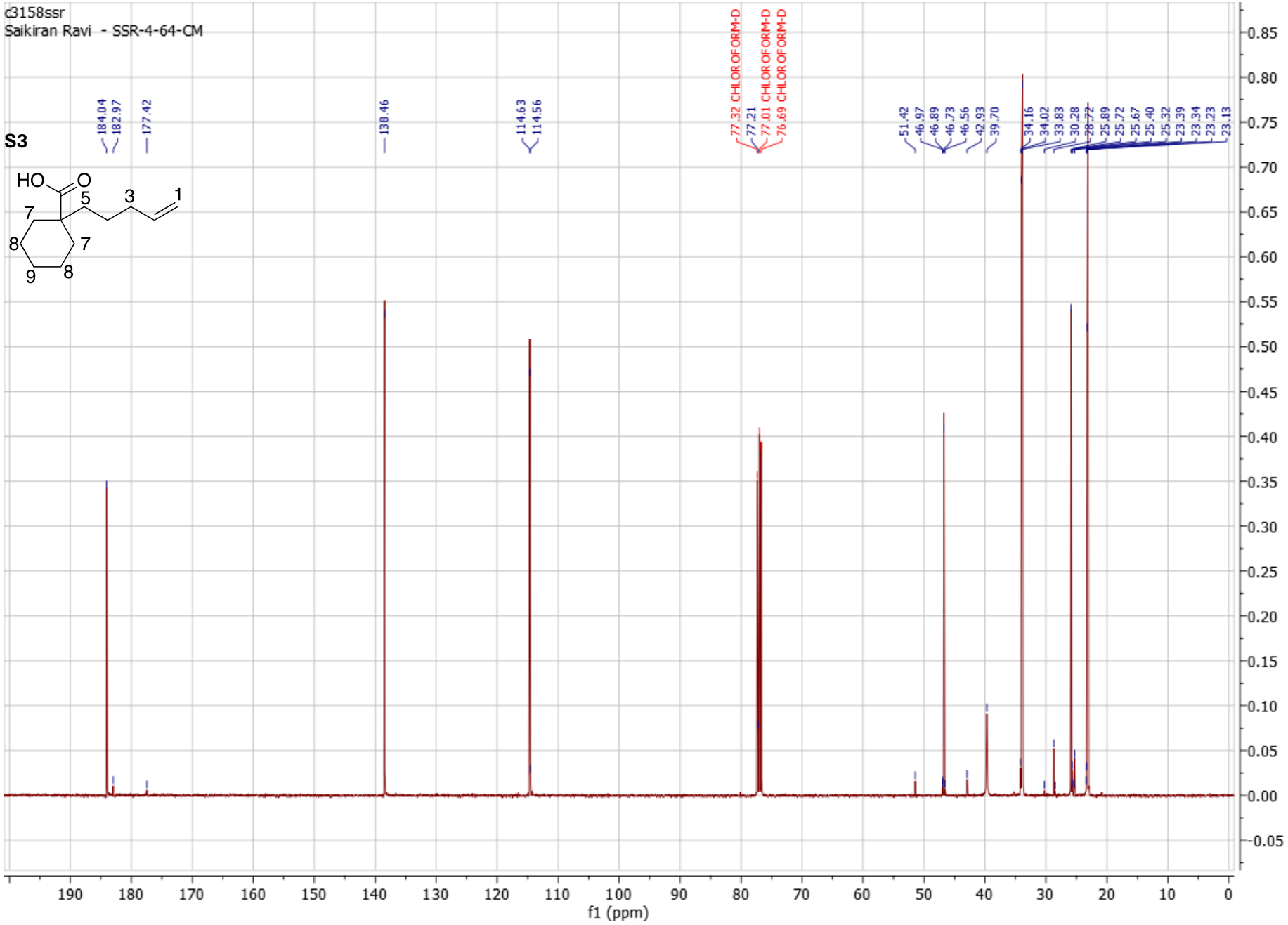
8

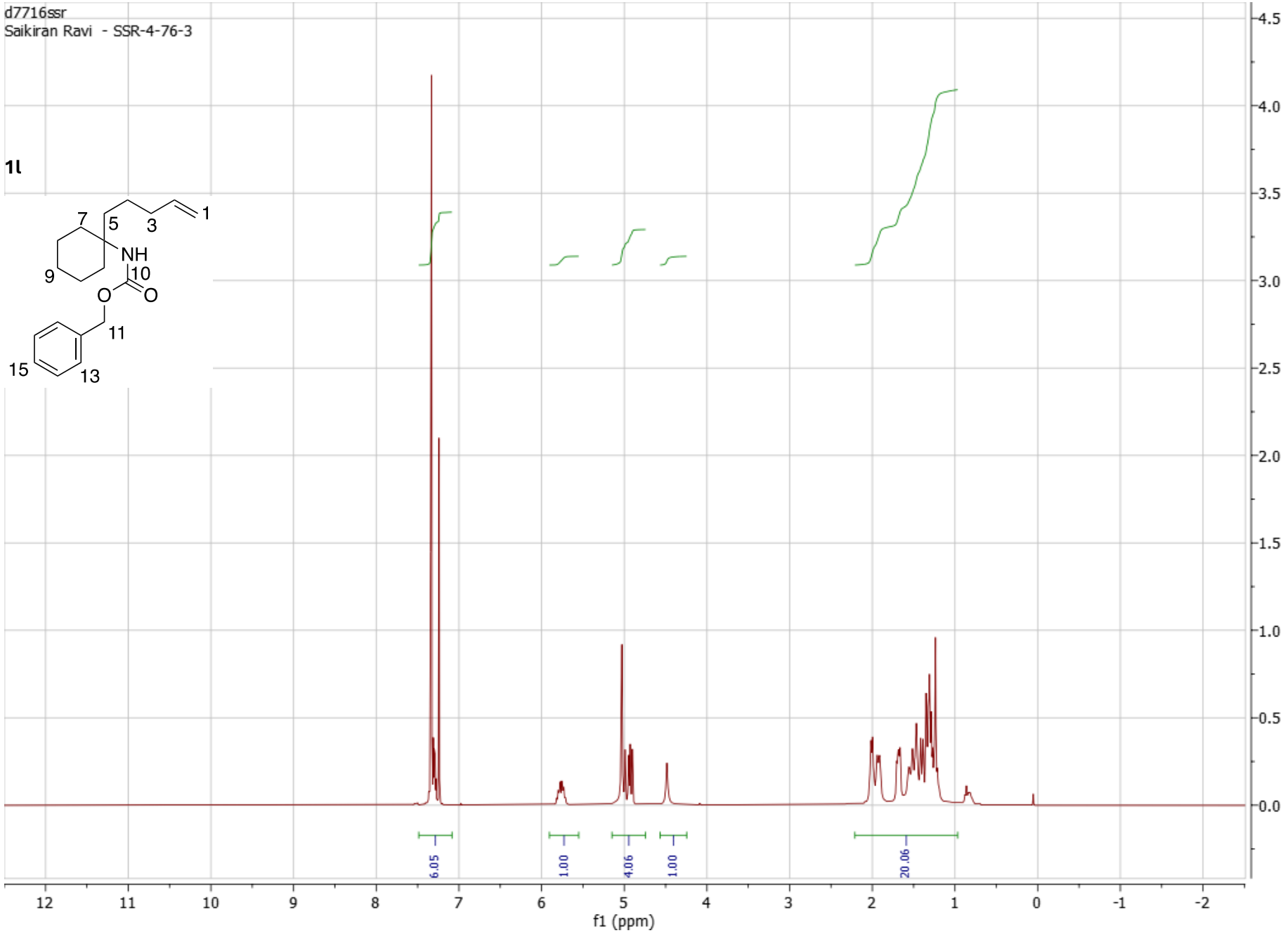

Chloroform-d 101 MHz
175.85
155.64
136.82
128.61
128.09
127.96
77.48
77.16
76.84
67.37
48.12
39.78
35.14
28.37
25.30
18.87
O
OH
N
O
O
8
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

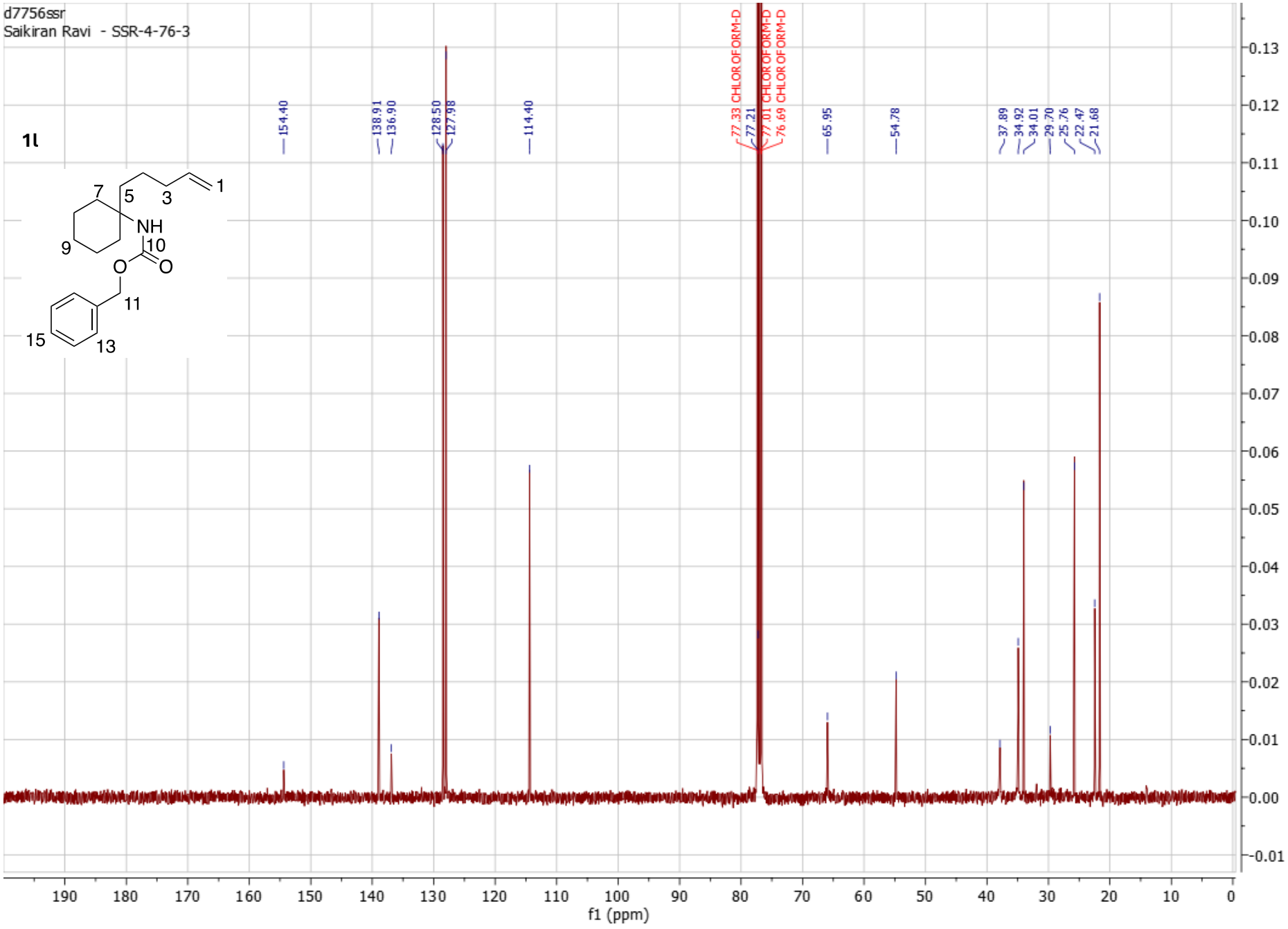

a6186ssr
Saikiran Ravi SSR-2-85-2
S2
11
O
O
5
3
1
7
8
7
9
8
0.99
2.05
2.90
4.18
5.93
8.95
f1 (ppm)

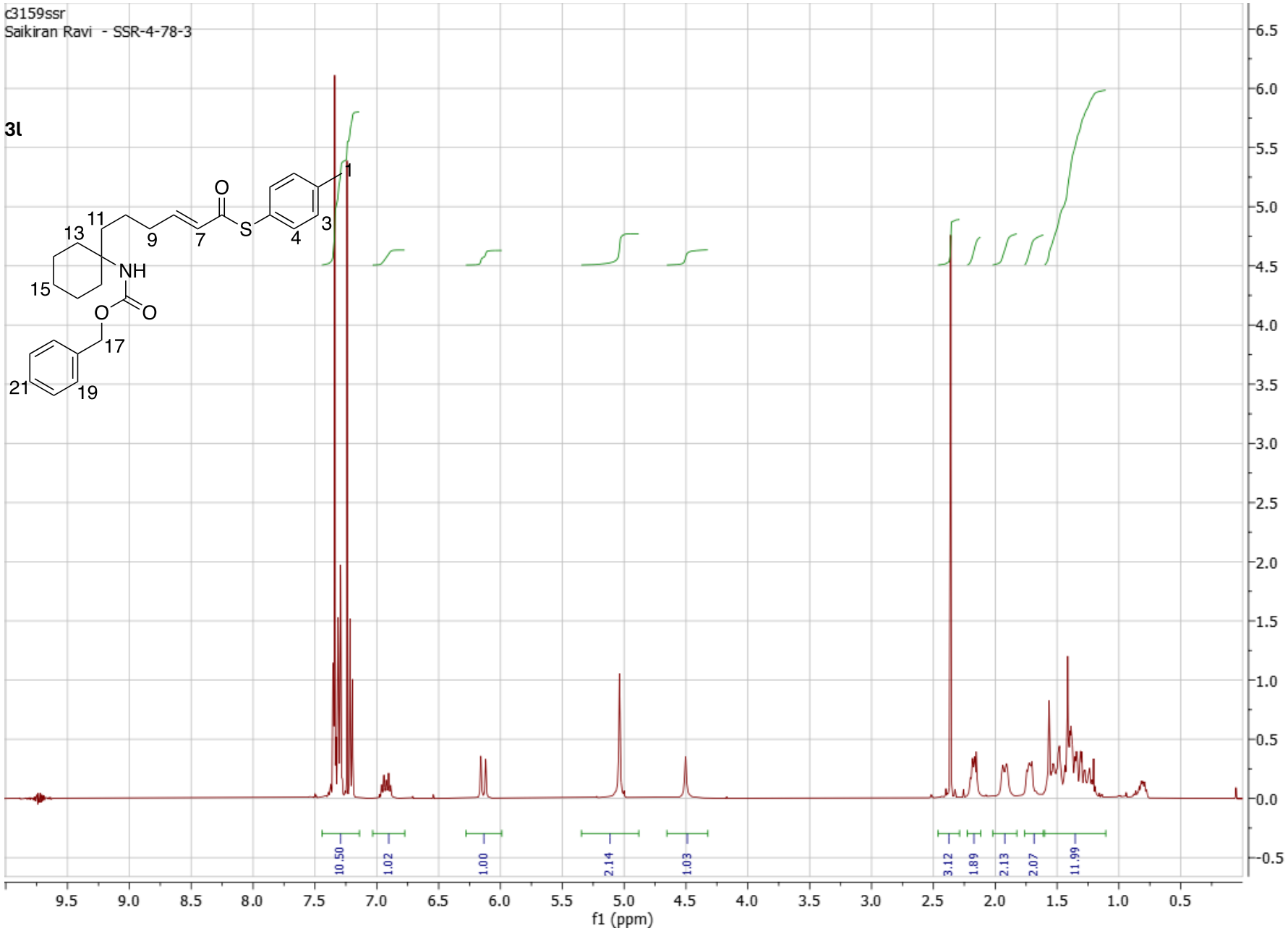

a6186ssr
Saikiran Ravi SSR-2-85-2
S2
177.36
138.56
114.56
77.32 CHLOROFORM-D
76.69 CHLOROFORM-D
51.41
50.81
46.97
40.37
40.06
34.17
34.05
25.96
25.87
25.84
25.71
23.36
23.27
22.44
13.91
f1 (ppm)

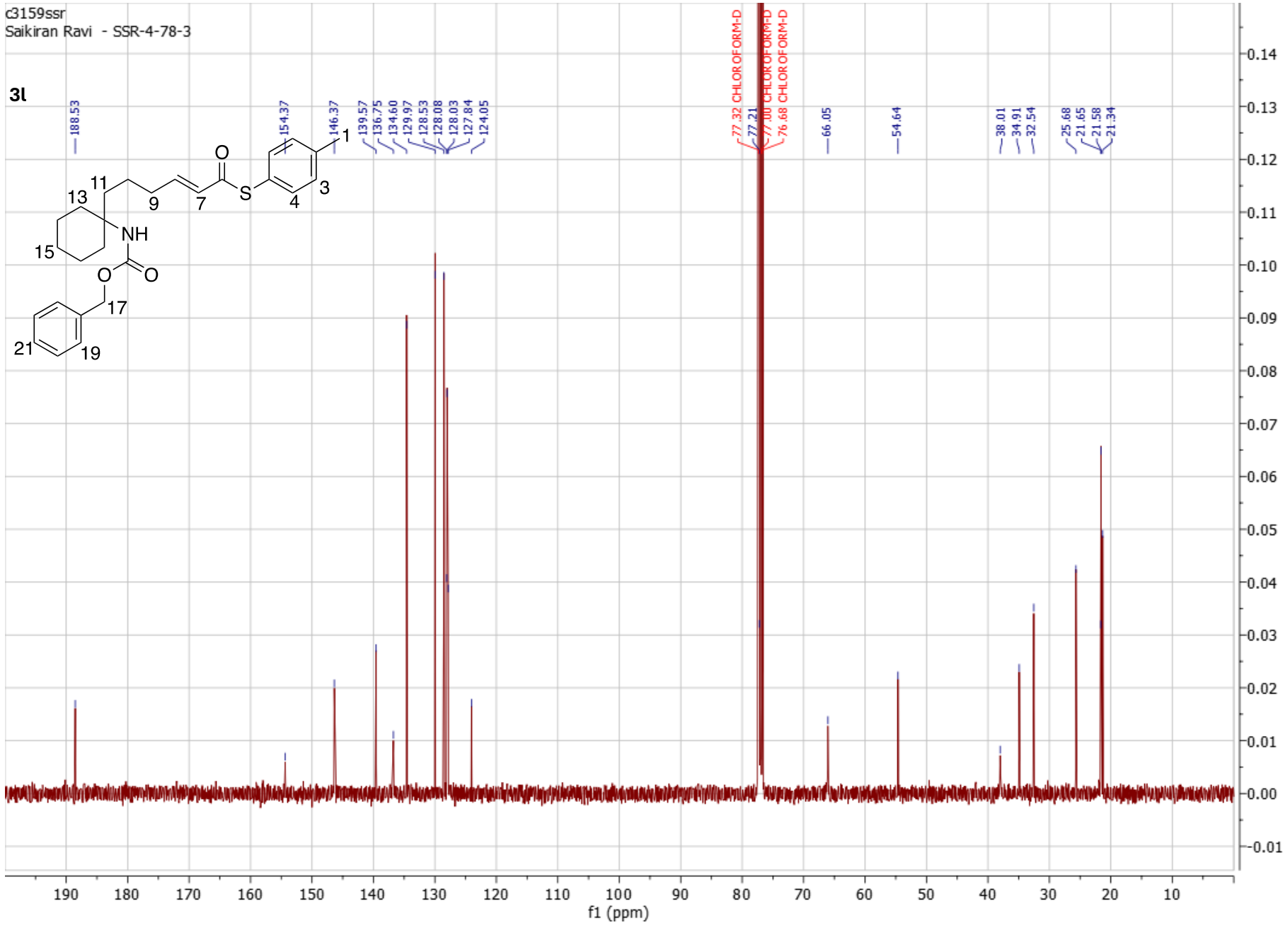

c3158ssr
Saikiran Ravi - SSR-4-64-CM
S3
HO
O
1
3
5
7
8
7
9
8
7.24 CHLOROFORM-D
1.97 H2O
0.78
1.00
2.02
4.35
13.04
f1 (ppm)


c3158ssr
Saikiran Ravi - SSR-4-64-CM
S3
184.04
182.97
177.42
138.46
114.63
114.56
77.32 CHLOROFORM-D
77.21
77.01 CHLOROFORM-D
76.69 CHLOROFORM-D
51.42
46.97
46.89
46.73
46.56
42.93
39.70
34.16
34.02
33.83
30.28
28.72
25.89
25.72
25.67
25.40
25.32
23.39
23.34
23.23
23.13
HO
O
1
3
5
7
7
8
8
9
f1 (ppm)


d7716ssr
Saikiran Ravi - SSR-4-76-3
1l
NH
O
O
6.05
1.00
4.06
1.00
20.06
f1 (ppm)


d7756ssr
Saikiran Ravi - SSR-4-76-3
1l
154.40
138.91
136.90
128.50
127.98
114.40
77.33 CHLOROFORM-D
77.21
77.01 CHLOROFORM-D
76.69 CHLOROFORM-D
65.95
54.78
37.89
34.92
34.01
29.70
25.76
22.47
21.68
NH
O
O
f1 (ppm)


c3159ssr
Saikiran Ravi - SSR-4-78-3
3l
O
S
NH
O
O
1
3
4
7
9
11
13
15
17
19
21
10.50
1.02
1.00
2.14
1.03
3.12
1.89
2.13
2.07
11.99
f1 (ppm)


c3159ssr
Saikiran Ravi - SSR-4-78-3
3l
188.53
154.37
146.37
139.57
136.75
134.60
129.97
128.53
128.08
128.03
127.84
124.05
77.32 CHLOROFORM-D
77.21
77.00 CHLOROFORM-D
76.68 CHLOROFORM-D
66.05
54.64
38.01
34.91
32.54
25.68
21.65
21.58
21.34
NH
O
S
1
3
4
7
9
11
13
15
17
19
21
f1 (ppm)