nature chemistry

Supplementary information

https://doi.org/10.1038/s41557-026-02072-2

Hetero[3.1.1]propellanes

In the format provided by the authors and unedited

Table of Contents

1. General Experimental Information

NMR Spectroscopy: Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker AVIII HD 400, NEO 600, AVIII HD 500, and AVII 500 spectrometers (University of Oxford). ^{1}H, and ^{13} chemical shifts (δ) are quoted in parts per million (ppm). ^{1}H NMR spectra were recorded using an internal deuterium lock for the residual protons in benzene-*d* (δ = 7.16) or chloroform-*d* (δ = 7.26). ^{13}C NMR spectra were recorded using an internal deuterium lock in benzene-*d* (δ = 128), chloroform-*d* (δ = 77.16). Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HSQC, HMBC and/or NOESY experiments. Peak multiplicities are defined as s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet) and br (broad). Coupling constants (*J*) are reported to the nearest 0.1 Hz.

Mass Spectroscopy: High-resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Thermo Scientific Exactive Mass Spectrometer (Waters Equity autosampler and pump) for electrospray ionization (ESI) and an Agilent 7200 Accurate Mass QTOF GCMS (using a SIM Direct Insertion Probe) for electron ionization (EI) and chemical ionization (CI). HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument (IISC India). High-resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Infrared Spectroscopy: Infrared spectra were obtained on a Bruker Tensor 27 FT-IR spectrometer, as a thin film by evaporation of a solution onto a diamond ATR module. Wavelengths of maximum absorbance (υ_{max}) are quoted in cm^{-1}.

Chromatography: Column chromatography refers to normal phase column chromatography and was performed on silica gel (Merck Si 60, 0.040–0.063 mm) under a positive pressure of nitrogen, using the stated solvent system. Analytical thin-layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254} plates) with visualization by ultraviolet light (254 nm) and/or by staining with potassium permanganate or vanillin. Retention factors (R_f) are reported with the solvent system in parentheses.

Materials/procedures: All air- or moisture-sensitive reactions were carried out in anhydrous solvents under an inert atmosphere of argon or nitrogen. Light-sensitive reactions were carried out under aluminium foil protection. Heating was performed using a silicone oil bath. Dry tetrahydrofuran, CH_2Cl_2, pyridine, triethylamine and diethyl ether were collected from an mBraun SPS-800 solvent purification system, having been passed through anhydrous alumina columns. "rt" refers to room (ambient) temperature, typically 23 °C.

Photochemical setup: Photochemical reactions were carried out in an EvoluChem PhotoRedOx Box with an LED lamp (HCK1012-01-010 405 nm or HCK1012-01-002 450-455 nm or Kessil PR160, 456 nm) positioned 10 cm away from the vial, with fan cooling.

Melting points: Recorded using a Gallenkamp melting point apparatus, and are uncorrected.

X-ray crystallography: See section 6 for details of X-ray crystallography.

Safety note: all reactions involving diazo compounds or azides were carried out behind a blast shield, although no uncontrolled decomposition has been observed.

2. Retrosynthesis of 3-oxa[3.1.1]propellane

We investigated a number of possible disconnections of 3-oxa[3.1.1]propellane before arriving at the successful route described in the Main Text. We first considered an equivalent disconnection to that used for the synthesis of carbocyclic [3.1.1]propellane (Fig. 1a). Several routes were attempted to achieve this precursor, however we were not able to install the required chloromethoxy group. This was deemed to be a non-ideal precursor as the chloromethoxy group is likely to be unstable and susceptible to nucleophilic attack.

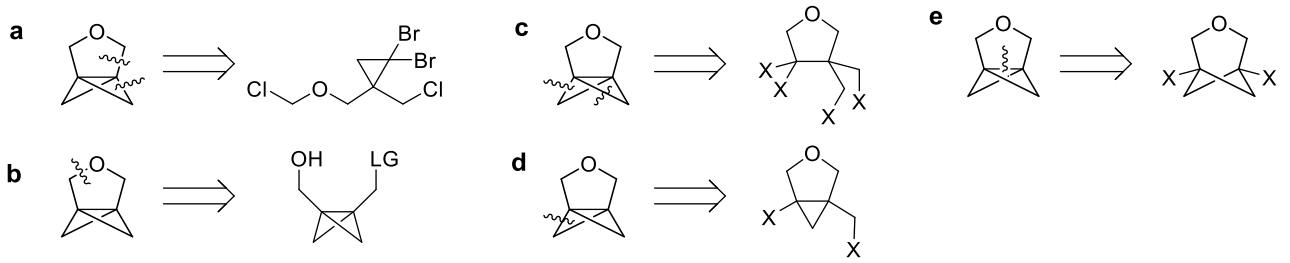


Fig. 1. Disconnections explored for the synthesis of 3-oxa[3.1.1]propellane.

The second disconnection we considered (Fig. 1b) focuses on the tetrahydrofuran ring, having already formed a bicyclo[1.1.0]butane (BCB). However, without a stabilising (electron-withdrawing) group on the BCB, such precursors could not be reliably isolated. It was decided that it would be inconvenient for any synthesis to involve a precursor to the propellane that is unstable / non-scalable.

Consequently, we realised that disconnection of one or both of the cyclopropane rings (Fig. 1c-d) would lead to a stable precursor which has the tetrahydrofuran ring already formed. However, we were unable to identify a scalable / concise synthetic route to the required tetrahalogenated precursor for the approach in Fig. 1c, and therefore decided to focus efforts towards the synthesis of the dihalogenated precursor in Fig. 1d. We further recognised the possibility to access the propellane by cyclisation of a dihalogenated BCHep, as is discussed in the Main Text, and outlined on page S38. We did not develop an independent synthetic route to this dihalide, although this would be an interesting target for further investigations.

Details of the development of the strategy of Fig. 1d are shown in Fig. 2. The first route we investigated (Fig. 2a) started with a Wittig reaction of 1,3-dichloroacetone, followed by bromination and then elimination, which proceeded smoothly to form intermediate **S1**. However, attempted cyclopropanation of this intermediate, either by Corey-Chaykovsky or Simmons-Smith methods proved unsuccessful.

We then explored alternative routes that would form the cyclopropane earlier in the synthesis. We attempted a cyclopropanation of 3-chloro-2-(chloromethyl)prop-1-ene using α-bromodiazoacetate (Fig. 2b), which would lead, after ester reduction, to the same intermediate **S2** as targeted in Fig. 2a. We found that the cyclopropanation did proceed, but only in 12% yield, as decomposition of the diazo compound was faster than the cyclopropanation. This route is limited by the poor stability of this particular diazo compound.

This promising result prompted us to reverse the 'direction' of cyclopropanation, with the substituents on the alkene and diazo compound essentially switched around (Fig. 2c). This now involved the more stable malonate-derived diazo compound, and the cyclopropanation worked well. Of several catalysts investigated (including $Rh_2(OAc)_4$, $Rh_2(TFA)_4$ and $Rh_2(TPA)_4$), $Rh_2(TPA)_4$ performed best. The cyclopropanation was the key step here because it essentially introduced all the necessary functional groups in the correct places, from which a series of functional group manipulations smoothly led to the propellane precursor **5**. After some investigation, we found that we could utilise intermediates **2** and **3** to access the corresponding 3-aza- and 3-thia[3.1.1]propellanes.

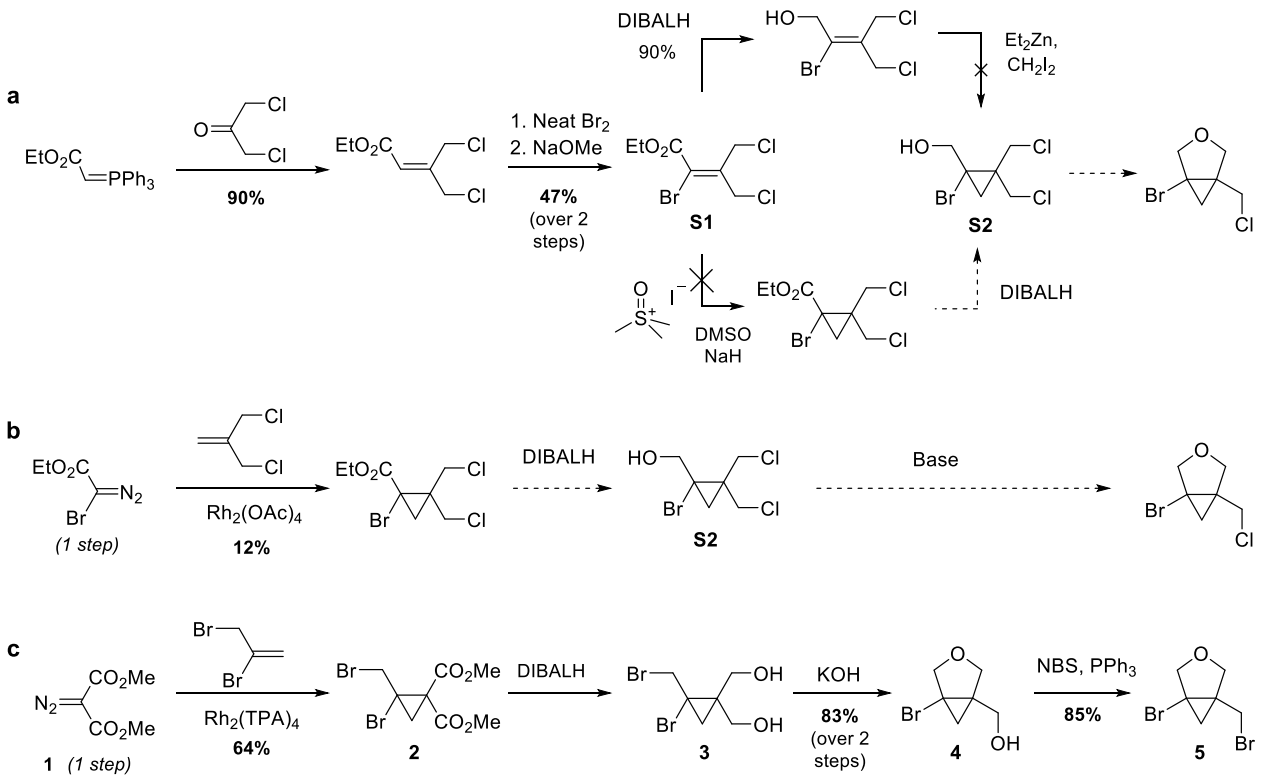


Fig. 2. Evolution of a route to 3-oxa[3.1.1]propellane precursor **5**.

3. Selection of unsuccessful substrates for ring-opening reactions

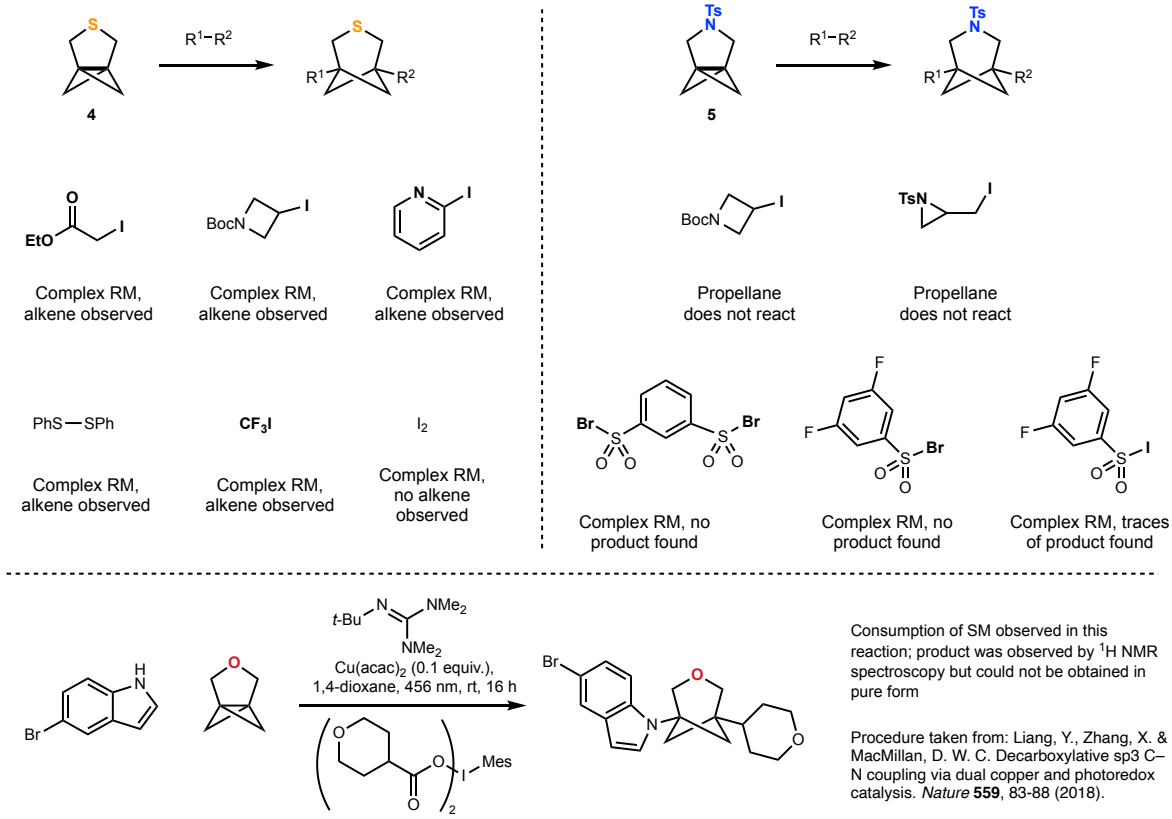
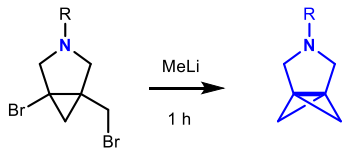


Fig. 3. Unsuccessful substrates for ring-opening reactions.

4. Exploration of 3-aza[3.1.1]propellane substituents



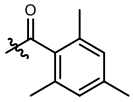
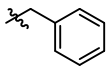
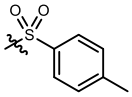
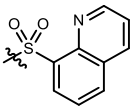
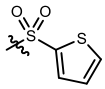
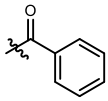
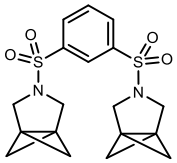
R Group	Result	R Group	Result
	No reaction, SM remains		45% product + 10% SM + decomposition
	MeLi – No reaction, SM remains PhLi – 14% product + SM		98% product
	No reaction, SM remains		81% product
	8% product + SM		70% product
	Amide bond cleaved		99% product

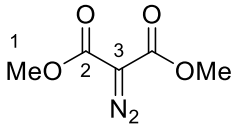
Table 1. Scope of N-substituent in 3-aza[3.1.1]propellane synthesis.

A variety of nitrogen atom substituents were tested in 3-aza[3.1.1]propellane synthesis. We found that the propellane formation performed better with electron-withdrawing groups on the nitrogen which would likely have a stabilising effect on the tertiary bridgehead carbanion that forms as a result of lithium-halogen exchange. Sulfonamide groups performed best, although sterically bulky amides (to protect the amide from attack by MeLi) were also possible, albeit proceeding with lower yields.

5. Experimental Procedures and Characterisation Data

5.1. Routes to Hetero[3.1.1]propellanes

Dimethyl 2-diazomalonate (6)



The product was prepared according to a modified literature procedure[1]. To a solution of dimethyl malonate (17.3 mL, 151 mmol, 1.0 equiv.) and *p*-ABSA (40.0 g, 167 mmol, 1.1 equiv.) in dry MeCN (150 mL) at 0 °C was added DBU (24.9 mL, 167 mmol, 1.1 equiv.) dropwise over 30 min, keeping the internal temperature below 20 °C. The mixture was then warmed to rt and stirred for 3 h. NH_4Cl sat. (20 mL) was added, then the solvent was removed under reduced pressure. Water (400 mL) was added and the mixture was extracted with Et_2O (3 x 400 mL), then the combined organic layers were washed with brine (600 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was filtered through a silica plug and eluted with a 4:1 mixture of hexane/EtOAc until all of the yellow substance was removed from the silica. Concentration under reduced pressure gave the product (20.6 g, 130 mmol, 86%) as a yellow oil.

R_f 0.20 (4:1 pentane / EtOAc).

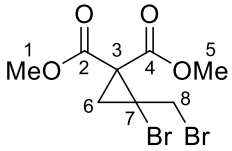
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.83 (6H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.2, 52.7.

Analytical data matches that previously recorded[1].

Note: For safety reasons, to avoid isolation of neat diazo compound, the product is not concentrated until completely free of solvent, but is taken forward to the next step with around 10% residual solvent remaining. The amount of product was determined by NMR spectroscopy.

Dimethyl 2-bromo-2-(bromomethyl)cyclopropane-1,1-dicarboxylate (7)



To a solution of rhodium(II) triphenylacetate dimer (93.8 mg, 65.1 µmol, 0.050 mol%) in dry CH_2Cl_2 (100 mL) was added 2,3-dibromoprop-1-ene (25.5 mL, 80%, 208 mmol, 1.6 equiv.). A solution of dimethyl 2-diazomalonate **6** (20.6 g, 130 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20.0 mL) was added *via* a syringe pump over 8 h at rt then the mixture was stirred at rt for an additional 8 h. The solvent was removed under reduced pressure, then purification by column chromatography (SiO_2, pentane/Et_2O 19:1 $\rightarrow$ 8:2) gave the product (29.1 g, 88.2 mmol, 68%) as a colourless oil.

R_f 0.26 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.07 (2H, s, H8), 3.84 (3H, s, H1 or 5), 3.80 (3H, s, H1 or 5), 2.29 (1H, d, *J* = 7.2 Hz, H6), 2.06 (1H, d, *J* = 7.2 Hz, H6).

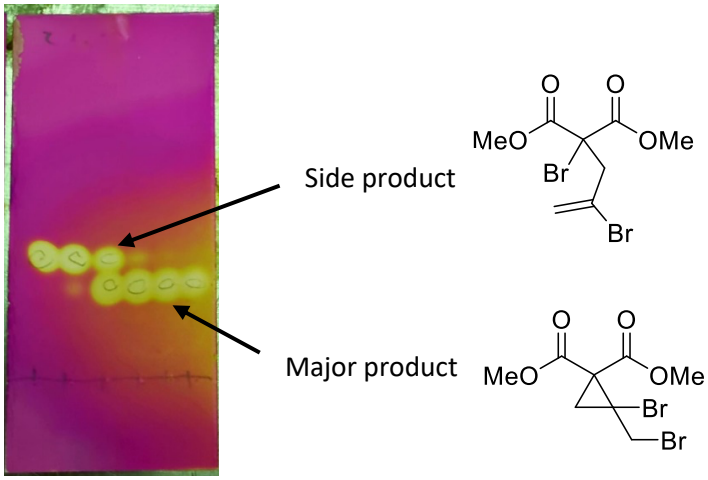
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.9, 165.9, 53.6, 53.5, 42.3, 41.2, 38.3, 30.8.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2955, 1743, 1438, 1345, 1258.

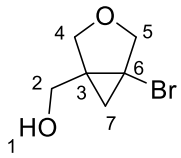
HRMS (ES^+) calc. for $C_8H_{11}Br_2O_4$ $[M+H]^+$ 328.9019, found 328.9006.

Note: some product fractions contained traces of catalyst, giving them a blue colour, but this did not impact the following steps.

Note: the following TLC plate shows a typical result from a column for this step. The second fraction contains the product. To achieve good separation, the column should be eluted with pentane/Et_2O 19:1 until the first fraction has eluted, then the solvent mixture may be increased to pentane/Et_2O 8:2.



(5-Bromo-3-oxabicyclo[3.1.0]hexan-1-yl)methanol (9)



To a solution of **7** (15.0 g, 46.0 mmol, 1.0 equiv.) in dry THF (150 mL) at -78 °C was added DIBALH (200 mL, 1.0 M solution in hexanes, 200 mmol, 4.3 equiv.). The mixture was stirred at -78 °C for 2.5 h, allowed to warm slowly to rt and stirred for an additional 30 min. The mixture was cooled to 0 °C and Rochelle's salt (250 mL, aq. sat.) was added slowly. The cloudy mixture was stirred at rt for 5 h until it became clear. THF was removed under reduced pressure, then the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford (2-Bromo-2-(bromomethyl)cyclopropane-1,1-diyl)dimethanol (**8**).

The crude product **8** from the first step was dissolved in MeOH (100 mL) and added to a solution of KOH (4.50 g, 80.0 mmol, 1.8 equiv.) in MeOH (150 mL). The mixture was heated to 60 °C for 1 h, then the solvent was removed under reduced pressure. Water (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product **9** (7.40 g, 38.0 mmol, 84%) as a yellow oil, which required no further purification.

R_f 0.45 (4:6 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.09 (1H, d, *J* = 8.2 Hz, H4 or H5), 4.00 (1H, d, *J* = 8.7 Hz, H4 or H5), 3.98 (1H, d, *J* = 12.5 Hz, H2), 3.88 (1H, d, *J* = 8.3 Hz, H4 or H5), 3.83 (1H, d, *J* = 9.1 Hz, H 4 or H5),

3.82 (1H, d, *J* = 11.8 Hz, H2), 1.69 (1H, br s, H1), 1.33 (1H, d, *J* = 6.1 Hz, H7), 1.19 (1H, d, *J* = 6.1 Hz, H7).

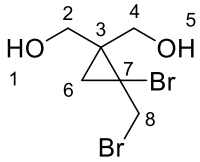
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 75.1, 70.0, 63.5, 37.2, 34.0, 20.8.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3422, 2870, 1074, 1040, 998.

HRMS (ES^+) Not found.

If desired, the product **3** of the first step can be isolated by trituration. A representative procedure is as follows:

(2-Bromo-2-(bromomethyl)cyclopropane-1,1-diyl)dimethanol (8)



To a solution of **7** (6.69 g, 20.3 mmol, 1.0 equiv.) in dry THF (50.0 mL) at -78 °C was added DIBALH (83.1 mL, 1.0 M solution in hexanes). The mixture was stirred at -78 °C for 2 h, then stirred at 0 °C for a further 1 h. Rochelle's salt (100 mL, aq., sat.) was added and the cloudy mixture was stirred at rt for 3 h until it became clear. THF was removed under reduced pressure, then the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Trituration from a 7:3 mixture of pentane:Et_2O gave the product (2.59 g, 9.45 mmol, 47%) as a white amorphous solid which was collected by filtration.

R_f 0.24 (4:6 pentane / EtOAc).

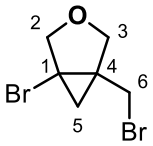
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.15 (1H, d, *J* = 11.9 Hz, H2), 4.08 (1H, d, *J* = 12.2 Hz, H4), 4.03 (1H, d, *J* = 12.0 Hz, H8), 3.93 (1H, d, *J* = 12.0 Hz, H8), 3.89 (1H, d, *J* = 12.0 Hz, H2), 3.76 (1H, d, *J* = 12.2 Hz, H4), 2.23 (2H, br s, H1/H5), 1.36 (1H, d, *J* = 7.1 Hz, H6), 1.23 (1H, d, *J* = 7.1 Hz, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 69.9, 64.1, 44.2, 42.6, 37.1, 26.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3373, 2947, 1436, 1229, 1025.

HRMS (ES^+) calc. for $C_6H_{11}Br_2O_2$ $[M+H]^+$ 272.9120, found 272.9122.

1-Bromo-5-(bromomethyl)-3-oxabicyclo[3.1.0]hexane (10)



To a solution of **9** (7.59 g, 39.3 mmol, 1.0 equiv.) in dry CH_2Cl_2 (100 mL), was added NBS (8.40 g, 47.2 mmol, 1.2 equiv.). PPh_3 (12.4 g, 47.2 mmol, 1.2 equiv.) was then added in portions at 0 °C and the mixture was stirred at rt for 1 h. Pentane (150 mL) was added to the reaction mixture and stirred for 10 minutes at room temperature. The mixture was filtered through a celite pad, and the filtrate was concentrated. Purification by column chromatography (SiO_2, pentane/Et_2O 19:1) gave the product (7.43 g, 29.0 mmol, 74%) as a pale yellow oil.

R_f 0.33 (19:1 pentane / Et_2O).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.99 (1H, d, *J* = 8.4 Hz, H2/3), 3.81 (1H, d, *J* = 8.6 Hz, H2/3), 3.77 (1H, d, *J* = 8.6 Hz, H2/3), 3.76 (1H, dd, *J* = 8.4, 1.2 Hz, H2/3), 3.54 (1H, d, *J* = 11.0 Hz, H6), 3.51 (1H, d, *J* = 11.0 Hz, H6), 1.42 (1H, d, *J* = 6.3 Hz, H5), 1.14 (1H, d, *J* = 6.3 Hz, H5).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 75.0, 71.4, 40.1, 34.2, 33.1, 23.6.

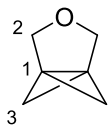
IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2939, 2869, 1442, 1358, 1177, 948.

HRMS (ES^+) Not found.

Note: the product is relatively volatile and must be concentrated carefully with pressure not lower than 250 mbar. However, we have not observed any stability issues with the storage of this propellane precursor over a period of several months.

3-Oxa[3.1.1]propellane (3)

Method 1 (filtration):



To a stirred solution of **10** (5.03 g, 15.7 mmol, 1.0 equiv.) in dry Et_2O (80 mL) at rt was added MeLi (12.1 mL, 1.3 M in Et_2O, 15.7 mmol, 1.0 equiv.). The mixture was stirred at rt for 4 h, then $NaHCO_3$ (1.32 g, 15.7 mmol, 1.0 equiv.) was added. The mixture was cooled to 0 °C, then passed through a celite pad and eluted with Et_2O (100 mL). The mixture was partially concentrated under reduced pressure to give the product as a solution in Et_2O (72.0 mL, 0.16 M, 11.7 mmol, 74%), which was stored in an amber glass bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^{1}H peak at 2.51 ppm relative to the Et_2O peaks.

^{1}H NMR (600 MHz, C_6D_6) δ_H 3.68 (4H, s, H2), 2.51 (2H, s, H3), 1.62 (2H, s, H3).

^{13}C NMR (151 MHz, C_6D_6) δ_C 73.8 (C2), 53.9 (C3), 28.6 (C1).

Note: the solution of product contains a white precipitate, presumed to be LiBr, which does not affect subsequent reactions.

Caution: During the partial concentration process, bromomethane will be released.

Storage: It is recommended to store the propellane solution in the freezer (-20 °C) at <0.5 M concentration, under which conditions it is stable for a period of (at least) several weeks–months. See Section 6 for further discussion on stability.

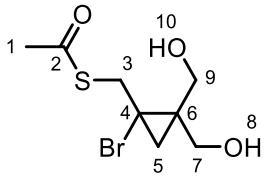
Method 2 (distillation):

To a stirred solution of **10** (1.02 g, 3.19 mmol, 1.0 equiv.) in dry Et_2O (16 mL) at rt was added MeLi (2.45 mL, 1.3 M in Et_2O, 3.19 mmol, 1.0 equiv.). The mixture was stirred at rt for 4 h, then $NaHCO_3$ (268 mg, 3.19 mmol, 1.0 equiv.) was added. *n*Bu_2O (30 mL) was added and the mixture was distilled using a rotary evaporator (30 °C water bath) with a dry ice cold finger condenser and a receiving flask immersed in an acetone/dry ice bath. The Et_2O fraction containing bromomethane was removed by slowly decreasing the pressure to 150 mbar and this fraction was discarded. The *n*Bu_2O fraction containing 3-oxa[3.1.1]propellane was then distilled by slowly decreasing the pressure to <10 mbar. This gave the product as a solution in *n*Bu_2O (27.0 mL, 0.065 M, 1.76 mmol, 55%), which was stored in an amber bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^{1}H peak at 2.42 ppm relative to the Et_2O peaks.

^{1}H NMR (400 MHz, C_6D_6) δ_H 3.51 (4H, s, H2), 2.42 (2H, t, *J* = 1.4 Hz, H3), 1.64 (2H, t, *J* = 1.4 Hz, H3)

^{13}C NMR (101 MHz, C_6D_6) δ_C 73.2 (C2), 53.9 (C3), 22.8 (C1).

(1-Bromo-2,2-bis(hydroxymethyl)cyclopropyl)methyl ethanethioate (11)



To a solution of **7** (8.51 g, 25.8 mmol, 1.0 equiv.) in dry THF (65 mL) at -78 °C was added DIBALH (106 mL, 1.0 M solution in hexanes, 106 mmol, 4.1 equiv.). The mixture was stirred at -78 °C for 2 h, then 0 °C for 1 h, then rt for 1 h. Rochelle's salt (100 mL, aq., sat.) was added and the cloudy mixture was stirred at rt for 16 h until it became clear. THF was removed under reduced pressure, then the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product **8**.

The crude product **8** was dissolved in MeOH (30 mL) and potassium thioacetate (2.95 g, 25.8 mmol, 1.0 equiv.) was added. The mixture was stirred at rt for 3 h, then the solvent was removed under reduced pressure. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 4:6) gave the product **11** (3.75 g, 13.9 mmol, 54%) as a white solid.

R_f 0.30 (4:6 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.18 (1H, d, *J* = 11.9 Hz, H7/9), 4.12 (1H, d, *J* = 12.0 Hz, H7/9), 3.85 (1H, dd, *J* = 12.0, 1.6 Hz, H7/9), 3.83 (1H, d, *J* = 14.8 Hz, H3), 3.73 (1H, dd, *J* = 12.0, 1.7 Hz, H7/9), 3.54 (1H, d, *J* = 14.7 Hz, H3), 2.39 (3H, s, H1), 1.14 (1H, d, *J* = 7.0 Hz, H5), 1.12 (1H, d, *J* = 6.9 Hz, H5).

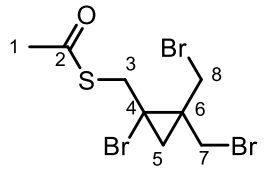
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 195.2, 71.0, 65.6, 45.0, 39.7, 35.6, 30.6, 24.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3395, 2943, 1692, 1422, 1137, 1029.

HRMS (ES^+) calc. for $C_8H_{13}BrO_3SNa$ $[M+Na]^+$ 290.9661, found 290.9664.

m.p. 54 °C

(1-Bromo-2,2-bis(bromomethyl)cyclopropyl)methyl ethanethioate (12)



To a stirred solution of **11** (3.16 g, 11.7 mmol, 1.0 equiv.) and NBS (5.22 g, 29.4 mmol, 2.5 equiv.) in dry CH_2Cl_2 (120 mL) at 0 °C was added PPh_3 (7.70 g, 29.4 mmol, 2.5 equiv.) portionwise. The mixture was stirred at rt for 10 min, then H_2O_2 (30%, 3.6 mL) and water (100 mL) were added. The

organic layer was removed and mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was diluted with pentane / Et_2O (9:1), filtered through a silica pad and concentrated under reduced pressure to give the product (2.70 g, 6.84 mmol, 58%) as a white solid.

R_f 0.27 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) 4.01 (1H, dd, *J* = 10.9, 1.0 Hz, H7/8), 3.85 (1H, d, *J* = 10.9 Hz, H7/8), 3.85 (1H, dd, *J* = 11.3, 0.9 Hz, H7/8), 3.82 (1H, d, *J* = 13.5 Hz, H3), 3.77 (1H, dd, *J* = 11.1, 1.0 Hz, H7/8), 3.50 (1H, d, *J* = 14.9 Hz, H3), 2.42 (3H, s, H1), 1.43 (2H, s, H5).

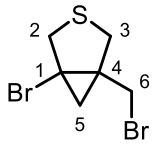
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 194.8, 48.0, 40.0, 39.0, 35.2, 34.8, 30.8, 30.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2970, 1693, 1428, 1354, 1293, 1135.

HRMS (ES^+) Not found.

m.p. 75 °C

1-Bromo-5-(bromomethyl)-3-thiabicyclo[3.1.0]hexane (13)



To a suspension of **12** (2.70 g, 6.84 mmol, 1.0 equiv.) in MeOH (35 mL) was added KOH (767 mg, 13.7 mmol, 2.0 equiv.) and the mixture was stirred at 50 °C for 1 h. The solvent was removed under reduced pressure, then water (60 mL) was added and the mixture was extracted with Et_2O (3 x 60 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (1.77 g, 6.51 mmol, 95%) as a low melting point pale yellow solid. We have not observed any stability issues with the storage of this propellane precursor over a period of several months.

R_f 0.59 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) 3.73 (1H, d, *J* = 10.8 Hz, H2/3), 3.63 (1H, d, *J* = 10.8 Hz, H2/3), 3.45 (1H, d, *J* = 11.2 Hz, H2/3), 3.31 (1H, d, *J* = 10.9 Hz, H2/3), 3.29 (1H, d, *J* = 11.3 Hz, H6), 2.89 (1H, d, *J* = 11.3 Hz, H6), 2.07 (1H, d, *J* = 6.6 Hz, H5), 1.13 (1H, d, *J* = 6.6 Hz, H5).

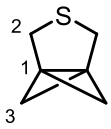
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 44.3, 41.0, 38.7, 35.9, 34.6, 22.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2927, 1432, 1343, 1224, 1105, 1018.

HRMS (ES^+) Not found.

m.p. 33 °C

3-Thia[3.1.1]propellane (4)



To a stirred solution of **13** (0.961 g, 3.53 mmol, 1.0 equiv.) in dry Et_2O (18 mL) at rt was added MeLi (2.72 mL, 1.3 M in Et_2O, 3.53 mmol, 1.0 equiv.). The mixture was stirred at rt for 4 h, then $NaHCO_3$ (297 mg, 3.53 mmol, 1.0 equiv.) was added. The mixture was cooled to 0 °C, then passed through a celite pad and eluted with Et_2O (50 mL). The mixture was partially concentrated under reduced pressure to give the product as a solution in Et_2O (18.5 mL, 0.13 M, 2.41 mmol, 68%), which was stored in an amber glass bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^1H peak at 2.79 ppm relative to the Et_2O peaks.

^{1}H NMR (400 MHz, C_6D_6) δ_H ^{1}H NMR (400 MHz, C_6D_6) δ 2.78 (2H, t, *J* = 1.4 Hz, H3), 2.70 (4H, s, H2), 1.58 (2H, t, *J* = 1.4 Hz, H3).

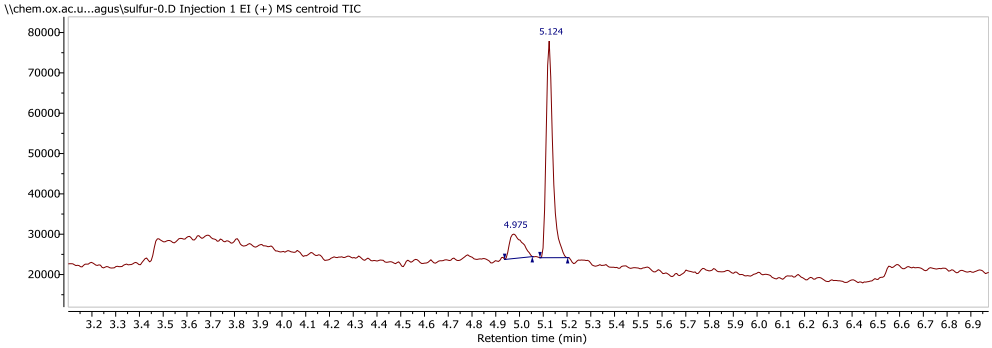
^{13}C NMR (101 MHz, C_6D_6) δ_C 52.4 (C2), 37.7 (C1), 37.7 (C3).

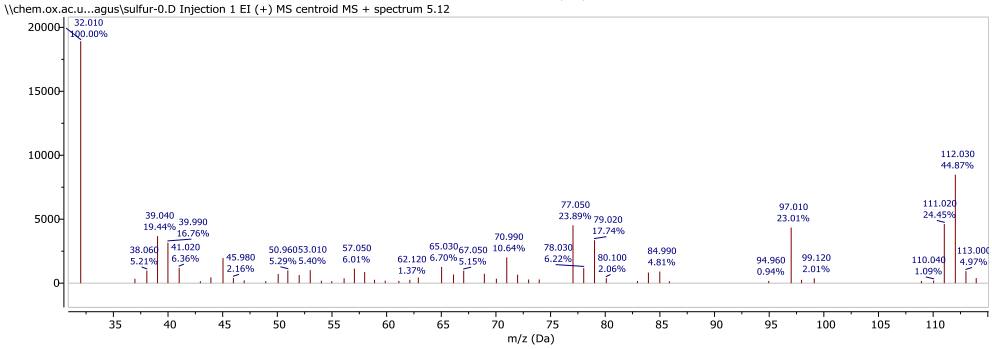
Note: the solution of product contains a white precipitate, presumed to be LiBr, which does not affect subsequent reactions.

Caution: During the partial concentration process, bromomethane will be released.

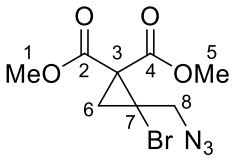
Storage: It is recommended to store the propellane solution in the freezer (-20 °C) at <0.5 M concentration, under which conditions it is stable for a period of (at least) several weeks–months. See Section 6 for further discussion on stability; the thia[3.1.1]propellane solution will degrade over a period of ~4-5 days if stored at room temperature.

GCMS calc. for C_6H_8S $[M]^+$ 112.035, found 112.030.





Dimethyl 2-(azidomethyl)-2-bromocyclopropane-1,1-dicarboxylate (14)



To a mixture of **7** (14.3 g, 43.3 mmol, 1.0 equiv.) in dry DMF (70 mL) was added NaN_3 (2.82 g, 43.3 mmol, 1.0 equiv.) and the mixture was stirred at 40 °C for 4 h. Et_2O (500 mL) was added and the mixture was washed with water (3 x 500 mL). Each water wash was back-extracted with Et_2O (2 x 500 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (12.2 g, 41.8 mmol, 96%) as a yellow oil.

R_f 0.40 (6:4 pentane / Et_2O).

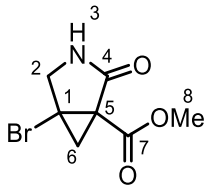
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.03 (1H, d, *J* = 13.8 Hz, H8), 3.89 (1H, d, *J* = 13.8 Hz, H8), 3.83 (3H, s, H1/5), 3.79 (3H, s, H1/5), 2.16 (1H, d, *J* = 7.2 Hz, H6), 1.93 (1H, d, *J* = 7.2 Hz, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 167.3, 166.1, 56.4, 53.7, 53.4, 39.7, 39.6, 27.8.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2956, 2109, 1731, 1436, 1250.

HRMS (ES^+) calc. for $C_8H_{10}BrN_3O_4Na$ $[M+Na]^+$ 313.9747, found 313.9747.

Methyl 5-bromo-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (15)



To a stirred solution of PBu_3 (11.2 mL, 44.8 mmol, 1.0 equiv.) and water (0.808 mL, 44.8 mmol, 1.0 equiv.) in THF (110 mL) at 0 °C was added a solution of **14** (13.1 g, 44.8 mmol, 1.0 equiv.) in THF (20 mL) dropwise over 45 min, keeping the internal temperature below 5 °C. The mixture was stirred at 0 °C for a further 30 min, then slowly warmed to rt over 30 min and stirred at rt for 1 h. The mixture was then concentrated under reduced pressure. Trituration from THF/pentane (1:5) gave the product (6.40 g, 27.3 mmol, 61%) as a white solid.

R_f 0.17 (3:7 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.07 (1H, s, H3), 3.85 (3H, s, H8), 3.82 (2H, d, *J* = 0.9 Hz, H2), 2.38 (1H, d, *J* = 6.2 Hz, H6), 1.66 (1H, d, *J* = 6.2 Hz, H6).

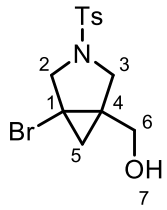
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.8, 165.4, 53.2, 51.8, 37.8, 34.4, 27.0.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3210, 1730, 1708, 1439, 1248.

HRMS (ES^+) calc. for $C_7H_9BrNO_3$ $[M+H]^+$ 233.9760, found 233.9768.

m.p. 109 °C (dec.)

(5-Bromo-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (16)



To a stirred solution of **15** (3.10 g, 13.2 mmol, 1.0 equiv.) in dry THF (125 mL) at 0 °C was added Red-Al (10.8 mL, 60%, 33.1 mmol, 2.5 equiv.) and the mixture was stirred at rt for 5 h. Rochelle's salt (70 mL) was added slowly at 0 °C (note: vigorous quenching) and the mixture was stirred for 10 min at rt until it became clear. The mixture was diluted with water (50 mL), then Na_2CO_3 (2.10 g, 19.8 mmol, 1.5 equiv.) was added. The mixture was cooled to 0 °C and TsCl (2.52 g, 13.2 mmol, 1.0 equiv.) was added. The mixture was stirred at 0 °C for another 5 min, then at rt for 1 h. The THF was removed under reduced pressure and the mixture was extracted with EtOAc (3 x 120 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (6:4 pentane / EtOAc) gave the product (1.82 g, 5.26 mmol, 40%) as a white solid.

R_f 0.24 (6:4 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, Ts), 7.35 (2H, d, *J* = 8.0 Hz, Ts), 3.95 (1H, d, *J* = 9.2 Hz, H2/3), 3.90 (1H, dd, *J* = 12.4, 7.6 Hz, H6), 3.66 (1H, dd, *J* = 12.4, 4.6 Hz, H6), 3.56 (1H, d, *J* = 9.4 Hz, H2/3), 3.32 (1H, d, *J* = 9.4 Hz, H2/3), 3.26 (1H, dd, *J* = 9.2, 1.2 Hz, H2/3), 2.45 (3H, s, Ts), 1.52 (1H, dd, *J* = 7.8, 4.9 Hz, H7), 1.38 (1H, d, *J* = 6.6 Hz, H5), 1.12 (1H, d, *J* = 6.5 Hz, H5).

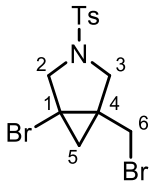
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 133.2, 130.0, 127.7, 64.0, 56.6, 49.9, 35.2, 33.7, 21.7, 21.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3535, 2924, 1346, 1167, 1030.

HRMS (ES^+) calc. for $C_{13}H_{17}BrNO_3S$ $[M+H]^+$ 346.0107, found 346.0111.

m.p. 130 °C

1-Bromo-5-(bromomethyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (17)



To a stirred solution of **16** (5.80 g, 16.8 mmol, 1.0 equiv.) and NBS (3.58 g, 20.1 mmol, 1.2 equiv.) in dry CH_2Cl_2 (80 mL) at 0 °C was added a solution of PPh_3 (5.27 g, 20.1 mmol, 1.2 equiv.) in CH_2Cl_2 (10 mL) dropwise. The mixture was stirred at rt for 1 h, then concentrated under reduced pressure. Purification by column chromatography (8:2 pentane / Et_2O) gave the product (6.32 g, 15.4 mmol, 92%) as a white solid. We have not observed any stability issues with the storage of this propellane precursor over a period of several months.

R_f 0.21 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, Ts), 7.36 (2H, d, *J* = 7.9 Hz, Ts), 3.95 (1H, d, *J* = 9.4 Hz, H2/3), 3.65 (1H, d, *J* = 9.5 Hz, H2/3), 3.52 (1H, d, *J* = 11.1 Hz, H6), 3.47 (1H, d, *J* = 11.1

Hz, H6), 3.24 (1H, d, *J* = 15.9 Hz, H2/3), 3.22 (1H, d, *J* = 16.2 Hz, H2/3), 2.45 (3H, s, Ts), 1.54 (1H, d, *J* = 6.7 Hz, H5), 1.19 (1H, d, *J* = 6.8 Hz, H5).

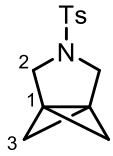
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 133.2, 130.1, 127.6, 56.5, 51.7, 38.1, 34.8, 32.8, 24.5, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2923, 1351, 1166, 1100, 1013.

HRMS (ES^+) calc. for $C_{13}H_{16}Br_2NO_2S$ $[M+H]^+$ 407.9263, found 407.9251.

m.p. 124 °C

3-(*N*-Tosyl)aza[3.1.1]propellane (5)



To a stirred solution of **17** (2.00 g, 4.89 mmol, 1.0 equiv.) in dry THF (40 mL) at -78 °C was added MeLi (3.76 mL, 1.3 M in Et_2O, 4.89 mmol, 1.0 equiv.). The mixture was stirred at -78 °C for 10 min then at rt for 1 h. $NaHCO_3$ (411 mg, 4.89 mmol, 1.0 equiv.) was added, then the mixture was cooled to 0 °C, passed through a celite pad and eluted with THF (100 mL). The mixture was partially concentrated under reduced pressure to give the product as a solution in THF (26.0 mL, 0.18 M, 4.79 mmol, 98%), which was stored in an amber glass bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^{1}H peak at 3.17 ppm relative to the THF peaks.

^{1}H NMR (500 MHz, C_6D_6) δ_H 7.62 (2H, d, *J* = 8.2 Hz, Ts), 6.99 (2H, d, *J* = 8.0 Hz, Ts), 3.17 (4H, s, H2), 2.04 (3H, s, Ts), 2.03 (2H, t, *J* = 1.7 Hz, H3), 1.31 (2H, t, *J* = 1.7 Hz, H3).

^{13}C NMR (126 MHz, C_6D_6) δ_C 143.3 (Ts), 135.0 (Ts), 129.8 (Ts), 127.9 (Ts), 53.6 (C2), 52.1 (C3), 22.4 (C1), 21.1 (Ts Me).

HRMS (ES^+) calc. for $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.0896, found 250.0900.

Caution: During the partial concentration process, bromomethane will be released.

Storage: It is recommended to store the propellane solution in the freezer (-20 °C) at <0.5 M concentration, under which conditions it is stable for a period of (at least) several weeks–months. See Section 6 for further discussion on stability.

5.2. General procedures for Ring-opening Reaction of Hetero[3.1.1]propellanes

General procedure 1: Reaction with chalcogen (RXH)[2]

Hetero[3.1.1]propellane (1.0 equiv.) was added dropwise to a solution of thiol/benzeneselenol (1.1 equiv.) in anhydrous diethyl ether. The reaction mixture was stirred for 1 h at ambient temperature, then diluted with diethyl ether and washed with 1 M aqueous NaOH solution (x3), followed by brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel.

General procedure 2: BEt_3-initiated atom transfer radical addition[3]

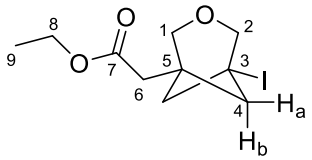
An alkyl iodide (1 equiv.) was added to a stirred diethyl ether solution of hetero[3.1.1]propellane (1.2-1.5 equiv.) at 0 °C. Et_3B (10 mol%, 1 M in hexane) was then added. The mixture was stirred until complete consumption of the alkyl iodide, as monitored by TLC. The reaction mixture was then concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel.

General procedure 3: Photoredox-catalysed atom transfer radical addition[4]

To a 4 mL screw-capped vial equipped with a stirrer bar were added *fac*-Ir(ppy)$_3$ (2.5 mol%), an alkyl or aryl halide (1.0 equiv.), and *t*-BuCN (0.13 M). Hetero[3.1.1]propellane (1.5-2.0 equiv.) was added and the mixture was degassed with N_2 for 5 minutes. The vial was placed in the photobox, and the stirred reaction mixture was irradiated with blue LEDs (HCK1012-01-002 450-455 nm or Kessil PR160, 456 nm) with fan cooling for the specified time. After the consumption of the iodides as monitored by TLC, the reaction mixture was concentrated, and the product was purified by column chromatography on silica gel.

5.3. Ring-opening Reactions of Hetero[3.1.1]propellanes

Ethyl 2-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetate (18a)



Method 1: Synthesised in accordance with *General Procedure 3* using iodomethyl propionate (43.0 mg, 0.200 mmol, 1.0 equiv.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.5 equiv., 0.25 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 2 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column gel (SiO_2, pentane/Et_2O 8:2) to afford the title compound **18a** (51.0 mg, 0.160 mmol, 82%) as a colourless oil.

Method 2: Synthesised in accordance with *General Procedure 2* using iodomethyl propionate (43.0 mg, 0.200 mmol, 1 equiv.), oxa[3.1.1]propellane (1.2 mL, 0.300 mmol, 1.5 equiv., 0.25 M in diethyl ether) and BEt_3 (20.0 µL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 45 min. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane / Et_2O 8:2) to afford the title compound **18a** (43.0 mg, 0.140 mmol, 69%) as a colourless oil.

$\mathbf{R_f}$ = 0.5 (8:2 pentane/Et_2O).

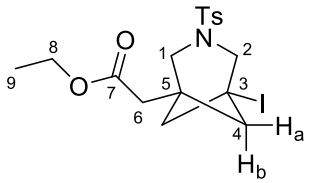
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.13-4.09 (4H, singlet from H1/H2 and quartet from H8 overlapped), 3.80 (2H, s, H1/H2), 2.60-2.58 (2H, m, $H4_b$), 2.51-2.49 (2H, m, $H4_a$), 2.36 (2H, s, H6), 1.25 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 170.2, 77.8, 72.1, 60.8, 48.7, 44.6, 41.4, 27.6, 14.4.

IR (thin film, ν_{max} / cm^{-1}): 2944, 2859, 1733, 1273, 1246, 1196, 1086.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{10}H_{16}IO_3]^+$ 311.0139, found 311.0135.

Ethyl 2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetate (18b)



Synthesised in accordance with *General Procedure 2*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.25 mL, 0.15 M in THF, 0.288 mmol, 2.0 equiv.), ethyl 2-iodoacetate (17.4 µL, 0.147 mmol, 1.0 equiv.) and BEt_3 (14.7 µL, 1.0 M solution in hexanes, 14.7 µmol, 0.1 equiv.). The mixture was stirred for 1 h. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product **18b** (58.7 mg, 0.127 mmol, 86%) as a colourless oil.

R_f 0.29 (8:2 pentane / EtOAc).

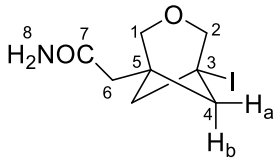
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, Ts), 7.33 (2H, d, *J* = 7.7 Hz, Ts), 4.09 (2H, q, *J* = 7.1 Hz, H8), 3.84 (2H, s, H1/2), 3.36 (2H, s, H1/2), 2.51-2.46 (2H, m, $H4_b$), 2.43 (3H, s, Ts), 2.40 (2H, s, H6), 2.18-2.10 (2H, m, $H4_a$), 1.22 (3H, t, *J* = 7.2 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.9, 143.9, 134.3, 130.0, 127.4, 60.9, 59.2, 52.2, 48.7, 42.0, 41.5, 22.5, 21.7, 14.3.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2943, 1731, 1345, 1160, 1094.

HRMS (ES^+) calc. for $C_{17}H_{23}INO_4S$ $[M+H]^+$ 464.0387, found 464.0395.

2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetamide (18c)



Synthesised in accordance with *General Procedure 3* using 2-iodoacetamide (37.0 mg, 0.200 mmol, 1 equiv.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.2 equiv., 0.25 M in Et_2O) and *fac*-$Ir(ppy)_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 3 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/EtOAc 8:2) to afford **18c** (35.0 mg, 0.120 mmol, 62%) as a white solid.

R_f = 0.2 (8:2 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.49 (1H, s, H8), 5.34 (1H, s, H8), 4.14 (2H, s, H1/H2), 3.85 (2H, s, H1/H2), 2.62-2.61 (2H, m, $H4_b$), 2.55-2.52 (2H, m, $H4_a$), 2.28 (2H, s, H6).

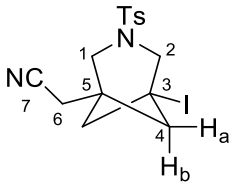
^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ_C 171.4, 77.8, 72.2, 48.7, 44.9, 42.6, 27.7.

IR (thin film, ν_{max} / cm^{-1}): 3381, 2945, 2861, 1732, 1666, 1419, 1242, 1198, 1024.

HRMS (ESI+) $[M+Na]^+$ calculated for $[C_8H_{12}INO_2Na]^+$ 303.9805, found 303.9805.

m.p. 113-115 °C

2-(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetonitrile (18d)



Synthesised in accordance with *General Procedure 2*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (2.13 mL, 0.15 M in THF, 0.320 mmol, 2.0 equiv.), 2-iodoacetonitrile (11.6 µL, 0.160 mmol, 1.0 equiv.) and BEt_3 (16.0 µL, 16.0 µmol, 10 mol%). The mixture was stirred for 1 h. Purification by column chromatography (SiO_2, pentane/EtOAc 7:3) gave the product **18d** (23.3 mg, 56.0 µmol, 35%) as a white solid.

R_f 0.27 (7:3 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, J = 8.3 Hz, Ts), 7.36 (2H, d, J = 8.1 Hz, Ts), 3.86 (2H, s, H1/2), 3.36 (2H, s, H1/2), 2.59-2.50 (2H, m, $H4_b$), 2.46 (2H, s, H6), 2.45 (3H, s, Ts), 2.18-2.09 (2H, m, $H4_a$).

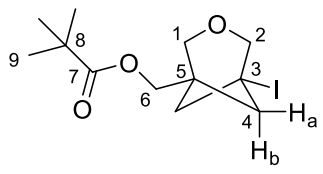
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 133.9, 130.2, 127.4, 115.8, 58.9,51.8, 47.5, 40.8, 25.5, 21.7, 19.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2920, 1343, 1159, 1011.

HRMS (ES^+) calc. for $C_{15}H_{18}IN_2O_2S$ $[M+H]^+$ 417.0128, found 417.0126.

m.p. 126 °C

(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (18e)



Method 1: Synthesised in accordance with *General Procedure 3* using iodomethyl pivalate (48.0 mg, 0.200 mmol, 1 equiv.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.2 equiv., 0.25 M in Et_2O) and *fac*-$Ir(ppy)_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product **18e** (51.0 mg, 0.150 mmol, 75%) as a colourless oil.

Method 2: Synthesised in accordance with *General Procedure 2* using iodomethyl pivalate (48.0 mg, 0.200 mmol, 1 equiv.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.5 equiv., 0.25 M in diethyl ether) and BEt_3 (20 µL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 8 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product **18e** (39.0 mg, 0.120 mmol, 58%) as a colourless oil.

R_f = 0.3 (8:2 pentane / Et_2O)

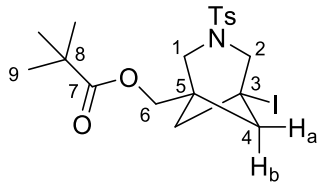
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.16 (2H, s, H1/2/6), 3.92 (2H, s, H1/2/6), 3.81 (2H, s, H1/2/6), 2.59-2.55 (2H, m, $H4_b$), 2.41-2.37 (2H, m, $H4_a$), 1.20 (9H, s, H9).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ_C 178.2, 78.2, 70.4, 66.1, 47.0, 46.2, 39.1, 27.4, 27.3.

IR (thin film, ν_{max} / cm^{-1}): 2986, 2863, 1732, 1600, 1503, 1479, 1363, 1282, 1155, 1085.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{12}H_{20}IO_3]^+$ 339.0452, found 339.0459.

(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (18f)



Synthesised in accordance with *General Procedure 3*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.54 mL, 0.15 M in THF, 0.354 mmol, 2.0 equiv.), iodomethyl pivalate (28.2 µL, 0.182 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (3.0 mg, 4.5 µmol, 2.5 mol%). The mixture was stirred and irradiated with blue LED (450-455 nm) for 4 h. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product **18f** (18.3 mg, 37.2 µmol, 21%) as a white solid.

R_f 0.16 (9:1 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.3 Hz, Ts), 7.34 (2H, d, *J* = 8.1 Hz, Ts), 3.93 (2H, s, H1/2), 3.89 (2H, s, H1/2), 3.33 (2H, s, H6), 2.50-2.45 (2H, m, $H4_b$), 2.45 (3H, s, Ts), 2.03-1.97 (2H, m, $H4_a$), 1.18 (9H, s, H9).

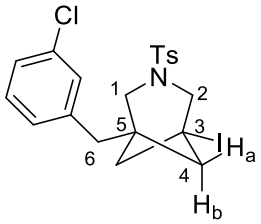
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.0, 144.0, 134.3, 130.0, 127.4, 66.3, 59.6, 50.3, 46.2, 44.0, 39.1, 27.3, 22.1, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2974, 1733, 1344, 1283, 1163.

HRMS (ES^+) calc. for $C_{19}H_{27}INO_4S$ $[M+H]^+$ 492.0700, found 492.0686.

m.p. 137 °C

1-(3-Chlorobenzyl)-5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptane (18g)



Synthesised in accordance with *General Procedure 2*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.60 mL, 0.15 M in THF, 0.240 mmol, 1.2 equiv.), 1-chloro-3-(iodomethyl)benzene (50.5 mg, 0.200 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (3.3 mg, 5.0 µmol, 2.5 mol%). The mixture was stirred and irradiated with 450-455 nm blue light in a photobox with fan cooling for 4 h. Purification by column chromatography (SiO_2, pentane/Et_2O 8:2) gave the product **16j** (25.2 mg, 50.2 µmol, 25%) as a yellow solid.

R_f 0.17 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, *J* = 8.3 Hz, Ts), 7.29 (2H, d, *J* = 8.0 Hz, Ts), 7.25-7.21 (2H, m, Ar H), 6.97 (1H, s, Ar H), 6.93-6.84 (1H, m, Ar H), 3.85 (2H, s, H1/2/6), 3.21 (2H, s, H1/2/6), 2.66 (2H, s, H1/2/6), 2.43 (3H, s, Ts), 2.42-2.37 (2H, m, H4$_b$), 2.00-1.91 (2H, m, H4$_b$).

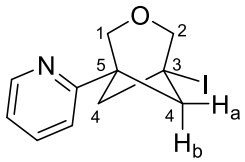
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.8, 138.4, 134.6, 134.3, 130.0, 130.0, 129.3, 127.7, 127.3, 127.2, 59.5, 52.2, 48.3, 44.7, 43.3, 23.2, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2943, 1597, 1342, 1160, 1094.

HRMS (ES$^+$) calc. for $C_{20}H_{22}ClINO_2S$ $[M+H]^+$ 502.0099, found 502.0087.

m.p. 156 °C

2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)pyridine (18h)



Synthesised in accordance with *General Procedure 3* using 2-iodopyridine (41.0 mg, 0.200 mmol, 1.0 equiv.), oxa[3.1.1]propellane (1.30 mL, 0.240 mmol, 1.5 equiv., 0.23 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 3 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product **18h** (39.0 mg, 0.130 mmol, 65%) as a yellow oil.

R_f = 0.3 (6:4 pentane / Et_2O).

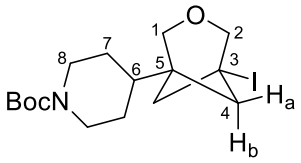
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.54 (1H, dd, *J* = 4.9, 1.9 Hz, ArH), 7.66 (1H, td, *J* = 7.7, 1.8 Hz, ArH), 7.17 (1H, ddd, *J* = 7.5, 4.9, 1.2 Hz, ArH), 7.07 (1H, dt, *J* = 7.9, 1.1 Hz, ArH), 4.26 (2H, s, H1/H2), 4.06 (2H, s, H1/H2), 3.01-2.97 (2H, m, H4$_b$), 2.84-2.80 (2H, m, H4$_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 161.0, 149.5, 136.9, 122.1, 120.0, 77.9, 72.8, 52.4, 48.3, 27.3.

IR (thin film, ν_{max} / cm^{-1}): 2946, 2858, 1589, 1471, 1423, 1216, 1040.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{11}H_{13}INO]^+$ 302.0036, found 302.0039.

***tert*-Butyl 4-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)piperidine-1-carboxylate (18i)**



Synthesised in accordance with *General Procedure 3* using *tert*-butyl 4-iodopiperidine-1-carboxylate (62.0 mg, 0.200 mmol, 1.0 equiv.), oxa[3.1.1]propellane (1.40 mL, 0.300 mmol, 1.5 equiv., 0.22 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 4 h.

All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product **18i** (52.0 mg, 0.130 mmol, 64%) as a crystalline solid.

R_f = 0.45 (8:2 pentane/ EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.15 (2H, m, H8), 4.12 (2H, s, H1/H2), 3.75 (2H, s, H1/H2), 2.59-2.54 (2H, m, H8, 2.48-2.44 (2H, m, H4$_b$), 2.38-2.35 (2H, m, H4$_a$), 1.48-1.36 (3H, m, H6/7), 1.44 (9H, s, Boc), 1.11 (1H, dd, *J* = 12.6, 4.4 Hz, H7), 1.06 (1H, dd, *J* = 12.5, 4.4 Hz, H7).

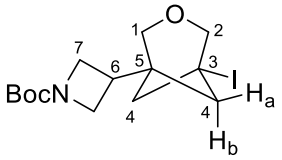
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 154.8, 79.7, 78.3, 70.9, 50.3, 46.9, 42.7, 28.8, 28.6, 26.9.

IR (thin film, ν_{max} / cm^{-1}): 2936, 2857, 1688, 1426, 1367, 1242, 1038.

HRMS (ESI+) $[M+Na]^+$ calculated for $[C_{16}H_{26}INO_3Na]^+$ 430.0850, found 430.0862.

m.p. 72-75 °C

***tert*-Butyl 3-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)azetidine-1-carboxylate (18j)**



Synthesised in accordance with *General Procedure 2* using *tert*-butyl 3-iodoazetidine-1-carboxylate (57.0 mg, 0.200 mmol, 1.0 equiv.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.5 equiv., 0.25 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 4 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product **18j** (49.0 mg, 0.130 mmol, 65%) as a light yellow oil.

R_f = 0.3 (8:2 pentane / Et_2O).

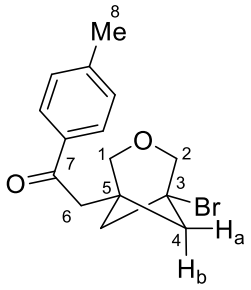
^{1}H NMR (600 MHz, $CDCl_3$) δ_H 4.16 (2H, s, H1/H2), 3.87 (2H, t, *J* = 8.2 Hz, H7), 3.68-3.65 (4H, m, H1/H2+H7), 2.58-2.55 (2H, m, H4$_b$), 2.38-2.35 (1H, m, H6), 2.35-2.31 (2H, m, H4$_a$), 1.43 (9H, s, Boc).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 156.3, 79.9, 78.3, 71.1, 50.0, 48.3, 44.4, 31.4, 28.5, 27.4.

IR (thin film, ν_{max} / cm^{-1}): 2974, 2882, 1698, 1478, 1404, 1301, 1252, 1084.

HRMS (ESI+) $[M+Na]^+$ calculated for $[C_{14}H_{22}INO_3Na]^+$ 402.0537, found 402.0538.

2-(5-Bromo-3-oxabicyclo[3.1.1]heptan-1-yl)-1-(p-tolyl)ethan-1-one (18k)



Synthesised in accordance with *General Procedure 3* using 2-bromo-1-(*p*-tolyl)ethan-1-one (43.0 mg, 0.200 mmol, 1.0 equiv.), oxa[3.1.1]propellane (1.30 mL, 0.300 mmol, 1.5 equiv., 0.23 M in diethyl ether) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 9:1) to give the product **18k** (32.0 mg, 0.100 mmol, 52%) as a crystalline solid.

R_f = 0.5 (9:1 pentane / Et_2O).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.3 Hz, ArH), 7.26 (2H, d, *J* = 7.9 Hz, ArH), 4.05 (2H, s, H1/H2), 3.82 (2H, s, H1/H2), 3.06 (2H, s, H6), 2.54-2.50 (2H, m, $H4_a$), 2.45-2.42 (2H, m, $H4_b$), 2.41 (3H, s, H8).

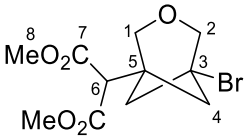
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 196.9, 144.5, 134.6, 129.6, 128.3, 75.5, 72.2, 52.2, 47.5, 44.6, 41.4, 21.8.

IR (thin film, ν_{max} / cm^{-1}): 2949, 2859, 1681, 1606, 1572, 1406, 1180, 1036.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{15}H_{18}BrO_2]^+$ 309.0485, found 309.0482.

m.p. 93-95 °C

Dimethyl 2-(5-bromo-3-oxabicyclo[3.1.1]heptan-1-yl)malonate (18l)



Synthesised in accordance with *General Procedure 2* using dimethyl bromomalonate (42.0 mg, 0.200 mmol, 1.0 equiv.), oxa[3.1.1]propellane (1.30 mL, 0.300 mmol, 1.5 equiv., 0.24 M in diethyl ether) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 4 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product **18l** (33.0 mg, 0.110 mmol, 54%) as a colourless oil.

R_f = 0.5 (8:2 pentane / Et_2O)

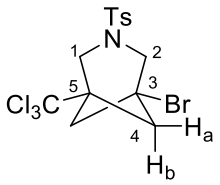
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.01 (2H, s, H1/H2), 3.85 (2H, s, H1/H2), 3.73 (6H, s, H8), 3.45 (1H, s, H6), 2.53-2.47 (4H, m, H4).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ_C 167.2, 75.4, 70.2, 56.9, 52.7, 50.9, 46.2, 42.4.

IR (thin film, ν_{max} / cm^{-1}): 2955, 2867, 1740, 1437, 1332, 1239, 1087.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{11}H_{16}BrO_5]^+$ 307.0176, found 307.0178.

1-Bromo-3-tosyl-5-(trichloromethyl)-3-azabicyclo[3.1.1]heptane (18m)



To a stirred solution of 3-(*N*-tosyl)-aza[3.1.1]propellane (1.33 mL, 0.15 M in THF, 0.200 mmol, 1.0 equiv.) at -78 °C was added CCl_3Br (59.2 µL, 0.600 mmol, 3.0 equiv.). The mixture was stirred at -78 °C for 15 min, then at rt for 1 h. The mixture was then concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 9:1) gave the product **18m** (37.7 mg, 84.2 µmol, 42%) as a white solid.

R_f 0.31 (9:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.1 Hz, Ts), 7.37 (2H, d, *J* = 8.0 Hz, Ts), 3.77 (2H, s, H1/2), 3.75 (2H, s, H1/2), 2.92-2.82 (2H, m, $H4_b$), 2.46 (3H, s, Ts), 2.14-2.04 (2H, m, $H4_a$).

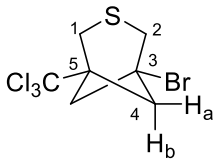
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 134.1, 130.2, 127.5, 101.6, 56.4, 55.5, 49.8, 44.6, 44.3, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2872, 1344, 1162, 1035, 1014.

HRMS (ES^+) calc. for $C_{14}H_{16}BrCl_3NO_2S$ $[M+H]^+$ 445.9145, found 445.9130.

m.p. 136 °C

1-Bromo-5-(trichloromethyl)-3-thiabicyclo[3.1.1]heptane (18n)



To a solution of 3-thia[3.1.1]propellane (1.00 mL, 0.12 M, 0.12 mmol, 1.0 equiv.) in Et_2O at -78 °C was added CCl_3Br (59.2 µL, 0.60 mmol, 5.0 equiv.), then BEt_3 (12.0 µL, 1.0 M solution in hexanes, 12.0 µmol, 10 mol%). The mixture was stirred at -78 °C for 15 min then rt for 1 h. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane 100%) gave the product **18n** (11.9 mg, 38.3 µmol, 32%) as a white solid.

R_f 0.29 (100% pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.43 (2H, s, H1/2), 3.27 (2H, s, H1/2), 3.12-3.03 (2H, m, $H4_b$), 2.69-2.60 (2H, m, $H4_a$).

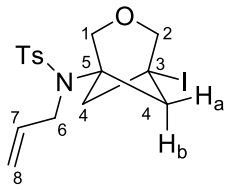
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 104.2, 57.1, 49.3, 45.1, 40.3, 31.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2934, 1272, 1137, 775.

HRMS (ES^+) Not found

m.p. 77 °C

N-allyl-N-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)-4-methylbenzene sulfonamide (18o)



Prepared according to the literature procedure[5] and in accordance with *General Procedure 3*, using 2-(iodomethyl)-1-tosylaziridine (67.0 mg, 0.200 mmol, 1.0 equiv.), *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%), *t*-BuCN (1.5 mL) and oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 0.25 M in Et_2O, 1.5 equiv.). The mixture was irradiated with 456 nm light for 4 h. The crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product **18o** (46.0 mg 0.110 mmol, 53%) as a colourless oil.

R_f = 0.3 (8:2 pentane / Et_2O).

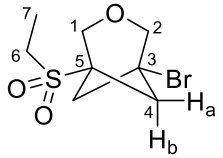
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, ArH), 7.31 (2H, d, *J* = 7.8 Hz, ArH), 5.75 (1H, ddt, *J* = 17.2, 10.1, 6.3 Hz, H7), 5.16 (1H, dd, *J* = 11.0, 1.3 Hz, H8), 5.13 (1H, dd, *J* = 10.5, 1.2 Hz, H8), 3.98 (2H, s, H1/H2), 3.93 (2H, s, H1/H2), 3.77 (2H, dt, *J* = 6.3, 1.4 Hz, H6), 2.83-2.80 (2H, m, $H4_b$), 2.82-2.75 (2H, m, $H4_a$), 2.44 (3H, s, H9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 143.8, 138.7, 135.3, 130.0, 127.3, 118.6, 76.8, 71.7, 62.7, 49.8, 49.3, 22.1, 21.7.

IR (thin film, ν_{max} / cm^{-1}): 2954, 2862, 1437, 1335, 1238, 1087.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{16}H_{21}INO_3S]^+$ 434.0281, found 434.0281.

1-Bromo-5-(ethylsulfonyl)-3-oxabicyclo[3.1.1]heptane (18p)



The reaction was carried out according to the literature procedure[6]. To an oven-dried vial, ethanesulfonyl bromide (35.0 mg, 0.200 mmol, 1.0 equiv.) was added. The vial was sealed with a PTFE cap, and Et_2O (1.50 mL) was added. The reaction mixture was degassed for 10 min, after which oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 0.24 M in Et_2O, 1.5 equiv.) was added, and degassing was continued with argon for an additional 5 min. The reaction mixture was stirred at ambient temperature overnight. The solvent was then removed under reduced pressure, and the crude reaction mixture was treated with Et_2O (5.0 mL) and cooled in an ice bath for 30 min. The resulting cloudy solution was filtered, and the solvent was removed under reduced pressure, to give the product **18p** (35.0 mg 0.120 mmol, 62%) as a thick, colourless oil.

Note: The product is not stable on silica gel.

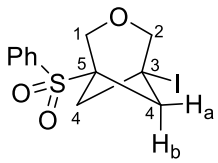
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.09 (2H, s, H1/H2), 4.06 (2H, s, H1/H2), 3.01-3.07 (2H, m, $H4_b$), 2.86 (2H, q, *J* = 7.5 Hz, H6), 2.53-2.49 (2H, m, $H4_a$), 1.39 (3H, t, *J* = 7.5 Hz, H7).

^{13}C NMR (151MHz, $CDCl_3$) δ_C 75.0, 67.0, 60.6, 48.4, 44.0, 42.8, 5.7.

IR (thin film, ν_{max} / cm^{-1}): 2953, 2866, 1599, 1436, 1312, 1237, 1040.

HRMS not found.

1-Iodo-5-(phenylsulfonyl)-3-oxabicyclo[3.1.1]heptane (18q)



The reaction was carried out according to the literature procedure[6]. A solution of sodium benzenesulfinate salt (0.50 mL, 0.500 mmol, 1.0 M in H_2O, 2.5 equiv.) was added dropwise to a suspension of 1,3-diiodo-5,5-dimethylhydantoin (76.0 mg, 0.200 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL) at -5 °C (ice/NaCl). The mixture was stirred vigorously for 15 minutes, then a solution of oxa[3.1.1]propellane (0.8 mL, 0.20 mmol, 0.25 M in Et_2O, 1.0 equiv.) was added. The slurry was stirred at -5 °C for 10 minutes and then sonicated for a few seconds at ambient temperature to ensure complete mixing. The reaction was quenched at ambient temperature by addition of saturated aqueous $Na_2S_2O_3$ (0.50 mL). The biphasic mixture was poured into H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were concentrated in vacuo. The crude reaction mixture was treated with Et_2O (5 mL) and cooled in an ice bath for 30 minutes. The resulting cloudy solution was filtered, and the solvent was removed under reduced pressure, yielding the product **16q** (50.0 mg 0.140 mmol, 69%) as a thick colourless liquid.

Note: The product is not stable on silica gel.

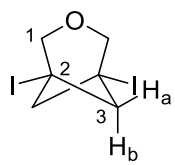
^{1}H NMR (600 MHz, C_6D_6) δ_H 7.46 (2H, dd, *J* = 8.3, 1.3 Hz, ArH), 6.94-6.86 (1H, m, ArH), 6.82 (2H, dd, *J* = 8.4, 7.2 Hz, ArH), 3.70 (2H, s, H1/H2), 3.68 (2H, s, H1/H2), 3.08-3.05 (2H, m, $H4_b$), 1.94-1.91 (2H, m $H4_a$).

^{13}C NMR (151 MHz, C_6D_6) δ_C 136.6, 133.7, 129.2, 129.1, 77.1, 66.7, 64.9, 44.3, 23.0.

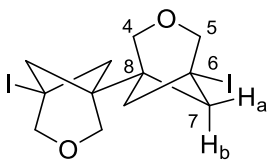
IR (thin film, ν_{max} / cm^{-1}): 2925, 2872, 1690, 1583, 1450, 1300, 1159, 1081.

HRMS (ESI+) $[M+H]^+$calculated for $[C_{12}H_{14}IO_3S]^+$ 364.9703, found 364.9685.

1,5-Diiodo-3-oxabicyclo[3.1.1]heptane (18r) and 5,5'-Diiodo-3,3'-dioxa-1,1'-bi(bicyclo[3.1.1]heptane) (18r')



18r



18r'

To a stirred solution of 3-oxa-[3.1.1]propellane (0.60 mL, 0.14 M in THF, 84.0 µmol, 1.0 equiv.) was added iodine (21.3 mg, 84.0 µmol, 1.0 equiv.) and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane/Et_2O 19:1) gave the inseparable products **18r** and **18r'** (17.3 mg) as a yellow solid in a 1.0:0.15 ratio of **18r**:**18r'** as determined from the ^{1}H NMR spectrum, with 64% overall yield.

R_f 0.42 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.12 (4H, s, H1), 4.05 (4H, s, H4/5), 4.03 (4H, s, H4/5), 3.25-3.15 (2H, m, $H3_b$), 3.14-3.08 (4H, m, $H7_b$), 3.04-2.95 (2H, m, $H3_a$), 2.94-2.86 (4H, m, $H7_a$)

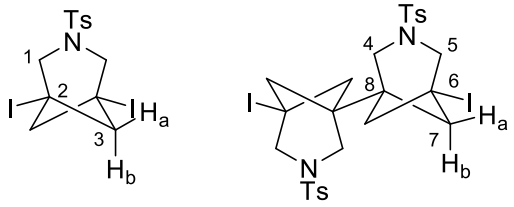
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 76.5, 55.7, 24.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2862, 1456, 1244, 1072, 976.

HRMS (ES^+) Not found

m.p. 43 °C

1,5-Diiodo-3-tosyl-3-azabicyclo[3.1.1]heptane (18s) and 5,5'-Diiodo-3,3'-ditosyl-3,3'-diaza-1,1'-bi(bicyclo[3.1.1]heptane) (18s')



18s **18s'**

To a stirred solution of 3-(*N*-tosyl)-aza[3.1.1]propellane (1.32 mL, 0.15 M in THF, 0.198 mmol, 1.1 equiv.) was added iodine (45.7 mg, 0.180 mmol, 1.0 equiv.) and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane/EtOAc 19:1) gave the inseparable products **18s** and **18s'** (58.1 mg) as a yellow solid in a 1.4:1.0 ratio of **18s**:**18s'** as determined from the ^{1}H NMR spectrum, with 75% overall yield.

R_f 0.20 (19:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (6H, d, *J* = 8.3 Hz, Ts), 7.36 (6H, d, *J* = 8.1 Hz, Ts), 3.80 (4H, s, H1), 3.76 (4H, s, H4/5), 3.69 (4H, s, H4/5), 3.18-3.05 (2H, m, $H3_b$), 3.04-2.96 (4H, m, $H7_b$), 2.70-2.59 (2H, m, $H3_a$), 2.58-2.50 (4H, m, $H7_a$), 2.45 (9H, s, Ts).

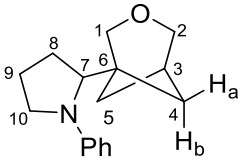
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.3, 144.3, 134.1, 130.2, 127.4, 127.4, 58.2, 58.0, 55.8, 55.6, 54.3, 47.2, 21.7, 19.4, 16.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2869, 1344, 1160, 1012.

HRMS (ES^+) calc. for $C_{13}H_{15}I_2NO_2SNa$ [M(**18s**)+Na]$^+$ 525.8805, found 525.8807.

m.p. 167 °C

2-(3-Oxabicyclo[3.1.1]heptan-1-yl)-1-phenylpyrrolidine (18t)



The reaction was carried out according to the literature procedure[7]. To an oven-dried vial containing 1-(4-bromophenyl)pyrrolidine (450 mg, 0.200 mmol, 10.0 equiv.) and 4CzIPN (4.0 mg, 2.5 mol%) was added anhydrous DMA (0.50 mL) and H_2O (36.0 µL, 2.0 mmol, 10.0 equiv.). The solution was deggased with argon for 15 minutes before adding oxa[3.1.1]propellane (0.80 mL, 0.300 mmol, 1.0 equiv., 0.25 M in Et_2O). The vial was sealed and irradiated with a 440 nm Kessil PR160L LED lamp.

After stirring at ambient temperature for 18 h, the solution was diluted with EtOAc (5.0 mL) and washed with 5% LiCl solution (10.0 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude reaction mixture was purified via column chromatography using silica gel to afford the product **18t** (44.0 mg, 0.140 mmol, 68%) as a colourless crystalline solid.

m.p. 88-90 °C

R_f = 0.5 (19:1 pentane / Et_2O).

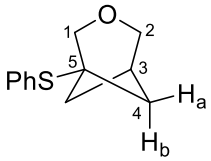
^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.22-7.20 (2H, m, ArH), 6.69 (1H, t, *J* = 7.3 Hz, ArH), 6.58 (2H, d, *J* = 8.1 Hz, ArH), 3.91–3.86 (4H, m, H1/2), 3.61 (1H, td, *J* = 8.7, 2.5 Hz, H10), 3.45 (1H, dd, *J* = 7.0, 3.5 Hz, H7), 3.18 (1H, td, *J* = 9.3, 7.4 Hz, H10), 2.18 (1H, tt, *J* = 6.5, 3.3 Hz, H3), 2.02–1.92 (4H, m, $H4_b/5_b$/9), 1.82–1.78 (2H, m, H8), 1.62 (1H, t, *J* = 8.2 Hz, $H4_a/5_a$), 1.56 (1H, t, J = 8.4 Hz, $H4_a/5_a$).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 149.4, 129.0, 116.1, 112.8, 73.8, 70.9, 61.2, 50.3, 48.7, 34.5, 32.5, 31.4, 28.0, 24.4.

IR (thin film, ν_{max} / cm^{-1}): 2954, 2853, 1600, 1503, 1341, 1238, 1055.

HRMS (ESI-) $[M-H]^-$ calculated for $[C_{16}H_{20}NO]^-$ 242.1550, found 242.1539.

1-(Phenylthio)-3-oxabicyclo[3.1.1]heptane (18u)



Synthesised in accordance with *General Procedure 1* using thiophenol (24.0 mg, 0.220 mmol, 1.1 equiv.) and oxa[3.1.1]propellane (0.80 mL, 0.200 mmol, 1.0 equiv., 0.24 M in diethyl ether), stirred at ambient temperature for 1 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 9:1) to afford the product **18u** (38.0 mg, 0.180 mmol, 91%) as a colourless solid.

R_f = 0.2 (99:1 pentane / Et_2O).

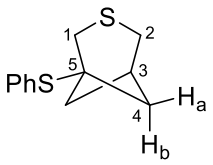
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.42–7.40 (2H, m, ArH), 7.32 –7.30 (3H, m, ArH), 3.89 (2H, s, H1), 3.85 (2H, d, *J* = 2.2 Hz, H2), 2.46 (1H, tt, *J* = 6.8, 2.2 Hz, H3), 2.22–2.19 (2H, m, $H4_b$), 1.93–1.89 (2H, m, $H4_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 134.9, 131.7, 129.0, 128.3, 74.6, 69.9, 50.4, 38.3, 32.9.

IR (thin film, ν_{max} / cm^{-1}): 2951, 2858, 1474, 1233, 1124, 1024.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{12}H_{15}OS]^+$ 207.0838, found 207.0835.

1-(Phenylthio)-3-thiabicyclo[3.1.1]heptane (18v)



A solution of 3-thia[3.1.1]propellane (1.67 mL, 0.12 M, 0.200 mmol, 1.0 equiv.) in Et_2O was added dropwise to stirred neat PhSH (0.205 mL, 2.00 mmol, 10 equiv.). The mixture was stirred at rt for 30 min then diluted with Et_2O (2 mL), washed with 1 M aq NaOH (3 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 98:2) gave the product **18v** (18.5 mg, 83.2 µmol, 42%) as a colourless oil.

R_f 0.24 (98:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44-7.36 (2H, m, Ar H), 7.35-7.28 (3H, m, Ar H), 3.16 (2H, s, H1), 3.03 (2H, d, *J* = 3.3 Hz, H2), 2.77-2.70 (1H, m, H3), 2.40-2.29 (2H, m, $H4_b$), 2.18-2.08 (2H, m, $H4_a$).

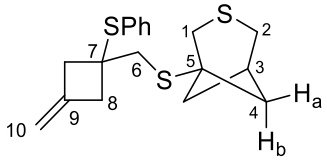
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 134.8, 132.3, 129.0, 128.3, 50.0, 38.5, 37.9, 32.8, 31.0.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2933, 1583, 1438, 1202, 1097.

HRMS (ES^+) calc. for $C_{12}H_{15}S_2$ $[M+H]^+$ 223.0610, found 223.0614.

A side product was observed in this reaction, where upon reaction with PhSH, the resulting BCHep radical fragmented, forming a new sulfur-based radical, which attacked a second molecule of propellane. The proportion of this side product in the reaction mixture decreased with increasing amounts of PhSH added. When 1 equiv. PhSH was used, the ratio of **18v:18v'** was 1:0.5. When 10 equiv. PhSH was used, the ratio was 1:0.1.

Fragmentation product, 1-(((3-methylene-1-(phenylthio)cyclobutyl)methyl)thio)-3-thiabicyclo[3.1.1]heptane (18v')



R_f 0.19 (98:2 pentane / Et_2O).

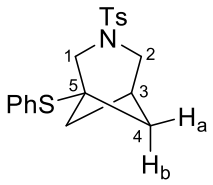
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.55-7.49 (2H, m, Ar H), 7.37-7.30 (3H, m, Ar H), 4.90 (2H, p, *J* = 2.3 Hz, H10), 3.17 (2H, s, H1), 3.04 (2H, d, *J* = 3.3 Hz, H2), 2.95-2.91 (2H, m, H8), 2.84-2.79 (2H, m, H8), 2.82 (2H, s, H6), 2.75 (1H, tt, *J* = 7.3, 3.4 Hz, H3), 2.27-2.19 (2H, m, $H4_b$), 2.12-2.05 (2H, m, $H4_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 141.9, 135.1, 132.7, 129.1, 128.7, 108.8, 47.8, 47.3, 44.6, 38.5, 38.4, 38.0, 32.8, 30.6, 29.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3073, 2935, 1678, 1475, 1438, 1260.

HRMS (ES^+) calc. for $C_{18}H_{22}S_3Na$ $[M+Na]^+$ 357.0776, found 357.0768.

1-(Phenylthio)-3-tosyl-3-azabicyclo[3.1.1]heptane (18w)



Synthesised in accordance with *General Procedure 1*, using 3-(*N*-tosyl)-aza[.3.1.1]propellane (1.33 mL, 0.15 M in THF, 0.200 mmol, 1.0 equiv.) and PhSH (20.5 µL 0.200 mmol, 1.0 equiv.). Purification by column chromatography (SiO_2, pentane/Et_2O 7:3) gave the product **18w** (35 mg, 97 µmol, 48%) as a white solid.

R_f 0.23 (7:3 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.3 Hz, Ar H), 7.42–7.24 (7H, m, Ar H), 3.53 (2H, s, H1), 3.42 (2H, d, *J* = 2.6 Hz, H2), 2.49 (1H, tt, *J* = 6.5, 2.7 Hz, H3), 2.43 (3H, s, Ts), 2.16–2.05 (2H, m, $H4_b$), 1.50–1.40 (2H, m, $H4_a$).

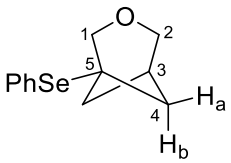
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.4, 135.1, 134.7, 131.2, 129.8, 129.1, 128.7, 127.3, 54.8, 49.6, 48.5, 38.0, 29.7, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2943, 1340, 1164, 1123, 1012.

HRMS (ES^+) calc. for $C_{19}H_{22}NO_2S_2$ $[M+H]^+$ 360.1087, found 360.1089.

m.p. 99 °C

1-(Phenylselenyl)-3-oxabicyclo[3.1.1]heptane (18x)



Synthesised in accordance with *General Procedure 1* using benzeneselenol (35.0 mg, 0.220 mmol, 1.1 equiv.) and oxa[3.1.1]propellane (0.80 mL, 0.200 mmol, 1.0 equiv., 0.24 M in Et_2O), stirred at ambient temperature for 1 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 9:1) to afford the product **18x** (47.0 mg, 0.190 mmol, 93%) as a colourless solid.

R_f = 0.2 (99:1 pentane / Et_2O)

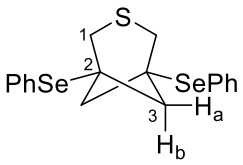
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.54–7.53 (2H, m, ArH), 7.35–7.27 (3H, m, ArH), 3.99 (2H, s, H1), 3.88 (2H, d, *J* = 2.1 Hz, H2), 2.52 (1H, tt, *J* = 6.8, 2.2 Hz, H3), 2.33–2.27 (2H, m, $H4_b$), 1.98–1.94 (2H, m, $H4_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 136.6, 129.1, 128.4, 126.9, 75.5, 69.9, 46.4, 39.1, 34.7.

IR (thin film, ν_{max} / cm^{-1}): 2947, 2855, 1578, 1473, 1435, 1232, 1122, 1038.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{12}H_{15}OSe]^+$ 255.0283, found 255.0274.

1,5-Bis(phenylselanyl)-3-thiabicyclo[3.1.1]heptane (18y)



To a solution of 3-thia[3.1.1]propellane (1.15 mL, 0.13 M, 0.150 mmol, 1.0 equiv.) in Et_2O was added diphenyl diselenide (46.8 mg, 0.150 mmol, 1.0 equiv.) and the mixture was stirred for 3 h at rt. The mixture was concentrated under reduced pressure, and the residue purified by column chromatography (SiO_2, pentane/Et_2O 98:2) to give the product **18y** (43.4 mg, 0.102 mmol, 68% approx.) as a pale yellow oil, which contained a small unidentified impurity that co-eluted with the product. Trituration from pentane removed this impurity with some loss of yield to give the product (21.8 mg, 51.4 μmol, 34%) as a white crystalline solid.

R_f 0.12 (98:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 (4H, d, *J* = 6.6 Hz, Ar H), 7.39-7.32 (2H, m, Ar H), 7.32-7.27 (4H, m, Ar H), 3.21 (4H, s, H1), 2.73-2.63 (2H, m, $H3_b$), 2.61-2.52 (2H, m, $H3_a$).

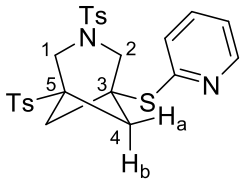
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.7, 129.3, 128.8, 127.2, 47.4, 43.9, 38.1.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3070, 2930, 1475, 1436, 1200, 1065.

HRMS (ES^+) calc. for $C_{18}H_{19}SSe_2$ $[M+H]^+$ 426.9532, found 426.9544.

m.p. 87 °C

1-(Pyridin-2-ylthio)-3,5-ditosyl-3-azabicyclo[3.1.1]heptane (18z)



Prepared according to the literature procedure[8]. To a solution of *S*-2-pyridyl tolylthiosulfonate (54.3 mg, 0.205 mmol, 1.0 equiv.) in dry MeCN (1.5 mL) was added of 3-(*N*-tosyl)-aza[3.1.1]propellane (2.05 mL, 0.15 M in THF, 0.307 mmol, 1.5 equiv.) and the mixture was stirred at 60 °C for 16 h. The mixture was then cooled to rt, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, pentane/EtOAc 7:3) to give the product **18z** (51.9 mg, 0.101 mmol, 49%) as a white solid.

R_f 0.29 (7:3 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.29 (1H, ddd, *J* = 4.9, 1.9, 0.9 Hz, Ar H), 7.67 (2H, d, *J* = 8.3 Hz, Ts), 7.63 (2H, d, *J* = 8.3 Hz, Ts), 7.49 (1H, td, *J* = 7.7, 1.9 Hz, Ar H), 7.37 (2H, d, *J* = 8.0 Hz, Ts), 7.29 (2H, d, *J* = 8.0 Hz, Ts), 7.11 (1H, d, *J* = 8.0 Hz, Ar H), 7.02 (1H, ddd, *J* = 7.4, 4.9, 1.1 Hz, Ar H), 3.82 (2H, s, H1/2), 3.55 (2H, s, H1/2), 2.81-2.71 (2H, m, $H4_b$), 2.49 (3H, s, Ts), 2.45 (3H, s, Ts), 2.00-1.90 (2H, m, $H4_a$).

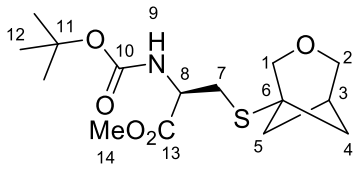
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.9, 149.7, 145.7, 143.9, 136.6, 134.4, 132.3, 130.3, 129.9, 129.3, 127.5, 123.7, 120.6, 60.6, 53.8, 48.0, 43.1, 39.0, 21.9, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2926, 1578, 1416, 1317, 1160.

HRMS (ES$^+$) calc. for $C_{25}H_{27}N_2O_4S_3$ [M+H]$^+$ 515.1128, found 515.1136.

m.p. 164 °C

Methyl *S*-(3-oxabicyclo[3.1.1]heptan-1-yl)-N-(*tert*-butoxycarbonyl) cysteinate (18aa)



Synthesised in accordance with *General Procedure 1* using *N*-(*tert*-Butoxycarbonyl)-L-cysteine methyl ester (47.0 mg, 0.200 mmol, 1 equiv.), oxa[3.1.1]propellane (1.00 mL, 0.260 mmol, 1.3 equiv., 0.27 M in diethyl ether) and BEt_3 (20.0 µL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 2.5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to afford **18aa** (44.0 mg, 0.130 mmol, 67%) as a colourless oil.

Scaled up synthesis:

Synthesised in accordance with *General Procedure 1* using *N*-(*tert*-Butoxycarbonyl)-L-cysteine methyl ester (240 mg, 1.00 mmol, 1 equiv.), oxa[3.1.1]propellane (4.80 mL, 1.30 mmol, 1.3 equiv., 0.27 M in diethyl ether) and BEt_3 (0.10 mL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 2.5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to afford **18aa** (200 mg, 0.610 mmol, 61%) as a light yellow oil.

$\mathbf{R_f}$ = 0.3 (8:2 pentane / Et_2O)

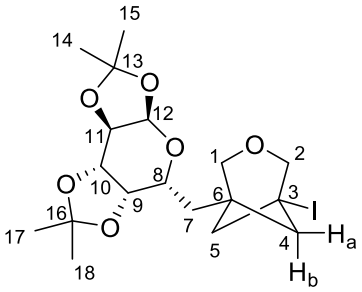
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.28 (1H, d, *J* = 7.9 Hz, H9), 4.52 (1H, d, *J* = 5.5 Hz, H8), 3.88 (2H, s, H1), 3.87 (2H, d, *J* = 2.2 Hz, H2), 3.77 (3H, s, H14), 2.95 (1H, dd, *J* = 13.4, 4.9 Hz, H7), 2.90 (1H, dd, *J* = 13.2, 5.3 Hz, H7), 2.50 (1H, tt, *J* = 6.9, 2.2 Hz, H3), 2.17 (2H, m, H4/5), 1.90 (2H, m, H4/5), 1.45 (9H, s, H12).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 171.3, 155.2, 80.4, 74.8, 69.7, 53.5, 52.8, 48.0, 38.0, 37.9, 32.7, 31.2, 28.5.

IR (thin film, ν_{max} / cm^{-1}): 3352, 2975, 2861, 1748, 1714, 1508, 1439, 1362, 1314, 1167, 1044.

HRMS (ESI+) [M+H]$^+$ calculated for $[C_{15}H_{26}NO_5S]^+$ 332.1526, found 332.1520.

(3aR,5R,5aS,8aS,8bR)-5-((5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (18ab)



Synthesised in accordance with *General Procedure 3*, using 3-oxa[3.1.1]propellane (1.61 mL, 0.14 M in Et_2O, 0.225 mmol, 1.5 equiv.), (3aR,5S,5aR,8aS,8bR)-5-(iodomethyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran[9] (55.5 mg, 0.150 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (2.5 mg, 3.8 µmol, 2.5 mol%). The mixture was stirred and irradiated with 456 nm blue light in a photobox with fan cooling for 16 h. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product **18ab** (24.5 mg, 52.5 µmol, 35%) as a white solid.

R_f 0.16 (9:1 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.48 (1H, d, *J* = 5.2 Hz, H12), 4.56 (1H, dd, *J* = 7.9, 2.4 Hz, H10), 4.27 (1H, dd, *J* = 5.1, 2.4 Hz, H11), 4.13 (2H, s, H2), 4.01 (1H, dd, *J* = 7.9, 1.9 Hz, H9), 3.84 (1H, dd, *J* = 9.7, 1.4 Hz, H1), 3.76 (1H, dd, *J* = 9.6, 1.5 Hz, H1), 3.73 (1H, dt, *J* = 10.2, 2.2 Hz, H8), 2.64 (1H, d, *J* = 8.8 Hz, H4$_b$/H5$_b$), 2.55 (1H, d, *J* = 8.9 Hz, H4$_b$/H5$_b$), 2.45 (1H, t, *J* = 8.3 Hz, H4$_a$/H5$_a$), 2.41 (1H, t, *J* = 8.3 Hz, H4$_a$/H5$_a$), 1.80 (1H, dd, *J* = 14.9, 10.2 Hz, H7), 1.55 (3H, s, H14/15), 1.49 (1H, dd, *J* = 14.9, 2.3 Hz, H7), 1.43 (3H, s, H14/15/17/18), 1.33 (3H, s, H14/15/17/18), 1.32 (3H, s, H14/15/17/18).

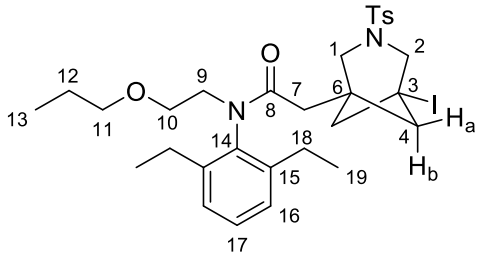
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 109.3, 108.6, 96.7, 78.1, 73.7, 73.0, 71.1, 70.3, 64.4, 49.2, 48.6, 46.3, 36.9, 29.4, 26.3, 26.1, 25.0, 24.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2986, 1383, 1212, 1169, 1071.

HRMS (ES$^+$) calc. for $C_{18}H_{28}IO_6$ $[M+H]^+$ 467.0925, found 467.0928.

m.p. 149 °C

N-(2,6-Diethylphenyl)-2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)-N-(2-propoxyethyl)acetamide (18ac)



Synthesised in accordance with *General procedure 3*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.07 mL, 0.14 M in THF, 0.150 mmol, 1.5 equiv.), N-(2,6-diethylphenyl)-2-iodo-N-(2-propoxyethyl)acetamide[4] (40.3 mg, 0.100 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 µmol, 2.5 mol%). The mixture was stirred and irradiated with 456 nm blue light in a photobox with fan cooling

for 16 h. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product **18ac** (30.9 mg, 47.3 µmol, 47%) as a colourless oil.

R_f 0.34 (8:2 pentane / EtOAc).

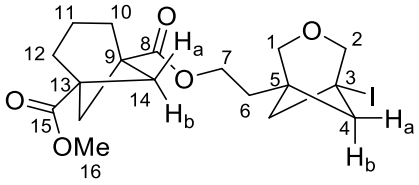
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.3 Hz, Ts Ar), 7.37-7.30 (3H, m, H17, Ts Ar), 7.20 (2H, d, *J* = 7.7 Hz, H16), 3.80 (2H, s, H1/2), 3.67 (2H, t, *J* = 6.3 Hz, H9/10), 3.53 (2H, t, *J* = 6.2 Hz, H9/10), 3.37 (2H, s, H1/2), 3.31 (2H, t, *J* = 6.7 Hz, H11), 2.56 (2H, m, H18), 2.49-2.40 (5H, m, H18/Ts Me), 2.40-2.34 (2H, m, $H4_b$), 2.21-2.14 (2H, m, $H4_a$), 1.96 (2H, s, H7), 1.51 (2H, qt, *J* = 7.2, 7.1 Hz, H12), 1.26 (6H, t, *J* = 7.5 Hz, H19), 0.86 (3H, t, *J* = 7.4 Hz, H13)

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 170.4, 143.7, 141.2, 139.0, 134.6, 130.0, 128.8, 127.4, 126.8, 72.9, 67.6, 59.2, 52.4, 49.4, 49.3, 42.1, 41.3, 24.0, 23.4, 23.0, 21.7, 14.4, 10.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2970, 1654, 1459, 1400, 1342, 1160.

HRMS (ES^+) calc. for $C_{30}H_{42}IN_2O_4S$ $[M+H]^+$ 653.1905, found 653.1895.

1-(2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)ethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (18ad)



Synthesised in accordance with *General Procedure 3*, using 3-oxa[3.1.1]propellane (1.07 mL, 0.14 M in Et_2O, 0.150 mmol, 1.5 equiv.), 1-(2-iodoethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate **S1** (35.2 mg, 0.100 mmol, 1.0 equiv.) and *fac*-$Ir(ppy)_3$ (1.6 mg, 2.5 µmol, 2.5 mol%). The mixture was stirred and irradiated with 456 nm blue light in a photobox with fan cooling for 16 h. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product **18ad** (19.8 mg, 44.2 µmol, 44%) as a colourless oil.

R_f 0.30 (8:2 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.13 (2H, s, H1/2), 4.02 (2H, t, *J* = 6.4 Hz, H7), 3.76 (2H, s, H1/2), 3.68 (3H, s, H16), 2.55-2.50 (2H, m, $H4_b$), 2.50-2.46 (2H, m, $H14_b$), 2.46-2.41 (2H, m, $H4_a$), 2.01-1.87 (6H, m, H10/11/12), 1.85-1.77 (2H, m, $H14_a$), 1.73 (2H, t, *J* = 6.4 Hz, H6).

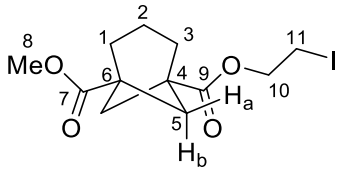
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 175.5, 175.0, 78.0, 72.5, 61.0, 52.0, 48.8, 46.0, 42.4, 38.1, 35.3, 29.6, 29.5, 28.2, 16.1.

Note: both C9 and C13 appear at 42.4 ppm.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2952, 1731, 1287, 1220, 1128.

HRMS (ES^+) calc. for $C_{18}H_{26}IO_5$ $[M+H]^+$ 449.0820, found 449.0814.

1-(2-Iodoethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (S3)



To a stirred solution of 5-(methoxycarbonyl)bicyclo[3.1.1]heptane-1-carboxylic acid [10,11] (198 mg, 1.00 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) at 0 °C was added 2-iodoethanol (0.156 mL, 2.00 mmol, 2.0 equiv.), DMAP (183 mg, 1.50 mmol, 1.5 equiv.) and EDCI.HCl (383 mg, 2.00 mmol, 2.0 equiv.). The mixture was stirred at 0 °C for 2 h, then $NaHCO_3$ sat. (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL), then the organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product **S3** (208 mg, 0.591 mmol, 59%) as a colourless oil.

R_f 0.25 (9:1 pentane / EtOAc).

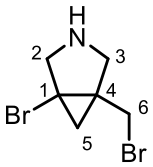
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.30 (2H, t, *J* = 6.7 Hz, H10), 3.66 (3H, s, H8), 3.28 (2H, t, *J* = 6.7 Hz, H11), 2.56-2.46 (2H, m, $H5_b$), 2.05-1.96 (4H, m, H1/3), 1.94-1.85 (2H, m, H2), 1.87-1.78 (2H, m, $H5_a$)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 175.5, 174.4, 64.4, 51.9, 42.4, 42.4, 38.1, 29.6, 29.6, 16.0, 0.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2952, 1731, 1455, 1286, 1219, 1125.

HRMS (ES^+) calc. for $C_{12}H_{18}IO_4$ $[M+H]^+$ 353.0244, found 353.0244.

1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (19)



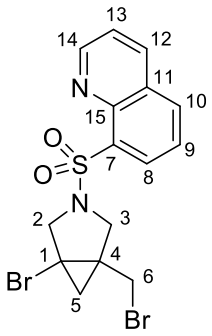
To a solution of HBr in acetic acid (33%, 12.1 mL, 73.3 mmol, 30 equiv.) was added phenol (2.30 g, 24.4 mmol, 10 equiv.). 1-Bromo-5-(bromomethyl)-3-tosyl-3-azabicyclo[3.1.0]hexane **17** (1.00 g, 2.44 mmol, 1.0 equiv.) was added and the mixture was stirred at 70 °C for 2 h. The mixture was then made adjusted to pH 8 with 1 M aq NaOH (250 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product **19** (2.45 g, 25% w/w, 2.40 mmol, 98%) as an orange oil. The yield was determined by NMR; the doublet at 3.39 ppm was integrated relative to a CH_2Cl_2 internal standard. The crude product was taken forward without further purification to all subsequent amine functionalisation steps.

R_f 0.19 (3:7 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.64 (2H, s, H6), 3.43 (1H, d, *J* = 11.8 Hz, H2/3), 3.27 (1H, d, *J* = 11.8 Hz, H2/3), 3.20 (1H, d, *J* = 11.9 Hz, H2/3), 3.10 (1H, d, *J* = 11.9 Hz, H2/3), 1.37 (1H, d, *J* = 7.1 Hz, H5), 1.27 (3H, d, *J* = 6.9 Hz, H5)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 56.4, 50.6, 41.8, 35.9, 33.8, 22.9.

8-((1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)quinoline (20a)



To a solution of **19** (812 mg, 16% w/w, 0.500 mmol, 1.0 equiv.) and Na_2CO_3 (79.5 mg, 0.750 mmol, 1.5 equiv.) in THF (0.8 mL) and water (0.8 mL) was added quinoline-8-sulfonyl chloride (171 mg, 0.750 mmol, 1.5 equiv.) and the mixture was stirred at rt for 1 h. The THF was removed under reduced pressure and the mixture was diltued with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organicc extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Recrystallisation from Et_2O at -20 °C gave the product **20a** (102 mg, 0.229 mmol, 46%) as a colourless crystalline solid.

R_f 0.17 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.08 (1H, dd, *J* = 4.2, 1.8 Hz, Ar H), 8.44 (1H, dd, *J* = 7.4, 1.5 Hz, Ar H), 8.24 (1H, dd, *J* = 8.3, 1.8 Hz, Ar H), 8.03 (1H, dd, *J* = 8.2, 1.5 Hz, Ar H), 7.60 (1H, t, *J* = 7.8 Hz, Ar H), 7.53 (1H, dd, *J* = 8.3, 4.2 Hz, Ar H), 4.34 (1H, d, *J* = 9.9 Hz, H2/3), 4.00 (1H, d, *J* = 9.9 Hz, H2/3), 3.81 (1H, d, *J* = 9.9 Hz, H2/3), 3.76 (1H, d, *J* = 10.0 Hz, H2/3), 3.55 (1H, d, *J* = 11.0 Hz, H6), 3.51 (1H, d, *J* = 11.1 Hz, H6), 1.27 (1H, d, *J* = 6.7 Hz, H5), 1.12 (1H, d, *J* = 6.9 Hz, H5).

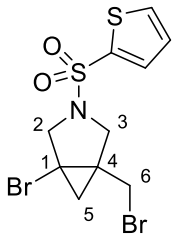
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.5, 144.1, 137.1, 136.7, 133.9, 133.1, 129.2, 125.7, 122.4, 56.9, 52.0, 38.7, 35.3, 32.8, 24.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2877, 1494, 1338, 1164, 1145.

HRMS (ES^+) calc. for $C_{15}H_{15}N_2O_2S$ $[M+H]^+$ 444.9216, found 444.9211.

m.p. 130 °C

1-Bromo-5-(bromomethyl)-3-(thiophen-2-ylsulfonyl)-3-azabicyclo[3.1.0]hexane (20b)



To a solution of **19** (810 mg, 16% w/w, 0.500 mmol, 1.0 equiv.) and Na_2CO_3 (79.5 mg, 0.750 mmol, 1.5 equiv.) in THF (0.8 mL) and water (0.8 mL) was added thiophene-2-sulfonyl chloride (137 mg, 0.750 mmol, 1.5 equiv.) and the mixture was stirred at rt for 1 h. The THF was removed under reduced pressure and the mixture was diltued with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Recrystallisation from Et_2O at -20 °C gave the product **20b** (111 mg, 0.277 mmol, 55%) as a white crystalline solid.

R_f 0.21 (7:3 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (1H, d, *J* = 5.1 Hz, Ar H), 7.60 (1H, dd, *J* = 3.8, 1.3 Hz, Ar H), 7.18 (1H, dd, *J* = 5.0, 3.7 Hz, Ar H), 3.99 (2H, d, *J* = 9.5 Hz, H2/3), 3.67 (2H, d, *J* = 9.7 Hz, H2/3), 3.56 (2H, d, *J* = 11.1 Hz, H6), 3.49 (2H, d, *J* = 11.1 Hz, H6), 3.38 (2H, d, *J* = 9.6 Hz, H2/3), 3.36 (2H, d, *J* = 9.6 Hz, H2/3), 1.49 (2H, d, *J* = 6.8 Hz, H5), 1.23 (2H, d, *J* = 6.8 Hz, H5).

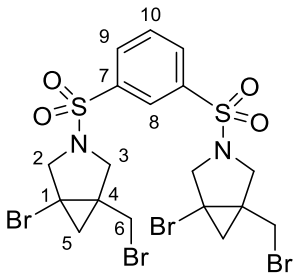
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.2, 132.9, 132.7, 128.0, 56.8, 52.0, 37.8, 34.7, 32.9, 24.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2861, 1722, 1358, 1228, 1165, 1045, 1018.

HRMS (ES^+) calc. for $C_{10}H_{12}NO_2S_2$ $[M+H]^+$ 399.8671, found 399.8670.

m.p. 98 °C

1,3-Bis((1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)benzene (20c)



To a solution of **19** (510 mg, 25% w/w, 0.500 mmol, 2.0 equiv.) and Na_2CO_3 (79.5 mg, 0.750 mmol, 3.0 equiv.) in THF (0.8 mL) and water (0.8 mL) was added benzene-1,3-disulfonyl dichloride (68.8 mg, 0.250 mmol, 1.0 equiv.) and the mixture was stirred at rt for 1 h. The THF was removed under reduced pressure and the mixture was diltued with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Trituration from Et_2O at gave the product **20c** (43.9 mg, 61.6 µmol, 25%) as a white solid.

R_f 0.21 (1:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.21 (1H, s, H8), 8.05 (2H, dd, J = 7.9, 1.8 Hz, H9), 7.81 (1H, t, J = 7.8 Hz, H10), 4.04 (2H, d, J = 9.5 Hz, H2/3), 3.72 (2H, d, J = 9.6 Hz, H2/3), 3.55 (2H, d, J = 11.2 Hz, H2/3), 3.49 (2H, d, J = 11.0 Hz, H2/3), 3.35-3.24 (4H, m), 1.56 (2H, d, J = 6.9 Hz, H5), 1.27 (2H, d, J = 6.9 Hz, H5)

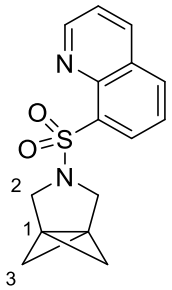
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.7, 138.6, 131.7, 131.7, 130.9, 126.2, 56.6, 56.6, 51.8, 37.5, 37.5, 34.5, 34.5, 32.8, 32.8, 24.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3060, 1438, 1358, 1184, 1120.

HRMS (ES^+) calc. for $C_{18}H_{20}Br_4N_2O_4S_2Na$ $[M+Na]^+$ 730.7490, found 730.7513.

m.p. 97 °C

3-(Quinolin-8-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (21a)



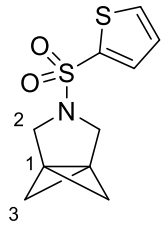
To a stirred solution of **20a** (95.5 mg, 0.214 mmol, 1.0 equiv.), in dry THF (2.1 mL) at -78 °C was added MeLi (0.165 mL, 1.3 M, 0.214 mmol, 1.0 equiv.). The mixture was stirred at -78 °C for 10 min, then at rt for 1 h. $MgSO_4$ (200 mg) was added to the reaction mixture and this was stirred for 10 min. Then the mixture was passed through a celite filter, eluted with THF (1.0 mL). The mixture was partially concentrated under reduced pressure (120 mbar) to remove MeBr and Et_2O, giving the product as a solution in THF (1.80 mL, 0.10 M, 0.173 mmol, 81%), which was stored under nitrogen at -20 °C. The yield was determined by integrating the singlet at 3.79 ppm relative to the THF peak.

^{1}H NMR (500 MHz, C_6D_6) δ_H 8.67 (1H, dd, *J* = 4.2, 1.8 Hz, Ar H), 8.48 (1H, dd, *J* = 7.3, 1.5 Hz, Ar H), 7.62 (1H, dd, *J* = 8.3, 1.8 Hz, Ar H), 7.45 (1H, dd, *J* = 8.2, 1.5 Hz, Ar H), 7.10 (1H, dd, *J* = 8.2, 7.3 Hz, Ar H), 6.90 (1H, dd, *J* = 8.3, 4.2 Hz, Ar H), 3.79 (4H, s, H2), 2.10 (2H, t, *J* = 1.6 Hz, H3), 1.35 (2H, t, *J* = 1.5 Hz, H3).

^{13}C NMR (126 MHz, C_6D_6) δ_C 150.9, 144.6, 139.3, 136.4, 133.1, 133.0, 129.2, 125.7, 122.0, 53.7, 52.1, 23.2.

HRMS (ES^+) calc. for $C_{15}H_{15}N_2O_2S$ $[M+H]^+$ 287.0849, found 287.0853.

3-(Thiophen-2-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (21b)



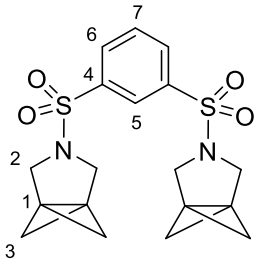
To a stirred solution of **20b** (85.5 mg, 0.213 mmol, 1.0 equiv.), in dry THF (2.1 mL) at -78 °C was added MeLi (0.158 mL, 1.35 M in Et_2O, 0.213 mmol, 1.0 equiv.). The mixture was stirred at -78 °C for 10 min, then at rt for 1 h. $MgSO_4$ (200 mg) was added to the reaction mixture and this was stirred for 10 min. Then the mixture was passed through a celite filter and eluted with THF (1.0 mL). The mixture was partially concentrated under reduced pressure (120 mbar) to remove MeBr and Et_2O, giving the product as a solution in THF (1.14 mL, 0.13 M, 0.150 mmol, 70%), which was stored under nitrogen at -20 °C. The yield was determined by integrating the triplet at 1.94 ppm relative to the THF peak.

^{1}H NMR (400 MHz, C_6D_6) δ_H 7.33 (1H, dd, *J* = 3.7, 1.3 Hz, Ar H), 7.01 (1H, dd, *J* = 5.0, 1.3 Hz, Ar H), 6.62 (1H, dd, *J* = 5.0, 3.7 Hz, Ar H), 3.23 (4H, s, H2), 1.94 (2H, t, *J* = 1.7 Hz, H3), 1.29 (2H, t, *J* = 1.6 Hz, H3).

^{13}C NMR (101 MHz, C_6D_6) δ_C 138.2, 132.2, 131.7, 126.2, 53.8, 52.2, 22.7.

HRMS (ES^+) calc. for $C_{10}H_{12}NO_2S_2$ $[M+H]^+$ 242.0304, found 242.0301.

1,3-Bis((3-azatricyclo[3.1.1.01,5]heptan-3-yl)sulfonyl)benzene (21c)

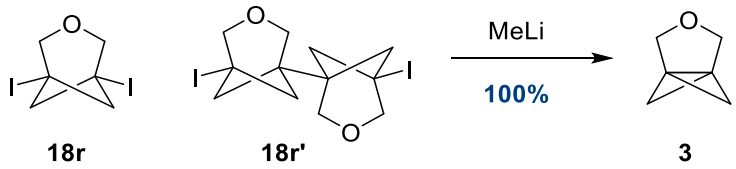


To a stirred solution of **20c** (50.8 mg, 71.3 µmol, 1.0 equiv.), in dry THF (1.0 mL) at -78 °C was added MeLi (0.110 mL, 1.3 M in Et_2O, 0.143 mmol, 2.0 equiv.). The mixture was stirred at -78 °C for 10 min, then at rt for 1 h. $MgSO_4$ (100 mg) was added to the reaction mixture and this was stirred for 10 min. Then the mixture was passed through a celite filter and eluted with THF (1.0 mL). The mixture was partially concentrated under reduced pressure (120 mbar) to remove MeBr and Et_2O, giving the product as a solution in THF (0.40 mL, 0.18 M, 70.9 µmol, 99%), which was stored under nitrogen at -20 °C. The yield was determined by integrating the triplet at 1.98 ppm relative to a $CHCl_3$ internal standard.

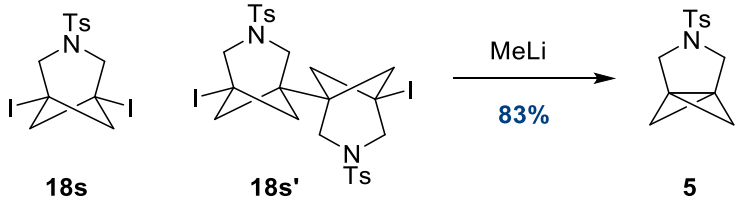
^{1}H NMR (400 MHz, C_6D_6) δ_H 8.37 (1H, t, *J* = 1.8 Hz, H5), 7.82 (2H, dd, *J* = 7.8, 1.8 Hz, H6), 7.25 (1H, t, *J* = 7.8 Hz, H7), 3.17 (8H, s, H2), 1.98 (4H, t, *J* = 1.7 Hz, H3), 1.30 (4H, t, *J* = 1.7 Hz, H3).

^{13}C NMR (101 MHz, C_6D_6) δ_C 139.6, 131.2, 130.6, 126.1, 53.8, 52.1, 22.6.

5.4. Alternative method for propellane formation:

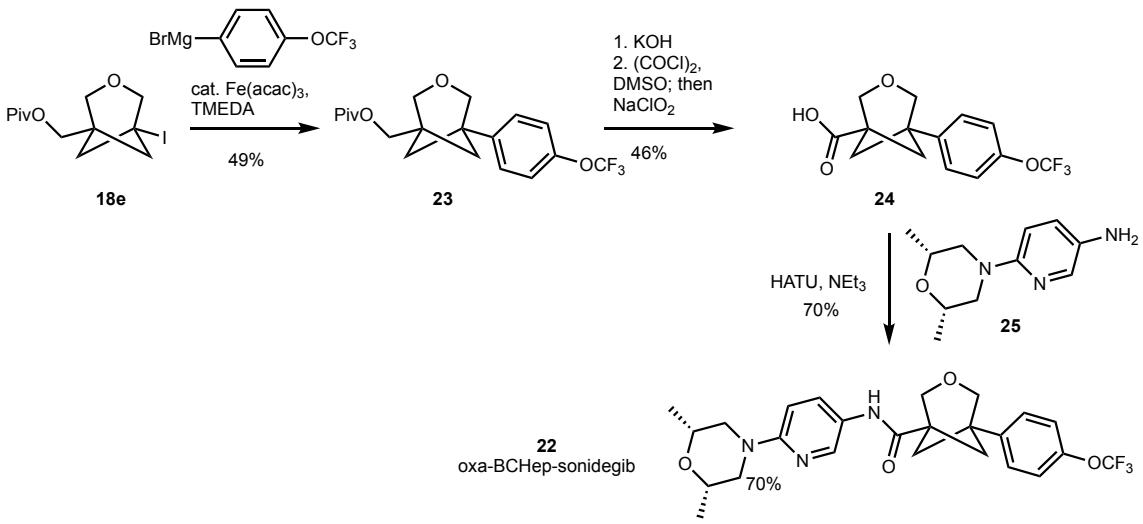


A 1.4:1.0 mixture of **18r:18r'** (10.9 mg total, including **18r** (9.14 mg, 26.1 µmol, 1.0 equiv.) and **18r'** (1.75 mg, 3.92 µmol, 0.15 equiv.)) was dissolved in Et_2O (0.40 mL) and cooled to -78 °C. MeLi (26.0 µL, 1.35 M solution in Et_2O, 35.1 µmol, 1.3 equiv.) was added and the mixture was stirred at -78 °C for 10 min. The mixture was then stirred at rt for 1 h. The yield was determined directly from the reaction mixture by ^1H NMR spectroscopy using a CH_2Cl_2 internal standard (5.0 µL). The mixture contained 34.1 µmol product, 100% yield, and the NMR spectra matched that reported above for compound **3**.

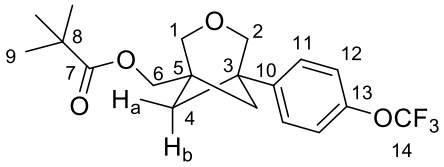


A 1.4:1.0 mixture of **18s:18s'** (21.0 mg total, including **18s** (10.2 mg, 20.3 µmol, 1.0 equiv.) and **18s'** (10.8 mg, 14.4 µmol, 0.70 equiv.)) was dissolved in THF (0.17 mL) and cooled to -78 °C. MeLi (32.1 µL, 1.3 M solution in Et_2O, 41.7 µmol, 2.1 equiv.) was added and the mixture was stirred at -78 °C for 10 min. The mixture was then stirred at rt for 1 h. The yield was determined directly from the reaction mixture by ^1H NMR spectroscopy using a CH_2Cl_2 internal standard (2.5 µL). The mixture contained 40.6 µmol product, 83% yield, and the NMR spectra matched that reported above for compound **5**.

5.5 Synthesis of Sonidegib analogue



(5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (23)



To prepare the Grignard reagent, Mg turnings (88.0 mg, 3.62 mmol, 1.2 equiv.) were added to a flask which was heated under vacuum for 1 minute. THF (2.5 mL) and I_2 (one crystal) were added, then 1-bromo-4-(trifluoromethoxy)benzene (0.448 mL, 3.02 mmol, 1.0 equiv.) was added dropwise. The mixture was heated under reflux for 2 h, then cooled to room temperature. The concentration of the reagent was determined by iodometric titration.

To a solution of **18e** (134 mg, 0.396 mmol, 1.0 equiv.) and $Fe(acac)_3$ (28.1 mg, 79.2 µmol, 0.2 equiv.) in THF (0.2 mL) was added TMEDA (24.0 µL, 0.158 mmol, 0.4 equiv.) and the mixture was stirred for 5 min. A solution of (4-(trifluoromethoxy)phenyl)magnesium bromide in THF (0.81 mL, 0.98 M, 2.0 equiv.) was added slowly over 2 h. The mixture was stirred at room temperature for an additional 2 h, then quenched with NH_4Cl sat. (3 mL). The mixture was extracted with Et_2O (3 x 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the title compound **23** (71.7 mg, 0.193 mmol, 49%) as a colourless oil.

R_f 0.22 (9:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.16 (1H, d, *J* = 8.0 Hz, H11/12), 7.13-7.08 (2H, m, H11/12), 3.96 (2H, s, H6), 3.89 (2H, s, H1/2), 3.85 (2H, s, H1/2), 2.16-2.08 (2H, m, $H4_b$), 2.07-2.00 (2H, m, $H4_a$), 1.20 (9H, s, H9).

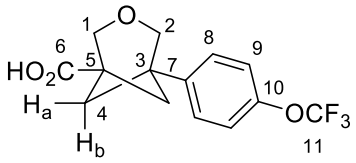
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.5, 148.0, 143.3, 127.0, 120.6 (q, *J* = 258.3 Hz), 121.2, 76.3, 71.8, 67.0, 43.8, 39.4, 39.1, 37.5, 27.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F -57.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2934, 1730, 1511, 1260, 1161.

HRMS (ES^+) calc. for $C_{19}H_{24}F_3O_4$ $[M+H]^+$ 373.1621, found 373.1640.

5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxylic acid (24)



To a solution of **23** (71.7 mg, 0.193 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added KOH (23.0 mg, 0.410 mmol, 2.1 equiv.) and the mixture was heated at 50 °C for 20 h. The mixture was then concentrated under reduced pressure and water (3 mL) was added. The mixture was extracted with EtOAc (3 x 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used directly in the next step.

The oxidation was carried out according to the literature procedure[12]. To a solution of oxalyl chloride (21.0 µL, 0.251 mmol, 1.3 equiv.) in CH_2Cl_2 (4 mL) at -78 °C was added a solution of DMSO (20.6 µL, 0.290 mmol, 1.5 equiv.) in CH_2Cl_2 (0.5 mL) dropwise and the mixture was stirred at -78 °C for 1 h. The crude product from the previous step was dissolve in CH_2Cl_2 (0.5 mL) and added to the reaction mixture dropwise. The mixture was stirred at -78 °C for 4 h. NEt_3 (0.11 mL, 0.772 mmol, 4.0 equiv.) was added and the mixture was stirred at rt overnight. The mixture was washed with water (2 x 2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. THF (2 mL) was added, followed by 2-methylbut-2-ene (63.4 µL, 0.598 mmol, 3.1 equiv.). A solution of NaH_2PO_4 (27.8 mg, 0.232 mmol, 1.2 equiv.) in water (0.5 mL) was added. The mixture was cooled to 0 °C, then a solution of $NaClO_2$ (20.9 mg, 0.232 mmol, 1.2 equiv.) in water (0.5 mL) was added dropwise. The mixture was stirred at rt overnight, then concentrated under reduced pressure. The residue was diluted with water (3 mL) then acidified with conc. HCl to pH 5. The mixture was extracted with EtOAc (3 x 3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product (26.8 mg, 88.6 µmol, 46%) as an orange oil which was used directly in the next step without further purification.

R_f 0.28 (2:1 hexane / THF).

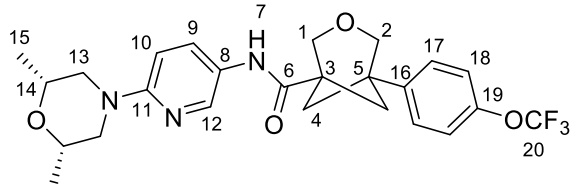
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18-7.08 (4H, m, H8/9), 4.12 (2H, s, H1/2), 3.85 (2H, s, H1/2), 2.56-2.50 (2H, m, $H4_b$), 2.32-2.26 (2H, m, $H4_a$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 176.9, 148.1, 142.5, 126.9, 121.2, 120.6 (q, *J* = 258.2 Hz), 75.5, 69.6, 43.3, 42.9, 38.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F -58.0.

Analytical data matches that previously recorded [12].

N-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxamide (22)



The amide coupling was carried out according to the lietature procedure[12]. To a solution of **24** (26.8 mg, 88.7 µmol, 1.0 equiv.), 6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-amine **25** (18.4 mg, 88.7 µmol, 1.0 equiv.) and HATU (40.5 mg, 0.106 mmol, 1.2 equiv.) in DMF (0.5 mL) was added NEt_3

(49.4 µL, 0.355 mmol, 4.0 equiv.) and the mixture was stirred at 50 °C for 8 h. Water (2 mL) and EtOAc (2 mL) were added. The layers were separated and the organic layer was washed with water (2 x 2 mL) and each wash was back-extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexane / THF 2:1) gave the product (30.5 mg, 62.1 µmol, 70%) as a yellow solid.

R_f 0.24 (2:1 hexane / THF).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.13 (1H, d, *J* = 2.8 Hz, H12), 7.86 (1H, dd, *J* = 9.1, 2.8 Hz, H9), 7.23-7.08 (4H, m, H17/18/7), 6.61 (1H, d, *J* = 9.1 Hz, H10), 4.16 (2H, s, H1/2), 3.97 (1H, dd, *J* = 12.7, 1.8 Hz, H13), 3.88 (2H, s, H1/2), 3.71 (2H, dqd, *J* = 10.5, 6.2, 2.5 Hz, H14), 2.55-2.40 (6H, m, H4/13), 1.26 (3H, s, H15), 1.25 (3H, s, H15).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.1, 156.7, 148.2, 142.4, 140.0, 131.8, 127.0, 125.1, 121.3, 120.6 (q, *J* = 258.5 Hz), 107.1, 75.6, 71.7, 71.3, 51.3, 45.1, 42.4, 38.5, 19.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F -57.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2867, 1651, 1511, 1493, 1256, 1224.

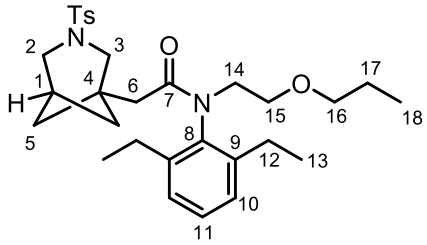
HRMS (ES^+) calc. for $C_{25}H_{28}F_3N_3O_4Na$ $[M+Na]^+$ 514.1924, found 514.1932.

m.p. 202 °C.

Analytical data matches that previously recorded [12].

5.6 Detosylation studies

N-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)-2-(3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetamide (26)



Prepared according to the literature procedure[5]. To a solution of **18ac** (85.5 mg, 0.131 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (2.1 mg, 3.3 µmol, 2.5 mol%) in *t*BuCN (1.0 mL) was added Si(SiMe$_3$)H (72.7 µL, 0.236 mmol, 1.8 equiv.) and the mixture was degassed with N_2 for 5 min. The vial was placed in a photobox and the stirred reaction was irradiated with blue LEDs (Kessil PR160, 456 nm) with fan cooling for 1 h. The reaction mixture was concentrated under reduced pressure and the product was purified by column chromatography (SiO_2, pentane/EtOAc 8:2) to give the product (49.7 mg, 94.4 µmol, 72%) as a pale yellow oil.

R_f 0.23 (8:2 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.70 (d, *J* = 8.2 Hz, 2H, Ts), 7.33 – 7.27 (m, 3H, Ts/H11), 7.19 (d, *J* = 7.7 Hz, 2H, H10), 3.68 (t, *J* = 6.3 Hz, 2H, H14/15), 3.55 (t, *J* = 6.3 Hz, 2H, H14/15), 3.40 (s, 4H, H2/3), 3.31 (t, *J* = 6.8 Hz, 2H, H16), 2.60-2.52 (m, 2H, H12), 2.50 – 2.40 (m, 2H, H12), 2.42 (s, 3H, Ts), 2.34 (tt, *J* = 6.1, 2.7 Hz, 1H, H1), 1.87 (s, 2H, H6), 1.84 – 1.77 (m, 2H, H5), 1.51 (h, *J* = 7.2 Hz, 2H, H17), 1.41 – 1.33 (m, 2H, H5), 1.25 (t, *J* = 7.6 Hz, 6H, H13), 0.85 (t, *J* = 7.4 Hz, 3H, H18).

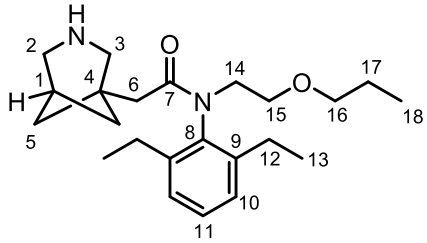
^{13}C NMR ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 171.4, 143.2, 141.3, 139.4, 135.0, 129.7, 128.6, 127.5, 126.7, 72.9, 67.7, 54.6, 50.1, 49.3, 41.1, 39.4, 36.0, 29.8, 23.4, 23.0, 21.7, 14.4, 10.7.

Note: the ^{1}H and ^{13}C spectra show additional peaks due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2964, 1656, 1459, 1396, 1341, 1159.

HRMS (ES^+) calc. for $C_{30}H_{43}N_2O_4S$ $[M+H]^+$ 527.2938, found 527.2938.

2-(3-Azabicyclo[3.1.1]heptan-1-yl)-*N*-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)acetamide (27)



To a solution of **26** (27.6 mg, 52.4 µmol, 1.0 equiv.) in MeOH (1.5 mL) was added Mg powder (25.5 mg, 1.05 mmol, 20 equiv.) and the mixture was sonicated for 2 h. Another portion of Mg was added and the mixture was sonicated for a further 1 h, then stirred at rt for 16 h. HCl (aq., 1M) was added until the mixture became clear and then the mixture was adjusted to pH 8 with sat. $NaHCO_3$ solution. The mixture was extracted with EtOAc (3 x 15 mL), then the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, CH_2Cl_2/NH_3 (7 M, in MeOH) 9:1) gave the product (15.3 mg, 41.2 µmol, 79%) as a yellow oil.

R_f 0.40 (9:1 CH_2Cl_2/NH_3 (7 M, in MeOH) 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 (dd, *J* = 8.3, 7.0 Hz, 1H, H11), 7.19 (d, *J* = 7.7 Hz, 2H, H10), 5.49 (br s, 1H, N-H), 3.67 (t, *J* = 6.3 Hz, 2H, H14/15), 3.52 (t, *J* = 6.2 Hz, 2H, H14/15), 3.49 (s, 2H, H3), 3.40 (d, *J* = 2.5 Hz, 2H, H2), 3.30 (t, *J* = 6.7 Hz, 2H, H16), 2.63 – 2.37 (m, 5H, H1/12), 1.96-1.89 (m, 2H, H5), 1.91 (s, 2H, H6), 1.88 – 1.81 (m, 2H, H5), 1.50 (h, *J* = 7.2 Hz, 2H, H17), 1.25 (t, *J* = 7.6 Hz, 6H, H13), 0.84 (t, *J* = 7.4 Hz, 3H, H18).

^{13}C NMR ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.2, 141.2, 139.0, 128.8, 126.8, 72.9, 67.6, 51.7, 49.3, 47.5, 41.5, 39.4, 35.9, 29.9, 23.4, 22.9, 14.4, 10.6.

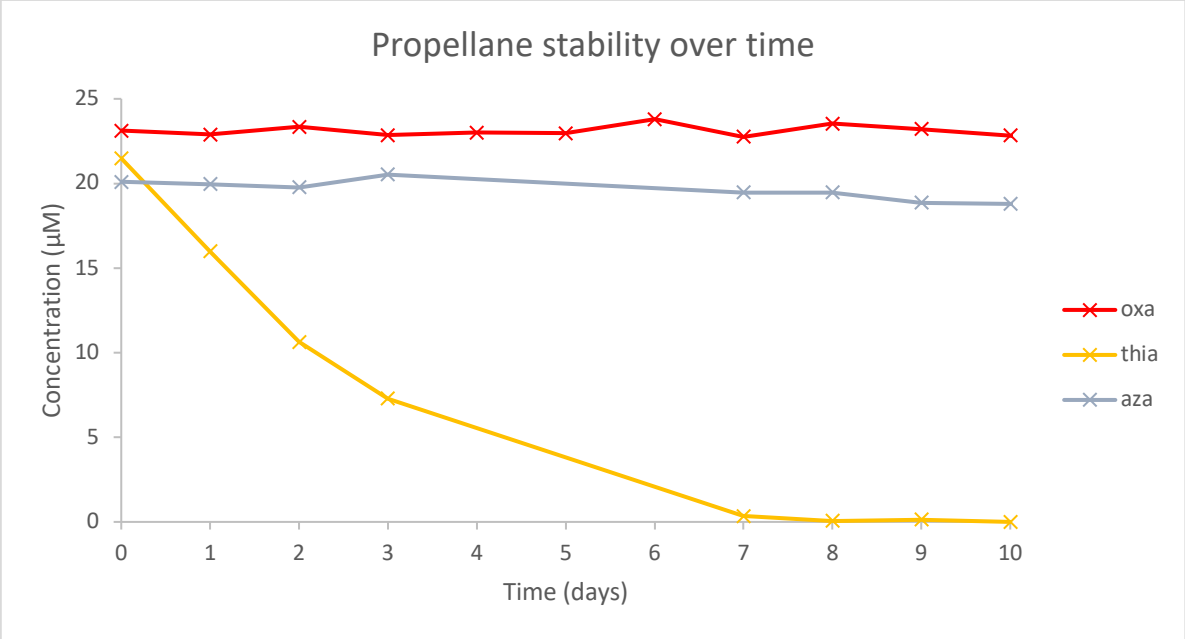
Note: the ^{1}H and ^{13}C spectra show additional peaks due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3462, 2965, 1652, 1457, 1400, 1113.

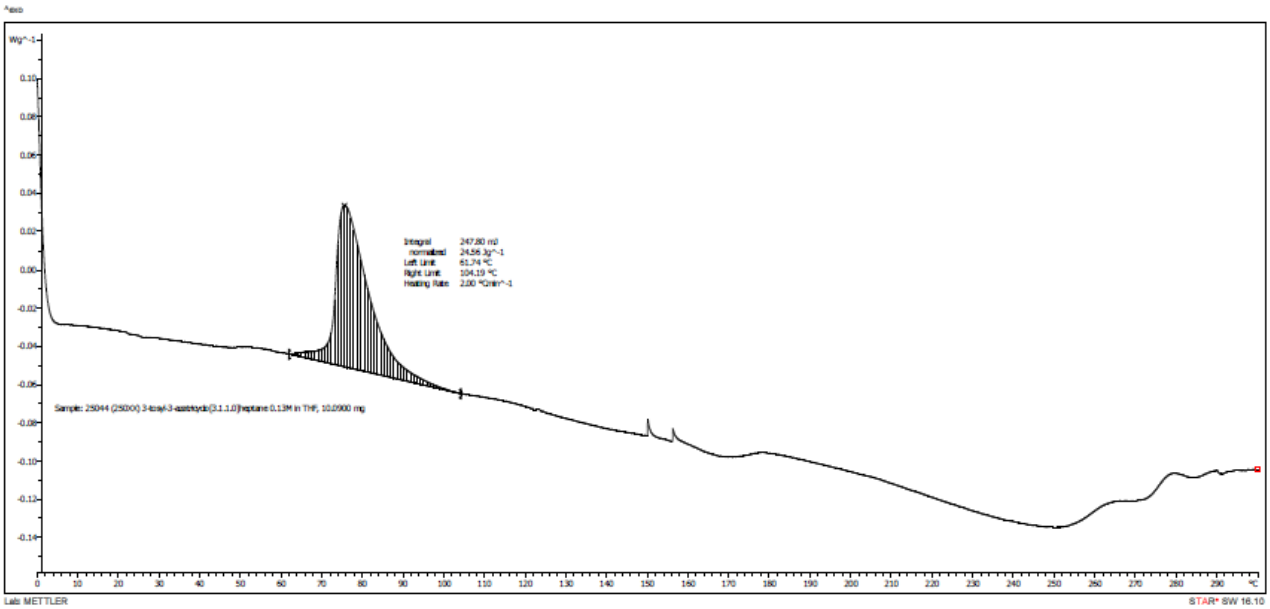
HRMS (ES^+) calc. for $C_{23}H_{37}N_2O_2$ $[M+H]^+$ 373.2850, found 373.2850.

6. Propellane stability

We have analysed the stability of the hetero[3.1.1]propellane solutions by preparing an NMR sample of each propellane and measuring the ^{1}H NMR spectrum of the same sample each day. The samples were prepared in C_6D_6 in air, and the concentrations were calculated by integrating the propellane peaks relative to a DCE internal standard (5 µL). The concentration of each sample was adjusted to be roughly the same by adjusting the amount of C_6D_6 added. Between measurements, the NMR samples were left at rt under air. The concentration of the oxa- and azapropellanes remained essentially constant over the timeframe measured (10 days), however the thiapropellane degraded relatively quickly under ambient conditions.



To further explore the stability of propellane solutions, we have carried out DSC analysis on a standard (0.13 M) solution of 3-NTs[3.1.1]propellane (**5**) in THF. The calorimetry trace is shown below; the major peak observed corresponds to evaporation of THF, and no other significant exothermic event occurs. As such, we believe that solutions of heteropropellanes are likely quite safe to handle and unlikely to decompose with an uncontrolled exotherm.



In terms of the propellane solutions, in light of the above DSC results and NMR results, we do not believe there are any especial hazards in terms of storage. As solutions of propellanes are typically stored at -20 °C under an inert atmosphere, we therefore believe that solutions of **3** and **5** will be stable for several months if stored in this way. However, it is recommended that the concentration of any propellane solution should not exceed 0.5 M, to minimise the risk of decomposition by polymerisation.

7 X-ray Crystallographic Data

Single crystal X-ray diffraction data for **5** were collected using a Rigaku Oxford SuperNova diffractometer and for **18i** using a Rigaku Synergy-DW. Raw frame data was reduced using CrysAlisPro. The structure was solved using 'Superflip'[13] before refinement with CRYSTALS[14,15] as per the SI (CIF). Full refinement details are given in the Supplementary Information CIF file; Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre (CCDC 2412510-2412511) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

Table S2. Crystal data and structure refinement for **5**:

CCDC identification code	2412510	
Empirical formula	C13 H15 N1 O2 S	
Formula weight	249.33	
Temperature	210 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.5561(4)	α = 107.620(5)°
	b = 8.6377(5)	β = 94.191(4)°
	c = 8.8534(4)	γ = 101.295(5)°
Volume	605.37(6) Å³	
Z	2	
Crystal size	0.07 × 0.23 × 0.36 mm³	
Reflections collected	5628	
Independent reflections	2487 [R(int) = 0.028]	
Completeness to theta = 73.913°	99.5%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2485 / 0 / 154	
Goodness-of-fit on F^2	0.9868	
Final R indices [I>2sigma(I)]	R1 = 0.0458, wR2 = 0.1269	
R indices (all data)	R1 = 0.0489, wR2 = 0.1333	

Alerts:

PLAT008_ALERT_5_B No _iucr_refine_reflections_details in the CIF Please Do !

• *This card is present in the data block, but is not recognised by some of the online checking facilities.*

PLAT995_ALERT_1_B Can not Recreate .fcf from Embedded .res & .hkl ! Check

• *The data are included in CRYSTALS format. The .fcf file has been uploaded separately.*

PLAT995_ALERT_1_B Can not Recreate .fcf from Embedded .res & .hkl ! Check

• *The data are included in CRYSTALS format. The .fcf file has been uploaded separately.*

Table S3. Crystal data and structure refinement for **18i**:

CCDC identification code	2412511	
Empirical formula	C16 H26 I N O3	
Formula weight	407.29	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 40.8370(6) Å	α = 90°
	b = 5.9142(1) Å	β = 107.493(2)°
	c = 30.9152(5) Å	γ = 90°
Volume	7121.3(2) Å³	
Z	16	
Crystal size	0.03 × 0.06 × 0.11 mm³	
Reflections collected	155737	
Independent reflections	7350 [R(int) = 0.064]	
Completeness to theta = 73.805°	99.9%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7350 / 0 / 379	
Goodness-of-fit on F^2	0.9920	
Final R indices [I>2sigma(I)]	R1 = 0.0684, wR2 = 0.1657	
R indices (all data)	R1 = 0.0756, wR2 = 0.1760	

Alerts:

PLAT008_ALERT_5_B No _iucr_refine_reflections_details in the CIF Please Do !

• *This card is present in the data block, but is not recognised by some of the online checking facilities.*

PLAT094_ALERT_2_B Ratio of Maximum / Minimum Residual Density .... 4.75 Report

• *These are very close to the iodine atom.*

PLAT995_ALERT_1_B Can not Recreate .fcf from Embedded .res & .hkl ! Check

• *The data are included in CRYSTALS format. The .fcf file has been uploaded separately.*

PLAT995_ALERT_1_B Can not Recreate .fcf from Embedded .res & .hkl ! Check

• *The data are included in CRYSTALS format. The .fcf file has been uploaded separately.*

Table S4. Bond lengths for **5**:

N1	C2	1.491(3) Å	S8	O9	1.4349(13) Å
N1	C5	1.485(2) Å	S8	O10	1.4355(13) Å
N1	S8	1.6298(17) Å	S8	C11	1.7635(19) Å
C2	C3	1.482(3) Å	C11	C12	1.390(2) Å
C2	H21	0.973 Å	C11	C16	1.391(2) Å
C2	H22	0.967 Å	C12	C13	1.382(3) Å
C3	C4	1.559(3) Å	C12	H121	0.923 Å
C3	C6	1.479(3) Å	C13	C14	1.390(3) Å
C3	C7	1.483(3) Å	C13	H131	0.926 Å
C4	C5	1.494(3) Å	C14	C15	1.392(3) Å
C4	C6	1.475(3) Å	C14	C17	1.504(3) Å
C4	C7	1.481(3) Å	C15	C16	1.381(3) Å
C5	H51	0.967 Å	C15	H151	0.920 Å
C5	H52	0.984 Å	C16	H161	0.941 Å
C6	H61	0.951 Å	C17	H171	0.930 Å
C6	H62	0.953 Å	C17	H172	0.946 Å
C7	H71	0.949Å	C17	H173	0.947 Å
C7	H72	0.950 Å			

Table S5. Bond angles for **5**:

C2	N1	C5	111.38(17)°	C4	C7	H71	117.2°
C2	N1	S8	118.93(14)°	H71	C7	H72	110.8°
C5	N1	S8	119.95(14)°	C3	C7	H72	120.0°
N1	C2	C3	106.72(16)°	C4	C7	H72	119.7°
N1	C2	H21	110.7°	N1	S8	O9	106.23(9)°
C3	C2	H21	109.8°	N1	S8	O10	106.35(9)°
N1	C2	H22	111.8°	O9	S8	O10	120.45(9)°
C3	C2	H22	109.0°	N1	S8	C11	106.78(9)°
H21	C2	H22	108.9°	O9	S8	C11	108.36(9)°
C2	C3	C4	107.88(17)°	O10	S8	C11	107.92(9)°
C2	C3	C6	121.7(2)°	S8	C11	C12	120.22(14)°
C4	C3	C6	58.02(14)°	S8	C11	C16	118.87(14)°
C2	C3	C7	121.9(2)°	C12	C11	C16	120.77(18)°
C4	C3	C7	58.20(15)°	C11	C12	C13	118.89(18)°
C6	C3	C7	98.5(2)°	C11	C12	H121	120.8°
C3	C4	C5	107.29(16)°	C13	C12	H121	120.3°
C3	C4	C6	58.24(14)°	C12	C13	C14	121.74(18)°
C5	C4	C6	121.9(2)°	C12	C13	H131	119.3°
C3	C4	C7	58.31(14)°	C14	C13	H131	118.9°
C5	C4	C7	121.1(2)°	C13	C14	C15	118.01(18)°
C6	C4	C7	98.8(2)°	C13	C14	C17	122.0(2)°

C4	C5	N1	106.73(17)°	C15	C14	C17	120.0(2)°
C4	C5	H51	107.6°	C14	C15	C16	121.59(18)°
N1	C5	H51	110.7°	C14	C15	H151	119.9°
H51	C5	H52	110.2°	C16	C15	H151	118.5°
C4	C5	H52	110.5°	C11	C16	C15	118.99(18)°
N1	C5	H52	111.0°	C11	C16	H161	121.6°
C3	C6	C4	63.73(15)°	C15	C16	H161	119.4°
C3	C6	H61	118.4°	C14	C17	H171	110.3°
C4	C6	H61	120.9°	C14	C17	H172	111.9°
H61	C6	H62	110.8°	H171	C17	H172	108.4°
C3	C6	H62	117.3°	H171	C17	H173	108.8°
C4	C6	H62	118.6°	H172	C17	H173	108.5°
C3	C7	C4	63.49(15)°	C14	C17	H173	108.8°
C3	C7	H71	118.6°				

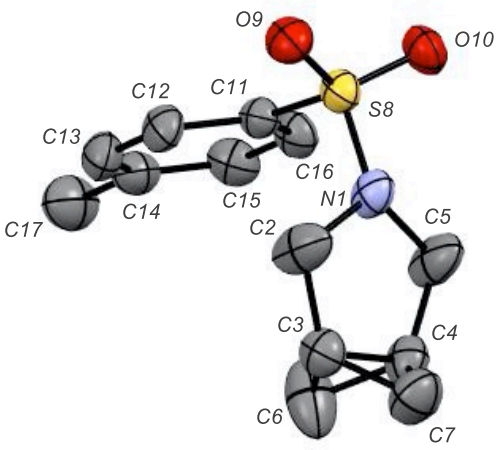


Fig. 4. Solid state structure of **5**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms are omitted for clarity.

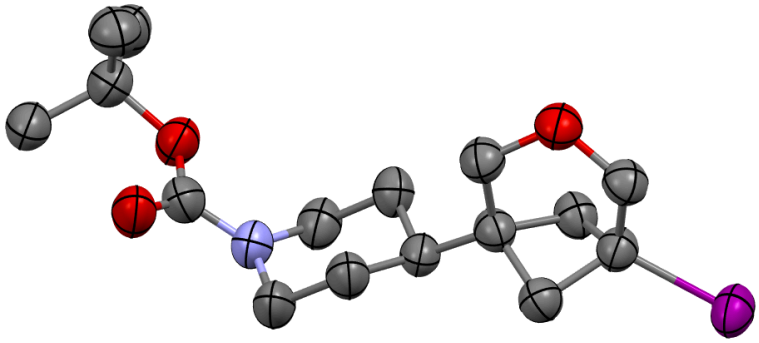
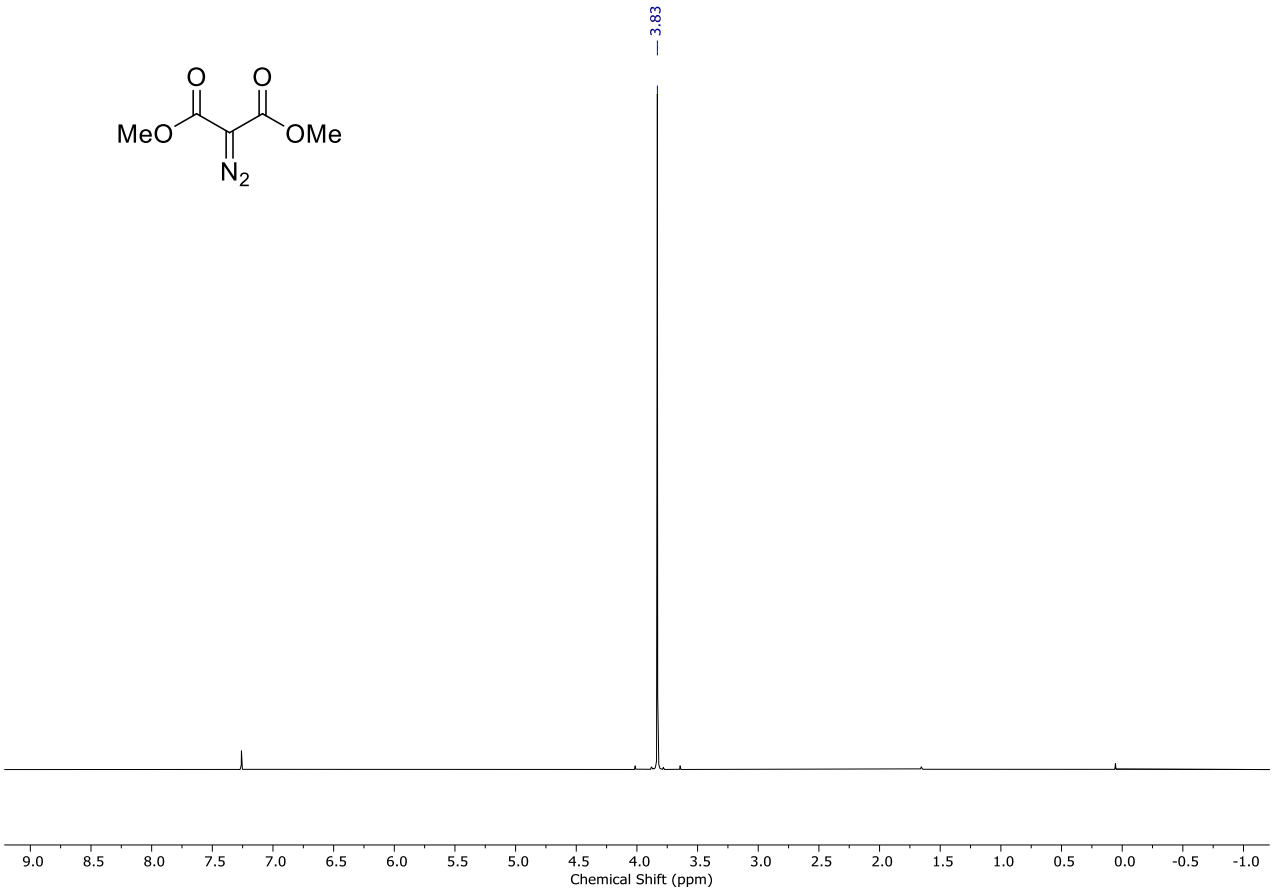


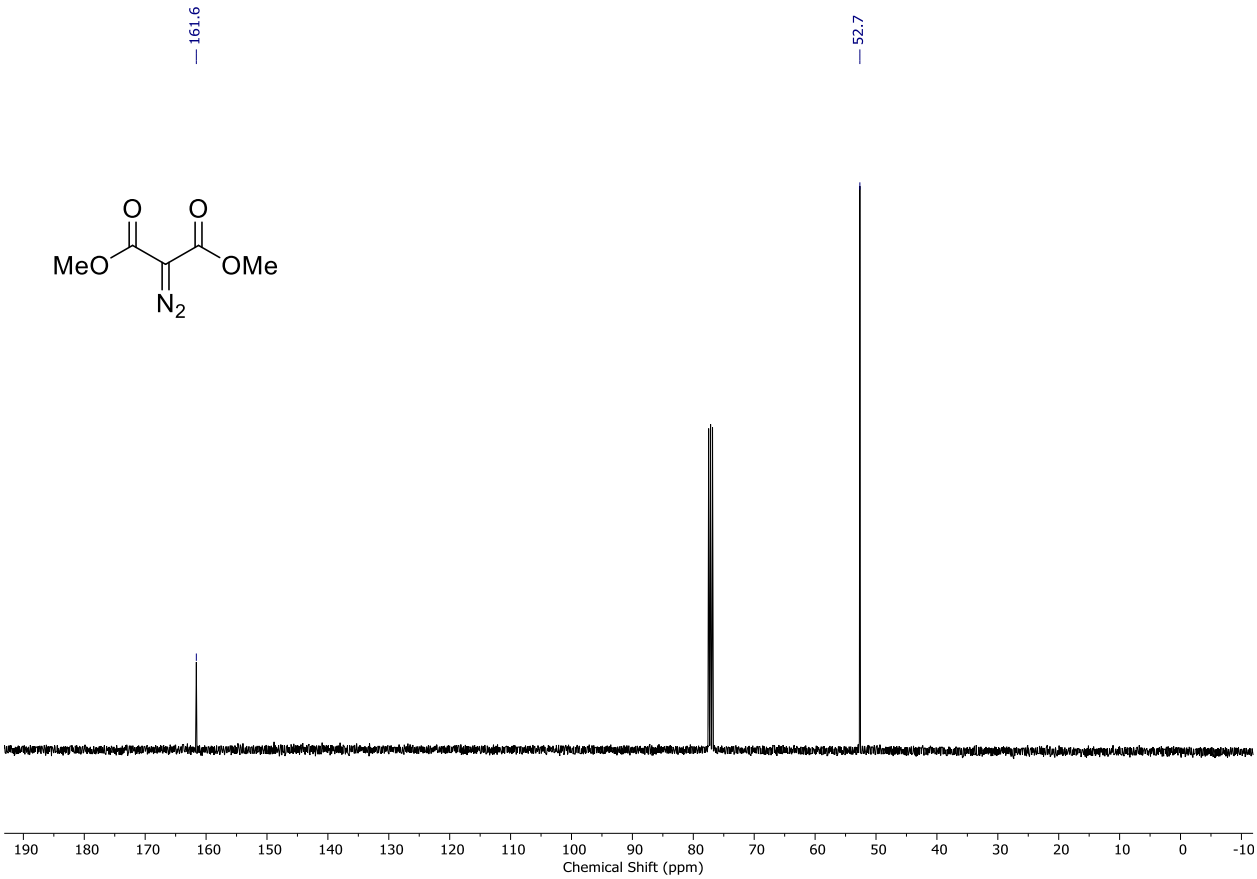
Fig. 5. Solid state structure of **18i**. Displacement ellipsoids are drawn at 50% probability. Hydrogen atoms are omitted for clarity.

8. NMR Spectra

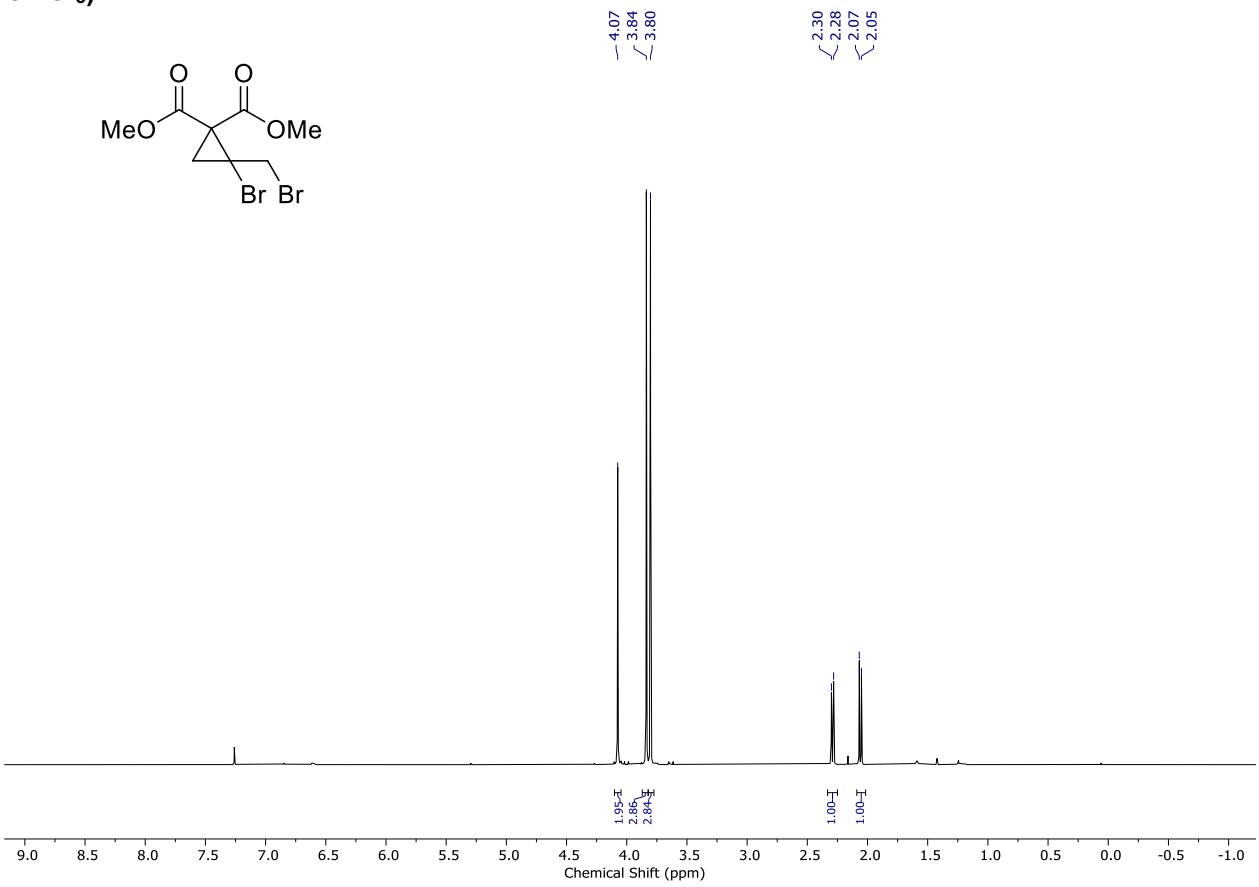
Dimethyl 2-diazomalonate (6) ^{1}H NMR (400 MHz, $CDCl_3$)



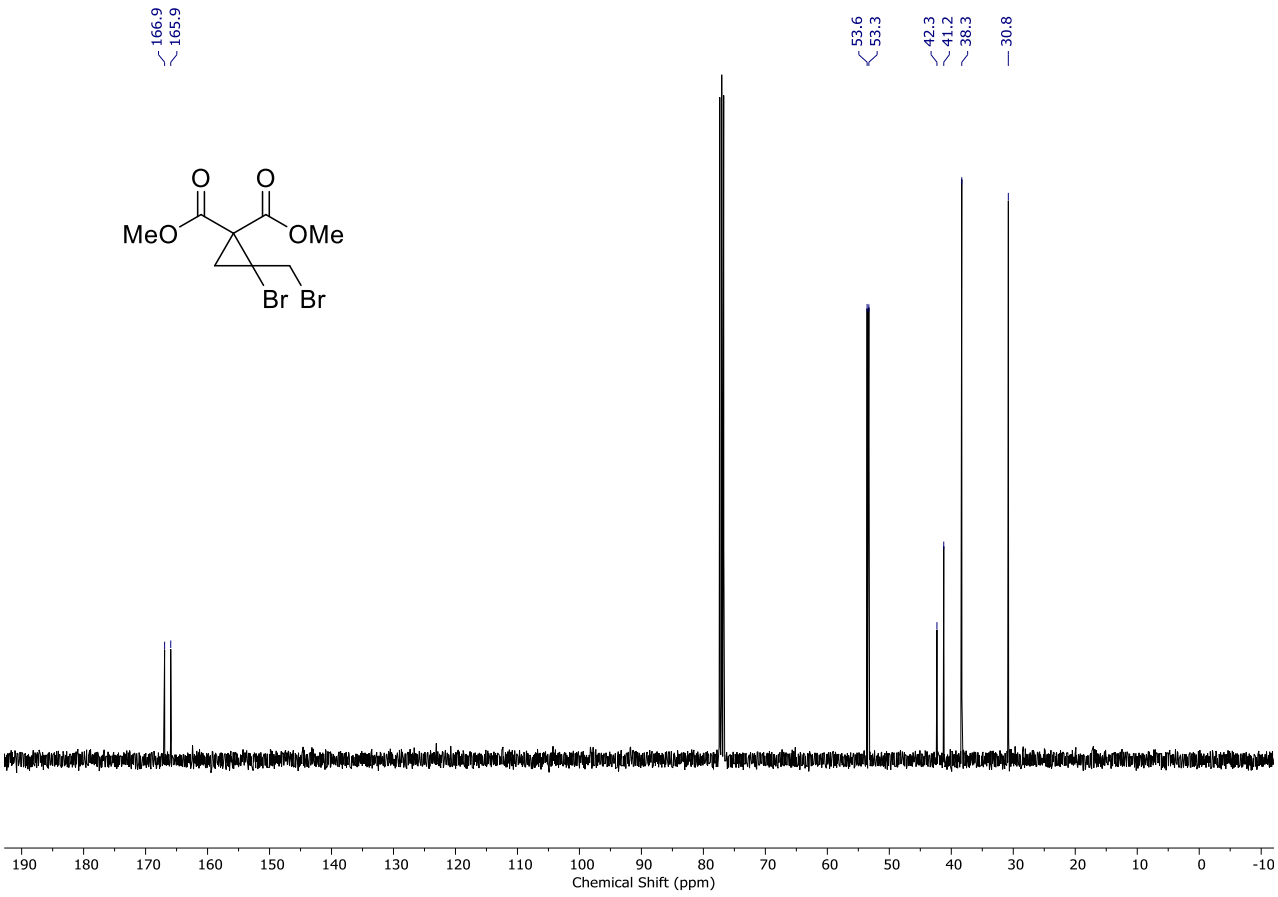
Dimethyl 2-diazomalonate (6) ^{13}C NMR (101 MHz, $CDCl_3$)



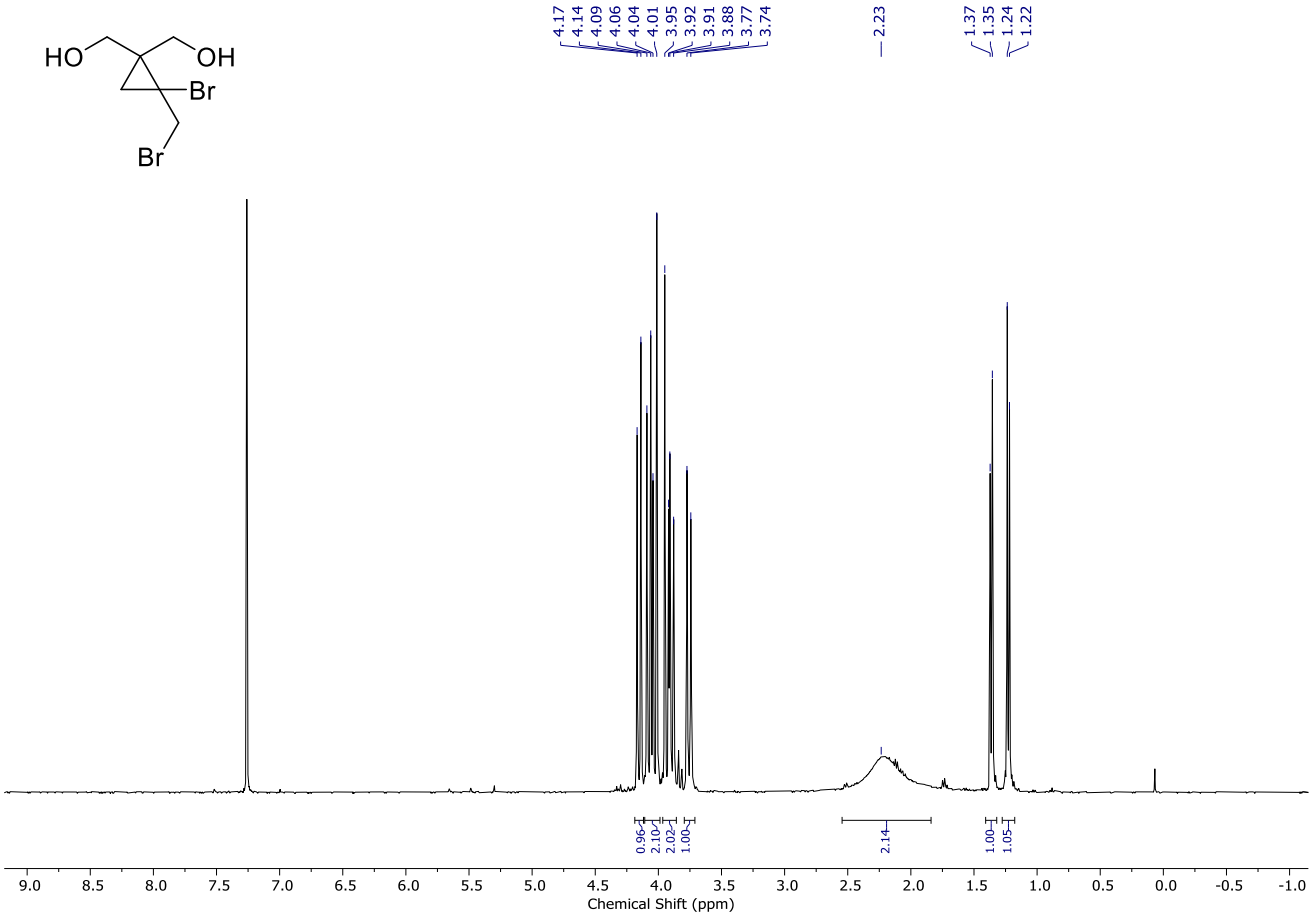
Dimethyl 2-bromo-2-(bromomethyl)cyclopropane-1,1-dicarboxylate (7) ^{1}H NMR (400 MHz, $CDCl_3$)



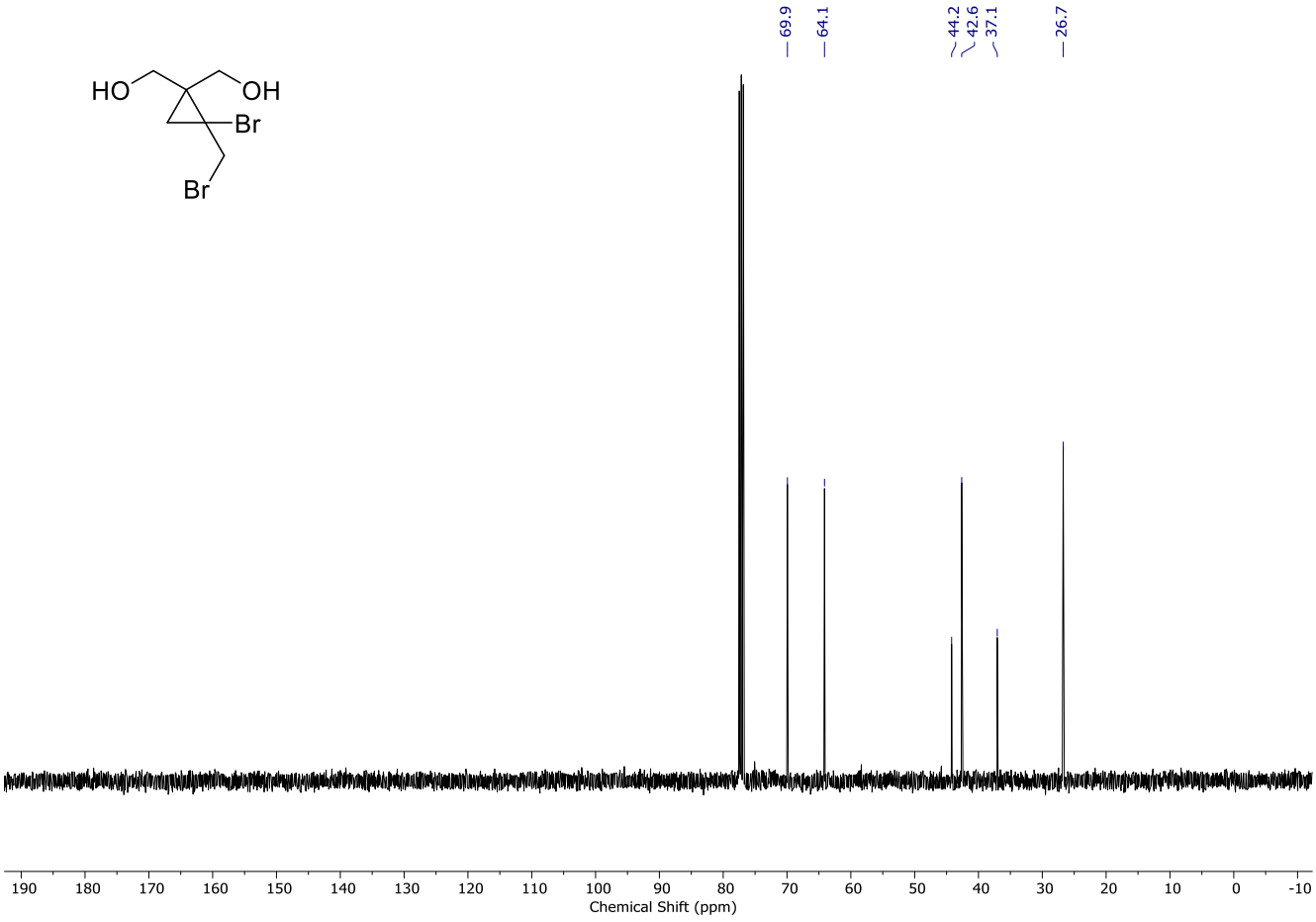
Dimethyl 2-bromo-2-(bromomethyl)cyclopropane-1,1-dicarboxylate (7) ^{13}C NMR (101 MHz, $CDCl_3$)



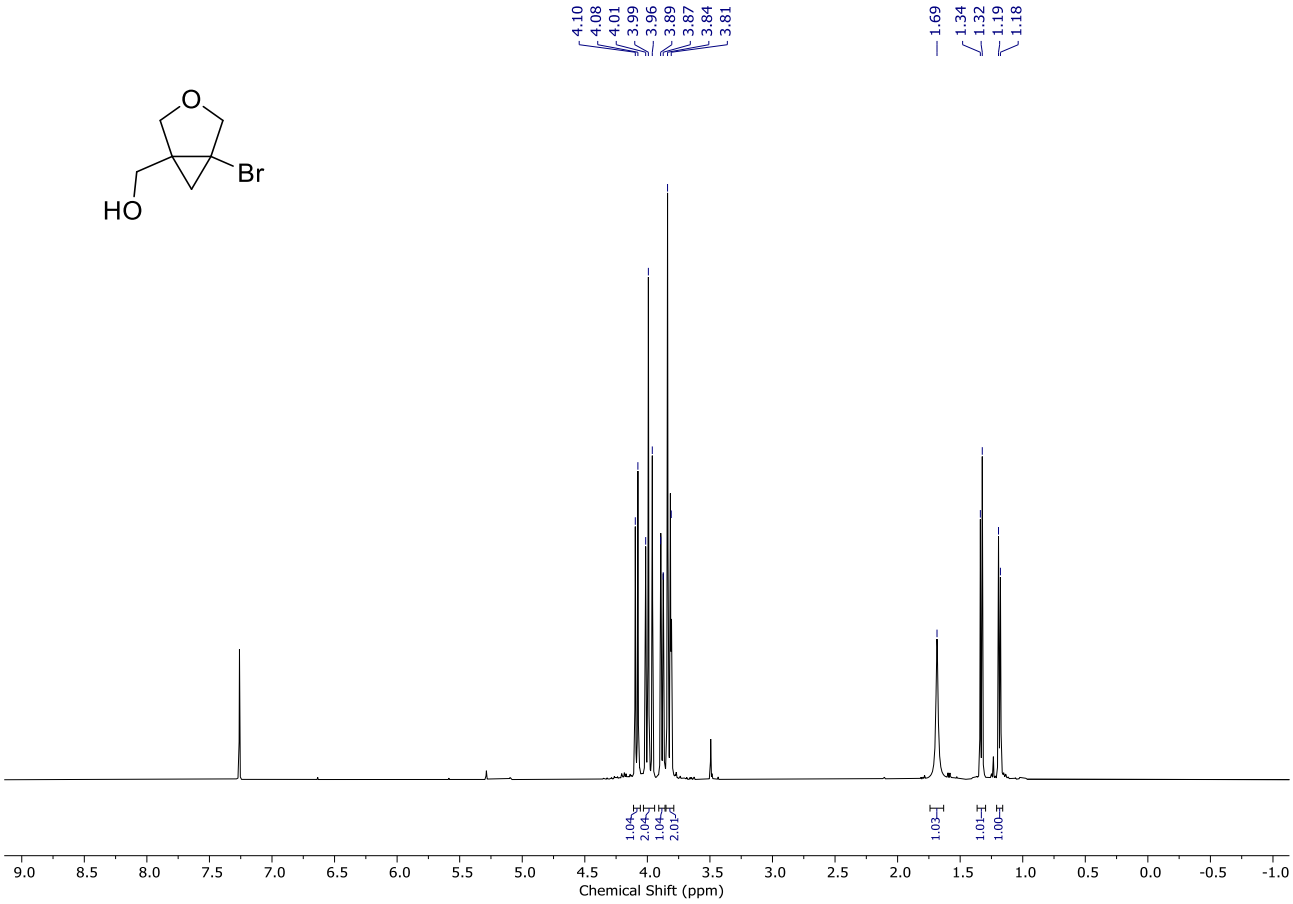
(2-Bromo-2-(bromomethyl)cyclopropane-1,1-diyl)dimethanol **(8) ^{1}H NMR (400 MHz, $CDCl_3$)**



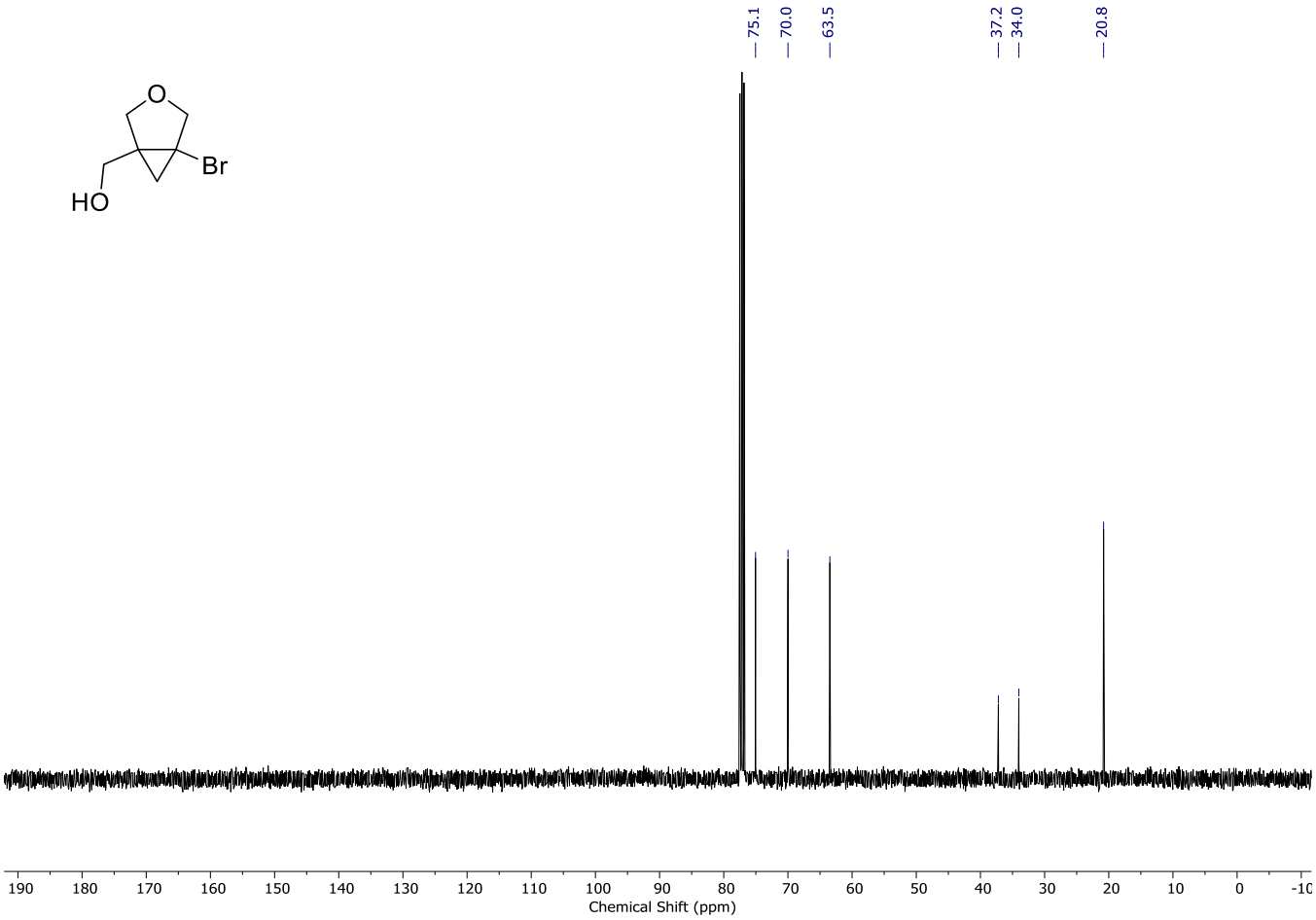
(2-Bromo-2-(bromomethyl)cyclopropane-1,1-diyl)dimethanol (8) ^{13}C NMR (101 MHz, $CDCl_3$)



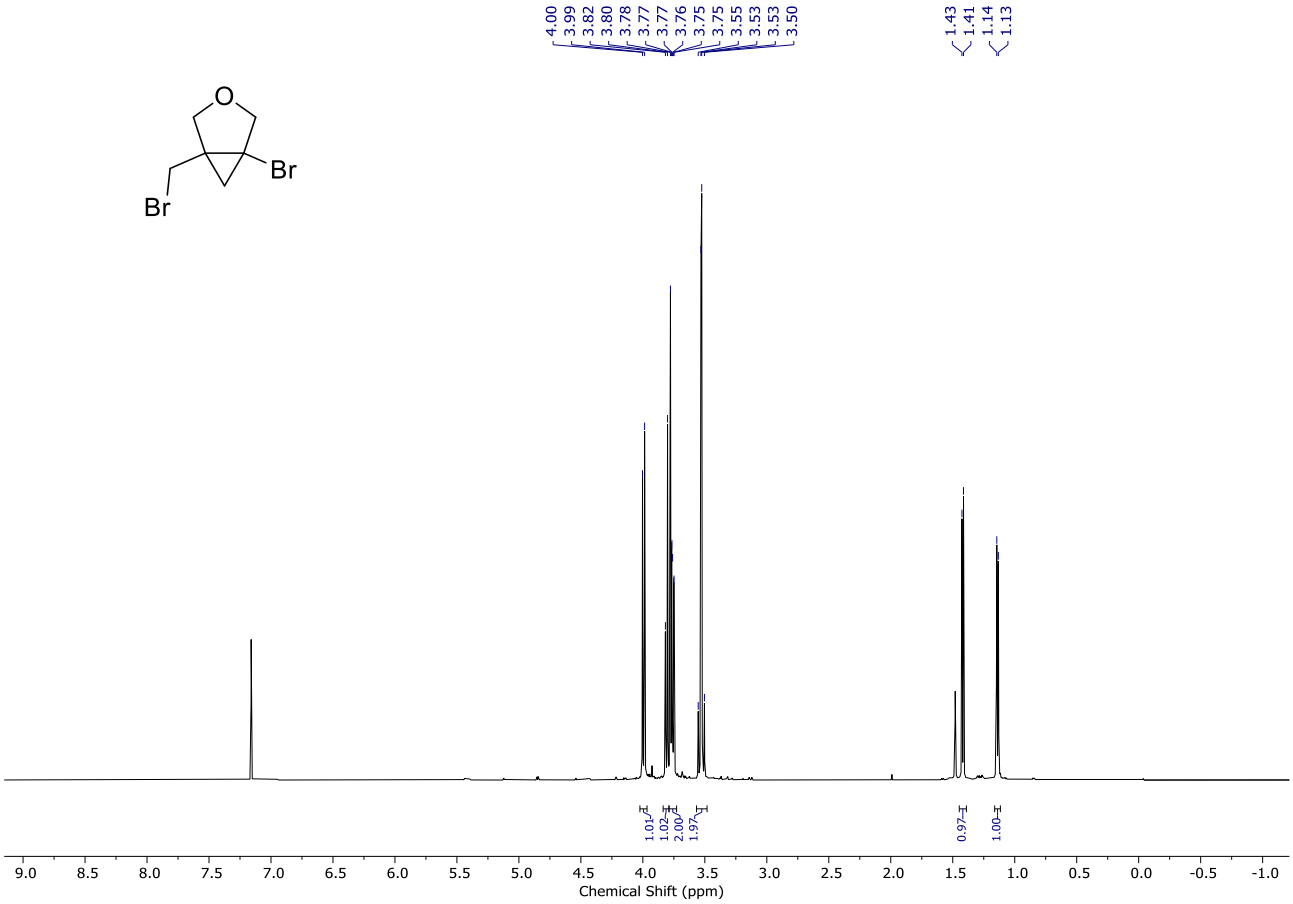
(5-Bromo-3-oxabicyclo[3.1.0]hexan-1-yl)methanol (9) ^{1}H NMR (400 MHz, $CDCl_3$)



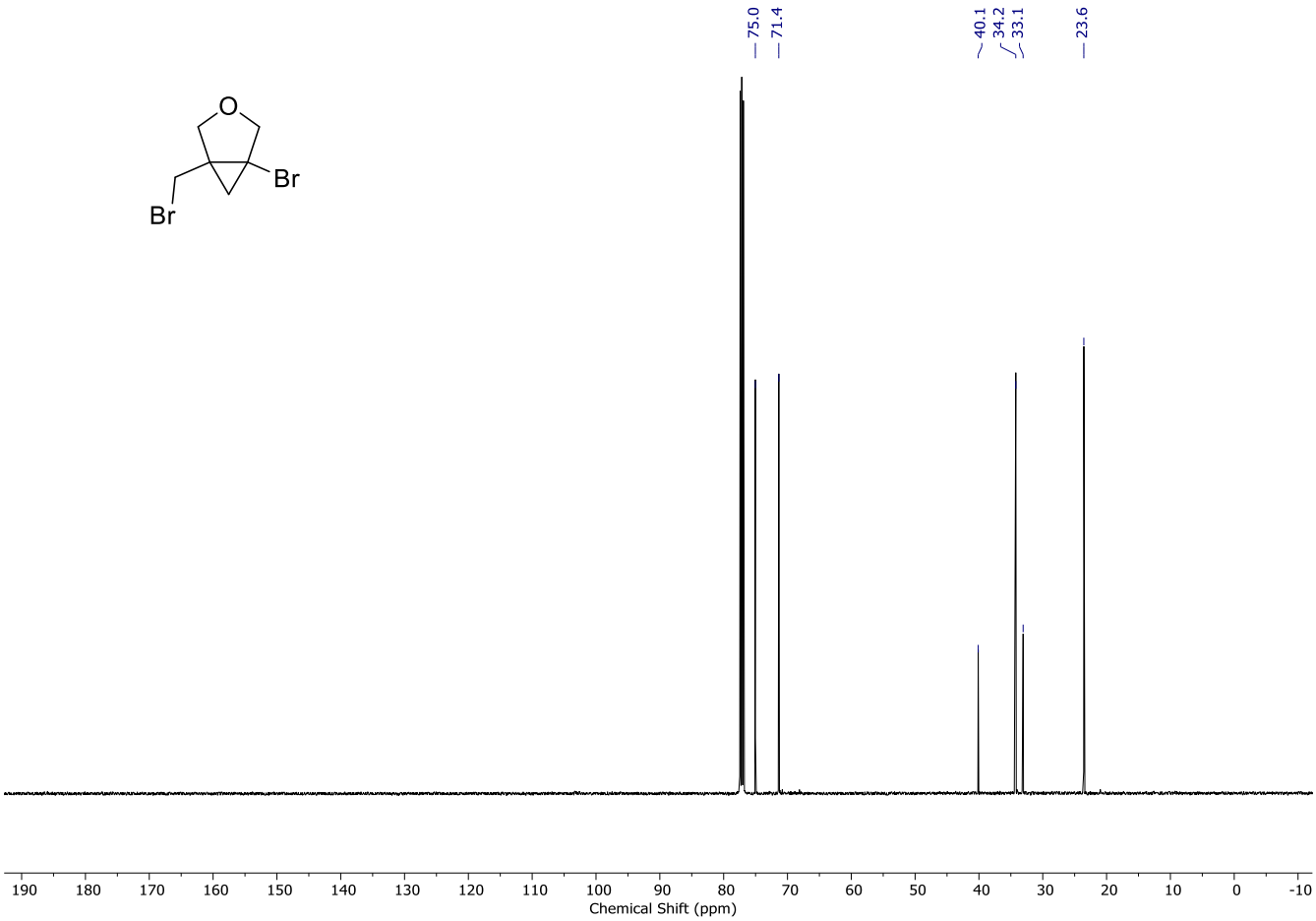
(5-Bromo-3-oxabicyclo[3.1.0]hexan-1-yl)methanol (9) ^{13}C NMR (101 MHz, $CDCl_3$)



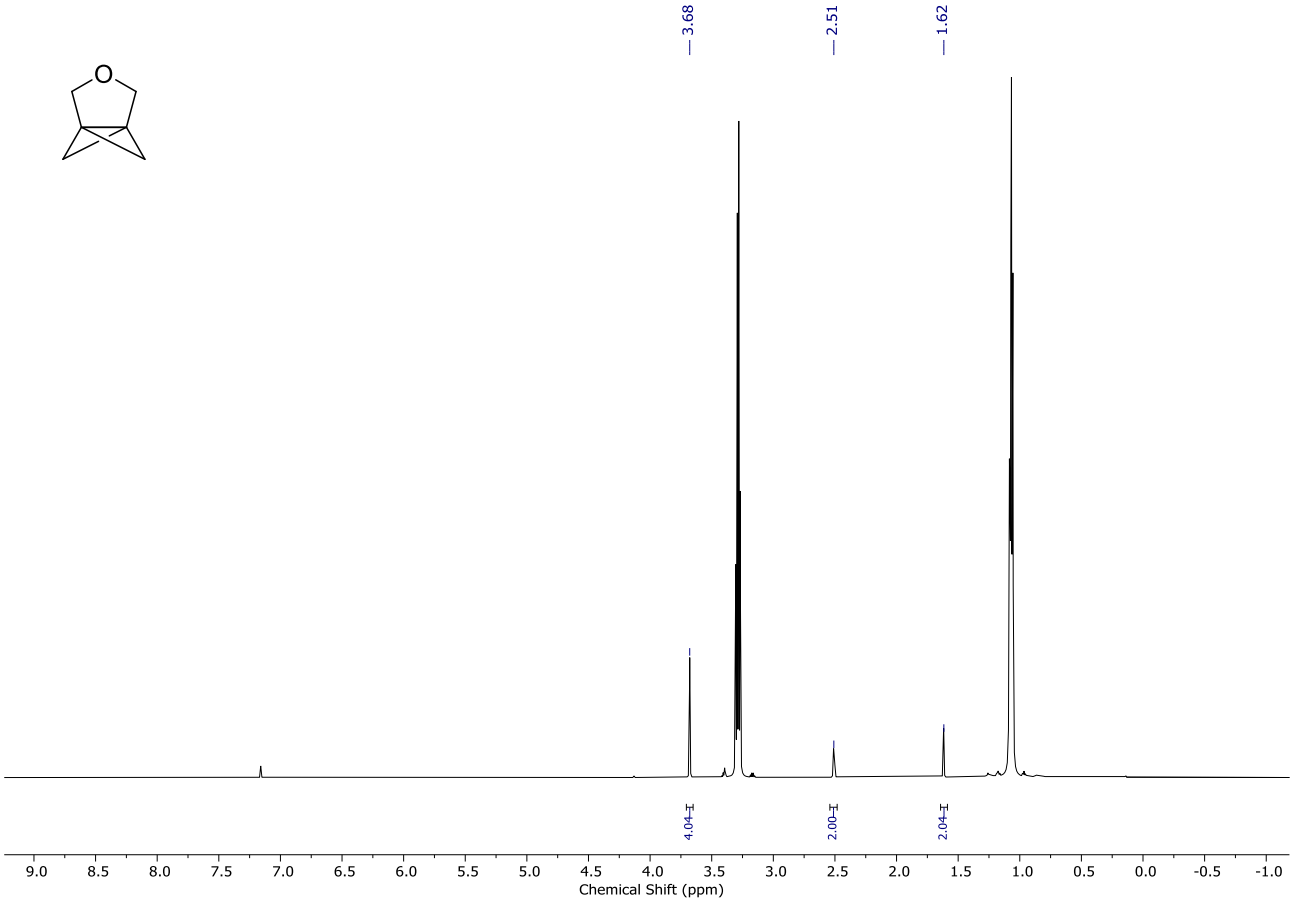
1-Bromo-5-(bromomethyl)-3-oxabicyclo[3.1.0]hexane (10) ^{1}H NMR (500 MHz, $CDCl_3$)



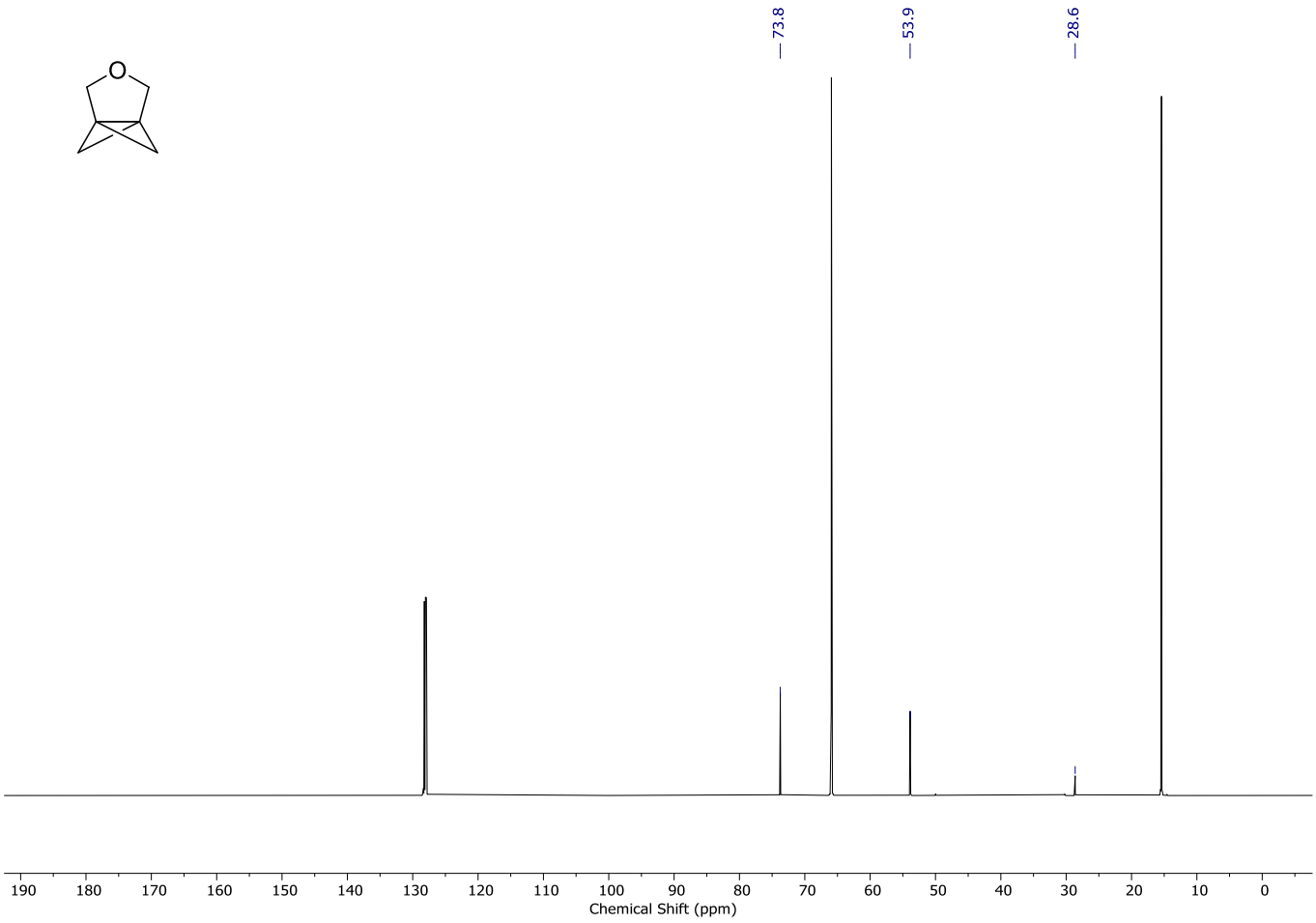
1-Bromo-5-(bromomethyl)-3-oxabicyclo[3.1.0]hexane (10) ^{13}C NMR (126 MHz, $CDCl_3$)



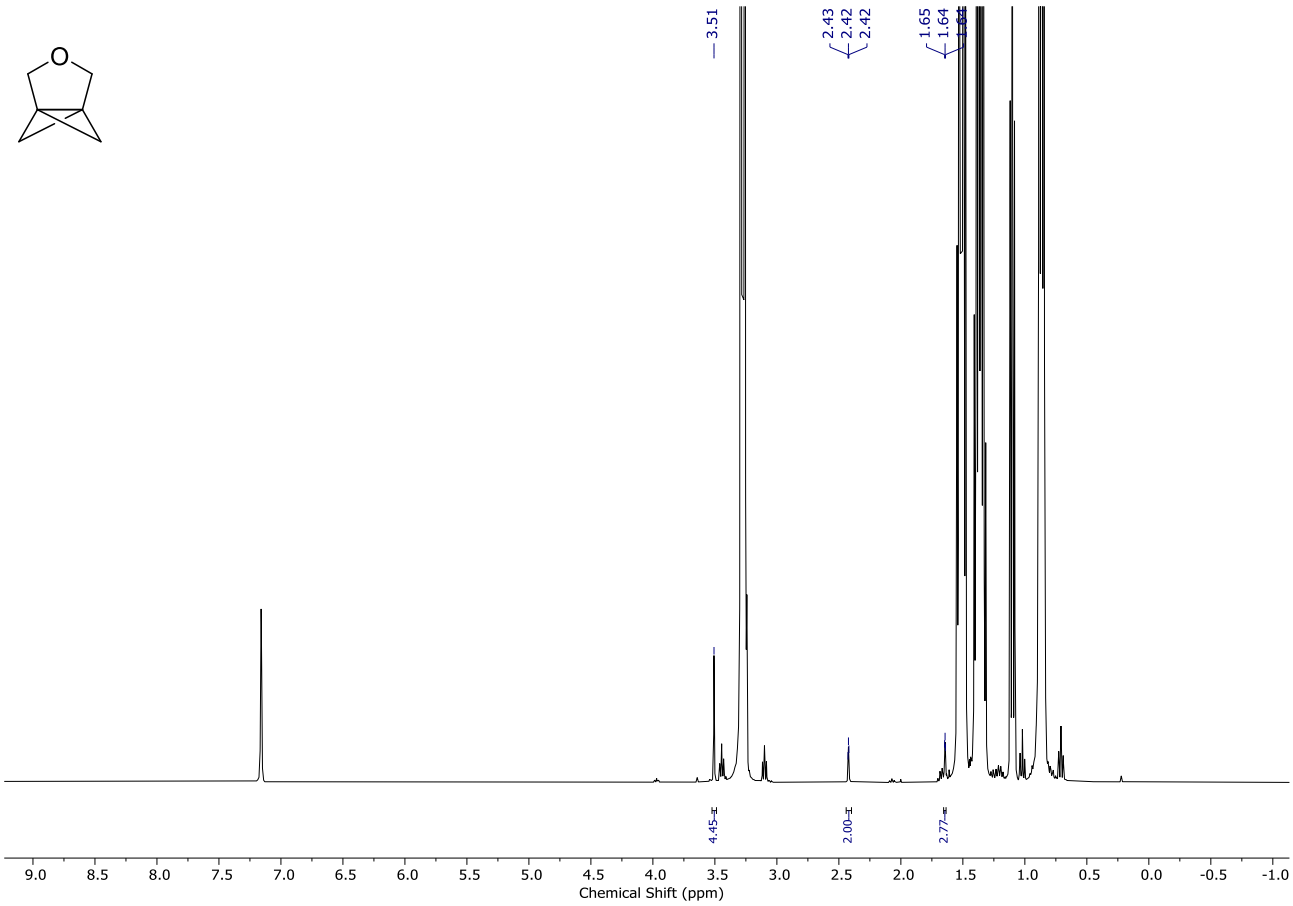
3-Oxa[3.1.1]propellane (3) in Et_2O ^1H NMR (600 MHz, C_6D_6)



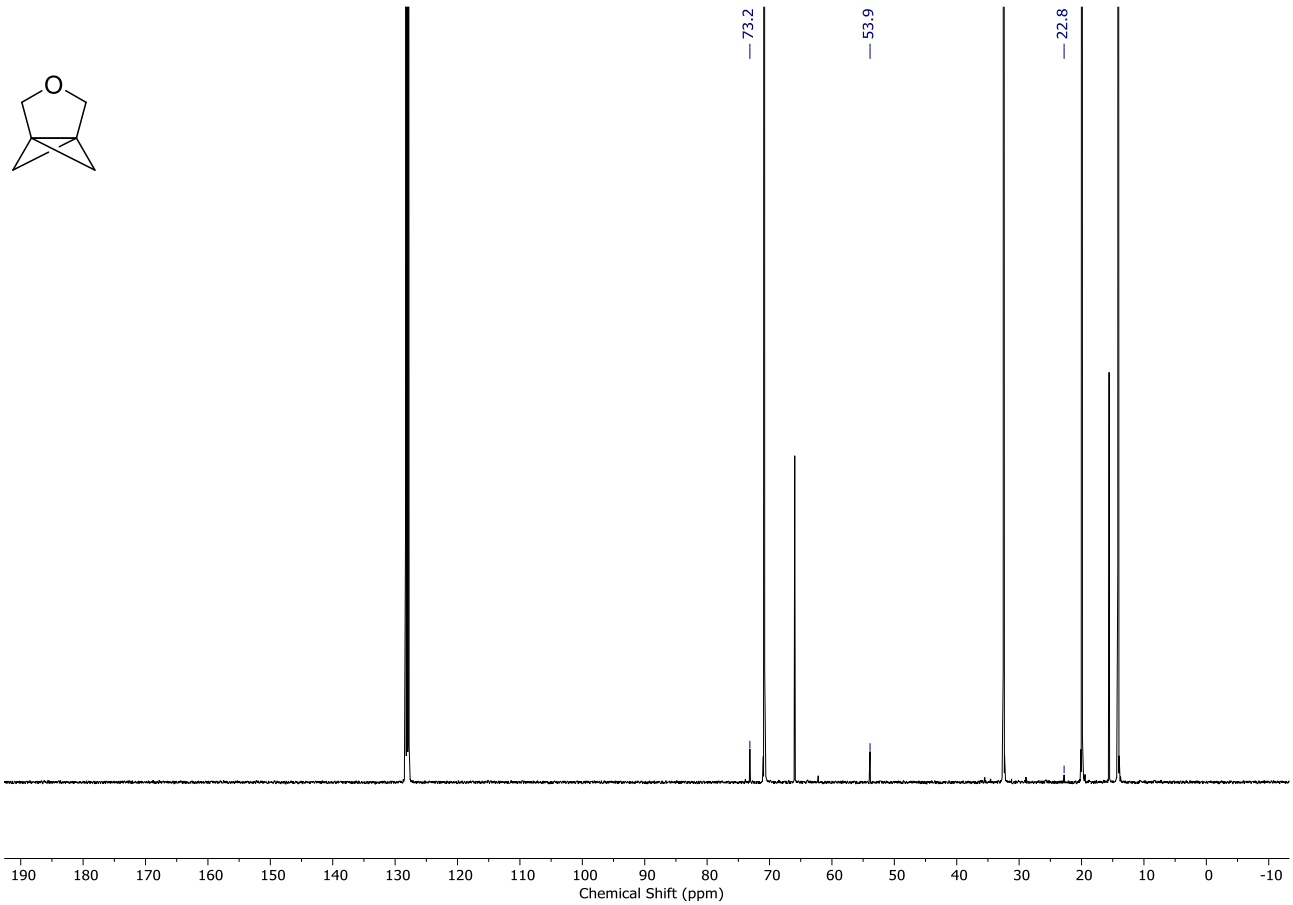
3-Oxa[3.1.1]propellane (3) in Et_2O ^{13}C NMR (151 MHz, C_6D_6)



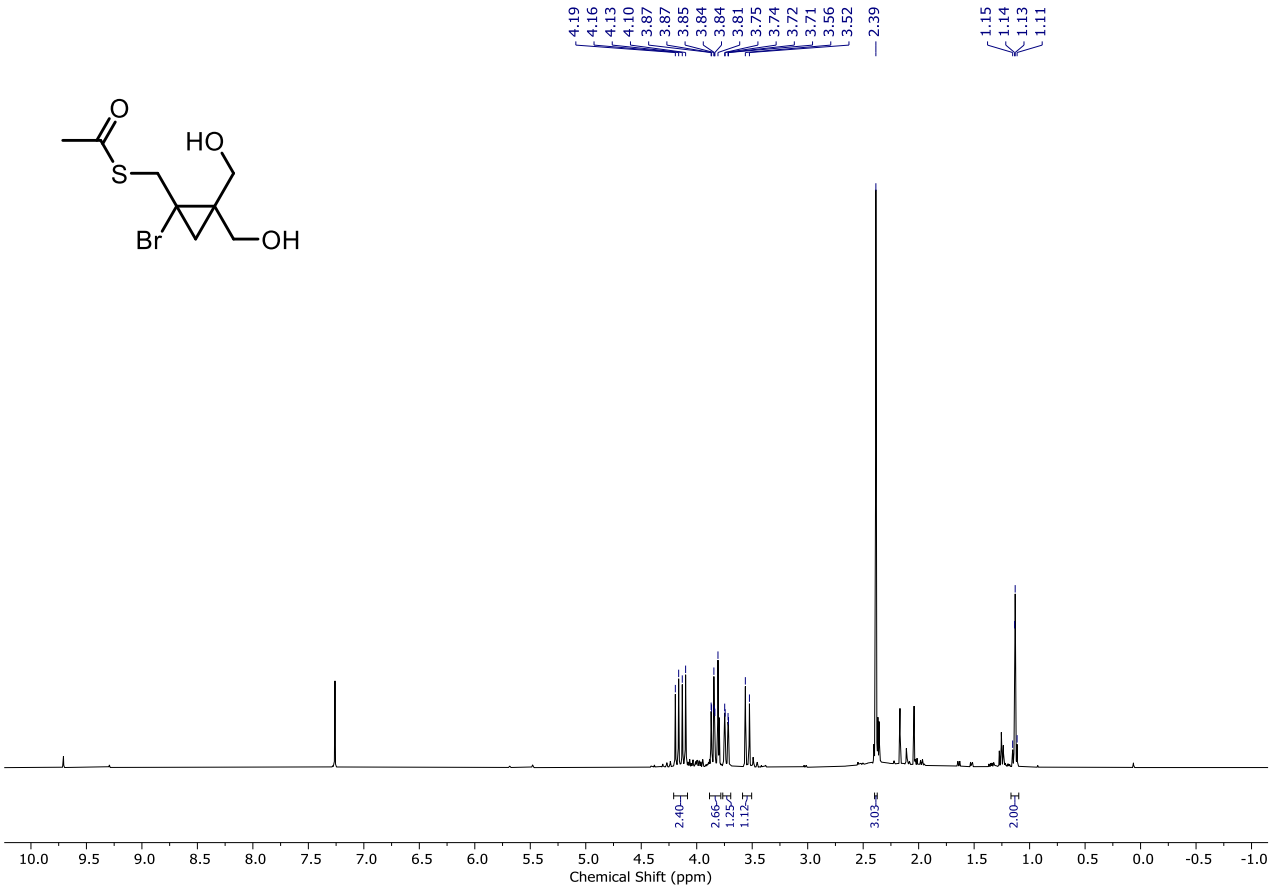
3-Oxa[3.1.1]propellane (3) in *n*Bu_2O ^1H NMR (400 MHz, C_6D_6)



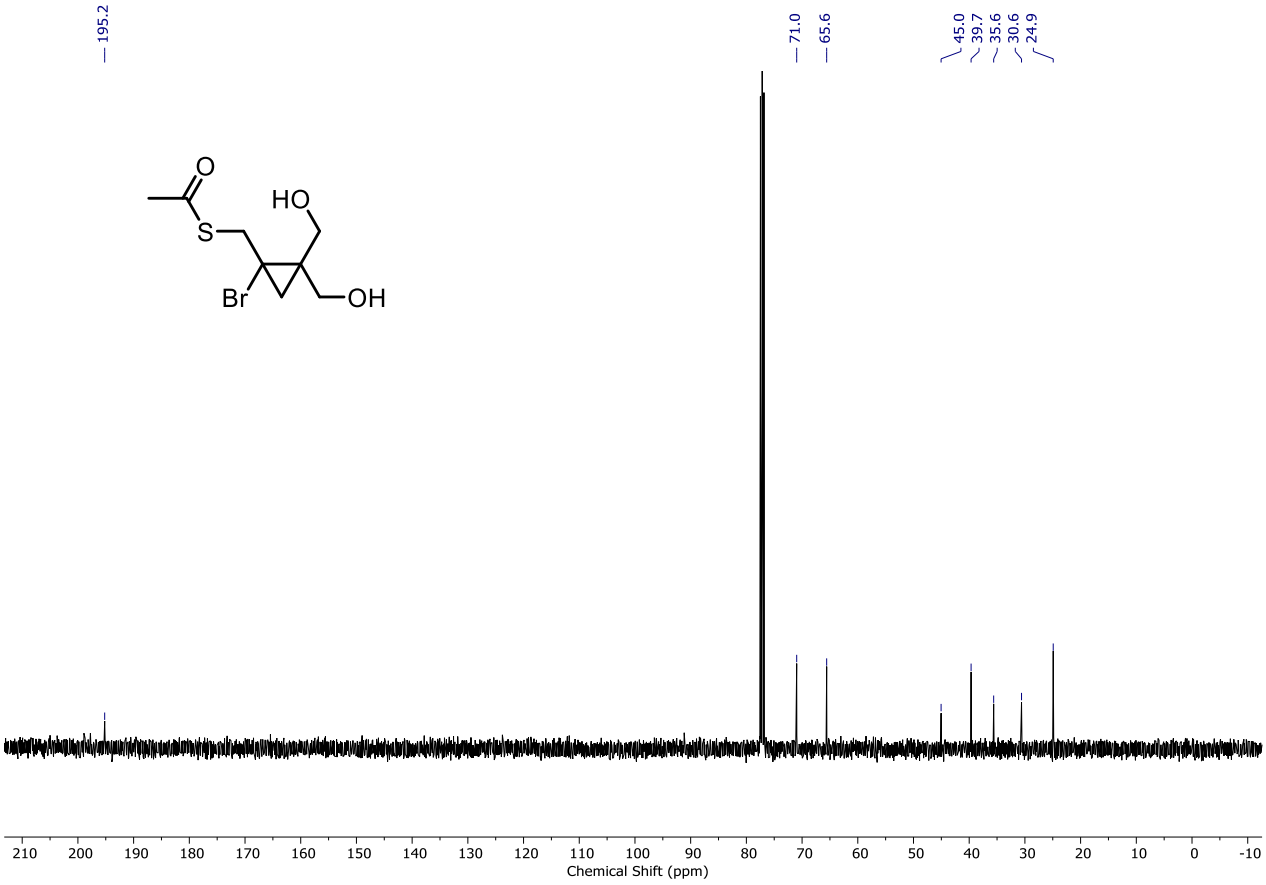
3-Oxa[3.1.1]propellane (3) in *n*Bu_2O ^{13}C NMR (101 MHz, C_6D_6)



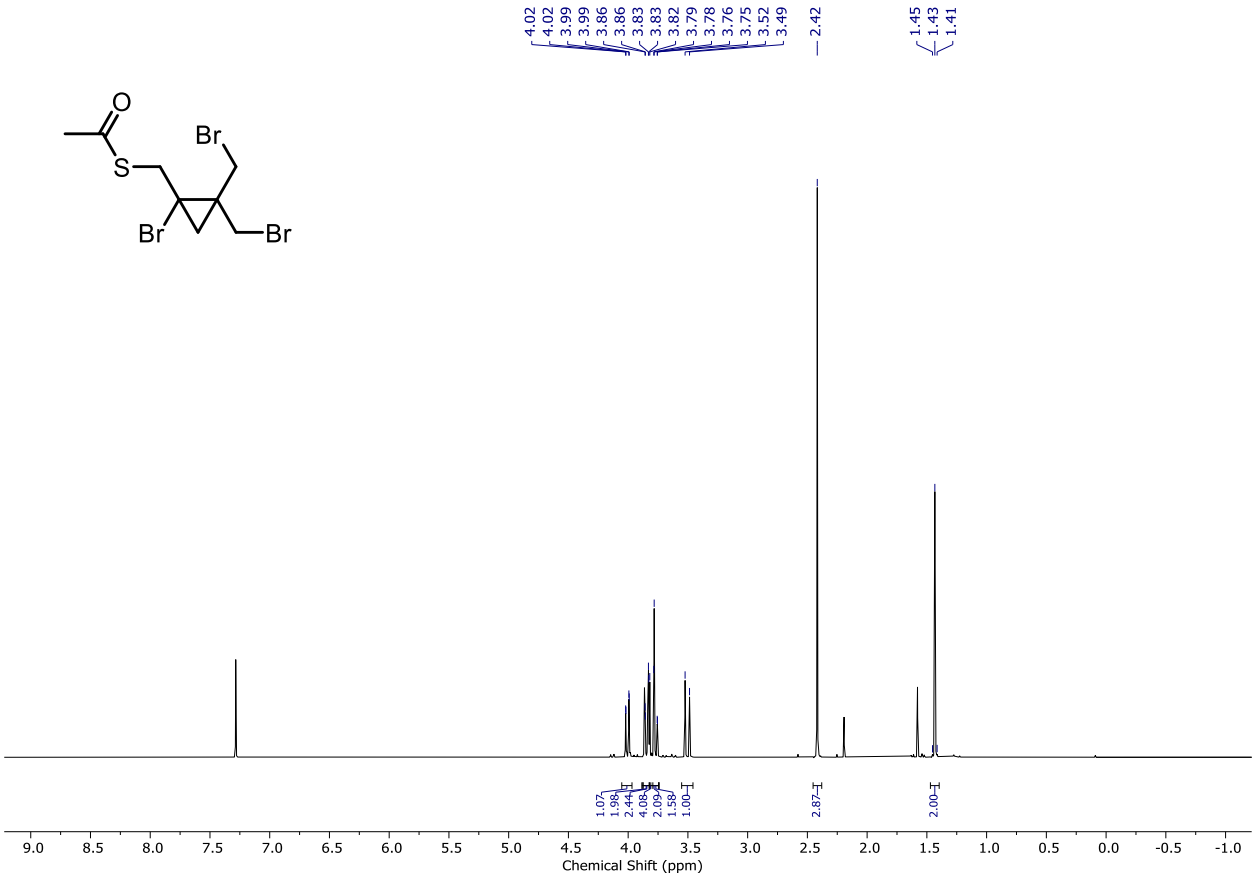
(1-Bromo-2,2-bis(hydroxymethyl)cyclopropyl)methyl ethanethioate (11) ^{1}H NMR (400 MHz, $CDCl_3$)



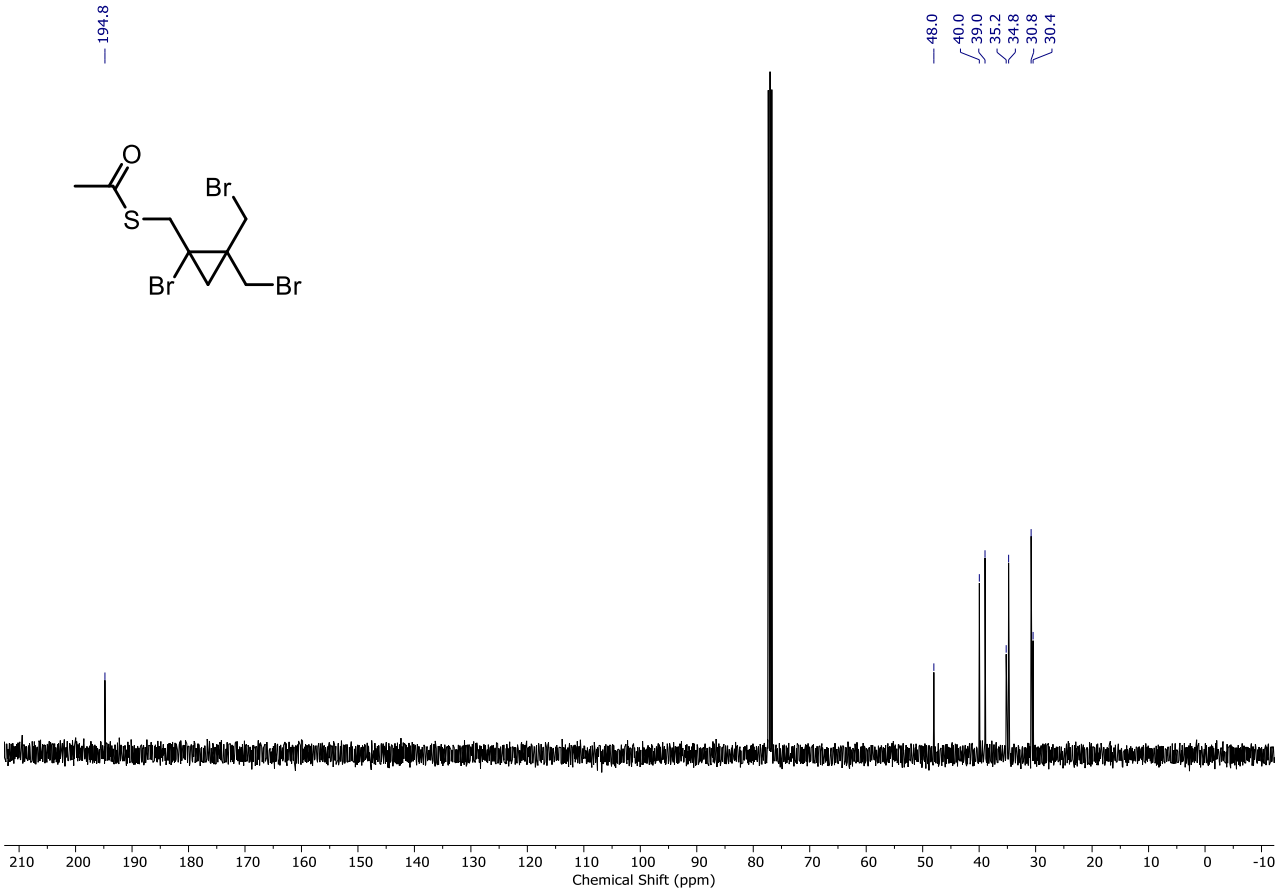
(1-Bromo-2,2-bis(hydroxymethyl)cyclopropyl)methyl ethanethioate (11) ^{13}C NMR (101 MHz, $CDCl_3$)



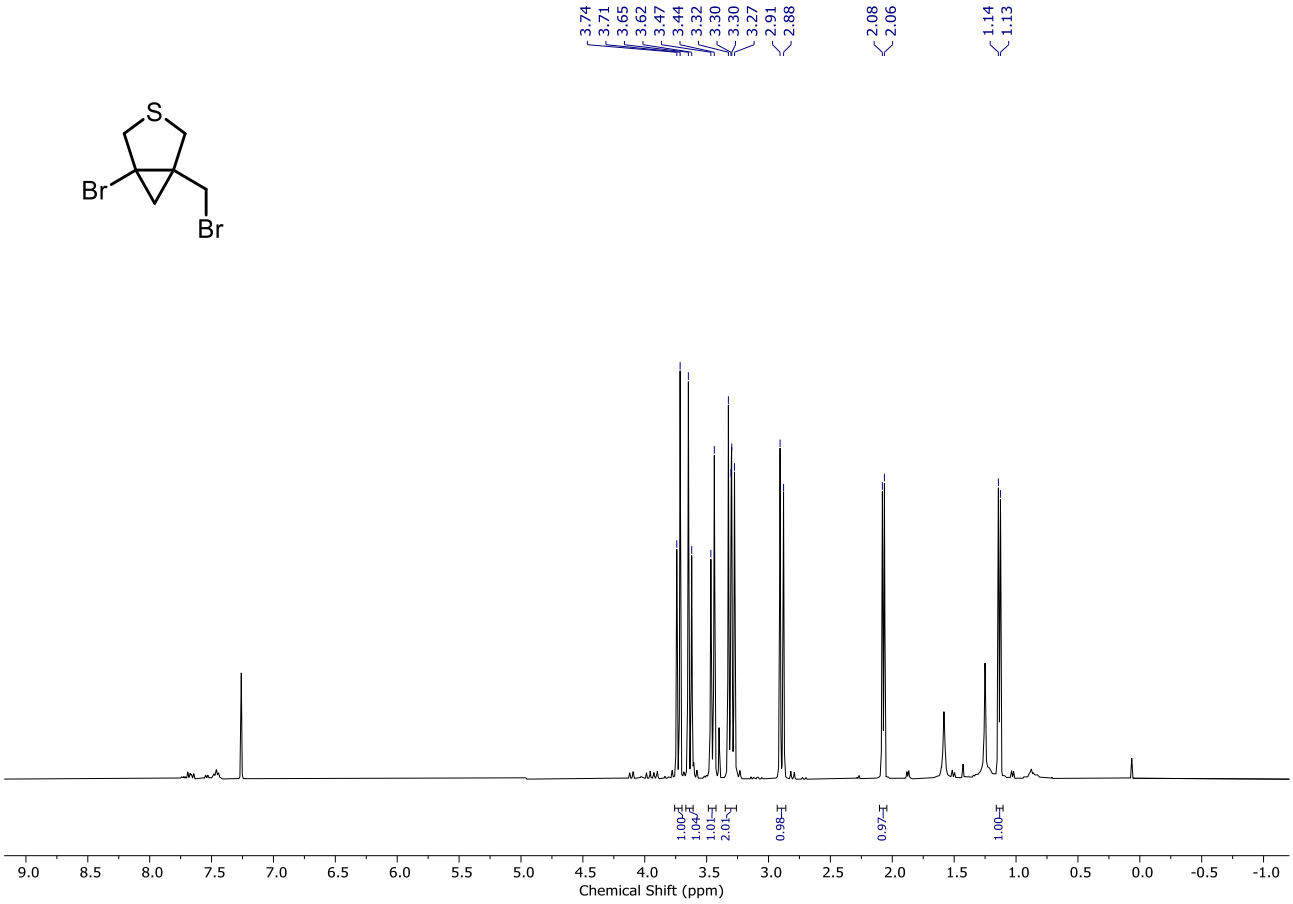
(1-Bromo-2,2-bis(bromomethyl)cyclopropyl)methyl ethanethioate (12) ^{1}H NMR (400 MHz, $CDCl_3$)



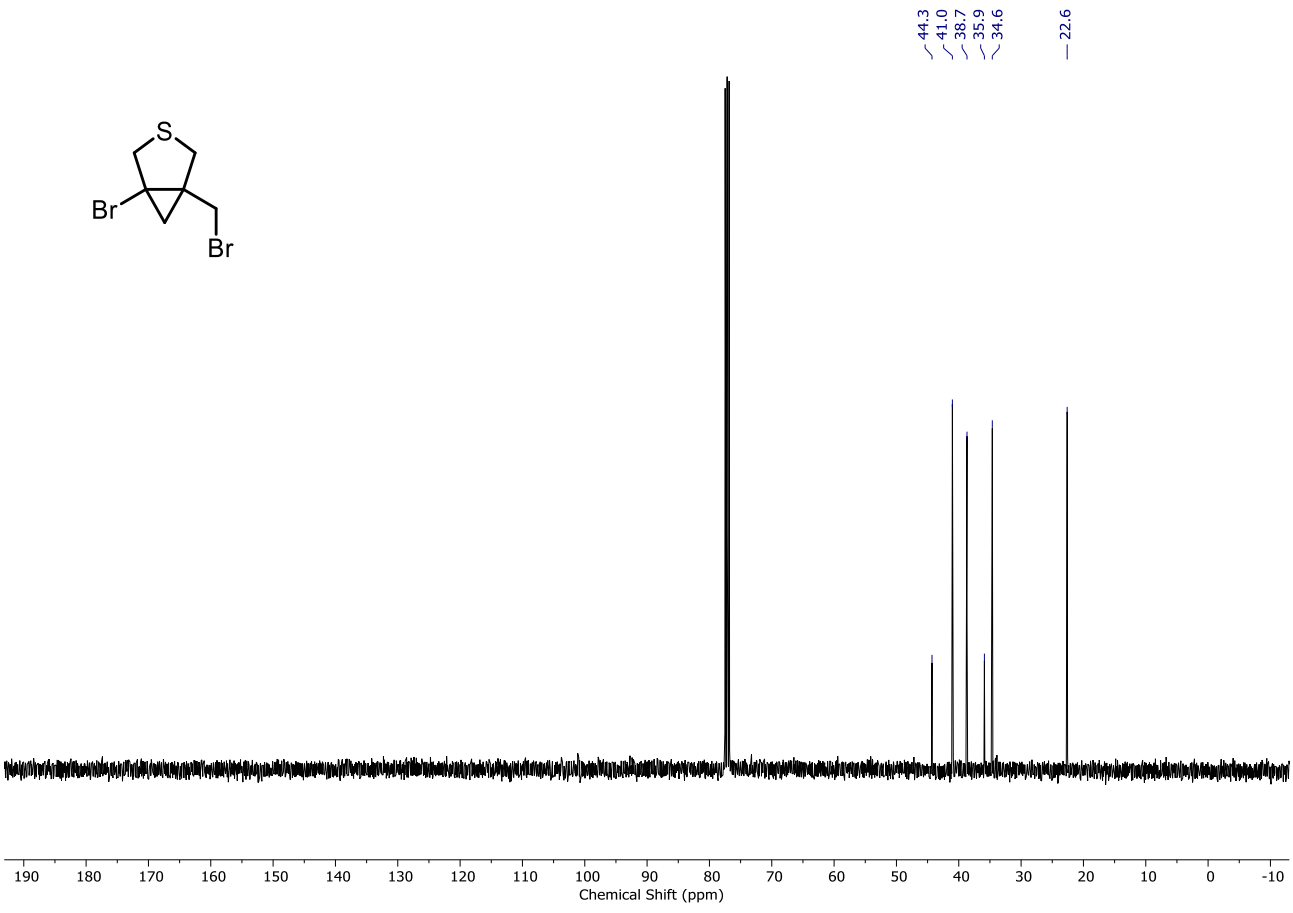
(1-Bromo-2,2-bis(bromomethyl)cyclopropyl)methyl ethanethioate (12) ^{13}C NMR (101 MHz, $CDCl_3$)



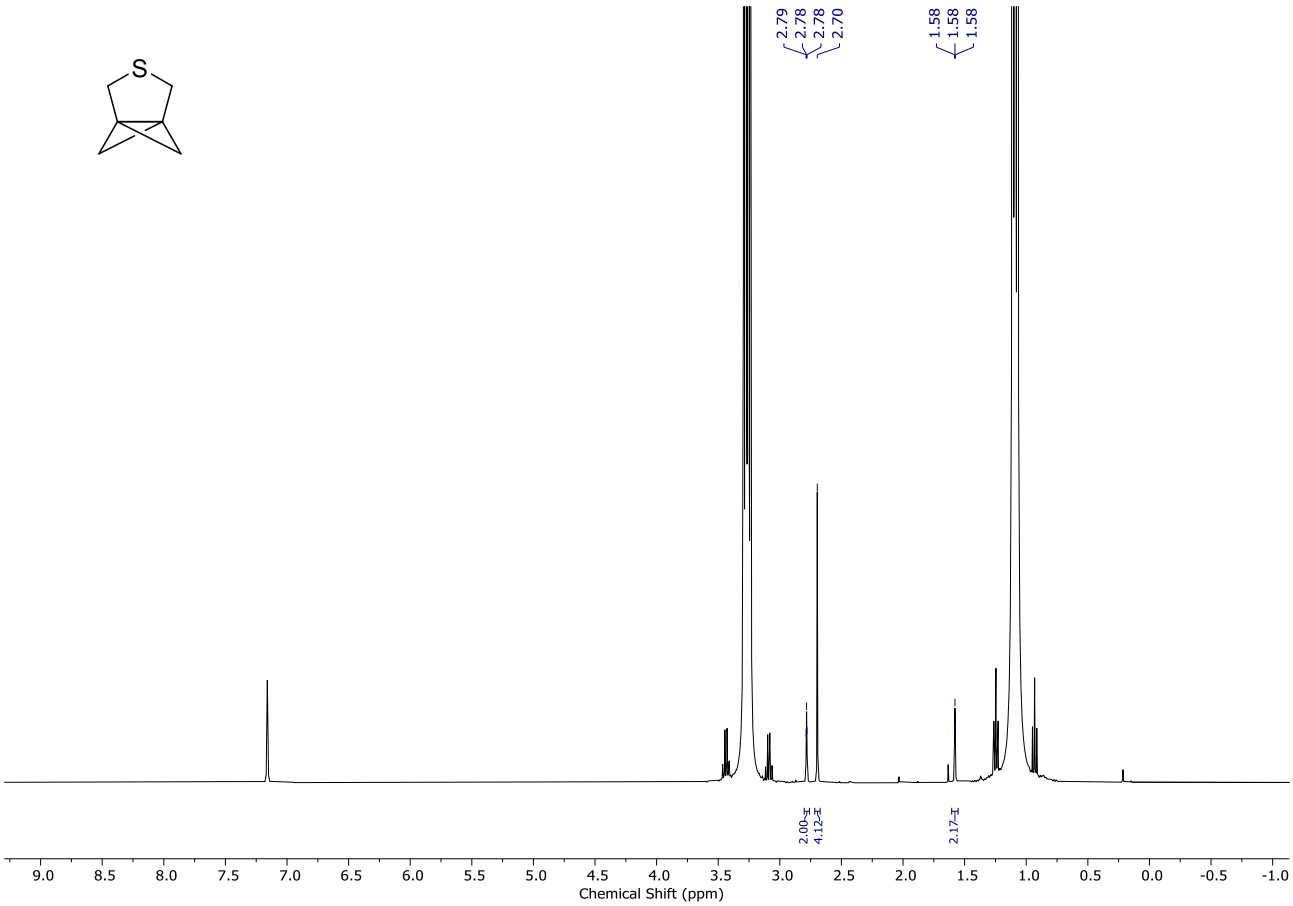
1-Bromo-5-(bromomethyl)-3-thiabicyclo[3.1.0]hexane (13) ^{1}H NMR (200 MHz, $CDCl_3$)



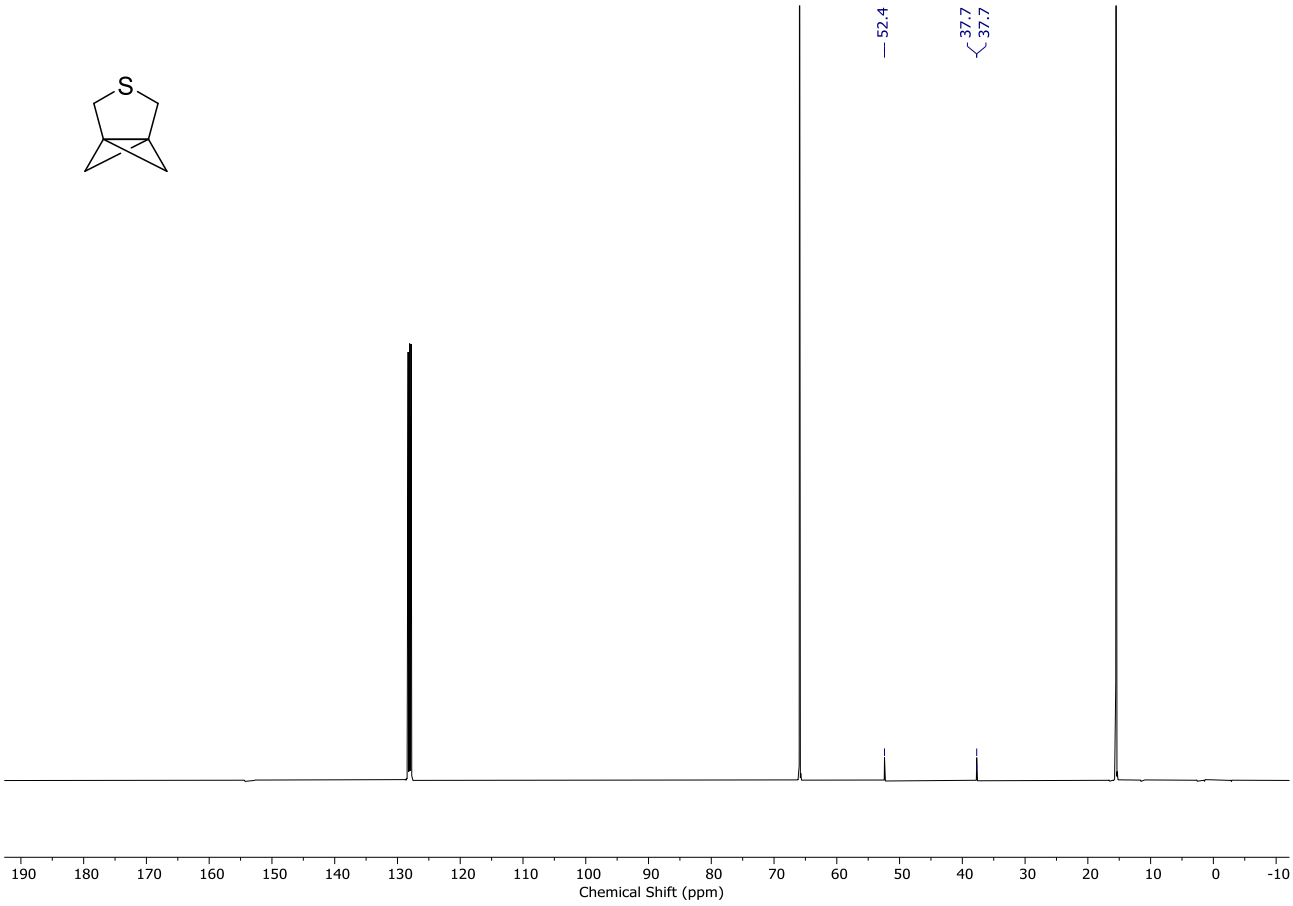
1-Bromo-5-(bromomethyl)-3-thiabicyclo[3.1.0]hexane (13) ^{13}C NMR (101 MHz, $CDCl_3$)



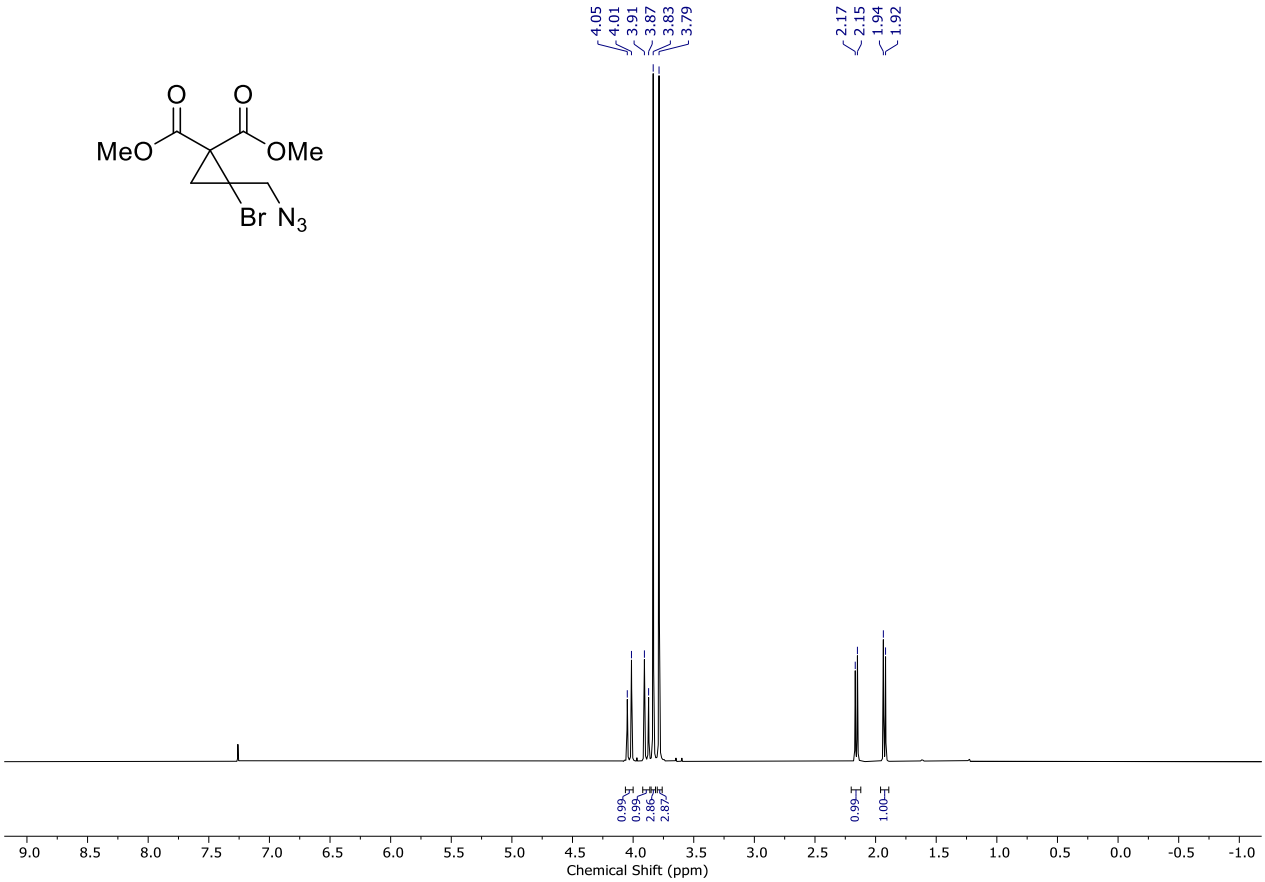
3-Thia[3.1.1]propellane (4) ^{1}H NMR (400 MHz, C_6D_6)



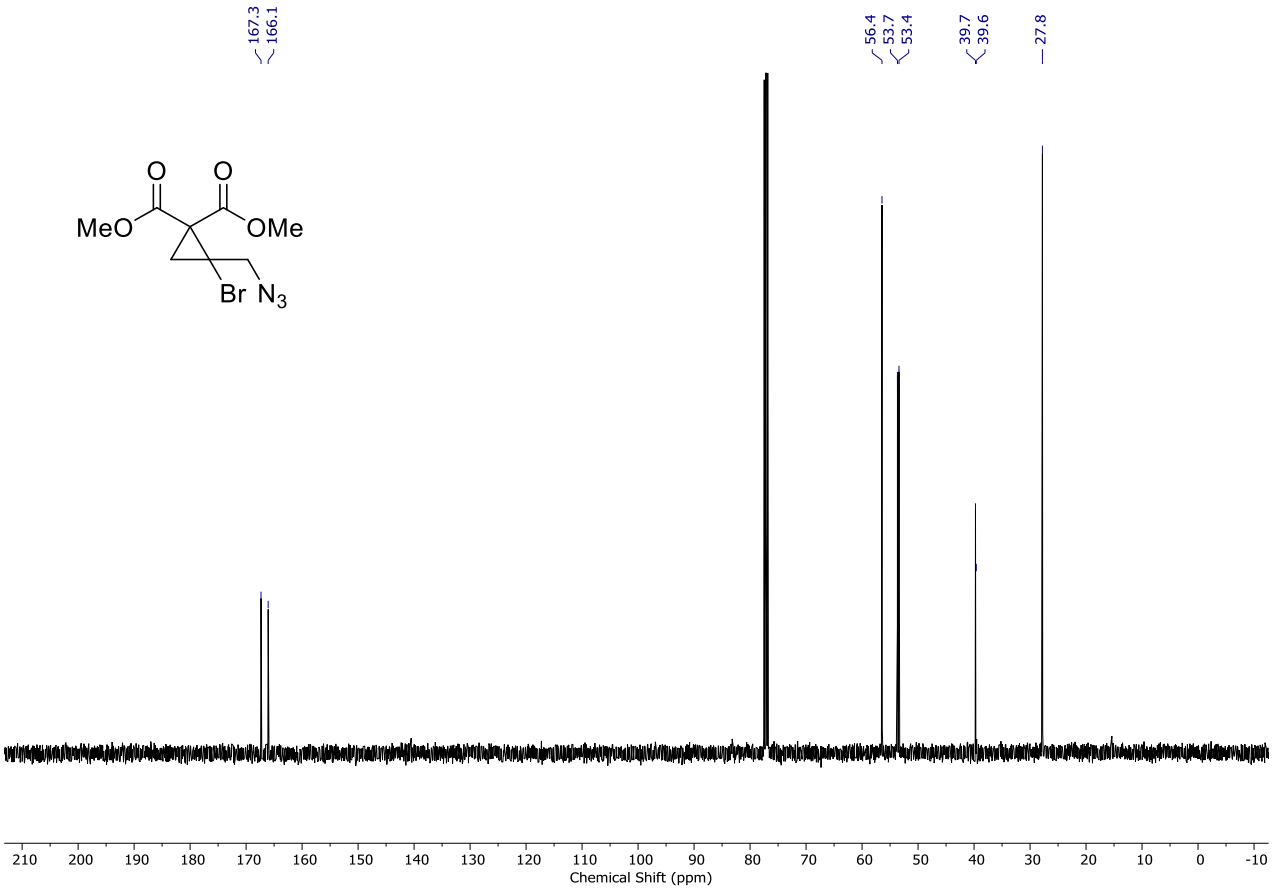
3-Thia[3.1.1]propellane (4) ^{13}C NMR (101 MHz, C_6D_6)



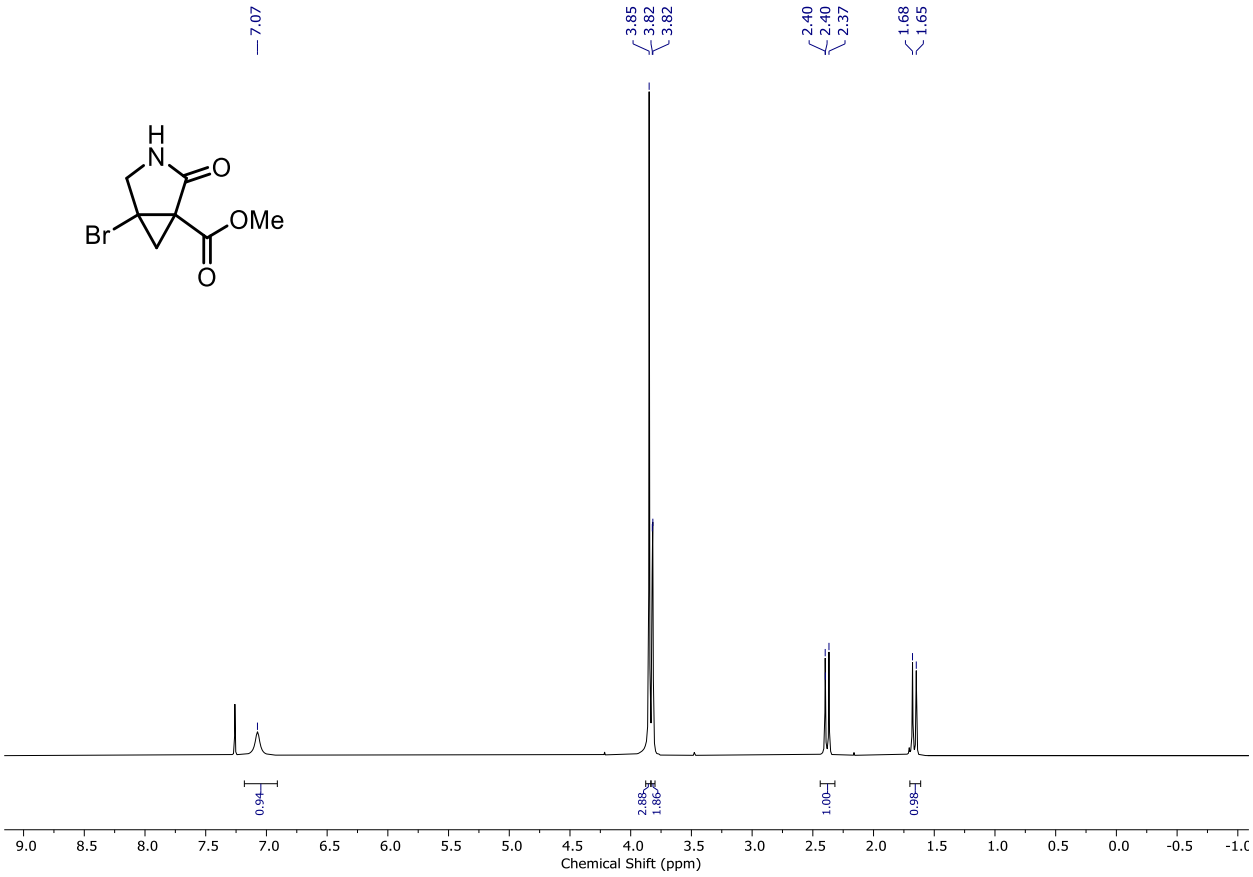
Dimethyl 2-(azidomethyl)-2-bromocyclopropane-1,1-dicarboxylate (14) ^{1}H NMR (400 MHz, $CDCl_3$)



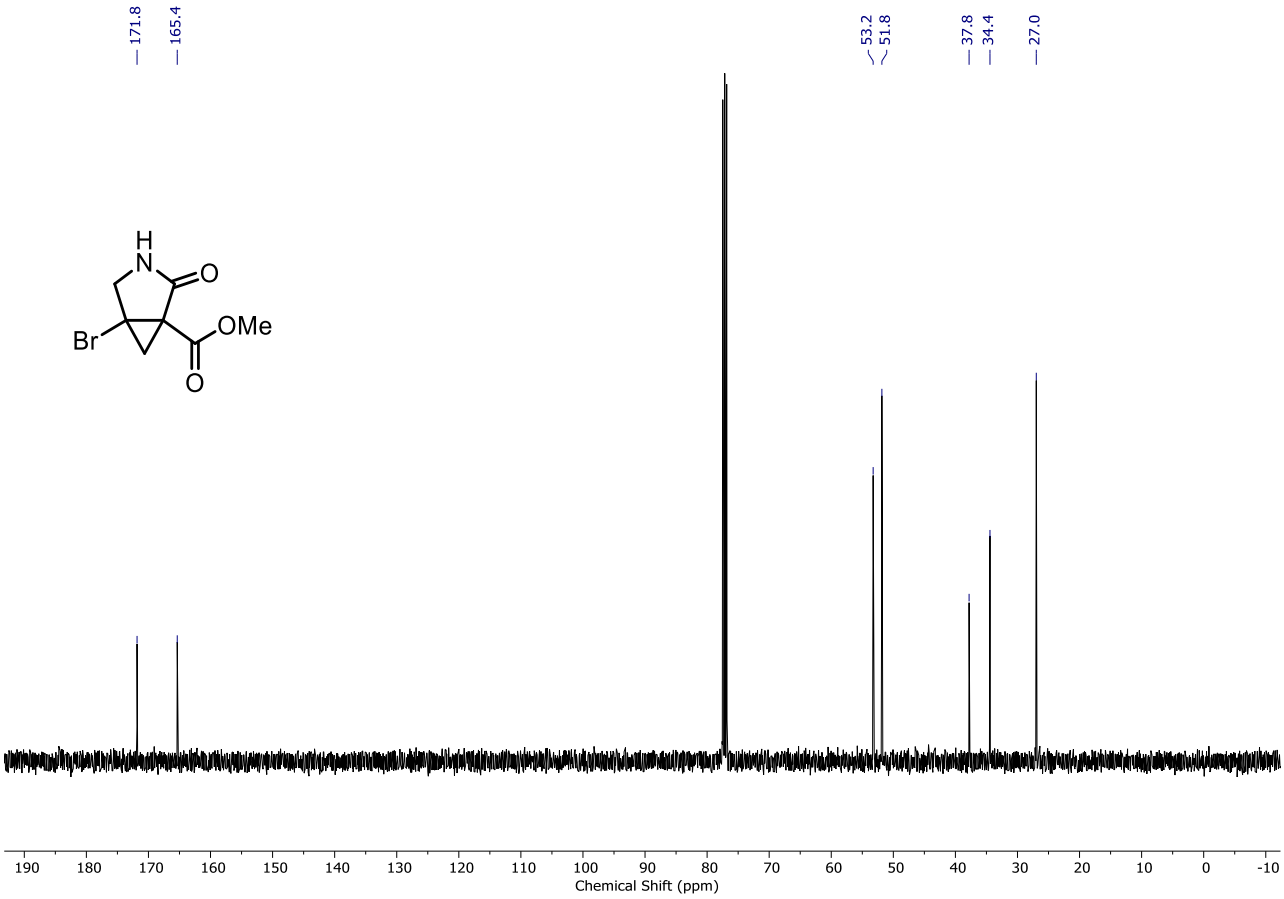
Dimethyl 2-(azidomethyl)-2-bromocyclopropane-1,1-dicarboxylate (14) ^{13}C NMR (101 MHz, $CDCl_3$)



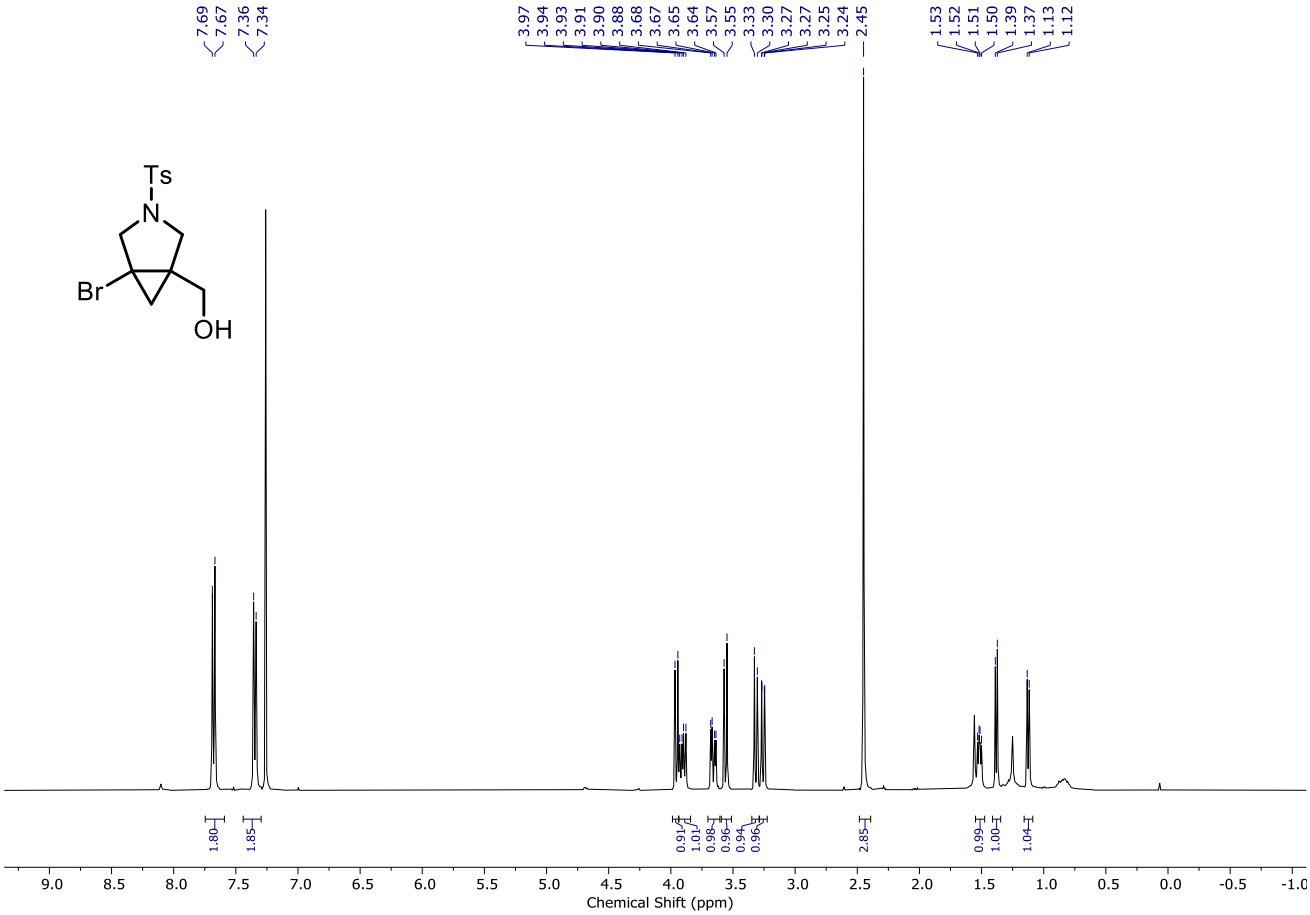
Methyl 5-bromo-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (15) ^{1}H NMR (400 MHz, $CDCl_3$)



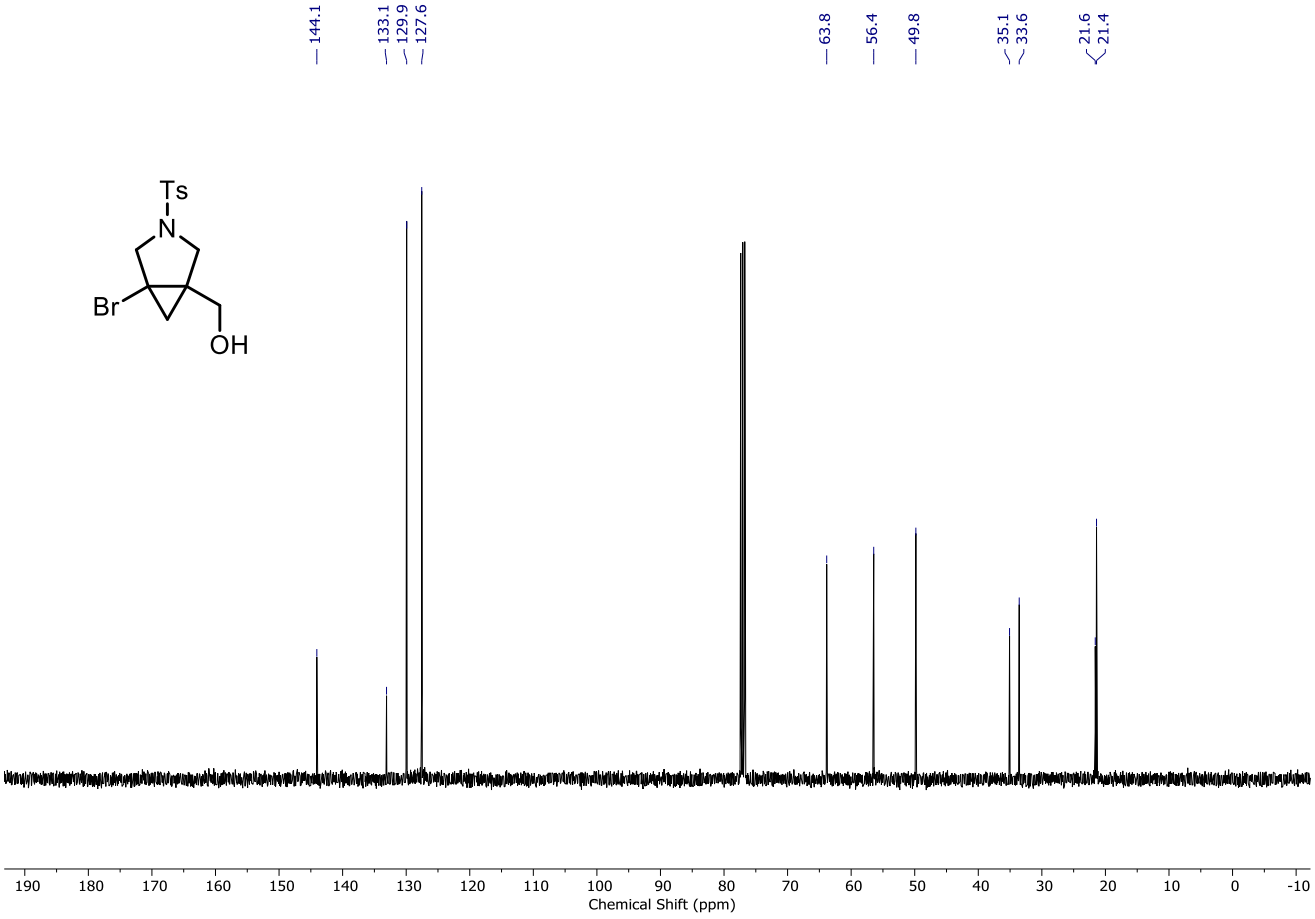
Methyl 5-bromo-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (15) ^{13}C NMR (101 MHz, $CDCl_3$)



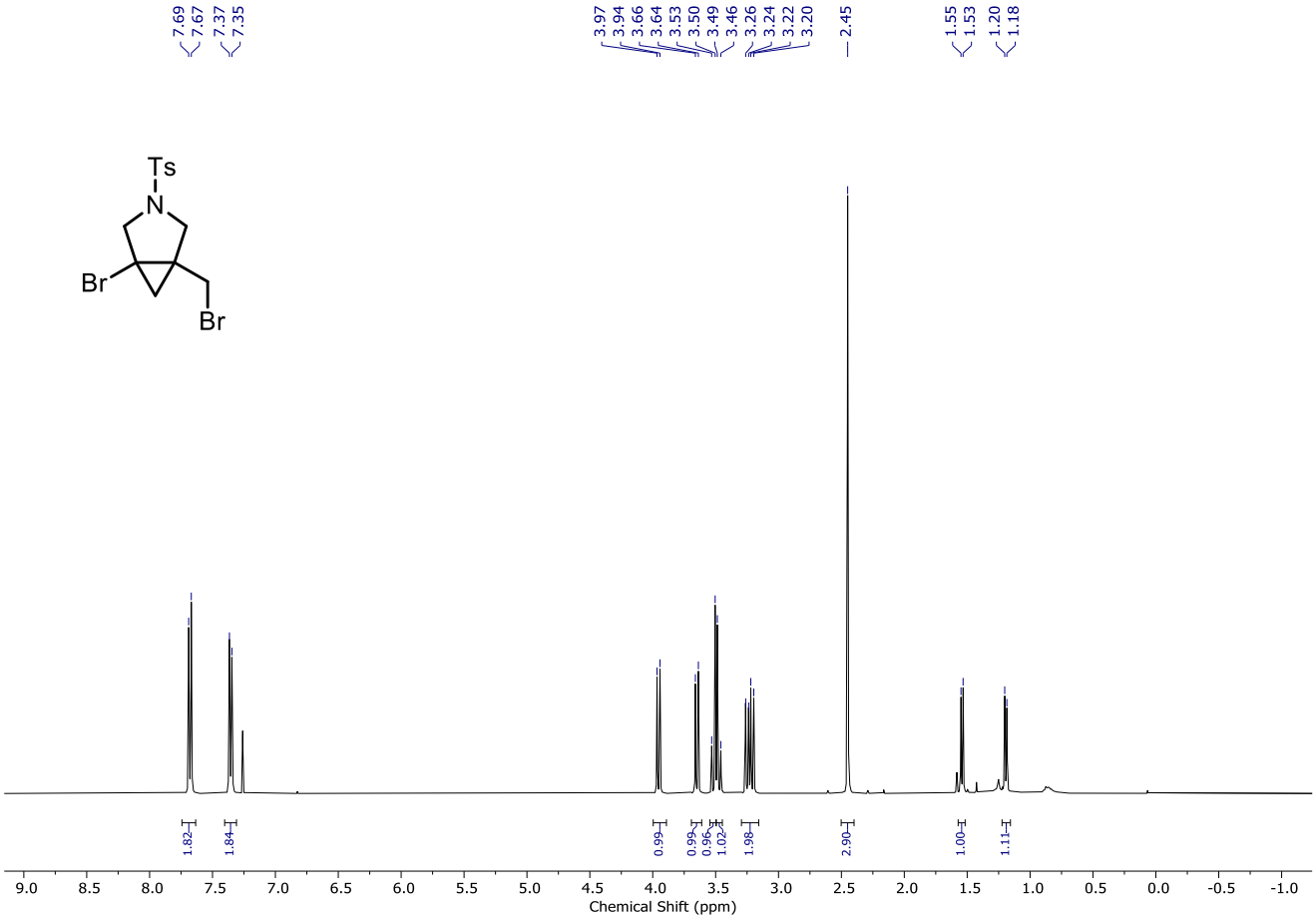
(5-Bromo-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (16) ^{1}H NMR (400 MHz, $CDCl_3$)



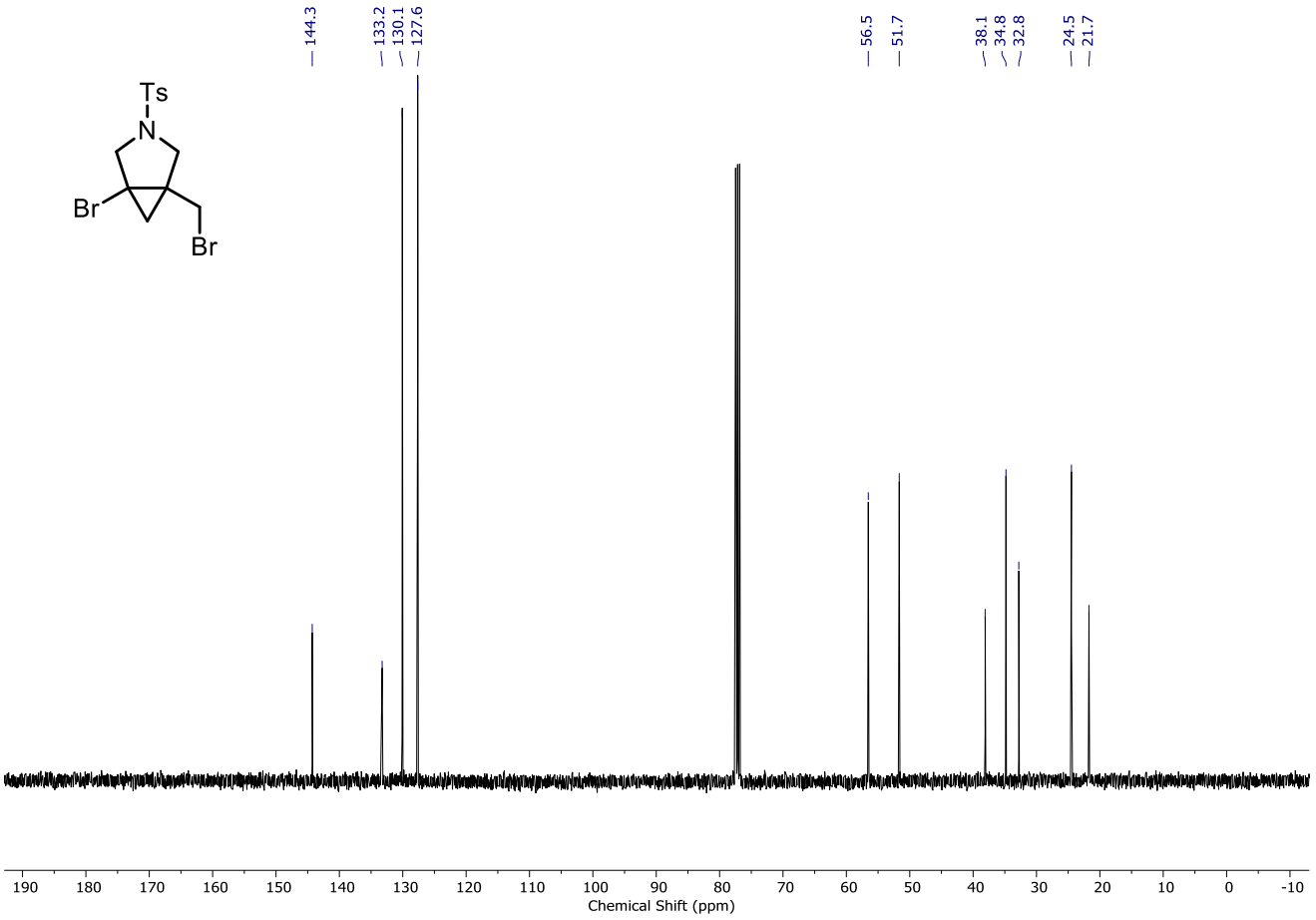
(5-Bromo-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (16) ^{13}C NMR (101 MHz, $CDCl_3$)



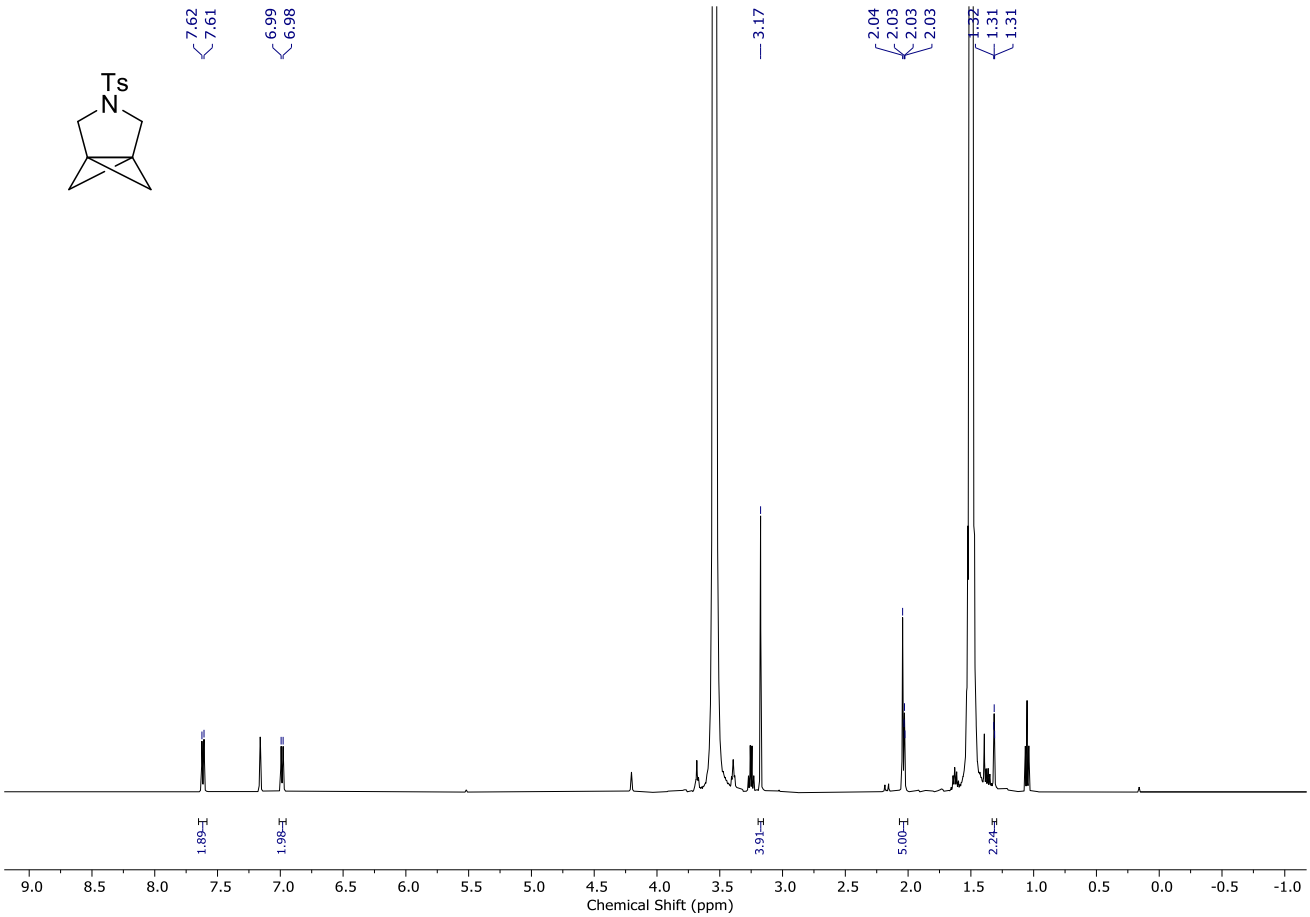
1-Bromo-5-(bromomethyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (17) ^{1}H NMR (400 MHz, $CDCl_3$)



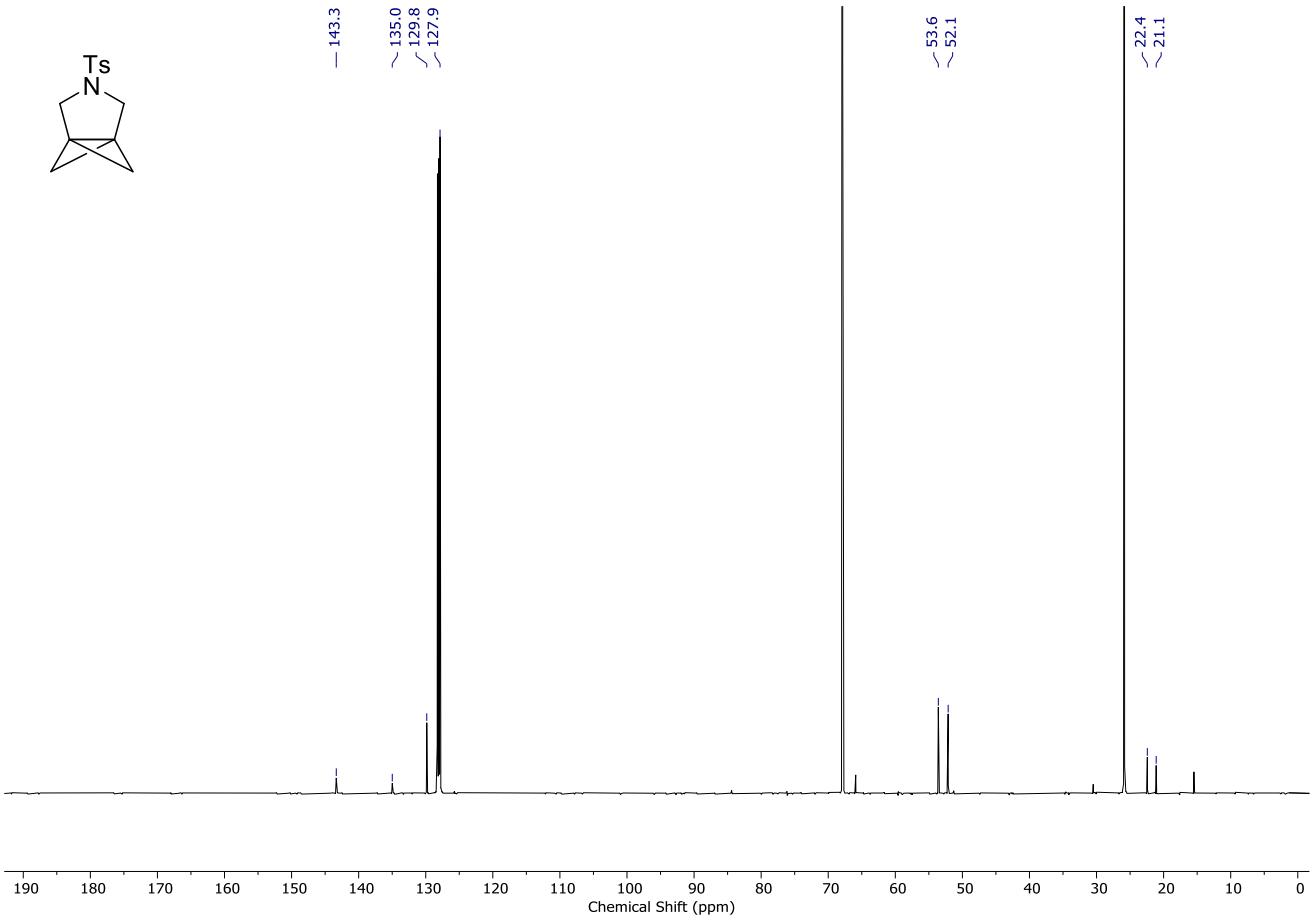
1-Bromo-5-(bromomethyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (17) ^{13}C NMR (101 MHz, $CDCl_3$)



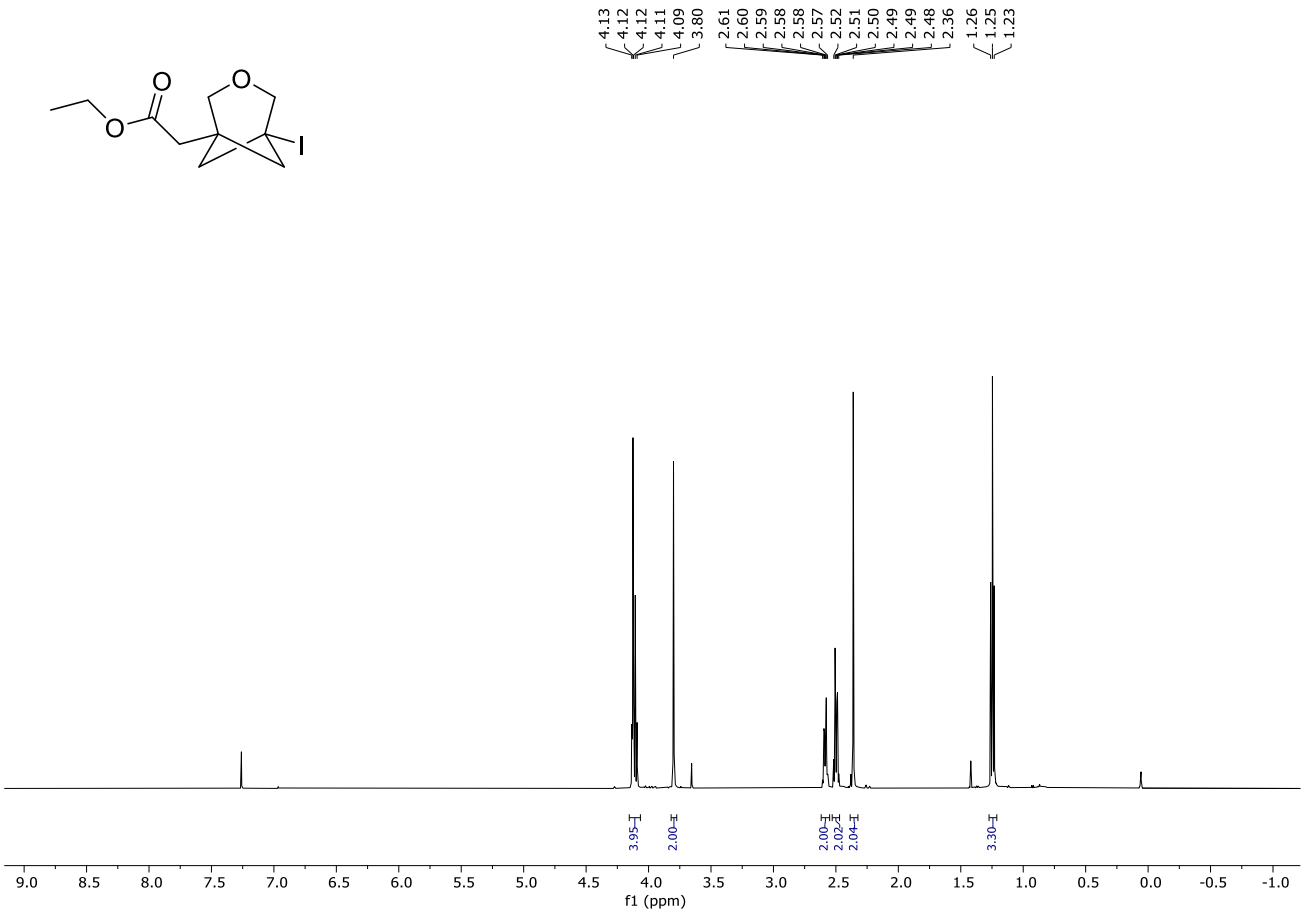
3-(Tosyl)-aza[3.1.1]propellane (15) ^{1}H NMR (500 MHz, C_6D_6) (contains some residual Et_2O)



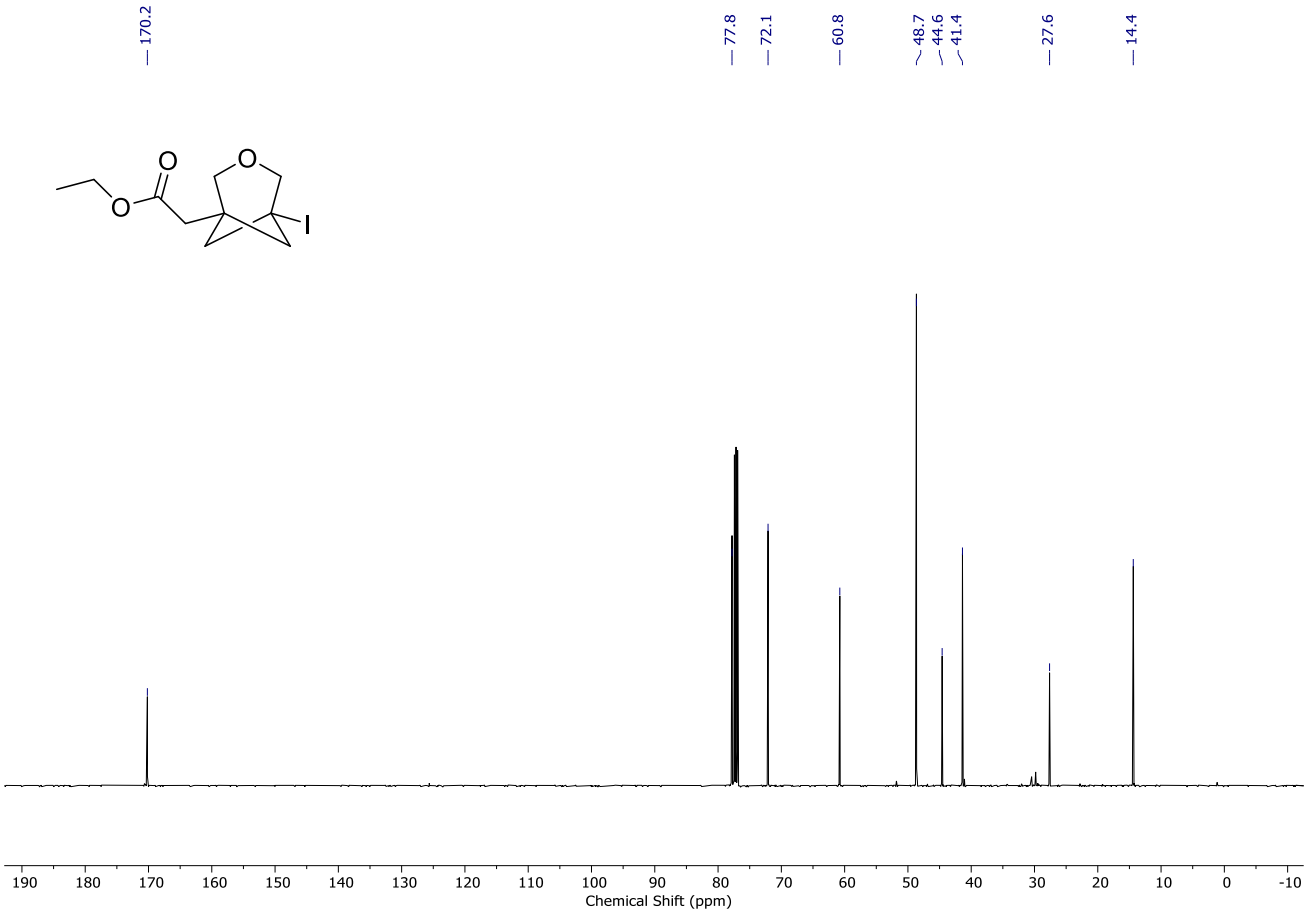
3-(Tosyl)-aza[3.1.1]propellane (15) ^{13}C NMR (126 MHz, C_6D_6) (contains some residual Et_2O)



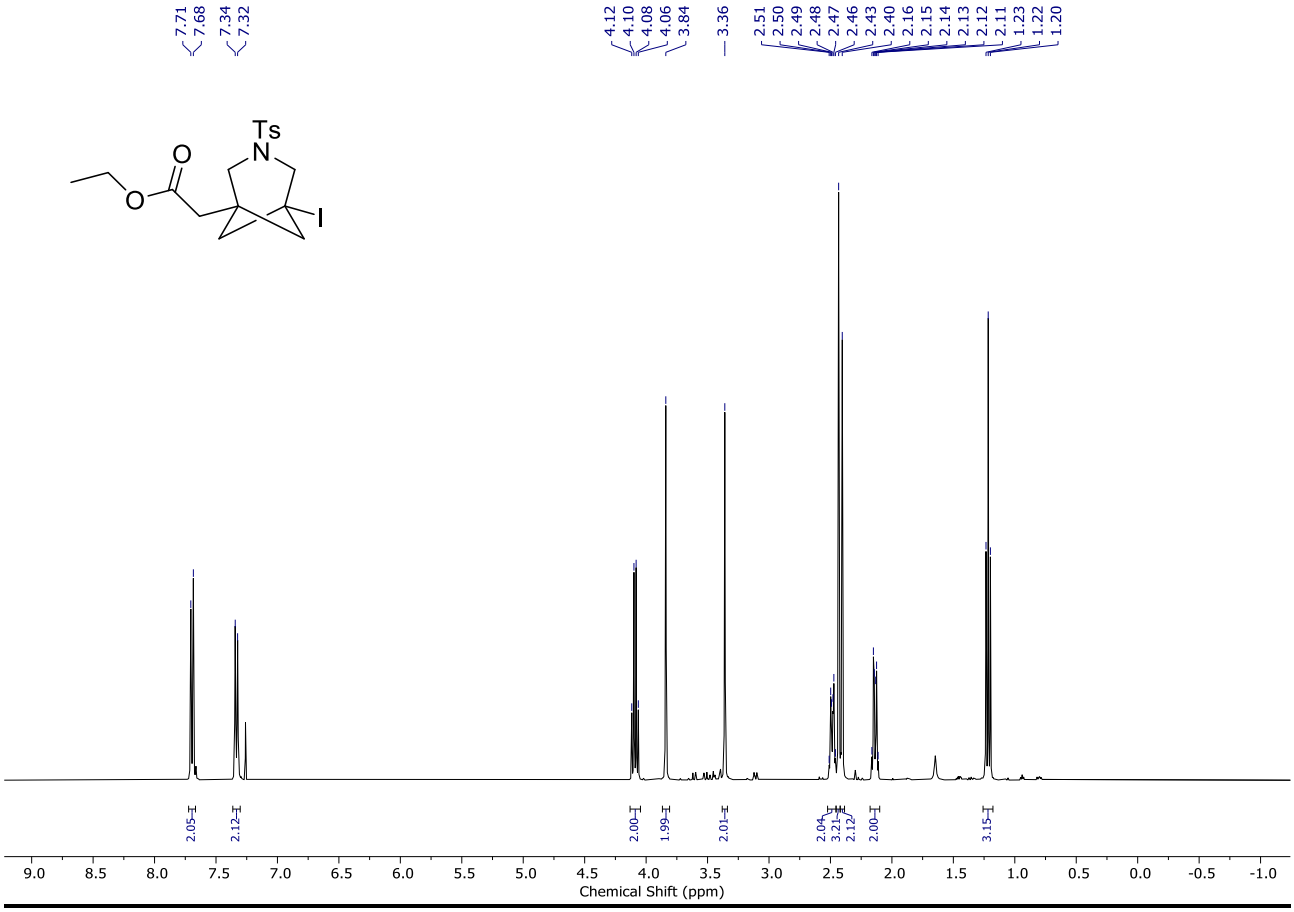
Ethyl 2-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetate (18a) ^{1}H NMR (500 MHz, $CDCl_3$)



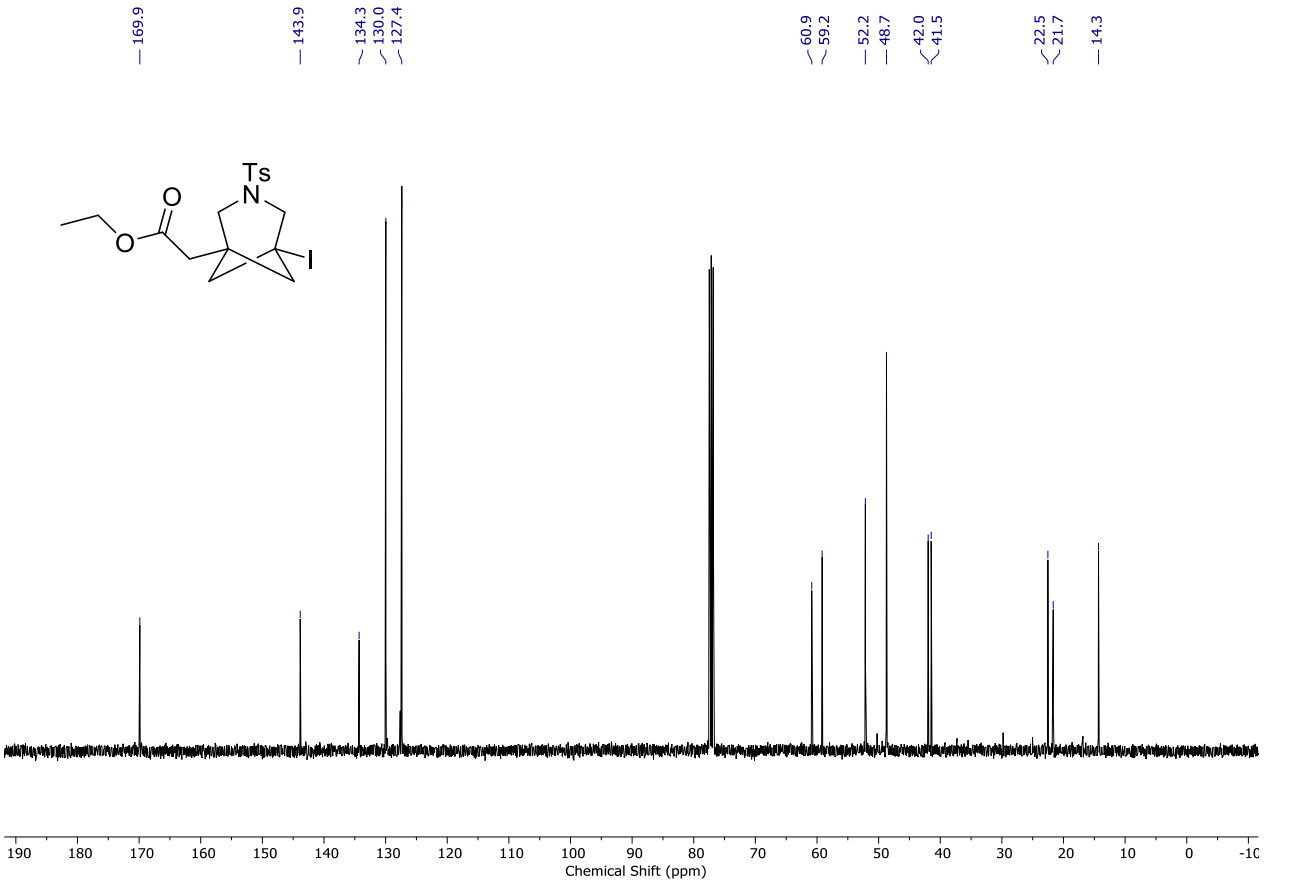
Ethyl 2-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetate (18a) ^{13}C NMR (126 MHz, $CDCl_3$)



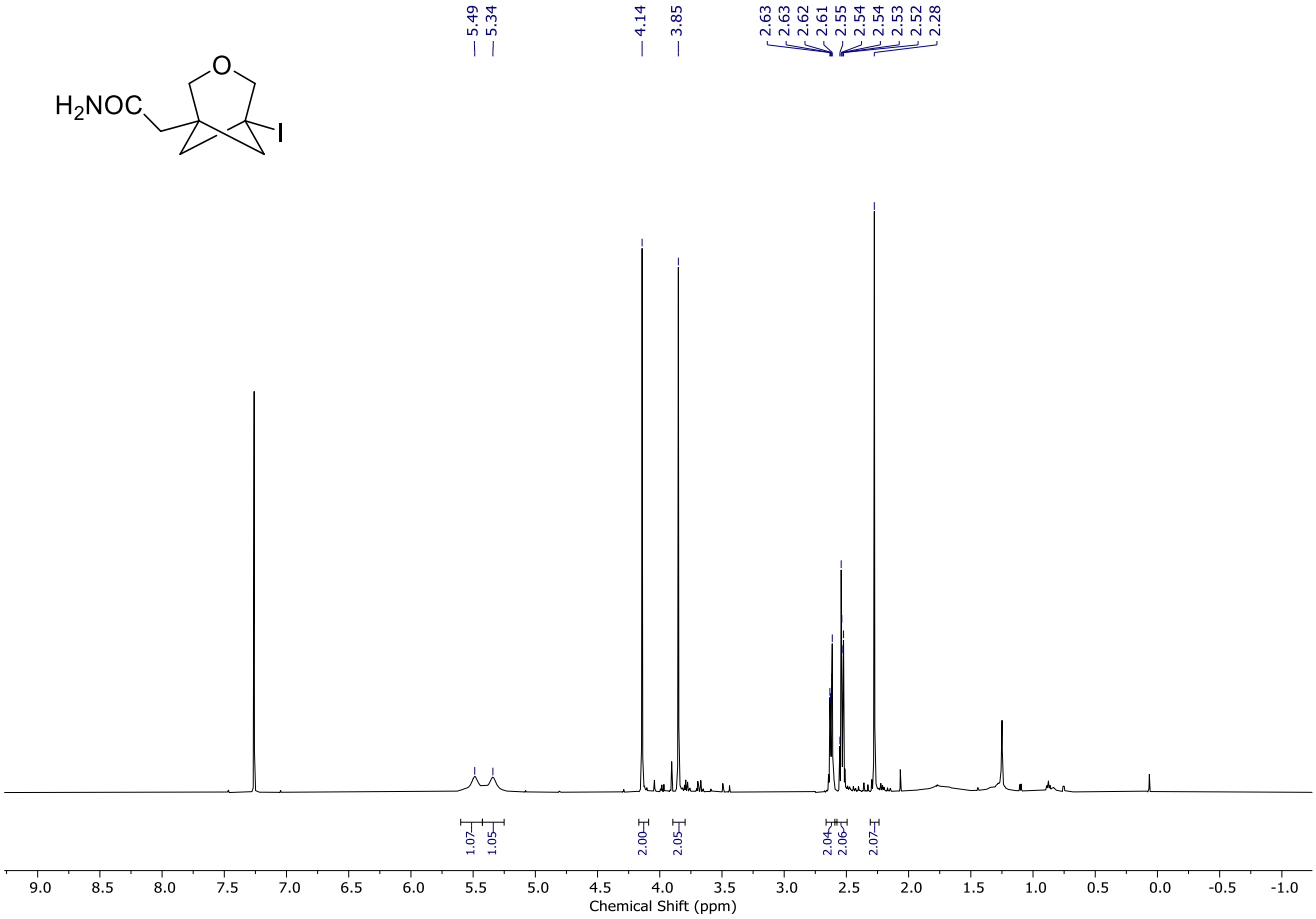
Ethyl 2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetate (18b) ^{1}H NMR (400 MHz, $CDCl_3$)



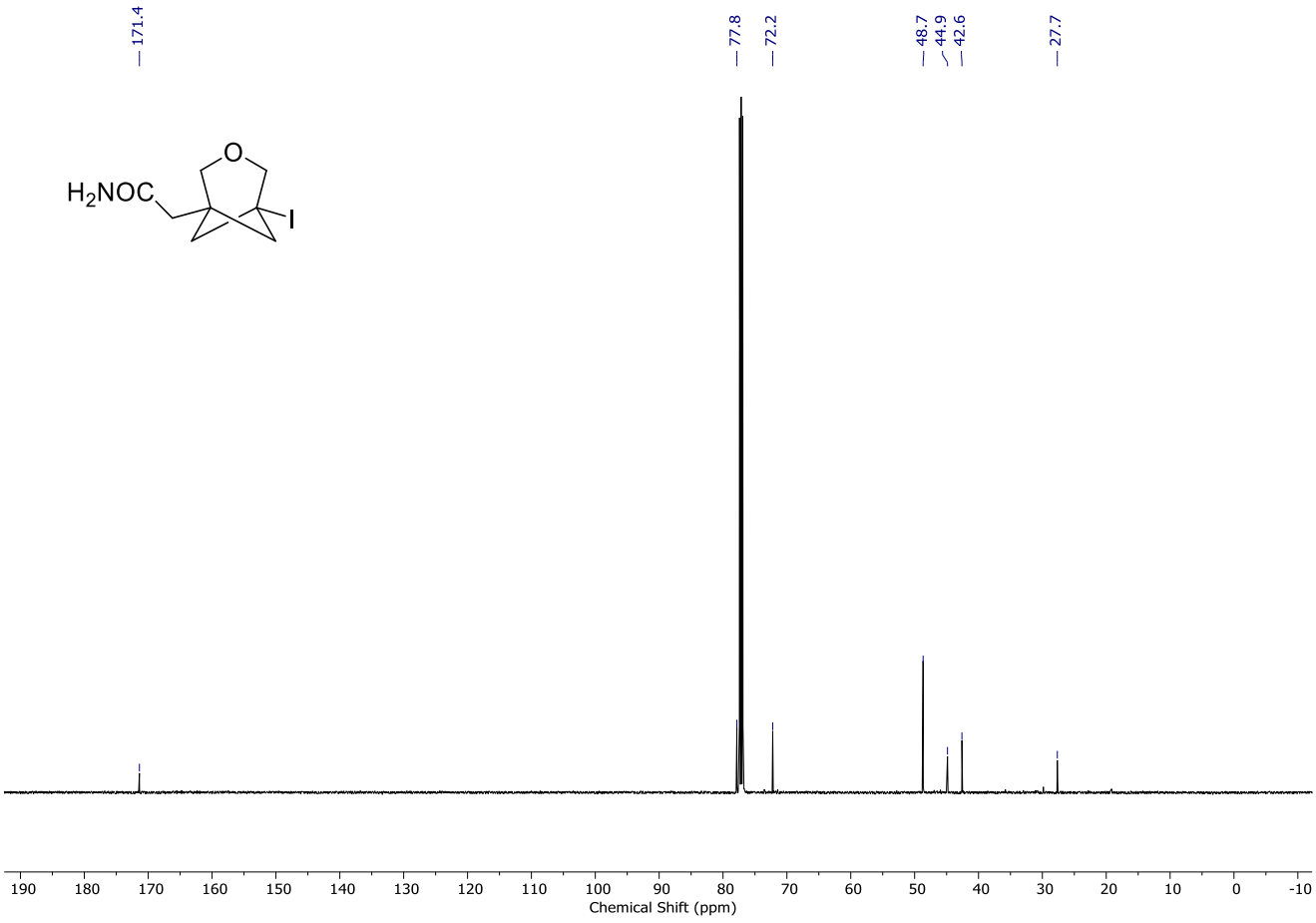
Ethyl 2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetate (18b) ^{13}C NMR (101 MHz, $CDCl_3$)



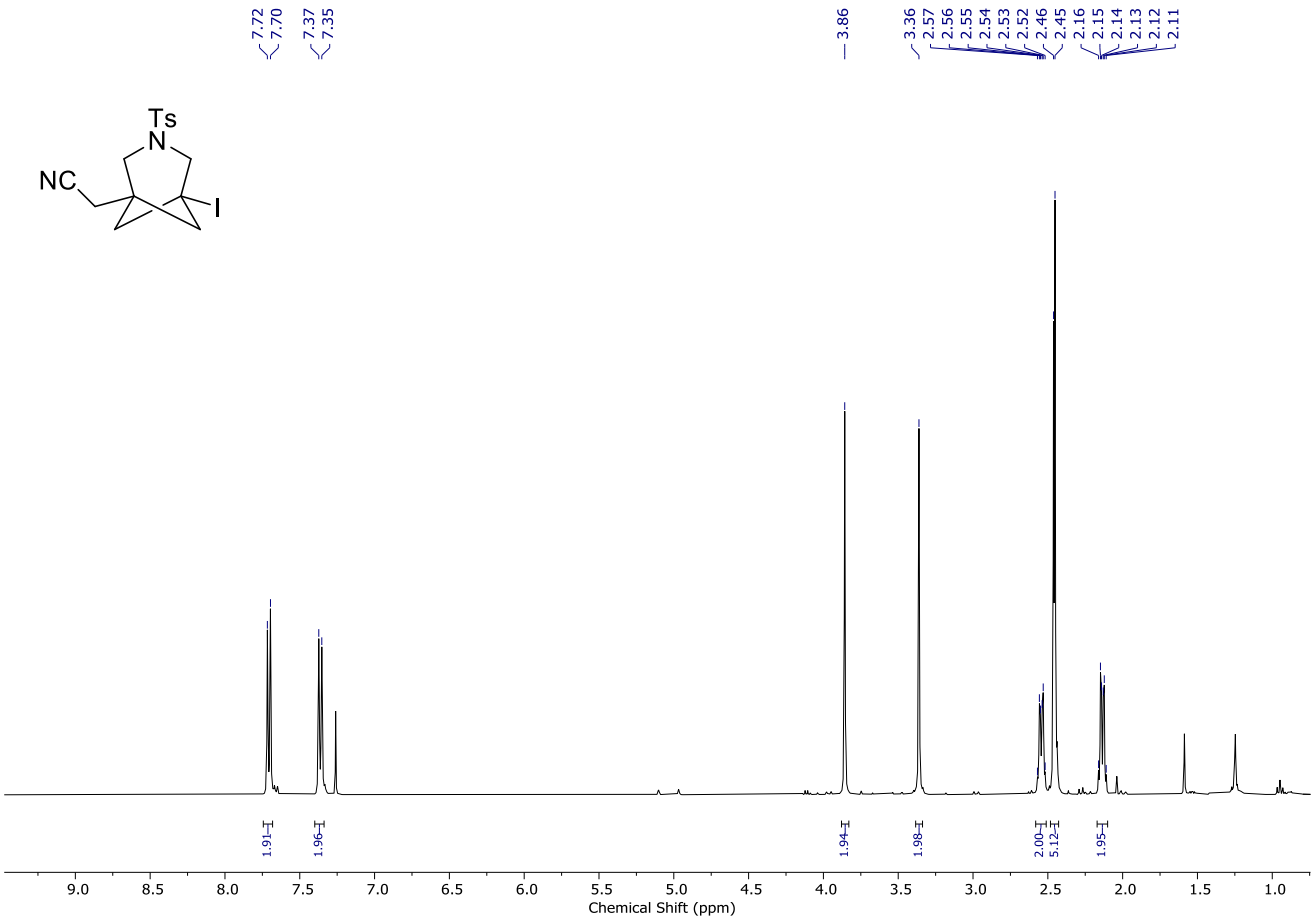
2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetamide (18c) ^{1}H NMR (500 MHz, $CDCl_3$)



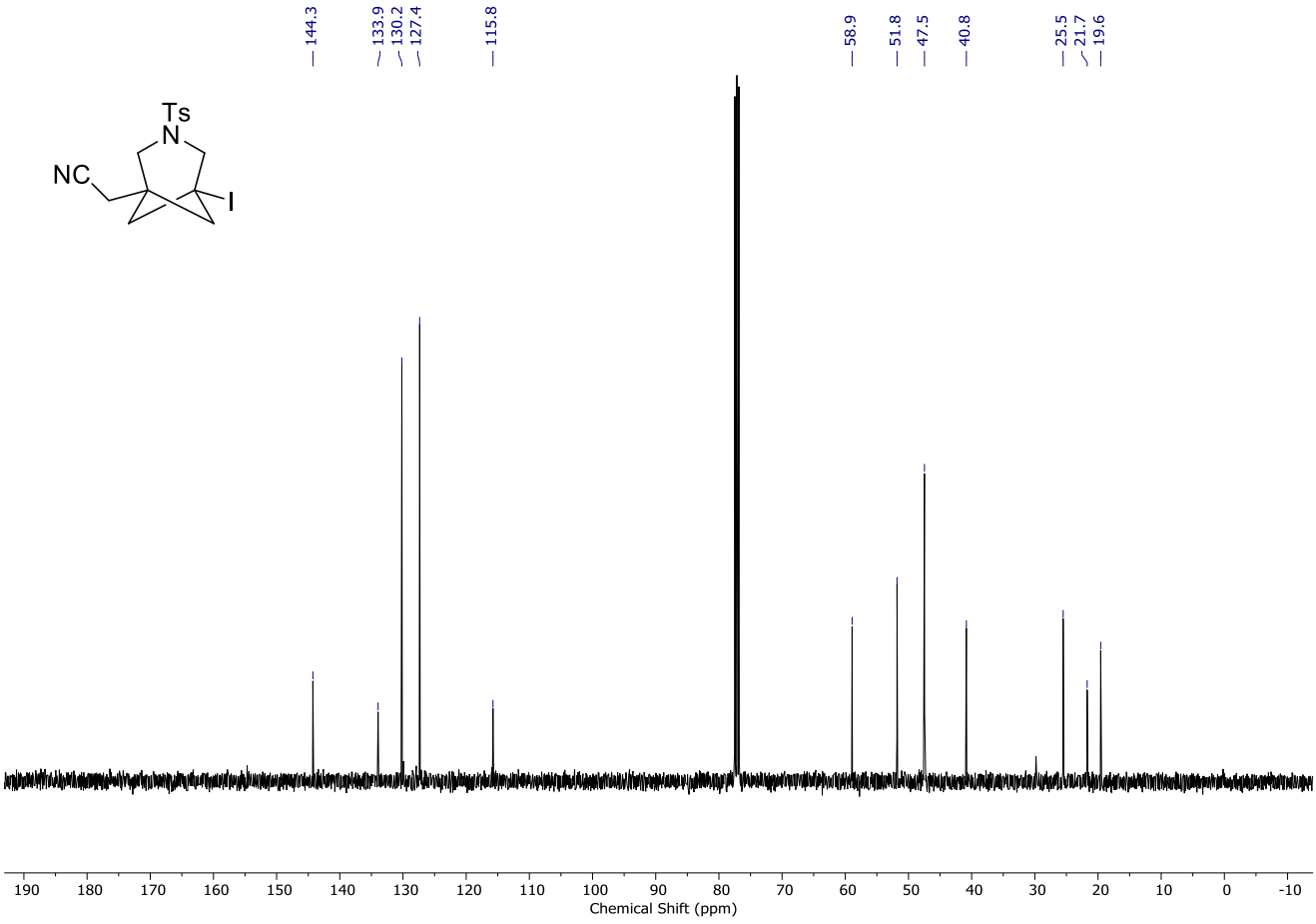
2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetamide (18c) ^{13}C NMR (126 MHz, $CDCl_3$)



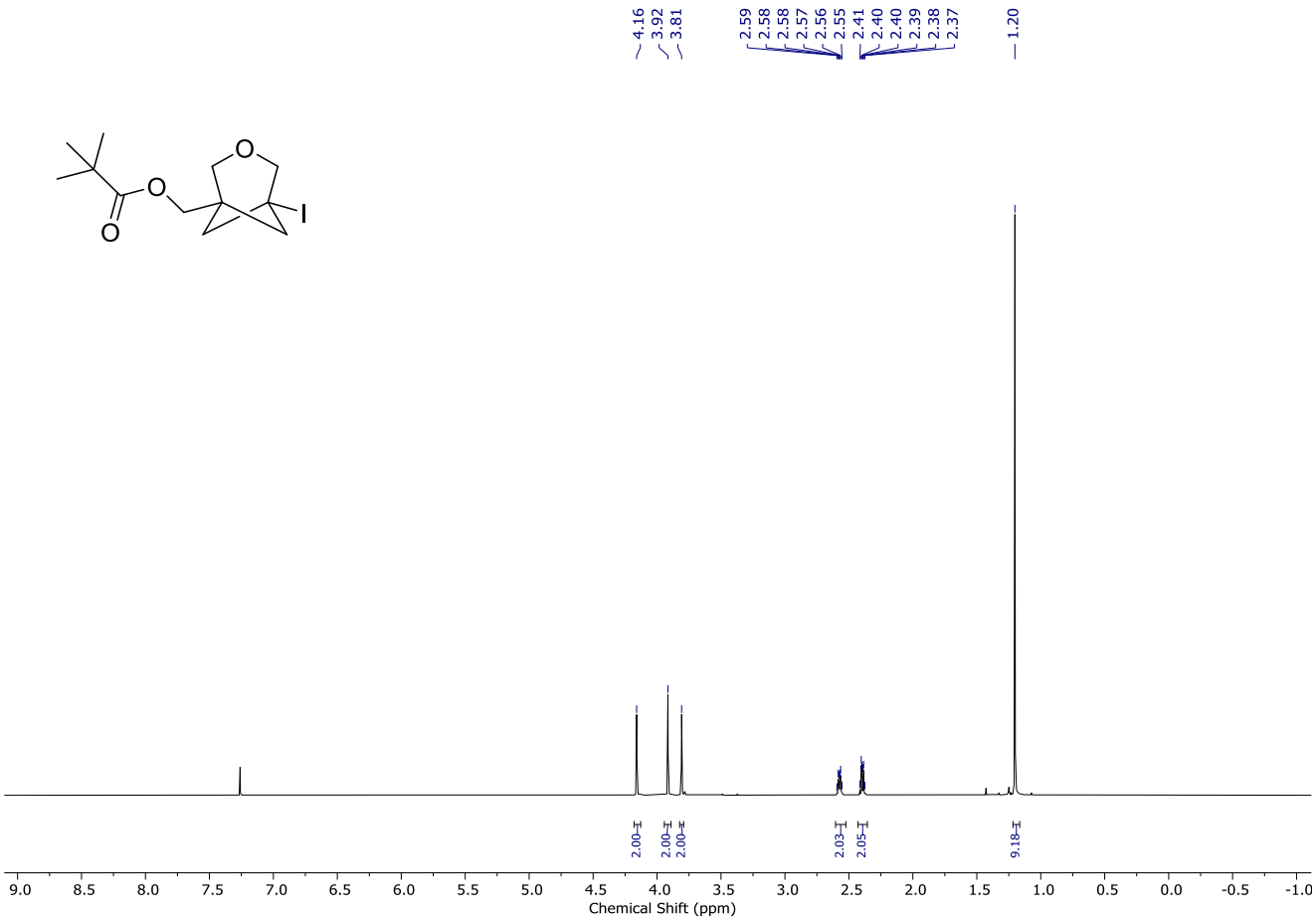
2-(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetonitrile (18d) ^{1}H NMR (400 MHz, $CDCl_3$)



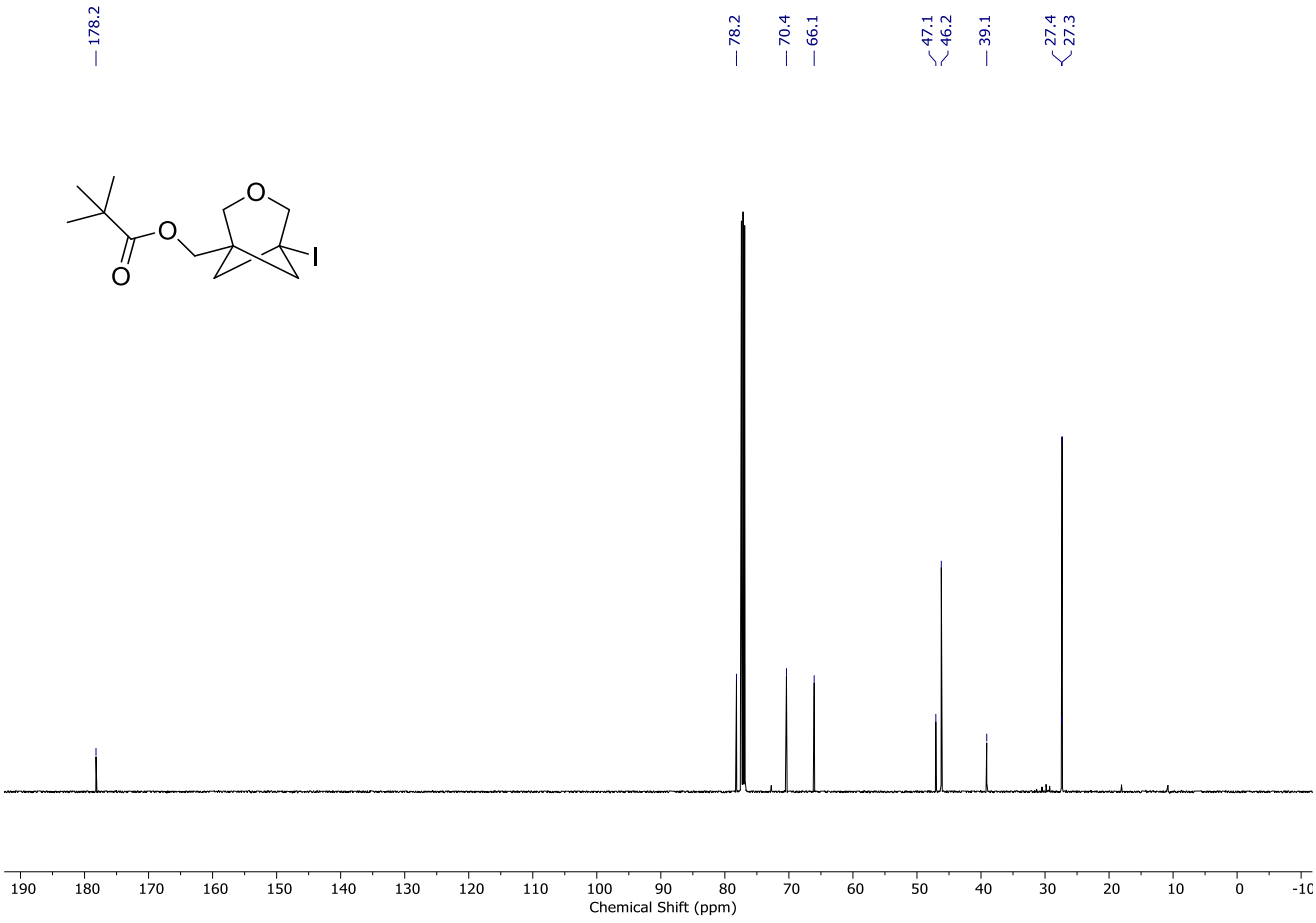
2-(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetonitrile (18d) ^{13}C NMR (101 MHz, $CDCl_3$)



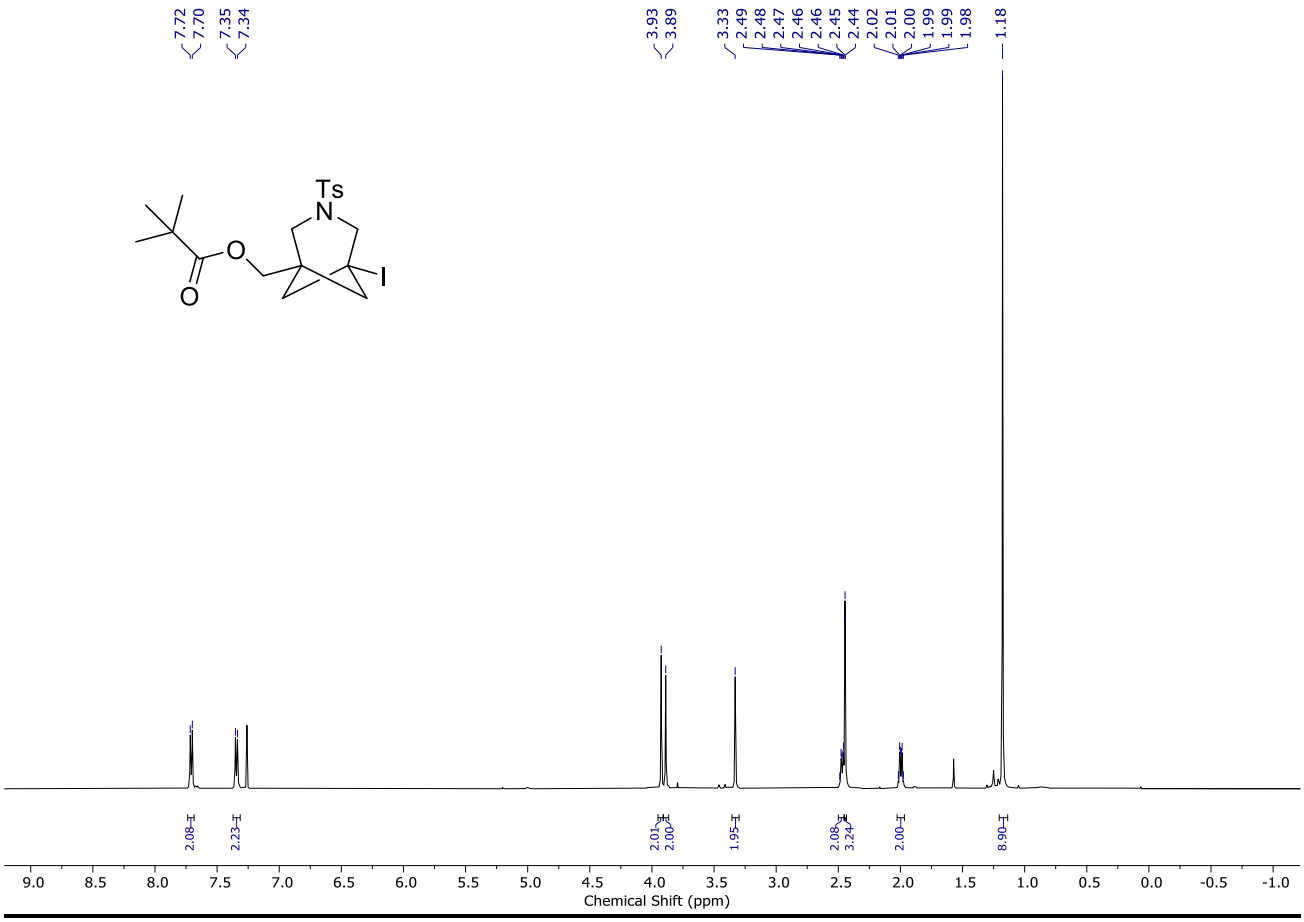
(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (18e) ^{1}H NMR (500 MHz, $CDCl_3$)



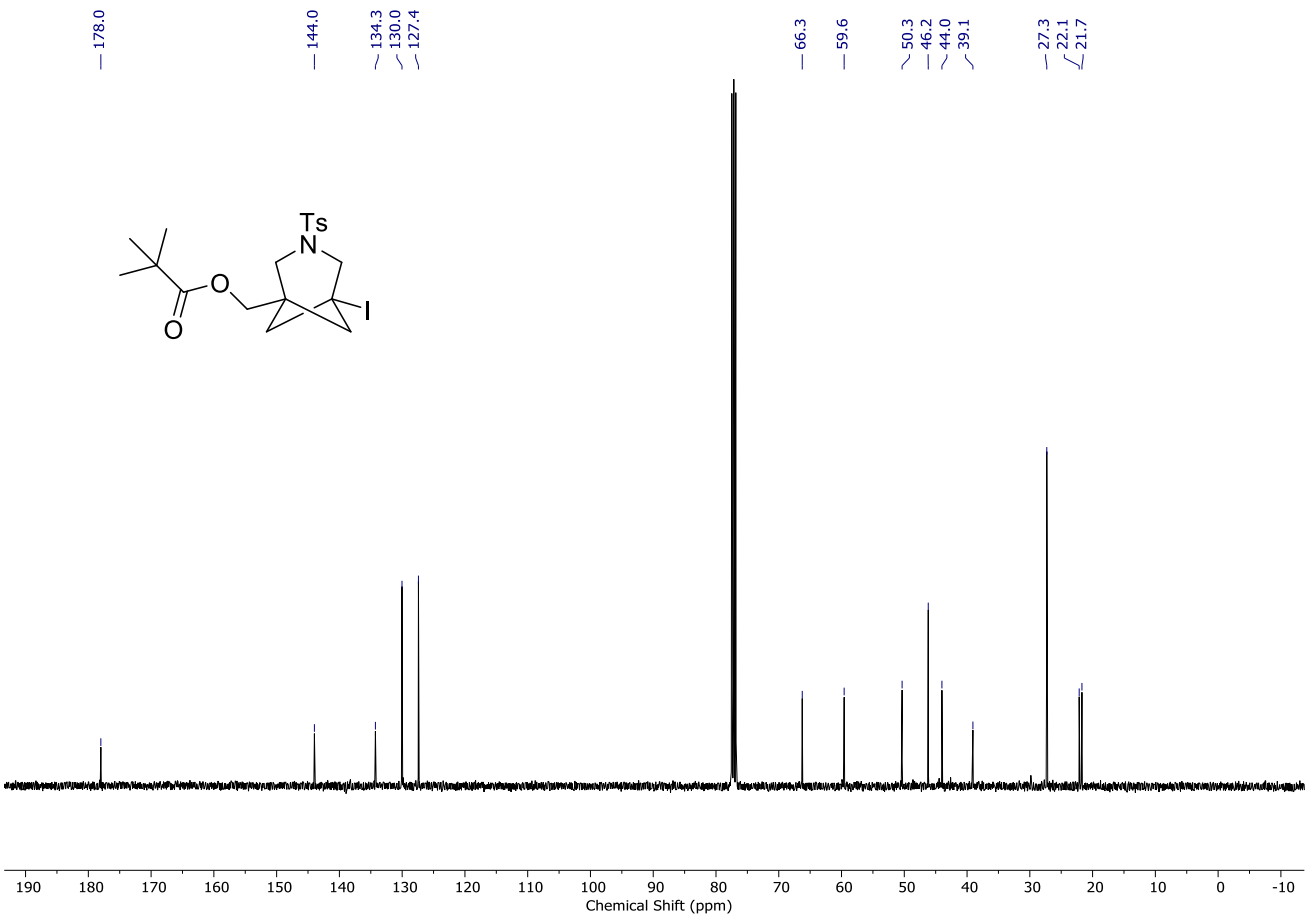
(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (18e) ^{13}C NMR (126 MHz, $CDCl_3$)



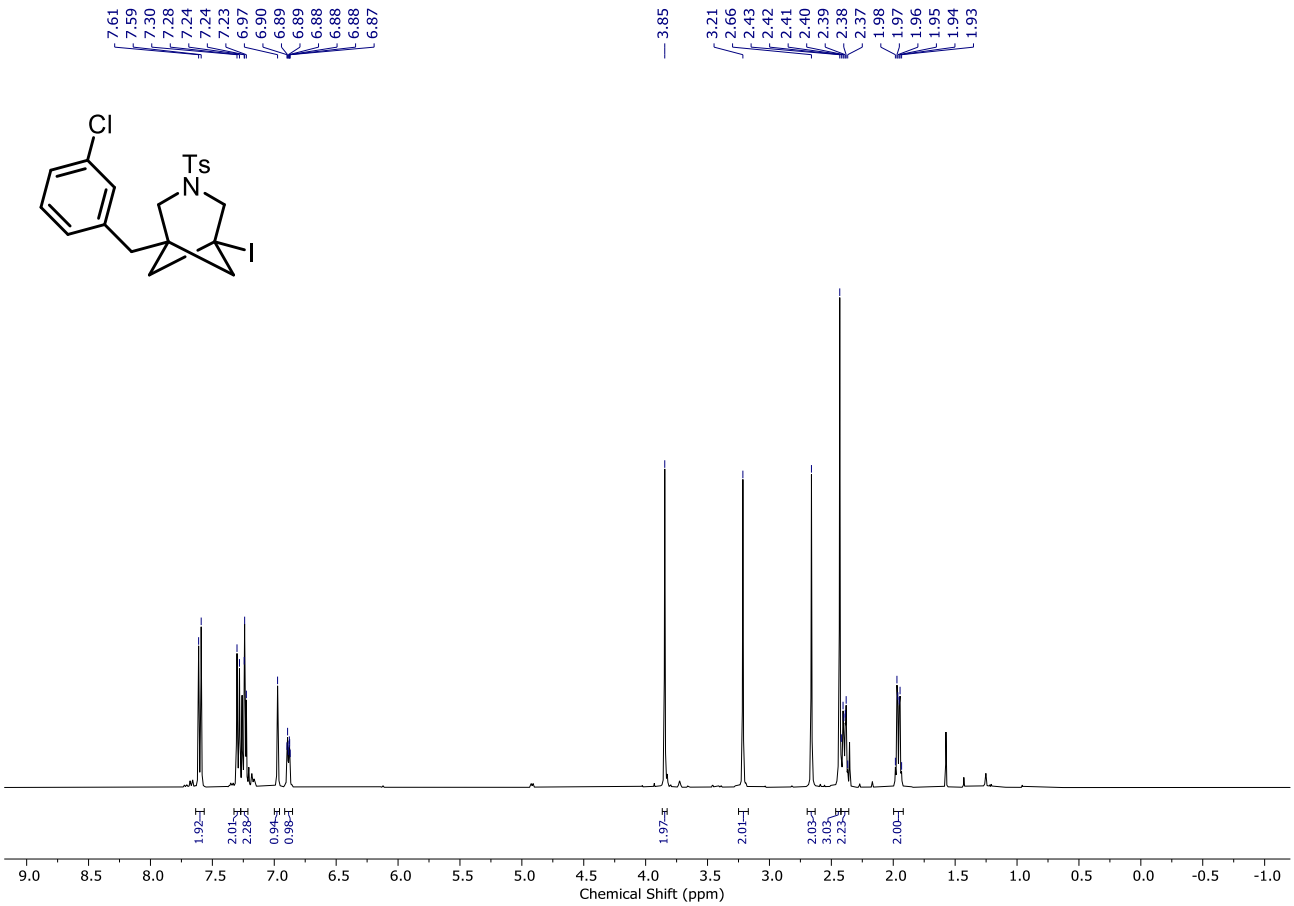
(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (18f) ^{1}H NMR (500 MHz, $CDCl_3$)



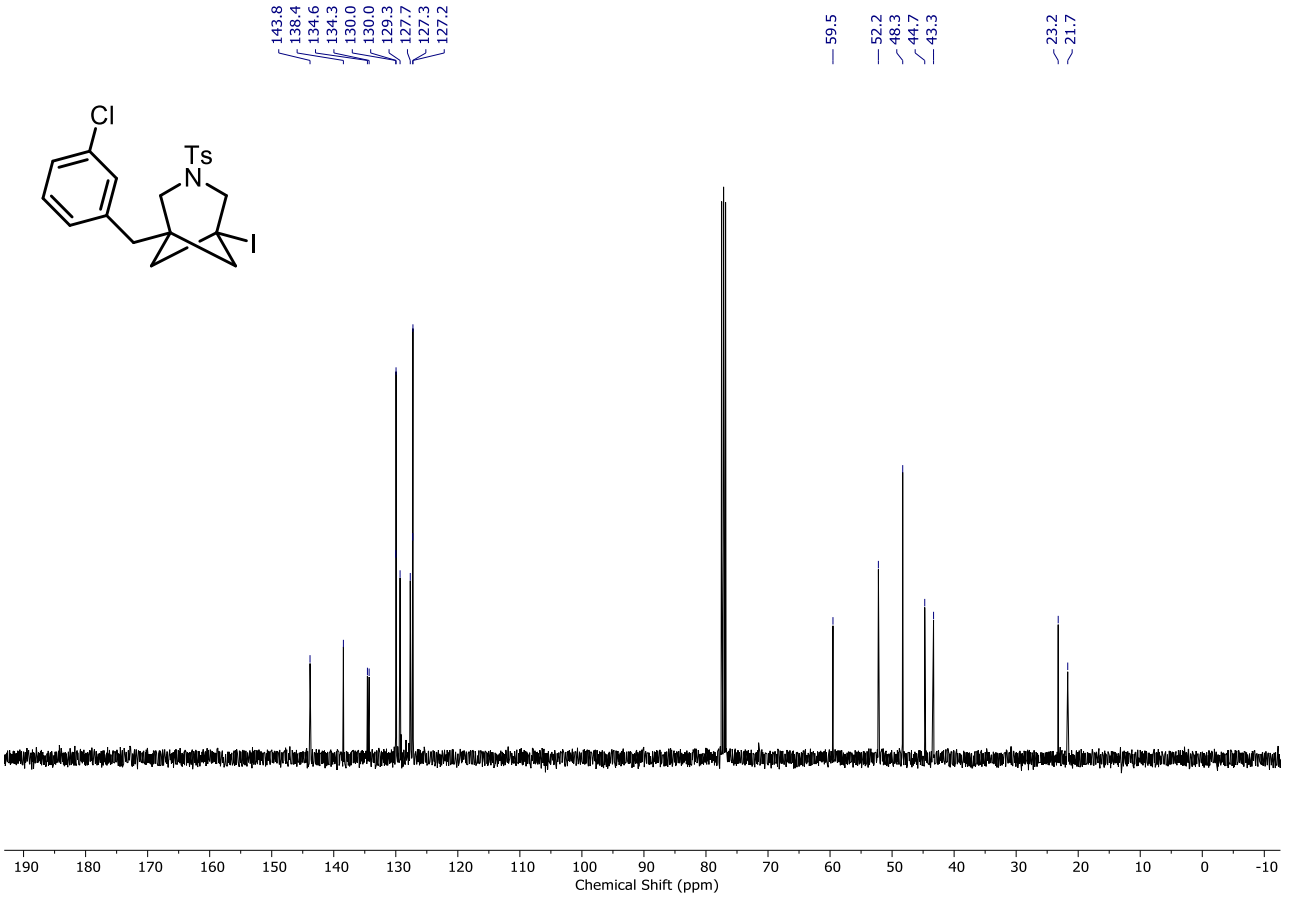
(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (18f) ^{13}C NMR (101 MHz, $CDCl_3$)



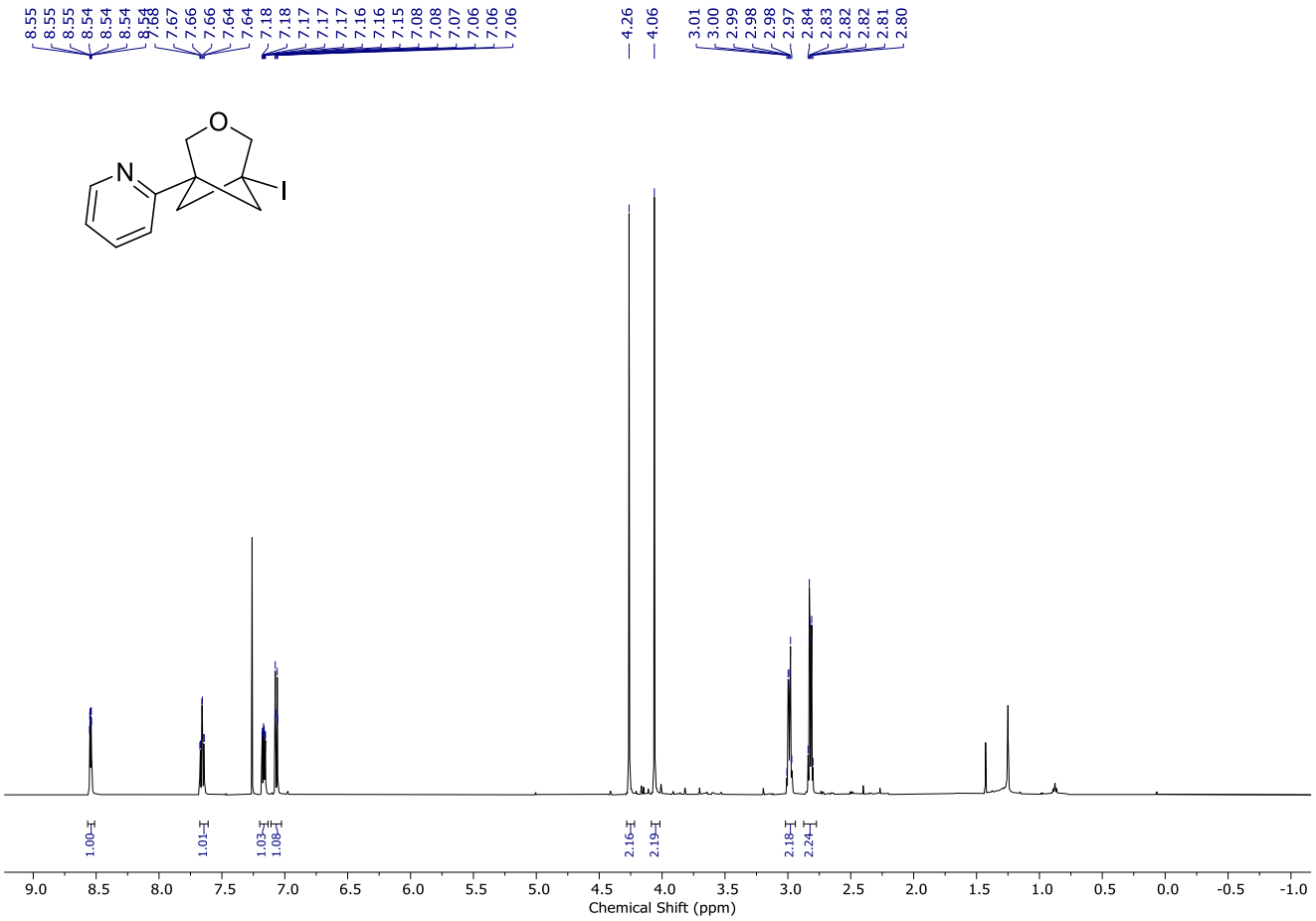
1-(3-Chlorobenzyl)-5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptane (18g) ^{1}H NMR (400 MHz, $CDCl_3$)



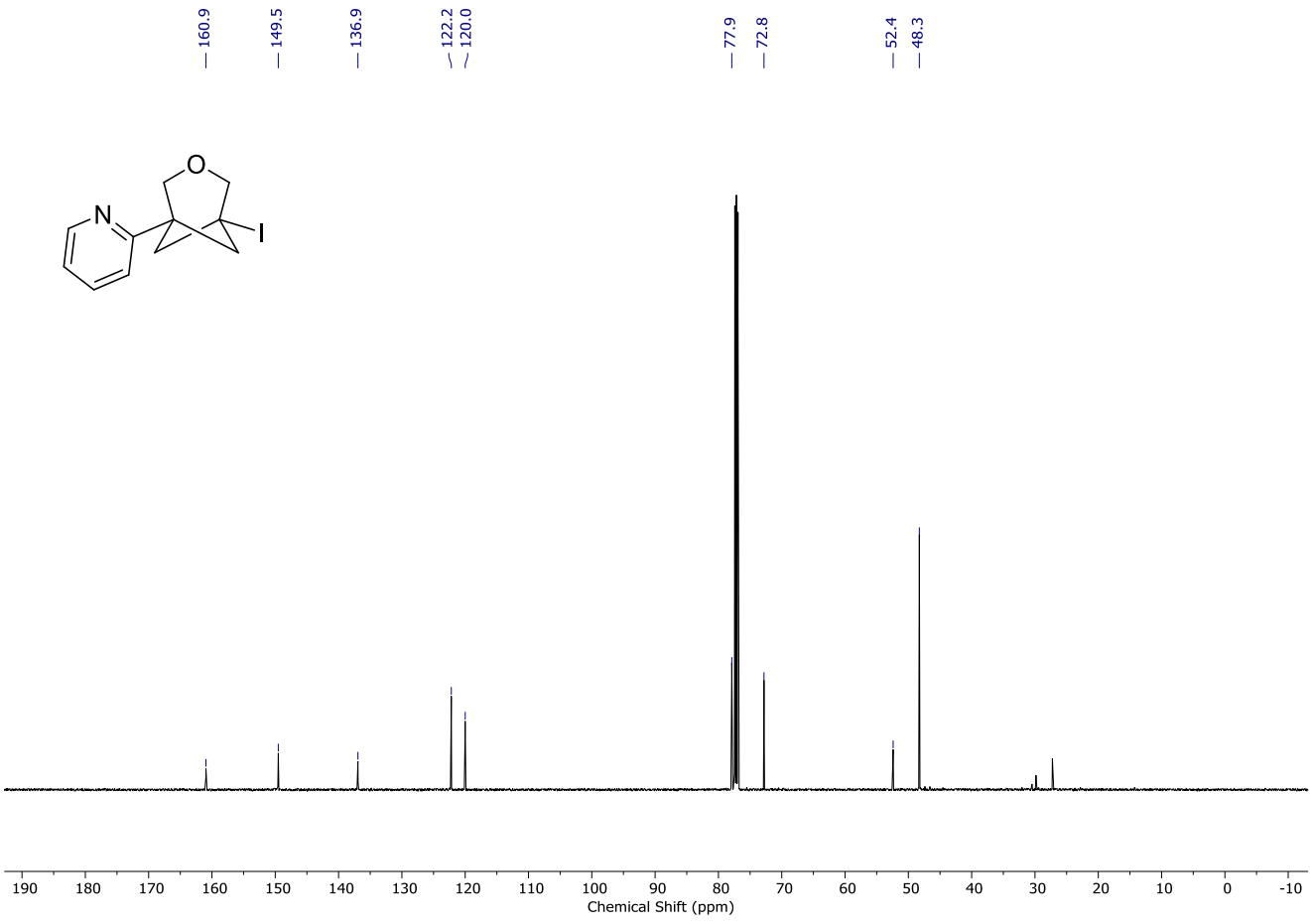
1-(3-Chlorobenzyl)-5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptane (18g) ^{13}C NMR (101 MHz, $CDCl_3$)



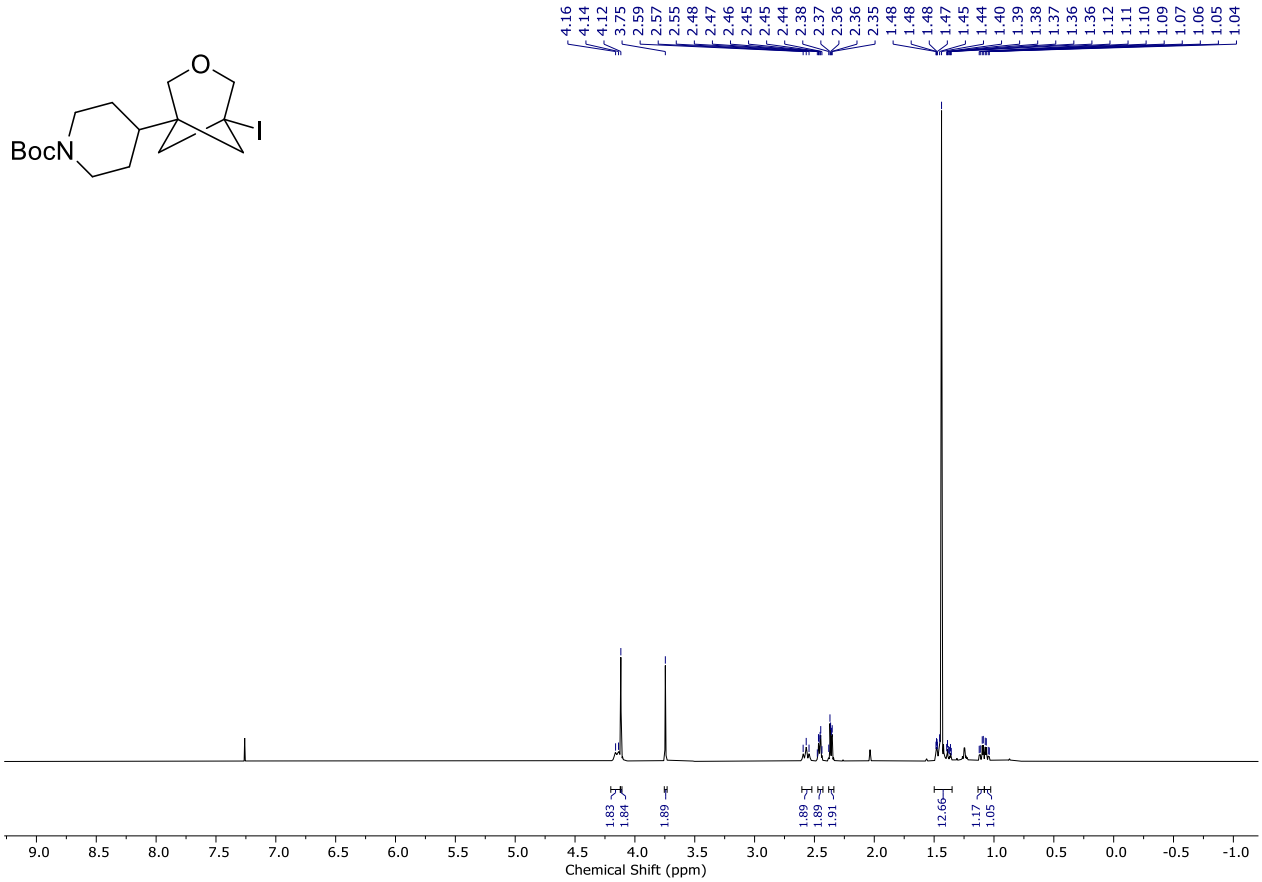
2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)pyridine (18h) ^{1}H NMR (500 MHz, $CDCl_3$)



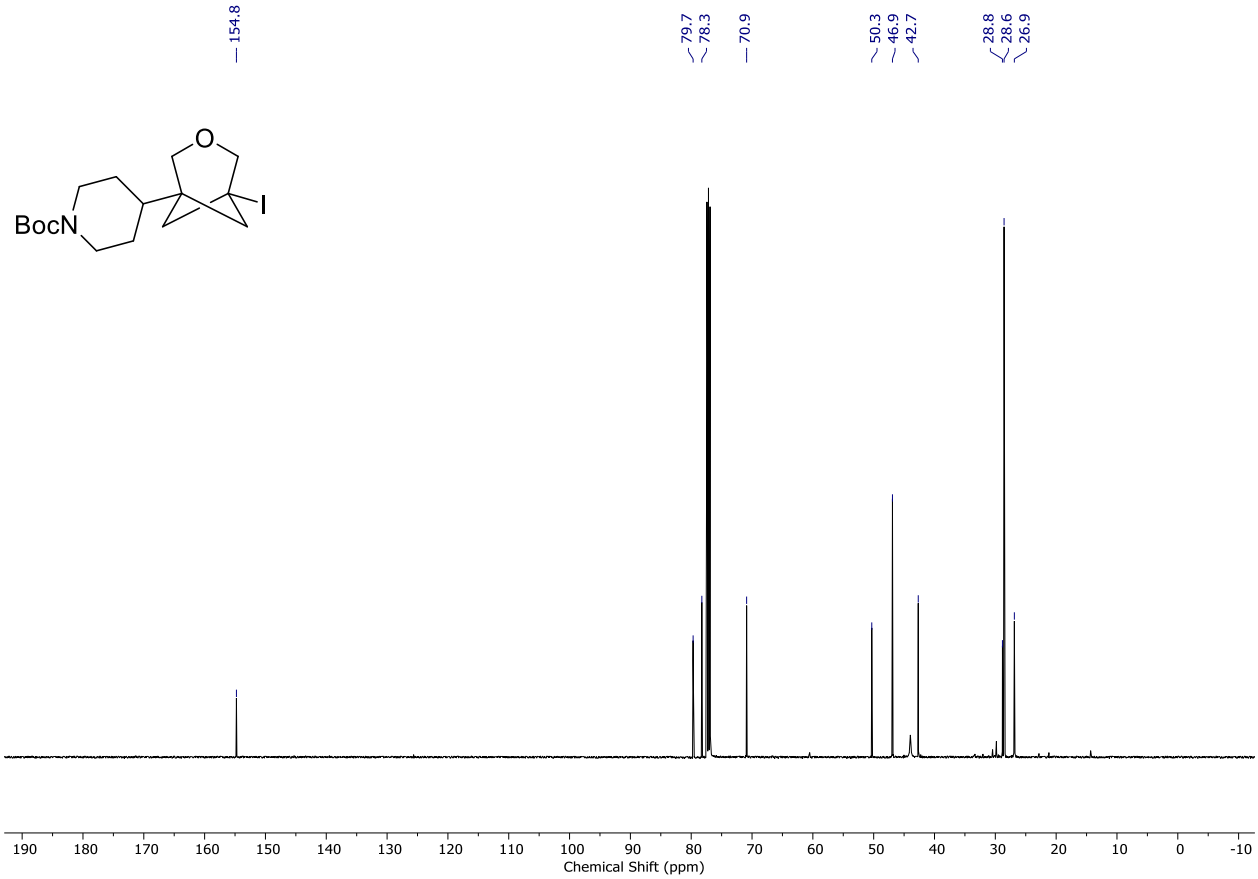
2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)pyridine (18h) ^{13}C NMR (126 MHz, $CDCl_3$)



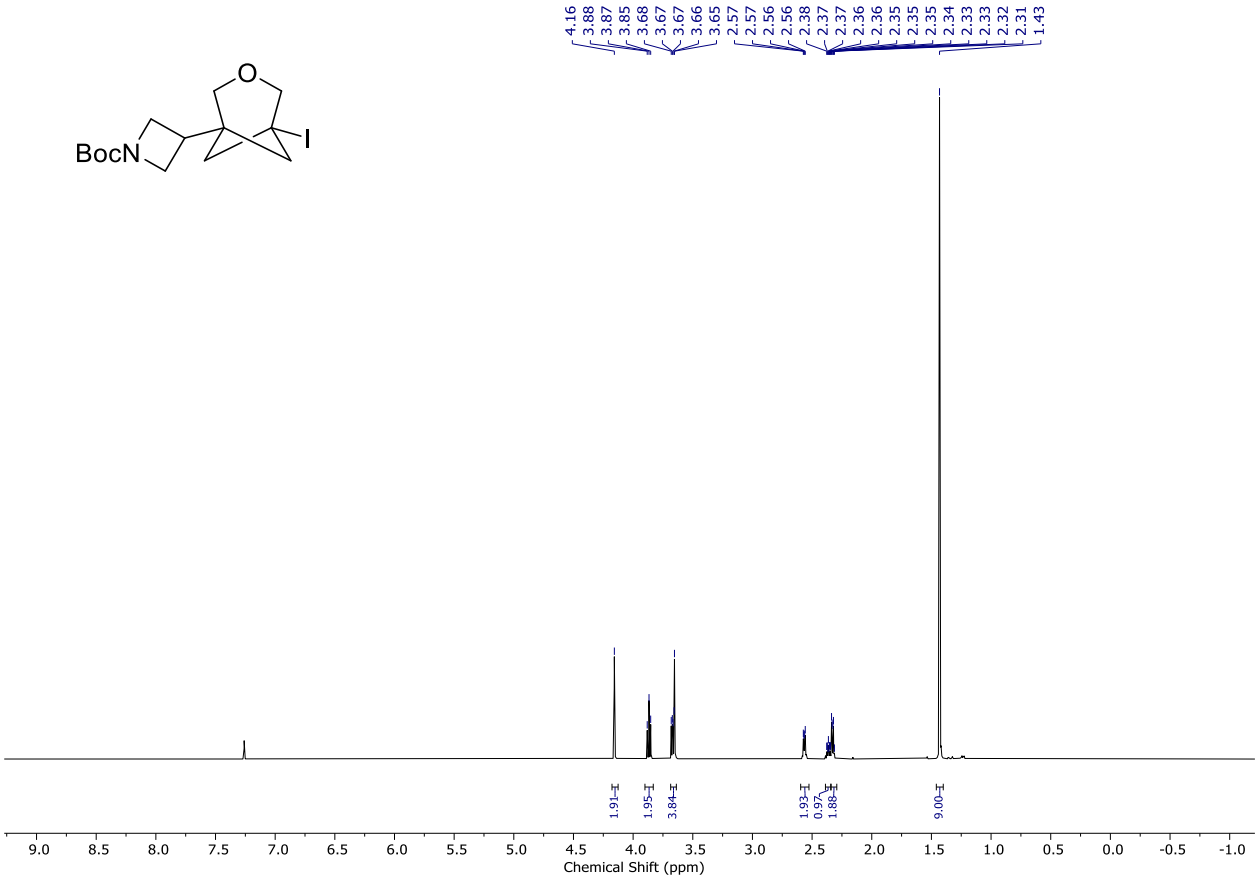
***tert*-Butyl 4-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)piperidine-1-carboxylate (18i) ^{1}H NMR (500 MHz, $CDCl_3$)**



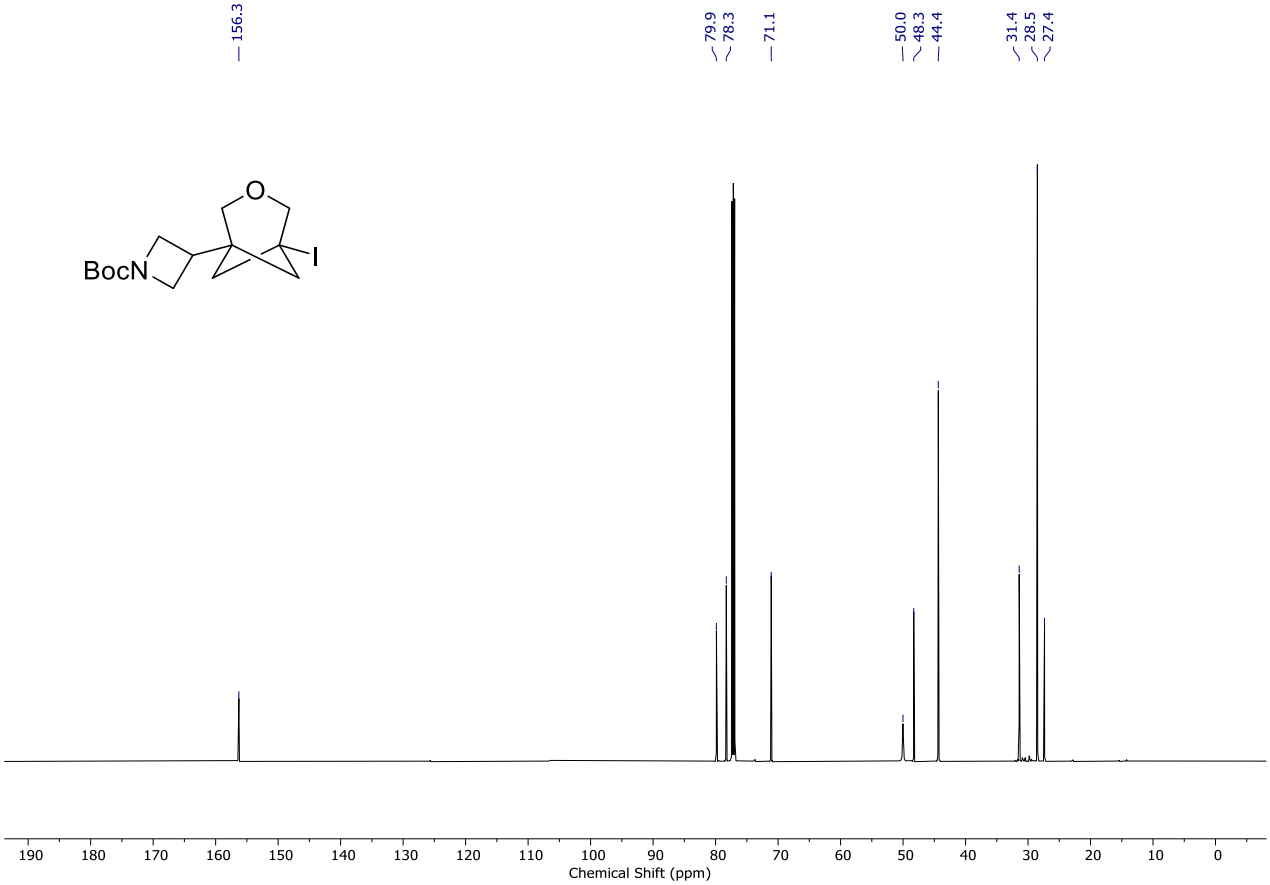
***tert*-Butyl 4-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)piperidine-1-carboxylate (18i) ^{13}C NMR (126 MHz, $CDCl_3$)**



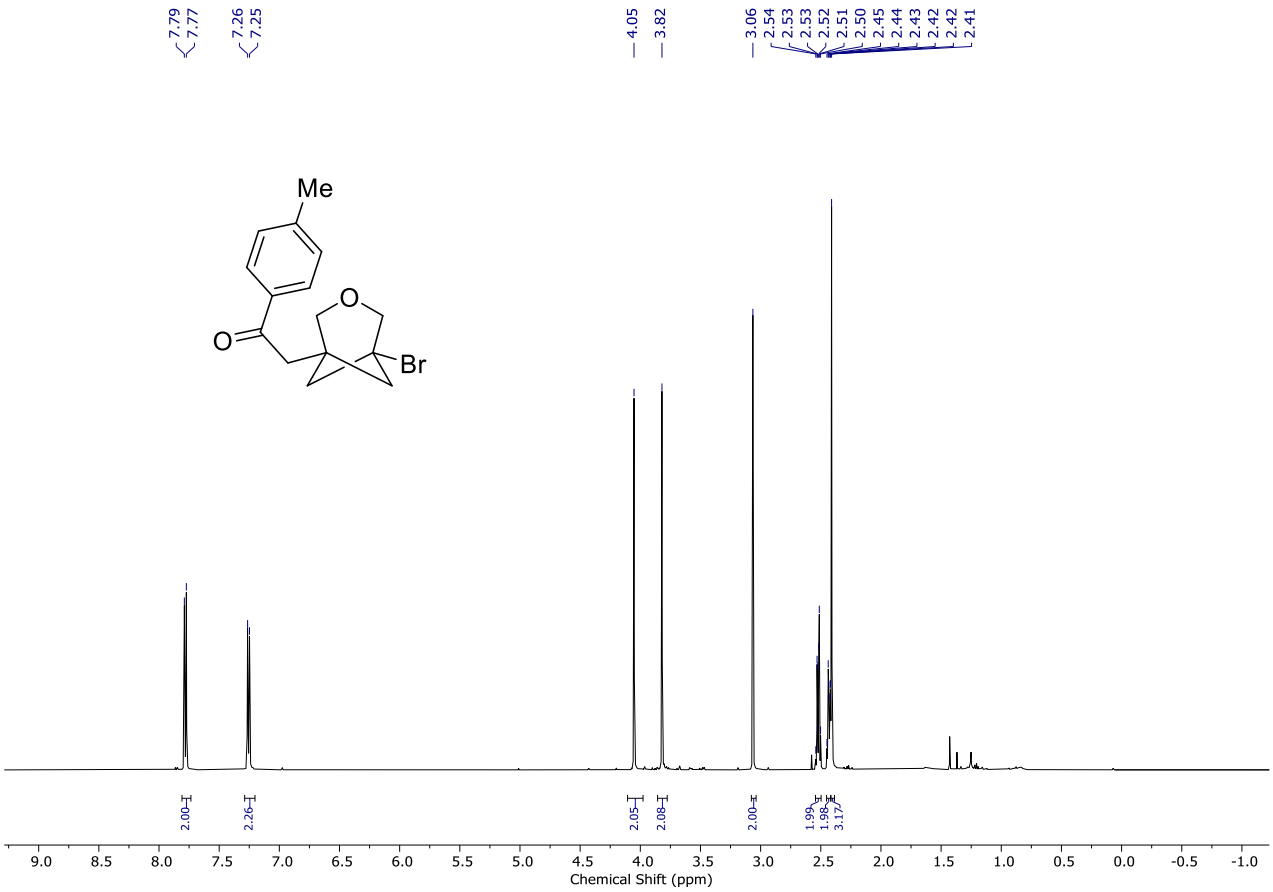
tert-Butyl 3-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)azetidine-1-carboxylate (18j) ^{1}H NMR (600 MHz, $CDCl_3$)



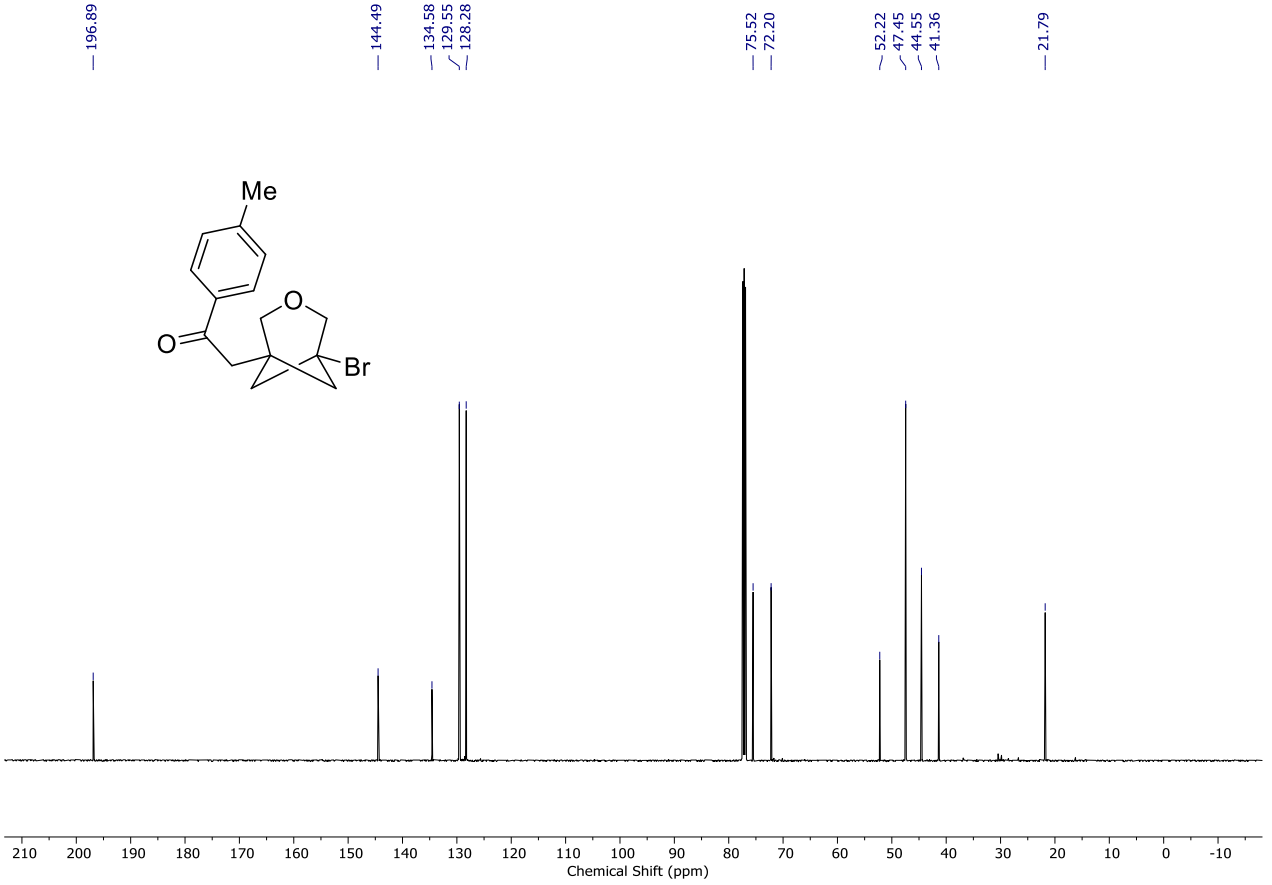
tert-Butyl 3-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)azetidine-1-carboxylate (18j) ^{13}C NMR (151 MHz, $CDCl_3$)



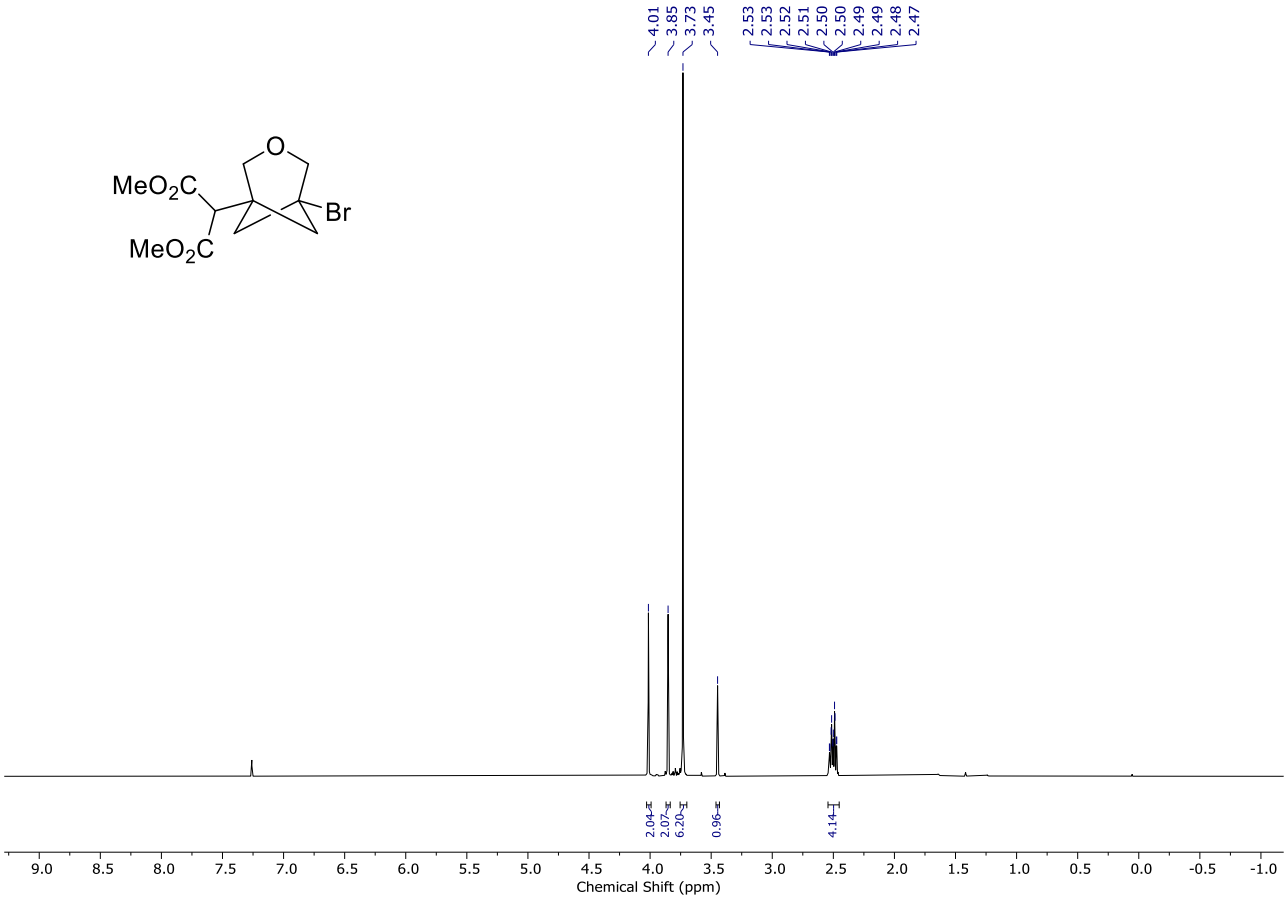
2-(5-Bromo-3-oxabicyclo[3.1.1]heptan-1-yl)-1-(p-tolyl)ethan-1-one (18k) ^{1}H NMR (500 MHz, $CDCl_3$)



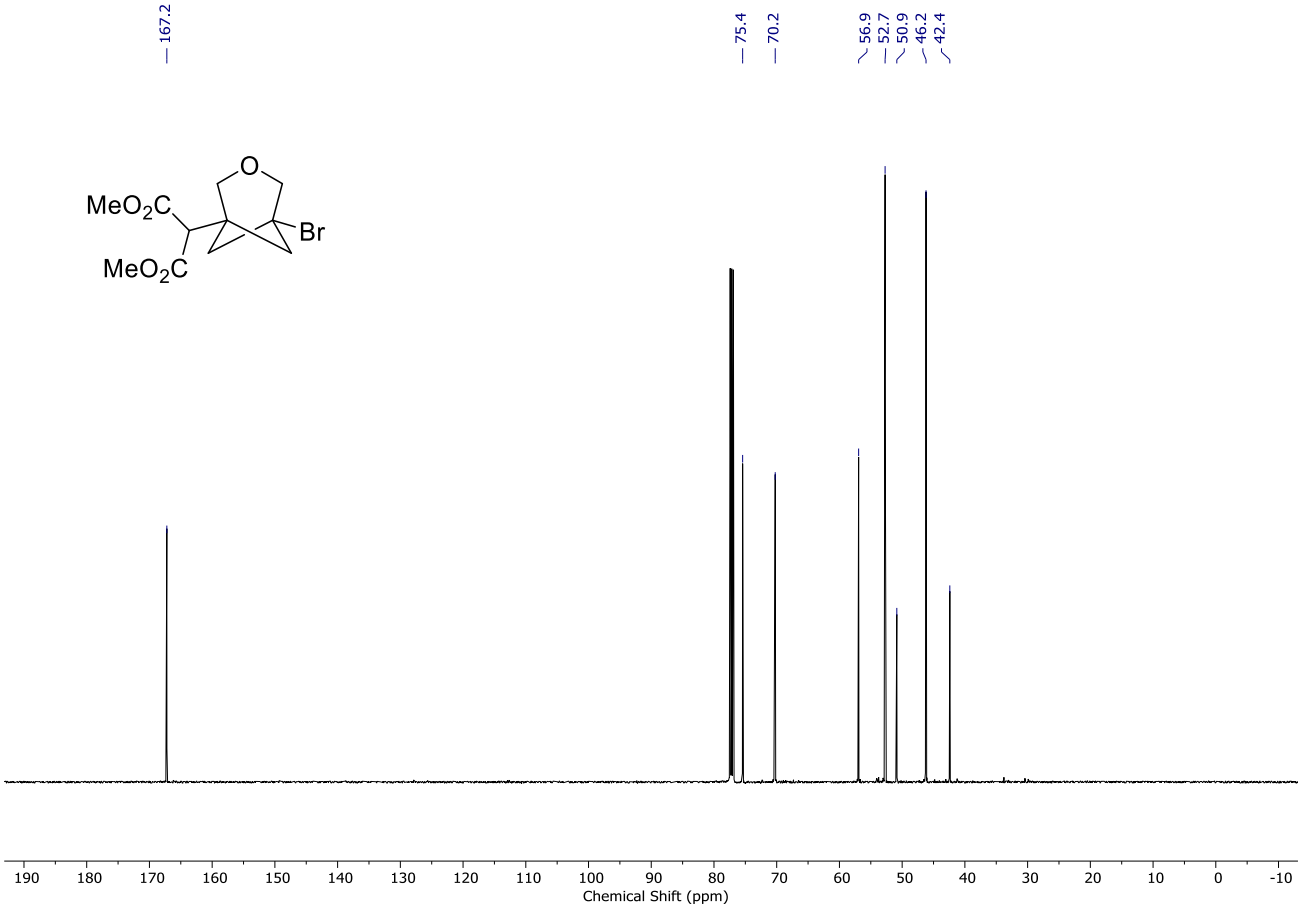
2-(5-Bromo-3-oxabicyclo[3.1.1]heptan-1-yl)-1-(p-tolyl)ethan-1-one (18k) ^{13}C NMR (126 MHz, $CDCl_3$)



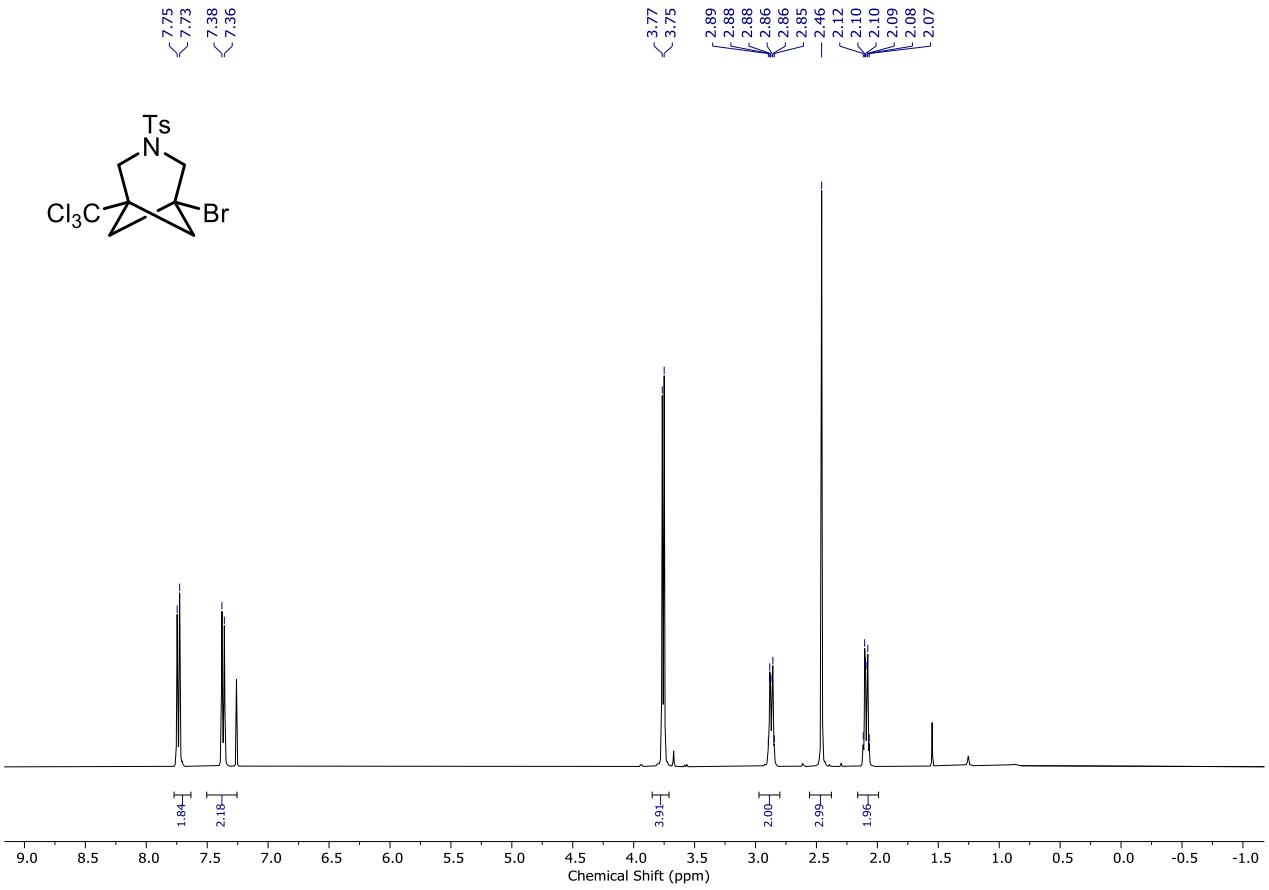
Dimethyl 2-(5-bromo-3-oxabicyclo[3.1.1]heptan-1-yl)malonate (18l) ^{1}H NMR (500 MHz, $CDCl_3$)



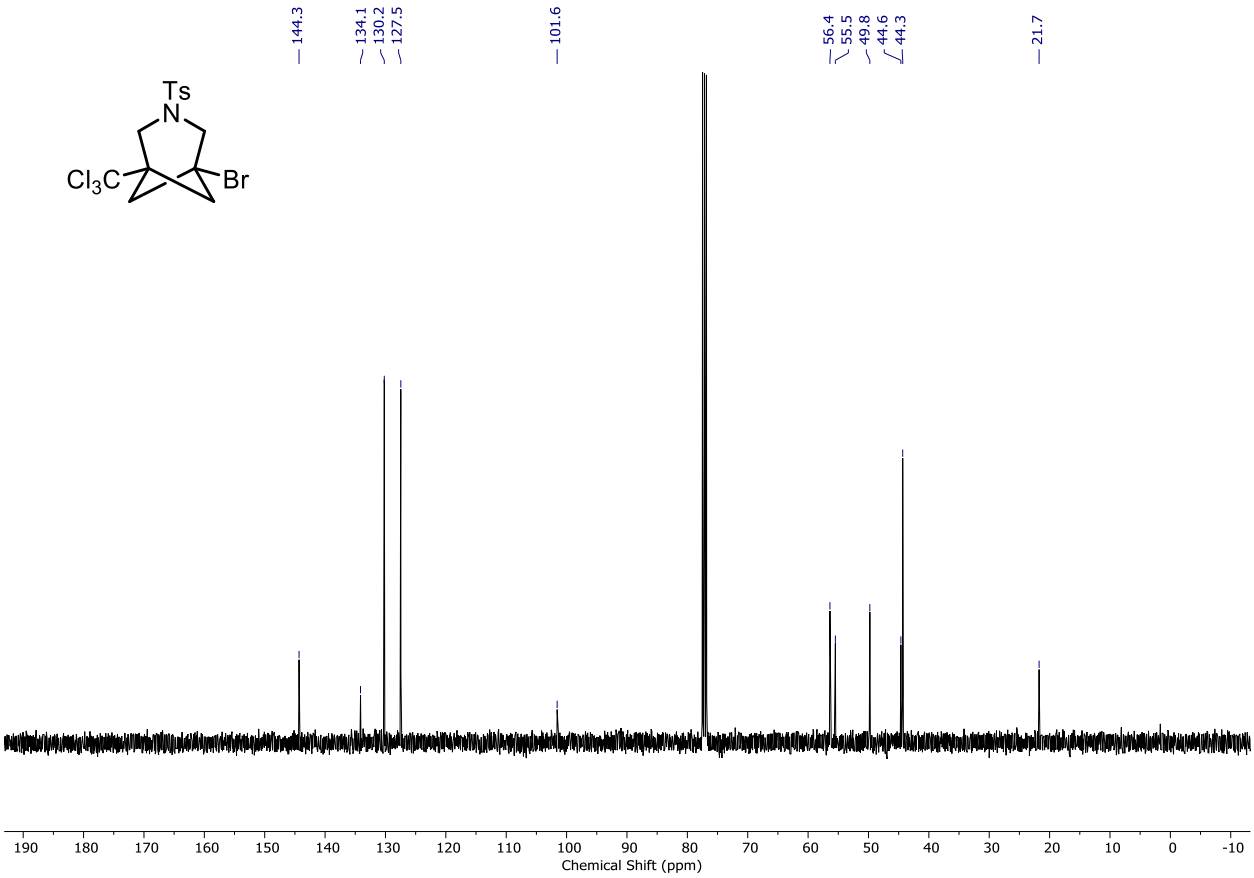
Dimethyl 2-(5-bromo-3-oxabicyclo[3.1.1]heptan-1-yl)malonate (18l) ^{13}C NMR (126 MHz, $CDCl_3$)



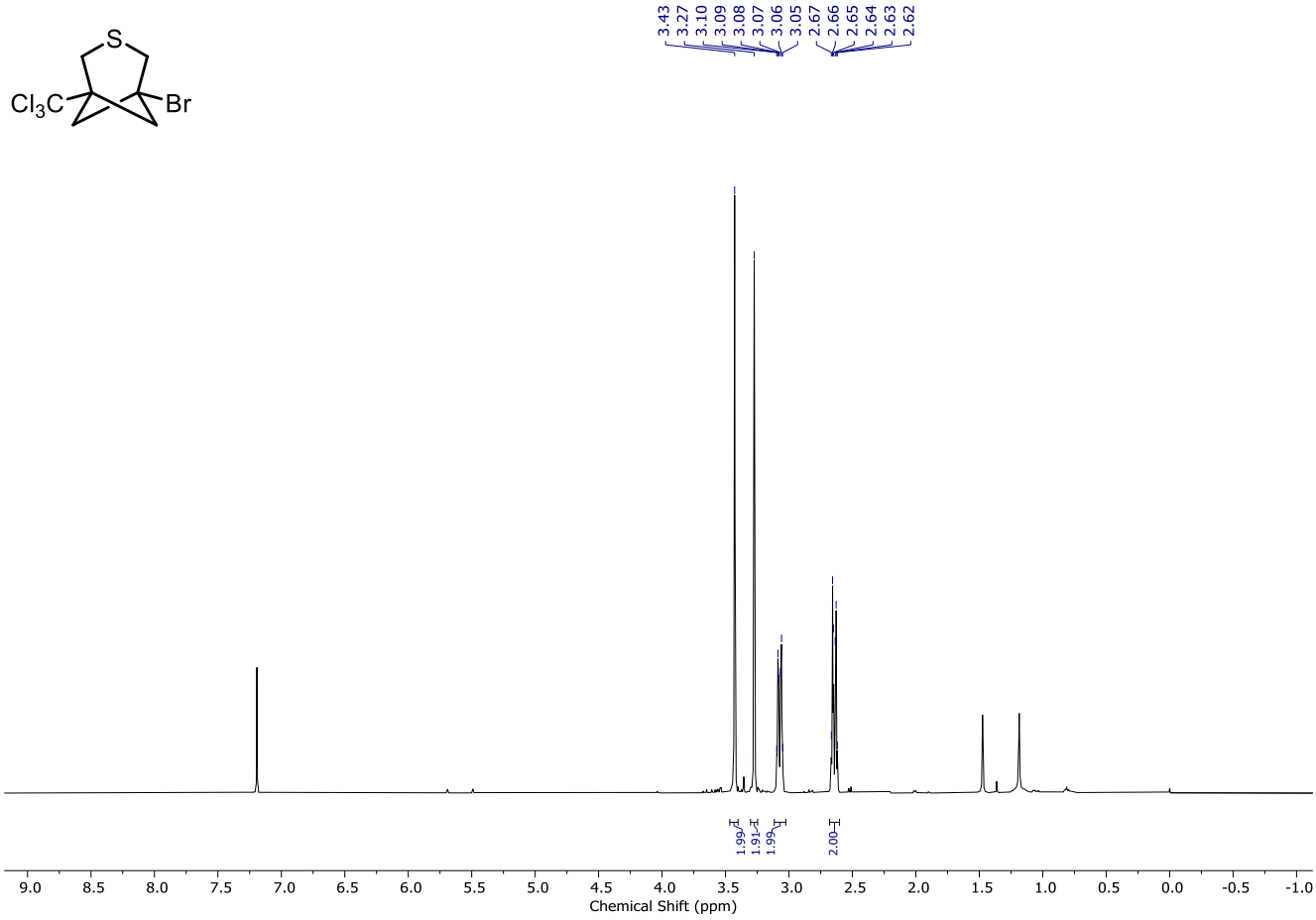
1-Bromo-3-tosyl-5-(trichloromethyl)-3-azabicyclo[3.1.1]heptane (18m) ^{1}H NMR (400 MHz, $CDCl_3$)



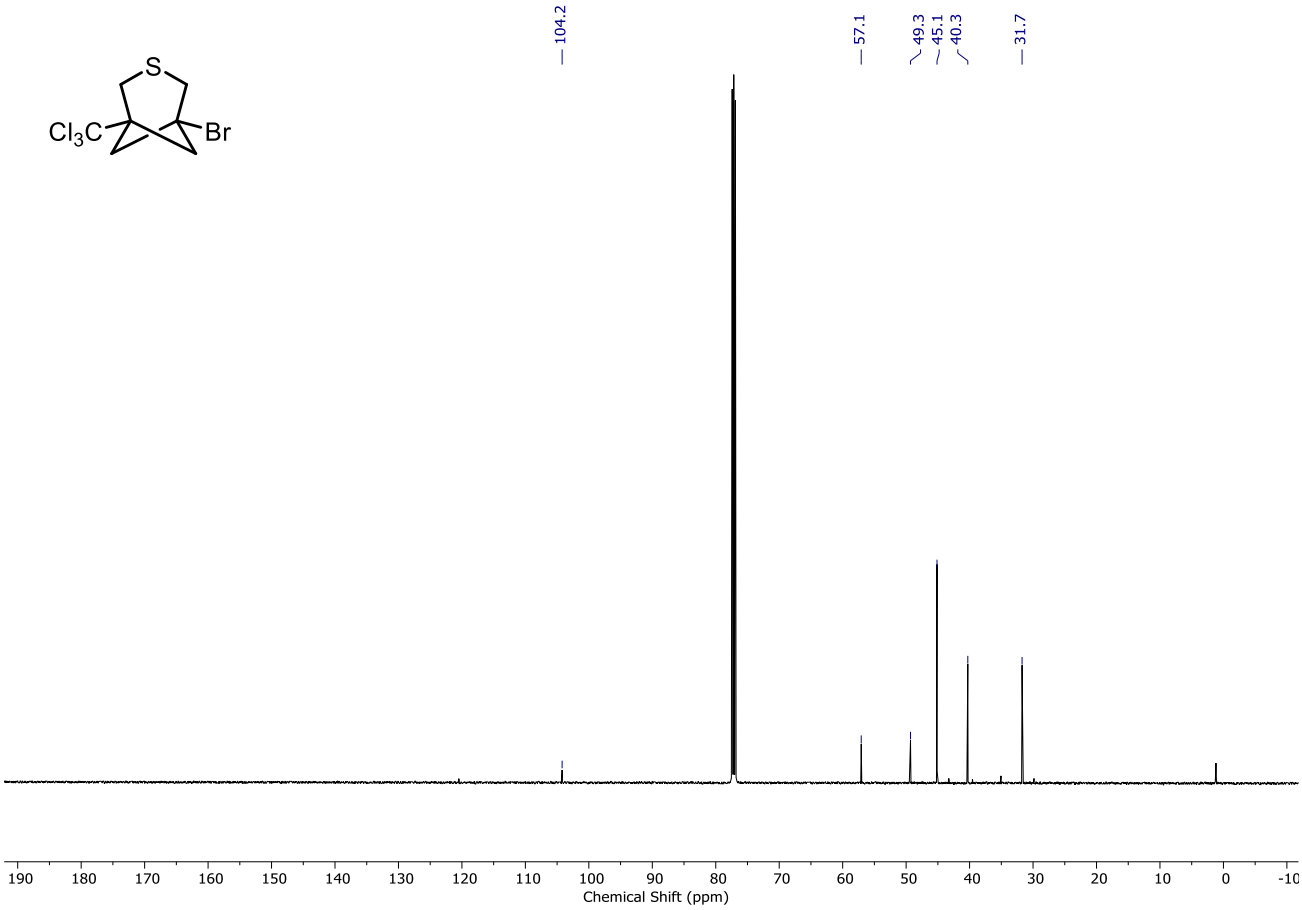
1-Bromo-3-tosyl-5-(trichloromethyl)-3-azabicyclo[3.1.1]heptane (18m) ^{13}C NMR (101 MHz, $CDCl_3$)



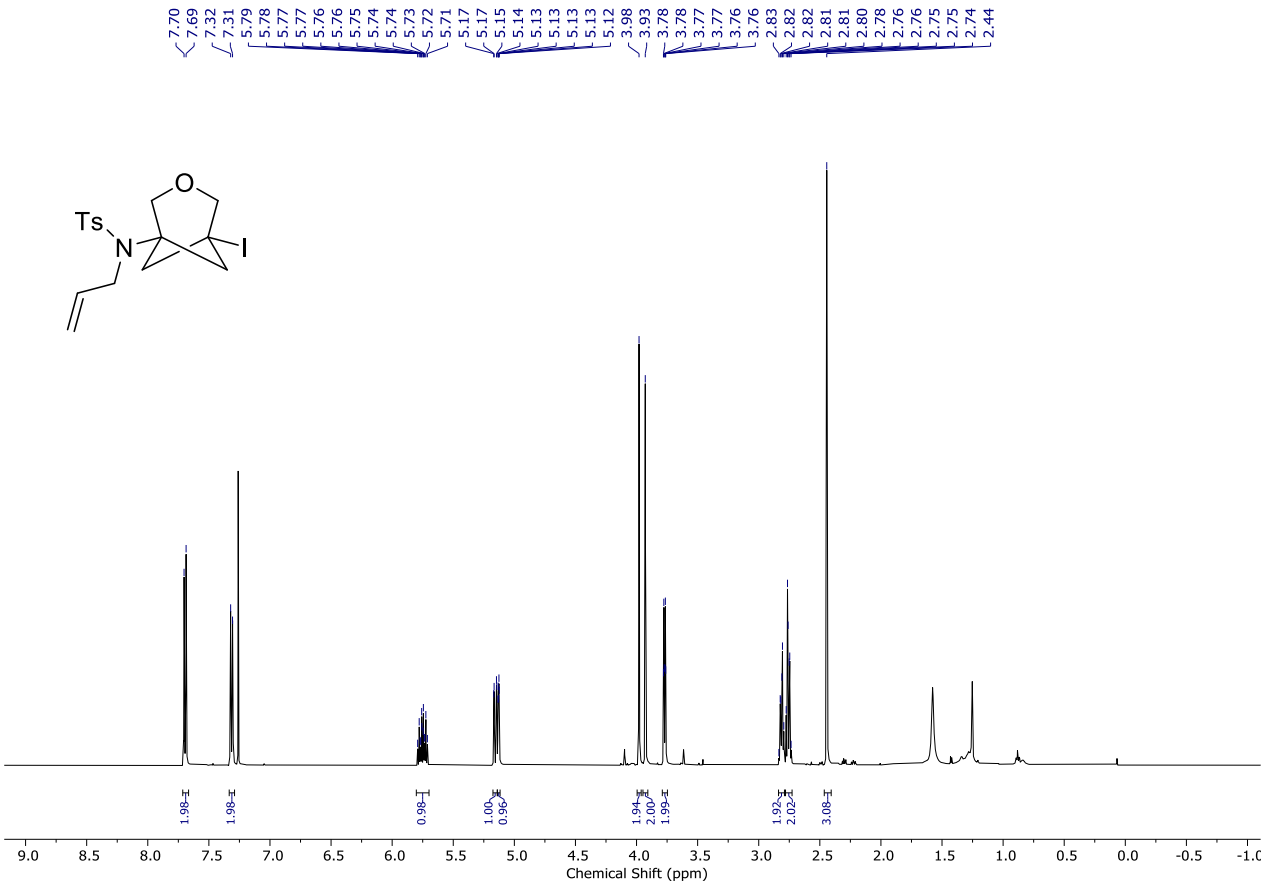
1-Bromo-5-(trichloromethyl)-3-thiabicyclo[3.1.1]heptane (18n) ^{1}H NMR (400 MHz, $CDCl_3$)



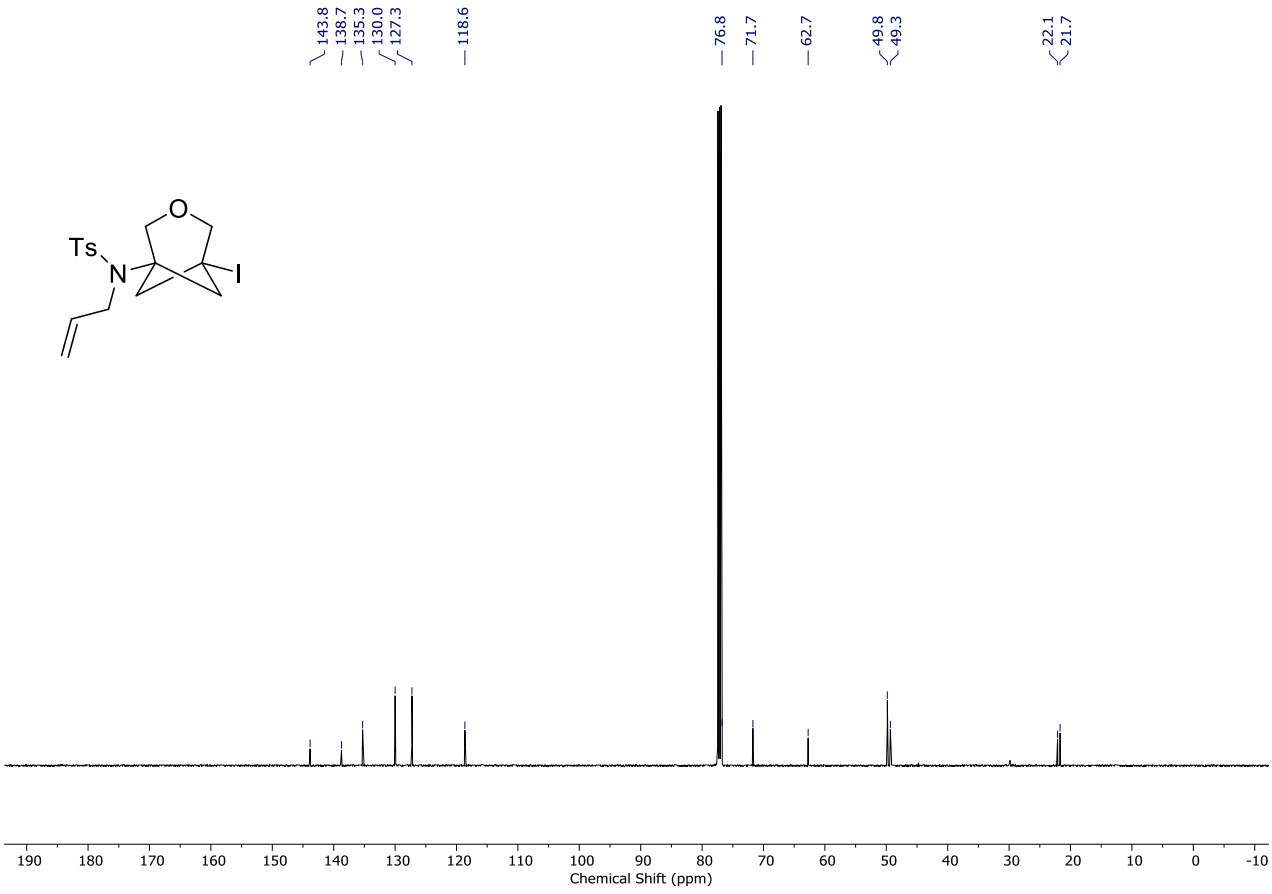
1-Bromo-5-(trichloromethyl)-3-thiabicyclo[3.1.1]heptane (18n) ^{13}C NMR (126 MHz, $CDCl_3$)



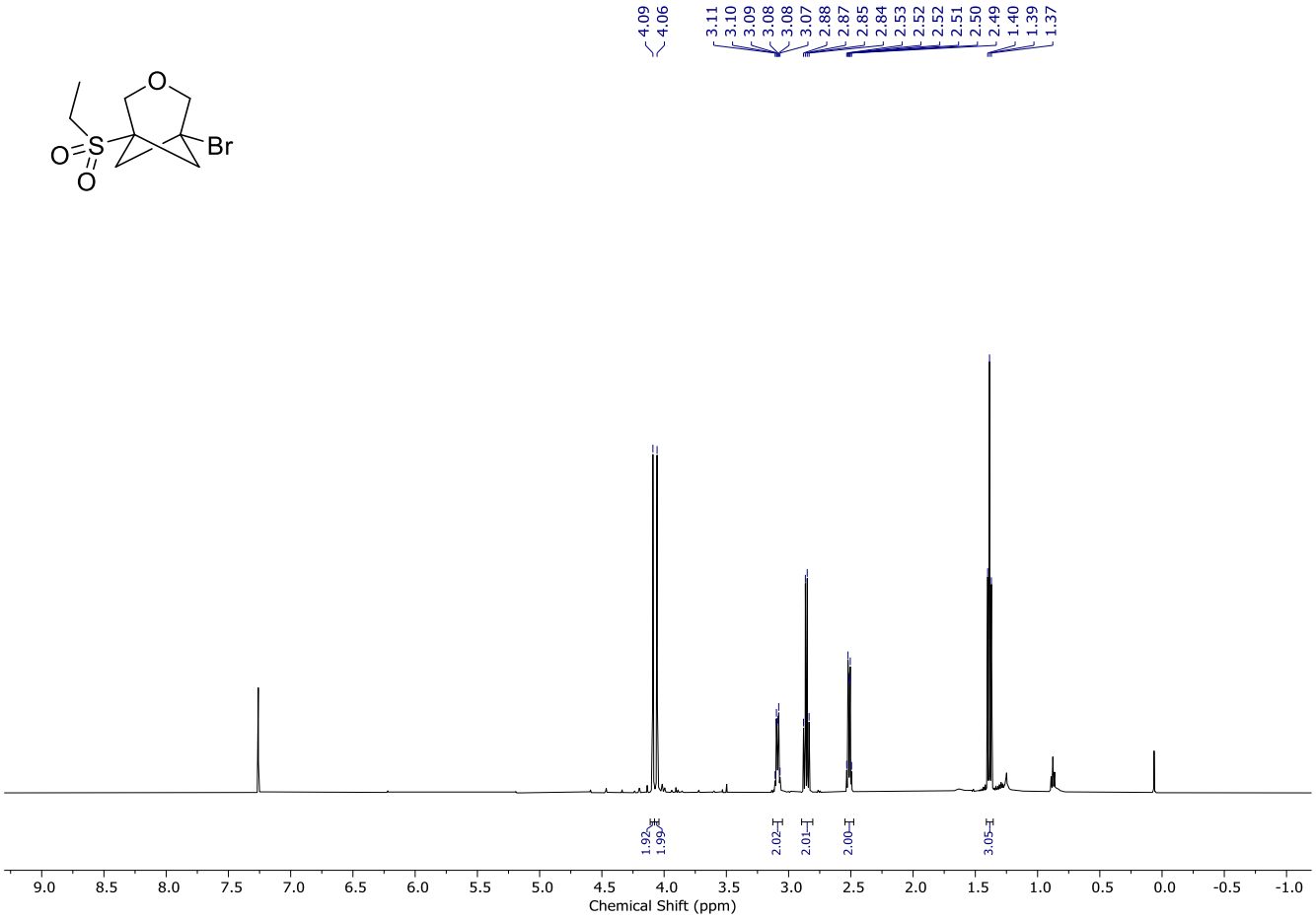
N-allyl-N-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)-4-methylbenzene sulfonamide (18o) ^{1}H NMR (500 MHz, $CDCl_3$)



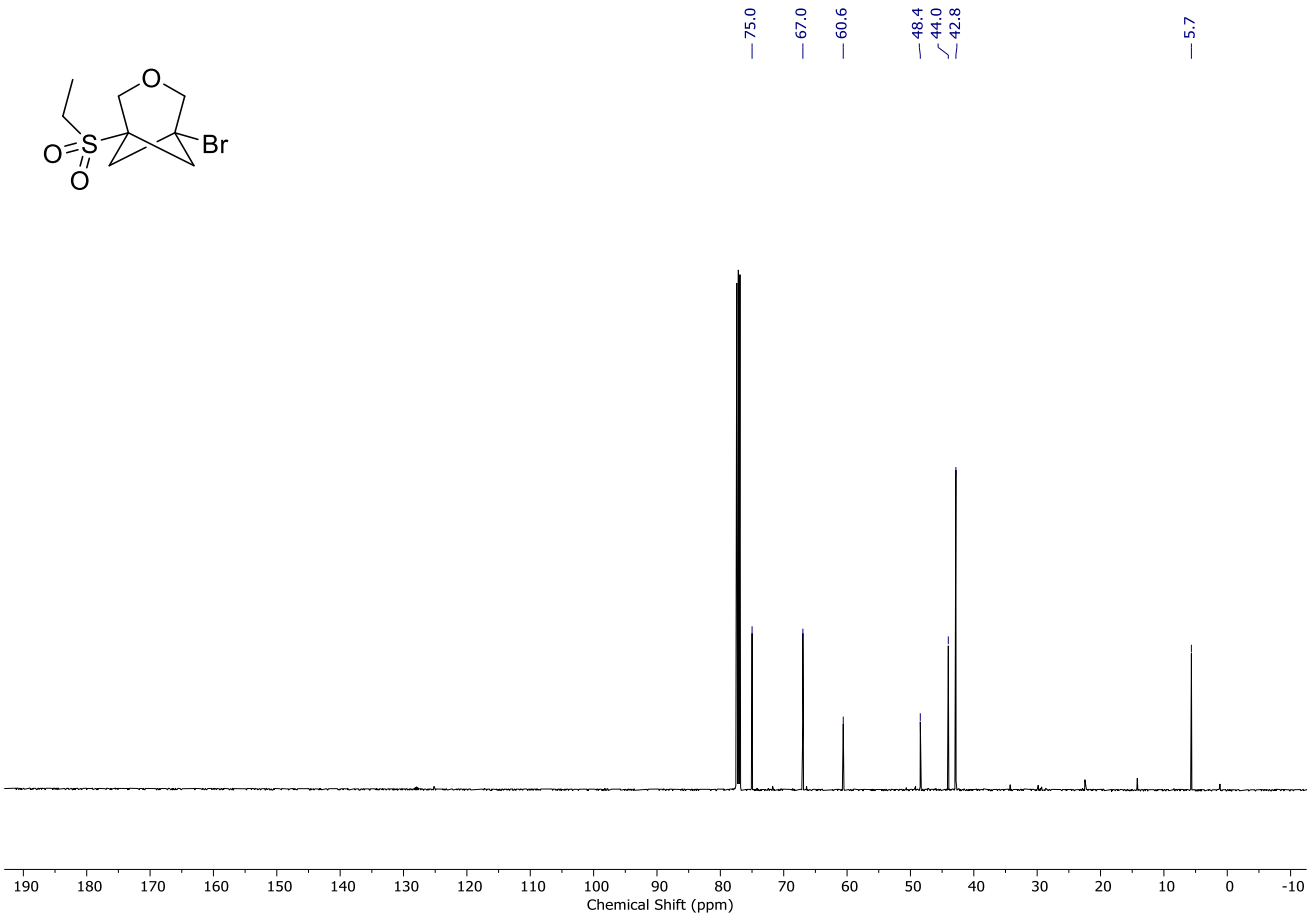
N-allyl-N-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)-4-methylbenzene sulfonamide (18o) ^{13}C NMR (126 MHz, $CDCl_3$)



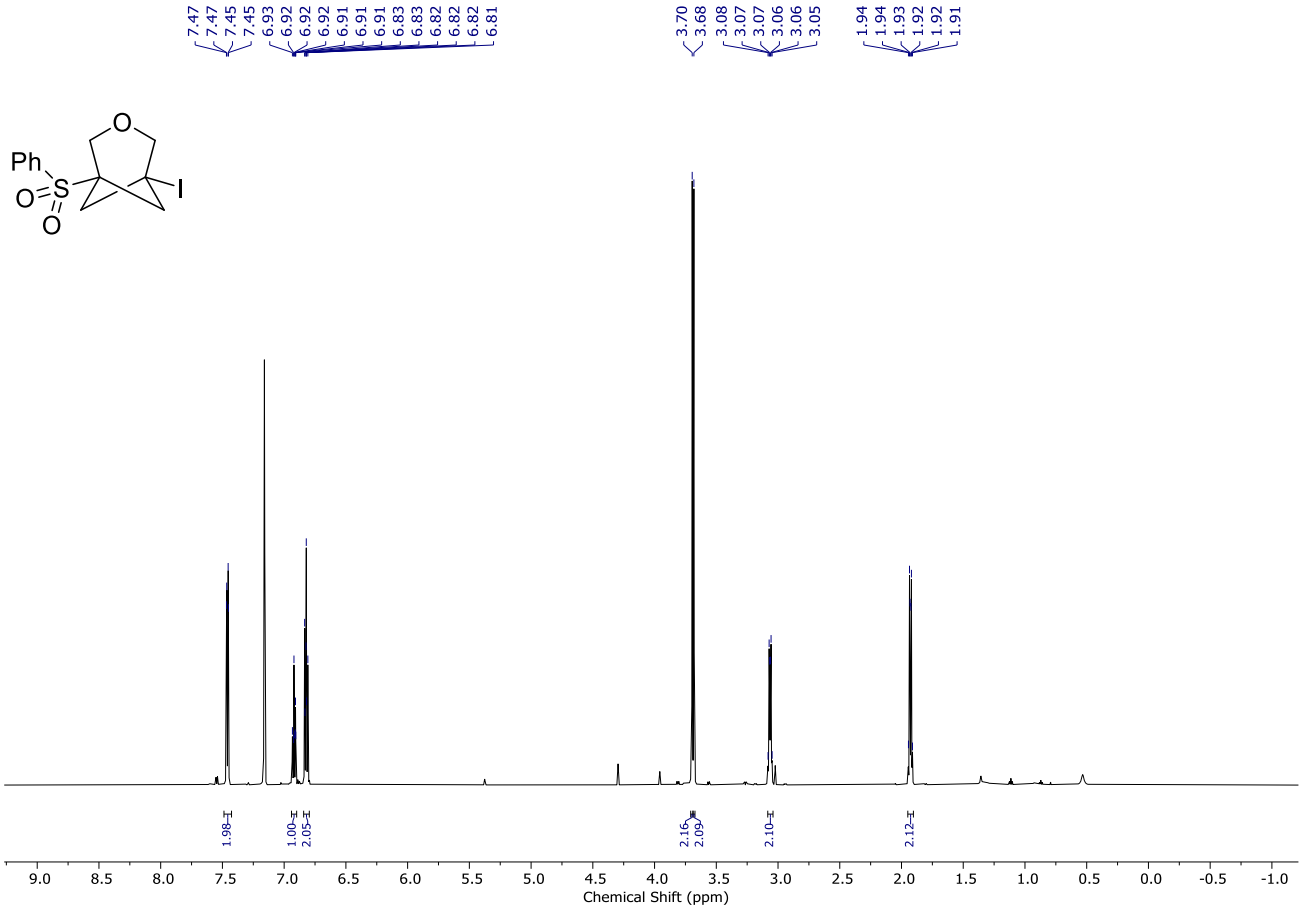
1-Bromo-5-(ethylsulfonyl)-3-oxabicyclo[3.1.1]heptane (18p) ^{1}H NMR (500 MHz, $CDCl_3$)



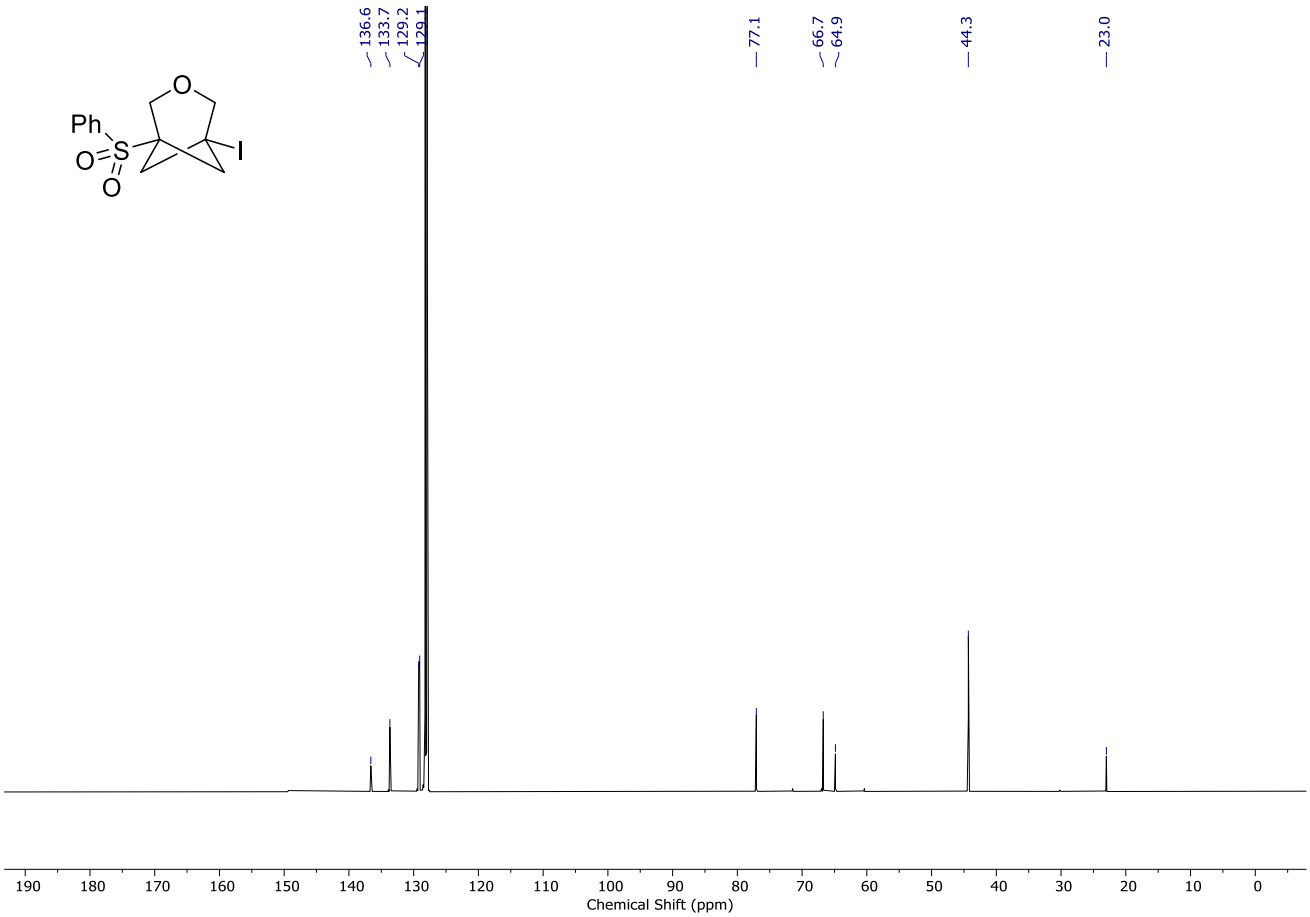
1-Bromo-5-(ethylsulfonyl)-3-oxabicyclo[3.1.1]heptane (18p) ^{13}C NMR (126 MHz, $CDCl_3$)



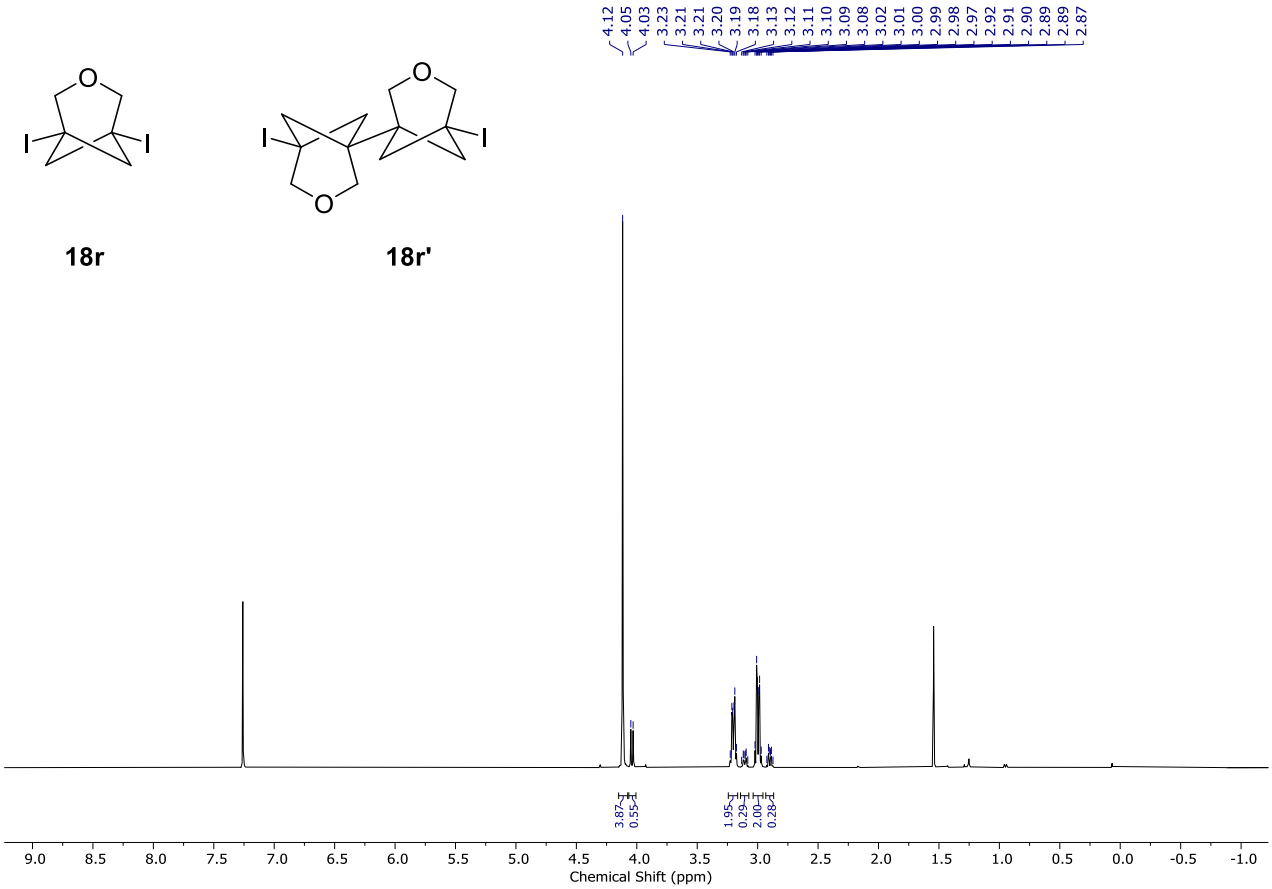
1-Iodo-5-(phenylsulfonyl)-3-oxabicyclo[3.1.1]heptane (18q) ^{1}H NMR (600 MHz, $CDCl_3$)



1-Iodo-5-(phenylsulfonyl)-3-oxabicyclo[3.1.1]heptane (18q) ^{13}C NMR (151 MHz, $CDCl_3$)

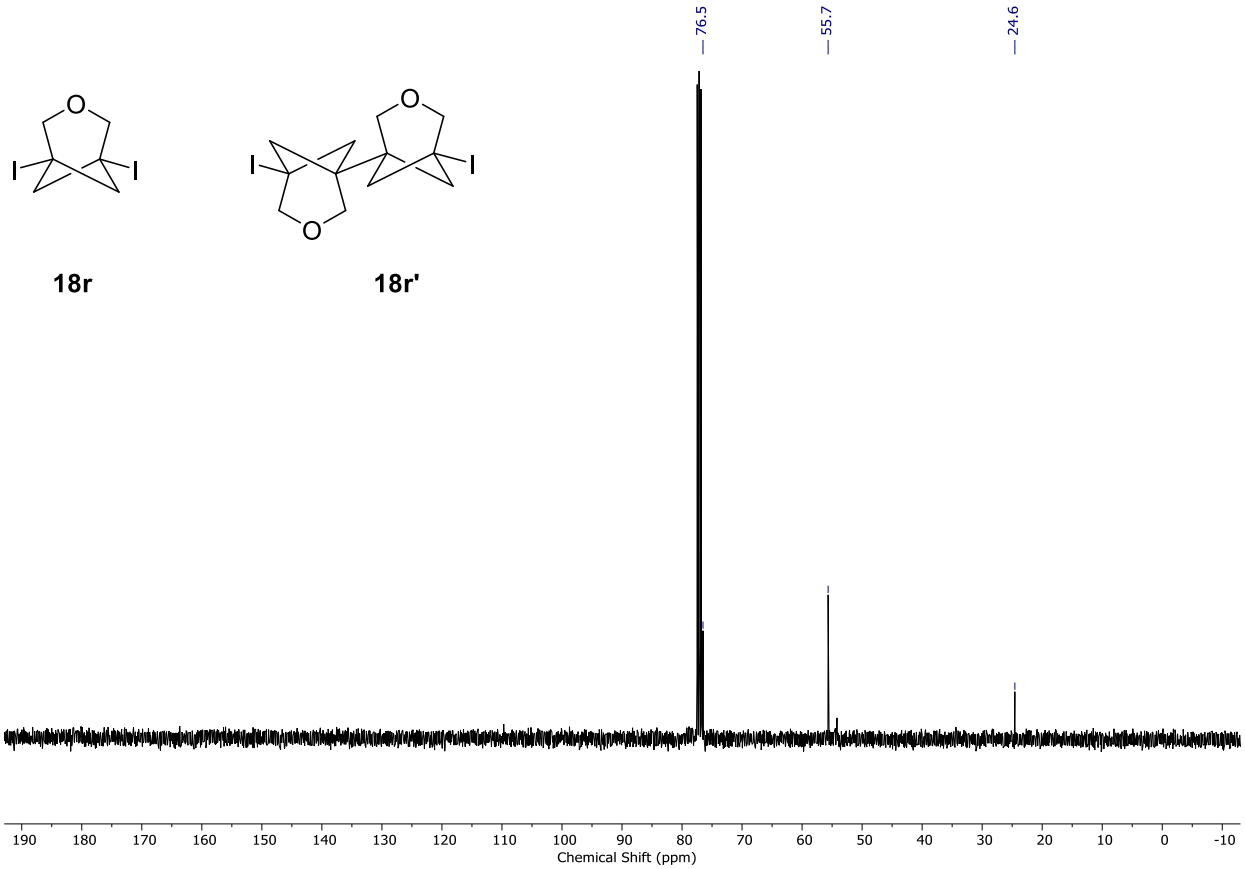


1,5-Diiodo-3-oxabicyclo[3.1.1]heptane (18r) and 5,5'-Diiodo-3,3'-dioxa-1,1'-bi(bicyclo[3.1.1]heptane) (18r') ^{1}H NMR (400 MHz, $CDCl_3$)



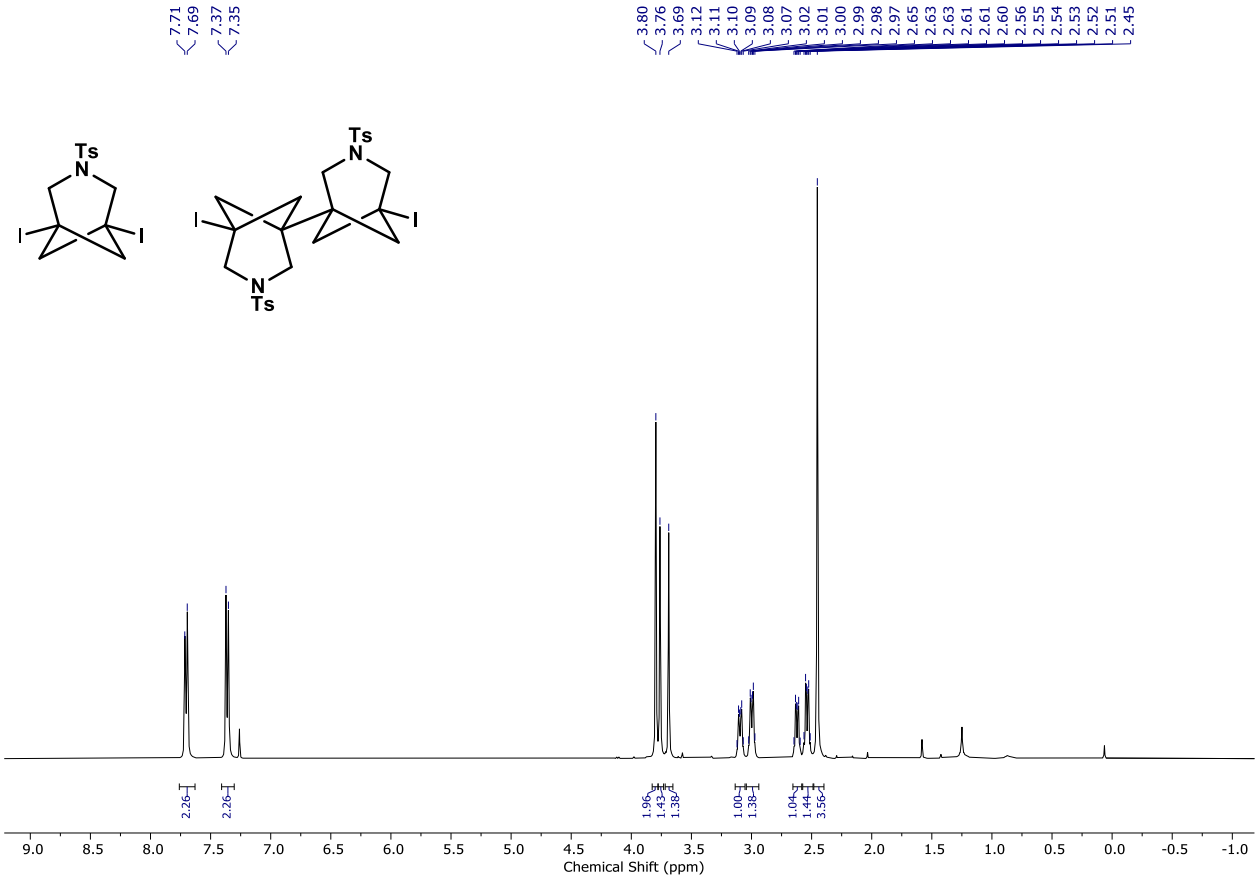
18r 18r'

1,5-Diiodo-3-oxabicyclo[3.1.1]heptane (18r) and 5,5'-Diiodo-3,3'-dioxa-1,1'-bi(bicyclo[3.1.1]heptane) (18r') ^{13}C NMR (400 MHz, $CDCl_3$)

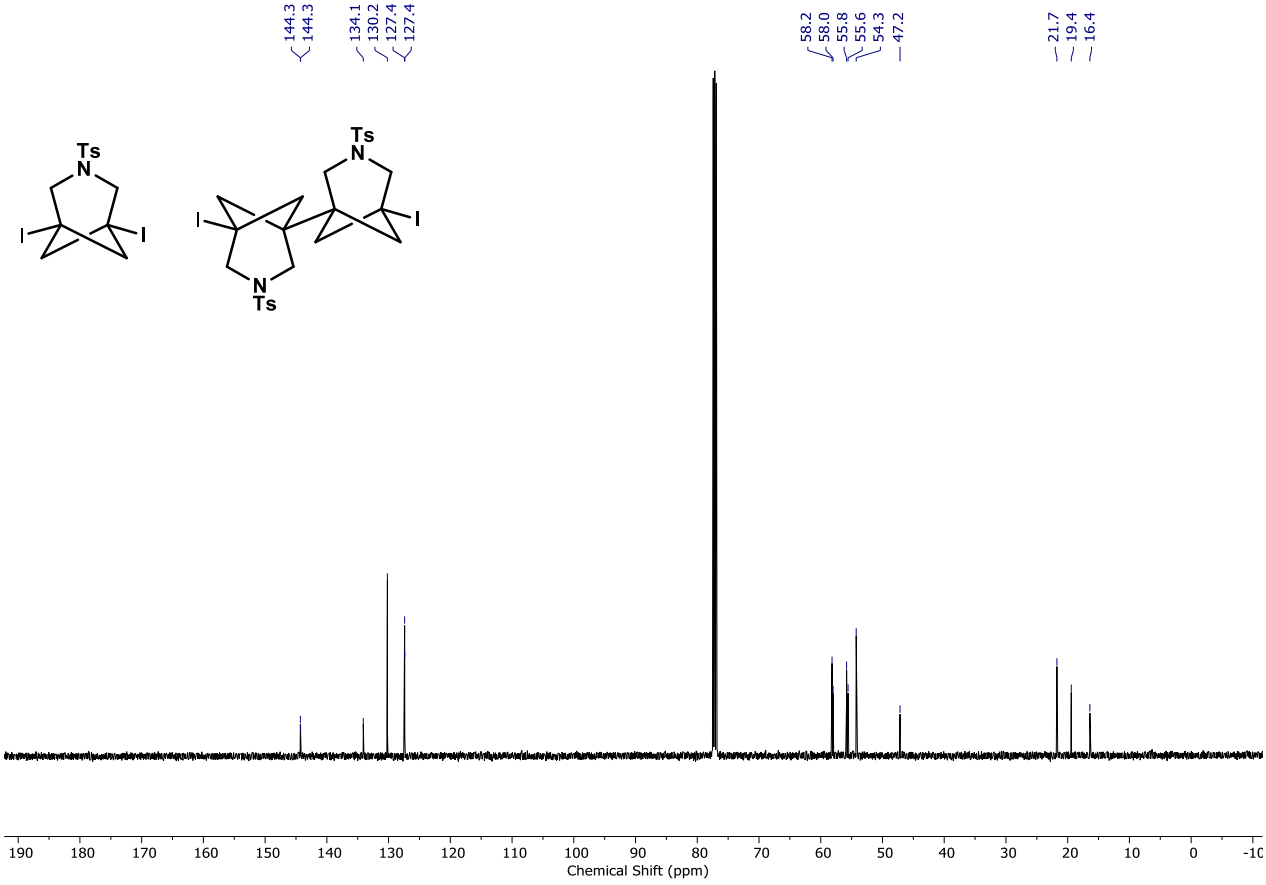


18r 18r'

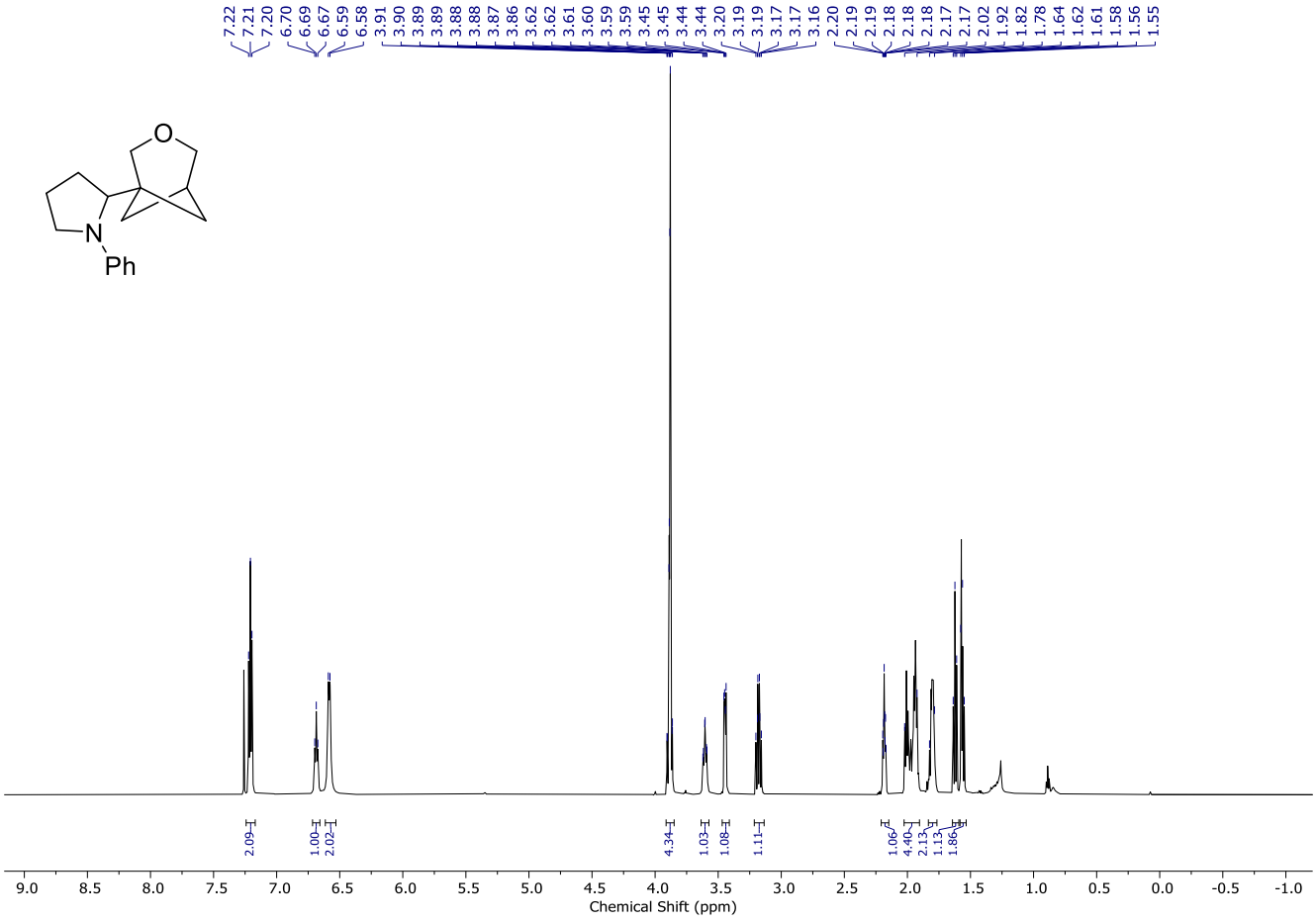
1,5-Diiodo-3-tosyl-3-azabicyclo[3.1.1]heptane (18s) and 5,5'-Diiodo-3,3'-ditosyl-3,3'-diaza-1,1'-bi(bicyclo[3.1.1]heptane) (18s') ^{1}H NMR (400 MHz, $CDCl_3$)



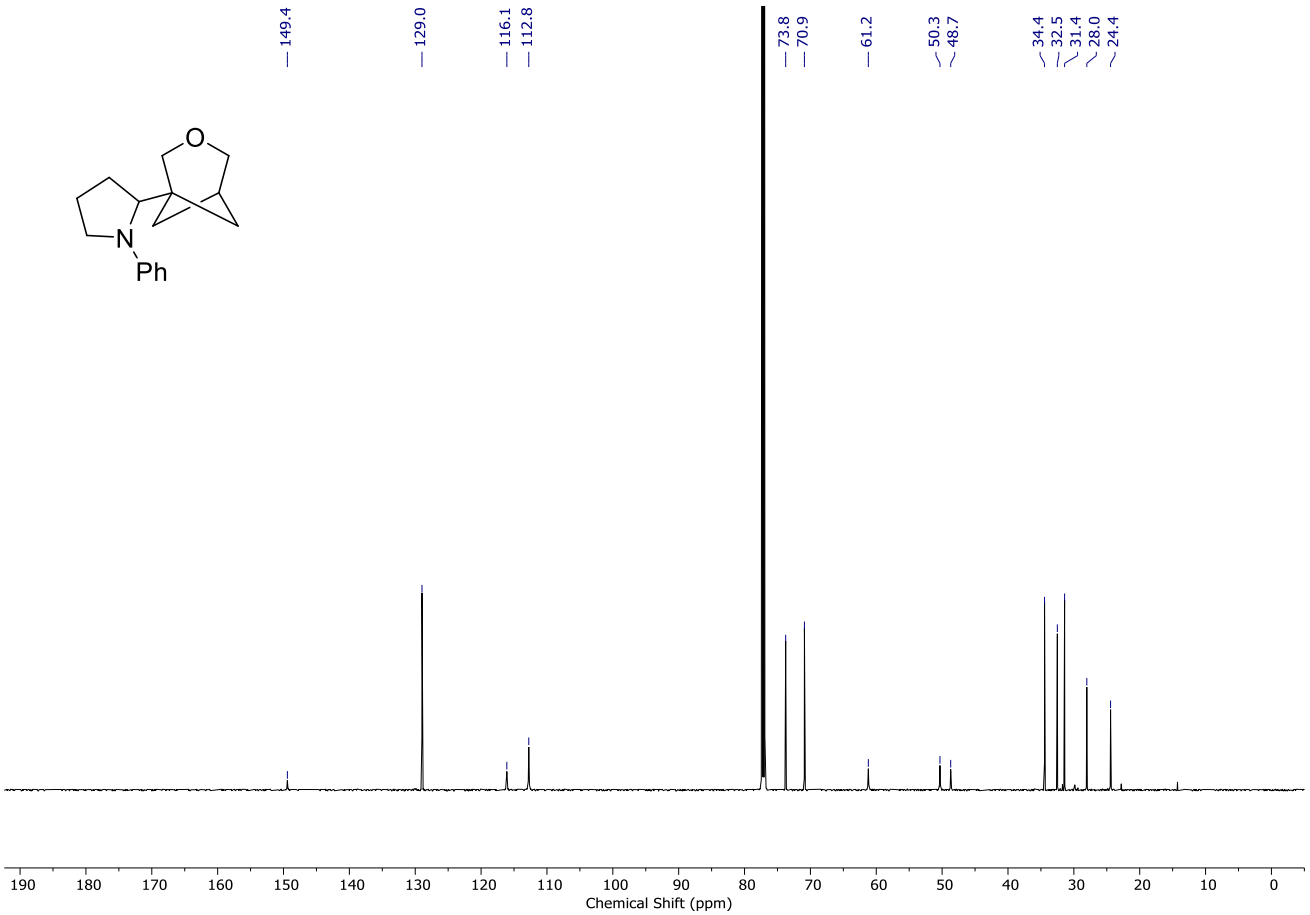
1,5-Diiodo-3-tosyl-3-azabicyclo[3.1.1]heptane (18s) and 5,5'-Diiodo-3,3'-ditosyl-3,3'-diaza-1,1'-bi(bicyclo[3.1.1]heptane) (18s') ^{13}C NMR (126 MHz, $CDCl_3$)



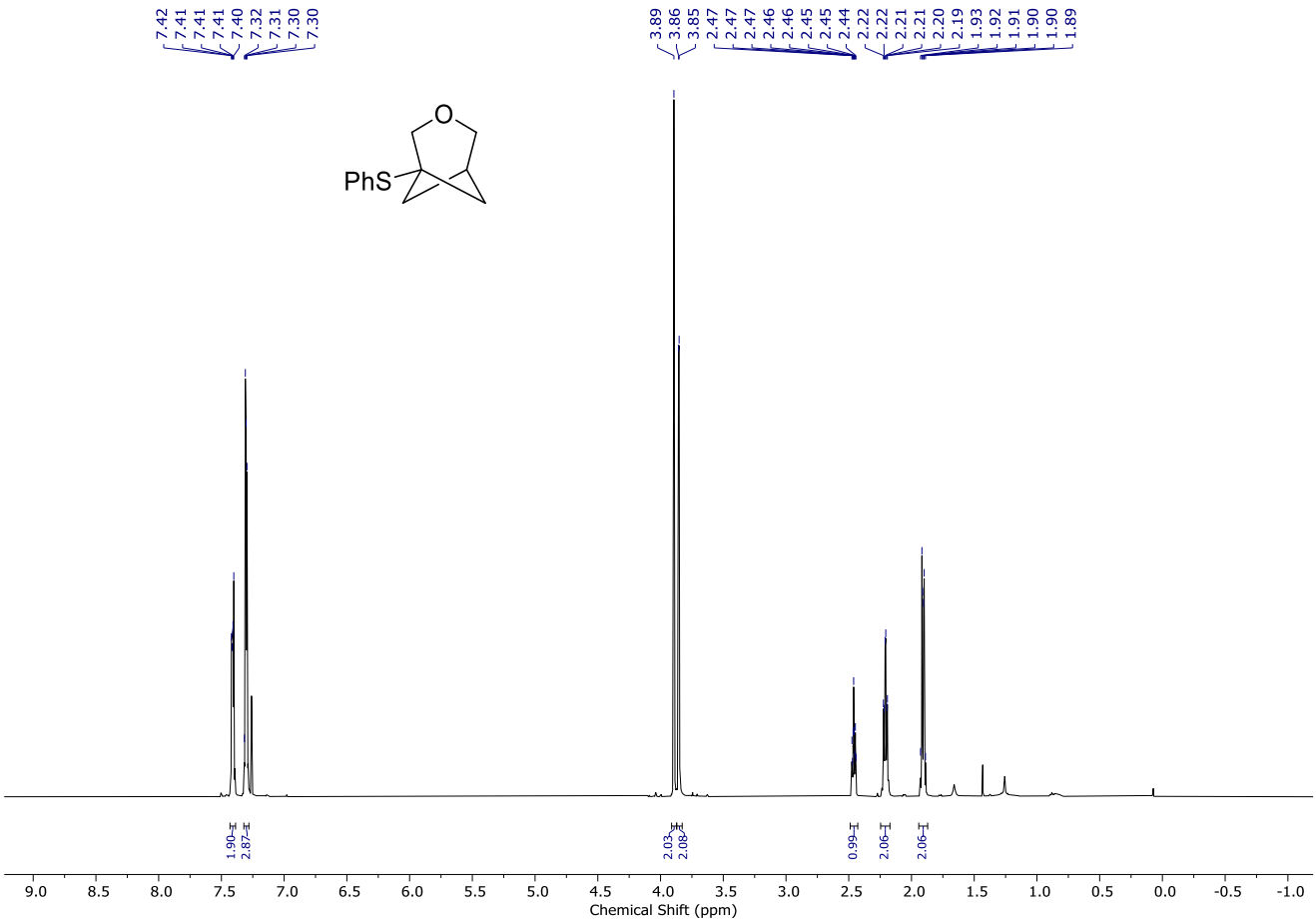
2-(3-Oxabicyclo[3.1.1]heptan-1-yl)-1-phenylpyrrolidine (18t) ^{1}H NMR (600 MHz, $CDCl_3$)



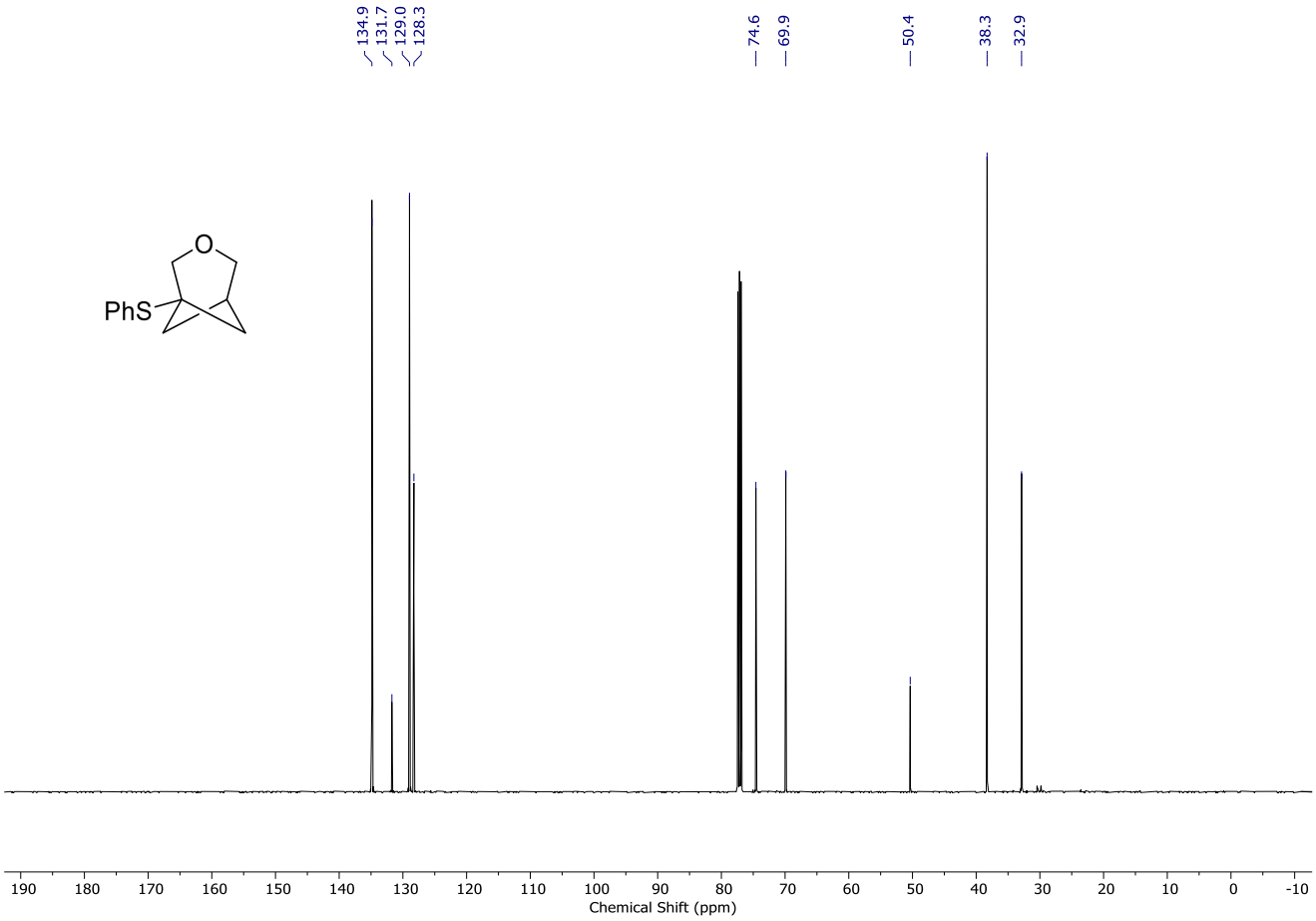
2-(3-Oxabicyclo[3.1.1]heptan-1-yl)-1-phenylpyrrolidine (18t) ^{13}C NMR (151 MHz, $CDCl_3$)



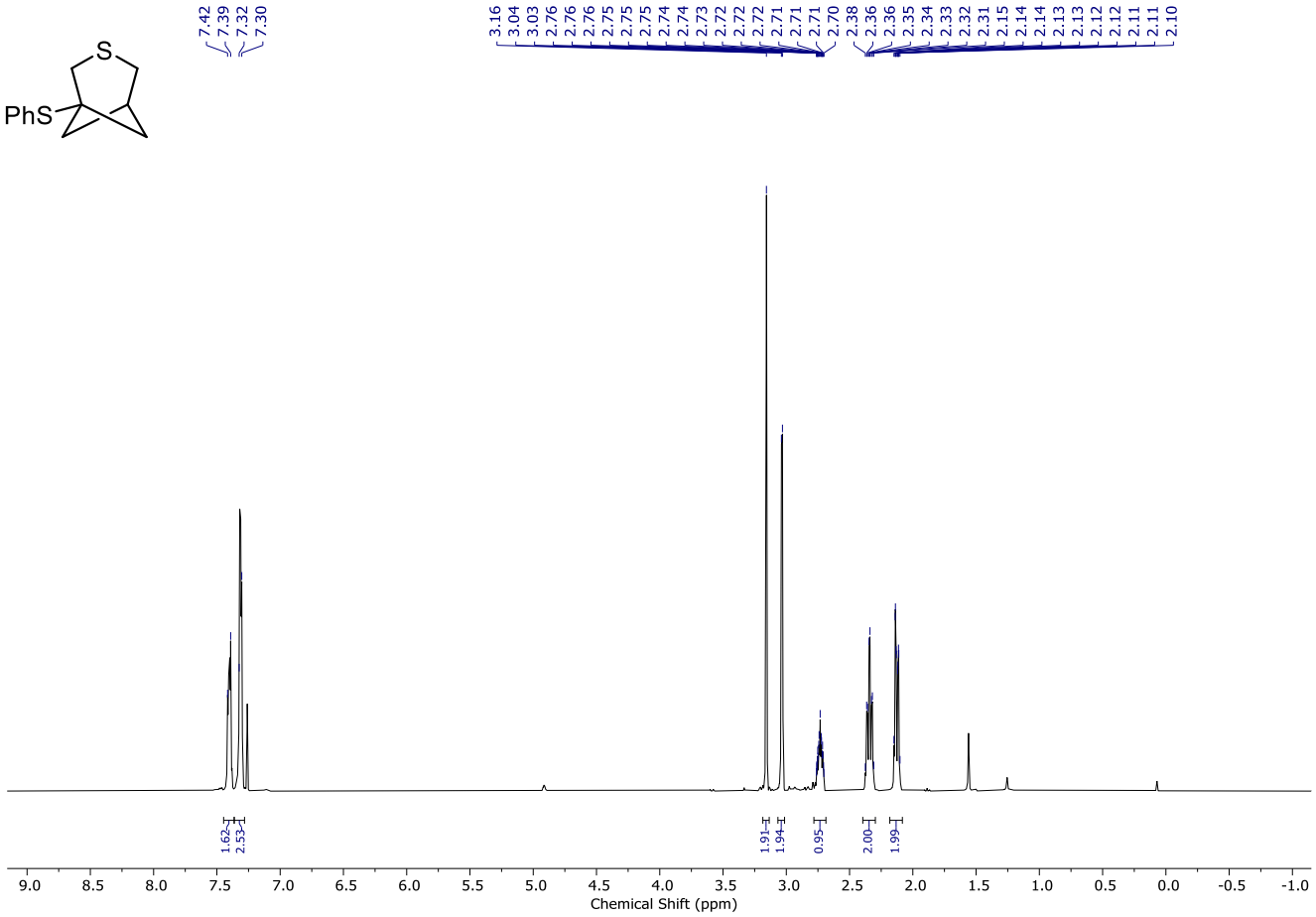
1-(Phenylthio)-3-oxabicyclo[3.1.1]heptane (18u) ^{1}H NMR (500 MHz, $CDCl_3$)



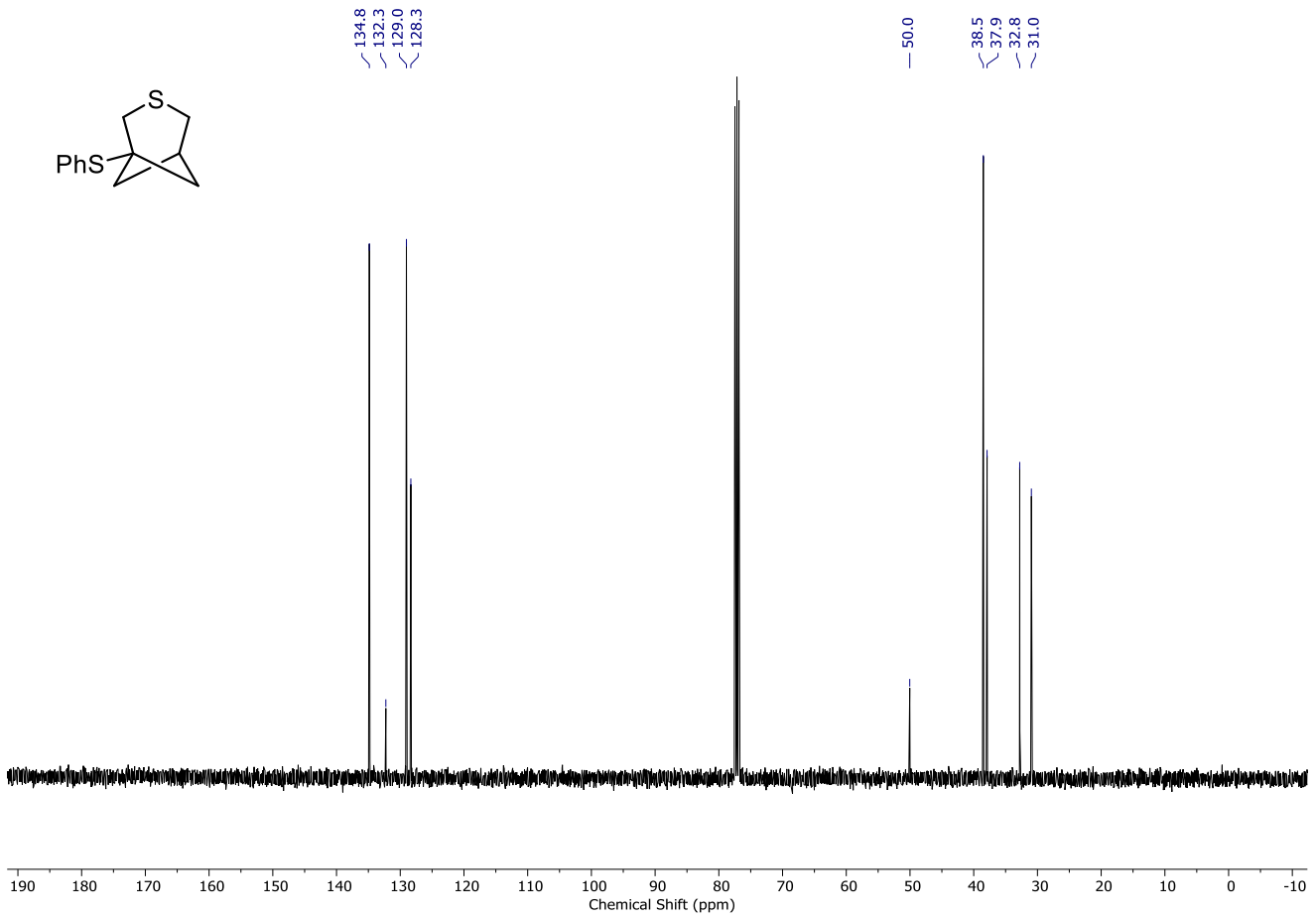
1-(Phenylthio)-3-oxabicyclo[3.1.1]heptane (18u) ^{13}C NMR (126 MHz, $CDCl_3$)



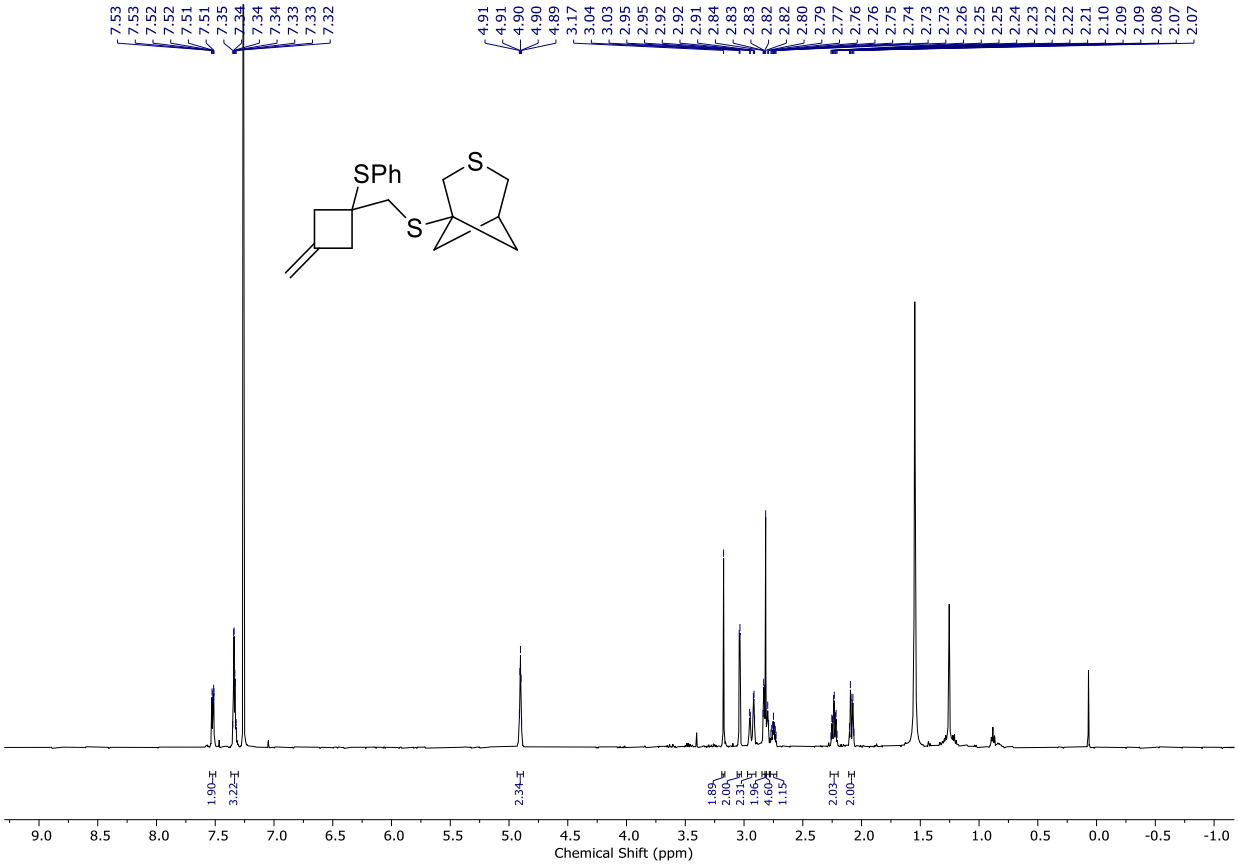
1-(Phenylthio)-3-thiabicyclo[3.1.1]heptane (18v) ^{1}H NMR (400 MHz, $CDCl_3$)



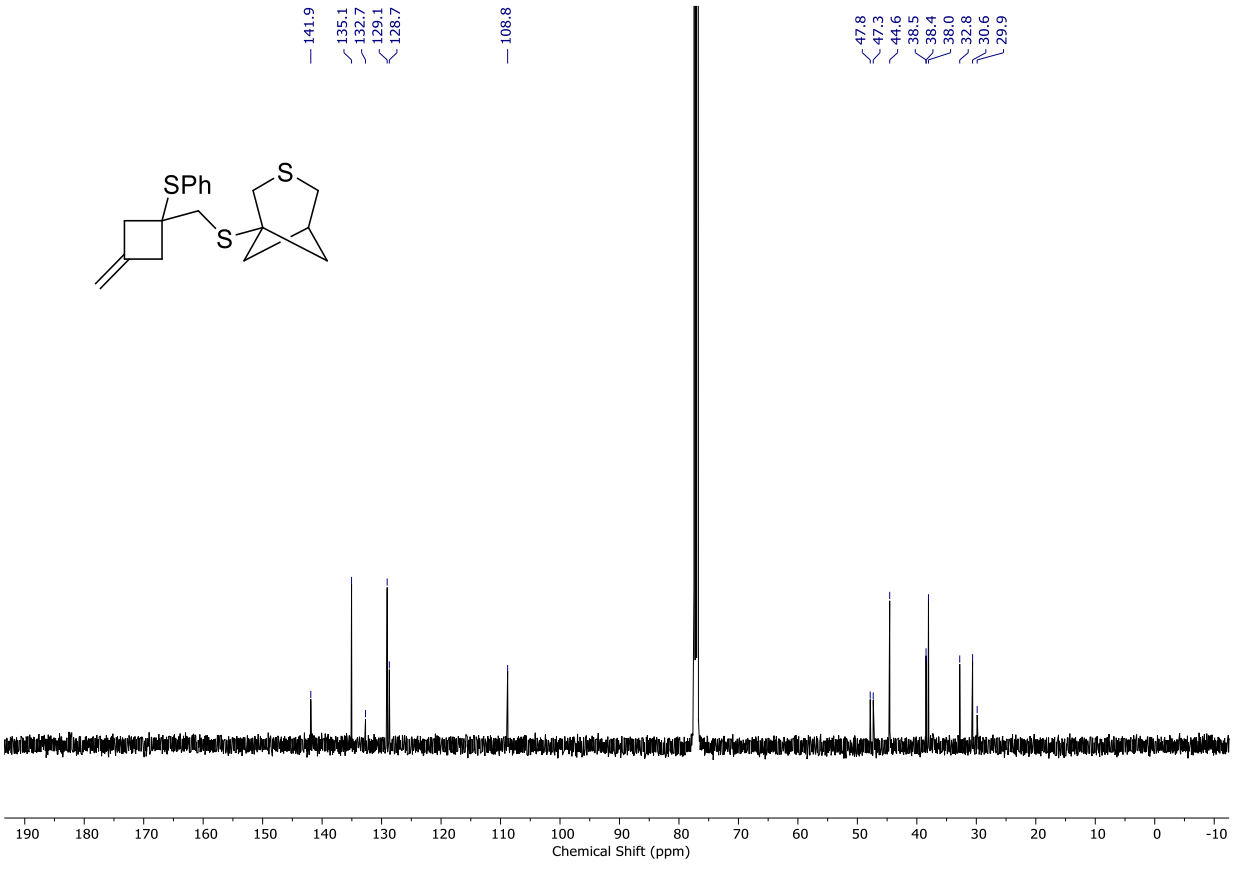
1-(Phenylthio)-3-thiabicyclo[3.1.1]heptane (18v) ^{13}C NMR (101 MHz, $CDCl_3$)



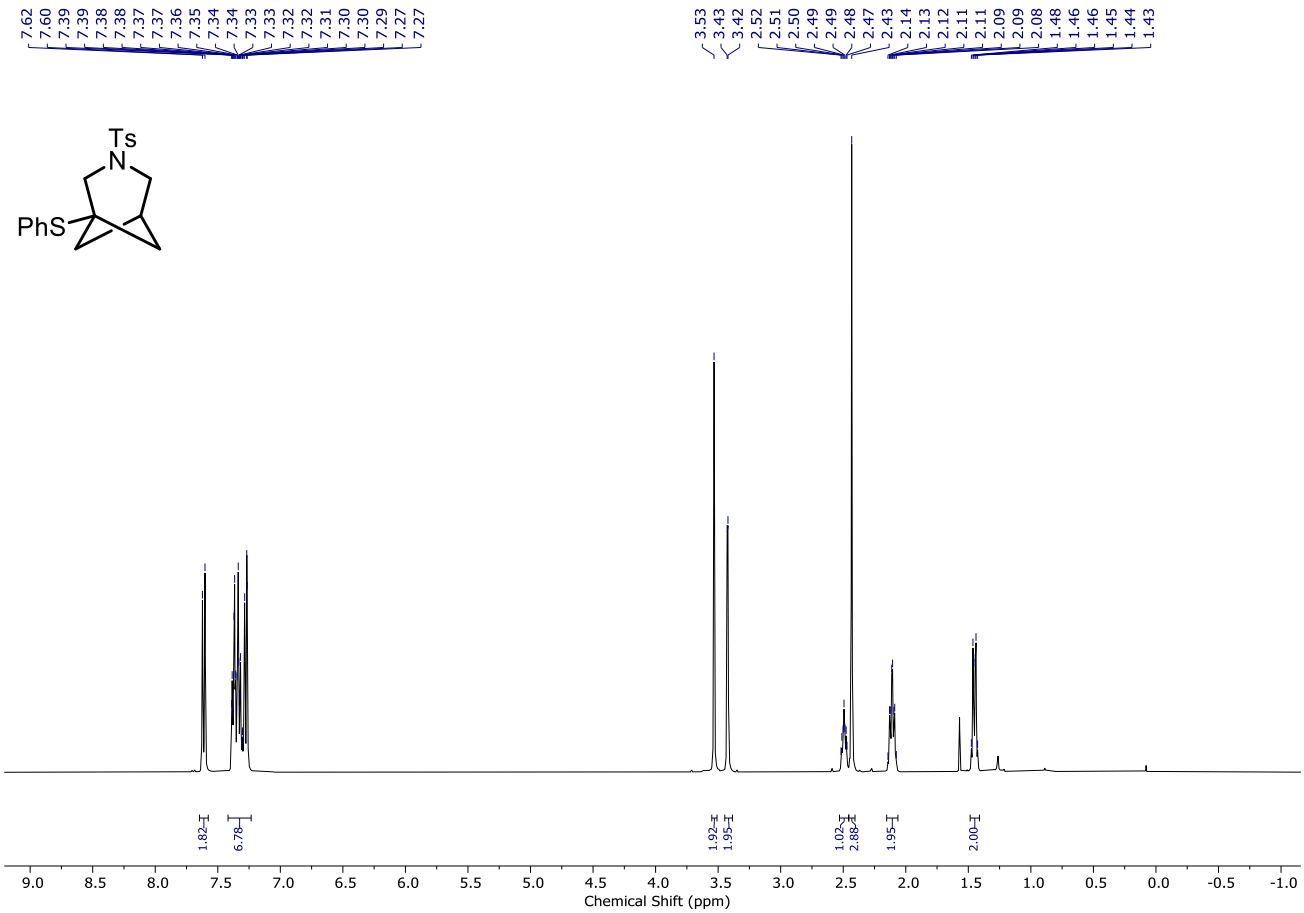
Fragmentation product, 1-(((3-methylene-1-(phenylthio)cyclobutyl)methyl)thio)-3-thiabicyclo[3.1.1]heptane (18v') ^{1}H NMR (500 MHz, $CDCl_3$)



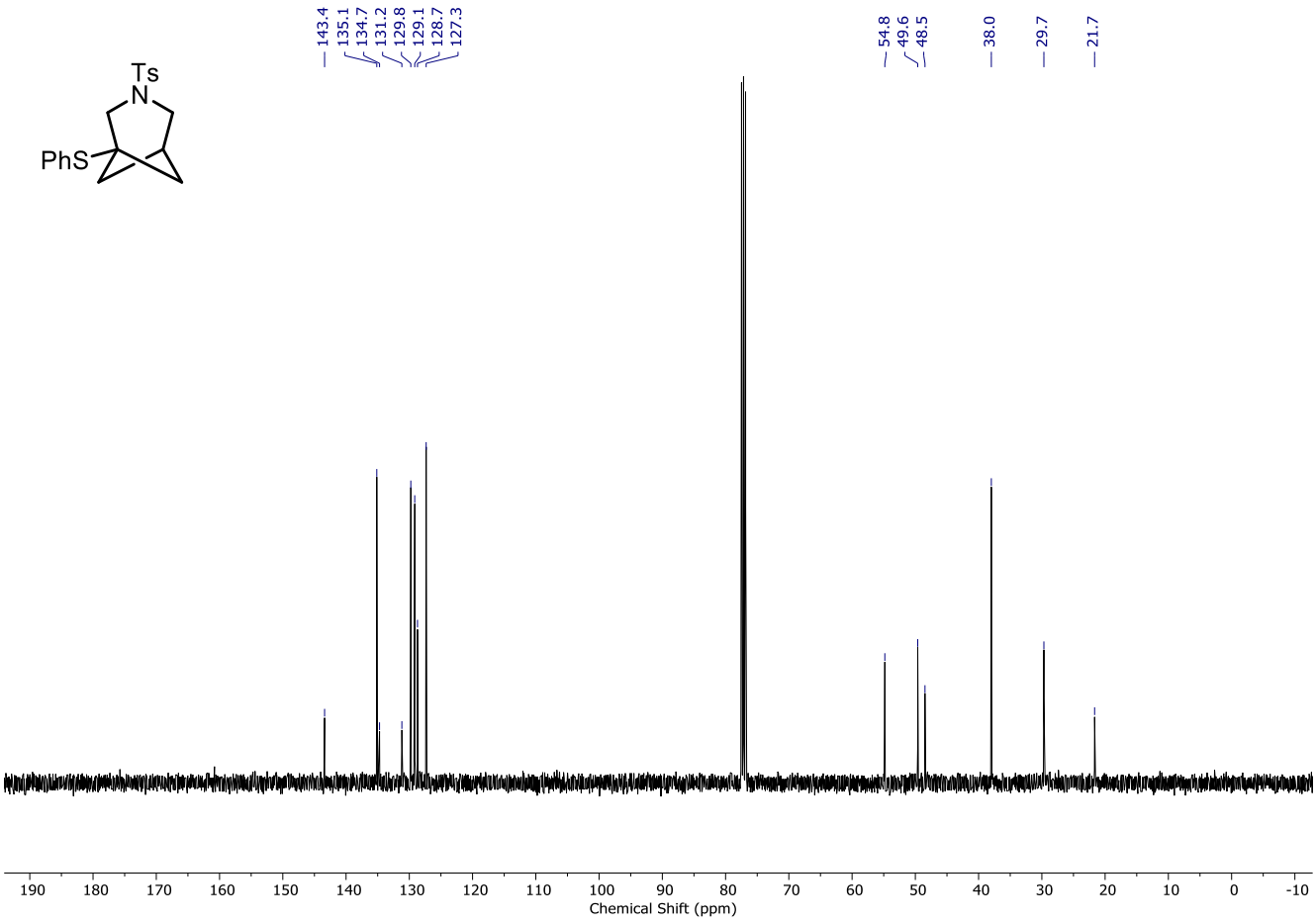
Fragmentation product, 1-(((3-methylene-1-(phenylthio)cyclobutyl)methyl)thio)-3-thiabicyclo[3.1.1]heptane (18v') ^{13}C NMR (126 MHz, $CDCl_3$)



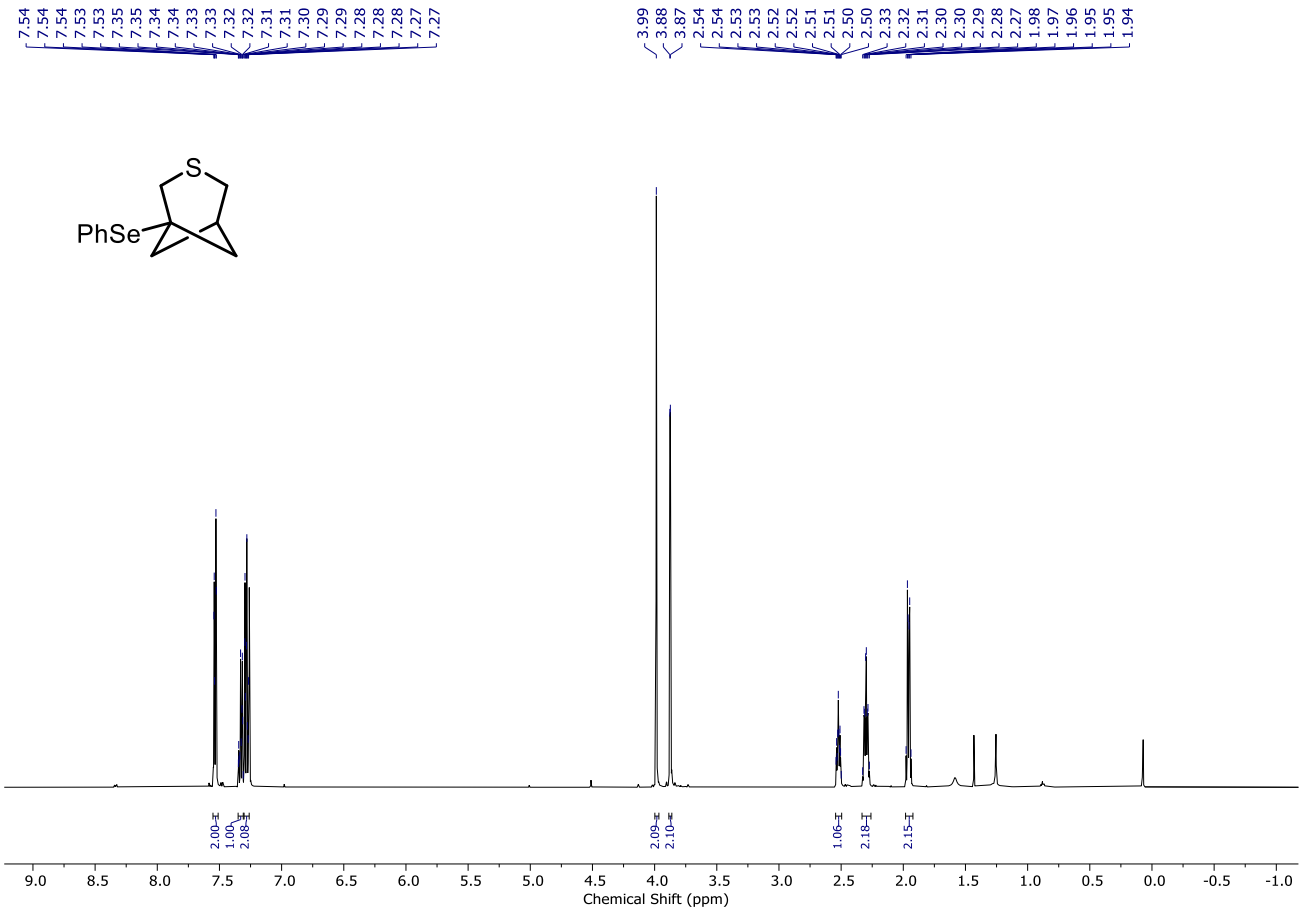
1-(Phenylthio)-3-tosyl-3-azabicyclo[3.1.1]heptane (18w) ^{1}H NMR (400 MHz, $CDCl_3$)



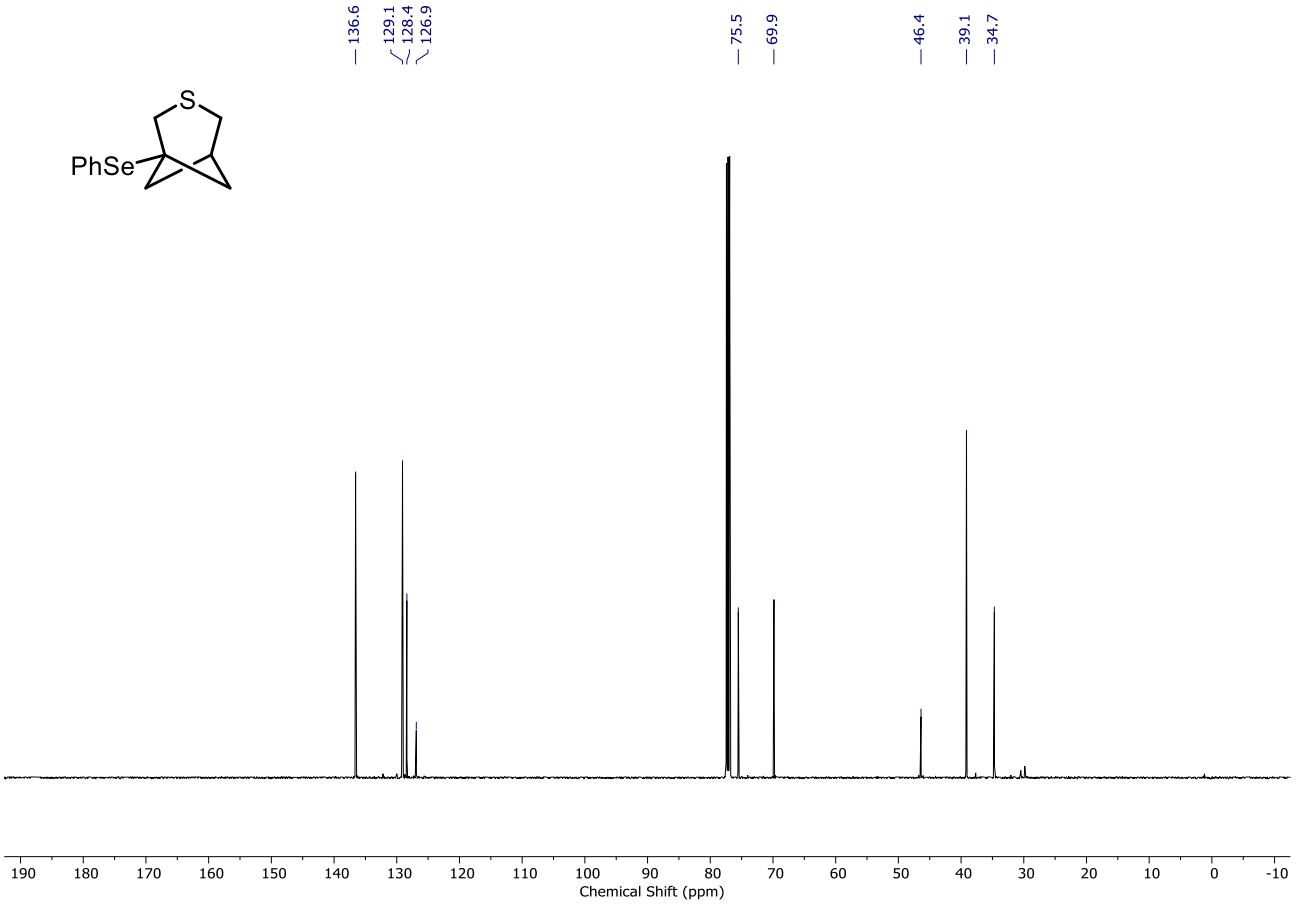
1-(Phenylthio)-3-tosyl-3-azabicyclo[3.1.1]heptane (18w) ^{13}C NMR (101 MHz, $CDCl_3$)



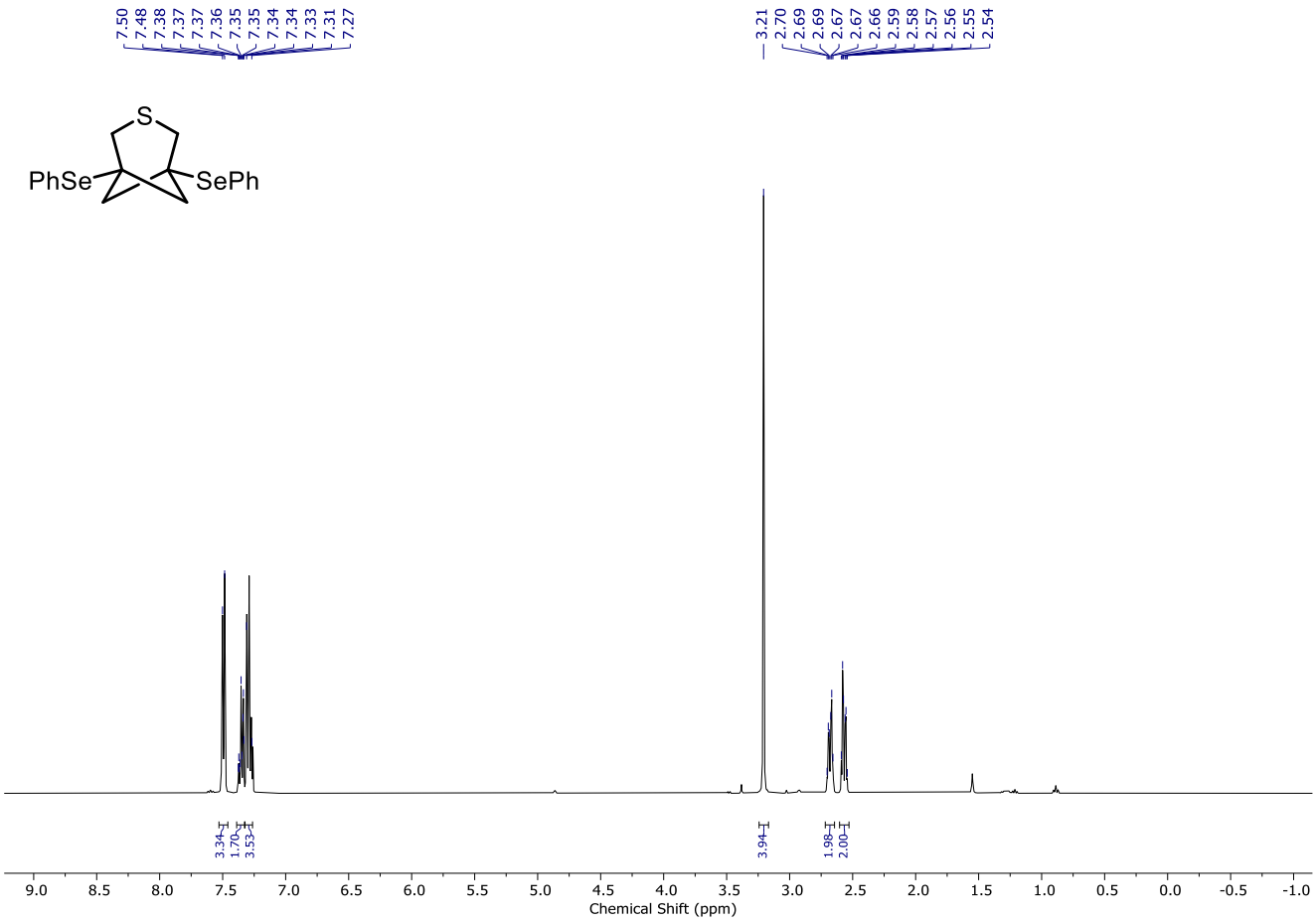
1-(Phenylselenyl)-3-oxabicyclo[3.1.1]heptane (18x) ^{1}H NMR (500 MHz, $CDCl_3$)



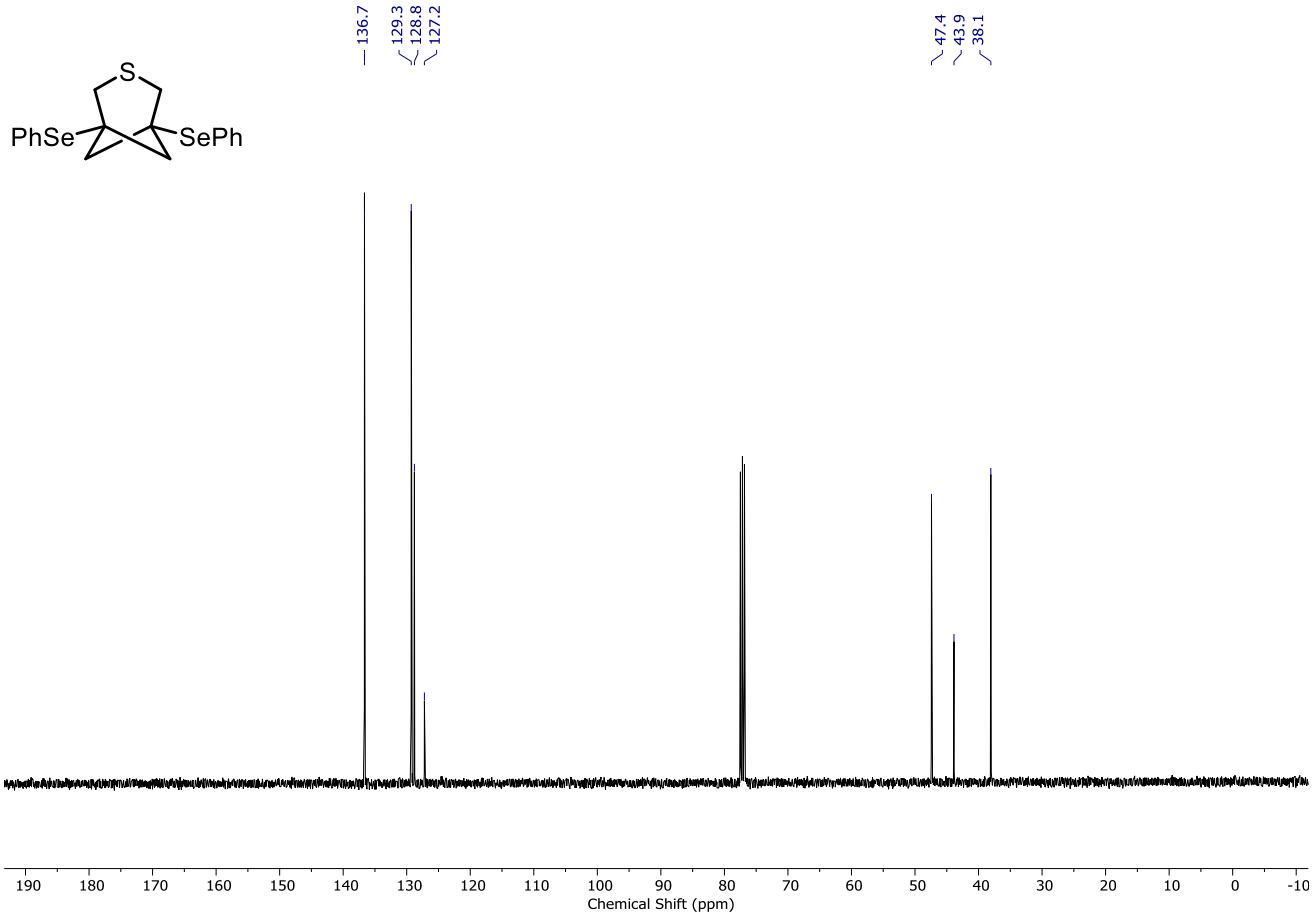
1-(Phenylselenyl)-3-oxabicyclo[3.1.1]heptane (18x) ^{13}C NMR (126 MHz, $CDCl_3$)



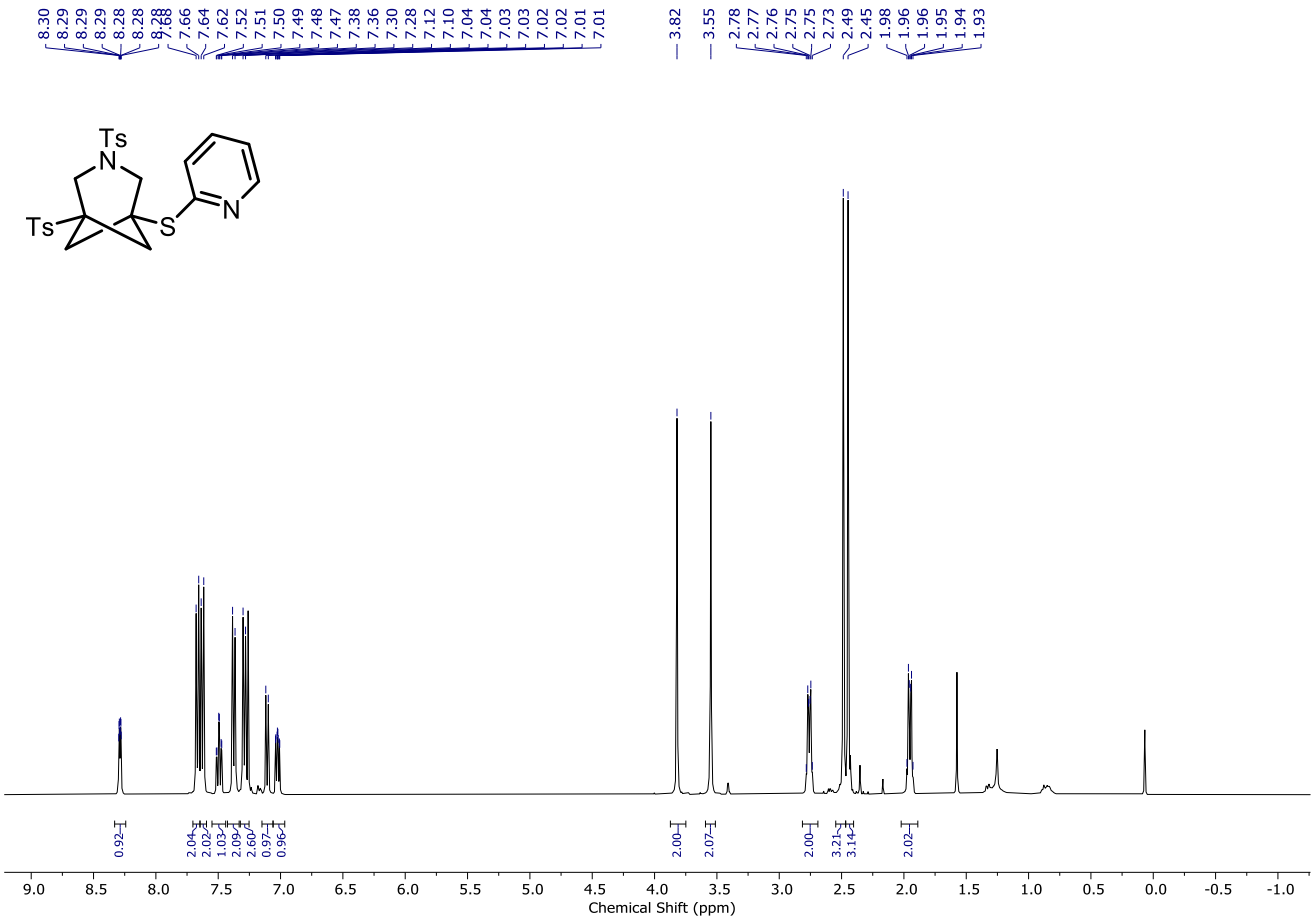
1,5-Bis(phenylselanyl)-3-thiabicyclo[3.1.1]heptane (18y) ^{1}H NMR (400 MHz, $CDCl_3$)



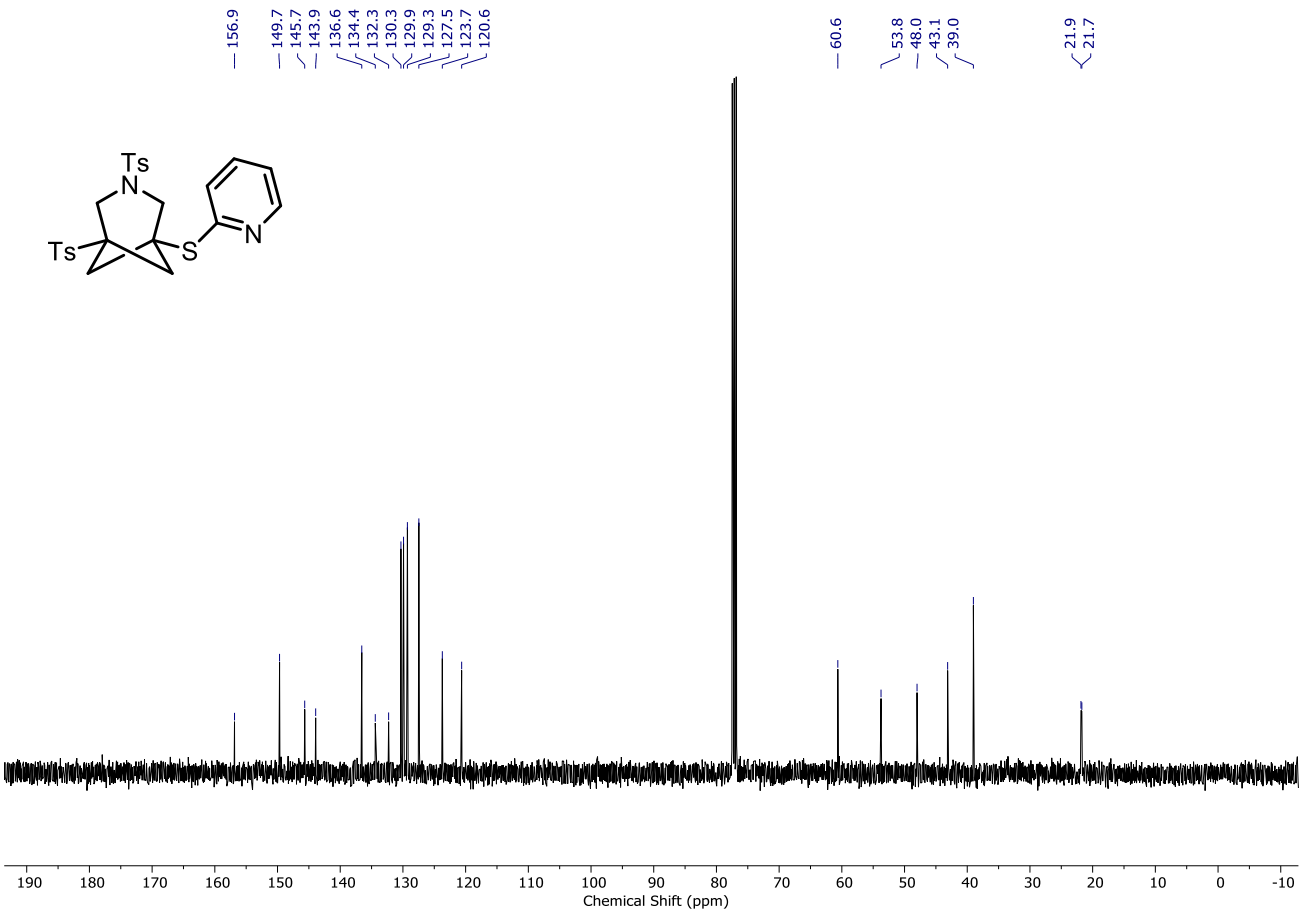
1,5-Bis(phenylselanyl)-3-thiabicyclo[3.1.1]heptane (18y) ^{13}C NMR (101 MHz, $CDCl_3$)



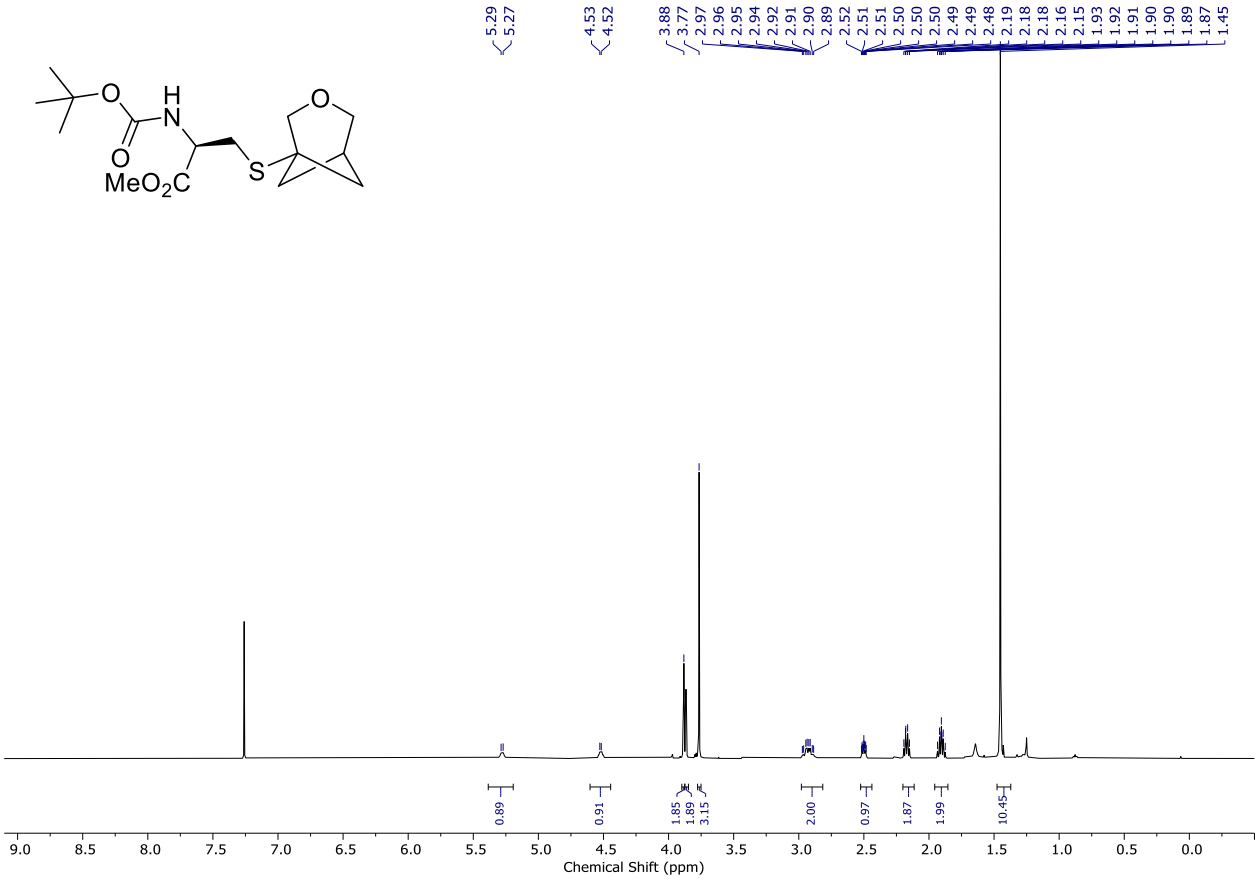
1-(Pyridin-2-ylthio)-3,5-ditosyl-3-azabicyclo[3.1.1]heptane (18z) ^{1}H NMR (400 MHz, $CDCl_3$)



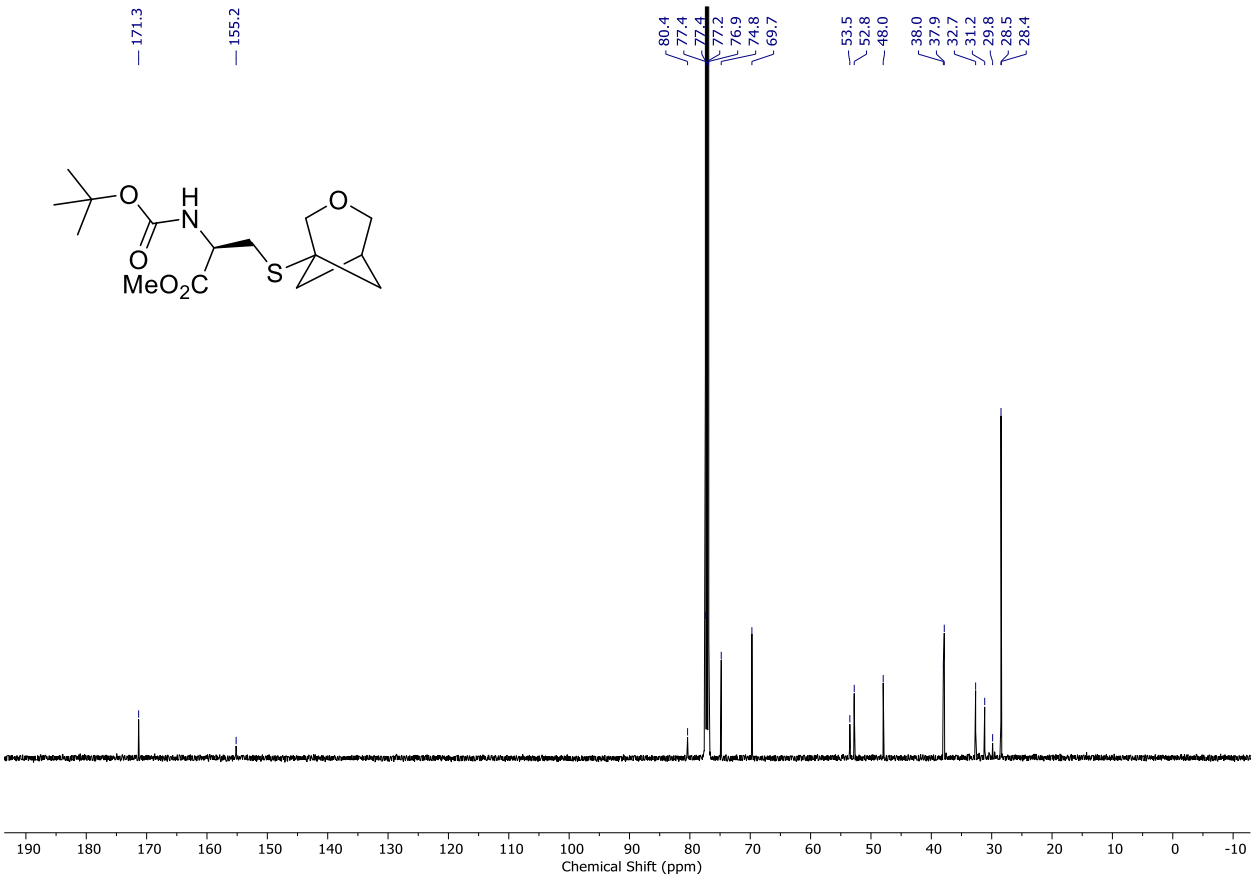
1-(Pyridin-2-ylthio)-3,5-ditosyl-3-azabicyclo[3.1.1]heptane (18z) ^{13}C NMR (101 MHz, $CDCl_3$)



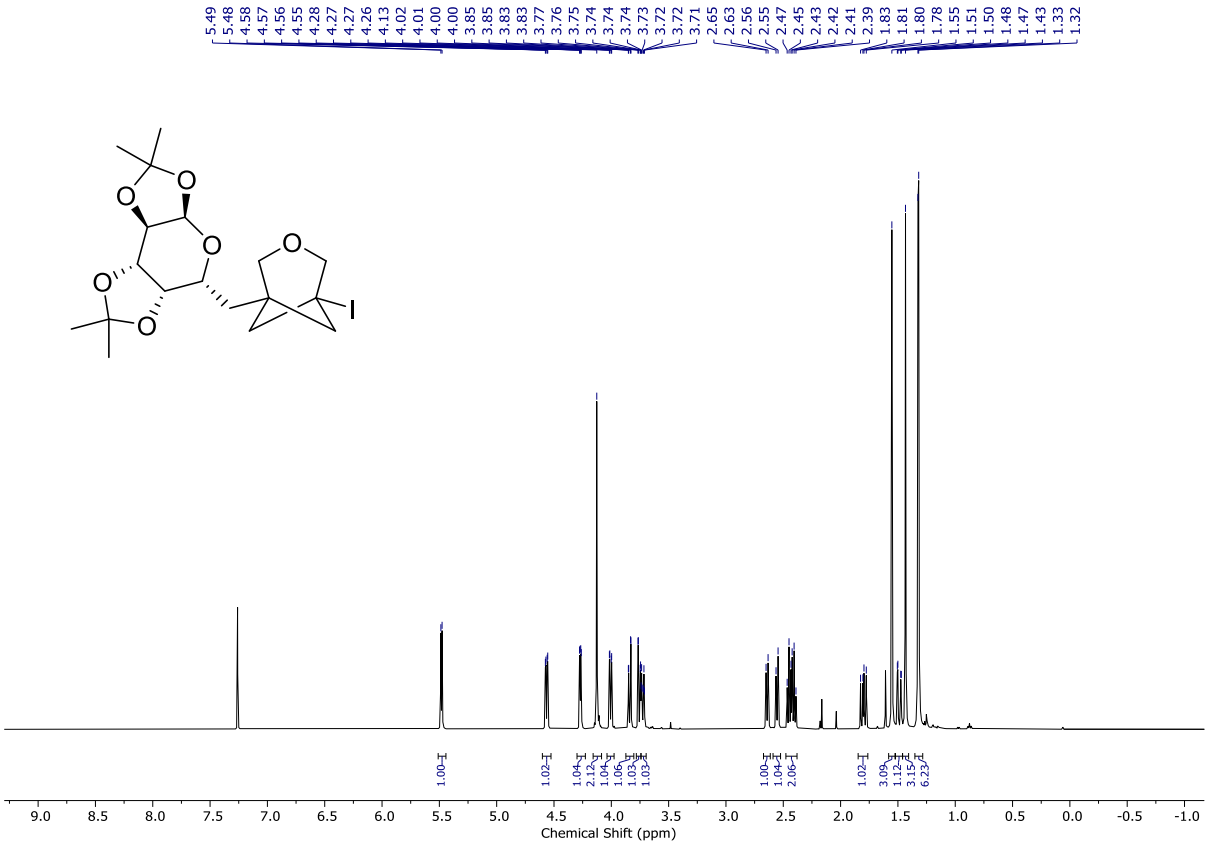
Methyl *S*-(3-oxabicyclo[3.1.1]heptan-1-yl)-N-(*tert*-butoxycarbonyl) cysteinate (18aa) ^{1}H NMR (500 MHz, $CDCl_3$)



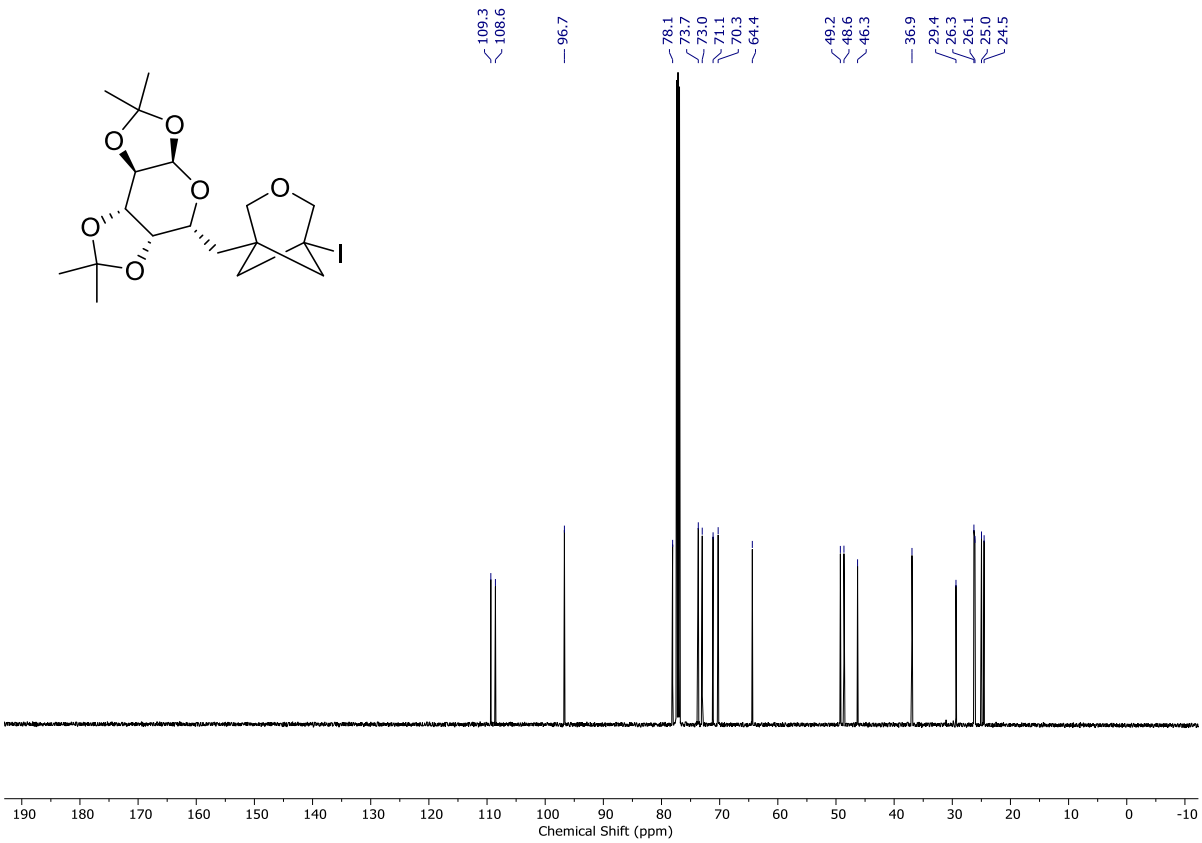
Methyl *S*-(3-oxabicyclo[3.1.1]heptan-1-yl)-N-(*tert*-butoxycarbonyl) cysteinate (18aa) ^{13}C NMR (126 MHz, $CDCl_3$)



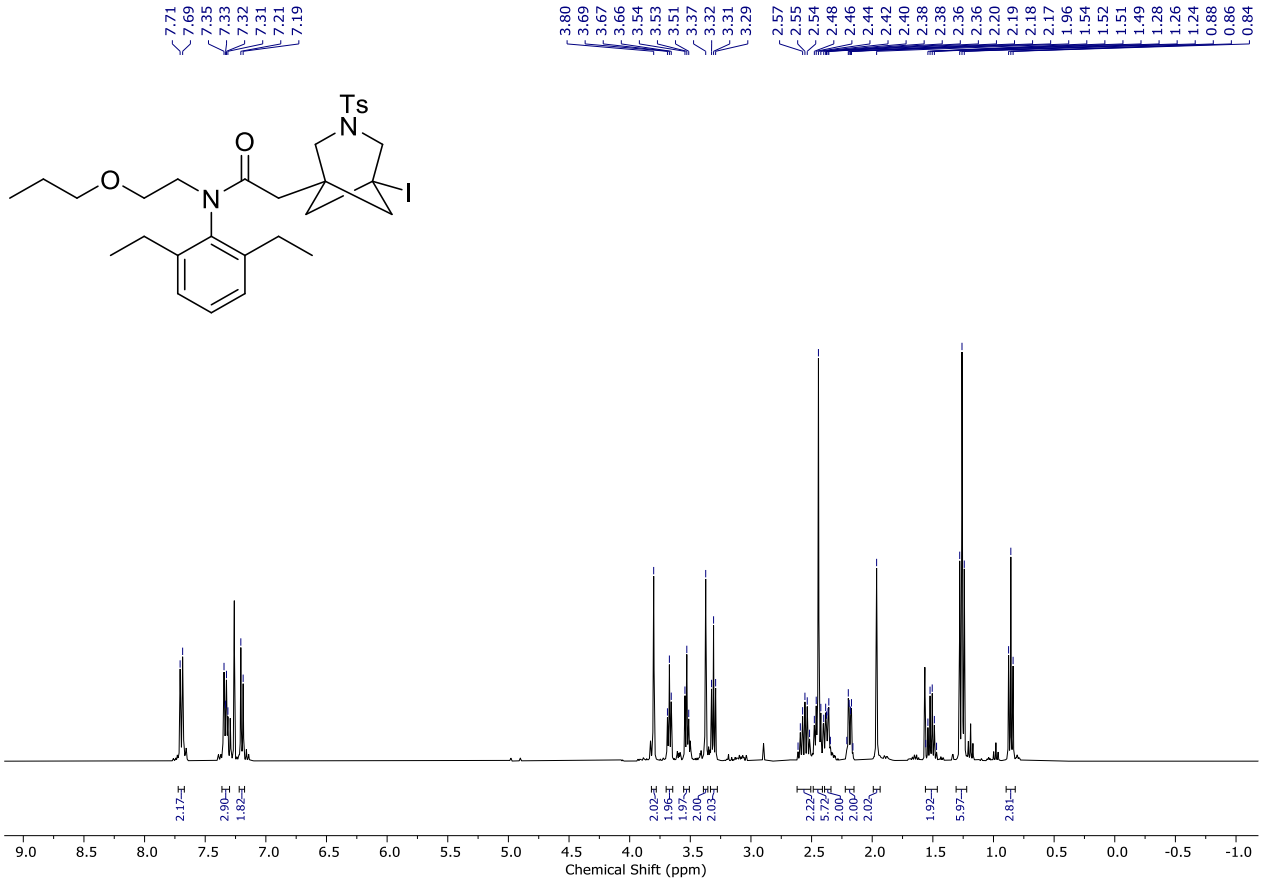
(3aR,5R,5aS,8aS,8bR)-5-((5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (18ab) ^{1}H NMR (500 MHz, $CDCl_3$)



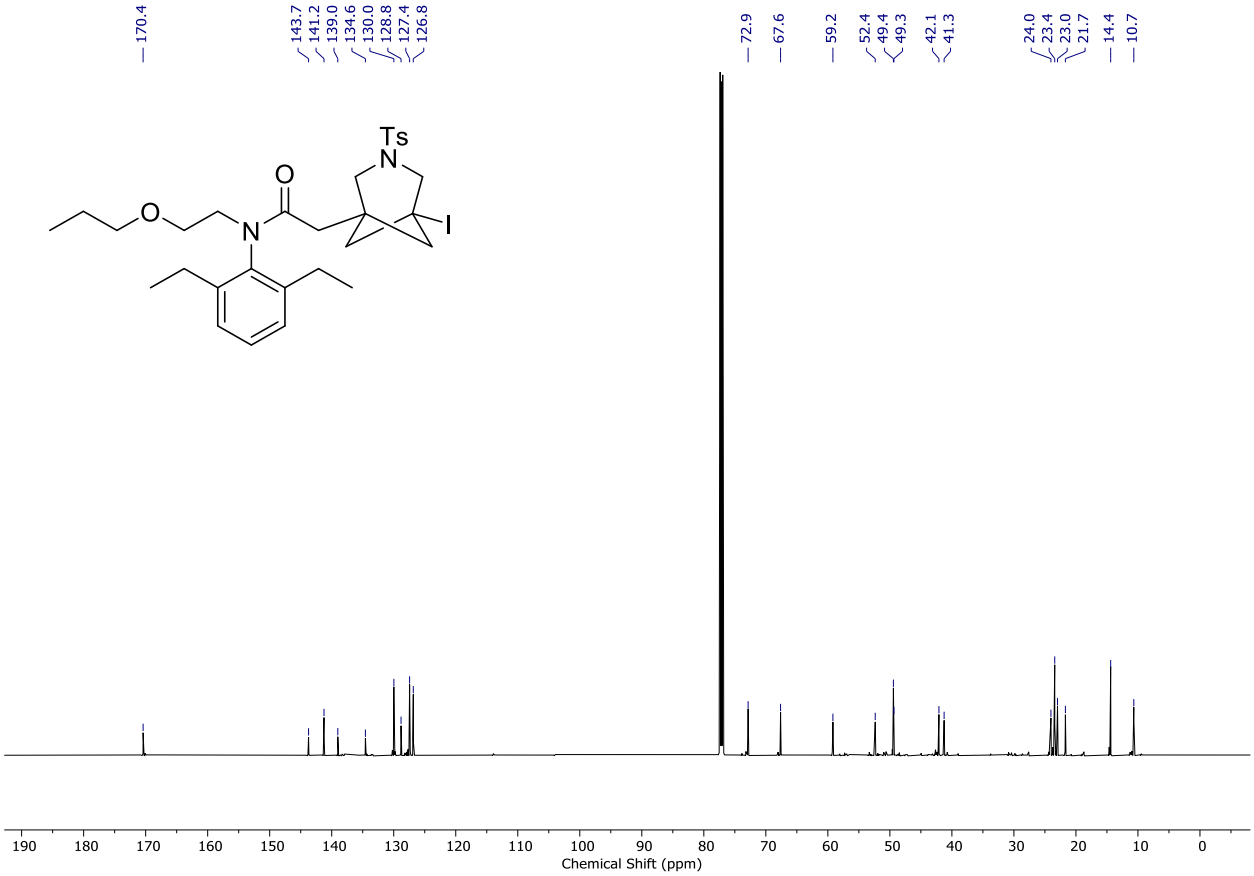
(3aR,5R,5aS,8aS,8bR)-5-((5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (18ab) ^{13}C NMR (126 MHz, $CDCl_3$)



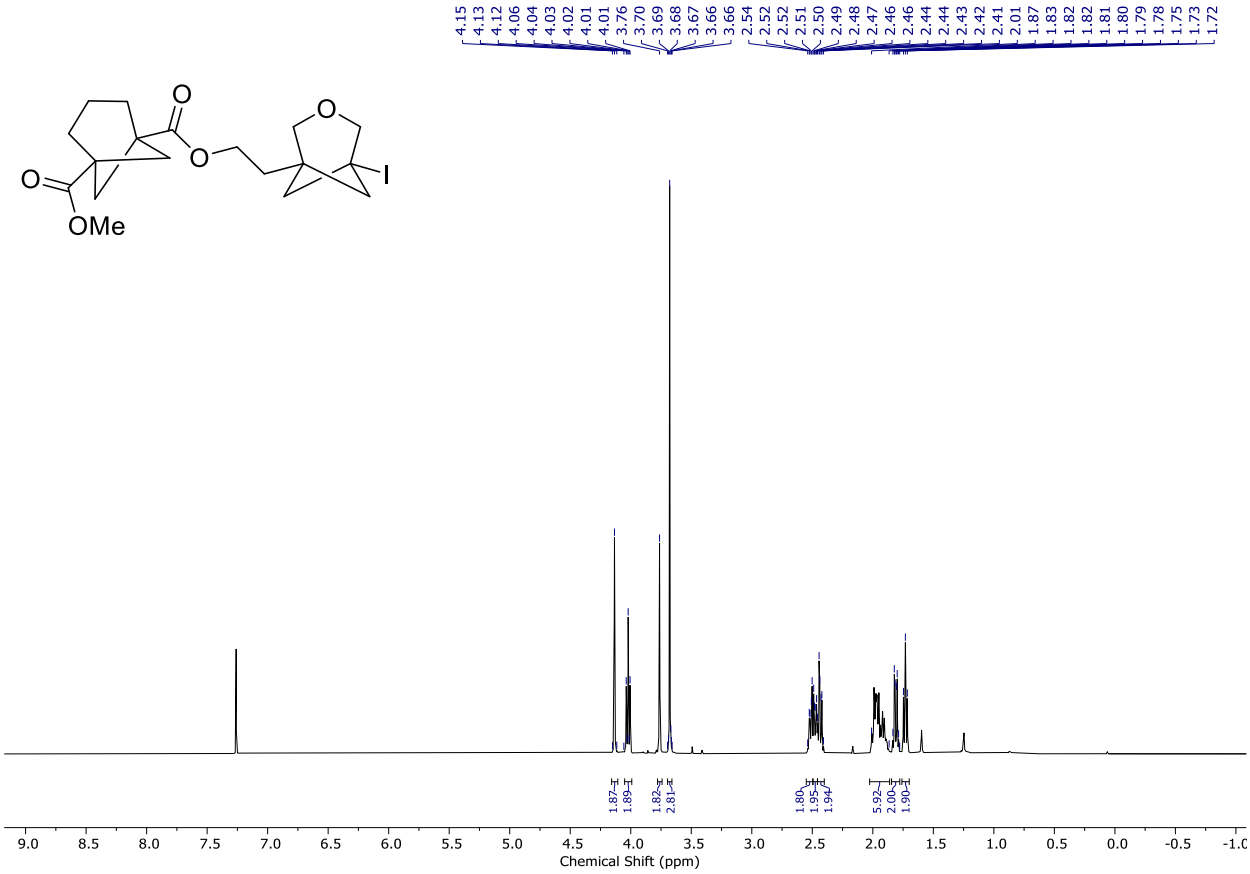
N-(2,6-Diethylphenyl)-2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)-N-(2-propoxyethyl)acetamide (18ac) ^{1}H NMR (400 MHz, $CDCl_3$)



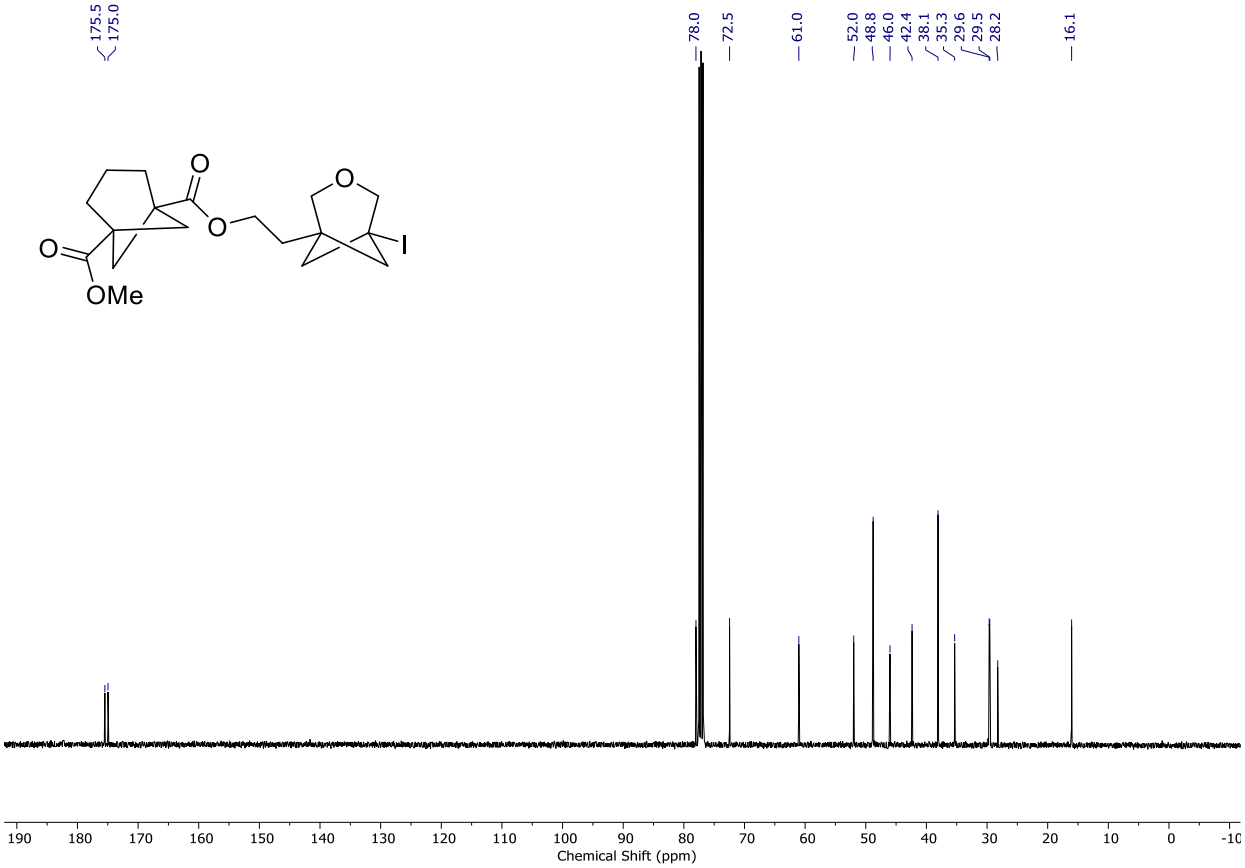
N-(2,6-Diethylphenyl)-2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)-N-(2-propoxyethyl)acetamide (18ac) ^{13}C NMR (151 MHz, $CDCl_3$)



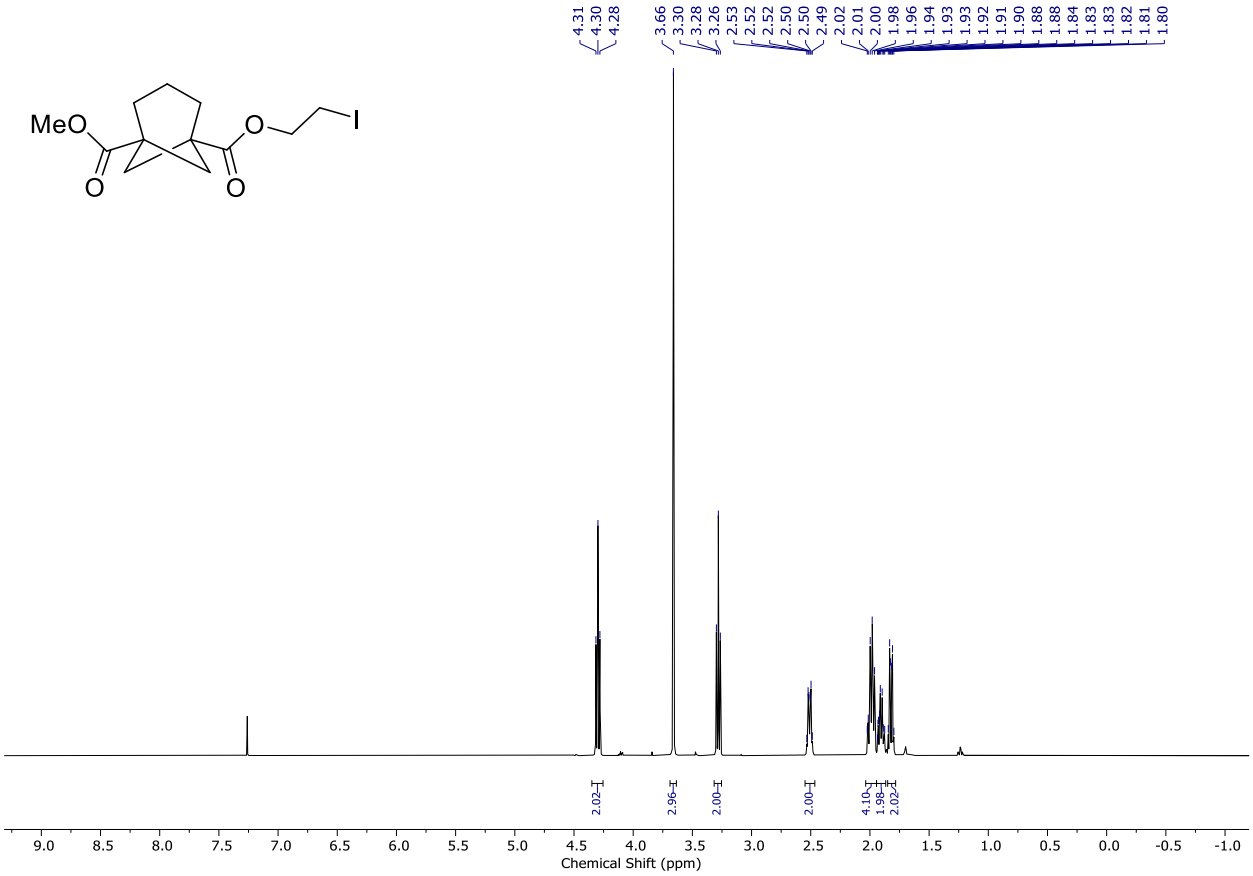
1-(2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)ethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (18ad) ^{1}H NMR (400 MHz, $CDCl_3$)



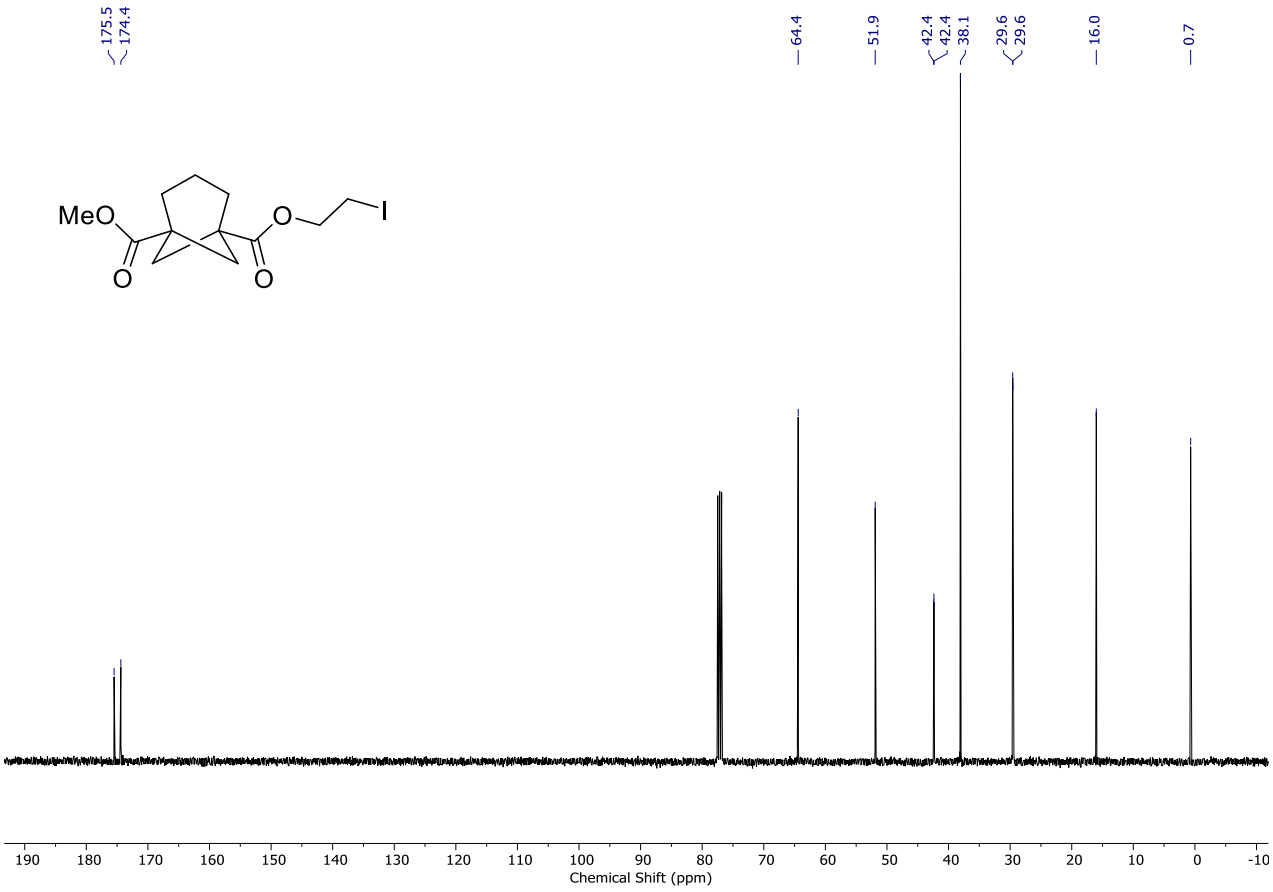
1-(2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)ethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (18ad) ^{13}C NMR (101 MHz, $CDCl_3$)



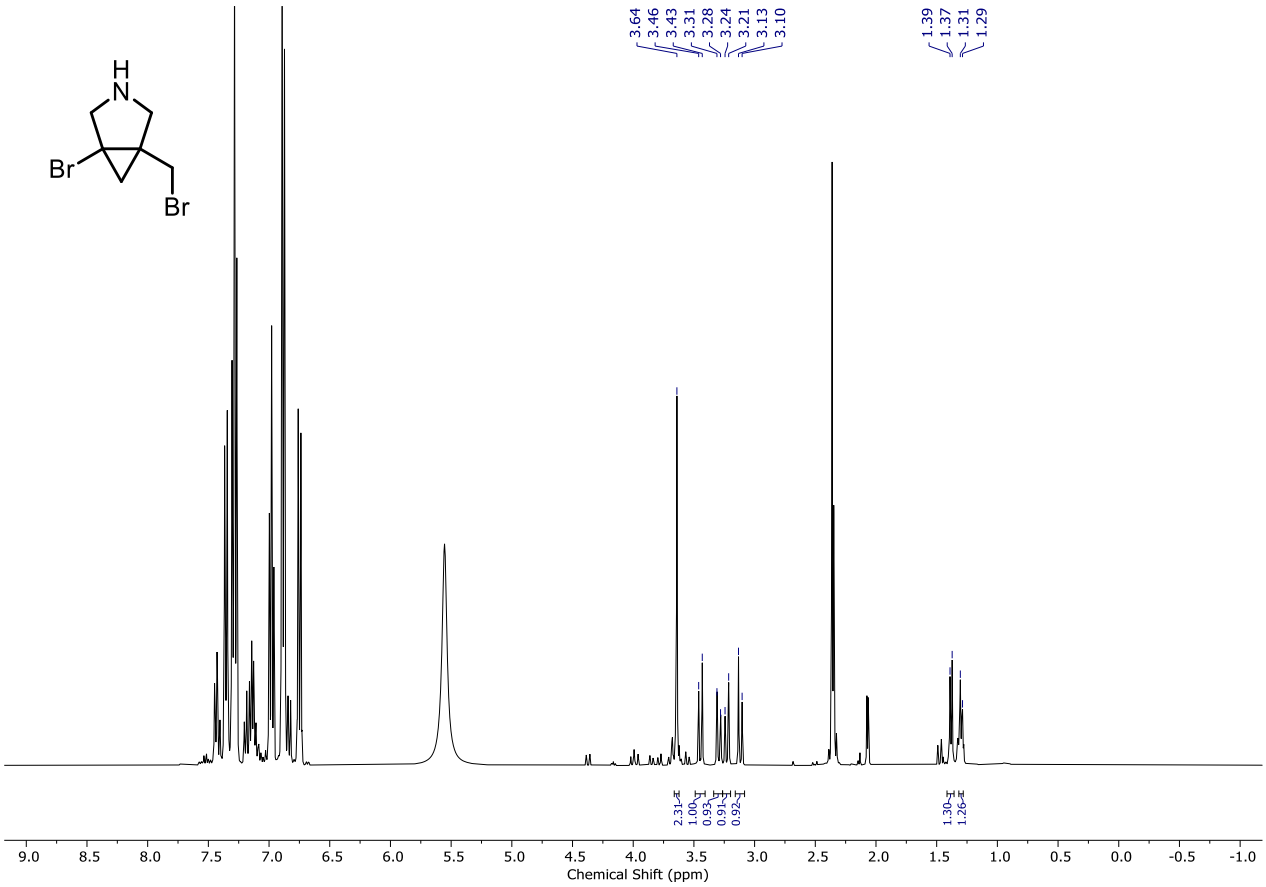
1-(2-Iodoethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (S3) ^{1}H NMR (400 MHz, $CDCl_3$)



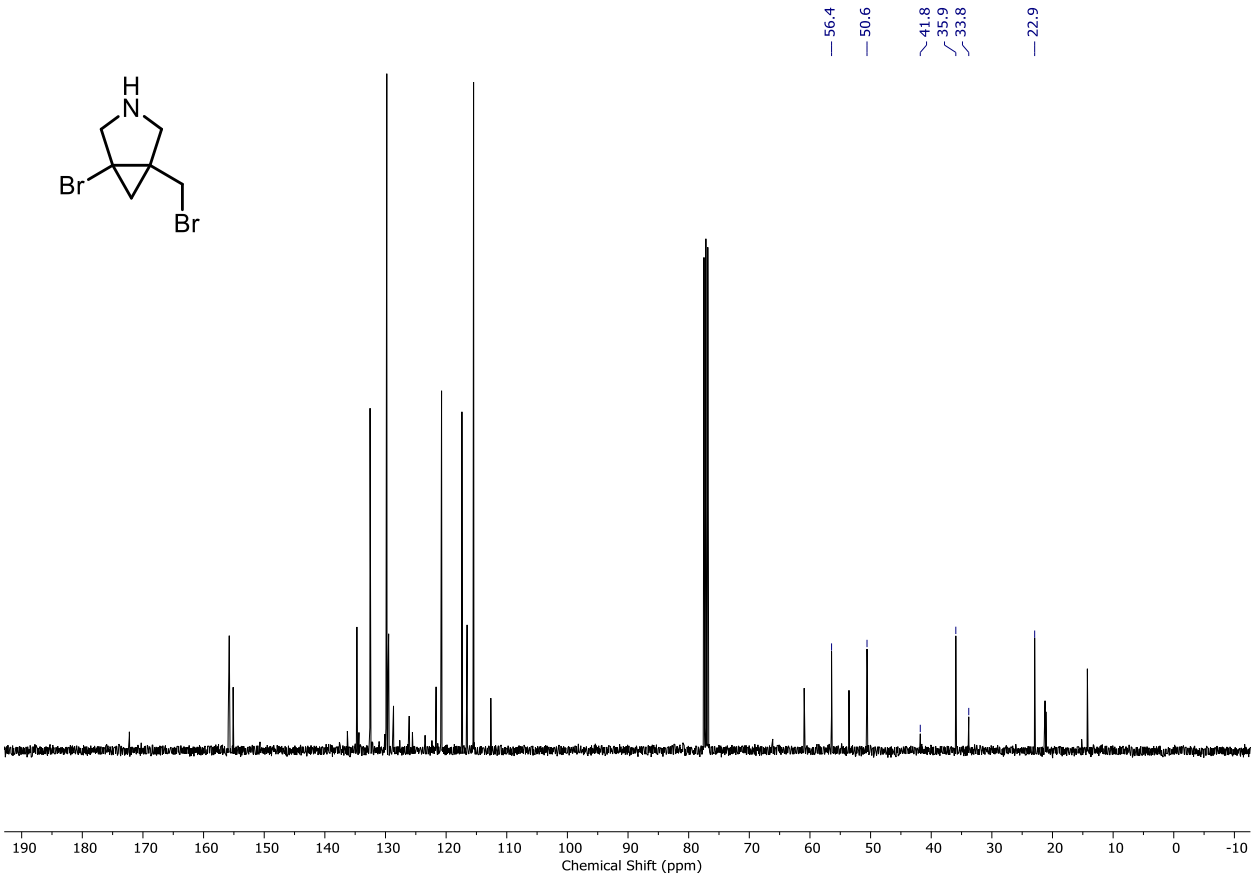
1-(2-Iodoethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (S3) ^{13}C NMR (101 MHz, $CDCl_3$)



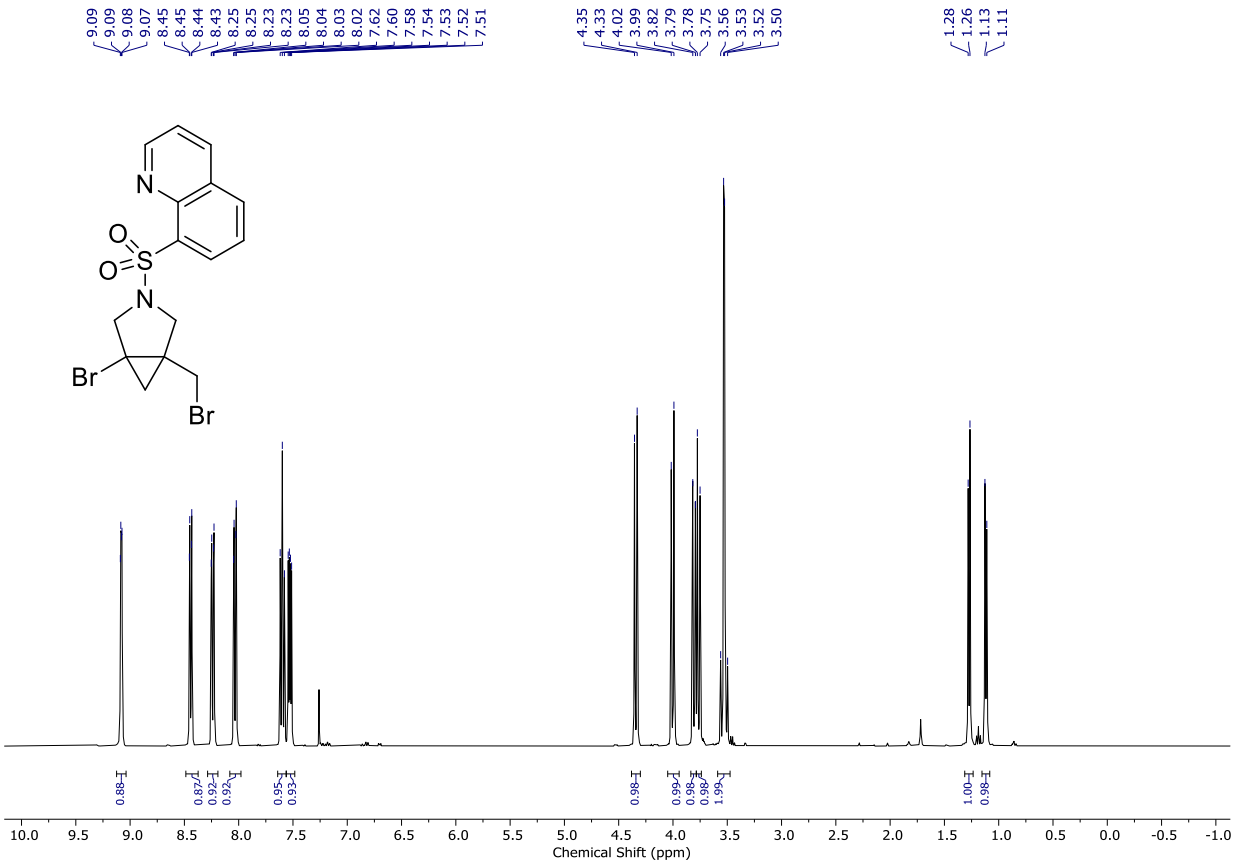
1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (19) (as used for next step) ^{1}H NMR (400 MHz, $CDCl_3$)



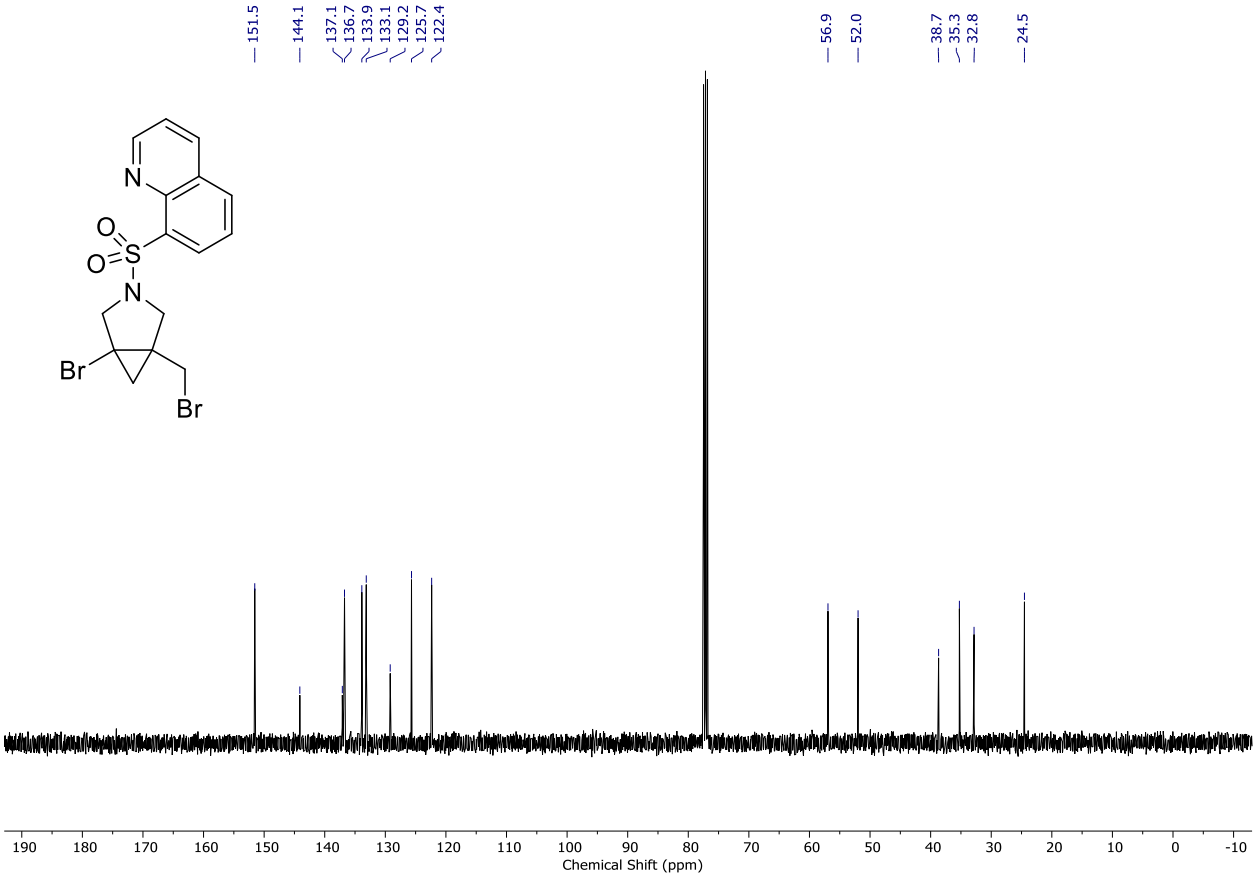
1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (19) (as used for next step) ^{13}C NMR (101 MHz, $CDCl_3$)



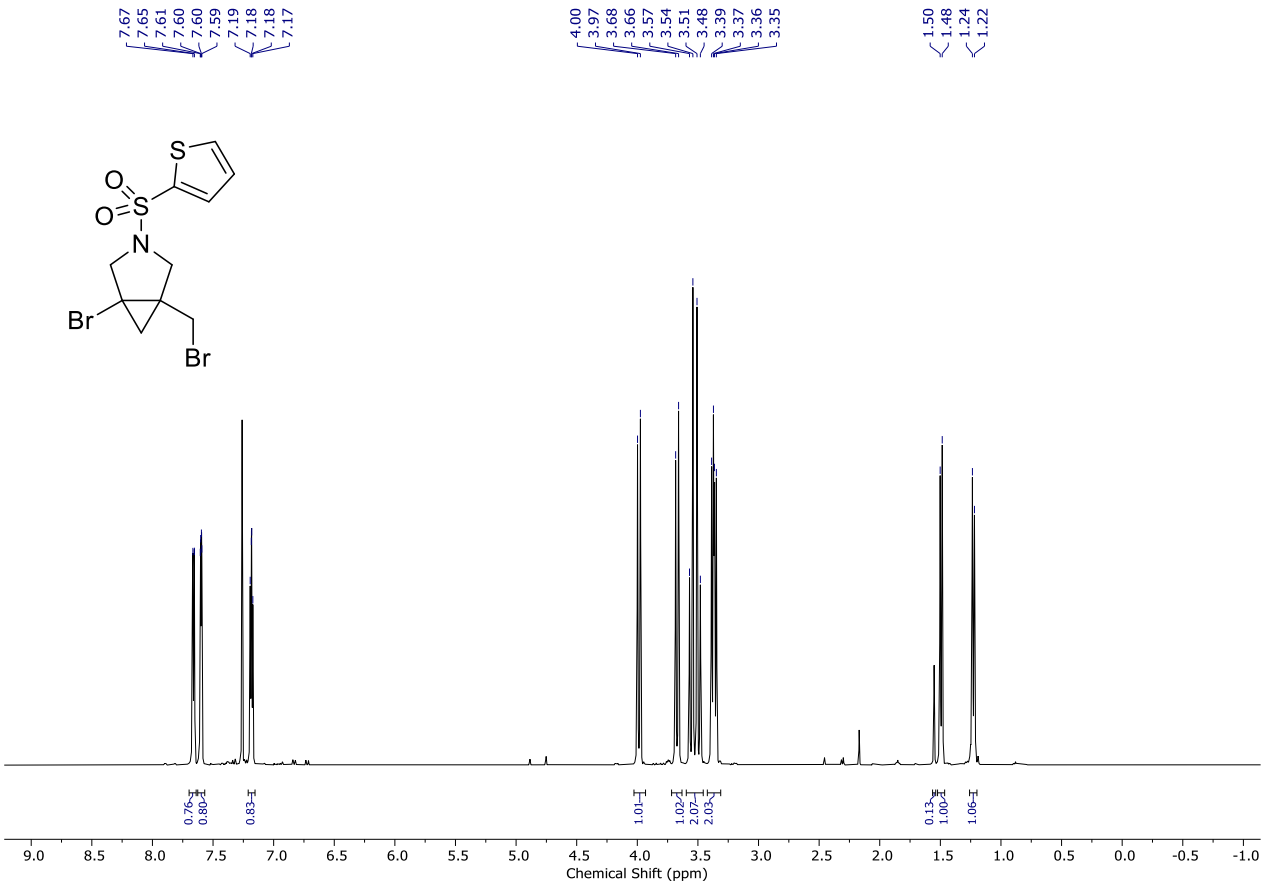
8-((1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)quinoline (20a) ^{1}H NMR (400 MHz, $CDCl_3$)



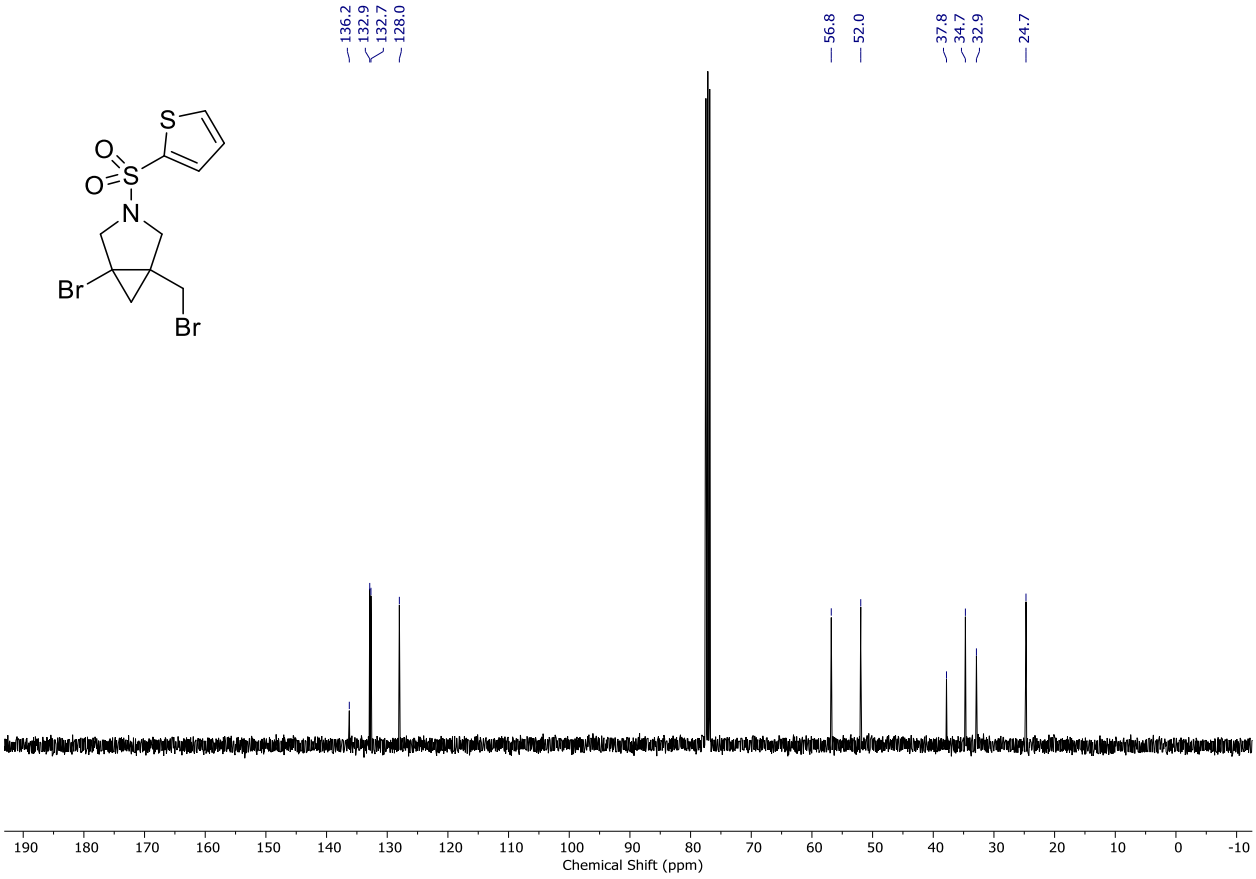
8-((1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)quinoline (20a) ^{13}C NMR (101 MHz, $CDCl_3$)



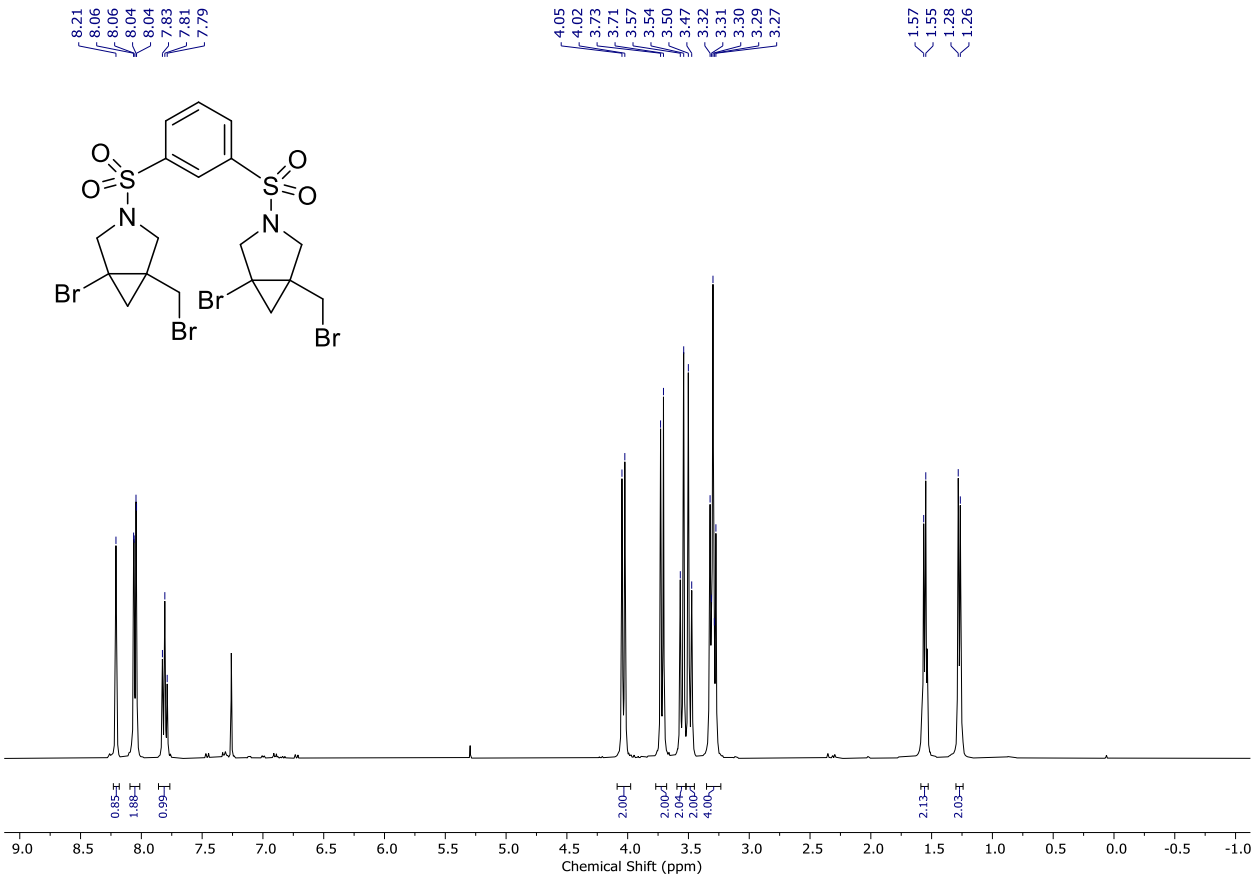
1-Bromo-5-(bromomethyl)-3-(thiophen-2-ylsulfonyl)-3-azabicyclo[3.1.0]hexane (20b) ^{1}H NMR (400 MHz, $CDCl_3$)



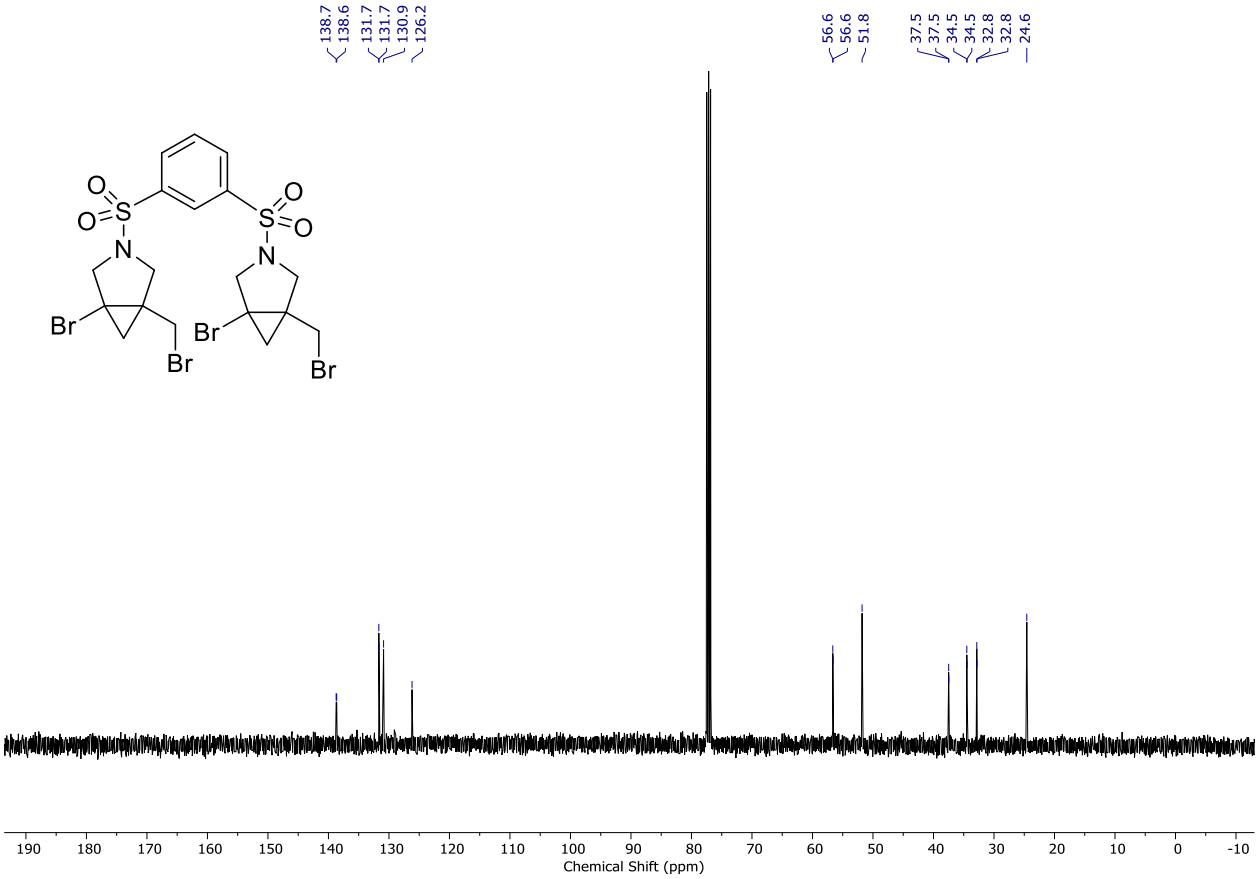
1-Bromo-5-(bromomethyl)-3-(thiophen-2-ylsulfonyl)-3-azabicyclo[3.1.0]hexane (20b) ^{13}C NMR (101 MHz, $CDCl_3$)



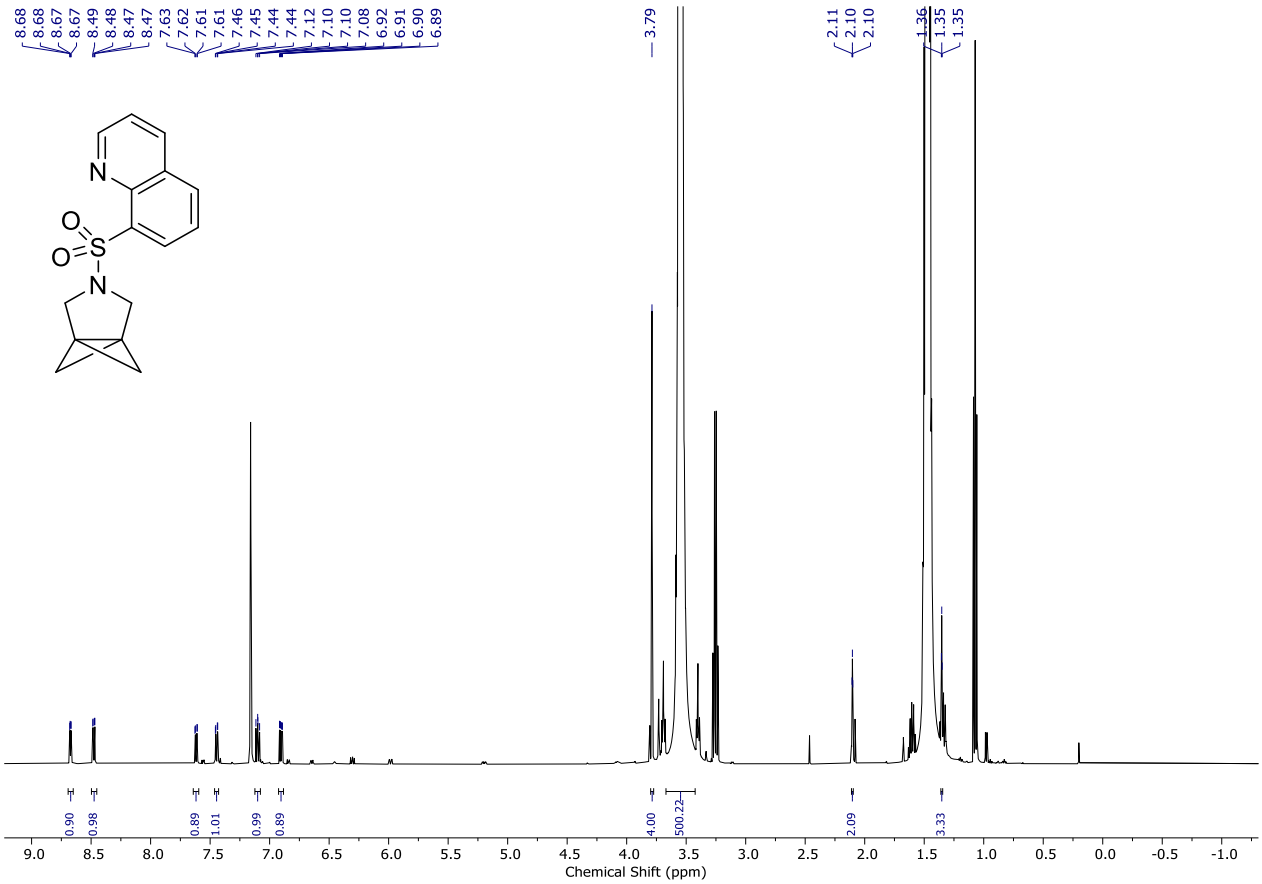
1,3-Bis((1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)benzene (20c) ^{1}H NMR (400 MHz, $CDCl_3$)



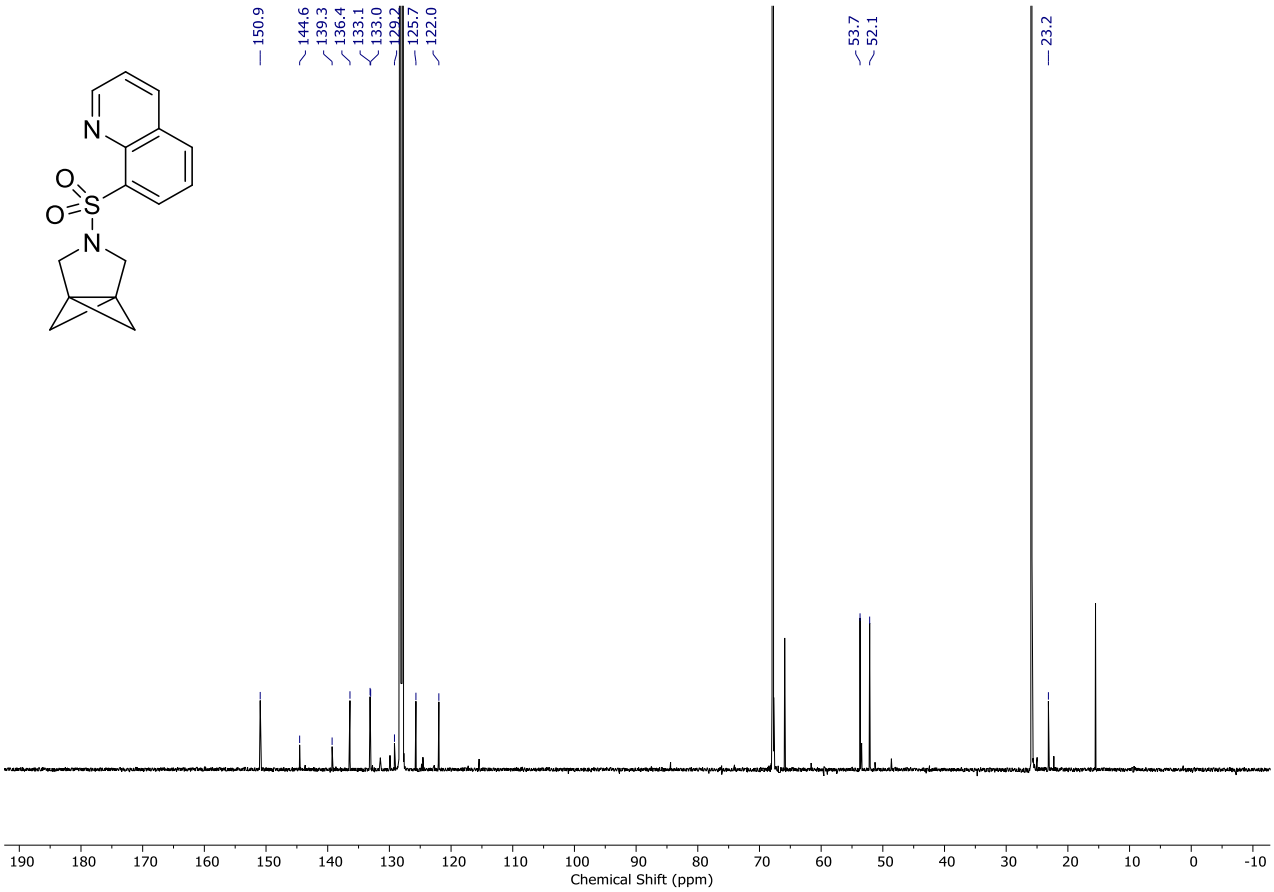
1,3-Bis((1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)benzene (20c) ^{13}C NMR (101 MHz, $CDCl_3$)



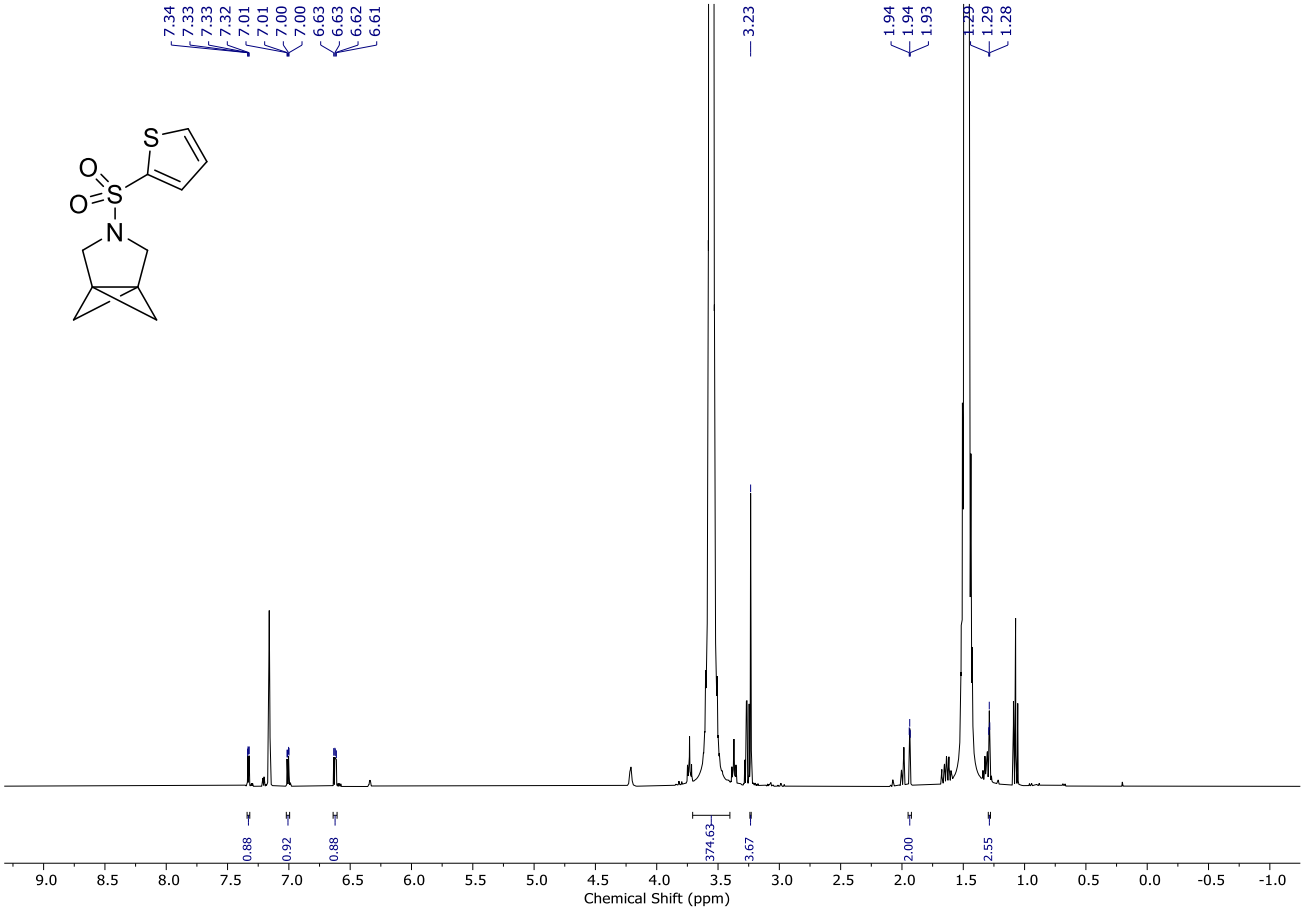
3-(Quinolin-8-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (21a) (contains some Et_2O) ^1H NMR (500 MHz, $CDCl_3$)



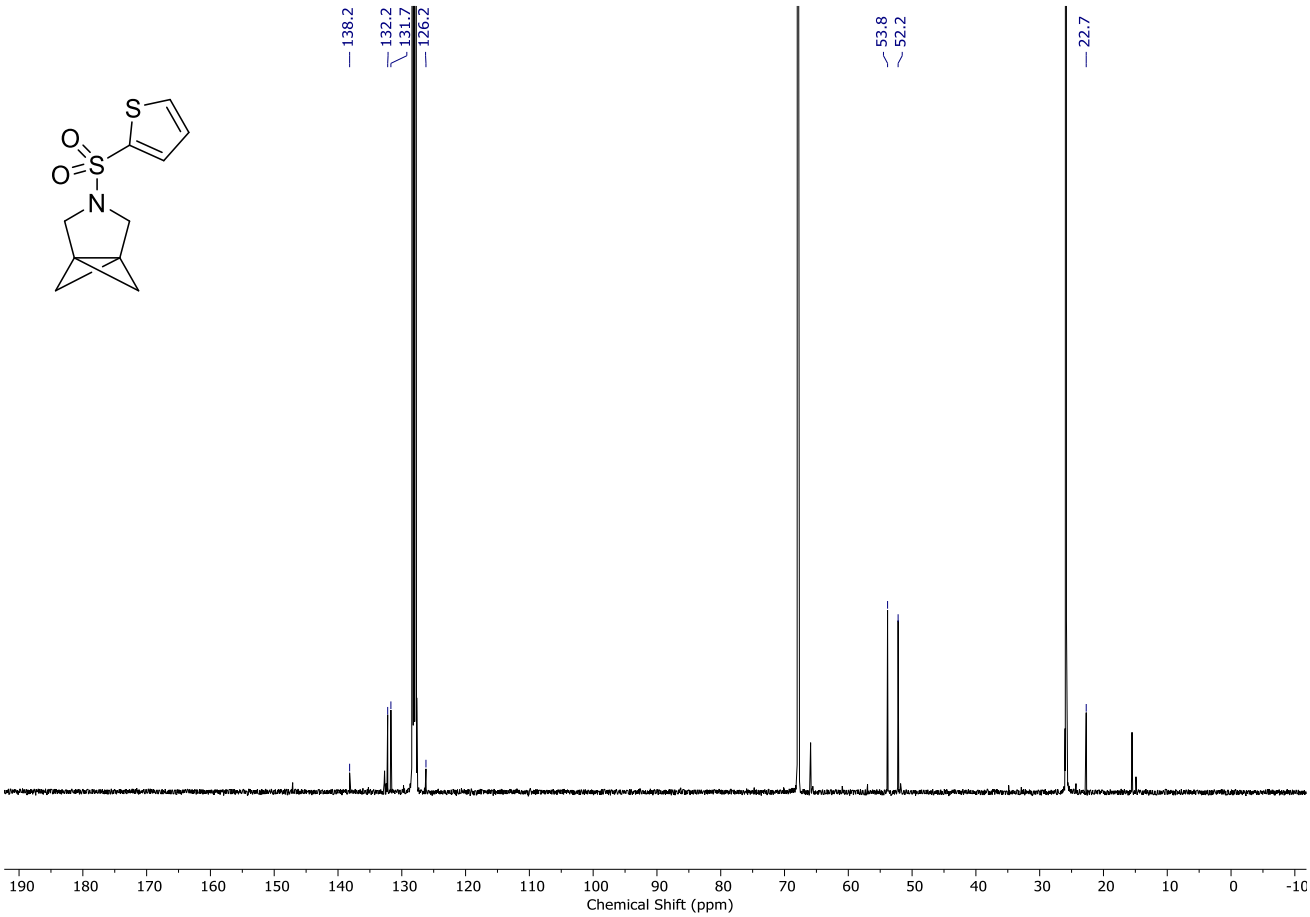
3-(Quinolin-8-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (21a) (contains some Et_2O) ^{13}C NMR (126 MHz, $CDCl_3$)



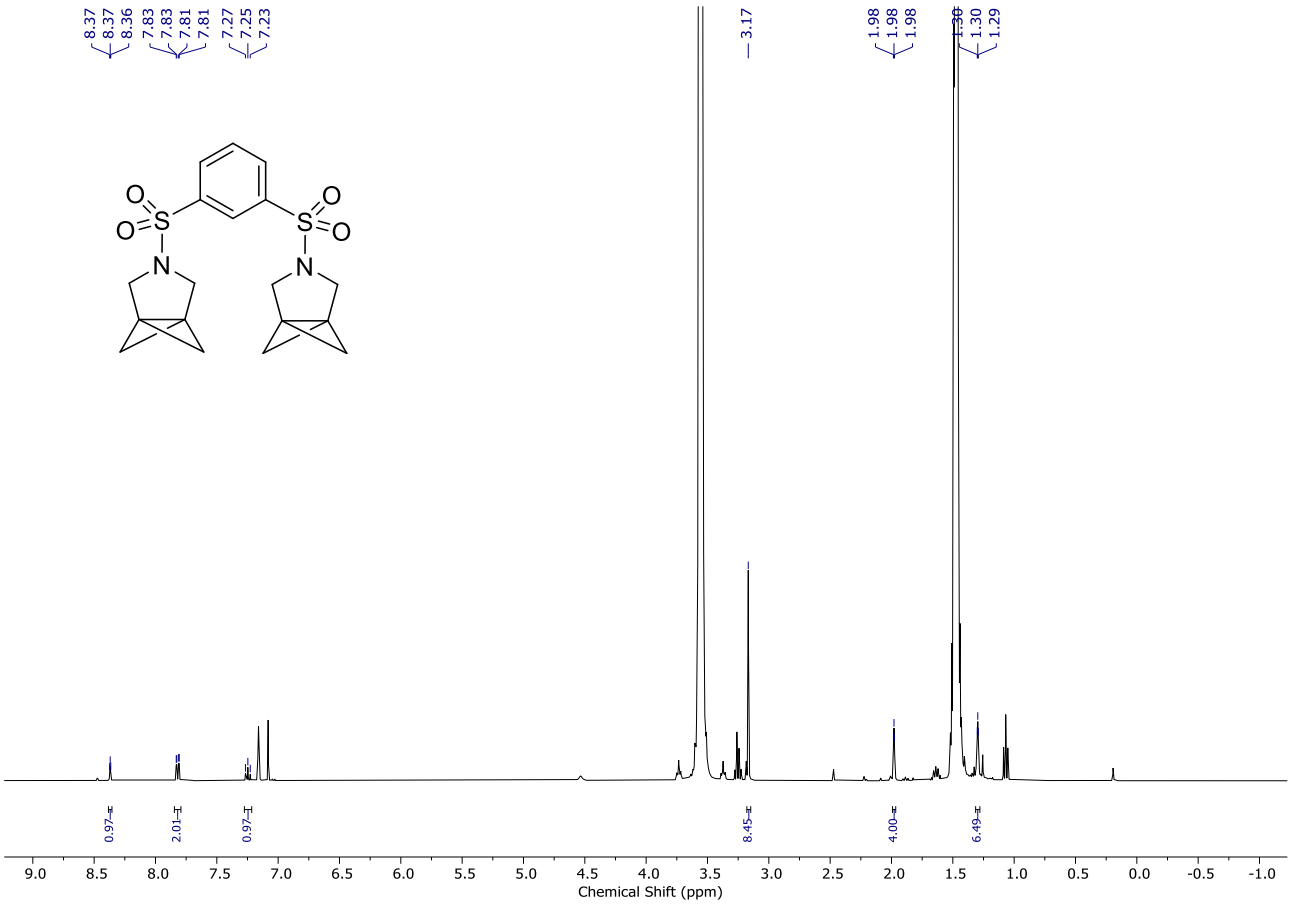
3-(Thiophen-2-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (21b) ^{1}H NMR (400 MHz, $CDCl_3$)



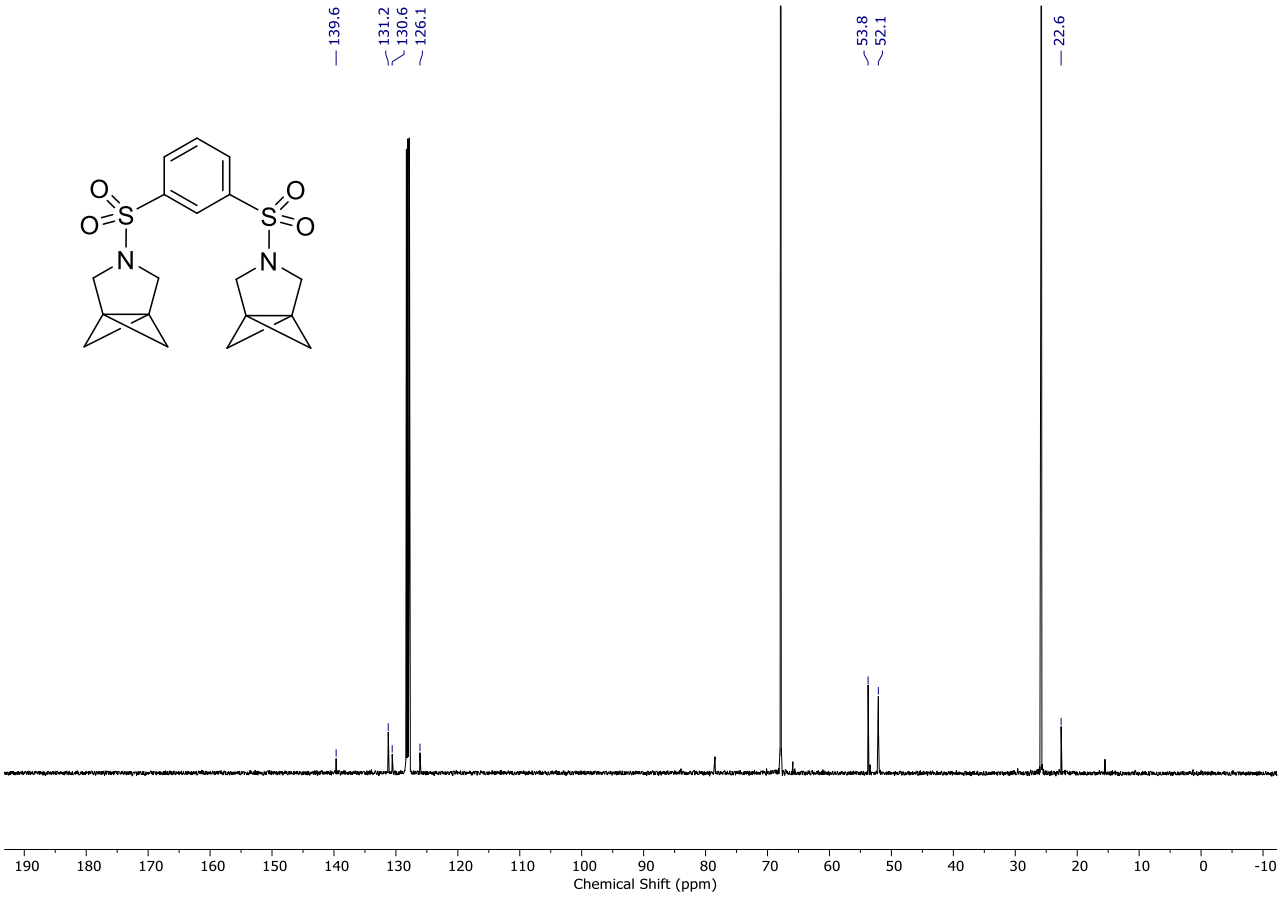
3-(Thiophen-2-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (21b) ^{13}C NMR (101 MHz, $CDCl_3$)



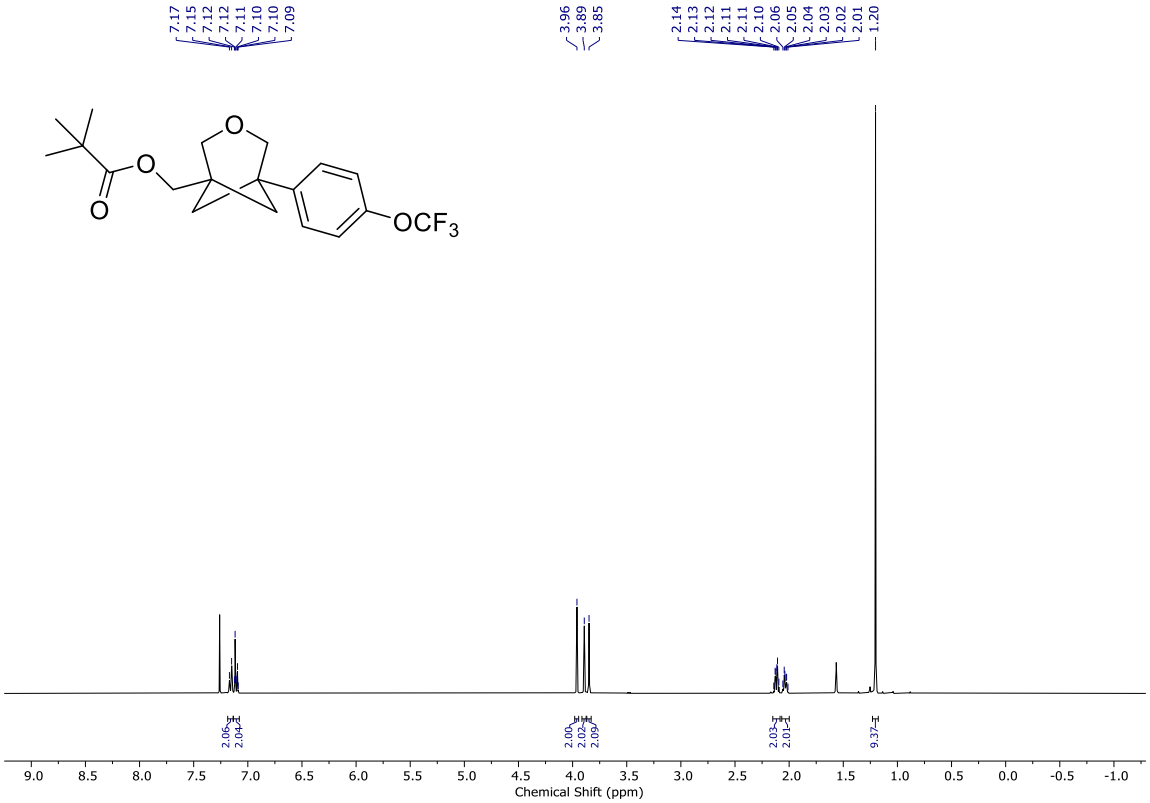
1,3-Bis((3-azatricyclo[3.1.1.01,5]heptan-3-yl)sulfonyl)benzene (21c) ^{1}H NMR (400 MHz, $CDCl_3$)



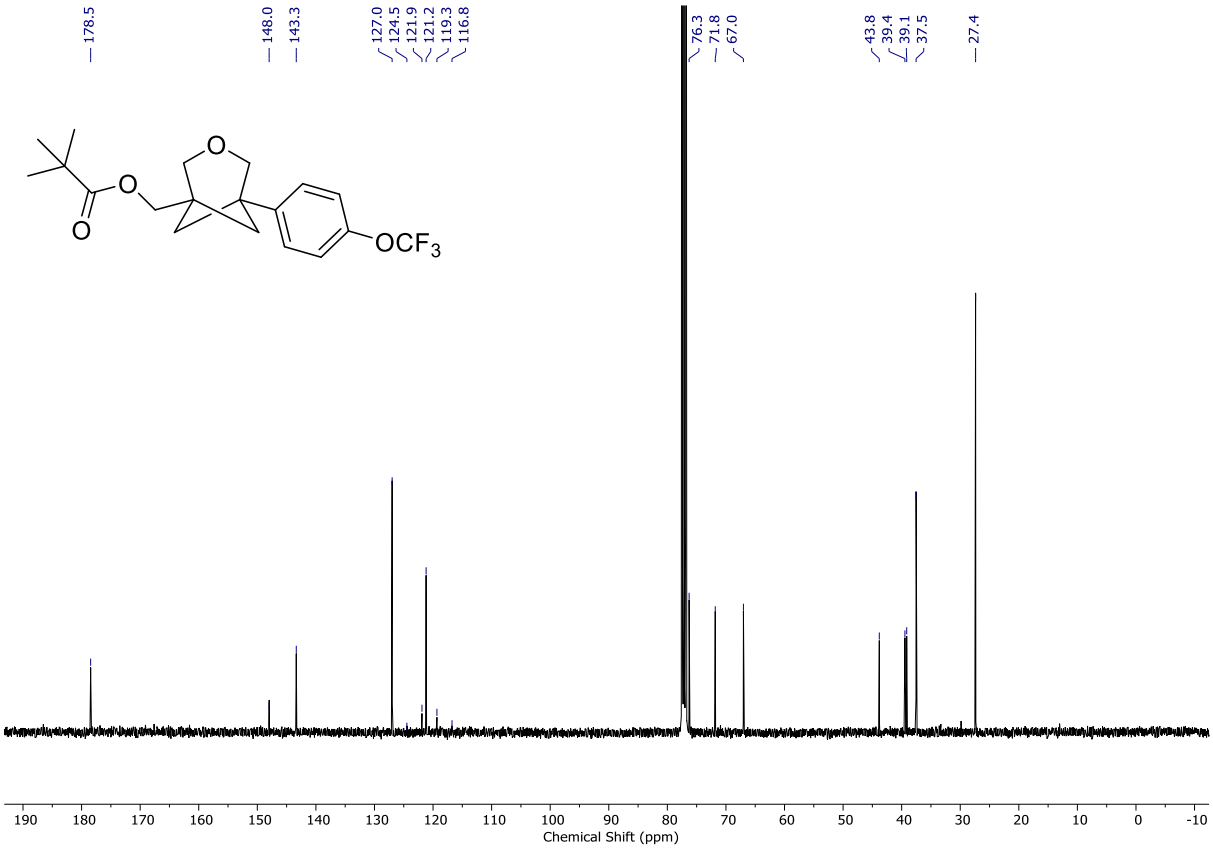
1,3-Bis((3-azatricyclo[3.1.1.01,5]heptan-3-yl)sulfonyl)benzene (21c) ^{13}C NMR (101 MHz, $CDCl_3$)



(5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (23) ^{1}H NMR (400 MHz, $CDCl_3$)

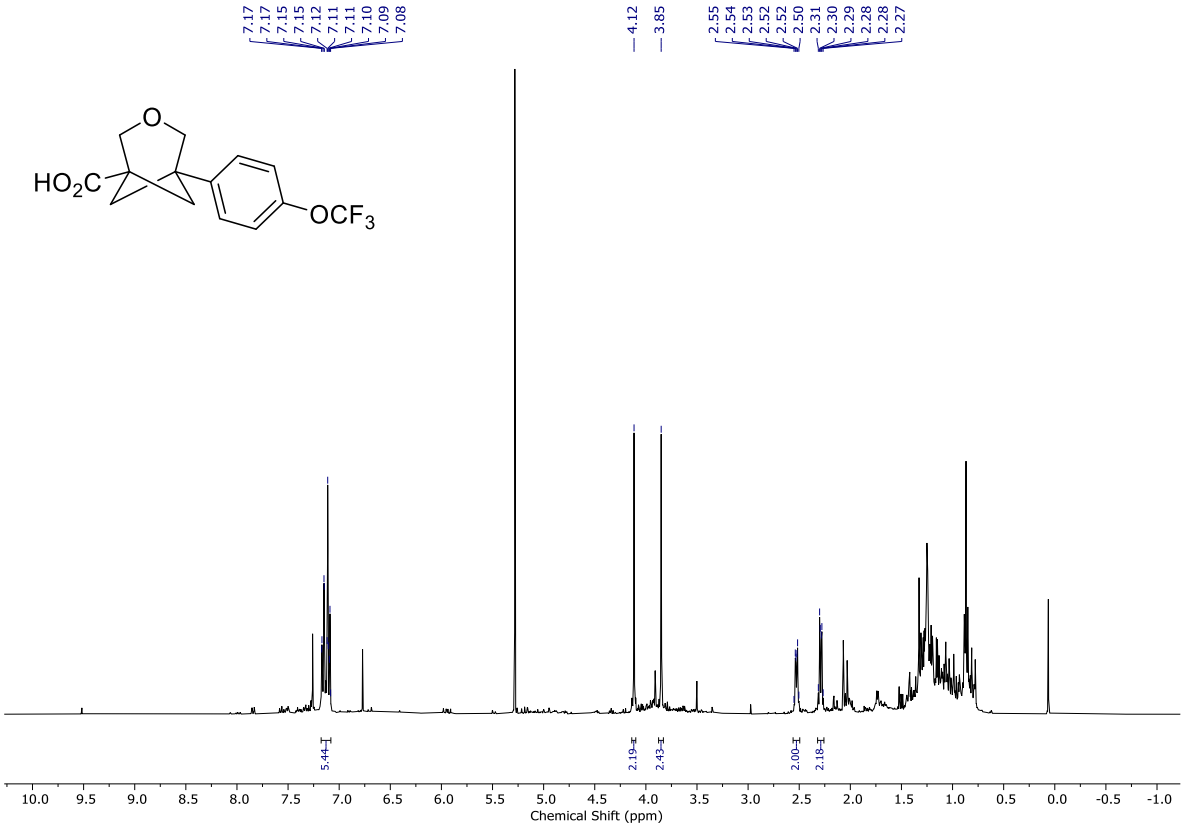


(5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (23) ^{13}C NMR (101 MHz, $CDCl_3$)

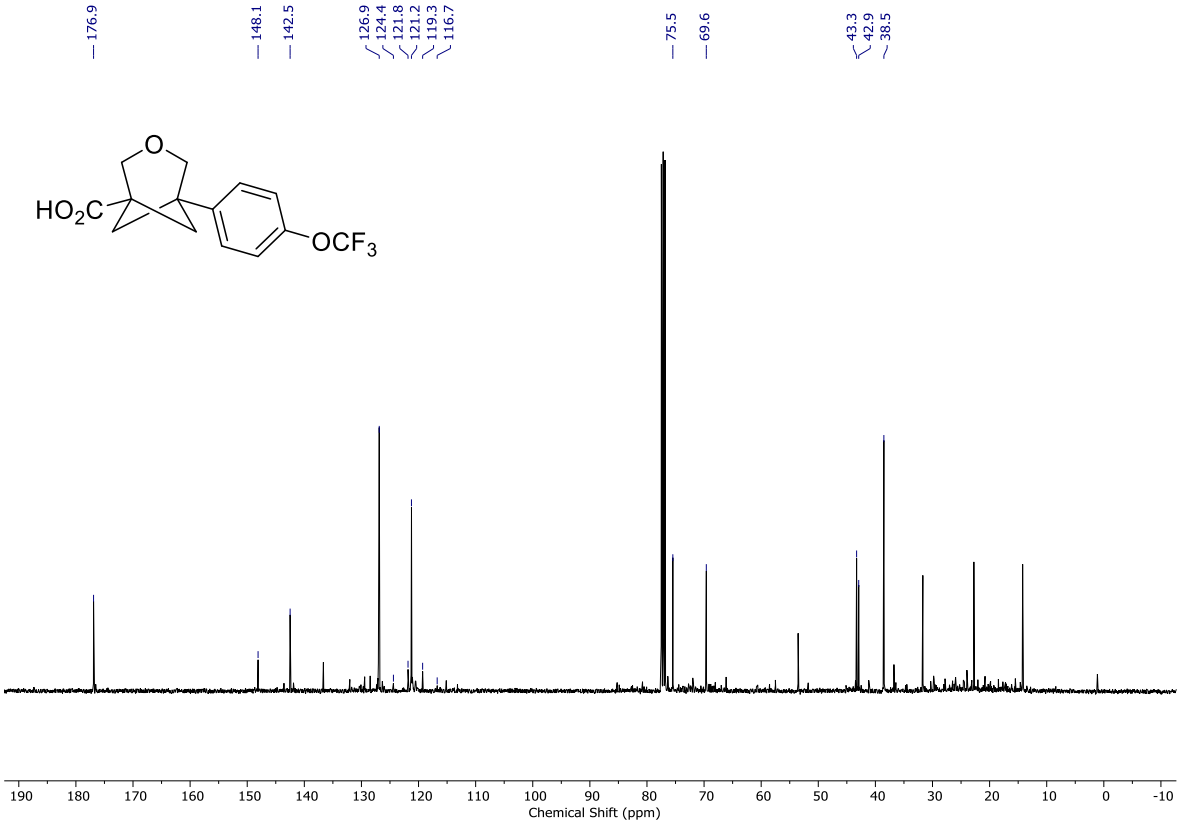


(5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (23) ^{19}F NMR (376 MHz, $CDCl_3$)

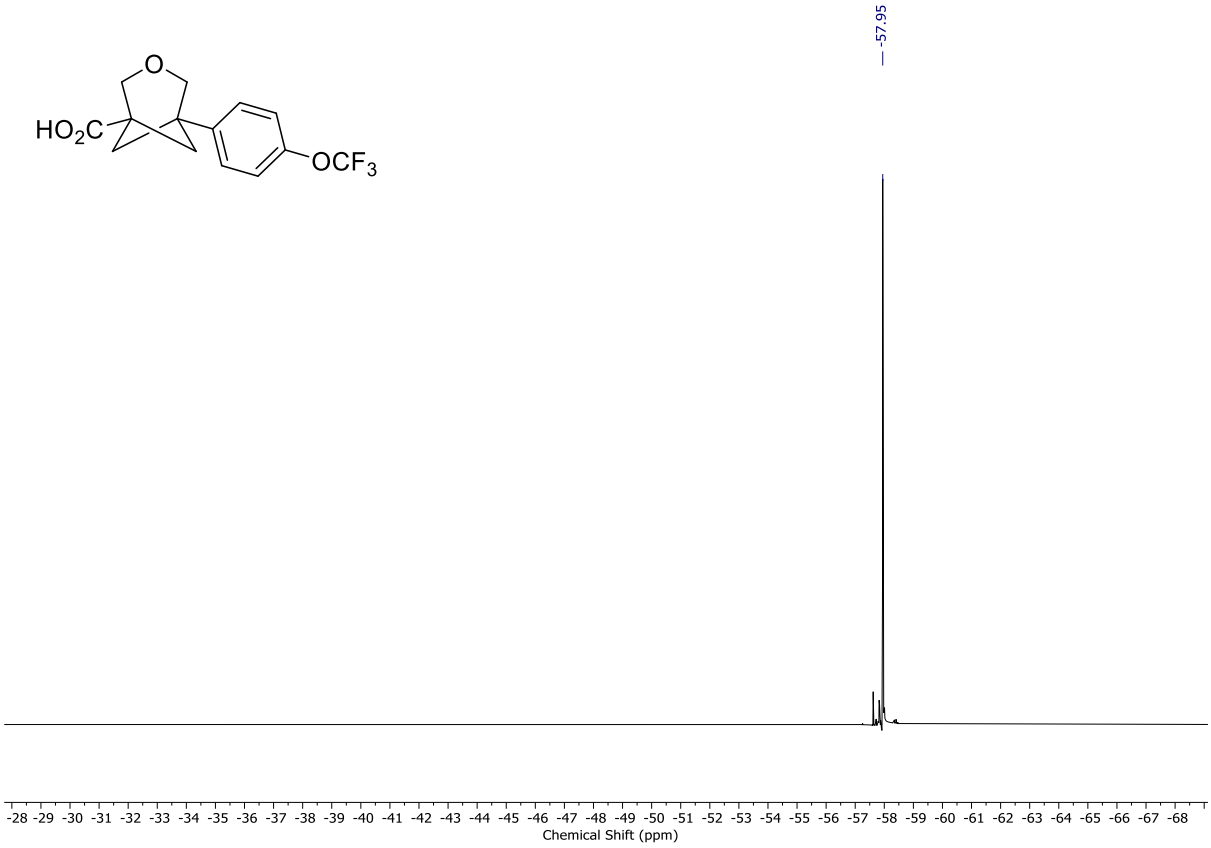
5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxylic acid (24) ^{1}H NMR (400 MHz, $CDCl_3$) (as used for next step)



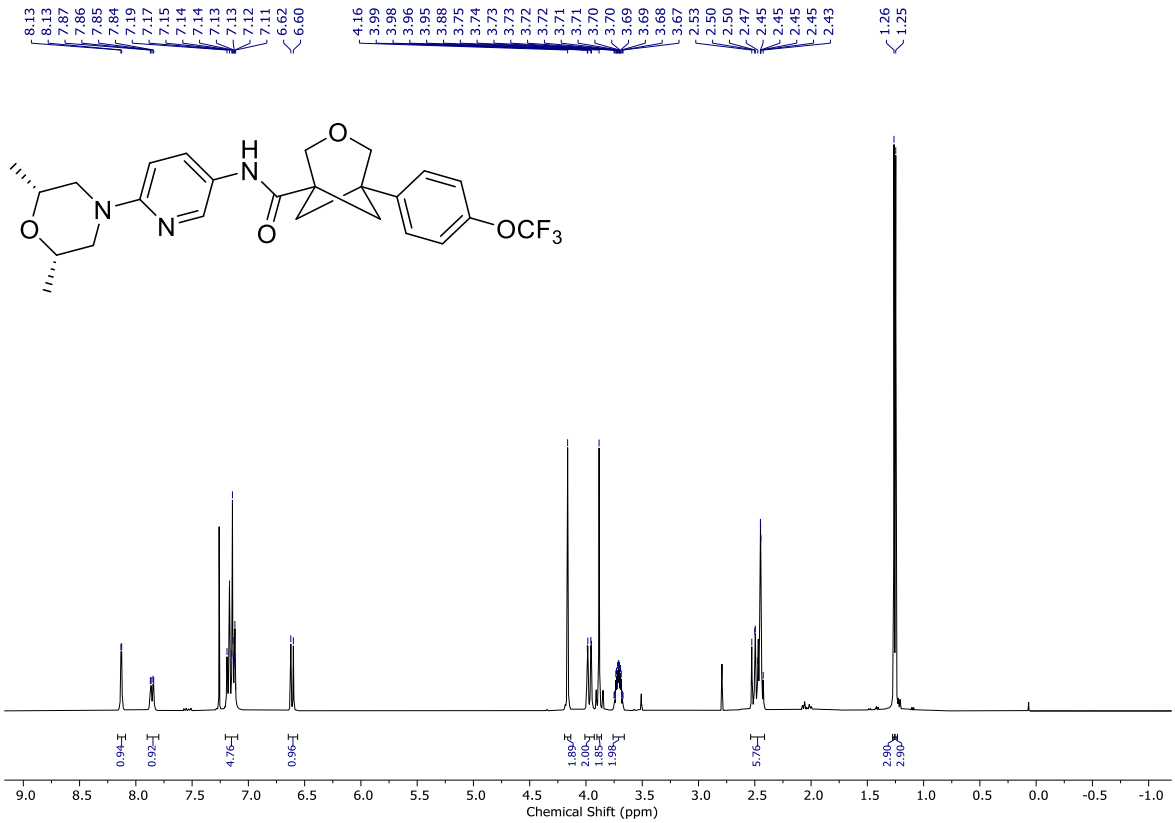
5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxylic acid (24) ^{13}C NMR (101 MHz, $CDCl_3$) (as used for next step)



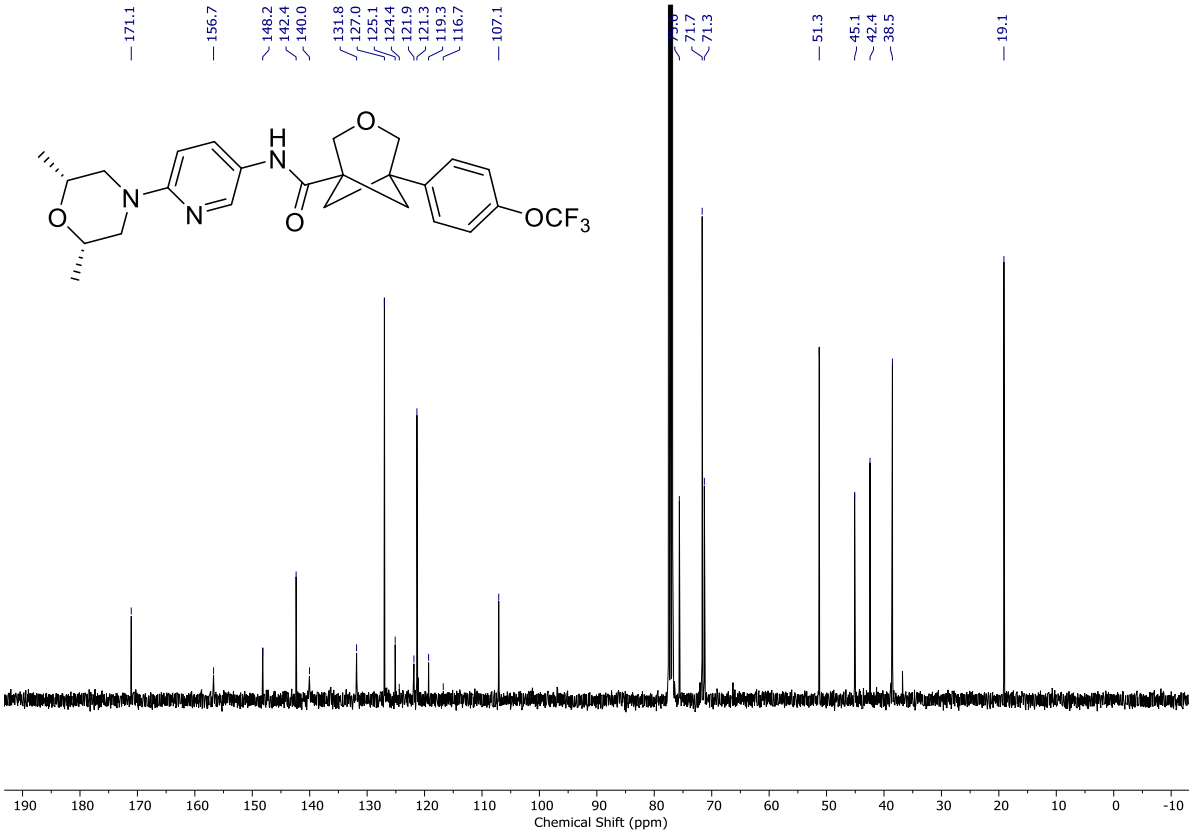
5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxylic acid (24) ^{19}F NMR (376 MHz, $CDCl_3$) (as used for next step)



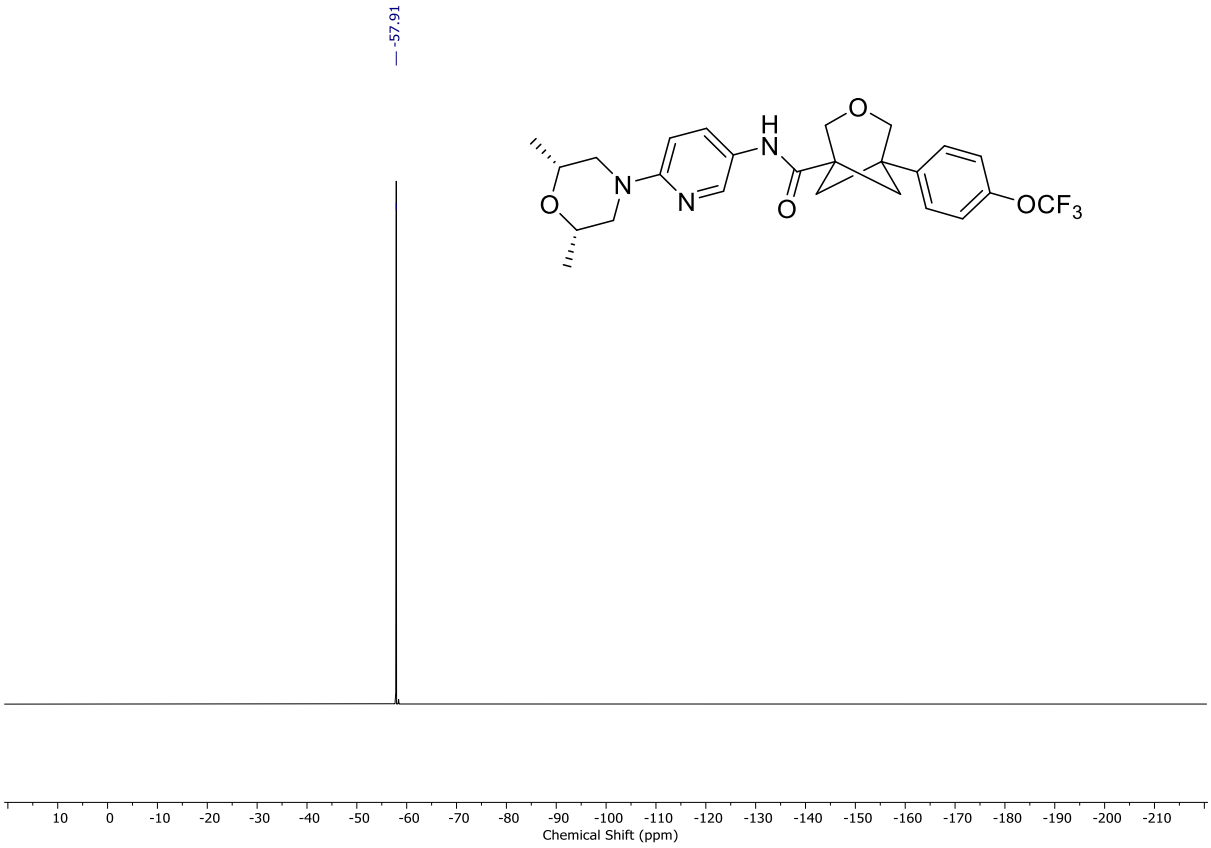
N-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxamide (22) ^{1}H NMR (400 MHz, $CDCl_3$)



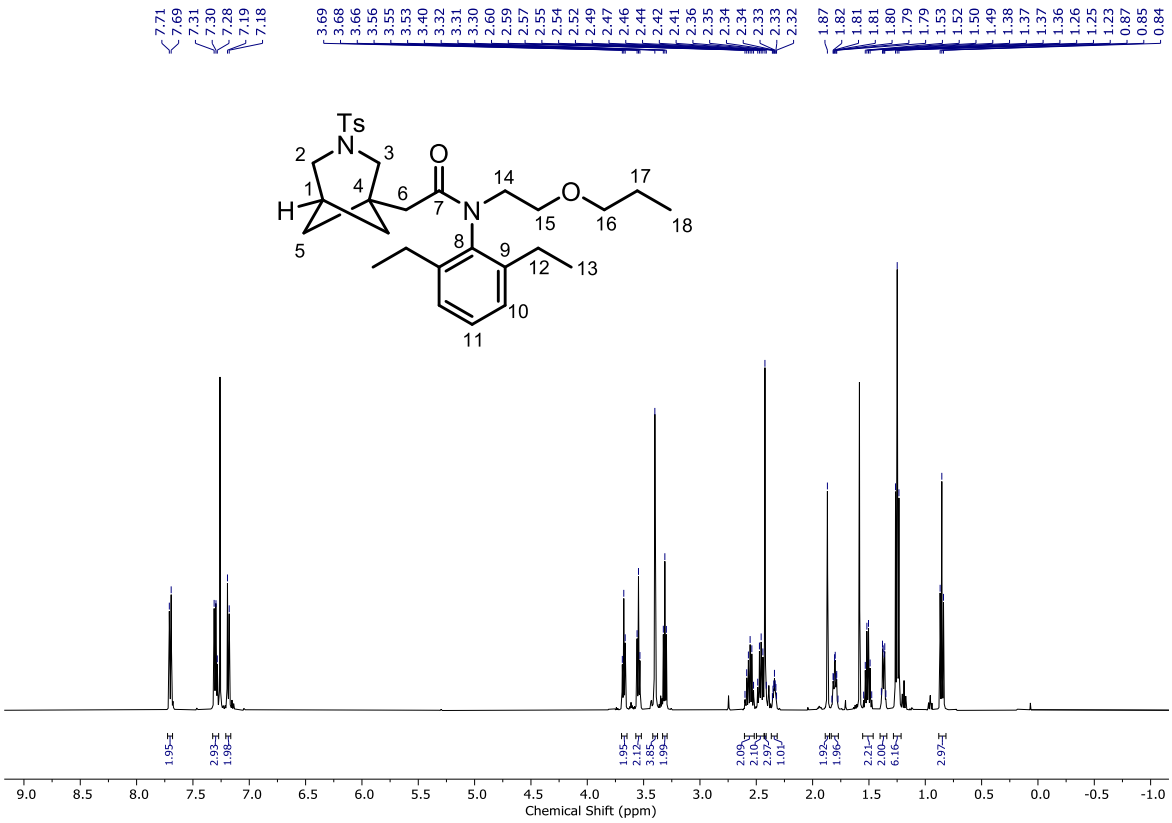
N-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxamide (22) ^{13}C NMR (101 MHz, $CDCl_3$)



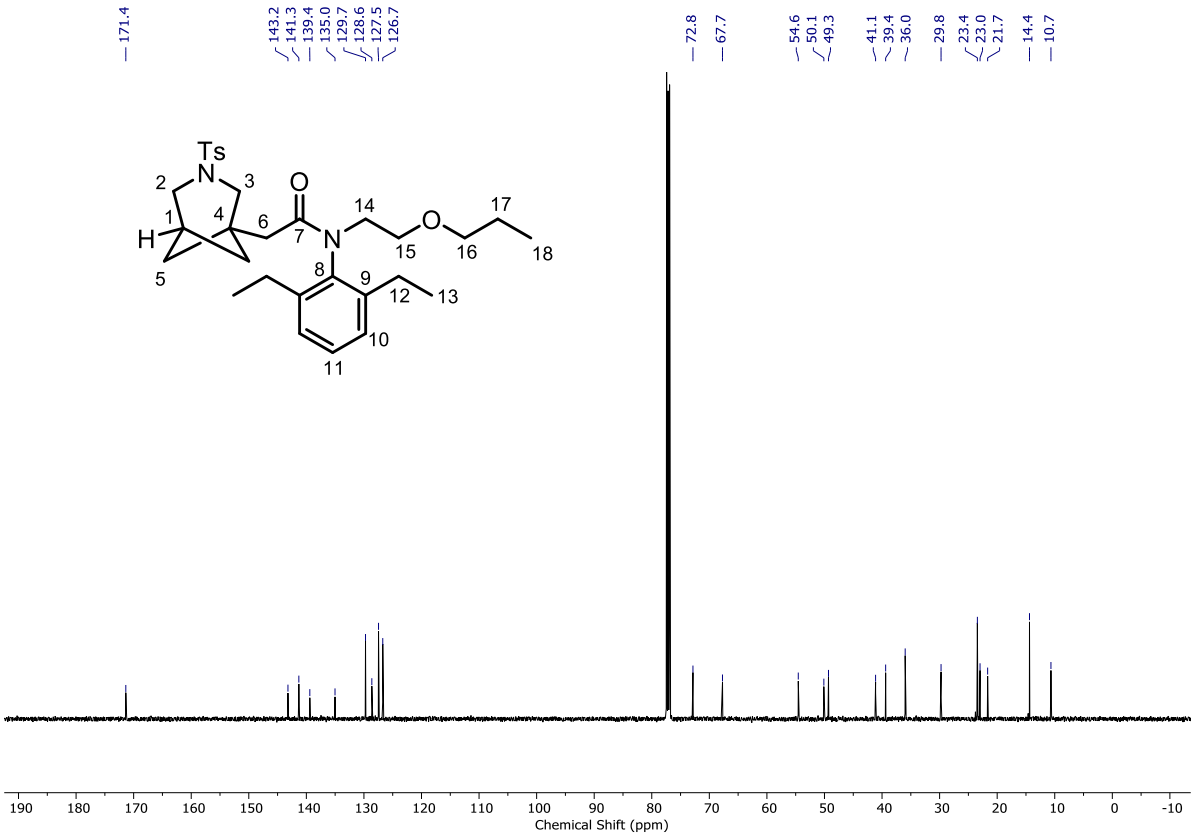
N-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxamide (22) ^{19}F NMR (376 MHz, $CDCl_3$)



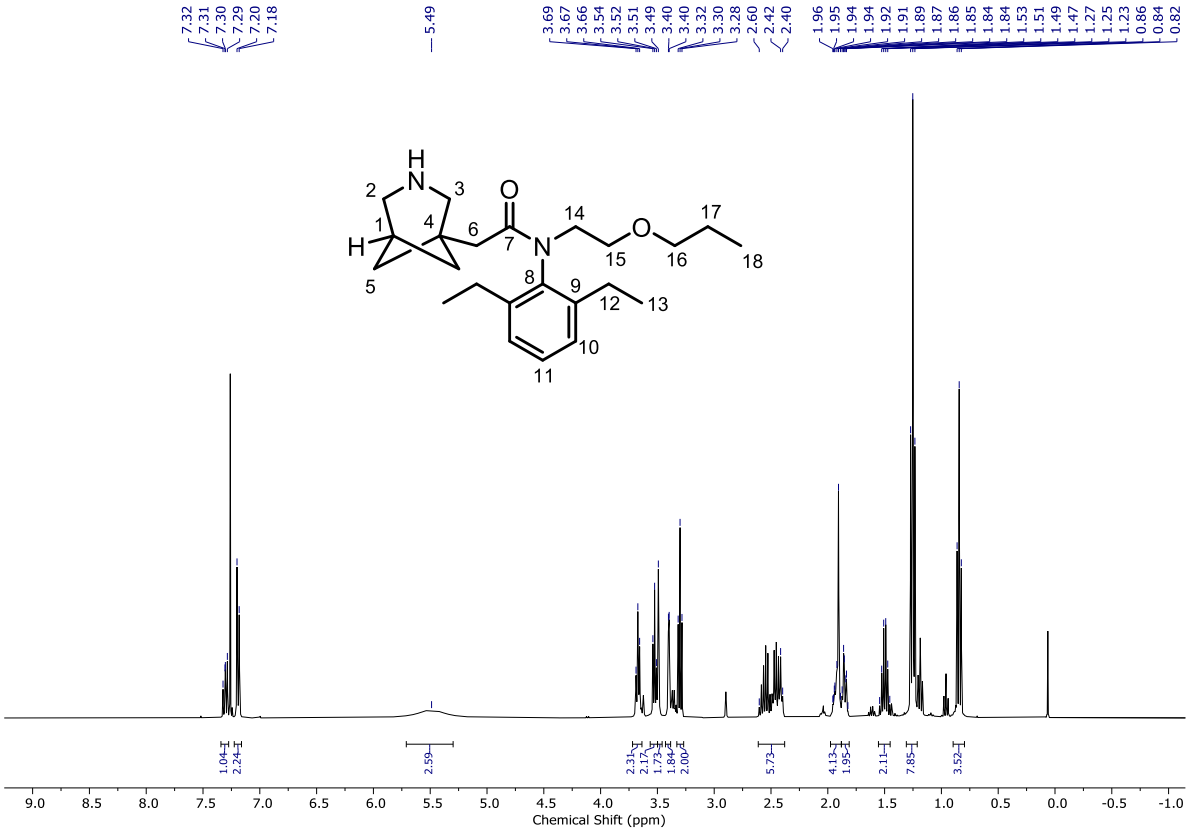
***N*-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)-2-(3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetamide (26) ^{1}H NMR (500 MHz, $CDCl_3$).**



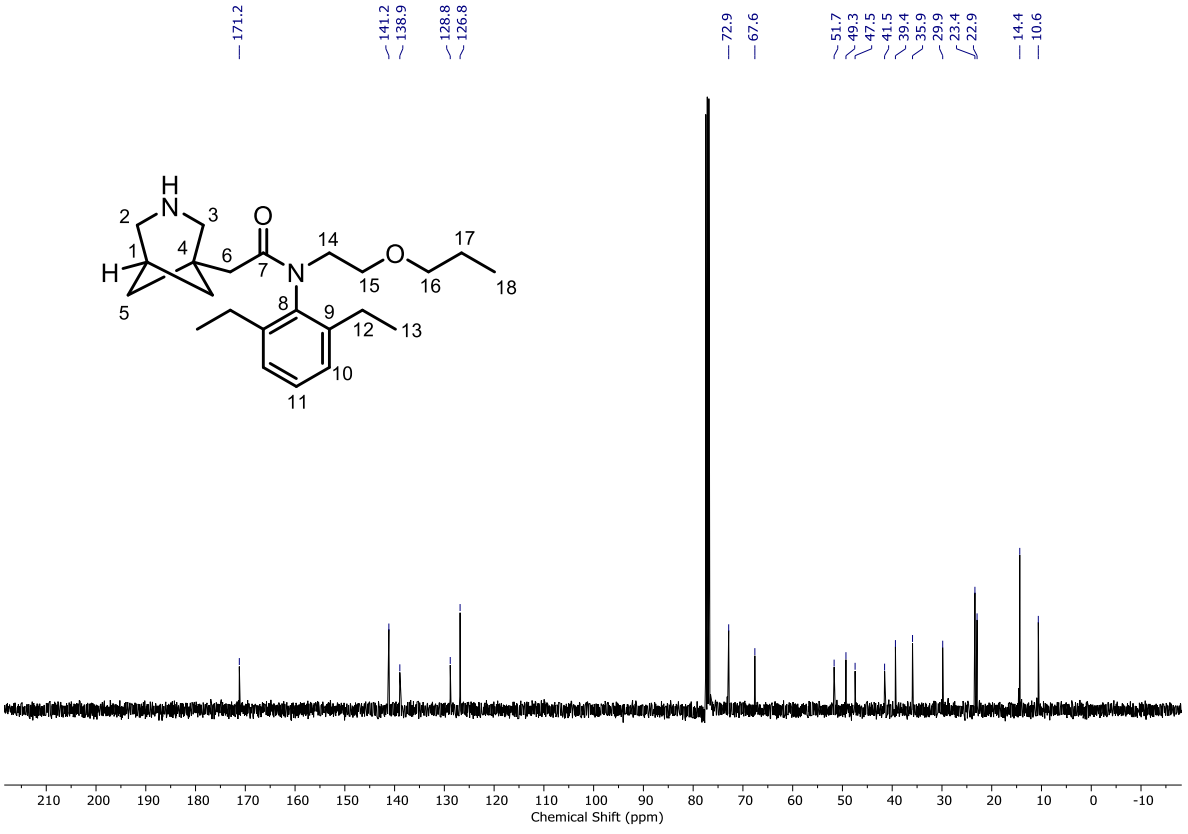
***N*-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)-2-(3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetamide (26) ^{13}C NMR (126 MHz, $CDCl_3$).**



2-(3-Azabicyclo[3.1.1]heptan-1-yl)-*N*-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)acetamide (27) ^{1}H NMR (400 MHz, $CDCl_3$).



2-(3-Azabicyclo[3.1.1]heptan-1-yl)-*N*-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)acetamide (27)
^{13}C NMR (101 MHz, $CDCl_3$).



9. References

1 Dasgupta, A. *et al.* Borane Catalyzed Selective Diazo Cross‐Coupling Towards Pyrazoles. *Adv. Synth. Catal.* **364**, 773-780 (2022).

2 Frank, N. *et al.* Synthesis of meta-substituted arene bioisosteres from [3.1.1]propellane. *Nature* **611**, 721-726 (2022).

3 Caputo, D. F. J. *et al.* Synthesis and applications of highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes. *Chem. Sci.* **9**, 5295-5300 (2018).

4 Nugent, J. *et al.* A general route to bicyclo[1.1.1]pentanes through photoredox catalysis. *ACS Catal.* **9**, 9568-9574 (2019).

5 Pickford, H. D. *et al.* Twofold radical-based synthesis of N,C-difunctionalized bicyclo[1.1.1]pentanes. *J. Am. Chem. Soc.* **143**, 9729-9736 (2021).

6 Pickford, H. D. *et al.* Rapid and Scalable Halosulfonylation of Strain-Release Reagents. *Angew. Chem. Int. Ed.* **62**, e202213508 (2023).

7 Nugent, J. *et al.* α-Amino bicycloalkylation through organophotoredox catalysis. *Chem. Sci.* **15**, 10918-10925 (2024).

8 Zhen, W., Yaohui, X., Xinxin, W. & Chen, Z. Synthesis of selenoether and thioether functionalized bicyclo 1.1.1 pentanes. *Tetrahedron* **76**, 131692 (2020).

9 Sennari, G., Hirose, T., Iwatsuki, M., Ōmura, S. & Sunazuka, T. A concise total synthesis of puberulic acid, a potent antimalarial agent. *Chem. Commun.* **50**, 8715-8718 (2014).

10 Iida, T. *et al.* Practical and Facile Access to Bicyclo[3.1.1]heptanes: Potent Bioisosteres of meta-Substituted Benzenes. *J. Am. Chem. Soc.* **144**, 21848-21852 (2022).

11 Revie, R. I., Whitaker, B. J., Paul, B., Smith, R. C. & Anderson, E. A. Synthesis of Heterocycle-Substituted Bicyclo[3.1.1]heptanes and Aza-bicyclo[3.1.1]heptanes via Photocatalytic Minisci Reaction. *Org. Lett.* **26**, 2843–2846 (2024).

12 Dibchak, D. & Mykhailiuk, P. Water-soluble Bioisosteres of meta-Benzenes. *ChemRxiv* (2025) doi: 10.26434/chemrxiv-2024-j5wcs.

13 Palatinus, L. & Chapuis, G. SUPERFLIP - a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions. *J. Appl. Cryst.* **40**, 786-790 (2007).

14 Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. CRYSTALS version 12: software for guided crystal structure analysis. *J. Appl. Cryst.* **36**, 1487 (2003).

15 Cooper, R. I., Thompson, A. L. & Watkin, D. J. CRYSTALS enhancements: dealing with hydrogen atoms in refinement. *J. Appl. Cryst.* **43**, 1100-1107 (2010).