

## Supporting Information

# Synthesis and Structural Analysis of a New Class of Azaspiro[3.3]heptanes as Building Blocks for Medicinal Chemistry

Johannes A. Burkhard,<sup>†</sup> Carine Guérot,<sup>†,‡</sup> Henner Knust,<sup>‡</sup> Mark Rogers-Evans,<sup>‡</sup>  
and Erick M. Carreira<sup>\*,†</sup>

<sup>†</sup> Laboratorium für Organische Chemie, ETH Hönggerberg, CH-8093 Zürich, Switzerland, and

<sup>‡</sup> F. Hoffmann-La Roche AG, Discovery Chemistry, CH-4070 Basel, Switzerland

### CONTENTS

General Information.....	2
Experimental Procedures .....	3
Copies of NMR Spectra of New Compounds .....	14
Crystallographic Data .....	38

## GENERAL INFORMATION

All non-aqueous reactions were carried out using oven-dried (90 °C) or heat gun dried glassware under a positive pressure of dry argon unless otherwise noted. CH<sub>2</sub>Cl<sub>2</sub>, THF, Et<sub>2</sub>O, CH<sub>3</sub>CN, and toluene were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H<sub>2</sub>O content < 30 ppm, *Karl–Fischer* titration). Triethylamine was distilled from KOH under an atmosphere of dry nitrogen. All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate, potassium permanganate, ninhydrin or Dragendorff's stain. Chromatographic purification of products (flash chromatography) was performed on Brunschwig silica 32-63, 60 Å using a forced flow of eluent at 0.3-0.5 bar. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried under high vacuum. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

**Melting points:** measured on a Büchi SMP-20 or Büchi B-540 apparatus. All melting points were measured in open capillaries and are uncorrected.

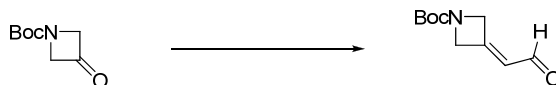
**NMR spectra:** NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for <sup>1</sup>H and <sup>13</sup>C acquisitions, respectively, or on Bruker DRX400 (or AV400) spectrometers operating at 400 MHz (<sup>1</sup>H) and 101 MHz (<sup>13</sup>C). Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) or water (δ 4.79) for <sup>1</sup>H, and chloroform (δ 77.0) for <sup>13</sup>C. All <sup>13</sup>C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal; coupling constants in Hz.

**IR spectra:** recorded on a Perkin Elmer Spectrum RX-I FT-IR (as thin film), PerkinElmer Spectrum BX FT-IR (neat) or Varian 800 FT-IR (neat) spectrometer. Absorptions are given in wavenumbers (cm<sup>-1</sup>).

**Mass spectra:** recorded by the MS service at ETH Zürich. EI-MS (*m/z*): VG-TRIBRID spectrometer. ESI-MS (*m/z*): Varian IonSpec spectrometer. MALDI-MS (*m/z*): IonSpec Ultima Fourier Transform Mass Spectrometer.

**Chemical names:** generated with ChemBioDraw Ultra 11.0 (CambridgeSoft) and modified where appropriate.

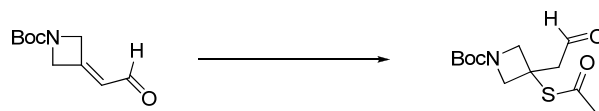
## EXPERIMENTAL PROCEDURES



**tert-Butyl 3-(2-oxoethylidene)azetidine-1-carboxylate (2).** To a solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (680 mg, 3.97 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (14.6 ml) was added at RT (formylmethylene)triphenylphosphorane (1370 mg, 4.37 mmol, 1.1 equiv), and the reaction mixture was stirred at 40 °C for 5 h, when it was concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1) to afford the pure title compound.

Yield: 735 mg (3.73 mmol, 94%). Colorless oil.

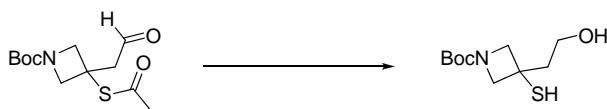
**TLC:**  $R_f$  = 0.35 (hexanes : EtOAc 2:1; UV,  $\text{KMnO}_4$ );  **$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.60 (d,  $J$ =6.4, 1H), 6.13-5.95 (m, 1H), 5.00-4.84 (m, 2H), 4.80-4.61 (m, 2H), 1.47 (s, 9H);  **$^{13}\text{C-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 188.7, 157.0, 156.0, 122.5, 80.5, 58.8 (br), 28.3; **IR** (thin film): 2978, 2932, 1697, 1391, 1367, 1155, 1119, 914, 744  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{15}\text{NNaO}_3$  ( $[\text{M}+\text{Na}]^+$ ), 220.0944; found 220.0939.



**tert-Butyl 3-(acetylthio)-3-(2-oxoethyl)azetidine-1-carboxylate (S-1).** To a solution of  $\alpha,\beta$ -unsaturated aldehyde **2** (57 mg, 0.29 mmol, 1.0 equiv) in THF (0.2 ml) was added piperidine (2  $\mu\text{l}$ , 0.02 mmol, 0.07 equiv), when the solution turned slightly yellow. Thioacetic acid (31  $\mu\text{l}$ , 0.43 mmol, 1.5 equiv) was added and the mixture was stirred at RT for 6 h. At this point, the mixture was directly purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1) to afford the title compound.

Yield: 66 mg (0.24 mmol, 84%). Colorless oil.

**TLC:**  $R_f$  = 0.32 (hexanes : EtOAc 2:1; UV, CAM);  **$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.67 (t,  $J$ =0.8, 1H), 4.06 (q,  $J$ =10.0, 4H), 3.29 (s, 2H), 2.29 (s, 3H), 1.42 (s, 9H);  **$^{13}\text{C-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 198.4, 195.3, 155.8, 80.1, 61.2 (br), 50.8, 41.4, 30.6, 28.3; **IR** (thin film): 2977, 2887, 1698, 1393, 1367, 1151, 1124, 1087, 633  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$  ( $[\text{M}+\text{NH}_4]^+$ ), 291.1373; found 291.1373.

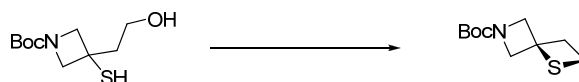


**tert-Butyl 3-(2-hydroxyethyl)-3-mercaptoazetidine-1-carboxylate (3).** To a solution of aldehyde **S-1** (73 mg, 0.25 mmol, 1.0 equiv) in  $\text{Et}_2\text{O}$  (4 ml) was added dropwise  $\text{LiAlH}_4$  (4 M in  $\text{Et}_2\text{O}$ ; 73  $\mu\text{l}$ , 0.29 mmol, 1.15 equiv), upon which the mixture immediately turned to a colorless suspension. The mixture was stirred at RT for 25 min, then it was diluted with  $\text{Et}_2\text{O}$  (10 ml) and quenched by addition of saturated aqueous  $\text{NaHCO}_3$  (10 ml). The organic phase was diluted with EtOAc (20 ml) and to the aqueous phase was added a saturated aqueous solution of Rochelle's salt (5 ml), and the phases were separated. The aqueous phase was saturated with NaCl and

extracted with EtOAc (10 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to afford the pure title compound.

Yield: 59 mg (0.25 mmol, quantitative). Colorless oil.

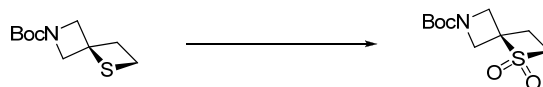
**TLC:**  $R_f$  = 0.16 (hexanes : EtOAc 1:1; KMnO<sub>4</sub>); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.08 (d,  $J$ =8.6, 2H), 3.92 (d,  $J$ =8.6, 2H), 3.86 (t,  $J$ =6.2, 2H), 2.22 (s, 1H), 2.10 (t,  $J$ =6.2, 2H), 2.11-2.01 (m, 1H), 1.43 (s, 9H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.2, 79.9, 64.9 (br), 59.7, 43.2, 40.7, 28.3; **IR** (thin film): 3416, 2977, 2880, 2543, 1685, 1478, 1416, 1367, 1255, 1155, 914, 744 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>10</sub>H<sub>20</sub>NO<sub>3</sub>S ([M+H]<sup>+</sup>), 234.1158; found 234.1155.



**tert-Butyl 1-thia-6-azaspiro[3.3]heptane-6-carboxylate (S-2).** To a solution of diethoxytriphenylphosphorane<sup>1</sup> (59 mg, 0.10 mmol, 1.2 equiv) in toluene (1 ml) was added at -30 °C a solution of the alcohol **3** (20 mg, 0.09 mmol, 1.0 equiv) in toluene (1 ml), and the mixture was stirred at -30 °C for 1 h, then it was allowed to slowly warm to RT overnight. After stirring for 13 h, the mixture was diluted with EtOAc (20 ml) and quenched with saturated aqueous NaCl (15 ml). The phases were separated and the organic phase was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 5:1).

Yield: 11 mg (0.05 mmol, 60%). Colorless oil.

**TLC:**  $R_f$  = 0.42 (hexanes : EtOAc 3:1; KMnO<sub>4</sub>); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.20-4.01 (m, 4H), 3.21-2.96 (m, 4H), 1.51-1.32 (m, 9H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.9, 79.7, 65.3 (br), 44.4, 39.7, 28.3, 19.3; **IR** (thin film): 3005, 2857, 1702, 1392, 1366, 1172, 913, 773, 744 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>10</sub>H<sub>10</sub>NO<sub>2</sub>S ([M+H]<sup>+</sup>), 216.1053; found 216.1049.



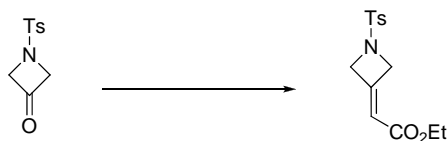
**tert-Butyl 1,1-dioxo-1-thia-6-azaspiro[3.3]heptane-6-carboxylate (4).** To a solution of thioether **S-2** (30 mg, 0.14 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was added at 0 °C *m*-CPBA (77%; 66 mg, 0.29 mmol, 2.1 equiv), and the mixture was stirred at 0 °C for 15 min, when it was allowed to warm to RT, and stirring was continued for 3.5 h. It was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and saturated aqueous NaHCO<sub>3</sub> (15 ml) was added. The phases were separated, and the organic phase was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure sulfone was obtained after FC (SiO<sub>2</sub>; hexanes : EtOAc 2:3).

Yield: 33 mg (0.13 mmol, 96%). Colorless solid.

**TLC:**  $R_f$  = 0.24 (hexanes : EtOAc 1:1; ninhydrin); **Melting Point:** 143-144 °C; **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.55 (dd,  $J$ =10.3, 1.3, 2H), 4.15-3.91 (m, 4H), 2.49-2.26 (m, 2H), 1.43 (s, 9H); **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$

(1) Prepared from PPh<sub>3</sub>, Br<sub>2</sub>, then NaOEt; slightly lower yields were obtained when a toluene solution of PPh<sub>3</sub>(OEt)<sub>2</sub>, generated from PPh<sub>3</sub> and diethyl peroxide, was used. References: (a) Robinson, P. L.; Kelly, J. W.; Evans, S. A. *Phosphorus Sulfur* **1987**, *31*, 59-70. (b) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 5210-5219.

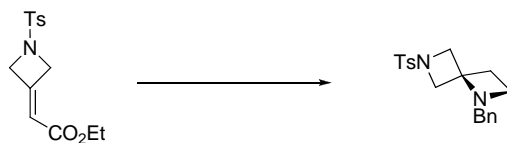
= 155.6, 80.6, 75.6, 62.5, 55.5 (br), 28.2, 19.6; **IR** (thin film): 2975, 2877, 1701, 1387, 1316, 1201, 1166, 1146, 783  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{18}\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 248.0951; found 248.0948.



**Ethyl 2-(1-tosylazetidin-3-ylidene)acetate (7).** To a solution of *N*-tosylazetidin-3-one<sup>2</sup> (9.45 g, 41.95 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (900 ml) was added at 0 °C (carbethoxymethylene)triphenylphosphorane (16.08 g, 46.16 mmol, 1.1 equiv). The mixture was allowed to warm to RT and after stirring for 15 min filtered through silica gel (hexanes : EtOAc 2:1) to give the pure title compound.

Yield: 11.42 g (38.7 mmol, 92%). Colorless crystalline solid.

**TLC:**  $R_f$  = 0.36 (hexanes : EtOAc 7:3; UV,  $\text{KMnO}_4$ ); **Melting Point:** 114-115 °C;  **$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.76 (d,  $J$ =8.2, 2H), 7.37 (d,  $J$ =8.2, 2H), 5.68 (p,  $J$ =2.4, 1H), 4.73 (dd,  $J$ =5.7, 2.4, 2H), 4.54-4.47 (m, 2H), 4.13 (q,  $J$ =7.1, 2H), 2.45 (s, 3H), 1.24 (t,  $J$ =7.1, 3H);  **$^{13}\text{C-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 164.8, 149.3, 144.5, 131.7, 129.9, 128.4, 114.6, 61.4, 60.5, 59.0, 21.6, 14.2; **IR** (neat): 2992, 2908, 1714, 1688, 1598, 1427, 1373, 1339, 1254, 1217, 1161, 1104, 1027, 918, 815, 710, 671  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{14}\text{H}_{18}\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 296.0951; found 296.0946.



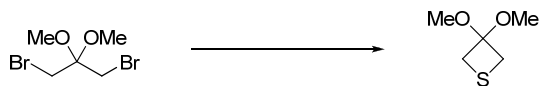
**1-Benzyl-6-tosyl-1,6-diazaspiro[3.3]heptane (16).** To a solution of ethyl 2-(1-tosylazetidin-3-ylidene)acetate (**7**) (10.5 g, 35.6 mmol, 1.0 equiv) in THF (70 ml) was added benzylamine (4.66 ml, 42.7 mmol, 1.2 equiv). The resulting mixture was heated at 60 °C under argon atmosphere for 24 h. TLC-analysis of the reaction mixture indicated some unreacted starting material, therefore was added benzylamine (0.78 ml, 7.11 mmol, 0.2 equiv), and it was heated to reflux for 24 h to assure complete conversion. Dry  $\text{Et}_2\text{O}$  (450 ml) was then added to the reaction mixture cooled to 0 °C.  $\text{LiAlH}_4$  (4 M in  $\text{Et}_2\text{O}$ ; 39.1 ml, 156 mmol, 4.4 equiv) was dropwise added, and the reaction mixture left to stir for a further 2 h. At this point the reaction was carefully quenched with  $\text{H}_2\text{O}$  (6 ml), aqueous NaOH (15%; 6 ml), and  $\text{H}_2\text{O}$  (18 ml). The formed precipitate was filtered, and the filter cake was thoroughly washed with EtOAc and  $\text{Et}_2\text{O}$ . The filtrate was concentrated *in vacuo* and filtered through silica gel ( $\text{CH}_2\text{Cl}_2$  : MeOH 96:4) to give the crude alcohol **11** (11.92 g).

To a solution of the alcohol **11** (11.92 g, 33.1 mmol, 1.0 equiv) in dry  $\text{CH}_3\text{CN}$  (550 ml) was added triphenylphosphine (13.0 g, 49.6 mmol, 1.5 equiv), carbon tetrabromide (16.45 g, 49.6 mmol, 1.5 equiv), followed by distilled triethylamine (9.3 ml, 66.1 mmol, 2.0 equiv). The mixture was stirred at RT for 60 h, and then at 80 °C for 1 h. Brine (500 ml) and  $\text{Et}_2\text{O}$  (500 ml) were added, the phases were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3  $\times$  500 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 7:3).

Yield: 7.75 g (22.6 mmol, 64% over the three steps). Colorless crystalline solid.

(2) (a) Katritzky, A. R.; Cundy, D. J.; Chen J. *J. Heterocycl. Chem.* **1994**, *34*, 271-275. (b) Axenrod, T.; Watnick, C.; Yazdekhashti, H. *J. Org. Chem.* **1995**, *60*, 1959-1964. (c) Singh, A.; Sikder, N.; Sikder, A. K. *Indian. J. Chem.* **2005**, *44B*, 2560-2563.

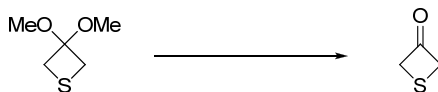
**TLC:**  $R_f$  = 0.61 (hexane : EtOAc 1:1; UV, Dragendorff's reagent); **Melting Point:** 100-101 °C;  **$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.72 (d,  $J$ =8.0, 2H), 7.35 (d,  $J$ =8.0, 2H), 7.28-7.18 (m, 3H), 7.16-7.08 (m, 2H), 3.97 (d,  $J$ =9.7, 1H), 3.80 (d,  $J$ =9.7, 1H), 3.25 (s, 1H), 3.00 (t,  $J$ =6.8, 1H), 2.42 (s, 1H), 2.21 (t,  $J$ =6.8, 1H);  **$^{13}\text{C-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 144.1, 137.4, 131.3, 129.7, 128.5, 128.4, 128.2, 127.1, 63.6, 60.0, 55.5, 49.8, 30.0, 21.6; **IR** (neat): 2936, 2833, 1598, 1496, 1449, 1339, 1161, 1089, 1044, 819, 709, 674  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 343.1475; found 343.1477.



**3,3-Dimethoxythietane (S-3).** To a solution of 1,3-dibromo-2,2-dimethoxypropane (10.2 g, 38.9 mmol, 1.0 equiv) in DMF (120 ml) was added sodium sulfide (about trihydrate; 6.68 g, *ca.* 50.6 mmol, *ca.* 1.3 equiv), and the mixture was heated to 130 °C and stirred for 24 h (shortly after heating started, the mixture turned dark-brown to black). Then it was cooled to RT and  $\text{Et}_2\text{O}$  (200 ml) was added, upon which a colorless precipitate formed, which was filtered. The filtrate was washed with  $\text{H}_2\text{O}$  (150 ml). The  $\text{Et}_2\text{O}$ -phase was washed with  $\text{H}_2\text{O}$  ( $2 \times 100$  ml), brine (50 ml), then dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo* to give product as yellowish oil (3.54 g). The  $\text{H}_2\text{O}$ /DMF phase from the first washing was extracted with  $\text{Et}_2\text{O}$  (150 ml). The organic phase was washed with  $\text{H}_2\text{O}$  ( $2 \times 80$  ml) and brine (50 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo* to give more product (0.37 g). The title compound was obtained in good purity, requiring no further purification.

Yield: 3.91 g (29.1 mmol, 75%). Slightly yellowish and low viscous oil.

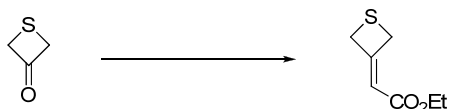
**$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.34-3.31 (m, 4H), 3.18-3.15 (m, 6H);  **$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 102.3, 48.0, 47.9, 37.1; **IR** (thin film): 2949, 2831, 1437, 1253, 1192, 1114, 1040, 964  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_5\text{H}_{10}\text{O}_2\text{S}$  ( $\text{M}^+$ ), 134.0396; found 134.0397.



**Thietan-3-one (6).** To a solution of 3,3-dimethoxythietane **S-3** (10.6 g, 79.0 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (590 ml) was added montmorillonite K10 clay (46.7 g), and the mixture was heated to 55 °C and stirred for 3 h. It was cooled to RT, and the solids were filtered. The filtrate was concentrated *in vacuo* to give the crude title compound as a light yellow solid. The pure title compound was obtained after recrystallization from pentane. *Important: The title compound sublimates readily under reduced pressure, therefore it is recommended to minimize drying under vacuum.*

Yield: 5.15 g (58.5 mmol, 74%). Slightly yellowish crystals.

**Melting Point:** 63-64 °C;  **$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.30 (s, 4H);  **$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 194.7, 55.2; **IR** (thin film): 1761, 1220, 773  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_3\text{H}_4\text{OS}$  ( $\text{M}^+$ ), 87.9978; found 87.9977.

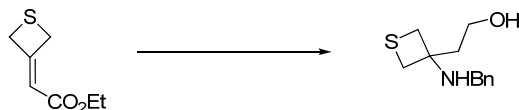


**Ethyl 2-(thietan-3-ylidene)acetate (8).** To a solution of thietan-3-one (**6**) (1.00 g, 11.35 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (50 ml) was added at RT in portions (carboxymethylene)triphenylphosphorane (4.35 g, 12.48 mmol),

and the mixture was stirred at RT for 21.5 h, when it was concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 8:1) to afford the pure title compound.

Yield: 1.71 g (10.81 mmol, 95%). Colorless oil.

**TLC:**  $R_f$  = 0.60 (hexanes : EtOAc 3:1; UV, CAM); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.48 (quint,  $J$ =2.5, 1H), 4.35 (dd,  $J$ =5.6, 2.5, 2H), 4.14 (quart,  $J$ =7.1, 2H), 4.03-3.94 (m, 2H), 1.26 (t,  $J$ =7.1, 3H); **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 165.3, 159.0, 114.7, 60.0, 37.9, 35.4, 14.2; **IR** (thin film): 2984, 2925, 1713, 1669, 1337, 1216, 1162, 1108, 1036, 773 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>7</sub>H<sub>10</sub>O<sub>2</sub>S (M<sup>+</sup>), 158.0396; found 158.0398.

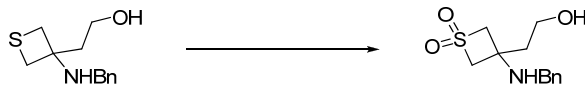


**2-(3-(Benzylamino)thietan-3-yl)ethanol (12).** Ethyl 2-(thietan-3-ylidene)acetate **8** (438 mg, 2.77 mmol, 1.0 equiv) and benzylamine (317  $\mu$ l, 2.91 mmol, 1.05 equiv) were mixed, and the oil was stirred at RT for 2 d. <sup>1</sup>H-NMR analysis of an aliquot of the reaction mixture showed incomplete conversion, therefore the oil was dissolved in THF (2 ml) and the solution was heated to 60 °C for 1 d. This mixture was directly purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 7:1) to afford pure ethyl 2-(3-(benzylamino)thietan-3-yl)acetate (524 mg, 1.98 mmol; 71% yield), which was directly used for the next step.

To a solution of ethyl 2-(3-(benzylamino)thietan-3-yl)acetate (524 mg, 1.98 mmol, 1.0 equiv) in Et<sub>2</sub>O (25 ml), cooled to 0 °C, was added LiAlH<sub>4</sub> (4 M in Et<sub>2</sub>O; 1.98 ml, 7.90 mmol), and the reaction mixture was stirred at 0 °C for 15 min. At this point, the reaction was quenched by careful addition of H<sub>2</sub>O (0.5 ml), aqueous NaOH (15%; 0.5 ml), and H<sub>2</sub>O (1.5 ml). The resulting colorless suspension was thoroughly stirred at RT for 10 min, when the solids were filtered off and the filter cake was thoroughly washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo* to yield the pure title compound.

Yield: 400 mg (1.79 mmol, 91%; 67% over the 2 steps). Colorless oil.

**TLC:**  $R_f$  = 0.18 (hexanes : EtOAc 1:1; UV, CAM); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.47-7.15 (m, 5H), 3.95-3.83 (m, 2H), 3.80 (s, 2H), 3.33 (d,  $J$ =10.2, 2H), 3.10 (d,  $J$ =10.2, 2H), 2.27-2.10 (m, 2H); **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 138.7, 128.5, 128.0, 127.2, 64.3, 58.8, 45.9, 37.1, 36.5; **IR** (thin film): 3290, 2399, 2849, 1453, 1175, 1088, 1055, 913, 744 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>18</sub>NOS ([M+H]<sup>+</sup>), 224.1104; found 224.1099.

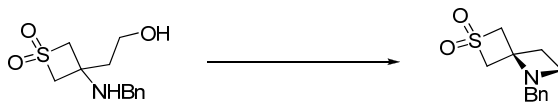


**2-(3-(Benzylamino)(S,S-dioxo-thietan)-3-yl)ethanol (S-4).** To a solution of thioether **12** (32 mg, 0.14 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 ml), cooled to 0 °C, was added titanium(IV)isopropoxide (42  $\mu$ l, 0.14 mmol, 1.0 equiv) followed by hydrogen peroxide (30%; 58  $\mu$ l, 0.56 mmol, 4 equiv), and the solution was stirred at 0 °C for 15 min. The ice-bath was removed and stirring was continued at RT for 1 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and quenched by addition of H<sub>2</sub>O (10 ml). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and H<sub>2</sub>O (10 ml), the phases were separated, and the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to afford a colorless oil, which represented almost pure title compound that can be used for further transformations without purification.

Yield: 34 mg (0.13 mmol, 94%). Colorless oil.

An analytically pure sample can be obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:2 → 0:1 gradient).

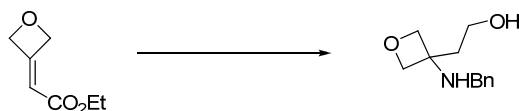
**TLC:**  $R_f$  = 0.23 (hexanes : EtOAc 1:2; UV, ninhydrin); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.46-7.23 (m, 5H), 4.08 (s, 4H), 3.85 (t,  $J$ =5.5, 2H), 3.74 (s, 2H), 2.16 (t,  $J$ =5.5, 2H); **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 137.7, 128.7, 128.1, 127.7, 72.9, 59.7, 48.2, 47.9, 37.7; **IR** (thin film): 3528, 3322, 3028, 2949, 2876, 1454, 1392, 1311, 1202, 1106, 1074, 742 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>18</sub>NO<sub>3</sub>S ([M+H]<sup>+</sup>), 256.1002; found 256.1002.



**1-Benzyl-6,6-dioxo-6-thia-1-azaspiro[3.3]heptane (17).** To a solution of alcohol **S-4** (63 mg, 0.25 mmol, 1.0 equiv) in CH<sub>3</sub>CN (5 ml) was added triphenylphosphine (97 mg, 0.37 mmol, 1.5 equiv) and carbon tetrabromide (123 mg, 0.37 mmol, 1.5 equiv), and the mixture was stirred at RT for 1.5 h. H<sub>2</sub>O (1 ml) was added followed by potassium carbonate (68 mg, 0.49 mmol, 2.0 equiv), and the colorless mixture was heated to 60 °C and stirred for 18 h. The mixture was cooled to RT and concentrated to 1/4 of the initial volume. The residue was partitioned between EtOAc (20 ml) and saturated aqueous NaHCO<sub>3</sub> (10 ml), and the phases were separated. The organic phase was washed with saturated aqueous NaHCO<sub>3</sub> (5 ml), then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2).

Yield: 44 mg (0.19 mmol, 75%). Colorless crystalline solid.

**TLC:**  $R_f$  = 0.16 (hexanes : EtOAc 2:1; UV, ninhydrin); **Melting Point:** 86-88 °C; **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.43-7.19 (m, 5H), 4.53-4.32 (m, 2H), 4.21-3.99 (m, 2H), 3.68 (s, 2H), 3.16 (t,  $J$ =6.8, 2H), 2.47 (t,  $J$ =6.8, 2H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 136.3, 128.4, 128.3, 127.4, 71.8, 55.8, 55.5, 50.1, 32.0; **IR** (thin film): 2950, 2833, 1389, 1316, 1219, 1189, 1086, 772 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>16</sub>NO<sub>2</sub>S ([M+H]<sup>+</sup>), 238.0896; found 238.0895.



**2-(3-(Benzylamino)oxetan-3-yl)ethanol (13).** To ethyl 2-(oxetan-3-ylidene)acetate<sup>3</sup> (1.47 g, 10.3 mmol, 1.0 equiv) was added benzylamine (1.19 ml, 10.9 mmol, 1.05 equiv), and the now slightly yellowish liquid was stirred at RT for 20 h, then it was heated to 40 °C for 30 min to assure complete conversion. The oil was now dissolved in Et<sub>2</sub>O (80 ml) and the mixture was cooled to 0 °C. LiAlH<sub>4</sub> (4 M in Et<sub>2</sub>O; 10.34 ml, 41.4 mmol, 4.0 equiv) was dropwise added, when after 4/5 of the addition a yellowish precipitate formed. The addition was completed, THF (20 ml) was added to redissolve the precipitate. The slightly yellowish suspension was further stirred at 0 °C for 30 min. At this point the reaction was carefully quenched with H<sub>2</sub>O (1.57 ml), aqueous NaOH (15%; 1.57 ml), and H<sub>2</sub>O (3 × 1.57 ml). The resulting mixture was thoroughly stirred at RT for 10 min, when the precipitate was filtered, and the filter cake was thoroughly washed with EtOAc and Et<sub>2</sub>O. The filtrate was concentrated *in vacuo*. The title compound was obtained after purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5).

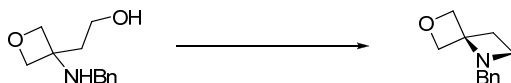
Yield: 1.60 g (7.72 mmol, 75%). Colorless oil.

**TLC:**  $R_f$  = 0.14 (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 96:5; UV, CAM); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48-7.11 (m, 5H), 4.55 (d,  $J$ =6.8, 2H), 4.48 (d,  $J$ =6.8, 2H), 3.89-3.70 (m, 2H), 3.79 (s, 2H), 3.21 (br s, 2H), 2.23-2.03 (m, 2H); **<sup>13</sup>C-**

(3) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736-7739.



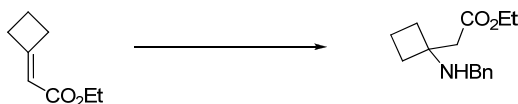
**NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 138.8, 128.5, 128.0, 127.3, 81.2, 60.9, 59.3, 47.1, 35.2; **IR** (thin film): 3396, 3305, 2941, 2870, 1454, 1052, 974, 913, 744, 701 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>18</sub>NO<sub>2</sub> ([M+H]<sup>+</sup>), 208.1332; found 208.1332.



**1-Benzyl-6-oxa-1-azaspiro[3.3]heptane (18).** To a solution of alcohol **13** (116 mg, 0.560 mmol, 1.0 equiv) in CH<sub>3</sub>CN (6 ml) was added at RT triphenylphosphine (220 mg, 0.839 mmol, 1.5 equiv) followed by carbon tetrabromide (278 mg, 0.839 mmol, 1.5 equiv), and the colorless solution was stirred at RT for 2 h. H<sub>2</sub>O (1.2 ml) was added followed by potassium carbonate (155 mg, 1.12 mmol, 2.0 equiv). The solution was heated to 60 °C and stirred for 3.75 h, when it was concentrated to 1/4 of the initial volume. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and saturated aqueous NaHCO<sub>3</sub> (10 ml). The phases were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 8 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The crude material was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2) to give the pure title compound.

Yield: 87 mg (0.46 mmol, 82%). Colorless oil.

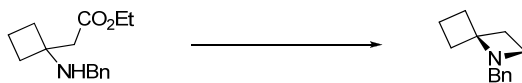
**TLC:**  $R_f$  = 0.19 (hexanes : EtOAc 2:1; UV, ninhydrin); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.44-7.16 (m, 5H), 5.00 (dd,  $J$ =7.5, 0.7, 2H), 4.64 (dd,  $J$ =7.5, 0.7, 2H), 3.82 (s, 2H), 3.06 (t,  $J$ =6.8, 2H), 2.38 (t,  $J$ =6.8, 2H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 137.9, 128.5, 128.4, 127.1, 81.4, 69.2, 56.3, 49.8, 29.4; **IR** (thin film): 2944, 2861, 1495, 1453, 1362, 1215, 1120, 974, 913, 746, 696 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>16</sub>NO ([M+H]<sup>+</sup>), 190.1226; found 190.1227.



**Ethyl 2-(1-(benzylamino)cyclobutyl)acetate (S-5).** A mixture of ethyl 2-cyclobutylideneacetate<sup>4</sup> (162 mg, 1.16 mmol) and benzylamine (253  $\mu$ l, 2.32 mmol) was heated to 60 °C and stirred for 2 d. At this point the oil was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to give the pure title compound.

Yield: 203 mg (0.82 mmol, 71%). Colorless oil.

**TLC:**  $R_f$  = 0.17 (hexanes : EtOAc 5:1; UV, ninhydrin); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48-7.10 (m, 5H), 4.15 (q,  $J$ =7.1, 2H), 3.70 (s, 2H), 2.72 (s, 2H), 2.20-1.67 (m, 7H), 1.26 (t,  $J$ =7.1, 3H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.8, 141.0, 128.3, 128.2, 126.7, 60.1, 58.7, 46.8, 41.5, 32.4, 14.3, 13.8; **IR** (thin film): 3028, 2981, 2936, 1729, 1454, 1368, 1245, 1193, 1114, 1029, 699 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>15</sub>H<sub>22</sub>NO<sub>2</sub> ([M+H]<sup>+</sup>), 248.1645; found 248.1643.



**1-Benzyl-1-azaspiro[3.3]heptane (19).** To a solution of ethyl ester **S-5** (173 mg, 0.70 mmol, 1.0 equiv) in Et<sub>2</sub>O (8 ml), cooled to 0 °C, was added LiAlH<sub>4</sub> (4 M in Et<sub>2</sub>O; 0.70 ml, 2.80 mmol, 4.0 equiv), and the reaction mixture

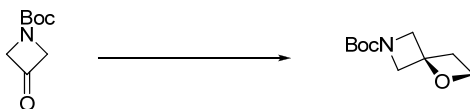
(4) Afzal, M.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 937-945.

was stirred at 0 °C for 15 min. The reaction was quenched by addition of H<sub>2</sub>O (0.11 ml), aqueous NaOH (15%; 0.11 ml), and H<sub>2</sub>O (0.33 ml). The resulting colorless suspension was thoroughly stirred at RT for 15 min, when the solids were filtered off and the filter cake was thoroughly washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo* to give the pure alcohol **14** (140 mg, 0.68 mmol; 97%), which was directly used for next step without purification.

To a solution of the alcohol **14** (140 mg, 0.68 mmol, 1.0 equiv) in CH<sub>3</sub>CN (10 ml) was added triphenylphosphine (268 mg, 1.02 mmol, 1.5 equiv) and carbon tetrabromide (339 mg, 1.02 mmol, 1.5 equiv), and the mixture was stirred at RT for 1.5 h. H<sub>2</sub>O (2 ml) was added followed by potassium carbonate (188 mg, 1.36 mmol, 2.0 equiv), and the colorless mixture was heated to 60 °C and stirred for 16.5 h. The reaction mixture was cooled to RT and concentrated to 1/4 of the initial volume. The residue was partitioned between EtOAc (20 ml) and aqueous HCl (1 M; 20 ml) and the phases were separated. To the aqueous phase was added EtOAc (30 ml) and the aqueous layer was basified with aqueous KOH (6 M) until the pH was basic. The phases were separated, and the aqueous layer was extracted with EtOAc (10 ml). The combined organic phases from the basic extraction were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5).

Yield: 95 mg (0.51 mmol, 74%; 72% over the two steps). Colorless oil.

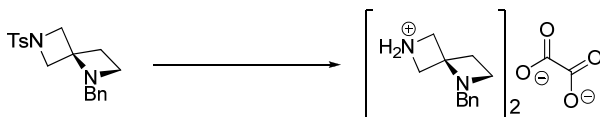
**TLC:**  $R_f = 0.09$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5; UV, ninhydrin); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.48$ -7.11 (m, 5H), 3.65 (s, 2H), 3.12 (t,  $J=6.9$ , 2H), 2.43-2.21 (m, 2H), 2.22 (t,  $J=6.9$ , 2H), 2.09-1.85 (m, 2H), 1.77-1.49 (m, 2H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 138.0$ , 128.8, 128.3, 126.9, 69.6, 56.1, 49.6, 32.4, 31.5, 13.4; **IR** (thin film): 3027, 2977, 2955, 2823, 1454, 1360, 1273, 1114, 725, 697 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>13</sub>H<sub>18</sub>N ([M+H]<sup>+</sup>), 188.1434; found 188.1435.



***tert*-Butyl 1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (20).** To a suspension of trimethylsulfoxonium iodide (0.643 g, 2.92 mmol, 2.5 equiv) in dry *tert*-BuOH (12 ml) was added at 50 °C potassium *tert*-butoxide (0.328 g, 2.92 mmol, 2.5 equiv), upon which the mixture turned to a cloudy suspension. The mixture was stirred at that temperature for 1.5 h, then was added *tert*-butyl 3-oxoazetidine-1-carboxylate (0.200 g, 1.17 mmol, 1.0 equiv). The suspension was stirred at 50 °C for 48 h. It was cooled to RT and the mixture was partitioned between saturated aqueous NH<sub>4</sub>Cl (30 ml) and EtOAc (50 ml). The phases were separated and the aqueous phase was extracted with EtOAc (50 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 2:1 → 0:1 gradient).

Yield: 95 mg (0.48 mmol, 41%). Colorless oil.

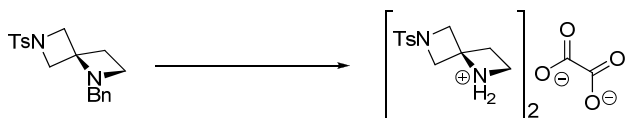
**TLC:**  $R_f = 0.23$  (hexanes : EtOAc 2:1; ninhydrin);  **$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.49$  (t,  $J=7.5$ , 2H), 4.07 (q,  $J=10.9$ , 4H), 2.80 (t,  $J=7.5$ , 2H), 1.40 (s, 9H);  **$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 156.0$ , 82.5, 79.5, 66.2, 63.8 (br), 31.7, 28.2; **IR** (thin film): 2976, 2893, 1705, 1400, 1366, 1171, 1095, 978, 772  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_6\text{H}_9\text{NO}_3$  ( $[\text{M}-\text{C}_4\text{H}_8]^+$ ), 143.0577; found 143.0578.



**1-(Benzyl-1-aza-6-azoniaspiro[3.3]heptane) oxalate (22).** In a 250 ml flask equipped with a condenser, Mg powder (2.84 g, 117 mmol, 10 equiv) was added to a solution of 1-benzyl-6-tosyl-1,6-diazaspiro[3.3]heptane (**16**) (4.0 g, 11.7 mmol, 1.0 equiv) in MeOH (70 ml). After about 30 min, the reaction mixture started to boil violently, and therefore it was cooled down with an ice bath. The crude mixture was concentrated under reduced pressure to afford a gray suspension. This was suspended in Et<sub>2</sub>O (280 ml) and Na<sub>2</sub>SO<sub>4</sub>·10 H<sub>2</sub>O (*ca.* 36 g) was added. The suspension was vigorously stirred at room temperature for 1 h, then filtered, the filtrate dried (Na<sub>2</sub>SO<sub>4</sub>), and filtered. To the filtrate was added under stirring a solution of anhydrous oxalic acid (0.526 g, 5.84 mmol, 0.5 equiv) in EtOH (1.2 ml), upon which immediately a precipitate formed. The solid was filtered and dried under reduced pressure to give the pure title compound.

Yield: 1.98 g (4.24 mmol, 73%). Colorless solid.

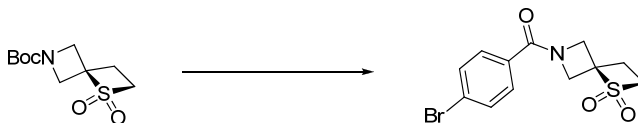
**TLC:**  $R_f$  = 0.00 (EtOAc; UV, Dragendorff's reagent); **Melting Point:** 179-181 °C; **<sup>1</sup>H-NMR** (400 MHz, D<sub>2</sub>O):  $\delta$  = 7.60-7.35 (m, 5H), 4.60 (dd,  $J$ =11.1, 2.1, 2H), 4.25-4.18 (m, 2H), 3.99 (s, 2H), 3.31 (t,  $J$ =7.3, 2H), 2.56 (t,  $J$ =7.3, 2H); **<sup>13</sup>C-NMR** (101 MHz, D<sub>2</sub>O):  $\delta$  = 173.0, 134.6, 129.4, 129.0, 128.3, 66.3, 55.3, 54.6, 48.9, 28.6; **IR** (neat): 2920, 2834, 2660, 1582, 1438, 1333, 1219, 1137, 760, 710 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>17</sub>N<sub>2</sub> ([M+H]<sup>+</sup>), 189.1386; found 189.1377.



**6-(Tosyl-6-aza-1-azoniaspiro[3.3]heptane) oxalate (23).** 1-Benzyl-6-tosyl-1,6-diazaspiro[3.3]heptane **16** (3.0 g, 8.76 mmol, 1.0 equiv) was dissolved in methanol (45 ml), and palladium (10% on carbon; 886 mg, 0.832 mmol, 0.095 equiv) was added. A hydrogen atmosphere (balloon) was built up, and the mixture was stirred at RT for 16 h. The crude suspension was filtered over celite and the filter cake thoroughly washed with MeOH. The filtrate was concentrated and then Et<sub>2</sub>O (200 ml) was added. To this solution under stirring was added a solution of anhydrous oxalic acid (0.394 g, 4.38 mmol, 0.5 equiv) in EtOH (0.9 ml), upon which immediately a precipitate formed. The solid was filtered and dried under reduced pressure to give the pure title compound.

Yield: 2.29 g (3.85 mmol, 88%). Colorless solid.

**TLC:**  $R_f$  = 0.00 (EtOAc; UV, Dragendorff's reagent); **Melting Point:** 195-196 °C; **<sup>1</sup>H-NMR** (400 MHz, D<sub>2</sub>O):  $\delta$  = 7.83 (d,  $J$ =7.8, 2H), 7.60 (d,  $J$ =7.8, 2H), 4.37 (d,  $J$ =10.7, 2H), 4.12 (d,  $J$ =10.7, 2H), 3.89 (t,  $J$ =8.5, 2H), 2.54 (t,  $J$ =8.5, 2H), 2.50 (s, 3H); **<sup>13</sup>C-NMR** (101 MHz, D<sub>2</sub>O):  $\delta$  = 146.8, 130.48, 128.48, 128.18, 62.1, 60.2, 41.7, 28.4, 20.8; **IR** (neat): 2909, 2656, 1576, 1341, 1288, 1158, 1092, 1030, 813, 762, 682 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>17</sub>N<sub>2</sub> O<sub>2</sub>S ([M+H]<sup>+</sup>), 253.1005; found 253.0996.

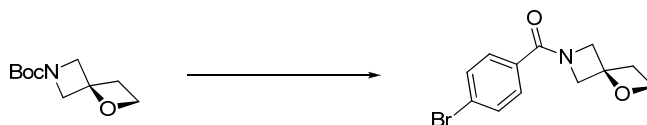


**(4-Bromophenyl)(1,1-dioxo-1-thia-6-azaspiro[3.3]heptan-6-yl)methanone (24).** To a solution of *tert*-butyl carbamate **4** (20 mg, 0.08 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was added at RT trifluoroacetic acid (0.2 ml), and the colorless solution was stirred at RT for 20 min. The volatiles were removed *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 ml), triethylamine (23  $\mu$ l, 0.16 mmol, 2.0 equiv) was added followed by 4-bromobenzoyl

chloride (20 mg, 0.09 mmol, 1.1 equiv), and the mixture was stirred at RT for 3 h. The mixture was directly purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:3 → 0:1 gradient) to give the pure title compound.

Yield: 26.5 mg (0.080 mmol, 99%). Colorless crystalline solid.

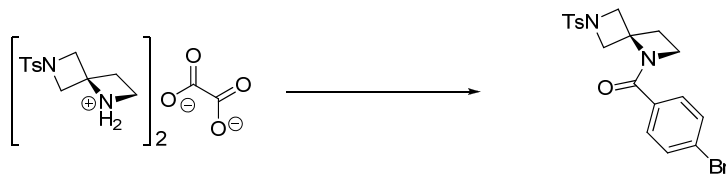
**TLC:**  $R_f$  = 0.13 (hexanes : EtOAc 1:2; UV); **Melting Point:** 180-182 °C; **<sup>1</sup>H-NMR**  $\delta$  = 7.71-7.39 (m, 4H), 4.84 (d,  $J$ =10.4, 2H), 4.34 (d,  $J$ =10.4, 2H), 4.07 (t,  $J$ =8.7, 2H), 2.42 (t,  $J$ =8.7, 2H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.7, 131.9, 130.9, 129.5, 126.4, 75.8, 62.7, 58.6 (br), 55.1 (br), 19.7; **IR** (thin film): 2940, 2872, 1638, 1589, 1415, 1313, 1206, 1122, 1011, 913, 748 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>13</sub>BrNO<sub>3</sub>S ([M+H]<sup>+</sup>), 329.9794; found 329.9788.



**(4-Bromophenyl)(1-oxa-6-azaspiro[3.3]heptan-6-yl)methanone (25).** To a solution of *tert*-butyl carbamate **20** (17.0 mg, 0.085 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was added at 0 °C trifluoroacetic acid (0.4 ml), and the mixture was stirred at 0 °C for 15 min, when the volatiles were removed *in vacuo*. The residue (colorless oil) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 ml), and triethylamine (24  $\mu$ l, 0.171 mmol, 2.0 equiv) followed by 4-bromobenzoyl chloride (22.5 mg, 0.102 mmol, 1.2 equiv) was added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then it was allowed to warm to RT and stirring was continued for 16 h. At this point, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (25 ml) and quenched by addition of saturated aqueous NaHCO<sub>3</sub> (10 ml). The phases were separated and the organic phase was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; EtOAc : hexanes 2:1).

Yield: 14.0 mg (0.050 mmol, 58%). Colorless crystalline solid.

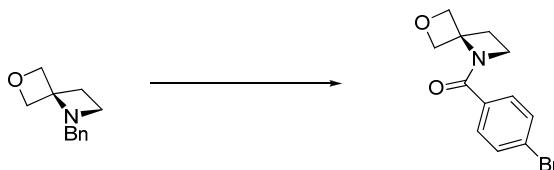
**TLC:**  $R_f$  = 0.19 (hexanes : EtOAc 1:2; UV); **Melting Point:** 157-158 °C; **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.68-7.36 (m, 4H), 4.71-4.18 (m, 6H), 2.87 (dd,  $J$ =13.8, 6.4, 2H); **<sup>13</sup>C-NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.1, 132.0, 131.7, 129.5, 125.7, 82.8, 67.6 (br), 66.3, 63.5 (br), 31.8; **IR** (thin film): 2931, 2891, 1638, 1418, 958, 913, 748 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>13</sub>BrNO<sub>2</sub> ([M+H]<sup>+</sup>), 282.0124; found 282.0125.



**(4-Bromophenyl)(6-tosyl-1,6-diazaspiro[3.3]heptan-1-yl)methanone (26).** To a suspension of 6-(tosyl-6-aza-1-azoniaspiro[3.3]heptane) oxalate **23** (50 mg, 0.084 mmol, 0.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1.6 ml) was added triethylamine (35  $\mu$ l, 0.252 mmol, 1.5 equiv) and then 4-bromobenzoyl chloride (44.3 mg, 0.202 mmol, 1.2 equiv) at RT. The reaction mixture (white suspension) turned immediately to a clear solution. After 30 min, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and quenched with saturated aqueous NaHCO<sub>3</sub> (5 ml). The phases were separated, the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 ml), and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1).

Yield: 50 mg (0.115 mmol, 68%). Colorless crystalline solid.

**TLC:**  $R_f$  = 0.79 ( $\text{CH}_2\text{Cl}_2$  : MeOH 9:1; UV, Dragendorff's reagent); **Melting Point:** 153-154°C;  **$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.74 (d,  $J$ =7.6, 1H), 7.51-7.46 (m, 2H), 7.40-7.34 (m, 4H), 4.68 (bs, 2H), 4.07 (t,  $J$ =7.5, 2H), 3.87 (d,  $J$ = 9.0, 2H), 2.47 (t,  $J$ =7.5, 2H), 2.44 (s, 3H);  **$^{13}\text{C-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 168.2, 144.1, 132.4, 131.9, 131.6, 129.7, 129.0, 128.3, 125.6, 62.6, 60.3, 49.6, 29.9, 21.6; **IR** (neat): 3060, 2968, 2936, 2888, 1620, 1587, 1414, 1342, 1301, 1161, 1091, 1028, 1008, 839, 814, 744, 689, 655  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{19}\text{H}_{20}\text{BrN}_2\text{O}_3\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 435.0373; found 435.0364.

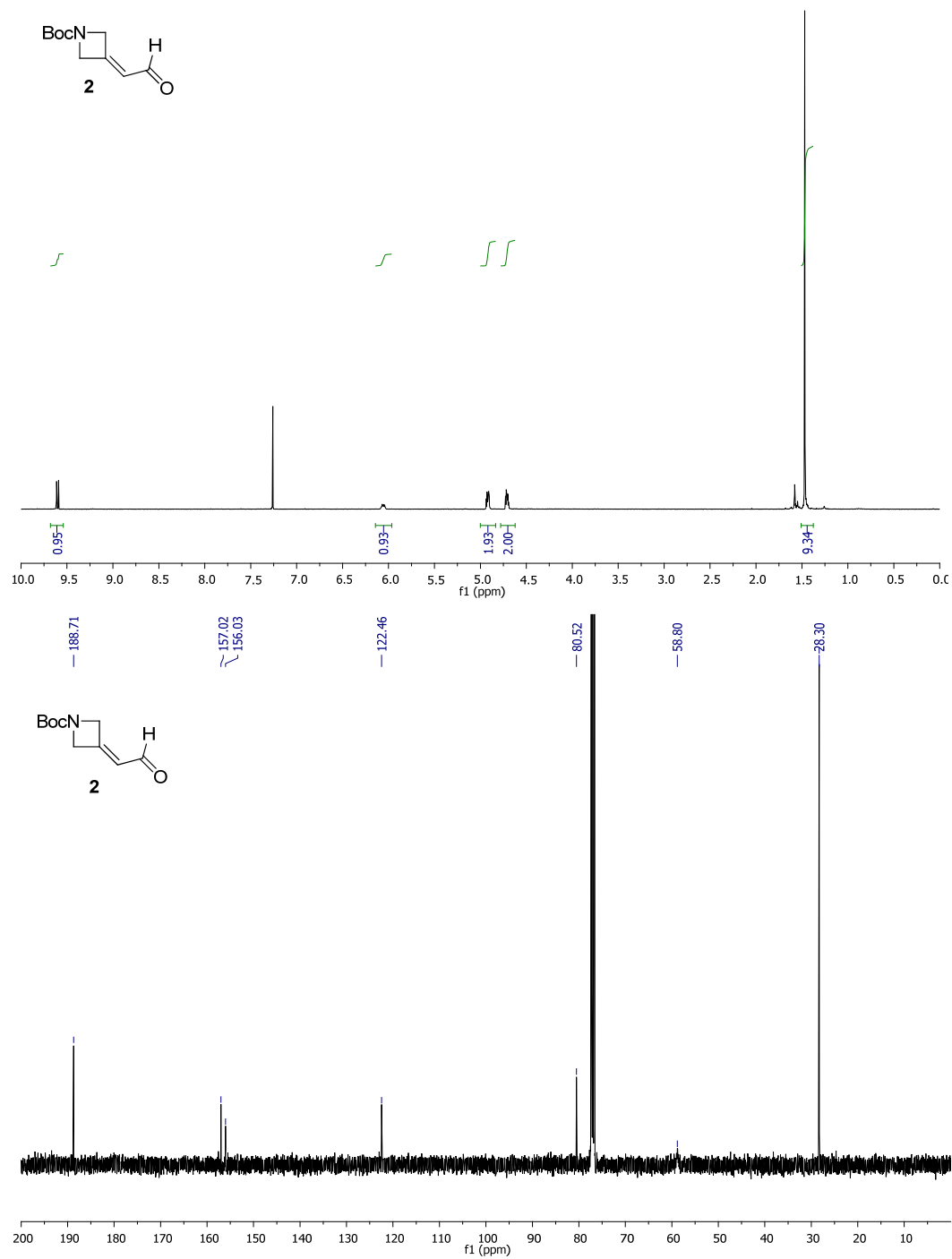


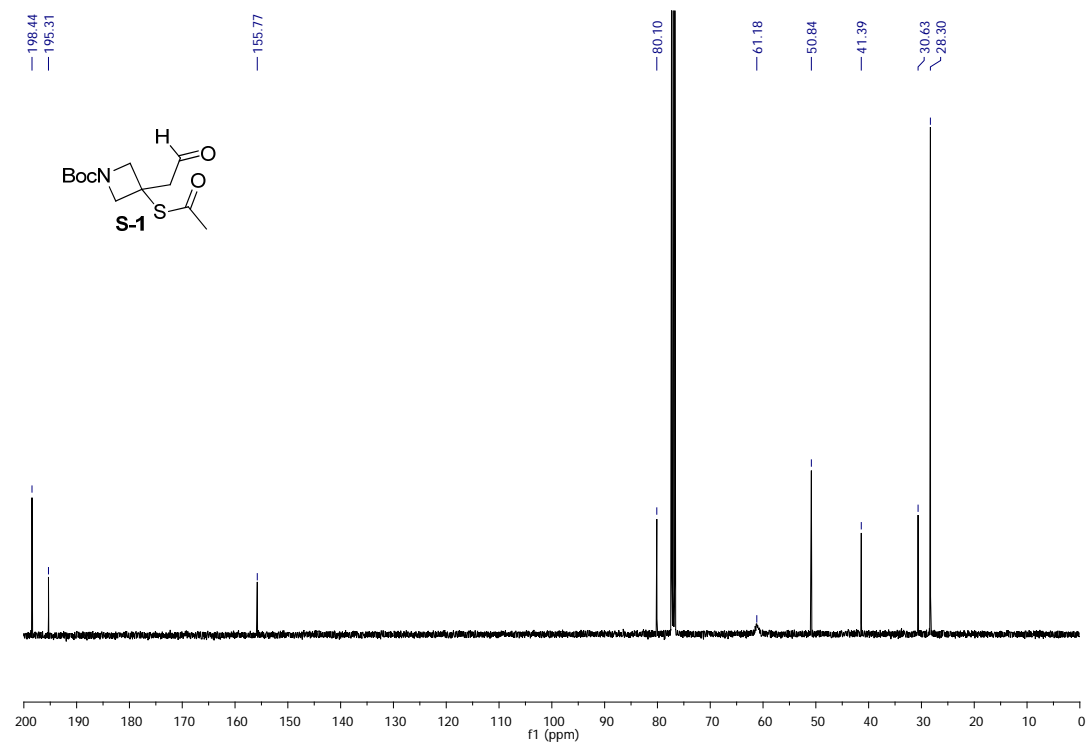
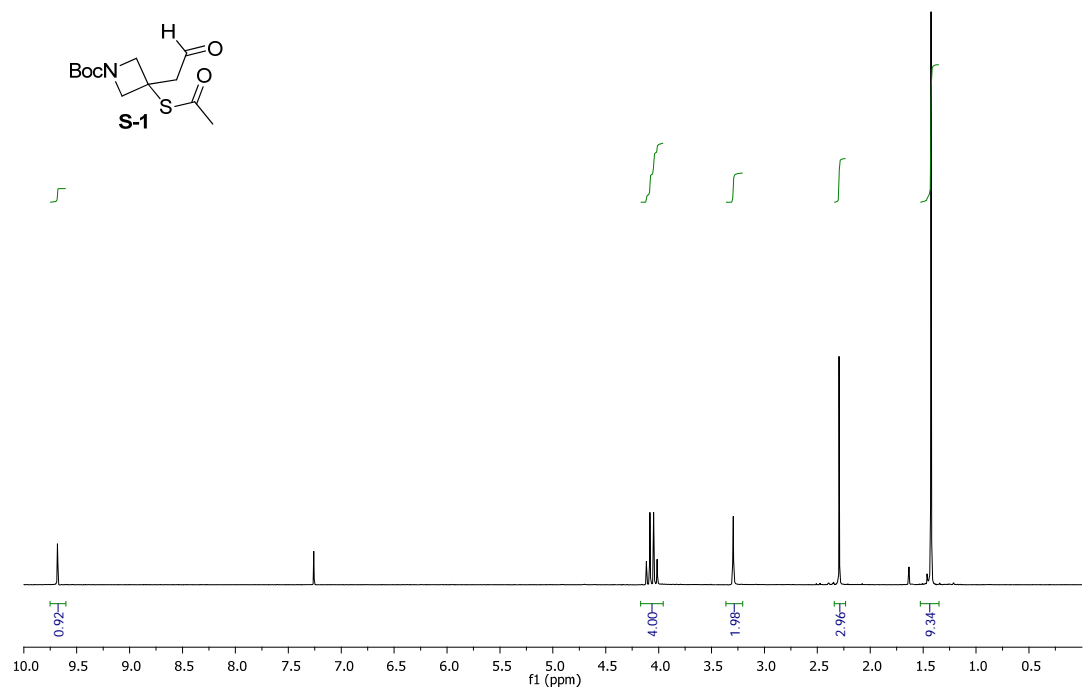
**(4-Bromophenyl)(6-oxa-1-azaspiro[3.3]heptan-1-yl)methanone (27).** To a solution of benzyl amine **18** (79 mg, 0.42 mmol, 1.0 equiv) in MeOH (4 ml) was added palladium (10% on carbon; 89 mg, 0.083 mmol, 0.2 equiv), and a  $\text{H}_2$  atmosphere was built up. The mixture was stirred at RT for 36 h. At this point the mixture was filtered over celite and thoroughly washed with MeOH. The filtrate was co-evaporated with  $\text{CHCl}_3$  multiple times and briefly dried under high vacuum. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 ml), when triethylamine (88  $\mu\text{l}$ , 0.63 mmol, 1.5 equiv) was added followed by 4-bromobenzoyl chloride (101 mg, 0.46 mmol, 1.1 equiv), and the mixture was stirred at RT for 18.5 h. It was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and quenched with saturated aqueous  $\text{NaHCO}_3$  (10 ml). The phases were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; EtOAc).

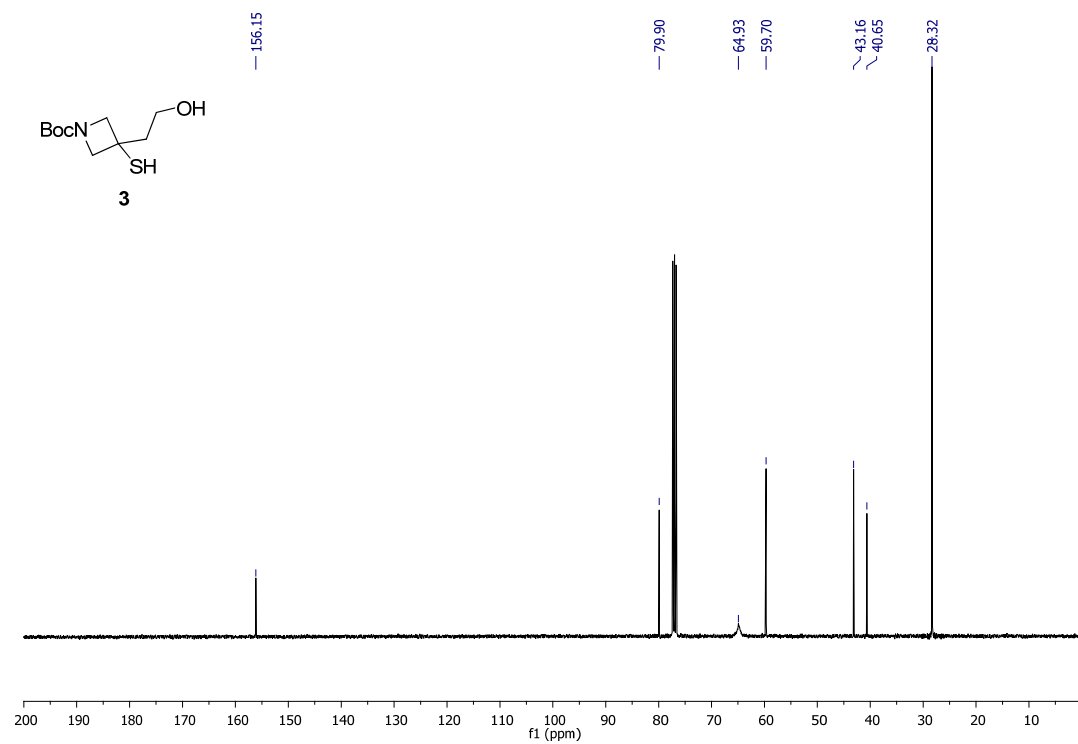
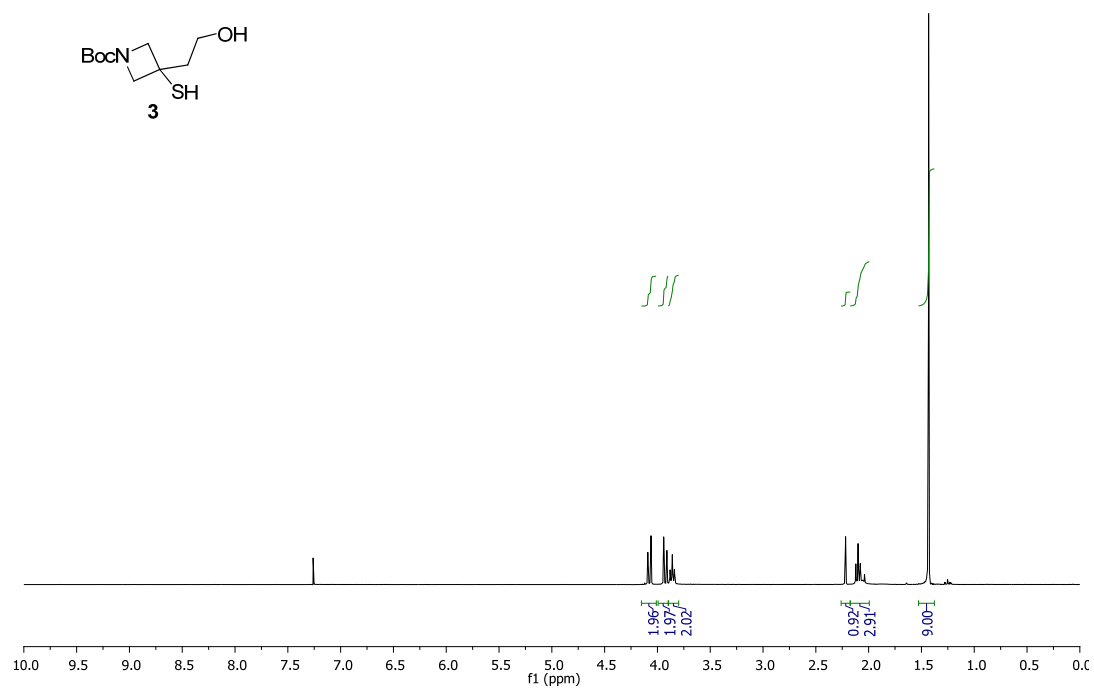
Yield: 56 mg (0.20 mmol, 48%). Colorless crystalline solid.

**TLC:**  $R_f$  = 0.31 (EtOAc; UV, DNP); **Melting Point:** 158-159 °C;  **$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.71-7.35 (m, 4H), 5.61 (br s, 2H), 4.63 (d,  $J$ =7.2, 2H), 4.11 (t,  $J$ =7.5, 2H), 2.61 (d,  $J$ =7.5, 2H);  **$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.9, 132.6, 131.4, 128.8, 125.2, 80.6, 68.5, 49.5, 29.1; **IR** (thin film): 2962, 2870, 1619, 1558, 1416, 970, 913, 851, 748  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{13}\text{BrNO}_2$  ( $[\text{M}+\text{H}]^+$ ), 282.0124; found 282.0125.

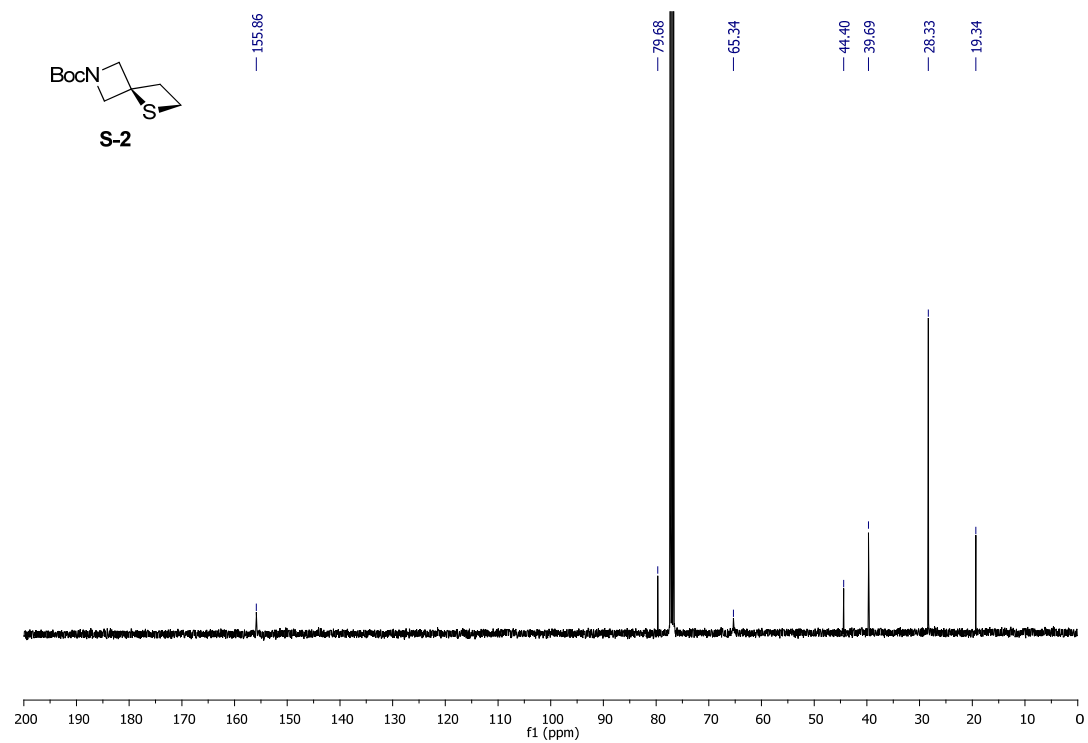
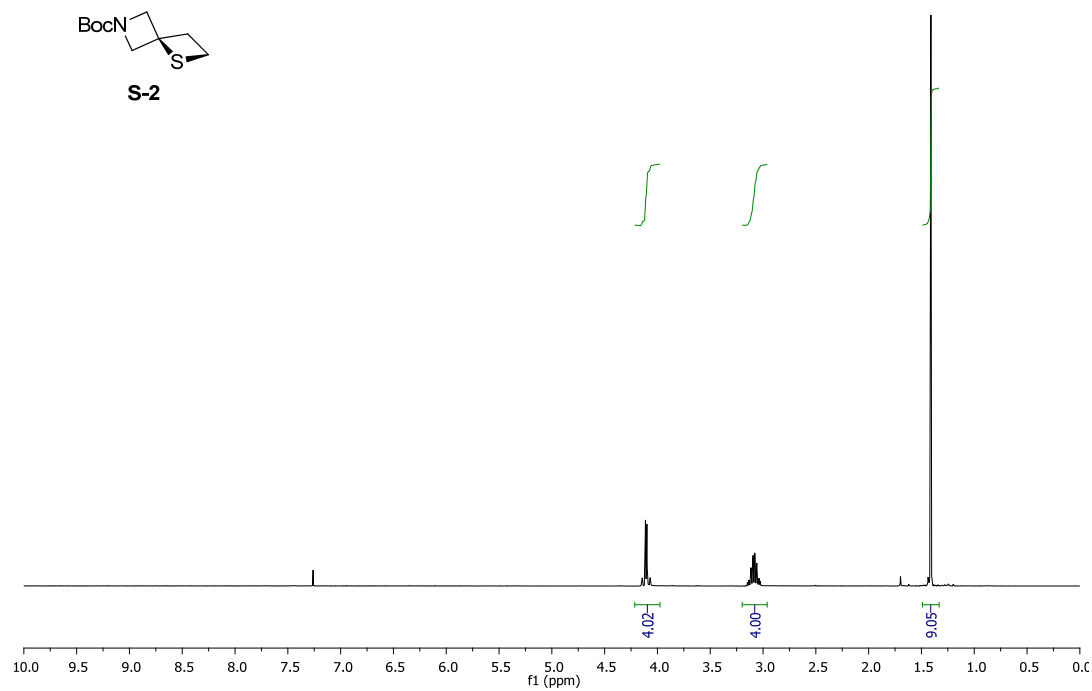
# COPIES OF NMR SPECTRA OF NEW COMPOUNDS

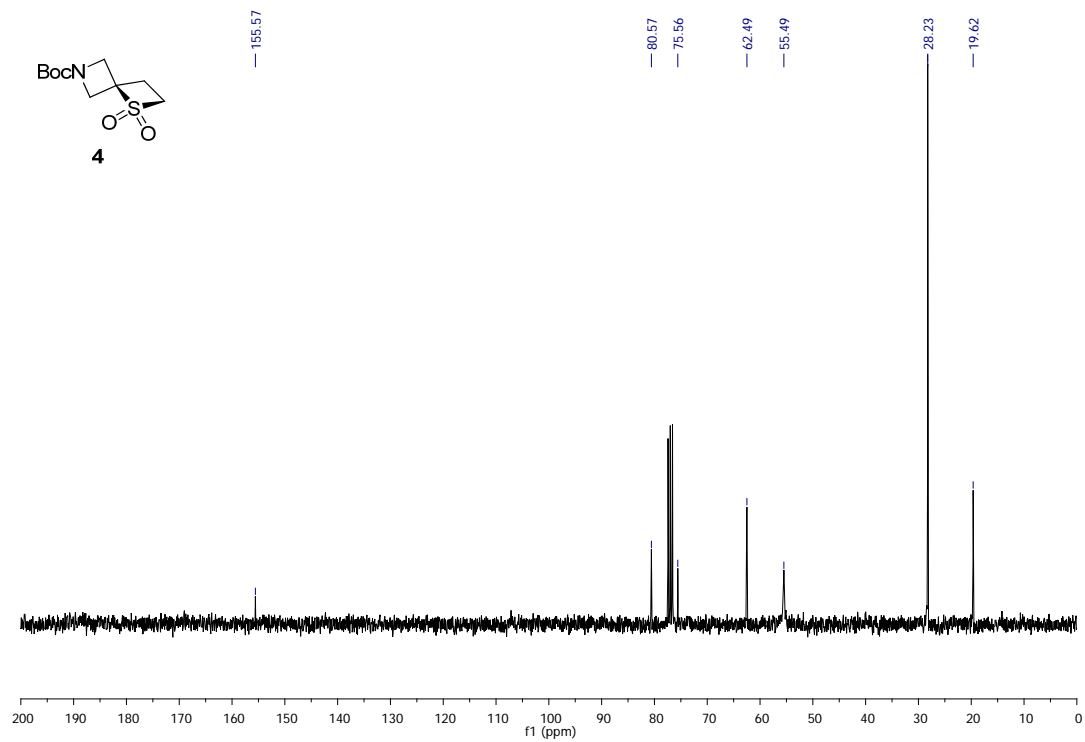
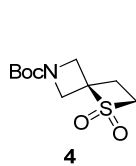
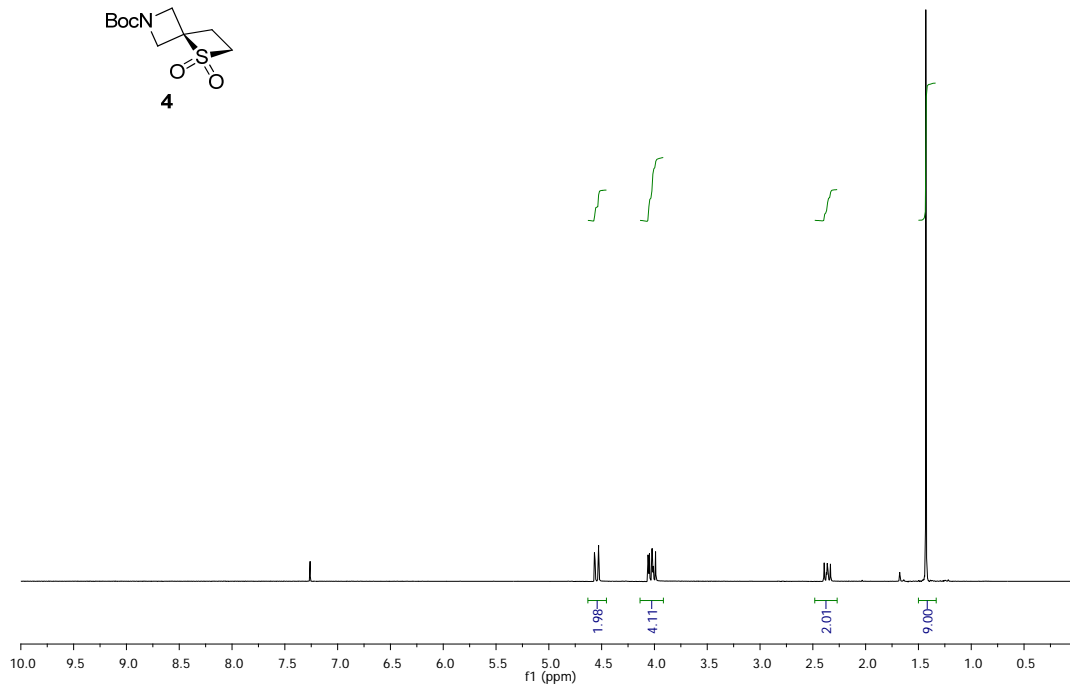
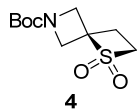


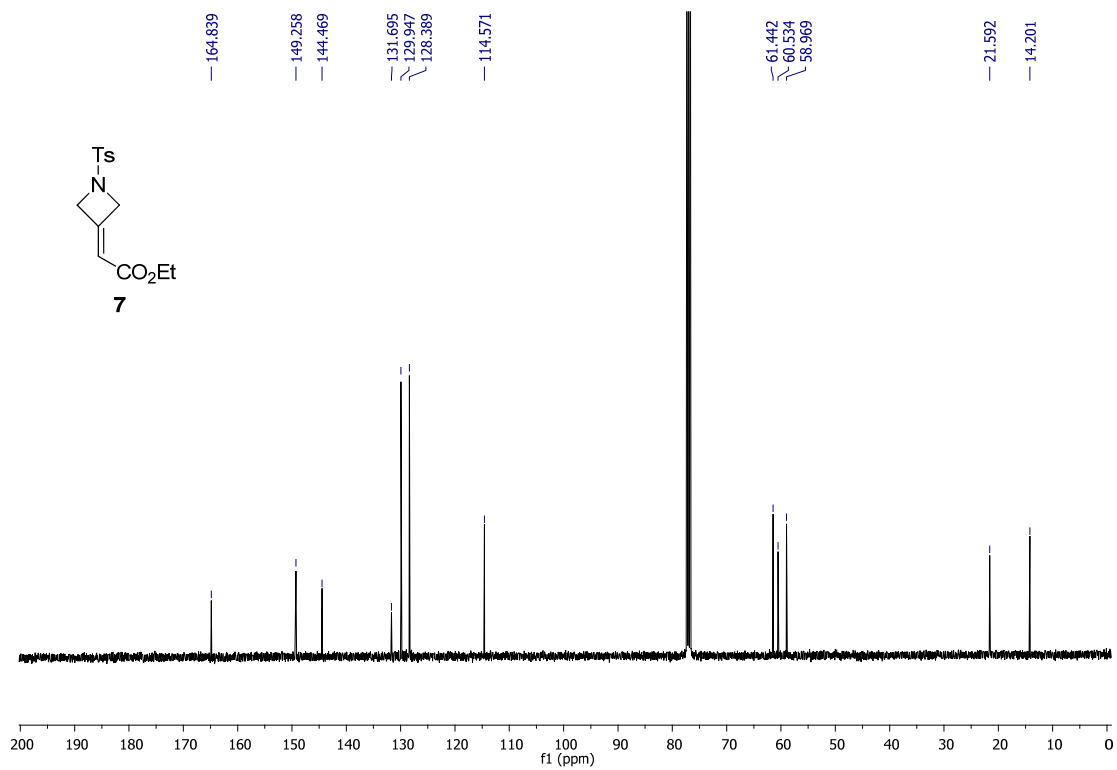
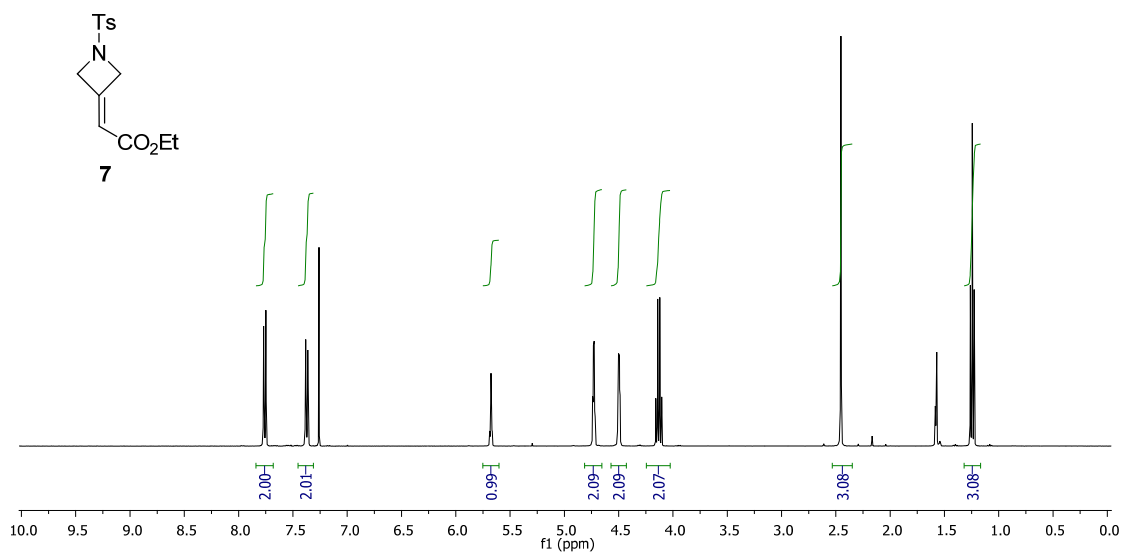


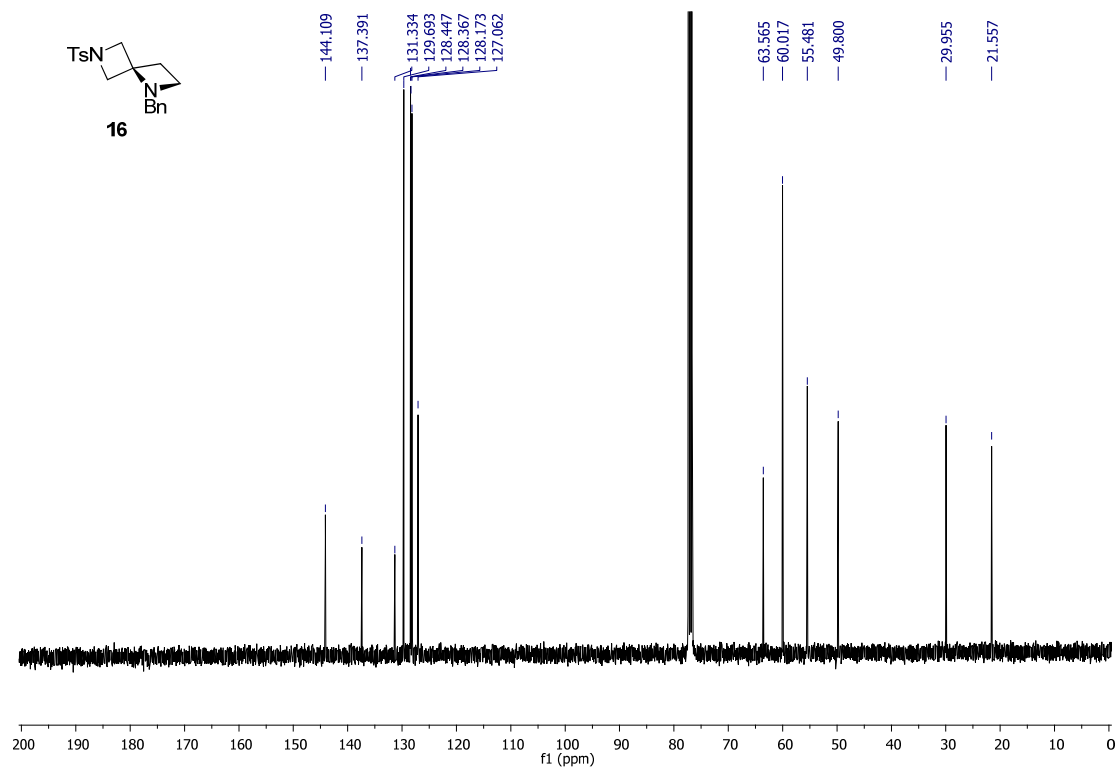
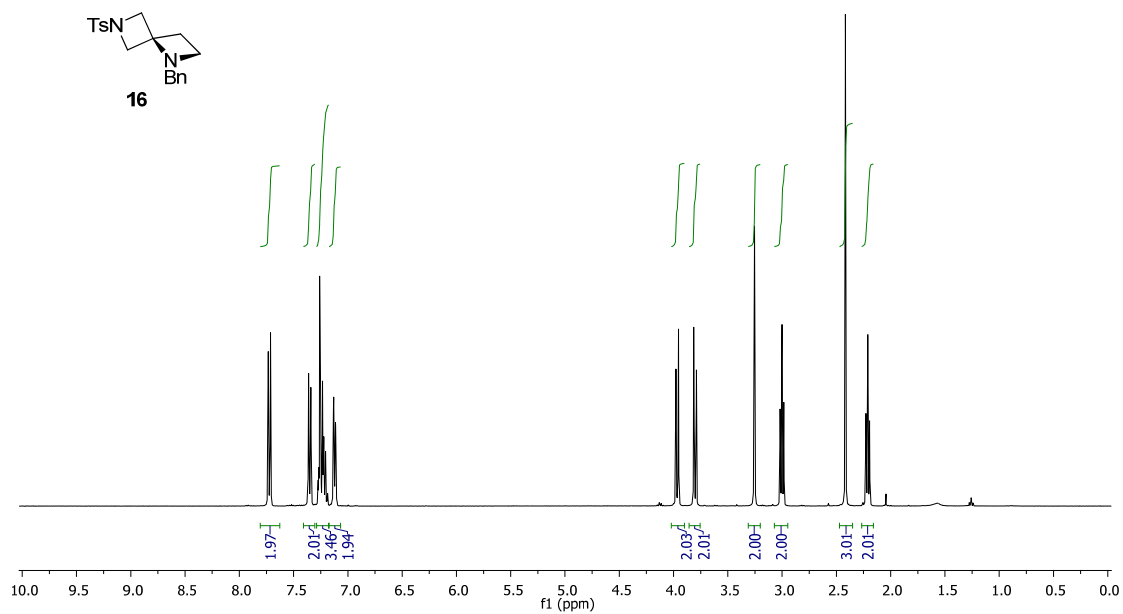


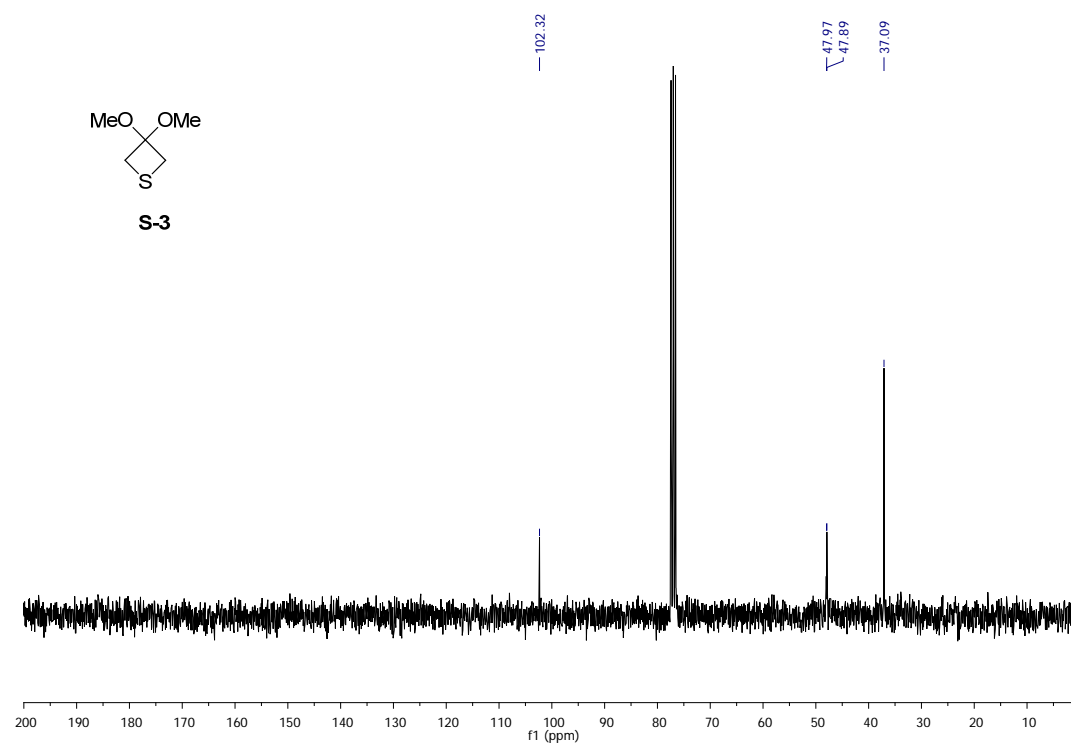
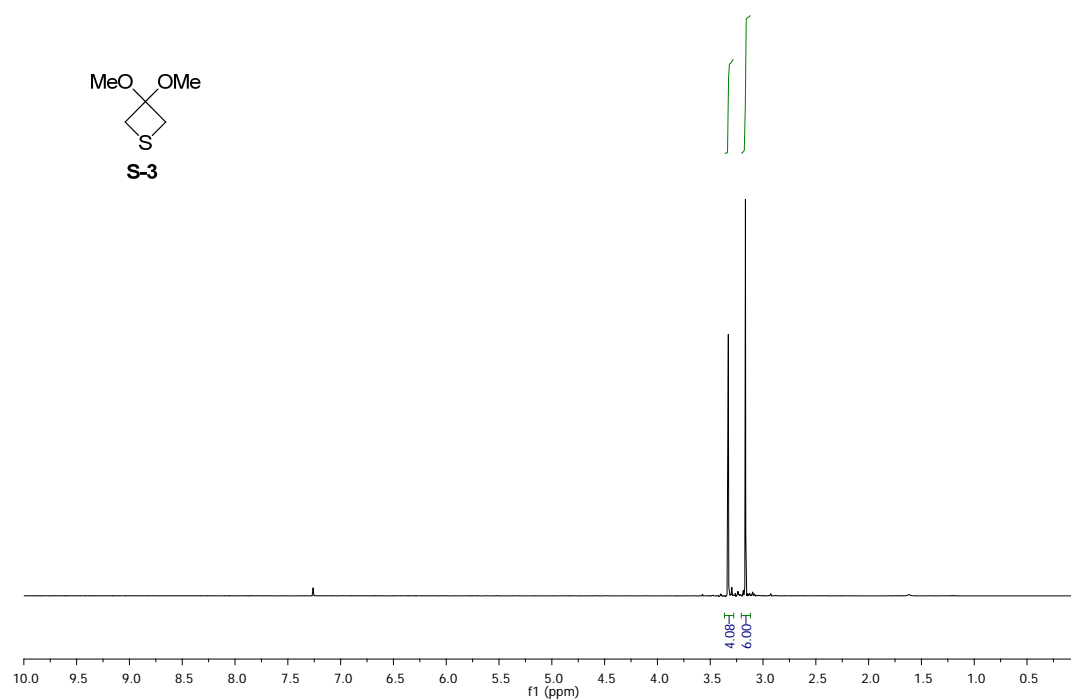


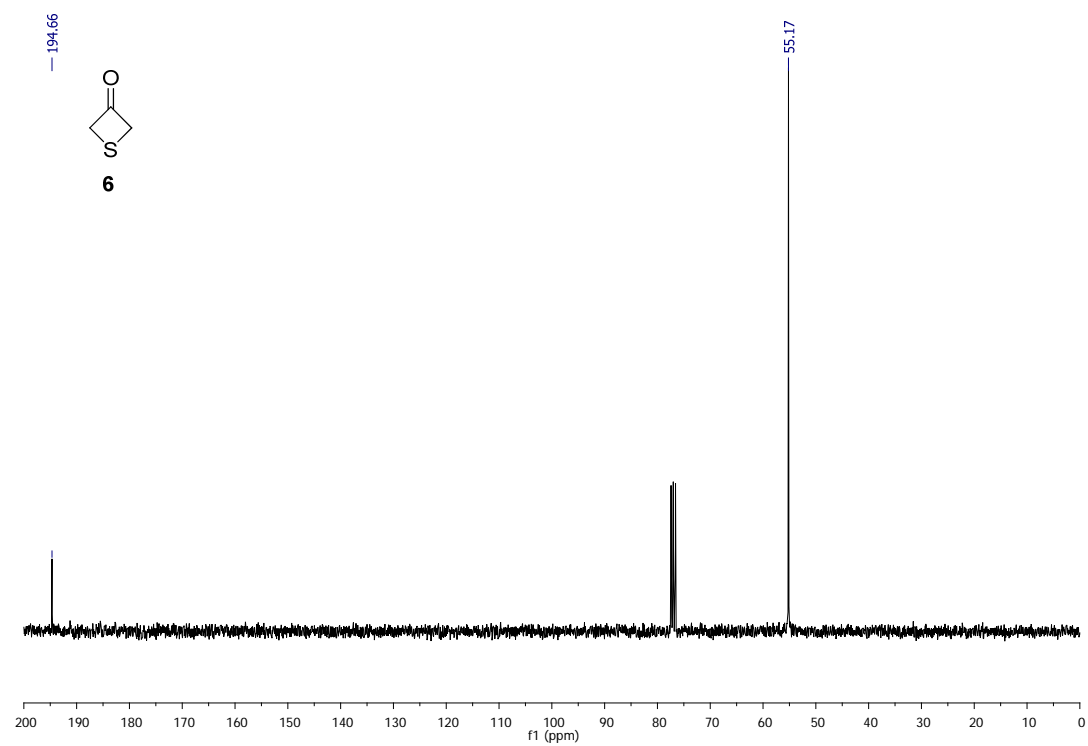
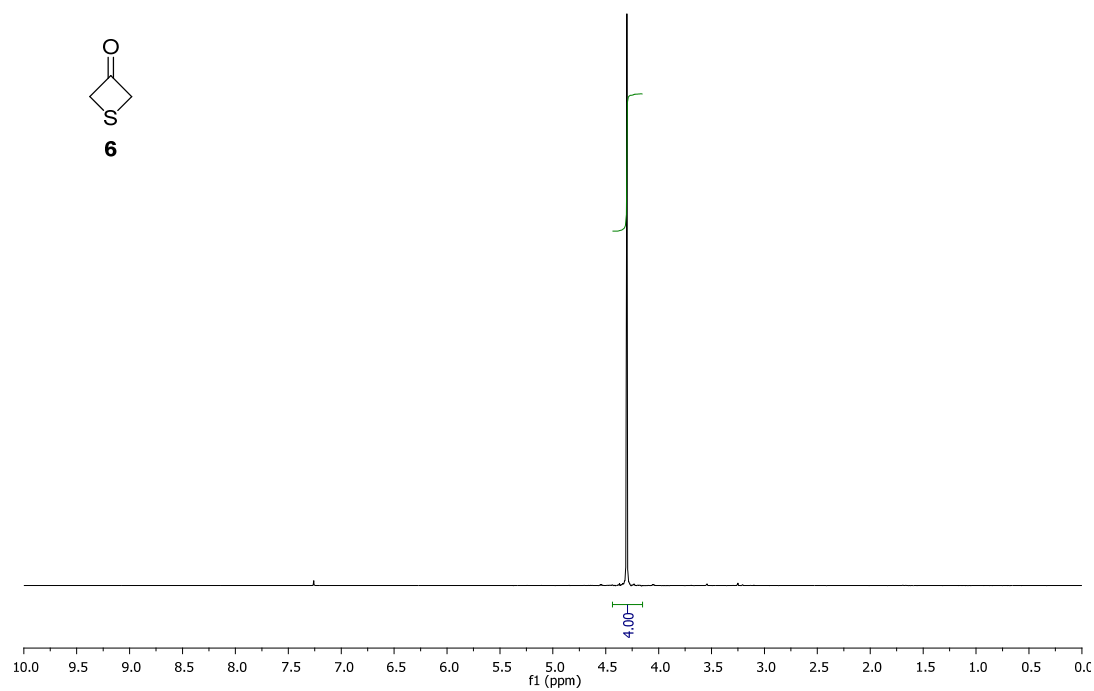


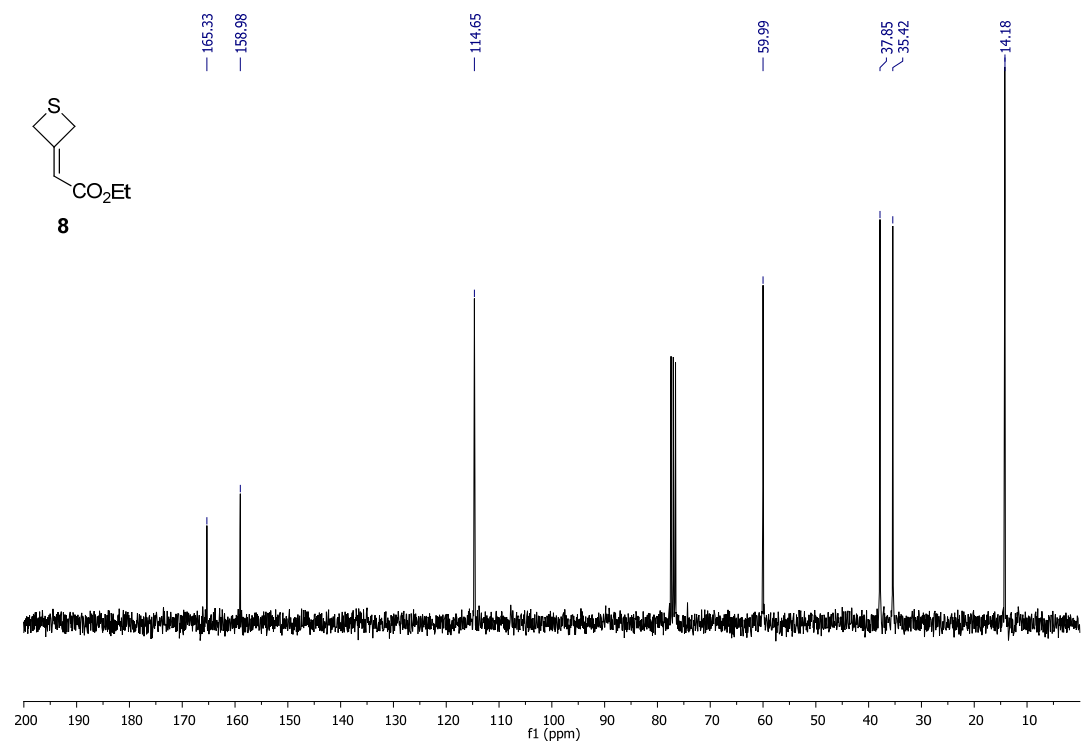
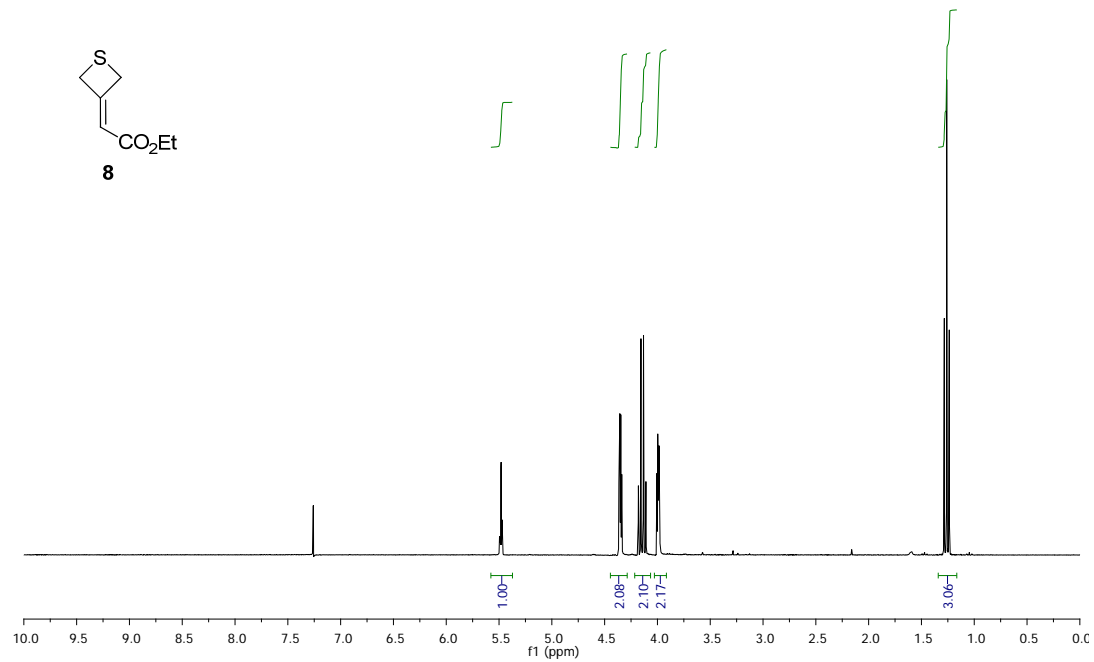


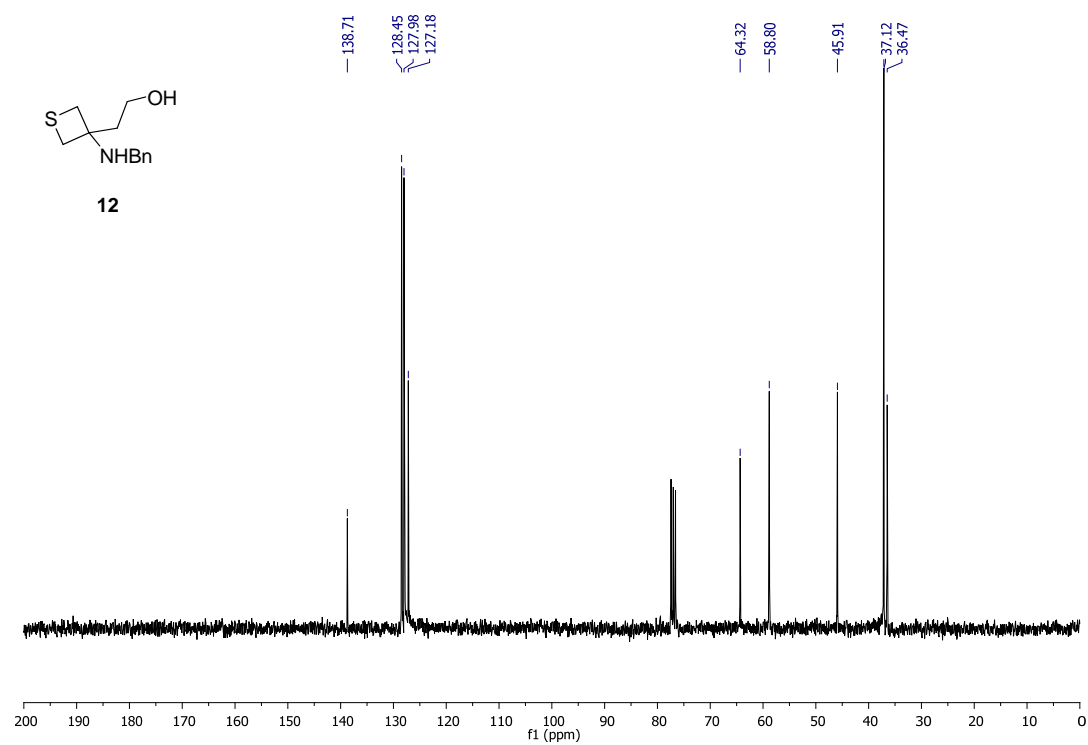
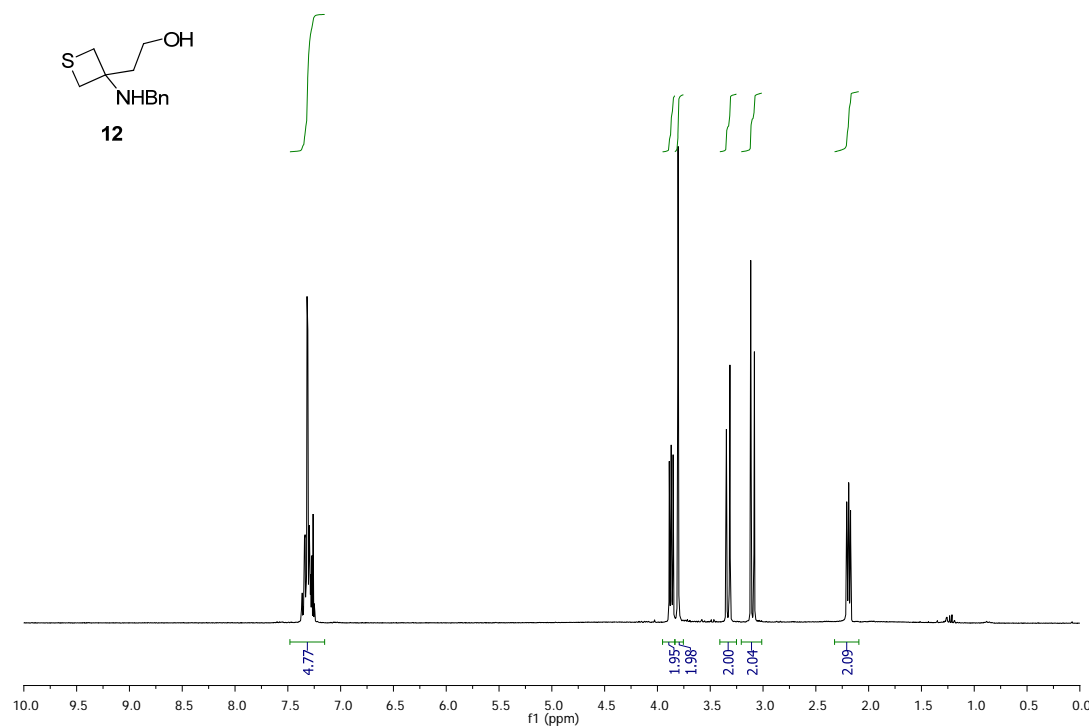




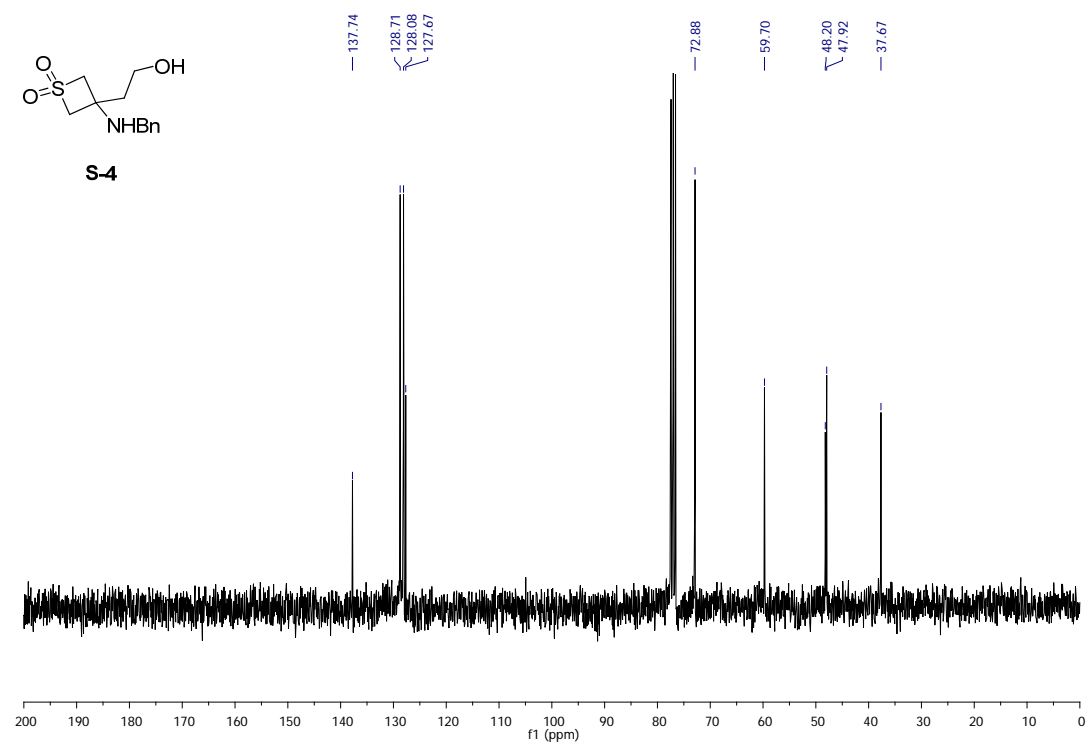
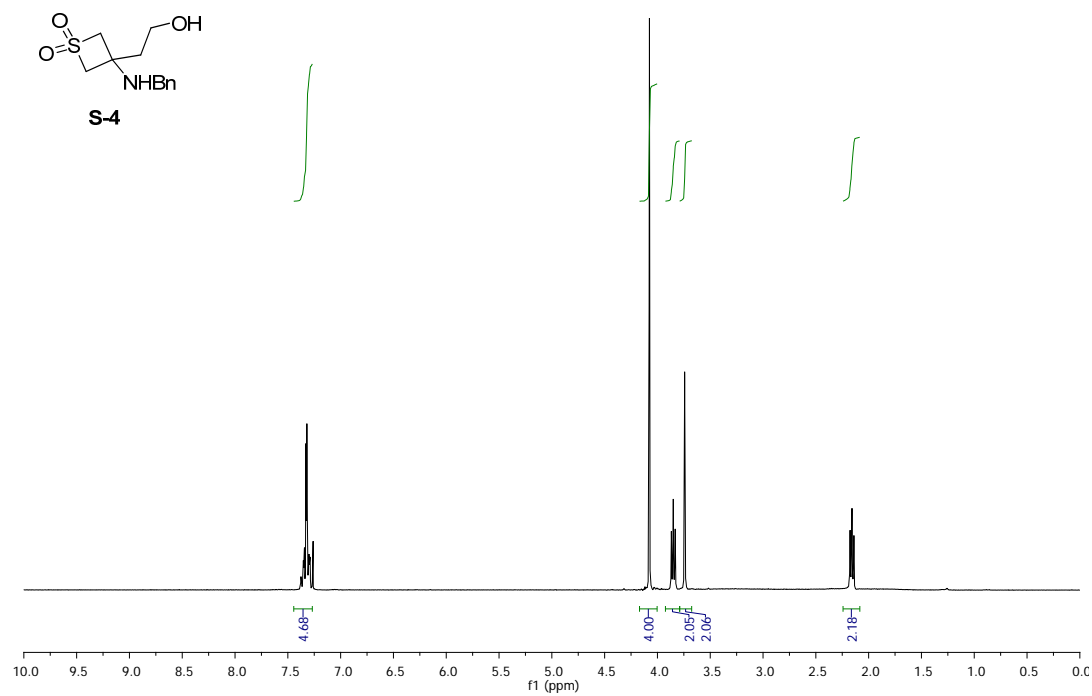


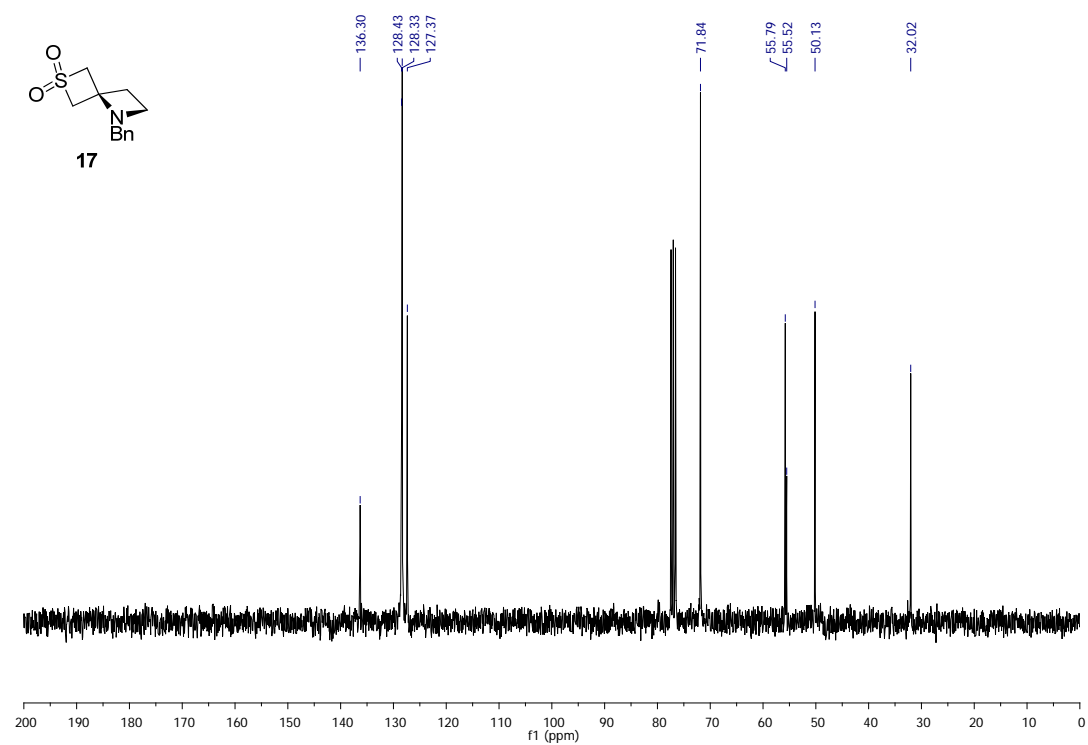
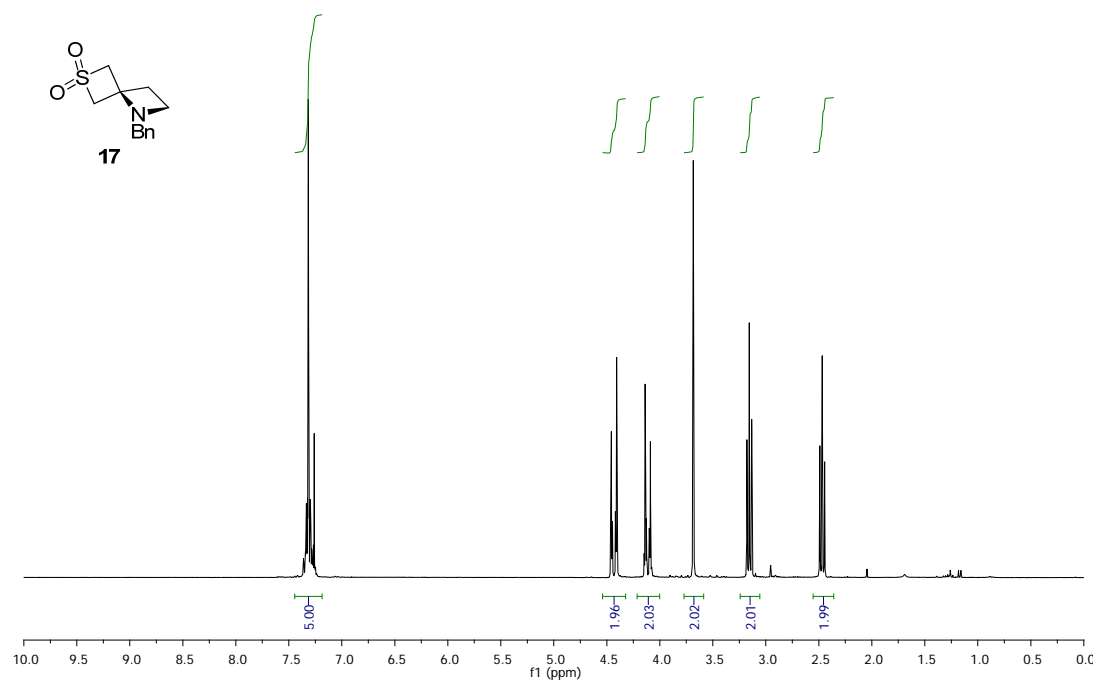


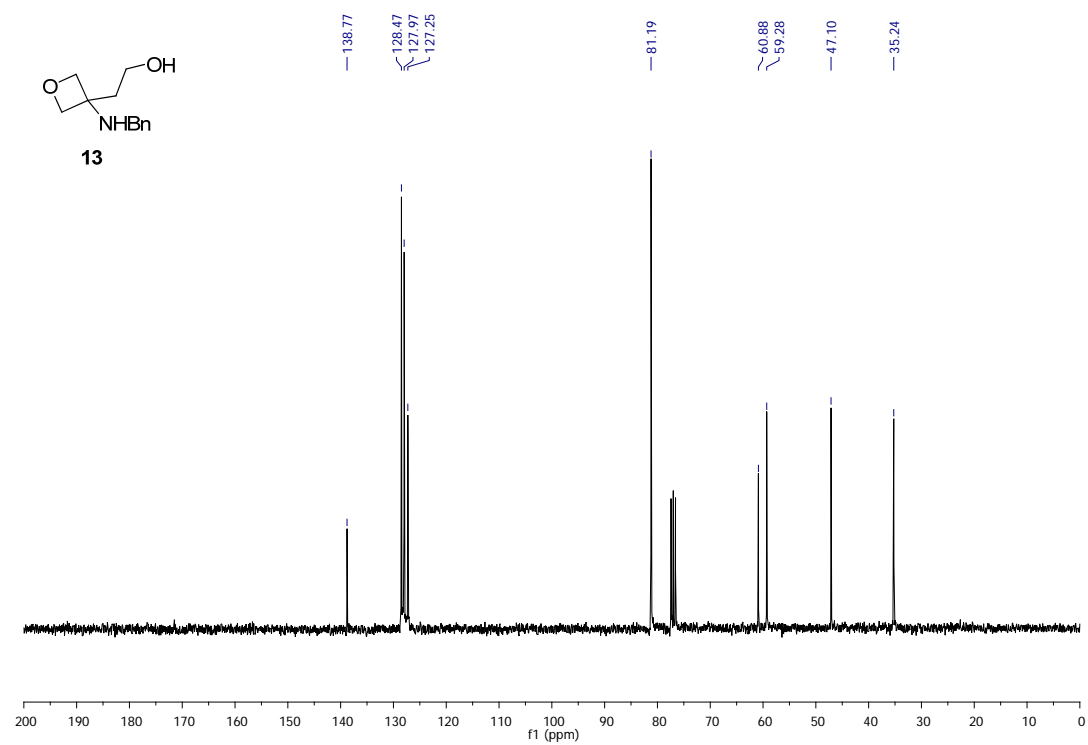
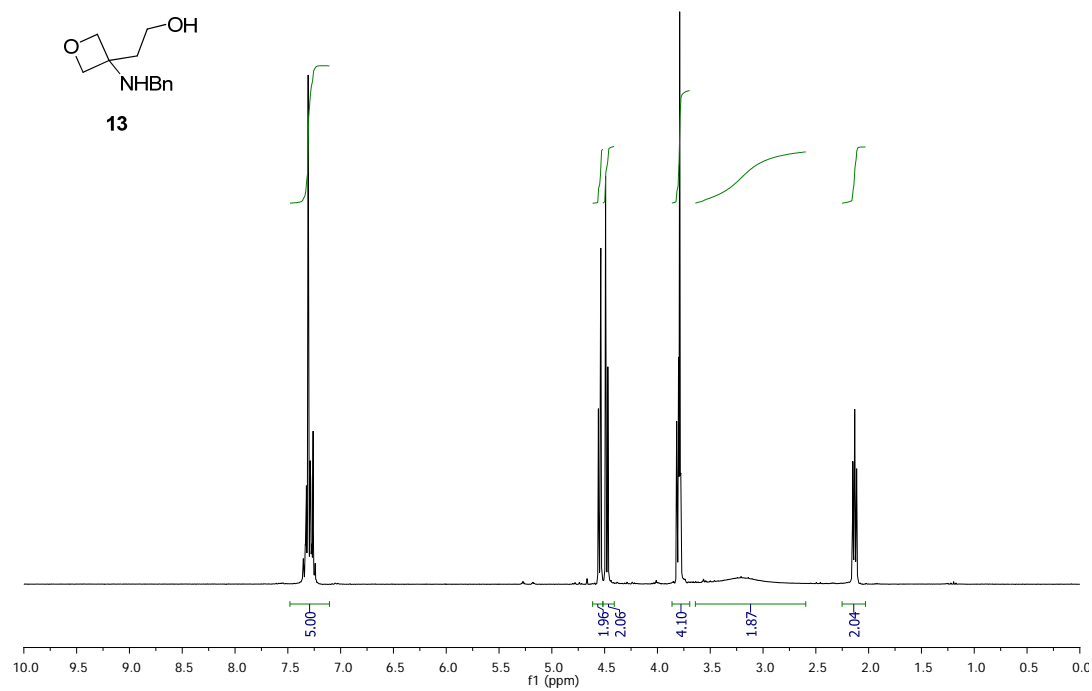


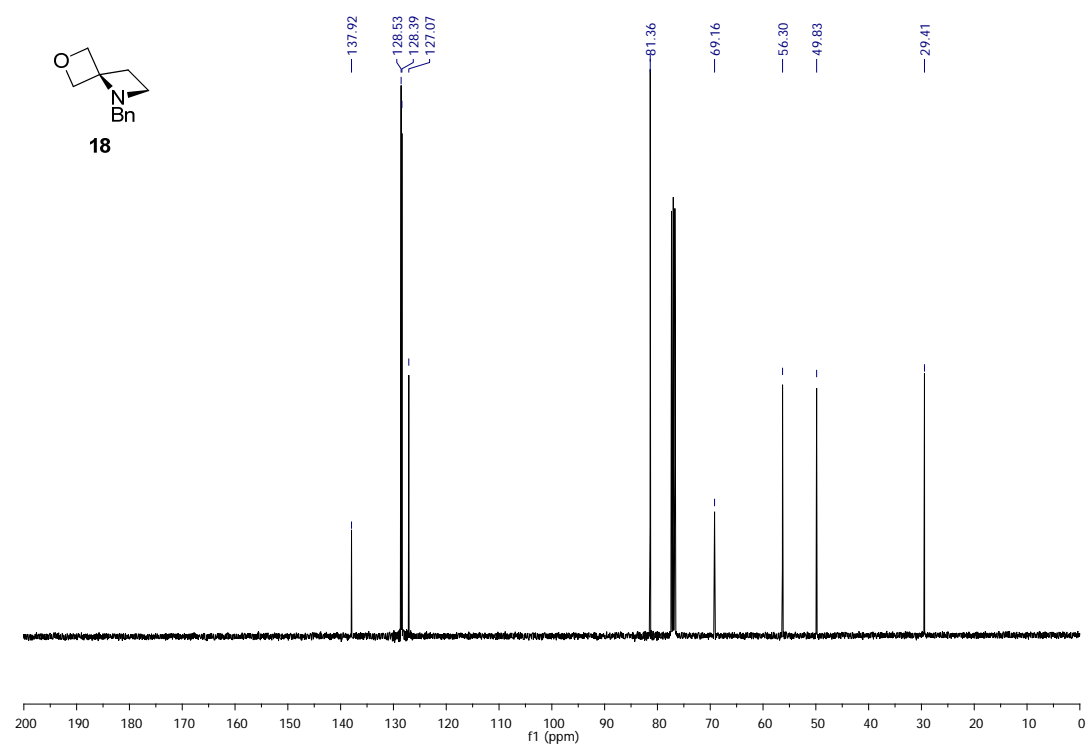
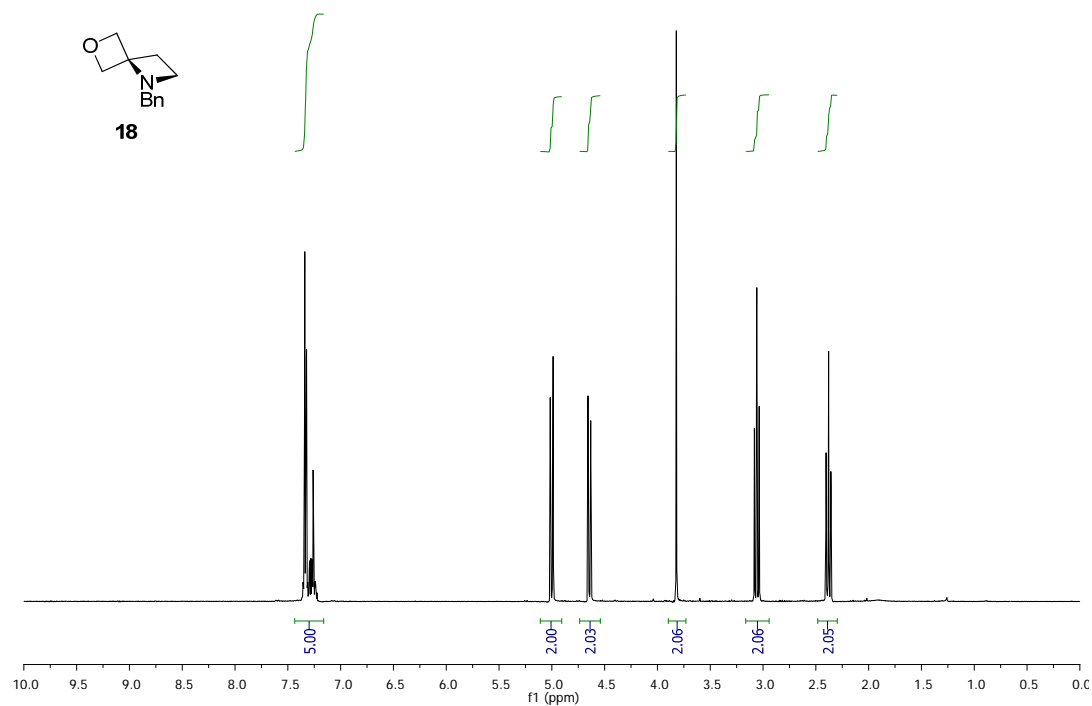


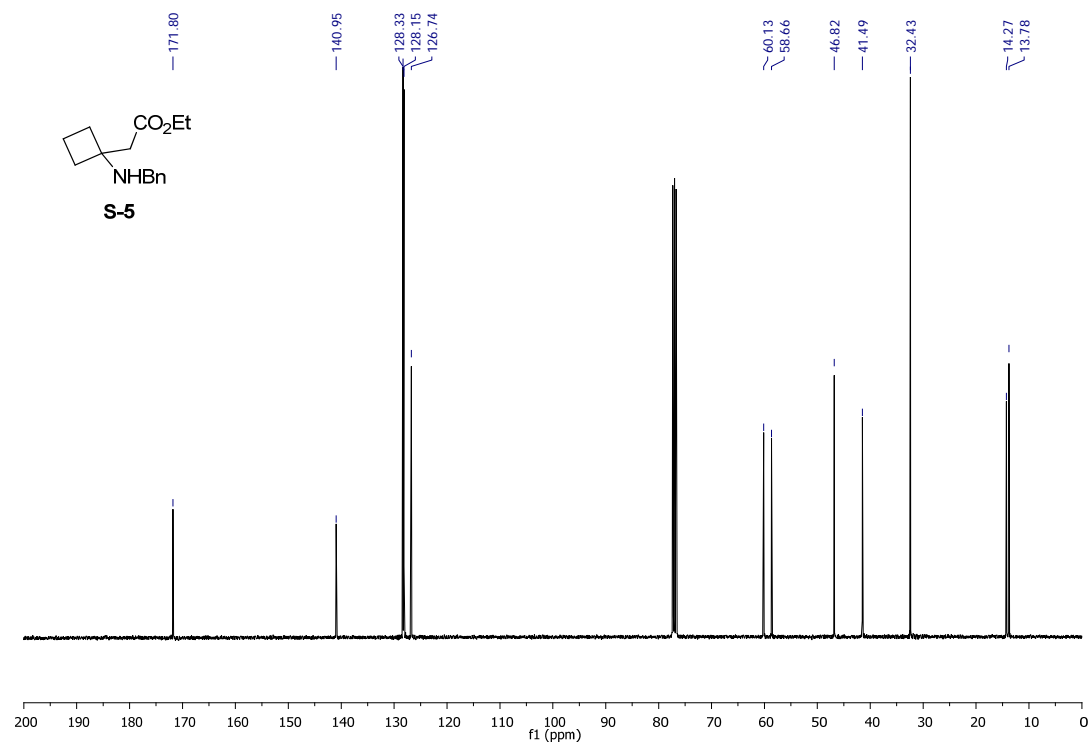
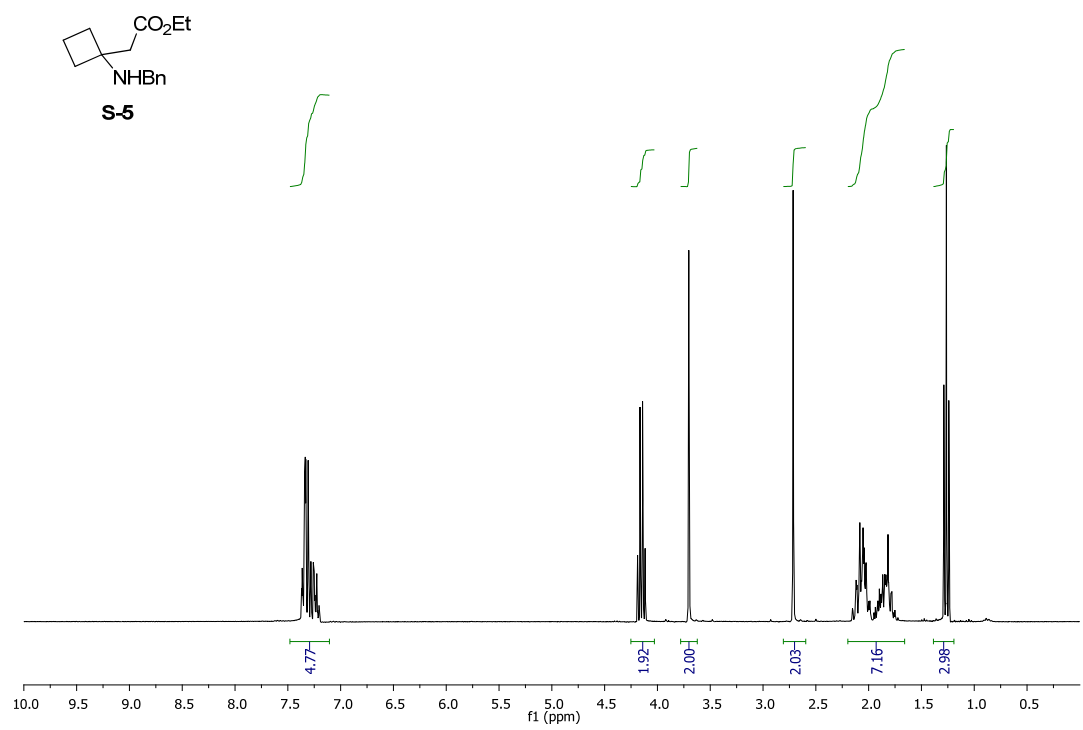


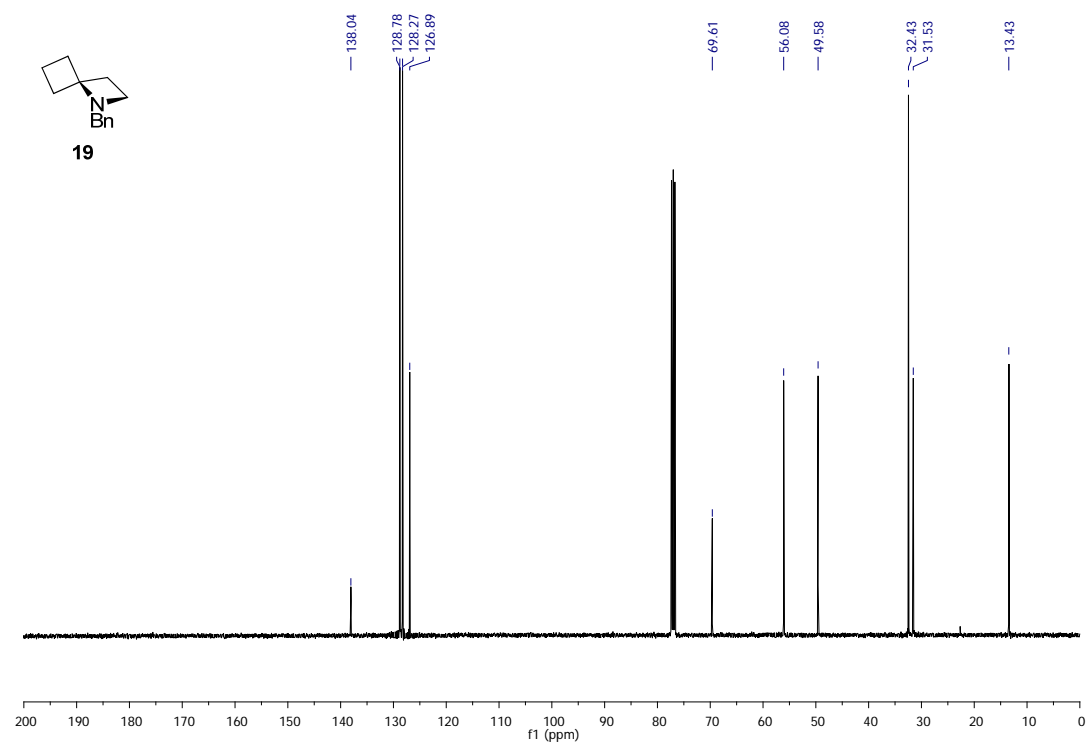
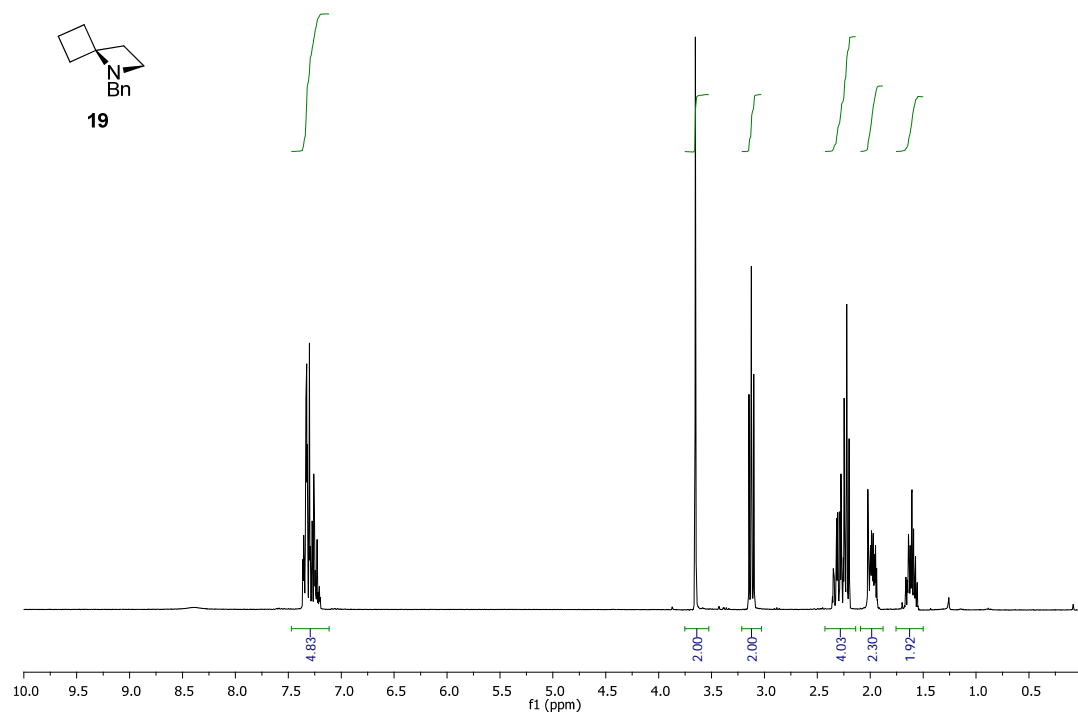


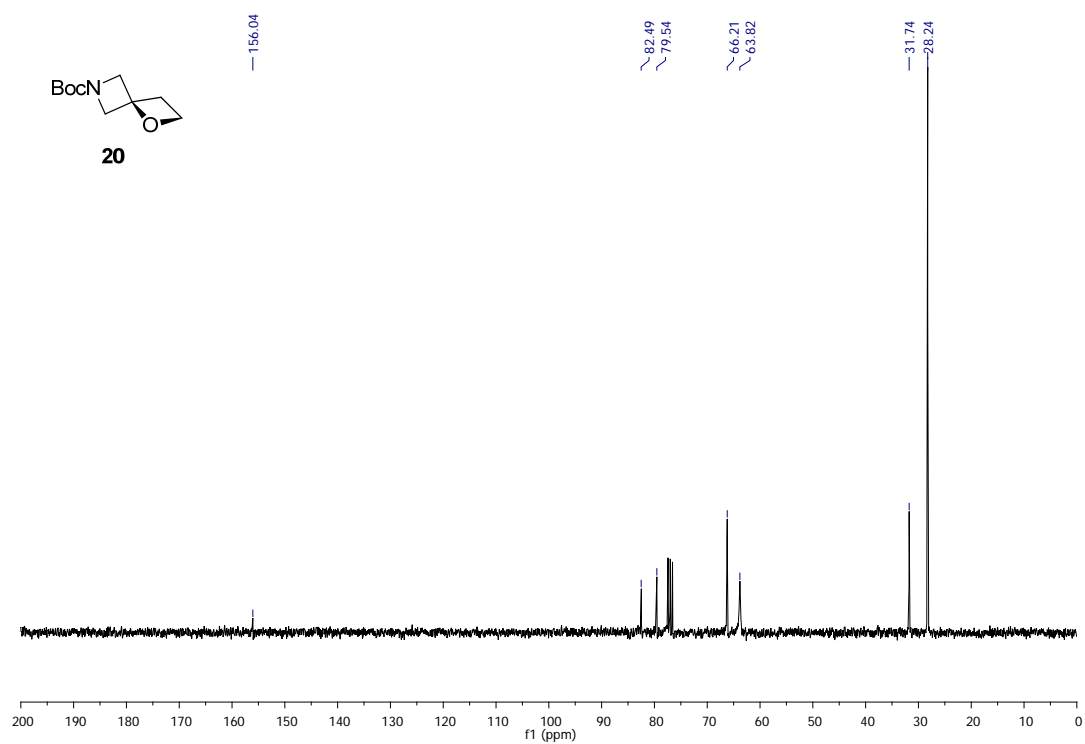
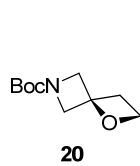
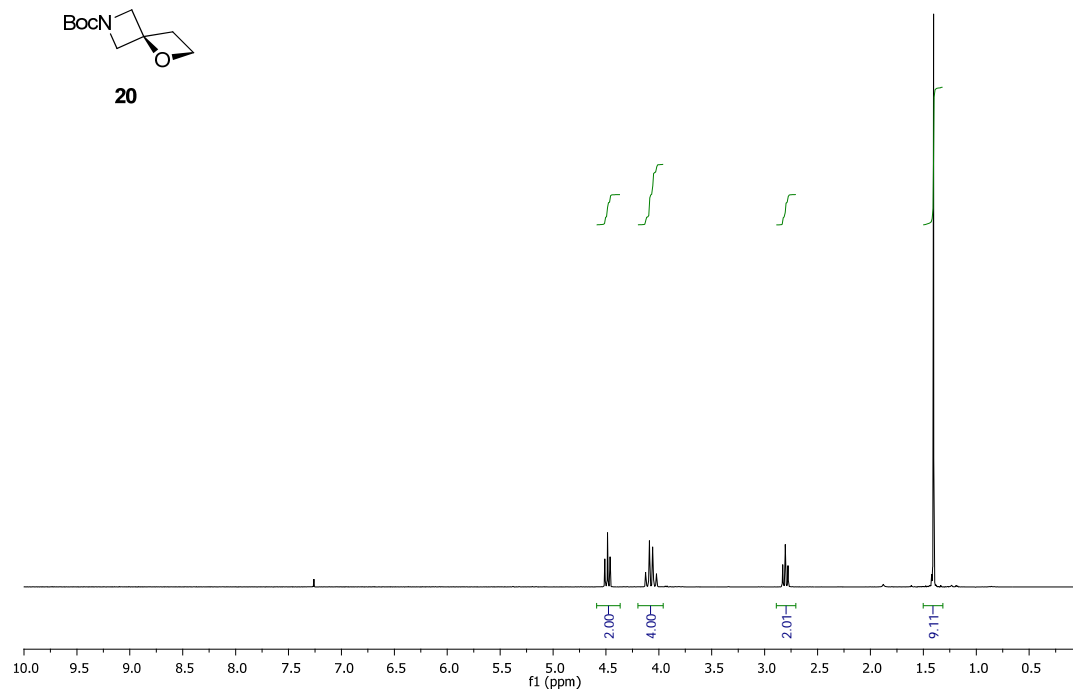
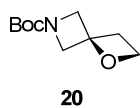


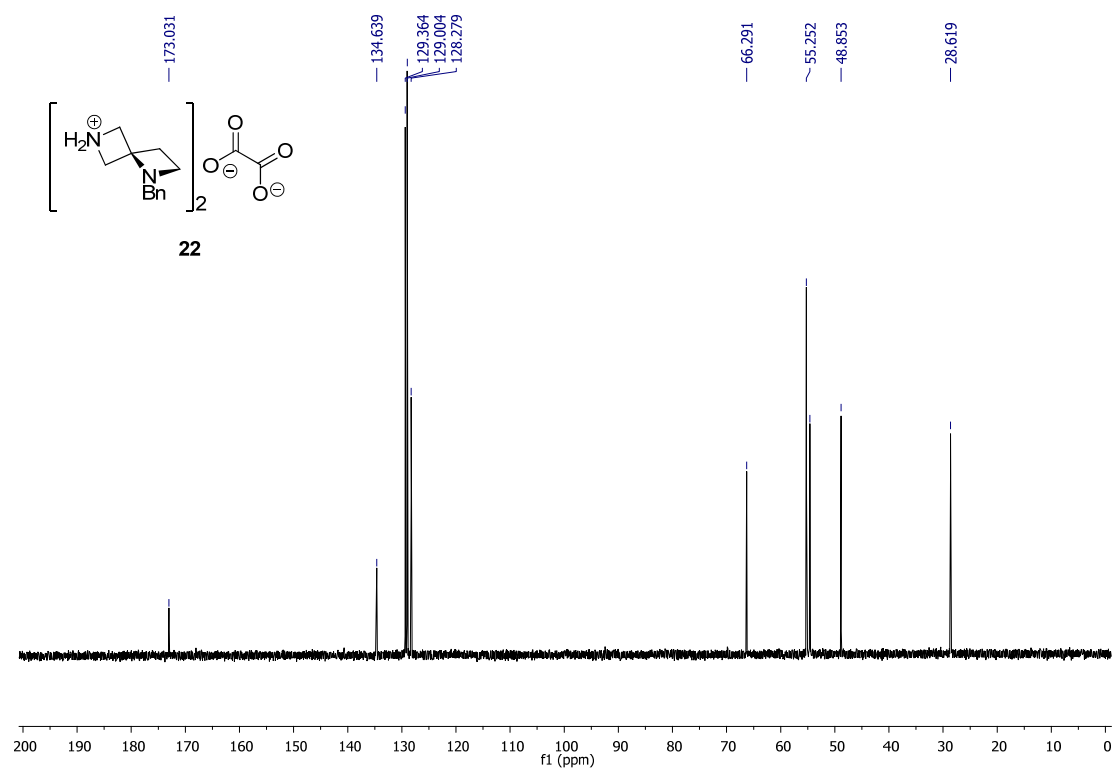
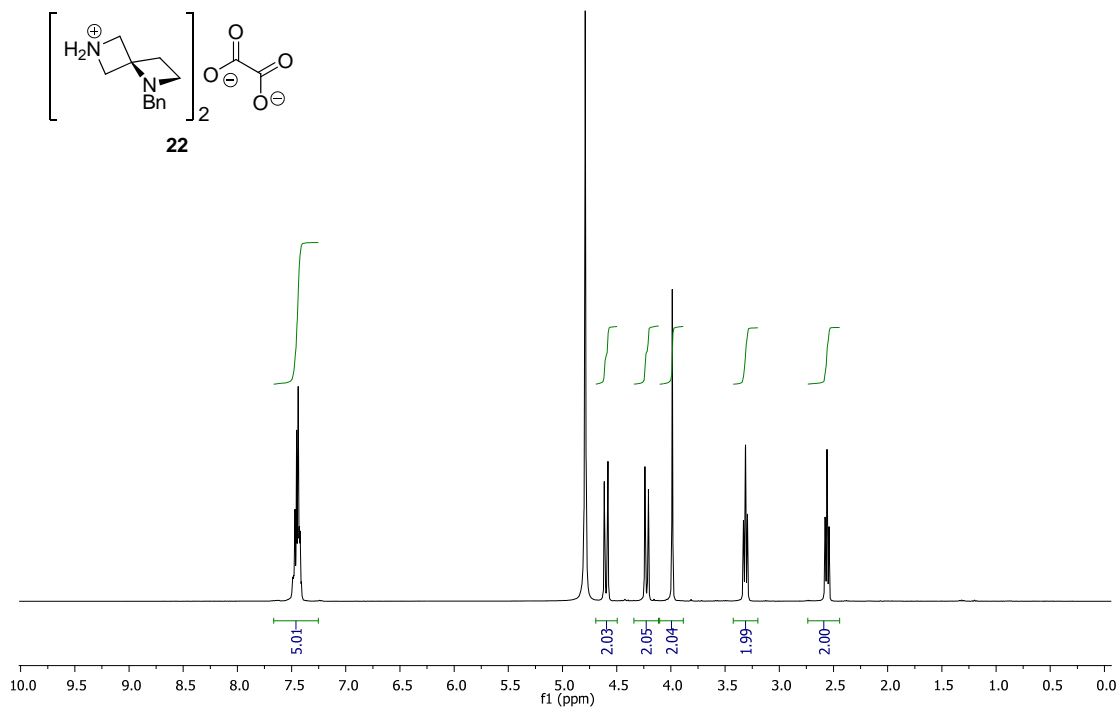




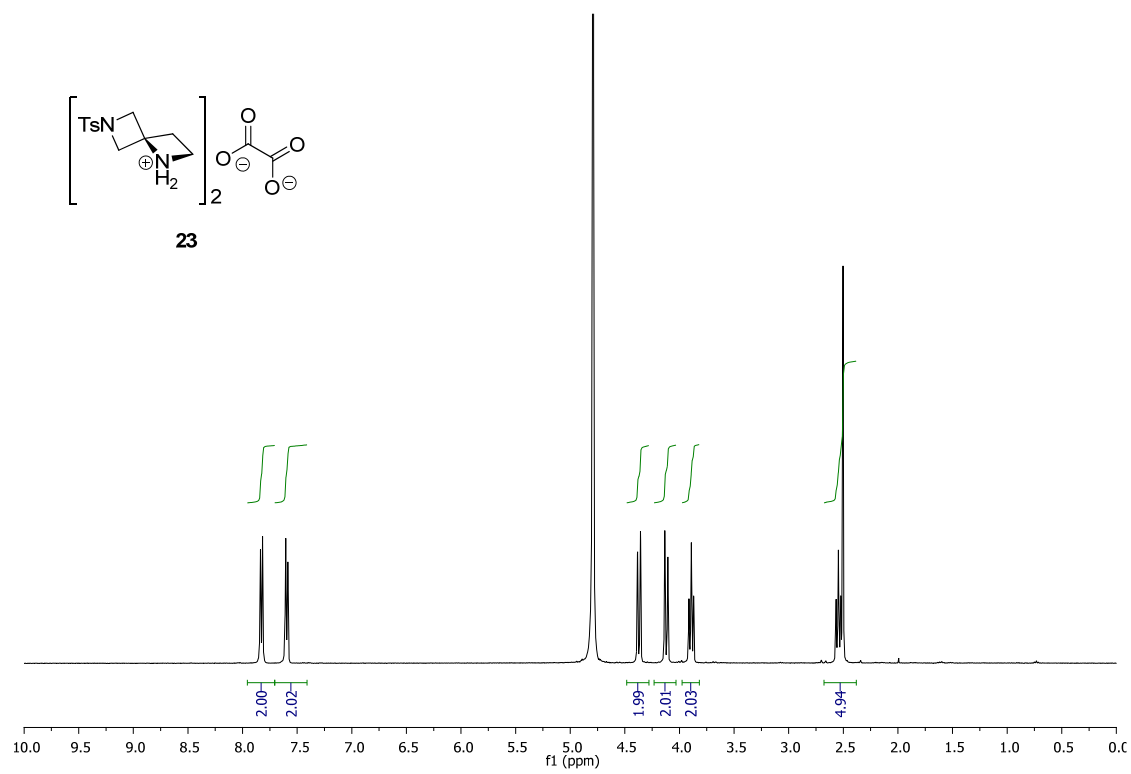












— 146.755

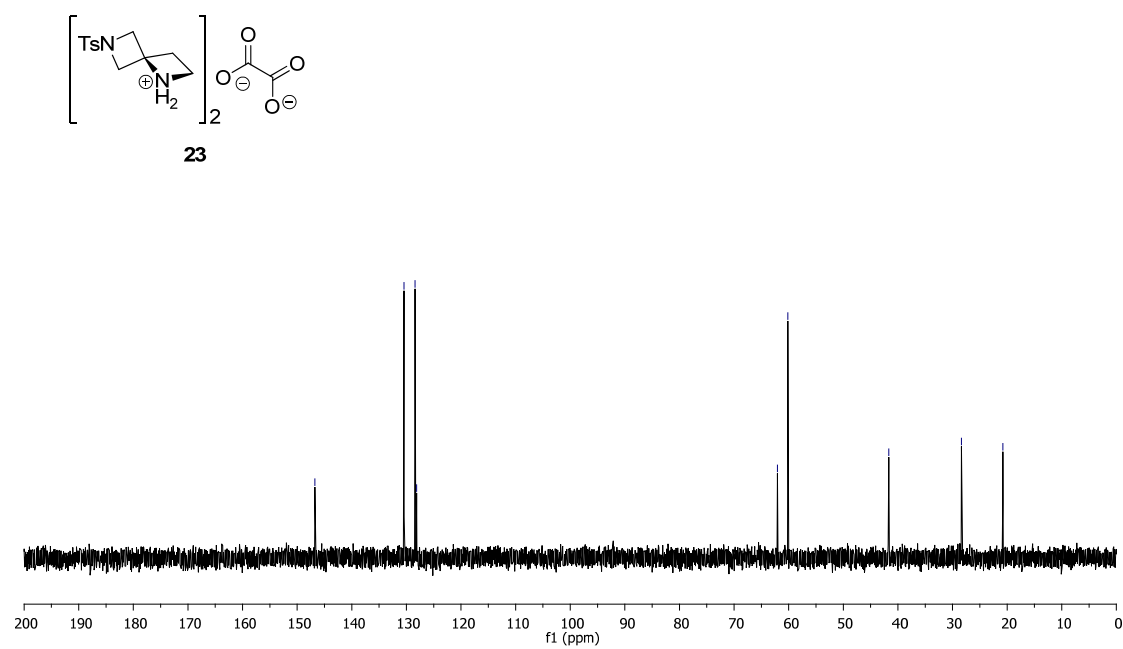
— 130.430  
— 128.433  
— 128.133

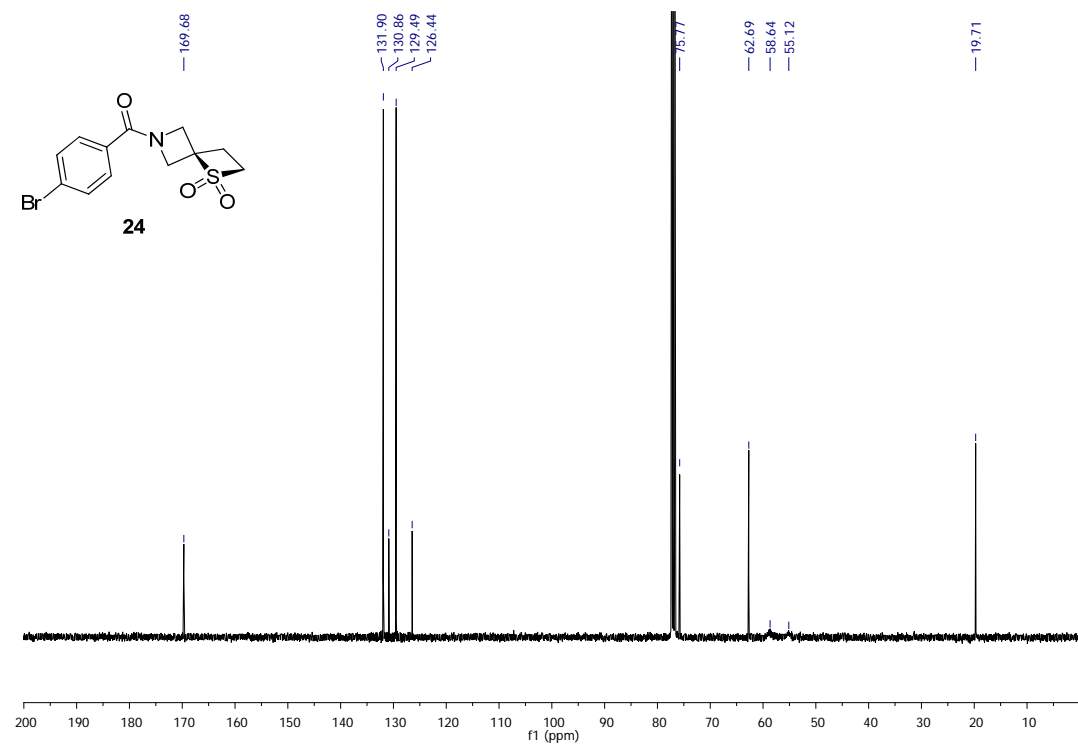
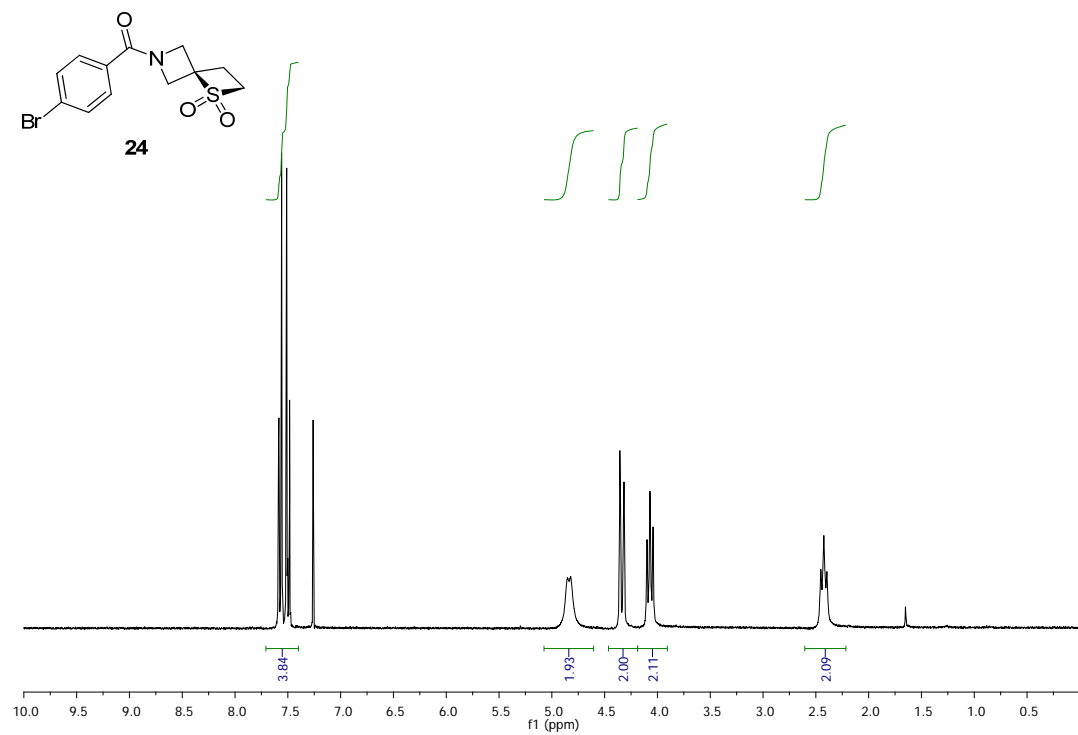
— 62.054  
— 60.165

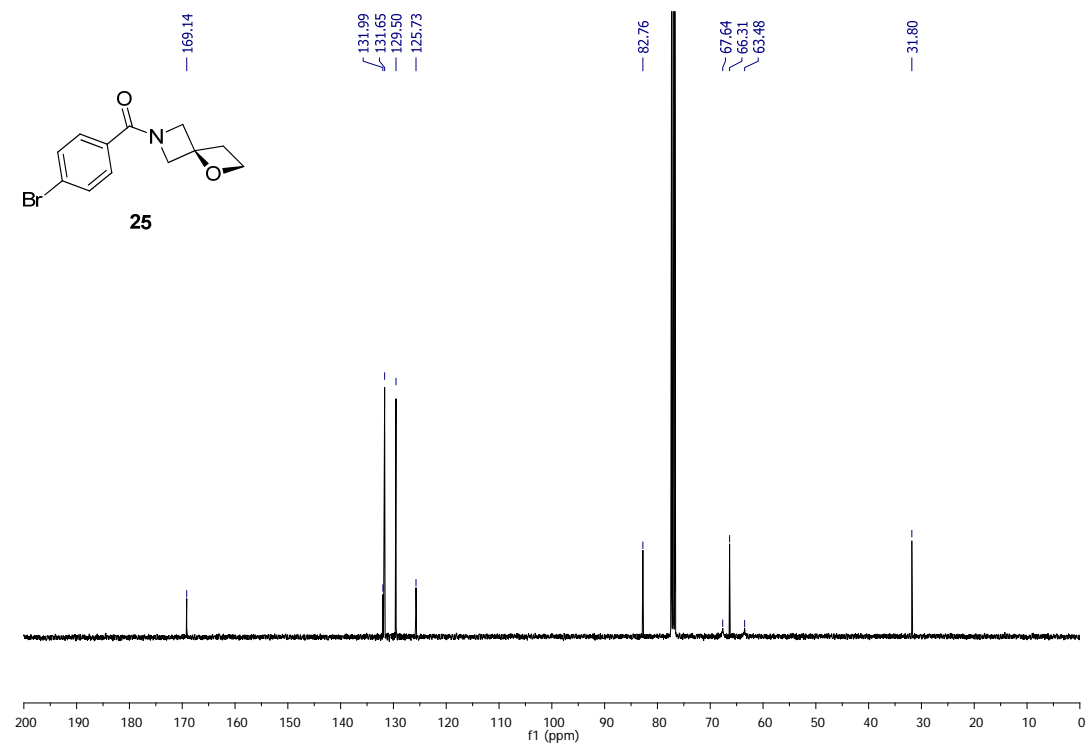
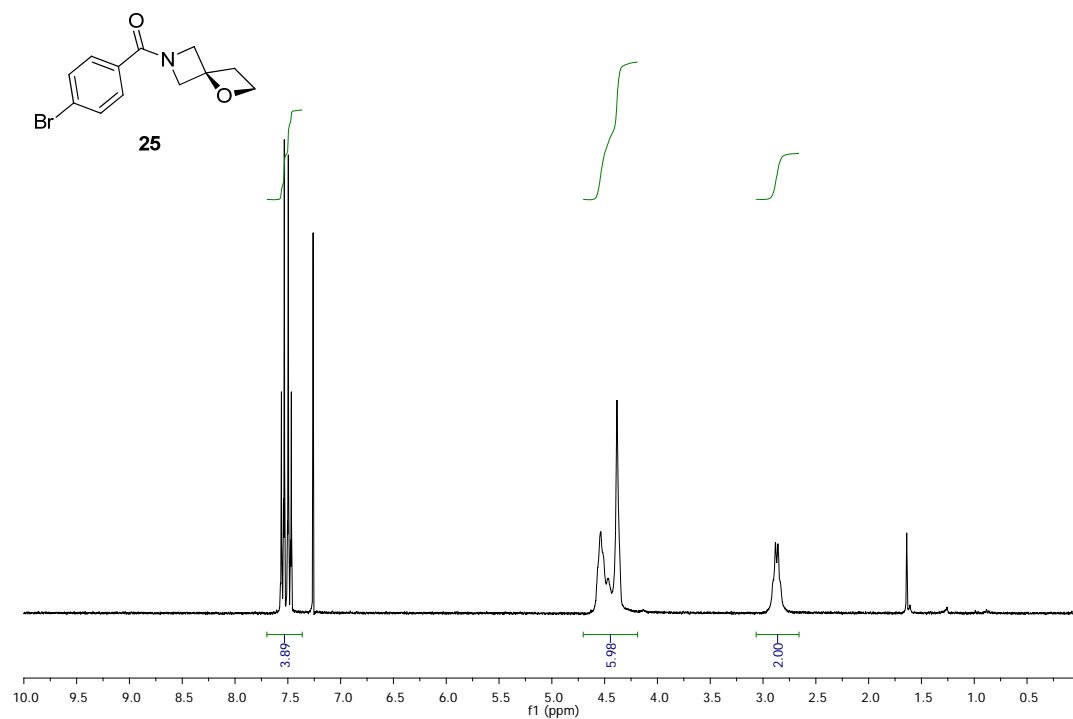
— 41.668

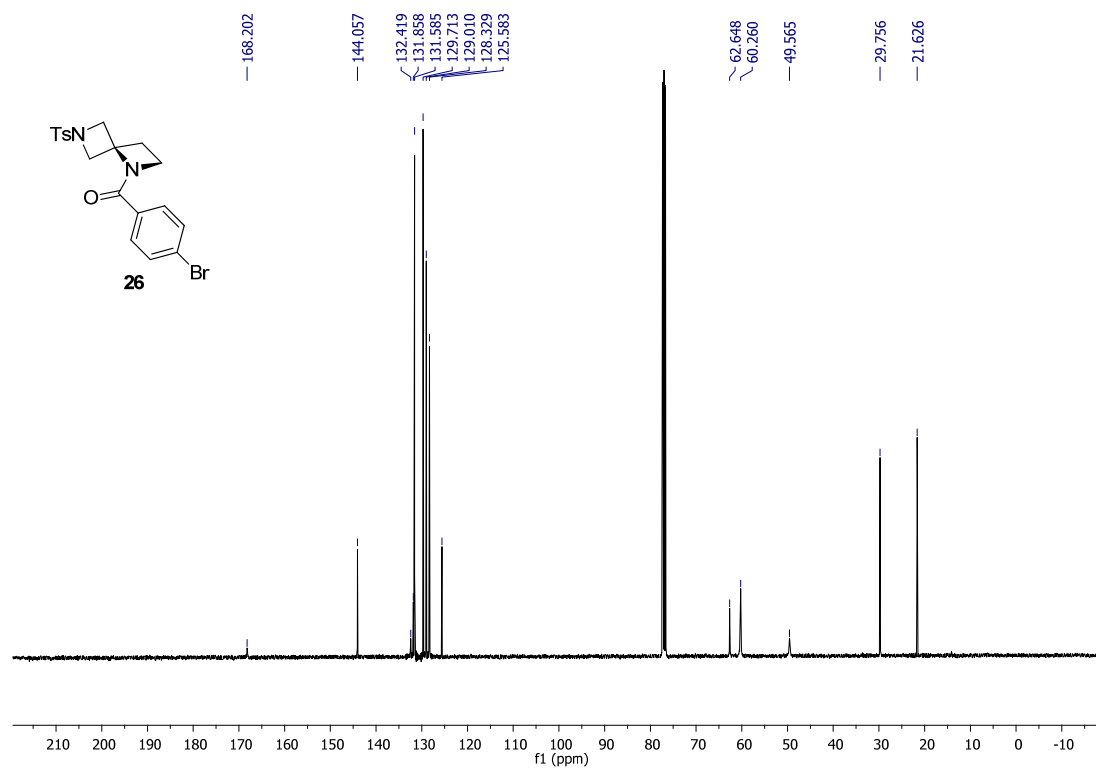
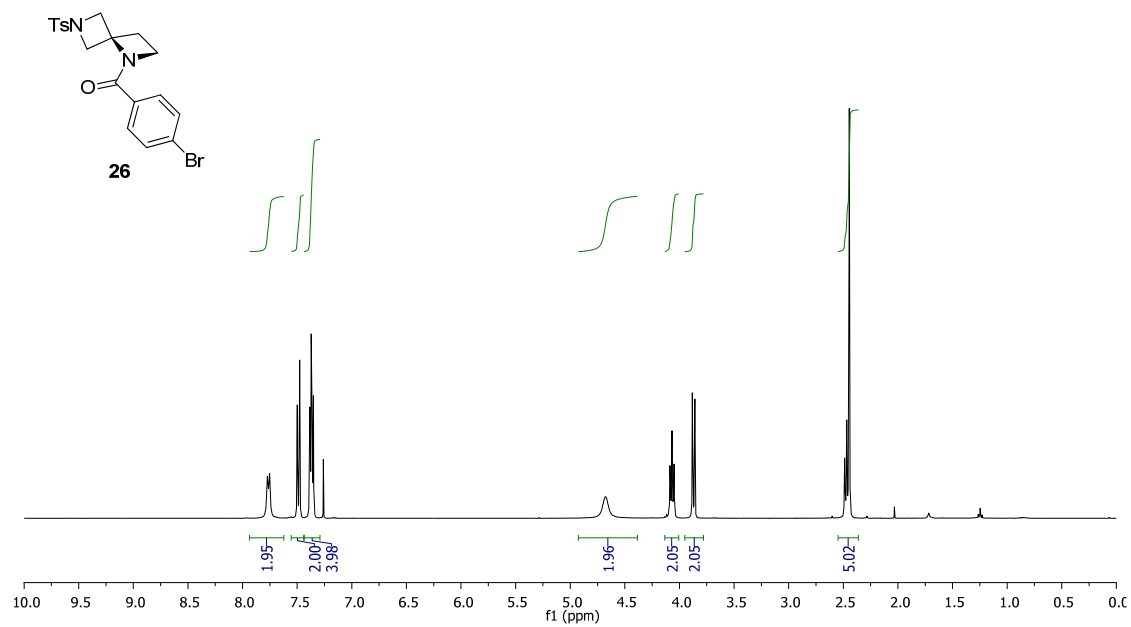
— 28.368

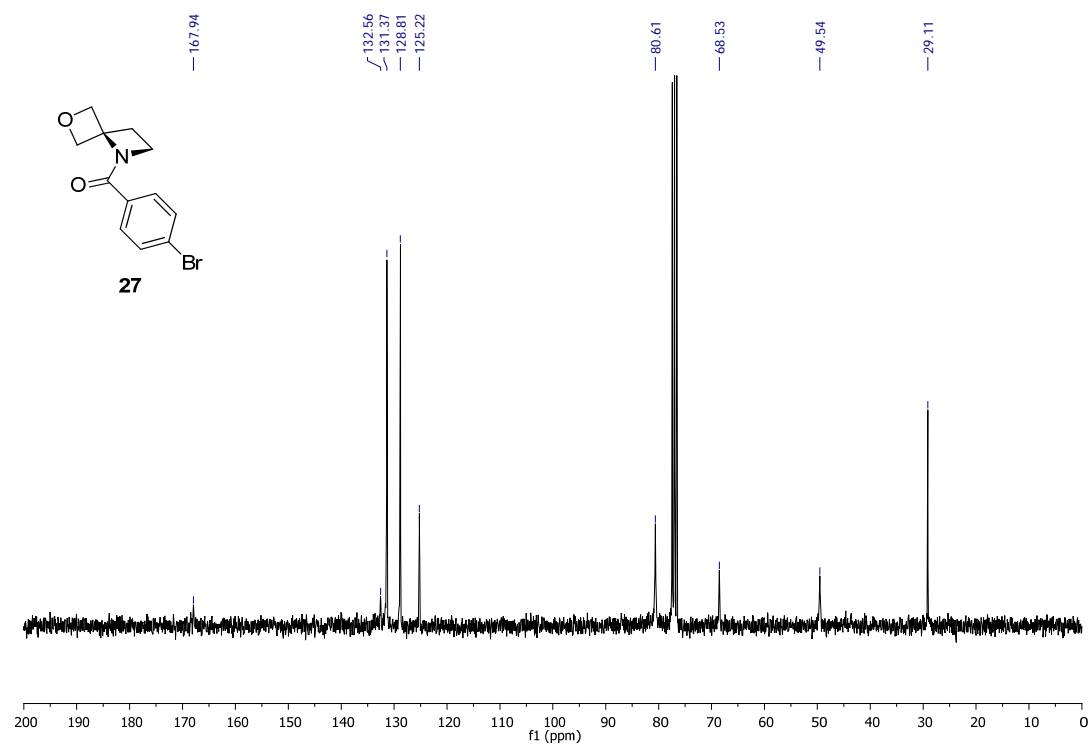
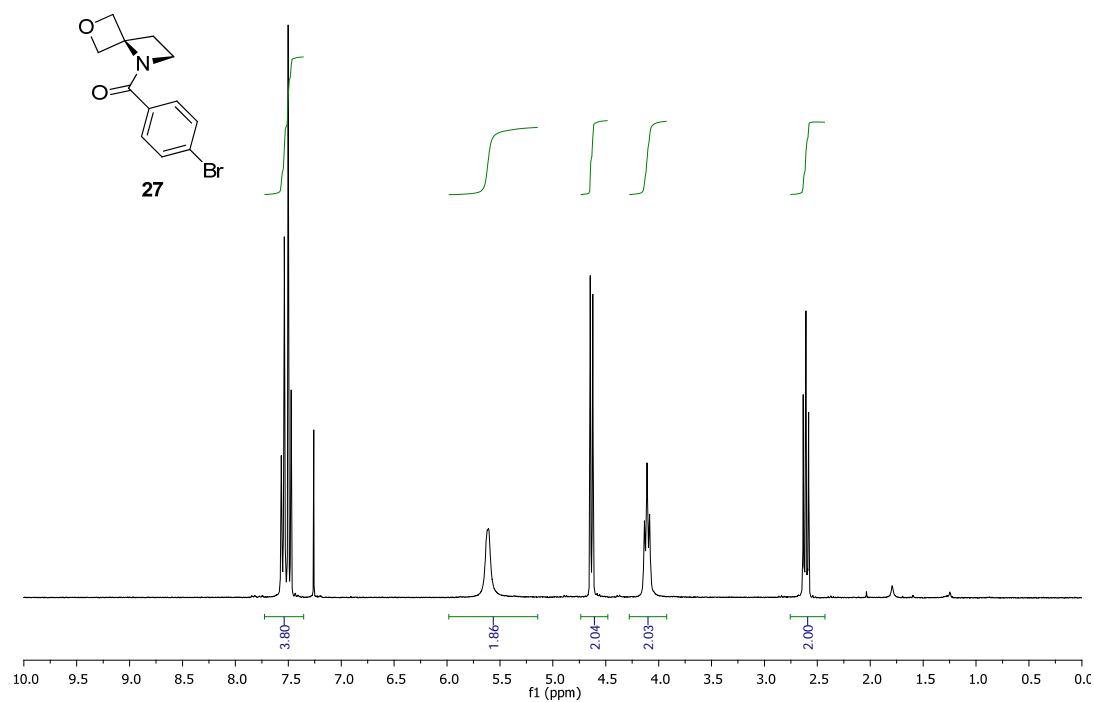
— 20.786





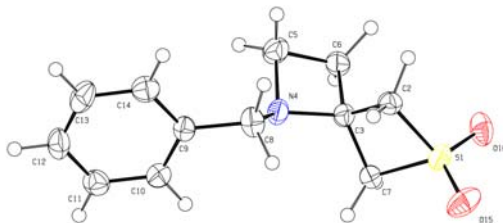






## CRYSTALLOGRAPHIC DATA

### Crystallographic data of compound **17**



#### Crystal data

$C_{12}H_{15}NO_2S$   
 $C_{12}H_{15}NO_2S$   
 $M_r = 237.321$   
 Monoclinic  $P2_1/c$   
 $a = 11.3919 (2) \text{ \AA}$   
 $b = 28.3759 (6) \text{ \AA}$   
 $c = 18.3852 (5) \text{ \AA}$   
 $\alpha = 90.00^\circ$   
 $\beta = 95.9248 (14)^\circ$   
 $\gamma = 90.00^\circ$   
 $V = 5911.4 (2) \text{ \AA}^3$   
 $Z = 20$   
 $F(000) = 2520.0$

$D_x = 1.333 \text{ Mg m}^{-3}$   
 Density measured by: not measured  
 fine-focus sealed tube  
 Mo  $K\alpha$  radiation  $\lambda = 0.71073$   
 Cell parameters from 68275 refl.  
 $\theta = 2.425\text{--}27.485^\circ$   
 $\mu = 0.258 \text{ mm}^{-1}$   
 $T = 173 \text{ K}$   
 Cube  
 $0.27 \times 0.24 \times 0.18 \text{ mm}$   
 Colourless  
 Crystal source: LOC ETH Zurich

#### Data collection

KappaCCD CCD diffractometer  
 Absorption correction: none  
 29576 measured reflections  
 12319 independent reflections  
 6313 observed reflections  
 Criterion:  $>2\sigma(I)$

$R_{\text{int}} = 0.077$   
 $\theta_{\text{max}} = 27.48^\circ$   
 $h = -14 \rightarrow 14$   
 $k = -23 \rightarrow 36$   
 $l = -23 \rightarrow 23$

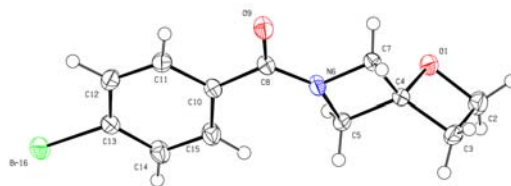
#### Refinement

Refinement on  $F^2$   
 fullmatrix least squares refinement  
 $R(\text{all}) = 0.1633$   
 $R(\text{gt}) = 0.0725$   
 $wR(\text{ref}) = 0.2140$   
 $wR(\text{gt}) = 0.1642$   
 $S(\text{ref}) = 1.017$   
 12319 reflections  
 796 parameters  
 0 restraints

Only H-atom  $U$ 's refined  
 Calculated weights  $1/[\sigma^2(I_o) + (I_o + I_c)^2/900]$   
 $\Delta/\sigma_{\text{max}} = 0.024$   
 $\Delta\rho_{\text{max}} = 0.575 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.440 \text{ e \AA}^{-3}$   
 Extinction correction: none  
 Atomic scattering factors from International Tables Vol  
 C Tables 4.2.6.8 and 6.1.1.4

Data collection: KappaCCD  
 Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)  
 Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)  
 Program(s) used to solve structure: *SIR97* (Altomare et al., *J. Appl. Cryst.*, 1999)  
 Program(s) used to refine structure: *SHELXL-97* (Sheldrick, 1997)

## Crystallographic data of compound **25**



### Crystal data

$C_{12}H_{12}BrNO_2$   
 $C_{12}H_{12}BrNO_2$   
 $M_r = 282.142$   
Triclinic  
P $\bar{1}$   
 $a = 8.02570 (10) \text{ \AA}$   
 $b = 11.3647 (2) \text{ \AA}$   
 $c = 12.6017 (2) \text{ \AA}$   
 $\alpha = 90.2638 (6)^\circ$   
 $\beta = 91.1398 (7)^\circ$   
 $\gamma = 106.7051 (7)^\circ$   
 $V = 1100.61 (3) \text{ \AA}^3$   
 $Z = 4$

$F(000) = 568.0$   
 $D_x = 1.703 \text{ Mg m}^{-3}$   
Density measured by: not measured  
fine-focus sealed tube  
Mo  $K\alpha$  radiation  $\lambda = 0.71073$   
Cell parameters from 12925 refl.  
 $\theta = 2.425\text{--}27.485^\circ$   
 $\mu = 3.718 \text{ mm}^{-1}$   
 $T = 123 \text{ K}$   
Cube  
 $0.27 \times 0.195 \times 0.135 \text{ mm}$   
Colourless  
Crystal source: LOC ETH Zurich

### Data collection

KappaCCD CCD diffractometer  
Absorption correction: integration  
 $T_{\min} = 0.389$ ,  $T_{\max} = 0.631$   
19915 measured reflections  
5032 independent reflections  
4564 observed reflections  
Criterion:  $>2\sigma(I)$

$R_{\text{int}} = 0.059$   
 $\theta_{\max} = 27.47^\circ$   
 $h = -10 \rightarrow 10$   
 $k = -14 \rightarrow 14$   
 $l = -16 \rightarrow 16$

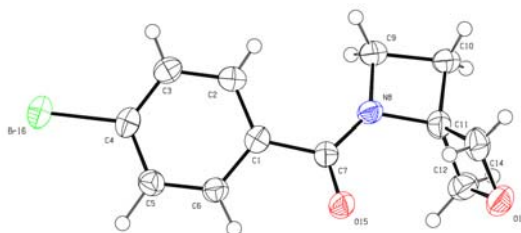
### Refinement

Refinement on  $F^2$   
fullmatrix least squares refinement  
 $R(\text{all}) = 0.0348$   
 $R(\text{gt}) = 0.0305$   
 $wR(\text{ref}) = 0.1061$   
 $wR(\text{gt}) = 0.0994$   
 $S(\text{ref}) = 0.873$   
5032 reflections  
385 parameters  
0 restraints

All H-atom parameters refined  
Calculated weights  $1/[\sigma^2(I_o) + (I_o + I_c)^2/900]$   
 $\Delta/\sigma_{\max} = 0.001$   
 $\Delta\rho_{\max} = 0.948 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\min} = -0.843 \text{ e \AA}^{-3}$   
Extinction correction: none  
Atomic scattering factors from International Tables Vol  
C Tables 4.2.6.8 and 6.1.1.4

Data collection: KappaCCD  
Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)  
Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)  
Program(s) used to solve structure: *SIR97* (Altomare et al., *J. Appl. Cryst.*, 1999)  
Program(s) used to refine structure: *SHELXL-97* (Sheldrick, 1997)

## Crystallographic data of compound **27**



### Crystal data

$C_{12}H_{12}BrNO_2$   
 $C_{12}H_{12}BrNO_2$   
 $M_r = 282.142$   
Orthorhombic  
Pbca  
 $a = 9.9717(3) \text{ \AA}$   
 $b = 8.8126(3) \text{ \AA}$   
 $c = 25.5594(11) \text{ \AA}$   
 $\alpha = 90.00^\circ$   
 $\beta = 90.00^\circ$   
 $\gamma = 90.00^\circ$   
 $V = 2246.07(14) \text{ \AA}^3$   
 $Z = 8$

$F(000) = 1136.0$   
 $D_x = 1.669 \text{ Mg m}^{-3}$   
Density measured by: not measured  
fine-focus sealed tube  
Mo  $K\alpha$  radiation  $\lambda = 0.71073$   
Cell parameters from 20614 refl.  
 $\theta = 2.425\text{--}27.485^\circ$   
 $\mu = 3.644 \text{ mm}^{-1}$   
 $T = 173 \text{ K}$   
plate  
 $0.3 \times 0.15 \times 0.009 \text{ mm}$   
Colourless  
Crystal source: LOC ETH Zurich

### Data collection

KappaCCD CCD diffractometer  
Absorption correction: integration  
 $T_{\min} = 0.451$ ,  $T_{\max} = 0.936$   
12140 measured reflections  
2565 independent reflections  
1701 observed reflections  
Criterion:  $>2\sigma(I)$

$R_{\text{int}} = 0.093$   
 $\theta_{\max} = 27.49^\circ$   
 $h = -12 \rightarrow 11$   
 $k = -11 \rightarrow 9$   
 $l = -33 \rightarrow 31$

### Refinement

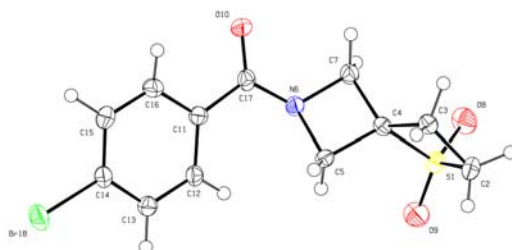
Refinement on  $F^2$   
fullmatrix least squares refinement  
 $R(\text{all}) = 0.0853$   
 $R(\text{gt}) = 0.0467$   
 $wR(\text{ref}) = 0.1472$   
 $wR(\text{gt}) = 0.1216$   
 $S(\text{ref}) = 0.886$   
2565 reflections  
193 parameters  
0 restraints

All H-atom parameters refined  
Calculated weights  $1/[\sigma^2(I_o) + (I_o + I_c)^2/900]$   
 $\Delta/\sigma_{\max} = 0.008$   
 $\Delta\rho_{\max} = 0.384 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\min} = -0.676 \text{ e \AA}^{-3}$   
Extinction correction: none  
Atomic scattering factors from International Tables Vol  
C Tables 4.2.6.8 and 6.1.1.4

Data collection: KappaCCD  
Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)  
Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)  
Program(s) used to solve structure: *SIR97* (Altomare et al., *J. Appl. Cryst.*, 1999)  
Program(s) used to refine structure: *SHELXL-97* (Sheldrick, 1997)



## Crystallographic data of compound **24**



### Crystal data

$C_{12}H_{12}BrNO_3S$   
 $C_{12}H_{12}BrNO_3S$   
 $M_r = 330.205$   
Orthorhombic  
 $Pna2_1$   
 $a = 20.7240 (8) \text{ \AA}$   
 $b = 5.8436 (2) \text{ \AA}$   
 $c = 10.4288 (4) \text{ \AA}$   
 $\alpha = 90.00^\circ$   
 $\beta = 90.00^\circ$   
 $\gamma = 90.00^\circ$   
 $V = 1262.96 (8) \text{ \AA}^3$   
 $Z = 4$

$F(000) = 664.0$   
 $D_x = 1.737 \text{ Mg m}^{-3}$   
Density measured by: not measured  
fine-focus sealed tube  
Mo  $K\alpha$  radiation  $\lambda = 0.71073$   
Cell parameters from 5158 refl.  
 $\theta = 2.425\text{--}27.485^\circ$   
 $\mu = 3.419 \text{ mm}^{-1}$   
 $T = 173 \text{ K}$   
plate  
 $0.33 \times 0.255 \times 0.021 \text{ mm}$   
Colourless  
Crystal source: LOC ETH Zurich

### Data collection

KappaCCD CCD diffractometer  
Absorption correction: integration  
 $T_{\min} = 0.457$ ,  $T_{\max} = 0.911$   
4954 measured reflections  
2143 independent reflections  
2044 observed reflections  
Criterion:  $>2\sigma(I)$

$R_{\text{int}} = 0.086$   
 $\theta_{\max} = 27.54^\circ$   
 $h = -26 \rightarrow 20$   
 $k = -7 \rightarrow 5$   
 $l = -11 \rightarrow 13$

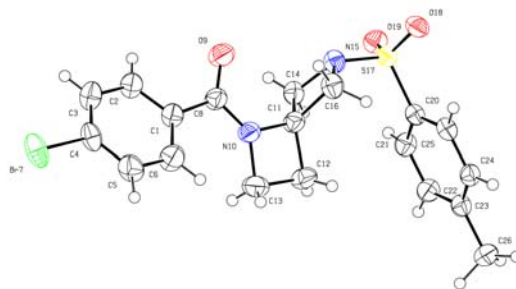
### Refinement

Refinement on  $F^2$   
fullmatrix least squares refinement  
 $R(\text{all}) = 0.0333$   
 $R(\text{gt}) = 0.0313$   
 $wR(\text{ref}) = 0.0952$   
 $wR(\text{gt}) = 0.0917$   
 $S(\text{ref}) = 0.791$   
2143 reflections  
200 parameters  
1 restraints  
All H-atom parameters refined

Calculated weights  $1/[\sigma^2(I_o) + (I_o + I_c)^2/900]$   
 $\Delta/\sigma_{\max} = 0.000$   
 $\Delta\rho_{\max} = 0.293 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\min} = -0.727 \text{ e \AA}^{-3}$   
Extinction correction: none  
Atomic scattering factors from International Tables Vol  
C Tables 4.2.6.8 and 6.1.1.4  
Flack parameter =  $-0.003 (11)$   
Flack H D (1983), *Acta Cryst.* A39, 876-881

Data collection: KappaCCD  
Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)  
Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)  
Program(s) used to solve structure: *SIR97* (Altomare et al., *J. Appl. Cryst.*, 1999)  
Program(s) used to refine structure: *SHELXL-97* (Sheldrick, 1997)

### Crystallographic data of compound 26



### Crystal data

$\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{O}_3\text{S}$   
 $\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{O}_3\text{S}$   
 $M_r = 435.345$   
 Monoclinic  $P2_1/c$   
 $a = 16.3389 \text{ (5) \AA}$   
 $b = 17.2034 \text{ (6) \AA}$   
 $c = 6.7010 \text{ (2) \AA}$   
 $\alpha = 90.00^\circ$   
 $\beta = 100.420 \text{ (2) }^\circ$   
 $\gamma = 90.00^\circ$   
 $V = 1852.49 \text{ (10) \AA}^3$   
 $Z = 4$   
 $F(000) = 888.0$

$D_x = 1.561 \text{ Mg m}^{-3}$   
 Density measured by: not measured  
 fine-focus sealed tube  
 Mo  $K\alpha$  radiation  $\lambda = 0.71073$   
 Cell parameters from 14007 refl.  
 $\theta = 2.425\text{--}27.485^\circ$   
 $\mu = 2.353 \text{ mm}^{-1}$   
 $T = 173 \text{ K}$   
 needle  
 $0.27 \times 0.06 \times 0.009 \text{ mm}$   
 Colourless  
 Crystal source: LOC ETH Zurich

### Data collection

KappaCCD CCD diffractometer  
Absorption correction: integration  
 $T_{\min} = 0.689$ ,  $T_{\max} = 0.965$   
16779 measured reflections  
4227 independent reflections  
3117 observed reflections  
Criterion:  $>2\sigma(I)$

$$\begin{aligned} R_{\text{int}} &= 0.12 \\ \theta_{\text{max}} &= 27.46^\circ \\ h &= -21 \rightarrow 21 \\ k &= -17 \rightarrow 22 \\ l &= -8 \rightarrow 8 \end{aligned}$$

### Refinement

Refinement on  $F^2$   
 fullmatrix least squares refinement  
 R(all) = 0.0721  
 R(gt) = 0.0466  
 wR(ref) = 0.1546  
 wR(gt) = 0.1340  
 S(ref) = 0.977  
 4227 reflections  
 303 parameters  
 0 restraints

H position refinement mixed  
 Calculated weights  $1/[\sigma^2(I_o)+(I_o+I_c)^2/900]$   
 $\Delta/\sigma_{\max} = 0.001$   
 $\Delta\rho_{\max} = 0.482\text{e}\text{\AA}^3$   
 $\Delta\rho_{\min} = -0.866\text{e}\text{\AA}^3$   
 Extinction correction: none  
 Atomic scattering factors from International Tables Vol  
 C Tables 4.2.6.8 and 6.1.1.4

Data collection: KappaCCD  
Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)  
Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)  
Program(s) used to solve structure: *SIR97* (Altomare et al., *J. Appl. Cryst.*, 1999)  
Program(s) used to refine structure: *SHELXL-97* (Sheldrick, 1997)