

Supporting Information

Expanding the Azaspiro[3.3]heptane Family: Synthesis of Novel Highly Functionalized Building Blocks

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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_2Cl_2 , THF, Et_2O , CH_3CN , and toluene were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O 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 or Fluka 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.

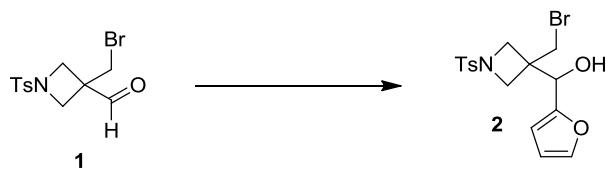
NMR spectra: NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for ^1H and ^{13}C acquisitions, respectively, or on Bruker DRX400 (or AV400) spectrometers operating at 400 MHz (^1H) and 101 MHz (^{13}C). Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) for ^1H , and to chloroform (δ 77.0) for ^{13}C . All ^{13}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^{-1}).

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.

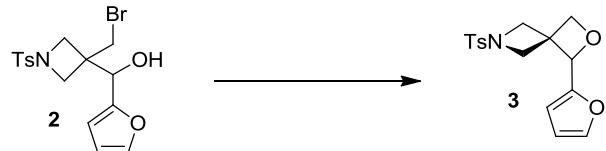
Chemical names: generated with ChemBioDraw Ultra 12.0 (*CambridgeSoft*) and modified where appropriate.

EXPERIMENTAL PROCEDURES



(3-(Bromomethyl)-1-tosylazetidin-3-yl)(furan-2-yl)methanol (2). To a solution of freshly distilled furan (0.27 ml, 3.63 mmol, 6.0 equiv) in THF (8 ml), cooled to -78°C , was added over 3 min BuLi (1.6 M in hexanes; 1.51 ml, 2.42 mmol, 4.0 equiv), and the resulting solution was allowed to warm to -10°C over 60 min, when it was cooled again to -78°C . At this point was added a solution of aldehyde **1**¹ (201 mg, 0.61 mmol, 1.0 equiv) in THF (1.5 ml; rinsed with 0.5 ml) over 5 min. The mixture was stirred at -78°C for 10 min, when it was quenched with H_2O (5 ml) and diluted with EtOAc (20 ml) and halfsaturated aqueous NaCl (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (25 ml). The combined organic phases were dried (MgSO_4), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO_2 ; hexanes : EtOAc 5:2). Yield: 215 mg (0.54 mmol, 89%). Colorless oil.

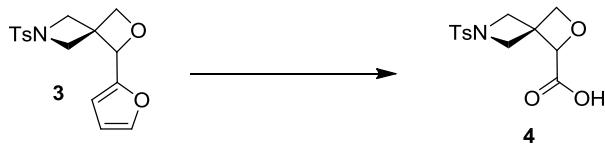
TLC: $R_f = 0.32$ (hexanes : EtOAc 2:1; UV, CAM); **¹H NMR** (300 MHz, CDCl_3): $\delta = 7.72$ (d, $J=8.1$, 2H), 7.35 (d, $J=8.1$, 2H), 7.31 – 7.28 (m, 1H), 6.35 – 6.21 (m, 2H), 4.85 (d, $J=4.6$, 1H), 4.02 (dd, $J=14.3$, 8.4, 2H), 3.64 (dd, $J=14.3$, 10.0, 2H), 3.53 (d, $J=8.4$, 1H), 3.14 (d, $J=10.0$, 1H), 2.45 (s, 3H), 2.02 (d, $J=4.6$, 1H); **¹³C NMR** (101 MHz, CDCl_3): $\delta = 152.2$, 144.0, 142.9, 131.7, 129.7, 128.4, 110.3, 109.0, 67.4, 54.9, 54.4, 42.1, 36.7, 21.6; **IR** (thin film): 3498, 2952, 2878, 1598, 1340, 1161, 1089, 914, 816, 744, 672, 550 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{16}\text{H}_{19}\text{BrNO}_4\text{S}$ ($[\text{M}+\text{H}]^+$), 400.0213; found 400.0210.



1-(Furan-2-yl)-6-tosyl-2-oxa-6-azaspiro[3.3]heptane (3). The bromoalcohol **2** (202 mg, 0.51 mmol, 1.0 equiv) was dissolved in MeOH (15 ml) and potassium carbonate (349 mg, 2.52 mmol, 5.0 equiv) was added, and the suspension was heated to 60°C and the resulting solution was stirred at that temperature for 5 h and subsequently was held at 50°C for 14 h. At this point the mixture was concentrated to approximately $1/5$ of the initial volume, after which it was partitioned between EtOAc (30 ml) and halfsaturated aqueous NaCl (15 ml). The phases were separated, and the organic phase was washed with saturated aqueous NaCl (10 ml), dried (MgSO_4), filtered, and concentrated *in vacuo*. The title compound was obtained in good purity (>95% by ¹H NMR) after purification by FC (SiO_2 ; hexanes : EtOAc 2:1). Yield: 98 mg (0.31 mmol, 61%).

TLC: $R_f = 0.21$ (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 132–133 $^{\circ}\text{C}$; **¹H NMR** (300 MHz, CDCl_3): $\delta = 7.63$ (d, $J=8.2$, 2H), 7.48 – 7.40 (m, 1H), 7.31 (d, $J=8.2$, 2H), 6.34 (dd, $J=3.3$, 1.8, 1H), 6.26 – 6.20 (m, 1H), 5.31 (s, 1H), 4.71 (d, $J=6.9$, 1H), 4.57 (d, $J=6.9$, 1H), 3.97 (q, $J=9.1$, 2H), 3.81 (d, $J=9.5$, 1H), 3.60 (d, $J=9.5$, 1H), 2.44 (s, 3H); **¹³C NMR** (101 MHz, CDCl_3): $\delta = 150.8$, 144.1, 143.8, 130.9, 129.6, 128.1, 110.4, 110.3, 82.2, 78.4, 59.2, 57.4, 42.0, 21.7; **IR** (thin film): 2939, 2882, 1335, 1162, 1044, 964, 813, 749, 709, 675 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{16}\text{H}_{18}\text{NO}_4\text{S}$ ($[\text{M}+\text{H}]^+$), 320.0951; found 320.0961.

(1) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524–3527.



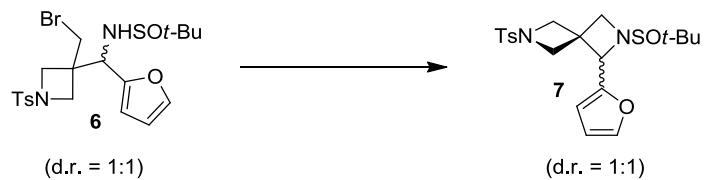
6-Tosyl-2-oxa-6-azaspiro[3.3]heptane-1-carboxylic acid (4). To a mixture of furan **3** (35 mg, 0.11 mmol, 1.0 equiv) and sodium periodate (234 mg, 1.10 mmol, 10.0 equiv) in CCl_4 (0.8 ml)/ CH_3CN (0.8 ml)/ H_2O (1.0 ml) was added at RT $\text{RuCl}_3\cdot\text{H}_2\text{O}$ (1.2 mg, 5.5 μmol , 0.05 equiv), and the now dark brown mixture was vigorously stirred at RT for 40 min. Then it was diluted with EtOAc (10 ml) and filtered over celite (thoroughly washed with EtOAc). Then was added H_2O (10 ml) and HCl (1 M in H_2O ; 5 ml), and the phases were separated. The aqueous layer was extracted with EtOAc (15 ml), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO_2 ; CH_2Cl_2 : MeOH : AcOH 95:4:1) to afford the pure title compound. Yield: 22 mg (0.07 mmol, 68%). Colorless amorphous solid.

TLC: R_f = 0.24 (CH_2Cl_2 : MeOH : AcOH 95:4:1; UV, CAM); **$^1\text{H NMR}$** (300 MHz, CDCl_3 : CD_3OD 7:2): δ = 7.59 (d, J =8.0, 2H), 7.29 (d, J =8.0, 2H), 4.82 (s, 1H), 4.50 (s, 2H), 4.00 – 3.51 (m, 4H), 2.36 (s, 3H); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3 : CD_3OD 7:2): δ = 170.8, 144.6, 130.6, 129.7, 128.1, 83.9, 79.1, 59.1, 56.7, 39.6, 21.3; **IR** (neat): 3498, 2955, 2924, 2885, 1719, 1615, 1598, 1338, 1156, 1090, 957, 814, 678 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{13}\text{H}_{16}\text{NO}_5\text{S}$ ($[\text{M}+\text{H}]^+$), 298.0744; found 298.0752.



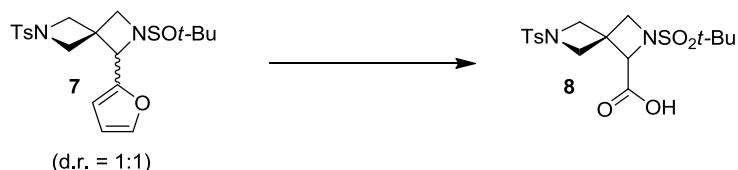
(R)-*N*-(3-(Bromomethyl)-1-tosylazetidin-3-yl)(furan-2-yl)methyl-2-methylpropane-2-sulfinamide (6). To a solution of freshly distilled furan (0.30 ml, 4.13 mmol, 6.0 equiv) in THF (5 ml), cooled to -78 °C, was added over 5 min BuLi (1.6 M in hexanes; 1.72 ml, 2.76 mmol, 4.0 equiv), and the resulting solution was allowed to warm to -50 °C over 60 min, when it was cooled again to -78 °C. At this point was added a solution of imine **5** (300 mg, 0.69 mmol, 1.0 equiv) in THF (2.5 ml; rinsed with 0.3 ml) over 5 min. The mixture was stirred at -78 °C for 15 min, when it was quenched with saturated aqueous NH_4Cl (3 ml) and diluted with EtOAc (25 ml) and water (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (MgSO_4), filtered, and concentrated *in vacuo*. **$^1\text{H NMR}$** analysis of the residue revealed an almost pure mixture of diastereomeric addition products (d.r. ~1:1). Yield: 348 mg (0.69 mmol, quantitative). This material was used for the next step without further purifications.

TLC: R_f = 0.37 (hexanes : EtOAc 1:2; UV, CAM) and 0.31 (hexanes : EtOAc 1:2; UV, CAM).



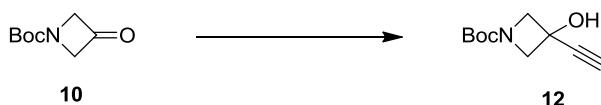
(R)-2-(*tert*-Butylsulfinyl)-1-(furan-2-yl)-6-tosyl-2,6-diazaspiro[3.3]heptane (7). To a solution of unpurified sulfinamide **6** (348 mg, 0.69 mmol, 1.0 equiv) in THF (15 ml), cooled to 0 °C, was added in one portion KO*t*-Bu (171 mg, 1.52 mmol, 2.2 equiv). The now brown solution was stirred at 0 °C for 30 min, when it was quenched by the addition of saturated aqueous NH₄Cl (5 ml). The mixture was diluted with EtOAc (40 ml) and H₂O (20 ml), and the phases were separated. The aqueous phase was extracted with EtOAc (20 ml), and the combined organic phases were dried (MgSO₄), filtered, and concentrated *in vacuo* to afford the crude product as a brownish solid. The title compound (as a mixture of diastereomers) was obtained after purification by FC (SiO₂; hexanes : EtOAc 2:3 → 1:2 gradient). Yield: 179 mg (0.42 mmol, 61% over 2 steps). Colorless solid.

TLC: R_f = 0.35 (hexanes : EtOAc 1:1; UV, CAM) and 0.29 (hexanes : EtOAc 1:1; UV, CAM).



2-(*tert*-Butylsulfonyl)-6-tosyl-2,6-diazaspiro[3.3]heptane-1-carboxylic acid (8). RuCl₃·H₂O (1.0 mg, 3.0 µmol, 0.05 equiv) was added to a mixture of NaIO₄ (0.17 g, 0.78 mmol, 15.0 equiv), CH₂Cl₂ (1 ml), CH₃CN (0.04 ml), and H₂O (0.7 ml). The now brownish mixture was stirred at RT for 1 h. At this point was added more H₂O (0.7 ml) and then in one portion a solution of furan **7** (mixture of diastereomers; 22 mg, 0.05 mmol, 1.0 equiv) in CH₂Cl₂ (1 ml). The now dark brown to black mixture was vigorously stirred at RT for 12 h. Then it was diluted with CH₂Cl₂ (5 ml), acidified to pH ~1 with NaHSO₄ (1 M in H₂O), and the mixture was filtered over celite (rinsed with CH₂Cl₂). The phases were then separated, and the organic phase was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to afford the title compound in good purity. Yield: 18 mg (0.04 mmol, 83%). An analytically pure sample can be obtained after purification by FC (SiO₂; CH₂Cl₂ : MeOH : AcOH 100:1:1). Colorless solid.

TLC: R_f = ~0.35 (CH₂Cl₂ : MeOH 9:1; UV, CAM); **Melting Point:** 197-199 °C (decomp.); **¹H NMR** (400 MHz, CDCl₃ : CD₃OD 6:1): δ = 7.59 (d, *J*=8.2, 2H), 7.29 (d, *J*=8.2, 2H), 4.60 (s, 1H), 4.08 (d, *J*=8.5, 1H), 3.91 – 3.59 (m, 4H), 3.53 (d, *J*=8.5, 1H), 2.36 (s, 3H), 1.25 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃ : CD₃OD 6:1): δ = 169.0, 144.7, 130.4, 129.8, 128.1, 66.3, 60.1, 59.8, 59.1, 57.5, 34.0, 23.4, 21.3; **IR** (neat): 3340, 3265, 2928, 1756, 1330, 1311, 1150, 1124, 1087, 1030, 812, 674 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₇H₂₅N₂O₆S₂ ([M+H]⁺), 417.1149; found 417.1151.

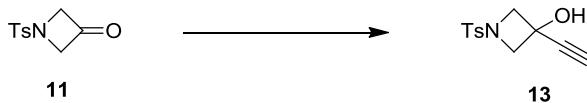


***tert*-Butyl 3-ethynyl-3-hydroxyazetidine-1-carboxylate (12).** To a solution of ethynyltrimethylsilane (0.24 ml, 1.74 mmol, 1.5 equiv) in THF (13 ml) was added at -78 °C BuLi (1.6 M in hexanes; 1.05 ml, 1.68 mmol, 1.45 equiv), and the mixture was stirred at -78 °C for 15 min, when a solution of *tert*-butyl 3-oxoazetidine-1-

carboxylate (199 mg, 1.16 mmol, 1.0 equiv) in THF (2 ml; rinsed with 0.3 ml) was added over 2 min. The reaction mixture was stirred at -78°C for 15 min, when it was allowed to warm to -20°C over 60 min. At this point it was quenched with halfsaturated aqueous NaCl (15 ml) and diluted with EtOAc (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (MgSO_4), filtered, and concentrated *in vacuo*. The residue was directly used for the next step.

To a solution of *tert*-butyl 3-hydroxy-3-((trimethylsilyl)ethynyl)azetidine-1-carboxylate (313 mg, 1.16 mmol, 1.0 equiv) in THF (13 ml) was added at 0°C TBAF (1 M in THF; 1.39 ml, 1.39 mmol, 1.2 equiv), and the mixture was stirred at 0°C for 15 min. At this point was added halfsaturated aqueous NH_4Cl (15 ml) followed by EtOAc (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (MgSO_4), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO_2 ; hexanes : EtOAc 3:1) to afford the pure title compound. Yield: 213 mg (1.08 mmol, 93% over 2 steps). Colorless oil.

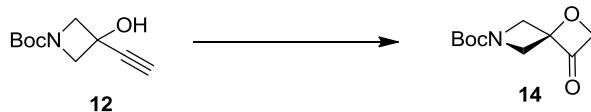
TLC: $R_f = 0.61$ (hexanes : EtOAc 1:1; CAM, ninhydrin); **¹H NMR** (300 MHz, CDCl_3): $\delta = 4.19$ (d, $J=9.1$, 2H), 4.02 (d, $J=9.1$, 2H), 3.63 (br s, 1H), 2.67 (s, 1H), 1.44 (s, 9H); **¹³C NMR** (101 MHz, CDCl_3): $\delta = 156.2$, 83.8, 80.2, 74.1, 63.9, 61.9, 28.3; **IR** (neat): 3294, 2979, 1672, 1418, 1367, 1156, 1080, 646 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{10}\text{H}_{15}\text{NNaO}_3$ ($[\text{M}+\text{Na}]^+$), 220.0944; found 220.0946.



3-Ethynyl-1-tosylazetidin-3-ol (13). To a solution of ethynyltrimethylsilane (0.092 ml, 0.666 mmol, 1.5 equiv) in THF (5 ml) was added at -78°C BuLi (1.6 M in hexanes; 0.40 ml, 0.64 mmol, 1.45 equiv), and the mixture was stirred at -78°C for 15 min, when a solution of ketone **11** (100 mg, 0.44 mmol, 1.0 equiv) in THF (2 ml; rinsed with 0.3 ml) was added over 2 min. The mixture was stirred at -78°C for 15 min, then it was allowed to warm to -20°C over 60 min. At this point it was quenched with halfsaturated aqueous NaCl (15 ml) and diluted with EtOAc (20 ml). The phases were separated and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (MgSO_4), filtered, and concentrated *in vacuo*. The residue did not require any further purification and was used as such for the next step.

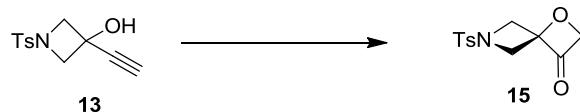
To a solution of this material (138 mg, 0.43 mmol, 1.0 equiv) in THF (5 ml) was added at 0°C TBAF (1 M in THF; 0.51 ml, 0.51 mmol, 1.2 equiv), and the mixture was stirred at 0°C for 15 min. At this point was added halfsaturated aqueous NH_4Cl (15 ml) followed by EtOAc (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (MgSO_4), filtered, and concentrated *in vacuo*. The pure product was obtained after purification by FC (SiO_2 ; hexanes : EtOAc 2:1). Yield: 83 mg (0.33 mmol, 74% over 2 steps). Colorless solid.

TLC: $R_f = 0.15$ (hexanes : EtOAc 2:1; CAM); **¹H NMR** (300 MHz, CDCl_3): $\delta = 7.73$ (d, $J=8.1$, 2H), 7.37 (d, $J=8.1$, 2H), 4.07 (dd, $J=8.0$, 1.3, 2H), 3.83 (dd, $J=8.0$, 1.3, 2H), 2.61 (s, 1H), 2.58 (s, 1H), 2.46 (s, 3H); **¹³C NMR** (101 MHz, CDCl_3): $\delta = 144.4$, 131.4, 129.8, 128.4, 82.6, 74.7, 64.6, 61.2, 21.6; **IR** (thin film): 3461, 3334, 1597, 1445, 1301, 1293, 1160, 1090, 914 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{12}\text{H}_{14}\text{NO}_3\text{S}$ ($[\text{M}+\text{H}]^+$), 252.0689; found 252.0690.



tert-Butyl 3-oxo-1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (14). To a solution of *tert*-butyl 3-ethynyl-3-hydroxyazetidine-1-carboxylate (**12**) (81 mg, 0.41 mmol, 1.0 equiv), 8-ethylquinoline 1-oxide² (142 mg, 0.82 mmol, 2.0 equiv), and [BrettPhosAuNTf₂]³ (20.8 mg, 0.021 mmol, 0.05 equiv) in DCE (10 ml) was added at RT methanesulfonic acid (0.04 ml, 0.62 mmol), and the mixture was stirred at RT for 3 h. At this point the mixture was partitioned between CH₂Cl₂ (30 ml) and HCl (1 M in H₂O; 10 ml). The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (20 ml). The combined organic phases were washed with saturated aqueous NaCl (15 ml), dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO₂; hexanes : EtOAc 2:1) to afford the pure title compound. Yield: 46 mg (0.22 mmol, 53%). Slightly yellowish oil.

TLC: R_f = 0.21 (hexanes : EtOAc 2:1; CAM, ninhydrin); **¹H NMR** (300 MHz, CDCl₃): δ = 5.28 (s, 2H), 4.35 (dd, J =10.6, 1.5, 2H), 4.24 (dd, J =10.6, 1.5, 2H), 1.44 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ = 199.3, 155.7, 99.9, 89.2, 80.4, 58.9, 28.3; **IR** (thin film): 2974, 2937, 1826, 1705, 1393, 1369, 1243, 1169, 950, 913, 745 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₀H₁₅NNaO₄ ([M+Na]⁺), 236.0893; found 236.0889.

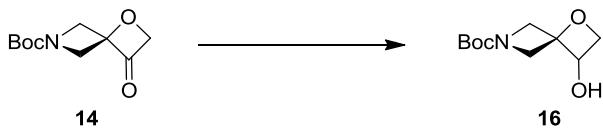


6-Tosyl-1-oxa-6-azaspiro[3.3]heptan-3-one (15). To a solution of 3-ethynyl-1-tosylazetidin-3-ol (102 mg, 0.406 mmol, 1.0 equiv), 8-ethylquinoline 1-oxide² (141 mg, 0.812 mmol, 2.0 equiv), and [BrettPhosAuNTf₂]³ (33 mg, 0.03 mmol, 0.08 equiv) in DCE (13 ml) was added at RT methanesulfonic acid (0.040 ml, 0.609 mmol, 1.5 equiv), and the flask was immersed into an oil bath preheated to 40 °C. Heating was continued for 3 h. At this point the mixture was partitioned between CH₂Cl₂ (30 ml) and HCl (1 M in H₂O; 15 ml). The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (20 ml). The combined organic phases were dried (MgSO₄), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO₂; hexanes : EtOAc 3:2). Yield: 42 mg (0.16 mmol, 39%). Slightly yellowish oil that solidifies upon standing.

TLC: R_f = 0.27 (hexanes : EtOAc 1:1; CAM); **¹H NMR** (300 MHz, CDCl₃): δ = 7.72 (d, J =8.1, 2H), 7.39 (d, J =8.1, 2H), 5.21 (s, 2H), 4.20 (dd, J =9.2, 1.9, 2H), 4.07 (dd, J =9.2, 1.9, 2H), 2.48 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ = 197.7, 144.7, 131.3, 130.0, 128.4, 98.0, 89.4, 59.6, 21.6; **IR** (neat): 2925, 1827, 1597, 1342, 1158, 1090, 1038, 947, 679 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₂H₁₄NO₄S ([M+H]⁺), 268.0638; found 268.0628.

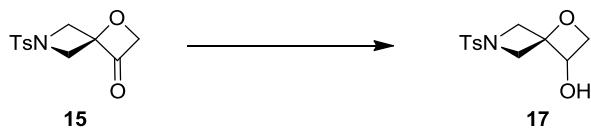
(2) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070-14072.

(3) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236-3239.



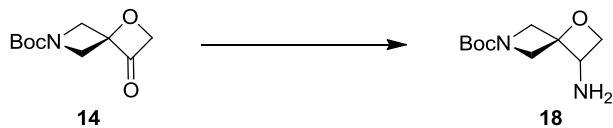
tert-Butyl 3-hydroxy-1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (16). To a solution of ketone **14** (10.5 mg, 0.049 mmol, 1.0 equiv) in MeOH (1 ml), cooled to 0 °C, was added sodium borohydride (3.6 mg, 0.09 mmol, 1.9 equiv) and the mixture was stirred at 0 °C for 20 min, when it was allowed to warm to RT and stirring was continued for another 20 min. At this point it was partitioned between EtOAc (20 ml) and H₂O (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (Na₂SO₄), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 10.5 mg (0.049 mmol, 99%). Colorless oil.

TLC: R_f = 0.23 (hexanes : EtOAc 1:1; CAM, ninhydrin); **¹H NMR** (300 MHz, CDCl₃): δ = 4.74 (dd, J =11.5, 5.7, 1H), 4.63 (t, J =6.7, 1H), 4.49 (d, J =11.5, 1H), 4.33 (dd, J =6.7, 5.7, 1H), 4.05 (q, J =10.6, 2H), 3.93 (d, J =10.6, 1H), 3.43 (br s, 1H), 1.43 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃): δ = 156.4, 87.5, 80.0, 76.1, 69.7, 61.2, 57.0, 28.3; **IR** (thin film): 3397, 2978, 2941, 2876, 1674, 1423, 1367, 1167, 1097, 957, 855 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₀H₁₈NO₄ ([M+H]⁺), 216.1230; found 216.1237.



6-Tosyl-1-oxa-6-azaspiro[3.3]heptan-3-ol (17). To a solution of ketone **15** (10.0 mg, 0.04 mmol, 1.0 equiv) in MeOH (1 ml), cooled to 0 °C, was added sodium borohydride (3.0 mg, 0.08 mmol, 2.0 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 another 60 min. At this point it was partitioned between EtOAc (20 ml) and H₂O (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (Na₂SO₄), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 10.0 mg (0.04 mmol, quantitative). Colorless oil.

TLC: R_f = 0.08 (hexanes : EtOAc 3:2; UV, CAM); **¹H NMR** (300 MHz, CDCl₃): δ = 7.73 (d, J =8.1, 2H), 7.38 (d, J =8.1, 2H), 4.76 (dd, J =12.1, 5.6, 1H), 4.54 (t, J =6.7, 1H), 4.47 (dt, J =9.6, 1.4, 1H), 4.24 (dd, J =6.7, 5.6, 1H), 4.03 (dt, J =9.6, 1.4, 1H), 3.77 (dd, J =9.6, 1.0, 1H), 3.61 (dd, J =9.6, 1.0, 1H), 3.05 (d, J =5.6, 1H), 2.46 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃): δ = 144.6, 130.7, 129.9, 128.5, 86.0, 75.9, 69.5, 62.3, 58.3, 21.6; **IR** (thin film): 3480, 2966, 2881, 1597, 1342, 1160, 1092, 959, 817, 709, 675, 552 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₂H₁₆NO₄S ([M+H]⁺), 270.0795; found 270.0794.

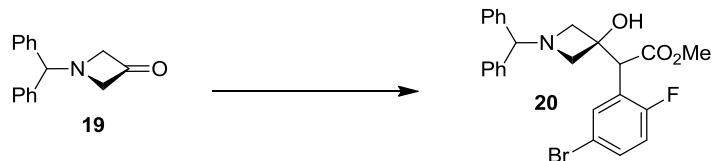


tert-Butyl 3-amino-1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (18). To a solution of ketone **14** (23.4 mg, 0.110 mmol, 1.0 equiv) in EtOH (1 ml) and H₂O (1 ml) was added hydroxylamine hydrochloride (11.4 mg, 0.165 mmol, 1.5 equiv) and sodium acetate (22.5 mg, 0.274 mmol, 2.5 equiv), and the mixture was placed in a preheated oil bath (80 °C), and stirring at that temperature was continued for 5.5 h. Then it was cooled to RT and stirred overnight. At this point it was partitioned between EtOAc (20 ml) and H₂O (10 ml). The phases were

separated, and the aqueous phase was extracted with EtOAc (20 ml). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the crude product (25 mg) as a slightly yellowish oil (*ca.* 14:11 ratio of oxime isomers). This material was pure enough for the next step.

Raney nickel (50% slurry in H_2O ; *ca.* 100 mg) was placed in a flask equipped with a stir bar under Ar. It was washed with EtOH (3×1 ml). The residue was suspended in EtOH (1 ml) and a solution of the above mentioned mixture of oxime isomers (25 mg, 0.11 mmol, 1.0 equiv) in EtOH (1.4 ml) was added. A hydrogen atmosphere was built up, and the mixture was vigorously stirred at RT for 3.5 h. At this point the atmosphere was changed to nitrogen, and the mixture was filtered over celite and thoroughly washed with MeOH. The filtrate was concentrated *in vacuo* and the residue filtered again over a small pad of celite using CH_2Cl_2 as the eluent. The filtrate was concentrated *in vacuo* to afford the title compound in good purity. Purification by FC (SiO_2 ; CH_2Cl_2 : MeOH 98:2 \rightarrow 95:5 \rightarrow 90:10 gradient) afforded the pure title compound. Yield: 13.5 mg (0.063 mmol, 58% over 2 steps). Colorless oil.

TLC: $R_f = 0.30$ (CH_2Cl_2 : MeOH 95:5; ninhydrin); **¹H NMR** (300 MHz, CDCl_3): $\delta = 4.69$ (dd, $J = 7.3, 6.3, 1\text{H}$), 4.37 (dd, $J = 10.3, 1.4, 1\text{H}$), 4.19 – 4.06 (m, 2H), 4.06 – 3.95 (m, 2H), 3.89 (dd, $J = 10.3, 1.4, 1\text{H}$), 1.57 (br s, 2H), 1.44 (s, 9H); **¹³C NMR** (101 MHz, CDCl_3): $\delta = 156.2, 87.7, 79.7, 76.7, 61.9, 56.9, 53.3, 28.3$; **IR** (thin film): 3366, 2974, 2872, 1695, 1411, 1216, 1174, 1090, 960, 913, 773 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$), 237.1210; found 237.1209.



Methyl 2-(1-benzhydryl-3-hydroxyazetidin-3-yl)-2-(5-bromo-2-fluorophenyl)acetate (20). A solution of methyl 2-(5-bromo-2-fluorophenyl)acetate⁴ (500 mg, 2.02 mmol, 1.6 equiv) in dry THF (3.6 ml) was treated with BuLi (1.6 M in hexanes; 1.26 ml, 2.02 mmol, 1.6 equiv) at -78°C . After stirring for 20 min, a solution of 1-benzhydrylazetidin-3-one (300 mg, 1.26 mmol, 1.0 equiv) in dry THF (2.4 ml) was added dropwise. The resulting reaction mixture was stirred at -78°C for a further hour, and then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO_2 ; hexanes : EtOAc 8:2) to give the pure title compound.

Yield: 449 mg (0.93 mmol, 73%). Colorless foam.

TLC: $R_f = 0.30$ (hexanes : EtOAc 85:15; UV, CAM); **¹H-NMR** (400 MHz, CDCl_3): $\delta = 7.61$ (dd, $J = 2.5, 6.4, 1\text{H}$), 7.43–7.31 (m, 5H), 7.29–7.22 (m, 4H), 7.21–7.14 (m, 2H), 6.99 (dd, $J = 9.1, 9.1, 1\text{H}$), 4.55 (s, 1H), 4.36 (s, 1H), 3.82 (bs, 1H), 3.72 (s, 3H), 3.29 (d, $J = 7.9, 1\text{H}$), 3.15 (d, $J = 7.9, 1\text{H}$), 3.09 (d, $J = 8.1, 1\text{H}$), 2.86 (d, $J = 8.1, 1\text{H}$); **¹³C-NMR** (101 MHz, CDCl_3): $\delta = 173.0, 160.0$ (d, $J = 246.4$), 142.0, 142.0, 133.3 (d, $J = 3.4$), 132.3 (d, $J = 8.4$), 128.4, 128.4, 127.4, 127.3, 127.1, 127.1, 124.3 (d, $J = 16.1$), 117.2 (d, $J = 24.8$), 116.7 (d, $J = 3.3$), 77.4, 70.7, 65.5, 62.6, 52.6, 49.2; **IR** (neat): 3543, 3061, 3027, 2952, 2840, 1727, 1599, 1484, 1452, 1236, 1201, 1171, 1105, 1073, 1082, 1004 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{25}\text{H}_{24}\text{BrFNO}_3$ ($[\text{M}+\text{H}]^+$), 484.0918; found 484.0916.

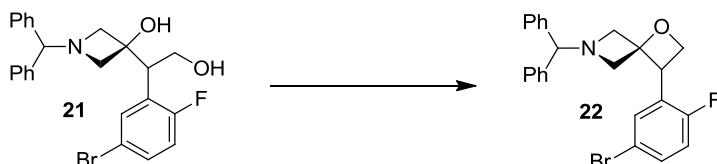
(4) Lim, S.; Harris, K. J.; Stefany, D.; Gardner, C. J.; Cao, B.; Boffey, R.; Gillespy, T. A.; C., A. J.; Hunt, H. J.; Dechaux, E. A. (Aventis Pharma, Inc.), WO 2006/044732, 2006.



1-Benzhydryl-3-(1-(5-bromo-2-fluorophenyl)-2-hydroxyethyl)azetidin-3-ol (21). To a solution of LiAlH₄ (4 M in Et₂O; 0.15 ml, 0.60 mmol, 0.75 equiv) in dry THF (0.5 ml) at 0 °C was added dropwise a solution of methyl ester **20** (390 mg, 0.805 mmol, 1.0 equiv) in THF (8 ml). After 5 h, the reaction mixture was carefully quenched with H₂O (40 µl), NaOH (15% in H₂O; 40 µl), and H₂O (120 µl). The formed precipitate was filtered, and the filter cake was thoroughly washed with EtOAc and Et₂O. The filtrate was concentrated *in vacuo* and the residue was purified by FC (SiO₂; hexanes : EtOAc 6:4) to give the pure title compound.

Yield: 220 mg (0.48 mmol, 60%). Colorless foam.

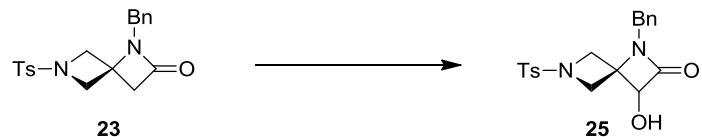
TLC: R_f = 0.49 (hexanes : EtOAc 6:4; UV, KMnO₄); **¹H-NMR** (400 MHz, CDCl₃): δ = 7.78 (dd, J = 2.5, 6.5, 1H), 7.39–7.31 (m, 5H), 7.30–7.23 (m, 5H), 7.22–7.15 (m, 2H), 6.95 (dd, J = 8.8, 9.6, 1H), 4.38 (s, 1H), 4.10–4.00 (m, 2H), 3.62 (t, J = 5.4, 1H), 3.50 (d, J = 8.4, 1H), 3.23 (d, J = 8.5, 1H), 3.16 (d, J = 8.4, 1H), 3.03 (d, J = 8.5, 1H), 2.79–2.31 (m, 2H); **¹³C-NMR** (101 MHz, CDCl₃): δ = 160.2 (d, J = 245.0), 141.5, 141.4, 133.1 (d, J = 4.1), 131.5 (d, J = 8.6), 128.6, 128.5, 128.1 (d, J = 15.8), 127.3, 127.3, 117.0 (d, J = 25.2), 116.8 (d, J = 3.3), 77.7, 72.7, 66.3, 65.2, 63.4, 45.3 (d, J = 0.9); **IR** (neat): 3200, 3109, 2956, 2926, 2842, 1483, 1451, 1349, 1314, 1260, 1234, 1172, 1111, 1071, 1037 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₂₄H₂₄BrFNO₂ ([M+H]⁺), 456.0969; found 456.0970.



6-Benzhydryl-3-(5-bromo-2-fluorophenyl)-1-oxa-6-azaspiro[3.3]heptane (22). To a solution of diol **21** (210 mg, 0.46 mmol, 1.0 equiv) in THF (2.4 ml) at 0 °C was added KO*t*-Bu (25.8 mg, 0.230 mmol, 0.5 equiv) followed by dropwise addition of a solution of *p*-toluenesulfonyl chloride (43.9 mg, 0.230 mmol, 0.5 equiv) in THF (0.4 ml). After 1 h at 0 °C another portion of KO*t*-Bu (25.8 mg, 0.230 mmol, 0.5 equiv) followed by a solution of *p*-toluenesulfonyl chloride (43.9 mg, 0.230 mmol, 0.5 equiv) in THF (0.4 ml) were added. After 1 h, KO*t*-Bu (51.6 mg, 0.460 mmol, 1.0 equiv) was added and the resulting reaction mixture was allowed to warm to rt for 2 h, and then diluted with water (5 ml) and Et₂O (10 ml). The aqueous layer was extracted with Et₂O (3 × 10 ml), and the combined organic layers dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO₂; hexanes : EtOAc 95:5) to give the pure title compound.

Yield: 132 mg (0.30 mmol, 65%). Light brown oil.

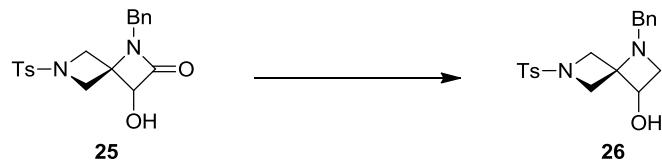
TLC: R_f = 0.50 (hexanes : EtOAc 9:1; UV, KMnO₄); **¹H-NMR** (400 MHz, CDCl₃): δ = 7.67 (dd, J = 2.4, 6.5, 1H), 7.45–7.31 (m, 5H), 7.31–7.10 (m, 6H), 7.01 (dd, J = 9.2, 9.2, 1H), 4.80 (dd, J = 6.2, 8.3, 1H), 4.66 (t, J = 6.5, 1H), 4.38 (t, J = 7.6, 1H), 4.27 (s, 1H), 3.54 (d, J = 9.0, 1H), 3.36 (d, J = 9.0, 1H), 3.12 (d, J = 9.4, 1H), 3.05 (d, J = 9.4, 1H); **¹³C-NMR** (101 MHz, CDCl₃): δ = 159.9 (d, J = 246.8), 142.3, 142.2, 131.7 (d, J = 8.7, 1H), 131.6 (d, J = 4.2, 1H), 128.4, 128.4, 127.5 (d, J = 16.1), 127.3, 127.3, 127.1, 127.1, 117.4 (d, J = 24.0), 117.0 (d, J = 3.4), 86.1, 77.7, 70.8 (d, J = 3.5), 66.9, 62.8, 41.5 (d, J = 1.1); **IR** (neat): 3061, 2953, 2891, 2825, 1598, 1488, 1415, 1401, 1346, 1318, 1237, 1158, 1113, 1027 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₂₄H₂₂BrFNO ([M+H]⁺), 438.0863; found 438.0866.



1-Benzyl-3-hydroxy-6-tosyl-1,6-diazaspiro[3.3]heptan-2-one (25). To a stirred solution of KHMDS (0.5 M in toluene; 2.22 ml, 1.11 mmol, 2.0 equiv) in THF (6 ml) at -78°C was added dropwise a solution of β -lactam **23**⁵ (198 mg, 0.56 mmol, 1.0 equiv) in THF (2 ml). After 15 min, a solution of 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (**24**) (363 mg, 1.39 mmol, 2.5 equiv) in THF (2 ml) was dropwise added. The resulting mixture was stirred at -78°C for additional 2 h, when it was quenched with saturated aqueous NH_4Cl (10 ml) and diluted with EtOAc. The two layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by FC (SiO₂; hexanes : EtOAc 3:7) to give the pure title compound.

Yield: 130 mg (0.349 mmol, 63%). Colorless solid.

TLC: R_f = 0.23 (hexanes : EtOAc 4:6; UV, KMnO₄); **Melting Point:** 168-170 °C; **¹H-NMR** (400 MHz, CDCl₃): δ = 7.67 (d, J = 8.1, 2H), 7.37 (d, J = 8.1, 2H), 7.33-7.27 (m, 3H), 7.12-7.01 (m, 2H), 4.70 (s, 1H), 4.26 (d, J = 15.4, 1H), 4.18 (d, J = 15.4, 1H), 4.05 (d, J = 9.5, 1H), 3.95 (br s, 1H), 3.86-3.77 (m, 2H), 3.68 (d, J = 9.5, 1H), 2.49 (s, 3H); **¹³C-NMR** (101 MHz, CDCl₃): δ = 167.2, 144.6, 135.4, 131.1, 129.9, 129.0, 128.4, 128.2, 127.9, 80.7, 60.8, 55.8, 53.3, 43.4, 21.7; **IR** (neat): 3297, 3066, 2938, 1732, 1595, 1498, 1442, 1343, 1212, 1185, 1156, 1129, 1185, 1156, 1129, 1086, 1039 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₉H₂₁N₂O₄S ([M+H]⁺), 373.1217; found 373.1225.

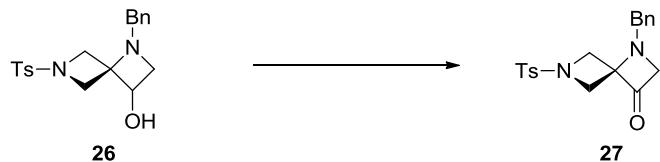


1-Benzyl-6-tosyl-1,6-diazaspiro[3.3]heptan-3-ol (26). AlCl₃ (13.3 mg, 0.10 mmol, 1.5 equiv) was dissolved in anhydrous Et₂O (0.6 ml) and then LiAlH₄ (1 M in Et₂O; 100 μl , 0.10 mmol, 1.5 equiv) was added dropwise at rt. The reaction mixture was stirred for 45 min at reflux temperature and then a solution of β -lactam **25** (25 mg, 0.067 mmol, 1.0 equiv) in anhydrous Et₂O/THF (1:1; 2.4 ml) was added dropwise over 10 min, and stirring was continued for 1.5 h at 60 °C. The reaction was then allowed to cool to rt and was quenched by addition of saturated aqueous NaHCO₃ (5 ml). The mixture was extracted with EtOAc (3 \times 10 ml), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO₂; hexanes : EtOAc 1:1) to give the pure title compound.

Yield: 16 mg (0.045 mmol, 67%). Colorless foam.

TLC: R_f = 0.24 (hexanes : EtOAc 1:1; UV, KMnO₄); **¹H-NMR** (400 MHz, CDCl₃): δ = 7.77 (d, J = 8.1, 2H), 7.39 (d, J = 8.1, 2H), 7.32-7.22 (m, 3H), 7.19-7.11 (m, 2H), 4.32 (dd, J = 6.0, 6.0, 1H), 4.26 (d, J = 9.2, 1H), 3.99 (d, J = 9.2, 1H), 3.86 (d, J = 9.4, 1H), 3.80 (d, J = 9.4, 1H), 3.41 (dd, J = 6.0, 7.2, 1H), 3.39 (d, J = 13.0, 1H), 3.31 (d, J = 13.0, 1H), 2.71 (dd, J = 6.0, 7.2, 1H), 2.45 (s, 3H); **¹³C-NMR** (101 MHz, CDCl₃): δ = 144.3, 137.2, 131.2, 129.7, 128.5, 128.4, 128.2, 127.2, 68.6, 67.8, 60.0, 58.9, 54.9, 51.5, 21.6; **IR** (neat): 3068, 3030, 2969, 2857, 1596, 1454, 1335, 1308, 1213, 1165, 1093, 1049 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₉H₂₃N₂O₃S ([M+H]⁺), 359.1424; found 359.1421.

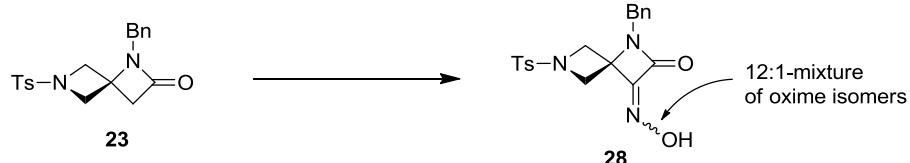
(5) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780-783.



1-Benzyl-6-tosyl-1,6-diazaspiro[3.3]heptan-3-one (27). To a solution of oxalyl chloride (12 μ l, 0.134 mmol, 1.5 equiv) in CH_2Cl_2 (1.25 ml), cooled to -78°C , was added DMSO (16 μ l, 0.223 mmol, 2.5 equiv), and the mixture was stirred at -78°C for 10 min, when a solution of alcohol **26** (32 mg, 0.089 mmol, 1.0 equiv) in CH_2Cl_2 (1 ml) was slowly added. The mixture was stirred at -78°C for 45 min, when triethylamine (62 μ l, 0.446 mmol, 5.0 equiv) was added. The reaction mixture was allowed to warm to rt, and then was partitioned between CH_2Cl_2 (15 ml) and saturated aqueous NH_4Cl (10 ml). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (10 ml). The combined organic phases were washed with saturated aqueous NaCl , dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by FC (SiO_2 ; hexanes : EtOAc 7:3) to give the pure title compound.

Yield: 26 mg (0.073 mmol, 82%). Light yellow solid.

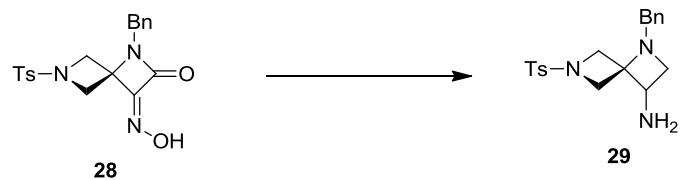
TLC: $R_f = 0.66$ (hexanes : EtOAc 1:1; UV, KMnO_4); **Melting Point:** 117–119 $^\circ\text{C}$; **$^1\text{H-NMR}$** (400 MHz, CDCl_3): $\delta = 7.72$ (d, $J = 8.1$, 2H), 7.37 (d, $J = 8.1$, 2H), 7.34–7.22 (m, 5H), 4.13 (d, $J = 9.8$, 2H), 4.02 (d, $J = 9.7$, 2H), 3.91 (s, 2H), 3.73 (s, 2H), 2.43 (s, 3H); **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3): $\delta = 200.2$, 144.6, 136.8, 131.4, 129.9, 128.7, 128.4, 128.1, 127.7, 78.6, 72.2, 56.0, 55.2, 21.6.; **IR** (neat): 2927, 2852, 1807, 1597, 1497, 1458, 1346, 1305, 1162, 1119, 1039, 1001 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$), 357.1267; found 357.1281.



1-Benzyl-3-(hydroxyimino)-6-tosyl-1,6-diazaspiro[3.3]heptan-2-one (28). To a stirred solution of β -lactam **23**⁵ (1.00 g, 2.81 mmol, 1.0 equiv) in THF (30 ml) at -78°C was added dropwise a solution of KHMDS (0.5 M in toluene; 11.2 ml, 5.61 mmol, 2.0 equiv) in THF (20 ml). After stirring for 15 min, a solution of isoamyl nitrite (0.76 ml, 5.61 mmol, 2.0 equiv) was added dropwise. The resulting mixture was stirred at -78°C for a further hour, and then quenched with saturated aqueous NH_4Cl (50 ml), and diluted with EtOAc (50 ml). The layers were separated, and the aqueous phase was extracted with EtOAc . The combined organic phases were washed with saturated aqueous NaCl , dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO_2 ; hexanes : EtOAc 1:1) to give the pure title compound.

Yield: 752 mg (1.95 mmol, 69%). Colorless foam.

TLC: $R_f = 0.32$ (hexanes : EtOAc 1:1; UV, KMnO_4); **$^1\text{H-NMR}$** (400 MHz, CDCl_3 , major isomer): $\delta = 8.68$ (br s, 1H), 7.67 (d, $J = 8.1$, 2H), 7.37 (d, $J = 8.1$, 2H), 7.34–7.28 (m, 3H), 7.20–7.12 (m, 2H), 4.45 (s, 2H), 3.99 (dd, $J = 0.9$, 9.6, 2H), 3.86 (dd, $J = 0.9$, 9.6, 2H), 2.49 (s, 3H); **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3 , major isomer): $\delta = 155.6$, 154.0, 144.7, 134.9, 131.2, 130.0, 129.1, 128.5, 128.4, 128.1, 61.9, 55.9, 43.9, 21.7; **IR** (neat): 3264, 2627, 2869, 1749, 1597, 1455, 1442, 1386, 1345, 1160, 1120, 1092, 1030 cm^{-1} ; **HRMS** (ESI): exact mass calculated for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$), 386.1169; found 386.1186.

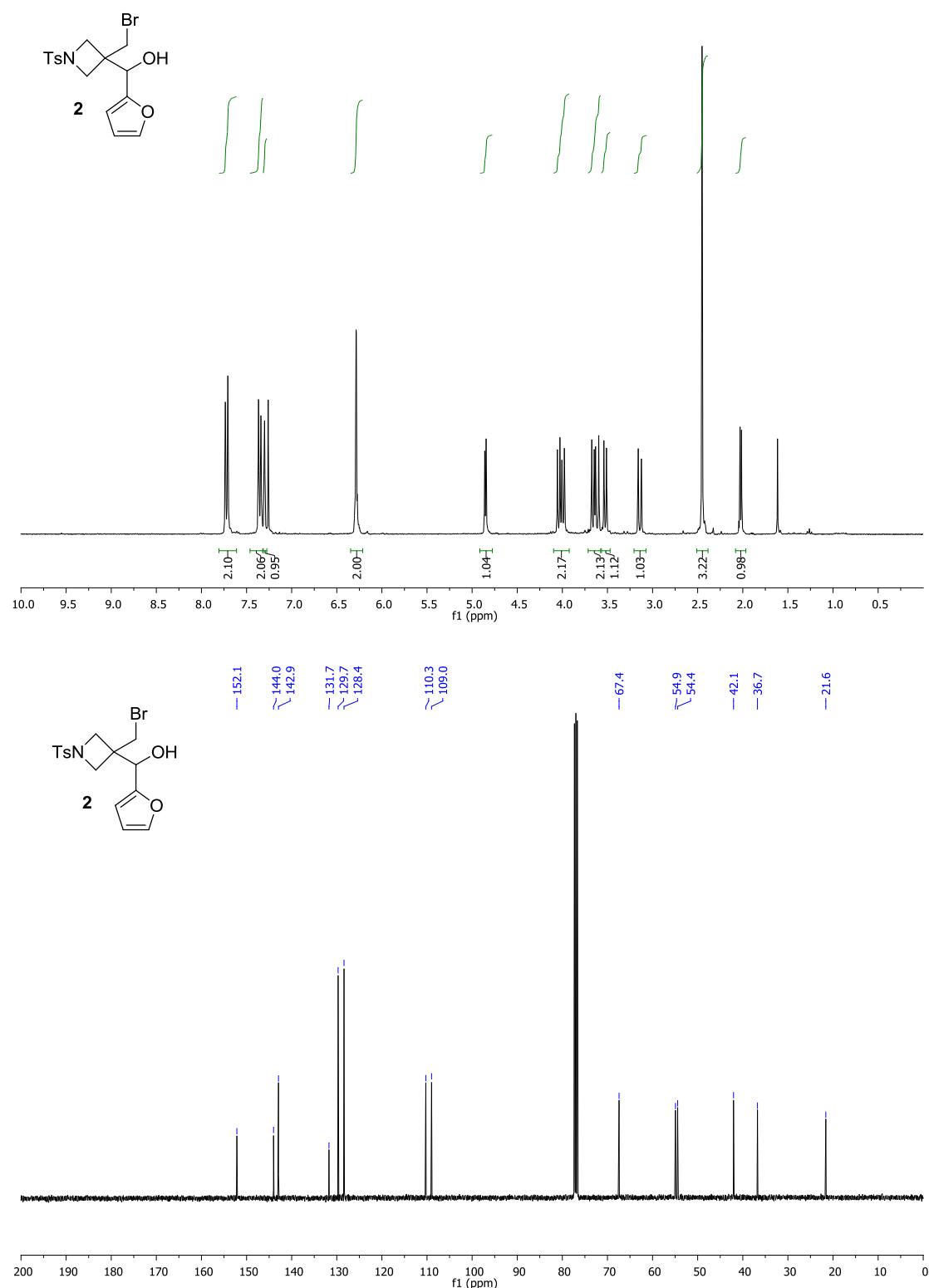


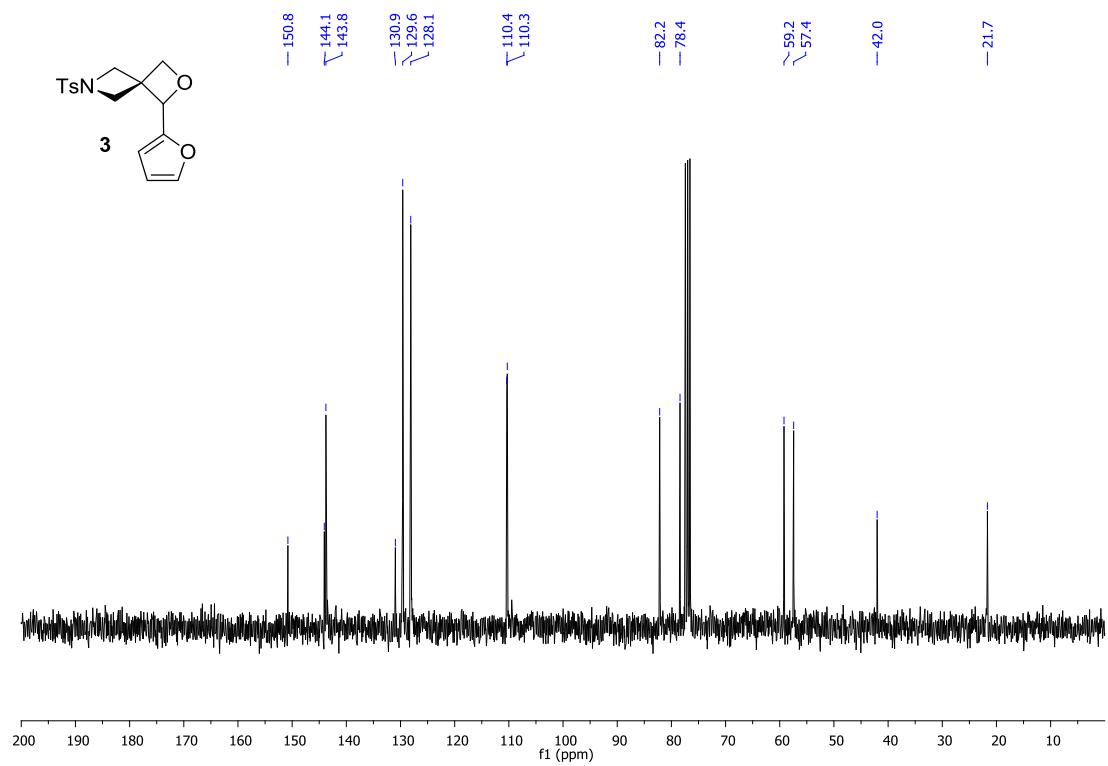
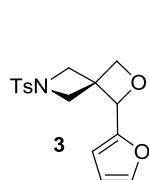
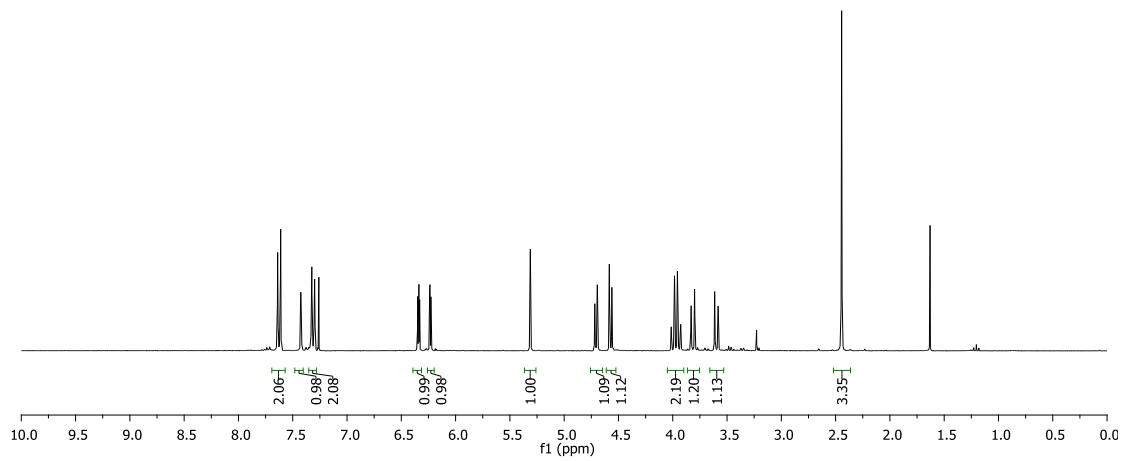
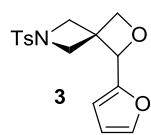
1-Benzyl-6-tosyl-1,6-diazaspiro[3.3]heptan-3-amine (29). AlCl_3 (104 mg, 0.78 mmol, 3.0 equiv) was dissolved in anhydrous Et_2O (5 ml) and then LiAlH_4 (1 M in Et_2O ; 0.78 ml, 0.78 mmol, 3.0 equiv) was added dropwise at rt. The reaction mixture was stirred at reflux temperature for 45 min, and then a solution of oxime **28** (100 mg, 0.26 mmol, 1.0 equiv) in anhydrous $\text{Et}_2\text{O}/\text{THF}$ (1:1; 10 ml) was added dropwise over 10 min. Stirring was continued at 40 °C for an additional period of 45 min. The reaction was then allowed to cool to rt, and it was quenched by addition of saturated aqueous NaHCO_3 (20 ml). The mixture was extracted with EtOAc (3 × 40 ml), the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO_2 ; CH_2Cl_2 : MeOH 95:5) to give the pure title compound.

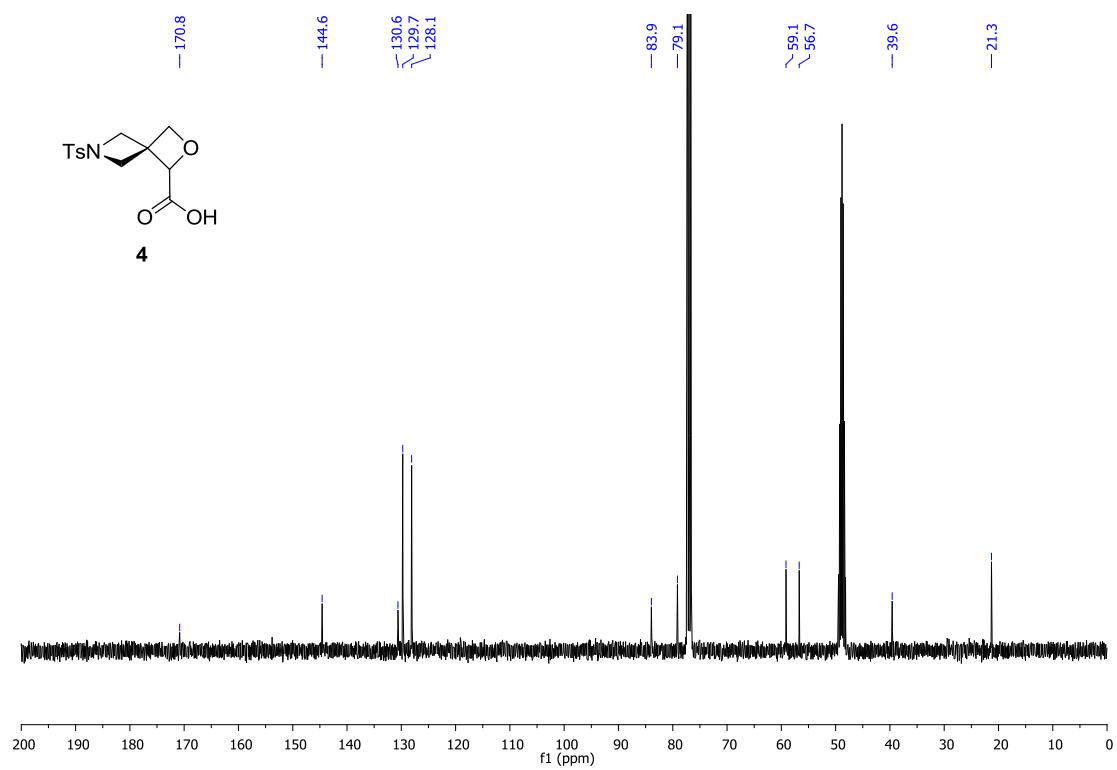
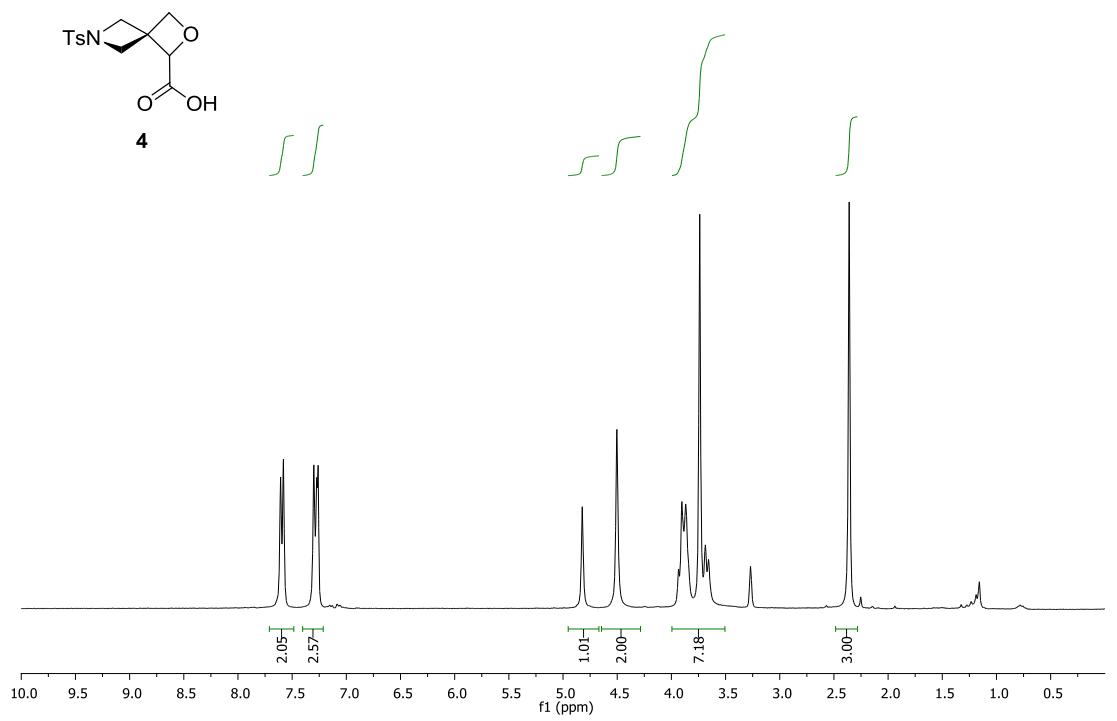
Yield: 61 mg (0.171 mmol, 66%). Colorless oil.

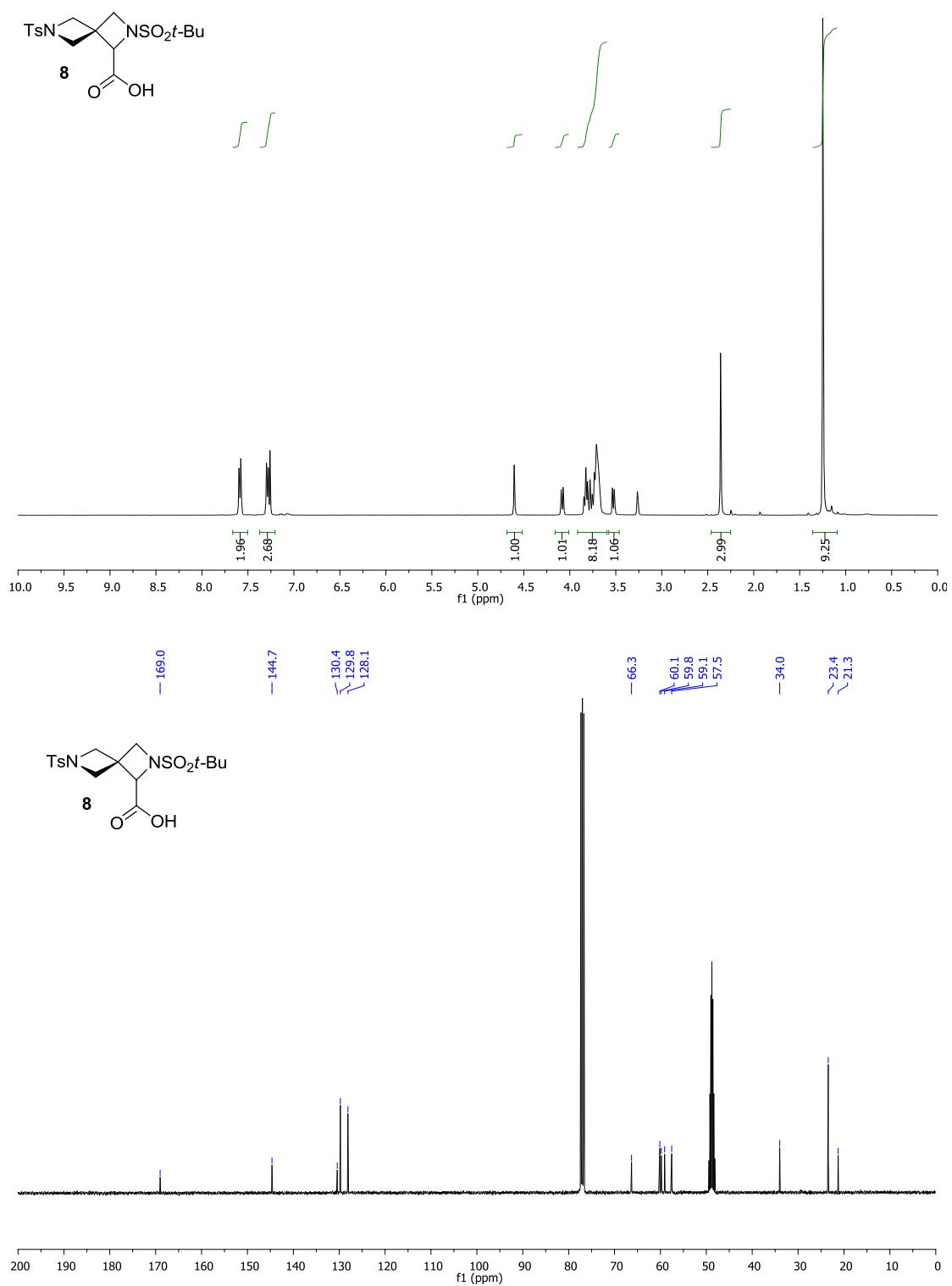
TLC: $R_f = 0.33$ (CH₂Cl₂ : MeOH 95:5; UV, KMnO₄); **¹H-NMR** (400 MHz, CDCl₃): $\delta = 7.74$ (d, $J = 8.1$, 2H), 7.36 (d, $J = 8.1$, 2H), 7.28–7.19 (m, 3H), 7.14–7.10 (m, 2H), 4.05 (d, $J = 9.2$, 1H), 3.89–3.82 (m, 2H), 3.76 (d, $J = 9.2$, 1H), 3.48 (t, $J = 6.4$, 1H), 3.36 (t, $J = 6.9$, 1H), 3.34 (d, $J = 13.0$, 1H), 3.25 (d, $J = 13.0$, 1H), 2.51 (dd, $J = 6.0$, 6.8, 1H), 2.42 (s, 3H)); **¹³C-NMR** (101 MHz, CDCl₃): $\delta = 144.2$, 137.4, 131.2, 129.7, 128.5, 128.4, 128.2, 127.1, 68.2, 60.0, 59.5, 55.0, 52.2, 51.3, 21.6; **IR** (neat): 3376, 2932, 2863, 2829, 1597, 1495, 1453, 1337, 1159, 1091, 1038 cm⁻¹; **HRMS** (ESI): exact mass calculated for C₁₂H₁₇N₂ ([M+H]⁺), 358.1584; found 358.1573.

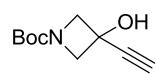
Copies of NMR spectra of new compounds



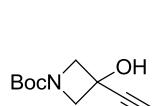
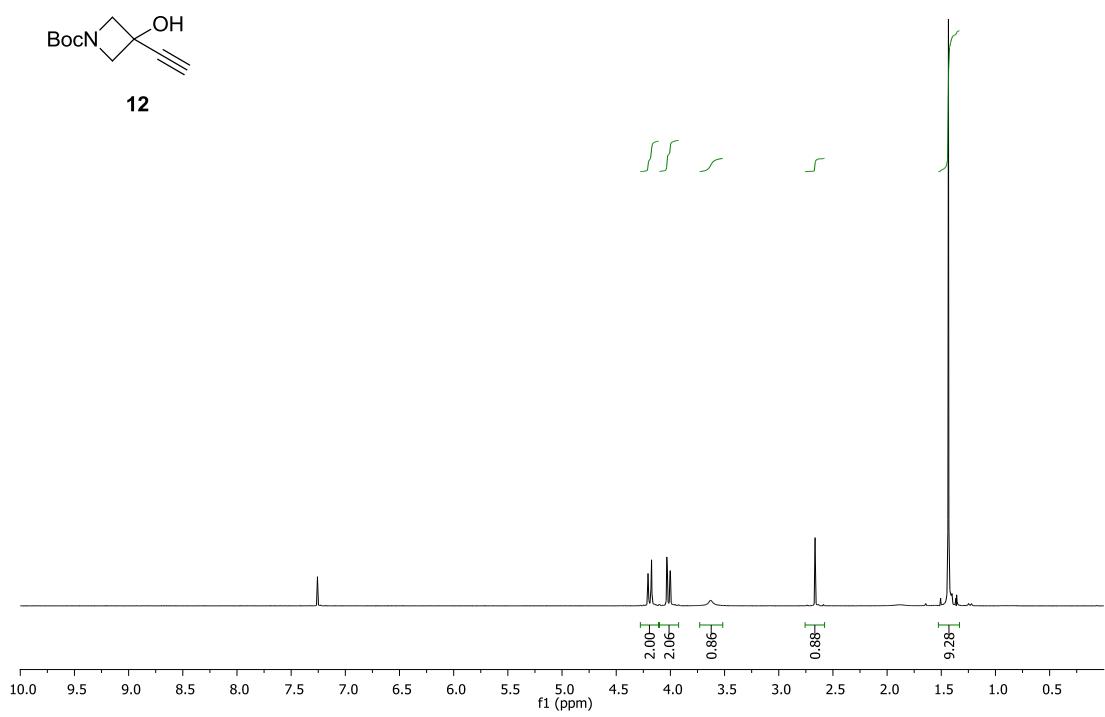






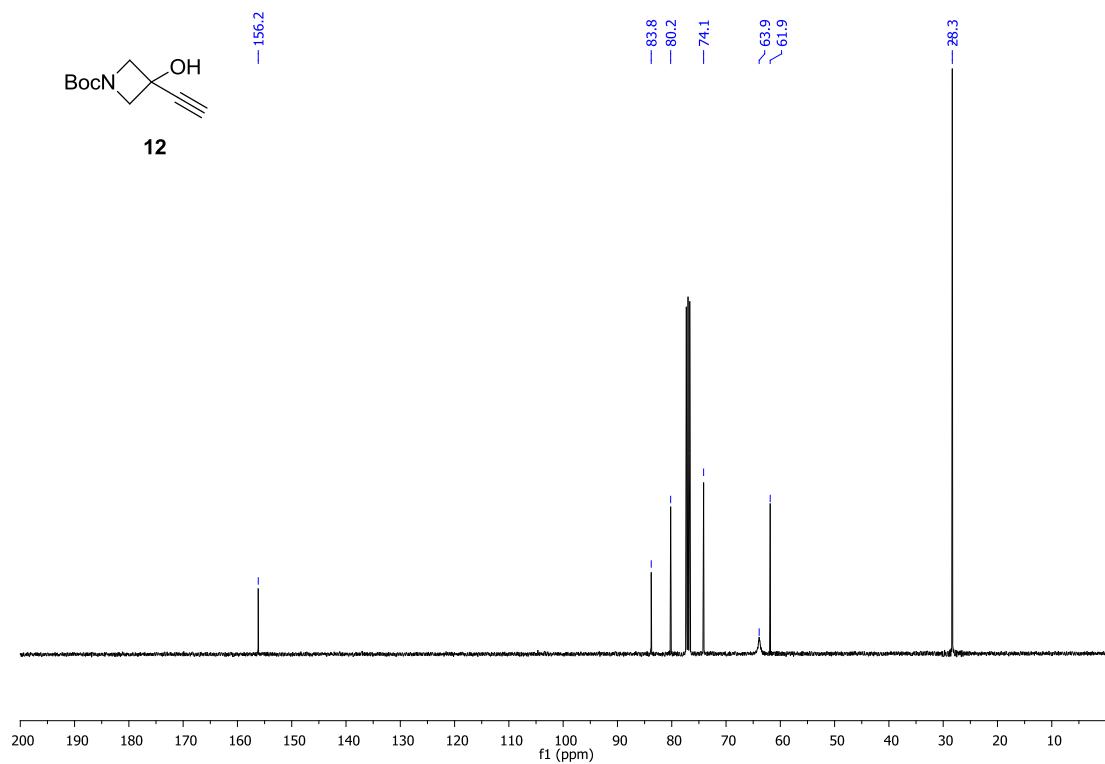


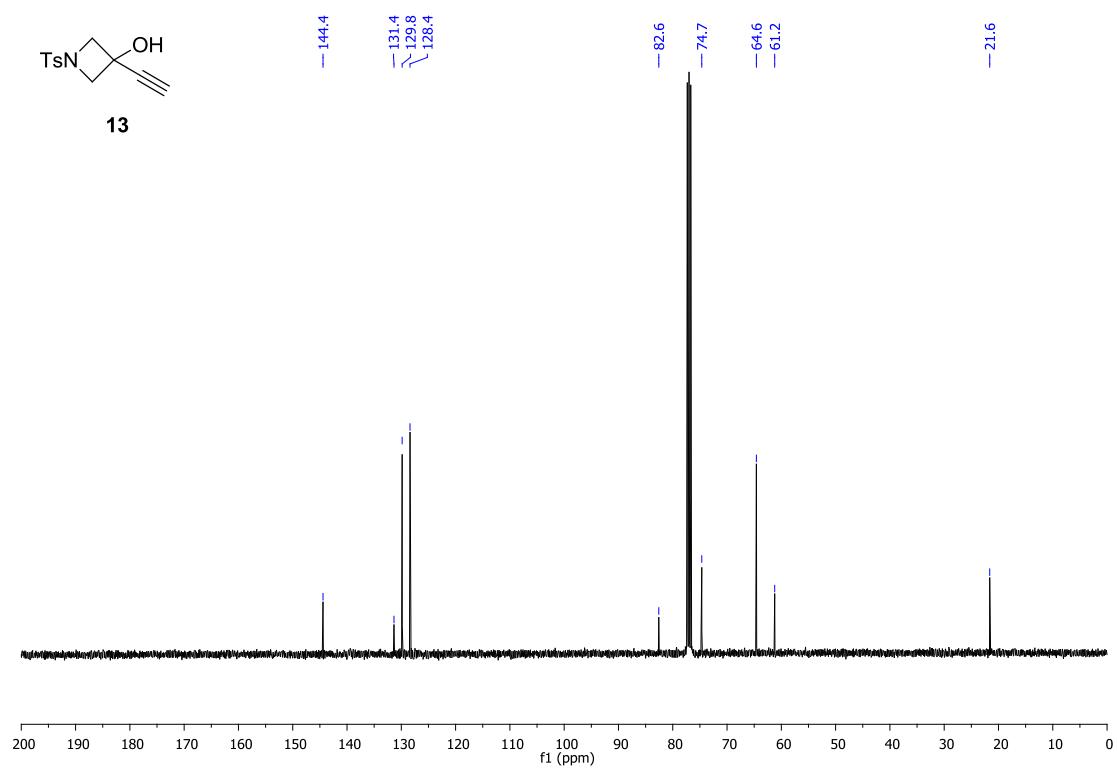
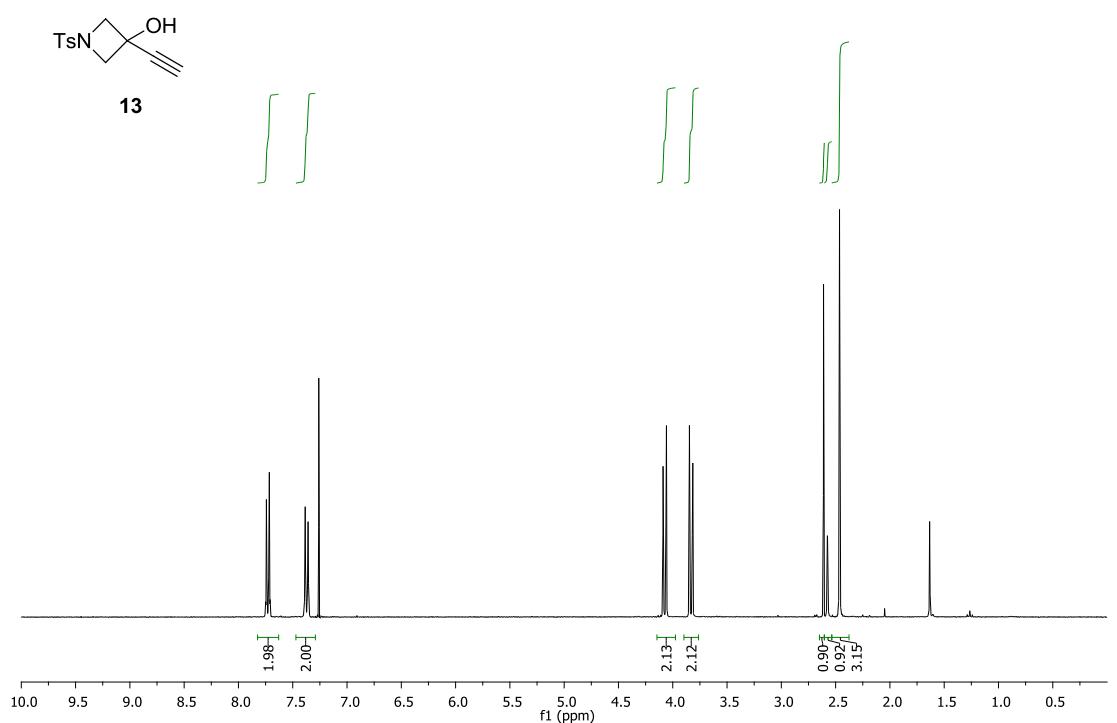
12

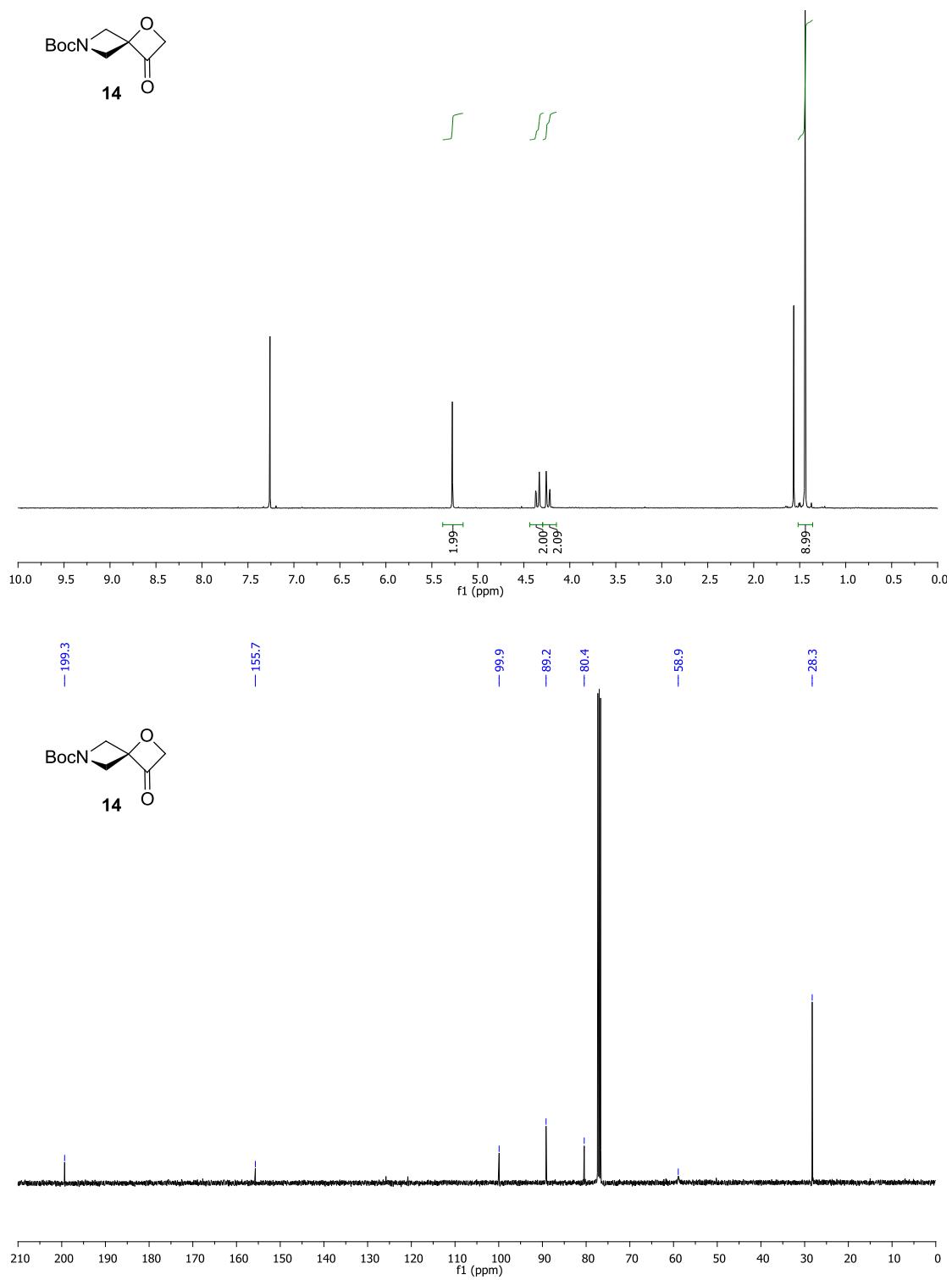


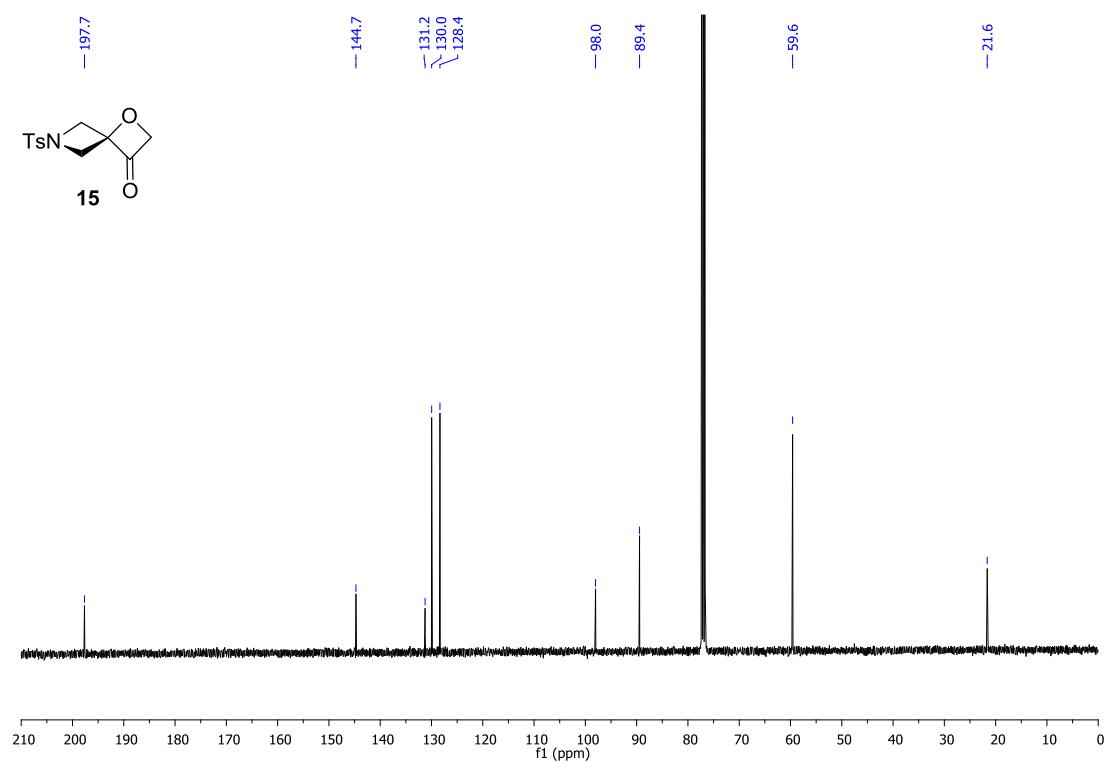
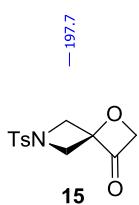
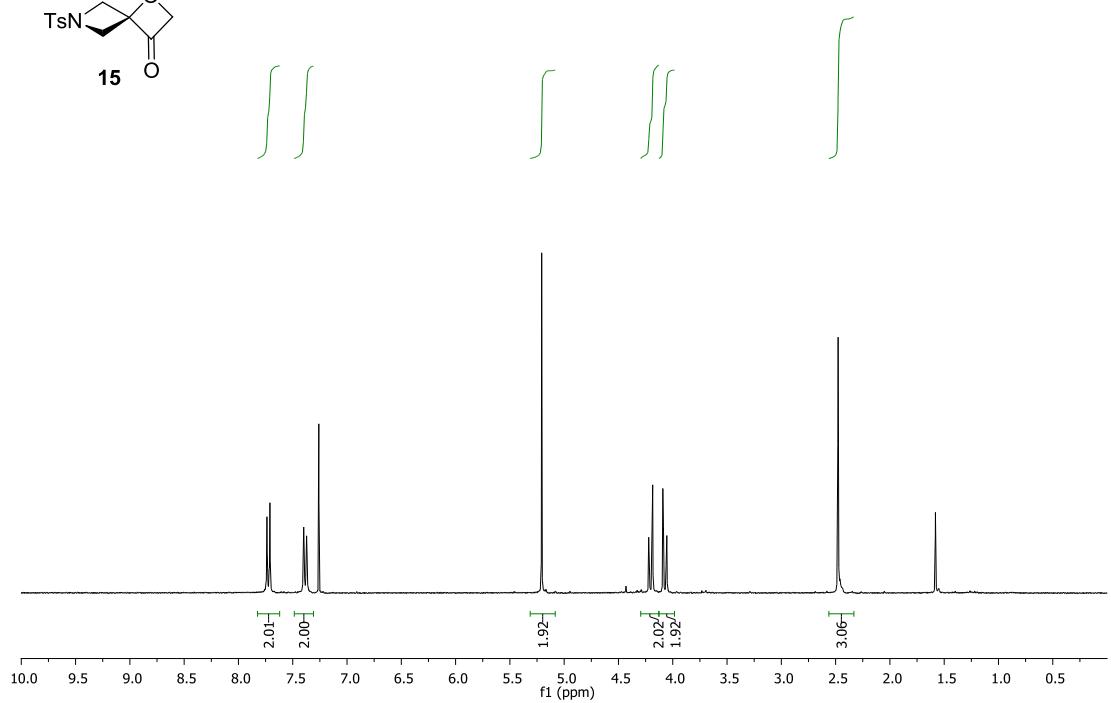
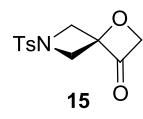
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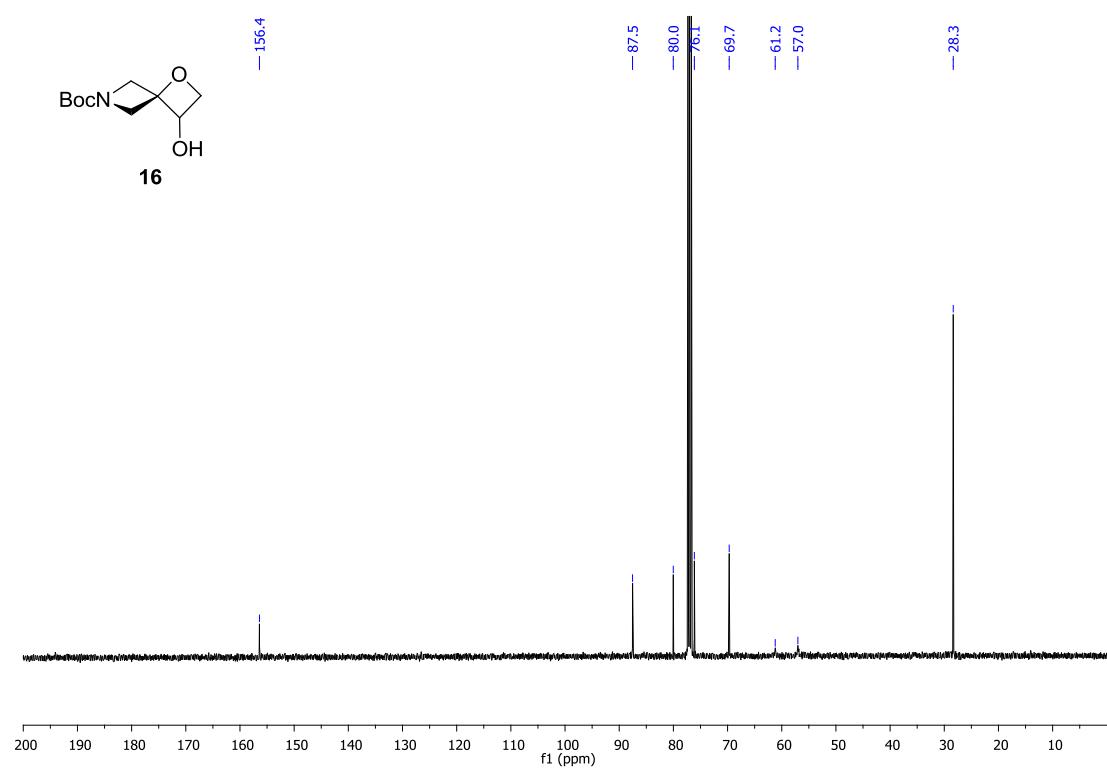
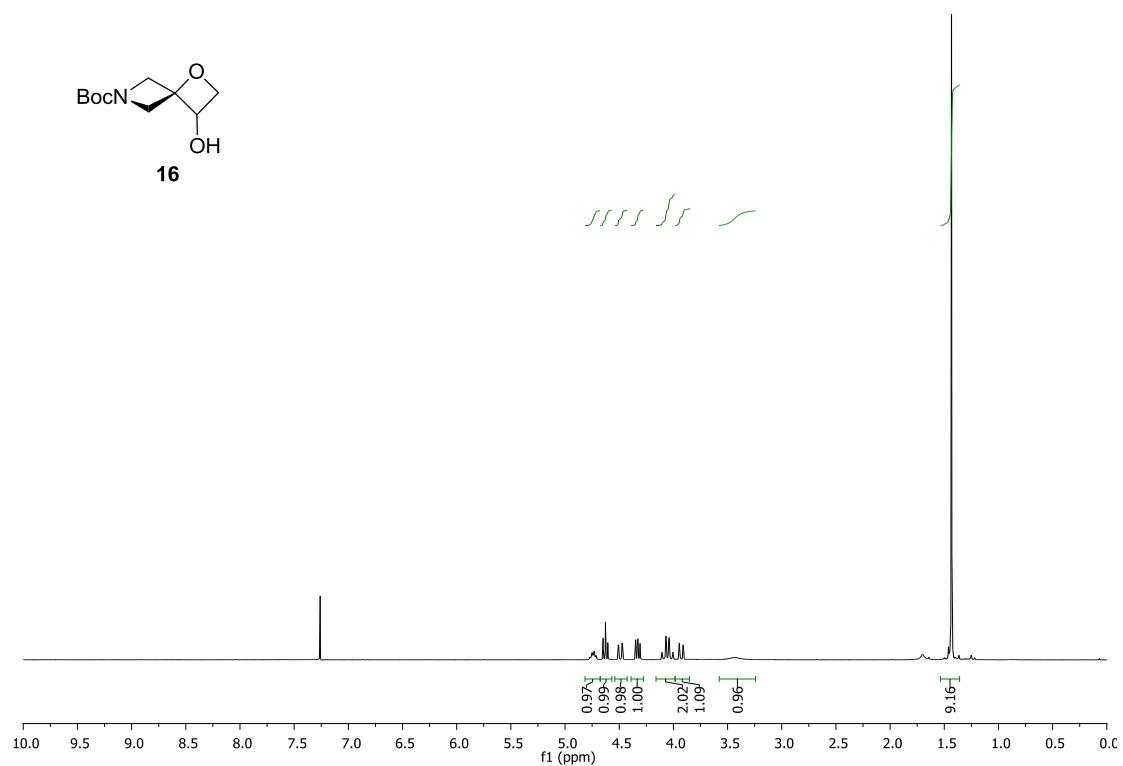
— 156.2
— 83.8
— 80.2
— 74.1
— 63.9
— 61.9
— 28.3

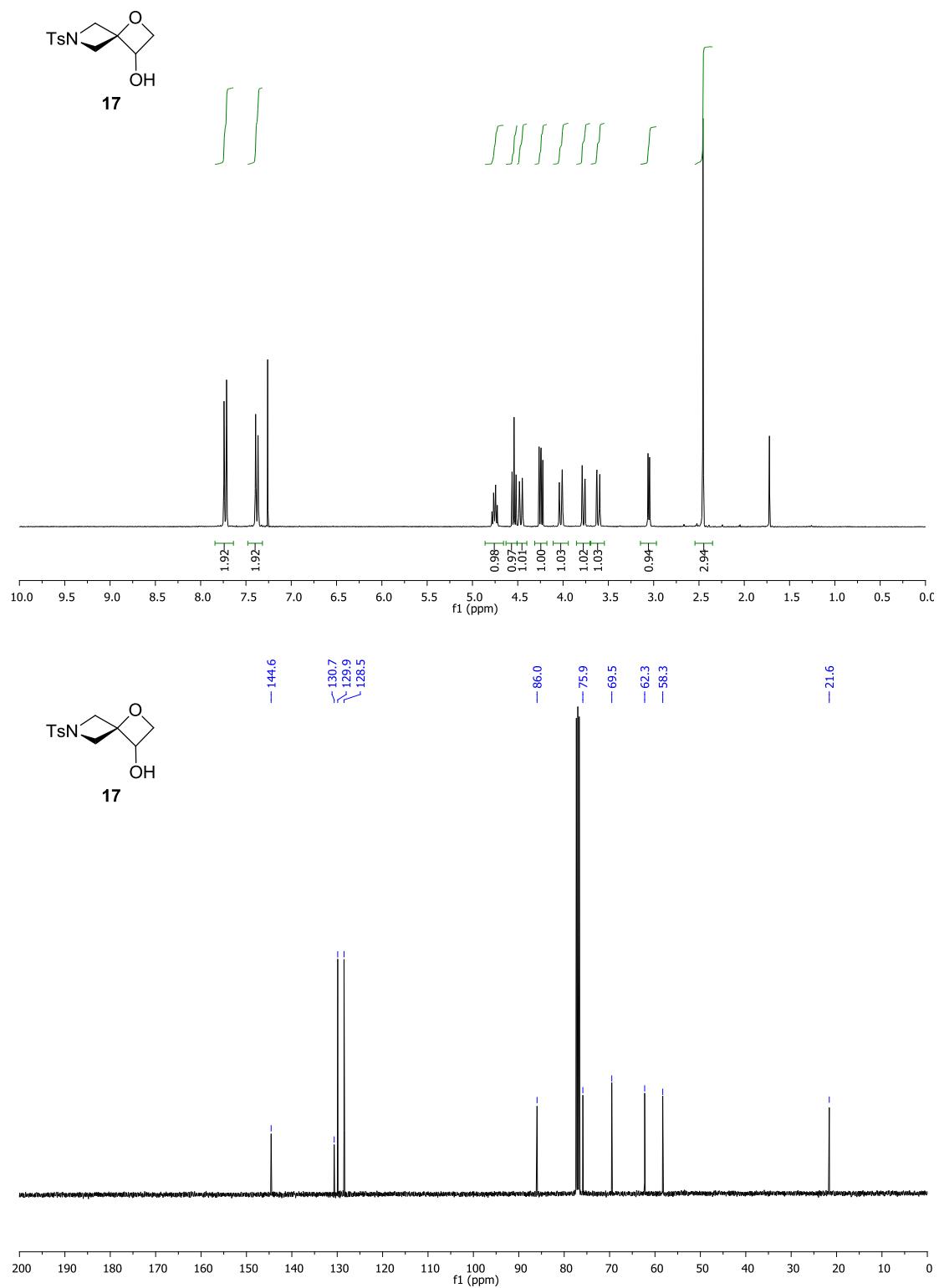


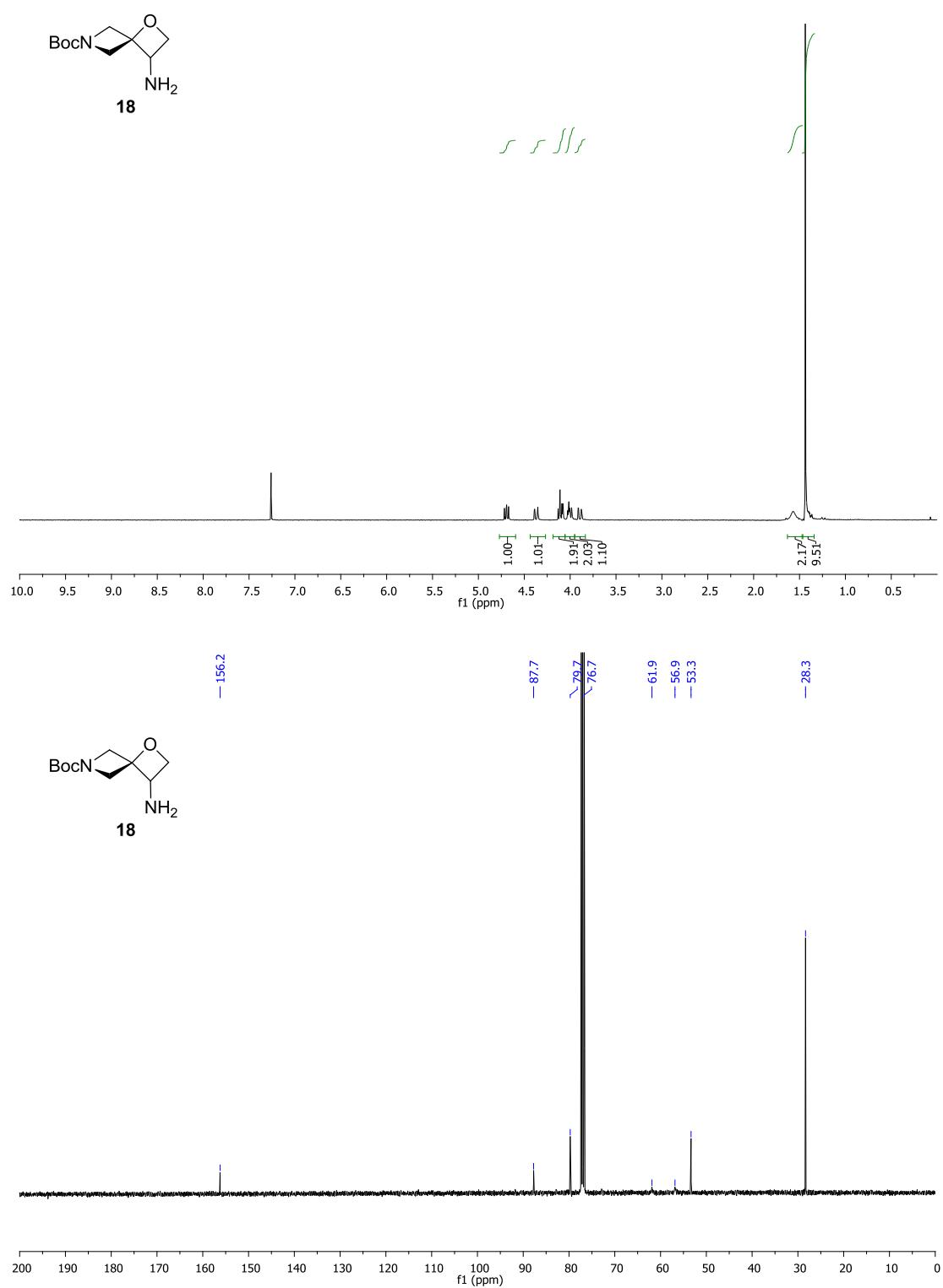


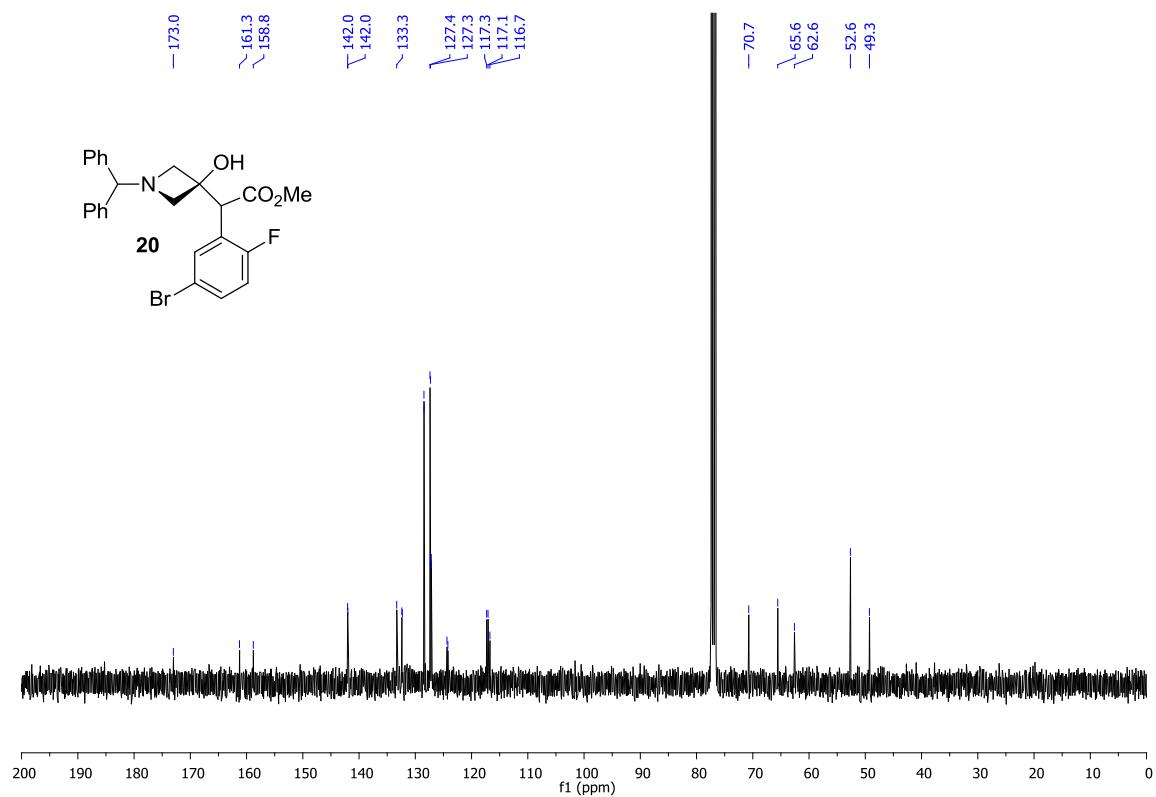
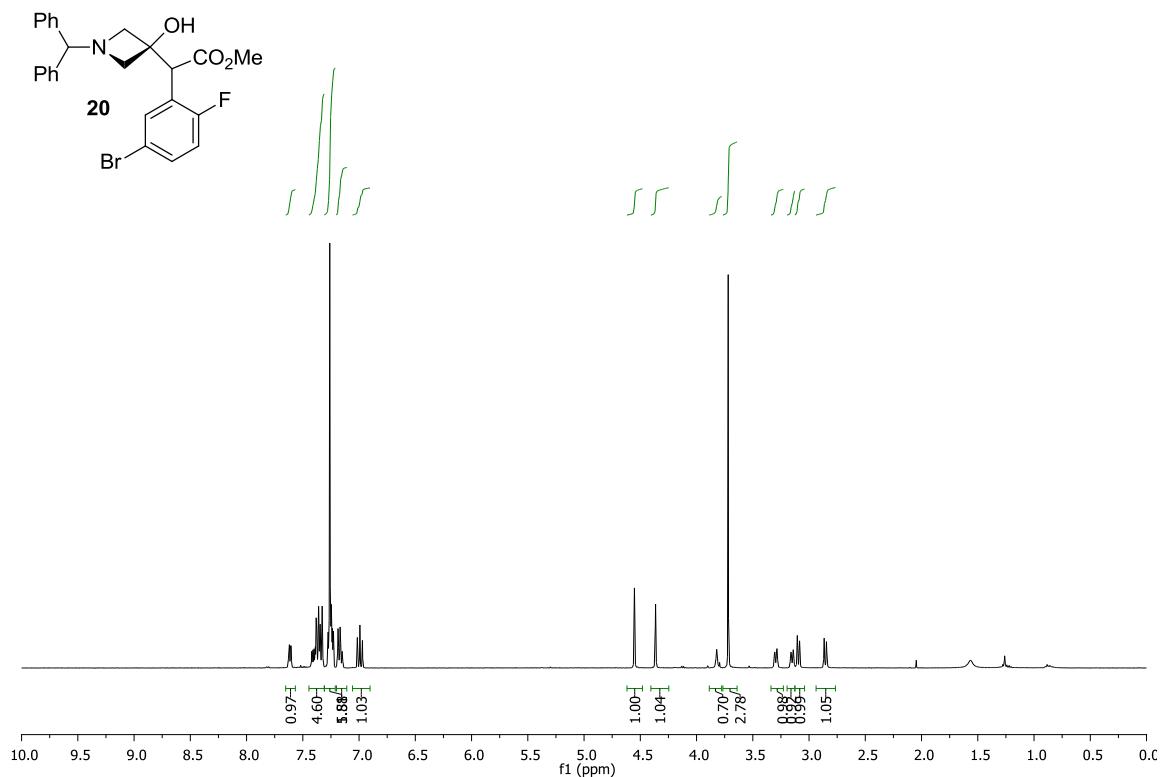


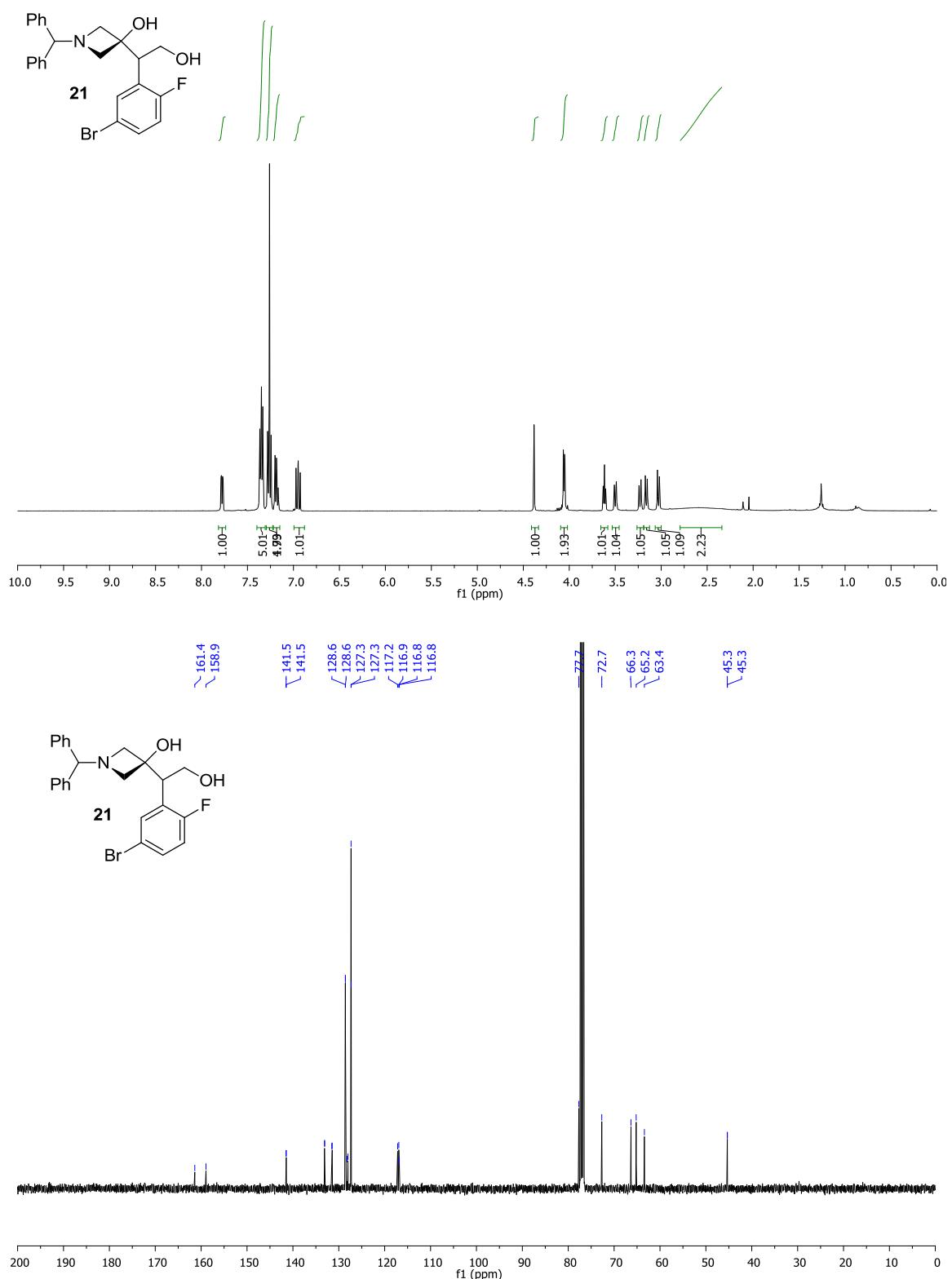


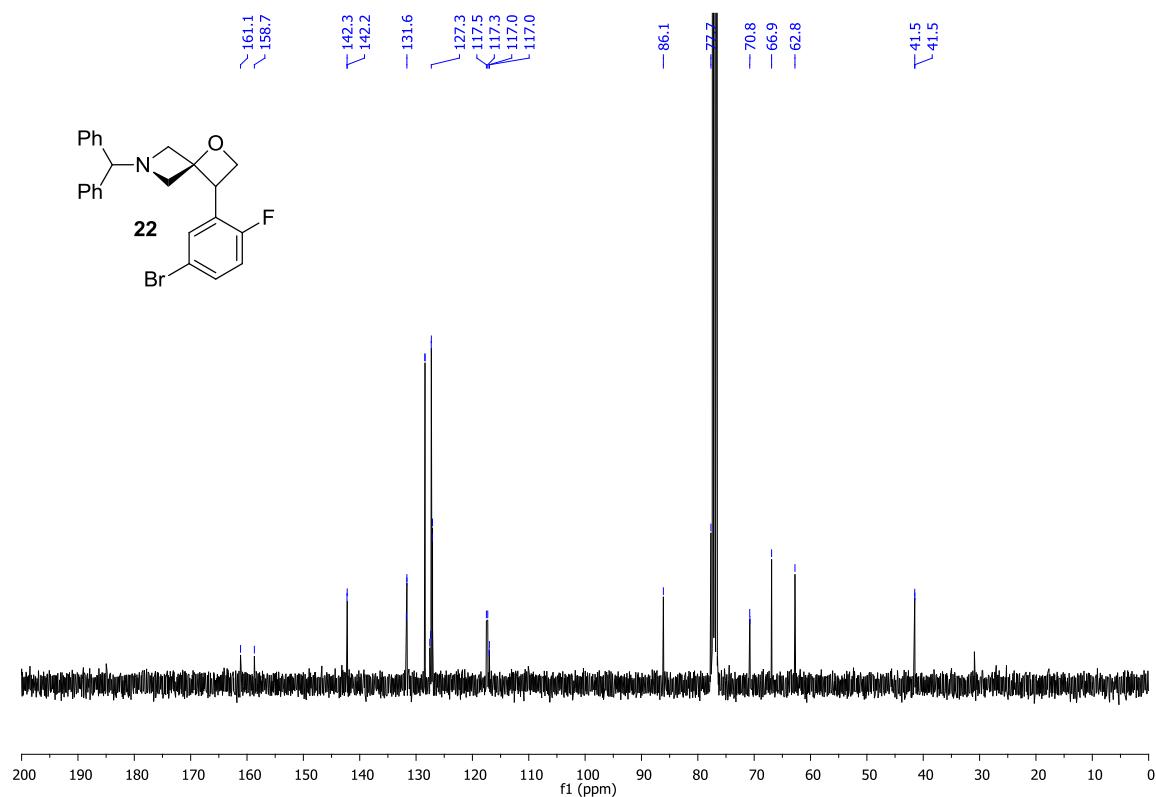
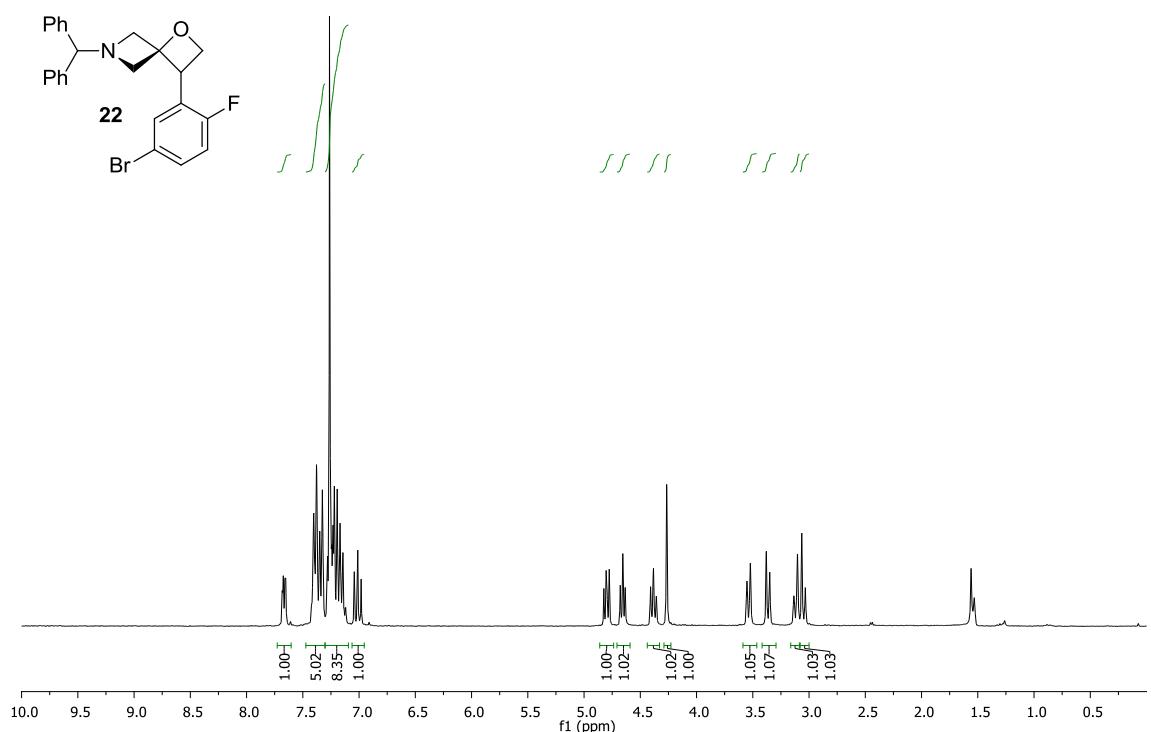


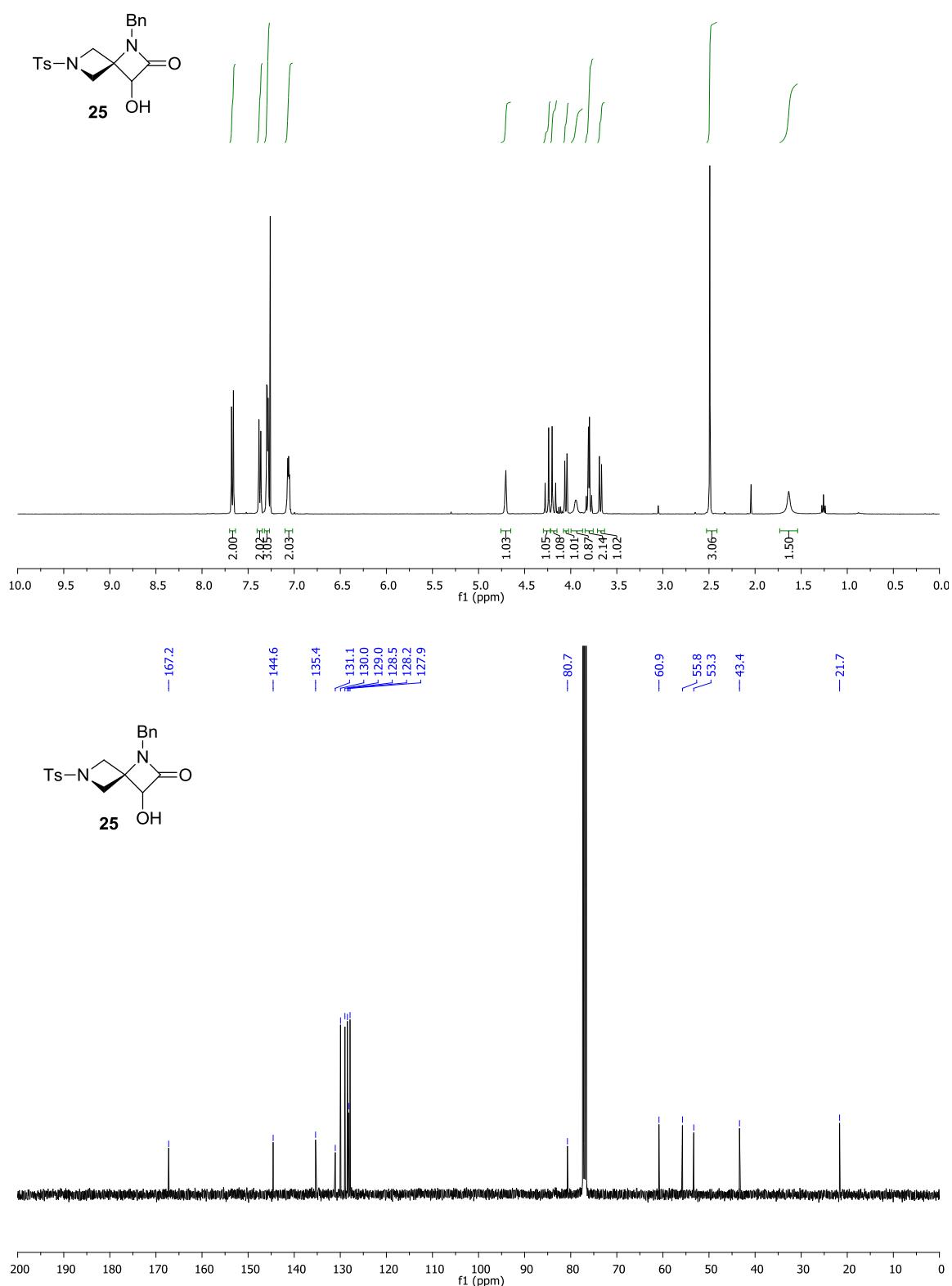


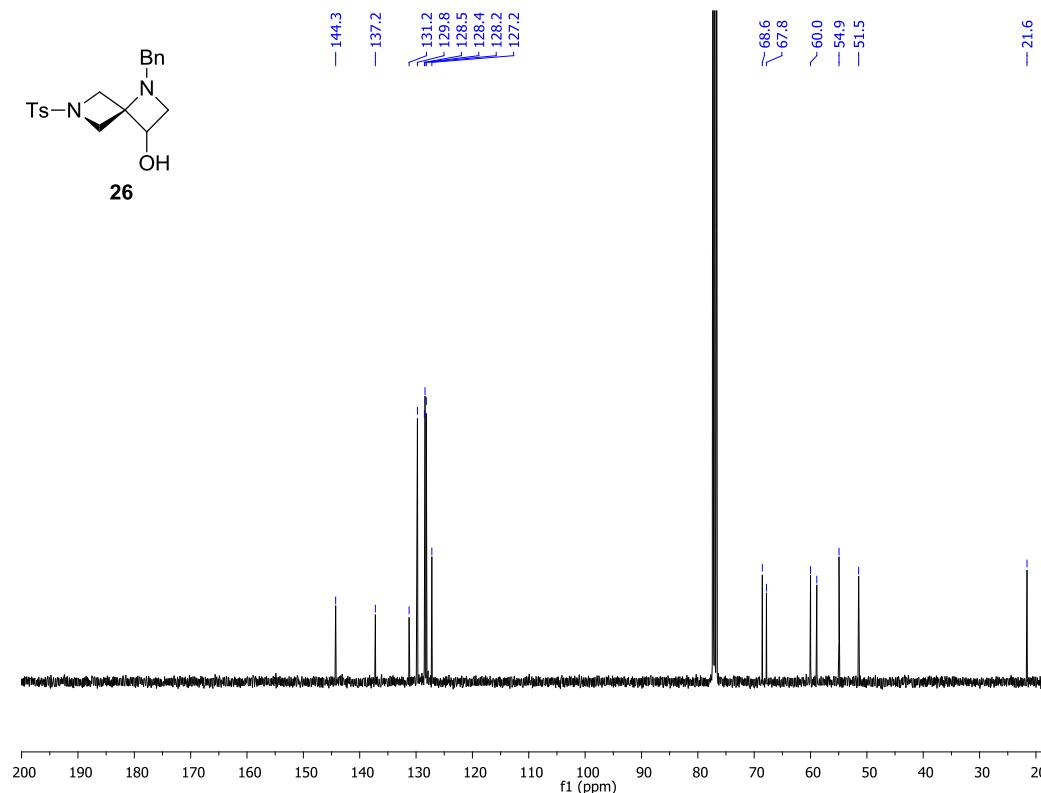
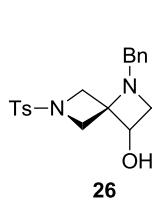
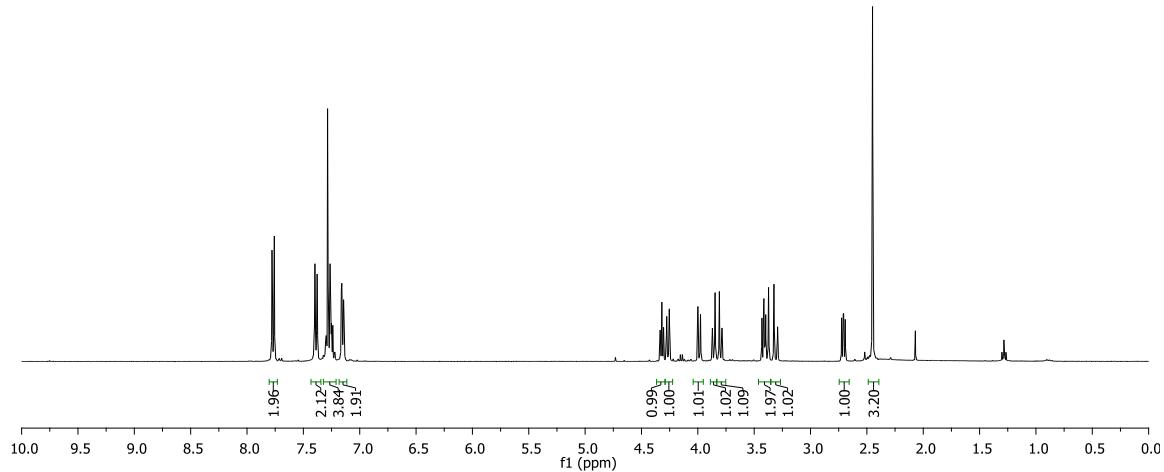
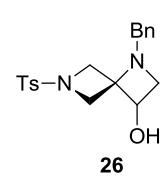


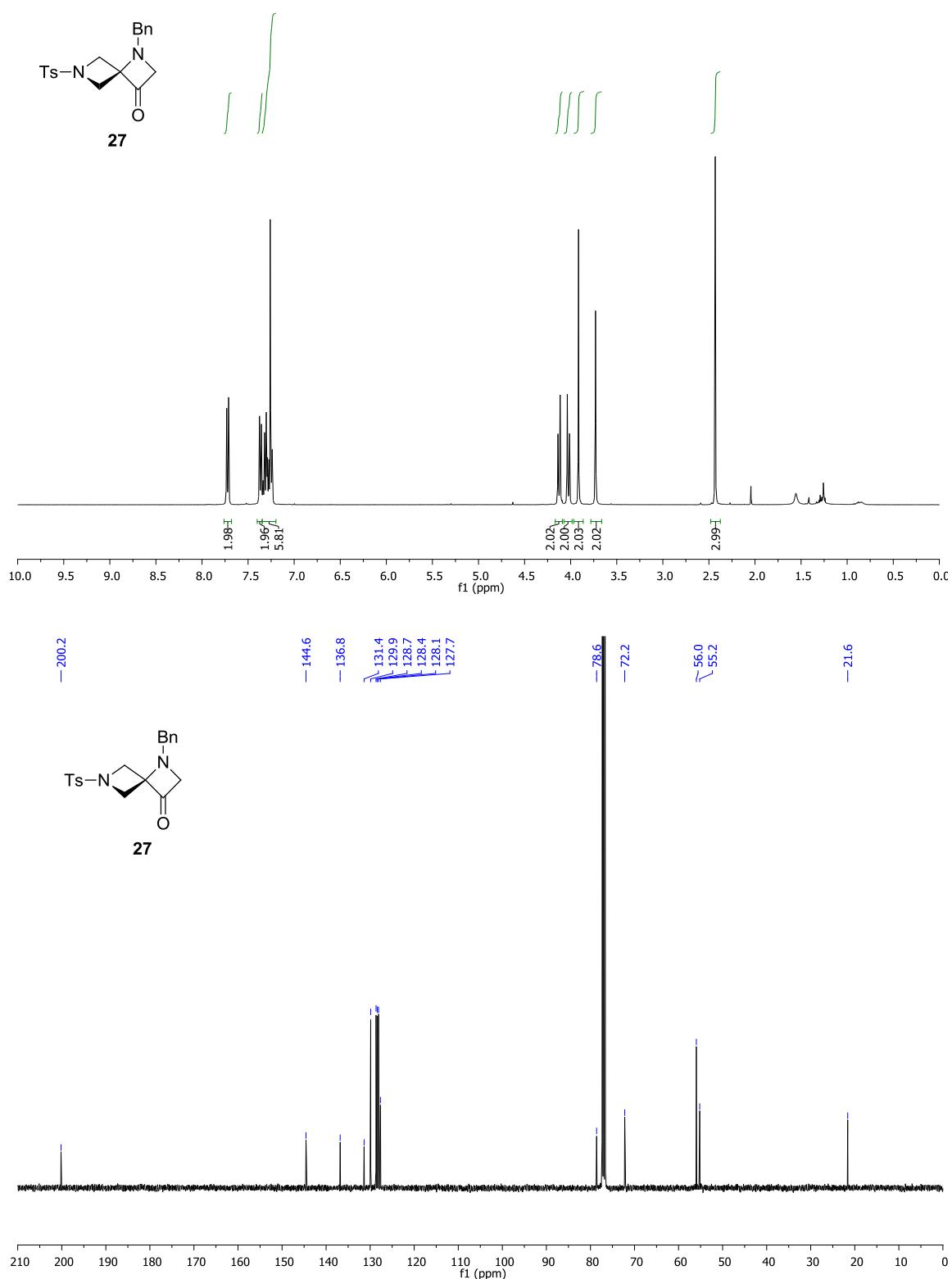


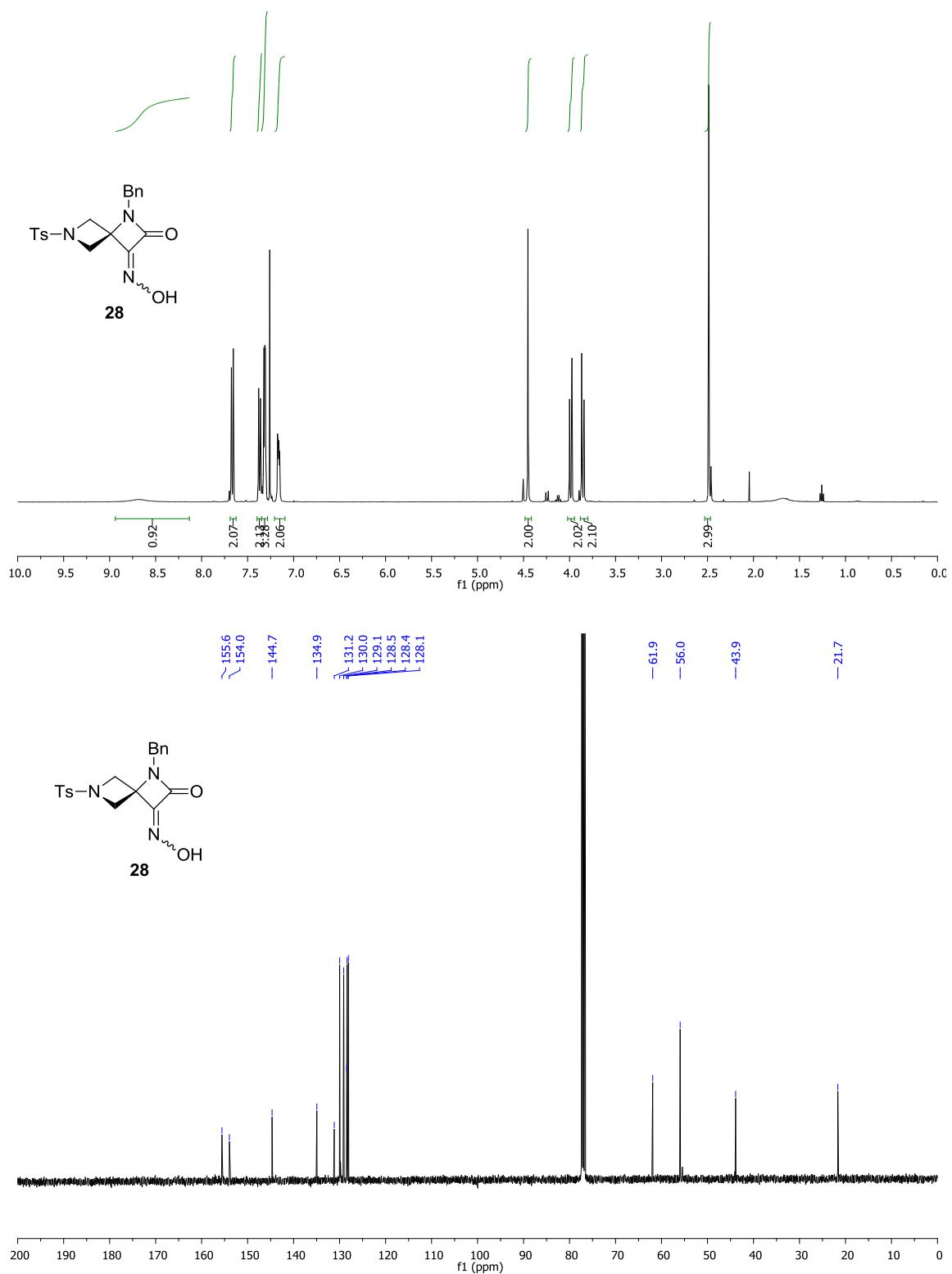


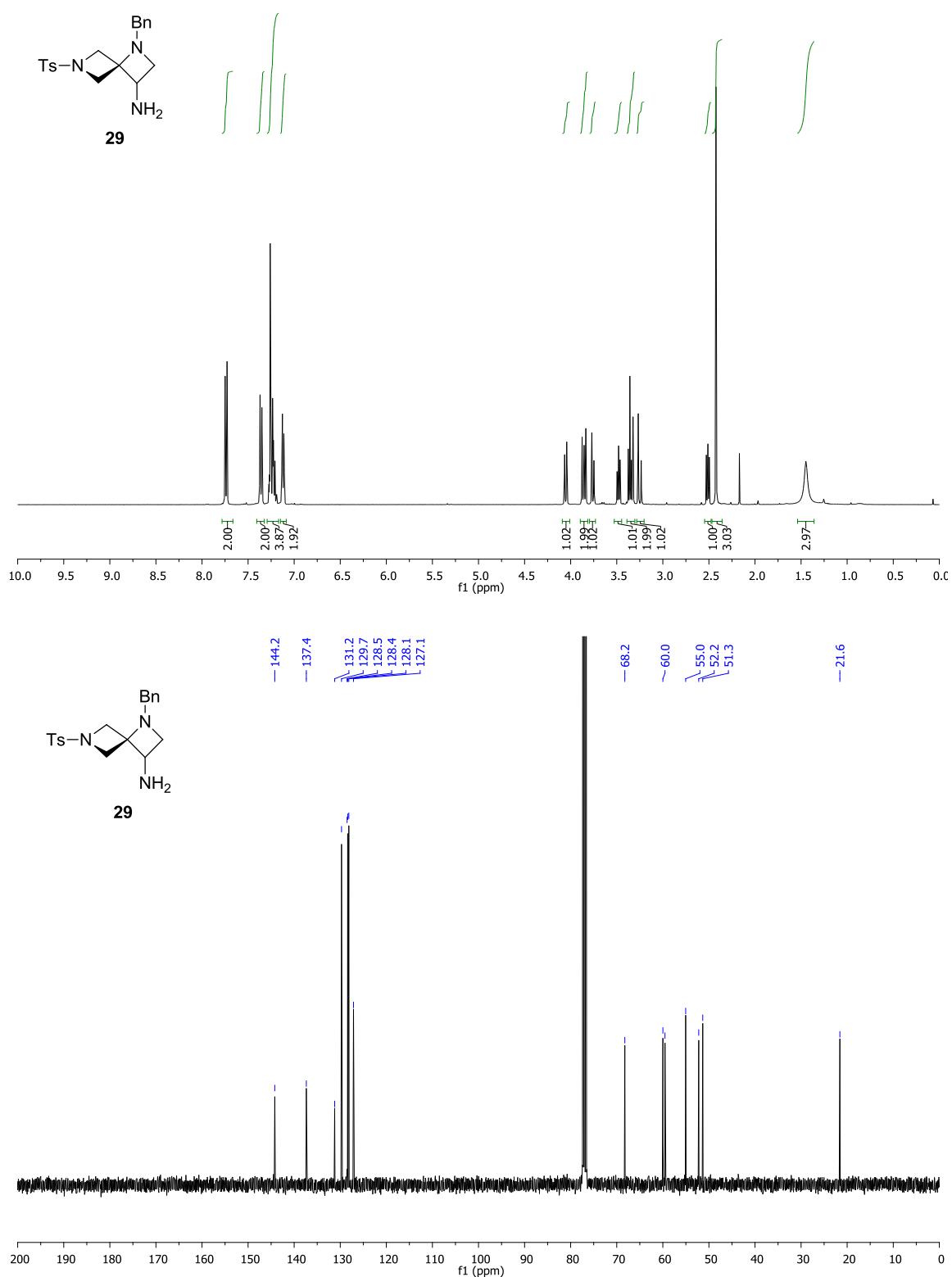






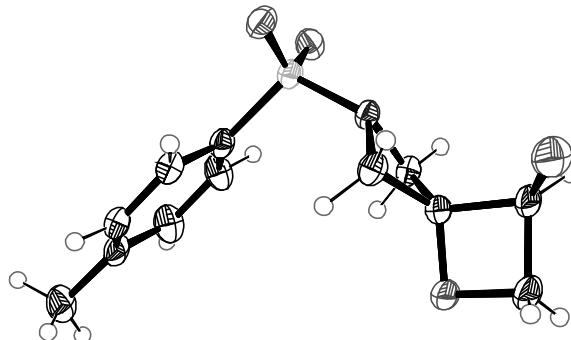






CRYSTALLOGRAPHIC DATA

Crystallographic Data of Compound 17



Crystal data

$C_{12}H_{15}NO_4S$	$D_x = 1.415 \text{ Mg m}^{-3}$
$C_{12}H_{15}NO_4S$	Density measured by: not measured
$M_r = 272.31$	fine-focus sealed tube
Triclinic P1	Mo $K\alpha$ radiation $\lambda = 0.71073$
$a = 12.0406(13) \text{ \AA}$	Cell parameters from 12664 refl.
$b = 14.1356(15) \text{ \AA}$	$\theta = 2.62\text{--}24.83^\circ$
$c = 14.145(3) \text{ \AA}$	$\mu = 0.261 \text{ mm}^{-1}$
$\alpha = 112.222(4)^\circ$	$T = 100 \text{ K}$
$\beta = 106.419(4)^\circ$	Plate
$\gamma = 106.584(3)^\circ$	$0.04 \times 0.2 \times 0.2 \text{ mm}$
$V = 1917.8(4) \text{ \AA}^3$	Colorless
$Z = 6$	Crystal source: LOC ETH Zurich
$F(000) = 862.0$	

Data collection

KappaCCD CCD diffractometer	$R_{\text{int}} = 0.038$
Absorption correction: none	$\theta_{\text{max}} = 24.83^\circ$
12664 measured reflections	$h = -14 \rightarrow 14$
6242 independent reflections	$k = -11 \rightarrow 16$
4734 observed reflections	$l = -16 \rightarrow 14$
Criterion: $>2\sigma(I)$	

Refinement

Refinement on F^2	All H-atom parameters refined
fullmatrix least squares refinement	Calculated weights $1/[\sigma^2(I_o)+(I_o+I_c)^2/900]$
$R(\text{all}) = 0.0765$	$\Delta/\sigma_{\text{max}} = 0.040$
$R(\text{gt}) = 0.0571$	$\Delta\rho_{\text{max}} = 0.780 \text{ e\AA}^{-3}$
$wR(\text{ref}) = 0.1695$	$\Delta\rho_{\text{min}} = -0.611 \text{ e\AA}^{-3}$
$wR(\text{gt}) = 0.1533$	Extinction correction: none
$S(\text{ref}) = 0.780$	Atomic scattering factors from International Tables Vol C
6242 reflections	Tables 4.2.6.8 and 6.1.1.4
679 parameters	
3 restraints	

Data collection: KappaCCD

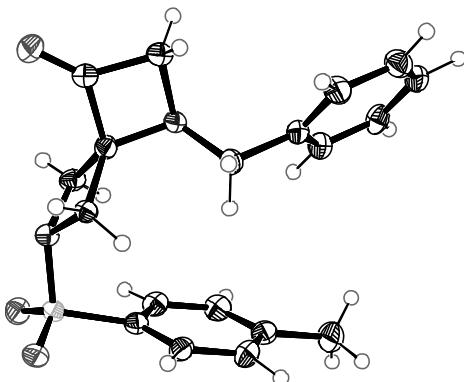
Cell refinement: HKL Scalepack (Otwinowski & Minor, 1997)

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

$C_{19}H_{20}N_2O_3S$	Density measured by: not measured
$C_{19}H_{20}N_2O_3S$	fine-focus sealed tube
$M_r = 356.439$	Mo $K\alpha$ radiation $\lambda = 0.71073$
Orthorhombic $Pna2_1$	Cell parameters from 11301 refl.
$a = 9.2975 (3) \text{ \AA}$	$\theta = 2.91-27.485^\circ$
$b = 9.6020 (3) \text{ \AA}$	$\mu = 0.202 \text{ mm}^{-1}$
$c = 19.9856 (8) \text{ \AA}$	$T = 100 \text{ K}$
$\alpha = 90.00^\circ$	Cube
$\beta = 90.00^\circ$	$0.33 \times 0.3 \times 0.21 \text{ mm}$
$\gamma = 90.00^\circ$	Pale yellow
$V = 1784.21 (11) \text{ \AA}^3$	Crystal source: LOC ETH Zurich
$Z = 4$	
$F(000) = 752.0$	

Data collection

KappaCCD CCD diffractometer	$R_{\text{int}} = 0.047$
Absorption correction: none	$\theta_{\text{max}} = 27.48^\circ$
11301 measured reflections	$h = -25 \rightarrow 25$
9219 independent reflections	$k = -12 \rightarrow 12$
2030 observed reflections	$l = -12 \rightarrow 12$
Criterion: $>2\sigma(I)$	

Refinement

Refinement on F^2	All H-atom parameters refined
fullmatrix least squares refinement	Calculated weights $1/[\sigma^2(I_o)+(I_o+I_c)^2/900]$
$R(\text{all}) = 0.0633$	$\Delta/\sigma_{\text{max}} = 0.001$
$R(\text{gt}) = 0.0423$	$\Delta\rho_{\text{max}} = 0.271 \text{ e\AA}^3$
$wR(\text{ref}) = 0.1185$	$\Delta\rho_{\text{min}} = -0.371 \text{ e\AA}^3$
$wR(\text{gt}) = 0.1041$	Extinction correction: none
$S(\text{ref}) = 0.816$	Atomic scattering factors from International Tables Vol C
3715 reflections	Tables 4.2.6.8 and 6.1.1.4
306 parameters	Flack parameter = 0.43 (8)
1 restraint	Flack H D (1983), <i>Acta Cryst. A</i> 39, 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)