Bromoethylsulfonium salt – a more effective annulation agent for the synthesis of 6- and 7-membered 1,4-heterocyclic compounds

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Supporting Information

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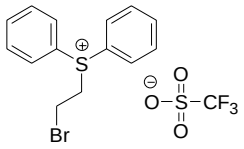
General Directions

Chromatography: Flash chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) unless otherwise stated. TLC was performed on aluminium-backed silica plates (60F254, 0.2 mm). The units of the specific rotation, (deg mL)/(g dm), are implicit and are not included with the reported value. Chemical shifts (δ_H) are quoted in parts per million (ppm), *J* values are given in Hz. Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. COSY, HMBC and HMQC were used where necessary in assigning NMR spectra. Anhydrous THF, CH_2Cl_2, Et_2O and toluene were obtained from a purification column composed of activated alumina (A- 2).[1] Other anhydrous solvents were used as obtained from Aldrich. Sodium hydride was purchased as a 60% dispersion in mineral oil and was used without removal of the mineral oil (similar results were obtained using NaH that had been washed).

Compounds **5a**–**c**, **5e**, **5j**, **5k**[2] and **11**[3] were prepared according to previously reported procedures. MP (where appropriate), ^{1}H NMR and ^{13}C NMR spectra were recorded and were in agreement with literature reports.

Synthesis of sulfonium salt 4

(2-Bromoethyl)diphenylsulfonium trifluoromethanesulfonate 4[2,4]

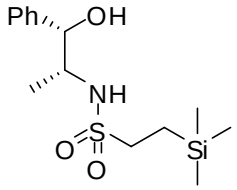


A solution of 2-bromoethyl trifluoromethanesulfonate[2] (3.24 g, 12.6 mmol) in anhydrous toluene (10 mL) was treated with phenyl sulfide (2.81 g, 15.1 mmol) at RT under nitrogen with stirring. The reaction mixture was then heated at 100 °C under nitrogen for 5 h. The solution was allowed to cool to RT and diethyl ether (20 mL) was added to precipitate the product **4** which was isolated by filtration as a white powder (4.51 g, 81%) after washing with Et_2O and used in the next step without further purification. mp 85–87 °C (precipitated from toluene/Et_2O) [lit.[5] 86.5–88 °C (precipitated from Et_2O/CH_2Cl_2)]; R_f (MeOH-CH_2Cl_2, 1:9) 0.20; δ_H (400 MHz; $CDCl_3$) 8.13–8.06 (4 H, m, ArH), 7.78–7.67 (6 H, m, ArH), 4.86 (2 H, t, *J* 6.5, S^+CH_2), 3.67 (2 H, t, *J* 6.5, $BrCH_2$); δ_c (100.5 MHz; $CDCl_3$) 135.3 (C), 131.9 (CH), 131.2 (CH), 122.9 (CH), 48.3 (CH_2), 23.8 (CH_2).

The above reaction can also be performed using trifluorotoluene instead of toluene. On cooling white crystals form. Et_2O was added to assist mobilization. Filtration and washing with Et_2O afforded **4** as white crystals (80% yield). mp 84–87 °C (trifluorotoluene). NMR spectra were identical to when toluene was used.

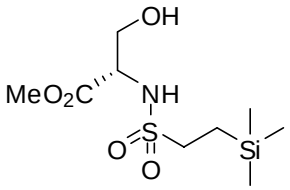
Synthesis of *N*-tosyl and *N*-SES-protected amino alcohols and diamines

Synthesis of *N*-((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-2-(trimethylsilyl) ethanesulfonamide 5d



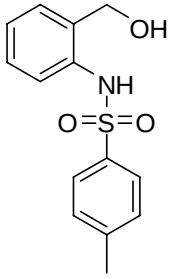
According to the procedure reported by Weinreb et al.,[6] D-(+)-norephedrine (0.500 g, 3.31 mmol) was dissolved in dry DMF (4 mL), cooled to 0 °C and triethylamine (1.67 g, 16.5 mmol) was added under argon. The reaction mixture was then treated with a solution of β-trimethylsilylethanesulfonyl chloride (0.664 g, 3.31 mmol) in DMF (2 mL). After stirring for 2 h at 0 °C the reaction mixture was poured into water (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (60 mL) and dried over Na_2SO_4, filtered, concentrated under vacuum and purified by silica gel chromatography (EtOAc-PE, 1:4) to afford the target compound **5d** as a white solid (0.850 g, 81%); R_f 0.32 (EtOAc-PE, 1:4); mp 71–73 °C (CH_2Cl_2); $[\alpha]_D^{22}$ +26 (*c*. 1.0, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3493 (OH), 3281 ($NHSO_2$), 1317 ($NHSO_2$); δ_H (300 MHz; $CDCl_3$) 7.40–7.28 (5 H, m, ArH), 4.89 (1 H, d, *J* 3.5, PhCH), 4.50 (1 H, br d, *J* 9.0, NH), 3.80–3.67 (1 H, m, NCH), 3.01–2.79 (2 H, m, SO_2CH_2), 2.68 (1 H, br s, OH), 1.09 (3 H, d, *J* 6.5, CH_3), 1.06–0.96 (2 H, m, $SiCH_2$), 0.05 (9 H, s, $Si(CH_3)_3$); δ_c (67.5 MHz; $CDCl_3$) 140.7 (C), 128.4 (CH), 127.8 (CH), 126.3 (CH), 76.5 (CH), 55.3 (CH), 50.0 (CH_2), 16.0 (CH_3), 10.6 (CH_2), –1.9 $Si(CH_3)_3$); *m/z* (ESI^+) 338 $[M+Na]^+$; HRMS (ESI^+) $C_{14}H_{25}NO_3SSiNa$ ($M+Na^+$) requires: 338.1222; found: 338.1217.

(*S*)-Methyl 3-hydroxy-2-(2-(trimethylsilyl)ethylsulfonamido)propanoate 5f



According to the procedure reported by Weinreb et al.,[6] L-serine methyl ester hydrochloride (0.515 g, 3.31 mmol) was dissolved in dry DMF (4 mL), cooled to 0 °C and triethylamine (1.67 g, 16.5 mmol) was added under argon. The reaction mixture was then treated with a solution of β-trimethylsilylethanesulfonyl chloride (0.664 g, 3.31 mmol) in DMF (2 mL). After stirring for 2 h at 0 °C the reaction mixture was poured into water (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (60 mL) and dried over Na_2SO_4, filtered, concentrated under vacuum and purified by silica gel chromatography (EtOAc-PE 2:8) to afford the target compound **5f** as a gummy white solid (0.415 g, 44% (unoptimized)); R_f 0.13 (EtOAc-PE, 3:7); $[\alpha]_D^{23}$ –4.0 (*c*. 1.0, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3502 (OH), 3291 ($NHSO_2$), 1746 (CO), 1329 ($NHSO_2$); δ_H (400 MHz; $CDCl_3$) 5.57 (1 H, d, *J* 8.5, NH), 4.22 (1 H, ddd, *J* 8.5, 3.8, 3.8, NCH), 4.02–3.95 (2 H, m, C*H*$_2$OH), 3.81 (3 H, s, OCH_3), 3.05–2.92 (2 H, m, C*H*$_2$$SO_2$), 2.75 (1 H, t, *J* 6.5, OH), 1.16–0.99 (2 H, m, C*H*$_2$Si), 0.05 (9 H, s, $Si(CH_3)_3$); δ_c (100.5 MHz; $CDCl_3$) 170.9 (C=O), 64.0 (CH_2), 57.9 (CH), 53.0 (OCH_3), 50.0 (CH_2), 10.3 (CH_2), –2.0 $Si(CH_3)_3$); *m/z* (ESI^+) 306 $[M+Na]^+$; HRMS (ESI^+) $C_9H_{21}NO_5SSiNa$ ($M+Na^+$) requires: 306.0807; found: 306.0802.

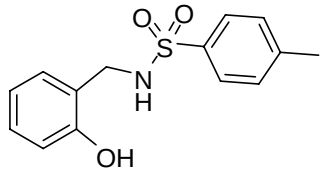
***N*-(2-(Hydroxymethyl)phenyl)-4-methylbenzenesulfonamide, 8a**[7]



The procedure reported by Fonseca et al.[8] was modified slightly. To a solution of (2-aminophenyl)methanol (1.00 g, 8.12 mmol) and pyridine (0.963 g, 12.2 mmol) in dry CH_2Cl_2 (50 mL) was added tosyl chloride (1.70 g, 8.92 mmol) in CH_2Cl_2 (30 mL) dropwise over 5 min. The reaction mixture was stirred for 3 h and then concentrated

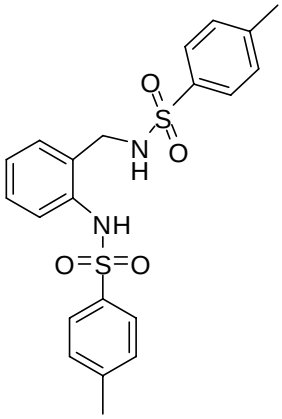
under vacuum. The residue was dissolved into EtOAc (150 mL) and washed with saturated aqueous ammonium chloride (3 × 50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum to give the title compound **8a** as a white solid (1.28 g, 56%); R_f 0.16 (EtOAc-PE, 3:7); mp 148–150 °C ($CHCl_3$) [lit.[7] mp 148–150 °C (isopropyl ether)]; δ_H (300 MHz; $CDCl_3$) 7.90 (1 H, s, NH), 7.65 (2 H, d, *J* 8.5, ArH), 7.44 (1 H, d, *J* 8.5, ArH), 7.33–7.20 (3 H, m, ArH), 7.15–7.05 (2 H, m, ArH), 4.40 (2 H, br d, *J* 5.5), 2.39 (3 H, s, CH_3), 2.25–2.12 (1 H, m, OH); δ_c (75 MHz; $CDCl_3$) 143.8 (C), 136.9 (C), 136.4 (C), 131.6 (C), 129.6 (CH), 129.2 (CH), 129.0 (CH), 127.0 (CH), 125.4 (CH), 123.4 (CH), 63.9 (CH_2), 21.5 (CH_3);

_N_-(2-Hydroxybenzyl)-4-methylbenzenesulfonamide, 8b[9]



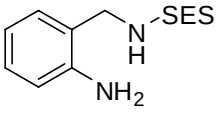
A modification of the procedure reported by Inoue et al.[9] was used. 2-(Aminomethyl)phenol (0.085 g, 0.69 mmol) was dissolved in dry CH_2Cl_2 (15 mL), cooled to 0 °C and triethylamine (0.104 g, 1.03 mmol) was added under argon and the reaction stirred for 5 min. The reaction mixture was then treated with tosyl chloride (0.144 g, 0.755 mmol) and stirred for 3 h. After that the reaction mixture was allowed to warm to RT. After stirring for 3 h, the reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 3 N NaOH (50 mL), and the aqueous layer was neutralized with conc. HCl and extracted with CH_2Cl_2 (3 × 50 mL) washed with brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated under vacuum and recrystallization (EtOAc-PE) afforded the title compound **8b** as a white crystals (0.120 g, 63%); R_f 0.24 (EtOAc-PE, 3:7); mp 112–114 °C (CH_2Cl_2) [lit.[10] mp 110 °C (CH_2Cl_2/petrol)]; δ_H (400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.5, ArH), 7.26 (2 H, d, *J* 7.5, ArH), 7.16–7.10 (1 H m, ArH), 6.99 (1 H, d, *J* 6.5, ArH), 6.81–6.74 (2 H, m, ArH), 6.22 (1 H, s, OH) 5.17 (1 H, br t, *J* 5.5, NH), 4.12 (2 H, d, *J* 5.5, NHC*H*$_2$), 2.41 (3 H, s, CH_3); δ_c (100.5 MHz; $CDCl_3$) 154.4 (C), 143.7 (C), 136.2 (C), 130.0 (CH), 129.7 (CH), 129.6 (CH), 127.1 (CH), 122.0 (C), 120.6 (CH), 116.1 (CH), 44.2 (CH_2), 21.5 (CH_3).

4-Methyl-*N*-(2-(4-methylphenylsulfonamido)benzyl)benzenesulfonamide, 8c[11]



According to the procedure reported by Beddoes et al.,[11] a solution of 2-(aminomethyl)aniline (0.500 g, 4.09 mmol), pyridine (9 mL) and tosyl chloride (2.34 g, 12.3 mmol) was heated at reflux for 30 min. The reaction mixture was allowed to cool to RT, poured into crushed ice and then conc. HCl was added slowly until pH ~0. The mixture was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with dil. HCl (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated under vacuum to afford the target compound **8c** as a white solid (0.850 g, 81%); R_f 0.20 (EtOAc-PE, 3:7); mp 129–131 °C (toluene) [lit.[11] mp 130–132 °C (toluene)]; δ_H (400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.5, ArH), 7.57 (2 H, d, *J* 8.5, ArH), 7.31 (2 H, d, *J* 8.0, ArH), 7.20 (2 H, dd, *J* 8.5, 0.6, ArH), 7.19–7.13 (2 H, m, ArH), 7.12–7.07 (2 H, m, ArH), 5.17 (1 H, t, *J* 6.5, NH), 3.80 (2 H, d, *J* 6.5, NHCH_2), 2.44 (3 H, s, CH_3), 2.39 (3 H, s, CH_3); δ_c (100.5 MHz; $CDCl_3$) 143.9 (C), 143.8 (C), 136.2 (C), 136.0 (C), 134.9 (C), 130.9 (C), 130.8 (CH), 129.8 (CH), 129.6 (CH), 129.2 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 125.9 (CH), 44.0 (CH_2), 21.5 (2 × CH_3);

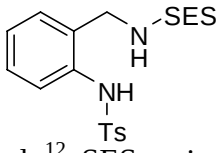
***N*-(2-Aminobenzyl)-2-(trimethylsilyl)ethanesulfonamide, 10**



Using the procedure of Weinreb et al.,[6] 2-aminobenzyl amine (0.608 g, 4.98 mmol) was dissolved in dry DMF (10 mL), cooled to 0 °C and then triethylamine (2.52 g, 24.9 mmol) was added under argon. The reaction mixture was then treated with a solution of β-trimethylsilylethanesulfonyl chloride (1.00 g, 4.98 mmol) in DMF (2 mL). After stirring for 2 h at 0 °C the reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were

washed with very dilute HCl (pH = 5, a few drops of dil. HCl were added to 300 mL of water) (3 × 100 mL), and then with aqueous 1 N HCl solution (3 × 100 mL). The latter aqueous phase was basified until pH = 14 and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (60 mL) and dried over Na_2SO_4, filtered, concentrated under vacuum and purified by recrystallization (CH_2Cl_2-PE) to afford the target compound **10** as a white crystals (0.985 g, 69%); R_f 0.56 (CH_2Cl_2-MeOH, 9:1); mp 142–144 °C (CH_2Cl_2-PE); ν_{max} (neat)/cm^{-1} 3488 (NH_2), 3394 (NH_2), 3287 ($NHSO_2$), 1309 ($NHSO_2$); δ_H (300 MHz; $CDCl_3$) 7.18–7.05 (2 H, m, ArH), 6.76–6.67 (2 H, m, ArH), 4.68 (1 H, t, *J* 5.9, N*H*CH_2), 4.20 (2 H, d, *J* 5.9, NHC*H*$_2$), 4.08 (2 H, br s, NH_2), 2.91–2.83 (2 H, m, CH_2SO_2), 0.98–0.90 (2 H, m, CH_2Si), 0.01 (9 H, s, $Si(CH_3)_3$), δ_c (100.5 MHz; $CDCl_3$) 145.3 (C), 130.3 (CH), 129.7 (CH), 120.5 (CH), 118.4 (CH), 116.4 (C), 49.0 (CH_2), 45.0 (CH_2), 10.4 (CH_2), –2.1 ($Si(CH_3)_3$); *m/z* (ESI$^+$) 309 [M+Na]$^+$; HRMS (ESI$^+$) $C_{12}H_{22}N_2O_2SSiNa$ (M+Na$^+$) requires: 309.1064; found: 309.1072.

4-Methyl-*N*-(2-((2-(trimethylsilyl)ethylsulfonamido)methyl)phenyl)benzenesulfonamide, 8d

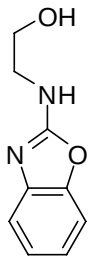


Using the procedure of Hara et al.,[12] SES-amine **10** (0.128 g, 0.447 mmol) was dissolved in pyridine (2 mL), stirred under argon, cooled to 0 °C and treated with tosyl chloride (0.128 g, 0.670 mmol). The reaction was then allowed to warm to RT and stirred for 12 h. After 12 h the reaction mixture was treated with water (1 mL) and further stirred for 30 min at RT, diluted with EtOAc, and washed with dil. HCl solution (3 × 100 mL), brine (50 mL) and dried over $MgSO_4$. After concentrating under vacuum, the title compound **8d** was obtained as a white gummy solid (0.196 g, 99%); R_f 0.27 (EtOAc-PE, 3:7); ν_{max} (neat)/cm^{-1} 3271 ($NHSO_2$), 1322 ($NHSO_2$); δ_H (400 MHz; $CDCl_3$) 7.60 (2 H, d, *J* 8.5, ArH), 7.39 (1 H, s, N*H*Ts), 7.34–7.28 (1 H, m, ArH), 7.22 (2 H, d, *J* 8.5, ArH), 7.20–7.14 (2 H, m, ArH), 7.08–7.02 (1 H, m, ArH), 5.18 (1 H, t, *J* 6.5, N*H*CH_2), 4.08 (2 H, d, *J* 6.5, NHC*H*$_2$), 2.86–2.80 (2 H, m, CH_2SO_2), 2.40 (3 H, s, CH_3), 0.98–0.91 (2 H, m, CH_2Si), –0.00 (9 H, s, $Si(CH_3)_3$); δ_c (100.5 MHz; $CDCl_3$) 144.0 (C), 136.1 (C), 134.6 (C), 132.4 (C), 131.0 (CH), 129.6 (CH), 129.2 (CH), 127.3 (CH), 127.0 (CH), 126.2 (CH), 49.3 (CH_2), 43.6 (CH_2), 21.5

(CH_3), 10.3 (CH_2), –2.09 ($Si(CH_3)_3$); *m/z* (ESI^+) 463 $[M+Na]^+$; HRMS (ESI^+) $C_{19}H_{28}N_2O_4S_2SiNa$ ($M+Na^+$) requires: 463.1152; found: 463.1151.

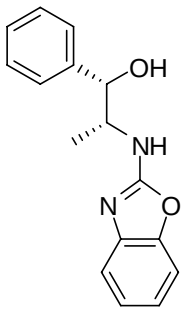
Synthesis of *N*-aromatic and *N*-heteroaromatic β-amino alcohols

2-(Benzo[*d*]oxazol-2-ylamino)ethanol, 5h[13]



According to the procedure reported by Kim et al.,[13] 2-chlorobenzoxazole (1.00 g, 6.51 mmol) was dissolved into THF (15 mL) and treated with 2-hydroxyethylamine (0.840 g, 13.8 mmol) at RT. The reaction mixture was stirred for 3 h, poured into water (100 mL), and extracted with EtOAc (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to obtain the title compound **5h** as a white solid (1.10 g, 95%); R_f 0.12 (EtOAc-PE, 8:2); mp 158–160 °C (EtOAc-PE) [lit.[13] mp 156–157 °C (hexane-Et_2O)]; δ_H (400 MHz, CD_3OD) 7.27–7.23 (m, 2 H) 7.14 (ddd, *J* 7.5, 7.5, 1.1, 1 H) 7.02 (ddd, *J* 7.8, 7.5, 1.2, 1 H), 3.75 (t, *J* 5.7, 2 H), 3.50 (t, *J* 5.7, 2 H); δ_c (100.5 MHz; CD_3OD) 164.5 (C), 149.8 (C), 143.7 (C), 125.2 (CH), 122.2 (CH), 116.5 (CH), 109.8 (CH), 61.5 (CH_2), 46.3 (CH_2).

(1*S*,2*R*)-2-(Benzo[*d*]oxazol-2-ylamino)-1-phenylpropan-1-ol, 5i



According to the procedure reported by Kim et al.,[13] 2-chlorobenzoxazole (0.242 g, 1.58 mmol) was dissolved into THF (20 mL) and treated with D-(+)-norephedrine (0.500 g, 3.31 mmol) at RT. The reaction mixture was stirred for 3 h, poured into water (100 mL), and extracted with EtOAc (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to obtain the title compound **5i** as a white solid (0.386

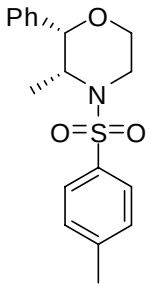
g, 91%); R_f 0.37 (EtOAc-PE, 6:4); mp 78–80 °C (EtOAc-PE); $[\alpha]_D^{22}$ 55 (*c*. 2.0, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3397, 1645, 1584, 1461; δ_H (400 MHz, $CDCl_3$) 7.44–7.35 (5 H, m, ArH), 7.33–7.25 (2 H, m, ArH), 7.19 (1 H, ddd, *J* 7.5, 7.5, 1.5, ArH), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.5, ArH), 5.29–5.19 (1 H, m), 5.08 (1 H, d, *J* 2.8, PhCH), 4.36–4.26 (1 H, m, NCH), 1.18 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 161.8 (C), 148.3 (C), 142.3 (C), 140.8 (C), 128.2 (CH), 127.5 (CH), 126.1 (CH), 124.0 (CH), 120.9 (CH), 116.1 (CH), 108.8 (CH), 75.6 (CH), 54.6 (CH), 14.2 (CH_3); *m/z* (CI^+) 269 $[M+H]^+$; HRMS (CI^+) $C_{16}H_{17}N_2O_2$ (MH^+) requires: 269.1290; found: 269.1289.

Synthesis of morpholines 6a–i, thiomorpholine 6j, piperazine 6k, benzoxazepines 9a and 9b, benzodiazepines 9c and 9d

General method A

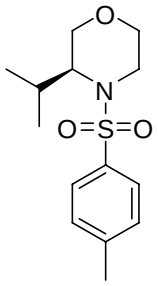
A stirring solution of the requisite amino alcohol, amino thiol or diamine (0.079–0.41 mmol) in CH_2Cl_2 (10–30 mL) was treated with NaH or DBU (3.5–7.5 eq) at 0 °C under argon. After 5 min, 2-bromoethyldiphenylsulfonium salt **4** (1.2–3.75 eq) was added and the reaction was stirred for 3 h at 0 °C, followed by 12 h at RT. The reaction was then quenched with saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The product was then purified using chromatography on silica.

(2*S*,3*R*)-3-Methyl-4-[(4-methylphenyl)sulfonyl]-2-phenylmorpholine 6a[2]



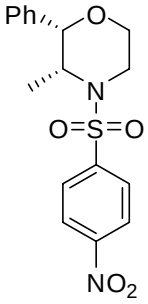
Following general method **A**, using *N*-tosyl-β-amino alcohol **5a** (0.050 g, 0.16 mmol), NaH (0.014 g, 0.58 mmol) and bromoethyldiphenylsulfonium salt **4** (0.085 g, 0.19 mmol), after chromatography (EtOAc-PE, 2:8) the title compound **6a** was isolated as a white gummy solid (0.047 g, 86%); R_f 0.67 (EtOAc-PE, 2:8); δ_H (400 MHz; $CDCl_3$) 7.74 (2 H, d, *J* 8.5, ArH), 7.35–7.22 (7 H, m, ArH), 4.63 (1 H, d, *J* 3.0, PhCH), 4.20 (1 H, dq, *J* 7.0, 3.0, NC*H*Me), 4.05 (1 H, dd, *J* 12.5, 3.0, OCH_{eq}H), 3.70 (1 H, ddd, *J* 12.5, 12.5, 3.0, OCHH_{ax}), 3.60 (1 H, dd, *J* 12.5, 3.0, NCH_{eq}H), 3.25 (1 H, ddd, *J* 12.5, 12.5, 3.0, NCHH_{ax}), 2.43 (3 H, s, Ar-CH_3), 0.72 (3 H, d, *J* 7.0, CH-CH_3); δ_c (100.5 MHz; $CDCl_3$) 143.4 (C), 138.7 (C), 137.9 (C), 129.8 (CH), 128.3 (CH), 127.4 (CH), 127.2 (CH), 125.4 (CH), 80.4 (CH), 67.1 (CH_2), 53.3 (CH), 39.5 (CH_2), 21.4 (CH_3), 9.2 (CH_3).

(3*S*)-3-Isopropyl-4-[(4-methylphenyl)sulfonyl]morpholine 6b[2]



Following general method **A**, using *N*-tosyl-β-amino alcohol **5b** (0.050 g, 0.19 mmol), NaH (0.017 g, 0.71 mmol) and bromoethyldiphenylsulfonium salt **4** (0.103 g, 0.232 mmol), after chromatography (EtOAc-PE, 2:8) the title compound **6b** was isolated as colorless crystals (0.051 g, 93%); R_f 0.62 (EtOAc-PE, 3:7); mp 98–100 °C (EtOAc-PE) [lit.[2] mp 99–101 °C (EtOAc-PE)]; δ_H (400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.5, ArH), 7.31 (2 H, d, *J* 8.5, ArH), 3.82 (1 H, d, *J* 11.5, CHCH*H*O), 3.66–3.59 (2 H, m, NCH*H*, OCH*H*CH), 3.35–3.10 (4 H, m, NCH*H*CH*H*OCH*H*C*H*), 2.43 (3 H, s, Ar-CH_3), 2.35–2.20 (1 H, m, Me_2CH), 0.99 (3 H, d, *J* 6.5, CH_3), 0.97 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 143.2 (C), 138.9 (C), 129.8 (CH), 126.9 (CH), 66.2 (CH_2), 65.5 (CH_2), 59.7 (CH), 41.2 (CH_2), 25.3 (CH), 21.5 (CH_3), 19.9 (CH_3), 19.8 (CH_3).

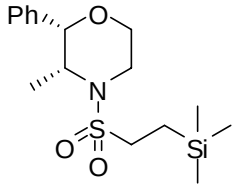
(2*S*,3*R*)-3-Methyl-4-[(4-nitrophenyl)sulfonyl]-2-phenylmorpholine 6c[2]



Following general method **A**, using *N*-nosyl-β-amino alcohol **5c** (0.028 g, 0.083 mmol), NaH (0.010 g, 0.42 mmol) and bromoethyldiphenylsulfonium salt **4** (0.092 g, 0.21 mmol), after chromatography (EtOAc-PE, 3:7) the title compound **6c** was isolated as pale yellow crystals (0.027 g, 90%); R_f 0.56 (EtOAc-PE, 3:7); mp 133–134 °C (EtOAc-PE) [lit.[2] mp 133–134 °C (EtOAc-PE)]; δ_H (400 MHz; $CDCl_3$) 8.40 (2 H, d, *J* 8.5, ArH), 8.06 (2 H, d, *J* 8.5, ArH), 7.37–7.23 (5 H, m, ArH), 4.69 (1 H, d, *J* 2.5, PhCH), 4.26 (1 H, qd, *J* 6.5, 2.5, NC*H*Me), 4.14 (1 H, dd, *J* 12.5, 3.5, OCH_{eq}H), 3.77 (1 H, ddd, *J* 12.5, 12.5, 3.5, OCH_{ax}H), 3.66 (1 H, dd, *J* 12.5, 3.5, NCH_{eq}H), 3.31 (1 H, ddd, *J* 12.5, 12.5, 3.5, NCH_{ax}H), 0.75 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$)

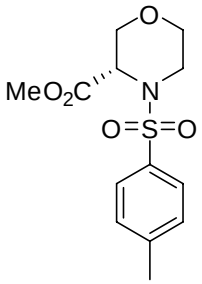
150.2 (C), 146.6 (C), 138.2 (C), 128.6 (CH), 128.3 (CH), 127.8 (CH), 125.4 (CH), 124.7 (CH), 80.6 (CH), 67.3 (CH_2), 53.8 (CH), 39.7 (CH_2), 9.4 (CH_3).

(2*S*,3*R*)-3-Methyl-2-phenyl-4-(2-(trimethylsilyl)ethylsulfonyl)morpholine, 6d



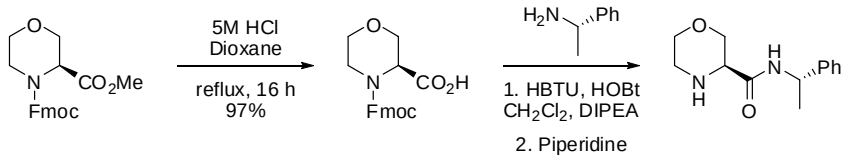
Following general method **A**, using *N*-SES-β-amino alcohol **5d** (0.025 g, 0.079 mmol), NaH (0.007 g, 0.3 mmol) and bromoethyldiphenylsulfonium salt **4** (0.042 g, 0.095 mmol), after chromatography (EtOAc-PE, 1:9) the title compound **6d** was obtained as a gummy solid (0.025 g, 93%); R_f 0.49 (EtOAc-PE, 1:9); $[\alpha]_D^{22}$ –13 (*c*. 0.68, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3293 ($NHSO_2$), 1327 ($NHSO_2$); δ_H (400 MHz; $CDCl_3$) 7.40–7.26 (5 H, m, ArH), 4.78 (1 H, d, *J* 3.0, PhCH), 4.17–4.07 (2 H, m, CH_3CH, OCH*H*), 3.81 (1 H, ddd, *J* 12.0, 12.0, 3.5, OCHH_{ax}), 3.54 (1 H, dddd, *J* 13.5, 3.5, 0.9, 0.9, NCHH_{eq}), 3.43 (1 H, ddd, 13.5, 12.0, 3.5, NCHH_{ax}), 2.99–2.89 (2 H, m, SO_2CH_2), 1.15–0.99 (2 H, m, $SiCH_2$) 1.02 (3 H, d, *J* 6.8 Hz, CH_3), 0.09 (s, 9H, $Si(CH_3)_3$); δ_c (100 MHz; $CDCl_3$) 138.8 (C), 128.3 (CH), 127.5 (CH), 125.3 (CH), 80.7 (CH), 67.8 (CH_2), 53.2 (CH), 49.2 (CH_2), 39.9.0 (CH_2), 10.6 (CH_3), 10.4 (CH_2), –2.0 (3 × CH_3); *m/z* (ESI^+) 364 $[M+Na]^+$; HRMS (ESI^+) $C_{16}H_{27}NO_3SSiNa$ ($M+Na^+$) requires: 364.1379; found: 364.1373.

Methyl (3*S*)-4-[(4-methylphenyl)sulfonyl]morpholine-3-carboxylate 6e[2]



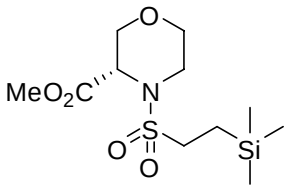
Following general method **A**, using *N*-tosyl-β-amino alcohol **5e** (0.050 g, 0.18 mmol), NaH (0.016 g, 0.67 mmol) and bromoethyldiphenylsulfonium salt **4** (0.097 g, 0.22 mmol), after chromatography (EtOAc-PE, 3:7), the title compound **6e** was isolated as a colorless crystals (0.051 g, 93%); R_f 0.64 (EtOAc-PE, 4:6); mp 98–100 °C (EtOAc-PE) [lit.[2] mp 98–99 °C (EtOAc-PE)]; $[\alpha]_D^{24}$ –68 (*c* 1.0, CH_2Cl_2) [lit.[2] $[\alpha]_D^{22}$ –68 (*c* 1.0, CH_2Cl_2)]; δ_H (400 MHz; $CDCl_3$) 7.66 (2 H, d, *J* 8.5, ArH), 7.30 (2 H, d, *J* 8.5, ArH),

4.50 (1 H, d, *J* 3.0, NCH), 4.26 (1 H, d, *J* 11.5, NCHCH*H*), 3.85 (1 H, dd, *J* 11.5, 3.0, NCH_2CH*H*), 3.69 (1 H, dd, *J* 11.5, 3.0, NCHCH*H*), 3.61–3.39 (3 H, m, NC*H*$_2CH$*H*), 3.55 (3 H, s, OCH_3), 2.42 (3 H, s, Ar-CH_3); δ_c (100.5 MHz; $CDCl_3$) 169.5 (C), 143.7 (C), 136.4 (C), 129.6 (CH), 127.4 (CH), 68.8 (CH_2), 66.7 (CH_2), 55.4 (CH), 52.4 (CH_3), 42.0 (CH_2), 21.7 (CH_3). Morpholine **6e** was further transformed into Fmoc-protected morpholine **7** using previously described procedures.[2] The optical rotation and other characterization data were identical to those described by Guarna and co-workers.[14] They reported the hydrolysis of **7**, followed by derivatization with (*S*)-1-phenylethylamine (98% pure) and Fmoc-deprotection (see Scheme 1). They demonstrated that the resulting amide had a diastereomeric purity of >96% by HPLC. Thus, the stereogenic center of **6e** has not been racemized during the reaction.



Scheme 1 Derivatization of Fmoc-protected morpholine 7 for determination of enantiopurity

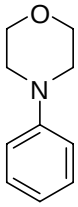
(*S*)-Methyl 4-(2-(trimethylsilyl)ethylsulfonyl)morpholine-3-carboxylate, 6f



Following general method **A**, using *N*-SES-β-amino alcohol **5f** (0.056 g, 2.0 mmol), NaH (0.017 g, 0.71 mmol) and bromoethyldiphenylsulfonium salt **4** (0.105 g, 0.237 mmol), after chromatography (EtOAc-PE, 3:7) the title compound **6f** was obtained as a gummy solid (0.058 g, 95%); R_f 0.43 (EtOAc-PE, 3:7); $[\alpha]_D^{22}$ –40 (*c*. 1.0, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 1747 (CO), 1327, 1329 ($NHSO_2$); δ_H (300 MHz; $CDCl_3$) 4.48 (1 H, d, *J* 3.5, NCH), 4.41–4.37 (1 H, m, NCHCH*H*O), 3.90–3.87 (1 H, m, OCH*H*CH_2N), 3.81 (3 H, s, OCH_3), 3.74 (1 H, dd, *J* 3.5, 11.5, NCHC*H*HO), 3.63–3.53 (3 H, m, C*H*$_2$CH*H*), 3.08–2.98 (1 H, m, SO_2CH_2), 1.18–1.02 (2 H, m, $SiCH_2$), 0.07 (9 H, s, $Si(CH_3)_3$); δ_c (100.5 MHz; $CDCl_3$) 170.2 (C=O), 68.9 (CH_2), 67.1 (CH_2), 55.8 (CH), 52.6 (CH_3), 49.0 (CH_2), 42.6 (CH_2), 10.1 (CH_2), –2.0 (3 × CH_3); *m/z* (CI^+) 310 $[M+H]^+$; HRMS (CI^+) $C_{11}H_{24}NO_5SSi$ (MH^+) requires: 310.1144; found: 310.1153. Morpholine **6f** was further transformed into Fmoc-protected morpholine **7** (see below for details). The optical rotation and other characterization data were identical to those

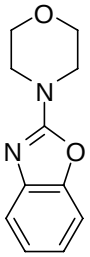
described by Guarna and co-workers.[14] They reported the hydrolysis of **7**, followed by derivatization with (*S*)-1-phenylethylamine (98% pure) and Fmoc-deprotection (see Scheme 1). They demonstrated that the resulting amide had a diastereomeric purity of >96% by HPLC. Thus, the stereogenic center of **6f** has not been racemized during the reaction.

4-Phenylmorpholine, 6g[15]



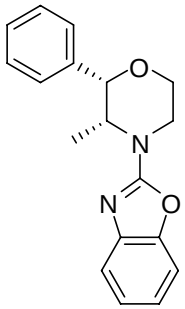
Following general method **A**, using 2-(phenylamino)ethanol **5g** (0.056 g, 0.41 mmol), NaH (0.049 g, 2.0 mmol) and bromoethyldiphenylsulfonium salt **4** (0.452 g, 1.02 mmol), after chromatography (EtOAc-PE, 2.5:7.5) the title compound **6g** was obtained as a white solid (0.062 g, 93%); R_f 0.68 (EtOAc-PE, 1:1); mp 51–53 °C (EtOAc-PE) [lit.[15] mp 53–55 °C]; δ_H (400 MHz; $CDCl_3$) 7.32–7.26 (m, 2 H), 6.95–6.87 (m, 3 H), 3.89–3.86 (m, 4 H), 3.18–3.15 (m, 4 H); δ_c (100.5 MHz; $CDCl_3$) 151.3 (C), 129.2 (CH), 120.0 (CH), 115.7 (CH), 66.9 (CH_2), 49.4 (CH_2);

2-Morpholinobenzo[*d*]oxazole, 6h[16,17]



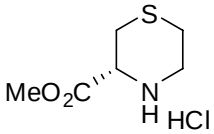
Following general method **A**, using 2-(benzofuran-2-ylamino)ethanol **5h** (0.020 g, 0.11 mmol), NaH (0.020 g, 0.83 mmol) and bromoethyldiphenylsulfonium salt **4** (0.186 g, 0.420 mmol), after chromatography (EtOAc-PE, 8:2) the title compound **6h** was obtained as a white solid (0.021 g, 92%); R_f 0.48 (EtOAc-PE, 8:2); mp 84–86 °C (EtOAc) [lit.[16] mp 84–85 °C (CH_3OH-H_2O)]; δ_H (400 MHz, $CDCl_3$) 7.39 (1 H, ddd, *J* 7.5, 1.5, 0.5, ArH), 7.29–7.26 (1 H, m, ArH), 7.19 (1 H, ddd, *J* 7.5, 7.5, 1.5, ArH), 7.06 (1 H, ddd, *J* 7.5, 1.5, 0.5, ArH), 3.86–3.82 (4 H, m, CH_2), 3.72–3.69 (4 H, m, CH_2); δ_c (100.5 MHz; $CDCl_3$) 162.1 (C), 148.7 (C), 142.8 (C), 124.1 (CH), 120.9 (CH), 116.5 (CH), 108.8 (CH), 66.2 (CH_2), 45.7 (CH_2).

2-((2*S*,3*R*)-3-Methyl-2-phenylmorpholino)benzo[*d*]oxazole, 6i



Following general method **A**, using (1*S*,2*R*)-2-(benzofuran-2-ylamino)-1-phenylpropan-1-ol **5i** (0.040 g, 0.15 mmol), NaH (0.027 g, 1.1 mmol) and bromoethyldiphenylsulfonium salt **4** (0.248 g, 0.559 mmol), after chromatography (EtOAc-PE, 6:4) the title compound **6i** was obtained as a gummy solid (0.030 g, 68%); R_f 0.53 (EtOAc-PE, 6:4); $[\alpha]_D^{22}$ –60 (*c*. 0.2, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 1633, 1574, 1459; δ_H (400 MHz; $CDCl_3$) 7.45–7.35 (5 H, m, ArH), 7.33–7.28 (2 H, m, ArH), 7.20 (1 H, ddd, *J* 7.5, 7.5, 1.5, ArH), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.5, ArH), 4.87 (1 H, d, *J* 3.0, PhCH), 4.54 (1 H, qd, *J* 6.5, 3.0, NC*H*CH_3), 4.24 (1 H, dd, *J* 12.0, 3.5, OCHH_{eq}), 3.99 (1 H, dd, *J* 12.0, 3.5, NCHH_{eq}), 3.91 (1 H, ddd, *J* 12.0, 12.0, 3.5, OCHH_{ax}), 3.58 (1 H, ddd, *J* 12.0, 12.0, 3.5, NCHH_{ax}), 1.03 (3 H, d, *J* 6.5, CH_3); δ_c (100.5 MHz; $CDCl_3$) 161.8 (C), 148.7 (C) 143.0 (C) 138.8 (C) 128.3 (CH) 127.5 (CH) 125.5 (CH) 124.1 (CH) 120.8 (CH), 116.4 (CH), 108.8 (CH), 79.7 (CH) 66.9 (CH_2) 53.4 (CH) 39.9 (CH_2), 9.7 (CH_3); *m/z* (CI^+) 295 $[M+H]^+$; HRMS (CI^+) $C_{18}H_{19}N_2O_2$ (MH^+) requires: 295.1447; found: 295.1452.

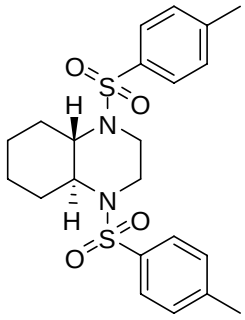
Thiomorpholine-(3*R*)-carboxylic acid methyl ester hydrochloride, 6j[2]



General method **A** was followed using L-cysteine methyl ester hydrochloride **5j** (0.050 g, 0.29 mmol), NaH (0.034 g, 1.4 mmol) and bromoethyldiphenylsulfonium salt **4** (0.154 g, 0.350 mmol). After 15 h the reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was basified with 5% Na_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). All the six organic layers were combined and dried over anhydrous K_2CO_3, filtered and evaporated under vacuum. The resulting residue was

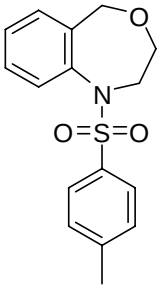
dissolved into dry diethyl ether (2 mL) and treated with 2 M HCl in diethylether (3 mL). The hydrochloride **6j**[2,18] was isolated by filtration as a colorless solid (0.057 g, 99%); mp 171–173 °C (MeOH-Et_2O) [lit.[18] mp 172–173 °C (MeOH-Et_2O)]; $[\alpha]_D^{23}$ –21 (*c*. 1.0, CH_3OH) [lit.[18] $[\alpha]_D^{25}$ –20.4 (*c*. 1, CH_3OH)]; δ_H (400 MHz; D_2O) 4.32 (1 H, dd, *J* 9.5, 3.5, NC*H*), 3.78 (3 H, s, OCH_3), 3.67 (1 H, ddd, *J* 13.0, 5.0, 3.5, NCH*H*), 3.32 (1 H, ddd, 13.0, 8.5, 3.5, NCH*H*), 3.18–2.68 (4 H, m, CH_2SCH_2); δ_c (100 MHz; $CDCl_3$) 168.2 (C), 56.6 (CH), 54.0 (CH_3), 45.1 (CH_2), 26.2 (CH_2), 23.5 (CH_2). The optical rotation of the pure **6j** is the same as that reported by Sakai and Yoneda[18] and is the same as that of a sample we made using vinyl sulfonium salt **1** and triethylamine as base.[2] Thus, the stereogenic center of **6j** has not been racemized during the reaction.

(±)-1,4-Bis(toluene-4-sulfonyl)decahydroquinoxaline 6k[2]



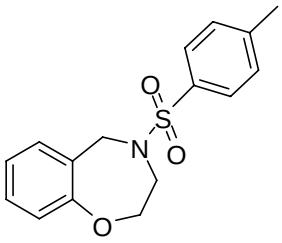
Following general method **A**, using (±)-*N*,*N*-bistosyl-1,2-diamine **5k** (0.050 g, 0.12 mmol), DBU (0.063 g, 0.41 mmol) and bromoethyldiphenylsulfonium salt **4** (0.063 g, 0.14 mmol), after chromatography (EtOAc-PE, 4:6) the title compound **6k** was isolated as a colorless crystalline solid (0.052 g, 98%); R_f 0.55 (EtOAc-PE, 4:6); mp 127–129 °C (EtOAc-PE) [lit.[2] mp 127–129 °C (EtOAc-PE)]; δ_H (400 MHz; $CDCl_3$) 7.61 (4 H, d, *J* 8.0, ArH), 7.29 (4 H, d, *J* 8.0, ArH), 3.96–3.82 (2 H, m NCH*H*), 3.24–3.10 (2 H, m, NC*H*H), 2.92–2.81 (2 H, m, NC*H*), 2.42 (6 H, s, 2 × CH_3), 2.36–2.26 (2 H, m), 1.70–1.58 (2 H, m), 1.54–1.38 (2 H, m), 1.20–1.12 (2 H, m); δ_c (100.5 MHz; $CDCl_3$) 143.8 (C), 137.9 (C), 129.9 (CH), 127.2 (CH), 62.1(CH), 46.8 (CH_2), 31.0 (CH_2), 24.8 (CH_2), 21.6 (CH_3).

1-Tosyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine, 9a



Following general method **A**, using *N*-tosyl-2-aminobenzylalcohol **8a** (0.050 g, 0.18 mmol), NaH (0.024 g, 1.0 mmol) and bromoethyldiphenylsulfonium salt **4** (0.184 g, 0.215 mmol), after chromatography (EtOAc-PE, 3:7) the title compound **9a** was obtained as a white solid (0.054 g, 99%); R_f 0.45 (EtOAc-PE, 3:7); mp 107–109 °C (PE-EtOAc); ν_{max} (nujol)/cm^{-1} 1345 (SO_2), 1162 (SO_2); δ_H (400 MHz; $CDCl_3$ at 50 °C) 7.62 (2 H, d, *J* 8.5, ArH), 7.42 (1 H, dd, *J* 7.5, 1.5, ArH), 7.32–7.19 (5 H, m, ArH), 4.28 (2 H, s), 4.10–3.60 (4 H, m), 2.44 (s, 3 H, CH_3); δ_C (100.5 MHz; $CDCl_3$) 143.6 (C), 140.0 (C), 138.6 (C), 138.0 (C), 129.8 (CH), 129.7 (CH), 129.0 (CH), 128.8 (CH), 127.8 (CH), 127.1 (CH), 73.5 (CH_2), 71.0 (CH_2), 52.2 (CH_2), 21.5 (CH_3); *m/z* (CI$^+$) 304 [M+H]$^+$; HRMS (CI$^+$) $C_{16}H_{18}NO_3S$ (MH$^+$) requires: 304.1007; found: 304.1008.

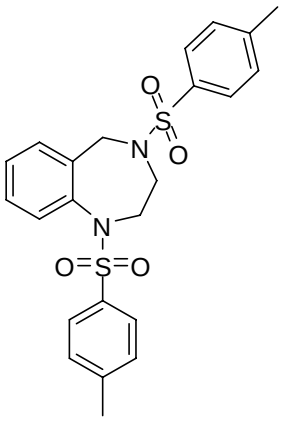
4-Tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine, 9b



Following general method **A**, using *N*-(2-hydroxybenzyl)-4-methylbenzenesulfonamide **8b** (0.021 g, 0.076 mmol), NaH (0.007 g, 0.3 mmol) and bromoethyldiphenylsulfonium salt **4** (0.040 g, 0.090 mmol), after chromatography (EtOAc-PE, 2:8) the title compound **9b** was obtained as a white solid (0.015 g, 64%); R_f 0.58 (EtOAc-PE, 2:8); mp 115–117 °C (EtOAc-PE); ν_{max} (nujol)/cm^{-1} 1377 (SO_2), 1162 (SO_2); δ_H (400 MHz; $CDCl_3$) 7.63 (2 H, d, *J* 8.5, ArH), 7.31–7.20 (4 H, m, ArH), 7.07 (1 H, ddd, *J* 7.5, 7.5, 1.5, ArH), 6.95 (1 H, dd, *J* 7.5, 1.5, ArH), 4.42 (2 H, s, NCH_2C), 4.04–4.01 (2 H, m, CH_2), 3.66–3.62 (2 H, m, CH_2), 2.42 (3 H, s, CH_3); δ_c (100.5 MHz; $CDCl_3$) 159.3 (C), 143.4 (C), 135.9 (C), 130.0 (C), 129.9 (CH), 129.6 (CH), 129.3 (CH), 127.2 (CH), 123.9 (CH), 121.0 (CH), 71.7 (CH_2), 51.6 (2 × CH_2),

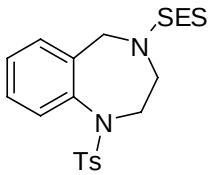
21.5 (CH_3); *m/z* (CI^+) 304 $[M+H]^+$; HRMS (CI^+) $C_{16}H_{18}NO_3S$ (MH^+) requires: 304.1007; found: 304.1011.

1,4-Ditosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine, 9c



Following general method **A**, using *N*,*N*-*bis*-tosyl-2-aminobenzylamine **8c** (0.050 g, 0.12 mmol), NaH (0.010 g, 0.42 mmol) and bromoethyldiphenylsulfonium salt **4** (0.062 g, 0.14 mmol), after chromatography (EtOAc-PE, 3:7) the title compound **9c** was obtained as a white solid (0.052 g, 98%); R_f 0.39 (EtOAc-PE, 3:7); mp 143–145 °C (CH_2Cl_2) ν_{max}(neat)/cm^{-1} 1377 (SO_2), 1158 (SO_2); δ_H (300 MHz; DMSO-d^6 at 60 °C) 7.60–7.52 (4 H, m, ArH) 7.42–7.26 (7 H, m, ArH), 7.18–7.10 (1 H, m, ArH), 3.91 (2 H, br s), 3.76–3.60 (2 H, m), 3.44–3.32 (2 H, m), 2.40 (3 H, s, CH_3), 2.37 (3 H, s, CH_3); δ_c (100.5 MHz; DMSO-d^6 at RT) 143.8 (C), 143.5 (C), 139.6 (C), 137.6 (C), 135.8 (C), 134.7 (C), 130.4 (CH), 130.0 (CH), 129.8 (CH), 129.0 (CH), 128.5 (CH), 128.2 (CH), 127.0 (CH), 126.7 (CH), 51.4 (CH_2), 49.9 (CH_2), 49.5 (CH_2), 21.0 (CH_3), 20.9 (CH_3); *m/z* (CI^+) 457 $[M+H]^+$; HRMS (CI^+) $C_{23}H_{25}N_2O_4S_2$ (MH^+) requires: 457.1256; found: 457.1248.

1-Tosyl-4-(2-(trimethylsilyl)ethylsulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine, 9d

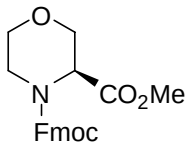


Following general method **A**, using *N*-SES, *N*-tosyl-2-aminobenzyl amine **8d** (0.133 g, 0.302 mmol), NaH (0.025 g, 1.0 mmol) and bromoethyldiphenylsulfonium salt **4** (0.161 g, 0.362 mmol), after chromatography (EtOAc-PE, 3:7) the title compound **9d** was obtained as a white solid (0.140 g, 99%); R_f 0.42 (EtOAc-PE, 3:7); mp 71–73 °C decomposed (EtOAc-n-Pentane); ν_{max} (neat)/cm^{-1} 1330 (SO_2), 1158 (SO_2); δ_H (400

MHz; $CDCl_3$, at 50 °C) 7.68 (2 H, d, *J* 8.5, ArH), 7.37–7.22 (6 H, m, ArH), 4.23 (2 H, br s), 3.96–3.76 (2 H, m), 3.74–3.65 (2 H, m), 2.78–2.71 (2 H, m, CH_2SO_2), 2.47 (3 H, s), 0.86 (2 H, m, CH_2Si), 0.00 (9 H, s, $(Si(CH_3)_3)$; δ_c (100.5 MHz; $CDCl_3$, at 50 °C) 143.8 (C), 139.8 (C), 138.5 (C), 137.8 (C), 130.1 (CH), 129.8 (CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 127.2 (CH), 51.7 (CH_2), 51.5 (CH_2), 49.9 (CH_2), 49.1 (CH_2), 21.4 (CH_3), 10.2 (CH_2), –2.2 ($Si(CH_3)_3$); *m/z* (CI^+) 467 $[M+H]^+$; HRMS (CI^+) $C_{21}H_{31}N_2O_4S_2Si$ (MH^+) requires: 467.1495; found: 467.1497.

Synthesis of Fmoc-protected morpholine 7

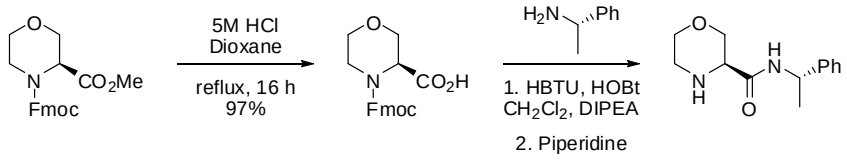
(*S*)-4-(9*H*-Fluoren-9-yl)methyl 3-methyl morpholine-3,4-dicarboxylate, 7[2]



CsF (23 mg, 0.15 mmol) was added to a stirred solution of (*S*)-methyl 4-(2-(trimethylsilyl)ethylsulfonyl)morpholine-3-carboxylate **6f** (0.015 g, 0.048 mmol) in dry DMF (1 mL) at RT under argon. The reaction mixture was then heated at 95 °C for 4 h. After cooling the reaction was quenched with methanol (0.5 mL) and dry diethyl ether (3 mL) was added which resulted in a white precipitate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a gummy residue. The residue was dissolved in a mixture of dioxane/water (1:1, 2 mL) and $NaHCO_3$ (12 mg, 0.14 mmol) was added. Then it was cooled to 0 °C and treated with Fmoc-Cl (0.015 g, 0.058 mmol), allowed to warm to RT and stirred for 12 h at RT. The reaction mixture was then diluted with water and extracted with Et_2O (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by preparative TLC (Et_2O-PE, 4:6) gave the title compound **7** as white foam (0.016 g, 91%).

R_f 0.47 (EtOAc-PE, 3:7); $[\alpha]_D^{22}$ –51 (*c*. 1.0, CH_2Cl_2) [lit.[14] $[\alpha]_D^{22}$ –51.5 (*c*. 1.0, CH_2Cl_2)]; δ_H (400 MHz; $CDCl_3$) (mixture of rotamers) 7.76 (2 H, t, *J* 7.0), 7.59 (1 H, t, *J* 8.5), 7.50 (1 H, t, *J* 7.0), 7.43-7.37 (2 H, m) 7.35-7.27 (2 H, m), 4.65 (0.5 H, br d, *J* 3.5), 4.56-4.20 (4.5 H, m), 3.94-3.80 (1.5 H, m), 3.78 (3 H, s), 3.72 (3 H, s), 3.66 (1 H, dd, *J* 12.0, 3.5), 3.58 (0.5 H, dd, *J* 12.0, 3.5), 3.50-3.40 (1.5 H, m), 3.27 (0.5 H, ddd, *J* 12.5, 12.5, 3.5); δ_c (100.5 MHz; $CDCl_3$) 170.1 (C), 156.2 (C), 155.7 (C), 143.9 (C), 143.8 (C), 143.7 (C), 143.6 (C), 141.31 (C), 141.29 (C), 127.74 (CH), 127.72

(CH), 127.68 (CH), 127.08 (CH), 127.04 (CH), 127.02 (CH), 125.0 (CH), 124.7 (CH), 120.0 (CH), 67.9 (CH_2), 67.65 (CH_2), 67.60 (CH_2), 67.2 (CH_2), 66.6 (CH_2), 66.3 (CH_2), 54.9 (CH), 54.4 (CH), 52.6 (CH_3), 47.15 (CH), 47.12 (CH), 41.6 (CH_2), 41.0 (CH_2). The optical rotation and other characterization data were identical to those described by Guarna and co-workers.[14] They reported the hydrolysis of **7**, followed by derivatization with enantiopure (*S*)-phenylethylamine and deprotection (see Scheme 2). They demonstrated that the resulting amide had a diastereomeric purity of >96% by HPLC.



Scheme 2 Derivatization of Fmoc-protected morpholine 7 for determination of enantiopurity

References

[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

[2] M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2008**, *47*, 3784–3786; *Angew. Chem.* **2008**, *120*, 3844–3846.

[3] K. Kamei, N. Maeda, K. Nomura, M. Shibata, R. Katsuragi-Ogino, M. Koyama, M. Nakajima, T. Inoue, T. Ohno, T. Tatsuoka, *Bioorg. Med. Chem.* **2006**, *14*, 1978–1992.

[4] M. G. Unthank, N. Hussain, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2006**, *45*, 7066–7069; *Angew. Chem.* **2006**, *118*, 7224–7227.

[5] Y. Wang, W. Zhang, V. J. Colandrea, L. S. Jimenez, *Tetrahedron* **1999**, *55*, 10659–10672.

[6] S. M. Weinreb, D. M. Demko, T. A. Lessen, *Tetrahedron Lett.* **1986**, *27*, 2099–2102.

[7] A. Nishiguchi, T. Ikemoto, I. Tatsuya, M. Shotaro, T. Kiminori, *Heterocycles* **2007**, *71*, 1183–1192.

[8] M. H. Fonseca, E. Eibler, M. Zabel, B. Konig, *Tetrahedron: Asymmetry* **2003** *14*, 1989–1994.

[9] T. Inoue, J.-F. Liu, D. C. Buske, A. Abiko, *J. Org. Chem.* **2002**, *67*, 5250–5256.

[10] W. R. McKay, G. R. Proctor, *J. Chem. Soc. Perkin Trans.* 1 **1981**, *9*, 2443–2450.

[11] R. L. Beddoes, W. D. Edwards, J. A. Joule, O. S. Mills, J. D. Street *Tetrahedron* **1987**, *43*, 1903–1920.

[12] O. Hara, T. Koshizawa, K. Makino, I. Kunimune, A. Namiki, Y. Hamada, *Tetrahedron* **2007**, *63*, 6170–6181.

[13] S.-H. Kim, S. D. Jonson, M. J. Welch, J. A. Katzenellenbogen, *Bioconjugate Chem.* **2001**, *12*, 439–450.

[14] F. Sladojevich, A. Trabocchi, A. Guarna, *J. Org. Chem.* **2007**, *72*, 4254–4257

[15] A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2006**, *71*, 219–224.

[16] G. Wagner, *Pharmazie* **1976**, *31*, 345–347.

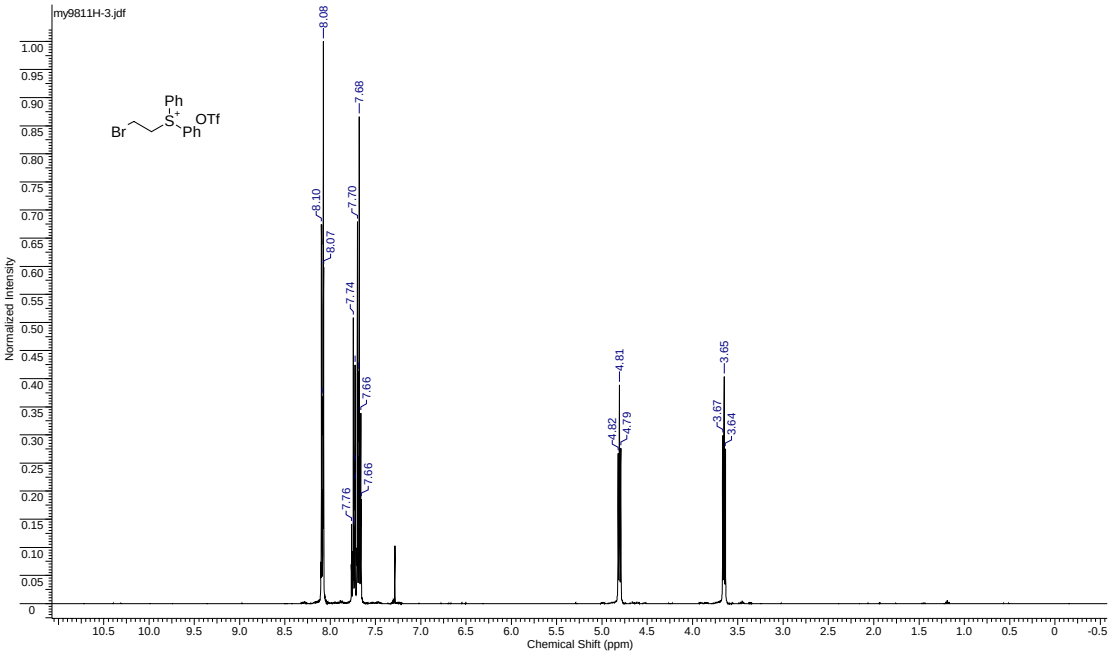
[17] M. W. Hooper, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem.* **2003**, *68*, 2861–2873.

[18] K. Sakai, N. Yoneda, *Chem. Pharm. Bull.* **1981**, *29*, 1554–1560.

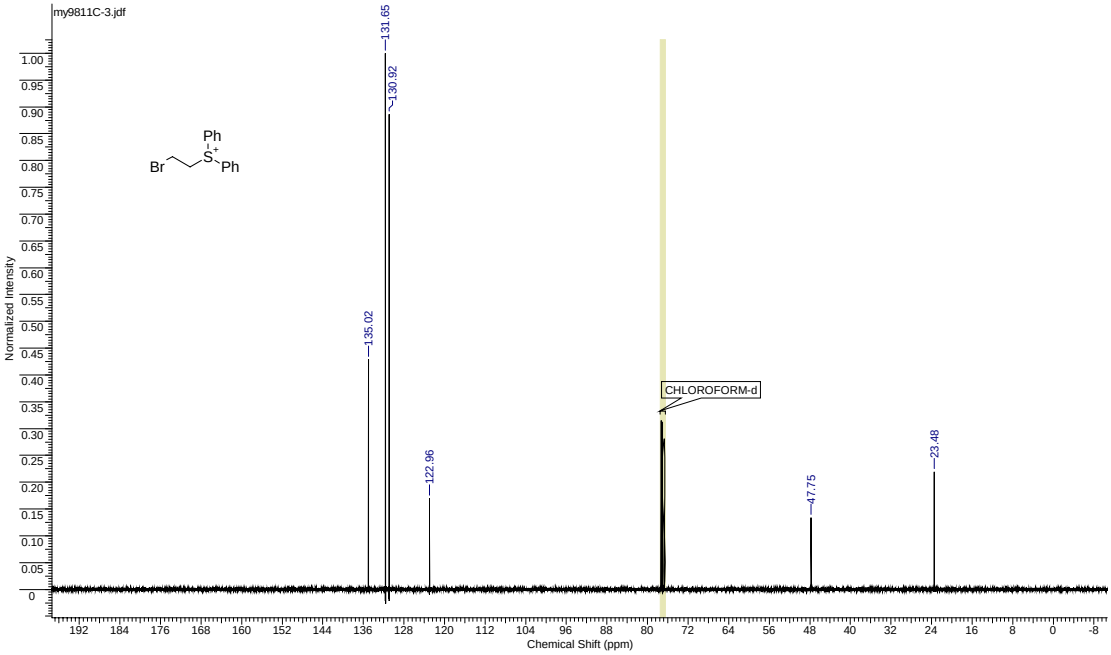
NMR Spectrum of 4–11

(2-Bromoethyl)diphenylsulfonium trifluoromethanesulfonate, 4

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

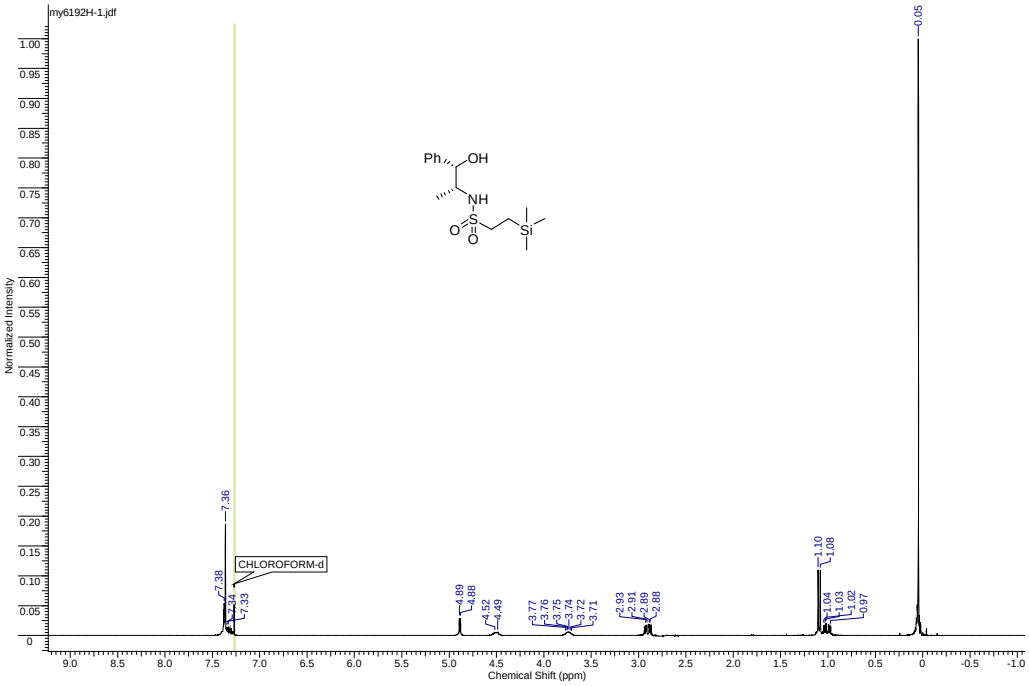


^{13}C NMR (100.5 MHz, $CDCl_3$)

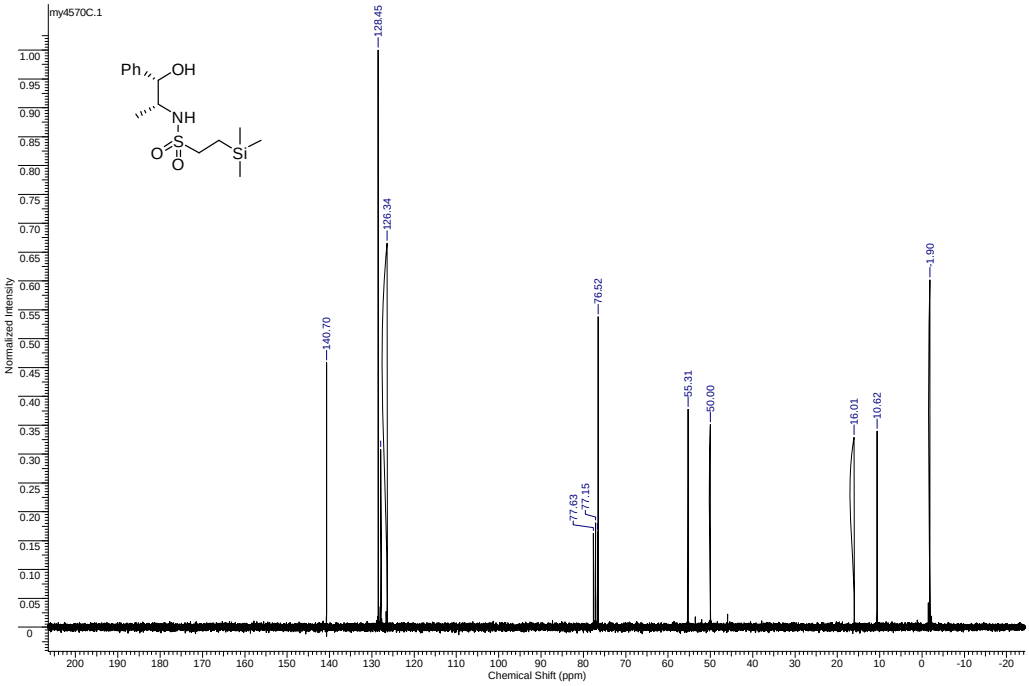


N-((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-2-(trimethylsilyl) ethanesulfonamide, 5d

^{1}H NMR (300 MHz, $CDCl_3$)

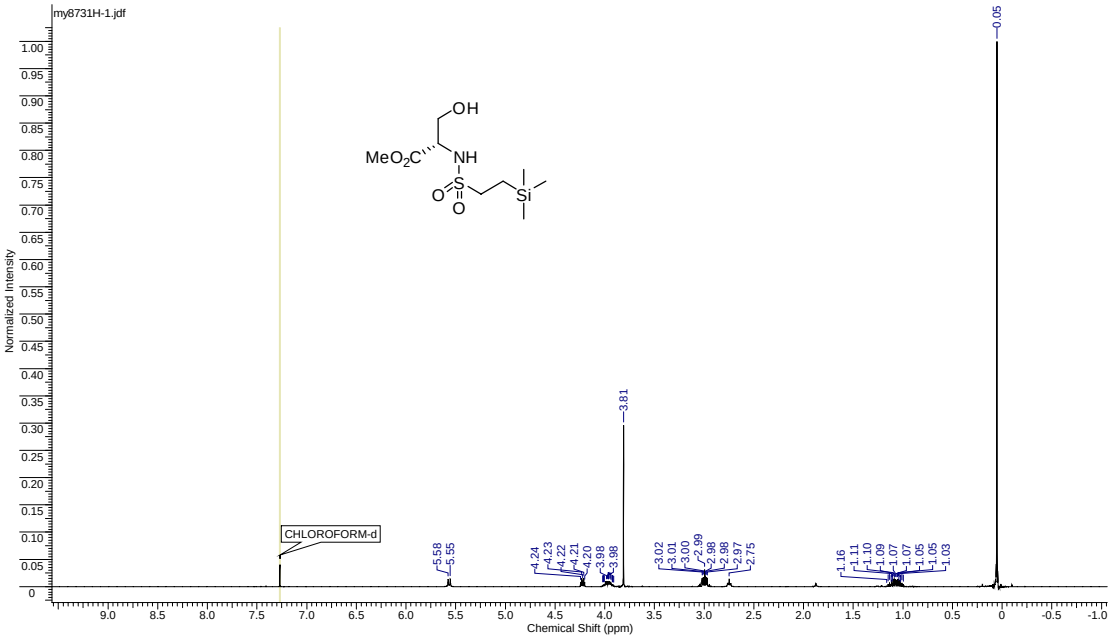


^{13}C NMR (67.5 MHz, $CDCl_3$)

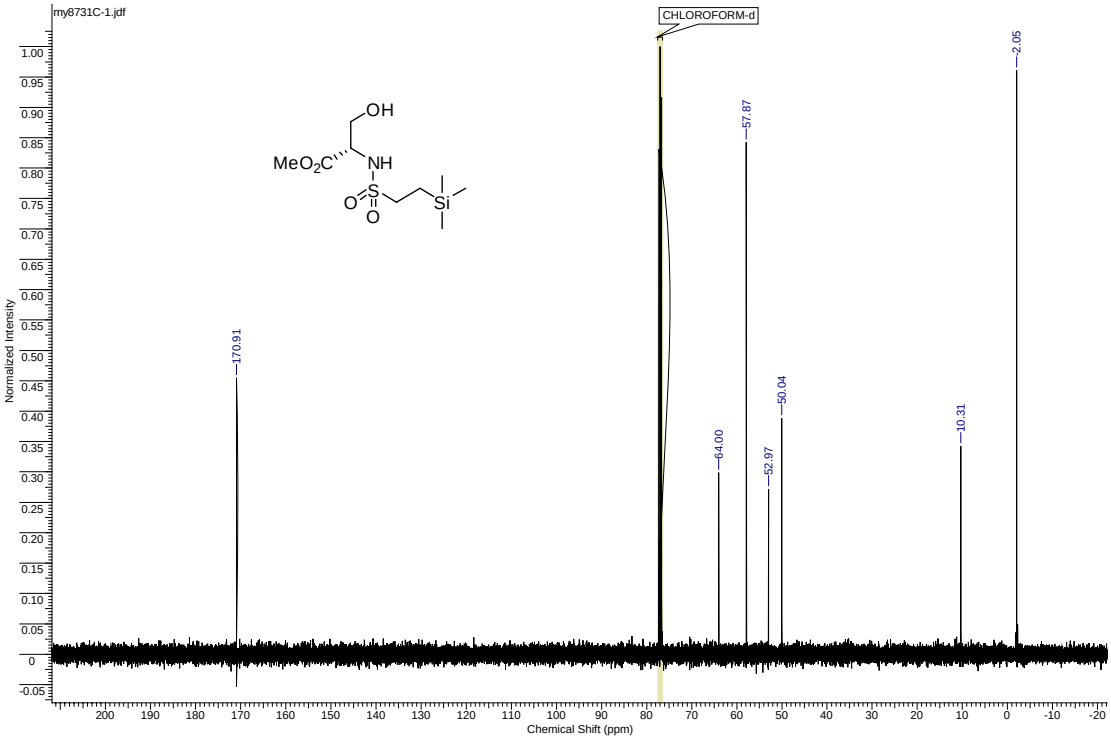


(*S*)-Methyl 3-hydroxy-2-(2-(trimethylsilyl)ethylsulfonamido)propanoate, 5f

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

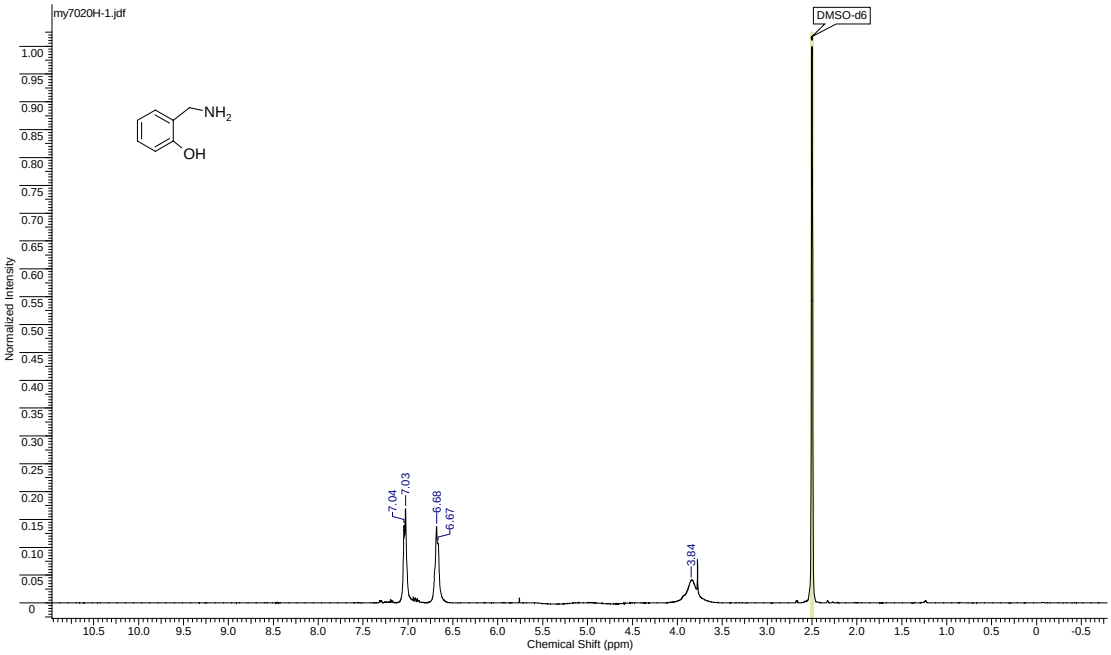


^{13}C NMR (100.5 MHz, $CDCl_3$)

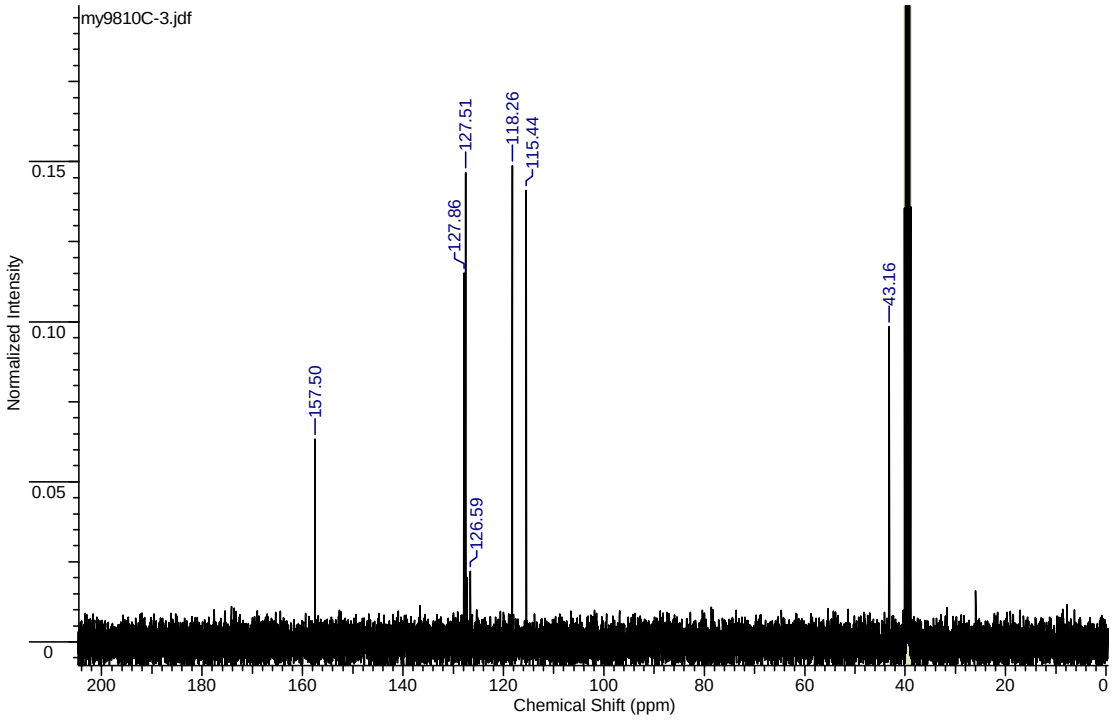


2-(Aminomethyl)phenol, 11[3]

^{1}H NMR (400 MHz, DMSO-d^{6})

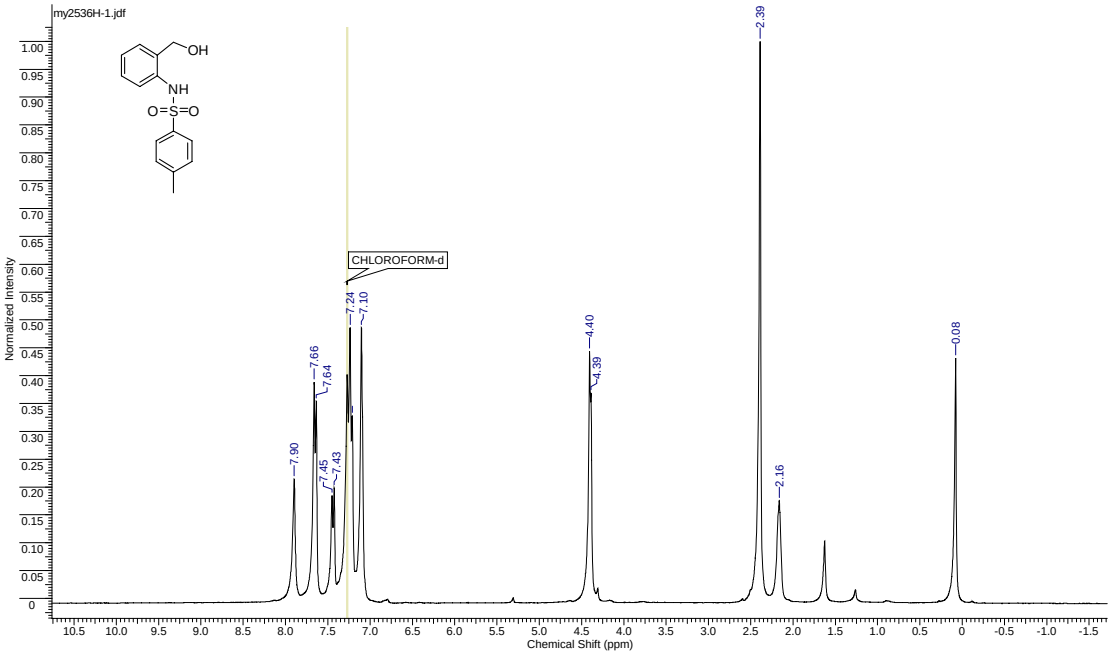


^{13}C NMR (75 MHz, DMSO-d^{6})

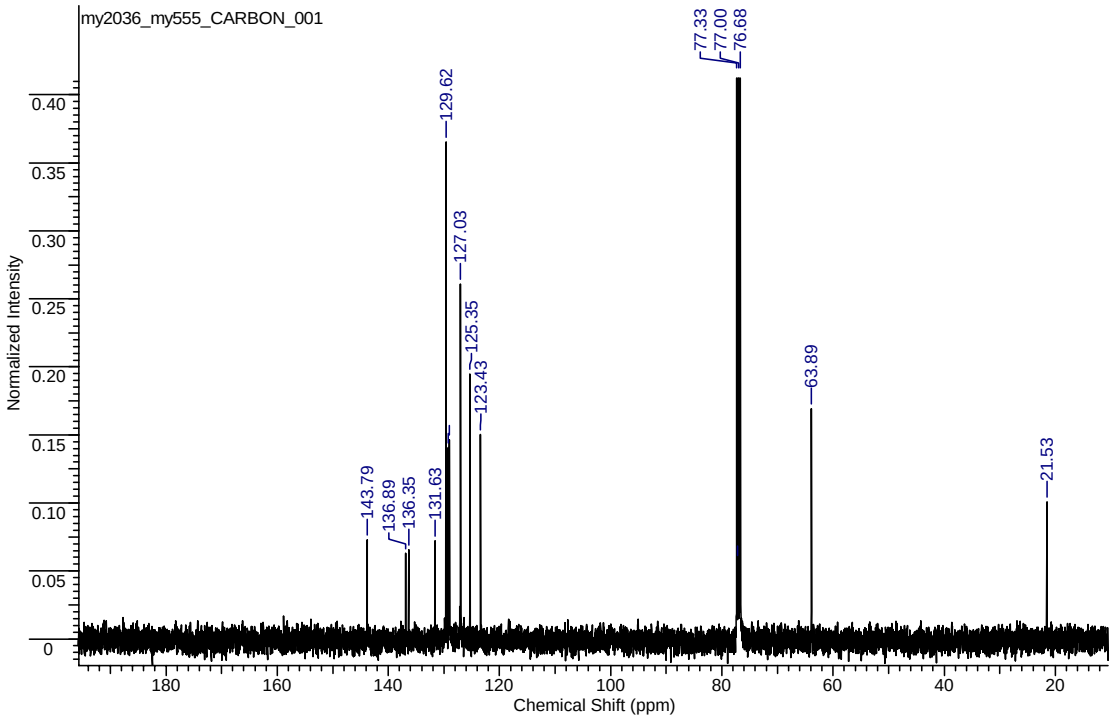


N-(2-(Hydroxymethyl)phenyl)-4-methylbenzenesulfonamide, 8a

^{1}H NMR (300 MHz, $CDCl_3$)

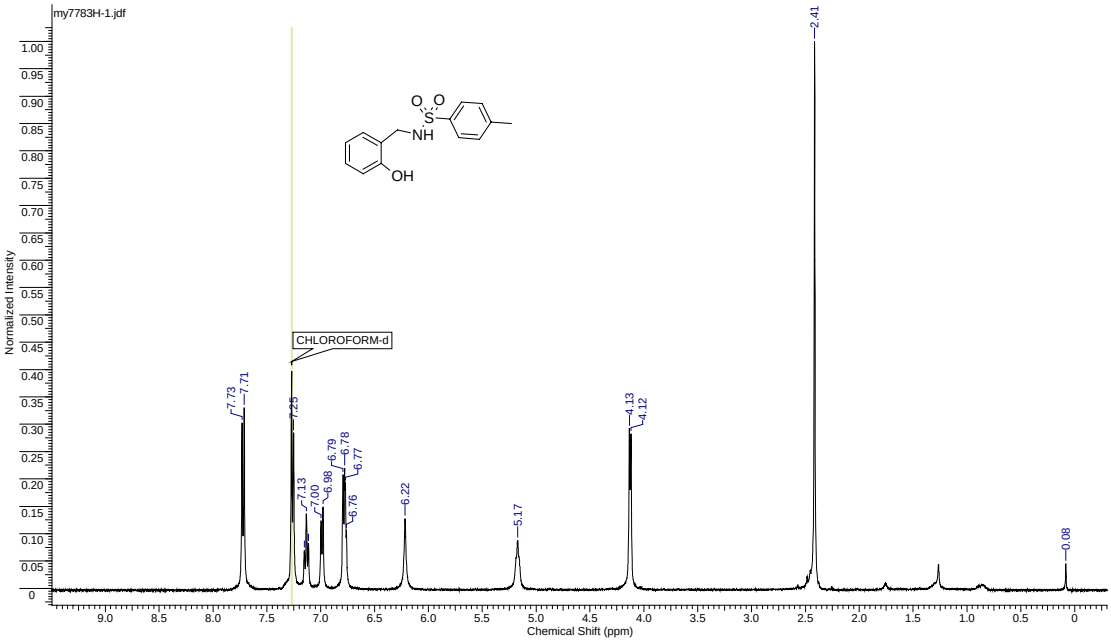


^{13}C NMR (100.5 MHz, $CDCl_3$)

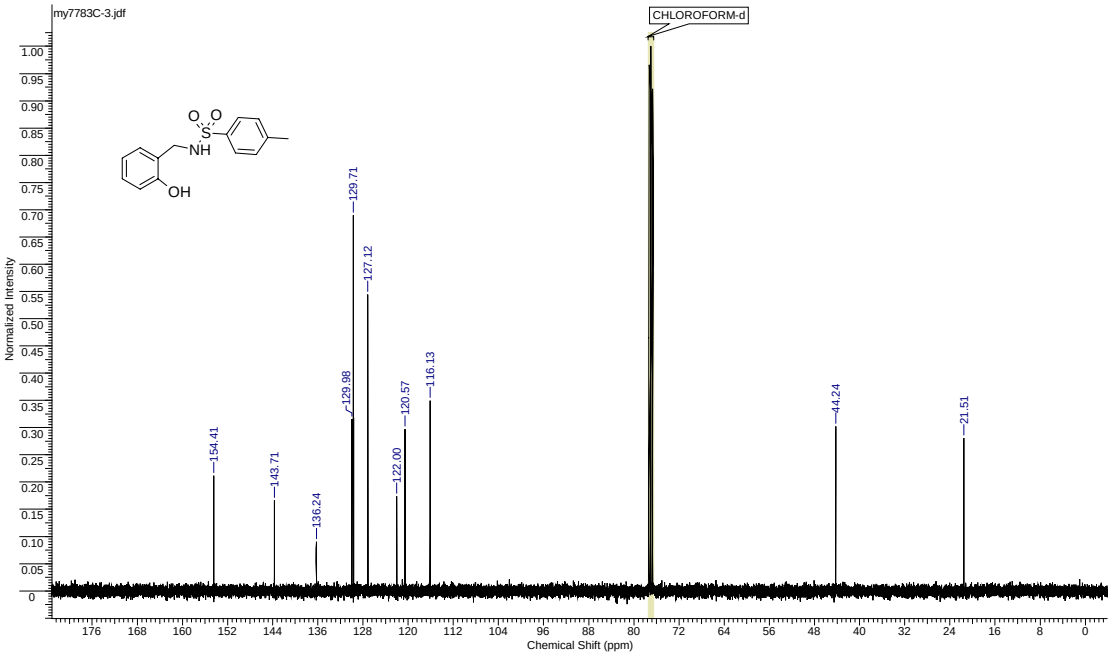


N-(2-Hydroxybenzyl)-4-methylbenzenesulfonamide, 8b

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

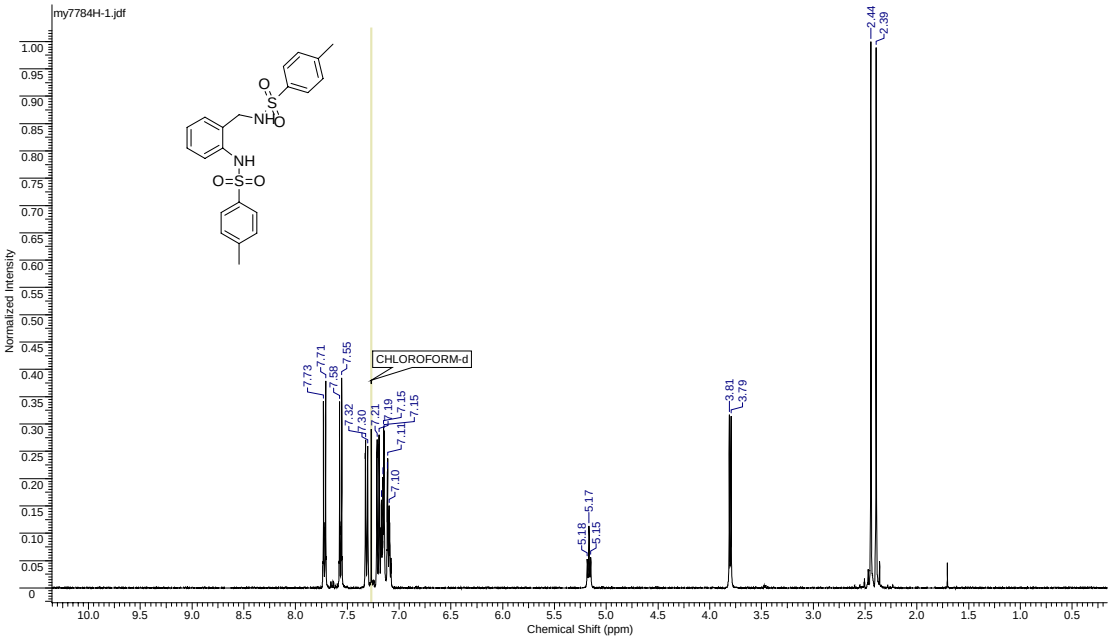


^{13}C NMR (100.5 MHz, $CDCl_3$)

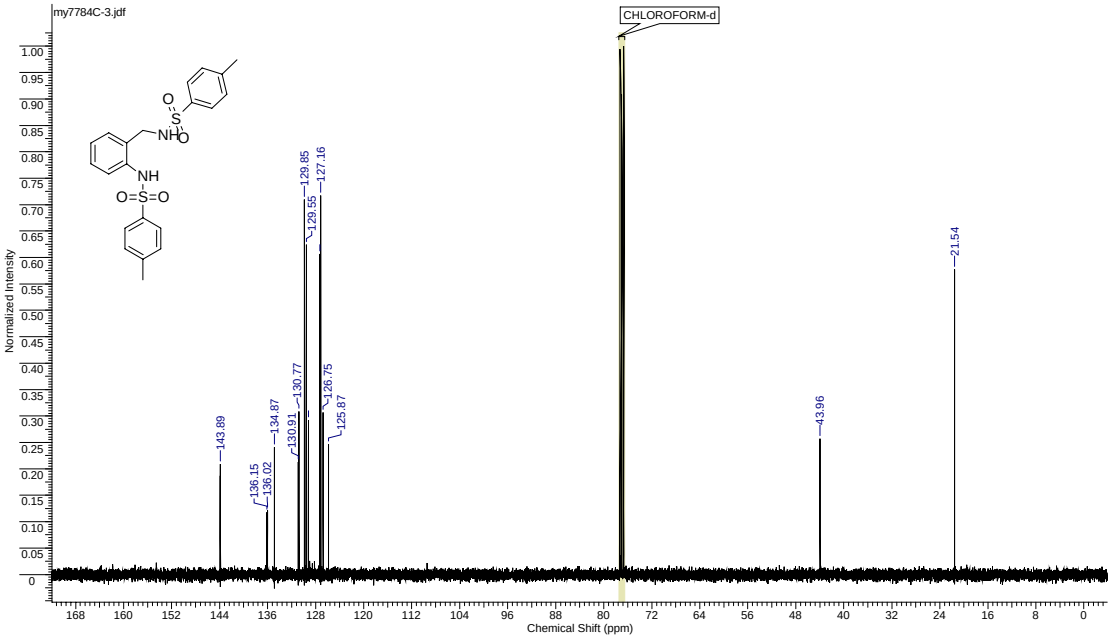


4-Methyl-*N*-(2-(4-methylphenylsulfonamido)benzyl)benzenesulfonamide, 8c

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

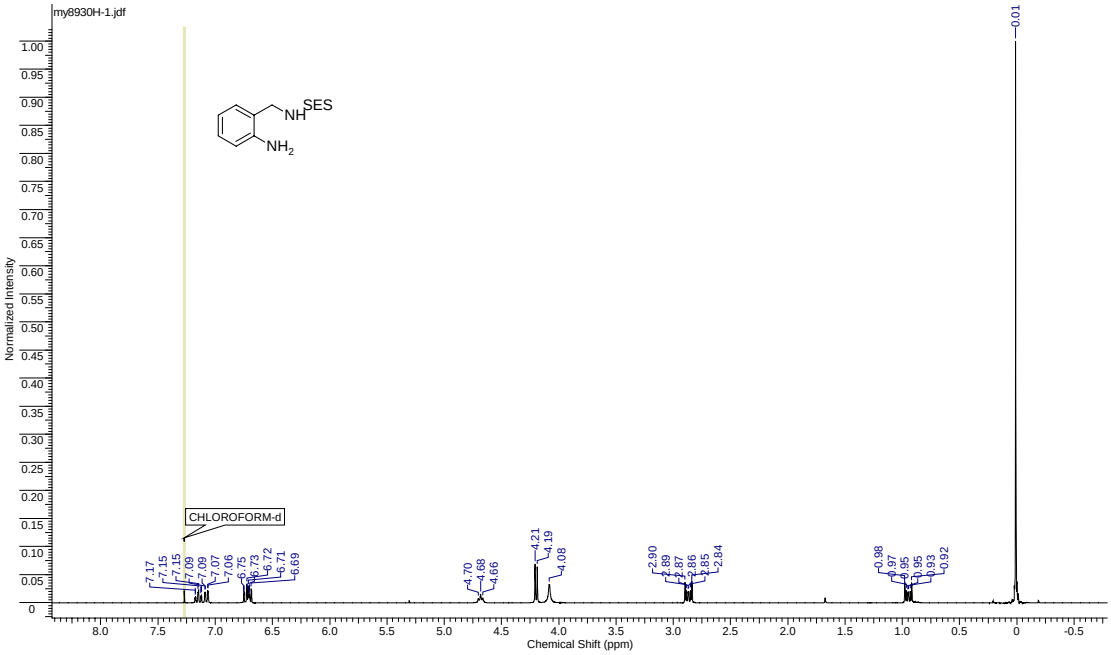


^{13}C NMR (100.5 MHz, $CDCl_3$)

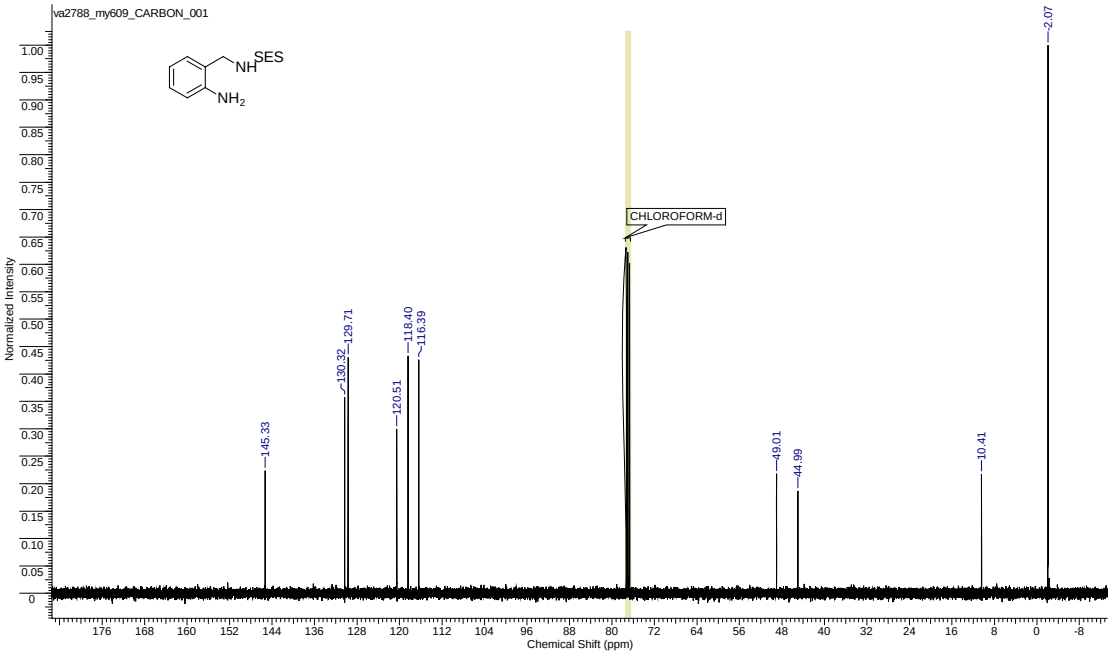


N-(2-Aminobenzyl)-2-(trimethylsilyl)ethanesulfonamide, 10

^{1}H NMR (300 MHz, $CDCl_3$)

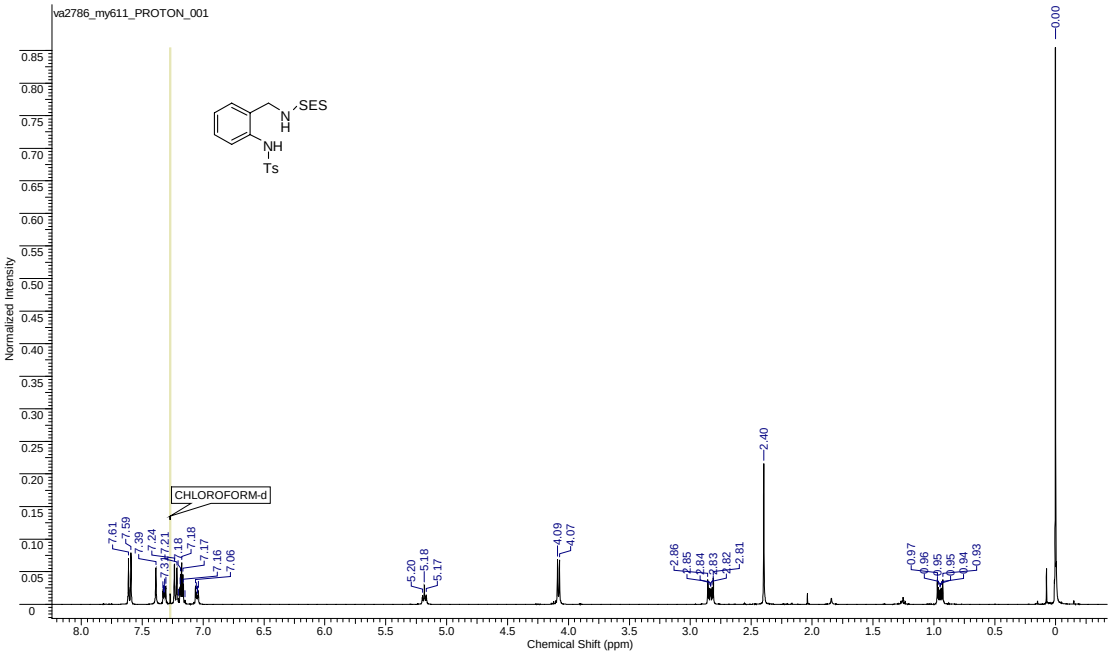


^{13}C NMR (100.5 MHz, $CDCl_3$)

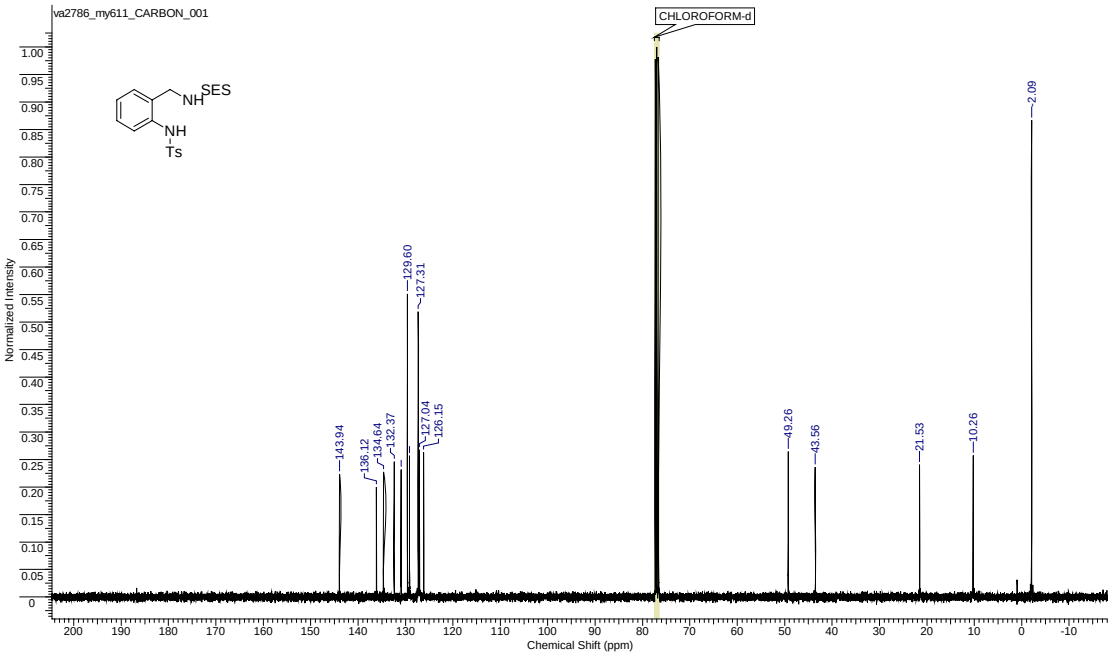


4-Methyl-*N*-(2-((2-(trimethylsilyl)ethylsulfonamido)methyl)phenyl)benzenesulfonamide, 8d

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

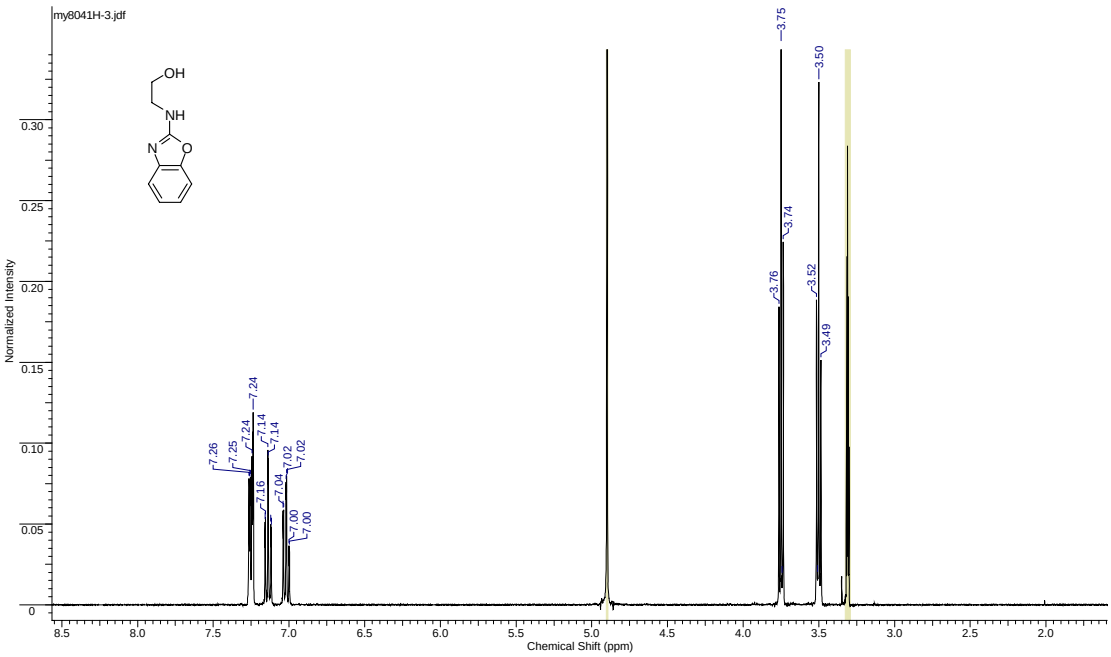


^{13}C NMR (100.5 MHz, $CDCl_3$)

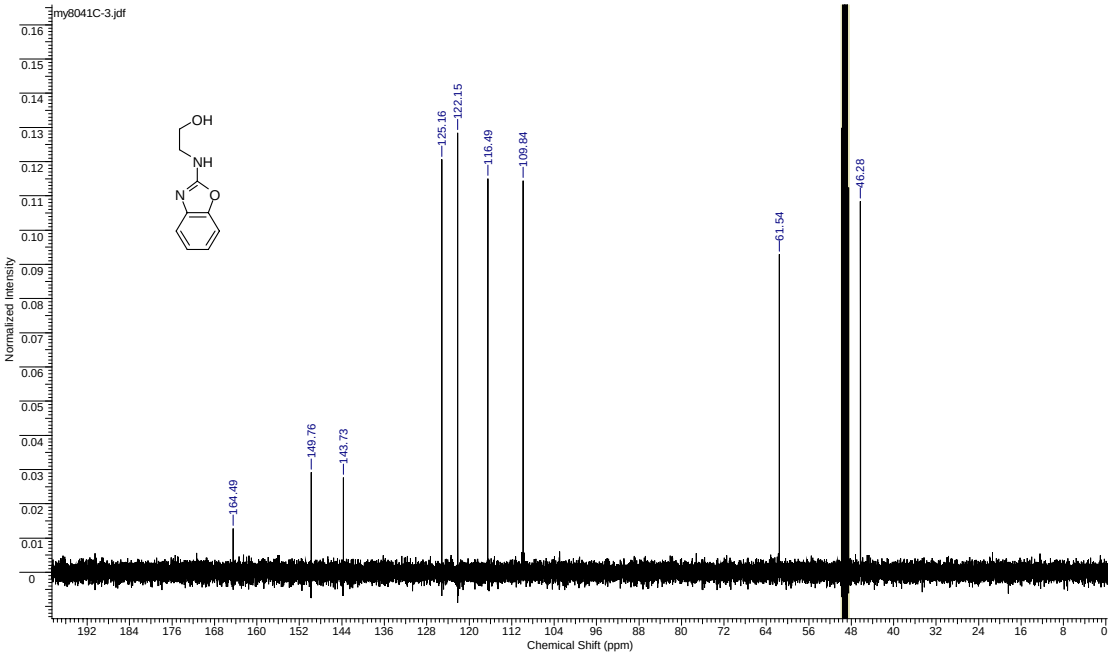


2-(Benzo[*d*]oxazol-2-ylamino)ethanol, 5h

^{1}H NMR (400 MHz, CD_3OD)

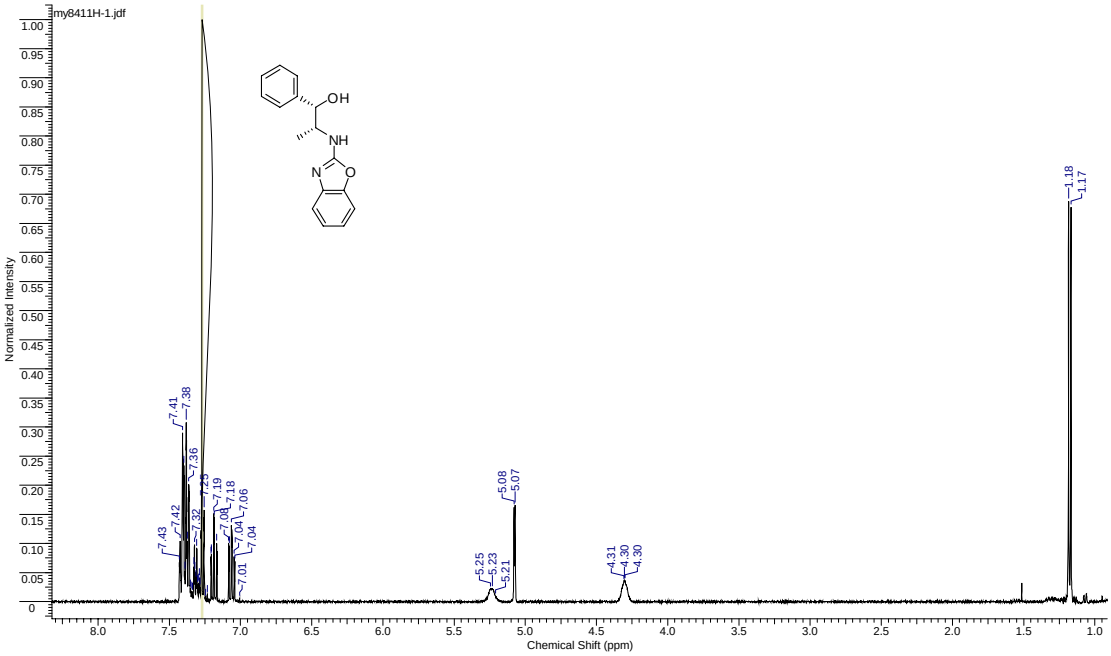


^{13}C NMR (100.5 MHz, CD_3OD)

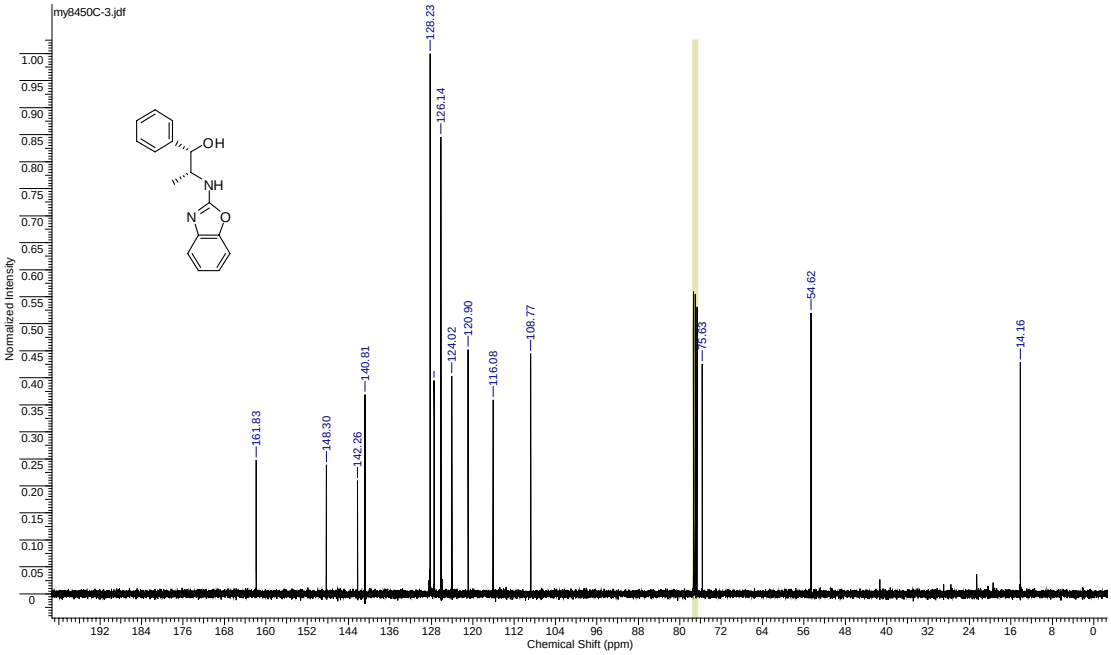


(1*S*,2*R*)-2-(Benzo[*d*]oxazol-2-ylamino)-1-phenylpropan-1-ol, 5i

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

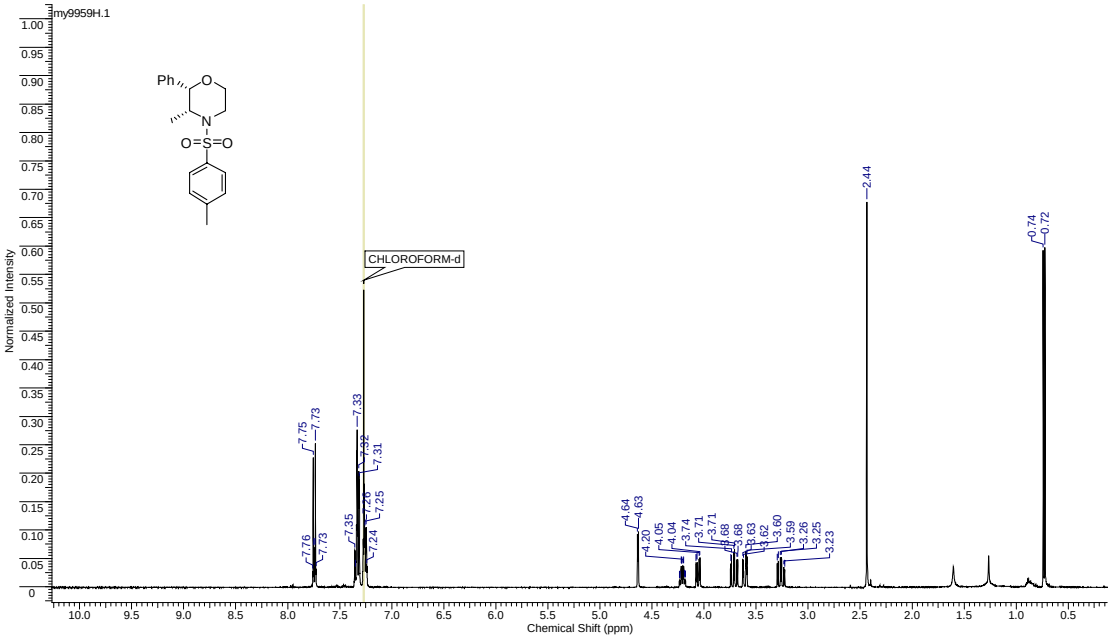


^{13}C NMR (100.5 MHz, $CDCl_3$)

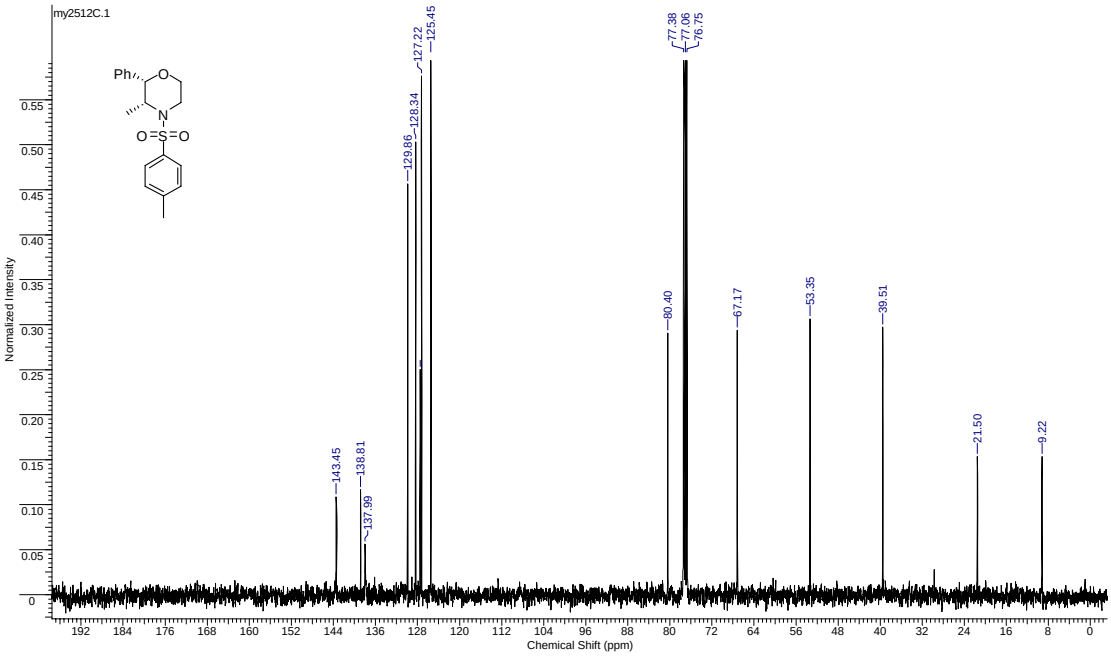


(2*S*,3*R*)-3-Methyl-4-[(4-methylphenyl)sulfonyl]-2-phenylmorpholine, 6a

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

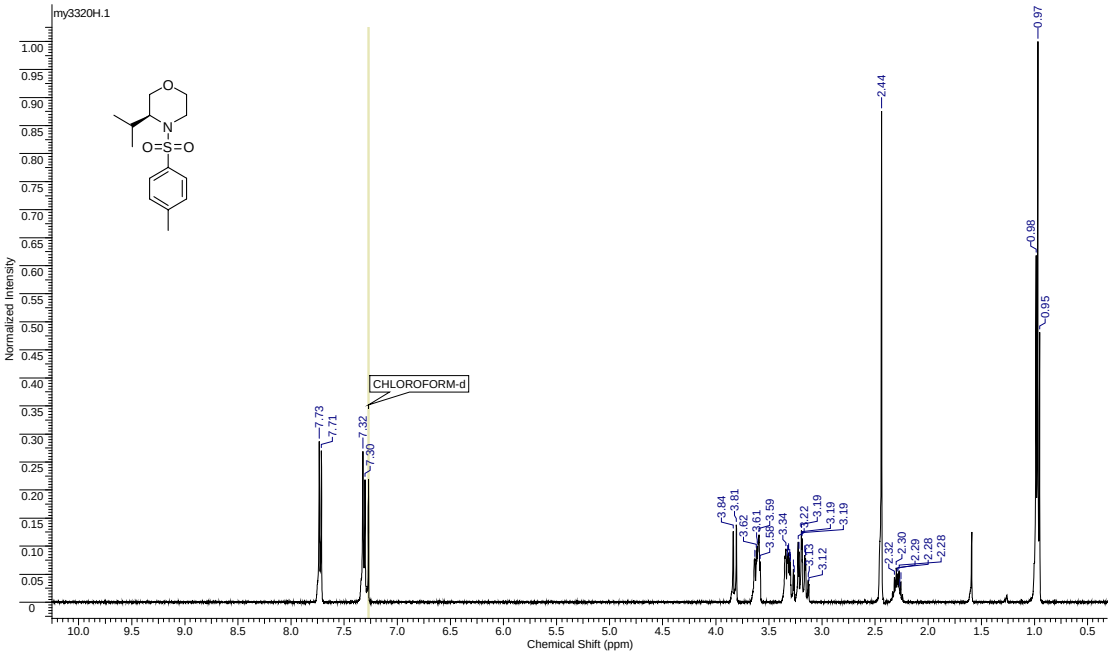


^{13}C NMR (100.5 MHz, $CDCl_3$)

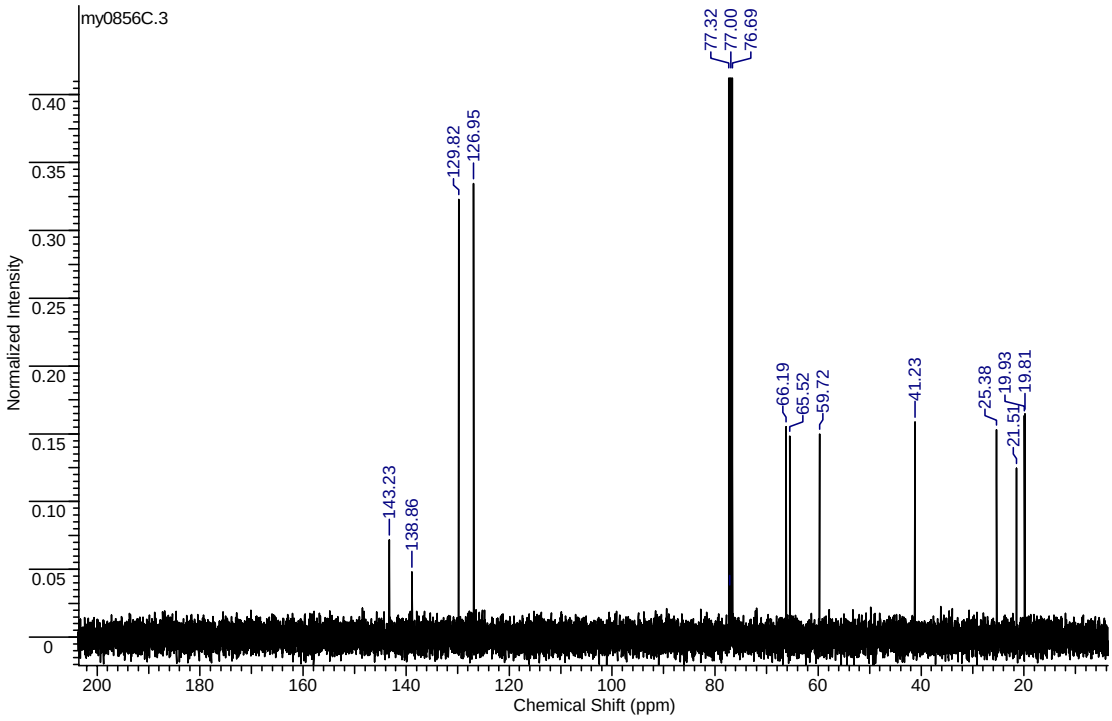


(3*S*)-3-Isopropyl-4-[(4-methylphenyl)sulfonyl]morpholine, 6b

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

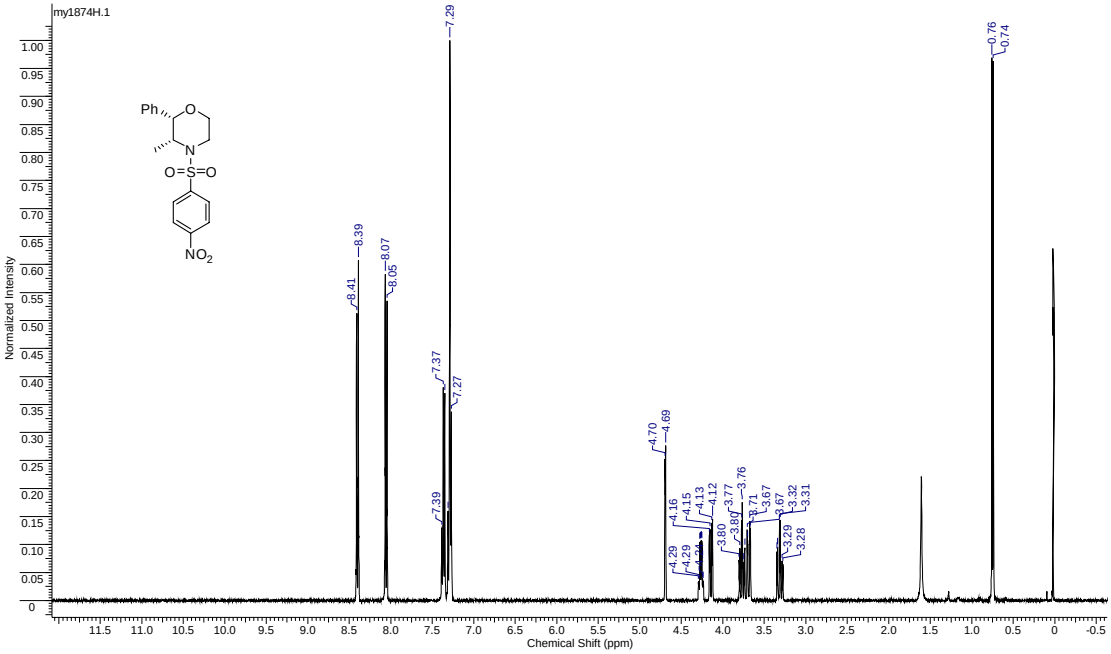


^{13}C NMR (100 MHz, $CDCl_3$)

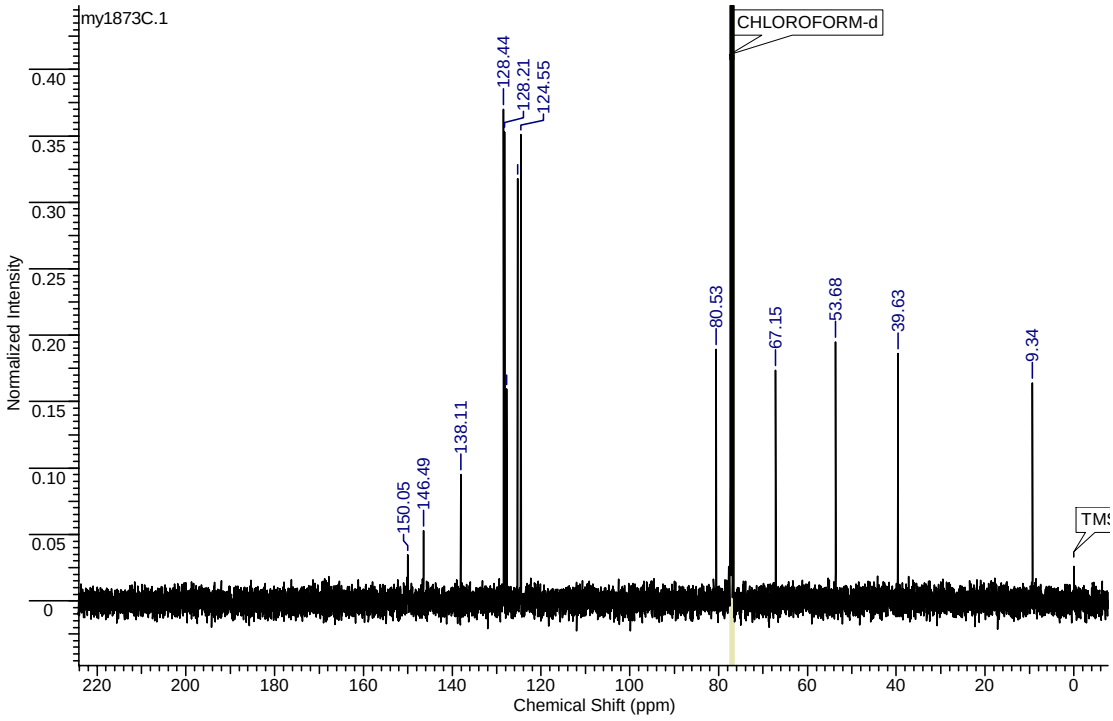


(2*S*,3*R*)-3-Methyl-4-[(4-nitrophenyl)sulfonyl]-2-phenylmorpholine, 6c

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

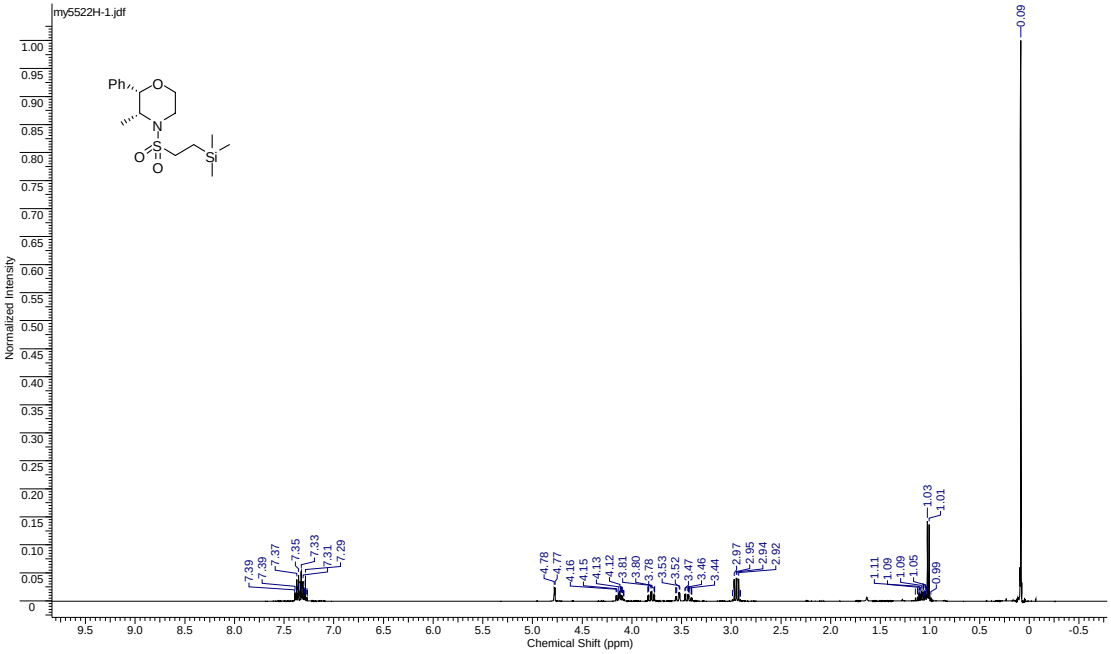


^{13}C NMR (100 MHz, $CDCl_3$)

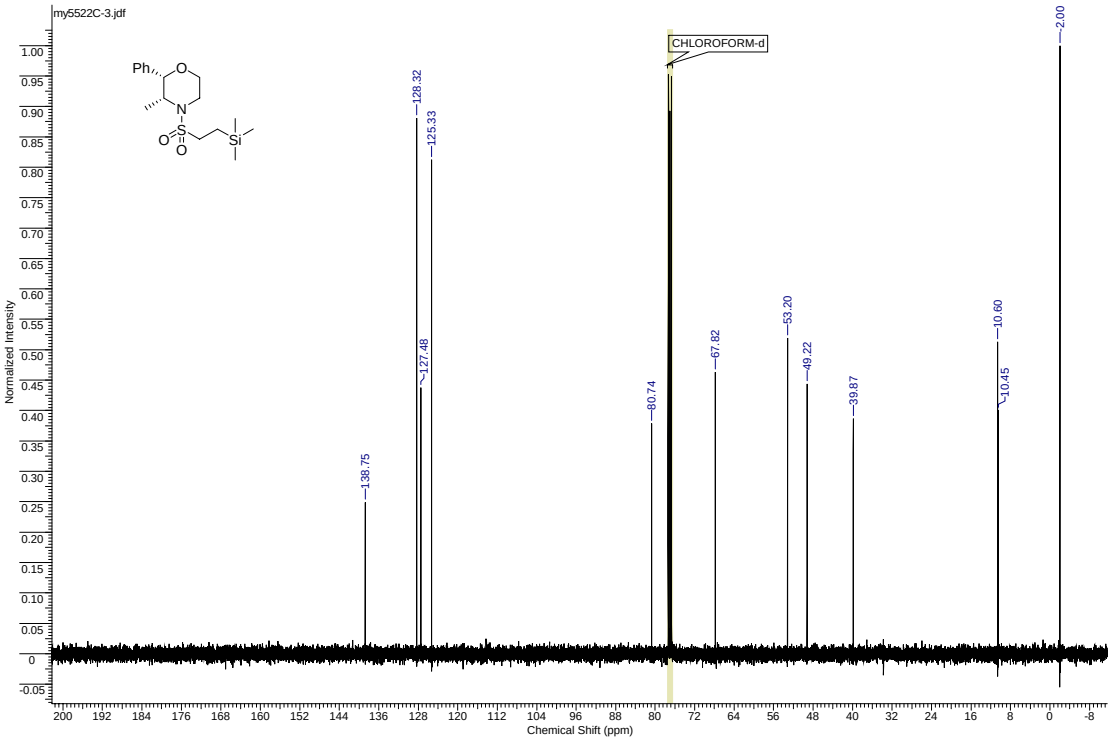


(2*S*,3*R*)-3-Methyl-2-phenyl-4-(2-(trimethylsilyl)ethylsulfonyl)morpholine, 6d

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

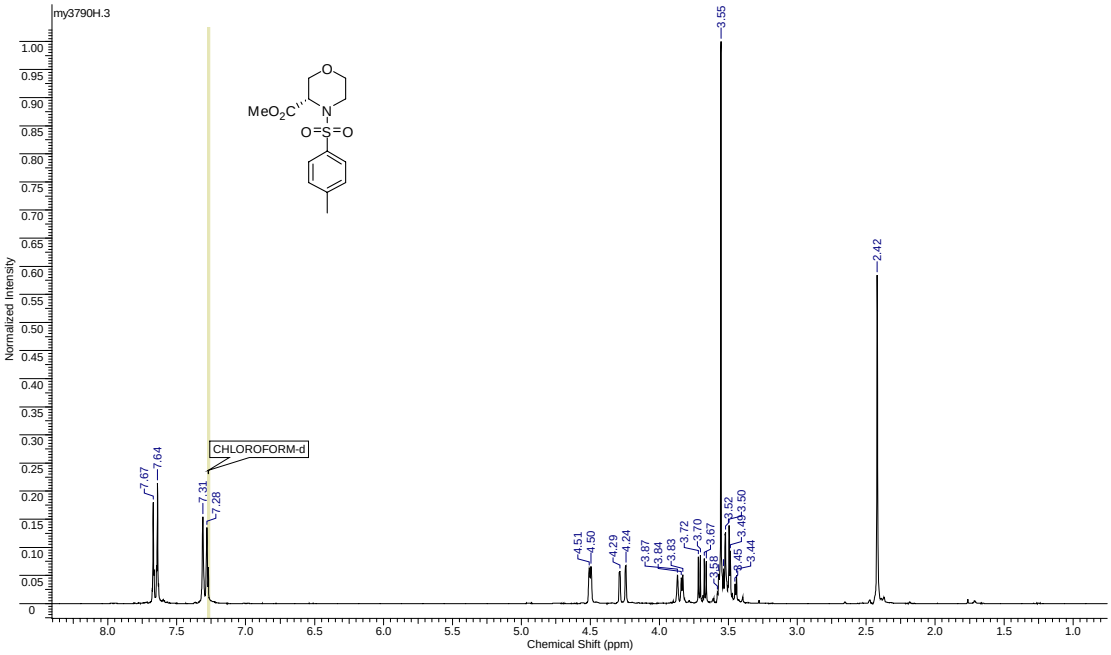


^{13}C NMR (100 MHz, $CDCl_3$)

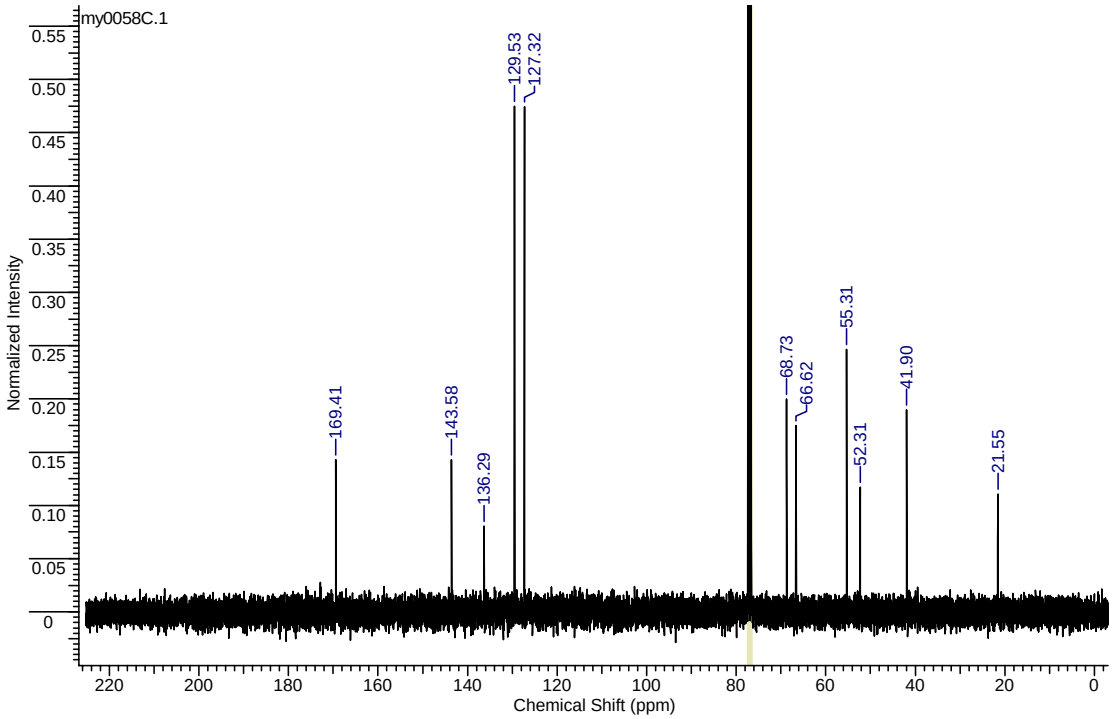


Methyl (3*S*)-4-[(4-methylphenyl)sulfonyl]morpholine-3-carboxylate, 6e

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

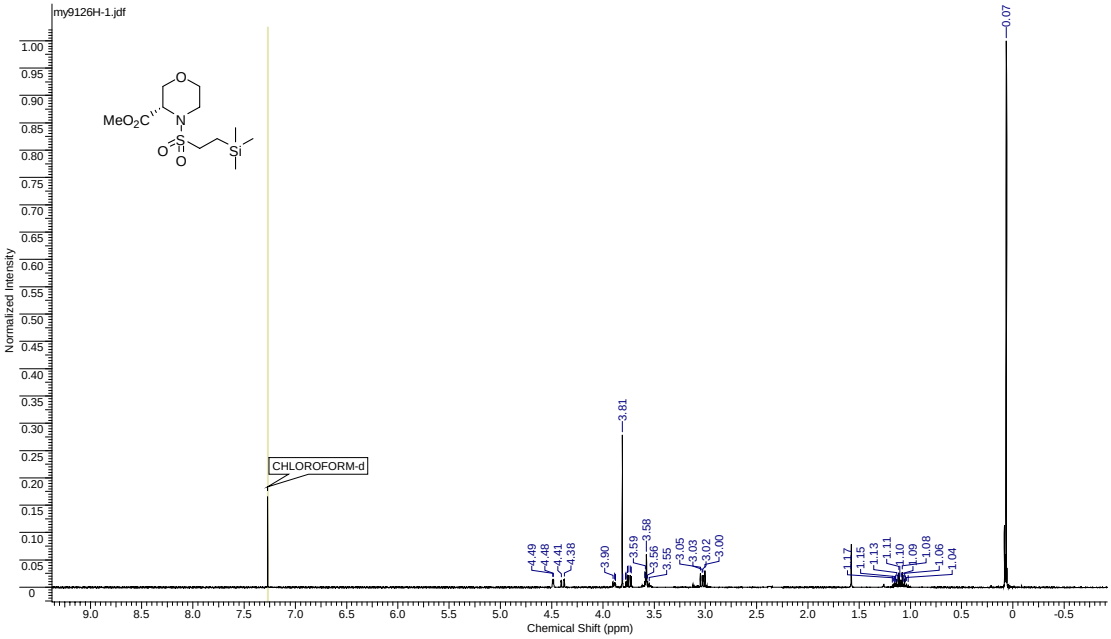


^{13}C NMR (100 MHz, $CDCl_3$)

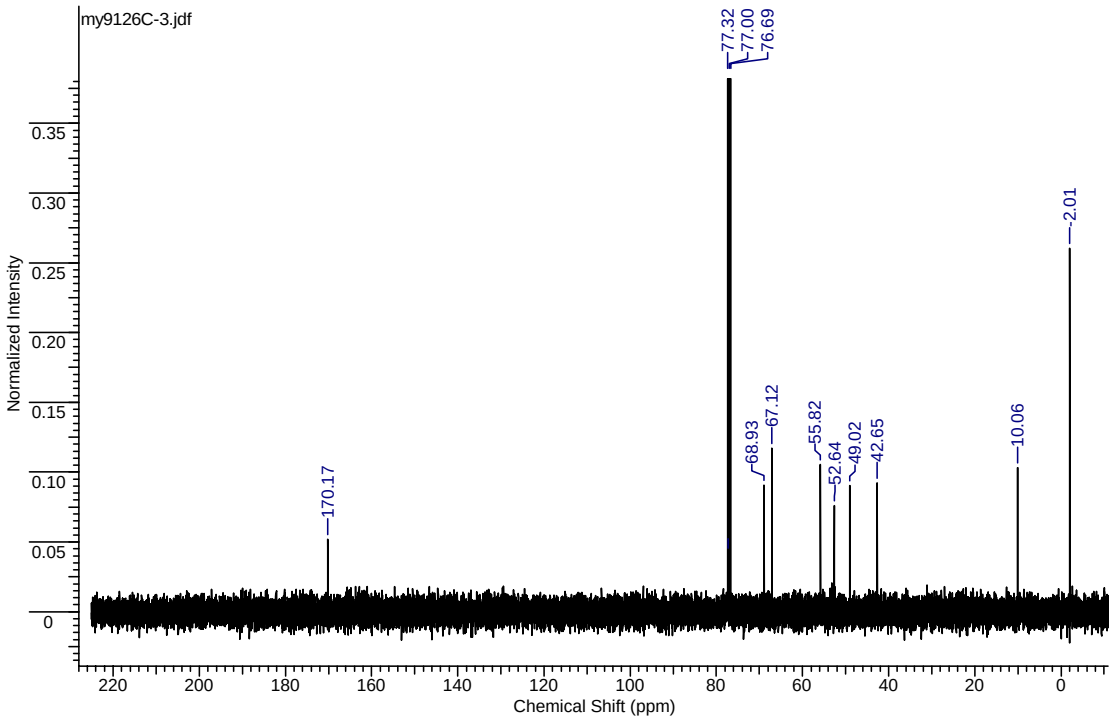


(*S*)-Methyl 4-(2-(trimethylsilyl)ethylsulfonyl)morpholine-3-carboxylate, 6f

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

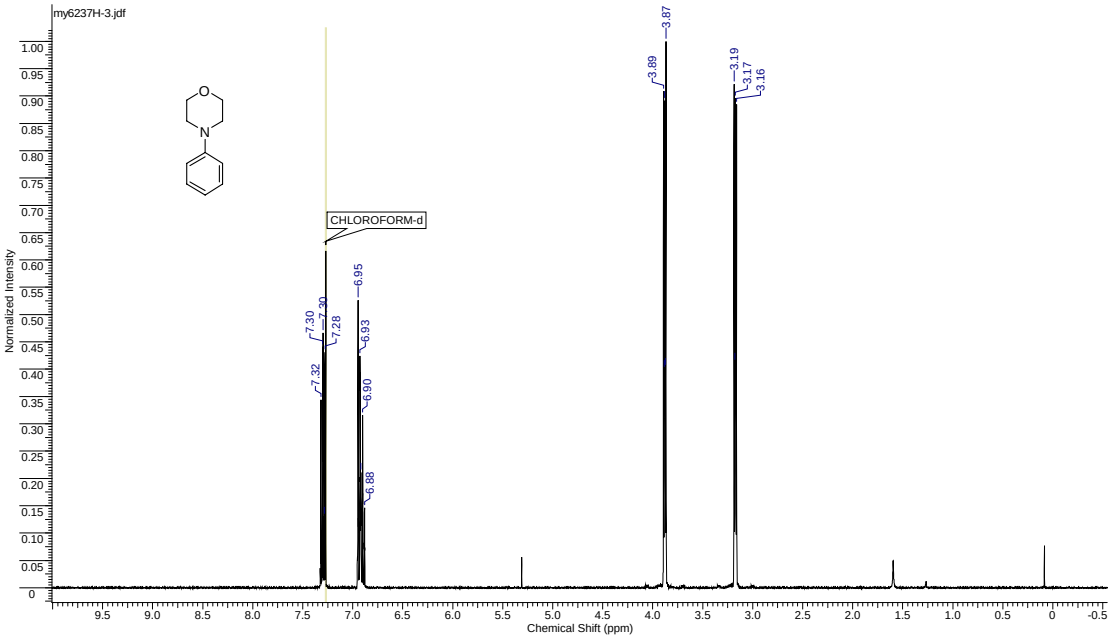


^{13}C NMR (100.5 MHz, $CDCl_3$)

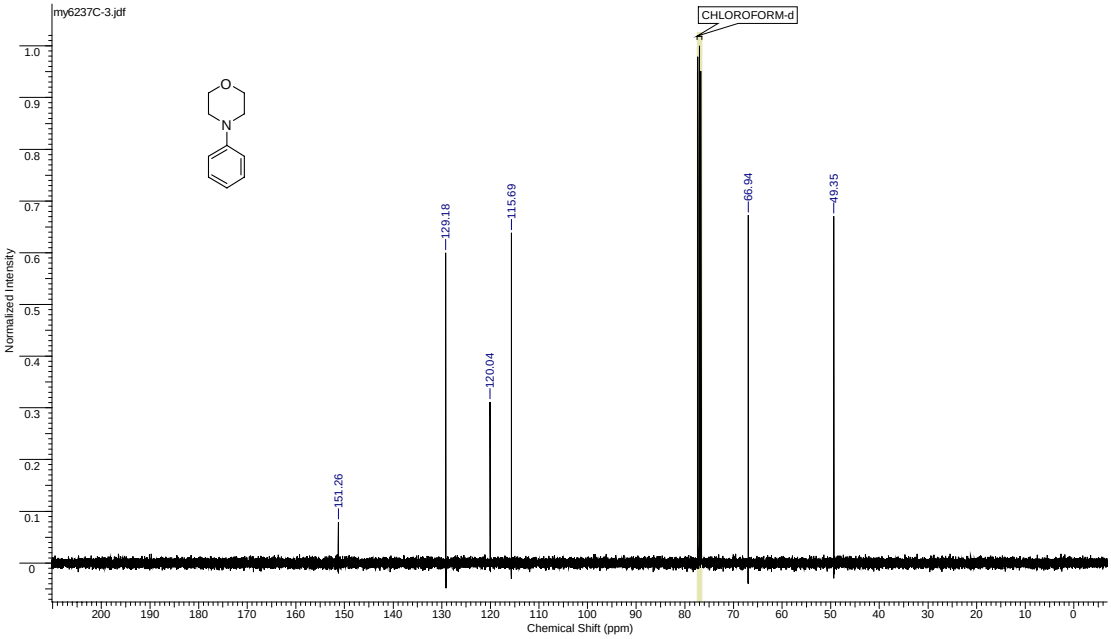


4-Phenylmorpholine, 6g

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

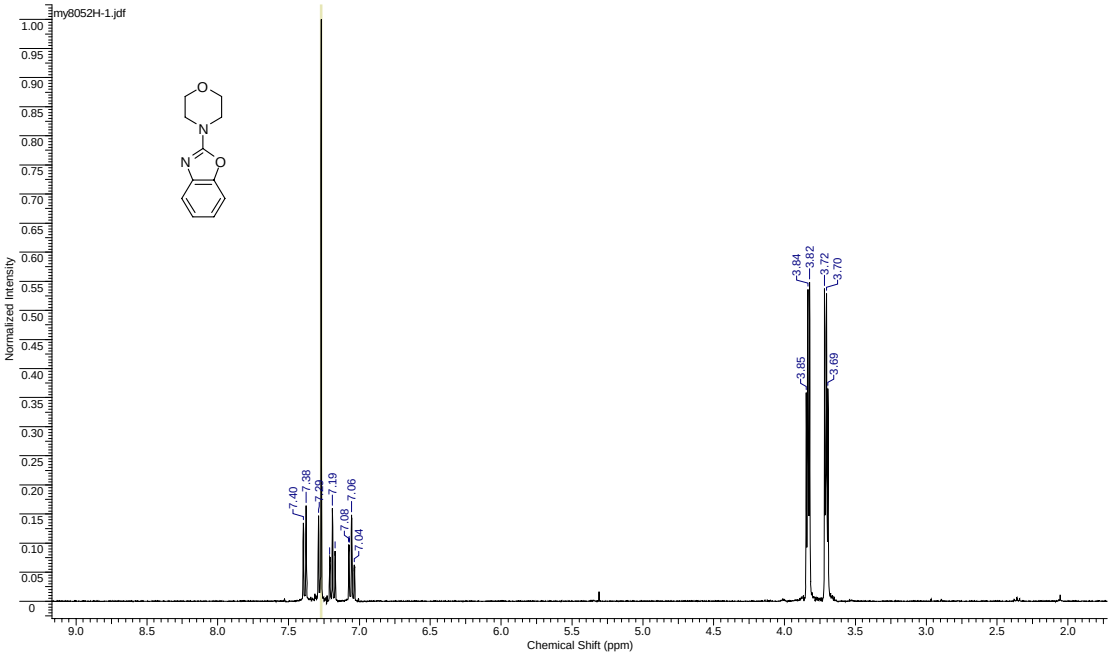


^{13}C NMR (100.5 MHz, $CDCl_3$)

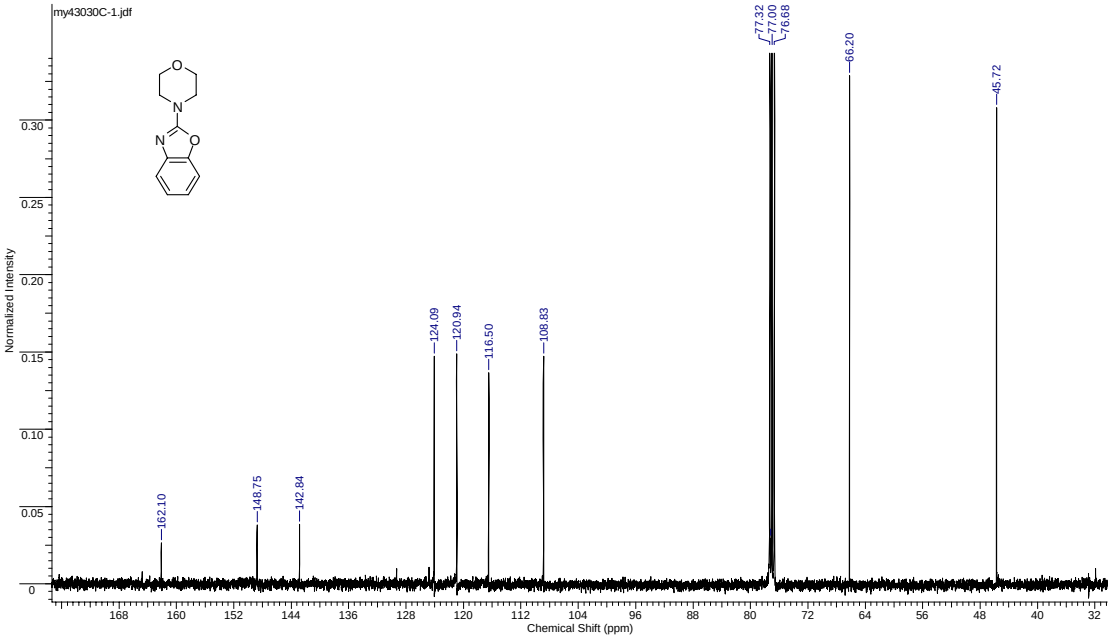


2-Morpholinobenzo[*d*]oxazole, 6h

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

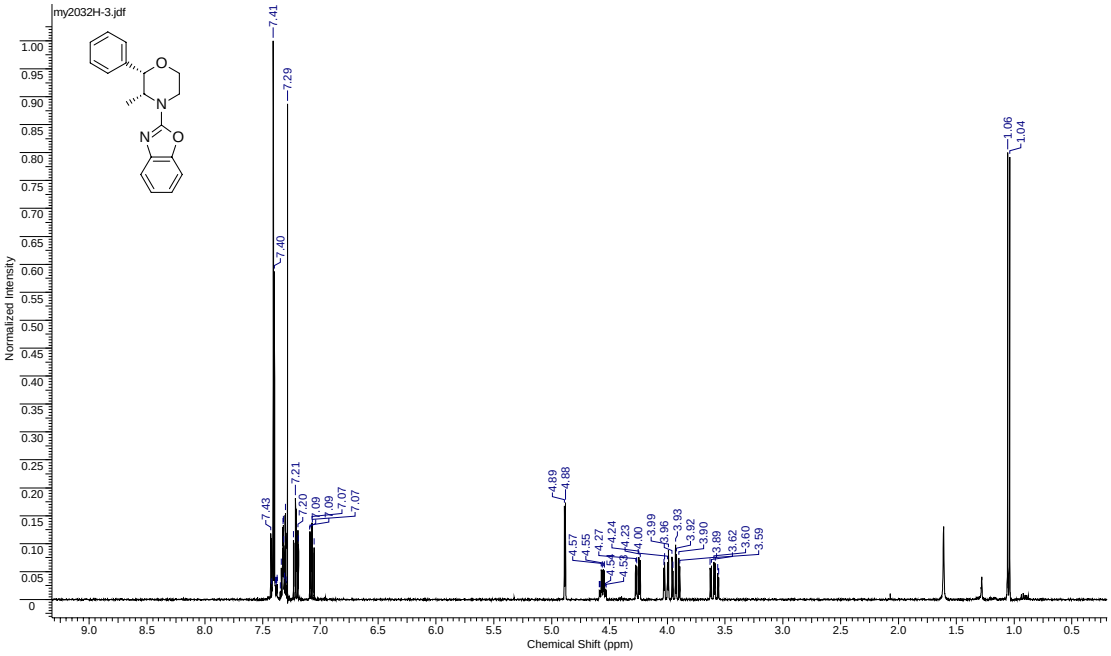


^{13}C NMR (100.5 MHz, $CDCl_3$)

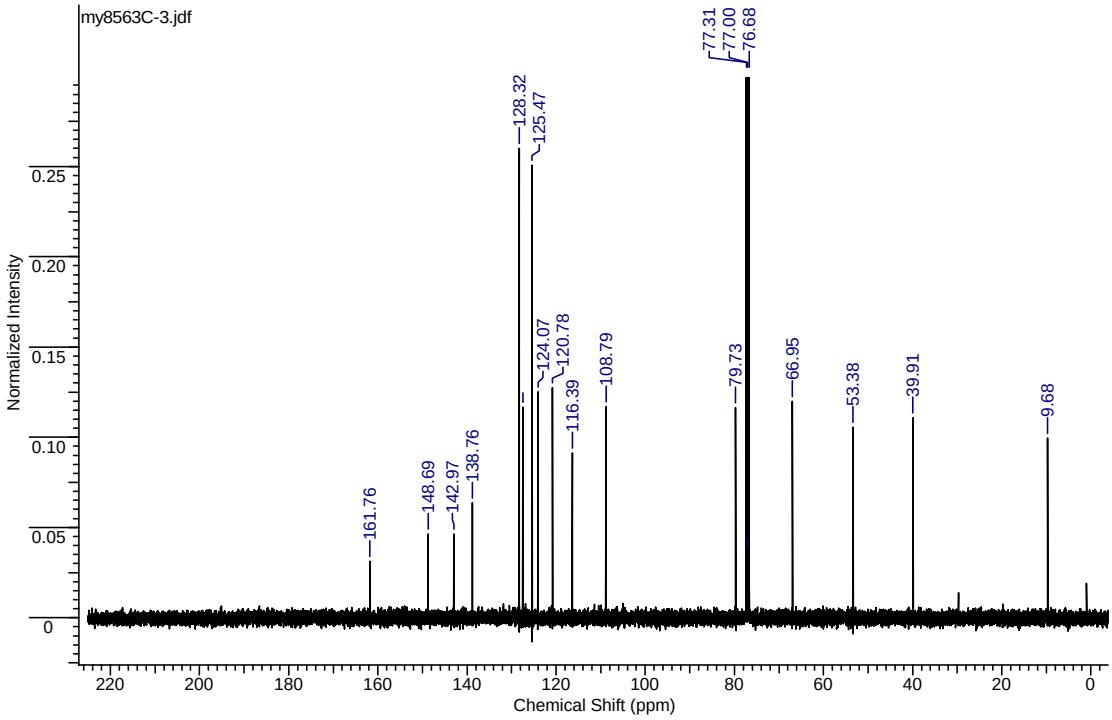


2-((2*S*,3*R*)-3-Methyl-2-phenylmorpholino)benzo[*d*]oxazole, 6i

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

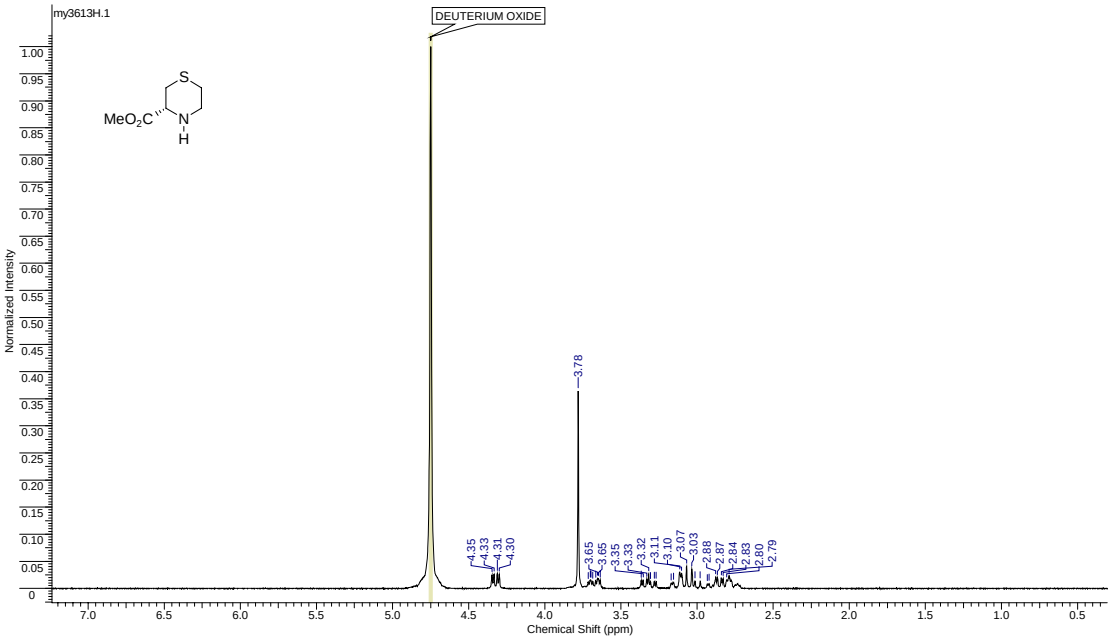


^{13}C NMR (100.5 MHz, $CDCl_3$)

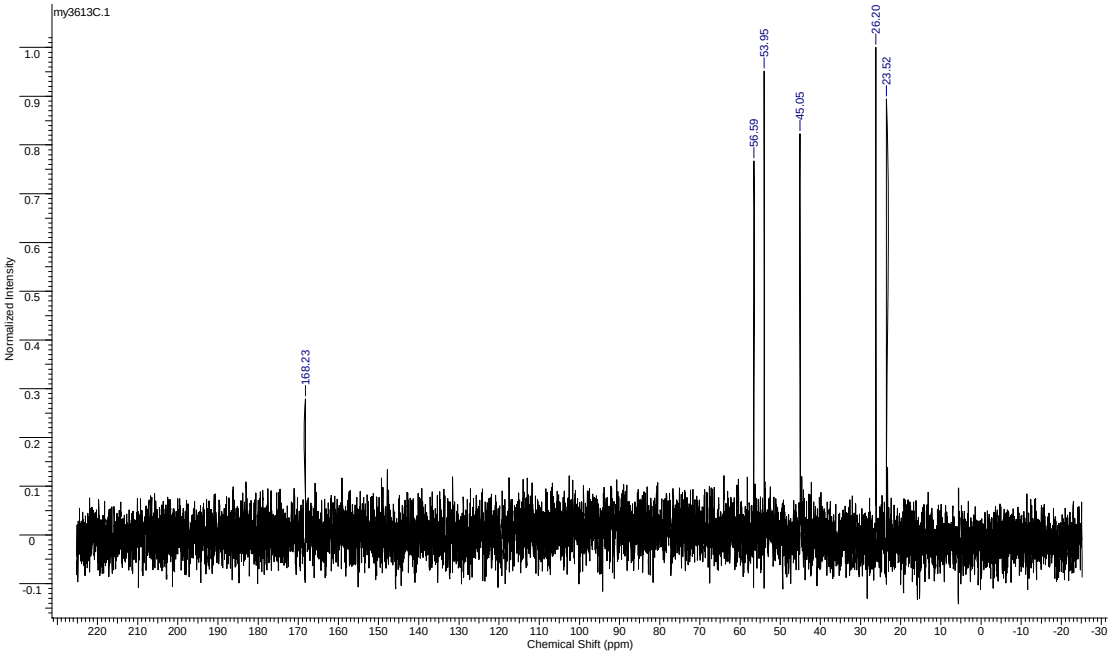


Thiomorpholine-(3*R*)-carboxylic acid methyl ester hydrochloride, 6j

^{1}H NMR (300 MHz, D_2O)

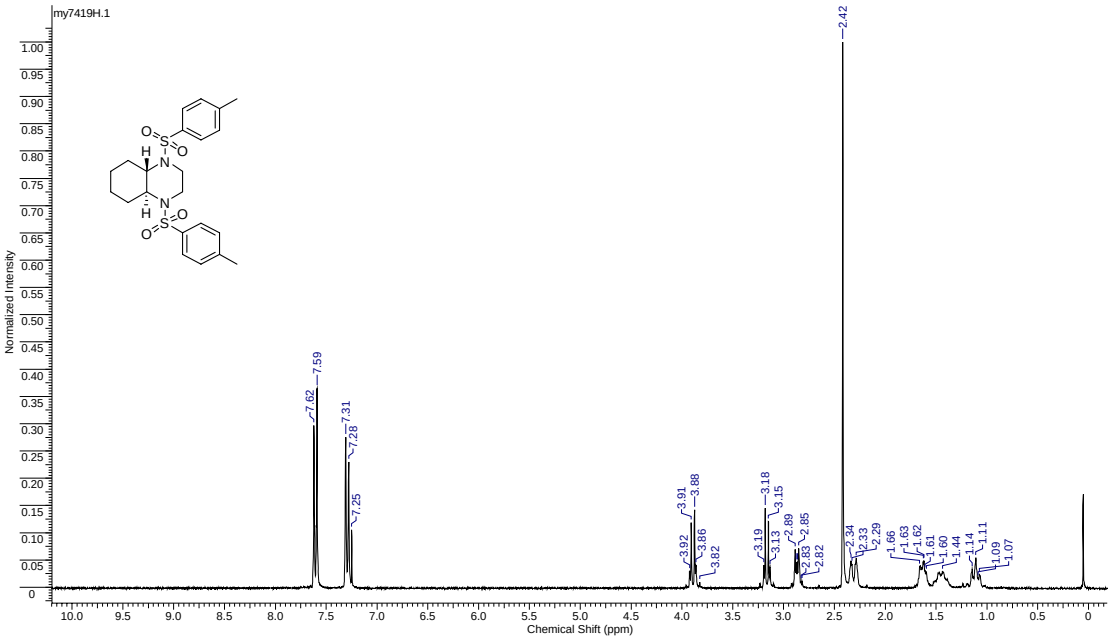


^{13}C NMR (100 MHz, D_2O)

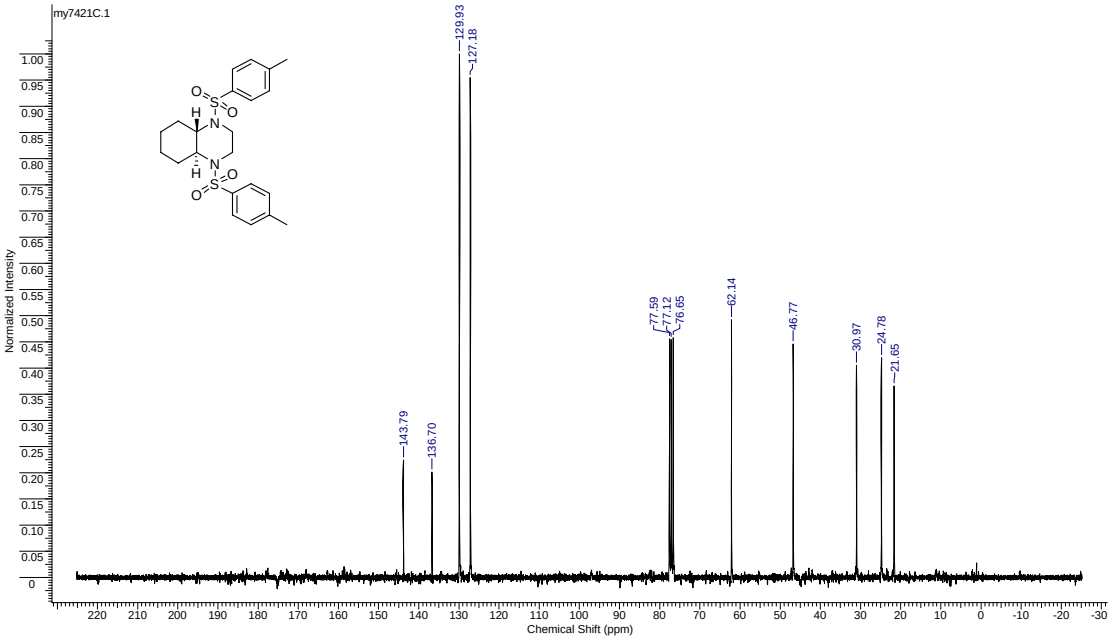


(±)-1,4-Bis(toluene-4-sulfonyl)decahydroquinoxaline, 6k

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

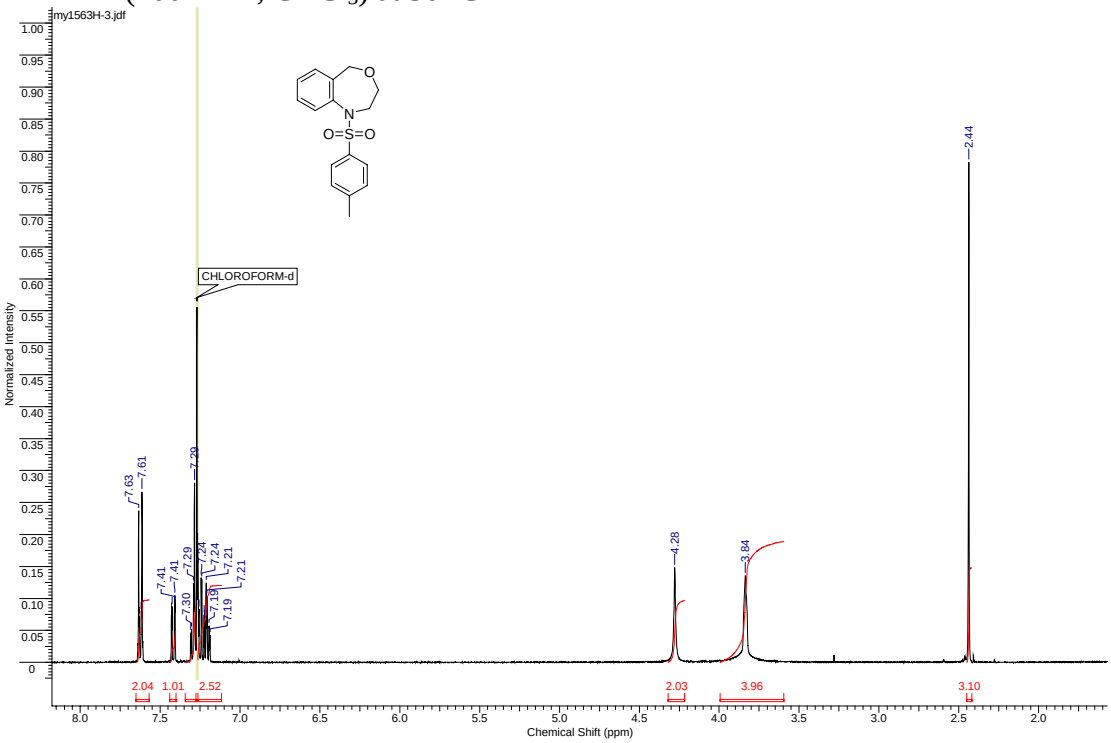


^{13}C NMR (100.5 MHz, $CDCl_3$)

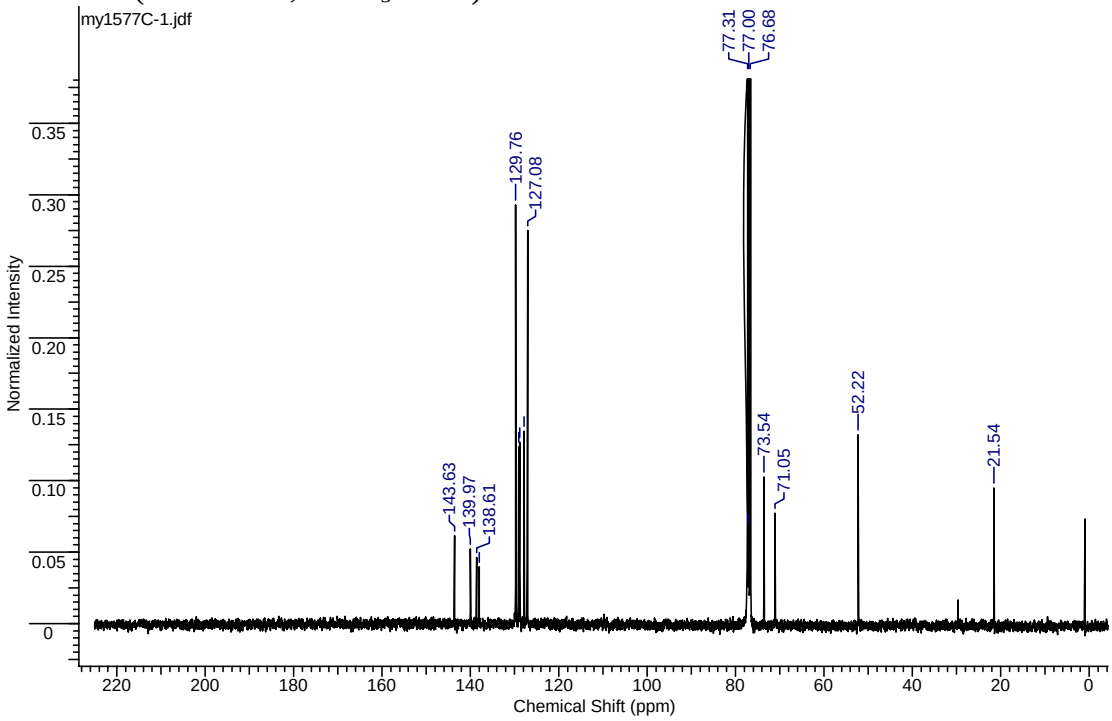


1-Tosyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine, 9a

^{1}H NMR (400 MHz, $CDCl_3$) at 50 ^{o}C

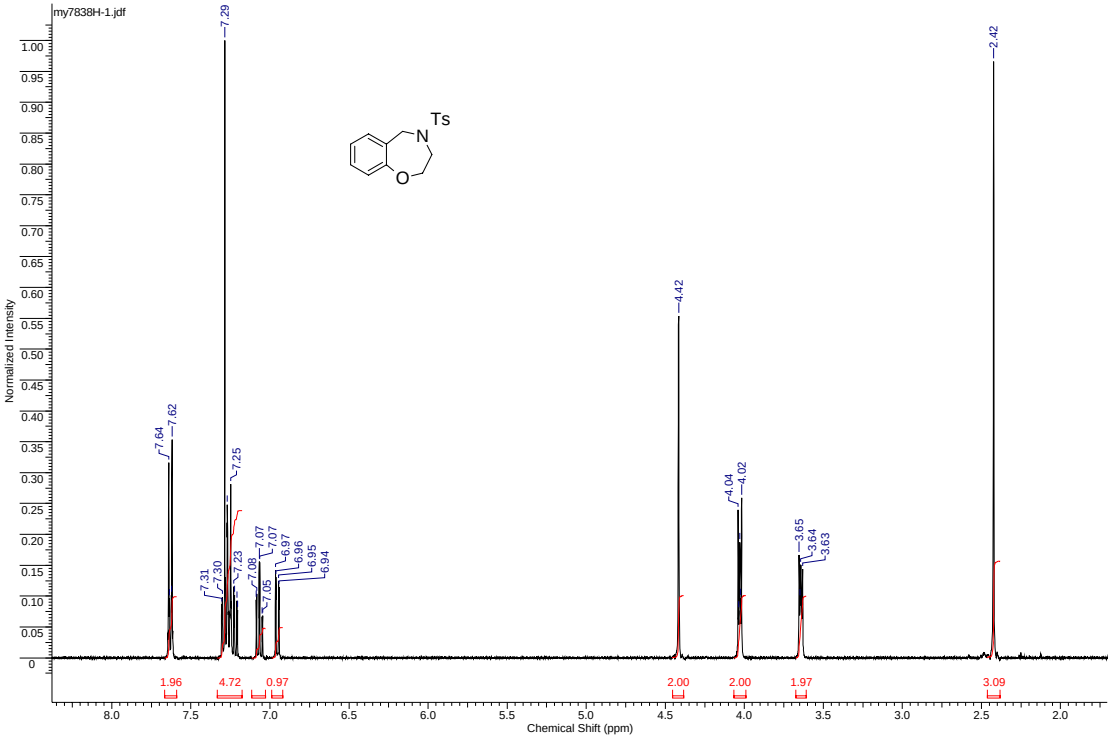


^{13}C NMR (100.5 MHz, $CDCl_3$ at RT)

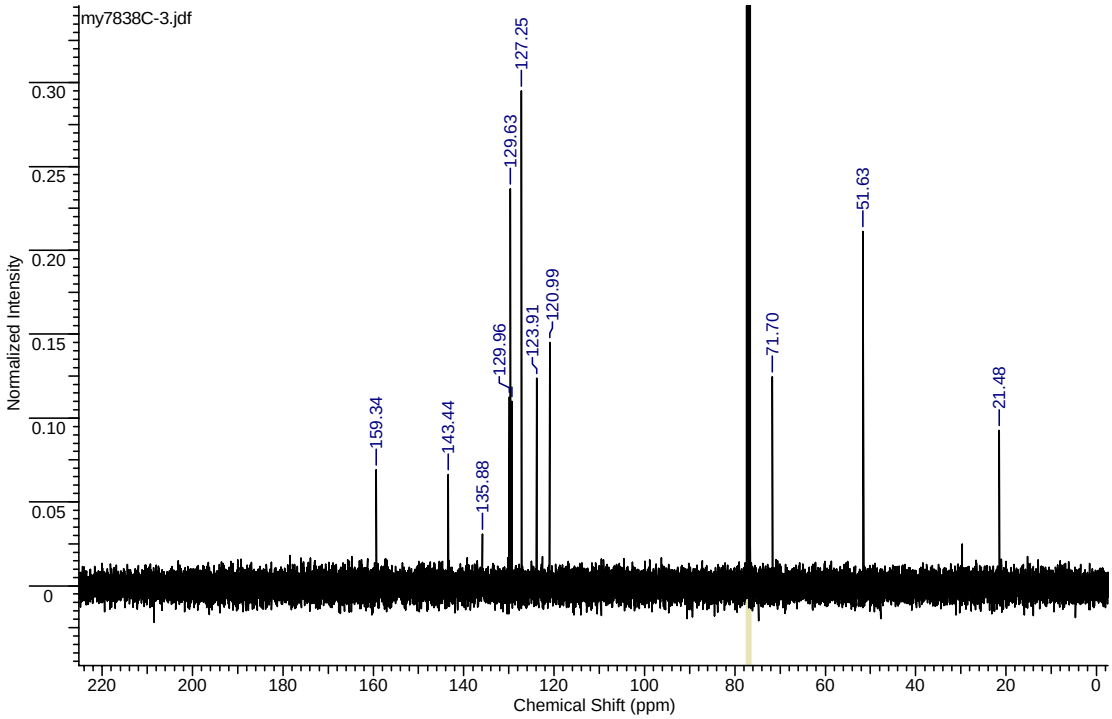


4-Tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine, 9b

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

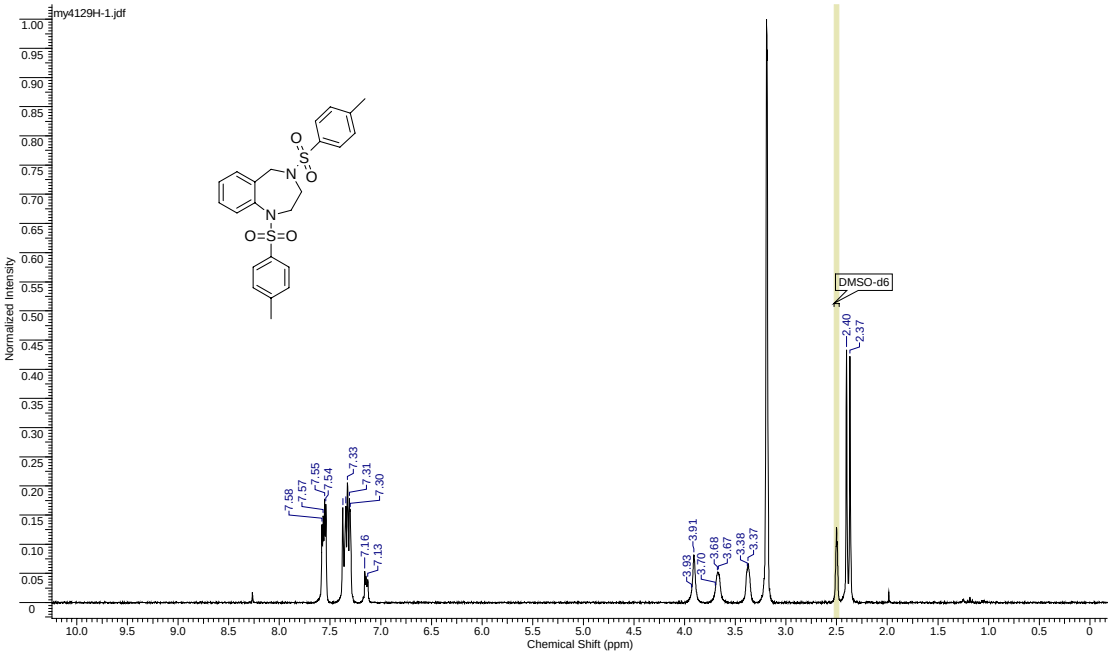


^{13}C NMR (100.5 MHz, $CDCl_3$)

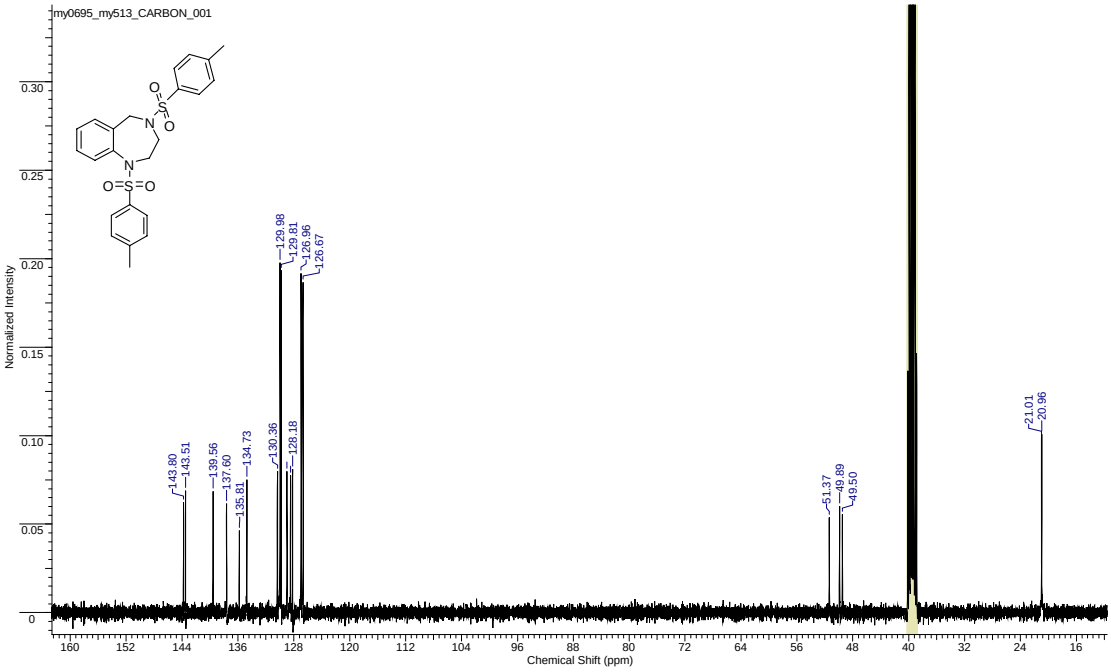


1,4-Ditosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine, 9c

^{1}H NMR (400 MHz, DMSO-d^{6}, run at 60 °C)

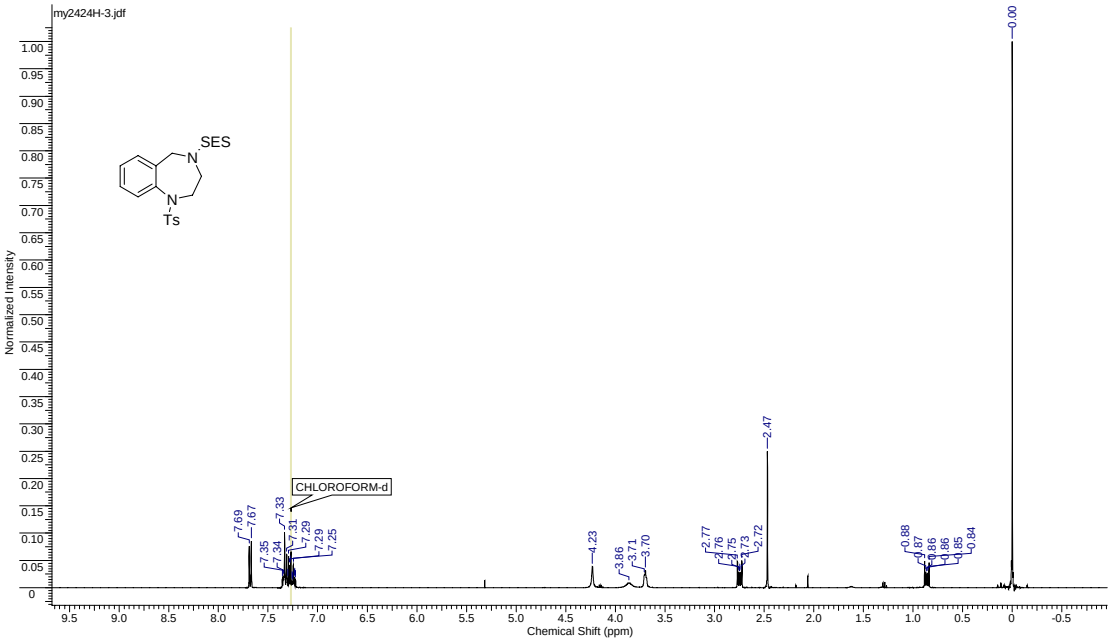


^{13}C NMR (100.5 MHz, DMSO-d^{6} at RT)

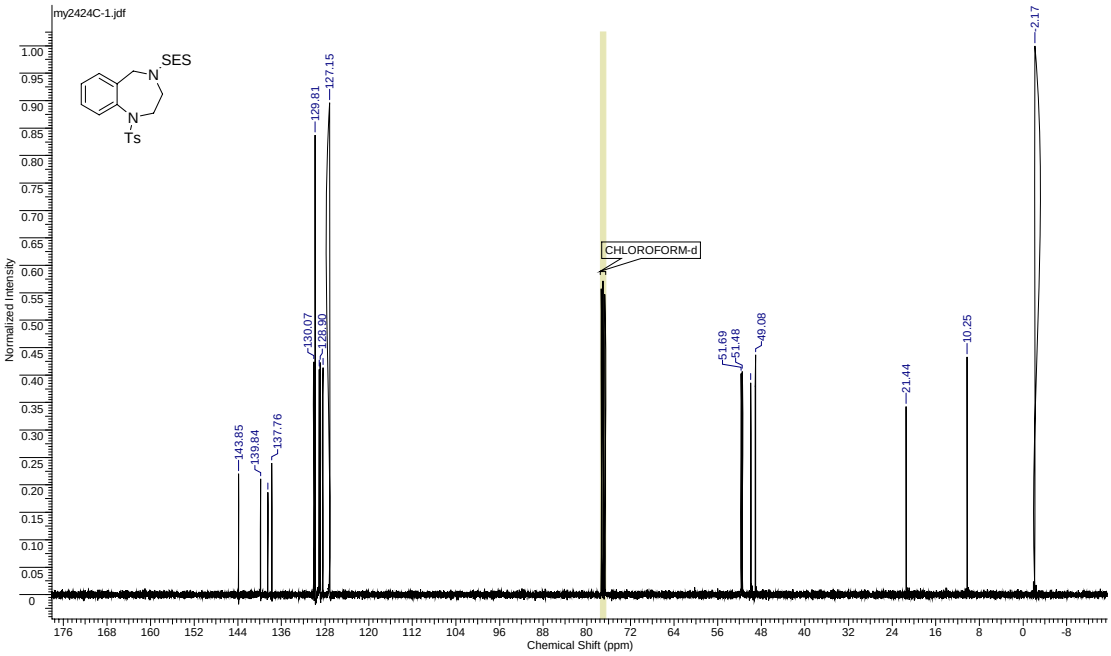


1-Tosyl-4-(2-(trimethylsilyl)ethylsulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine, 9d

^{1}H NMR (400 MHz, $CDCl_3$ at 50 ^{o}C)

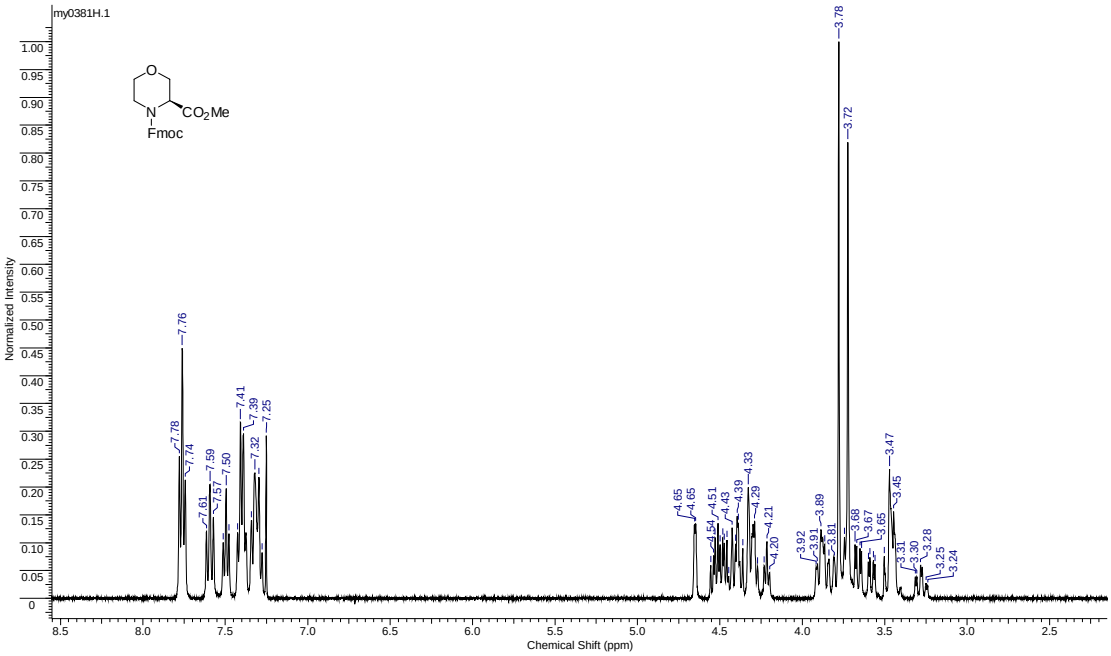


^{13}C NMR (100.5 MHz, $CDCl_3$ at 50 ^{o}C)

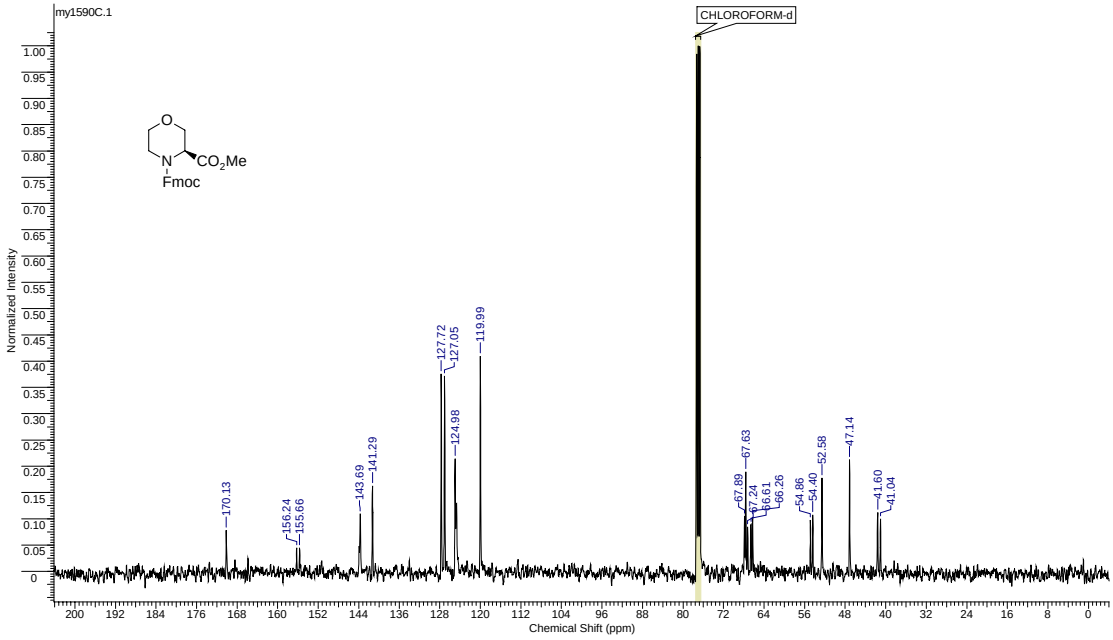


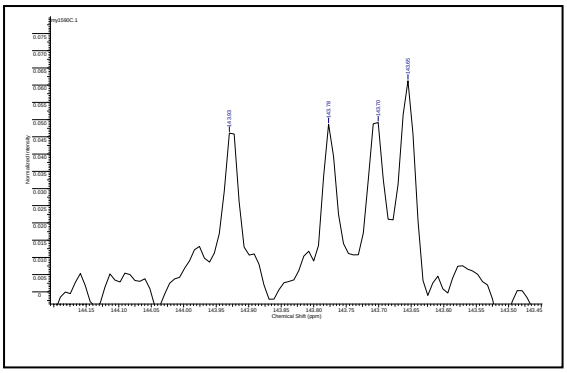
(*S*)-4-(9*H*-Fluoren-9-yl)methyl 3-methyl morpholine-3,4-dicarboxylate, 7

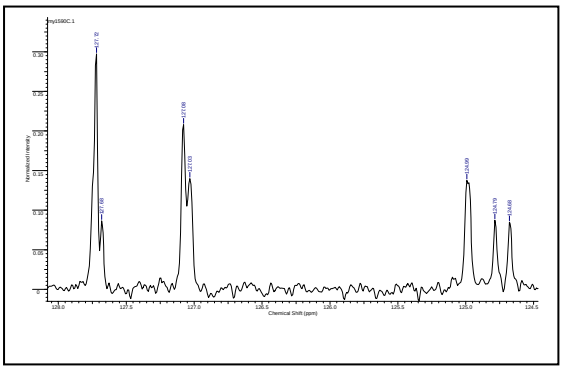
^{1}H NMR (400 MHz, $CDCl_3$)

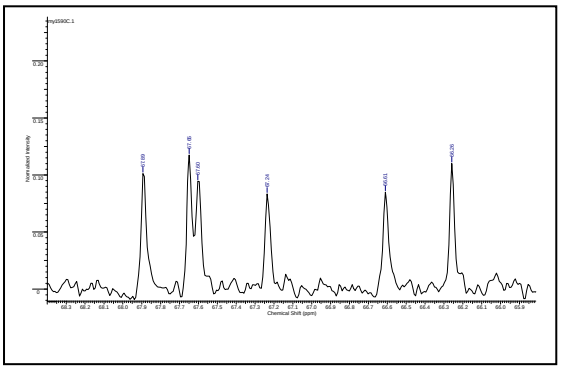


^{13}C NMR (100.5 MHz, $CDCl_3$)





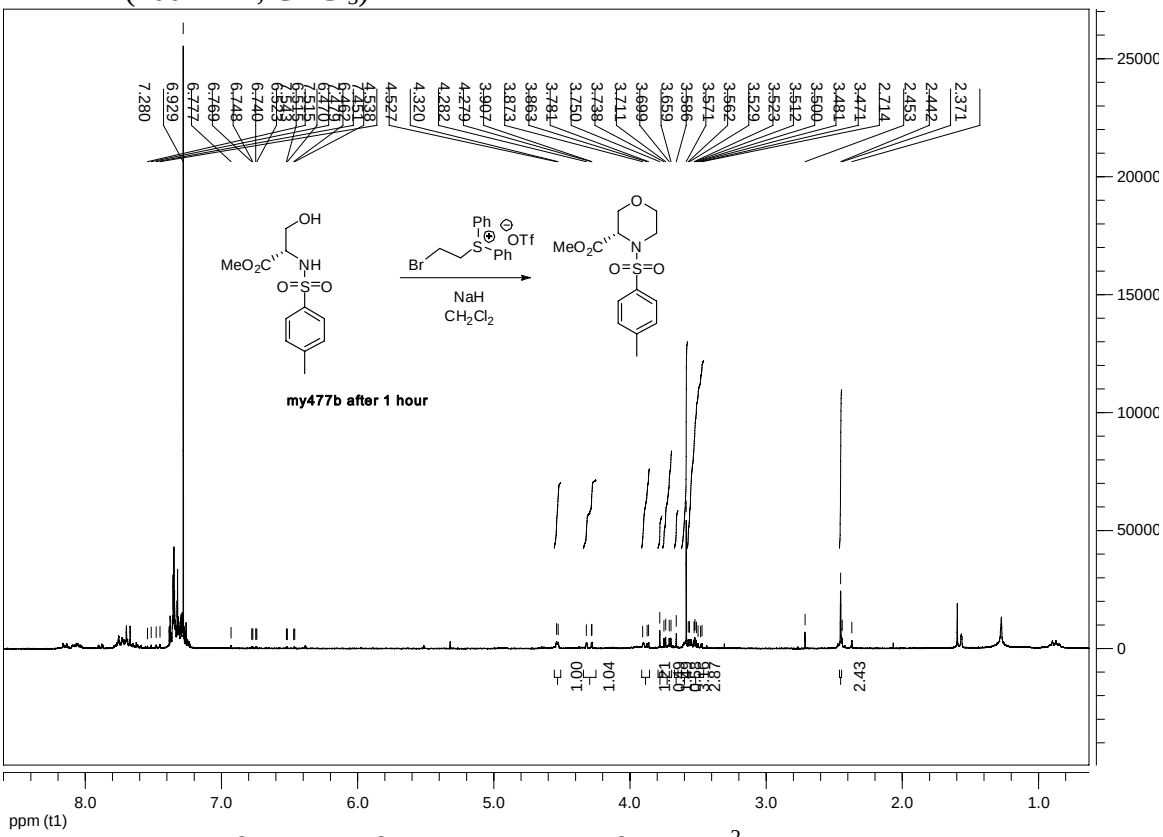




Formation of 1 under reaction conditions

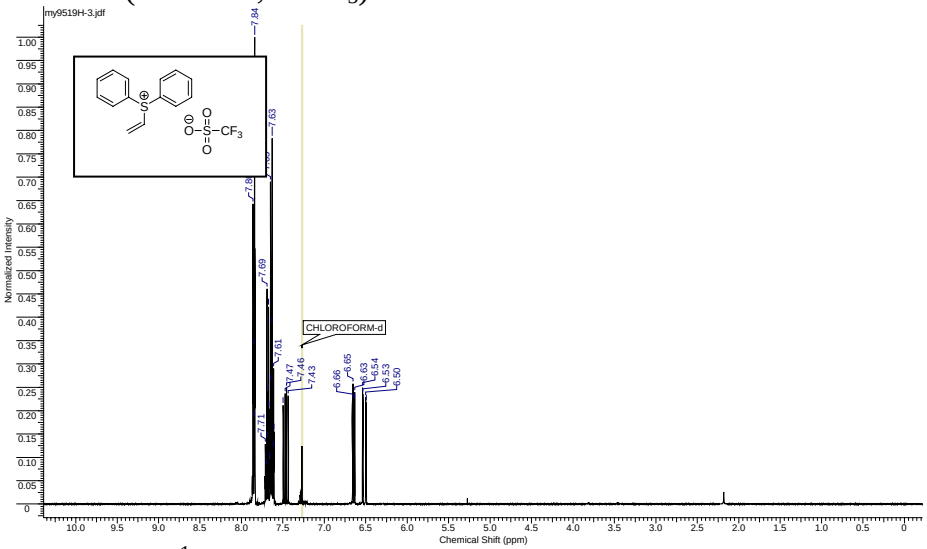
Following general method **A**, amino alcohol **5e** was reacted with bromoethylsulfonium salt **4**. After one hour the solvent was removed on a rotary evaporator. A sample of the residue was dissolved in $CDCl_3$ and a ^1H NMR spectrum was obtained. Peaks corresponding to vinyl sulfonium salt **1** were observed. See spectra below.

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



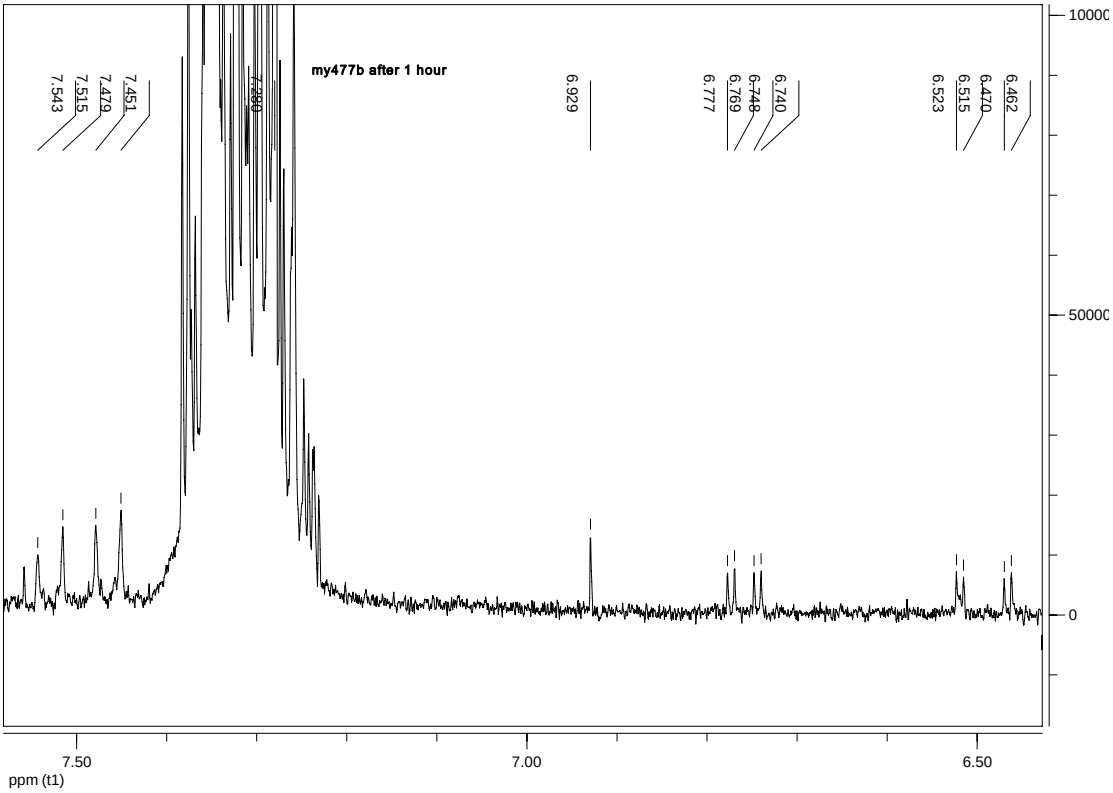
Diphenylvinylsulfonium trifluoromethanesulfonate, 1[2]

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



Expansion of ^1H NMR (400 MHz), $CDCl_3$

Reaction after 1 hour:



Diphenylvinylsulfonium trifluoromethanesulfonate, 1[2]

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