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Functionalization of terpene alcohols with 1-sulfonyl-1,2,3-triazoles: synthesis of *N*-(2-terpenyloxyethenyl/ethyl)sulfonamides

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Experimental Section

General

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) at 298 K. Chemical shifts are reported in parts per million (δ, ppm) and are referenced to 7.28 ($CDCl_3$) for ^{1}H NMR and 77.0 ($CDCl_3$) for ^{13}C NMR. High-resolution mass-spectra with Electrospray ionization (ESI) were measured on a Bruker MaXis HRMS-ESI-QTOF mass spectrometer. Melting points were determined on a melting point apparatus Stuart® SMP30 and are uncorrected. Optical rotations were acquired on a Polaar 3005 Polarimeter (Optical Activity, Huntingdon, Great Britain) using a 2.5 cm cell with a Na 589 nm filter and the concentration of samples was denoted as *c* (mg/ml). Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Column chromatography was performed on a silica gel Kieselgel 60 (0.04−0.063 mm). All solvents were distilled and dried prior to use. Commercial isoborneol (Sigma-Aldrich, ≥ 95%) and (−)-menthol (Sigma-Aldrich, 99%) were used.

Synthesis 4-aryl-1-arylsulfonyl-1,2,3-triazoles

4-Aryl-1-arylsulfonyl-1,2,3-triazoles were synthesized according to a known procedure[S1]. To a solution of the corresponding alkyne (10 mmol) in 60 ml toluene were added arylsulfonyl azide (10 mmol) and copper(I) thiophene-2-carboxylate (1 mmol, 190 mg). The reaction mixture was stirred for 12 h at 20 °C. After the reaction was complete (TLC monitoring), 50 ml of dichloromethane were added to the reaction mixture, and it was filtered through Celite. The solvent was evaporated under reduced pressure. The resulting crystalline product was washed first with an Et_2O – hexane mixture (10 ml, ratio 1/2, 1/4 and 1/8) and then with only hexane.

Synthesis betulin [lup-20(29)-ene-3β,28-diol, (3β,28-dihydroxy-20(29)-lupene)]

Betulin was obtained by extraction from crushed birch bark with a toluene-petroleum ether mixture (70−100°C) according to a known method[S2,S3]. Cream-colored solid, m.p. 254-256 °C, lit. data: m.p. 256−258 °C[S2]. According to the ^{1}H NMR spectrum, the product contains ≥95% of the main substance.

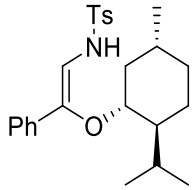
Synthesis of allobetulin [19,28-epoxyoleanan-3-ol]

Allobetulin was obtained by isomerization of betulin in the presence of cationite Amberlyst 15 according to the method[S4]. Light beige solid, m. p. 260−262 °C, lit. data: m.p. 263−265 °C[S4]. According to the ^{1}H NMR spectrum data, the product contains ≥95% of the main substance.

General Procedure for the synthesis of enamides 3a−o
(only stable compounds 3a and 3j−l are characterized)

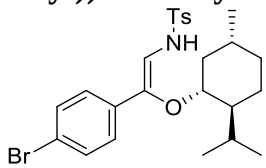
To a solution of terpene alcohol (0.55 mmol), 4-aryl-1-sulfonyl-1,2,3-triazole (0.5 mmol) and 0.5 ml of chloroform in a screw cap tube, $Rh_2(piv)_4$ (1 mol %) was added. The reaction was carried out under argon atmosphere. The mixture was stirred at 75 °C for 30-60 min depending on the substrate. The completion of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure. The product was isolated by column chromatography on silica gel using a hexane – ethyl acetate mixture (15:1) as an eluent.

***N*-((*Z*)-2-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-2-phenylvinyl)-4-methylbenzenesulfonamide (3a)**



To avoid decomposition, the chromatographic purification of the product should be carried out quickly. Yield 47 mg (65%), colorless solid, $[\alpha]_D^{22}$= -3.25 (*c* = 12.31, CH_2Cl_2). Spectral data correspond to literature data[S5].

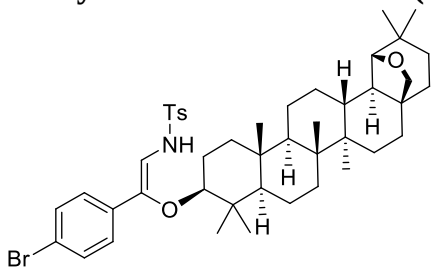
***N*-((*Z*)-2-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-2-(4-bromophenyl-vinyl))-4-methylbenzenesulfonamide (3j)**



To avoid decomposition, the chromatographic purification of the product should be carried out quickly. The final product contains a small amount of (−)-menthol. Yield 228 mg (49%), colorless solid, m. p. 129–130 °C, $[\alpha]_D^{22}$= -13.08 (*c* = 2.14, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.46 – 0.60 (m, 1H), 0.69 – 0.77 (m, 6H), 0.96 (d, 3H, *J* 7.0 Hz, CH_3), 1.29– 1.40 (m, 1H), 1.52 – 1.69 (m, 4H), 2.26 – 2.38 (m, 1H), 2.43 (s, 3H, CH_3), 3.39 (m, 1H, $C_{terp}HO$), 6.13 (d, 1H, ^3J 10.9 Hz, HC=), 6.63 (d, 1H, ^3J 10.9 Hz, NH), 7.12 – 7.20 (m, 2H, Ar), 7.33 (d, 2H, ^3J 8.1 Hz, Ar), 7.43 – 7.51 (m, 2H, Ar), 7.75 – 7.82 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 16.2, 21.2, 21.6, 22.1, 22.8, 25.1, 31.0,

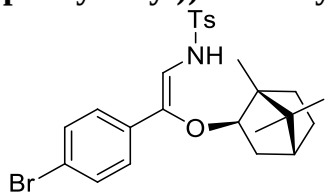
34.1, 40.1, 48.3, 111.0 (HC=), 121.9, 126.8, 127.7, 129.8, 131.7, 132.9, 137.0, 139.5, 143.8 (O–C=). HRMS (ESI), *m/z*: Found 530.1154 $[M+Na]^+$. (Calcd for $C_{25}H_{32}BrNO_3SNa^+$, *m/z*: 530.1159).

_N_-((_Z_)-2-([19-β,28-Epoxy-18α-olean-3β-yl]oxy)-2-(4-bromophenyl)vinyl))-4-methylbenzenesulfonamide (3k)



To avoid decomposition, the chromatographic purification of the product should be carried out quickly. The final product contains a small amount of allobetulin. Yield 194 mg (49%), colorless solid, m. p. 149–151°C, $[\alpha]_D^{22}$= -26.72 (*c* = 15.42, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.46 – 0.61 (m, 2H), 0.78 (m, 6H), 0.86 (m, 6H), 0.95 (m, 6H), 1.05 (s, 3H, CH_3), 1.06 – 1.16 (m, 2H), 1.17 – 1.70 (m, 22H), 2.43 (s, 3H, CH_3), 3.20 (m, 1H, $C_{terp}HO$), 3.45 (d, 1H, ^3J 7.7 Hz), 3.52 (s, 1H), 3.78 (d, 1H, ^3J 7.9 Hz), 6.16 (d, 1H, ^3J 10.8 Hz, HC=), 6.42 (d, 1H, ^3J 10.8 Hz, NH), 7.18 (d, 2H, ^3J 8.4 Hz, Ar), 7.33 (d, 2H, ^3J 8.0 Hz, Ar), 7.47 (d, 2H, ^3J 8.4 Hz, Ar), 7.79 (d, 2H, ^3J 8.3 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.4, 15.7, 16.3, 16.6, 18.0, 20.9, 21.5, 22.3, 24.6, 26.2, 26.3, 26.4, 27.8, 28.8, 32.7, 33.8, 34.1, 36.2, 36.7, 37.1, 38.1, 38.7, 40.6, 40.7, 41.5, 46.8, 50.9, 55.6, 71.2, 84.5, 87.9, 111.2 (HC=), 122.0, 126.8, 127.6, 129.9, 131.7, 132.7, 136.9, 140.3, 143.8 (O–C=). HRMS (ESI), *m/z*: Found 794.3636 $[M+H]^+$. (Calcd for $C_{45}H_{63}BrNO_4S^+$, *m/z*: 794.3638).

_N_-((_Z_)-2-(((1_S_,2_S_,4_S_)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)oxy)-2-(4-bromo-phenylvinyl))-4-methylbenzenesulfonamide (3l)

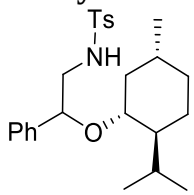


To avoid decomposition, the chromatographic purification of the product should be carried out quickly. The final product contains a small amount of isoborneol. Yield 159 mg (63%), colorless solid, m. p. 166–168°C, $[\alpha]_D^{22}$= -1.15 (*c* = 13.91, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.81 – 0.89 (m, 6H), 1.08 (s, 3H, CH_3), 1.26 – 1.36 (m, 1H), 1.41 (td, 1H, ^3J 11.9, 3.6 Hz), 1.55 – 1.67 (m, 4H), 2.45 (s, 3H, CH_3), 3.57 (m, 1H, $C_{terp}HO$), 5.92 (d, 1H, ^3J 10.8 Hz, HC=), 6.42 (d, 1H, ^3J 10.8 Hz, NH), 7.09 – 7.13 (m, 2H, Ar), 7.33 (d, 2H, ^3J 7.9 Hz, Ar), 7.74 – 7.79 (m, 2H, Ar), 7.45 – 7.49 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 11.6, 20.1, 20.6, 21.6, 26.8, 34.1, 38.5, 44.9, 46.8, 49.5, 86.4, 109.0 (HC=), 121.9, 126.8, 128.2, 129.8, 131.7, 132.9, 136.9, 141.7, 143.8 (O–C=). HRMS (ESI), *m/z*: Found 528.1023 $[M+Na]^+$. (Calcd for $C_{25}H_{30}BrNO_3SNa^+$, *m/z*: 528.1022).

General Procedure for the synthesis of sulfonamides 4a−g

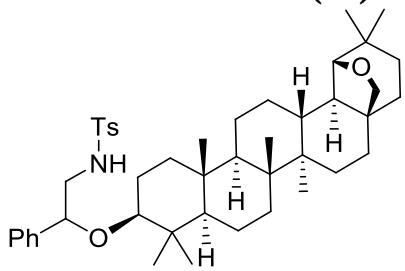
To a solution of enamide (0.3 mmol) in methanol (5 ml) in a Schlenk flask equipped with a glass Vigreux column and a hydrogen injection outlet, Pd/C (10 wt%) was added (if the substance was poorly soluble, THF was additionally added in an amount of 1/2 of the methanol volume). The reaction was carried out at 50 °C with constant hydrogen flow for 8−12 h. The reaction progress was monitored by TLC. The solvent was evaporated under reduced pressure. The product was isolated using column chromatography on silica gel using a hexane − ethyl acetate mixture (18:1) as an eluent.

***N*-(2-((((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-2-phenylethyl)-4-methylbenzenesulfonamide (4a)**



Compound **4a** was obtained as two diastereomers A:B (1:0.13) after column chromatography on silica gel and further recrystallization from a petroleum ether – ethyl acetate mixture (20:1). Yield 40 mg (31%), colorless solid, m. p. 114–115 °C, $[\alpha]_D^{22}$= -2.08 (*c* = 13.48, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.29 (m, 3H), 0.86 (m, 3H), 0.93 (m, 3H), 1.09 – 1.28 (m, 2H), 1.65 – 1.52 (m, 2H), 2.00 – 2.07 (m, 1H), 2.11 – 2.19 (m, 1H), 2.19 (s, 5H), 2.46 (s, 3H, CH_3), 2.90 (m, 1H, C_{terp}.HO), 3.02 – 3.13 (m, 1H), 3.26 – 3.15 (m, 2H, CH_2N), 4.47 (dd, 1H, ^3J 9.4, 3.9 Hz, ArC<u>H</u>O), 4.88 (dd, 1H, ^3J 9.4, 3.1 Hz, NH), 7.20 – 7.25 (m, 2H), 7.30 – 7.36 (m, 5H), 7.76 (d, 2H, ^3J 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.4, 15.8, 21.2, 21.5, 22.2, 22.3, 22.7, 22.8, 24.8, 25.5, 31.3, 31.5, 34.2, 34.4, 39.7, 42.4, 48.4, 49.1, 49.1, 74.9, 75.8, 77.2, 79.9, 126.6, 127.1, 127.2, 127.4, 128.0, 128.4, 128.5, 128.5, 129.7, 129.7, 137.2, 139.0, 143.4. HRMS (ESI), *m/z*: Found 430.2416 $[M+H]^+$. (Calcd for $C_{25}H_{36}NO_3S^+$, *m/z*: 430.2410).

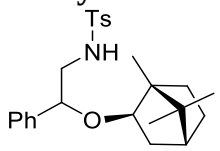
***N*-(-2-([19-β,28-Epoxy-18α-olean-3β-yl]oxy)-2-phenylethyl)-4-methyl-benzenesulfonamide (4b)**



The product was additionally purified by column chromatography on silica gel using a toluene – DCM mixture (5:1) as an eluent. Compound **4b** was obtained as two diastereomers A:B (1:0.7). Yield 107 mg (50%), colorless solid, m. p. 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.39 – 2.47 (m, 5H, $CH_3^{(A+B)}$), 2.70 (dd, 1H, ^3J 11.7, 4.0 Hz, C_{terp}.HO^B), 2.92 (dd, 1H, ^3J 11.7, 4.5 Hz, C_{terp}.HO^A), 3.04 (m, 2H, CH_2N^B), 3.18 (m, 2H, CH_2N^A), 3.42 (dd, 2H, ^3J 7.8, 2.2 Hz,), 3.51 (s, 1H), 3.50 (s, 1H), 3.76 (d, 2H, ^3J 7.7 Hz,), 4.41 (dd, 1H, ^3J 8.3, 4.3 Hz, ArC<u>H</u>O^B), 4.47 (dd, 1H, ^3J 9.3, 3.8 Hz, ArC<u>H</u>O^A), 4.71 (dd, 1H, ^3J 8.3, 4.3 Hz, NH^A), 4.82 (dd, 1H, ^3J 9.2, 3.0 Hz, NH^B), 7.18 – 7.25 (m, 4H, Ar), 7.25 – 7.34 (m, 10H, Ar), 7.69 (d, 2H, ^3J 8.1 Hz, Ar^A), 7.73 (d, 2H, ^3J 8.1 Hz, Ar^B). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.4, 13.5, 14.1, 15.7, 16.4, 16.5, 16.5, 16.6,

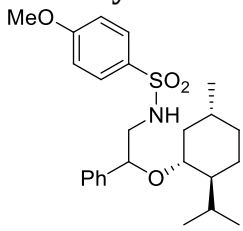
18.1, 18.2, 20.9, 21.0, 21.5, 22.0, 22.3, 24.5, 24.8, 26.2, 26.3, 26.4, 26.4, 28.0, 28.5, 28.8, 32.7, 33.9, 33.9, 34.1, 36.3, 36.8, 37.0, 37.1, 38.5, 38.6, 38.8, 39.5, 40.6, 40.6, 40.7, 40.7, 41.5, 41.5, 46.8, 49.4, 49.6, 51.0, 51.0, 55.6, 55.7, 71.3, 75.9, 80.2, 82.2, 87.8, 87.9, 126.6, 127.1, 127.1, 127.5, 128.0, 128.4, 128.4, 129.7, 137.0, 137.2, 138.7, 141.0, 143.4. HRMS (ESI), *m/z*: Found 716.4716 $[M+Na]^+$. (Calcd for $C_{45}H_{65}NO_4SNa^+$, *m/z*: 716.4707).

_N_-(2-(((1*S*,2*S*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)oxy)-2-phenylethyl)-4-methylbenzenesulfonamide (4c)



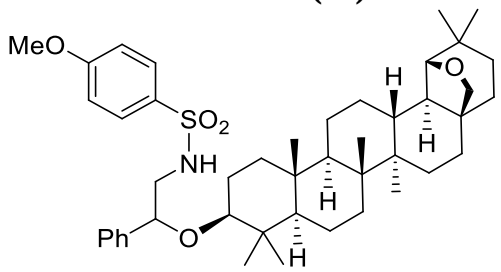
Compound **4c** was obtained as two diastereomers A:B (1:1). Yield 125 mg (97%), colorless solid, m. p. 78–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.74 – 0.82 (m, 1H), 0.83 (m, 6H, CH_3), 0.84 – 0.95 (m, 6H, CH_3), 1.02 (m, 6H, CH_3), 1.06 (s, 3H), 1.30 – 1.53 (m, 4H), 1.56 – 1.69 (m, 4H), 1.68 – 1.78 (m, 2H), 2.45 (s, 6H, CH_3), 2.91 – 3.06 (m, 2H, C_{terp}.HO), 3.09 – 3.25 (m, 4H, CH_2N), 4.35 (dd, 1H, ^3J 9.0, 3.8 Hz, ArC<u>H</u>O^B), 4.43 (dd, 1H, ^3J 8.8, 3.9 Hz, ArC<u>H</u>O^A), 4.68 (dd, 1H, ^3J 8.8, 3.7 Hz, NH^B), 4.80 (dd, 1H, ^3J 8.7, 3.5 Hz, NH^A), 7.16 – 7.26 (m, 4H, Ar), 7.27 – 7.38 (m, 10H, Ar), 7.66 – 7.76 (m, 4H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 12.1, 12.6, 20.3, 20.3, 20.3, 20.8, 21.7, 27.1, 27.2, 34.3, 34.4, 38.0, 39.9, 45.1, 45.2, 46.6, 46.8, 49.1, 49.7, 49.7, 49.9, 77.0, 81.2, 83.3, 86.7, 127.0, 127.2, 127.2, 128.3, 128.3, 128.6, 128.7, 129.8, 129.9, 137.1, 137.3, 139.1, 140.1, 143.5, 143.5. HRMS (ESI), *m/z*: Found 450.2069 $[M+Na]^+$. (Calcd for $C_{24}H_{33}NO_3SNa^+$, *m/z*: 450.2079).

_N_-(2-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-2-phenylethyl)-4-methoxybenzenesulfonamide (4d)



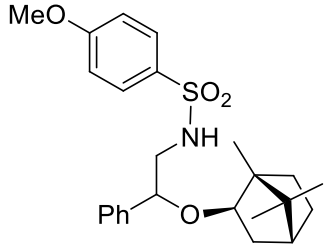
Compound **4d** was obtained as two diastereomers A:B (1:1). Yield 99 mg (74%), colorless solid, m. p. 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.26 – 0.31 (m, 3H), 0.64 – 0.73 (m, 1H), 0.72 – 0.76 (m, 3H), 0.74 – 0.84 (m, 2H), 0.84 – 0.88 (m, 6H), 0.90 – 0.96 (m, 3H), 0.95 – 1.00 (m, 3H), 1.12 – 1.23 (m, 4H), 1.24 – 1.32 (m, 1H), 1.50 – 1.66 (m, 6H), 2.01 – 2.10 (m, 1H), 2.11 – 2.23 (m, 1H), 2.21 – 2.31 (m, 1H), 2.90 (m, 1H, C_{terp}.HO), 3.01 – 3.11 (m, 2H, CH_2N), 3.11 – 3.24 (m, 3H), 3.89 (s, 3H, CH_3O^B), 3.90 (s, 3H, CH_3O^A), 4.44 (dd, 1H, ^3J 8.0, 4.5 Hz, ArC<u>H</u>O^B), 4.48 (dd, 1H, ^3J 9.4, 3.8 Hz, ArC<u>H</u>O^A), 4.67 (dd, 1H, ^3J 8.0, 4.6 Hz, NH^B), 4.87 (dd, 1H, ^3J 9.4, 3.1 Hz, NH^A), 6.94 – 7.00 (m, 2H, Ar), 6.97 – 7.03 (m, 2H, Ar), 7.20 – 7.25 (m, 2H, Ar), 7.23 – 7.29 (m, 2H, Ar), 7.28 – 7.37 (m, 6H, Ar), 7.72 – 7.78 (m, 2H, Ar), 7.78 – 7.84 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.5, 16.0, 21.4, 21.4, 22.3, 22.5, 22.8, 22.9, 24.9, 25.6, 31.4, 31.6, 34.4, 34.5, 39.9, 42.5, 48.5, 49.2, 49.2, 49.6, 55.8, 75.0, 75.9, 80.0, 114.4, 114.4, 126.8, 127.5, 128.2, 128.5, 128.6, 128.6, 129.3, 129.4, 131.6, 131.9, 139.1, 141.0, 163.0. HRMS (ESI), *m/z*: Found 446.2368 $[M+H]^+$. (Calcd for $C_{25}H_{36}NO_4S^+$, *m/z*: 446.2360).

***N*-(-2-([19-β,28-Epoxy-18α-olean-3β-yl]oxy)-2-phenylethyl)-4-methoxybenzenesulfonamide (4e)**



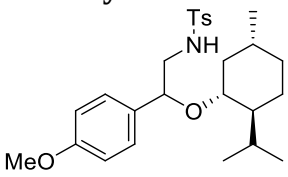
Compound **4e** was obtained as two diastereomers A:B (1:1). Yield 176 mg (60%), colorless solid, m. p. 66–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.76 – 0.82 (m, 16H), 0.83 – 0.90 (m, 10H), 0.90 – 0.98 (m, 16H), 1.15 – 1.79 (m, 48H), 2.73 (dd, 1H, ^{3}J 11.7, 4.1 Hz, C_{terp}.HO^{B}), 2.94 (dd, 1H, ^{3}J 11.6, 4.5 Hz, C_{terp}.HO^{A}), 3.00 – 3.12 (m, 2H, CH_2N^{B}), 3.13 – 3.25 (m, 2H, CH_2N^{A}), 3.45 (dd, 2H, ^{3}J 7.8, 2.1 Hz), 3.53 (d, 2H, ^{3}J 4.9 Hz), 3.78 (d, 2H, ^{3}J 7.8 Hz), 3.89 (s, 3H, CH_3O^{B}), 3.90 (s, 3H, CH_3O^{A}), 4.43 (dd, 1H, ^{3}J 8.3, 4.3 Hz, ArC<u>H</u>O^{A}), 4.50 (dd, 1H, ^{3}J 9.3, 3.8 Hz, ArC<u>H</u>O^{A}), 4.70 (dd, 1H, ^{3}J 8.2, 4.4 Hz, NH^{A}), 4.80 (dd, 1H, ^{3}J 9.2, 3.0 Hz, NH^{B}), 6.94 – 7.03 (m, 4H, Ar), 7.20 – 7.29 (m, 4H, Ar), 7.27 – 7.38 (m, 6H), 7.73– 7.80 (m, 2H, Ar), 7.77 – 7.83 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.4, 13.5, 14.1, 15.7, 16.5, 16.5, 16.7, 18.1, 18.2, 21.0, 21.0, 22.0, 22.3, 24.6, 24.8, 26.3, 26.4, 26.4, 28.0, 28.5, 28.8, 32.7, 33.9, 33.9, 34.1, 36.3, 36.8, 37.0, 37.1, 38.5, 38.6, 38.8, 39.5, 40.6, 40.7, 41.5, 46.8, 49.4, 49.6, 51.0, 51.0, 55.6, 55.7, 55.7, 71.3, 75.9, 80.2, 82.2, 87.8, 87.9, 114.3, 126.6, 127.5, 128.0, 128.4, 128.4, 129.2, 129.2, 131.6, 131.7, 138.8, 141.0, 162.9, 162.9. HRMS (ESI), *m/z*: Found 732.4652 $[M+H]^{+}$. (Calcd for $C_{45}H_{66}NO_5S^{+}$, *m/z*: 732.4656).

***N*-(2-(((1*S*,2*S*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)oxy)-2-phenylethyl)-4-methoxybenzenesulfonamide (4f)**



Compound **4f** was obtained as two diastereomers A:B (1:1). Yield 109 mg (82%), colorless solid, m. p. 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.81 – 0.85 (m, 6H), 0.87 (s, 3H), 1.02 (m, 6H), 1.06 (s, 3H), 1.31 – 1.53 (m, 6H), 1.57 – 1.68 (m, 5H), 1.69 – 1.80 (m, 2H), 2.45 (s, 6H, CH_3O^{A+B}), 2.90 – 3.04 (m, 2H, C_{terp}.HO$^{(A+B)}$), 3.09 – 3.24 (m, 4H, $CH_2N^{(A+B)}$), 4.36 (dd, 1H, ^{3}J 8.9, 3.8 Hz, ArC<u>H</u>O^{A}), 4.43 (dd, 1H, ^{3}J 8.7, 3.9 Hz, ArC<u>H</u>O^{B}), 4.66 (dd, 1H, ^{3}J 8.9, 3.7 Hz, NH), 4.77 (dd, 1H, ^{3}J 8.8, 3.5 Hz, NH), 6.93 – 7.02 (m, 4H, Ar), 7.18 – 7.26 (m, 4H, Ar), 7.27 – 7.39 (m, 6H, Ar), 7.72 – 7.81 (m, 4H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 12.0, 12.5, 20.1, 20.2, 20.2, 20.7, 27.0, 27.1, 34.2, 34.3, 37.9, 39.8, 45.0, 45.1, 46.5, 46.6, 49.0, 49.5, 49.5, 49.7, 55.6, 55.6, 76.9, 81.0, 83.2, 86.6, 114.2, 114.3, 126.9, 127.1, 128.1, 128.2, 128.5, 128.5, 129.2, 131.5, 131.7, 139.1, 140.0, 162.9, 162.9. HRMS (ESI), *m/z*: Found 466.2016 $[M+Na]^{+}$. (Calcd for $C_{24}H_{33}NO_4SNa^{+}$, *m/z*: 466.2028).

***N*-(2-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-2-(4-methoxyphenyl)ethyl)-4-methylbenzenesulfonamide (4g)**



Compound **4g** was obtained as two diastereomers A:B (1:1). Yield 94 mg (68%), colorless solid, m.p. 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.31 (d, ^{3}J 6.9 Hz, 3H), 0.62 – 0.75 (m, 2H), 0.75 (d, 5H, ^{3}J 6.5 Hz), 0.78 – 0.88 (m, 8H), 0.90 – 1.01 (m, 7H), 1.09 – 1.31 (m, 5H), 1.52 – 1.66 (m, 3H), 1.98 – 2.06 (m, 1H), 2.09 – 2.018 (m, 1H), 2.31 – 2.19 (m, 1H), 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.89 (m, 1H, C_{terp}.HO), 2.98 – 3.27 (m, 5H), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.34 – 4.46 (m, 2H, ArC<u>H</u>O$^{(A+B)}$), 4.61 – 4.69 (m, 1H, NH^{A}), 4.85 (dd, 1H, ^{3}J 9.1, 3.2 Hz, NH^{B}), 6.81 – 6.88 (m, 4H), 7.09 – 7.20 (d, 4H, Ar), 7.27 – 7.36 (m, 4H, Ar), 7.70 (d, 2H, ^{3}J 8.0 Hz, Ar), 7.76 (d, 2H, ^{3}J 8.1 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.5, 15.9, 21.3, 21.3, 21.5, 21.6, 22.2, 22.4, 22.7, 22.8, 24.8, 25.5, 31.3, 31.5, 34.2, 34.4, 39.7, 42.5, 48.4, 49.1, 49.2, 49.5, 55.3, 55.3, 74.5, 75.2, 77.3, 79.5, 79.5, 113.8, 113.8, 127.1, 127.2, 127.9, 128.6, 129.7, 129.7, 130.9, 132.7, 136.9, 137.2, 143.4, 159.4, 159.7. HRMS (ESI), *m/z*: Found 460.2522 $[M+H]^{+}$. (Calcd for $C_{26}H_{38}NO_4S^{+}$, *m/z*: 460.2516).

Study of Biological Activity

Antiproliferative assay

Cell culture. SK-BR-3 breast cancer cells, PC-3 prostate cancer cells, A549 lung carcinoma cells, HCT116 colorectal carcinoma cells, A375 melanoma cells, and WI-26 VA4 embryonic lung fibroblast cells were purchased from the ATCC. PC-3 cells and A549 cells were maintained in F12-K medium (Gibco, UK) supplemented with 10% fetal bovine serum (FBS, Gibco, UK), penicillin (100 U/ml), streptomycin (100 μg/ml), and GlutaMax (2 mM, Gibco, UK). HCT116 and SK-BR-3 cells were maintained in McCoy's 5A medium (Gibco, UK) supplemented with 10% fetal bovine serum (FBS, Gibco, UK), penicillin (100 U/ml), streptomycin (100 μg/mL), and GlutaMax (1.5 mM, Gibco, UK). A375 cells were maintained in DMEM (Gibco, UK) supplemented with 10% fetal bovine serum (FBS, Gibco, UK), penicillin (100 U/mL), streptomycin (100 μg/ml), and GlutaMax (4.0 mM, Gibco, UK). WI-26 VA4 cells were maintained in Advanced MEM (Gibco, UK) supplemented with 5% fetal bovine serum (FBS, Gibco, UK), penicillin (100 U/ml), streptomycin (100 μg/ml), and GlutaMax (1.87 mM, Gibco, UK). All cell lines were cultivated under a humidified atmosphere of 95% air/5% CO_2 at 37 °C. Subconfluent monolayers in the log growth phase were harvested by a brief treatment with TrypLE Express solution (Gibco, UK) in phosphate-buffered saline (PBS, Capricorn Scientific, Germany) and washed three times in serum-free PBS. The number of viable cells was determined by trypan blue exclusion.

Antiproliferative assay. The effects of the synthesized compounds on cell viability were determined using the MTT colorimetric assay[S6,S7]. All examined cells were diluted with growth medium to a concentration of 3.5×10^4 cells/ml. Aliquots containing 7×10^3 cells per 200 μl were placed into individual wells of 96-well plates (Eppendorf, Germany) and incubated for 24 hours. Triplicate wells were treated with test compounds at a final concentration of 30 μM. DMSO (Sigma, USA) was used as a control at a final concentration of 0.1%. The plates were incubated for 72 hours at 37°C in a 5% CO_2 atmosphere. After incubation, the cells were treated with 40 μl of MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, 5 mg/ml in PBS) and incubated for an additional 4 hours. Following this, the medium containing MTT was removed, and 150 μL of DMSO was added to each well to dissolve the formazan crystals. The plates were shaken for 10 minutes to ensure complete dissolution. The optical density of each well was measured at 560 nm using a GloMax Multi+ microplate reader (Promega, USA). The cytotoxicity of each tested compound was evaluated in three separate experiments.

Determination of Antibacterial Activity *in vitro*

ESKAPE bacterial strains used for experiments: *Enterococcus faecalis* (ATCC 29812), *Staphylococcus aureus* (ATCC 25912), *Klebsiella pneumonia* (ATCC 13882), *Acinetobacter baumannii* (ATCC 19606), *Pseudomonas aeruginosa* (ATCC 27853), *Enterobacter cloacae* (ATCC 13048).

Disk diffusion method. Testing of the susceptibility of above microorganisms to compounds **4** as well as Sulfamethoxazole (positive control) was performed using the conventional Kirby–Bauer disk diffusion test[S8] under the Standard Operating Procedure of The European Committee on Antimicrobial Susceptibility Testing (EUCAST)[S9]. Disks containing 5 μg of Sulfamethoxazole were used. The tested compound (1 mg) was dissolved in dimethyl sulfoxide (10 μl) and diluted to a volume of 1 ml with deionized water. To a Petri dish containing Muller-Hilton agar inoculated with a bacterial suspension (McFarland OD = 0.5) 5 μl of this solution were added. After drying of the compound solution, the Petri dish was incubated at 37 °C for 24 h. The susceptibility to a drug was assessed by measuring the bacterial growth inhibition zone diameter around the disc with Sulfamethoxazole or the tested compound dried solution circular spot.

Determination of the minimum inhibitory concentration (MIC). The test was performed under the Standard Operating Procedure of The European Committee on Antimicrobial Susceptibility Testing (EUCAST)[S10] at a final volume of 0.2 mL in a 96-well sterile immunology plate with sterile lids. The nutrient medium for this method is the Muller–Hinton medium. A standard microbial suspension equivalent to 0.5 according to the Mcfarland standard was used for inoculation, diluted 100 times on a nutrient broth, after which the concentration of the microorganism in it was approximately 10^6 CFU/ml.

The working solution of the antibiotic compound was prepared from the basic solution using a liquid nutrient medium. The first concentration was the maximum. In all wells of the plate 100 μl of nutrient medium were placed. Then 100 μl of the maximum concentration solution of the compound were placed in the first well of the horizontal row of the plate. The contents of the well were mixed and 100 μl from the first well of the

first horizontal row was transferred to the second well of the first horizontal row. So it was continued to the well number 10, from which 100 μl of the contents were removed after mixing. Thus, a number of wells with a solution of antibacterial compound was obtained, the concentrations of which differed in neighboring tubes by 2 times. Then, in the first 10 wells 100 μl of the prepared suspension of bacteria was placed. Wells 11 and 12 were controls. Well 11 was a control of bacteria, it contained 100 μl of the nutrient medium and 100 μl of the bacteria suspension, which was used in the first horizontal row. Well 12 was a control of the broth, it contained 200 μl of the nutrient medium. Each horizontal row of the plate corresponded to a separate antibacterial compound or a separate microorganism. One or two rows of the plate were used to establish controls of the respective antibiotics selected as reference for the compound under study with each microorganism.

The plates were incubated at +37 °C in the thermostat during 18–24 h. The results were taken into account visually, comparing the growth of microorganisms in the presence of an antibacterial compound with the growth of culture in the cell without it. The minimum concentration providing complete suppression of the visible growth of the studied strain was used for MIC value.

References

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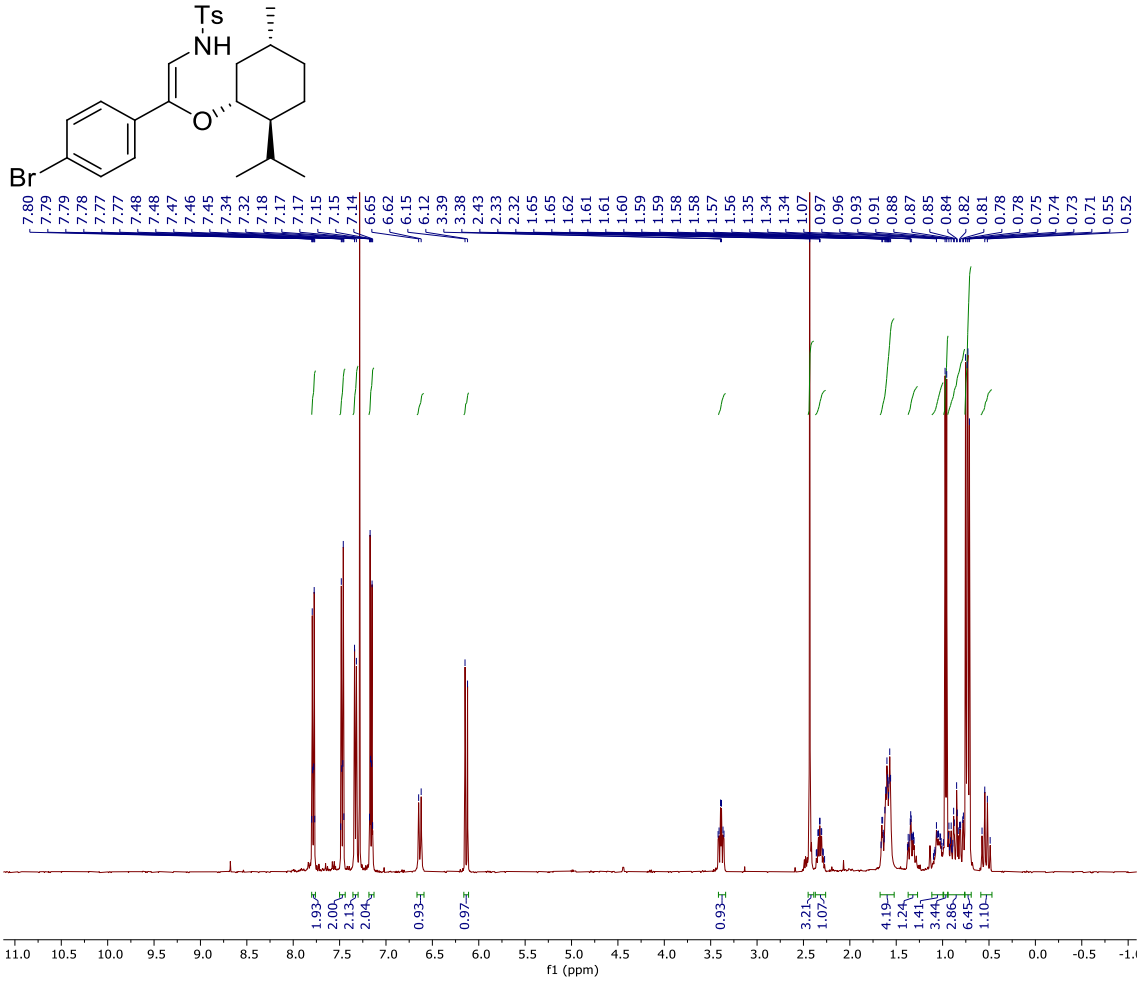
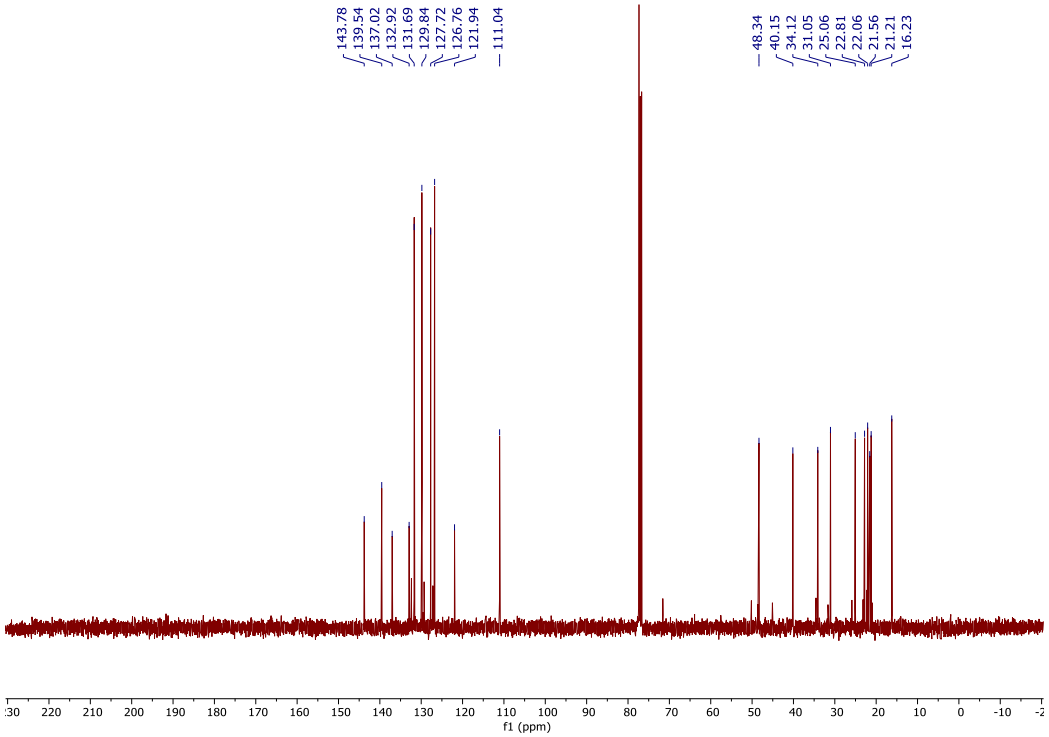
S10. *MIC Determination of Non-Fastidious and Fastidious Organisms*, EUCAST, version 1.0, 2019.

^{1}H and ^{13}C NMR Spectra

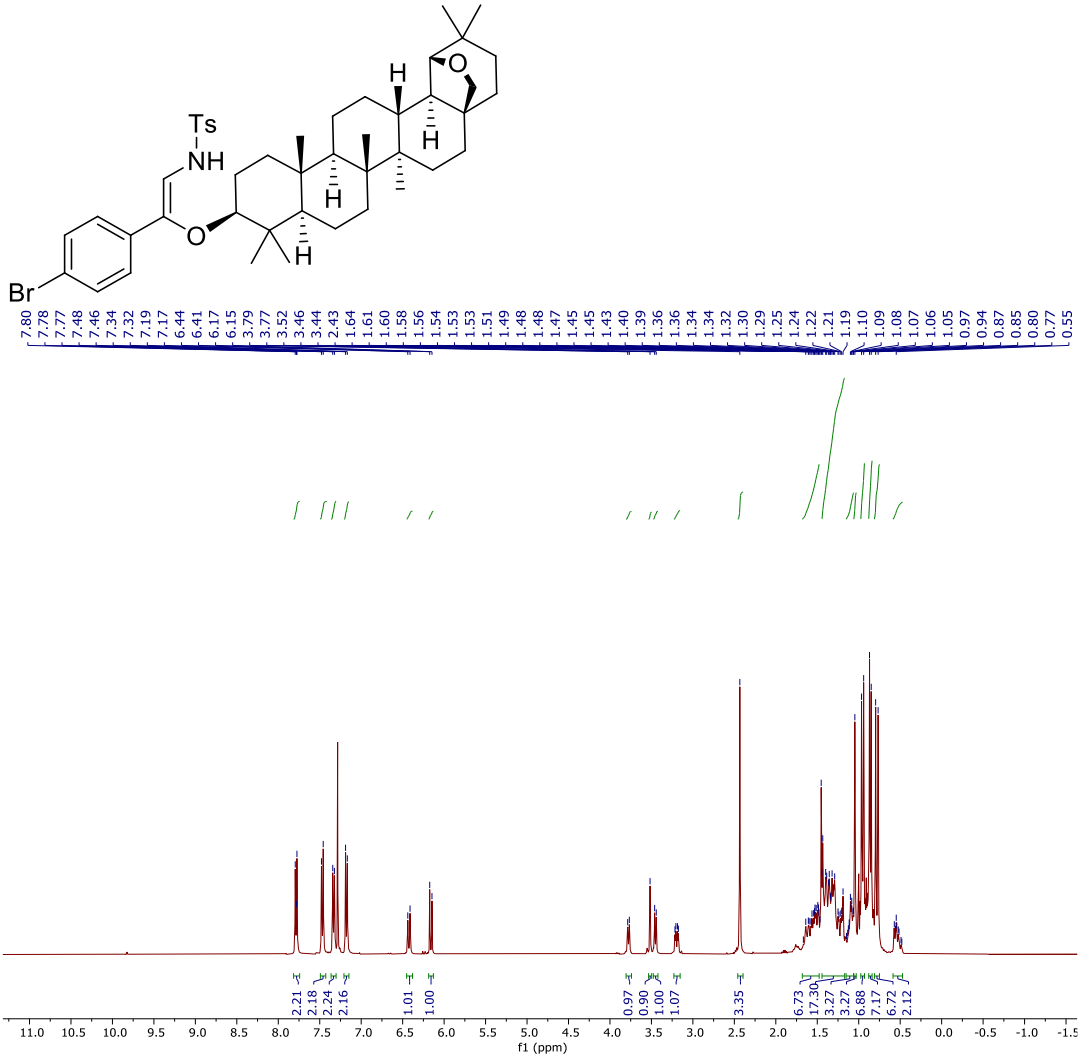
^{1}H NMR spectrum of **3j** (400 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR spectrum of **3j** (100 MHz, $CDCl_3$)



^{1}H NMR spectrum of **3k** (400 MHz, $CDCl_3$)



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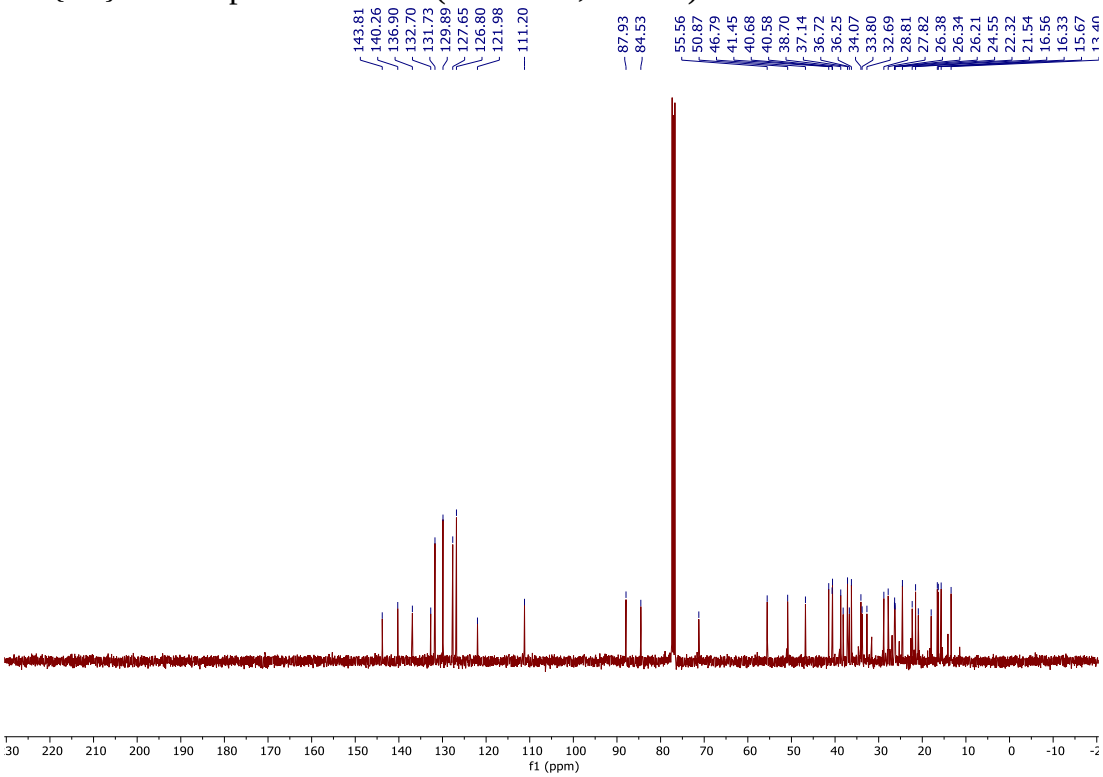
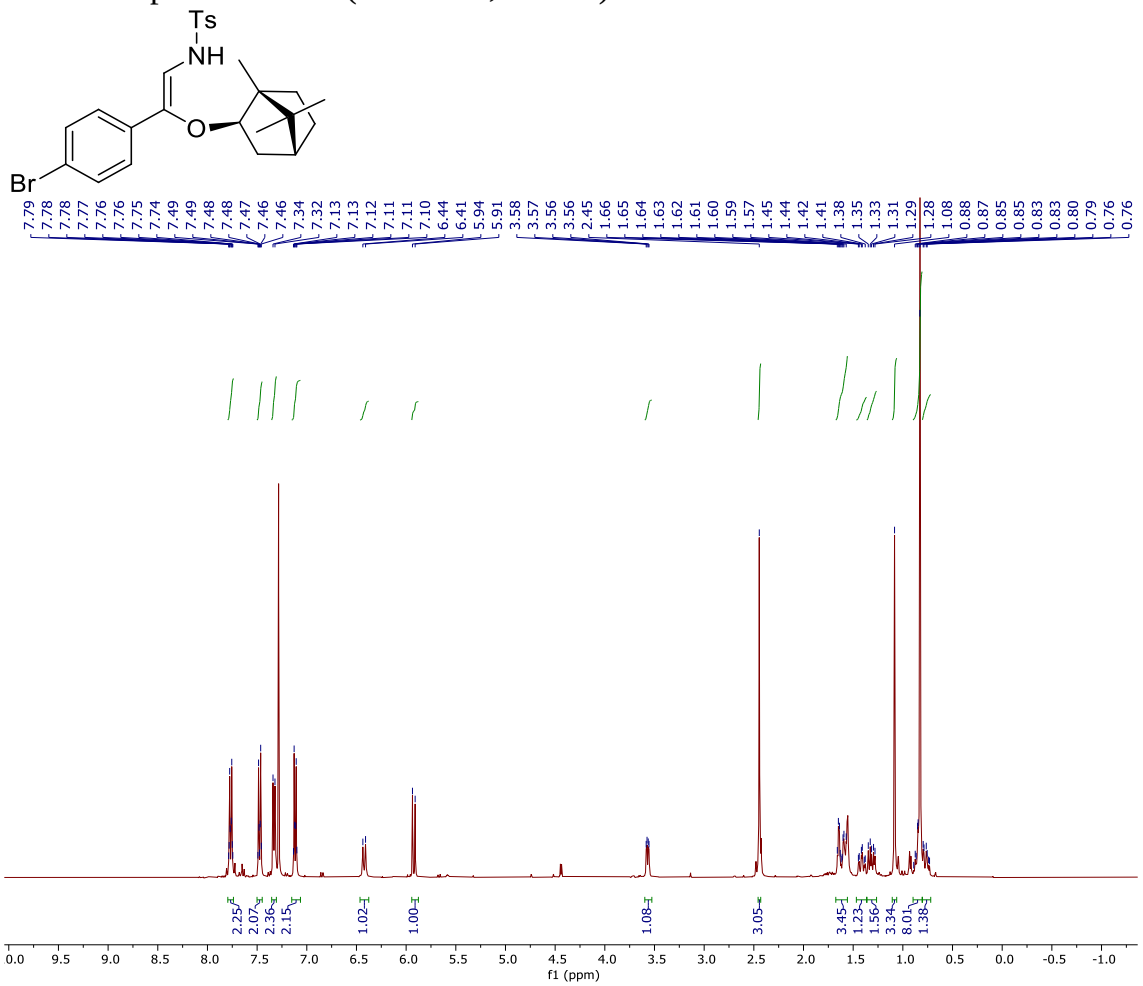


^{1}H NMR spectrum of **3l** (400 MHz, $CDCl_3$)



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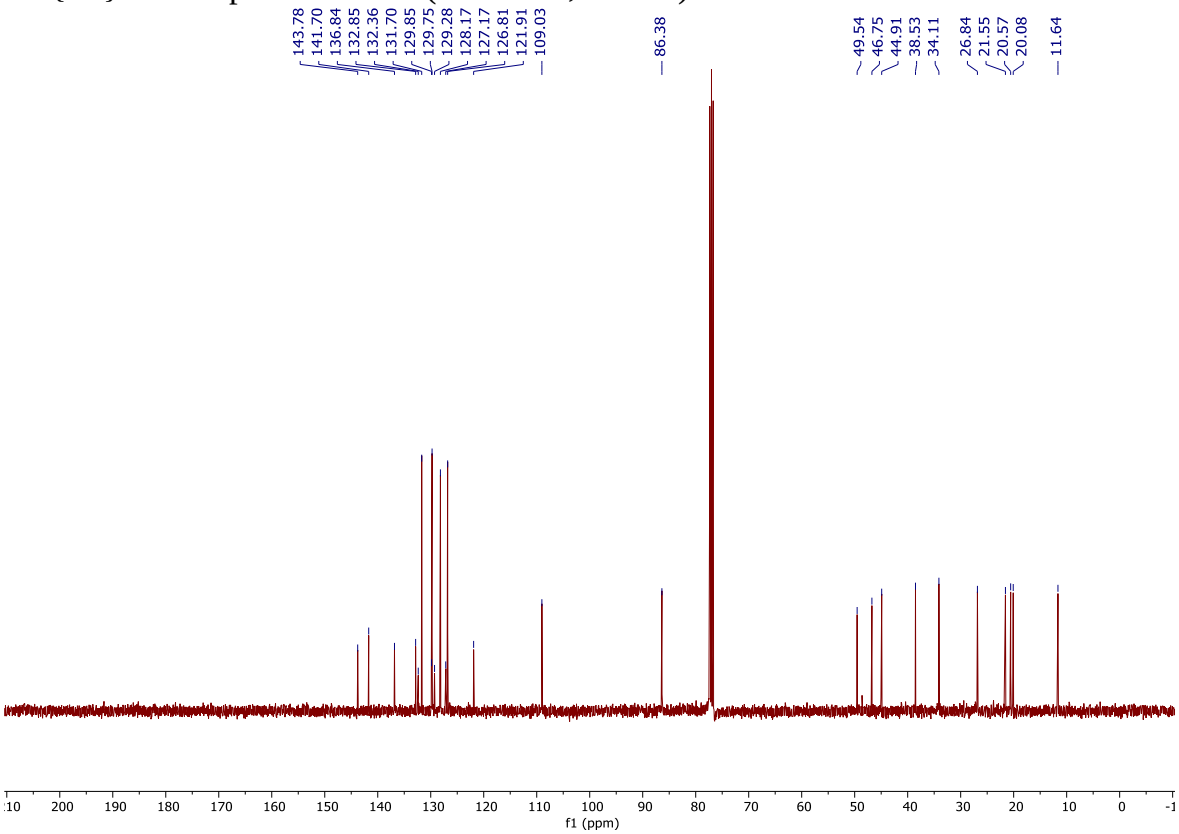
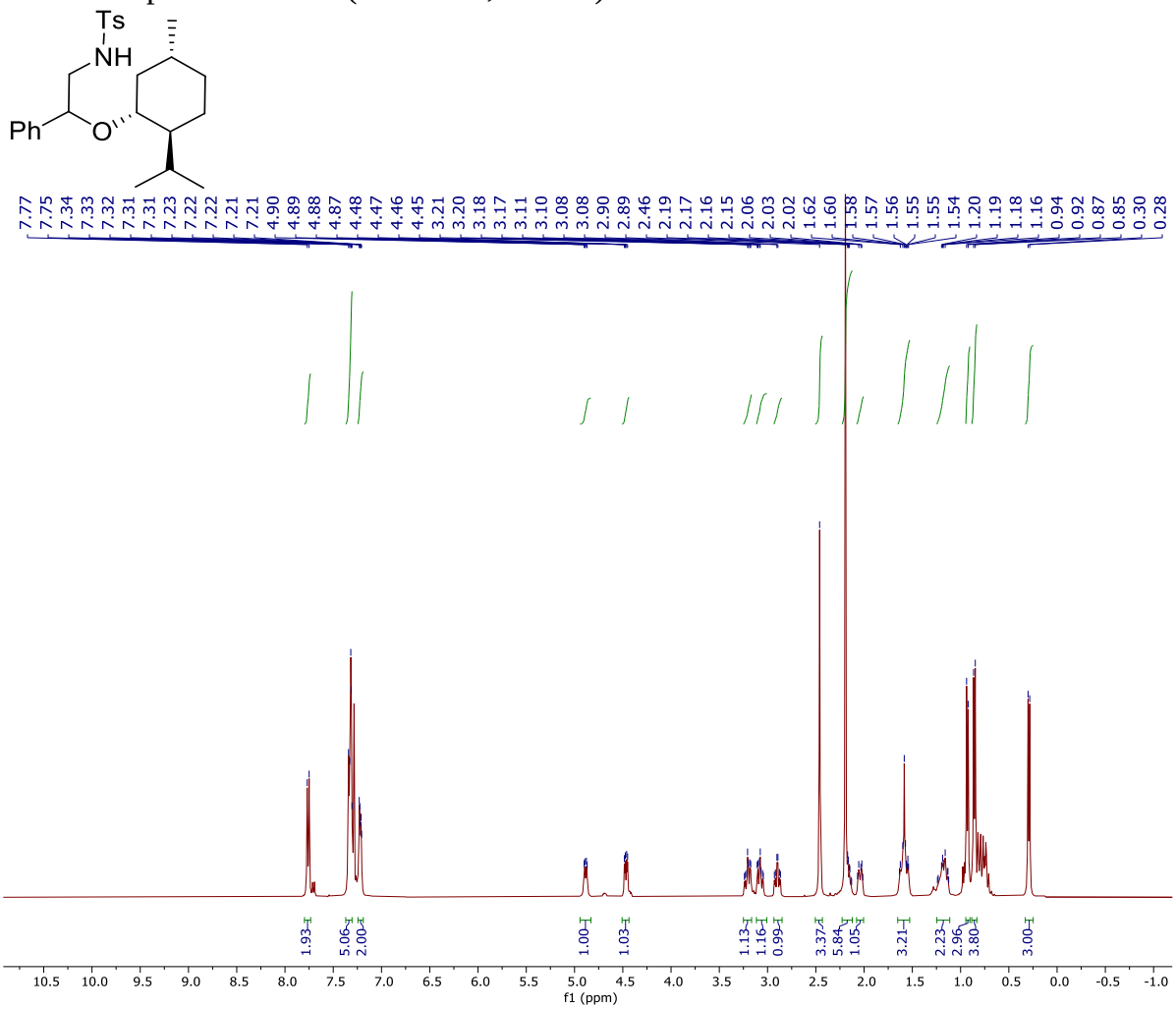
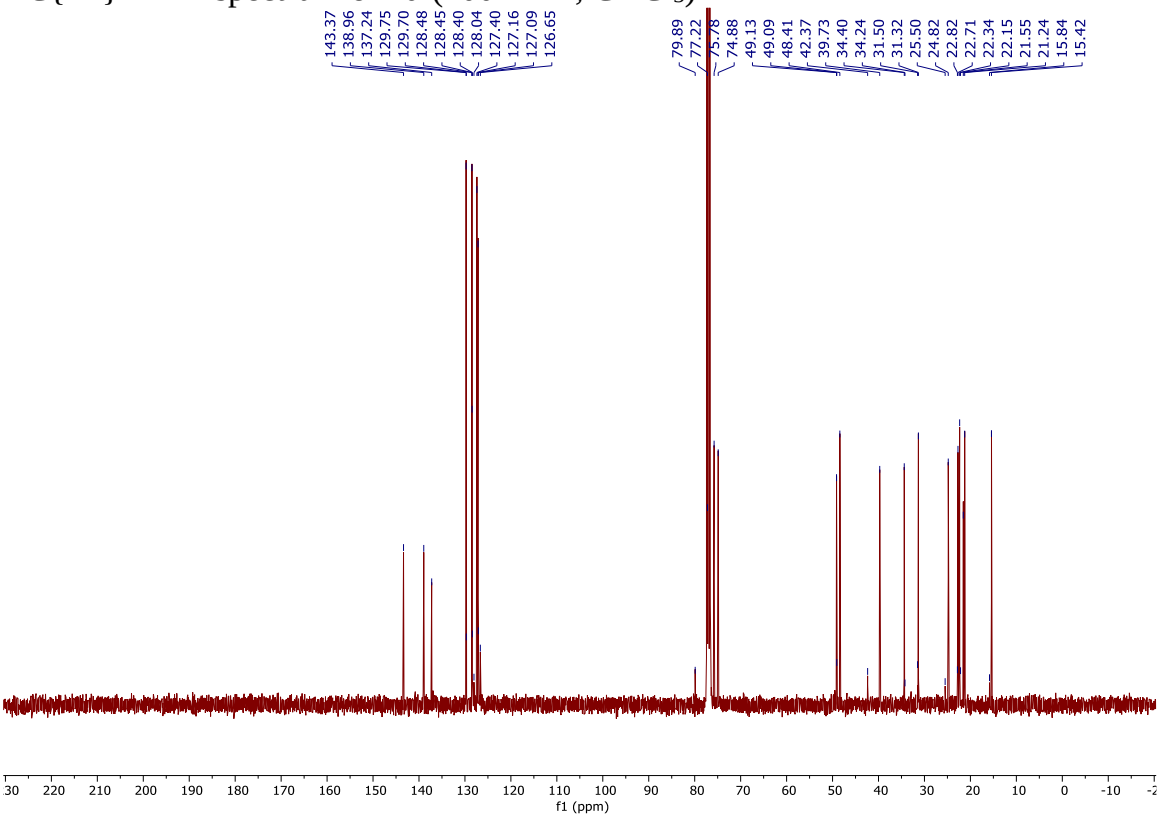


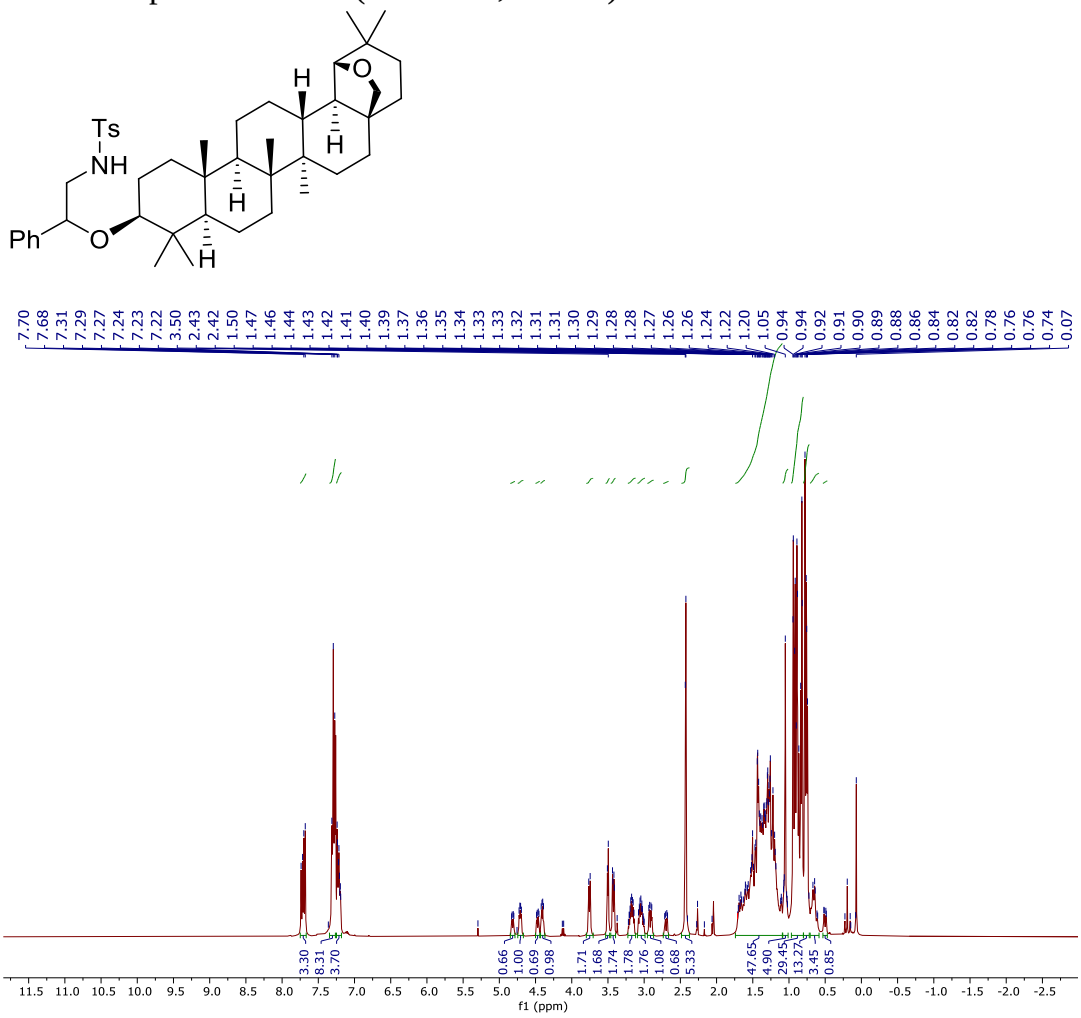
^{1}H NMR spectrum of **4a** (400 MHz, $CDCl_3$)



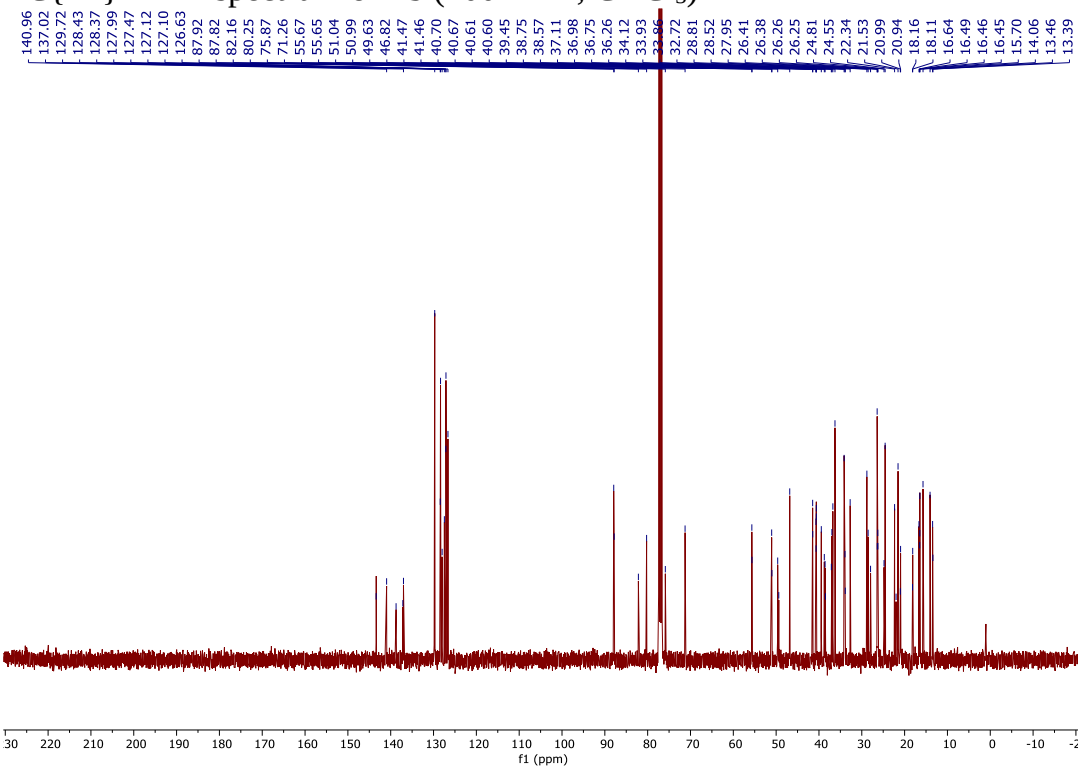
^{13}C{^{1}H} NMR spectrum of **4a** (100 MHz, $CDCl_3$)



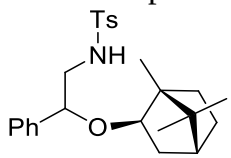
^{1}H NMR spectrum of **4b** (400 MHz, $CDCl_3$)

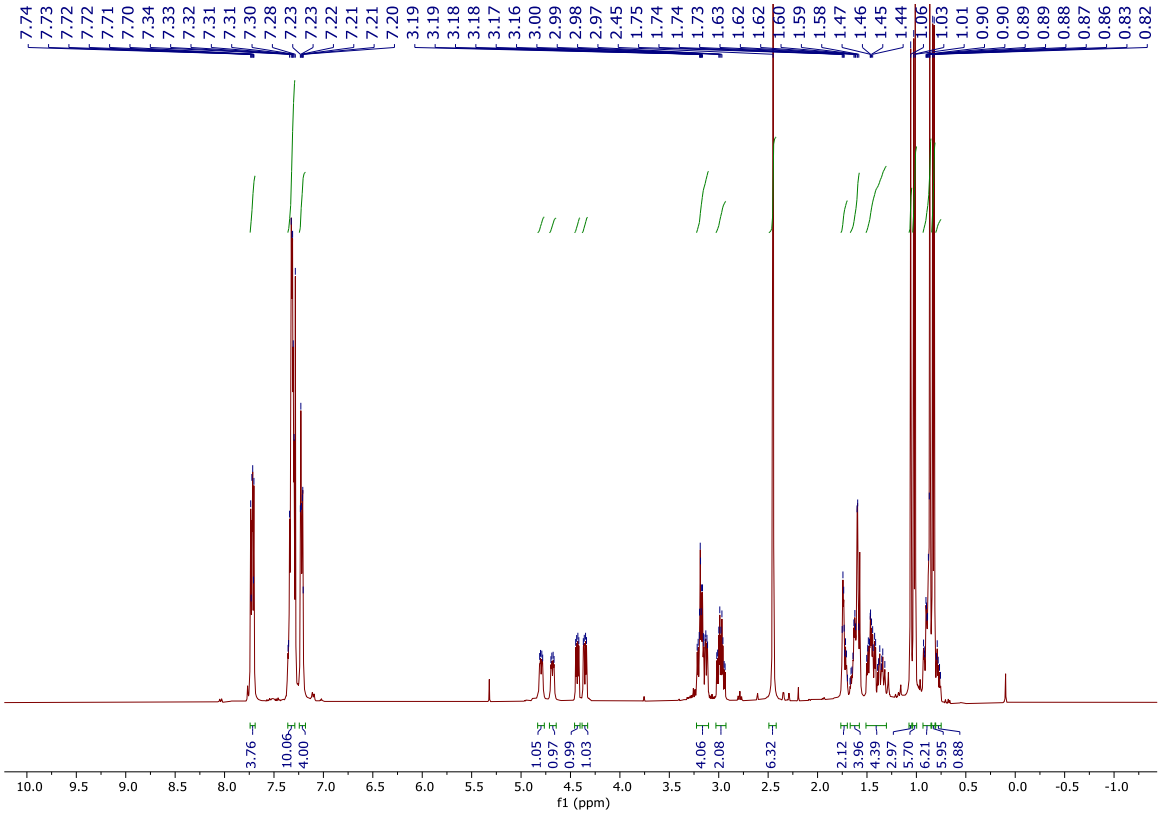


^{13}C{^{1}H} NMR spectrum of **4b** (100 MHz, $CDCl_3$)

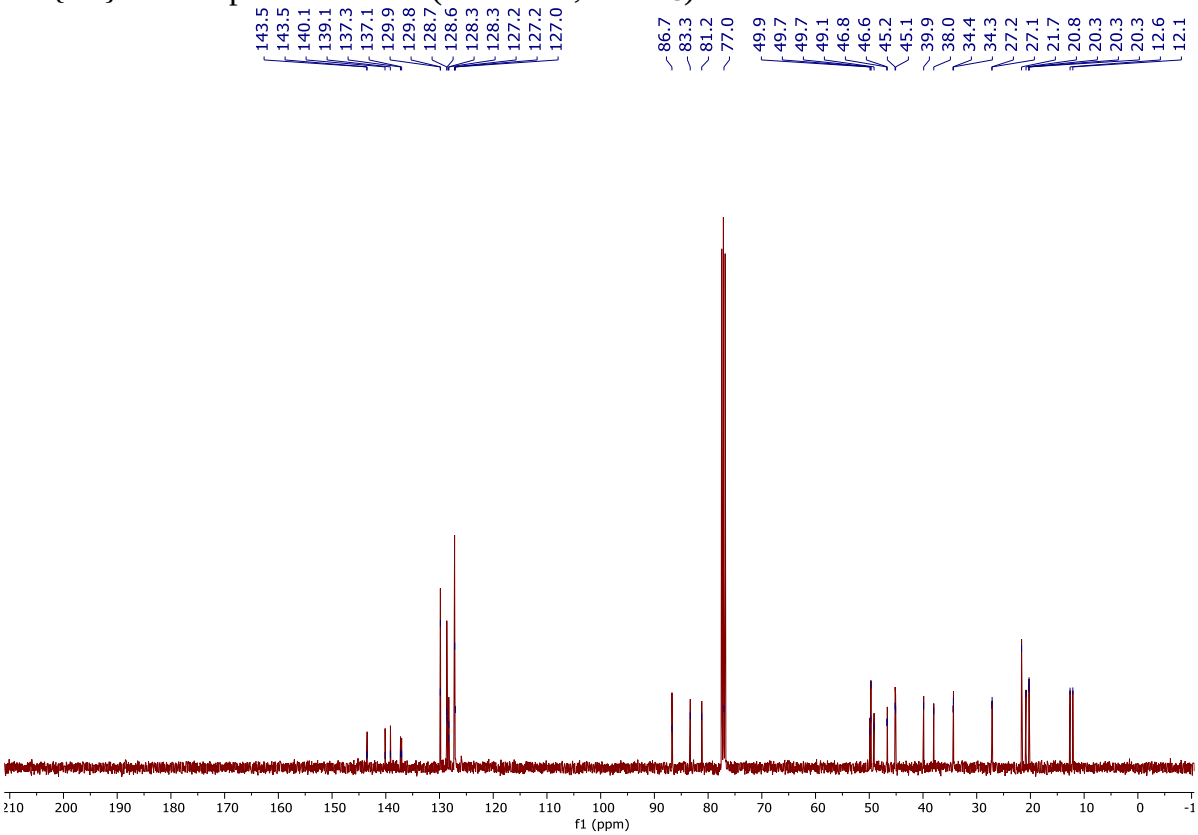


^{1}H NMR spectrum of **4c** (400 MHz, $CDCl_3$)

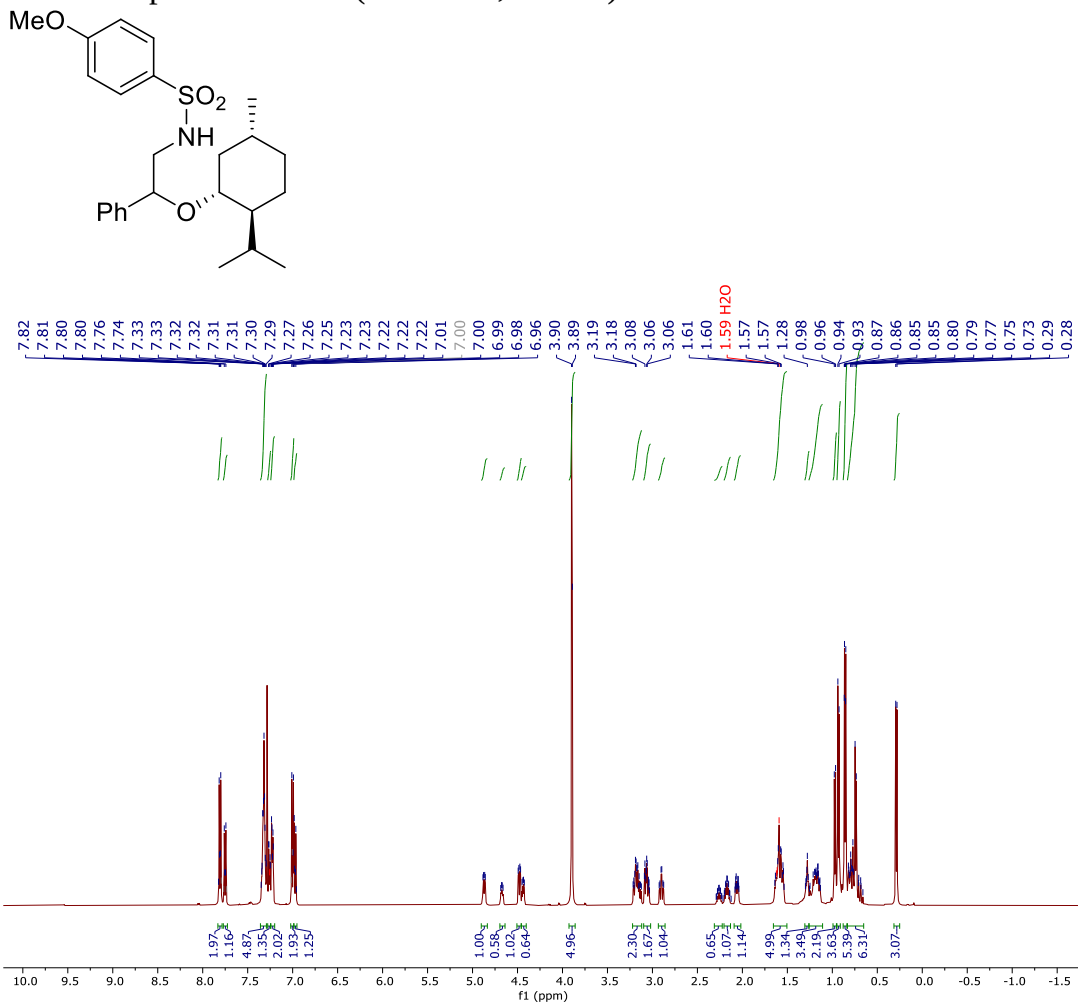




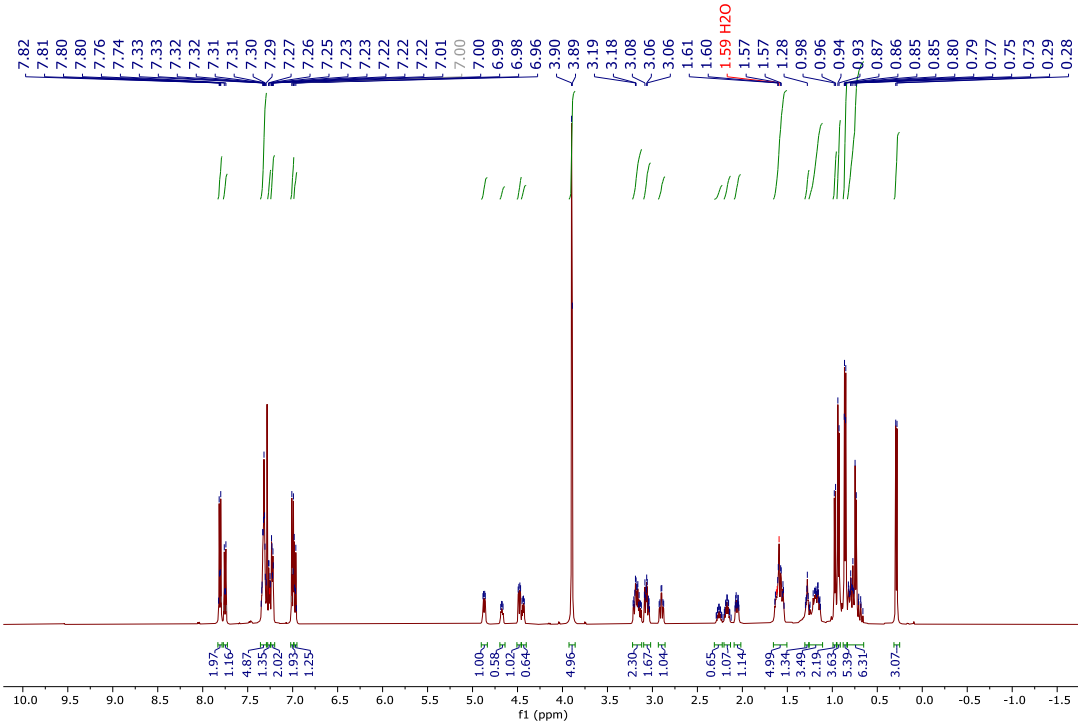
^{13}C{^{1}H} NMR spectrum of **4c** (100 MHz, $CDCl_3$)



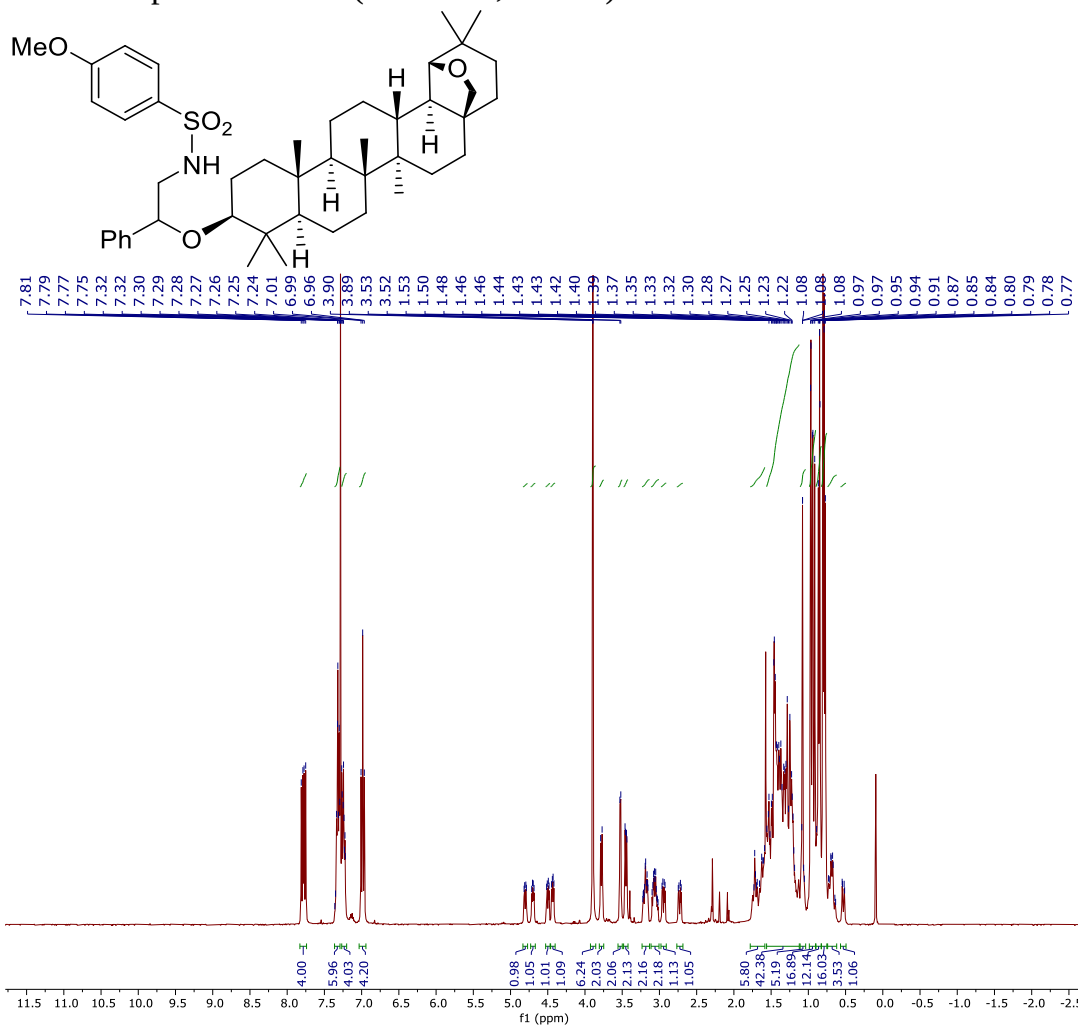
^{1}H NMR spectrum of **4d** (400 MHz, $CDCl_3$)



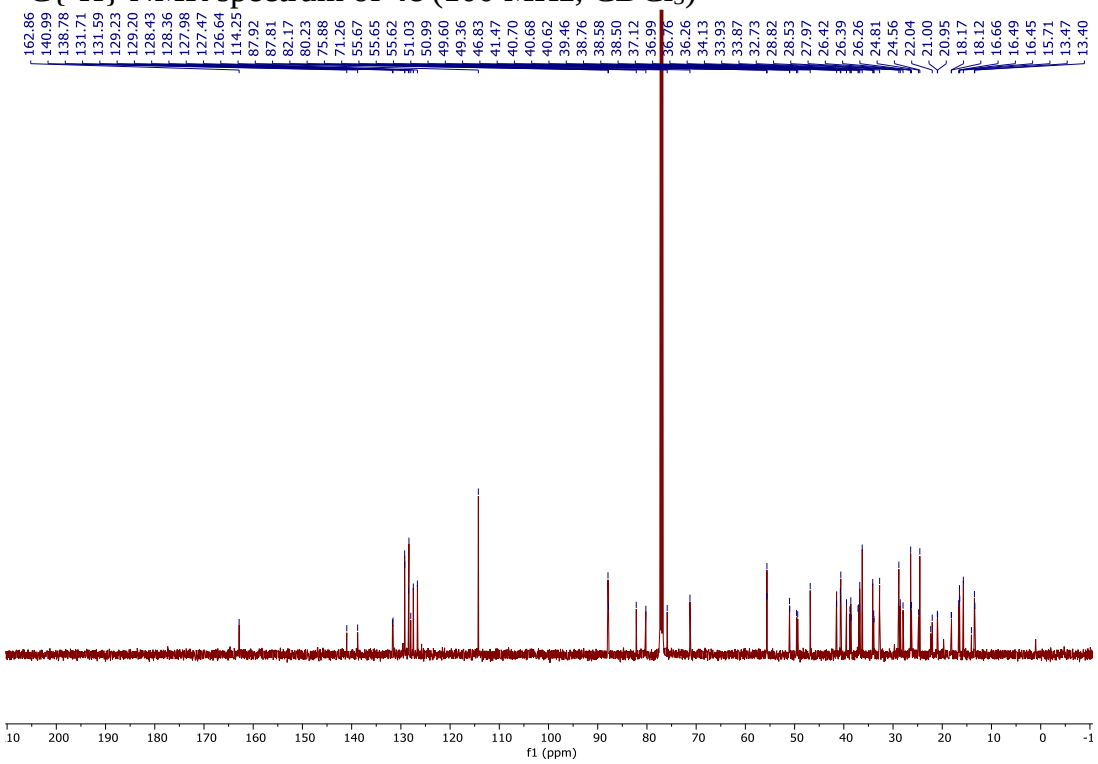
^{13}C{^{1}H} NMR spectrum of **4d** (100 MHz, $CDCl_3$)



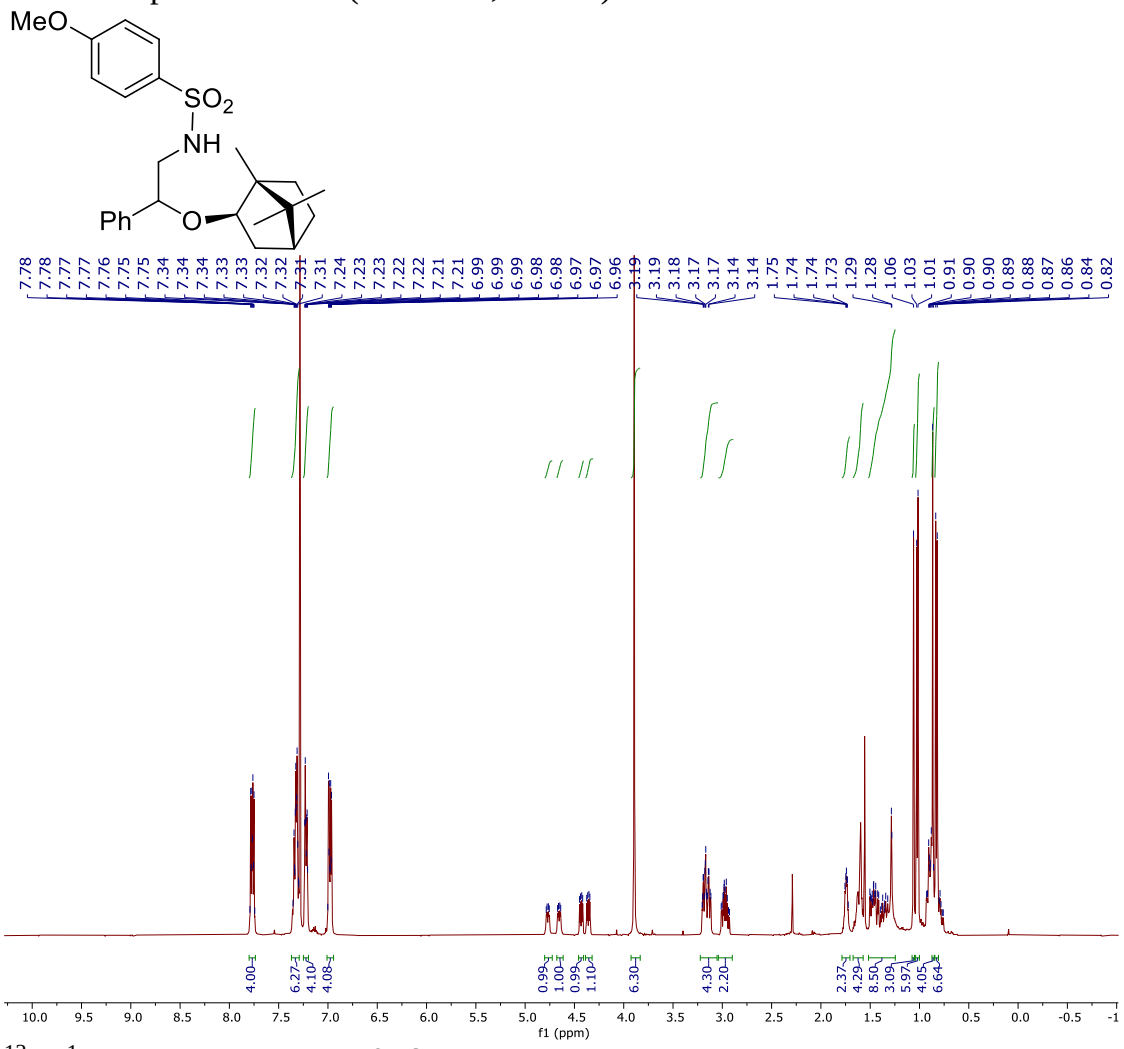
^{1}H NMR spectrum of **4e** (400 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR spectrum of **4e** (100 MHz, $CDCl_3$)



^{1}H NMR spectrum of **4f** (400 MHz, $CDCl_3$)



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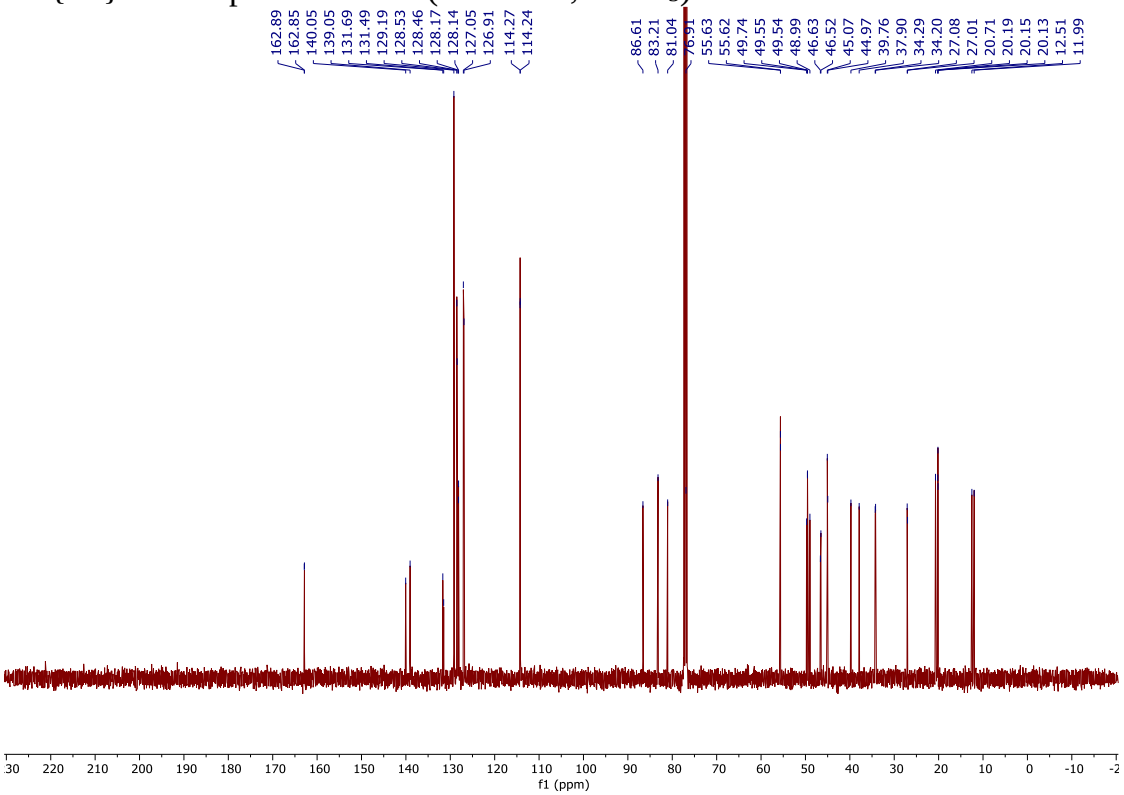
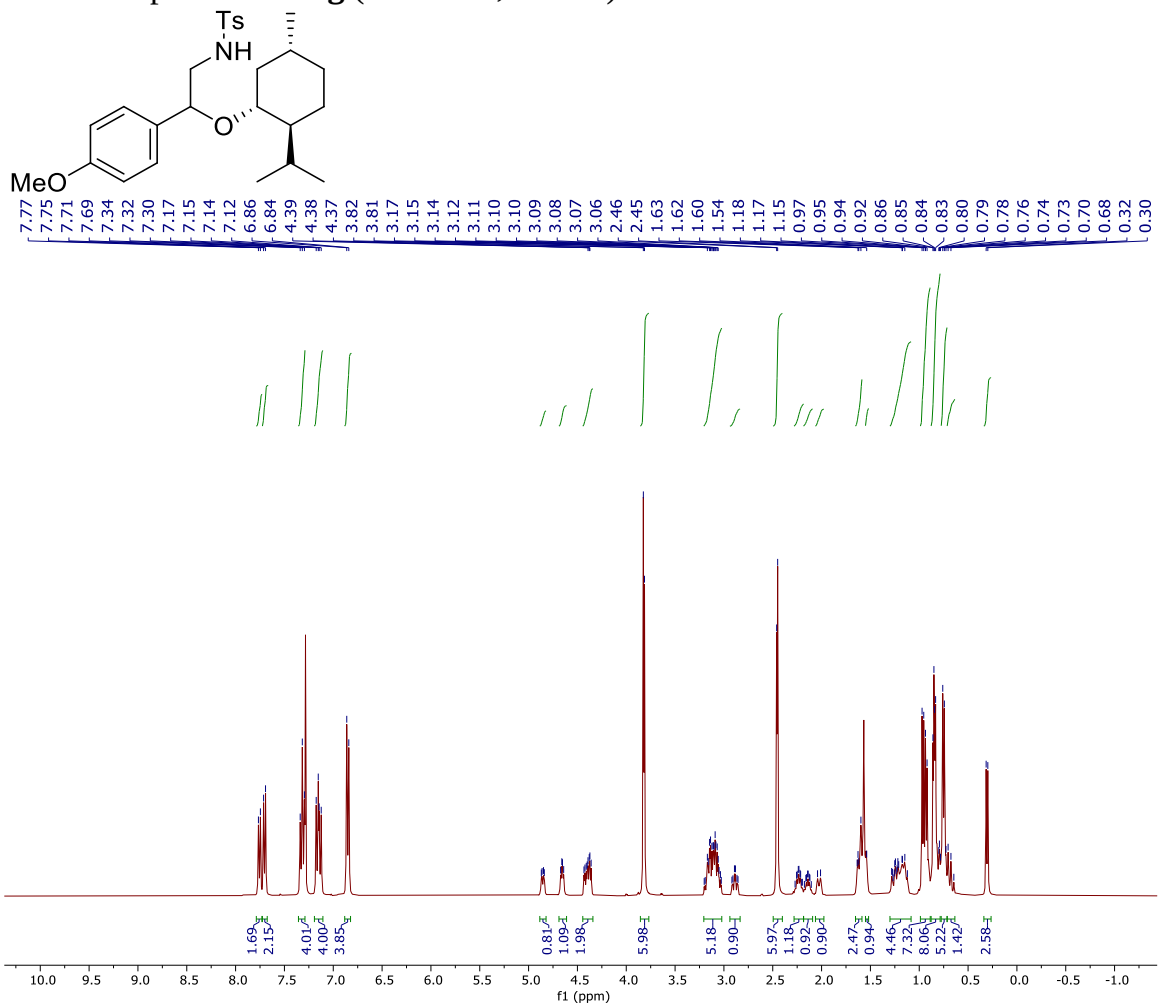
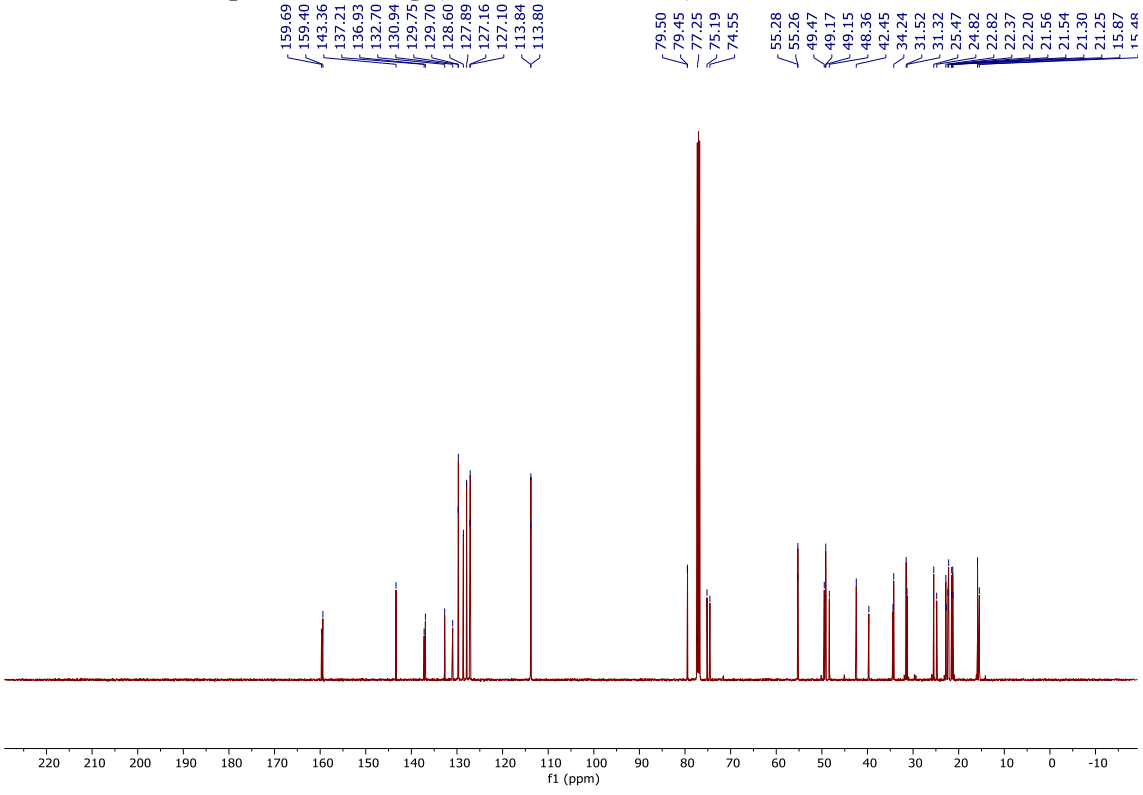


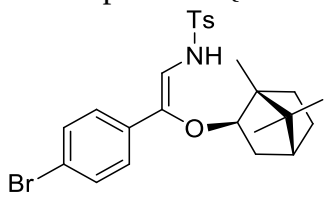
^{1}H NMR spectrum of **4g** (400 MHz, $CDCl_3$)

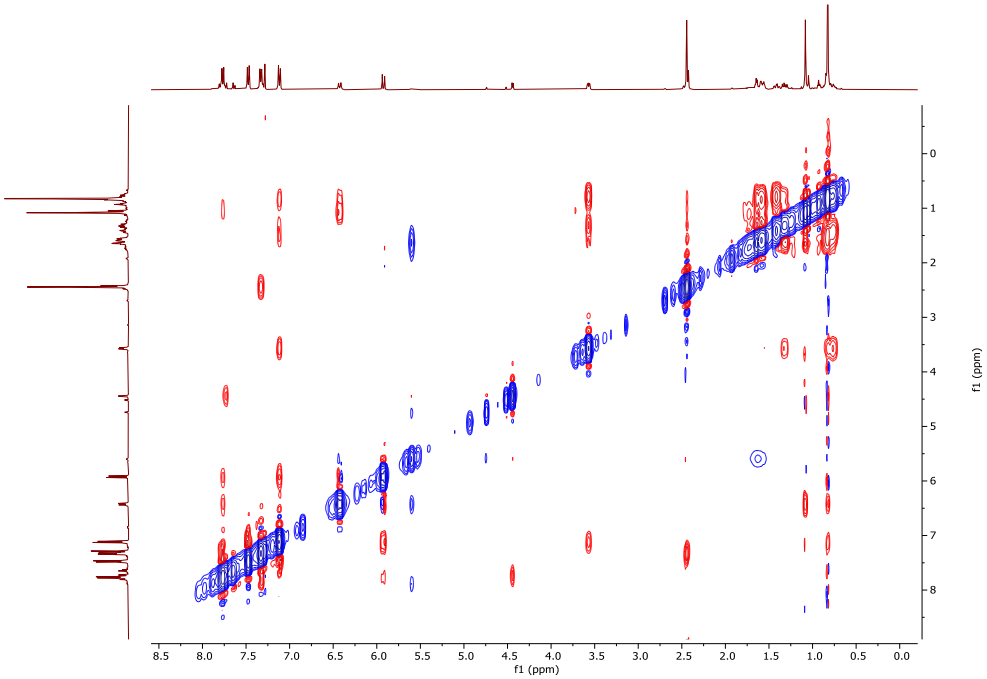


^{13}C{^{1}H} NMR spectrum of **4g** (100 MHz, $CDCl_3$)

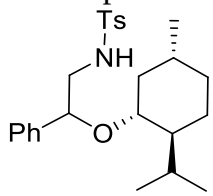


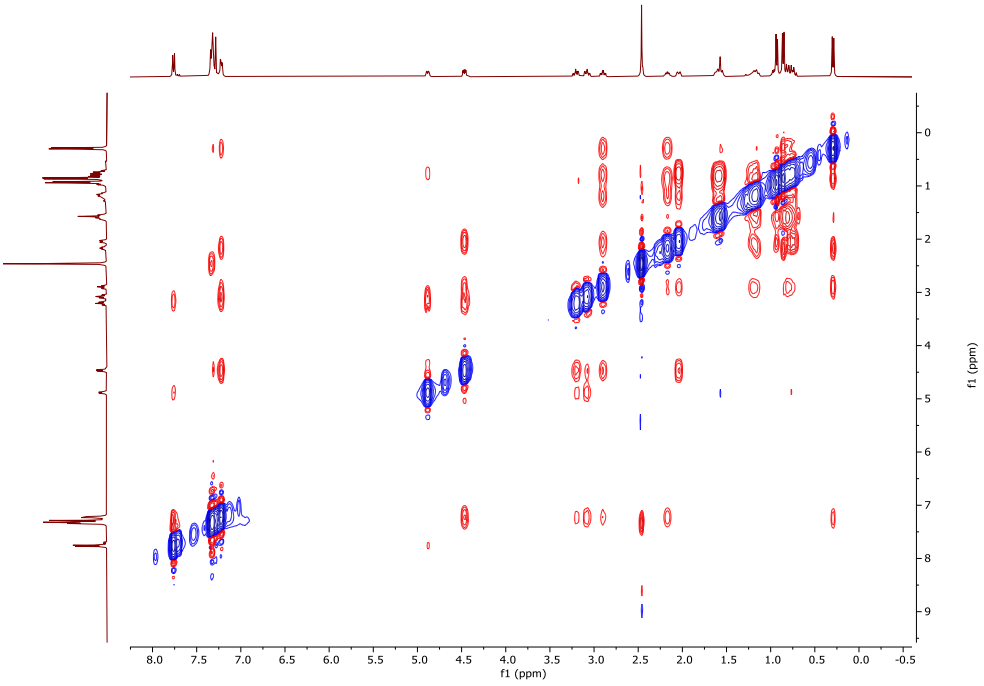
NMR spectrum {^{1}H-^{1}H}-NOESY of **3l**



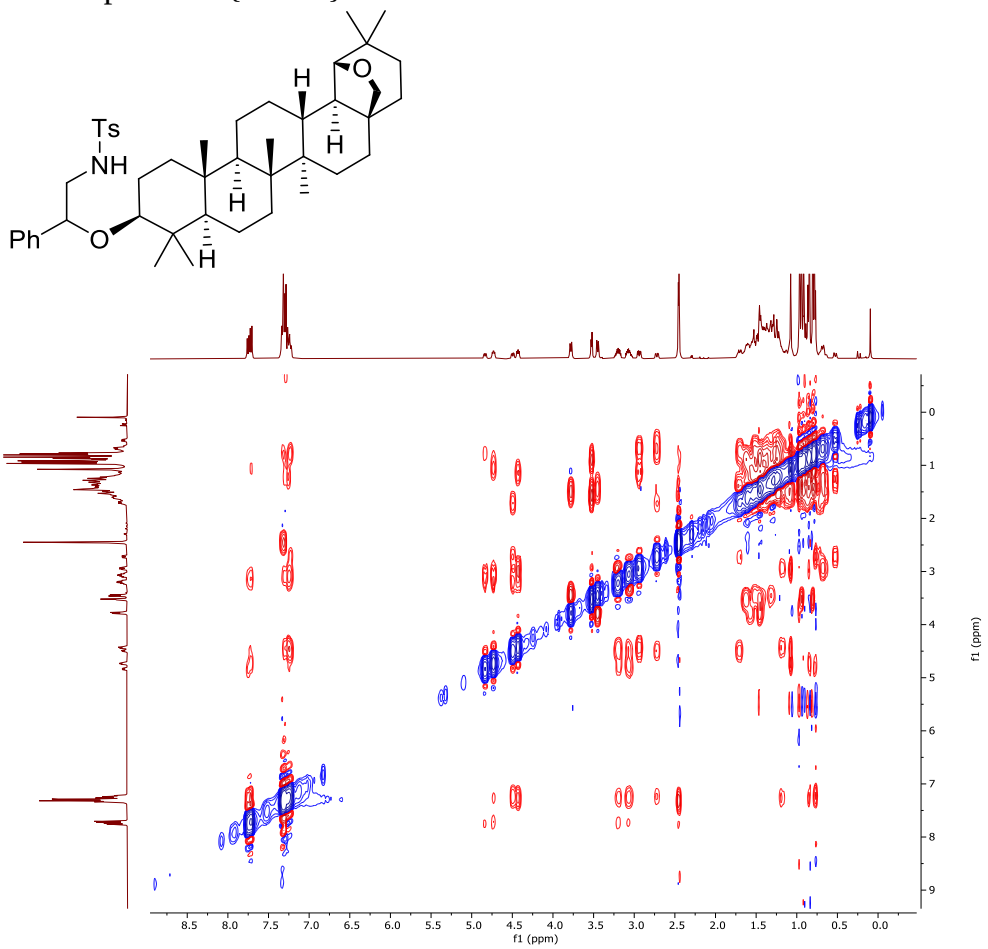


NMR spectrum {^{1}H-^{1}H}-NOESY of **4a**

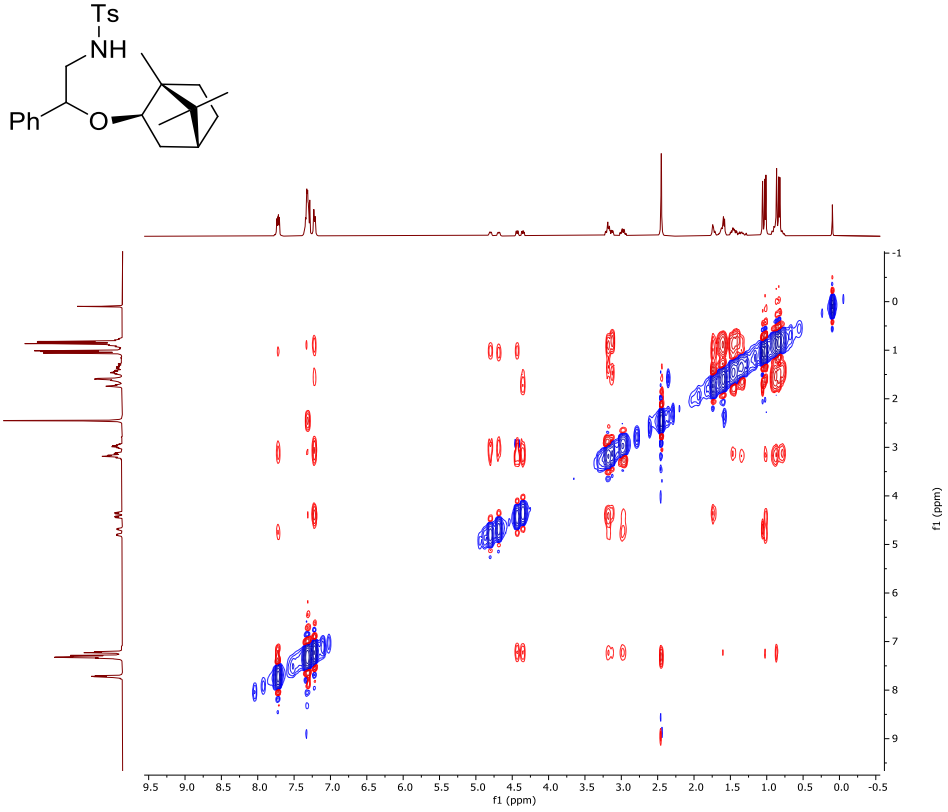




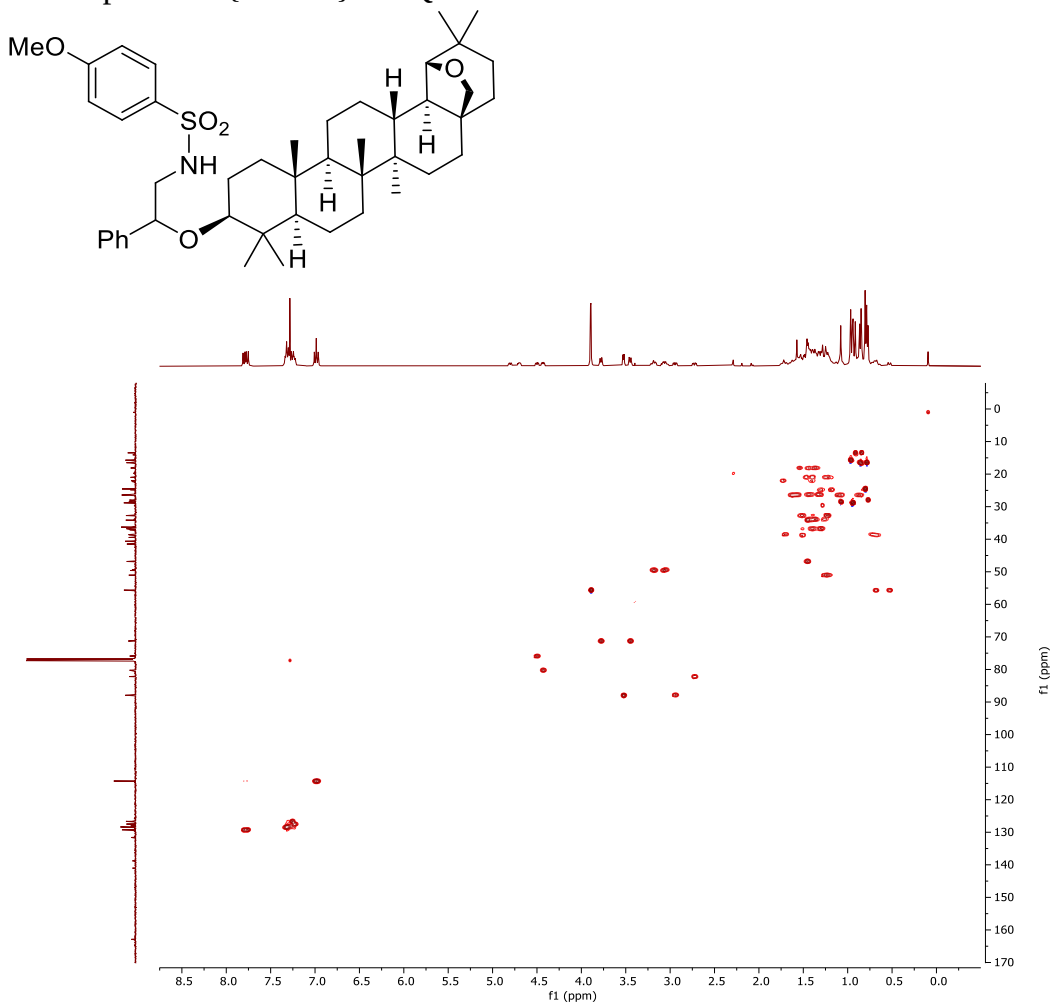
NMR spectrum {^{1}H-^{1}H}-NOESY of **4b**



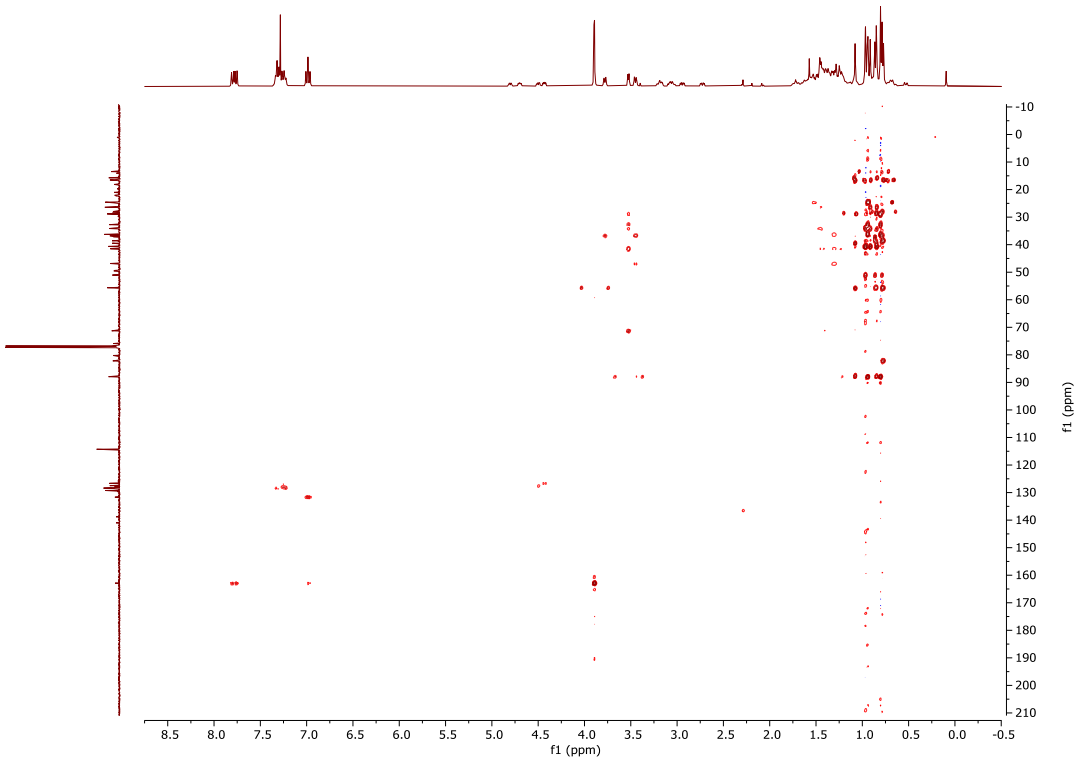
NMR spectrum {^{1}H-^{1}H}-NOESY of **4c**



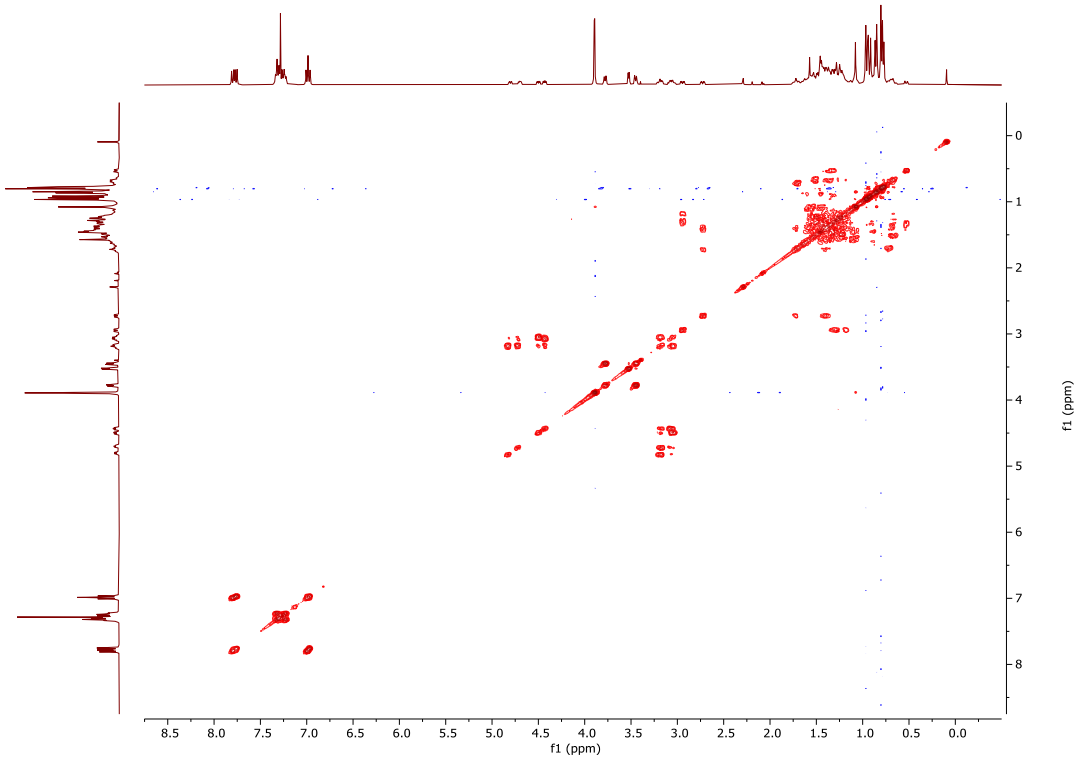
NMR spectrum {^{1}H-^{13}C}-HSQC of **4e**



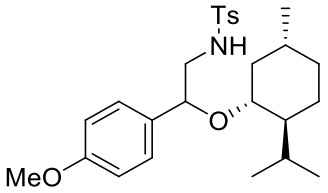
NMR spectrum {^{1}H-^{13}C}-HMBC of **4e**

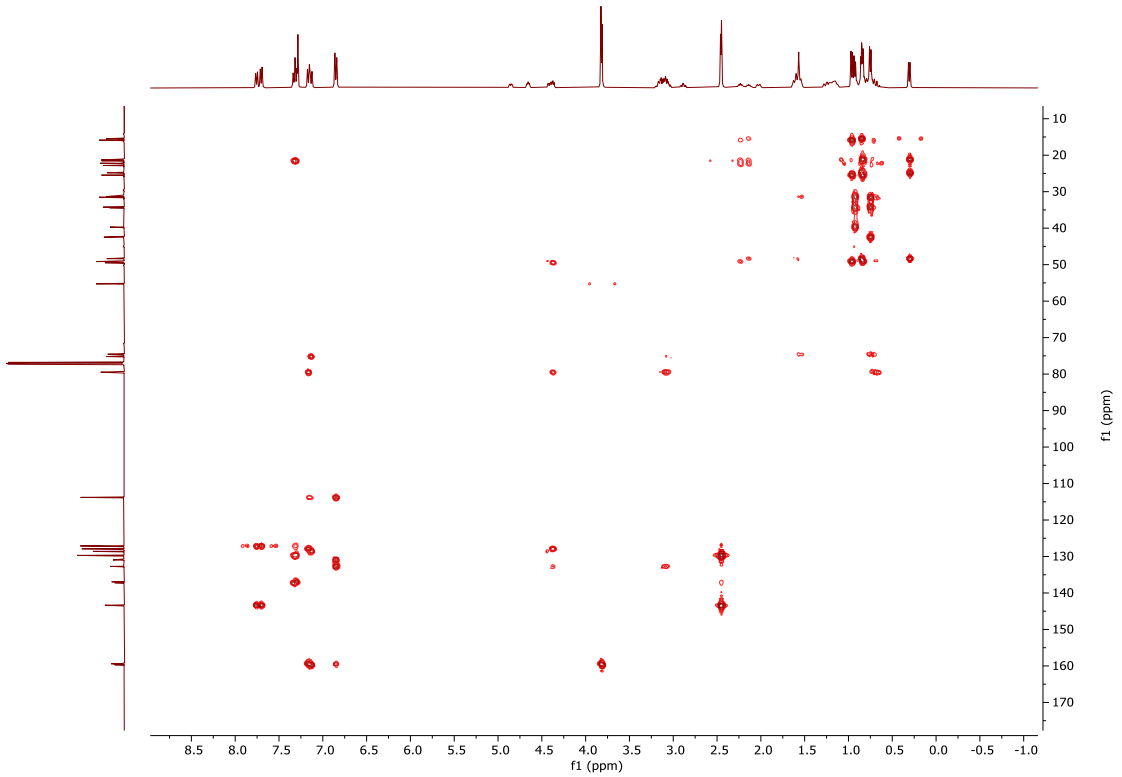


NMR spectrum {^{1}H-^{1}H}-COSY of **4e**

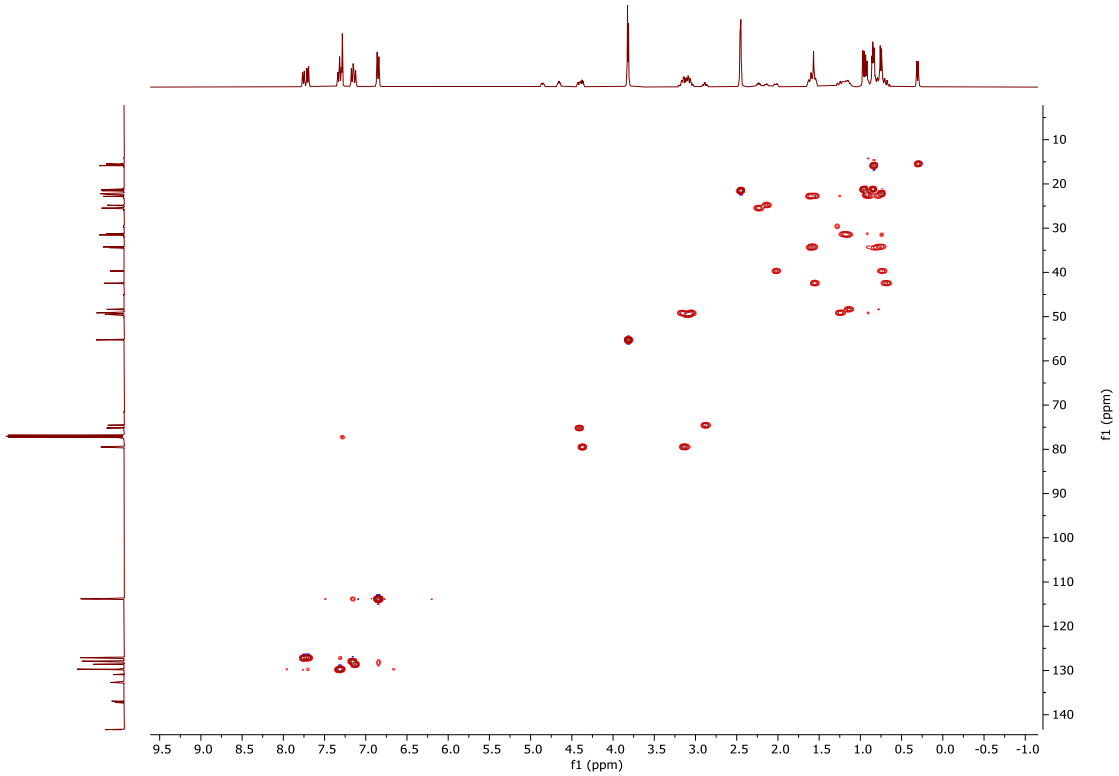


NMR spectrum {^{1}H-^{13}C}-HMBC of **4g**





NMR spectrum {^{1}H-^{13}C}-HSQC of **4g**



NMR spectrum {^{1}H-^{1}H}-COSY of **4g**