# Supporting Information

# Discovery of bis-sulfonamides as novel inhibitors of mitochondrial NADH-quinone oxidoreductase (complex I)

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## Table of Contents

## 1. Supplementary Figures

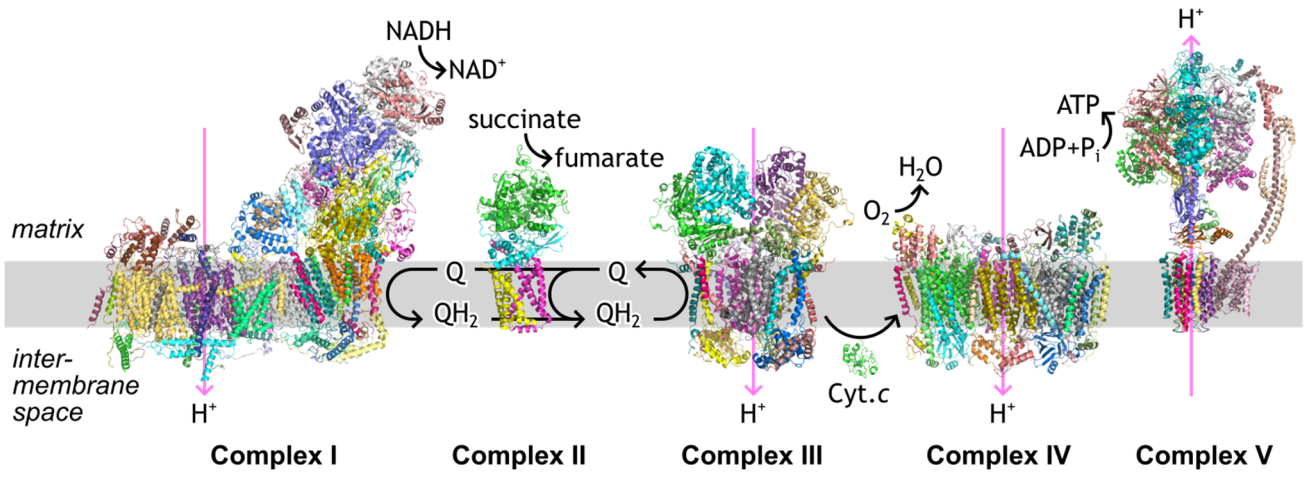



**Figure S1. Mitochondrial respiratory chain enzymes and $F_oF_1$-ATP synthase.** The mammalian mitochondrial respiratory chain consists of complex I (NADH-quinone oxidoreductase, PDB ID: 5O31), complex II (succinate dehydrogenase, PDB ID: 3AEF), complex III (quinol-cytochrome *c* oxidoreductase, PDB ID: 1BGY), complex IV (cytochrome c oxidase, PDB ID: 1OCC), and complex V ($F_oF_1$-ATP synthase, PDB ID: 5FIL). Electron transfer between complexes is mediated by quinone (Q) and cytochrome c (Cyt. *c*, PDB ID: 1AKK).

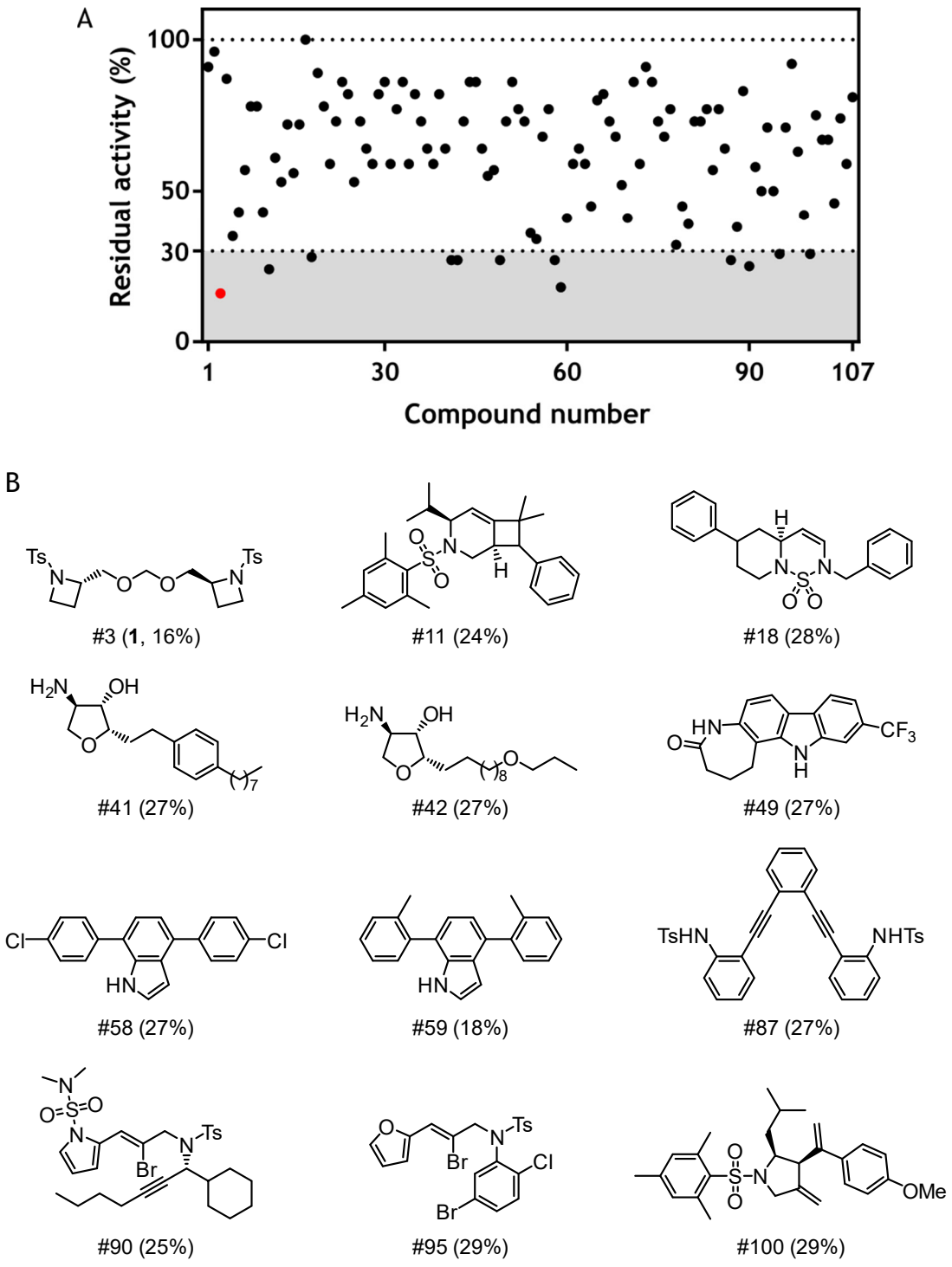



**Figure S2. Results of initial screening.** Each compound was evaluated at 5 μM. (A) Scatter plot of residual activity from the initial screen. The shaded area highlights the activities that were defined as initial hits. KPYC01112 (#3, **1**) is highlighted in *red*. (B) Chemical structures of hit compounds from the initial screening. Compound number and residual activity percentage is shown below each structure.

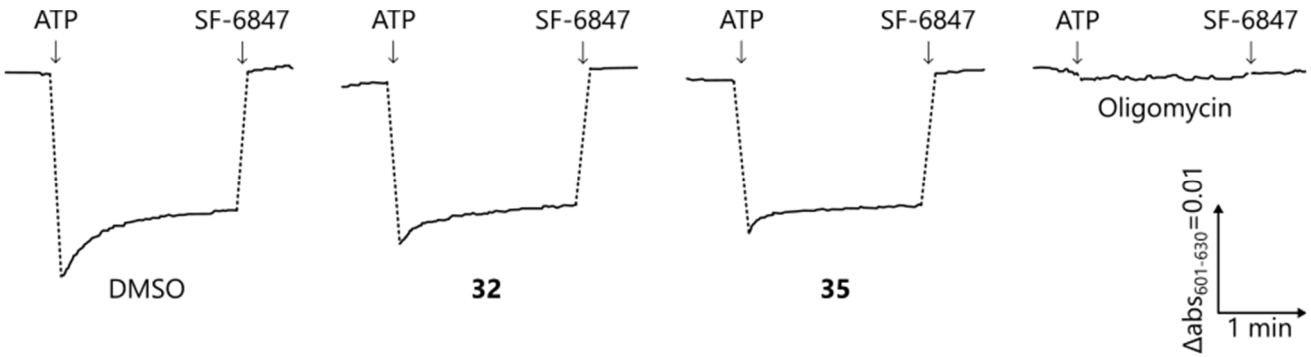



**Figure S3. Effects on membrane potential generated by ATP hydrolysis.** Membrane potential generated by ATP hydrolysis by ATPase was monitored via following the changes in absorbance of oxonol VI. SMPs (90 μg of proteins/mL) were incubated with compounds (20 μM) for 3 min in the reaction medium (200 mM sucrose, 2.5 mM $MgCl_2$, 0.10 μM nigericin, and 50 mM Tricine-KOH (pH 7.5)). The arrows indicate the addition of ATP (4.0 mM) and protonophoric uncoupler SF6847 (0.10 μM). The ATPase inhibitor oligomycin was used as a control to inhibit membrane potential formation. Dashed lines indicate unrecorded sections. Data shown are representative of two independent measurements.

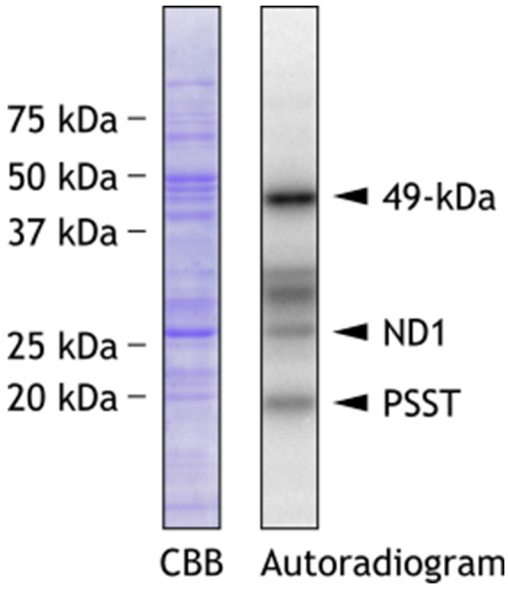



**Figure S4. Photoaffinity labeling of subunits of bovine complex I with [$^{125}$I]-43.** SMPs were labeled with [$^{125}$I]-**43** as described in Experimental Procedures. An autoradiogram of SDS-PAGE analysis (a 12.5% gel) of [$^{125}$I]-**43**-labeled SMPs is shown. Based on the autoradiogram of BN/SDS-PAGE (a 4–16% BN gel/a 12.5% SDS gel) two-dimensional analysis, we confirmed that the bands between the 49-kDa and the ND1 bands are the labeling of small proteins except complexes I-V.

## 2. Experimental Procedures of Medicinal and Biological Study

### Materials

Bullatacin was kindly provided by J. L. McLaughlin (Purdue University, West Lafayette, IN). Protein standards (Precision Plus Protein Standards) for SDS-PAGE were purchased from Bio-Rad.

### Preparation of Bovine Heart Submitochondrial Particles (SMPs) and Enzyme Assay

Mitochondria were isolated from bovine heart.[1] Submitochondrial particles (SMPs) were prepared by the method of Matsuno-Yagi and Hatefi[2] using a sonication medium containing 250 mM sucrose, 1 mM succinate, 1.5 mM ATP, 10 mM $MgCl_2$, 10 mM $MnCl_2$, and 10 mM Tris-HCl (pH 7.4) and stored in a buffer containing 250 mM sucrose and 10 mM Tris-HCl (pH 7.4) at −80 °C until used.

The NADH oxidase activity in SMPs was measured spectrometrically with a Shimadzu UV-2600i instrument (340 nm, $\epsilon$ = 6.2 $mM^{-1}$ $cm^{-1}$) at 30 °C.[3] The reaction medium (2.0 mL) contained 250 mM sucrose, 1 mM $MgCl_2$, and 50 mM $KP_i$ buffer (pH 7.4), and the final protein concentration was 30 μg/mL. The reaction was initiated by adding 50 μM NADH after the equilibration of SMPs with a test compound for 4 min.

NADH-$Q_1$ oxidoreductase activity (complex I) in SMPs was measured under the same experimental conditions, except that the reaction medium contained 50 μM $Q_1$, 0.2 μM antimycin A, and 2 mM KCN.

Succinate-cytochrome *c* oxidoreductase activity (complex II-III) in SMPs (solubilized in 0.9% sodium deoxycholate on ice for 1 h) was measured spectrometrically with a Shimadzu UV-3000 instrument (550-540 nm, $\epsilon$ = 21 $mM^{-1}$ $cm^{-1}$) at 30°C. The reaction medium (2.0 mL) contained 250 mM sucrose, 1.0 mM $MgCl_2$, 1.0 μM rotenone, 4 mM KCN, 30 μM cytochrome *c* (from horse heart, Sigma-Aldrich), and 50 mM $KP_i$ buffer (pH 7.4), and the final protein concentration was 30 μg/mL. The reaction was initiated by adding 5 mM sodium succinate after equilibration of SMPs with a test compound for 4 min.

The $IC_{50}$ values of inhibitors were calculated by Prism (version 9, GraphPad Software, La Jolla, CA) using sigmoid dose-response curve fitting.

### Measurement of Membrane Potential Formation

Membrane potential formation driven by ATP hydrolysis in bovine heart SMPs was determined by following changes in the absorbance of oxonol VI, an optical indicator of the membrane potential, at 601–630 nm with a Shimadzu UV-3000 instrument in dual-wavelength mode.[4] SMPs (90 μg of proteins/mL) were suspended in the reaction medium (2.5 mL) containing 200 mM sucrose, 2.5 mM $MgCl_2$, 0.10 μM nigericin, and 50 mM Tricine-KOH (pH 7.5). The reaction was initiated by adding 4.0 mM ATP after the equilibration of SMPs with an inhibitor for 3 min at 30 °C. The protonophoric uncoupler SF6847 was used at a final concentration of 0.10 μM to confirm complete dissipation of the membrane potential.

### Photoaffinity Labeling of Complex I in SMPs by [$^{125}$I]-43

Bovine SMPs (2.0 mg/mL, 100 μL), which were previously incubated with a competitor of choice at room temperature for 10 min, were incubated with [$^{125}$I]-**43** (5.0 nM) in buffer containing 250 mM sucrose, 50 mM $KP_i$ (pH 7.4), and 5.0 mM $MgCl_2$ at room temperature for 10 min. The mixture was then irradiated with a long wavelength

UV-lamp (Black-lay model B-100A, UVP, Upland, CA) on ice for 10 min at a distance of 10 cm from the light source.[5] The reaction was quenched by the addition of 4 × Laemmli sample buffer (34 μL). Samples were separated on a 12.5% Laemmli gel, which was stained with CBB, dried, exposed to an imaging plate (BAS-MS2040, Fujifilm, Tokyo, Japan), and visualized with the Bio-imaging analyzer Typhoon-FLA 9500 (GE Healthcare, Buckinghamshire, UK). The incorporated radioactivity of each band was quantified using Multi Gauge (Fujifilm).

**Identification of the Subunit Labeled by [$^{125}$I]-43**

SMPs labeled by [$^{125}$I]-**43** (10 nM) were solubilized in sample buffer containing 50 mM Bistris-HCl (pH 7.2),50 mM NaCl, 10% (w/v) glycerol, 1.0% (w/v) dodecyl maltoside, and 0.001% (w/v) Ponceau S on ice for 1 h, and the samples were separated by BN-PAGE[3] using a NativePAGE™ 4–16% BisTris precast gel system (Thermo Fischer Scientific) according to the manufacturer's protocol. The isolated complex I was further solved on a Laemmli-type 12.5% SDS gel[6] or Schägger-type 10% SDS gel containing 6.0 M urea.[7]

Doubled SDS-PAGE was conducted as described previously.[3,8] In brief, the labeled complex I was separated on a first-dimensional 10% Schägger-type gel (10% T, 3% C, containing 6.0 M urea). The gel slice was then acidified with 100 mM Tris-HCl (pH 2.0) for 30 min, followed by second-dimensional separation on a 16% Schägger-type gel (16% T, 3% C). Typically, complex I equivalent to 200 μg of SMPs was separated on a mini-size gel (8090 mm, 1 mm). The resolved proteins were visualized by MS-compatible silver staining (Wako Silver stain MS kit, Wako Pure Chemicals, Osaka), followed by autoradiography.

## 3. Chemical Synthesis and Compound Characterization

### 3.1. General Methods

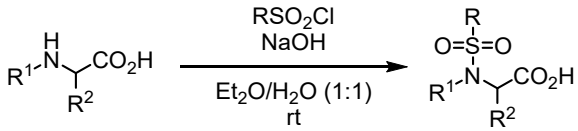
$^1$H NMR spectra were recorded using JEOL ECA-500 at 500 MHz frequency, or JEOL ECZ600R at 600 MHz frequency. Chemical shifts were reported in $\delta$ (ppm) relative to $Me_4Si$ (in $CDCl_3$, DMSO-$d_6$ and $CD_3OD$) or $Me_3Si(CD_2)_2CO_2Na$ (in $D_2O$) as internal standard. $^{13}$C NMR spectra were recorded using JEOL AL-500 at 125 MHz frequency, or JEOL ECZ600R at 150 MHz frequency. Chemical shifts were reported in $\delta$ (ppm) relative to the residual solvent signal (in $CDCl_3$ and DMSO-$d_6$), or $Me_3Si(CD_2)_2CO_2Na$ (in $D_2O$) as internal standard. IR spectra were obtained on a JASCO FT/IR-4100 spectrometer. Exact mass (HRMS) spectra were recorded on Shimadzu LC-ESI-IT-TOF-MS equipment or Thermo Scientific Exactive™ Plus Orbitrap mass spectrometer. Column chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on a Wakogel® C-200E (Wako), Wakogel® C-300E (Wako), CHROMATOREX® NH-DM1020 (Fuji Silysia), or Biotage Isolera™ flash purification system on Biotage® Sfär D. All the heating experiments were performed in an oil bath. All tested compounds were at least 95% pure, as determined by $^1$H NMR spectroscopy. Methods for assessing enantiomeric and diastereomeric excess (ee and de) values of the prolinol derivatives are described in the compound **4**, *ent*-**4** and **6** sections.

No unexpected or unusually high safety hazards were encountered.

### 3.2. Synthesis

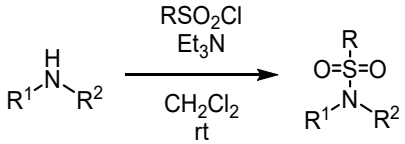
**General Procedures**

**GP1: *N*-Sulfonylation of Amino Acid**



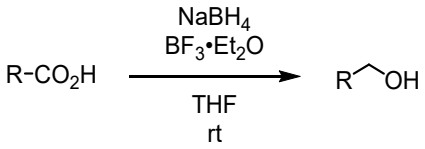

To an ice-cooled solution of amino acid (1.0 equiv) in 2 M aqueous NaOH was added a solution of sulfonyl chloride (1.1 equiv) in diethyl ether, and the mixture was stirred on ice for 1 h and then stirred at rt for 18 h. The aqueous layer was collected, washed with diethyl ether, acidified to pH 1 using 3 M aqueous HCl, and extracted with EtOAc. The extract was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated *in vacuo* to afford the product.

**GP2: *N*-Sulfonylation of Amine (2)**



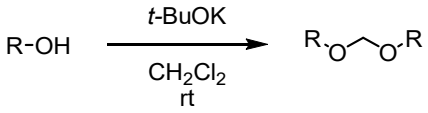

To an ice-cooled solution of amine (1.0 equiv) in anhydrous $CH_2Cl_2$ were added $Et_3N$ (2.1 equiv) and sulfonyl chloride (1.0 equiv), and the mixture was stirred at rt for 2-24 h. The mixture was diluted with 3 M aqueous HCl and extracted with $CH_2Cl_2$. The extract was dried over $Na_2SO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography to afford the product.

**GP3: Reduction of Carboxylic Acid to Alcohol**



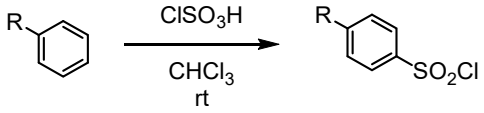

To an ice-cooled suspension of $NaBH_4$ (2.0 equiv) in THF was added dropwise $BF_3 \cdot OEt_2$ (2.6 equiv). A solution of carboxylic acid (1.0 equiv) in THF was added dropwise to the reaction mixture at 0 °C, and the mixture was stirred at the same temperature for 1 h, then at rt for 18 h. The mixture was diluted with methanol and 2 M aqueous HCl, and further stirred at 60 °C for 30 min. The mixture was carefully neutralized with 2 M aqueous NaOH and the volatiles were removed *in vacuo*. The remaining aqueous layer was extracted with $CH_2Cl_2$, and the extract was washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo*. When needed, the crude product was purified by silica gel column chromatography to afford the product.

**GP4: Formation of Symmetrical Dialkoxymethane**



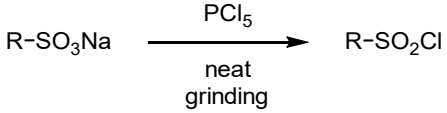

To an ice-cooled solution of alcohol (1.0 equiv) in anhydrous $CH_2Cl_2$ was added *t*-BuOK (4.0 equiv), and the mixture was stirred at rt for 1 h. The mixture was diluted with 5% aqueous $NH_4Cl$ under vigorous stirring. The mixture was extracted with EtOAc, and the extract was washed with water, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography or by reverse phase HPLC to afford the product.

**GP5: Chlorosulfonylation of Alkylbenzene**



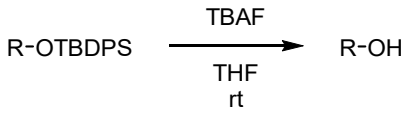

To a solution of alkylbenzene (1.0 equiv) in anhydrous $CHCl_3$ was added $ClSO_3H$ (8.0 equiv) dropwise. The mixture was stirred at rt for 18 h, poured into ice, and extracted with $CH_2Cl_2$. The extract was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. When needed, the crude product was purified by silica gel column chromatography to afford the *para*-substituted product, containing a small amount of the *ortho*-substituted isomer.

**GP6: Chlorination of Alkanesulfonate Salt**



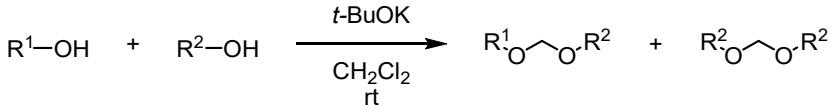
A mixture of sodium sulfonate (1.0 equiv) and $PCl_5$ (4.0 equiv) was grinded with mortar and pestle for 2 min. $Et_2O$ was poured to the mortar to dissolve materials, and the solution was filtered through a pad of Celite to remove $PCl_5$. The filtrate was concentrated *in vacuo*.

**GP7: Removal of *O*-TBDPS Group**



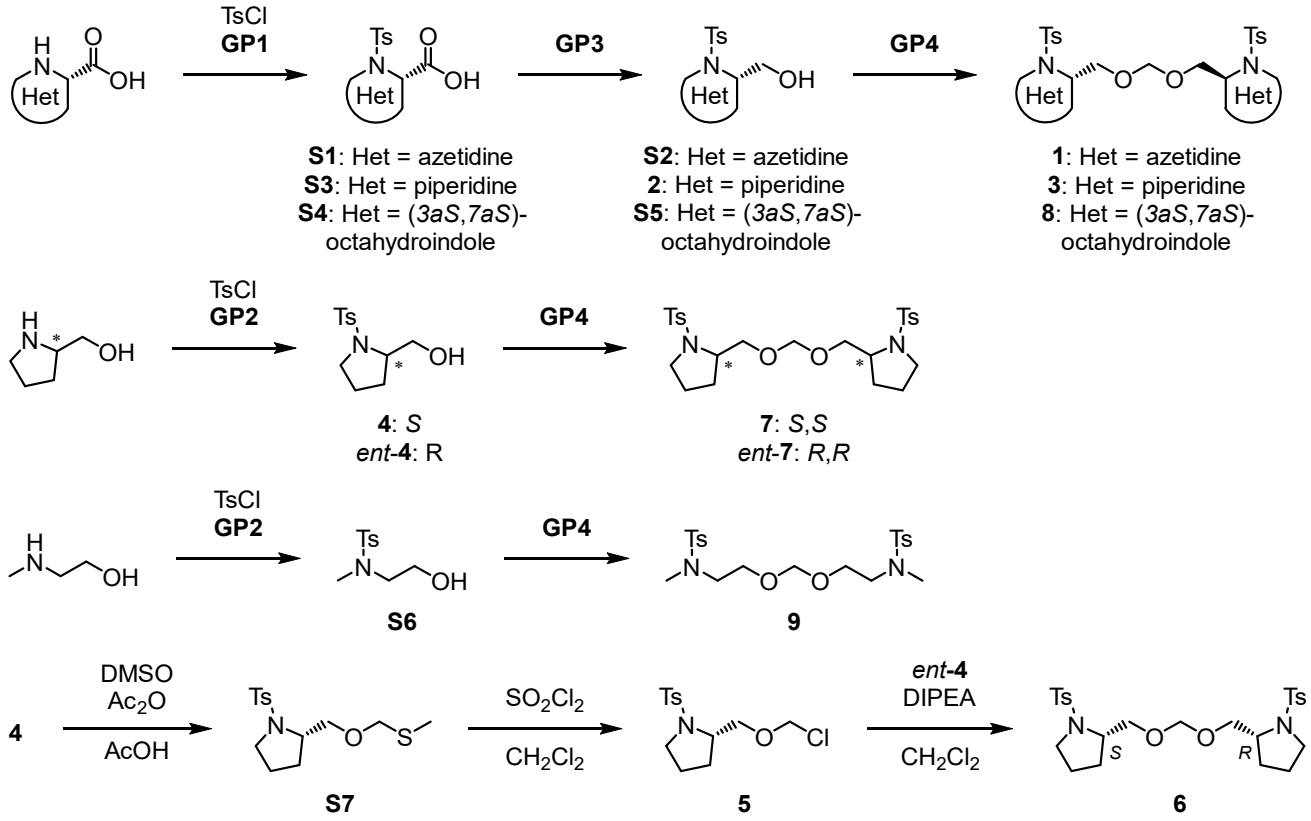

To an ice-cooled solution of *O*-TBDPS-protected alcohol (1.0 equiv) in THF was added TBAF (1.0 M solution in THF; 1.5 equiv). The mixture was stirred at rt for 1.5 h, diluted with saturated aqueous $NH_4Cl$, and extracted with EtOAc. The extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to afford the product.

**GP8: Simultaneous Formation of Symmetrical and Asymmetrical Dialkoxymethane**



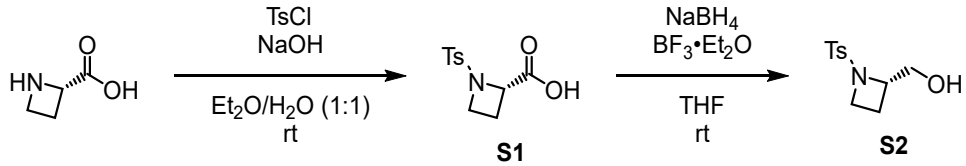

To an ice-cooled solution of alcohol A ($R^1$-OH, 1.0 equiv) and alcohol B ($R^2$-OH, 2.0 equiv) in anhydrous $CH_2Cl_2$ was added *t*-BuOK (12.0 equiv), and the mixture was stirred at rt for 1 h. The mixture was diluted with 5% aqueous $NH_4Cl$ under vigorous stirring. The mixture was extracted with EtOAc, and the extract was washed with water, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography or by reverse phase HPLC to afford the asymmetrical product ($R^1$-$OCH_2O$-$R^2$) and the symmetrical product ($R^2$-$OCH_2O$-$R^2$).

**Synthetic Scheme of the Compounds 1-9**



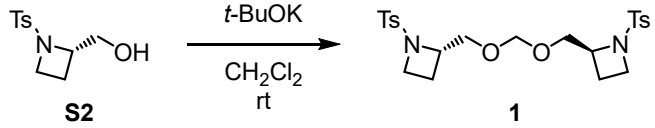

**Compounds (1-9)**

**(*S*)-1-(Tosylazetidin-2-yl)methanol (S2)**




According to **GP1**, (*S*)-2-azetidinecarboxylic acid (303 mg, 3.00 mmol) was converted to **S1** as a crude white solid by the reaction with TsCl (630 mg, 3.30 mmol, 1.1 equiv) in 2 M aqueous NaOH (9 mL) and diethyl ether (9 mL). The crude product was used in next reaction without further purification. According to **GP3**, the crude **S1** <3.00 mmol, 1.0 equiv) was converted to **S2** (661 mg, 2.74 mmol, 91% in 2 steps) as a colorless oil by the reaction with $NaBH_4$ (227 mg, 6.00 mmol, 2.0 equiv) and $BF_3{\cdot}OEt_2$ (1.11 g, 7.80 mmol, 2.6 equiv) in THF (12 mL). The spectral data were in good agreement with those previously reported.[9]

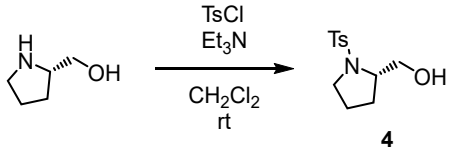
**Bis{[(*S*)-1-tosylazetidin-2-yl]methoxy}methane (KPYC01112, 1)**




According to **GP4**, **S2** (241 mg, 1.00 mmol) was converted to **1** (184 mg, 0.372 mmol, 74%) as a white solid by

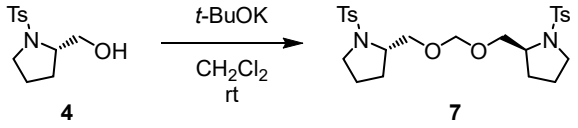
the reaction with *t*-BuOK (449 mg, 4.00 mmol, 4.0 equiv) in $CH_2Cl_2$ (10 mL). Purification by silica gel column chromatography was performed with Wakogel® C-200E and 20–40% EtOAc/*n*-hexane eluent. The spectral data were in good agreement with those previously reported.[10]

**(*S*)-(1-Tosylpyrrolidin-2-yl)methanol (4)**



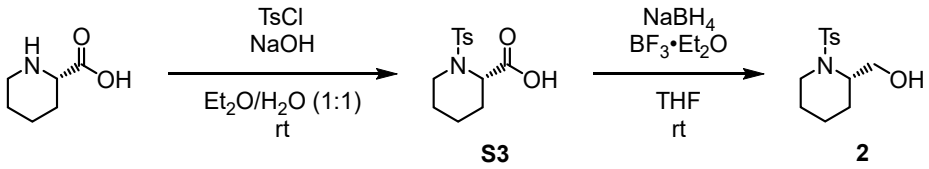

According to **GP2**, (*S*)-prolinol (1.01 g, 10.0 mmol) was converted to **4** (2.39 g, 9.36 mmol, 94%) as a white solid by the reaction with TsCl (1.91 g, 10.0 mmol, 1.0 equiv) and $Et_3N$ (2.12 g, 21.0 mmol, 2.1 equiv) in $CH_2Cl_2$ (20 mL). Purification by silica gel column chromatography was performed with Wakogel® C-200E and 0–5% MeOH/$CHCl_3$ eluent. The spectral data were in good agreement with those previously reported.[11] Based on chiral HPLC, we confirmed that the enantiomeric excess of **4** is >95%.

**Bis{[(*S*)-1-tosylpyrrolidin-2-yl]methoxy}methane (7)**



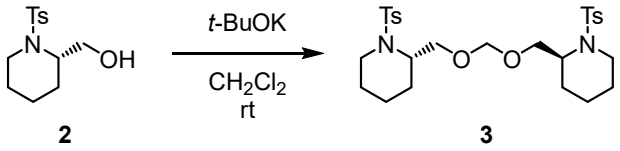

According to **GP4**, **4** (128 mg, 0.500 mmol) was converted to **7** (116 mg, 0.223 mmol, 89%) as a colorless oil by the reaction with *t*-BuOK (224 mg, 2.00 mmol, 4.0 equiv) in $CH_2Cl_2$ (8 mL). Purification by column chromatography was performed with Wakogel® C-200E and 20–40% EtOAc/*n*-hexane eluent. The spectral data were in good agreement with those previously reported.[10]

**(*S*)-(1-Tosylpiperidin-2-yl)methanol (2)**




According to **GP1**, (*S*)-piperidine-2-carboxylic acid (258 mg, 2.00 mmol) was converted to **S3** (177 mg, <0.625 mmol) as a crude white solid by the reaction with TsCl (419 mg, 2.20 mmol, 1.1 equiv) in 2 M aqueous NaOH (5 mL) and diethyl ether (5 mL). The crude product was used in next reaction without further purification. According to **GP3**, the crude **S3** (177 mg, <0.625 mmol, 1.0 equiv) was converted to **2** (104 mg, 0.387 mmol, 19% in 2 steps) as a colorless oil by the reaction with $NaBH_4$ (49 mg, 1.30 mmol, 2.0 equiv) and $BF_3{\cdot}OEt_2$ (241 mg, 1.70 mmol, 2.6 equiv) in THF (4 mL). Column chromatography was performed with Wakogel® C-200E and 0–5% MeOH/$CHCl_3$ eluent. The spectral data were in good agreement with those previously reported.[12]

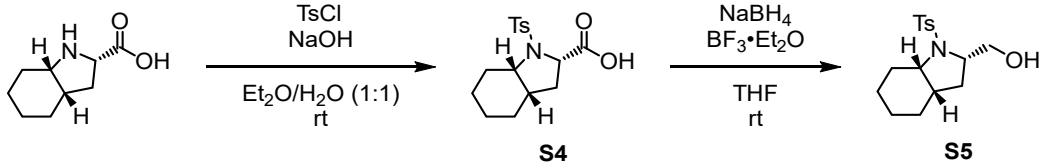
**Bis{[(*S*)-1-tosylpiperidin-2-yl]methoxy}methane (3)**




**2** **3**

According to **GP4**, **2** (52.9 mg, 0.200 mmol) was converted to **3** (22.6 mg, 0.0410 mmol, 41%) by the reaction with *t*-BuOK (89.8 mg, 0.800 mmol, 4.0 equiv) in $CH_2Cl_2$ (4 mL). Purification by preparative TLC was performed with a plate (PLC Silica gel 60 F254, 1mm) and 30% EtOAc/*n*-hexane: colorless oil; $[\alpha]^{24}_D$ −49.1° (*c* 1.07, $CHCl_3$); IR (neat) 1338 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.23−1.70 (m, 12H), 2.42 (s, 6H), 2.98 (ddd, *J* = 13.5, 13.5, 2.5 Hz, 2H), 3.54−3.60 (m, 4H), 3.75 (dd, *J* = 13.7, 3.4 Hz, 2H), 4.19−4.24 (m, 2H), 4.51 (s, 2H), 7.28 (d, *J* = 8.0 Hz, 4H), 7.73 (d, *J* = 8.0 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 18.8 (2C), 21.5 (2C), 24.5 (2C), 25.1 (2C), 41.5 (2C), 51.6 (2C), 65.8 (2C), 95.1, 127.0 (4C), 129.5 (4C), 138.6 (2C), 142.8 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{27}H_{38}N_2NaO_6S_2$, 573.2064; found, 573.2063.

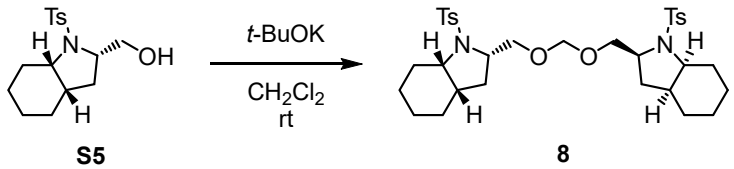
**[(2*S*,3a*S*,7a*S*)-1-Tosyloctahydro-1*H*-indol-2-yl]methanol (S5)**




**S4** **S5**

According to **GP1**, (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (326 mg, 2.00 mmol) was converted to **S4** (649 mg, <2.00 mmol) as a white rubbery solid by the reaction with TsCl (419 mg, 2.20 mmol, 1.1 equiv) in 2 M aqueous NaOH (5 mL) and diethyl ether (5 mL). The crude product was used in next reaction without further purification. According to **GP3**, the crude **S4** (649 mg, <2.00 mmol) was converted to **S5** (463 mg, 1.50 mmol, 89% in 2 steps) by the reaction with $NaBH_4$ (151 mg, 4.00 mmol, 2.4 equiv) and $BF_3{\cdot}OEt_2$ (738 mg, 5.2 mmol, 3.1 equiv) in THF (8 mL). Column chromatography was performed with Wakogel® C-200E and $CHCl_3$ eluent: white solid; mp 131−132 °C; $[\alpha]^{25}_D$ +3.2° (*c* 0.97, $CHCl_3$); IR (neat) 3444 (O–H), 1335 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.09−1.25 (m, 2H), 1.33−1.59 (m, 5H), 1.65−1.72 (m, 2H), 1.81 (ddd, *J* = 12.9, 12.9, 9.7 Hz, 1H), 1.94−1.98 (m, 1H), 2.43 (s, 3H), 3.19 (dd, *J* = 8.0, 4.2 Hz, 1H), 3.53−3.58 (m, 1H), 3.63−3.69 (m, 2H), 3.78−3.83 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 20.2, 21.6, 24.4, 25.8, 30.97, 31.01, 36.1, 61.8, 62.8, 66.7, 127.5 (2C), 129.9 (2C), 134.8, 143.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{23}NO_3S$, 310.1470; found, 310.1471.

**Bis{[(2*S*,3a*S*,7a*S*)-1-tosyloctahydro-1*H*-indol-2-yl]methoxy}methane (8)**

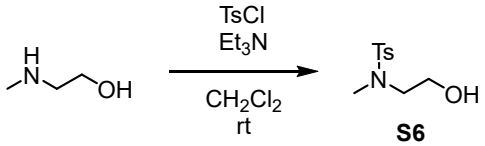



**S5** **8**

According to **GP4**, **S5** (92.8 mg, 0.300 mmol) was converted to **8** (88.7 mg, 0.141 mmol, 94%) by the reaction

with *t*-BuOK (135 mg, 1.20 mmol, 4.0 equiv) in $CH_2Cl_2$ (1.5 mL). Purification by reverse phase HPLC was performed with COSMOSIL 5$C_{18}$-AR-II and 87% MeCN/$H_2O$ eluent: white solid; mp 102−104 °C; $[\alpha]^{20}_D$ −62.7° (*c* 1.14, $CHCl_3$); IR (neat) 1342 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.08−1.16 (m, 2H), 1.23−1.31 (m, 2H), 1.38−1.51 (m, 8H), 1.60 (s, 2H), 1.60−1.66 (m, 2H), 1.78−1.84 (m, *J* = 6.6 Hz, 2H), 1.88−1.90 (m, 2H), 1.99 (td, *J* = 12.9, 9.2 Hz, 2H), 2.41 (s, 6H), 3.57−3.72 (m, 6H), 3.97 (dd, *J* = 9.2, 3.4 Hz, 2H), 4.75 (s, 2H), 7.29 (d, *J* = 7.7 Hz, 4H), 7.74 (d, *J* = 8.6 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 20.2 (2C), 21.6 (2C), 24.5 (2C), 26.0 (2C), 30.6 (2C), 32.0 (2C), 36.4 (2C), 59.8 (2C), 61.0 (2C), 71.9 (2C), 95.9, 127.5 (4C), 129.8 (4C), 135.3 (2C), 143.3 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{33}H_{46}N_2NaO_6S_2$, 653.2690; found, 653.2690.

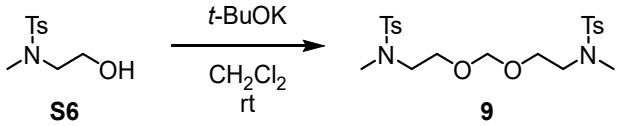
**_N_-(2-Hydroxyethyl)-_N_,4-dimethylbenzenesulfonamide (S6)**




**S6**

According to **GP2**, 2-(methylamino)ethan-1-ol (150 mg, 2.00 mmol) was converted to **S6** (455 mg, 1.99 mmol, 99%) as a colorless oil by the reaction with TsCl (381 mg, 2.00 mmol, 1.0 equiv) and $Et_3N$ (425 mg, 4.2 mmol, 2.1 equiv) in $CH_2Cl_2$ (5 mL). Column chromatography was performed with Wakogel® C-200E and 0–2% MeOH/$CHCl_3$ eluent. The spectral data were in good agreement with those previously reported.[13]

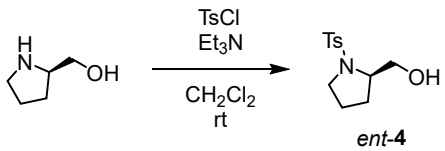
**_N_,_N_'-{[Methylenebis(oxy)]bis(ethane-2,1-diyl)}bis(_N_,4-dimethylbenzenesulfonamide) (9)**




**S6** **9**

According to **GP4**, **S6** (45.9 mg, 0.200 mmol) was converted to **9** (29.6 mg, 0.629 mmol, 63%) by the reaction with *t*-BuOK (135 mg, 1.20 mmol, 6.0 equiv) in $CH_2Cl_2$ (3 mL). Purification by reverse phase HPLC was performed with COSMOSIL 5$C_{18}$-AR-II and 62% MeCN/$H_2O$: colorless oil; IR (neat) 1339 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.43 (s, 6H), 2.82 (s, 6H), 3.21 (t, *J* = 5.7 Hz, 4H), 3.67 (t, *J* = 5.7 Hz, 4H), 4.62 (s, 2H), 7.32 (d, *J* = 8.0 Hz, 4H), 7.67 (d, *J* = 8.0 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.60, 21.64, 36.26, 36.33, 50.0 (2C), 66.5 (2C), 95.4, 127.47 (2C), 127.50 (2C), 129.75 (2C), 129.83 (2C), 134.7 (2C), 143.5 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{30}N_2NaO_6S_2$, 493.1437; found, 493.1436.

**(_R_)-(1-Tosylpyrrolidin-2-yl)methanol (*ent*-4)**

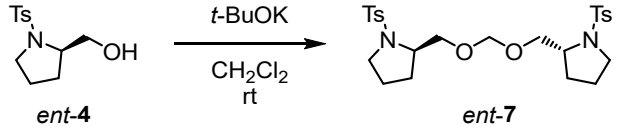



*ent*-**4**

According to **GP2**, (*R*)-prolinol (101 mg, 1.00 mmol) was converted to *ent*-**4** (174 mg, 0.681 mmol, 68%) by the reaction with TsCl (191 mg, 1.00 mmol, 1.0 equiv) and $Et_3N$ (212 mg, 2.10 mmol, 2.1 equiv) in $CH_2Cl_2$ (3 mL).

Column chromatography was performed with Wakogel® C-200E and 0-5% MeOH/$CHCl_3$ eluent: white solid; mp 79−83 °C; $[\alpha]^{20}_D$ +61.8° (*c* 0.71, $CHCl_3$); IR (neat) 3525 (O–H), 1339 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.40−1.48 (m, 1H), 1.64−1.71 (m, 2H), 1.74−1.82 (m, 1H), 2.43 (s, 3H), 2.76−2.78 (m, 1H), 3.23−3.28 (m, 1H), 3.43−3.47 (m, 1H), 3.60−3.71 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 21.6, 24.3, 29.0, 50.2, 61.9, 66.0, 127.7 (2C), 129.9 (2C), 134.0, 143.9; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{17}NNaO_3S$, 278.0821; found, 278.0821. Based on chiral HPLC, we confirmed that the enantiomeric excess of *ent*-**4** is >95%.

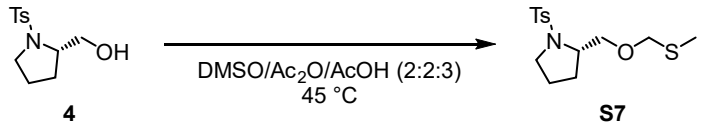
**Bis{[(*R*)-1-tosylpyrrolidin-2-yl]methoxy}methane (*ent*-7)**




*ent*-**4** *ent*-**7**

According to **GP4**, *ent*-**4** (59.3 mg, 0.232 mmol) was converted to *ent*-**7** (49.2 mg, 0.0941 mmol, 81%) by the reaction with *t*-BuOK (104 mg, 0.928 mmol, 4.0 equiv) in $CH_2Cl_2$ (3 mL). Purification by reverse phase HPLC was performed with COSMOSIL 5$C_{18}$-AR-II and 70% MeCN/$H_2O$ eluent: colorless oil; $[\alpha]^{20}_D$ +115.5° (*c* 1.48, $CHCl_3$); IR (neat) 1344 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.52−1.63 (m, 4H), 1.82−1.92 (m, 4H), 2.42 (s, 6H), 3.05−3.10 (m, 2H), 3.42−3.46 (m, 2H), 3.53 (dd, *J* = 9.2, 8.0 Hz, 2H), 3.73−3.80 (m, 4H), 4.68 (s, 2H), 7.31 (d, *J* = 8.0 Hz, 4H), 7.74 (dd, *J* = 6.3, 1.7 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6 (2C), 24.1 (2C), 28.9 (2C), 49.4 (2C), 59.2 (2C), 70.5 (2C), 95.6, 127.7 (4C), 129.8 (4C), 134.3 (2C), 143.5 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{34}N_2NaO_6S_2$, 545.1750; found, 545.1750.

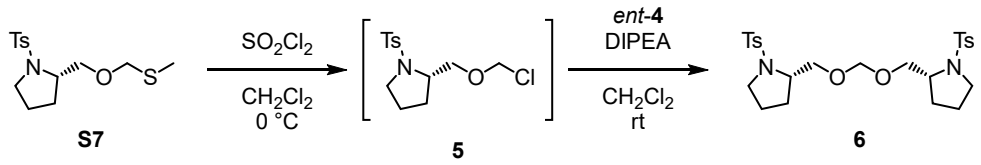
**(*S*)-2-{[(Methylthio)methoxy]methyl}-1-tosylpyrrolidine (S7)**




**4** **S7**

A mixture of **4** (255 mg, 1.00 mmol), anhydrous DMSO (2 mL), $Ac_2O$ (2 mL) and AcOH (3 mL) was stirred at 45 °C for 5 h under Ar atmosphere. The mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The extract was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (Wakogel® C-200E, 10% EtOAc/*n*-hexane eluent) to afford **S7** (187 mg, 0.592 mmol, 59%) as a colorless oil: $[\alpha]^{26}_D$ −112° (*c* 1.23, $CHCl_3$); IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.54−1.63 (m, 2H), 1.80−1.91 (m, 2H), 2.15 (s, 3H), 2.43 (s, 3H), 3.09−3.14 (m, 1H), 3.40−3.46 (m, 1H), 3.54 (dd, *J* = 9.2, 8.0 Hz, 1H), 3.73−3.80 (m, 2H), 4.64 (d, *J* = 14.9, 1H), 4.66 (d, *J* = 14.9, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.1, 21.5, 24.0, 28.9, 49.2, 58.8, 70.8, 75.7, 127.6 (2C), 129.7 (2C), 134.3, 143.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{21}NNaO_3S_2$, 338.0855; found, 338.0855.

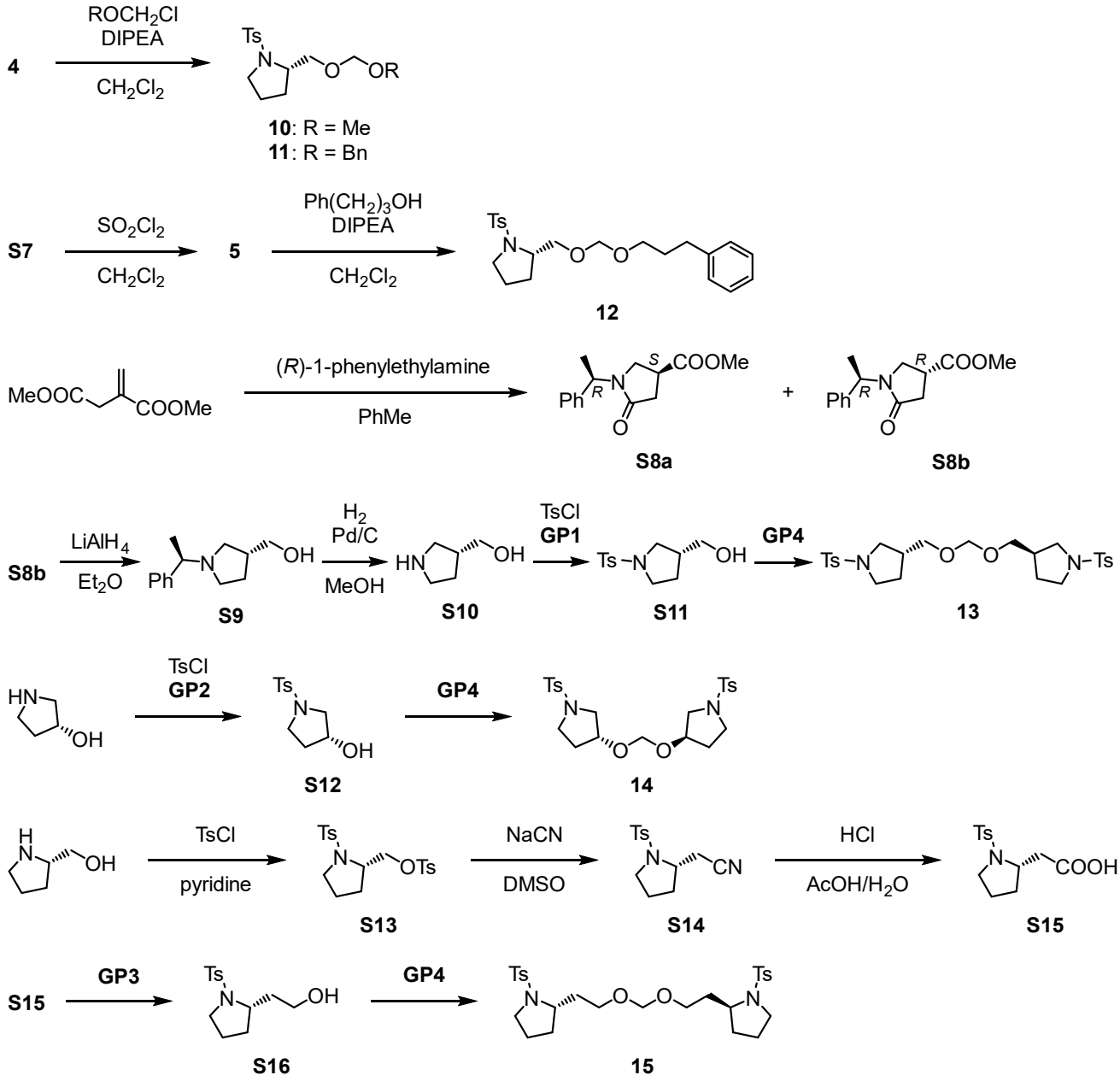
**{[(*R*)-1-Tosylpyrrolidin-2-yl]methoxy}{[(*S*)-1-tosylpyrrolidin-2-yl]methoxy}methane (6)**




To an ice-cooled solution of **S7** (63.1 mg, 0.200 mmol) in anhydrous $CH_2Cl_2$ (2 mL) was added dropwise $SO_2Cl_2$ (27.0 mg, 0.200 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 20 min, concentrated *in vacuo*, and diluted with anhydrous $CH_2Cl_2$ (2 mL). This chloromethyl ether (**5**) solution was added to an ice-cooled solution of *ent*-**4** (51.1 mg, 0.200 mmol, 1.0 equiv) and DIPEA (38.8 mg, 0.300 mmol, 1.5 equiv) in anhydrous $CH_2Cl_2$ (1 mL) at 0 °C. The mixture was stirred at rt for 21 h and then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 70% MeCN/$H_2O$ eluent) to afford **6** (37.0 mg, 0.0707 mmol, 35%) as a white solid: mp 97−102 °C; IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.52−1.62 (m, 4H), 1.82−1.91 (m, 4H), 2.42 (s, 6H), 3.06−3.10 (m, 2H), 3.42−3.46 (m, 2H), 3.51 (dd, $J$ = 9.2, 8.0 Hz, 2H), 3.72−3.79 (m, 4H), 4.66 (d, $J$ = 6.6 Hz, 1 H), 4.71 (d, $J$ = 6.6 Hz, 1H), 7.31 (d, $J$ = 8.0 Hz, 4H), 7.72 (d, $J$ = 8.6 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6 (2C), 24.1 (2C), 28.9 (2C), 49.4 (2C), 59.2 (2C), 70.6 (2C), 95.8, 127.7 (4C), 129.8 (4C), 134.3 (2C), 143.6 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{34}N_2NaO_6S_2$, 545.1750; found, 545.1753.

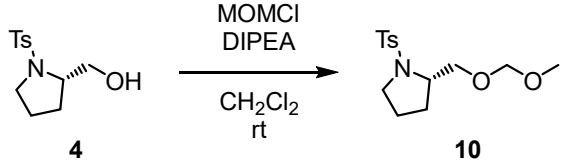
Assessment of diastereomeric excess (de) of **6**: The acetal methylene group of diastereomerically pure **6** with (*S*,*R*)-stereochemistry shows two doublet peaks (4.66 and 4.71 ppm), while those of **7** with (*S*,*S*)-stereochemistry and *ent*-**7** with (*R*,*R*)-stereochemistry show one singlet peak (4.68 ppm). Based on the integration ratio of these peaks in the $^1$H NMR spectra, we confirmed that the compound **6** is >90% de, which means that ee values of each component (compound **5** and *ent*-**4**) is >90% ee.

**Synthetic Scheme of the Compounds 10-15**




**Compounds (10-15)**

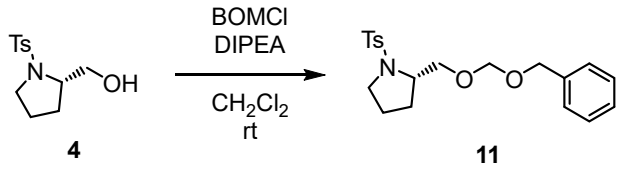
**(*S*)-2-[(Methoxymethoxy)methyl]-1-tosylpyrrolidine (10)**




To a solution of **4** (38.3 mg, 0.150 mmol) in anhydrous $CH_2Cl_2$ (1 mL) were added DIPEA (29.1 mg, 0.225 mmol, 1.5 equiv) and MOMCl (18.1 mg, 0.225 mmol, 1.5 equiv). The mixture was stirred at rt for 19 h and then concentrated. The crude product was purified by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 55% MeCN/$H_2O$

eluent) to afford **10** (33.3 mg, 0.111 mmol, 74%) as a white solid: mp 56−58 °C; $[\alpha]^{25}_{D}$ −79.5° (*c* 0.43, $CHCl_3$); IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.52−1.60 (m, 2H), 1.80−1.88 (m, 2H), 2.42 (s, 3H), 3.09−3.14 (m, 1H), 3.35 (s, 3H), 3.39−3.44 (m, 1H), 3.52 (dd, *J* = 10.3, 9.2 Hz, 1H), 3.74−3.77 (m, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6, 24.1, 28.9, 49.4, 55.5, 59.2, 70.6, 96.9, 127.7 (2C), 129.7 (2C), 134.5, 143.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{21}NNaO_4S$, 322.1084; found, 322.1084.

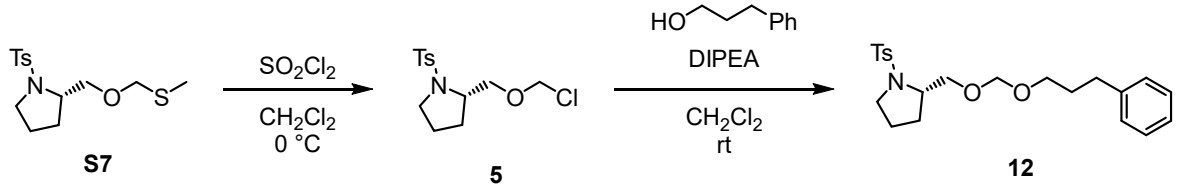
**(*S*)-2-{[(Benzyloxy)methoxy]methyl}-1-tosylpyrrolidine (11)**




**4** **11**

To a solution of **4** (38.3 mg, 0.150 mmol) in anhydrous $CH_2Cl_2$ (1 mL) were added DIPEA (29.1 mg, 0.225 mmol, 1.5 equiv) and BOMCl (35.2 mg, 0.225 mmol, 1.5 equiv). The mixture was stirred at rt for 19 h and then concentrated. The crude product was purified by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 70% MeCN/$H_2O$ eluent) to afford **11** (23.1 mg, 0.0615 mmol, 41%) as a colorless oil; $[\alpha]^{27}_{D}$ −71.3° (*c* 0.38, $CHCl_3$); IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.52−1.58 (m, 2H), 1.78−1.85 (m, 2H), 2.42 (s, 3H), 3.08−3.14 (m, 1H), 3.40−3.44 (m, 1H), 3.58 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.76−3.83 (m, 2H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.76 (d, *J* = 6.5 Hz, 1H), 4.78 (d, *J* = 6.5 Hz, 1H), 7.27−7.31 (m, 3H), 7.34−7.36 (m, 4H), 7.72 (d, *J* = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6, 24.1, 28.9, 49.4, 59.2, 69.7, 70.9, 95.2, 127.7 (2C), 127.8, 127.9 (2C), 128.5 (2C), 129.7 (2C), 134.5, 137.9, 143.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}NO_4S$, 376.1577; found, 376.1576.

**(*S*)-2-{[(3-Phenylpropoxy)methoxy]methyl}-1-tosylpyrrolidine (12)**

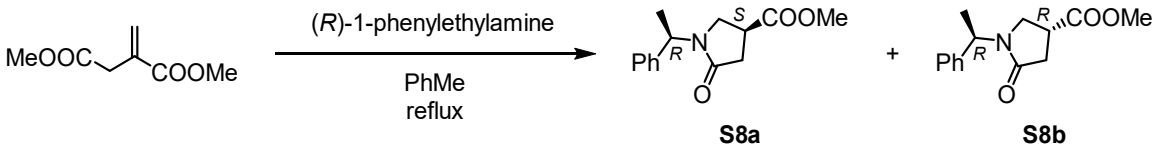



**S7** **5** **12**

To an ice-cooled solution of **S7** (63.1 mg, 0.200 mmol) in anhydrous $CH_2Cl_2$ (2 mL) was added dropwise $SO_2Cl_2$ (27.0 mg, 0.200 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 20 min, concentrated *in vacuo*, and diluted with anhydrous $CH_2Cl_2$ (2 mL). The resulting solution of chloromethyl ether (**5**) was added to an ice-cooled mixture of 3-phenylpropan-1-ol (27.2 mg, 0.200 mmol, 1.0 equiv) and DIPEA (38.8 mg, 0.300 mmol, 1.5 equiv) in anhydrous $CH_2Cl_2$ (1 mL) at 0 °C. The mixture was stirred at rt for 20 h and then concentrated *in vacuo*. The crude product was purified by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 77% MeCN/$H_2O$ eluent) to afford **12** (37.1 mg, 0.0920 mmol, 46%) as a colorless oil: $[\alpha]^{23}_{D}$ −68.7° (*c* 0.80, $CHCl_3$); IR (neat) 1347 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.50−1.56 (m, 2H), 1.77−1.85 (m, 2H), 1.88−1.94 (m, 2H), 2.41 (s, 3H), 2.70 (t, *J* = 7.7 Hz, 2H), 3.08−3.13 (m, 1H), 3.40−3.44 (m, 1H), 3.51−3.57 (m, 3H), 3.73-3.79 (m, 2H), 4.68 (d, *J* = 10.6 Hz, 1H), 4.69 (d, *J* = 10.6 Hz, 1H),

7.16−7.20 (m, 3H), 7.26−7.30 (m, 4H), 7.72 (d, $J$ = 8.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta$ 21.6, 24.0, 28.9, 31.4, 32.5, 49.4, 59.2, 67.4, 70.7, 95.9, 125.9, 127.7 (2C), 128.4 (2C), 128.5 (2C), 129.8 (2C), 134.4, 141.9, 143.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{29}NNaO_4S$, 426.1710; found, 426.1710.

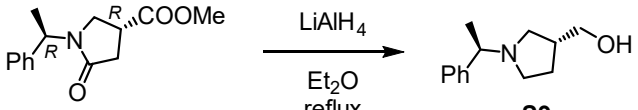
**Methyl (*S*)-5-Oxo-1-[(*R*)-1-phenylethyl]pyrrolidine-3-carboxylate (S8a) and Its (*R*,*R*)-Isomer (S8b)**




**S8a** **S8b**

To a solution of dimethyl itaconate (1.58 g, 10.0 mmol) in anhydrous toluene (5 mL) was added (*R*)-1-phenylethylamine (1.58 mg, 13.0 mmol, 1.3 equiv) under Ar atmosphere. The mixture was refluxed for 2 days and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Wakogel® C-200E, 50-70% EtOAc/*n*-hexane eluent) to afford **S8a** (823 mg, 3.33 mmol, 33%) and **S8b** (739 mg, 2.96 mmol, 30%) both as a colorless oil. The spectral data were in good agreement with those previously reported.[14]

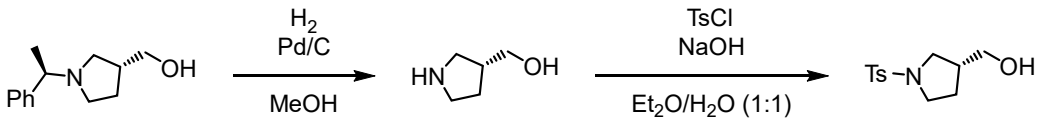
**{(*R*)-1-[(*R*)-1-Phenylethyl]pyrrolidin-3-yl}methanol (S9)**




**S8b** **S9**

To a suspension of 95% $LiAlH_4$ (89.9 mg, 2.25 mmol, 1.5 equiv) in anhydrous $Et_2O$ (2 mL) was added dropwise a solution of **S8b** (371 mg, 1.50 mmol) in anhydrous $Et_2O$ (2 mL). The mixture was refluxed for 2 h, cooled to rt and diluted with $Et_2O$/water (4:1, 3 mL). The mixture was stirred at rt for 30 min and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Wakogel® C-200E, 0–30% MeOH/$CHCl_3$ eluent) to afford **S9** (283 mg, 1.38 mmol, 92%) as a yellowish oil. The spectral data were in good agreement with those previously reported.[14]

**(*R*)-(1-Tosylpyrrolidin-3-yl)methanol (S11)**

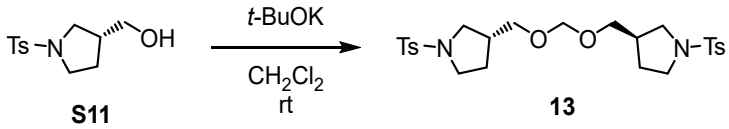



**S9** **S10** **S11**

To a solution of **S9** (139 mg, 0.677 mmol) in anhydrous MeOH (5 mL) was added 10% Pd/C (67.7 mg, 0.1 g/mol substrate). The mixture was stirred at rt for 5 days under $H_2$ atmosphere and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give the crude product (**S10**), which was used in next reaction without further purification. According to **GP2**, the crude **S10** (<0.677 mmol) was converted to **S11** (99.8 mg, 0.391 mmol, 58%) by the reaction with NaOH (67.2 mg, 1.68 mmol) and TsCl (103 mg, 0.542 mmol) in water (1 mL) and $Et_2O$ (1 mL). Column chromatography was performed with Wakogel® C-200E and 0–2% MeOH/$CHCl_3$ eluent: white solid; mp

58−61 °C; $[\alpha]^{24}_D$ +5.3° (*c* 1.03, $CHCl_3$); IR (neat) 3554 (O–H), 1339 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.54−1.61 (m, 2H), 1.86−1.92 (m, 1H), 2.27−2.33 (m, 1H), 2.43 (s, 3H), 3.06 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.15−3.20 (m, 1H), 3.29-3.34 (m, 2H), 3.39−3.50 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6, 27.6, 40.8, 47.4, 50.4, 64.2, 127.7 (2C), 129.8 (2C), 133.4, 143.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{17}NO_3S$, 256.1002; found, 256.1001.

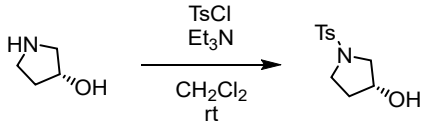
**Bis{[(*R*)-1-tosylpyrrolidin-3-yl]methoxy}methane (13)**




**S11** **13**

According to **GP4**, **S11** (66.4 mg, 0.260 mmol) was converted to **13** (53.0 mg, 0.101 mmol, 30%) by the reaction with *t*-BuOK (117 mg, 1.04 mmol, 4.0 equiv) in $CH_2Cl_2$ (1.5 mL). Chromatography was performed with Wakogel® C-200E and 30% EtOAc/*n*-hexane eluent: colorless oil; $[\alpha]^{24}_D$ −8.6° (*c* 0.89, $CHCl_3$); IR (neat) 1341 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.50−1.57 (m, 2H), 1.85−1.91 (m, 2H), 2.28−2.36 (m, 2H), 2.43 (s, 6H), 3.02 (dd, *J* = 9.7, 6.3 Hz, 2H), 3.12−3.17 (m, 2H), 3.25 (dd, *J* = 9.5, 7.7 Hz, 2H), 3.29−3.34 (m, 6H), 4.48 (s, 2H), 7.32 (d, *J* = 8.0 Hz, 4H), 7.70 (d, *J* = 8.6 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6 (2C), 28.1 (2C), 38.5 (2C), 47.4 (2C), 50.7 (2C), 69.3 (2C), 95.5, 127.7 (4C), 129.7 (4C), 133.5 (2C), 143.6 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{34}N_2NaO_6S_2$, 545.1750; found, 545.1751.

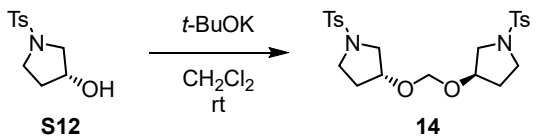
**(*R*)-1-Tosylpyrrolidin-3-ol (S12)**




**S12**

According to **GP2**, (*R*)-3-pyrrolidinol (174 mg, 2.00 mmol) was converted to **S12** (357 mg, 1.06 mmol, 53%) by the reaction with TsCl (381 mg, 2.00 mmol, 1.0 equiv) and $Et_3N$ (425 mg, 4.20 mmol, 2.1 equiv) in $CH_2Cl_2$ (6 mL). Column chromatography was performed with Wakogel® C-200E and 50% EtOAc/*n*-hexane eluent: white solid; mp 112−114 °C; $[\alpha]^{26}_D$ −5.7° (*c* 0.80, $CHCl_3$); IR (neat) 3528 (O–H), 1328 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.53 (d, *J* = 4.6 Hz, 1H), 1.80−1.85 (m, 1H), 1.89−1.95 (m, 1H), 2.42 (s, 3H), 3.23 (ddd, *J* = 10.9, 1.7, 1.7 Hz, 1H), 3.32−3.41 (m, 3H), 4.35−4.39 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6, 34.4, 46.0, 56.2, 70.9, 127.7 (2C), 129.8 (2C), 133.7, 143.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{15}NNaO_3S$, 264.0665; found, 264.0665.

**Bis{[(*R*)-1-tosylpyrrolidin-3-yl]oxy}methane (14)**

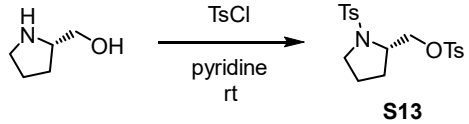



**S12** **14**

According to **GP4**, **S12** (96.5 mg, 0.400 mmol) was converted to **14** (62.7 mg, 0.127 mmol, 63%) by the reaction

with *t*-BuOK (180 mg, 1.60 mmol, 4.0 equiv) in $CH_2Cl_2$ (2 mL). Purification by preparative TLC was performed with a plate (PLC Silica gel 60 F254, 1 mm) and 40% EtOAc/*n*-hexane eluent: white solid; mp 115−117 °C; $[\alpha]^{24}_D$ +8.50° (*c* 0.87, $CHCl_3$); IR (neat) 1337 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.79−1.85 (m, 4H), 2.42 (s, 6H), 3.17−3.20 (m, 2H), 3.24 (ddd, $J$ = 8.4, 8.4, 8.4 Hz, 2H), 3.31−3.35 (m, 4H), 4.05−4.08 (m, 2H), 4.38 (s, 2H), 7.31 (d, $J$ = 8.0 Hz, 4H), 7.69 (d, $J$ = 8.0 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6 (2C), 31.7 (2C), 46.1 (2C), 53.1 (2C), 75.4 (2C), 92.1, 127.7 (4C), 129.7 (4C), 133.8 (2C), 143.6 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_6S_2$, 517.1437; found, 517.1436.

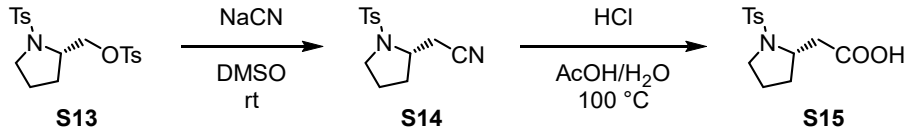
**(*S*)-(1-Tosylpyrrolidin-2-yl)methyl 4-Methylbenzenesulfonate (S13)**




**S13**

To an ice-cooled solution of (*S*)-prolinol (506 mg, 5.00 mmol, 1.0 equiv) in anhydrous pyridine (1 mL) was added a solution of TsCl (2.10 g, 11.0 mmol, 2.2 equiv) in anhydrous pyridine (9 mL). The mixture was stirred at rt for 13 h, acidified on ice to pH 3 with 3 M aqueous HCl, and extracted with $CH_2Cl_2$. The extract was dried over $Na_2SO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (Wakogel® C-200E, 20–30% EtOAc/*n*-hexane eluent) to afford **S13** (1.57 mg, 3.85 mmol, 77%) as a white solid. The spectral data were in good agreement with those previously reported.[9]

**(*S*)-2-(1-Tosylpyrrolidin-2-yl)acetic Acid (S15)**

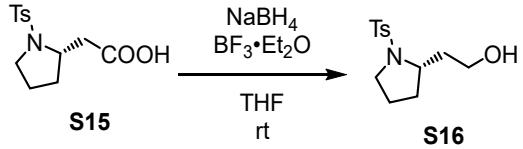



**S13** **S14** **S15**

A solution of **S13** (1.15 g, 2.80 mmol) and NaCN (206 mg, 4.20 mmol, 1.5 equiv) in anhydrous DMSO (9 mL) was stirred at rt for 64 h under Ar atmosphere. The mixture was diluted with 5% aqueous $NH_4Cl$, and extracted with $CH_2Cl_2$. The extract was washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product (**S14**) containing a small amount of unreacted starting material was used in next reaction without further purification.

A mixture of the crude **S14** (crude, <2.80 mmol) in AcOH (0.8 mL) and concentrated aqueous HCl (4 mL) was stirred at 100 °C for 4 h, cooled to rt, and extracted with $Et_2O$. The organic layer was washed with water and extracted with 1 M aqueous NaOH. The aqueous layer was acidified to pH 2 using 3 M aqueous HCl and extracted with toluene. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford **S15** (315 mg, 1.11 mmol, 40% in 2 steps) as a white solid. The spectral data were in good agreement with those previously reported.[15]

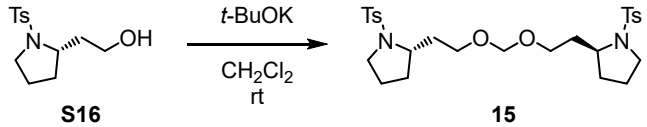
**(*S*)-2-(1-Tosylpyrrolidin-2-yl)ethan-1-ol (S16)**




**S15** **S16**

According to **GP3**, **S15** (283 mg, 1.00 mmol) was converted to **S16** (269 mg, 1.00 mmol, quant) as a colorless oil by the reaction with $NaBH_4$ (75.6 mg, 2.00 mmol, 2.0 equiv) and $BF_3{\cdot}OEt_2$ (370 mg, 2.60 mmol, 2.6 equiv) in THF (7 mL). Column chromatography was performed with Wakogel® C-200E and 50% EtOAc/*n*-hexane eluent. The spectral data were in good agreement with those previously reported.[15]

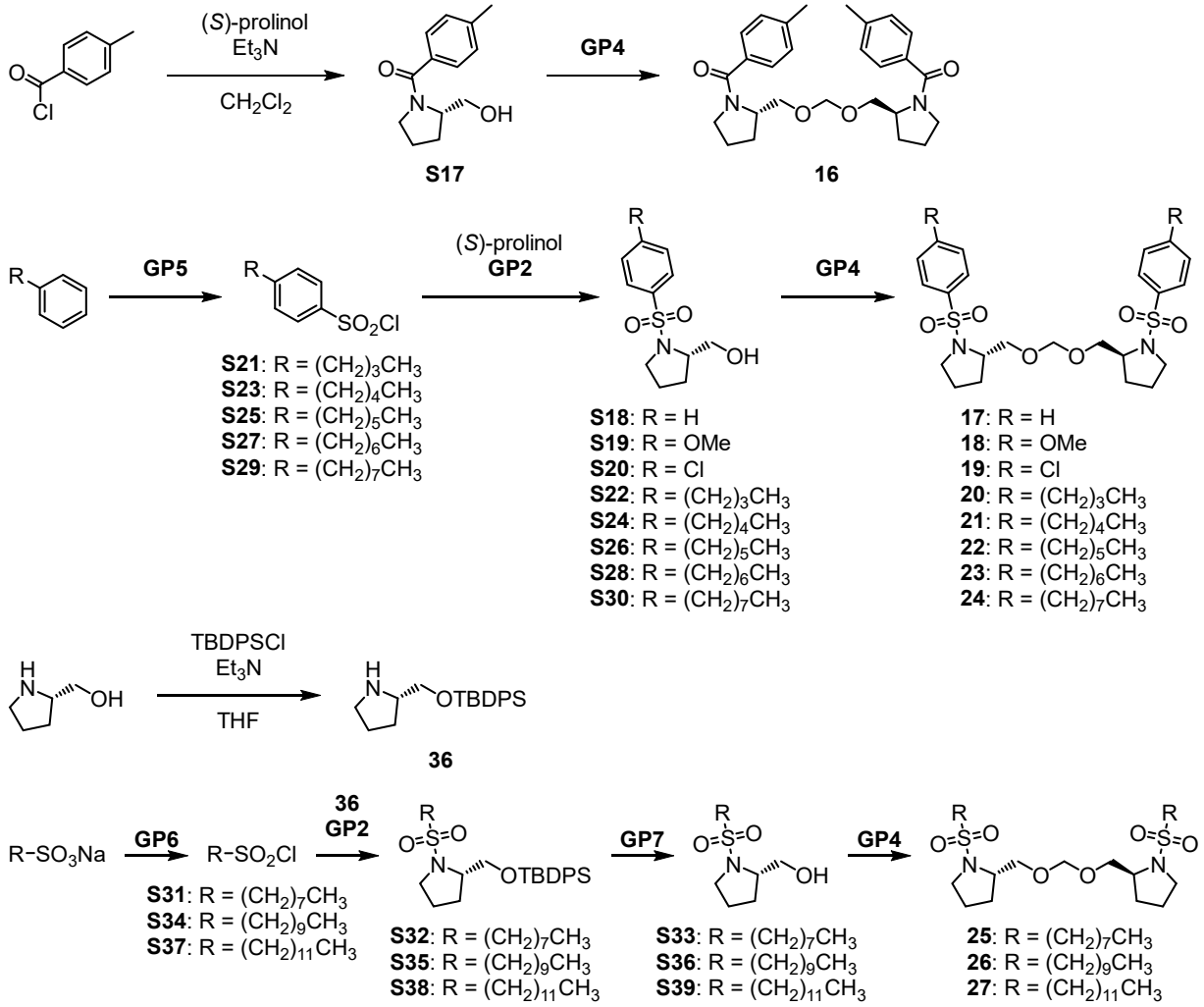
**Bis{2-[(*S*)-1-tosylpyrrolidin-2-yl]ethoxy}methane (15)**




**S16** **15**

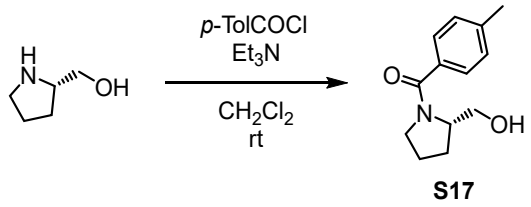
According to **GP4**, **S16** (46.3 mg, 0.172 mmol) was converted to **15** (34.6 mg, 0.0628 mmol, 73%) by the reaction with *t*-BuOK (89.8 mg, 0.800 mmol, 4.7 equiv) in $CH_2Cl_2$ (1 mL). Purification by reverse phase HPLC was performed with COSMOSIL $5C_{18}$-AR-II and 65% MeCN/ $H_2O$ eluent: colorless oil; $[\alpha]^{23}_D$ −106° (*c* 0.38, $CHCl_3$); IR (neat) 1343 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.45−1.52 (m, 2H), 1.53−1.59 (m, 2H), 1.60−1.66 (m, 2H), 1.68−1.80 (m, 4H), 2.09−2.16 (m, 2H), 2.41 (s, 6H), 3.15−3.20 (m, 2H), 3.36−3.40 (m, 2H), 3.61−3.69 (m, 4H), 3.75−3.80 (m, 2H), 4.69 (s, 2H), 7.30 (d, $J$ = 8.0 Hz, 4H), 7.71 (d, $J$ = 8.0 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 21.6 (2C), 24.2 (2C), 31.2 (2C), 36.4 (2C), 48.9 (2C), 58.3 (2C), 65.2 (2C), 95.5, 127.7 (4C), 129.8 (4C), 134.8 (2C), 143.4 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{27}H_{38}N_2NaO_6S_2$, 573.2064; found, 573.2065.

**Synthetic Scheme of the Compounds 16-27**



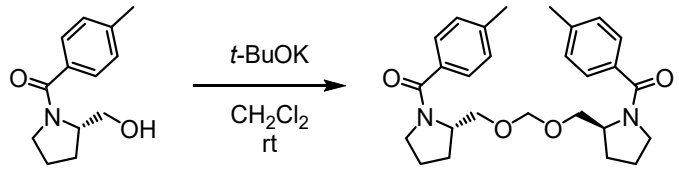

**Compounds (16-27)**

**(*S*)-[2-(Hydroxymethyl)pyrrolidin-1-yl](*p*-tolyl)methanone (S17)**




To a solution of (*S*)-prolinol (202 mg, 2.00 mmol) and $Et_3N$ (202 mg, 2.00 mmol, 1.0 equiv) in anhydrous $CH_2Cl_2$ (8 mL) was added *p*-toluoyl chloride (309 mg, 2.0 mmol, 1.0 equiv) at −10 °C. The mixture was stirred at the same temperature for 4 h and then at rt for 4 h, diluted with $CH_2Cl_2$, washed with 10% aqueous citric acid, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Wakogel® C-200E, 50–70% EtOAc/*n*-hexane eluent) to afford **S17** (289 mg, 1.32 mmol, 66%) as a colorless oil. The spectral data were in good agreement with those previously reported.[16]

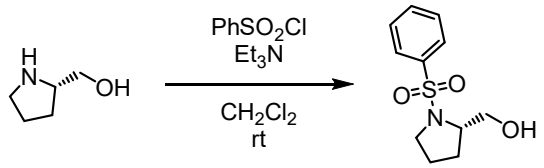
**[(2*S*,2'*S*)-{[Methylenebis(oxy)]bis(methylene)}bis(pyrrolidine-2,1-diyl)]bis(*p*-tolylmethanone) (16)**




**S17** **16**

According to **GP4**, **S17** (87.7 mg, 0.400 mmol) was converted to **16** (72.0 mg, 0.160 mmol, 80%) by the reaction with *t*-BuOK (180 mg, 1.60 mmol, 4.0 equiv) in $CH_2Cl_2$ (2 mL). Column chromatography was performed with Wakogel® C-200E and 30–100% EtOAc/*n*-hexane eluent: white solid; mp 118−119 °C; $[\alpha]^{27}_D$ −193° (*c* 0.51, $CHCl_3$); IR (neat) 1623 (C=O); $^1$H NMR (500 MHz, DMSO-$d_6$, 95 °C) $\delta$ 1.69−1.74 (m, 2H), 1.80−1.88 (m, 4H), 1.93−1.99 (m, 2H), 2.31 (s, 6H), 3.34−3.36 (m, 4H), 3.47 (br s, 2H), 3.56 (br s, 2H), 4.19 (br s, 2H), 4.55 (br s, 2H), 7.18 (d, *J* = 8.0 Hz, 4H), 7.32 (d, *J* = 8.0 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, DMSO-$d_6$, 95 °C) $\delta$ 21.3 (2C), 24.3 (2C), 28.2 (2C), 49.3 (2C), 57.1 (2C), 68.4 (2C), 95.8, 127.4 (4C), 129.1 (4C), 135.3 (2C), 139.7 (2C), 169.4 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{27}H_{34}N_2NaO_4$, 473.2411; found, 473.2409.

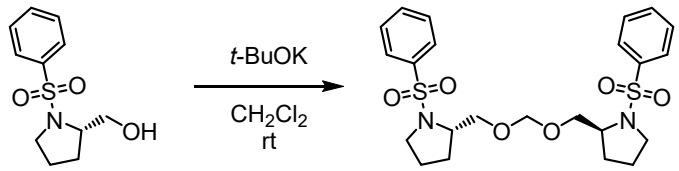
**(*S*)-[1-(Phenylsulfonyl)pyrrolidin-2-yl]methanol (S18)**




**S18**

According to **GP2**, (*S*)-prolinol (202 mg, 2.00 mmol) was converted to **S18** (483 mg, 2.00 mmol, quant) as a colorless oil by the reaction with benzenesulfonyl chloride (353 mg, 2.00 mmol, 1.0 equiv) and $Et_3N$ (425 mg, 4.20 mmol, 2.1 equiv) in $CH_2Cl_2$ (5 mL). Column chromatography was performed with Wakogel® C-200E and 5% MeOH/$CHCl_3$ eluent. The spectral data were in good agreement with those previously reported.[17]

**Bis{[(*S*)-1-(phenylsulfonyl)pyrrolidin-2-yl]methoxy}methane (17)**

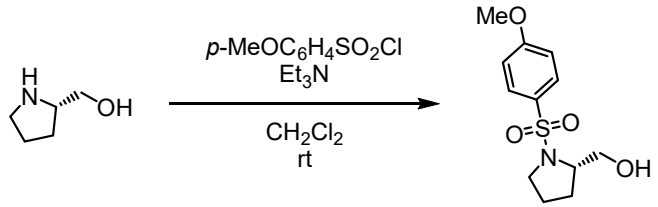



**S18** **17**

According to **GP4**, **S18** (72.4 mg, 0.300 mmol) was converted to **17** (37.4 mg, 0.0757 mmol, 50%) by the reaction with *t*-BuOK (135 mg, 1.20 mmol, 4.0 equiv) in $CH_2Cl_2$ (1.5 mL). Purification by reverse phase HPLC was performed with COSMOSIL 5$C_{18}$-AR-II and 58% MeCN/$H_2O$ eluent: colorless oil; $[\alpha]^{21}_D$ −94.5° (*c* 1.07, $CHCl_3$); IR (neat) 1345 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.54−1.61 (m, 4H), 1.85−1.93 (m, 4H), 3.08−3.13 (m, 2H), 3.43−3.48 (m, 2H), 3.52−3.56 (m, 2H), 3.75−3.80 (m, 4H), 4.68 (s, 2H), 7.50−7.54 (m, 4H), 7.57−7.60 (m, 2H), 7.83−7.87 (m, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 24.1 (2C), 28.9 (2C), 49.5 (2C), 59.3 (2C), 70.5 (2C), 95.7,

127.6 (4C), 129.2 (4C), 132.8 (2C), 137.3 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_6S_2$, 517.1437; found, 517.1434.

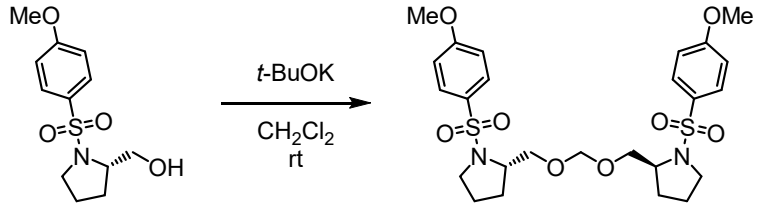
**(*S*)-{1-[(4-Methoxyphenyl)sulfonyl]pyrrolidin-2-yl}methanol (S19)**




**S19**

According to **GP2**, (*S*)-prolinol (202 mg, 2.00 mmol) was converted to **S19** (303 mg, 1.12 mmol, 56%) as white solid by the reaction with *p*-methoxybenzenesulfonyl chloride (413 mg, 2.00 mmol, 1.0 equiv) and $Et_3N$ (425 mg, 4.20 mmol, 2.0 equiv) in $CH_2Cl_2$ (6 mL). Column chromatography was performed with Wakogel® C-200E and 0–5% MeOH/$CHCl_3$ eluent. The spectral data were in good agreement with those previously reported.[18]

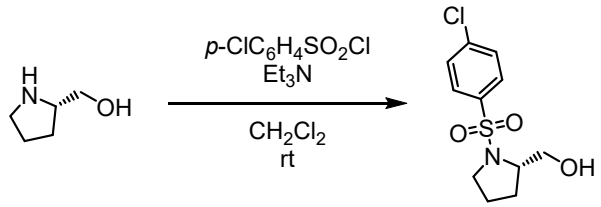
**Bis({(*S*)-1-[(4-methoxyphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (18)**




**S19** **18**

According to **GP4**, **S19** (54.3 mg, 0.200 mmol) was converted to **18** (43.9 mg, 0.0791 mmol, 79%) by the reaction with *t*-BuOK (89.8 mg, 0.800 mmol, 4.0 equiv) in $CH_2Cl_2$ (2 mL). Purification by reverse phase HPLC was performed with COSMOSIL 5$C_{18}$-AR-II and 70% MeCN/$H_2O$ eluent: colorless foam; $[\alpha]^{24}_D$ −109° (*c* 1.77, $CHCl_3$); IR (neat) 1341 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.53−1.63 (m, 4H), 1.82−1.92 (m, 4H), 3.04−3.09 (m, 2H), 3.41−3.45 (m, 2H), 3.51 (dd, $J$ = 9.2, 8.0 Hz, 2H), 3.72−3.77 (m, 2H), 3.80 (dd, $J$ = 9.5, 3.7 Hz, 2H), 3.86 (s, 6H), 4.69 (s, 2H), 6.96−6.99 (m, 4H), 7.77−7.81 (m, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 24.1 (2C), 28.9 (2C), 49.4 (2C), 55.7 (2C), 59.2 (2C), 70.5 (2C), 95.6, 114.3 (4C), 129.0 (2C), 129.7 (4C), 163.0 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{34}N_2NaO_8S_2$, 577,1649; found, 577.1652.

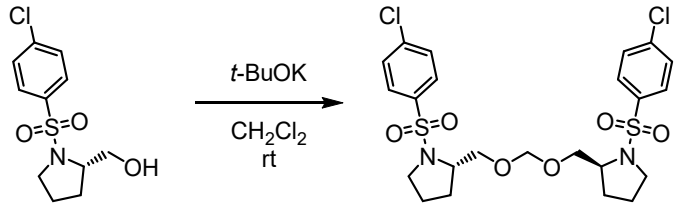
**(*S*)-{1-[(4-Chlorophenyl)sulfonyl]pyrrolidin-2-yl}methanol (S20)**




**S20**

According to **GP2**, (*S*)-prolinol (202 mg, 2.00 mmol) was converted to **S20** (371 mg, 1.35 mmol, 67%) by the reaction with *p*-chlorobenzenesulfonyl chloride (422 mg, 2.00 mmol, 1.0 equiv) and $Et_3N$ (425 mg, 4.20 mmol, 2.1 equiv) in $CH_2Cl_2$ (5mL). Column chromatography was performed with Wakogel® C-200E and 0–5% MeOH/$CHCl_3$ eluent: colorless oil; $[\alpha]^{23}_D$ −55.4° (*c* 0.83, $CHCl_3$); IR (neat) 3524 (O–H), 1344 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.45–1.52 (m, 1H), 1.66-1.77 (m, 2H), 1.79–1.87 (m, 1H), 2.65 (dd, $J$ = 6.9, 5.2 Hz, 1H), 3.20-3.25 (m, 1H), 3.45–3.50 (m, 1H), 3.59–3.72 (m, 3H), 7.50–7.53 (m, 2H), 7.77–7.80 (m, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 24.4, 29.0, 50.2, 62.1, 65.9, 129.1 (2C), 129.6 (2C), 135.5, 139.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}ClNNaO_3S$, 298.0275; found, 298.0273.

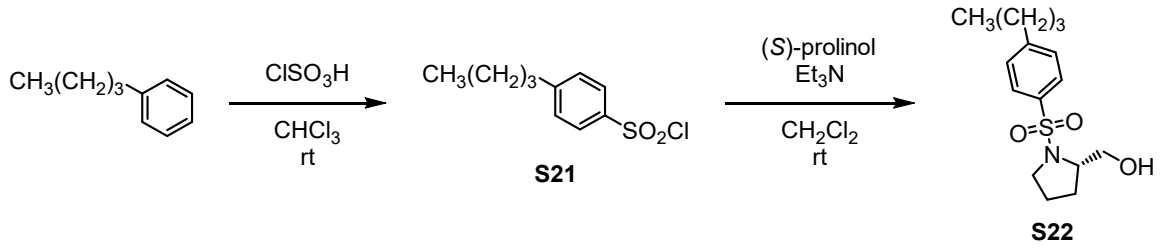
**Bis({(*S*)-1-[(4-chlorophenyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (19)**




**S20** **19**

According to **GP4**, **S20** (82.7 mg, 0.300 mmol) was converted to **19** (46.2 mg, 0.0819 mmol, 55%) by the reaction with *t*-BuOK (50.5 mg, 0.450 mmol, 1.5 equiv) in $CH_2Cl_2$ (3 mL). Purification by reverse phase HPLC was performed with COSMOSIL 5$C_{18}$-AR-II and 70% MeCN/$H_2O$ eluent: colorless oil; $[\alpha]^{25}_D$ −95.1° (*c* 1.46, $CHCl_3$); IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.59–1.66 (m, 4H), 1.87–1.94 (m, 4H), 3.04–3.09 (m, 2H), 3.44–3.48 (m, 2H), 3.51 (dd, $J$ = 9.2, 7.4 Hz, 2H), 3.73–3.80 (m, 4H), 4.67 (s, 2H), 7.48–7.51 (m, 4H), 7.79–7.82 (m, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 24.1 (2C), 29.0 (2C), 49.5 (2C), 59.3 (2C), 70.3 (2C), 95.5, 129.0 (4C), 129.5 (4C), 135.8 (2C), 139.3 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{28}Cl_2N_2NaO_6S_2$, 585.0658; found, 585.0662.

**(*S*)-{1-[(4-Butylphenyl)sulfonyl]pyrrolidin-2-yl}methanol (S22)**

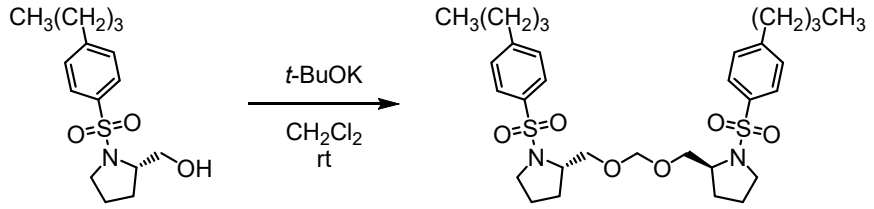



**S21** **S22**

According to **GP5**, *n*-butylbenzene (268 mg, 2.00 mmol) was converted to **S21** (410 mg, 1.76 mmol, 88%, containing a small amount of *ortho*-substituted by-product) by the reaction with $ClSO_3H$ (1.86 mg, 16.0 mmol, 8.0 equiv) in $CHCl_3$ (4 mL). Column chromatography was performed with Wakogel® C-200E and 20–30% EtOAc/*n*-hexane eluent. According to **GP2**, **S21** (410 mg, 1.76 mmol, containing *ortho*-substituted by-product) was converted to **S22** (512 mg, 1.72 mmol, 98%; containing *ca*. 5 % of the *ortho*-substituted by-product) by the reaction with (*S*)-prolinol (182 mg, 1.80 mmol, 1.02 equiv) and $Et_3N$ (374 mg, 3.70 mmol, 2.1 equiv) in $CH_2Cl_2$ (5 mL). The *para*-

isomer was separated from *ortho*-isomer by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 50% MeCN/$H_2O$ eluent): colorless oil; $[\alpha]^{23}_D$ −49.6° (*c* 0.44, $CHCl_3$); IR (neat) 3528 (O–H), 1341 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.93 (t, *J* = 7.4 Hz, 3H), 1.35 (qt, *J* = 7.6, 7.6 Hz, 2H), 1.40–1.48 (m, 1H), 1.60–1.70 (m, 4H), 1.75–1.83 (m, 1H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.76 (dd, *J* = 7.5, 4.0 Hz, 1H), 3.24–3.29 (m, 1H), 3.43–3.48 (m, 1H), 3.61–3.72 (m, 3H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.74 (dt, *J* = 8.4, 2.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.0, 22.4, 24.4, 29.0, 33.3, 35.6, 50.2, 62.0, 66.0, 127.8 (2C), 129.2, 129.3, 134.1, 148.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{23}NNaO_3S$, 320.1291; found, 320.1287.

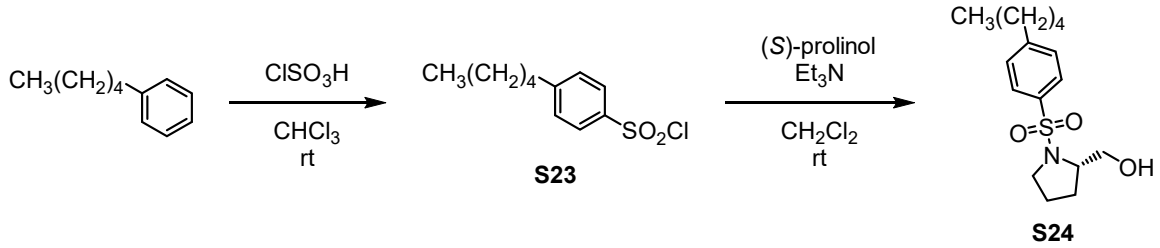
**Bis({(*S*)-1-[(4-butylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (20)**




**S22** **20**

According to **GP4**, **S22** (33.8 mg, 0.114 mmol) was converted to **20** (25.4 mg, 0.0419 mmol, 74%) by the reaction with *t*-BuOK (51.0 mg, 0.455 mmol, 4.0 equiv) in $CH_2Cl_2$ (1 mL). Column chromatography was performed with Biotage® Sfär D and 7–30% EtOAc/*n*-hexane eluent: colorless oil; $[\alpha]^{24}_D$ −83.8° (*c* 1.00, $CHCl_3$); IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.92 (t, *J* = 7.2 Hz, 6H), 1.34 (qt, *J* = 7.4, 7.4 Hz, 4H), 1.53–1.63 (m, 8H), 1.84–1.91 (m, 4H), 2.66 (t, *J* = 7.7 Hz, 4H), 3.06–3.11 (m, 2H), 3.42–3.46 (m, 2H), 3.54 (dd, *J* = 8.6, 7.4 Hz, 2H), 3.74–3.80 (m, 4H), 4.68 (s, 2H), 7.31 (d, *J* = 8.0 Hz, 4H), 7.75 (d, *J* = 8.6 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.0 (2C), 22.4 (2C), 24.1 (2C), 28.9 (2C), 33.3 (2C), 35.6 (2C), 49.4 (2C), 59.2 (2C), 70.5 (2C), 95.6, 127.7 (4C), 129.1 (4C), 134.4 (2C), 148.4 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{46}N_2NaO_6S_2$, 629.2690; found, 629.2687.

**(*S*)-{1-[(4-Pentylphenyl)sulfonyl]pyrrolidin-2-yl}methanol (S24)**

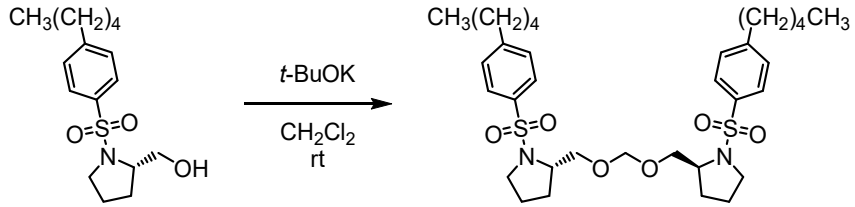



**S23** **S24**

According to **GP5**, *n*-pentylbenzene (297 mg, 2.00 mmol) was converted to **S23** (crude, containing a small amount of *ortho*-substituted by-product) by the reaction with $ClSO_3H$ (1.86 mg, 16.0 mmol, 8.0 equiv) in $CHCl_3$ (4 mL). The crude product was used in next reaction without further purification. According to **GP2**, the crude **S23** (<2.00 mmol, containing *ortho*-substituted by-product) was converted to **S24** (563 mg, 1.81 mmol, 91%, containing *ca*. 6% of the *ortho*-substituted by-product) by the reaction with (*S*)-prolinol (202 mg, 2.00 mmol, 1.0 equiv) and $Et_3N$ (425 mg, 4.20 mmol, 2.1 equiv) in $CH_2Cl_2$ (5 mL). Short column chromatography was performed with Biotage®

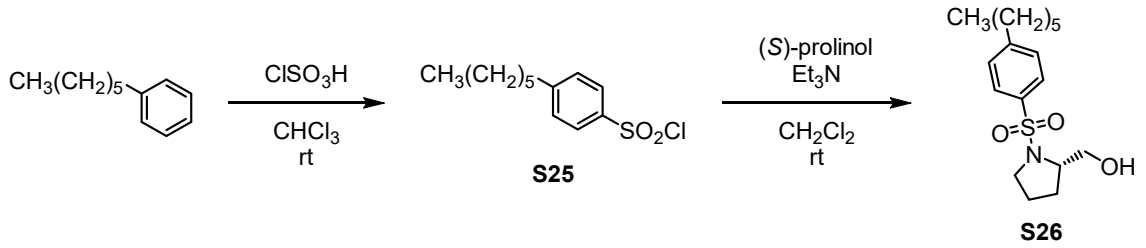
Sfär D and 0–3% MeOH/$CHCl_3$ eluent. The *para*-isomer was separated from *ortho*-isomer by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 55% MeCN/$H_2O$ eluent): colorless oil; $[\alpha]^{26}_D$ −46.9° (*c* 0.62, $CHCl_3$); IR (neat) 3539 (O–H), 1343 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.27–1.37 (m, 4H), 1.40–1.47 (m, 1H), 1.60–1.70 (m, 4H), 1.74–1.81 (m, 1H), 2.67 (t, $J$ = 8.0 Hz, 2H), 2.78–2.79 (m, 1H), 3.24–3.29 (m, 1H), 3.43–3.47 (m, 1H), 3.61–3.70 (m, 3H), 7.32 (d, $J$ = 8.6 Hz, 2H), 7.74 (d, $J$ = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.1, 22.5, 24.4, 29.0, 30.8, 31.5, 35.9, 50.1, 61.9, 66.0, 127.7 (2C), 129.2 (2C), 134.1, 148.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{25}NNaO_3S$, 334.1447; found, 334.1446.

**Bis({(*S*)-1-[(4-pentylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (21)**




According to **GP4**, **S24** (30.6 mg, 0.0983 mmol) was converted to **21** (22.7 mg, 0.0358 mmol, 37%) by the reaction with *t*-BuOK (44.1 mg, 0.393 mmol, 4.0 equiv) in $CH_2Cl_2$ (1.5 mL). Column chromatography was performed with Biotage® Sfär D and 7–40% EtOAc/*n*-hexane eluent: colorless oil; $[\alpha]^{27}_D$ −103° (*c* 0.61, $CHCl_3$); IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 7.2 Hz, 6H), 1.26–1.35 (m, 8H), 1.53–1.65 (m, 8H), 1.84–1.92 (m, 4H), 2.65 (t, $J$ = 7.7 Hz, 4H), 3.07–3.12 (m, 2H), 3.42-3.46 (m, 2H), 3.54 (dd, $J$ = 8.9, 7.7 Hz, 2H), 3.74–3.80 (m, 4H), 4.68 (s, 2H), 7.31 (d, $J$ = 8.0 Hz, 4H), 7.75 (d, $J$ = 8.0 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.1 (2C), 22.5 (2C), 24.1 (2C), 28.9 (2C), 30.8 (2C), 31.5 (2C), 35.9 (2C), 49.4 (2C), 59.2 (2C), 70.5 (2C), 95.6, 127.7 (4C), 129.1 (4C), 134.4 (2C), 148.5 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{33}H_{50}N_2NaO_6S_2$, 657.3003; found, 657.3003.

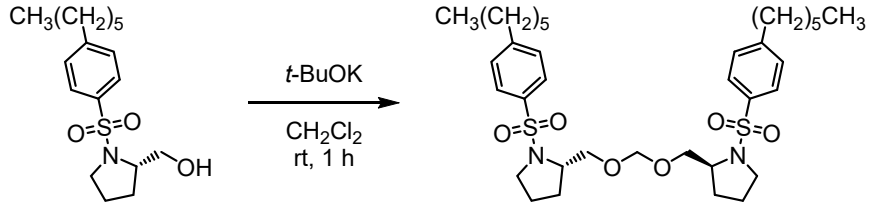
**(*S*)-{1-[(4-Hexylphenyl)sulfonyl]pyrrolidin-2-yl}methanol (S26)**




According to **GP5**, *n*-hexylbenzene (325 mg, 2.00 mmol) was converted to **S25** (465 mg, 1.78 mmol, 89%, containing a small amount of *ortho*-substituted by-product) by the reaction with $ClSO_3H$ (1.86 mg, 16.0 mmol, 8.0 equiv) in $CHCl_3$ (4 mL). Column chromatography was performed with Wakogel® C-200E and 20–30% $CH_2Cl_2$/*n*-hexane eluent. According to **GP2**, **S25** (465 mg, 1.78 mmol, containing *ortho*-substituted by-product) was converted to **S26** (580 mg, 1.78 mmol, quant, containing *ca*. 7% of the *ortho*-substituted by-product) by the reaction with (*S*)-prolinol (202 mg, 2.00 mmol, 1.1 equiv) and $Et_3N$ (425 mg, 4.20 mmol, 2.4 equiv) in $CH_2Cl_2$ (5 mL). Short column

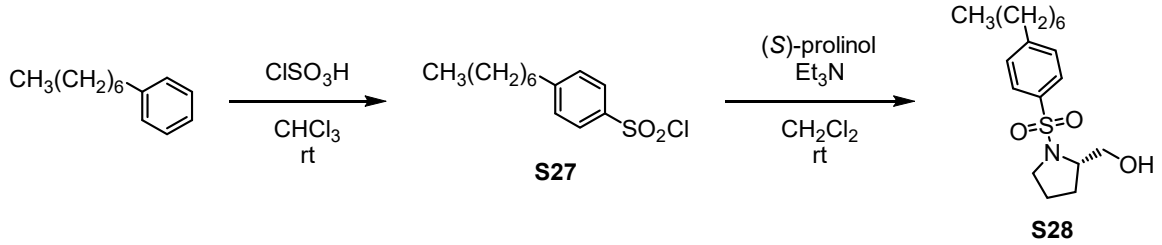
chromatography was performed with Biotage® Sfär D and 0–3% MeOH/$CHCl_3$ eluent. The *para*-isomer was separated from the *ortho*-isomer by reverse phase HPLC (COSMOSIL $5C_{18}$-AR-II, 60% MeCN/$H_2O$ eluent): colorless oil; $[\alpha]^{26}_D$ −41.4° (*c* 0.32, $CHCl_3$); IR (neat) 3491 (O–H), 1342 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.9 Hz, 3H), 1.24–1.35 (m, 6H), 1.39–1.47 (m, 1H), 1.59–1.70 (m, 4H), 1.75–1.83 (m, 1H), 2.67 (t, $J$ = 7.7 Hz, 2H), 2.77 (dd, $J$ = 6.5, 4.0 Hz, 1H), 3.24-3.29 (m, 1H), 3.43-3.48 (m, 1H), 3.60–3.72 (m, 3H), 7.33 (d, $J$ = 8.6 Hz, 2H), 7.74 (d, $J$ = 8.6 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2, 22.6, 24.4, 28.98, 29.03, 31.1, 31.7, 36.0, 50.2, 62.0, 66.0, 127.8 (2C), 129.3 (2C), 134.1, 148.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{27}NNaO_3S$, 348.1604; found, 348.1603.

**Bis({(*S*)-1-[(4-hexylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (22)**




According to **GP4**, **S26** (38.5 mg, 0.118 mmol) was converted to **22** (18.4 mg, 0.0278 mmol, 47%) by the reaction with *t*-BuOK (53.1 mg, 0.473 mmol, 4.0 equiv) in $CH_2Cl_2$ (2 mL). Column chromatography was performed with Biotage® Sfär D and 7–30% EtOAc/*n*-hexane eluent.: colorless oil; $[\alpha]^{27}_D$ −96.8° (*c* 0.66, $CHCl_3$); IR (neat) 1347 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.9 Hz, 6H), 1.24–1.34 (m, 12H), 1.51–1.64 (m, 8H), 1.82–1.92 (m, 4H), 2.65 (t, $J$ = 7.7 Hz, 4H), 3.06–3.11 (m, 2H), 3.42–3.46 (m, 2H), 3.54 (dd, $J$ = 8.9, 7.7 Hz, 2H), 3.74–3.80 (m, 4H), 4.68 (s, 2H), 7.31 (d, $J$ = 8.0 Hz, 4H), 7.75 (d, $J$ = 8.0 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.1 (2C), 22.6 (2C), 24.1 (2C), 28.9 (2C), 29.0 (2C), 31.1 (2C), 31.7 (2C), 35.9 (2C), 49.4 (2C), 59.2 (2C), 70.5 (2C), 95.6, 127.7 (4C), 129.1 (4C), 134.4 (2C), 148.5 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{35}H_{54}N_2NaO_6S_2$, 685.3316; found, 685.3314.

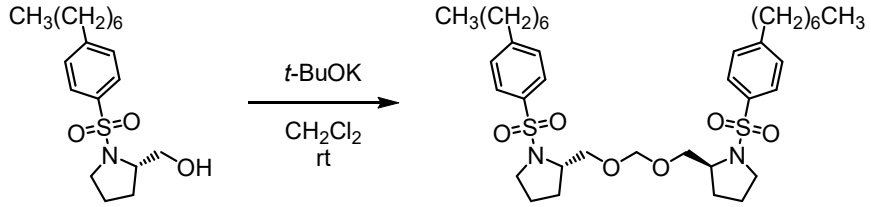
**(*S*)-{1-[(4-Heptylphenyl)sulfonyl]pyrrolidin-2-yl}methanol (S28)**




According to **GP5**, *n*-heptylbenzene (353 mg, 2.00 mmol) was converted to **S27** (crude, containing a small amount of *ortho*-substituted by-product) by the reaction with $ClSO_3H$ (1.86 mg, 16.0 mmol, 8.0 equiv) in $CHCl_3$ (4 mL). The crude product was used in next reaction without further purification. According to **GP2**, the crude **S27** (<2.00 mmol, containing *ortho*-substituted by-product) was converted to **S28** (242 mg, 0.713 mmol, 36%, containing *ca*. 6% of the *ortho*-substituted by-product) by the reaction with (*S*)-prolinol (202 mg, 2.00 mmol, 1.0 equiv) and

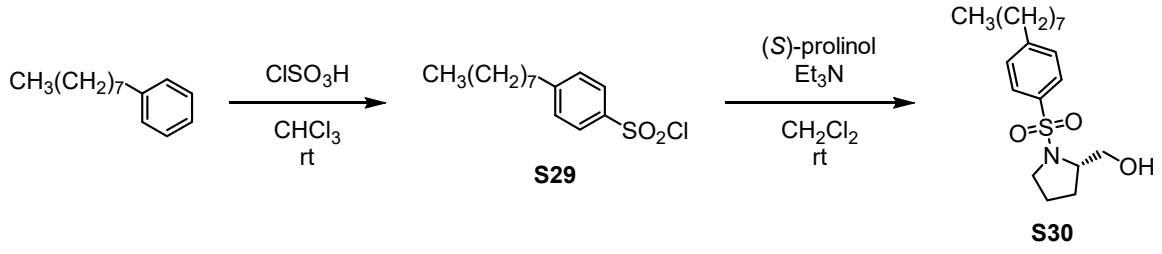
$Et_3N$ (425 mg, 4.20 mmol, 2.1 equiv) in $CH_2Cl_2$ (5 mL). Short column chromatography was performed with Biotage® Sfär D and 0–3% MeOH/$CHCl_3$ eluent. The *para*-isomer was separated from the *ortho*-isomer by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 68% MeCN/$H_2O$ eluent): colorless oil; $[\alpha]^{26}_D$ −40.6° (*c* 0.45, $CHCl_3$); IR (neat) 3553 (O–H), 1345 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 7.2 Hz, 3H), 1.24–1.32 (m, 8H), 1.40–1.47 (m, 1H), 1.61–1.70 (m, 4H), 1.75–1.81 (m, 1H), 2.67 (t, $J$ = 7.7 Hz, 2H), 2.77 (dd, $J$ = 4.0, 4.0 Hz, 1H), 3.24–3.29 (m, 1H), 3.43–3.47 (m, 1H), 3.61–3.71 (m, 3H), 7.32 (d, $J$ = 8.0 Hz, 2H), 7.74 (d, $J$ = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.2, 22.7, 24.4, 29.0, 29.1, 29.3, 31.1, 31.8, 35.9, 50.2, 61.9, 66.0, 127.7 (2C), 129.3 (2C), 134.1, 148.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{29}NNaO_3S$, 362.1760; found, 362.1761.

**Bis({(*S*)-1-[(4-heptylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (23)**




According to **GP4**, **S28** (34.7 mg, 0.102 mmol) was converted to **23** (26.9 mg, 0.0389 mmol, 38%) by the reaction with *t*-BuOK (45.8 mg, 0.408 mmol, 4.0 equiv) in $CH_2Cl_2$ (2 mL). Column chromatography was performed with Biotage® Sfär D and 7–40% EtOAc/*n*-hexane eluent: colorless oil; $[\alpha]^{25}_D$ −96.8° (*c* 0.74, $CHCl_3$); IR (neat) 1346 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.9 Hz, 6H), 1.25–1.31 (m, 16H), 1.53–1.64 (m, 8H), 1.84–1.91 (m, 4H), 2.65 (t, $J$ = 7.7 Hz, 4H), 3.07–3.12 (m, 2H), 3.42–3.46 (m, 2H), 3.54 (dd, $J$ = 8.9, 7.7 Hz, 2H), 3.74–3.80 (m, 4H), 4.68 (s, 2H), 7.30 (d, $J$ = 8.0 Hz, 4H), 7.75 (d, $J$ = 8.6 Hz, 4H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2 (2C), 22.7 (2C), 24.1 (2C), 28.9 (2C), 29.2 (2C), 29.3 (2C), 31.1 (2C), 31.8 (2C), 35.9 (2C), 49.4 (2C), 59.2 (2C), 70.5 (2C), 95.6, 127.7 (4C), 129.1 (4C), 134.4 (2C), 148.5 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{37}H_{58}N_2NaO_6S_2$, 713.3629; found, 713.3627.

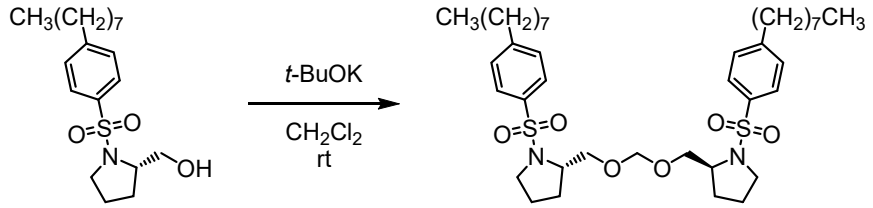
**(*S*)-{1-[(4-Octylphenyl)sulfonyl]pyrrolidin-2-yl}methanol (S30)**




According to **GP5**, *n*-octylbenzene (381 mg, 2.00 mmol) was converted to **S29** (538 mg, 1.86 mmol, 93%, containing a small amount of *ortho*-substituted by-product) by the reaction with $ClSO_3H$ (1.86 mg, 16.0 mmol, 8.0 equiv) in $CHCl_3$ (4 mL). Column chromatography was performed with Wakogel® C-200E and 20–30% $CH_2Cl_2$/*n*-hexane eluent. According to **GP2**, **S29** (538 mg, 1.86 mmol, containing *ca*. 6% of the *ortho*-substituted by-product) was converted to **S30** (658 mg, 1.86 mmol, quant, containing *ortho*-substituted by-product) by the reaction with (*S*)-

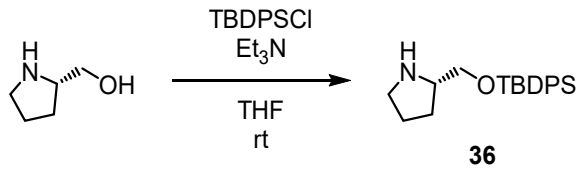
prolinol (202 mg, 2.00 mmol, 1.1 equiv) and $Et_3N$ (425 mg, 4.20 mmol, 2.3 equiv) in $CH_2Cl_2$ (5 mL). Short column chromatography was performed with Biotage® Sfär D and 0–3% MeOH/$CHCl_3$ eluent. The *para*-isomer was separated from the *ortho*-isomer by reverse phase HPLC (COSMOSIL 5$C_{18}$-AR-II, 75% MeCN/$H_2O$ eluent): colorless oil; $[\alpha]^{26}_D$ −36.9° (*c* 1.25, $CHCl_3$); IR (neat) 3428 (O–H), 1341 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.9 Hz, 3H), 1.25–1.30 (m, 10H), 1.39–1.47 (m, 1H), 1.61–1.70 (m, 4H), 1.75–1.83 (m, 1H), 2.67 (t, $J$ = 8.0 Hz, 2H), 2.77 (dd, $J$ = 7.2, 4.9 Hz, 1H), 3.24–3.29 (m, 1H), 3.43–3.48 (m, 1H), 3.61–3.72 (m, 3H), 7.33 (d, $J$ = 8.6 Hz, 2H), 7.74 (d, $J$ = 8.6 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2, 22.7, 24.4, 29.0, 29.29, 29.32, 29.5, 31.1, 31.9, 36.0, 50.2, 62.0, 66.0, 127.7 (2C), 129.2, 129.3, 134.1, 148.8; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{19}H_{31}NNaO_3S$, 376.1917; found, 376.1918.

**Bis({(*S*)-1-[(4-octylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (24)**



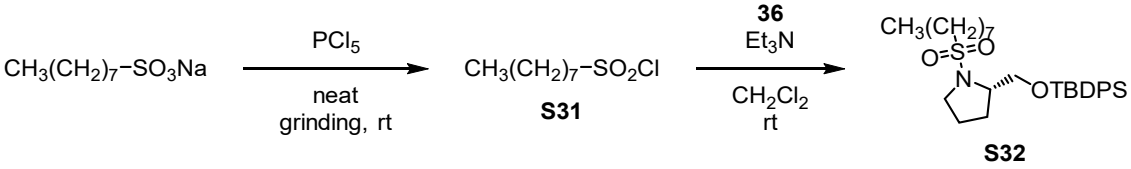

According to **GP4**, **S30** (50.7 mg, 0.143 mmol) was converted to **24** (20.7 mg, 0.0289 mmol, 40%) by the reaction with *t*-BuOK (64.4 mg, 0.574 mmol, 4.0 equiv) in $CH_2Cl_2$ (2 mL). Column chromatography was performed with Biotage® Sfär D and 7–30% EtOAc/*n*-hexane eluent: colorless oil; $[\alpha]^{27}_D$ −87.0° (*c* 0.70, $CHCl_3$); IR (neat) 1348 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 7.2 Hz, 6H), 1.25–1.30 (m, 20H), 1.52–1.62 (m, 8H), 1.84–1.92 (m, 4H), 2.65 (t, $J$ = 7.7 Hz, 4H), 3.06–3.11 (m, 2H), 3.42–3.46 (m, 2H), 3.54 (dd, $J$ = 8.6, 7.4 Hz, 2H), 3.74–3.80 (m, 4H), 4.68 (s, 2H), 7.30 (d, $J$ = 8.0 Hz, 4H), 7.75 (d, $J$ = 8.6 Hz, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.2 (2C), 22.7 (2C), 24.1 (2C), 28.9 (2C), 29.3 (2C), 29.3 (2C), 29.5 (2C), 31.1 (2C), 31.9 (2C), 35.9 (2C), 49.4 (2C), 59.2 (2C), 70.5 (2C), 95.6, 127.7 (4C), 129.1 (2C), 129.2 (2C), 134.4 (2C), 148.5 (2C); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{39}H_{62}N_2NaO_6S_2$, 741.3942; found, 741.3943.

**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}pyrrolidine (36)**



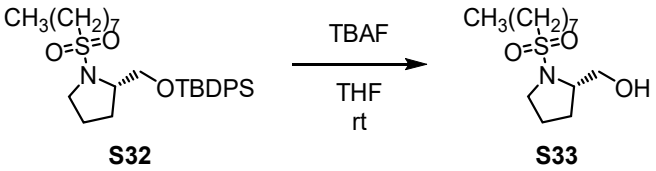

To a solution of (*S*)-prolinol (405 mg, 4.00 mmol) in anhydrous THF (15 mL) were added $Et_3N$ (1.01 g, 10.0 mmol, 2.5 equiv) and TBDPSCl (1.21 g, 4.40 mmol, 1.1 equiv). The mixture was stirred at rt for 18 h and filtered to remove $Et_3N$·HCl. The filtrate was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (CHROMATOREX® NH-DM1020, 10–30% EtOAc/*n*-hexane eluent) to afford **36** (1.11 mg, 3.27 mmol, 82%) as a colorless oil. The spectral data were in good agreement with those previously reported.[19]

**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-(octylsulfonyl)pyrrolidine (S32)**



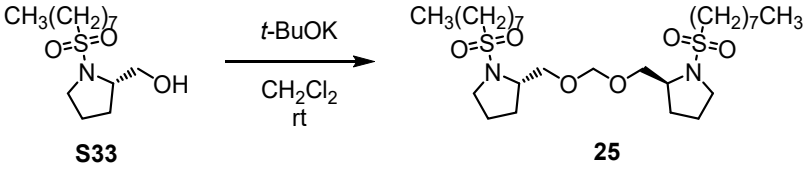

According to **GP6**, sodium 1-octanesulfonate (217 mg, 1.00 mmol) was converted to crude **S31** by the reaction with $PCl_5$ (833 mg, 4.00 mmol, 4.0 equiv). The crude product was used in next reaction without further purification. According to **GP2**, the crude **S31** (<1.00 mmol) was converted to **S32** (169 mg, 0.328 mmol, 33%) by the reaction with **36** (340 mg, 1.00 mmol) and $Et_3N$ (212 mg, 2.10 mmol, 2.1 equiv) in $CH_2Cl_2$ (3mL): colorless oil; $[\alpha]^{27}_D$ −14.8° (*c* 1.14, $CHCl_3$); IR (neat) 1336 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 9H), 1.26–1.35 (m, 10H), 1.72–2.06 (m, 6H), 2.83–2.88 (m, 2H), 3.30 (ddd, *J* = 10.7, 5.9, 3.9 Hz, 1H), 3.37–3.42 (m, 1H), 3.58 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.77 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.88–3.92 (m, 1H), 7.36–7.44 (m, 6H), 7.63–7.66 (m, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.2, 19.3, 22.7, 23.3, 24.7, 27.0 (3C), 28.6 (2C), 29.1, 29.2, 31.8, 49.0, 50.3, 60.6, 66.0, 127.8 (2C), 129.8 (2C), 133.4 (2C), 133.5 (2C), 135.68 (2C), 135.71 (2C);HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{29}H_{45}NNaO_3SSi$, 538.2782; found, 538.2781.

**(*S*)-[1-(Octylsulfonyl)pyrrolidin-2-yl]methanol (S33)**




According to **GP7**, **S32** (103 mg, 0.200 mmol) was converted to **S33** (40.7 mg, 0.147 mmol, 73%) by the reaction with TBAF (1.0 M solution in THF; 0.30 mL, 0.300 mmol, 1.5 equiv) in THF (2 mL). Column chromatography was performed with Biotage® Sfär D and 10–50% EtOAc/*n*-hexane eluent: colorless oil; $[\alpha]^{27}_D$ −25.8° (*c* 0.74, $CHCl_3$); IR (neat) 3528 (O–H), 1330 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 7.2 Hz, 3H), 1.24–1.33 (m, 8H), 1.38–1.44 (m, 2H), 1.78–1.89 (m, 4H), 1.93–1.99 (m, 1H), 2.02-2.08 (m, 1H), 2.59 (t, *J* = 6.0 Hz, 1H), 2.97 (td, *J* = 8.2, 1.9 Hz, 2H), 3.37–3.47 (m, 2H), 3.56–3.67 (m, 2H), 3.83–3.87 (m, 1H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2, 22.7, 23.2, 25.0, 28.6, 29.1, 29.16, 29.24, 31.8, 49.2, 49.6, 61.7, 66.0; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{13}H_{27}NNaO_3S$, 300.1604; found, 300.1604.

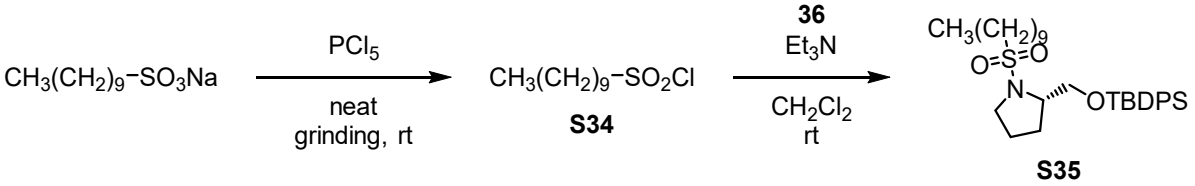
**Bis{[(*S*)-1-(octylsulfonyl)pyrrolidin-2-yl]methoxy}methane (25)**




According to **GP4**, **S33** (25.0 mg, 0.0901 mmol) was converted to **25** (17.9 mg, 0.0315 mmol, 35%) by the reaction with *t*-BuOK (40.4 mg, 0.360 mmol, 4.0 equiv) in $CH_2Cl_2$ (1 mL). Column chromatography was performed with Biotage® Sfär D and 7–30% EtOAc/*n*-hexane eluent: white solid; $[\alpha]^{25}_D$ −40.2° (*c* 0.32, $CHCl_3$); IR (neat) 1340

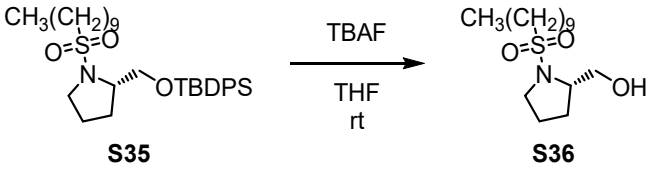
(S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 7.2 Hz, 6H), 1.19–1.29 (m, 16H), 1.37–1.43 (m, 4H), 1.76–2.02 (m, 12H), 2.95 (t, $J$ = 8.0 Hz, 4H), 3.33–3.40 (m, 4H), 3.48 (dd, $J$ = 9.7, 7.4 Hz, 2H), 3.64 (dd, $J$ = 10.0, 4.6 Hz, 2H), 3.92–3.96 (m, 2H), 4.67 (s, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.2 (2C), 22.7 (2C), 23.3 (2C), 24.8 (2C), 28.6 (2C), 29.1 (2C), 29.2 (4C), 31.8 (2C), 49.0 (2C), 49.8 (2C), 58.8 (2C), 70.4 (2C), 95.7; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{27}H_{54}N_2NaO_6S_2$, 589.3316; found, 589.3314.

**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-(decylsulfonyl)pyrrolidine (S35)**



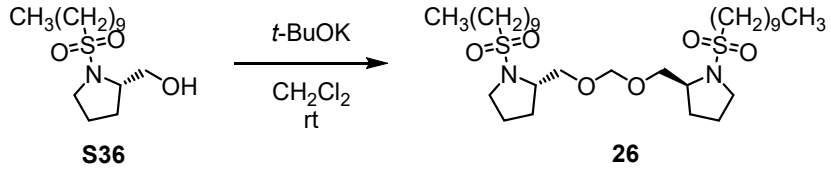

According to **GP6**, sodium 1-decanesulfonate (489 mg, 2.00 mmol) was converted to crude **S34** (crude) by the reaction with $PCl_5$ (1.67 g, 8.00 mmol, 4.0 equiv). According to **GP2**, the crude **S34** (<2.00 mmol) was converted to **S35** (593 mg, 1.09 mmol, 61%) by the reaction with **36** (611 mg, 1.80 mmol, 1.0 equiv) and $Et_3N$ (382 mg, 3.80 mmol, 2.1 equiv) in $CH_2Cl_2$ (5 mL). Column chromatography was performed with Wakogel® C-200E and 10–15% $Et_2O$/*n*-hexane eluent: colorless oil; $[\alpha]^{27}_D$ −19.1° (*c* 1.34, $CHCl_3$); IR (neat) 1334 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.06 (s, 9H), 1.25–1.35 (m, 14H), 1.70–2.07 (m, 6H), 2.81–2.91 (m, 2H), 3.28–3.32 (m, 1H), 3.36–3.41 (m, 1H), 3.58 (dd, $J$ = 9.9, 7.3 Hz, 1H), 3.77 (dd, $J$ = 10.0, 3.7 Hz, 1H), 3.88–3.93 (m, 1H), 7.36–7.44 (m, 6H), 7.63–7.66 (m, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.2, 19.3, 22.8, 23.3, 24.7, 27.0 (3C), 28.6 (2C), 29.2 (2C), 29.4, 29.6, 32.0, 49.0, 50.3, 60.6, 66.0, 127.8 (4C), 129.8 (4C), 133.5 (2C), 135.7 (2C); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{31}H_{49}NNaO_3SSi$, 566.3095; found, 566.3095.

**(*S*)-{1-(Decylsulfonyl)pyrrolidin-2-yl}methanol (S36)**




According to **GP7**, **S35** (326 mg, 0.600 mmol) was converted to **S36** (183 mg, 0.600 mmol, quant) by the reaction with TBAF (1.0 M solution in THF; 0.90 mL, 0.900 mmol, 1.5 equiv) in THF (4 mL). Column chromatography was performed with Biotage® Sfär D and 0–15% MeOH/$CHCl_3$ eluent: white solid; mp 28−31 °C; $[\alpha]^{26}_D$ −21.5° (*c* 1.00, $CHCl_3$); IR (neat) 3524 (O–H), 1331 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.9 Hz, 3H), 1.22–1.30 (m, 12H), 1.38–1.44 (m, 2H), 1.78–1.89 (m, 4H), 1.91–1.99 (m, 1H), 2.02–2.09 (m, 1H), 2.61 (dd, $J$ = 6.9, 5.7 Hz, 1H), 2.92–2.99 (m, 2H), 3.36–3.46 (m, 2H), 3.56–3.66 (m, 2H), 3.82–3.87 (m, 1H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2, 22.8, 23.2, 25.0, 28.6, 29.20, 29.23, 29.3, 29.4, 29.6, 31.9, 49.2, 49.6, 61.7, 66.0; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{15}H_{31}NNaO_3S$, 328.1917; found, 328.1918.

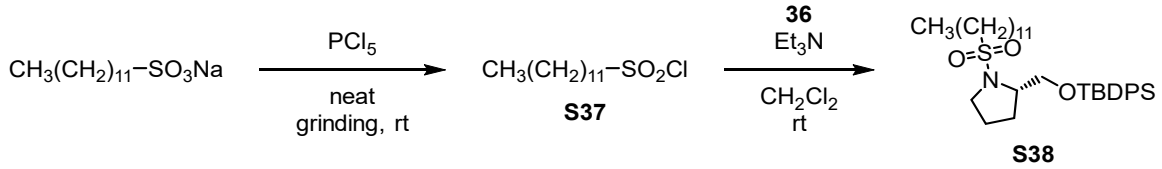
**Bis{[(*S*)-1-(octylsulfonyl)pyrrolidin-2-yl]methoxy}methane (26)**




**S36** **26**

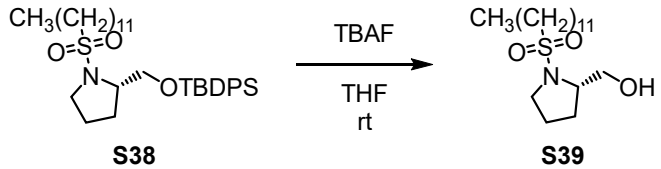
According to **GP4**, **S36** (61.1 mg, 0.200 mmol) was converted to **26** (42.4 mg, 0.0681 mmol, 68%) by the reaction with *t*-BuOK (67.3 mg, 0.800 mmol, 4.0 equiv) in $CH_2Cl_2$ (1 mL). Column chromatography was performed with Wakogel® C-300E and 20–30% EtOAc/*n*-hexane eluent: white solid; mp 65−69 °C; $[\alpha]^{25}_D$ −33.9° (*c* 1.21, $CHCl_3$); IR (neat) 1339 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.9 Hz, 6H), 1.25–1.29 (m, 24H), 1.36–1.42 (m, 4H), 1.77–2.02 (m, 12H), 2.95 (t, $J$ = 8.0 Hz, 4H), 3.34–3.37 (m, 4H), 3.48 (dd, $J$ = 9.7, 7.4 Hz, 2H), 3.64 (dd, $J$ = 10.0, 4.8 Hz, 2H), 3.92–3.96 (m, 2H), 4.67 (s, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2 (2C), 22.8 (2C), 23.3 (2C), 24.8 (2C), 28.6 (2C), 29.2 (2C), 29.3 (2C), 29.36 (2C), 29.43 (2C), 29.6 (2C), 32.0 (2C), 49.0 (2C), 49.8 (2C), 58.8 (2C), 70.4 (2C), 95.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{62}N_2NaO_6S_2$, 645.3942; found, 645.3944.

**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-(dodecylsulfonyl)pyrrolidine (S38)**




According to **GP6**, sodium 1-dodecanesulfonate (273 mg, 1.00 mmol) was converted to crude **S37** by the reaction with $PCl_5$ (833 mg, 4.00 mmol, 4.0 equiv). According to **GP2**, the crude **S37** (<1.00 mmol) was converted to **S38** (83.3 mg, 0.146 mmol, 15%) by the reaction with **36** (340 mg, 1.00 mmol, 1.0 equiv) and $Et_3N$ (212 mg, 2.10 mmol, 2.1 equiv) in $CH_2Cl_2$ (3 mL). Column chromatography was performed with Biotage® Sfär D and 10–100% $CHCl_3$/*n*-hexane eluent: colorless oil; $[\alpha]^{27}_D$ −19.2° (*c* 0.80, $CHCl_3$); IR (neat) 1337 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 7.2 Hz, 3H), 1.06 (s, 9H), 1.25–1.35 (m, 18H), 1.70-2.07 (m, 6H), 2.83-2.89 (m, 2H), 3.28-3.32 (m, 1H), 3.37–3.42 (m, 1H), 3.58 (dd, $J$ = 10.0, 7.2 Hz, 1H), 3.77 (dd, $J$ = 10.0, 3.7 Hz, 1H), 3.89–3.93 (m, 1H), 7.36–7.43 (m, 6H), 7.63–7.66 (m, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.2, 19.3, 22.8, 23.3, 24.7, 27.0 (3C), 28.6 (2C), 29.2, 29.4 (2C), 29.6, 29.7 (2C), 32.0, 49.0, 50.3, 60.6, 66.0, 127.8 (2C), 129.8 (2C), 133.4 (2C), 133.5 (2C), 135.7 (2C), 135.7 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{33}H_{53}NNaO_3SSi$, 594.3408; found, 594.3410.

**(*S*)-[1-(Dodecylsulfonyl)pyrrolidin-2-yl]methanol (S39)**

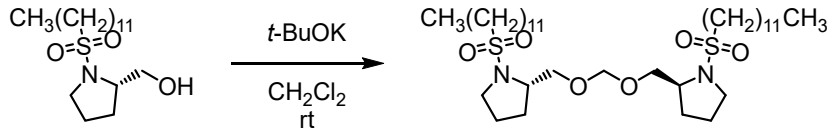



**S38** **S39**

According to **GP7**, **S38** (57.2 mg, 0.100 mmol) was converted to **S39** (23.8 mg, 0.0714 mmol, 71%) by the

reaction with TBAF (1.0 M solution in THF; 0.15 mL, 0.150 mmol, 1.5 equiv) in THF (1 mL). Column chromatography was performed with Biotage® Sfär D and 10–50% EtOAc/*n*-hexane eluent: white solid; mp 43−45 °C; $[\alpha]^{26}_{D}$ −22.3° (*c* 1.09, $CHCl_3$); IR (neat) 3489 (O–H), 1331 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 7.2 Hz, 3H), 1.19–1.30 (m, 16H), 1.38–1.44 (m, 2H), 1.78–1.88 (m, 4H), 1.93–1.98 (m, 1H), 2.03–2.08 (m, 1H), 2.56 (dd, *J* = 7.4, 5.2 Hz, 1H), 2.95–2.99 (m, 2H), 3.37–3.48 (m, 2H), 3.57–3.67 (m, 2H), 3.833.87 (m, 1H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2, 22.8, 23.2, 25.0, 28.6, 29.21, 29.25, 29.40, 29.43, 29.6, 29.7 (2C), 32.0, 49.2, 49.6, 61.7, 66.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{35}NO_3S$, 334.2410; found, 334.2409.

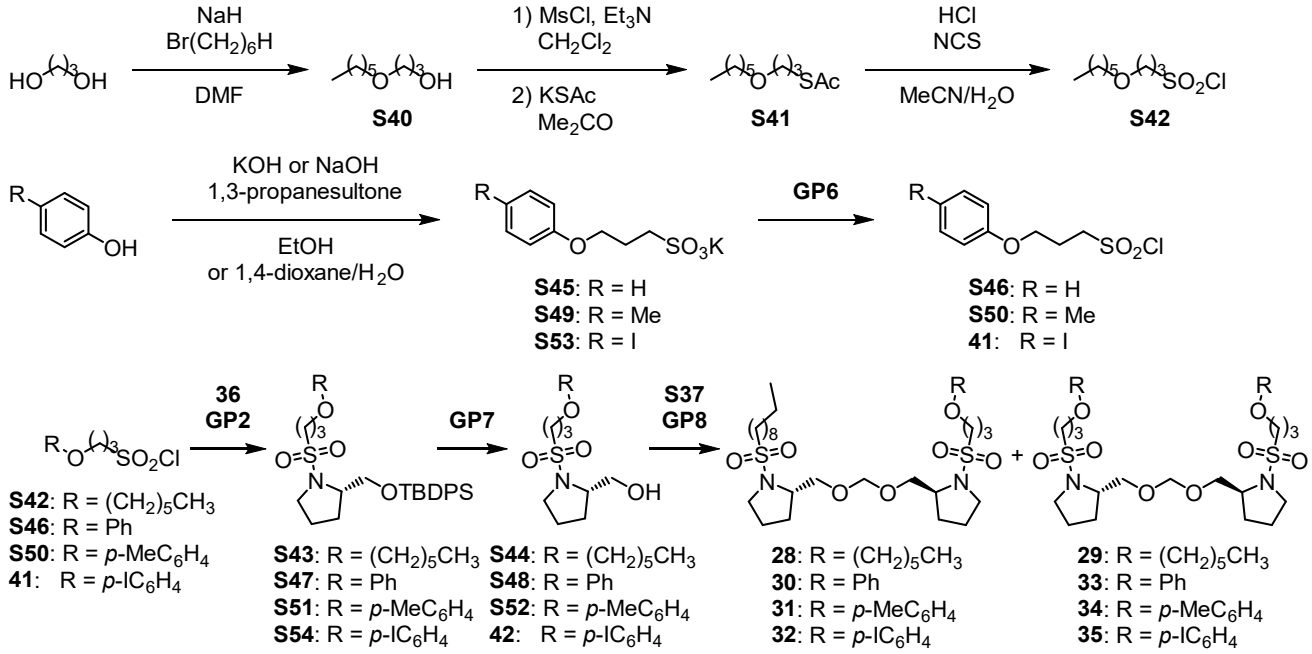
**Bis{[(*S*)-1-(Dodecylsulfonyl)pyrrolidin-2-yl]methoxy}methane (27)**




**S39** **27**

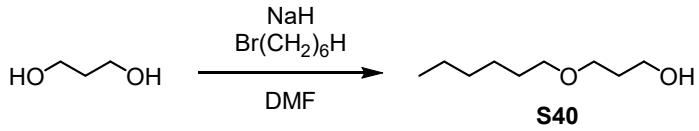
According to **GP4**, **S39** (20.0 mg, 0.0600 mmol) was converted to **27** (8.00 mg, 0.0118 mmol, 20%) by the reaction with *t*-BuOK (26.9 mg, 0.240 mmol, 4.0 equiv) in $CH_2Cl_2$ (1 mL). Column chromatography was performed with Biotage® Sfär D and 7–30% EtOAc/*n*-hexane eluent: a white solid; mp 75−78 °C; $[\alpha]^{27}_{D}$ −35.3° (*c* 0.27, $CHCl_3$); IR (neat) 1340 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 6.9 Hz, 6H), 1.19–1.29 (m, 32H), 1.37–1.42 (m, 4H), 1.76–2.02 (m, 12H), 2.95 (t, *J* = 7.7 Hz, 4H), 3.34–3.39 (m, 4H), 3.48 (dd, *J* = 9.6, 7.6 Hz, 2H), 3.64 (dd, *J* = 9.8, 4.8 Hz, 2H), 3.91–3.96 (m, 2H), 4.67 (s, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.2 (2C), 22.8 (2C), 23.3 (2C), 24.8 (2C), 28.6 (2C), 29.2 (2C), 29.3 (2C), 29.4 (4C), 29.6 (2C), 29.7 (4C), 32.0 (2C), 49.0 (2C), 49.8 (2C), 58.8 (2C), 70.4 (2C), 95.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{35}H_{70}N_2NaO_6S_2$, 701.4568; found, 701.4570.

**Schemes of Synthesis (28-35)**



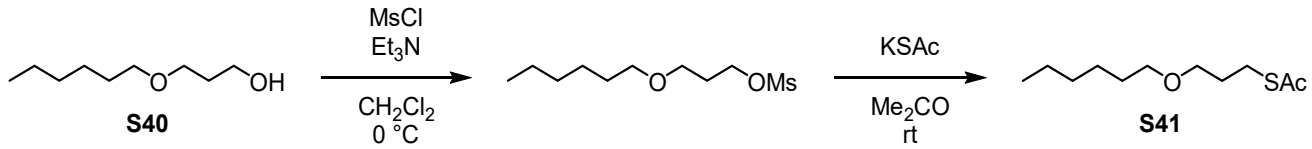

**Compounds (28-35)**

**3-(Hexyloxy)propan-1-ol (S40)**




NaH (60% dispersion in mineral oil; 240 mg, 6.00 mmol, 1.2 equiv) in a flask was washed with hexane under $N_2$ atmosphere, and cooled on ice after removal of solvent. To the washed NaH were added anhydrous DMF (10 mL) and 1,3-propanediol (381 mg, 5.00 mmol). The mixture was stirred at rt for 30 min and then cooled on ice. To the mixture was added 1-bromohexane (990 mg, 6.00 mmol, 1.2 equiv). The mixture was stirred at rt for 21 h, diluted with water, and extracted with $Et_2O$. The extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Wakogel® C-200E, 10–20% EtOAc/*n*-hexane eluent) to afford **S40** (436 mg, 2.72 mmol, 54%) as a colorless liquid: IR (neat) 3420 (O–H); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 7.2 Hz, 3H), 1.23–1.34 (m, 6H), 1.52–1.58 (m, 2H), 1.79–1.84 (m, 2H), 2.59 (s, 1H), 3.41 (t, $J$ = 6.6 Hz, 2H), 3.60 (t, $J$ = 5.7 Hz, 2H), 3.75–3.78 (m, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 14.1, 22.7, 25.9, 29.7, 31.7, 32.0, 62.6, 70.6, 71.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_9H_{20}NaO_2$, 183.1356; found, 183.1359.

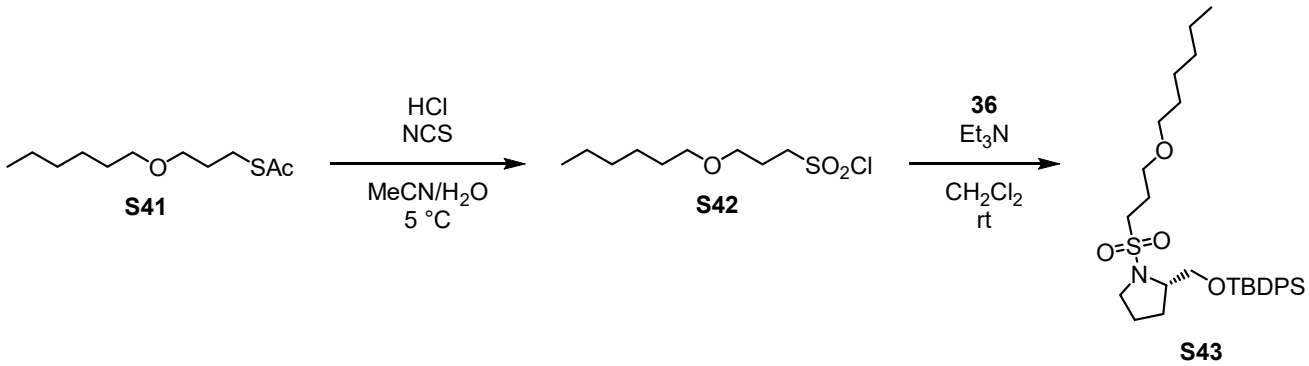
***S*-[3-(Hexyloxy)propyl] Ethanethioate (S41)**




To a mixture of **S40** (320 mg, 2.00 mmol) and $Et_3N$ (405 mg, 4.00 mmol, 2.0 equiv) in anhydrous $CH_2Cl_2$ (5

mL) was added MsCl (458 mg, 4.0 equiv 2.0 equiv) at −10 °C. The mixture was stirred at 0 °C for 1 h, diluted with 2 M aqueous HCl, diluted with saturated aqueous $NaHCO_3$, and extracted with $CH_2Cl_2$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. To the crude mesylate were added anhydrous $Me_2CO$ (10 mL) and KSAc (274 mg, 2.40 mmol, 1.2 equiv). The mixture was stirred at rt for 21 h and filtered. The filtrate was concentrated *in vacuo*, and the residue was diluted with $CH_2Cl_2$ and brine, extracted with $CH_2Cl_2$, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Biotage® Sfär D, 2–20% $CHCl_3$/*n*-hexane eluent) to afford **S41** (304 mg, 1.39 mmol, 70%) as a yellow oil; IR (neat) 1695 (C=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.9 Hz, 3H), 1.25–1.33 (m, 6H), 1.53 (tt, $J$ = 7.3, 7.3 Hz, 2H), 1.80–1.86 (m, 2H), 2.31 (s, 3H), 2.94 (t, $J$ = 7.2 Hz, 2H), 3.38 (t, $J$ = 6.6 Hz, 2H), 3.44 (t, $J$ = 6.3 Hz, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.1, 22.7, 25.9, 26.2, 29.7 (2C), 30.7, 31.8, 69.1, 71.2, 196.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{22}NaO_2S$, 241.1233; found, 241.1230.

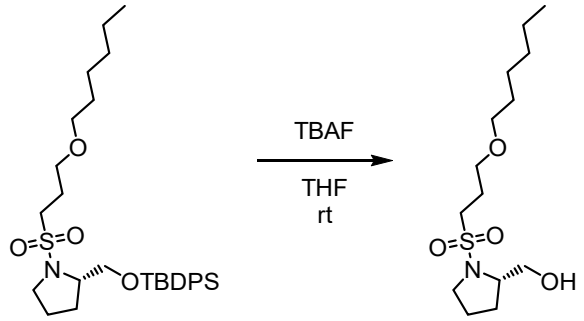
**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-{[3-(hexyloxy)propyl]sulfonyl}pyrrolidine (S43)**




To a solution of *N*-chlorosuccinimide (267 mg, 2.00 mmol, 4.0 equiv) in 2 M aqueous HCl (0.5 mL) and MeCN (2.5 mL) was added a solution of **S41** (109 mg, 0.500 mmol) in MeCN (0.5 mL) at 5 °C. The mixture was stirred at 5 °C for 20 min, diluted with water, and extracted with EtOAc. The extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Biotage® Sfär D, 2–20% EtOAc/*n*-hexane eluent) to afford **S42** (110 mg, 0.451 mmol, 90%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.24–1.35 (m, 6H), 1.54 (tt, $J$ = 7.3, 7.3 Hz, 2H), 2.25–2.31 (m, 2H), 3.41 (t, $J$ = 6.6 Hz, 2H), 3.56 (t, $J$ = 5.7 Hz, 2H), 3.78–3.81 (m, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.1, 22.7, 25.1, 25.9, 29.6, 31.7, 62.9, 67.1, 71.4.

According to **GP2**, **36** (102 mg, 0.300 mmol) was converted to **S43** (122 mg, 0.224 mmol, 75%) by the reaction with **S42** (80.1 mg, 0.330 mmol, 1.1 equiv) and $Et_3N$ (45.5 mg, 0.450 mmol, 1.5 equiv) in $CH_2Cl_2$ (1.5 mL): colorless oil; $[\alpha]^{27}_D$ −22.2° (*c* 1.14, $CHCl_3$); IR (neat) 1335 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.06 (s, 9H), 1.24–1.33 (m, 6H), 1.52 (dt, $J$ = 14.7, 6.7 Hz, 2H), 1.83–2.06 (m, 6H), 2.97–3.01 (m, 2H), 3.29–3.33 (m, 1H), 3.35–3.39 (m, 3H), 3.42–3.47 (m, 2H), 3.57 (dd, $J$ = 10.3, 6.9 Hz, 1H), 3.77 (dd, $J$ = 10.3, 4.0 Hz, 1H), 3.88–3.92 (m, 1H), 7.36–7.44 (m, 6H), 7.63–7.66 (m, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.1, 19.3, 22.7, 23.9, 24.7, 25.9, 27.0 (3C), 28.6, 29.7, 31.8, 47.1, 49.0, 60.6, 66.0, 68.5, 71.1, 127.8 (2C), 129.8 (2C), 133.4 (2C), 133.5 (2C), 135.68 (2C), 135.71 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{47}NNaO_4SSi$, 568.2887; found, 568.2887.

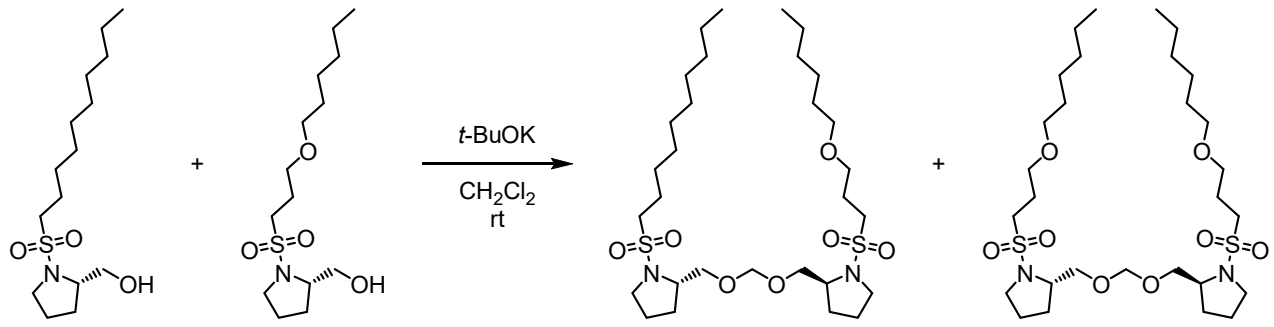
**(*S*)-{1-[(3-(Hexyloxy)propyl)sulfonyl]pyrrolidin-2-yl}methanol (S44)**




**S43** **S44**

According to **GP7**, **S43** (71.6 mg, 0.131 mmol) was converted to **S44** (34.3 mg, 0.112 mmol, 85%) by the reaction with TBAF (1.0 M solution in THF; 0.3 mL, 0.300 mmol, 2.3 equiv) in THF (1 mL). Column chromatography was performed with Biotage® Sfär D and 6–60% EtOAc/*n*-hexane eluent: colorless oil; $[\alpha]^{27}_{D}$ −34.3° (*c* 0.18 $CHCl_3$); IR (neat) 3526 (O–H), 1329 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, *J* = 6.9 Hz, 3H), 1.23–1.34 (m, 6H), 1.52–1.57 (m, 2H), 1.79–1.88 (m, 2H), 1.90–1.99 (m, 1H), 2.03–2.11 (m, 3H), 2.70 (t, *J* = 6.0 Hz, 1H), 3.09–3.12 (m, 2H), 3.36–3.42 (m, 3H), 3.45–3.54 (m, 3H), 3.55–3.60 (m, 1H), 3.64–3.68 (m, 1H), 3.85–3.89 (m, 1H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.1, 22.7, 23.9, 25.0, 25.9, 29.2, 29.6, 31.7, 46.7, 49.7, 61.7, 65.8, 68.4, 71.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{29}NNaO_4S$, 330.1710; found, 330.1709.

**(*S*)-1-(Decylsulfonyl)-2-[({[(*S*)-1-{[3-(hexyloxy)propyl]sulfonyl}pyrrolidin-2-yl]methoxy}methoxy)methyl]-pyrrolidine (28) and Bis{[(*S*)-1-{[3-(hexyloxy)propyl]sulfonyl}pyrrolidin-2-yl]methoxy}methane (29)**




**S36** **S44** **28** **29**

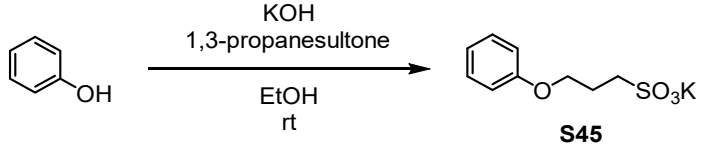
According to **GP8**, **S36** (17.0 mg, 0.0557 mmol) and **S44** (29.2 mg, 0.0950 mmol, 1.7 equiv) was converted to **28** (17.2 mg, 0.0274 mmol, 36%) and **29** (15.5 mg, 0.248 mmol, 33%) by the reaction with *t*-BuOK (75.0 mg, 0.668 mmol, 12.0 equiv) in anhydrous $CH_2Cl_2$ (1 mL).

Compound **28**: white solid; mp 39−41 °C; $[\alpha]^{27}_{D}$ −35.2° (*c* 0.52, $CHCl_3$); IR (neat) 1334 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (td, *J* = 7.0, 4.4 Hz, 6H), 1.25–1.34 (m, 18H), 1.36–1.42 (m, 2H), 1.51–1.56 (m, 2H), 1.75–2.09 (m, 12H), 2.95 (t, *J* = 8.0 Hz, 2H), 3.07 (t, *J* = 7.7 Hz, 2H), 3.34–3.40 (m, 6H), 3.46–3.51 (m, 4H), 3.62–3.65 (m, 2H), 3.92–3.95 (m, 2H), 4.66 (s, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.1, 14.2, 22.7, 22.8, 23.3, 24.0, 24.8 (2C), 25.9, 28.6, 29.17 (2C), 29.24, 29.3, 29.4, 29.6, 29.7, 31.8, 31.9, 46.9, 49.0 (2C), 49.8, 58.8, 58.9, 68.5, 70.36, 70.38, 71.2, 95.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{60}N_2NaO_7S_2$, 647.3734; found, 647.3735.

Compound **29**: colorless oil; $[\alpha]^{25}_{D}$ −33.3° (*c* 0.45, $CHCl_3$); IR (neat) 1332 (S=O); $^1$H NMR (500 MHz, $CDCl_3$)

$\delta$ 0.86–0.91 (m, 6H), 1.23–1.36 (m, 12H), 1.51–1.56 (m, 4H), 1.85–2.11 (m, 12H), 3.07 (t, $J$ = 7.7 Hz, 4H), 3.33–3.42 (m, 8H), 3.47–3.54 (m, 6H), 3.63 (dd, $J$ = 10.0, 4.6 Hz, 2H), 3.92–3.96 (m, 2H), 4.66 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 14.1 (2C), 22.7 (2C), 24.0 (2C), 24.8 (2C), 25.9 (2C), 29.2 (2C), 29.7 (2C), 31.8 (2C), 46.9 (2C), 49.0 (2C), 58.9 (2C), 68.5 (2C), 70.3 (2C), 71.2 (2C), 95.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{58}N_2NaO_8S_2$, 649.3527; found, 649.3526.

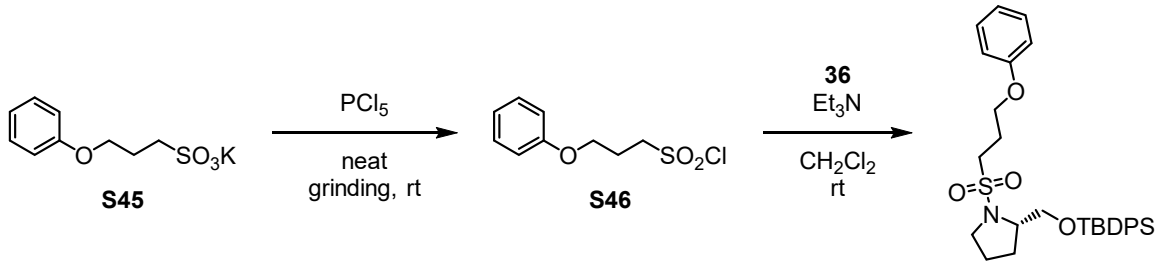
**Potassium 3-Phenoxypropane-1-sulfonate (S45)**




**S45**

To a solution of phenol (188 mg, 2.00 mmol) in anhydrous EtOH (5 mL) were added KOH (135 mg, 2.40 mmol, 1.2 equiv) and 1,3-propanesultone (269 mg, 2.20 mmol, 1.1 mmol). The mixture was stirred at rt for 17 h and filtered to collect solid materials. The residue was washed with EtOH and dried on air to afford **S45** (499 mg, 1.96 mmol, 98%) as a white solid: mp 255−256 °C; IR (neat) 1190 (S=O); $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 2.20–2.25 (m, 2H), 3.09–3.12 (m, 2H), 4.20 (t, $J$ = 6.3 Hz, 2H), 7.05–7.09 (m, 3H), 7.40 (t, $J$ = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $D_2O$) $\delta$ 27.1, 50.7, 69.5, 117.8 (2C), 124.4, 132.7 (2C), 160.9; HRMS (ESI-TOF) *m/z*: $[M - K]^-$ calcd for $C_9H_{11}O_4S$, 215.0384; found, 215.0384.

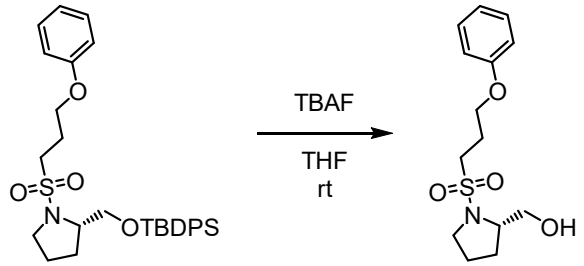
**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-[(3-phenoxypropyl)sulfonyl]pyrrolidine (S47)**




**S45** **S46** **S47**

According to **GP6**, **S45** (137 mg, 0.573 mmol) was converted to **S46** (crude) by the reaction with $PCl_5$ (477 mg, 2.29 mmol, 4.0 equiv). The crude product was used in next reaction without further purification. According to **GP2**, **36** (177 mg, 0.521 mmol) was converted to **S47** (177 mg, 0.329 mmol, 63%) by the reaction with the crude **S46** (<0.573 mmol, 1.1 equiv) and $Et_3N$ (116 mg, 1.15 mmol, 2.2 equiv) in $CH_2Cl_2$ (1 mL): white solid; mp 51−56 °C; $[\alpha]^{25}_D$ −25.0° (*c* 0.85, $CHCl_3$); IR (neat) 1331 (S=O); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.06 (s, 9H), 1.84–1.98 (m, 3H), 2.04–2.07 (m, 1H), 2.21–2.27 (m, 2H), 3.08–3.11 (m, 2H), 3.31–3.35 (m, 1H), 3.38–3.43 (m, 1H), 3.59 (dd, $J$ = 10.3, 7.4 Hz, 1H), 3.78 (dd, $J$ = 10.0, 3.7 Hz, 1H), 3.91–3.95 (m, 1H), 3.97–4.03 (m, 2H), 6.85 (dd, $J$ = 8.6, 1.1 Hz, 2H), 6.94–6.97 (m, 1H), 7.24–7.29 (m, 2H), 7.35–7.43 (m, 6H), 7.63–7.66 (m, 4H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 19.3, 23.7, 24.7, 27.0 (3C), 28.6, 47.1, 49.0, 60.6, 65.7, 66.0, 114.6 (2C), 121.1, 127.8 (2C), 129.6 (2C), 129.9 (2C), 133.36 (2C), 133.42 (2C), 135.69 (2C), 135.72 (2C), 158.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{39}NNaO_4SSi$, 560.2261; found, 560.2260.

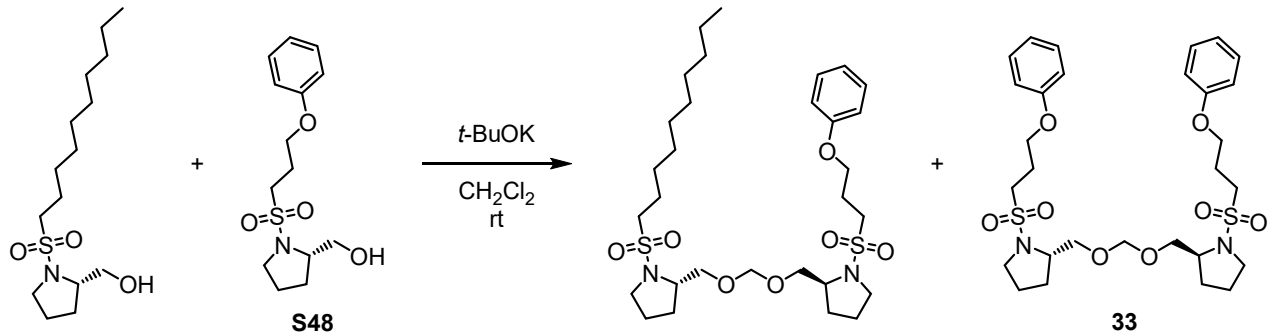
**(*S*)-{1-[(3-Phenoxypropyl)sulfonyl]pyrrolidin-2-yl}methanol (S48)**




**S47** **S48**

According to **GP7**, **S47** (129 mg, 0.240 mmol) was converted to **S48** (58.1 mg, 0.194 mmol, 81%) by the reaction with TBAF (1.0 M solution in THF; 0.36 mL, 0.36 mmol, 1.5 equiv) in THF (1 mL): colorless oil; $[\alpha]^{26}_{D}$ −26.3° (*c* 0.80, $CHCl_3$); IR (neat) 3523 (O−H), 1325 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.79–1.90 (m, 2H), 1.91–1.99 (m, 1H), 2.02–2.09 (m, 1H), 2.30–2.35 (m, 2H), 2.61 (br s, 1H), 3.17–3.26 (m, 2H), 3.37–3.42 (m, 1H), 3.45–3.50 (m, 1H), 3.57–3.61 (m, 1H), 3.64–3.68 (m, 1H), 3.86–3.90 (m, 1H), 4.09 (t, *J* = 6.0 Hz, 2H), 6.88–6.89 (m, 2H), 6.96 (t, *J* = 7.2 Hz, 1H), 7.26–7.30 (m, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 23.6, 25.0, 29.1, 46.3, 49.6, 61.7, 65.6, 65.8, 114.5 (2C), 121.3, 129.7 (2C), 158.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{21}NNaO_4S$, 322.1084; found, 322.1083.

**(*S*)-1-(Decylsulfonyl)-2-{[({(*S*)-1-[(3-phenoxypropyl)sulfonyl]pyrrolidin-2-yl}methoxy)methoxy]methyl}pyrrolidine (30) and Bis({(*S*)-1-[(3-phenoxypropyl)sulfonyl]pyrrolidin-2-yl}methoxy)methane (33)**




**S36** **S48** **30** **33**

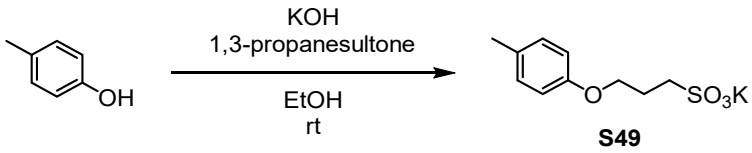
According to **GP8**, **S36** (15.7 mg, 0.0500 mmol) and **S48** (29.9 mg, 0.100 mmol, 2.0 equiv) was converted to **30** (13.9 mg, 0.0225 mmol, 30%) and **33** (12.8 mg, 0.0209 mmol, 28%) by the reaction of *t*-BuOK (67.3 mg, 0.600 mmol, 12 equiv) in anhydrous $CH_2Cl_2$ (1 mL).

Compound **30**: white solid; mp 34−38 °C; $[\alpha]^{26}_{D}$ −37.2° (*c* 0.37, $CHCl_3$); IR (neat) 1332 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 6.9 Hz, 3H), 1.25–1.29 (m, 12H), 1.38 (q, *J* = 7.3 Hz, 2H), 1.75–2.03 (m, 10H), 2.27–2.33 (m, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 3.20 (t, *J* = 7.4 Hz, 2H), 3.32–3.44 (m, 4H), 3.45–3.52 (m, 2H), 3.64 (dd, *J* = 10.0, 4.6 Hz, 2H), 3.92–3.96 (m, 1H), 3.97–4.00 (m, 1H), 4.08 (t, *J* = 5.7 Hz, 2H), 4.67 (s, 2H), 6.88 (d, *J* = 7.7 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 7.26–7.29 (m, 2H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 14.2, 22.8, 23.3, 23.7, 24.7, 24.8, 28.6, 29.17 (2C), 29.24, 29.3, 29.4, 29.6, 31.9, 46.9, 48.9, 49.0, 49.8, 58.8, 58.9, 65.7, 70.3, 70.4, 95.7, 114.5 (2C), 121.2, 129.6 (2C), 158.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{52}N_2NaO_7S_2$, 639.3108; found,

639.3110.

Compound **33**: white solid; mp 91−92 °C; $[\alpha]^{26}_{D}$ −38.0° (*c* 0.47, $CHCl_3$); IR (neat) 1331 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.86–2.02 (m, 8H), 2.26–2.32 (m, 4H), 3.17–3.20 (m, 4H), 3.34–3.42 (m, 4H), 3.49 (dd, *J* = 9.7, 6.9 Hz, 2H), 3.65 (dd, *J* = 9.7, 4.8 Hz, 2H), 3.94–3.99 (m, 2H), 4.07 (t, *J* = 5.7 Hz, 4H), 4.67 (s, 2H), 6.87–6.89 (m, 4H), 6.95 (t, *J* = 7.2 Hz, 2H), 7.27–7.30 (m, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 23.7 (2C), 24.8 (2C), 29.1 (2C), 46.9 (2C), 49.0 (2C), 58.9 (2C), 65.7 (2C), 70.3 (2C), 95.7, 114.5 (4C), 121.2 (2C), 129.6 (4C), 158.5 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{42}N_2NaO_8S_2$, 633.2275; found, 633.2276.

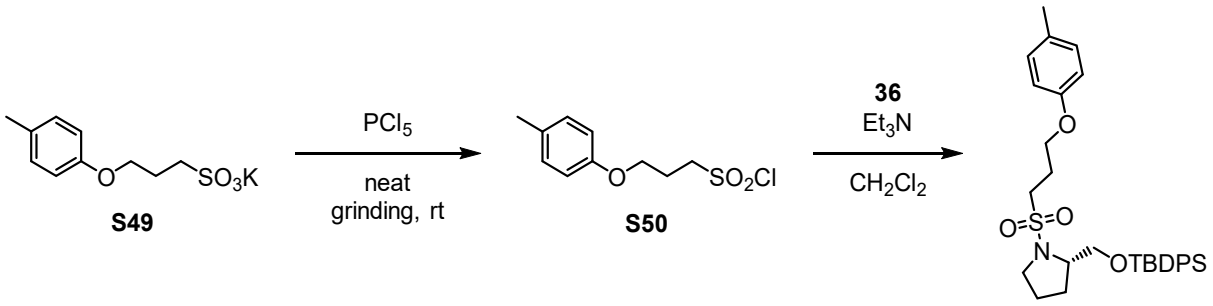
**Potassium 3-(*p*-Tolyloxy)propane-1-sulfonate (S49)**



**S49**

To a solution of *p*-cresol (216 mg, 2.00 mmol) in anhydrous EtOH (5 mL) were added KOH (135 mg, 2.40 mmol, 1.2 equiv) and 1,3-propanesultone (269 mg, 2.20 mmol, 1.1 mmol). The mixture was stirred at rt for 17 h and filtered to collect solid materials. The residue was washed with EtOH and dried on air to afford **S49** (503 mg, <1.87 mmol, <94%; containing some impurities) as a white solid; mp 254−255 °C; IR (neat) 1190 (S=O); $^1$H NMR (500 MHz, $D_2O$) $\delta$ 2.16–2.22 (m, 2H), 2.28 (s, 3H), 3.06–3.10 (m, 2H), 4.15 (t, *J* = 6.3 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $D_2O$) $\delta$ 22.3, 27.1, 50.7, 69.7, 117.9 (2C), 133.0 (2C), 134.2, 158.6; HRMS (ESI-TOF) *m/z*: $[M - K]^-$ calcd for $C_{10}H_{13}O_4S$, 229.0540; found, 229.0541.

**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-{[3-(*p*-tolyloxy)propyl]sulfonyl}pyrrolidine (S51)**

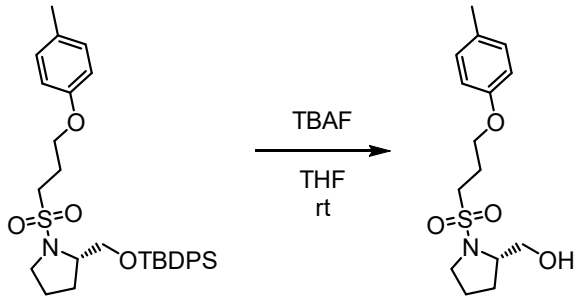


**S49** **S50** **S51**

According to **GP6**, the crude **S49** (145 mg, <0.573 mmol) was converted to crude **S50** by the reaction with $PCl_5$ (477 mg, 2.29 mmol, 4.0 equiv). According to **GP2**, **36** (177 mg, 0.521 mmol) was converted to **S51** (221 mg, 0.400 mmol, 77%) by the reaction with the crude **S50** (<0.573 mmol, <1.1 equiv) and $Et_3N$ (116 mg, 1.15 mmol, 2.2 equiv) in $CH_2Cl_2$ (1 mL): colorless oil; $[\alpha]^{26}_{D}$ −24.3° (*c* 1.11, $CHCl_3$); IR (neat) 1335 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.06 (s, 9H), 1.83–1.99 (m, 3H), 2.03–2.06 (m, 1H), 2.19–2.25 (m, 2H), 2.28 (s, 3H), 3.08 (dd, *J* = 8.0, 6.9 Hz, 2H), 3.30–3.34 (m, 1H), 3.37–3.42 (m, 1H), 3.59 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.78 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.90–4.00 (m, 3H), 6.75 (ddd, *J* = 9.2, 2.4, 2.4 Hz, 2H), 7.05–7.07 (m, 2H), 7.35–7.43 (m, 6H), 7.63–7.66 (m, 4H); $^{13}$C{$^1$H} NMR (150 MHz, $CDCl_3$) $\delta$ 19.3, 20.6, 23.7, 24.7, 27.0 (3C), 28.6, 47.1, 49.0, 60.6, 65.9, 66.0, 114.4 (2C), 127.8

(2C), 129.9 (2C), 130.0 (2C), 130.4, 133.36 (2C), 133.43 (2C), 135.69 (2C), 135.72 (2C), 156.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{41}NNaO_4SSi$, 574.2418; found, 574.2422.

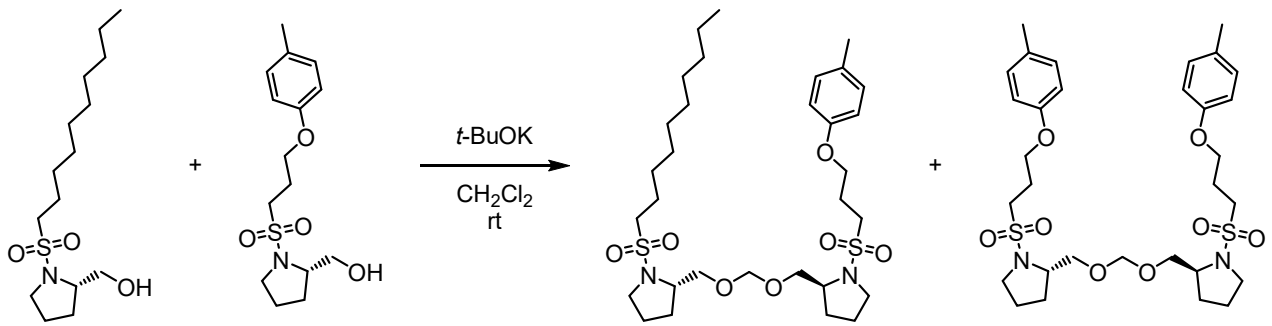
**(*S*)-(1-{[3-(*p*-Tolyloxy)propyl]sulfonyl}pyrrolidin-2-yl)methanol (S52)**




**S51** **S52**

According to **GP7**, **S51** (132 mg, 0.240 mmol) was converted to **S52** (59.5 mg, 0.190 mmol, 79%) by the reaction with TBAF (1.0 M solution in THF; 0.36 mL, 0.36 mmol, 1.5 equiv) in THF (1 mL): white solid; mp 57−59 °C; $[\alpha]^{27}_D$ −24.6° (*c* 0.48, $CHCl_3$); IR (neat) 3523 (O–H), 1325 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.79–1.90 (m, 2H), 1.91–1.99 (m, 1H), 2.02–2.09 (m, 1H), 2.28 (s, 3H), 2.25–2.33 (m, 2H), 2.59 (s, 1H), 3.16–3.25 (m, 2H), 3.37–3.42 (m, 1H), 3.45–3.50 (m, 1H), 3.57–3.61 (m, 1H), 3.64–3.67 (m, 1H), 3.85–3.90 (m, 1H), 4.06 (t, *J* = 6.0 Hz, 2H), 6.78 (dt, *J* = 8.0, 2.4 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 20.6, 23.7, 25.0, 29.1, 46.3, 49.6, 61.7, 65.8, 65.9, 114.4 (2C), 130.1 (2C), 130.5, 156.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{23}NNaO_4S$, 336.1240; found, 336.1241.

**(*S*)-1-(Decylsulfonyl)-2-{[([(*S*)-1-{[3-(*p*-tolyloxy)propyl]sulfonyl}pyrrolidin-2-yl]methoxy)methoxy]methyl}-pyrrolidine (31) and Bis{[(*S*)-1-{[3-(*p*-tolyloxy)propyl]sulfonyl}pyrrolidin-2-yl]methoxy}methane (34)**




**S36** **S52** **31** **34**

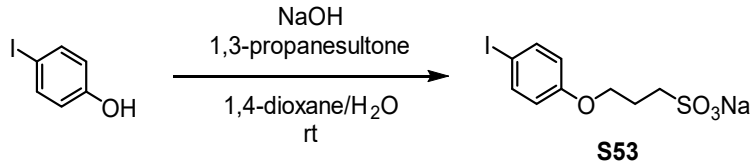
According to **GP8**, **S36** (19.6 mg, 0.0642 mmol) and **S52** (40.3 mg, 0.129 mmol, 2 equiv) was converted to **31** (17.0 mg, 0.0269 mmol, 28%) and **34** (20.1 mg, 0.0315 mmol, 33%) by the reaction of *t*-BuOK (86.6 mg, 0.772 mmol, 12.0 equiv) in anhydrous $CH_2Cl_2$ (1.5 mL).

Compound **31**: white solid; mp 55−59 °C; $[\alpha]^{27}_D$ −39.2° (*c* 0.47, $CHCl_3$); IR (neat) 1338 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 6.9 Hz, 3H), 1.25–1.29 (m, 12H), 1.36–1.41 (m, 2H), 1.75–2.03 (m, 10H), 2.25–2.31 (m, 2H), 2.27 (s, 3H), 2.94 (t, *J* = 7.4 Hz, 2H), 3.17–3.20 (m, 2H), 3.32–3.43 (m, 4H), 3.45–3.51 (m, 2H), 3.64 (dd, *J* = 9.7, 3.4 Hz, 2H), 3.91–4.00 (m, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 4.67 (s, 2H), 6.76–6.79 (m, 2H), 7.07 (d, *J* = 8.0 Hz,

2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 14.2, 20.5, 22.8, 23.3, 23.7, 24.75, 24.78, 28.6, 29.17 (2C), 29.24, 29.3, 29.4, 29.6, 31.9, 46.9, 48.9, 49.0, 49.8, 58.8, 58.9, 65.9, 70.3, 70.4, 95.7, 114.4 (2C), 130.0 (2C), 130.4, 156.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{54}N_2NaO_7S_2$, 653.3265; found, 653.3265.

Compound **34**: white solid; mp 63−65 °C; $[\alpha]^{27}_D$ −37.8° (*c* 0.44, $CHCl_3$); IR (neat) 1338 (S=O); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.85–2.04 (m, 8H), 2.24–2.31 (m, 4H), 2.27 (s, 6H), 3.16–3.19 (m, 4H), 3.32–3.42 (m, 4H), 3.48 (dd, *J* = 9.7, 6.9 Hz, 2H), 3.64 (dd, *J* = 10.0, 4.8 Hz, 2H), 3.95–3.99 (m, 2H), 4.04 (t, *J* = 6.0 Hz, 4H), 4.67 (s, 2H), 6.75-6.78 (m, 4H), 7.07 (d, *J* = 8.0 Hz, 4H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 20.5 (2C), 23.7 (2C), 24.8 (2C), 29.1 (2C), 46.9 (2C), 49.0 (2C), 58.9 (2C), 65.9 (2C), 70.3 (2C), 95.7, 114.4 (4C), 130.0 (4C), 130.4 (2C), 156.4 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{46}N_2NaO_8S_2$, 661.2588; found, 661.2590.

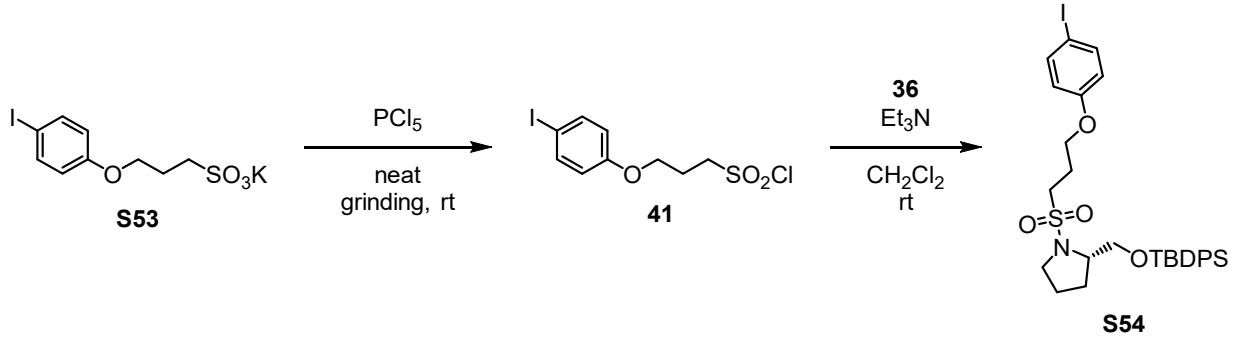
**Sodium 3-(4-Iodophenoxy)propane-1-sulfonate (S53)**



**S53**

To a solution of *p*-iodophenol (440 mg, 2.00 mmol, 1.0 equiv) in water (2 mL) and 1,4-dioxane (2 mL) were added NaOH (200 mg, 5.00 mmol, 2.5 equiv) and 1,3-propanesultone (318 mg, 2.60 mmol, 1.3 mmol). The mixture was stirred at rt for 50 h and filtered to gather the solid. The residue was washed with acetone and dried on air to afford **S53** (479 mg, 1.31 mmol, 66%) as a white solid. mp 285−287 °C; IR (neat) 1203 (S=O); $^1H$ NMR (600 MHz, $CD_3OD$) $\delta$ 2.18–2.23 (m, 2H), 2.93–2.95 (m, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 6.71–6.74 (m, 2H), 7.50–7.53 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-$d_6$) $\delta$ 25.7, 48.3, 67.4, 83.3, 117.8 (2C), 138.4 (2C), 159.1; HRMS (ESI-TOF) *m/z*: $[M - Na]^-$ calcd for $C_9H_{10}IO_4S$, 340.9350; found, 340.9351.

**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-{[3-(4-iodophenoxy)propyl]sulfonyl}pyrrolidine (S54)**

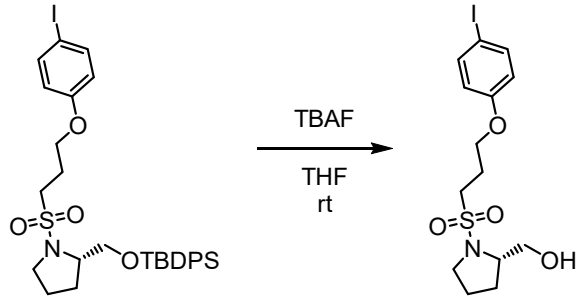


**S53** **41** **S54**

According to **GP6**, **S53** (209 mg, 0.574 mmol) was converted to crude **41** by the reaction with $PCl_5$ (477 mg, 2.29 mmol, 4.0 equiv). According to **GP2**, **36** (177 mg, 0.521 mmol) was converted to **S54** (160 mg, 0.241 mmol, 46%) by the reaction with the crude **41** (<0.574 mmol) and $Et_3N$ (116 mg, 1.15 mmol, 2.2 equiv) in $CH_2Cl_2$ (1 mL): colorless oil; $[\alpha]^{26}_D$ −15.9° (*c* 0.41, $CHCl_3$); IR (neat) 1338 (S=O); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.05 (s, 9H), 1.83-2.06 (m, 4H), 2.19–2.25 (m, 2H), 3.04–3.08 (m, 2H), 3.29–3.34 (m, 1H), 3.39–3.44 (m, 1H), 3.60 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.77 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.91–4.00 (m, 3H), 6.60–6.63 (m, 2H), 7.35–7.43 (m, 6H), 7.51–7.55 (m,

2H), 7.62–7.65 (m, 4H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 19.3, 23.6, 24.8, 27.0 (3C), 28.6, 47.0, 49.0, 60.7, 65.9, 65.9, 83.2, 116.9 (2C), 127.8 (2C), 129.9 (2C), 133.3 (2C), 133.4 (2C), 135.67 (2C), 135.70 (2C), 138.3 (2C), 158.5; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{39}INO_4SSi$, 664.1408; found, 664.1404.

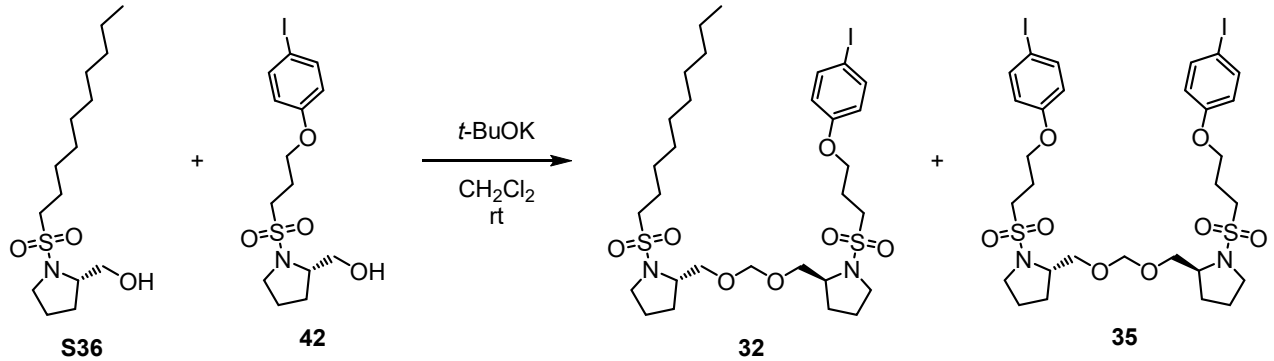
**(*S*)-(1-{[3-(4-Iodophenoxy)propyl]sulfonyl}pyrrolidin-2-yl)methanol (42)**




**S54** **42**

According to **GP7**, **S54** (133 mg, 0.200 mmol) was converted to **42** (63.8 mg, 0.150 mmol, 75%) by the reaction with TBAF (1.0 M solution in THF; 0.3 mL, 0.300 mmol, 1.5 equiv) in THF (1 mL): white solid; mp 34−37 °C; $[\alpha]^{25}_D$ −17.4° (*c* 1.43, $CHCl_3$); IR (neat) 3496 (O–H), 1326 (S=O); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.79–1.90 (m, 2H), 1.91–2.00 (m, 1H), 2.02–2.10 (m, 1H), 2.28–2.34 (m, 2H), 2.55 (br s, 1H), 3.14–3.23 (m, 2H), 3.37–3.42 (m, 1H), 3.44–3.49 (m, 1H), 3.59 (dd, *J* = 11.5, 5.9 Hz, 1H), 3.66 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.85–3.90 (m, 1H), 4.04–4.09 (m, 2H), 6.64–6.68 (m, 2H), 7.53–7.56 (m, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 23.5, 25.0, 29.1, 31.0, 46.1, 49.6, 61.7, 65.8, 83.3, 116.9 (2C), 138.4 (2C), 158.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{20}INNaO_4S$, 448.0050; found, 448.0051.

**(*S*)-1-(Decylsulfonyl)-2-{[([(*S*)-1-{[3-(4-iodophenoxy)propyl]sulfonyl}pyrrolidin-2-yl]methoxy)methoxy]-methyl}pyrrolidine (32) and Bis{[(*S*)-1-{[3-(4-iodophenoxy)propyl]sulfonyl}pyrrolidin-2-yl]methoxy}methane (35)**




**S36** **42** **32** **35**

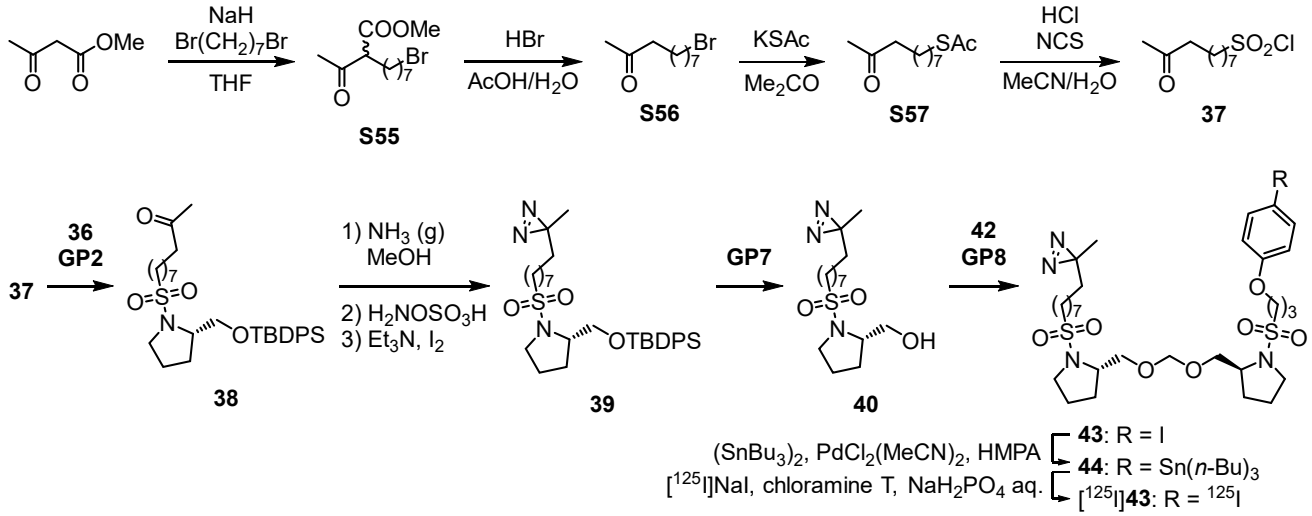
According to **GP8**, **S36** (22.9 mg, 0.0750 mmol) and **42** (63.8 mg, 0.150 mmol, 2.0 equiv) was converted to **32** (25.8 mg, 0.0347 mmol, 31%) and **35** (18.8 mg, 0.0218 mmol, 22%) by the reaction of *t*-BuOK (101 mg, 0.900 mmol, 12.0 equiv) in anhydrous $CH_2Cl_2$ (1.5 mL).

Compound **32**: white solid; mp 67−68 °C; $[\alpha]^{26}_D$ −31.6° (*c* 0.34, $CHCl_3$); IR (neat) 1332 (S=O); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 6.9 Hz, 3H), 1.25–1.29 (m, 12H), 1.36–1.41 (m, 2H), 1.75–2.04 (m, 10H), 2.26–2.32 (m,

2H), 2.94 (t, $J$ = 8.0 Hz, 2H), 3.17 (t, $J$ = 7.4 Hz, 2H), 3.33–3.52 (m, 6H), 3.62–3.66 (m, 2H), 3.90–3.94 (m, 1H), 3.96–4.01 (m, 1H), 4.05 (t, $J$ = 6.0 Hz, 2H), 4.66 (s, 2H), 6.66 (d, $J$ = 9.2 Hz, 2H), 7.54 (d, $J$ = 9.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 14.2, 22.8, 23.3, 23.6, 24.7, 24.8, 28.6, 29.16, 29.18, 29.24, 29.3, 29.4, 29.6, 31.9, 46.8, 48.96, 49.01, 49.7, 58.8, 58.9, 66.0, 70.3, 70.4, 83.2, 95.7, 117.0 (2C), 138.4 (2C), 158.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{51}IN_2NaO_7S_2$, 765.2075; found, 765.2076.

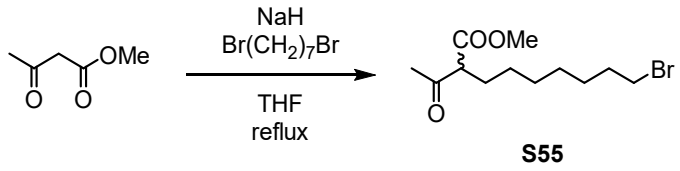
Compound **35**: white solid; mp 88−90 °C; $[\alpha]^{27}_D$ −27.5° (*c* 0.48, $CHCl_3$); IR (neat) 1329 (S=O); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.85–2.04 (m, 8H), 2.25–2.33 (m, 4H), 3.16 (t, $J$ = 7.4 Hz, 4H), 3.32–3.42 (m, 4H), 3.48 (dd, $J$ = 9.7, 6.9 Hz, 2H), 3.63 (dd, $J$ = 9.7, 4.6 Hz, 2H), 3.94–3.99 (m, 2H), 4.04 (t, $J$ = 6.0 Hz, 4H), 4.66 (s, 2H), 6.65 (d, $J$ = 9.2 Hz, 4H), 7.54 (d, $J$ = 8.6 Hz, 4H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 23.6 (2C), 24.8 (2C), 29.2 (2C), 46.7 (2C), 49.0 (2C), 58.9 (2C), 65.9 (2C), 70.3 (2C), 83.2 (2C), 95.6, 117.0 (4C), 138.4 (4C), 158.5 (2C); HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{40}I_2N_2NaO_8S_2$, 885.0208; found, 885.0201.

**Schemes of Synthesis (43 and [$^{125}$I]-43)**



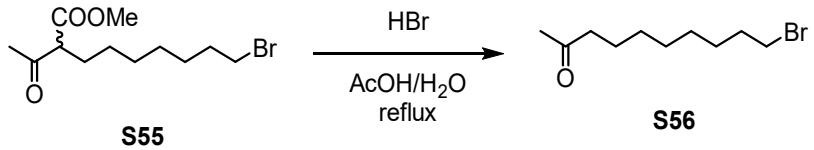

**Compounds (43 and [$^{125}$I]-43)**

**Methyl 2-Acetyl-9-bromononanoate (S55)**




NaH (60% dispersion in mineral oil; 468 mg, 11.7 mmol, 1.05 equiv) in a flask was washed with hexane under $N_2$ atmosphere, and cooled on ice. To the washed NaH were added THF (20 mL) and methyl acetoacetate (1.29 g, 11.1 mmol) dropwise. The mixture was stirred on ice until $H_2$ gas evolution was ceased. To the mixture was added 1,7-dibromoheptane (3.16 g, 12.2 mmol, 1.1 equiv). The mixture was refluxed for 25 h, diluted with saturated aqueous $NH_4Cl$, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Biotage® Sfär D, 2–10% EtOAc/*n*-hexane eluent) to afford **S55** (1.17 g, 4.00 mmol, 36%, 67% brsm) and recovered 1,7-dibromoheptane (1.62 g, 6.26 mmol). Compound **S55**: colorless oil; IR (neat) 1745 (C=O), 1717 (C=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.23–1.31 (m, 6H), 1.38–1.43 (m, 2H), 1.80–1.86 (m, 4H), 2.21 (s, 3H), 3.38–3.42 (m, 3H), 3.73 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 27.4, 28.1, 28.3, 28.5, 28.9, 29.2, 32.8, 34.0, 52.5, 59.8, 170.5, 203.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{21}BrNaO_3$, 315.0566; found, 315.0566.

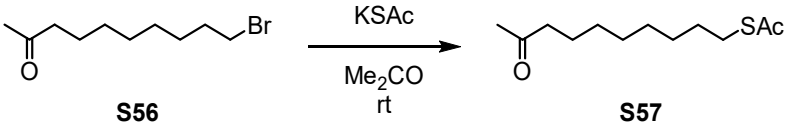
**10-Bromodecan-2-one (S56)**




A mixture of **S55** (1.49 g, 5.07 mmol) in 48% aqueous HBr (7.5 mL) and AcOH (5 mL) was refluxed for 45 min, cooled to rt, extracted with toluene, washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

The crude product was purified by silica gel column chromatography (Biotage® Sfär D, 1–10% EtOAc/*n*-hexane eluent) to afford **S56** (1.10 g, 4.69 mmol, 93%) as a colorless oil. The spectral data were in good agreement with those previously reported.[20]

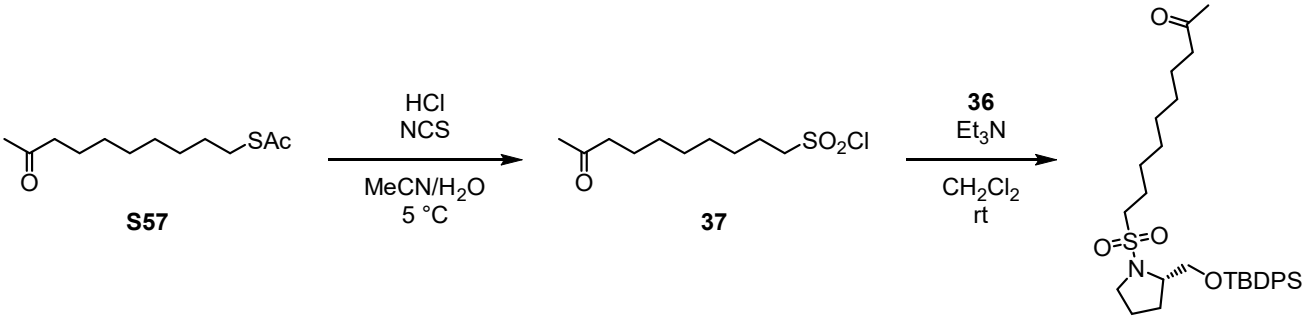
**S-(9-Oxodecyl) Ethanethioate (S57)**




**S56** **S57**

To a mixture of **S56** (1.10 g, 4.69 mmol) in anhydrous $Me_2CO$ (30 mL) was added KSAc (643 mg, 5.63 mmol, 1.2 equiv). The mixture was stirred at rt for 1 h and filtered. The filtrate was concentrated *in vacuo*, and the residue was diluted with $CH_2Cl_2$ and brine, extracted with $CH_2Cl_2$, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Biotage® Sfär D, 1–7% $CHCl_3$/*n*-hexane eluent) to afford **S57** (933 mg, 4.01 mmol, 86%) as a colorless oil: IR (neat) 1715 (C=O), 1692 (C=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.23–1.36 (m, 8H), 1.51–1.57 (m, 4H), 2.12 (s, 3H), 2.31 (s, 3H), 2.40 (t, $J$ = 7.4 Hz, 2H), 2.84 (t, $J$ = 7.4 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 23.9, 28.8, 29.0, 29.1, 29.2, 29.3, 29.5, 30.0, 30.7, 43.8, 196.2, 209.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{22}NaO_2S$, 253.1233; found, 253.1233.

**(*S*)-10-[(2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}pyrrolidin-1-yl)sulfonyl]decan-2-one (38)**



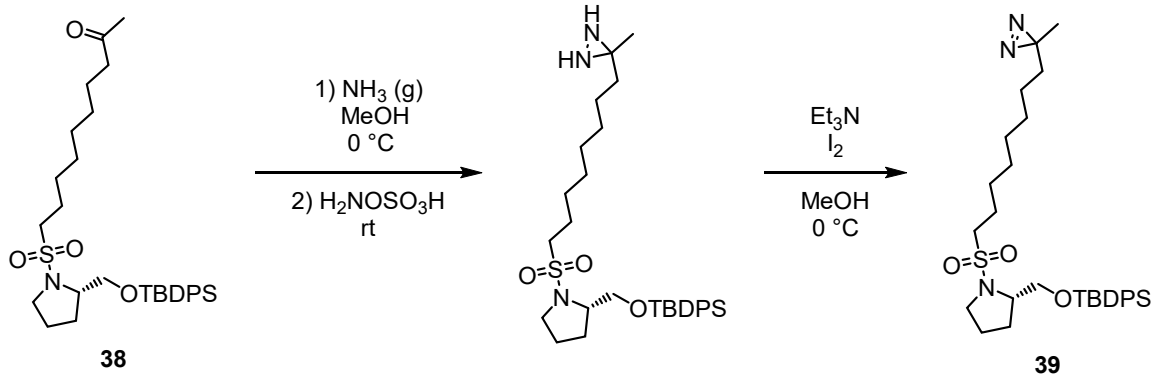

**S57** **37** **38**

To a mixture of *N*-chlorosuccinimide (1.60 g, 12.0 mmol, 4.0 equiv) in 2 M aqueous HCl (3 mL) and MeCN (17 mL) was added a solution of **S57** (691 mg, 3.00 mmol) in MeCN (4 mL) at 5 °C. The mixture was stirred at 5 °C for 30 min, diluted with water, and extracted with EtOAc. The extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Biotage® Sfär D, 2–15% EtOAc/*n*-hexane eluent) to afford **37** (591 mg, 2.32 mmol, 77%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.23–1.38 (m, 6H), 1.44–1.50 (m, 2H), 1.53–1.59 (m, 2H), 1.99–2.05 (m, 2H), 2.13 (s, 3H), 2.42 (t, $J$ = 7.4 Hz, 2H), 3.63–3.66 (m, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 23.7, 24.3, 27.6, 28.8, 29.0, 29.0, 30.0, 43.7, 65.5, 209.2.

According to **GP2**, **36** (944 mg, 2.78 mmol) was converted to **38** (1.23 g, 2.20 mmol, 95%) by the reaction with **37** (591 mg, 2.32 mmol) and $Et_3N$ (470 mg, 4.64 mmol, 2.0 equiv) in $CH_2Cl_2$ (12 mL): colorless oil; $[\alpha]^{26}_D$ −22.9° (*c* 1.15, $CHCl_3$); IR (neat) 1715 (C=O), 1334 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.06 (s, 9H), 1.26–1.34 (m, 8H), 1.52–1.57 (m, 2H), 1.71–2.05 (m, 6H), 2.13 (s, 3H), 2.41 (t, $J$ = 7.4 Hz, 2H), 2.83–2.87 (m, 2H), 3.28–3.32 (m, 1H), 3.35-3.40 (m, 1H), 3.57 (dd, $J$ = 10.3, 7.4 Hz, 1H), 3.76 (dd, $J$ = 10.3, 3.7 Hz, 1H), 3.87–3.91 (m, 1H), 7.36–7.43 (m,

6H), 7.63–7.66 (m, 4H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) $\delta$ 19.3, 23.3, 23.8, 24.7, 27.0 (3C), 28.5, 28.6, 29.0, 29.1, 29.2, 30.0, 43.8, 49.0, 50.1, 60.6, 66.0, 127.8 (2C), 129.8 (2C), 133.4 (2C), 133.5 (2C), 135.7 (2C), 135.7 (2C), 209.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{47}NNaO_4SSi$, 580.2887; found, 580.2888.

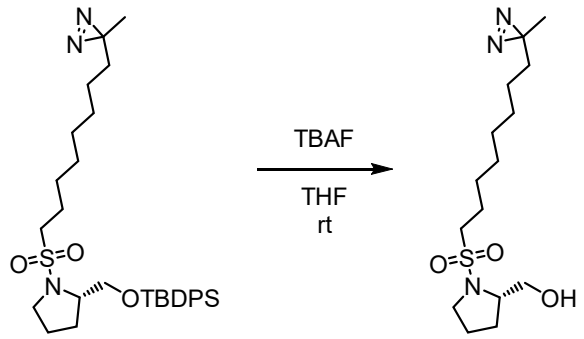
**(*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-{[8-(3-methyl-3*H*-diazirin-3-yl)octyl]sulfonyl}pyrrolidine (39)**




**38** **39**

An ice-cooled solution of **38** (566 mg, 1.01 mmol) in anhydrous MeOH (10 mL) was bubbled with $NH_3$ gas for 3 h under $N_2$ atmosphere, followed by the careful addition of a solution of hydroxylamine-*O*-sulfonic acid (124 mg, 1.10 mmol, 1.1 equiv) in anhydrous MeOH (1 mL). The mixture was stirred at rt for 15 h and dried by blowing $N_2$ gas, suspended with anhydrous MeOH, and filtered. The filtrate was concentrated *in vacuo*, and the crude diaziridine residue was diluted with anhydrous MeOH (10 mL) and $Et_3N$ (2 mL) and cooled on ice. To the mixture was added dropwise a solution of $I_2$ (0.6 M solution in MeOH) until a dark brown color was persisted in the solution for more than 10 min. The mixture was stirred at rt for 2 h, diluted with brine, and extracted with EtOAc. The extract was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Biotage® Sfär D, 2–15% EtOAc/*n*-hexane eluent) to afford **39** (150 mg, 0.264 mmol, 26%) as a colorless oil: $[\alpha]^{25}_D$ −17.4° (*c* 0.38, $CHCl_3$); IR (neat) 1339 (S=O); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.99 (s, 3H), 1.06 (s, 9H), 1.09–1.34 (m, 12H), 1.71–1.77 (m, 2H), 1.83–1.95 (m, 3H), 2.03–2.05 (m, 1H), 2.84–2.87 (m, 2H), 3.28–3.32 (m, 1H), 3.36–3.41 (m, 1H), 3.57 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.76 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.88–3.92 (m, 1H), 7.36–7.44 (m, 6H), 7.63–7.66 (m, 4H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) $\delta$ 19.4, 20.0, 23.3, 24.1, 24.7, 26.0, 27.0 (3C), 28.5, 28.6, 29.07, 29.11, 29.2, 34.3, 49.0, 50.2, 60.6, 66.0, 127.8 (2C), 129.8 (2C), 133.4 (2C), 133.5 (2C), 135.67 (2C), 135.71 (2C); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{47}N_3NaO_3SSi$, 592.3000; found, 592.2999.

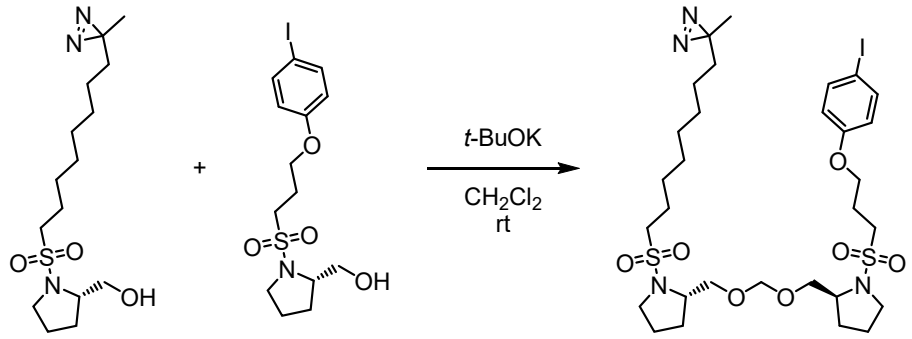
**(*S*)-(1-{[8-(3-Methyl-3*H*-diazirin-3-yl)octyl]sulfonyl}pyrrolidin-2-yl)methanol (40)**




**39** **40**

According to **GP7**, **39** (150 mg, 0.264 mmol) was converted to **40** (49.5 mg, 0.149 mmol, 56%) by the reaction with TBAF (1.0 M solution in THF; 0.528 mL, 0.528 mmol, 2.0 equiv) in THF (3 mL): colorless oil; $[\alpha]^{25}_{D}$ −22.6° (*c* 0.22, $CHCl_3$); IR (neat) 3466 (O–H), 1329 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.99 (s, 3H), 1.11–1.43 (m, 12H), 1.78–1.88 (m, 4H), 1.93–1.98 (m, 1H), 2.02–2.08 (m, 1H), 2.58 (dd, $J$ = 6.9, 5.2 Hz, 1H), 2.95–2.98 (m, 2H), 3.37–3.47 (m, 2H), 3.56–3.67 (m, 2H), 3.82–3.87 (m, 1H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 20.0, 23.2, 24.0, 25.0, 26.0, 28.5, 29.0, 29.08, 29.14, 29.2, 34.3, 49.2, 49.6, 61.7, 66.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{29}N_3NaO_3S$, 354.1822; found, 354.1823.

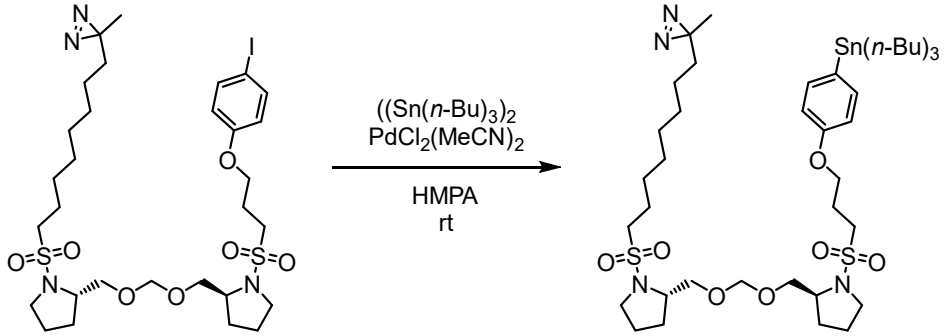
**(*S*)-1-{[3-(4-Iodophenoxy)propyl]sulfonyl}-2-[({[(*S*)-1-{[8-(3-methyl-3*H*-diazirin-3-yl)octyl]sulfonyl}-pyrrolidin-2-yl]methoxy}methoxy)methyl]pyrrolidine (43)**




**40** **42** **43**

To an ice-cooled solution of **40** (42.4 mg, 0.128 mmol, 1.06 equiv) and **42** (51.2 mg, 0.120 mmol) in anhydrous $CH_2Cl_2$ (3 mL) was added *t*-BuOK (108 mg, 0.960 mmol, 8.0 equiv), and the mixture was stirred at rt for 1 h. The mixture was diluted with 5% aqueous $NH_4Cl$ under vigorous stirring. The mixture was extracted with EtOAc, and the extract was washed with water, dried over $Na_2SO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (Wakogel® C-300E, 30% EtOAc/*n*-hexane eluent) to afford **43** (17.2 mg, 0.0224 mmol, 19%) as a white amorphous; IR (neat) 1332 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.98 (s, 3H), 1.13–1.41 (m, 14H), 1.74–2.04 (m, 8H), 2.26–2.32 (m, 2H), 2.93 (t, $J$ = 8.0 Hz, 2H), 3.16–3.19 (m, 2H), 3.33–3.42 (m, 4H), 3.44–3.51 (m, 2H), 3.62–3.65 (m, 2H), 3.91–3.93 (m, 1H), 3.96–4.00 (m, 1H), 4.05 (t, $J$ = 6.0 Hz, 2H), 4.66 (s, 2H), 6.64–6.68 (m, 2H), 7.51–7.56 (m, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 20.0, 23.3, 23.6, 24.1, 24.75, 24.81, 26.0, 28.5, 29.1 (2C), 29.2 (3C), 34.3, 46.7, 48.97, 49.02, 49.6, 58.8, 58.9, 65.9, 70.3, 70.4, 83.2, 95.7, 117.0 (2C), 138.4 (2C), 158.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{49}IN_4NaO_7S_2$, 791.1980; found, 791.1979.

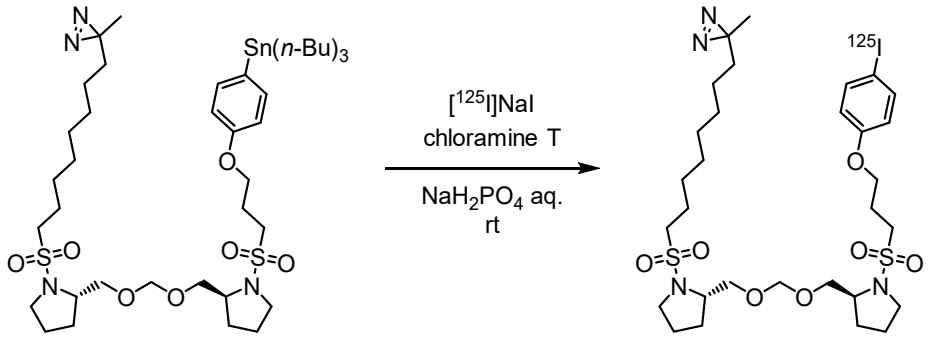
**(*S*)-1-{[8-(3-Methyl-3*H*-diazirin-3-yl)octyl]sulfonyl}-2-[({[(*S*)-1-({3-[4-(tributylstannyl)phenoxy]propyl}-sulfonyl)pyrrolidin-2-yl]methoxy}methoxy)methyl]pyrrolidine (44)**




**43** **44**

To a solution of **43** (12.3 mg, 0.0159 mmol) in distilled HMPA (0.5 mL) were added bis(tributyltin) (92.2 mg, 0.159 mmol, 10 equiv) and $PdCl_2(MeCN)_2$ (2.06 mg, 0.00795 mmol, 0.5 equiv). The mixture was stirred at rt for 16 h, diluted with saturated aqueous $NH_4Cl$, and extracted with $Et_2O$. The extract was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by reverse phase HPLC (COSMOSIL $5C_{18}$-AR-II, MeCN eluent) to afford **44** (4.02 mg, 0.00432 mmol, 27%) as a white amorphous: IR (neat) 1335 (S=O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 7.2 Hz, 9H), 0.98–1.03 (m, 8H), 1.11–1.42 (m, 22H), 1.48–1.54 (m, 5H), 1.77–2.03 (m, 10H), 2.28–2.34 (m, 2H), 2.94 (t, $J$ = 8.0 Hz, 2H), 3.19 (t, $J$ = 7.7 Hz, 2H), 3.32–3.42 (m, 4H), 3.46–3.52 (m, 2H), 3.62–3.66 (m, 2H), 3.91–3.99 (m, 2H), 4.08 (t, $J$ = 5.7 Hz, 2H), 6.87 (d, $J$ = 8.6 Hz, 2H), 7.35 (d, $J$ = 8.6 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 9.7 (3C), 13.8 (3C), 20.0, 23.3, 23.7, 24.0, 24.8, 25.9, 27.5 (3C), 28.5, 29.1 (2C), 29.2 (6C), 29.8, 34.3, 46.9, 48.95, 49.01, 49.8, 58.85, 58.95, 65.5, 70.3, 70.4, 95.7, 114.5 (2C), 132.7, 137.6 (2C), 158.7; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{42}H_{77}N_4O_7S_2Sn$, 933.4250; found, 933.4244.

**(*S*)-[$^{125}$I]-1-{[3-(4-Iodophenoxy)propyl]sulfonyl}-2-[({[(*S*)-1-{[8-(3-methyl-3*H*-diazirin-3-yl)octyl]sulfonyl}-pyrrolidin-2-yl]methoxy}methoxy)methyl]pyrrolidine ([$^{125}$I]-43)**




**44** [$^{125}$I]**43**

To an ethanolic solution of the tin-precursor **44** (1.0 mM, 20 μL) in a screw-capped 1.5 mL plastic-tube, [$^{125}$I]NaI (PerkinElmer, NEZ033A, 1 mCi, 2000 Ci/mmol, 10 μL) was added, and the radio-iodination was initiated by the addition of freshly prepared aqueous chloramine T (3.0 mM in 0.2 M aqueous $NaH_2PO_4$, 20 μL). The mixture was incubated at rt for 10 min, then the reaction was quenched with 10% aqueous $NaHSO_3$ (100 μL).[5] The resulting

mixture was extracted 3 times with $CHCl_3$ (100 µL × 3), and the combined organic layer was concentrated using vacuum-centrifugal evaporator. The crude product was dissolved in MeOH (50 µL) and subjected to HPLC purification using a $C_{18}$ column (Shimazu LC10 AS, COSMOSIL 5C18-MS-II, 4.6 × 150 mm, Nacalai Tesque) at a flow rate of 800 µL/min with 90% methanol/water system as an eluent. The fraction was collected every 30 s (~ 400 µL) and the radioactivity was measured by γ-counting system (ARC-8001, Aloka). The strong radioactive fraction (fr. 10 and 11 in Figure S5) corresponding to the HPLC retention time of [$^{125}$I]-**43** (6.9 min) was collected, and the solvent was evaporated by vacuum-centrifugal concentrator. [$^{125}$I]-**43** was stored as an ethanolic solution (1 mCi/mL) at 4 °C. The radiochemical yield of [$^{125}$I]-**43** from the initial [$^{125}$I]NaI was 43%. The radiochemical purity and the specific activity were >99% and ~2000 Ci/mmol, respectively (judged from HPLC and TLC analyses).

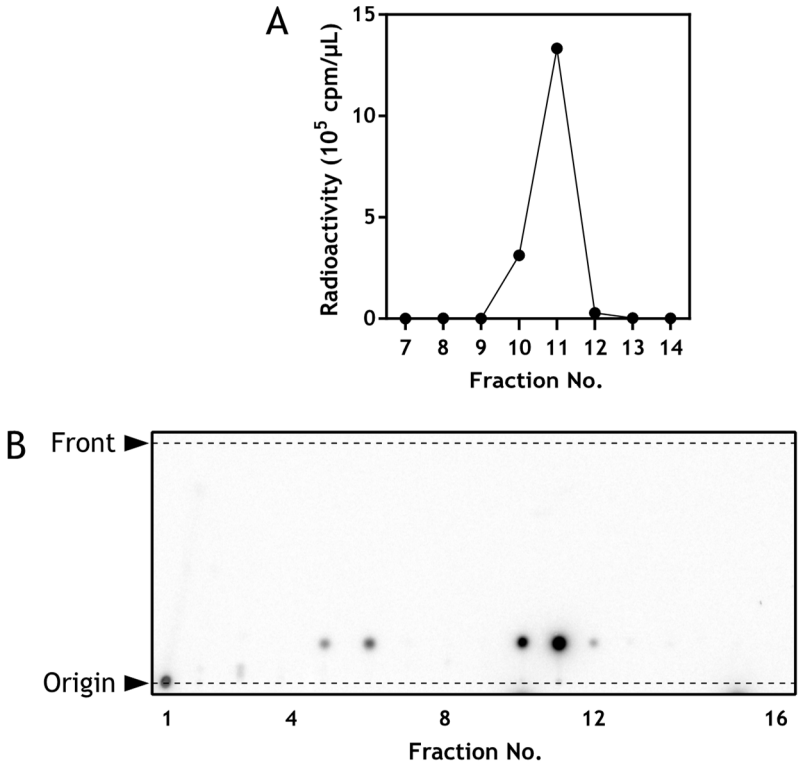



**Figure S5. Purification of [$^{125}$I]-43 using reverse-phase HPLC.** (A) Radioactivity distribution in HPLC chromatogram. The fractions were collected every 400 µL, and 2 µL aliquot from each fraction was transferred to RIA tubes, then the radioactivity was measured using γ-counting system. (B) TLC analysis of the collected fractions. The fractions were analyzed on TLC plate (Merck TLC Plate Silica-gel 60F$^{254}$) using 40% EtOAc/*n*-hexane (v/v) as a mobile phase. The plate was exposed to an Imaging Plate® for 1 h and analyzed by Bio-Imaging analyzer FLA-5100 (Fuji Film).

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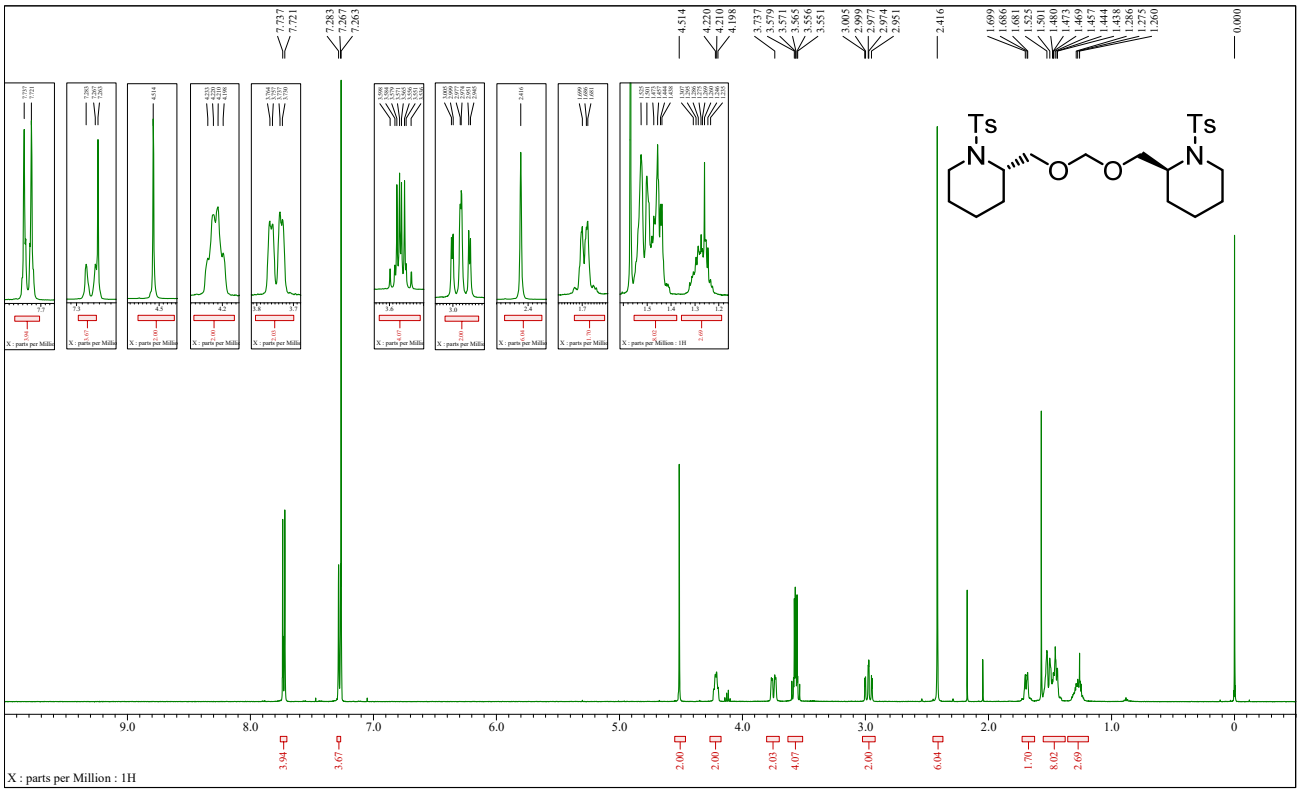
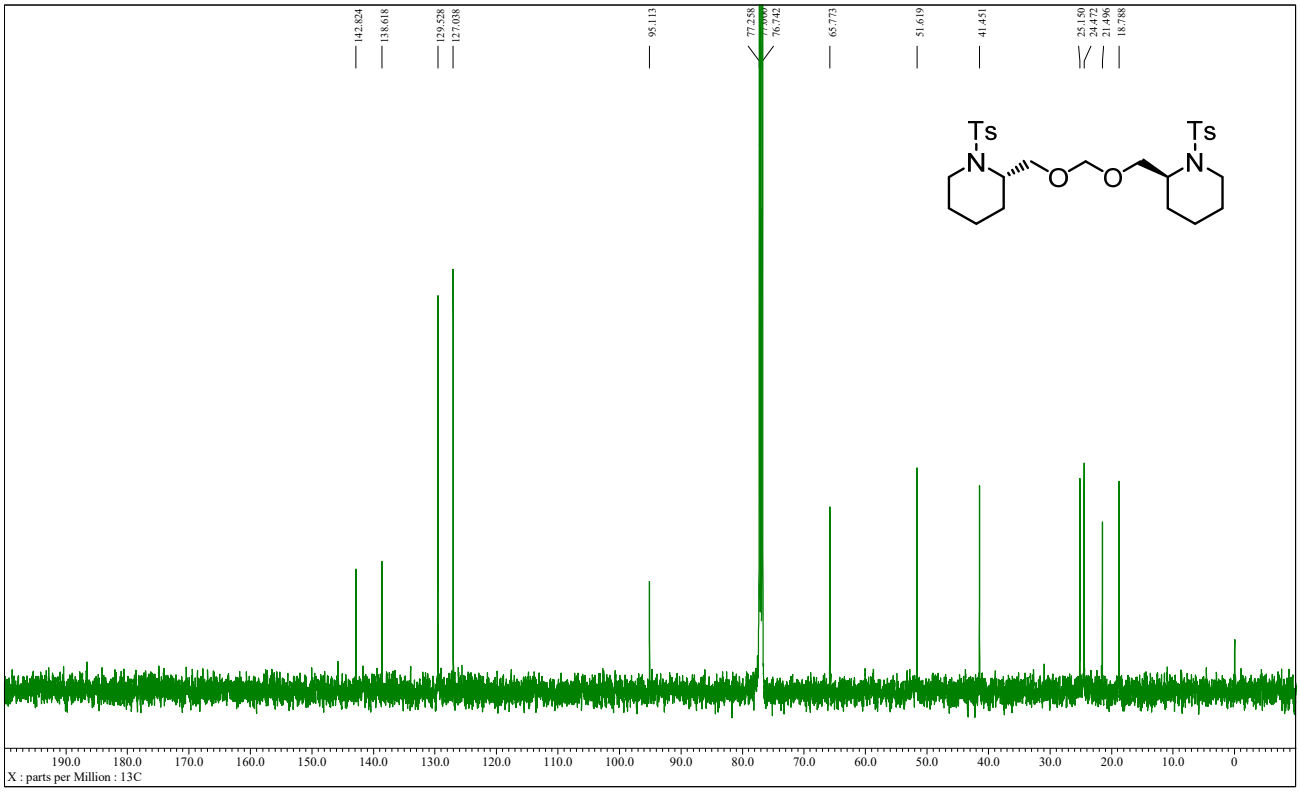
## 5. NMR Spectra

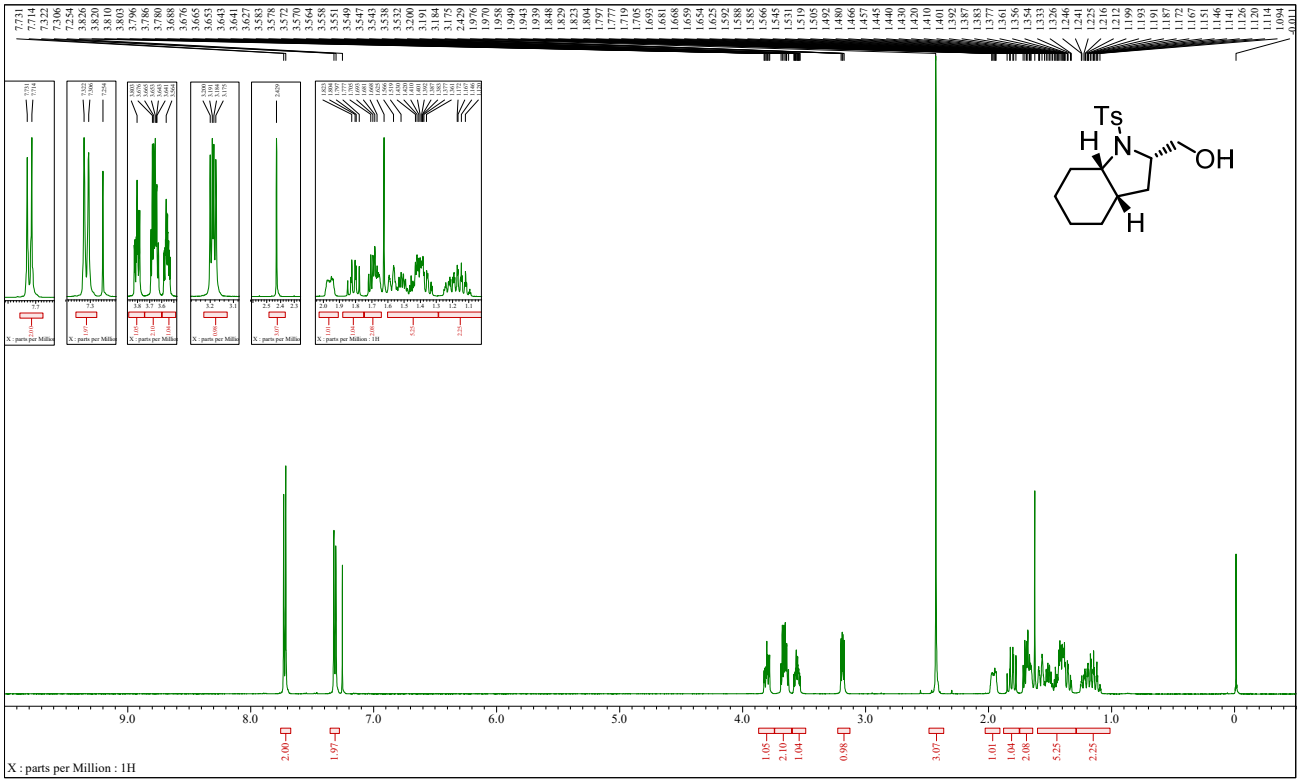
$^{1}$H NMR spectrum of compound **3** (500 MHz, $CDCl_3$)



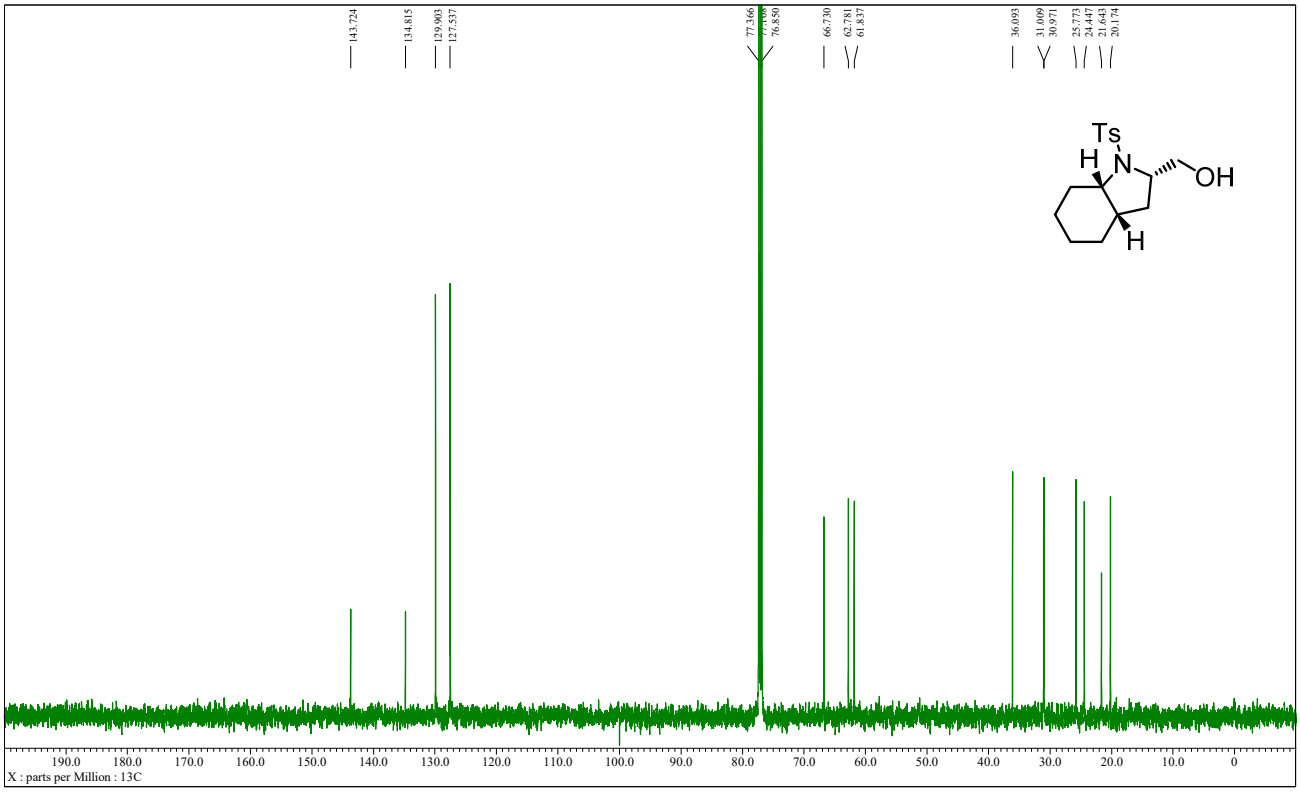

$^{13}$C NMR spectrum of compound **3** (125 MHz, $CDCl_3$)



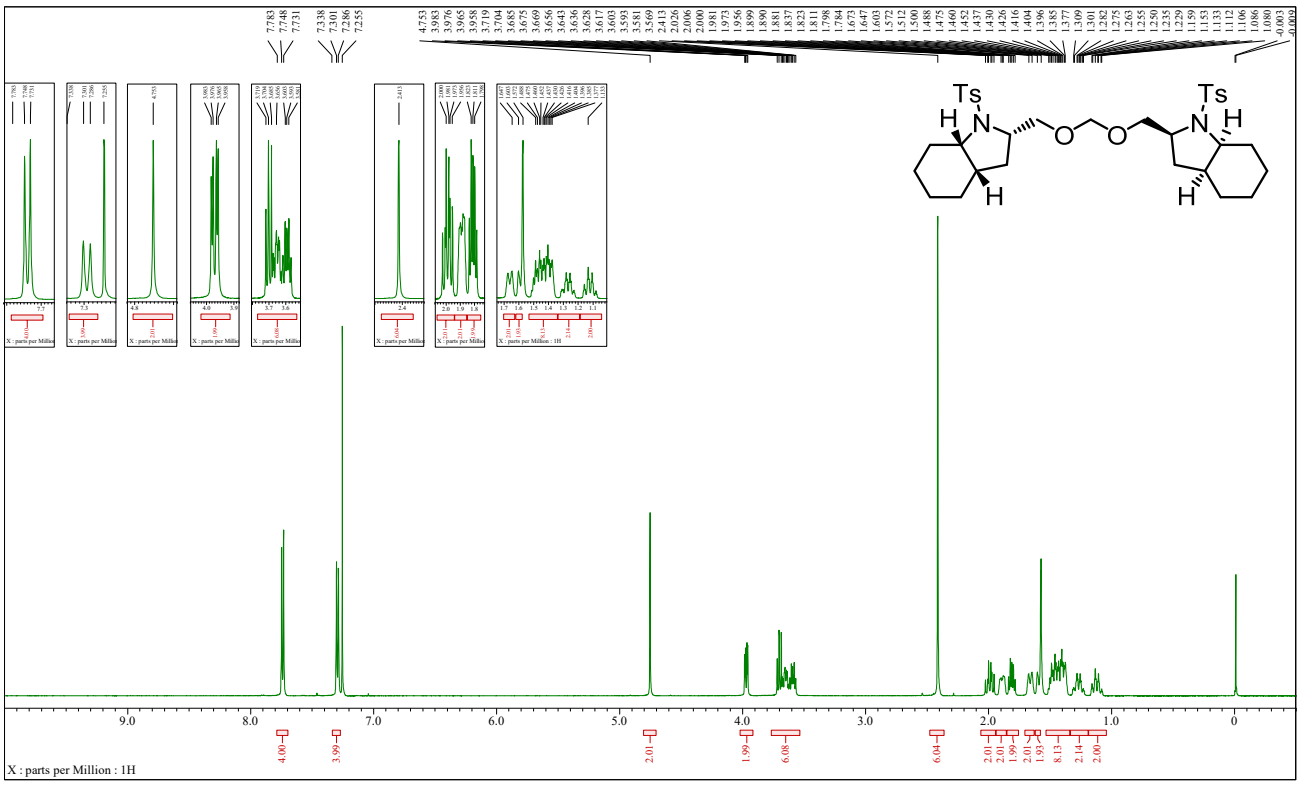
$^{1}$H NMR spectrum of compound **S5** (500 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of compound **S5** (125 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of compound **8** (500 MHz, $CDCl_3$)

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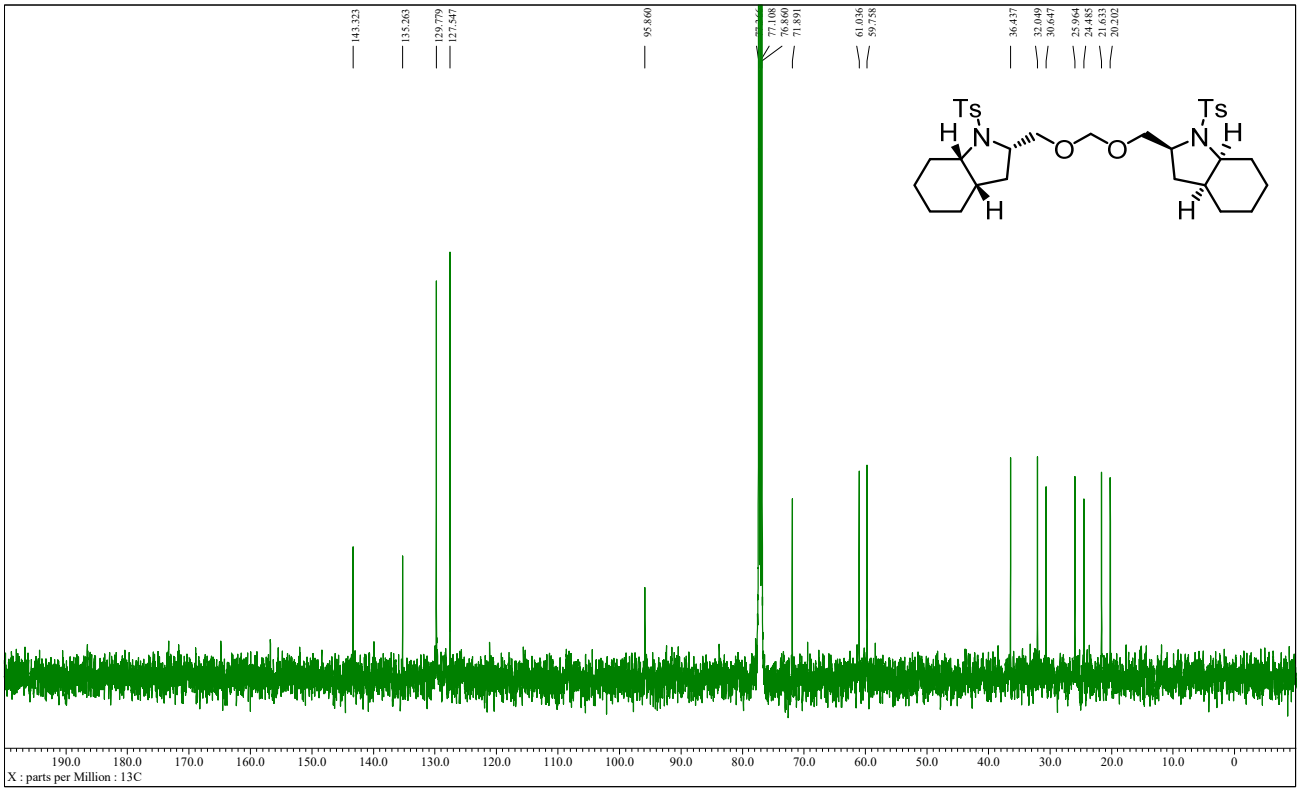
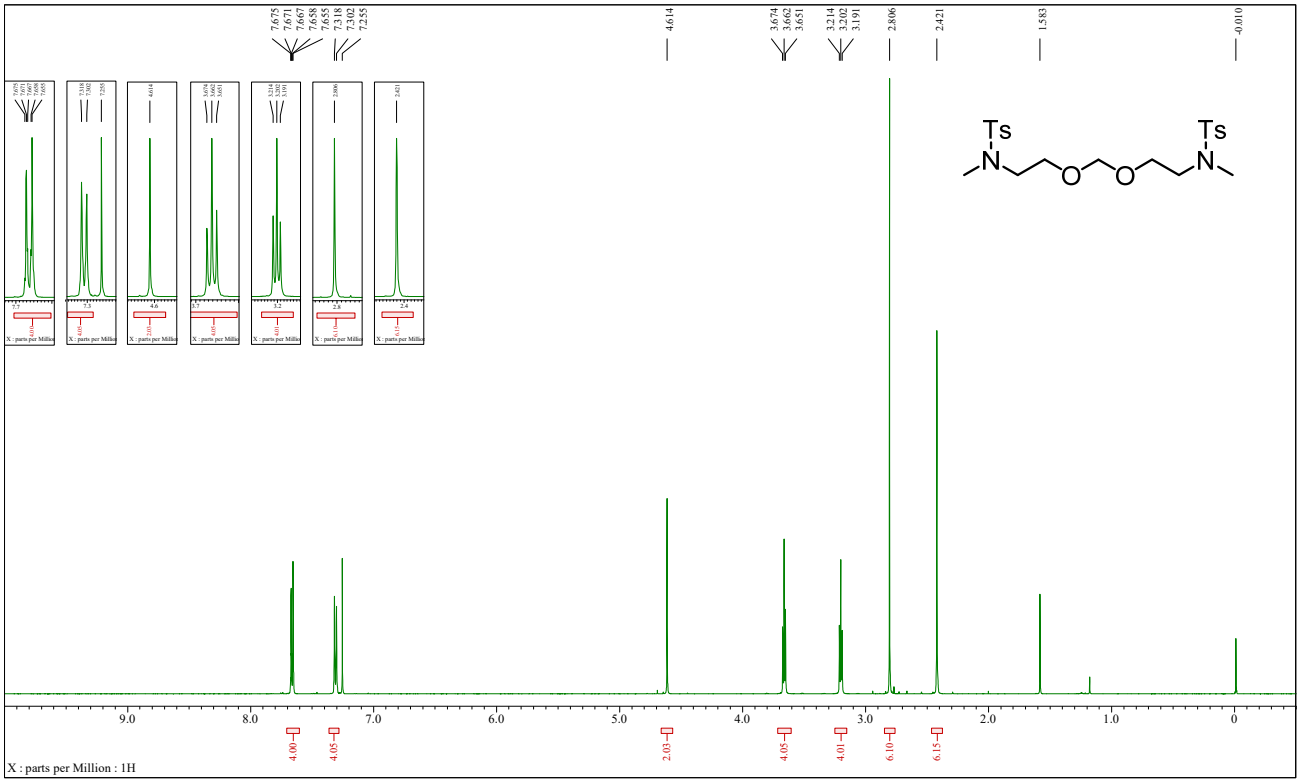
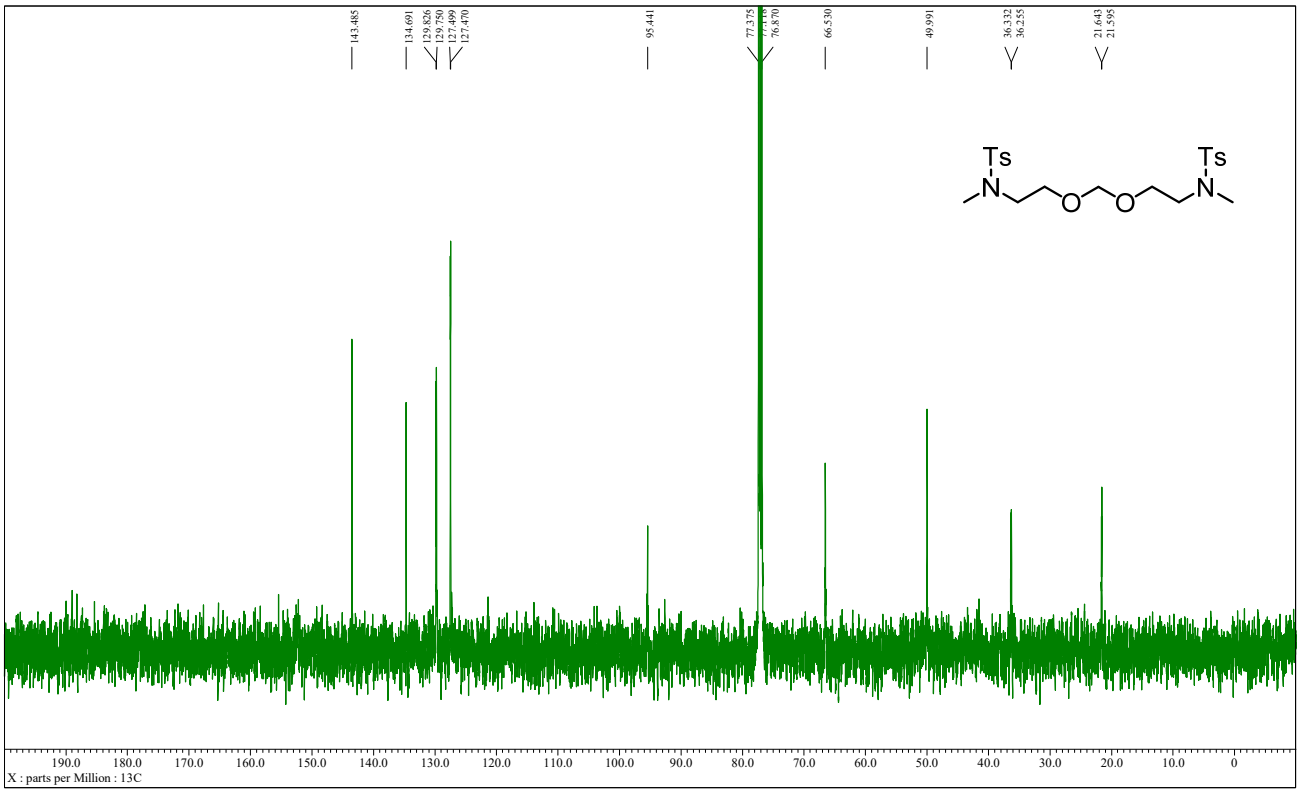


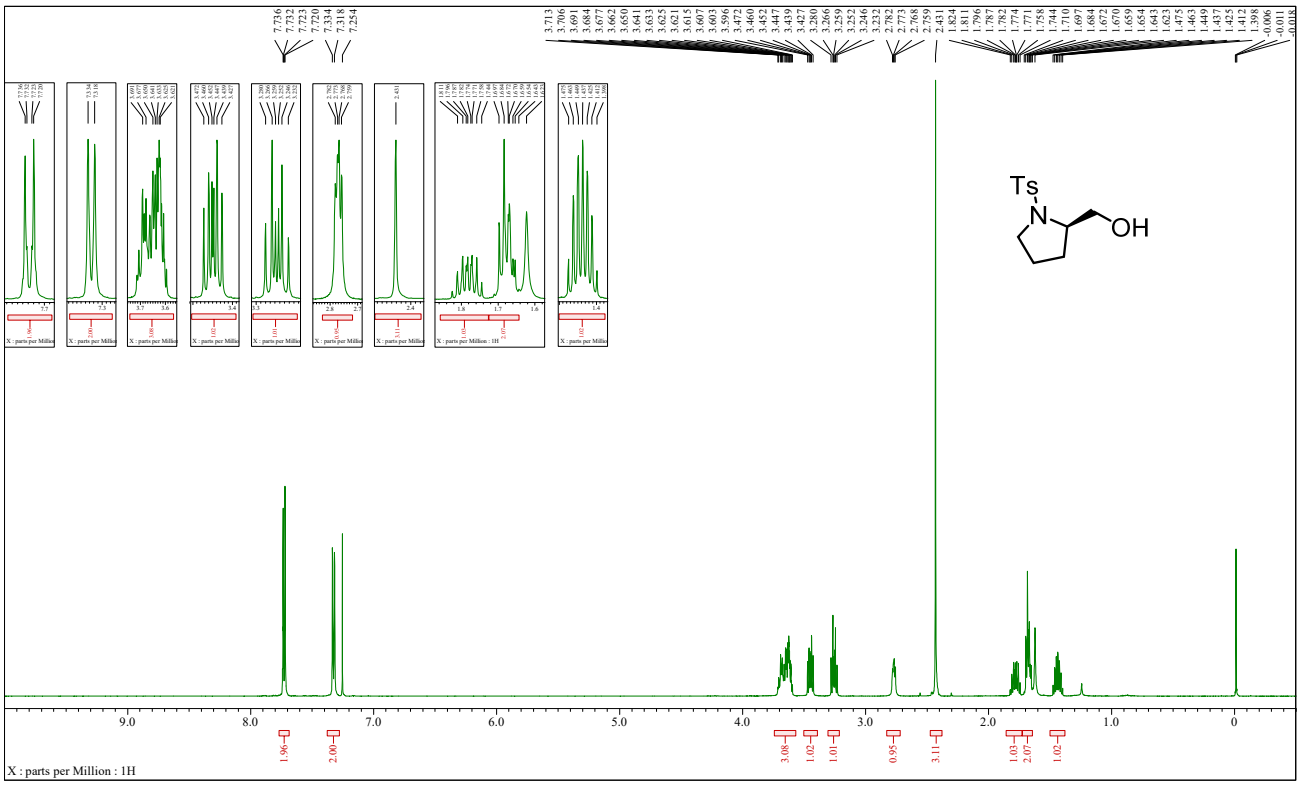
$^{1}$H NMR spectrum of compound **9** (500 MHz, $CDCl_3$)



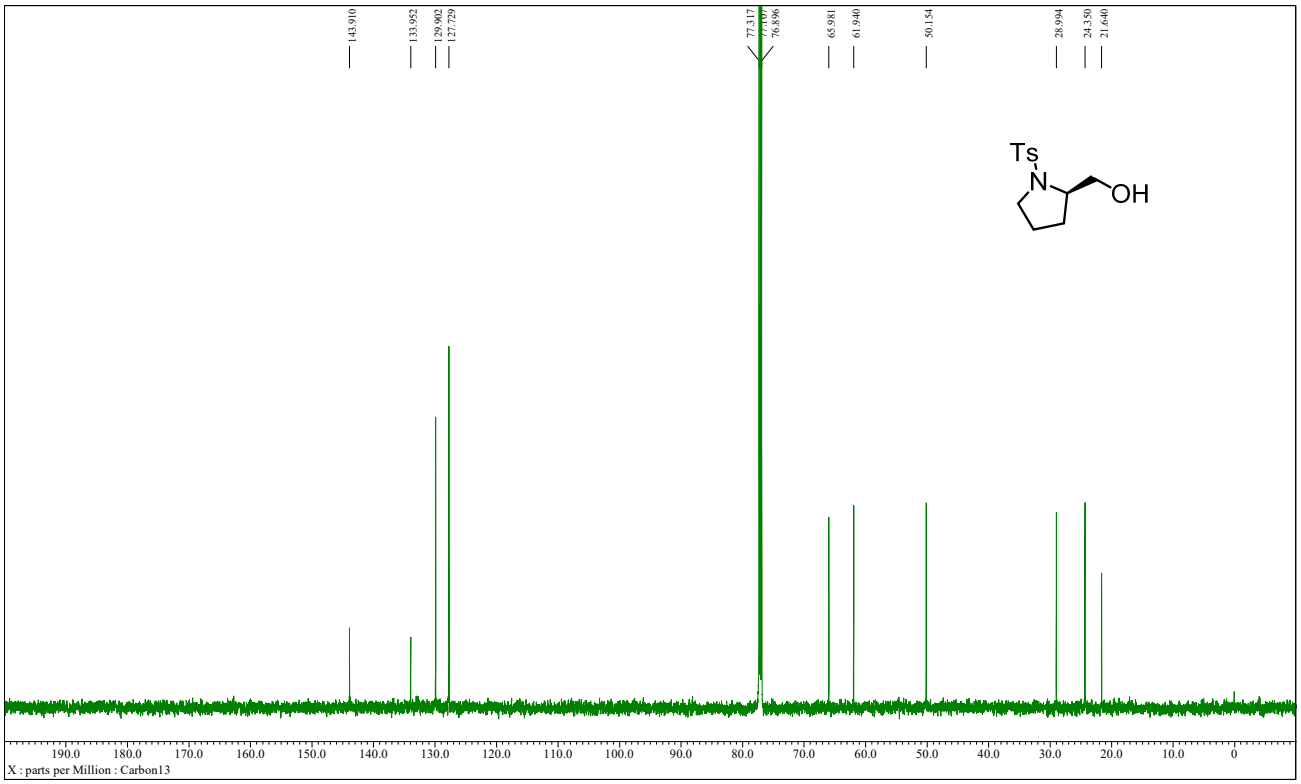

$^{13}$C NMR spectrum of compound **9** (125 MHz, $CDCl_3$)



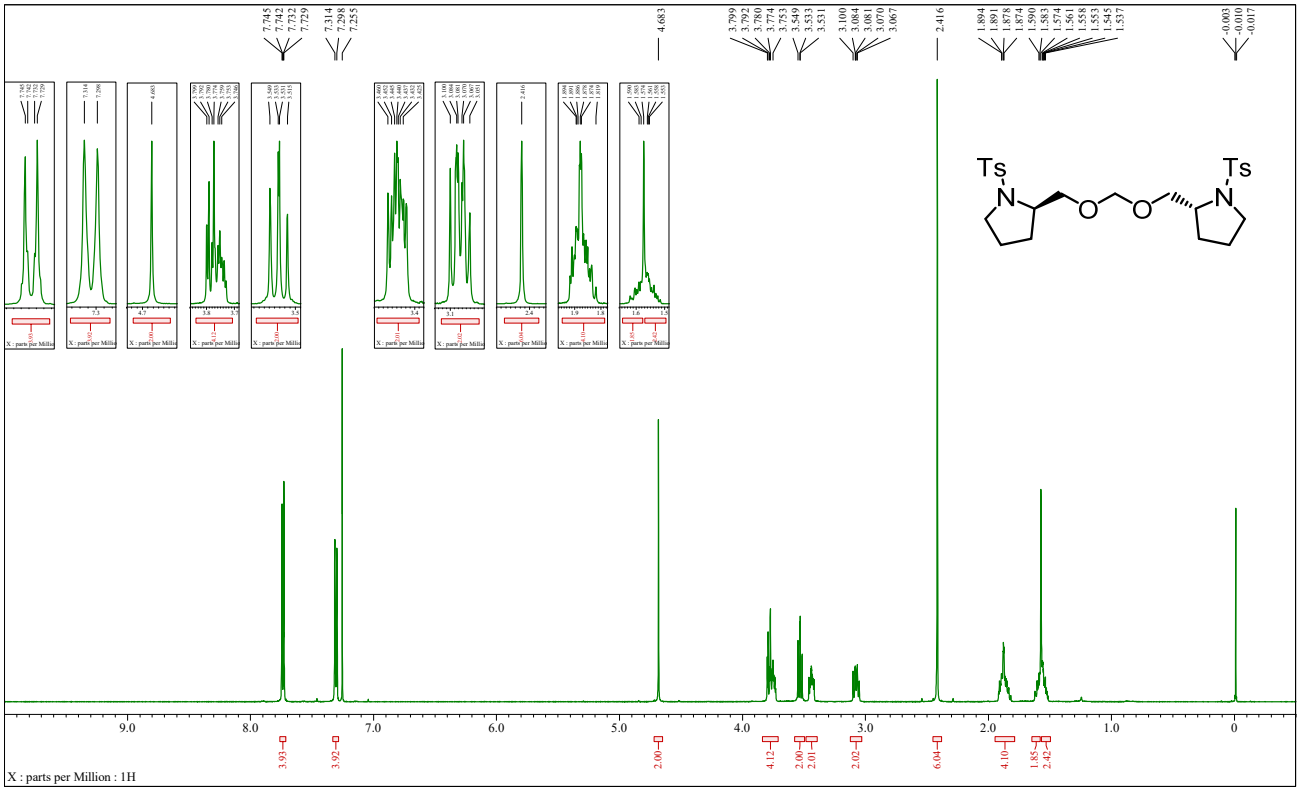
$^{1}$H NMR spectrum of compound *ent*-**4** (500 MHz, $CDCl_3$)



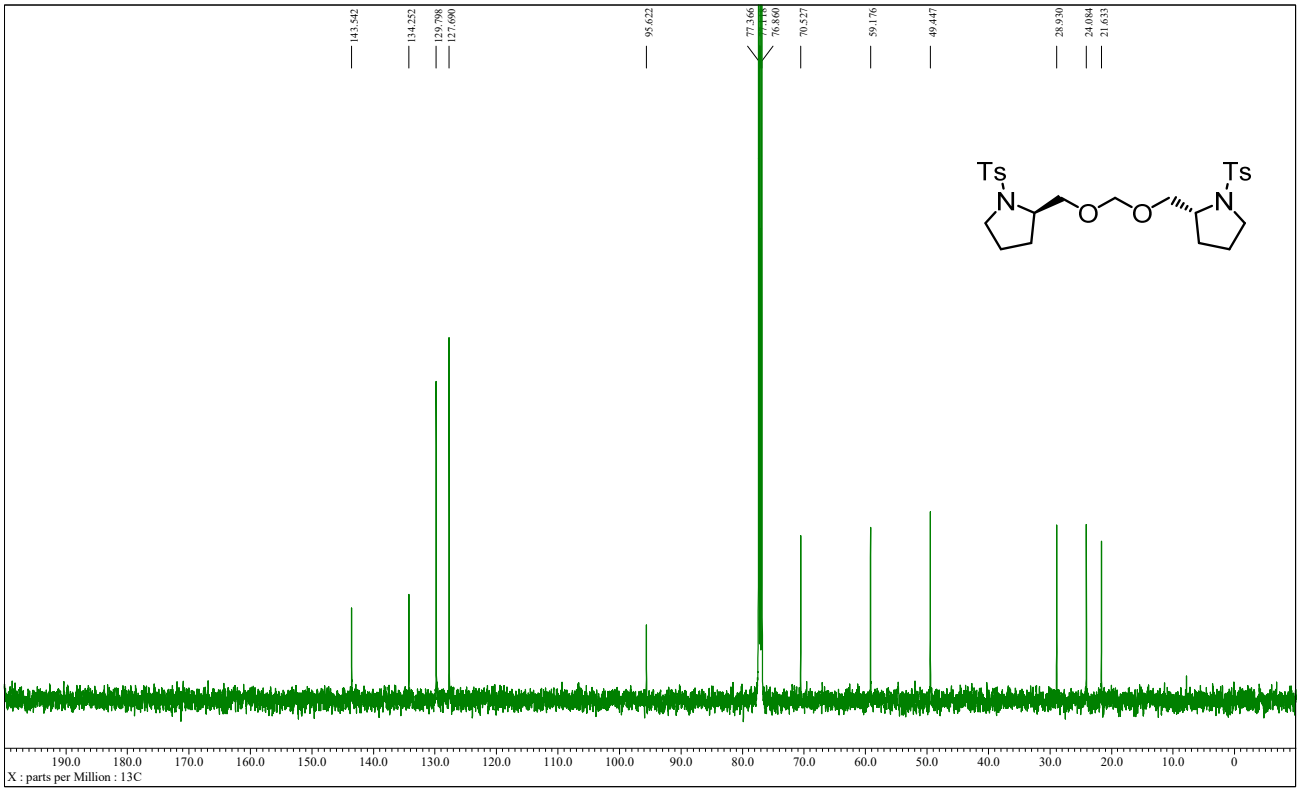

$^{13}$C NMR spectrum of compound *ent*-**4** (150 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of compound *ent*-**7** (500 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of compound *ent*-**7** (125 MHz, $CDCl_3$)



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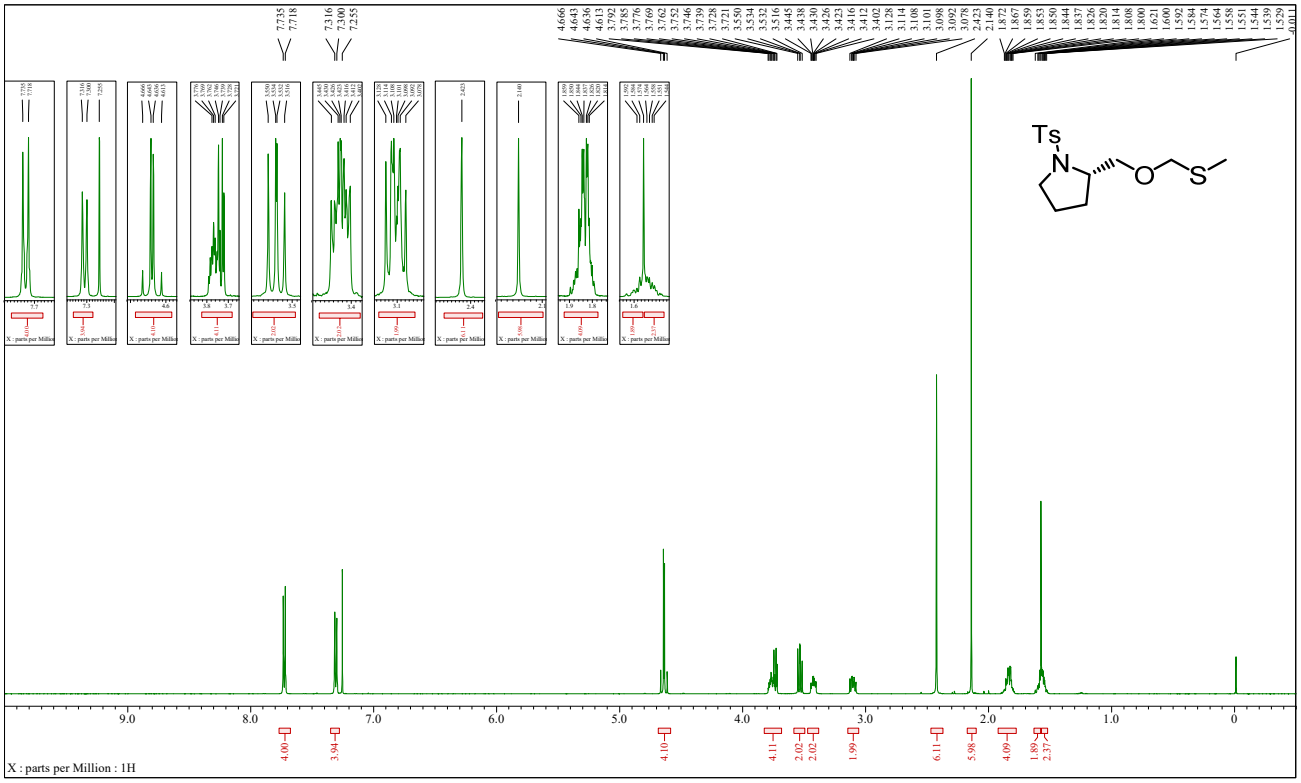
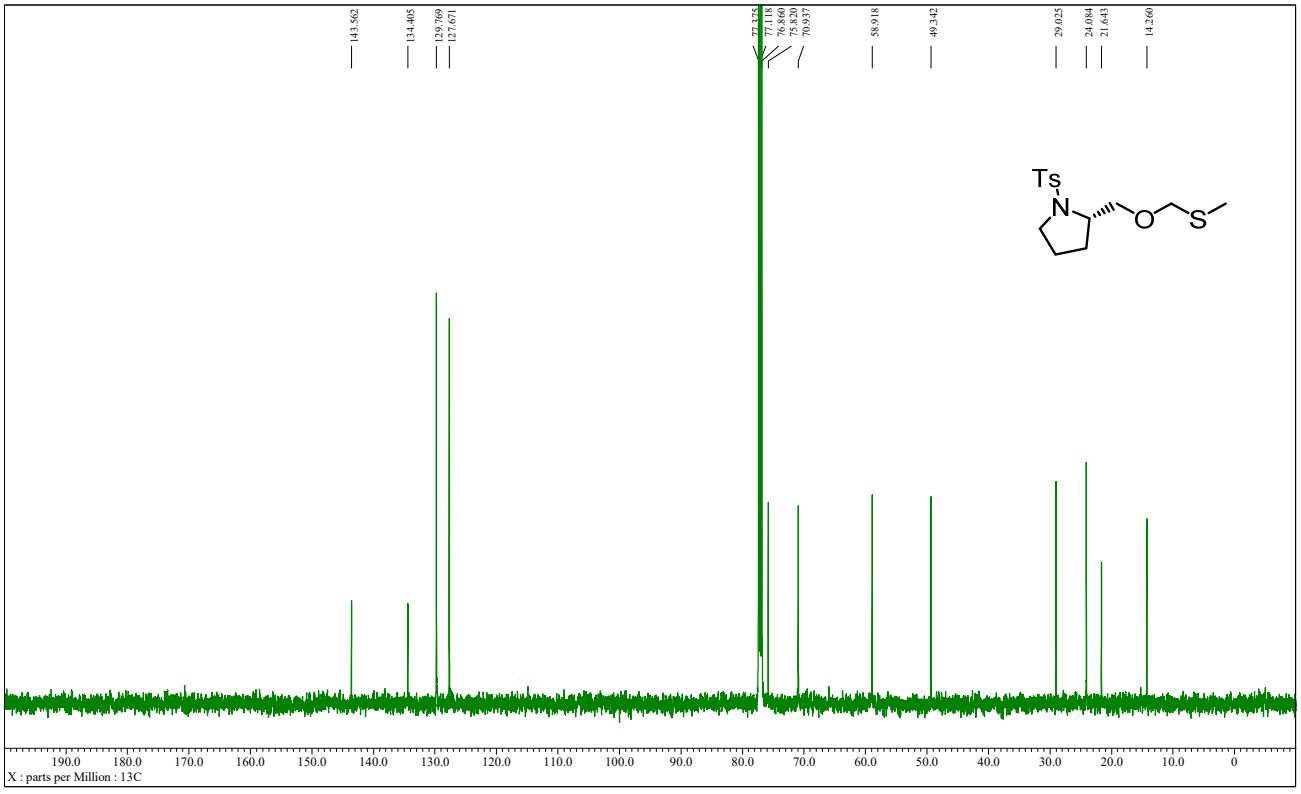
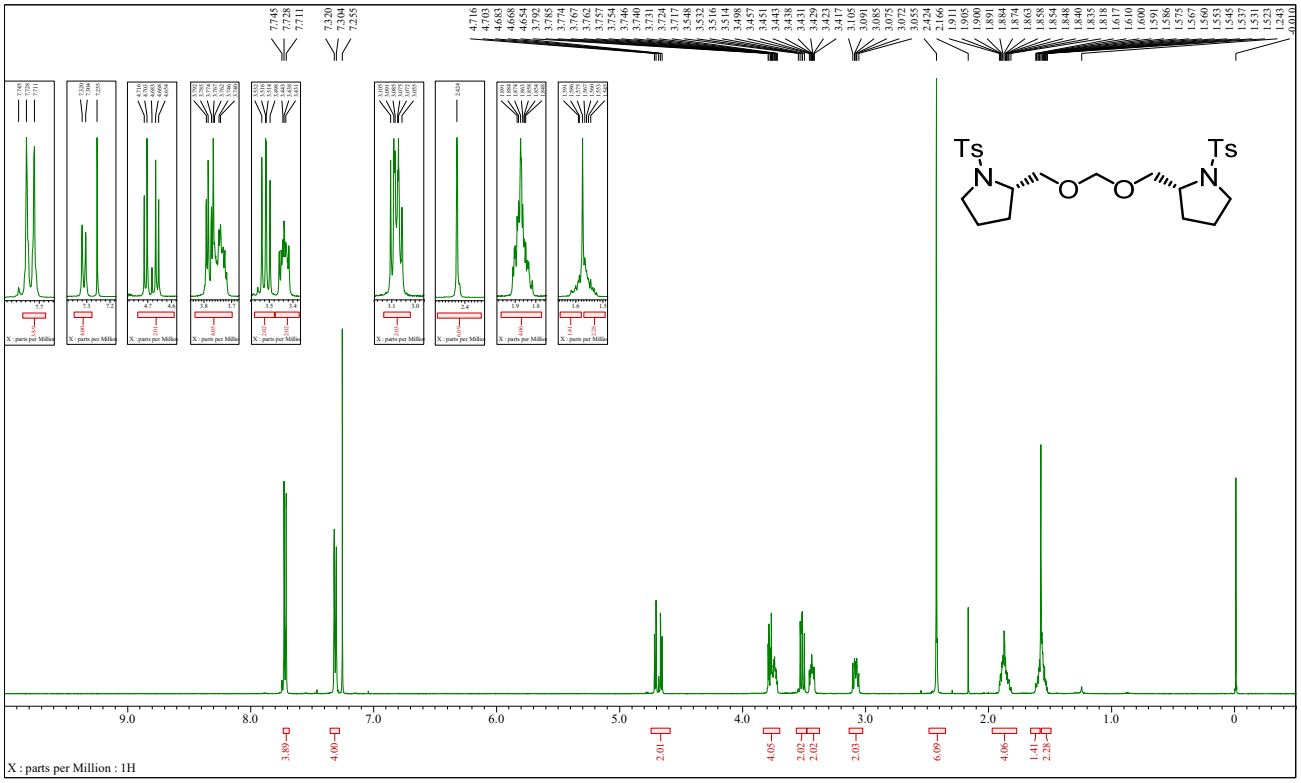


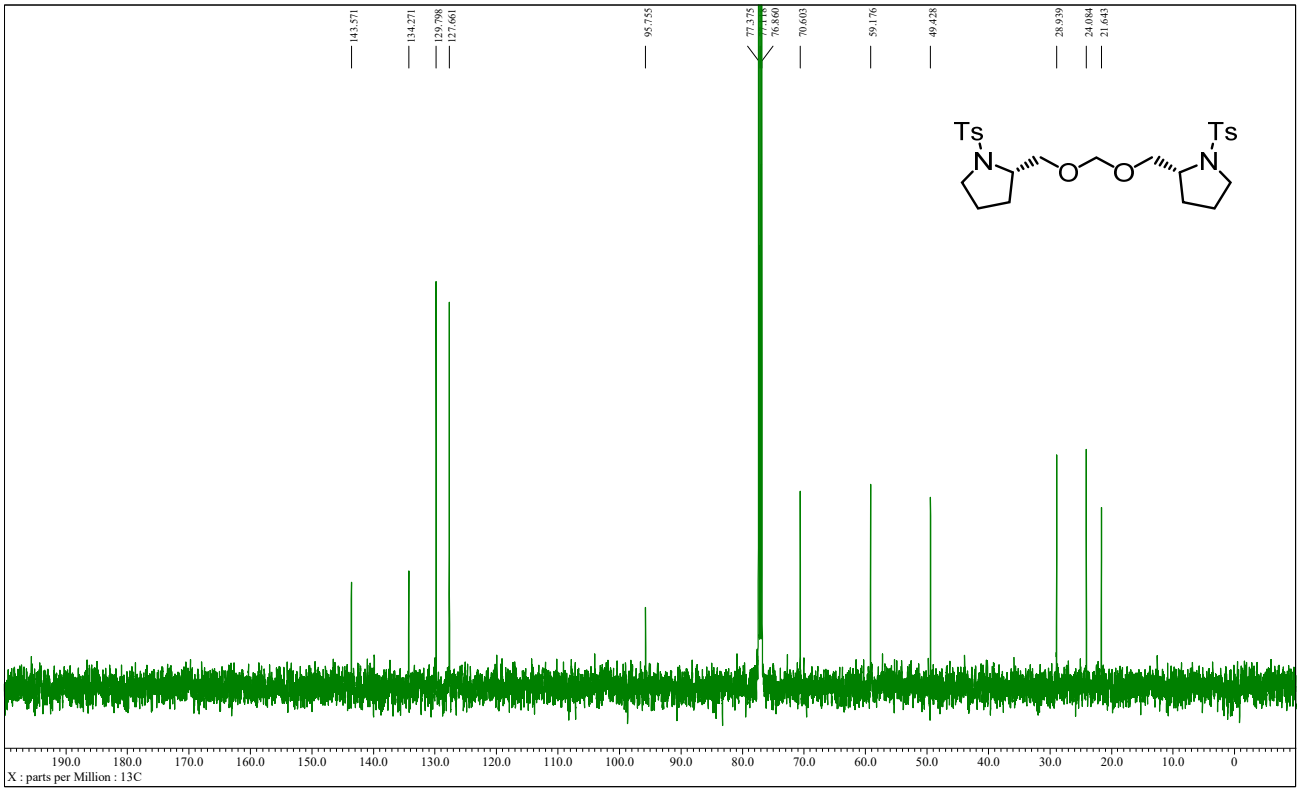

$^{13}$C NMR spectrum of compound **S7** (125 MHz, $CDCl_3$)



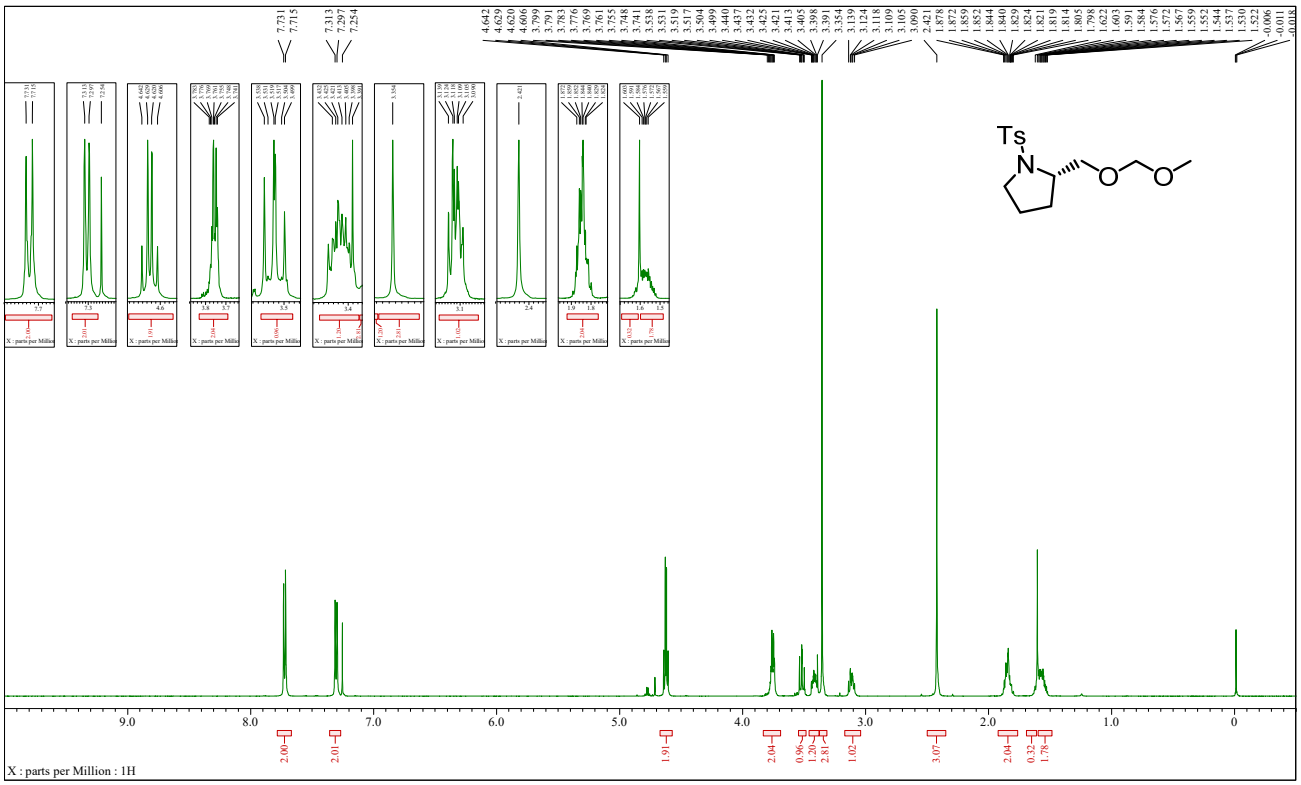
$^{1}$H NMR spectrum of compound **6** (500 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of compound **6** (125 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of compound **10** (500 MHz, $CDCl_3$)

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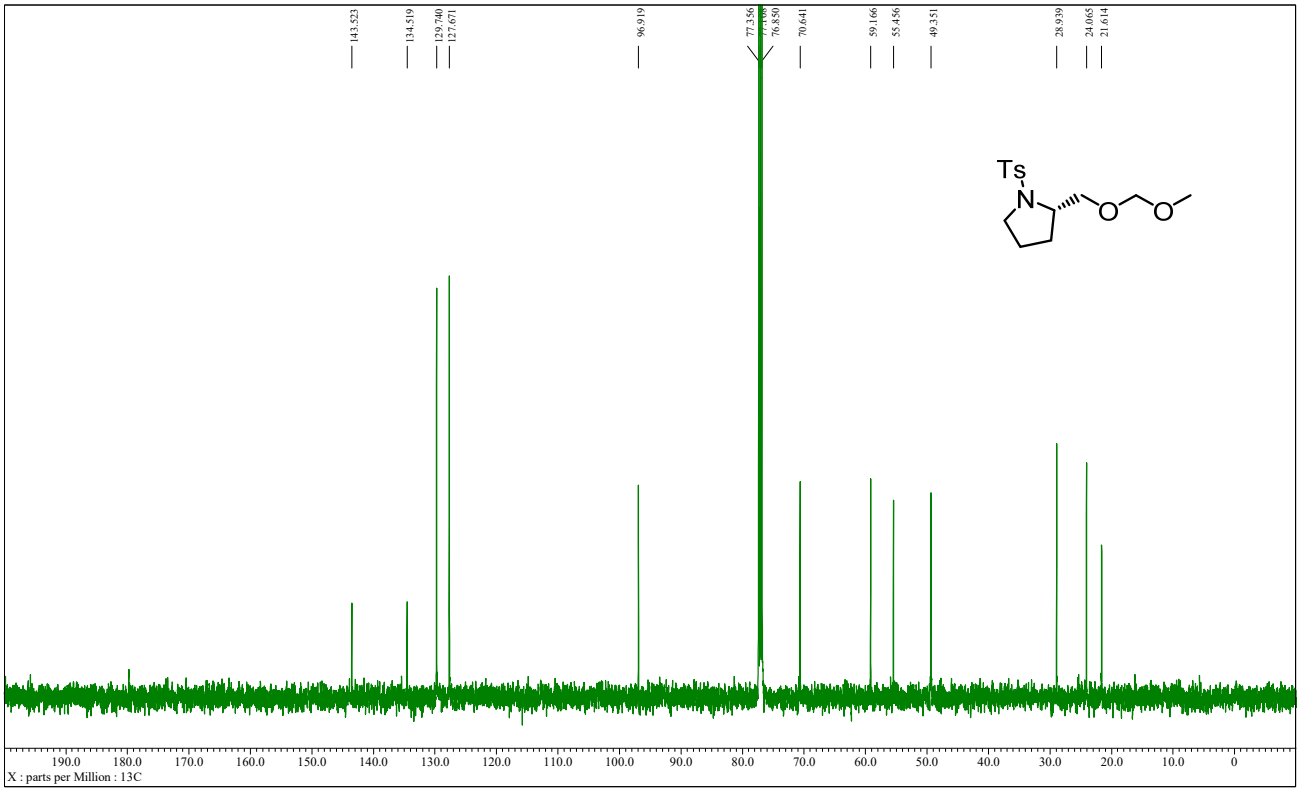
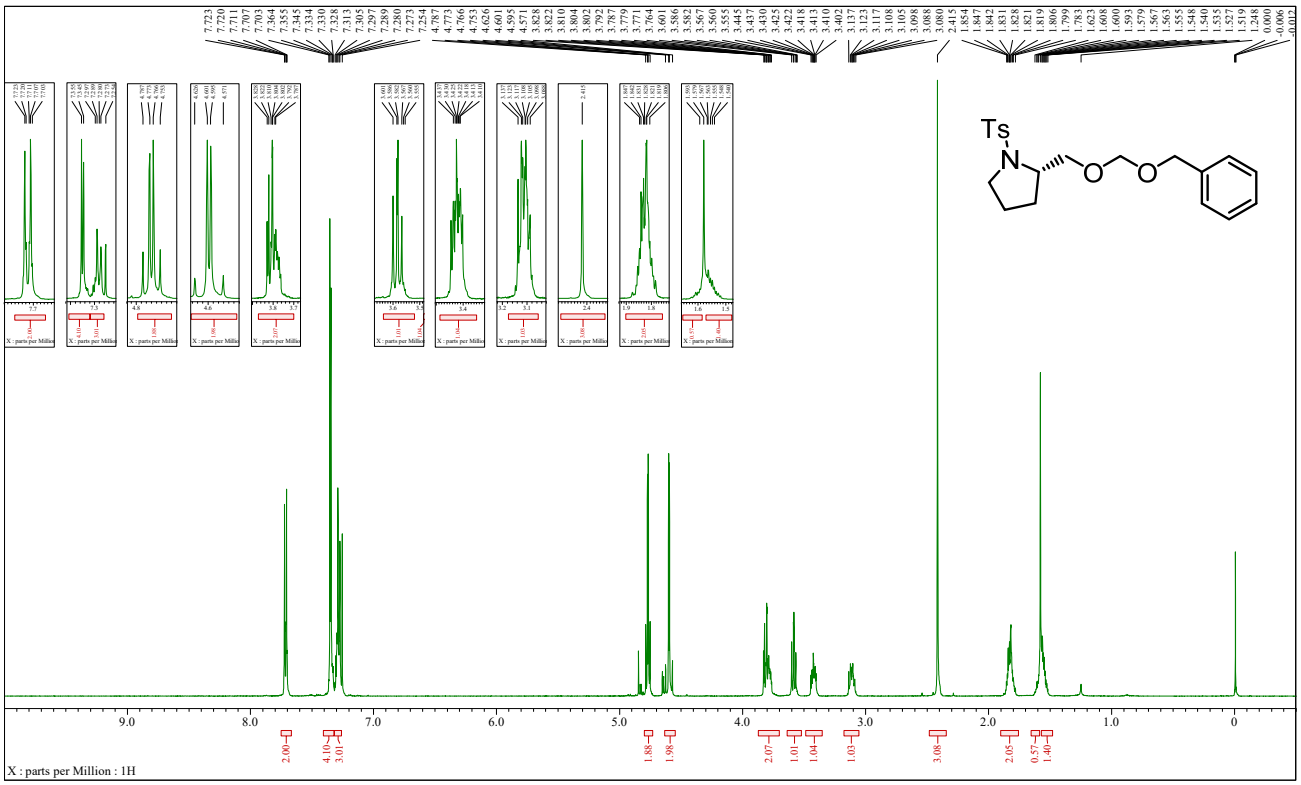


$^{1}$H NMR spectrum of compound **11** (500 MHz, $CDCl_3$)

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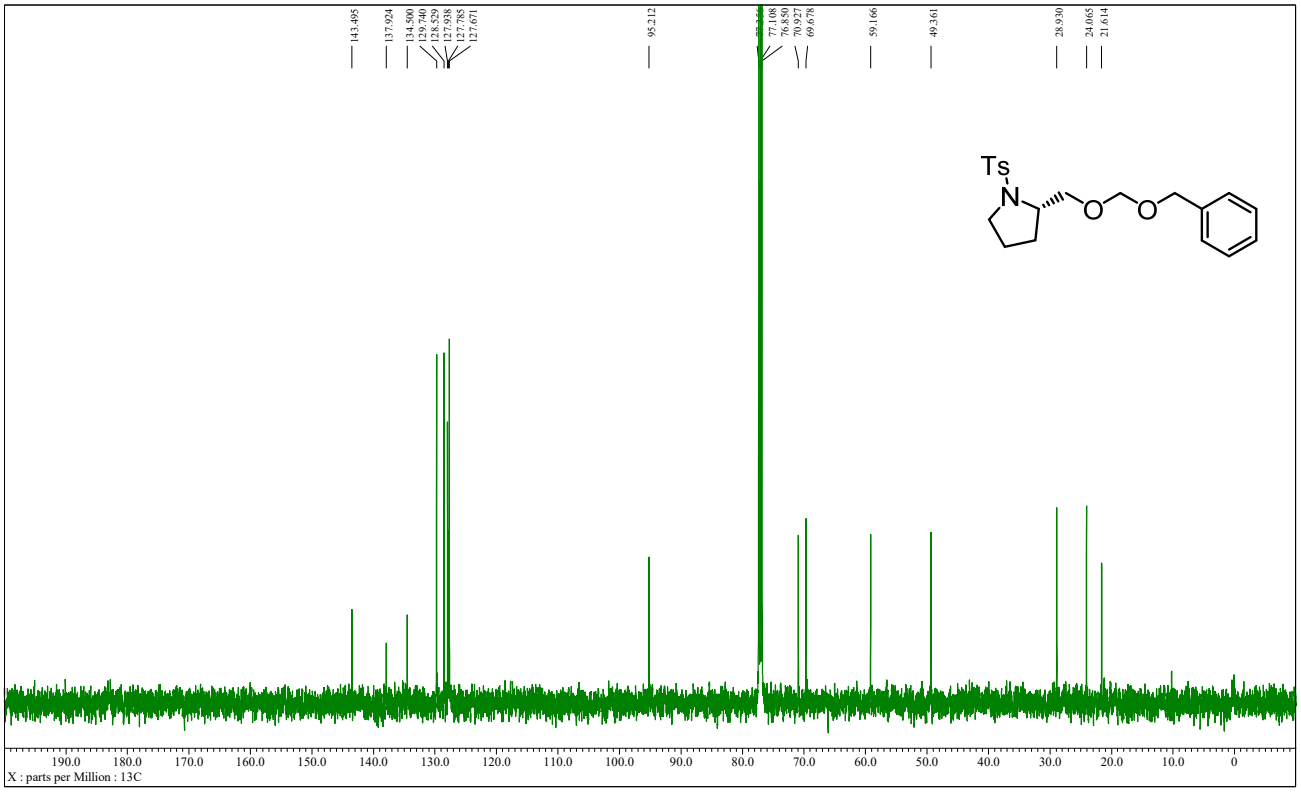

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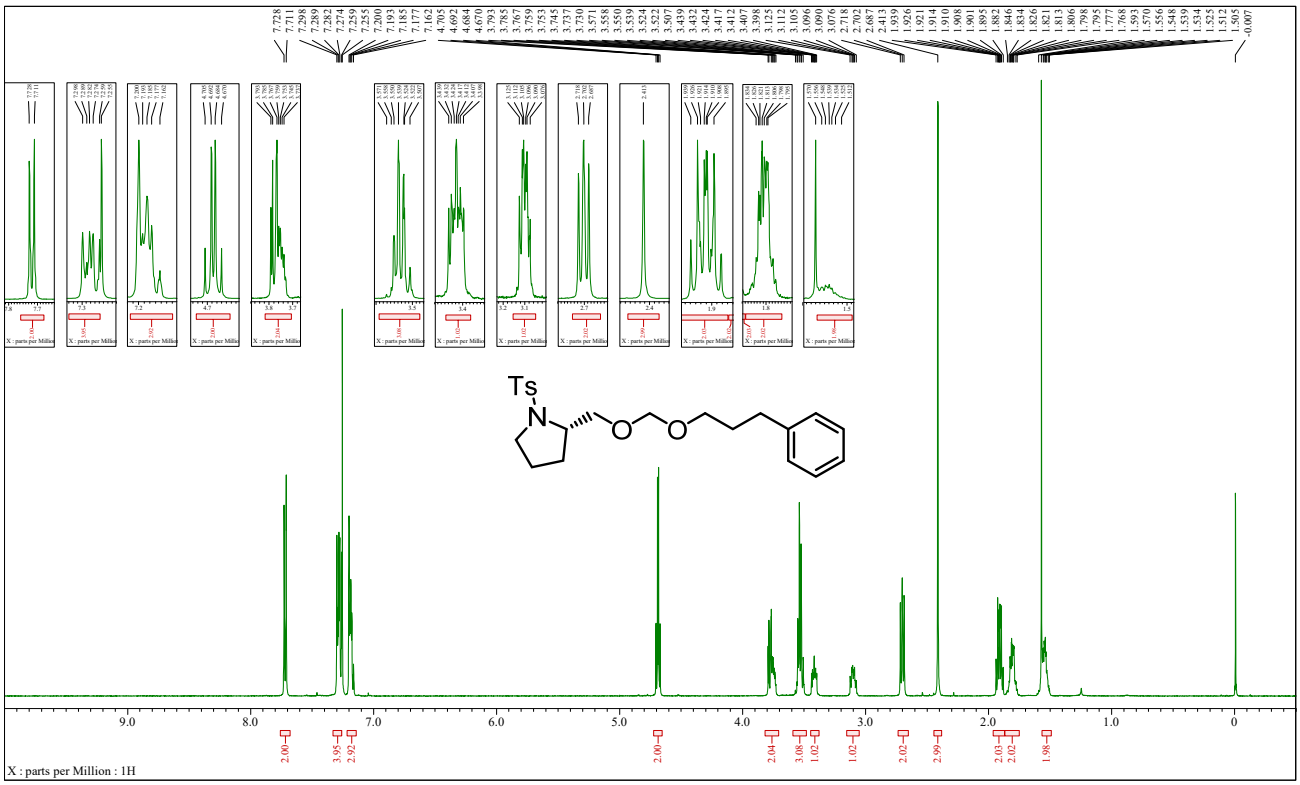
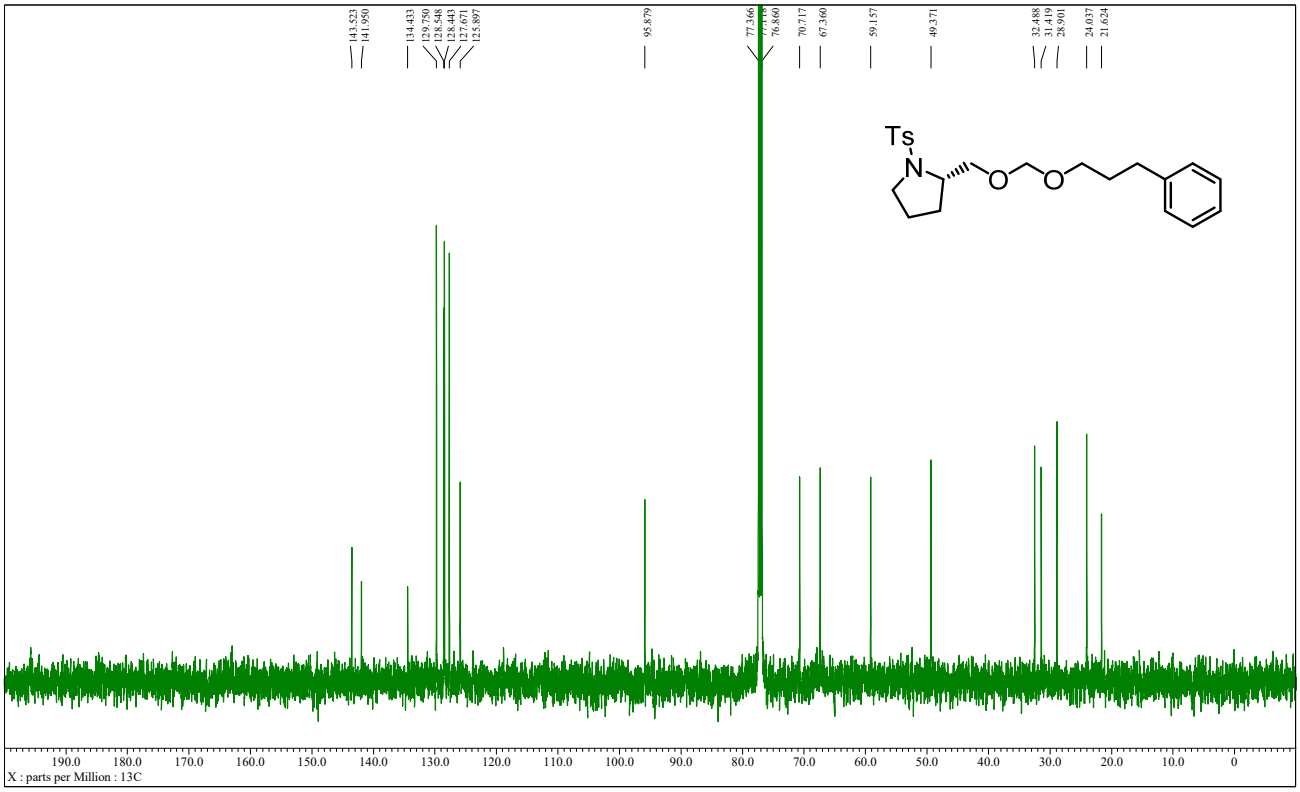
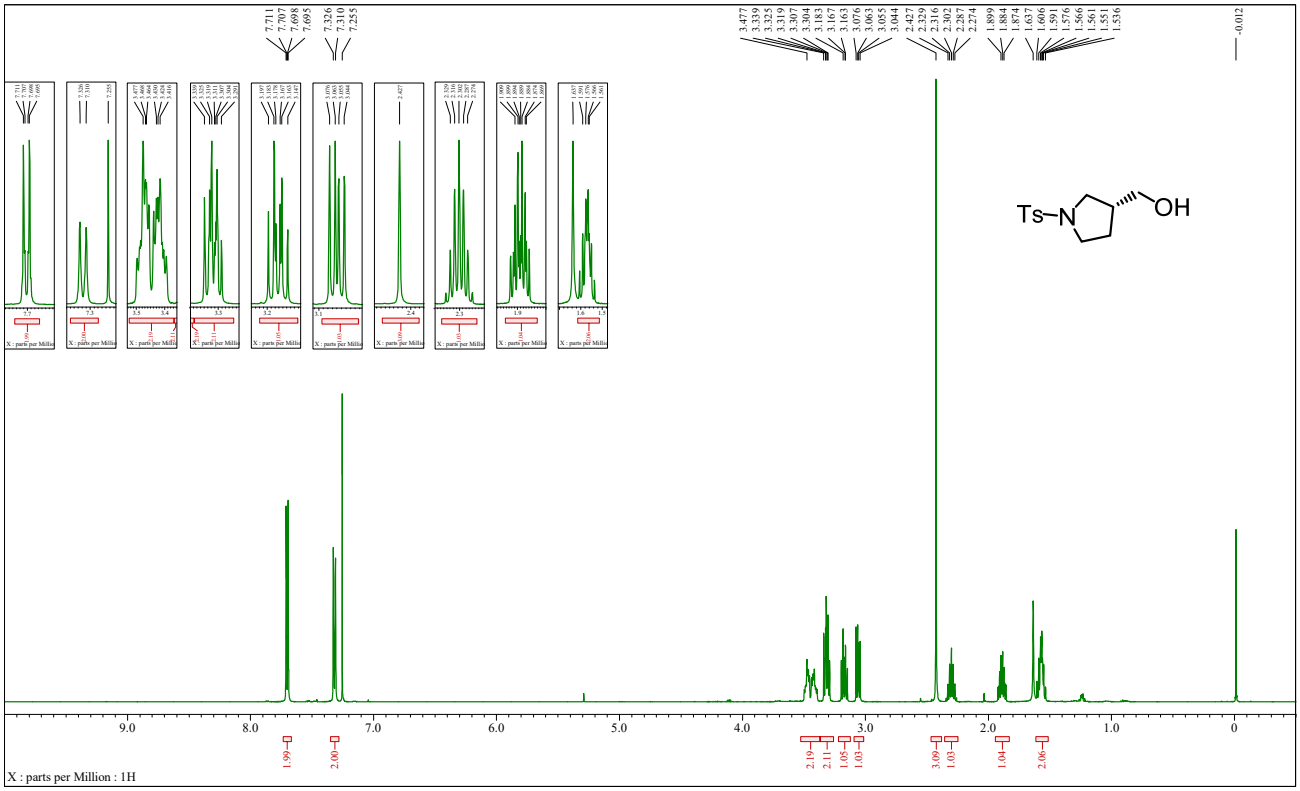



$^{13}$C NMR spectrum of compound **12** (125 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of compound **S11** (500 MHz, $CDCl_3$)

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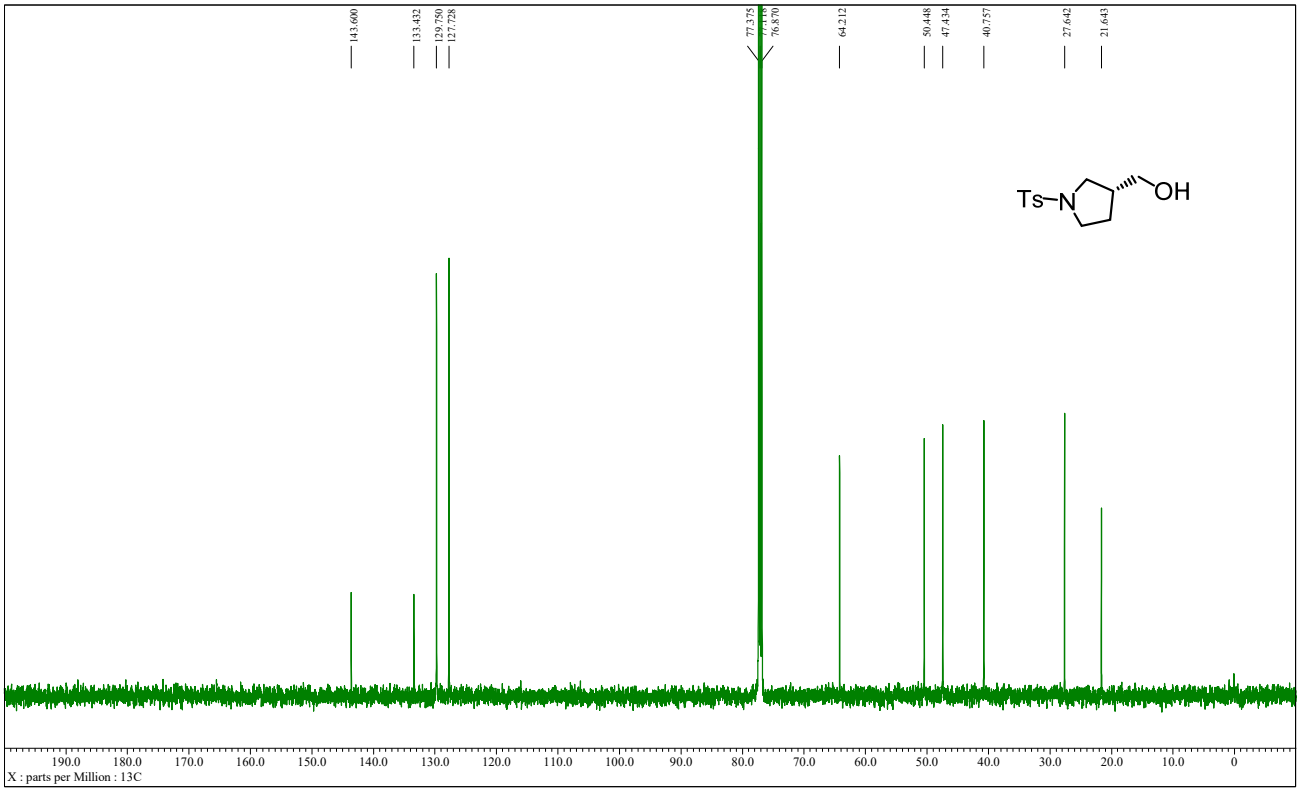
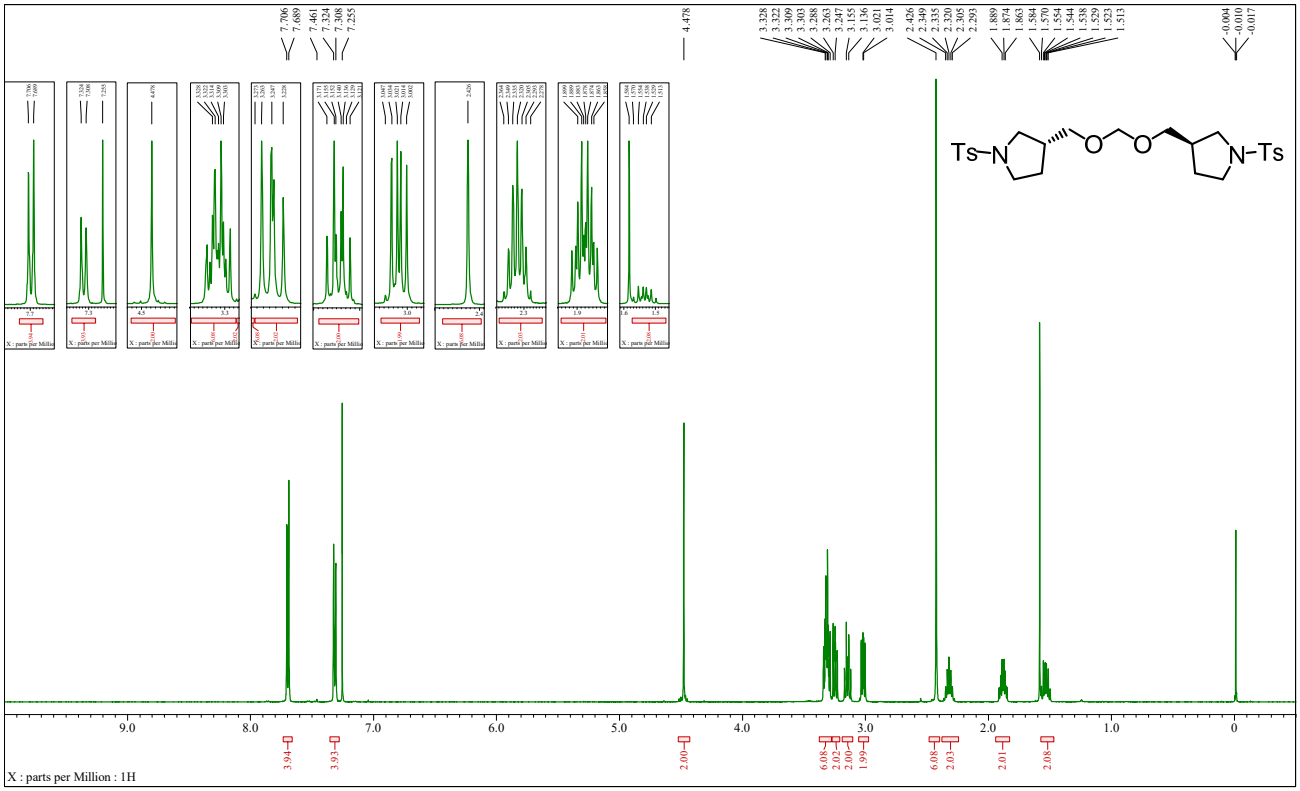
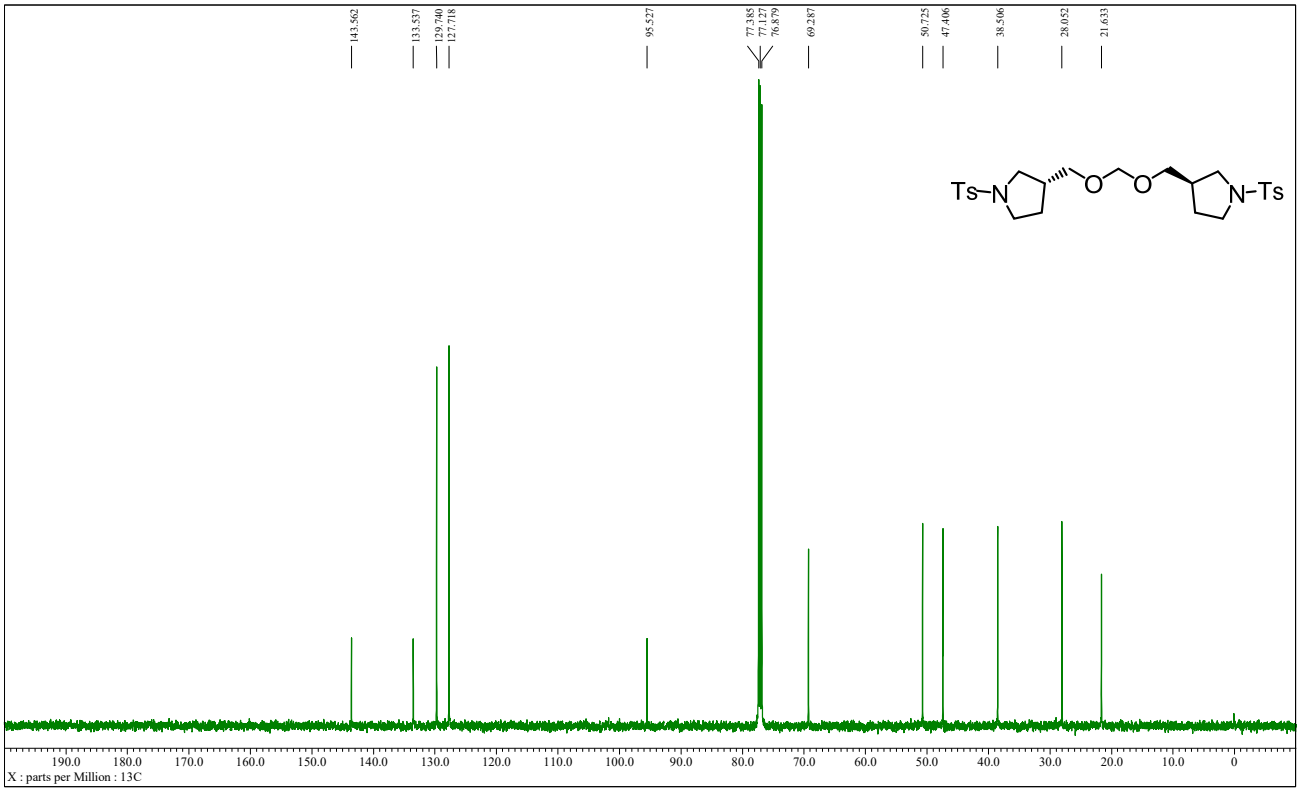


$^{1}$H NMR spectrum of compound **13** (500 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of compound **13** (125 MHz, $CDCl_3$)



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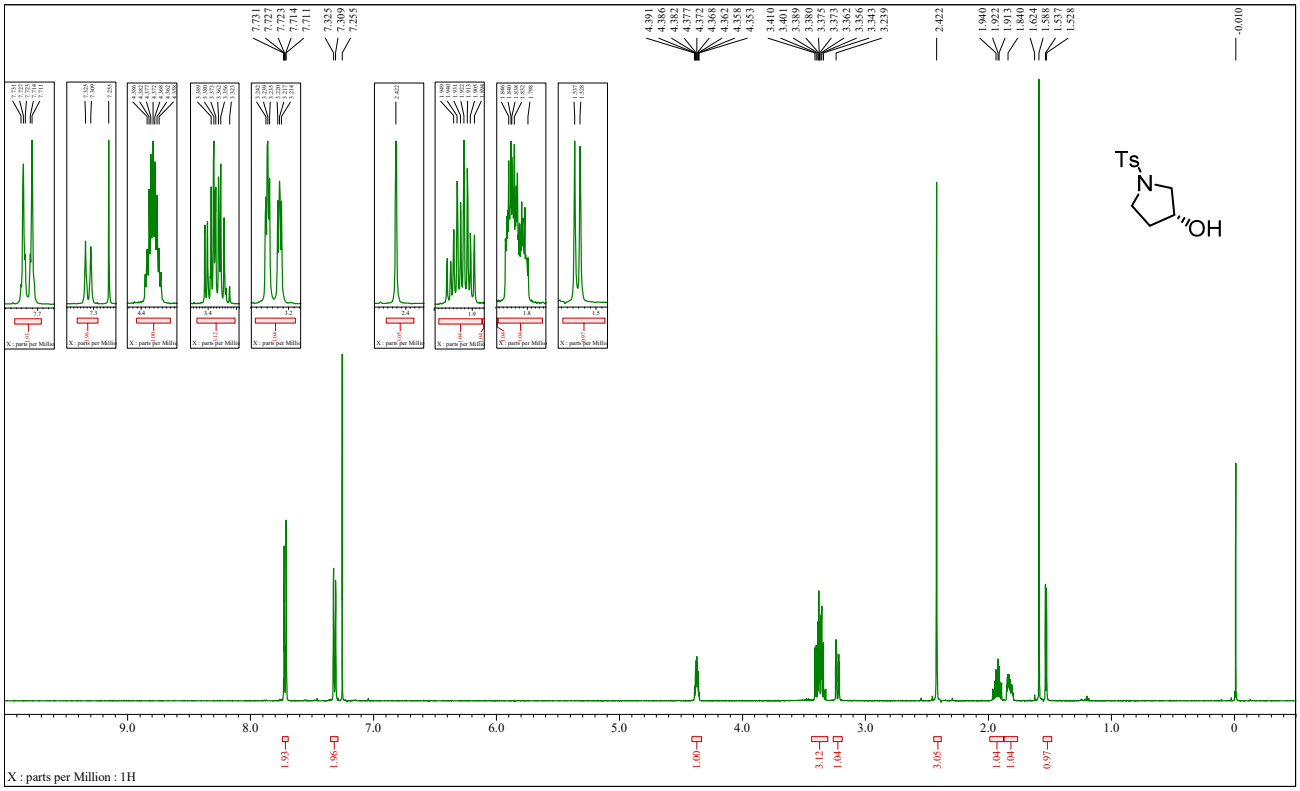


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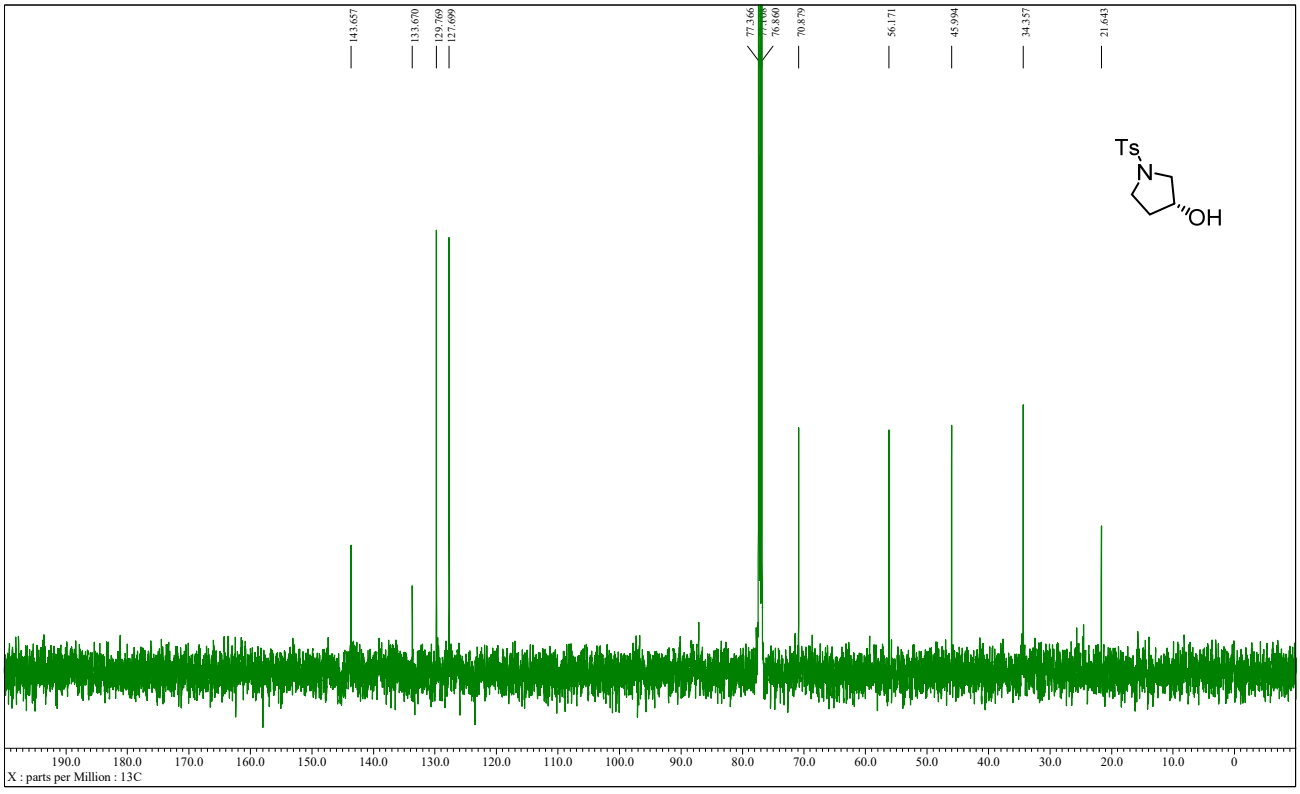
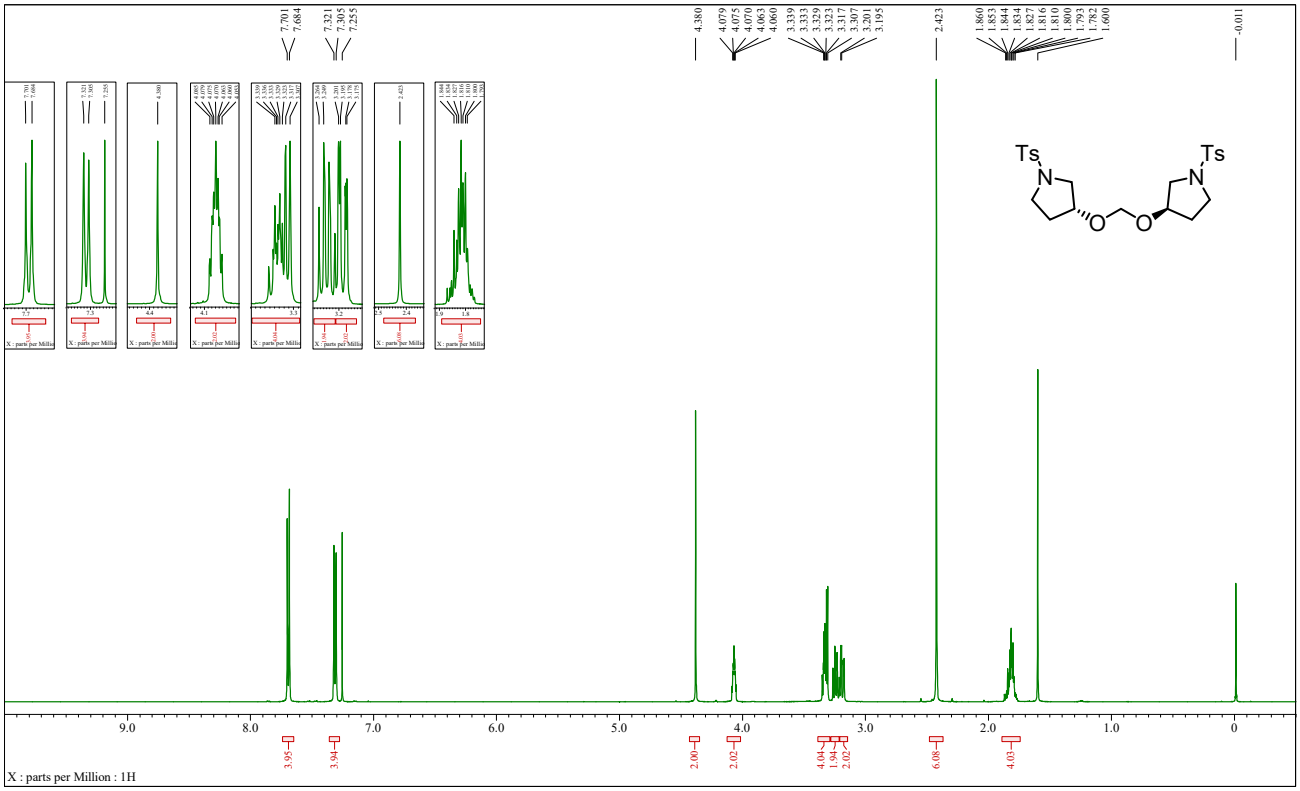
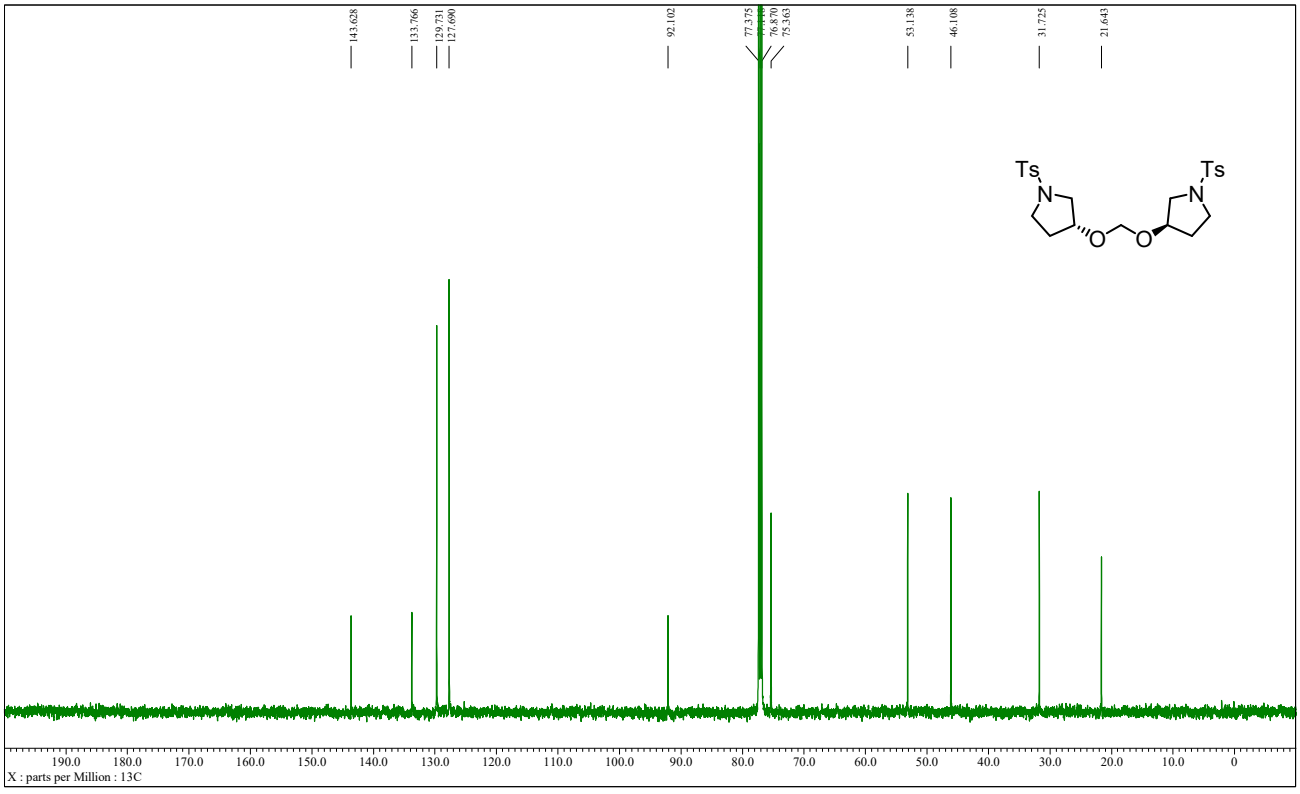


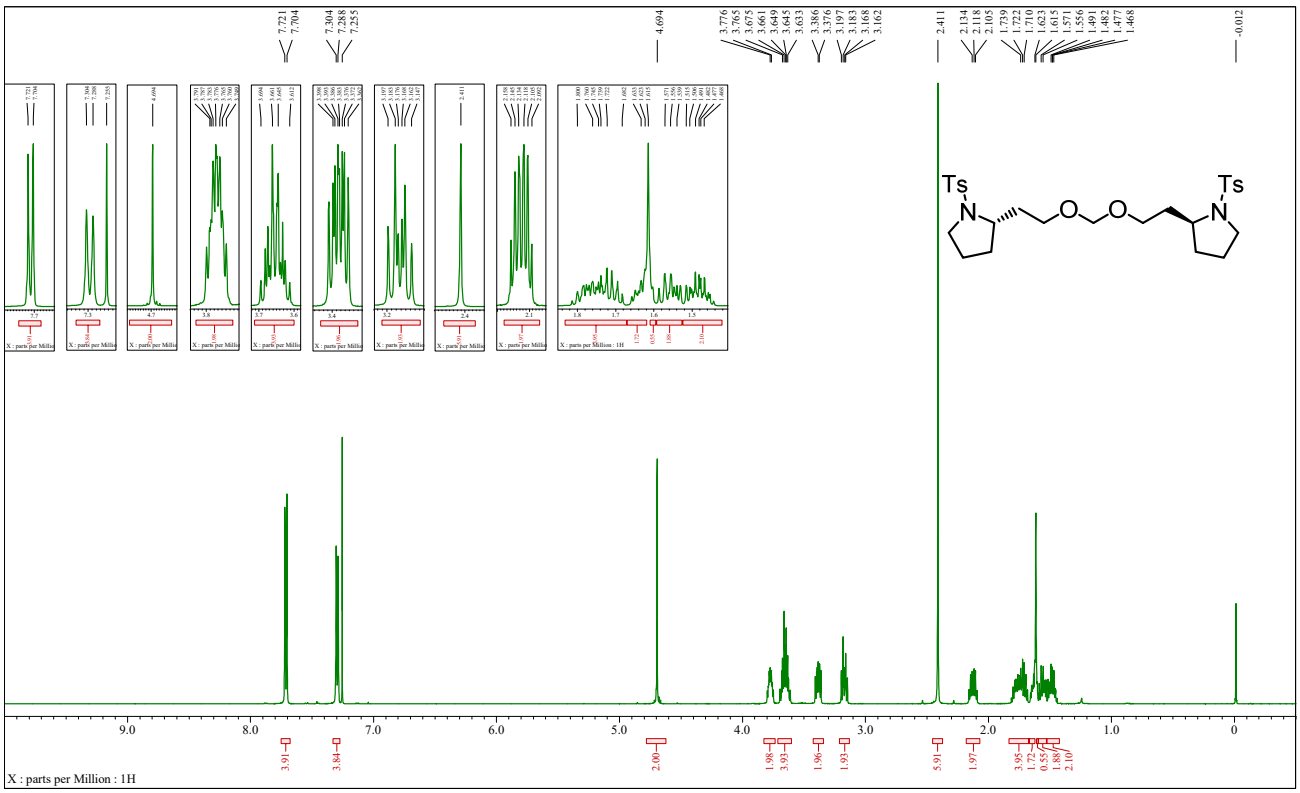
$^{1}$H NMR spectrum of compound **14** (500 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of compound **14** (125 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of compound **15** (500 MHz, $CDCl_3$)

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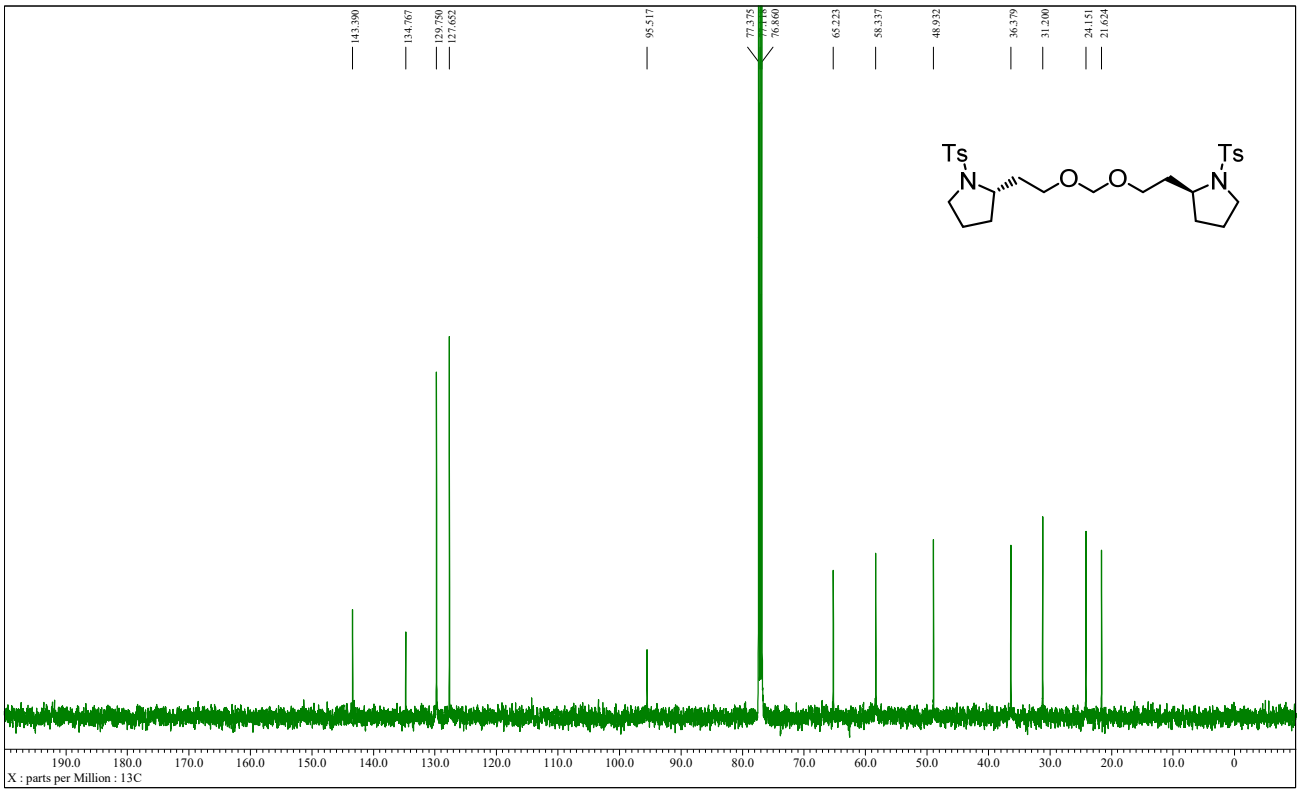
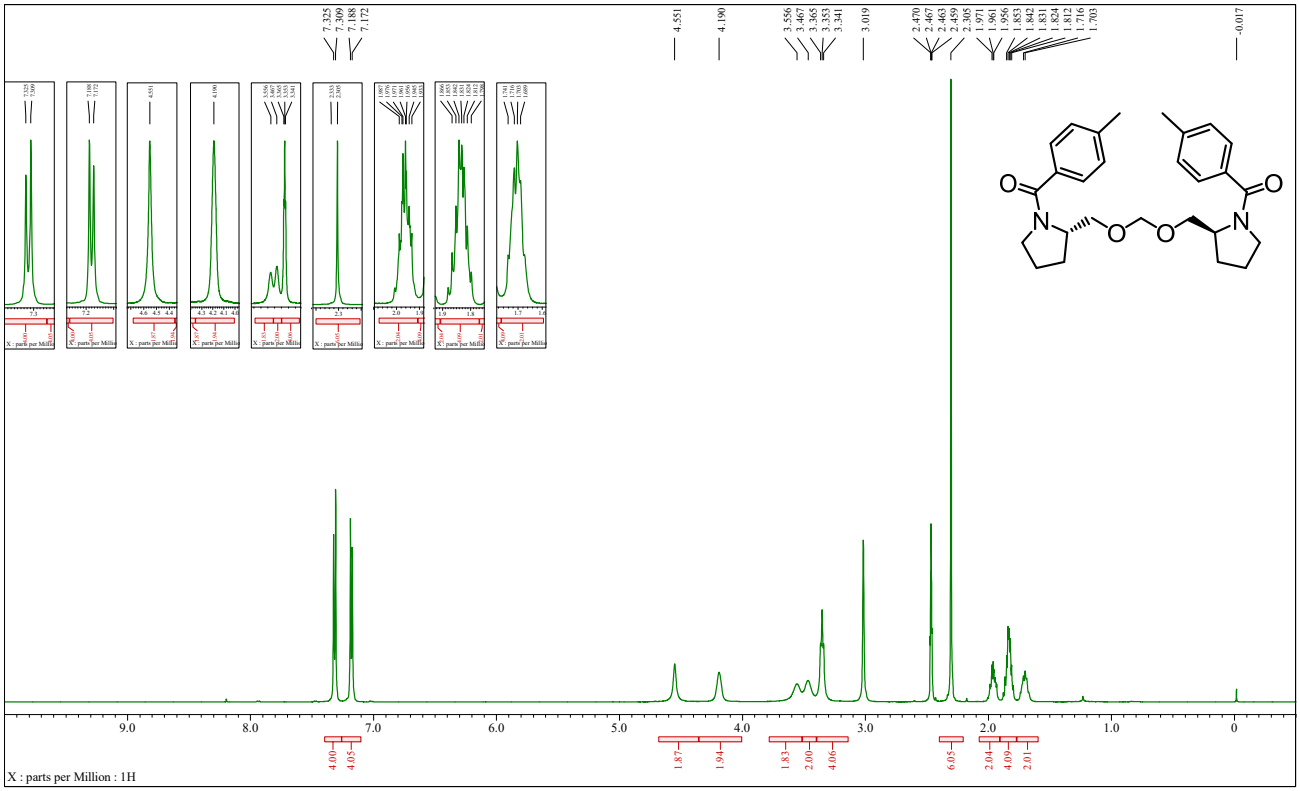
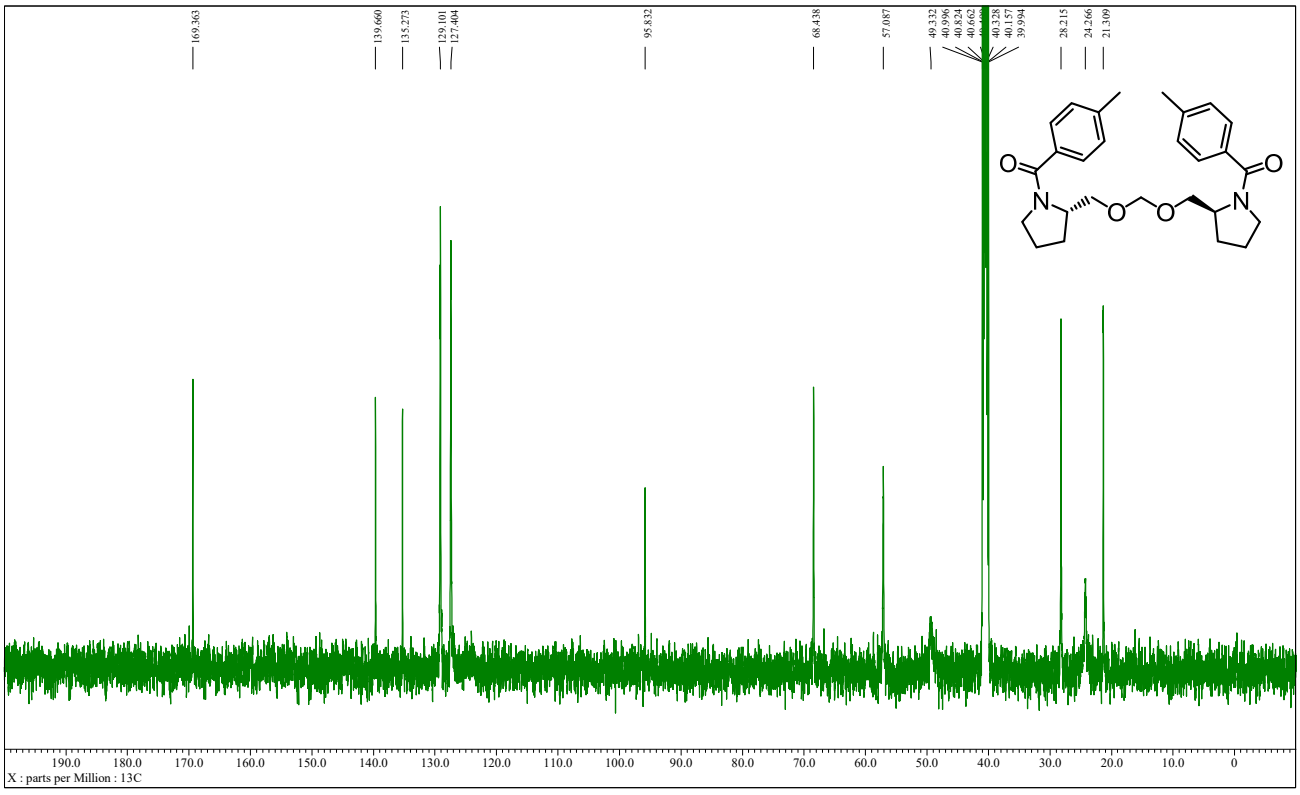


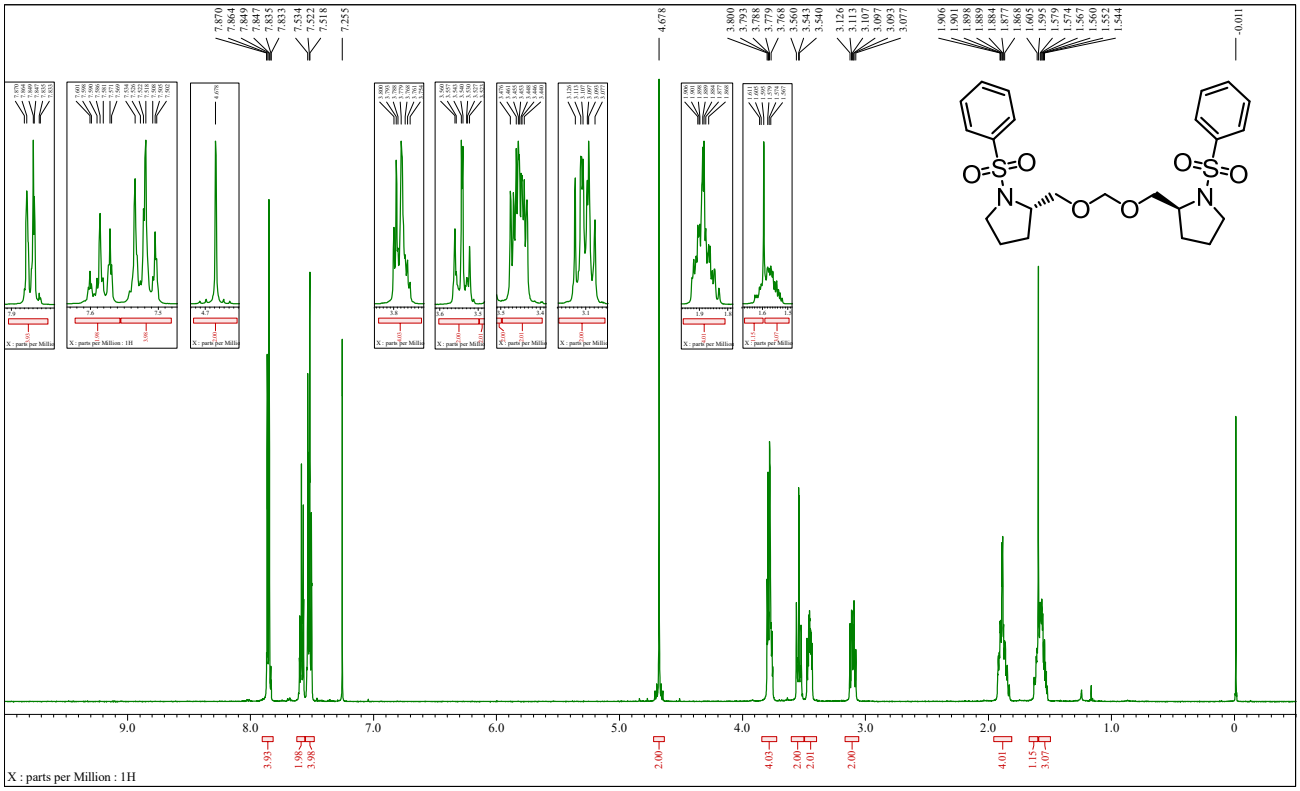
$^{1}$H NMR spectrum of compound **16** (500 MHz, DMSO-$d_6$, 95 °C)




$^{13}$C NMR spectrum of compound **16** (125 MHz, DMSO-$d_6$, 95 °C)



$^{1}$H NMR spectrum of compound **17** (500 MHz, $CDCl_3$)

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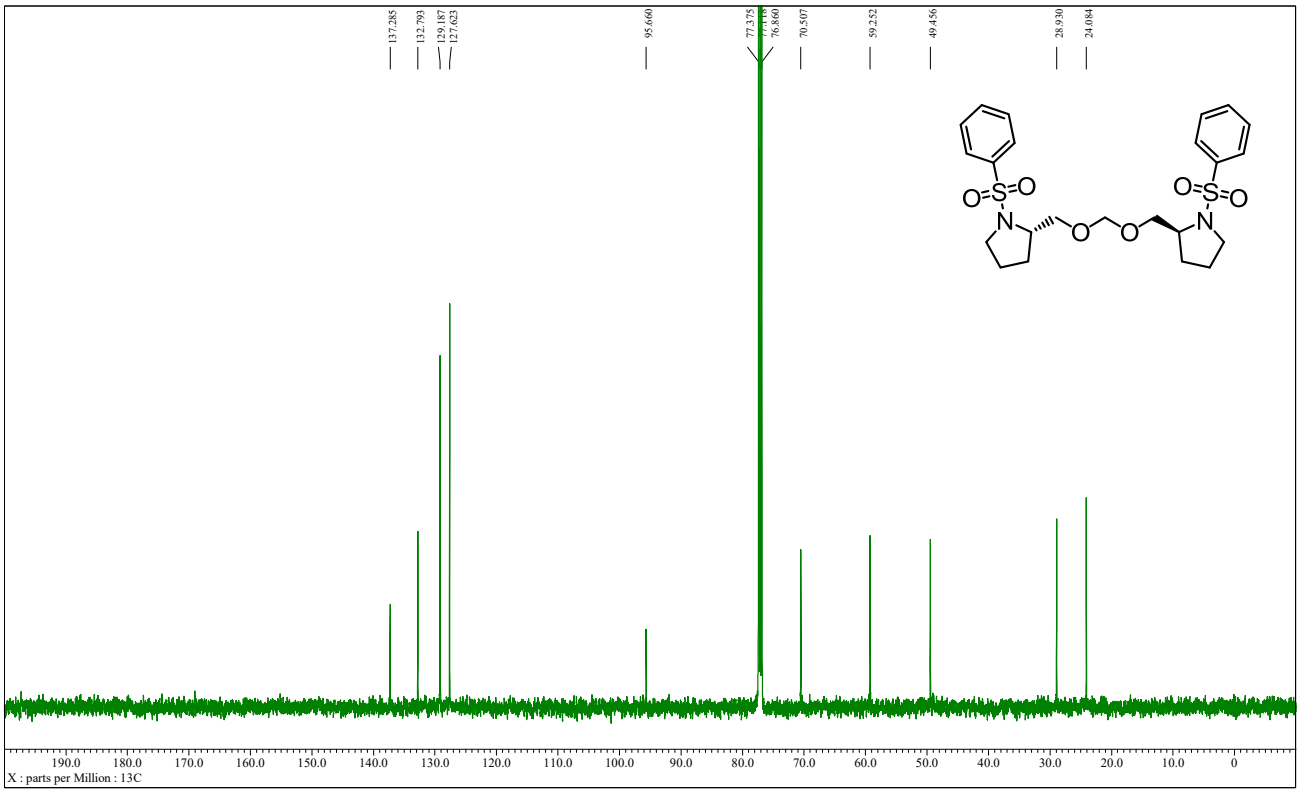
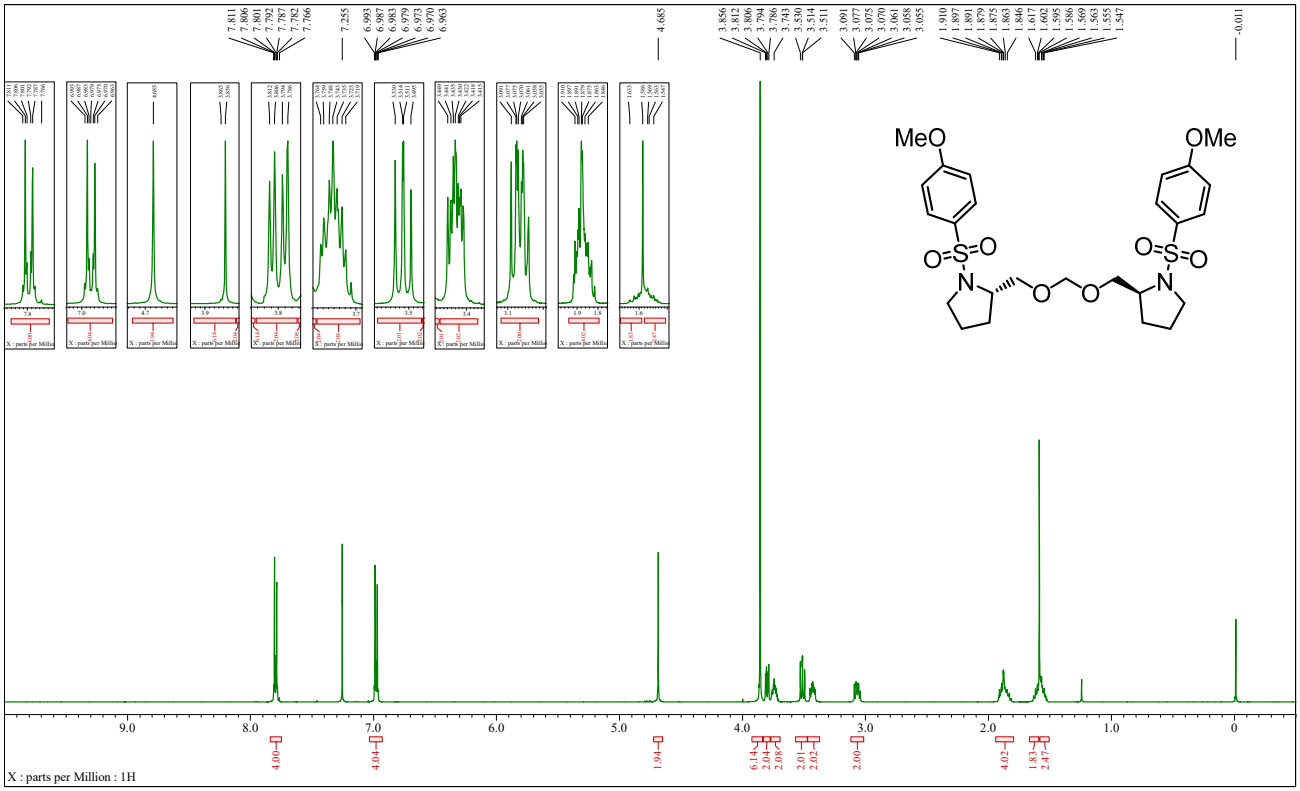
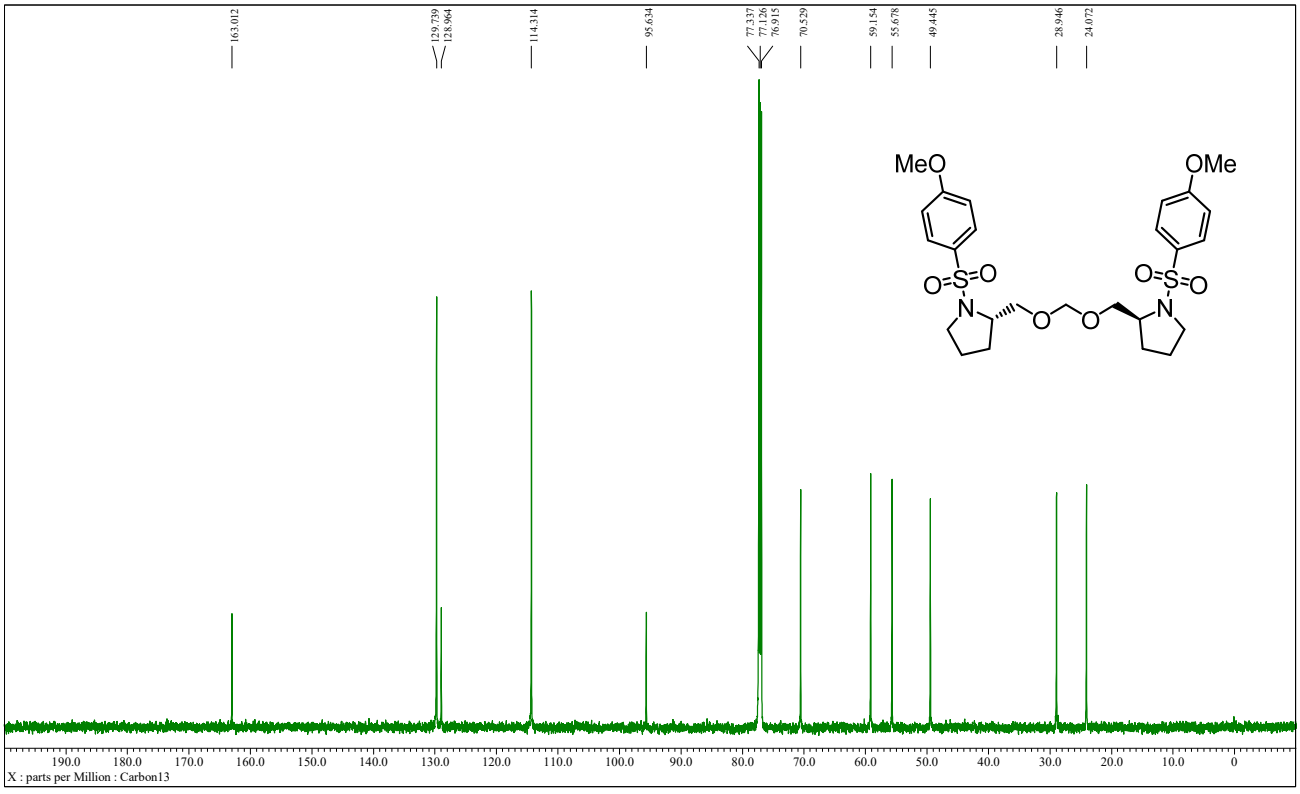


$^{1}$H NMR spectrum of compound **18** (500 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of compound **18** (150 MHz, $CDCl_3$)



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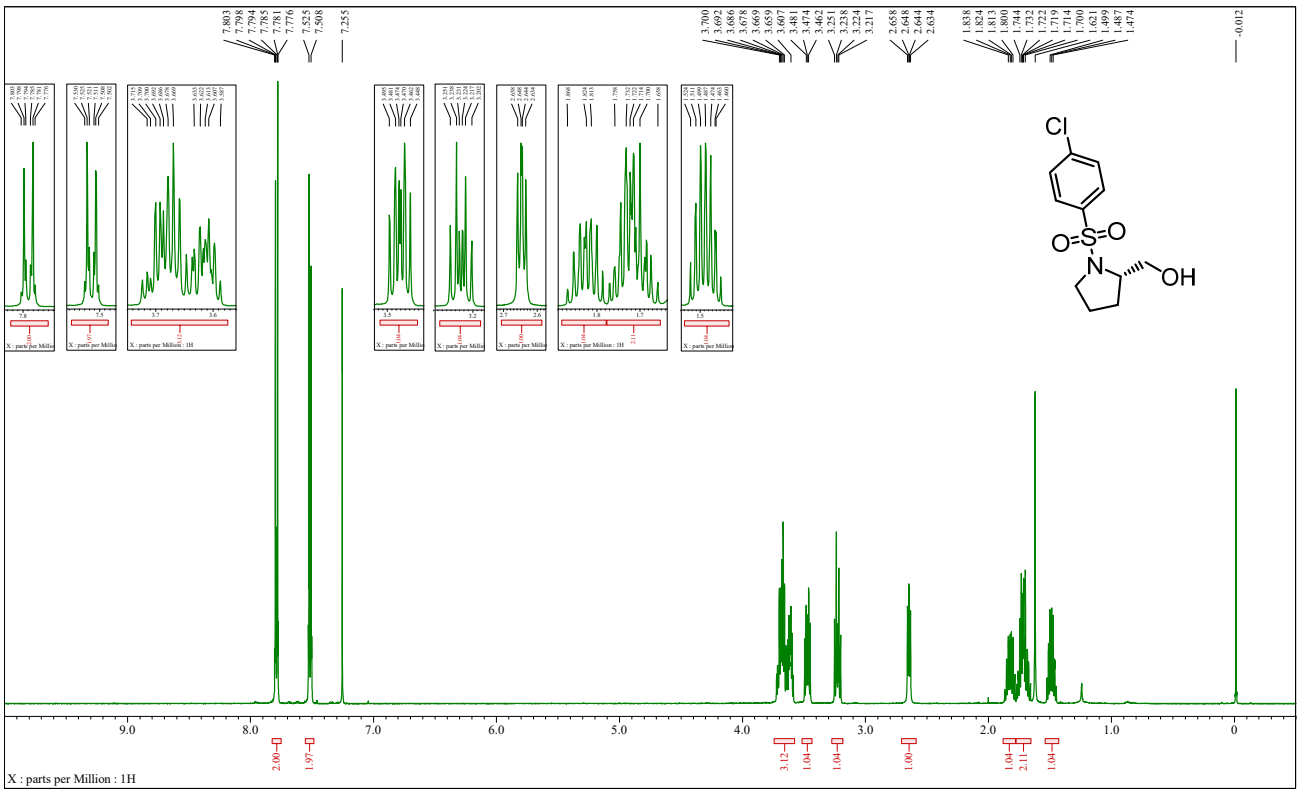
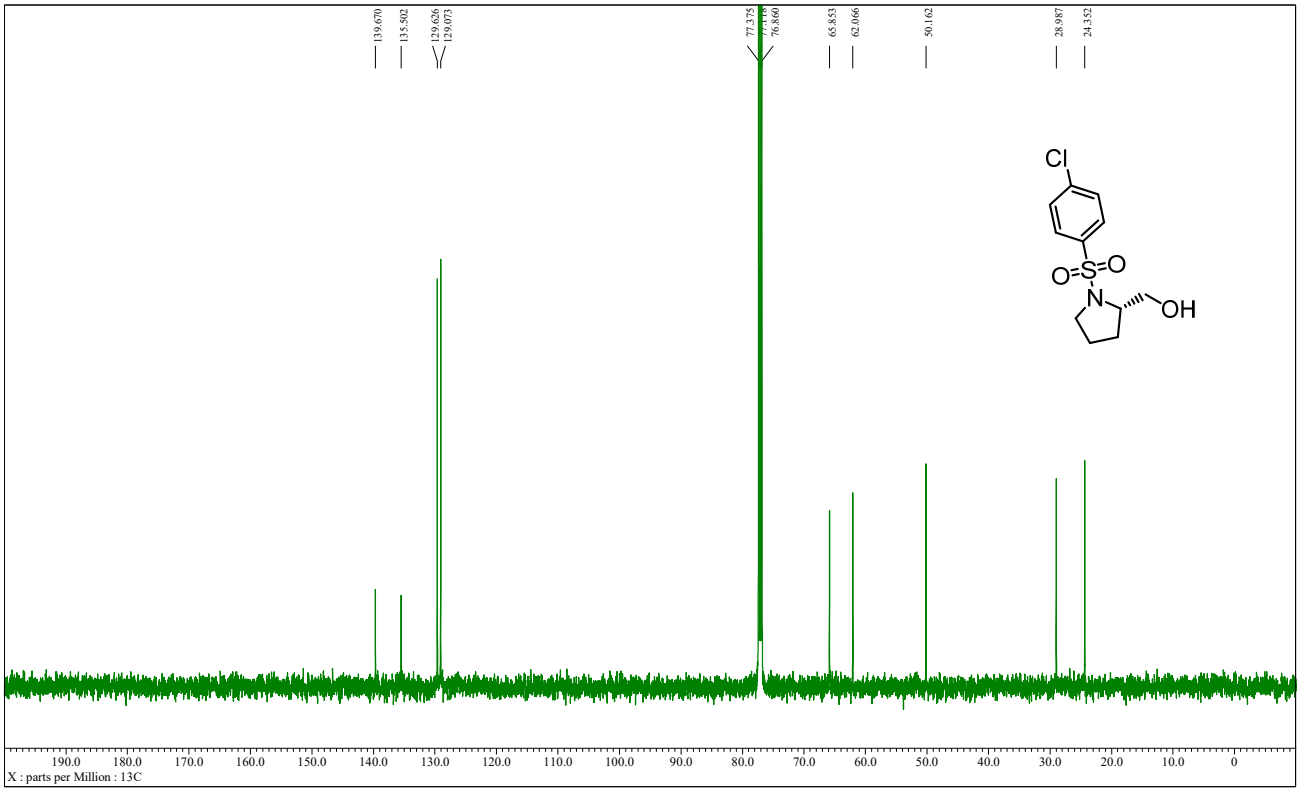
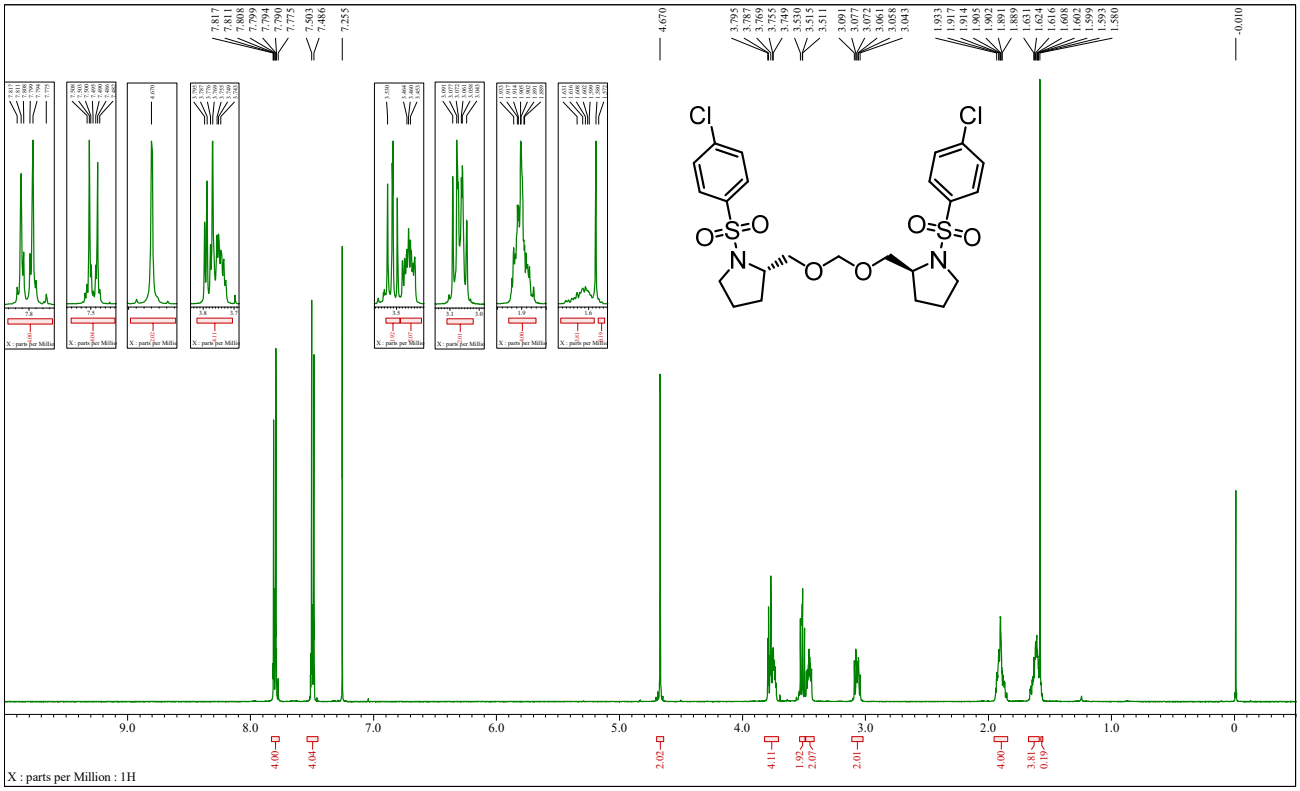



$^{13}$C NMR spectrum of compound **S20** (125 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of compound **19** (500 MHz, $CDCl_3$)

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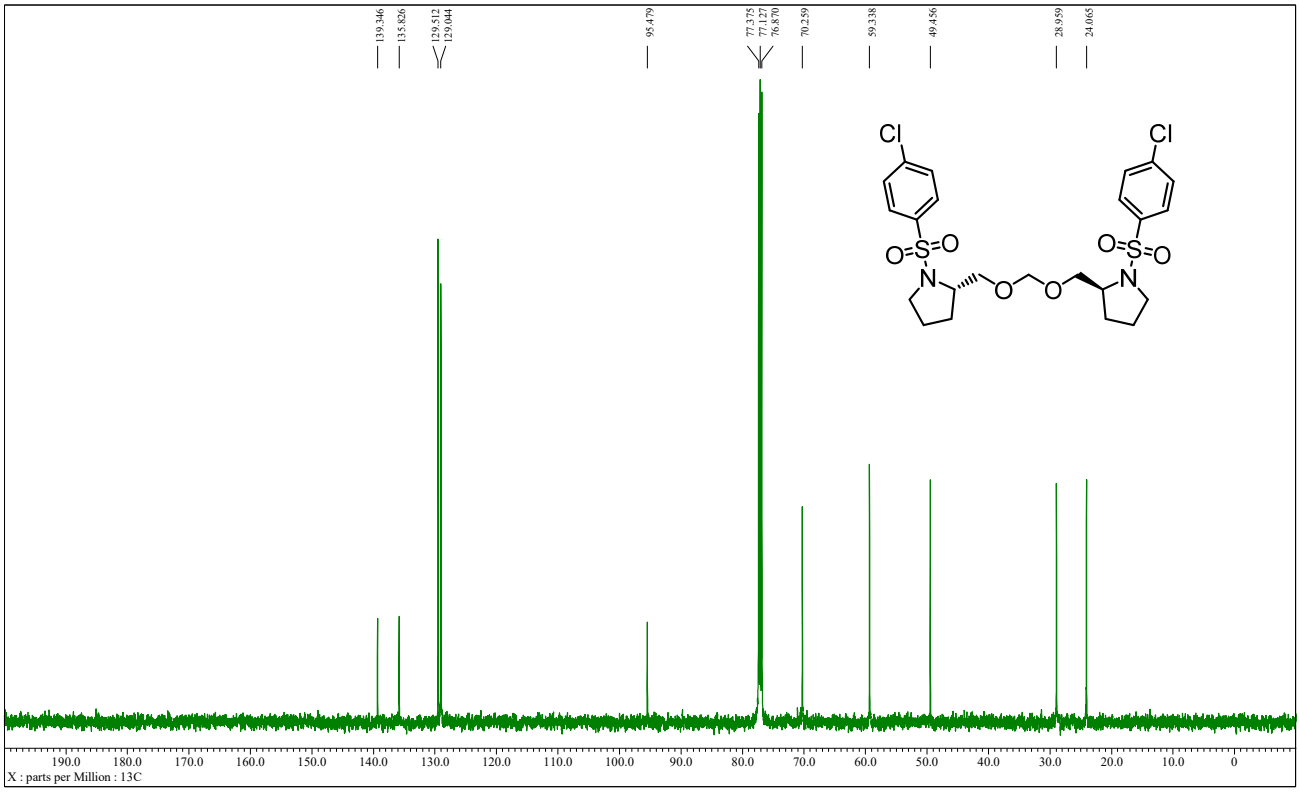

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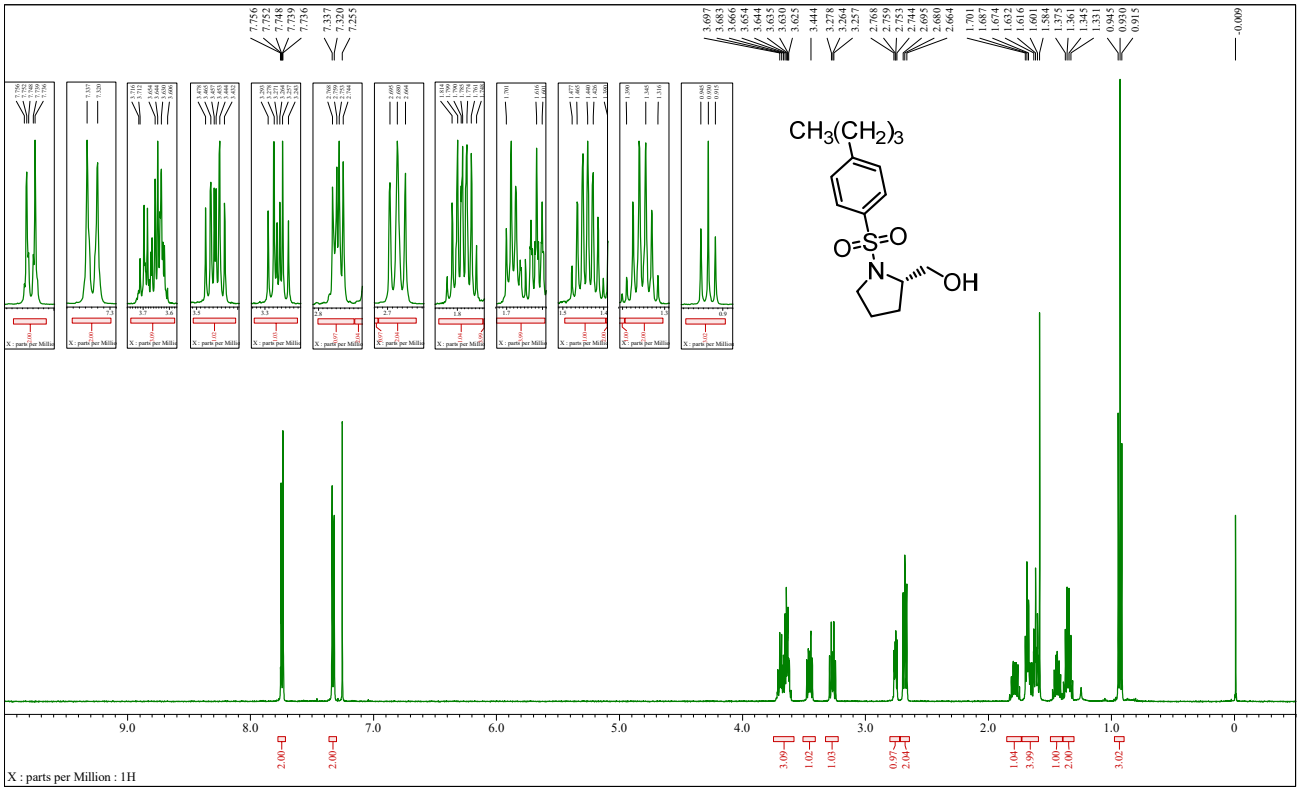


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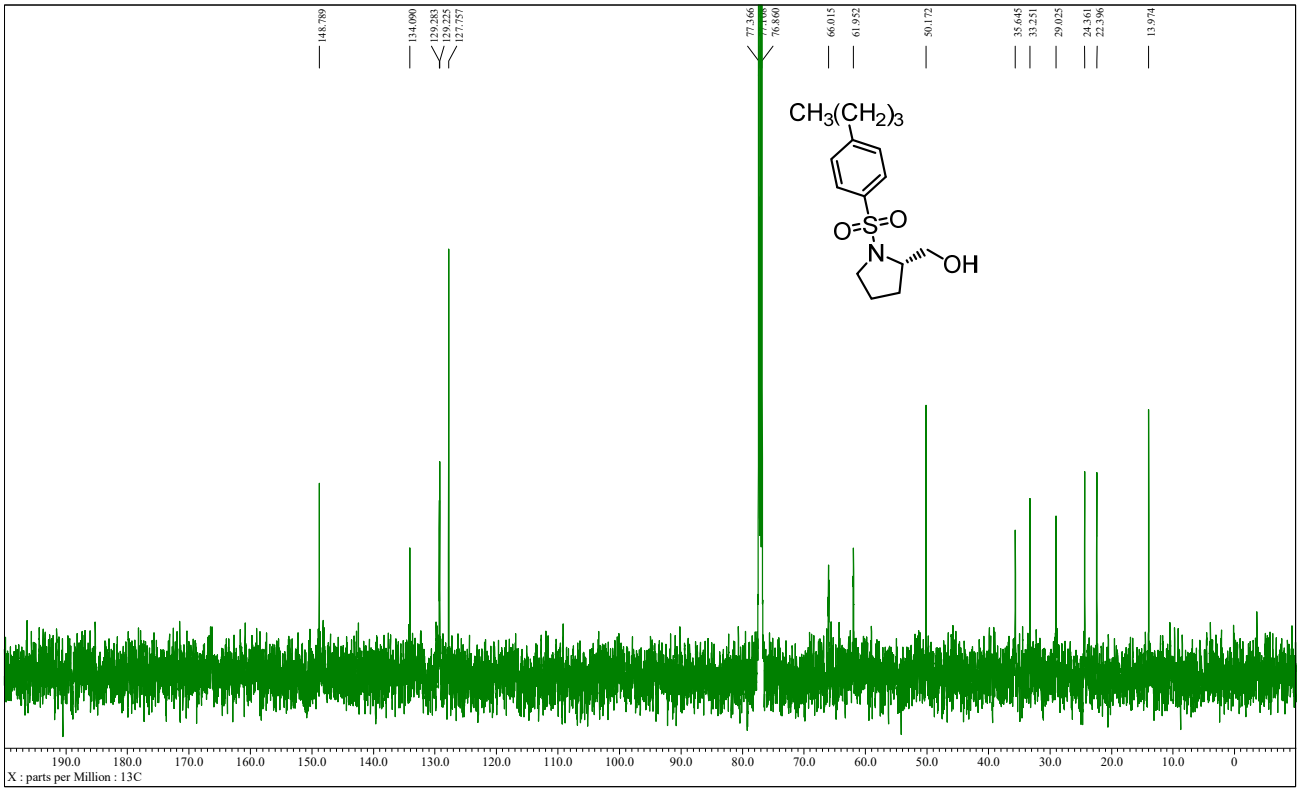

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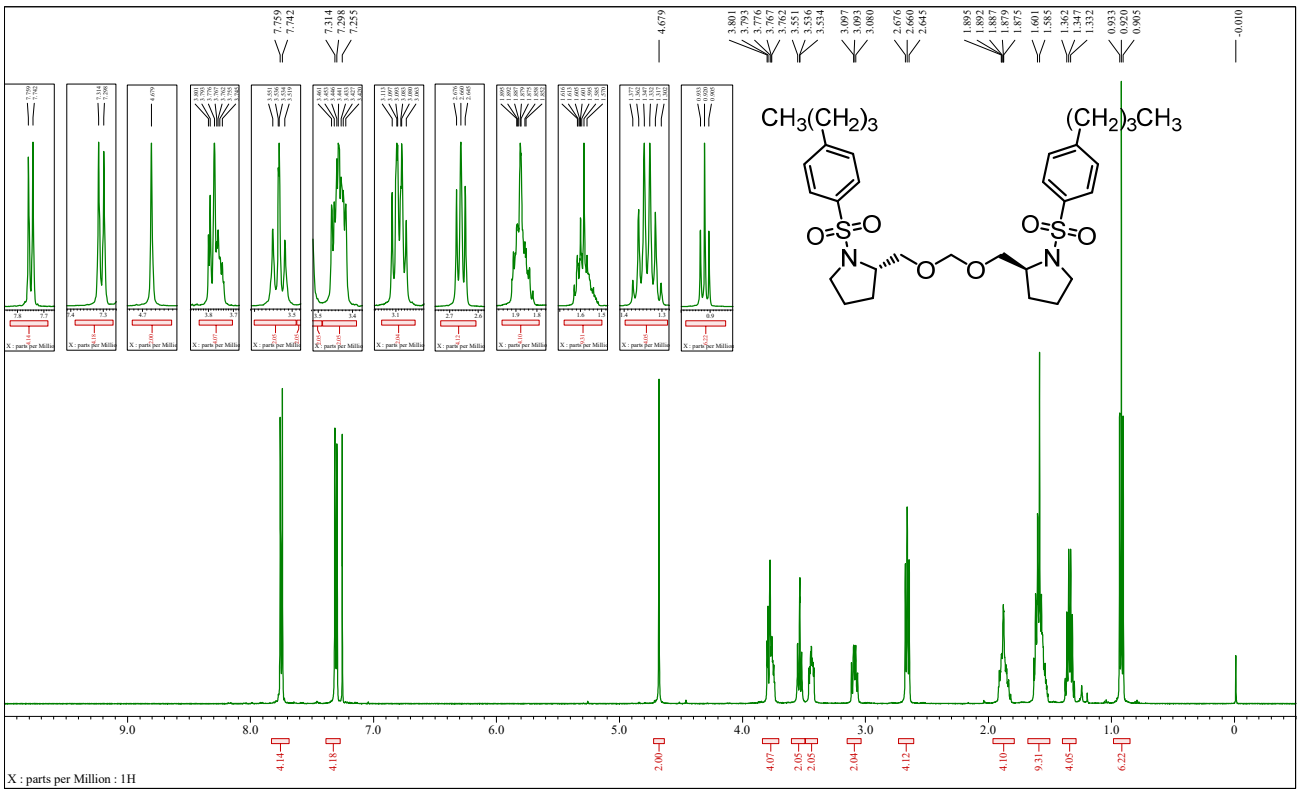


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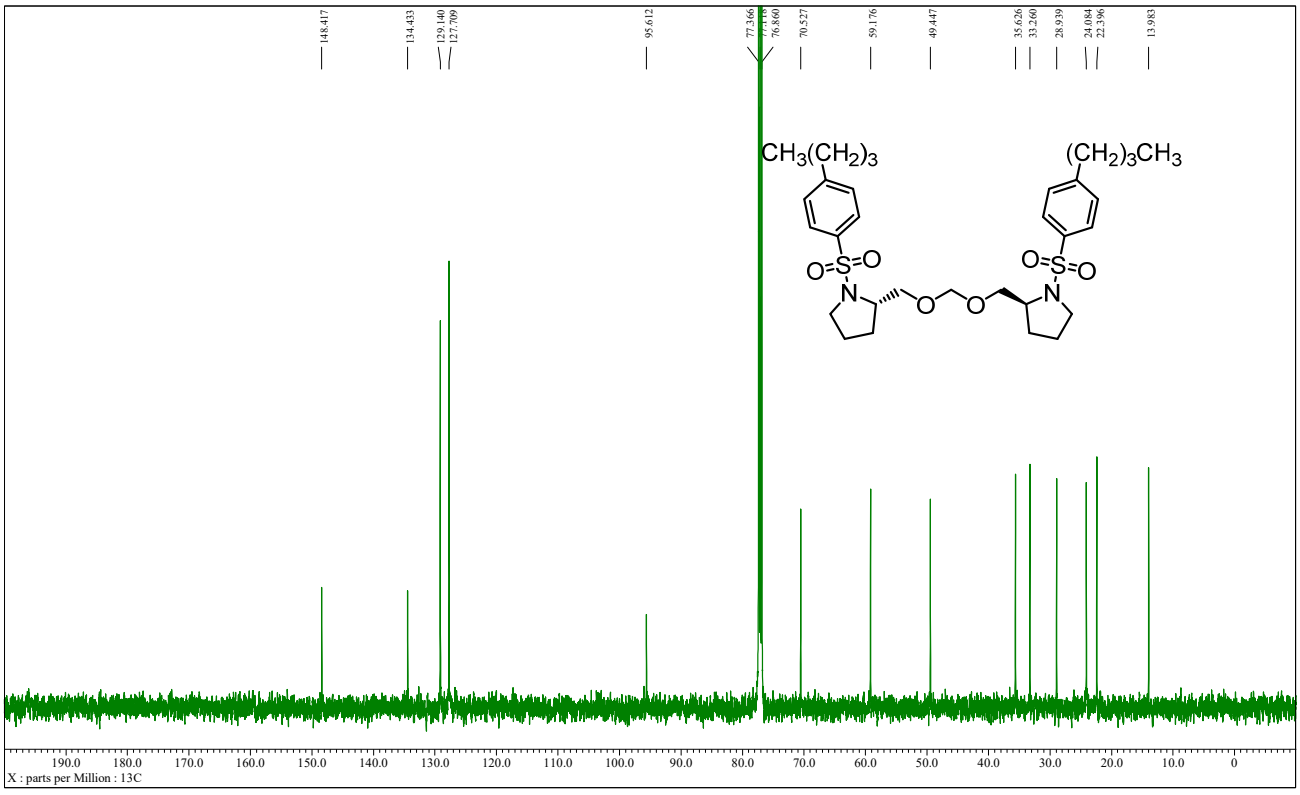
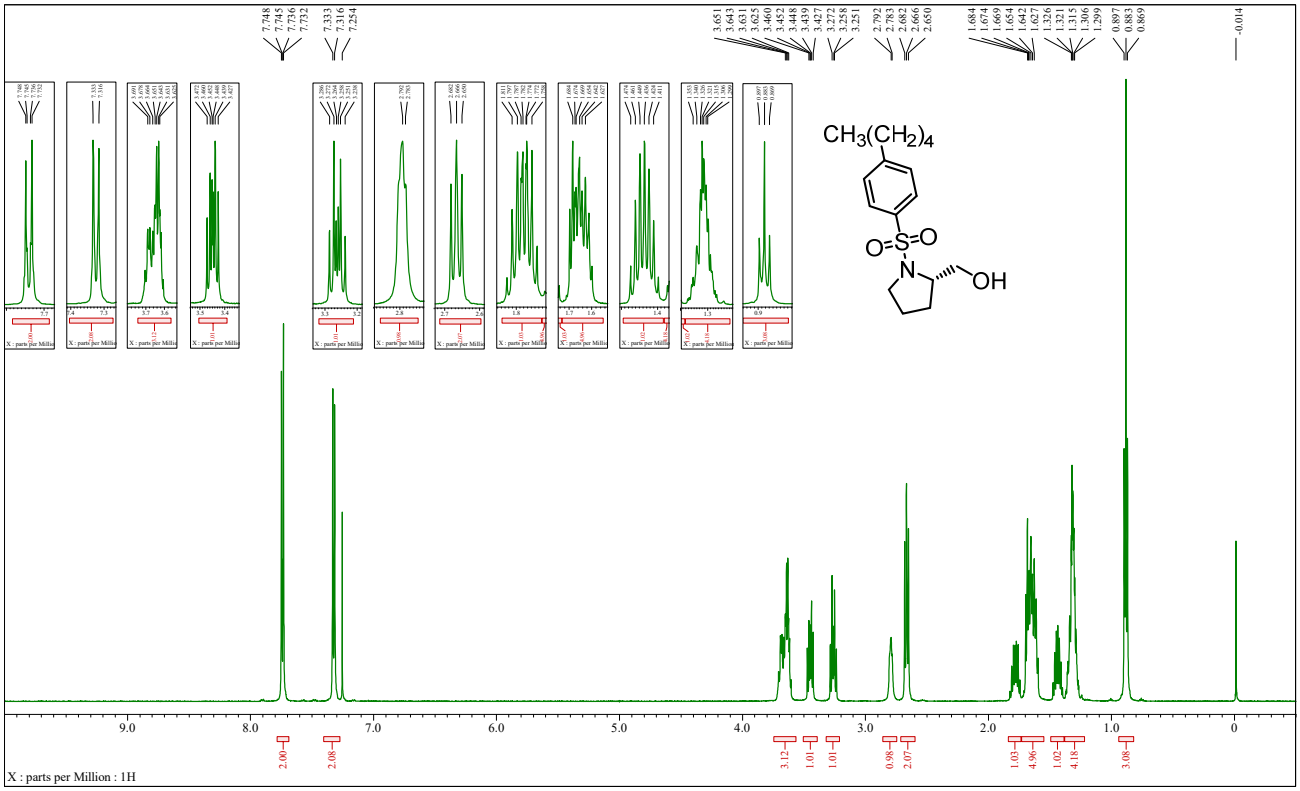
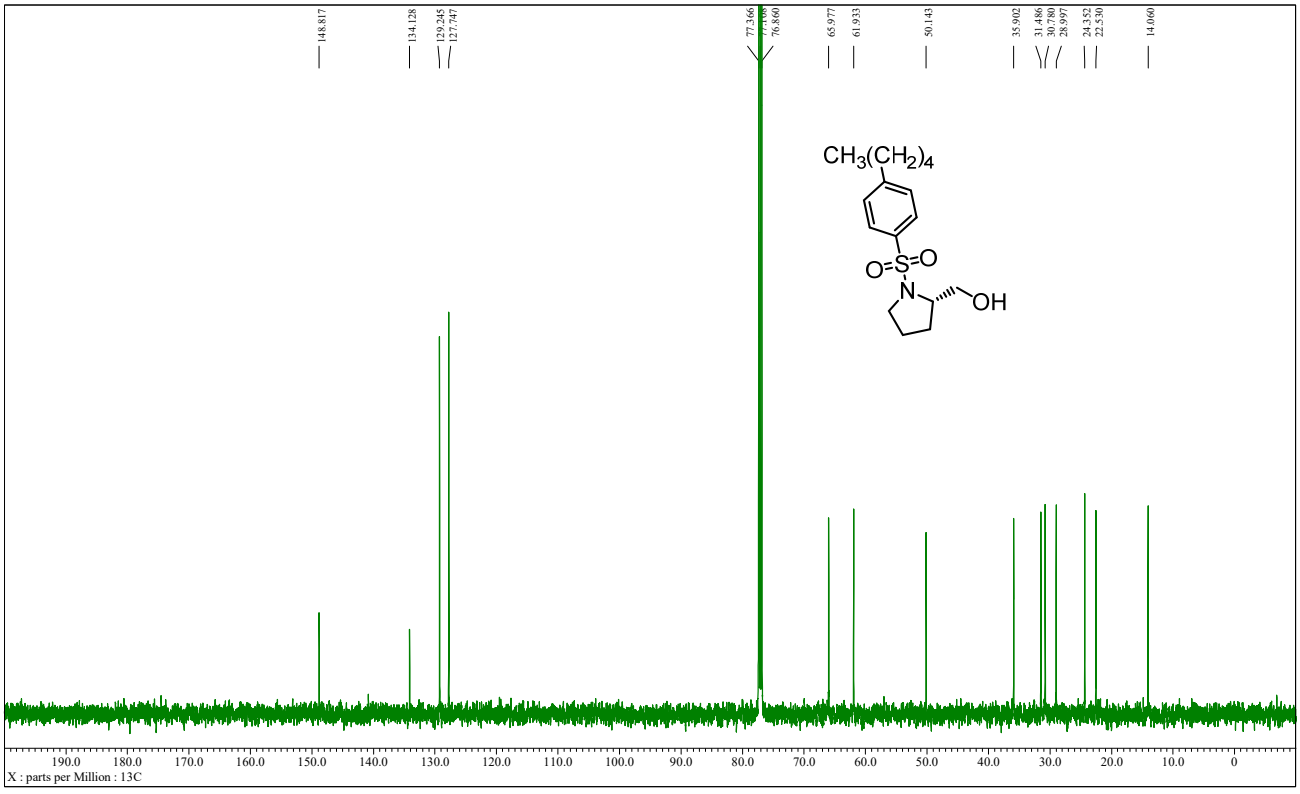


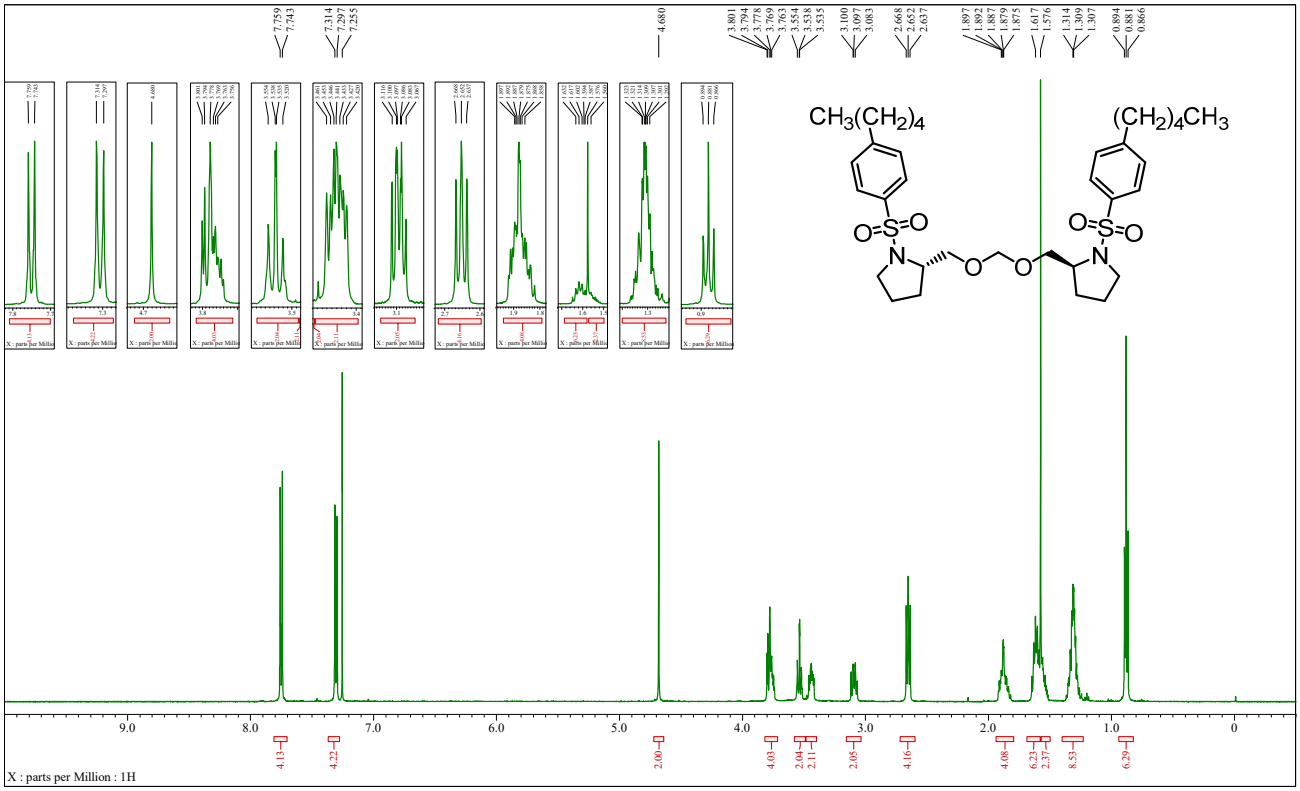
$^{1}$H NMR spectrum of compound **S24** (500 MHz, $CDCl_3$)



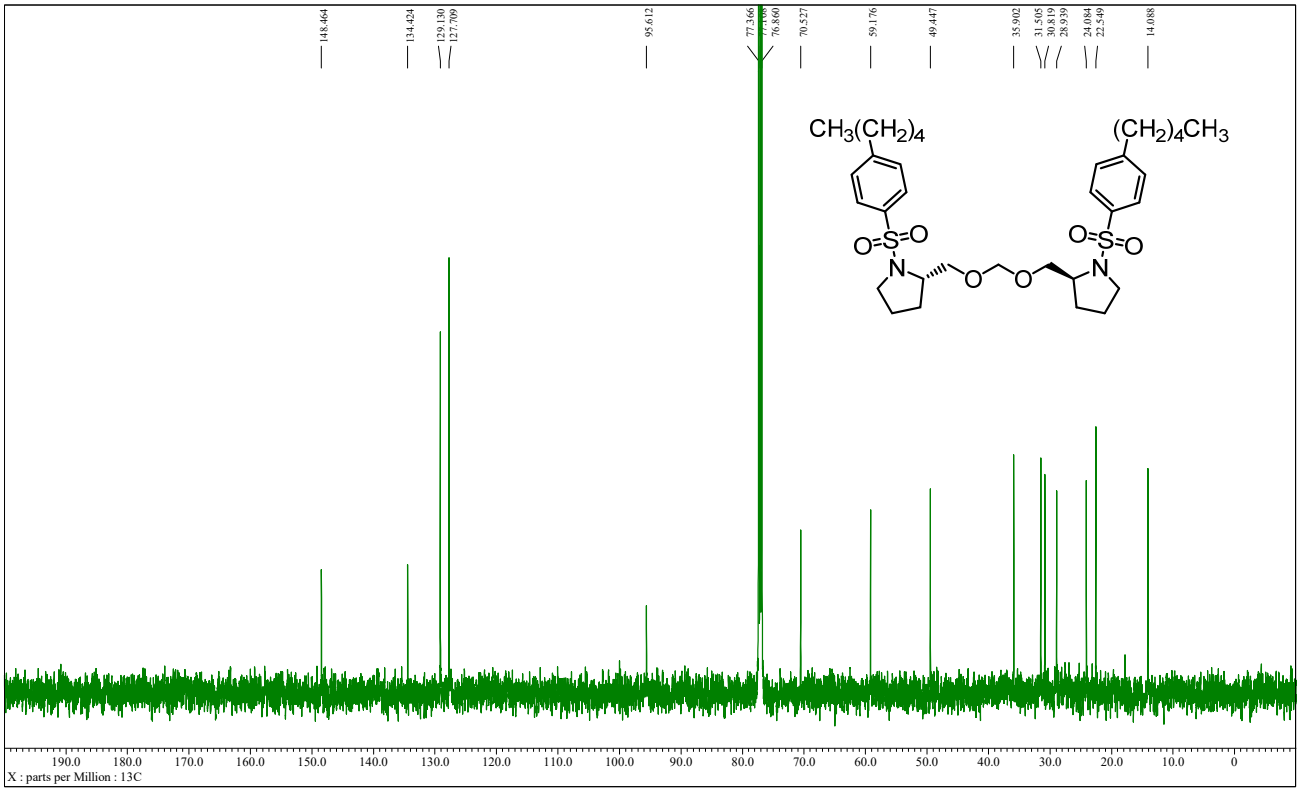

$^{13}$C NMR spectrum of compound **S24** (125 MHz, $CDCl_3$)



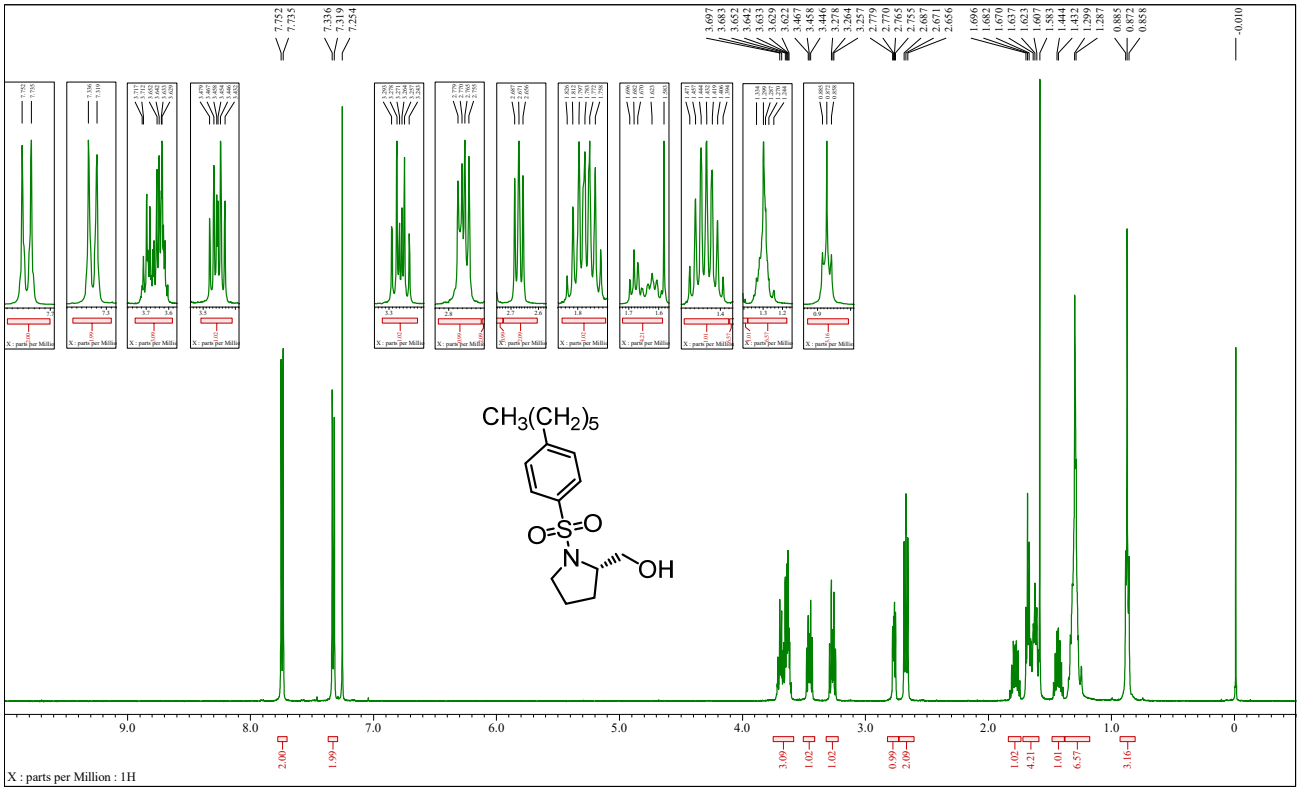
$^{1}$H NMR spectrum of compound **21** (500 MHz, $CDCl_3$)



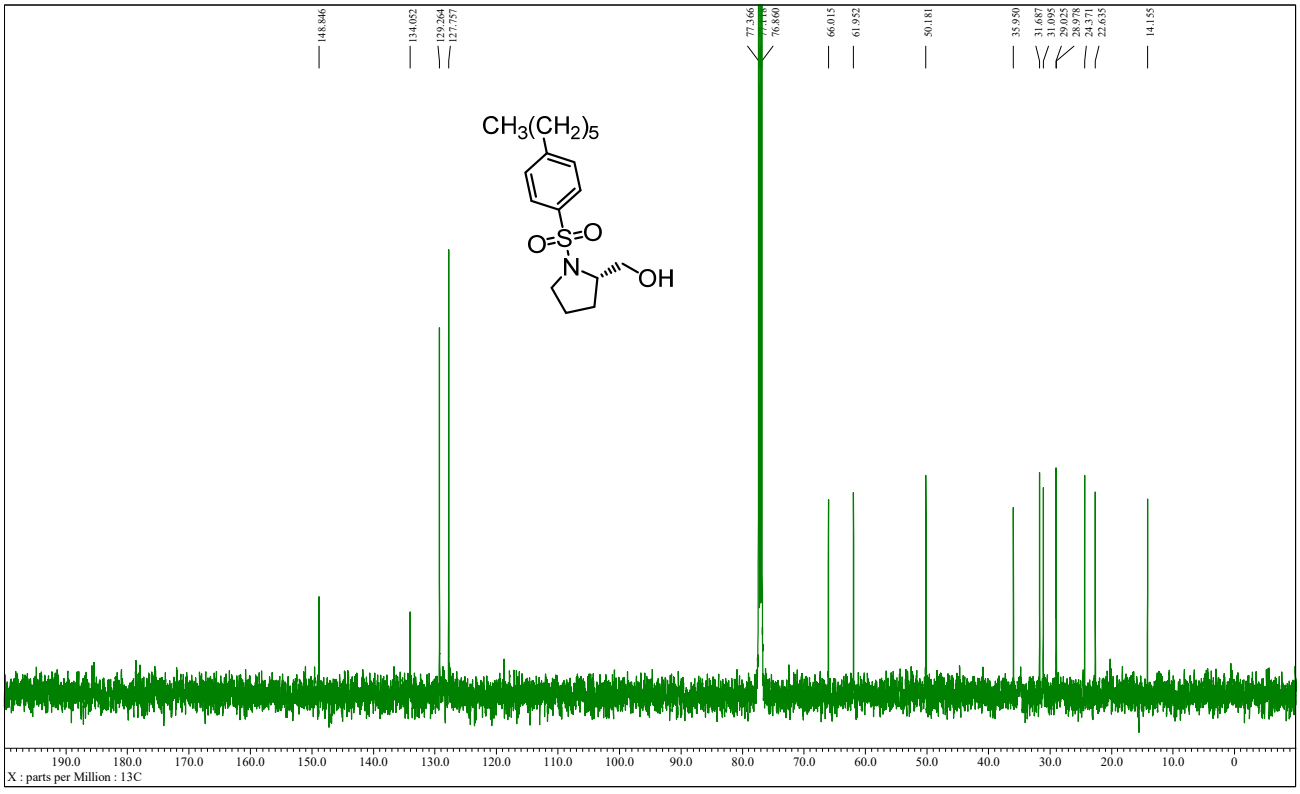

$^{13}$C NMR spectrum of compound **21** (125 MHz, $CDCl_3$)



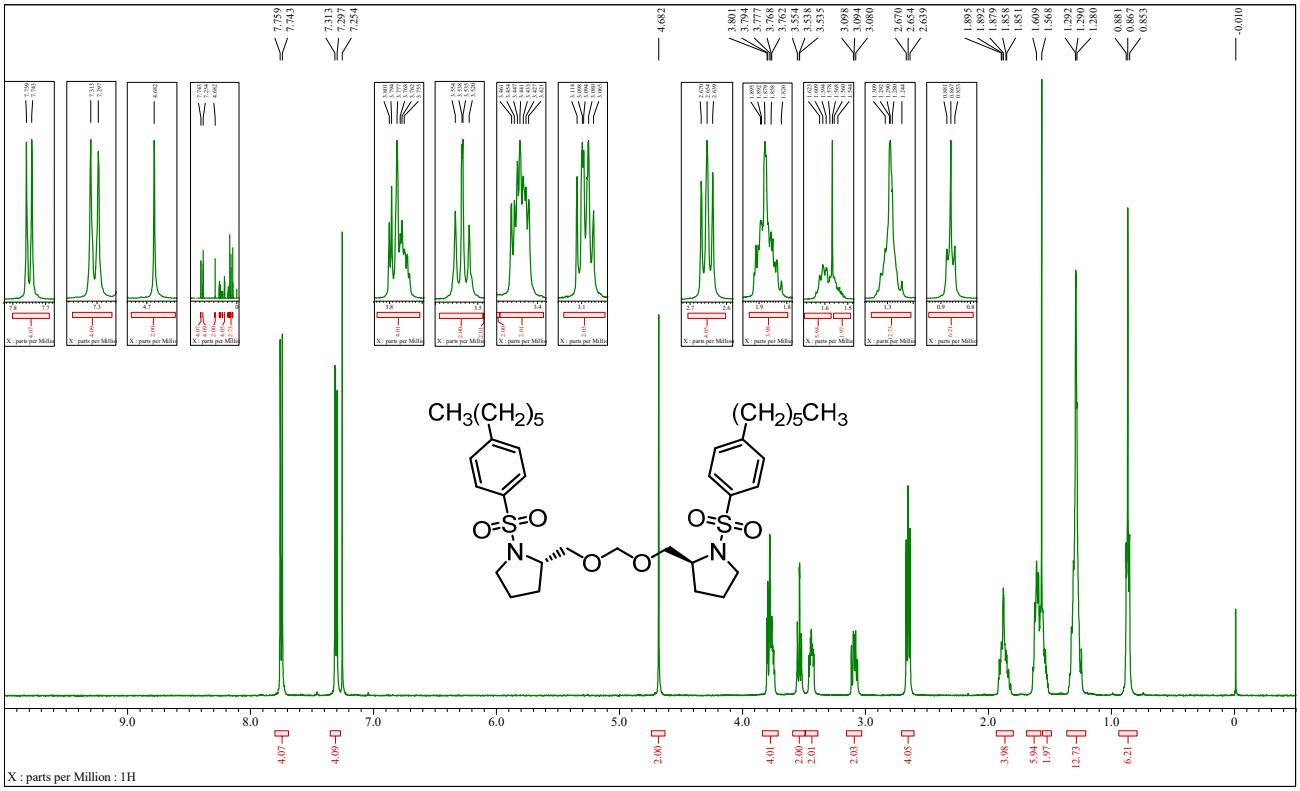
$^{1}$H NMR spectrum of compound **S26** (500 MHz, $CDCl_3$)



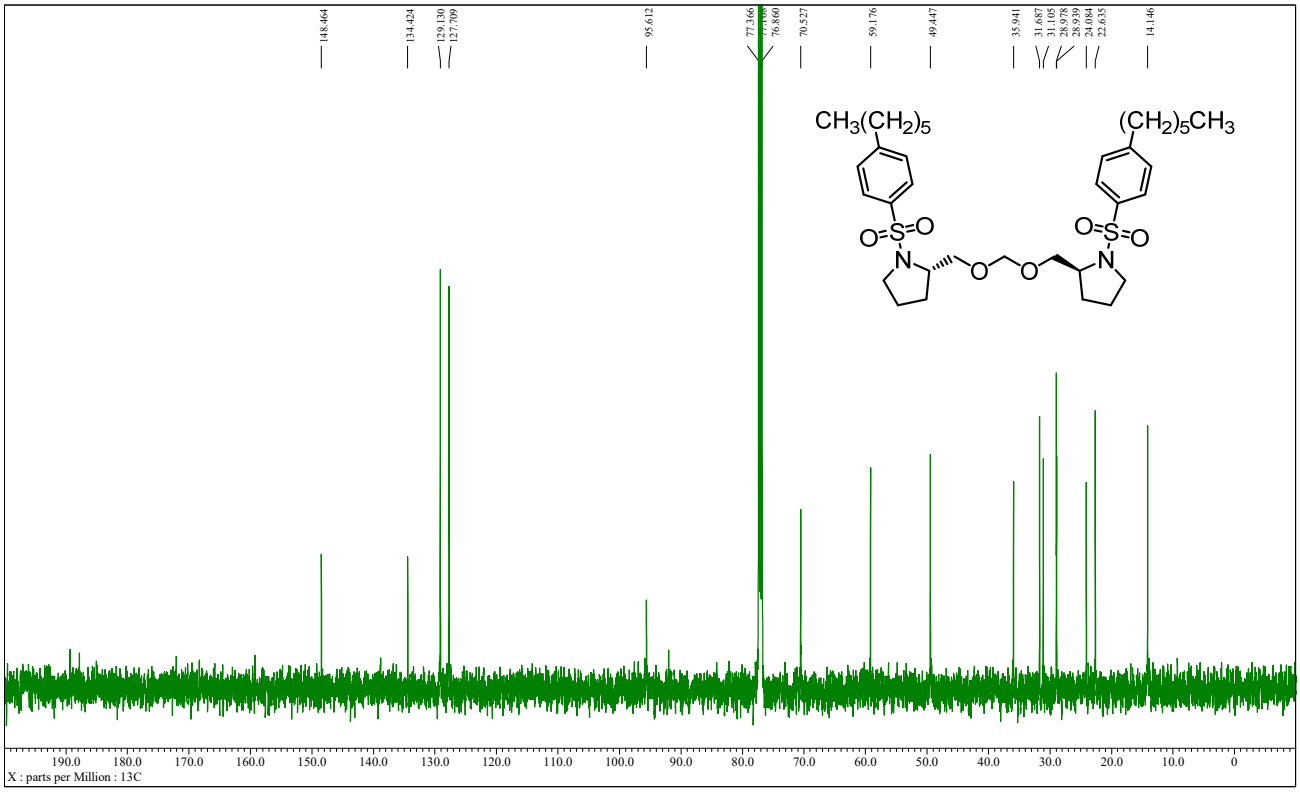

$^{13}$C NMR spectrum of compound **S26** (125 MHz, $CDCl_3$)



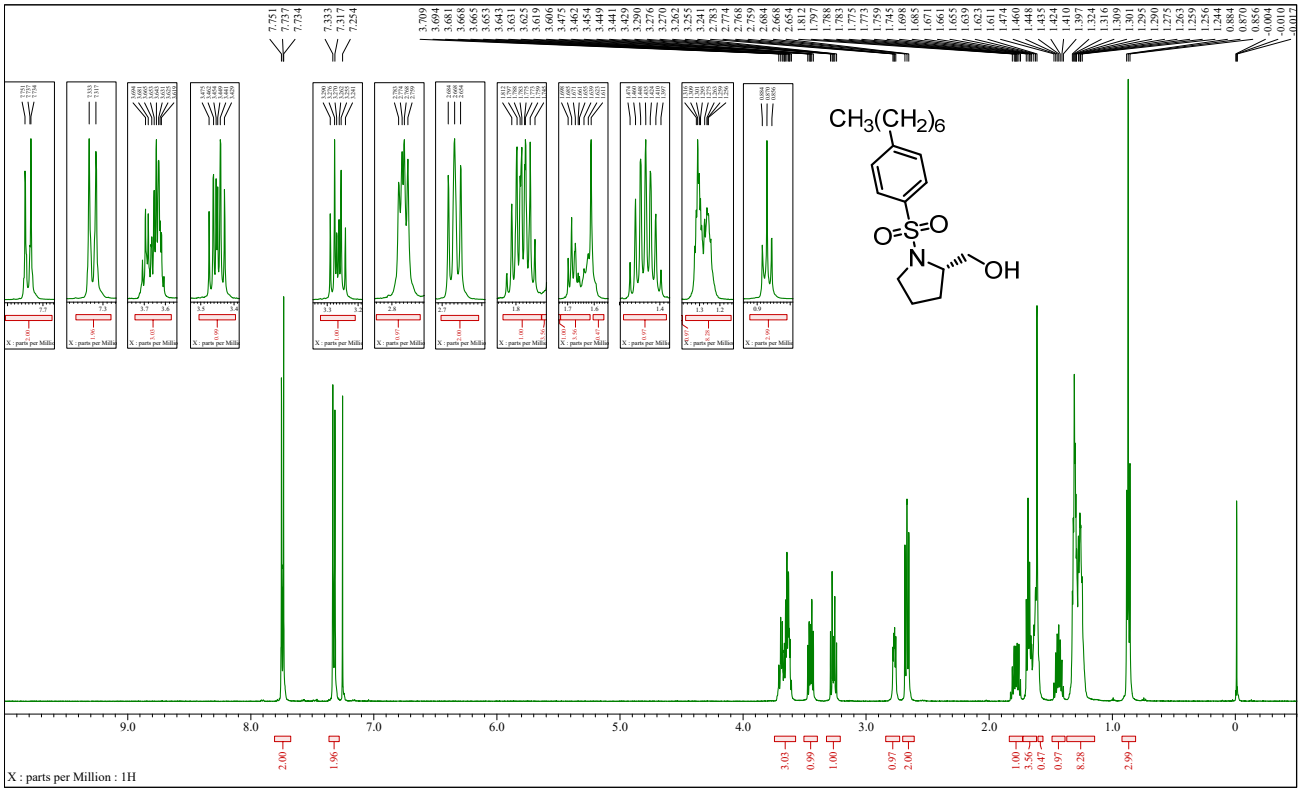
$^{1}$H NMR spectrum of compound **22** (500 MHz, $CDCl_3$)



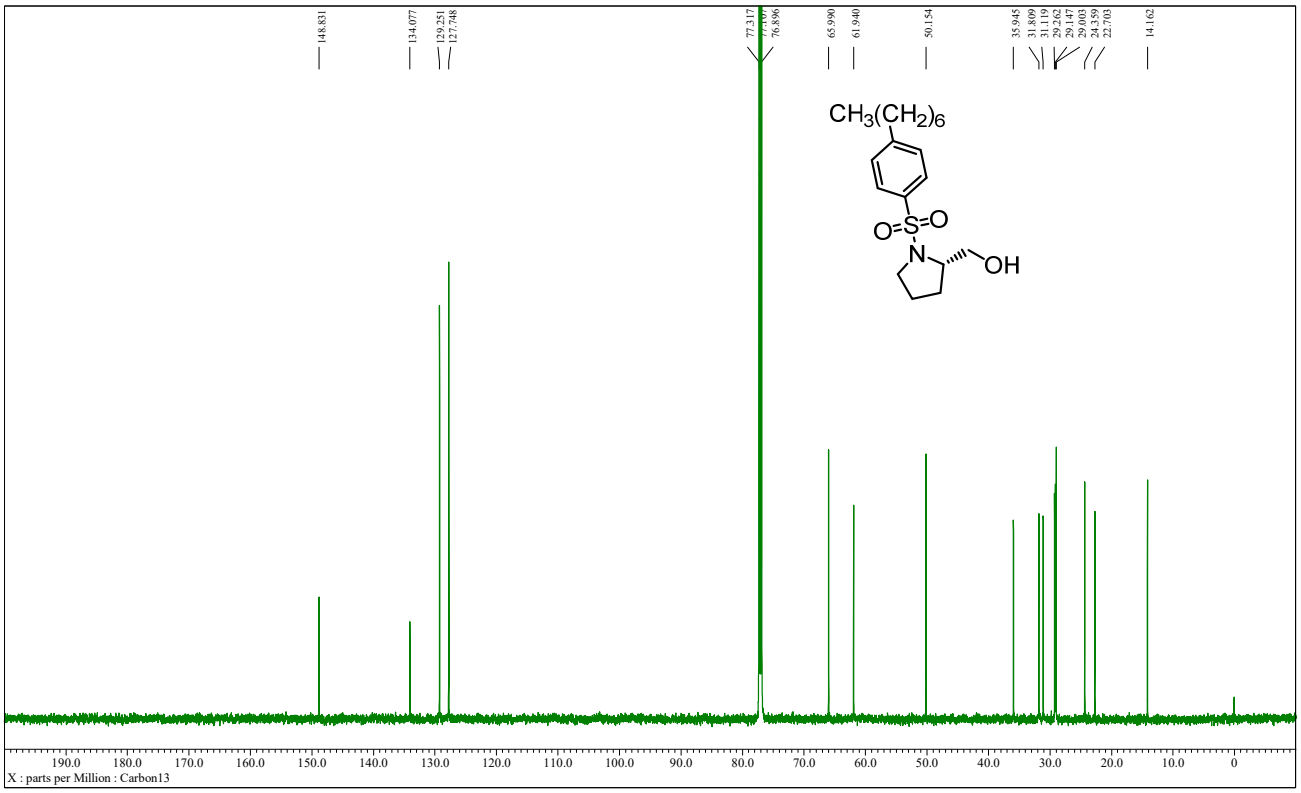

$^{13}$C NMR spectrum of compound **22** (125 MHz, $CDCl_3$)



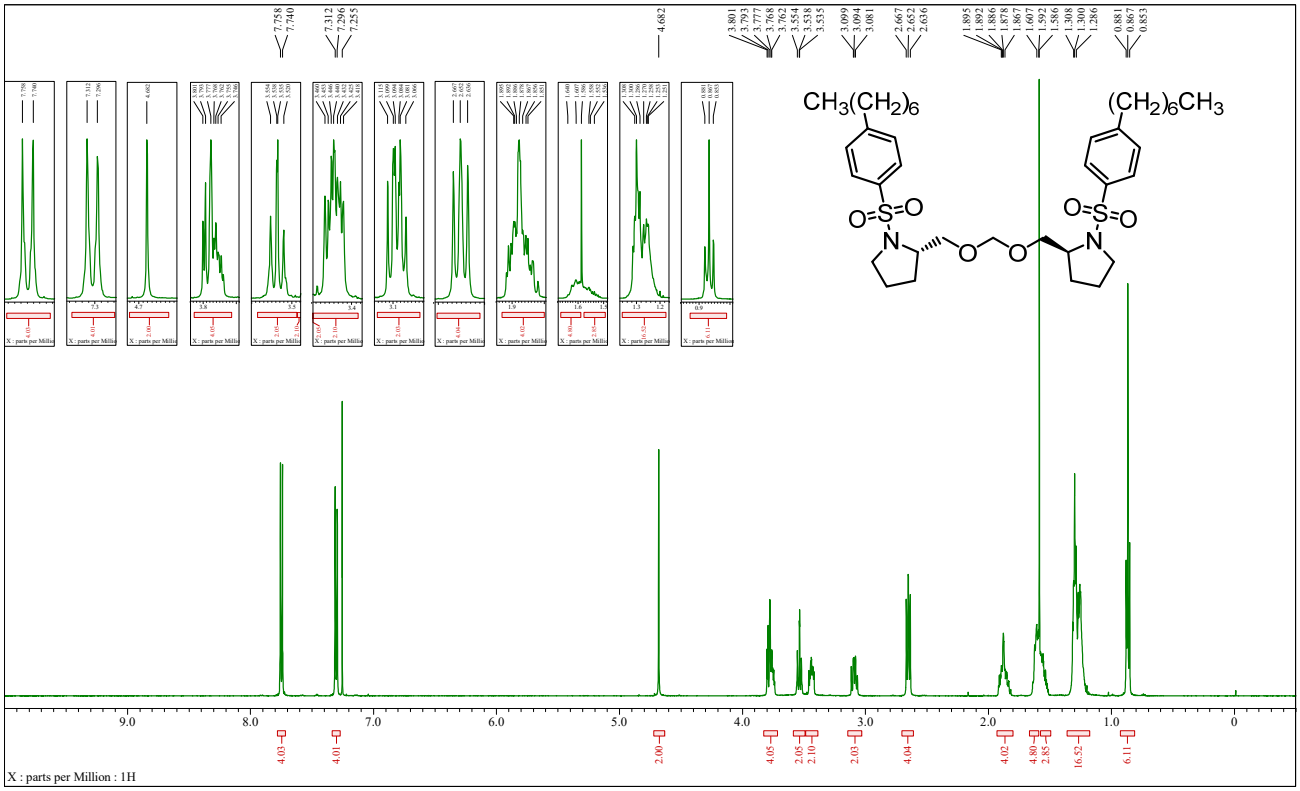
$^{1}$H NMR spectrum of compound **S28** (500 MHz, $CDCl_3$)



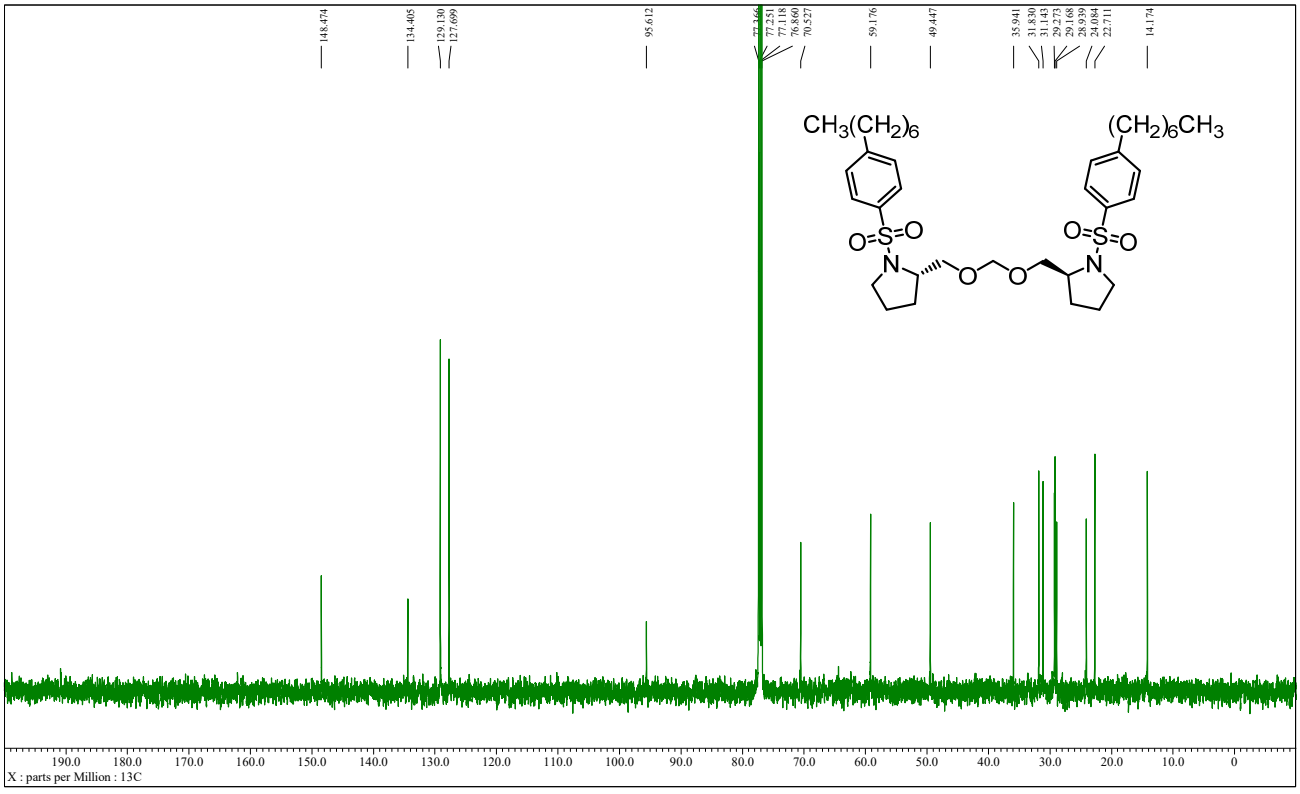

$^{13}$C NMR spectrum of compound **S28** (150 MHz, $CDCl_3$)



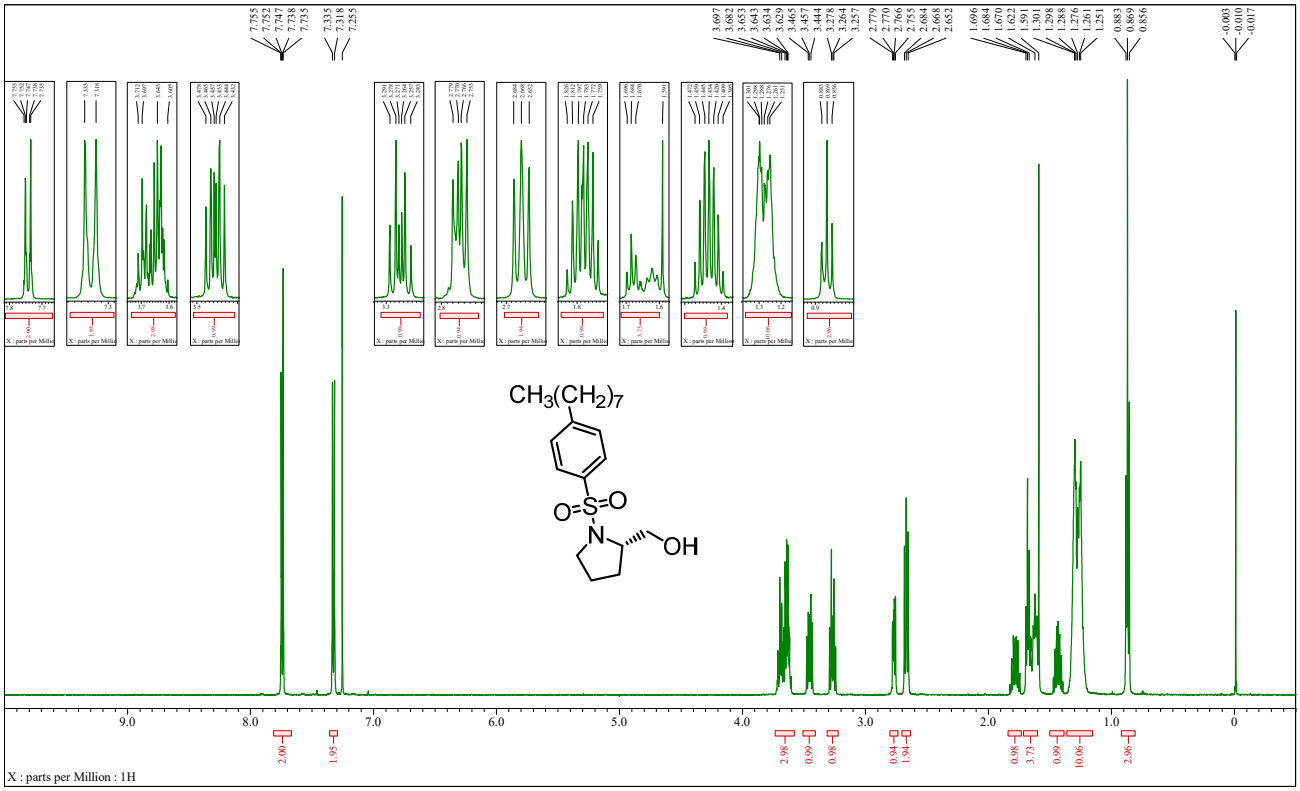
$^{1}$H NMR spectrum of compound **23** (500 MHz, $CDCl_3$)



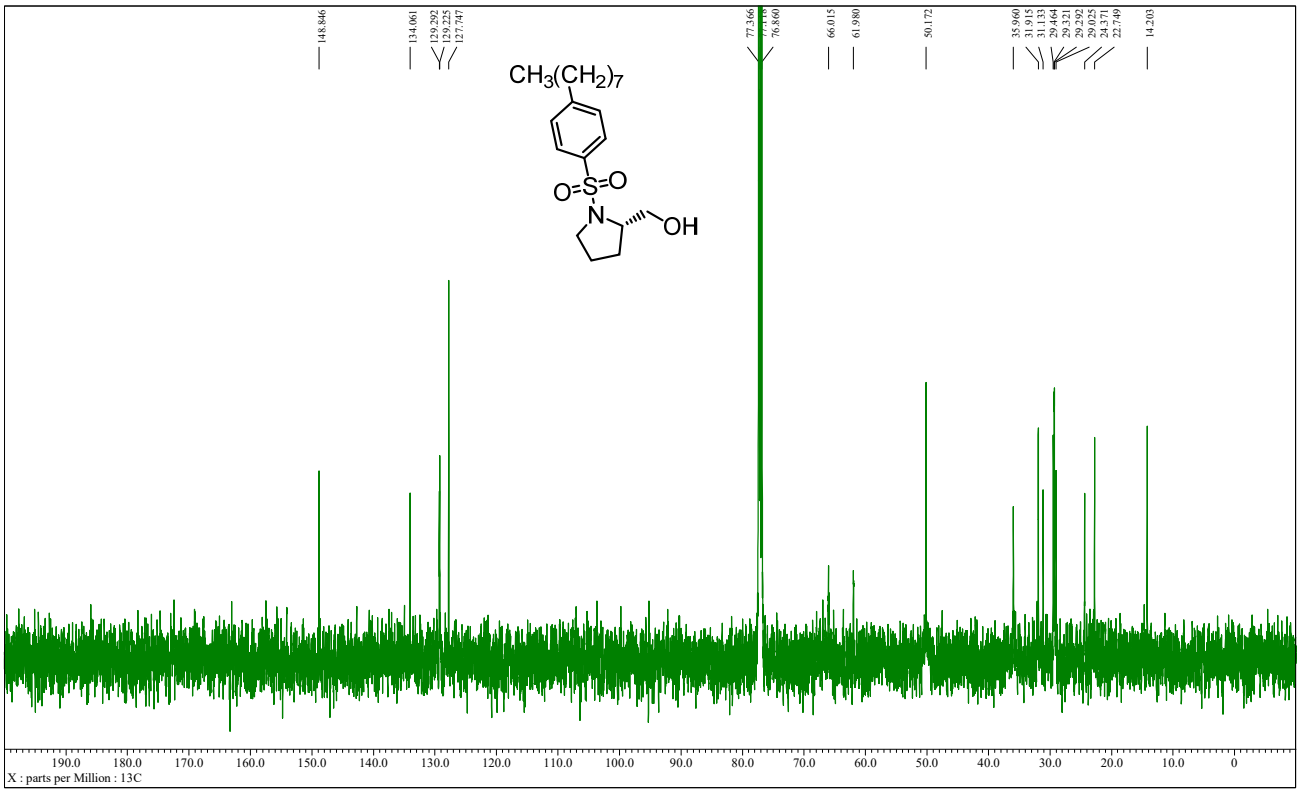

$^{13}$C NMR spectrum of compound **23** (125 MHz, $CDCl_3$)



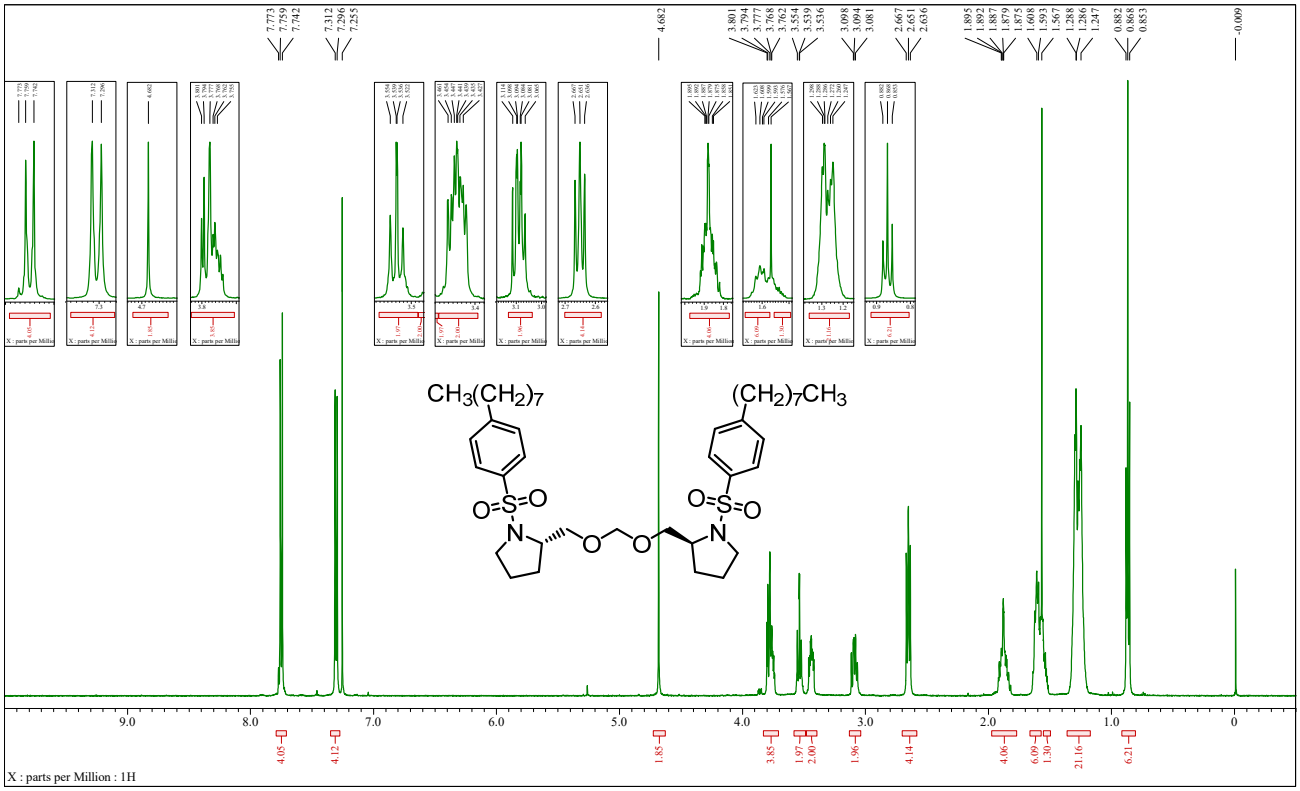
$^{1}$H NMR spectrum of compound **S30** (500 MHz, $CDCl_3$)



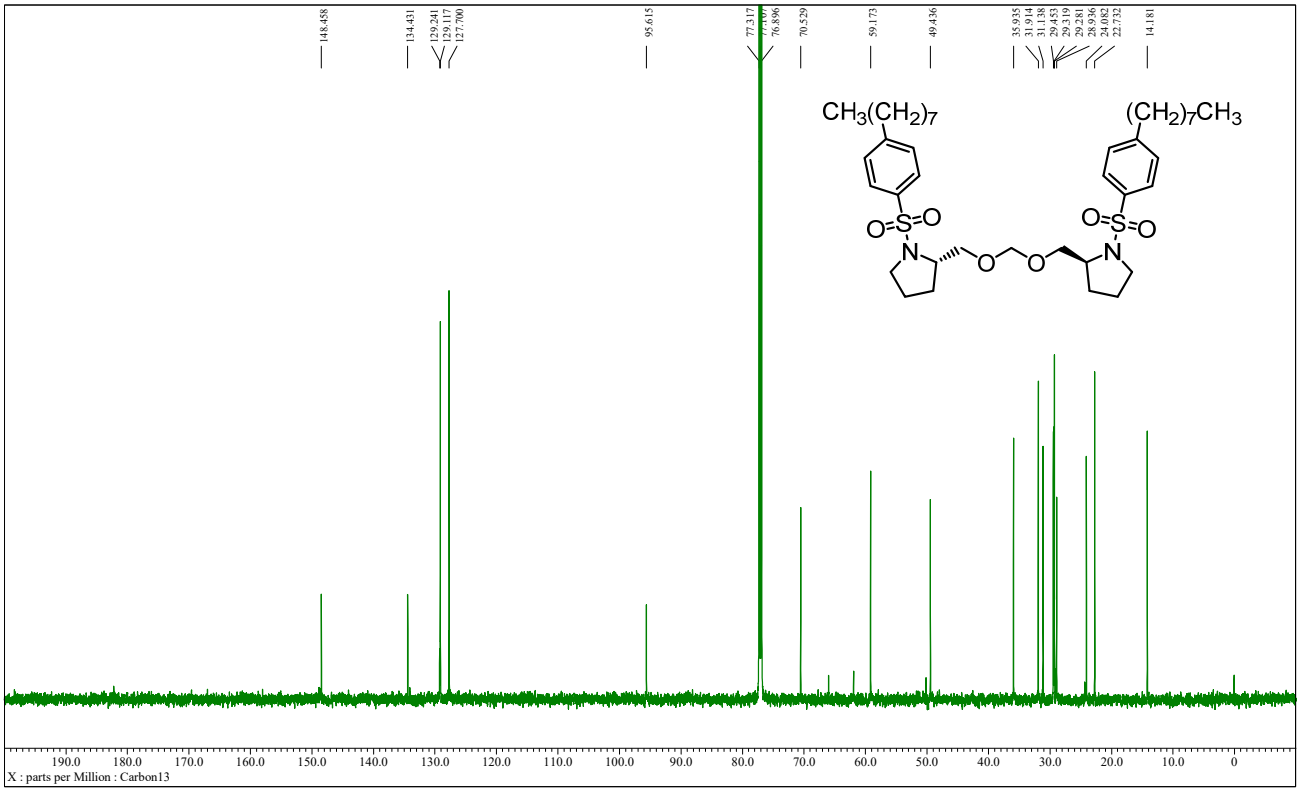

$^{13}$C NMR spectrum of compound **S30** (125 MHz, $CDCl_3$)



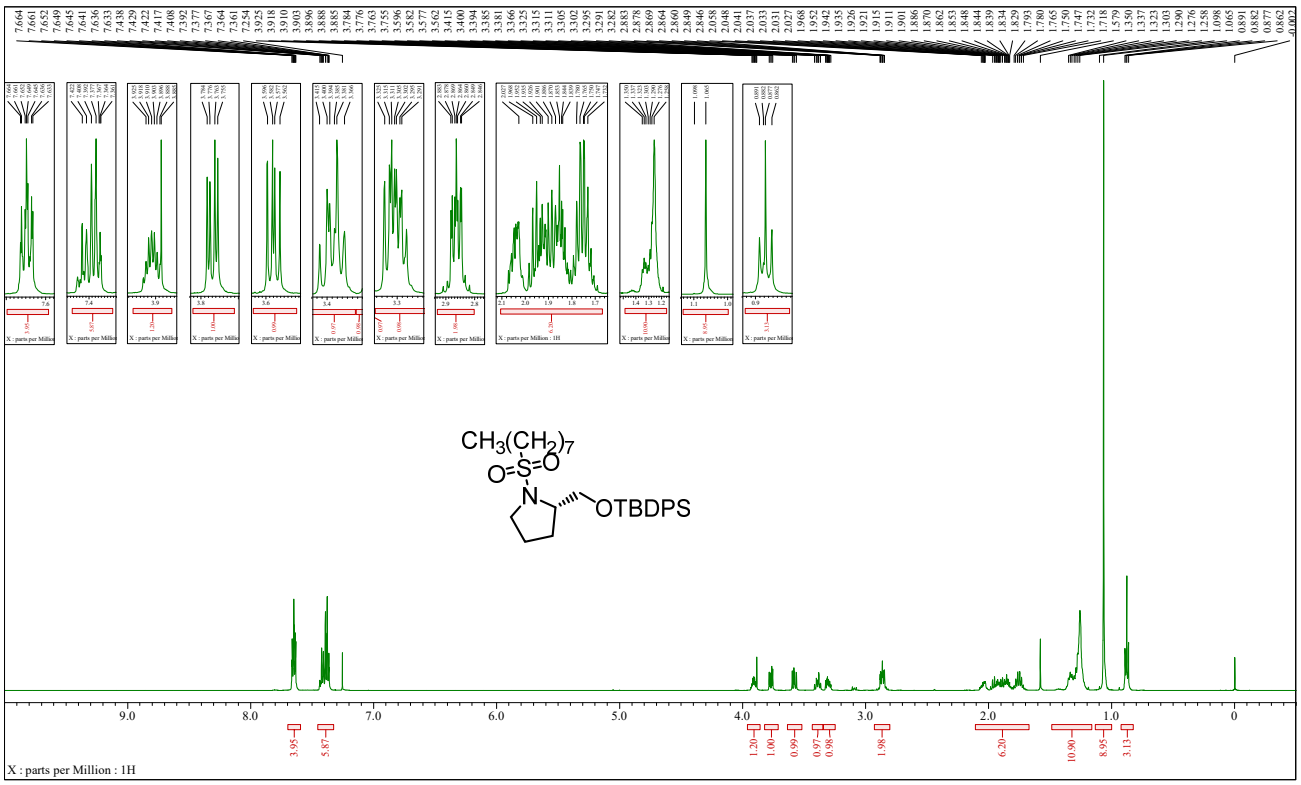
$^{1}$H NMR spectrum of compound **24** (500 MHz, $CDCl_3$)



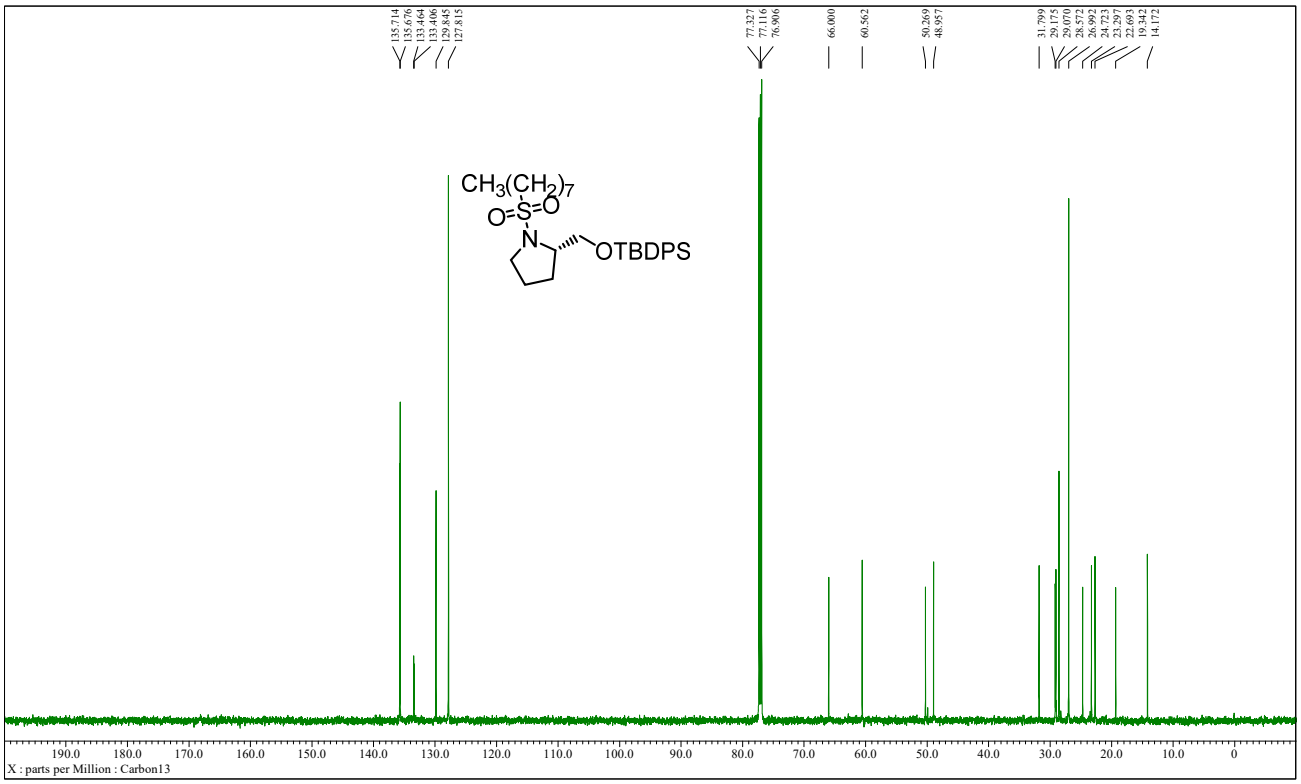

$^{13}$C NMR spectrum of compound **24** (150 MHz, $CDCl_3$)



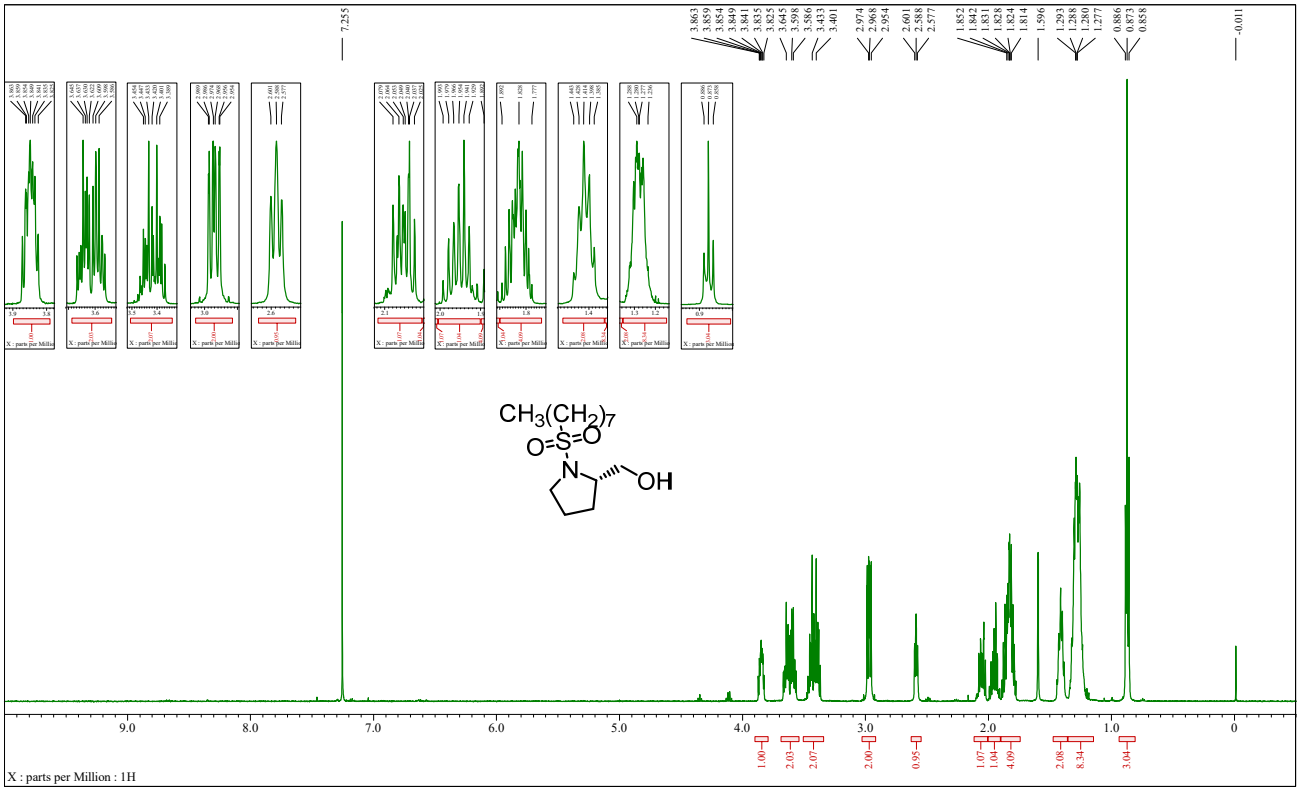
$^{1}$H NMR spectrum of compound **S32** (500 MHz, $CDCl_3$)



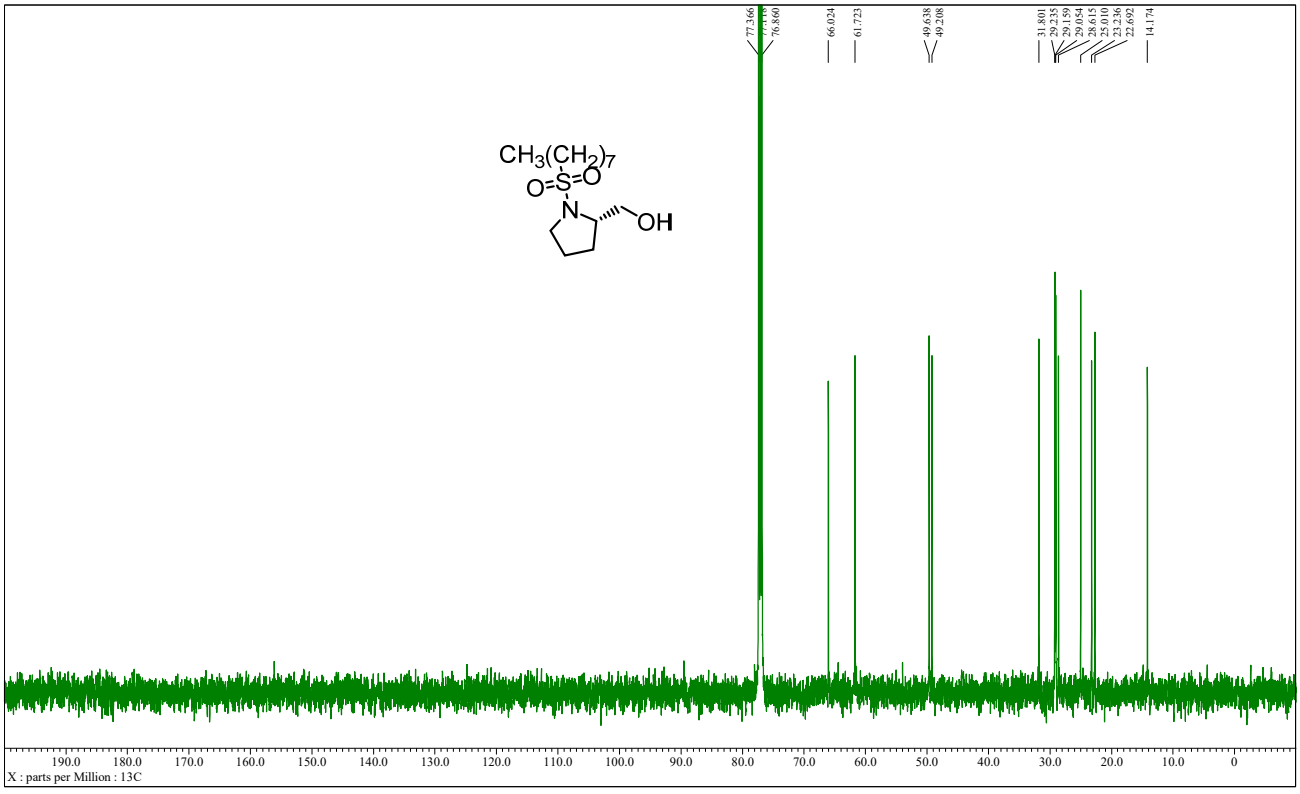

$^{13}$C NMR spectrum of compound **S32** (150 MHz, $CDCl_3$)



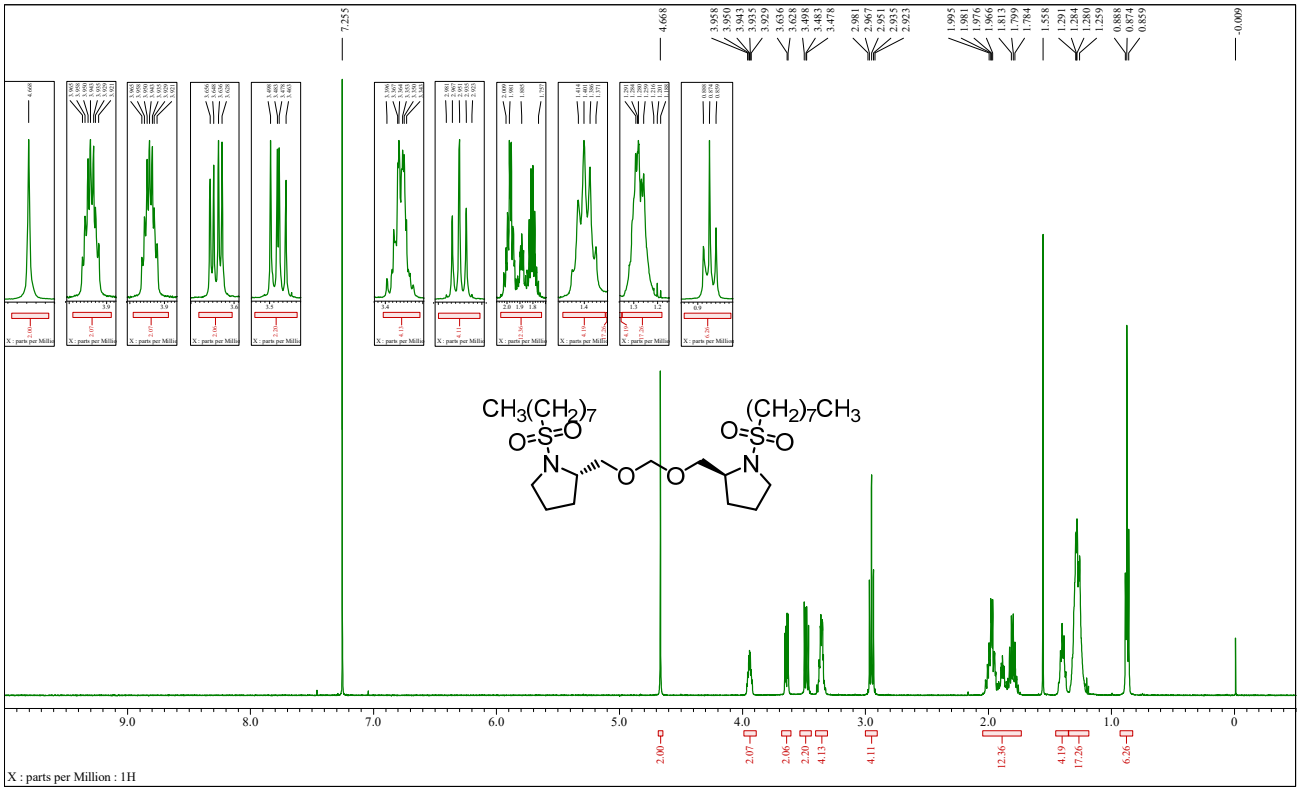
$^{1}$H NMR spectrum of compound **S33** (500 MHz, $CDCl_3$)



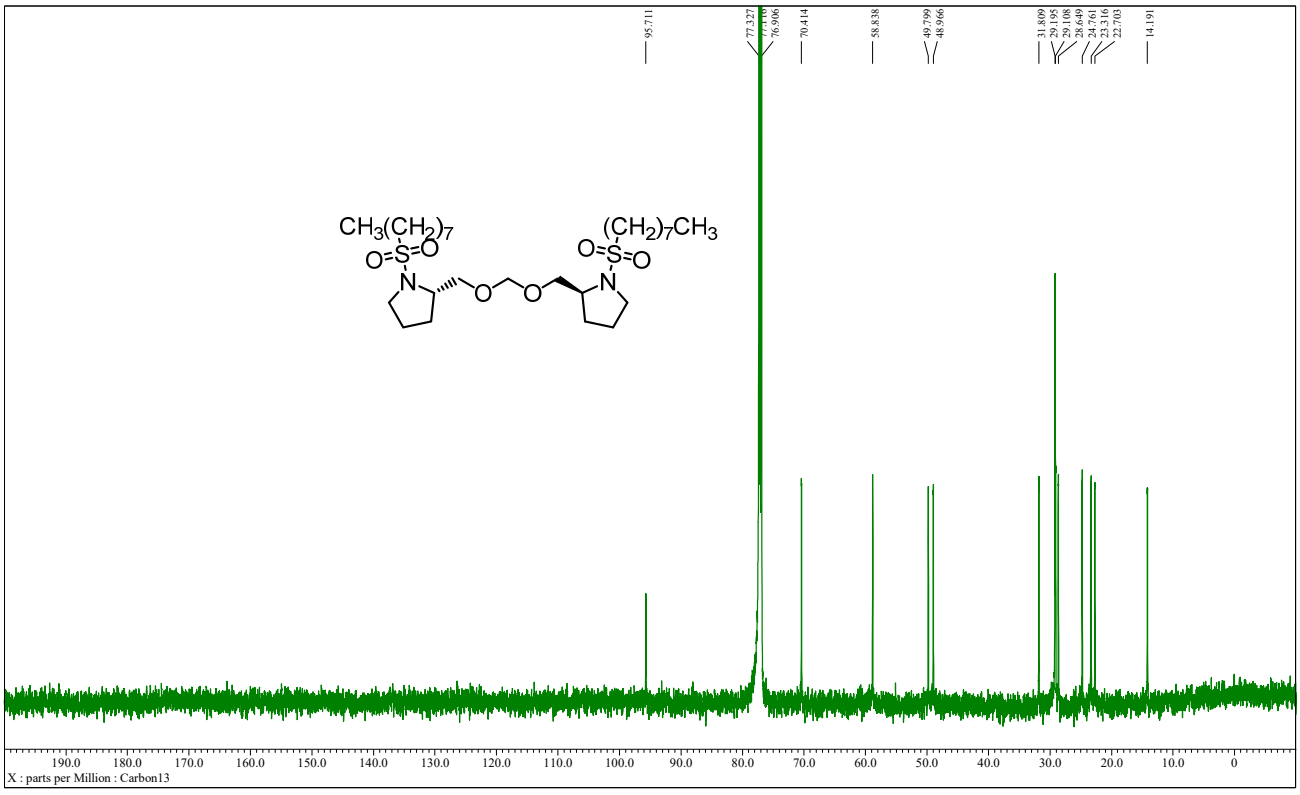

$^{13}$C NMR spectrum of compound **S33** (125 MHz, $CDCl_3$)



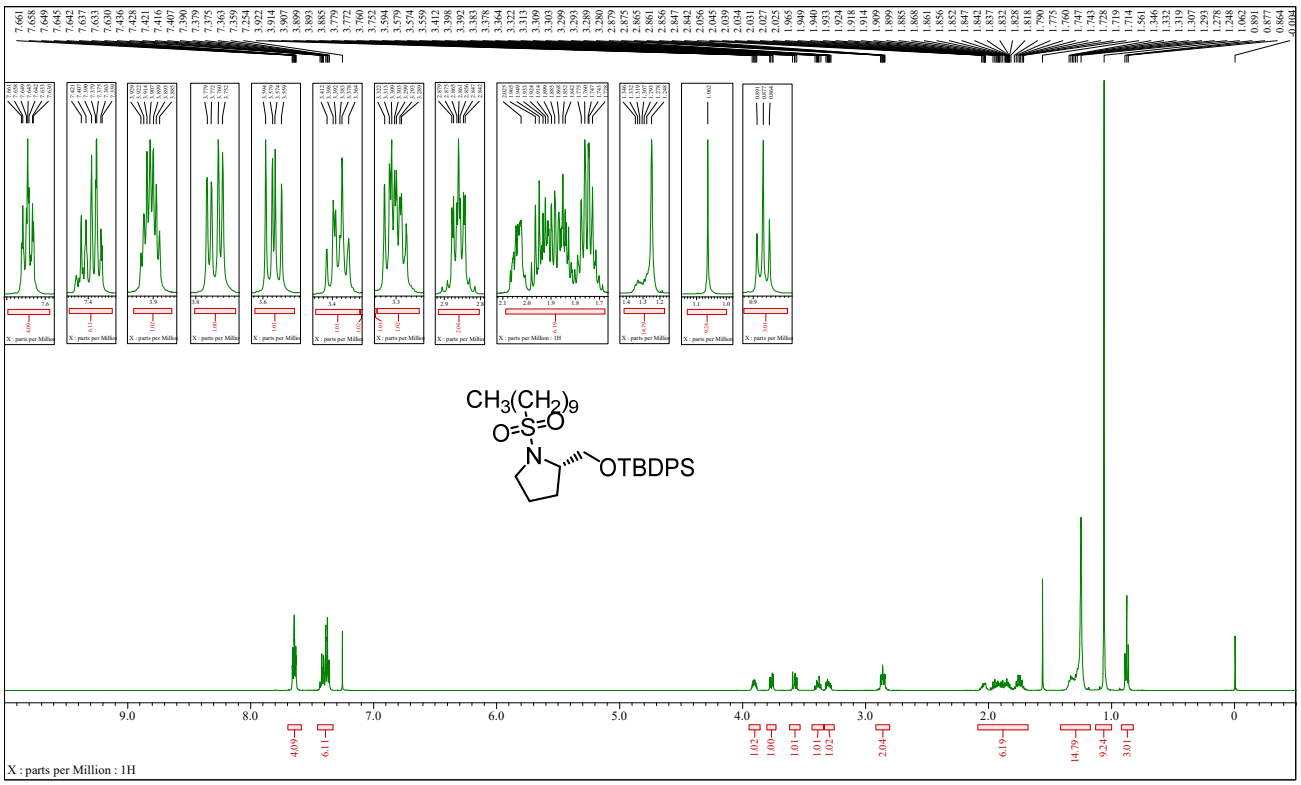
$^{1}$H NMR spectrum of compound **25** (500 MHz, $CDCl_3$)



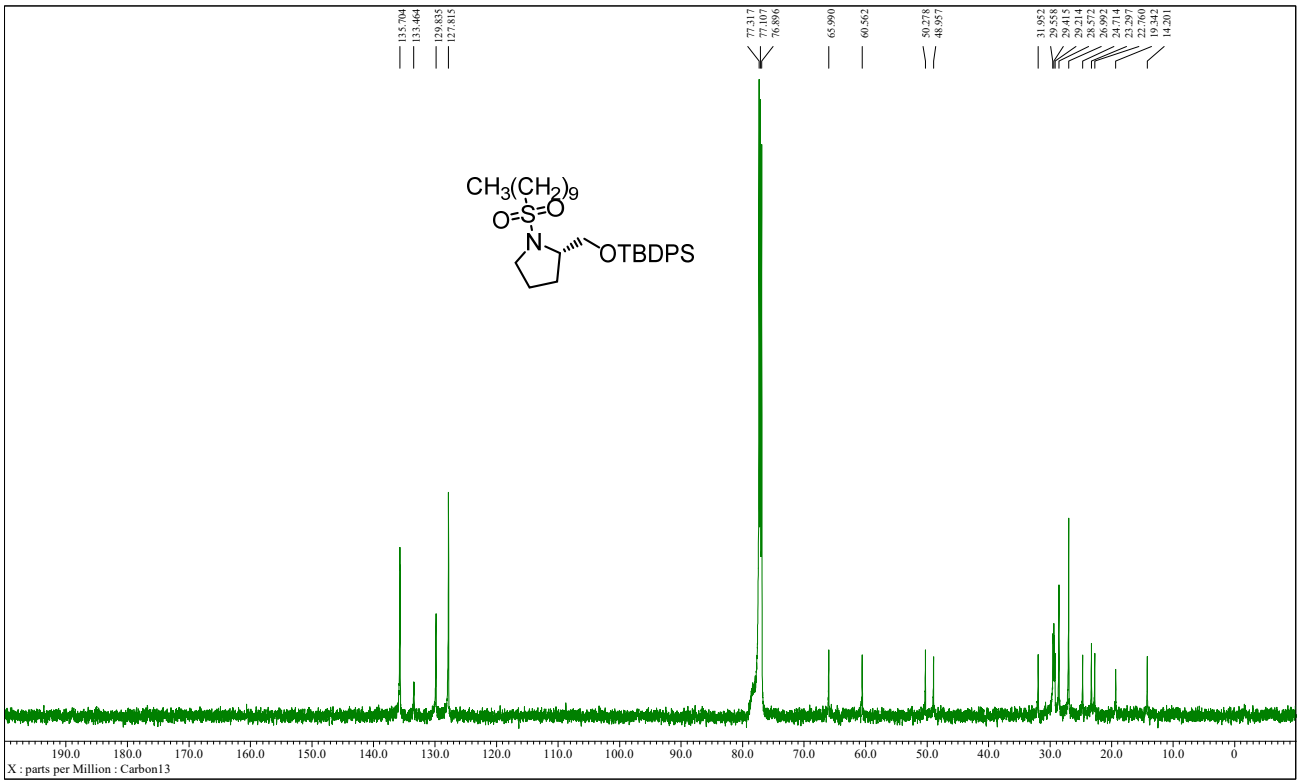

$^{13}$C NMR spectrum of compound **25** (150 MHz, $CDCl_3$)



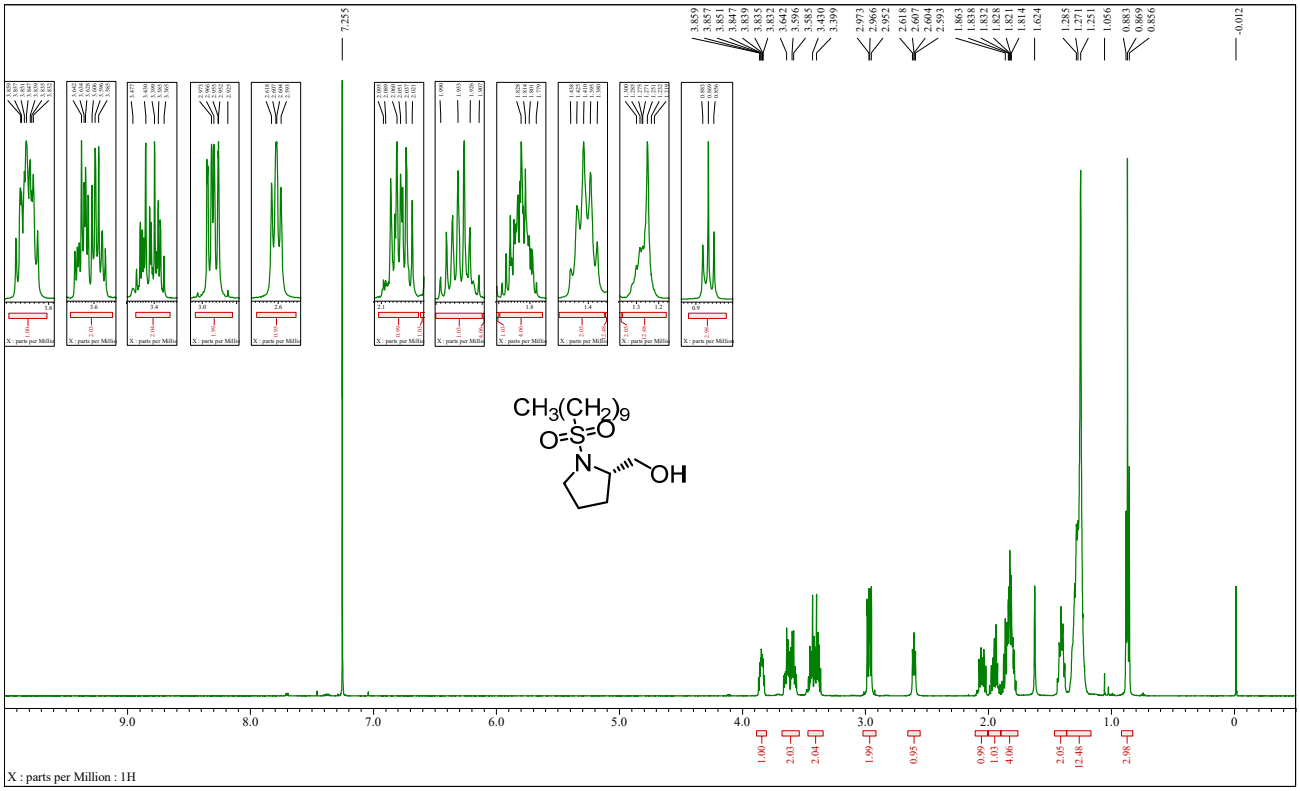
$^{1}$H NMR spectrum of compound **S35** (500 MHz, $CDCl_3$)



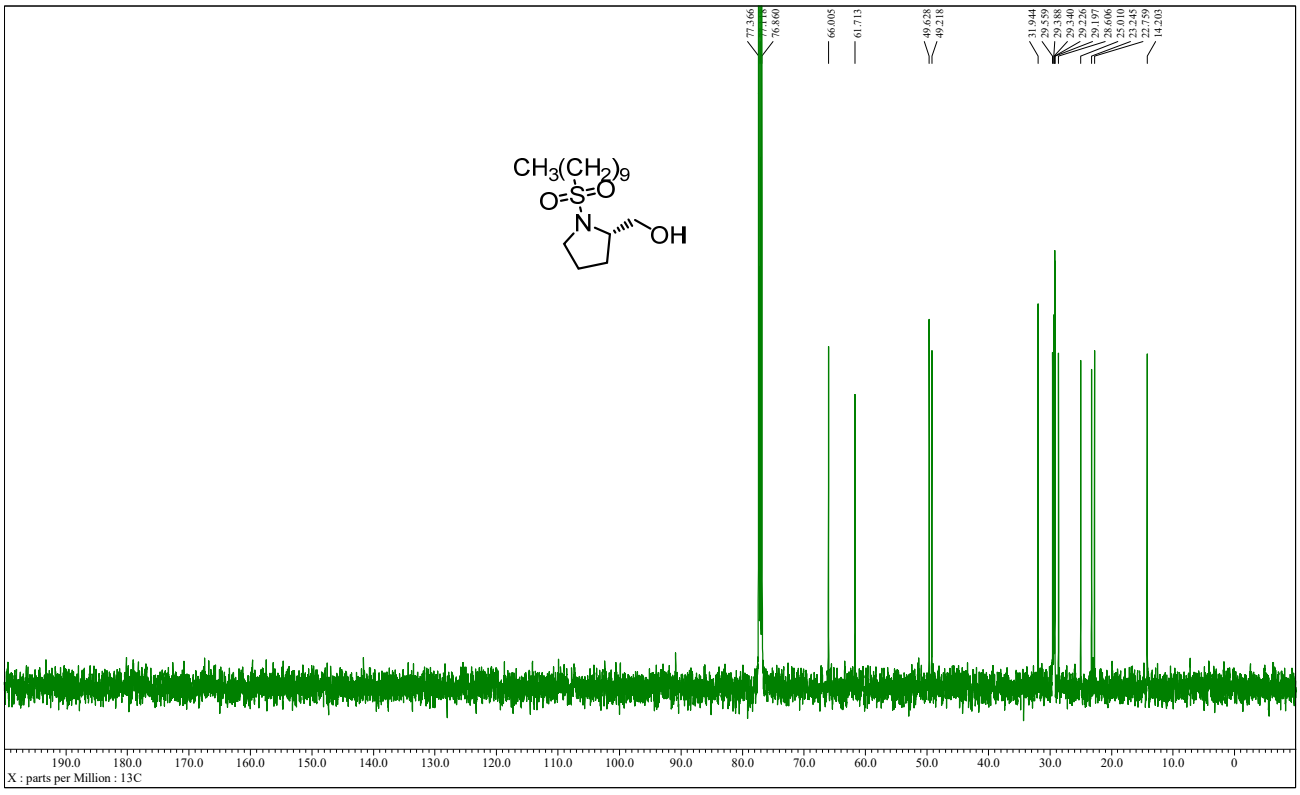

$^{13}$C NMR spectrum of compound **S35** (150 MHz, $CDCl_3$)



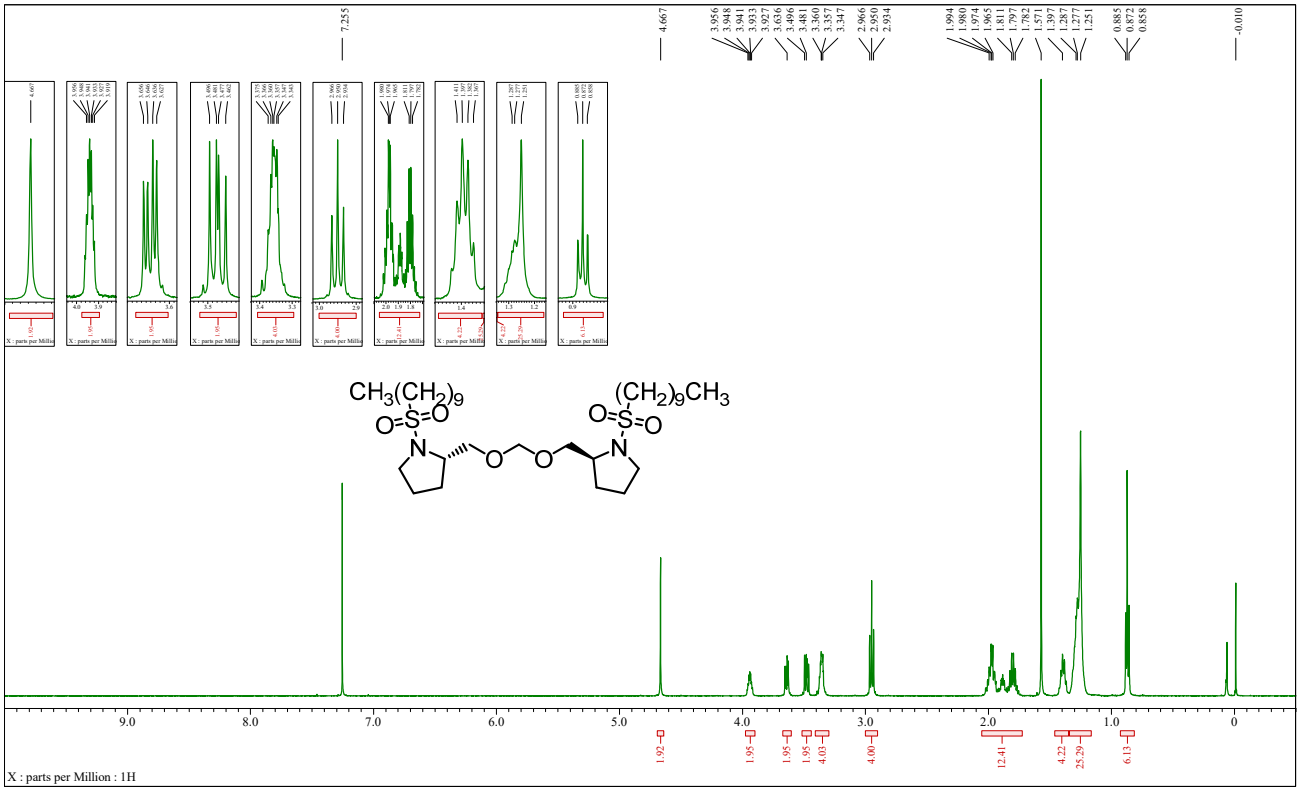
$^{1}$H NMR spectrum of compound **S36** (500 MHz, $CDCl_3$)



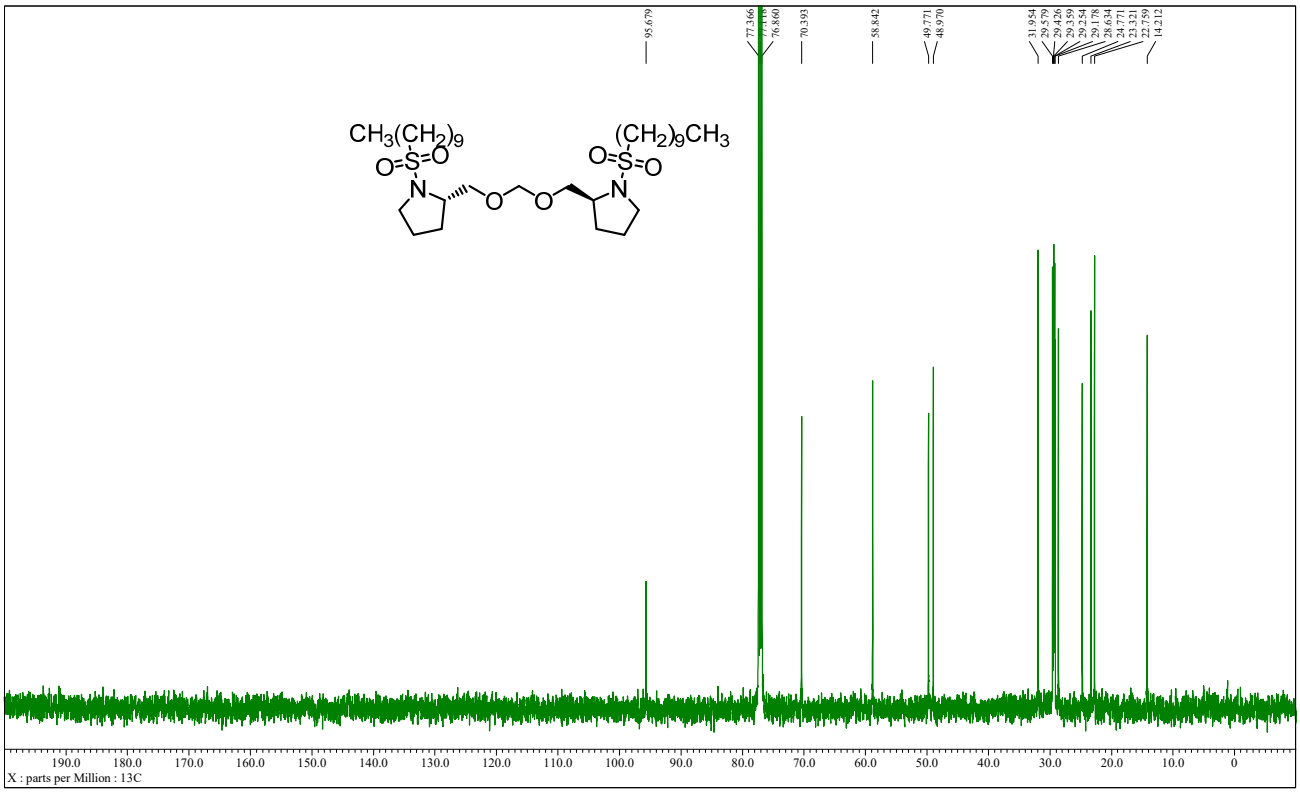

$^{13}$C NMR spectrum of compound **S36** (125 MHz, $CDCl_3$)



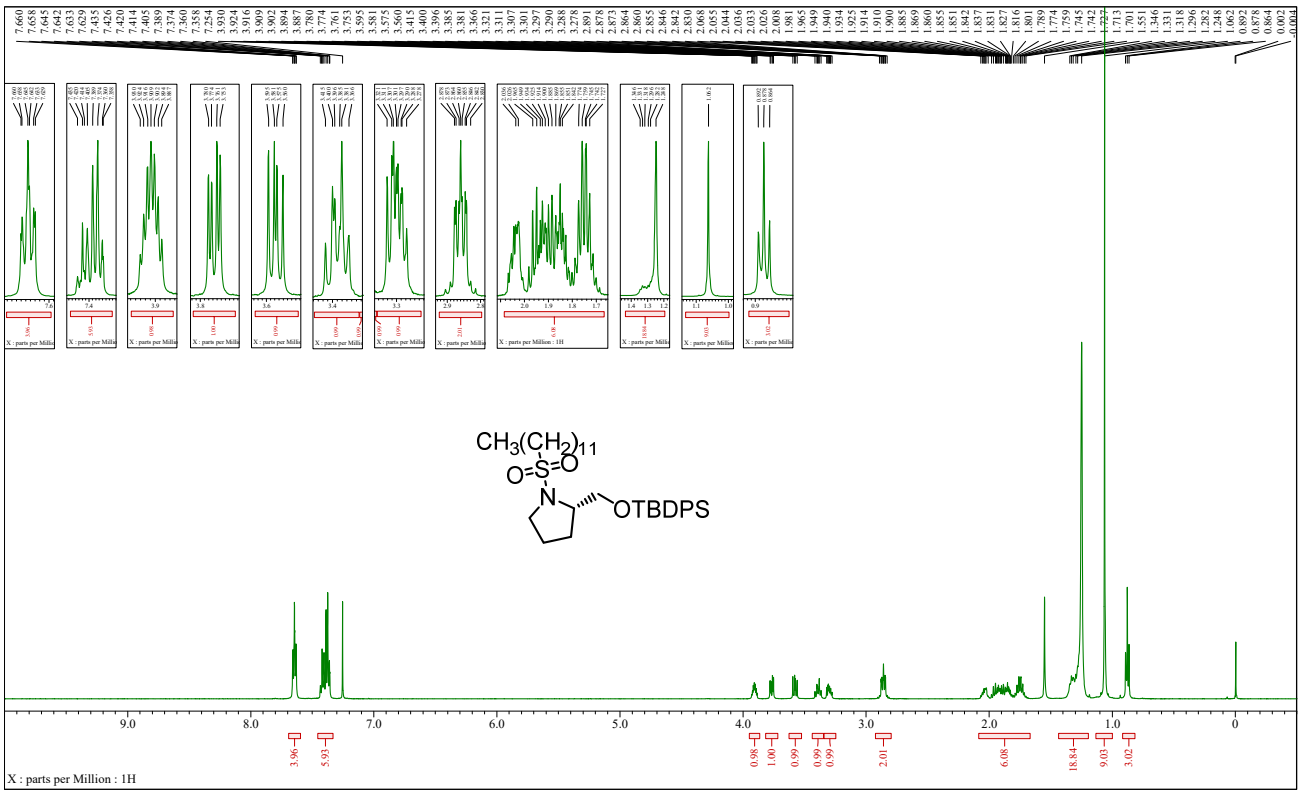
$^{1}$H NMR spectrum of compound **26** (500 MHz, $CDCl_3$)



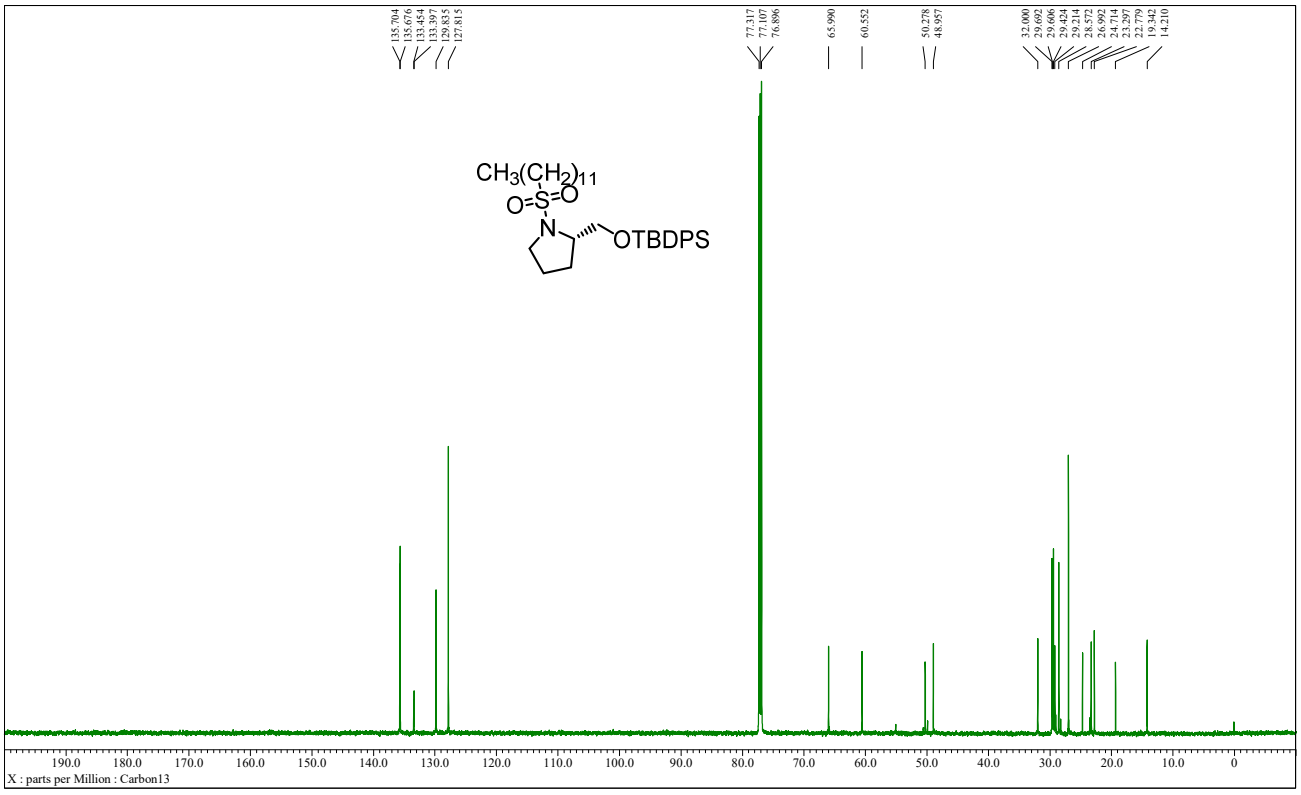

$^{13}$C NMR spectrum of compound **26** (125 MHz, $CDCl_3$)



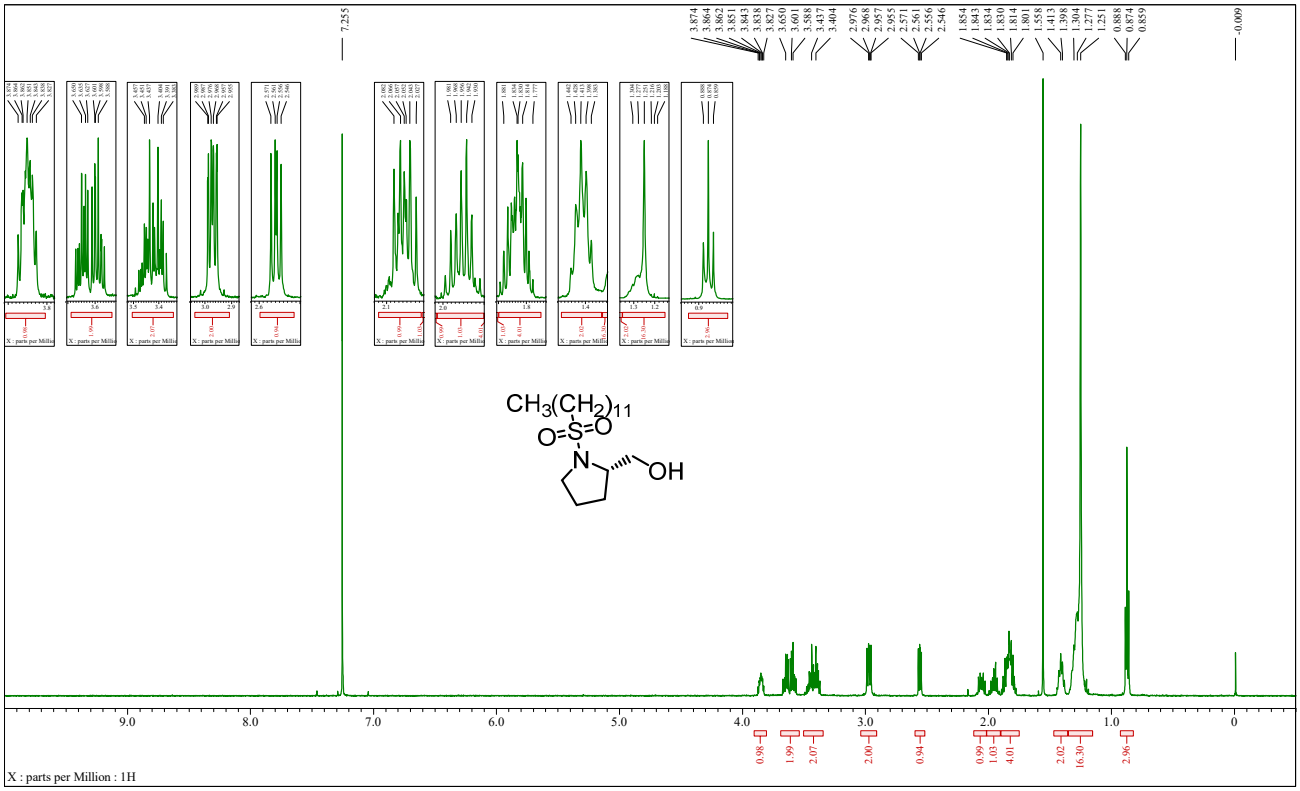
$^{1}$H NMR spectrum of compound **S38** (500 MHz, $CDCl_3$)



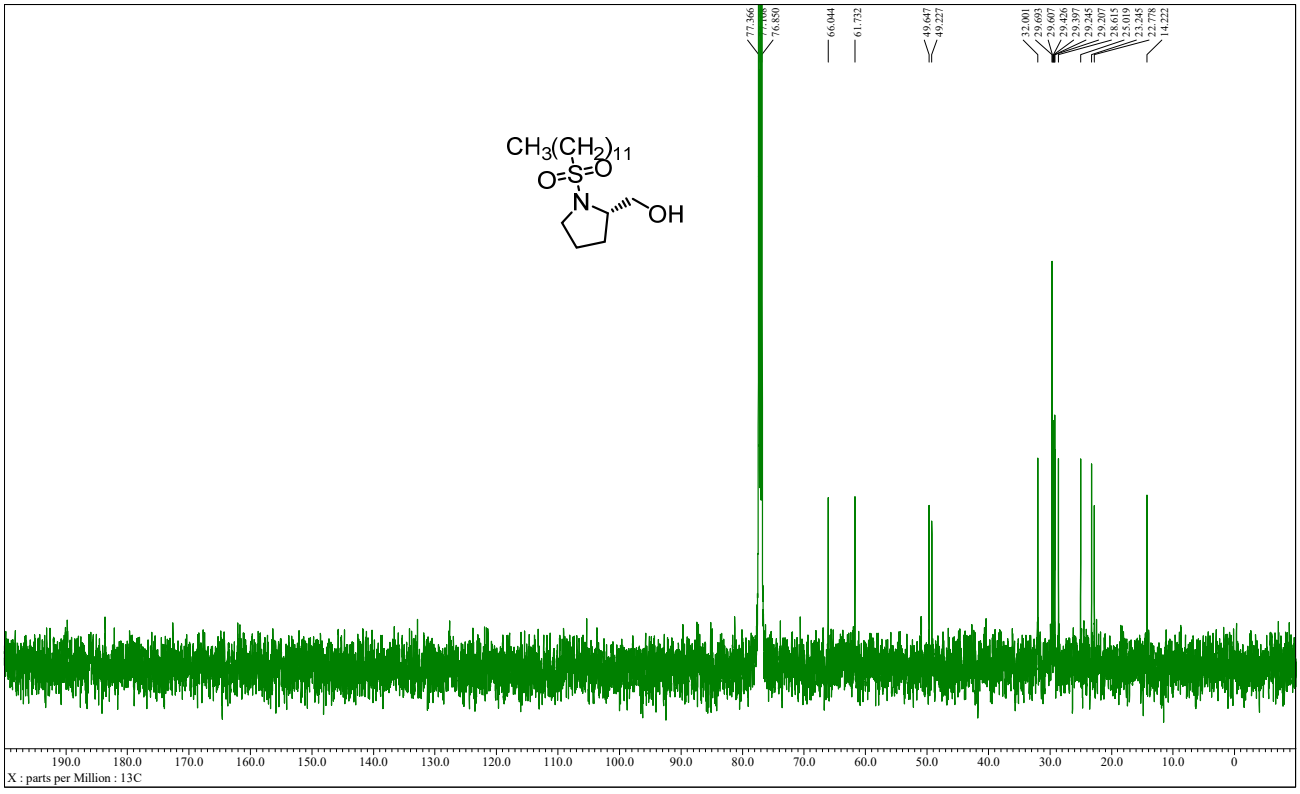

$^{13}$C NMR spectrum of compound **S38** (150 MHz, $CDCl_3$)



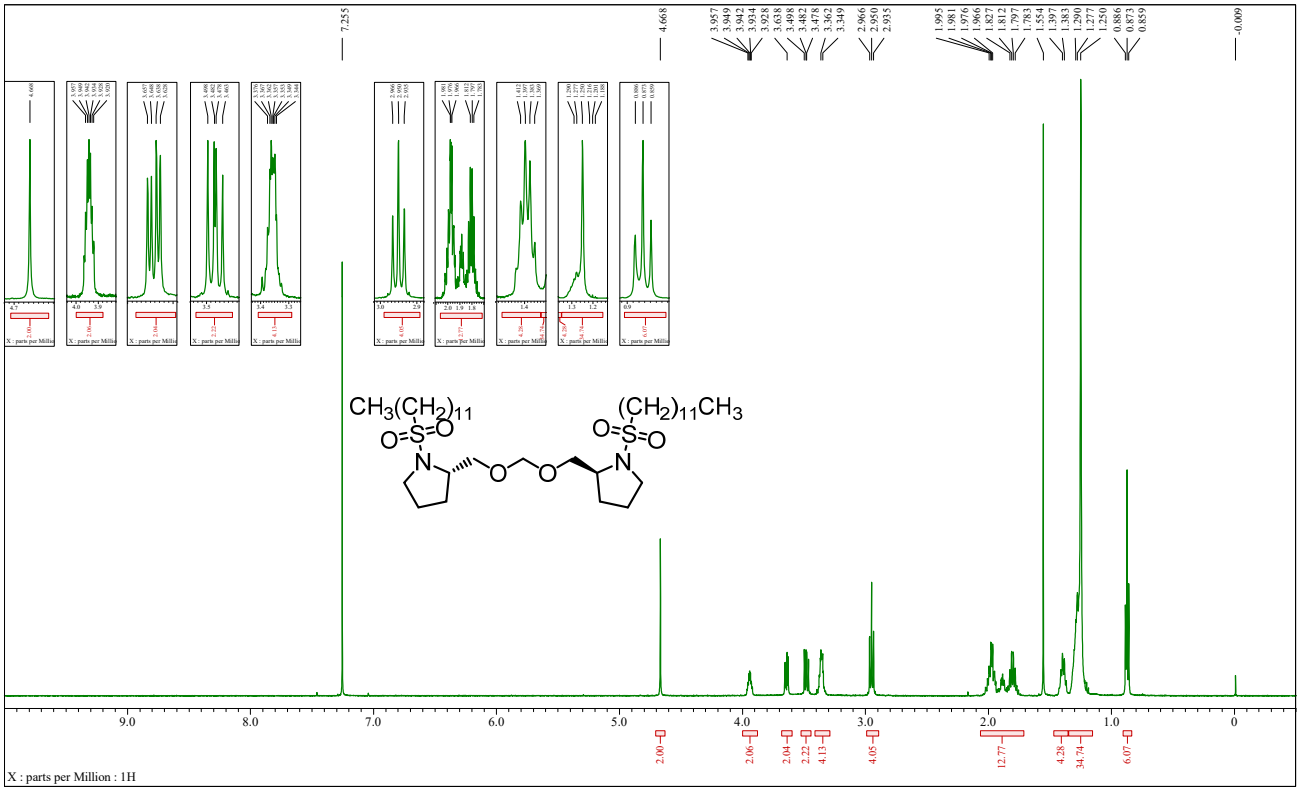
$^{1}$H NMR spectrum of compound **S39** (500 MHz, $CDCl_3$)



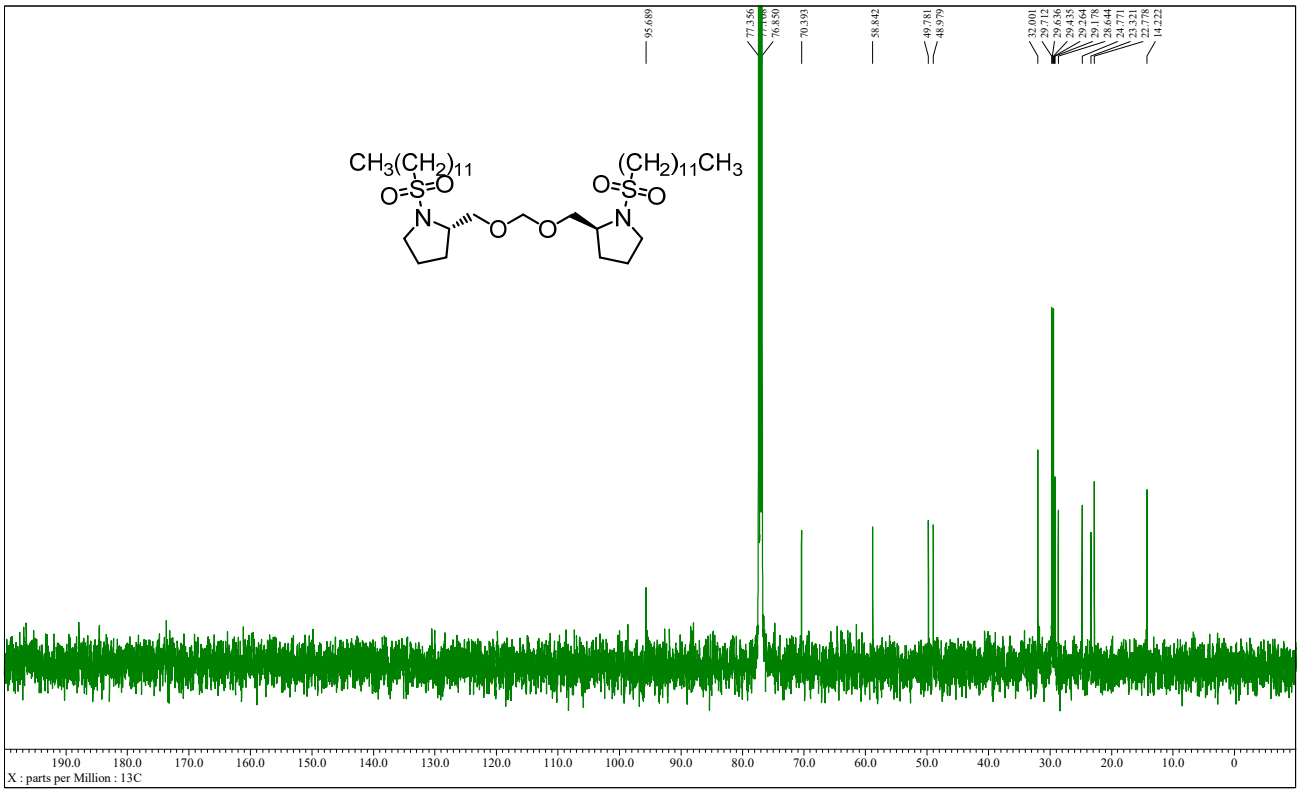

$^{13}$C NMR spectrum of compound **S39** (125 MHz, $CDCl_3$)



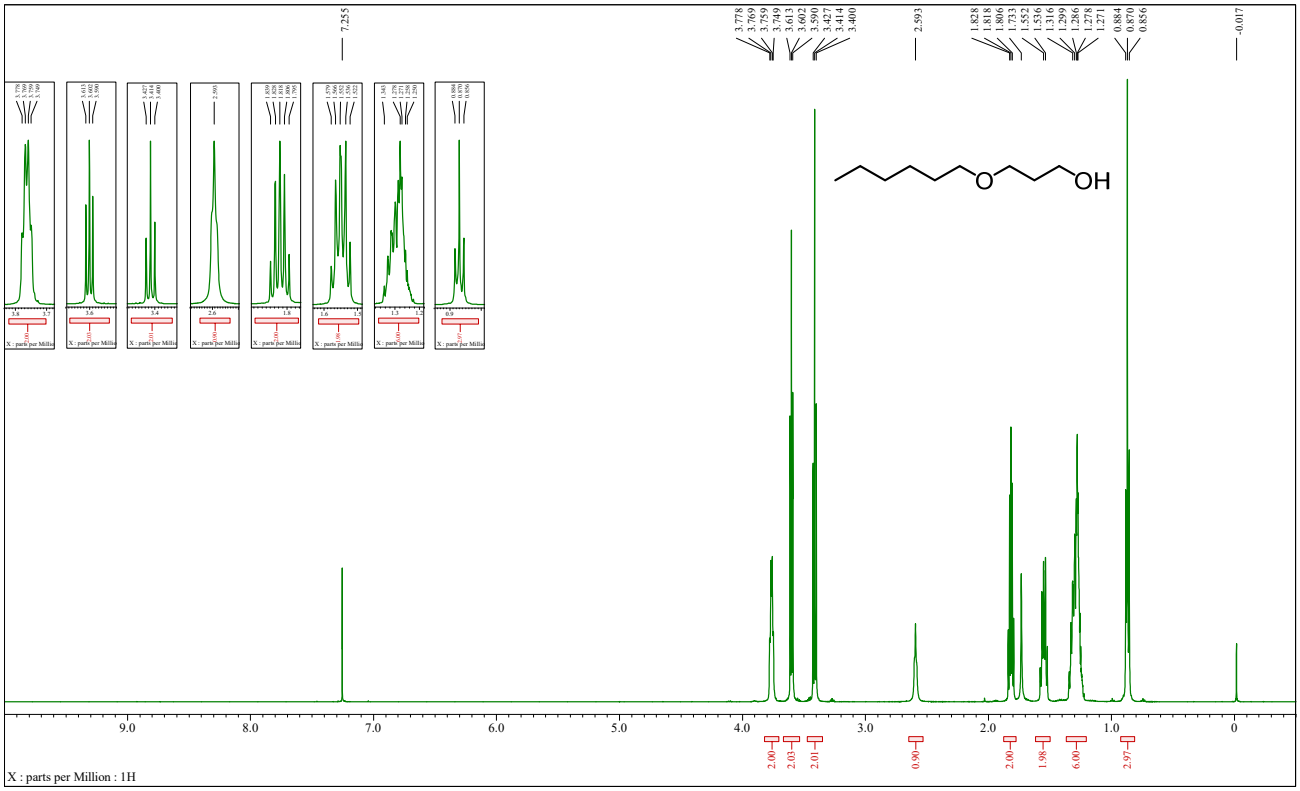
$^{1}$H NMR spectrum of compound **27** (500 MHz, $CDCl_3$)



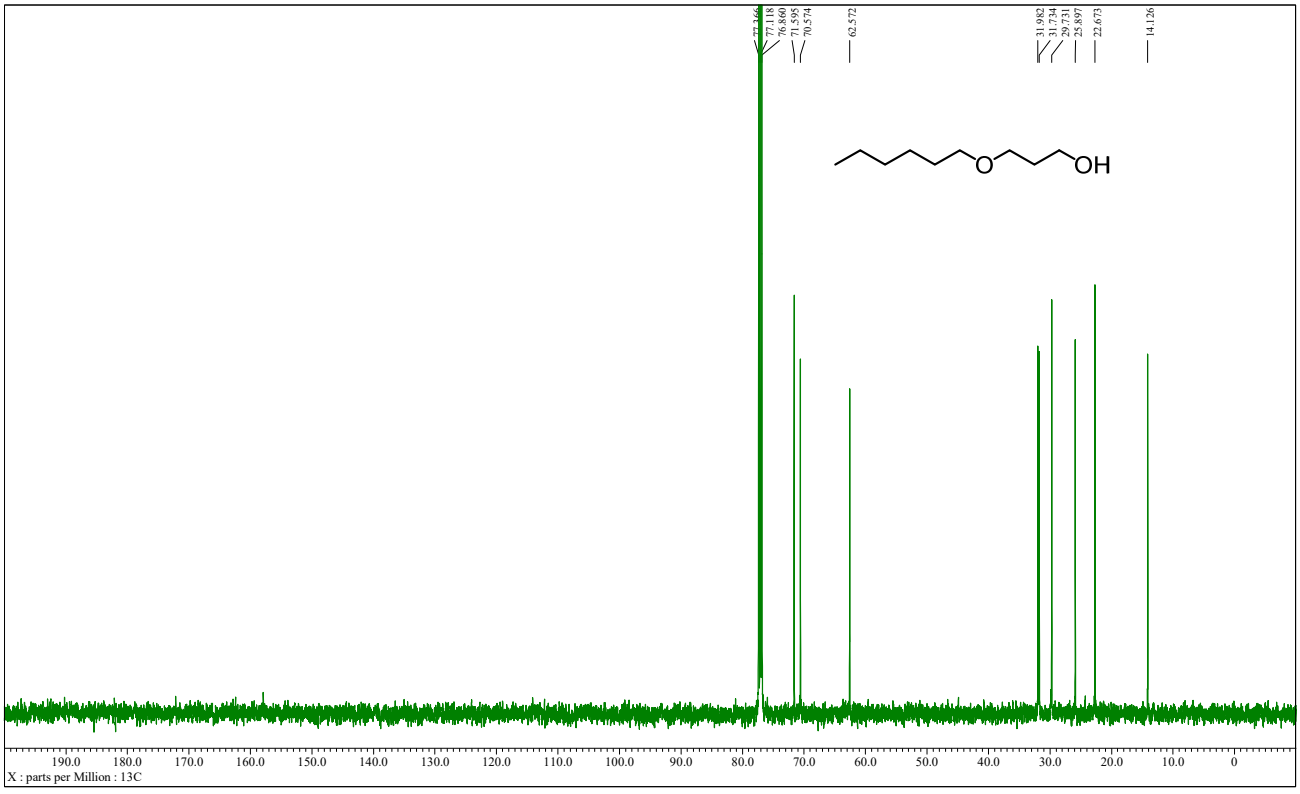

$^{13}$C NMR spectrum of compound **27** (125 MHz, $CDCl_3$)



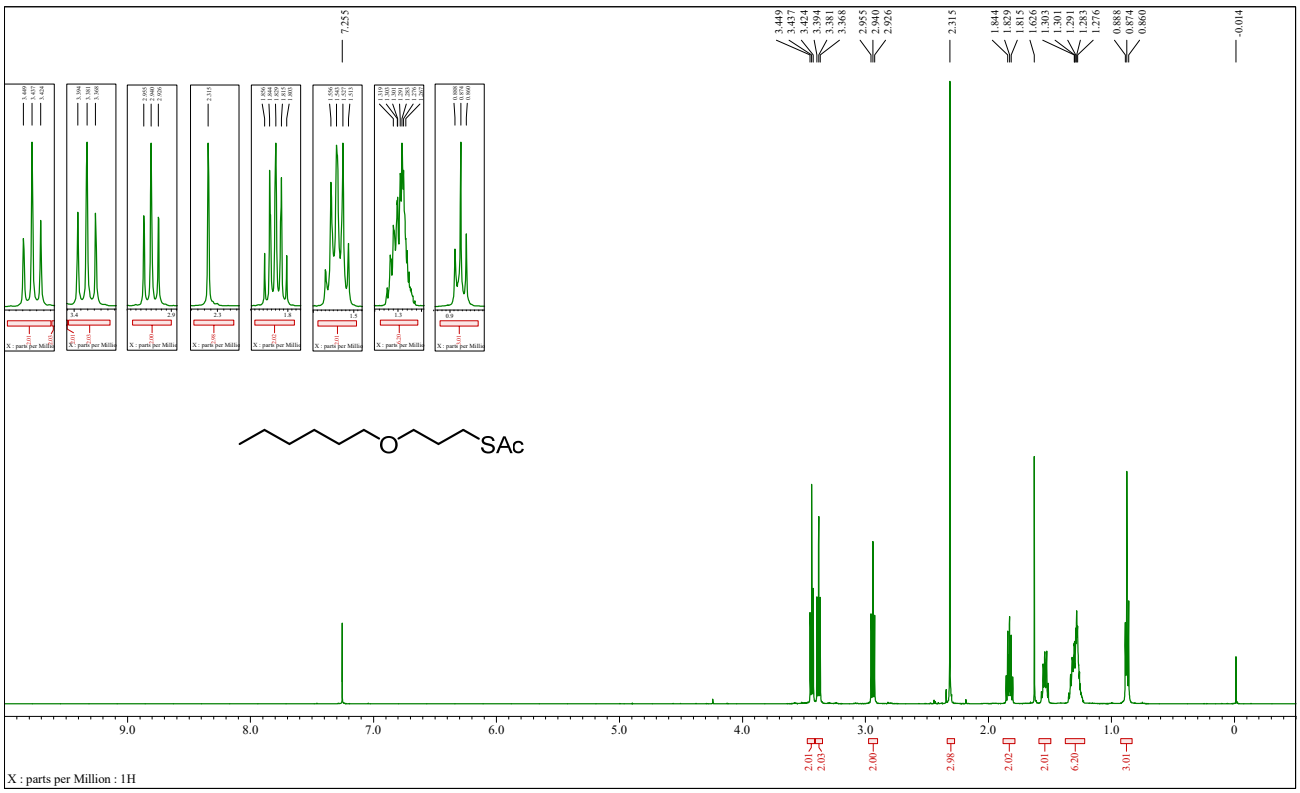
$^{1}$H NMR spectrum of compound **S40** (500 MHz, $CDCl_3$)



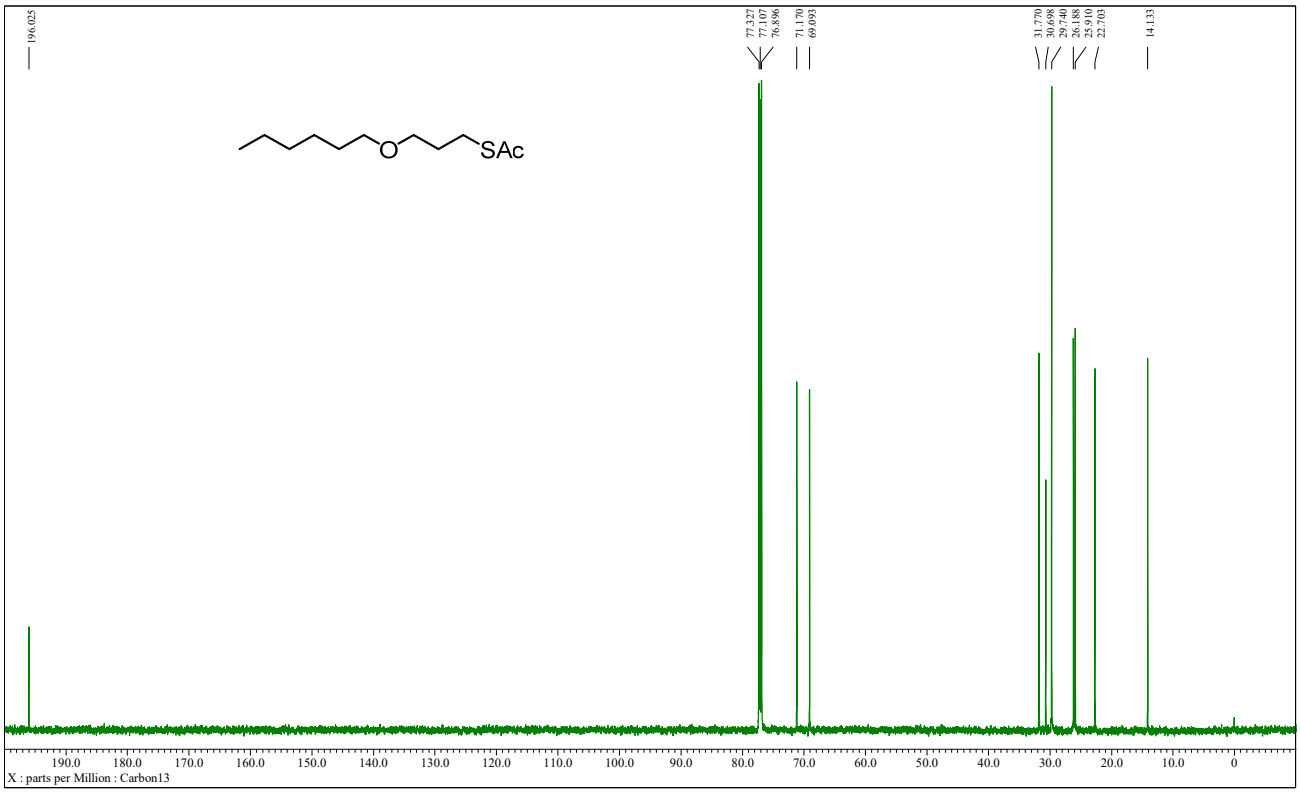

$^{13}$C NMR spectrum of compound **S40** (125 MHz, $CDCl_3$)



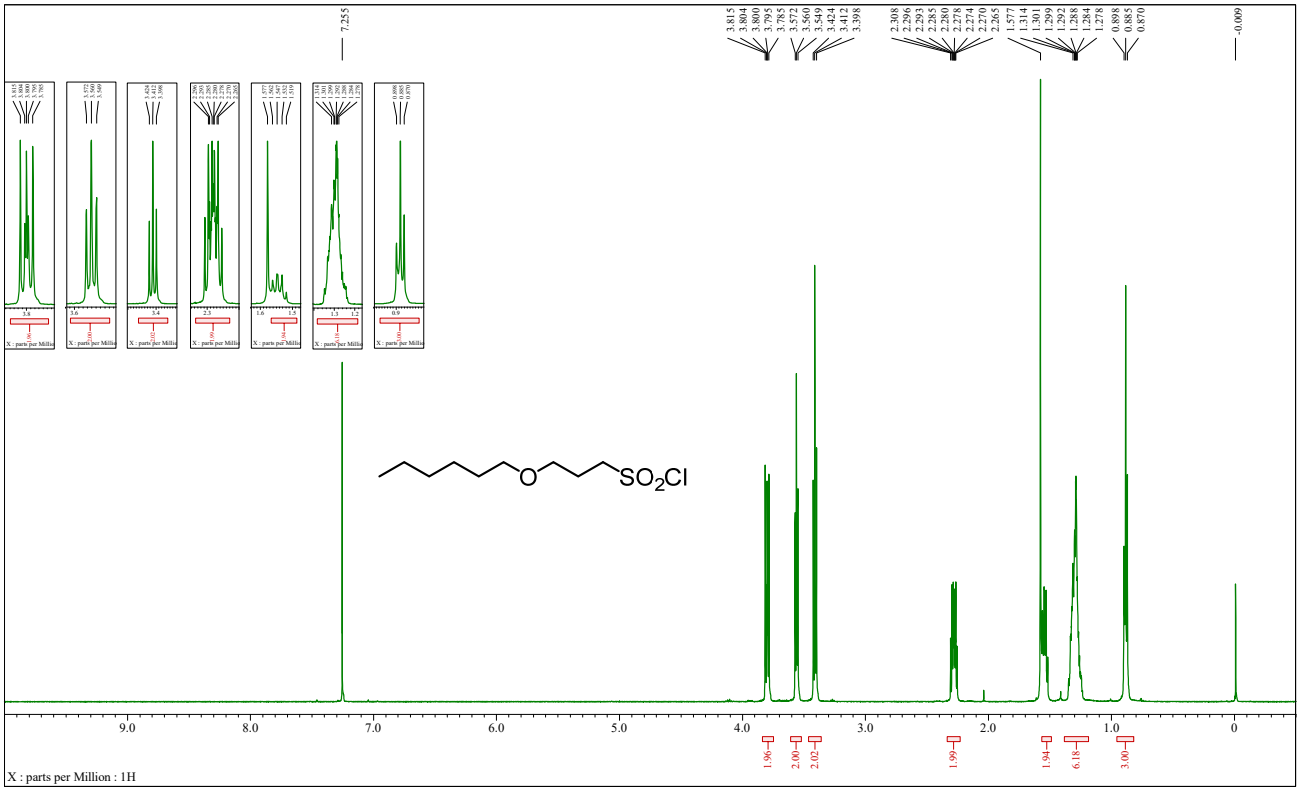
$^{1}$H NMR spectrum of compound **S41** (500 MHz, $CDCl_3$)



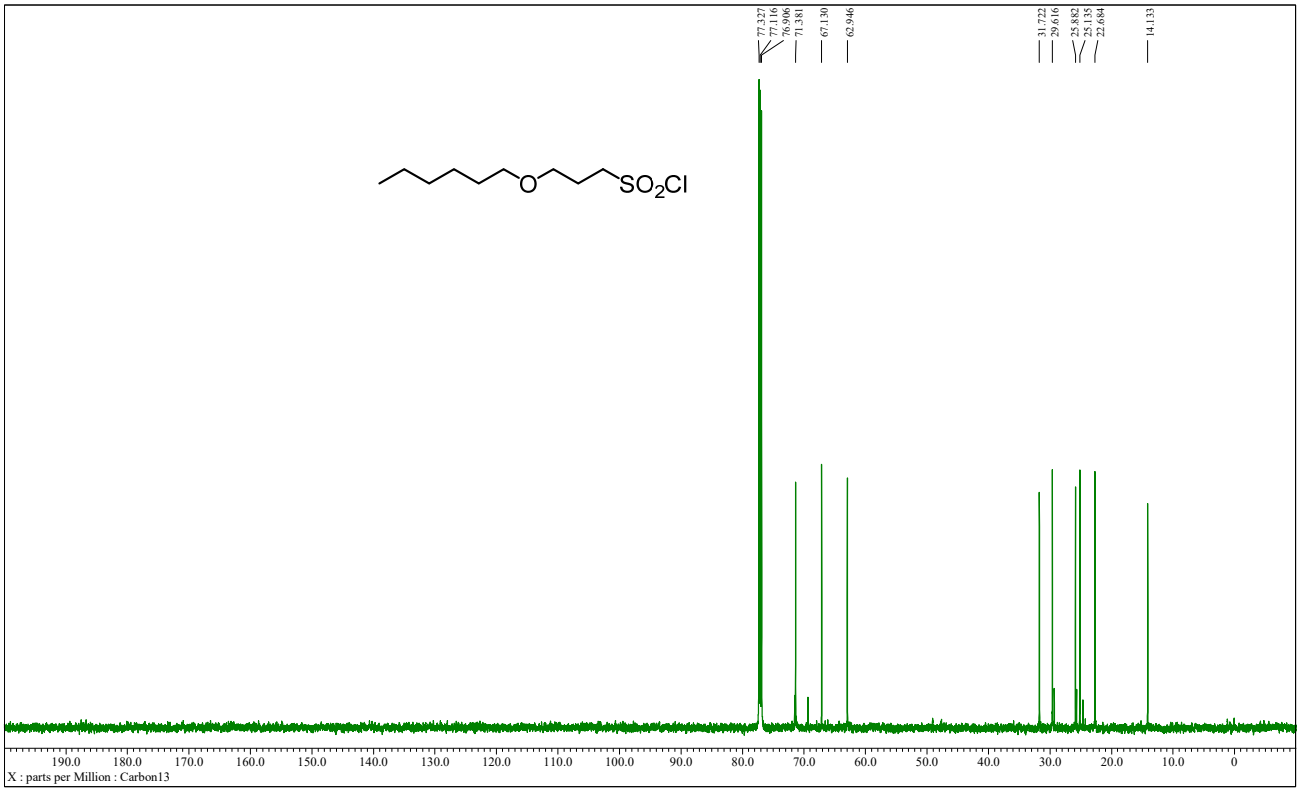

$^{13}$C NMR spectrum of compound **S41** (150 MHz, $CDCl_3$)



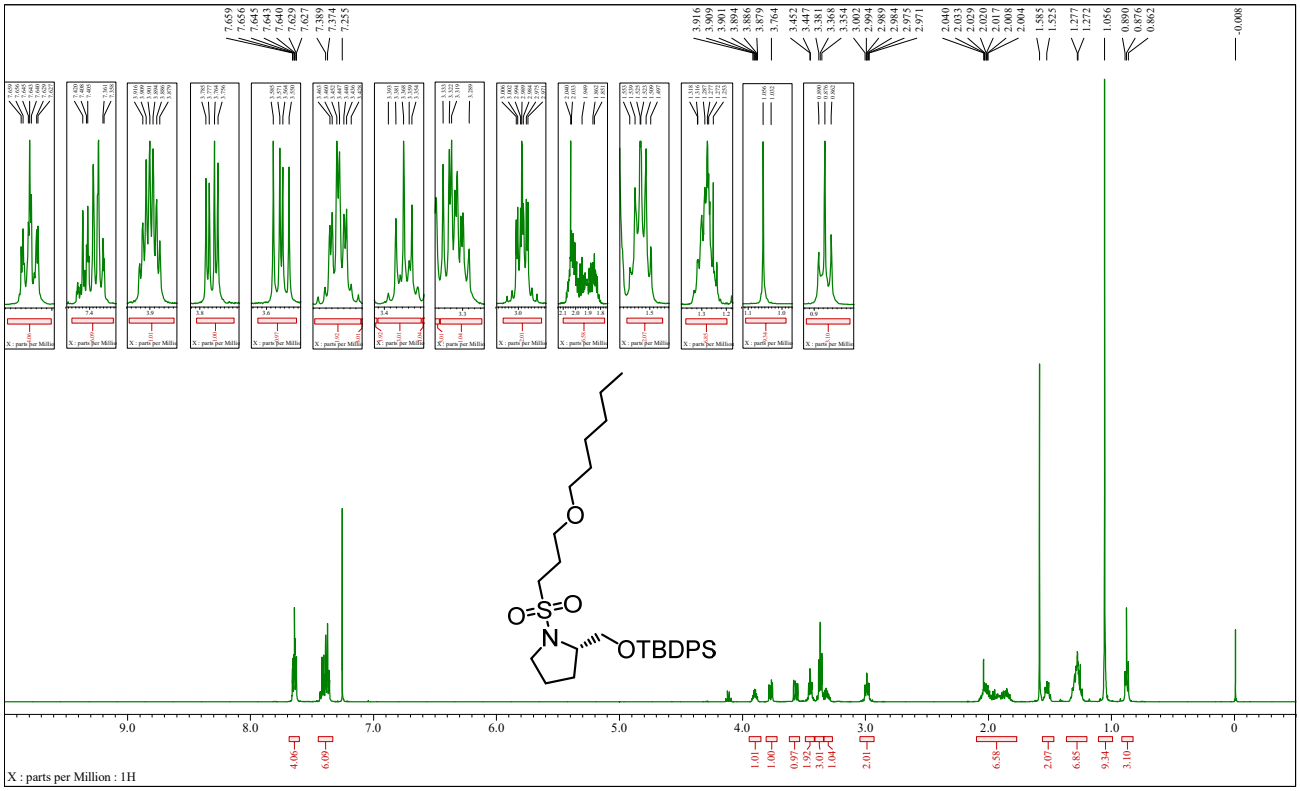
$^{1}$H NMR spectrum of compound **S42** (500 MHz, $CDCl_3$)



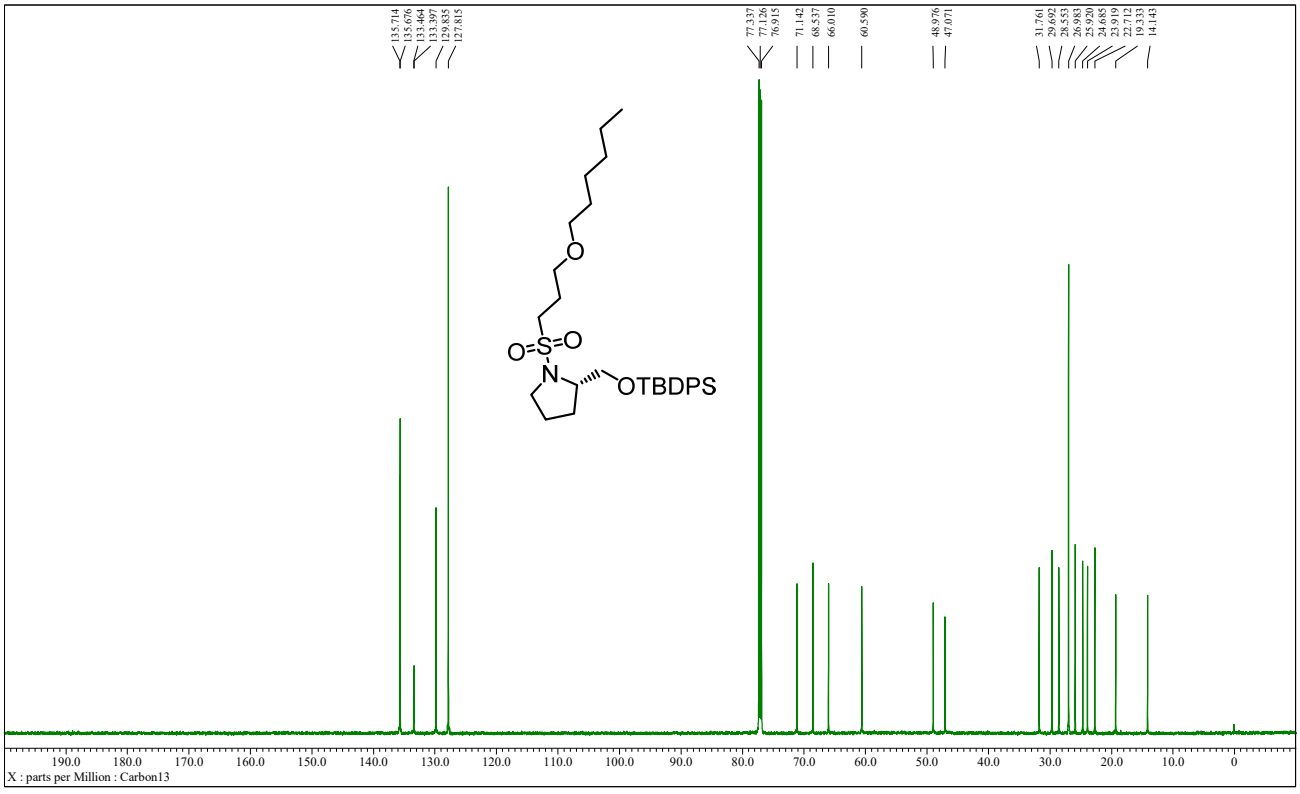

$^{13}$C NMR spectrum of compound **S42** (150 MHz, $CDCl_3$)



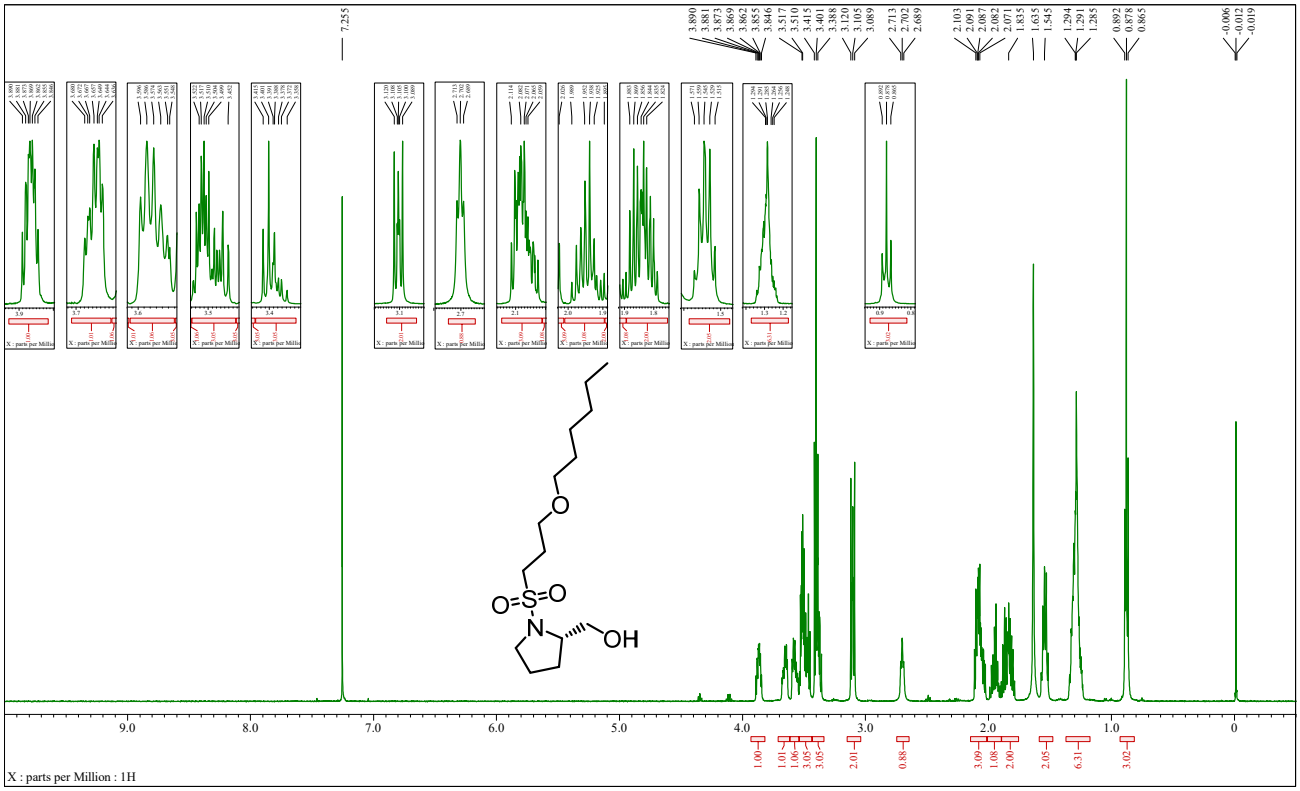
$^{1}$H NMR spectrum of compound **S43** (500 MHz, $CDCl_3$)



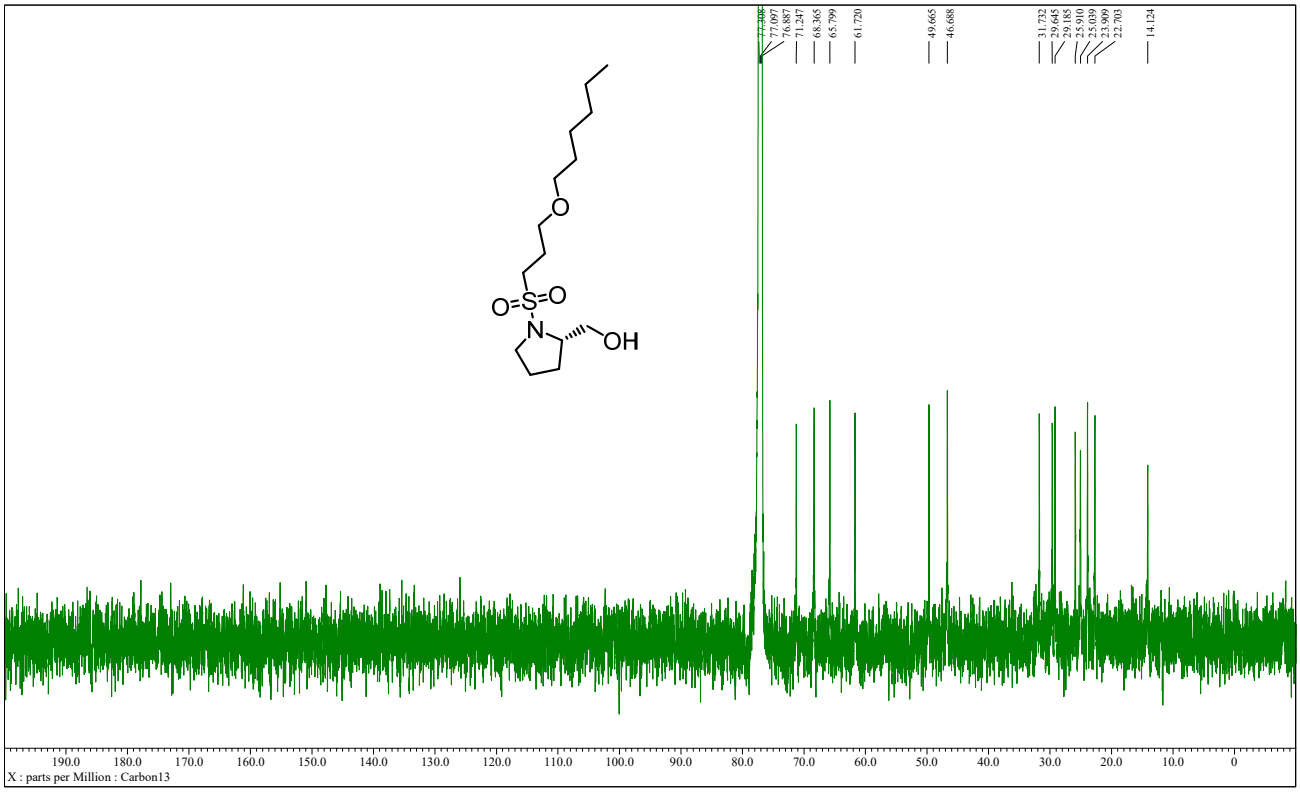

$^{13}$C NMR spectrum of compound **S43** (150 MHz, $CDCl_3$)



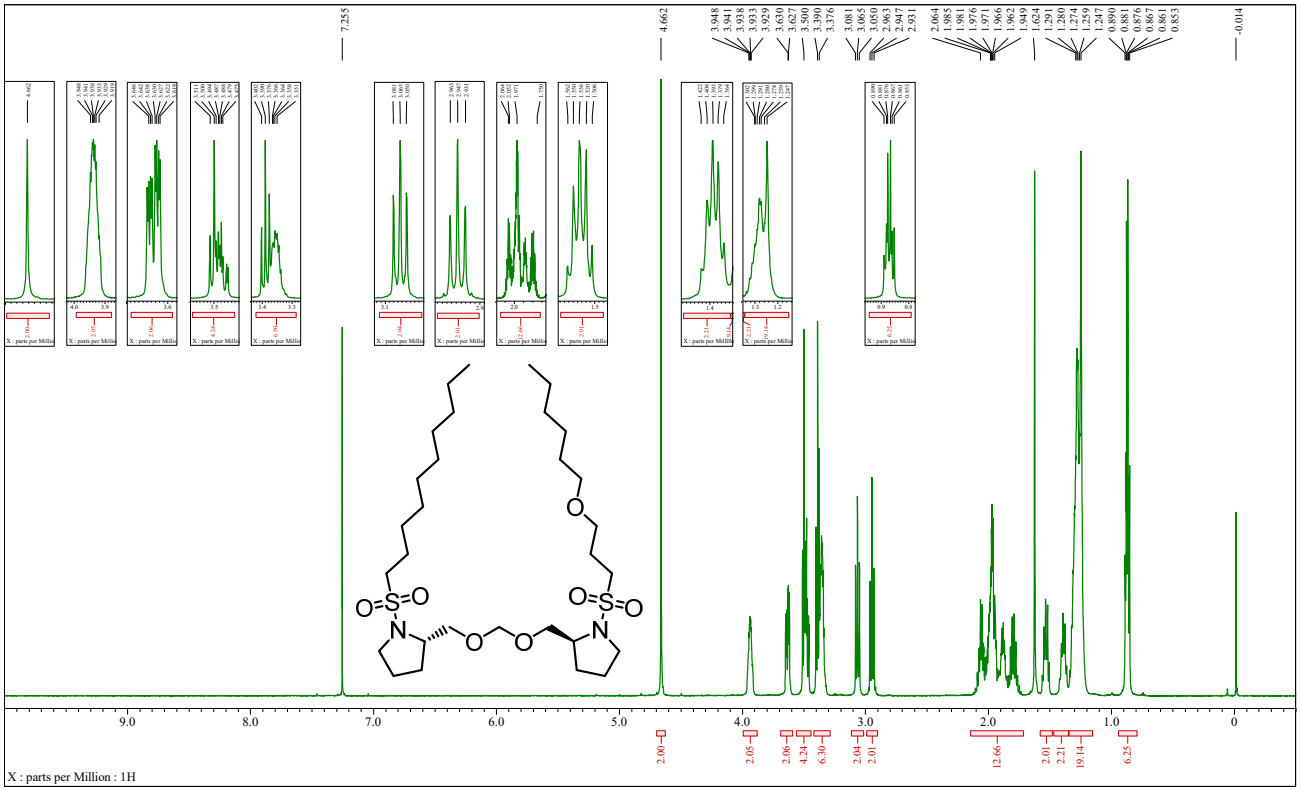
$^{1}$H NMR spectrum of compound **S44** (500 MHz, $CDCl_3$)



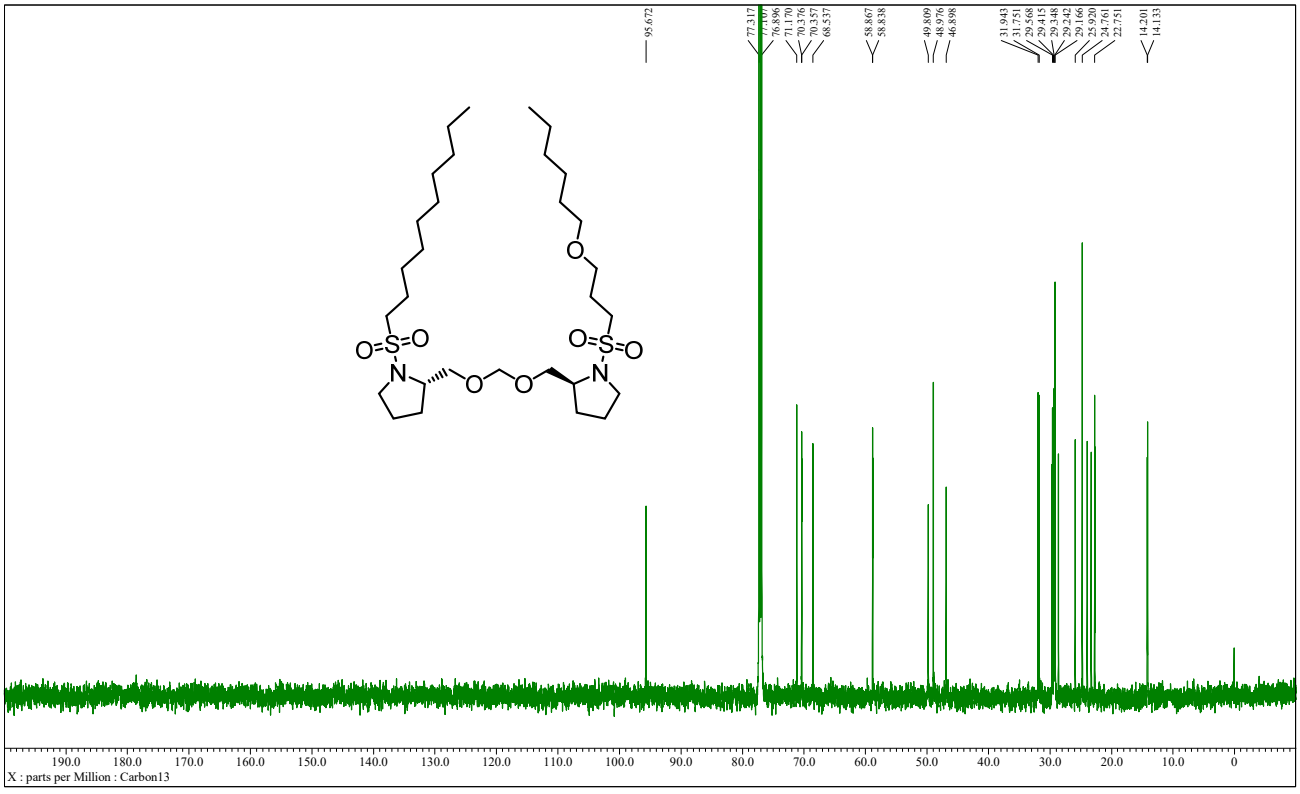

$^{13}$C NMR spectrum of compound **S44** (150 MHz, $CDCl_3$)



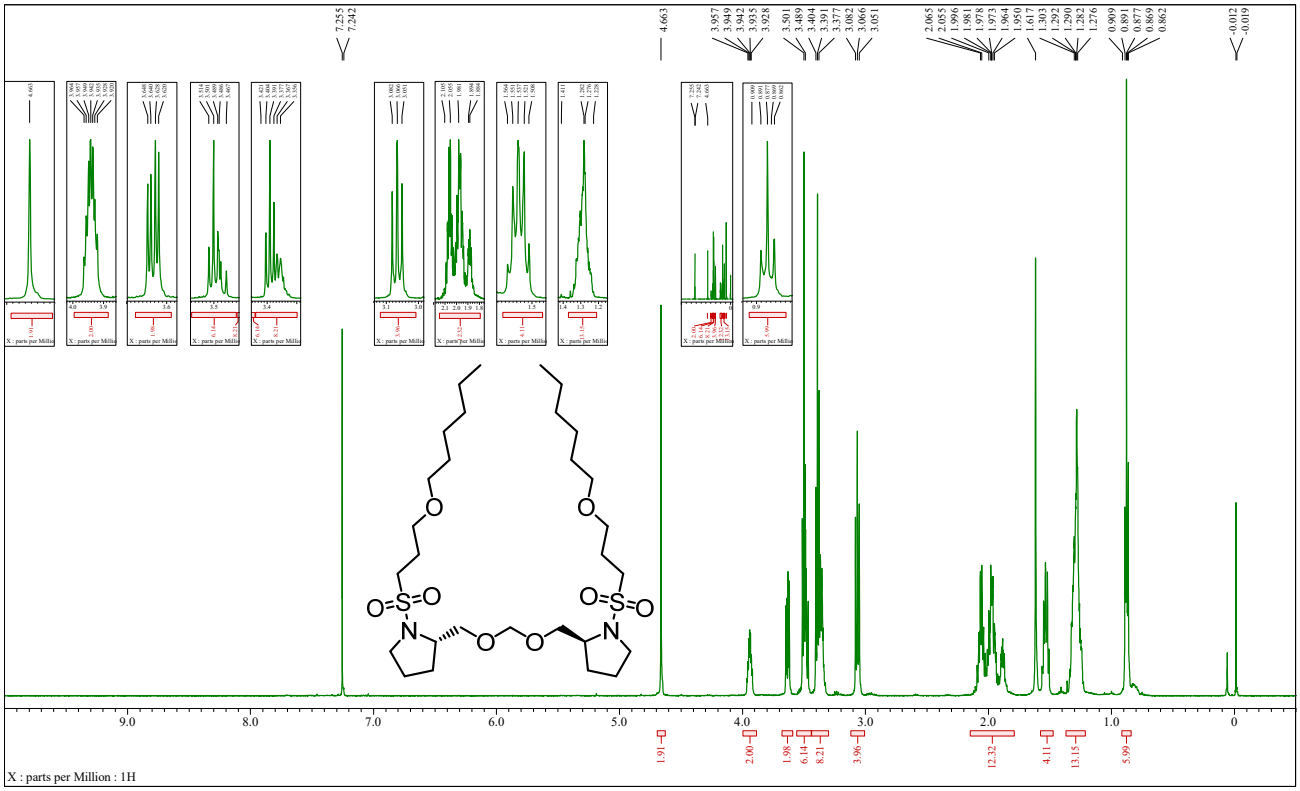
$^{1}$H NMR spectrum of compound **28** (500 MHz, $CDCl_3$)



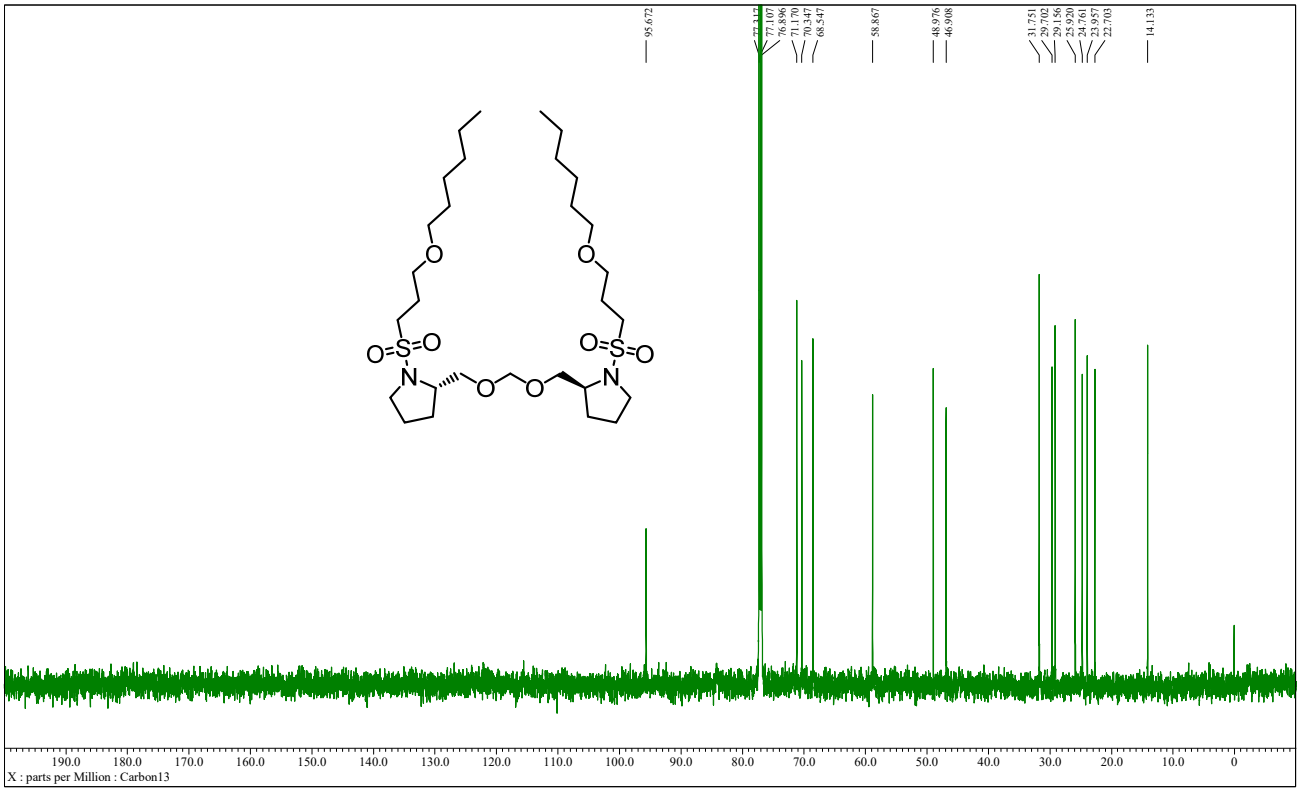

$^{13}$C NMR spectrum of compound **28** (150 MHz, $CDCl_3$)



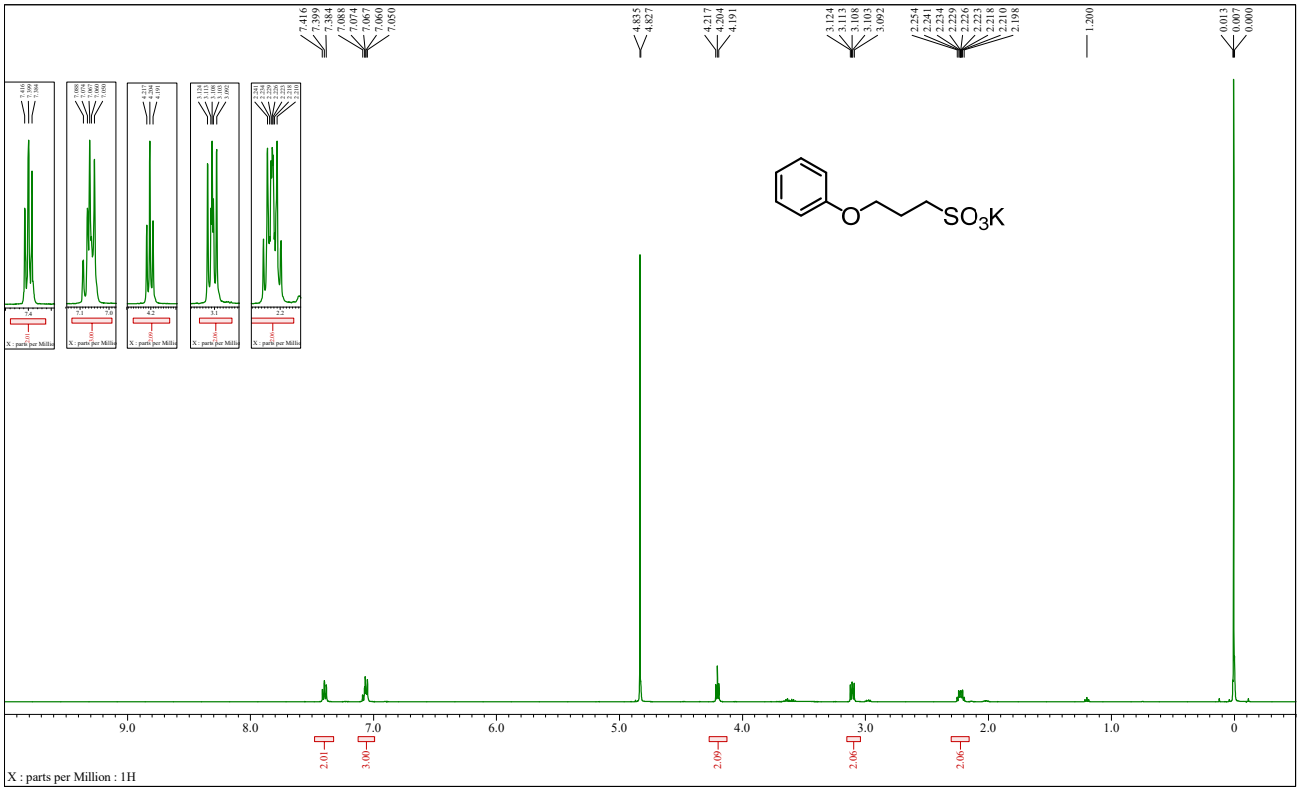
$^{1}$H NMR spectrum of compound **29** (500 MHz, $CDCl_3$)



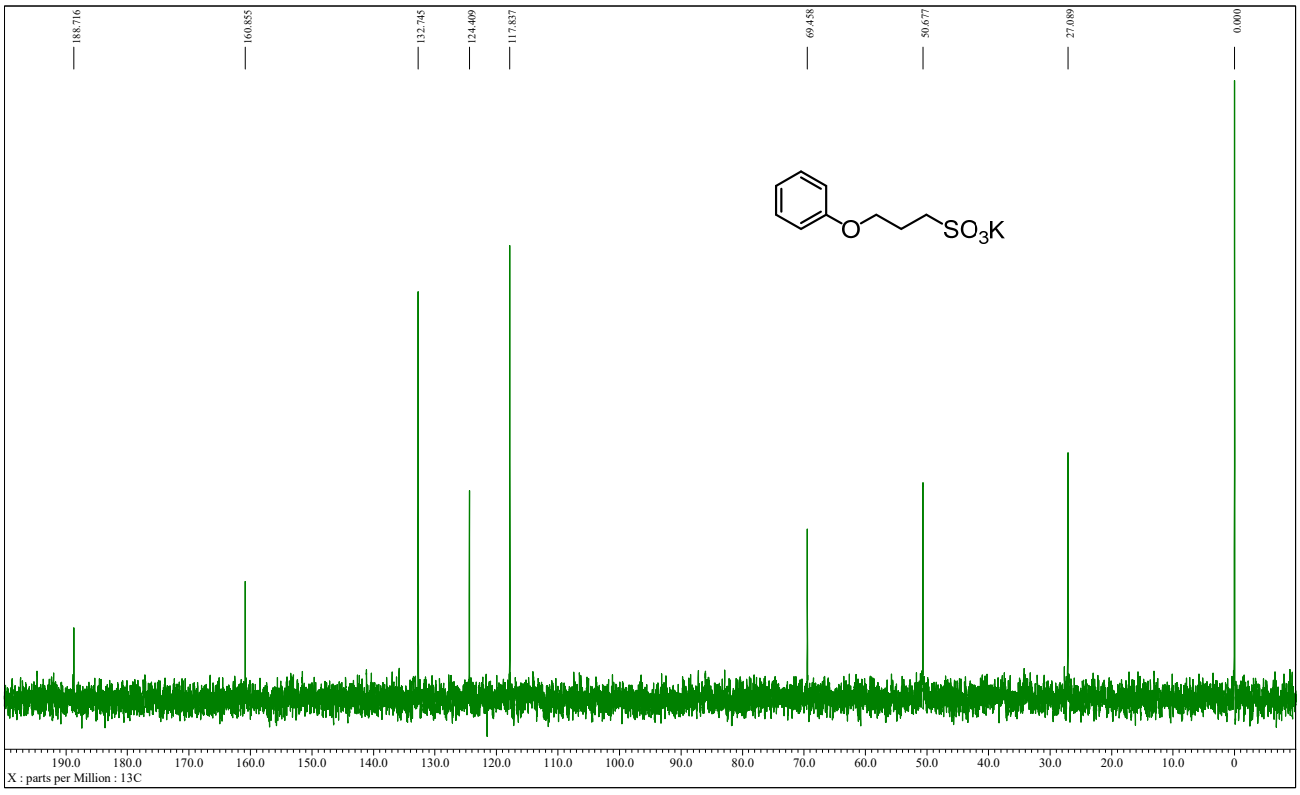

$^{13}$C NMR spectrum of compound **29** (150 MHz, $CDCl_3$)



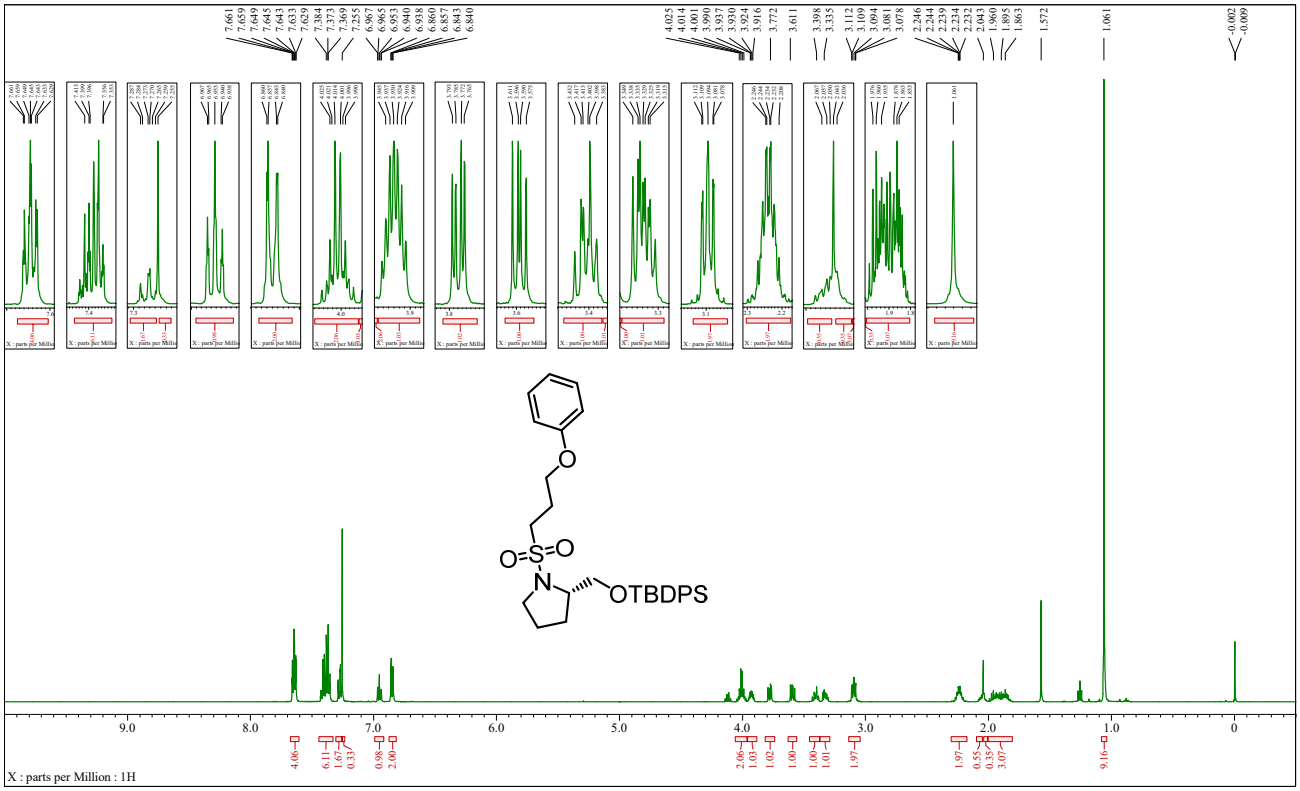
$^{1}$H NMR spectrum of compound **S45** (500 MHz, $D_2O$)



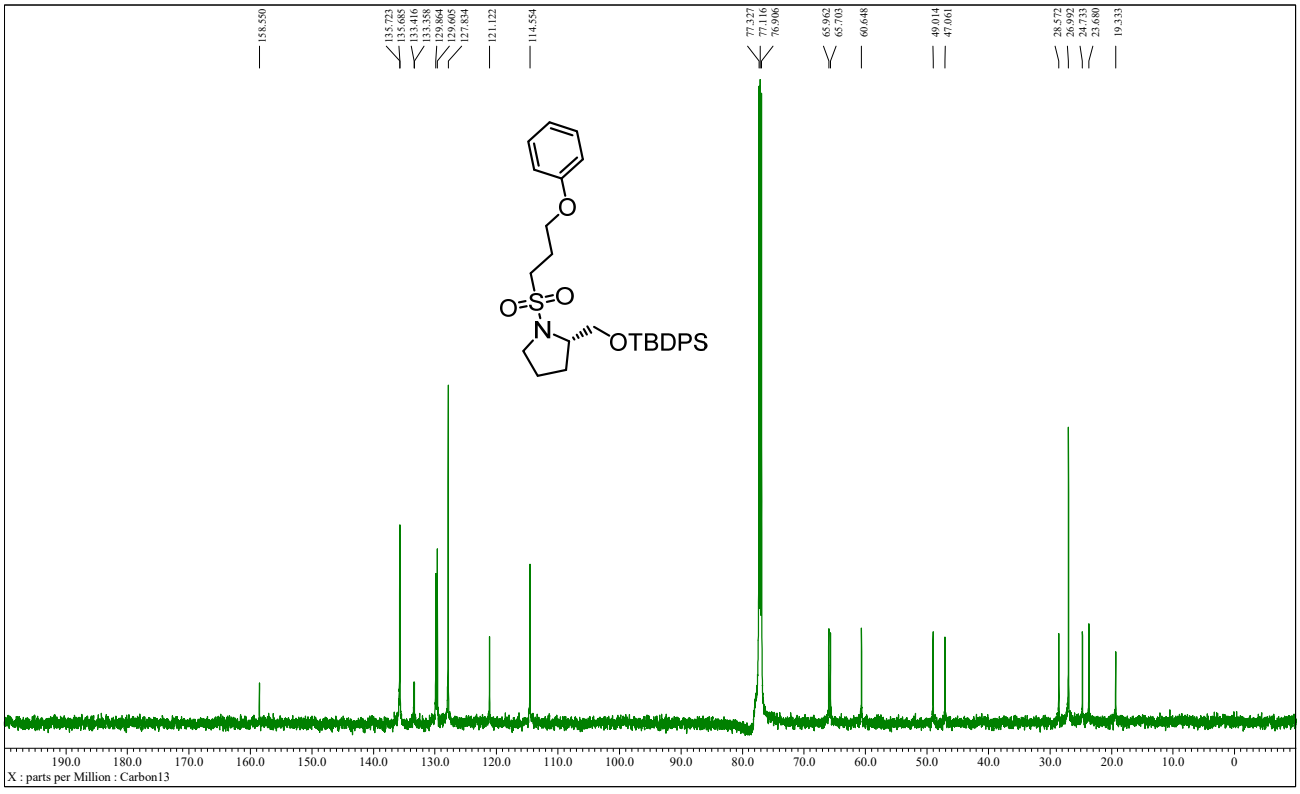

$^{13}$C NMR spectrum of compound **S45** (125 MHz, $D_2O$)



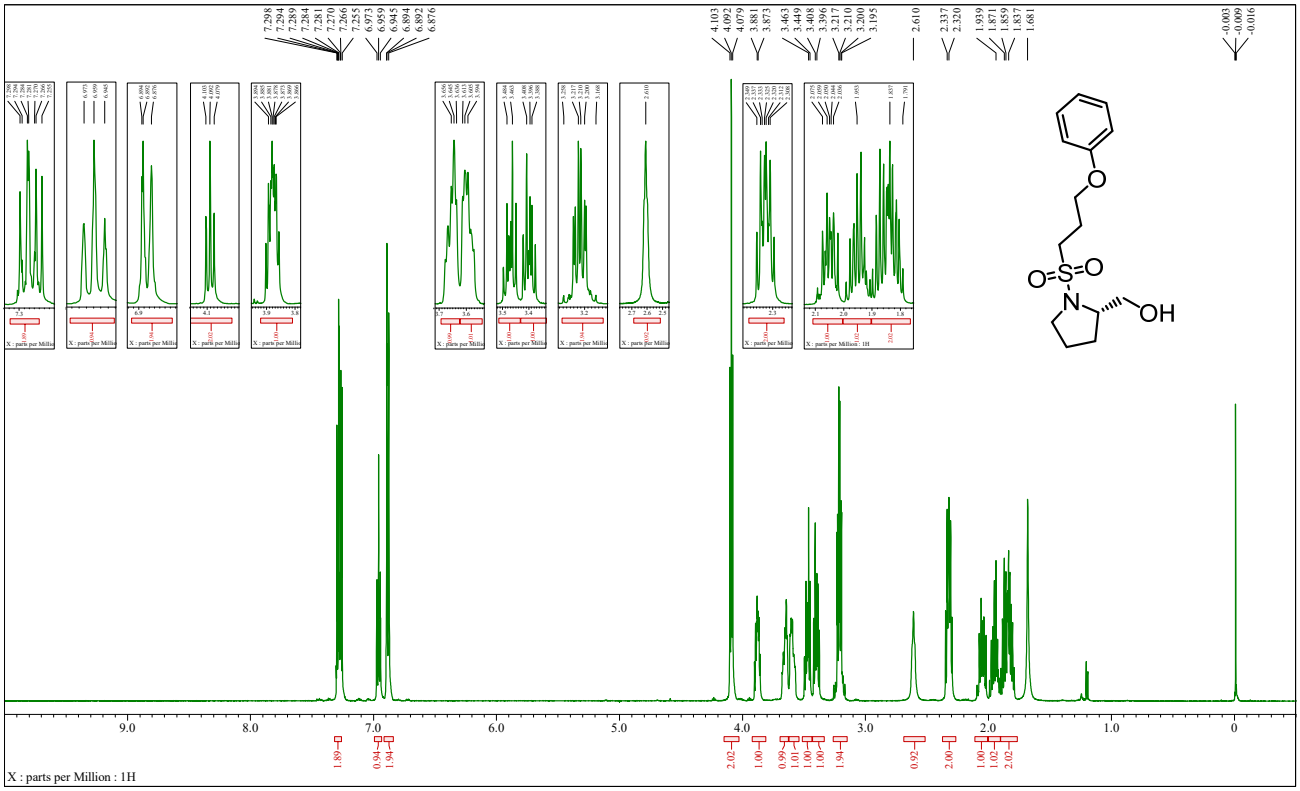
$^{1}$H NMR spectrum of compound **S47** (500 MHz, $CDCl_3$)



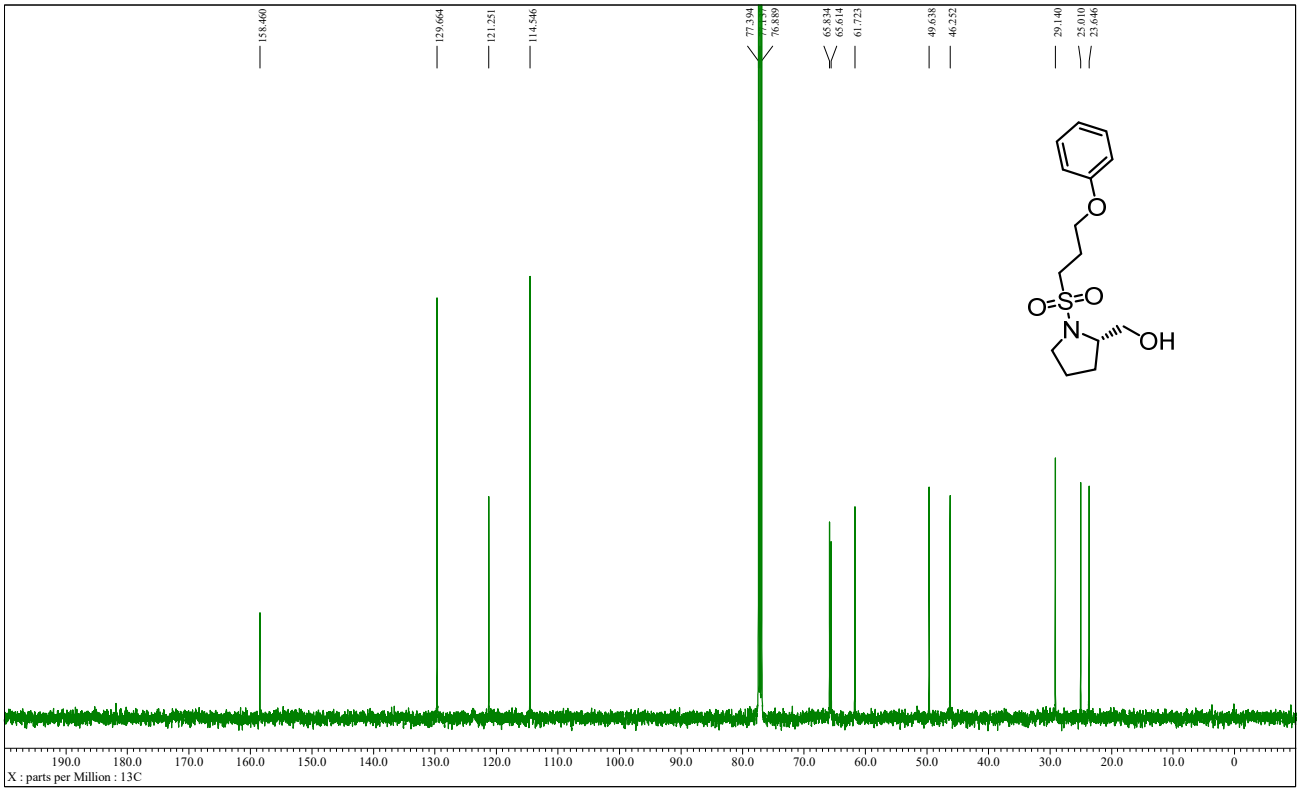

$^{13}$C NMR spectrum of compound **S47** (150 MHz, $CDCl_3$)



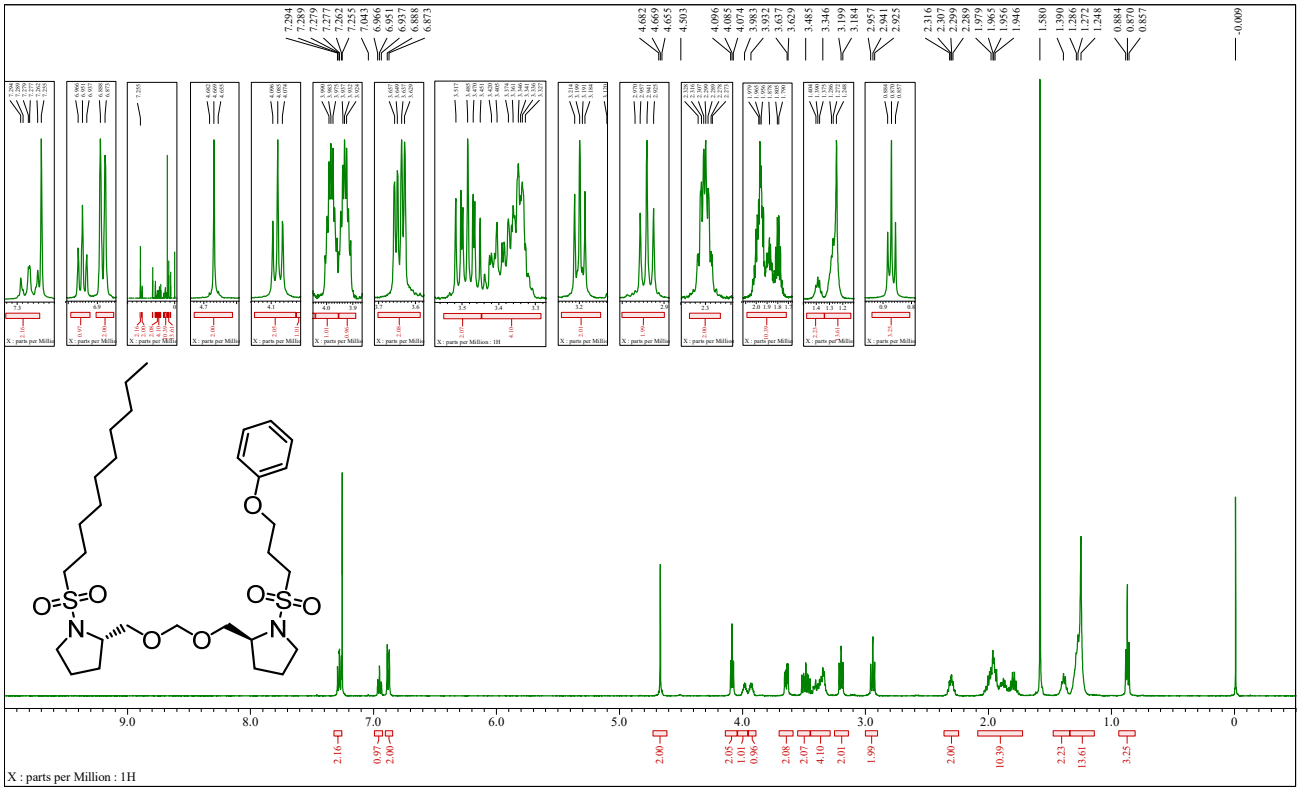
$^{1}$H NMR spectrum of compound **S48** (500 MHz, $CDCl_3$)



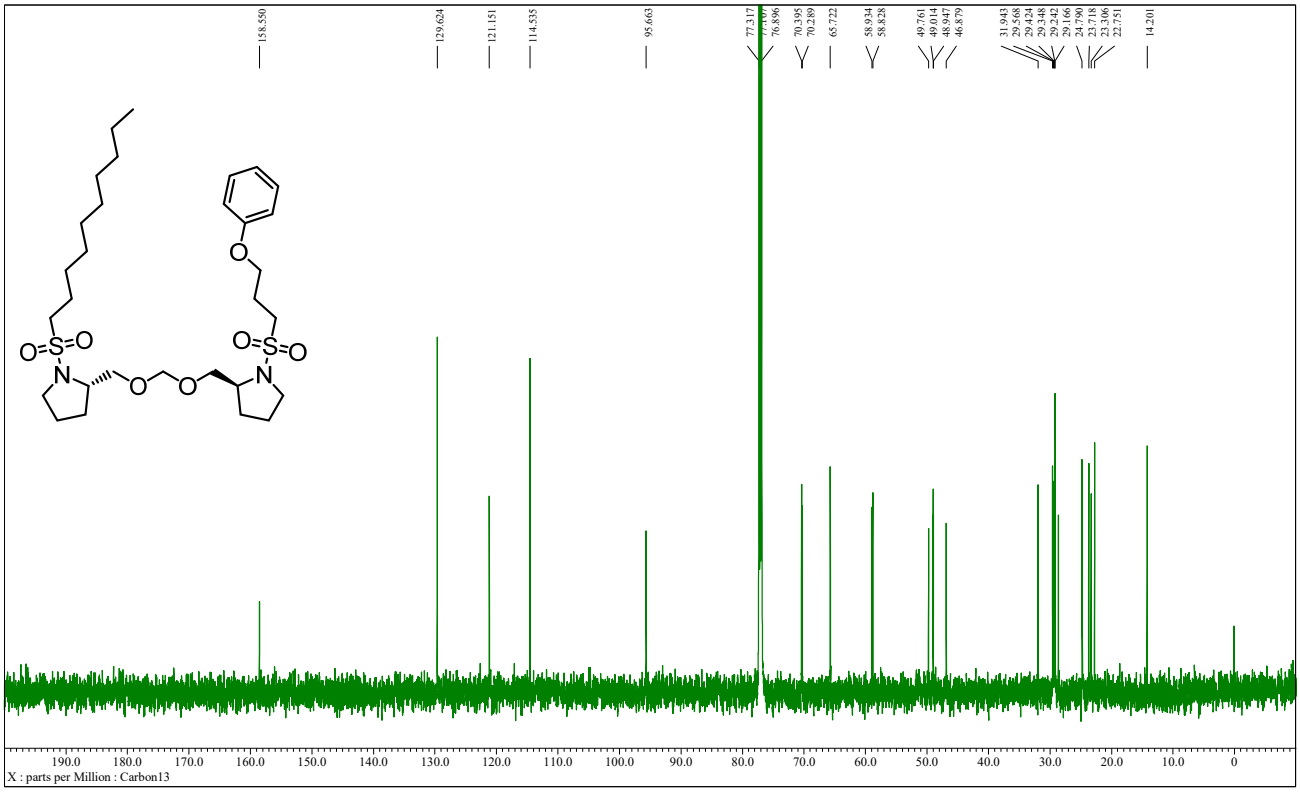

$^{13}$C NMR spectrum of compound **S48** (125 MHz, $CDCl_3$)



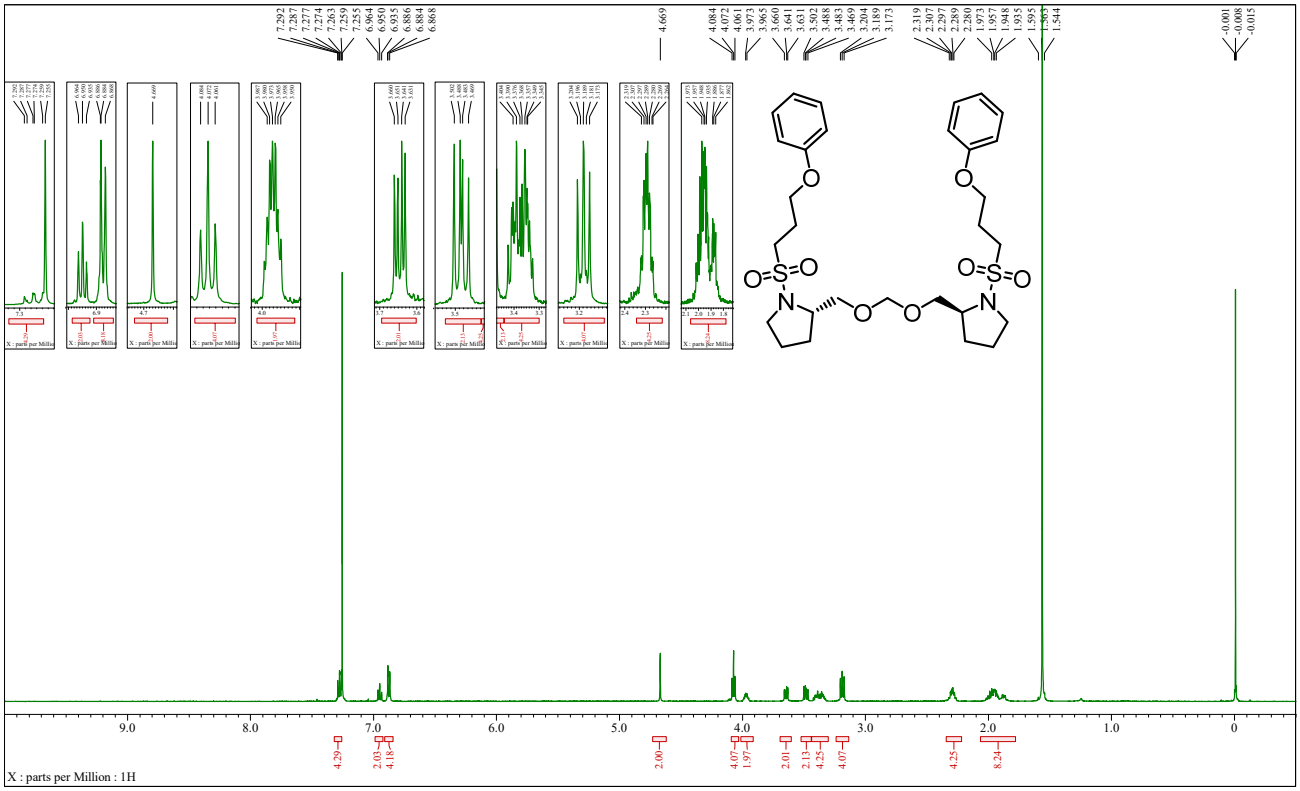
$^{1}$H NMR spectrum of compound **30** (500 MHz, $CDCl_3$)



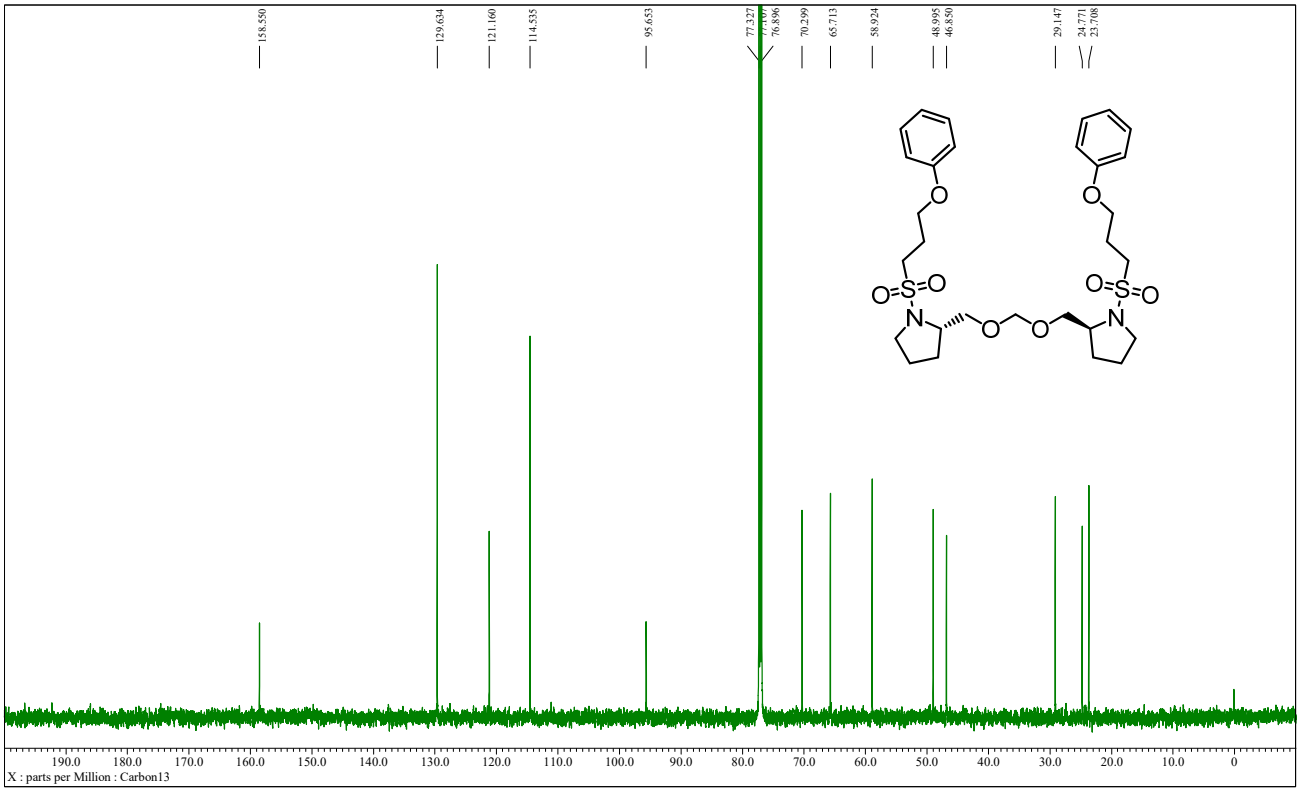

$^{13}$C NMR spectrum of compound **30** (150 MHz, $CDCl_3$)



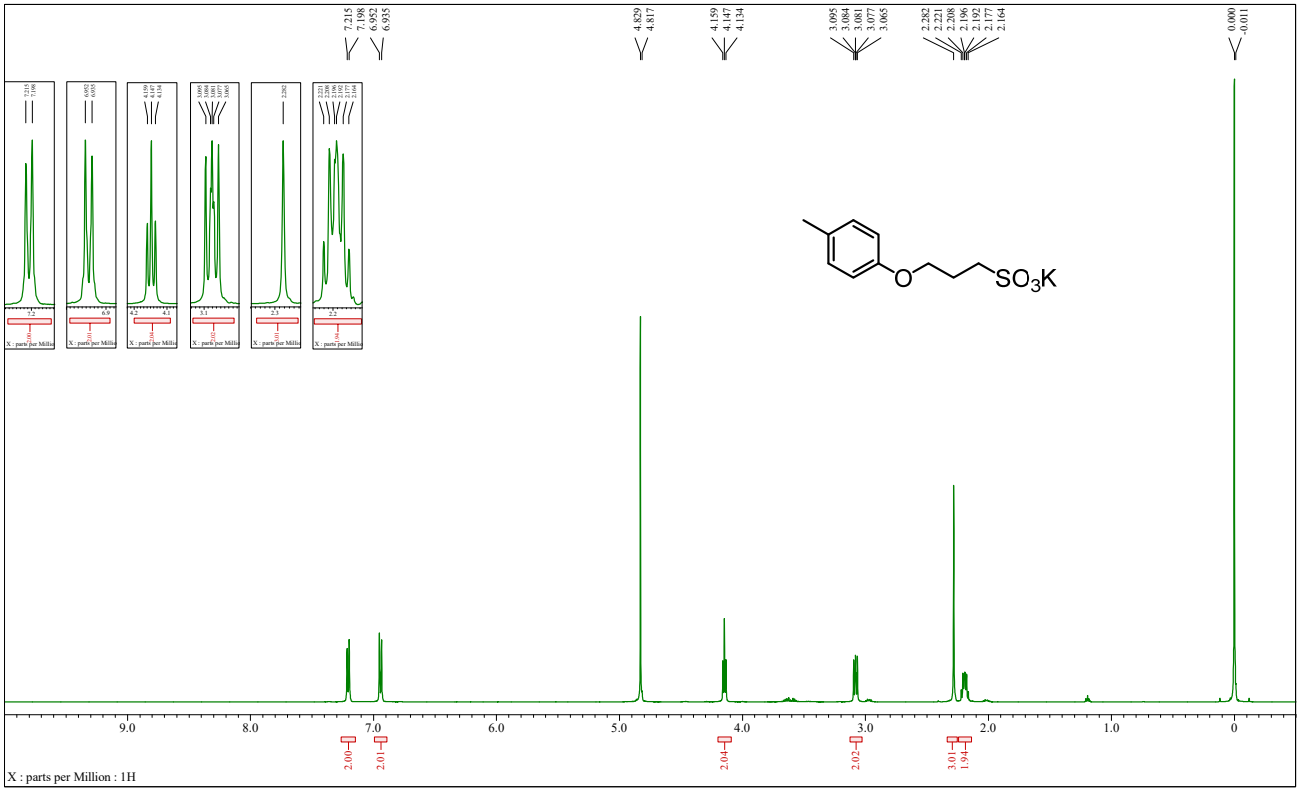
$^{1}$H NMR spectrum of compound **33** (500 MHz, $CDCl_3$)



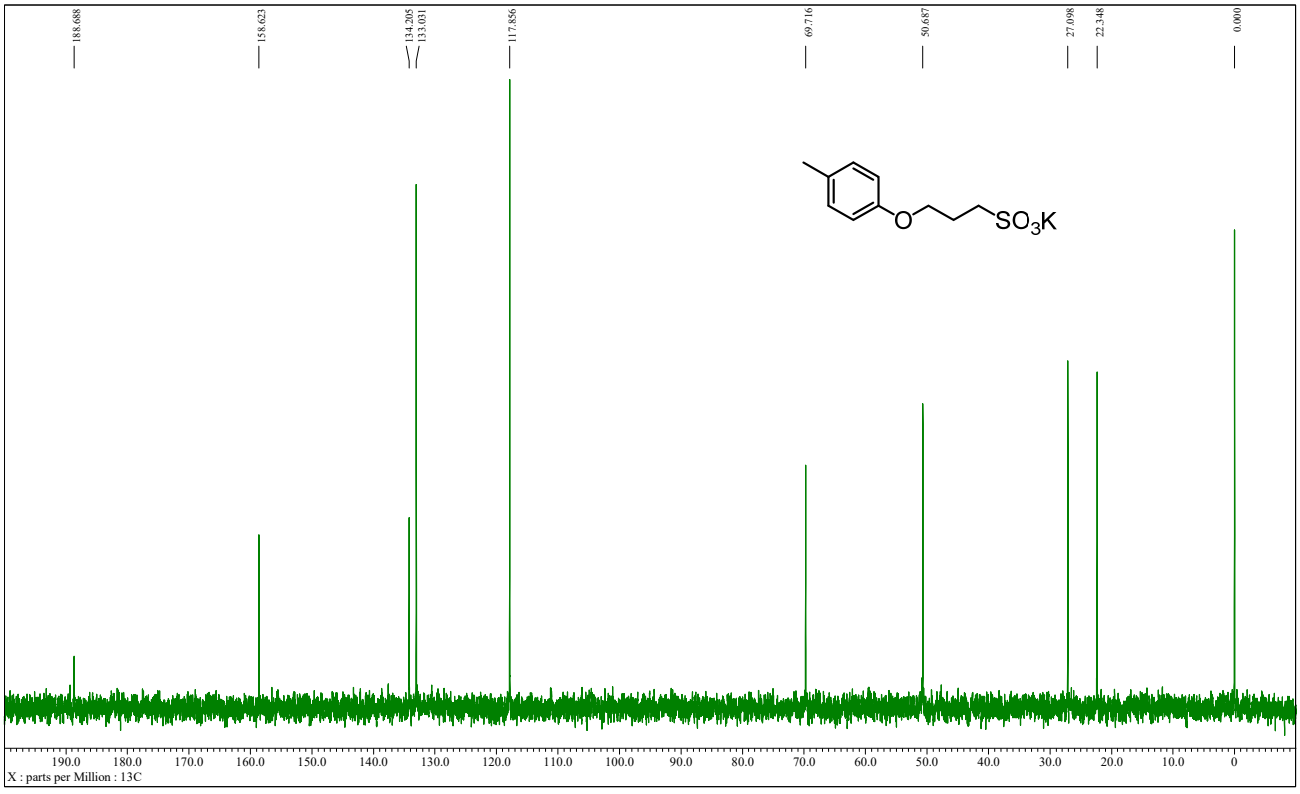

$^{13}$C NMR spectrum of compound **33** (150 MHz, $CDCl_3$)



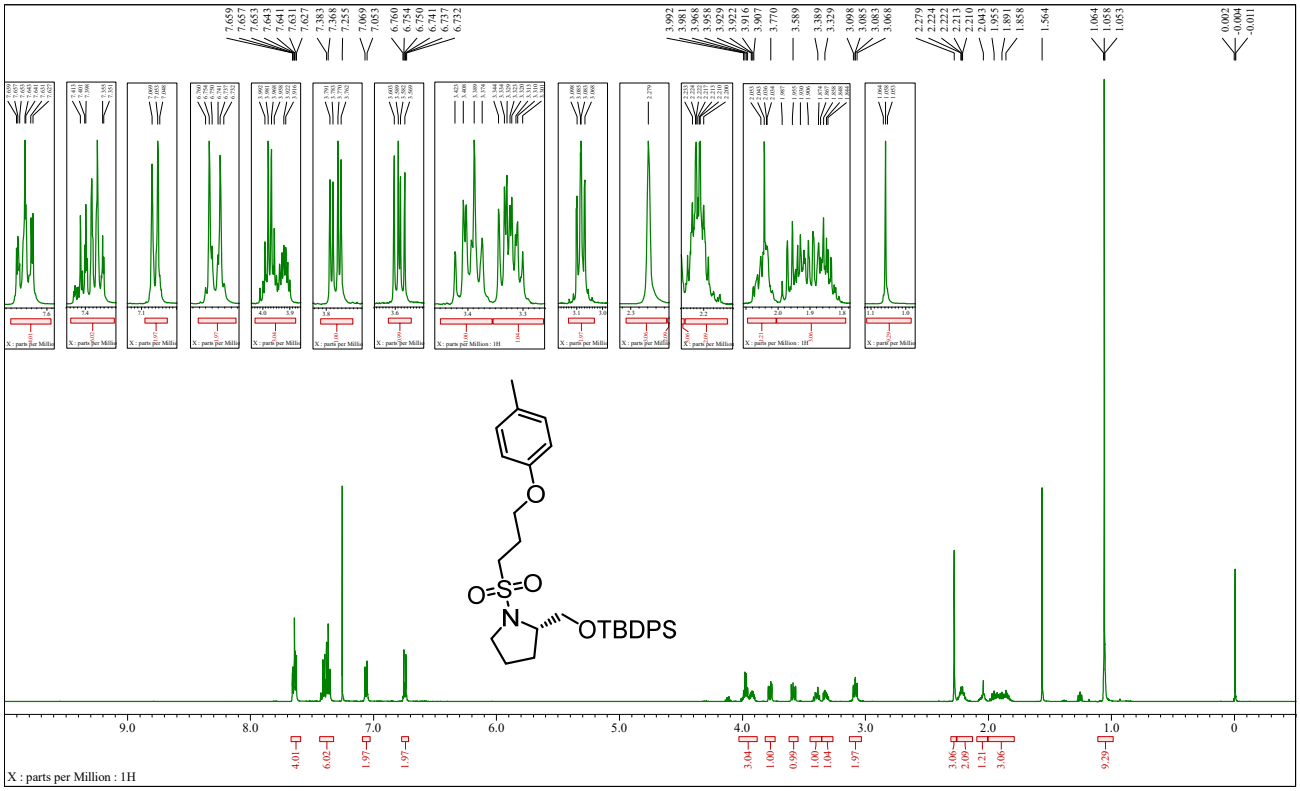
$^{1}$H NMR spectrum of compound **S49** (500 MHz, $D_2O$)



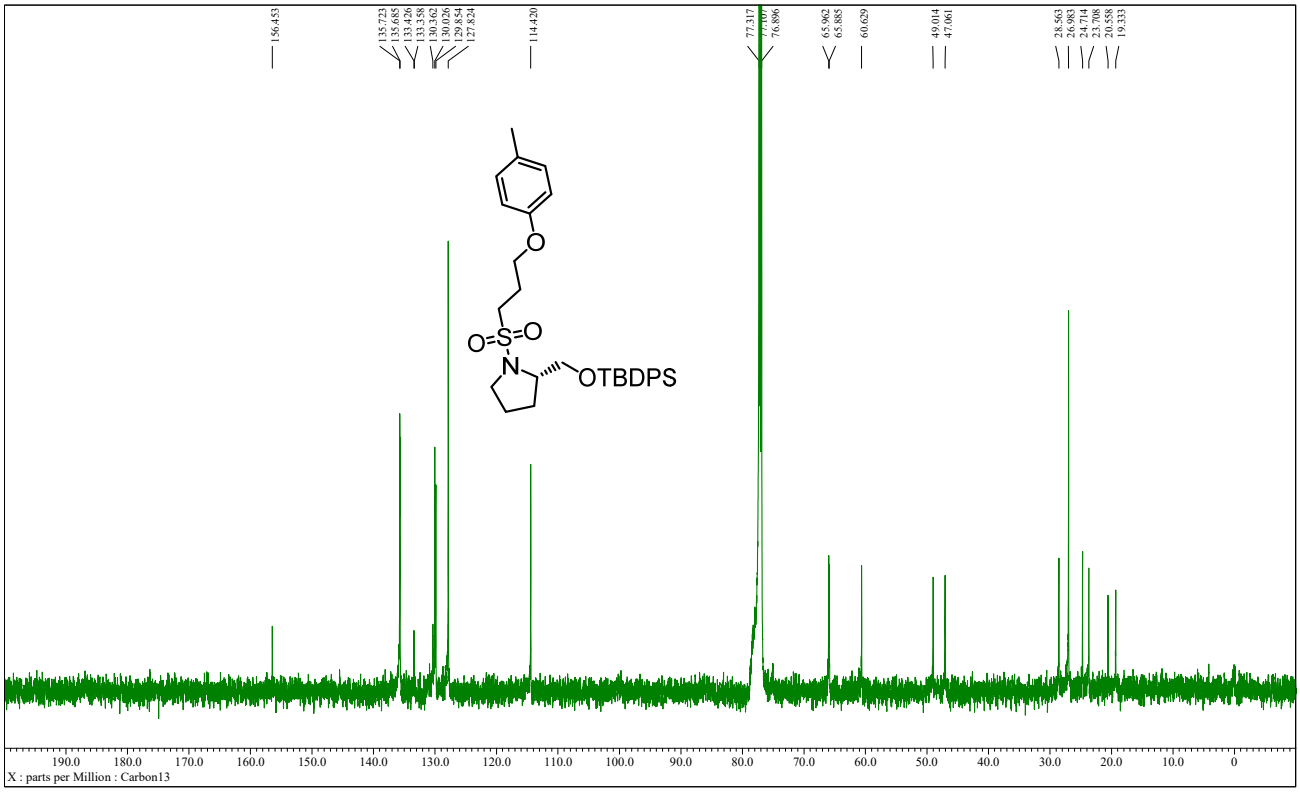

$^{13}$C NMR spectrum of compound **S49** (125 MHz, $D_2O$)



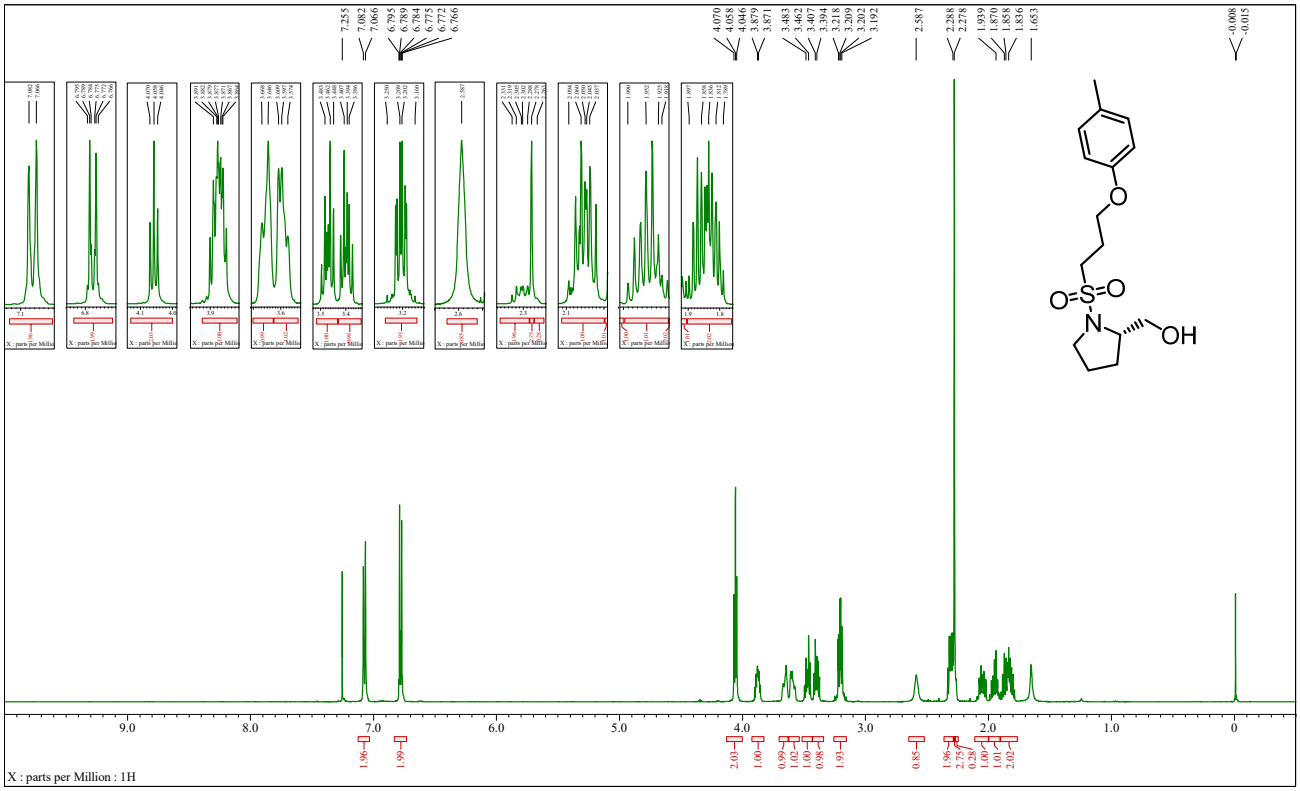
$^{1}$H NMR spectrum of compound **S51** (500 MHz, $CDCl_3$)



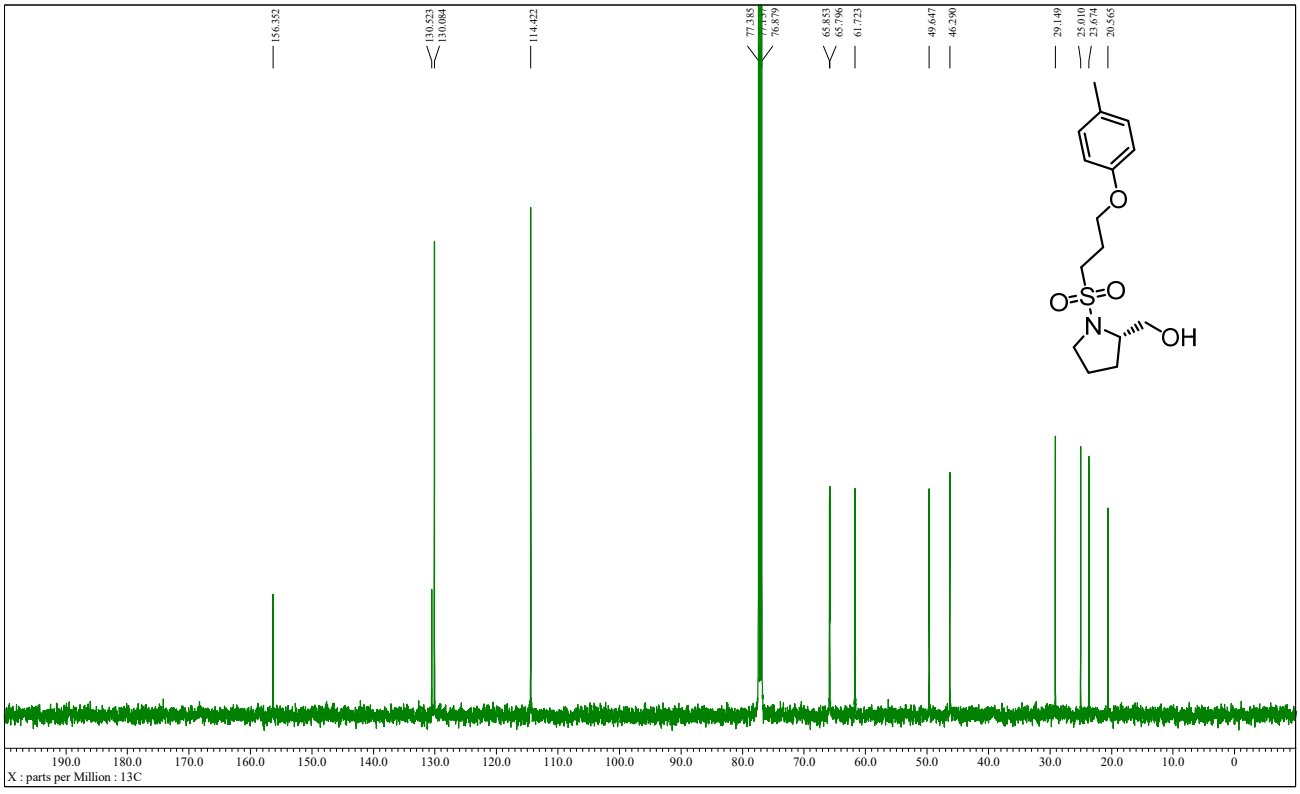

$^{13}$C NMR spectrum of compound **S51** (150 MHz, $CDCl_3$)



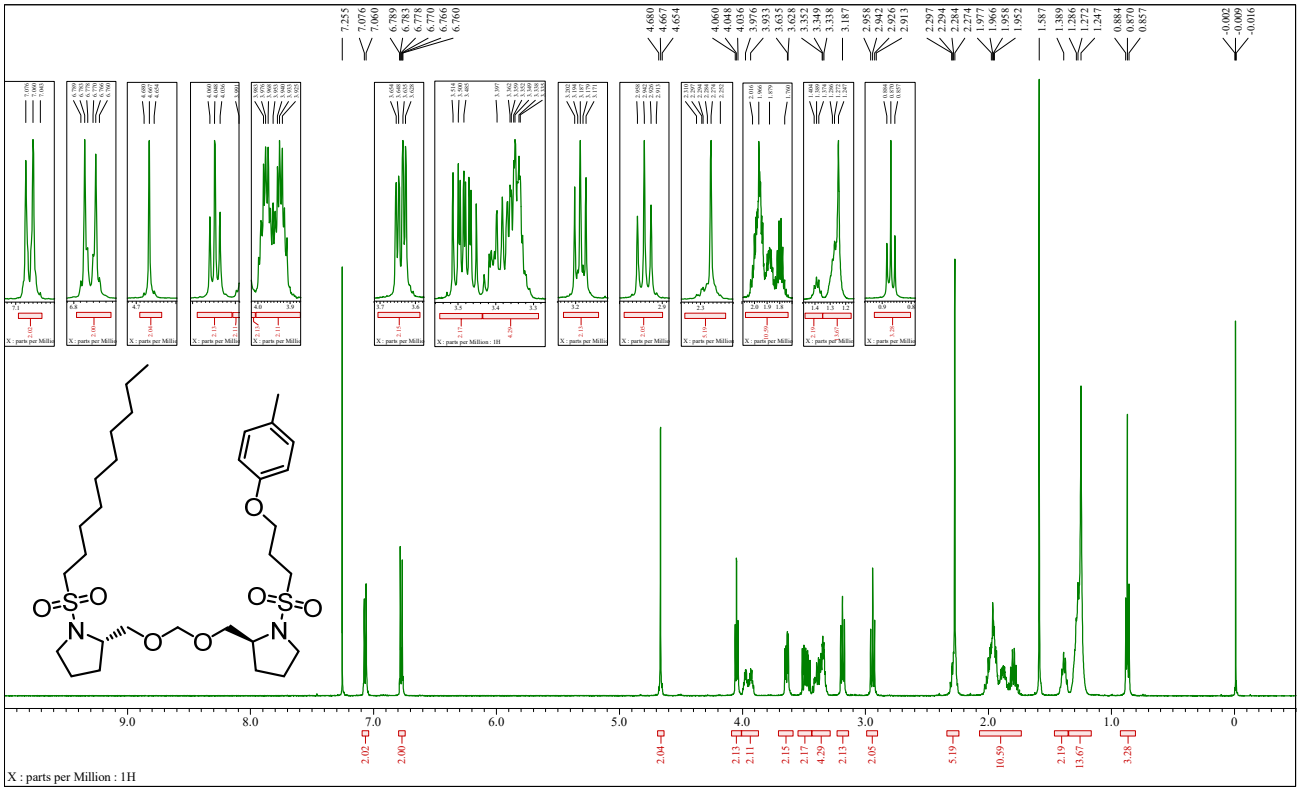
$^{1}$H NMR spectrum of compound **S52** (500 MHz, $CDCl_3$)



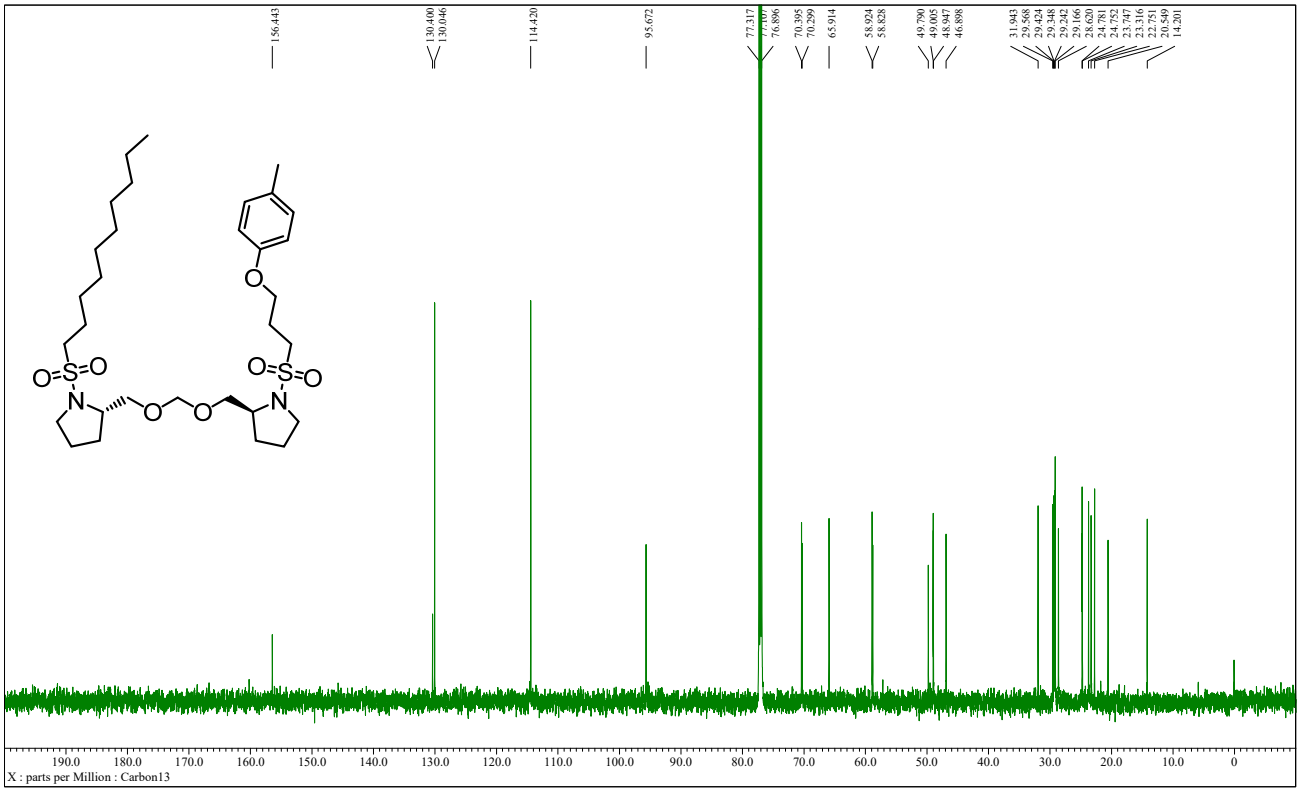

$^{13}$C NMR spectrum of compound **S52** (125 MHz, $CDCl_3$)



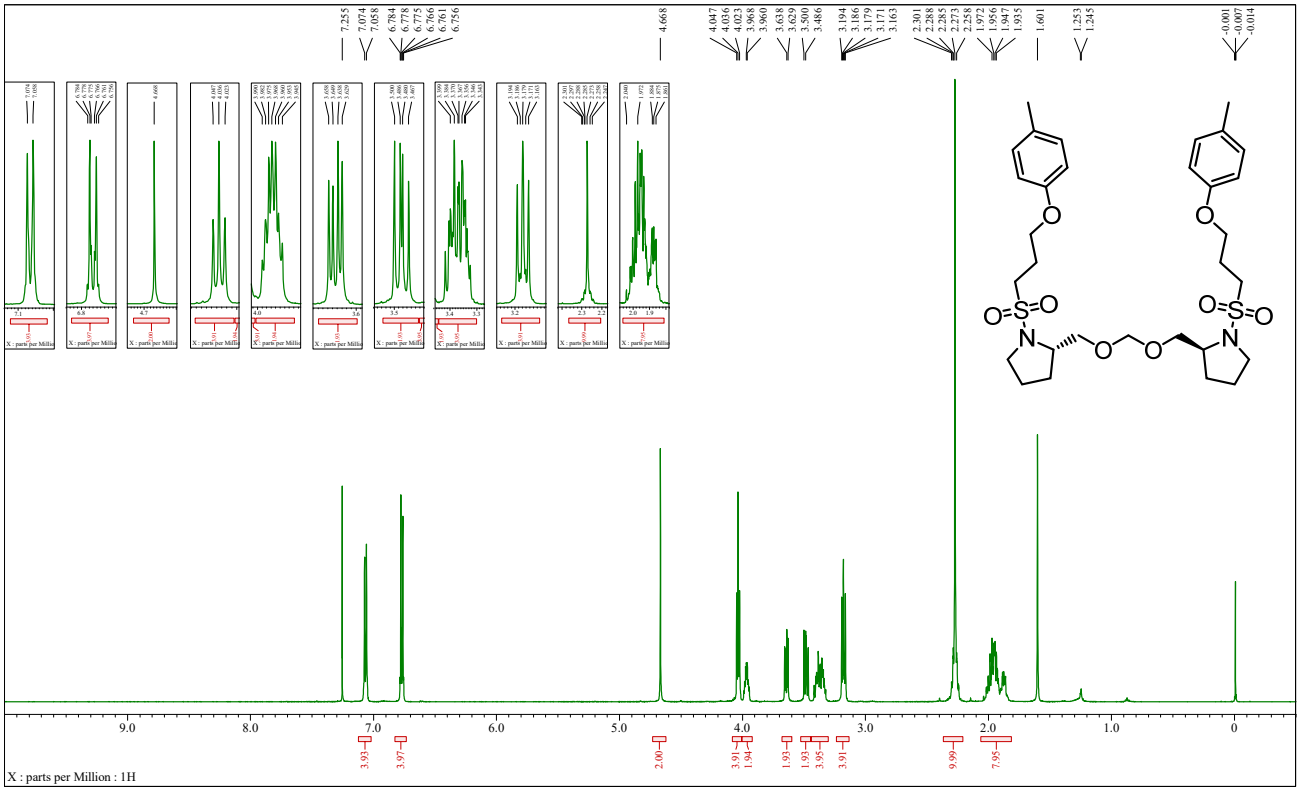
$^{1}$H NMR spectrum of compound **31** (500 MHz, $CDCl_3$)



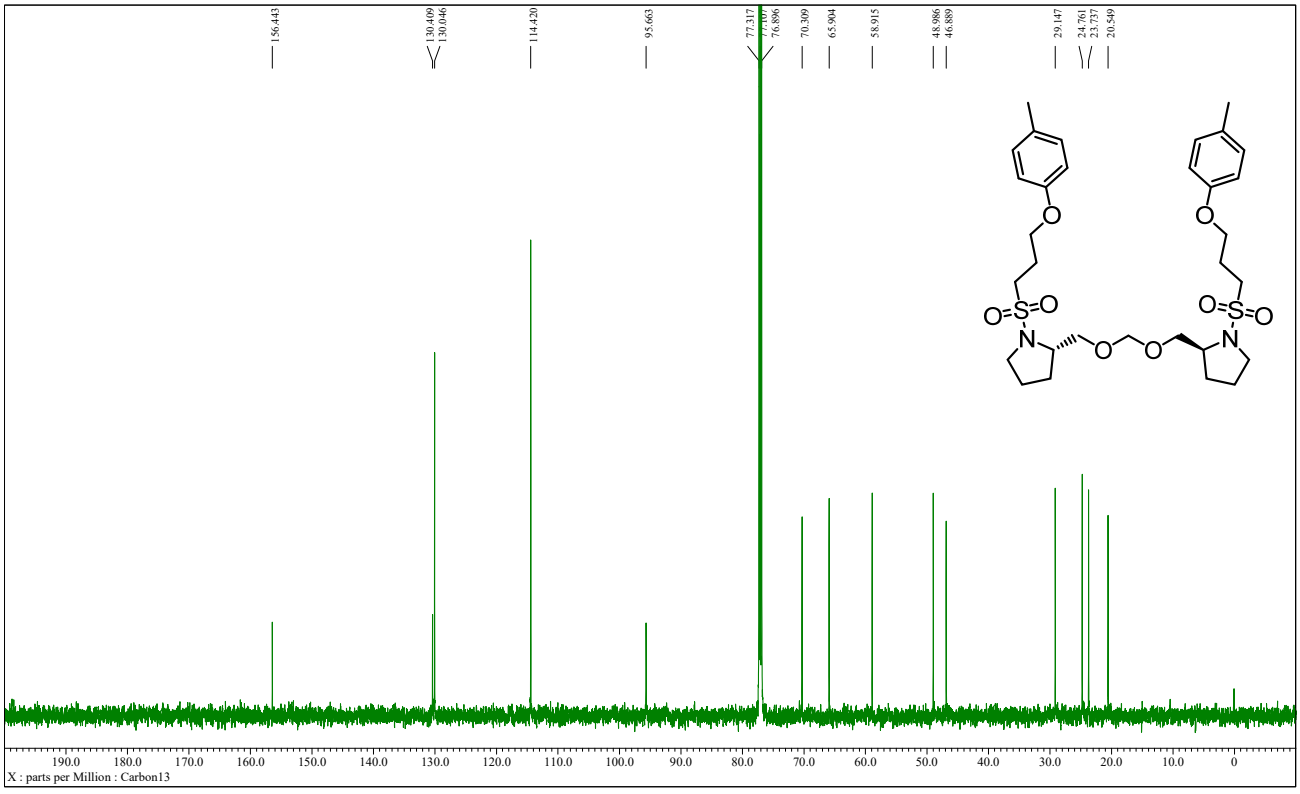

$^{13}$C NMR spectrum of compound **31** (150 MHz, $CDCl_3$)



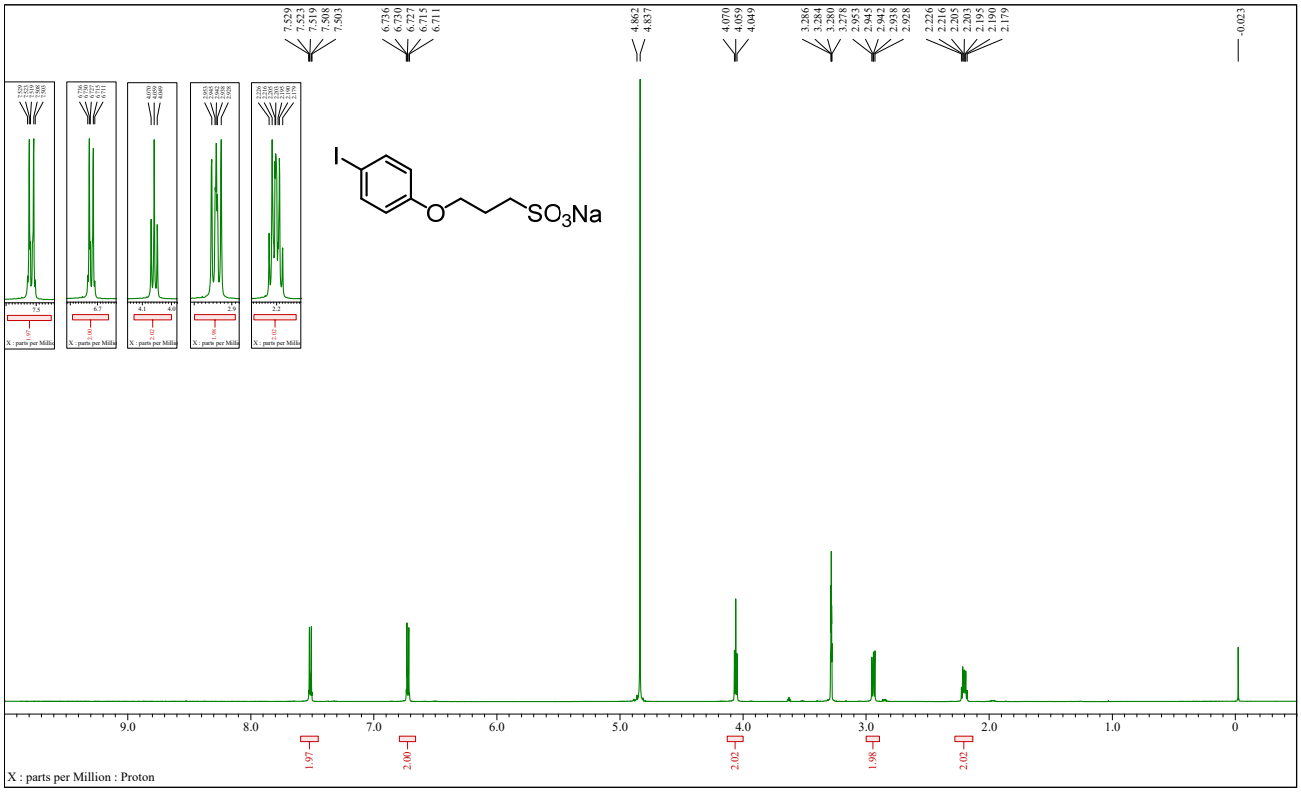
$^{1}$H NMR spectrum of compound **34** (500 MHz, $CDCl_3$)



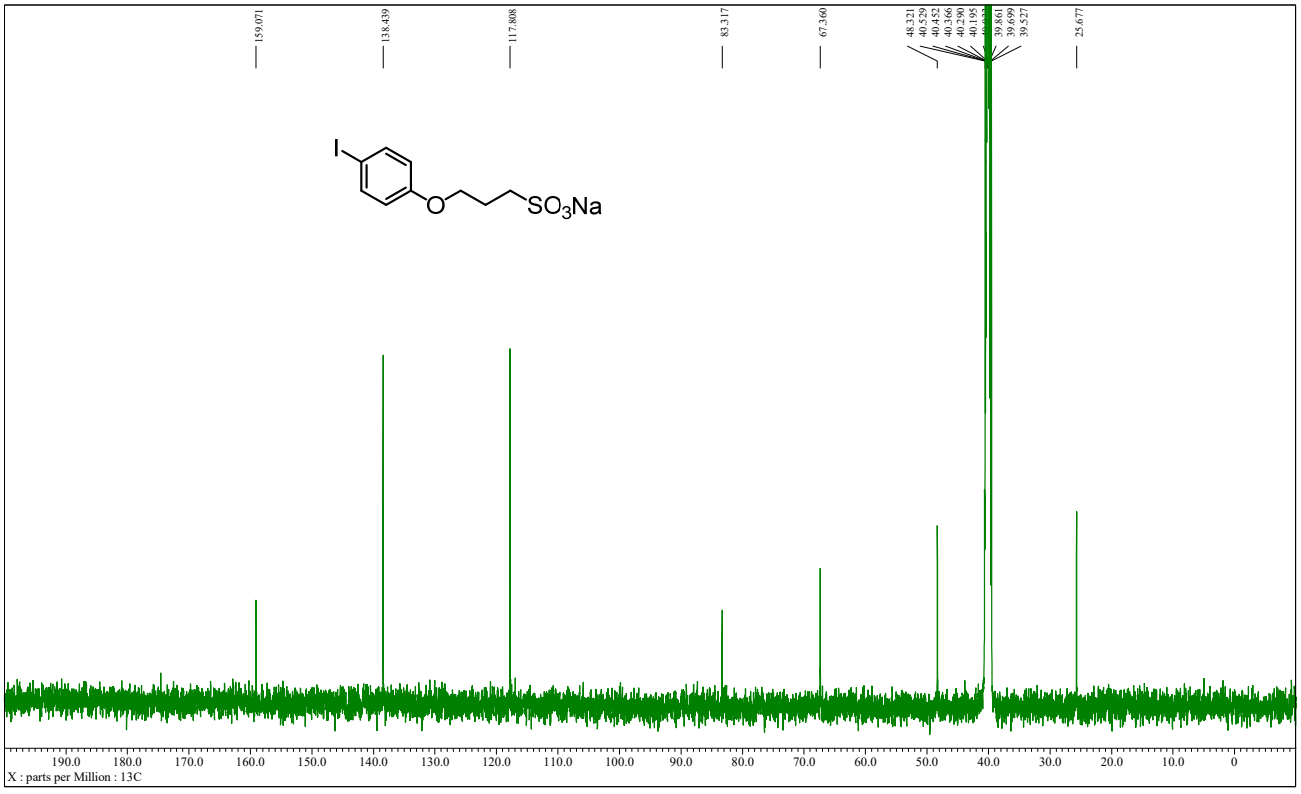

$^{13}$C NMR spectrum of compound **34** (150 MHz, $CDCl_3$)



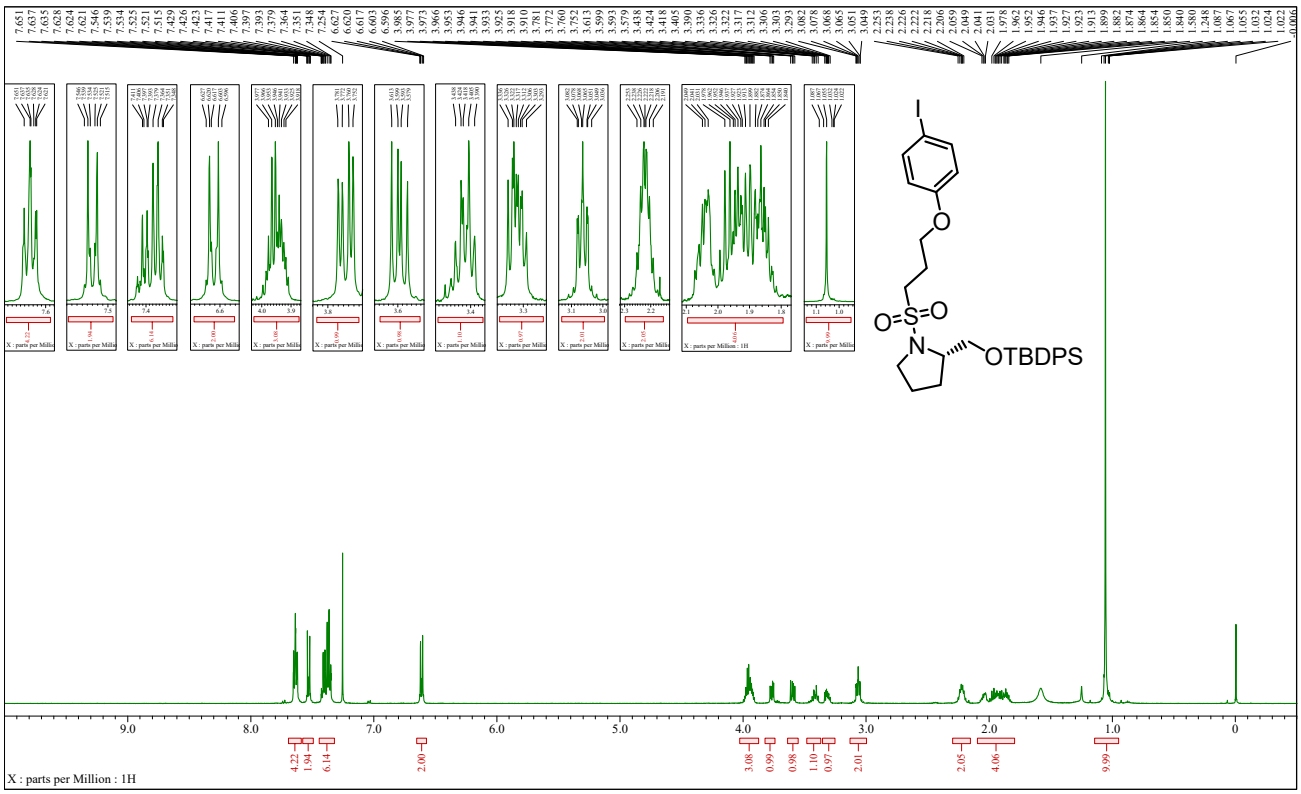
$^{1}$H NMR spectrum of compound **S53** (600 MHz, $CD_3OD$)



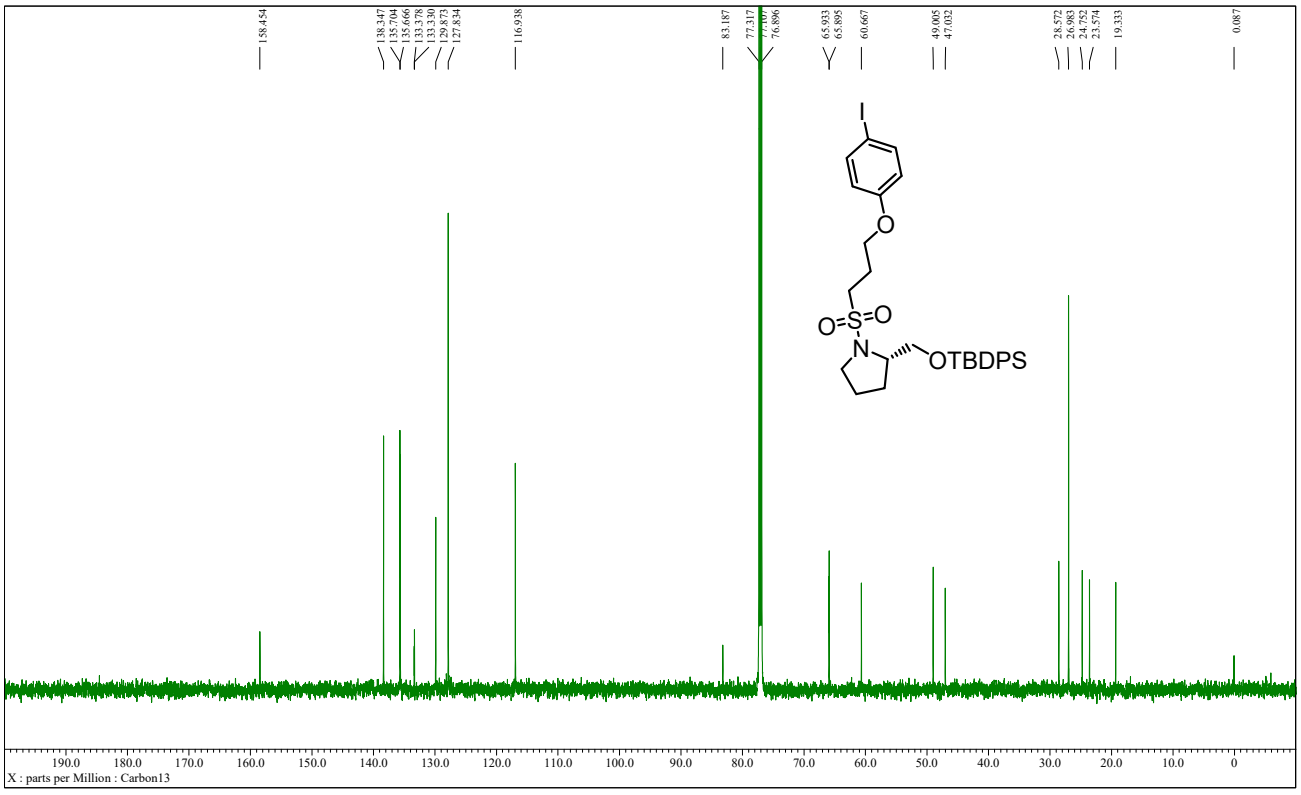

$^{13}$C NMR spectrum of compound **S53** (125 MHz, DMSO-$d_6$)



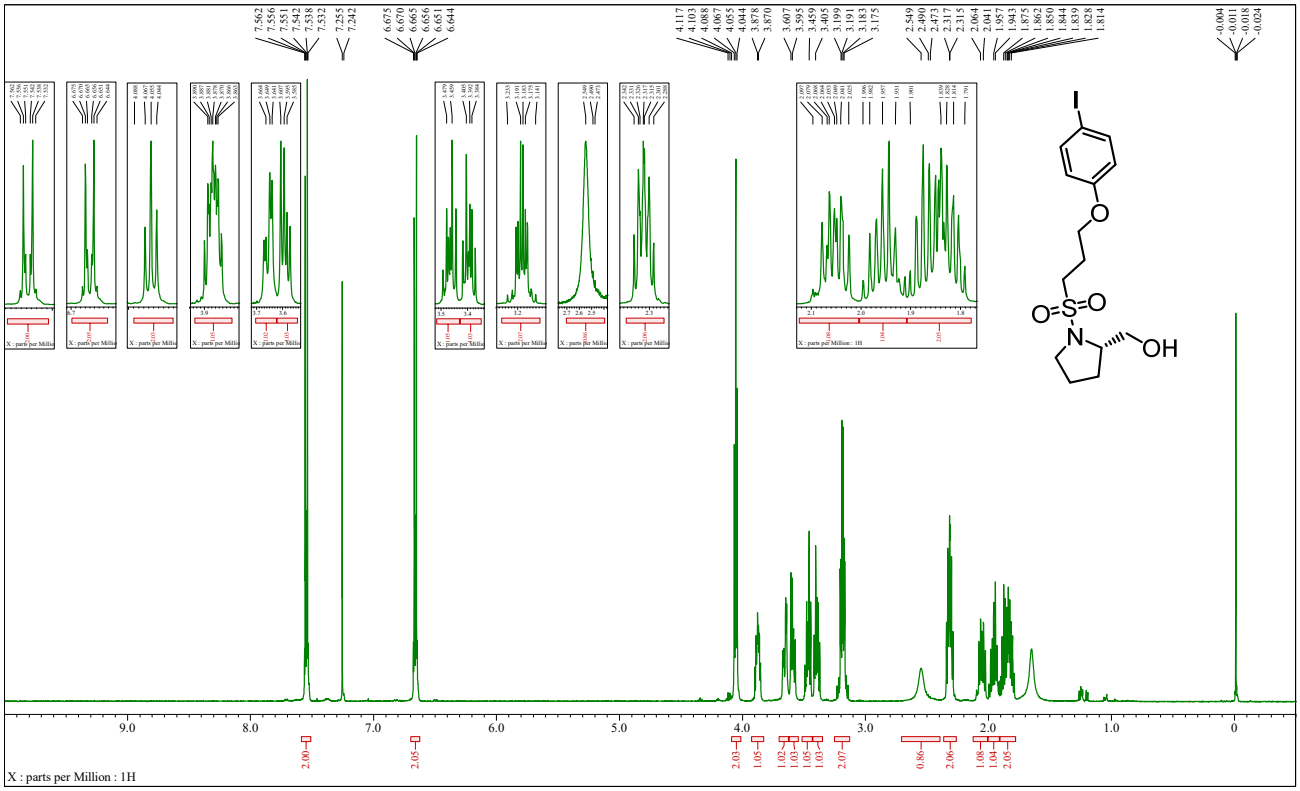
$^{1}$H NMR spectrum of compound **S54** (500 MHz, $CDCl_3$)



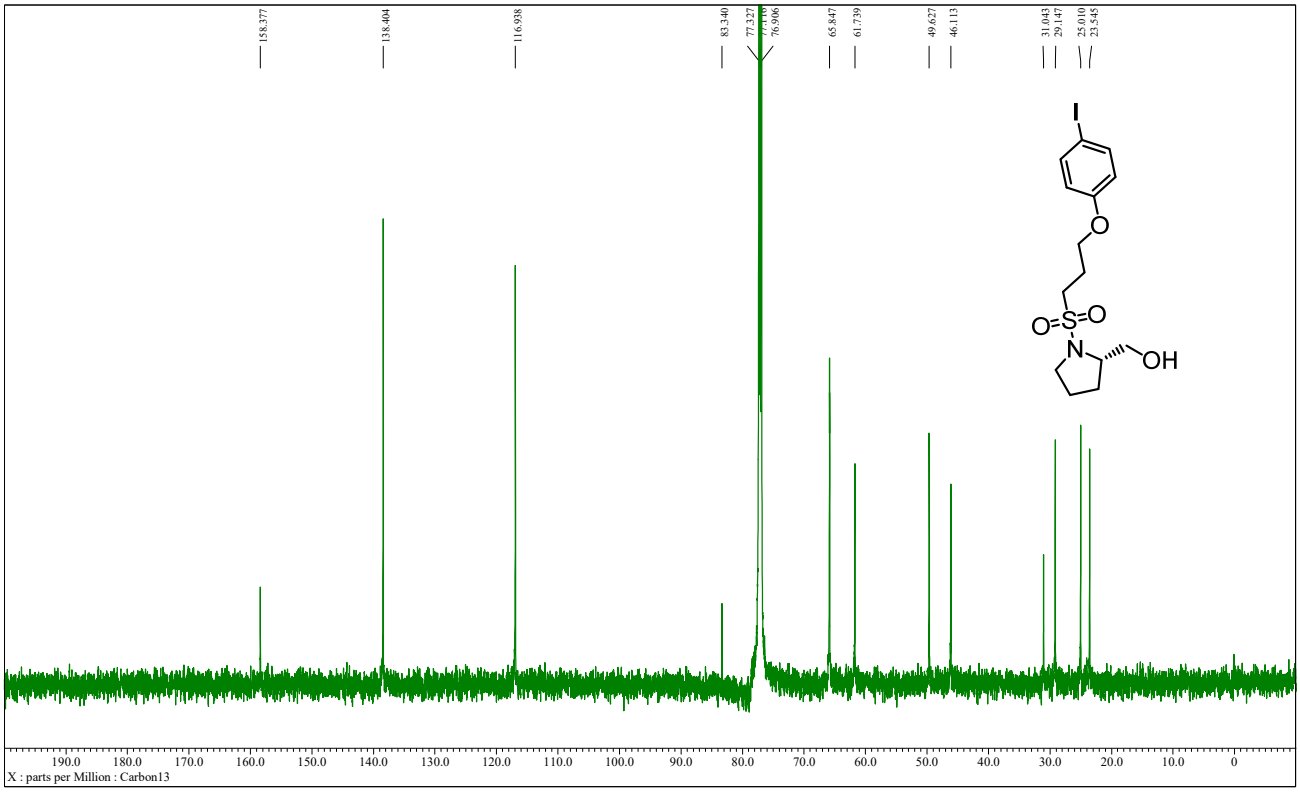

$^{13}$C NMR spectrum of compound **S54** (150 MHz, $CDCl_3$)



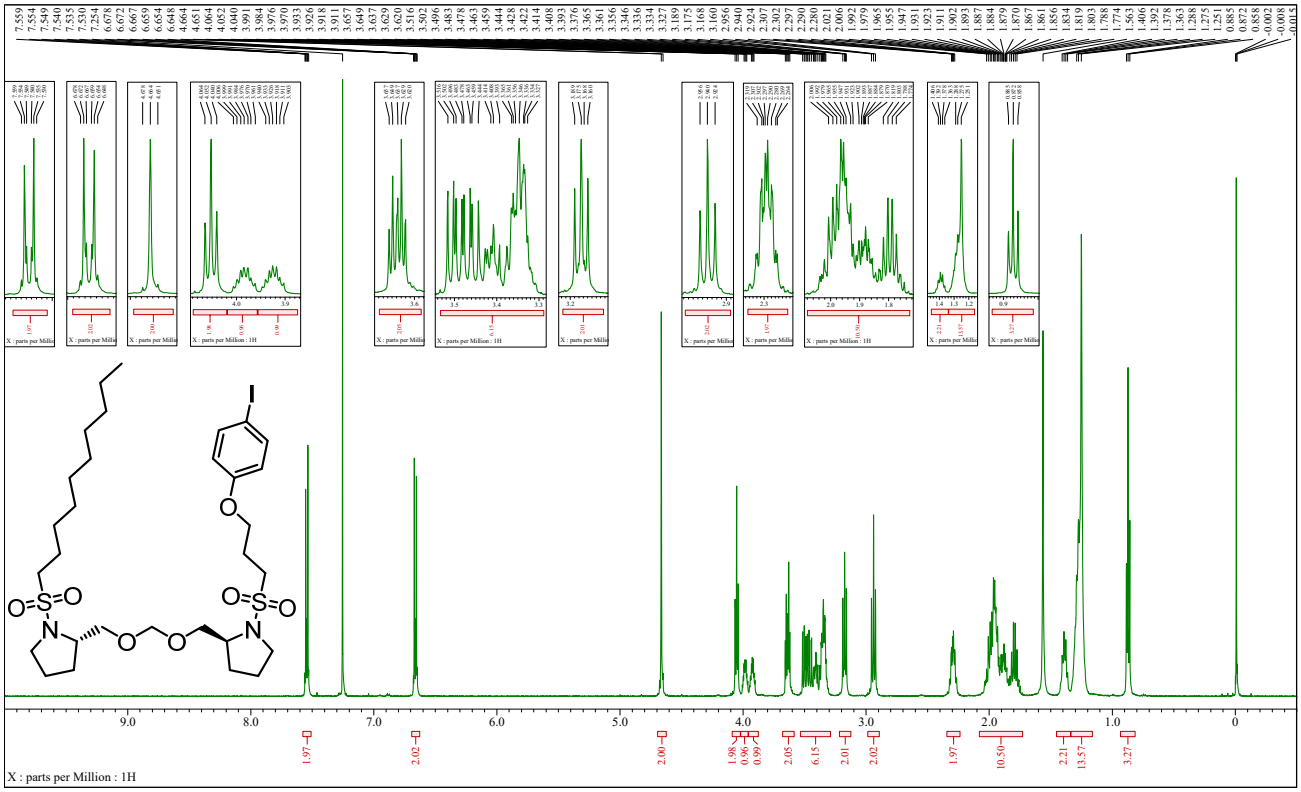
$^{1}$H NMR spectrum of compound **42** (500 MHz, $CDCl_3$)



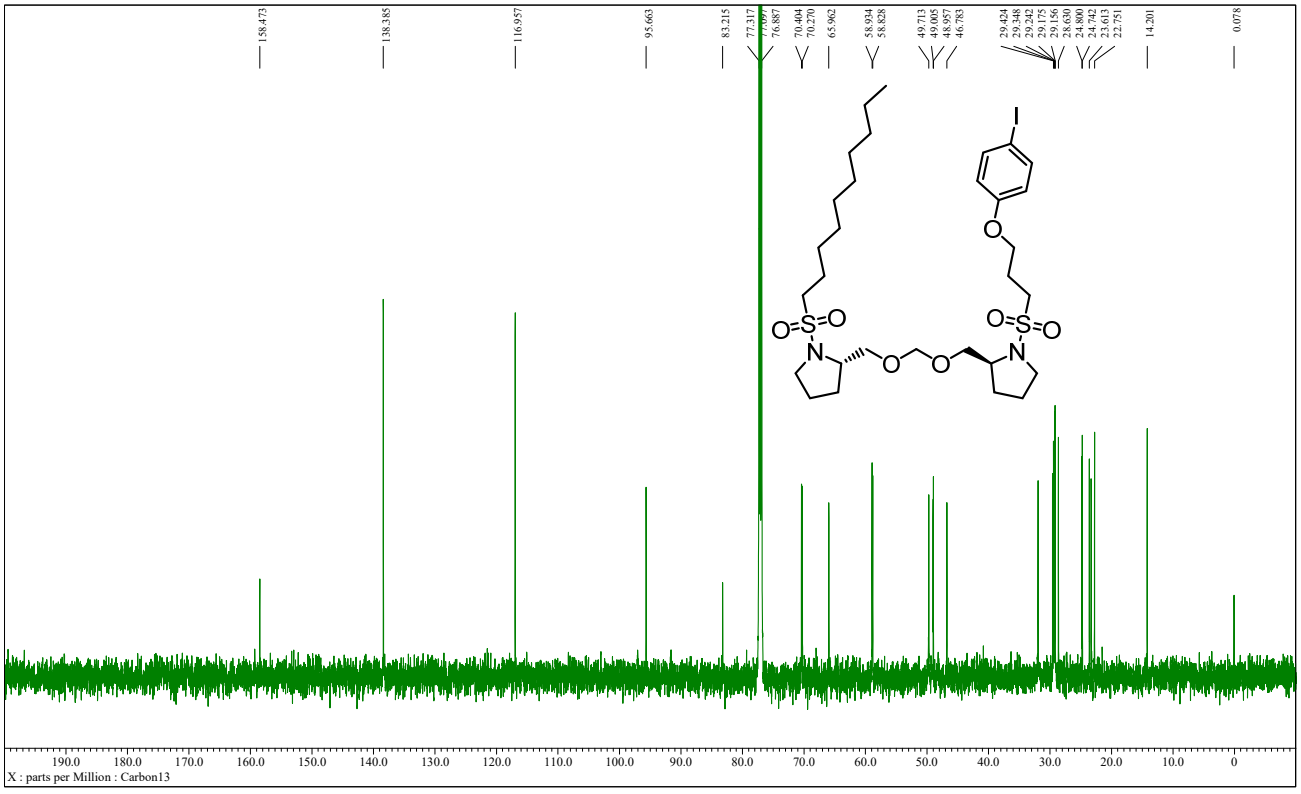

$^{13}$C NMR spectrum of compound **42** (150 MHz, $CDCl_3$)



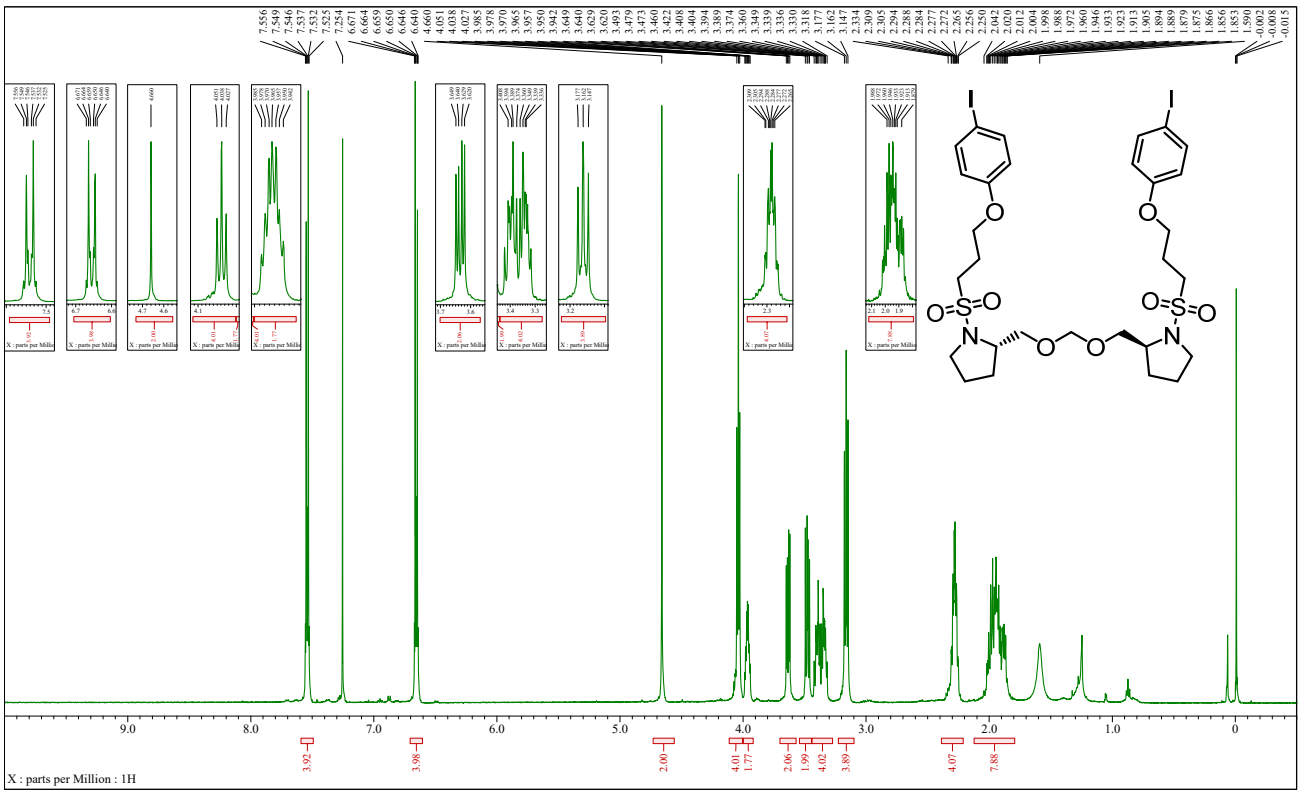
$^{1}$H NMR spectrum of compound **32** (500 MHz, $CDCl_3$)



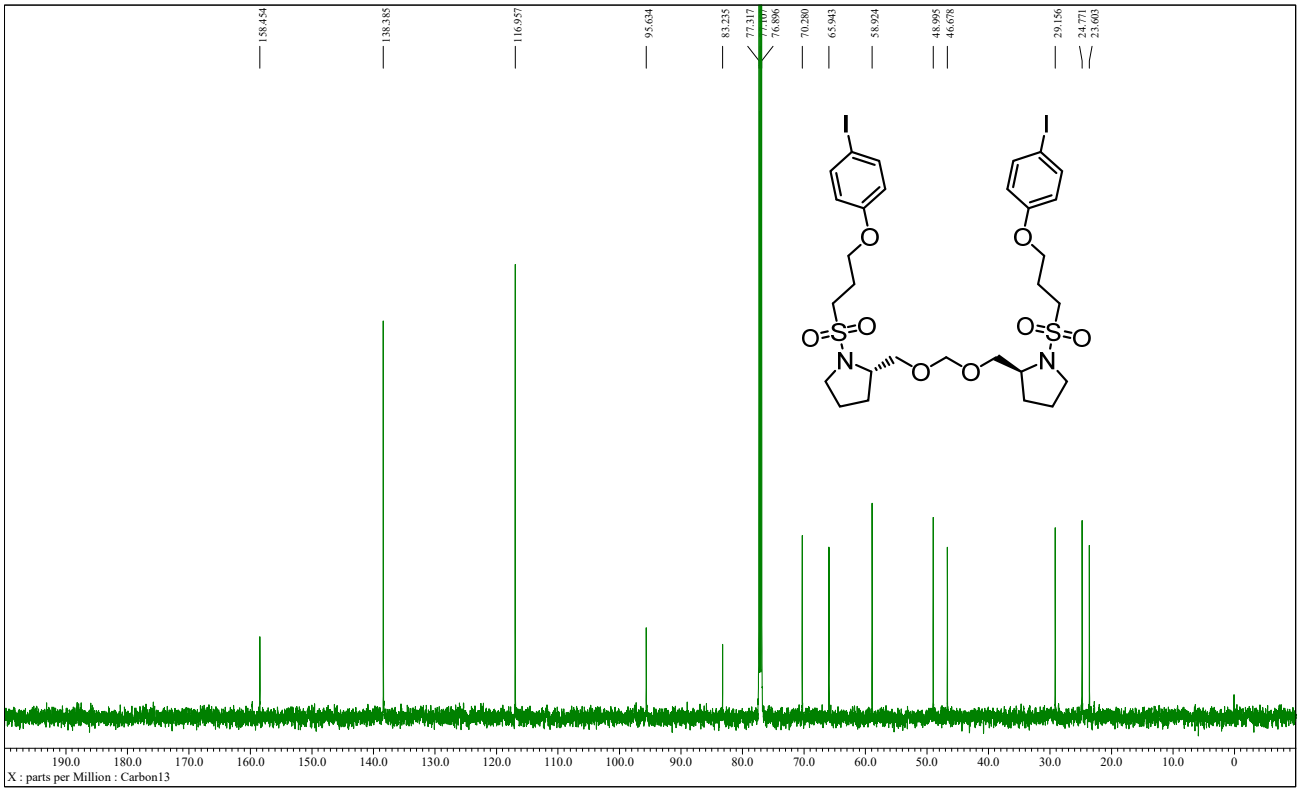
$^{13}$C NMR spectrum of compound **32** (150 MHz, $CDCl_3$)



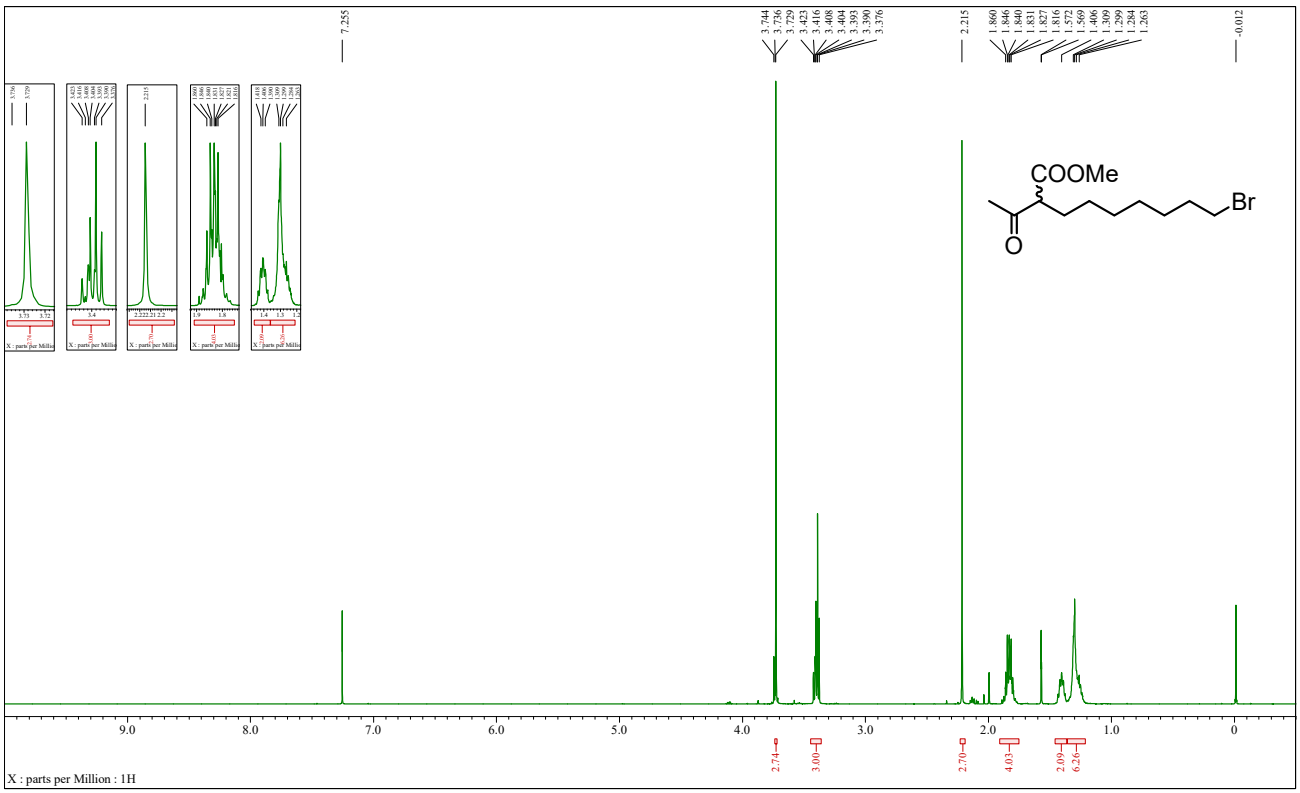
$^{1}$H NMR spectrum of compound **35** (500 MHz, $CDCl_3$)



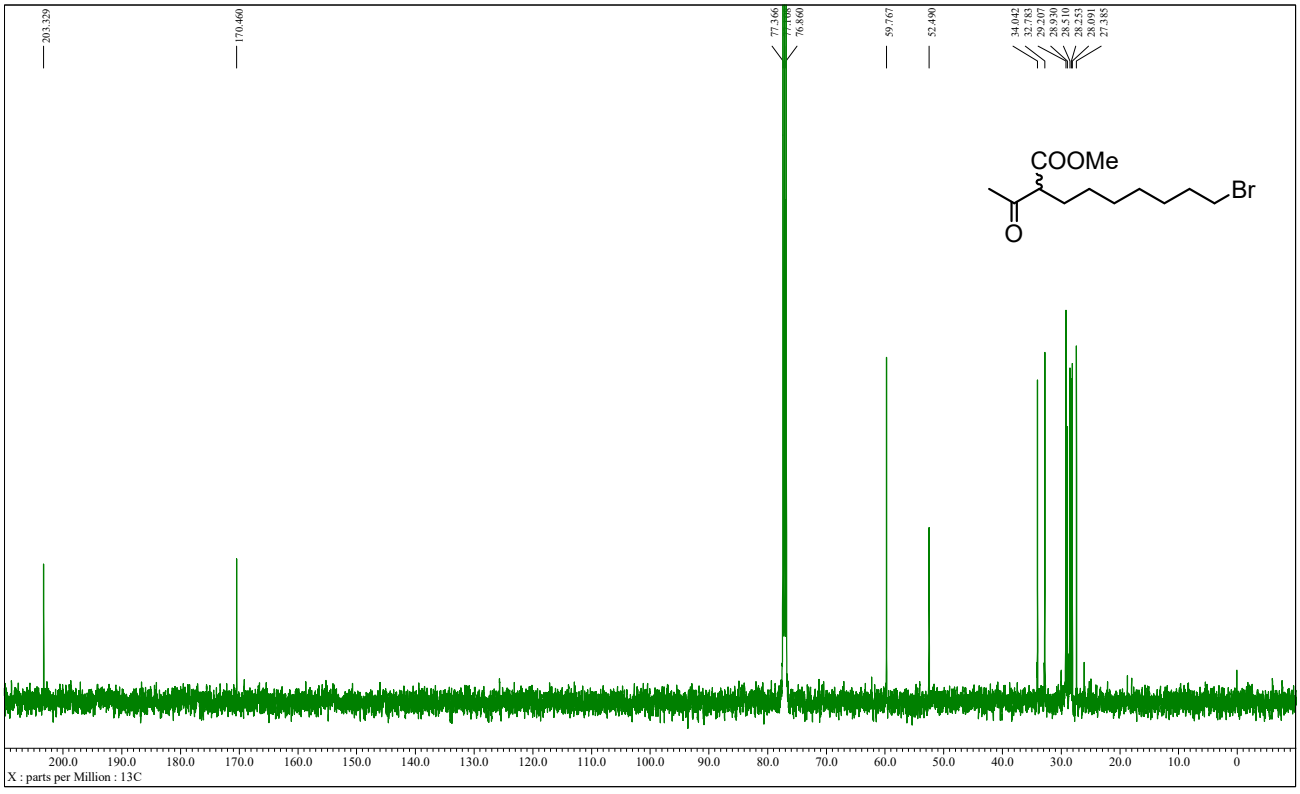
$^{13}$C NMR spectrum of compound **35** (150 MHz, $CDCl_3$)



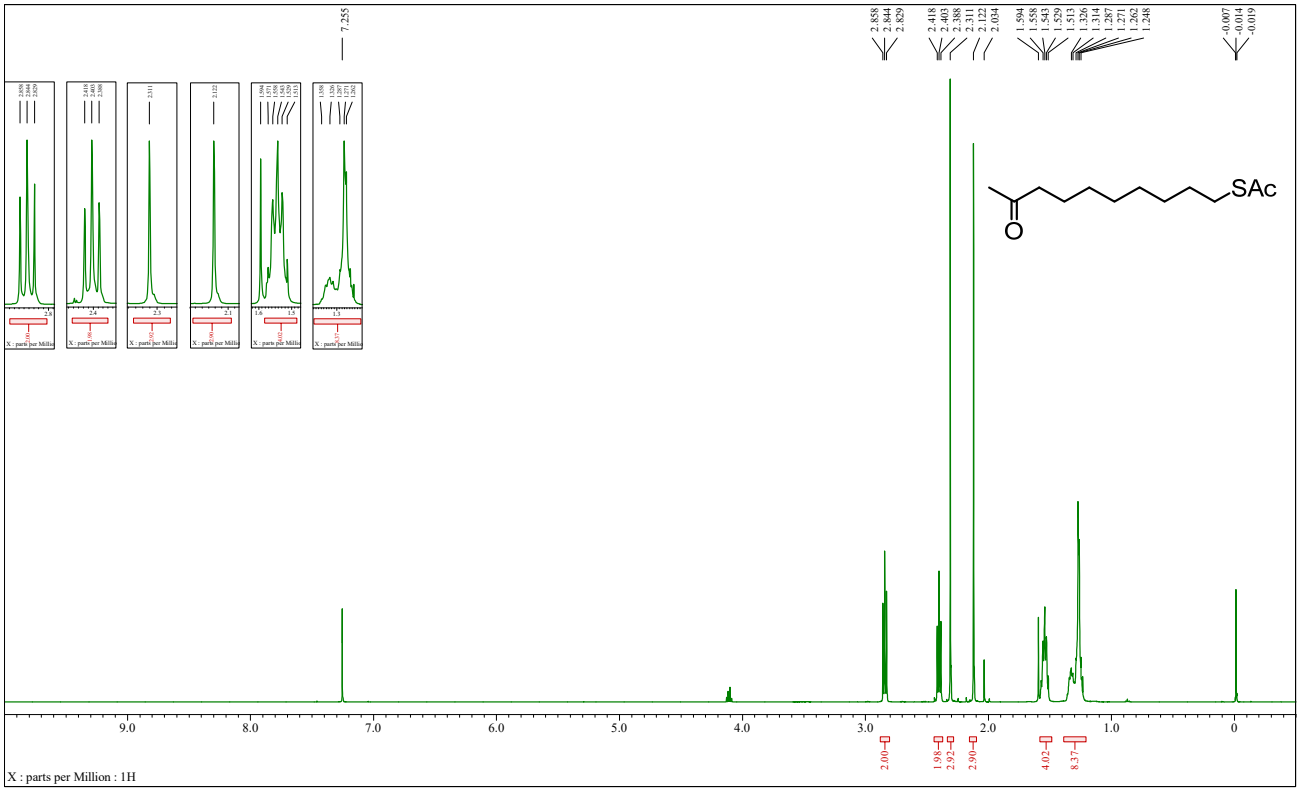
$^{1}$H NMR spectrum of compound **S55** (500 MHz, $CDCl_3$)



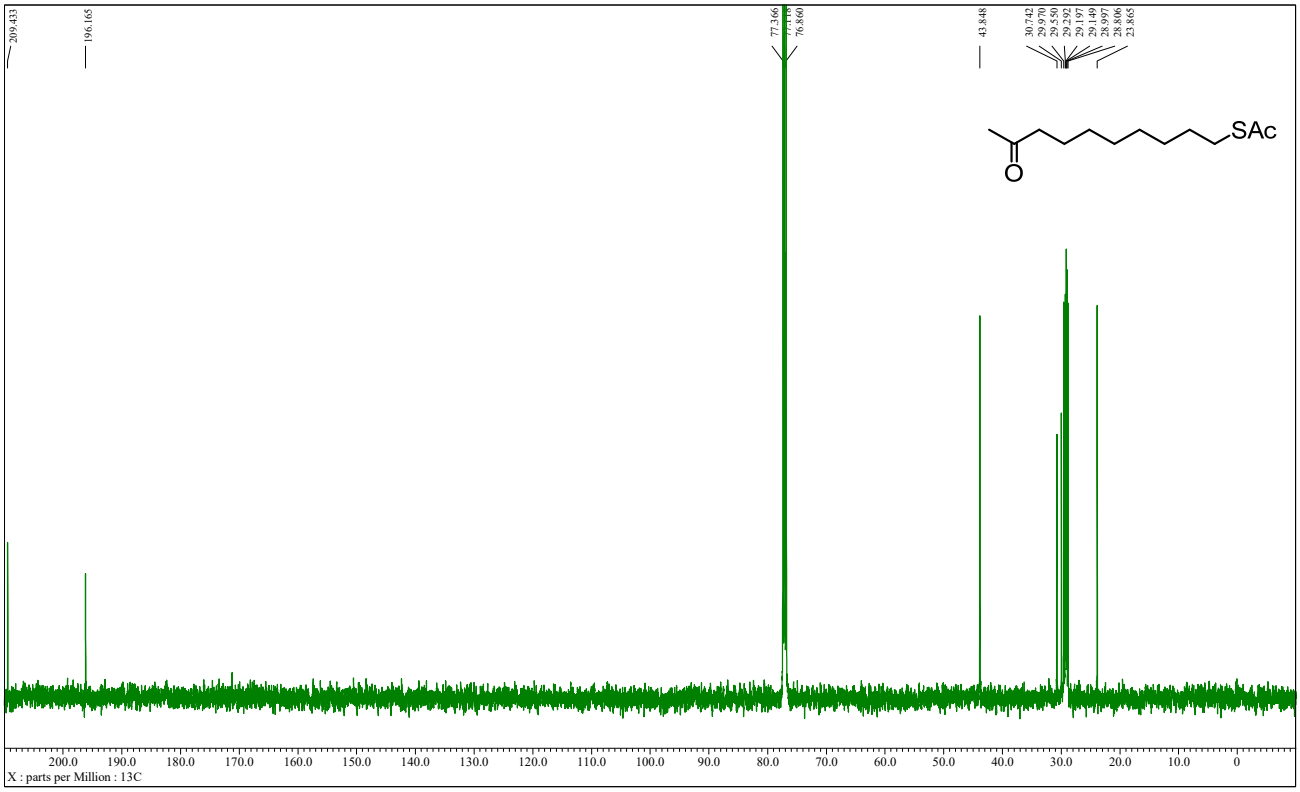

$^{13}$C NMR spectrum of compound **S55** (125 MHz, $CDCl_3$)



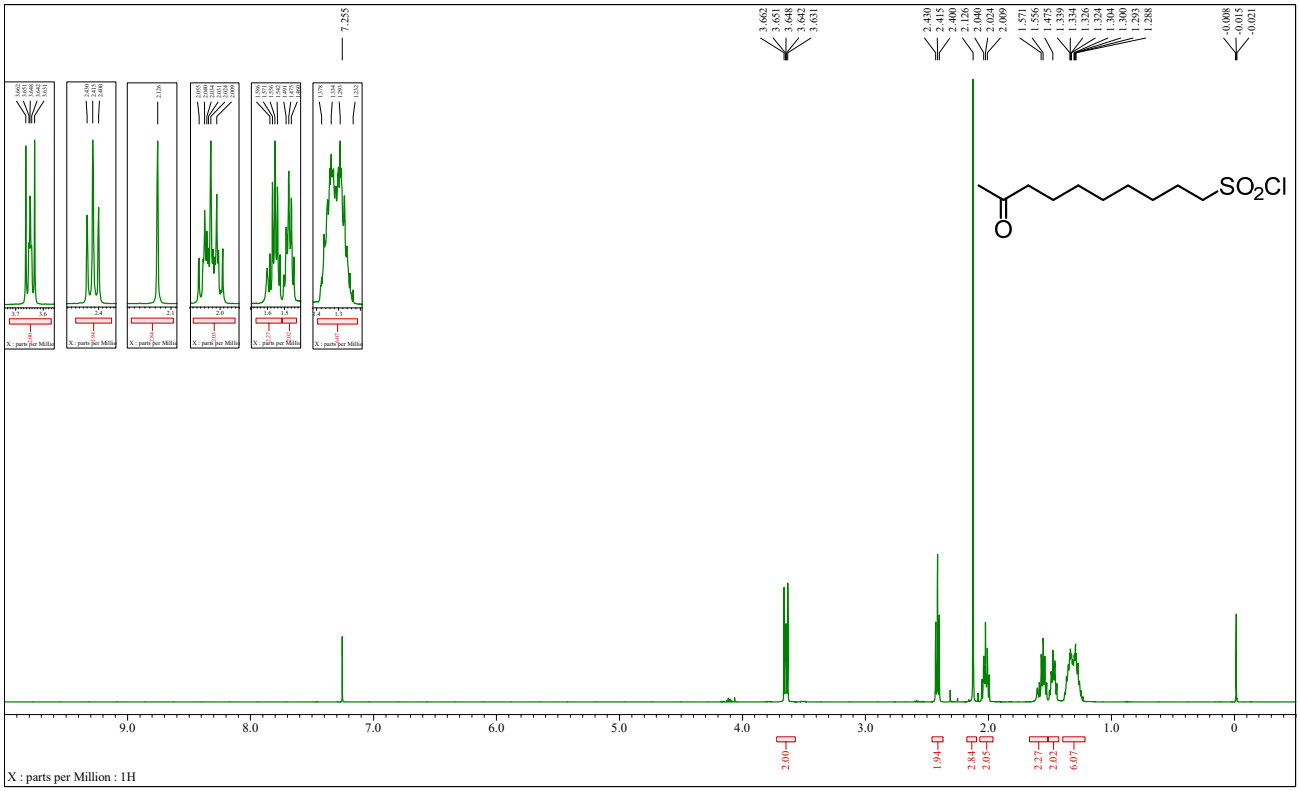
$^{1}$H NMR spectrum of compound **S57** (500 MHz, $CDCl_3$)



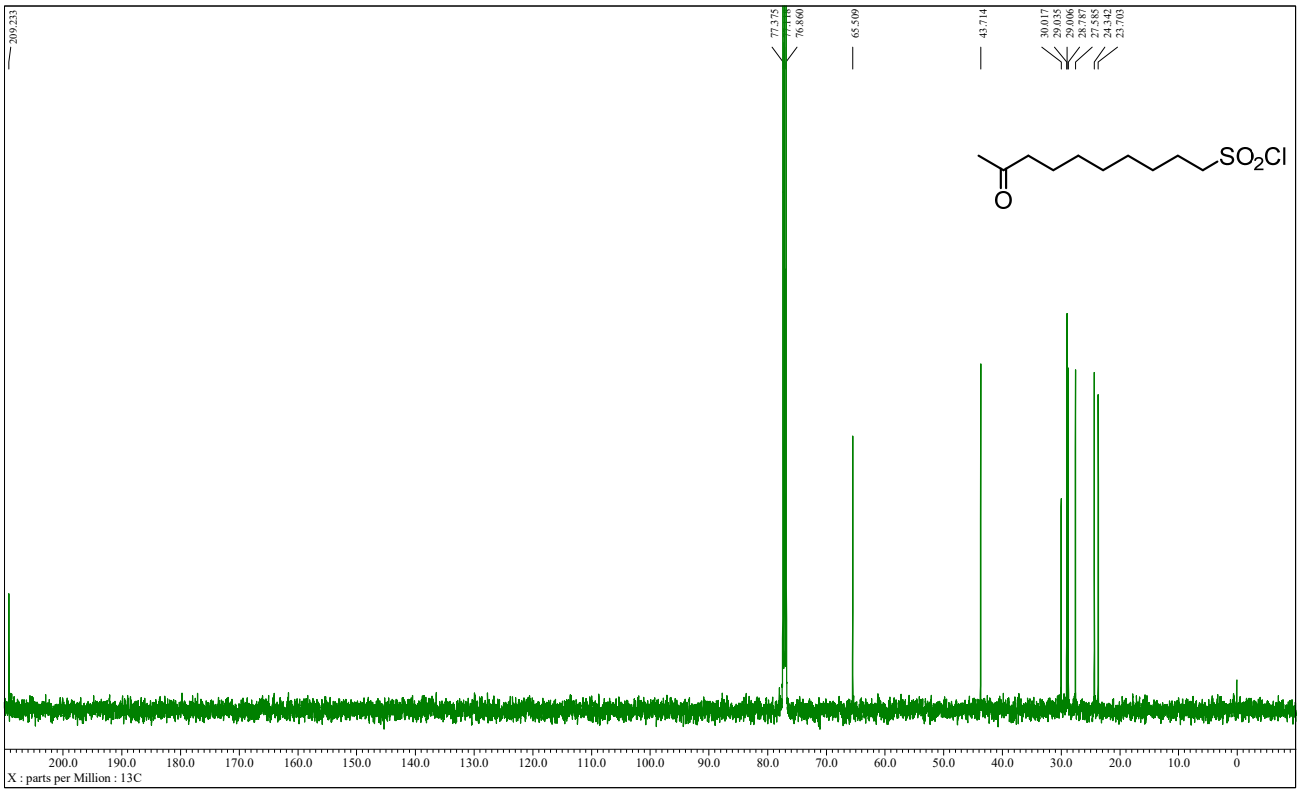

$^{13}$C NMR spectrum of compound **S57** (125 MHz, $CDCl_3$)



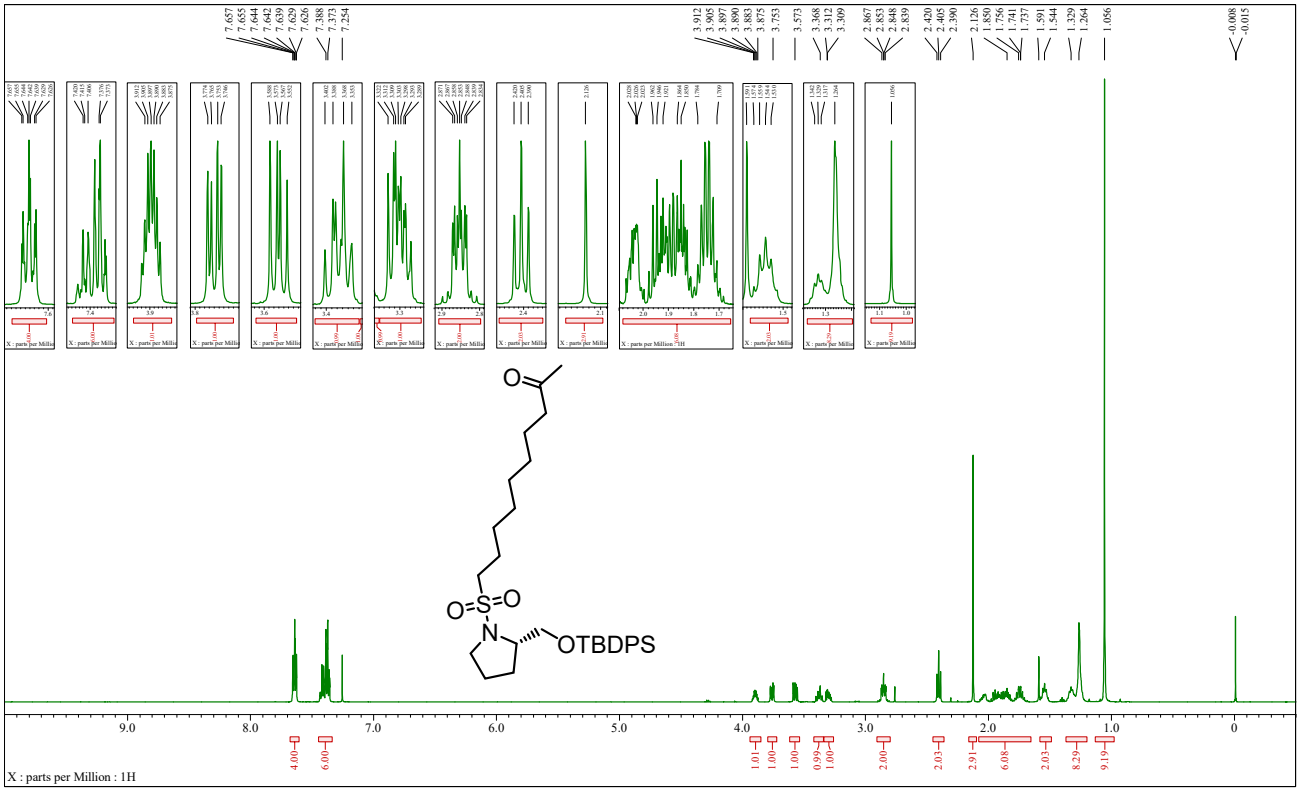
$^{1}$H NMR spectrum of compound **37** (500 MHz, $CDCl_3$)



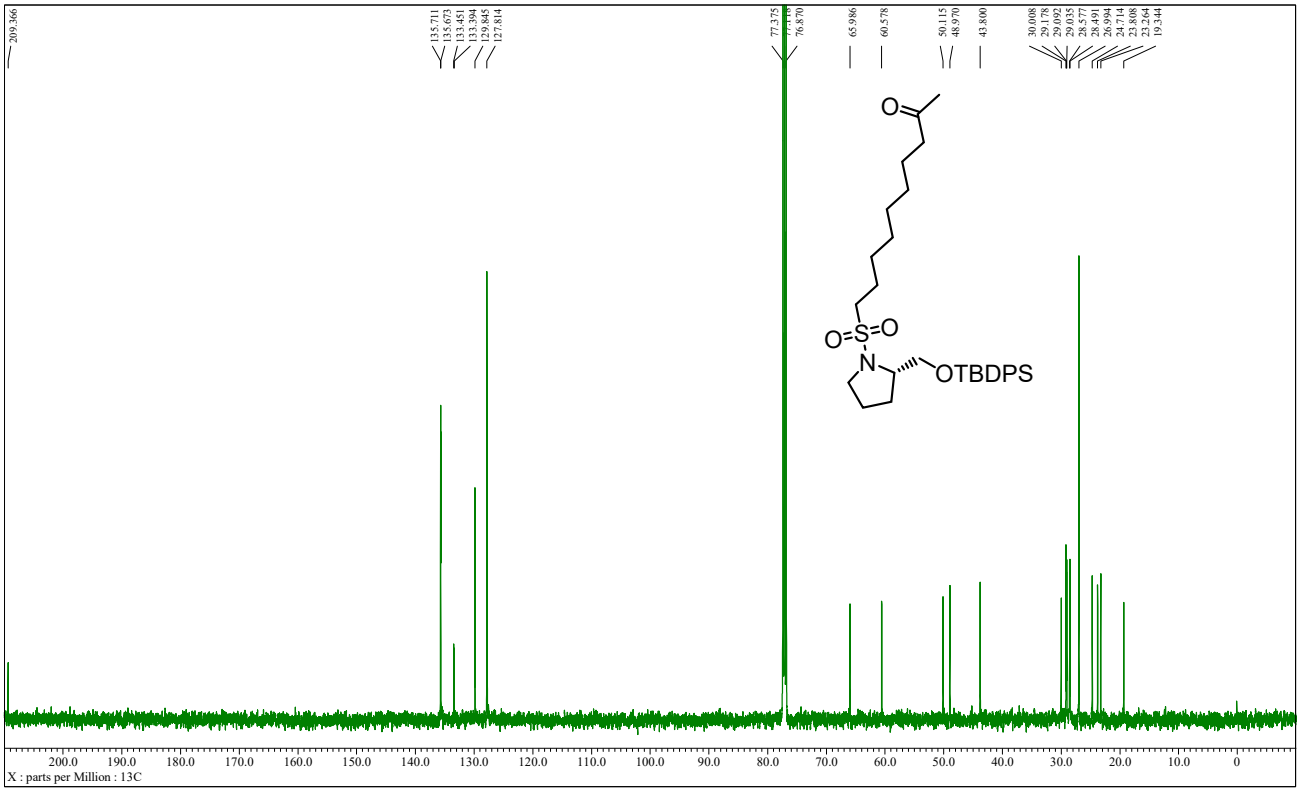

$^{13}$C NMR spectrum of compound **37** (125 MHz, $CDCl_3$)



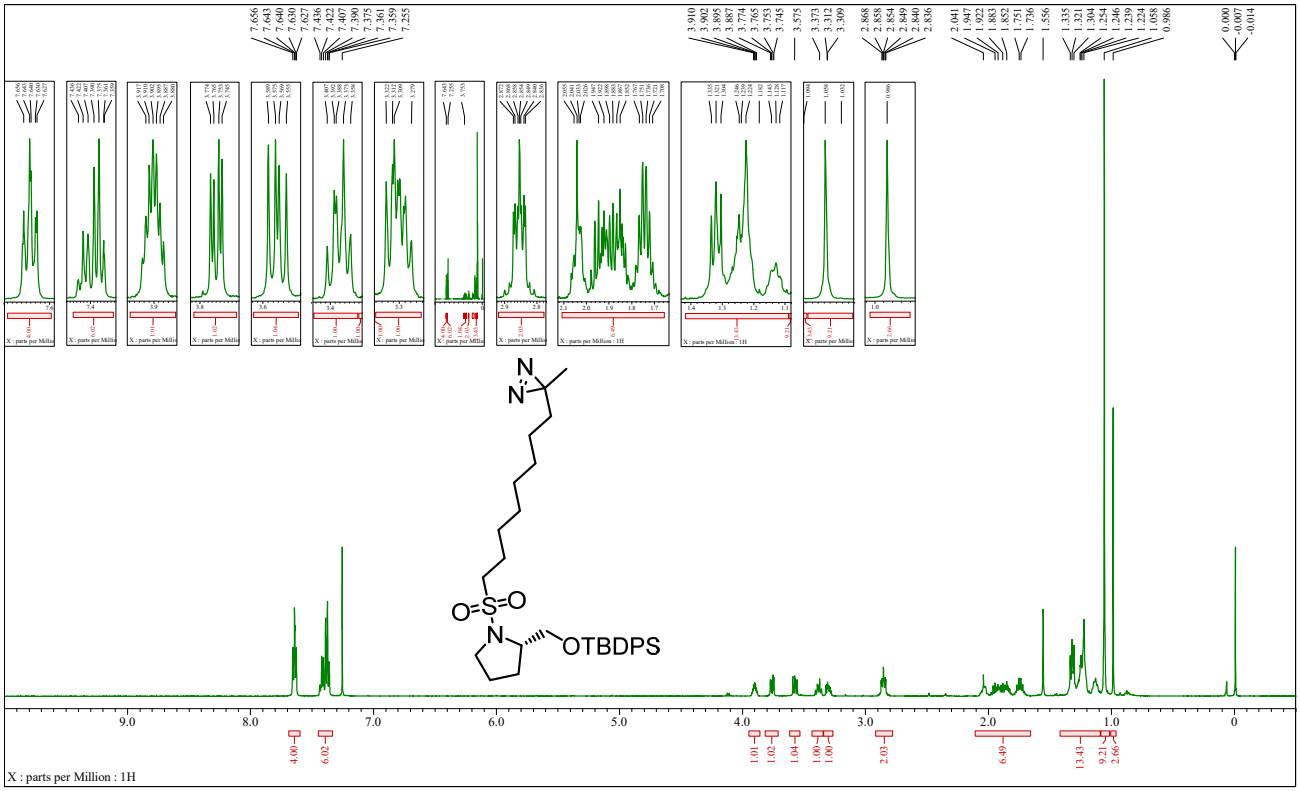
$^{1}$H NMR spectrum of compound **38** (500 MHz, $CDCl_3$)



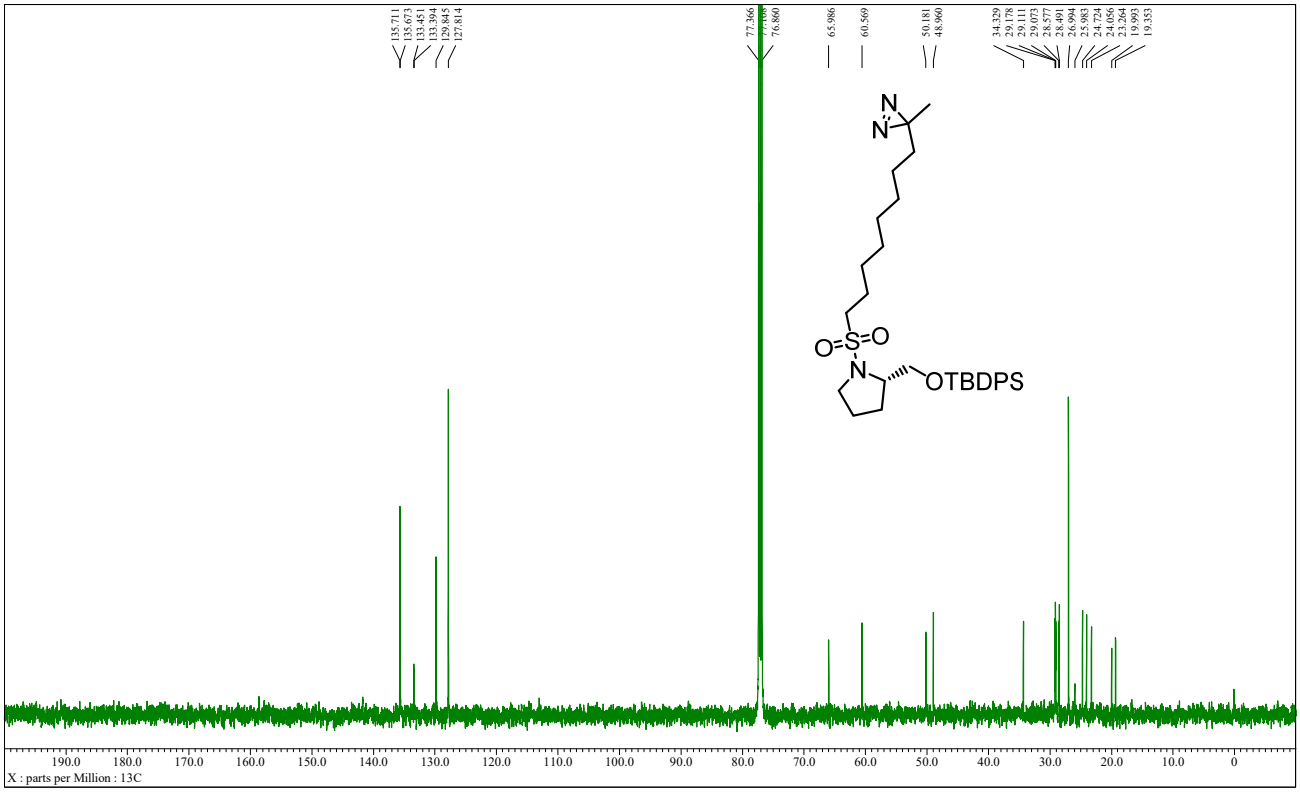

$^{13}$C NMR spectrum of compound **38** (125 MHz, $CDCl_3$)



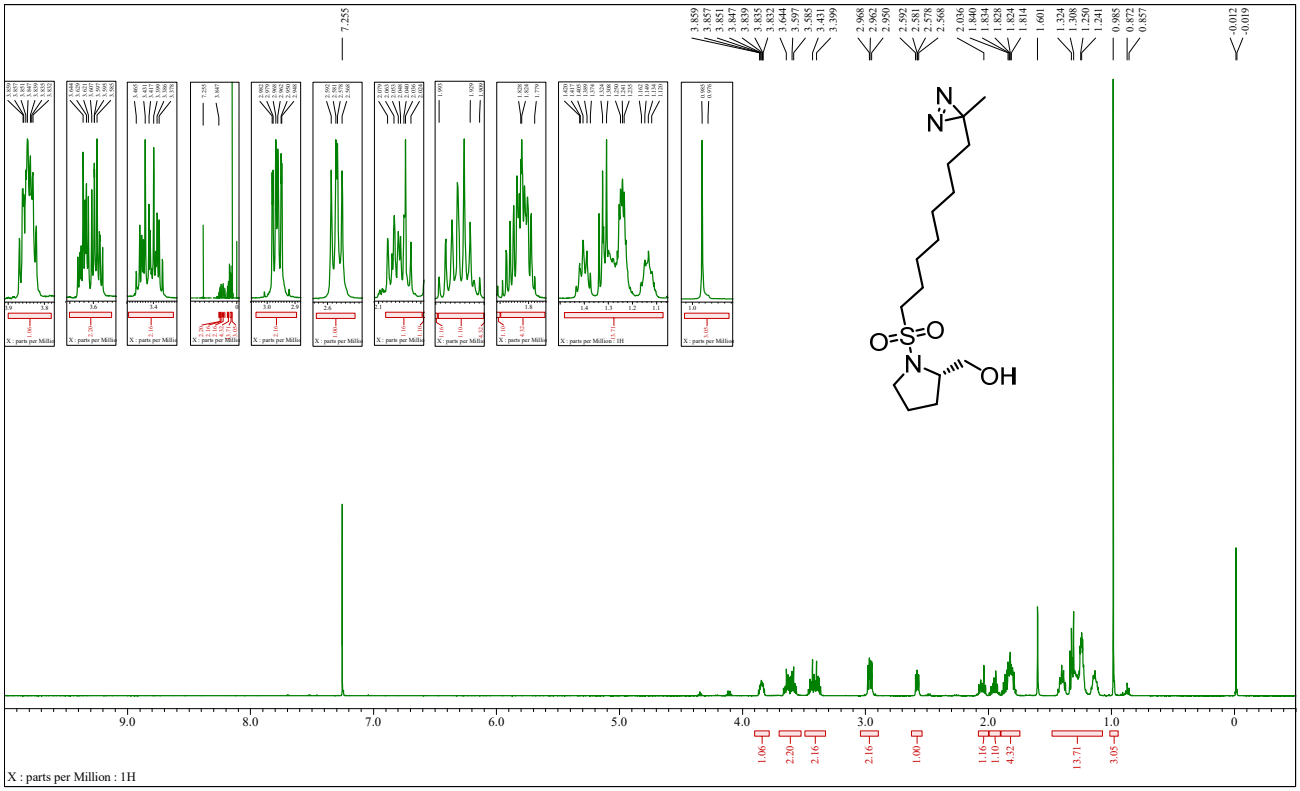
$^{1}$H NMR spectrum of compound **39** (500 MHz, $CDCl_3$)



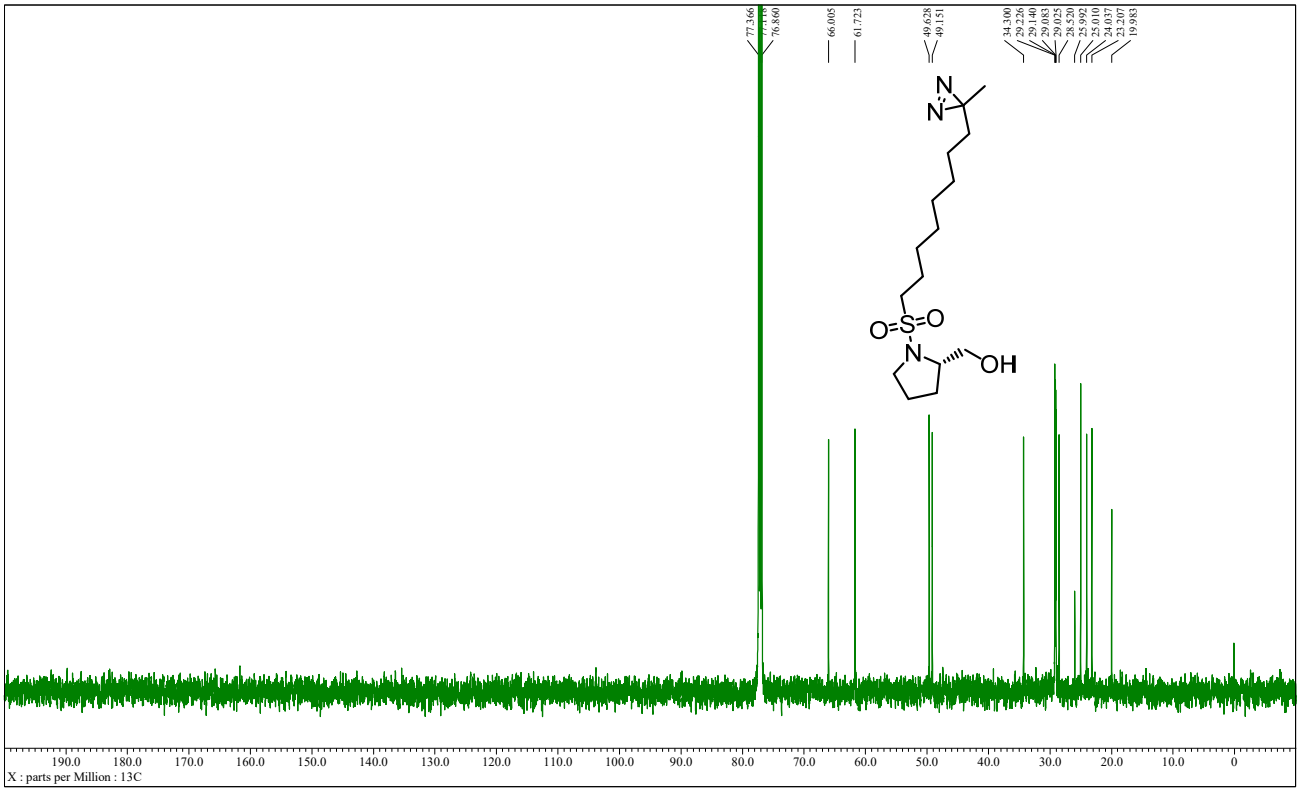

$^{13}$C NMR spectrum of compound **39** (125 MHz, $CDCl_3$)



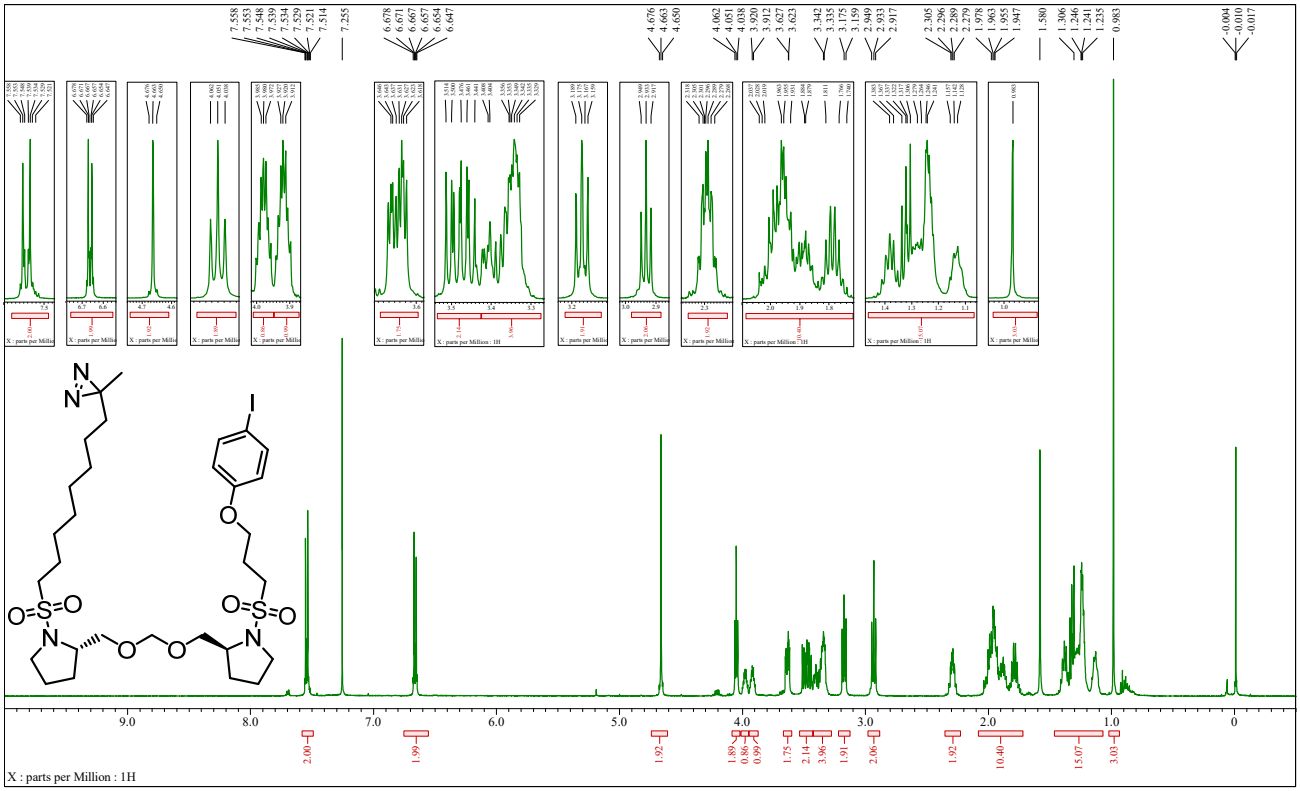
$^{1}$H NMR spectrum of compound **40** (500 MHz, $CDCl_3$)



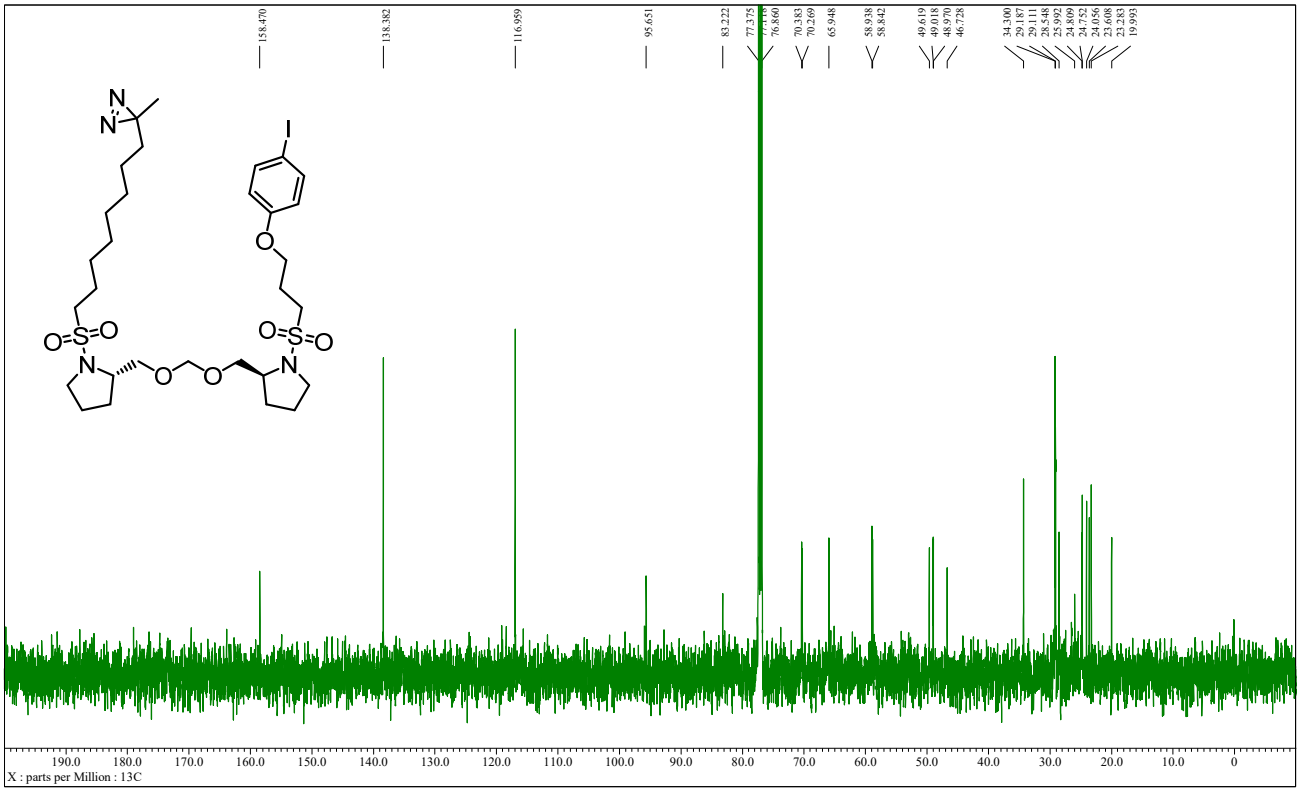

$^{13}$C NMR spectrum of compound **40** (125 MHz, $CDCl_3$)



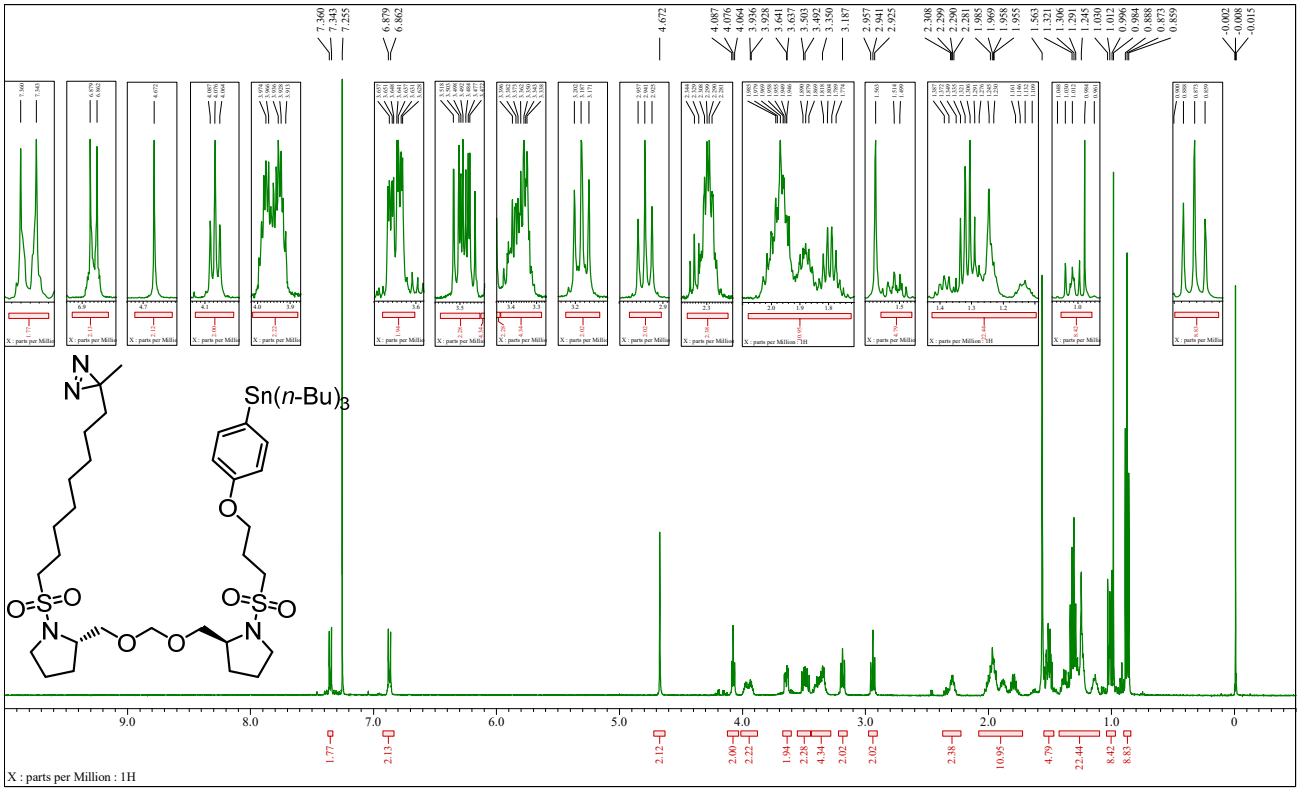
$^{1}$H NMR spectrum of compound **43** (500 MHz, $CDCl_3$)



$^{13}$C NMR spectrum of compound **43** (125 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of compound **44** (500 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of compound **44** (125 MHz, $CDCl_3$)