Ti(III)-mediated radical cyclization of epoxy-β-aminoacrylate in the synthesis of substituted pyrrolidine core of necine bases: synthesis of 2-*epi*-rosmarinecine.

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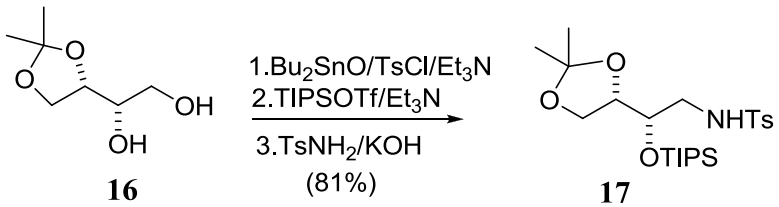
General Experimental Procedures. All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I2, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Optical rotations were measured using Autopol III manufactured by Rudolph using sodium (589, D line) lamp and are reported as follows: $[\alpha]^{D}_{25}$ (*c* = g/100 ml, solvent). IR spectra were recorded as neat liquids or KBr pellets. Mass spectra were obtained under electron impact ionisation (EI), liquid secondary ion mass spectrometric (LSIMS) technique, electron spray ionisation (ESI) and MALDI techniques. NMR spectra were recorded on 500, 400 and 300 MHz spectrometers at 30 °C with 2-10 mM solutions in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded on 125, 100 and 75 MHz spectrometers with complete proton decoupling.

Procedures:

Synthesis of 17.



16 **17**

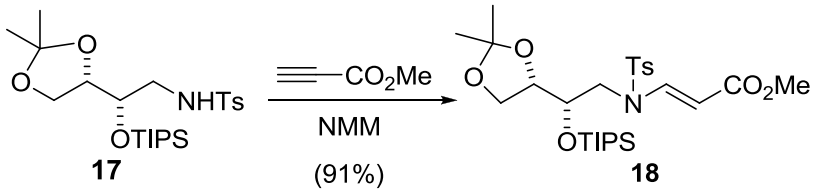
To a solution of diol **16 (**10 gm, 61.73 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (17.2 mL, 123.46 mmol), Bu_2SnO (3.1 gm, 12.346 mmol) and TsCl (14.12 gm, 74.07 mmol) sequentially at 0 °C. After 15 min, temperature was raised to room temperature and stirred for another 1 h. Then the reaction was diluted with EtOAc and filtered through a pad of Celite. The filtrate was

concentrated under *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-hexane, 4:6) gave tosylate (17.2 gm, 93%) as a yellow liquid. $\mathbf{R_f}$ = 0.4 (silica, EtOAc:hexane, 1:1).

The tosylate (17.2 gm, 57.41 mmol) was dissolved in CH_2Cl_2 (120 mL) and cooled to 0 °C. Et_3N (16.0 mL, 114.82 mmol) and triisopropylsilyltriflate (17.1 mL, 63.151 mmol) were added sequentially and stirring was continued for another 4 h at the same temperature. Then the reaction was quenched with satd. NH_4Cl (50 mL) and extracted with EtOAc (800 mL). EtOAc layer was washed sequentially with H_2O (2x100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated in *vacuo* to provide crude silyl ether which was used for next reaction without further purification. $\mathbf{R_f}$ = 0.6 (silica, EtOAc:hexane, 1:9).

The silyl ether was dissolved in DMSO (80 mL) and $TsNH_2$ (19.63 gm, 114.82 mmol) and KOH (3.67 gm, 172.23 mmol) were added to it. The resulting mixture was heated to 80 °C and stirring was continued for 10 h at that temperature. Then the temperature of the reaction mixture was brought down to room temperature and water was added to it. The reaction mixture was extracted with diethyl ether (500 mL) and washed sequentially with water (3x100 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated in *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-hexane, 2:8) gave the protected amino-alcohol **17** (21.2 gm, 87% from tosylate) as a pale yellow liquid. $\mathbf{R_f}$ = 0.4 (silica, EtOAc:hexane, 3:7); $[\alpha]^{25}_D$ +1.92 (*c* 1.93, $CHCl_3$); **IR** (neat): ν 3401, 3019, 1216, 1161, 757, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.73 (d, *J* = 8.09 Hz, 2 H), 7.31 (d, *J* = 8.09 Hz, 2 H), 4.93 (dd, *J* = 7.30, 4.54 Hz, 1 H), 4.20 (dd, *J* = 12.75, 6.68 Hz, 1 H), 4.03-3.92 (m, 2 H), 3.75 (dd, *J* = 8.24, 7.20 Hz, 1 H), 3.09-2.93 (m, 2 H), 2.43 (s, 3 H), 1.37 (s, 3H), 1.32 (s, 3 H), 1.01 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 143.5, 136.4, 129.7, 127.1, 109.5, 70.9, 65.0, 45.2, 26.1, 24.8, 21.5, 17.9, 12.3 ppm; **MS** (ESI) *m/z* (%): 414 (100) $[M+H–C_3H_6O]^+$, 494 (10) $[M+Na]^+$.

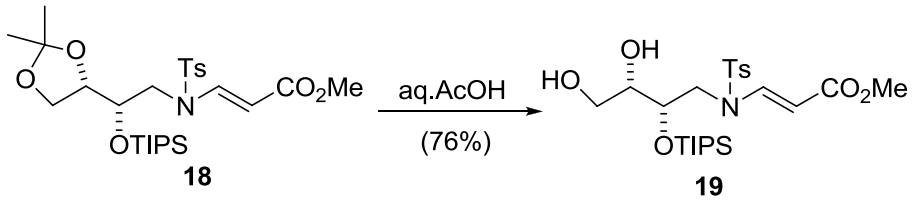
Synthesis of 18.



To a solution of the protected amino-alcohol **17** (21.2 gm, 44.95 mmol) in dry CH_2Cl_2 (120 mL), methyl propiolate (4.8 mL, 53.94 mmol) and *N*-methyl morpholine (NMM) (1.0 mL, 9.0 mmol) were added sequentially under nitrogen atmosphere at room temperature and stirred for another 8 h. It was then quenched with saturated aqueous NH_4Cl (25 mL) and extracted with EtOAc (500 mL). The combined organic layer was washed with water (2x100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated in *vacuo*. Chromatographic purification of the residue (SiO_2, with EtOAc-hexane, 2:8) afforded the pure epoxy-β-aminoacrylate **18** (22.7 gm, 91%) as colorless liquid. $\mathbf{R_f}$ = 0.5 (silica, EtOAc:hexane, 3:7); $[\alpha]^{25}_D$ - 6.86 (*c* 2.21, $CHCl_3$); **IR** (neat): ν 3019,

1705, 1626, 1215, 1164, 757, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.07 (d, *J* = 13.98 Hz, 1 H), 7.68 (d, *J* = 8.23 Hz, 2 H), 7.32 (d, *J* = 8.23 Hz, 2 H), 5.48 (d, *J* =13.98 Hz, 1H), 4.37-4.32 (m, 1 H), 4.17-4.11 (m, 1 H), 4.01-3.90 (m, 2 H), 3.71 (s, 3 H), 3.47 (dd, *J* = 14.87, 5.46 Hz, 1H), 3.38 (dd, *J* = 14.87, 7.37 Hz, 1 H), 2.43 (s, 3 H), 1.39 (s, 3 H), 1.31 (s, 3 H), 1.07 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 167.8, 145.2, 143.3, 135.0, 130.5, 127.4, 109.4, 99.8, 76.2, 70.8, 64.9, 51.5, 48.6, 26.4, 24.6, 21.9, 18.5, 13.0 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{46}NO_7SSi$, 556.2764; found 556.2761.

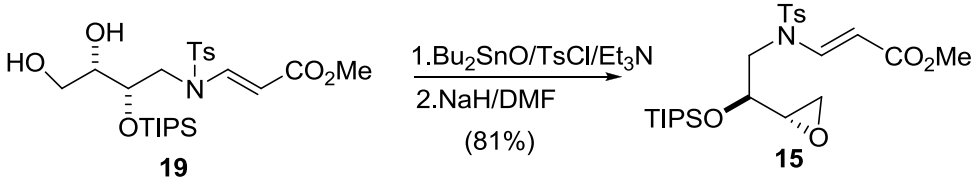
Synthesis of 19.



18 **19**

To the epoxy-β-aminoacrylate **18** (22.7 gm, 40.9 mmol) a solution of AcOH:H_2O (7:3,100 mL) was added and the resulting mixture was heated at 100 °C for 1 h. Then the reaction mixture was concentrated under *vacuo* and residual AcOH was quenched with solid $NaHCO_3$. The reaction mixture was diluted with EtOAc (600 mL) and washed sequentially with water (3x100 mL) and brine (50 ml) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic purification of the residue (SiO_2, with EtOAc-hexane, 4:6) afforded the pure diol **19** (16.0 gm, 76%) as colorless liquid. **R_f** = 0.4 (silica, EtOAc:hexane, 6:4); **[α]**$^{25}_D$ - 12.77 (*c* 1.28, $CHCl_3$); **IR** (neat): ν 3019, 1626, 1215, 1164, 757, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.06 (d, *J* = 14.10 Hz, 1 H), 7.68 (d, *J* = 8.20 Hz, 2 H), 7.34 (d, *J* = 8.20 Hz, 2 H), 5.53 (d, *J* =14.10 Hz, 1H), 4.28 (dd, *J* = 8.51, 5.58 Hz, 1 H), 3.71 (s, 3 H), 3.70-3.58 (m, 3 H), 3.48 (dd, *J* = 14.53, 5.51 Hz, 1 H), 2.44 (s, 3 H), 1.09 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 167.7, 145.2, 142.9, 134.6, 130.3, 129.8, 127.3, 99.4, 70.8, 70.4, 64.1, 51.6, 47.8, 21.7, 18.1, 12.9 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{42}NO_7SSi$, 516.2451; found 516.2440.

Synthesis of 15.



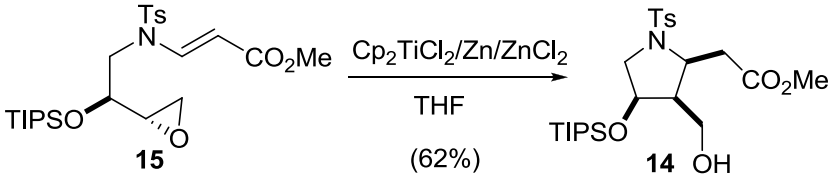
19 **15**

To a solution of diol **19 (**16.0 gm, 31.1 mmol) in CH_2Cl_2 (75 mL) were added Et_3N (8.6 mL, 62.2 mmol), Bu_2SnO (3.87 gm, 15.55 mmol) and TsCl (6.52 gm, 34.21 mmol) sequentially at 0 °C. After 15 min, temperature was raised to room temperature and stirred for another 1 hr. Then the reaction was diluted with EtOAc and filtered through a pad of Celite. The filtrate was

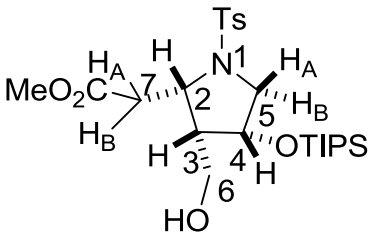
concentrated under *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-Hexane, 2:8) gave tosylate (18.3 gm, 88%) as a yellow liquid. $\mathbf{R_f}$ = 0.3 (silica, EtOAc:hexane, 3:7).

The tosylate (18.3 gm, 27.36 mmol) was dissolved in DMF (60 mL) and cooled to 0 °C and then NaH (1.31 gm, 32.83 mmol) was added into it portion wise. After 30 min, saturated aqueous NH_4Cl solution (10 mL) was added into it slowly. The reaction mixture was diluted with EtOAc (300 mL) and washed sequentially with water (3x40 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and chromatographic purification of the residue (SiO_2, with EtOAc-Hexane, 2:9) afforded the pure epoxy-β-aminoacrylate **15** (12.5 gm, 92% from tosylate) as colorless liquid. $\mathbf{R_f}$ = 0.5 (silica, EtOAc:hexane, 3:7); $\mathbf{[\alpha]}^{25}_D$ - 2.66 (*c* 1.82, $CHCl_3$); **IR** (neat): ν 3435, 3019, 1626, 1216, 1162, 758, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.04 (d, *J* = 14.27 Hz, 1 H), 7.68 (d, *J* = 8.23 Hz, 2 H), 7.35 (d, *J* = 8.23 Hz, 2 H), 5.27 (d, *J* = 14.27 Hz, 1H), 3.84-3.77 (m, 1 H), 3.71 (s, 3 H), 3.52 (dd, *J* = 14.94, 9.13 Hz, 1 H), 3.37 (dd, *J* = 14.94, 5.39 Hz, 1 H), 2.98 (m, 1 H), 2.82 (t, *J* = 4.48 Hz, 1 H), 2.62 (dd, *J* = 4.69, 2.64 Hz, 1 H), 2.44(s, 3 H), 1.08 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 167.3, 145.2, 142.4, 134.8, 130.3, 127.2, 99.1, 72.5, 54.4, 51.5, 49.0, 44.9, 21.6, 18.0, 12.4 ppm; **HRMS** (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{39}NO_6SSiNa$, 520.2165; found 520.2153.

Synthesis of 14.

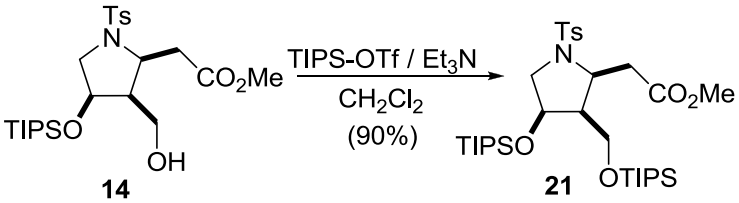


Activated Zn powder (4.73 gm, 72.42 mmol), freshly fused $ZnCl_2$ (4.9 gm, 36.21 mmol) and Cp_2TiCl_2 (9.01 gm, 36.21 mmol) were taken in dry THF (350 mL) and stirred for 1 hr at room temperature. The color of the reaction mixture turned into deep green. Then it was cooled to -20 °C and compound **15** (6.0 gm, 12.07 mmol) in dry THF (60 mL) was cannulated into it. The reaction mixture was allowed to come at room temperature slowly. Then it was stirred for 8 h. Reaction was quenched with 1 N HCl (50 mL) and extracted with EtOAc (2 x 250mL). The organic layer was washed sequentially with 1 N HCl (2x100 mL), H_2O (2x100 mL), and brine (100 mL), and dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-hexane, 3:7) provided the pyrrolidine ester **14** (3.73 gm, 62%) as a yellow liquid. $\mathbf{R_f}$ = 0.4 (silica, EtOAc:Hexane, 4:6); $\mathbf{[\alpha]}^{25}_D$ 11.47 (*c* 0.55, $CHCl_3$); **IR** (neat): ν 3435, 3019, 1215, 757, 668 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.72 (d, *J* = 8.08 Hz, 2 H), 7.33 (d, *J* = 8.08 Hz, 2 H), 4.08 (m, 1 H, C_4-H), 3.827 (m, 1 H, C_2-H), 3.68 (s, 3 H, -OMe), 3.468 (dd, *J* = 10.75, 2.0 Hz, 1 H, C_5-H_A), 3.24 (dd, *J* = 10.75, 4.72 Hz, 1 H, C_5-H_B), 3.16 (dd, *J*



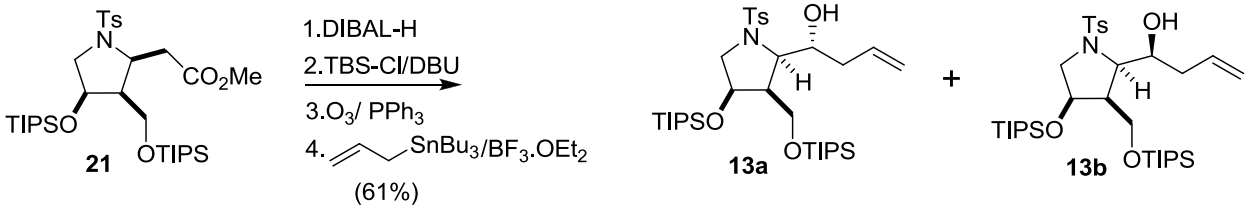
= 17.10, 3.74 Hz, 1 H, C_7-H_A), 3.06 (dd, *J* = 17.10, 10.31 Hz, 1 H, C_7-H_B), 2.94 (d, *J* = 7.03 Hz, 2 H, C_6-H_A&H_B), 2.43 (s, 3 H, -CH_3), 2.17 (m, 1 H, C_3-H), 1.01 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 50 MHz): 173.2, 143.9, 133.6, 129.8, 127.5, 72.8, 61.6, 58.2, 55.9, 55.7, 51.6, 40.9, 21.6, 17.9, 11.9 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{42}NO_6SSi$, 500.2502; found 500.2512.

Synthesis of 21.



Pyrrolidine **14** (3.73 gm, 7.48 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. Et_3N (1.1 mL, 15.0 mmol) and triisopropylsilyl triflate (2.5 mL, 9.0 mmol) were added sequentially and stirring was continued for another 4 h at same temperature. Then the reaction was quenched with satd. NH_4Cl (30 mL) and extracted with EtOAc (300 mL). EtOAc layer was washed sequentially with H_2O (2x50 mL), brine (100 mL) and dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-hexane, 1:9) provided the silyl-ether **21** (4.4 gm, 90%) as a yellow liquid. $\mathbf{R_f}$ = 0.5 (silica, EtOAc:hexane, 1:9); $[\alpha]^{25}_D$ 3.78 (*c* 0.46, $CHCl_3$); **IR** (neat): ν 3019, 1215, 757, 668 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.73 (d, *J* = 8.04 Hz, 2 H), 7.32 (d, *J* = 8.04 Hz, 2 H), 4.42 (m, 1 H), 3.69 (s, 3 H), 3.58-3.51 (m, 2 H), 3.26-3.07 (m, 4 H), 2.43 (s, 3 H), 2.29-2.16 (m, 2 H), 1.06 (s, 24 H), 0.92 (s, 18 H) ppm; **^{13}C NMR** ($CDCl_3$, 50 MHz): 172.3, 143.7, 133.2, 129.7, 127.5, 72.5, 62.2, 58.6, 55.6, 55.0, 51.4, 41.0, 21.5, 17.9, 17.8, 17.7, 12.3, 11.9, 11.5 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{62}NO_6SSi_2$, 656.3836; found 656.3830.

Synthesis of 13a and 13b.



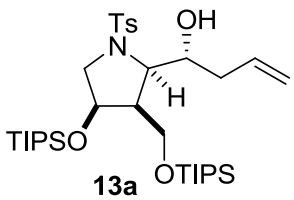
Silyl-ether **21** (2.2 gm, 3.35 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to -78 °C. After 5 min, DIBAL-H (1 M in toluene, 3.7 mL, 3.7 mmol) was added into it and stirring was continued for another 30 min at the same temperature. Then the temperature was raised to 0 °C and the reaction was quenched with slow addition of saturated solution of saturated sodium potassium tartrate. Then the reaction mixture was stirred at room temperature for another 1 h.

The resulting mixture was extracted with EtOAc (200 mL), washed sequentially with H_2O (2x50 mL), brine (100 mL) and dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (SiO_2, with EtOAc-Hexane, 1:9) to furnish the corresponding aldehyde (1.725 gm, 82%).

To a stirred solution of aldehyde (1.72 gm, 2.76 mmol) in CH_2Cl_2 (25 mL) at 25 °C were added DBU (13.7 mL, 55.2 mmol) and TBSCl (4.15 gm, 27.6 mmol). The resulting mixture was stirred for 10 h at that temperature and then quenched with saturated aqueous $NaHCO_3$ solution (100 mL). The resulting mixture was extracted with EtOAc (250 mL), washed sequentially with H_2O (2x50 mL), brine (100 mL) and dried over anhydrous Na_2SO_4 and concentrated in *vacuo* The crude residue was purified by flash column chromatography (SiO_2, with EtOAc-Hexane, 1:15) to furnish the corresponding silyl enol ether. To a solution of this enol ether in MeOH:CH_2Cl_2 (1:1, 40 mL) at –78 °C was added pyridine (0.25 mL, 2.76 mmol). Ozone was gently bubbled into the reaction mixture until the solution took on a light blue color. The reaction mixture was stirred for 2 min and then purged with oxygen until it became colorless. Ph_3P (3.61 gm, 13.8 mmol) was added and the reaction mixture was warmed up to 25 °C, stirred for an additional 1 h, and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, with EtOAc-hexane, 1:9) to furnish α-aminoaldehyde.

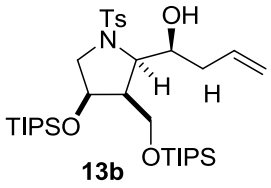
Aldehyde was dissolved in CH_2Cl_2 (20 mL) and allyltributylstannane (1.28 mL, 4.14 mmol) were added into it and the the reaction mixture was cooled to -78 °C. After colling for 10 min, a solution of $BF_3.OEt_2$ (0.38 mL, 3.036 mmol) in CH_2Cl_2 (5 mL) was added into it and stirring was continued for another 1 h. Then the reaction was quenched with satd. $NaHCO_3$ (20 mL) and extracted with EtOAc (100 mL). EtOAc layer was washed sequentially with H_2O (2x30mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-hexane, 1:20) gave homo allylalcohols **13a** (1.08 gm, 60%) and **13b** (0.27 gm, 15%) as separable diastreomers. $\mathbf{R_f}$ = 0.4 (silica, EtOAc:hexane, 1:9).

Characterization of compounds :



13a

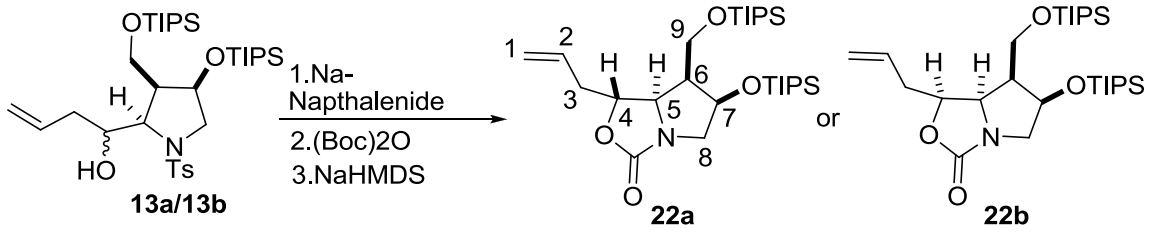
[α]$^{25}_{D}$ 10.82 (*c* 0.4, $CHCl_3$); **IR** (neat): ν 3019, 1217, 771, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.24 Hz, 2 H), 7.34 (d, *J* = 8.24 Hz, 2 H), 6.00 (m, 1 H), 5.15-5.11 (m, 2 H), 4.09-4.04 (m, 2 H), 3.52 (dd, *J* = 11.42, 5.43 Hz, 1 H), 3.45 (d, *J* = 3.09 Hz, 1 H), 3.42 (dd, *J* = 6.60, 2.75 Hz, 1 H), 3.01 (dd, *J* = 9.90, 7.43 Hz, 1 H), 2.76 (td, *J* = 9.83, 8.81 Hz, 1 H), 2.53-2.48 (m, 1 H), 2.44 (s, 3 H), 2.33-2.23 (m, 2 H), 1.03 (s, 21 H), 0.98 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.1, 135.1, 134.2, 129.9, 127.8, 117.2, 72.5, 72.2, 66.9, 63.0, 56.5, 53.4, 38.6, 21.6, 18.09, 18.06, 17.9, 12.1, 11.8 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{64}NO_5SSi_2$, 654.4044; found 654.4010.



13b

[α]$^{25}_{D}$ 7.26 (*c* 0.475, $CHCl_3$); **IR** (neat): ν 3019, 1215, 771, 668 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.18 Hz, 2 H), 7.31 (d, *J* = 8.18 Hz, 2 H), 5.99-5.89 (m, 1 H), 5.12-5.07 (m, 2 H), 4.26 (m, 1 H), 4.19 (m, 1 H), 3.816 (m, 1 H), 3.45 (d, *J* = 11.17 Hz), 3.37 (m, 1 H), 3.29 (dd, J = 10.93, 4.37 Hz, 1 H), 3.15 (dd, *J* = 10.20, 6.31 Hz, 1 H), 2.67 (t, *J* = 9.91 Hz, 1 H), 2.47-2.33 (m, 2 H), 2.42 (s, 3 H), 2.25-2.18 (m, 1 H), 1.05 (s, 21 H), 0.95 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 143.9, 135.4, 133.5, 129.7, 117.1, 72.4, 72.2, 65.9, 62.9, 56.2, 50.6, 39.9, 21.6, 18.2, 18.0, 17.9, 12.1, 11.8 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{64}NO_5SSi_2$, 654.4044; found 654.4010.

Syntheses of 22a and 22b.



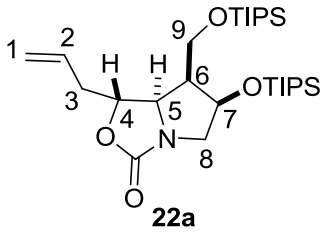
13a/13b **22a** **22b**

To a solution of naphthalene (180 mg, 1.4 mmol) in dry THF (4 mL), sodium (35 mg, 1.4 mmol) was added at RT. The reaction mixture was stirred at room temperature for 1 h. A deep green color appeared. Then the stirring was stopped and the solution was allowed to stand for 30 min. Homoallyl alcohol **13a** (or, **13b**) (90 mg, 0.14 mmol) was dissolved in THF (5 mL) and cooled to -78 °C. Then the Na-napthalenide solution that was prepared initially was cannulated into it with stirring. After 15 min, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc (50 mL). EtOAc layer was washed sequentially with H_2O (2x10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo* and preceded to next reaction without further purification.

The free amine obtained above was dissolved in CH_2Cl_2 (5 mL) and Et_3N (0.1 mL, 0.7 mmol) and $(Boc)_2O$ (0.1 mL, 0.42 mmol) were added into sequentially at room temperature. After 4 h, the reaction was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (50 mL). EtOAc layer was washed sequentially with H_2O (2x10 mL), Brine (10 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo* and purification by column chromatography (SiO_2, with EtOAc-hexane, 1:9) gave Boc-carbamate (64 mg, 77%) as a pale yellow liquid.

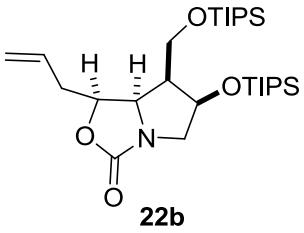
The Boc carbamate (60 mg, 0.1 mmol) obtained in the above reaction was dissolved in THF and cooled to 0 °C. After 5 min, NaHMDS (1 M in THF, 0.3 mL, 0.3 mmol) was added into it and stirred for another 15 min at the same temperature. Then the temperature of the reaction mixture was raised to room temperature and stirred for 10 h. After completion of the reaction, it was quenched by adding saturated NH_4Cl (5 mL) and extracted with EtOAc (30 mL). EtOAc layer was washed sequentially with H_2O (2x10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and

concentrated in *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-hexane, 1:9) gave **22a** (32 mg, 62%) (**22b**, 40 mg, 79%) as a colorless liquid.



22a

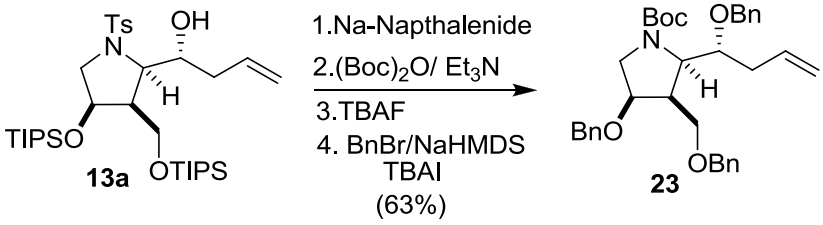
R_f = 0.5 (silica, EtOAc:hexane, 2:8); **IR** (neat): ν 1638, 1384, 1216 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.38 (m, 1 H, C_2-H), 5.20-5.16 (m, 2 H, C_1-H_a&H_b), 4.50 (m, 1 H, C_4-H), 4.32 (m, 1 H, C_7-H), 3.74 (dd, *J* = 10.07, 5.87 Hz, 1 H, C_9-H_a), 3.66 (m, 1 H, C_8-H_a), 3.63(dd, *J* = 10.07, 7.08 Hz, 1 H, C_9-H_b), 3.49 (dd, *J* = 5.31, 4.84 Hz, 1 H, C_5-H), 3.22 (dd, *J* = 11.96, 4.7 Hz, 1 H, C_8-H_b), 2.60-2.55 (m, 1 H, C_3-H_a), 2.52-2.46 (m, 1 H, C_3-H_b), 2.16 (m, 1 H, C_6-H), 1.06 (m, 42 H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.02, 131.8, 119.3 81.2, 76.1, 65.4, 63.5, 57.0, 55.6, 39.3, 29.8, 18.11, 18.06, 18.03, 12.13, 11.98 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{56}NO_4Si_2$, 526.3748; found 526.3707.



22b

R_f = 0.4 (silica, EtOAc:hexane, 2:8); **IR** (neat): ν 1638, 1384, 1216 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.85 (m, 1 H, C_2-H), 5.14 (m, 2 H, C_1-H_a&H_b), 4.76 (dt, *J* = 8.47, 5.84 Hz, 1 H, C_4-H), 4.32 (m, 1 H, C_7-H), 3.94 (dd, *J* = 8.47, 4.93 Hz, 1 H, C_5-H), 3.77 (d, *J* = 12.10 Hz, 1 H, C_8-H_a), 3.66 (d, *J* = 5.93 Hz, 2 H, C_9-H_a&H_b), 3.14 (dd, *J* = 12.10, 3.71 Hz, 1 H, C_8-H_b), 2.56 (m, 1 H, C_3-H_a), 2.45 (m, 1 H, C_3-H_b), 2.38 (m, 1 H, C_6-H), 1.068 (s, 21 H), 1.059 (s, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.59, 133.24, 118.34, 76.51, 76.08, 63.76, 63.57, 56.05, 51.28, 36.61, 29.91, 18.11, 18.07, 12.16, 12.01 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{56}NO_4Si_2$, 526.3748; found 526.3707.

Synthesis of 23.



13a **23**

To a solution of naphthalene (840 mg, 6.57 mmol) in dry THF (8 mL), sodium (151 mg, 6.57 mmol) was added at RT. The reaction mixture was stirred at room temperature for 1 h. A deep green colour appeared. Then the stirring was stopped and the solution was allowed to stand for 30 min. Homoallyl alcohol **13a** (430 mg, 0.657 mmol) was dissolved in THF (10 mL) and cooled to -78 °C and stirred for 10 min at that temperature. Then the Na-napthalenide solution that was prepared initially was cannulated into it. After 15 min, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc (50 mL). EtOAc layer was washed sequentially with H_2O (2x15

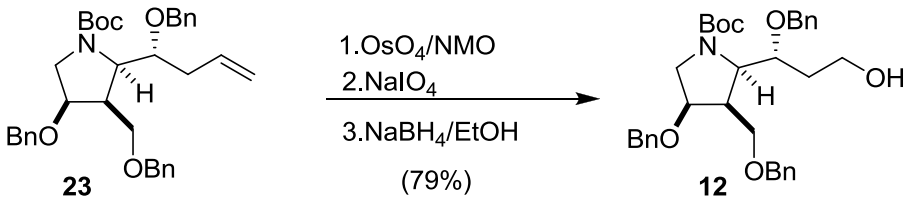
mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo* and used in the next reaction without further purification.

The free amine obtained above was dissolved in CH_2Cl_2 (5 mL) and Et_3N (0.45 mL, 2.0 mmol) and $(Boc)_2O$ (0.45 mL, 3.28 mmol) were added into sequentially at room temperature. After 4 h, the reaction was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (50 mL). EtOAc layer was washed sequentially with H_2O (2x10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo* and purification by column chromatography (SiO_2, with EtOAc-hexane, 1:9) gave Boc-carbamate (303 mg, 77%) as a pale yellow liquid. $\mathbf{R_f}$ = 0.5 (silica, EtOAc:hexane, 1:20).

The carbamate (303 mg, 0.506 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. To it a solution of TBAF in THF (3.1 mL, 3.036 mmol) was added and the reaction temperature was raised to room temperature and stirred overnight. Then the reaction was quenched by addition of saturated NH_4Cl (5 mL) and extracted with EtOAc (100 mL). EtOAc layer was washed sequentially with H_2O (2x20 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo* and purification by column chromatography (SiO_2, with EtOAc-hexane, 8:2) gave triol (133 mg, 92%) as a colorless liquid. $\mathbf{R_f}$ = 0.3 (silica, EtOAc:hexane, 8:2).

The triol (133 mg, 0.465 mmol) obtained in the above reaction was dissolved in a 2:1 mixture of THF:DMF (6 mL). BnBr (0.67 mL, 5.58 mmol) and TBAI (510 mg, 1.39 mmol) were added into it sequentially at room temperature. After 15 min, the reaction mixture was cooled to 0 °C and NaHMDS (1 M in THF, 2.8 mL, 2.79 mmol) was added into it and stirred for another 30 min at the same temperature. Then the temperature of the reaction mixture was raised to room temperature and stirred for 16 h. After completion of the reaction, it was quenched by adding saturated NH_4Cl (10mL) and extracted with EtOAc (100 mL). EtOAc layer was washed sequentially with H_2O (2x20 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo* and purification by column chromatography (SiO_2, with EtOAc-hexane, 1:9) gave tribenzylated product **23** (230 mg, 89%) as a pale yellow liquid. $\mathbf{R_f}$ = 0.4 (silica, EtOAc:hexane, 2:8); $\mathbf{[\alpha]}^{25}_{D}$ 11.52 (*c* 0.396, $CHCl_3$); **IR** (neat): ν 1638, 1384, 1216, 770, 670 cm^{-1}; **Rotamers ^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.31-7.28 (m, 15 H), 5.92-5.81 (m, 1 H), 5.09-4.99 (m, 2 H), 4.61-4.45 (m, 6 H), 4.16-3.80 (m, 4 H), 3.52 (dd, *J* = 9.14, 4.64 Hz, 1 H), 3.44-3.36 (m, 1 H), 3.21-3.18 (m, 1 H), 2.55 (m, 1 H), 2.32-2.29 (m, 2 H), 1.44 (s, 9 H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.2, 138.3, 138.2, 135.1, 128.3, 127.68, 127.62, 127.60, 116.94, 80.01, 79.80, 79.5, 79.19, 78.95, 78.52, 73.05, 72.68, 71.76, 70.26, 61.40, 51.87, 51.05, 45.46, 44.45, 36.55, 28.52, 22.70, 14.13 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{44}NO_5$, 558.3219; found 558.3228.

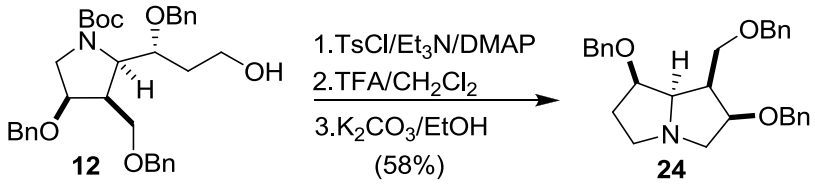
Synthesis of 12.



To a solution of the alkene **23** (124 mg, 0.22 mmol) in acetone-water mixture (3:1, 8 mL) were added NMO (77 mg, 0.66 mmol) and OsO_4 (0.04 M in toluene, 0.55 mL, 0.022 mmol) sequentially at room temperature. After being stirred for 6 h at the same temperature, the reaction mixture was concentrated in *vacuo* and diluted with EtOAc (50 mL), washed with water (2x10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and preceded to the next reaction. $\mathbf{R_f}$ = 0.3 (silica, EtOAc:hexane, 1:1).

The diol obtained above was dissolved in THF-H_2O (1:1, 10 mL) and treated with $NaIO_4$ (188 mg, 0.88 mmol) at 0 ºC and stirred for 45 min at the same temperature. Then the reaction mixture was diluted with EtOAc and solid Na_2SO_4 was added into it. The resulting reaction mixture was filtered and the solids were washed with EtOAc. The filtrate and washings were combined, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude reaction mixture was dissolved in MeOH (5 mL) and cooled to 0 °C. Then $NaBH_4$ (25 mg, 0.66 mmol) was added to it and stirred for another 1 h. After completion of the reaction, it was quenched with satd. NH_4Cl (5 mL) and extracted with EtOAc (30 mL). The organic layer was washed sequentially with water (2x10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in *vacuo*. Purification by column chromatography (SiO_2, with EtOAc-hexane, 1:1) gave the alcohol **12** (97 mg, 79%). $\mathbf{R_f}$ = 0.5 (silica, EtOAc:hexane, 1:1); $\mathbf{[\alpha]}^{25}_{D}$ 6.54 (*c* 1.33, $CHCl_3$); **IR** (neat): ν 3430, 3018, 1215, 757, 669 cm^{-1}; **Rotamers ^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.35-7.28 (m, 15 H), 4.75-4.45 (m, 6 H), 4.15 (m, 2 H), 4.04-3.94 (m, 2 H), 3.76-3.69 (m, 3 H), 3.52 (dd, *J* = 9.26, 4.84 Hz, 1 H), 3.45 (dd, *J* = 9.12, 5.82 Hz, 1 H), 3.25 (m, 1 H), 2.60 (m, 1 H), 1.81-1.73 (m, 2 H), 1.47 (s, 1 H) ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{44}NO_6$, 562.3169; found 562.3157.

Synthesis of 24.

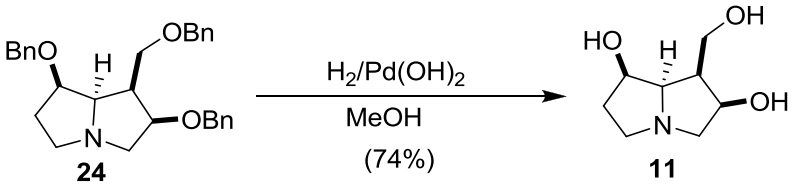


To the solution of the alcohol **12** (76 mg, 0.135 mmol) in CH_2Cl_2 (6 mL) were added Et_3N (0.1 mL, 0.7 mmol), TsCl (52 mg, 0.27 mmol) and DMAP (12 mg, 0.1 mmol) sequentially at room

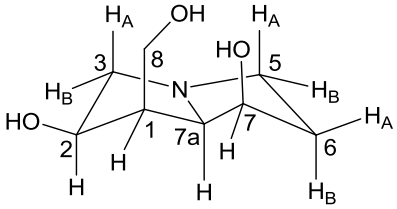
temperature. The reaction was stirred for another 2 h at the same temperature. Then it was quenched with satd.NH_4Cl (5 mL) and extracted with EtOAc (30 mL). The organic layer was washed sequentially with water (2 x 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (SiO_2, with EtOAc-hexane, 1:9) to give the tosylated product (85 mg, 88%) as a colorless liquid. $\mathbf{R_f}$ = 0.6 (silica, EtOAc:hexane, 2:8).

To the solution of the tosylate (85 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL) and stirred at 0 °C for 1 h. The reaction mixture was then concentrated in *vacuo* to give TFA salt of the tosylate. This TFA salt was dissolved in EtOH (10 mL) and K_2CO_3 (50 mg, 0.36 mmol) was added into it and the resulting reaction mixture was refluxed for 36 h. The reaction was cooled and the crude mixture was filtered through a short Celite pad and the filter cake was washed with ethanol. The filtrate and the washings were combined and concentrated in *vacuo*. Purification by column chromatography (silica gel, 4% MeOH in chloroform eluant) afforded protected pyrrolizidine **24** (35 mg, 66%). $\mathbf{R_f}$ = 0.4 (silica gel, MeOH:$CHCl_3$, 1:9); **IR** (neat): ν 3019, 1215, 757, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33-7.26 (m, 15 H), 4.59 (d, *J* = 12.16 Hz, 1 H), 4.51-4.44 (m, 5 H), 4.10 (ddd, *J* = 13.61, 7.72, 5.69 Hz, 1 H), 3.97 (m, 1 H), 3.61 (dd, *J* = 9.29, 4.77 Hz, 1 H), 3.51 (dd, *J* = 9.23, 7.14 Hz, 1 H), 3.46 (dd, *J* = 7.65, 4.68 Hz, 1 H), 3.38 (dd, *J* = 9.10, 5.80 Hz, 1 H), 3.17 (m, 1 H), 2.88 (ddd, *J* = 12.43, 7.56, 4.87 Hz, 1 H), 2.78 (td, *J* = 10.22, 6.41 Hz, 1 H), 2.64 (t, *J* = 8.51 Hz, 1 H), 2.20-2.14 (m, 1 H), 1.92-1.83 (m, 1 H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 138.77, 138.64, 138.54, 128.48, 128.43, 127.85, 127.76, 127.64, 127.59, 127.51, 127.43, 82.74, 78.54, 73.15, 72.43, 71.34, 70.91, 70.38, 59.61, 52.44, 42.75, 32.82 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{34}NO_3$, 444.2539; found 444.2542.

Synthesis of 11.



To a solution of the protected pyrrolizidine **24** (35 mg, 0.08 mmol) in MeOH (10 mL), was added 20% $Pd(OH)_2$ (20 mg) and subjected to hydrogenation under atmospheric pressure using a hydrogen filled balloon. After 48 h the reaction mixture was filtered through a short Celite pad and the filter cake was washed with methanol. The filtrate and the washings were combined and concentrated in *vacuo* to give 2-*epi*-rosmarinecine **11** (9 mg, 74%) which was sufficiently pure for characterization. $\mathbf{R_f}$ = 0.4 (silica gel, NH_4OH:MeOH:$CHCl_3$, 0.5:2.5:7); **^{1}H NMR** (D_2O, 500 MHz): δ 4.60 (m, 1 H, C_7-H), 4.45 (m, 1 H, C_2-H), 4.03 (dd, *J* = 7.38, 4.94 Hz, C_{7a}-H), 3.86 (dd, *J* = 11.46, 5.88 Hz, 1 H, C_3-H_A), 3.81-3.74 (m, 3 H, C_8-H_A & H_B, C_5-H_B), 3.35 (dt, *J* =



11.37, 6.43 Hz, 1 H, C_5-H_A), 3.08 (dd, *J* = 11.51, 7.94 Hz, 1 H, C_3-H_B), 2.68 (m, 1 H, C_1-H), 2.34-2.22 (m, 2 H, C_6- H_A & H_B) ppm; **^{13}C NMR** (D_2O, 125 MHz): δ 75.40, 74.72, 72.28, 62.66, 62.15, 55.79, 48.36, 37.42 ppm; **HRMS** (ESI) (*m/z*): $[M+H]^+$ calcd for $C_8H_{16}NO_3$, 174.1130; found 174.1126.

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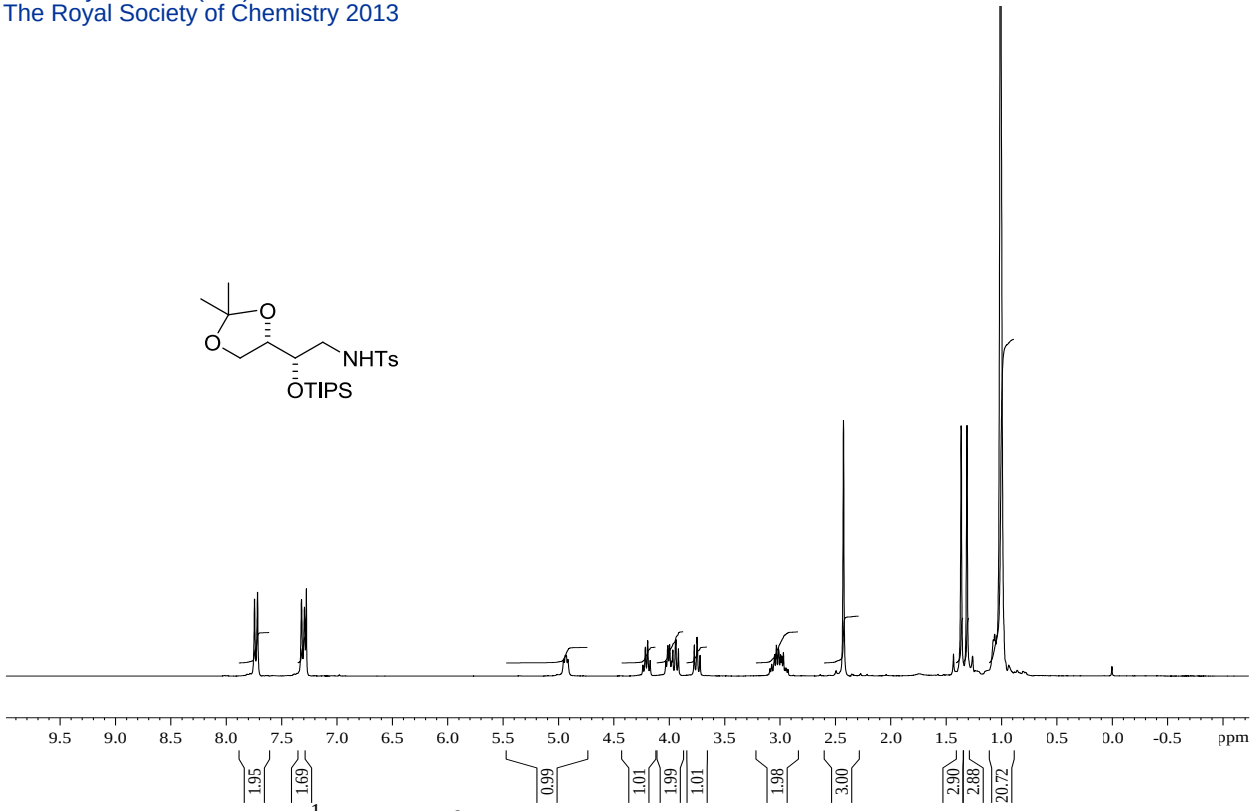
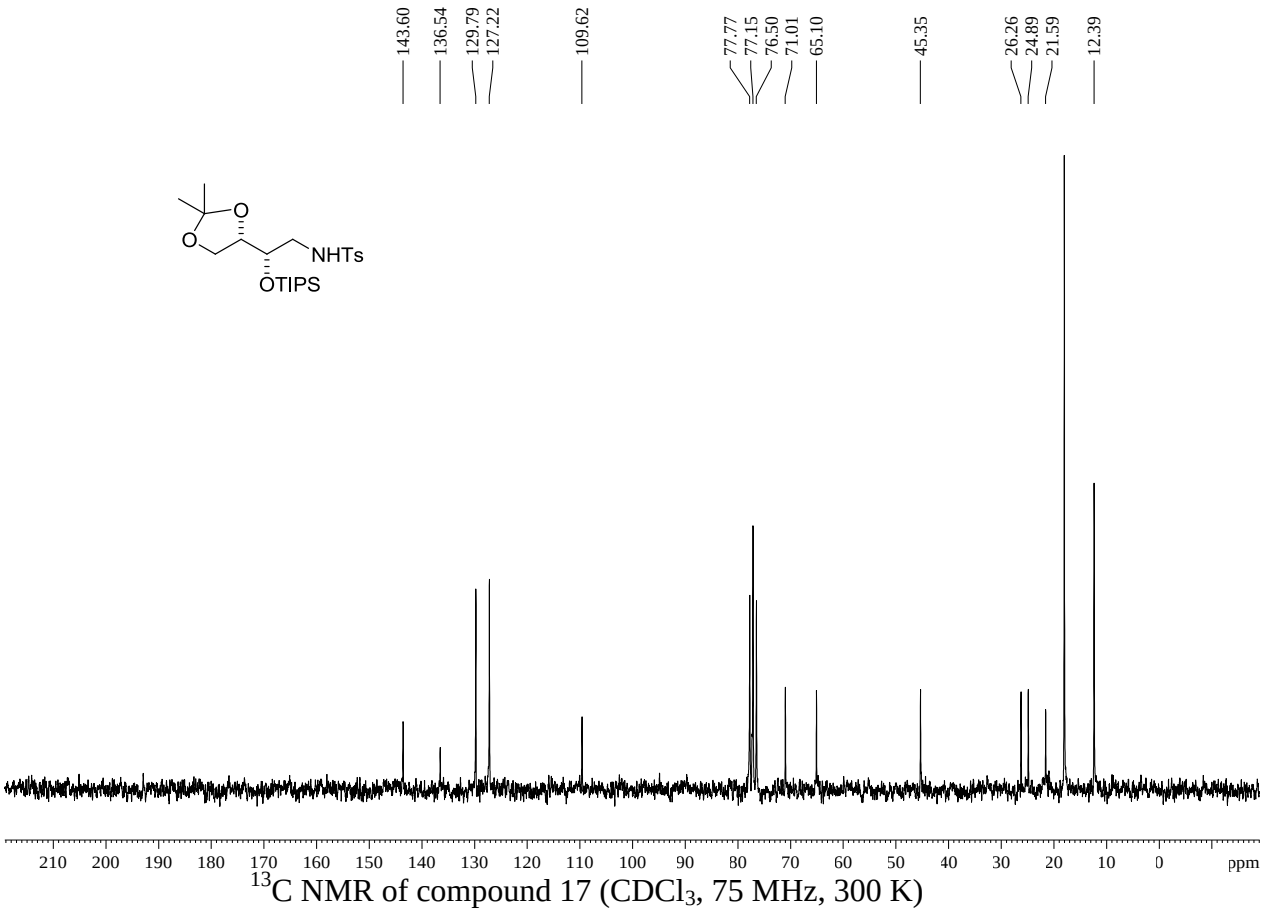
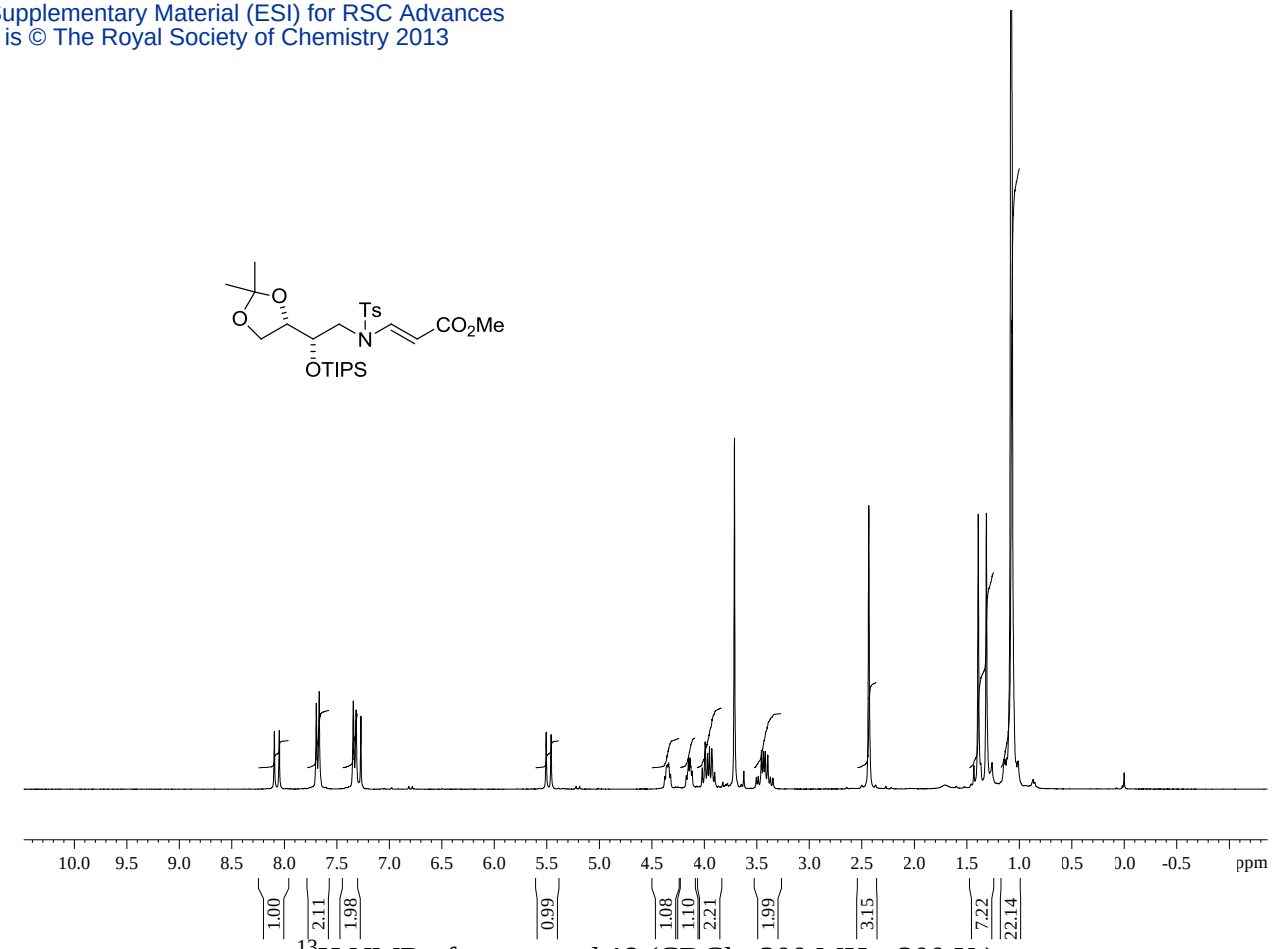


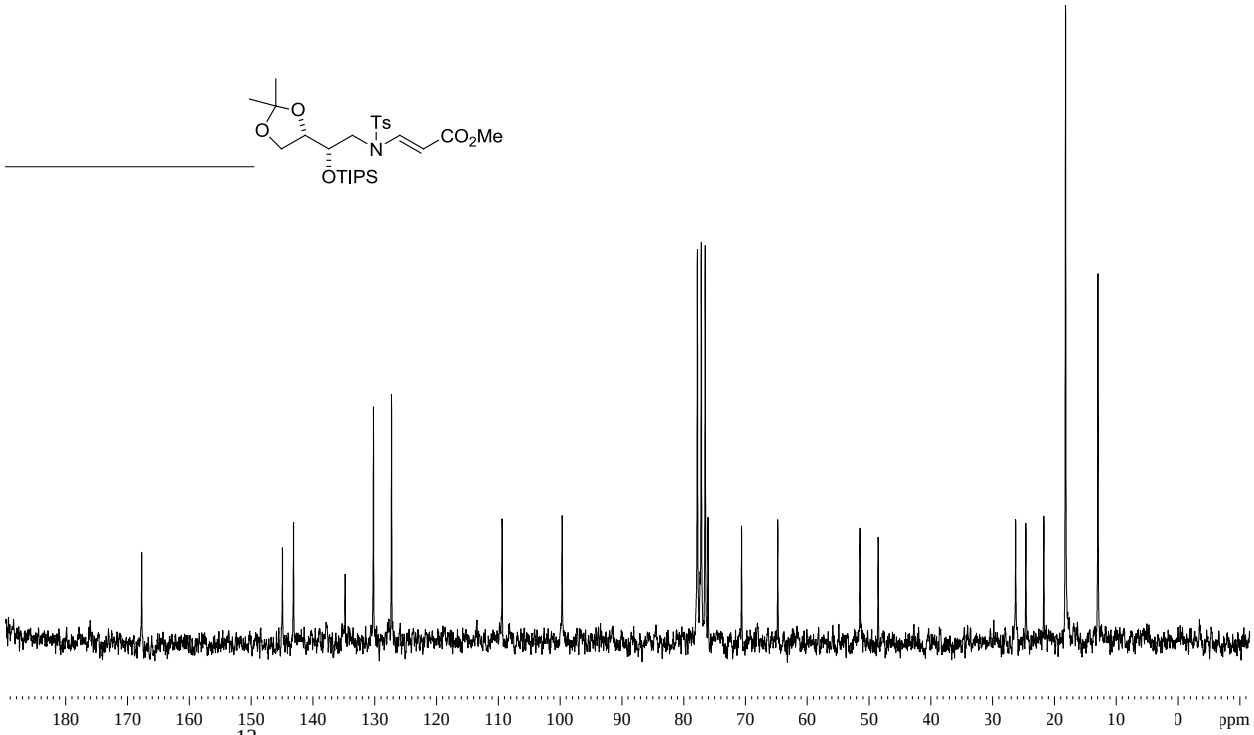
^{1}H NMR of compound 17 ($CDCl_3$, 300 MHz, 300 K)



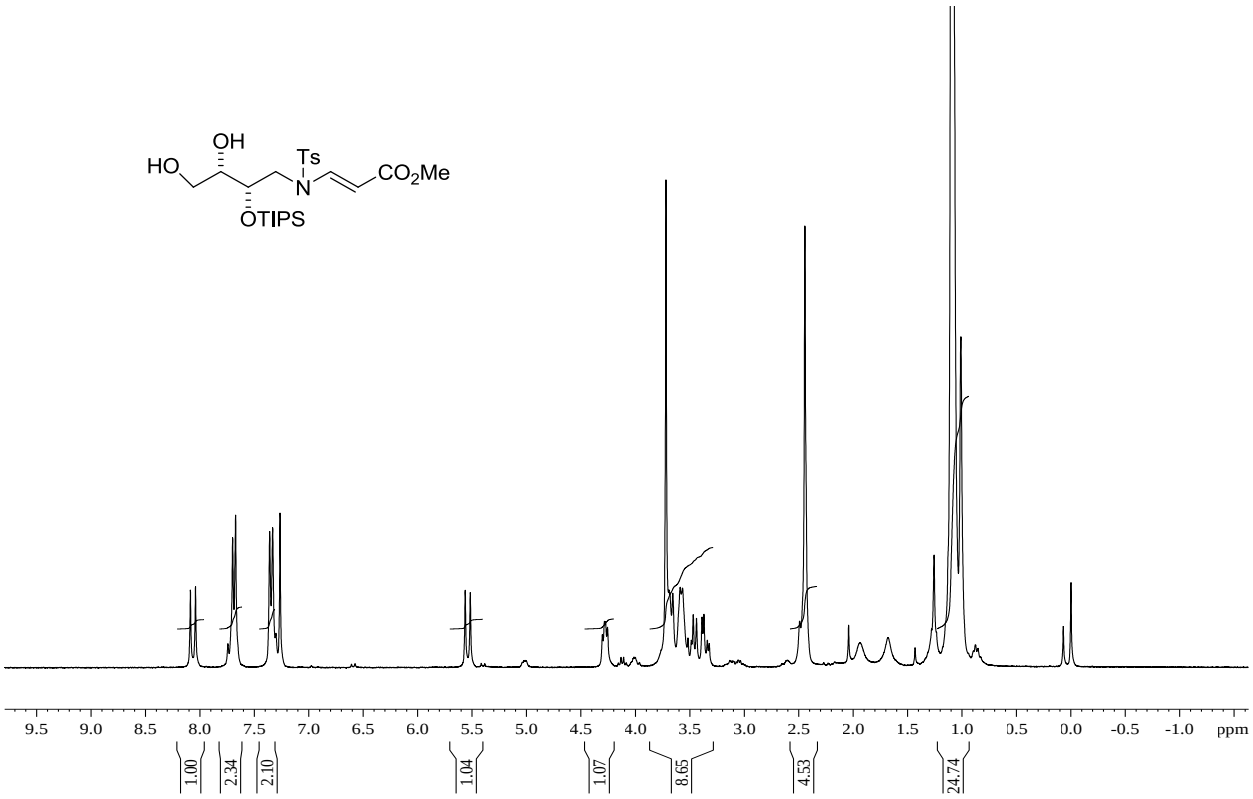
^{13}C NMR of compound 17 ($CDCl_3$, 75 MHz, 300 K)



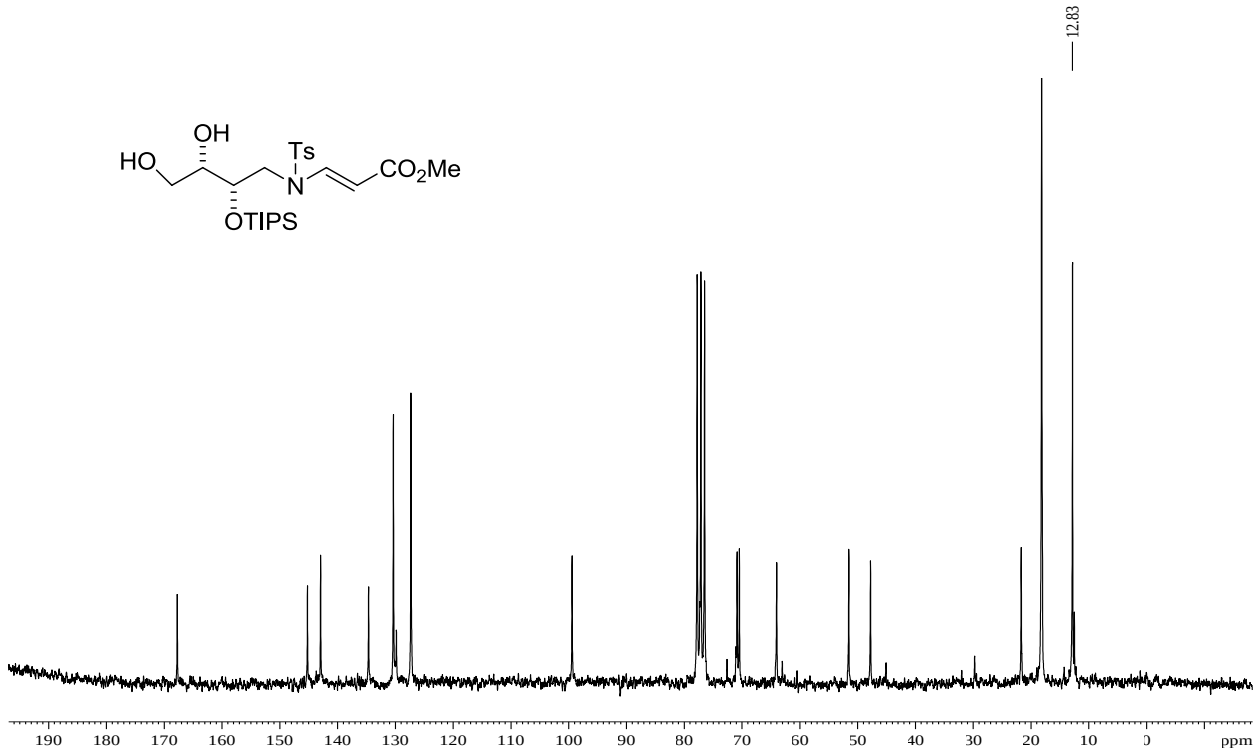
^{13}H NMR of compound **18** ($CDCl_3$, 300 MHz, 300 K)



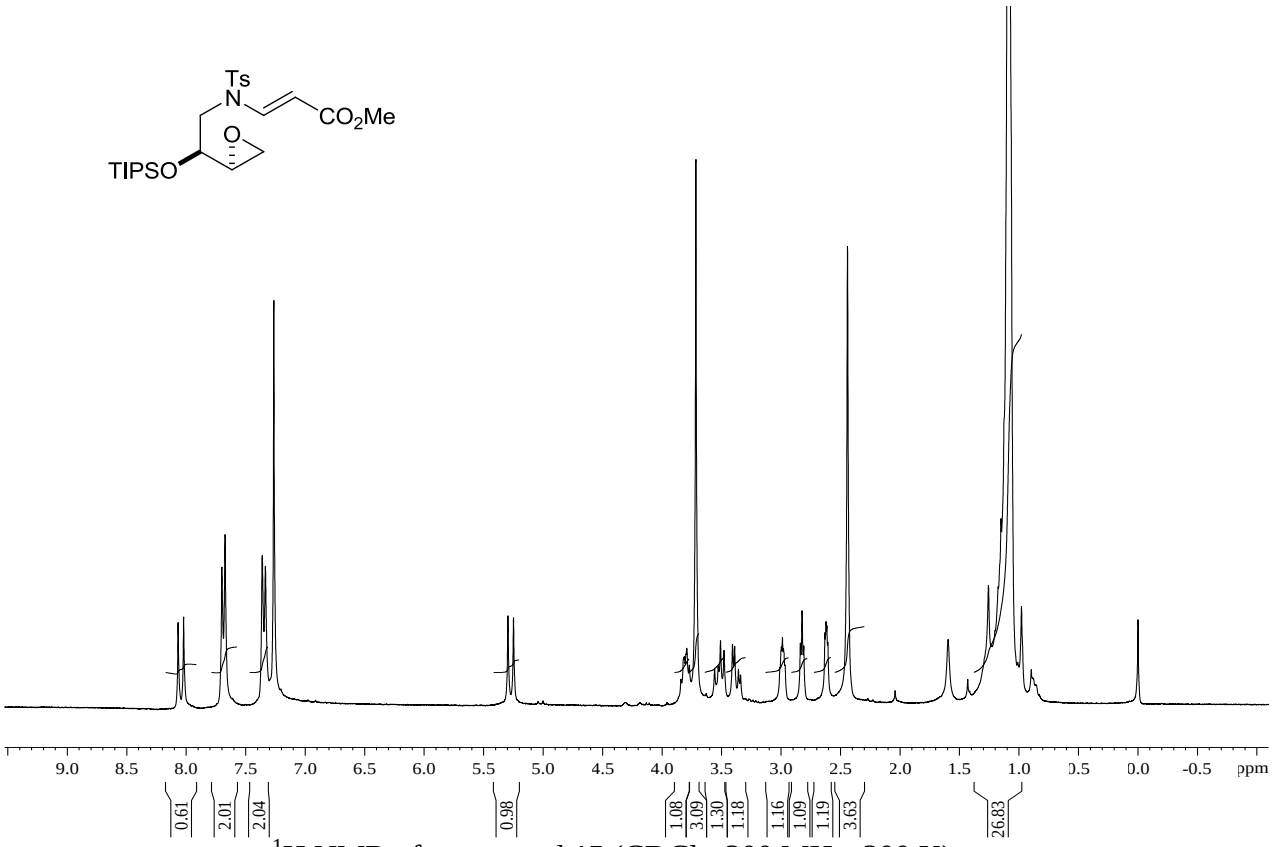
^{13}C NMR of compound **18** ($CDCl_3$, 75 MHz, 300 K)



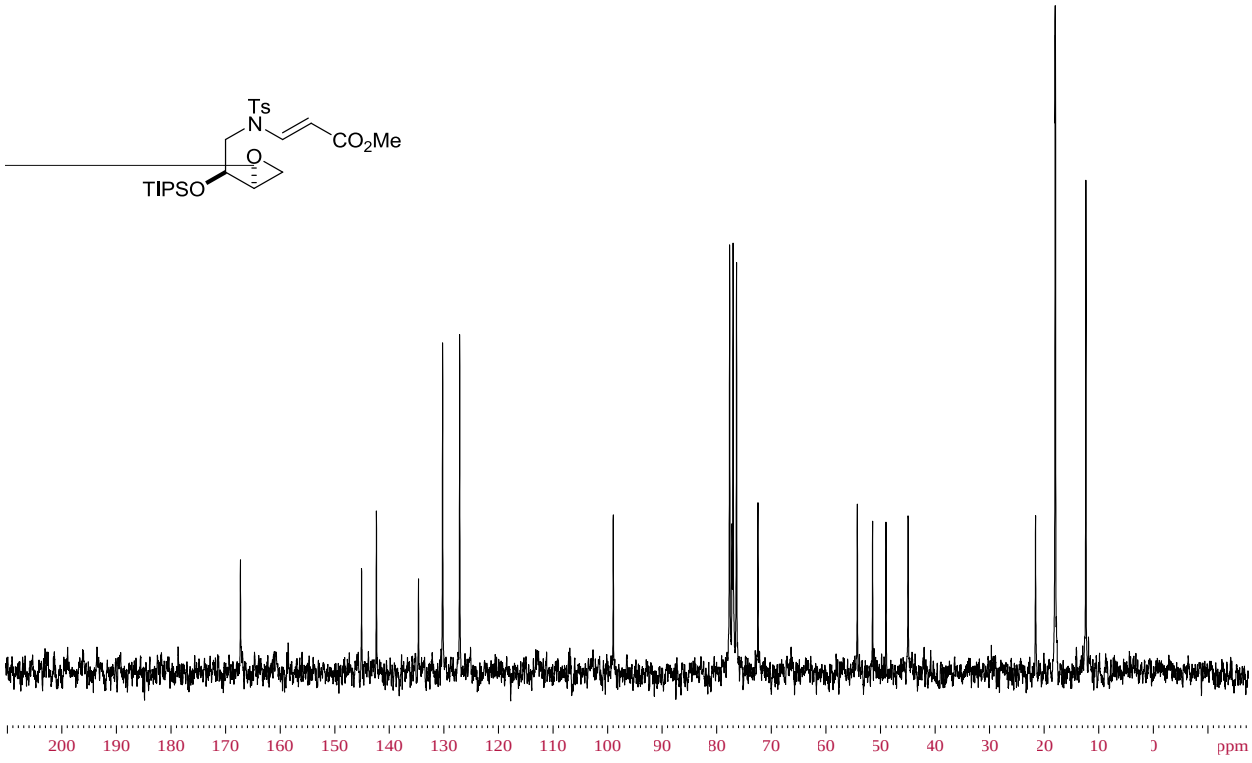
^{1}H NMR of compound **19** ($CDCl_3$, 300 MHz, 300 K)



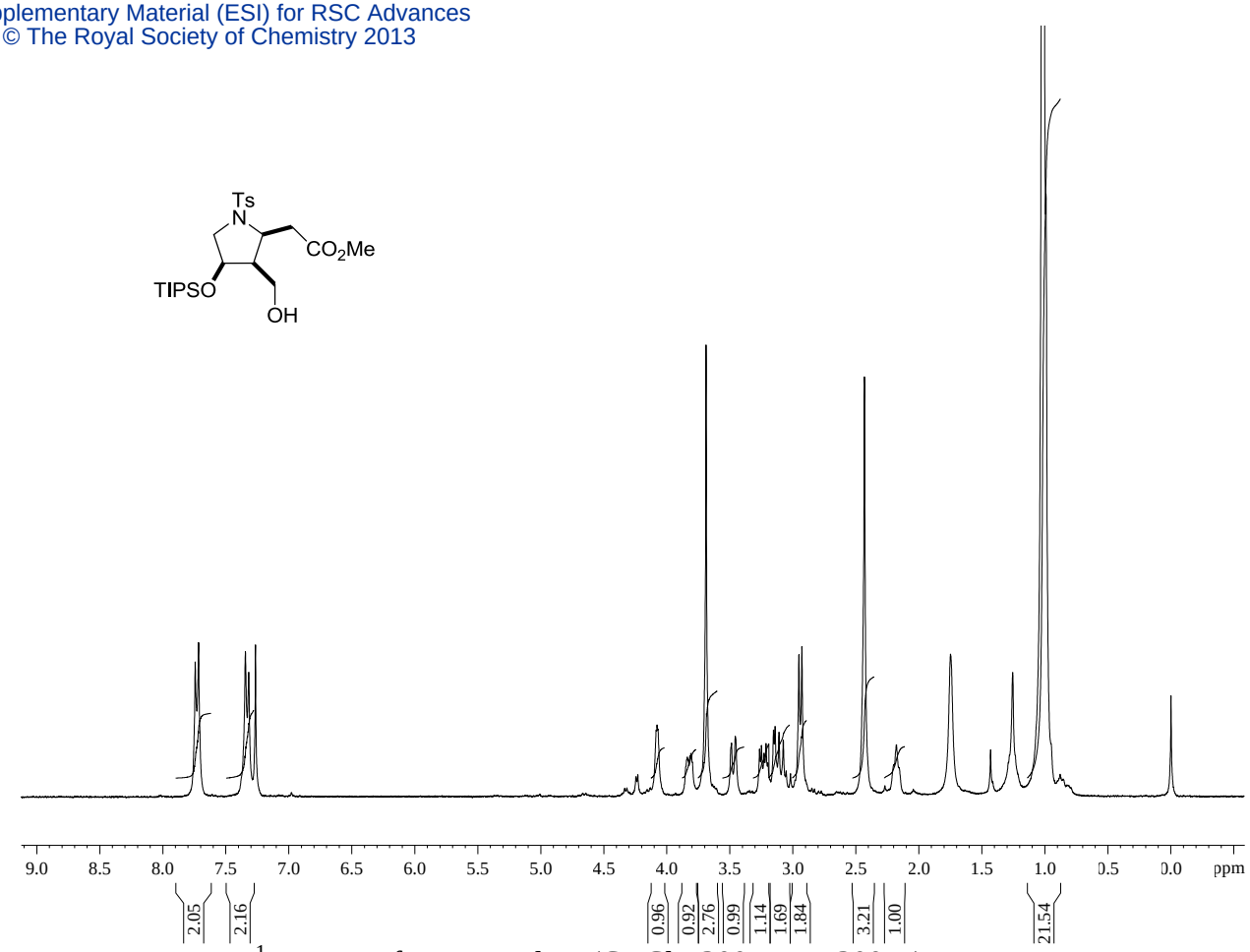
^{13}C NMR of compound **19** ($CDCl_3$, 75 MHz, 300 K)



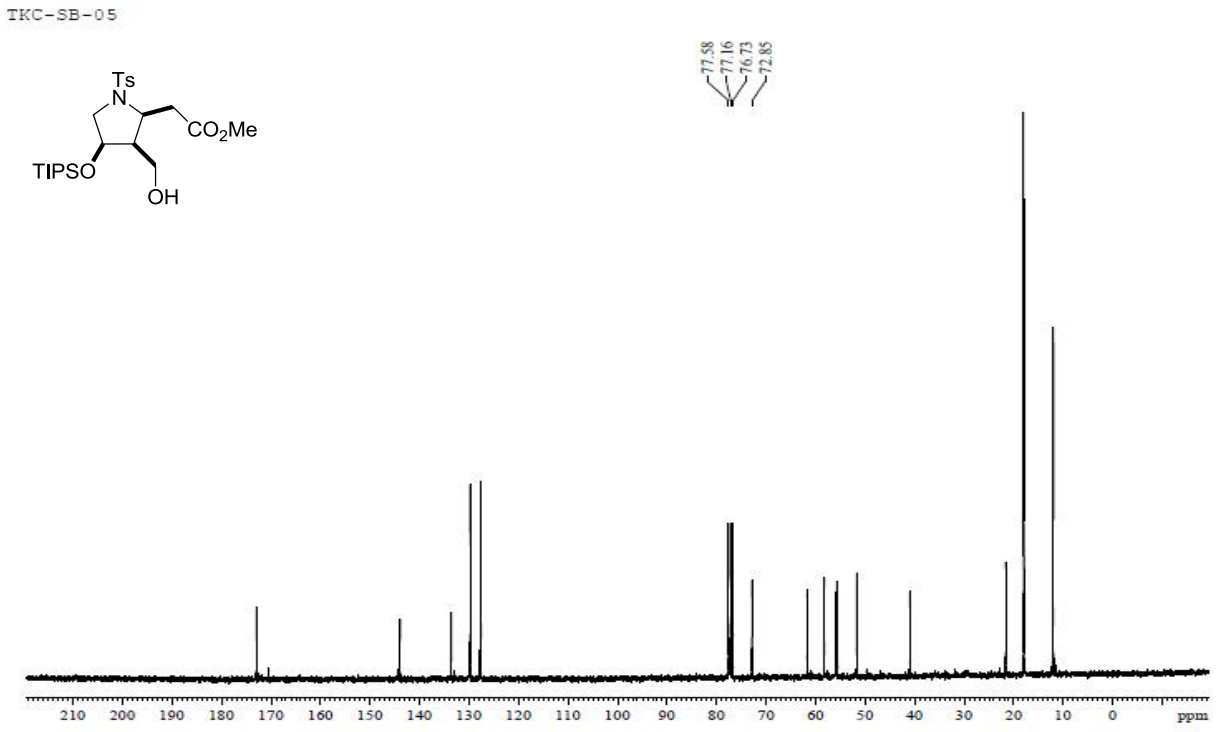
^{1}H NMR of compound **15** ($CDCl_3$, 300 MHz, 300 K)



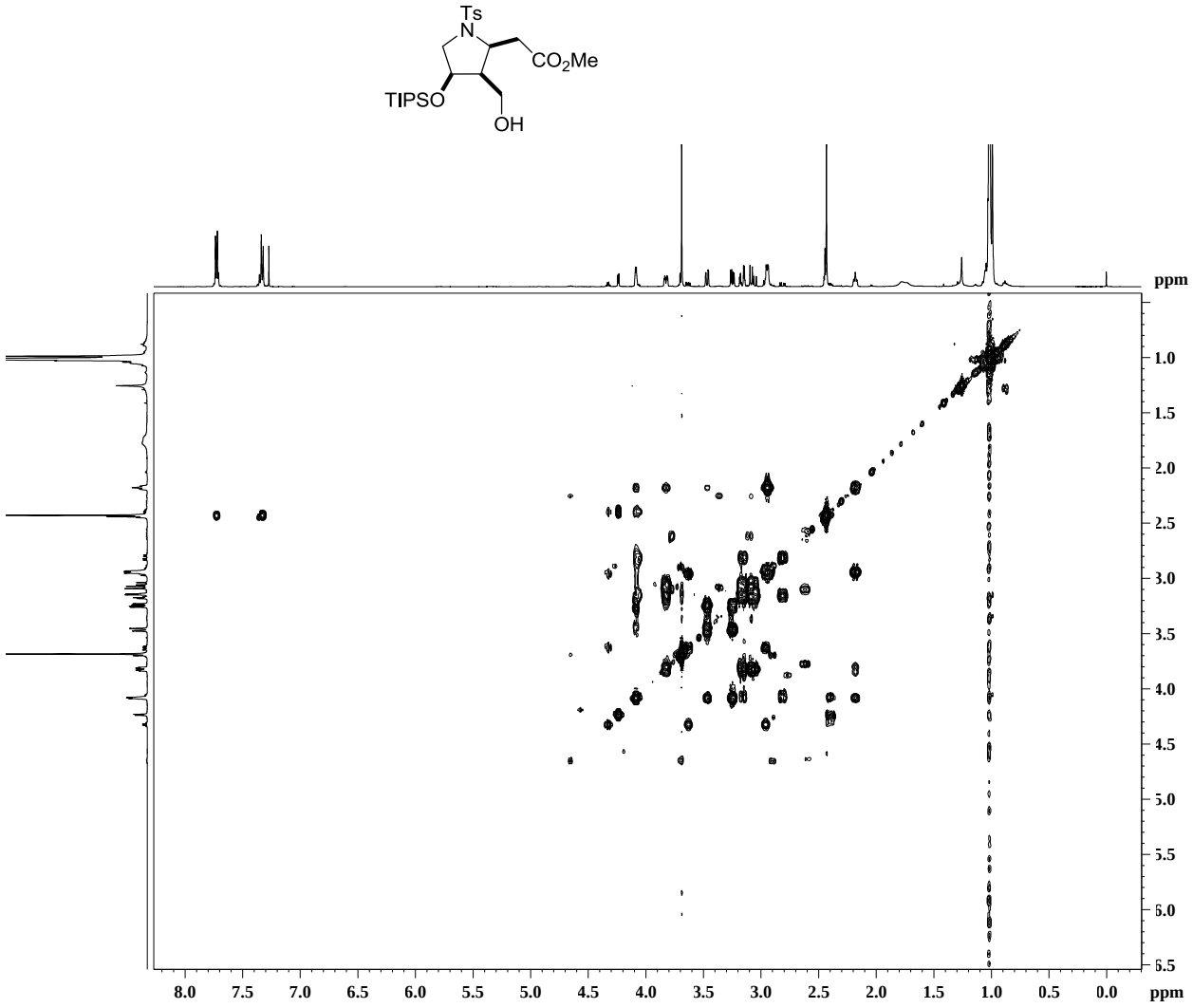
^{13}C NMR of compound **15** ($CDCl_3$, 75 MHz, 300 K)



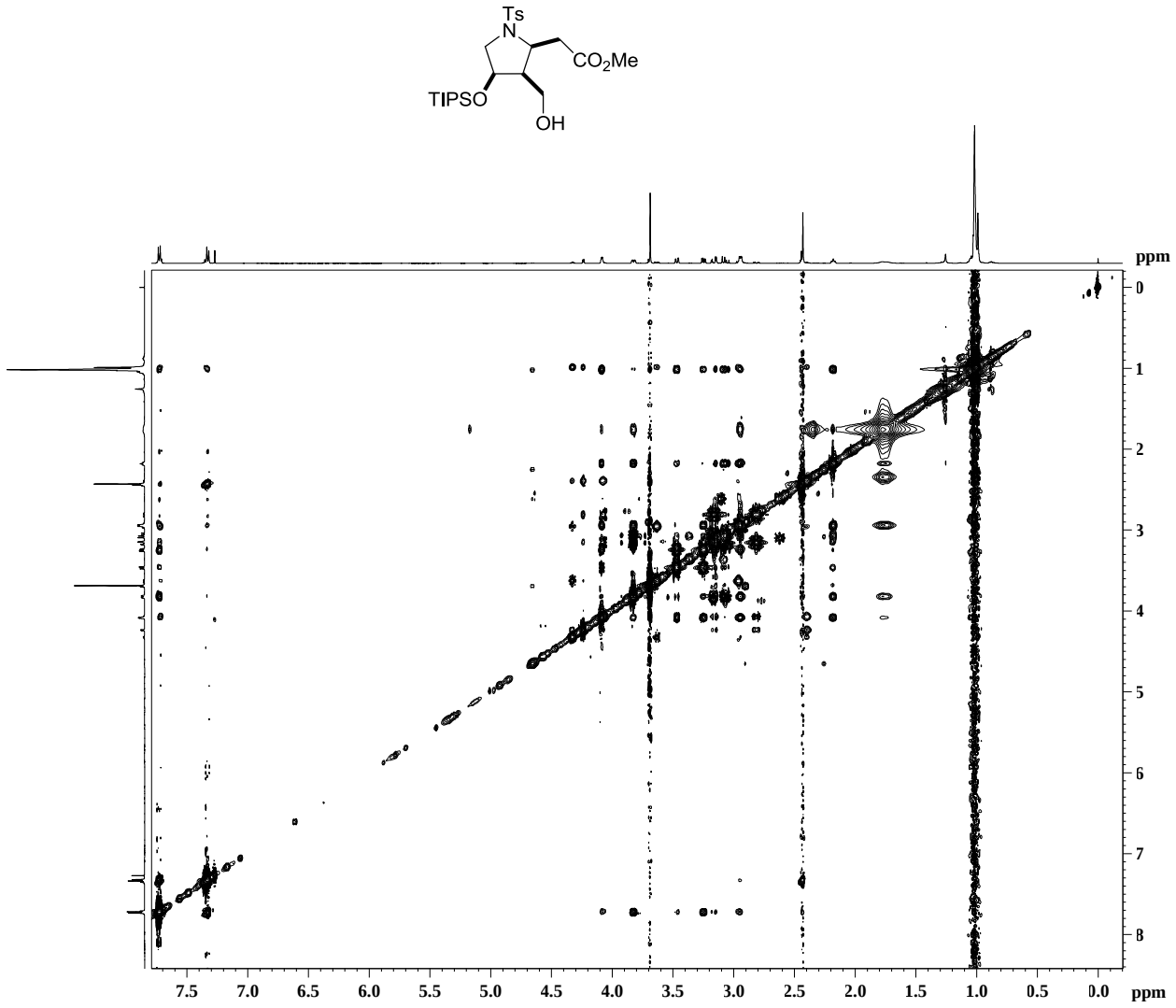
^{1}H NMR of compound **14** ($CDCl_3$, 300 MHz, 300 K)



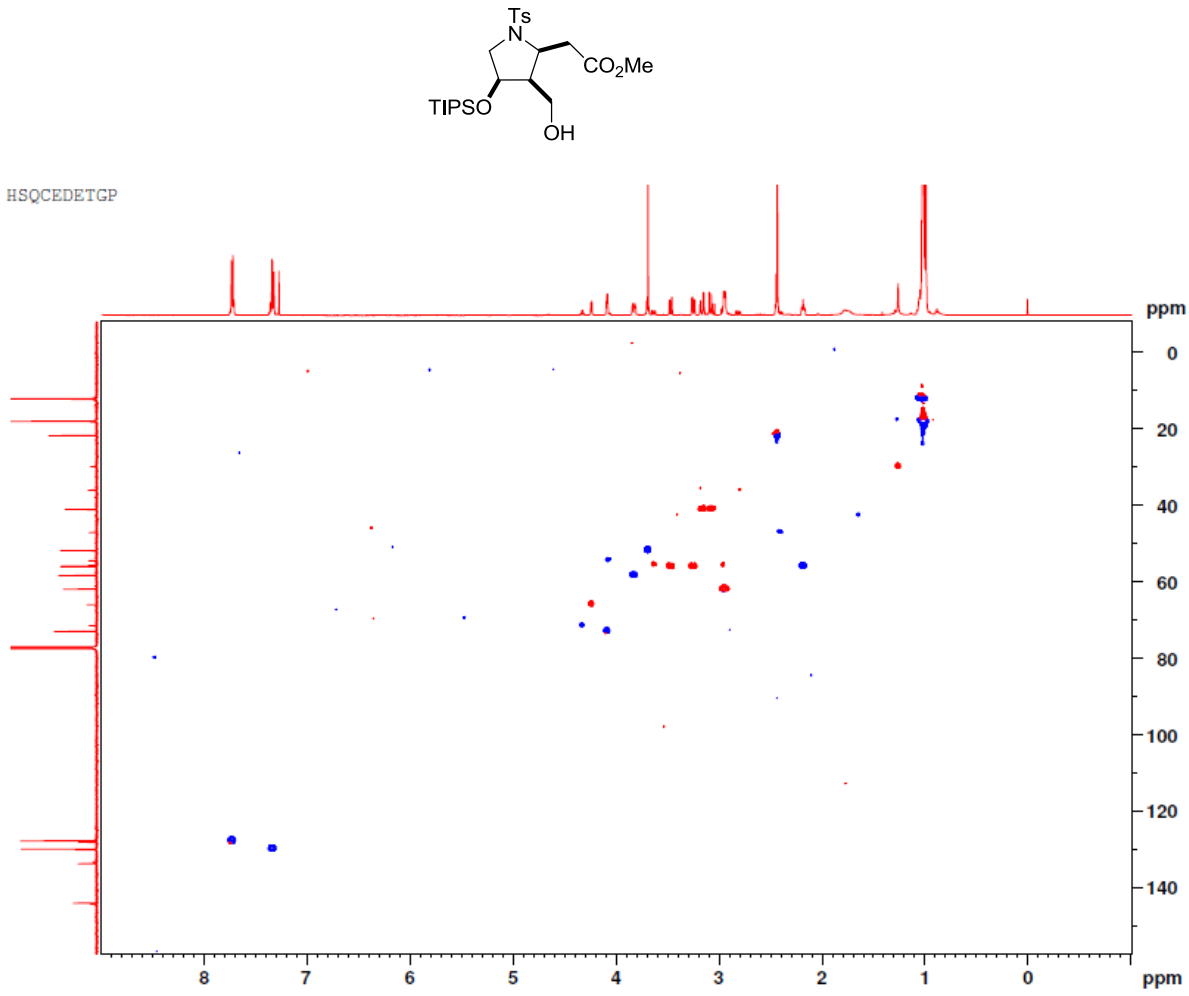
^{13}C NMR of compound **14** ($CDCl_3$, 75 MHz, 300 K)



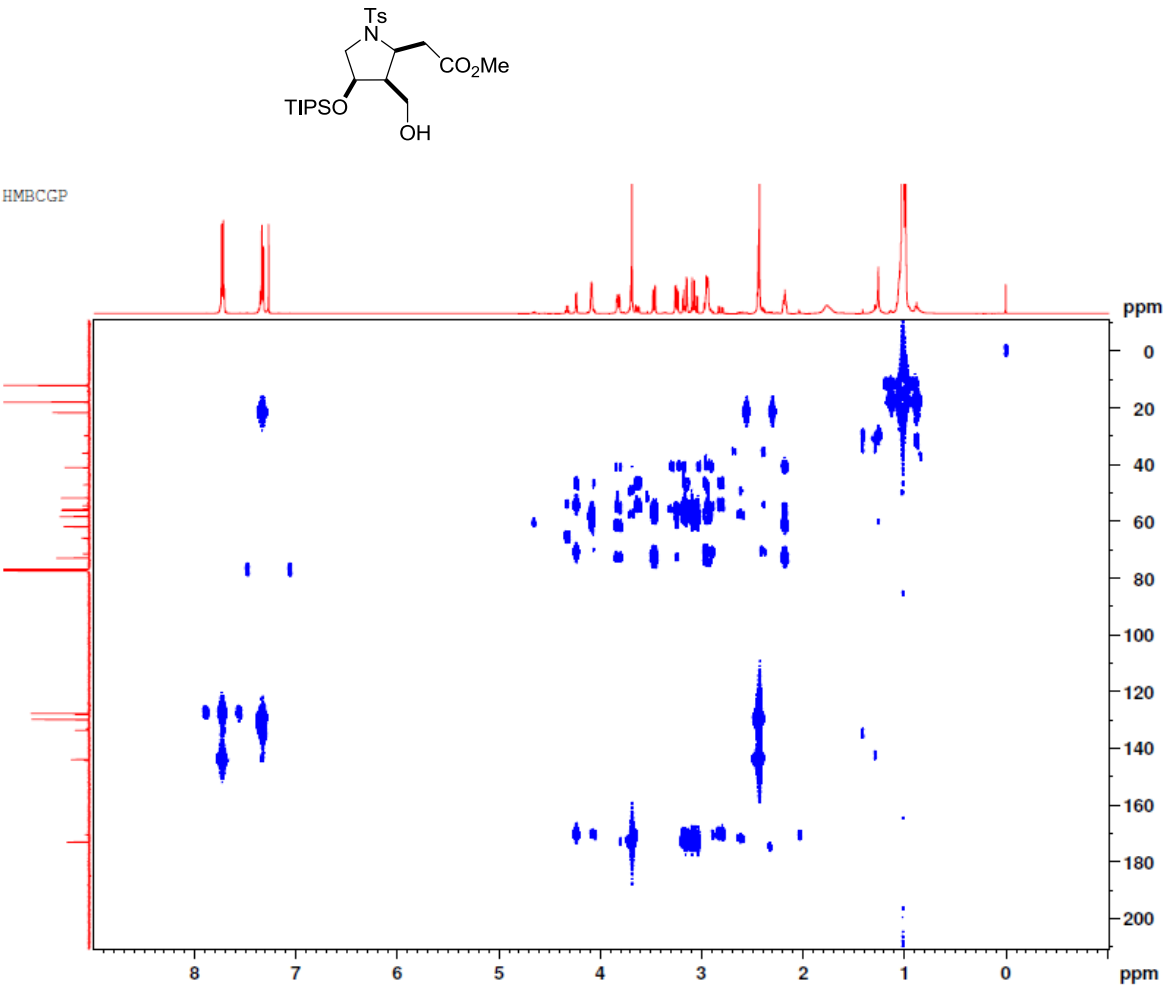
2D-COSY of compound **14** ($CDCl_3$, 500 MHz, 300K)



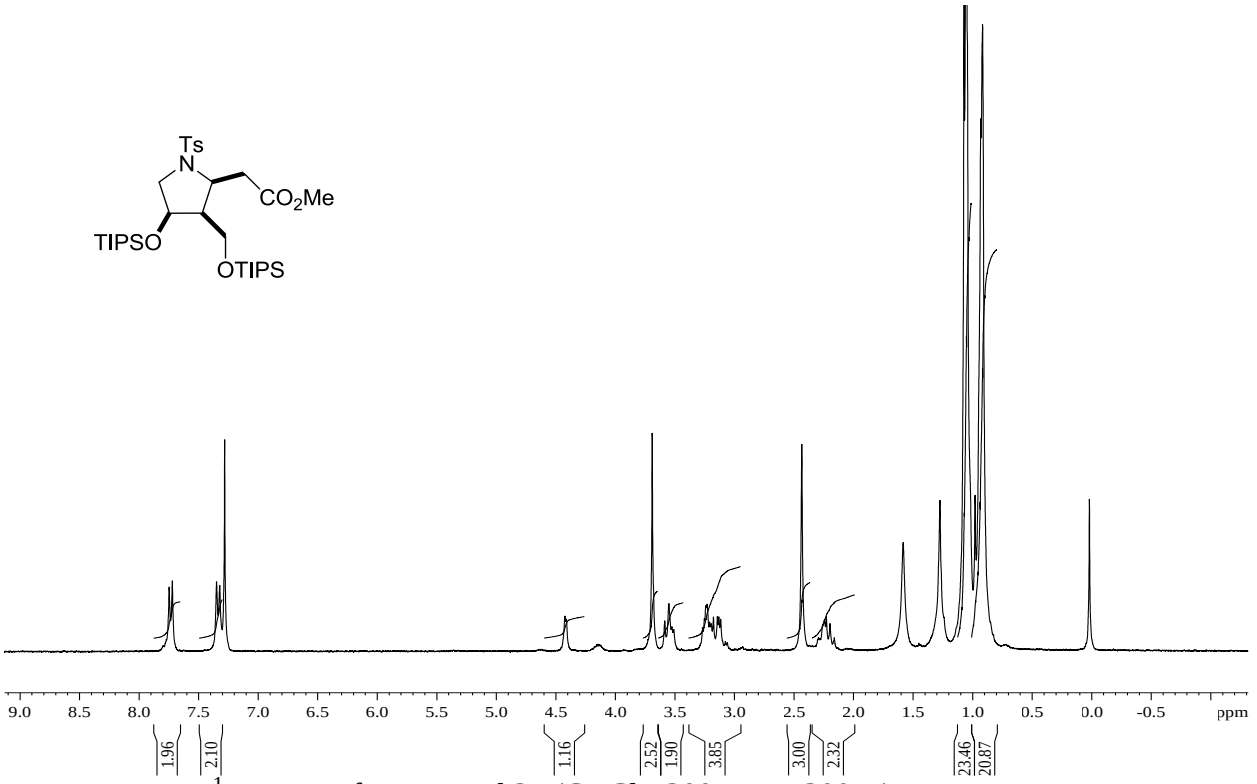
2D-NOESY of compound **14** ($CDCl_3$, 500 MHz, 300K)



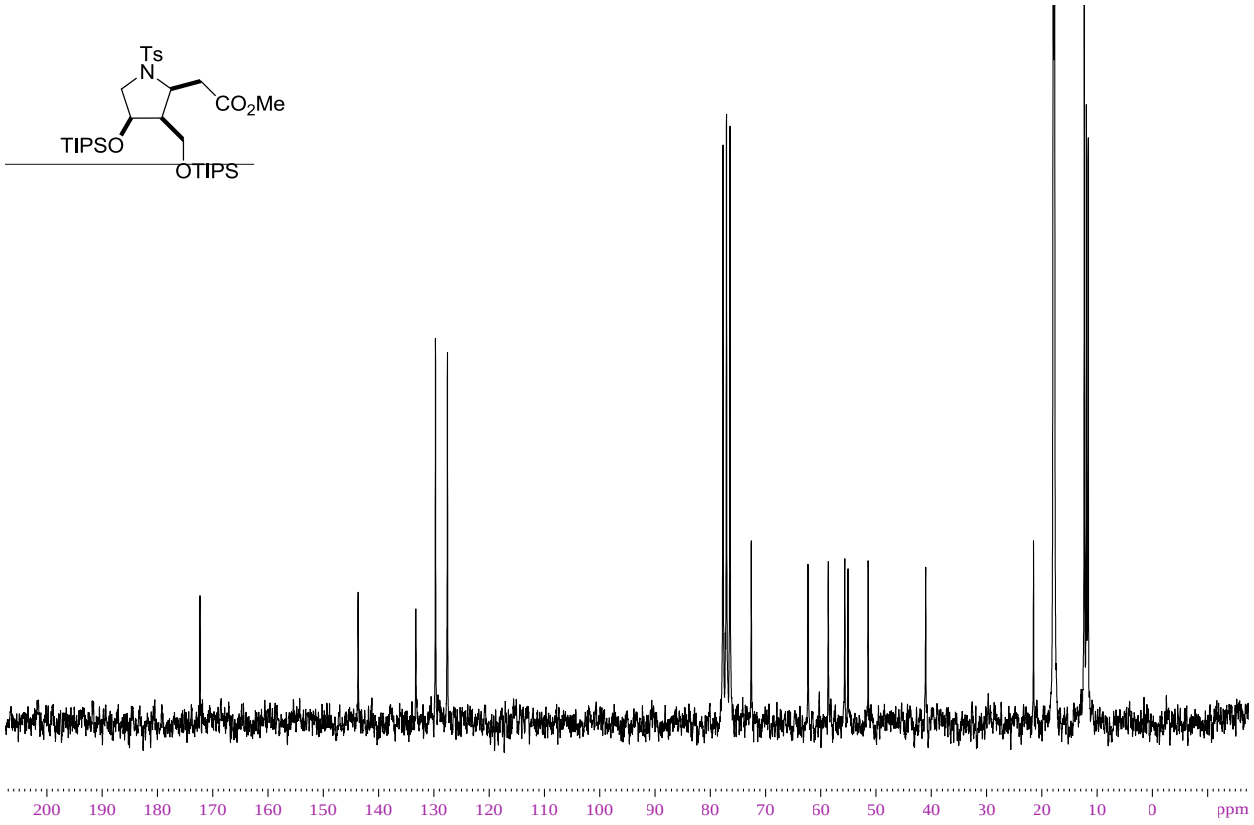
HSQC of compound **14** ($CDCl_3$, 500 MHz, 300K)



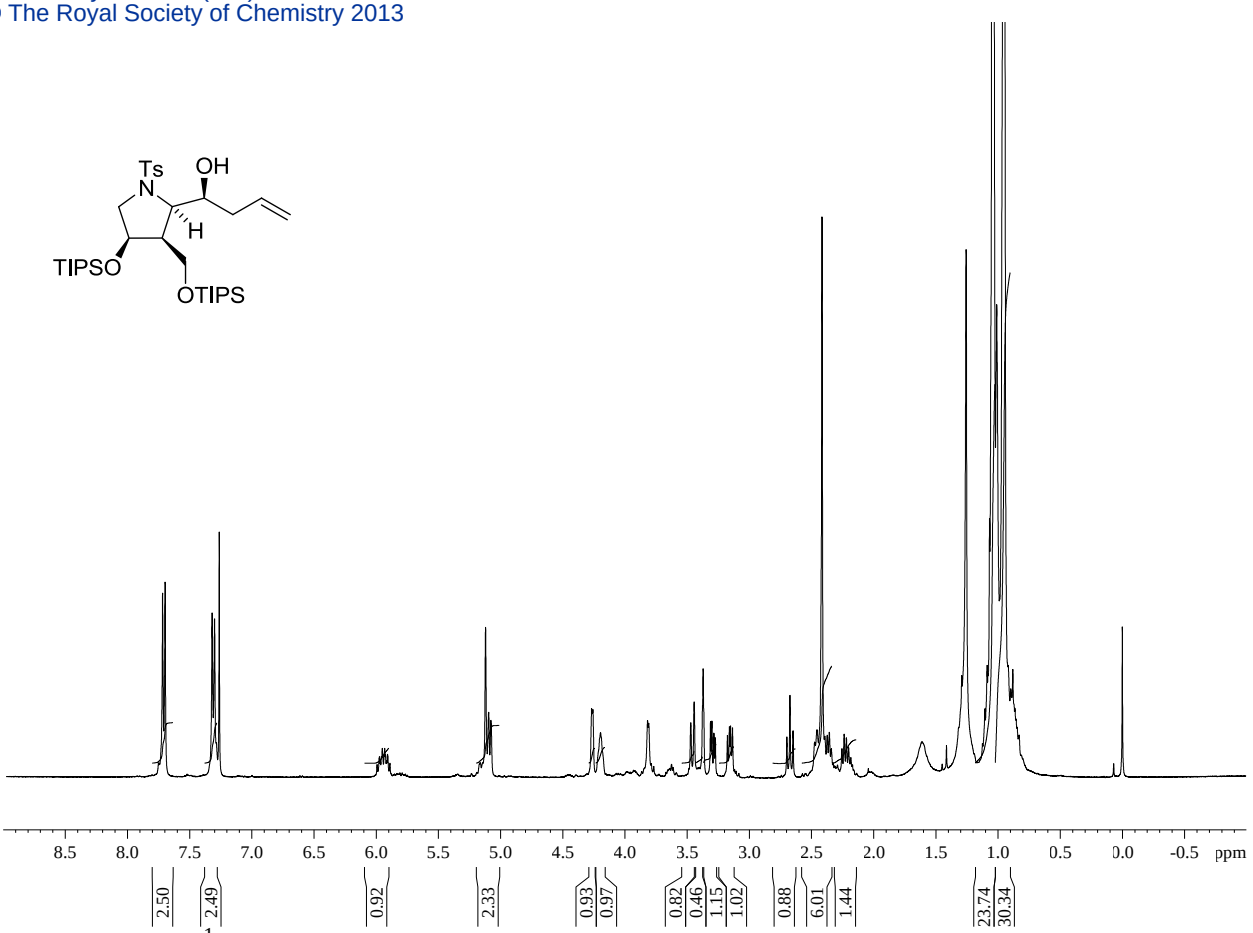
HMBC of compound **14** ($CDCl_3$, 500 MHz, 300K)



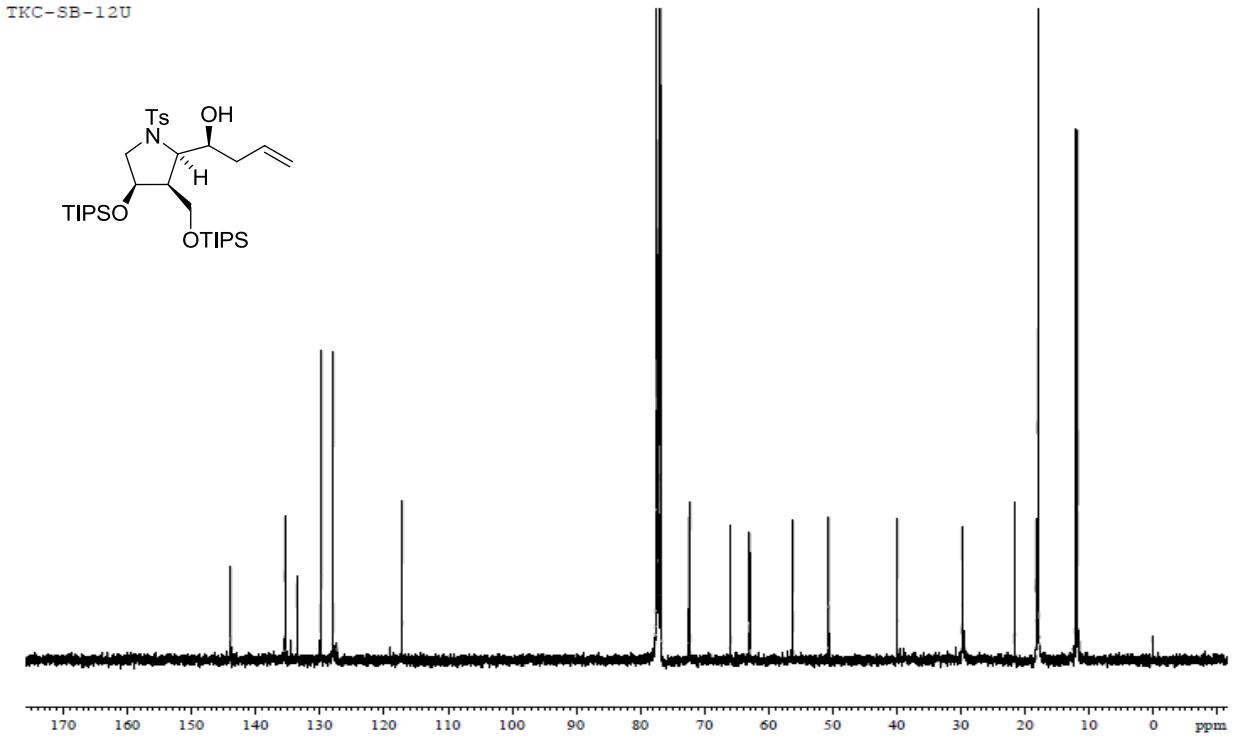
^{1}H NMR of compound **21** ($CDCl_3$, 300 MHz, 300 K)



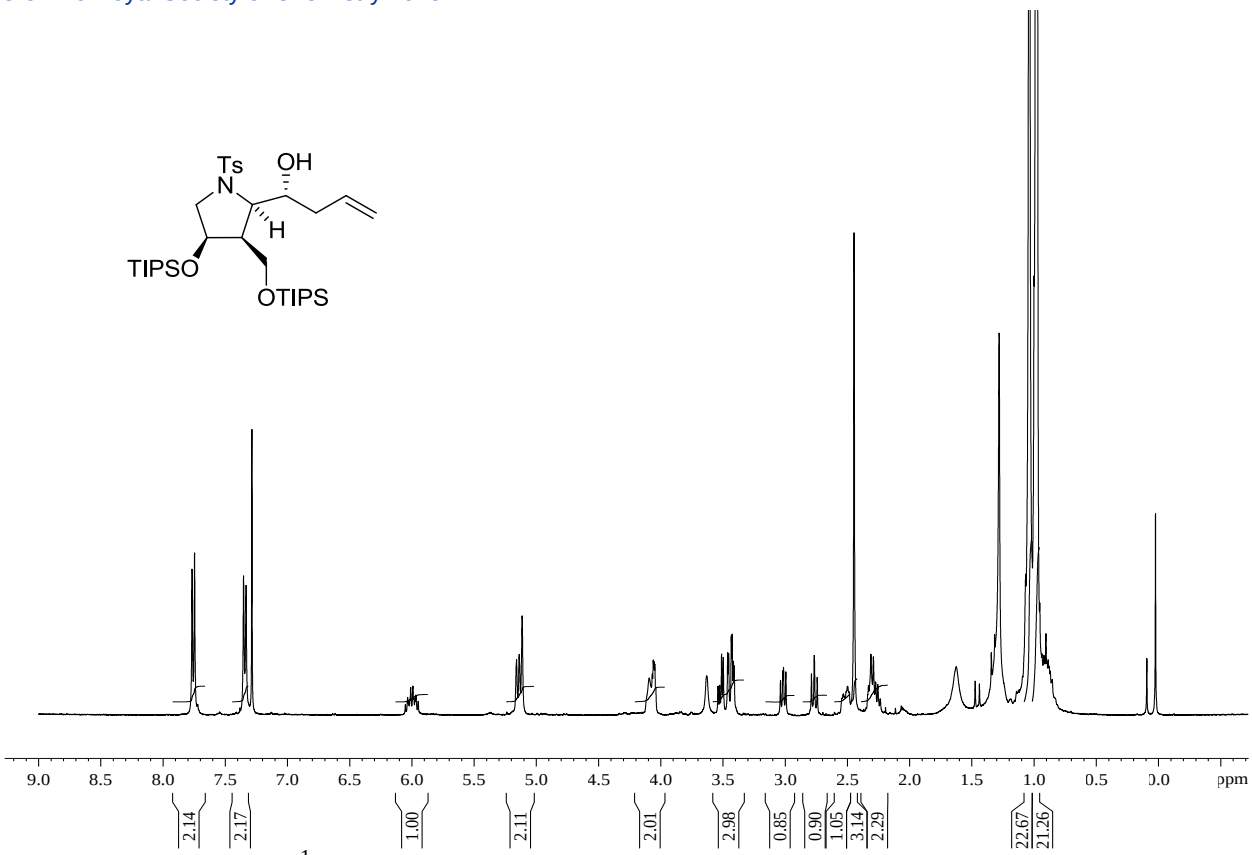
^{13}C NMR of compound **21** ($CDCl_3$, 75 MHz, 300 K)



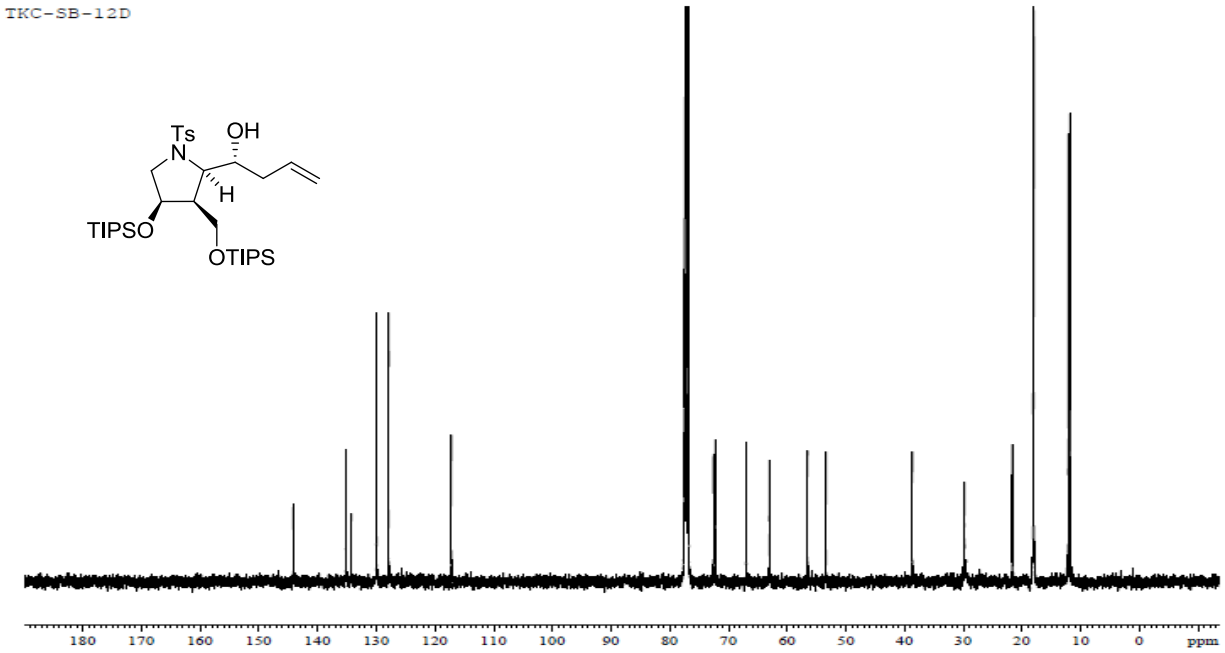
^{1}H NMR of compound **13b** ($CDCl_3$, 400 MHz, 300 K)



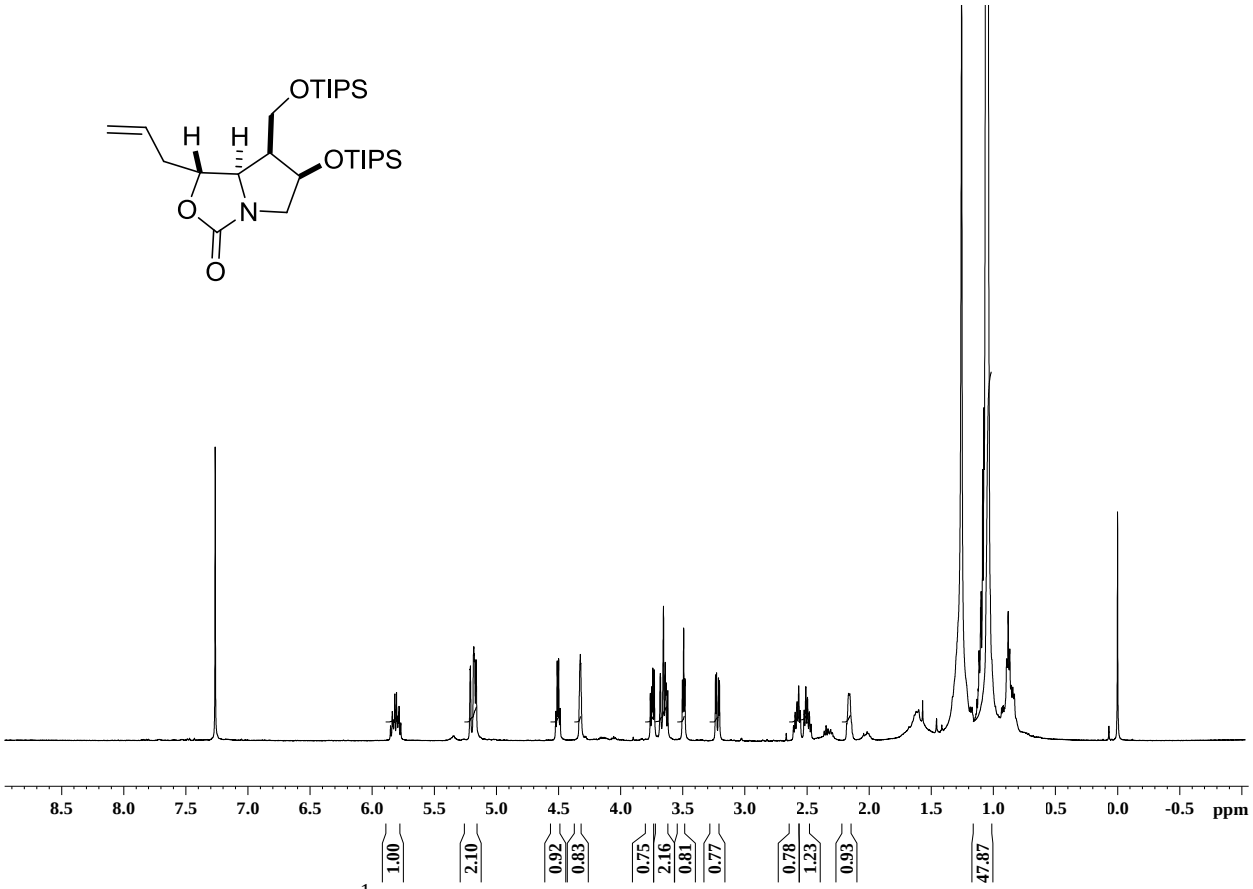
^{13}C NMR of compound **13b** ($CDCl_3$, 100 MHz, 300 K)



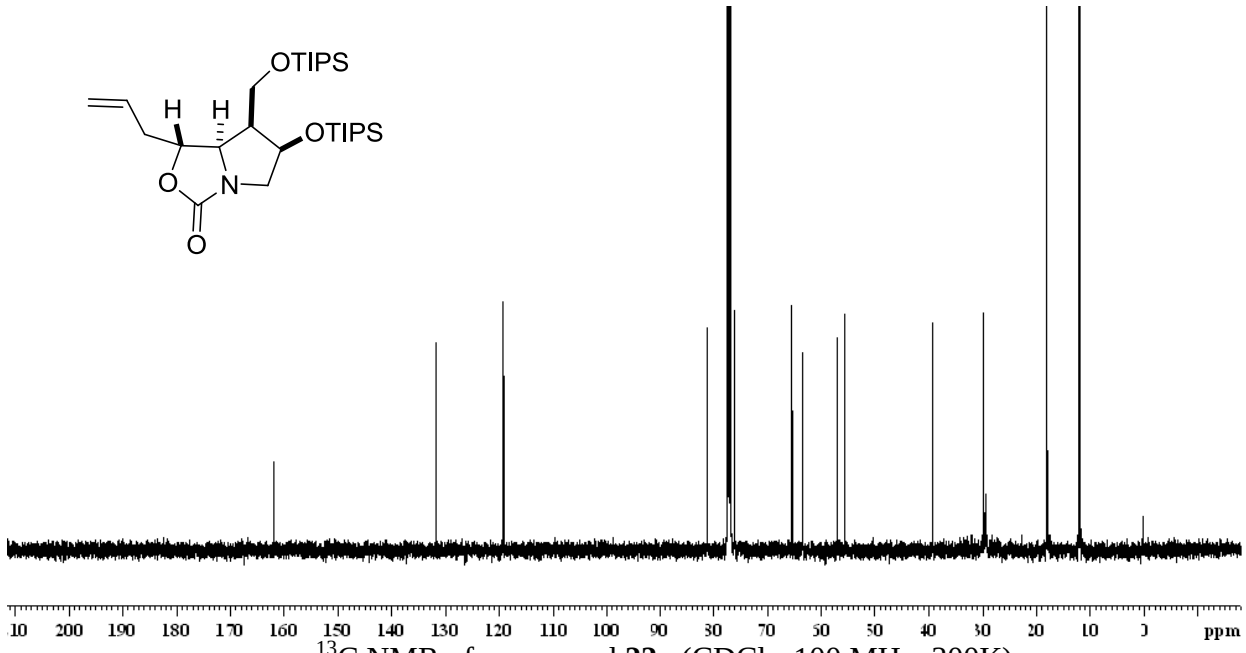
^{1}H NMR of compound **13a** ($CDCl_3$, 400 MHz, 300 K)



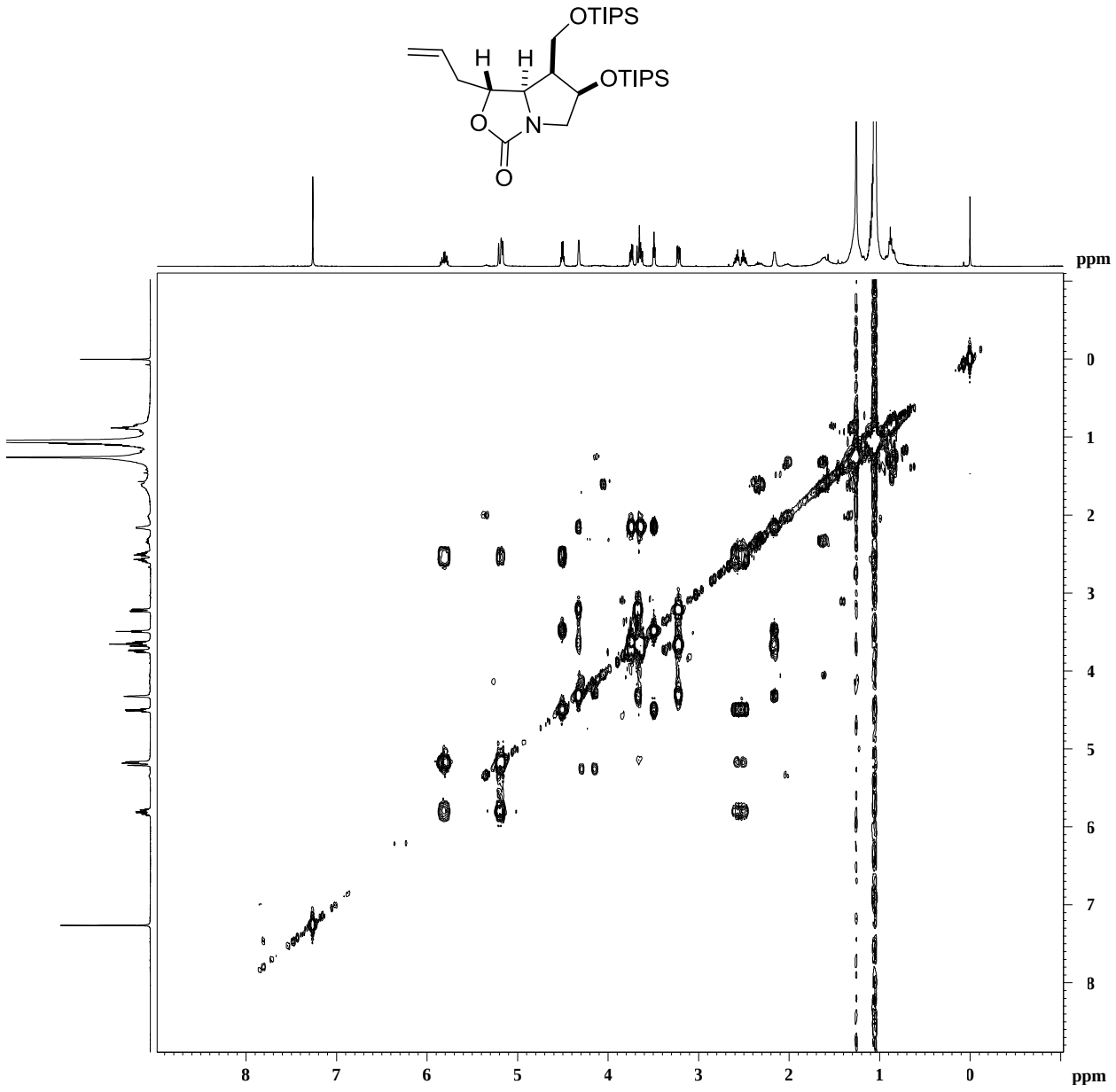
^{13}C NMR of compound **13a** ($CDCl_3$, 100 MHz, 300 K)



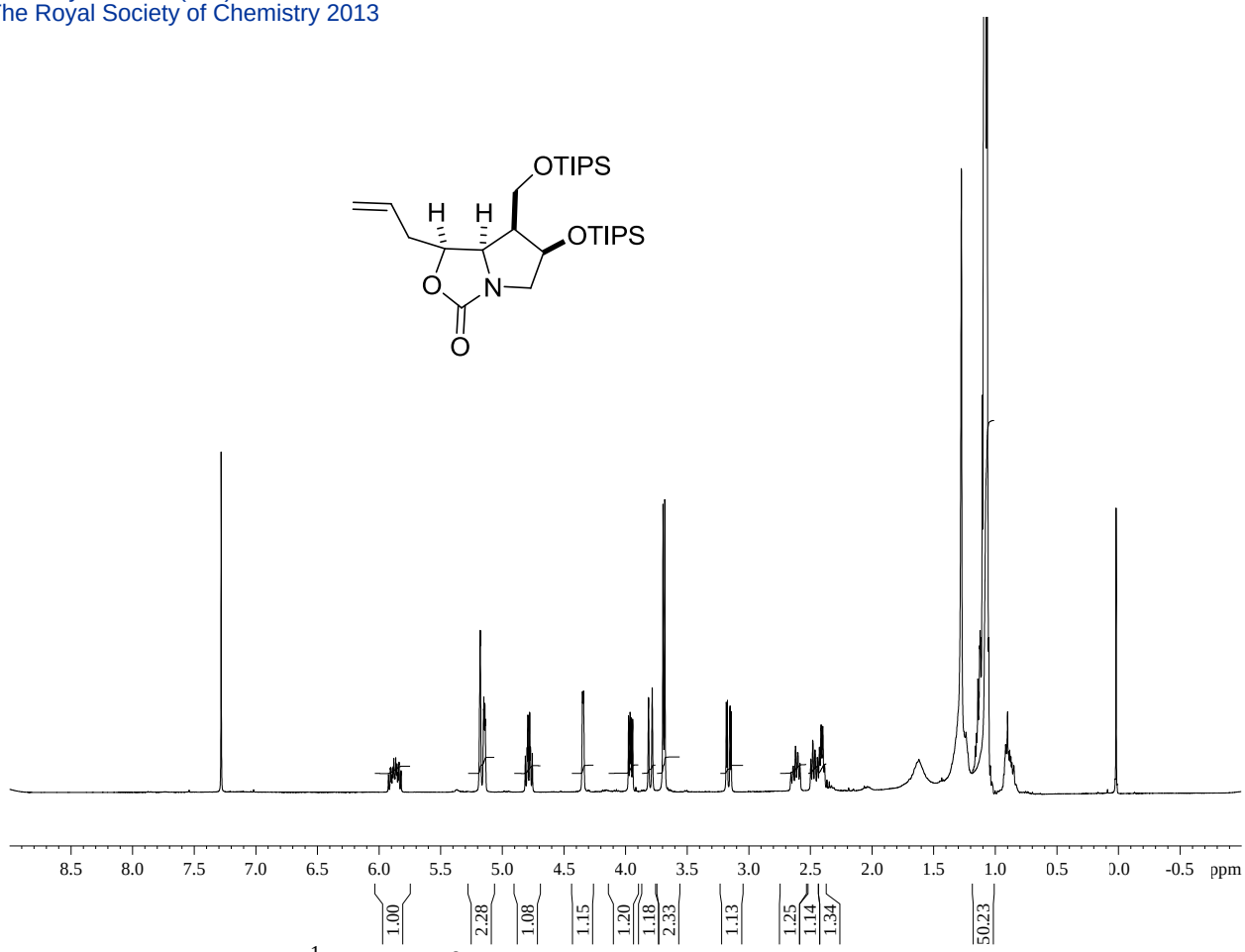
^{1}H NMR of compound **22a** ($CDCl_3$, 400 MHz, 300K)



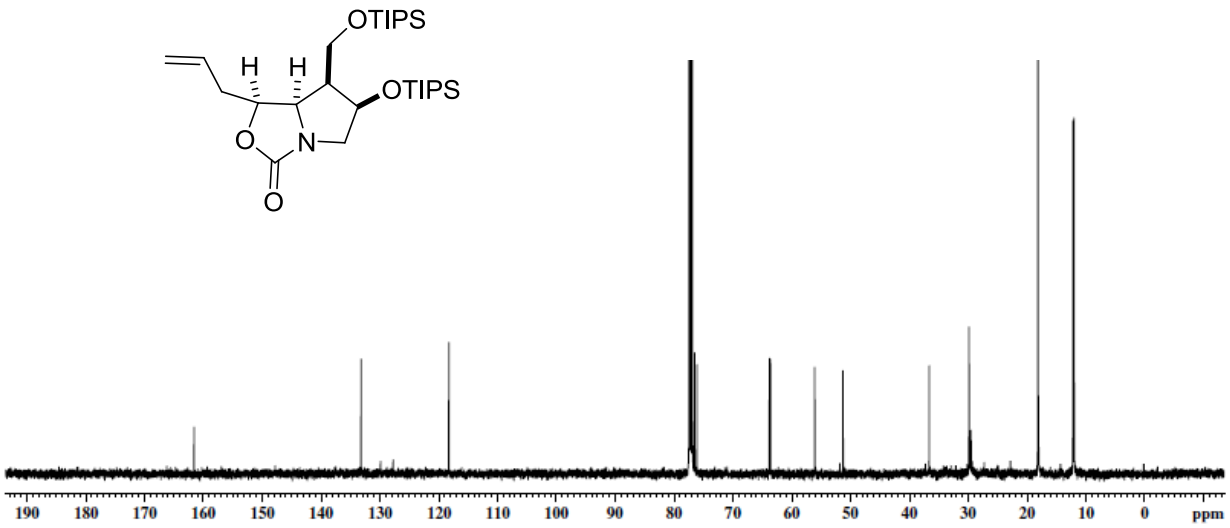
^{13}C NMR of compound **22a** ($CDCl_3$, 100 MHz, 300K)



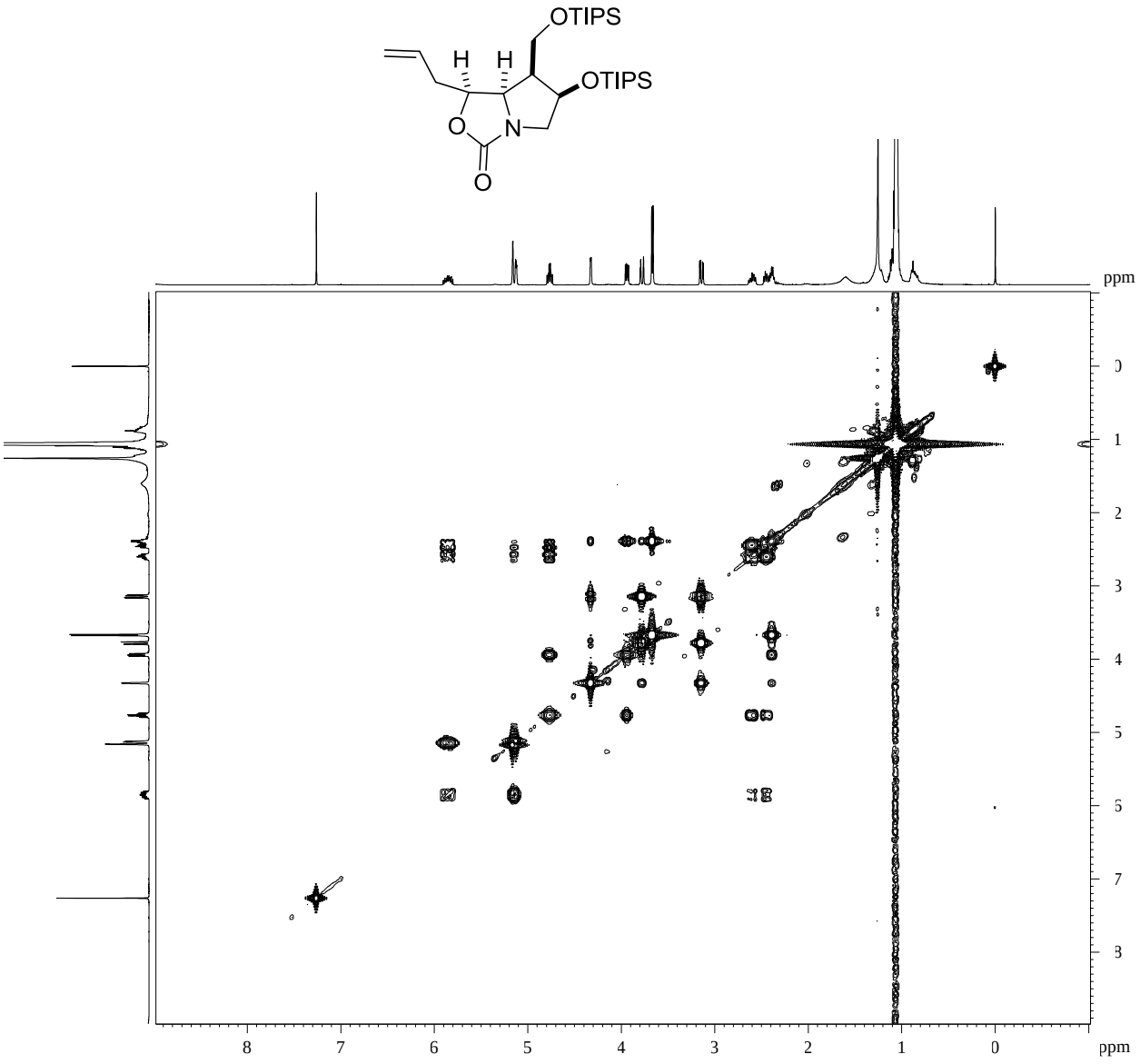
2D-COSY of compound **22a** ($CDCl_3$, 300K)



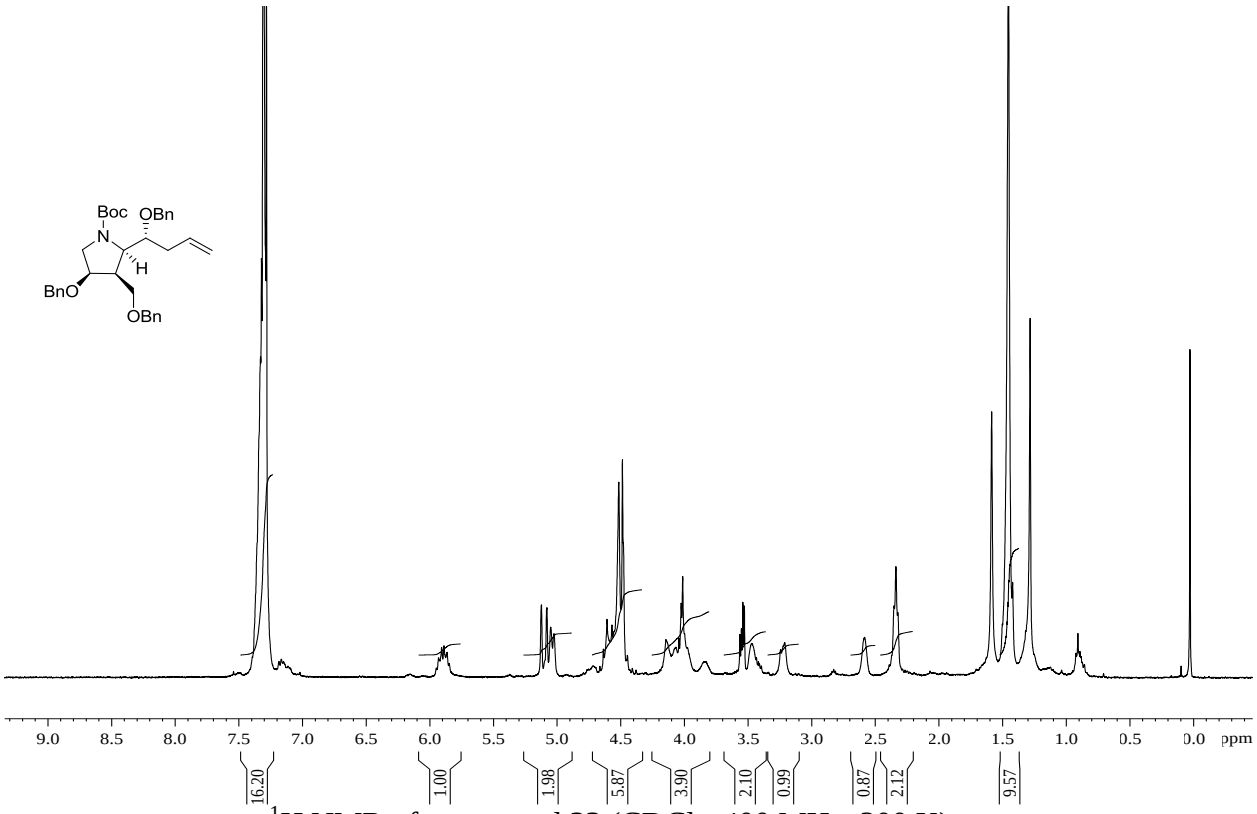
^{1}H NMR of compound **22b** ($CDCl_3$, 400 MHz, 300K)



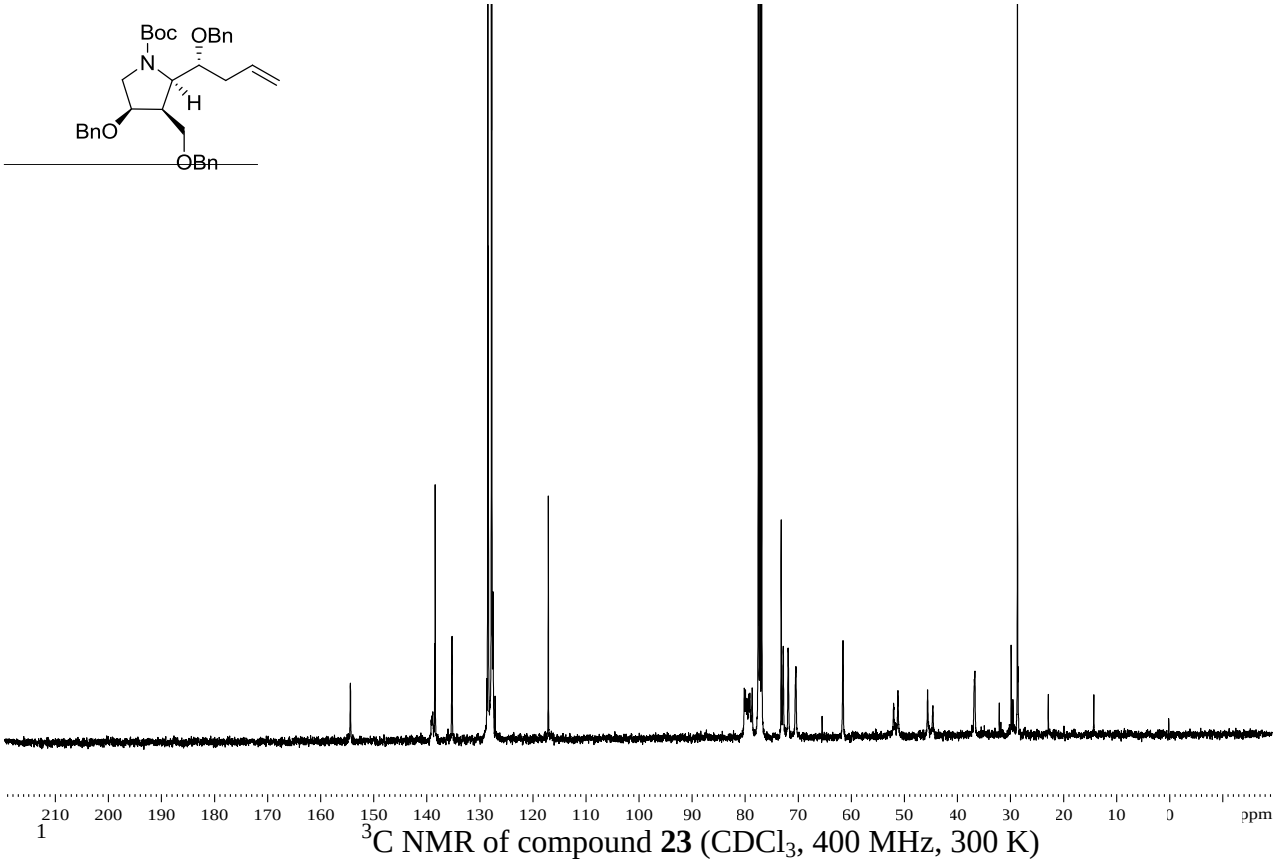
^{13}C NMR of compound **22b** ($CDCl_3$, 100 MHz, 300K)



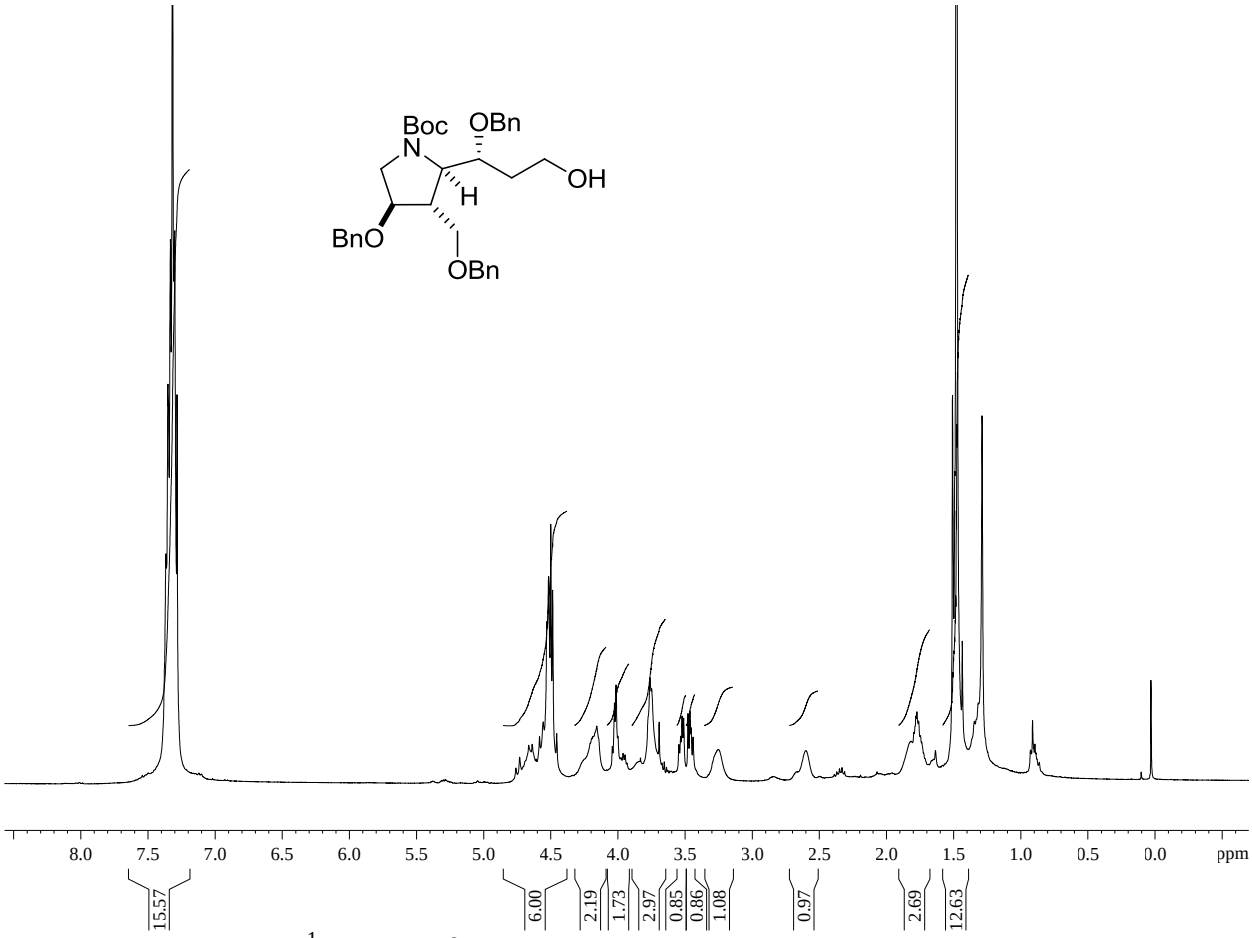
2D-COSY of compound **22b** ($CDCl_3$, 300K)



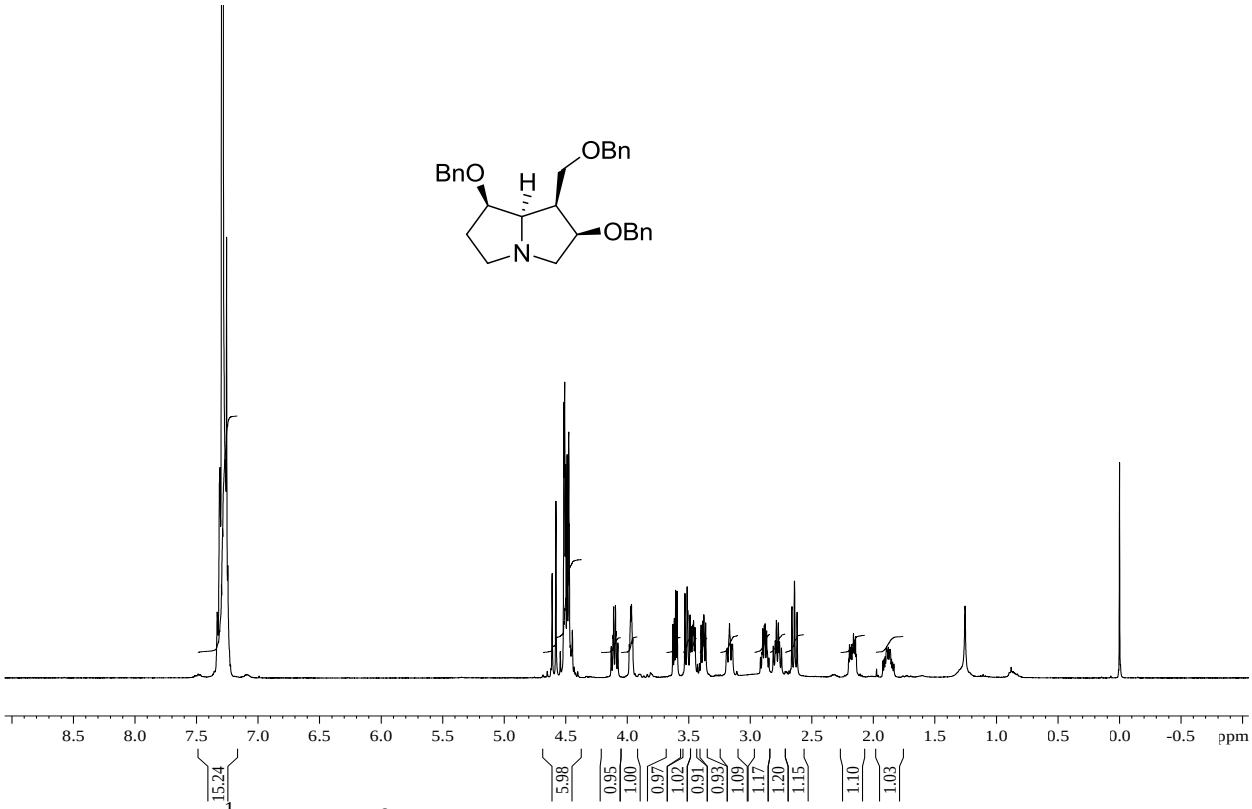
^{1}H NMR of compound **23** ($CDCl_3$, 400 MHz, 300 K)



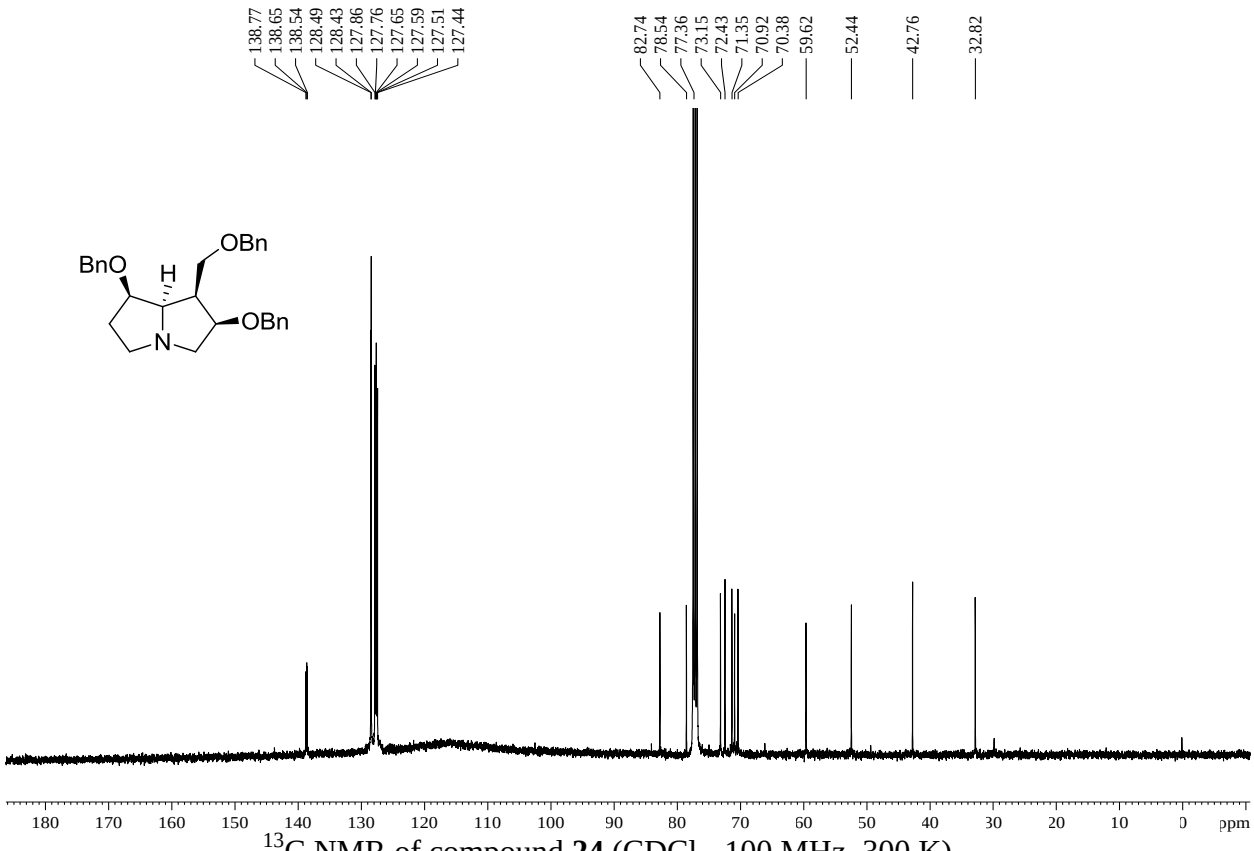
^{13}C NMR of compound **23** ($CDCl_3$, 400 MHz, 300 K)



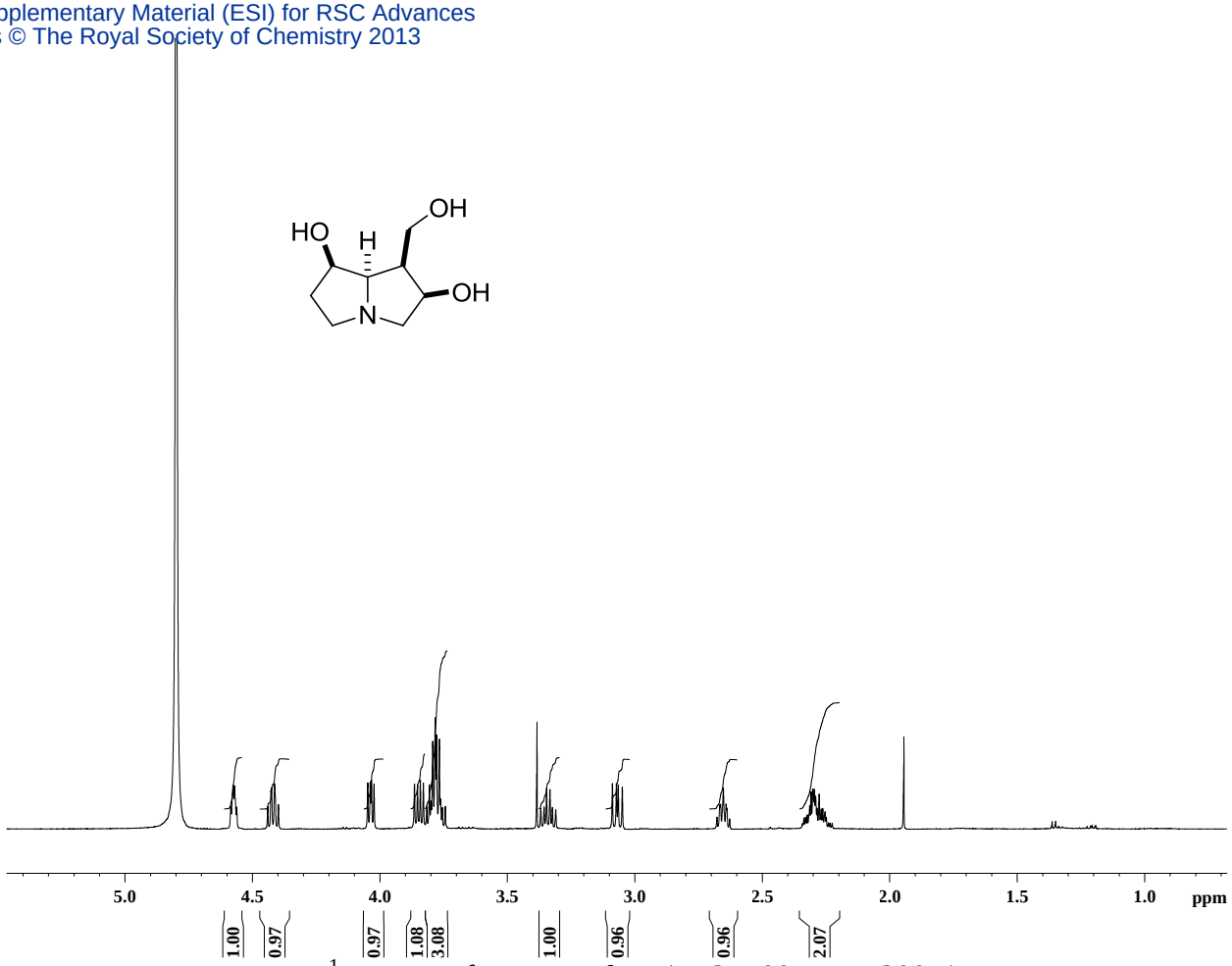
^{1}H NMR of compound **12** ($CDCl_3$, 400 MHz, 300K)



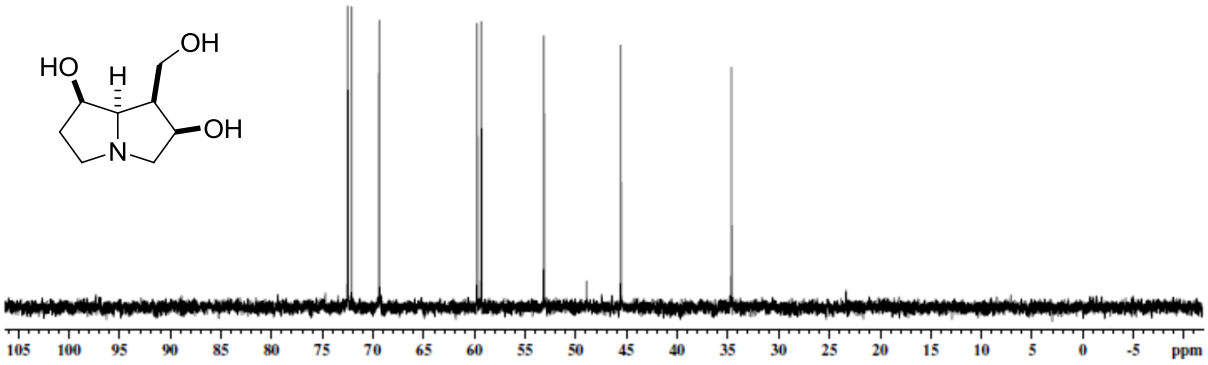
^{1}H NMR of compound **24** ($CDCl_3$, 400 MHz, 300 K)



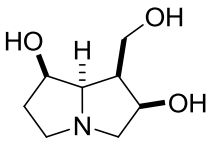
^{13}C NMR of compound **24** ($CDCl_3$, 100 MHz, 300 K)

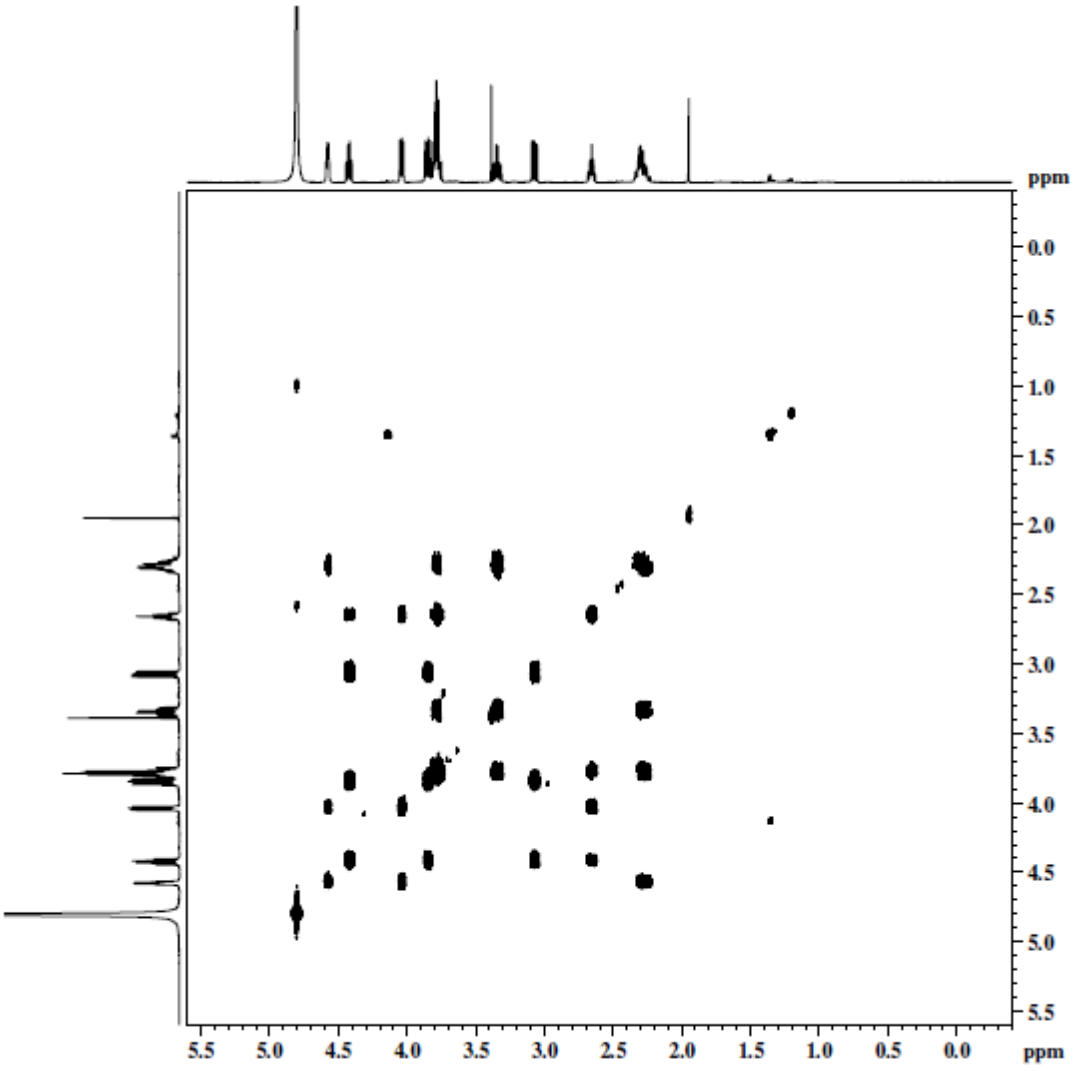


^{1}H NMR of compound **11** (D_2O, 500 MHz, 300K)

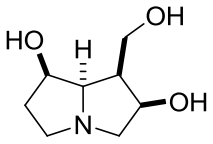


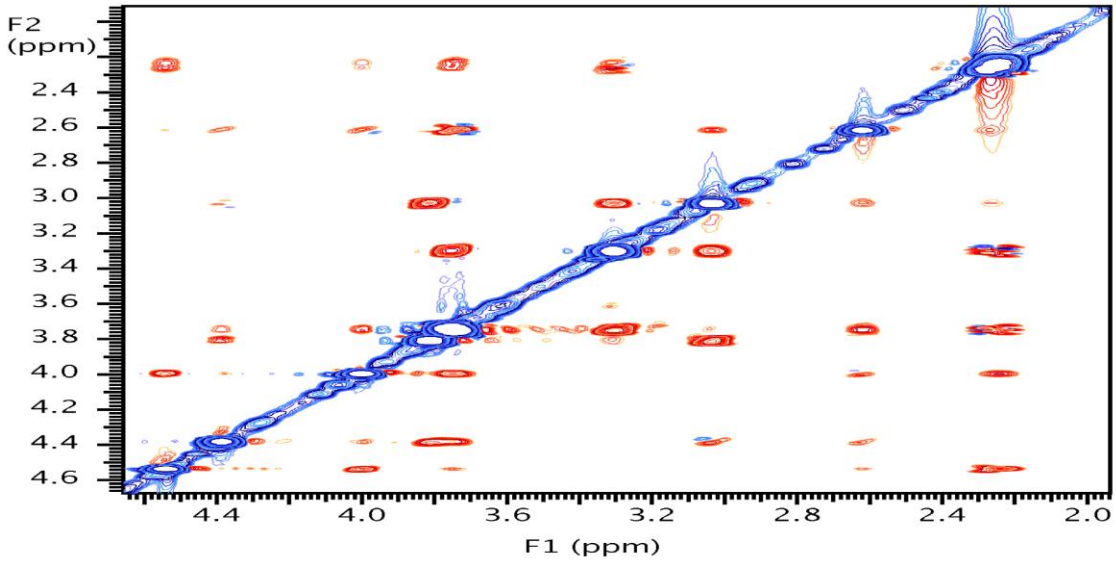
^{13}C NMR of compound **11** (D_2O, 125 MHz, 300K)





2D-COSY of compound **11** (D_2O, 500 MHz, 300K)





2D-NOESY of compound **11** (D_2O, 500 MHz, 300K)