Electronic Supplementary Material (ESI) for ChemComm.


# Supplementary Information

# A concise [C+NC+CC] coupling-enabled synthesis of kaitocephalin

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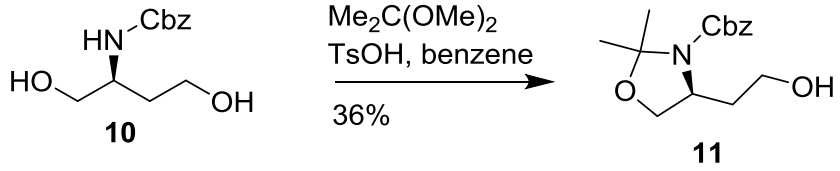
**Contents**

## 1. General experimental considerations.

All moisture sensitive reactions were performed in flame dried glassware under an inert, dry atmosphere of argon (Ar). Air sensitive liquids were transferred via syringe or cannula through rubber septa. Reagent grade solvents were used for extraction and flash chromatography. Anhydrous solvents were prepared as follows: THF was distilled from Na/benzophenone under Ar; dichloromethane ($CH_2Cl_2$ or DCM) was distilled from $CaH_2$ under Ar. Triethylamine (TEA) was distilled from $CaH_2$ under Ar. All other reagents and solvents were purchased from commercial sources and used directly without further purification. The progress of reactions was monitored by analytical thin-layer chromatography (TLC, silica gel F-254 plates). TLC plates were visualized first with UV illumination (254 nm) followed by charring using either ninhydrin stain (0.3% ninhydrin (w/v) in 97:3 EtOH/AcOH) or a modification of Hanessian's stain (10 g ammonium molybdate ($(NH_4)_6Mo_7O_{24}\bullet 4H_2O$) and 5 g cerium sulfate ($Ce(SO_4)_2$) in 1 L 10% aq. $H_2SO_4$). Flash column chromatography was performed on flash grade (230-400 mesh) silica gel. The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. High performance liquid chromatography (HPLC) was carried out using an X-Bridge C18 (3x250 mm) column for analytical separations and an X-Bridge prep C18 (19x150 mm) column for semi-preparative separations. Melting points are uncorrected. Optical rotations were recorded at room temperature at the sodium D line (589 nm). $^1$H-NMR spectra were recorded at 600 MHz and are reported in parts per million (ppm) on the δ scale relative to tetramethylsilane (TMS) as an internal standard (δ 0.00). $^{13}$C-NMR spectra were recorded at 150.8 MHz and are reported in parts per million (ppm) on the δ scale relative to $CDCl_3$ as an internal standard (δ 77.00). Unless indicated otherwise, NMR spectra were acquired at ambient temperature. High resolution mass spectrometry (HRMS) was performed with ESI and MALDI using either α-cyano-4-hydroxycinnamic acid or 3,5-dimethoxy-4-hydroxycinnamic acid matrices.

## II. Synthetic procedures for key compounds

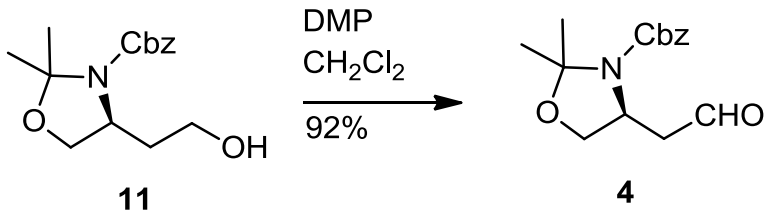
The *N*-Cbz-protected (*S*)-2-amino-1,4-butanediol **10** was provided by Vertex Pharmaceuticals, It was prepared from aspartic acid in 4 steps in 24% overall yield following previously reported methods.[1]




**Alcohol 11:** 2,2-Dimethoxypropane (300 mL) and p-toluenesulfonic acid monohydrate ( 1.3 g, 7.5 mmol) were added to a stirred solution of diol **10** (60.0 g, 251 mmol) in benzene (900 mL). After stirring for 1.5 h at 100 °C with the constant removal of methanol formed during the reaction by distillation, the reaction mixture was concentrated and the black residue was purified by silica gel flash chromatography eluting with petroleum ether to afford **11** (25 g, 36%) as a colorless oil. $R_f$ 0.5 (7:3 $CHCl_3$/ EtOAc); $[\alpha]_D$ +10.0 (c 0.68, MeOH) lit[2] $[\alpha]_D$ +9.4 (c 0.66, MeOH). $^1$H NMR (600 MHz, DMSO-$d_6$, 45 °C) δ 7.38 – 7.32 (m, 3H), 7.32 – 7.26 (m, 1H), 5.07 (s, 2H), 4.30 (t, *J* = 5.0 Hz, 1H), 3.93 (t, *J* = 8.8 Hz, 1H), 3.89 (dd, *J* = 8.7, 5.7 Hz, 1H), 3.82 (d, *J* = 8.3 Hz, 1H), 3.46 – 3.36 (m, 2H), 1.88 – 1.74 (m, 1H), 1.66 – 1.56 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (150.8 MHz, $CDCl_3$, major rotamer) δ 151.9, 137.3, 128.8, 128.1, 127.7, 93.3, 67.2, 66.0, 58.6, 55.4, 36.6, 26.9, 23.3.[2]

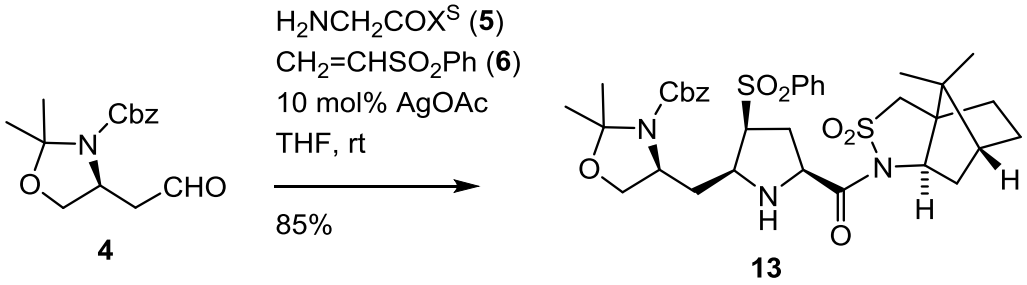
The spectroscopic data were consistent with those reported.

(1) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2000**, *66*, 206-215.
(2) Yonezawa,; Konn, A.; Shin, C. *Heterocycles.* **2004**, *63*, 2735



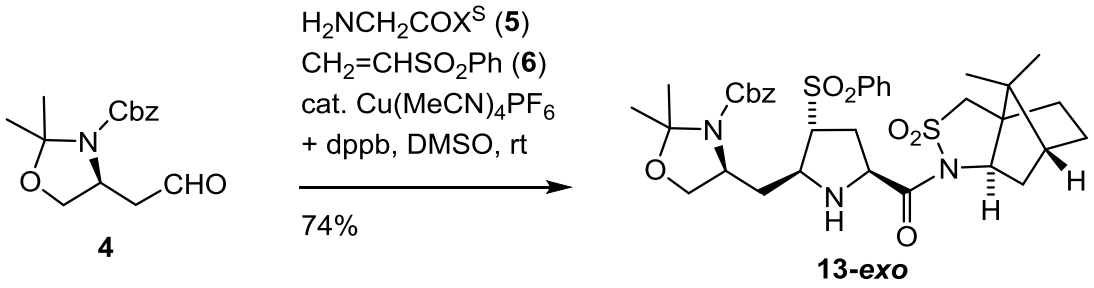

**11** **4**

**Aldehyde 4:** To a stirred mixture of alcohol **11** (15.0 g, 53.7 mmol) in $CH_2Cl_2$ (120 mL) at room temperature was added Dess-Martin periodinane (29.6 g, 68.7 mmol). The reaction mixture was stirred at room temperature for 3 h, when TLC analysis showed the reaction to be complete. The reaction mixture was partitioned between $CH_2Cl_2$ (250 mL) and a solution of $Na_2S_2O_3$ (8 g) in saturated aq $NaHCO_3$ (250 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 200 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (3:1 hexanes/EtOAc) gave the aldehyde **4** as a colorless oil (13.7 g, 92 %). $R_f$ 0.48 (7:3 hexanes/EtOAc); $[\alpha]_D$ -28.8 (c 1.82, $CHCl_3$); $^1$H NMR (600 MHz, DMSO-$d_6$, 45 °C) δ 9.60 (s, 1H), 7.39 – 7.25 (m, 5H), 5.06 (s, 2H), 4.34 – 4.26 (m, 1H), 4.02 (dd, $J$ = 8.1, 1.0 Hz 1H), 3.72 (d, $J$ = 9.4 Hz, 1H), 2.81 – 2.63 (m, 2H), 1.48 (s, 3H), 1.40 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$, mixture of rotomers) δ 200.2, 200.1, 152.6, 151.7, 136.3, 136.1, 128.5, 128.1, 128.0, 127.9, 94.2, 93.7, 67.9, 67.5, 67.2, 66.7, 53.1, 52.0, 47.9, 47.0, 27.4, 26.5, 24.5, 23.0; HRMS (MALDI) $m/z$ calcd for $C_{15}H_{19}NO_4$ $[M+H]^+$ 278.1314; found, 278.1322.

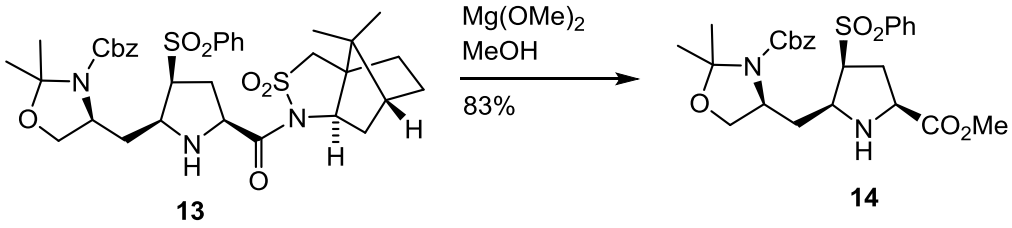



**4** **13**

**Cycloadduct 13:** To a stirred solution of phenyl vinyl sulfone **6** (6.8 g, 41 mmol) and (1*S*)-Glycyl sultam **5** (8.9 g, 32 mmol) in THF (75 mL) were added **4** (7.5 g, 27 mmol) and AgOAc (0.45 g, 3.2 mmol). The mixture was stirred at room temperature for 4 h in the dark. When the TLC analysis confirmed the complete consumption of aldehyde **4**, sat'd aqueous $NH_4Cl$ (200 mL) was added, the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellowish oil. Flash column chromatography of the residue eluting 3:1 hexanes/acetone yielded **13** as a white solid (16 g, 85%). $R_f$ 0.58 (1:1 acetone/hexanes); mp 104-107 °C; $[\alpha]_D$ -75.6 (c 0.85, $CHCl_3$); $^1$H NMR (600 MHz, DMSO-$d_6$, 90 °C) δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 7.4 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.41 – 7.15 (m, 5H), 5.09 (d, *J* = 12.9 Hz, 1H), 5.03 (d, *J* = 12.9 Hz, 1H), 4.18 (t, *J* = 8.3 Hz, 1H), 4.02 – 3.92 (m, 3H), 3.92 – 3.77 (m, 2H), 3.71 (d, *J* = 11.9 Hz, 1H), 3.61 (d, *J* = 11.9 Hz, 1H), 3.53 – 3.46 (m, 1H), 2.42 – 2.29 (m, 2H), 2.05 – 1.73 (m, 8H), 1.48 (s, 3H), 1.46 – 1.43 (m, 1H), 1.41 (s, 3H), 1.29 (t, *J* = 10.7 Hz, 1H), 0.97 (s, 3H), 0.93 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$, 90 °C) δ 171.5, 152.4, 140.6, 137.3, 134.0, 129.8, 128.8, 128.1, 128.0, 127.9, 93.5, 68.8, 66.5, 66.0, 65.0, 60.3, 59.7, 57.6, 52.9, 49.1, 47.8, 44.9, 38.2, 35.6, 33.8, 32.4, 27.3, 26.3, 24.4, 20.8, 19.9, 15.4; HRMS (MALDI) *m*/*z* calcd for $C_{35}H_{46}N_3O_8S_2$ $[M+H]^+$ 700.2726; found, 700.2729. HPLC: C18 (3 × 250 mm) XBridge column, gradient 50% to 80% $CH_3CN$ in $H_2O$ over 30 min, flow rate 0.5 mL/min, UV detection at 215 nm, $t_R$: 10.2 min (minor isomer) and 11.0 min (**13**) in a ratio of 1:9.

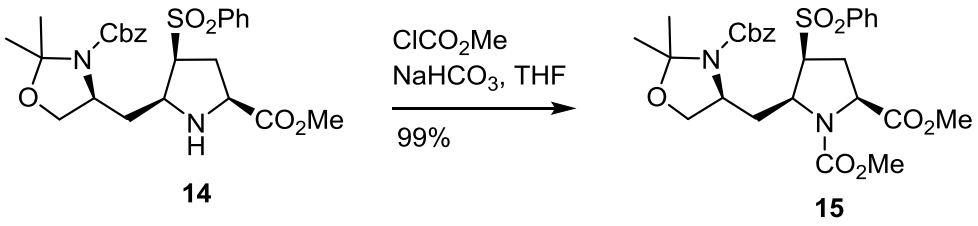



***Exo*-diastereomer 13:** A mixture of $Cu(MeCN)_4PF_6$ (33 mg, 90 μmol) and dppb (43.0 mg, 100 μmol) in DMSO (2 mL) was stirred at room temperature for 1 h in the dark. To this solution phenyl vinyl sulfone **6** (0.30 g, 1.8 mmol), (1*S*)-glycyl sultam **5** (0.30 g, 1.1 mmol) and **4** (0.2 g, 0.9 mmol) were added. The reaction mixture was stirred at room temperature for 10 h and when the TLC analysis confirmed the reaction was complete, sat'd aqueous $NH_4Cl$ (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a yellowish oil. Flash column chromatography of the residue eluting 3:1 hexanes/acetone yielded ***exo*-13** as a white solid (0.5 g, 74%). $R_f$ 0.58 (1:1 acetone/hexanes); mp 117-119 °C; $^1$H NMR (600 MHz, DMSO-$d_6$, 90 °C) δ 7.79 – 7.70 m, 3H), 7.69 – 7.60 (m, 2H), 7.58 (s, 2H), 7.50 – 7.44 (m, 3H), 7.44 – 7.32 (m, 3H), 5.00 (brs, 2H), 4.14 – 3.86 (m, 4H), 3.82 – 3.77 (m, 1H), 3.73 (d, $J$ = 14.2 Hz, 1H), 3.57 (d, $J$ = 14.2 Hz, 1H), 3.24 – 3.14 (m, 1H), 2.69 – 2.51 (m, 1H), 2.39 – 2.19 (m, 1H), 1.98 – 1.63 (m, 9H), 1.60 (s, 3H), 1.53 (s, 3H), 1.40 (t, $J$ = 9.8 Hz, 1H), 1.24 (t, $J$ = 9.8 Hz, 1H), 0.92 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$, 90 °C) δ 170.7, 163.5, 151.0, 137.5, 135.7, 135.1, 133.7, 129.1, 128.6, 127.8, 126.9, 94.1, 74.5, 67.5, 67.2, 63.9, 59.2, 56.6, 51.9, 48.2, 46.9, 43.9, 37.3, 32.7, 31.5, 26.1, 25.4, 23.3, 19.0, 15.4; HRMS (MALDI) *m*/*z* calcd for $C_{35}H_{46}N_3O_8S_2$ $[M+H]^+$ 700.2726; found, 700.2759. HPLC: C18 (3 × 250 mm) XBridge column, gradient 50% to 80% $CH_3CN$ in $H_2O$ over 30 min, flow rate 0.5 mL/min, UV detection at 215 nm, $t_R$: 10.5 min (**13-*exo***).



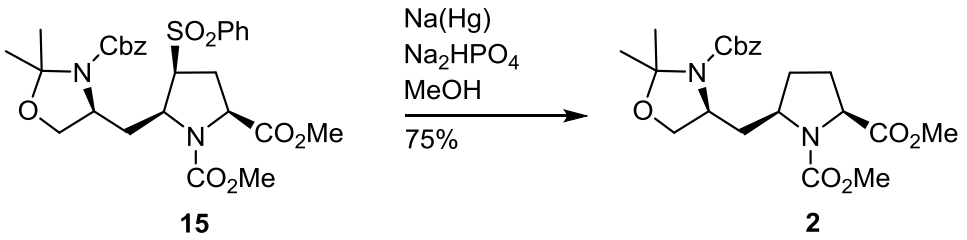

13 14

**Pyrrolidine ester 14**: To a solution of **13** (15.0 g, 21.4 mmol) in dry MeOH (100 mL) was added 1.5 M $Mg(OMe)_2$/MeOH (36 mL, 54 mmol) at 0 °C. The resulting yellow solution was stirred for 2 h at 0 °C to room temperature, when TLC analysis confirmed the complete consumption of the starting material. The reaction mixture was concentrated and partitioned between the $CH_2Cl_2$ (6 × 250 mL) and sat. $NH_4Cl$ (250 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give the crude product as yellowish oil. Purification by flash chromatography eluting with 7:3 hexanes/EtOAc, provided the methyl ester **14** as white foam (8.6 g, 83%). mp 111-114 °C; $R_f$ 0.4 (1:1 hexanes/EtOAc), $^1$H NMR (600 MHz, DMSO-$d_6$, 90 °C) δ 7.83 (d, $J$ = 7.8 Hz, 2H), 7.74 – 7.67 (m, 1H), 7.65 – 7.58 (m, 2H), 7.40 – 7.32 (m, 4H), 7.32 – 7.26 (m, 1H), 5.10 (d, $J$ = 12.5 Hz, 1H), 5.03 ($J$ = 12.5 Hz, 1H), 3.99 – 3.90 (m, 3H), 3.90 – 3.75 (m, 1H), 3.69 (t, $J$ = 8.2 Hz, 1H), 3.64 (s, 3H), 3.44 – 3.37 (m, 1H), 2.31 – 2.22 (m, 1H), 2.17 (td, $J$ = 8.2, 3.7 Hz, 2H), 1.88 – 1.79 (m, 1H), 1.47 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$, 90 °C) δ 173.3, 152.5, 140.8, 137.2, 134.0, 129.8, 128.8,128.2, 128.0, 127.9, 93.5, 68.8, 66.5, 65.9, 59.4, 58.6, 57.3, 52.1, 35.9, 31.5, 27.3, 24.4; HRMS (MALDI) $m/z$ calcd for $C_{26}H_{32}N_2O_7SNa$ $[M+Na]^+$ 539.1714; found, 539.1728. HPLC: C18 (3 × 250 mm) XBridge column, gradient 20% to 80% $CH_3CN$ in $H_2O$ over 30 min, flow rate 0.5 mL/min, UV detection at 215 nm, $t_R$: 19.5 min (**14**).




**14** **15**

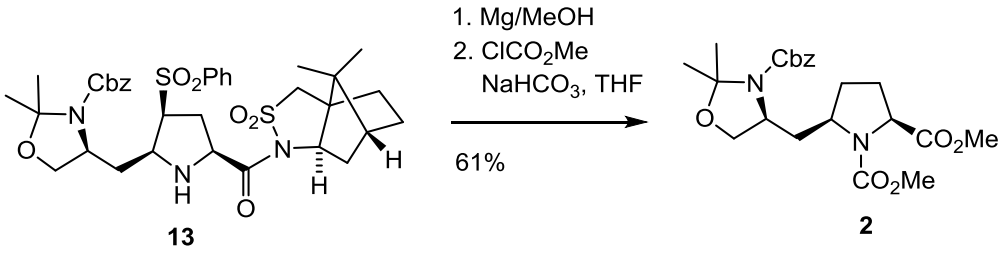
**Methyl carbamate 15:** To a solution of **14** (7.50 g, 14.5 mmol) in THF (50 mL) were added 1M $NaHCO_3$ (50 mL) and methyl chloroformate (2.75 g, 29.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h, when TLC analysis showed reaction is to be complete. The reaction mixture was partitioned between EtOAc (150 mL) and water (200 mL). The organic layer was separated and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography eluting with 2:1 hexanes/EtOAc to give the product as a white solid (8.1 g, 99%). mp 117-119 °C $^1$H NMR (600 MHz, DMSO-$d_6$, 75 °C) δ $^1$H NMR (600 MHz, dmso) δ 7.87 (d, $J$ = 7.2 Hz, 2H), 7.74 (t, $J$ = 7.5 Hz, 1H), 7.64 (t, $J$ = 7.2 Hz, 2H), 7.39 (d, $J$ = 7.6 Hz, 2H), 7.35 (t, $J$ = 7.1 Hz, 2H), 7.29 (t, $J$ = 6.8 Hz, 1H), 5.18 (d, $J$ = 13.2 Hz, 1H), 5.04 (d, $J$ = 12.3 Hz, 1H), 4.44 (t, $J$ = 8.5 Hz, 1H), 4.33 (t, $J$ = 9.1 Hz, 1H), 4.23 – 4.13 (m, 3H), 3.79 (dd, $J$ = 7.2, 1.0 Hz, 1H), 3.68 (s, 3H), 3.56 (s, 3H), 2.42 – 2.25 (m, 3H), 1.92- 1.83 (m, 1H), 1.47 (s, 3H), 1.40 (s, 3H).; $^{13}$C NMR (150 MHz, DMSO-$d_6$, 75 °C) δ 171.9, 155.2, 152.2, 139.9, 137.4, 134.5, 129.9, 128.7, 128.2, 128.0, 127.9, 93.0, 67.5, 66.5, 63.3, 58.53, 58.50, 56.9, 53.0, 52.5, 35.4, 29.7, 27.4, 24.2; HRMS (MALDI) $m/z$ calcd for $C_{28}H_{34}N_2O_9SNa$ $[M+Na]^+$ 597.1885; found, 597.1894.



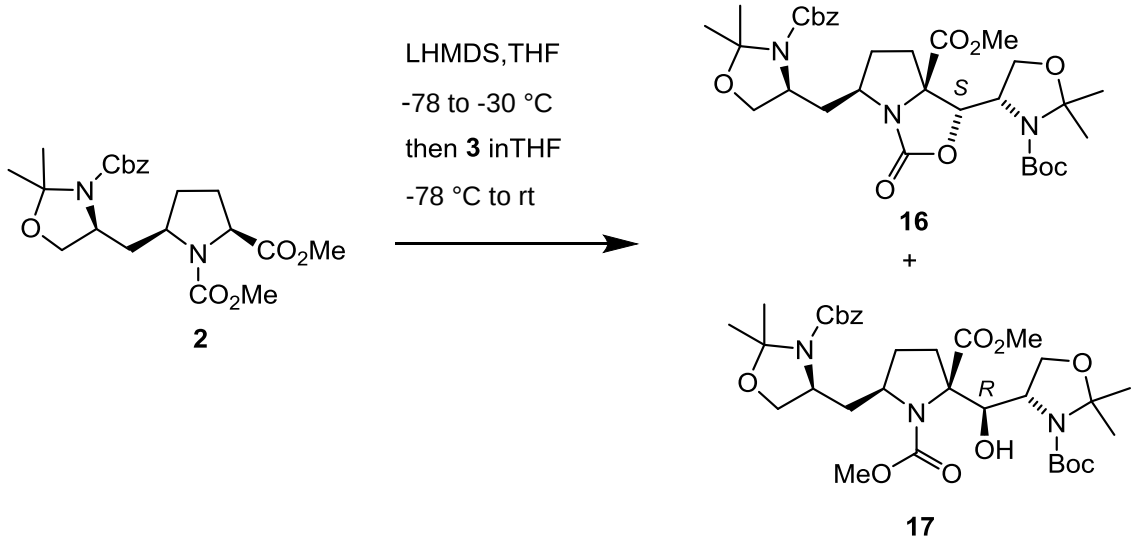

**15** **2**

**Desulfonated pyrrolidine 2:** A mixture of **15** (9.00 g, 15.7 mmol), Na(Hg) (10 g, 78 mmol) and $Na_2HPO_4$ (6.7 g, 47 mmol) in dry MeOH (100 mL) was stirred for 24 h at 0 °C to room temperature, when the TLC analysis showed reaction to be complete. The reaction mixture was concentrated and partitioned between $H_2O$ (200 mL) and $CH_2Cl_2$ (200 mL). The organic layer was washed with water (2 x 50 mL). The combined aqueous layers were extracted with $CH_2Cl_2$ (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with 5:1 EtOAc/hexanes to afford **2** as white foam (5.1 g, 75%). $R_f$ 0.3 (2:1 hexanes/EtOAc); $[\alpha]_D$ +53.8 (c 1.0, $CHCl_3$); $^1$H NMR (600 MHz, DMSO-$d_6$, 90 °C) δ 7.36 – 7.21 (m, 4H), 7.30 – 7.26 (m, 1H), 5.10 (d, $J$ = 12.3 Hz, 1H), 5.03 (d, $J$ = 12.3 Hz, 1H), 4.43 (t, $J$ = 7.7 Hz, 1H), 3.93 (t, $J$ = 6.6, 1.9 Hz, 1H), 3.90 – 3.83 (m, 2H), 3.79 – 3.72 (m, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 2.14 – 2.06 (m, 1H), 2.00 – 1.86 (m, 2H), 1.79 – 1.69 (m, 2H), 1.65 – 1.56 (m, 1H), 1.50 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR (151 MHz, DMSO-d6, 90 °C ) δ 173.1, 154.8, 152.1, 137.1, 128.7, 128.2, 93.5, 67.4, 66.6, 59.9, 57.0, 55.9, 52.4, 52.1, 38.9, 29.8, 28.6, 27.3, 24.0; HRMS (MALDI) $m/z$ calcd for $C_{22}H_{30}N_2O_7Na$ $[M+Na]^+$ 457.1945; found, 457.1949.

Alternatively,

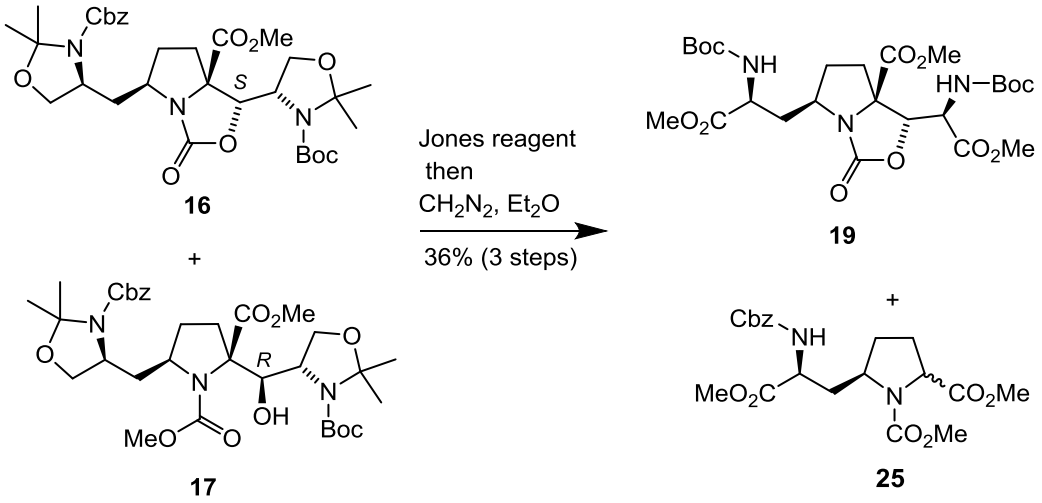



To a solution of **13** (2.0 g, 2.9 mmol) in dry MeOH (30 mL) was added Mg (2.1 g, 36 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h when TLC showed reaction is to be complete, the reaction mixture was concentrated and partitioned between $CH_2Cl_2$ (200 mL) and water (200 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 3:1 hexane/acetone to give desulfonated methyl ester as a colorless oil. To a solution of crude methyl ester in THF (30 mL) were added 1M $NaHCO_3$ (30 mL) and methyl chloroformate (0.30 g, 2.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h when TLC showed the reaction to be complete. The reaction mixture was partitioned between EtOAc (150 mL) and water (150 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 5:1 EtOAc/hexanes to afford **2** as white foam (0.7 g, 61%).




**Aldol reaction (16+17):** To a solution of methyl ester **2** (1.04 g, 2.40 mmol) in dry THF (2 mL) was added a solution of LHMDS (1.0 M in THF, 3.1 mL) at -78 °C. The resulting reaction mixture was stirred for 1 h under Ar at the same temperature and then warmed to -30 °C over 1 h. Then the reaction mixture was cooled to -78 °C. To the enolate, a solution of **3** (0.71 g, 3.1 mmol) in dry THF (0.8 mL) was added dropwise. The reaction mixture was stirred for 2 h at -78 °C and then warmed to room temperature over 4 h. The reaction mixture was quenched by adding 10 mL of 1 M HCl. The organic layer was separated and aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to get the crude product as thick yellowish oil. The crude product was purified by flash chromatography (2:3 hexanes/EtOAc) to yield an inseparable 2:1 mixture of aldol product (**16**+**17)** as white foam (1.1 g, 73% combined yield). $R_f$ 0.35 (2:1 hexanes/EtOAc); HPLC: C18 (3 × 250 mm) XBridge column, gradient 50% to 100% $CH_3CN$ in $H_2O$ (0.1% TFA) over 30 min, flow rate 0.5 mL/min, UV detection at 215 nm, $t_R$: 19.5 min (**17**)

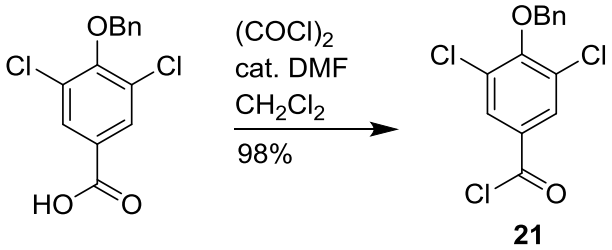
and 20.1 min (**16**) in a ratio of 1:2. LC/MS analysis $t_R$: 19.5 min (m/z cald for $[M+H]^+$ 663.3) and $t_R$: 20.1 min (m/z calcd for $[M+H]^+$ 632.4).




**Trimethyl ester 19**: To a solution of (**16**+**17**) (200 mg, 0.30 mmol) in acetone (6 mL) was added freshly prepared Jones reagent (1.9 M) (1.3 mL, 1.5 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 5 h at room temperature and quenched by adding i-PrOH (15 mL) at 0 °C. Stirring was continued for 1 h and the mixture was partitioned between brine (30 mL) and $CHCl_3$ (30 mL). The organic layer was separated, aqueous layer was extracted with $CHCl_3$ (3 X 30 mL), Combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude diacid residue was dissolved in THF (8 mL) and treated with a solution of $CH_2N_2$ in $Et_2O$ (0.6 M) at 0 °C until the reaction mixture remained yellow. The stirring was continued for 1 h at 0 °C and the reaction was quenched with HOAc (2 drops). The reaction mixture was treated with a 1:1 mixture of ether/hexanes (10 mL), concentrated and purified by silica gel flash column eluting with 1:1 hexanes/EtOAc to give pure **19** as white foam (61 mg, 49%). $R_f$ 0.3 (1:1 EtOAc/hexanes); $^1$H NMR (600 MHz, DMSO-$d_6$, 27 °C) δ 7.67 (d, $J$ = 7.3 Hz, 1H), 7.61 (d, $J$ =

9.1 Hz, 1H), 7.38 – 7.22 (m, 5H), 5.00 (brs, 2H), 4.92 (d, *J* = 10.0 Hz, 1H), 4.33 (dd, *J* = 10.0, 8.4 Hz 1H), 4.14 – 4.01 (m, 1H), 3.91 – 3.84 (m, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 3.61 (s, 3H), 2.26 -2.11 (m, 2H), 1.94 – 1.84 (m, 2H), 1.74 – 1.62 (m, 1H), 1.55 – 1.44 (m, 1H), 1.35 (s, 9H); HRMS (MALDI) *m*/*z* calcd for $C_{28}H_{37}N_3NaO_{12}$+ $[M+Na]^+$ 630.2040; found, 630.2048. HPLC: C18 (3 × 250 mm) XBridge column, gradient 40% to 90% $CH_3CN$ in $H_2O$ (0.1%TFA) over 30 min, flow rate 0.5 mL/min, UV detection at 215 nm, $t_R$: 14.7 min.

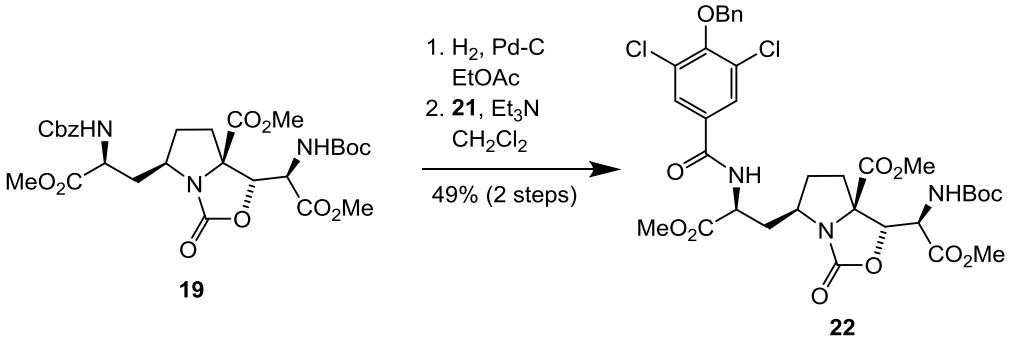
**Compound 25:** $R_f$ 0.5 (1:1 EtOAc/hexanes); $^1$H NMR (600 MHz, DMSO-$d_6$, 75 °C) δ 7.40 – 7.24 (m, 5H), 5.04 (s, 2H), 4.26 (t, *J* = 7.4 Hz, 1H), 4.14 (dd, *J* = 13.9, 6.5 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 3.52 (s, 3H), 2.30 – 2.13 (m, 2H), 2.00 – 1.80 (m, 1H), 1.76 – 1.77 (m, 1H), 1.60 (m, 2H); $^{13}$C NMR (151 MHz, DMSO-d6, 75 °C) δ 172.9, 172.7, 172.6, 137.5, 128.6, 128.1, 127.9, 66.1, 66.0,60.8, 52.5, 52.1, 52.0, 36.4, 30.5, 28.5, 16.3; HRMS (MALDI) *m*/*z* calcd for $C_{19}H_{26}N_2NaO_7$ $[M+Na]^+$ 417.1632; found, 417.1642.




**21**

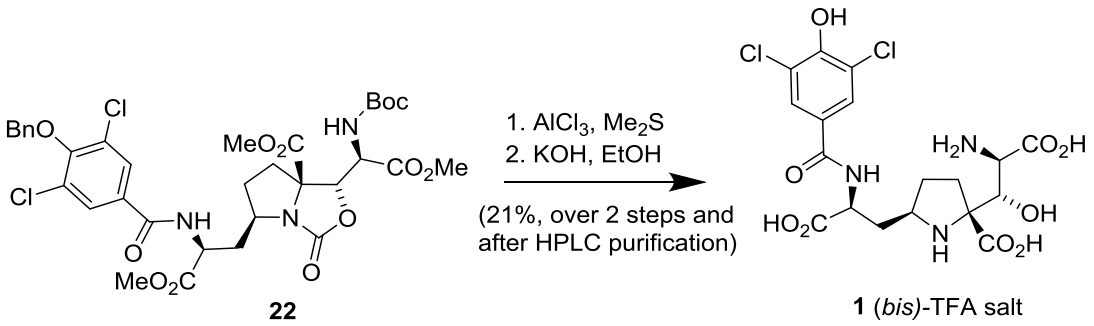
**Acid chloride 21:** To a heterogeneous solution of carboxylic acid (2.0 g, 6.8 mmol) in dry $CH_2Cl_2$ (35 mL) were added oxalyl chloride (1.2 mL, 8.1 mmol) and two drops of DMF at 0 °C. The reaction mixture was stirred for 30 min, warmed up to room temperature and continuously stirred for 2 h. Then the yellowish homogeneous reaction mixture was concentrated under reduced pressure and dried over high vacuum overnight to give **21** as a yellowish solid (2.02 g, 98%). mp 82-84 °C (sm 214-217 °C); $^1$H NMR (600 MHz, $CDCl_3$) δ 8.08 (s, 2H), 7.54 (d, *J* = 6.7 Hz, 2H), 7.45 – 7.36 (m, 3H), 5.16 (s, 2H); $^{13}$C NMR (150.8 MHz, $CDCl_3$) δ 165.7, 156.9,

135.3, 131.8, 103.6, 129.9, 128.8, 128.62, 128.61, 75.6.




**Ma's advanced intermediate 22:** To a solution of **19** (20 mg, 0.030 mmol) in EtOAc (1 mL) was added 10% Pd/C (4 mg). The reaction mixture was purged with $H_2$ gas and stirred under $H_2$ atmosphere for 2 h when the TLC analysis confirmed the complete consumption of the starting material. The reaction mixture was filtered by Celite washing with $CH_2Cl_2$ (10 mL) and the resulting solution was concentrated under reduced pressure to afford the free amine as colorless liquid. The free amine was immediately dissolved in dry $CH_2Cl_2$ (1 mL) and to this was added $Et_3N$ (0.04 mmol, 3.6 mg), **21** (0.20 mmol, 63 mg) in $CH_2Cl_2$ (1 mL) was added at 0 °C and stirred overnight at room temperature. The consumption of the free amine was monitored by LC/MS ($C_{18}$-RP HPLC, isocratic elution (50:50 $CH_3CN$: $H_2O$ (0.1% TFA), 214 nm). The reaction mixture was concentrated and purified by silica gel flash column eluting with 3:1 hexanes/EtOAc to give pure **22** as white foam (12 mg, 49%); $R_f$ (1:1 EtOAc/hexanes); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.4 Hz, 1H), 7.81 (s, 2H), 7.53 (d, *J* = 7.1 Hz, 2H), 7.42 – 7.32 (m, 3H), 5.22 (brs, 1H), 5.07 (s, 2H), 4.82 (d, *J* = 9.1 Hz, 1H), 4.56 – 4.45 (m, 2H), 3.95 – 3.88 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.46 -2.39 (m, 1H), 2.39 – 2.33 (m, 1H), 2.25 (dd, *J* = 12.6, 6.9 Hz, 1H), 2.22 – 2.14 (m, 1H), 2.01 (ddd,), 1.88 – 1.78 (m, 1H), 1.42 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$ ) δ 171.1, 164.0, 159.6, 153.7, 135.8, 130.9, 130.1, 129.9, 128.6, 128.3, 128.1, 75.1, 74.3, 57.5, 53.7, 53.2, 52.6, 52.0, 36.2, 32.8, 31.9, 30.9, 29.7, 29.3, 28.2, 22.7,

14.1; HRMS (MALDI) *m/z* calcd for $C_{34}H_{39}Cl_2N_3O_{12}K$ $[M+K]^+$ 790.1547; found, 790.1545. HPLC: C18 (3 × 250 mm) XBridge column, gradient 5% to 100% $CH_3CN$ in $H_2O$ (0.1%TFA) over 30 min, flow rate 0.5 mL/min, UV detection at 215 nm, $t_R$: 20.0 min (**22**).

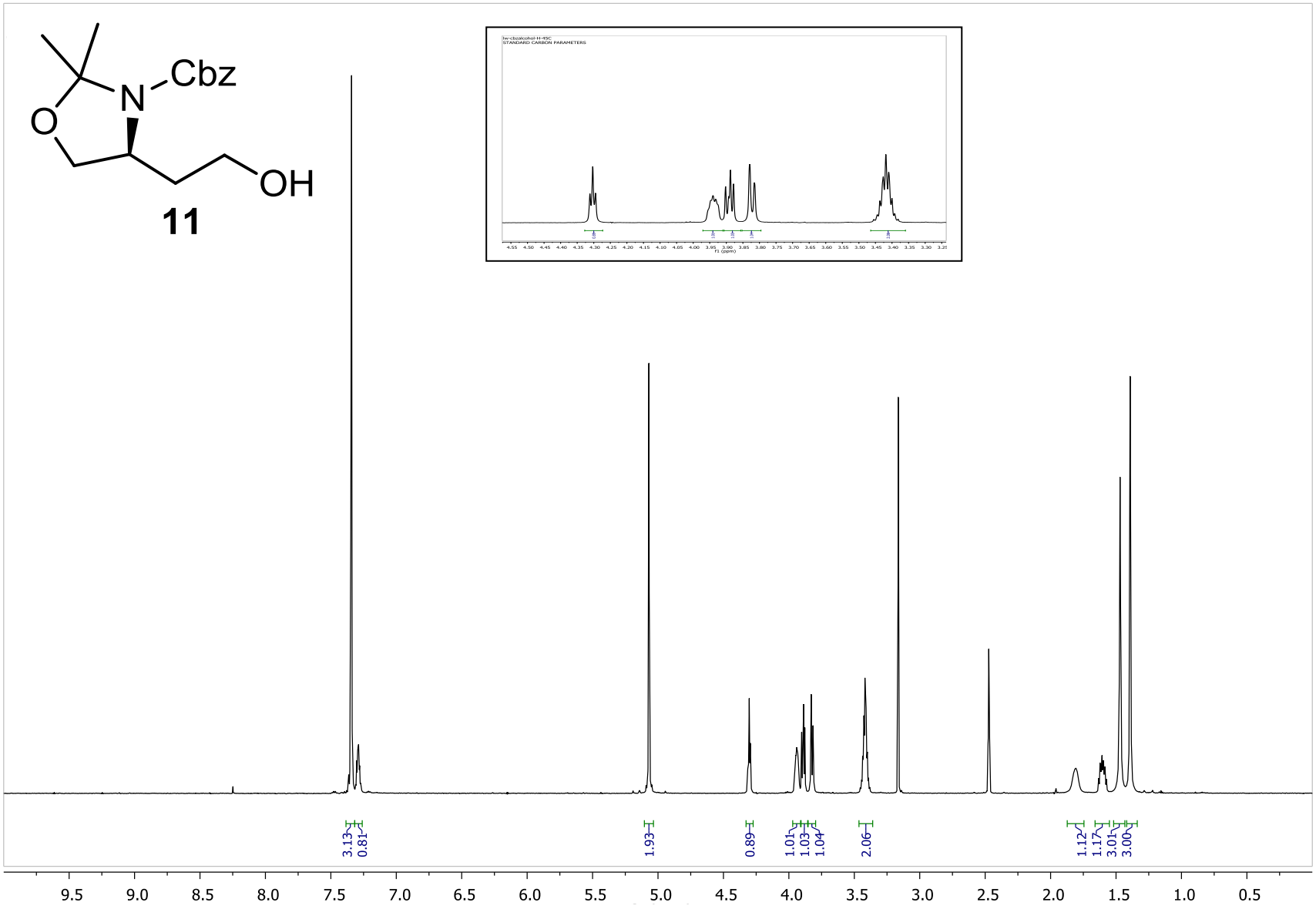



**1 (*bis*)-TFA salt:** To a solution of **22** (10.0 mg, 13.2 μmol) and $Me_2S$ (0.5 mL) in a scrw capped vial was added $AlCl_3$ (50 mg, 0.38 mmol) at room temperature. The mixture was stirred at room temperature for 36 h when the LC/MS analysis confirmed the reaction to be complete. (At about halfway point, additional $Me_2S$ was added to maintain the volume). The reaction mixture was quenched with $H_2O$ (0.5 mL) and concentrated under reduced pressure. The residue was passed through a Dowex 50WX2 column (eluting with 1N $NH_4OH$) to give the crude product **23**. To a solutionof crude **23** in EtOH (0.5 mL) was added 1N KOH (0.5 mL) and the solution was stirred for 9 h at 40 °C. The reaction mixture was cooled to room temperature, quenched with 1N HCl (0.5 mL) and concentrated. The residue was passed through a Dowex 50WX2 column (eluting with 1N $NH_4OH$) and purified by reverse-phase HPLC (X-Bridge C18 (19x150 mm) column) eluting with 10:90 $CH_3CN$ in $H_2O$ (0.8% TFA), flow rate 16 mL/min. The collected fractions were freeze-dried to give the (*bis*)-TFA salt of **1** as a white powder (1.1 mg, 21%). $^1$H NMR (600 MHz, $D_2O$) δ 7.81 (s, 2H), 4.66 (dd, *J* = 8.5, 5.7 Hz, 1H), 4.55 (s, 1H), 4.30 (s, 1H), 3.91 – 3.83 (m, 1H), 2.62 (dt, *J* = 13.8, 6.7 Hz, 1H), 2.42 (ddd, *J* = 13.5, 6.2, 2.5 Hz, 1H), 2.30 – 2.20 (m, 2H), 2.15 (ddd, *J* = 13.4, 11.4, 6.7 Hz, 1H), 1.79 – 1.68 (m, 1H). HPLC:

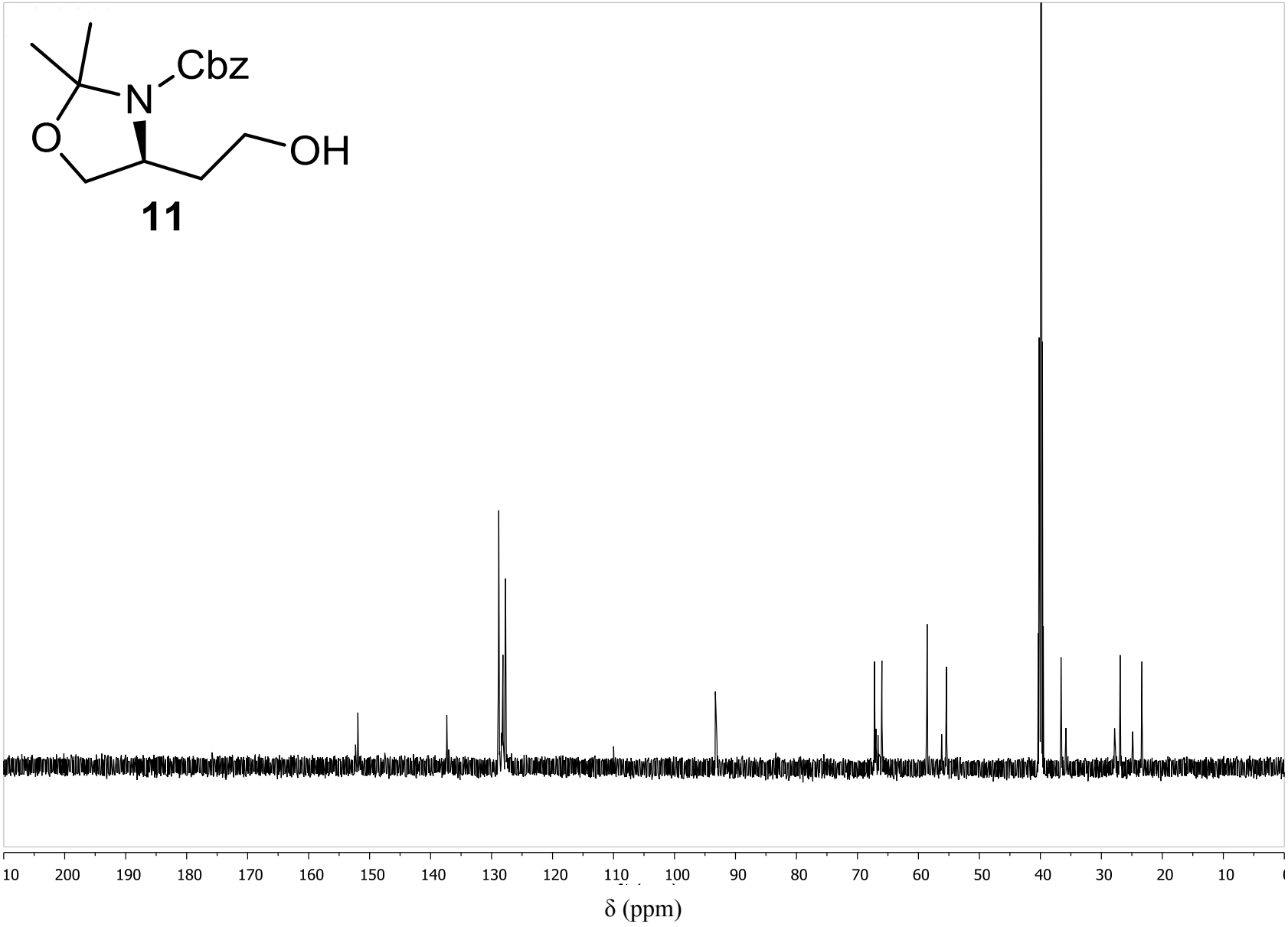
C18 (3 × 250 mm) XBridge column, isocratic 10:90 $CH_3CN$:$H_2O$ (0.8% TFA), flaw rate 0.5 mL/min, UV detection at 215 nm, $t_R$: 13.1 min (**1**).

## III. NMR and HPLC data for the key compounds

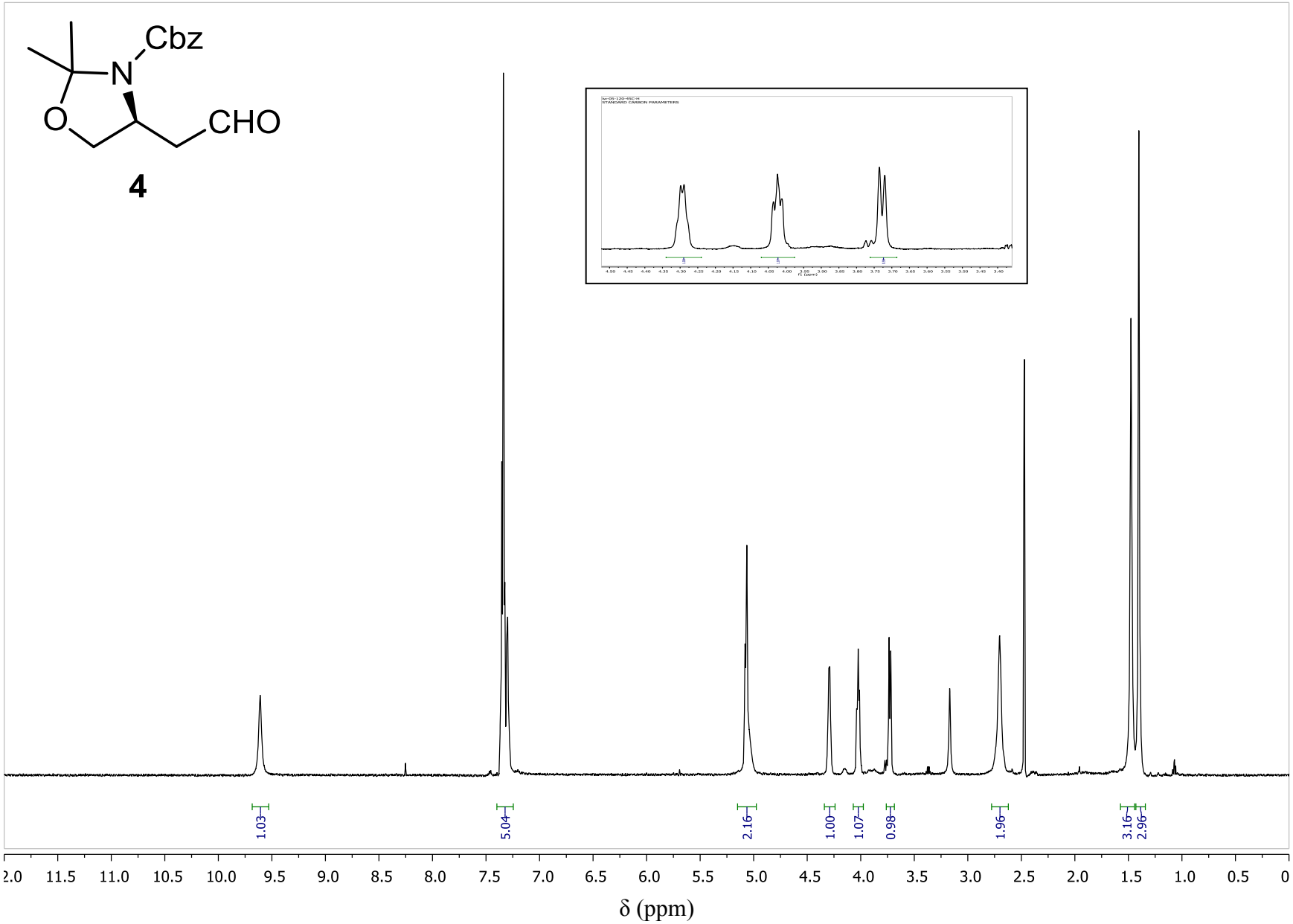
**600 MHz $^{1}$H NMR, DMSO-$d_6$ at 45 °C**



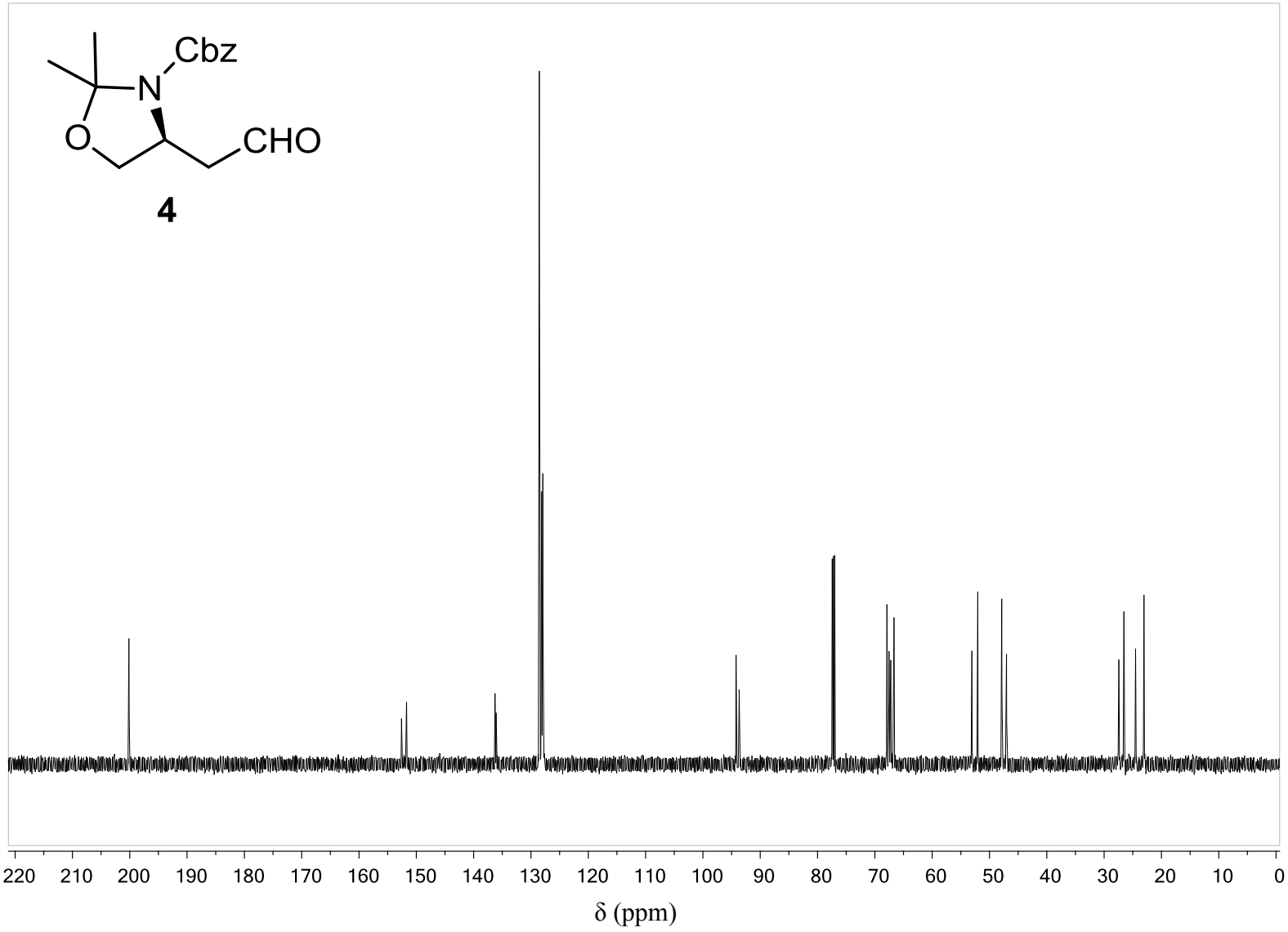
**150.8 MHz $^{13}$C NMR, DMSO-$d_6$**



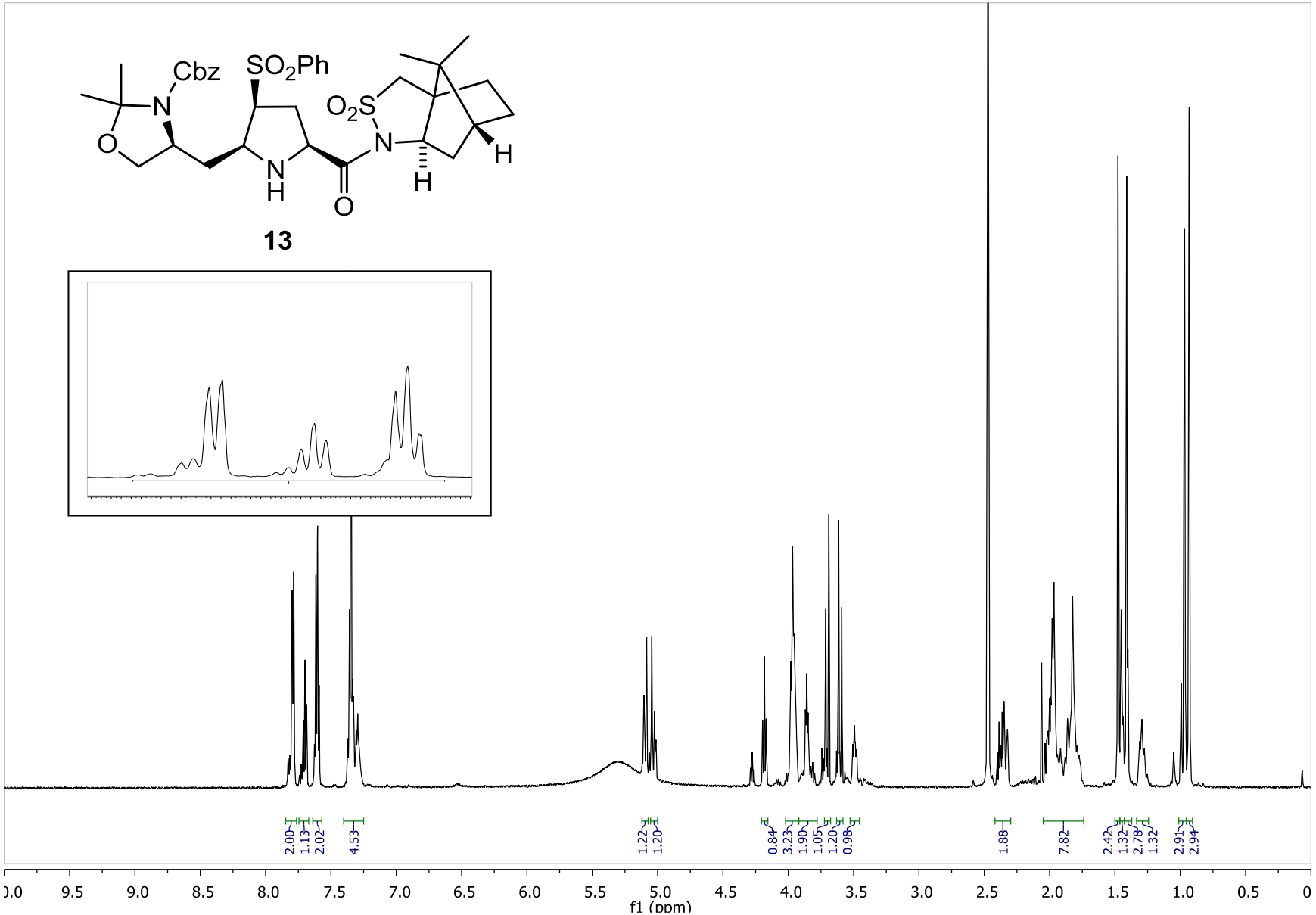
**600 MHz $^{1}$H NMR, DMSO-d6, 45 °C**



**150.8 MHz $^{13}$C NMR, $CDCl_3$**

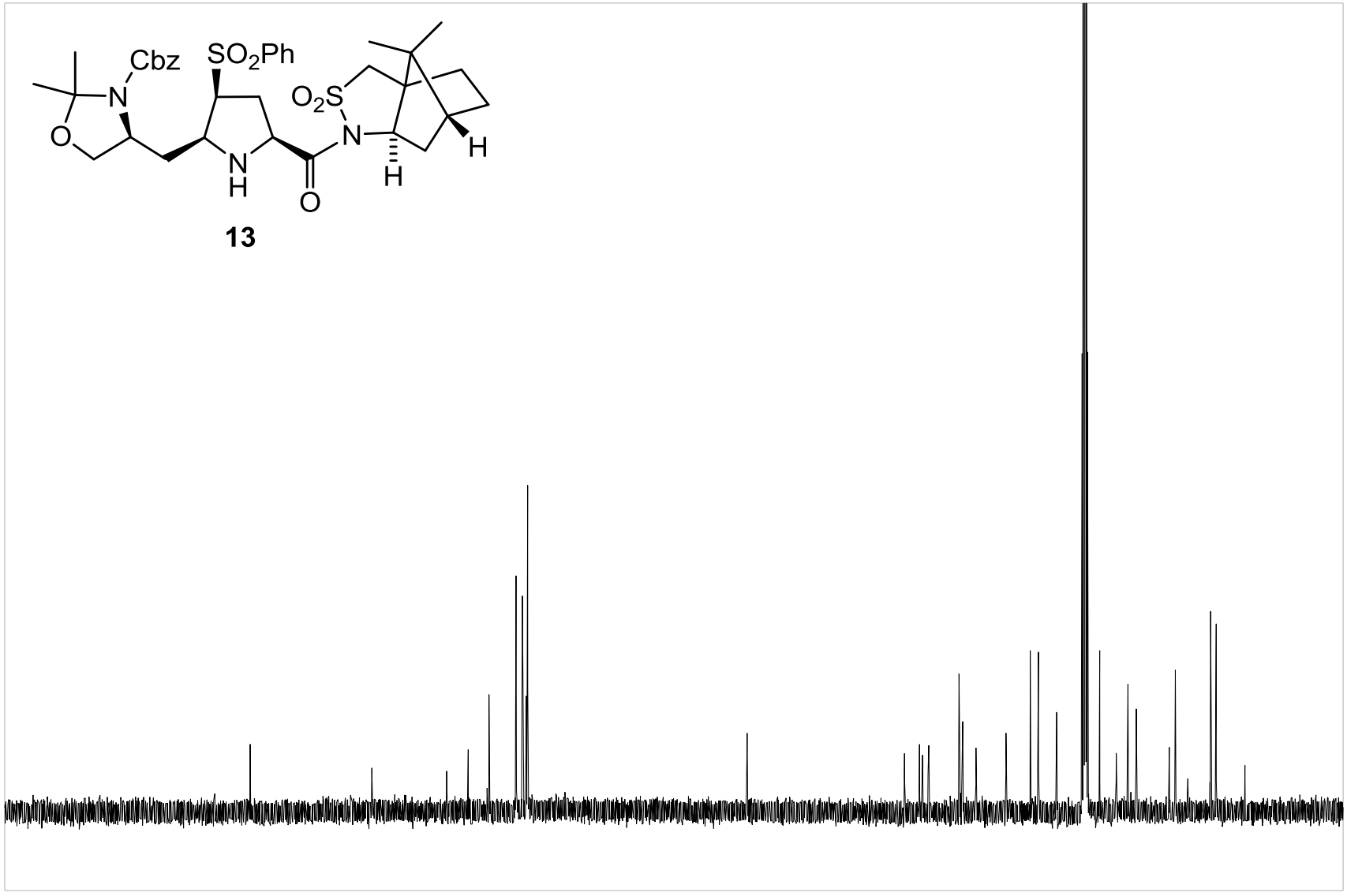


**600 MHz $^{1}$H NMR, DMSO-$d_6$ 90 $^{\circ}$C**

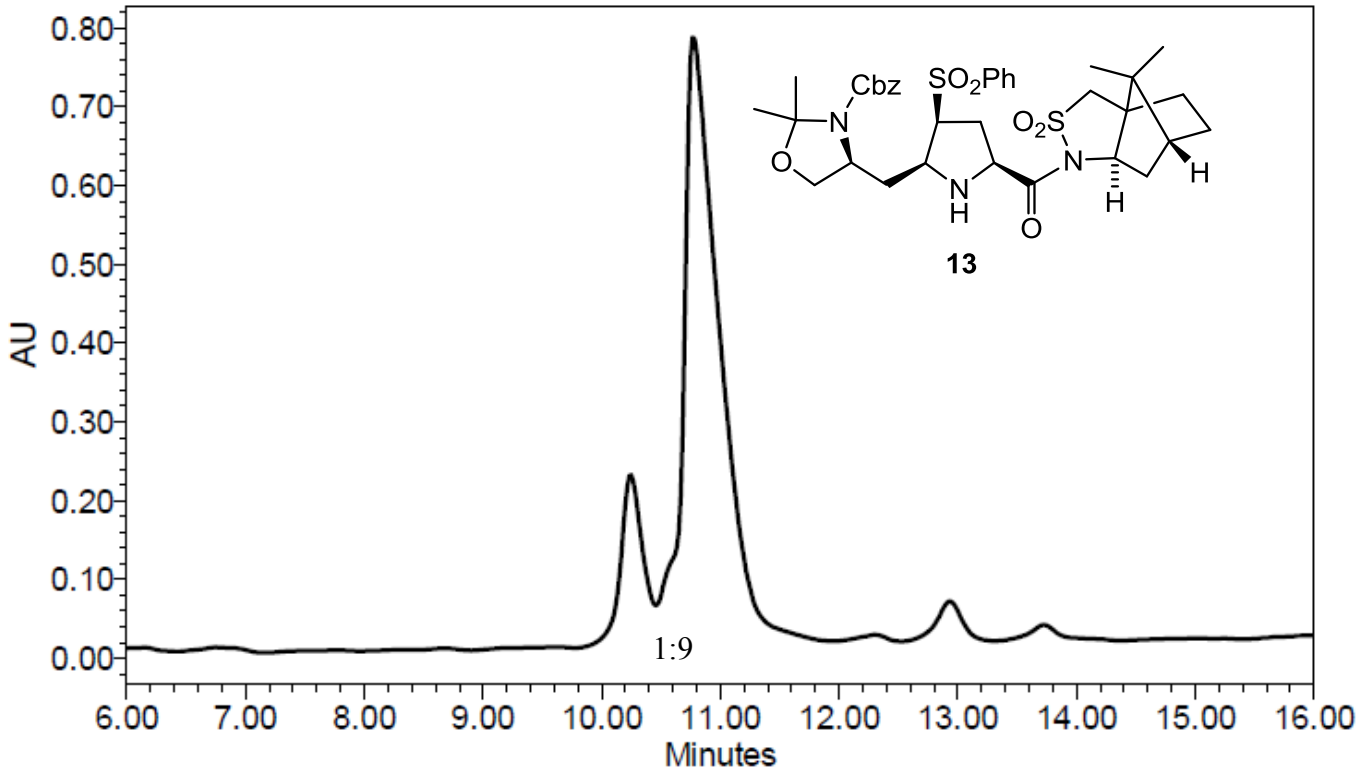



δ (ppm)

**150.8 MHz $^{13}$C NMR, DMSO-$d_6$ 90 °C**

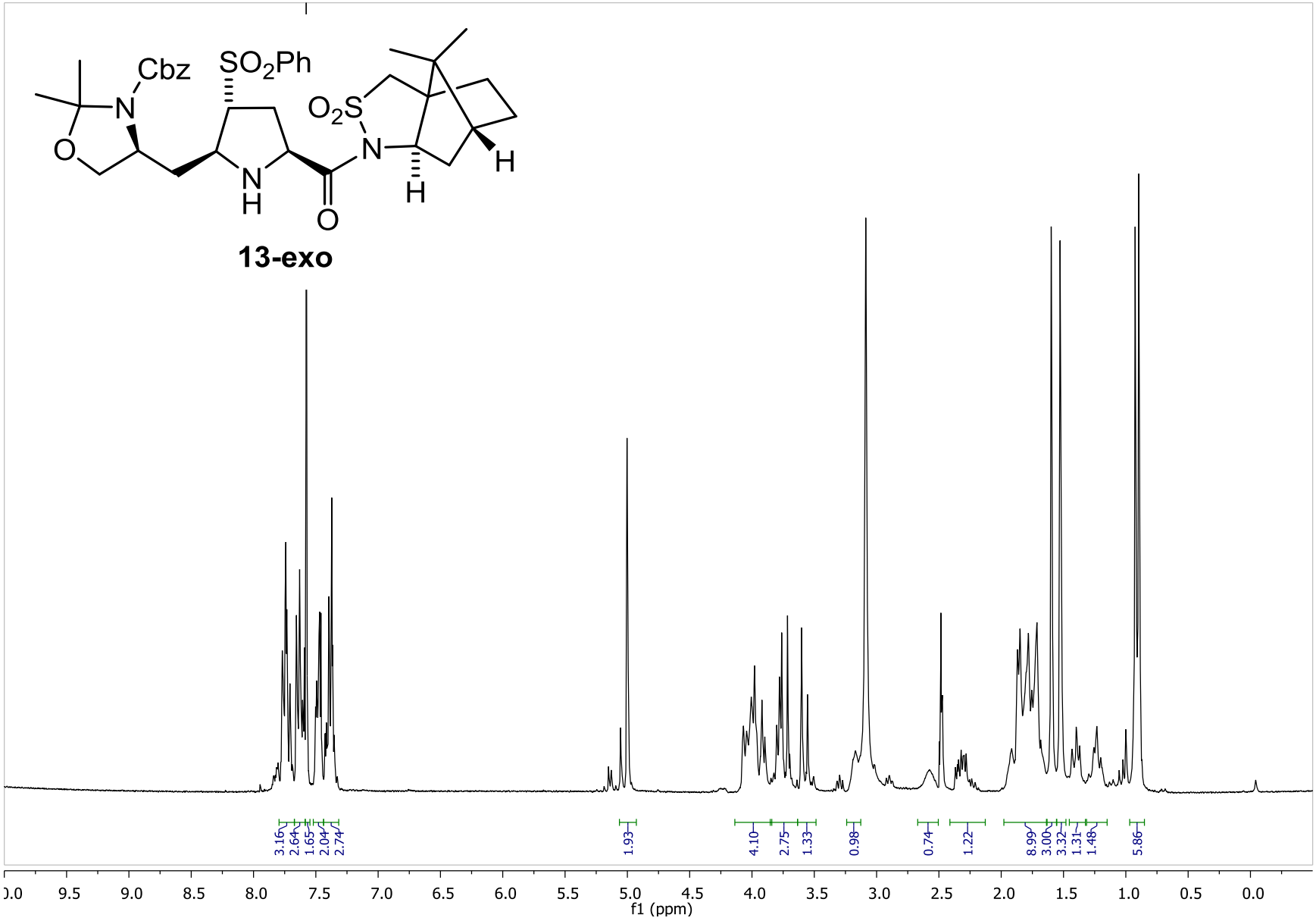


HPLC Chromatograph of the cycloadduct **13**

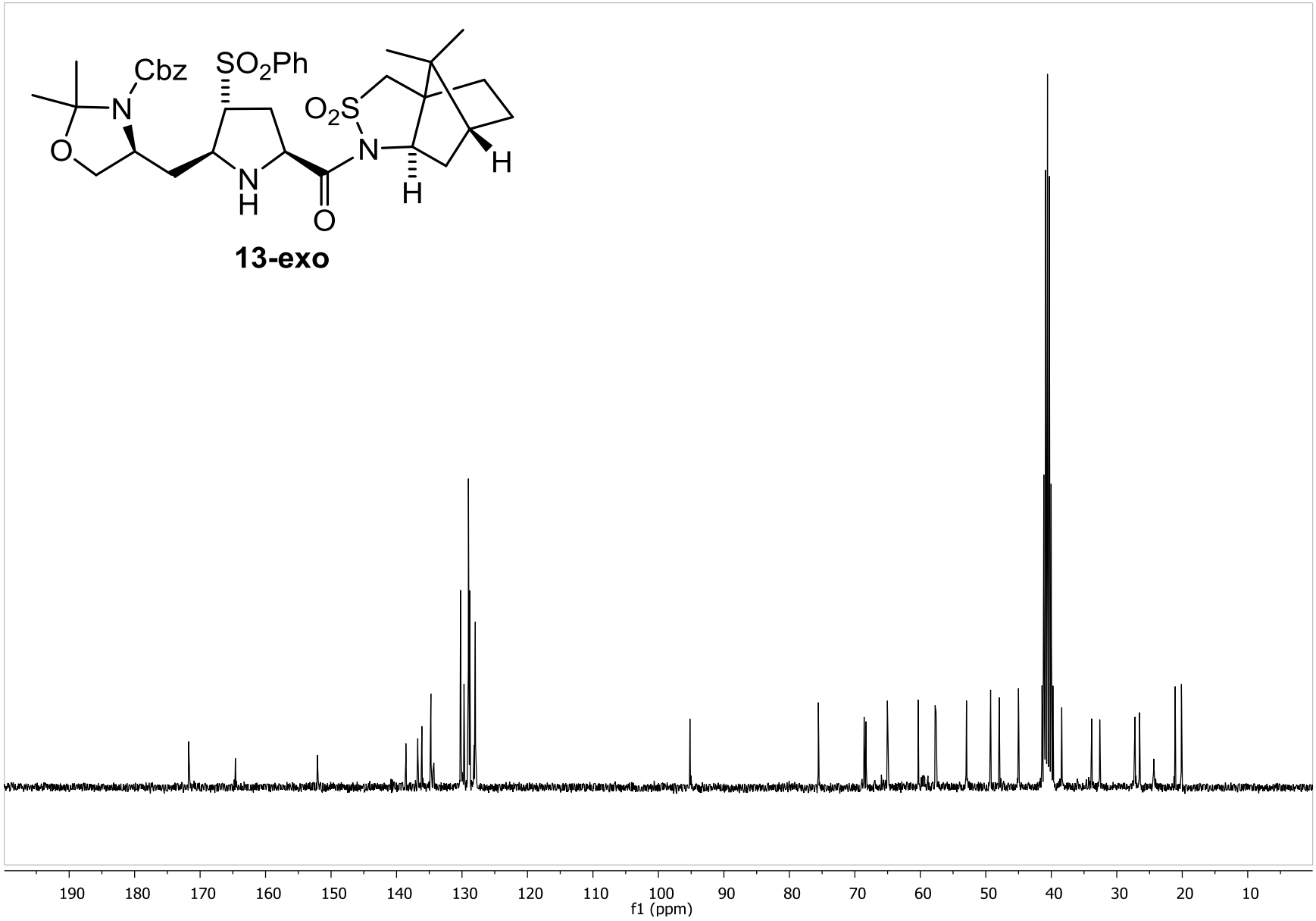



X-Bridge C18 (3x250 mm) column, 50-80% $CH_3CN/H_2O$ (0.1% TFA) over 30 min at 0.5 mL/min, 215 nm

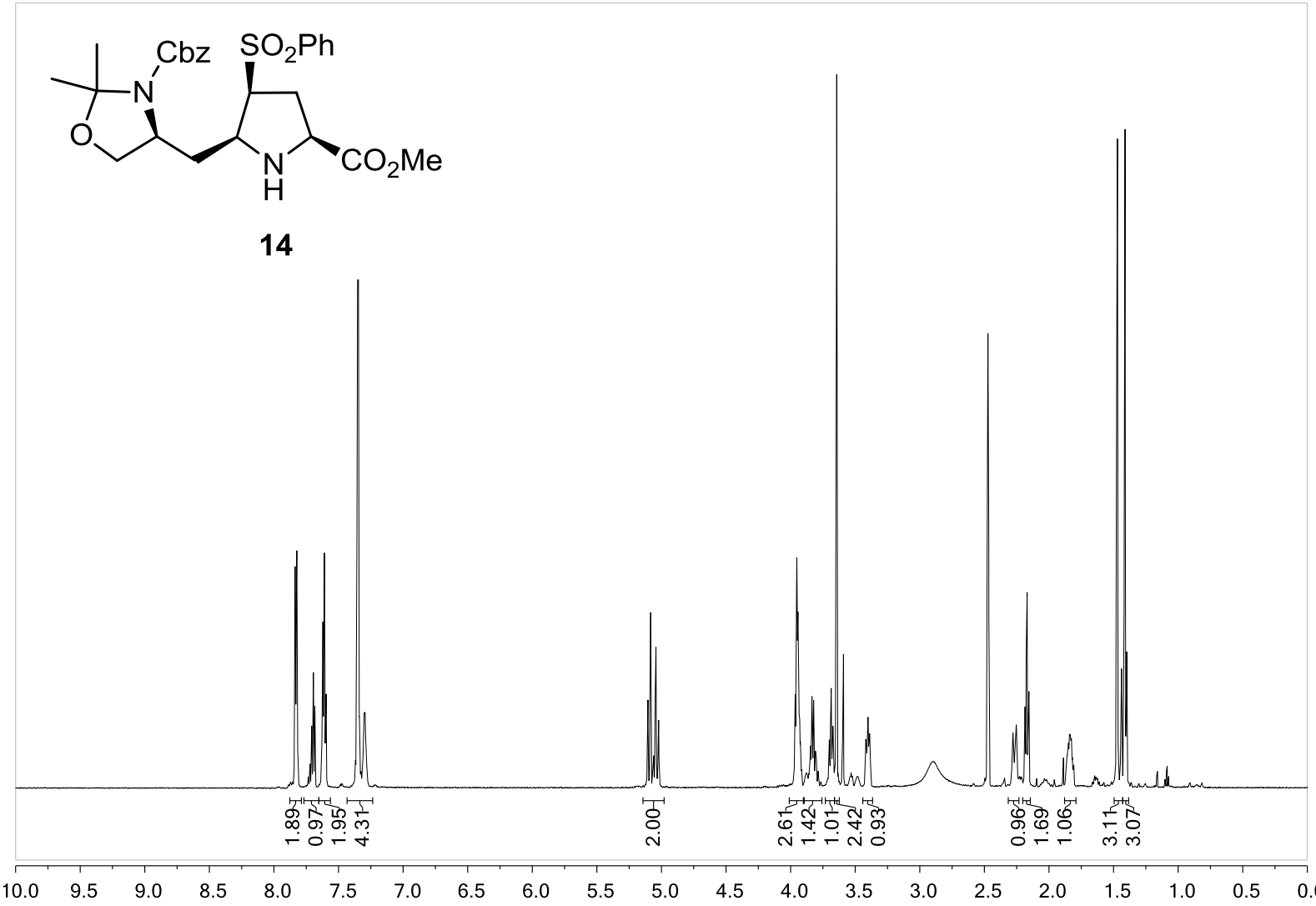
**600 MHz $^{1}$H NMR, DMSO-$d_6$ 90 °C**



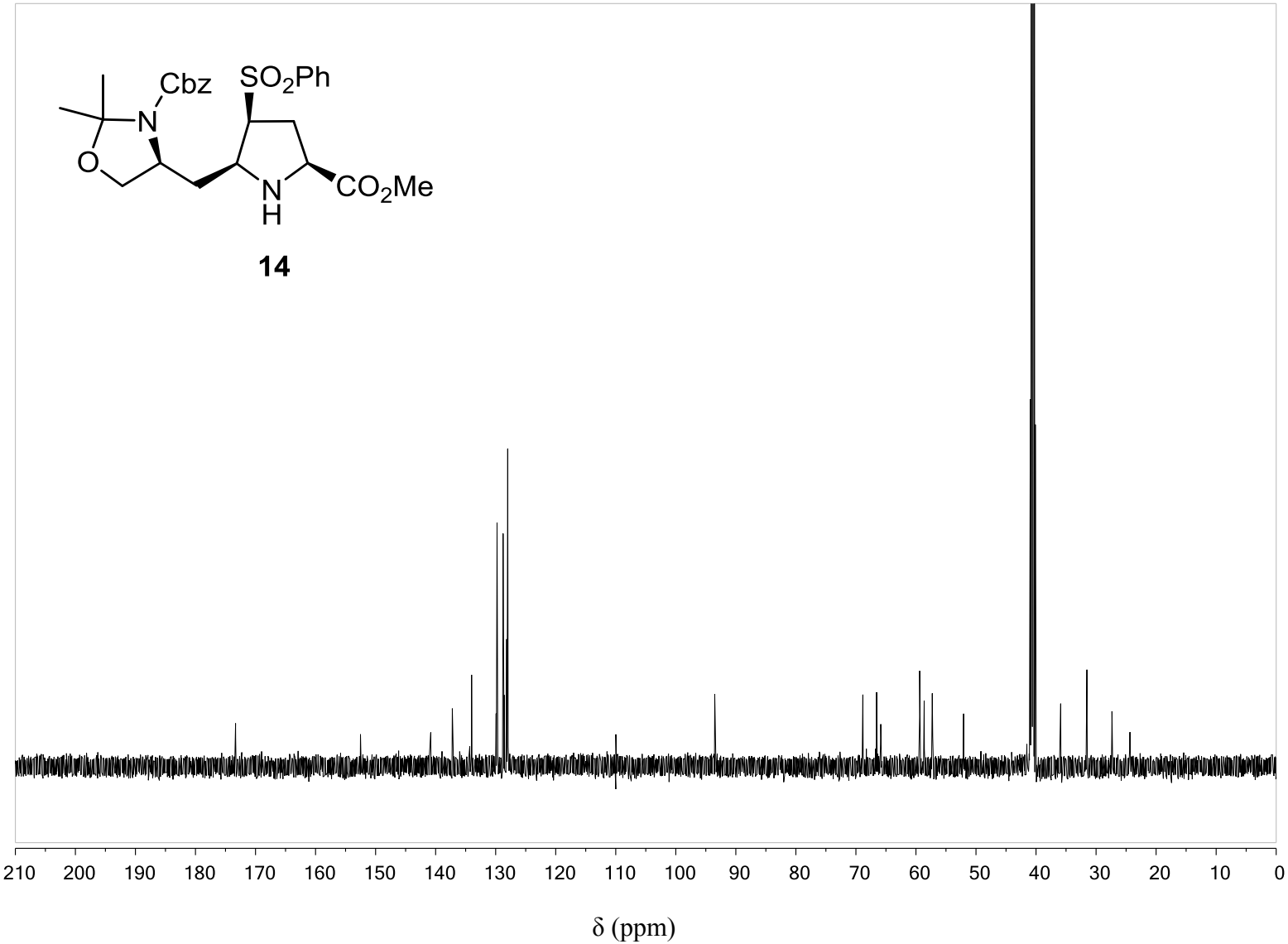
**150.8 MHz $^{13}$C NMR, DMSO-$d_6$ 90 °C**



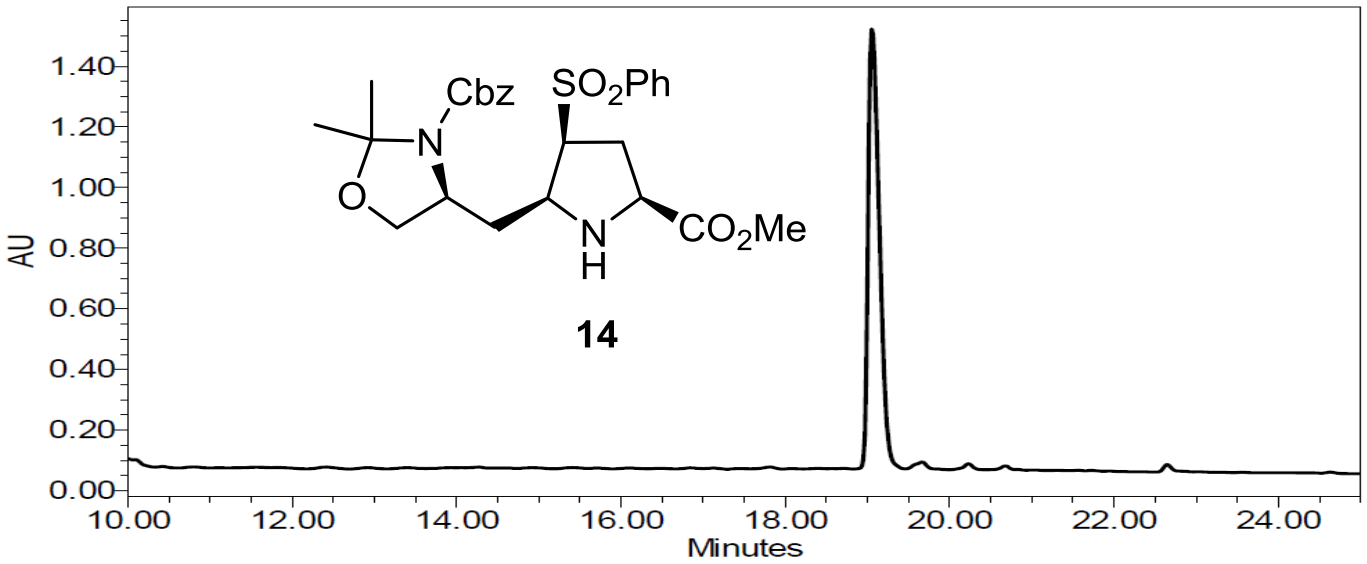
**600 MHz $^{1}$H NMR, DMSO-$d_6$ 90 °C**



**150.8 MHz $^{13}$C NMR, DMSO-$d_6$ 90 $^{\circ}$C**

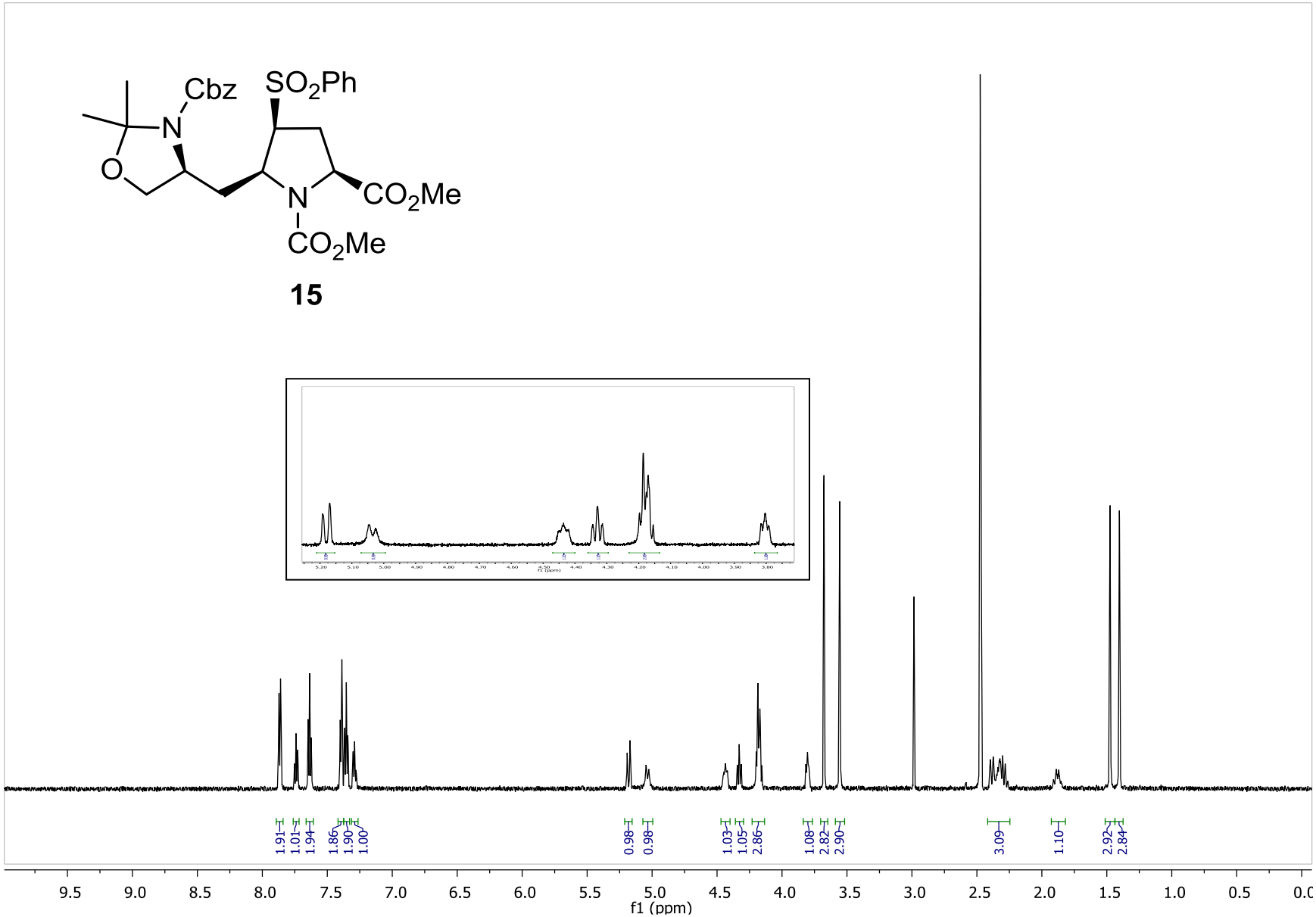


HPLC Chromatograph of the methylester **14**



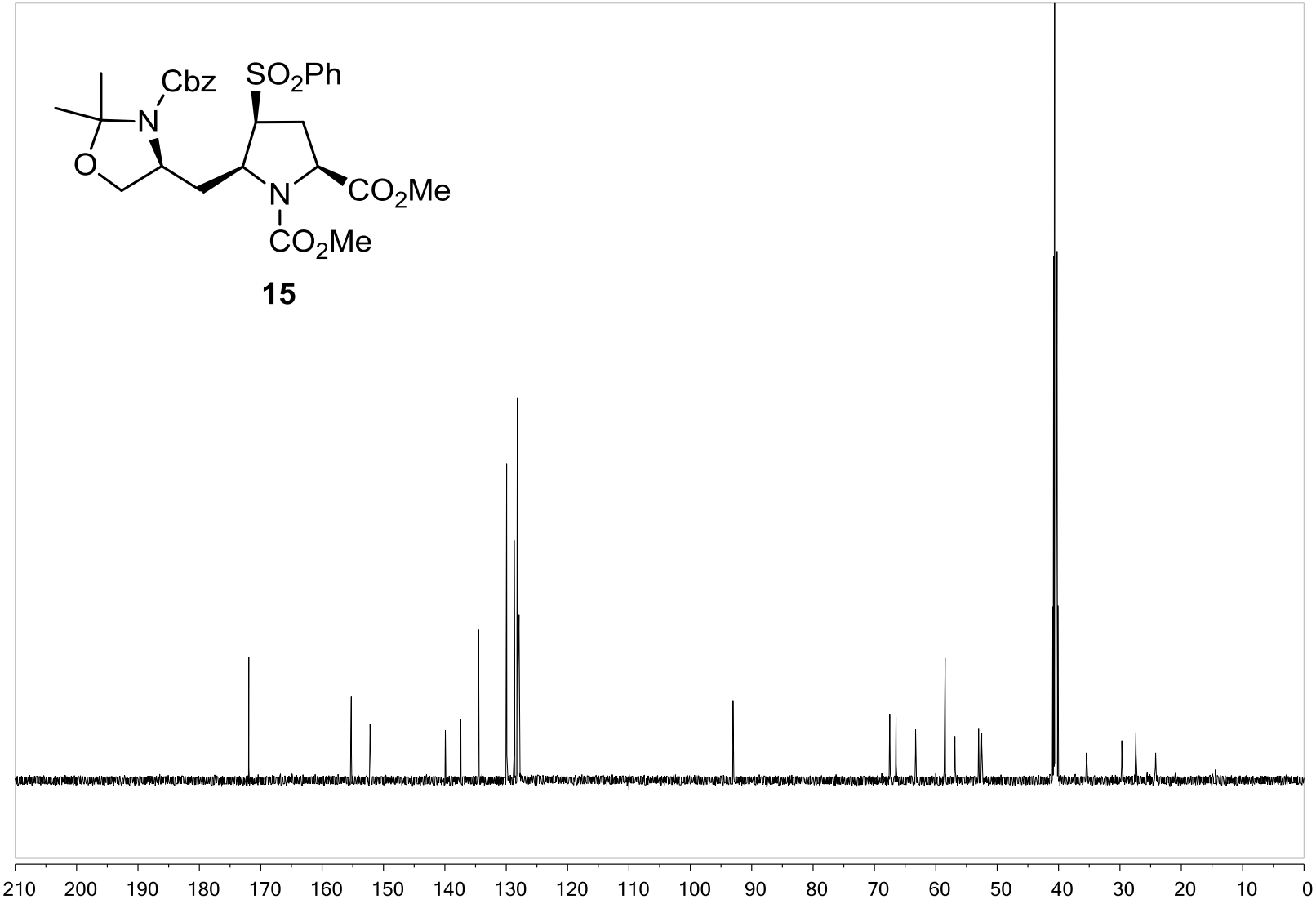

X-Bridge C18 (3x250 mm) column, 20-80% $CH_3CN$ /$H_2O$ (0.1% TFA) over 30 min at 0.5 mL/min, 215 nm

**600 MHz $^{1}$H NMR, DMSO-$d_6$ 75 $^{\circ}$C**



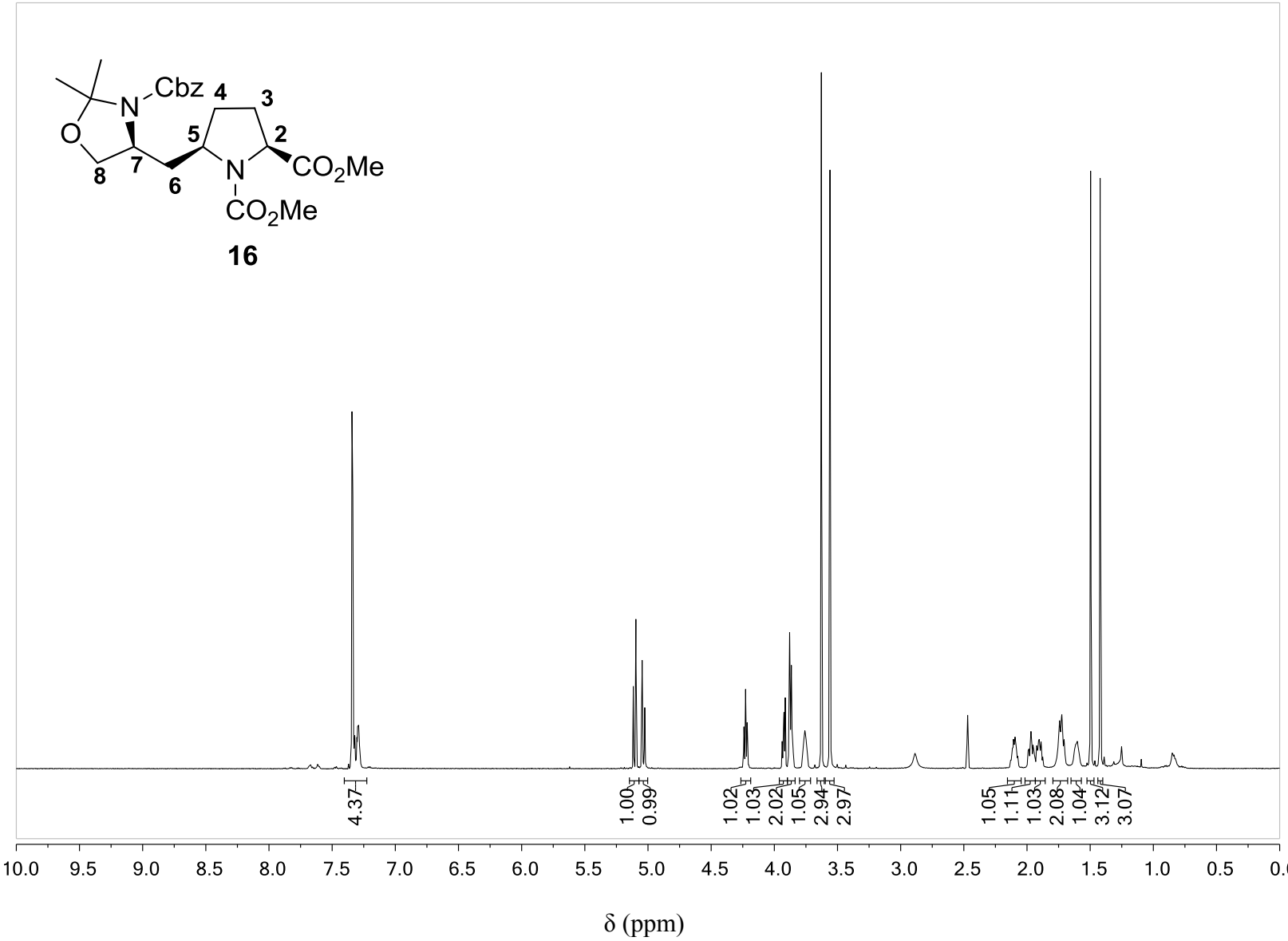

δ (ppm)

**150.8 MHz $^{13}$C NMR, DMSO-$d_6$ 75 °C**

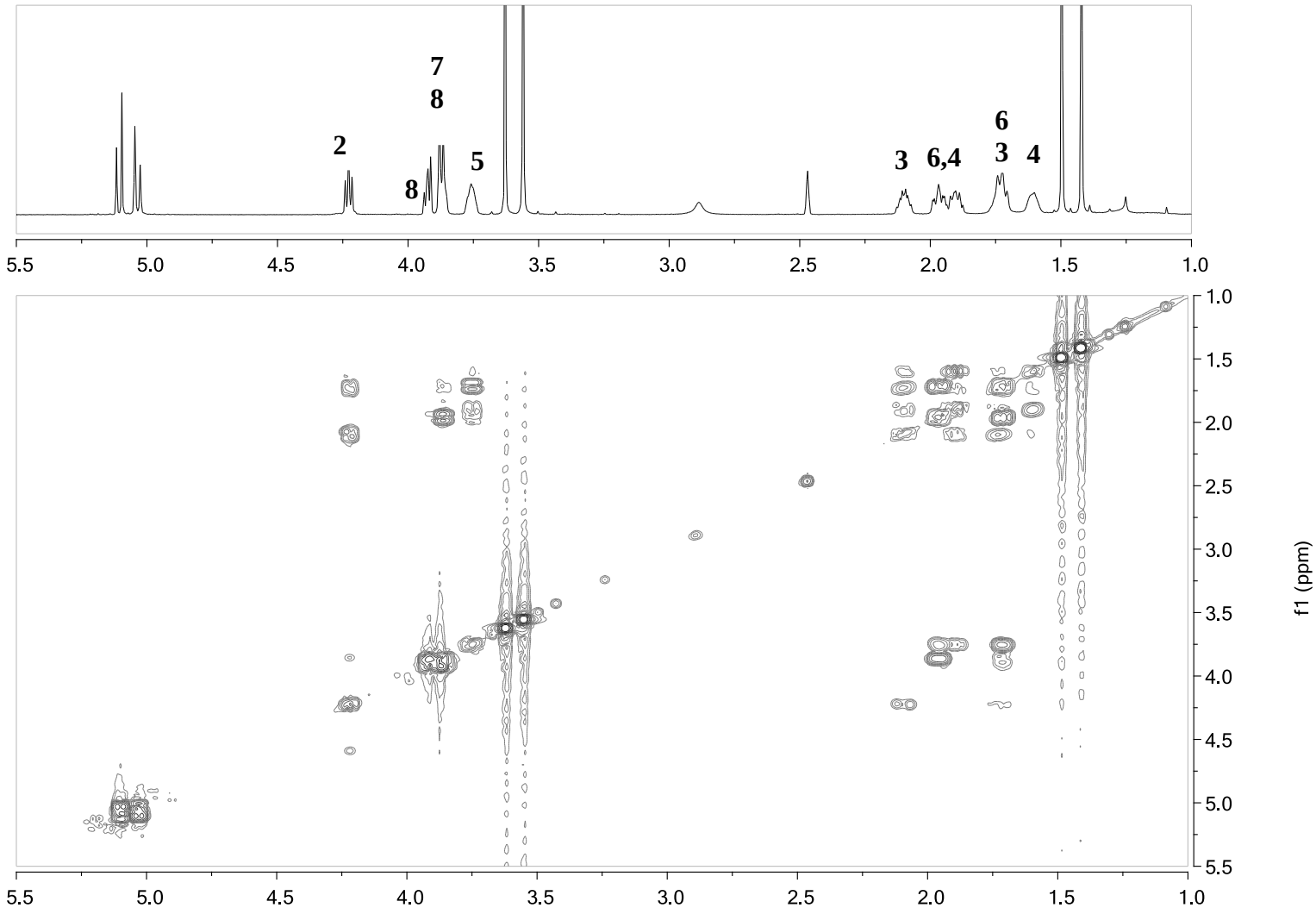



δ (ppm)

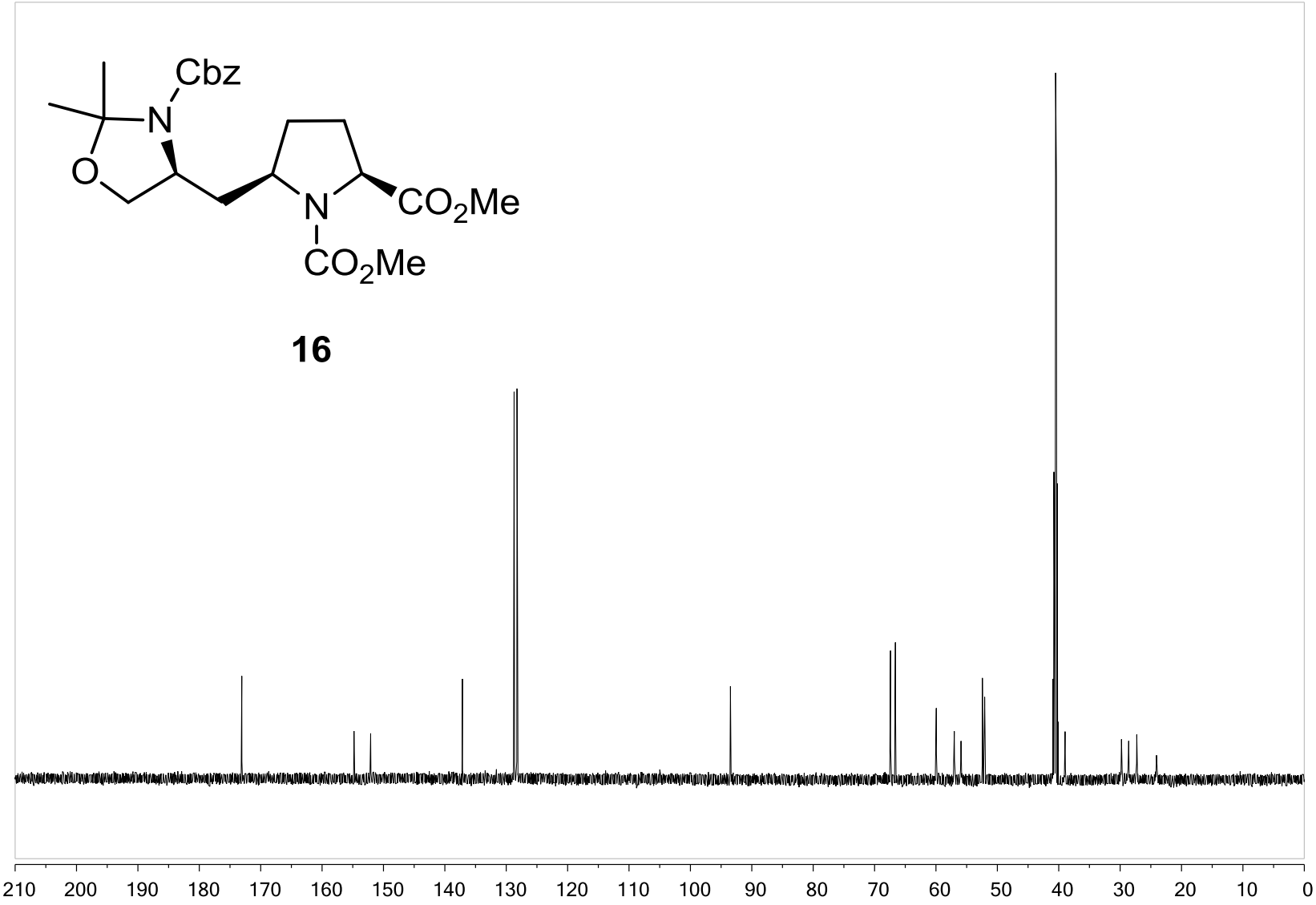
**600 MHz $^{1}$H NMR, DMSO-$d_6$ 90 °C**



**600 MHz gCOSY NMR, DMSO-$d_6$ 90 °C**

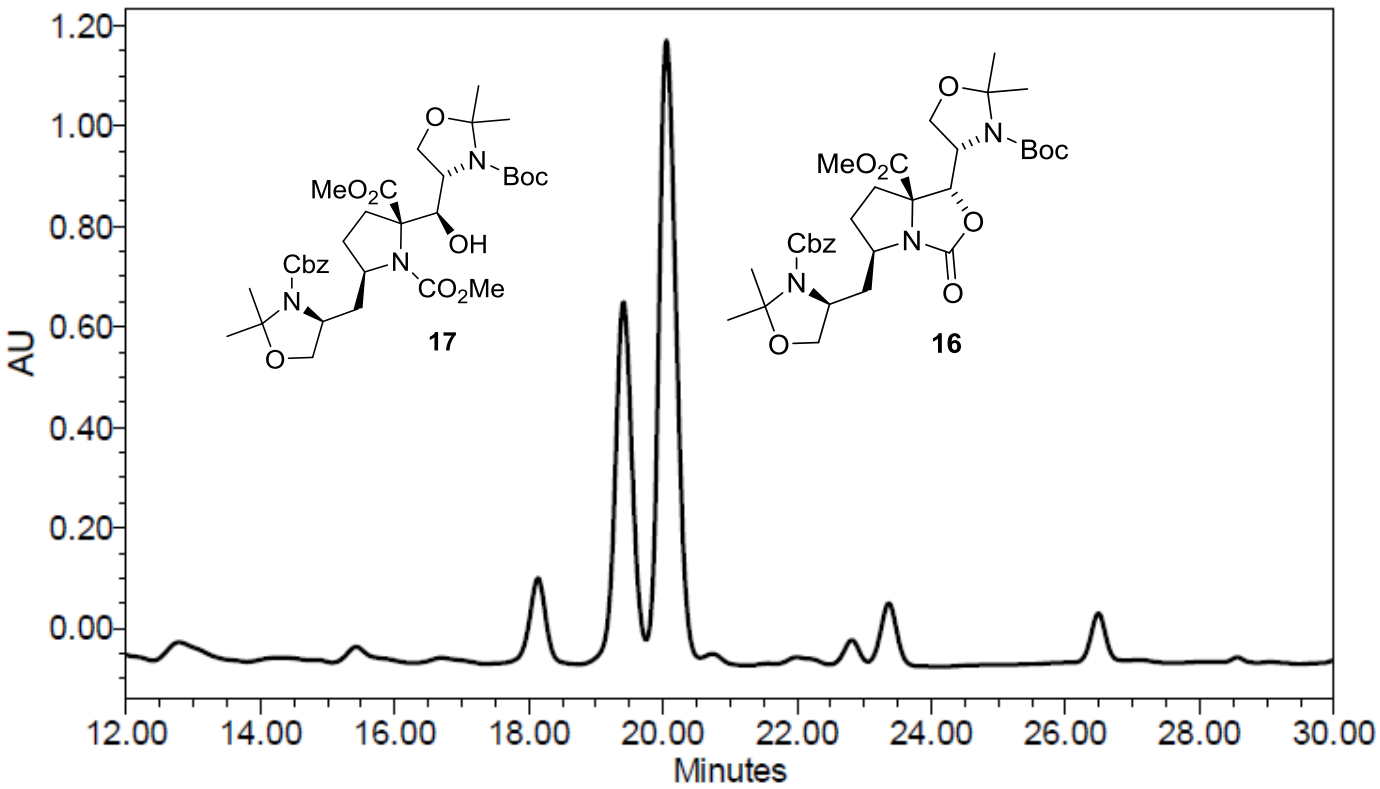


**150.8 MHz $^{13}$C NMR, DMSO-$d_6$ 90 °C**




δ (ppm)

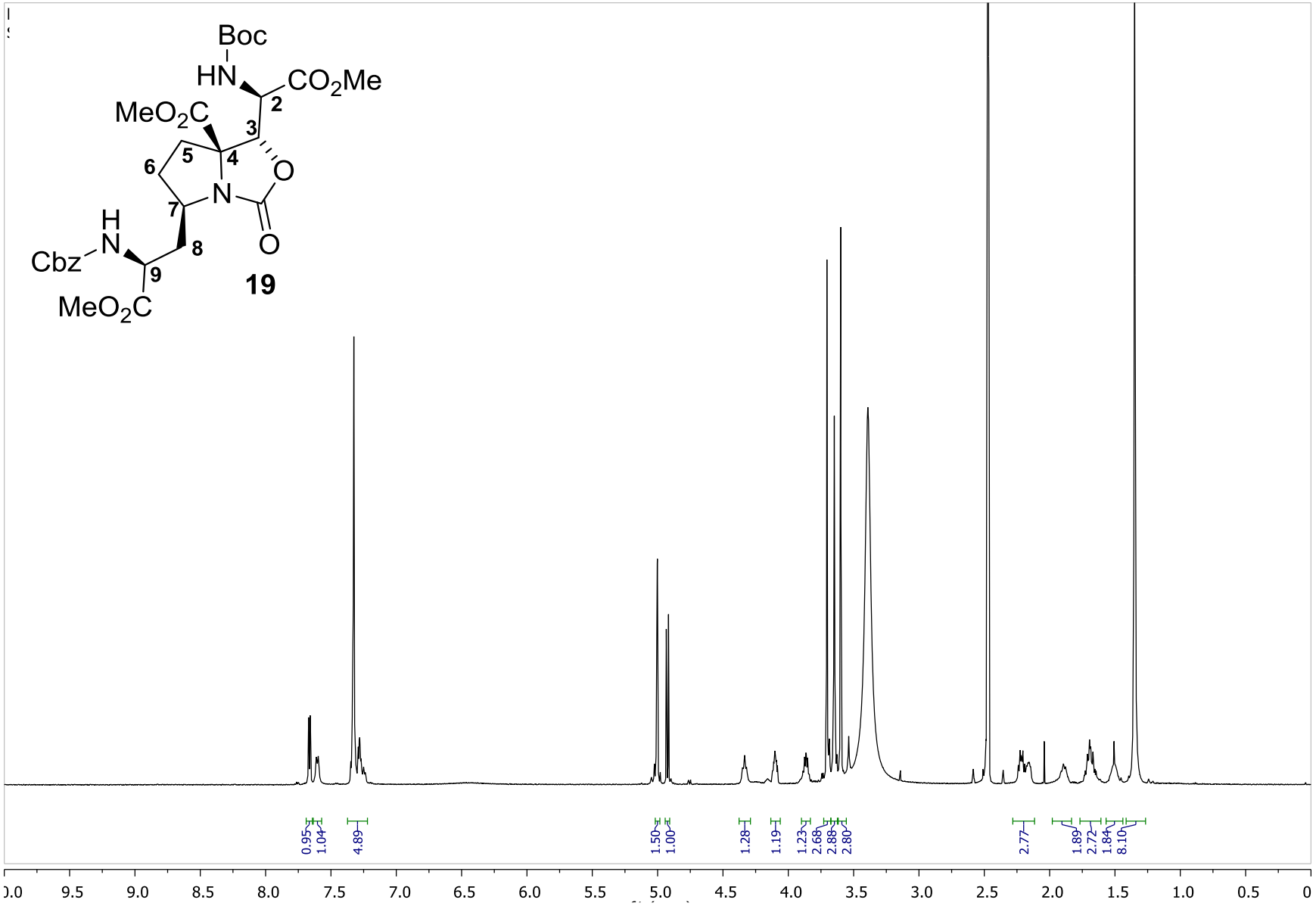
HPLC Chromatograph of the aldol product mixture **(16+17)**

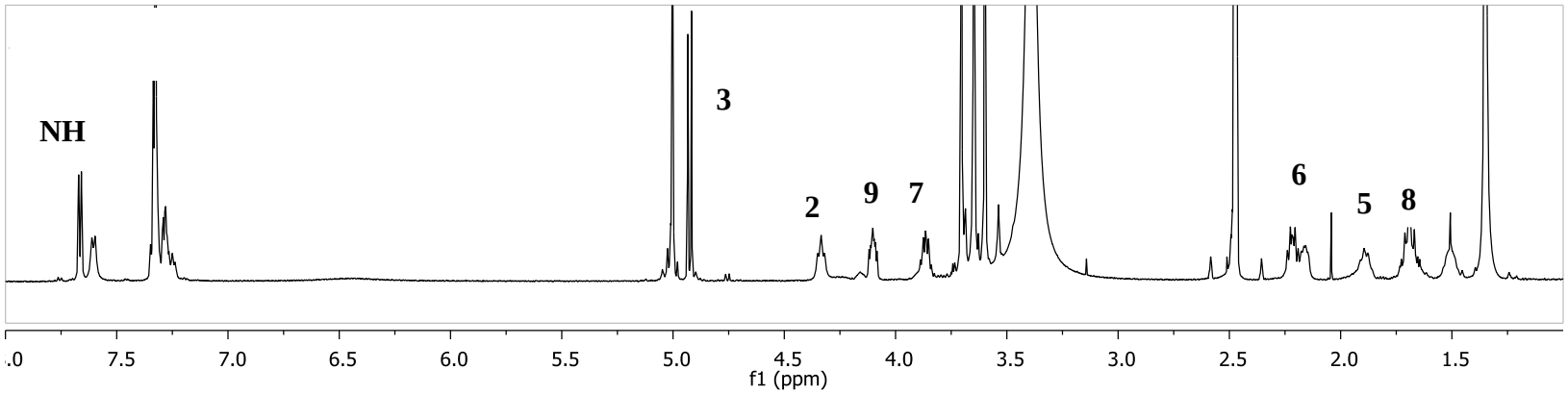


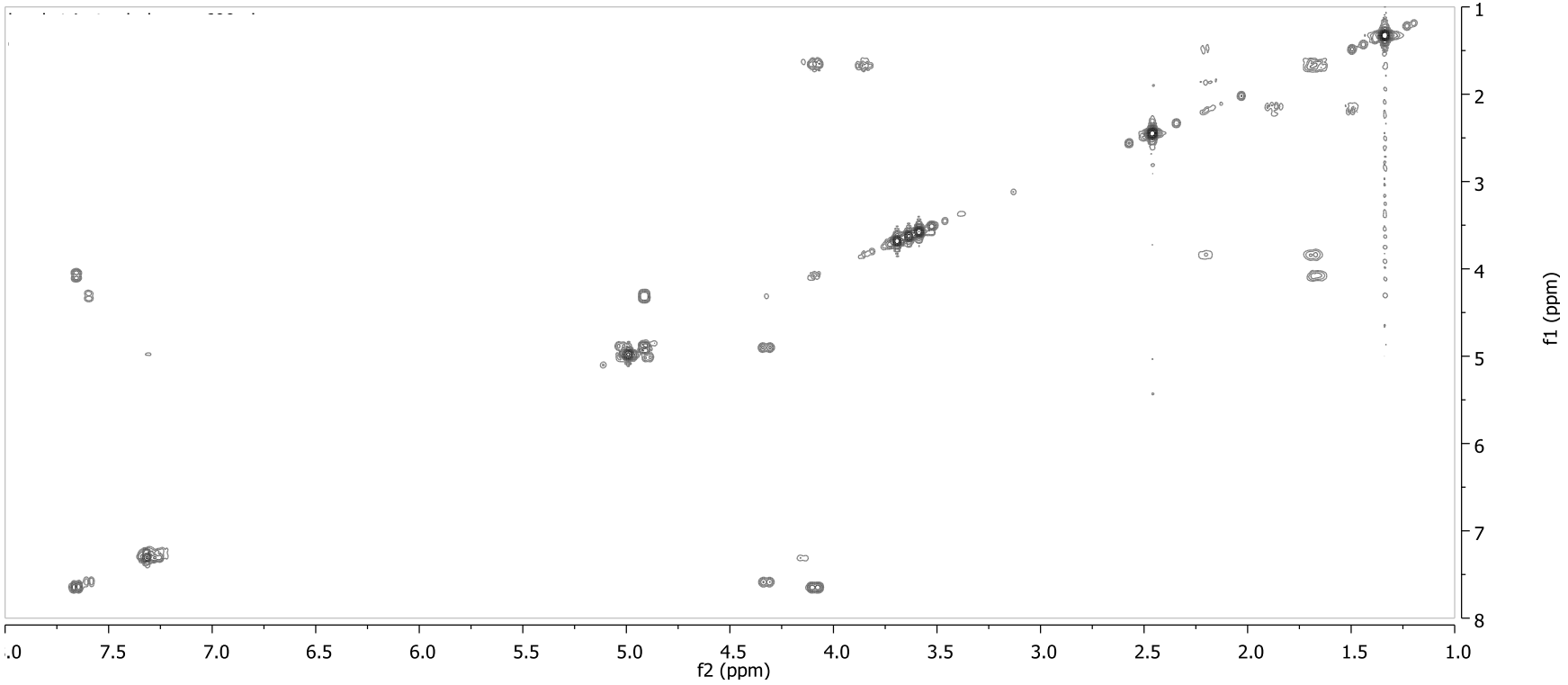

X-Bridge C18 (3x250 mm) column, 50-100% $CH_3CN$ /$H_2O$ (0.1% TFA) over 30 min at 0.5 mL/min, 215 nm

LCMS- $t_R$: 19.5 min, m/z cald for [M+1] 663.3 and $t_R$: 20.1 min (m/z calcd for [M+1] 632.4.

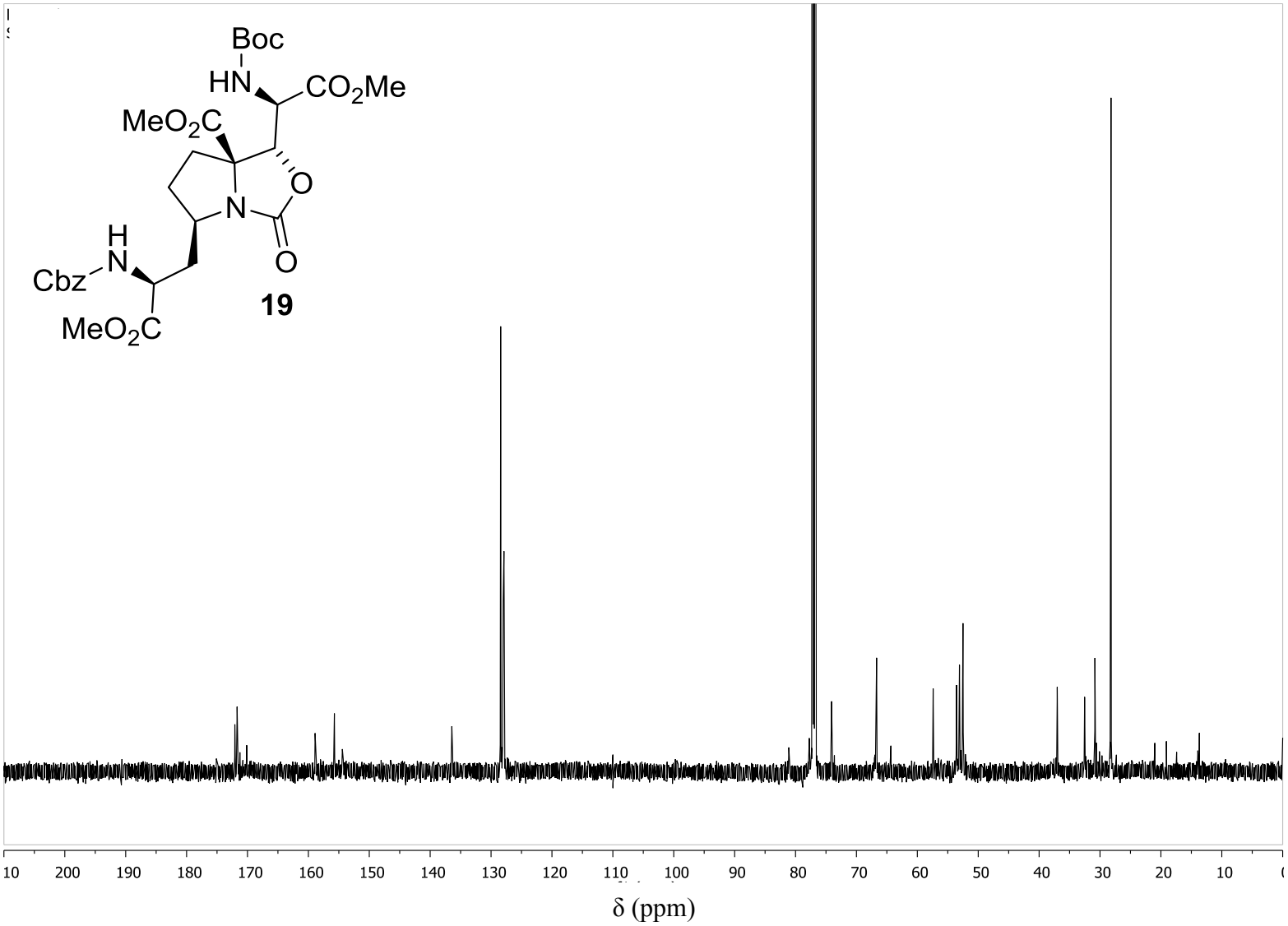
**600 MHz $^{1}$H NMR, DMSO-$d_6$ at 27° C**



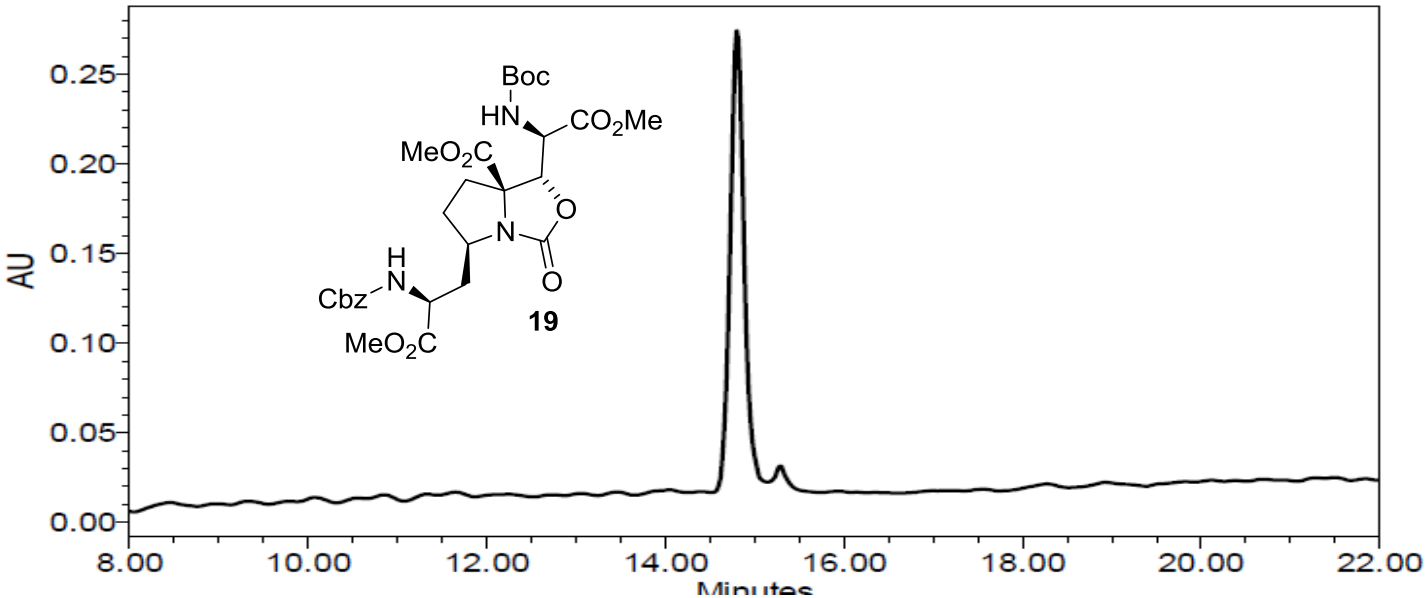

NH
3
2
9
7
6
5
8
f1 (ppm)


f2 (ppm)
f1 (ppm)

**600 MHz $^{1}$H NMR, $CDCl_3$**

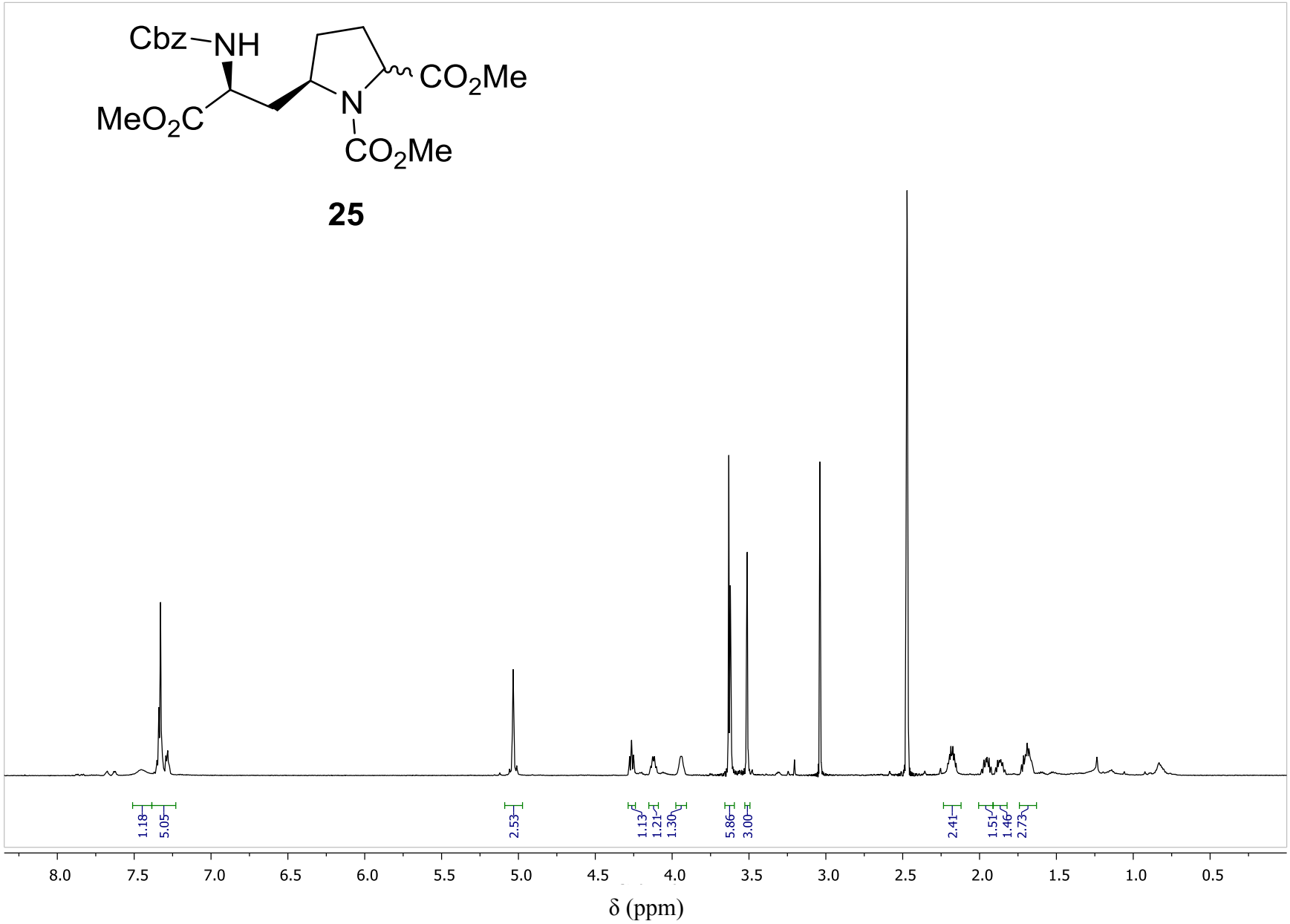


HPLC Chromatograph of the *N*-Cbz-*tri*-methyl ester **20**

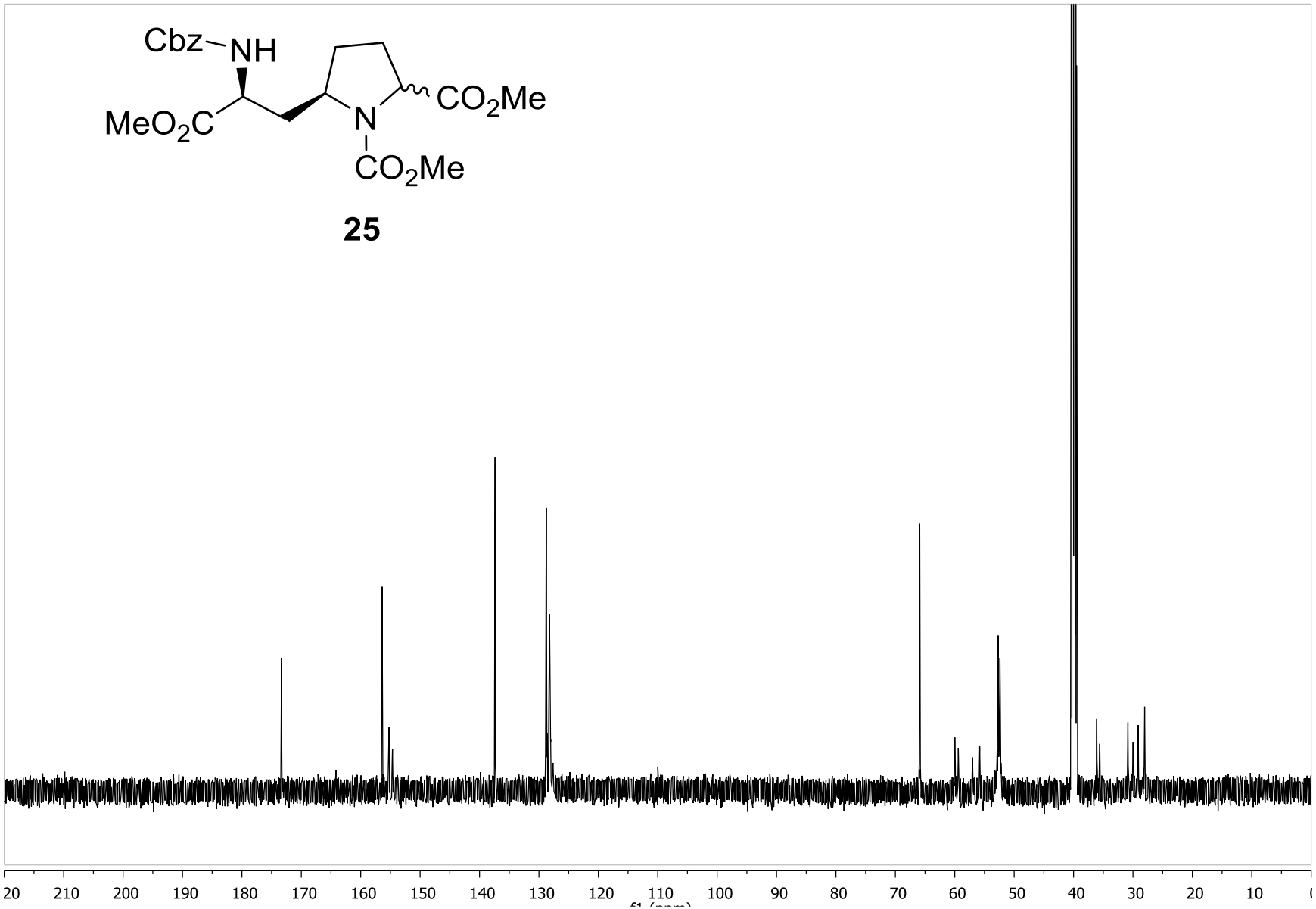



X-Bridge C18 (3x250 mm) column, 40-90% $CH_3CN$ /$H_2O$ (0.1% TFA) over 30 min at 0.5 ml/min, 215 nm

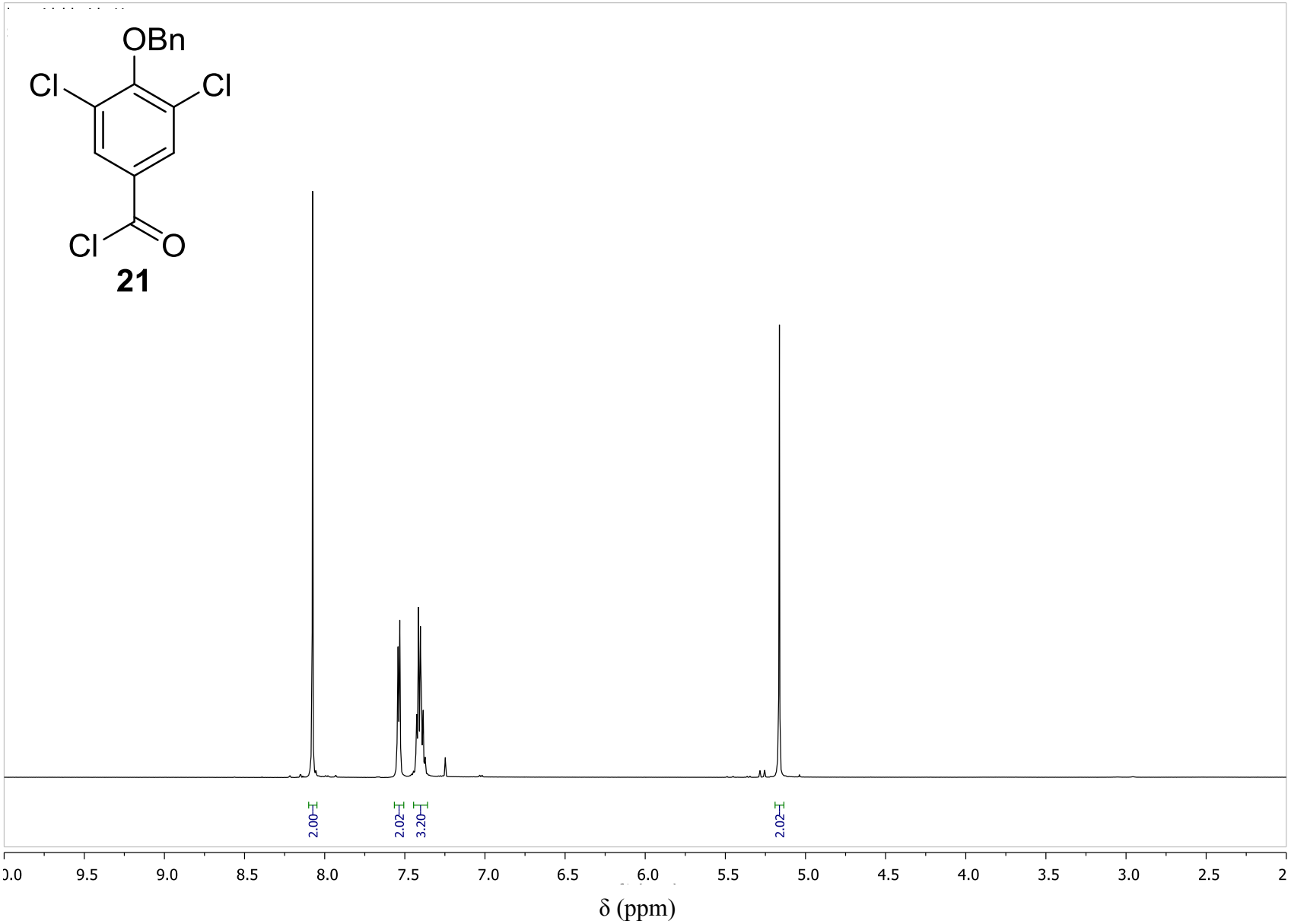
**600 MHz $^{1}$H NMR, DMSO-$d_6$ at 75° C**



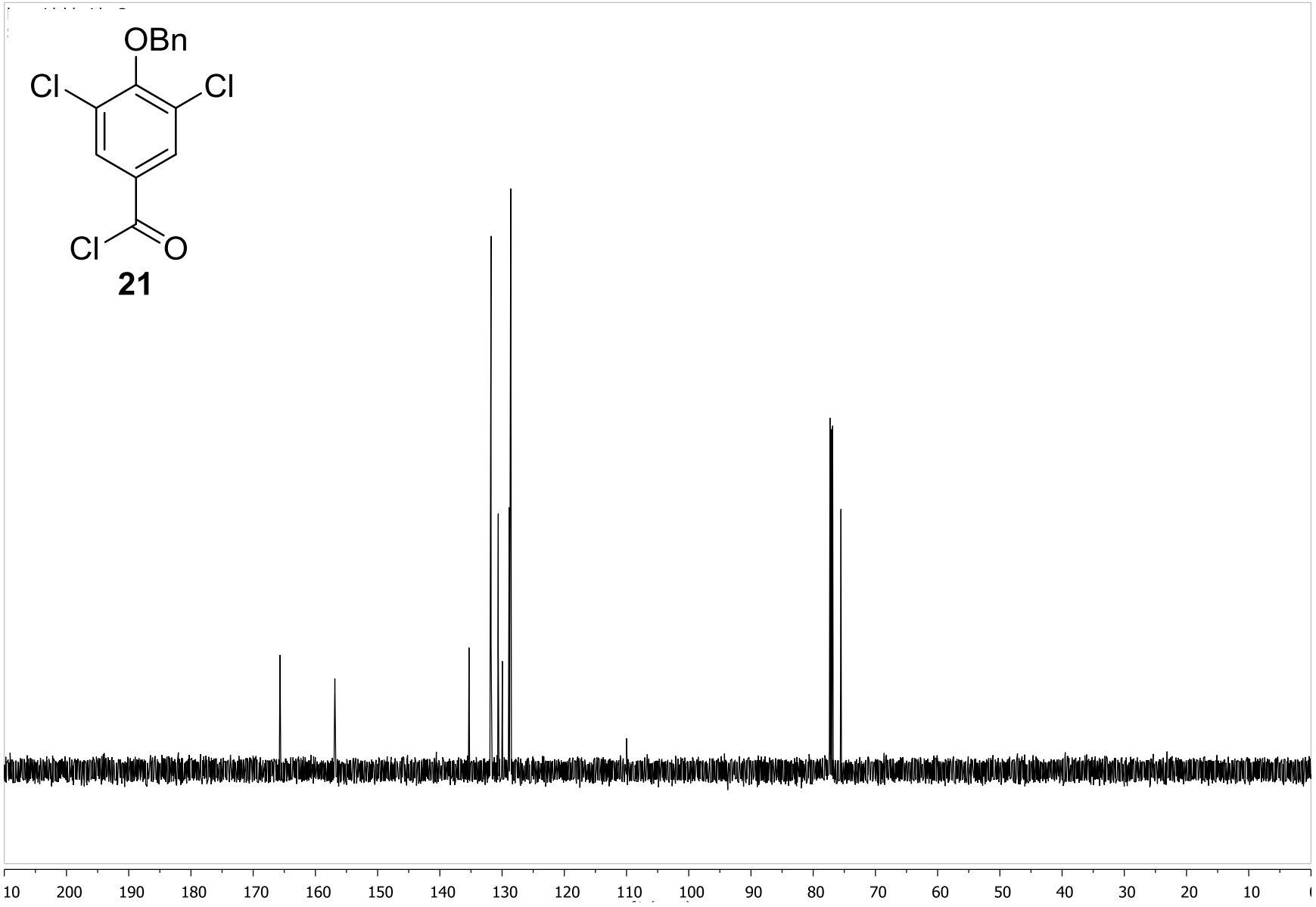
**150.8 MHz $^{13}$C NMR, DMSO-$d_6$**



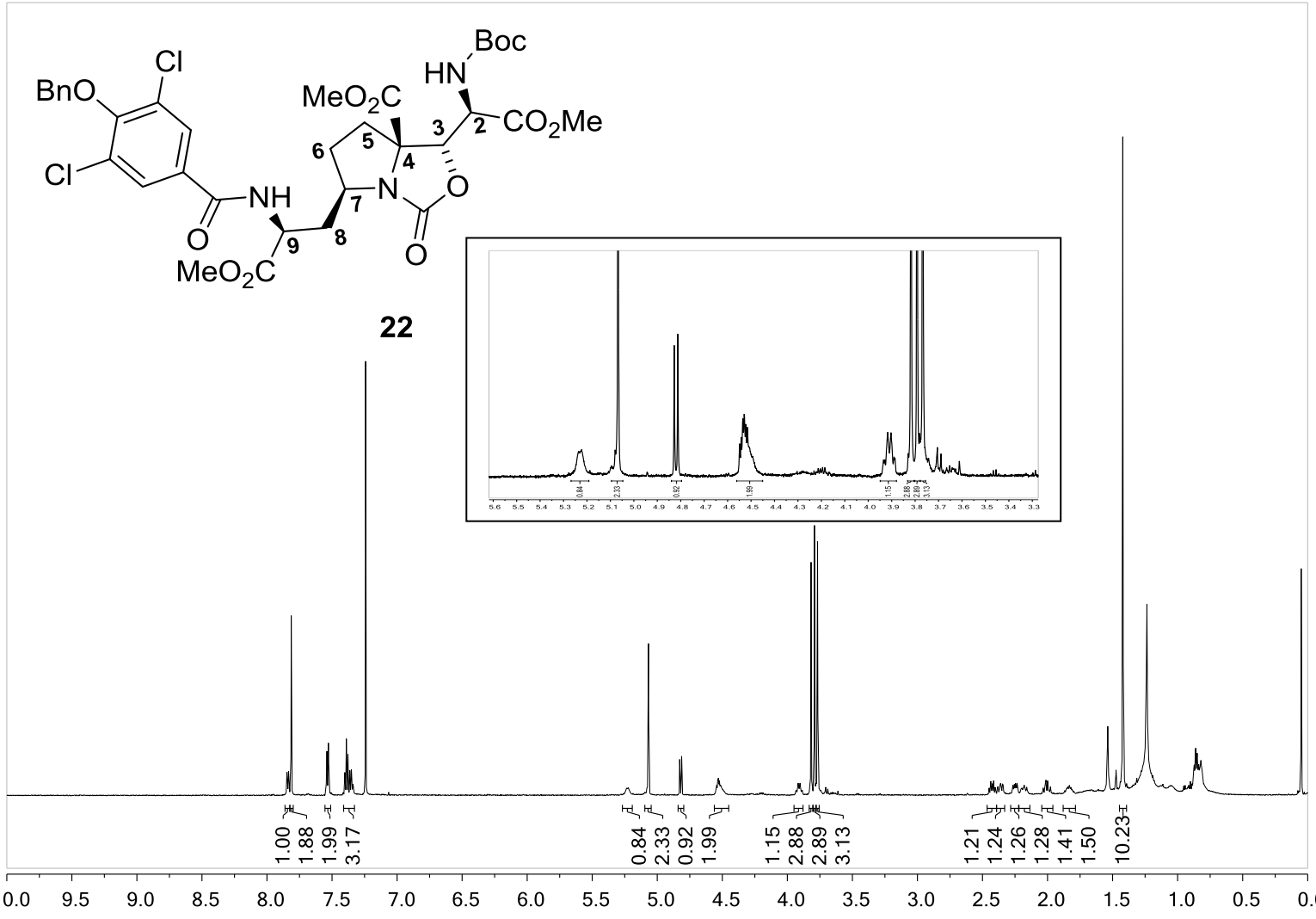
**600 MHZ $^{1}H$ NMR, $CDCl_3$**



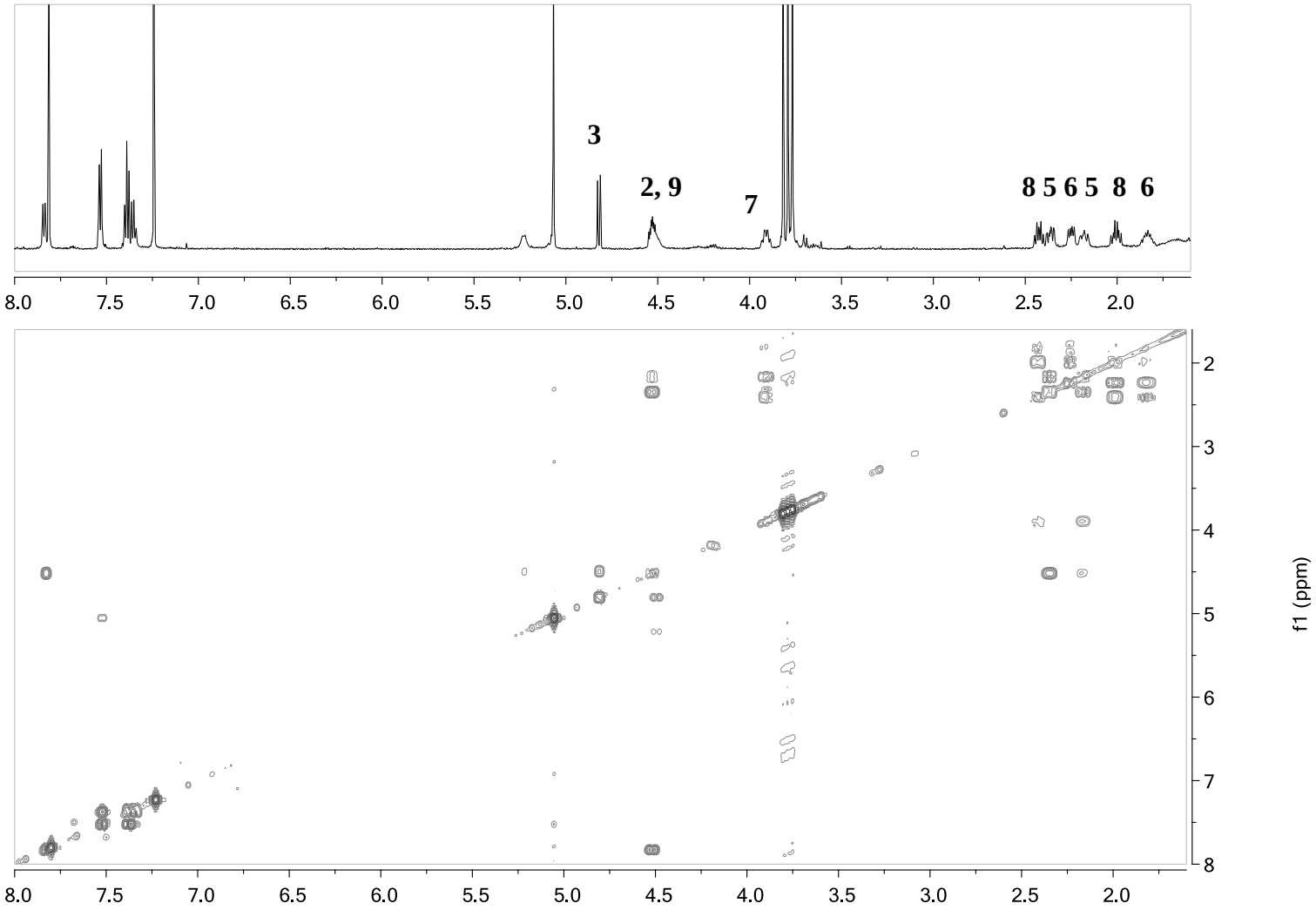
**150.8 MHZ $^{13}C$ NMR, $CDCl_3$**



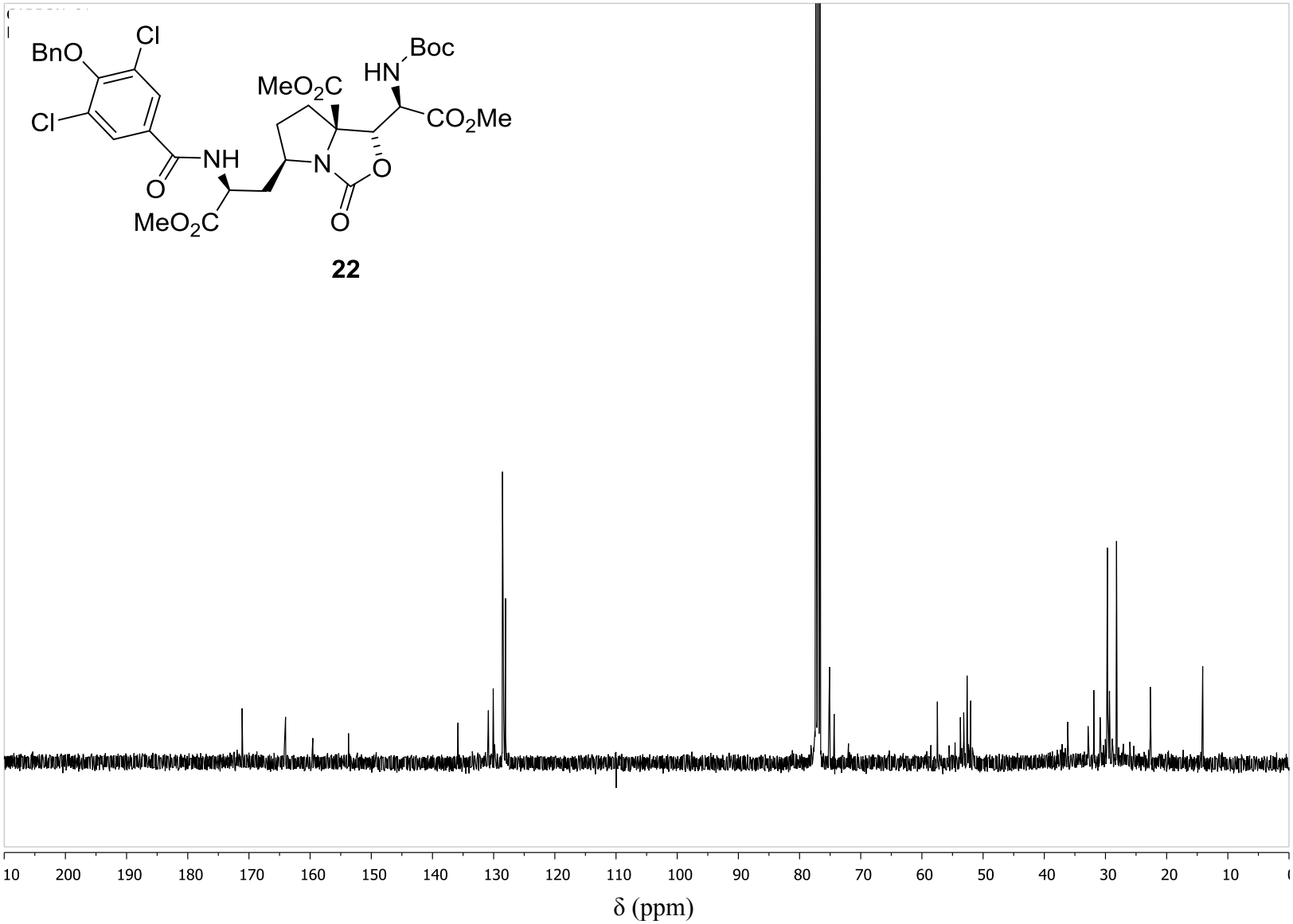
**600 MHz $^{1}$H NMR, $CDCl_3$**



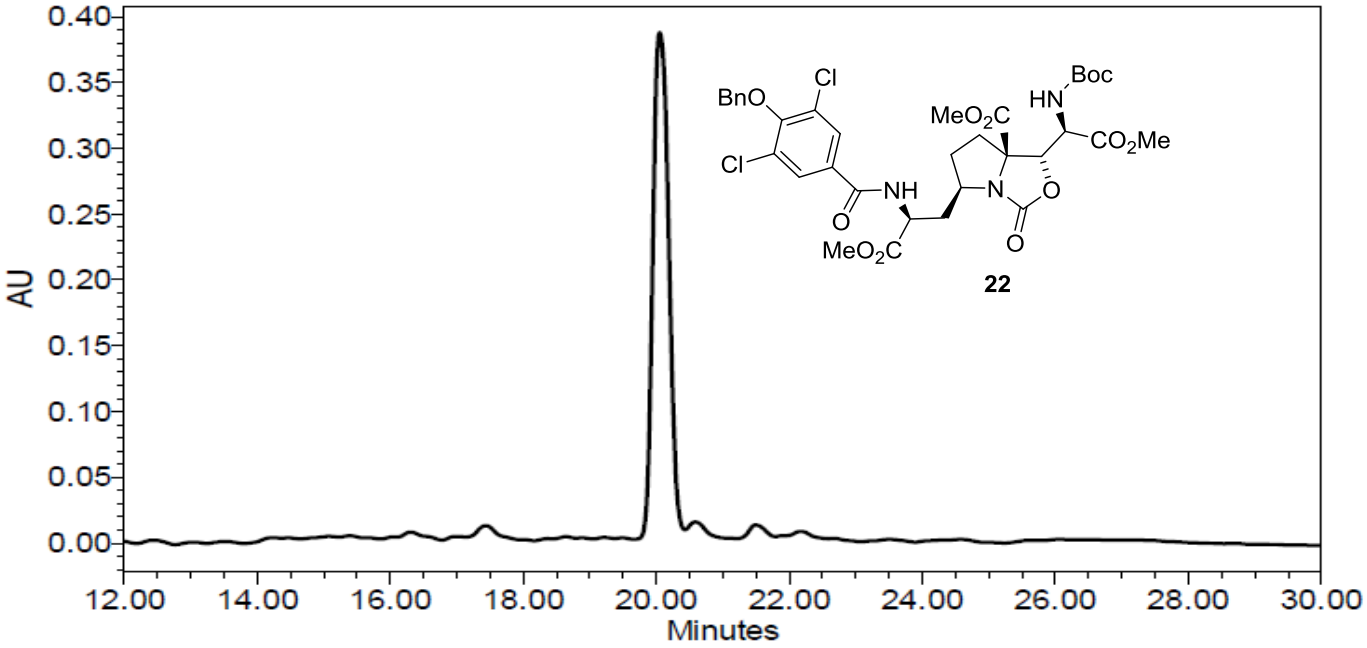
**600 MHz, gCOSY NMR, $CDCl_3$**



**125 MHz $^{13}$C NMR, $CDCl_3$**

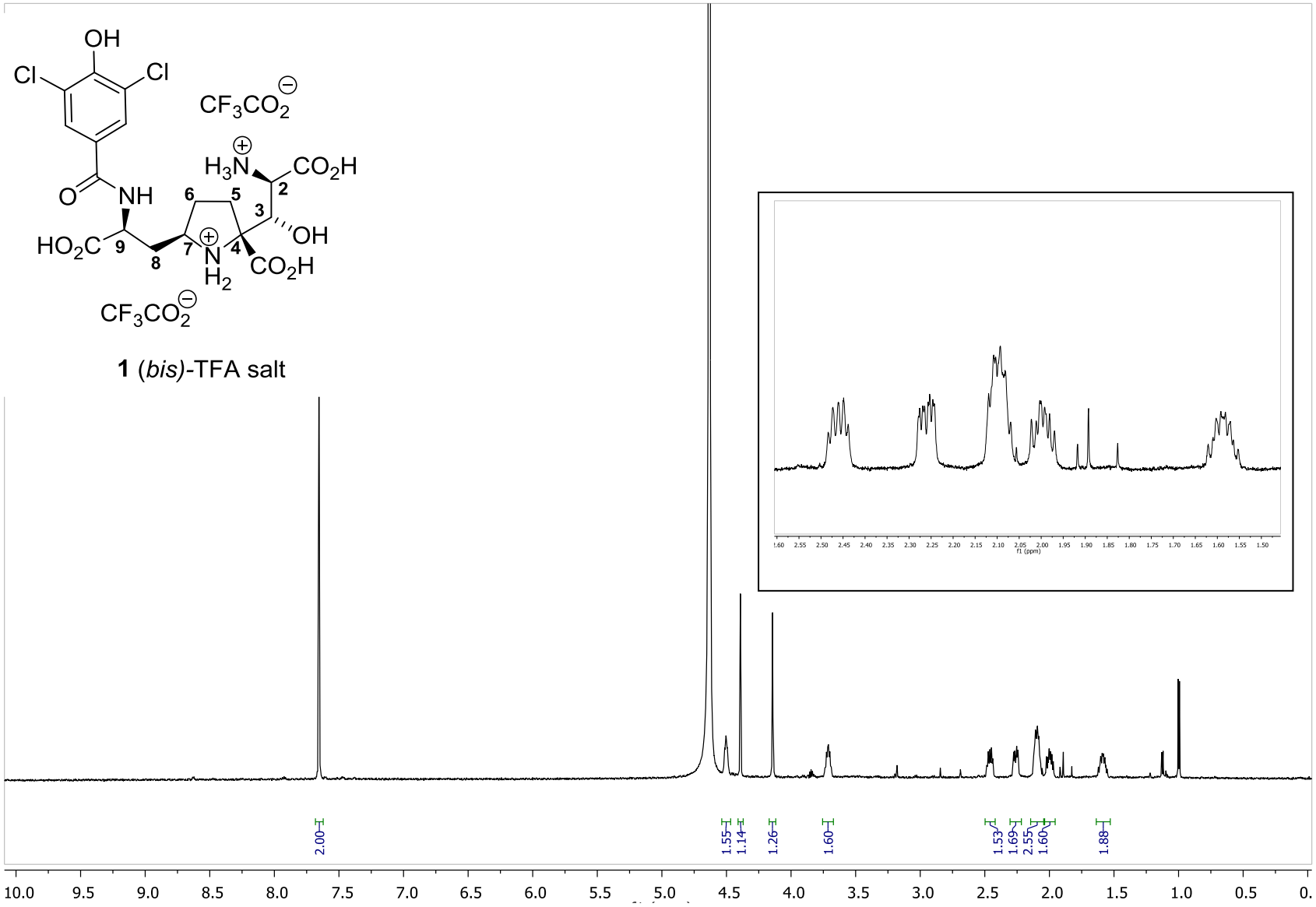


HPLC Chromatograph of the compound **22**



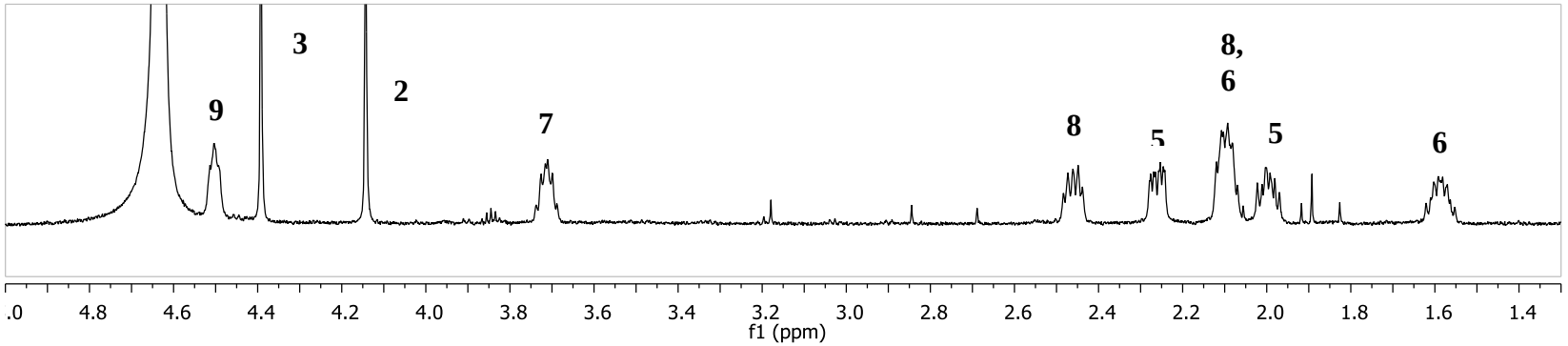

X-Bridge C18 (3x250 mm) column, 5-100% MeCN/$H_2O$ (0.1% TFA) over 30 min at 0.5 ml/min, 215 nm

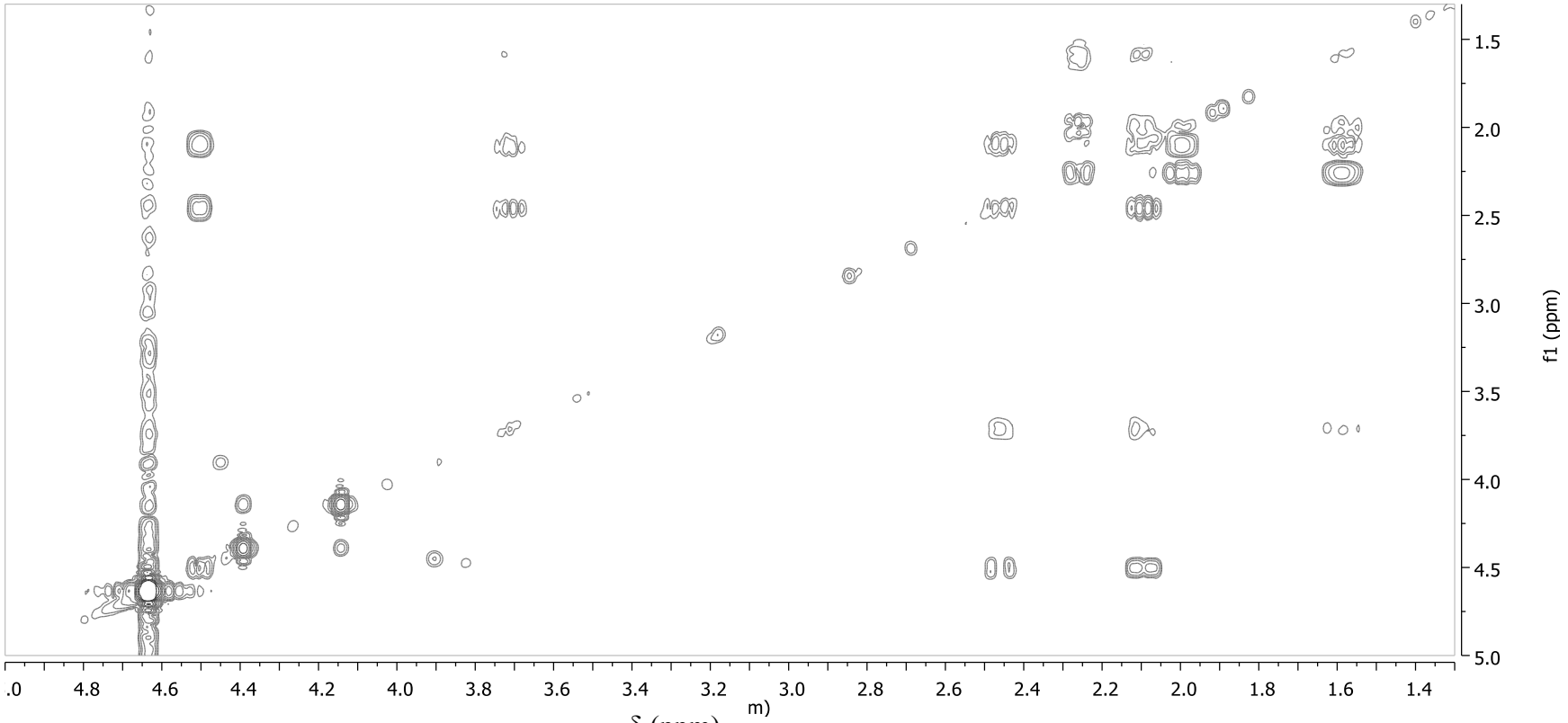
**600 MHz $^{1}$H NMR, $D_2O$**




**1** (*bis)*-TFA salt

**600 MHz gCOSY NMR, $D_2O$**



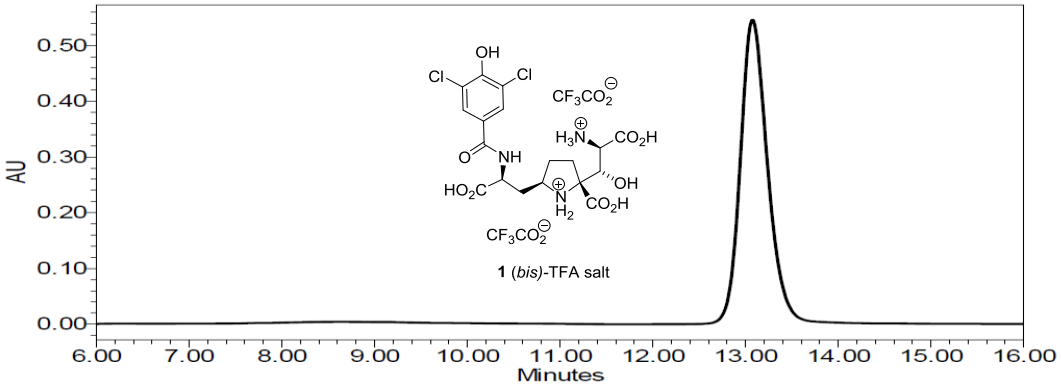
$^1$H NMR data comparison of **22** with Ma's advanced intermediate

| **Our Data ($^1$H 300 MHz, $CDCl_3$)** | **Ma's Data ($^1$H 300 MHz, $CDCl_3$)** |
|---|---|
| 7.88 (d, *J* = 7.6 Hz, 1H) | 7.88 (d, *J* = 7.5 Hz, 1H) |
| 7.84 (s, 2H) | 7.84 (s, 2H) |
| 7.59-7.50 (m, 2H) | 7.57-7.54 (m, 2H) |
| 7.46-7.32 (m, 3H) | 7.44-7.34 (m, 3H) |
| 5.26 (d, *J* = 8.6 Hz, 1H) | 5.27 (d, *J* = 8.7 Hz, 1H) |
| 5.08 (s, 2H) | 5.08 (s, 2H) |
| 4.84 (d, *J*= 9.1 Hz, 1H) | 4.85 (d, *J* = 9.3 Hz, 1H) |
| 4.59-4.44 (m, 2H) | |
| 3.99-3.86 (m, 1H) | 3.97-3.92 (m, 1H) |
| 3.84 (s, 3H) | 3.84 (s, 3H) |
| 3.81 (s, 3H) | 3.81 (s, 3H) |
| 3.78 (s, 3H) | 3.78 (s, 3H) |
| 2.50 – 2.34 (m, 2H) | 2.49-2.34 (m, 2H) |
| 2.28 – 2.14 (m, 2H), | 2.30-2.25 (m, 2H) |
| 2.06 -1.98 (m, 1H) | 2.08-1.91 (m, 1H) |
| 1.89 – 1.78 (m, 1H) | 1.91-1.78 (m, 1H) |
| 1.44 (s, 9H) | 1.44 (s, 9H |

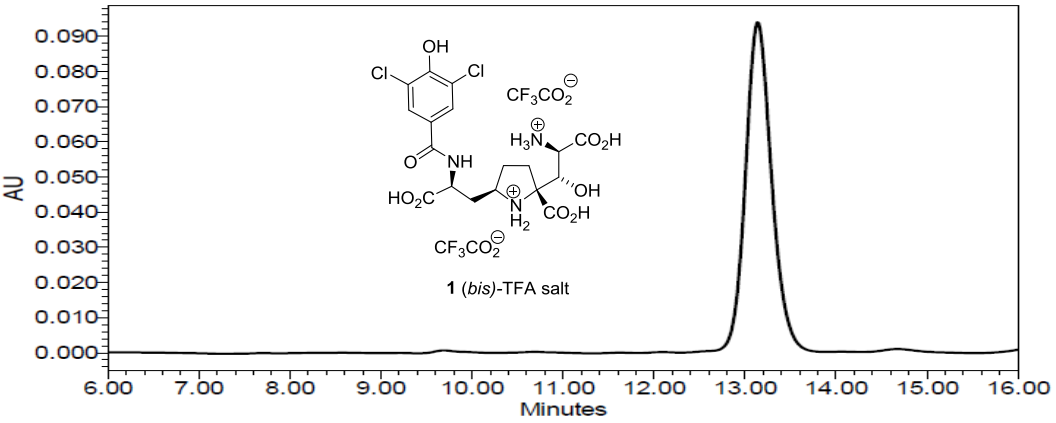
$^1$H NMR data comparison of **1** (*bis*)-TFA salt with Chamberlin's data

| **Chamberlin's data ($^1$H 500 MHz, $D_2O$)** | **Our data ($^1$H 600 MHz, $D_2O$)** |
|---|---|
| 7.81 (s, 2H) | 7.81 (s 2H) |
| 4.60 (dd, *J* = 8.4, 5.5 Hz, 1H) | 4.66 (dd, *J* = 8.5, 5.7 Hz, 1H) |
| 4.54 (s, 1H) | 4.55 (s, 1H) |
| 4.30 (s, 1H) | 4.30 (s, 1H) |
| 3.89 – 3.82 (m, 1H) | 3.91 – 3.83 (m, 1H) |
| 2.59 (ddd, *J* = 13.8, 6.8, 6.8 Hz, 1H) | 2.62 (dt, *J* = 13.8, 6.7 Hz, 1H) |
| 2.42 (ddd, *J* = 13.5, 6.4, 2.4 Hz, 1H) | 2.42 (ddd, *J* = 13.5, 6.2, 2.5 Hz, 1H) |
| 2.28 – 2.20 (m, 2H) | 2.30 – 2.20 (m, 2H) |
| 2.15 (ddd, *J* = 13.5, 11.2, 6.7 Hz, 1H) | 2.15 (ddd, *J* = 13.4, 11.4, 6.7 Hz, 1H) |
| 1.78 – 1.70 (m, 1H) | 1.79 – 1.69 (m, 1H) |

HPLC data comparison of **1** (*bis*)-TFA salt with authentic sample




(a)- kaitocephalin authentic sample[3]




(b)- **1** (*bis*)-TFA salt + authentic sample

X-Bridge C18 (3x250 mm) column, 10:90 % MeCN:$H_2O$ (0.8% TFA) at 0.5 ml/min, 215 nm

(3) We thank Prof. Yasufumi Ohfune for sending a sample of kaitocephalin.