Supporting Information

Synthesis of (–)-cotylenol, a 14-3-3 molecular glue component

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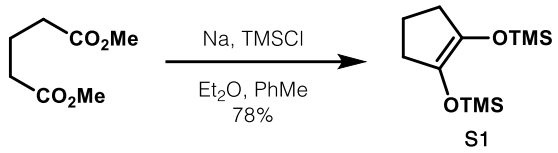
Materials and Methods

Diethyl ether (ACS grade), dichloromethane (DCM, ACS grade), ethyl acetate (EtOAc, ACS grade), hexanes (ACS grade), pentanes (ACS grade), MeOH (MeOH, ACS grade) and acetone (ACS grade) were purchased from Fisher Chemical and used without further purification. Anhydrous tetrahydrofuran (THF), anhydrous toluene (PhMe), anhydrous dichloromethane (DCM) and anhydrous 1,2-dichloroethane (DCE) were purchased from Sigma Aldrich in SureSeal bottles and used without further purification. Anhydrous MeOH (MeOH) was purchased from Acros in AcrosSeal bottles and used without further purification. Commercially available reagents were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using precoated silica plates from EMD Chemicals (TLC Silica gel 60 F254, 250 μm thickness). Flash column chromatography was performed over Silica gel 60 (particle size 0.04-0.063 mm) from EMD chemicals. Low resolution mass spectra were recorded on an Agilent 6120 Quadrupole LC/MS system with an ESI probe. Measurements for high-resolution mass spectrometry (HRMS) were performed on a Waters Xevo G2-XS TOF calibrated against sodium formate clusters and using a LeuEnk lockmass. Expected monoisotopic masses were calculated using MassLynx 4.1 and the *m*/*z* values for calibrant and lockmass were MassLynx-default values. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-400, DPX-400, AV-500, or AV-600 (equipped with ^{1}H or ^{13}C cryoprobe) spectrometers and referenced to residual solvent peaks ($CDCl_3$ @ 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; C_6D_6 @ 7.16 ppm ^{1}H NMR, 128.06 ppm ^{13}C NMR). Optical rotations were obtained on an Anton Paar MCP100 modular circular polarimeter.

Experimental Procedures
A. First-Generation Synthesis

Bis(trimethylsilyloxy)olefin S1 [1,2-bis((trimethylsilyl)oxy)cyclopent-1-ene]

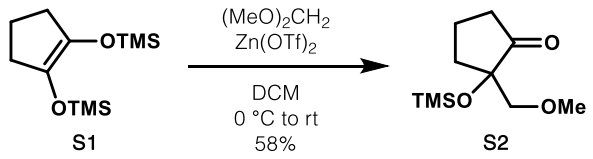


S1

The title compound was prepared according to the procedure of Bloomfield *et. al*., rewritten here for convenience.[1]

An oven dried 3 L 3-neck round bottom flask equipped with an addition funnel, reflux condenser, and mechanical stirrer was charged with freshly cut metallic sodium (27.6 g, 1.20 mol, 4 equiv) under a stream of dry nitrogen. The vessel was placed under an argon atmosphere, and anhydrous PhMe (270 mL, 10x v/w with respect to sodium) was cannulated into the reaction. The reaction was rapidly stirred and heated to reflux until the sodium (m.p. 98 °C) had formed finely dispersed droplets. Stirring was stopped and the reaction was allowed to cool to room temperature. Anhydrous Et_2O (750 mL) was then added via cannula to the reaction. The addition funnel was charged with dimethyl glutarate (44.1 mL, 300 mmol, 1 equiv), freshly distilled chlorotrimethylsilane (152 mL, 1.20 mol, 4 equiv), and Et_2O (360 mL). Stirring was resumed, and the addition funnel was emptied dropwise into the reaction over approximately 100 minutes. The reaction was then heated to a gentle reflux overnight and then cooled to room temperature. The mixture was filtered through a pad of celite under a stream of nitrogen, rinsing with Et_2O, and then concentrated. The crude product was purified via fractional distillation under vacuum (b.p. 64–65°, 4.3 Torr) to afford the product as a colorless oil (57.5 g, 78%). Analytical data were in agreement with those previously reported.[2]

Ketone S2 [2-(methoxymethyl)-2-((trimethylsilyl)oxy)cyclopentan-1-one]



To a stirred suspension of $Zn(OTf)_2$ (1.82 g, 5.0 mmol, 5 mol %) in anhydrous CH_2Cl_2 (200 mL, 0.5 M) at 0 °C under an argon atmosphere was added simultaneously bis(trimethylsilyloxy)olefin **S1** (26.9 mL, 100 mmol, 1 equiv) and dimethoxymethane (26.5 mL, 300 mmol, 3 equiv) via syringe over 10 minutes. After stirring for 1 hour at this temperature, the reaction was raised to room temperature and then stirred for an additional 2 hours. The reaction mixture was diluted with hexanes (400 mL, *ca.* 2 reaction volumes) and filtered through Celite, eluting with hexanes. The filtrate was concentrated. Purification by chromatography on silica gel (0 to 10% Et_2O/hexanes) afforded the product as a colorless oil (12.5 g, 58%).

R_f 0.63 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$)

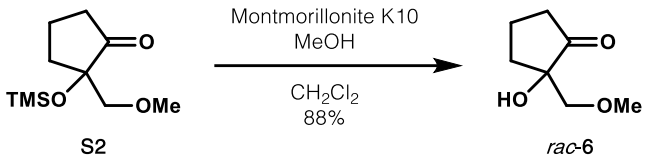
δ 3.42 (d, *J* = 9.3 Hz, 1H), 3.35 (d, *J* = 9.2 Hz, 1H), 3.30 (s, 3H), 2.33 – 2.27 (m, 1H), 2.25 – 2.16 (m, 2H), 1.97 – 1.89 (m, 2H), 1.88 – 1.81 (m, 1H), 0.09 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 217.4, 80.2, 75.2, 59.5, 36.5, 35.0, 17.9, 2.0.

HRMS Calculated $C_7H_{13}O_3$ $[M–TMS+2H]^+$: 145.0865 | Found: 145.0859

Racemic α-hydroxyketone *rac*-6 [2-hydroxy-2-(methoxymethyl)cyclopentan-1-one]



To a solution of ketone **S2** (11.98 g, 55.4 mmol, 1 equiv) in CH_2Cl_2 (110 mL, 0.5 M) was added montmorillonite K10 (13.85 g, 250 mg/mmol) and MeOH (13.4 mL, 332.4 mmol, 6 equiv) under air with no exclusion of air or moisture. After full consumption of the starting material as indicated by TLC (*ca.* 4 hours), the reaction mixture was filtered through a plug of KF/silica gel (10:90 w/w), eluting with CH_2Cl_2. The filtrate was then concentrated to afford the product as a pale yellow oil of sufficient purity to use in the next step (7.02 g, 88%).

R_f 0.31 (40% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$)

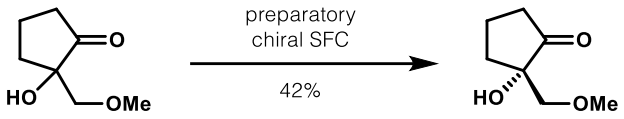
δ 3.44 (d, *J* = 9.6 Hz, 1H), 3.40 (d, *J* = 9.6 Hz, 1H), 3.35 (s, 3H), 2.90 (br s, 1H), 2.40 – 2.29 (m, 2H), 2.18 – 2.14 (m, 1H), 2.01 – 1.84 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 218.3, 78.3, 75.3, 59.8, 35.6, 33.2, 17.4.

HRMS Calculated $C_7H_{12}NaO_3$ $[M+Na]^+$: 167.0684 | Found: 167.0682

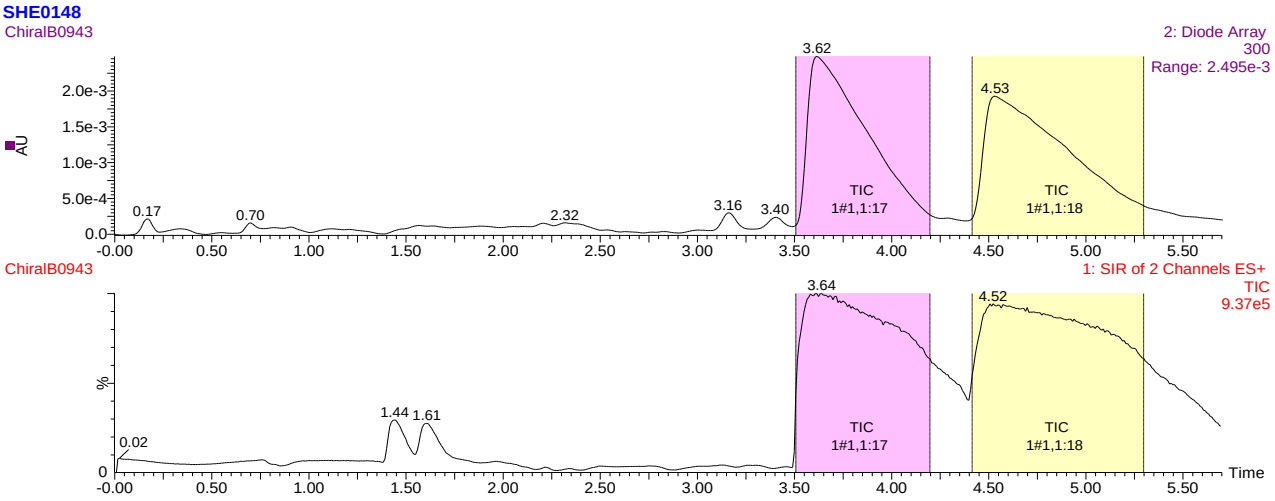
(*S*)-α-Hydroxyketone (*S*)-6 [(*S*)-2-hydroxy-2-(methoxymethyl)cyclopentan-1-one]



rac-6 (*S*)-6

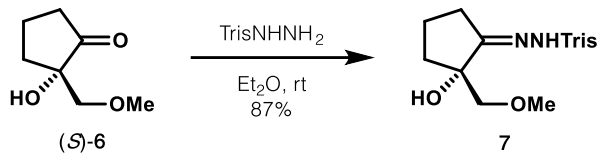
A solution of 5.68 g of *rac*-**6** (39.4 mmol) in MeOH was prepared at a concentration of 50 mg/mL (114 mL). The material was purified via preparative SFC (Waters 150 AP) on a Daicel IG column (21 mm inner diameter, 250 mm length, 5 micron particle size) using an isocratic solvent system of 95% CO_2 and 5% MeOH at 35 °C with a flow rate of 100 mL/min against a 110 bar backpressure. Fraction collection was triggered by MS monitoring (QDa mass detector) at $[M+Na]^+$ and $[M+H]^+$ (167.1 and 145.1 respectively). 400 µL injections were conducted every 6.5 minutes, resulting in 285 injections over approximately 31 hours of instrument time. Concentration of the fractions with shorter retention time (positive optical rotation) afforded the product as a colorless oil (2.37 g, 42%). Analytical data are in agreement with the racemate with exception of the observed optical rotation:

$[\alpha]_D^{20}$ +70.6 (*c* 0.5, $CHCl_3$)



Representative chromatogram from preparative SFC separation. Top: UV detector at 300 nm wavelength. Bottom: MS detector monitoring at $[M+H]^+$ and $[M+Na]^+$ (167.1 and 145.1 respectively)

Hydrazone 7 [(*R*)-*N*'-(2-hydroxy-2-(methoxymethyl)cyclopentylidene)-2,4,6-triisopropylbenzenesulfonohydrazide]



(*S*)-6 7

A solution of α-hydroxyketone (*S*)-**6** (365 mg, 2.53 mmol, 1 equiv) in Et_2O (5.0 mL, 0.5 M) was treated with 2,4,6-triisopropylbenzenesulfonyl hydrazide[13] (830 mg, 2.78 mmol, 1.1 equiv). An argon atmosphere was established, and the reaction mixture was stirred overnight then concentrated. Purification by chromatography on silica gel (10 to 40% EtOAc/hexanes), afforded the product as an amorphous foam with an inconsequential 4:1 mixture of unassigned *E*/*Z* isomers (934 mg, 87%).

Note: *rac*-**7** could be prepared in the same manner starting from *rac*-**6**, yielding identical analytical data with the exception of optical rotation.

R_f Major diastereomer: 0.54; minor diastereomer: 0.63 (40% EtOAc/hexanes, UV active)

$[\alpha]_D^{20}$ +32.6 (*c* 0.5, $CHCl_3$)

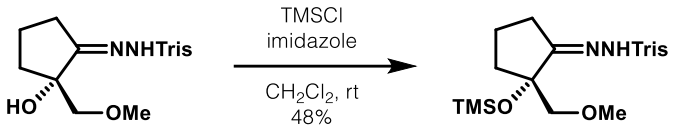
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.16 (s, 2H), 7.16* (s, 2H), 4.19 (hept, *J* = 6.8 Hz, 2H), 3.66* (d, *J* = 9.5 Hz, 1H), 3.46* (s, 3H), 3.40 (d, *J* = 9.5 Hz, 1H), 3.38* (d, *J* = 9.5 Hz, 1H), 3.23 (d, *J* = 9.5 Hz, 1H), 3.12 (s, 3H), 2.92 – 2.86 (m, 1H), 2.46 – 2.39* (m, 1H), 2.38 – 2.32 (m, 1H), 2.16 (dt, *J* = 17.9, 7.5 Hz, 1H), 1.98 – 1.91 (m, 2H), 1.86 – 1.76 (m, 3H), 1.29 – 1.24 (m, 18H). Distinguishable peaks for the minor isomer are denoted with a star (*).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 153.6, 151.4, 131.2, 123.9, 79.2, 76.7, 59.4, 35.8, 34.4, 30.1, 26.9, 24.9, 23.7, 20.6.

HRMS Calculated $C_{22}H_{37}N_2O_4S$ $[M+H]^+$: 425.2474 | Found: 425.2471

TMS-Protected hydrazone 8 [(*R*)-2,4,6-triisopropyl-*N*'-(2-(methoxymethyl)-2-((trimethylsilyl)oxy)cyclopentylidene)benzenesulfonohydrazide]



7 8

To a solution of hydrazone **7** (50 mg, 0.12 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1.2 mL, 0.1 M) was added trimethylsilyl chloride (44.6 μL, 0.35 mmol, 3 equiv) and imidazole (24 mg, 0.35 mmol, 3 equiv) at room temperature. After stirring for 3 hours, the mixture was diluted with hexane, filtered through a pad of Celite, and concentrated. Purification by chromatography on silica gel (11 to 20% EtOAc/hexanes), afforded the product (single unassigned *E*/*Z* isomer) as a white solid (28 mg, 48%).

R_f 0.41 (20% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ −18.4 (*c* 0.91 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

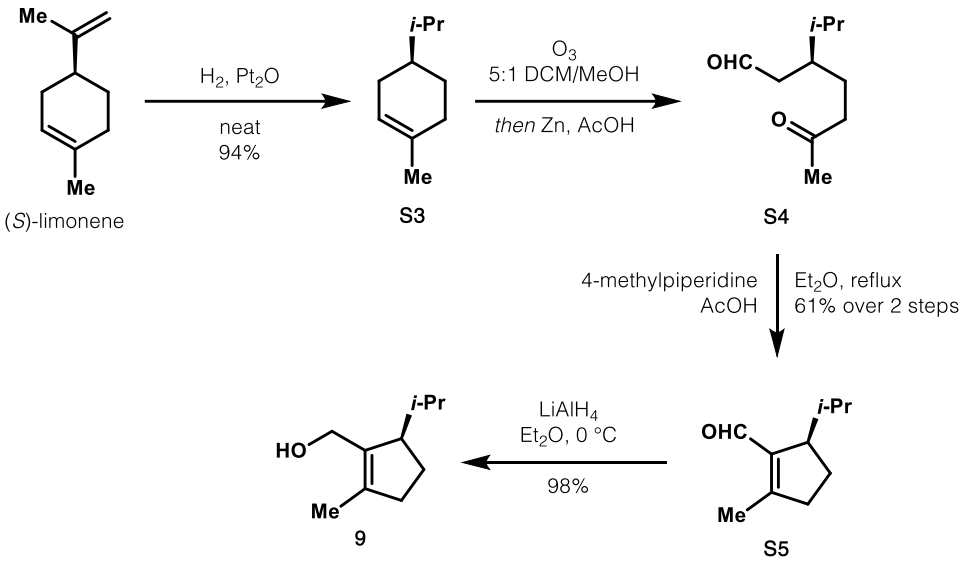
δ 7.71 (s, 1H), 7.16 (s, 2H), 4.26 (sept, *J* = 6.7 Hz, 2H), 3.43 (d, *J* = 9.4 Hz, 1H), 3.28 (d, *J* = 9.5 Hz, 1H), 3.00 (s, 3H), 2.88 (sept, *J* = 6.9 Hz, 1H), 2.29 (ddd, *J* = 18.2, 9.0, 2.7 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.88 – 1.76 (m, 4H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.28 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.9 Hz, 6H), -0.11 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 162.6, 153.5, 151.5, 131.2, 123.8, 81.6, 75.7, 59.0, 37.5, 34.4, 29.8, 27.4, 25.1, 24.8, 23.71, 23.70, 20.5, 1.62.

HRMS Calculated $C_{25}H_{45}N_2O_4SSi$ $[M+H]^+$: 497.2869 | Found: 497.2855

Alcohol 9 [(*R*)-(5-isopropyl-2-methylcyclopent-1-en-1-yl)methanol]



The title compound, alcohol **9**, was prepared via small modifications to published procedures,[3,4] described here for convenience.

S3: A 250 mL Parr hydrogenation apparatus was charged with (*S*)-limonene (120 mL, 741 mmol, 1 equiv) and PtO_2 (200 mg, 0.7 mmol, 0.1 mol %). The system was filled with hydrogen gas up to *ca.* 30 psi and shaken. The reaction was stopped and vented every 1.5 hours in order to monitor the reaction by ^1H NMR, and after 6 hours the starting material was found to be consumed. The crude material was filtered through a plug of Celite, affording **S3** as a pale yellow oil which was used in the next step without further purification (95.9 g, 94%). Analytical data match those previously reported.[3]

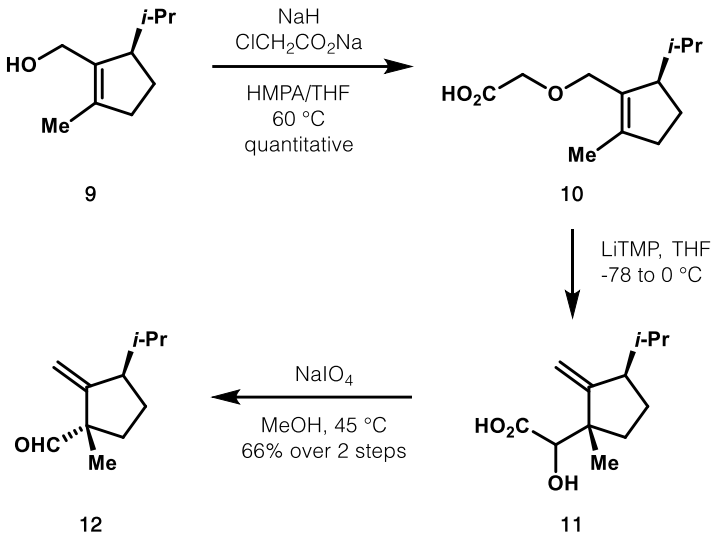
S4: A solution of **S3** (9.1 mL, 53.6 mmol, 1 equiv) in MeOH (28 mL) and CH_2Cl_2 (140 mL) was cooled to -78°C and a stream of ozone was bubbled through with stirring until a blue color persisted in the solution. Oxygen was bubbled through the solution until the blue color dissipated, and Zn powder (7.0 g) and AcOH (9.2 mL) were subsequently added. The solution was allowed to gradually warm to room temperature over roughly 1 hour. This procedure was repeated to yield a theoretical total of 107.4 mmol of **S4**. The combined reaction mixtures were filtered through Celite then washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated to afford ketoaldehyde **S4** which was used directly in the next step without further purification. Analytical data match those previously reported.[4]

S5: Crude **S4** (107.4 mmol theoretical, 1 equiv) was dissolved in Et_2O (600 mL, 0.17 M) and then treated with 4-methylpiperidine (4.2 mL, 35.4 mmol, 0.33 equiv) and AcOH (3.7 mL, 64.3 mmol, 0.6 equiv). The reaction vessel was equipped with a reflux condenser and placed under an argon atmosphere, then stirred at reflux for *ca.* 24 hours. After cooling to room temperature, the solution was washed with saturated aqueous $NaHCO_3$, 10 wt % aqueous citric acid, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (4 to 20% Et_2O/pentane) afforded

aldehyde **S5** as a light yellow oil (9.89 g, 61% over 2 steps). Analytical data match those previously reported.[3]

9: A solution of aldehyde **S5** (7.61 g, 50 mmol, 1 equiv) in Et_2O (100 mL, 0.5 M) under an argon atmosphere was cooled in an ice bath to 0 °C and then treated dropwise with a solution of $LiAlH_4$ (1.0 M in THF, 15.0 mL, 15.0 mmol, 0.3 equiv). After 15 minutes, the reaction was quenched with acetone (3.7 mL, 50 mmol, 1 equiv) and stirred at room temperature with a saturated solution of sodium potassium tartrate. After 30 minutes, the mixture was diluted with Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford alcohol **9** as a colorless solid with sufficient purity to use directly in the next step (7.52 g, 98%). Analytical data match those previously reported.[3]

Aldehyde 12 [(1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentane-1-carbaldehyde]



10: To a round bottom flask containing NaH (60% dispersion in mineral oil, 288 mg, 7.2 mmol, 1.2 equiv) under an argon atmosphere was added a solution of allylic alcohol **9** (924 mg, 6.0 mmol, 1 equiv) in anhydrous THF (12 mL, 0.5 M). HMPA (0.6 mL, 5% v/v with respect to THF) was added via syringe, and then the septum was removed and sodium chloroacetate (664 mg, 5.7 mmol, 0.95 equiv) was added quickly in one portion. The flask was equipped with a Vigreux column and then heated to 60 °C for 36 hours. The reaction mixture was then cooled to room temperature and diluted with Et_2O. The organic phase was extracted three times with 0.5 M aqueous NaOH to remove the product. The aqueous phase was acidified with 1 M HCl solution to pH <4, then extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to give of product of sufficient quality for use in the next step (1.351 g, *ca*. 100%). (Note: It is important that chloroacetic acid is minimally present in this crude material for the next step to proceed cleanly.)

11: LiTMP was first prepared by adding *n*-BuLi (2.4 M in hexanes, 2.33 mL, 5.61 mmol, 2.1 equiv) to a stirred solution of freshly distilled 2,2,6,6-tetramethylpiperidine (1.00 mL, 5.87 mmol, 2.2 equiv) in anhydrous THF that was previously degassed by sparging with argon (27 mL, 0.1 M) at -78 °C. After ~30 minutes, a solution of acid **10** (567 mg, 2.67 mmol, 1 equiv) in THF (2.7 mL, 1 M) was added dropwise at -78 °C. After 1 hour, the solution was warmed to 0 °C for 3 hours, then diluted with Et_2O and extracted three times with 0.5 M aqueous NaOH. The aqueous layer was acidified with 1 M HCl solution to pH <4, then extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to give crude material of sufficient quality to use in the next step (436 mg, 77%).

12: To a solution of the crude [2,3]-Wittig rearrangement product **11** (436 mg, 2.05 mmol) in MeOH (20 mL, 0.1 M) was added sodium periodate (1.31 g, 6.15 mmol, 3 equiv). The headspace was flushed briefly with argon, and the reaction was stirred at 45 °C for 8 hours. The solution was then cooled to room temperature, diluted with water until homogenous, and extracted three times with pentane. The organic phase was dried over $MgSO_4$, filtered, and concentrated under gentle vacuum to afford the volatile product as a colorless oil with a musky odor (294 mg, 86%; 66% over 2 steps).

R_f 0.52 (10% EtOAc/hexanes)

$[\alpha]_D^{25}$ +50.8 (*c* 0.81, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$)

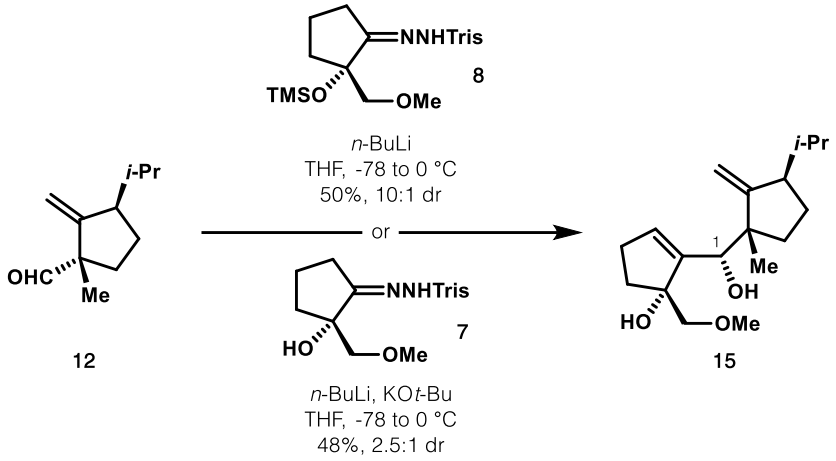
δ 9.29 (s, 1H), 5.04 (d, *J* = 2.5 Hz, 1H), 4.87 (d, *J* = 2.9 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.03 (ddd, *J* = 12.5, 9.3, 7.0 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.76 (ddt, *J* = 14.3, 6.6, 3.6 Hz, 1H), 1.57 (ddd, *J* = 12.3, 6.2, 2.8 Hz, 1H), 1.51 (ddd, *J* = 16.0, 6.8, 3.6 Hz, 1H), 1.16 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.5, 156.0, 109.5, 58.6, 51.5, 32.8, 29.2, 24.4, 22.0, 20.9, 17.0.

HRMS Calculated $C_{11}H_{18}NaO$ $[M+Na]^+$ 181.1255 | Found: 181.1251

Diol 15 [(*R*)-2-((*S*)-hydroxy((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methyl)-1-(methoxymethyl)cyclopent-2-en-1-ol]



Preparation from **8**: A solution of TMS-protected hydrazone **8** (270 mg, 0.54 mmol, 1.2 equiv) in anhydrous THF (5.4 mL, 0.1 M) under an argon atmosphere at -78 °C was treated with *n*-BuLi (2.42 M in hexanes, 0.67 mL, 1.62 mmol, 3.6 equiv). After 10 minutes, the reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was cooled to -78 °C and a solution of aldehyde **12** (75 mg, 0.45 mmol, 1 equiv) in THF (4.5 mL, 0.1 M) was added dropwise. After 20 minutes, the reaction mixture was stirred at 0 °C for 1 hour before being quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with brine and extracted three times with Et_2O. The combined extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (10 to 40% EtOAc/hexanes) afforded the product as a colorless oil (66 mg, 50%).

Preparation from **7**: A solution of hydrazone **7** (102 mg, 0.24 mmol, 1.2 equiv) in anhydrous THF (1.0 mL, 0.2 M) under an argon atmosphere at -78 °C was treated with *n*-BuLi (2.71 M in hexanes, 0.27 mL, 0.72 mmol, 3.6 equiv) and KO*t*-Bu (1.0 M in THF, 0.24 mL, 0.24 mmol, 1.2 equiv). After 5 minutes, the reaction mixture was stirred at 0 °C for 30 minutes. The reaction mixture was cooled to -78 °C and a solution of aldehyde **12** (62 mg, 0.2 mmol, 1 equiv) in THF (1.0 mL, 0.2 M) was added dropwise. After 20 minutes, the reaction mixture was stirred at 0 °C for 1 hour before being quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with brine and extracted three times with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (10 to 40% EtOAc/hexanes) afforded the product as a colorless oil (29 mg, 48%).

R_f 0.55 (40% EtOAc/hexanes)

$[\alpha]_D^{25}$ +59.0 (*c* 0.72 $CHCl_3$)

^{1}H NMR (500 MHz, C_6D_6)

δ 5.71 – 5.67 (m, 1H), 5.05 (d, *J* = 3.7 Hz, 1H), 4.85 (d, *J* = 3.2 Hz, 1H), 4.54 (d, *J* = 2.5 Hz, 1H), 4.04 (br s, 2H), 3.35 (d, *J* = 11.3 Hz, 1H), 3.32 (d, *J* = 11.1 Hz, 1H), 2.98 (s, 3H), 2.40 –

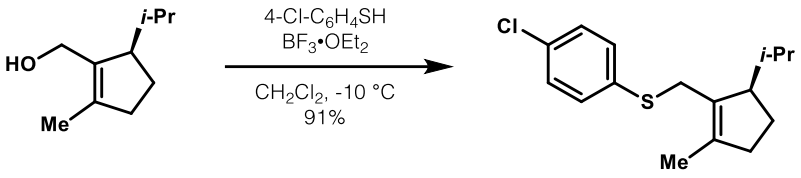
2.33 (m, 1H), 2.22 – 2.15 (m, 1H), 2.09 – 1.90 (m, 5H), 1.62 – 1.54 (m, 2H), 1.47 – 1.37 (m, 2H), 1.36 (s, 3H), 0.95 (d, J = 8.5 Hz, 3H), 0.83 (d, J = 8.4 Hz, 3H).

^{13}C NMR (126 MHz, C_6D_6)

δ 161.8, 145.0, 129.4, 105.8, 87.2, 78.8, 76.1, 59.0, 52.1, 51.8, 36.6, 33.9, 29.6, 28.5, 25.4, 23.4, 22.2, 16.4.

LRMS Calculated $C_{18}H_{30}NaO_3$ $[M+Na]^+$: 317.2 | Found: 317.2

Thioether 16 [(*R*)-(4-chlorophenyl)((5-isopropyl-2-methylcyclopent-1-en-1-yl)methyl)sulfane]



9 16

A flame dried flask was placed under an argon atmosphere and charged with alcohol **9** (7.68 g, 49.9 mmol, 1 equiv), 4-chlorothiophenol (10.85 g, 75 mmol, 1.5 equiv) and CH_2Cl_2 (500 mL, 0.1 M). The solution was cooled in an ice/methanol bath (bath temperature maintained between -14 and -10 °C over the reaction course). A solution of BF_3•OEt_2 (9.26 mL, 75 mmol, 1.5 equiv) in CH_2Cl_2 (~1.5:1 v:v with BF_3·OEt_2, *ca.* 15 mL) was added dropwise over 15 minutes. After stirring for 1 hour, the reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O (~1 L). The organic phase was washed twice with 1 M NaOH and once with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (100% hexanes) afforded the product as a colorless oil (12.67 g, 91%).

Note: In some batches, small amounts of aryl disulfide were formed over the course of the reaction that was difficult to remove chromatographically. In these cases, the organic phase was separated immediately following quenching and treated with zinc powder (4 g) and acetic acid (4 mL) and stirred until the disulfide impurity was depleted by TLC, typically 15 to 30 minutes. The solution was then filtered, washed twice with 1 M NaOH, and purified as above.

R_f 0.41 (100% hexanes, UV active)

$[\alpha]_D^{20}$ +16.9 (*c* 0.5, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

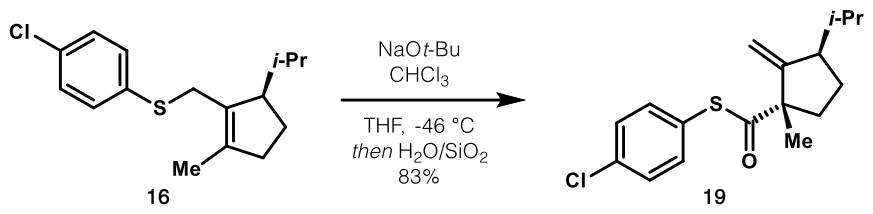
δ 7.27 – 7.25 (m, 2H), 7.24 – 7.21 (m, 2H), 3.77 (d, *J* = 12.3 Hz, 1H), 3.28 (br d, *J* = 12.5 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.23 – 2.12 (m, 2H), 1.96 (ddq, *J* = 10.3, 6.9, 3.4 Hz, 1H), 1.73 (dtd, *J* = 13.1, 9.2, 5.8 Hz, 1H), 1.55 (ddt, *J* = 13.1, 9.1, 5.7 Hz, 1H), 1.50 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 138.4, 135.6, 132.5, 132.1, 131.7, 128.8, 52.1, 37.7, 31.9, 28.4, 21.6, 21.5, 15.8, 14.2.

HRMS Calculated $C_{16}H_{22}ClS$ $[M+H]^+$: 281.1131 | Found: 281.1117

Thioester 19 [*S*-(4-chlorophenyl) (3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentane-1-carbothioate]



A flame dried flask was placed under an argon atmosphere and charged with thioether **16** (13.1 g, 46.8 mmol, 1 equiv) and anhydrous THF (100 mL, 0.5 M). The solution was cooled to -46° C (MeCN/dry ice) and a solution of NaO*t*-Bu (11.2 g, 117 mmol, 2.5 equiv) in THF (75 mL, 1.5 M) was added by cannula. A solution of chloroform (9.3 mL, 117 mmol, 2.5 equiv, deacidified by filtration through basic alumina) in THF (*ca*. 6 M with respect to chloroform, 20 mL) was then added dropwise over 10 minutes with vigorous stirring. The reaction was stirred at that -46 °C for 2 hours, then quenched by addition of saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on hydrated silica gel (12:88 w/w water/silica gel, 0 to 2% Et_2O/hexanes) afforded the product as a light yellow solid (12.0 g, 83% yield).

Note: Care must be taken that the $CHCl_3$ solution is not accidentally added in sudden spurts.

Note: While 12:88 w/w water/silica gel was used in this procedure, the use of 20:80 to 25:75 w/w water/silica gel has been found to more reliably avoid decomposition.

R_f 0.12 (100% hexanes, UV active)

$[\alpha]_D^{20}$ +33.2 (*c* 0.5, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

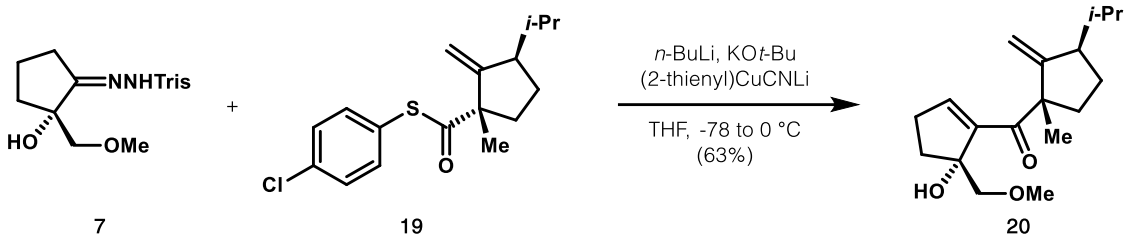
δ 7.37 – 7.35 (m, 2H), 7.30 – 7.28 (m, 2H), 5.23 (d, *J* = 2.9 Hz, 1H), 5.09 (d, *J* = 2.6 Hz, 1H), 2.70 – 2.66 (m, 1H), 2.31 (ddd, *J* = 12.8, 8.9, 7.0 Hz, 1H), 2.03 (dtd, *J* = 13.7, 6.8, 4.0 Hz, 1H), 1.81 (dtd, *J* = 12.3, 7.1, 4.6 Hz, 1H), 1.66 (ddd, *J* = 12.3, 7.1, 4.6 Hz, 1H), 1.56 – 1.49 (m, 1H), 1.37 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

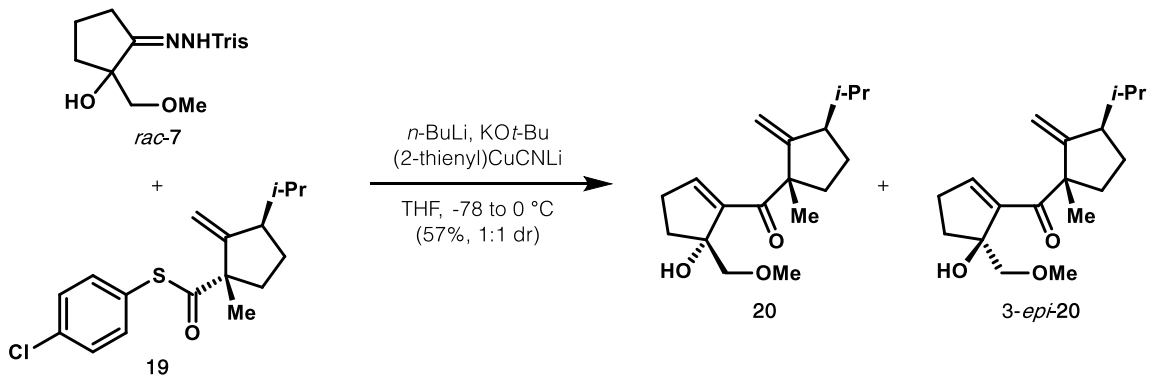
δ 202.3, 157.3, 136.2, 135.6, 129.4, 127.4, 109.7, 61.8, 50.9, 37.6, 28.9, 24.8, 23.9, 22.1, 16.6.

HRMS Calculated $C_{17}H_{22}ClOS$ $[M+H]^+$: 309.1080 | Found: 309.1085

Enones 20 and 3-*epi*-20 [((*R*)-5-hydroxy-5-(methoxymethyl)cyclopent-1-en-1-yl)((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methanone] and [((*S*)-5-hydroxy-5-(methoxymethyl)cyclopent-1-en-1-yl)((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methanone]



Preparation from **7**: A solution of (*R*)-hydrazone **7** (102 mg, 0.24 mmol, 1.2 equiv) in anhydrous THF (1.0 mL, 0.2 M) under an argon atmosphere at -78 °C was treated with *n*-BuLi (2.71 M in hexanes, 0.27 mL, 0.72 mmol, 3.6 equiv) and KO*t*-Bu (1.0 M in THF, 0.24 mL, 0.24 mmol, 1.2 equiv). After incubating for 5 minutes, the reaction was raised to 0 °C and stirred for 1 hour. Separately, a stirred suspension of CuCN (23 mg, 0.26 mmol, 1.3 equiv) in THF (1.0 mL, 0.2 M) under argon at -78 °C was treated with 2-lithiothiophene[5] (1 M in THF/hexanes, 0.26 mL, 0.26 mmol, 1.3 equiv) and then raised to 0 °C. The cuprate solution was transferred into the reaction, and the mixture was stirred at 0 °C for 5 minutes. A solution of thioester **19** (62 mg, 0.2 mmol, 1.0 equiv) in THF (1.0 mL, 0.2 M) was added dropwise, and the solution was stirred for 1 hour before being quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with brine and extracted three times with Et_2O. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (10 to 40% EtOAc in hexanes) afforded the desired product as a colorless oil that solidified upon standing (37 mg, 63%), along with recovered thioester **19** (6 mg, 0.019 mmol, 70% yield of **20** brsm).



Preparation from *rac*-**7**: A solution of *rac*-hydrazone **7** (1.02 g, 2.4 mmol, 1.2 equiv) in anhydrous THF (10 mL, 0.2 M) under an Ar atmosphere at -78 °C was treated with *n*-butyllithium (2.71 M in hexanes, 4.8 mL, 7.6 mmol, 3.8 equiv) and KO*t*-Bu (1.0 M in THF, 4.8 mL, 4.8 mmol, 2.4 equiv). After incubating for 5 minutes, the reaction was raised to 0 °C and stirred for 1 hour. A solution of lithium 2-thenylcyanocuprate (0.25 M in THF, 10.4 mL, 2.6 mmol, 1.3 equiv) was transferred into the reaction, and the mixture was stirred at 0 °C for 5 minutes. A solution of thioester **19** (618 mg, 2.0 mmol, 1.0 equiv) in THF (10 mL, 0.2 M) was added dropwise, and the solution was stirred for 1 hour before being quenched with saturated

sodium bicarbonate. The mixture was diluted with brine and extracted three times with Et_2O. The organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (10 to 40% EtOAc in hexanes), giving 332 mg (1.14 mmol, 57%) of an equal mixture of the epimeric products as a colorless oil and 230 mg (0.74 mmol) of recovered starting material (90% yield brsm). While the enones were found to be separable at this stage for characterization, it was found to be more convenient to carry through a mixture enriched in the desired epimer and purify completely after the subsequent step.

20:

R_f 0.32 (20% EtOAc/hexanes, UV active)

$[\alpha]_D^{20}$ +34.25 (*c* 0.4, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 6.67 (t, *J* = 2.7 Hz, 1H), 4.91 (d, *J* = 2.7 Hz, 1H), 4.84 (d, *J* = 3.1 Hz, 1H), 3.75 (s, 1H), 3.54 (d, *J* = 9.1 Hz, 1H), 3.45 (d, *J* = 9.1 Hz, 1H), 3.34 (s, 3H), 2.72 – 2.64 (m, 1H), 2.52 (ddt, *J* = 18.9, 9.2, 3.2 Hz, 1H), 2.40 (dddd, *J* = 18.9, 8.8, 6.6, 2.5 Hz, 1H), 2.31 – 2.21 (m, 2H), 2.10 – 2.01 (m, 1H), 1.88 (ddd, *J* = 13.4, 9.3, 6.6 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.62 – 1.52 (m, 2H), 1.22 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 205.5, 159.3, 145.1, 140.8, 108.2, 86.6, 77.6, 60.3, 59.4, 51.2, 38.1, 34.4, 30.5, 28.5, 25.1, 24.0, 22.1, 16.2.

HRMS Calculated $C_{18}H_{29}O_3$ $[M+H]^+$: 293.2117 | Found: 293.2121

3-*epi*-**20**:

R_f 0.44 (20% EtOAc in hexanes, UV active, *p*-anisaldehyde)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 6.57 – 6.54 (m, 1H), 4.93 – 4.88 (m, 2H), 3.43 (d, *J* = 9.0 Hz, 1H), 3.38 (d, *J* = 9.0 Hz, 1H), 3.29 (s, 3H), 2.70 – 2.66 (m, 1H), 2.57 – 2.51 (m, 1H), 2.42 – 2.37 (m, 1H), 2.27 – 2.20 (m, 1H), 2.13 (ddd, *J* = 13.7, 8.8, 4.8 Hz, 1H), 2.06 (h, *J* = 6.9 Hz, 1H), 1.90 (ddd, *J* = 13.9, 9.2, 4.9 Hz, 1H), 1.85 – 1.79 (m, 1H), 1.61 – 1.53 (m, 2H), 1.17 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

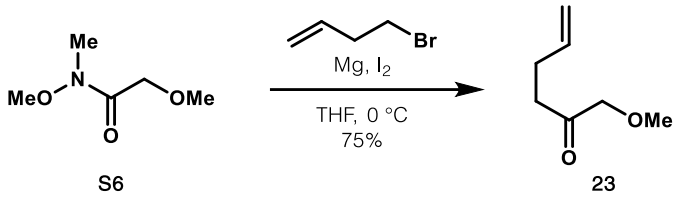
^{13}C NMR (151 MHz, $CDCl_3$)

δ 207.0, 159.4, 143.6, 141.0, 108.2, 86.9, 77.7, 60.5, 59.3, 51.9, 37.6, 34.3, 30.7, 28.5, 24.7, 24.5, 22.2, 16.2.

HRMS Calculated $C_{18}H_{28}NaO_3$ $[M+Na]^+$: 315.1936 | Found: 315.1929

B. Second-Generation Synthesis

***α*-Methoxyketone 23** [1-methoxyhex-5-en-2-one]



S6 23

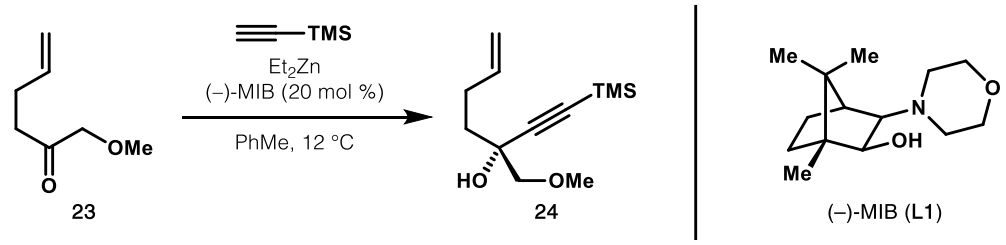
A flame-dried 3-neck 2 L flask was equipped with a mechanical stirrer, reflux condenser, and a rubber septum. The flask was placed under an argon atmosphere and charged with magnesium (13.5 g, 556 mmol, 1.2 equiv), THF (930 mL), and I_2 (267 mg, 1.05 mmol, 0.25 mol %). 4-bromo-1-butene (47.0 mL, 62.5 g, 463 mmol, 1.1 equiv) was added by syringe over 5 minutes, during which the reaction mixture warmed to reflux. After the reflux had begun to slow, the reaction vessel was lowered into an oil bath preheated to 70 °C and refluxed for 4 hours. The reaction mixture was cooled to 0 °C and cannulated over 1 h into a flame-dried 3 L flask containing a 0 °C solution of **S6**[6,7] (56.1 g, 421 mmol, 1 equiv) in THF (420 mL). After stirring at 0 °C for an additional 1 hour, the reaction mixture was quenched at 0 °C with 10 wt % aqueous citric acid (900 mL). The mixture was diluted with Et_2O (800 mL). The organic phase was collected and the aqueous phase was extracted with Et_2O (2 x 500 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 900 mL) and brine (1 x 900 mL), dried over Na_2SO_4, filtered, and concentrated to an orange oil. The crude product was purified by vacuum distillation (b.p. 66–69 °C, 18 Torr) to afford **23** as a colorless oil (40.70 g, 75%). Analytical data match those previously reported.[8]

Note: S6 can be prepared in large quantities (150 g) in 1 step from methoxyacetic acid under typical peptide coupling conditions (*N*,*O*-dimethylhydroxylamine hydrochloride, EDCl, HOBt, Et_3N, CH_2Cl_2, rt, 50% yield, no purification needed following workup).[6] A higher-yielding protocol via the acyl chloride has been reported as well on a reduced, albeit still large, scale (11 g, 81%, no purification needed following workup).[7]

Note: The crude reaction mixture was concentrated only to near-completion (25 °C and 60 Torr) due to the volatility of **23**.

Note: The preparation of **23** directly from methoxyacetonitrile has been reported.[8] However, in our hands this proceeds in low yield (~10%) with significant self-condensation of methoxyacetonitrile. This was not improved by the addition of Cu(I) salts.[9]

Trimethylsilyl alkyne 24 [(*R*)-3-(methoxymethyl)-1-(trimethylsilyl)hept-6-en-1-yn-3-ol]



Synthesis of **24**: A flame-dried 3-neck 2 L flask was equipped with an addition funnel, a rubber septum, and a thermometer inlet. The flask was charged with (–)-MIB[10] (2.80 g, 11.7 mmol, 0.2 equiv) and placed under an argon atmosphere. PhMe (585 mL) was added to the flask. The addition funnel was charged with Et_2Zn (1.0 M in heptane, 176 mmol, 176 mmol, 3 equiv), which was emptied into the flask at room temperature over 5 minutes. The addition funnel was rinsed with PhMe (5 mL), which was emptied into the flask. The reaction mixture was stirred at room temperature for 10 minutes, after which trimethylsilylacetylene (24.3 mL, 17.2 g, 176 mmol, 3 equiv) was added dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 30 minutes, then cooled in a dioxane/dry ice bath to an internal temperature of 12 °C. A solution of **23** (7.50 g, 58.5 mmol, 1 equiv) in PhMe (55 mL) was added dropwise by cannula over 3 minutes, completing the transfer with PhMe (4 mL). The reaction mixture was stirred at 12 °C for 2.5 hours, after which saturated aqueous NH_4Cl (400 mL) was carefully added, resulting in gas evolution and formation of a white precipitate. Once the rate of gas evolution decreased (after ~5 minutes), the reaction mixture was warmed to room temperature and stirred vigorously for 30 minutes, at which point gas evolution had essentially ceased. The entire mixture was filtered through a pad of Celite to remove precipitated solids, rinsing with EtOAc (3 x 100 mL) and H_2O (3 x 100 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (3 x 120 mL). The combined organic extracts were washed with 1 M HCl (2 x 100 mL), dried over $MgSO_4$, filtered, and concentrated to afford the product as a pale yellow oil, which was used without further purification.

Recovery of (–)-MIB: (–)-MIB could be routinely recovered in >90% yield according to the following procedure. The combined 1 M HCl washes were carefully basified with 10 wt % aqueous NaOH (~2 equiv relative to HCl). The mixture was extracted 3 times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting material was passed through a pad of silica gel using EtOAc and concentrated to afford (–)-MIB as a waxy solid.

Note: Partway through the addition of saturated aqueous NH_4Cl, gas evolution begins to occur. All rubber septa are removed during the quench to prevent over pressurization.

Note: Enantiomeric excess was determined after the following step, due to very poor retention of this compound on the chiral SFC column. Specific rotation was not measured at this stage due to the inability to determine enantiomeric excess.

R_f 0.49 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$)

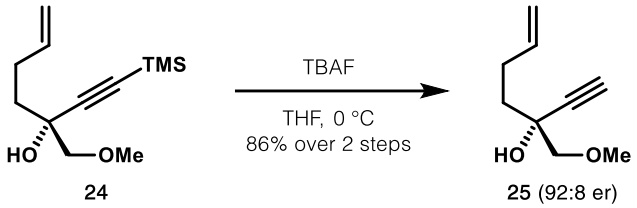
δ 5.88 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 (dq, *J* = 10.2, 1.5 Hz, 1H), 3.48 (d, *J* = 9.4 Hz, 1H), 3.46 (s, 3H), 3.39 (d, *J* = 9.4 Hz, 1H), 2.68 (s, 1H), 2.39 – 2.22 (m, 2H), 1.77 (ddd, *J* = 13.5, 10.9, 5.6 Hz, 1H), 1.70 (ddd, *J* = 13.4, 11.0, 5.5 Hz, 1H), 0.17 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 138.5, 114.8, 106.3, 89.6, 79.1, 70.7, 59.8, 37.7, 28.7, 0.1.

HRMS Calculated $C_{12}H_{23}O_2Si$ $[M+H]^+$: 227.1467 | Found: 227.1465

Terminal alkyne 25 [(*R*)-3-(methoxymethyl)hept-6-en-1-yn-3-ol]



A flask (not flame-dried) was charged with crude **24** (13.2 g, 58.3 mmol, 1 equiv, 100% yield assumed) and flushed with argon. THF (195 mL) was added, and the solution was cooled to 0 °C. TBAF (1.0 M in THF, 58.3 mL, 58.3 mmol, 1 equiv) was added to the reaction mixture over 10 minutes. The reaction mixture was stirred at 0 °C for 30 minutes then quenched at 0 °C with saturated aqueous NH_4Cl (200 mL). The mixture was warmed to room temperature and H_2O was added as needed to dissolve the precipitated NH_4Cl. The organic phase was collected and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (1 x 250 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (0 to 15% EtOAc/hexanes) afforded the product (92:8 er) as a pale yellow oil (7.73 g, 86% over 2 steps).

Note: 25 is slightly volatile, leading to slightly reduced yields on smaller scale and/or upon prolonged drying under high vacuum.

R_f 0.29 (20% EtOAc/hexanes)

$[\alpha]_D^{25}$ +6.8 (*c* 0.91 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 5.87 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.07 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.98 (dq, *J* = 10.3, 1.5 Hz, 1H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.47 (s, 3H), 3.38 (d, *J* = 9.2 Hz, 1H), 2.78 (s, 1H), 2.48 (s, 1H), 2.41 – 2.25 (m, 2H), 1.82 – 1.69 (m, 2H).

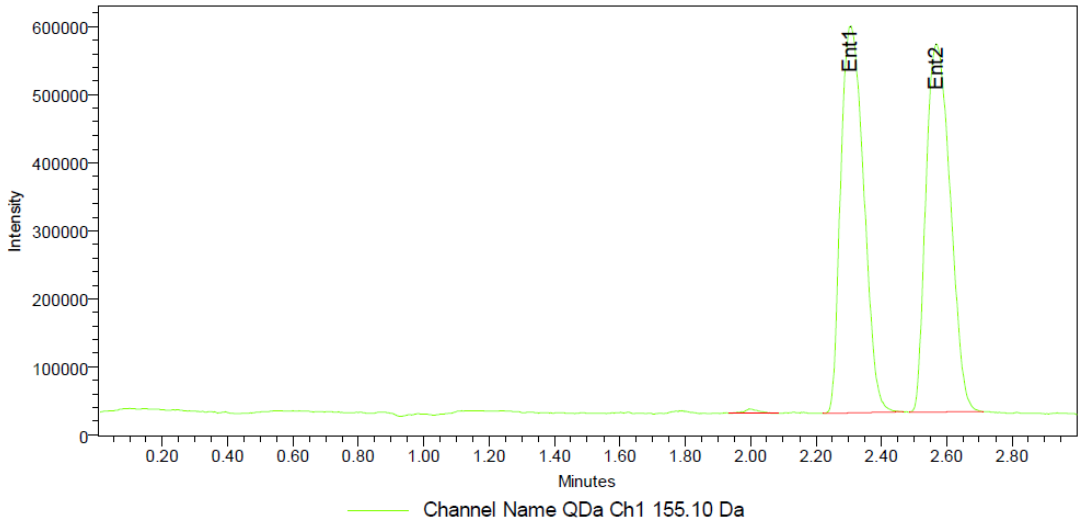
^{13}C NMR (151 MHz, $CDCl_3$)

δ 138.2, 115.0, 84.8, 79.3, 72.9, 70.3, 59.8, 37.5, 28.4.

HRMS Calculated $C_9H_{15}O_2$ $[M+H]^+$: 155.1072 | Found: 155.1070

SFC Analysis was performed on a Waters UPC2 SFC with a Diacel IG column (3 μm, 4.6 x 250 mm) under isocratic conditions (3.3 mL/min, 5% MeOH / CO_2, 1600 psi backpressure) at 30 °C. The enantiomers were detected by a Waters QDa mass spec (ESI^+, *m*/*z* = 155.1).

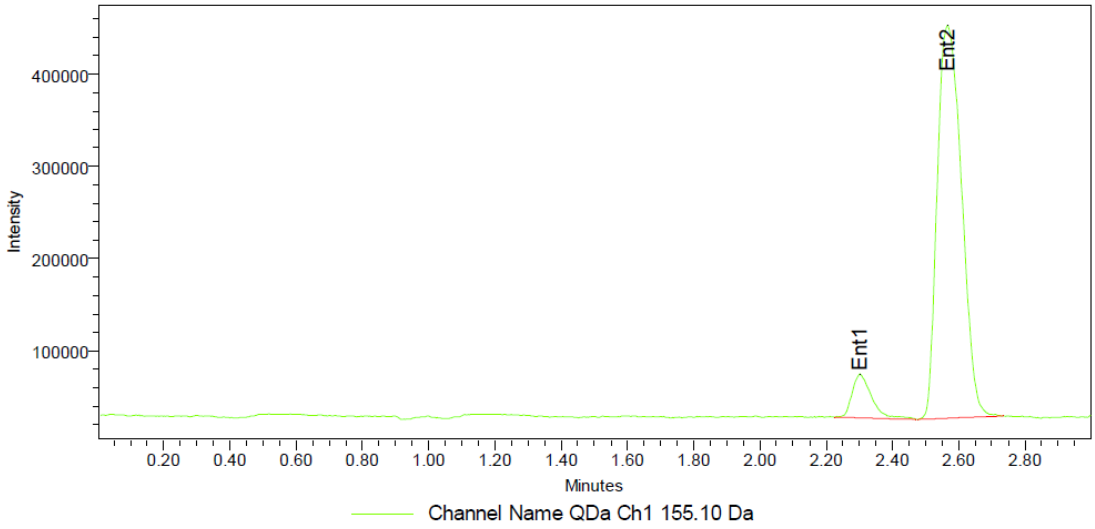
Racemic standard:



Peak Info

	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	QDa Ch1 155.10 Da		2.00	20177	6359	49.77	50.23	-0.46
2	QDa Ch1 155.10 Da	Ent1	2.31	2771900	568863	49.77	50.23	-0.46
3	QDa Ch1 155.10 Da	Ent2	2.57	2797438	540868	49.77	50.23	-0.46

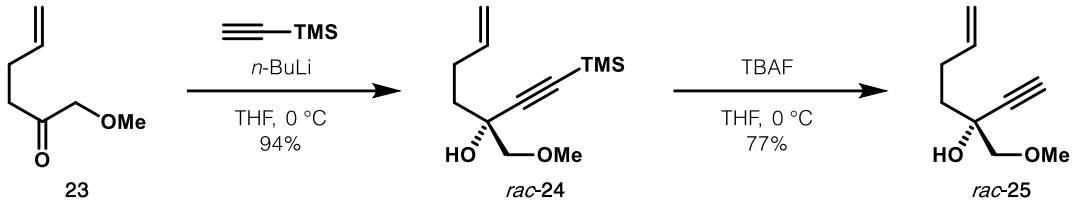
Enantioenriched product:



Peak Info

	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	QDa Ch1 155.10 Da	Ent1	2.30	194534	47111	8.23	91.77	-83.55
2	QDa Ch1 155.10 Da	Ent2	2.57	2170504	426027	8.23	91.77	-83.55

Racemic terminal alkyne *rac*-25 [3-(methoxymethyl)hept-6-en-1-yn-3-ol]

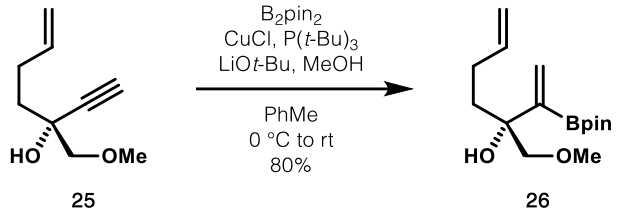


23 *rac*-24 *rac*-25

A flame-dried 250 mL flask was placed under an argon atmosphere. THF (23 mL) and trimethylsilylacetylene (3.24 mL, 2.30 g, 23.4 mmol, 3 equiv) were added, and the solution was cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 9.03 mL, 23.4 mmol, 3 equiv) was added dropwise over 5 minutes. The reaction mixture was stirred at 0 °C for 30 minutes. A solution of **23** (1.00 g, 7.80 mmol, 1 equiv) in THF (24 mL) was added dropwise by cannula over 8 minutes, completing the transfer with THF (2 mL). The reaction mixture was stirred at 0 °C for 1 h then quenched at 0 °C with saturated aqueous NH_4Cl (40 mL). The mixture was warmed to rt and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated to afford *rac*-**24** as a yellow oil, which was used without further purification (1.67 g, 94%). Analytical data are in agreement with enantioenriched **24**.

A flask (not flame-dried) was charged with *rac*-**24** (1.56 g, 6.89 mmol, 1 equiv) and flushed with argon. THF (23 mL) was added, and the solution was cooled to 0 °C. TBAF (1.0 M in THF, 6.89 mL, 6.89 mmol, 1 equiv) was added dropwise over 3 minutes. The reaction mixture was stirred at 0 °C for 2 h then quenched at 0 °C with saturated aqueous NH_4Cl (30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (0 to 15% EtOAc/hexanes) afforded *rac*-**25** as a pale yellow oil (819 mg, 77%). Analytical data are in agreement with enantioenriched **25** with the exception of optical rotation.

Boronic ester 26 [(*R*)-3-(methoxymethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,6-dien-3-ol]



25 26

A flame dried flask was placed under an argon atmosphere and charged with **25** (5.00 g, 32.4 mmol, 1 equiv) followed by anhydrous PhMe (600 mL). The solution was cooled to 0 °C before removing the septum and quickly adding LiO*t*-Bu (389 mg, 4.86 mmol, 0.15 equiv), CuCl (321 mg, 3.24 mmol, 0.1 equiv), and B_2pin_2 (9.06 g, 35.7 mmol, 1.1 equiv). Upon addition of the solids, the septum was quickly replaced and the headspace was flushed with argon for ~1 minute. A solution of P(*t*-Bu)$_3$ (787 mg, 3.89 mmol, 0.12 equiv) in PhMe (12 mL) was added, followed by MeOH (2.62 mL, 2.08 g, 64.9 mmol, 2 equiv). The reaction mixture stirred at room temperature. After 4 hours, the reaction mixture was passed through a silica plug, eluting with EtOAc, and the filtrate was concentrated. Purification by chromatography on silica gel (0 to 20% EtOAc/hexanes) afforded the product as a colorless oil (7.13 g, 80%).

Note: The use of P(*t*-Bu)$_3$ as opposed to P(*t*-Bu)$_3$•HBF_4 was necessary to reproducibly obtain high regioselectivity. The poor solubility of P(*t*-Bu)$_3$•HBF_4 and LiO*t*-Bu led to irreproducible generation of free P(*t*-Bu)$_3$ in situ.

R_f 0.43 (20% EtOAc/hexanes)

$[\alpha]_D^{25}$ +8.4 (*c* 0.90 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

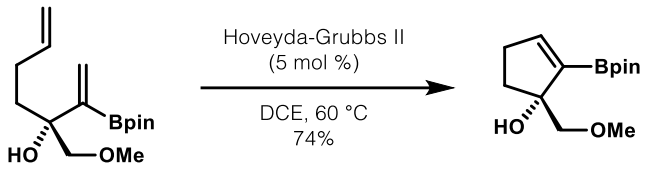
δ 6.00 (d, *J* = 3.2 Hz, 1H), 5.96 (d, *J* = 3.2 Hz, 1H), 5.82 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.90 (dm, *J* = 10.2 Hz, 1H), 3.52 (d, *J* = 9.0 Hz, 1H), 3.40 (d, *J* = 9.0 Hz, 1H), 3.35 (s, 3H), 2.71 (s, 1H), 2.13 – 2.05 (m, 1H), 2.01 – 1.91 (m, 1H), 1.79 (ddd, *J* = 13.7, 11.7, 4.8 Hz, 1H), 1.70 (ddd, *J* = 13.7, 11.5, 5.3 Hz, 1H), 1.26 (s, 6H), 1.25 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 139.4, 129.6, 114.1, 83.7, 79.6, 77.1, 59.4, 35.8, 27.8, 24.9, 24.7. The carbon attached to boron is not observed due to quadrupolar relaxation.

HRMS Calculated $C_{15}H_{27}BNaO_4$ $[M+Na]^+$: 304.1936 | Found: 304.1941

Cyclic boronic ester 27 [(*R*)-1-(methoxymethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-ol]



26 27

A flame dried flask was placed under an argon atmosphere and charged with **26** (3.36 g, 11.9 mmol, 1 equiv) and 1,2-dichloroethane (240 mL). The septum was then removed to add Hoveyda-Grubbs II (374 mg, 0.595 mmol, 5 mol %), and the septum was quickly replaced following the addition. The reaction mixture was then warmed to 60 °C and stirred at this temperature for 2 hours before cooling to room temperature. 1,3,5-Trimethoxybenzene (668 mg, 3.97 mmol, 0.33 equiv) was added and the reaction mixture was concentrated to afford a brown oil that was used without further purification (2.2 g of **27** as determined via ^{1}H NMR integration relative to 1,3,5-trimethoxybenzene, 74%).

Note: The material may be purified by chromatography on silica gel (0 to 20% EtOAc/hexanes) for characterization, but strong adsorption of the product on silica gel leads to a considerably lower isolated yield (53%).

Note: The quality of 1,2-dichloroethane is important, and 1,2-dichloroethane was used from an Aldrich SureSeal bottle. Reagent grade 1,2-dichloroethane led to significant formation of byproducts, which could not be suppressed by dilution or the addition of *p*-benzoquinone; we believe this observation is due to trace HCl present in the solvent.

R_f 0.36 (40% EtOAc/hexanes)

$[\alpha]_D^{25}$ –9.0 (*c* 1.2 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

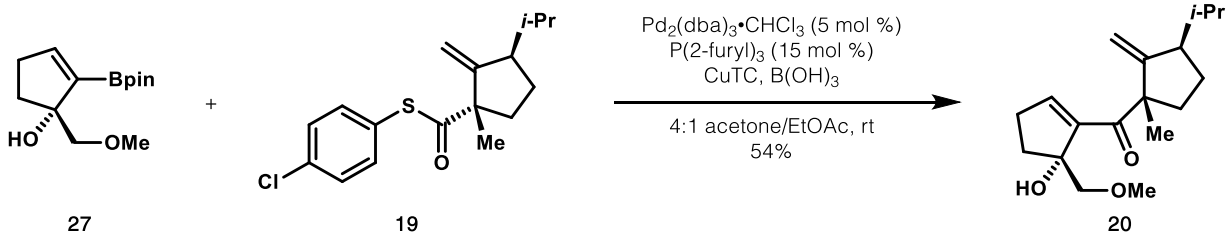
δ 6.61 (t, *J* = 2.4 Hz, 1H), 3.48 – 3.30 (m, 5H), 2.89 (br s, 1H), 2.53 (ddt, *J* = 18.1, 9.2, 3.0 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.12 (ddd, *J* = 13.5, 8.3, 3.3 Hz, 1H), 1.86 (ddd, *J* = 13.4, 9.2, 6.7 Hz, 1H), 1.28 (s, 6H), 1.27 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 149.6, 87.8, 83.5, 79.1, 59.4, 35.5, 32.9, 25.2, 24.5. The carbon attached to boron is not observed due to quadrupolar relaxation.

HRMS Calculated $C_{13}H_{23}BNaO_4$ $[M+Na]^+$: 276.1623 | Found: 276.1629

Enone 20 [((*R*)-5-hydroxy-5-(methoxymethyl)cyclopent-1-en-1-yl)((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methanone]



27 19 20

A flask was charged with crude **27** (91:9 er, 2.25 g, 8.85 mmol, 1 equiv determined from internal standard added in previous step), **19** (2.74 g, 8.85 mmol, 1 equiv), $Pd_2(dba)_3$•$CHCl_3$ (405.4 mg, 0.442 mmol, 5 mol %), P(2-furyl)$_3$ (308.3 mg, 1.33 mmol, 15 mol %), copper(I) thiophene-2-carboxylate (2.70 g, 14.17 mmol, 1.6 equiv) and boric acid (1.10 g, 17.71 mmol, 2 equiv). The vessel was evacuated and backfilled three times to exchange the atmosphere for argon. 4:1 Acetone/EtOAc (60 mL, 0.15 M, degassed by sparging with argon for ~15 minutes) was then added. Argon was bubbled through the resulting mixture for ~10 minutes, after which the argon inlet was removed and the pierced septum was coated with grease. The mixture was stirred at room temperature for 16 hours. After this time, the reaction mixture was diluted with a roughly equal volume of hexanes and passed through a pad of silica gel, eluting with Et_2O. The filtrate was concentrated and purified by chromatography on silica gel (0 to 40% EtOAc/hexanes) afforded a partially purified sample of **20**. To remove thiophene-2-carboxylic acid and hydrolyzed thioester (poorly separated by chromatography, especially the former), the resulting material was taken up in EtOAc (50 mL) and washed with 10 wt % aqueous Na_2CO_3 (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated. The product was obtained as a pale yellow oil (1.409 g, 54%). Analytical data match those obtained from the first-generation synthesis.

Note: $Pd_2(dba)_3$•$CHCl_3$ was recrystallized as described previously.[11] Successful reaction has been achieved using commercial $Pd_2(dba)_3$•$CHCl_3$ as received; however, it is known that the purity of commercial $Pd_2(dba)_3$•$CHCl_3$ can vary significantly (and be as low as ~60%).[11]

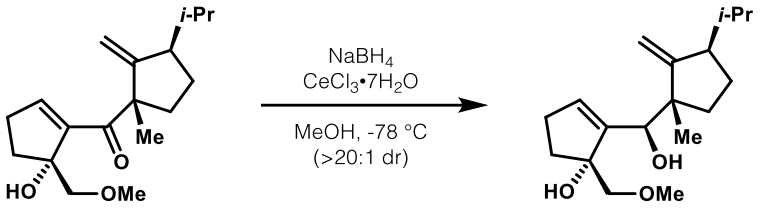
Note: The age of CuTC was found to be important. Our experiments used CuTC that was ~9 months old (the most recent lot available from the vendor). An older batch of CuTC (2.5 years, according to the certificate of analysis) failed to produce cross-coupled product.

Note: The water content of acetone was not found to impact the reaction, with reagent grade ("wet") acetone and anhydrous acetone performing similarly. Our experiments nonetheless use reagent grade acetone that is passed through a plug of silica gel before use, in an effort to reduce variability across different acetone drums.

Note: When aqueous workup is performed prior to chromatography, the carboxylic acid derived from **19** often partly coelutes with the product. This appears to be due to silica gel-promoted hydrolysis of higher R_f (mixed) anhydrides that are not fully destroyed during the silica plug or basic workup.

C. Successful Claisen Rearrangement and Completion of Cotylenol

Diol 21 [(*R*)-2-((*R*)-hydroxy((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methyl)-1-(methoxymethyl)cyclopent-2-en-1-ol]



20 21

To a -78 °C solution of enone **20** (1.409 g, 4.818 mmol) in MeOH (48.2 mL, 0.1 M) under an argon atmosphere was added $CeCl_3•7H_2O$ (2.69 g, 7.23 mmol, 1.5 equiv) followed by $NaBH_4$ (273.4 mg, 7.23mmol, 1.5 equiv). The reaction mixture was stirred at -78 °C for 30 minutes then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted three times with Et_2O, and the organic layer was concentrated to dryness. The material was resuspended in Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purified product can be obtained via chromatography on silica gel (10 to 30% EtOAc/hexanes) for characterization purposes. In practice, however, the material was used in the next step without further purification due to instability of the product.

R_f 0.47 (40% EtOAc/hexanes)

$[\alpha]_D^{20}$ +90.0 (*c* 0.5, MeOH)

^{1}H NMR (600 MHz, C_6D_6)

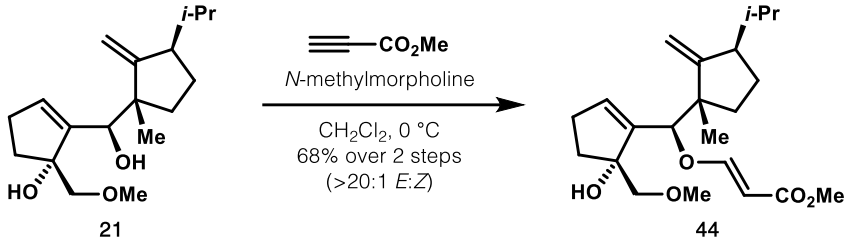
δ 5.93 (t, *J* = 2.3 Hz, 1H), 5.12 (d, *J* = 3.1 Hz, 1H), 4.86 (d, *J* = 2.7 Hz, 1H), 4.45 (s, 1H), 3.39 (dd, *J* = 9.1, 0.9 Hz, 1H), 3.25 (d, *J* = 9.0 Hz, 1H), 3.00 (s, 3H), 2.59 (br s, 1H), 2.44 (dtd, *J* = 11.5, 6.8, 3.1 Hz, 1H), 2.31 – 2.25 (m, 1H), 2.25 (br s, 1H), 2.22 – 2.14 (m, 2H), 2.07 – 2.01 (m, 1H), 1.99 – 1.91 (m 1H), 1.86 – 1.81 (m, 1H), 1.62 (dtd, *J* = 11.9, 7.2, 2.1 Hz, 1H), 1.47 (ddd, *J* = 12.0, 6.9, 2.1 Hz, 1H), 1.39 – 1.30 (m, 1H), 1.18 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6)

δ 162.3, 146.9, 131.3, 104.4, 85.6, 77.7, 72.5, 58.9, 52.5, 51.9, 36.6, 32.8, 29.4, 28.4, 26.0, 23.3, 22.2, 16.4.

HRMS Calculated $C_{18}H_{30}NaO_3$ $[M+Na]^+$: 317.2093 | Found: 317.2090

Enol ether 44 [methyl (*E*)-3-((*R*)-((*R*)-5-hydroxy-5-(methoxymethyl)cyclopent-1-en-1-yl)((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methoxy)acrylate]



To a solution of crude diol **21** (1.419 mg, 4.818 mmol, 1 equiv, quantitative yield from previous step assumed) in anhydrous CH_2Cl_2 (24.1 mL, 0.2 M) at 0 °C under an argon atmosphere was added sequentially methyl propiolate (1.29 mL, 14.45 mmol, 3 equiv) and *N*-methylmorpholine (2.65 mL, 24.1 mmol, 5 equiv). After stirring for 1 hour, the reaction was quenched with water, diluted with brine, and extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (0 to 8% acetone/PhMe) afforded the product as a white solid (1.24 g, 68% over two steps).

R_f 0.50 (40% EtOAc/hexanes, UV active)

$[\alpha]_D^{20}$ +89.4 (*c* 0.5, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

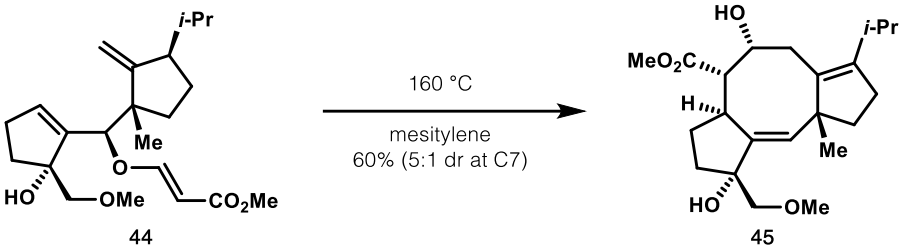
δ 7.51 (d, *J* = 12.1 Hz, 1H), 6.03 (t, *J* = 2.6 Hz, 1H), 5.20 (d, *J* = 12.1 Hz, 1H), 4.97 (d, *J* = 3.0 Hz, 1H), 4.90 (d, *J* = 2.6 Hz, 1H), 4.54 (s, 1H), 3.66 (s, 3H), 3.40 (s, 3H), 3.39 (d, *J* = 9.1 Hz, 1H), 3.36 (d, *J* = 9.1 Hz, 1H), 2.68 (s, 1H), 2.43 – 2.33 (m, 2H), 2.24 (dtd, *J* = 17.4, 7.7, 2.3 Hz, 1H), 2.10 – 2.02 (m, 2H), 2.02 – 1.92 (m, 1H), 1.78 (ddd, *J* = 13.1, 8.9, 7.5 Hz, 1H), 1.68 (dtd, *J* = 11.1, 7.2, 3.2 Hz, 1H), 1.47 – 1.40 (m, 1H), 1.39 – 1.33 (m, 1H), 1.04 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 169.0, 164.8, 160.8, 144.2, 133.7, 105.6, 96.3, 85.4, 84.7, 78.3, 59.4, 51.6, 51.3, 51.0, 36.6, 33.4, 29.2, 28.3, 24.8, 22.8, 22.1, 16.4.

HRMS Calculated $C_{22}H_{34}NaO_5$ $[M+Na]^+$: 401.2304 | Found: 401.2302

Tricycle 45 [methyl (1*R*,3a*S*,4*S*,5*R*,9a*R*,*E*)-1,5-dihydroxy-7-isopropyl-1-(methoxymethyl)-9a-methyl-1,2,3,3a,4,5,6,8,9,9a-decahydrodicyclopenta[*a*,*d*][8]annulene-4-carboxylate]



A flame dried flask was fitted with a reflux condenser, placed under an argon atmosphere, and charged with HMDS (60 mL). The apparatus was heated to 160 °C, with no water flowing through the condenser to ensure HMDS coated the entire interior of the condenser. After 1 hour, the condenser was briefly removed, the HMDS was poured out, and the condenser was quickly replaced. The entire apparatus was gently heated under vacuum to remove residual HMDS. The atmosphere was replaced with argon, and a solution of **44** (1.24 g, 3.28 mmol, 1 equiv, azeotropically dried three times with anhydrous benzene) in mesitylene (5 mL) was added, followed by additional mesitylene (160 mL). A flow of water through the condenser was established, and the reaction mixture was heated to 160 °C for 2 hours. The reaction mixture was cooled and directly loaded onto the column for purification by chromatography on silica gel (10 to 60% EtOAc/hexanes) afforded the product (5:1 dr at C7) as a foamy white solid (747 mg, 60%).

Note: Mesitylene was freshly distilled over CaH_2 then degassed by sparging with argon for ~30 minutes. This reaction has previously been run in PhMe (130 °C, 15 h, 55%, 5:1 dr), but was poorly reproducible even when using freshly distilled PhMe. We speculate that this may result from trace sulfur-containing impurities present in commercial PhMe that are not separated during distillation.[12]

Note: The product diastereomers were advanced without separation, as the C7 stereocenter is later ablated.

R_f 0.18 (40% EtOAc/hexanes)

$[\alpha]_D^{20}$ −43.8 (*c* 1.0, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

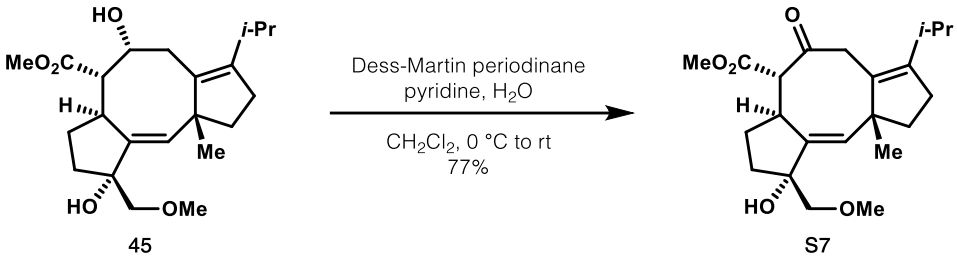
δ 5.65 (d, *J* = 2.0 Hz, 1H), 4.17 (dt, *J* = 12.2, 4.6 Hz, 1H), 3.74 (s, 3H), 3.71 – 3.66 (m, 1H), 3.38 (s, 3H), 3.29 (d, *J* = 9.2 Hz, 1H), 3.24 (d, *J* = 9.2 Hz, 1H), 2.85 – 2.79 (m, 2H), 2.57 (dd, *J* = 12.0, 5.1 Hz, 1H), 2.28 (dq, *J* = 14.2, 3.4, 1H), 2.17 – 2.12 (m, 2H), 1.97 – 1.83 (m, 2H), 1.80 (ddd, *J* = 12.4, 6.9, 3.7 Hz, 1H), 1.64 – 1.57 (m, 2H), 1.31 – 1.26 (m, 1H), 1.20 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 174.3, 144.1, 140.5, 136.1, 132.9, 81.1, 79.3, 69.1, 59.5, 54.6, 53.0, 51.9, 40.3, 37.5, 35.0, 32.1, 29.4, 27.9, 27.5, 27.2, 21.6, 19.8.

HRMS Calculated $C_{22}H_{34}NaO_5$ $[M+Na]^+$: 401.2304 | Found: 401.2298

β-Ketoester S7 [methyl (1*R*,3a*S*,4*S*,9a*R*,*E*)-1-hydroxy-7-isopropyl-1-(methoxymethyl)-9a-methyl-5-oxo-1,2,3,3a,4,5,6,8,9,9a-decahydrodicyclopenta[*a*,*d*][8]annulene-4-carboxylate]



To a 0 °C solution of tricycle **45** (5:1 dr at C7, 140 mg, 0.37 mmol, 1 equiv) in anhydrous CH_2Cl_2 (7.4 mL, 0.05 M) under an argon atmosphere was added pyridine (179 μL, 0.73 mmol, 6 equiv) and Dess-Martin periodinane (471 mg, 0.36 mmol, 3 equiv). H_2O (0.03 M in CH_2Cl_2, 23.1 mL, 0.74 mmol, 2 equiv) was added dropwise over 1 hour. The reaction was warmed to room temperature and stirred for 24 hours, then quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (10 to 40% EtOAc/hexanes) afforded the product as a colorless oil (107 mg, 77%).

R_f 0.36 (40% EtOAc/hexanes)

$[\alpha]_D^{25}$ +66.5 (*c* 0.49, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

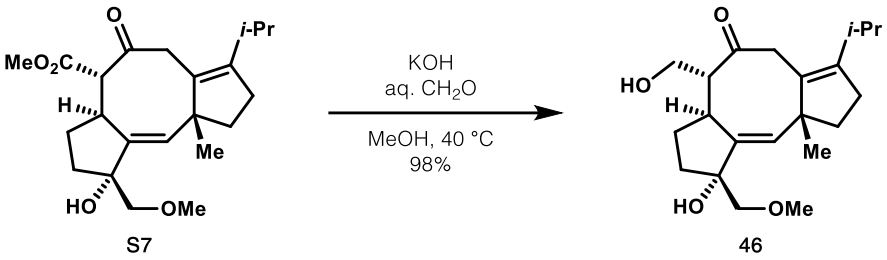
δ 5.67 (d, *J* = 1.9 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.77 – 3.72 (m, 4H), 3.40 (s, 3H), 3.28 (d, *J* = 9.7 Hz, 1H), 3.23 (d, *J* = 9.1 Hz, 1H), 3.14 (dd, *J* = 11.3, 1.7 Hz, 1H), 2.84 – 2.79 (m, 1H), 2.72 (hept, *J* = 6.9 Hz, 1H), 2.38 (br s, 1H), 2.36 – 2.28 (m, 1H), 2.28 – 2.21 (m, 1H), 2.00 (ddt, *J* = 13.4, 11.6, 7.3 Hz, 1H), 1.88 – 1.80 (m, 2H), 1.76 (ddd, *J* = 12.6, 8.3, 5.5 Hz, 1H), 1.71 (ddd, *J* = 13.9, 7.5, 3.0 Hz, 1H), 1.50 – 1.43 (m, 1H), 1.11 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 204.4, 169.8, 146.2, 142.7, 135.8, 131.5, 80.8, 79.7, 65.0, 59.5, 53.0, 52.5, 39.8, 39.74, 39.69, 35.3, 29.3, 27.9, 27.6, 26.9, 21.5, 19.9.

HRMS Calculated $C_{22}H_{32}NaO_5$ $[M+Na]^+$: 399.2147 | Found: 399.2159

β-Hydroxyketone 46 [(1*R*,3a*S*,4*R*,9a*R*,*E*)-1-hydroxy-4-(hydroxymethyl)-7-isopropyl-1-(methoxymethyl)-9a-methyl-2,3,3a,4,6,8,9,9a-octahydrodicyclopenta[*a*,*d*][8]annulen-5(1*H*)-one]



S7

A solution of β-keto ester **S7** (107 mg, 0.284 mmol, 1 equiv) in MeOH (14.2 mL, 0.02 M) under an argon atmosphere was treated with formalin (37 wt % in water with 10-15 wt % MeOH as stabilizer, 2.12 mL, 28.4 mmol, 100 equiv) and KOH (239 mg in 1 mL H_2O, 4.26 mmol, 15 equiv). The reaction was heated to 40 °C and stirred for 6 hours, then quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (40 to 60% EtOAc/hexanes) afforded the product as a white solid (97 mg, 98%).

R_f 0.1 (40% EtOAc/hexanes)

$[\alpha]_D^{25}$ +82.4 (*c* 0.46, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

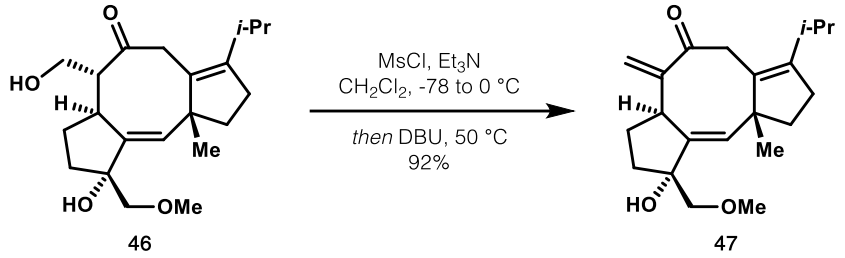
δ 5.64 (d, *J* = 1.8 Hz, 1H), 3.86 (d, *J* = 7.4 Hz, 2H), 3.65 (d, *J* = 15.4 Hz, 1H), 3.40 (s, 3H), 3.31 – 3.27 (m, 3H), 2.87 – 2.81 (m, 2H), 2.41 (br s, 1H), 2.39 – 2.34 (m, 1H), 2.33 – 2.20 (m, 2H), 1.93 – 1.85 (m, 2H), 1.81 – 1.77 (m, 2H), 1.74 – 1.67 (m, 1H), 1.46 – 1.39 (m, 2H), 1.11 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 211.1, 144.8, 143.7, 134.7, 132.6, 80.4, 79.5, 63.2, 62.6, 59.4, 52.9, 39.7, 39.2, 38.6, 35.6, 28.7, 27.60, 27.58, 26.7, 21.4, 20.1.

HRMS Calculated $C_{21}H_{32}NaO_4$ $[M+Na]^+$: 371.2198 | Found: 371.2198

Enone 47 [(1*R*,3a*R*,9a*R*,*E*)-1-hydroxy-7-isopropyl-1-(methoxymethyl)-9a-methyl-4-methylene-2,3,3a,4,6,8,9,9a-octahydrodicyclopenta[*a*,*d*][8]annulen-5(1*H*)-one]



46 47

A solution of β-hydroxyketone **46** (97 mg, 0.280 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5.6 mL, 0.05 M) under an argon atmosphere at -78 °C was treated with NEt_3 (121 μL, 0.84 mmol, 3 equiv) and MsCl (33 μL, 0.42 mmol, 1.5 equiv). The reaction was allowed to gradually warm to 0 °C over roughly 1 hour. After stirring for 1 hour at this temperature, DBU (0.42 mL, 2.8 mmol, 10 equiv) was added. The reaction was heated to 50 °C and stirred for 3 hours, then quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (20 to 60% EtOAc/hexanes) afforded the product as a white solid (85.0 mg, 92%).

R_f 0.58 (60% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ −124 (*c* 0.3, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

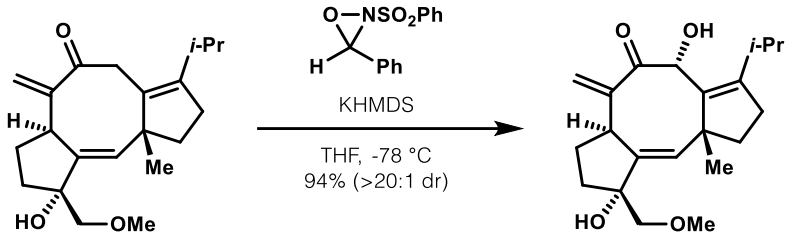
δ 5.72 (d, *J* = 1.8 Hz, 1H), 5.49 (d, *J* = 2.5 Hz, 1H), 5.07 (d, *J* = 2.4 Hz, 1H), 4.16 – 4.11 (m, 1H), 3.39 (d, *J* = 16.4 Hz, 1H), 3.35 (s, 3H), 3.18 (d, *J* = 9.3 Hz, 1H), 3.13 (d, *J* = 9.4 Hz, 1H), 2.96 (dt, *J* = 16.4, 2.2 Hz, 1H), 2.65 (hept, *J* = 7.0 Hz, 1H), 2.52 (s, 1H), 2.36 – 2.26 (m, 2H), 2.02 – 1.93 (m, 1H), 1.92 – 1.81 (m, 4H), 1.71 – 1.64 (m, 1H), 1.11 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 206.1, 153.0, 145.6, 144.7, 135.1, 133.3, 115.9, 80.6, 80.1, 59.4, 52.7, 41.2, 40.8, 39.6, 35.7, 28.4, 27.61, 27.58, 26.5, 21.1, 20.3.

HRMS Calculated $C_{21}H_{30}NaO_3$ $[M+Na]^+$: 353.2093 | Found: 353.2101

α-Hydroxyketone 48 [(1*R*,3a*R*,6*R*,9a*R*,*E*)-1,6-dihydroxy-7-isopropyl-1-(methoxymethyl)-9a-methyl-4-methylene-2,3,3a,4,6,8,9,9a-octahydrodicyclopenta[*a*,*d*][8]annulen-5(1*H*)-one]



47 48

A solution of enone **47** (24.9 mg, 0.0755 mmol, 1 equiv) in anhydrous THF (1.51 mL, 0.05 M) under an argon atmosphere at -78°C was treated with KHMDS (1.0 M in THF, 166 μL, 0.166 mmol, 2.2 equiv) and stirred for 1 hour. A solution of *rac*-2-(phenylsulfonyl)-3-phenyloxaziridine (39.5 mg, 0.151 mmol, 2 equiv) in anhydrous THF (1.00 mL, 0.15 M) was transferred into the reaction. The reaction was stirred at this temperature for 4 hours, then quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted three times with Et_2O. The combined organic extracts were washed with 1 M NaOH, H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (0 to 15% acetone/PhMe) afforded the product as a white solid (24.7 mg, 94%).

R_f 0.41 (50% EtOAc/hexanes, UV active, *p*-anisaldehyde)

$[\alpha]_D^{25}$ −79.1 (*c* 0.34, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

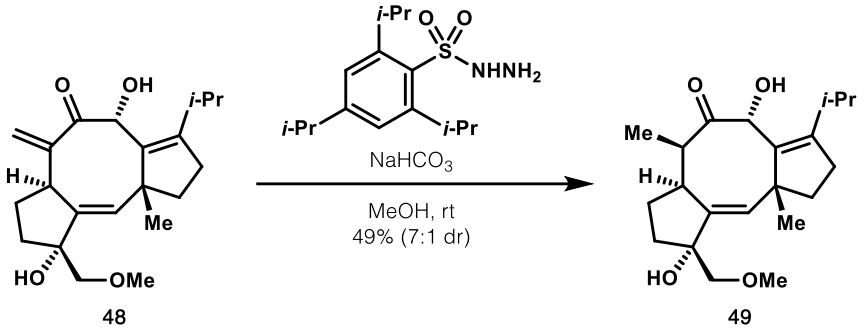
δ 6.20 (t, *J* = 1.1 Hz, 1H), 5.89 (d, *J* = 1.3 Hz, 1H), 5.47 (d, *J* = 1.9 Hz, 1H), 4.63 (d, *J* = 3.5 Hz, 1H), 4.14 (d, *J* = 3.5 Hz, 1H), 4.03 (d, *J* = 5.9 Hz, 1H), 3.36 (s, 3H), 3.24 (d, *J* = 9.0 Hz, 1H), 3.13 (d, *J* = 9.0 Hz, 1H), 2.69 (hept, *J* = 6.7 Hz, 1H), 2.63 (br s, 1H), 2.38 (ddd, *J* = 17.4, 10.4, 7.8 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.05 – 1.96 (m, 4H), 1.87 – 1.77 (m, 2H), 1.25 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 200.7, 148.8, 146.0, 144.9, 136.4, 136.1, 124.1, 82.1, 80.7, 73.4, 59.5, 52.6, 41.5, 38.9, 35.9, 28.2 (two overlapped resonances), 27.2, 25.5, 20.9, 19.8.

HRMS Calculated $C_{21}H_{30}NaO_4$ $[M+Na]^+$: 369.2042 | Found: 369.2035

α-Hydroxy-α′-methyl ketone 49 [(1*R*,3a*S*,4*R*,6*R*,9a*R*,*E*)-1,6-dihydroxy-7-isopropyl-1-(methoxymethyl)-4,9a-dimethyl-2,3,3a,4,6,8,9,9a-octahydrodicyclopenta[*a*,*d*][8]annulen-5(1*H*)-one]



A solution of α-hydroxyketone **48** (45.0 mg, 0.130 mmol, 1 equiv) in anhydrous MeOH (13 mL, 0.01 M) under an argon atmosphere was treated with 2,4,6-triisopropylbenzenesulfonyl hydrazide[13] (20 mg, 0.067 mmol, 5 equiv) and $NaHCO_3$ (193.82 mg, 0.649 mmol, 5 equiv). After stirring for 14 hours, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ and diluted with water. The mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (0 to 50% EtOAc/hexanes) afforded the product (7:1 dr) as a white foamy solid (22.1 mg, 49%).

R_f 0.42 (50% EtOAc/hexanes)

$[\alpha]_D^{25}$ −20.7 (*c* 0.14, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

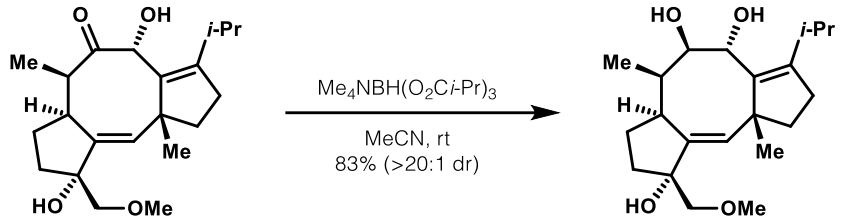
δ 5.82 (d, *J* = 2.3 Hz, 1H), 4.75 (d, *J* = 4.8 Hz, 1H), 3.82 (d, *J* = 5.2 Hz, 1H), 3.43 – 3.38 (m, 5H), 3.28 (d, *J* = 9.4 Hz, 1H), 2.75 (hept, *J* = 6.7 Hz, 1H), 2.69 (qd, *J* = 7.1, 1.6 Hz, 1H), 2.53 (br s, 1H), 2.26 – 2.18 (m, 2H), 2.07 (ddt, *J* = 12.5, 8.6, 7.8 Hz, 1H), 1.98 (ddd, *J* = 13.2, 7.3, 7.3 Hz, 1H), 1.88 – 1.78 (m, 2H), 1.58 (m, 1H), 1.39 (ddd, *J* = 13.0, 12.9, 7.3 Hz, 1H), 1.30 (s, 3H), 1.10 (d, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 211.8, 150.8, 140.6, 137.3, 133.7, 82.0, 78.0, 69.9, 59.5, 53.0, 50.9, 40.5, 39.7, 36.4, 31.1, 28.0, 27.2, 26.2, 21.1, 19.7, 14.6.

HRMS Calculated $C_{21}H_{33}O_4$ $[M+H]^+$: 349.2379 | Found: 349.2370

Cotylenol 3 [(1*R*,3a*S*,4*R*,5*R*,6*R*,9a*R*,*E*)-7-isopropyl-1-(methoxymethyl)-4,9a-dimethyl-1,2,3,3a,4,5,6,8,9,9a-decahydrodicyclopenta[*a*,*d*][8]annulene-1,5,6-triol]



49 cotylenol (**3**)

A solution of α-hydroxy-α′-methyl ketone **49** (5.2 mg, 0.015 mmol, 1 equiv) in anhydrous CH_3CN (0.77 mL, 0.02 M) under an argon atmosphere was treated with $Me_4NBH(O_2Ci\text{-}Pr)_3$[15] (1.0 M in CH_3CN, 0.62 mL, 0.62 mmol, 40 equiv). The reaction was stirred at room temperature for 24 hours, then quenched by addition of saturated aqueous $NaHCO_3$ (2 mL) and 5 M aqueous trimethylolethane (2 mL). After stirring for 12 hours, the mixture was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (0 to 50% EtOAc/hexanes) afforded the product as a white solid (4.5 mg, 83%).

Note: Trace HCl present in $CDCl_3$ was found to cause gradual conversion of cotylenol to an unidentified species. Basifying $CDCl_3$ before use is necessary, and use of C_6D_6 for NMR analysis is preferred.

R_f 0.43 (50% EtOAc/hexanes)

$[\alpha]_D^{25}$ −24.4 (*c* 0.10, MeOH)

^{1}H NMR (600 MHz, C_6D_6)

δ 5.72 (d, *J* = 2.5 Hz, 1H), 4.02 (d, *J* = 10.0 Hz, 1H), 3.94 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.35 (hept, *J* = 6.9 Hz, 1H), 3.28 (d, *J* = 9.2 Hz, 1H), 3.06 (s, 3H), 3.03 – 2.98 (m, 2H), 2.72 – 2.65 (m, 2H), 2.12 (ddd, *J* = 15.4, 10.1, 7.1 Hz, 1H), 2.03 (ddd, *J* = 12.4, 6.7, 3.2 Hz, 1H), 1.99 – 1.93 (m, 2H), 1.89 (ddd, *J* = 11.8, 7.1, 1.8 Hz, 1H), 1.85 – 1.78 (m, 1H), 1.66 – 1.59 (m, 1H), 1.53 – 1.46 (m, 2H), 1.15 (s, 3H), 1.14 – 1.06 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H).

(600 MHz, $CDCl_3$)

δ 5.52 (d, *J* = 2.6 Hz, 1H), 4.07 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.94 (dd, *J* = 9.9, 4.0 Hz, 1H), 3.40 (s, 3H), 3.36 (d, *J* = 9.5 Hz, 1H), 3.27 (hept, *J* = 6.6 Hz, 1H), 3.08 (dd, *J* = 9.4, 1.3 Hz, 1H), 2.96 – 2.92 (m, 2H), 2.52 (br s, 1H), 2.19 – 2.07 (m, 2H), 2.04 – 1.91 (m, 3H), 1.85 (ddd, *J* = 12.0, 6.9, 2.2 Hz, 1H), 1.74 (d, *J* = 2.8 Hz, 1H), 1.69 (ddd, *J* = 12.0, 10.0, 8.4 Hz, 1H), 1.45 – 1.37 (m, 1H), 1.31 – 1.26 (m, 1H), 1.22 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6)

δ 149.9, 139.9, 137.5, 134.4, 81.9, 77.95, 77.92, 68.1, 59.0, 52.0, 43.0, 42.2, 40.6, 35.7, 31.8, 28.3, 27.3, 26.7, 21.5, 20.4, 8.7.

(151 MHz, $CDCl_3$)

δ 150.5, 139.8, 137.0, 134.4, 82.1, 77.7, 77.4, 68.0, 59.5, 51.9, 42.6, 41.7, 40.3, 35.4, 31.7, 28.2, 27.2, 26.6, 21.6, 20.5, 8.5.

HRMS Calculated $C_{21}H_{34}NaO_4$ $[M+Na]^+$: 373.2355 | Found: 373.2343

Comparison of NMR Data for synthetic and natural cotylenol

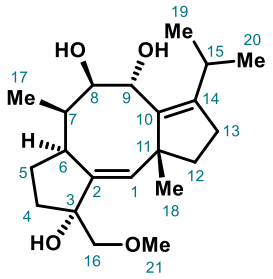


Table S1. Comparison of ^{1}H NMR data of synthetic cotylenol in C_6D_6

Uwamori *et al.* ^{1}H NMR (600 MHz, C_6D_6)[15]	This Work ^{1}H NMR (600 MHz, C_6D_6)
5.74 – 5.71 (m, 1H)	5.72 (d, *J* = 2.5 Hz, 1H)
4.02 (d, *J* = 10.5 Hz, 1H)	4.02 (d, *J* = 10.0 Hz, 1H)
3.93 (dd, *J* = 10.5, 4.0 Hz, 1H)	3.94 (dd, *J* = 10.0, 4.3 Hz, 1H)
3.41 – 3.31 (m, 1H)	3.35 (hept, *J* = 6.9 Hz, 1H)
3.28 (d, *J* = 9.0 Hz, 1H)	3.28 (d, *J* = 9.2 Hz, 1H)
3.06 (s, 3H)	3.06 (s, 3H)
3.05 – 2.96 (m, 2H)[a]	3.03 – 2.98 (m, 2H)
2.71 (br s, 1H)	2.72 – 2.65 (m, 2H)
2.16 – 2.07 (m, 1H)	2.12 (ddd, *J* = 15.4, 10.1, 7.1 Hz, 1H)
2.07 – 2.01 (m, 1H)	2.03 (ddd, *J* = 12.4, 6.7, 3.2 Hz, 1H)
2.00 – 1.88 (m, 3H)[b]	1.99 – 1.93 (m, 2H)
	1.89 (ddd, *J* = 11.8, 7.1, 1.8 Hz, 1H)
1.88 – 1.77 (m, 1H)	1.85 – 1.78 (m, 1H)
1.68 – 1.57 (m, 1H)	1.66 – 1.59 (m, 1H)
1.57 – 1.45 (m, 1H)	1.53 – 1.46 (m, 2H)
1.40 – 1.20 (m, 2H)	--
1.16 (s, 3H)	1.15 (s, 3H)
1.13 – 1.05 (m, 1H)	1.14 – 1.06 (m, 1H)
1.00 (d, *J* = 6.0 Hz, 3H)	1.00 (d, *J* = 6.7 Hz, 3H)
0.91 (d, *J* = 7.5 Hz, 3H)	0.91 (d, *J* = 7.3 Hz, 3H)
0.89 (d, *J* = 6.0 Hz, 3H)	0.89 (d, *J* = 6.9 Hz, 3H)

[a]The 1H integration stated in the reference was an error, as judged from the spectrum provided by the authors.

[b]The chemical shift of 2.00 – 1.95 stated in the reference was an error, as judged from the spectrum provided by the authors.

Table S2. Comparison ^{13}C NMR data of synthetic cotylenol in C_6D_6

Chemical Shift (ppm)		
Uwamori *et al.* ^{13}C NMR (150 MHz, C_6D_6)[15]	This Work ^{13}C NMR (151 MHz, C_6D_6)	Difference
149.9	149.9	0.0
139.9	139.9	0.0
137.5	137.5	0.0
134.4	134.4	0.0
81.9	81.9	0.0
77.96	77.95	-0.01
77.93	77.92	-0.01
68.1	68.1	0.0
58.9	59.0	0.1
52.0	52.0	0.0
43.0	43.0	0.0
42.2	42.2	0.0
40.6	40.6	0.0
35.7	35.7	0.0
31.8	31.8	0.0
28.3	28.3	0.0
27.3	27.3	0.0
26.7	26.7	0.0
21.5	21.5	0.0
20.4	20.4	0.0
8.7	8.7	0.0

Table S3. Comparison of ^{1}H NMR data of isolated and synthetic cotylenol in $CDCl_3$

C	Isolation ^{1}H NMR (100 MHz, $CDCl_3$)[14]	Uwamori *et al.* ^{1}H NMR (600 MHz, $CDCl_3$)[15]	This Work ^{1}H NMR (600 MHz, $CDCl_3$)
1	5.55 (d, *J* = 2.5 Hz, 1H)	5.52 (d, *J* = 2.6 Hz, 1H)	5.52 (d, *J* = 2.6 Hz, 1H)
9	3.8 – 4.2 (m, 2H)	4.07 (d, *J* = 10.2 Hz, 1H)	4.07 (dd, *J* = 10.1, 2.5 Hz, 1H)
8		3.94 (dd, *J* = 10.2, 4.4 Hz, 1H)	3.94 (dd, *J* = 9.9, 4.0 Hz, 1H)
21	3.42 (s, 3H)	3.40 (s, 3H)	3.40 (s, 3H)
16′	3.38 (d, *J* = 9.5 Hz, 1H)	3.36 (d, *J* = 9.7 Hz, 1H)	3.36 (d, *J* = 9.5 Hz, 1H)
15	3.28 (m)	3.29 – 3.25 (m, 1H)	3.27 (hept, *J* = 6.6 Hz, 1H)
16	3.08 (d, *J* = 9.5 Hz, 1H)	3.08 (dd, *J* = 9.5, 1.3 Hz, 1H)	3.08 (dd, *J* = 9.4, 1.3 Hz, 1H)
6	2.94 (br t, *J* = 7.5 Hz, 1H)	2.95 – 2.92 (m, 2H)	2.96 – 2.92 (m, 2H)
OH	not reported		
OH	2.48 (br s, 3H)	2.52 (br s, 1H)	2.52 (br s, 1H)
13	2.2 – 1.2 (m, 9H)	2.16 – 2.08 (m, 2H)	2.19 – 2.07 (m, 2H)
4′, 5		2.03 – 1.93 (m, 3H)	2.04 – 1.91 (m, 3H)
12′		1.85 (ddd, *J* = 11.9, 6.8, 2.0 Hz, 1H)	1.85 (ddd, *J* = 12.0, 6.9, 2.2 Hz, 1H)
OH		1.76 (s, 1H)	1.74 (d, *J* = 2.8 Hz, 1H)
12		1.71 – 1.66 (m, 1H)	1.69 (ddd, *J* = 12.0, 10.0, 8.4 Hz, 1H)
7		1.43 – 1.40 (m, 1H)	1.45 – 1.37 (m, 1H)
4		1.30 – 1.24 (m, 1H)	1.31 – 1.26 (m, 1H)
18	1.20 (s, 3H)	1.22 (s, 3H)	1.22 (s, 3H)
20	1.01 (d, *J* = 7.0 Hz, 3H)	1.04 (d, *J* = 6.9 Hz, 3H)	1.04 (d, *J* = 6.8 Hz, 3H)
19	0.94 (d, *J* = 7.0 Hz, 3H)	0.96 (d, *J* = 6.9 Hz, 3H)	0.96 (d, *J* = 6.9 Hz, 3H)
17	0.79 (d, *J* = 6.5 Hz, 3H)	0.81 (d, *J* = 7.2 Hz, 3H)	0.81 (d, *J* = 7.2 Hz, 3H)

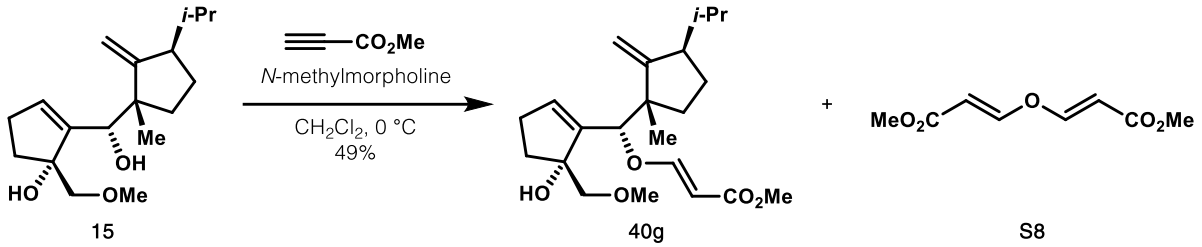
Table S4. Comparison ^{13}C NMR data of synthetic cotylenol in $CDCl_3$

Chemical Shift (ppm)		
Uwamori *et al.* ^{13}C NMR (150 MHz, $CDCl_3$)[15]	This Work ^{13}C NMR (151 MHz, $CDCl_3$)	Difference
150.4	150.5	0.1
139.7	139.8	0.1
136.9	137.0	0.1
134.2	134.4	0.2
81.9	82.1	0.2
77.5	77.6	0.1
77.3	77.4	0.1
67.8	68.0	0.2
59.3	59.5	0.2
51.8	51.9	0.1
42.5	42.6	0.1
41.6	41.7	0.1
40.2	40.3	0.1
35.3	35.4	0.1
31.6	31.7	0.1
28.0	28.2	0.2
27.1	27.2	0.1
26.5	26.6	0.1
21.4	21.6	0.2
20.3	20.5	0.2
8.4	8.5	0.1

Note: The ^{13}C NMR spectrum from Uwamori *et al.* referenced the $CDCl_3$ peak to 77.00 ppm instead of 77.16 ppm, accounting for the systematic chemical shift difference of 0.1–0.2 ppm.

D. Investigation of Alternative Claisen Rearrangement Substrates

Enol ether 40g [methyl (*E*)-3-((*S*)-((*R*)-5-hydroxy-5-(methoxymethyl)cyclopent-1-en-1-yl)((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methoxy)acrylate]



To a solution of diol **15** (15 mg, 0.05 mmol, 1 equiv) in anhydrous CH_2Cl_2 (0.25 mL, 0.2 M) at 0 °C under an argon atmosphere was added sequentially methyl propiolate (13 μL, 0.15 mmol, 3 equiv) and *N*-methylmorpholine (28 μL, 0.25 mmol, 5 equiv). After stirring for 1 hour, the reaction was quenched with water, diluted with brine, and extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by preparative thin layer chromatography (10% acetone/PhMe) afforded the product as a white solid (9 mg, 49%) along with poorly separable **S8** [dimethyl 3,3'-oxy(2*E*,2'*E*)-diacrylate].

R_f 0.31 (10% acetone/PhMe, UV active)

^{1}H NMR (600 MHz, $CDCl_3$)

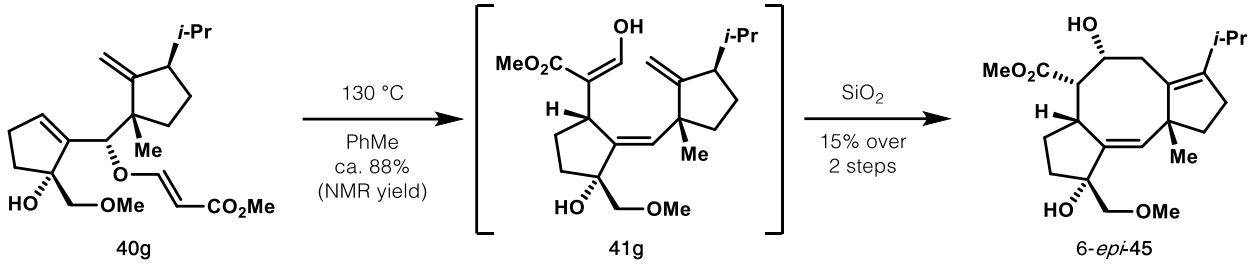
δ 7.59 (d, *J* = 12.1 Hz, 2H, **S8**), 7.58 (d, *J* = 12.2 Hz, 1H), 6.05 (td, *J* = 2.6, 0.8 Hz, 1H), 5.67 (d, *J* = 12.1 Hz, 2H, **S8**), 5.29 (d, *J* = 12.2 Hz, 1H), 4.94 (d, *J* = 2.9 Hz, 1H), 4.84 (d, *J* = 2.6 Hz, 1H), 4.50 (s, 1H), 3.74 (s, 6H, **S8**), 3.66 (s, 3H), 3.47 (d, *J* = 9.0 Hz, 1H), 3.38 (s, 3H), 3.27 (d, *J* = 9.0 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.39 – 2.36 (m, 1H), 2.28 – 2.23 (m, 1H), 2.09 (ddd, *J* = 13.2, 8.4, 4.8 Hz, 1H), 1.99 – 1.92 (m, *J* = 6.8, 4.0 Hz, 1H), 1.89 (ddd, *J* = 13.5, 8.6, 4.8 Hz, 1H), 1.78 – 1.72 (m, 1H), 1.63 – 1.59 (m, 1H), 1.43 – 1.33 (m, 2H), 1.17 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 168.8, 166.6 (**S8**), 164.3, 159.8, 157.5 (**S8**), 142.3, 137.1, 107.2, 104.1 (**S8**), 96.8, 87.7, 85.4, 78.0, 59.4, 51.8 (**S8**), 51.2, 51.1, 50.2, 37.1, 34.8, 29.4, 28.5, 24.2, 23.0, 22.2, 16.4.

LRMS Calculated $C_{22}H_{34}NaO_5$ $[M+Na]^+$: 401.2 | Found: 401.2

6-*epi*-Tricycle 6-*epi*-45 [methyl (1*R*,3a*R*,4*S*,5*R*,9a*R*,*E*)-1,5-dihydroxy-7-isopropyl-1-(methoxymethyl)-9a-methyl-1,2,3,3a,4,5,6,8,9,9a-decahydrodicyclopenta[*a*,*d*][8]annulene-4-carboxylate]



To a heavy walled glass tube under an argon atmosphere was added enol ether **40g** (96.2 mg, 0.25 mmol, 1 equiv) and anhydrous PhMe (5.1 mL, 0.05 M). The vessel was sealed and heated to 130 °C for 15 hours. The reaction vessel was then cooled to room temperature and concentrated. Purification by chromatography on silica gel (33% EtOAc/hexanes) afforded the product as a white foamy solid (15 mg, 15%).

R_f **41g**: 0.73 (33% EtOAc/hexanes)
6-*epi*-**45**: 0.19 (33% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$)

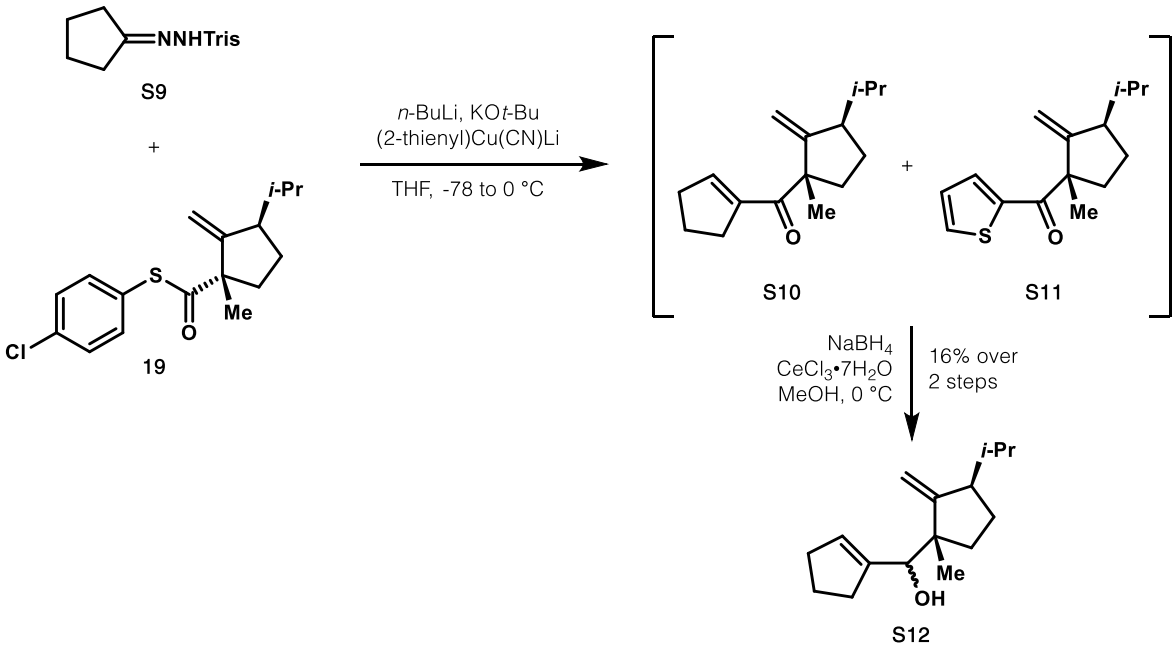
δ 5.74 (d, *J* = 2.1 Hz, 1H), 4.14 (td, *J* = 6.4, 2.2 Hz, 1H), 3.70 (m, 4H), 3.39 (m, 4H), 3.30 (d, *J* = 9.4 Hz, 1H), 3.22 (d, *J* = 9.4 Hz, 1H), 2.98 – 2.91 (m, 1H), 2.87 (dd, *J* = 9.7, 6.4 Hz, 1H), 2.78 – 2.70 (m, 2H), 2.42 (d, *J* = 14.6 Hz, 1H), 2.27 – 2.19 (m, 2H), 1.90 – 1.85 (m, 2H), 1.78 – 1.72 (m, 2H), 1.71 – 1.64 (m, 1H), 1.55 – 1.48 (m, 1H), 1.17 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 174.6, 146.7, 144.3, 134.5, 133.4, 81.6, 79.4, 71.1, 59.5, 57.7, 52.3, 51.8, 40.4, 40.3, 35.3, 29.4, 27.9, 27.7, 27.0, 25.5, 21.4, 21.2.

LRMS Calculated $C_{22}H_{34}NaO_5$ $[M+Na]^+$: 401.2 | Found: 401.2

Allylic alcohol S12 [cyclopent-1-en-1-yl((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methanol]



A solution of hydrazone **S9**[16] (408 mg, 1.12 mmol, 1 equiv) in anhydrous THF (5 mL, 0.2 M) under an argon atmosphere at -78 °C was treated with *n*-BuLi (2.71 M in hexanes, 0.88 mL, 2.24 mmol, 2 equiv). After incubating for 5 minutes, the reaction was raised to 0 °C and stirred for 40 minutes. A solution of lithium 2-thienylcyanocuprate (0.25 M in THF, 4.480 mL, 1.12 mmol, 1 equiv) was transferred into the reaction, and the mixture was stirred at 0 °C for 5 minutes. A solution of thioester **19** (346 mg, 1.12 mmol, 1 equiv) in THF (5 mL, 0.2 M) was added dropwise, and the solution was stirred for 2 hours before being quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with brine and extracted three times with Et_2O. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel (0 to 8% Et_2O/hexanes) afforded ketone **S10** as an inseparable mixture with **S11** (3:1 ratio favoring the desired product).

Without further purification, this mixture was dissolved in MeOH (9.1 mL, ca. 0.1 M) and cooled at 0 °C. $CeCl_3$•$7H_2O$ (510 mg, 1.37 mmol, 1.5 equiv) was added, followed by $NaBH_4$ (52 mg, 1.37 mmol, 1.5 equiv). The reaction was stirred for 5 minutes, then was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted three times with Et_2O and the combined organic extracts were concentrated to dryness. The material was resuspended in Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography silica gel (0 to 8% Et_2O/hexanes) afforded the **S12** (1.3:1 ratio of unassigned diastereomers) as a colorless oil (44 mg, 16% over 2 steps).

R_f 0.26 (10% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 5.70 (dt, *J* = 3.7, 1.8 Hz, 1H, minor isomer), 5.67 (dt, *J* = 4.2, 2.1 Hz, 1H, major isomer), 5.00 (d, *J* = 2.8 Hz, 1H, major isomer), 4.98 (d, *J* = 3.1 Hz, 1H, minor isomer), 4.93 (d, *J* = 2.7 Hz, 1H, minor isomer), 4.91 (d, *J* = 2.4 Hz, 1H, major isomer), 4.36 (s, 1H, minor isomer), 4.08 (s, 1H, major isomer), 2.47 – 2.36 (m, 4H), 2.34 – 2.25 (m, 5H), 2.03 (heptd, *J* = 6.8, 4.2 Hz, 1H, minor isomer), 1.99 – 1.93 (m, 2H), 1.90 – 1.82 (m, 5H), 1.75 (dt, *J* = 12.5, 7.4 Hz, 1H, major isomer), 1.66 – 1.60 (m, 2H), 1.43 – 1.25 (m, 4H), 1.07 (s, 3H, major isomer), 0.99 (d, *J* = 6.9 Hz, 3H, minor isomer), 0.98 (d, *J* = 6.7 Hz, 3H, major isomer), 0.89 (s, 3H, minor isomer), 0.78 (d, *J* = 6.7 Hz, 3H, minor isomer), 0.77 (d, *J* = 6.8 Hz, 3H, major isomer).

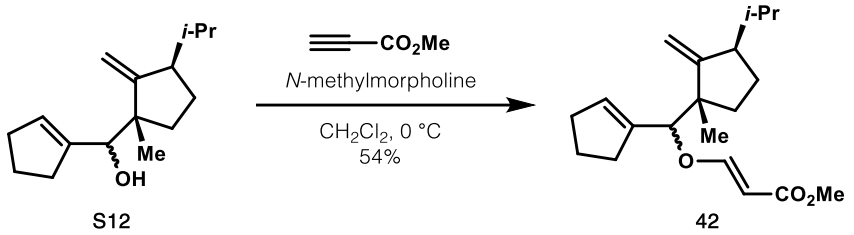
^{13}C NMR (151 MHz, $CDCl_3$)

δ 161.6, 161.3, 145.1, 144.2, 129.3, 128.0, 106.2, 104.4, 77.2, 76.0,

52.3, 51.6, 51.3, 50.5, 34.7, 34.5, 33.1, 32.11, 32.05, 32.0, 29.1, 28.2, 25.7, 24.1, 24.0, 23.2, 23.1, 22.6, 22.2, 22.0, 16.6, 16.2.

LRMS Calculated $C_{16}H_{25}$ $[M–OH]^+$: 217.2 | Found: 217.2

Enol ether 42 [methyl (*E*)-3-(cyclopent-1-en-1-yl((1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methoxy)acrylate]



To a solution of allylic alcohol **S12** (35 mg, 0.15 mmol, 1 equiv) in anhydrous CH_2Cl_2 (0.75 mL, 0.2 M) at 0 °C under an argon atmosphere was added sequentially methyl propiolate (40 μL, 0.45 mmol, 3 equiv) and *N*-methylmorpholine (82 μL, 0.75 mmol, 5 equiv). After stirring for 2 hours, an additional portion of both methyl propiolate and *N*-methylmorpholine was added. After stirring 1 additional hour, the reaction was quenched with water, diluted with brine, and extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, concentrated. Purification by preparative thin layer chromatography (10% EtOAc in *n*-heptane) afforded the product (mixture of diastereomers) as a colorless oil (28 mg, 54%). While the diastereomeric products were co-polar by TLC, splitting the preparatory TLC band into 2 segments allowed isolation of a small amount (5 mg) of material highly enriched (8:1 d.r.) in the major isomer for full characterization, with the remaining 23 mg as a nearly 1:1 mixture.

R_f 0.58 (10% EtOAc/hexanes, UV active)

^{1}H NMR (600 MHz, $CDCl_3$)

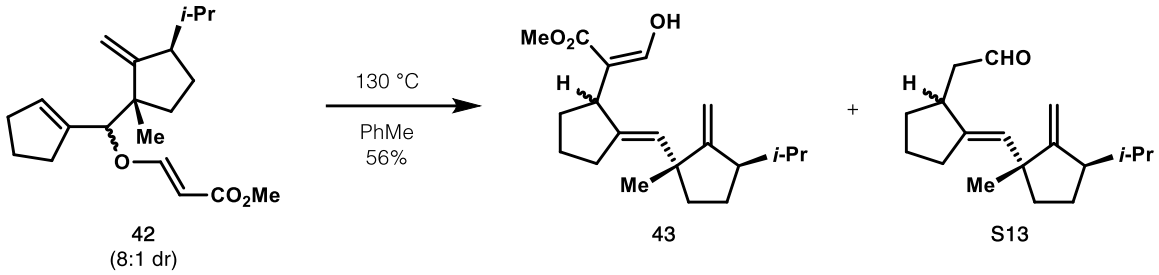
δ 7.49 (d, *J* = 12.4 Hz, 1H), 7.45 (d, *J* = 12.3 Hz, 1H), 5.75 – 5.73 (m, 1H), 5.63 – 5.60 (m, 1H), 5.21 (d, *J* = 12.3 Hz, 1H), 5.20 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 2.9 Hz, 1H), 4.87 (d, *J* = 3.0 Hz, 1H), 4.84 (d, *J* = 2.5 Hz, 1H), 4.79 (d, *J* = 2.6 Hz, 1H), 4.47 (s, 1H), 4.35 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 2.38 – 2.20 (m, 10H), 1.99 – 1.78 (m, 6H), 1.73 – 1.63 (m, 2H), 1.59 – 1.55 (m, 2H), 1.38 – 1.30 (m, 4H), 1.10 (s, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 3H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 168.91, 168.88, 163.2, 162.7, 160.2, 159.5, 141.2, 141.1, 132.6, 131.1, 106.8, 104.1, 96.8, 96.7, 89.4, 89.0, 51.8, 51.6, 51.13, 51.08, 49.9, 49.8, 34.7, 33.8, 33.0, 32.5, 32.2, 32.1, 28.6, 27.9, 25.7, 24.9, 24.0, 23.9, 23.3, 22.23, 22.15, 22.12, 16.6, 16.3.

LRMS Calculated $C_{20}H_{30}NaO_3$ $[M+Na]^+$: 341.2 | Found: 341.2

Enol 43 and aldehyde S13 [methyl (*Z*)-3-hydroxy-2-((*E*)-2-(((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methylene)cyclopentyl)acrylate] and [2-((*E*)-2-(((1*R*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentyl)methylene)cyclopentyl)acetaldehyde]



42 (8:1 dr) 43 S13

A solution of **42** (5 mg, 0.014 mmol, 1 equiv) in anhydrous PhMe (0.71 mL, 0.02 M) was sealed under an argon atmosphere in a vial that had previously been treated with refluxing HMDS for 30 minutes. The sealed vial was then heated to 130 °C for 2 hours, then cooled and concentrated. Purification by preparative thin layer chromatography (10% EtOAc/hexanes) afforded an inseparable 1:1 mixture of the title compounds as a colorless oil (3 mg, 56%).

R_f 0.62 (10% EtOAc/hexanes, UV active)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 11.59 (d, *J* = 12.6 Hz, 1H), 9.79 (t, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 12.5 Hz, 1H), 5.34 (d, *J* = 2.5 Hz, 1H), 5.24 (d, *J* = 2.7 Hz, 1H), 4.86 – 4.83 (m, 2H), 4.78 – 4.75 (m, 2H), 3.74 (s, 3H), 3.13 (t, *J* = 7.9 Hz, 1H), 2.87 – 2.82 (m, 1H), 2.60 (ddd, *J* = 16.3, 5.0, 2.1 Hz, 1H), 2.49 – 2.43 (m, 3H), 2.40 (ddd, *J* = 14.9, 7.9, 1.9 Hz, 2H), 2.31 – 2.20 (m, 2H), 2.02 – 1.96 (m, 2H), 1.88 (dq, *J* = 12.2, 6.8 Hz, 1H), 1.80 – 1.70 (m, 4H), 1.66 – 1.50 (m, 7H), 1.44 – 1.36 (m, 2H), 1.31 – 1.20 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 203.2, 162.6, 162.5, 162.2, 143.0, 131.6, 131.3, 104.6, 104.5, 51.4, 50.5, 50.4, 49.3, 48.4, 48.3, 45.4, 40.3, 39.4, 39.3, 33.0, 32.3, 29.7, 29.2, 28.83, 28.80, 28.0, 27.7, 25.1, 24.8, 23.4, 23.3, 22.10, 22.08, 16.5, 16.4.

Claisen rearrangement transition state analysis

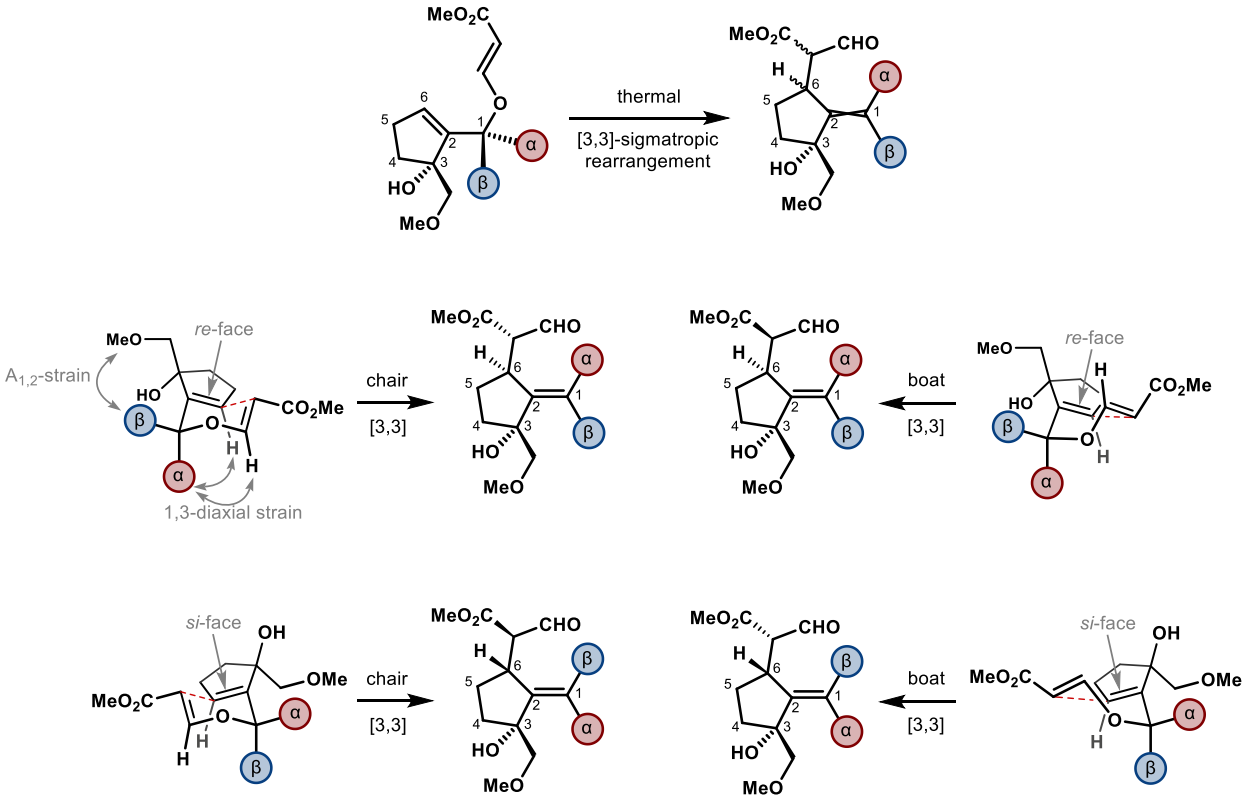


Figure S1. Analysis of possible Claisen transition states using generic substituents α and β.

A canonical concerted pericyclic Claisen rearrangement will have 4 available transition states for a given configurational isomer: 2 with chair conformations and 2 with boat conformations. Above is drawn the Claisen rearrangement pursued in this total synthesis and its corresponding 4 transition states. In order to elaborate the product to cotylenol, the C6 methine and the $\Delta^{1,2}$-olefin stereochemistry both needed to be correct. The C7 methine, however, is clearable and of minimal importance. Analysis of the above transition states leads to the following conclusions:

1: The C-ring needs to be in the α-position as drawn in the above enol ether. The C6 methine and the $\Delta^{1,2}$ olefin stereochemistries are evidently linked. When the C6 stereochemistry is correct, α-substituent is always *cis* relative to newly formed C-C bond. In order to have the correct olefin geometry for cyclization of the B-ring, the C-ring thus needs to be in the α-position.

2: $A^{1,2}$-strain must dominate to enforce a pseudo-axial orientation of the bulky C-ring and thus generate the correct $\Delta^{1,2}$-olefin stereochemistry.

Both of these points are consistent with the experimental observation (*vide infra*) that 1) inverted C1 stereochemistry in the starting material gives the inverted C6 stereochemistry in the product and that 2) the unsubstituted cyclopentene substrate gives exclusively products with the undesired olefin stereochemistry.

The distinction between chair and boat transition states is ultimately inconsequential and unknown in this case as rapid keto-enol tautomerism obfuscates any definitive C7 stereochemistry.

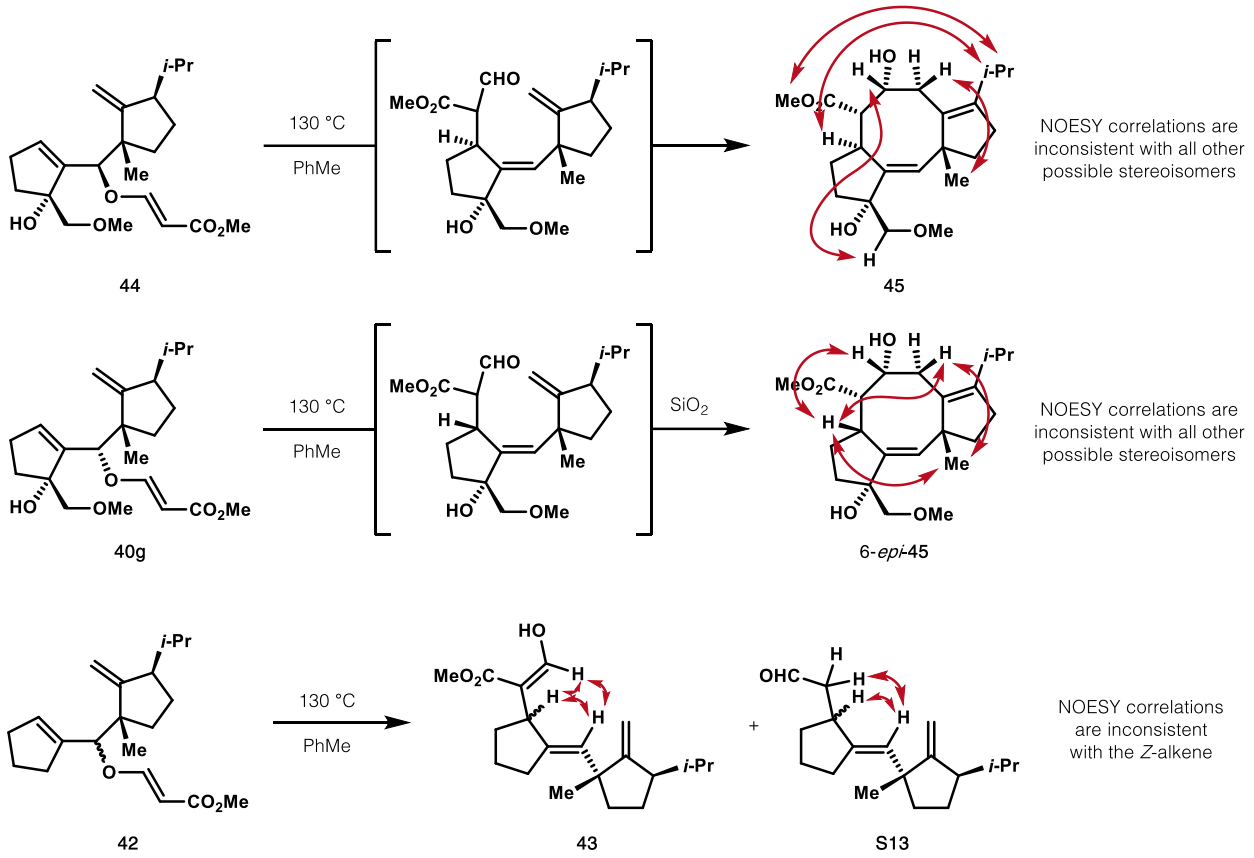
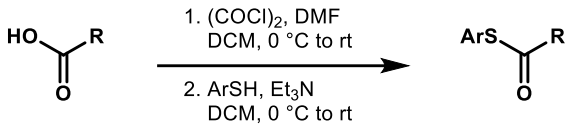


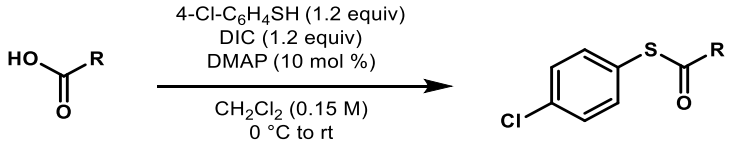
Figure S2. NOESY correlations exclude stereoisomers of interest but support the assigned structures.

E. Modified Liebeskind-Srogl Coupling

Synthesis of coupling substrates

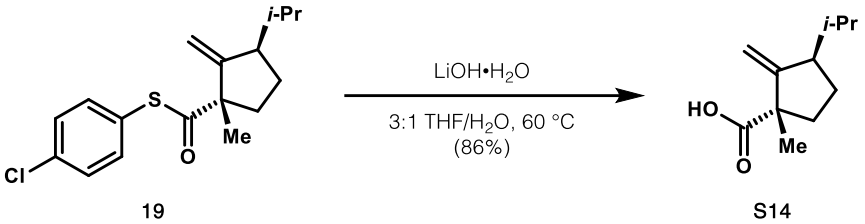


General Procedure A: A flame-dried reaction tube was charged with carboxylic acid (1 equiv) and placed under an argon atmosphere. CH_2Cl_2 (0.1 M with respect to carboxylic acid) and DMF (0.05 equiv) were added, and the reaction mixture was cooled to 0 °C. $(COCl)_2$ (2.0 M in CH_2Cl_2, 2 equiv) was added dropwise, and the reaction mixture was stirred at room temperature. After 2 hours, the reaction mixture was concentrated and placed under an argon atmosphere. CH_2Cl_2 (0.1 M with respect to carboxylic acid) was added, and the reaction mixture was cooled to 0 °C. Thiol (1.5 equiv) was then added, followed by Et_3N (2 equiv). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was passed through a pad of silica gel, eluting with Et_2O, and the filtrate was concentrated. Purification by chromatography on silica gel afforded the thioester.



General Procedure B: A flame-dried flask was charged with carboxylic acid (1 equiv), 4-chlorothiophenol (1.2 equiv) and 4-(dimethylamino)pyridine (0.1 equiv). The flask was placed under an argon atmosphere and charged with CH_2Cl_2 (0.15 M with respect to carboxylic acid). The solution was cooled to 0 °C, and *N*,*N*′-diisopropylcarbodiimide (1.2 equiv) was added dropwise over 1 minute. The reaction mixture was stirred at room temperature for 0.5–18 hours. The reaction mixture was passed through a pad of silica gel topped with Celite, eluting with Et_2O, and the filtrate was concentrated. Purification by chromatography on silica gel afforded the thioester.

Carboxylic acid S14 [(1*S*,3*R*)-3-isopropyl-1-methyl-2-methylenecyclopentane-1-carboxylic acid]



19 S14

Under ambient atmosphere, a solution of **19** (550 mg, 1.78 mmol, 1 equiv) in 3:1 THF/H_2O (18 mL) was treated with LiOH•H_2O (187 mg, 4.45 mmol, 2.5 equiv). The reaction mixture was stirred at 60 °C for 24 hours, then cooled to room temperature and carefully concentrated to remove THF (the reaction mixture is very prone to bumping). The material was diluted with CH_2Cl_2 (20 mL) and extracted with 1 M NaOH (2 x 10 mL), after which the organic phase was discarded. The combined aqueous extracts were acidified with 1 M HCl (50 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel (20% PhMe/hexanes, then 5 to 25% EtOAc/hexanes) afforded the product as a yellow solid (278 mg, 86%).

R_f 0.26 (20% EtOAc/hexanes)

$[\alpha]_D^{25}$ +77.1 (*c* 1.00 $CHCl_3$)

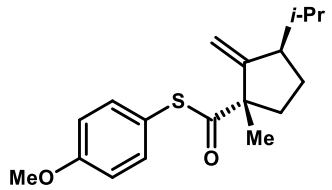
^{1}H NMR (600 MHz, $CDCl_3$)

δ 5.15 (d, *J* = 2.9 Hz, 1H), 4.93 (d, *J* = 2.5 Hz, 1H), 2.56 (tdd, *J* = 10.0, 4.9, 2.8 Hz, 1H), 2.26 (ddd, *J* = 12.6, 9.8, 7.0 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.80 (dtd, *J* = 11.8, 7.4, 4.0 Hz, 1H), 1.60 (ddd, *J* = 12.6, 7.0, 4.0 Hz, 1H), 1.47 (dtd, *J* = 12.4, 9.7, 7.0 Hz, 1H), 1.29 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 182.4, 158.2, 107.4, 53.1, 51.1, 36.4, 28.8, 24.7, 24.2, 22.1, 16.8.

HRMS Calculated $C_{11}H_{19}O_2$ $[M+H]^+$: 183.1385 | Found: 183.1384



S15: Prepared according to General Procedure A using **S14** (15.0 mg, 0.0823 mmol) and 4-methoxythiophenol (17.3 mg, 0.123 mmol, 1.5 equiv). Purification by chromatography on silica gel (50 to 100% PhMe/hexanes) afforded a mostly clean sample of **S15**. Further purification by chromatography on silica gel (6 to 10% Et_2O/hexanes) afforded the product as a colorless oil (19.8 mg, 79%).

R_f 0.34 (10% Et_2O/hexanes)

$[\alpha]_D^{25}$ +66.3 (*c* 1.00 $CHCl_3$)

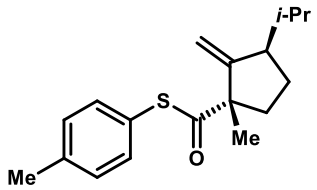
^1H NMR (600 MHz, $CDCl_3$)

δ 7.29 – 7.26 (m, 2H), 6.94 – 6.90 (m, 2H), 5.23 (d, *J* = 2.9 Hz, 1H), 5.07 (d, *J* = 2.6 Hz, 1H), 3.81 (s, 3H), 2.72 – 2.65 (m, 1H), 2.33 (ddd, *J* = 12.8, 8.9, 7.0 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.81 (dtd, *J* = 12.4, 7.4, 4.7 Hz, 1H), 1.68 – 1.61 (m, 1H), 1.50 (dtd, *J* = 12.5, 9.1, 7.2 Hz, 1H), 1.36 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 203.7, 160.5, 157.5, 136.5, 119.5, 114.9, 109.3, 61.6, 55.5, 50.8, 37.6, 28.9, 24.9, 23.8, 22.1, 16.6.

HRMS Calculated $C_{18}H_{25}O_2S$ $[M+H]^+$: 305.1575 | Found: 305.1585



S16: Prepared according to General Procedure A using **S14** (15.0 mg, 0.0823 mmol) and 4-methylthiophenol (15.3 mg, 0.123 mmol) Purification by chromatography on silica gel (10 to 30% PhMe/hexanes) afforded the product as a yellow oil (19.5 mg, 82%).

R_f 0.36 (20% PhMe/hexanes)

$[\alpha]_D^{25}$ +101 (*c* 0.91 $CHCl_3$)

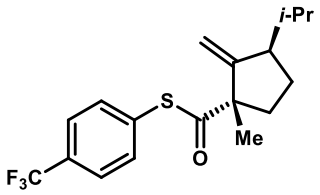
^{1}H NMR (600 MHz, $CDCl_3$)

7.26 – 7.24 (m, 2H), 7.22 – 7.18 (m, 2H), 5.23 (d, *J* = 2.9 Hz, 1H), 5.07 (d, *J* = 2.6 Hz, 1H), 2.72 – 2.66 (m, 1H), 2.36 (s, 3H), 2.36 – 2.30 (m, 1H), 2.07 – 1.98 (m, 1H), 1.81 (dtd, *J* = 12.4, 7.5, 4.7 Hz, 1H), 1.68 – 1.61 (m, 1H), 1.51 (dtd, *J* = 12.7, 9.2, 7.3 Hz, 1H), 1.37 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 203.2, 157.5, 139.4, 134.9, 130.0, 125.3, 109.4, 61.7, 50.8, 37.6, 28.9, 24.9, 23.8, 22.1, 21.5, 16.6.

HRMS Calculated $C_{18}H_{25}OS$ $[M+H]^+$: 289.1626 | Found: 289.1633



S17: Prepared according to General Procedure A using **S14** (16.3 mg, 0.0897 mmol) and 4-(trifluoromethyl)thiophenol (24.2 μL, 32.0 mg, 0.179 mmol, 2 equiv instead of 1.5 equiv). 3 equiv Et_3N (37.5 μL, 27.2 mg, 0.269 mmol) was used instead of 2 equiv. Purification by chromatography on silica gel (5 to 20% PhMe/hexanes) afforded the product as a pale yellow oil (28.1 mg, 92%).

R_f 0.33 (10% PhMe/hexanes)

$[\alpha]_D^{25}$ +86.5 (*c* 1.00 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 5.24 (d, *J* = 2.9 Hz, 1H), 5.11 (d, *J* = 2.6 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.32 (ddd, *J* = 12.8, 8.9, 7.1 Hz, 1H), 2.03 (heptd, *J* = 6.8, 4.0 Hz, 1H), 1.82 (dtd, *J* = 12.4, 7.5, 4.6 Hz, 1H), 1.68 (ddd, *J* = 12.3, 7.1, 4.6 Hz, 1H), 1.53 (dtd, *J* = 12.5, 9.1, 7.1 Hz, 1H), 1.38 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

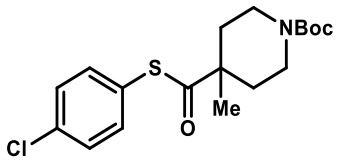
^{13}C NMR (151 MHz, $CDCl_3$)

δ 201.7, 157.2, 135.1, 133.8 (q, *J* = 1.2 Hz), 131.1 (q, *J* = 32.6 Hz), 125.9 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.3 Hz), 109.9, 62.0, 50.9, 37.6, 28.9, 24.8, 23.9, 22.1, 16.6.

^{19}F NMR (376 MHz, $CDCl_3$)

δ -63.3 (s, 3F).

HRMS Calculated $C_{18}H_{22}F_3OS$ $[M+H]^+$: 343.1343 | Found: 343.1345



38a: Prepared according to General Procedure B using 1-Boc-4-methylpiperidine-4-carboxylic acid (487 mg, 2.00 mmol) and a reaction time of 18 hours. Purification by chromatography on silica gel (50% PhMe/hexanes, then 0 to 15% EtOAc/hexanes) and further purification by chromatography on silica gel (5 to 8% Et_2O/PhMe) afforded the product as a white solid (717 mg, 97%).

R_f 0.34 (10% EtOAc/hexanes, UV active)

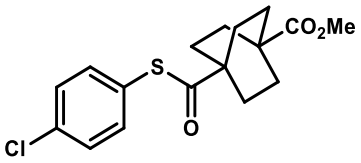
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.41 – 7.37 (m, 2H), 7.33 – 7.29 (m, 2H), 3.68 (br s, 2H), 3.22 (ddd, *J* = 13.5, 9.7, 3.3 Hz, 2H), 2.14 (br d, *J* = 13.8 Hz, 2H), 1.53 (br s, 2H), 1.46 (s, 9H), 1.35 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 202.9, 154.9, 136.4, 135.9, 129.6, 125.9, 79.8, 49.6, 41.2 and 40.5 (rotamers), 34.8, 28.6, 26.1.

HRMS Calculated $C_{13}H_{17}ClNOS$ $[M–Boc+2H]^+$: 270.0719 | Found: 270.0724



38b: Prepared according to General Procedure B using 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (424 mg, 2.00 mmol) and a reaction time of 3 hours. Purification by chromatography on silica gel (2 to 10% Et_2O/hexanes) and further purification by chromatography on silica gel (5 to 8% Et_2O/PhMe) afforded the product as a white solid (502 mg, 74%).

R_f 0.35 (20% Et_2O/hexanes, UV active)

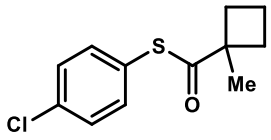
^1H NMR (600 MHz, $CDCl_3$)

δ 7.38 – 7.35 (m, 2H), 7.30 – 7.27 (m, 2H), 3.66 (s, 3H), 1.94 – 1.89 (m, 6H), 1.89 – 1.85 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 203.1, 177.6, 136.3, 135.8, 129.5, 126.3, 52.0, 47.5, 39.0, 28.4, 28.0.

HRMS Calculated $C_{17}H_{20}ClO_3S$ $[M+H]^+$: 339.0822 | Found: 339.0834



38c: Prepared according to General Procedure B using 1-methylcyclobutane-1-carboxylic acid (114 mg, 1.00 mmol) and a reaction time of 16 hours. Purification by chromatography on silica gel (0 to 20% PhMe/hexanes) afforded the product as a colorless oil (211 mg, 88%).

R_f 0.29 (10% PhMe/hexanes, UV active)

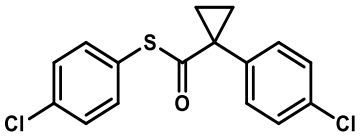
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.39 – 7.36 (m, 2H), 7.34 – 7.31 (m, 2H), 2.62 – 2.54 (m, 2H), 2.07 – 1.98 (m, 1H), 1.95 – 1.84 (m, 3H), 1.54 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 203.0, 136.2, 135.6, 129.5, 126.6, 51.6, 32.2, 24.7, 15.2.

HRMS Calculated $C_{12}H_{14}ClOS$ $[M+H]^+$: 241.0454 | Found: 241.0444



38d: Prepared according to General Procedure B using 1-(4-chlorophenyl)cyclopropane-1-carboxylic acid (400 mg, 2.03 mmol) and a reaction time of 2.5 hours. Purification by chromatography on silica gel (0 to 10% Et_2O/hexanes) afforded the product as a white solid (513 mg, 78%).

R_f 0.63 (20% Et_2O/hexanes, UV active)

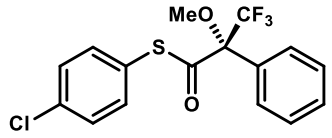
^1H NMR (600 MHz, $CDCl_3$)

δ 7.48 – 7.45 (m, 2H), 7.39 – 7.37 (m, 2H), 7.35 – 7.32 (m, 2H), 7.25 – 7.22 (m, 2H), 1.76 (q, *J* = 3.9 Hz, 2H), 1.28 (q, *J* = 3.9 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 198.7, 136.6, 135.9, 135.8, 134.8, 133.8, 129.5, 128.9, 127.3, 37.6, 19.7.

HRMS Calculated $C_{16}H_{13}Cl_2OS$ $[M+H]^+$: 323.0064 | Found: 323.0062



38e: Prepared according to General Procedure B using (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (234 mg, 1.00 mmol) and a reaction time of 16 hours. Purification by chromatography on silica gel (0 to 20% PhMe/hexanes) afforded the product as a pale yellow oil (300 mg, 83%).

R_f 0.34 (20% PhMe/hexanes, UV active)

$[\alpha]_D^{25}$ +263 (*c* 0.98 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.58 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.46 – 7.43 (m, 3H), 7.42 – 7.38 (m, 2H), 7.33 – 7.30 (m, 2H), 3.66 (q, *J* = 1.7 Hz, 3H).

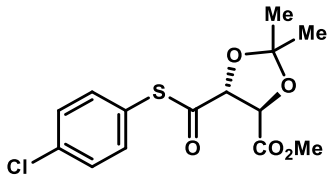
^{13}C NMR (151 MHz, $CDCl_3$)

δ 195.3, 136.4, 136.2, 131.9, 130.0, 129.8, 128.9, 127.5 (q, *J* = 1.4 Hz), 125.2, 123.1 (q, *J* = 291.0 Hz), 88.0 (q, *J* = 26.4 Hz), 55.9 (q, *J* = 1.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$)

δ -69.3 (s, 3F).

HRMS Calculated $C_{16}H_{13}ClF_3O_2S$ $[M+H]^+$: 361.0277 | Found: 361.0271



38f: Prepared according to General Procedure B using (4*R*,5*R*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid[17] (200 mg, 0.980 mmol) and a reaction time of 30 minutes. Purification by chromatography on silica gel (50% PhMe/hexanes, then 5 to 15% EtOAc/hexanes) afforded the product as a white solid (241 mg, 75%).

R_f 0.27 (10% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ –11.3 (*c* 0.75 $CHCl_3$)

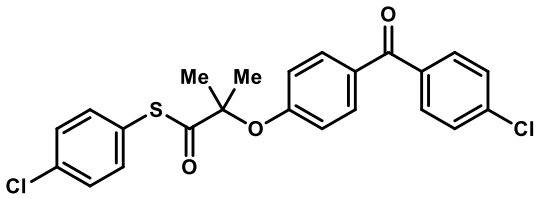
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.76 (d, *J* = 5.2 Hz, 1H), 3.82 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 198.0, 170.0, 136.3, 136.0, 129.7, 125.2, 114.8, 83.1, 77.6, 53.1, 26.7, 26.5.

HRMS Calculated $C_{14}H_{16}ClO_5S$ $[M+H]^+$: 331.0407 | Found: 331.0418



38g: Prepared according to General Procedure B using fenofibric acid (638 mg, 2.00 mmol) and a reaction time of 2.5 hours. Purification by chromatography on silica gel (0 to 10% Et_2O/hexanes) afforded the product as a white solid (714 mg, 80%).

R_f 0.49 (10% Et_2O/hexanes)

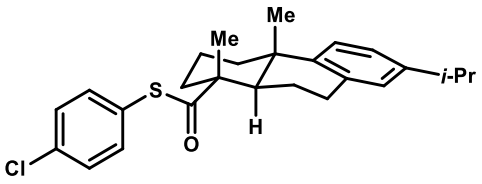
^1H NMR (600 MHz, $CDCl_3$)

δ 7.81 – 7.78 (m, 2H), 7.75 – 7.72 (m, 2H), 7.49 – 7.45 (m, 2H), 7.42 – 7.39 (m, 2H), 7.35 – 7.31 (m, 2H), 7.07 – 7.03 (m, 2H), 1.68 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 202.3, 194.4, 158.7, 138.8, 136.3, 136.2, 132.0, 131.8, 131.4, 129.7, 128.8, 125.9, 119.6, 86.4, 25.7. Note: 15 peaks are observed instead of the expected 16, likely due to two overlapping resonances. Attempts to verify this by 2D NMR were thwarted by extensive overlap of HMBC correlations.

HRMS Calculated $C_{23}H_{19}Cl_2O_3S$ $[M+H]^+$: 445.0432 | Found: 445.0433



38h: Prepared according to General Procedure B using dehydroabietic acid (451 mg, 1.50 mmol) and a reaction time of 16 hours. Purification by chromatography on silica gel (0 to 20% PhMe/hexanes) afforded the product as a white solid (313 mg, 49%).

R_f 0.27 (20% PhMe/hexanes, UV active)

$[\alpha]_D^{25}$ +59.3 (*c* 1.00 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

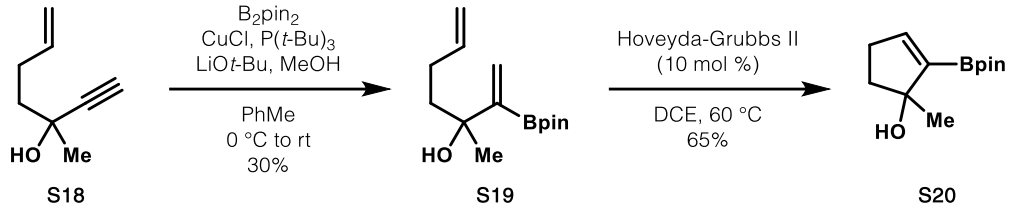
δ 7.39 – 7.35 (m, 2H), 7.31 – 7.28 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.02 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 2.96 (ddd, *J* = 18.4, 11.5, 7.3 Hz, 1H), 2.92 – 2.79 (m, 2H), 2.37 – 2.28 (m, 2H), 1.91 – 1.72 (m, 5H), 1.62 – 1.51 (m, 2H), 1.39 (s, 3H), 1.25 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 205.4, 146.6, 146.0, 136.5, 135.7, 134.7, 129.5, 127.2, 127.1, 124.3, 124.2, 55.8, 45.8, 37.9, 37.8, 37.5, 33.6, 30.2, 25.7, 24.12, 24.11, 21.7, 18.8, 16.9.

HRMS Calculated $C_{26}H_{32}ClOS$ $[M+H]^+$: 427.1862 | Found: 427.1865

Desmethoxy boronic ester S20 [1-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-ol]



A stock solution of P(*t*-Bu)$_3$ was prepared as follows: A flamed-dried flask was charged with P(*t*-Bu)$_3$•HBF$_4$ (294 mg, 1.01 mmol) and placed under an argon atmosphere. PhMe (19.1 mL) was added and the mixture was cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 0.34 mL, 0.845 mmol) was added dropwise over 1 minute, and the reaction mixture was stirred at room temperature for 20 minutes. During this time, the crystalline solid was converted to a finely dispersed solid, which was taken to reflect successful consumption of P(*t*-Bu)$_3$•HBF$_4$ with formation of LiBF$_4$. Stirring was stopped, allowing the LiBF$_4$ to mostly settle (the liquid remained cloudy).

Preparation of **S19**: A flame-dried flask was charged with **S18**[18] (673 mg, 5.42 mmol, 1 equiv) and placed under an argon atmosphere. PhMe (90 mL), B$_2$pin$_2$ (1.38 g, 5.42 mmol, 1 equiv), CuCl (53.7 mg, 0.542 mmol, 0.1 equiv) and MeOH (0.44 mL, 347 mg, 10.8 mmol, 2 equiv) were then added. A 15.0 mL aliquot of the P(*t*-Bu)$_3$ stock solution was then added, and the mixture was cooled to 0 °C. LiO*t*-Bu (65.1 mg, 0.813 mmol, 0.15 equiv) was added, and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was filtered through a pad of silica topped generously with Celite, flushing with Et$_2$O, and the filtrate was concentrated. Purification by chromatography on silica gel (0 to 25% EtOAc/hexanes) afforded the product as a pale yellow oil (415 mg, 30%).

R_f 0.47 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 5.87 (d, *J* = 2.7 Hz, 1H), 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.76 (d, *J* = 2.7 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.93 – 4.90 (m, 1H), 2.55 (s, 1H), 2.10 – 1.98 (m, 2H), 1.80 (ddd, *J* = 13.6, 10.1, 6.2 Hz, 1H), 1.67 (ddd, *J* = 13.6, 9.9, 6.9 Hz, 1H), 1.33 (s, 3H), 1.28 (s, 12H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 139.4, 127.2, 114.2, 83.9, 75.4, 41.3, 28.8, 27.4, 24.84, 24.79. The carbon attached to boron is not observed due to quadrupolar relaxation.

HRMS Calculated $C_{14}H_{24}BO_2$ $[M–OH]^+$: 234.1906 | Found: 234.1912

S20: A flame-dried flask was charged with **S19** (71.2 mg, 0.282 mmol, 1 equiv) and placed under an argon atmosphere. 1,2-Dichloroethane (5.6 mL) was added, followed by Hoveyda-Grubbs II (8.9 mg, 0.0141

mmol, 5 mol %). The reaction mixture was stirred at 60 °C for 2 hours, then cooled to room temperature and concentrated. The material was redissolved in 1,2-dichloroethane (5.6 mL) under an argon atmosphere, and treated with an additional portion of Hoveyda-Grubbs II (8.9 mg, 0.0141 mol, 5 mol %). The reaction mixture was stirred at 60 °C for 4 hours, then cooled to room temperature and concentrated to afford crude the product, which was used without further purification (41.3 mg, 65%, determined by ^{1}H NMR with CH_2Br_2 as an external standard).

Note: S20 is not stable to silica gel, which promotes facile 1,3-transposition of the allylic alcohol. Although this process can be avoided by using Et_3N-treated silica gel and Et_3N-doped eluent, **S20** is still almost quantitatively lost during attempts at chromatographic purification.

R_f 0.44 (30:79:1 EtOAc/hexanes/Et_3N)

^{1}H NMR (600 MHz, $CDCl_3$)

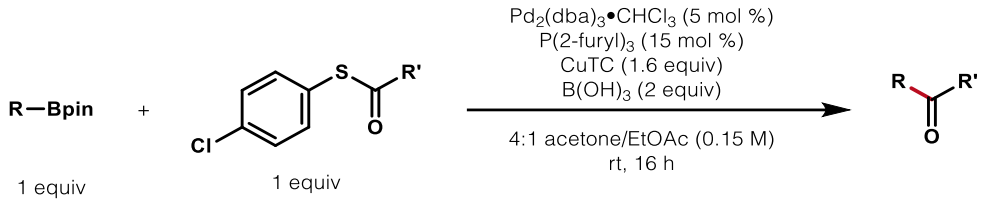
δ 6.52 (t, *J* = 2.4 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.40 – 2.32 (m, 2H), 2.02 – 1.91 (m, 2H), 1.41 (s, 3H), 1.29 (s, 6H), 1.28 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 147.7, 85.8, 83.5, 39.7, 32.7, 28.4, 25.1, 24.7. The carbon attached to boron is not observed due to quadrupolar relaxation.

HRMS Calculated $C_{12}H_{20}BO_2$ $[M–OH]^+$: 206.1593 | Found: 206.1595

Synthesis of coupling products

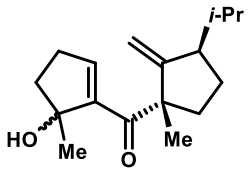


General Procedure C: A reaction tube (used without drying) was charged with boronic ester (0.120 mmol, 1 equiv), thioester (0.120 mmol, 1 equiv), $Pd_2(dba)_3$•$CHCl_3$ (6.2 mg, 0.0060 mmol, 5 mol %), P(2-furyl)$_3$ (4.2 mg, 0.018 mmol, 15 mol %), copper(I) thiophene-2-carboxylate (36.6 mg, 0.192 mmol, 1.6 equiv) and boric acid (14.8 mg, 0.240 mmol, 2 equiv). The vessel was evacuated and backfilled three times to exchange the atmosphere for argon. Acetone (0.64 mL) and EtOAc (0.16 mL), both of which were degassed by sparging with argon, were then added. Argon was bubbled through the resulting mixture for ~5 minutes, after which the argon inlet was removed and the pierced septum was coated with grease. The mixture was stirred at room temperature for 16 hours. After this time, the reaction mixture was diluted with a roughly equal volume of hexanes and passed through a pad of silica gel, eluting with Et_2O. The filtrate was concentrated. The silica gel plug was repeated if a significant amount of dark brown/black material was eluted. To remove thiophene-2-carboxylic acid (poorly separated by chromatography) and hydrolyzed thioester, the material was dissolved in EtOAc (10 mL) and washed with 10 wt % aqueous Na_2CO_3 (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on silica gel afforded the product.

Note: $Pd_2(dba)_3$•$CHCl_3$ was recrystallized as described previously.[11] Successful reaction has been achieved using commercial $Pd_2(dba)_3$•$CHCl_3$ as received; however, it is known that the purity of commercial $Pd_2(dba)_3$•$CHCl_3$ can vary significantly (and be as low as ~60%).[11]

Note: The age of CuTC was found to be important. Our experiments used CuTC that was ~9 months old, as indicated by the certificate of analysis for the particular lot number. An older batch of CuTC (2.5 years, according to the certificate of analysis) failed to produce cross-coupled product.

Note: The water content of acetone was not found to impact the reaction, with reagent grade "wet" acetone and anhydrous acetone performing similarly. Our experiments use reagent grade "wet" acetone that is passed through a plug of silica gel before use, in an effort to reduce variability across different acetone drums.



S21: Prepared from **S20** (racemic) and **19** according to General Procedure C. Prior to aqueous workup, the yield was determined to be 41% (1:1 dr) by ^{1}H NMR with CH_2Br_2 as an external standard. Purification by chromatography on silica gel (5 to 20% Et_2O/PhMe) afforded the product (1:1 dr) as a yellow oil (11.2 mg, 36%).

R_f 0.45 (UV active) and 0.53 (UV active) (20% EtOAc/hexanes)

$[\alpha]_D^{25}$ +0.191 (*c* 0.81 $CHCl_3$)

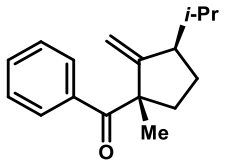
^{1}H NMR (600 MHz, $CDCl_3$)

δ 6.57 (dd, *J* = 3.1, 2.4 Hz, 1H), 6.53 (t, *J* = 2.7 Hz, 1H), 4.91 – 4.89 (m, 2H), 4.87 (d, *J* = 2.7 Hz, 1H), 4.79 (d, *J* = 3.1 Hz, 1H), 3.94 (br s, 1H), 3.72 (br s, 1H), 2.75 – 2.65 (m, 2H), 2.59 – 2.47 (m, 2H), 2.41 – 2.31 (m, 2H), 2.30 – 2.22 (m, 1H), 2.21 – 2.13 (m, 1H), 2.09 – 1.96 (m, 4H), 1.95 – 1.87 (m, 2H), 1.86 – 1.79 (m, 2H), 1.64 – 1.56 (m, 4H), 1.43 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 206.2, 204.8, 159.9, 159.3, 143.68, 143.67, 142.6, 142.3, 108.3, 107.8, 84.6, 84.3, 60.5, 60.4, 51.7, 51.3, 38.7, 38.4, 38.2, 37.7, 30.3, 29.9, 28.51, 28.49, 27.3, 27.2, 25.1, 24.8, 24.5, 24.1, 22.16, 22.15, 16.2, 16.1.

HRMS Calculated $C_{17}H_{26}NaO_2$ $[M+Na]^+$: 285.1830 | Found: 285.1830



S22: As General Procedure C afforded a low yield, the following alternative procedure was utilized to provide authentic material to enable the determination of NMR yields in separate experiments. A reaction tube (used without drying) was charged with $PhB(OH)_2$ (29.3 mg, 0.240 mmol, 2 equiv), **19** (37.1 mg, 0.120 mmol, 1 equiv), $Pd_2(dba)_3$•$CHCl_3$ (6.2 mg, 0.0060 mmol, 5 mol %), P(2-furyl)$_3$ (4.2 mg, 0.018 mmol, 15 mol %), and copper(I) thiophene-2-carboxylate (36.6 mg, 0.192 mmol, 1.6 equiv). The vessel was evacuated and backfilled three times to exchange the atmosphere for argon. THF (0.80 mL) was then added. Argon was bubbled through the resulting mixture for ~5 minutes, after which the argon inlet was removed and the pierced septum was coated with grease. The mixture was stirred at 50 °C for 16 hours. After this time, the reaction mixture was cooled to room temperature and diluted with a roughly equal volume of hexanes. The mixture was passed through a pad of silica gel, eluting with Et_2O, and the filtrate was concentrated. The silica gel plug was repeated once more. To remove thiophene-2-carboxylic acid (poorly separated by chromatography) and hydrolyzed thioester, the material was dissolved in EtOAc (10 mL) and washed with 10 wt % aqueous Na_2CO_3 (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by preparative TLC (50% PhMe/hexanes) afforded the product as a colorless oil (13.7 mg, 47%).

R_f 0.42 (50% PhMe/hexanes, UV active)

$[\alpha]_D^{25}$ +44.9 (*c* 1.00 $CHCl_3$)

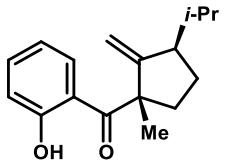
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.78 – 7.73 (m, 2H), 7.46 – 7.41 (m, 1H), 7.38 – 7.33 (m, 2H), 4.95 (d, *J* = 2.7 Hz, 1H), 4.93 (d, *J* = 3.1 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.25 (td, *J* = 11.8, 11.4, 6.8 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.86 (dt, *J* = 10.5, 7.1 Hz, 1H), 1.70 – 1.58 (m, 2H), 1.30 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 205.1, 159.5, 137.3, 131.3, 129.2, 128.0, 108.1, 59.8, 51.4, 37.4, 28.7, 25.6, 24.4, 22.2, 16.2.

HRMS Calculated $C_{17}H_{23}O$ $[M+H]^+$: 243.1749 | Found: 243.1744



S23: Prepared from 2-hydroxyphenylboronic acid and **19** on according to General Procedure C with slight modifications. The reaction was performed on 0.036 mmol scale, and after passing the reaction mixture through silica gel, the yield of **S23** was determined to be 75% by ^{1}H NMR with 1,3,5-trimethoxybenzene as an external standard. In place of an aqueous workup, the material was passed through silica gel once more, this time eluting with 3% Et_2O/hexanes, and the filtrate was concentrated. Purification by preparative thin layer chromatography (50% PhMe/hexanes) afforded the product as a colorless oil (5.7 mg, 61%).

R_f 0.53 (50% PhMe/hexanes, UV active)

$[\alpha]_D^{25}$ +82.0 (*c* 0.91 $CHCl_3$)

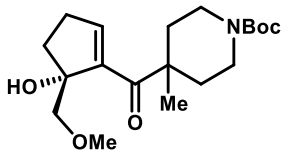
^{1}H NMR (600 MHz, $CDCl_3$)

δ 12.57 (s, 1H), 7.73 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.37 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.76 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 4.91 (d, *J* = 2.6 Hz, 1H), 4.84 (d, *J* = 3.1 Hz, 1H), 3.05 (ddt, *J* = 11.8, 8.2, 3.7 Hz, 1H), 2.43 – 2.34 (m, 1H), 2.20 – 2.10 (m, 1H), 1.96 (dt, *J* = 11.3, 7.7 Hz, 1H), 1.78 – 1.68 (m, 2H), 1.31 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 210.2, 163.8, 160.3, 135.2, 131.7, 119.3, 117.5, 116.8, 108.3, 60.3, 51.1, 38.9, 28.8, 25.8, 24.5, 22.1, 16.1.

HRMS Calculated $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1698 | Found: 259.1702



39a: Prepared from **27** (92:8 er) and **38a** according to General Procedure C. Purification by chromatography on silica gel (10 to 40% EtOAc/hexanes) afforded the product as a colorless oil (29.3 mg, 69%).

R_f 0.35 (40% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ –46.8 (*c* 0.98 $CHCl_3$)

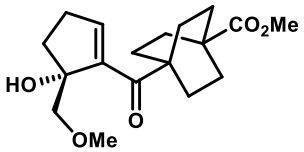
^{1}H NMR (600 MHz, $CDCl_3$)

δ 6.70 (t, *J* = 2.6 Hz, 1H), 3.94 (br s, 1H), 3.61 (br s, 2H), 3.48 (d, *J* = 8.9 Hz, 1H), 3.40 (d, *J* = 9.0 Hz, 1H), 3.29 (s, 3H), 3.19 – 3.08 (m, 2H), 2.62 (dddd, *J* = 18.9, 9.0, 4.9, 2.8 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.21 – 2.11 (m, 3H), 1.91 (ddd, *J* = 13.8, 9.1, 4.9 Hz, 1H), 1.52 (br s, 1H), 1.44 (s, 9H), 1.40 (br s, 1H), 1.30 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 207.9, 155.0, 143.7, 141.3, 87.0, 79.5, 77.3, 59.2, 47.1, 41.2 (br s), 40.3 (br s), 35.4, 35.1 (br s), 34.1, 30.8, 28.6, 25.9.

HRMS Calculated $C_{14}H_{24}NO_3^+$ $[M–Boc+2H]^+$: 254.1756 | Found: 254.1766



39b: Prepared from **27** (92:8 er) and **38b** according to General Procedure C. Purification by chromatography on silica gel (10 to 40% EtOAc/hexanes) afforded the product as a pale yellow oil (27.4 mg, 71%).

R_f 0.44 (40% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ –56.6 (*c* 1.00 $CHCl_3$)

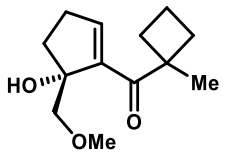
^{1}H NMR (600 MHz, $CDCl_3$)

δ 6.62 (t, *J* = 2.7 Hz, 1H), 3.91 (br s, 1H), 3.66 (s, 3H), 3.40 (d, *J* = 9.2 Hz, 1H), 3.38 (d, *J* = 9.2 Hz, 1H), 3.30 (s, 3H), 2.60 (dddd, *J* = 18.8, 9.1, 4.9, 2.7 Hz, 1H), 2.47 (dddd, *J* = 18.7, 8.8, 4.9, 2.6 Hz, 1H), 2.14 (ddd, *J* = 13.5, 8.7, 4.9 Hz, 1H), 1.92 – 1.79 (m, 13H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 208.7, 178.0, 142.8, 142.1, 87.1, 77.4, 59.4, 51.9, 45.5, 39.0, 34.1, 30.8, 28.1, 28.0.

HRMS Calculated $C_{18}H_{26}NaO_5$ $[M+Na]^+$: 345.1678 | Found: 345.1669



39c: Prepared from **27** (92:8 er) and **38c** according to General Procedure C. Purification by chromatography on silica gel (0 to 20% Et_2O/PhMe) afforded the product as a pale yellow oil (15.1 mg, 57%).

R_f 0.26 (20% Et_2O/PhMe, UV active)

$[\alpha]_D^{25}$ –83.0 (*c* 1.00 $CHCl_3$)

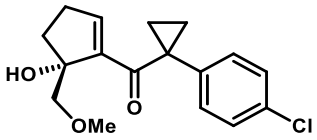
^1H NMR (600 MHz, $CDCl_3$)

δ 6.62 (t, *J* = 2.7 Hz, 1H), 3.83 (br s, 1H), 3.48 (s, 2H), 3.32 (s, 3H), 2.61 – 2.41 (m, 4H), 2.25 (ddd, *J* = 13.3, 8.5, 3.4 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.96 – 1.89 (m, 2H), 1.84 – 1.77 (m, 1H), 1.77 – 1.70 (m, 1H), 1.49 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 207.2, 146.5, 140.2, 85.8, 77.8, 59.5, 49.8, 34.7, 32.9, 31.2, 30.8, 25.9, 15.3.

HRMS Calculated $C_{13}H_{20}NaO_3$ $[M+Na]^+$: 247.1310 | Found: 247.1311



39d: Prepared from **27** (92:8 er) and **38d** according to General Procedure C. Purification by chromatography on silica gel (0 to 20% EtOAc/hexanes) afforded the product as a yellow oil (26.6 mg, 69%).

R_f 0.64 (20% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ –141 (*c* 1.00 $CHCl_3$)

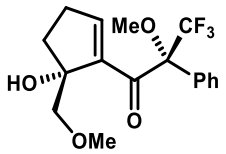
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.28 – 7.25 (m, 2H), 7.22 – 7.19 (m, 2H), 6.04 (t, *J* = 2.7 Hz, 1H), 3.87 (s, 1H), 3.49 (d, *J* = 9.0 Hz, 1H), 3.42 (d, *J* = 9.0 Hz, 1H), 3.37 (d, *J* = 0.7 Hz, 3H), 2.38 (dddd, *J* = 19.1, 9.2, 4.2, 2.9 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.10 (ddd, *J* = 13.1, 8.6, 4.2 Hz, 1H), 1.85 (ddd, *J* = 14.1, 9.2, 5.5 Hz, 1H), 1.77 (ddd, *J* = 9.7, 7.0, 3.8 Hz, 1H), 1.48 (ddd, *J* = 9.8, 7.2, 4.2 Hz, 1H), 1.43 (ddd, *J* = 9.3, 7.0, 4.2 Hz, 1H), 0.98 (ddd, *J* = 9.3, 7.1, 3.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 200.8, 147.6, 142.6, 139.8, 133.0, 130.8, 128.8, 86.1, 77.8, 59.4, 35.9, 34.6, 30.7, 18.3, 17.8.

HRMS Calculated $C_{17}H_{19}ClNaO_3$ $[M+Na]^+$: 329.0920 | Found: 329.0924



39e: Prepared from **27** (92:8 er) and **38e** according to General Procedure C. Purification by chromatography on silica gel (0 to 20% EtOAc/hexanes) afforded the product as a white solid (17.8 mg, 43%).

R_f 0.31 (20% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ +101 (*c* 1.00 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.52 – 7.49 (m, 2H), 7.40 – 7.35 (m, 3H), 6.70 (t, *J* = 2.8 Hz, 1H), 3.67 (d, *J* = 8.7 Hz, 1H), 3.64 (q, *J* = 1.9 Hz, 3H), 3.50 – 3.46 (m, 2H), 3.33 (s, 3H), 2.37 (ddd, *J* = 9.0, 5.9, 2.8 Hz, 2H), 2.21 – 2.14 (m, 1H), 1.90 – 1.83 (m, 1H).

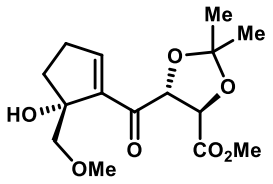
^{13}C NMR (151 MHz, $CDCl_3$)

δ 195.3, 153.1, 139.6, 134.3, 129.5, 128.6, 126.7, 123.6 (q, *J* = 291.2 Hz), 86.8 (q, *J* = 24.9 Hz), 86.0, 77.5, 59.2, 55.9 (q, *J* = 2.1 Hz), 34.8, 31.3.

^{19}F NMR (376 MHz, $CDCl_3$)

δ -70.1 (s, 3F).

HRMS Calculated $C_{17}H_{19}F_3NaO_4$ $[M+Na]^+$: 367.1133 | Found: 367.1141



39f: Prepared from **27** (92:8 er) and **38f** according to General Procedure C. Purification by chromatography on silica gel (0 to 40% EtOAc/hexanes) afforded the product as a colorless oil (13.1 mg, 35%).

Note: The product was obtained as part of 14.1 mg of an inseparable 14:1 mixture of diastereomers, arising from coupling of the minor enantiomer of **27**.

R_f 0.27 (20% EtOAc/hexanes , UV active)

$[\alpha]_D^{25}$ –42.3 (*c* 1.00 $CHCl_3$)

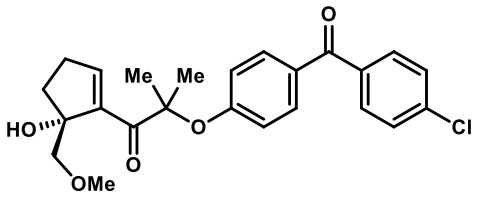
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.19 (t, *J* = 2.7 Hz, 1H), 5.19 (d, *J* = 5.0 Hz, 1H), 4.90 (d, *J* = 5.0 Hz, 1H), 3.81 (s, 3H), 3.56 (d, *J* = 9.0 Hz, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.33 (m, 4H), 2.65 (ddt, *J* = 19.5, 9.2, 3.3 Hz, 1H), 2.50 (dddd, *J* = 19.5, 8.6, 6.2, 2.5 Hz, 1H), 2.27 (ddd, *J* = 13.5, 8.6, 3.6 Hz, 1H), 1.99 (ddd, *J* = 13.5, 9.2, 6.2 Hz, 1H), 1.50 (d, *J* = 0.7 Hz, 3H), 1.46 (d, *J* = 0.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 195.5, 171.1, 151.1, 142.2, 113.9, 85.5, 81.1, 77.6, 76.1, 59.5, 52.9, 35.3, 31.2, 26.8, 26.5.

HRMS Calculated $C_{15}H_{22}NaO_7$ $[M+Na]^+$: 337.1263 | Found: 337.1261



39g: Prepared from **27** (92:8 er) and **38g** according to General Procedure C. Purification by chromatography on silica gel (10 to 35% EtOAc/hexanes) afforded the product as a pale yellow oil (35.4 mg, 69%).

R_f 0.36 (30% EtOAc/hexanes, UV active)

$[\alpha]_D^{25}$ –41.1 (*c* 1.00 $CHCl_3$)

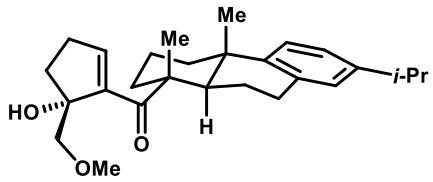
^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.73 – 7.69 (m, 4H), 7.47 – 7.43 (m, 2H), 7.32 (t, *J* = 2.8 Hz, 1H), 6.84 – 6.81 (m, 2H), 3.71 (br s, 1H), 3.52 (d, *J* = 8.9 Hz, 1H), 3.47 (d, *J* = 8.9 Hz, 1H), 3.33 (s, 3H), 2.52 (ddt, *J* = 19.7, 9.3, 3.3 Hz, 1H), 2.38 (dddd, *J* = 19.6, 8.8, 6.5, 2.5 Hz, 1H), 2.18 (ddd, *J* = 13.5, 8.5, 3.3 Hz, 1H), 1.89 (ddd, *J* = 13.5, 9.3, 6.6 Hz, 1H), 1.66 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 202.8, 194.3, 159.5, 150.9, 139.7, 138.6, 136.4, 132.2, 131.3, 130.7, 128.7, 117.9, 86.2, 85.4, 77.9, 59.5, 34.7, 31.1, 26.7, 25.2.

HRMS Calculated $C_{24}H_{25}ClNaO_5$ $[M+Na]^+$: 451.1288 | Found: 451.1284



39h: Prepared from **27** (92:8 er) and **38h** according to General Procedure C. Purification by chromatography on silica gel (0 to 10% Et_2O/PhMe) afforded the product as a colorless oil (15.6 mg, 32%).

Note: The product was obtained as part of 16.6 mg of an inseparable 16:1 mixture of diastereomers, arising from coupling of the minor enantiomer of **27**.

R_f 0.33 (10% Et_2O/PhMe, UV active)

$[\alpha]_D^{25}$ –18.3 (*c* 1.00 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

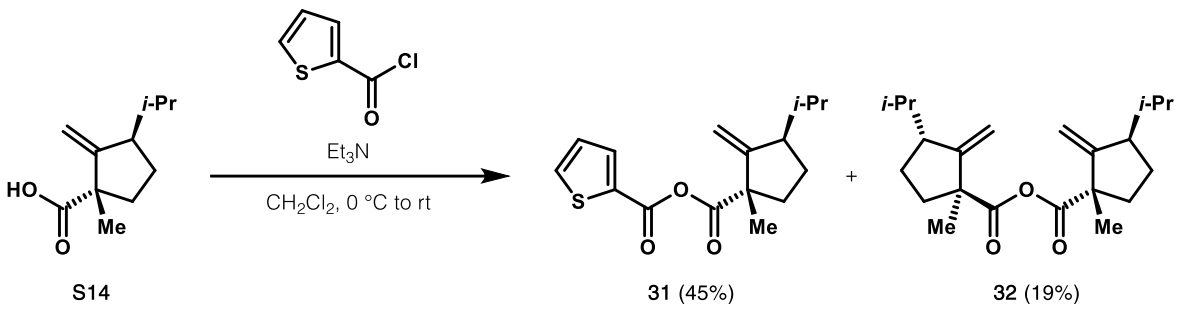
δ 7.17 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.51 (t, *J* = 2.7 Hz, 1H), 4.14 (s, 1H), 3.43 (d, *J* = 9.0 Hz, 1H), 3.39 (d, *J* = 9.0 Hz, 1H), 3.32 (s, 3H), 2.98 – 2.79 (m, 3H), 2.57 (dddd, *J* = 18.6, 9.1, 5.2, 2.6 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.32 (dt, *J* = 12.9, 3.3 Hz, 1H), 2.14 – 2.08 (m, 1H), 1.92 – 1.70 (m, 6H), 1.51 – 1.40 (m, 2H), 1.30 (s, 3H), 1.25 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 211.0, 147.1, 145.9, 141.8, 140.6, 134.9, 127.2, 124.2, 124.0, 87.6, 77.6, 59.2, 53.2, 43.5, 38.0, 37.2, 37.0, 34.0, 33.6, 30.6, 30.2, 25.6, 24.14, 24.10, 21.3, 18.9, 17.5.

HRMS Calculated $C_{27}H_{38}NaO_3$ $[M+Na]^+$: 433.2719 | Found: 433.2719

Independent synthesis of mixed anhydride 31 and anhydride 32



S14 **31** (45%) **32** (19%)

A stock solution of 2-thiophenecarbonyl chloride was prepared as follows: A flame-dried reaction tube was charged with thiophene-2-carboxylic acid (63.8 mg, 0.498 mmol, 1.42 equiv) and placed under an argon atmosphere. CH_2Cl_2 (3.5 mL) and DMF (1 drop, ~1 μL, ~0.05 equiv) were added, and the reaction mixture was cooled to 0 °C. $(COCl)_2$ (60.0 μL, 88.8 mg, 0.700 mmol, 2 equiv) was added dropwise, and the reaction mixture was stirred at room temperature. After 4 hours, the reaction mixture was concentrated, placed under an argon atmosphere, and redissolved in CH_2Cl_2 (1.4 mL).

Preparation of **31** and **32**: A separate flame-dried reaction tube was charged with **S14** (63.8 mg, 0.350 mmol, 1 equiv) and placed under an argon atmosphere. CH_2Cl_2 (2.5 mL) and Et_3N (0.98 mL, 70.8 mg, 0.700 mmol, 2 equiv) were added, and the reaction mixture was cooled to 0 °C. A 1.00 mL aliquot of the 2-thiophenecarbonyl chloride solution prepared above was then added dropwise. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with 5 wt % aqueous Na_2CO_3 (2 x 5 mL) and brine (1 x 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on hydrated silica gel (30:70 w/w water/silica gel, 3 to 5% Et_2O/hexanes) afforded **31** as a colorless oil (45.5 mg, 45%) and **32** as a colorless oil (11.2 mg, 19%).

Note: The anhydrides are poorly stable to silica gel, (partly) surviving rapid elution though a silica gel plug but hydrolyzing during chromatographic separations. Some stability is granted by deactivating the silica gel with water. Chromatography should be performed expediently to minimize hydrolysis.

Mixed anhydride **31**:

R_f 0.42 (10% Et_2O/hexanes, TLC plate wetted with 10% H_2O/MeCN and dried before use, UV active)

$[\alpha]_D^{25}$ +85.5 (*c* 1.00 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.85 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.68 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 5.20 (d, *J* = 2.9 Hz, 1H), 5.04 (d, *J* = 2.6 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.35 (ddd, *J* = 12.7, 9.7, 7.1 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.87 (dtd, *J* = 11.8, 7.4, 4.1 Hz, 1H), 1.73 (ddd, *J* = 12.7, 7.1,

4.0 Hz, 1H), 1.59 – 1.52 (m, 1H), 1.39 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$)

δ 171.2, 157.5, 157.1, 135.8, 135.0, 132.8, 128.5, 108.4, 54.4, 51.3, 36.3, 28.8, 24.44, 24.41, 22.0, 16.8.

HRMS Calculated $C_{16}H_{20}NaO_3S$ $[M+Na]^+$: 315.1031 | Found: 315.1023

Anhydride **32**:

R_f 0.60 (10% Et_2O/hexanes, TLC plate wetted with 10% H_2O/MeCN and dried before use)

$[\alpha]_D^{25}$ +99.9 (*c* 0.98 $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$)

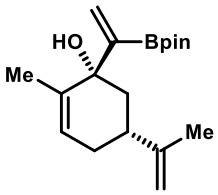
δ 5.07 (d, *J* = 2.9 Hz, 2H), 4.95 (d, *J* = 2.6 Hz, 2H), 2.54 – 2.48 (m, 2H), 2.19 (ddd, *J* = 12.8, 9.8, 7.1 Hz, 2H), 1.99 – 1.92 (m, 2H), 1.79 (dtd, *J* = 11.5, 7.4, 3.9 Hz, 2H), 1.63 (ddd, *J* = 12.7, 7.0, 3.8 Hz, 2H), 1.48 (dtd, *J* = 12.4, 9.9, 7.0 Hz, 2H), 1.29 (s, 6H), 0.99 (d, *J* = 6.9 Hz, 6H), 0.80 (d, *J* = 6.8 Hz, 6H).

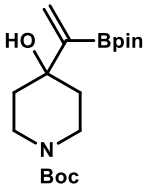
^{13}C NMR (151 MHz, $CDCl_3$)

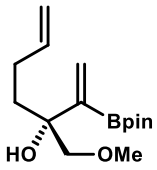
δ 171.8, 157.2, 108.0, 54.5, 51.3, 36.1, 28.7, 24.4, 24.3, 22.1, 16.8.

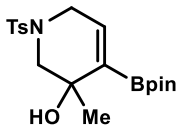
HRMS Calculated $C_{22}H_{35}O_3$ $[M+H]^+$: 347.2586 | Found: 347.2580

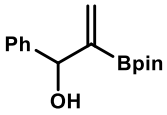
Unsuccessful substrates

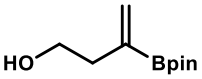












References

1. Bloomfield, J. J.; Nelke, J. M. Acyloin condensation in which chlorotrimethylsilane is used as a trapping agent: 1,2-bis(trimethylsiloxy)cyclobutene and 2-hydroxycyclobutanone. *Org. Synth.* **1977**, *57*, 1.
2. Jarkas, N.; Voll, R. J.; Williams, L.; Camp, V. M.; Goodman, M. M. (*R,S*)-*anti*-1-amino-2-[^{18}F]fluorocyclopentyl-1-carboxylic acid: synthesis from racemic 2-benzyloxycyclopentanone and biological evaluation for brain tumor imaging with positron emission tomography. *J. Med. Chem.* **2010**, *53*, 6603.
3. Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. Asymmetric Synthesis of the Tricyclic Core of Cyathane Diterpenes via a Transition Metal Catalyzed [5+2] Cycloaddition. *Org. Lett.* **2001**, *3*, 2105.
4. Daeppen, C.; Kaiser, M.; Neuburger, M.; Gademann, K. Preparation of Antimalarial Endoperoxides by a Formal [2+2+2] Cycloaddition. *Org. Lett.* **2015**, *17*, 5420.
5. Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. More Highly Mixed, Higher Order Cyanocuprates "R_T(2-thienyl)Cu(CN)Li_2". Efficient Reagents which Promote Selective Ligand Transfer. *J. Organomet. Chem.* **1985**, *285*, 437.
6. Leclercq, L. C. L.; Bartolome-Nebreda, J. M.; Conde-Ceide, S.; Van Gool, M. L. M. Inhibitors of Phosphodiesterase 10 Enzyme. WO 2014009305 A1, **2014**.
7. Tagat, J. R.; McCombie, S. W.; Nazareno, D.; Labroli, M. A.; Xiao, Y.; Steensma, R. W.; Strizki, J. M.; Baroudy, B. M.; Cox, K.; Lachowicz, J.; Varty, G.; Williams, R. Piperazine-Based CCR5 Antagonists as HIV-1 Inhibitors. IV. Discovery of 1-[(4,6-Dimethyl-5-pyrimidinyl)carbonyl]-4-[4-{2-methoxy-1(*R*)-4-(trifluoromethyl)phenyl}ethyl-3(*S*)-methyl-1-piperazinyl]-4-methylpiperidine (Sch-417690/Sch-D), a Potent, Highly Selective, and Orally Bioavailable CCR5 Antagonist. *J. Med. Chem.* **2004**, *47*, 2405.
8. Reznichenko, A. L.; Hampel, F.; Hultzsch, K. C. Kinetic Resolution of Aminoalkenes by Asymmetric Hydroamination: A Mechanistic Study. *Chem. Eur. J.* **2009**, *15*, 12819.
9. Weiberth, F. J.; Hall, S. S. Copper(I)-Activated Addition of Grignard Reagents to Nitriles. Synthesis of Ketimines, Ketones, and Amines. *J. Org. Chem.* **1987**, *52*, 3901.
10. Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A. (2*S*)-(–)-3-*exo*-(Morpholino)isoborneol [(–)-MIB]. *Org. Synth.* **2005**, *82*, 87.
11. Zalesskiy, S. S.; Ananikov, V. P. $Pd_2(dba)_3$ as a Precursor of Soluble Metal Complexes and Nanoparticles: Determination of Palladium Active Species for Catalysis and Synthesis. *Organometallics* **2012**, *31*, 2303.
12. Kadish, K. M.; Mu, X.; Anderson, J. E. Recommended Methods for the Purification of Solvents and Tests for Impurities: Benzene and Toluene. *Pure Appl. Chem.* **1989**, *61*, 1823.
13. Yang, M.-H.; Matikonda, S. S.; Altman, R. A. Preparation of Fluoroalkenes via the Shapiro Reaction: Direct Access to Fluorinated Peptidomimetics. *Org. Lett.* **2013**, *15*, 3894.
14. (a) Sassa, T.; Negoro, T.; Ueki, H. Production and Characterization of a New Fungal Metabolite, Cotylenol. *Agr. Biol. Chem.* **1972**, *36*, 2281. (b) Sassa, T. Structure of Cotylenol, the Aglycone of the Cotylenins Leaf Growth Substances. *Agr. Biol. Chem.* **1972**, *36*, 2037. (c) Sassa, T.; Takahama, A.; Shindo, T. The Stereostructure of Cotyelnol, the Aglycone of Cotylenins Leaf Growth Substances. *Agr. Biol. Chem.* **1975**, *39*, 1729.
15. Uwamori, M.; Osada, R.; Sugiyama, R.; Nagatani, K.; Nakada, M. Enantioselective Total Synthesis of Cotylenin A. *J. Am. Chem. Soc.* **2020**, *142*, 5556.
16. Engel, P. S.; Culotta, A. M. Photolysis of azoalkanes. Reactions and Kinetics of the 1-Cyclopropylcyclopentane-1,3-diyl Biradical and the 1-Cyclopropylcyclopentyl Radical. *J. Am. Chem. Soc.* **1991**, *113*, 2686.
17. Zhang, Q.; Cao, R.; Liu, A.; Lei, S.; Li, Y.; Yang, J.; Li, S.; Xiao, J. Design, Synthesis and Evaluation of 2,2-Dimethyl-1,3-dioxolane Derivatives as Human Rhinovirus 3C Protease Inhibitors. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4061.

18. Wulff, J. E.; Herzon, S. B.; Siegrist, R.; Myers, A. G. Evidence for the Rapid Conversion of Stephacidin B into the Electrophilic Monomer Avrainvillamide in Cell Culture. *J. Am. Chem. Soc.* **2007**, *129*, 4898.

Crystallographic Data

Crystal structure of enol ether **44**

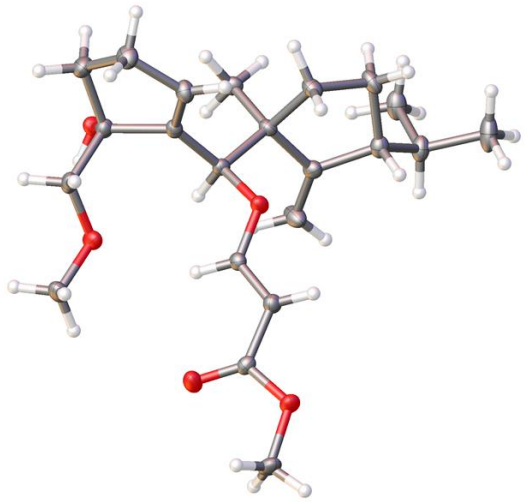


Table S5. Crystal data and structure refinement for Shenvi277.

Identification code	shenvi277_0m_a	
Empirical formula	C22 H34 O5	
Formula weight	378.49	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C 1 2 1	
Unit cell dimensions	a = 23.7955(11) Å	α= 90°.
	b = 7.1278(3) Å	β= 124.0150(10)°.
	c = 15.3100(7) Å	γ= 90°.
Volume	2152.40(17) $Å^3$	
Z	4	
Density (calculated)	1.168 Mg/m^3	
Absorption coefficient	0.654 mm^{-1}	
F(000)	824	
Crystal size	0.25 x 0.23 x 0.114 mm^3	
Theta range for data collection	3.483 to 70.138°.	
Index ranges	-28<=h<=27, -8<=k<=8, -16<=l<=18	
Reflections collected	13675	
Independent reflections	4060 [R(int) = 0.0302]	
Completeness to theta = 67.679°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.6921	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4060 / 1 / 250	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0272, wR2 = 0.0699	
R indices (all data)	R1 = 0.0279, wR2 = 0.0707	
Absolute structure parameter	0.00(5)	
Largest diff. peak and hole	0.199 and -0.148 $e.Å^{-3}$	

Table S6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Shenvi277. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3435(1)	3487(2)	2944(1)	19(1)
O(2)	3875(1)	3220(2)	660(1)	28(1)
O(3)	4930(1)	2342(2)	1961(1)	22(1)
O(4)	1371(1)	5655(2)	1042(1)	22(1)
O(5)	2078(1)	4259(2)	153(1)	23(1)
C(1)	3659(1)	8073(3)	3653(1)	30(1)
C(2)	3595(1)	6711(2)	4184(1)	19(1)
C(3)	4093(1)	6280(2)	5353(1)	21(1)
C(4)	4415(1)	8021(2)	6065(1)	24(1)
C(5)	4973(1)	7458(3)	7195(2)	38(1)
C(6)	3891(1)	9267(3)	6064(1)	29(1)
C(7)	3690(1)	4980(2)	5619(1)	24(1)
C(8)	3218(1)	3896(2)	4596(1)	21(1)
C(9)	2989(1)	5371(2)	3714(1)	16(1)
C(10)	2370(1)	6470(2)	3510(1)	21(1)
C(11)	2822(1)	4500(2)	2668(1)	15(1)
C(12)	3571(1)	3440(2)	2208(1)	16(1)
C(13)	4162(1)	2798(2)	2413(1)	19(1)
C(14)	4284(1)	2824(2)	1580(1)	17(1)
C(15)	5114(1)	2333(3)	1208(1)	26(1)
C(16)	2213(1)	3221(2)	2139(1)	16(1)
C(17)	2154(1)	1562(2)	2477(1)	22(1)
C(18)	1451(1)	744(3)	1782(1)	26(1)
C(19)	1037(1)	2445(3)	1114(1)	25(1)
C(20)	1550(1)	3728(2)	1092(1)	18(1)
C(21)	1567(1)	3212(2)	140(1)	20(1)
C(22)	2086(1)	3875(3)	-753(1)	26(1)

Table S7. Bond lengths [Å] and angles [°] for Shenvi277.

O(1)-C(11)	1.4629(18)	C(19)-H(19B)	0.9900
O(1)-C(12)	1.3362(18)	C(19)-C(20)	1.542(2)
O(2)-C(14)	1.215(2)	C(20)-C(21)	1.525(2)
O(3)-C(14)	1.3478(18)	C(21)-H(21A)	0.9900
O(3)-C(15)	1.4455(19)	C(21)-H(21B)	0.9900
O(4)-H(4)	0.8400	C(22)-H(22A)	0.9800
O(4)-C(20)	1.428(2)	C(22)-H(22B)	0.9800
O(5)-C(21)	1.418(2)	C(22)-H(22C)	0.9800
O(5)-C(22)	1.4254(19)		
C(1)-H(1A)	0.9500	C(12)-O(1)-C(11)	116.28(11)
C(1)-H(1B)	0.9500	C(14)-O(3)-C(15)	115.94(12)
C(1)-C(2)	1.328(3)	C(20)-O(4)-H(4)	109.5
C(2)-C(3)	1.527(2)	C(21)-O(5)-C(22)	111.37(12)
C(2)-C(9)	1.534(2)	H(1A)-C(1)-H(1B)	120.0
C(3)-H(3)	1.0000	C(2)-C(1)-H(1A)	120.0
C(3)-C(4)	1.543(2)	C(2)-C(1)-H(1B)	120.0
C(3)-C(7)	1.542(2)	C(1)-C(2)-C(3)	125.80(16)
C(4)-H(4A)	1.0000	C(1)-C(2)-C(9)	124.66(15)
C(4)-C(5)	1.532(2)	C(3)-C(2)-C(9)	109.50(13)
C(4)-C(6)	1.530(2)	C(2)-C(3)-H(3)	107.3
C(5)-H(5A)	0.9800	C(2)-C(3)-C(4)	114.79(14)
C(5)-H(5B)	0.9800	C(2)-C(3)-C(7)	103.95(13)
C(5)-H(5C)	0.9800	C(4)-C(3)-H(3)	107.3
C(6)-H(6A)	0.9800	C(7)-C(3)-H(3)	107.3
C(6)-H(6B)	0.9800	C(7)-C(3)-C(4)	115.67(14)
C(6)-H(6C)	0.9800	C(3)-C(4)-H(4A)	107.6
C(7)-H(7A)	0.9900	C(5)-C(4)-C(3)	111.16(15)
C(7)-H(7B)	0.9900	C(5)-C(4)-H(4A)	107.6
C(7)-C(8)	1.531(2)	C(6)-C(4)-C(3)	112.59(14)
C(8)-H(8A)	0.9900	C(6)-C(4)-H(4A)	107.6
C(8)-H(8B)	0.9900	C(6)-C(4)-C(5)	110.17(15)
C(8)-C(9)	1.549(2)	C(4)-C(5)-H(5A)	109.5
C(9)-C(10)	1.538(2)	C(4)-C(5)-H(5B)	109.5
C(9)-C(11)	1.547(2)	C(4)-C(5)-H(5C)	109.5
C(10)-H(10A)	0.9800	H(5A)-C(5)-H(5B)	109.5
C(10)-H(10B)	0.9800	H(5A)-C(5)-H(5C)	109.5
C(10)-H(10C)	0.9800	H(5B)-C(5)-H(5C)	109.5
C(11)-H(11)	1.0000	C(4)-C(6)-H(6A)	109.5
C(11)-C(16)	1.508(2)	C(4)-C(6)-H(6B)	109.5
C(12)-H(12)	0.9500	C(4)-C(6)-H(6C)	109.5
C(12)-C(13)	1.338(2)	H(6A)-C(6)-H(6B)	109.5
C(13)-H(13)	0.9500	H(6A)-C(6)-H(6C)	109.5
C(13)-C(14)	1.458(2)	H(6B)-C(6)-H(6C)	109.5
C(15)-H(15A)	0.9800	C(3)-C(7)-H(7A)	110.9
C(15)-H(15B)	0.9800	C(3)-C(7)-H(7B)	110.9
C(15)-H(15C)	0.9800	H(7A)-C(7)-H(7B)	109.0
C(16)-C(17)	1.329(2)	C(8)-C(7)-C(3)	104.04(13)
C(16)-C(20)	1.537(2)	C(8)-C(7)-H(7A)	110.9
C(17)-H(17)	0.9500	C(8)-C(7)-H(7B)	110.9
C(17)-C(18)	1.509(2)	C(7)-C(8)-H(8A)	110.9
C(18)-H(18A)	0.9900	C(7)-C(8)-H(8B)	110.9
C(18)-H(18B)	0.9900	C(7)-C(8)-C(9)	104.37(13)
C(18)-C(19)	1.536(3)	H(8A)-C(8)-H(8B)	108.9
C(19)-H(19A)	0.9900	C(9)-C(8)-H(8A)	110.9

C(9)-C(8)-H(8B)	110.9
C(2)-C(9)-C(8)	103.50(12)
C(2)-C(9)-C(10)	108.74(13)
C(2)-C(9)-C(11)	111.37(12)
C(10)-C(9)-C(8)	110.68(13)
C(10)-C(9)-C(11)	109.36(12)
C(11)-C(9)-C(8)	113.01(12)
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
O(1)-C(11)-C(9)	105.22(11)
O(1)-C(11)-H(11)	108.7
O(1)-C(11)-C(16)	111.11(12)
C(9)-C(11)-H(11)	108.7
C(16)-C(11)-C(9)	114.30(12)
C(16)-C(11)-H(11)	108.7
O(1)-C(12)-H(12)	119.0
O(1)-C(12)-C(13)	121.92(14)
C(13)-C(12)-H(12)	119.0
C(12)-C(13)-H(13)	120.4
C(12)-C(13)-C(14)	119.14(14)
C(14)-C(13)-H(13)	120.4
O(2)-C(14)-O(3)	122.75(14)
O(2)-C(14)-C(13)	126.47(14)
O(3)-C(14)-C(13)	110.78(13)
O(3)-C(15)-H(15A)	109.5
O(3)-C(15)-H(15B)	109.5
O(3)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(11)-C(16)-C(20)	122.36(14)
C(17)-C(16)-C(11)	127.44(14)
C(17)-C(16)-C(20)	110.20(14)
C(16)-C(17)-H(17)	123.7
C(16)-C(17)-C(18)	112.69(15)
C(18)-C(17)-H(17)	123.7
C(17)-C(18)-H(18A)	111.3
C(17)-C(18)-H(18B)	111.3
C(17)-C(18)-C(19)	102.15(14)
H(18A)-C(18)-H(18B)	109.2
C(19)-C(18)-H(18A)	111.3
C(19)-C(18)-H(18B)	111.3
C(18)-C(19)-H(19A)	110.7
C(18)-C(19)-H(19B)	110.7
C(18)-C(19)-C(20)	105.14(13)
H(19A)-C(19)-H(19B)	108.8
C(20)-C(19)-H(19A)	110.7
C(20)-C(19)-H(19B)	110.7
O(4)-C(20)-C(16)	112.56(13)
O(4)-C(20)-C(19)	110.84(13)
O(4)-C(20)-C(21)	110.33(13)
C(16)-C(20)-C(19)	101.57(13)
C(21)-C(20)-C(16)	112.38(12)
C(21)-C(20)-C(19)	108.82(13)
O(5)-C(21)-C(20)	109.90(12)
O(5)-C(21)-H(21A)	109.7
O(5)-C(21)-H(21B)	109.7
C(20)-C(21)-H(21A)	109.7
C(20)-C(21)-H(21B)	109.7
H(21A)-C(21)-H(21B)	108.2
O(5)-C(22)-H(22A)	109.5
O(5)-C(22)-H(22B)	109.5
O(5)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S8. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Shenvi277. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	17(1)	25(1)	16(1)	1(1)	10(1)	4(1)
O(2)	21(1)	45(1)	18(1)	1(1)	11(1)	7(1)
O(3)	17(1)	31(1)	22(1)	-1(1)	12(1)	3(1)
O(4)	25(1)	23(1)	22(1)	6(1)	15(1)	9(1)
O(5)	21(1)	31(1)	18(1)	-6(1)	12(1)	-4(1)
C(1)	35(1)	33(1)	21(1)	-4(1)	15(1)	-15(1)
C(2)	21(1)	21(1)	18(1)	-4(1)	12(1)	-3(1)
C(3)	20(1)	21(1)	20(1)	-2(1)	9(1)	2(1)
C(4)	21(1)	22(1)	20(1)	-4(1)	5(1)	0(1)
C(5)	30(1)	29(1)	26(1)	-7(1)	-2(1)	5(1)
C(6)	29(1)	23(1)	23(1)	-5(1)	8(1)	5(1)
C(7)	33(1)	21(1)	15(1)	-1(1)	12(1)	-2(1)
C(8)	28(1)	19(1)	18(1)	-1(1)	13(1)	-4(1)
C(9)	20(1)	17(1)	14(1)	-1(1)	11(1)	-1(1)
C(10)	23(1)	20(1)	22(1)	-5(1)	16(1)	-1(1)
C(11)	15(1)	17(1)	16(1)	0(1)	10(1)	2(1)
C(12)	17(1)	17(1)	15(1)	-4(1)	9(1)	-3(1)
C(13)	18(1)	21(1)	18(1)	0(1)	10(1)	1(1)
C(14)	16(1)	16(1)	21(1)	-3(1)	10(1)	-1(1)
C(15)	21(1)	37(1)	29(1)	-6(1)	18(1)	-3(1)
C(16)	17(1)	18(1)	14(1)	-2(1)	9(1)	2(1)
C(17)	23(1)	19(1)	18(1)	-1(1)	8(1)	0(1)
C(18)	27(1)	23(1)	24(1)	-3(1)	12(1)	-7(1)
C(19)	19(1)	31(1)	24(1)	-1(1)	11(1)	-3(1)
C(20)	15(1)	20(1)	17(1)	0(1)	8(1)	2(1)
C(21)	16(1)	25(1)	16(1)	-3(1)	6(1)	-1(1)
C(22)	27(1)	34(1)	18(1)	-1(1)	14(1)	4(1)

Table S9. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Shenvi277.

	x	y	z	U(eq)
H(4)	1418	6218	604	34
H(1A)	4042	8882	4004	36
H(1B)	3323	8238	2923	36
H(3)	4470	5520	5425	26
H(4A)	4631	8782	5780	29
H(5A)	4777	6691	7492	56
H(5B)	5177	8588	7624	56
H(5C)	5322	6734	7191	56
H(6A)	3516	9523	5335	43
H(6B)	4104	10452	6422	43
H(6C)	3718	8625	6433	43
H(7A)	3997	4116	6202	29
H(7B)	3427	5719	5821	29
H(8A)	2824	3388	4577	25
H(8B)	3461	2847	4522	25
H(10A)	2480	7063	4165	31
H(10B)	1987	5608	3257	31
H(10C)	2247	7437	2976	31
H(11)	2741	5537	2171	18
H(12)	3239	3875	1518	19
H(13)	4498	2331	3093	23
H(15A)	4835	1414	653	40
H(15B)	5594	1997	1566	40
H(15C)	5039	3583	894	40
H(17)	2515	956	3089	26
H(18A)	1284	265	2204	31
H(18B)	1440	-282	1336	31
H(19A)	829	3100	1437	31
H(19B)	672	2049	392	31
H(21A)	1659	1854	155	25
H(21B)	1120	3482	-517	25
H(22A)	1637	4129	-1391	39
H(22B)	2204	2555	-747	39
H(22C)	2424	4677	-745	39

Crystal structure of chloroform adduct of (*S*)-**6**.

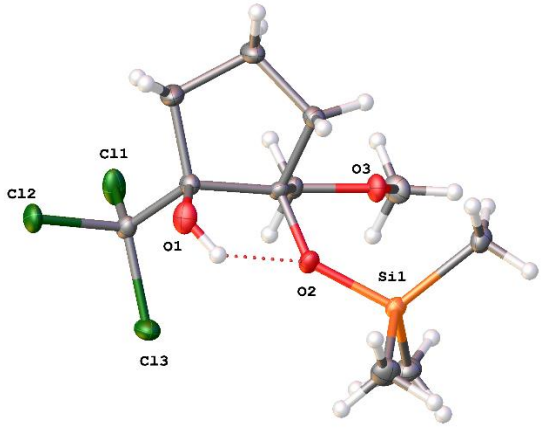


Table S10. Crystal data and structure refinement for Shenvi272.

Identification code	shenvi272	
Empirical formula	C11 H21 Cl3 O3 Si	
Formula weight	335.72	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.3108(6) Å	α= 90°.
	b = 10.5366(6) Å	β= 90°.
	c = 16.4028(8) Å	γ = 90°.
Volume	1609.18(16) $Å^3$	
Z	4	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.642 mm^{-1}	
F(000)	704	
Crystal size	0.23 x 0.225 x 0.21 mm^3	
Theta range for data collection	2.515 to 26.399°.	
Index ranges	-11<=h<=11, -13<=k<=13, -20<=l<=20	
Reflections collected	37345	
Independent reflections	3296 [R(int) = 0.0543]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7427 and 0.6864	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3296 / 0 / 168	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0211, wR2 = 0.0488	
R indices (all data)	R1 = 0.0227, wR2 = 0.0495	
Absolute structure parameter	-0.01(2)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.242 and -0.206 $e.Å^{-3}$	

Table S11. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Shenvi272. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	7649(1)	1194(1)	9679(1)	26(1)
Cl(3)	8648(1)	100(1)	8174(1)	23(1)
Cl(2)	10663(1)	1095(1)	9339(1)	22(1)
Si(1)	6836(1)	2552(1)	6284(1)	14(1)
O(1)	10113(2)	2661(2)	7921(1)	21(1)
O(2)	7752(1)	2530(1)	7154(1)	16(1)
O(3)	5038(2)	3162(1)	7783(1)	16(1)
C(1)	8935(2)	2666(2)	8461(1)	15(1)
C(2)	7563(2)	3053(2)	7943(1)	13(1)
C(3)	7711(2)	4506(2)	7940(1)	16(1)
C(4)	8179(2)	4844(2)	8804(1)	22(1)
C(5)	9162(3)	3747(2)	9078(1)	24(1)
C(6)	8937(2)	1343(2)	8884(1)	16(1)
C(7)	6117(2)	2645(2)	8295(1)	14(1)
C(8)	3639(2)	2790(2)	8033(1)	21(1)
C(9)	8281(3)	2177(2)	5536(1)	26(1)
C(10)	6026(2)	4121(2)	6043(1)	18(1)
C(11)	5456(2)	1282(2)	6265(1)	21(1)

Table S12. Bond lengths [Å] and angles [°] for Shenvi272.

Cl(1)-C(6)	1.778(2)	C(6)-C(1)-C(2)	118.02(16)
Cl(3)-C(6)	1.773(2)	O(2)-C(2)-C(1)	106.80(15)
Cl(2)-C(6)	1.791(2)	O(2)-C(2)-C(3)	111.85(17)
Si(1)-O(2)	1.6622(14)	O(2)-C(2)-C(7)	110.17(16)
Si(1)-C(9)	1.864(2)	C(3)-C(2)-C(1)	100.74(16)
Si(1)-C(10)	1.859(2)	C(7)-C(2)-C(1)	115.78(16)
Si(1)-C(11)	1.856(2)	C(7)-C(2)-C(3)	111.17(17)
O(1)-H(1)	0.8400	C(2)-C(3)-H(3A)	110.8
O(1)-C(1)	1.410(2)	C(2)-C(3)-H(3B)	110.8
O(2)-C(2)	1.418(2)	H(3A)-C(3)-H(3B)	108.9
O(3)-C(7)	1.419(2)	C(4)-C(3)-C(2)	104.72(17)
O(3)-C(8)	1.421(2)	C(4)-C(3)-H(3A)	110.8
C(1)-C(2)	1.587(3)	C(4)-C(3)-H(3B)	110.8
C(1)-C(5)	1.539(3)	C(3)-C(4)-H(4A)	110.6
C(1)-C(6)	1.557(3)	C(3)-C(4)-H(4B)	110.6
C(2)-C(3)	1.538(3)	C(3)-C(4)-C(5)	105.46(17)
C(2)-C(7)	1.527(3)	H(4A)-C(4)-H(4B)	108.8
C(3)-H(3A)	0.9900	C(5)-C(4)-H(4A)	110.6
C(3)-H(3B)	0.9900	C(5)-C(4)-H(4B)	110.6
C(3)-C(4)	1.525(3)	C(1)-C(5)-C(4)	106.34(17)
C(4)-H(4A)	0.9900	C(1)-C(5)-H(5A)	110.5
C(4)-H(4B)	0.9900	C(1)-C(5)-H(5B)	110.5
C(4)-C(5)	1.541(3)	C(4)-C(5)-H(5A)	110.5
C(5)-H(5A)	0.9900	C(4)-C(5)-H(5B)	110.5
C(5)-H(5B)	0.9900	H(5A)-C(5)-H(5B)	108.7
C(7)-H(7A)	0.9900	Cl(1)-C(6)-Cl(2)	106.67(11)
C(7)-H(7B)	0.9900	Cl(3)-C(6)-Cl(1)	108.30(11)
C(8)-H(8A)	0.9800	Cl(3)-C(6)-Cl(2)	107.60(11)
C(8)-H(8B)	0.9800	C(1)-C(6)-Cl(1)	113.86(14)
C(8)-H(8C)	0.9800	C(1)-C(6)-Cl(3)	111.63(14)
C(9)-H(9A)	0.9800	C(1)-C(6)-Cl(2)	108.50(14)
C(9)-H(9B)	0.9800	O(3)-C(7)-C(2)	106.99(15)
C(9)-H(9C)	0.9800	O(3)-C(7)-H(7A)	110.3
C(10)-H(10A)	0.9800	O(3)-C(7)-H(7B)	110.3
C(10)-H(10B)	0.9800	C(2)-C(7)-H(7A)	110.3
C(10)-H(10C)	0.9800	C(2)-C(7)-H(7B)	110.3
C(11)-H(11A)	0.9800	H(7A)-C(7)-H(7B)	108.6
C(11)-H(11B)	0.9800	O(3)-C(8)-H(8A)	109.5
C(11)-H(11C)	0.9800	O(3)-C(8)-H(8B)	109.5
		O(3)-C(8)-H(8C)	109.5
O(2)-Si(1)-C(9)	101.08(9)	H(8A)-C(8)-H(8B)	109.5
O(2)-Si(1)-C(10)	113.77(9)	H(8A)-C(8)-H(8C)	109.5
O(2)-Si(1)-C(11)	111.06(9)	H(8B)-C(8)-H(8C)	109.5
C(10)-Si(1)-C(9)	109.99(10)	Si(1)-C(9)-H(9A)	109.5
C(11)-Si(1)-C(9)	109.59(11)	Si(1)-C(9)-H(9B)	109.5
C(11)-Si(1)-C(10)	110.90(10)	Si(1)-C(9)-H(9C)	109.5
C(1)-O(1)-H(1)	109.5	H(9A)-C(9)-H(9B)	109.5
C(2)-O(2)-Si(1)	135.64(13)	H(9A)-C(9)-H(9C)	109.5
C(7)-O(3)-C(8)	111.86(15)	H(9B)-C(9)-H(9C)	109.5
O(1)-C(1)-C(2)	106.88(16)	Si(1)-C(10)-H(10A)	109.5
O(1)-C(1)-C(5)	108.01(17)	Si(1)-C(10)-H(10B)	109.5
O(1)-C(1)-C(6)	106.04(16)	Si(1)-C(10)-H(10C)	109.5
C(5)-C(1)-C(2)	105.78(16)	H(10A)-C(10)-H(10B)	109.5
C(5)-C(1)-C(6)	111.68(17)	H(10A)-C(10)-H(10C)	109.5

H(10B)-C(10)-H(10C)	109.5
Si(1)-C(11)-H(11A)	109.5
Si(1)-C(11)-H(11B)	109.5
Si(1)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5

Table S13. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Shenvi272. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	23(1)	38(1)	18(1)	11(1)	5(1)	8(1)
Cl(3)	26(1)	16(1)	27(1)	-5(1)	-6(1)	2(1)
Cl(2)	18(1)	26(1)	24(1)	2(1)	-7(1)	6(1)
Si(1)	15(1)	15(1)	12(1)	0(1)	0(1)	-1(1)
O(1)	11(1)	30(1)	23(1)	6(1)	1(1)	-2(1)
O(2)	14(1)	21(1)	12(1)	-2(1)	0(1)	3(1)
O(3)	9(1)	22(1)	19(1)	4(1)	-1(1)	1(1)
C(1)	12(1)	15(1)	17(1)	-1(1)	-2(1)	1(1)
C(2)	13(1)	15(1)	11(1)	-2(1)	0(1)	1(1)
C(3)	16(1)	14(1)	20(1)	1(1)	0(1)	0(1)
C(4)	23(1)	16(1)	27(1)	-6(1)	-7(1)	2(1)
C(5)	31(1)	17(1)	26(1)	-6(1)	-12(1)	3(1)
C(6)	13(1)	20(1)	15(1)	-1(1)	-1(1)	2(1)
C(7)	13(1)	17(1)	12(1)	0(1)	-1(1)	2(1)
C(8)	11(1)	24(1)	29(1)	0(1)	2(1)	-1(1)
C(9)	27(1)	31(1)	19(1)	-3(1)	4(1)	2(1)
C(10)	20(1)	19(1)	16(1)	3(1)	-3(1)	-2(1)
C(11)	24(1)	18(1)	22(1)	-1(1)	-2(1)	-4(1)

Table S14. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Shenvi272.

	x	y	z	U(eq)
H(1)	9836	2435	7455	32
H(3A)	8441	4781	7537	20
H(3B)	6783	4914	7805	20
H(4A)	7336	4917	9168	27
H(4B)	8708	5659	8809	27
H(5A)	10179	4022	9080	29
H(5B)	8902	3465	9634	29
H(7A)	6046	1707	8307	17
H(7B)	6007	2968	8859	17
H(8A)	3446	3125	8580	32
H(8B)	3578	1862	8043	32
H(8C)	2929	3127	7649	32
H(9A)	9042	2817	5574	38
H(9B)	7880	2178	4983	38
H(9C)	8682	1337	5656	38
H(10A)	5258	4306	6434	28
H(10B)	5628	4103	5490	28
H(10C)	6765	4781	6078	28
H(11A)	5798	551	6580	32
H(11B)	5280	1022	5700	32
H(11C)	4563	1601	6505	32

Table S15. Hydrogen bonds for Shenvi272 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(2)	0.84	2.00	2.536(2)	120.5

Crystal structure of 4-bromo-2-nitrophenylhydrazone of (*S*)-**6**.

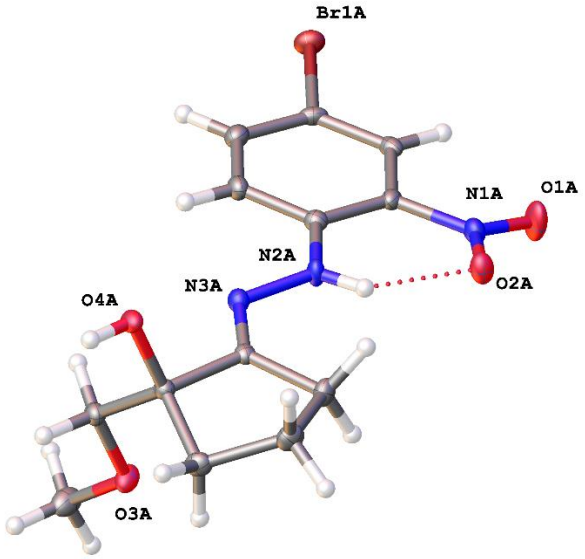


Table 15. Crystal data and structure refinement for Shenvi263.

Identification code	shenvi263	
Empirical formula	C13 H16 Br N3 O4	
Formula weight	358.20	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.7929(4) Å	α= 90°.
	b = 18.0102(8) Å	β= 107.250(2)°.
	c = 10.8860(6) Å	γ = 90°.
Volume	1459.14(13) $Å^3$	
Z	4	
Density (calculated)	1.631 Mg/m^3	
Absorption coefficient	2.837 mm^{-1}	
F(000)	728	
Crystal size	0.3 x 0.25 x 0.1 mm^3	
Theta range for data collection	1.959 to 26.410°.	
Index ranges	-9<=h<=9, -22<=k<=22, -13<=l<=13	
Reflections collected	16068	
Independent reflections	5985 [R(int) = 0.0323]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7454 and 0.6140	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5985 / 1 / 383	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0242, wR2 = 0.0569	
R indices (all data)	R1 = 0.0257, wR2 = 0.0575	
Absolute structure parameter	-0.005(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.521 and -0.223 $e.Å^{-3}$	

Table S16. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Shenvi263. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(01)	9505(1)	2921(1)	2614(1)	19(1)
Br(02)	-931(1)	7186(1)	2915(1)	20(1)
O(003)	6713(3)	4184(1)	9150(2)	18(1)
O(004)	5664(3)	5740(1)	8558(2)	15(1)
O(005)	2420(3)	3358(1)	9050(2)	19(1)
O(006)	5475(3)	6001(1)	2660(2)	20(1)
N(007)	3015(4)	4432(2)	5485(3)	16(1)
O(008)	10072(3)	6421(1)	8603(2)	19(1)
O(009)	2331(4)	4920(2)	1654(3)	30(1)
O(00A)	3300(4)	4140(1)	3208(3)	22(1)
N(00B)	6656(4)	5505(2)	5005(3)	15(1)
N(00C)	3482(4)	4358(2)	6802(3)	15(1)
N(00D)	7074(4)	5533(2)	6326(3)	14(1)
O(00E)	6458(4)	5516(2)	1184(3)	31(1)
N(00F)	2539(4)	4730(2)	2766(3)	18(1)
N(00G)	6304(4)	5509(2)	2274(3)	17(1)
C(00H)	2193(5)	5059(2)	4916(3)	14(1)
C(00I)	5591(5)	6791(2)	6056(4)	17(1)
C(00J)	7806(5)	4321(2)	2568(3)	14(1)
C(00K)	658(5)	6219(2)	5054(4)	17(1)
C(00L)	7280(5)	4930(2)	4449(3)	14(1)
C(00M)	5033(5)	7226(2)	7085(3)	19(1)
C(00N)	8629(5)	3744(2)	3343(3)	15(1)
C(00O)	6551(4)	6120(2)	6766(3)	12(1)
C(00P)	1561(5)	5594(2)	5632(4)	17(1)
C(00Q)	986(5)	5851(2)	3026(3)	17(1)
C(00R)	360(5)	6342(2)	3750(4)	17(1)
C(00S)	1894(5)	5214(2)	3597(4)	15(1)
C(00T)	5922(4)	2904(2)	8841(3)	16(1)
C(00U)	8165(5)	4323(2)	5197(4)	17(1)
C(00V)	8807(5)	3743(2)	4655(4)	17(1)
C(00W)	11862(5)	6210(2)	9252(4)	23(1)
C(00X)	7139(5)	4913(2)	3125(3)	14(1)
C(00Y)	6504(5)	7036(2)	8333(3)	17(1)
C(00Z)	3876(5)	3860(2)	9441(3)	16(1)
C(010)	5201(4)	3695(2)	8707(3)	14(1)
C(011)	6493(5)	2769(2)	7622(4)	19(1)
C(012)	5047(5)	3170(2)	6559(4)	17(1)
C(013)	6921(4)	6214(2)	8205(3)	13(1)
C(014)	4429(4)	3790(2)	7254(3)	14(1)
C(015)	8808(5)	5981(2)	8976(3)	15(1)
C(016)	1056(5)	3518(2)	9628(4)	23(1)

Table S17. Bond lengths [Å] and angles [°] for Shenvi263.

Br(01)-C(00N)	1.900(3)	C(00W)-H(00F)	0.9800
Br(02)-C(00R)	1.899(3)	C(00W)-H(00G)	0.9800
O(003)-H(003)	0.8400	C(00W)-H(00H)	0.9800
O(003)-C(010)	1.436(4)	C(00Y)-H(00I)	0.9900
O(004)-H(004)	0.8400	C(00Y)-H(00K)	0.9900
O(004)-C(013)	1.434(4)	C(00Y)-C(013)	1.531(4)
O(005)-C(00Z)	1.414(4)	C(00Z)-H(00O)	0.9900
O(005)-C(016)	1.416(4)	C(00Z)-H(00R)	0.9900
O(006)-N(00G)	1.241(4)	C(00Z)-C(010)	1.510(5)
N(007)-H(007)	0.8800	C(010)-C(014)	1.526(5)
N(007)-N(00C)	1.378(4)	C(011)-H(01C)	0.9900
N(007)-C(00H)	1.353(5)	C(011)-H(01D)	0.9900
O(008)-C(00W)	1.416(4)	C(011)-C(012)	1.535(5)
O(008)-C(015)	1.414(4)	C(012)-H(01E)	0.9900
O(009)-N(00F)	1.221(4)	C(012)-H(01F)	0.9900
O(00A)-N(00F)	1.244(4)	C(012)-C(014)	1.506(5)
N(00B)-H(00B)	0.8800	C(013)-C(015)	1.520(5)
N(00B)-N(00D)	1.378(4)	C(015)-H(01A)	0.9900
N(00B)-C(00L)	1.362(4)	C(015)-H(01B)	0.9900
N(00C)-C(014)	1.272(4)	C(016)-H(01G)	0.9800
N(00D)-C(00O)	1.275(4)	C(016)-H(01H)	0.9800
O(00E)-N(00G)	1.227(4)	C(016)-H(01I)	0.9800
N(00F)-C(00S)	1.448(5)		
N(00G)-C(00X)	1.441(4)	C(010)-O(003)-H(003)	109.5
C(00H)-C(00P)	1.417(5)	C(013)-O(004)-H(004)	109.5
C(00H)-C(00S)	1.413(5)	C(00Z)-O(005)-C(016)	112.2(3)
C(00I)-H(00A)	0.9900	N(00C)-N(007)-H(007)	120.0
C(00I)-H(00C)	0.9900	C(00H)-N(007)-H(007)	120.0
C(00I)-C(00M)	1.532(5)	C(00H)-N(007)-N(00C)	120.0(3)
C(00I)-C(00O)	1.509(4)	C(015)-O(008)-C(00W)	111.9(3)
C(00J)-H(00J)	0.9500	N(00D)-N(00B)-H(00B)	120.4
C(00J)-C(00N)	1.372(5)	C(00L)-N(00B)-H(00B)	120.4
C(00J)-C(00X)	1.400(5)	C(00L)-N(00B)-N(00D)	119.1(3)
C(00K)-H(00L)	0.9500	C(014)-N(00C)-N(007)	115.1(3)
C(00K)-C(00P)	1.375(5)	C(00O)-N(00D)-N(00B)	114.7(3)
C(00K)-C(00R)	1.387(5)	O(009)-N(00F)-O(00A)	122.0(3)
C(00L)-C(00U)	1.414(5)	O(009)-N(00F)-C(00S)	118.9(3)
C(00L)-C(00X)	1.413(5)	O(00A)-N(00F)-C(00S)	119.1(3)
C(00M)-H(00D)	0.9900	O(006)-N(00G)-C(00X)	119.7(3)
C(00M)-H(00E)	0.9900	O(00E)-N(00G)-O(006)	122.0(3)
C(00M)-C(00Y)	1.534(5)	O(00E)-N(00G)-C(00X)	118.2(3)
C(00N)-C(00V)	1.394(5)	N(007)-C(00H)-C(00P)	120.7(3)
C(00O)-C(013)	1.516(5)	N(007)-C(00H)-C(00S)	122.9(3)
C(00P)-H(00P)	0.9500	C(00S)-C(00H)-C(00P)	116.4(3)
C(00Q)-H(00Q)	0.9500	H(00A)-C(00I)-H(00C)	109.0
C(00Q)-C(00R)	1.367(5)	C(00M)-C(00I)-H(00A)	111.0
C(00Q)-C(00S)	1.394(5)	C(00M)-C(00I)-H(00C)	111.0
C(00T)-H(00M)	0.9900	C(00O)-C(00I)-H(00A)	111.0
C(00T)-H(00N)	0.9900	C(00O)-C(00I)-H(00C)	111.0
C(00T)-C(010)	1.524(5)	C(00O)-C(00I)-C(00M)	103.9(3)
C(00T)-C(011)	1.539(5)	C(00N)-C(00J)-H(00J)	120.8
C(00U)-H(00U)	0.9500	C(00N)-C(00J)-C(00X)	118.5(3)
C(00U)-C(00V)	1.365(5)	C(00X)-C(00J)-H(00J)	120.8
C(00V)-H(00V)	0.9500	C(00P)-C(00K)-H(00L)	119.8

C(00P)-C(00K)-C(00R)	120.4(3)
C(00R)-C(00K)-H(00L)	119.8
N(00B)-C(00L)-C(00U)	120.6(3)
N(00B)-C(00L)-C(00X)	122.7(3)
C(00X)-C(00L)-C(00U)	116.6(3)
C(00I)-C(00M)-H(00D)	111.1
C(00I)-C(00M)-H(00E)	111.1
C(00I)-C(00M)-C(00Y)	103.5(3)
H(00D)-C(00M)-H(00E)	109.0
C(00Y)-C(00M)-H(00D)	111.1
C(00Y)-C(00M)-H(00E)	111.1
C(00J)-C(00N)-Br(01)	119.6(3)
C(00J)-C(00N)-C(00V)	121.1(3)
C(00V)-C(00N)-Br(01)	119.3(3)
N(00D)-C(00O)-C(00I)	129.6(3)
N(00D)-C(00O)-C(013)	119.7(3)
C(00I)-C(00O)-C(013)	110.7(3)
C(00H)-C(00P)-H(00P)	119.4
C(00K)-C(00P)-C(00H)	121.3(3)
C(00K)-C(00P)-H(00P)	119.4
C(00R)-C(00Q)-H(00Q)	120.1
C(00R)-C(00Q)-C(00S)	119.7(3)
C(00S)-C(00Q)-H(00Q)	120.1
C(00K)-C(00R)-Br(02)	121.5(3)
C(00Q)-C(00R)-Br(02)	118.0(3)
C(00Q)-C(00R)-C(00K)	120.5(3)
C(00H)-C(00S)-N(00F)	122.2(3)
C(00Q)-C(00S)-N(00F)	116.2(3)
C(00Q)-C(00S)-C(00H)	121.7(3)
H(00M)-C(00T)-H(00N)	108.8
C(010)-C(00T)-H(00M)	110.8
C(010)-C(00T)-H(00N)	110.8
C(010)-C(00T)-C(011)	104.9(3)
C(011)-C(00T)-H(00M)	110.8
C(011)-C(00T)-H(00N)	110.8
C(00L)-C(00U)-H(00U)	119.3
C(00V)-C(00U)-C(00L)	121.4(3)
C(00V)-C(00U)-H(00U)	119.3
C(00N)-C(00V)-H(00V)	119.8
C(00U)-C(00V)-C(00N)	120.3(3)
C(00U)-C(00V)-H(00V)	119.8
O(008)-C(00W)-H(00F)	109.5
O(008)-C(00W)-H(00G)	109.5
O(008)-C(00W)-H(00H)	109.5
H(00F)-C(00W)-H(00G)	109.5
H(00F)-C(00W)-H(00H)	109.5
H(00G)-C(00W)-H(00H)	109.5
C(00J)-C(00X)-N(00G)	116.4(3)
C(00J)-C(00X)-C(00L)	122.1(3)
C(00L)-C(00X)-N(00G)	121.6(3)
C(00M)-C(00Y)-H(00I)	110.8
C(00M)-C(00Y)-H(00K)	110.7
H(00I)-C(00Y)-H(00K)	108.8
C(013)-C(00Y)-C(00M)	105.0(3)
C(013)-C(00Y)-H(00I)	110.7
C(013)-C(00Y)-H(00K)	110.8
O(005)-C(00Z)-H(00O)	109.8
O(005)-C(00Z)-H(00R)	109.8
O(005)-C(00Z)-C(010)	109.2(3)
H(00O)-C(00Z)-H(00R)	108.3
C(010)-C(00Z)-H(00O)	109.8
C(010)-C(00Z)-H(00R)	109.8
O(003)-C(010)-C(00T)	107.4(3)
O(003)-C(010)-C(00Z)	108.9(3)
O(003)-C(010)-C(014)	108.1(3)
C(00T)-C(010)-C(014)	103.0(3)
C(00Z)-C(010)-C(00T)	115.1(3)
C(00Z)-C(010)-C(014)	113.9(3)
C(00T)-C(011)-H(01C)	111.0
C(00T)-C(011)-H(01D)	111.0
H(01C)-C(011)-H(01D)	109.0
C(012)-C(011)-C(00T)	104.0(3)
C(012)-C(011)-H(01C)	111.0
C(012)-C(011)-H(01D)	111.0
C(011)-C(012)-H(01E)	110.9
C(011)-C(012)-H(01F)	110.9
H(01E)-C(012)-H(01F)	109.0
C(014)-C(012)-C(011)	104.0(3)
C(014)-C(012)-H(01E)	110.9
C(014)-C(012)-H(01F)	110.9
O(004)-C(013)-C(00O)	105.9(3)
O(004)-C(013)-C(00Y)	111.7(3)
O(004)-C(013)-C(015)	108.3(3)
C(00O)-C(013)-C(00Y)	102.8(3)
C(00O)-C(013)-C(015)	113.3(3)
C(015)-C(013)-C(00Y)	114.4(3)
N(00C)-C(014)-C(010)	119.7(3)
N(00C)-C(014)-C(012)	129.7(3)
C(012)-C(014)-C(010)	110.5(3)
O(008)-C(015)-C(013)	109.2(3)
O(008)-C(015)-H(01A)	109.8
O(008)-C(015)-H(01B)	109.8
C(013)-C(015)-H(01A)	109.8
C(013)-C(015)-H(01B)	109.8
H(01A)-C(015)-H(01B)	108.3
O(005)-C(016)-H(01G)	109.5
O(005)-C(016)-H(01H)	109.5
O(005)-C(016)-H(01I)	109.5
H(01G)-C(016)-H(01H)	109.5
H(01G)-C(016)-H(01I)	109.5
H(01H)-C(016)-H(01I)	109.5

Table S18. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Shenvi263. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(01)	21(1)	15(1)	23(1)	-4(1)	12(1)	0(1)
Br(02)	17(1)	15(1)	25(1)	5(1)	1(1)	1(1)
O(003)	15(1)	15(1)	20(1)	-2(1)	1(1)	-4(1)
O(004)	18(1)	17(1)	11(1)	0(1)	6(1)	-4(1)
O(005)	16(1)	21(1)	20(1)	-6(1)	5(1)	-6(1)
O(006)	24(1)	22(1)	15(1)	1(1)	5(1)	7(1)
N(007)	19(2)	16(1)	11(2)	-1(1)	1(1)	2(1)
O(008)	13(1)	21(1)	21(1)	7(1)	4(1)	0(1)
O(009)	54(2)	26(2)	12(2)	-1(1)	12(1)	-1(1)
O(00A)	24(1)	20(1)	21(1)	-3(1)	6(1)	6(1)
N(00B)	21(2)	16(1)	9(1)	2(1)	4(1)	5(1)
N(00C)	14(1)	16(1)	14(2)	-1(1)	1(1)	-1(1)
N(00D)	15(2)	16(1)	12(2)	1(1)	4(1)	0(1)
O(00E)	52(2)	30(1)	12(1)	4(1)	12(1)	10(1)
N(00F)	17(2)	20(2)	17(2)	-3(1)	3(1)	-5(1)
N(00G)	20(2)	19(2)	11(2)	0(1)	4(1)	-1(1)
C(00H)	10(2)	15(2)	17(2)	0(1)	2(1)	-3(1)
C(00I)	18(2)	17(2)	16(2)	5(1)	6(2)	4(1)
C(00J)	15(2)	17(2)	12(2)	-3(1)	6(1)	-6(1)
C(00K)	18(2)	14(2)	21(2)	-2(1)	6(2)	-2(1)
C(00L)	14(2)	15(2)	14(2)	-1(1)	5(1)	-2(1)
C(00M)	21(2)	14(2)	23(2)	1(2)	7(1)	4(2)
C(00N)	14(2)	11(2)	22(2)	-4(1)	8(1)	-2(1)
C(00O)	10(2)	14(2)	12(2)	0(1)	3(1)	-1(1)
C(00P)	18(2)	18(2)	15(2)	0(1)	2(1)	0(1)
C(00Q)	15(2)	19(2)	13(2)	3(1)	0(1)	-4(1)
C(00R)	12(2)	13(2)	22(2)	4(1)	0(1)	-1(1)
C(00S)	12(2)	15(2)	16(2)	-2(1)	3(1)	-3(1)
C(00T)	16(2)	13(1)	18(2)	2(2)	2(1)	1(2)
C(00U)	19(2)	18(2)	12(2)	1(1)	4(1)	-2(1)
C(00V)	18(2)	15(2)	18(2)	2(1)	4(1)	-2(1)
C(00W)	15(2)	22(2)	32(2)	6(2)	6(2)	1(1)
C(00X)	12(2)	13(2)	14(2)	2(1)	1(1)	-2(1)
C(00Y)	21(2)	16(2)	17(2)	-3(1)	9(2)	0(1)
C(00Z)	17(2)	12(2)	16(2)	-2(1)	1(1)	-2(1)
C(010)	13(2)	12(1)	16(2)	-1(1)	1(1)	-2(1)
C(011)	17(2)	18(2)	22(2)	-1(1)	6(2)	2(1)
C(012)	17(2)	17(2)	17(2)	-3(1)	5(2)	0(1)
C(013)	13(2)	13(2)	12(2)	0(1)	4(1)	-1(1)
C(014)	12(2)	12(2)	17(2)	-2(1)	3(1)	-3(1)
C(015)	17(2)	17(2)	11(2)	1(1)	3(1)	-2(1)
C(016)	18(2)	27(2)	27(2)	-5(2)	10(2)	-2(2)

Table S19. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Shenvi263.

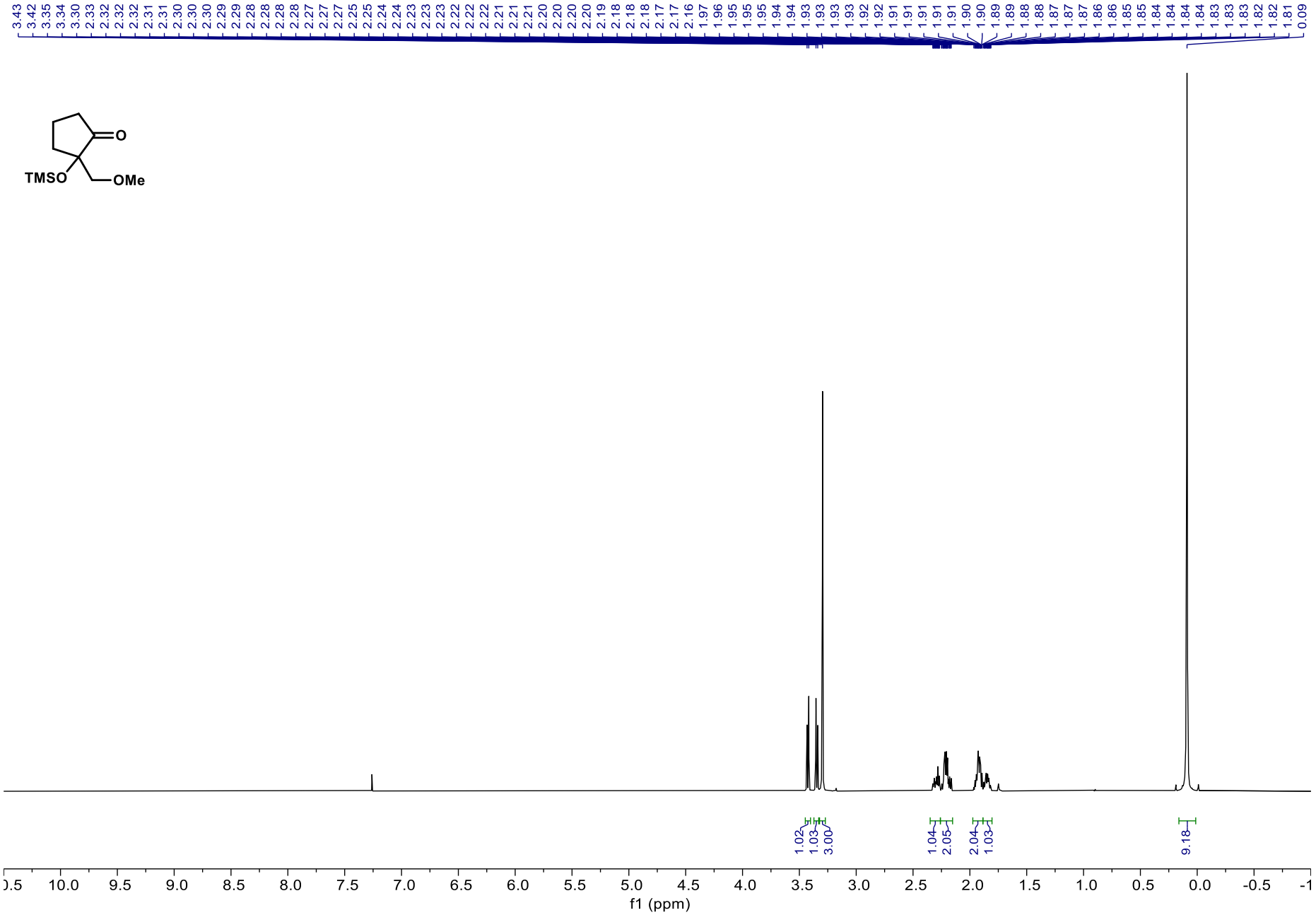
	x	y	z	U(eq)
H(003)	6388	4622	8936	26
H(004)	5733	5812	9333	22
H(007)	3251	4072	5013	19
H(00B)	5994	5855	4527	18
H(00A)	4527	6643	5343	20
H(00C)	6401	7090	5703	20
H(00J)	7691	4319	1674	17
H(00L)	235	6567	5552	21
H(00D)	3838	7065	7128	23
H(00E)	5000	7766	6911	23
H(00P)	1765	5521	6528	21
H(00Q)	803	5944	2137	20
H(00M)	4980	2546	8892	19
H(00N)	6961	2852	9623	19
H(00U)	8316	4319	6096	20
H(00V)	9379	3338	5175	20
H(00F)	12034	5686	9079	35
H(00G)	12096	6283	10180	35
H(00H)	12694	6515	8948	35
H(00I)	7586	7344	8425	21
H(00K)	6071	7118	9090	21
H(00O)	4473	3809	10376	19
H(00R)	3433	4376	9268	19
H(01C)	7697	2982	7716	23
H(01D)	6515	2232	7435	23
H(01E)	5556	3367	5893	20
H(01F)	4041	2831	6147	20
H(01A)	8967	6048	9906	18
H(01B)	8996	5450	8819	18
H(01G)	415	3969	9243	35
H(01H)	1598	3594	10554	35
H(01I)	210	3102	9486	35

Table S20. Hydrogen bonds for Shenvi263 [Å and °].

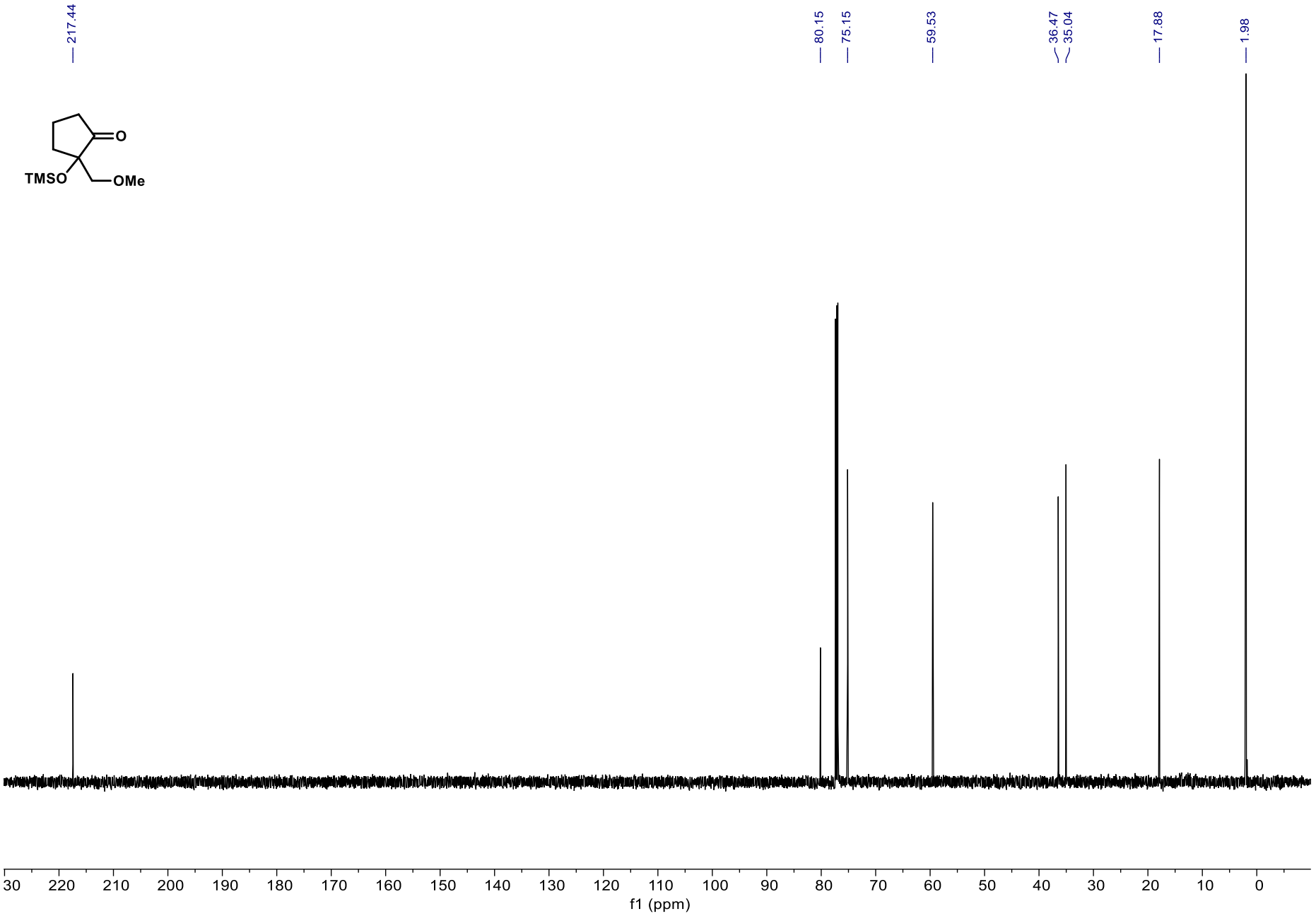
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(003)-H(003)...O(004)	0.84	2.10	2.937(3)	175.4
O(004)-H(004)...O(00E)#1	0.84	2.00	2.770(4)	152.6
N(007)-H(007)...O(00A)	0.88	1.98	2.607(4)	127.1
N(00B)-H(00B)...O(006)	0.88	1.97	2.602(4)	127.6

Symmetry transformations used to generate equivalent atoms:
#1 x,y,z+1

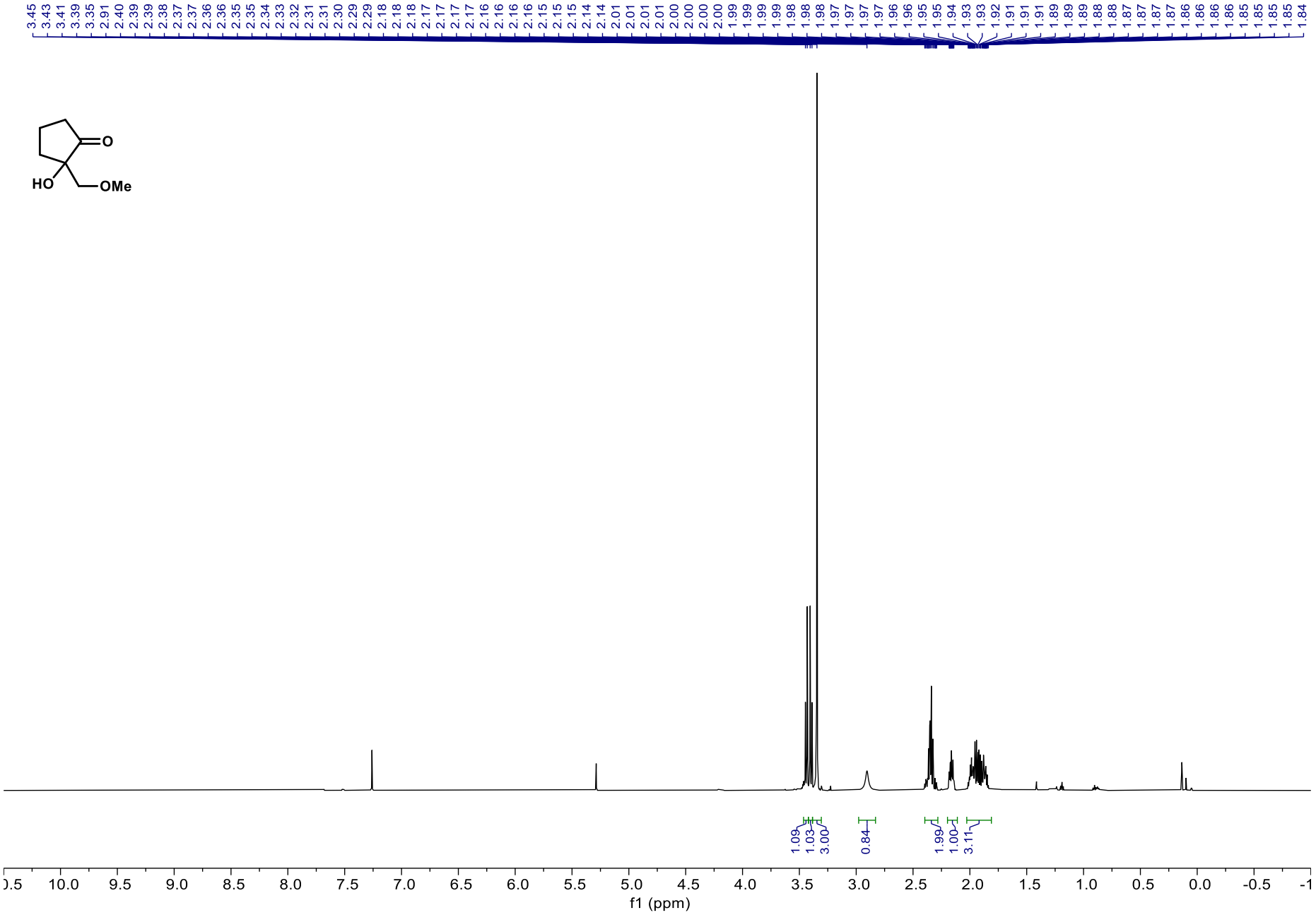
^{1}H NMR of **S2**, 600 MHz, $CDCl_3$



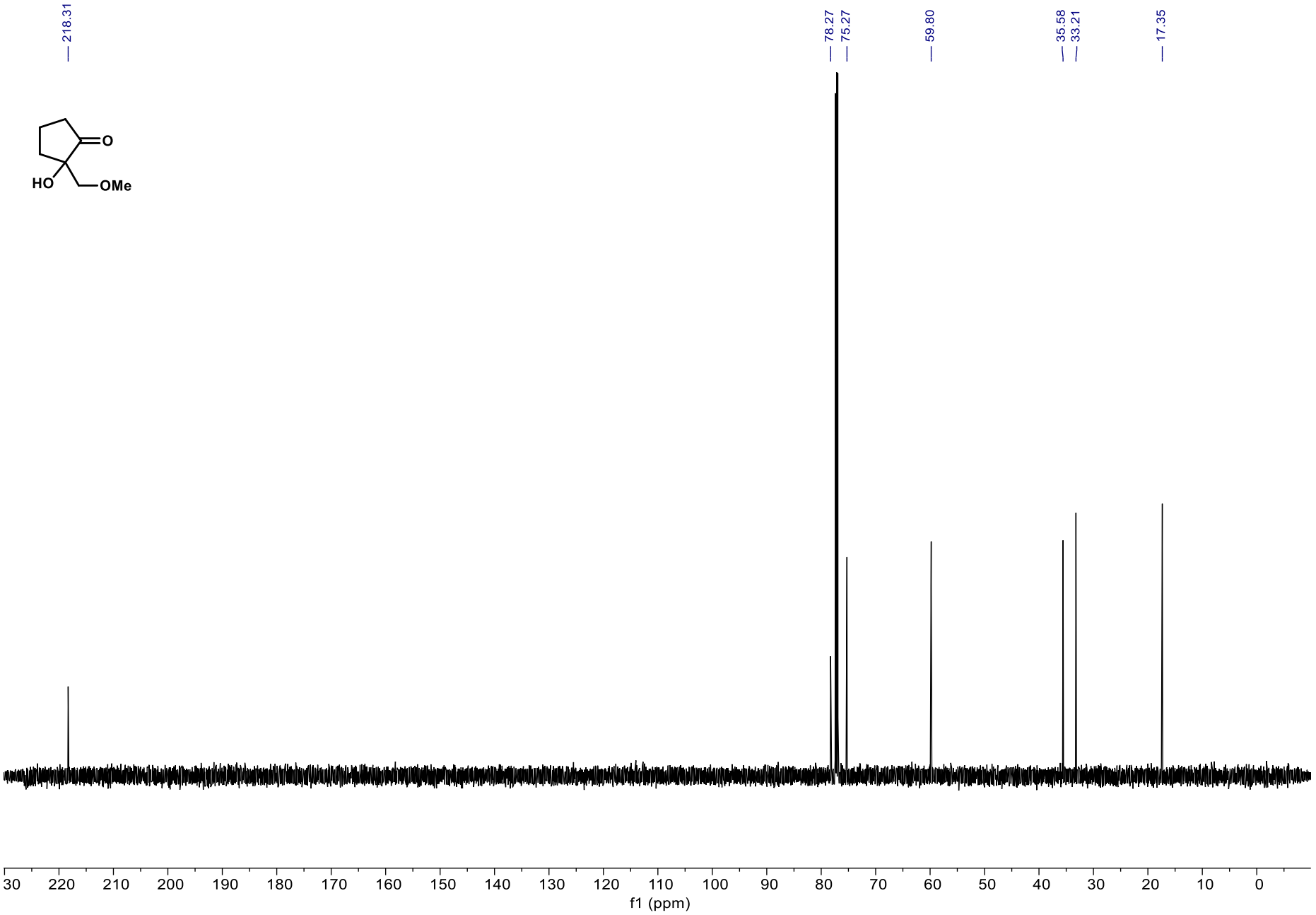
^{13}C NMR of **S2**, 151 MHz, $CDCl_3$



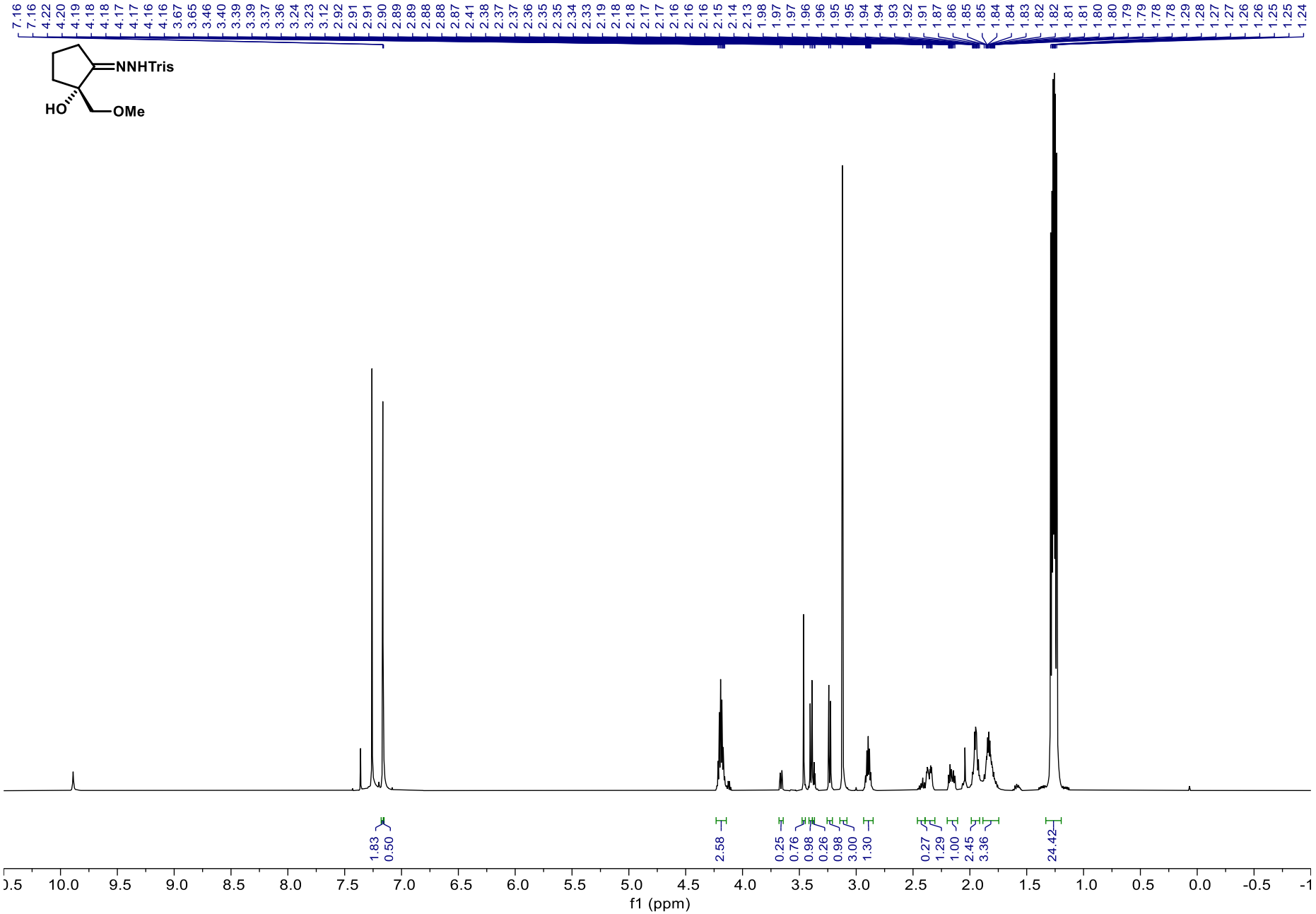
^{1}H NMR of ***rac*-6**, 600 MHz, $CDCl_3$



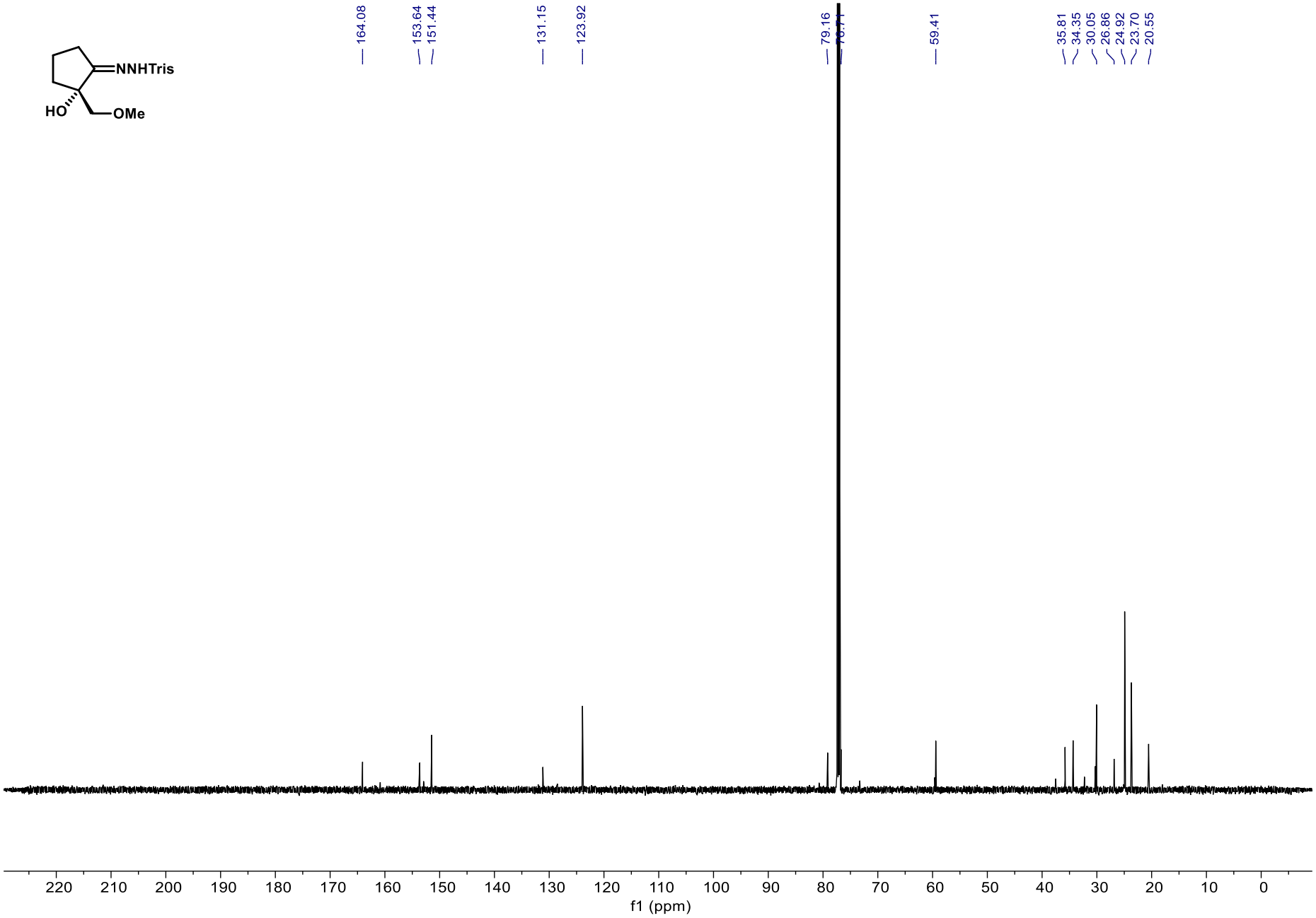
^{13}C NMR of ***rac*-6**, 151 MHz, $CDCl_3$



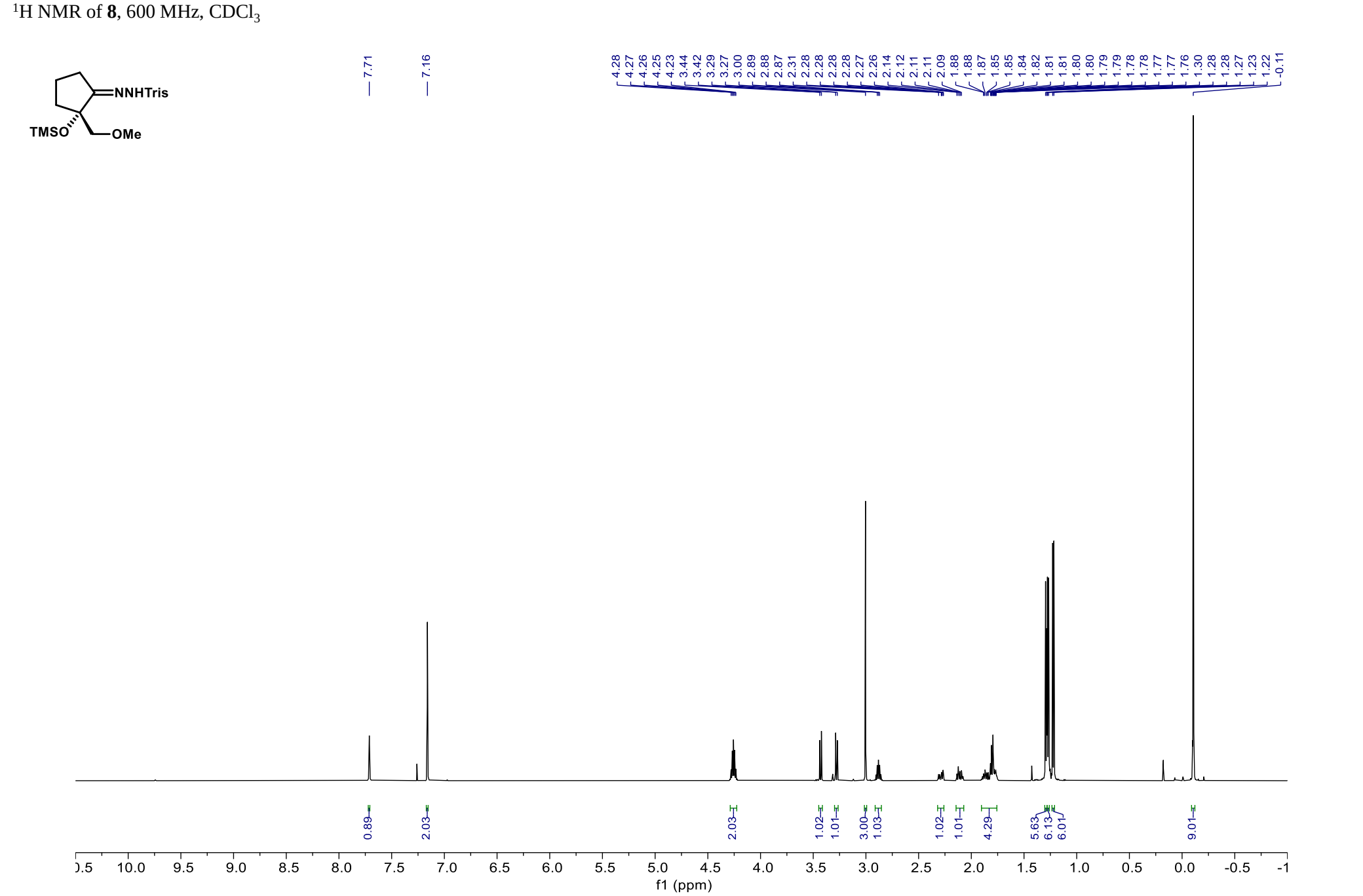
^{1}H NMR of **7**, 600 MHz, $CDCl_3$



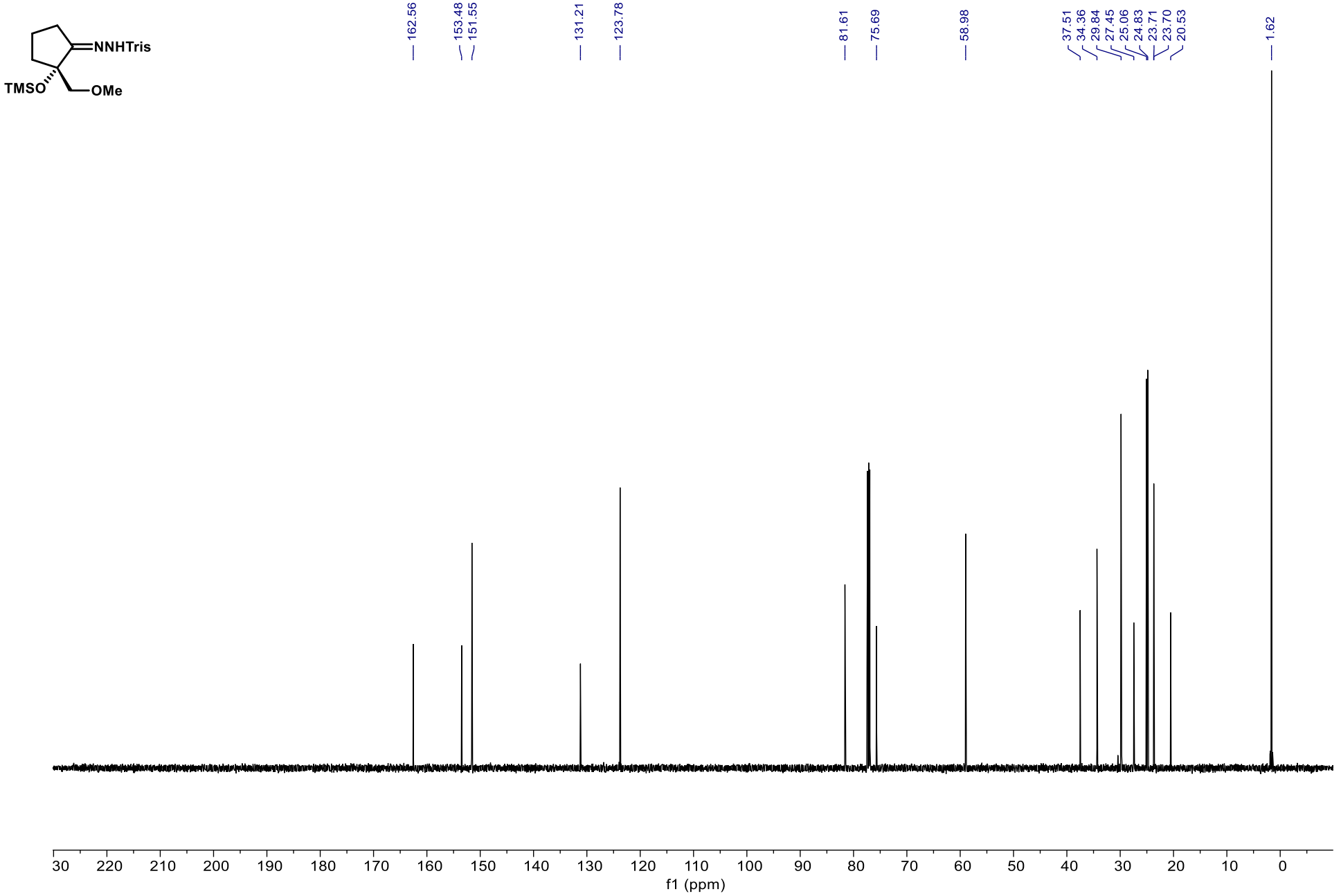
^{13}C NMR of **7**, 151 MHz, $CDCl_3$



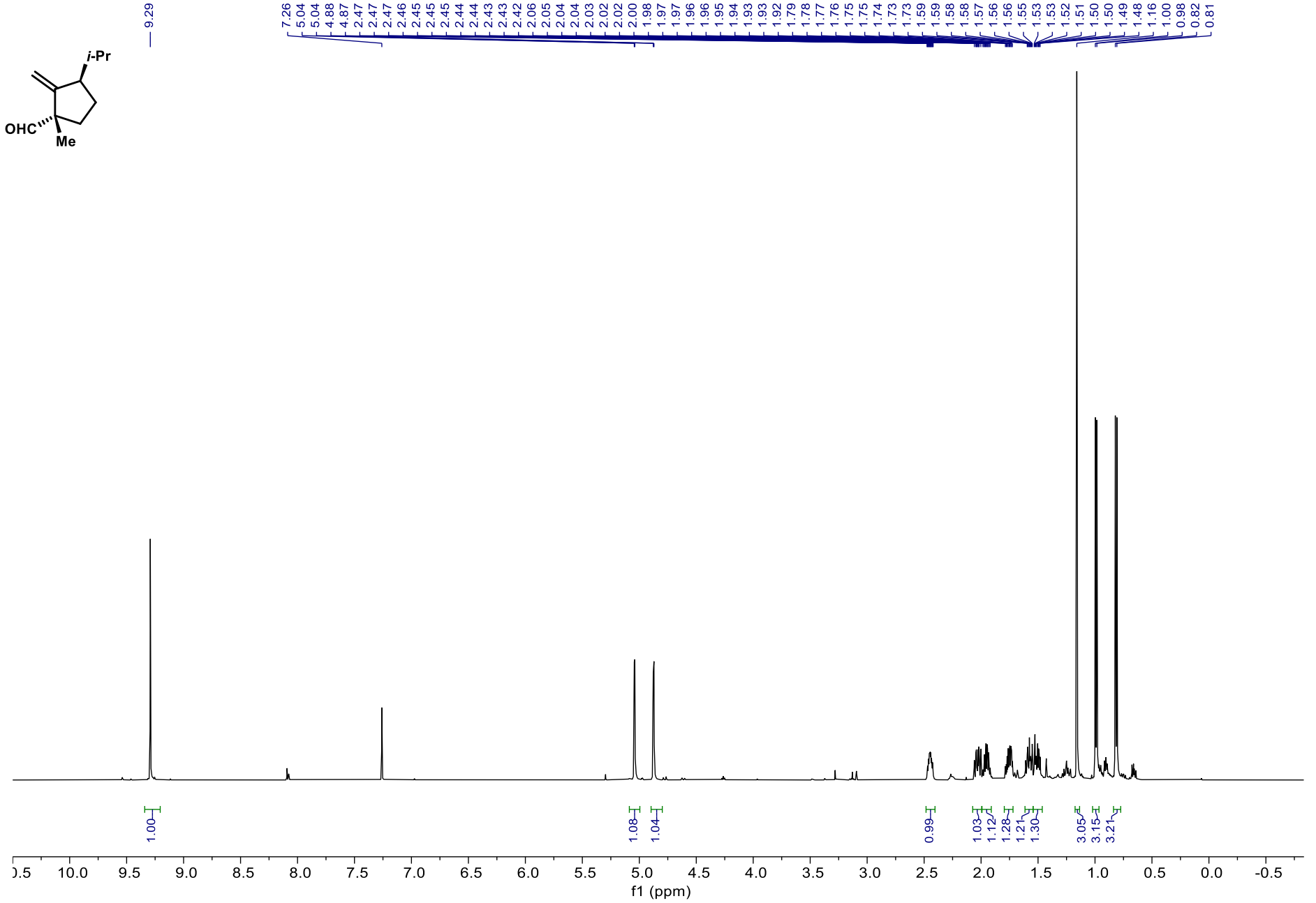
^{1}H NMR of **8**, 600 MHz, $CDCl_3$



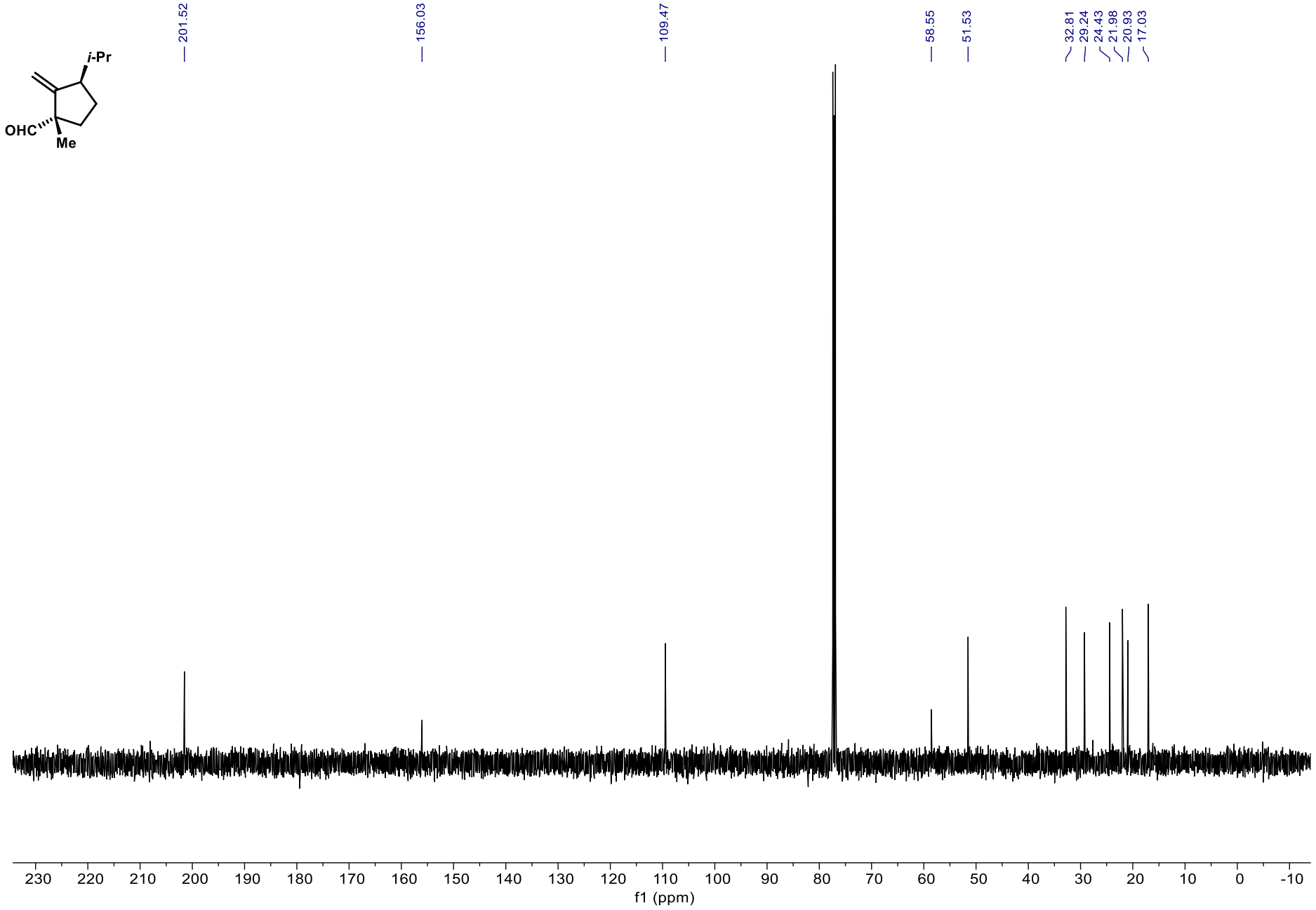
^{13}C NMR of **8**, 151 MHz, $CDCl_3$



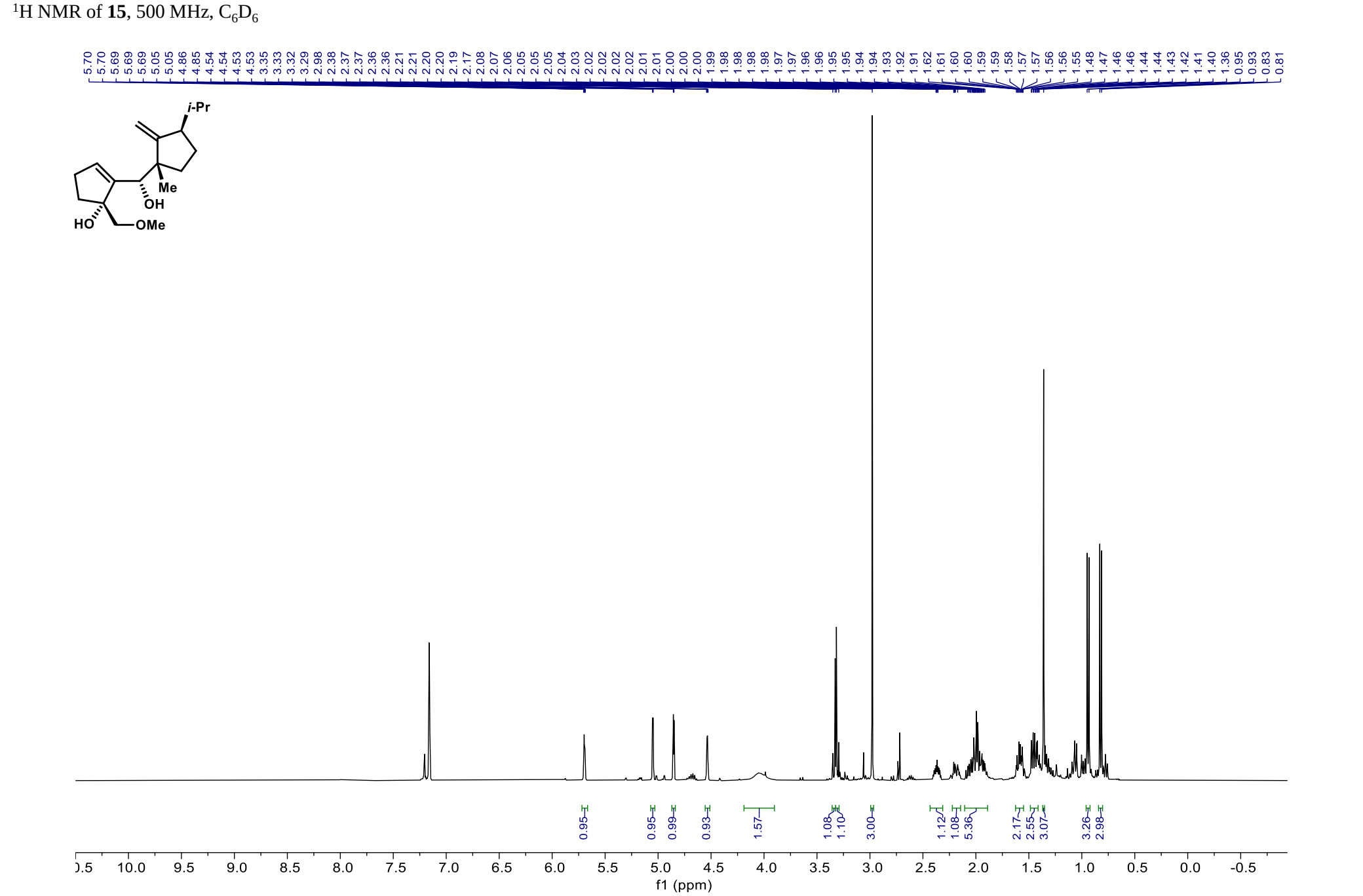
^{1}H NMR of **12**, 500 MHz, $CDCl_3$



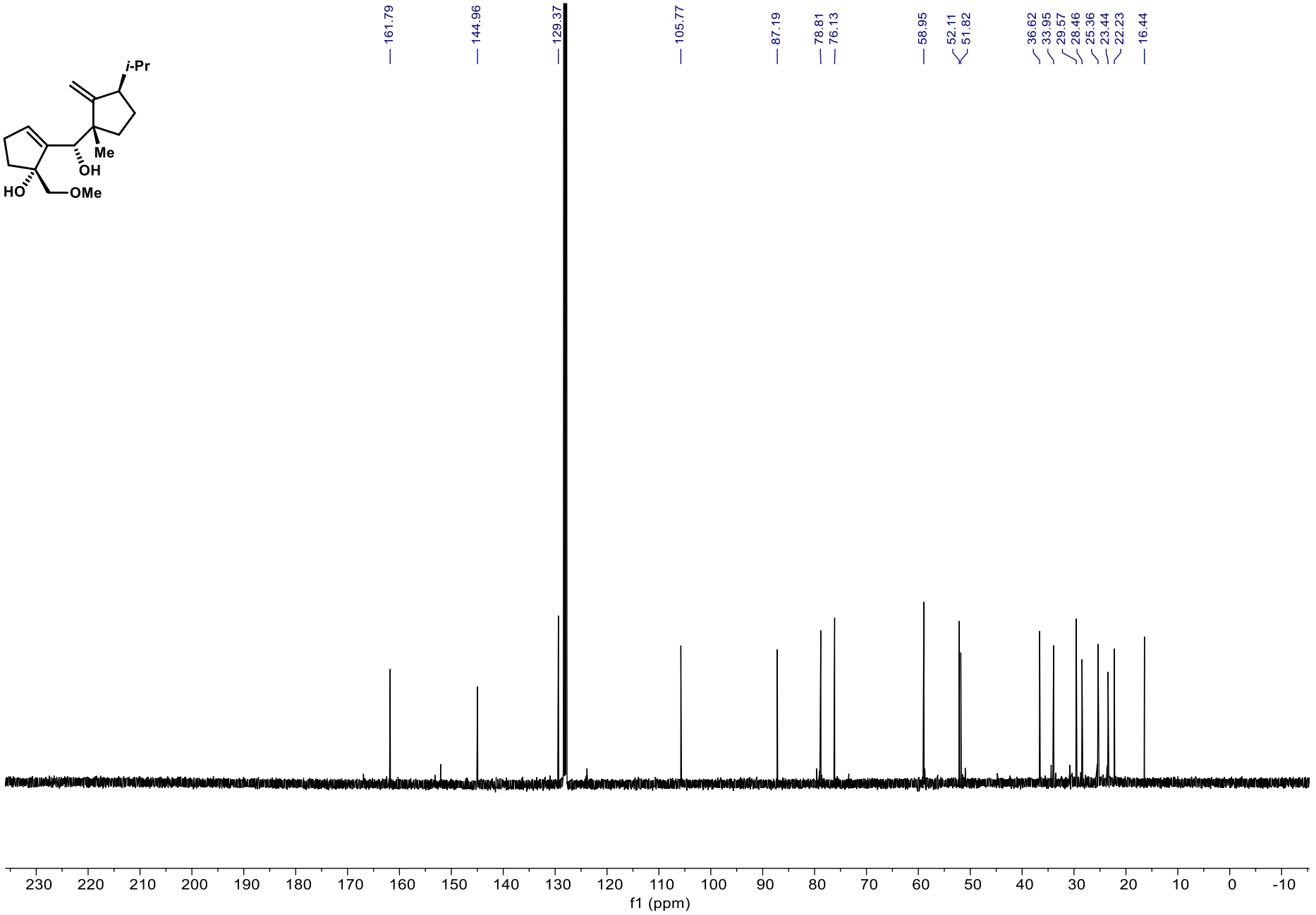
^{13}C NMR of **12**, 126 MHz, $CDCl_3$



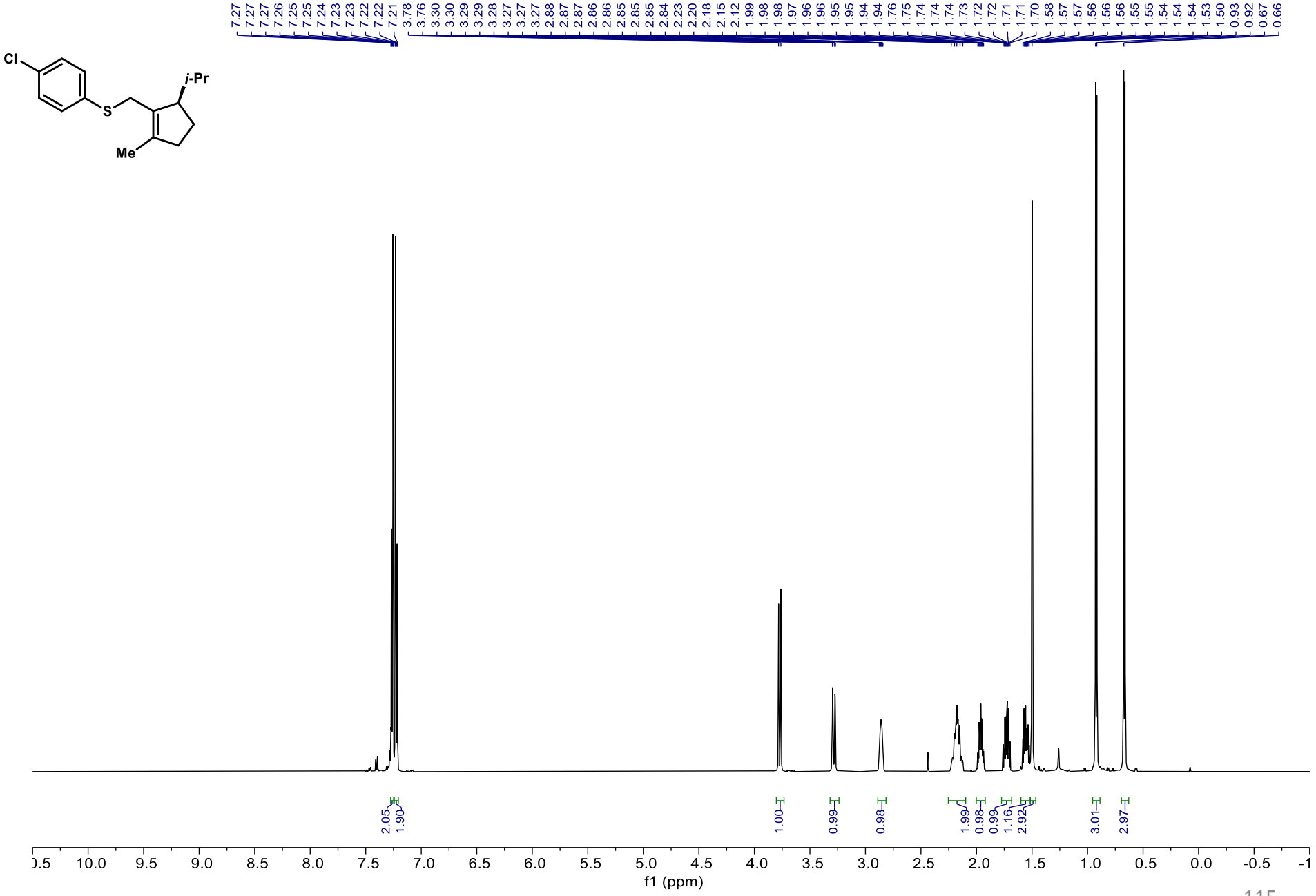
^{1}H NMR of **15**, 500 MHz, C_6D_6



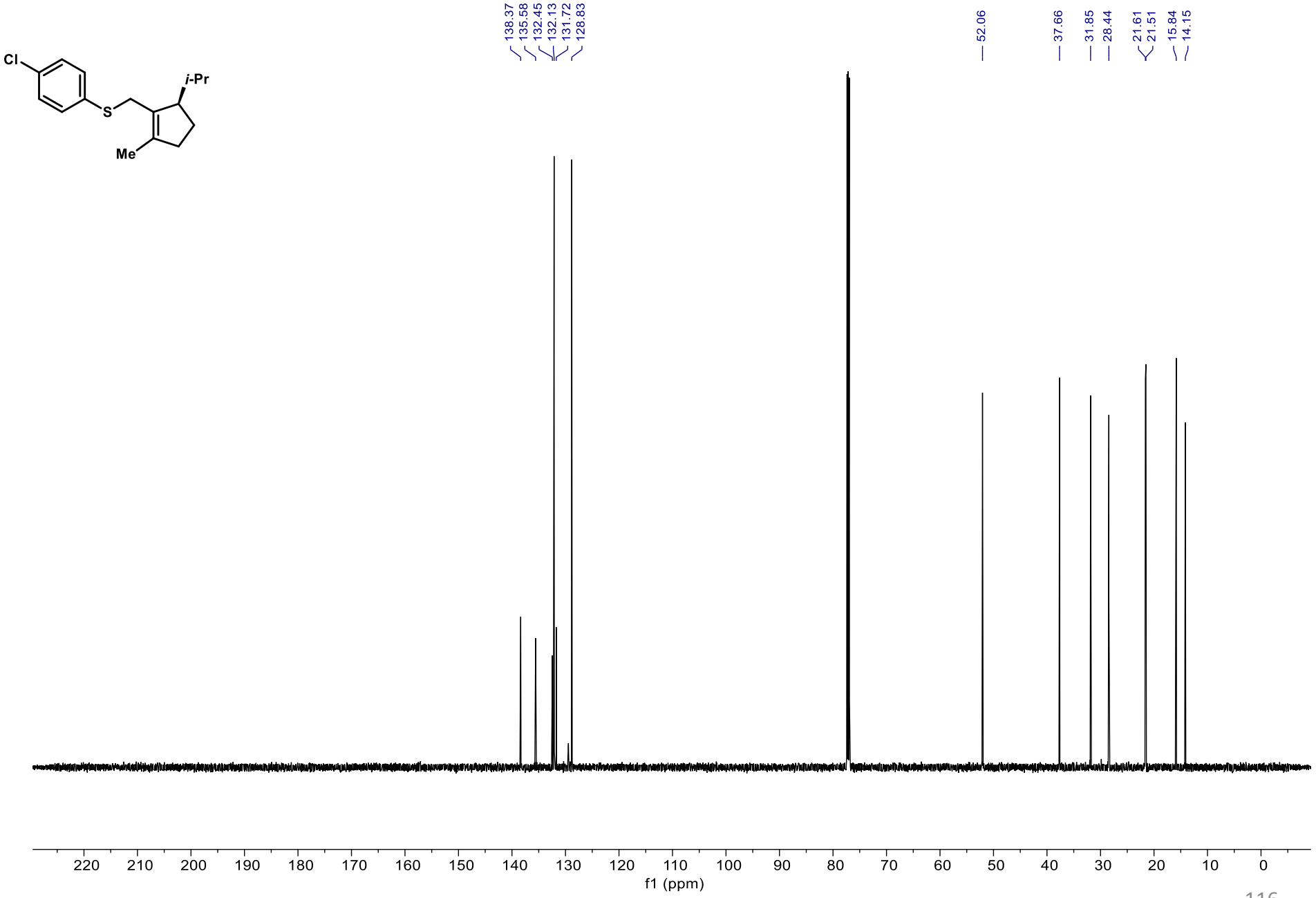
^{13}C NMR of **15**, 126 MHz, C_6D_6



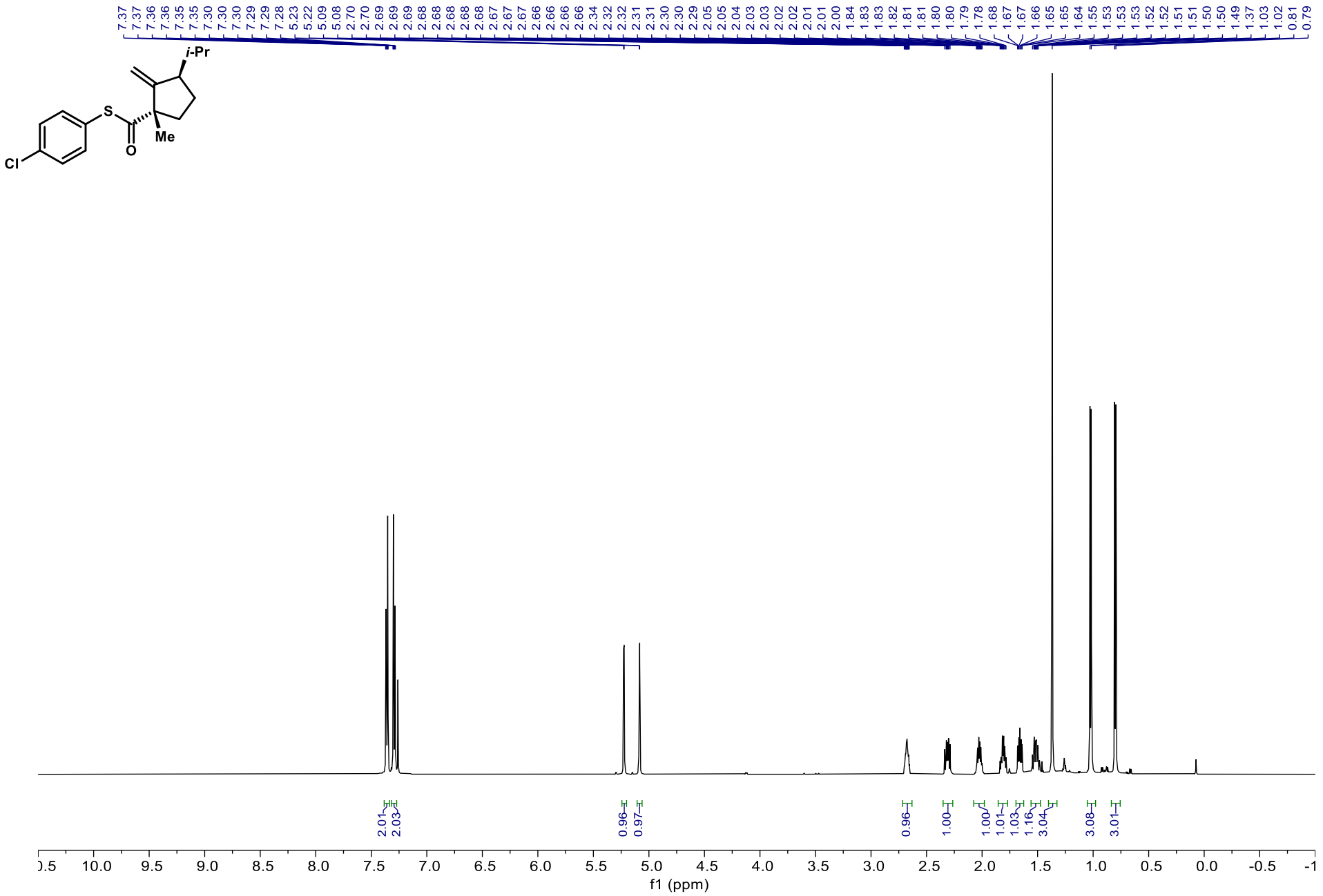
^{1}H NMR of **16**, 600 MHz, $CDCl_3$



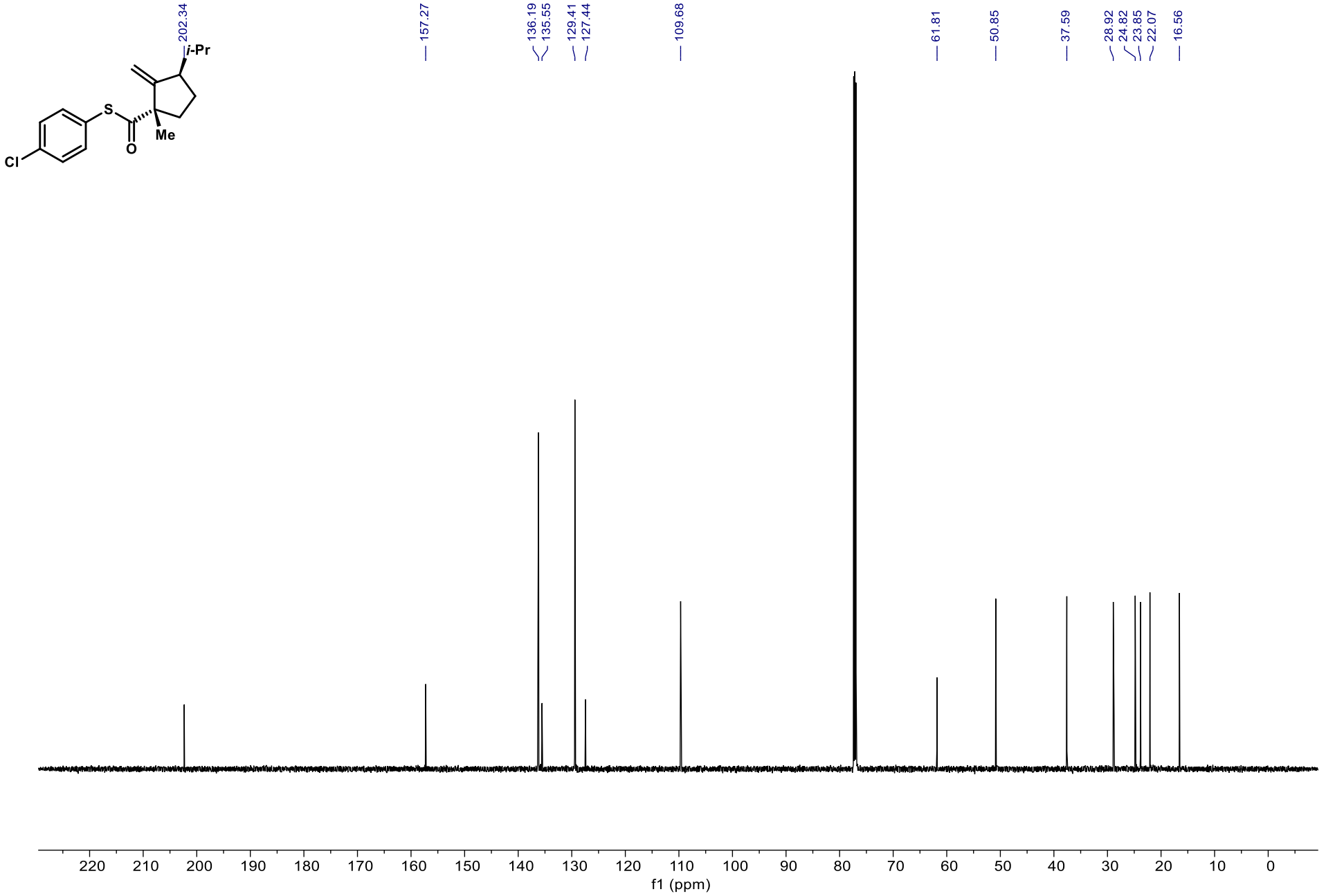
^{13}C NMR of **16**, 151 MHz, $CDCl_3$



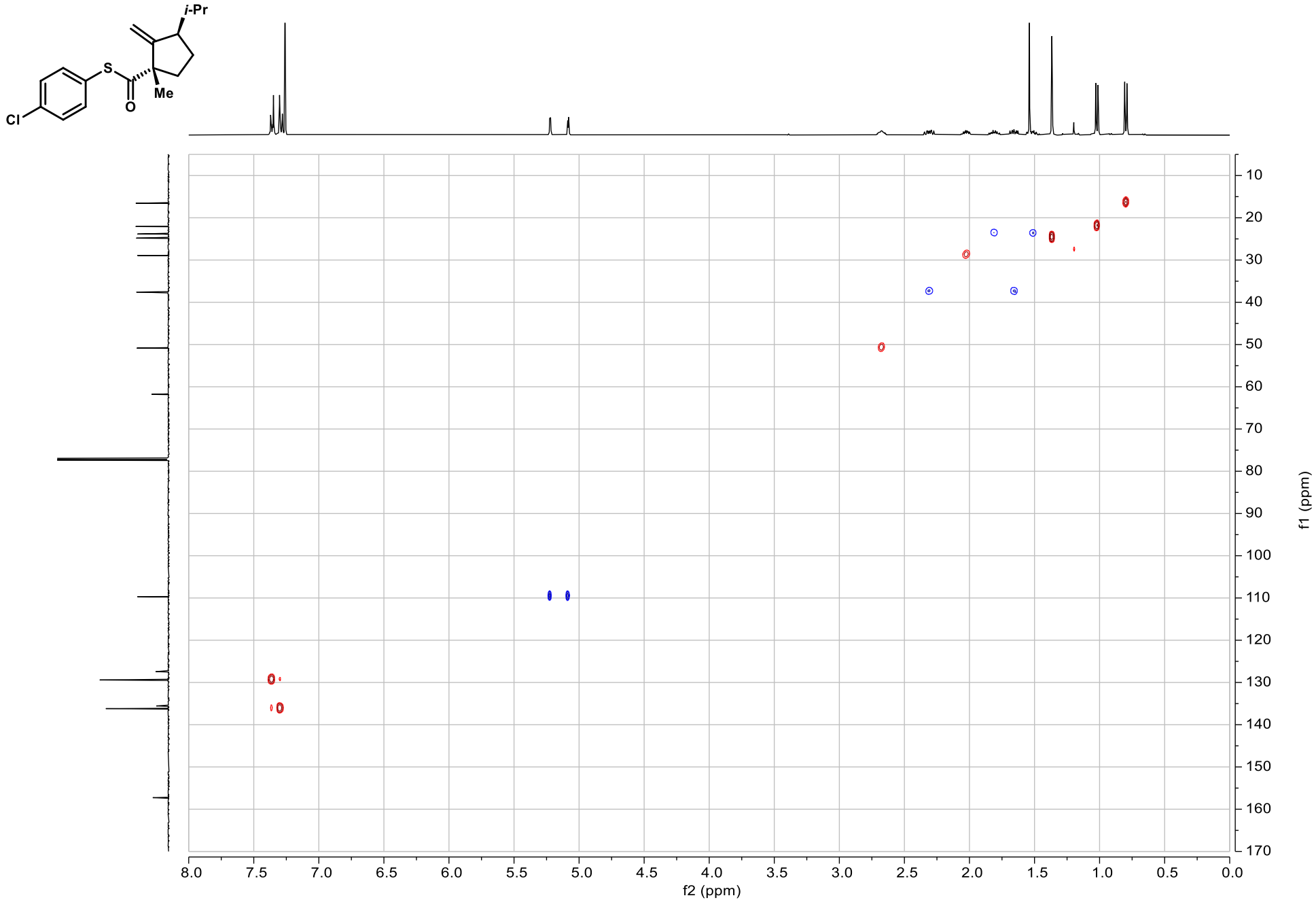
^{1}H NMR of **19**, 600 MHz, $CDCl_3$



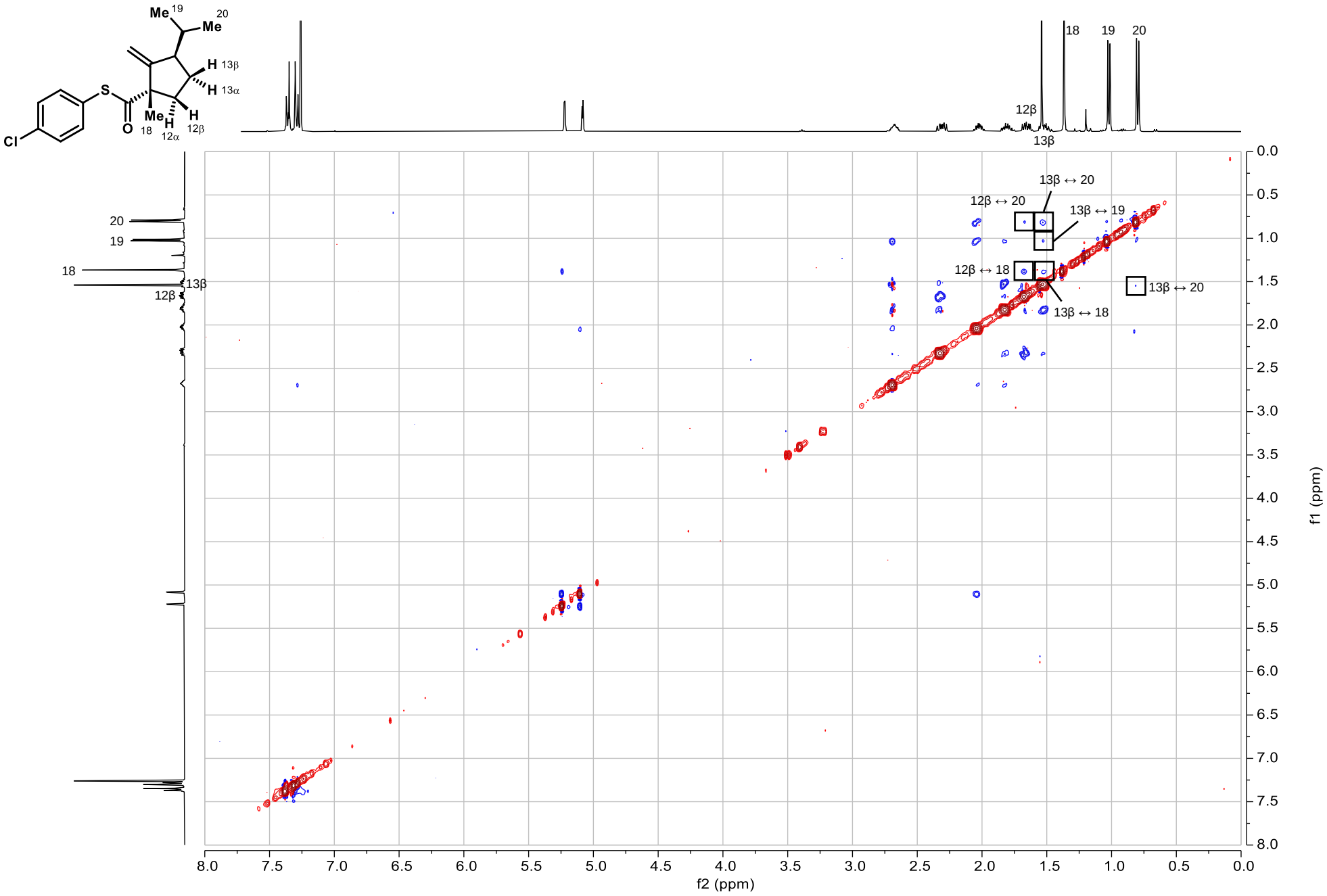
^{13}C NMR of **19**, 151 MHz, $CDCl_3$



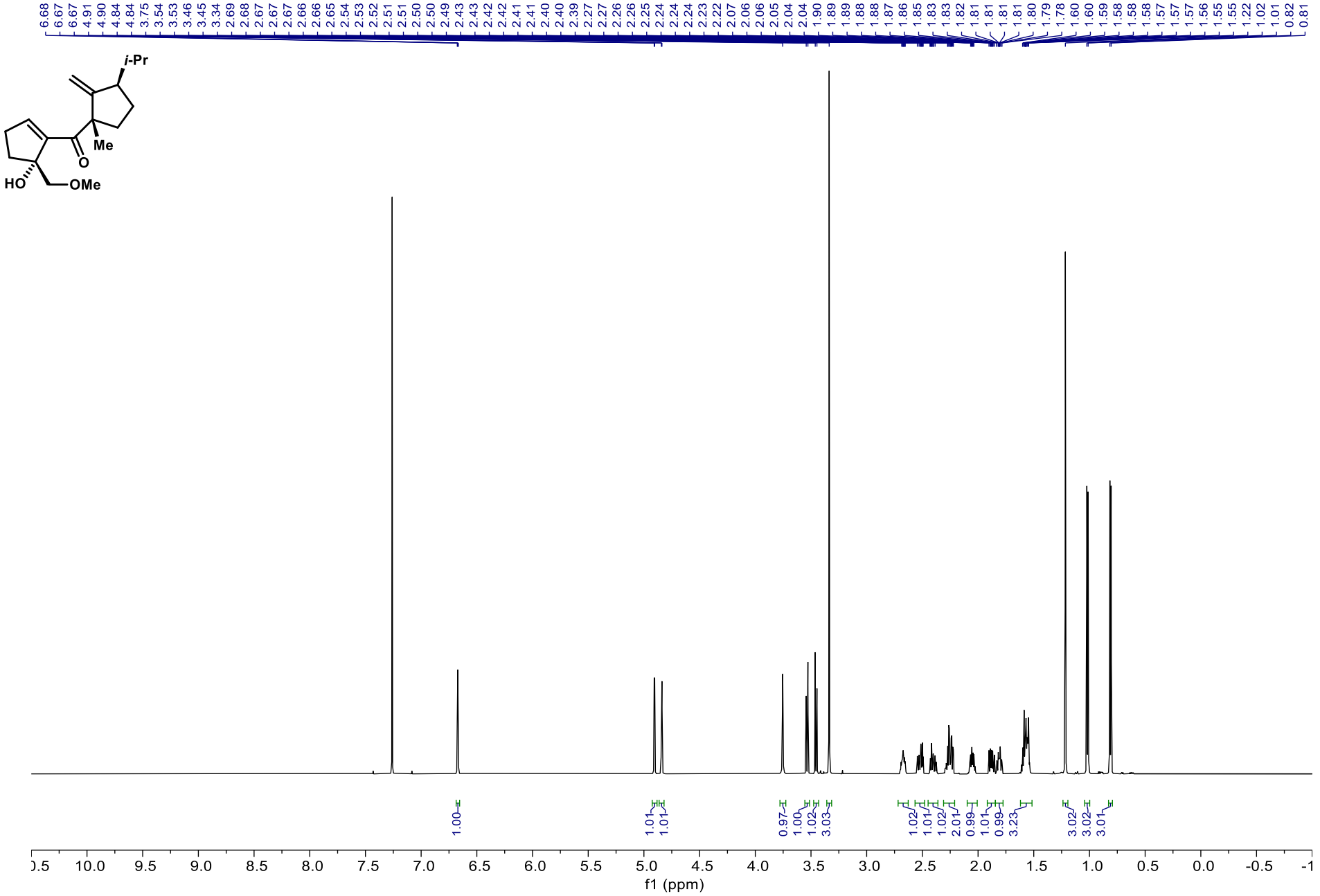
HSQC of **19**, 600 MHz, $CDCl_3$



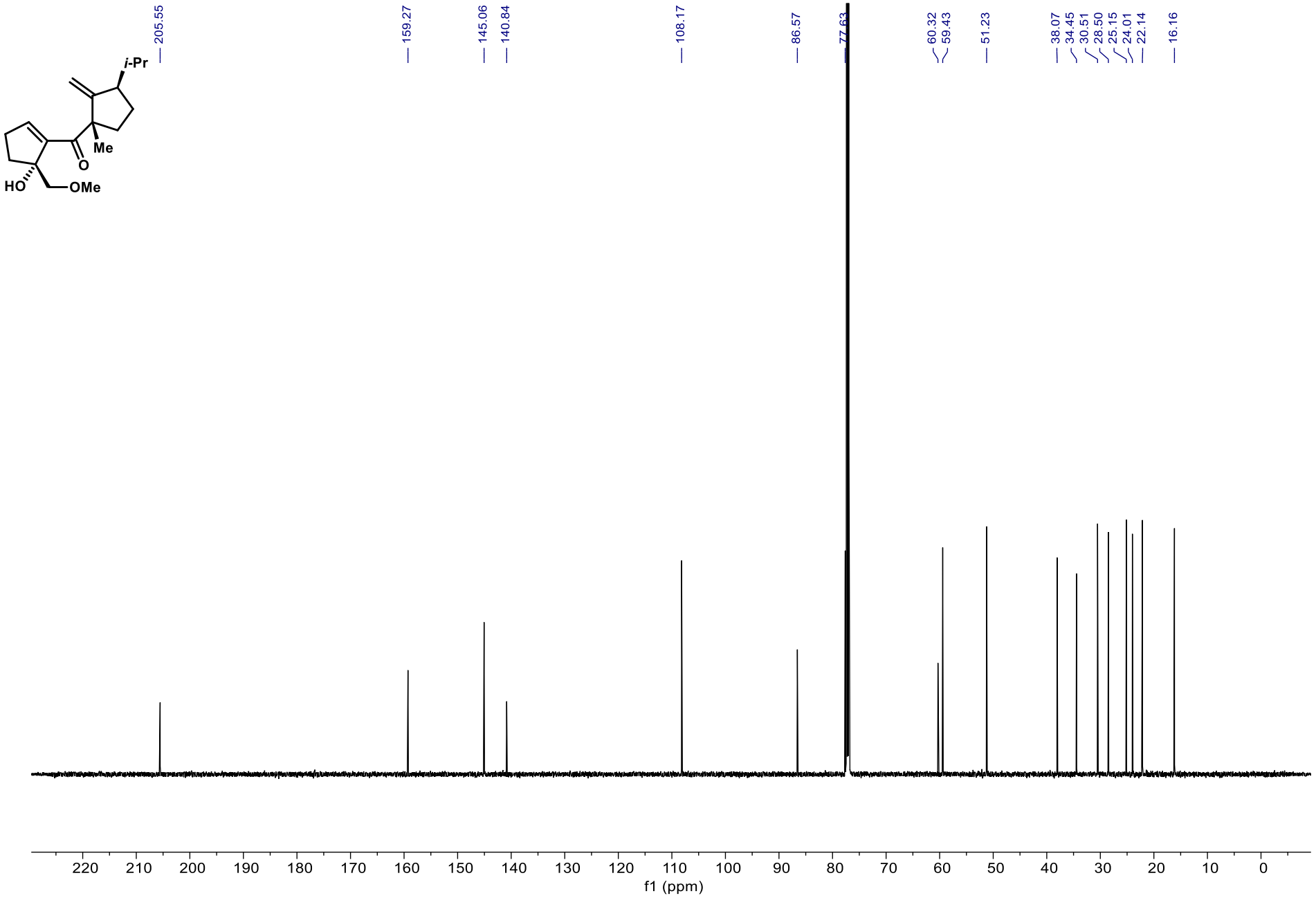
NOESY of **19**, 600 MHz, $CDCl_3$



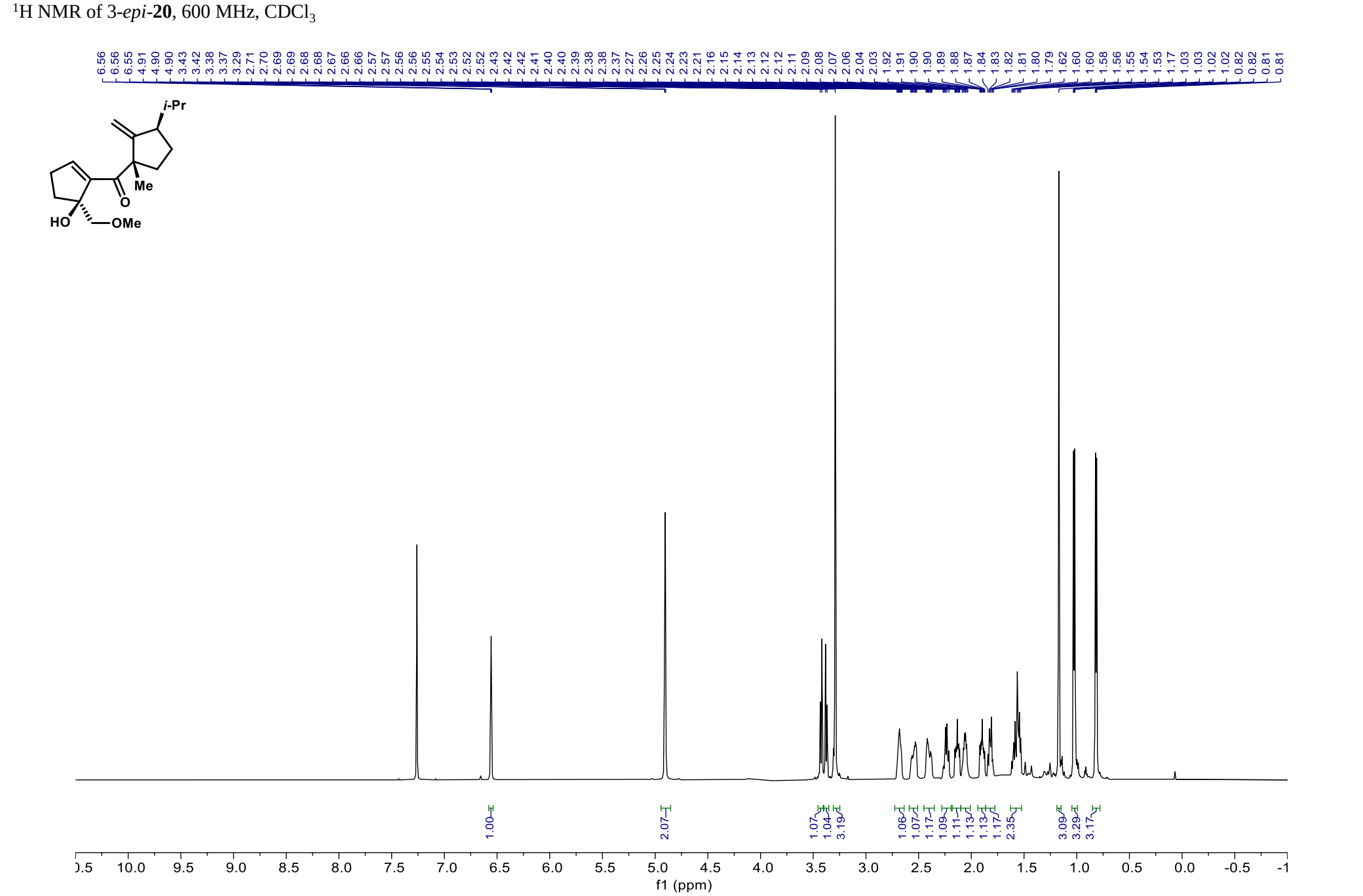
^{1}H NMR of **20**, 600 MHz, $CDCl_3$



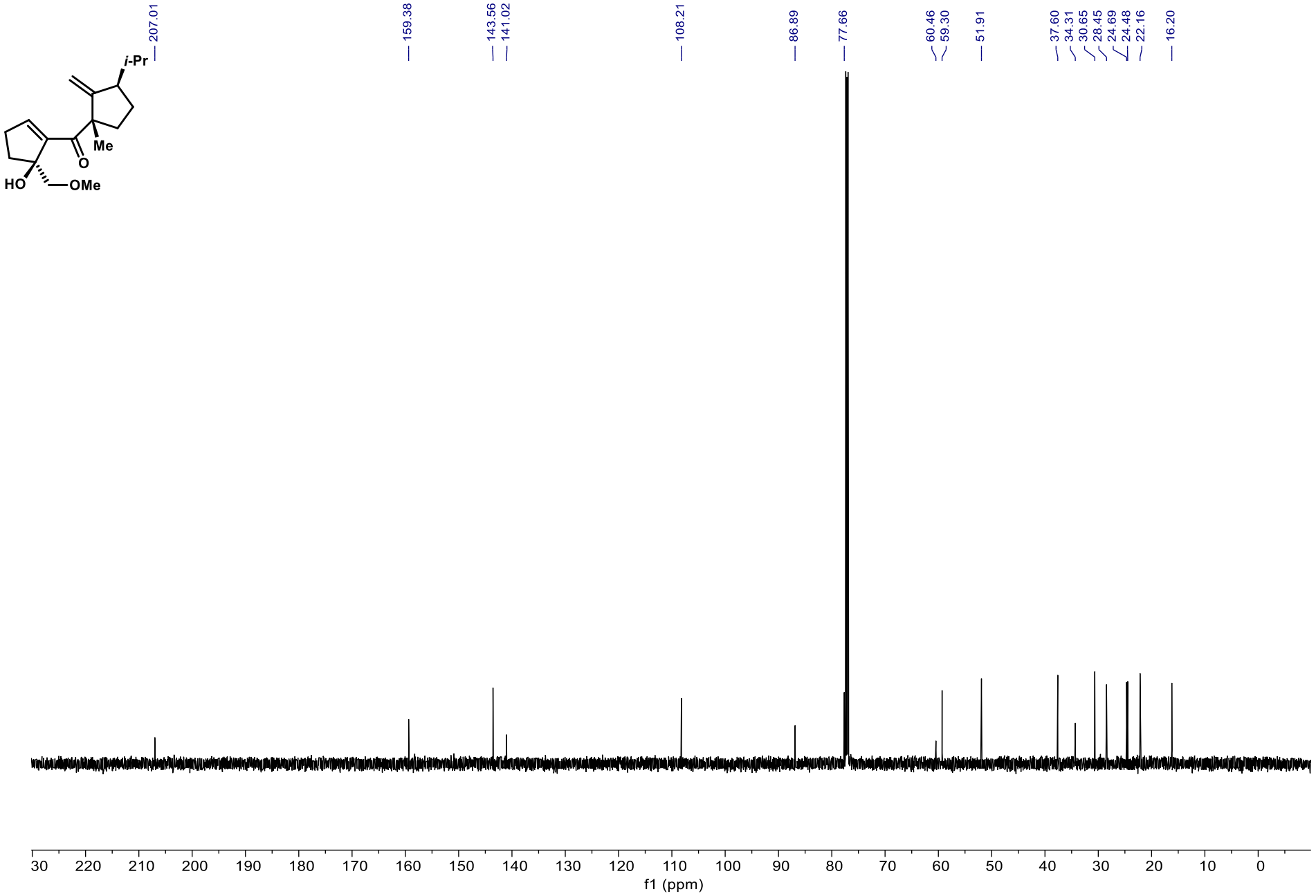
^{13}C NMR of **20**, 151 MHz, $CDCl_3$



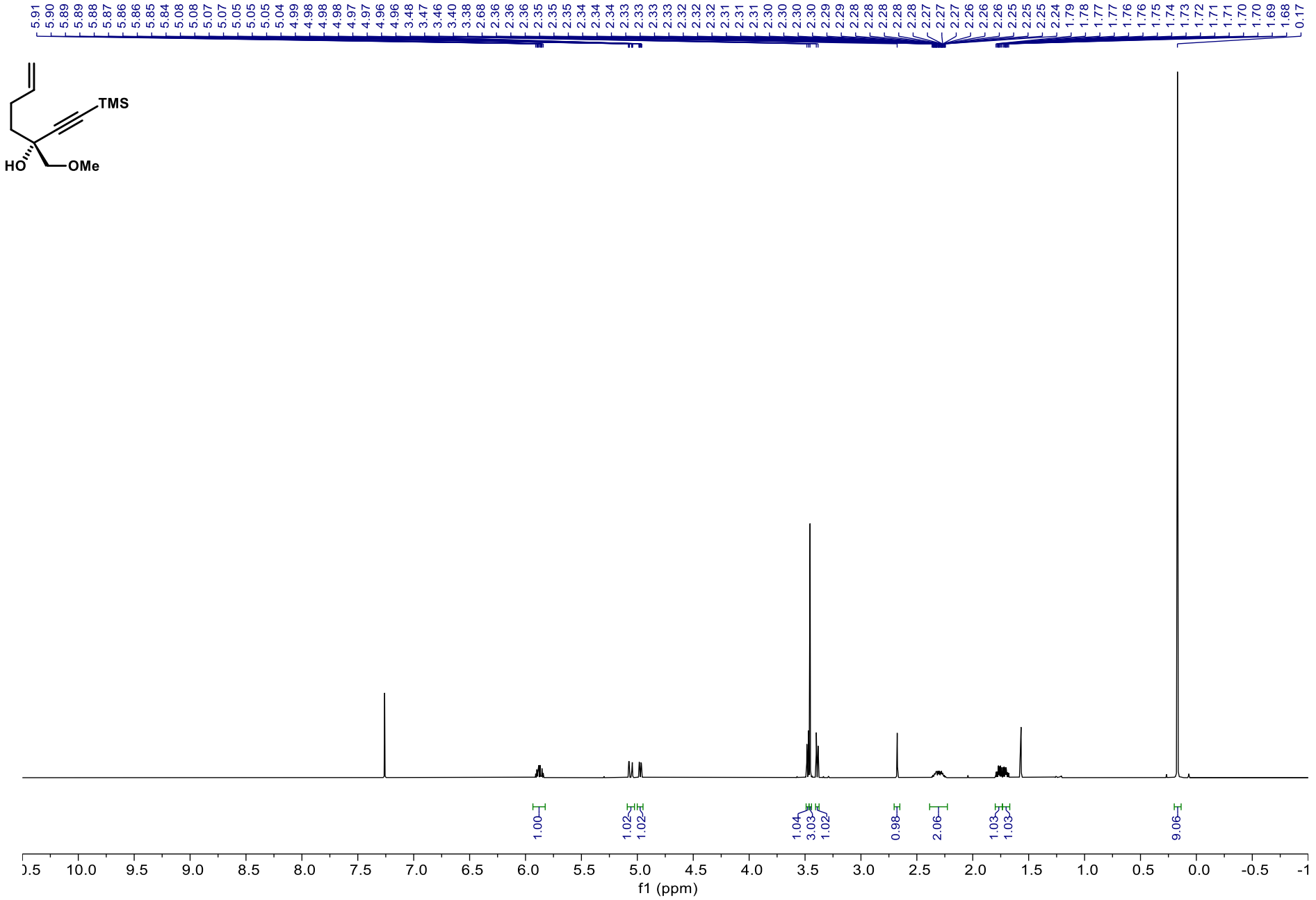
^{1}H NMR of 3-*epi*-**20**, 600 MHz, $CDCl_3$



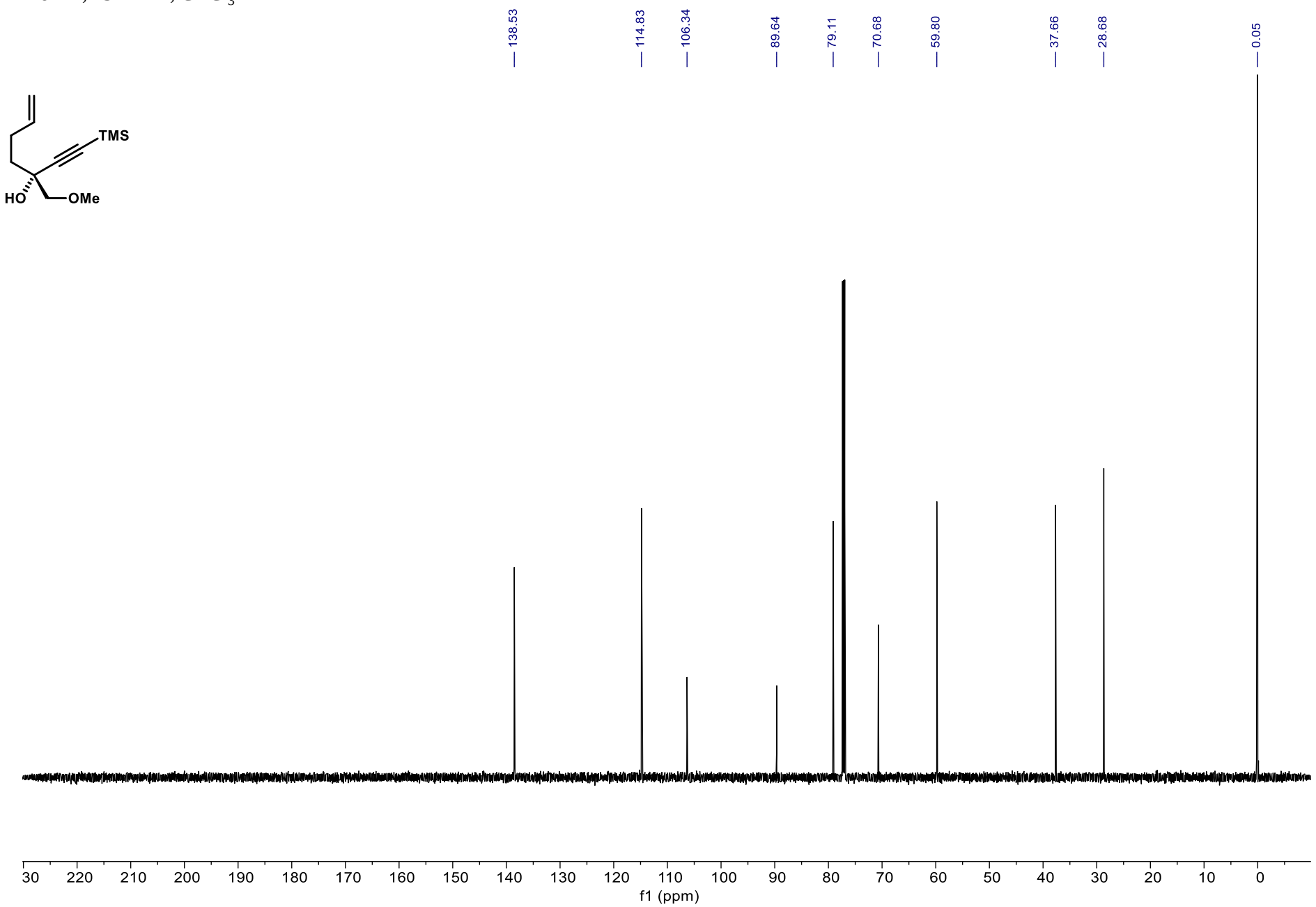
^{13}C NMR of 3-*epi*-**20**, 151 MHz, $CDCl_3$



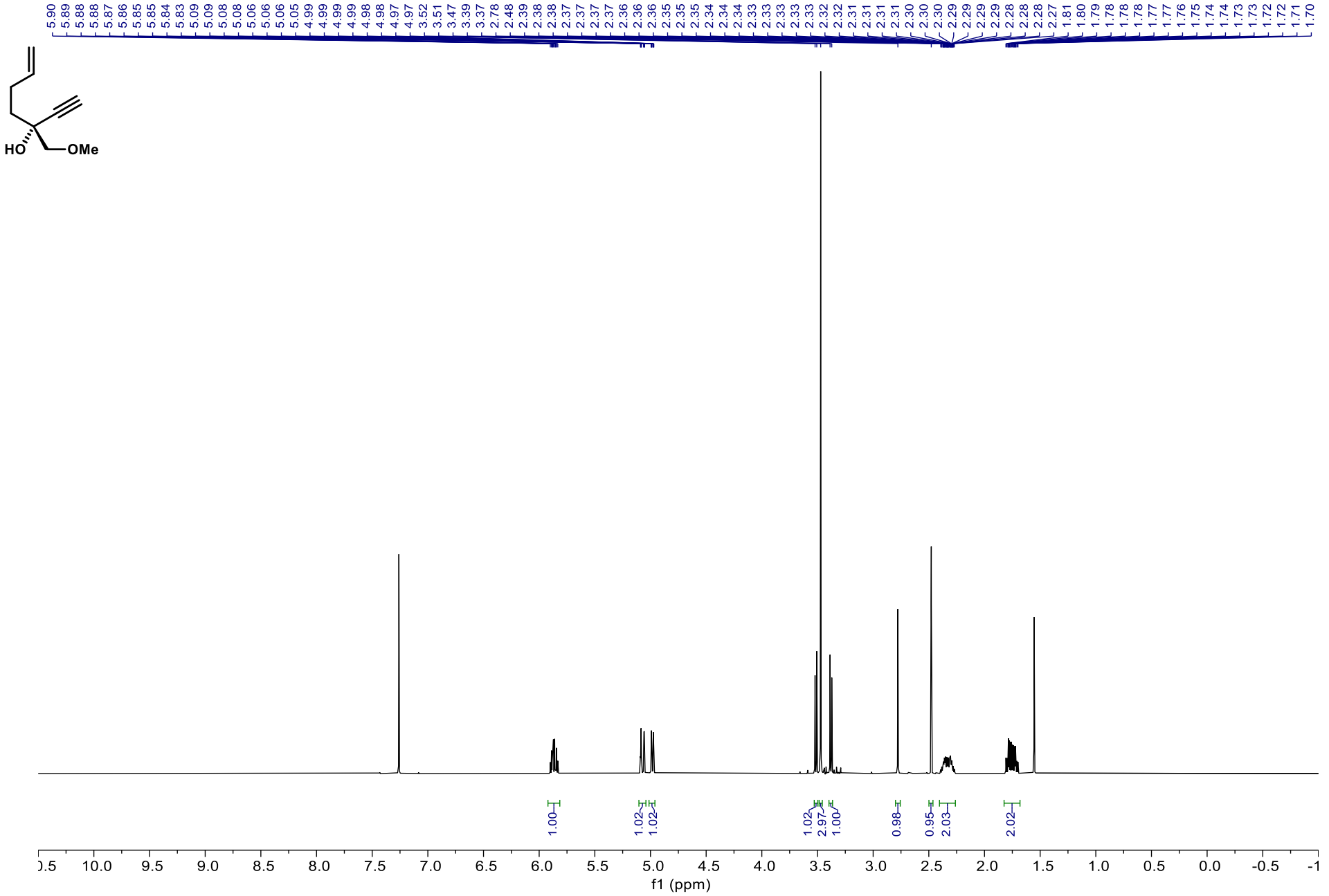
^{1}H NMR of **24**, 600 MHz, $CDCl_3$



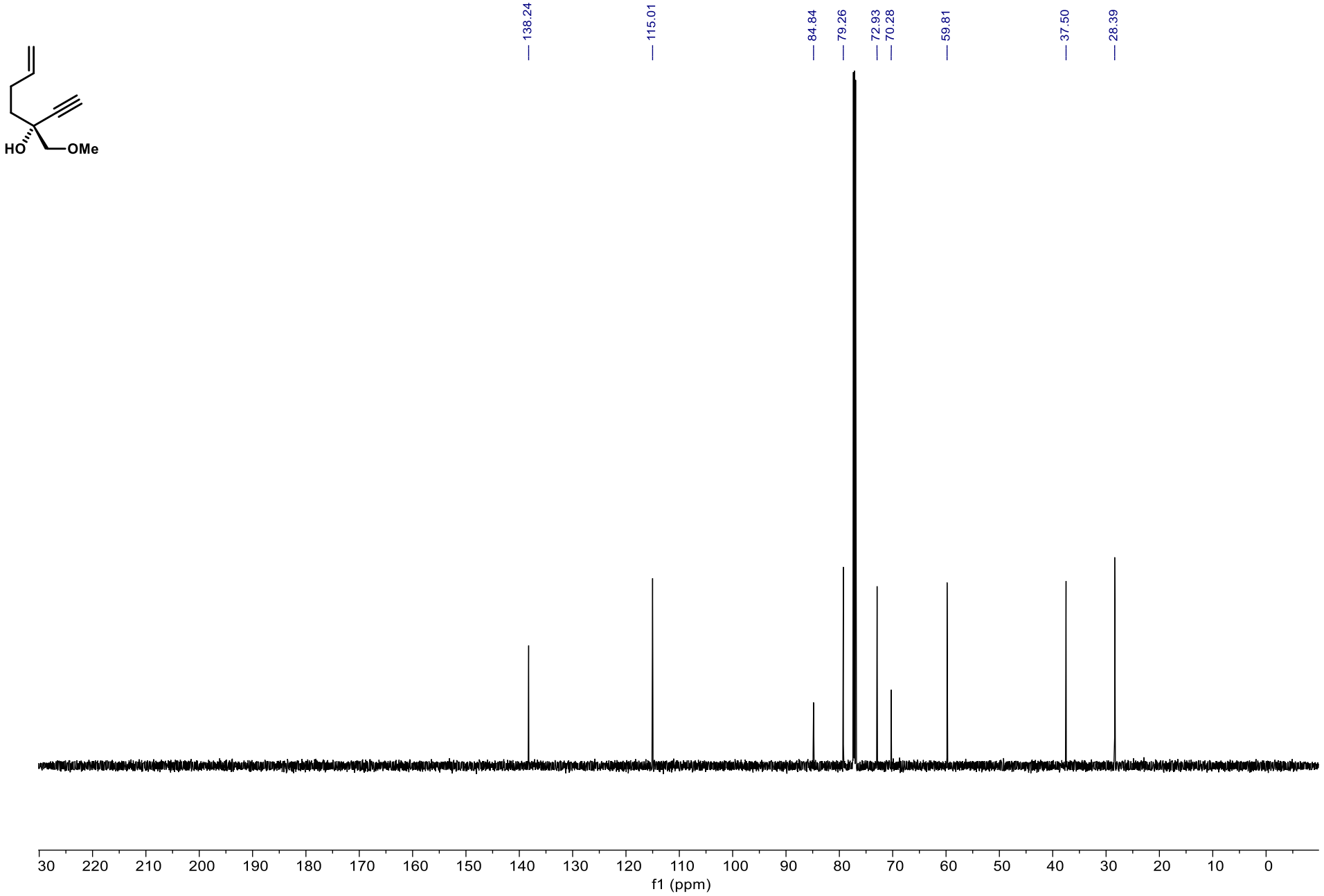
^{13}C NMR of **24**, 151 MHz, $CDCl_3$



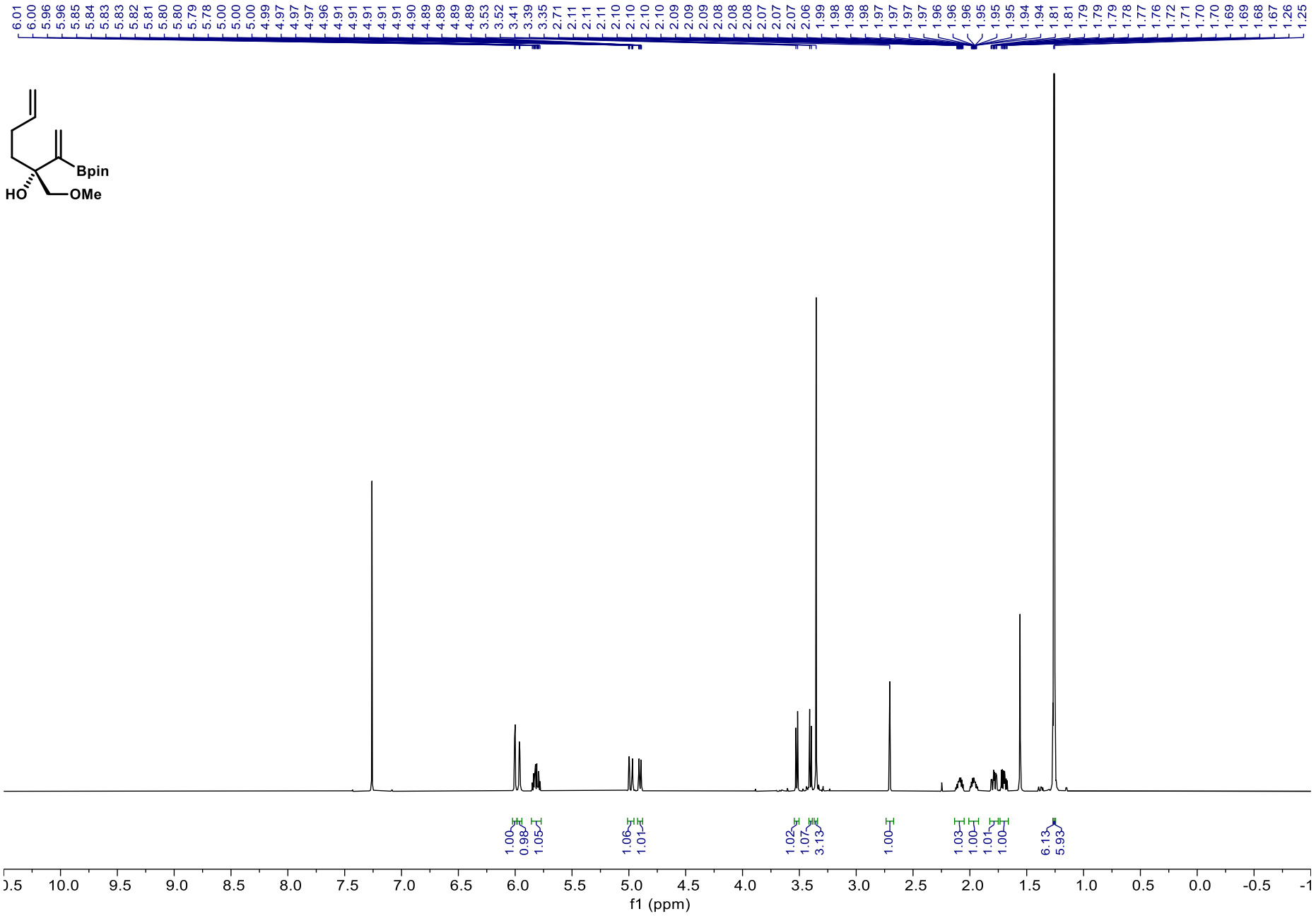
^{1}H NMR of **25**, 600 MHz, $CDCl_3$



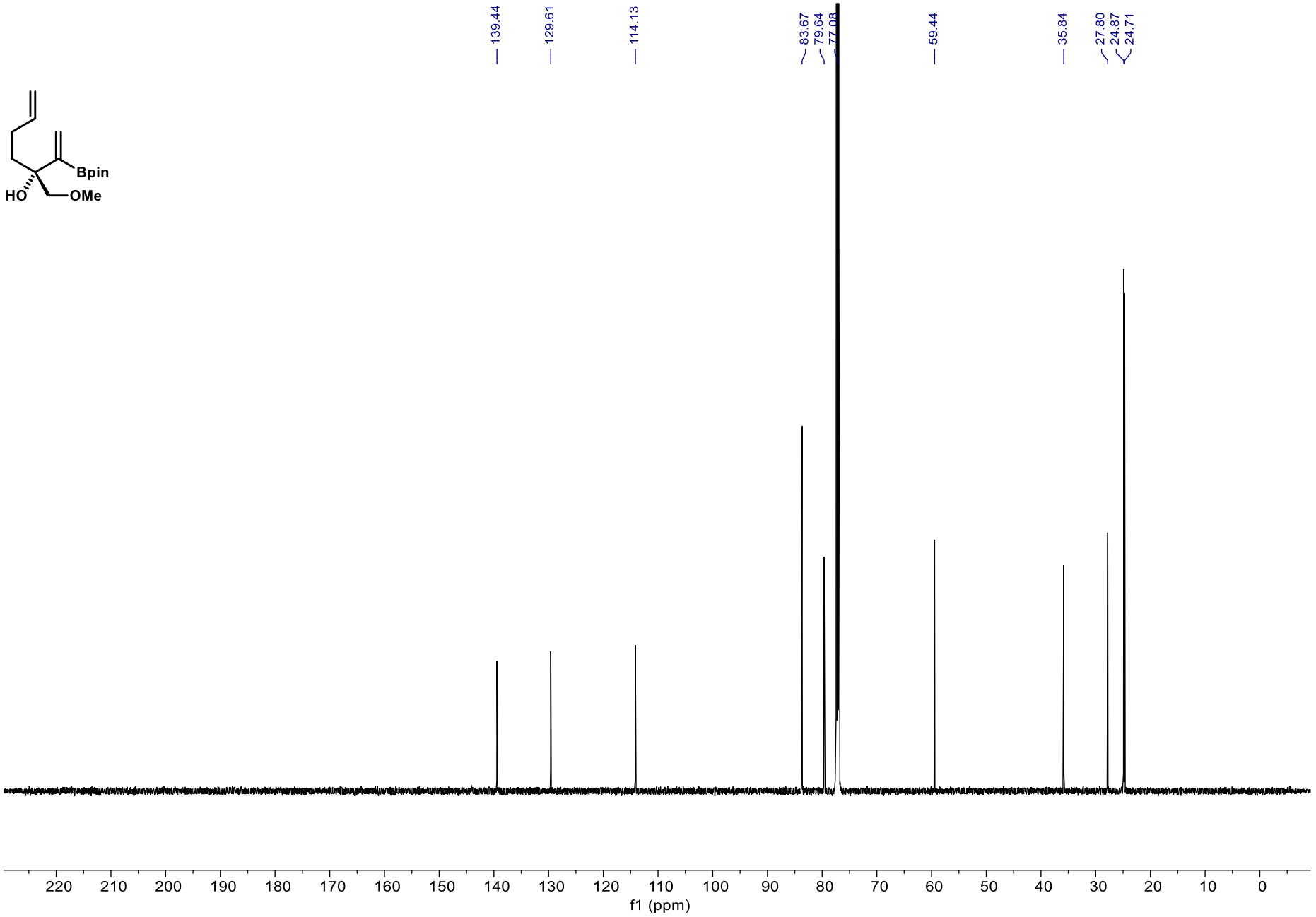
^{13}C NMR of **25**, 151 MHz, $CDCl_3$



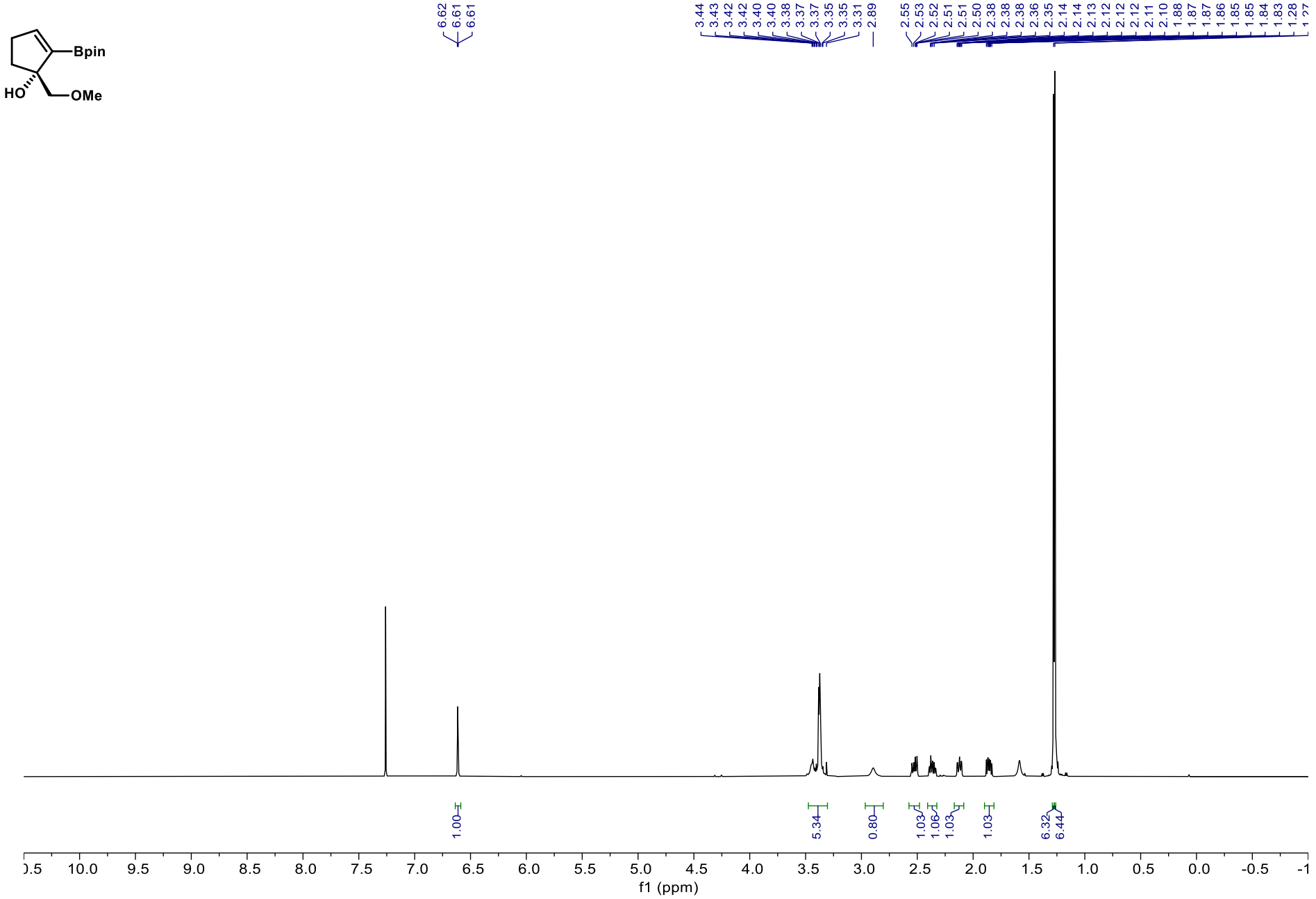
^{1}H NMR of **26**, 600 MHz, $CDCl_3$



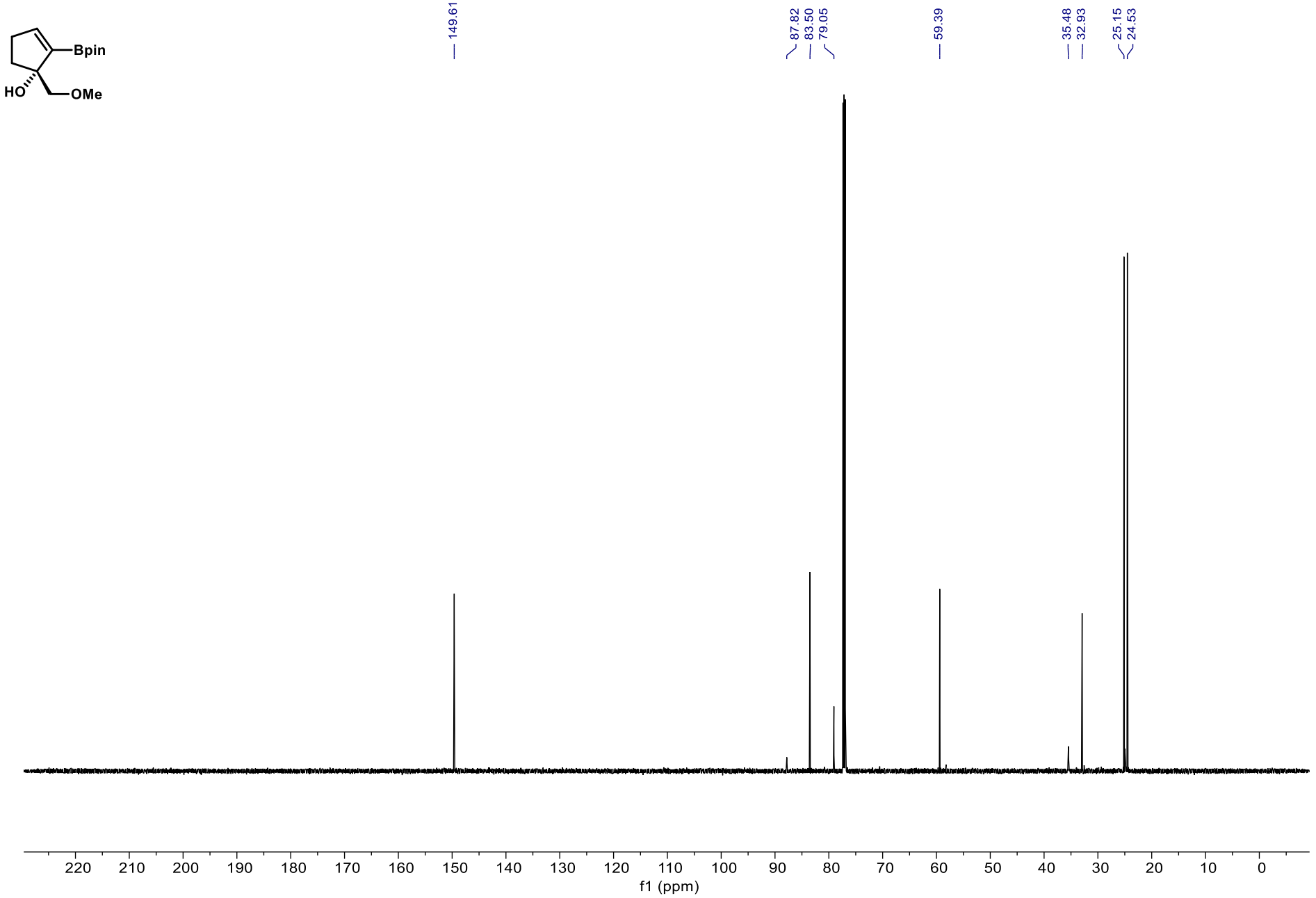
^{13}C NMR of **26**, 151 MHz, $CDCl_3$



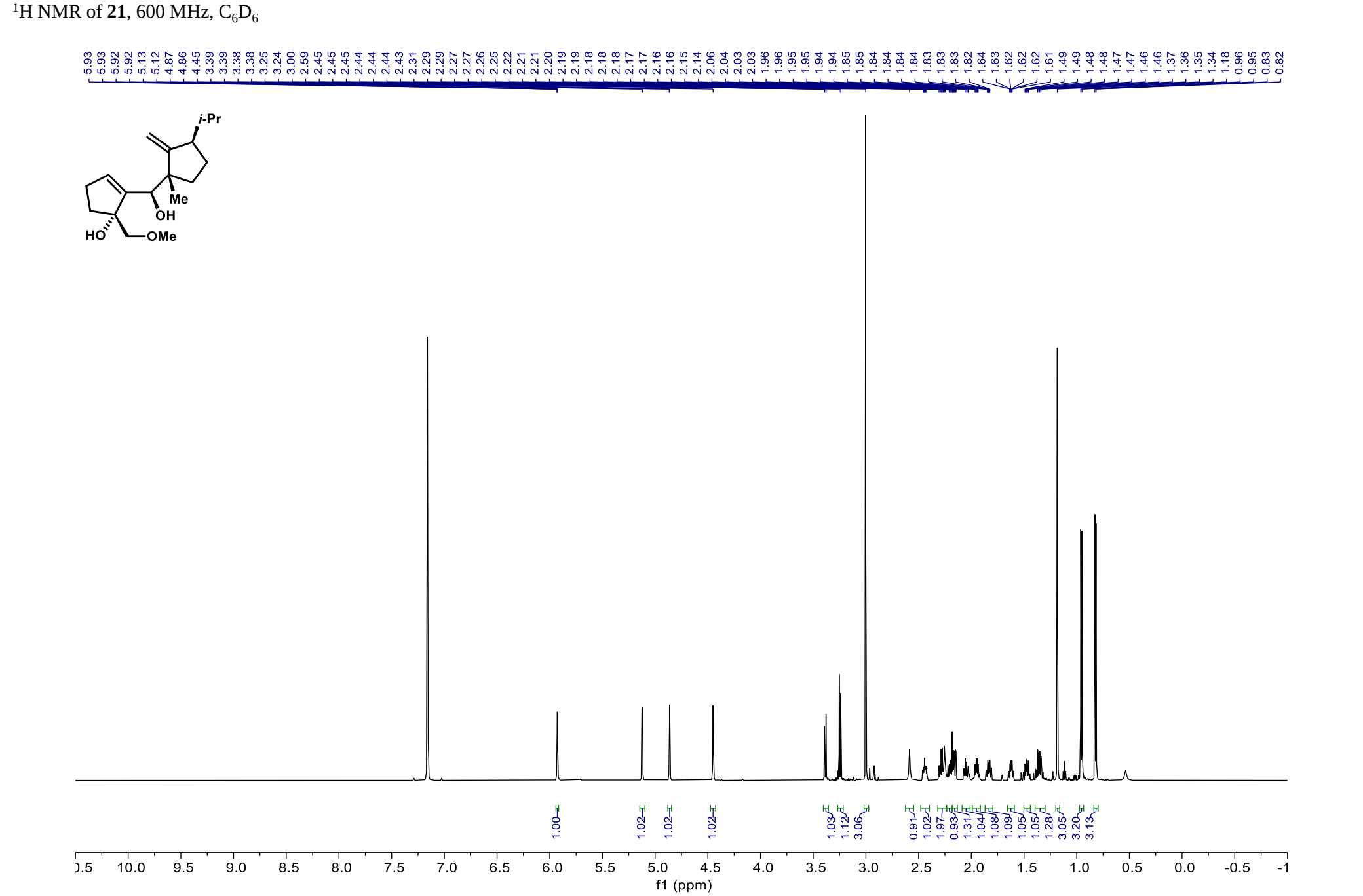
^{1}H NMR of **27**, 600 MHz, $CDCl_3$



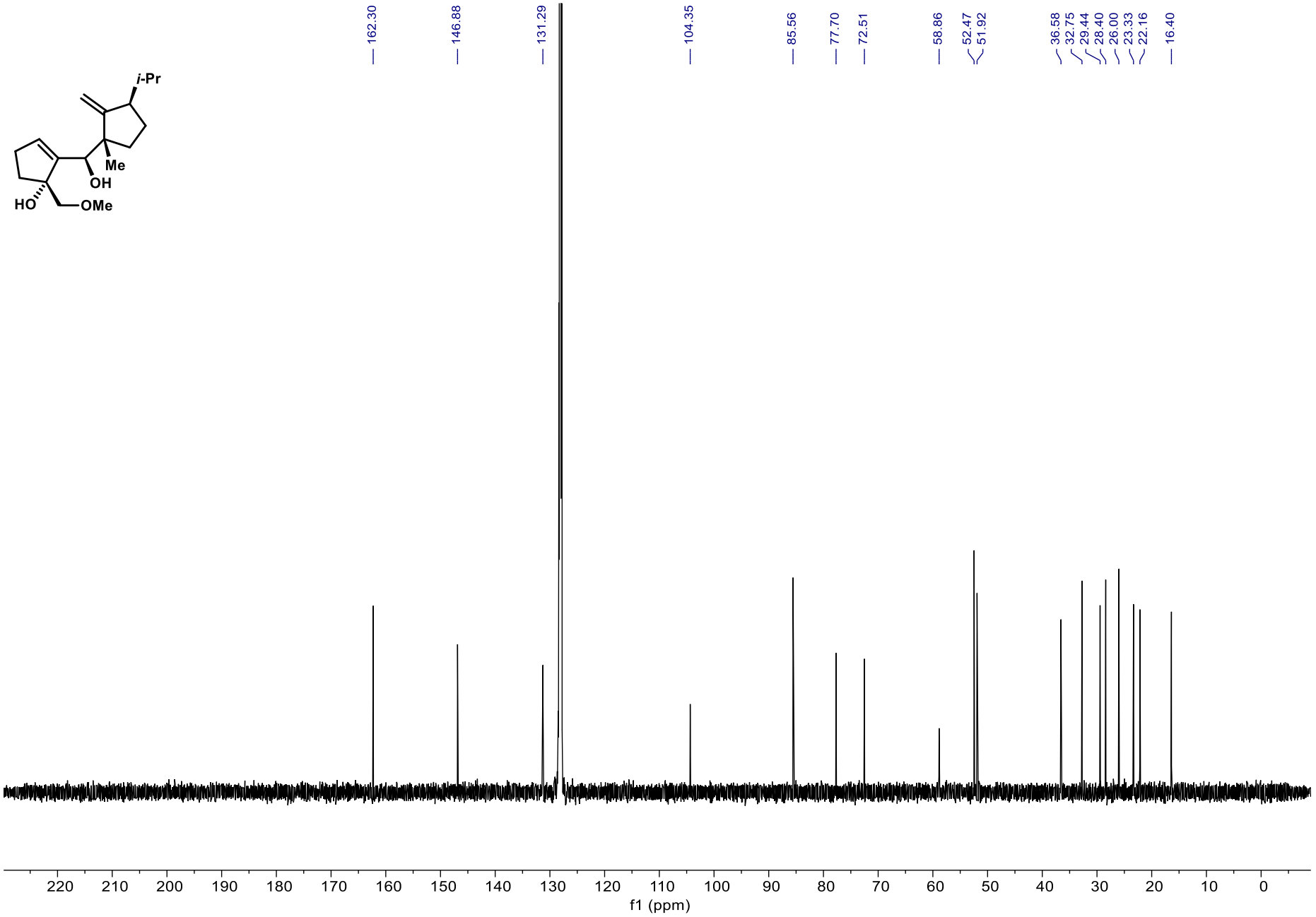
^{13}C NMR of **27**, 151 MHz, $CDCl_3$



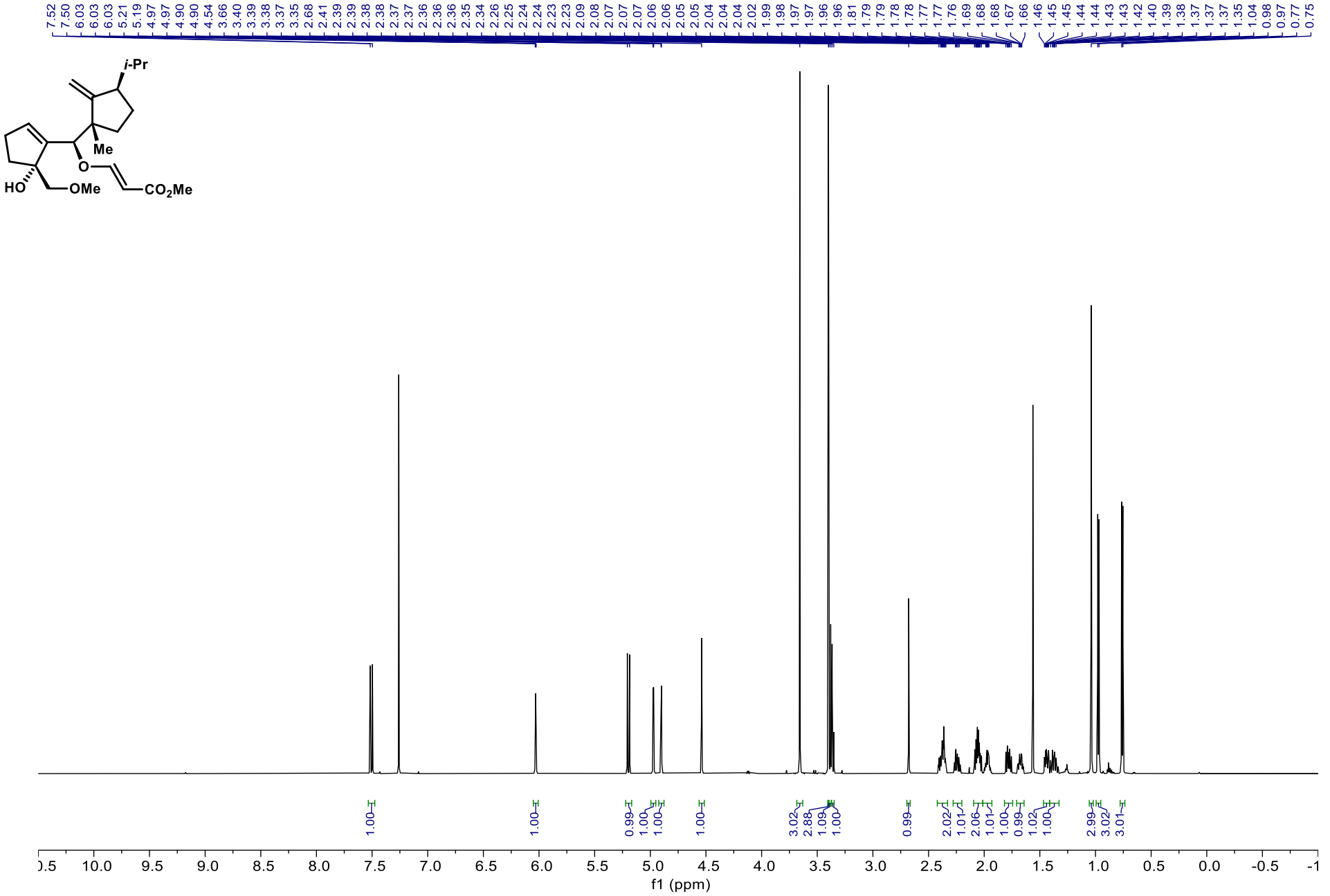
^{1}H NMR of **21**, 600 MHz, C_6D_6



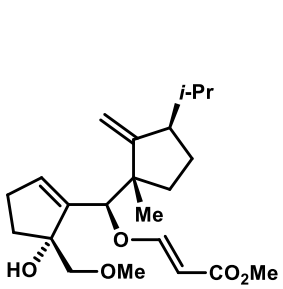
^{13}C NMR of **21**, 151 MHz, C_6D_6



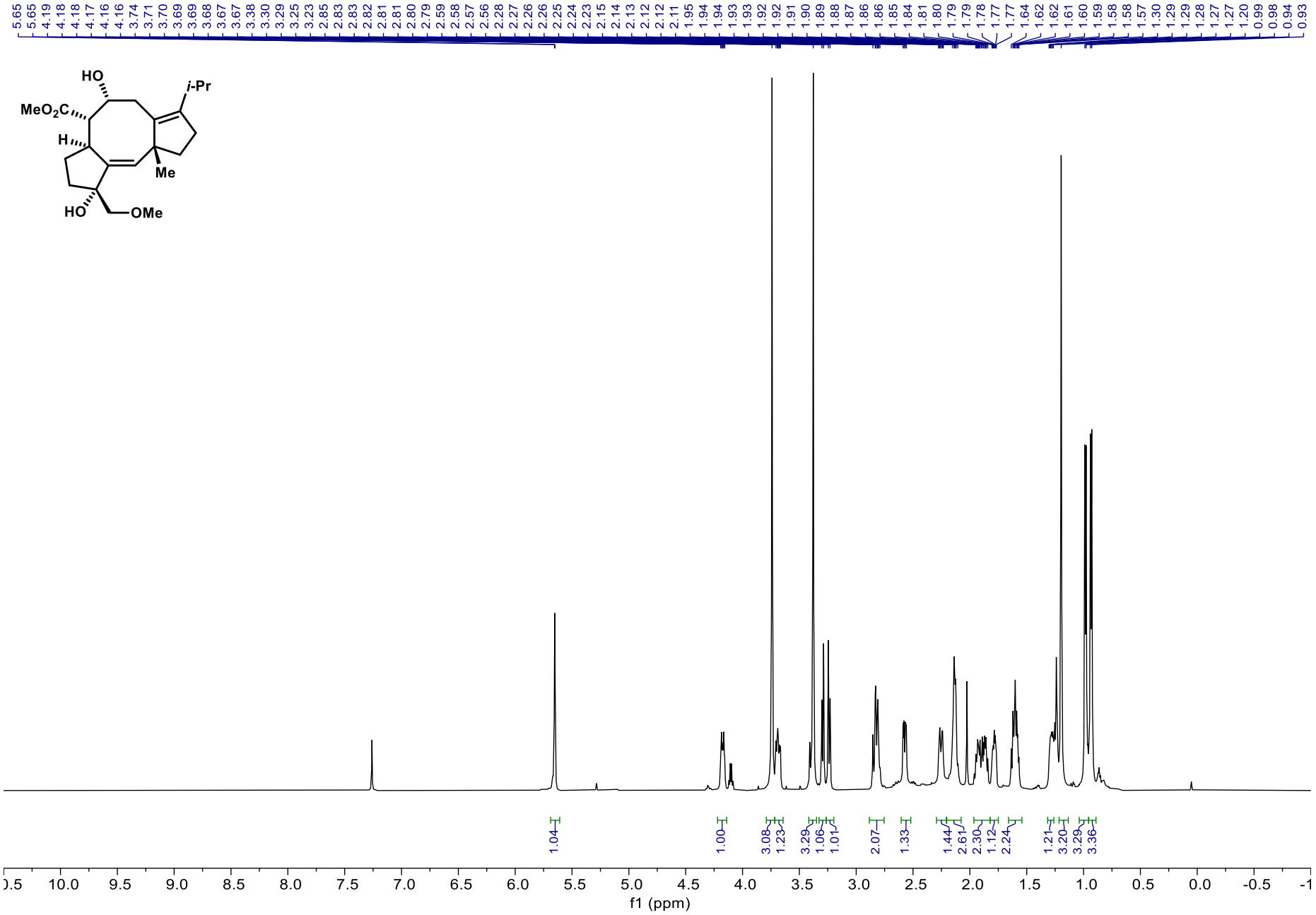
^{1}H NMR of **44**, 600 MHz, $CDCl_3$



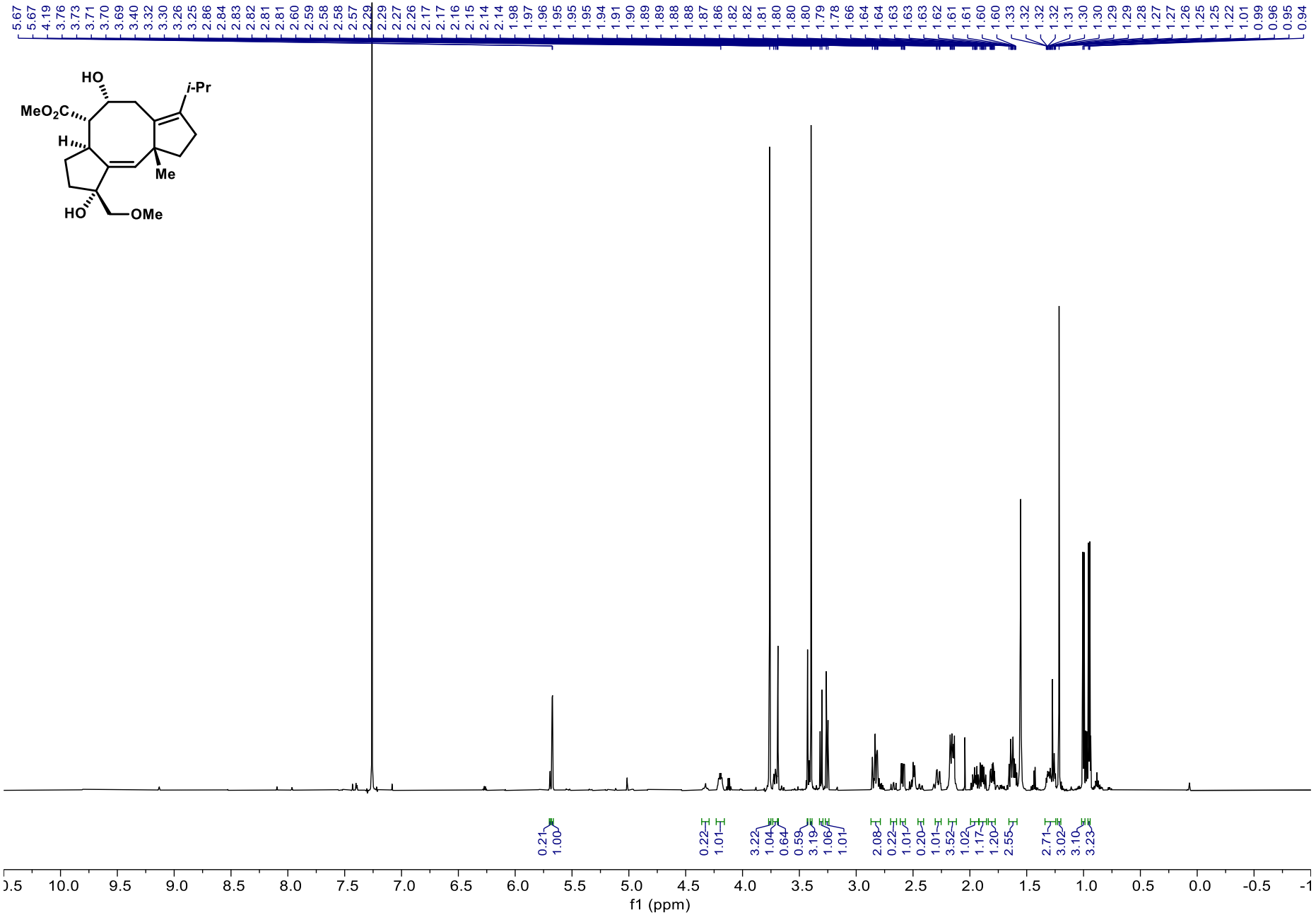
^{13}C NMR of **44**, 151 MHz, $CDCl_3$



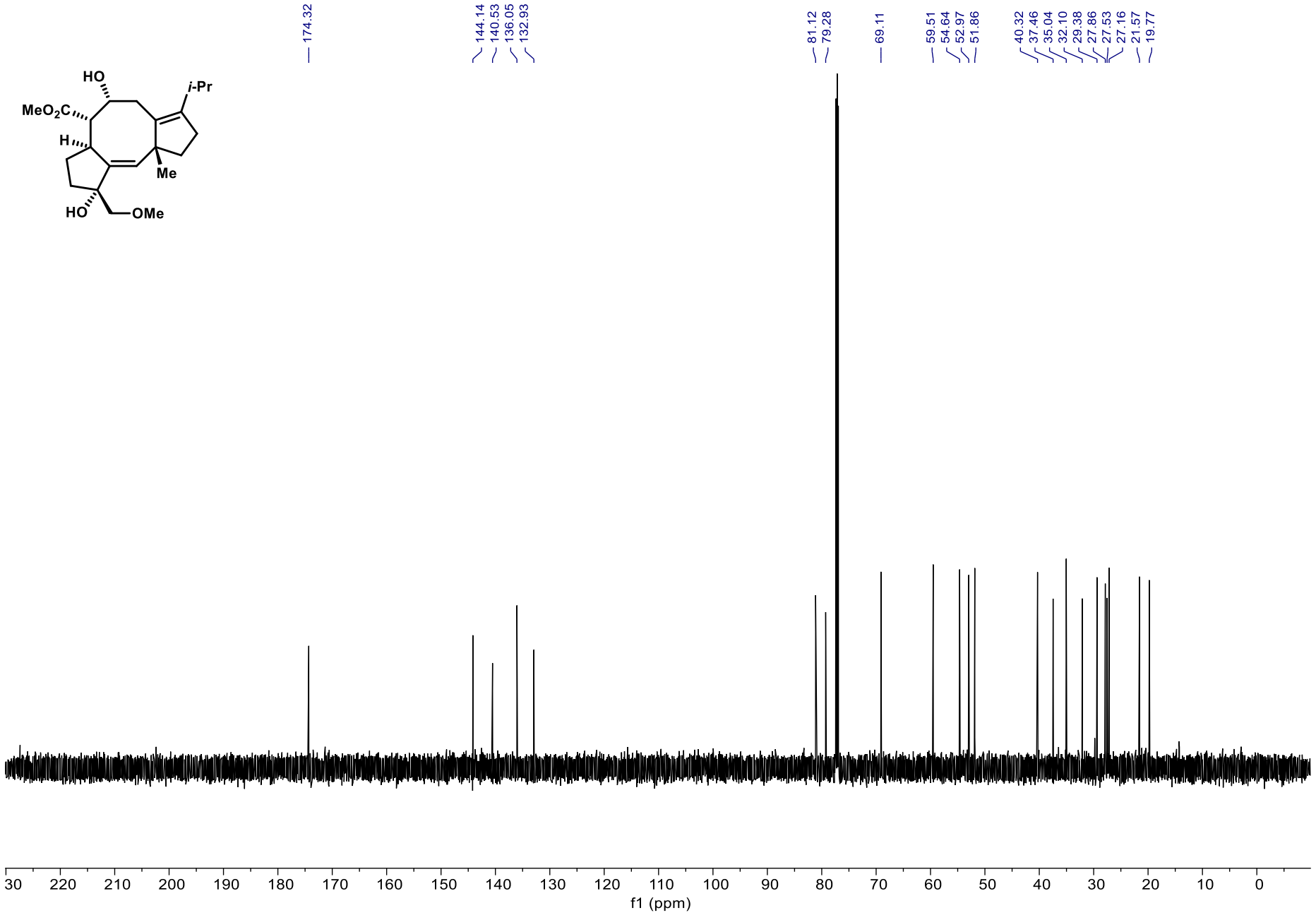
^{1}H NMR of **45**, 600 MHz, $CDCl_3$



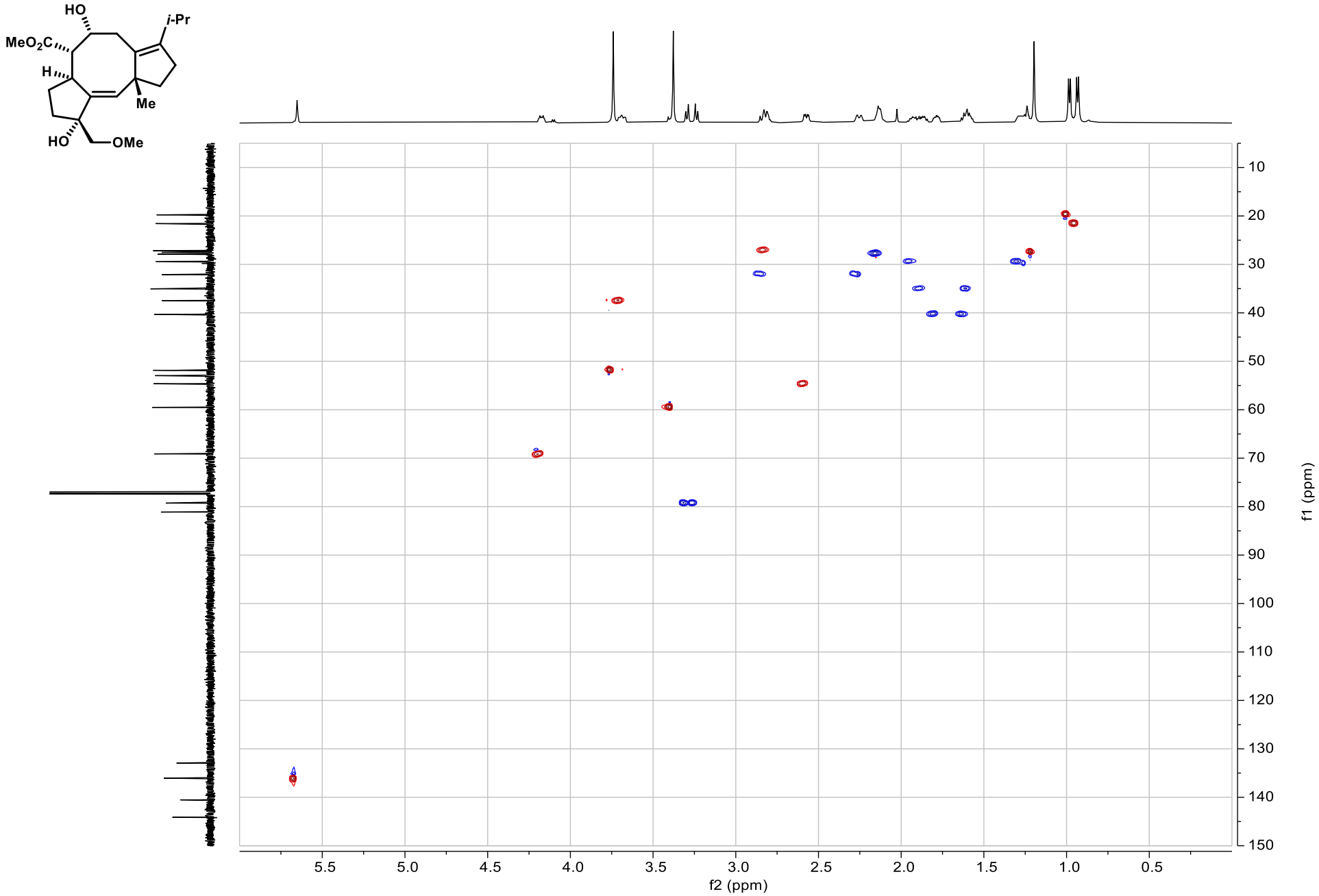
^{1}H NMR of **45** (5:1 dr), 600 MHz, $CDCl_3$



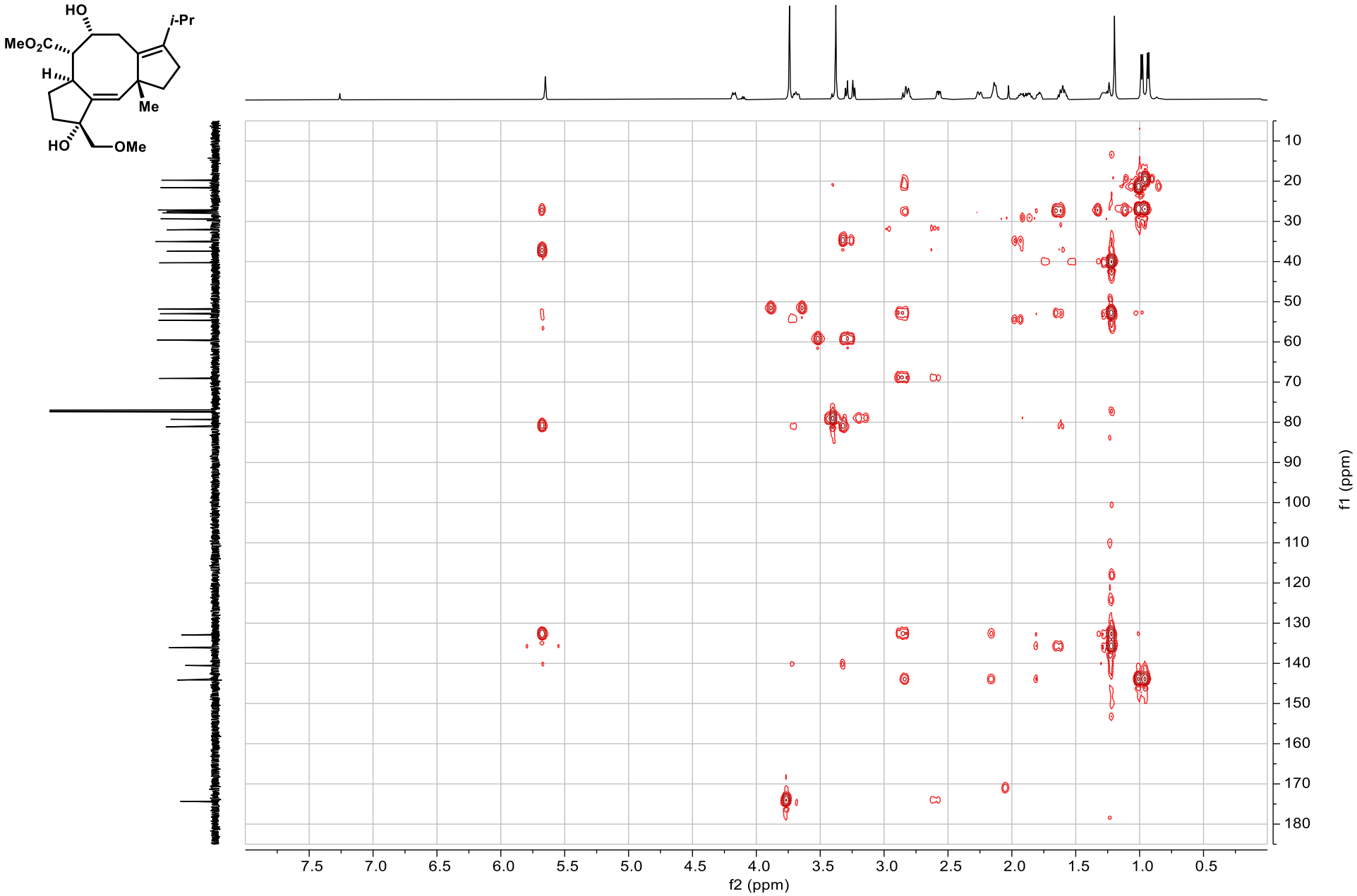
^{13}C NMR of **45**, 151 MHz, $CDCl_3$



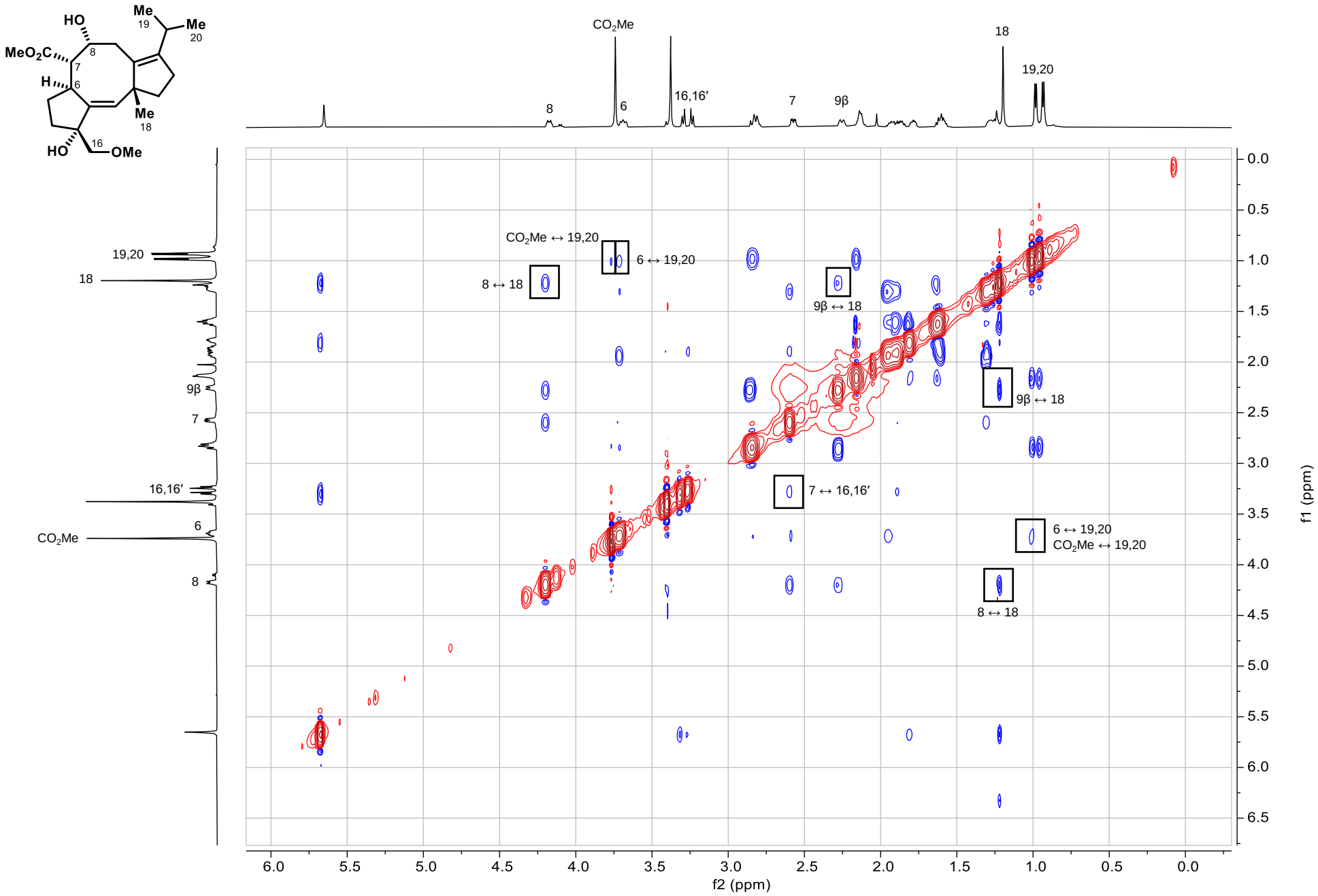
HSQC of **45**, 600 MHz, $CDCl_3$



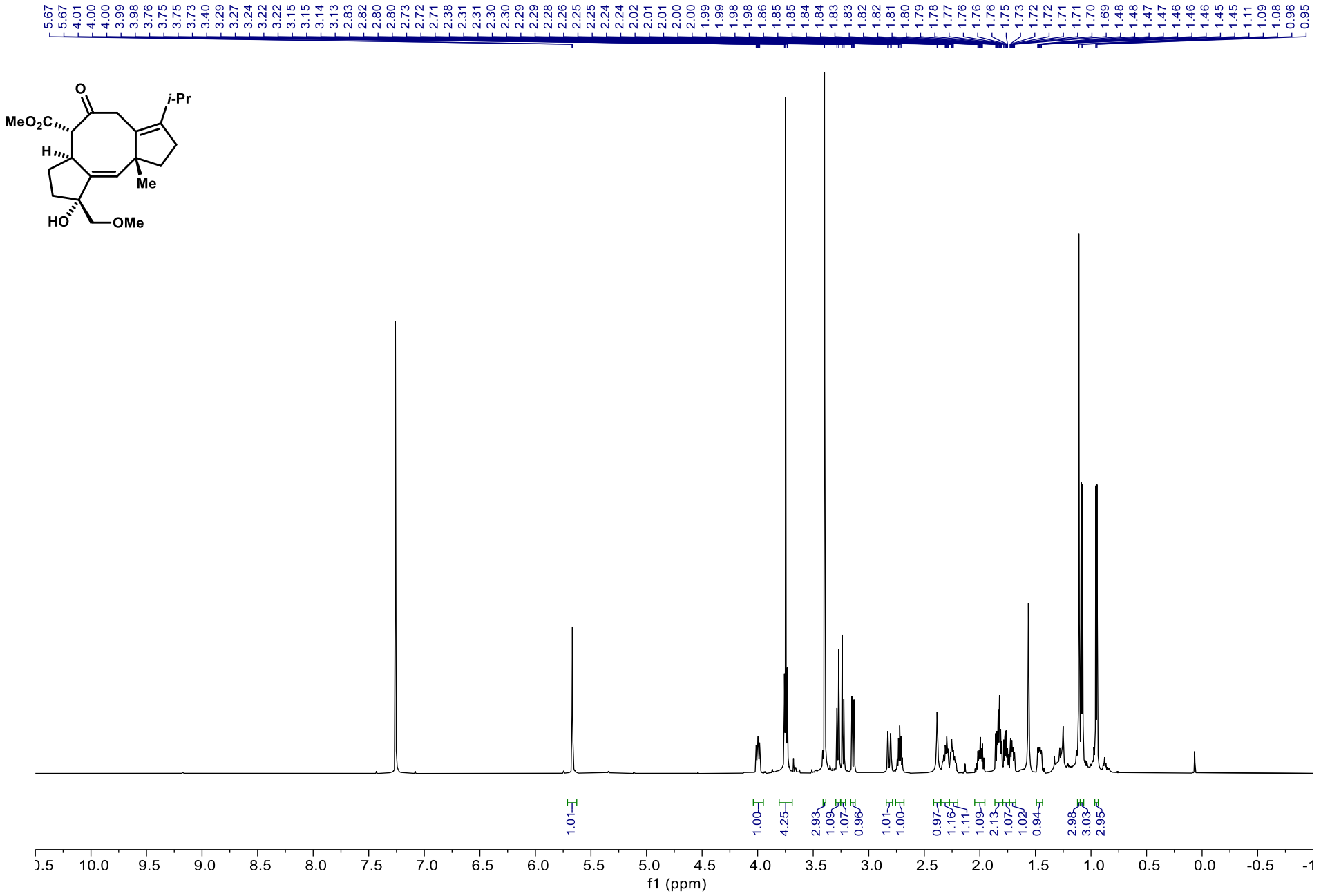
HMBC of **45**, 600 MHz, $CDCl_3$



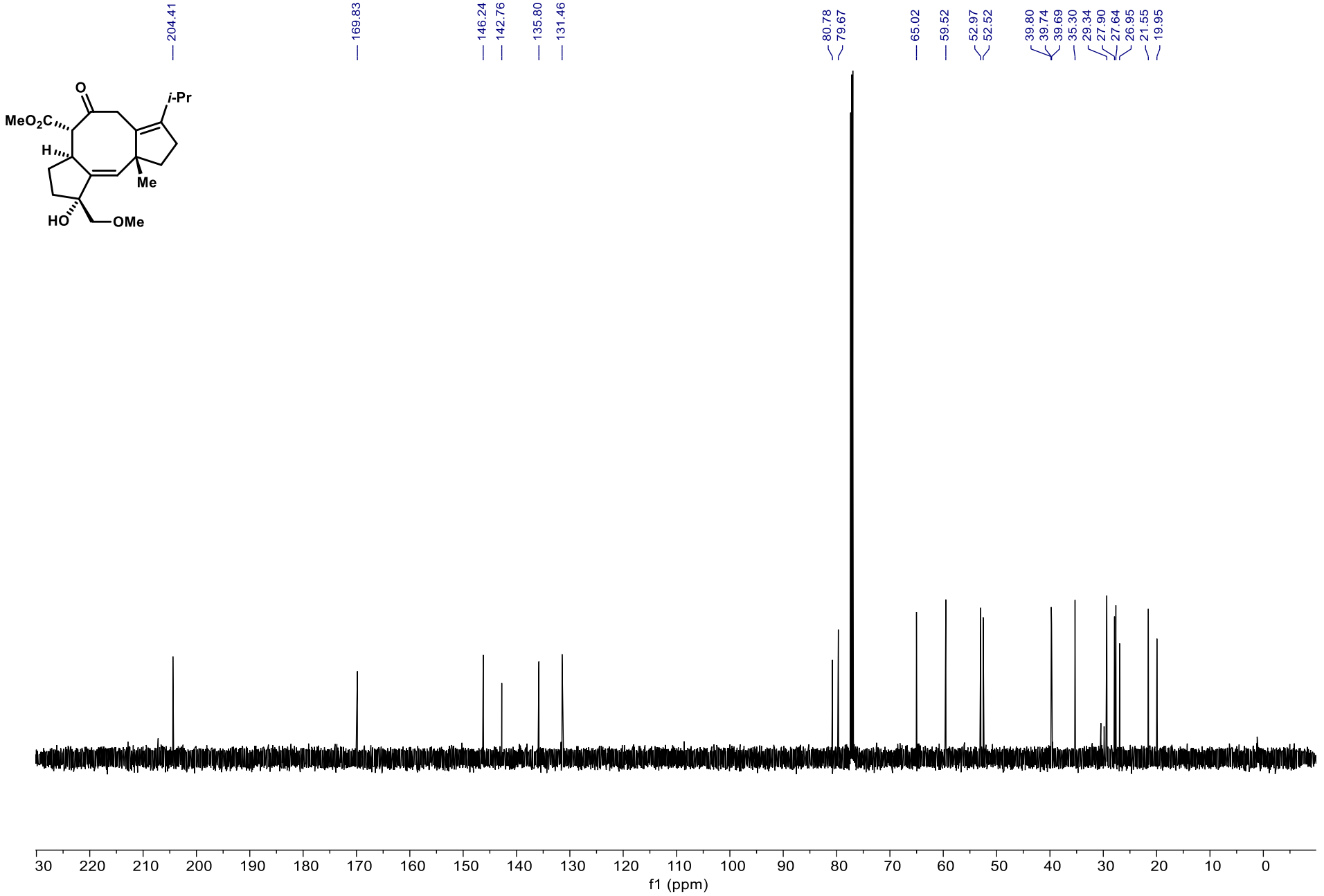
NOESY of **45**, 600 MHz, $CDCl_3$



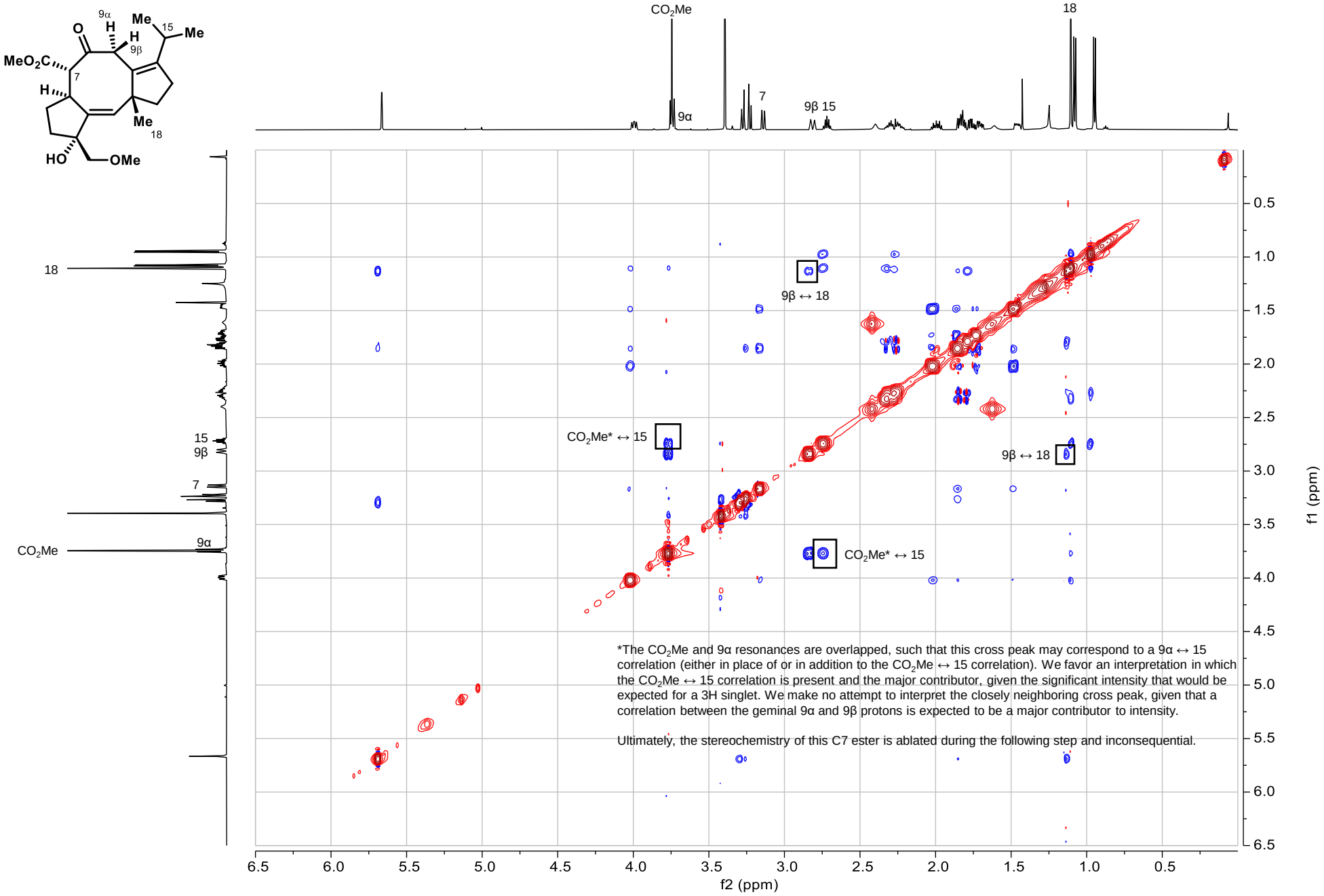
^{1}H NMR of **S7**, 600 MHz, $CDCl_3$



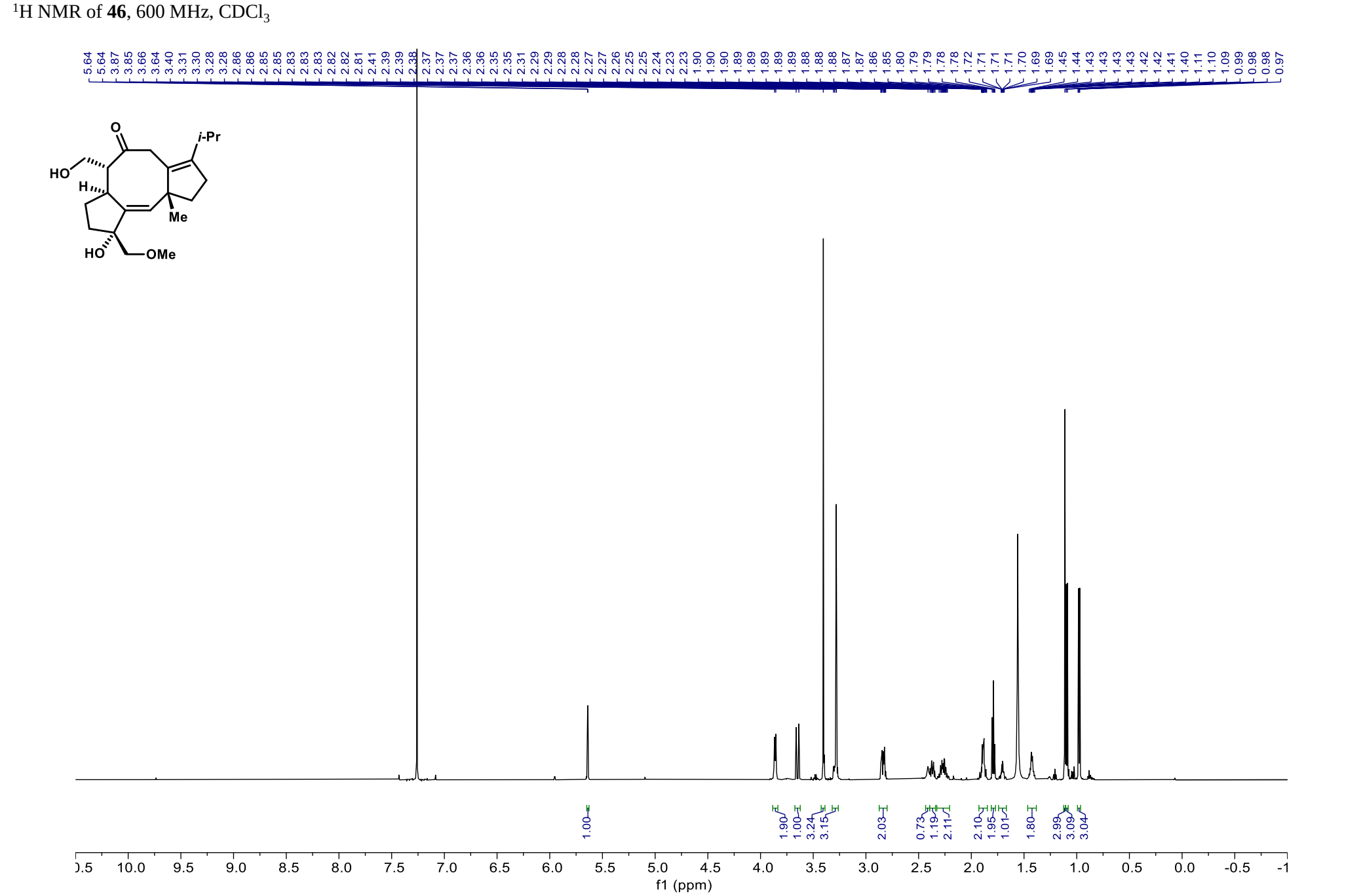
^{13}C NMR of **S7**, 151 MHz, $CDCl_3$



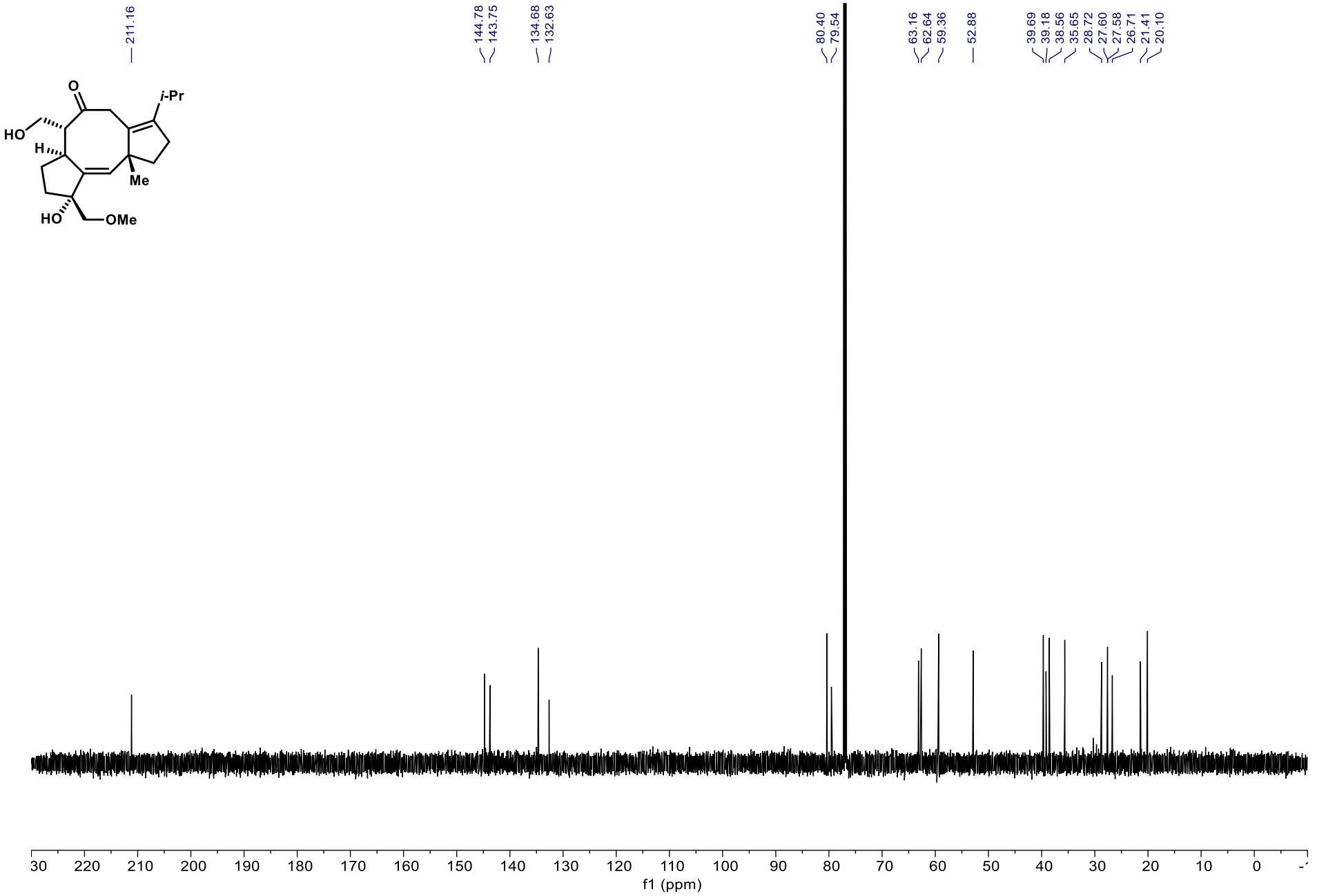
NOESY of **S7**, 600 MHz, $CDCl_3$



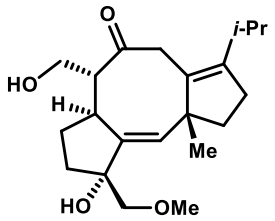
^{1}H NMR of **46**, 600 MHz, $CDCl_3$



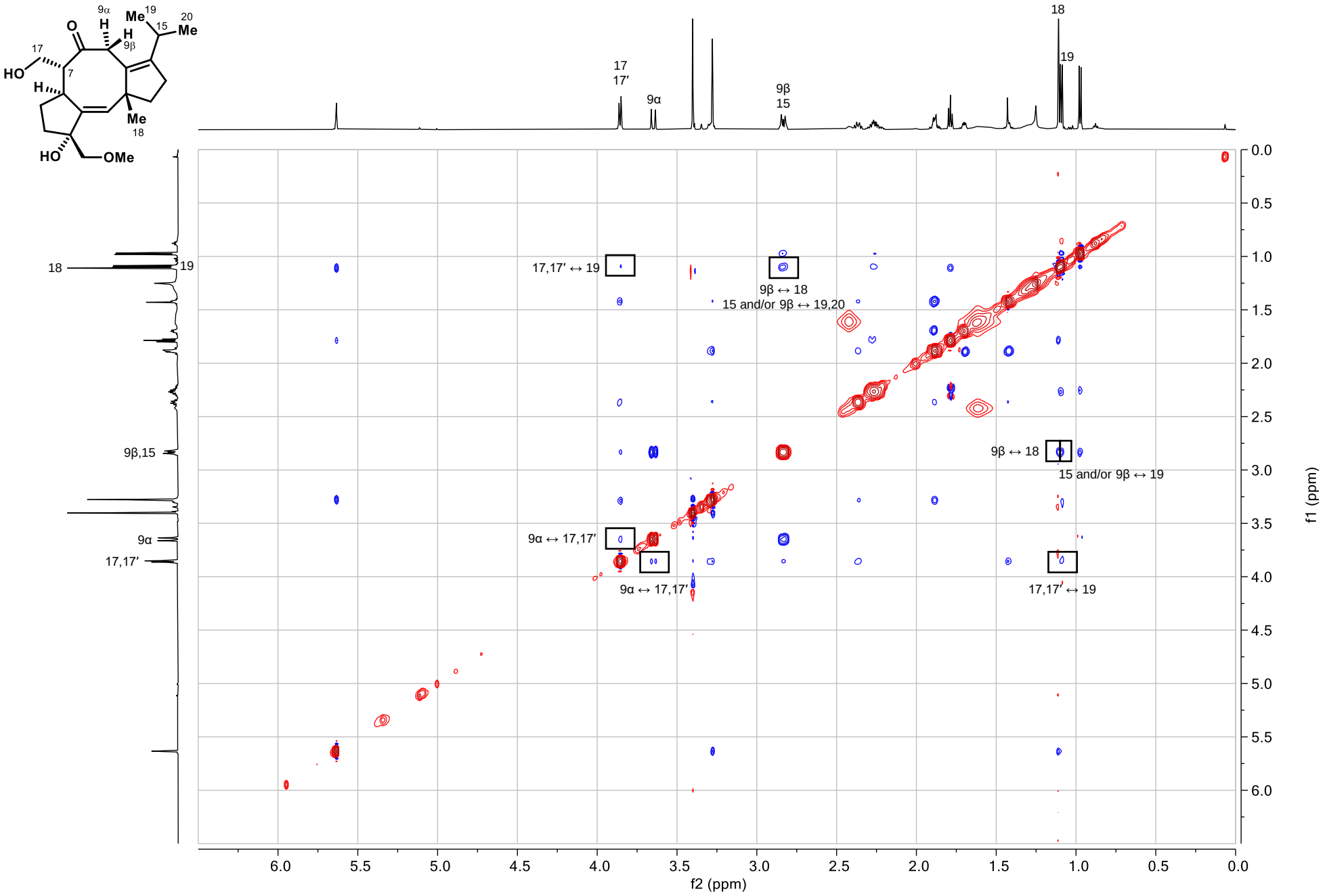
^{13}C NMR of **46**, 151 MHz, $CDCl_3$



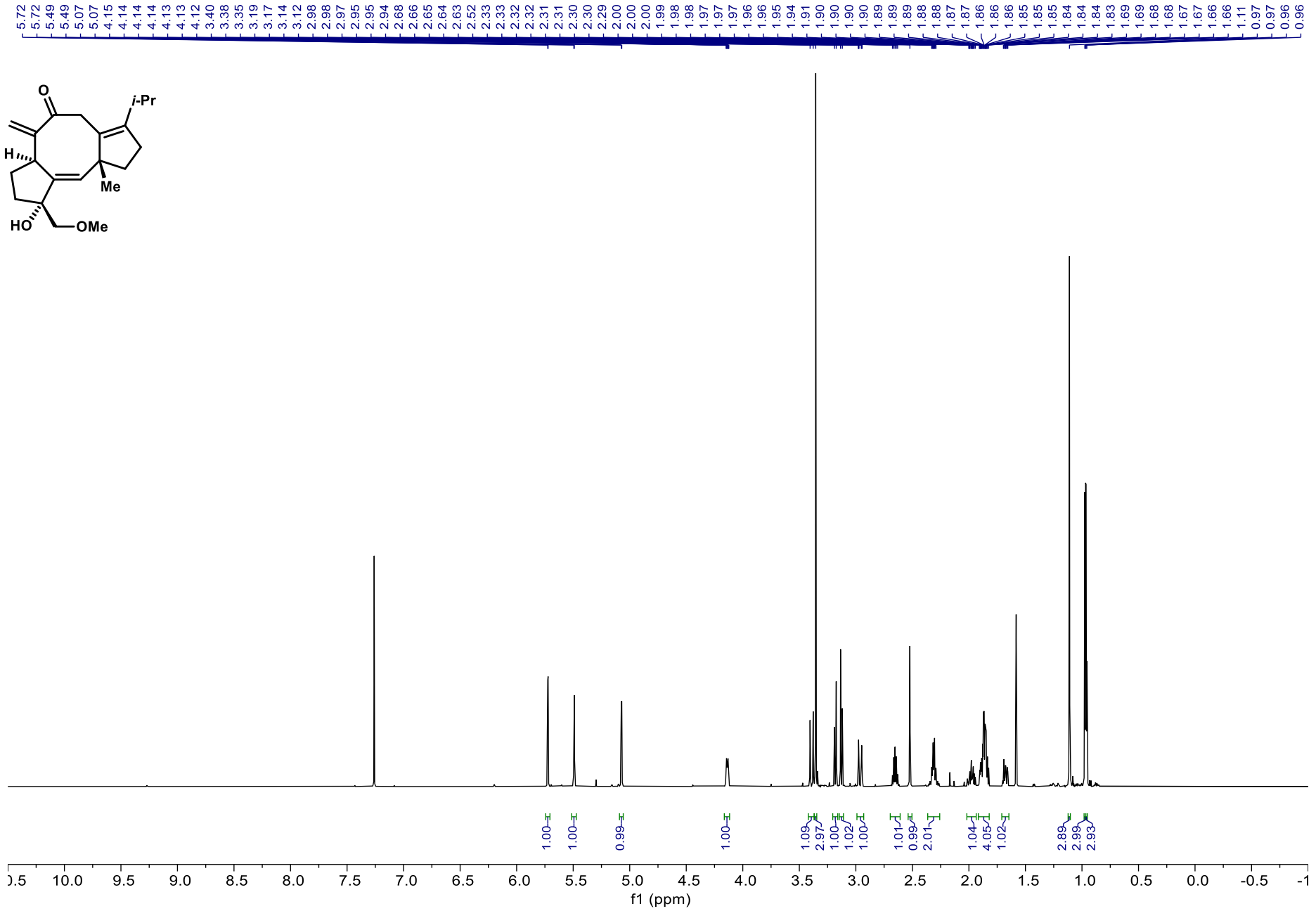
HSQC of **46**, 600 MHz, $CDCl_3$



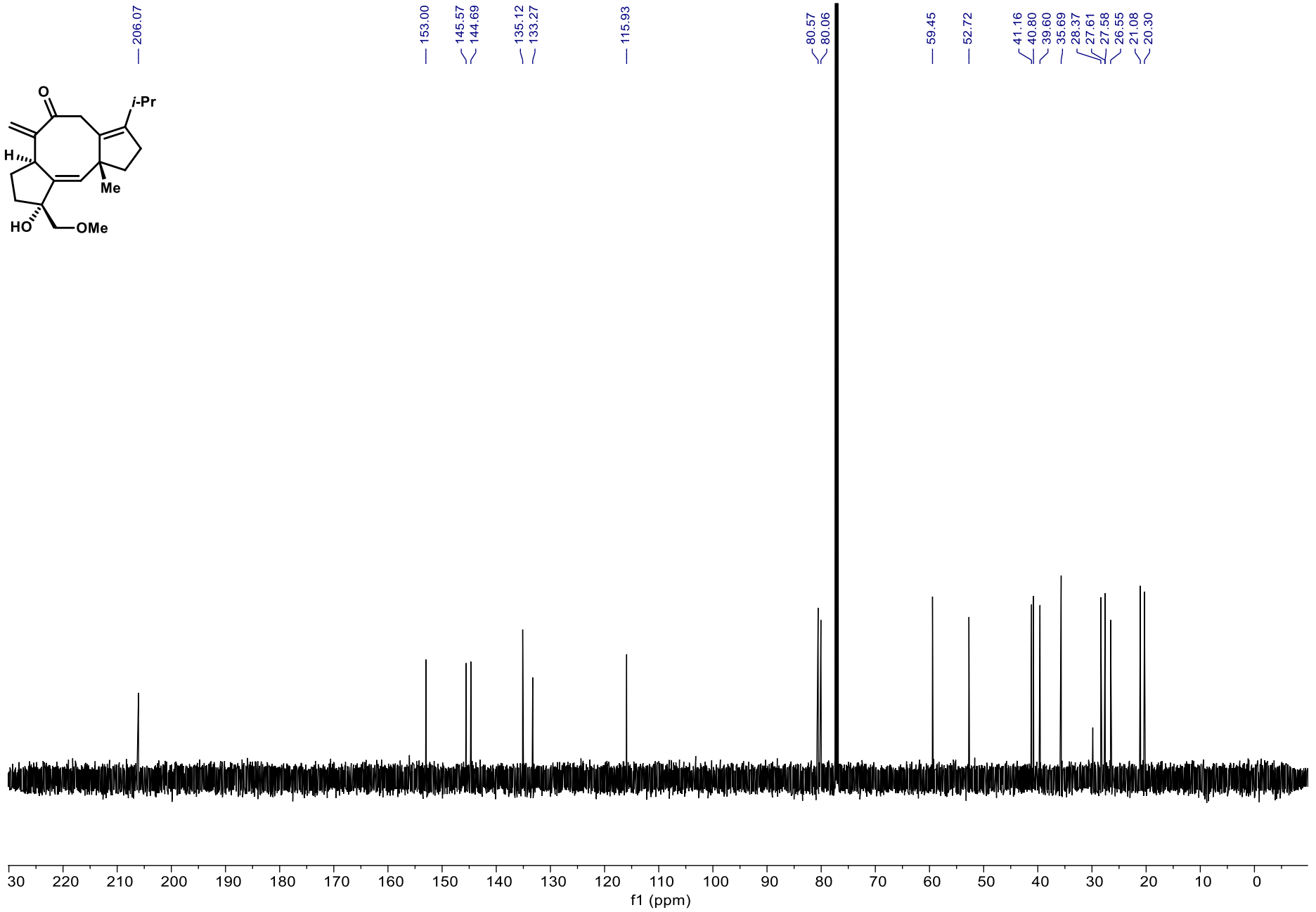
NOESY of **46**, 600 MHz, $CDCl_3$



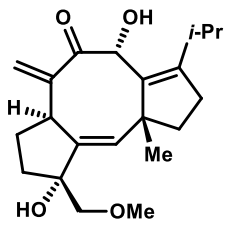
^{1}H NMR of **47**, 600 MHz, $CDCl_3$



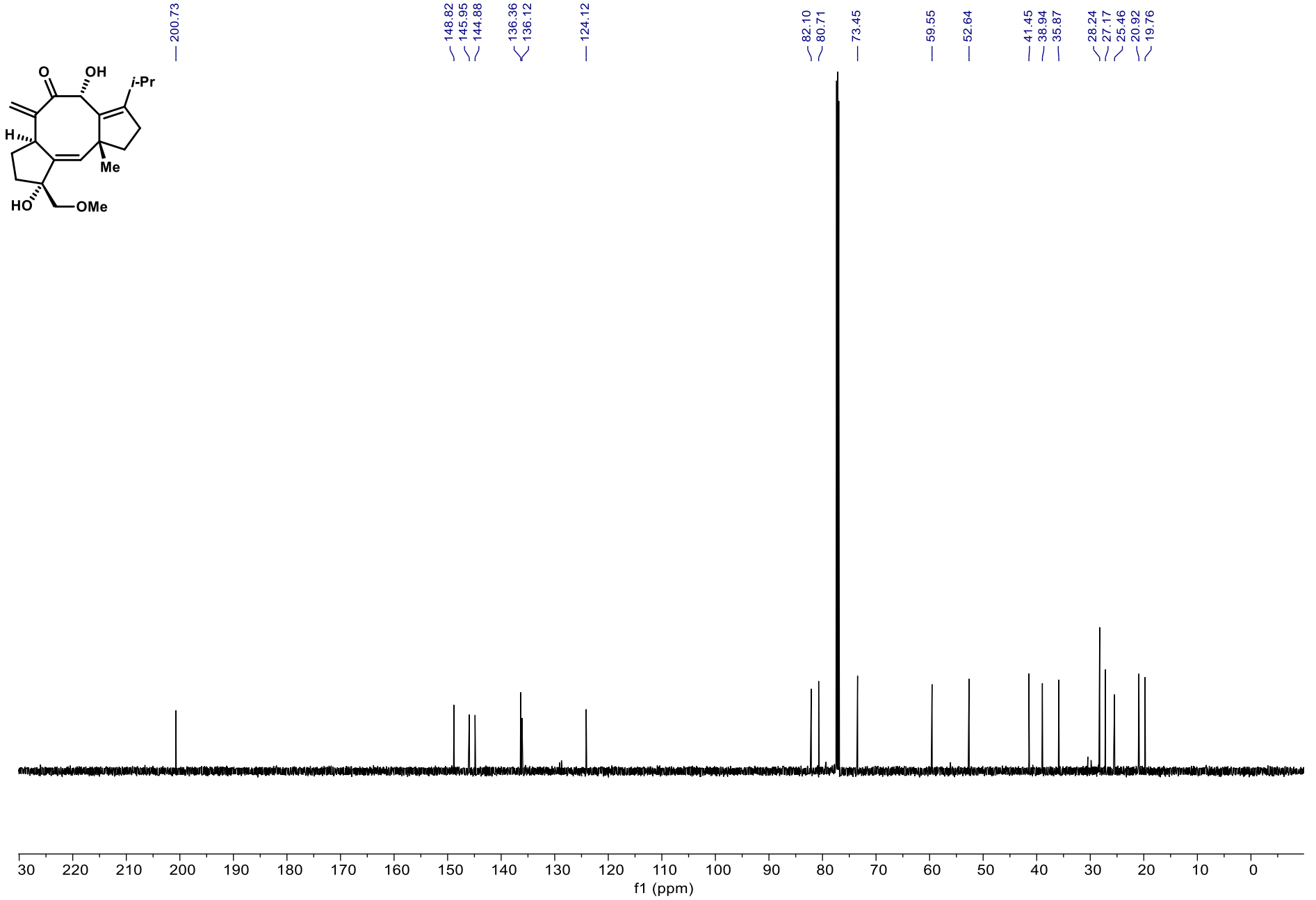
^{13}C NMR of **47**, 151 MHz, $CDCl_3$



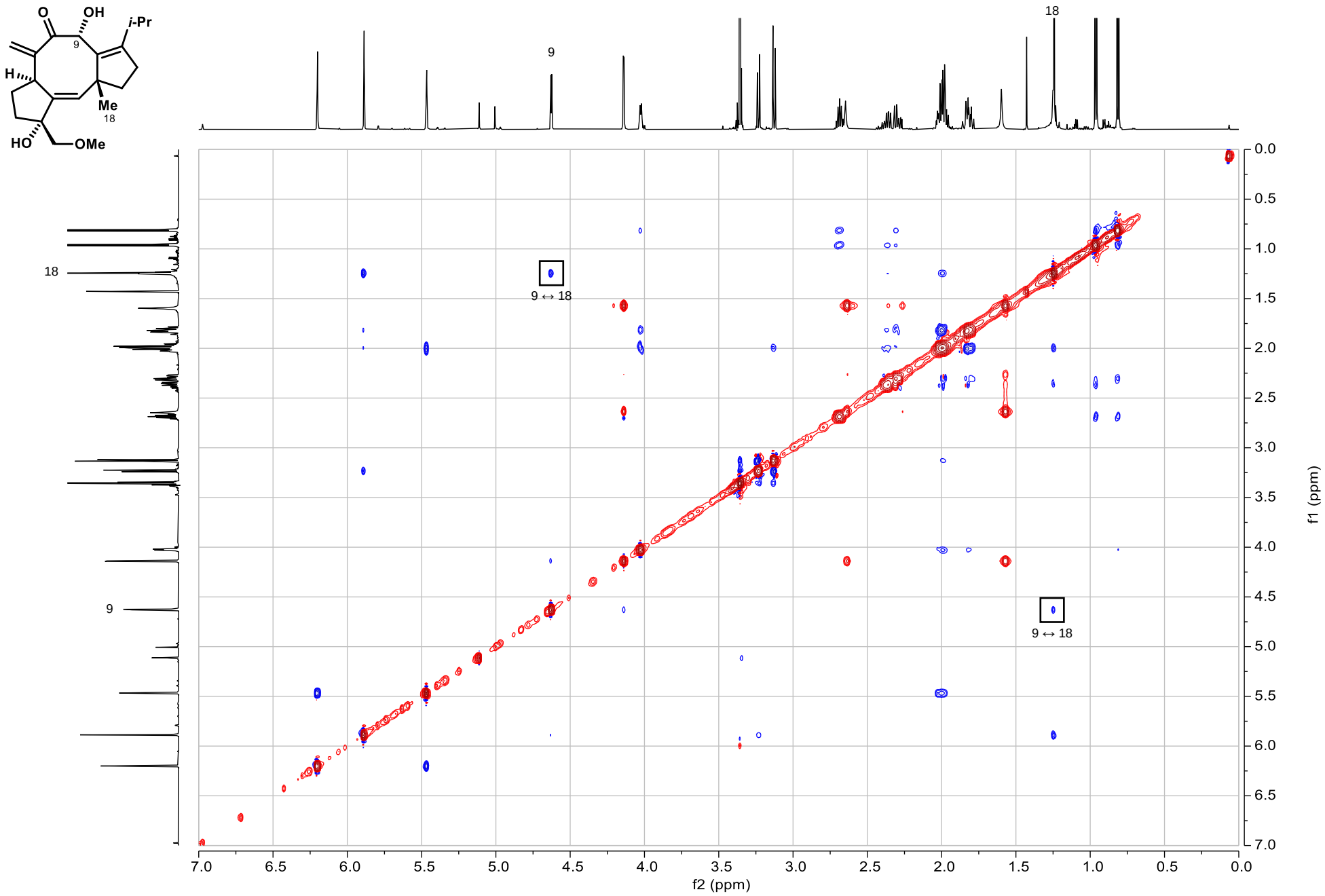
^{1}H NMR of **48**, 600 MHz, $CDCl_3$



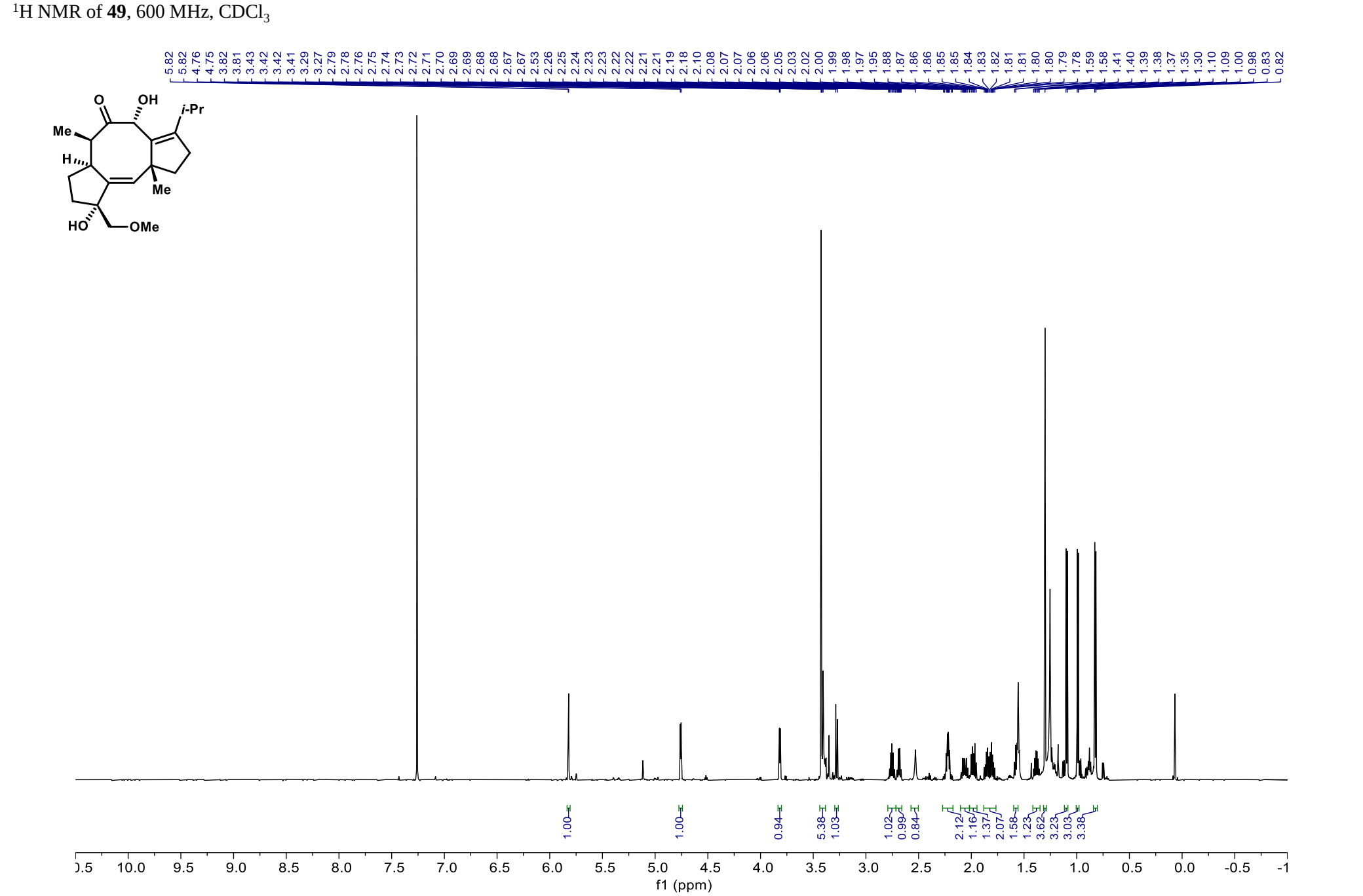
^{13}C NMR of **48**, 151 MHz, $CDCl_3$



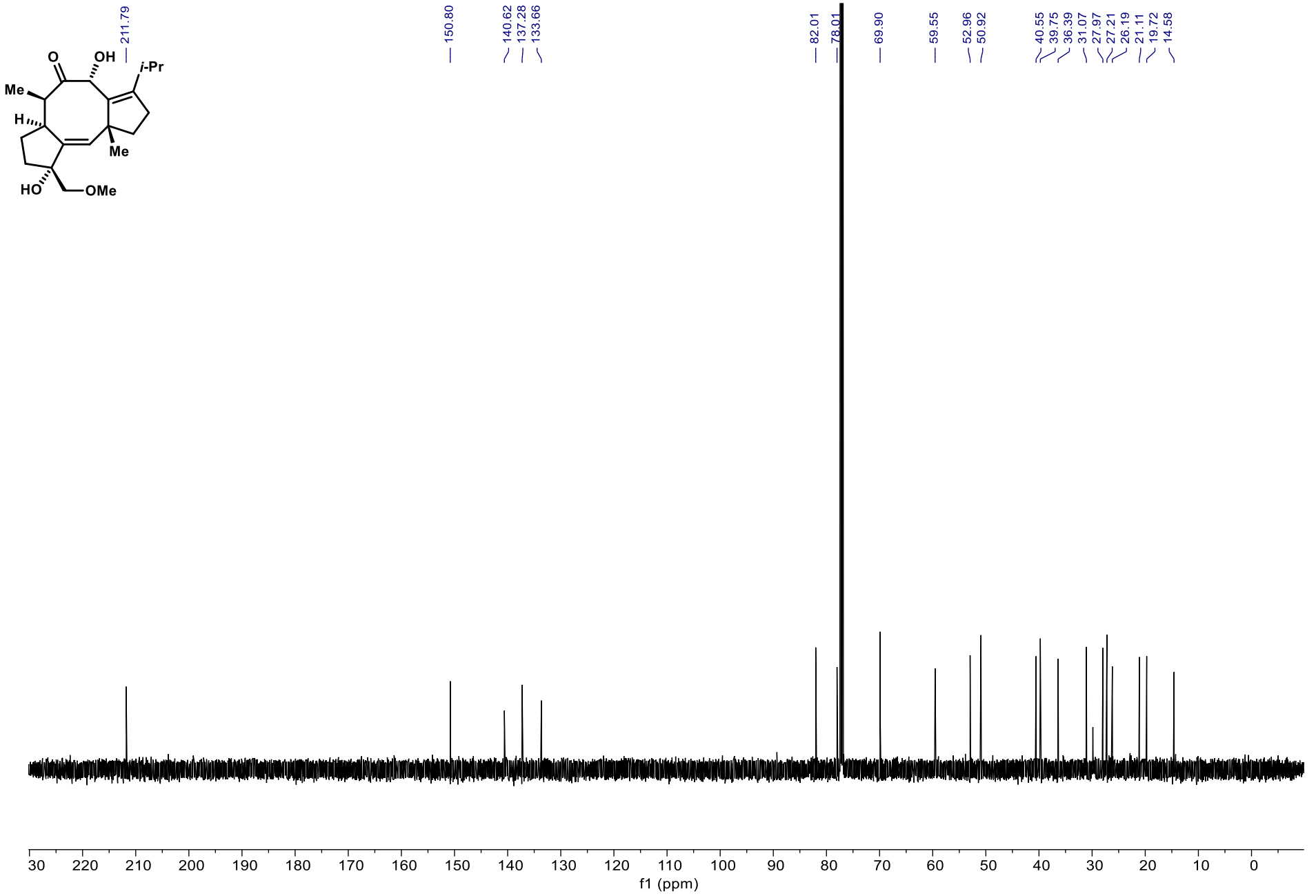
NOESY of **48**, 600 MHz, $CDCl_3$



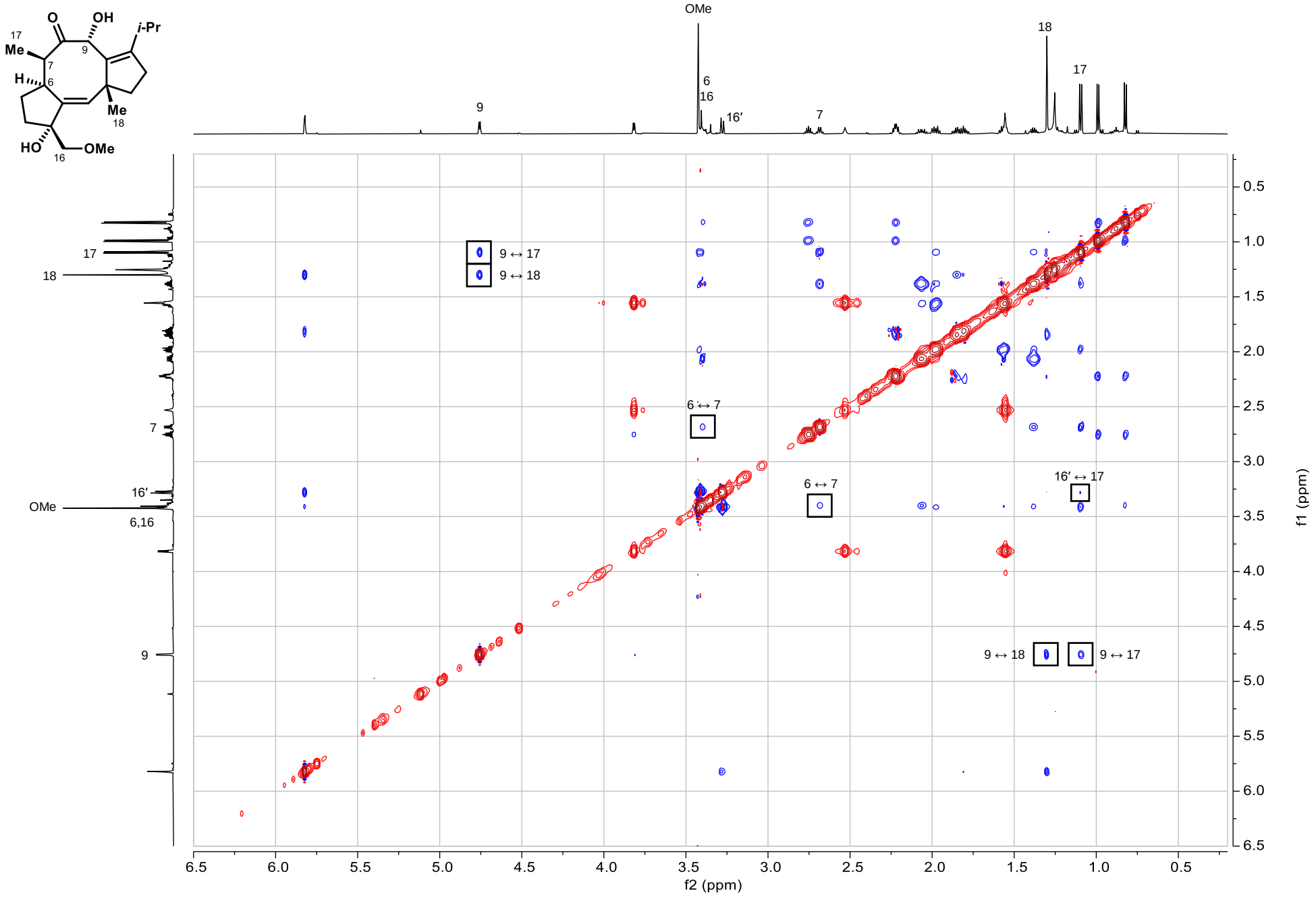
^{1}H NMR of **49**, 600 MHz, $CDCl_3$



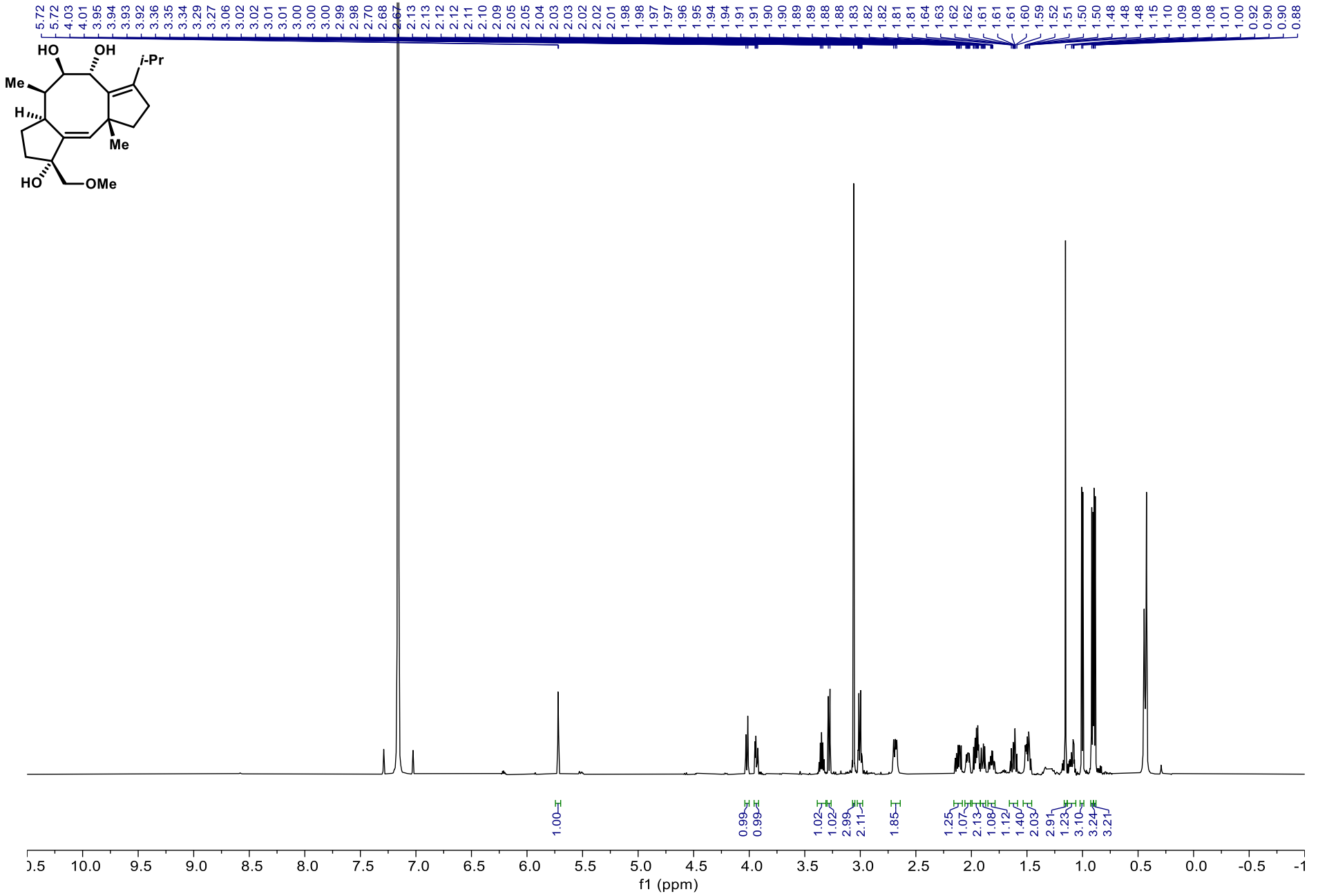
^{13}C NMR of **49**, 151 MHz, $CDCl_3$



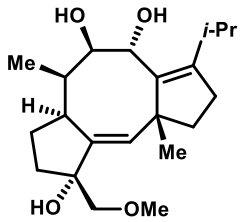
NOESY of **49**, 600 MHz, $CDCl_3$



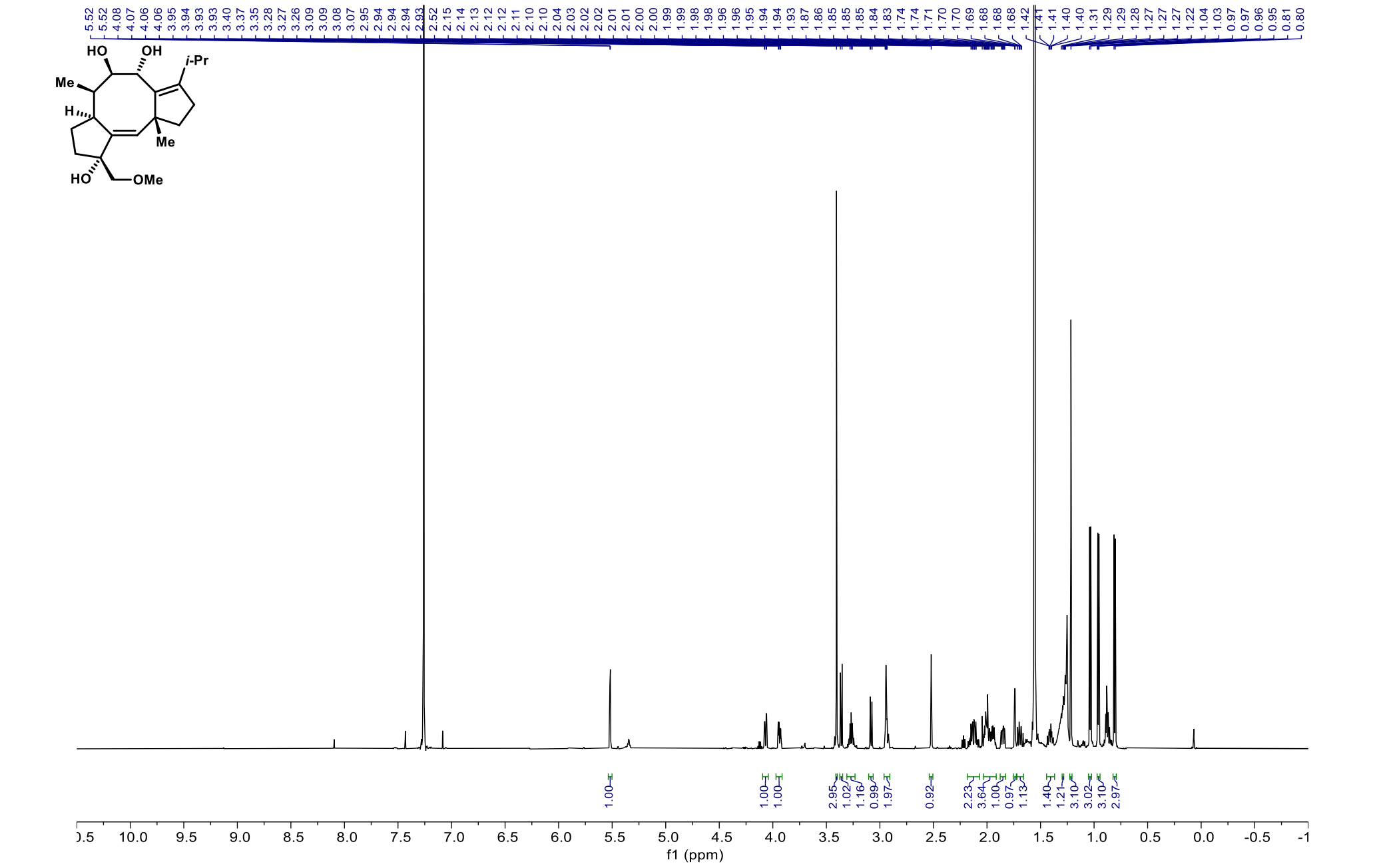
^{1}H NMR of cotylenol **3**, 600 MHz, C_6D_6



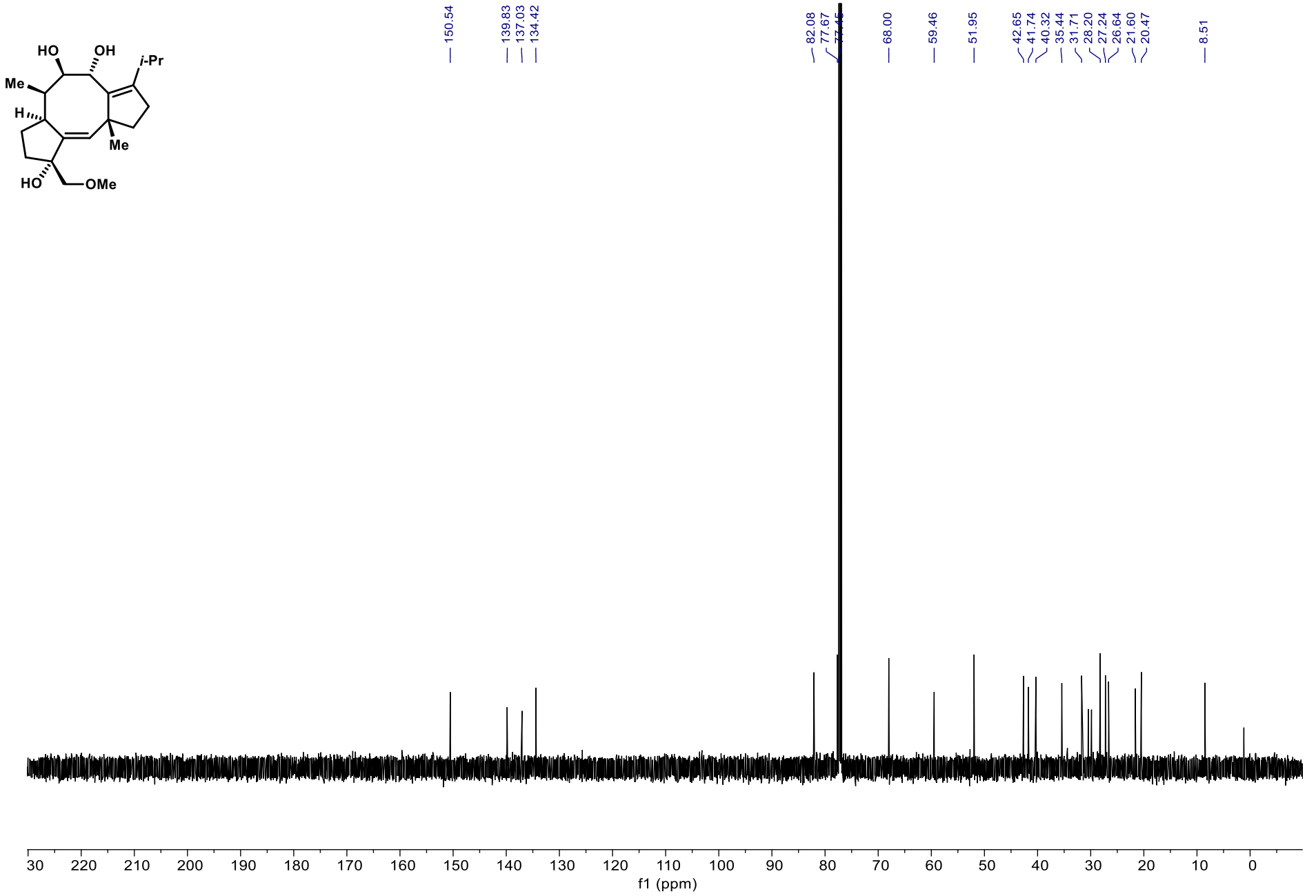
^{13}C NMR of cotylenol **3**, 151 MHz, C_6D_6



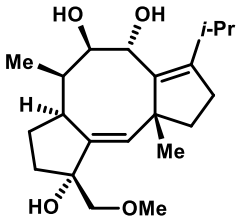
^{1}H NMR of cotylenol **3**, 600 MHz, $CDCl_3$

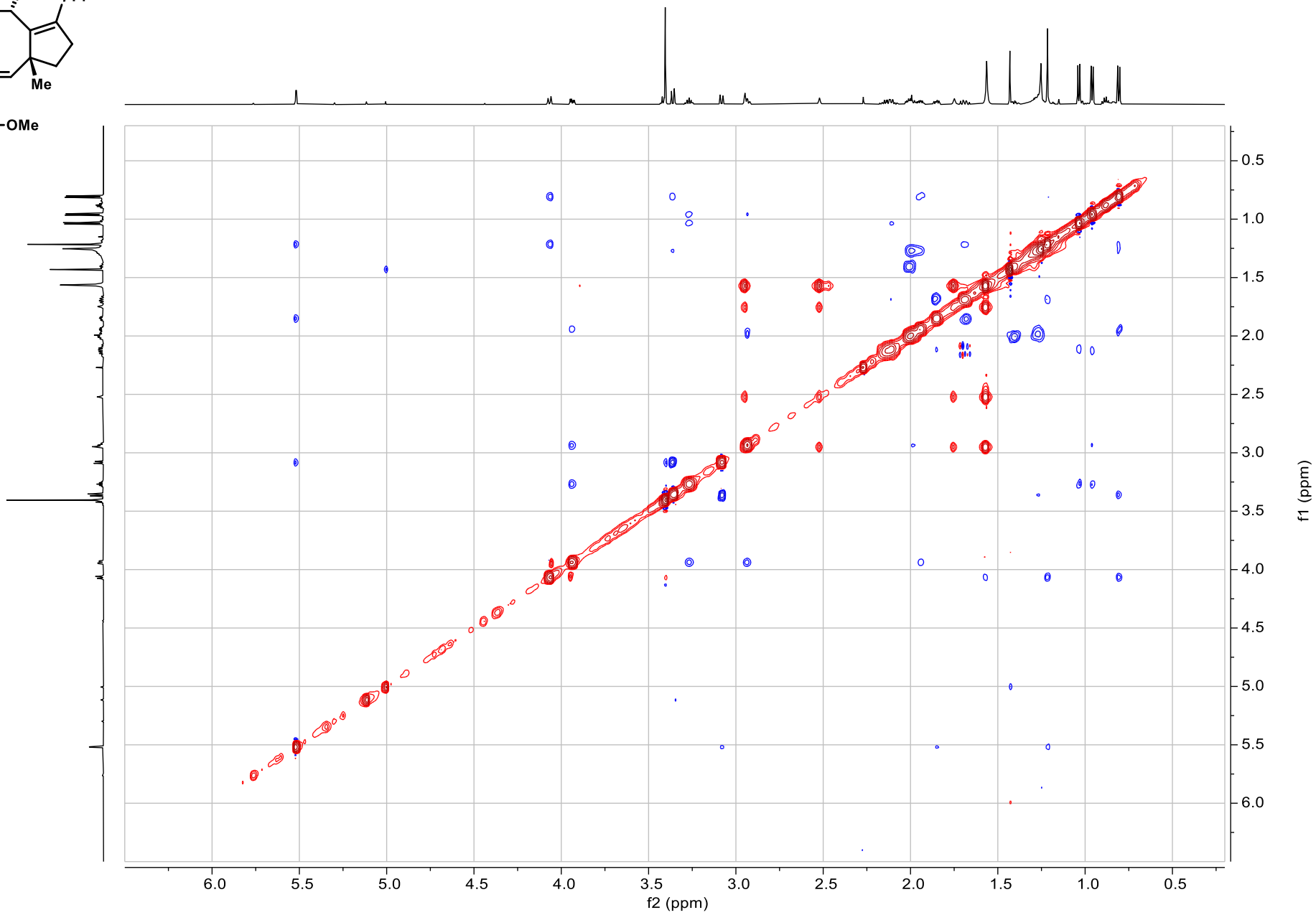


^{13}C NMR of cotylenol **3**, 151 MHz, $CDCl_3$

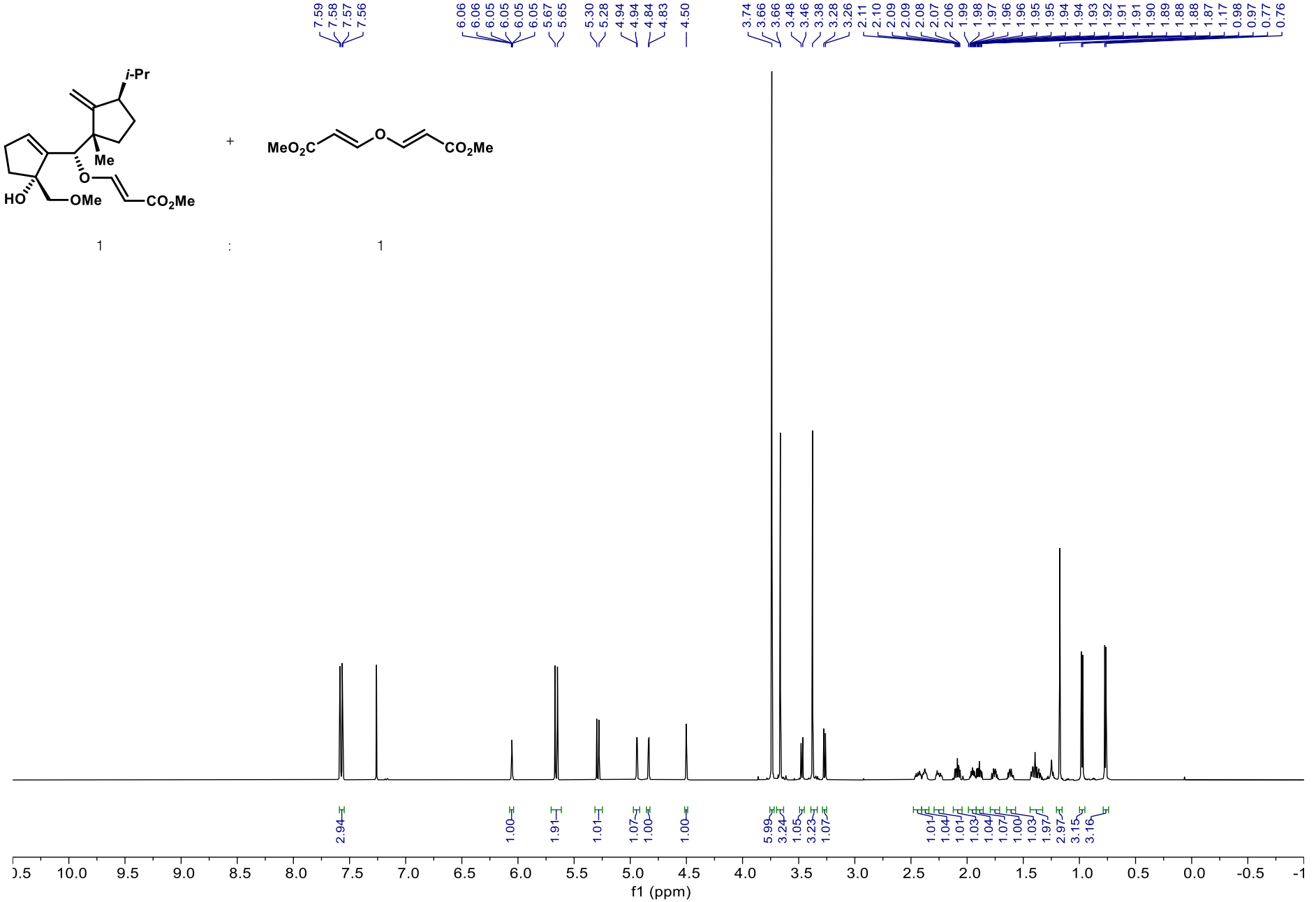


NOESY of cotylenol **3**, 600 MHz, $CDCl_3$

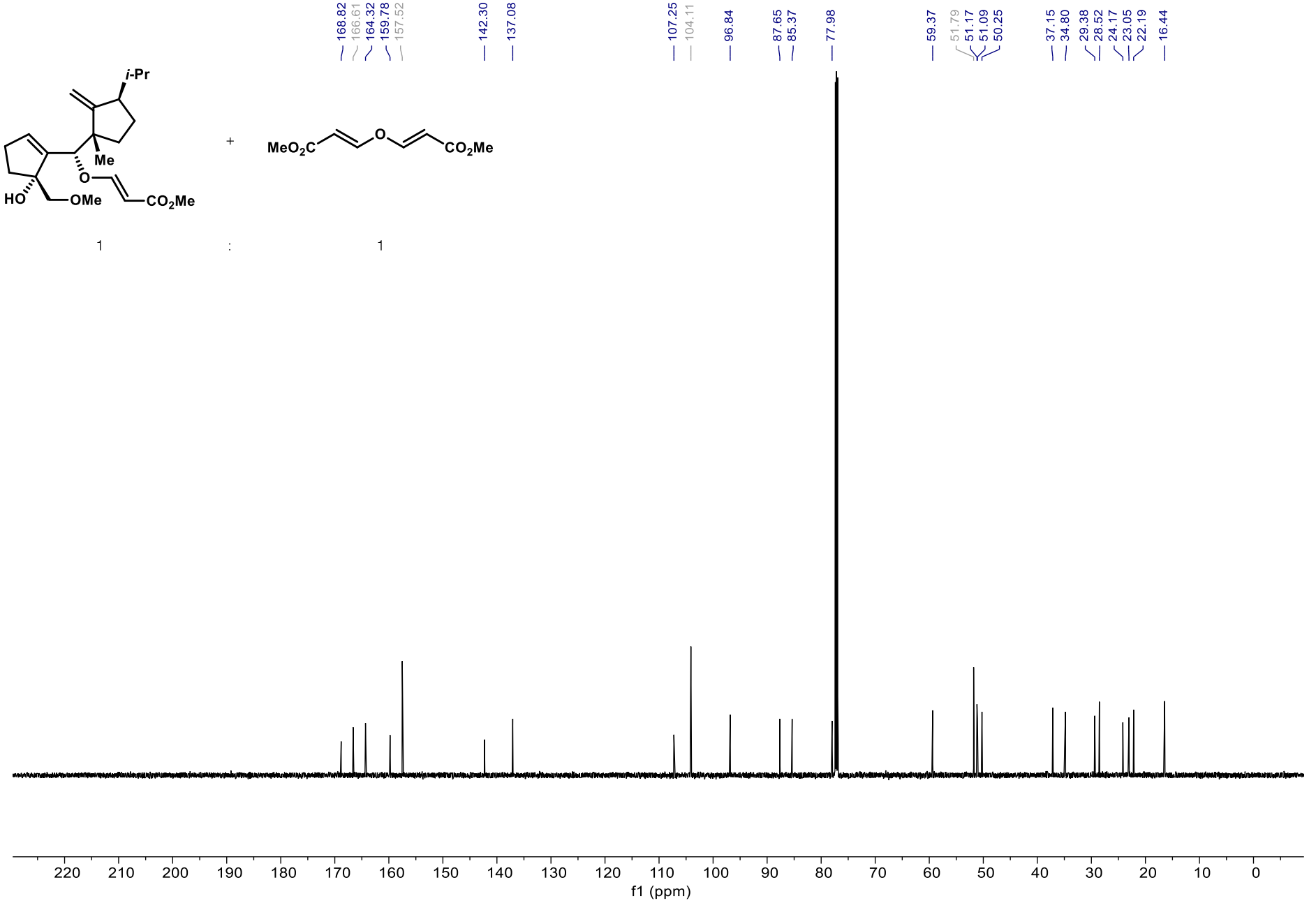




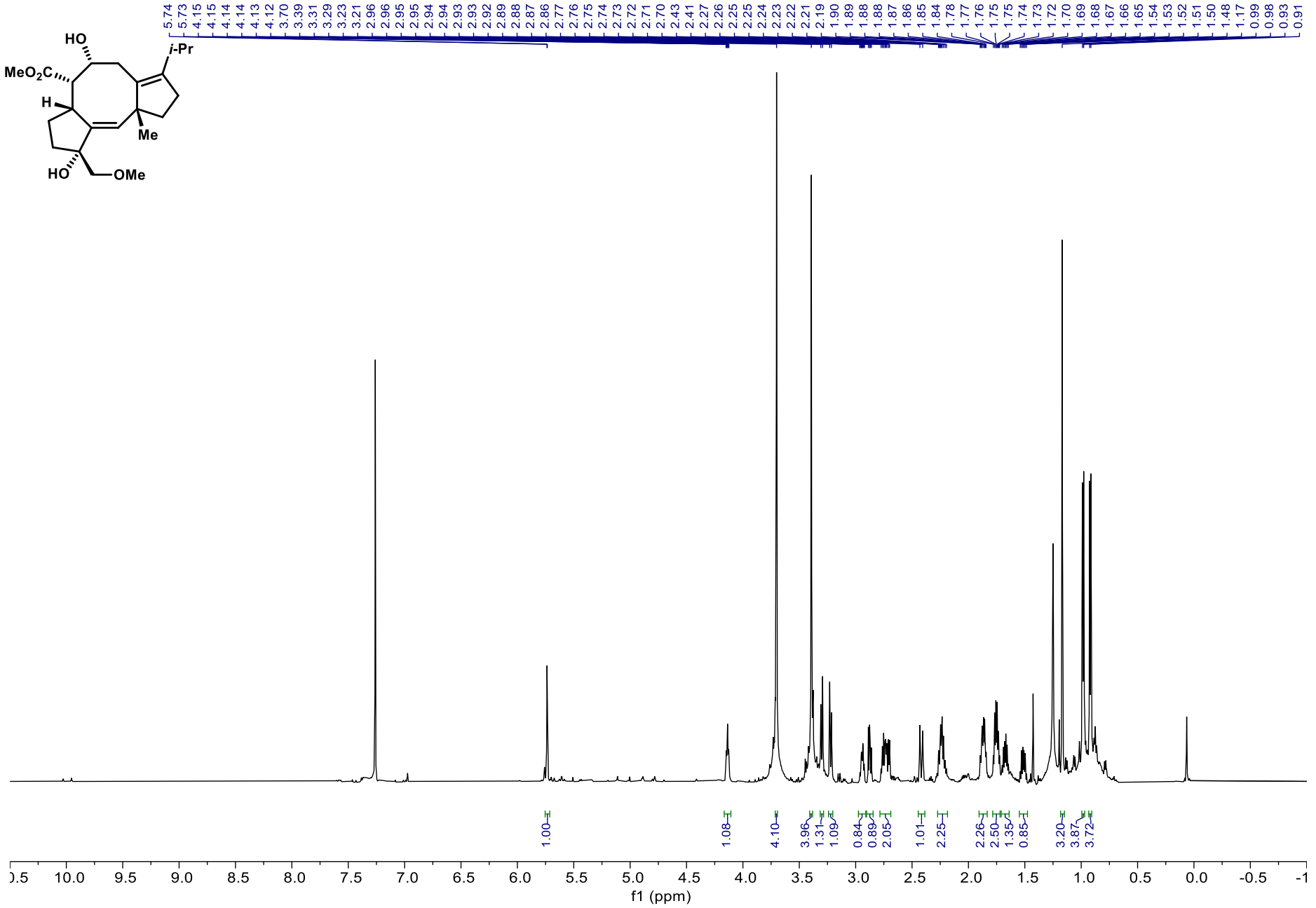
^{1}H NMR of **40g**, 600 MHz, $CDCl_3$



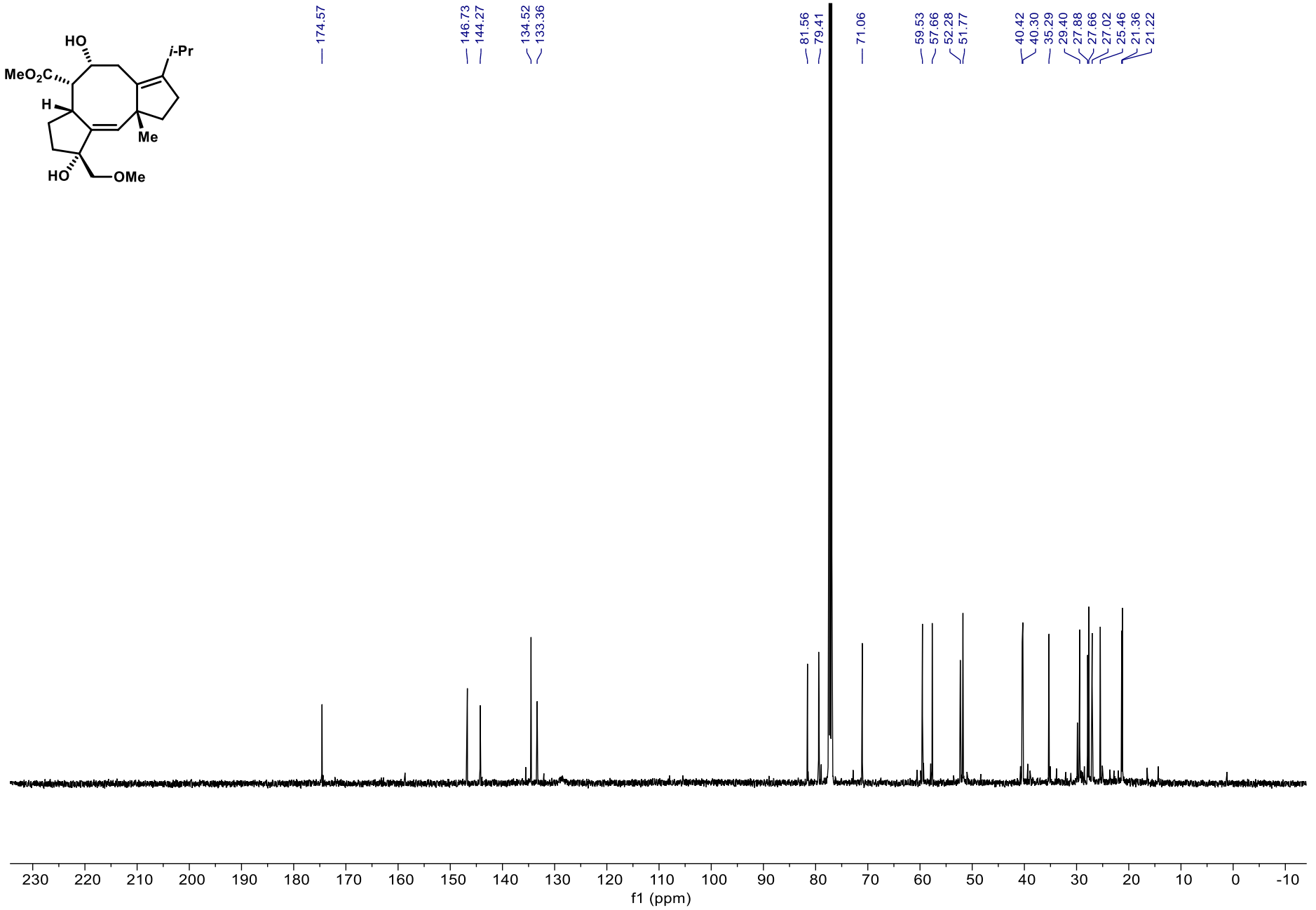
^{13}C NMR of **40g**, 151 MHz, $CDCl_3$



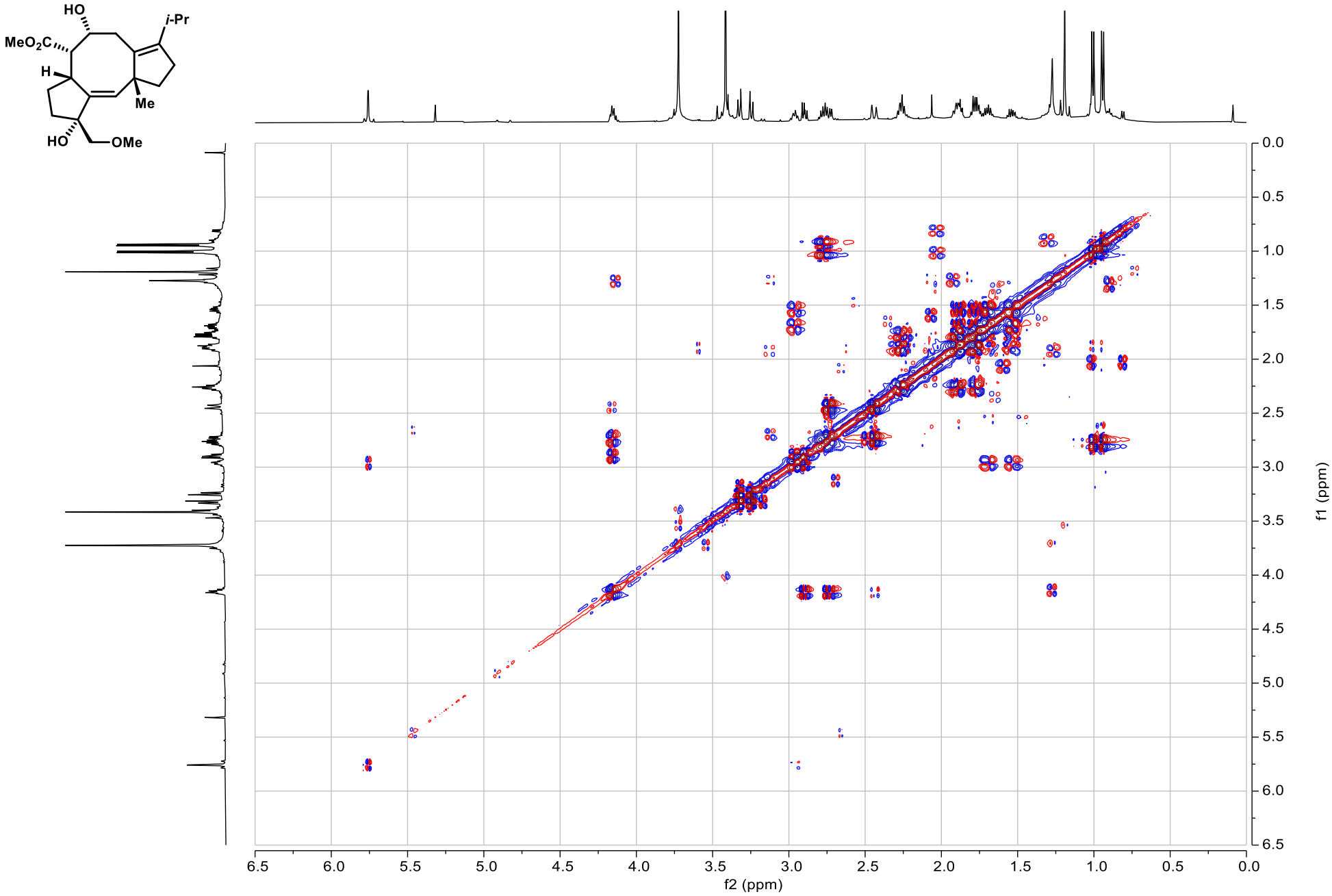
^{1}H NMR of 6-*epi*-**45**, 600 MHz, $CDCl_3$



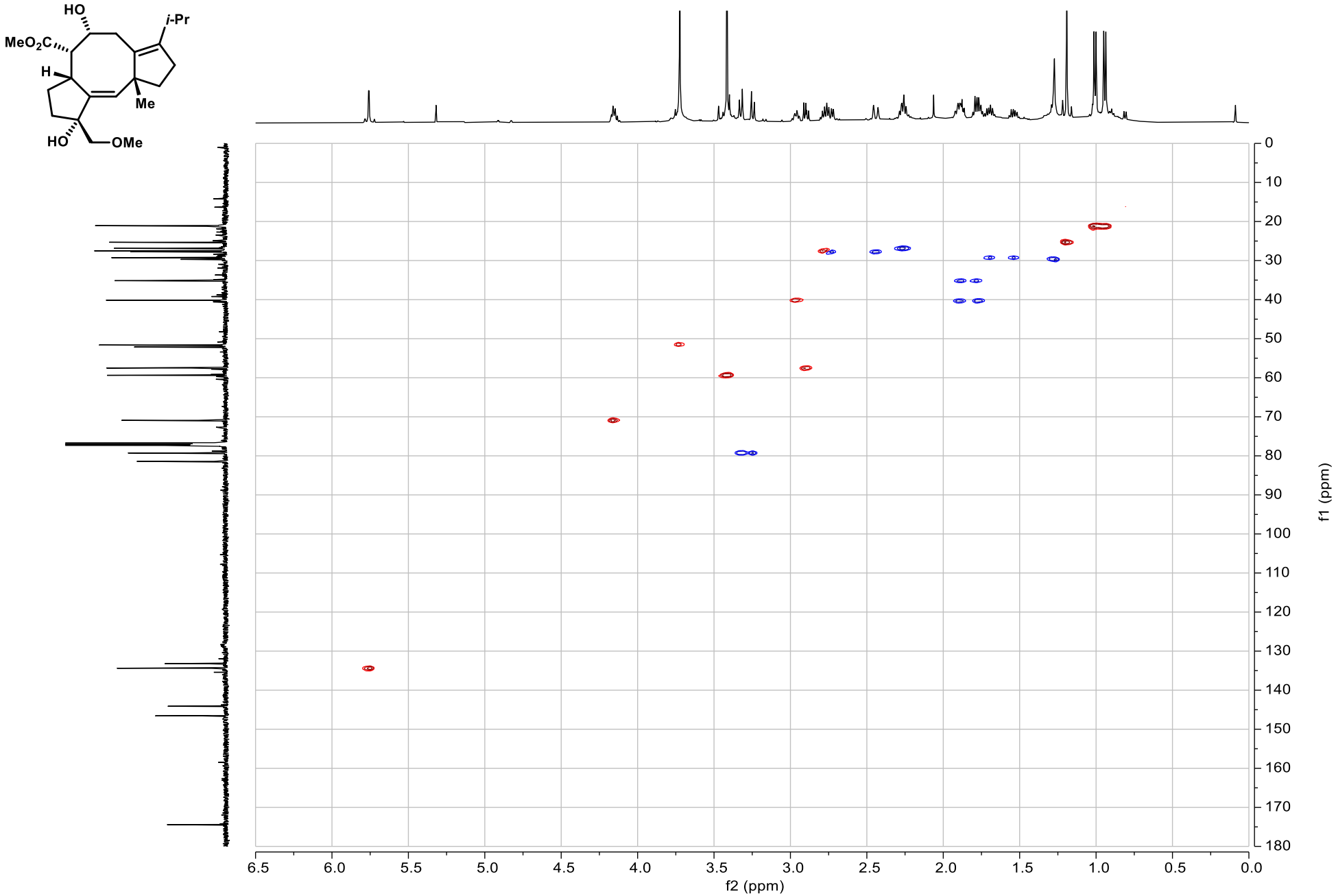
^{13}C NMR of 6-*epi*-**45**, 151 MHz, $CDCl_3$



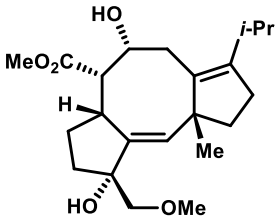
COSY of 6-*epi*-**45**, 600 MHz, $CDCl_3$



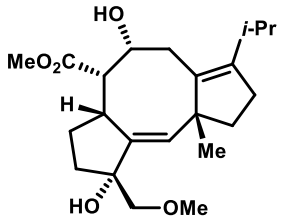
HSQC of 6-*epi*-**45**, 600 MHz, $CDCl_3$



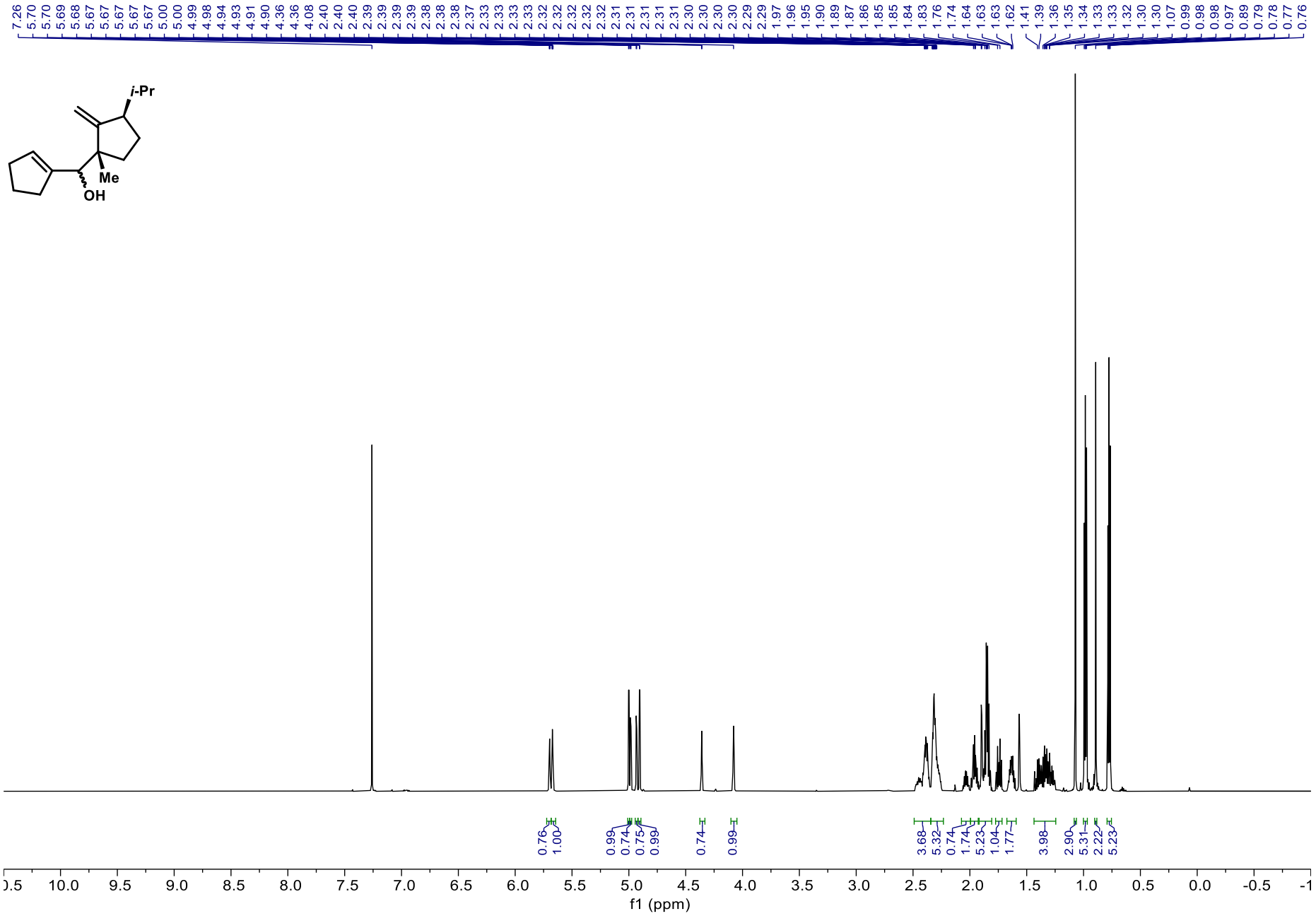
HMBC of 6-*epi*-**45**, 600 MHz, $CDCl_3$



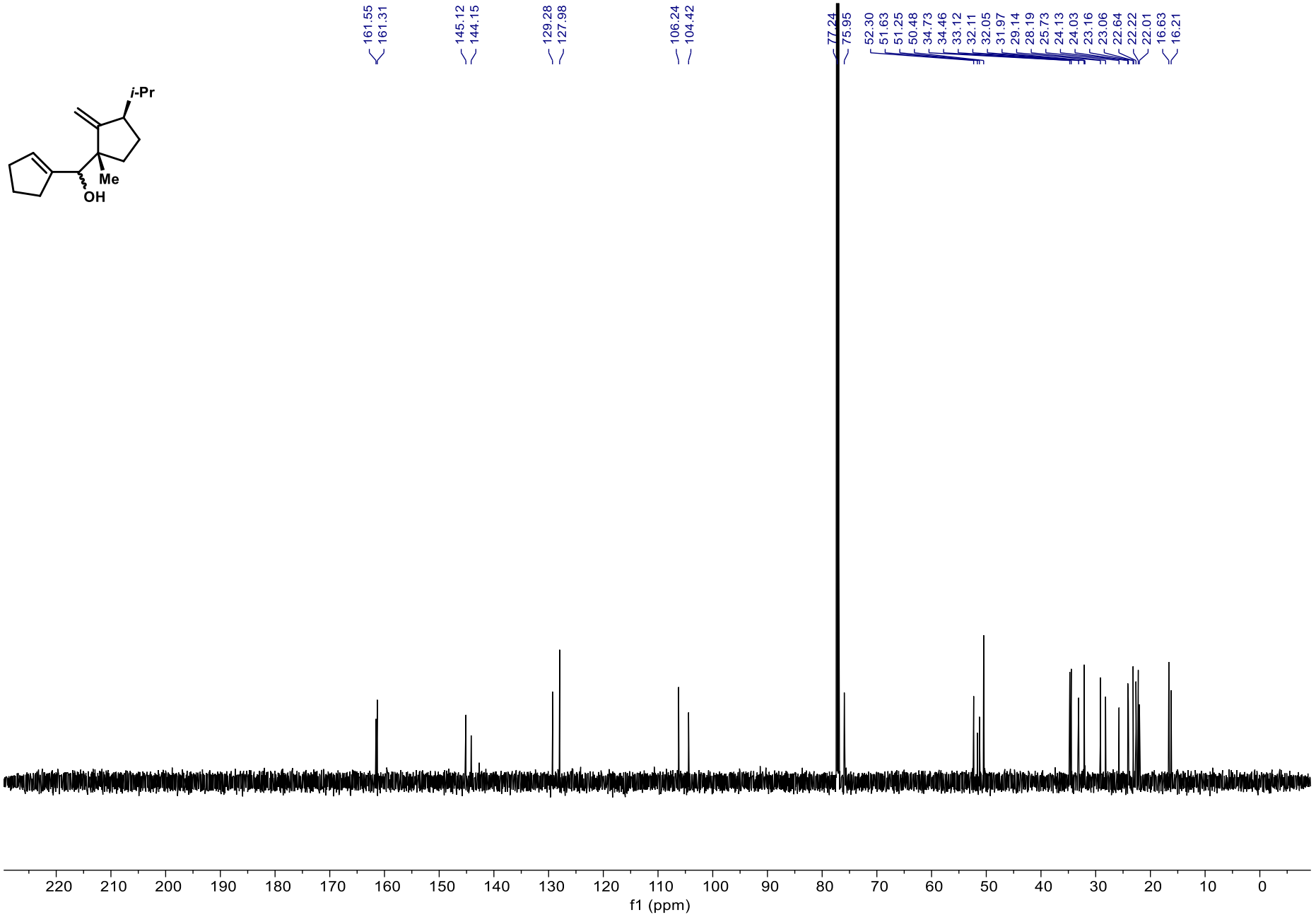
NOESY of 6-*epi*-**45**, 600 MHz, $CDCl_3$



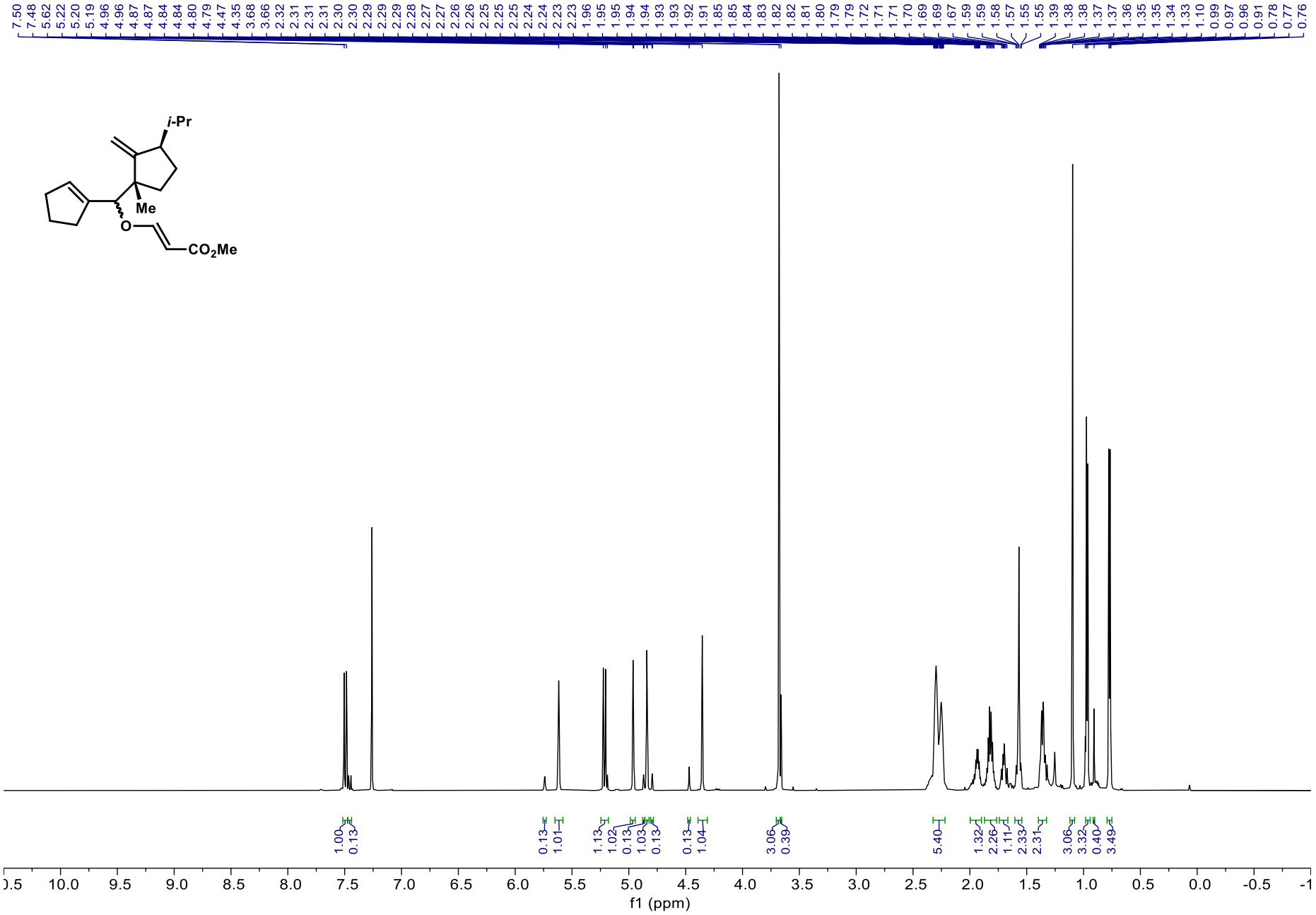
^{1}H NMR of **S12** (1.3:1 dr), 600 MHz, $CDCl_3$



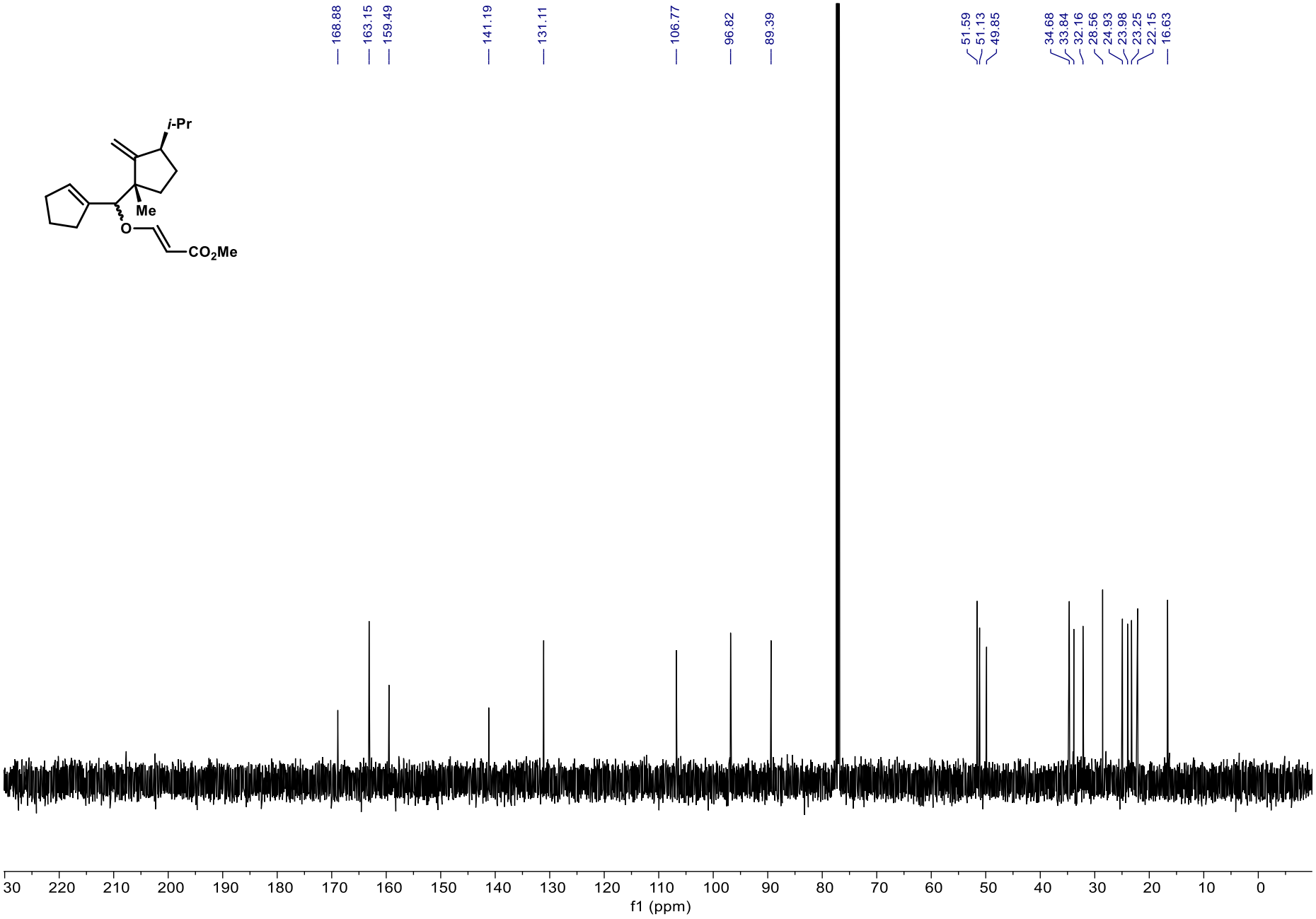
^{13}C NMR of **S12** (1.3:1 dr), 151 MHz, $CDCl_3$



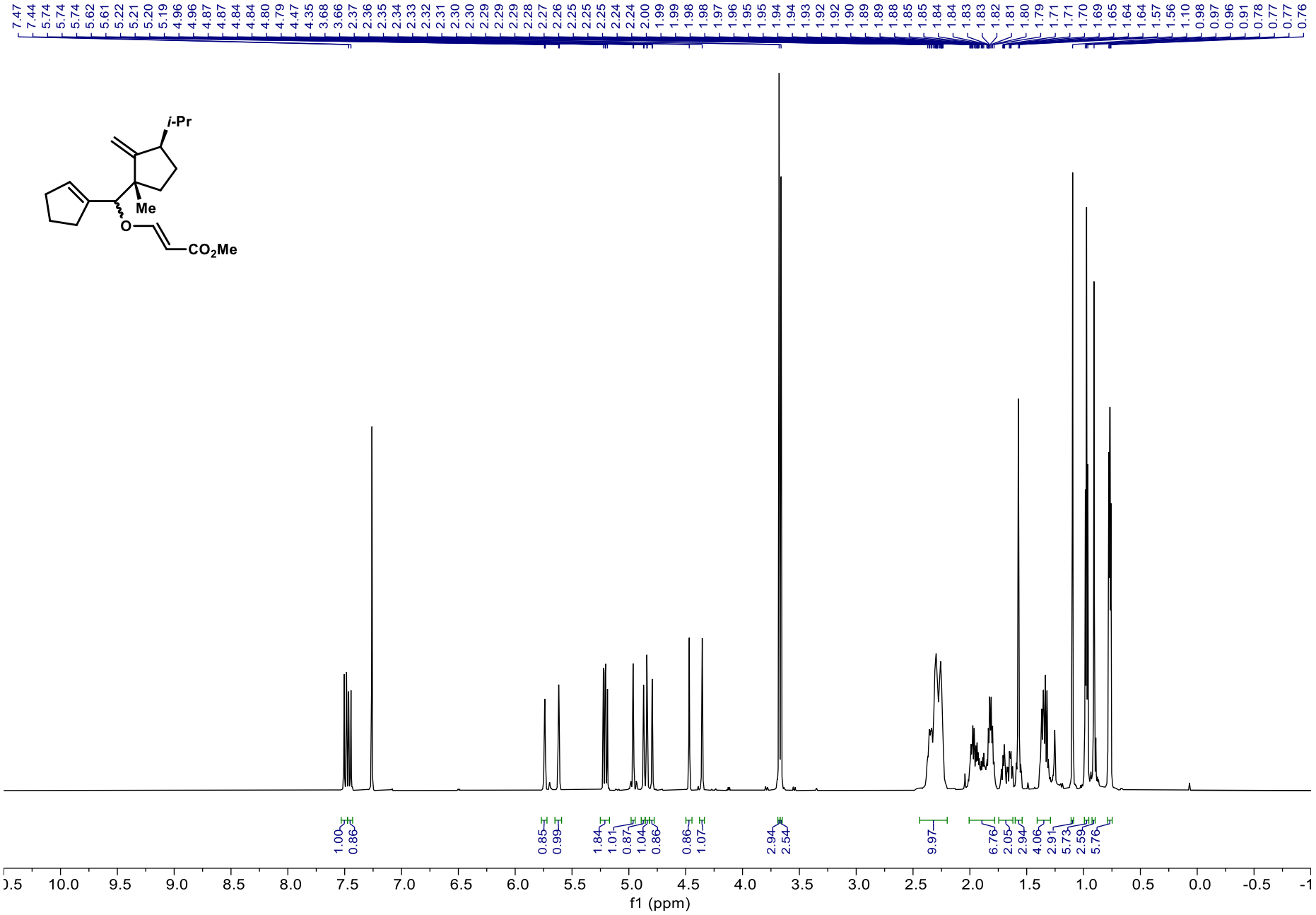
^{1}H NMR of 8:1 mixture of **42**, 600 MHz, $CDCl_3$



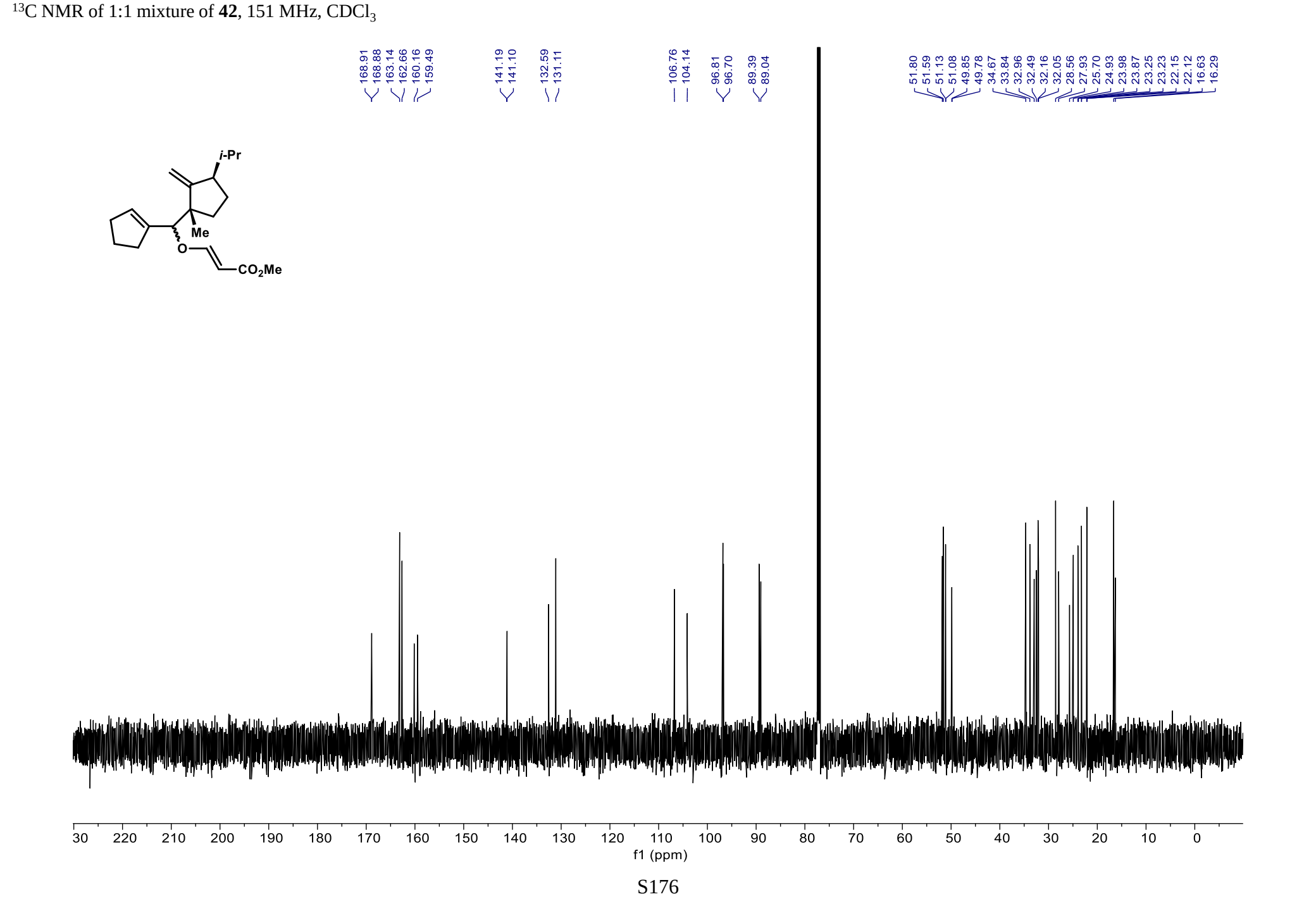
^{13}C NMR of 8:1 mixture of **42**, 151 MHz, $CDCl_3$



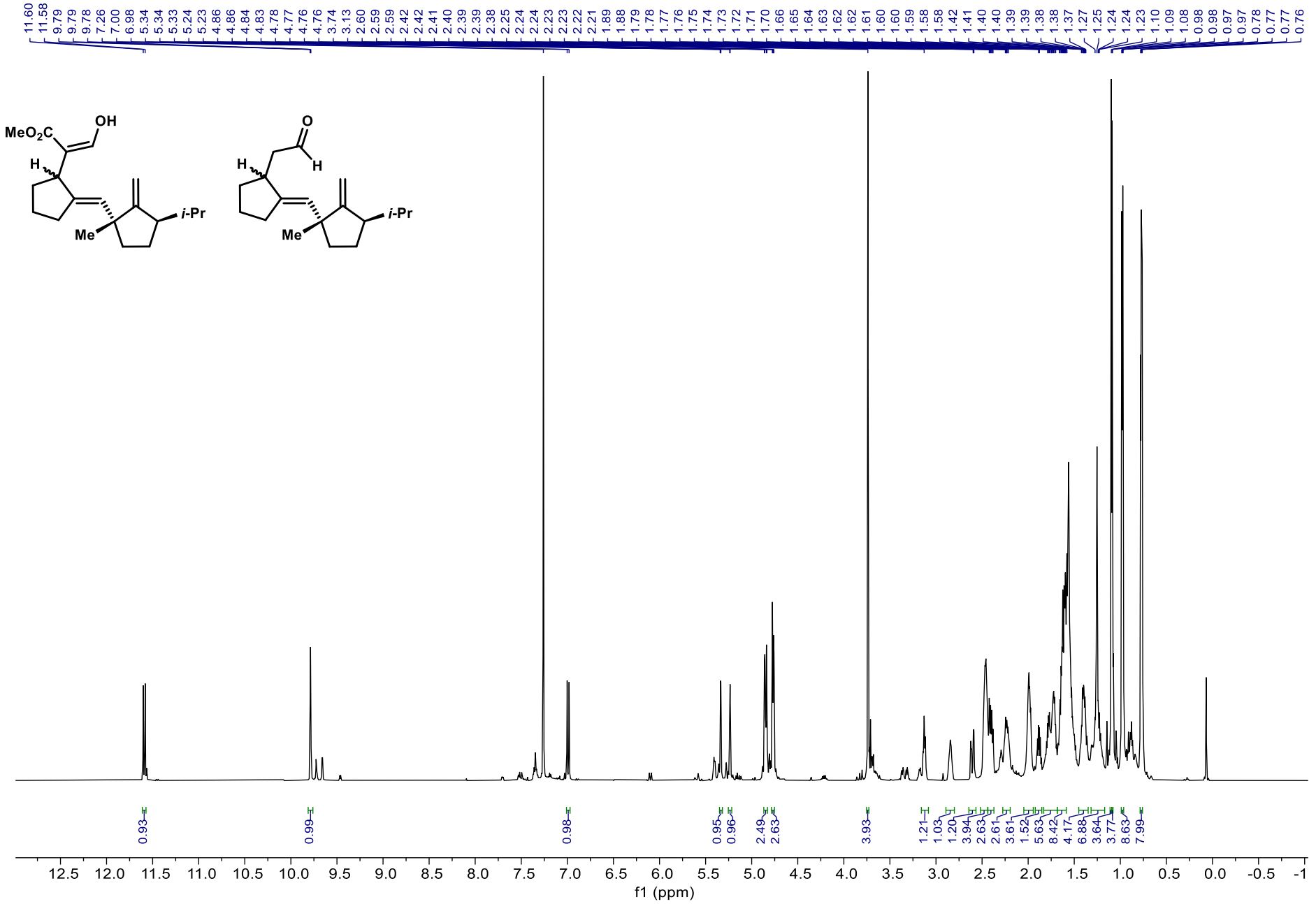
^{1}H NMR of 1:1 mixture of **42**, 600 MHz, $CDCl_3$



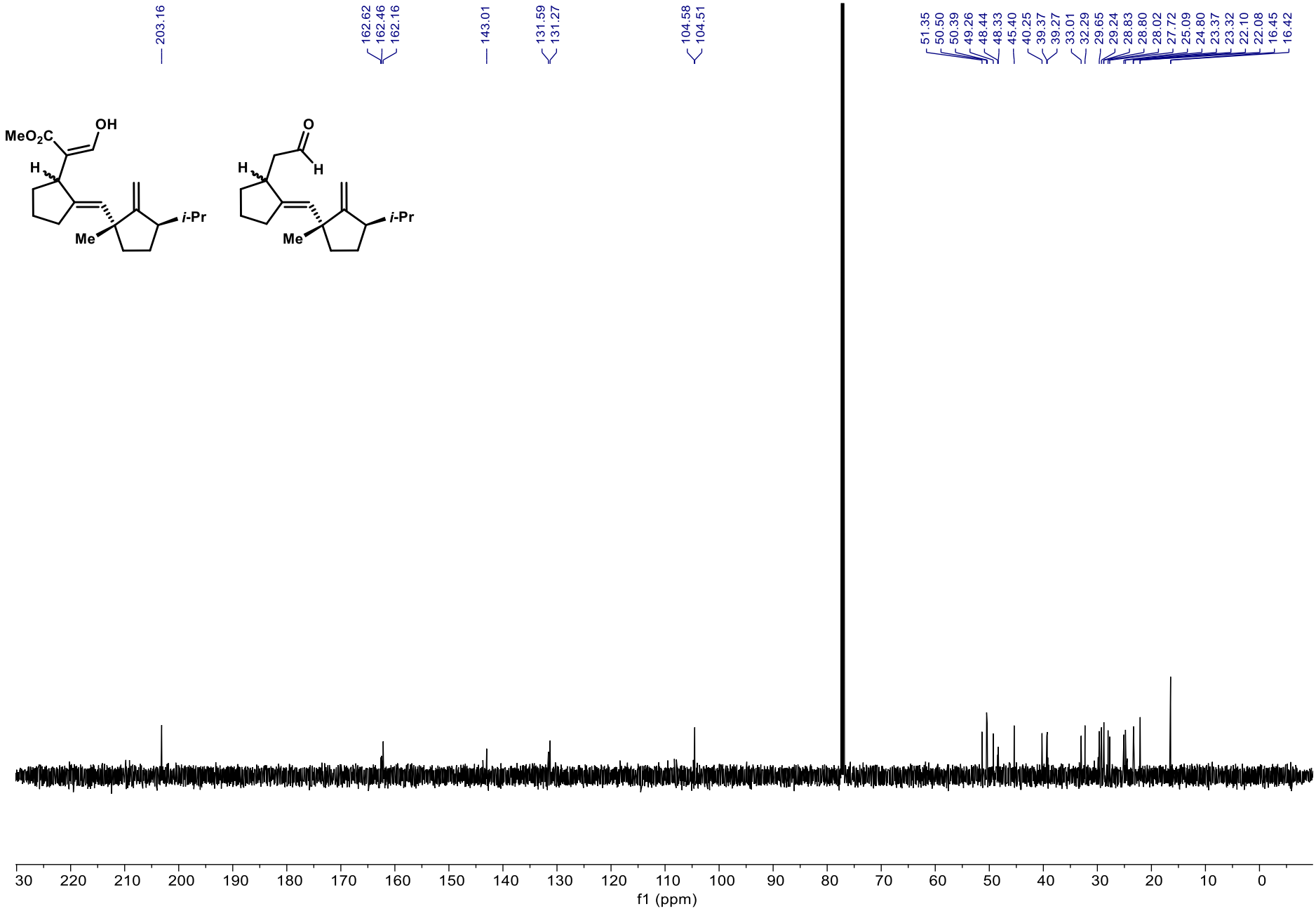
^{13}C NMR of 1:1 mixture of **42**, 151 MHz, $CDCl_3$



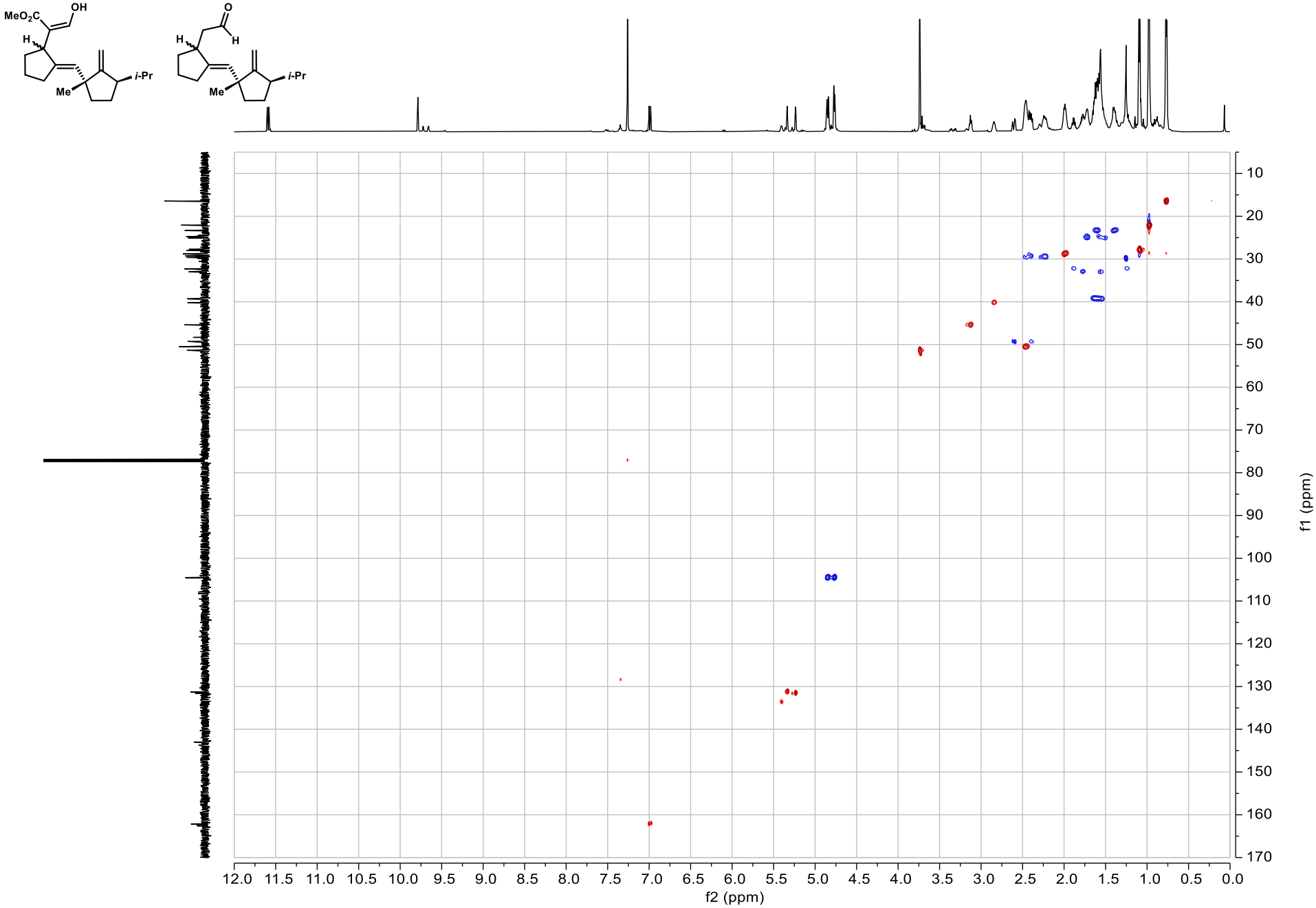
^{1}H NMR of 1:1 mixture of **43** and **S13**, 600 MHz, $CDCl_3$



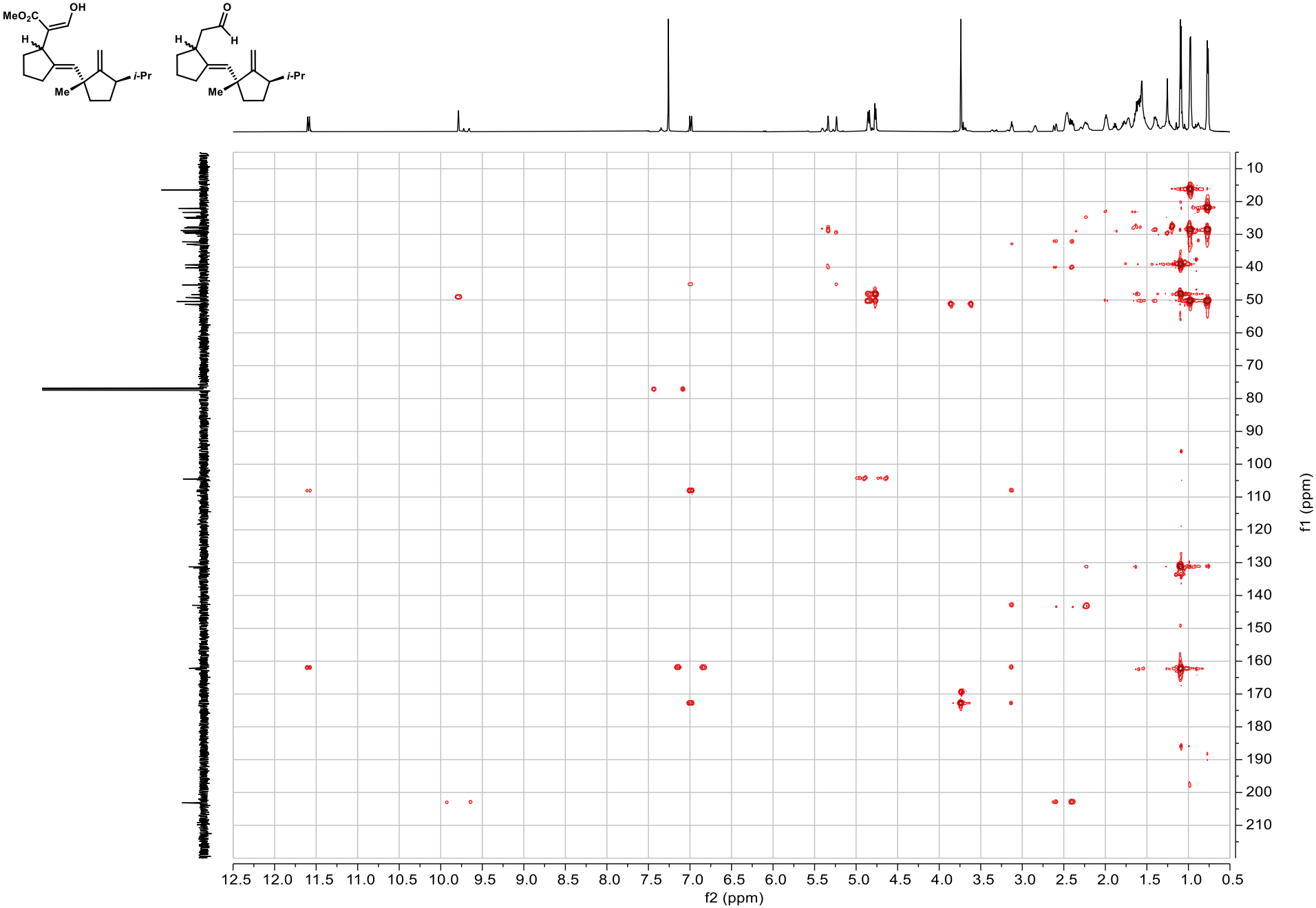
^{13}C NMR of 1:1 mixture of **43** and **S13**, 151 MHz, $CDCl_3$



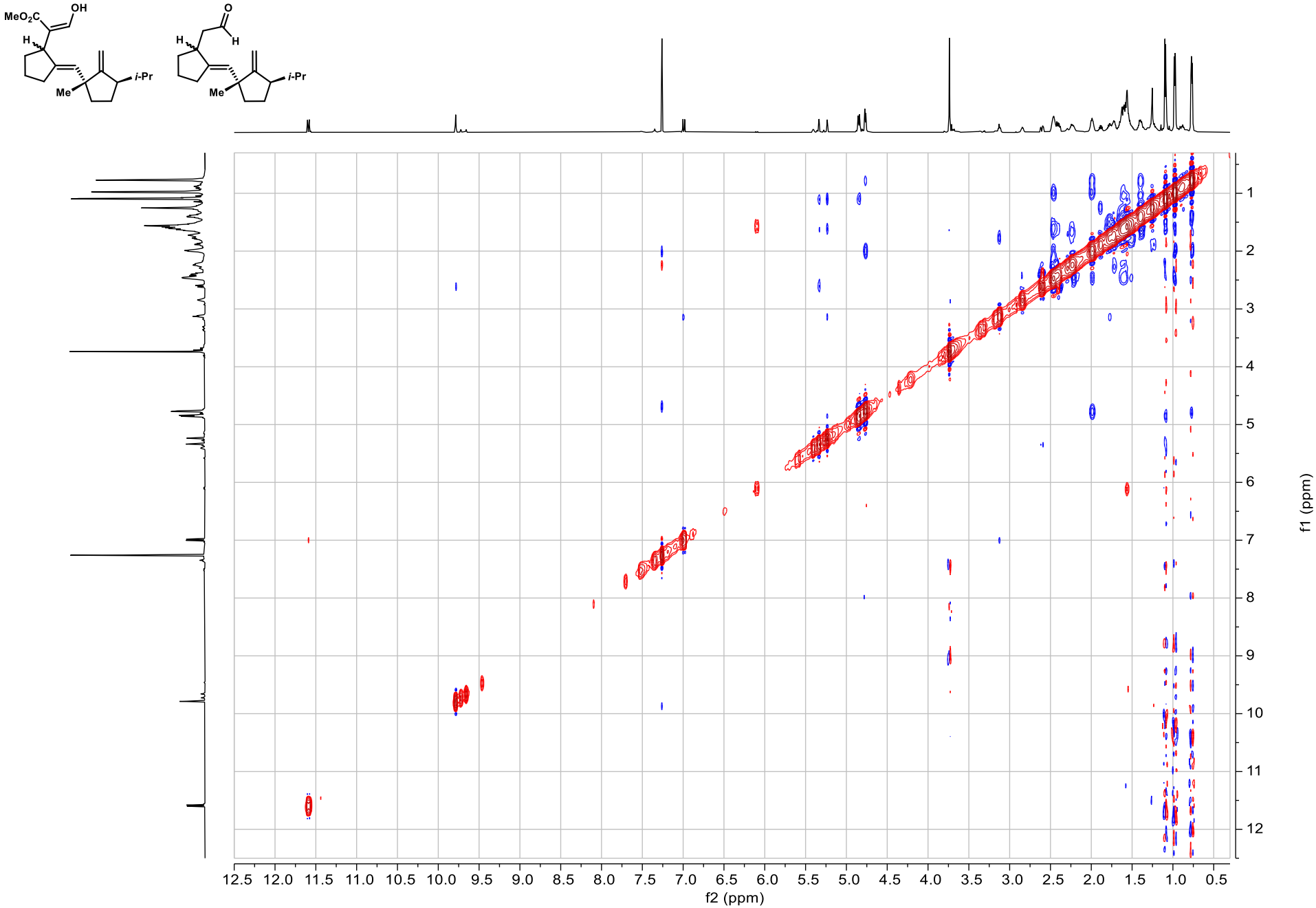
HSQC of 1:1 mixture of **43** and **S13**, 600 MHz, $CDCl_3$



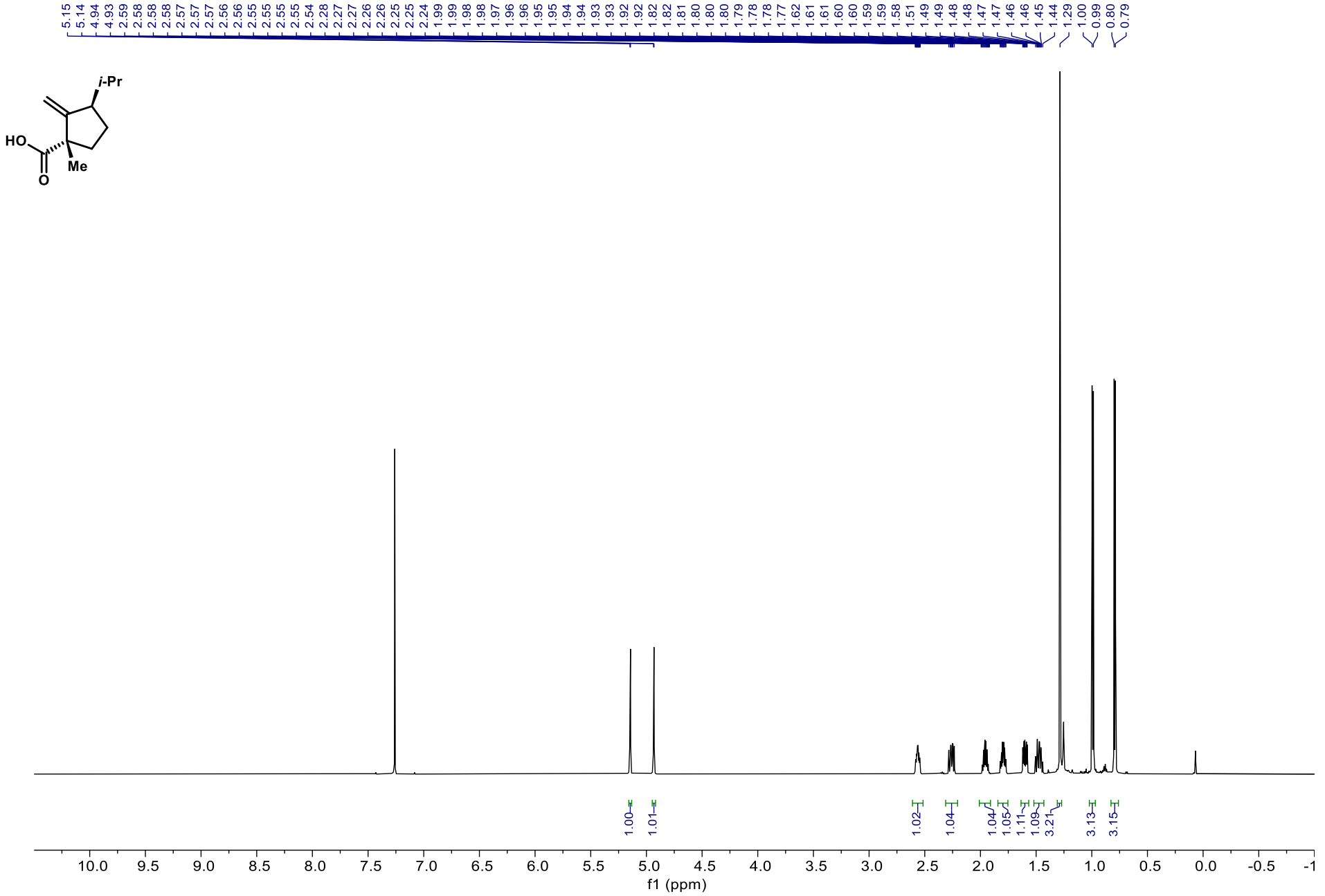
HMBC of 1:1 mixture of **43** and **S13**, 600 MHz, $CDCl_3$



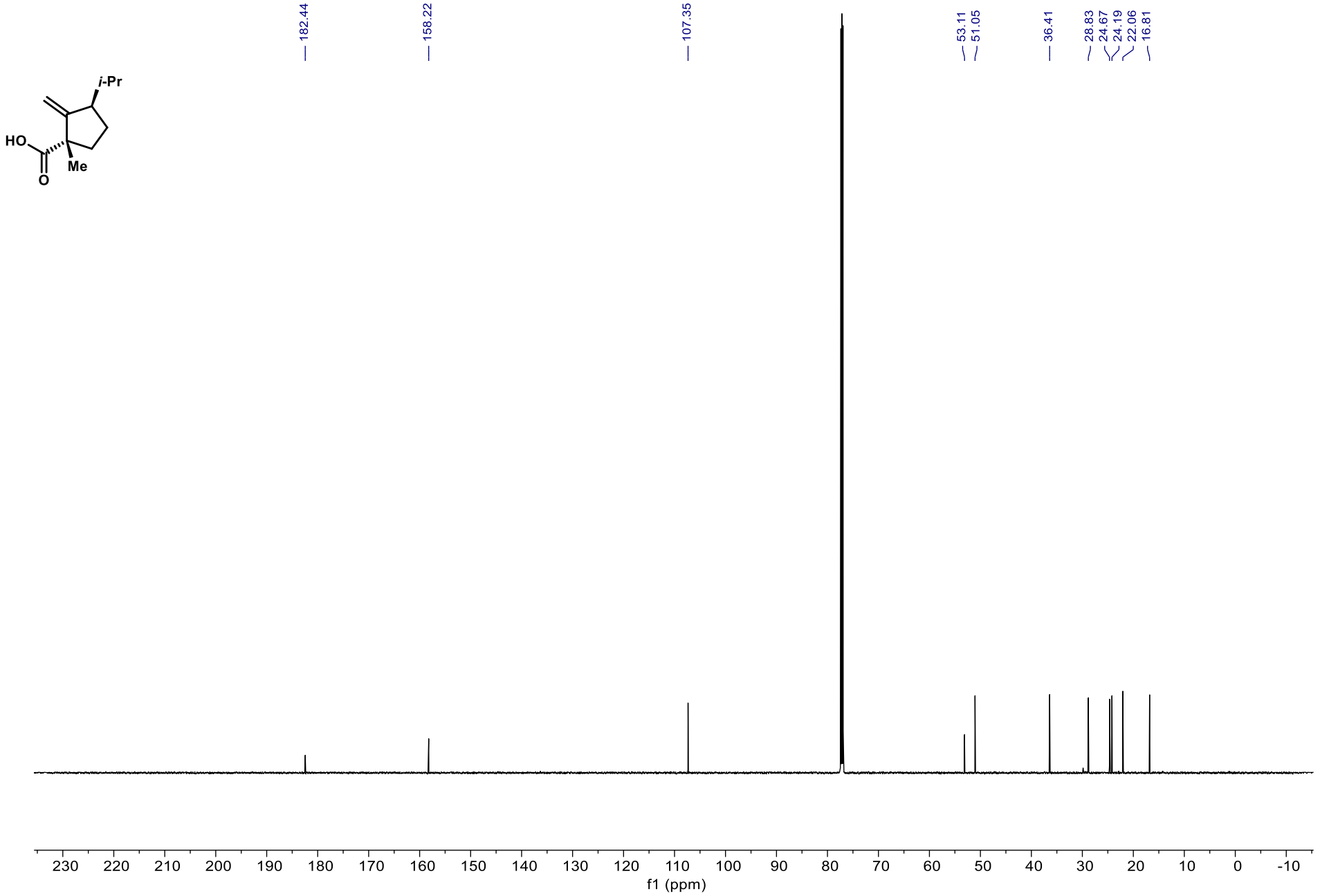
NOESY of 1:1 mixture of **43** and **S13**, 600 MHz, $CDCl_3$



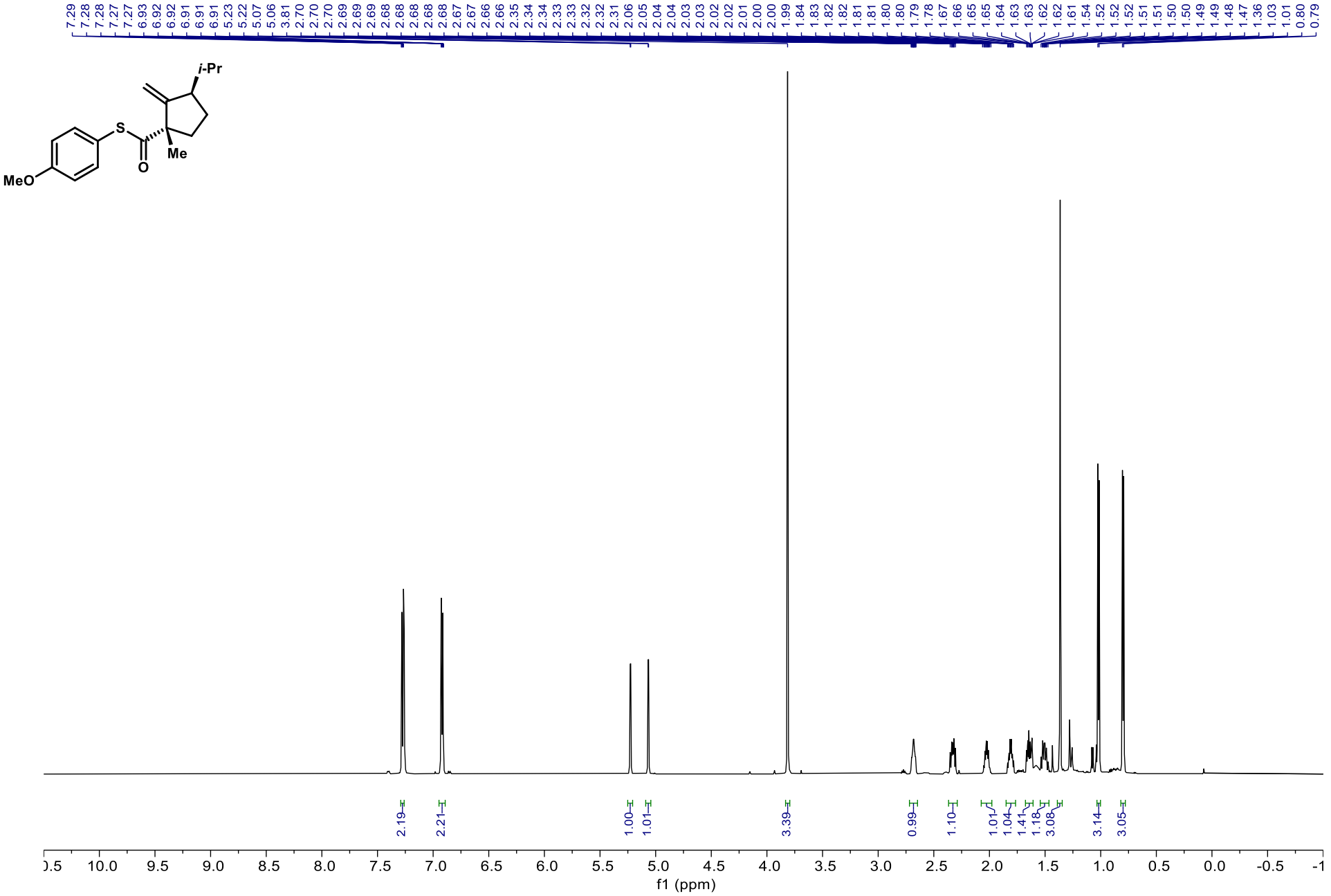
^{1}H NMR of **S14**, 600 MHz, $CDCl_3$



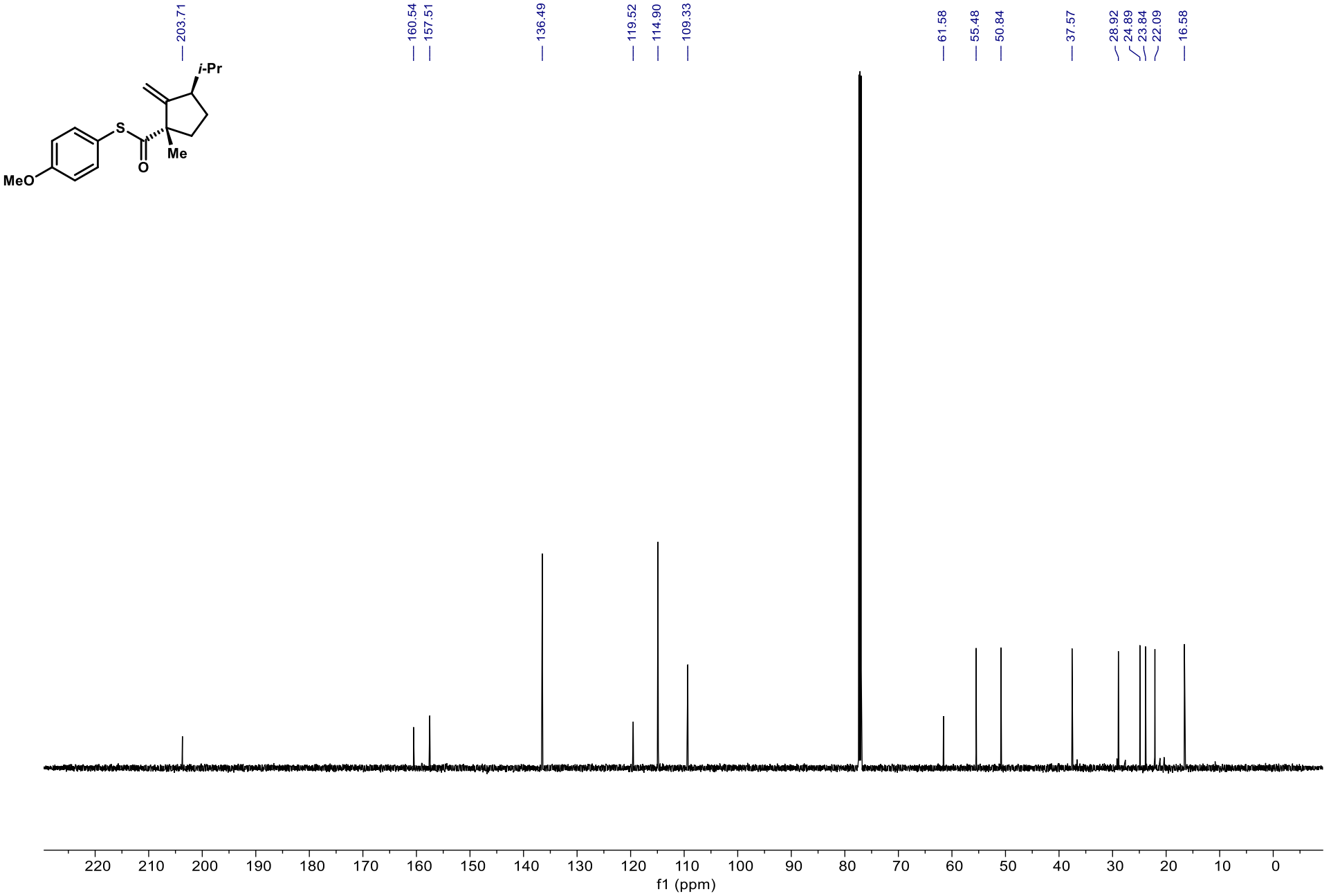
^{13}C NMR of **S14**, 151 MHz, $CDCl_3$



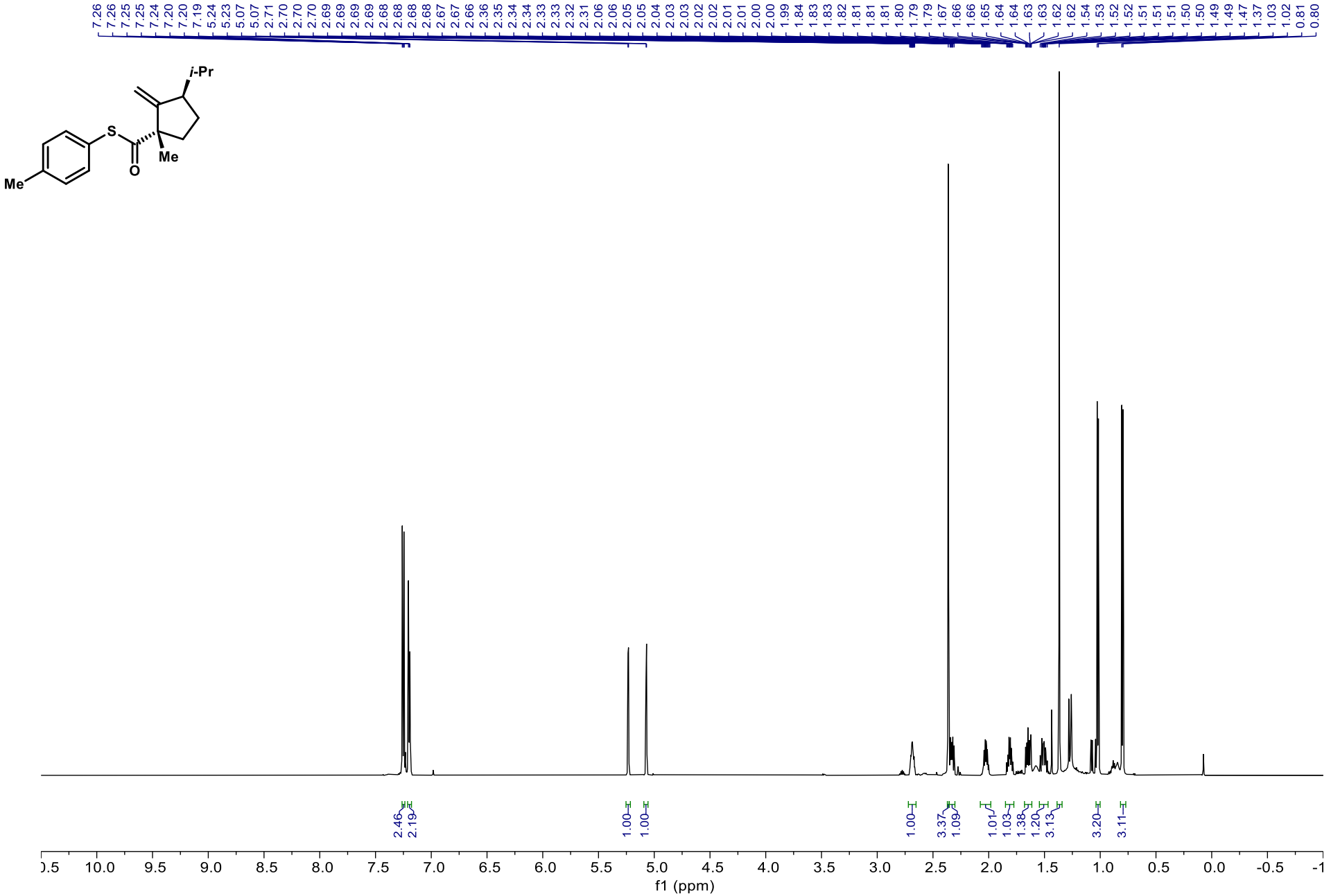
^{1}H NMR of **S15**, 600 MHz, $CDCl_3$



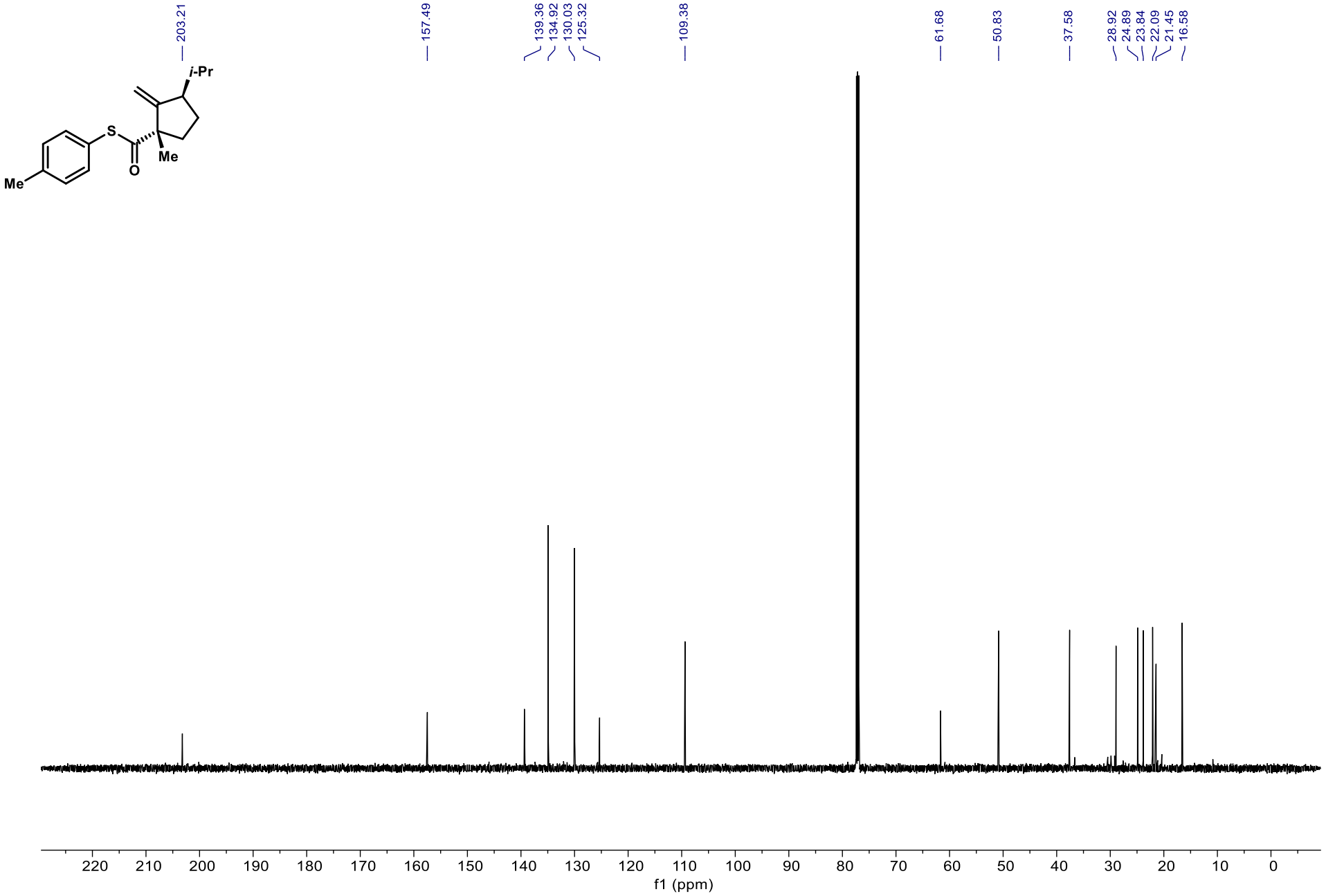
^{13}C NMR of **S15**, 151 MHz, $CDCl_3$



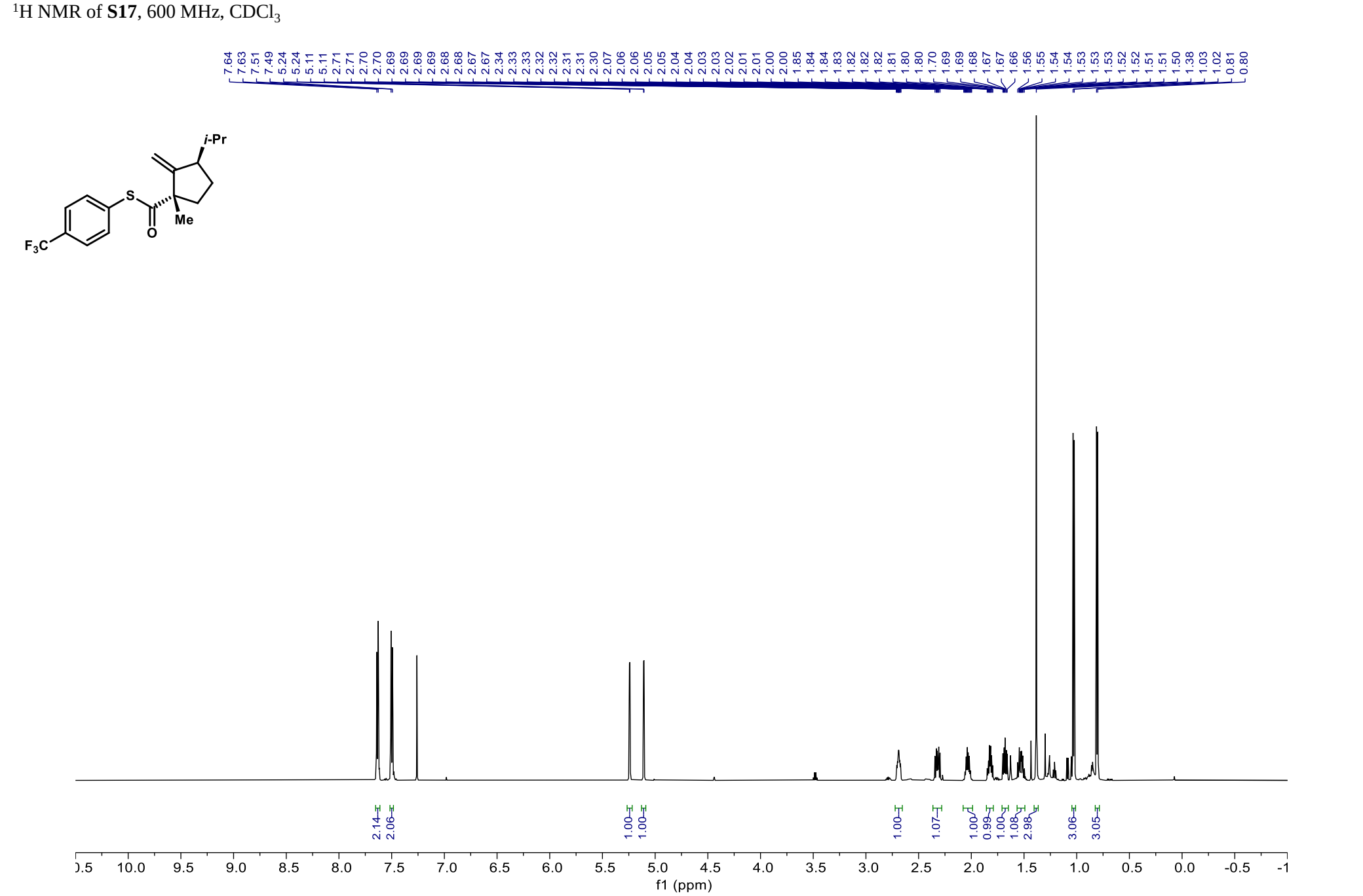
^{1}H NMR of **S16**, 600 MHz, $CDCl_3$



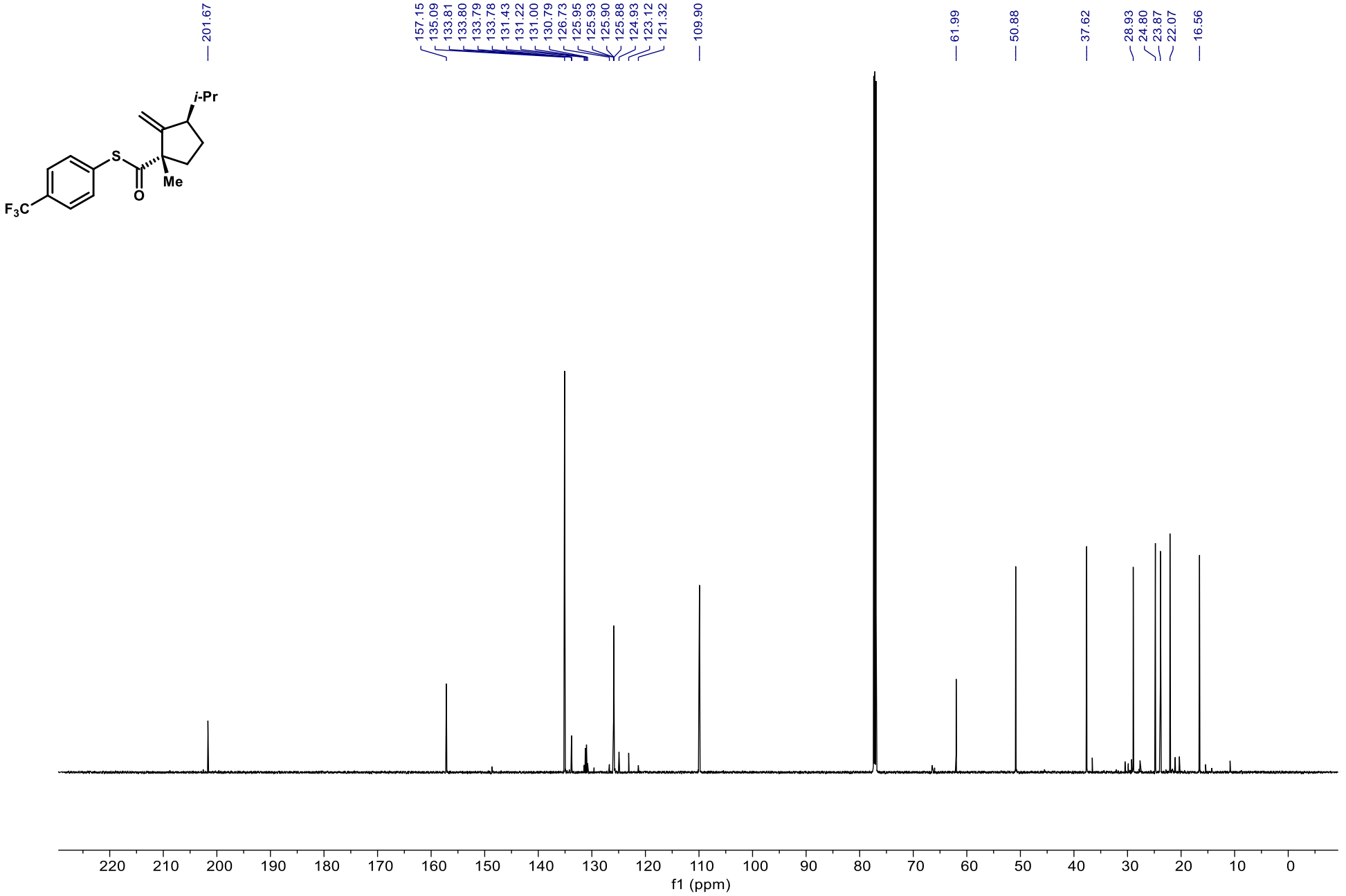
^{13}C NMR of **S16**, 151 MHz, $CDCl_3$



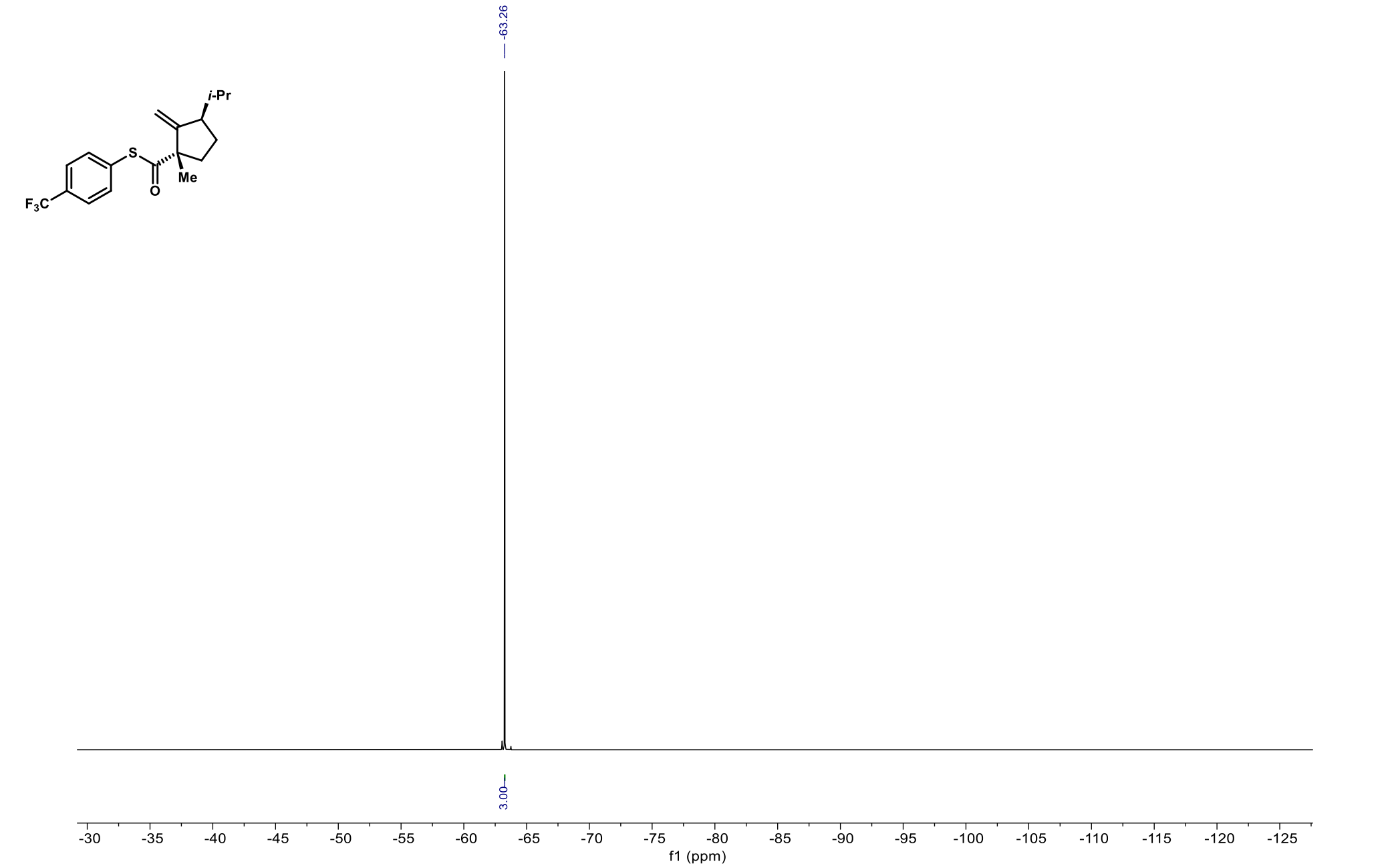
^{1}H NMR of **S17**, 600 MHz, $CDCl_3$



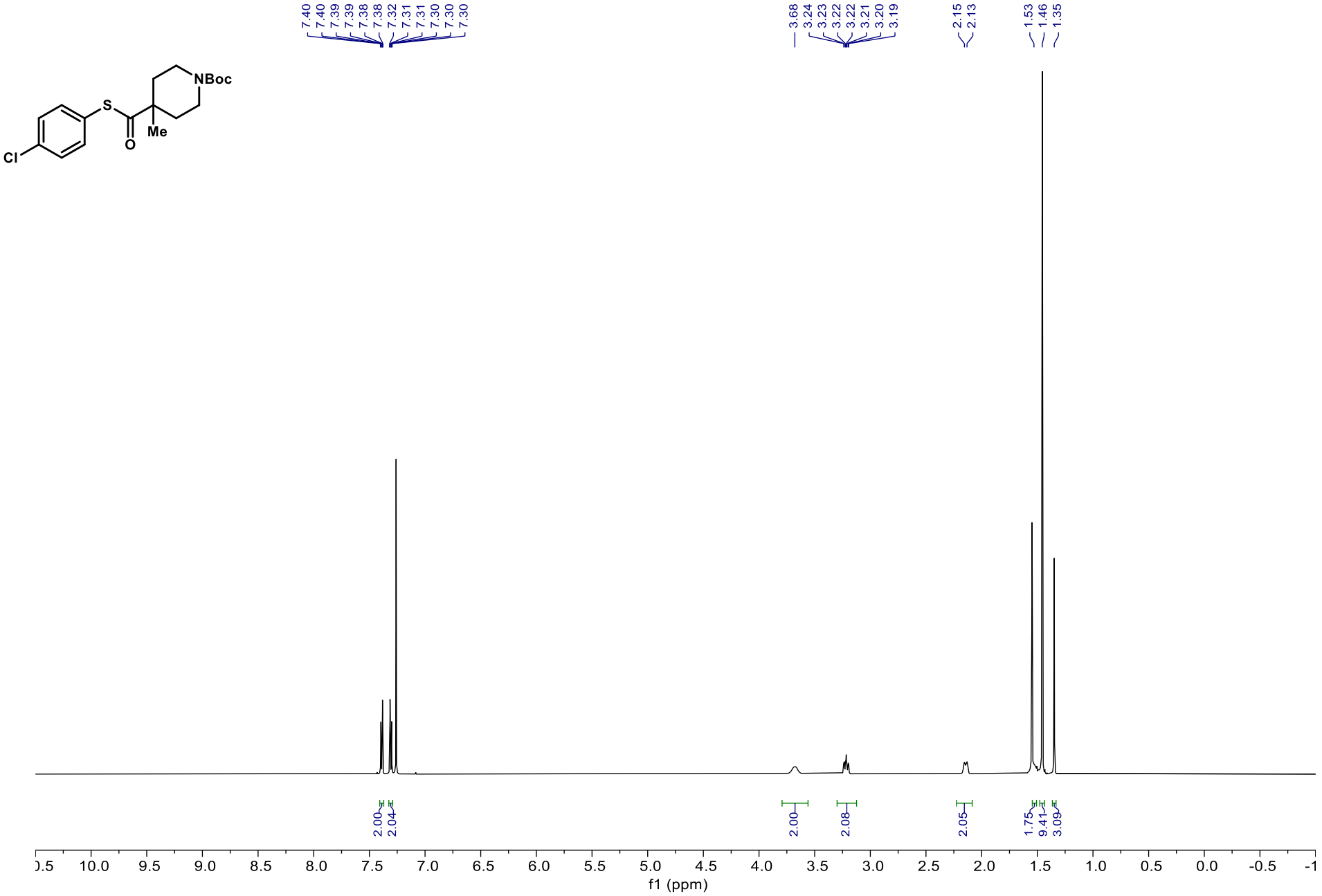
^{13}C NMR of **S17**, 151 MHz, $CDCl_3$



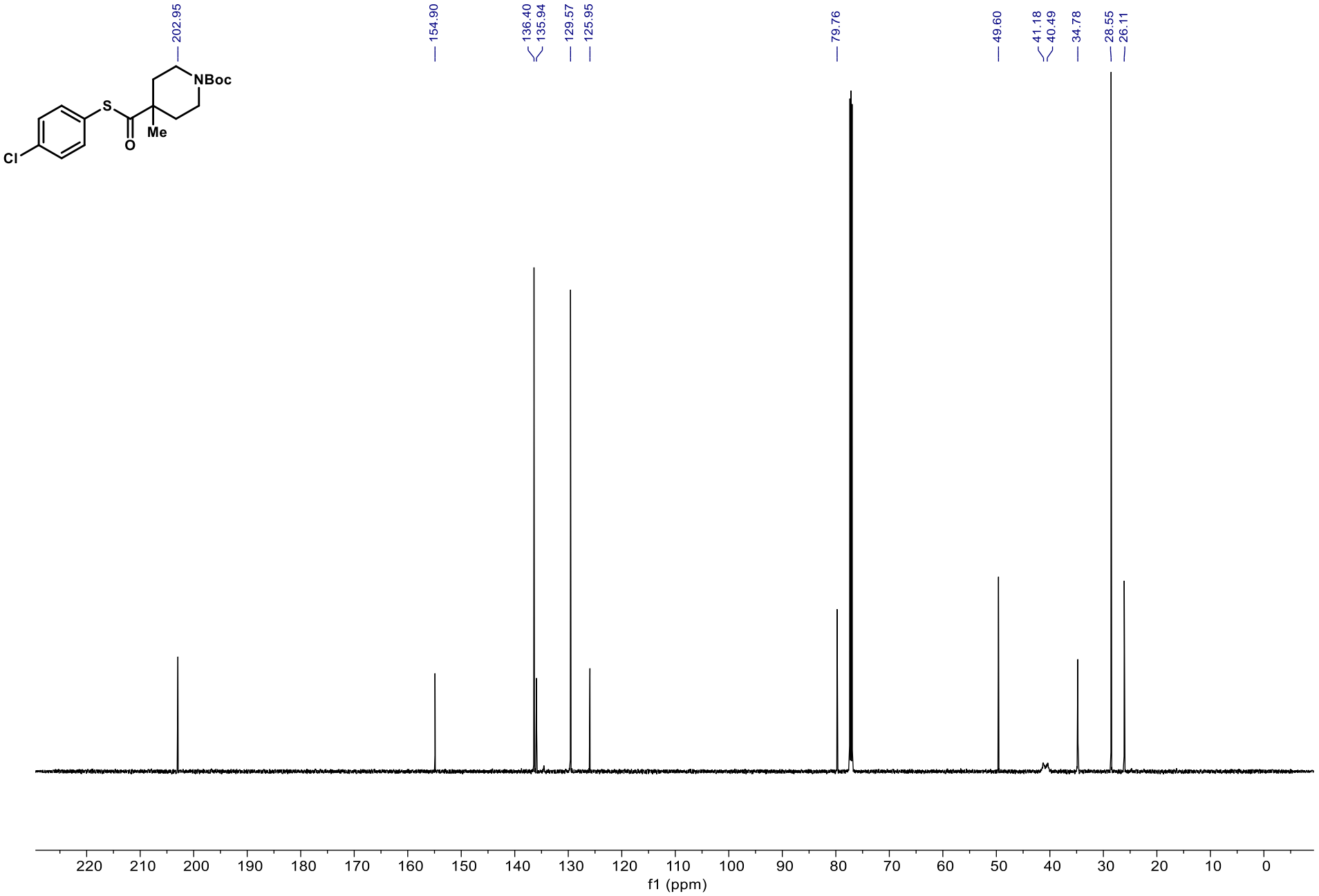
^{19}F NMR of **S17**, 376 MHz, $CDCl_3$



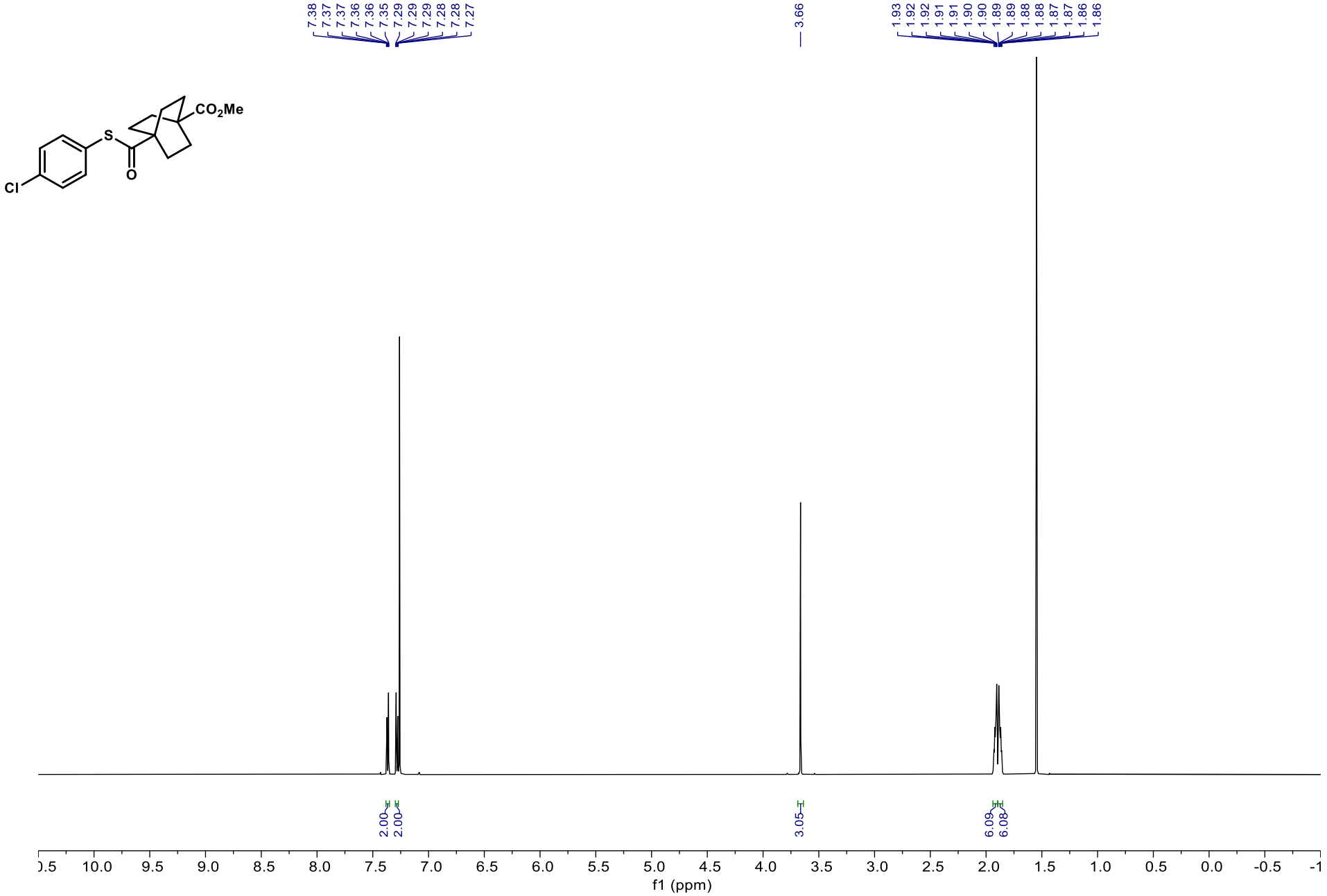
^{1}H NMR of **38a**, 600 MHz, $CDCl_3$



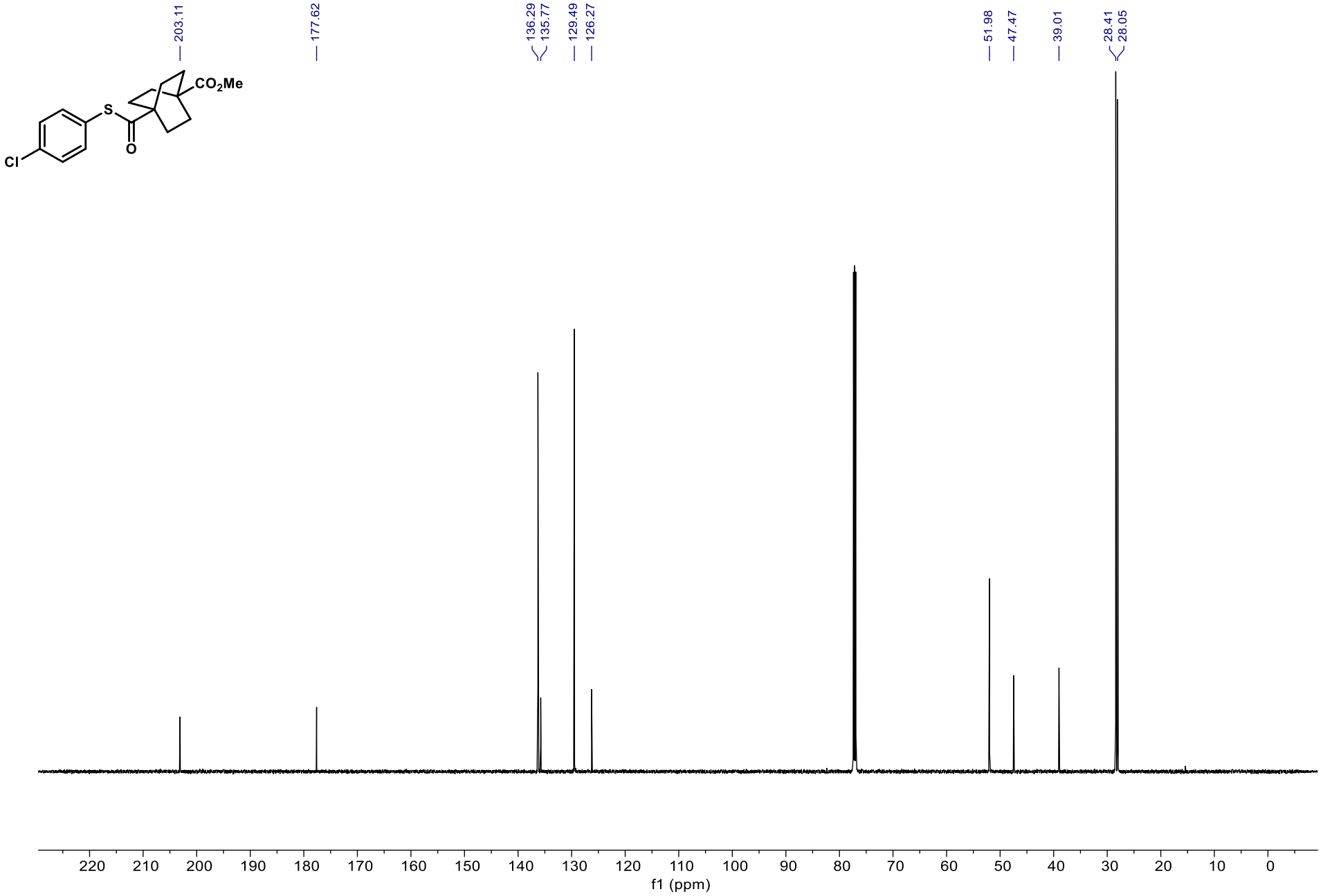
^{13}C NMR of **38a**, 151 MHz, $CDCl_3$



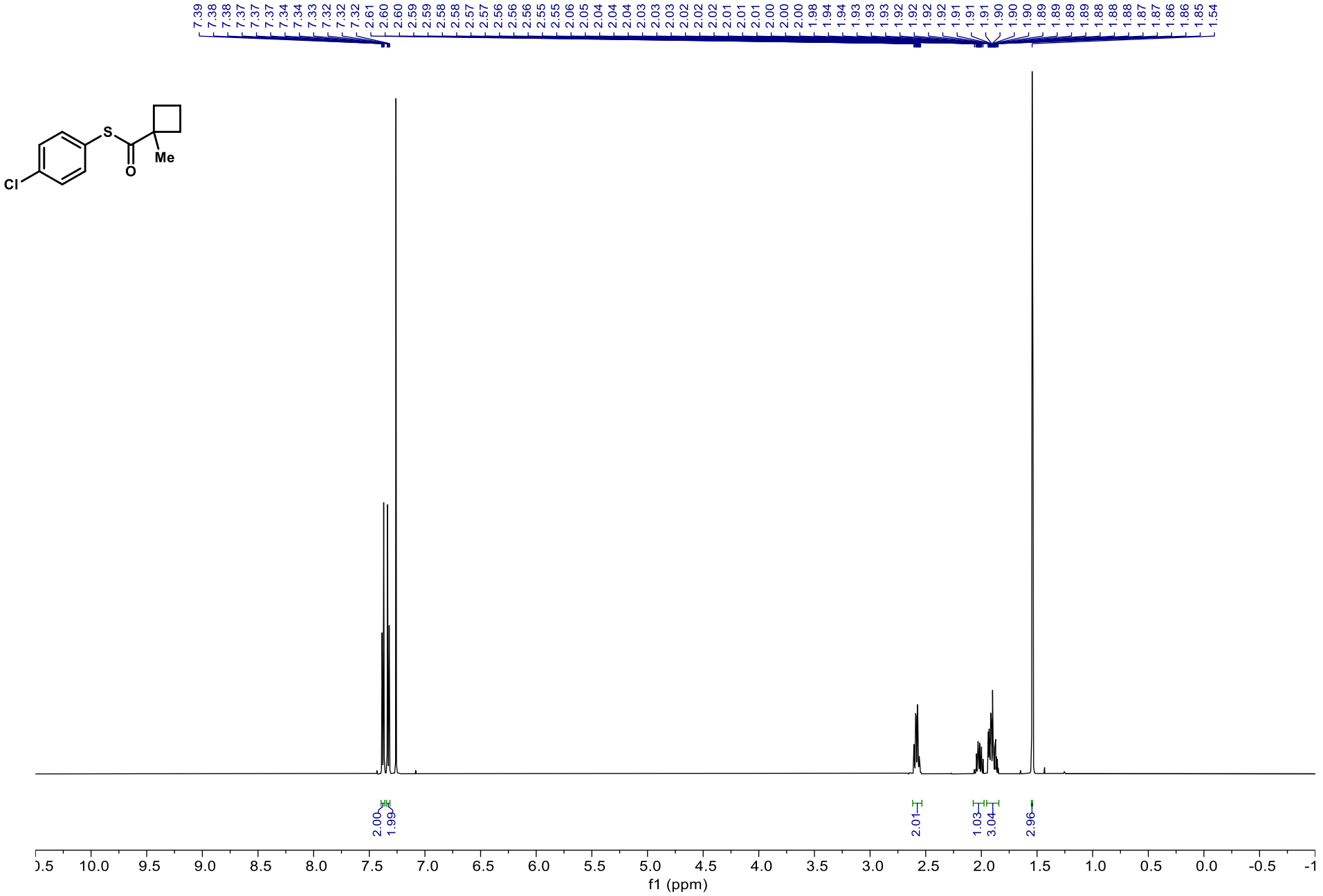
^{1}H NMR of **38b**, 600 MHz, $CDCl_3$



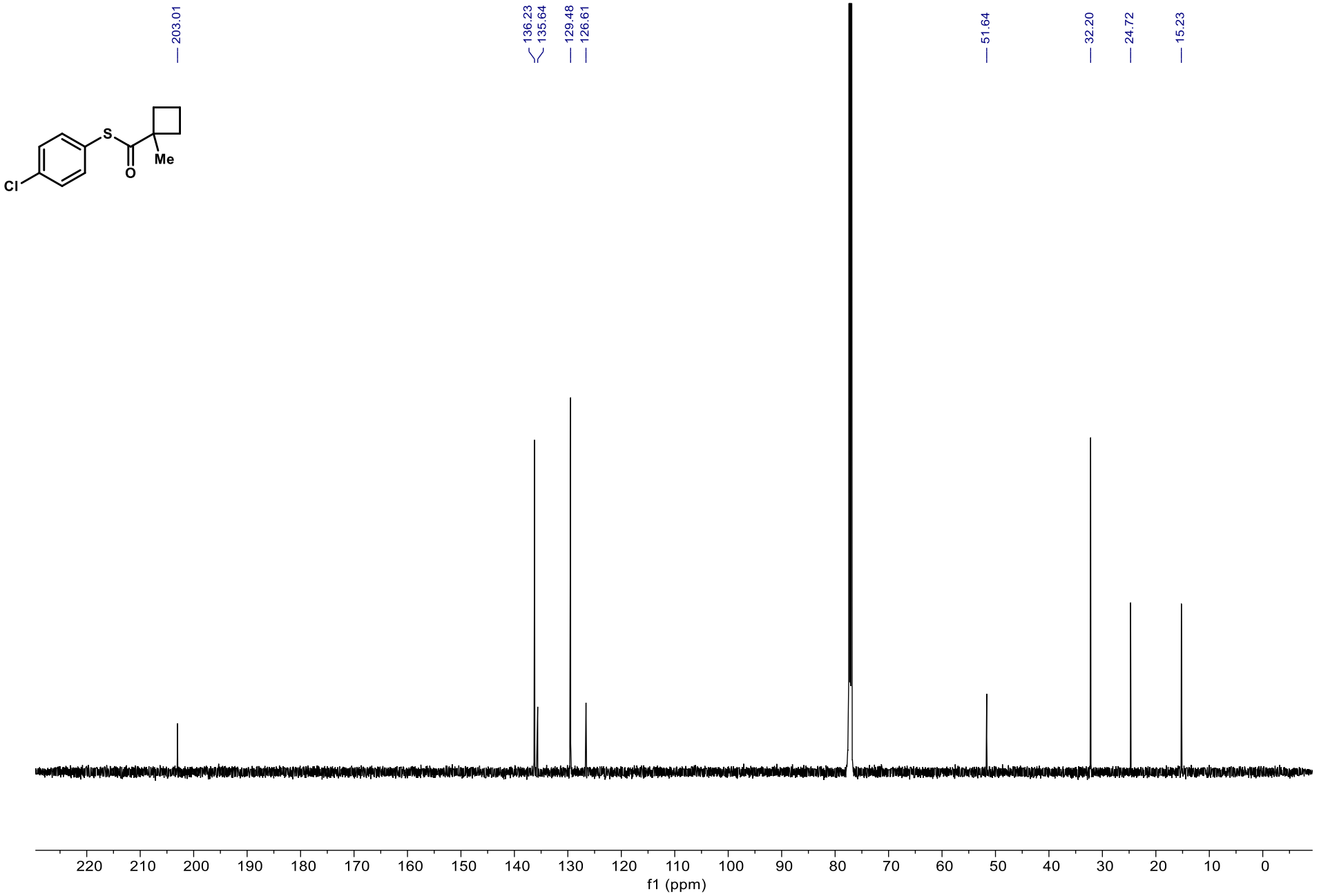
^{13}C NMR of **38b**, 151 MHz, $CDCl_3$



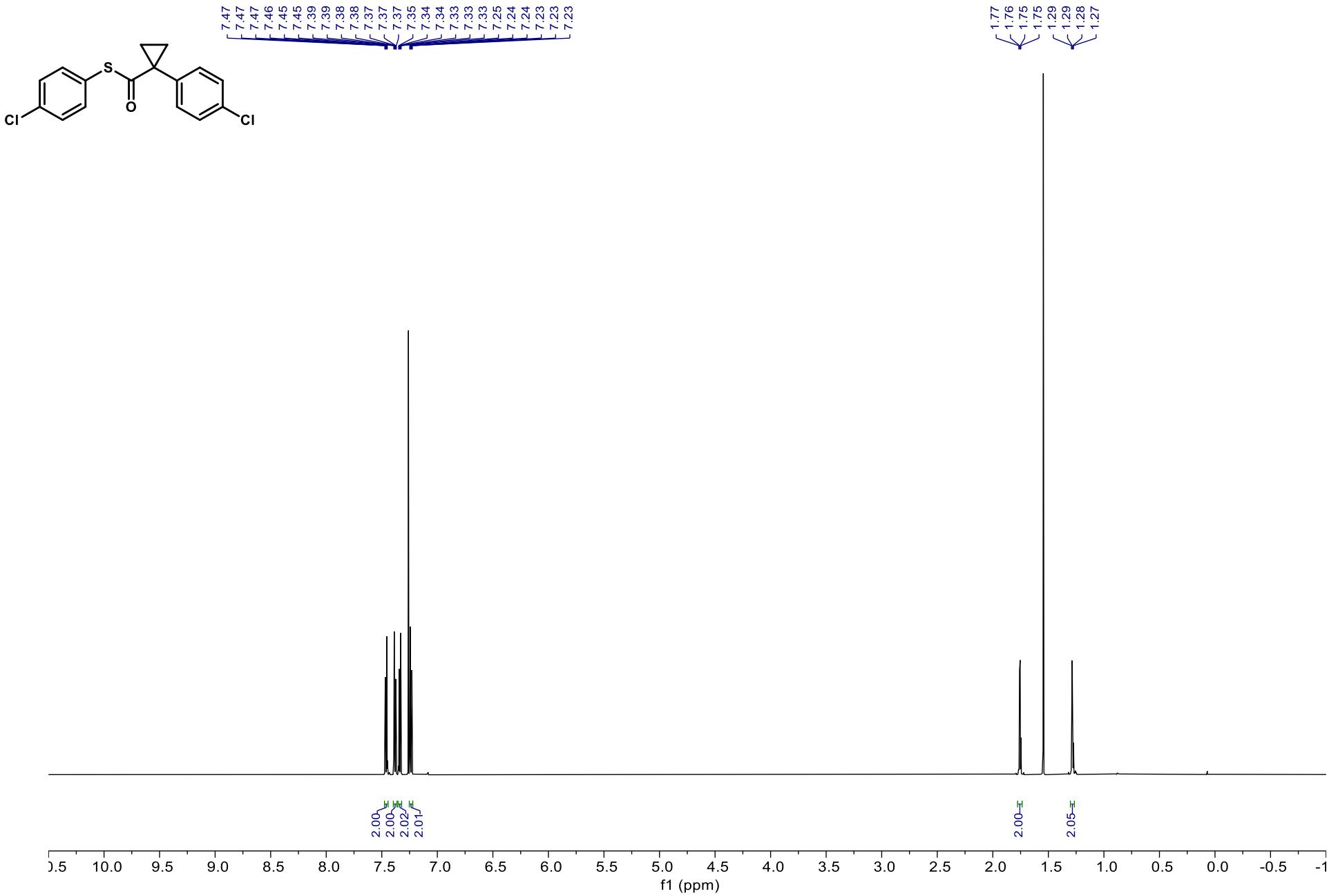
^{1}H NMR of **38c**, 600 MHz, $CDCl_3$



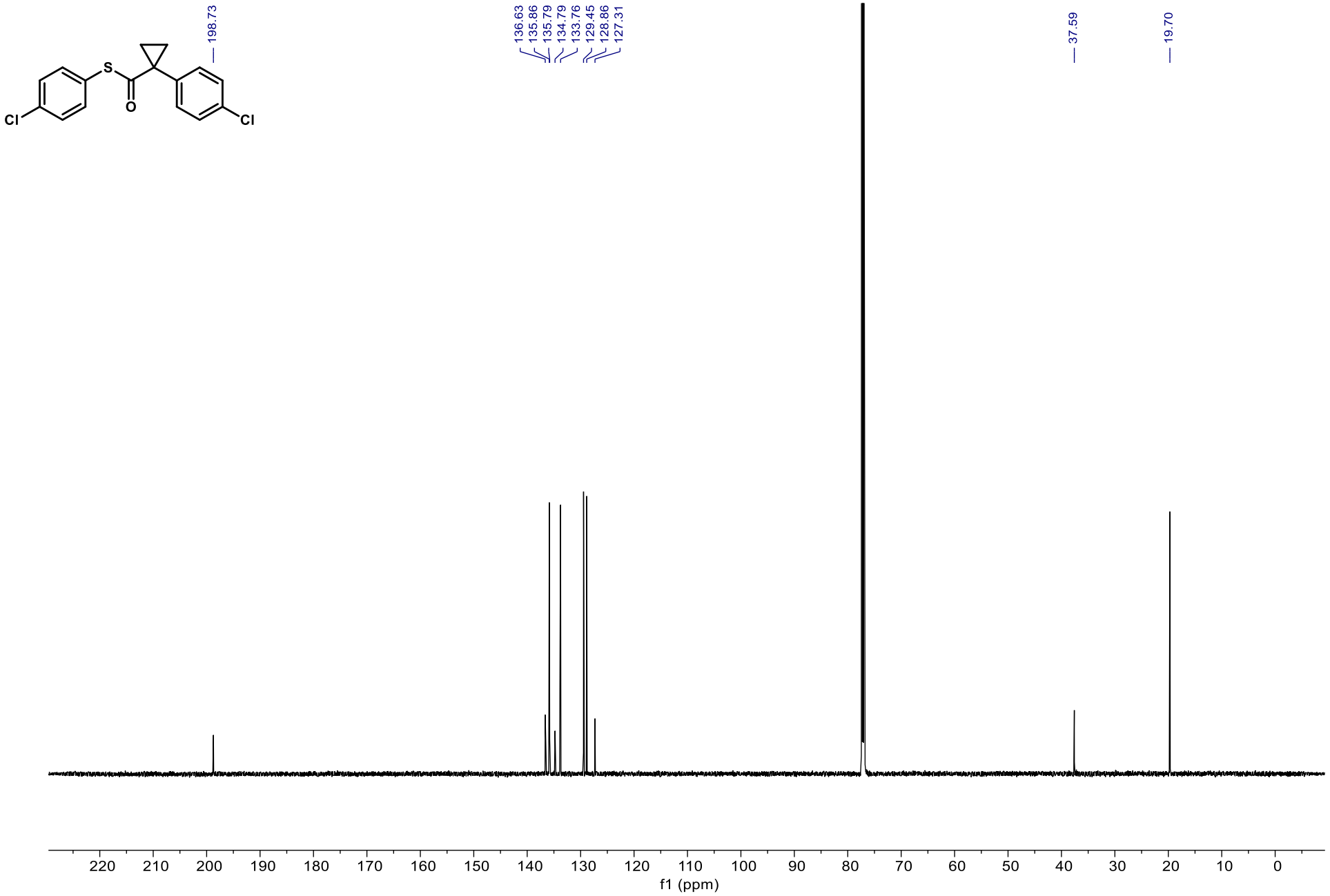
^{13}C NMR of **38c**, 151 MHz, $CDCl_3$



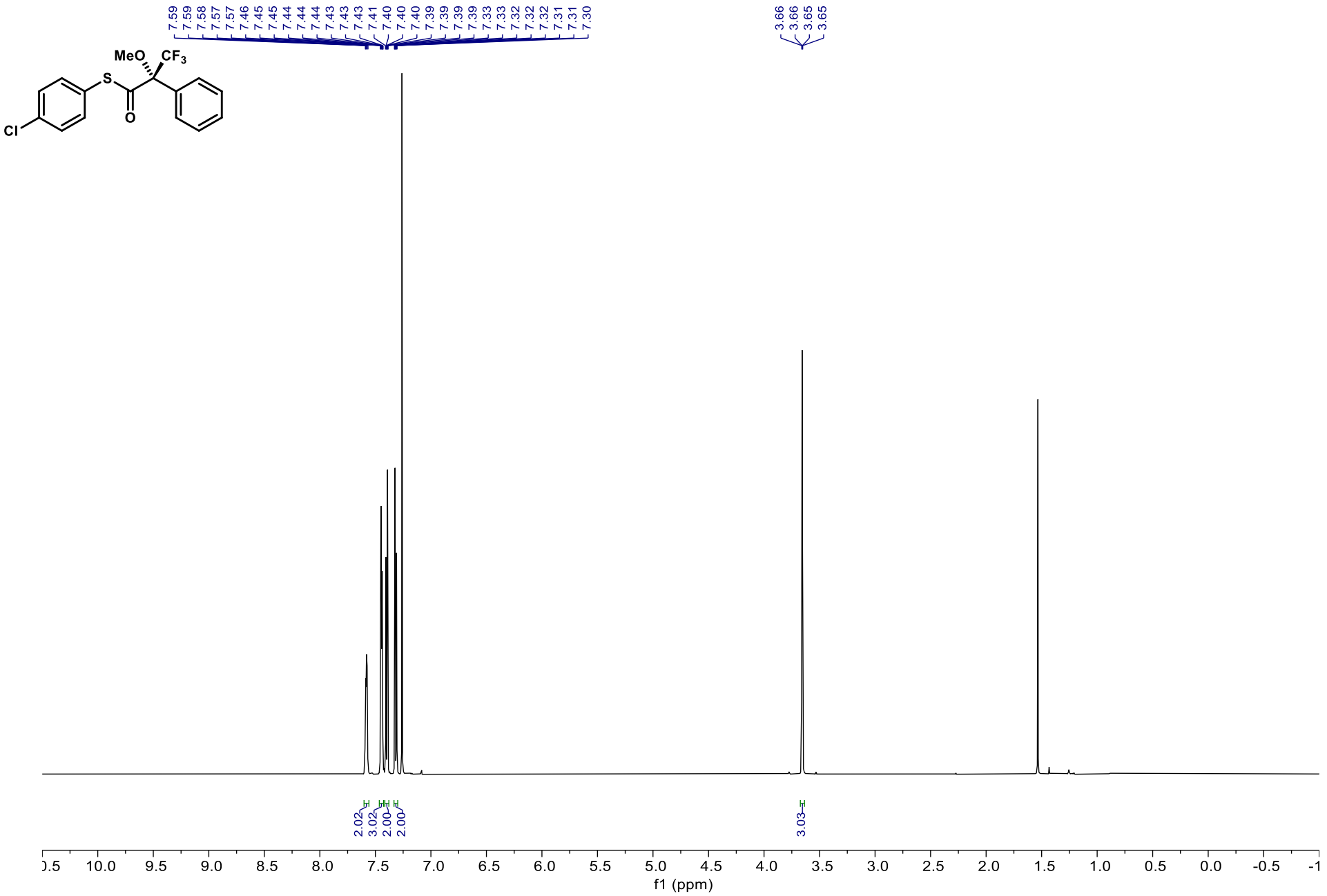
^{1}H NMR of **38d**, 600 MHz, $CDCl_3$



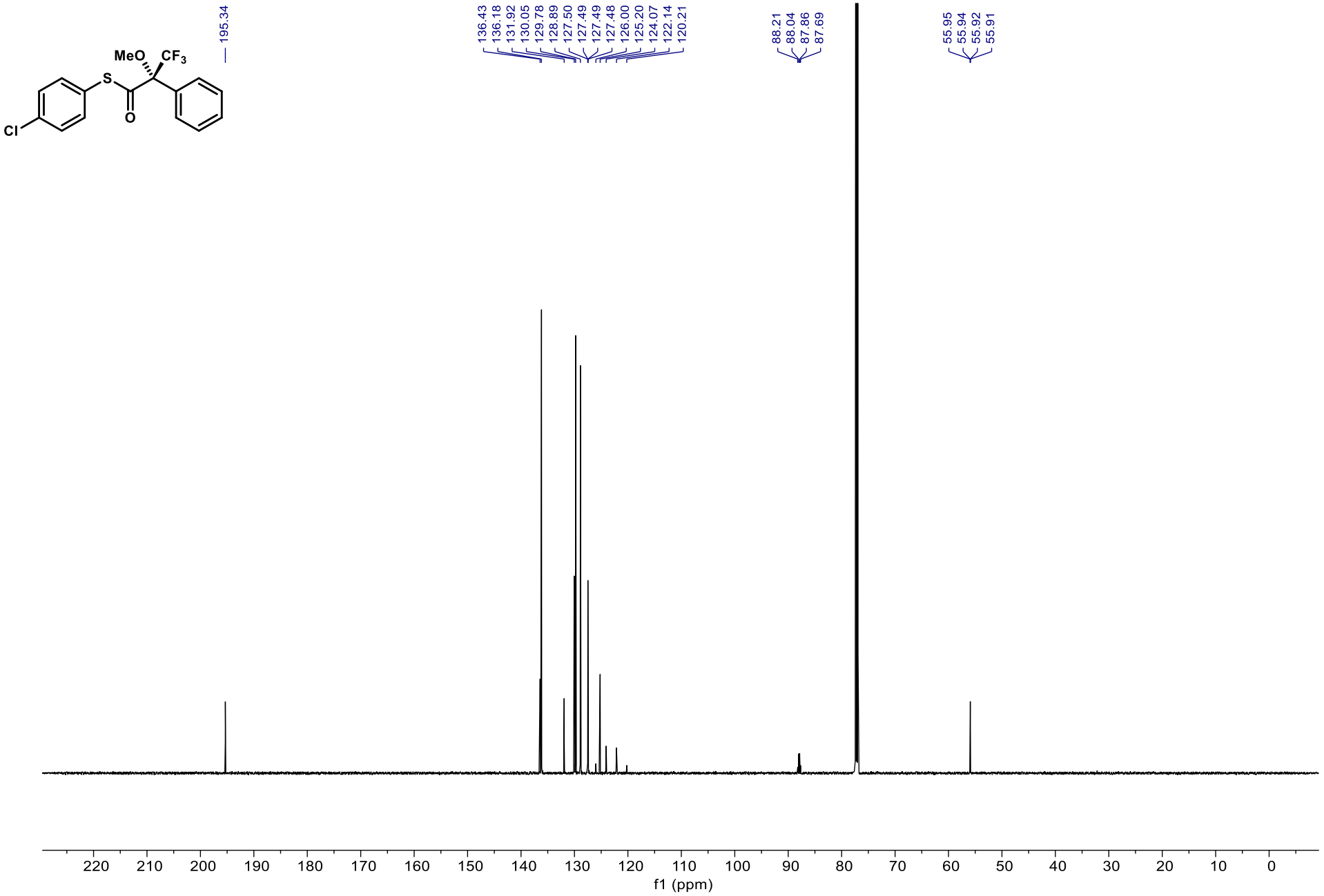
^{13}C NMR of **38d**, 151 MHz, $CDCl_3$



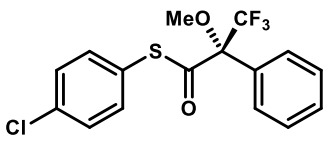
^{1}H NMR of **38e**, 600 MHz, $CDCl_3$



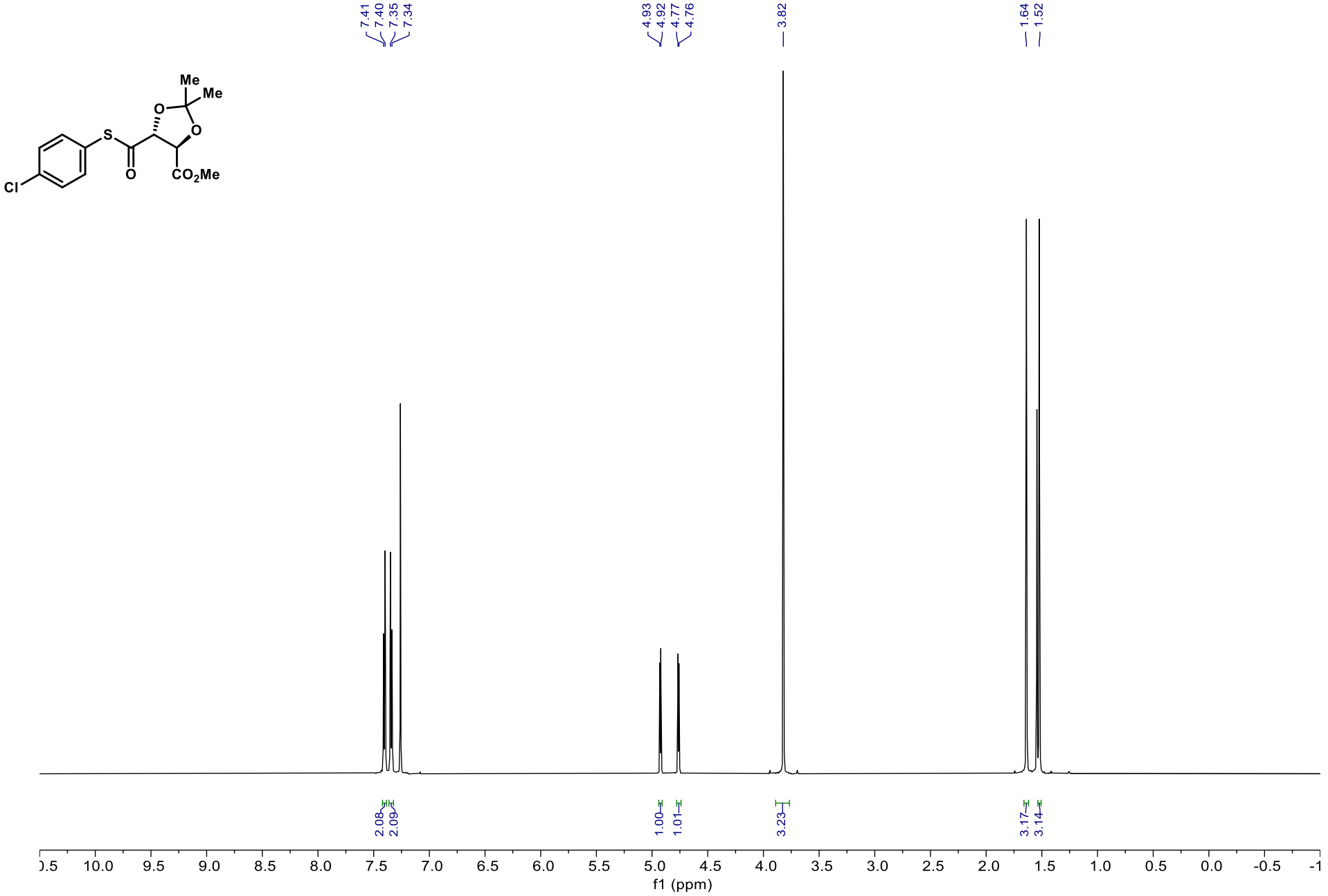
^{13}C NMR of **38e**, 151 MHz, $CDCl_3$



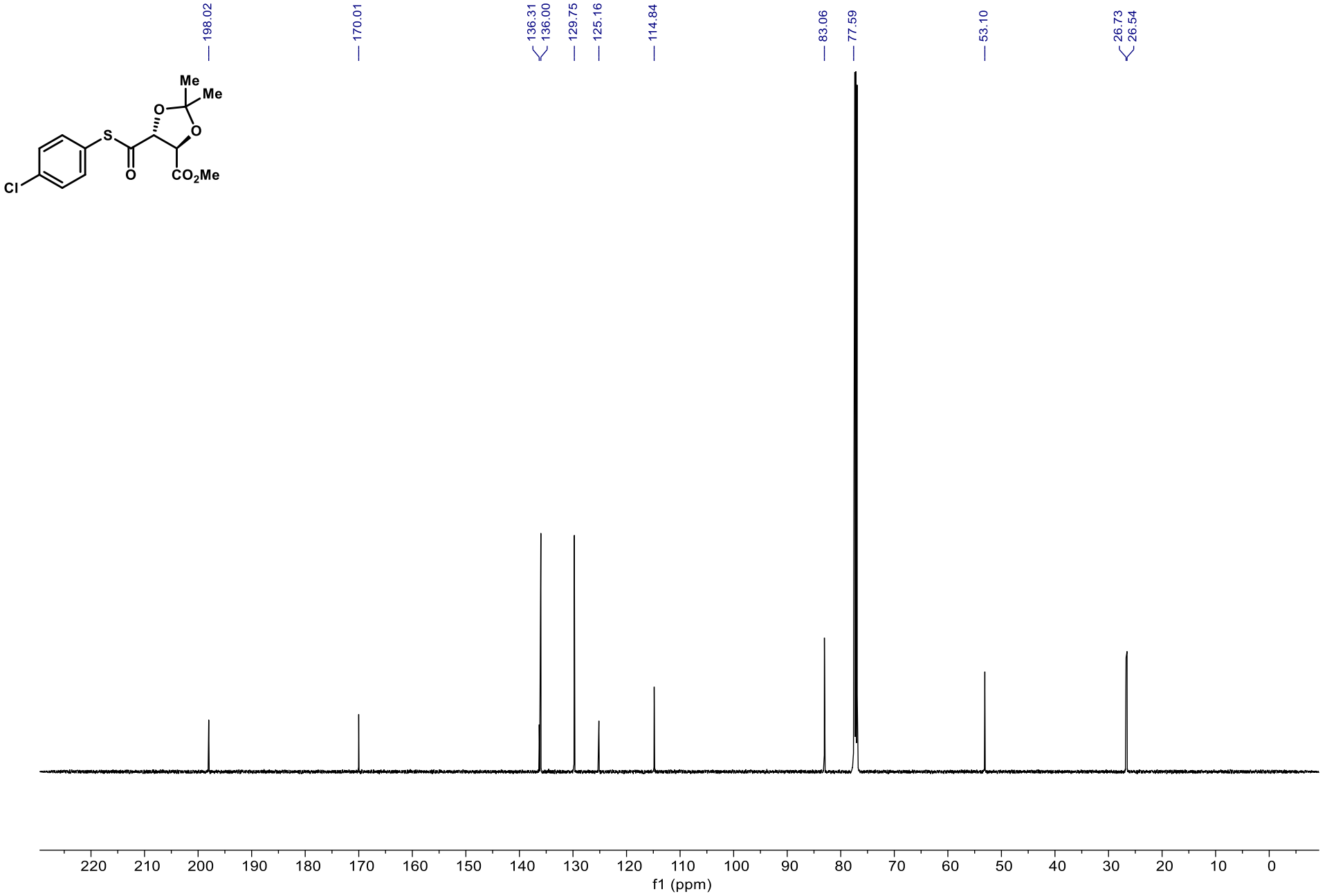
^{19}F NMR of **38e**, 376 MHz, $CDCl_3$



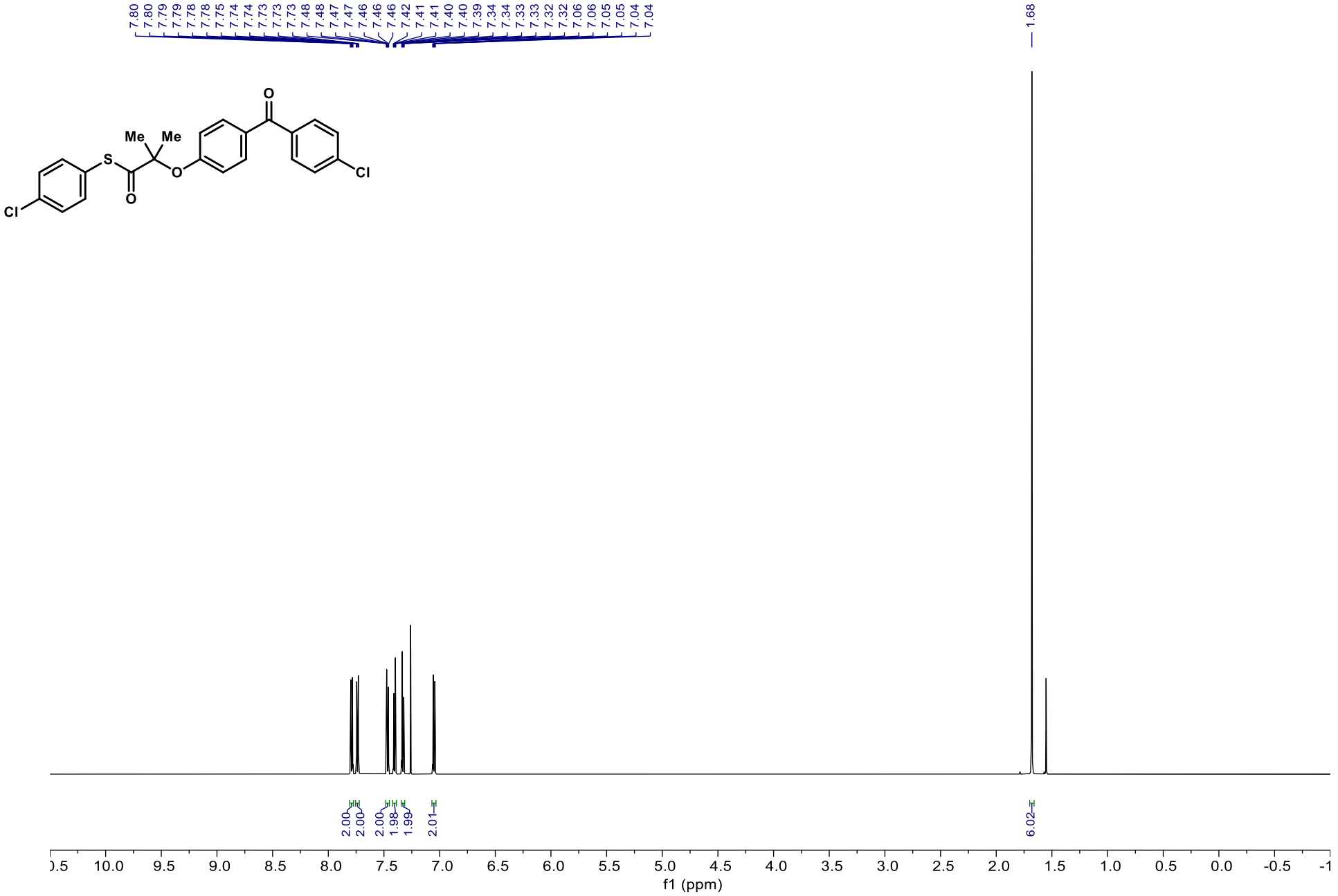
^{1}H NMR of **38f**, 600 MHz, $CDCl_3$



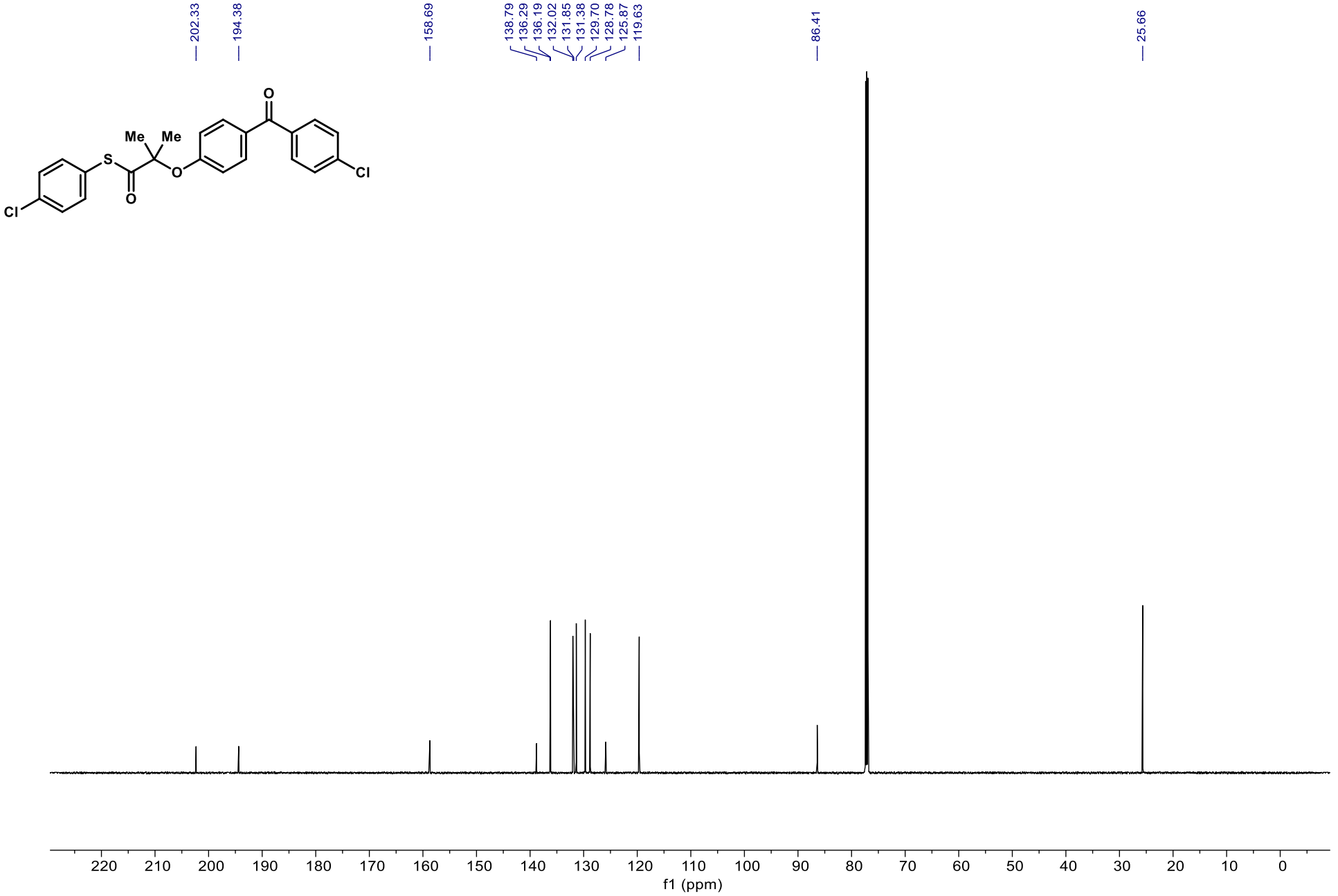
^{13}C NMR of **38f**, 151 MHz, $CDCl_3$



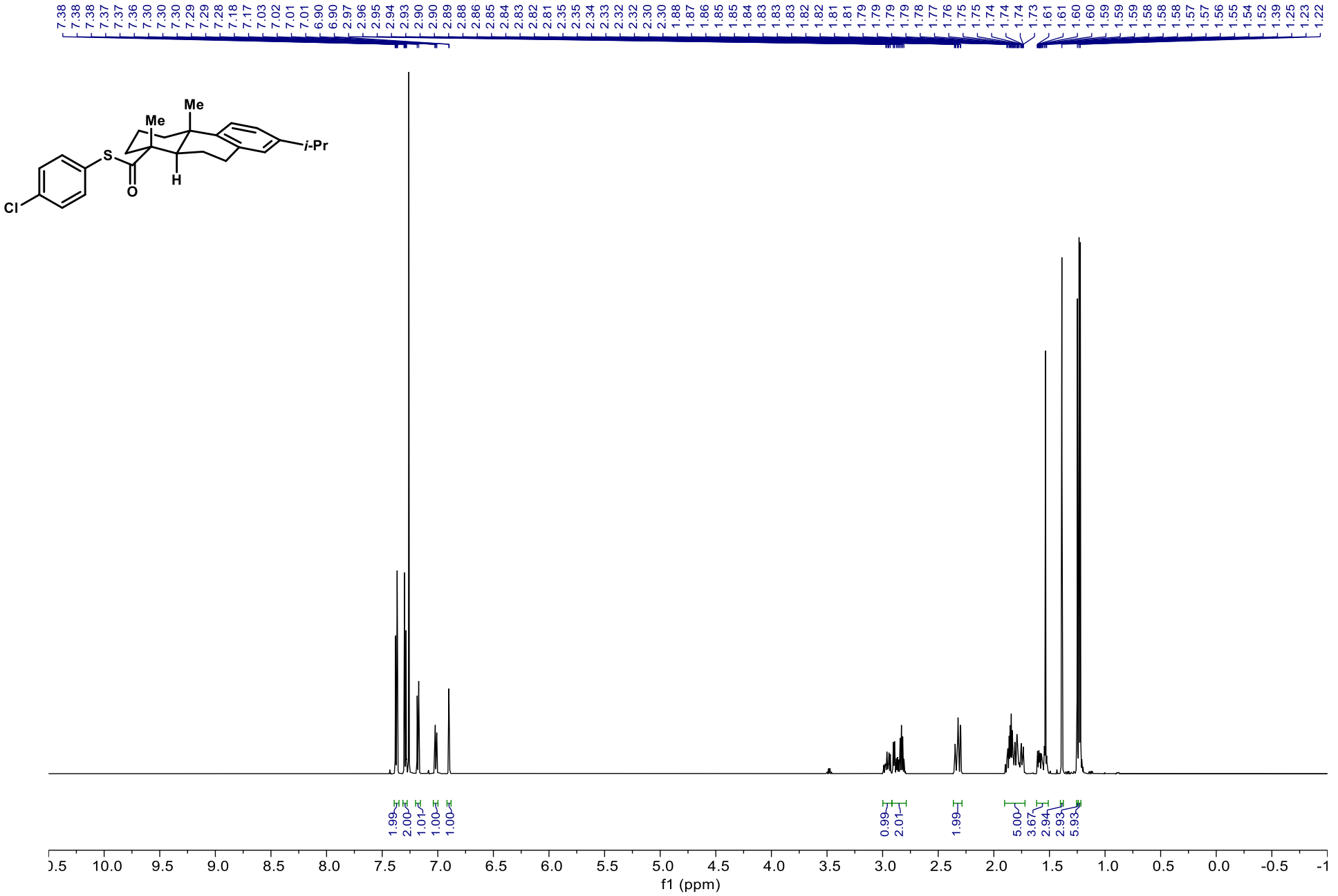
^{1}H NMR of **38g**, 600 MHz, $CDCl_3$



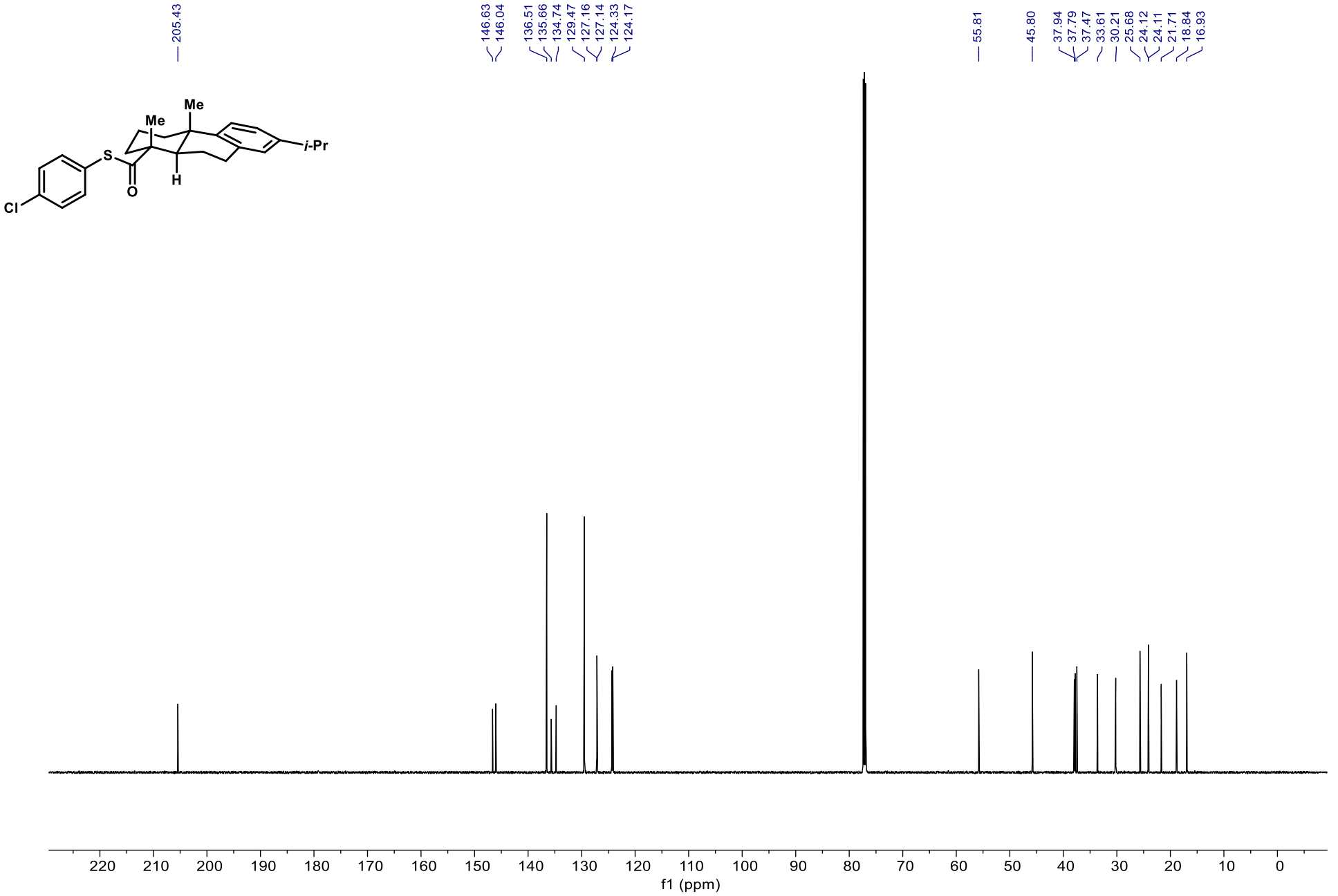
^{13}C NMR of **38g**, 151 MHz, $CDCl_3$



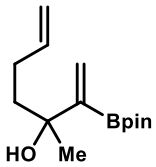
^{1}H NMR of **38h**, 600 MHz, $CDCl_3$



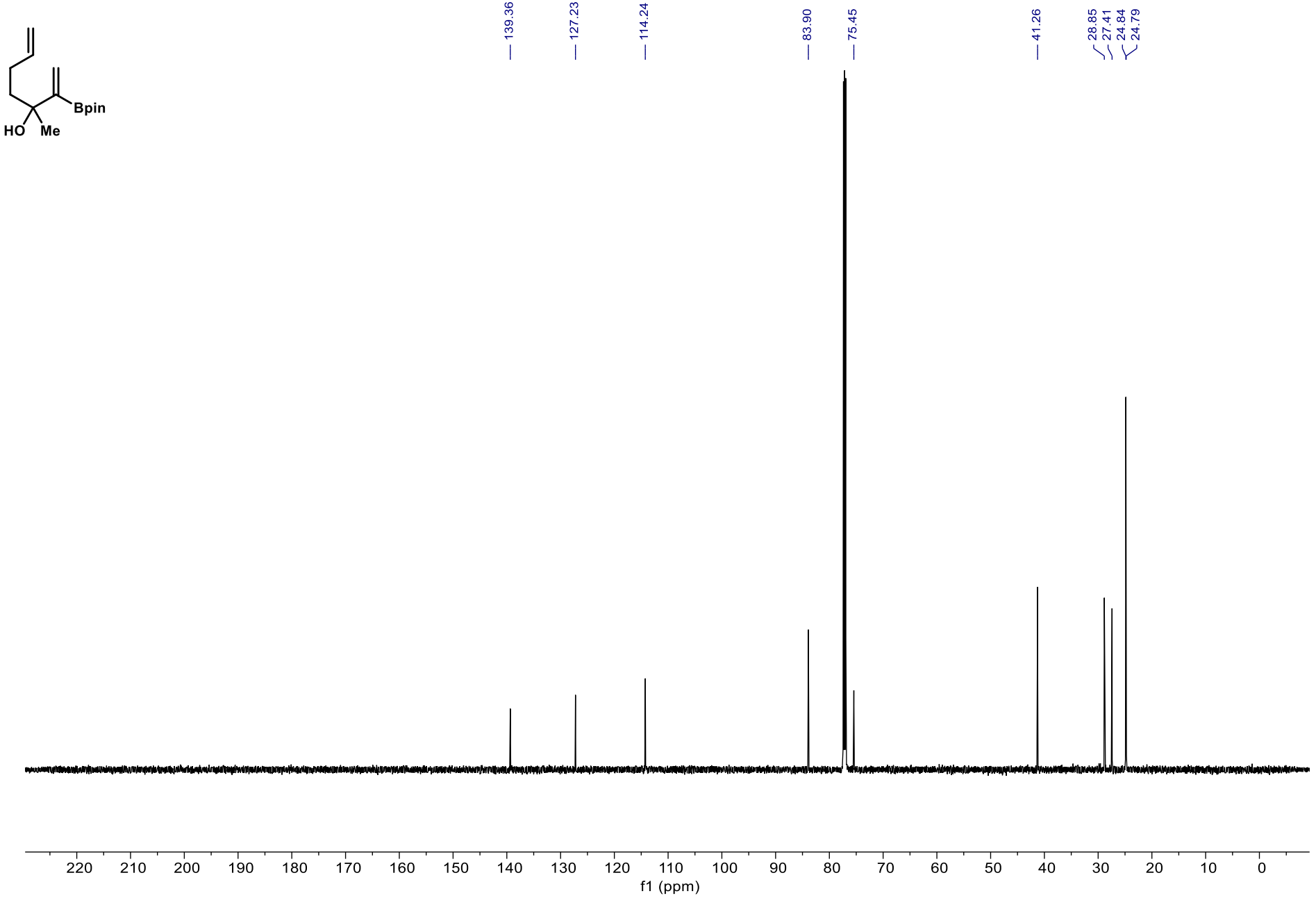
^{13}C NMR of **38h**, 151 MHz, $CDCl_3$



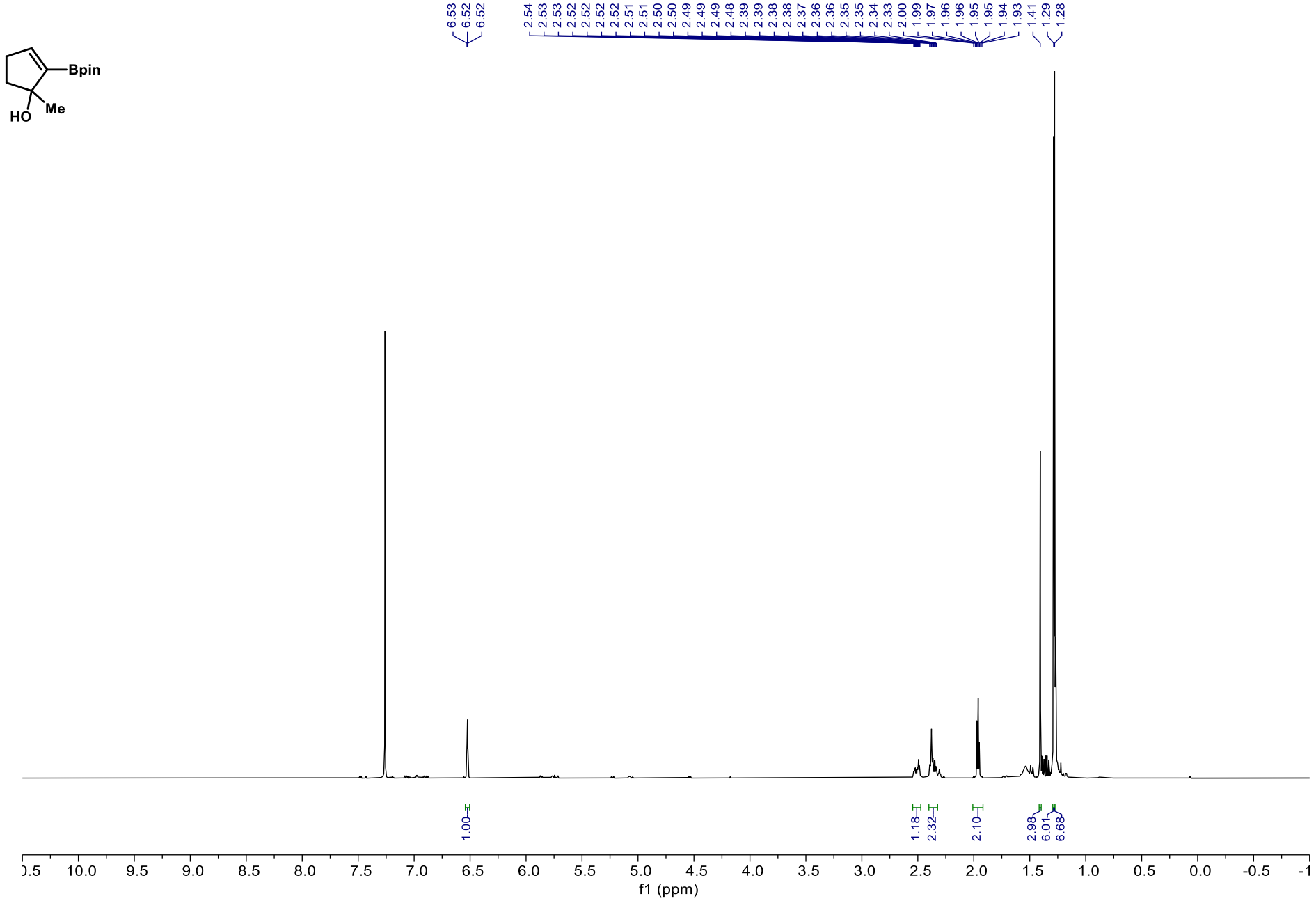
^{1}H NMR of **S19**, 600 MHz, $CDCl_3$



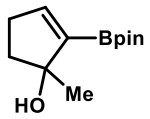
^{13}C NMR of **S19**, 151 MHz, $CDCl_3$



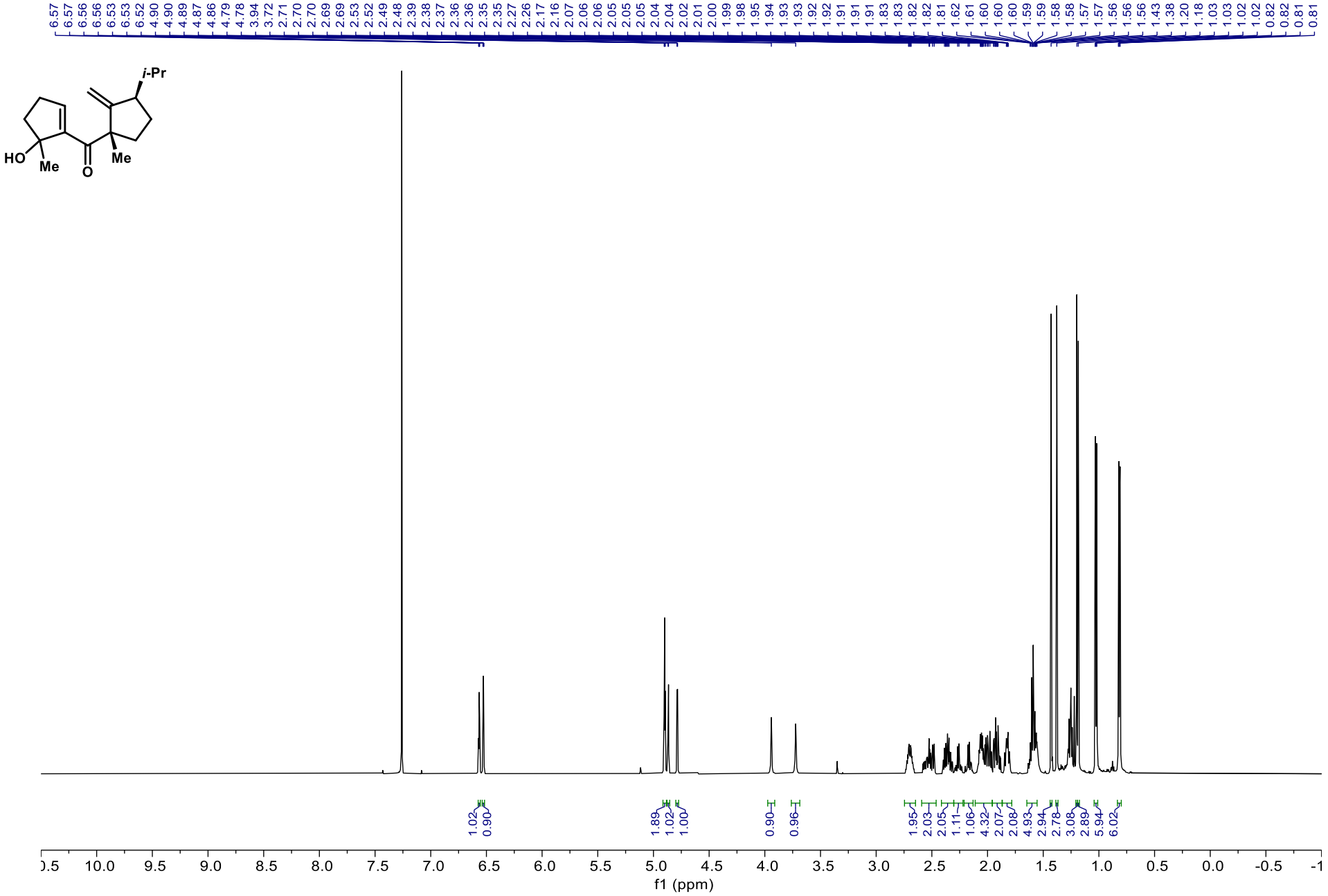
^{1}H NMR of **S20**, 600 MHz, $CDCl_3$



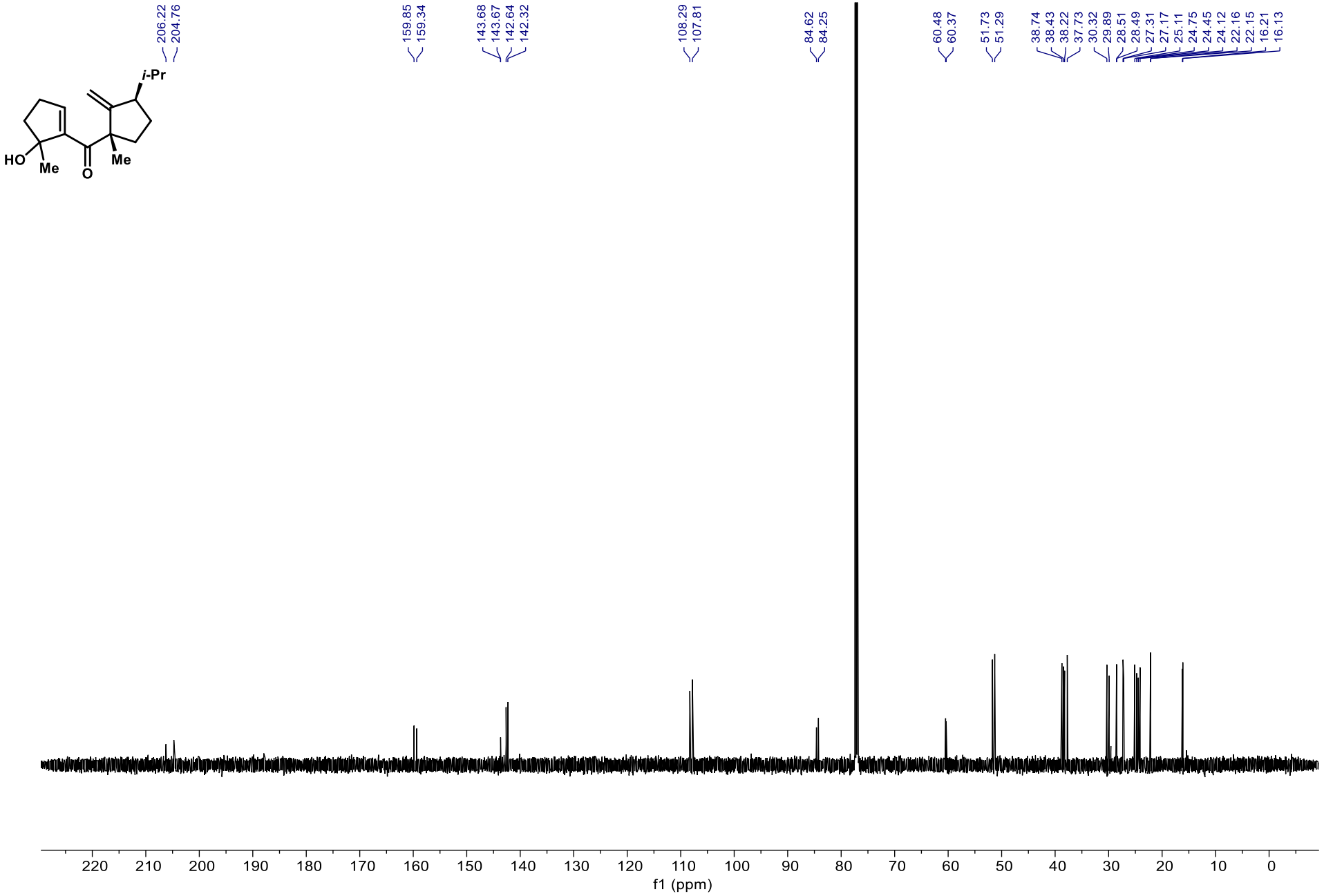
^{13}C NMR of **S20**, 151 MHz, $CDCl_3$



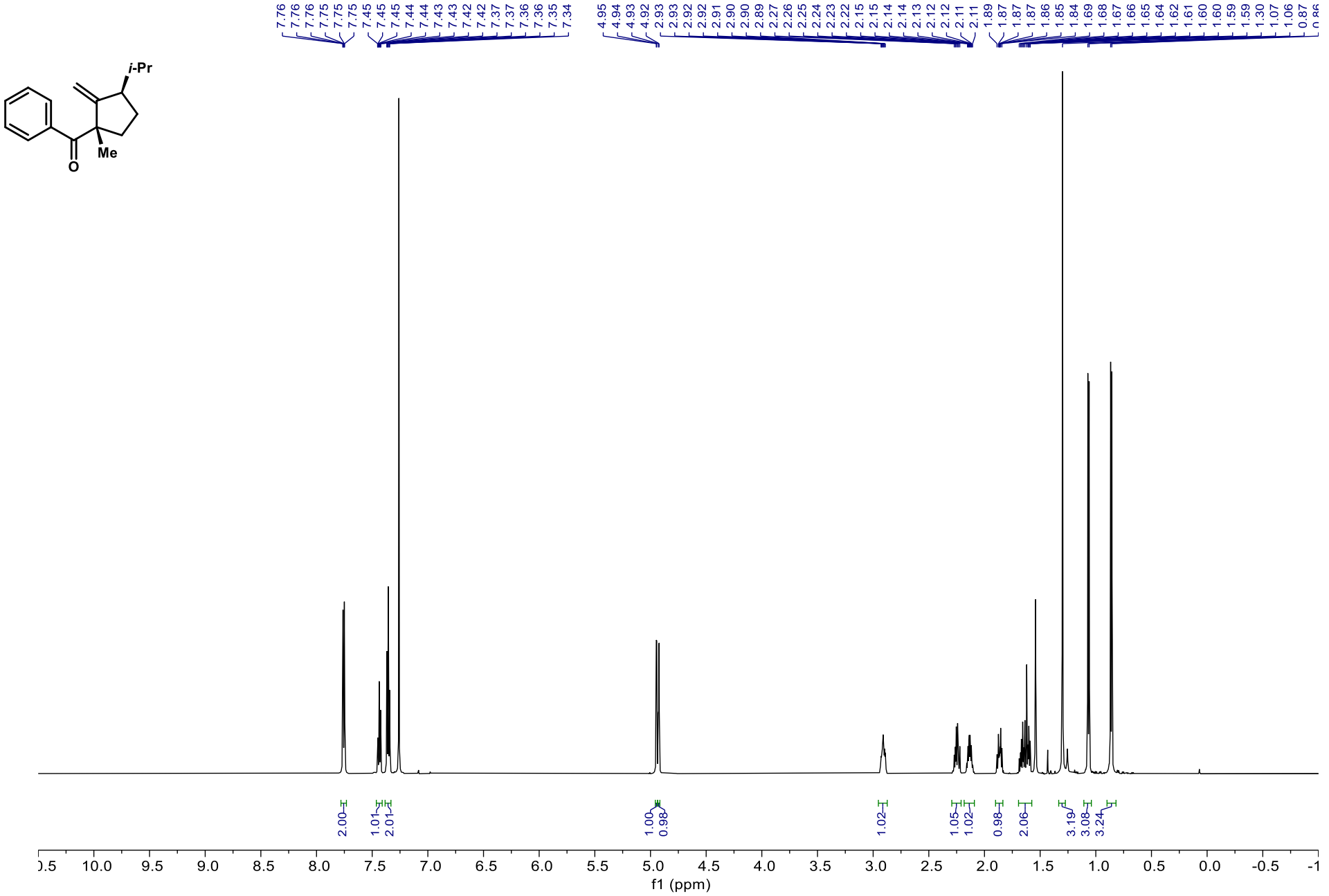
^{1}H NMR of **S21** (1:1 dr), 600 MHz, $CDCl_3$



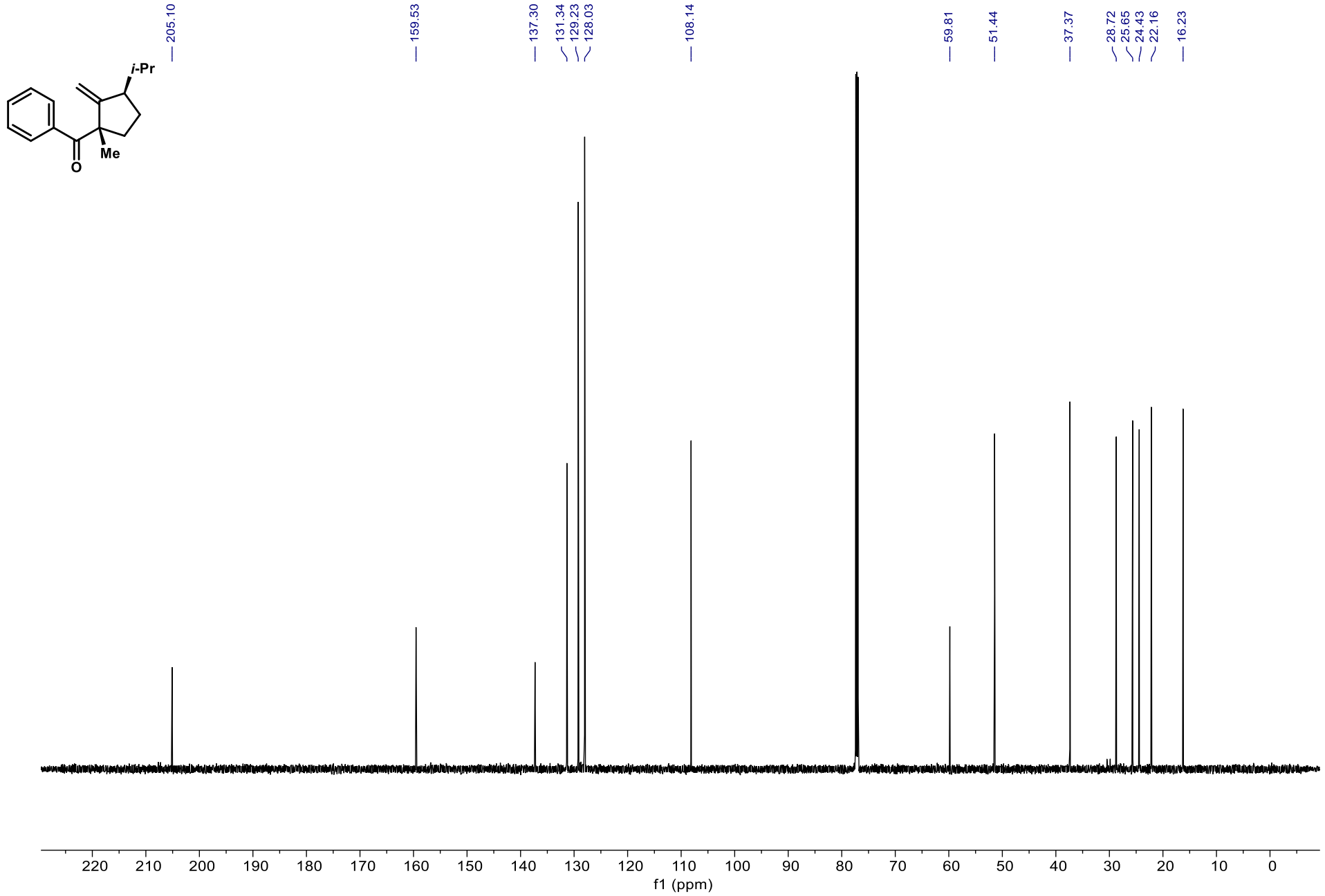
^{13}C NMR of **S21** (1:1 dr), 151 MHz, $CDCl_3$



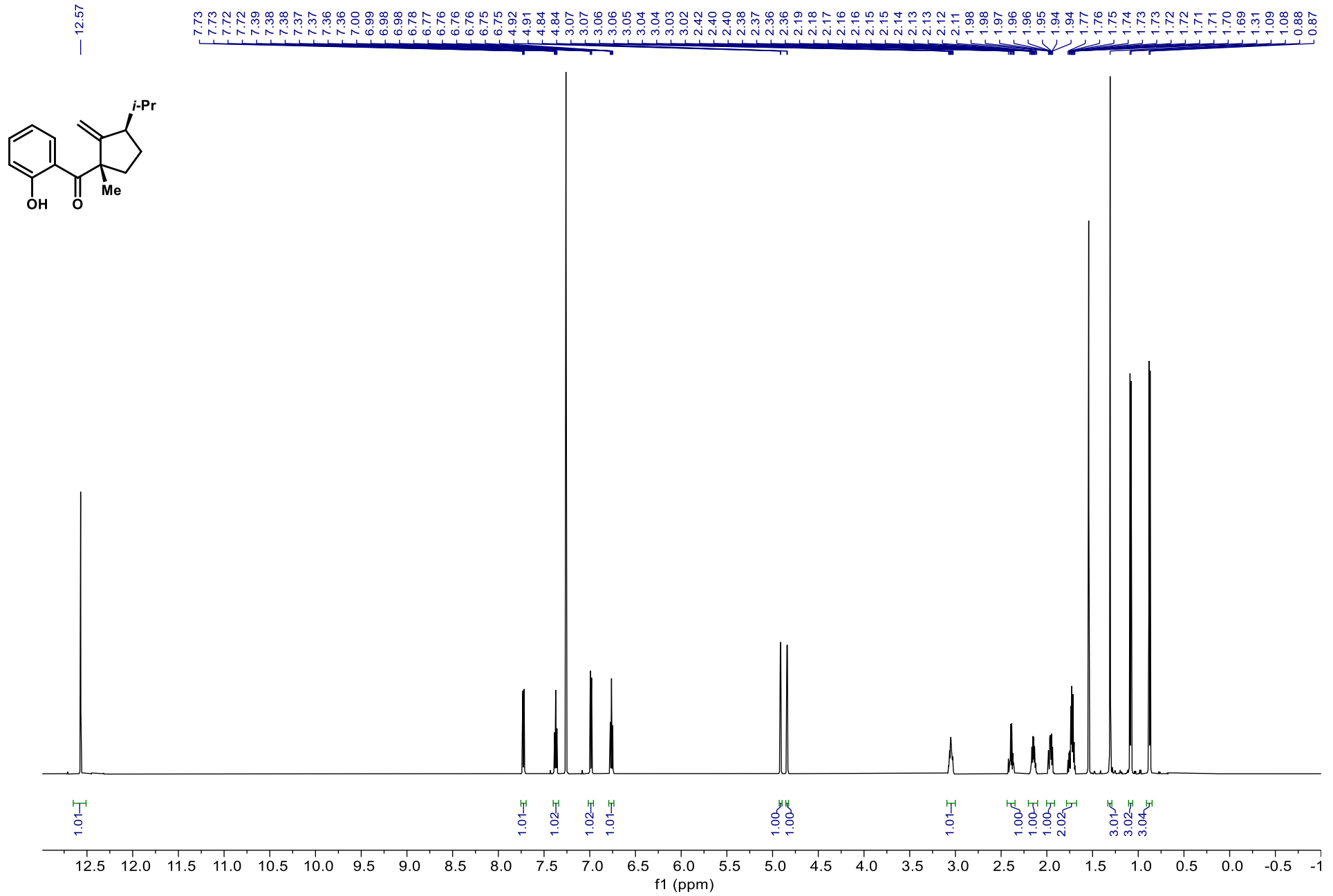
^{1}H NMR of **S22**, 600 MHz, $CDCl_3$



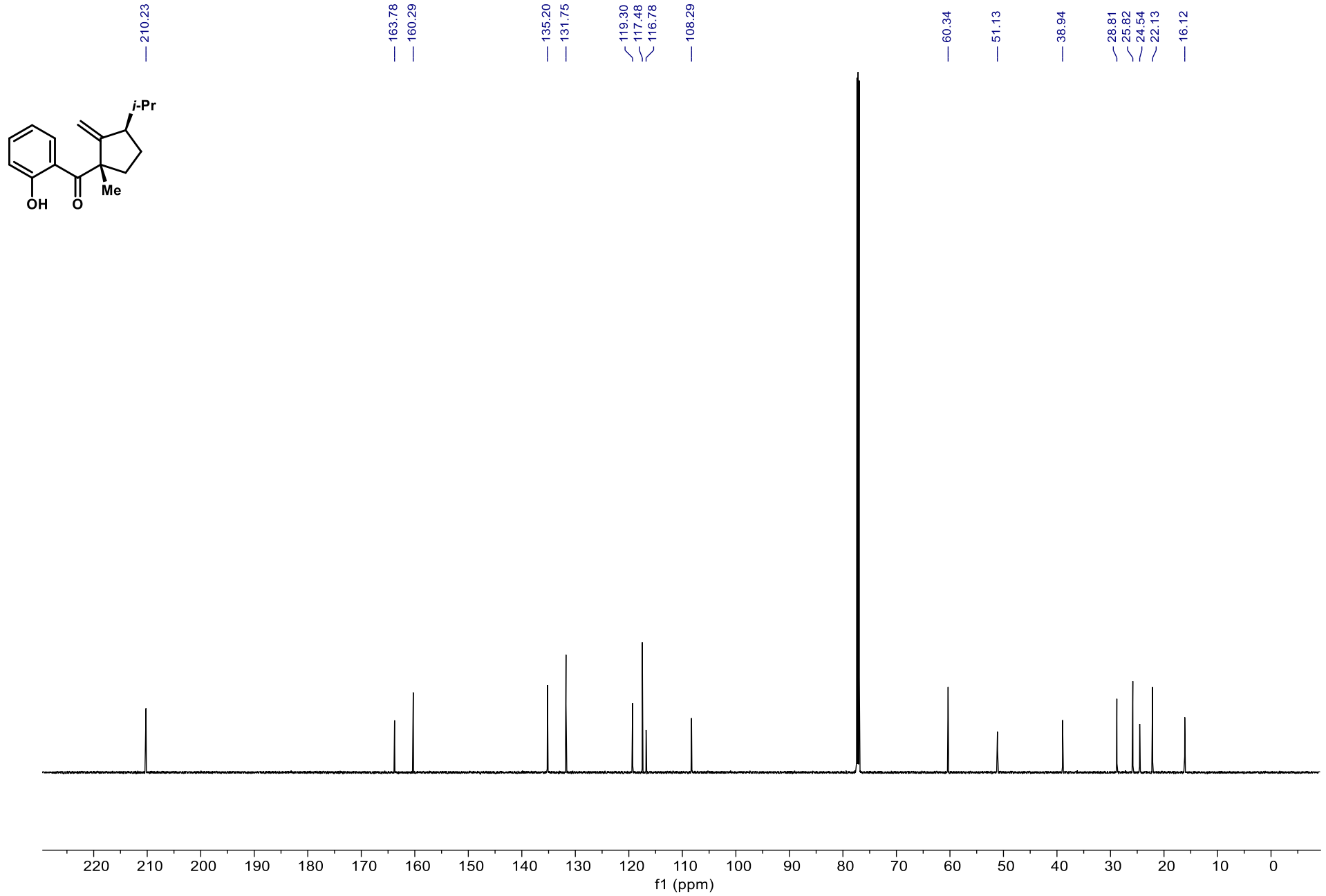
^{13}C NMR of **S22**, 151 MHz, $CDCl_3$



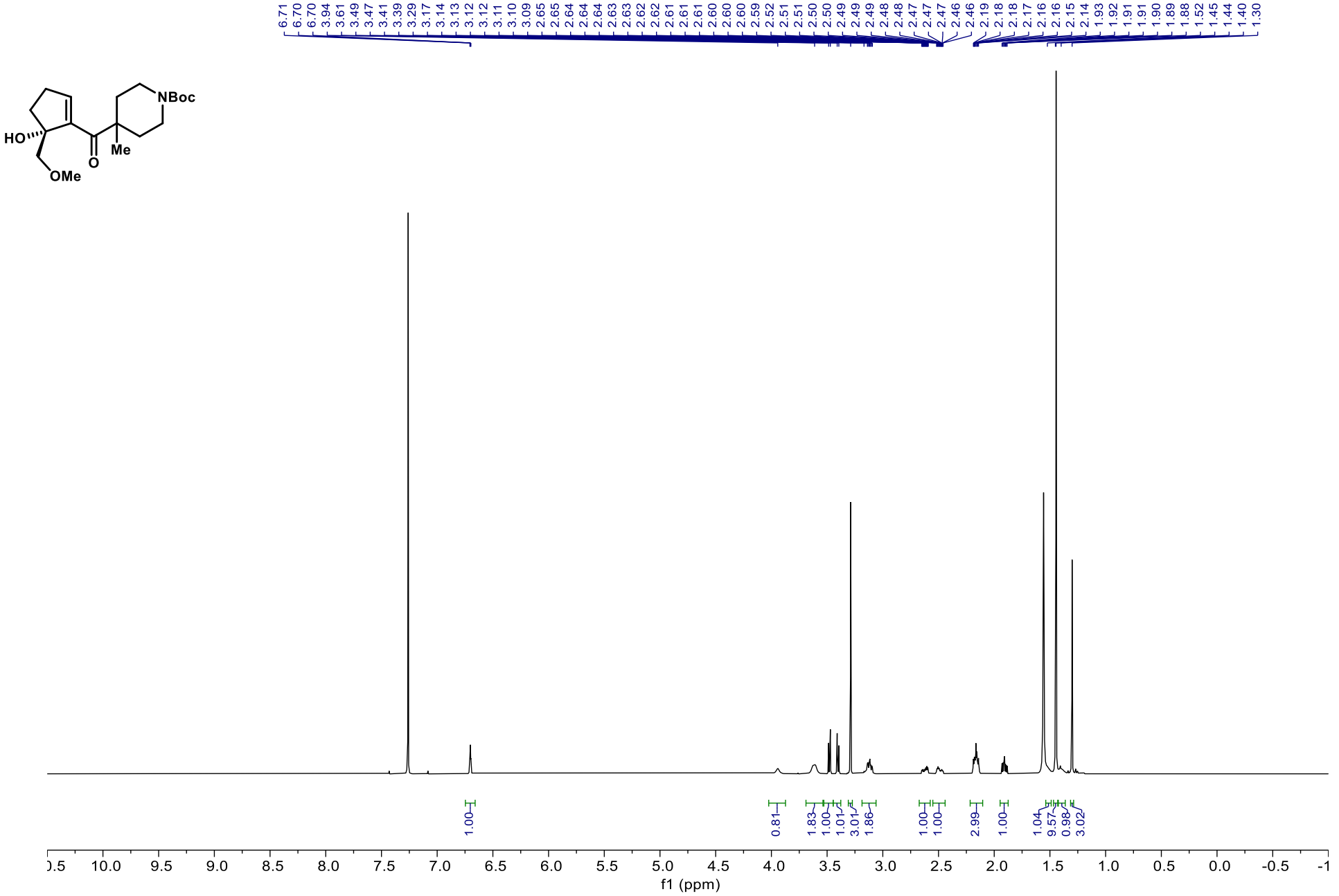
^{1}H NMR of **S23**, 600 MHz, $CDCl_3$



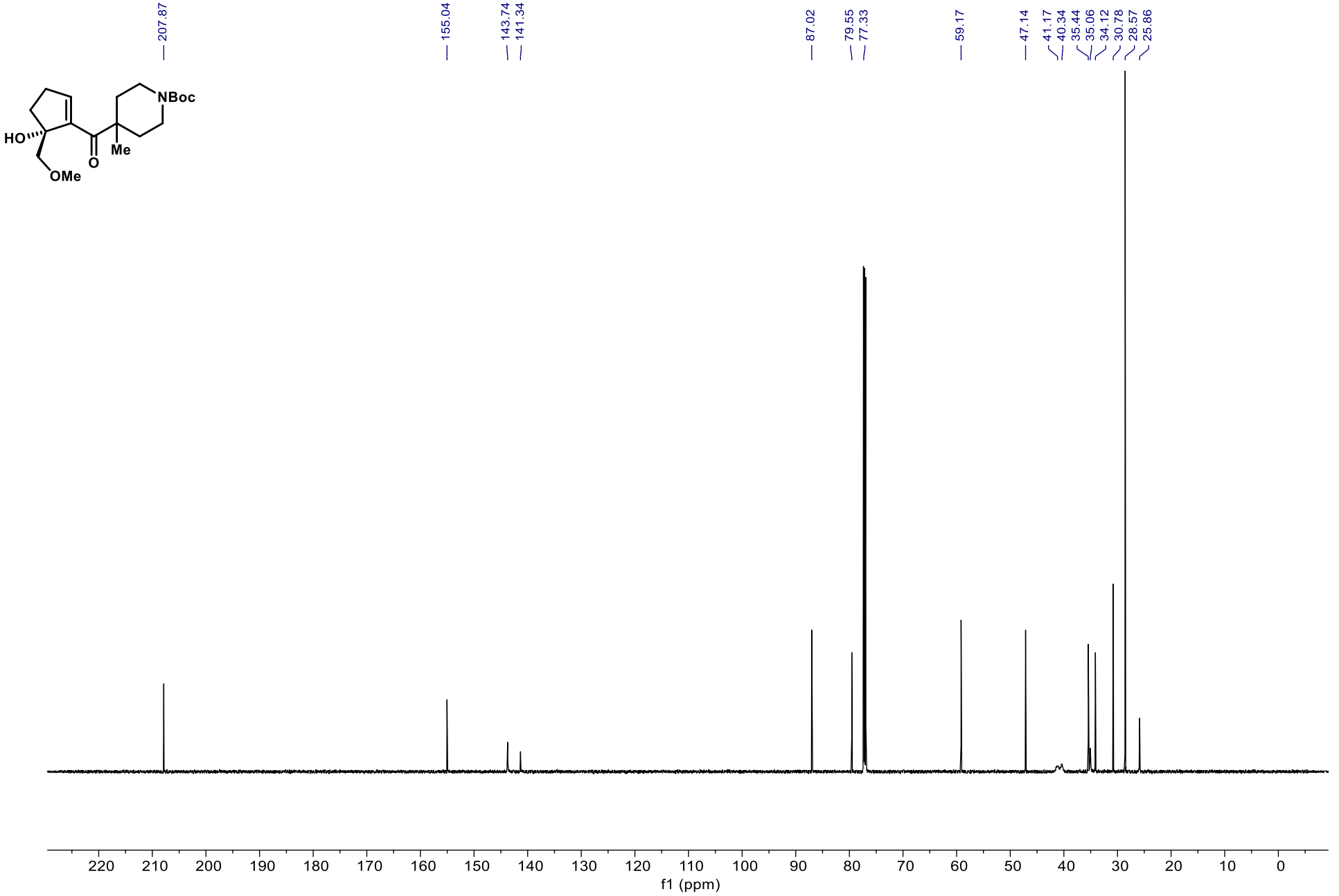
^{13}C NMR of **S23**, 151 MHz, $CDCl_3$



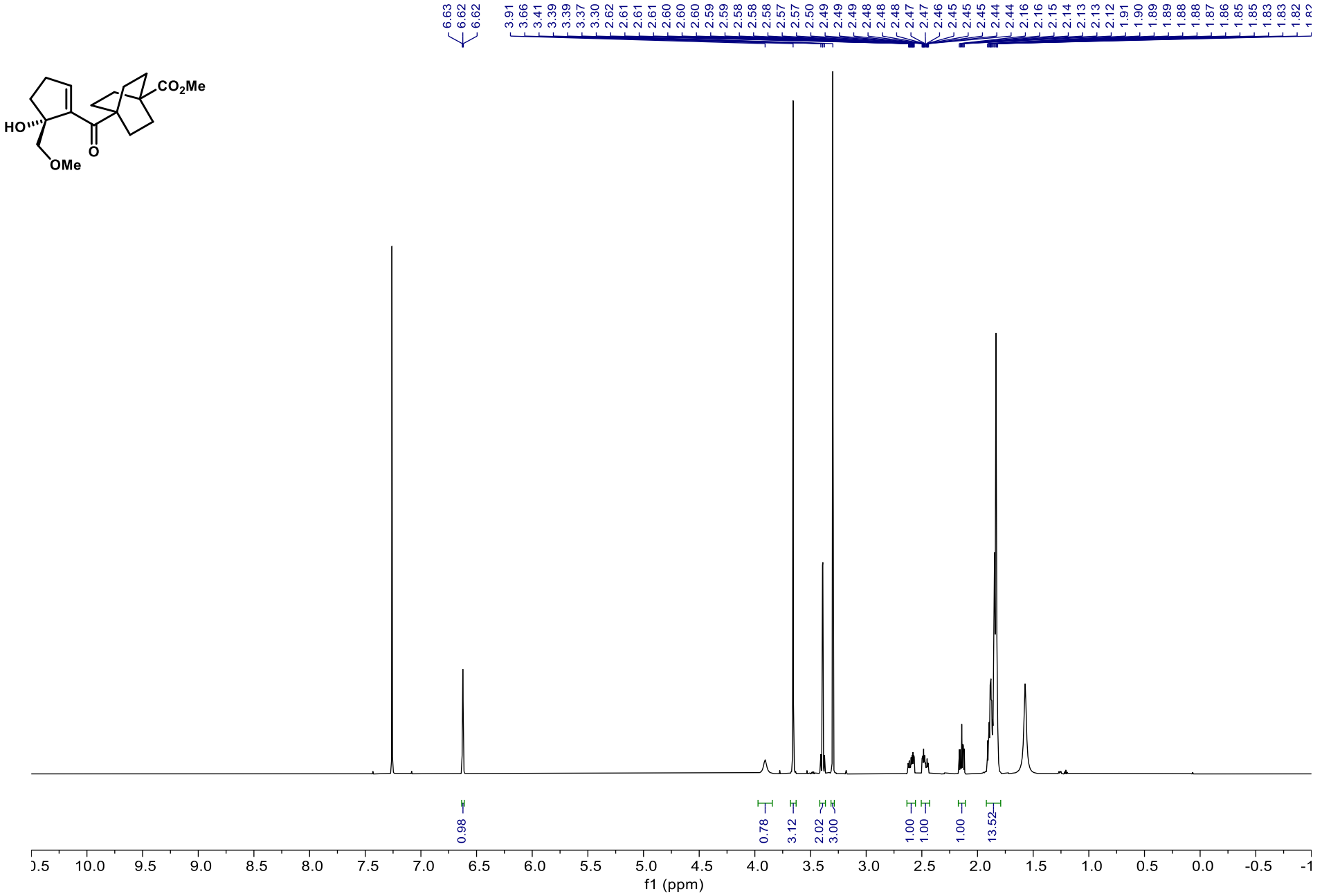
^{1}H NMR of **39a**, 600 MHz, $CDCl_3$



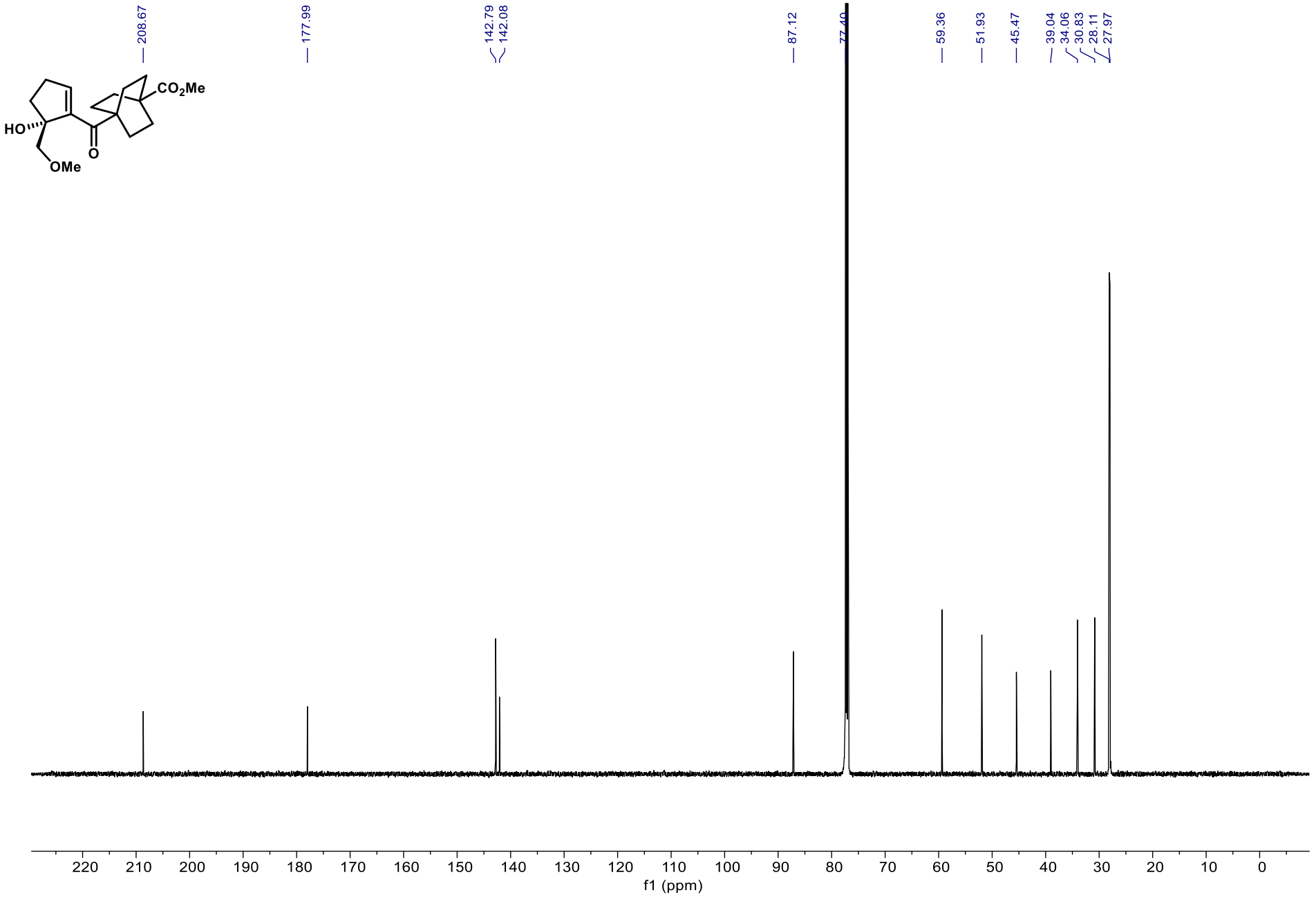
^{13}C NMR of **39a**, 151 MHz, $CDCl_3$



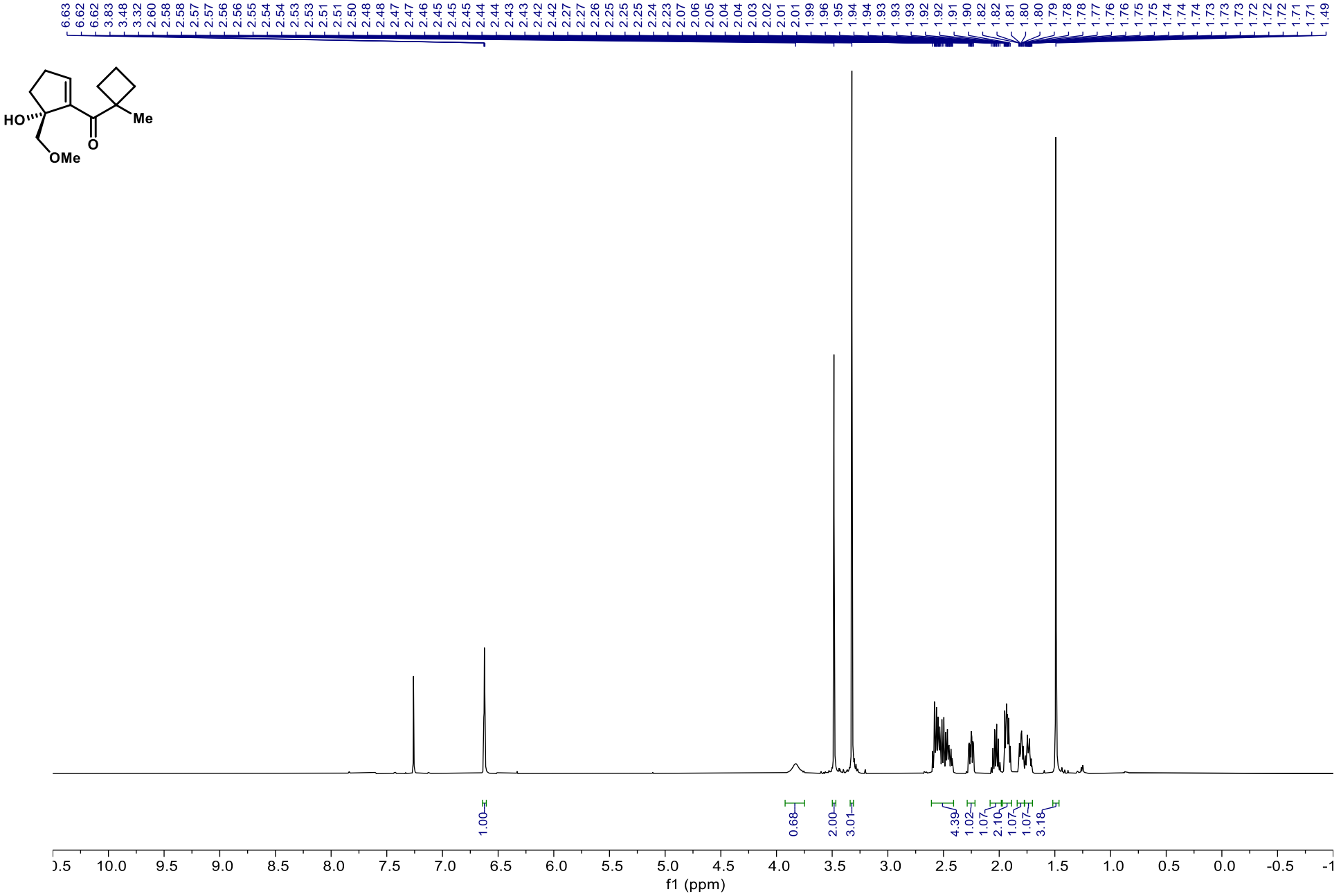
^{1}H NMR of **39b**, 600 MHz, $CDCl_3$



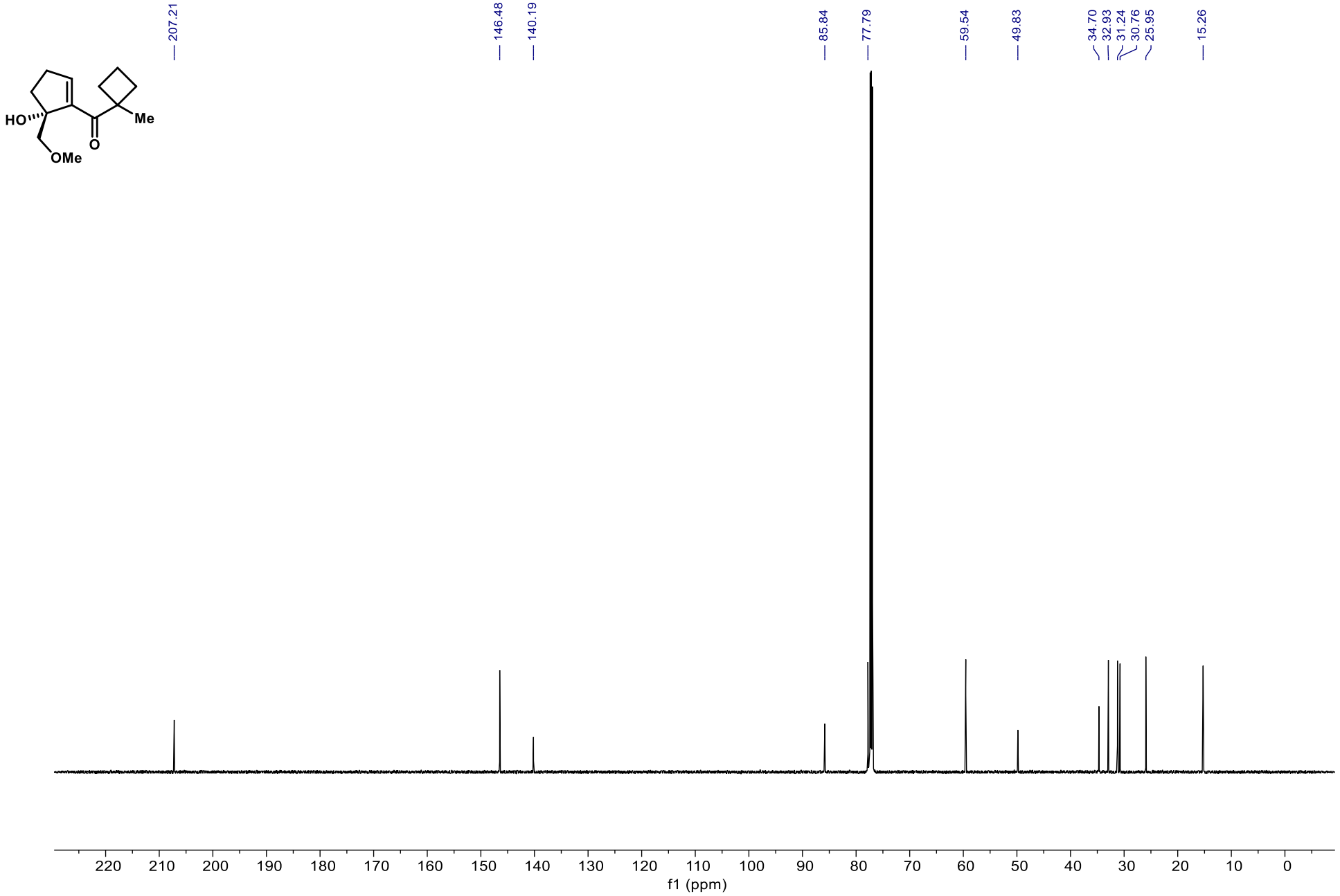
^{13}C NMR of **39b**, 151 MHz, $CDCl_3$



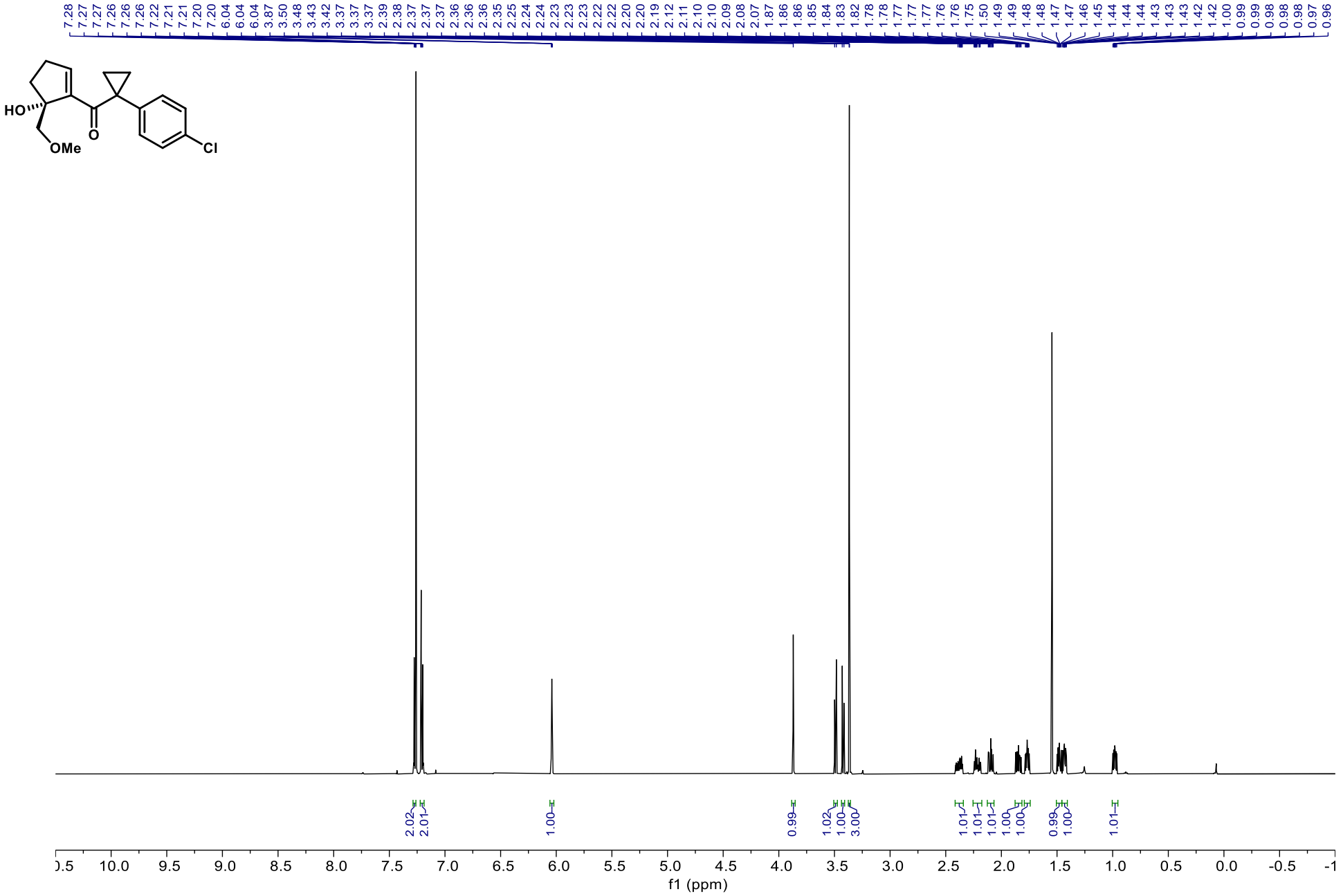
^{1}H NMR of **39c**, 600 MHz, $CDCl_3$



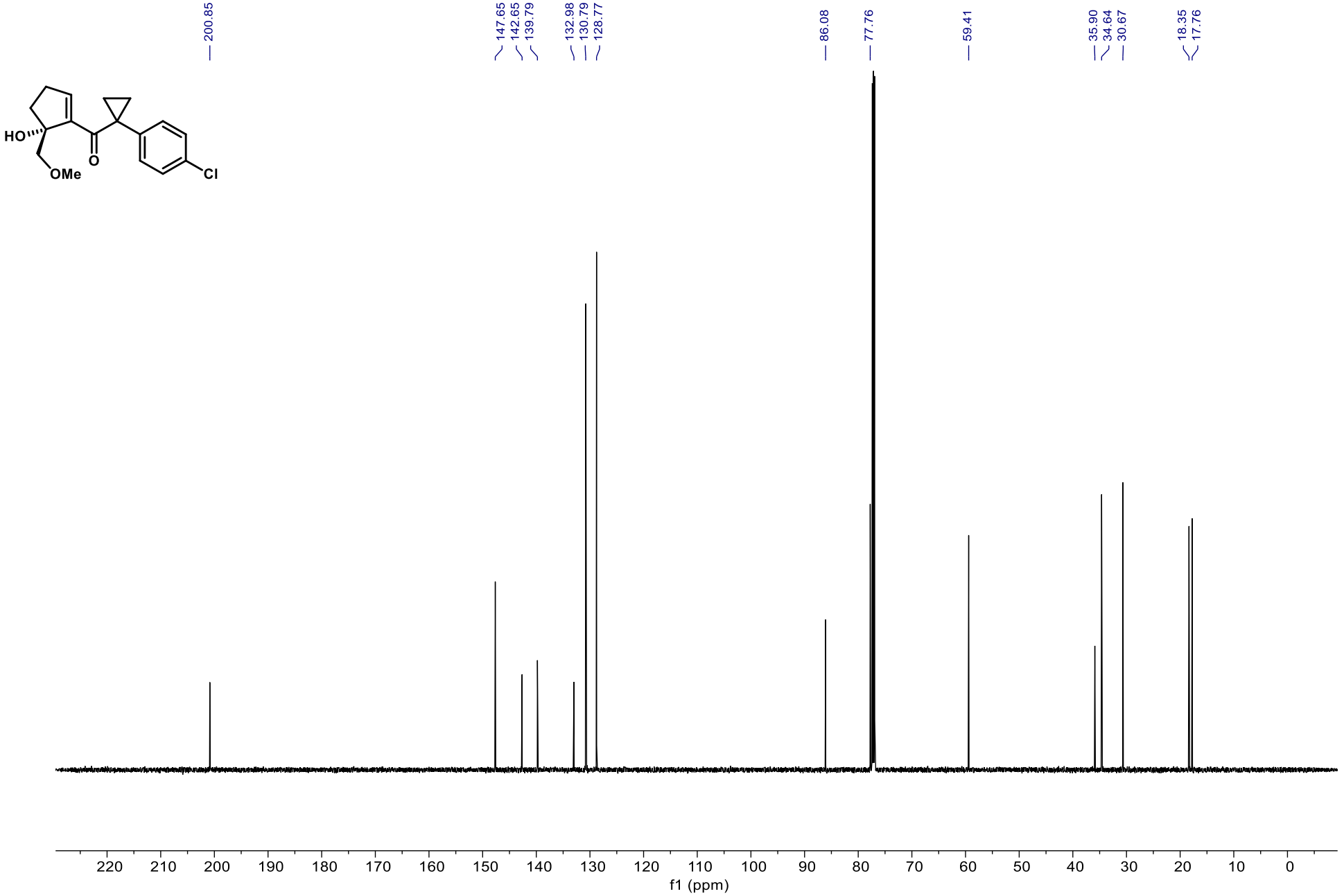
^{13}C NMR of **39c**, 151 MHz, $CDCl_3$



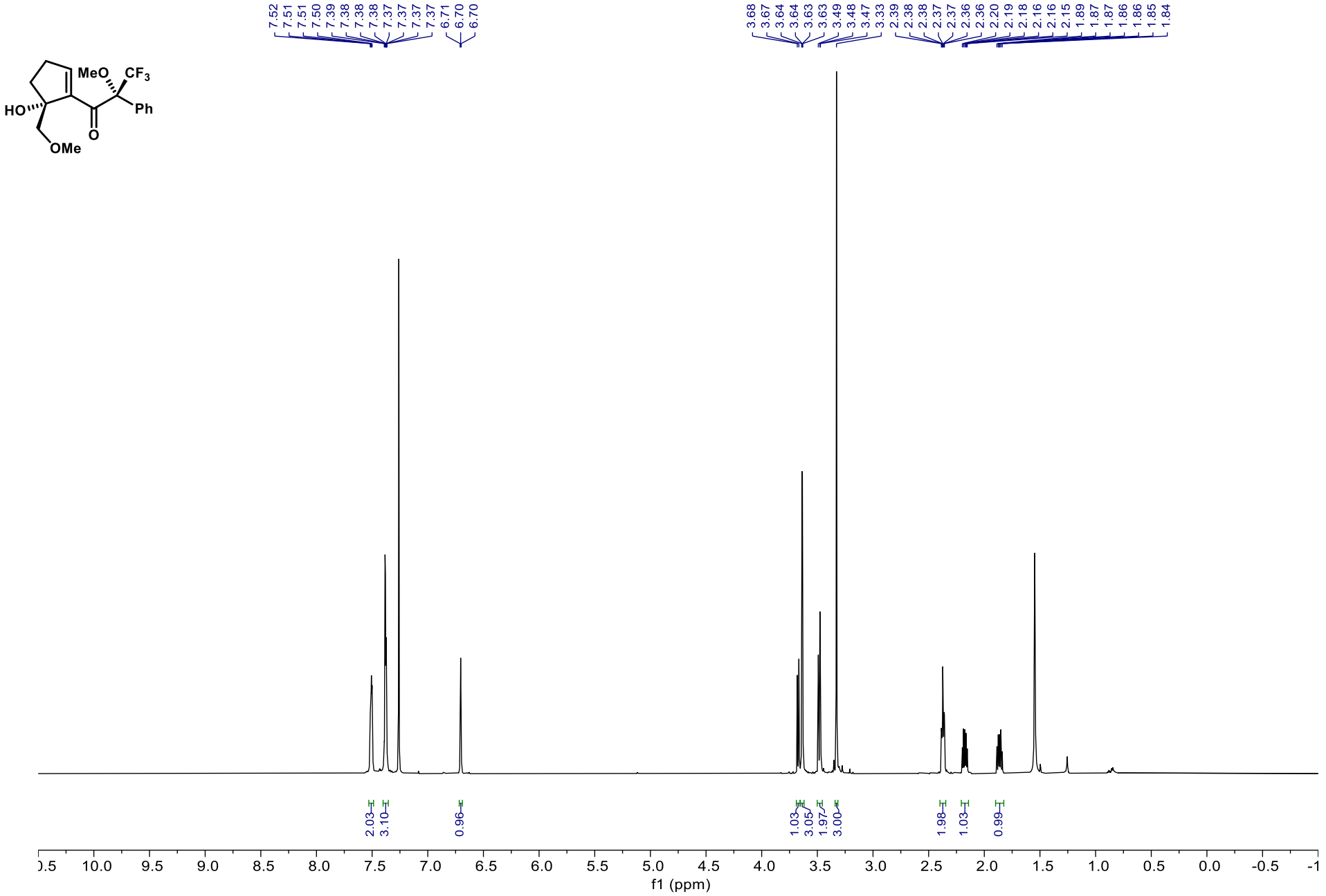
^{1}H NMR of **39d**, 600 MHz, $CDCl_3$



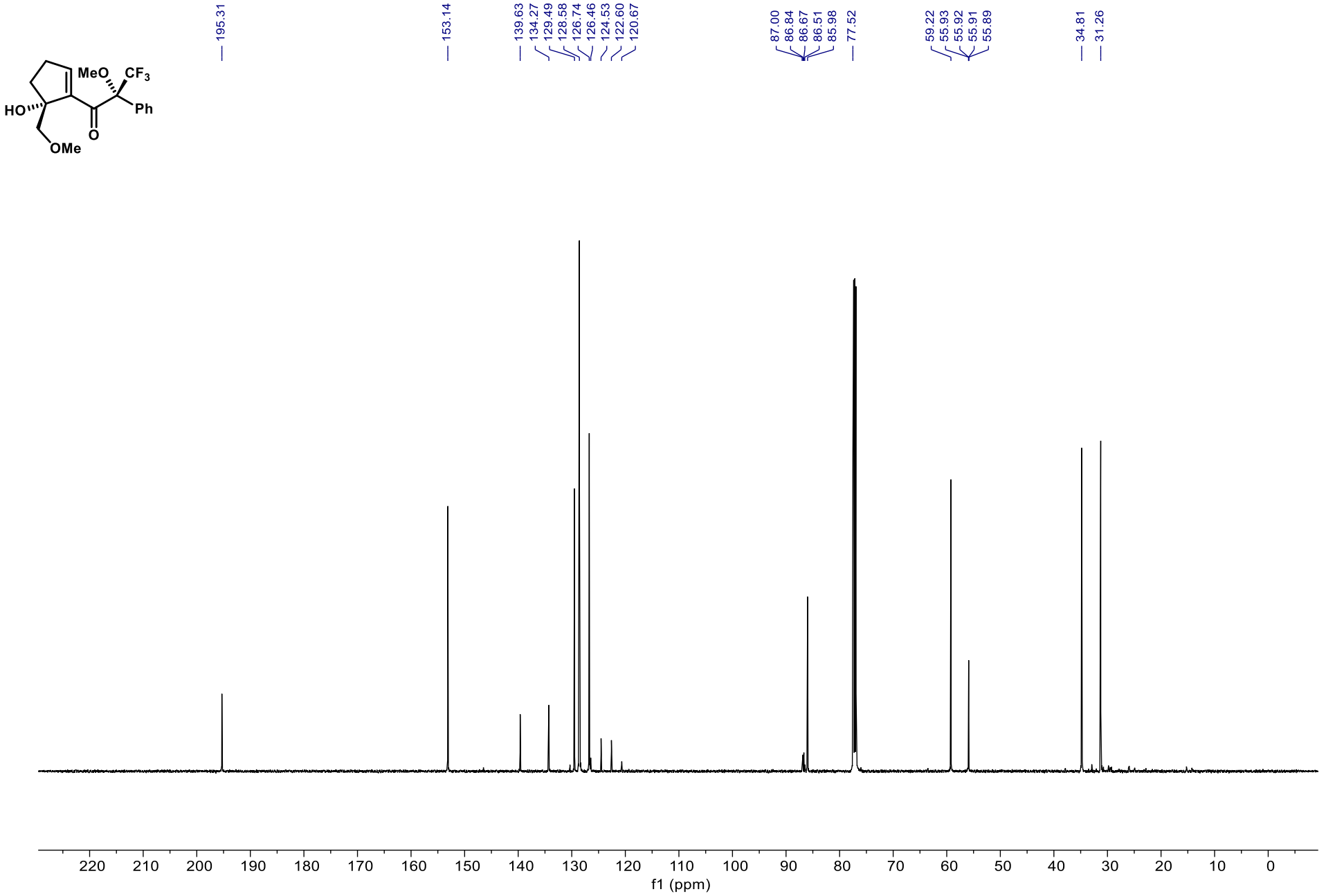
^{13}C NMR of **39d**, 151 MHz, $CDCl_3$



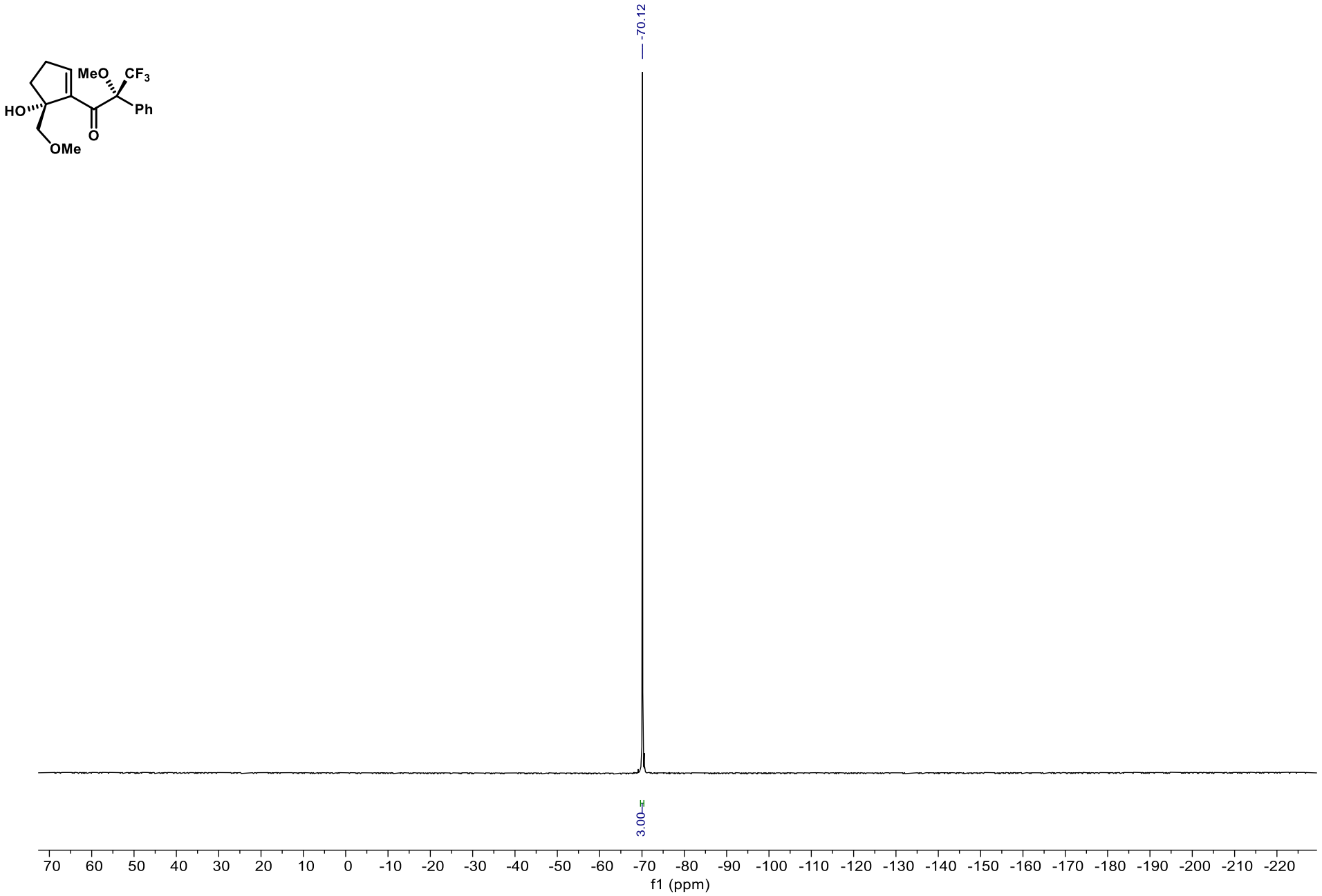
^{1}H NMR of **39e**, 600 MHz, $CDCl_3$



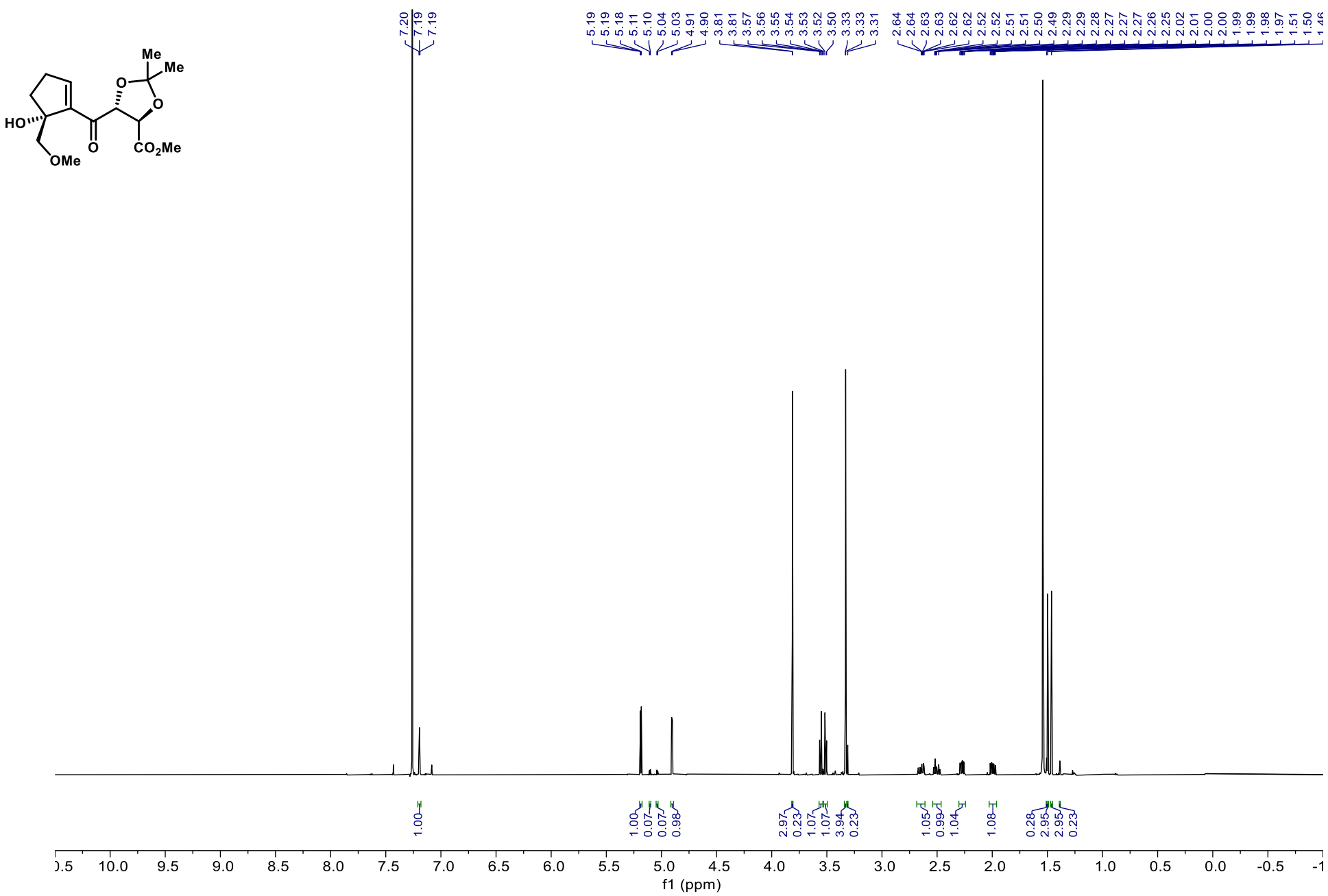
^{13}C NMR of **39e**, 151 MHz, $CDCl_3$



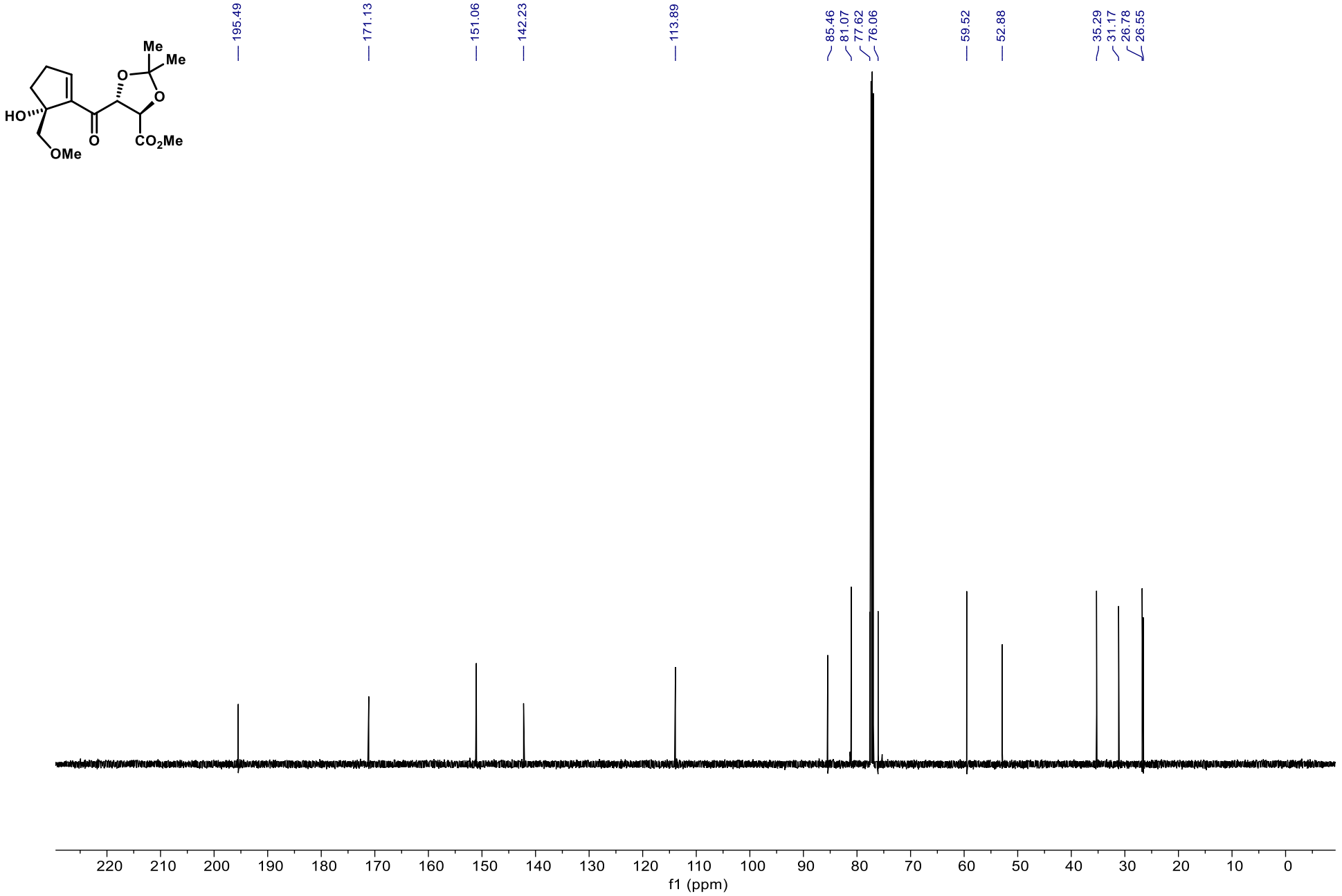
^{19}F NMR of **39e**, 376 MHz, $CDCl_3$



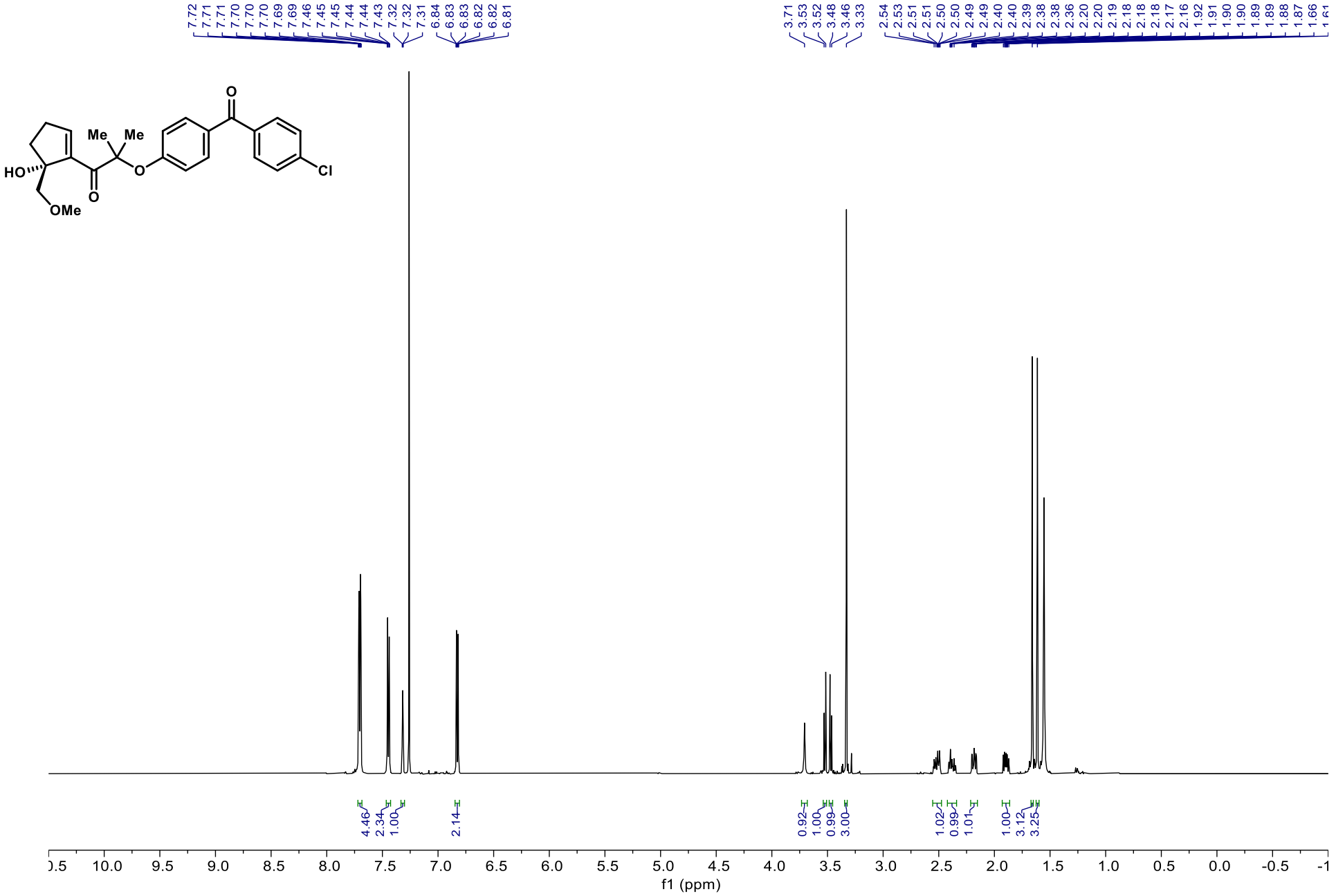
^{1}H NMR of **39f** (14:1 dr), 600 MHz, $CDCl_3$



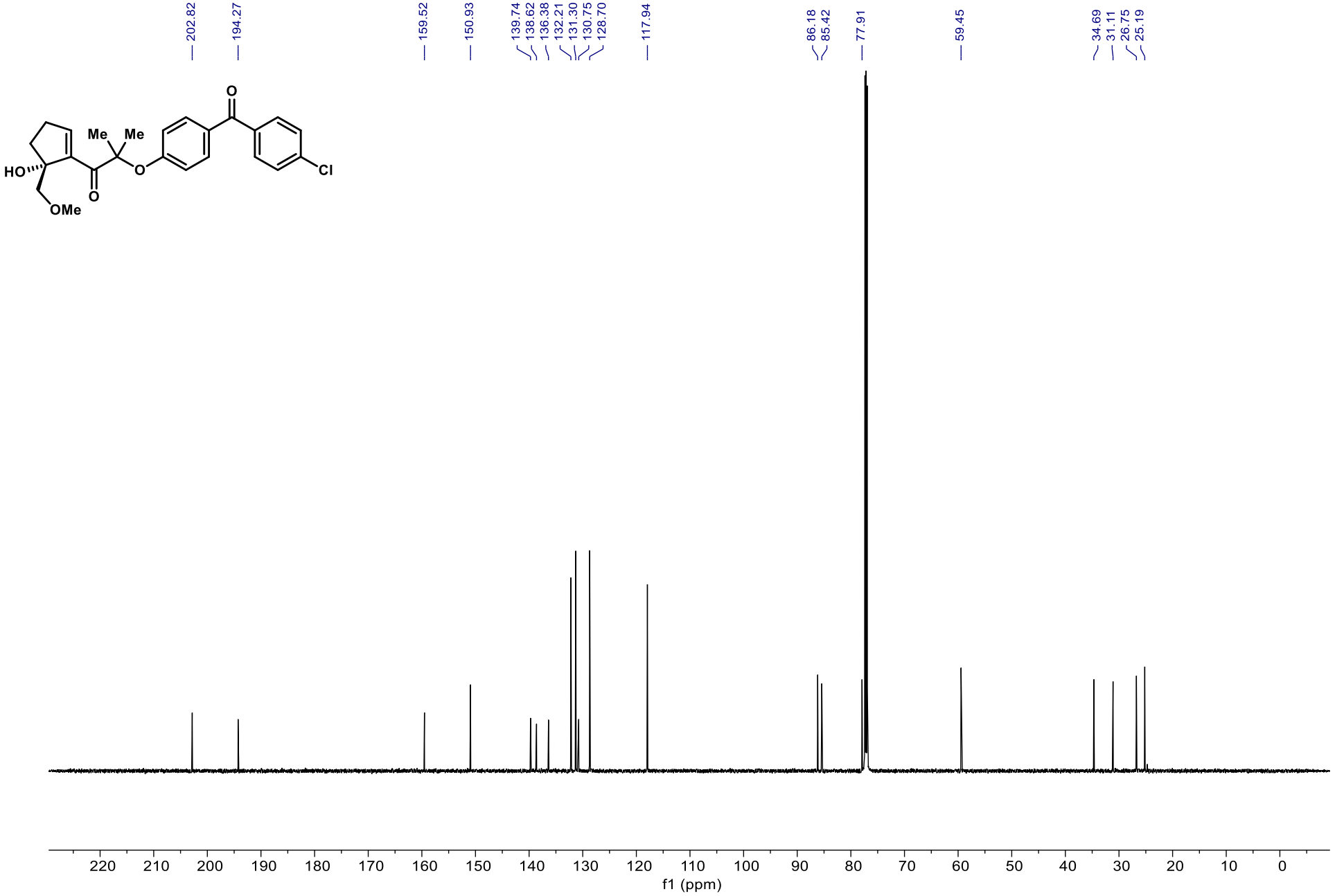
^{13}C NMR of **39f** (14:1 dr), 151 MHz, $CDCl_3$



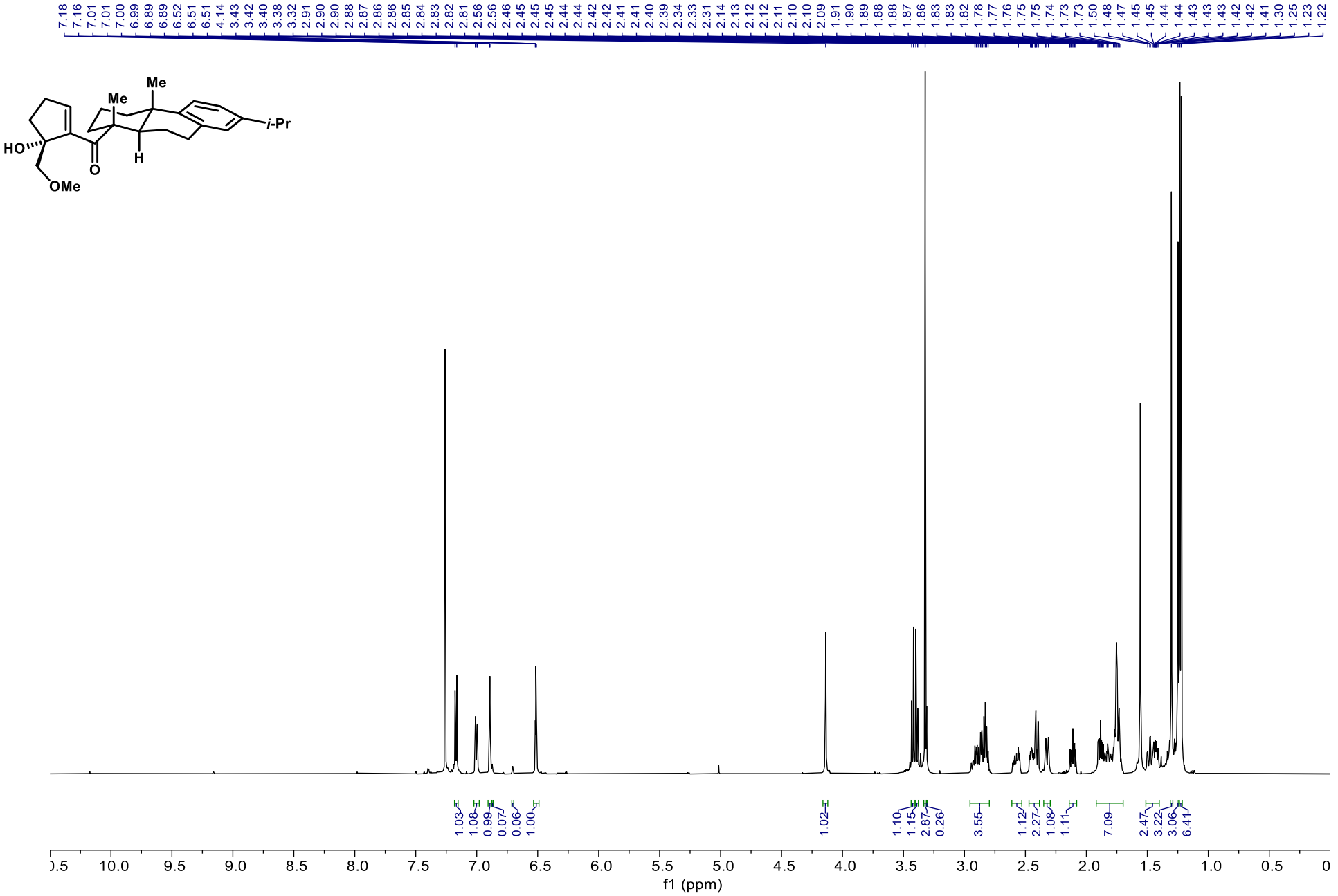
^{1}H NMR of **39g**, 600 MHz, $CDCl_3$



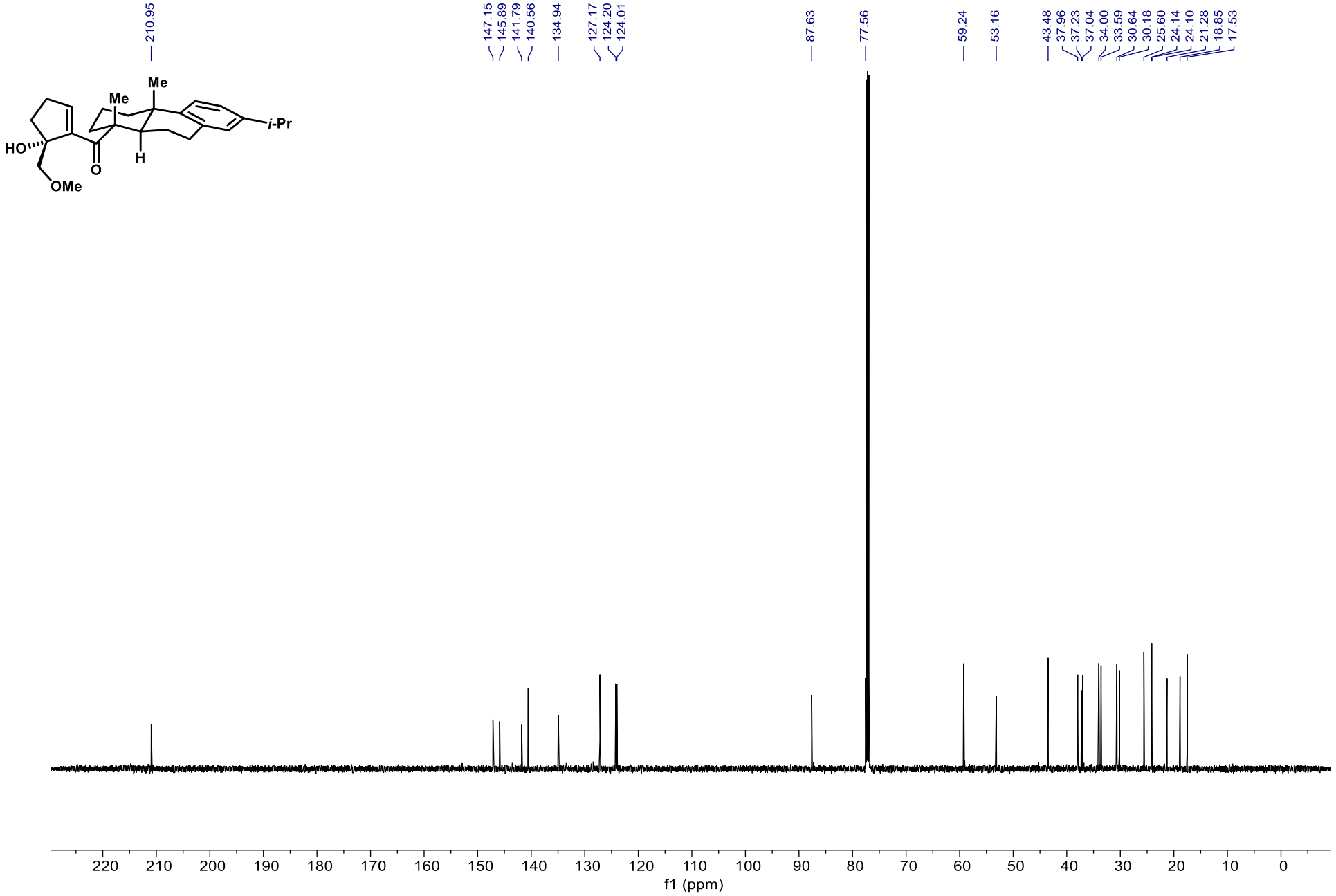
^{13}C NMR of **39g**, 151 MHz, $CDCl_3$



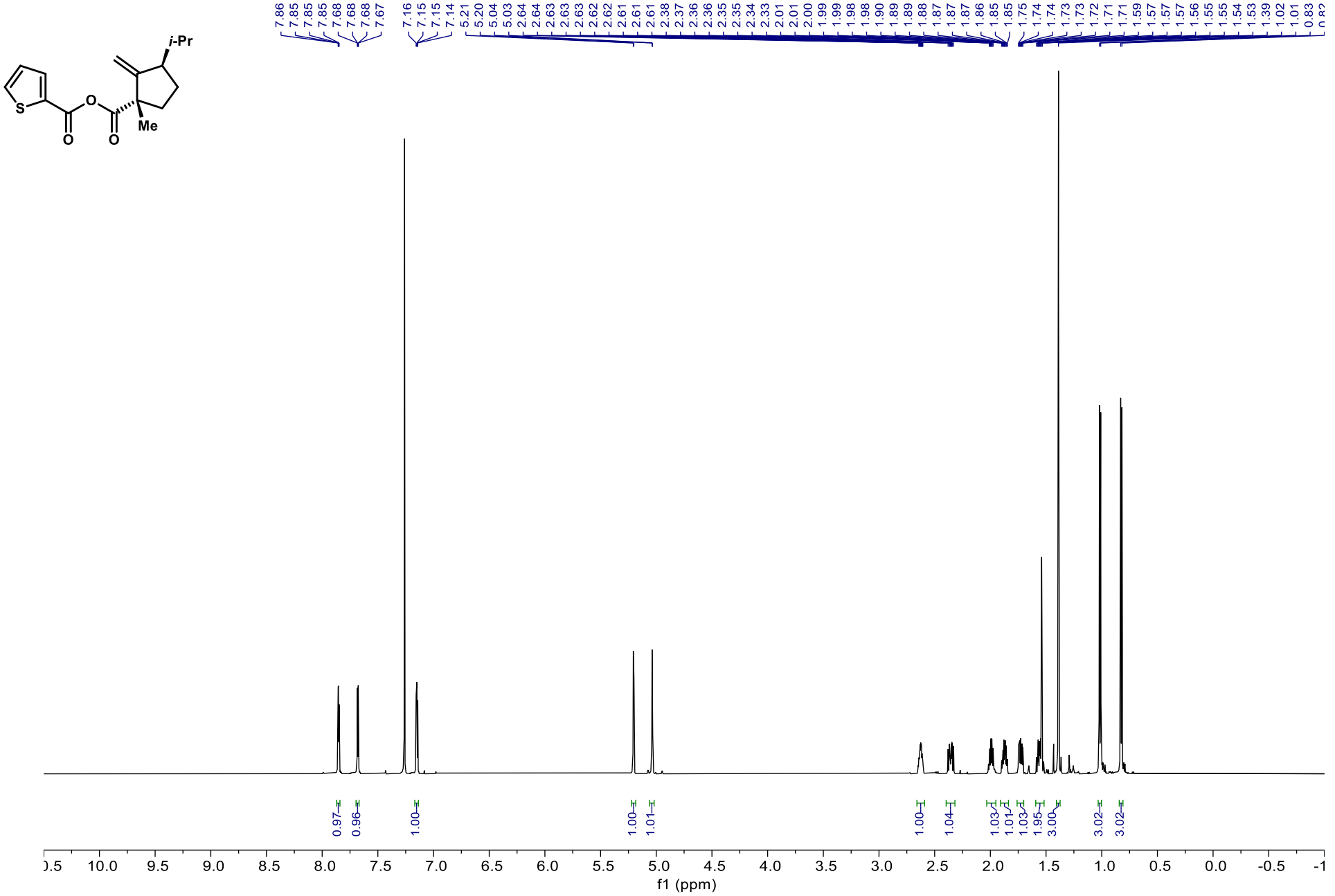
^{1}H NMR of **39h** (16:1 dr), 600 MHz, $CDCl_3$



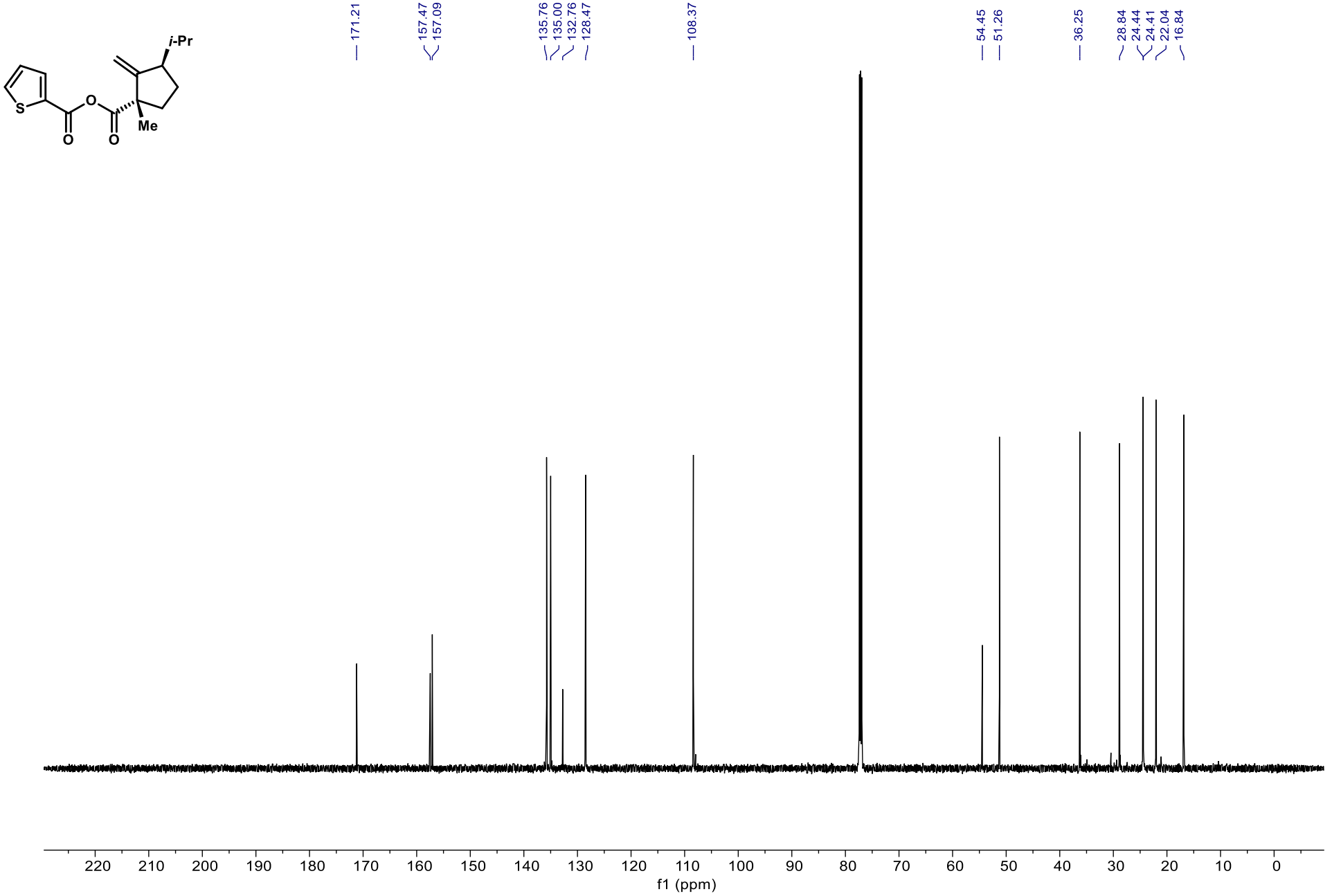
^{13}C NMR of **39h** (16:1 dr), 151 MHz, $CDCl_3$



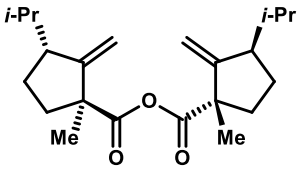
^{1}H NMR of **31**, 600 MHz, $CDCl_3$



^{13}C NMR of **31**, 151 MHz, $CDCl_3$



^{1}H NMR of **32**, 600 MHz, $CDCl_3$



^{13}C NMR of **32**, 151 MHz, $CDCl_3$