

SUPPORTING INFORMATION FOR

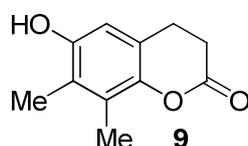
Enantioselective Total Synthesis of the Natural γ -Tocopherol Metabolite (*S*)- γ -CEHC [(*S*)-LLU- α]

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Experimental Procedures

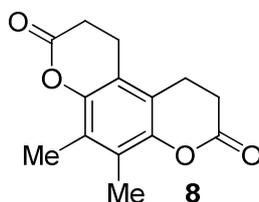
General: Melting points were obtained in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 at 300 and 75 MHz, respectively. All reactions were monitored by thin layer chromatography that was performed on pre-coated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230-400 mesh) of Merck. Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was dried by flaming in a stream of dry argon. Diisopropylamine was used freshly distilled over KOH. NaH was washed before use with several portions of hexane. CH_2Cl_2 was pre-dried over CaCl_2 , distilled over P_2O_5 and carefully kept under an argon atmosphere. Dry THF was distilled from sodium/benzophenone ketyl. All other reagent quality solvents were pre-dried over activated molecular sieves and kept under an argon atmosphere. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2 , and solvent drying with MgSO_4 .

6-Hydroxy-7,8-dimethylchroman-2-one (9).



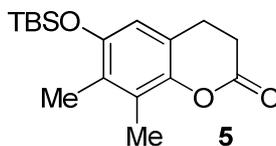
To a solution of 2,3-dimethylhydroquinone (**6**) (1 g, 7.24 mmol) and acidic resin “Amberlyst 15” (2.9 g) in toluene (21.7 mL), acrylic acid (**7**) (521 μ L, 7.60 mmol) was added dropwise, under argon. The reaction mixture was refluxed for two days, filtered, the solvent evaporated and the resulting residue diluted with EtOAc (100 mL). After filtration of the white precipitate, the filtrate was evaporated and the residue purified by flash chromatography (eluent hexane/EtOAc 4:1) to give compound **9** in 65% yield (906 mg), as a yellow solid: mp 123-125 $^{\circ}$ C; R_f 0.25 (hexane/EtOAc 2:1); ^1H NMR δ 2.16 (s, 3H), 2.21 (s, 3H), 2.71 (m, 2H), 2.88 (m, 2H), 4.98 (br s, 1H), 6.48 (s, 1H); ^{13}C NMR δ 11.8, 12.1, 23.9, 29.4, 111.2, 120.3, 122.7, 126.3, 144.2, 149.8, 169.5; MS (FAB $^+$) 154 (65), 192 (M^+ , 52), 193 (100); HRMS (FAB $^+$) calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$ (M^+) 192.0786, found 192.0779.

5,6-Dimethyl-1,2,9,10-tetrahydropyrano[3,2-f]chromene-3,8-dione (8).



Compound **8** was obtained as the white precipitate from above, in 10% yield: mp 244-246 $^{\circ}$ C; ^1H NMR δ 2.27 (s, 6H), 2.77-2.82 (m, 4H), 2.93-2.97 (m, 4H); ^{13}C NMR δ 12.0, 20.8, 28.7, 117.28, 125.3, 146.5, 168.1; MS (EI) m/z (%): 148 (11), 161 (24), 175 (19), 176 (100), 204 (33), 218 (18), 246 (M^+ , 91). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{14}\text{O}_4$ (M^+) 246.0892, found 246.0902.

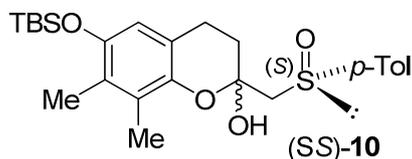
6-(*tert*-Butyldimethylsilyloxy)-7,8-dimethylchroman-2-one (5).



To a solution of phenol **9** (2.0 g, 10.42 mmol) and 2,6-lutidine (2.2 mL, 20.84 mmol) in CH_2Cl_2 (180 mL), *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.6 mL, 15.63 mmol) was added. The reaction mixture was stirred for 8 hours, hydrolyzed with a saturated aqueous ammonium chloride solution (70 mL) and extracted with EtOAc. After workup and flash chromatography (eluent hexane/EtOAc 2:1), compound **5** was obtained in 100% yield (3.5 g), as a white solid: mp 95-97 $^{\circ}$ C; R_f 0.69 (hexane/EtOAc 2:1); ^1H NMR δ 0.19 (s, 6H), 1.02 (s, 9H), 2.13 (s, 3H), 2.20 (s, 3H), 2.72 (m, 2H), 2.88 (m, 3H), 6.44 (s, 1H); ^{13}C NMR δ -4.2, 12.3, 12.8, 14.2, 18.3, 24.1, 25.8, 29.5, 114.8,

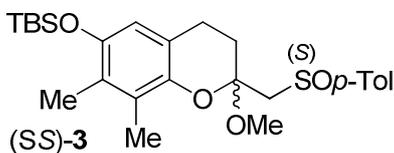
119.8, 126.2, 127.6, 144.5, 149.6, 169.3; MS (FAB⁺) 306 (M⁺, 100), 307 (61); HRMS (FAB⁺) calcd for C₁₇H₂₆O₃Si (M⁺) 306.1651, found 306.1662.

(SS)-6-(*tert*-Butyldimethylsilyloxy)-7,8-dimethyl-2-(*p*-tolylsulfinylmethyl)chroman-2-ol (10).



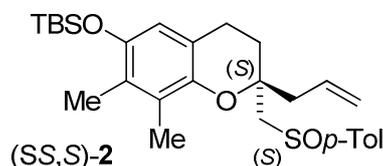
To a solution of dry diisopropylamine (302 μ L, 2.15 mmol) in THF (2 mL) at 0 °C, a solution of *n*-BuLi 2.5M in hexanes (0.9 mL, 2.15 mmol) was added, under N₂. The mixture was stirred for 30 min, cooled to -78 °C and a solution of (SS)-methyl-*p*-tolylsulfoxide (197 mg, 1.3 mmol) in THF (2 mL) was added dropwise. The reaction was allowed to reach -40 °C, stirred for 1 hour and added, via cannula, to a solution of chromanone **5** (300 mg, 1.0 mmol) in THF (3 mL), at -78 °C. The mixture was stirred for 1 hour, hydrolyzed with a saturated aqueous ammonium chloride solution (5 mL) and extracted with EtOAc. After workup, a pale orange syrup was obtained, and diethyl ether was added until a precipitate appeared. The solid was filtered, washed with several portions of diethyl ether/hexane and dried, to obtain compound (SS)-**10** as a white solid, in 74% yield (333 mg). When the reaction was performed in a smaller scale, the precipitation of the product was not observed and the final mixture was purified by flash chromatography (eluent hexane/EtOAc 2:1): mp 133-136 °C; R_f 0.26 (hexane/EtOAc 2:1); ¹H NMR δ 0.17 (s, 3H), 0.19 (s, 3H), 1.76 (ddt, $J = 2.0, 5.8$ and 13.1 Hz, 1H), 2.02-2.13 (m, 4H), 2.27 (s, 3H), 2.44 (s, 3H), 2.58 (ddd, $J = 2.5, 5.5$ and 15.9 Hz, 1H), 2.97-3.19 (m, 4H), 6.10 (d, $J = 1.9$ Hz, 1H), 6.39 (s, 1H), 7.49 (AA'BB' system, $J = 8.1$ Hz, 4H); ¹³C NMR δ -4.3, -4.1, 12.2, 12.8, 18.2, 21.0, 21.4, 25.9, 32.2, 63.9, 96.4, 115.7, 118.2, 124.0, 126.0, 126.6, 130.2, 140.5, 142.1, 143.9, 147.3; MS (FAB⁺) 385 (41), 460 (M⁺, 100), 461 (34); HRMS (FAB⁺) calcd for C₂₅H₃₆O₄SSi (M⁺) 460.2104, found 460.2098.

(SS)-6-(*tert*-Butyldimethylsilyloxy)-2-methoxy-7,8-dimethyl-2-(*p*-tolylsulfinylmethyl)chroman (3).



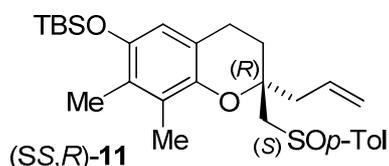
To a mixture of sulfinyl lactol (SS)-**10** (500 mg, 1.08 mmol), dry methanol (218 μ L) and anhydrous MgSO_4 (540 mg) in CH_2Cl_2 (5.4 mL), TMSOTf (39 μ L, 0.2 equiv) was added at 0 $^\circ\text{C}$, under N_2 . The solution was allowed to reach room temperature, stirred for 2 h and quenched with Et_3N (30 μ L). After evaporation of the solvent and flash chromatography (eluent hexane/EtOAc 2:1), compound (SS)-**3** was obtained as a yellow oil, in 85% yield (437 mg): R_f 0.46 (hexane/EtOAc 2:1); $[\alpha]_D^{20} = -71.6$ (c 2.0, CHCl_3); $^1\text{H NMR}$ δ 0.19 (s, 6H), 1.01 (s, 9H), 1.99 (m, 1H), 2.09 (s, 3H), 2.11 (s, 3H), 2.24 (m, 1H), 2.41 (s, 3H), 2.57 (m, 1H), 2.97 (m, 1H), 3.26 (m, 5H), 6.37 (s, 1H), 7.34 and 7.59 (AA'BB' system, $J = 8.2$ Hz, 4H); $^{13}\text{C NMR}$ δ -4.2, -4.1, 11.9, 12.7, 12.8, 14.2, 18.2, 21.3, 21.4, 25.7, 25.8, 25.9, 30.1, 30.4, 49.2, 49.3, 65.1, 65.6, 97.4, 97.8, 115.7, 115.8, 118.9, 119.0, 123.9, 124.0, 125.3, 126.3, 126.4, 130.0, 141.5, 141.6, 141.7, 141.9, 143.4, 143.5, 147.4; MS (FAB $^+$) 415 (65), 459 (58), 474 (M^+ , 100); HRMS (FAB $^+$) calcd for $\text{C}_{26}\text{H}_{38}\text{O}_4\text{SSi}$ (M^+) 474.2260, found 474.2263.

(SS,S)-2-Allyl-6-(tert-butyldimethylsilyloxy)-7,8-dimethyl-2-(p-tolylsulfinylmethyl)chroman (2).



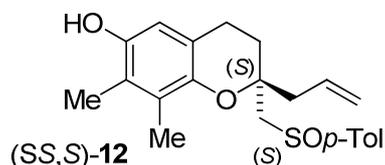
To a solution of sulfinyl ketal (SS)-**3** (1.49 g, 3.14 mmol) and allyltrimethylsilane (1.49 mL, 9.42 mmol, 3 equiv) in CH_2Cl_2 (46 mL) at -78 $^\circ\text{C}$, TiCl_4 (500 μ L, 4.39 mmol, 1.4 equiv) was added. After stirring for 1 hour, the reaction mixture was hydrolyzed with a saturated aqueous NaHCO_3 solution (20 mL) and extracted with EtOAc. After workup and flash chromatography (eluent hexane/EtOAc 4:1), compound (SS,S)-**2** was obtained in 67% yield (1.2 g), as a yellow oil: R_f 0.58 (hexane/EtOAc 2:1); $[\alpha]_D^{20} = -57.4$ (c 1.2, CHCl_3); $^1\text{H NMR}$ δ 0.17 (s, 6H), 1.01 (s, 9H), 2.04 (m, 2H), 2.09 (s, 6H), 2.39 (s, 3H), 2.78 (m, 4H), 2.86 and 3.12 (AB system, $J = 13.8$ Hz, 2H), 5.25-5.32 (m, 2H), 6.00 (dddd, $J = 6.4, 8.1, 10.1$ and 14.5 Hz, 1H), 6.36 (s, 1H), 7.27 and 7.44 (AA'BB' system, $J = 8.4$ Hz, 4H); $^{13}\text{C NMR}$ δ -4.2 (2C), 12.1, 12.8, 18.3, 21.3, 21.8, 25.8, 29.9, 41.9, 65.3, 115.9, 117.5, 119.5, 123.7 (2C), 125.9, 126.7, 129.9 (2C), 132.9, 141.2, 142.0, 144.5, 146.9; MS (FAB $^+$) 484 (M^+ , 75), 485 ($\text{M}^+ + 1$, 100); HRMS (FAB $^+$) calcd for $\text{C}_{28}\text{H}_{41}\text{O}_3\text{SSi}$ ($\text{M}^+ + 1$) 485.2546, found 485.2540.

(SS,R)-2-Allyl-6-(*tert*-butyldimethylsilyloxy)-7,8-dimethyl-2-(*p*-tolylsulfinylmethyl)chroman (11).

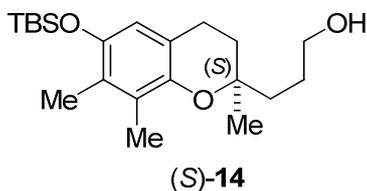


Compound (SS,R)-11 was obtained following the previously described protocol, in 12% yield (180 mg): $[\alpha]_D^{20} = -36.0$ (c 1.4, CHCl_3); $^1\text{H NMR}$ δ 0.19 (s, 6H), 1.01 (s, 9H), 2.04-2.10 (m, 2H), 2.08 (s, 3H), 2.11 (s, 3H), 2.39 (s, 3H), 2.57 (m, 1H), 2.75-2.81 (m, 1H), 2.99 and 3.12 (AB system, $J = 13.7$ Hz, 2H), 5.11-5.17 (m, 2H), 5.75-5.87 (m, 1H), 6.38 (s, 1H), 7.31 and 7.54 (AA'BB' system, $J = 7.9$ Hz, 4H); $^{13}\text{C NMR}$ δ -4.2 (2C), 12.1, 12.9, 18.3, 21.4, 21.9, 25.9, 28.4, 42.0, 66.7, 76.0, 115.8, 117.0, 119.6, 124.0, 126.0 (2C), 126.8, 129.9, 132.4 (2C), 141.3, 142.1, 144.7, 146.9; MS (FAB+) m/z (%): 345 (50), 467 (9), 484 (M^+ , 100), 485 ($\text{M}^+ + \text{H}$, 90). HRMS (FAB+) calcd for $\text{C}_{28}\text{H}_{41}\text{O}_3\text{SSi}$ ($\text{M}^+ + \text{H}$) 485.2546, found 485.2534.

(SS,S)-2-Allyl-6-hydroxy-7,8-dimethyl-2-(*p*-tolylsulfinylmethyl)chroman (12).

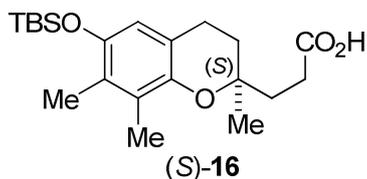


To a solution of OTBS-protected chroman (SS,S)-2 (106.5 mg, 0.22 mmol) in THF (4 mL), a solution of TBAF 1.0M in THF (265 μL , 0.26 mmol, 1.2 equiv) was added at 0 °C. The mixture was stirred for 5 min, hydrolyzed with NH_4Cl and extracted with EtOAc. After workup and flash chromatography (eluent hexane/EtOAc 2:1), phenol (SS,S)-12 was obtained in quantitative yield, as a crystalline white solid: mp 172-173 °C; $[\alpha]_D^{20} = -84.7$ (c 0.36, CHCl_3); $^1\text{H NMR}$ δ 2.02-2.22 (m, 2H), 2.13 (s, 3H), 2.18 (s, 3H), 2.41 (s, 3H), 2.65-2.88 (m, 2H), 2.88 and 3.16 (AB system, $J = 13.8$ Hz, 2H), 4.50-4.65 (m, 1H), 5.25-5.32 (m, 2H), 6.03 (dddd, $J = 18.3, 10.2, 8.2$ and 6.4 Hz, 1H), 6.38 (s, 1H), 7.30 and 7.48 (AA'BB' system, $J = 8.2$ Hz, 4H); $^{13}\text{C NMR}$ δ 11.8, 12.1, 20.2, 21.3, 30.0, 41.8, 65.0, 75.2, 117.1, 118.8, 119.4, 121.6, 122.8, 123.8 (2C), 129.9 (2C), 132.9, 141.2, 142.0, 144.2, 145.4; MS (FAB+) m/z (%): 55 (48), 231 (36), 371 ($\text{M}^+ + \text{H}$, 100). HRMS (FAB+) calcd for $\text{C}_{22}\text{H}_{27}\text{O}_3\text{S}$ ($\text{M}^+ + \text{H}$) 371.1681, found 371.1676.

(S)-3-[6-(*tert*-Butyldimethylsilyloxy)-2,7,8-trimethylchroman-2-yl]propan-1-ol (14).

To allyl sulfoxide (SS,S)-2 (400 mg, 0.83 mmol) without solvent at 0 °C, a solution of 9-BBN 0.5M in THF (6.7 mL, 3.32 mmol, 4 equiv) was added, under nitrogen. After stirring at room temperature for 48 h, the reaction mixture was cooled to 0 °C and a 50:50 solution of aqueous NaOH 3*N* and 30%-H₂O₂ (12 mL) was added. The mixture was stirred at room temperature for 3 h, diluted with EtOAc and washed with brine. After workup, compound (SS,S)-13 was obtained and used in the next step without further purification.

To a solution of the above obtained sulfinyl alcohol (SS,S)-13 in EtOH (4 mL), Ni Raney was added and the mixture was stirred at room temperature overnight. After filtration, evaporation of the solvent and flash chromatography in alumina (eluent hexane/EtOAc 4:1), compound (S)-14 was obtained in 87% yield for the two last steps, as a colorless oil: *R*_f 0.42 (hexane/EtOAc 2:1); [α]_D²⁰ = + 3.1 (*c* 1.4, CHCl₃); ¹H NMR δ 0.17 (s, 6H), 1.00 (s, 9H), 1.25 (s, 3H), 1.51-1.8 (m, 6H), 2.08 (s, 6H), 2.66-2.68 (m, 2H), 3.63-3.67 (m, 2H), 6.34 (s, 1H); ¹³C NMR δ -4.2, 12.1, 12.8, 18.2, 22.4, 22.7, 23.9, 25.2, 25.9, 27.0, 27.4, 31.6, 34.7, 36.2, 63.2, 72.2, 115.8, 117.6, 125.6, 126.2, 145.6, 146.2; MS (FAB⁺) 346 (48), 364 (M⁺, 100); HRMS (FAB⁺) calcd for C₂₁H₃₆O₃Si (M⁺) 364.2434, found 364.2431.

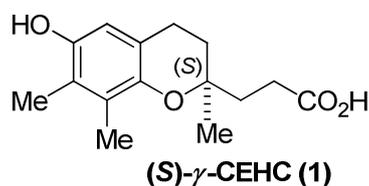
(S)-3-[6-(*tert*-Butyldimethylsilyloxy)-2,7,8-trimethylchroman-2-yl]propanoic acid (16).

To a solution of alcohol (S)-14 (100 mg, 0.274 mmol) in a 50:50 mixture of CH₂Cl₂ and DMSO (2.7 mL) at 0 °C, triethylamine (193 μL, 1.37 mmol) and the complex SO₃·pyridine (174 mg, 1.1 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, quenched with water,

extracted with EtOAc and washed with brine. After workup, the resulting residue was filtered over alumina (eluent EtOAc), to obtain compound (*S*)-**15** which was used directly in the next step without further purification: ^1H RMN: δ 0.17 (s, 6H), 1.00 (s, 9H), 1.23 (s, 3H), 1.70-2.10 (m, 4H), 2.06 (s, 3H), 2.08 (s, 3H), 2.62 (dt, $J = 1.6$ and 7.5 Hz, 2H), 2.67-2.73 (m, 2H), 6.34 (s, 1H), 9.80 (t, $J = 1.6$ Hz, 1H); ^{13}C RMN: δ -4.2 (2C), 12.1, 12.8, 18.2, 22.2, 23.7, 25.8, 31.7, 32.2, 38.6, 74.2, 115.8, 117.3, 125.7, 126.4, 145.3, 146.4, 202.5.

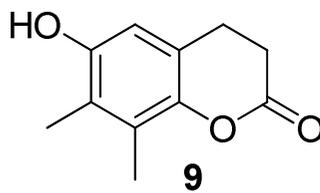
To a solution of the above obtained aldehyde (*S*)-**15** in a 80:20 mixture of *t*-BuOH and water (2.25 mL) at 0 °C, 2-methyl-2-butene (0.5 mL, 1 mmol), NaH_2PO_4 (31 mg, 0.22 mmol) and NaClO_2 (71 mg, 0.78 mmol) were successively added. The reaction mixture was stirred at 0 °C for 10 min, diluted with water and extracted with CH_2Cl_2 . After workup and flash chromatography, (eluent hexane/EtOAc 2:1, 5% MeOH), compound (*S*)-**16** was obtained in 76% yield (78 mg) for the two last steps, as a yellow oil: R_f 0.27 (hexane/EtOAc 2:1); $[\alpha]_D^{20} = +5.3$ (c 0.6, CHCl_3); ^1H NMR δ 0.17 (s, 6H), 1.00 (s, 9H), 1.24 (s, 3H), 1.73-2.05 (m, 6H), 2.07, (s, 3H), 2.08 (s, 3H), 2.56 (t, $J = 7.9$ Hz, 2H), 2.67-2.73 (m, 2H), 6.34 (s, 1H); ^{13}C NMR δ -4.2, 12.0, 12.8, 18.2, 22.2, 23.5, 25.8, 27.0, 28.4, 31.6, 34.7, 74.1, 115.8, 117.4, 125.7, 126.4, 145.4, 146.4, 178.7; MS (FAB^+) 378 (M^+ , 100); HRMS (FAB^+) calcd for $\text{C}_{21}\text{H}_{34}\text{O}_4\text{Si}$ (M^+) 378.2226, found 378.2233.

(*S*)-3-(6-Hydroxy-2,7,8-trimethylchroman-2-yl)propanoic acid (1) [(*S*)- γ -CEHC].

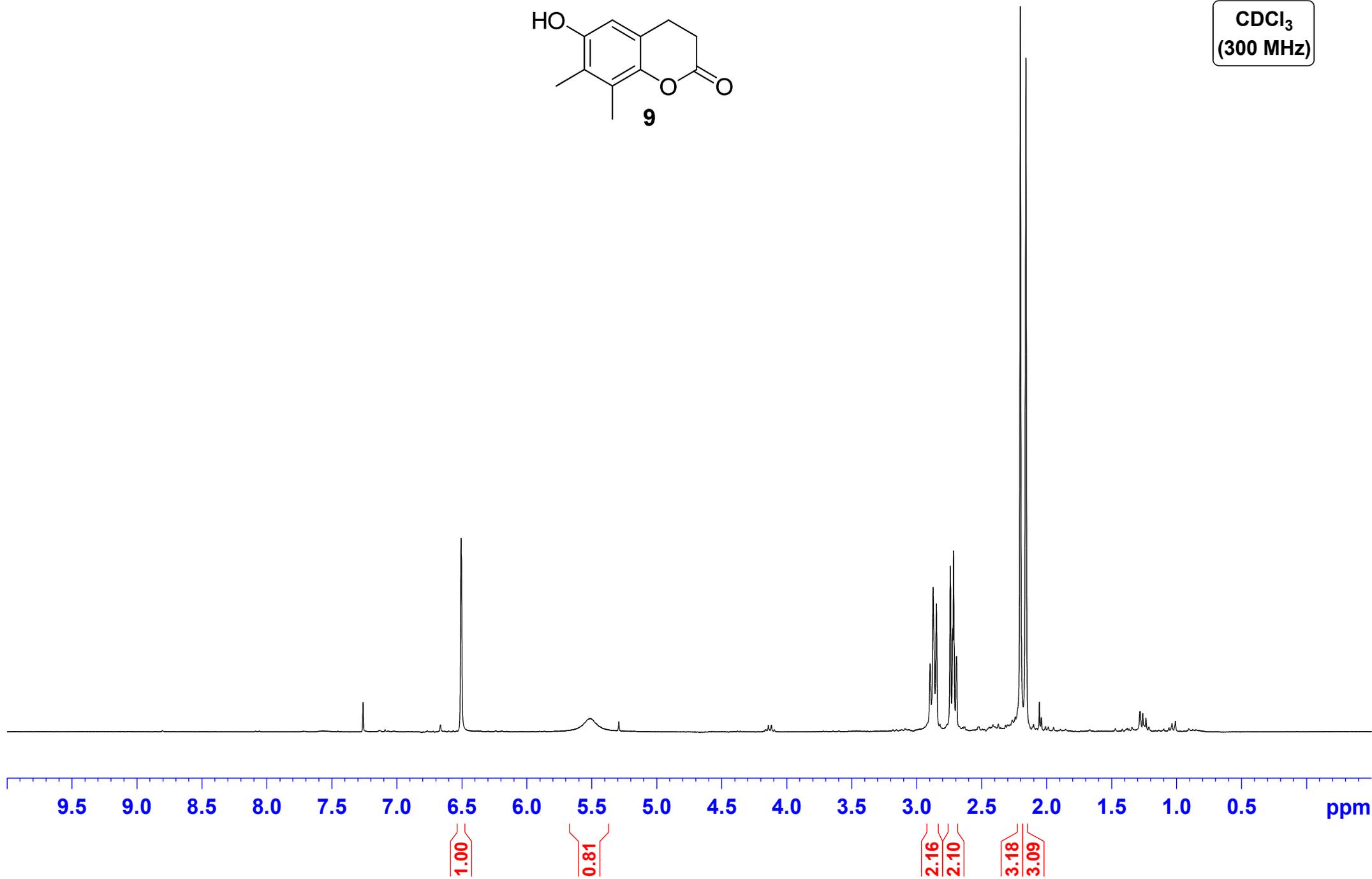


To a solution of carboxylic acid (*S*)-**16** (60 mg, 0.158 mmol) in THF (1.6 mL), tetrabutylammonium fluoride (0.2 mL, 0.205 mmol) was added, at 0 °C. The reaction mixture was stirred at 0 °C for 15 minutes, hydrolyzed with a saturated aqueous ammonium chloride solution and extracted with EtOAc. After workup and flash chromatography (eluent hexane/EtOAc 2:1, 5% MeOH, 0.01% AcOH), compound (*S*)-**1** [(*S*)- γ -CEHC] was obtained in 100% yield (42 mg), as a white solid: R_f 0.19 (hexane/EtOAc 2:1); $[\alpha]_D^{20} = +5.5$ (c 1.43, MeOH); ^1H NMR δ 1.24 (s, 3H), 1.72-1.82 (m, 2H), 1.89 (ddd, $J = 7.2$, 8.8 and 14.1 Hz, 1H), 1.99-2.05 (m, 1H), 2.09 (s, 3H), 2.12 (s, 3H), 2.55 (ddd, $J = 1.9$, 6.8 and 8.8 Hz, 2H), 2.66-2.75 (m, 2H), 6.37 (s, 1H); ^{13}C NMR δ 11.8, 11.9, 20.7, 22.1, 23.5, 28.4, 31.5, 34.6, 74.3, 112.1, 117.9, 121.8, 125.9, 145.2, 146.5, 176.8, 179.5; MS (FAB^+) 264 (M^+ , 100); HRMS (FAB^+) calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4$ (M^+) 264.1362, found 264.1364.

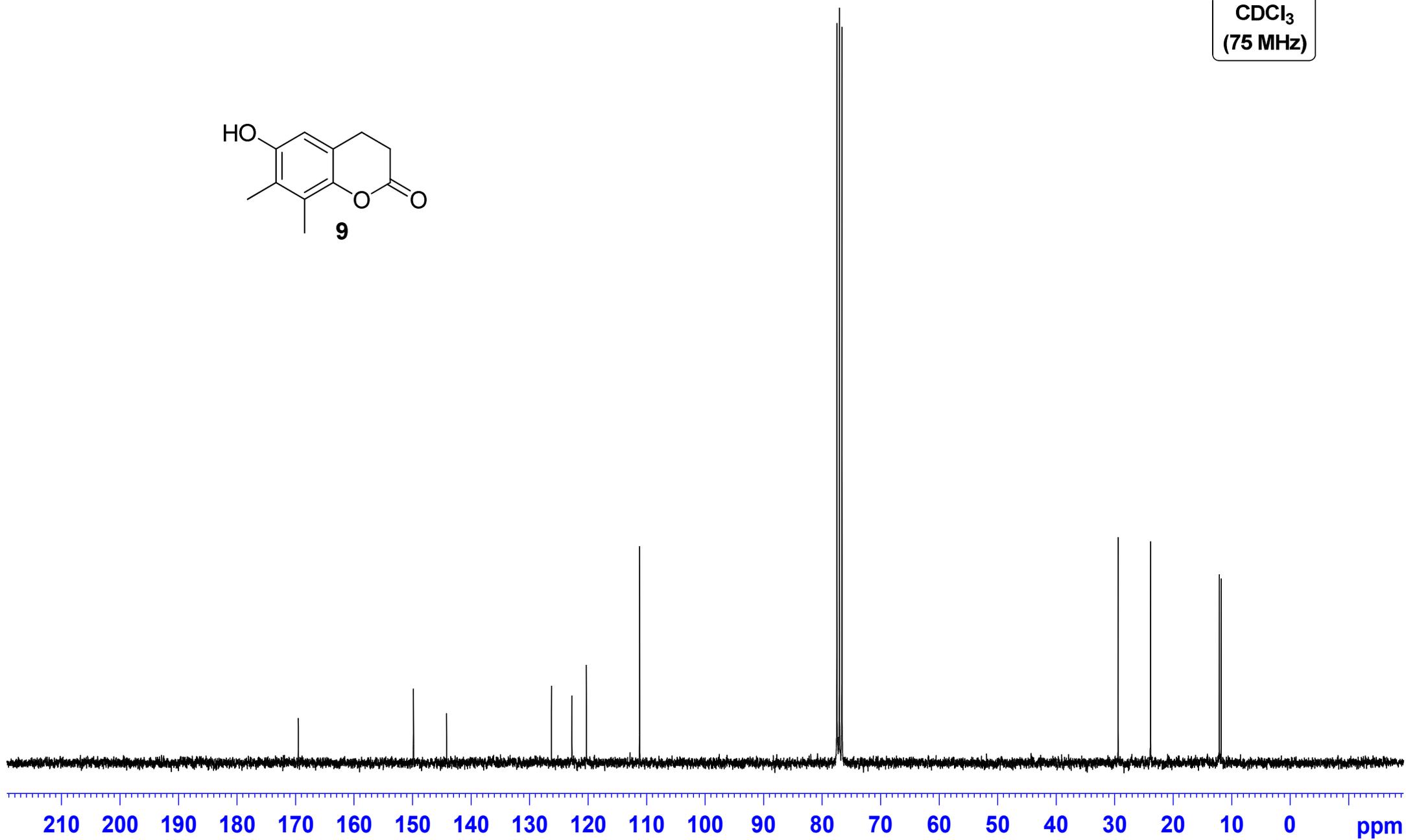
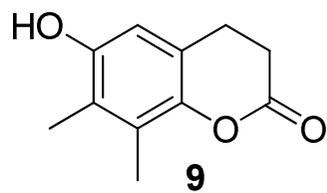
S-8

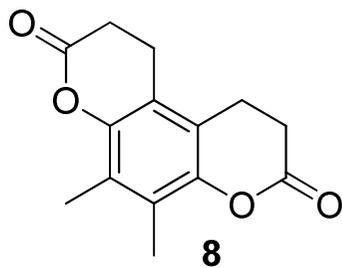


CDCl₃
(300 MHz)

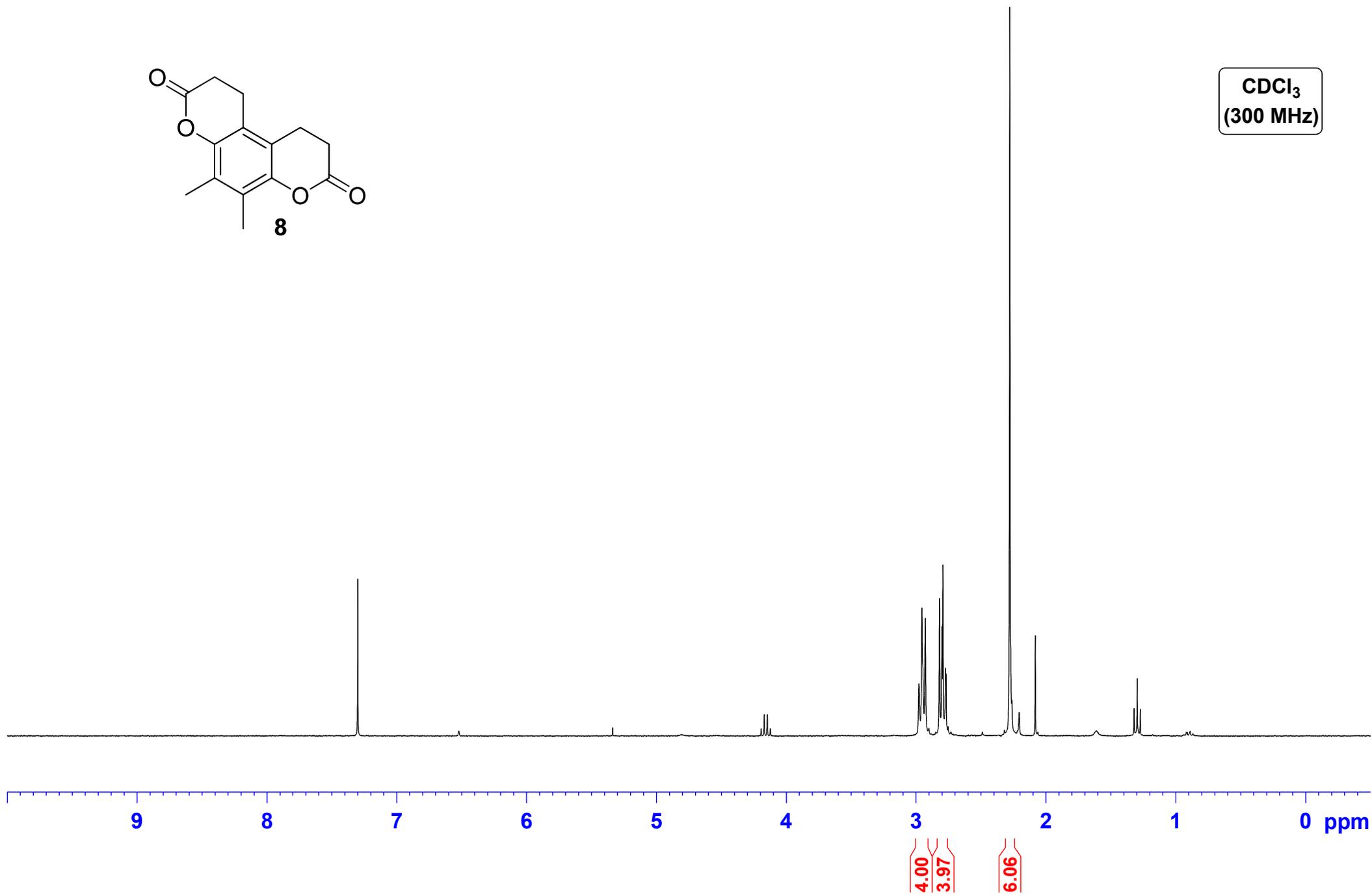


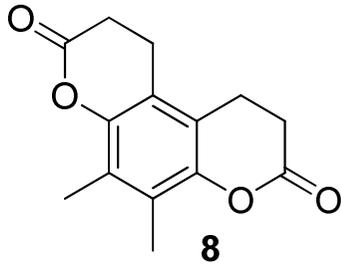
CDCl₃
(75 MHz)



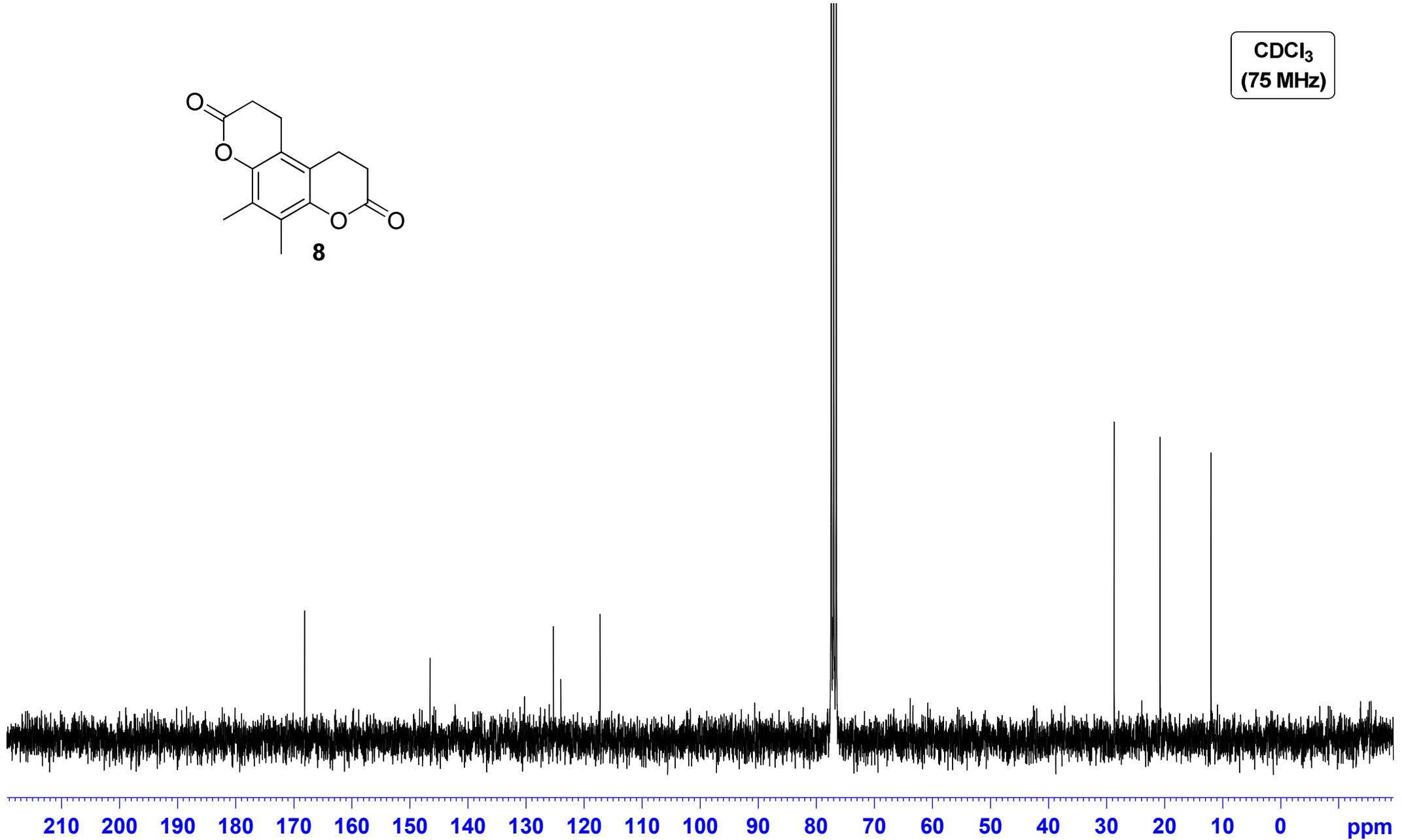


CDCl₃
(300 MHz)

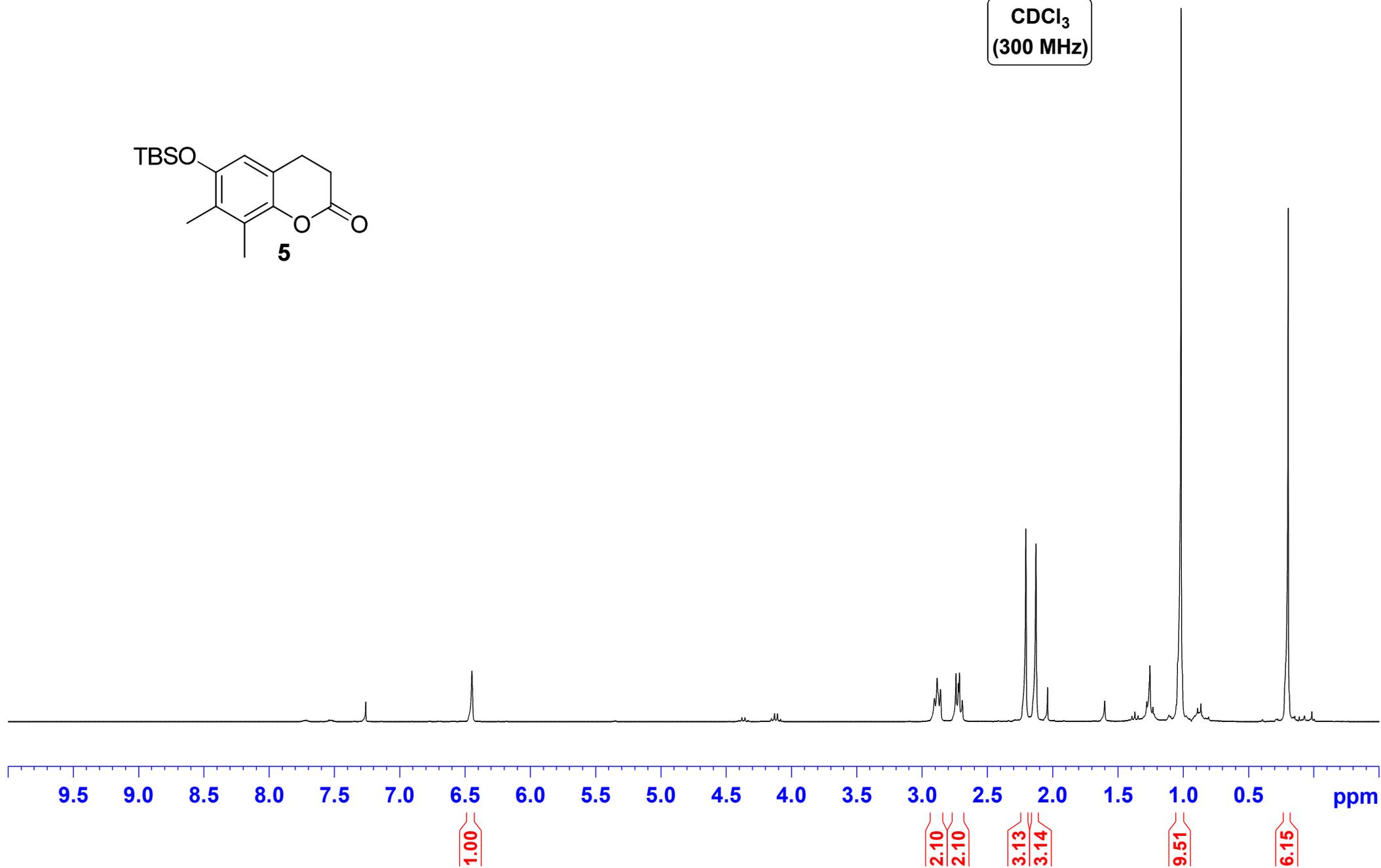
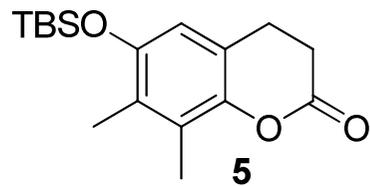


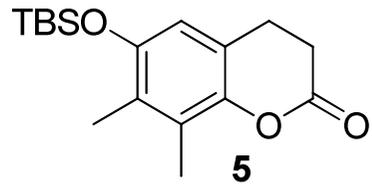


CDCl₃
(75 MHz)

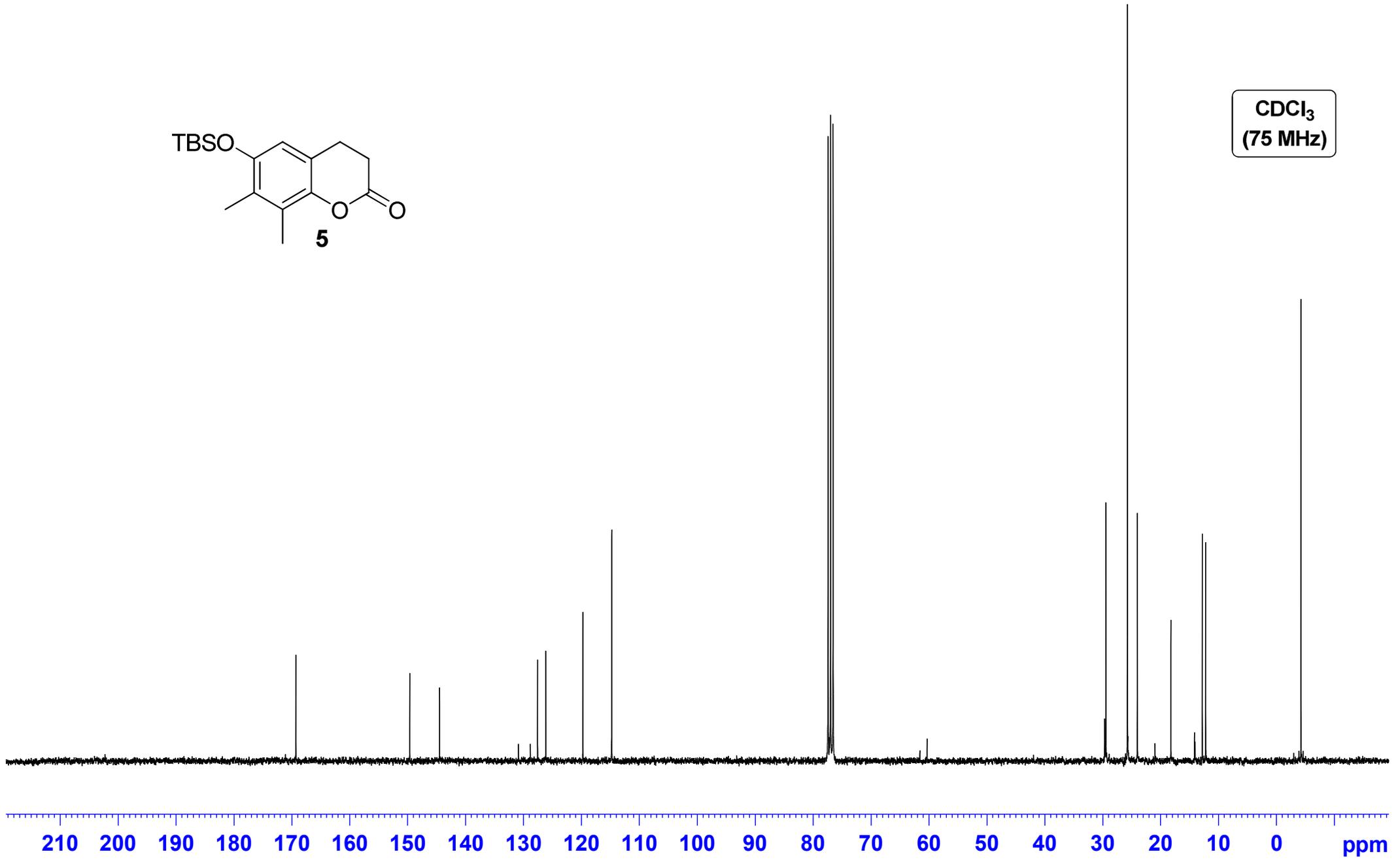


CDCl₃
(300 MHz)

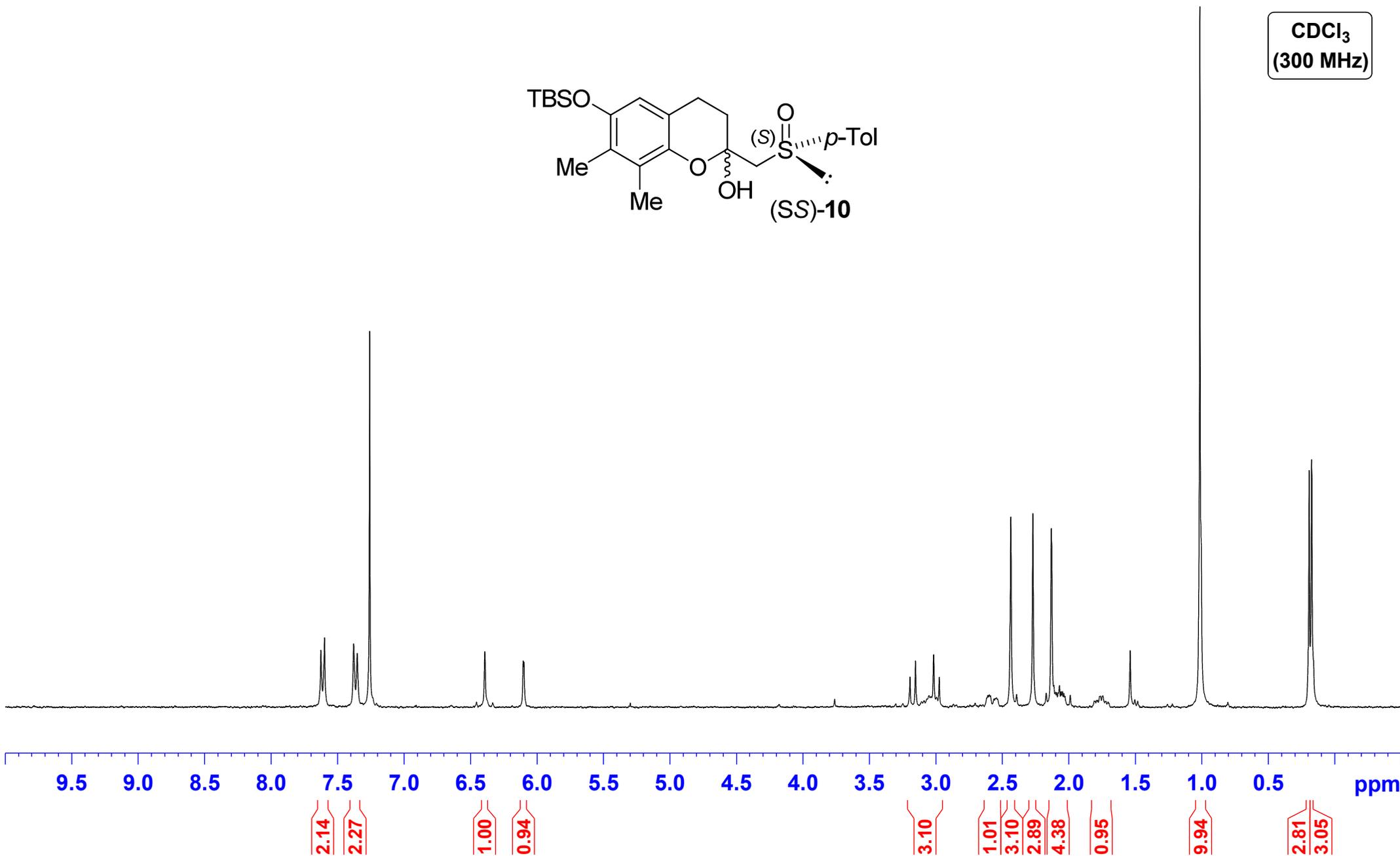
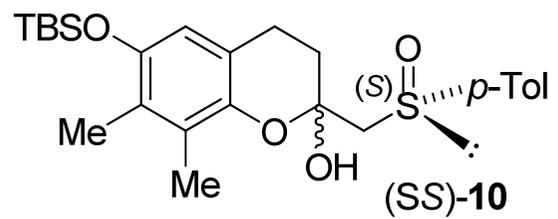




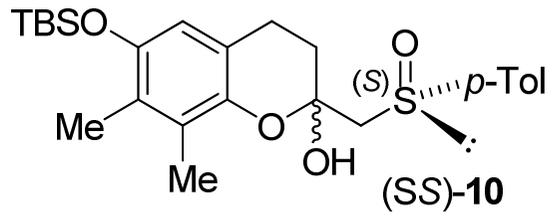
CDCl₃
(75 MHz)



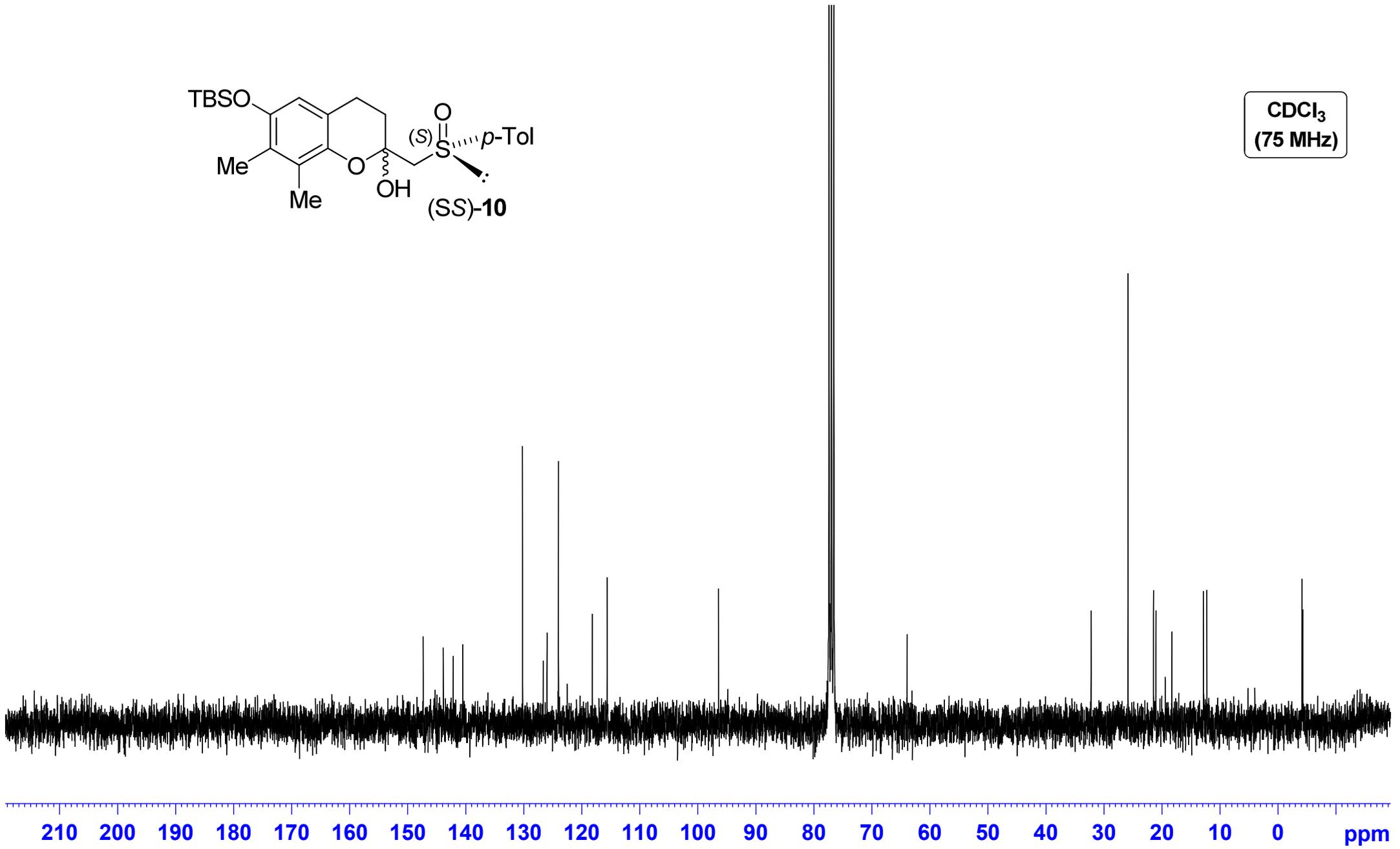
CDCl₃
(300 MHz)



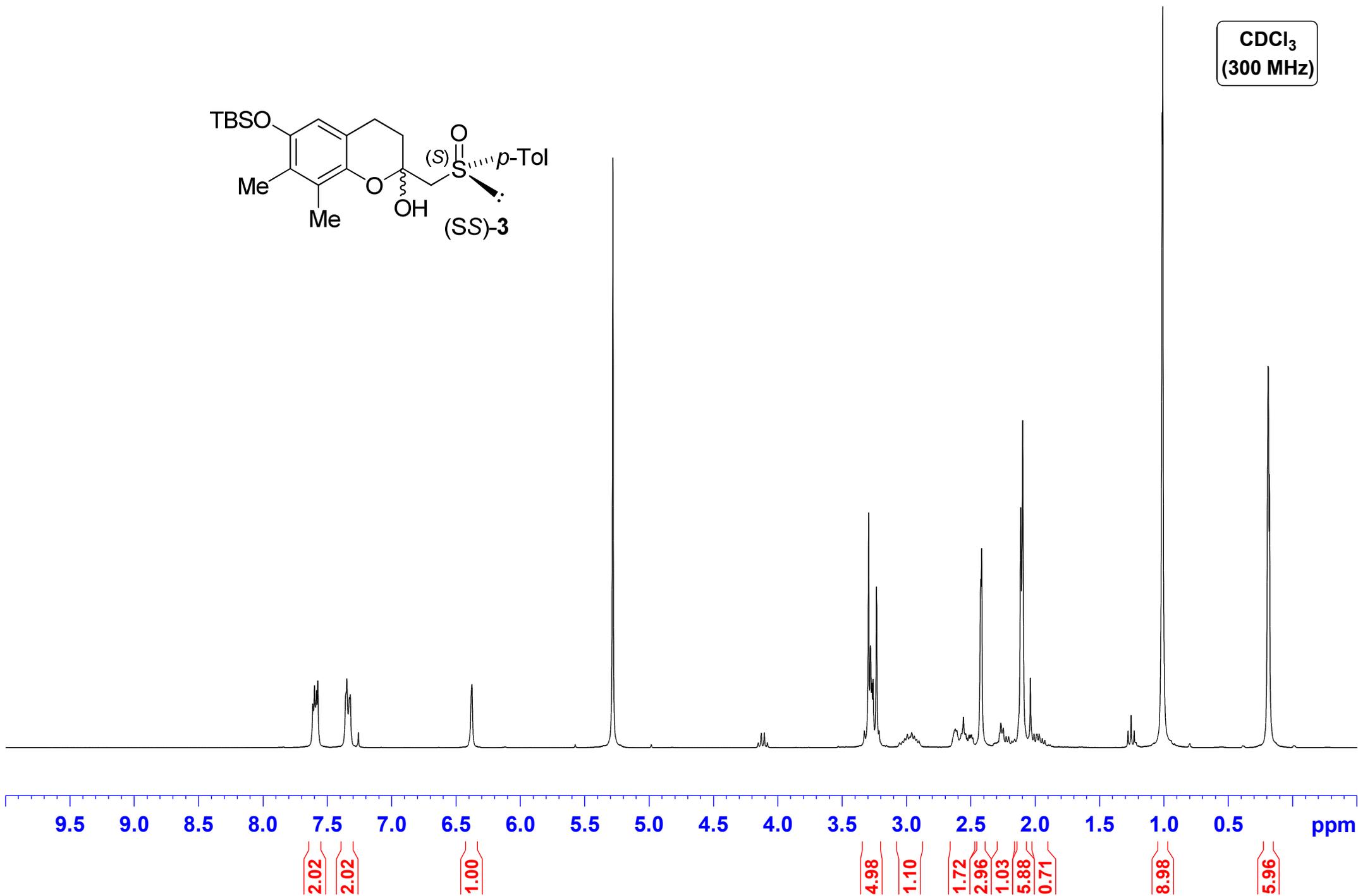
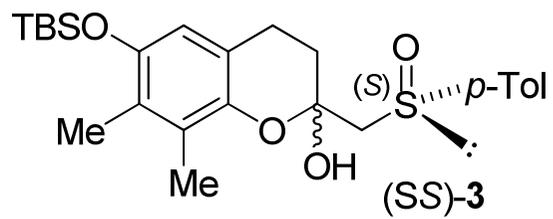
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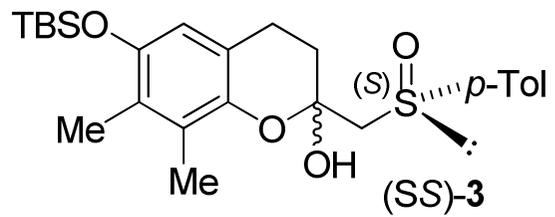


CDCl₃
(75 MHz)

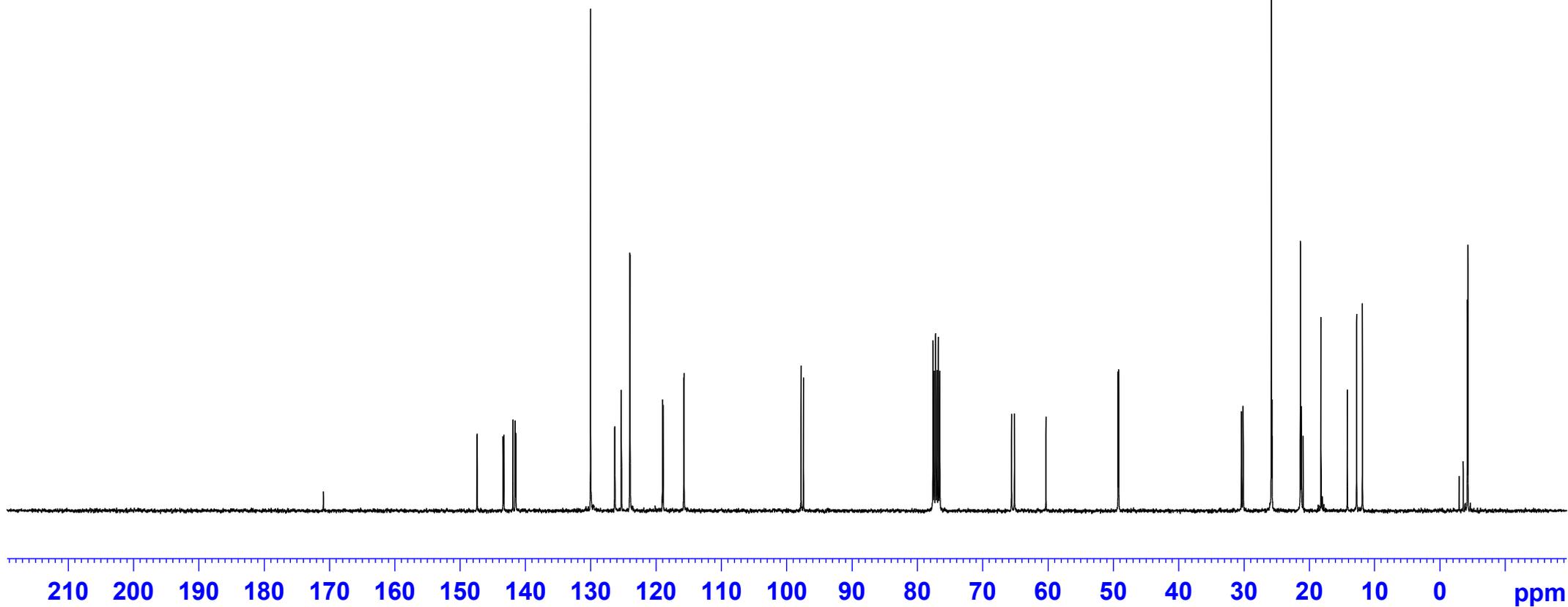


CDCl₃
(300 MHz)

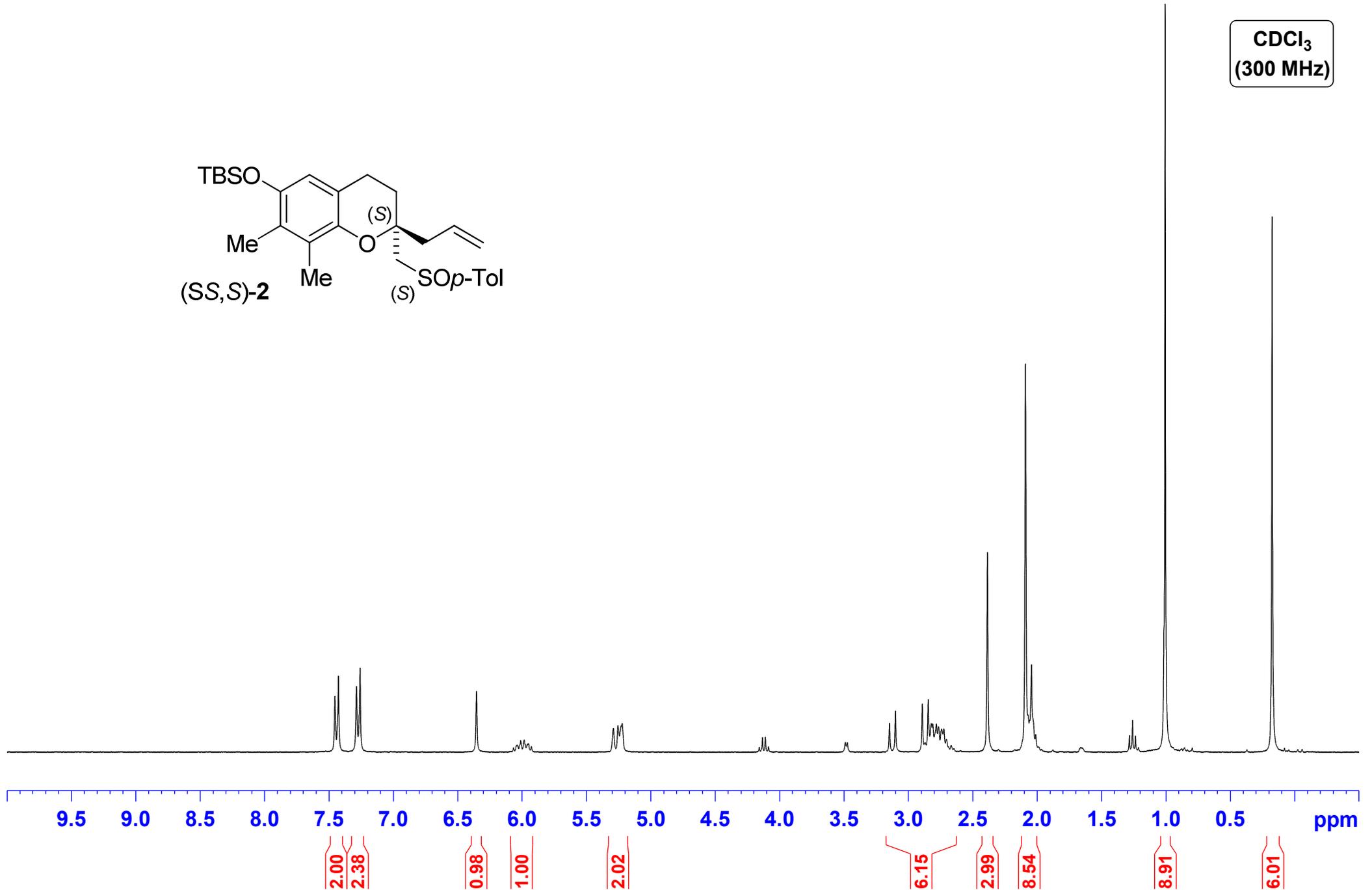
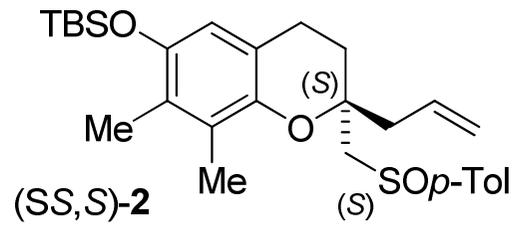


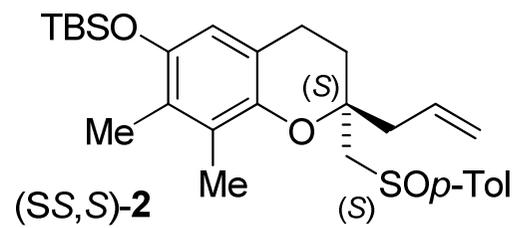


CDCl₃
(75 MHz)

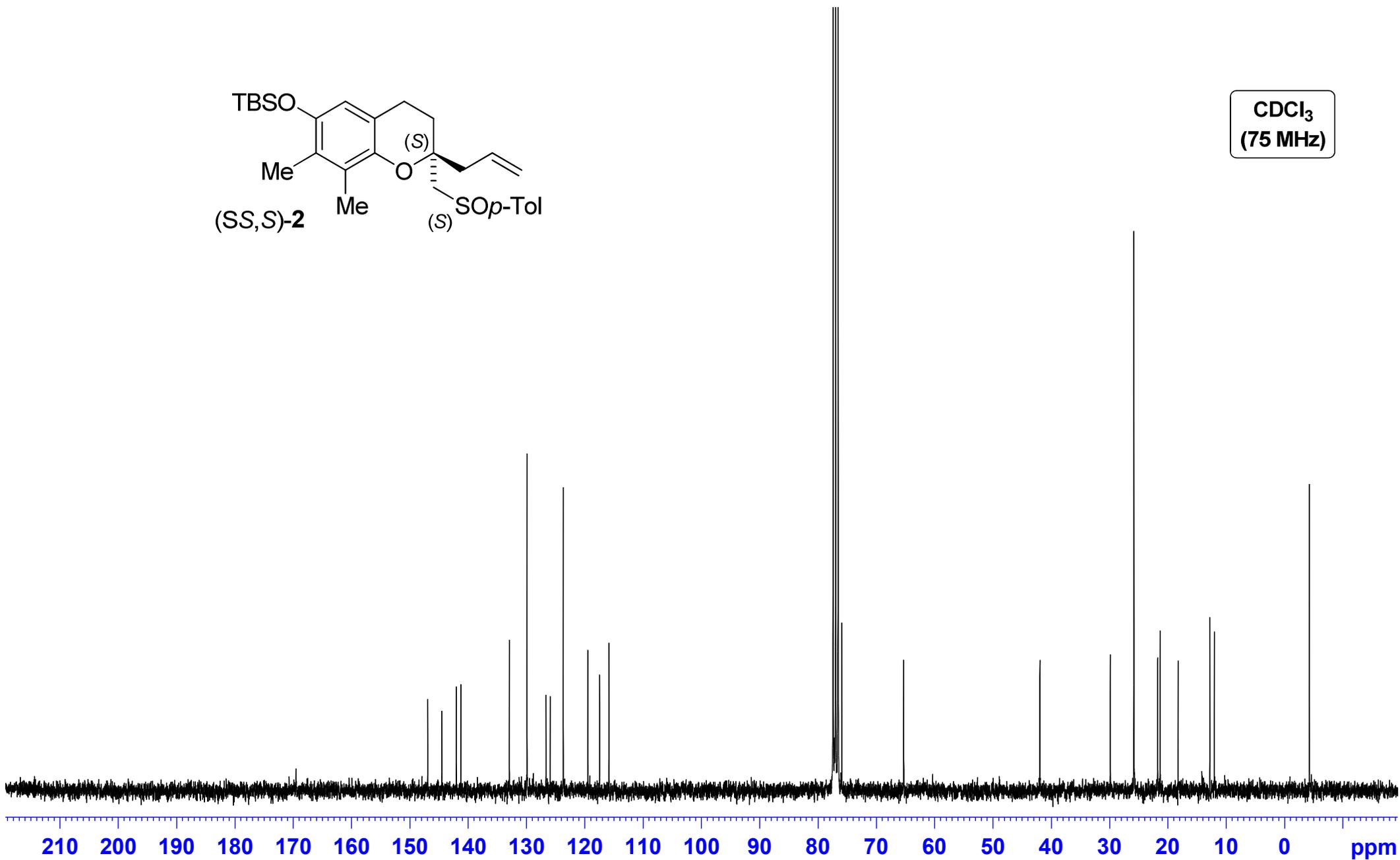


CDCl₃
(300 MHz)

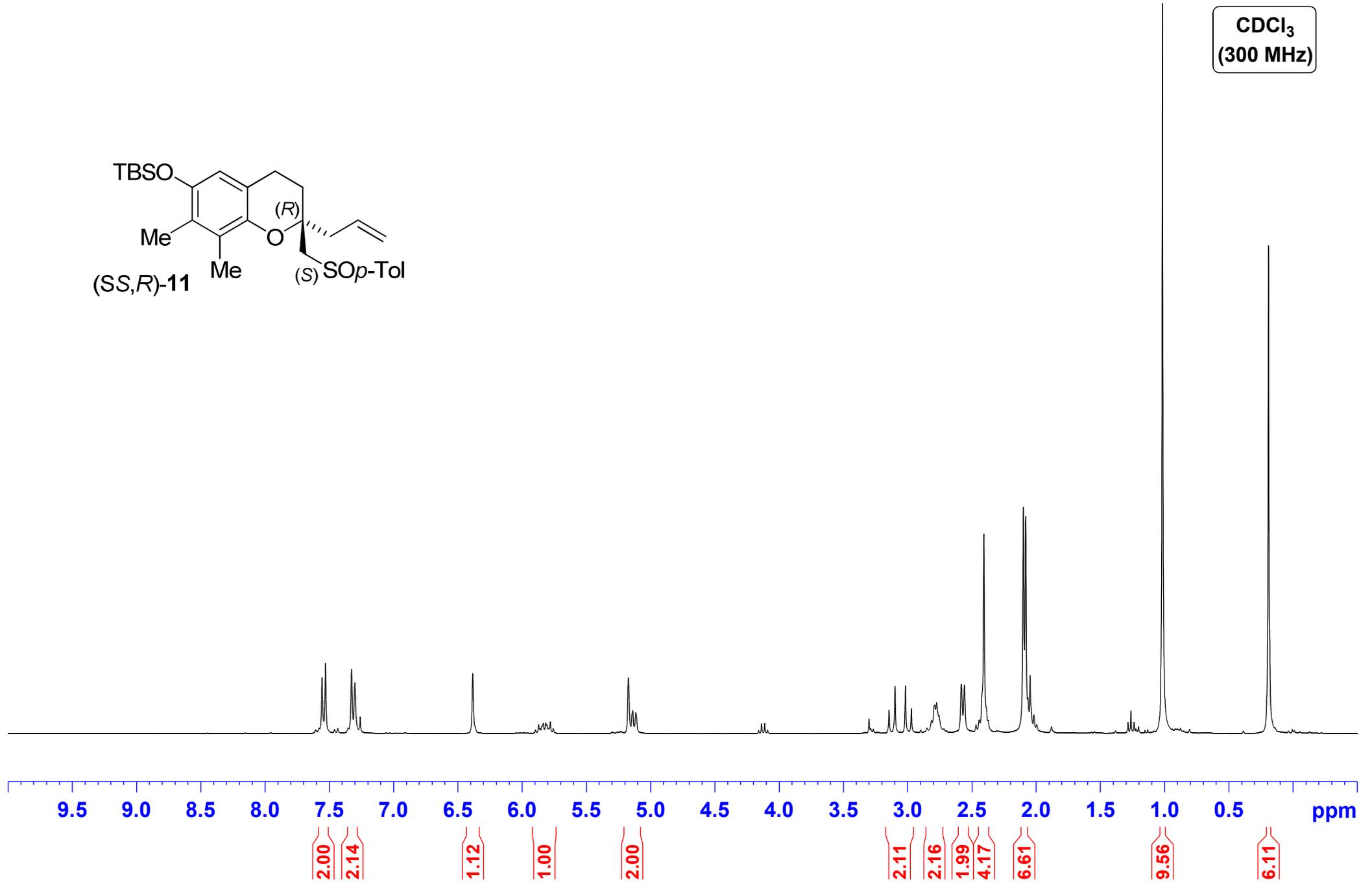
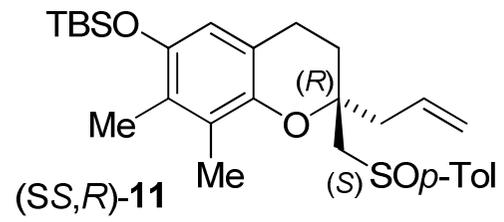




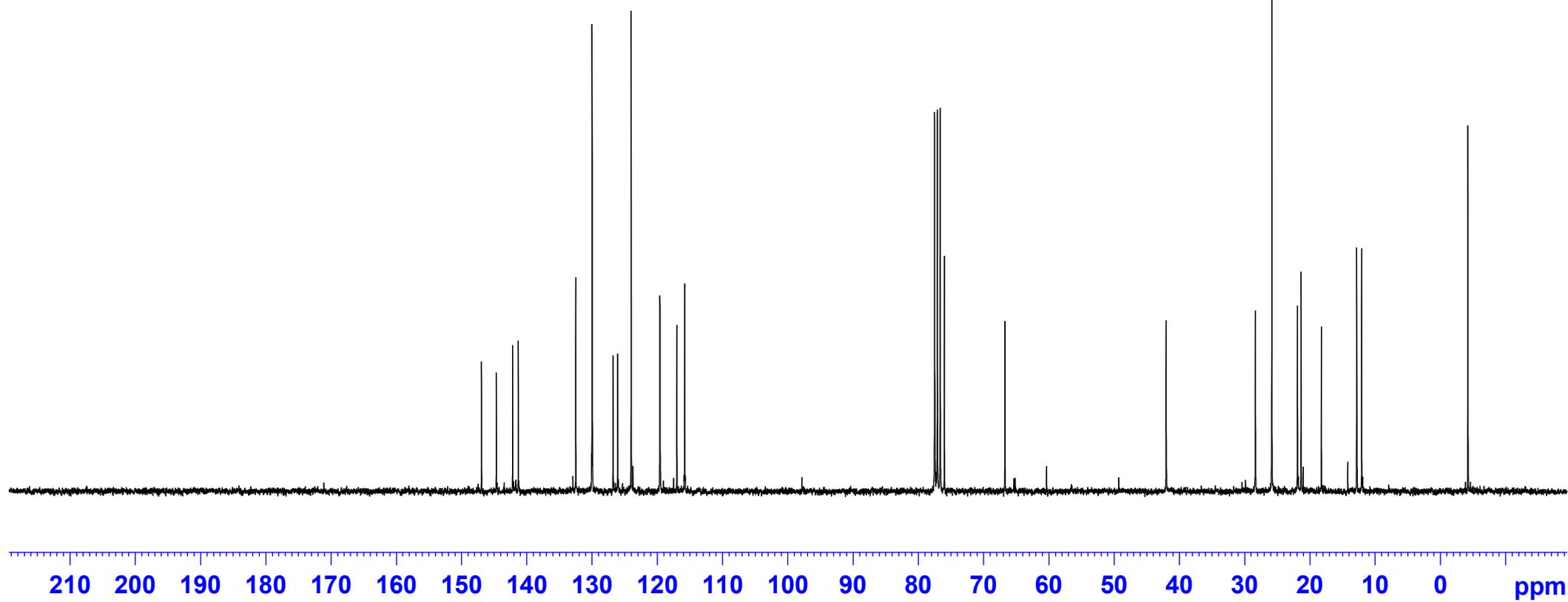
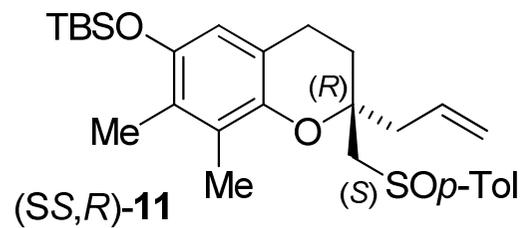
CDCl₃
(75 MHz)



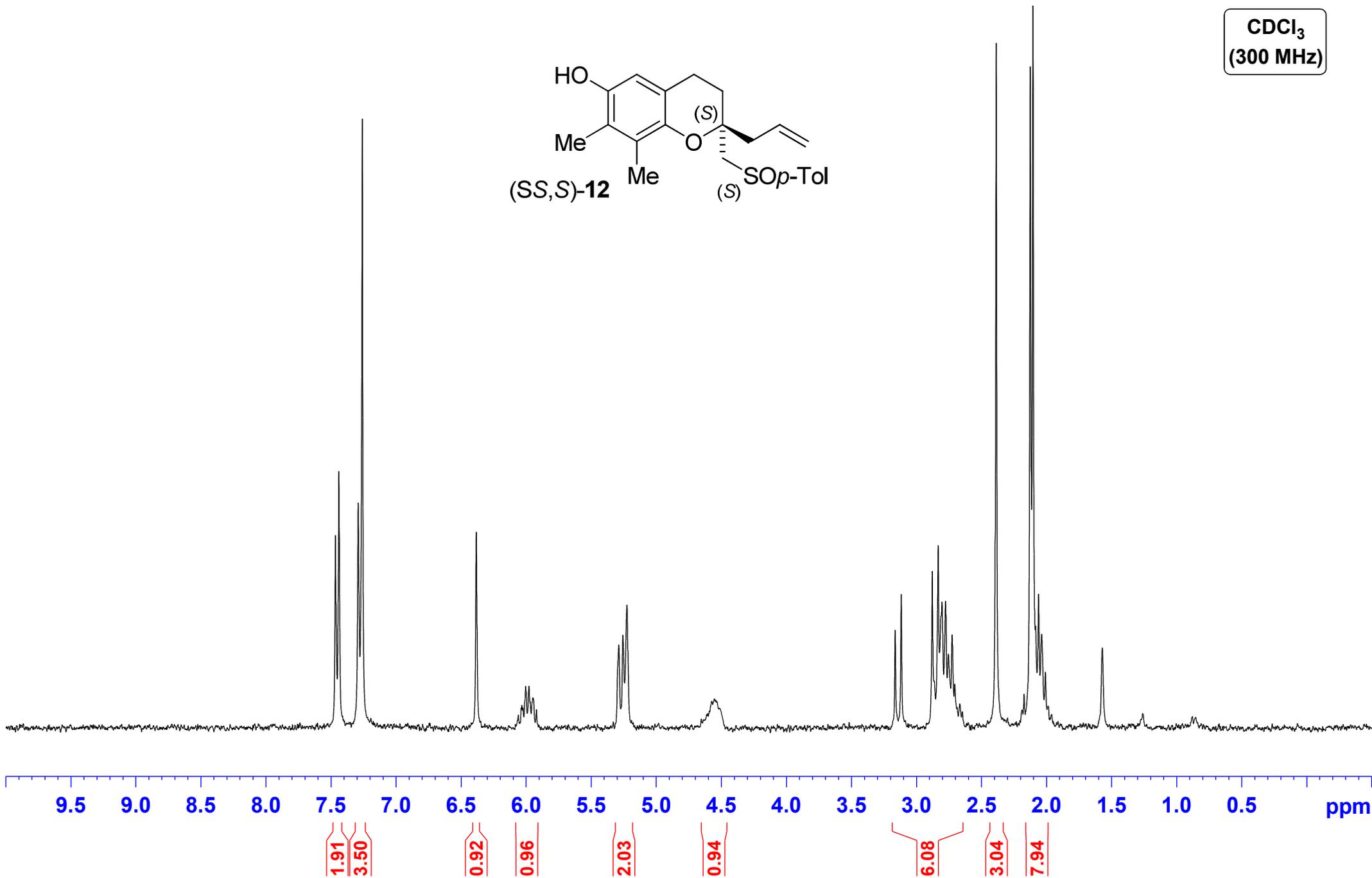
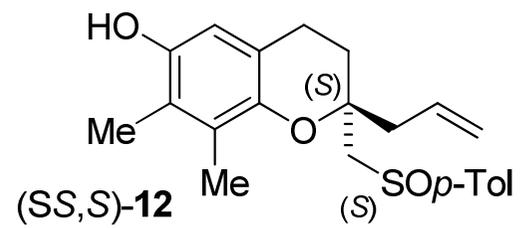
CDCl₃
(300 MHz)

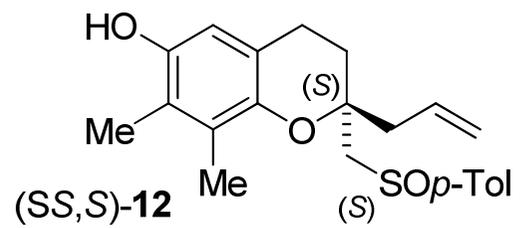


CDCl₃
(75 MHz)

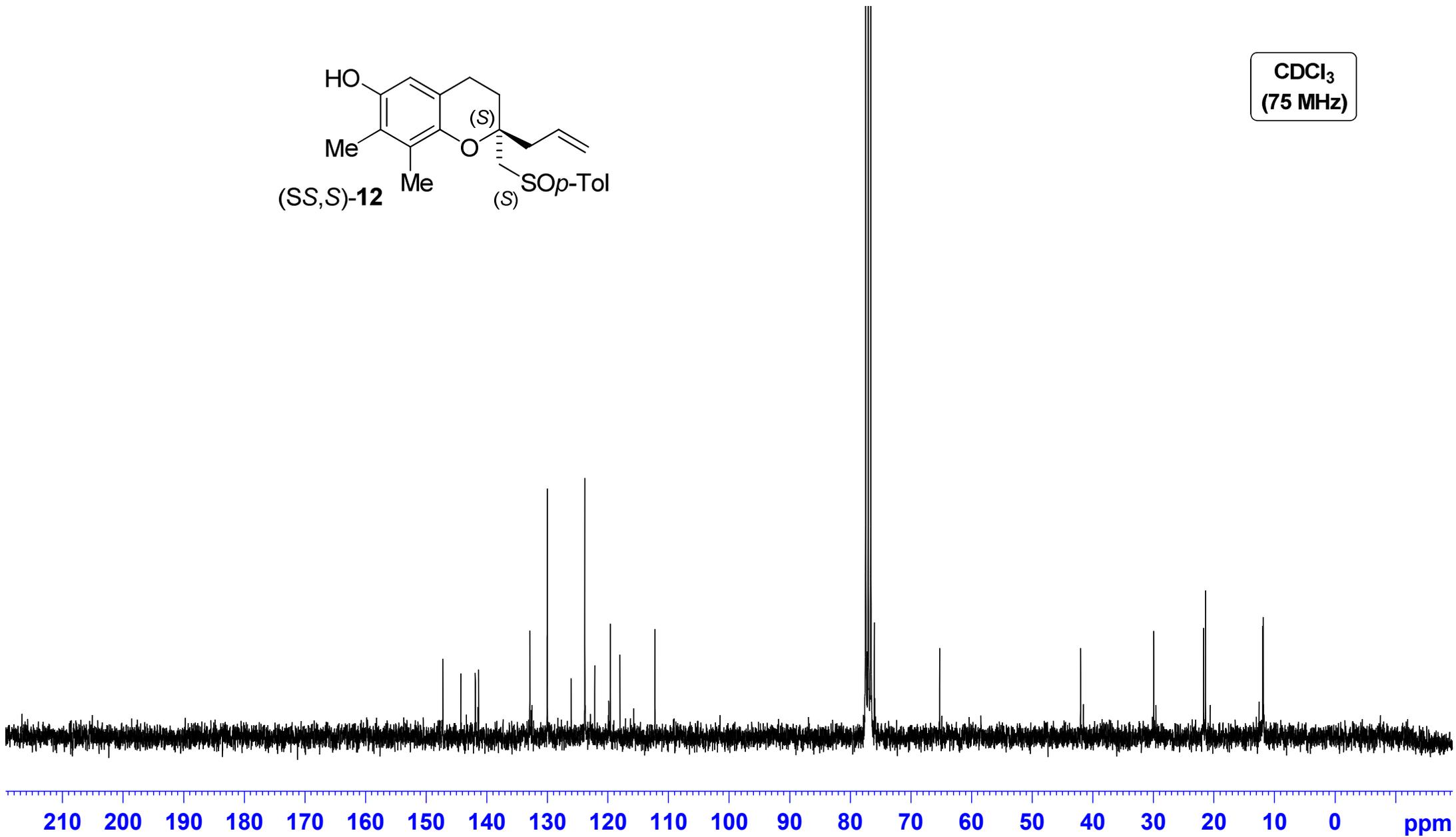


CDCl₃
(300 MHz)

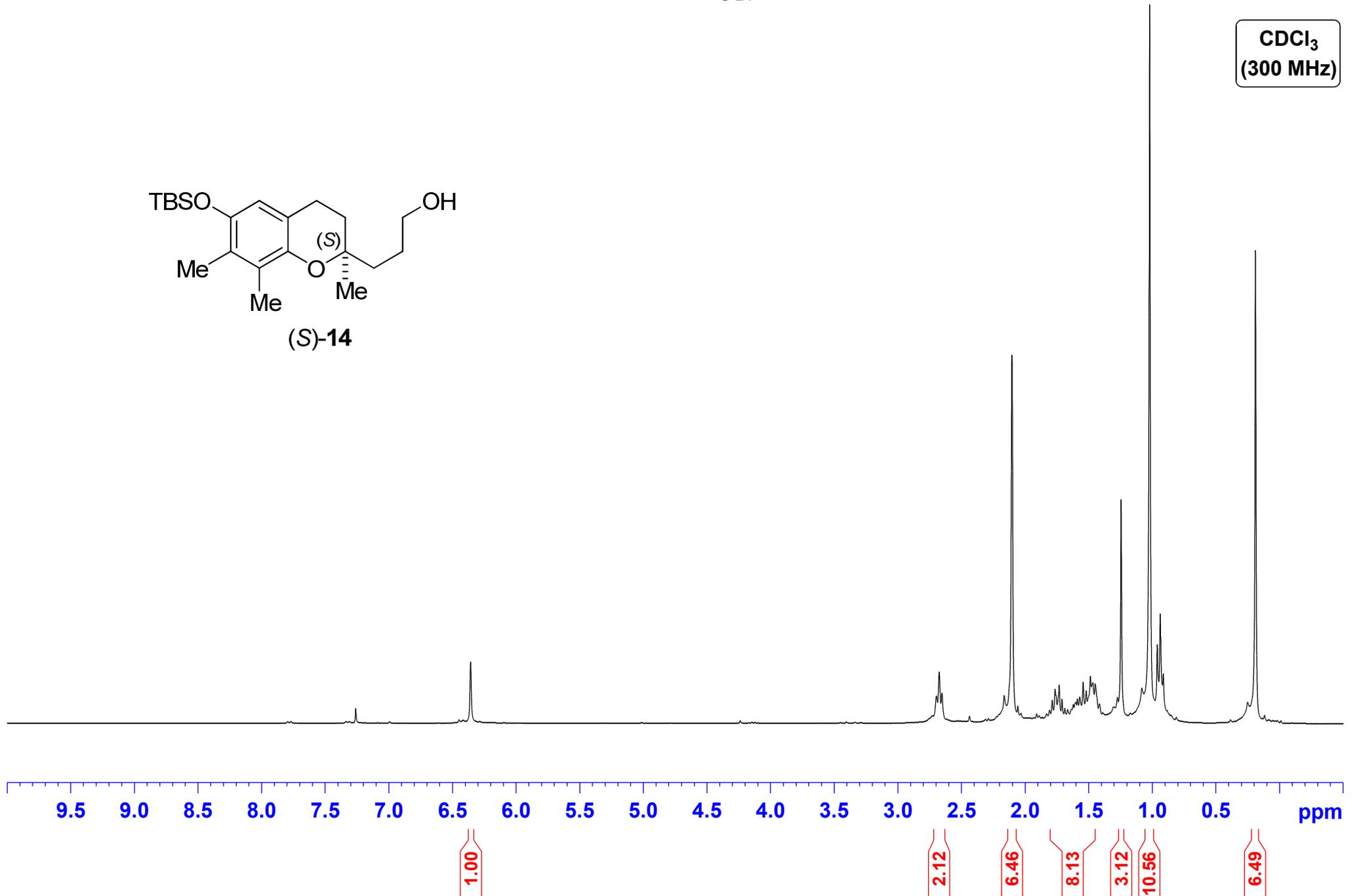
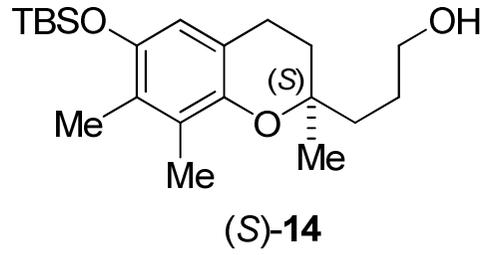


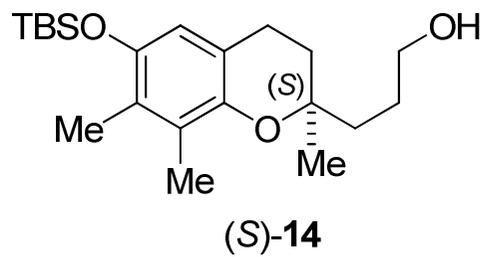


CDCl₃
(75 MHz)

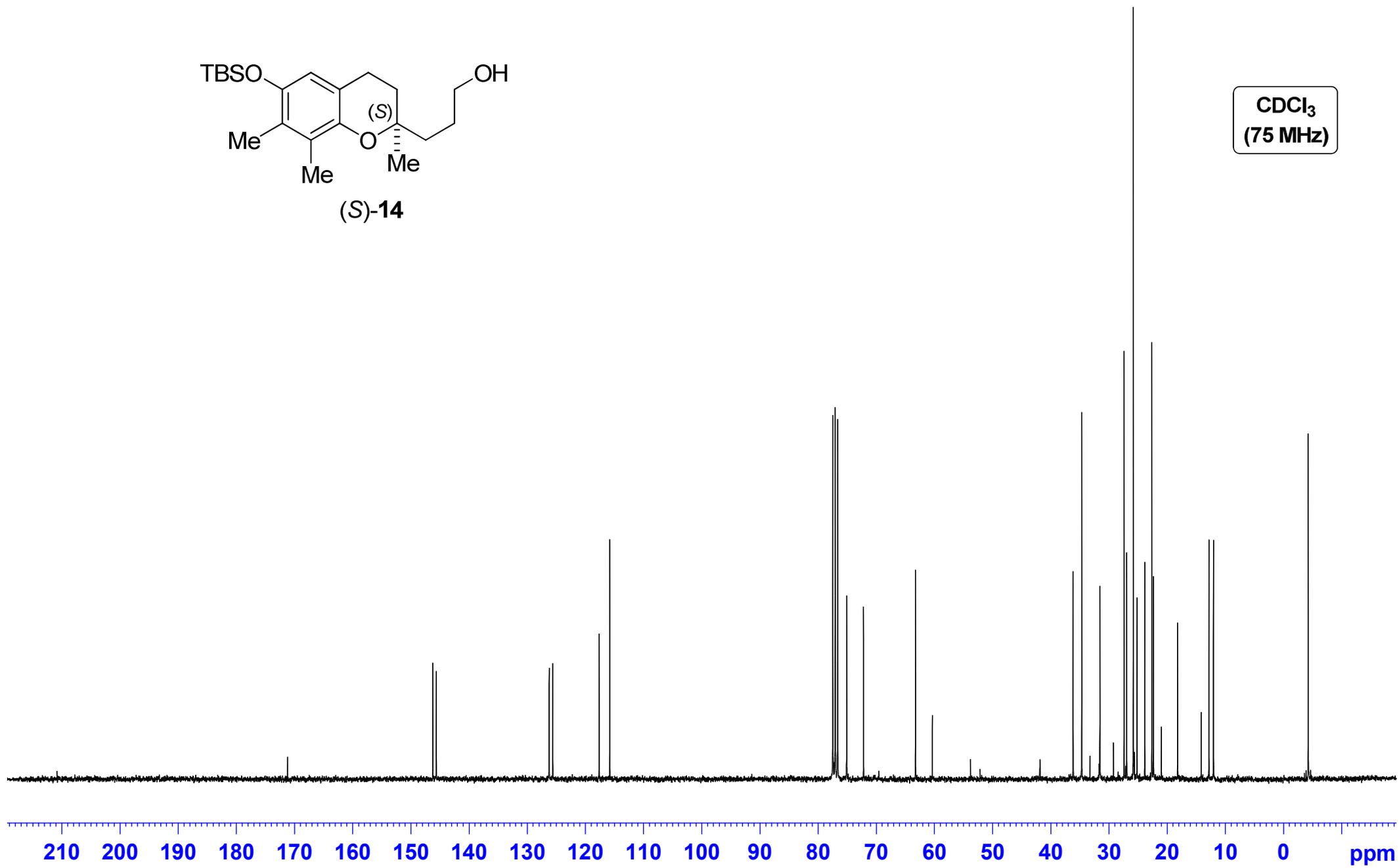


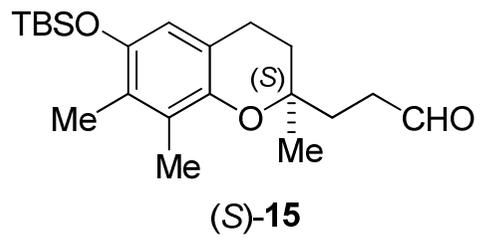
CDCl₃
(300 MHz)



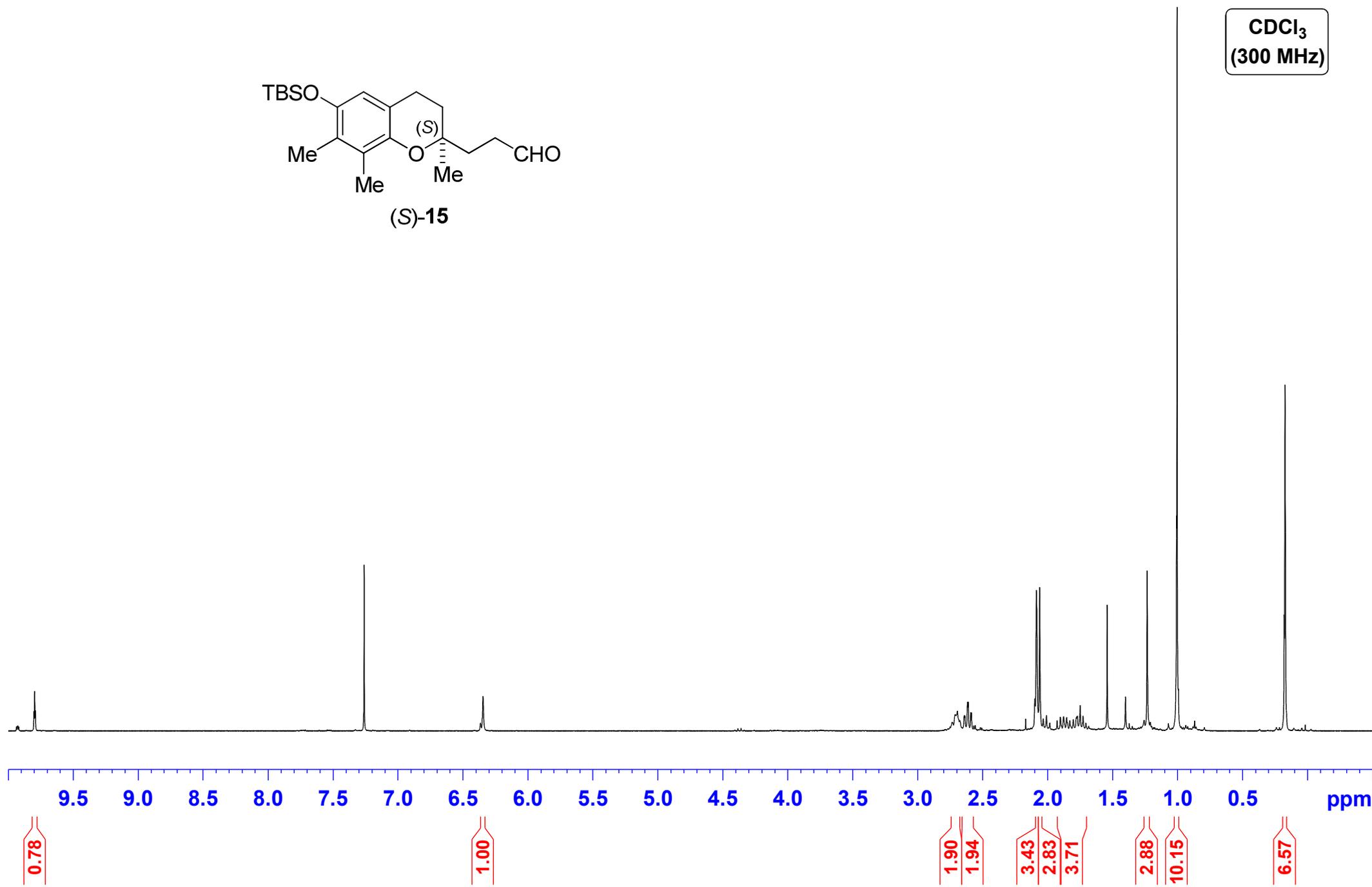


CDCl₃
(75 MHz)

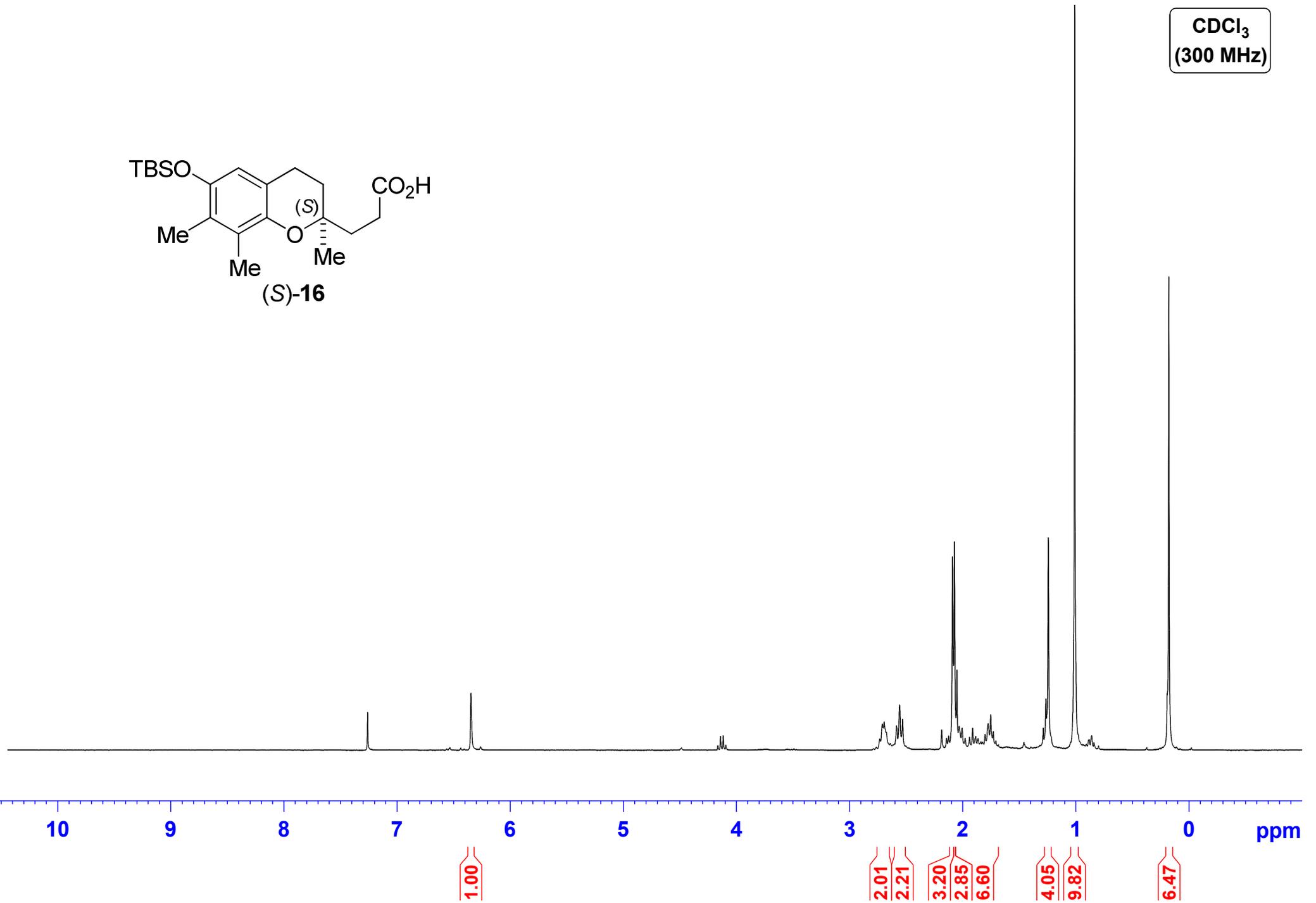
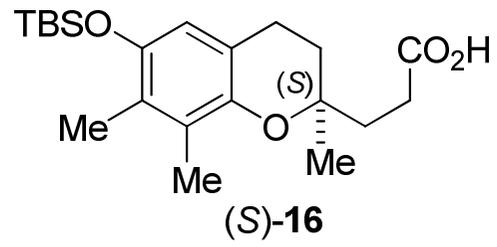




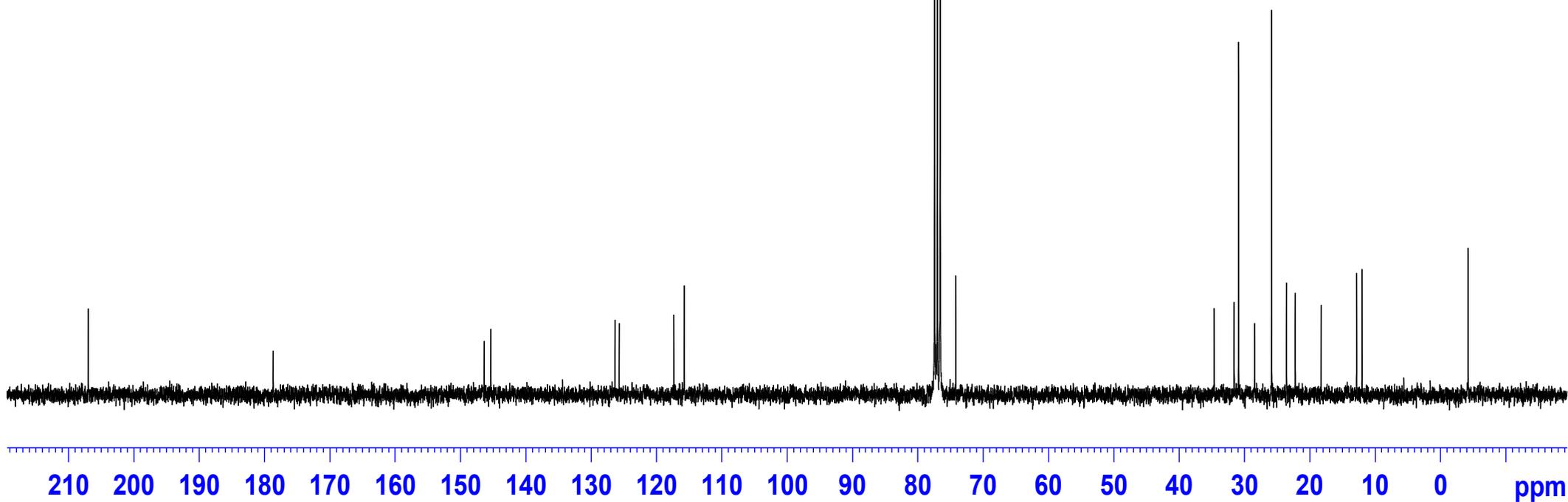
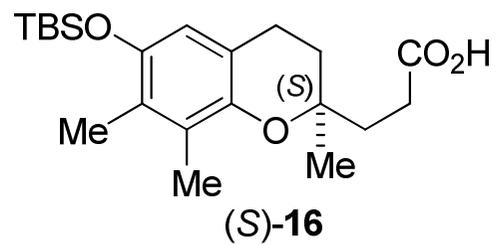
CDCl₃
(300 MHz)

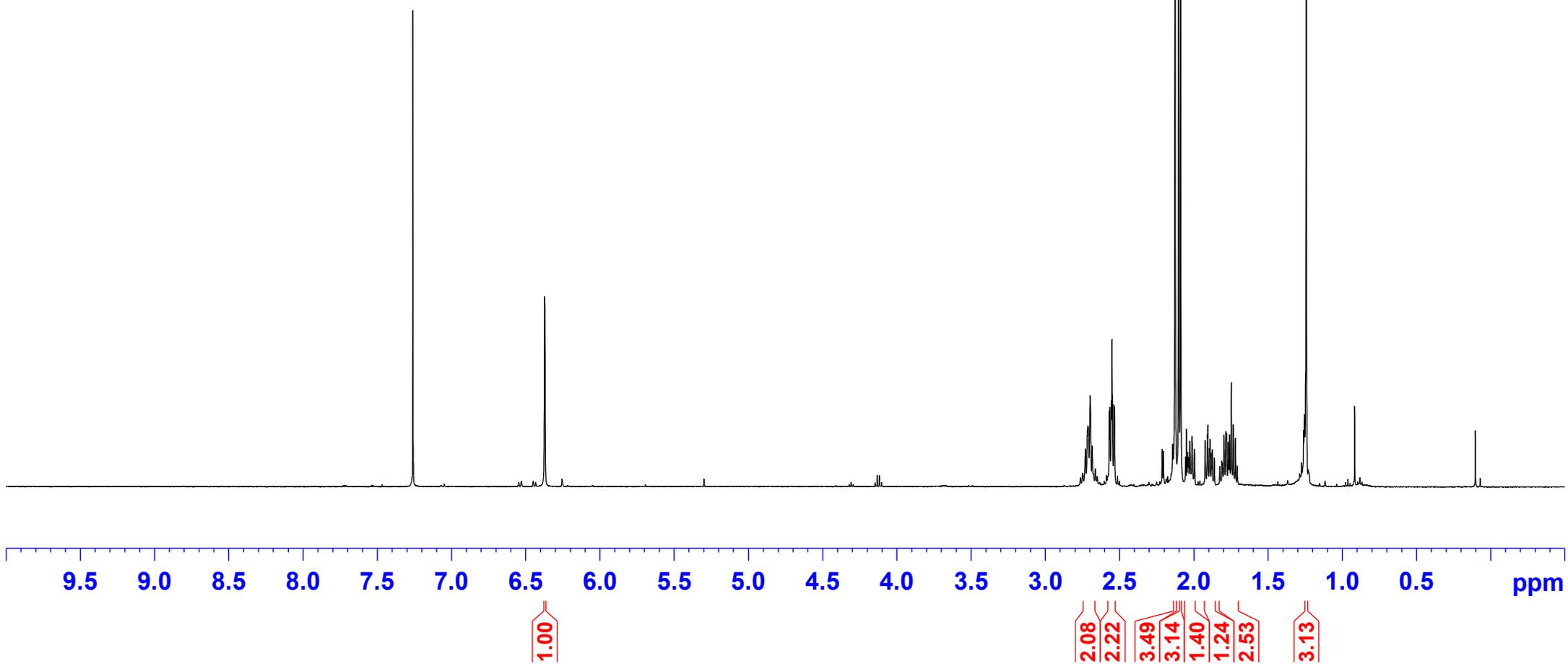
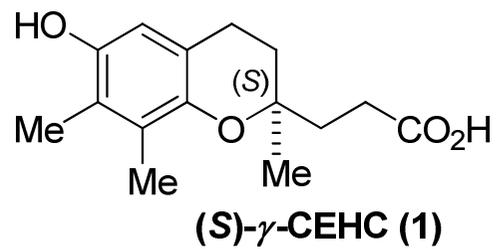


CDCl₃
(300 MHz)

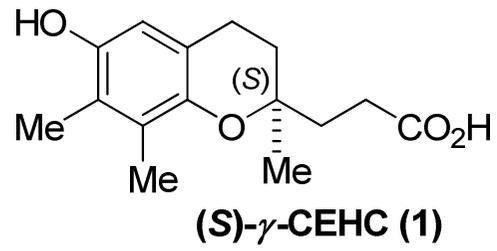


CDCl₃
(75 MHz)



CDCl₃
(300 MHz)

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CDCl₃
(75 MHz)

