Sulfur-Incorporating CTV Analogues: The Synthesis of Cyclotrithioguaiacylene.

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Experimental Section.

General. **1**,[1] **2**[2] and 4-(*N*,*N*-dimethylcarbamoylthio)-3-methoxybenzaldehyde (**7**)[2] were prepared according to literature procedures. Unless otherwise stated, all the reactions were run under an inert atmosphere of dinitrogen. CH_2Cl_2 and THF were distilled from P_2O_5 and sodium/benzophenone, respectively. ^{1}H NMR spectra of all new compounds (**3**-**6**, **8**, **9**, **11** and **12**) were assigned using 2D NOESY experiments, which confirmed that α'-H (or 5-H) are deshielded by comparison with α-H (or 2-H and 6-H), and that *ax*-H are deshielded by comparison with *eq*-H.[3] ^{13}C NMR spectra of all new compounds were assigned using 2D ^{1}H/^{13}C NMR HSQC and HMBC experiments. ^{1}H and ^{13}C NMR spectra of **1**[1], **2**,[2] and **10**[2] were in agreement with literature data.

4-(*N*,*N*-dimethylcarbamoylthio)-3-methoxybenzene methanol (8). $NaBH_4$ (0.250 g, 6.25 mmol) was added to a solution of 4-(*N*,*N*-dimethylcarbamoylthio)-3-methoxybenzaldehyde **7** (1.00 g, 4.18 mmol) in methanol (60 mL). After 2 hr stirring at room temperature, the reaction mixture was quenched by addition of H_2O (30 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered. Solvent removal by rotary evaporation followed by drying under vacuum afforded **8** (0.972 g) in 96% yield as a colorless solid. Mp. 129-130 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 3.00 (br s, 3H; NCH_3), 3.12 (br s, 3H; NCH_3), 3.86 (s, 3H; OCH_3), 4.66 (d, ^3J = 6.0 Hz, 2H; CH_2), 6.91 (d, ^3J = 7.8 Hz, 1H; 6-H), 6.99 (d, ^4J = 1.2 Hz, 1H; 2-H), 7.41 (dd, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1H; 5-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.1 (NCH_3), 56.2 (OCH_3), 65.0 (CH_2O), 109.9 (2-C), 115.7 (4-C), 119.1 (6-C), 138.2 (5-C), 145.2 (1-C), 160.4 (3-C), 166.6 (CO); IR (ATR) ν 1639 (SC=O) cm^{-1}; Anal. Calcd for $C_{11}H_{15}NO_3S \cdot 1/4H_2O$ (249.56): C, 53.8; H, 6.4; N, 5.7. Found: C, 54.0; H, 6.8; N, 5.7%.

4-(*N*,*N*-dimethylcarbamoylthio)-3-methoxybenzyl formate (9). A solution of **8** (0.500 g, 2.07 mmol) in formic acid (5 mL) was heated at 70 °C for 24 hr. The solvent was removed under reduced pressure and the solid residue washed with water to afford **9** (0.490 g, 1.82 mmol) in 90% yield. Mp. 93-94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (br s, 3H; NCH_3), 3.08 (br s, 3H; NCH_3), 3.85 (s, 3H; OCH_3); 5.18 (s, 2H; CH_2), 6.93 (s, 1H; 2-H), 6.95 (d, ^3J = 7.5 Hz, 1H; 6-H), 7.43 (d, ^3J = 7.5 Hz, 1H; 5-H), 8.12 (s, 1H; CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.9 ($N(CH_3)_2$), 56.1 (OCH_3), 65.2 (CH_2), 111.1 (2-C), 117.0 (4-C), 120.5 (6-C), 138.2 (5-C), 138.8 (1-C), 160.1 (3-C), 160.6 (HCO), 165.9 (SCO) ppm; IR (ATR) ν 1711 (HC=O), 1653 (SC=O) cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO_4S$ (269.32): C, 53.5; H, 5.6; N, 5.2; S, 11.9. Found: C, 53.6; H, 5.3; N, 5.0; S, 12.4%.

2,7,12-trihydroxy-3,8,13-trimethylsulfenyl-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (10).[1] *Tert*-butylthiol (0.225 mL, 2.08 mmol) was added to a suspension of NaH (0.050 g, 2.08 mmol) in THF at 0 °C. The mixture was stirred at this temperature for 15 min, then transferred to a solution of **2** (0.100 g, 0.200 mmol) in THF. The resulting reaction mixture was heated at reflux for 12 hr, and quenched by addition of 10% aqueous HCl. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5), which afforded **10** (0.090 g, 0.197 mmol) in 98% yield as a colorless solid.

Attempted deprotection of 6 to 3. Solid $AgNO_3$ (0.050 g, 0.255 mmol) was added to a solution of **6** (0.050 g, 0.085 mmol) in EtOH (50 mL), and the reaction mixture stirred at room temperature for 2 days. The resulting precipitate was removed by filtration, and the filtrate concentrated to dryness. It was subsequently retaken into CH_2Cl_2, and stirred for 6 hr with a 6 N aqueous HCl solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$) and concentrated to dryness.

X-ray crystallography of compound 12. The crystal structure analysis was performed at low temperature (T = 110K) on an Oxford Diffraction X'Calibur CCD diffractometer using CuKα radiation (λ = 1.5418 Å). The structure was solved by direct methods with the program SIR92,[4] and full matrix least-square refinements on F^2 in SHELXL-97[5] were performed with anisotropic displacements for non-H atoms. Hydrogen atoms were located in difference Fourier maps and refined isotropically according to a riding model. CCDC 800716 contains the detailed crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.ik/data_request/cif.

Table S 1. Crystal data and structure refinement for **12**.

Identification code	**12**	
Empirical formula	C29 H34 Cl4 O9 S3	
Formula weight	764.54	
Temperature	110(2) K	
Wavelength	1.54180 Å	
Crystal system	monoclinic	
Space group	$P\ 2_1\ /\ c$	
Unit cell dimensions	a = 16.8059(4) Å	α= 90°.
	b = 12.0718(2) Å	β= 127.012(3)°.
	c = 21.4038(5) Å	γ = 90°.
Volume	3467.4(2) $Å^3$	
Z	4	
Density (calculated)	1.465 Mg/m^3	
Absorption coefficient	5.244 mm^{-1}	
F(000)	1584	
Crystal size	0.130 × 0.089 × 0.043 mm^3	
Theta range for data collection	3.29 to 76.39°.	
Index ranges	-21<=h<=18, -14<=k<=15, -25<=l<=26	
Reflections collected	25730	
Independent reflections	7233 [R(int) = 0.0274]	
Completeness to theta = 76.39°	99.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7233 / 0 / 412	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.1102	
R indices (all data)	R1 = 0.0546, wR2 = 0.1147	
Largest diff. peak and hole	1.192 and -0.598 e.$Å^{-3}$	

References.

(1) a) Collet, A.; Gabard, J. *J. Org. Chem.* **1980**, *45*, 5400; b) Canceill, J.; Collet, A.; Gottarelli, G. *J. Am. Chem. Soc.* **1984**, *106*, 5997.
(2) Garcia, C.; Andraud, C.; Collet, A. *Supramol. Chem.* **1992**, *1*, 31.
(3) Collet, A. *Tetrahedron* **1987**, *43*, 5725.
(4) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343.
(5) Sheldrick, G. M. SHELXL-97, University of Göttingen, Germany, **1997**.

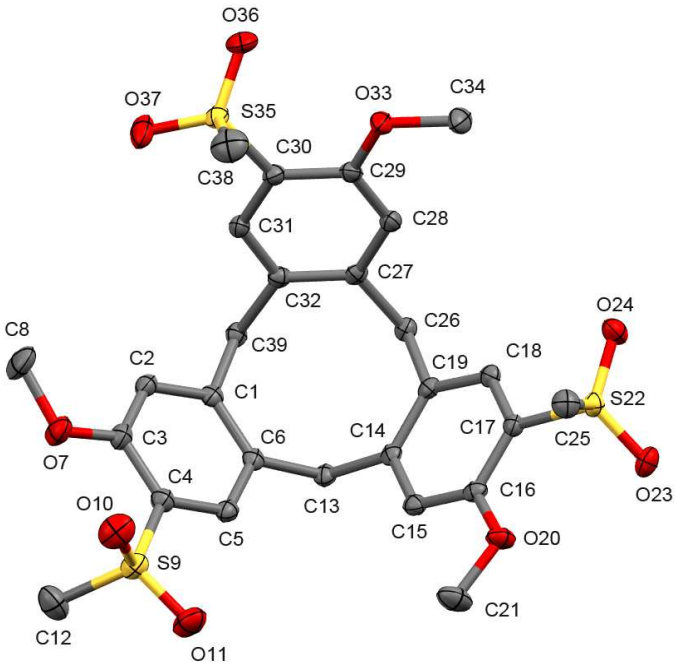

Figure S 1. ORTEP-3 view of **12** in space group $P2_1/c$. Atomic displacement ellipsoids are plotted at the 50% probability level. Hydrogen atoms and solvent molecules were removed for clarity. The dihedral angles formed by the least square planes of the three phenyl moieties are 66.87(6), 74.78(7)° and 74.05(7)°.

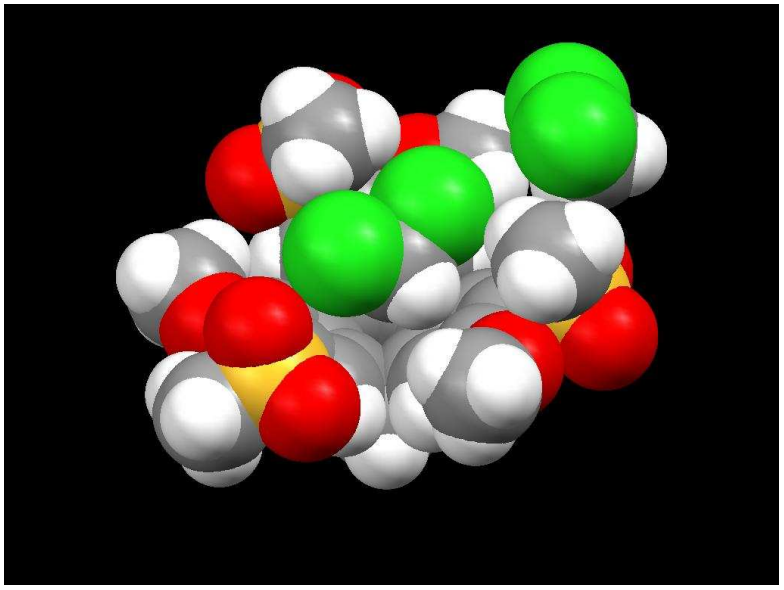

Figure S 2. CPK view of **12** with two co-crystallized CH_2Cl_2 molecules, one of them trapped within the molecular cavity, showing two edge-to-face aromatic CH···π interactions (both at 2.81

Å), and weaker CH···Cl (2.97 and 3.21 Å) and Cl···O interactions (3.80 Å) between guest and host.

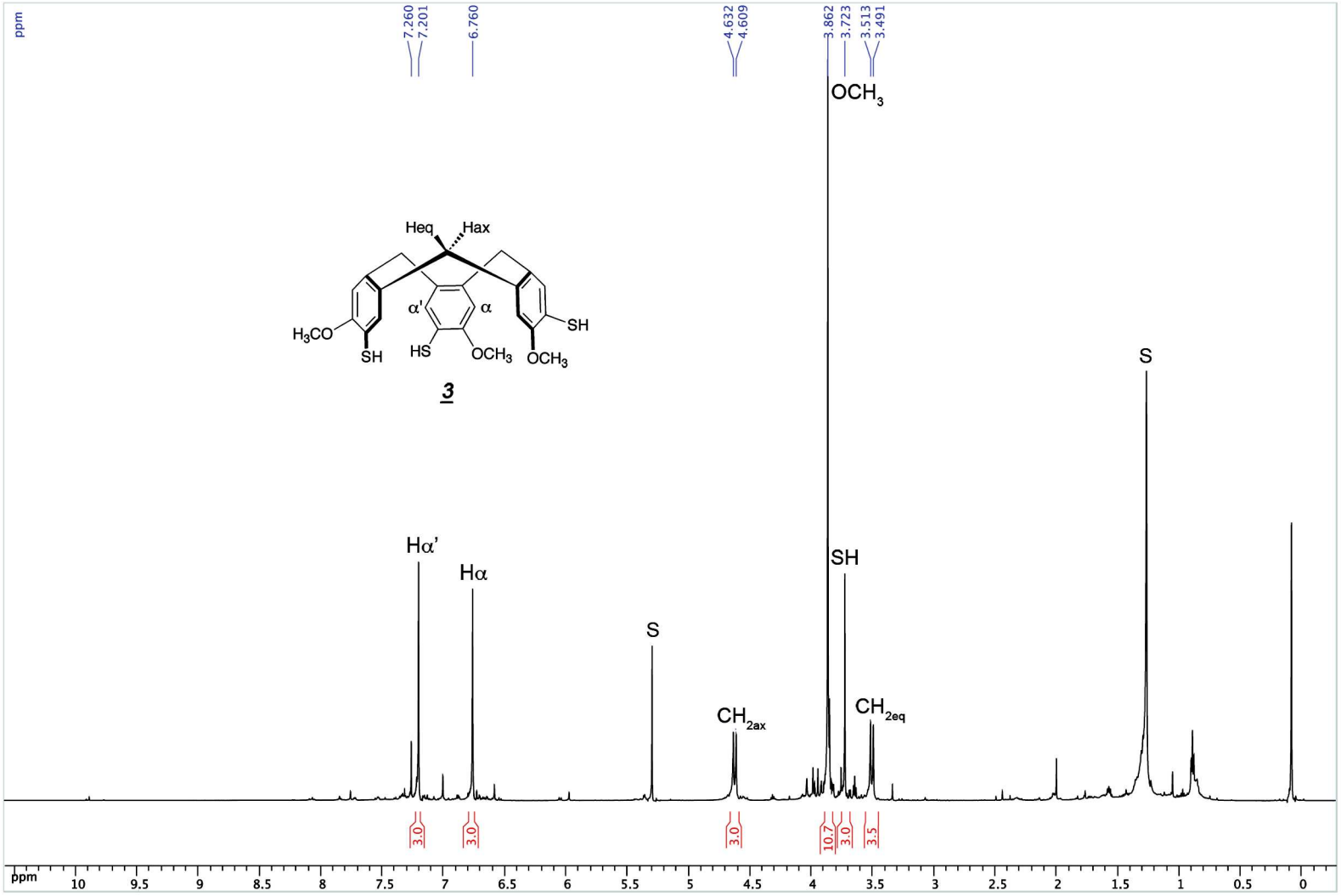

Figure S 3: ^{1}H NMR spectrum of cyclotrithioguaiacylene **3** obtained via Newman-Kwart rearrangement.

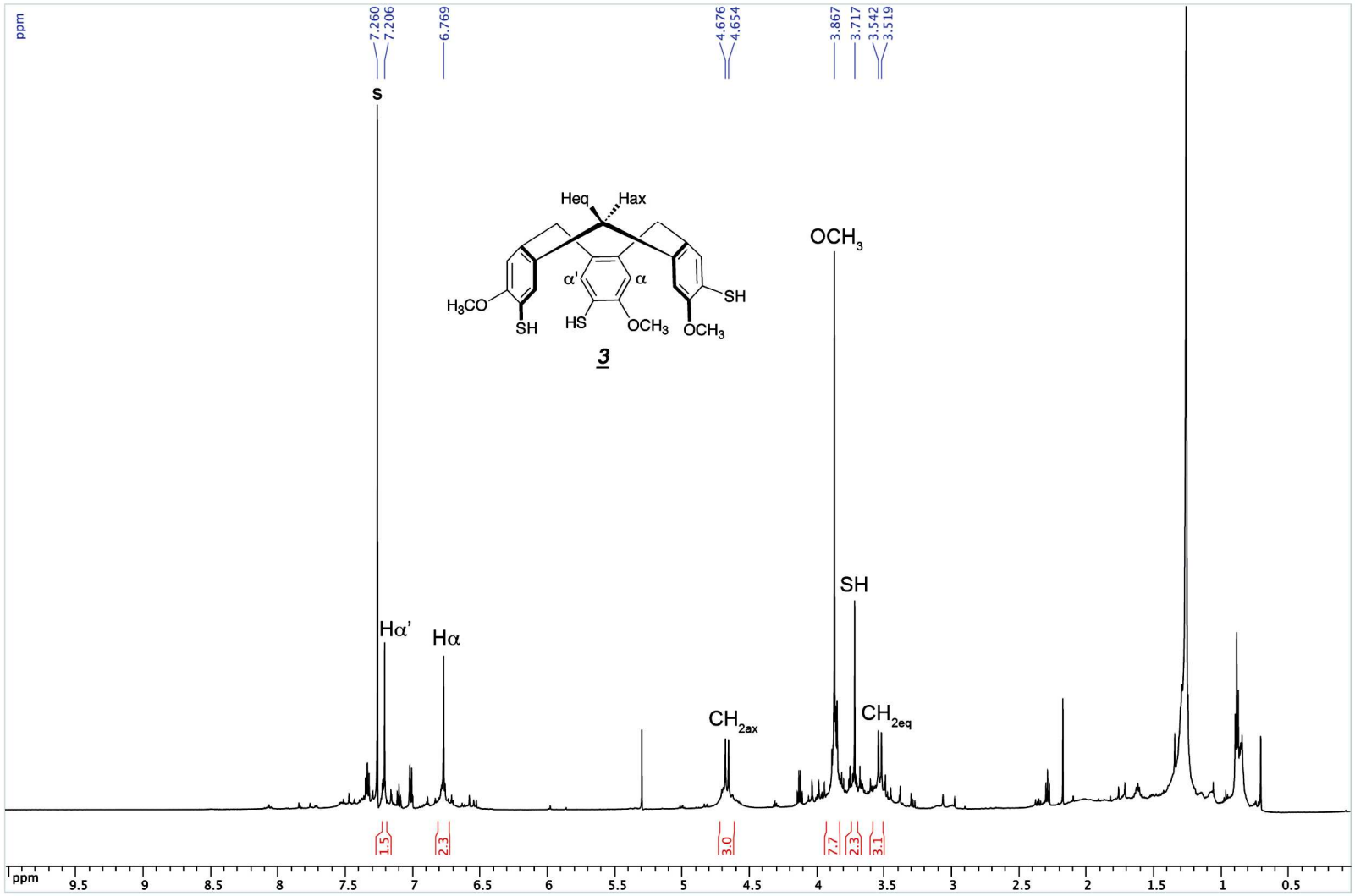

Figure S 4: ^{1}H NMR spectrum of cyclotrithioguaiacylene **3** obtained from **6**.

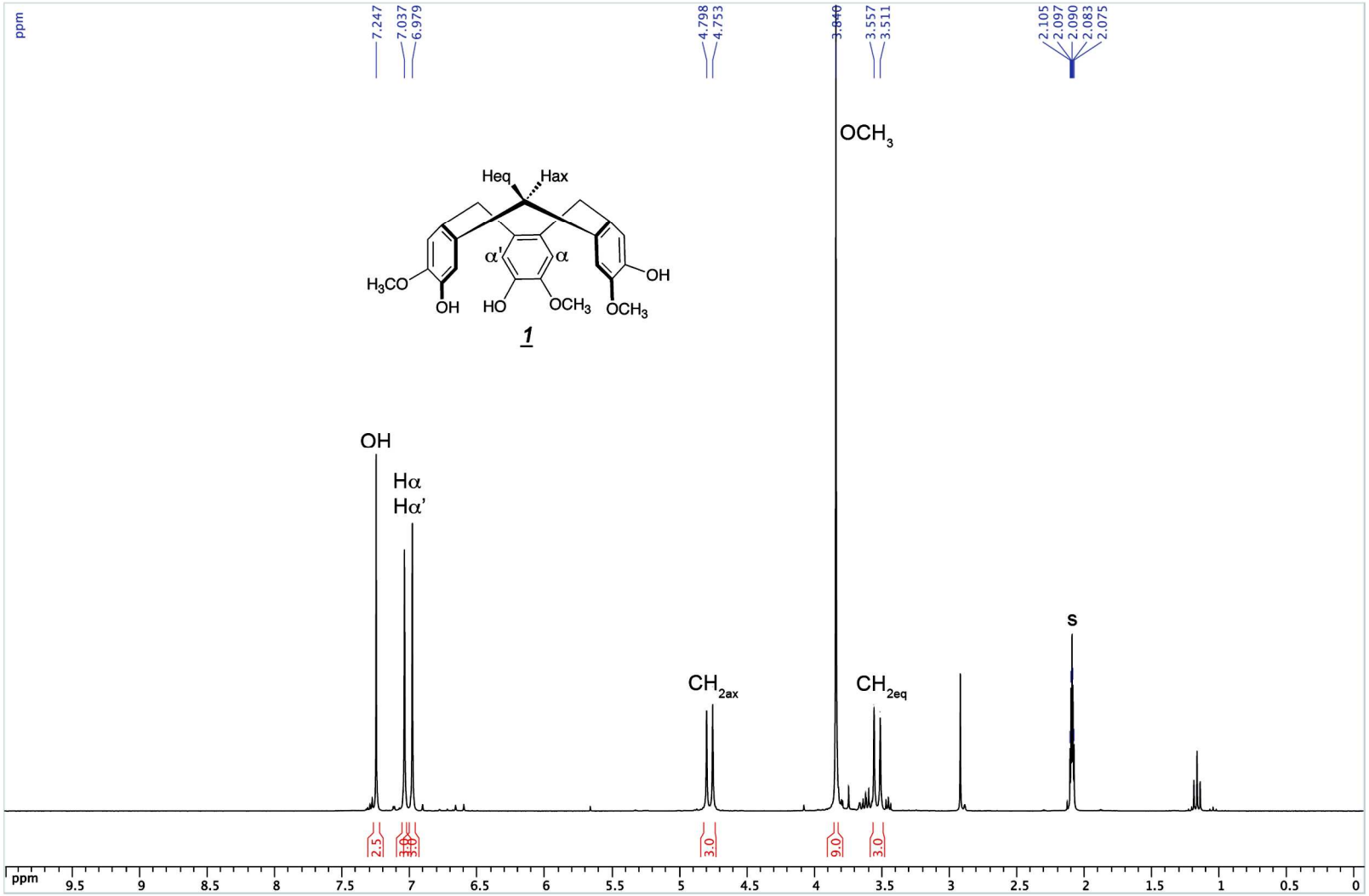

Figure S 5: ^{1}H NMR spectrum of compound **1** (300 MHz, d^{6}-acetone).

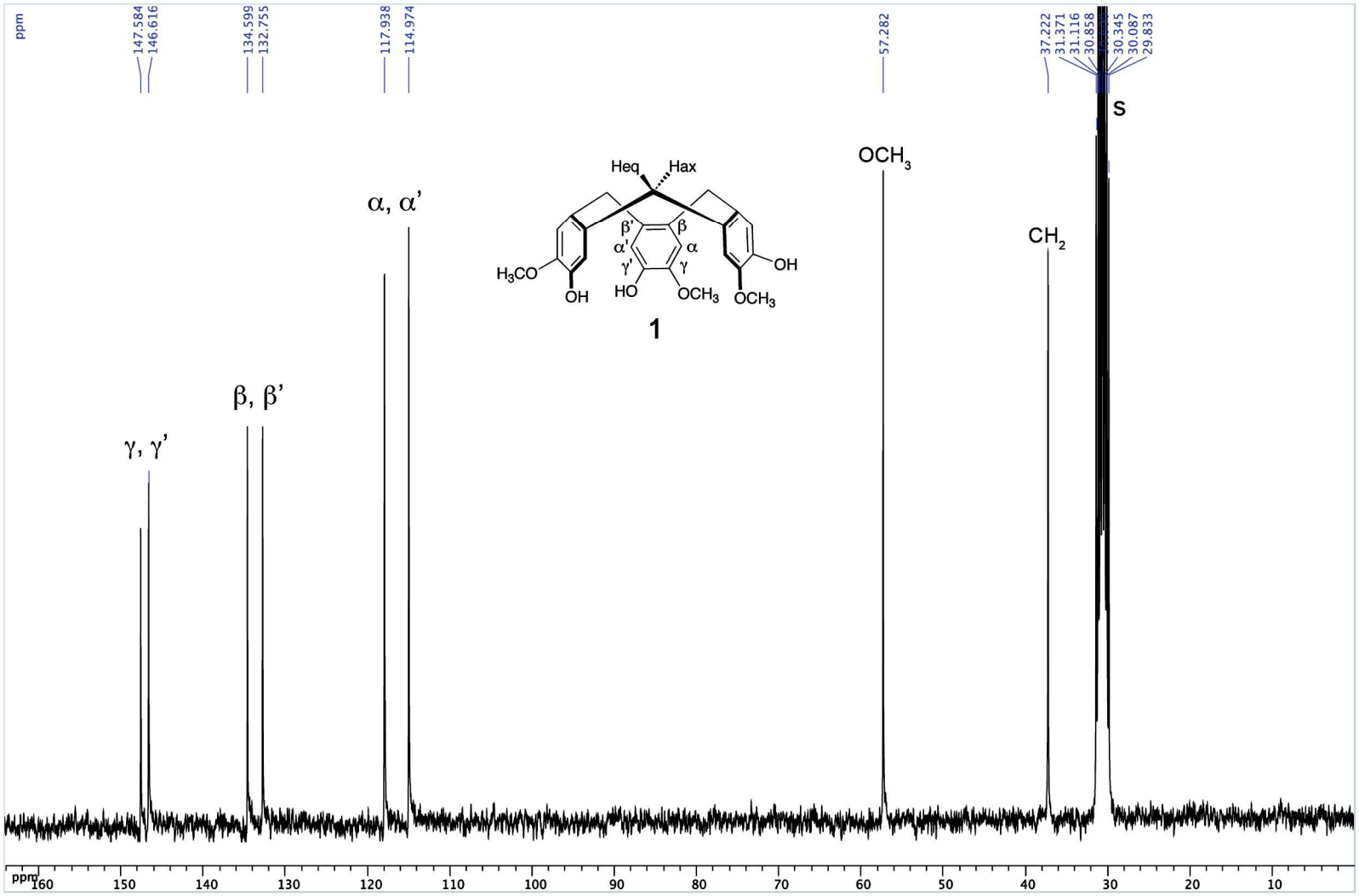

Figure S 6: ^{13}C NMR spectrum of compound **1** (75 MHz, d^6-acetone).

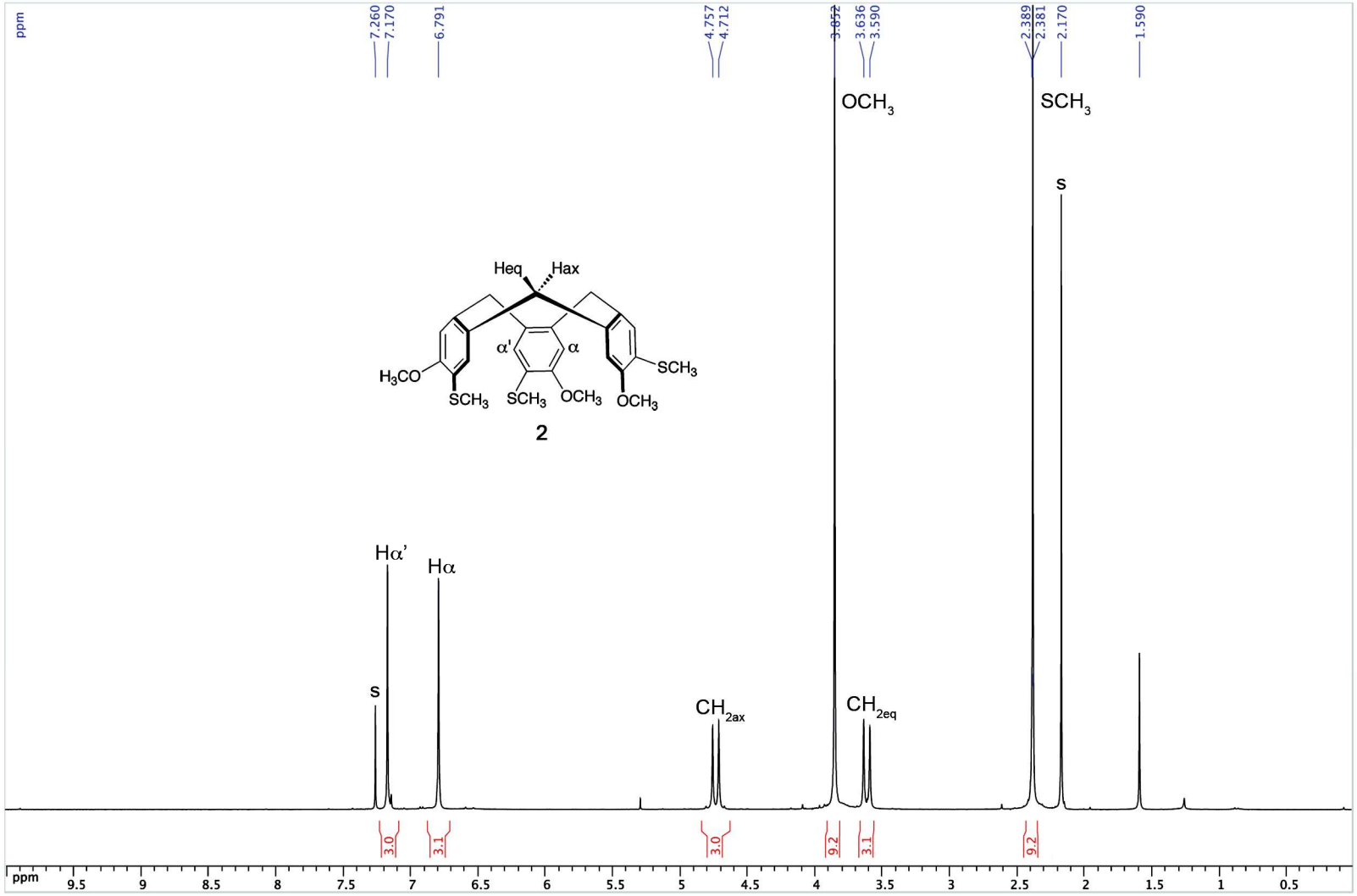

Figure S 7: ^{1}H NMR spectrum of compound **2** (300 MHz, $CDCl_3$).

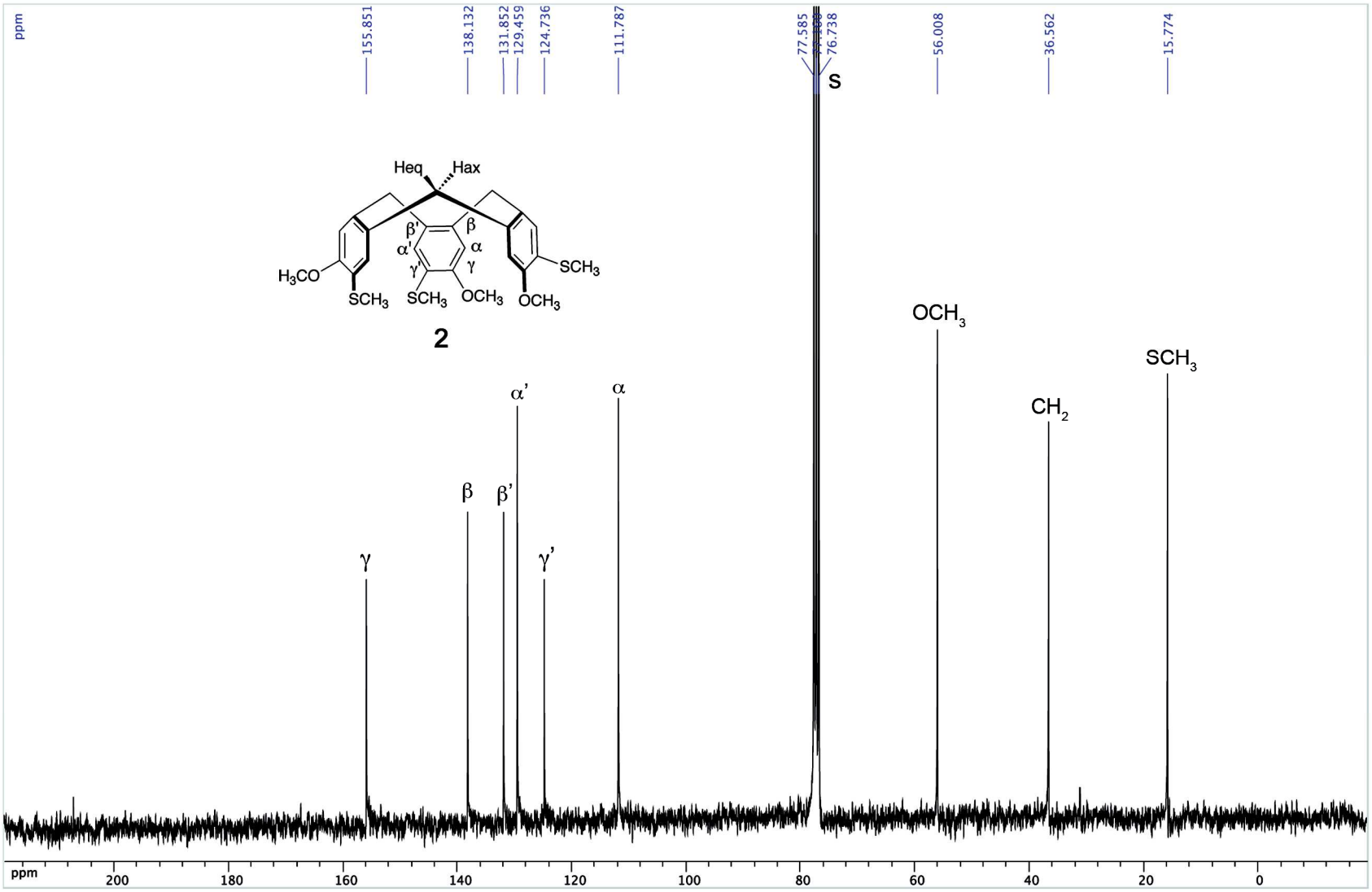

Figure S 8: ^{13}C NMR spectrum of compound **2** (75 MHz, $CDCl_3$).

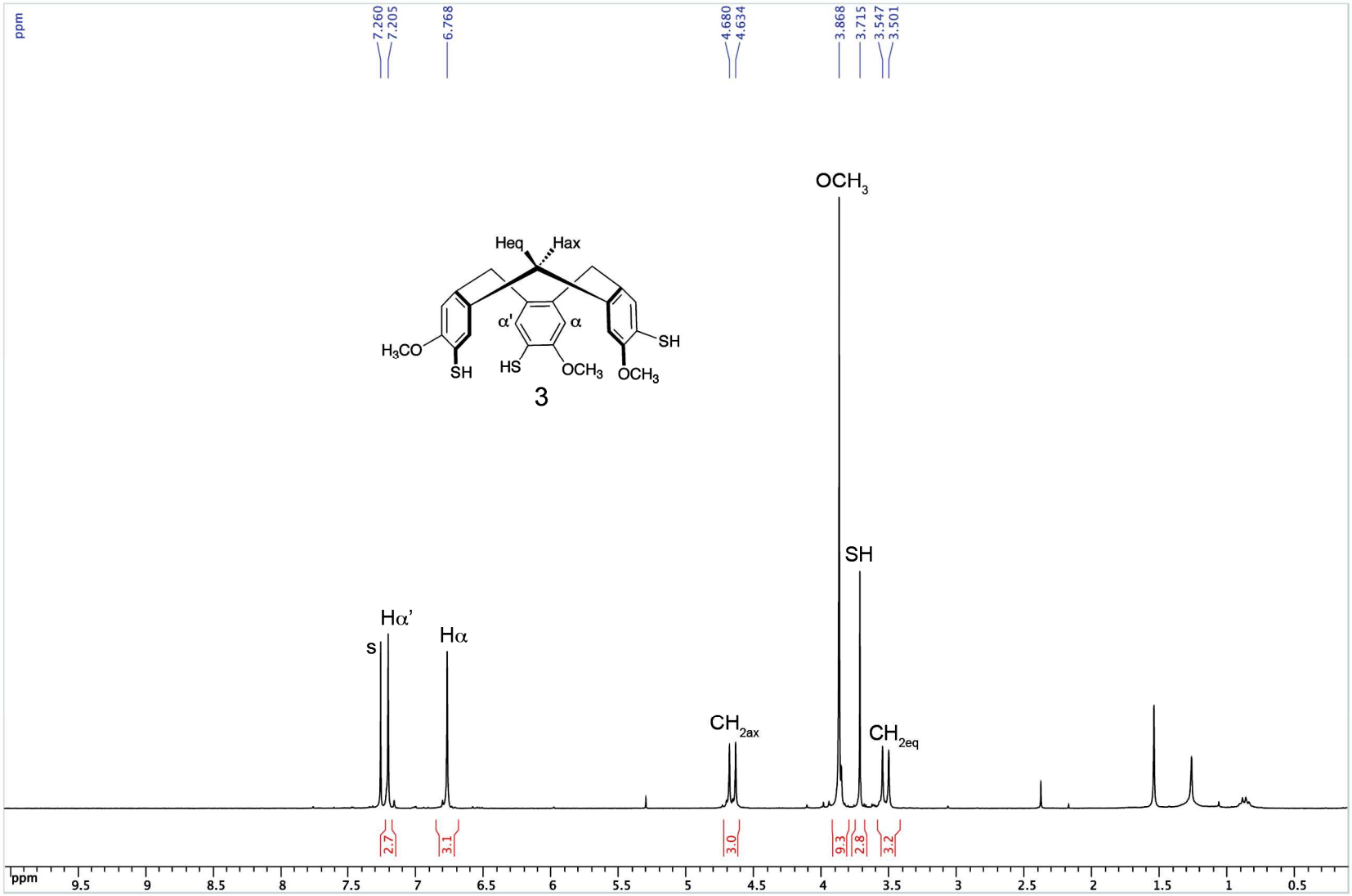

Figure S 9: ^{1}H NMR spectrum of compound **3** (300 MHz, $CDCl_3$).

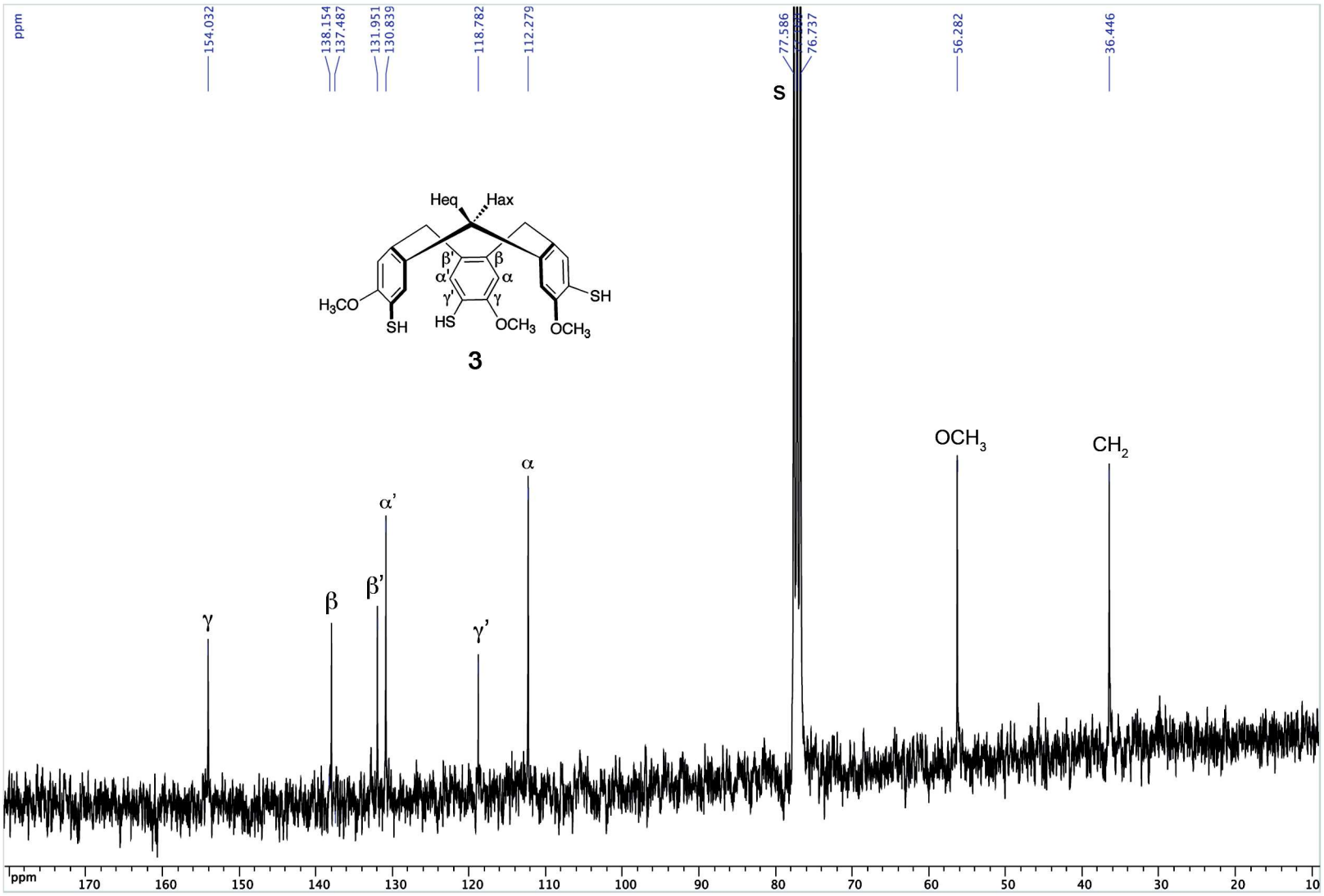

Figure S 10: ^{13}C NMR spectrum of compound **3** (75 MHz, $CDCl_3$).

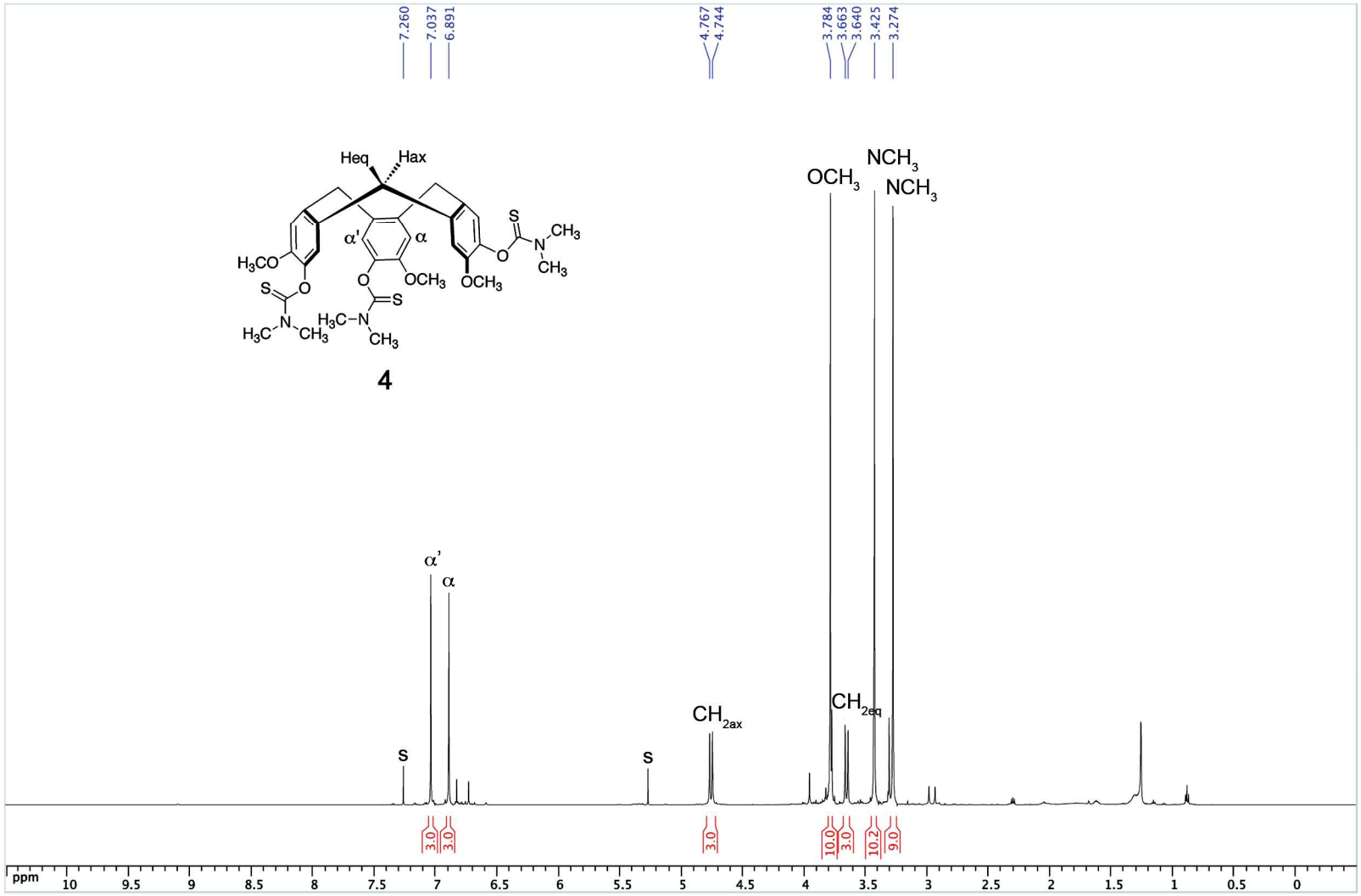

Figure S 11: ^{1}H NMR spectrum of compound **4** (600 MHz, $CDCl_3$).

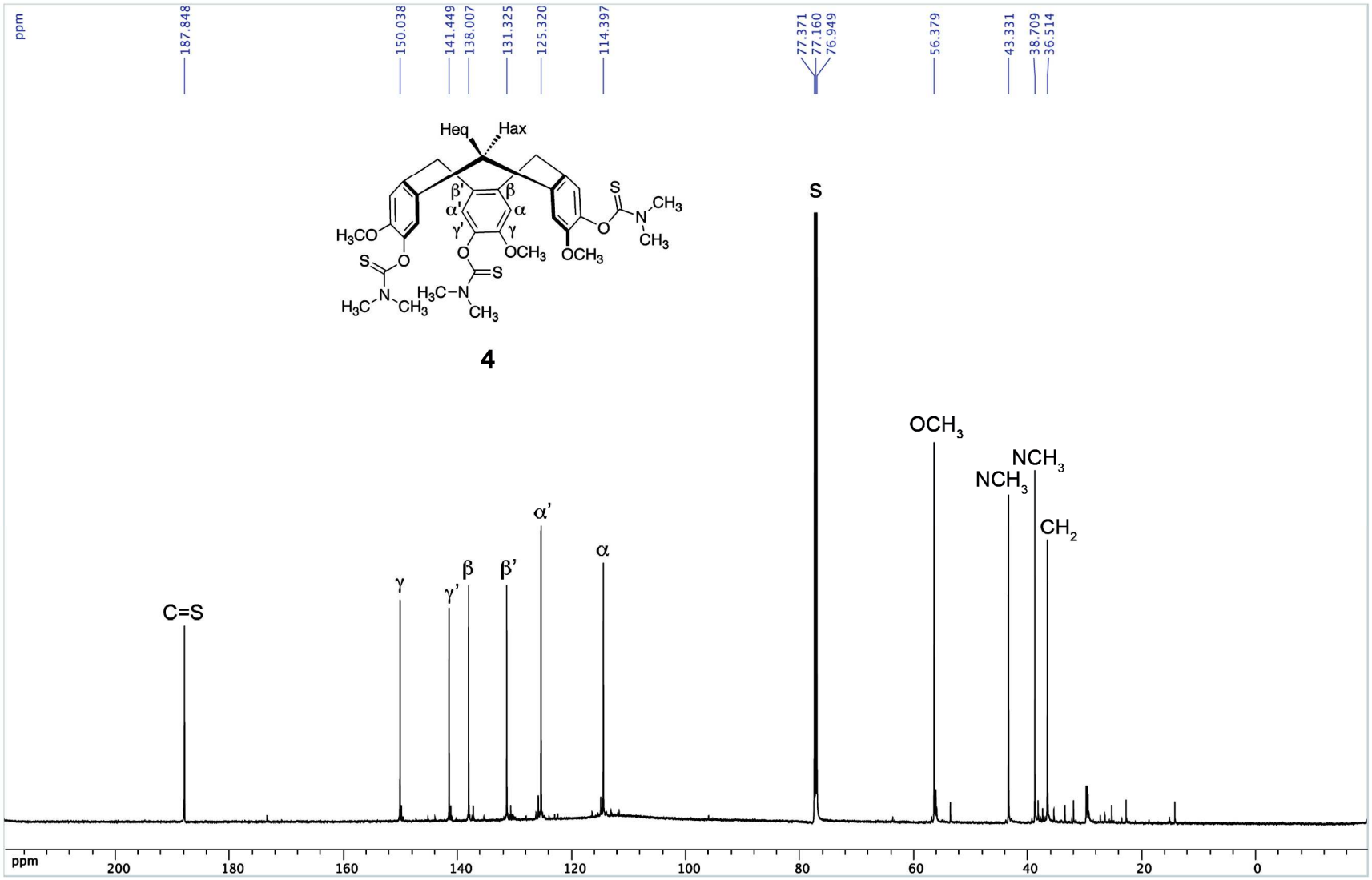

Figure S 12: ^{13}C NMR spectrum of compound **4** (75 MHz, $CDCl_3$).

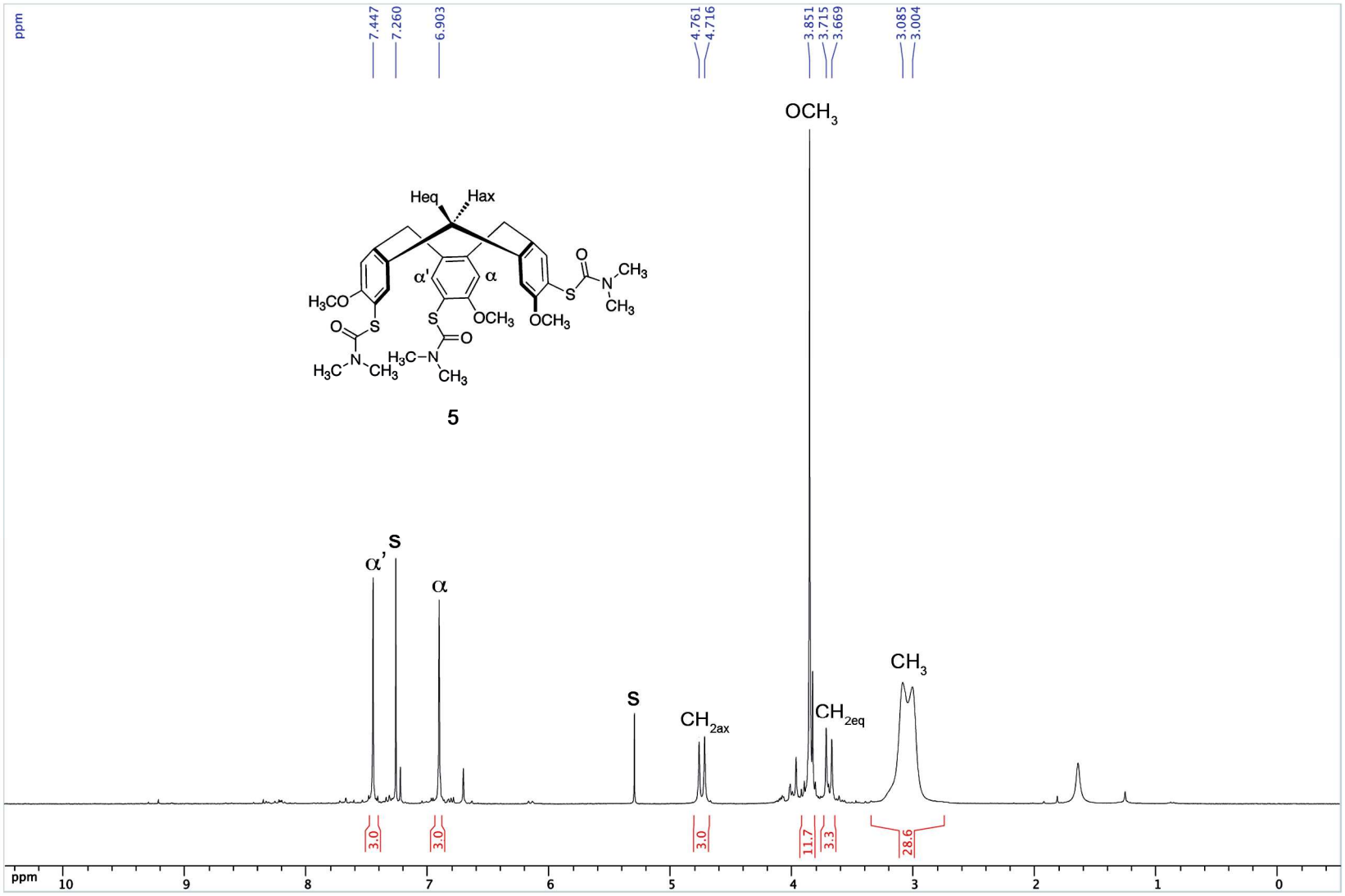

Figure S 13: ^{1}H NMR spectrum of compound **5** (300 MHz, $CDCl_3$).

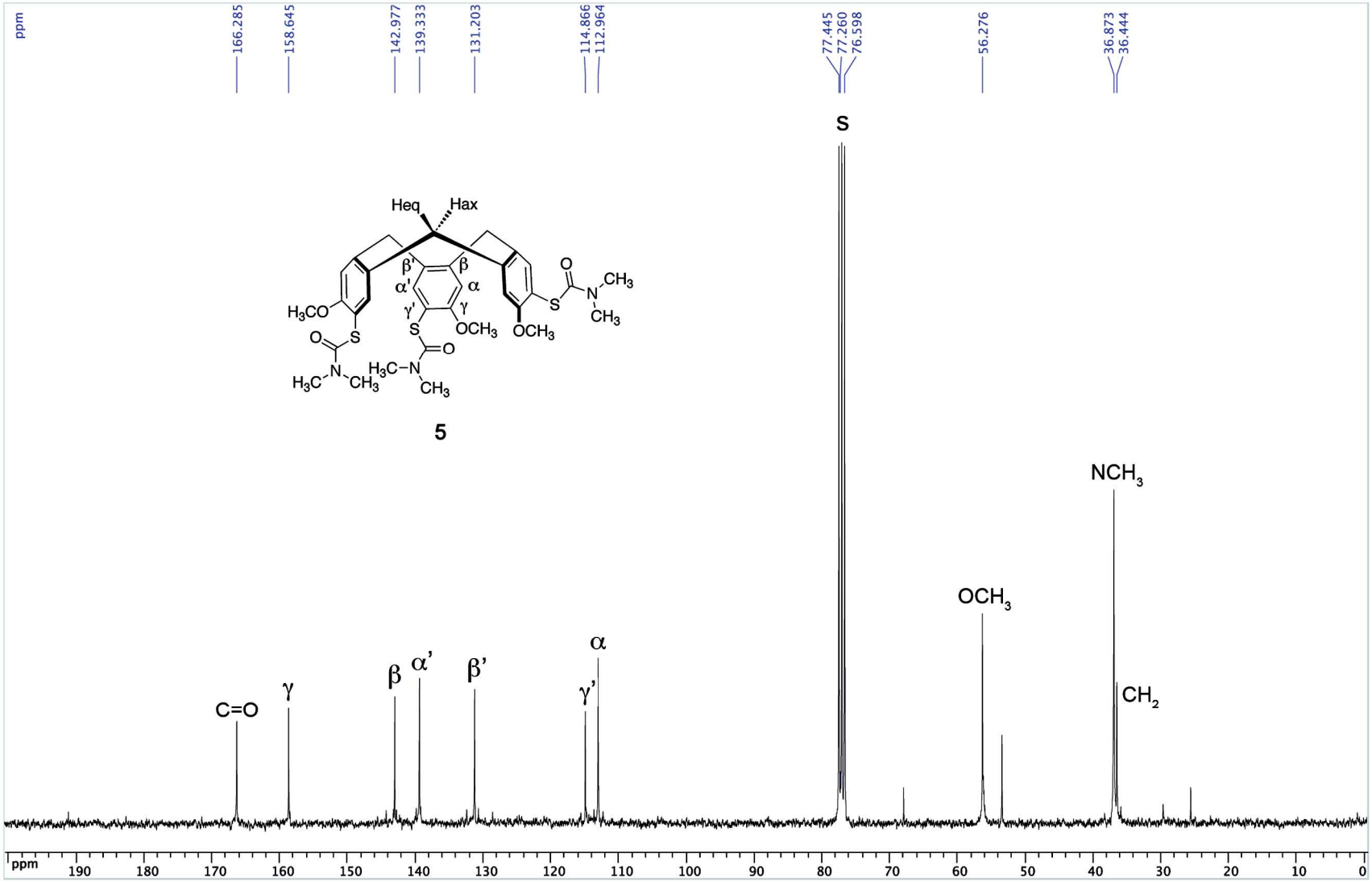

Figure S 14: ^{13}C NMR spectrum of compound **5** (75 MHz, $CDCl_3$).

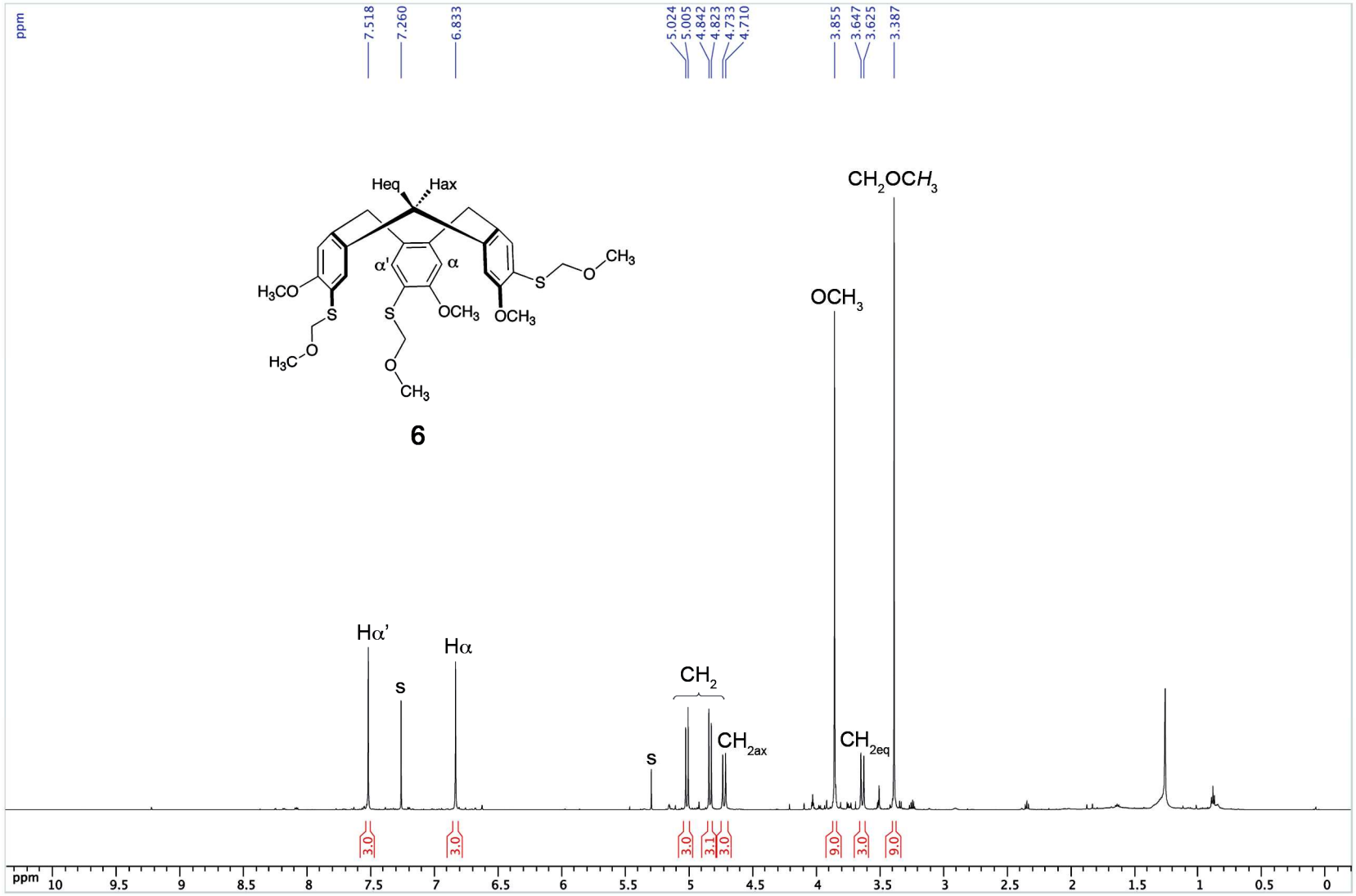

Figure S 15: ^{1}H NMR spectrum of compound **6** (600 MHz, $CDCl_3$).

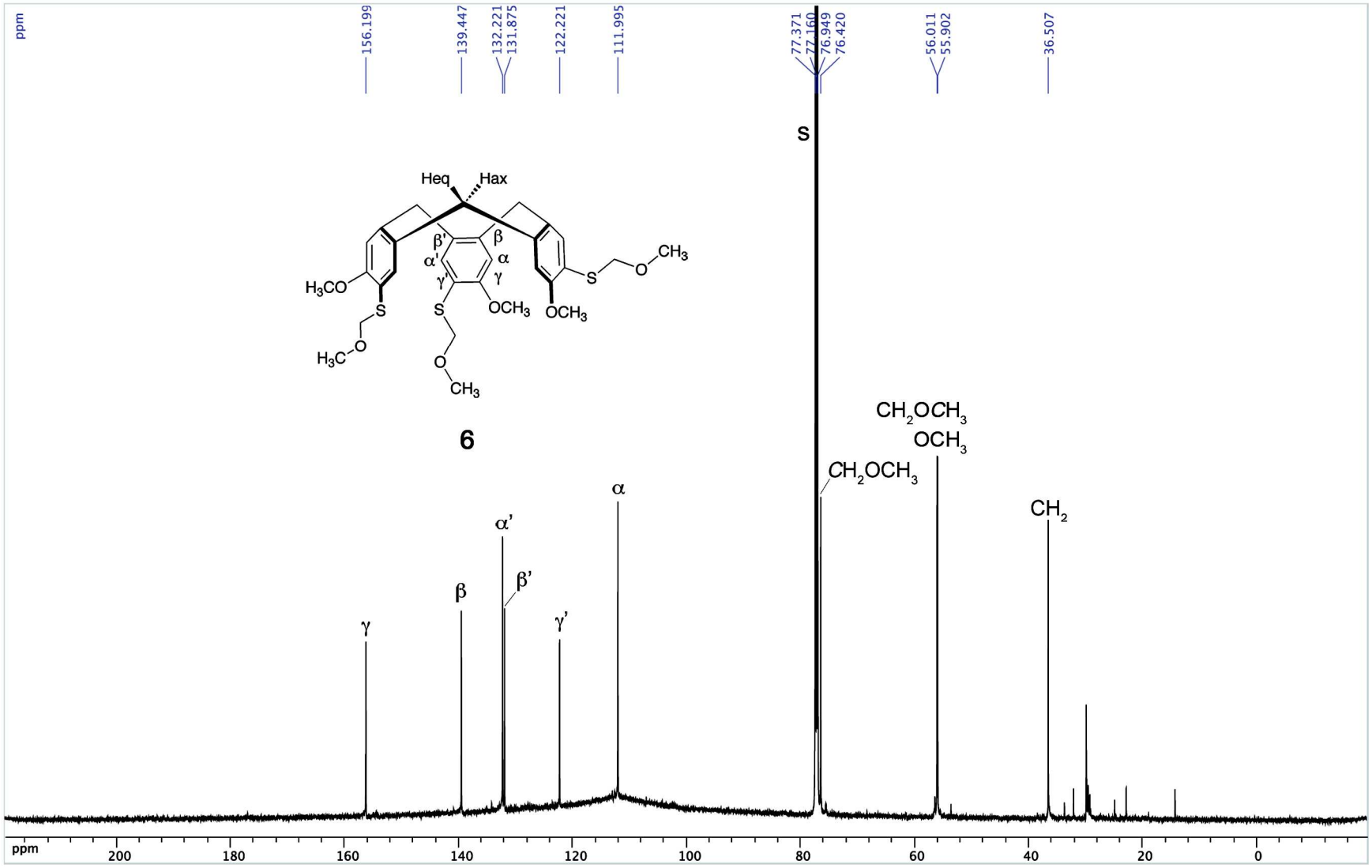

Figure S 16: ^{13}C NMR spectrum of compound **6** (75 MHz, $CDCl_3$).

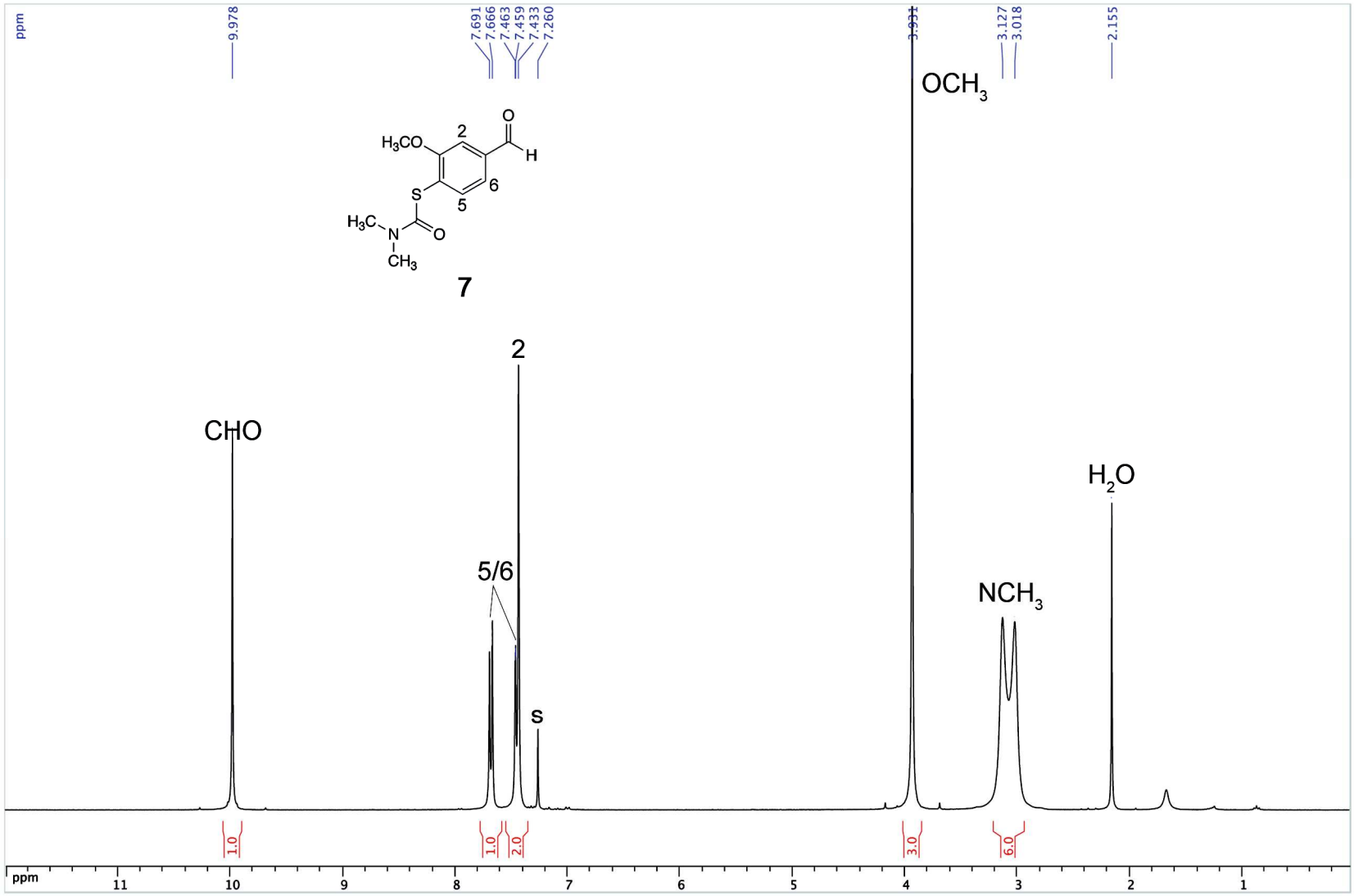

Figure S 17: ^{1}H NMR spectrum of compound **7** (300 MHz, $CDCl_3$).

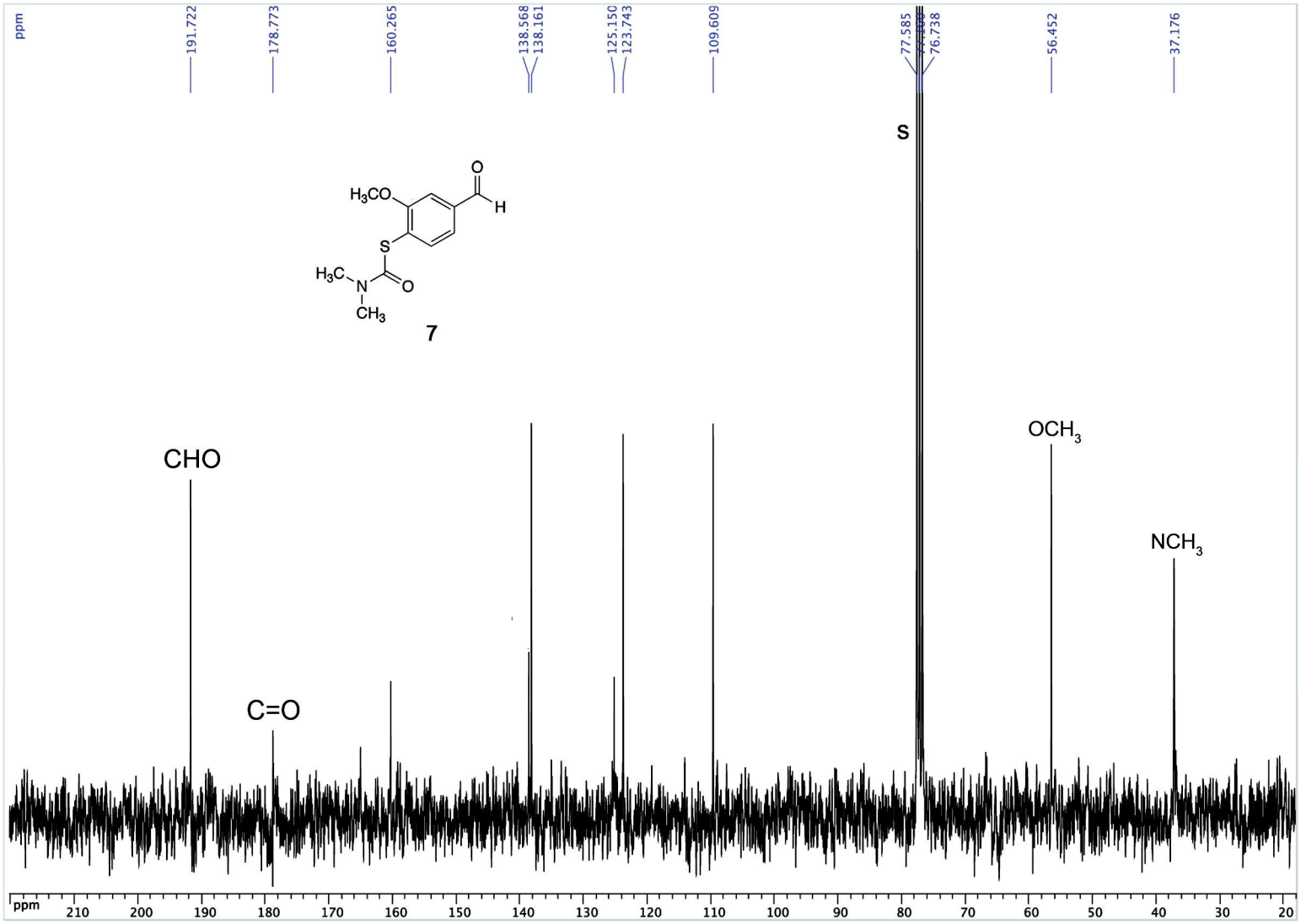

Figure S 18: ^{13}C NMR spectrum of compound **7** (75 MHz, $CDCl_3$).

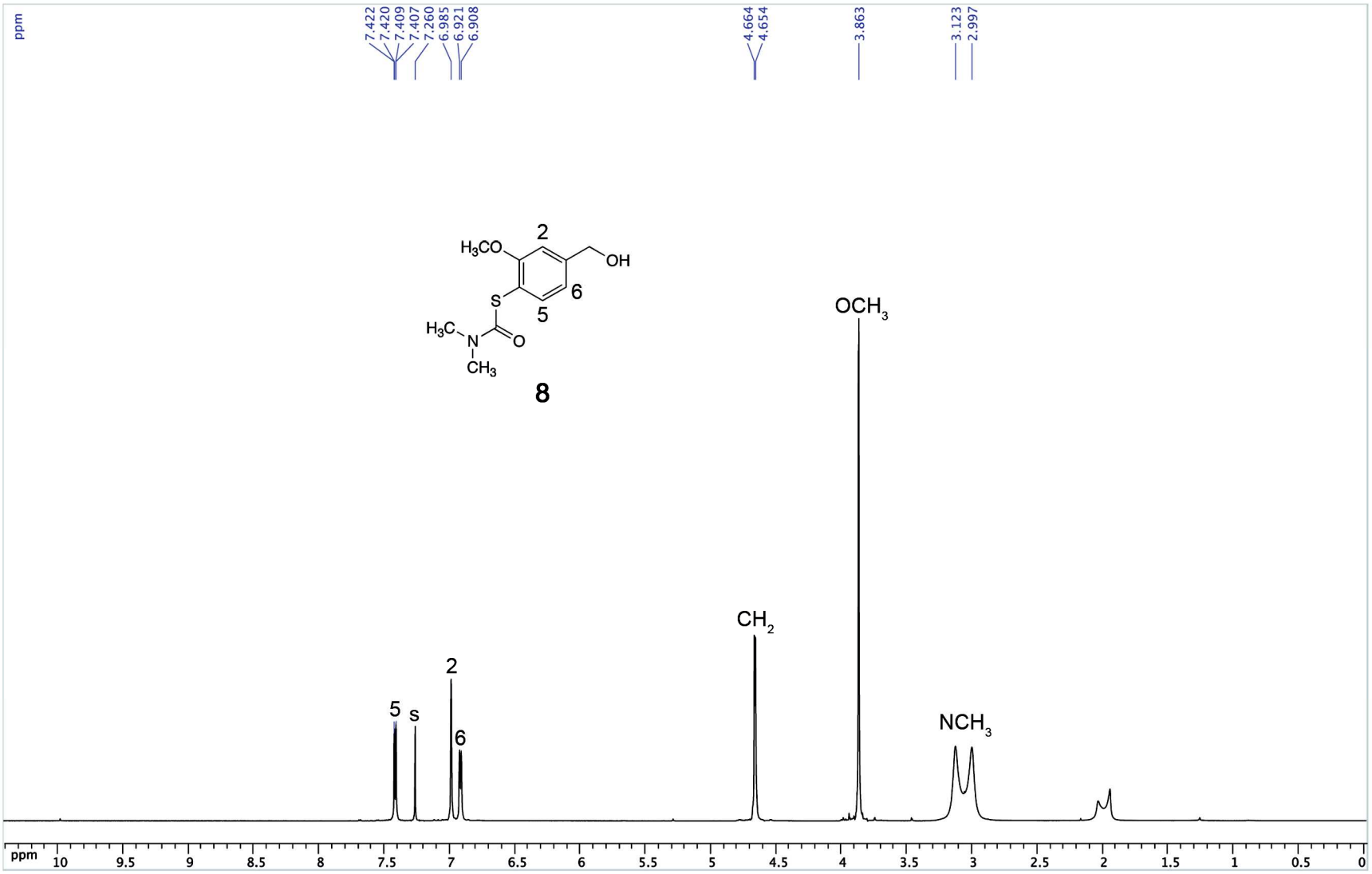

Figure S 19: ^{1}H NMR spectrum of compound **8** (300 MHz, $CDCl_3$).

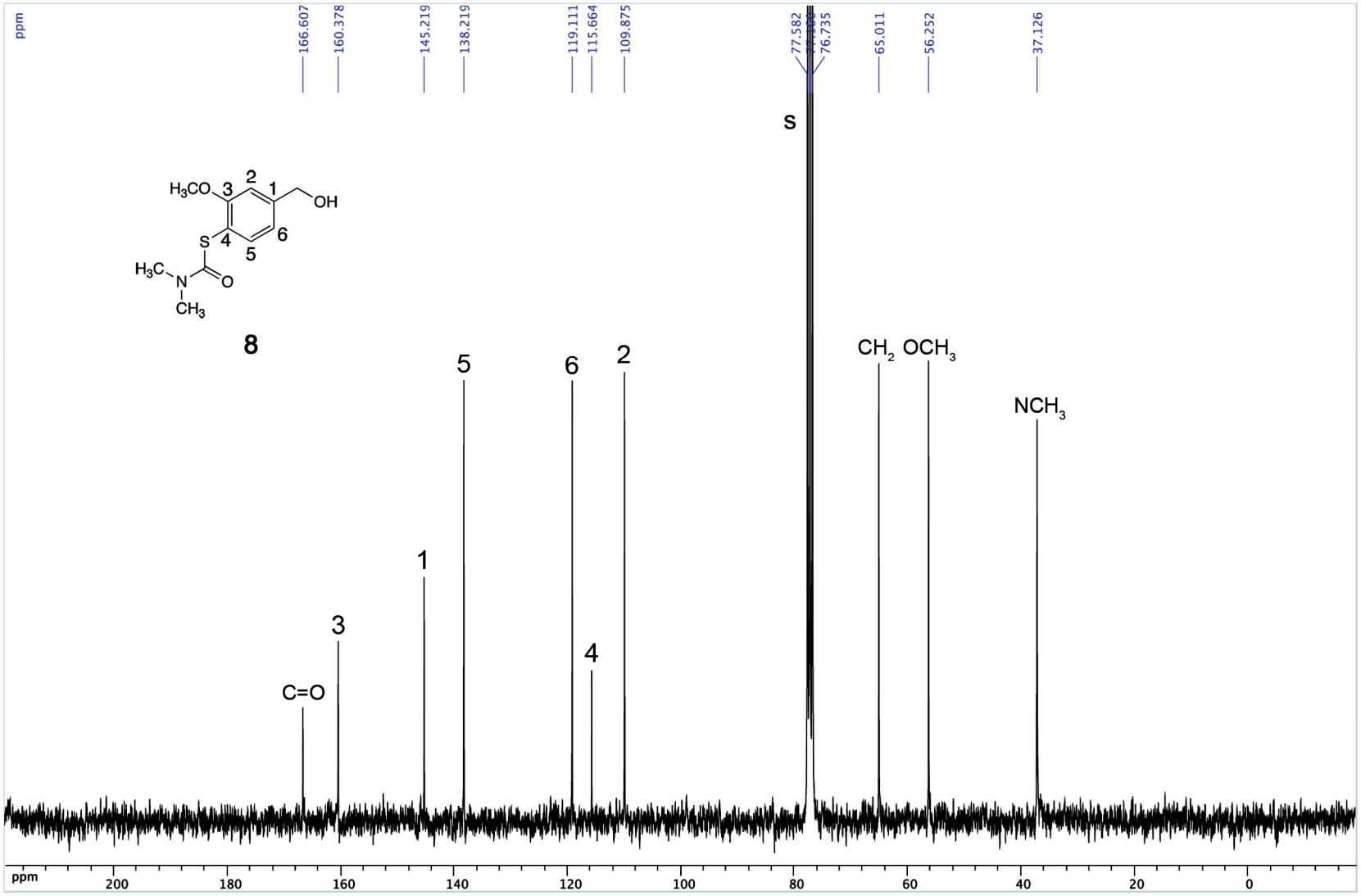

Figure S 20: ^{13}C NMR spectrum of compound **8** (75 MHz, $CDCl_3$).

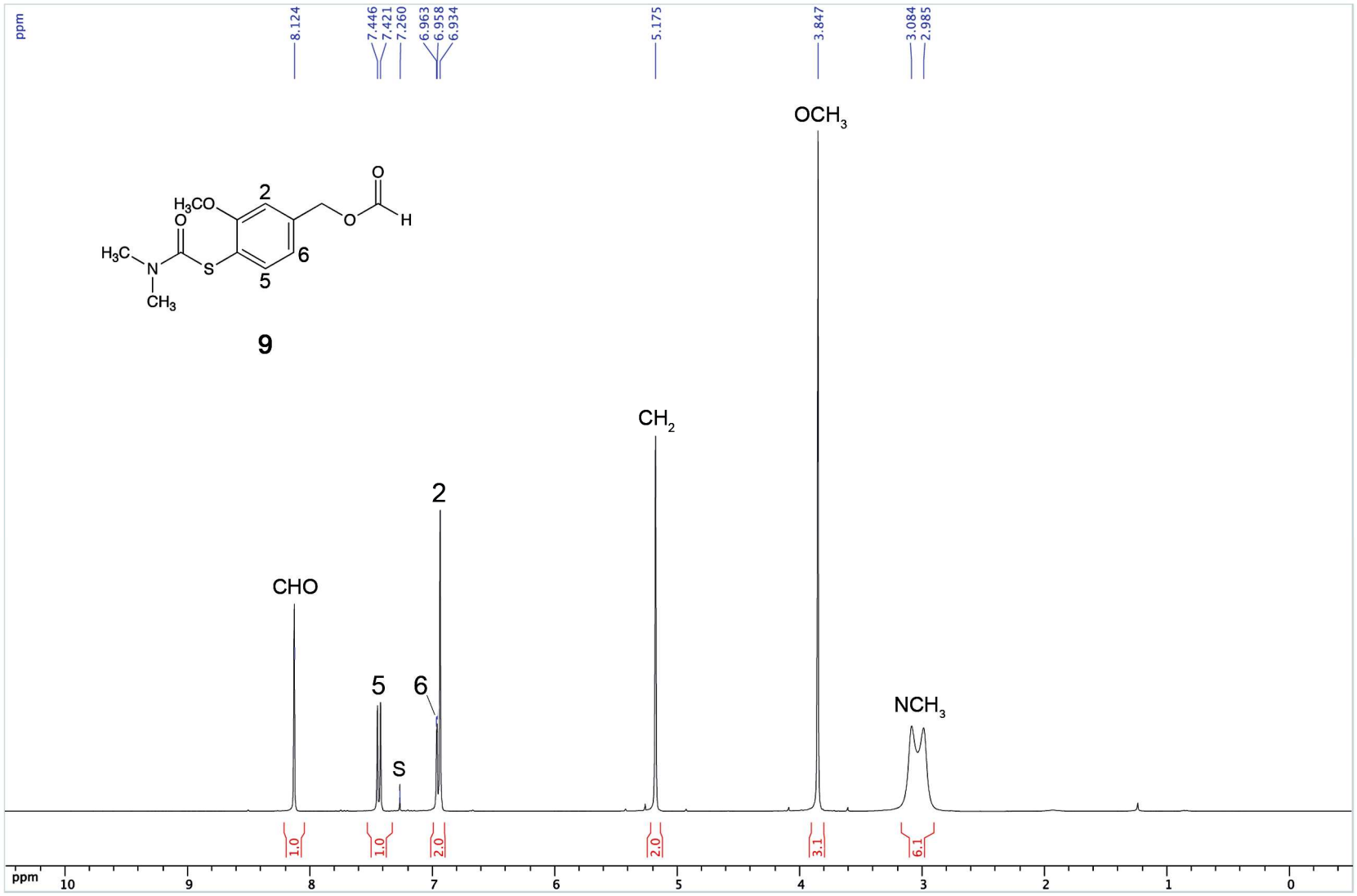

Figure S 21: ^{1}H NMR spectrum of compound **9** (300 MHz, $CDCl_3$).

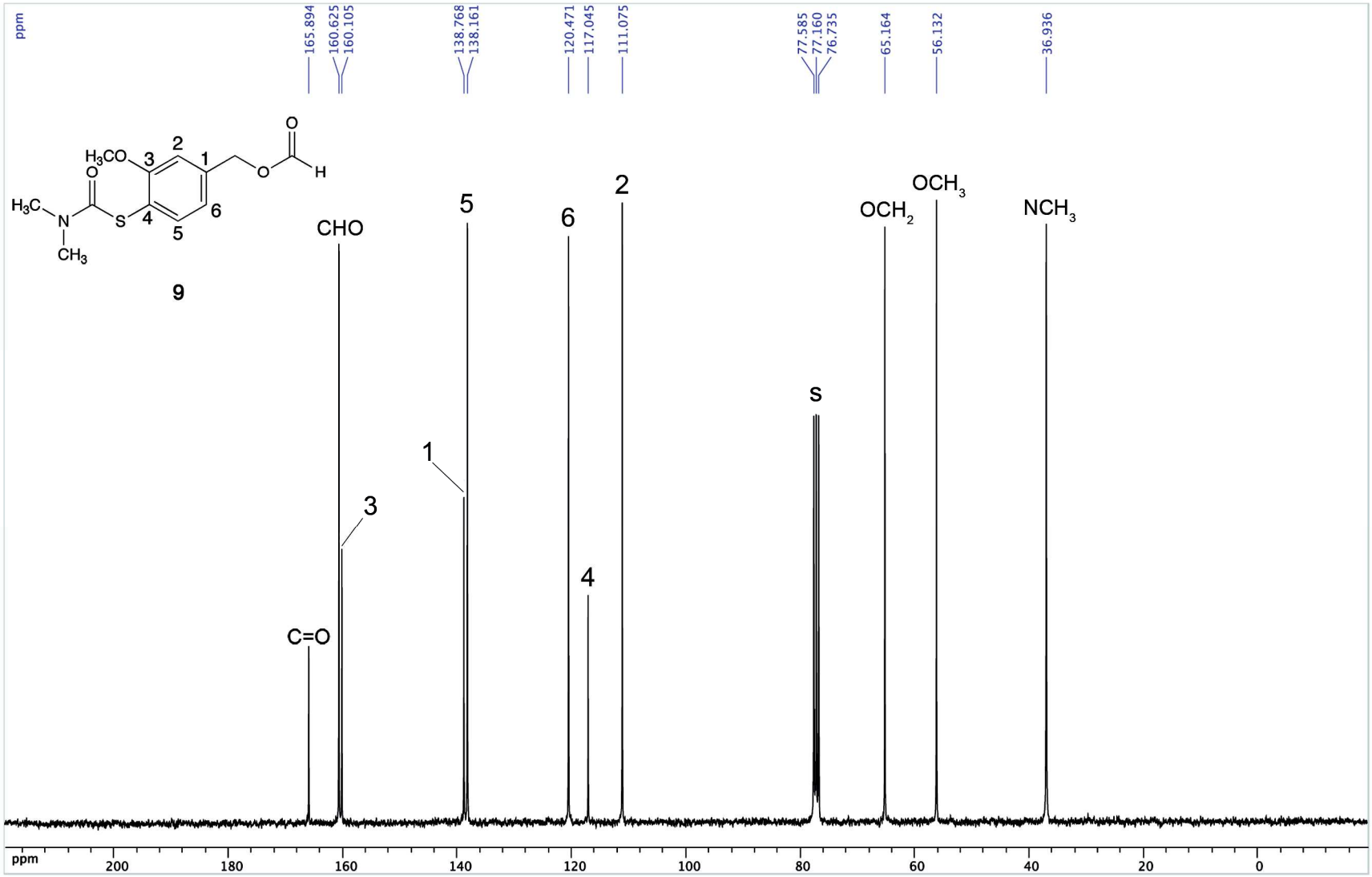

Figure S 22: ^{13}C NMR spectrum of compound **9** (75 MHz, $CDCl_3$).

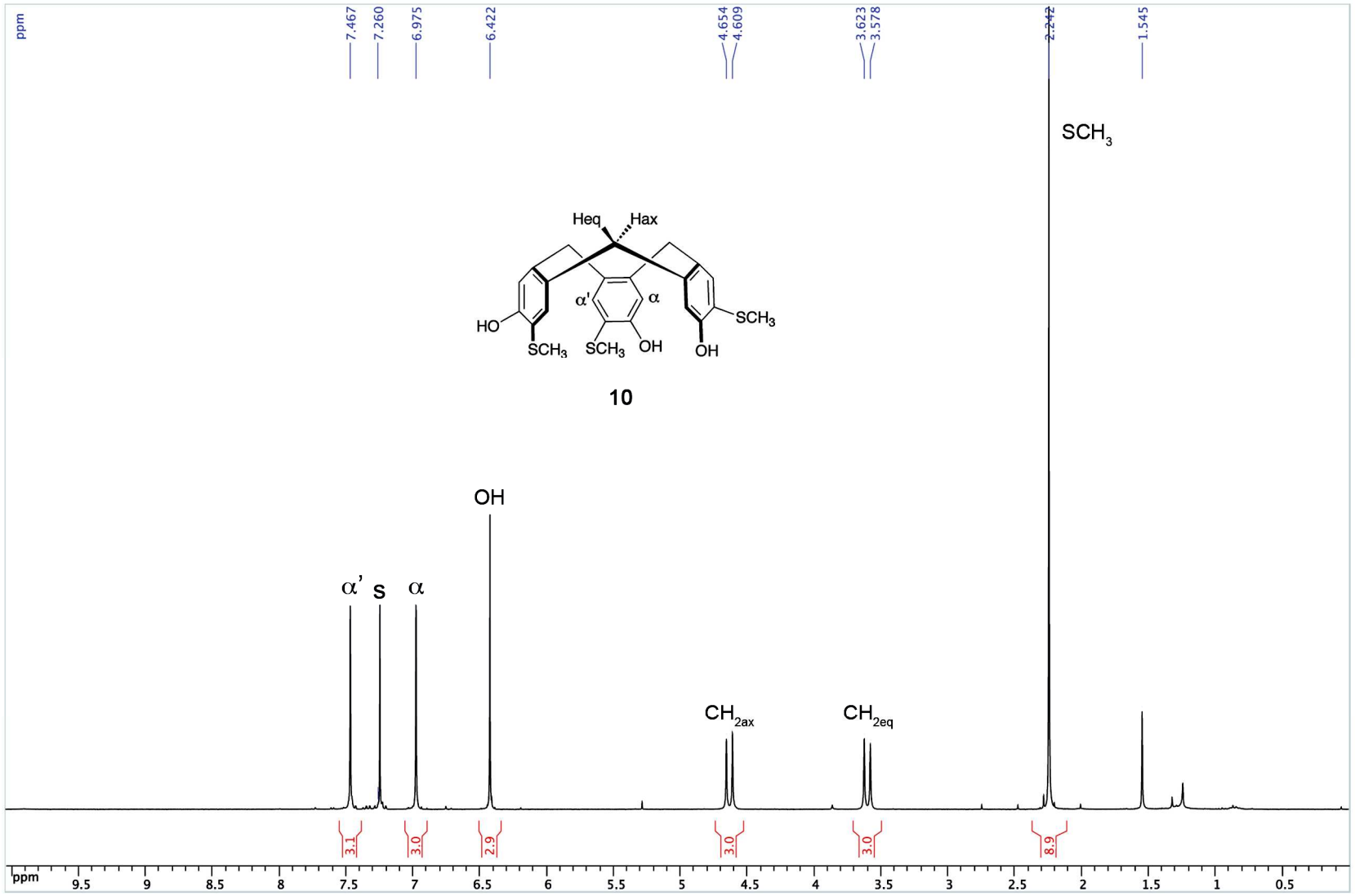

Figure S 23: ^{1}H NMR spectrum of compound **10** (300 MHz, $CDCl_3$).

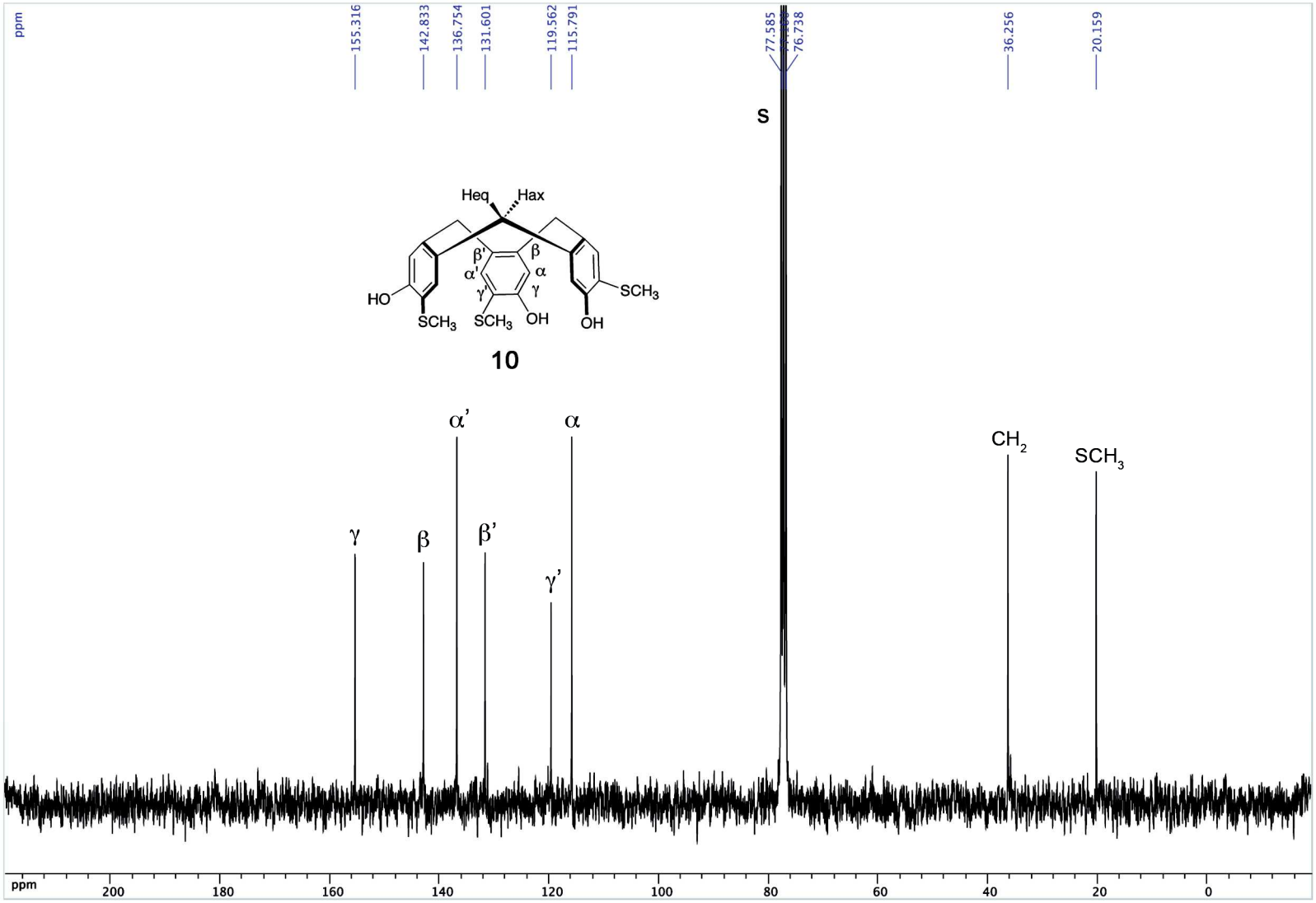

Figure S 24: ^{13}C NMR spectrum of compound **10** (75 MHz, $CDCl_3$).

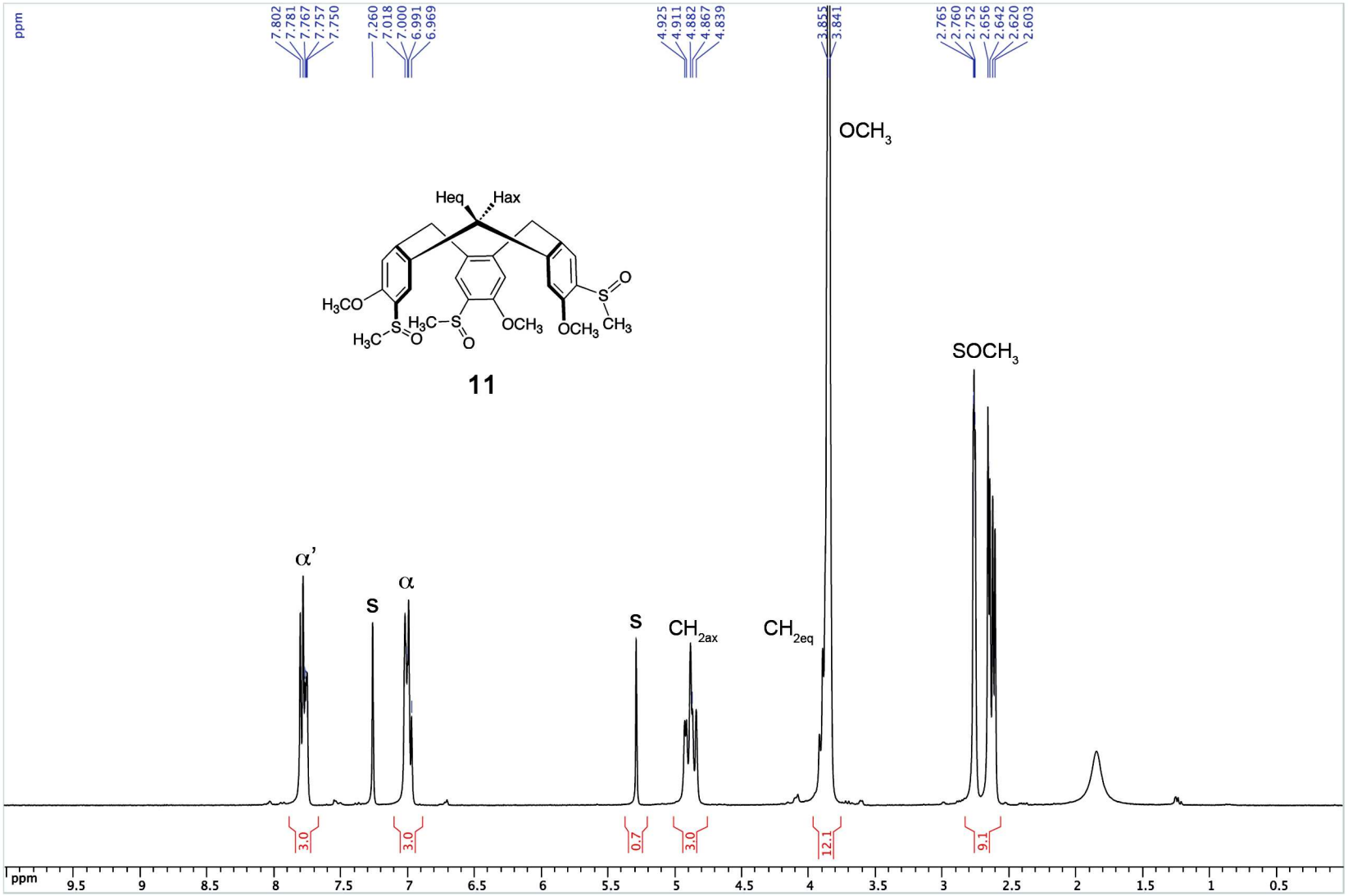

Figure S 25: ^{1}H NMR spectrum of compound **11** (300 MHz, $CDCl_3$).

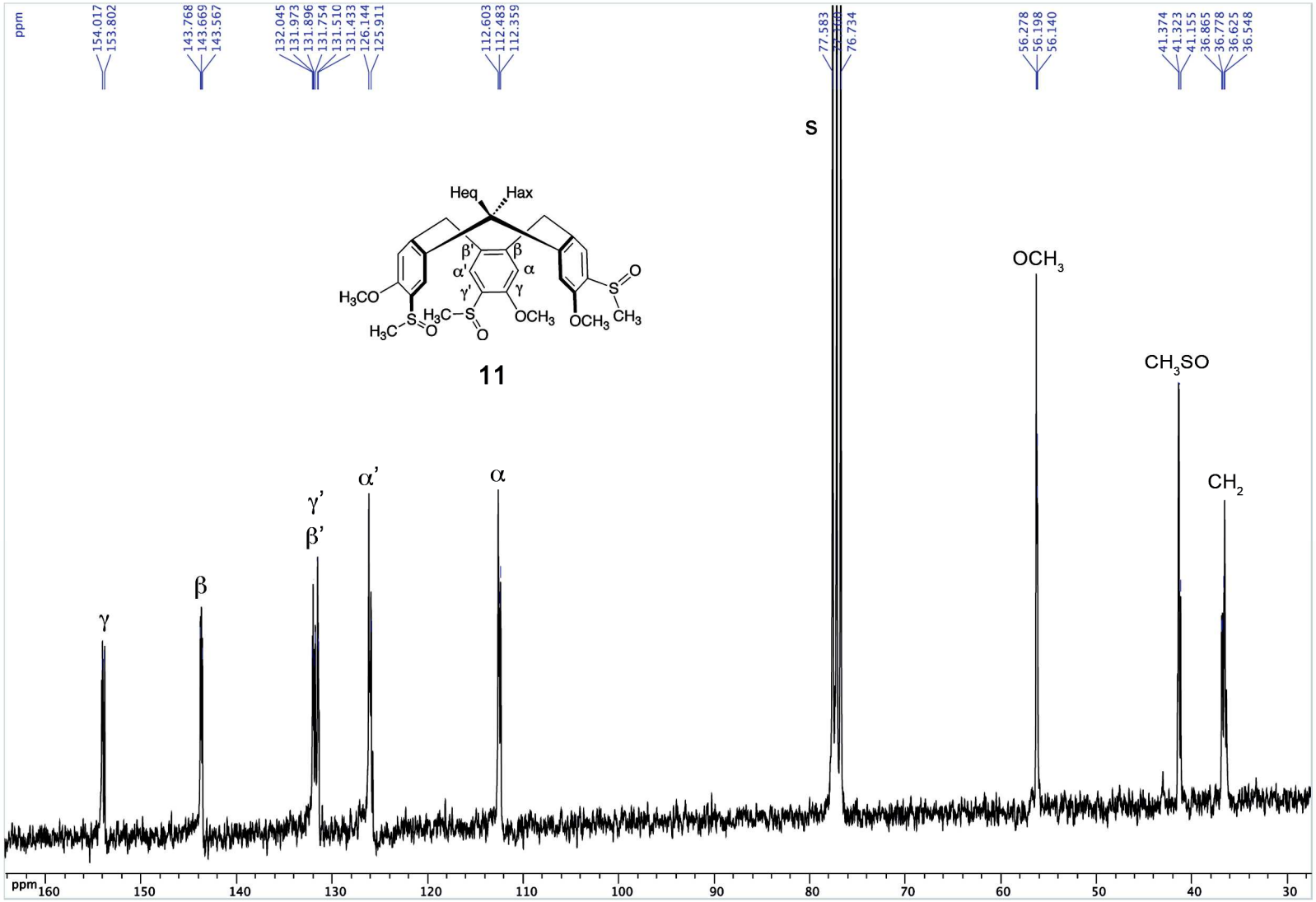

Figure S 26: ^{13}C NMR spectrum of compound **11** (75 MHz, $CDCl_3$).

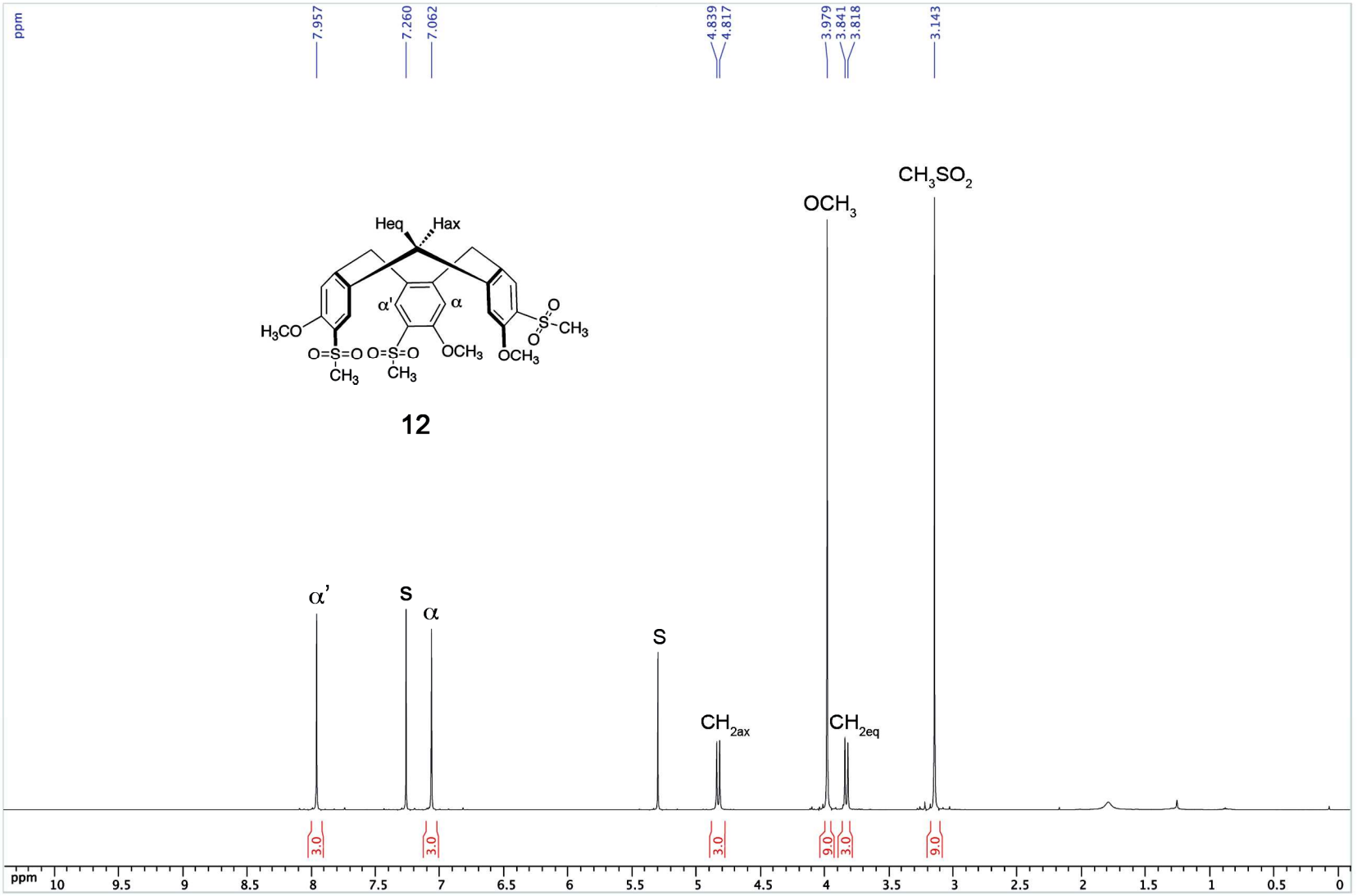

Figure S 27: ^{1}H NMR spectrum of compound **12** (300 MHz, $CDCl_3$).

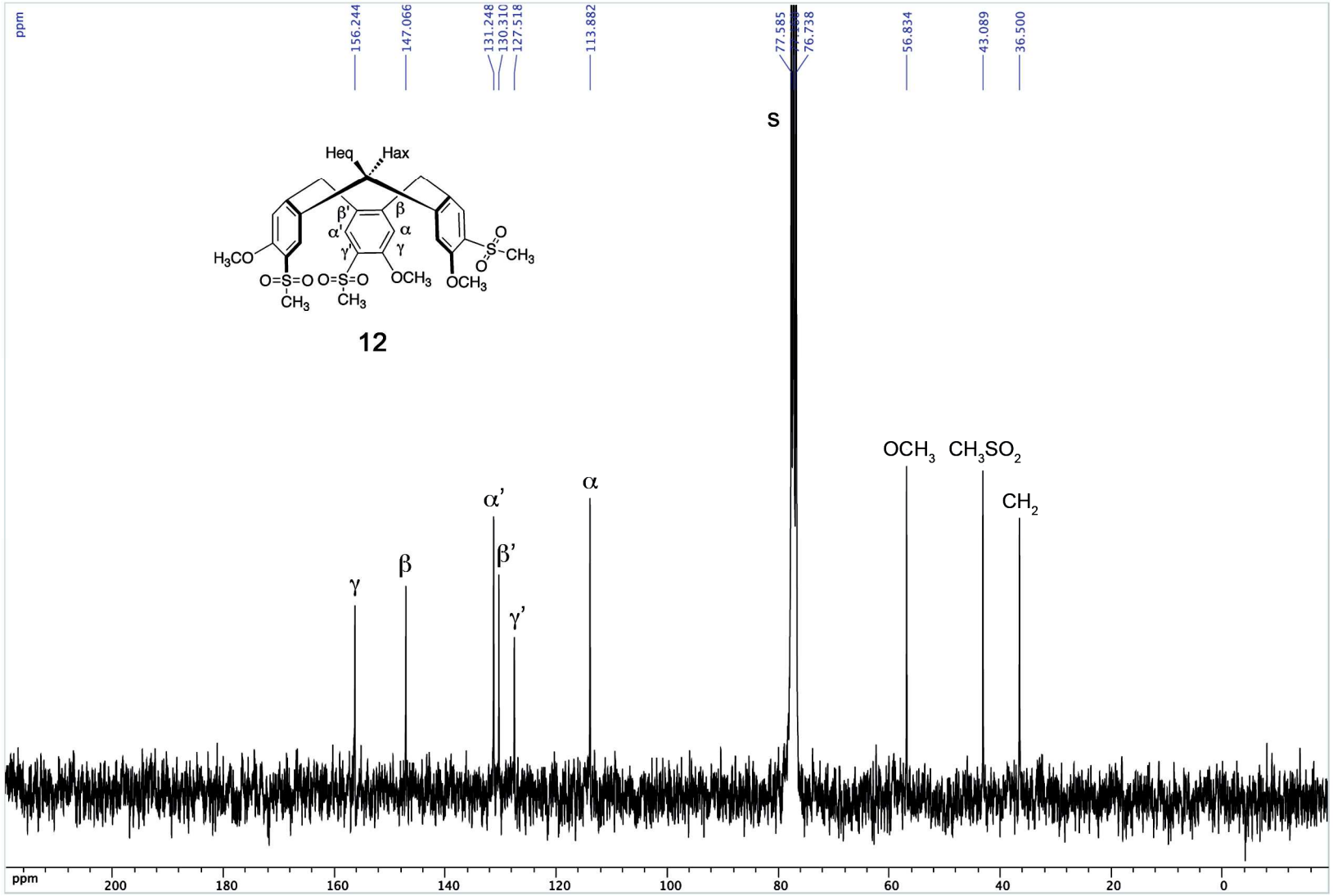

Figure S 28: ^{13}C NMR spectrum of compound **12** (75 MHz, $CDCl_3$).