Supporting Information

SYNTHESIS OF A 3-THIOMANNOSIDE

María B. Comba, Alejandra G. Suárez, Ariel M. Sarotti, María I. Mangione and Rolando A. Spanevello* and Enrique D. V. Giordano*

Instituto de Química Rosario, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario – CONICET. Suipacha 531, S2002RLK Rosario, Argentina.

Corresponding authors:

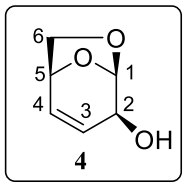
*spanevello@iquir-conicet.gov.ar and mangione@iquir-conicet.gov.ar

Table of contents

Experimental Section

All reagents and solvents were used directly as purchased or purified according to standard procedures. Analytical thin layer chromatography was carried out using commercial silica gel plates (Merck, Silica Gel 60 F254) and visualization was effected with short wavelength UV light (254 nm) and *p*-anysaldehyde solution with subsequent heating. Flash column chromatography was performed with silica gel 60 H (Merck) using EtOAc:hexanes mixtures. NMR spectra were recorded at 300 MHz for ^{1}H, and 75 MHz for ^{13}C on a Bruker Avance-300 DPX spectrometer with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H) as internal standard. Chemical shifts are reported in delta (δ) units in parts per million (ppm) and splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Coupling constants are recorded in Hertz (Hz). The structure of the products were determined by a combination of spectroscopic methods such as IR, 1D and 2D NMR (including NOE, COSY, HSQC and HMBC experiments) and HRMS. Infrared spectra were recorded on a Shimadzu IR Prestige-21 spectrometer using sodium chloride plate pellets. Absorbance frequencies are recorded in reciprocal centimeters (cm^{-1}). High resolution mass spectra (HRMS) were obtained on a Bruker microTOF-Q II LC-MS spectrometer. Optical rotations were determined using a JASCO DIP-1000 digital polarimeter in 100 mm cells and the sodium D line (589 nm) at room temperature in the solvent and concentration indicated. The melting points were taken on a Leitz Wetzlar Microscope Heating Stage Model 350 apparatus and are uncorrected. Levoglucosenone **3** was obtained according to the procedure previously described.[16]

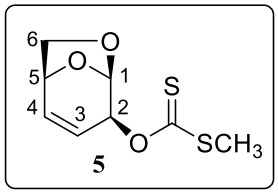
*Synthesis of Allylic alcohol **4***



4

Compound **3** (5.94 g, 47.13 mmoles) was dissolved in MeOH (32 mL) and cooled at 0 ºC. $CeCl_3$**.**$7H_2O$ (17.56 g, 47.13 mmoles) and $NaBH_4$ (1.42 g, 37.7 mmoles) were added and stirred for 2.5 h. The solution was neutralized with HCl 0.1 N to reach pH = 7. The mixture was diluted with water (5 mL) and extracted several times with 50 mL portions of EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography to afford **4** (5.59 g, 43.60 mmoles, 92%) as a white crystalline solid; Rf (60% hexane- EtOAc) 0.17; .mp = 67-68 ºC (ethyl ether) [Lit 67-69 ºC][29]; $[\alpha]_D^{25}$ -32.2 (*c* 0.995, $CHCl_3$) [Lit -34 (*c* 1.00, $CHCl_3$)][29]; ν_{max} (KBr) 3445 (OH), 3420, 1628 (C=C), 1122, 1066, 1045 cm^{-1}; δ_H (300 MHz $CDCl_3$) 6.12 (1H, dd, *J* 9.8, 4.3 Hz, H-4), 5.70 (1H, ddd, *J* 9.8, 2.4, 2.2 Hz, H-3), 5.51 (1H, dd, *J* 2.7, 2.2 Hz, H-1), 4.66 (1H, dd, *J* 4.3, 4.2 Hz, H-5), 4.33 (1H, s, H-2), 3.84 (1H, d, *J* 6.6 Hz, H-6*endo*), 3.75 (1H, dd, *J* 6.6, 4.2 Hz, H-6*exo*), 2.15 (1H, s, OH); δ_C (75 MHz $CDCl_3$) 130.6 (C-4), 129.0 (C-3), 101.1 (C-1), 71.1 (C-2), 70.5 (C-6), 68.6 (C-5).

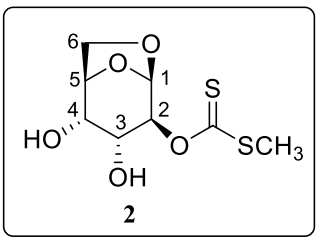
*Synthesis of Allylic xanthate **5***



5

To a solution of compound **4** (1.26 g, 9.84 mmoles) in 10 mL of anhydrous THF was added a suspension of NaH (60% dispersion in mineral oil) (0.86 g, 19.70 mmoles) in 40 mL of anhydrous THF. The mixture was cooled at 0 ºC. CS_2 (1.5 mL, 24.60 mmoles) and CH_3I (2.15 mL, 34.50 mmoles) were added. The mixture was stirred during 3 h and then a solution of NH_4Cl (sat) (2 mL) was added. The solution was extracted with EtOAc (100 mL) and then washed with 5 mL of brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography to afford **5** (2.01 g, 9.22 mmoles, 94%) as a white crystalline solid; Rf (60% hexane- EtOAc) 0.56; mp = 61-62 ºC (diisopropylether). $[\alpha]_D^{22}$ +18.2 (*c* 1.145, $CHCl_3$); ν_{max} (KBr) 3000, 2968, 2908, 1653 (C=C), 1288, 1208 (C=S), 1120, 882 cm^{-1}; δ_H (300 MHz $CDCl_3$) 6.36 (1H, s, H-2), 6.27 (1H, dd, *J* 9.8, 4.1 Hz, H-4), 5.79 (1H, s, H-1), 5.76 (1H, d, *J* 9.8 Hz, H-3), 4.73 (1H, dd, *J* 4.3, 4.1Hz, H-5), 4.02 (1H, d, *J* 6.4 Hz, H-6*endo*), 3.82 (1H, dd, *J* 6.4, 4.3 Hz, H-6*exo*), 2.59 (3H, s, SCH_3); δ_C (75 MHz $CDCl_3$) 215.8 (C=S), 133.2 (C-4), 123.8 (C-3), 98.3 (C-1), 79.3 (C-2), 71.3 (C-5), 71.1 (C-6), 19.1 (SCH_3); HRMS (EI, MH^+) MH^+ found 219.01384, $C_8H_{11}O_3S_2^+$ calcd 219.01441.

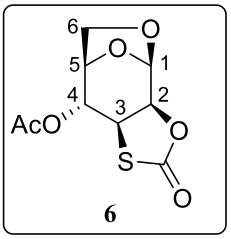
*Synthesis of Diol **2***



2

Compound **5** (795 mg, 3.64 mmoles) was dissolved in acetone:H_2O 95:5 mixture (25.7 mL), NMO was added and then a solution of OsO_4 in ^{t}BuOH was added (9.20 mg, 0.04 mmoles). The mixture was stirred during 72 h and then cooled at 0 ºC. Na_2SO_3 was added and after 10 min the solution was filtered. The residue was purified by flash chromatography to afford **2** (861 mg, 3.42 mmoles, 94%) a white crystalline solid; Rf (60% Hexane-EtOAc) 0.08; mp = 119-120 ºC (diisopropylether); $[\alpha]_D^{21}$ -155.6 (*c* 1.095, $CHCl_3$); ν_{max} (KBr) 3534 (OH), 3442 (OH), 2973, 2959, 2928, 2896, 1477, 1409, 1332, 1311, 1283, 1208 (C=S), 1088, 915cm^{-1}; δ_H (300 MHz $CDCl_3$) 5.63 (1H, dd, *J* 8.3, 1.7 Hz, H-2), 5.60 (1H, d, *J* 1.7 Hz, H-1), 4.72 (1H, ddd, *J* 5.1, 1.9, 1.6 Hz, H-5), 4.09 (1H, s, H-3), 4.00 (1H, s, H-4), 3.86 (1H, dd, *J* 8.1, 5.1 Hz, H-6*exo*), 3.81 (1H, dd, *J* 8.1, 1.6 Hz, H-6*endo*), 3.06 (1H, s, OH), 3.02 (1H, s, OH), 2.60 (3H, s, SCH_3); δ_C (75 MHz $CDCl_3$) 217.0 (C=S), 98.3 (C-1), 83.2 (C-2), 76.2 (C-5), 70.5 (C-3), 67.9 (C-4), 65.5 (C-6), 19.3 (SCH_3); HRMS (EI MNa^+) found 275.00115. $C_8H_{12}O_5S_2Na^+$ calcd 275.00184.

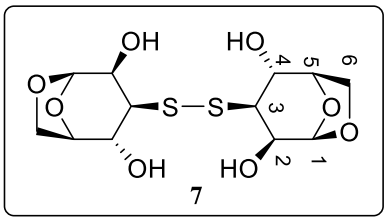
*Synthesis of Thiocarbonate **6***



6

Xanthate **2** (190 mg, 0.75 mmoles) was dissolved in AcOH (12 mL) and cooled at 0 ºC in an ice-bath. A solution of H_2SO_4/AcOH 50 % (7.8 mL) was added and the mixture was stirred for 6 h at room temperature. The mixture was cooled to 0º C in an ice bath and diluted with EtOAc (150 mL). Solid $NaHCO_3$ (10 g) was added and after 10 minutes of stirring, the base was dissolved with water and the phases were separated. The organic layer was washed with 5% aqueous $NaHCO_3$ (2 x 50 mL), brine (50 mL) and dried (Na_2SO_4 anh.). After filtration, the solvents were concentrated under reduced pressure. The residue was purified by flash chromatography to afford compound **6** (124.3 mg, 0.50 mmoles, 67%) as white crystalline solid; Rf (60%, hexane:EtOAc) 0.21; $[\alpha]_D^{23}$-112.4 (*c* 1.1, $CHCl_3$); ν_{max} (KBr) 2981, 2843, 1748 (C=O), 1357, 1223, 1206, 1160, 1023, 841 cm^{-1}; δ_H (300 MHz $CDC1_3$) 5.56 (1H, d, *J* 2.3 Hz, H-1), 5.00 (1H, s, H-4), 4.69 (1H, dd, *J* 8.6, 2.3 Hz, H-2), 4.66 (1H, dd, *J* 5.8 Hz, H-5), 4.32 (1H, dd, *J* 8.6 Hz, H-3), 4.30 (1H, dd, *J* 8.4 Hz, H-6*endo*), 3.88 (1H, dd, *J* 8.4 Hz, 5.8 Hz, H-6*exo*), 2.15 (3H, s, $COC\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 170.3 (C=O), 169.8 ($\underline{C}OCH_3$), 98.0 (C-1), 74.4 (C-5), 74.2 (C-2), 69.8 (C-4), 66.1 (C-6), 45.3 (C-3), 20.8 ($CO\underline{C}H_3$); HRMS (EI, MNa^+): MNa^+, found 269.00921 $C_9H_{10}O_6SNa^+$ calcd 269.00903.

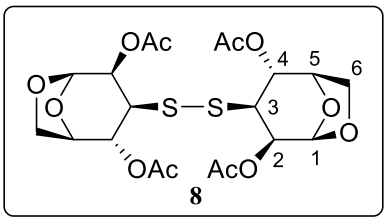
*Synthesis of Disulfide **7***



7

Compound **6 (**88 mg, 0.36 mmoles) was dissolved in anhydrous CH_3OH (12 mL) and anhydrous K_2CO_3 (86 mg, 0.62 mmoles) was added. The mixture was stirred for 3 h at room temperature under argon atmosphere. After completion (according to TLC analysis) the reaction mixture was filtered over a Celite pad and washed with aliquots of CH_3OH. The combine filtrates were concentrated under reduced pressure obtaining colorless oil. This compound was used without further purification in the next reaction step. For structural characterization an aliquot of crude product **7** was suspended in methyl *tert*-butyl ether and stirred overnight to obtain compound **7** as an off-white solid.; ν_{max} (KBr) 3342 (OH), 2926, 1635, 1558, 1386, 1078 cm^{-1}; δ_H (300 MHz, H_2O) 5.32 (1H, s, H-1), 4.55 (1H, d, *J* 5.1 Hz, H- 5), 4.43 (1H, d, *J* 8.1 Hz, H-6*endo*), 4.30 (1H, s, H-4), 4.11 (1H, d, *J* 6.7 Hz, H-2), 3.66 (1H, dd, *J* 5.1, 7.7 Hz, H-6*exo*), 3.36 (1H, d, *J* 6.7 Hz, H-3), 3.27 (1H, s, OH), 1.83 (1H, s, OH); δ_C (75 MHz, H_2O) 101.2 (C-1), 76.8 (C-5), 71.3 (C-4), 67.1 (C-2), 65.6 (C-6), 56.8 (C-3), HRMS (EI, MK^+): MK^+, found 393.00692. $C_{12}H_{18}KO_8S_2^+$ calcd 393.00747.

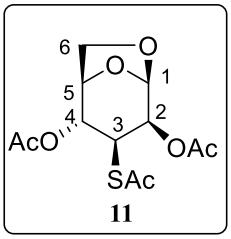
*Synthesis of Acetilated disulfide **8***



8

Crude product **7** (88 mg) was dissolved in anhydrous CH_2Cl_2 (1.8 mL) and the distilled pyridine (0.8 mL) was added at room temperature. Ac_2O (0.4 mL, 3.57 mmoles) and DMAP (11 mg, 0.09 mmoles) were added and the solution was stirred overnight under argon atmosphere. The mixture was treated with HCl 50% (1 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4 anh.) and concentrated under reduce pressure. The resulting residue was purified by flash chromatography to afford compound **8** (71 mg, 0.20 mmoles, 55% two steps) as a white crystalline solid.; **8**: R_f (60% hexane/ EtOAc) 0.32; $[\alpha]_D^{28}$+134.8 (*c* 1.1, $CDCl_3$); mp 199 – 200º C (CH_2Cl_2/hexane); ν_{max} (KBr) 1734 (C=O), 1375, 1361, 1247, 1236, 1153 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.41 (1H, bs, H-1), 5.24 (1H, s, H-4), 4.88 (1H, dd, *J* 1.3, 7.0 Hz, H-2), 4.63 (1H, d, *J* 5.1 Hz, H-5), 4.49 (1H, d, *J* 8.0 Hz, H-6*endo*), 3.77 (1H, dd, *J* 5.1, 8.0 Hz, H-6*exo*), 3.59 (1H, d, *J* 7.0, 8.0 Hz, H-3), 2.17 (3H, s, $COC\underline{H}_3$), 2.08 (3H, s, $COC\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 170.2 ($\underline{C}OCH3$), 170.1 ($\underline{C}OCH3$), 99.6 (C-1), 75.1 (C-5), 72.4 (C-4), 70.4 (C-2), 65.9 (C-6), 48.6 (C-3), 21.1 ($CO\underline{C}H_3$), 20.5 ($CO\underline{C}H_3$); HRMS (EI, MNa^+): MNa^+, found 545.07622. $C_{20}H_{26}NaO_{12}S_2^+$ calcd 545.07579.

*Synthesis of Triacetate **11***

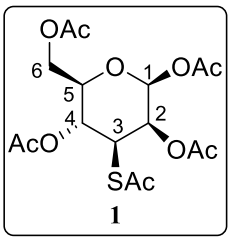


11

Compound **8** (25 mg, 0.05 mmoles) was dissolved in anhydrous THF (6 mL) and cooled to 0º C. $LiAlH_4$ (18 mg, 0.50 mmoles) was added and the resulting suspension was stirred at room temperature for 16 h. The mixture was cooled to 0º C, diluted with EtOAc (2.5 mL) and the excess of reducing agent was destroyed by addition of methanol (2.5 mL). Finally, the mixture was neutralized with AcOH and solvents were concentrated under reduced pressure. The resulting residue was dissolved in anhydrous pyridine (0.7 mL) and Ac_2O (0.7 mL) and catalytic amount of DMAP was added. The mixture was stirred for 16 h at room temperature. The reaction was concentrated and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (2 x 10 mL). The organic layer was dried (Na_2SO_4 anh.)

and the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography to give compound **11** (17.6 mg, 0.06 mmoles, 57% two steps) as a colorless oil; R_f (60% hexane/EtOAc) 0.39; $[\alpha]_D^{26}$-85.8 (*c* 0.6, $CDCl_3$); ν_{max} (liquid film) 1735 (C=O), 1691, 1373, 1217, 1062 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.45 (1H, s, H-1), 5.15 (1H, dd, *J* 1.6, 7.1 Hz, H-2), 4.86 (1H, bs, H-4), 4.57 (1H, d, *J* 5.4 Hz, H-5), 4.29 (1H, d, *J* 7.1 Hz, H-3), 4.27 (1H, d, *J* 8.4 Hz, H-6*endo*), 3.78 (1H, dd, *J* 5.4, 8.4 Hz, H-6*exo*), 2.35 (3H, s, $COCH_3$), 2.17 (3H, s, $COCH_3$), 2.10 (3H, s, $COCH_3$); δ_C (75 MHz, $CDCl_3$) 192.9 ($COCH_3$), 168.8 ($COCH_3$), 168.2 ($COCH_3$), 98.8 (C-1), 73.7 (C-5), 73.1 (C-4), 67.5 (C-2), 64.9 (C-6), 41.1 (C-3), 29.2 ($COCH_3$), 20.1 ($COCH_3$), 19.6 ($COCH_3$); HRMS (EI, MNa^+): MNa^+, found 327.04975. $C_{12}H_{16}NaO_7S^+$ calcd 327.05089.

*Synthesis of Thiomannopyranoside **1***



1

Compound **11** (55 mg, 0.18 mmoles) was dissolved in Ac_2O (1.8 mL) under argon atmosphere. The solution was cooled at 0 ºC and 2 drops of TMSOTf were added. The mixture was stirred for 1 h at room temperature. Then, the reaction mixture was treated with a saturated solution of $NaHCO_3$ (1 mL) and extracted with EtOAc (3 x 10 mL). The combine organic layers were dried (Na_2SO_4 anh.) and the solvent was concentrated under reduce pressure. The residue was purified by flash chromatography to give **1** (57.6 mg, 0.16 mmoles, 88%) as a colorless oil; R_f (60% hexane/EtOAc) 0.6; $[a]_D^{22}$+28.4 (*c* 1.1, $CDCl_3$); ν_{max} (liquid film) 1749 (C=O), 1371, 1217 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.01 (1H, d, *J* 1.7 Hz, H-1), 5.17 (1H, dd, *J* 9.7, 11.4 Hz, H-4), 5.00 (1H, dd, *J* 1.7, 3.0 Hz, H-2), 4.26 (1H, dd, *J* 3.0, 11.4 Hz, H-3), 4.22 (1H, m, H-6), 4.08 (1H, m, H-5), 4.05 (1H, m, H-6), 2.31 (3H, s, $COCH_3$), 2.17 (3H, s, $COCH_3$), 2.13 (3H, s, $COCH_3$), 2.05 (3H, s, $COCH_3$); 2.01 (3H, s, $COCH_3$); δ_C (75 MHz, $CDCl_3$) 193.4 ($COCH_3$), 170.6 ($COCH_3$), 169.6 (2 $COCH_3$), 168.2 ($COCH_3$), 89.6 (C-1), 71.3 (C-5), 70.8 (C-2), 65.6 (C-4), 62.3 (C-6), 43.7 (C-3), 30.5 ($COCH_3$), 20.9 ($COCH_3$), 20.7 ($COCH_3$), 20.6 ($COCH_3$), 20.5 ($COCH_3$); HRMS (EI, MNa^+): MNa^+, found 429.08385. $C_{16}H_{22}NaO_{10}S^+$ calcd 429.08259.

Selected spectra

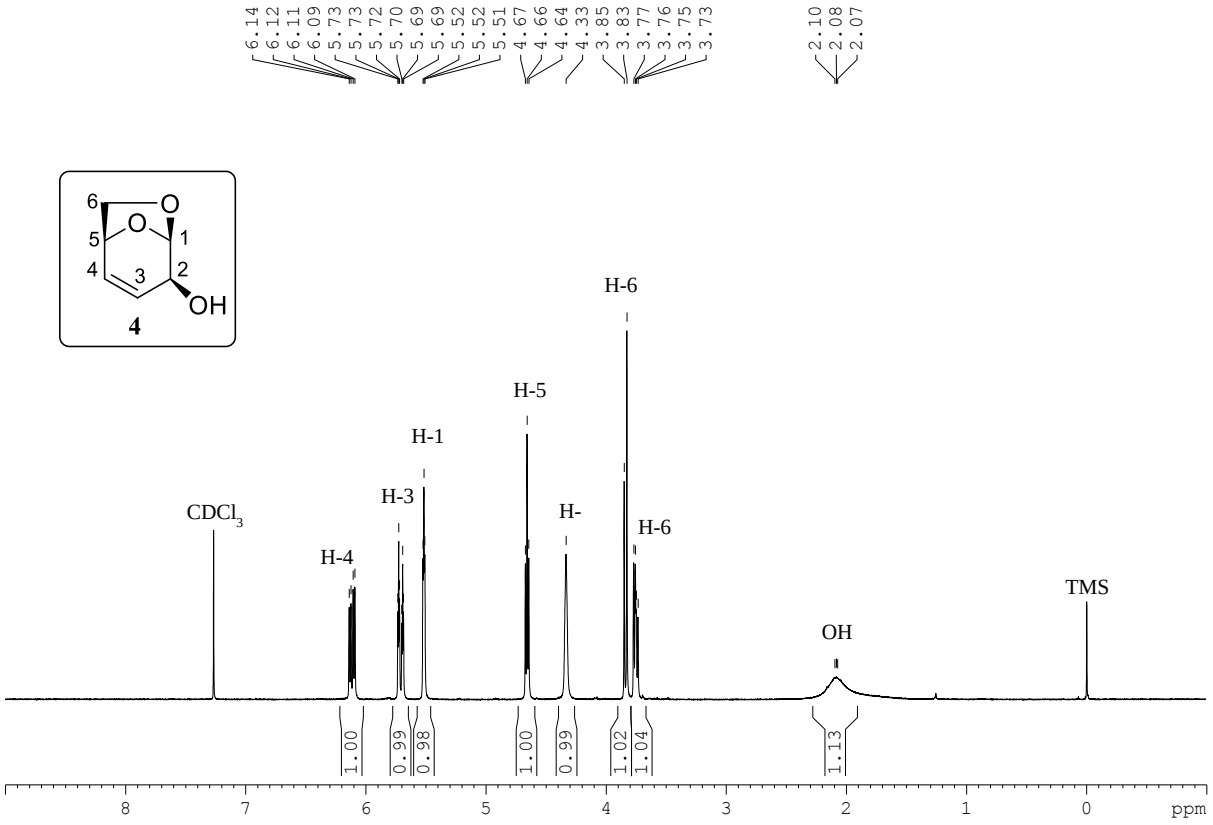


Figure S-1: ^{1}H spectrum of **4** in $CDCl_3$.

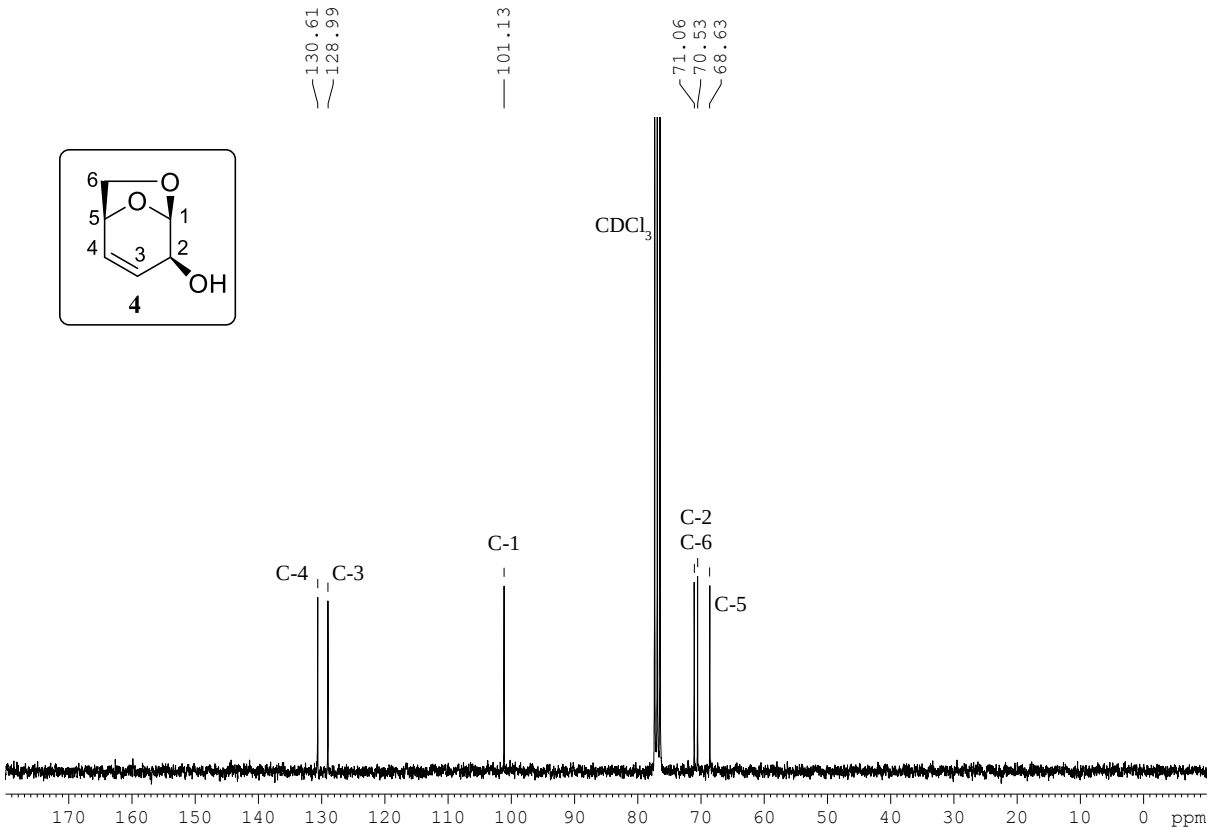


Figure S-2: ^{13}C spectrum of **4** in $CDCl_3$.

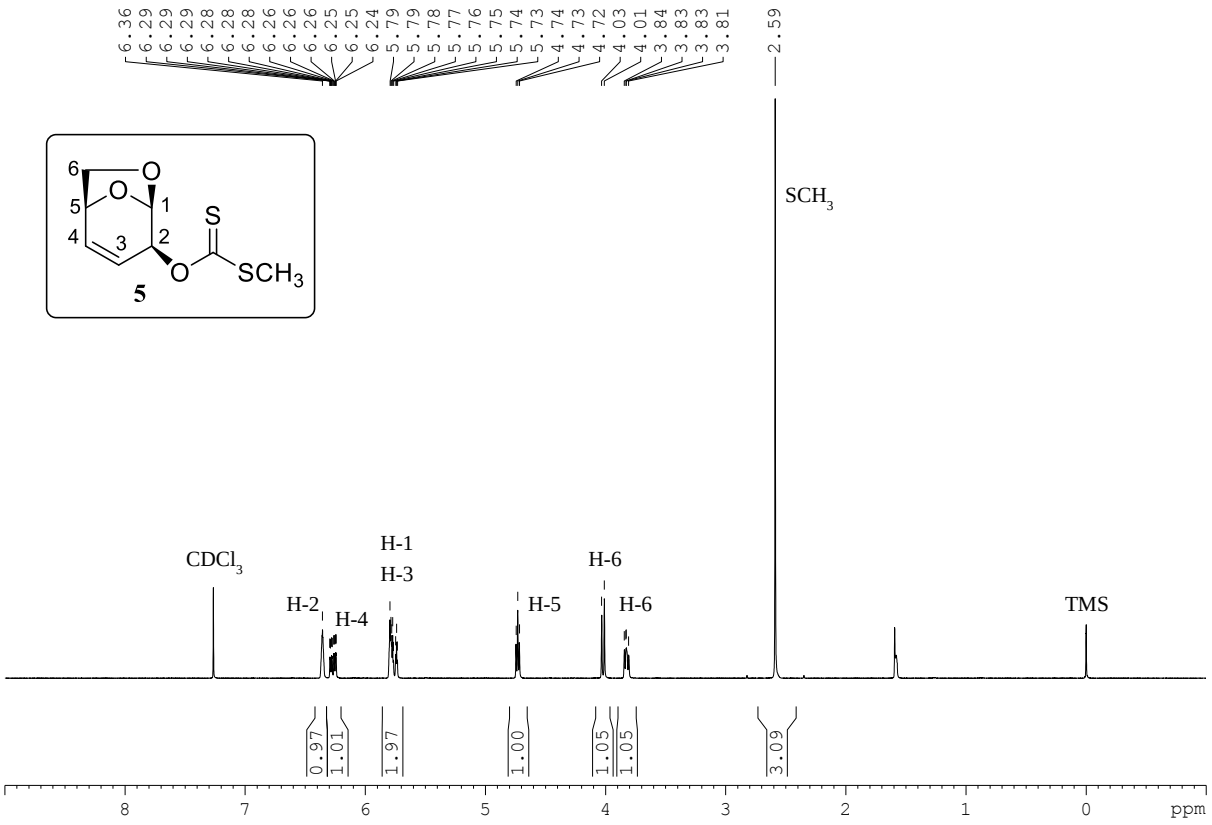


Figure S-3: ^{1}H spectrum of **5** in $CDCl_3$.

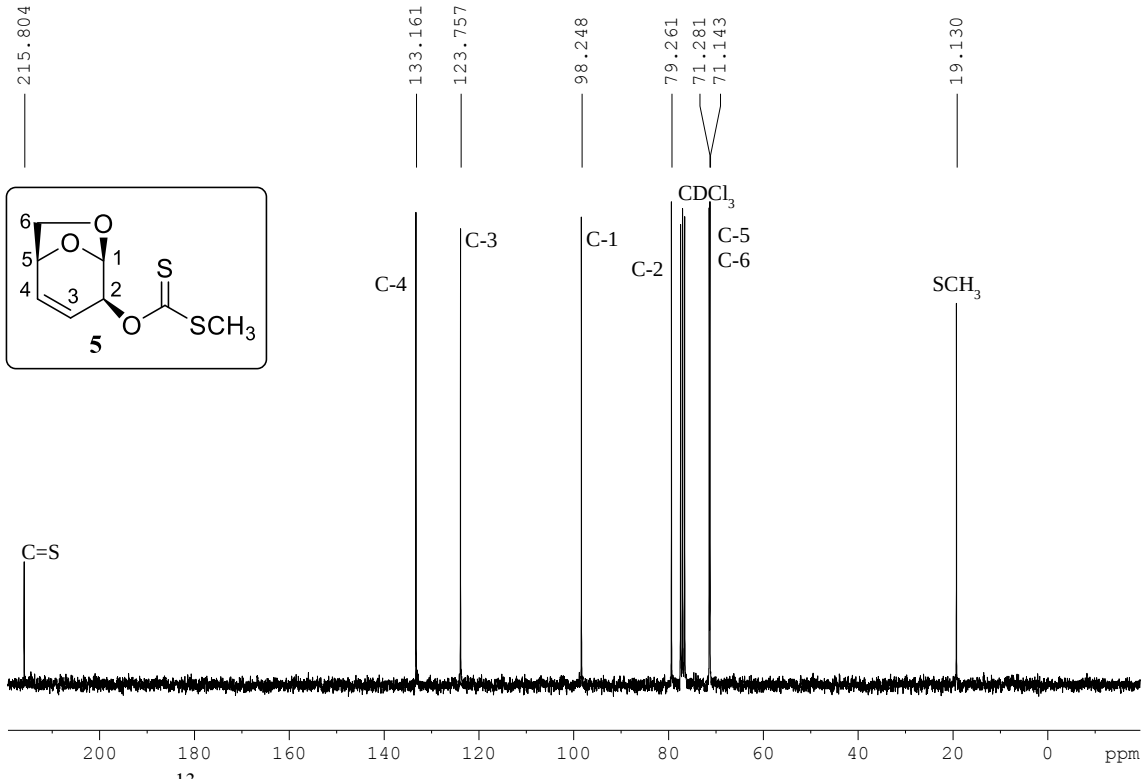


Figure S-4: ^{13}C spectrum of **5** in $CDCl_3$.

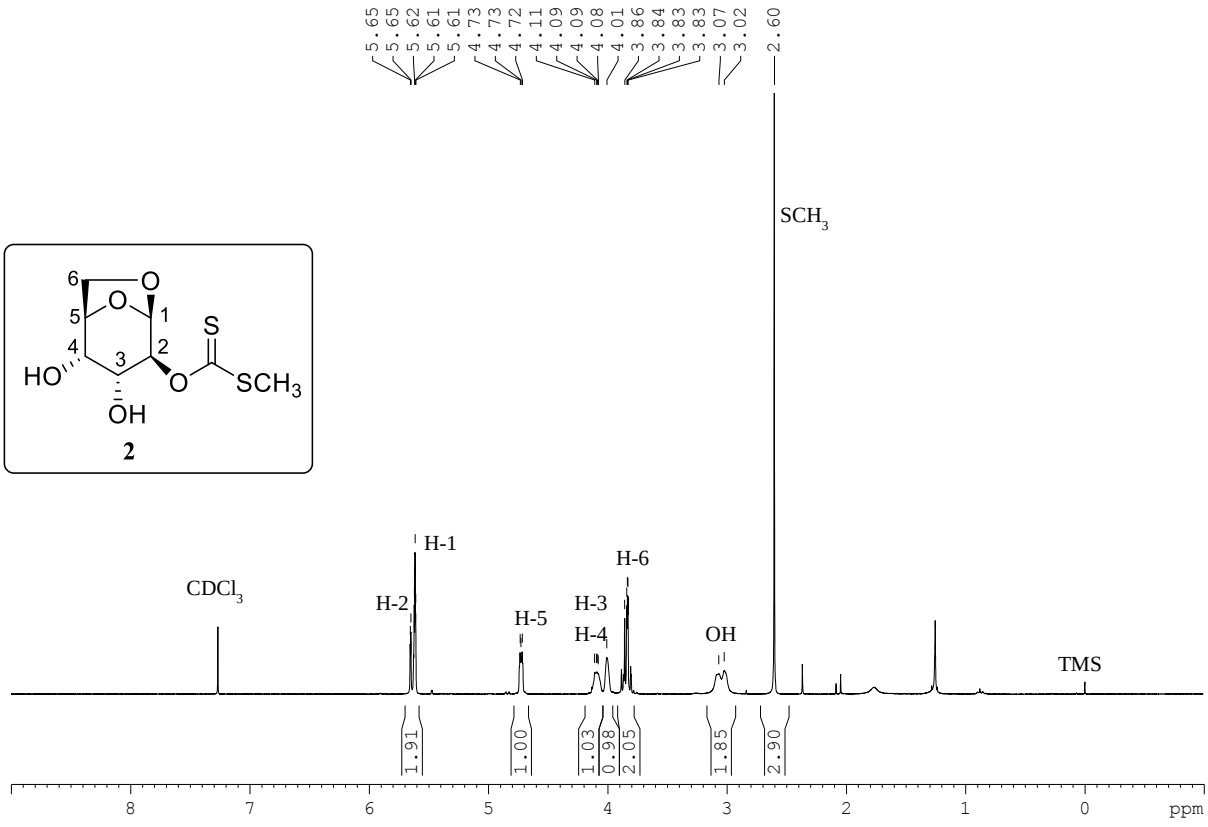


Figure S-5: ^{1}H spectrum of **2** in $CDCl_3$.

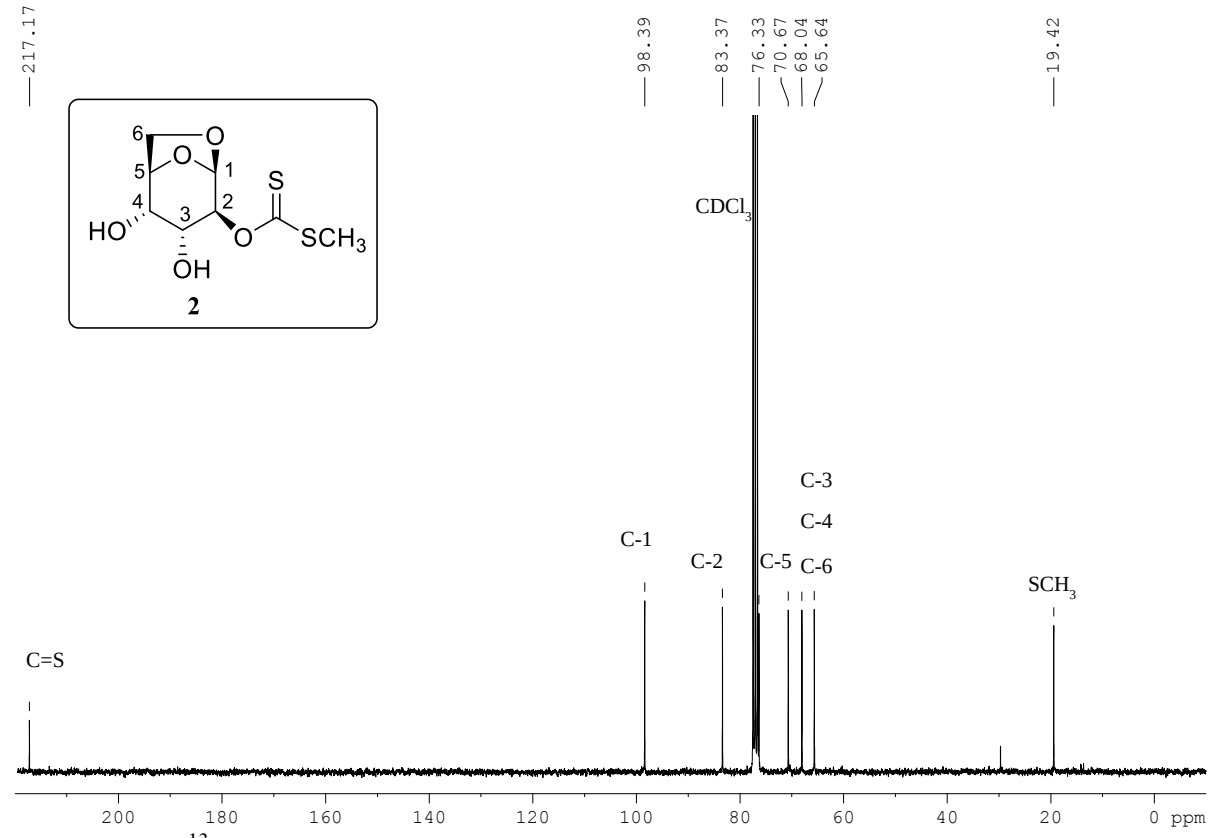


Figure S-6: ^{13}C spectrum of **2** in $CDCl_3$.

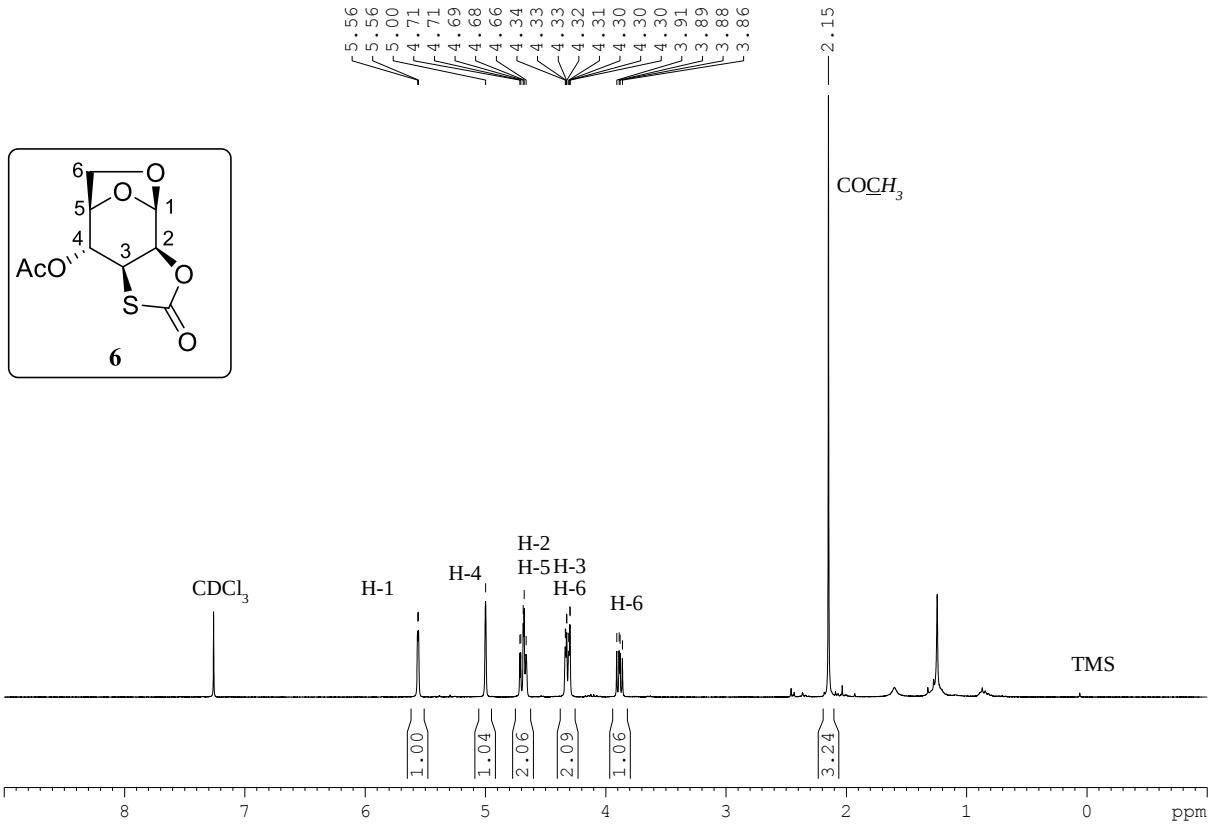


Figure S-7: ^{1}H spectrum of **6** in $CDCl_3$.

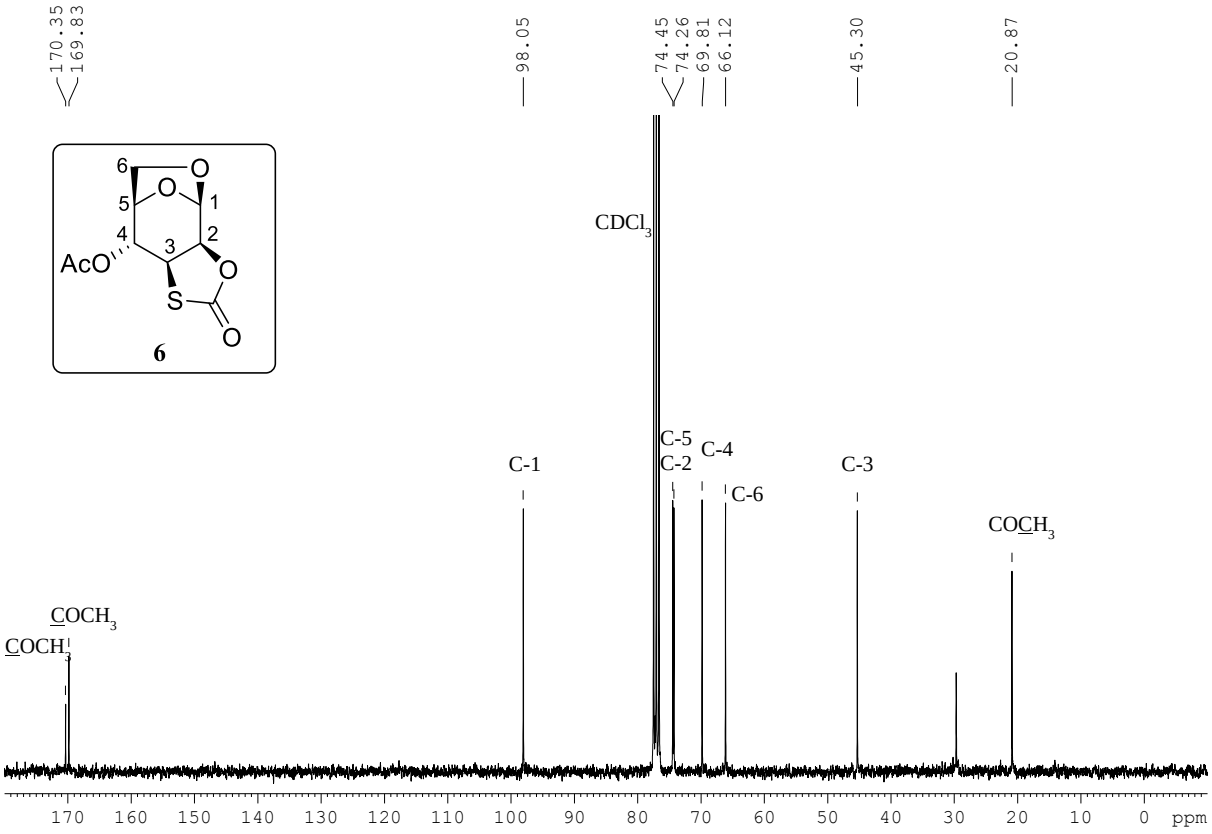


Figure S-8: ^{13}C spectrum of **6** in $CDCl_3$.

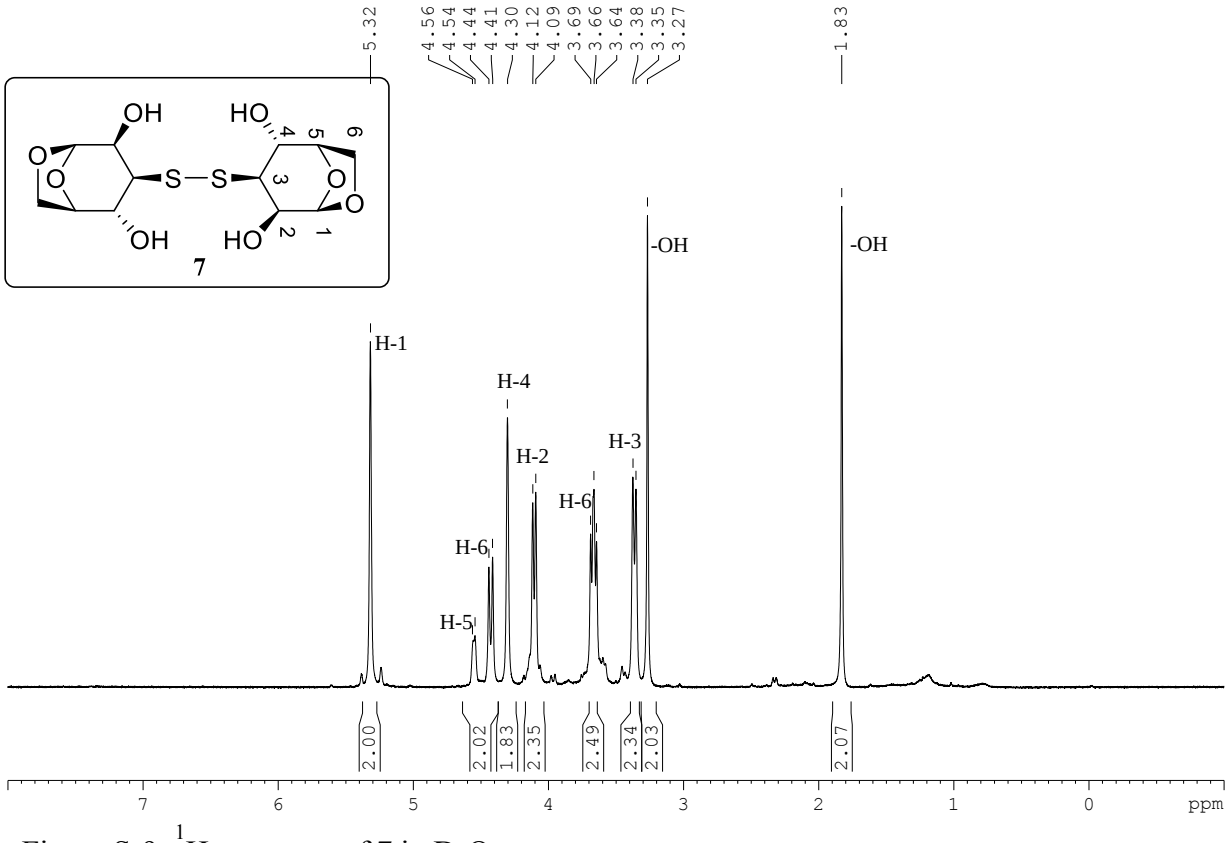


Figure S-9: ^{1}H spectrum of **7** in D_2O.

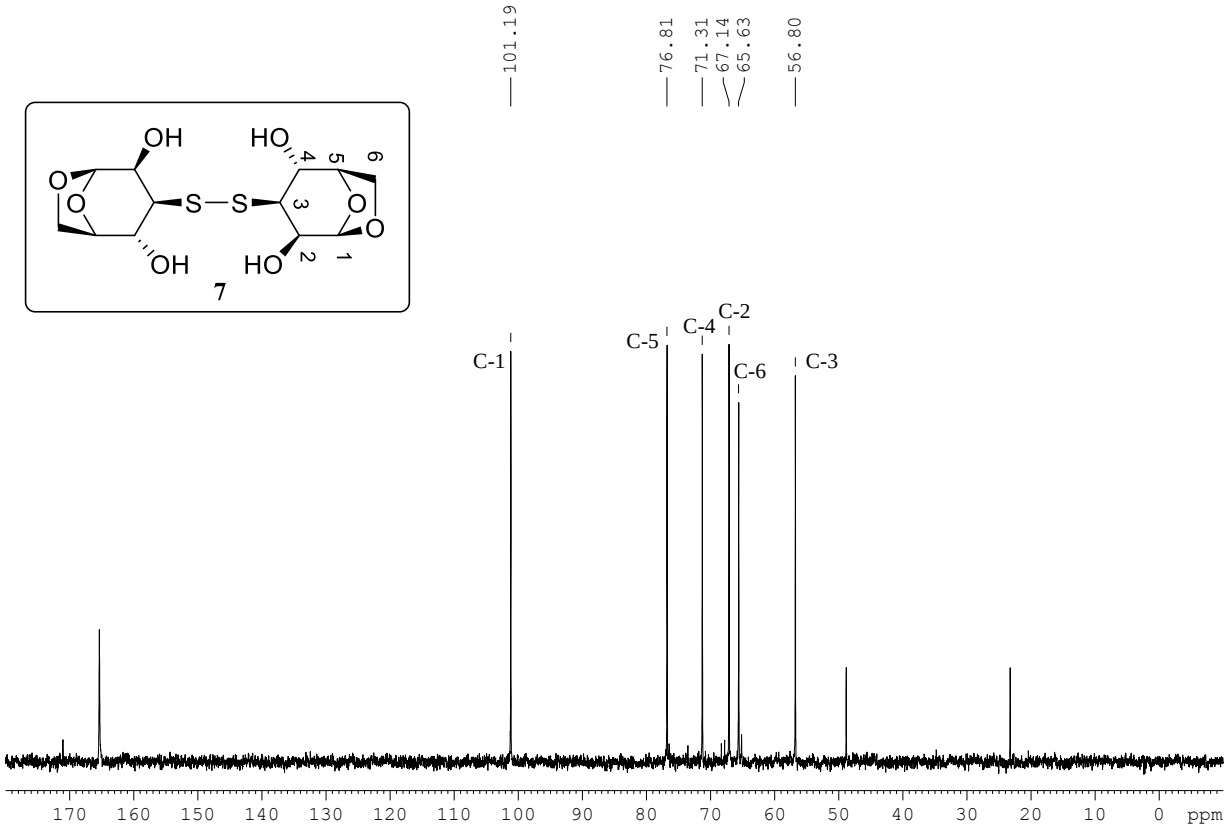


Figure S-10: ^{13}C spectrum of **7** in D_2O.

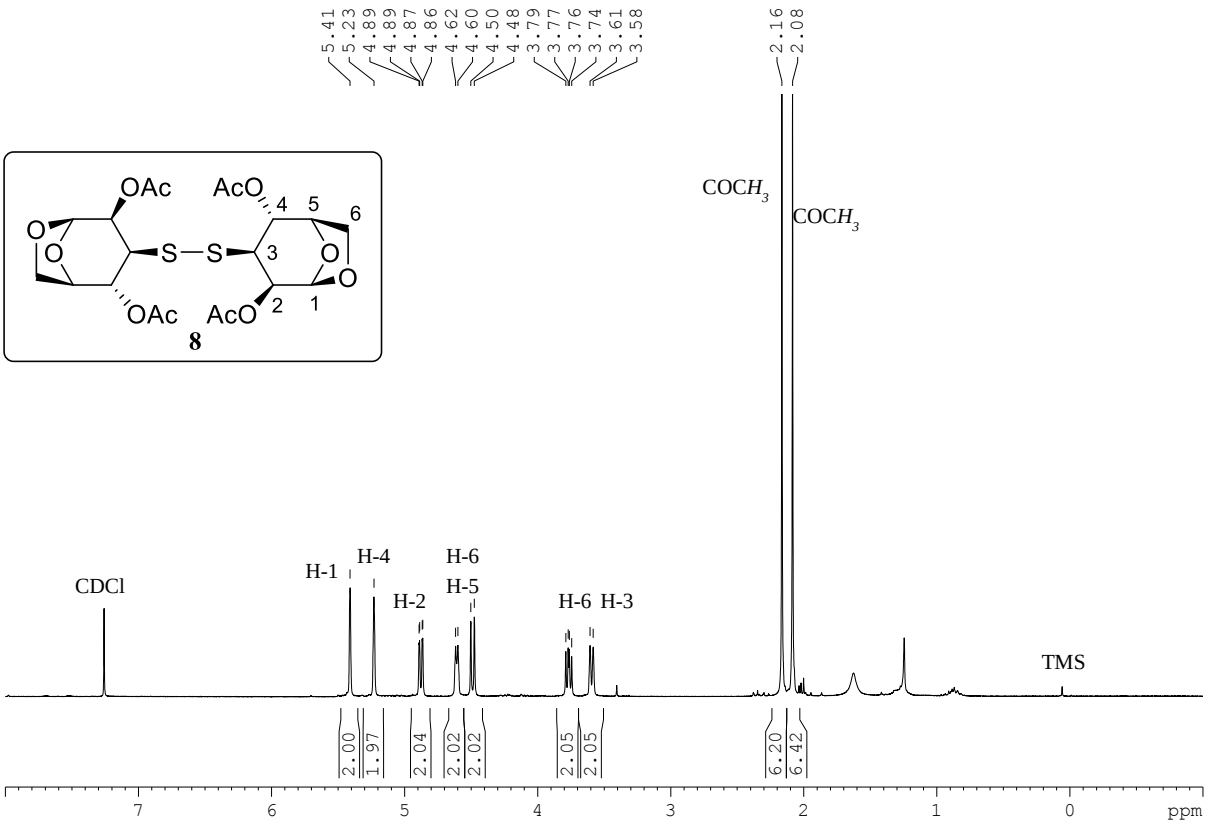


Figure S-11: ^{1}H spectrum of **8** in $CDCl_3$.

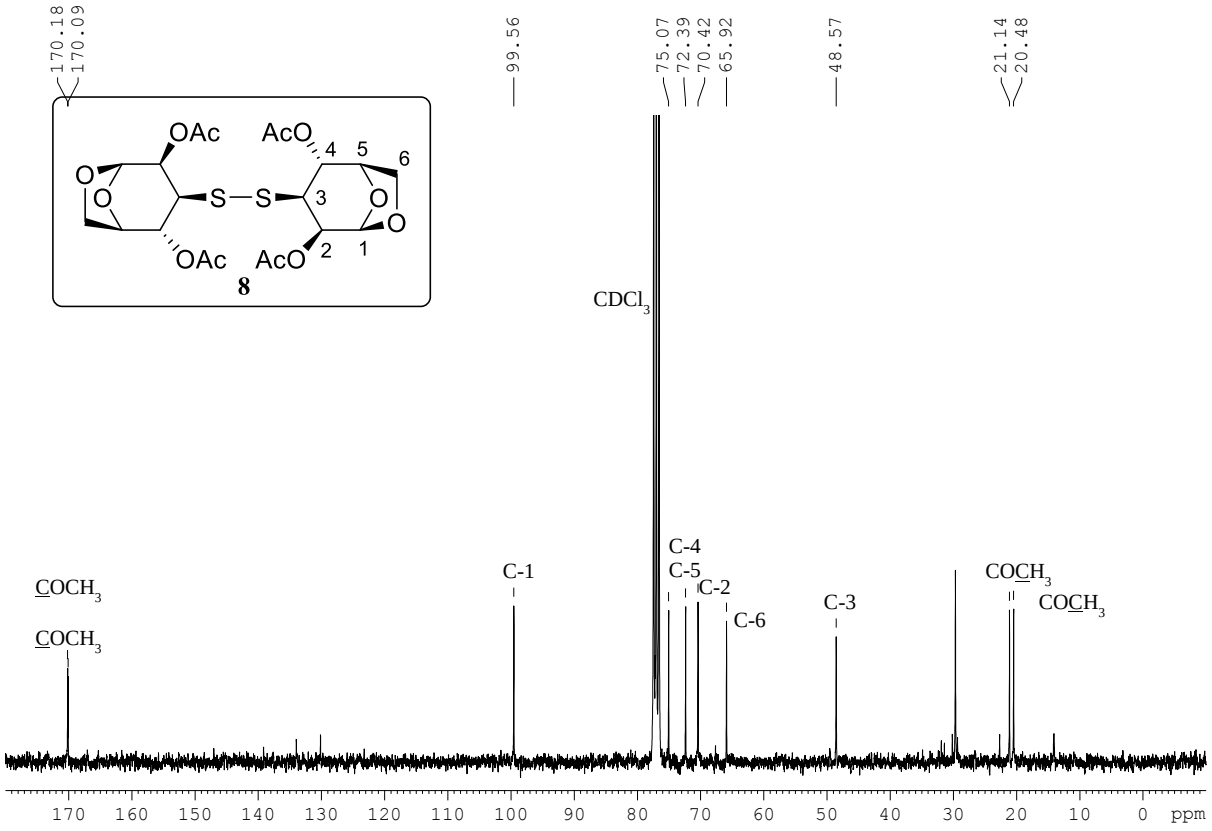


Figure S-12: ^{13}C spectrum of **8** in $CDCl_3$.

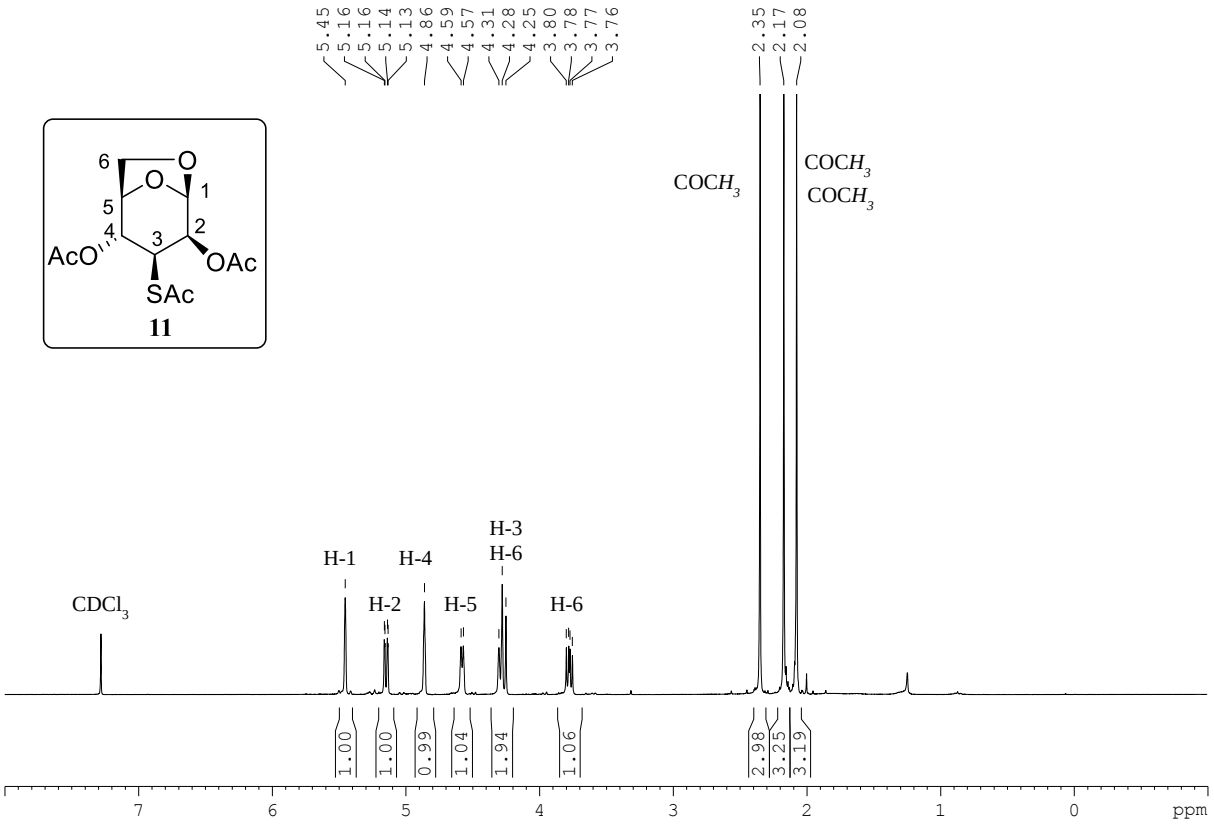


Figure S-13: ^{1}H spectrum of **11** in $CDCl_3$.

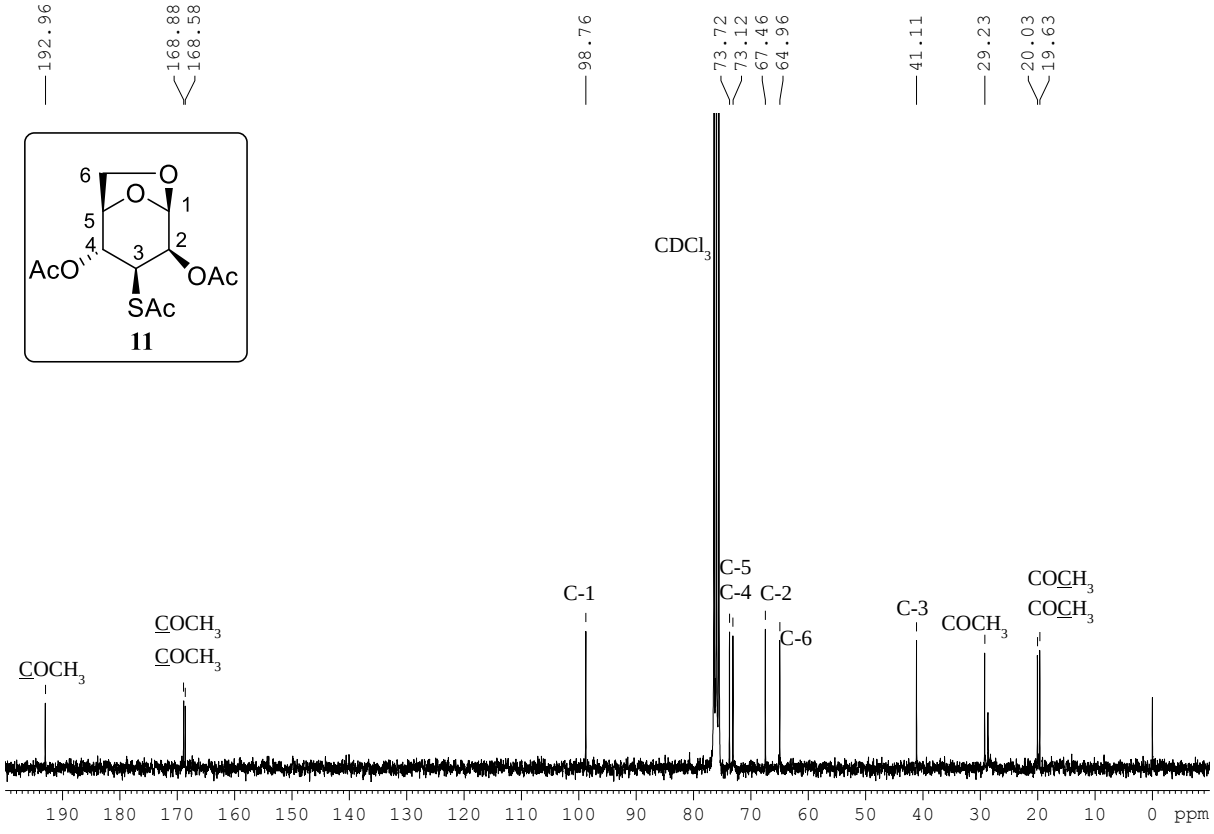


Figure S-14: ^{13}C spectrum of **11** in $CDCl_3$.

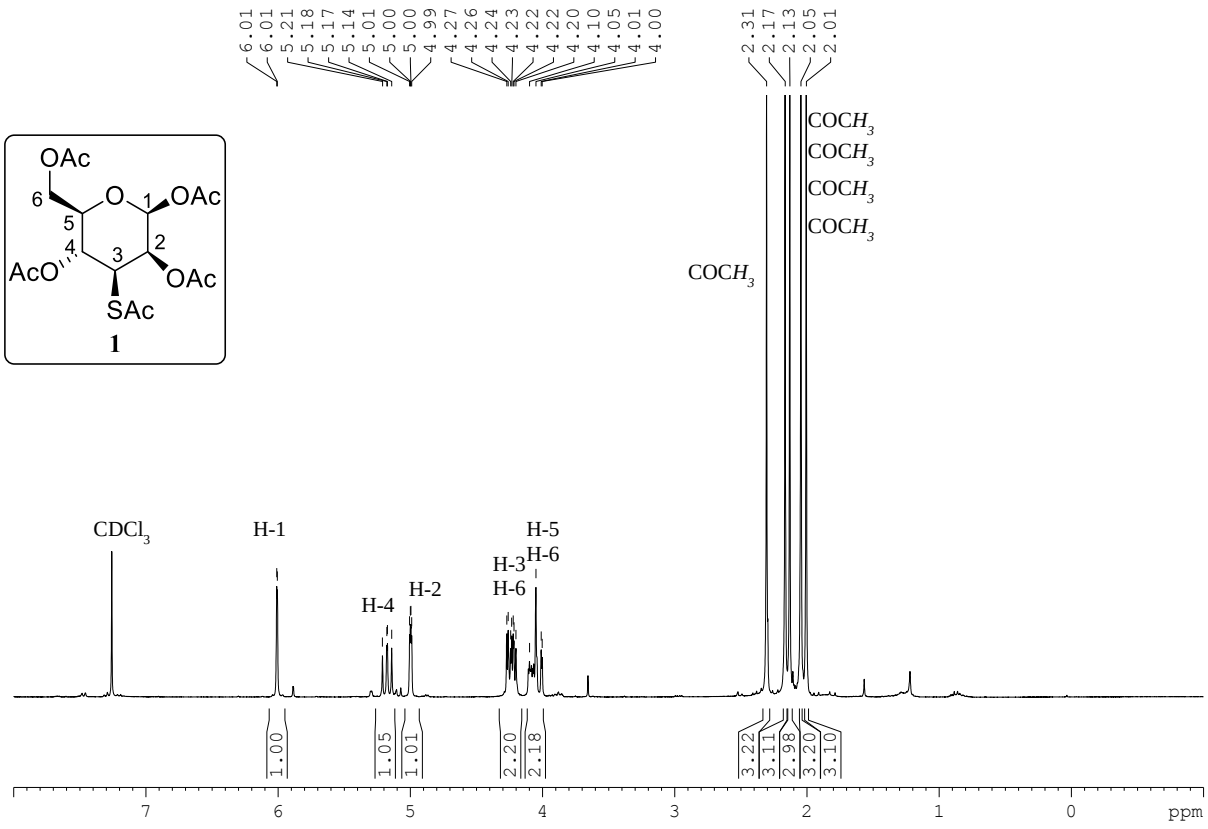


Figure S-15: ^{1}H spectrum of **1** in $CDCl_3$.

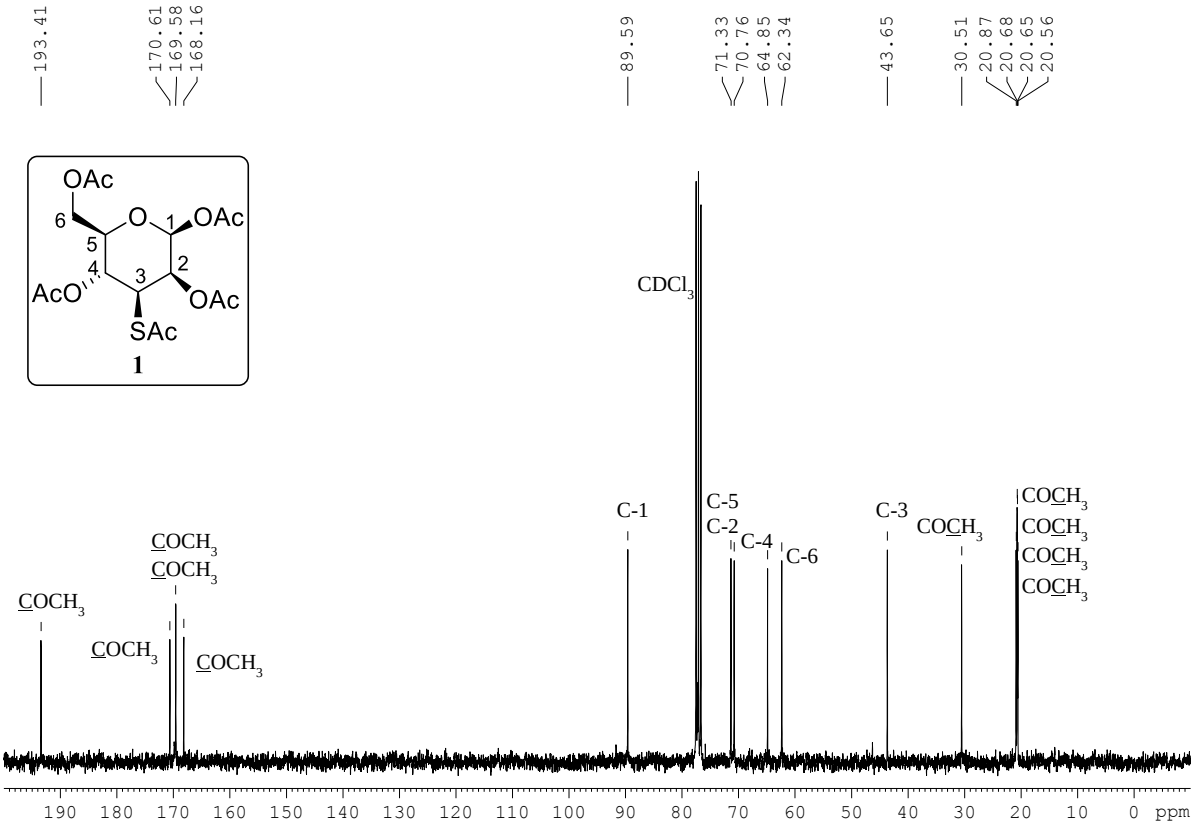


Figure S-16: ^{13}C spectrum of **1** in $CDCl_3$.