

Stereoselective Synthesis of a Dioxo-bicyclo[3.2.1]octane SGLT2 Inhibitor

Vincent Mascitti* and Cathy Prévaille

Pfizer Global Research and Development, Groton, CT 06340, USA

Supporting Information

Materials and methods	S1
Experimental part	S2
Copies of NMR spectra (¹H and ¹³C)	S9
X-ray data for compound 5	S25

Materials and methods

NMR spectra were recorded on a Varian Unity™ 400 (available from Varian Inc., Palo Alto, CA) at room temperature at 400 MHz for proton and 100 MHz for carbon. Chemical shifts are expressed in parts per million (δ) relative to residual solvent as an internal reference (for methanol-d δ H = 3.29 ppm and δ C = 47.8 ppm). The peak shapes are denoted as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; br.s., broad singlet. Electrospray ionization mass spectra (ES) were obtained on a Waters™ ZMD instrument (carrier gas: nitrogen; solvent A: water /0.01% formic acid, solvent B: acetonitrile/0.005% formic acid; available from Waters Corp., Milford, MA). High resolution mass spectra (HRMS) were obtained on an Agilent™ Model 6210 time of flight. Where the intensity of single chlorine or single bromine-containing ions are

described, the expected intensity ratio was observed (approximately 3:1 for $^{35}\text{Cl}/^{37}\text{Cl}$ -containing ions and 1:1 for $^{79}\text{Br}/^{81}\text{Br}$ -containing ions) and the intensity of only the lower mass ion is given. In some cases only representative ^1H NMR peaks are given.

Column chromatography was performed with a Combiflash[®] Companion[®] from Teledyne[™] Isco[™]; Redisep Rf silica (from Teledyne[™] Isco[™]) under low nitrogen pressure were used.

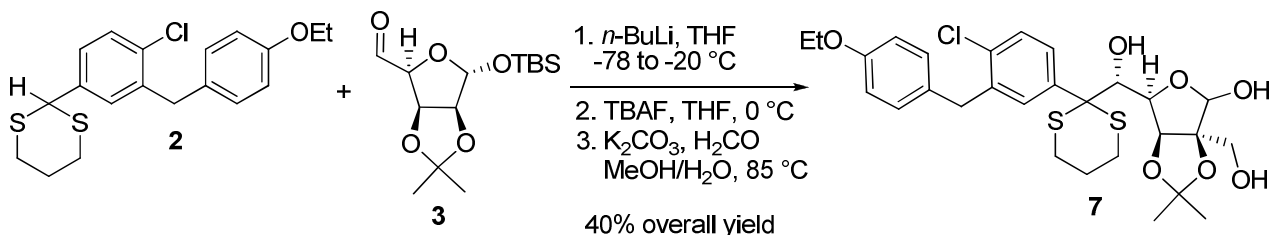
Except where otherwise noted, all reactions were run under an inert atmosphere of nitrogen gas using anhydrous solvents. Also, except where otherwise noted, all reactions were run at room temperature ($\sim 23^\circ\text{C}$).

Optical rotation was measured with a Perkin-Elmer[®] Polarimeter 343, Serial No. 9506 at 20°C .

R_t (retention time).

Experimental part

(3aS,6aS)-6-((R)-(2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1,3-dithian-2-yl)(hydroxymethyl)-3a-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (7)



To a solution of 2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1,3-dithiane (**2**¹, 6.70 g, 18.4 mmol) in THF (80 mL) cooled at -78 °C was added drop wise a solution of *n*-BuLi (2.5M in hexane, 7.56 mL, 19 mmol) and the reaction mixture was stirred at this temperature for 1.25 hours. The anion was then cannulated over 1.5 hours to a solution of aldehyde **3**² (5.55 g, 18.4 mmol) in THF (60 mL) cooled at -78 °C. The resulting solution was stirred at -78 °C for 1 hour and then warmed up to -20 °C over 2 hours before being quenched with a saturated aqueous solution of NH₄Cl. The mixture was diluted with CH₂Cl₂ and the aqueous phase was extracted 3 times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated to give intermediate **4**. The crude material was used in the next step without further purification. For characterization purposes, an aliquot was taken and purified by flash chromatography over silica gel (0% to 30% EtOAc in heptane) to give **4**. MS (LCMS) 689.4 (M+Na⁺; positive mode). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.08 (s, 3 H), 0.08 (s, 3 H), 0.86 (s, 9 H), 1.22 (s, 3 H), 1.38 (t, *J* = 7.0 Hz, 3 H), 1.41 (s, 3 H), 1.86 - 1.95 (m, 2 H), 2.55 - 2.74 (m, 4 H), 3.08 (d, *J* = 3.7 Hz, 1 H), 3.99 (q, *J* = 7.0 Hz, 2 H), 4.04 (2 H), 4.25 - 4.29 (m, 2 H), 4.41 (d, *J* = 5.8 Hz, 1 H), 4.45 (dd, *J* = 5.8 and 3.3 Hz, 1 H), 5.26 (s, 1 H), 6.78 - 6.82 (m, 2 H), 7.09 - 7.12 (m, 2 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.80 (dd, *J* = 8.6 and 2.5 Hz, 1 H), 7.92 (d, *J* = 2.5 Hz, 1 H). ¹³C NMR (100 MHz, CHLOROFORM-*d*) δ ppm -5.3, -4.2, 15.1, 18.1, 24.6, 25.2, 25.8 (3C), 26.1, 27.2, 27.3, 38.8, 63.6, 63.9, 75.1, 76.7, 81.4, 86.8, 100.9, 112.6, 114.6 (2C), 129.6, 129.8, 129.9 (2C), 131.9, 133.5 (2C), 138.1, 139.0, 157.5.

The above crude material (11.3 g, 17 mmol) was dissolved in 170 mL of THF, cooled to 0 °C and a solution of TBAF 1M in THF (34 mL, 34 mmol) was added. The reaction

¹ For the synthesis and X-ray crystal structure of **2** see: Samas, B.; Préville, C.; Thuma, B.; Mascitti, V. *Acta Cryst.* **2010**, E66, o1386.

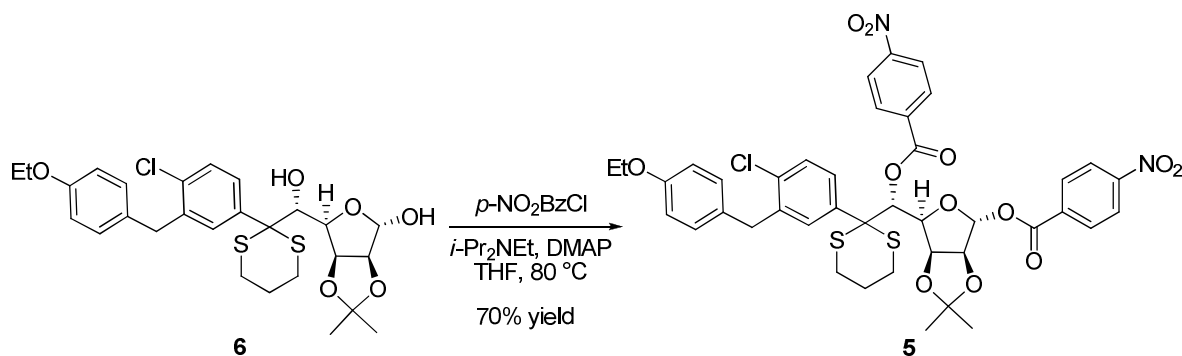
² Brewster, K.; Harrison, J. M.; Inch, T. D.; Williams, N. J. *Chem. Soc. Perkin Trans. I* **1987**, 21.

mixture was stirred at this temperature for 1 hour and then the reaction was quenched with the addition of a saturated aqueous solution of NH_4Cl . CH_2Cl_2 was added and the aqueous phase was extracted twice with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered and concentrated. The crude mixture was used in the next step without further purification. For characterization purposes, an aliquot was taken and purified by flash chromatography over silica gel (20% to 60% EtOAc in heptane) to give **6**. MS (LCMS) 575.2 ($\text{M}+\text{Na}^+$; positive mode). HRMS calculated for $\text{C}_{27}\text{H}_{33}\text{O}_6\text{NaS}_2\text{Cl}$ ($\text{M}+\text{Na}^+$) 575.1299 found 575.1306; $[\alpha]_{\text{D}}$ -0.8 (c 0.5, CHCl_3); ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 1.22 (s, 3 H), 1.37 (t, J = 7.0 Hz, 3 H), 1.39 (s, 3 H), 1.86 - 1.96 (m, 3 H), 2.55 - 2.74 (m, 4 H), 3.08 (d, J = 4.1 Hz, 1 H), 3.94 - 4.00 (m, 3 H), 4.12 (d, J = 15.0 Hz, 1 H), 4.30 - 4.36 (m, 2 H), 4.41 (d, J = 5.8 Hz, 1 H), 4.52 (dd, J = 5.8 and 3.6 Hz, 1 H), 5.16 (d, J = 2.3 Hz, 1 H), 6.76 - 6.82 (m, 2 H), 7.06 - 7.11 (m, 2 H), 7.36 (d, J = 8.4 Hz, 1 H), 7.83 (dd, J = 8.4 and 2.4 Hz, 1 H), 7.86 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, $\text{CHLOROFORM-}d$) δ ppm 15.0, 24.5, 25.1, 26.1, 27.2, 27.3, 38.6, 63.7, 63.8, 75.2, 76.1, 81.8, 84.9, 100.7, 112.8, 114.7 (2C), 129.6, 129.8 (2C), 130.2, 131.9, 133.5, 133.6, 137.6, 138.8, 157.7.

To a solution of the previous crude material (9.4 g, 17 mmol) dissolved in MeOH (90 mL) was added K_2CO_3 (11.9 g, 86.1 mmol) followed by a solution of 37% formaldehyde in water (52 mL, 690 mmol). The flask was flushed with N_2 and the reaction mixture was heated at 85 °C for 17 hours. The reaction mixture was diluted with MeOH cooled to 0°C and neutralized by the addition of 86 mL of 1M HCl aqueous solution. The solvent was evaporated and the residue was taken up in CH_2Cl_2 and water. The aqueous phase was extracted 3 times with CH_2Cl_2 and the combined organic layers were dried over MgSO_4 ,

filtered and concentrated. The crude product was purified by flash chromatography over silica gel (30% to 60% EtOAc in heptane) to give **7** as a white solid (α , β mixture of anomers) (4.29 g, 40% yield over 3 steps). Purity HPLC-MS: 95.2%, variable wavelength detection UV 210-450 nm range; MS (LCMS) 605.3 ($M+Na^+$; positive mode); HRMS calculated for $C_{28}H_{35}O_7NaS_2Cl$ ($M+Na^+$) 605.1404 found 605.1397. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.20 - 1.50 (m, 18 H), 1.69 (br. s., 1 H), 1.84 - 2.00 (m, 4 H), 2.48 - 2.88 (m, 11 H), 3.08 - 3.18 (1.5 H), 3.54 - 3.90 (m, 6 H), 3.92 - 4.15 (m, 8 H), 4.20 - 4.45 (m, 5 H), 4.68 (d, J = 11.1 Hz, 0.5 H), 5.20 (d, J = 2.5 Hz, 1 H), 6.75 - 6.82 (m, 4 H), 7.05 - 7.12 (m, 4 H), 7.32 - 7.38 (m, 2 H), 7.76 - 7.90 (m, 4 H). ^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 15.1 (2C), 25.0 (2C), 26.6 - 27.5 (8C), 38.7 (2C), 62.8, 63.5, 63.6, 63.7, 73.6, 74.9, 75.4, 77.2, 83.3, 85.0 (2C), 89.9, 93.4, 96.8, 103.2 (2C), 113.9, 114.1, 114.7 (4C), 129.6, 129.7, 129.8 (3C), 129.9 (2C), 130.2, 131.9, 132.1, 133.3, 133.5, 133.6, 133.7, 137.5, 138.0, 138.9, 139.1, 157.6, 157.7.

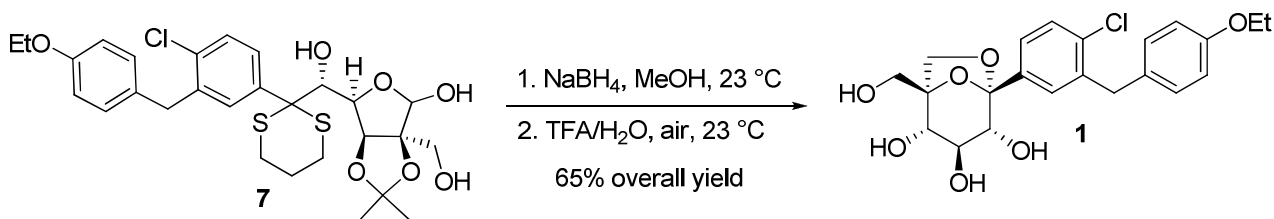
(1R)-(2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1,3-dithian-2-yl)((3aS,6R,6aS)-2,2-dimethyl-6-(4-nitrobenzoyloxy)tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl 4-nitrobenzoate (5)



To a solution of lactol **6** (14 mg, 0.025 mmol) in THF (1 mL) containing *N,N*-diisopropylethylamine (31 μ L, 0.18 mmol) and DMAP (3 mg, 0.025 mmol) was added *p*-nitrobenzoyl chloride (19 mg, 0.1 mmol) and the solution was stirred at 80 °C for 12 hours. The mixture was cooled to room temperature and water and EtOAc were added. The aqueous phase was extracted once with EtOAc and the combined organic phase was dried over MgSO_4 , filtered and concentrated. The crude product was purified by flash chromatography over silica gel (10% to 40% EtOAc in heptane) to give a yellow solid (15 mg, 70% yield). Single crystals were grown by slow evaporation from a mixture of MeCN/*i*-PrOH/EtOAc. m.p. = 177 °C. ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 1.29 (s, 6 H), 1.38 (t, J = 7.0 Hz, 3 H), 1.87 - 2.06 (m, 2 H), 2.56 - 2.77 (m, 2 H), 2.89 - 3.00 (m, 2 H), 3.89 - 4.02 (m, 4 H), 4.58 (dd, J = 5.7 and 3.4 Hz, 1 H), 4.77 (d, J = 5.8 Hz, 1 H), 4.83 (dd, J = 5.8 and 3.4 Hz, 1 H), 6.17 (d, J = 5.7 Hz, 1 H), 6.26 (s, 1 H), 6.70 - 6.75 (m, 2 H), 6.95 - 7.01 (m, 2 H), 7.19 (d, J = 8.5 Hz, 1 H), 7.72 (dd, J = 8.5 and 2.4 Hz, 1 H), 7.84 (d, J = 2.4 Hz, 1 H), 8.05 - 8.18 (m, 6 H), 8.28 - 8.34 (m, 2 H). ^{13}C NMR (100 MHz, $\text{CHLOROFORM-}d$) δ ppm 15.0, 24.6, 25.1, 26.2, 27.5, 27.8, 38.6, 60.4, 63.6, 72.8,

79.5, 81.0, 85.4, 101.5, 113.9, 114.6 (2C), 123.7 (2C), 123.9 (3C), 128.9, 129.6 (3C), 131.1 (2C), 131.3 (2C), 132.9, 134.5, 135.1, 135.5, 137.0, 139.0, 150.7, 151.0, 157.6, 163.1, 163.2.

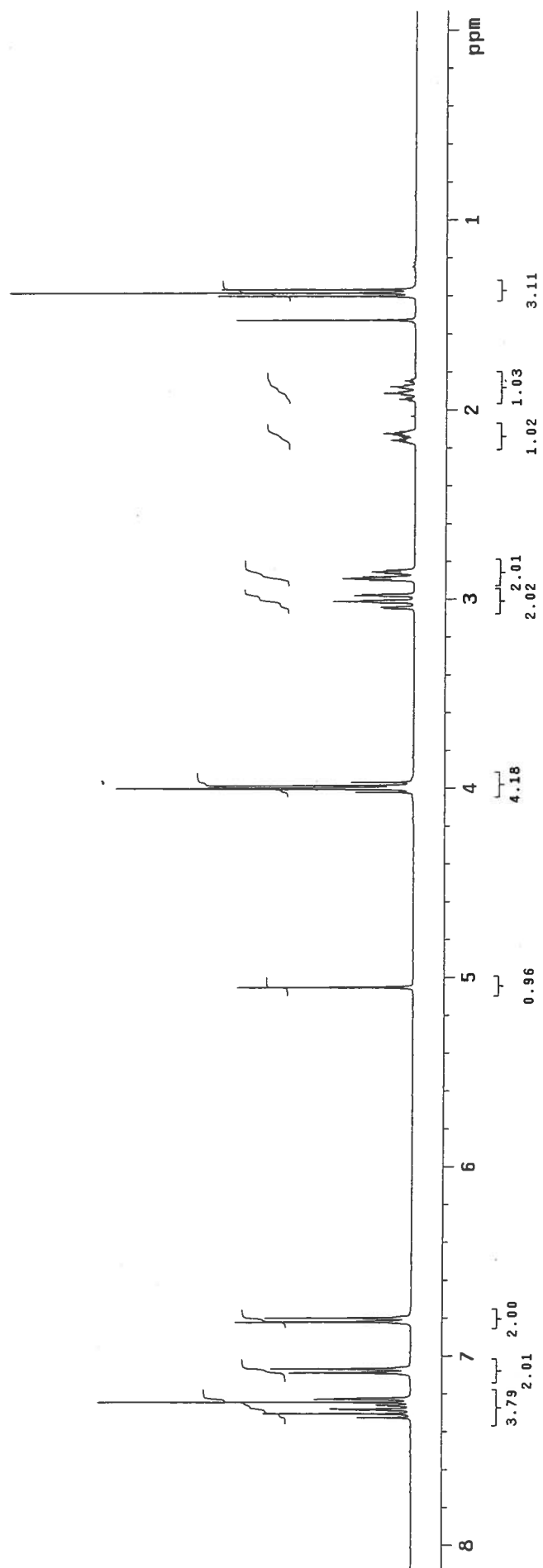
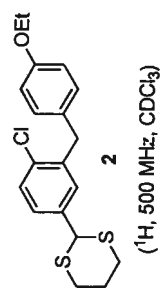
(1S,2S,3S,4R,5S)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (1)

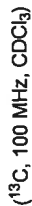


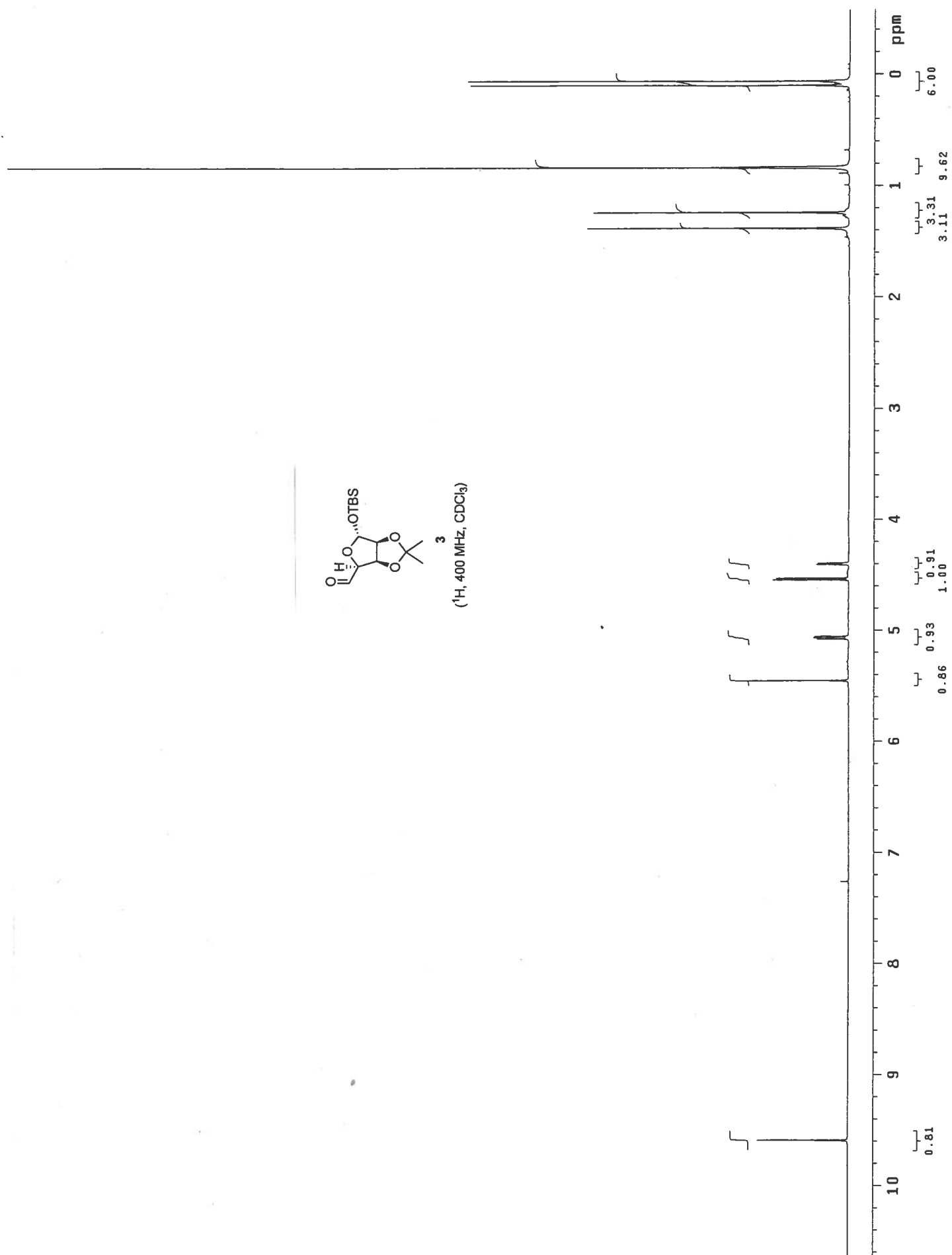
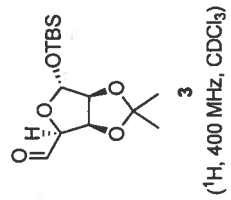
To a solution of **7** (1.01 g, 1.73 mmol) in MeOH (17 mL) cooled to 0 °C was added NaBH₄ (334 mg, 8.66 mmol). The reaction mixture was stirred at room temperature for 12 hours and a saturated aqueous solution of NH₄Cl was added. The solvent was evaporated and the residue was taken up in CH₂Cl₂ and water. The aqueous layer was extracted 3 times with CH₂Cl₂ and the combined organic layers were dried over MgSO₄, filtered and concentrated to give intermediate **8**. The crude mixture was used in the next step without further purification. For characterization purposes, an aliquot was taken and purified by flash chromatography over silica gel (30% to 80% EtOAc in heptane). MS (LCMS) 607.2 (M+Na⁺; positive mode). HRMS calculated for C₂₈H₃₇O₇NaS₂Cl (M+Na⁺) 607.1561 found 607.1547; [α]_D -1.71 (c 0.35, MeOH); ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.32 (s, 3 H), 1.37 (t, *J* = 7.0 Hz, 3 H), 1.41 (s, 3 H), 1.87 - 1.96 (m, 2 H), 2.03 (t, *J* = 6.5 Hz, 1 H), 2.54 - 2.78 (m, 4 H), 3.08 (t, *J* = 7.1 Hz, 1 H), 3.14 (d, *J* = 6.4 Hz, 1 H), 3.21(d, *J* = 4.4 Hz, 1 H), 3.40 (dd, *J* = 11.8 and 7.2 Hz, 1 H),

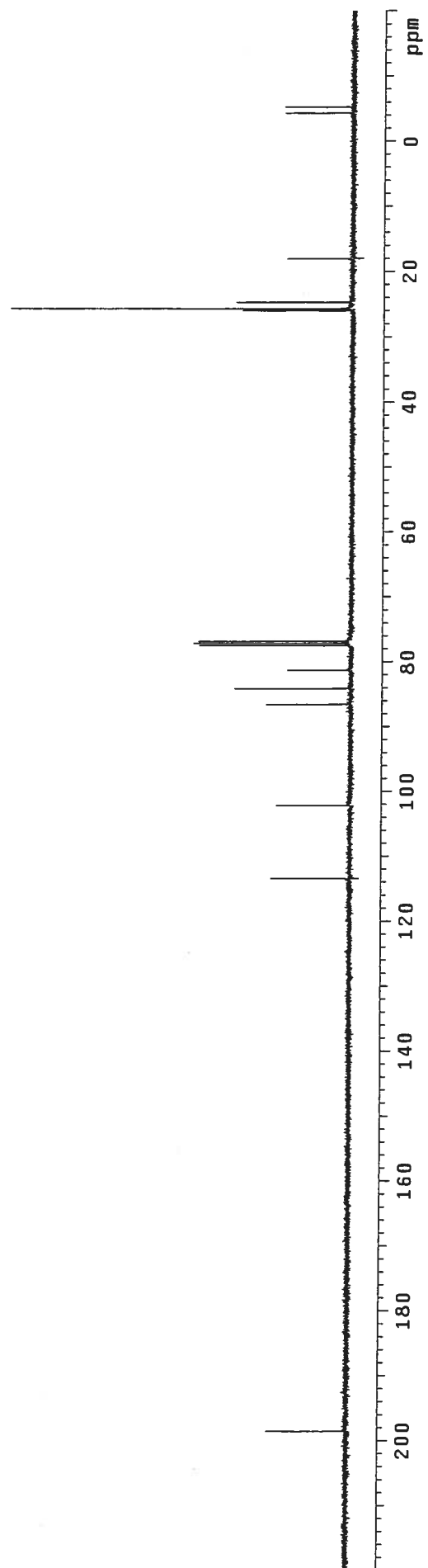
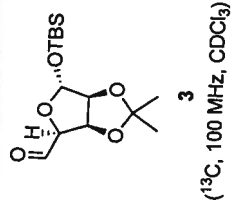
3.54 - 3.63 (m, 2 H), 3.66 (dd, $J = 12.0$ and 7.0 Hz, 1 H), 3.86 (d, $J = 2.0$ Hz, 1 H), 3.92 - 4.12 (m, 5 H), 4.23 (d, $J = 6.0$ Hz, 1 H), 6.77 - 6.83 (m, 2 H), 7.05 - 7.12 (m, 2 H), 7.37 (d, $J = 8.5$ Hz, 1 H), 7.80 (dd, $J = 8.5$ and 2.5 Hz, 1 H), 7.85 (d, $J = 2.5$ Hz, 1H); ^{13}C NMR (100 MHz, CHLOROFORM- d) δ ppm 15.1, 24.9, 26.7, 27.1, 27.4, 28.2, 38.7, 63.3, 63.4, 63.6, 64.9, 66.1, 79.9, 81.7, 83.5, 108.6, 114.7 (2C), 129.5, 129.8 (2C), 129.9, 131.7, 133.0, 134.0, 137.3, 139.6, 157.6.

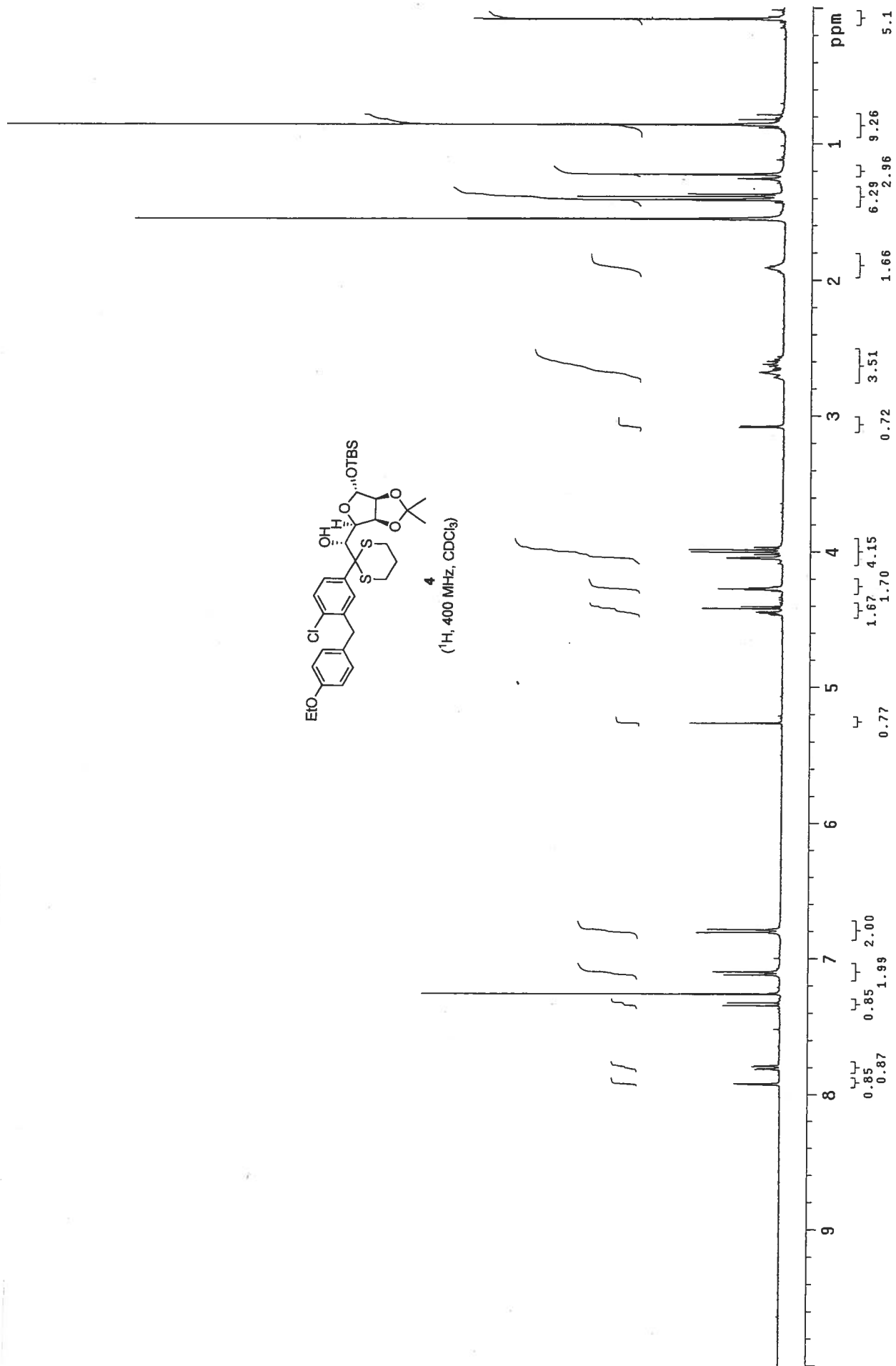
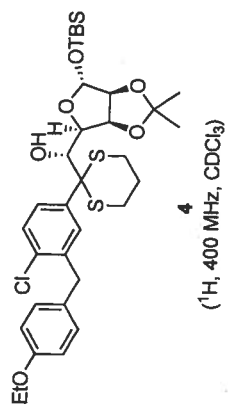
The crude material was redissolved in TFA (45 mL) and water (5 mL) and the resulting solution was stirred at 23 °C under an open atmosphere for 4 days. The solvent was evaporated and the residue was taken up in EtOAc. The organic phase was successively washed with water, 1M NaOH aqueous solution, brine, dried over MgSO_4 , filtered and concentrated. The crude product was purified by chromatography over silica gel (30% to 60% of [20% solution of MeOH in CH_2Cl_2] in CH_2Cl_2) to give **1** as a white solid precipitated from ethyl acetate and heptane (491 mg, 65% yield). MS (LCMS) 437.3 ($\text{M} + \text{H}^+$; positive mode). HRMS calculated for $\text{C}_{22}\text{H}_{26}\text{O}_7\text{Cl}$ ($\text{M} + \text{H}^+$) 437.1361 found 437.1378; $[\alpha]_{\text{D}} + 8.0$ (c 0.5, MeOH); ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 7.43 (d, 1H, $J = 1.9$ Hz), 7.36 (dd, 1H, $J = 8.3$ and 2 Hz), 7.32 (d, 1H, $J = 8.3$ Hz), 7.08-7.04 (m, 2H), 6.79-6.75 (m, 2H), 4.12 (d, 1H, $J = 7.5$ Hz), 4.00 (s, 2H), 3.96 (q, 2H, $J = 7.0$ Hz), 3.81 (d, 1H, $J = 12.5$ Hz), 3.75 (dd, 1H, $J = 8.3$ and 1.3 Hz), 3.65 (d, 1H, $J = 12.5$ Hz), 3.63 (t, 1H, $J = 8.2$ Hz), 3.57 (dd, 1H, $J = 7.5$ and 1.3 Hz), 3.52 (d, 1H, $J = 8.0$ Hz), 1.33 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, METHANOL- d_4) δ ppm 14.0, 38.1, 60.7, 63.2, 66.7, 71.9, 76.6, 78.1, 85.0, 108.4, 114.3 (2C), 125.9, 128.6, 129.3, 129.6 (2C), 131.6, 133.8, 137.4, 138.5, 157.7.

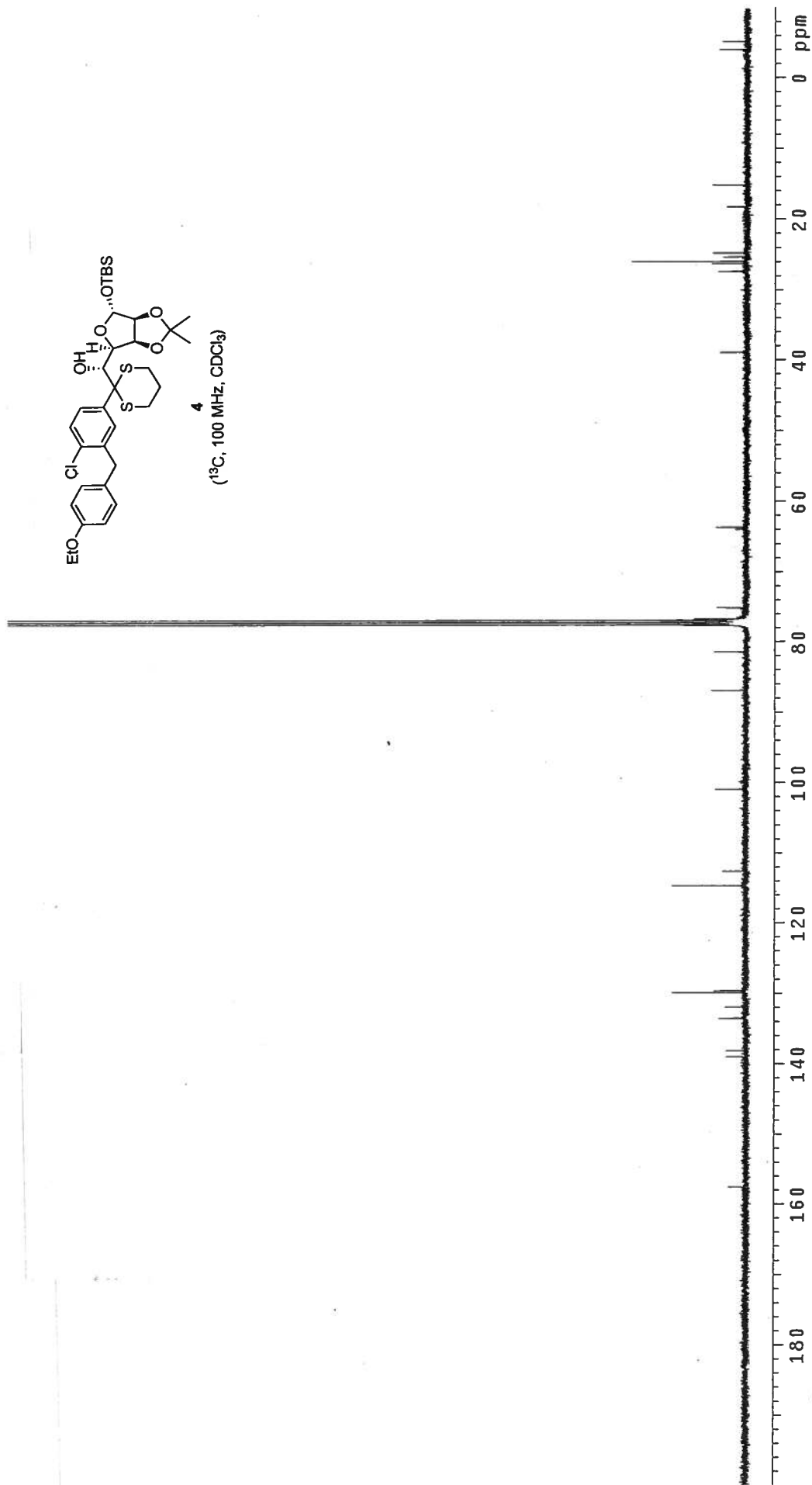
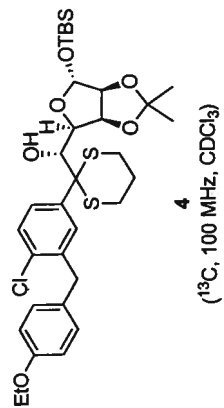


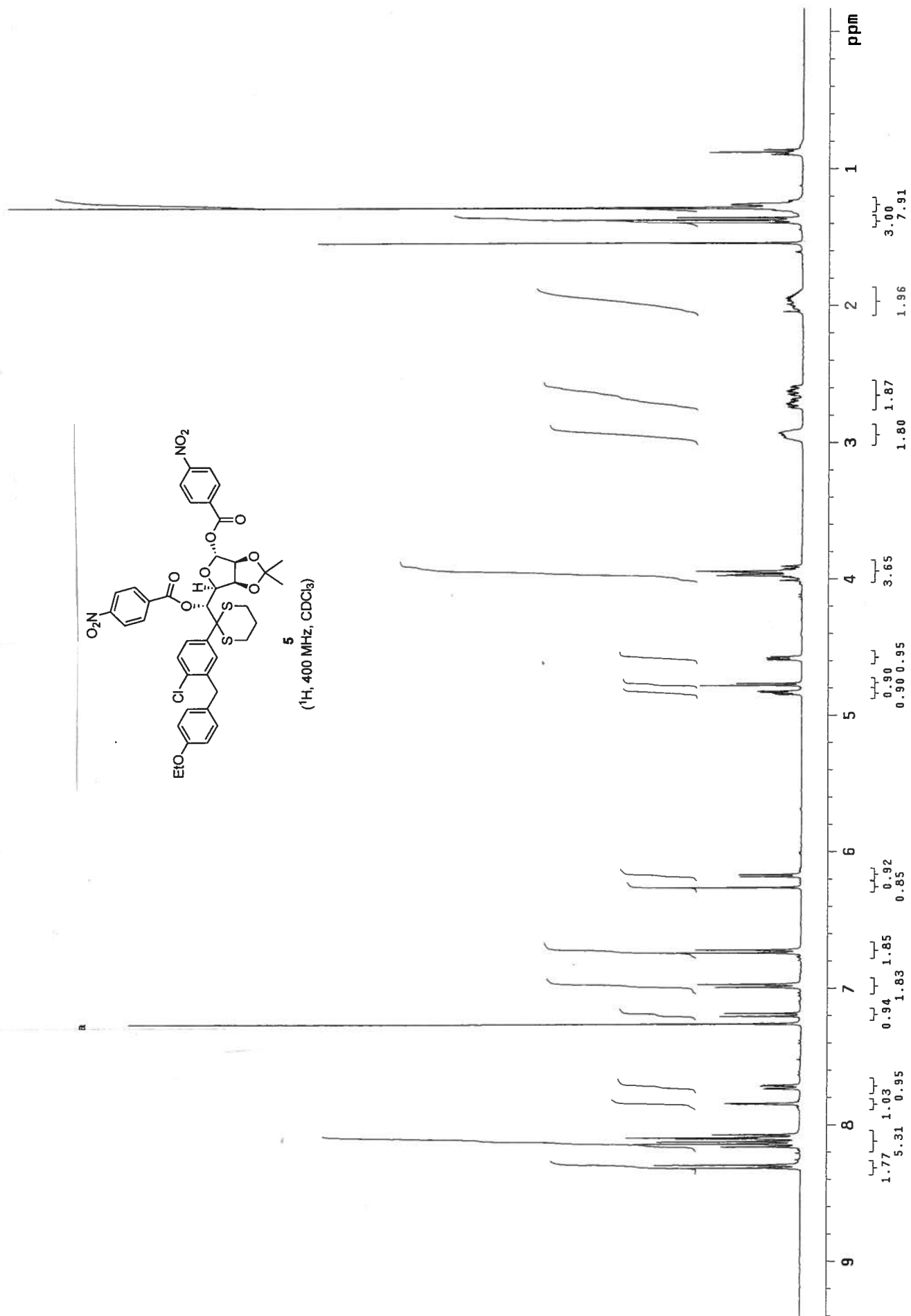


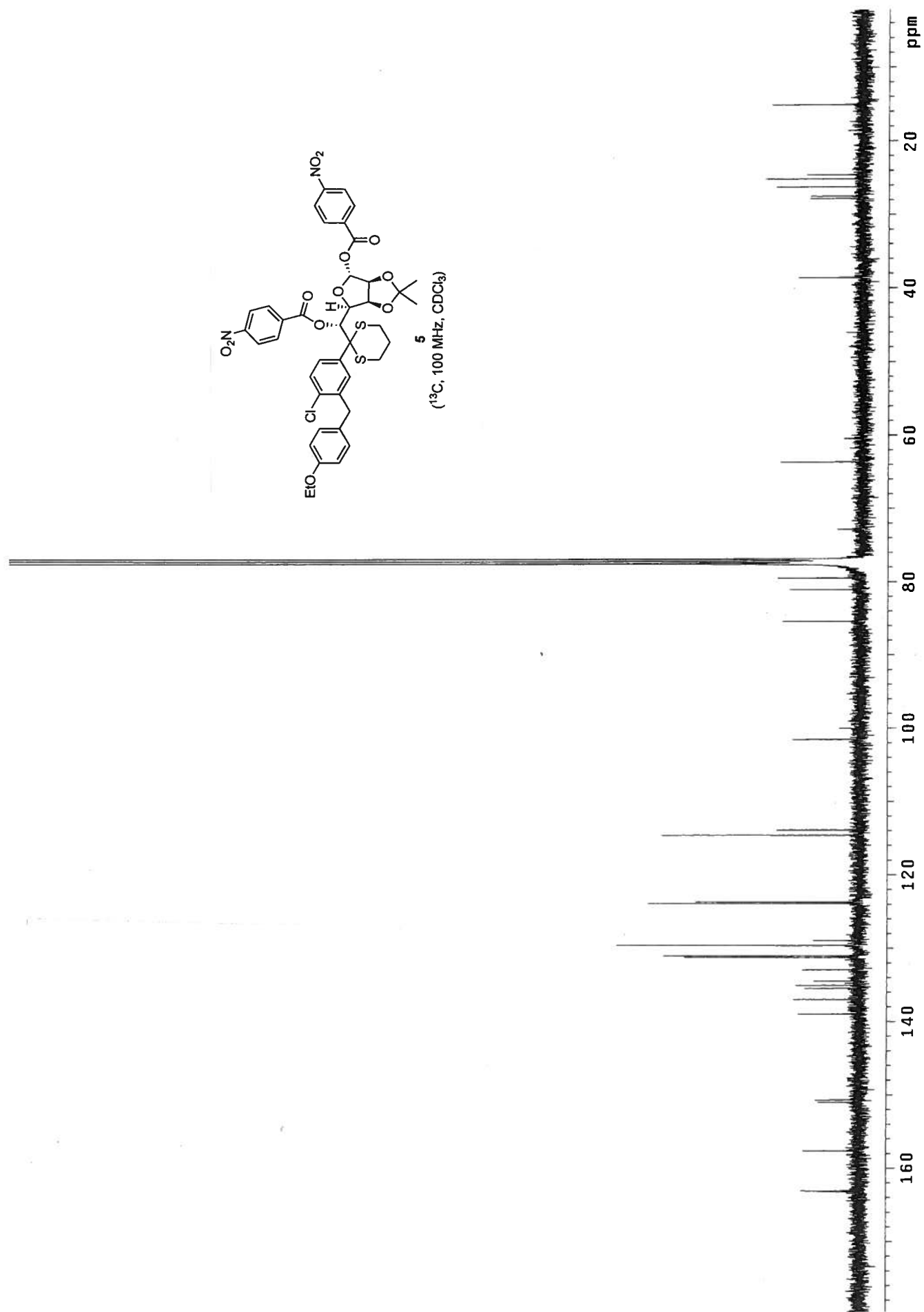


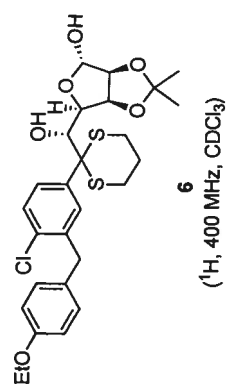


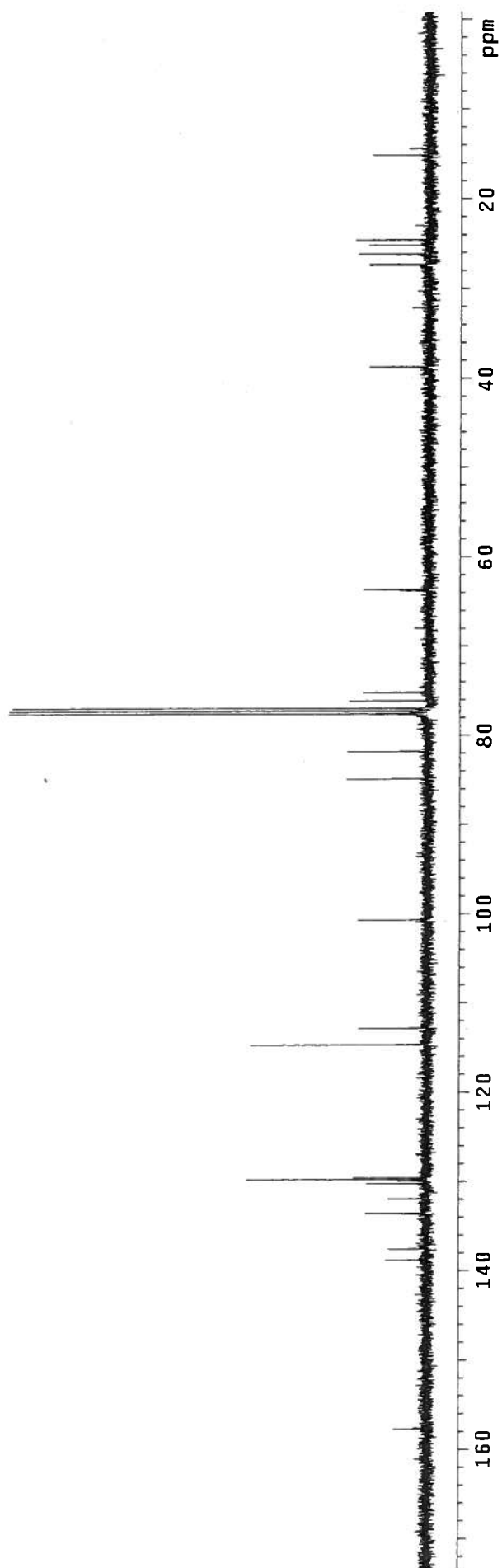
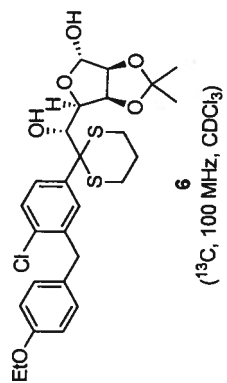


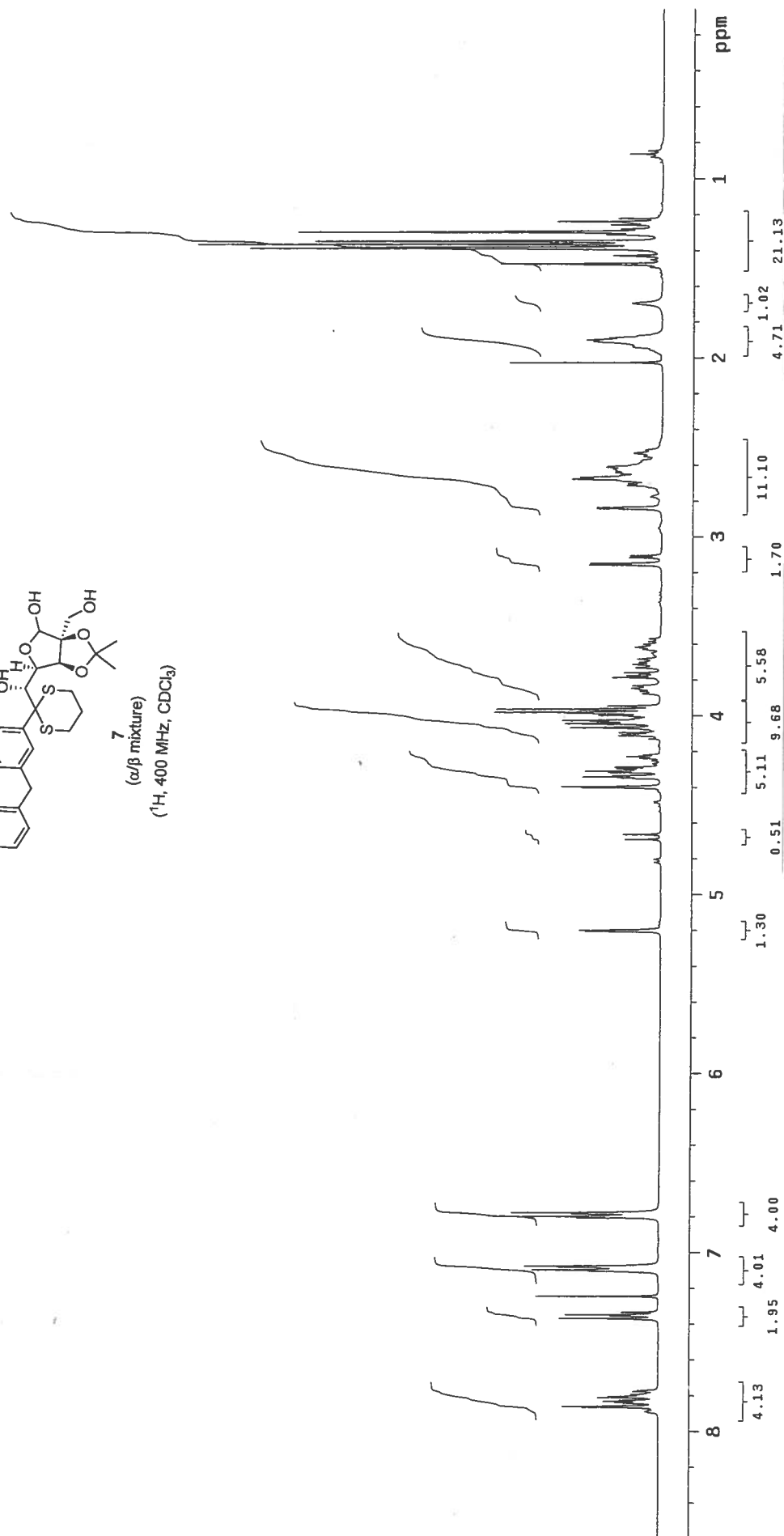
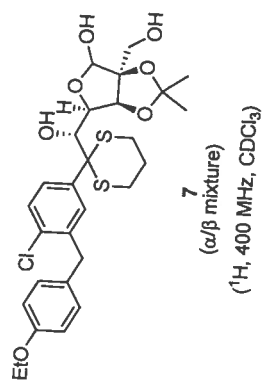


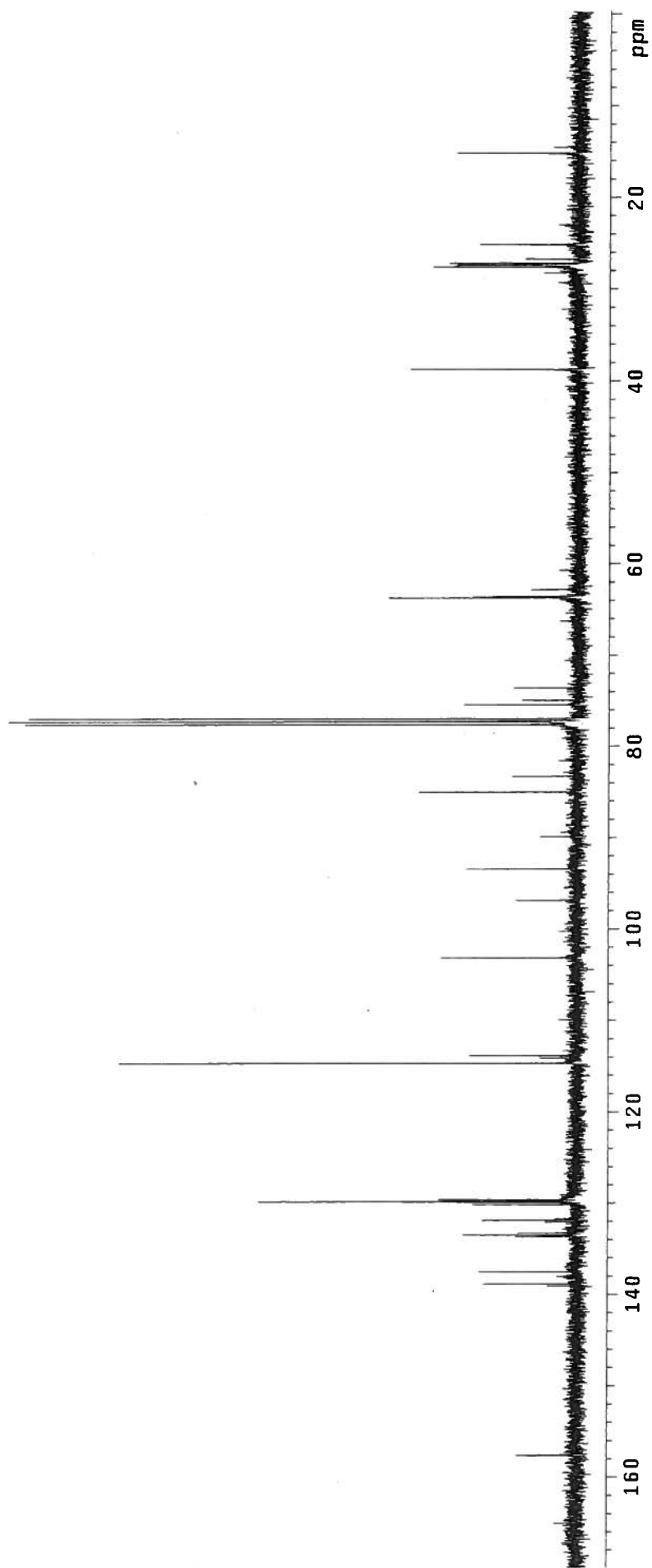
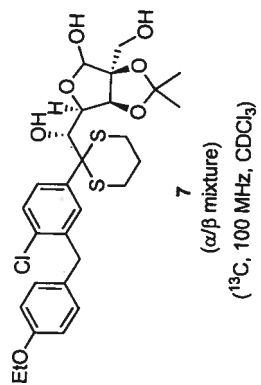


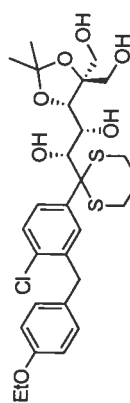




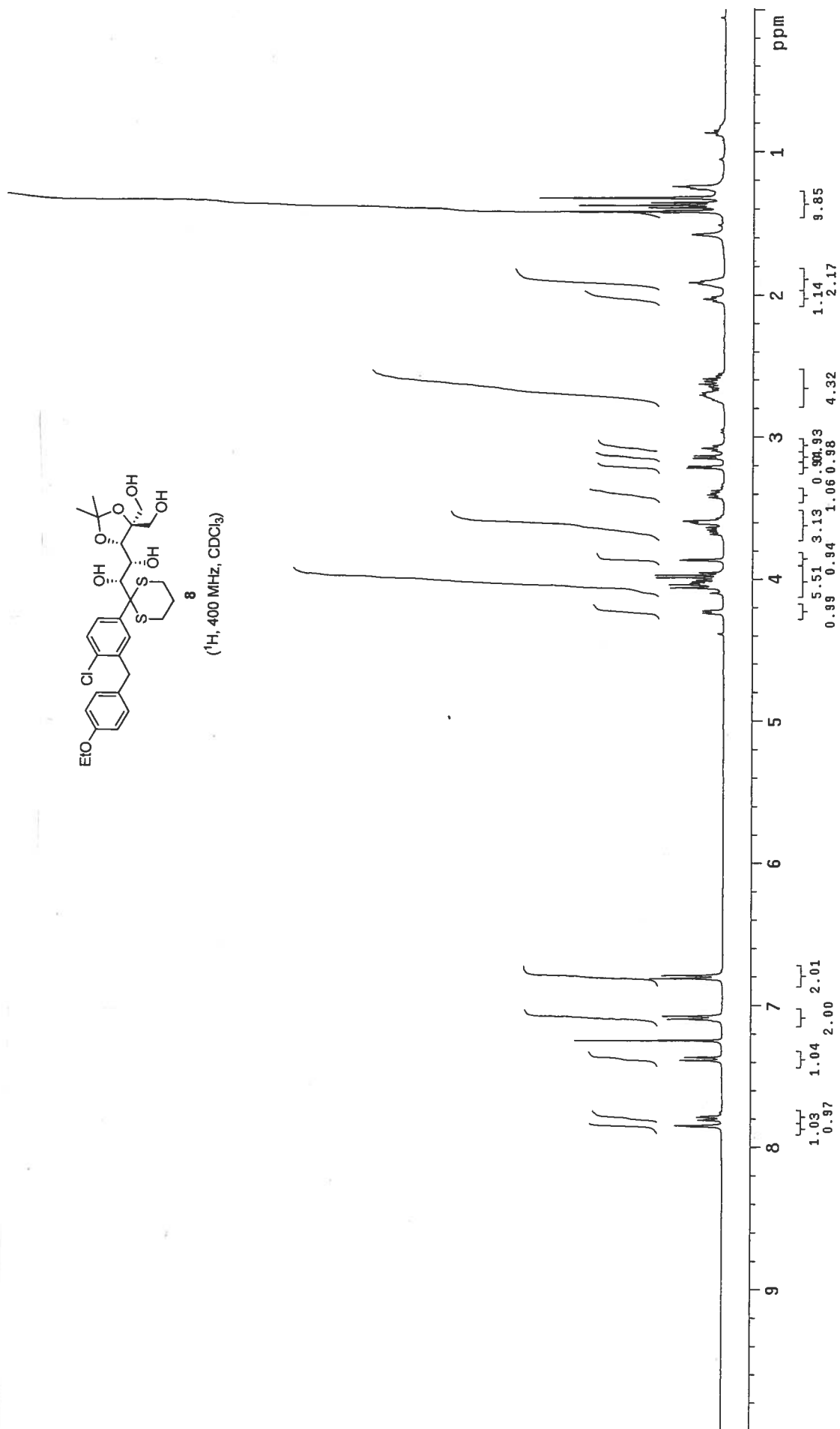


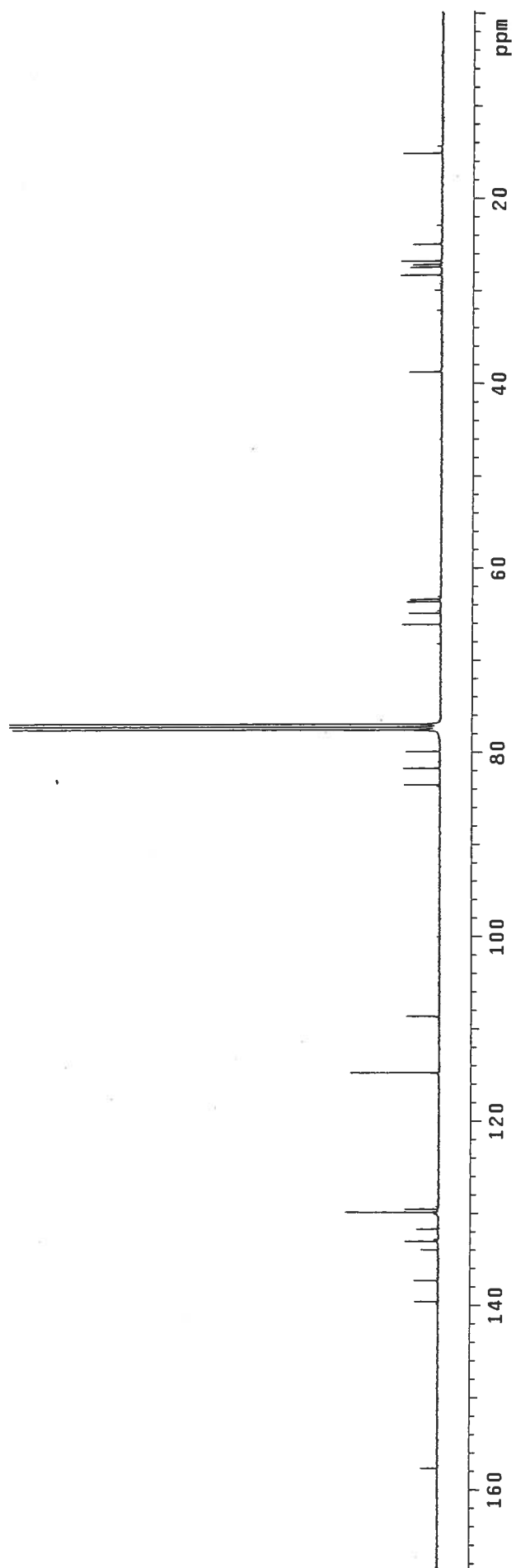
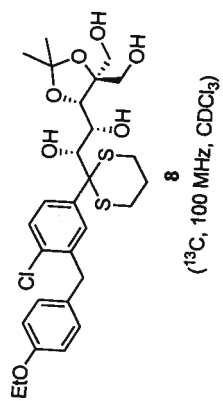


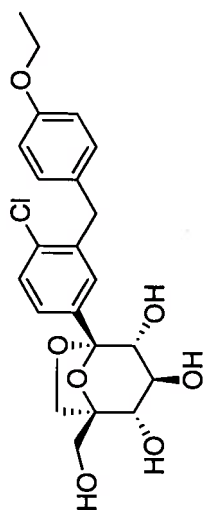




(^1H , 400 MHz, CDCl_3)

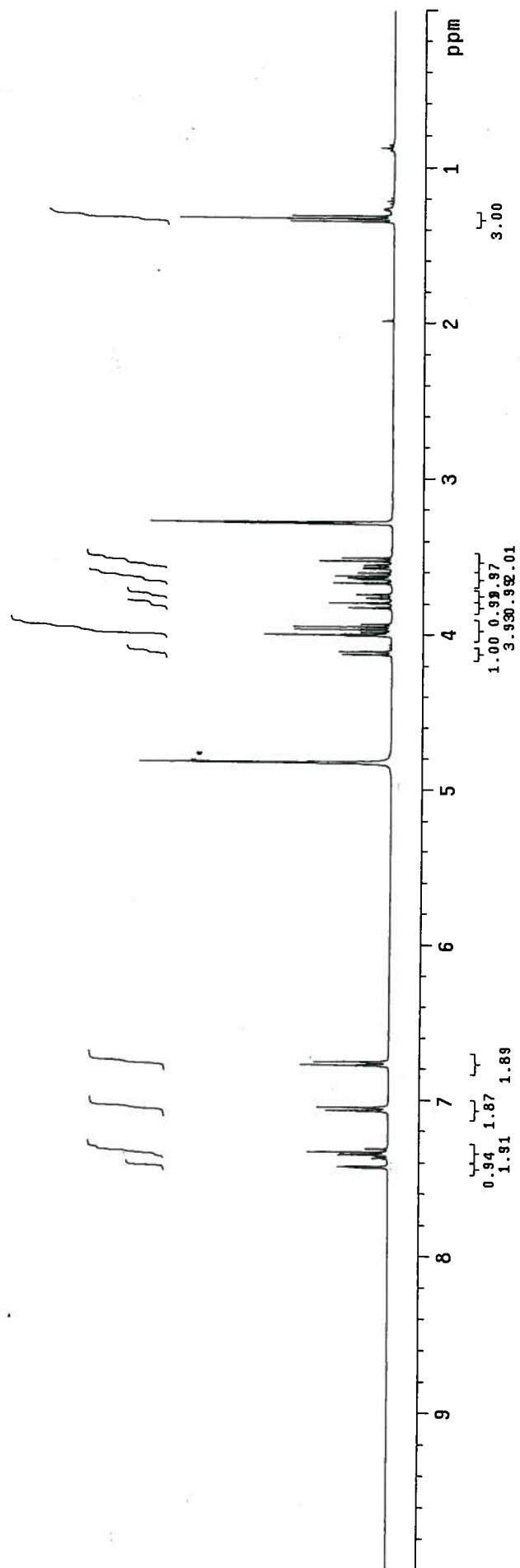


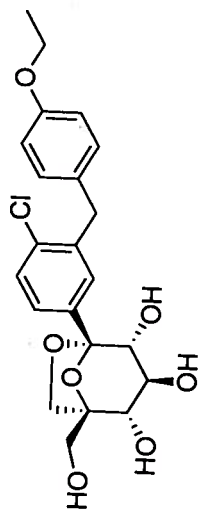




1

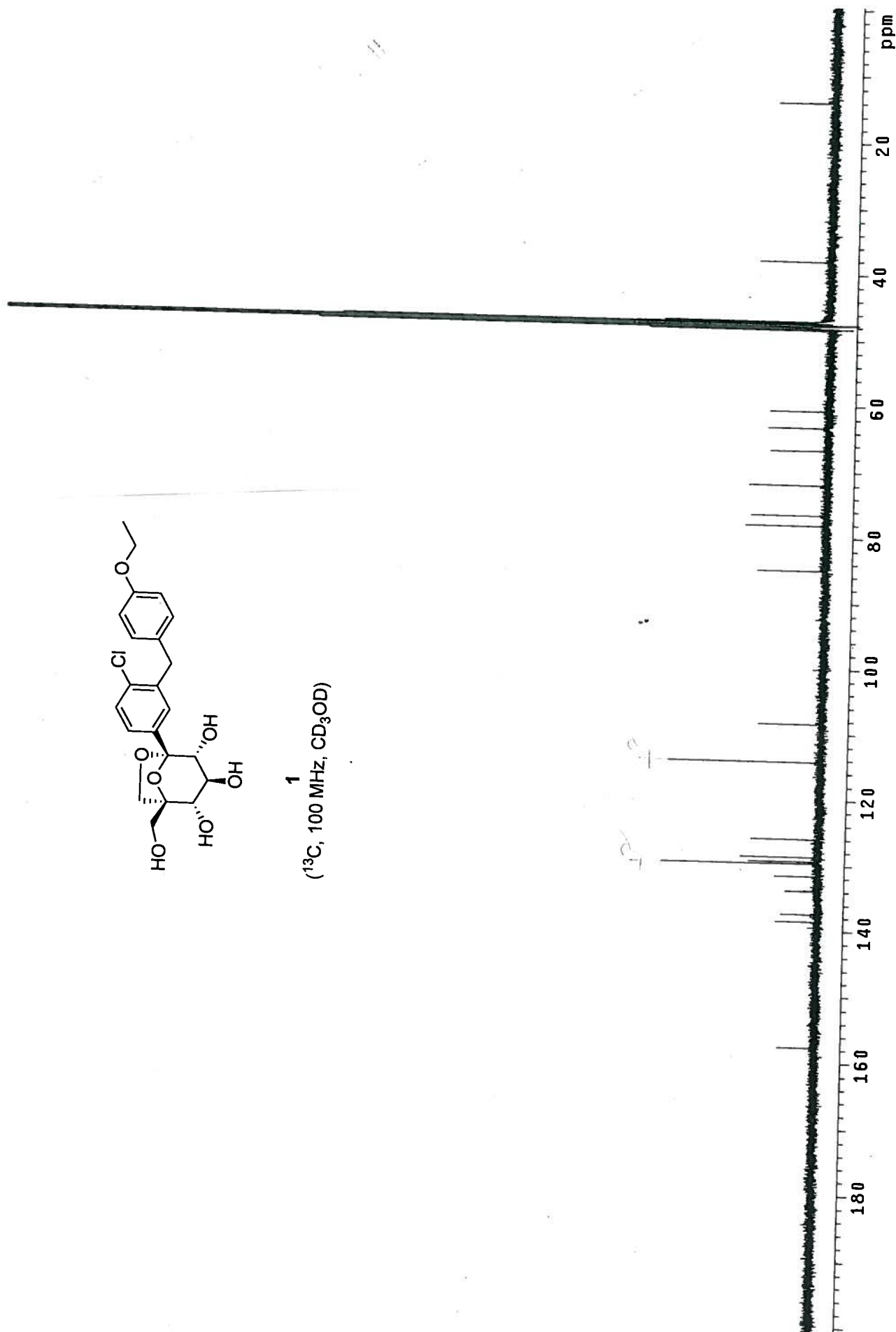
(¹H, 400 MHz, CD₃OD)



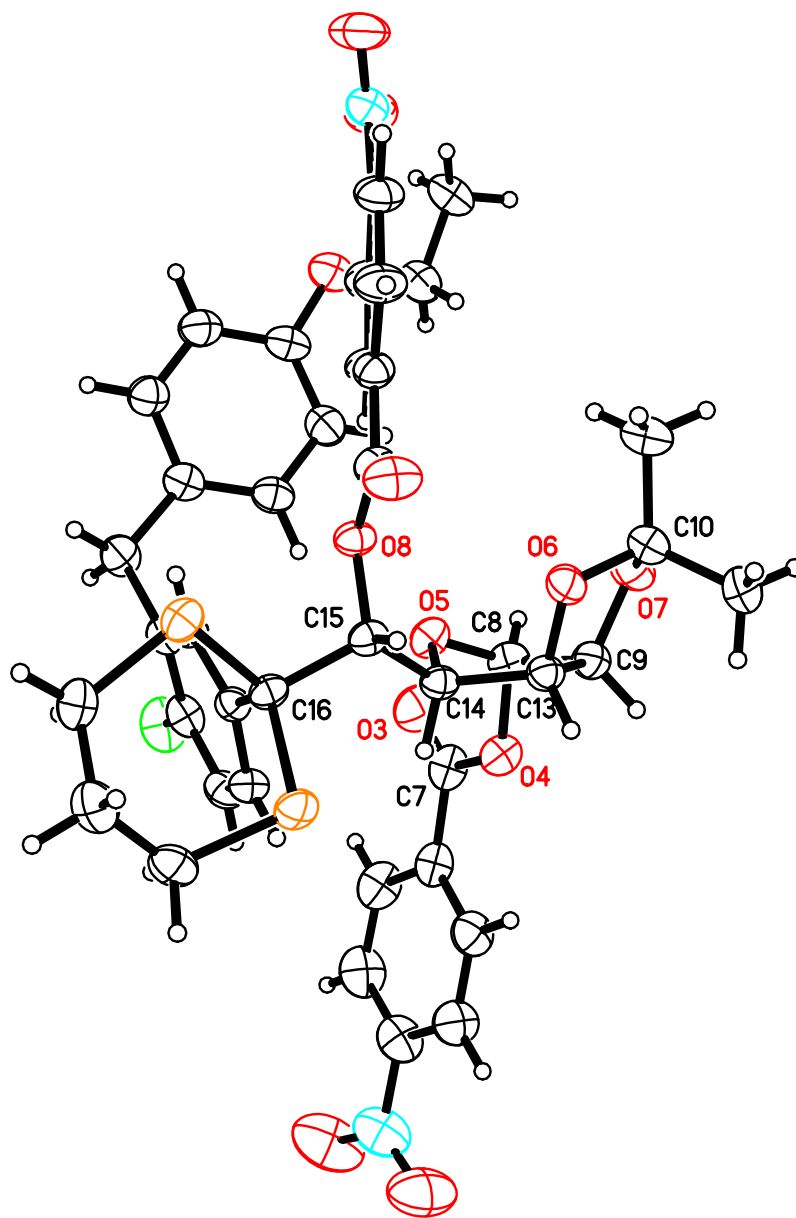


1

(^{13}C , 100 MHz, CD_3OD)



X-ray data for compound 5



ORTEP with ellipsoids drawn at 30% confidence level.

EXPERIMENTAL:

Data collection was performed on a Bruker APEX-II, diffractometer at room temperature. Data collection consisted of 3 omega scans and low angle and three at high angle; each with 0.5 step. In addition, 2 phi scans were collected to improve the quality of the absorption correction.

The structure was solved by direct methods using SHELX software suite in the space group P2(1)2(1)2(1). The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

All hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

From this crystal structure it has been possible to assign the absolute configuration of the molecule directly from the x-ray diffraction data. The structure was refined as depicted in figure 1 with the flack parameter = 0.013 (0.010). Additionally, the Hooft parameter = 0.028 (0.006).

Pertinent crystal, data collection and refinement are summarized in table 1. Atomic coordinates, bond lengths, bond angles, torsion angles and displacement parameters are listed in tables 2 –6.

Software and References

SHELXTL, Version 5.1, Bruker AXS, 1997

PLATON, A.L. Spek, *J. Appl. Cryst.* 2003, 36, 7-13.

MERCURY, C.F. Macrae, P.R. Edington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.* **39**, 453-457, 2006.

H.D. Flack, *Acta Cryst.* 1983, **A39**, 867-881.

R.W.W.Hooft, L.H. Straver, and A.L. Spek. *J. Appl Cryst.* 2008, **41**, 96-103.

Table 1. Crystal data and structure refinement.

Crystallization	ACN-IPA-EtOAc	
Empirical formula	C ₄₁ H ₃₉ Cl N ₂ O ₁₂ S ₂	
Formula Empirical weight	851.31	
Temperature	298(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.8049(2) Å	α = 90°.
	b = 17.5738(3) Å	β = 90°.
	c = 21.5909(4) Å	γ = 90°.
Volume	4099.75(13) Å ³	
Z	4	
Density (calculated)	1.379 Mg/m ³	
Absorption coefficient	2.330 mm ⁻¹	
F(000)	1776	
Crystal size	0.34 x 0.15 x 0.08 mm ³	
Theta range for data collection	3.24 to 67.05°.	
Index ranges	-12 ≤ h ≤ 11, -20 ≤ k ≤ 20, -24 ≤ l ≤ 25	
Reflections collected	23027	
Independent reflections	7078 [R(int) = 0.0233]	
Completeness to theta = 67.05°	98.7 %	
Absorption correction	Empirical	
Max. and min. transmission	0.8355 and 0.5046	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7078 / 0 / 526	
Goodness-of-fit on F ²	1.037	
Final R indices [I > 2σ(I)]	R1 = 0.0314, wR2 = 0.0859	
R indices (all data)	R1 = 0.0341, wR2 = 0.0887	
Absolute structure parameter	0.013(10)	
Largest diff. peak and hole	0.269 and -0.176 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	4031(2)	6266(1)	705(1)	66(1)
C(2)	2890(2)	6495(2)	486(1)	74(1)
C(3)	2006(3)	6715(1)	906(2)	74(1)
C(4)	2229(3)	6729(2)	1535(1)	80(1)
C(5)	3376(3)	6512(1)	1751(1)	72(1)
C(6)	4291(2)	6278(1)	1335(1)	57(1)
C(7)	5498(2)	6017(1)	1593(1)	58(1)
C(8)	7390(2)	5388(1)	1339(1)	54(1)
C(9)	8201(2)	5347(1)	767(1)	53(1)
C(10)	10007(2)	4714(1)	579(1)	63(1)
C(11)	10337(2)	4987(2)	-65(1)	72(1)
C(12)	11101(3)	4395(2)	930(2)	96(1)
C(13)	7916(2)	4550(1)	502(1)	46(1)
C(14)	6947(2)	4227(1)	939(1)	44(1)
C(15)	7016(2)	3371(1)	1058(1)	44(1)
C(16)	5729(2)	3015(1)	1203(1)	43(1)
C(17)	4412(2)	1699(1)	1467(1)	65(1)
C(18)	3705(3)	1740(1)	863(1)	71(1)
C(19)	3524(2)	2537(1)	629(1)	66(1)
C(20)	5046(2)	3466(1)	1704(1)	41(1)
C(21)	4187(2)	4024(1)	1558(1)	49(1)
C(22)	3662(2)	4468(1)	2016(1)	55(1)
C(23)	3995(2)	4355(1)	2621(1)	53(1)
C(24)	4819(2)	3788(1)	2796(1)	49(1)
C(25)	5332(2)	3352(1)	2322(1)	46(1)
C(26)	5185(2)	3635(1)	3456(1)	59(1)
C(27)	6414(2)	3964(1)	3649(1)	52(1)
C(28)	6952(2)	4582(1)	3371(1)	58(1)
C(29)	8070(2)	4887(1)	3596(1)	65(1)
C(30)	8639(2)	4543(1)	4096(1)	60(1)
C(31)	8125(2)	3913(2)	4368(1)	66(1)
C(32)	7028(2)	3627(1)	4151(1)	62(1)
C(33)	10342(2)	5434(2)	4105(1)	73(1)
C(34)	11545(2)	5528(2)	4447(1)	77(1)
C(35)	8848(2)	2800(1)	1477(1)	51(1)
C(36)	9701(2)	2851(1)	2017(1)	50(1)
C(37)	9543(2)	3388(1)	2478(1)	59(1)
C(38)	10360(2)	3419(1)	2964(1)	64(1)
C(39)	11323(2)	2911(1)	2985(1)	54(1)
C(40)	11512(2)	2377(2)	2535(1)	66(1)
C(41)	10697(2)	2352(1)	2041(1)	65(1)
Cl(1)	3354(1)	4963(1)	3176(1)	83(1)
N(1)	780(3)	6949(2)	670(2)	97(1)
N(2)	12149(2)	2923(1)	3529(1)	65(1)
O(1)	635(3)	6996(2)	116(2)	136(1)
O(2)	-20(2)	7074(2)	1054(2)	143(1)
O(3)	5763(2)	6013(1)	2130(1)	79(1)
O(4)	6261(2)	5763(1)	1138(1)	56(1)
O(5)	7115(1)	4640(1)	1509(1)	52(1)
O(6)	9056(1)	4153(1)	555(1)	56(1)

O(7)	9467(2)	5312(1)	936(1)	68(1)
O(8)	7842(1)	3246(1)	1567(1)	48(1)
O(9)	9014(2)	2418(1)	1025(1)	69(1)
O(10)	12903(2)	2412(1)	3577(1)	95(1)
O(11)	12045(2)	3436(1)	3896(1)	86(1)
O(12)	9735(2)	4787(1)	4361(1)	81(1)
S(1)	5997(1)	2020(1)	1425(1)	53(1)
S(2)	4962(1)	3026(1)	444(1)	55(1)

Table 3. Bond lengths [Å] and angles [°].

C(1)-C(2)	1.381(4)	C(36)-C(41)	1.390(3)
C(1)-C(6)	1.391(3)	C(37)-C(38)	1.374(3)
C(2)-C(3)	1.372(4)	C(38)-C(39)	1.372(3)
C(3)-C(4)	1.379(4)	C(39)-C(40)	1.367(3)
C(3)-N(1)	1.478(4)	C(39)-N(2)	1.475(3)
C(4)-C(5)	1.378(4)	C(40)-C(41)	1.382(3)
C(5)-C(6)	1.397(3)	N(1)-O(1)	1.210(4)
C(6)-C(7)	1.490(3)	N(1)-O(2)	1.217(4)
C(7)-O(3)	1.195(3)	N(2)-O(11)	1.207(3)
C(7)-O(4)	1.358(3)	N(2)-O(10)	1.216(3)
C(8)-O(5)	1.397(2)		
C(8)-O(4)	1.453(3)	C(2)-C(1)-C(6)	120.7(2)
C(8)-C(9)	1.516(3)	C(3)-C(2)-C(1)	118.5(3)
C(9)-O(7)	1.418(3)	C(2)-C(3)-C(4)	122.3(3)
C(9)-C(13)	1.543(3)	C(2)-C(3)-N(1)	118.3(3)
C(10)-O(6)	1.426(3)	C(4)-C(3)-N(1)	119.4(3)
C(10)-O(7)	1.427(3)	C(5)-C(4)-C(3)	119.0(2)
C(10)-C(12)	1.512(4)	C(4)-C(5)-C(6)	120.1(3)
C(10)-C(11)	1.513(3)	C(1)-C(6)-C(5)	119.3(2)
C(13)-O(6)	1.420(2)	C(1)-C(6)-C(7)	122.5(2)
C(13)-C(14)	1.519(3)	C(5)-C(6)-C(7)	118.1(2)
C(14)-O(5)	1.440(2)	O(3)-C(7)-O(4)	123.7(2)
C(14)-C(15)	1.528(3)	O(3)-C(7)-C(6)	125.0(2)
C(15)-O(8)	1.433(2)	O(4)-C(7)-C(6)	111.25(19)
C(15)-C(16)	1.557(3)	O(5)-C(8)-O(4)	109.02(18)
C(16)-C(20)	1.530(2)	O(5)-C(8)-C(9)	106.94(16)
C(16)-S(1)	1.8370(19)	O(4)-C(8)-C(9)	105.24(17)
C(16)-S(2)	1.8370(19)	O(7)-C(9)-C(8)	110.42(18)
C(17)-C(18)	1.513(4)	O(7)-C(9)-C(13)	104.37(17)
C(17)-S(1)	1.805(3)	C(8)-C(9)-C(13)	103.33(17)
C(18)-C(19)	1.502(4)	O(6)-C(10)-O(7)	103.56(17)
C(19)-S(2)	1.820(3)	O(6)-C(10)-C(12)	109.0(2)
C(20)-C(25)	1.384(3)	O(7)-C(10)-C(12)	108.8(2)
C(20)-C(21)	1.386(3)	O(6)-C(10)-C(11)	110.8(2)
C(21)-C(22)	1.381(3)	O(7)-C(10)-C(11)	111.1(2)
C(22)-C(23)	1.370(3)	C(12)-C(10)-C(11)	113.2(2)
C(23)-C(24)	1.388(3)	O(6)-C(13)-C(14)	111.38(16)
C(23)-Cl(1)	1.749(2)	O(6)-C(13)-C(9)	104.09(15)
C(24)-C(25)	1.395(3)	C(14)-C(13)-C(9)	104.26(16)
C(24)-C(26)	1.502(3)	O(5)-C(14)-C(13)	104.83(15)
C(26)-C(27)	1.507(3)	O(5)-C(14)-C(15)	110.22(15)
C(27)-C(28)	1.371(3)	C(13)-C(14)-C(15)	116.03(16)
C(27)-C(32)	1.400(3)	O(8)-C(15)-C(14)	108.13(15)
C(28)-C(29)	1.408(3)	O(8)-C(15)-C(16)	109.93(15)
C(29)-C(30)	1.380(3)	C(14)-C(15)-C(16)	112.69(15)
C(30)-C(31)	1.371(4)	C(20)-C(16)-C(15)	111.44(15)
C(30)-O(12)	1.383(3)	C(20)-C(16)-S(1)	112.60(13)
C(31)-C(32)	1.370(3)	C(15)-C(16)-S(1)	107.09(12)
C(33)-O(12)	1.426(3)	C(20)-C(16)-S(2)	114.07(13)
C(33)-C(34)	1.503(4)	C(15)-C(16)-S(2)	102.68(12)
C(35)-O(9)	1.198(3)	S(1)-C(16)-S(2)	108.29(10)
C(35)-O(8)	1.353(2)	C(18)-C(17)-S(1)	114.89(18)
C(35)-C(36)	1.488(3)	C(19)-C(18)-C(17)	113.66(19)
C(36)-C(37)	1.382(3)	C(18)-C(19)-S(2)	113.76(19)

C(25)-C(20)-C(21)	118.03(17)	O(8)-C(35)-C(36)	110.53(16)
C(25)-C(20)-C(16)	119.91(16)	C(37)-C(36)-C(41)	119.9(2)
C(21)-C(20)-C(16)	121.95(17)	C(37)-C(36)-C(35)	121.91(18)
C(22)-C(21)-C(20)	120.9(2)	C(41)-C(36)-C(35)	118.19(19)
C(23)-C(22)-C(21)	119.42(19)	C(38)-C(37)-C(36)	120.0(2)
C(22)-C(23)-C(24)	122.25(18)	C(39)-C(38)-C(37)	119.1(2)
C(22)-C(23)-Cl(1)	117.42(17)	C(40)-C(39)-C(38)	122.5(2)
C(24)-C(23)-Cl(1)	120.32(17)	C(40)-C(39)-N(2)	119.04(19)
C(23)-C(24)-C(25)	116.66(18)	C(38)-C(39)-N(2)	118.4(2)
C(23)-C(24)-C(26)	123.86(19)	C(39)-C(40)-C(41)	118.4(2)
C(25)-C(24)-C(26)	119.48(19)	C(40)-C(41)-C(36)	120.2(2)
C(20)-C(25)-C(24)	122.65(18)	O(1)-N(1)-O(2)	124.7(3)
C(24)-C(26)-C(27)	115.20(19)	O(1)-N(1)-C(3)	118.4(3)
C(28)-C(27)-C(32)	118.2(2)	O(2)-N(1)-C(3)	116.9(3)
C(28)-C(27)-C(26)	123.8(2)	O(11)-N(2)-O(10)	123.9(2)
C(32)-C(27)-C(26)	118.0(2)	O(11)-N(2)-C(39)	118.4(2)
C(27)-C(28)-C(29)	120.9(2)	O(10)-N(2)-C(39)	117.7(2)
C(30)-C(29)-C(28)	119.0(2)	C(7)-O(4)-C(8)	116.26(17)
C(31)-C(30)-C(29)	120.5(2)	C(8)-O(5)-C(14)	106.07(15)
C(31)-C(30)-O(12)	114.8(2)	C(13)-O(6)-C(10)	106.74(15)
C(29)-C(30)-O(12)	124.6(2)	C(9)-O(7)-C(10)	106.69(17)
C(32)-C(31)-C(30)	120.0(2)	C(35)-O(8)-C(15)	118.68(14)
C(31)-C(32)-C(27)	121.3(2)	C(30)-O(12)-C(33)	118.8(2)
O(12)-C(33)-C(34)	107.2(2)	C(17)-S(1)-C(16)	99.29(10)
O(9)-C(35)-O(8)	124.1(2)	C(19)-S(2)-C(16)	100.62(10)
O(9)-C(35)-C(36)	125.35(18)		

Symmetry transformations used to generate
equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	62(1)	74(1)	63(2)	-9(1)	14(1)	7(1)
C(2)	72(2)	82(2)	67(2)	-9(1)	8(1)	12(1)
C(3)	68(2)	62(1)	92(2)	-15(1)	12(2)	12(1)
C(4)	81(2)	74(2)	86(2)	-20(1)	28(2)	17(1)
C(5)	92(2)	63(1)	60(2)	-11(1)	17(1)	14(1)
C(6)	71(1)	45(1)	55(1)	-7(1)	13(1)	4(1)
C(7)	77(2)	45(1)	53(1)	-9(1)	12(1)	2(1)
C(8)	62(1)	49(1)	50(1)	-7(1)	-5(1)	3(1)
C(9)	51(1)	53(1)	54(1)	2(1)	-4(1)	-1(1)
C(10)	45(1)	75(1)	68(2)	8(1)	-3(1)	1(1)
C(11)	54(1)	85(2)	77(2)	13(1)	11(1)	-4(1)
C(12)	57(1)	124(3)	107(3)	27(2)	-16(2)	7(2)
C(13)	44(1)	52(1)	42(1)	0(1)	-1(1)	3(1)
C(14)	44(1)	50(1)	38(1)	-4(1)	-3(1)	5(1)
C(15)	49(1)	48(1)	36(1)	-3(1)	-1(1)	8(1)
C(16)	49(1)	45(1)	34(1)	-2(1)	-3(1)	5(1)
C(17)	78(2)	53(1)	64(2)	2(1)	10(1)	-7(1)
C(18)	77(2)	63(1)	73(2)	-17(1)	-1(1)	-14(1)
C(19)	63(1)	75(2)	60(2)	-14(1)	-16(1)	-9(1)
C(20)	41(1)	43(1)	40(1)	-3(1)	-2(1)	-2(1)
C(21)	46(1)	54(1)	45(1)	-3(1)	-5(1)	6(1)
C(22)	45(1)	51(1)	69(2)	-6(1)	1(1)	7(1)
C(23)	50(1)	54(1)	56(1)	-18(1)	11(1)	-6(1)
C(24)	47(1)	60(1)	41(1)	-9(1)	2(1)	-8(1)
C(25)	44(1)	52(1)	41(1)	-4(1)	-3(1)	2(1)
C(26)	60(1)	80(1)	38(1)	-9(1)	4(1)	-7(1)
C(27)	53(1)	62(1)	41(1)	-15(1)	1(1)	4(1)
C(28)	55(1)	65(1)	55(1)	-8(1)	-7(1)	4(1)
C(29)	57(1)	62(1)	75(2)	-4(1)	0(1)	-2(1)
C(30)	50(1)	72(1)	57(1)	-15(1)	-8(1)	11(1)
C(31)	62(1)	77(2)	58(1)	1(1)	-7(1)	9(1)
C(32)	62(1)	69(1)	53(1)	-2(1)	1(1)	4(1)
C(33)	61(1)	73(2)	85(2)	-5(1)	1(1)	-4(1)
C(34)	51(1)	92(2)	87(2)	-18(2)	-4(1)	-2(1)
C(35)	53(1)	51(1)	48(1)	-1(1)	4(1)	12(1)
C(36)	47(1)	51(1)	52(1)	2(1)	2(1)	12(1)
C(37)	58(1)	60(1)	59(1)	-4(1)	-5(1)	22(1)
C(38)	66(1)	62(1)	63(2)	-8(1)	-7(1)	12(1)
C(39)	46(1)	60(1)	55(1)	7(1)	-2(1)	1(1)
C(40)	51(1)	75(2)	72(2)	2(1)	-4(1)	22(1)
C(41)	60(1)	72(1)	62(2)	-9(1)	-2(1)	25(1)
Cl(1)	94(1)	76(1)	79(1)	-29(1)	29(1)	6(1)
N(1)	77(2)	88(2)	126(2)	-30(2)	-1(2)	23(1)
N(2)	52(1)	70(1)	74(1)	10(1)	-11(1)	-6(1)
O(1)	101(2)	174(3)	134(2)	-16(2)	-16(2)	53(2)
O(2)	85(2)	172(3)	172(3)	-70(2)	13(2)	51(2)
O(3)	97(1)	88(1)	51(1)	-12(1)	6(1)	8(1)
O(4)	67(1)	52(1)	50(1)	-6(1)	4(1)	12(1)
O(5)	65(1)	49(1)	41(1)	-4(1)	3(1)	3(1)
O(6)	45(1)	58(1)	64(1)	6(1)	6(1)	6(1)

O(7)	55(1)	79(1)	69(1)	-10(1)	-10(1)	-10(1)
O(8)	47(1)	54(1)	42(1)	-3(1)	-2(1)	12(1)
O(9)	73(1)	79(1)	56(1)	-19(1)	-5(1)	30(1)
O(10)	72(1)	96(1)	118(2)	6(1)	-36(1)	18(1)
O(11)	86(1)	94(1)	78(1)	-7(1)	-25(1)	-2(1)
O(12)	62(1)	93(1)	89(1)	7(1)	-19(1)	-7(1)
S(1)	64(1)	44(1)	53(1)	-1(1)	4(1)	7(1)
S(2)	67(1)	62(1)	35(1)	-4(1)	-9(1)	-4(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$).

	x	y	z	U(eq)
H(1)	4633	6102	427	80
H(2)	2723	6499	63	88
H(4)	1614	6882	1809	96
H(5)	3541	6522	2173	86
H(8)	7796	5667	1676	65
H(9)	8026	5756	471	63
H(11A)	10707	4578	-293	108
H(11B)	10911	5402	-36	108
H(11C)	9601	5154	-273	108
H(12A)	10887	4339	1360	144
H(12B)	11791	4736	892	144
H(12C)	11319	3908	762	144
H(13)	7621	4573	73	55
H(14)	6126	4347	773	52
H(15)	7357	3123	689	53
H(17A)	4407	1175	1610	78
H(17B)	3981	2002	1773	78
H(18A)	4146	1449	552	85
H(18B)	2900	1506	920	85
H(19A)	3083	2829	940	79
H(19B)	3011	2521	260	79
H(21)	3961	4100	1147	58
H(22)	3087	4842	1913	66
H(25)	5889	2968	2425	55
H(26A)	5210	3088	3518	71
H(26B)	4549	3838	3726	71
H(28)	6573	4803	3029	69
H(29)	8421	5313	3411	77
H(31)	8520	3680	4700	79
H(32)	6684	3202	4340	74
H(33A)	9833	5885	4155	88
H(33B)	10496	5358	3667	88
H(34A)	11381	5598	4880	115
H(34B)	11977	5964	4289	115
H(34C)	12044	5082	4390	115
H(37)	8884	3727	2459	71
H(38)	10262	3780	3275	76
H(40)	12171	2039	2559	79
H(41)	10817	2000	1725	78