Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information for

α-D-*Gal*-cyclophellitol cyclosulfamidate is a Michaelis complex analog that stabilizes therapeutic lysosomal α-galactosidase A in Fabry disease

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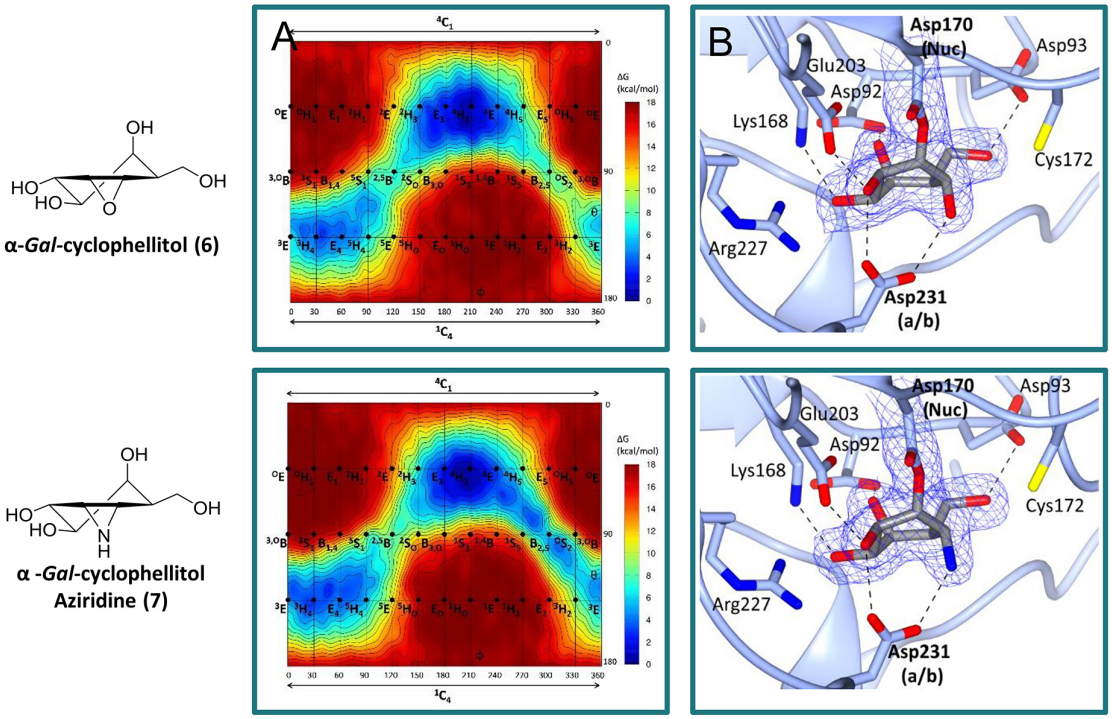


Figure S1. Conformational free energy landscapes of *gal*-cyclophellitol 6 and *gal*-cyclophellitol aziridine 7. A. α-G*al*-Cyclophellitol **6** (upper panel) and α-*gal*-cyclophellitol aziridine **7** (bottom panel) adopt $^{3}H_{4}$ ground state conformations, with a broad energy minimum extending toward $^{4}H_{3}$. The x and y axes of each graph correspond to the ϕ and θ Cremer−Pople puckering coordinates (in degrees), respectively. Isolines are 1 kcal/mol. **B**. Electron density for protein side chains and ligands is REFMAC maximum-likelihood/σA-weighted $2F_o - F_c$ contoured to 0.22 electron/Å^3 for **6** and **7**. nuc. = nucleophile; a./b. = acid/base.

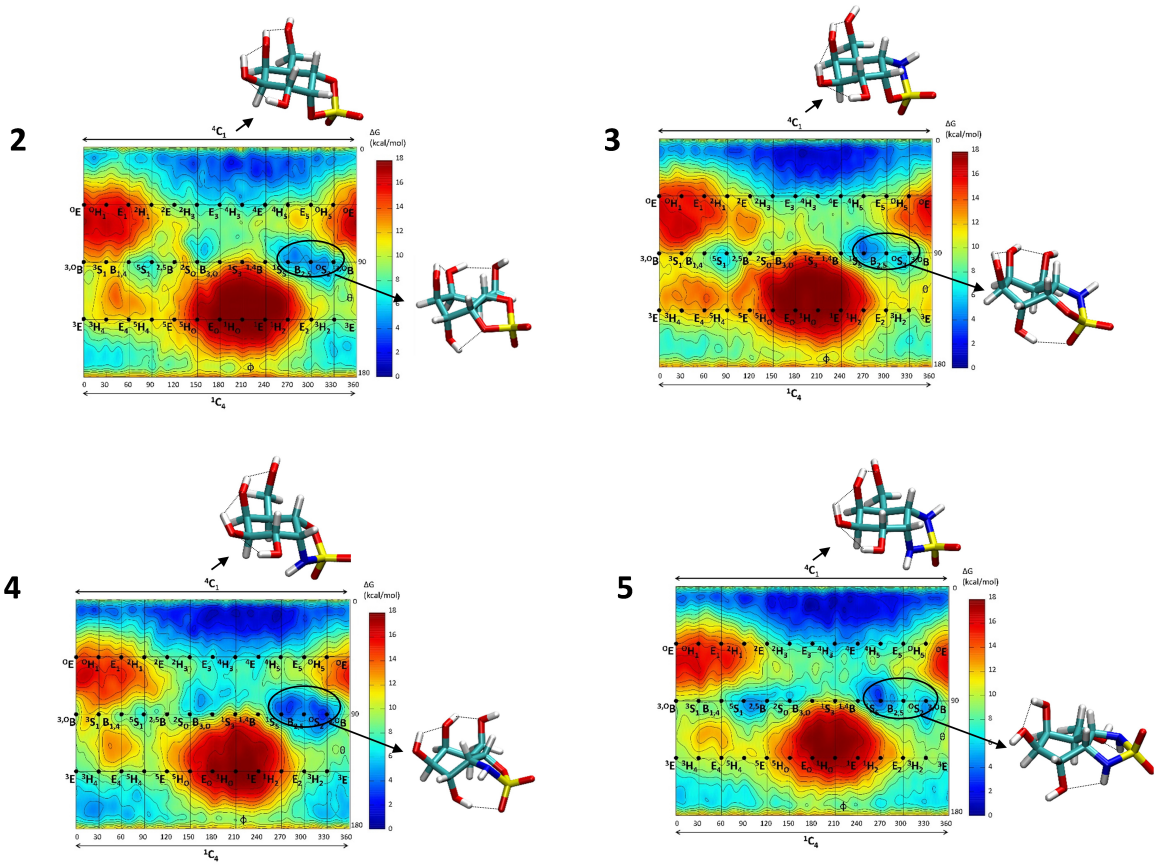


Figure S2. Comparison of the conformational free energy landscapes of α-*gal*-cyclosulfate 2, α-*gal*-cyclosulfamidates 3 and 4, and α-*gal*-cyclosulfamide 5. α-*Gal*-cyclosulfate **2** (top left), α-*gal*-cyclosulamidate **3** (top right), α-*gal*-cyclosulfamidate **4** (bottom left) and α-*gal*-cyclosulfamide **5** top (bottom right) adopt $^4C_1$ ground state conformations, with a secondary minimum around $B_{2,5}$. The x and y axes of each graph correspond to the ϕ and θ Cremer−Pople puckering coordinates (in degrees), respectively. Isolines are 1 kcal/mol.

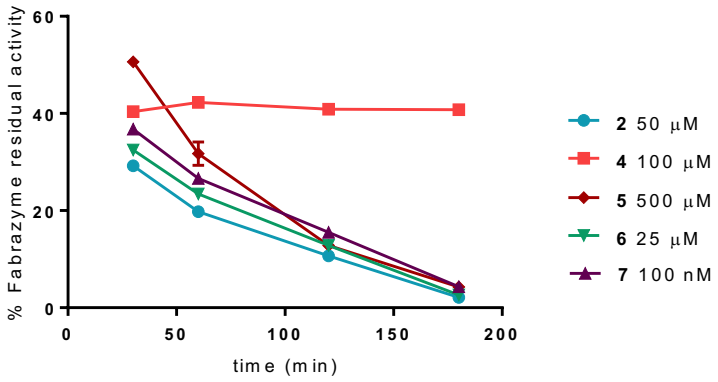


Figure S3. Time dependent inhibition of α-galactosidase A (agalsidase beta) by compounds 2, 4, 5, 6 and 7. Residual activity of human recombinant α-galactosidase A (agalsidase beta) with different incubation times (30, 60, 120 and 240 min) in the presence of inhibitors **2**, **4**, **5**, **6** and **7** at concentrations higher than their corresponding apparent IC_{50} values in α-gal A. Residual α-gal A activity was measured using fluorogenic 4-methylumbelliferyl (4MU)-α-D-galactopyranose substrate in 150 mM McIlvaine buffer pH 4.6, 0.1 % Bovine Serum albumin (BSA) (w/v).

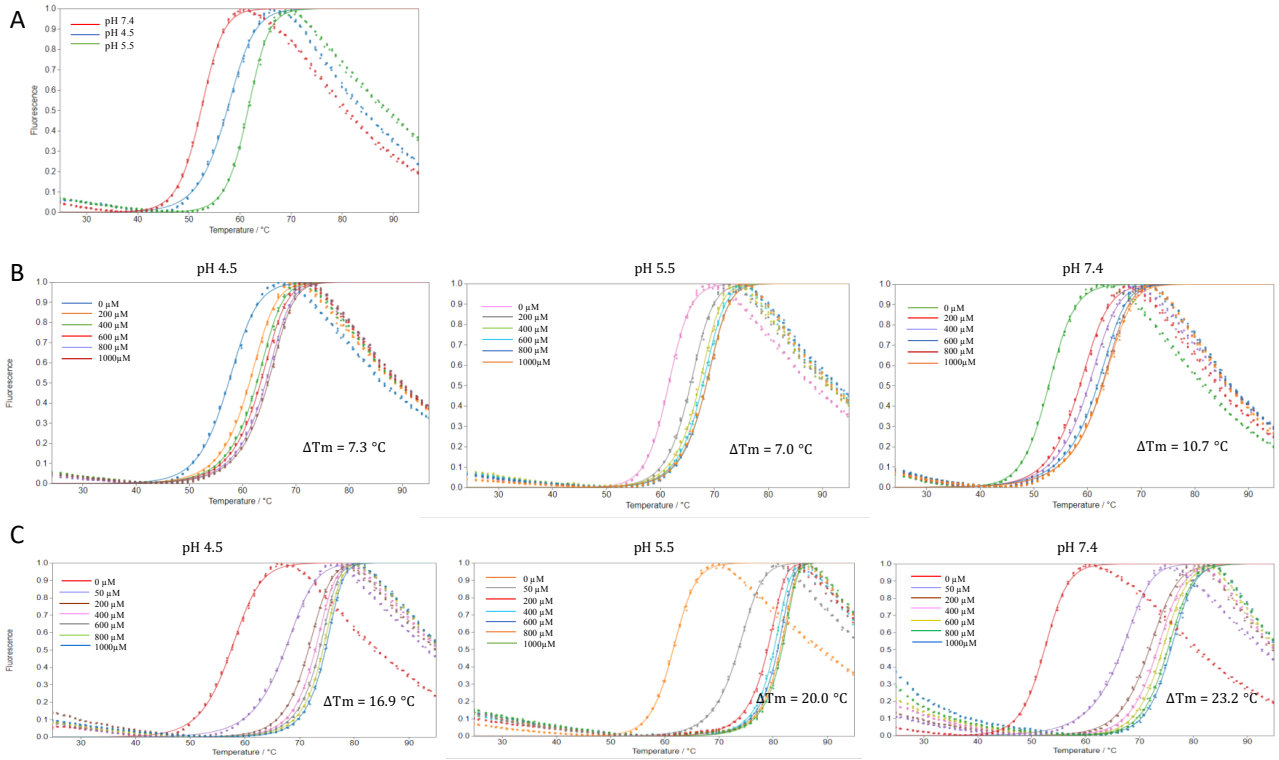
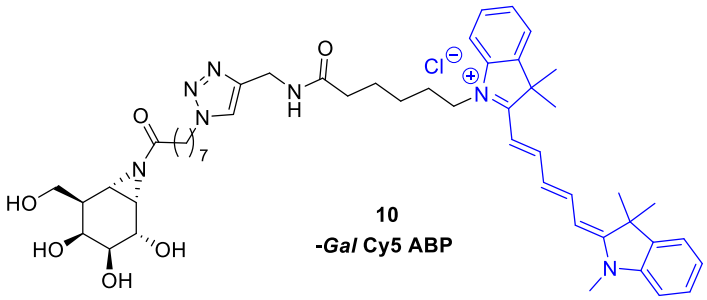


Figure S4. Stabilization of α-gal A by α-cyclosulfamidate 4 and Gal-DNJ 8 at different pHs. Heat-induced melting profiles of lysosomal agalsidase beta recorded by thermal shift at pH 4.5, 5.5 and 7.4 without pharmacological chaperone (**A**), with α-cyclosulfamidate **4** (**B**) and with Gal-DNJ **8** (**C**). The protein (45 µg/mL) was heated from 25 °C to 95 °C at 1 °C/min in the presence of Sypro Orange (5x). Data shown as normalized curves.



10
***-Gal* Cy5 ABP**

Figure S5. Chemical structure of α-galactosidase Cy5 ABP **10** used in this study.

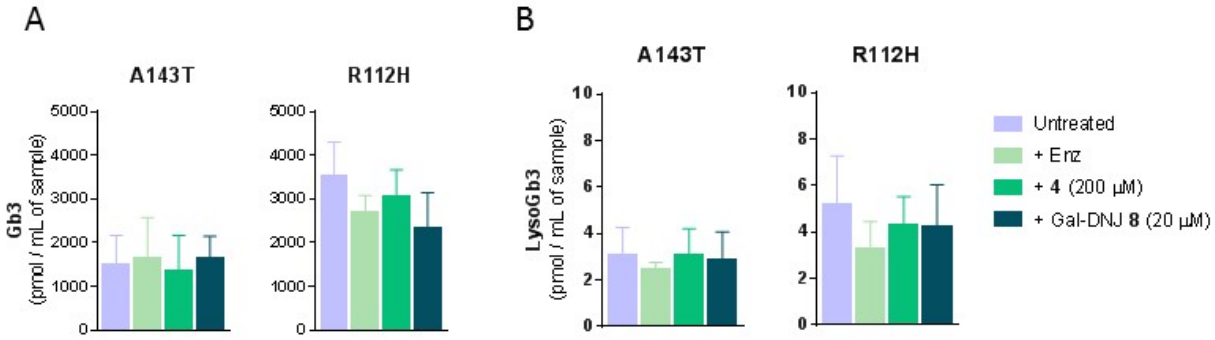


Figure S6. Gb3 and LysoGb3 quantification in cultured fibroblasts (A143T and R112H) treated with agalsidase beta co-administered with α-cyclosulfamidate 4 and Gal-DNJ 8. Gb3 (A) and lysoGb3 (B) levels measured by LC-MS/MS in variant Fabry fibroblasts (A143T and R112H), treated with agalsidase beta (50 µg/mL) with or without α-cyclosulfamidate **4** (200 µM) and Gal-DNJ **8** (20 µM) for 24 h. Data represented as mean ± standard deviation, n=4.

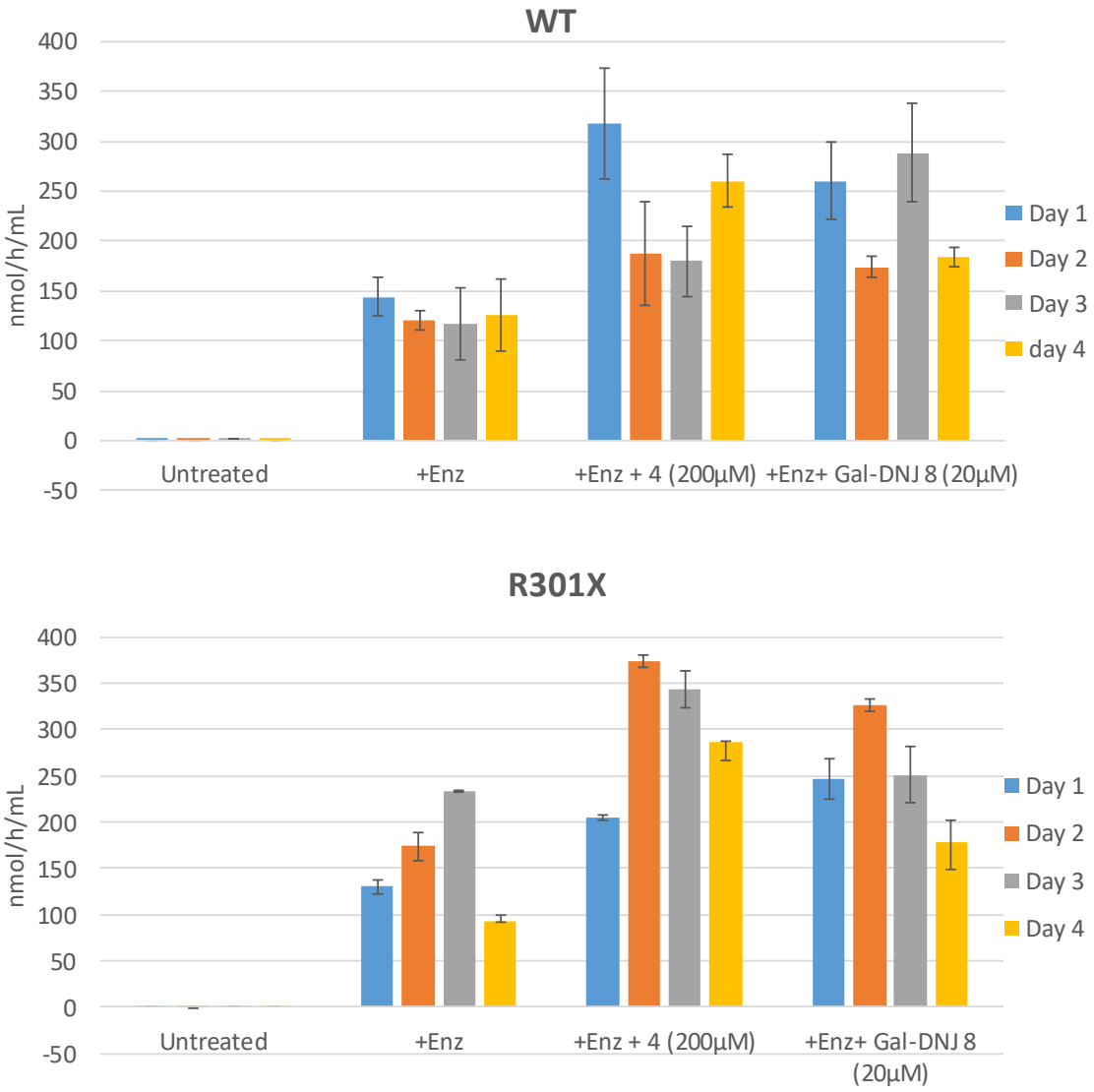


Figure S7. α-Gal A activity in cell culture medium samples. α-Gal A activity was measured in the cell medium of cultured FD fibroblasts of WT (c104) and classic Fabry (R301X) fibroblasts treated with agalsidase beta (200 ng/mL) or with a combination of enzyme (200 ng/mL) and α-cyclosulfamidate **4** (200 µM) or Gal-DNJ **8** (at 20 µM) for 4 days. α-Gal A activity is higher in all the cell mediums treated with α-cyclosulfamidate **4** (200 µM) or Gal-DNJ **8** (at 20 µM) in combination with agalsidase beta (200 ng). Reported activities are mean ± standard deviation from two biological replicates, each with two technical replicates.

Table S1. Apparent IC_{50} values for *in vitro* inhibition of in human plasma and human recombinant β-glucosidase GBA and α-glucosidase (GAA). Reported values are mean ± standard deviation from 3 technical replicates.

Compound	***In vitro* GBA IC_{50} (μM)**	***In vitro* GAA IC_{50} (μM)**
α-*Gal*-cyclosulfamidate 4	174 ± 10	>1000
Gal-DNJ 8	168 ± 8	1000 (65% inh.)

Table S2. Crystallographic data collection and refinement statistics.

	2	**4**	**6**	**7**
Data collection				
Space group	*P* 3_2 2 1	*P* 3_2 2 1	*P* 3_2 2 1	*P* 3_2 2 1
Cell dimensions				
a, *b*, *c* (Å)	90.3, 90.3, 216.0	90.6, 90.6, 216.3	90.4, 90.4, 216.3	90.3, 90.3, 216.2
α, β, γ, (°)	90, 90, 120	90, 90, 120	90, 90, 120	90, 90, 120
Resolution (Å)	78.24-2.07 (2.11-2.07)	63.51-1.99 (2.02-1.99)	63.40-2.02 (2.05-2.02)*	63.44-2.04 (2.08-2.04)
R_{merge}	0.09 (2.17)	0.08 (2.18)	0.11 (2.52)	0.13 (2.70)
R_{pim}	0.027 (0.669)	0.025 (0.684)	0.034 (0.778)	0.042 (0.844)
$CC_{1/2}$	0.999 (0.574)	0.999 (0.561)	0.999 (0.753)	0.998 (0.577)
I / σI	16.7 (1.1)	14.5 (1.2)	12.7 (1.1)	9.92 (0.9)
Completeness (%)	100.0 (100.0)	100.0 (99.8)	100.0 (100.0)	100 (100)
Redundancy	12.1 (12.4)	12.1 (11.9)	12.1 (12.2)	12.2 (11.9)
Refinement				
Resolution (Å)	78.24-2.07	63.51-1.99	63.40-2.02	63.44-2.04
No. reflections	63129	71432	67994	66147
R_{work} / R_{free}	0.19/0.24	0.22/0.28	0.20/0.26	0.20/0.26
No. atoms	6948	6966	6837	6839
Protein	6267	6290	6259	6282
Ligand/ion	409	402	345	317
Water	272	274	233	240
B-factors (Å^2)				
Protein	58	60	55	58
Ligand/ion	92	91	82	88
Water	59	63	57	58
R.m.s. deviations				
Bond lengths (Å)	0.008	0.008	0.008	0.007
Bond angles (°)	1.57	1.58	1.54	1.53
Ramachandran Plot Residues				
In most favourable regions (%)	96.0	96.3	95.6	95.2
In allowed regions (%)	3.1	2.8	3.2	4.0
PDB	6IBM	6IBK	6IBR	6IBT

*Values in parentheses are for highest resolution shell

3. Materials and Methods

Chemical probes and inhibitors. 4MU-α-galactopyranoside and 4MU-β-galactopyranoside were obtained from Melford Biolaboratories and Sigma-Aldrich, respectively. Gal-DNJ **8** [1,2], α-*glc*-cyclosulfate **1**[3], α-*gal*-cyclophellitol **6**[4], α-*gal*-cyclophellitol aziridine **7**[4], α-galactosidase Cy5 ABP **10**, 2,4-dinitrophenyl-β-D-galactopyranoside[5], 2,4-dinitrophenyl-α-D-galactopyranoside[5] were synthesized according to described procedures and their spectroscopic data are in agreement with those previously reported. All final compounds were lyophilized and aliquoted in 100-1000 nmol tubes before tested.

3.1. Biochemical and Biological Methods

Tissue and cell samples. Patients with Fabry disease were diagnosed on the basis of reduced α-gal A activity and/or demonstration of an abnormal genotype. Wild-type male human fibroblasts (c104) were obtained from Cambrex-Lonza (CC-2511, lot nr 104564, East Rutherford, NJ, USA). Fibroblast cell lines from classical FD (R301X and D136Y) and variant FD (A143T and R112H) individuals were obtained from the Lysosomal Outpatient Clinic of the Academic Medical Center in Amsterdam (AMC). Informed consent was obtained from all patients for investigations in accordance with the Declaration of Helsinki. For lysis, cells were washed three times with PBS, subsequently lysed by scraping in potassium phosphate buffer [K_2HPO_4–KH_2PO_4, 25 mM, pH 6.5, supplemented with 0.1 % (v/v) Triton X-100 and protease inhibitor cocktail (Roche, Basel, Switzerland)], aliquoted and stored at -20 °C until use. Lysate protein concentrations were determined with a Bradford assay using BSA as a standard. Naga enzyme was produced in Nicotiana benthamiana plants and purified in house as described earlier[6].

***In vitro* apparent IC_{50} measurements.** Enzyme preparations used for IC_{50} and kinetics measurements were as follows. Recombinant human α-gal A (agalsidase beta), recombinant human GBA1 (Cerezyme) and recombinant human GAA (Myozyme) were obtained from Genzyme. β-Galactosidase GLB1 was measured in human fibroblasts lysates (prepared in potassium phosphate buffer [K_2HPO_4–KH_2PO_4, 25 mM, pH 6.5, supplemented with 0.1 % (v/v) Triton X-100 and protease inhibitor cocktail (Roche, Basel, Switzerland)], using 5.5 µg total protein. For GALC measurements, recombinant murine GALC with 83% homology to human GALC was over-expressed in human embryonic kidney 293 (HEK293) and the secreted GALC to the culture medium (DMEM high glucose, Gibco) was used (5 µL of culture medium). To determine *in vitro* apparent IC_{50} values, 12.5 µL of enzyme mixture was pre-incubated with 12.5 µL of inhibitor for 30 min, in the following buffers: α-gal A in 150 mM McIlvaine buffer pH 4.6, 0.1 % Bovine Serum albumin (BSA) (w/v), GLB1 and GALC in 150 mM McIlvaine buffer pH 4.3, 0.1 % Bovine Serum albumin (BSA) (w/v) with 0.2 M NaCl, GBA1 in 150 mM McIlvaine buffer pH 5.2, 0.2% Taurocholate (w/v), 0.1% Triton X-100 (v/v), 0.1% Bovine Serum albumin (BSA) (w/v) and GAA in 150 mM McIlvaine buffer pH 4.0, 0.1% BSA (w/v). Following pre-incubation, 100 µL of substrate solution in the same buffer was added to 25 µL of the E + I mix and incubated for 30 minutes at 37 °C. α-Gal A residual activity was measured using final concentration of agalsidase beta (1 nM) and 4.2 mM 4-methylumbeliferone(4MU)-α-D-

galactopyranoside. GLB1 and GALC residual activities were measured using final concentrations of 1 mM 4MU-β-D-galactopyranoside, for 30 min at 37 °C. Finally, all enzyme reactions were quenched with 200 µL 1M NaOH-Glycine (pH 10.3), and liberated 4MU fluorescence was measured with a LS55 fluorescence spectrophotometer (Perkin Elmer; λ_{EX} 366 nm, λ_{EM} 445 nm). Values plotted for [I] are those in the final reaction mixture, containing E + I + S. *In vitro* IC_{50} values were determined in technical triplicate.

Kinetic studies. 12.5 µL of agalsidase beta (6.25 nM final concentration) and 12.5 µL of relevant inhibitor dilution were pre-incubated for 10, 30, 60, 120, 180, and 240 min at 37 °C in 150 mM McIlvaine buffer pH 4.6, supplemented with 0.1 % (w/v) BSA. Following inhibitor pre-incubations, reactions were started by addition of 50 µL of substrate mix containing 200 µM 2,4-dinitrophenyl-α-D-galactopyranoside in 150 mM McIlvaine buffer pH 4.6, supplemented with 0.1 % (w/v) BSA. Release of 2,4-dinitrophenolate was monitored via absorbance at 400 nm for 10 minutes to determine the hydrolysis rate in the presence of inhibitor (V_i), and in the absence of inhibitor (V_o). Pseudo-first order rate constants (k_{obs}) for each value of [I] were obtained from the gradient of a plot of $-\ln V_i/V_0$ against time. k_{obs} were then plotted against [I], and fitted to the equation $k_{obs} = (k_{inact}[I]/K_I + [I])$ in GraphPad Prism 7. For cases in which fast inhibition is observed at high [I] (> 50 % inhibition after 30s), a combined k_{inact}/K_I ratio was determined using the approximation $k_{obs} = k_{inact}[I]/K_I$, where k_{inact}/K_I is the slope of a linear fit of k_{obs} *vs* [I]. For irreversible inhibition kinetics, values plotted for [I] are those in the initial inhibition mixture, containing only E + I.

When reversible inhibition was observed (no variation of V_i/V_0 with time), 12.5 µL of agalsidase beta (6.25 nM final concentration) and 12.5 µL of relevant inhibitor dilution and a range of concentrations (0.05 – 2.0 mM) of 2,4-dinitrophenyl-α-D-galactopyranoside substrate was added to the enzyme-inhibitor mixture and the release of 2,4-dinitrophenolate was monitored via absorbance at 400 nm 10 minutes to determine the hydrolysis rate. K_I values of reversible inhibition were determined by linear mixed inhibition kinetics.[7] For reversible inhibition, values plotted for [I] are those in the final reaction mixture, containing E + I + S.

Thermo-stability assays (TSAs). Agalsidase beta (2.98 µL, 8.43 µM) was mixed with inhibitor (20 mM in HEPES pH 7) at concentrations ranging from 0 µM to 1000 µM in PCR tubes. Buffer (20mM HEPES, 100 mM NaCl, pH 7.4) was added to make a total reaction volume of 24 µL and a final enzyme concentration of 1 µM. The enzyme and inhibitor were incubated for 1 hour at room temperature, after which Sypro orange dye (1 µL, 125x) was added. The PCR tubes were placed in an Agilent Stratagene Mx3005P qPCR instrument. The Sypro orange dye was excited at λ_{ex} 517 nm and the resulting fluorescence signal was monitored at λ_{em} 585 nm as the temperature was ramped from 25 °C to 95 °C in 1 °C increments every 30 seconds. The fluorescence signal was measured in triplicates at each temperature increment and the average taken. The averaged fluorescence signal was plotted against temperature for each concentration of inhibitor and the data fitted to a sigmoid-5 function to yield thermal stability

curves. The melting temperature (T_m) of agalsidase beta was determined at each inhibitor concentration by taking the mid-point value of the thermal stability curves. The change in melting temperature (ΔT_m) was calculated by taking the difference in T_m at each inhibitor concentration relative to a control.

***In vitro* stabilization of agalsidase beta in cell culture medium.** Inhibitors' stabilization effect was studied in Dulbecco's Modified Eagles Medium/Nutrient Mixture F-12 (DMEM/F12, Sigma-Aldrich) medium, supplemented with 10 % fetal calf serum and 1 % penicillin/streptomycin at pH 7.2, mimicking fibroblasts cell culture conditions. Agalsidase beta (25 µL, 2.5 mg/mL) was incubated at 37 °C in cell culture medium at pH 7.2 for 5, 10, 15, 20, 30 and 60 min. After 15 min, 80 % degradation was observed, and this time point was used for further analysis. Thus, inhibitors (12.5 µL) at increasing concentrations (starting around the IC_{50} value of the corresponding inhibitor) were incubated with agalsidase beta (12.5 µL, 5 mg/mL) in cell medium conditions at pH 7.2 for 15 min and 0 min (for 100 % hydrolytic activity reference). Then, in duplicates 25 µL of sample (12.5 µL enzyme plus 12.5 µL inhibitor in cell culture medium and 1 % DMSO) were incubated in a shaker at 4 °C for 1 hour with 25 µL of ConA beads. The samples were next centrifuged at 16000 rcf for 10 minutes at 4 °C and the supernatant was discarded. The ConA beads were likewise washed 3x with 500 µL of washing buffer (sodium acetate buffer pH 6 supplemented with 0.1 M NaCl, 1 mM $CaCl_2$ and 1 mM $MnCl_2$). Afterwards, 100 µL of 4MU-α-D-galactopyranoside substrate (4.2 mM) in 150 mM McIlvaine buffer pH 4.6 supplemented with 0.1 % BSA (w/v) was added to the ConA beads and the mixture was incubated for 30 min at 37 ^{o}C. Finally, all enzyme reactions were quenched with 200 µL 1 M NaOH-Glycine (pH 10.3), and liberated 4MU fluorescence was measured with a LS55 fluorescence spectrophotometer (Perkin Elmer; λ_{EX} 366 nm, λ_{EM} 445 nm). Values plotted for [I] are those in the final reaction mixture, containing E + I + S and the percentage of α-galactosidase activity was calculated considering incubation time 0 min as 100 % activity.

Competitive activity-based protein profile (ABPP) in recombinant α-galactosidases. Agalsidase beta or alpha (200 ng), or N-acetylgalactosaminidase (NAGA, 200 ng) were incubated with different concentrations of both inhibitor **4** and GalDNJ **8**, ranging from 1 to 1000 µM, for 15 min. Then, enzymes were also incubated with 0.2 µM of ABP **10**, (Cy5 α-Gal), for 30 min in a water bath at 37 °C. After ABP incubation, proteins were denatured by boiling the samples with Laemmli buffer (50 % (v/v) 1 M Tris-HCl, pH 6.8, 50 % (v/v) 100 % glycerol, 10 % (w/v) DTT, 10 % (w/v) SDS, 0.01 % (w/v) bromophenol blue) for 5 min at 98 °C, and separated by electrophoresis on sodium dodecyl Sulphate-polyacrylamide gels, 10 % (SDS-PAGE), following fluorescent scanning of the gels as previously described.[4,6] Coomassie brilliant blue staining of the gels was performed in order to show equal protein loading.

***In situ* treatment of cultured fibroblasts from patients with Fabry disease.**

24 h Treatment. Fibroblasts (5 cell lines (males): WT, Fabry variants R112H and A143T, and Fabry classic D136Y and R301X) were grown in 12 well plates (0.5 mL of medium) in a humidified incubator at 37 °C with 5 % CO_2. Experiments were performed in triplicates. Fibroblasts were untreated as control (1 µL DMSO), or treated with 1 µL of 100 µg/mL of agalsidase beta, with inhibitor **4** (1 µL of 100 mM stock solution, final concentration 200 µM) or Gal-DNJ **8** (1 µL of 10 mM stock solution, final concentration 20 µM), or with the combination of 1 µL of 100 µg/mL of agalsidase beta and inhibitor **4** or Gal-DNJ **8** at 200 or 20 µM, respectively, followed by 24 h incubation. Next, the medium was collected for α-galactosidase activity assays and cells were washed, collected (combine the triplicates) and lysed in ice-cold 25 mM phosphate buffer, pH 6.5, supplemented with 0.1 % Triton X-100 and protease inhibitor cocktail table (Roche). The lysates were stored at -20 ^{o}C until further use.

4-day Treatment. Fibroblasts WT and classic Fabry (R301X) cell lines were grown in 12 well plates (0.5 mL of medium) in a humidified incubator at 37 °C with 5 % CO_2. Experiments were performed in triplicates. Fibroblasts were untreated as control (1 µL DMSO), or treated with 1 µL of 100 ng/µL of agalsidase beta, or with the combination of 1 µL of·100 ng/µL agalsidase beta and inhibitor **4** (1 µL of 100 mM stock solution, final concentration 200 µM) or Gal-DNJ **8** (1 µL of 10 mM stock solution, final concentration 20 µM), followed by a 4-day incubation. The medium was collected for α-galactosidase activity assays every 24 h and new medium supplemented with DMSO, agalsidase beta or the combination of enzyme and inhibitor was added. On the fifth day, cells were washed, collected (combine the triplicates) and lysed in ice-cold 25 mM phosphate buffer, pH 6.5, supplemented with 0.1 % Triton X-100 and protease inhibitor cocktail table (Roche). The lysates were stored at -20 ^{o}C until further use. A second experiment was performed in treated fibroblast WT and classic Fabry (R301X) with 1 µL of DMSO as control, or treated with 1 µL of·100 ng/µL of agalsidase beta, or with the combination of half amount of enzyme (1 µL of·50 ng/µL agalsidase beta) and inhibitor **4** (1 µL of 100 mM stock solution, final concentration 200 µM) or Gal-DNJ **8** (1 µL of 10 mM stock solution, final concentration 20 µM), followed by 4-day incubation.

Released 4-MU was fluorometrically quantified in fibroblast lysates as described above[8,9]. Reactions were performed in duplicates for 30 min at 37 ^{o}C at 4.2 mM of 4-methylumbeliferone(4MU)-α-D-galactopyranoside in 150 mM citrate-phosphate buffer pH 4.6 supplemented with 0.1 % (w/v) BSA. Reaction were as follow: 15 µL of Buffer with α-GAL B inhibitor NAGA (100 µM) was incubated for 30 minutes at 37 ^{o}C with 10 µL of fibroblast lysate, then 100 µL of 4MU substrate (4.2 mM) was added and the mixture was incubated for 30 min. Finally, stop buffer was added (200 µL) and fluorescence was measured.

α-Galactosidase activity in the cell medium samples was measured with a ConA purification pre-step to wash away the competitive inhibitors. Thus, in duplicate 25 µL of sample medium was incubated in a shaker at 4 °C for 1 hour with 25 µL of ConA beads. Then, the samples were centrifuged at 16000 rcf for 5 minutes at 4 °C and the supernatant was discarded. The conA

beads were likewise washed 3x with 200 µL of washing buffer (sodium acetate buffer pH 6 supplemented with 0.1 M NaCl, 1 mM $CaCl_2$ and 1 mM $MnCl_2$). Afterwards, 100 µL of 4MU substrate (4.2 mM) was added to the ConA beads and the mixture was incubated for 30 min at 37 ^oC. Finally, stop buffer was added (200 µL) and fluorescence was measured.

Gb3 and LysoGb3 determination. Gb3 and LysoGb3 were extracted as previously described by a modification of the Bligh and Dyer method using acidic buffer (100 mM ammonium formate buffer pH 3.1). Prior to extraction, 20 µL of the internal standard C17-dh-Ceramide (20 µM) and 20 µL of $^{13}C_5$-LysoGb3 (0.1 µM) were added to 50 µL of cell homogenate.[10]

Briefly, lipids were extracted by adding methanol, chloroform, and ammonium formate buffer (1:1:0.9; v/v/v) which resulted in 2 phases. The upper phase was dried under N_2 stream and further extracted with water/butanol (1:1; v/v) before being applied to the UPLC-MS. The lower phase was transferred to a Pyrex tube and de-acylated in a microwave for 1 h with 500 µL of methanolic NaOH (0.1 M). De-acylated lipids were additionally extracted with water/butanol (1:1; v/v) before being applied to the UPLC-MS. Lipids were analysed by reverse-phase liquid Chromatography using a Waters UPLC-Xevo-TQS micro and a BEH C18 column, 2.1 × 50 mm with 1.7 µm particle size (Waters, USA). Data was processed with MassLynx 4.1 Software (Waters Corporation, USA).

3.2. Molecular Modeling

Conformational free energy landscapes

Conformational free energy landscapes (FELs) were computed for α-*gal*-cyclosulfate **2**, α-*gal*-cyclosulfamidates **3** and **4**, α-*gal*-cyclosulfamide **5**, α-*gal*-cyclophellitol **6** and α-*gal*-cyclophellitol aziridine **7**, using quantum mechanical calculations, in particular Density Functional Theory-based molecular dynamics (MD), according to the Car-Parrinello (CP) method[11]. Each molecule was enclosed in an isolated cubic box of 12.0 Å × 12.0 Å × 12.0 Å. A fictitious electron mass of 700 au was used for the CP Lagrangian and a time step of 0.12 fs was used in all CPMD simulations. The Kohn-Sham orbitals were expanded in a plane wave (PW) basis set with a kinetic energy cutoff of 70 Ry. *Ab initio* pseudopotentials, generated within the Troullier-Martins scheme, were employed[12]. The Perdew, Burke and Ernzerhoff generalized gradient-corrected approximation (PBE)[13] was selected in view of its good performance in previous work on isolated sugars[14], glycosidases[15] and glycosyltransferases[16].

The metadynamics algorithm[17], provided by the Plumed 2 plugin[18], was used to explore the conformational free energy landscape of the systems, taking as collective variables θ and ϕ of the puckering coordinates of Cremer and Pople[19], in the spirit of the pioneering work by Dowd, French and Reilly[20]. Initially, the height of these Gaussian terms was set at 0.6 kcal mol^{-1} and a new Gaussian-like potential was added every 250 MD steps. Once the whole free energy space was explored, the height of the Gaussian terms was reduced to half of its initial value (0.1-0.3 kcal·mol^{-1}) and a new Gaussian-like potential was added every 500 MD steps. The width of the Gaussian terms was set to 0.10 radians. The simulations were stopped when energy differences among wells remain constant. For all molecules, the phase space was fully

explored in less than 80 ps and the simulations were further extended up to 450 ps for α-*gal*-cyclosulfate **2**, α-*gal*-cyclosulfamidate **3**, α-*gal*-cyclosulfamidate **4** and α-*gal*-cyclosulfamide **5**. In the case of α-*gal*-cyclophellitol **6** and α-*gal*-cyclophellitol aziridine **7** (**Figure S2, S3**), the simulation was extended to 160 ps. The errors in the principal minima, taken as a standard deviation (SD) from the last 60 ps, are below 1 kcal mol^{-1}.

3.3. Crystallographic data collection and refinement statistics

Crystallographic data collection and refinement of α-gal A (agalsidase beta)

Initial crystallization screening was carried out using sitting-drop vapour-diffusion, set up using a *Mosquito Crystal* liquid handling robot. Parent conditions were taken from Guce *et al* (2010)[21] and JCSG D4 with microseeding.

A seed stock was prepared from JCSG D4 conditions containing 0.2 M lithium sulfate, 0.1 M sodium acetate (pH 4.6) and 30 % PEG 8K. A seeding solution containing 0.2 M lithium sulfate, 0.1 M sodium acetate (pH 4.6), 30 % PEG 8K and crushed agalsidase beta crystals were prepared and mixed with the seed stock at 1, 1:10, 1:100, 1:1000, 1:10000 and 1:100000 seeding-solution:seed-stock ratios. The well solution comprised 25 % PEG 4K (50 %), 0.1 M sodium acetate (pH 4.6) and 0.2 M lithium sulfate. Crystallisation drops consisted of 500 nL agalsidase beta (20 mg/mL), 100 nL microseeding solution and 400 µL well solution. The best crystals were produced using 1:1000 microseeding.

Inhibitor was prepared at 20 mM in HEPES buffer (20 mM, pH 7.0) and diluted to 4 mM in mother liquor comprising of 0.2 M lithium sulfate, 0.1 M sodium acetate (pH 4.6) and 25 % PEG 4K (50 %). Crystals were soaked in 5 µL of inhibitor-mother liquor solution for 4 hours at 18 °C. Crystals were transferred to 5 µL of ethylene glycol cryoprotectant, containing 25 % EG (100 %), 50 % PEG 4K (50 %), 0.1 M sodium acetate (pH 4.6) and 0.2 M lithium sulfate, before freezing in liquid nitrogen for in-house data collection. Crystals were sent to the Diamond Light Source facility for full data collection.

Data was collected at the i04 (α-*gal*-cyclosulfate **2**) and i03 (α-*gal*-cyclosulfamidate **4**) beamline of the Diamond Light Source facility. The data were processed using XIA2[22,23] and AIMLESS data reduction pipelines through the CCP4i2 software[24]. All diffraction data were re-indexed to the appropriate space group ($P\,3_2\,2\,1$) and solved by molecular replacement using MOLREP[25] with PDB 1R46[26] as the search model. Refinement was performed using REFMAC[27], followed by several rounds of manual model building with COOT[28]. Idealized coordinate sets and refinement dictionaries for the inhibitors were generated using JLIGAND[29] and sugar conformations were validated using Privateer[30]. Crystal structure figures were generated using ccp4mg[31] (**Table S1**).

4. Chemical Synthesis

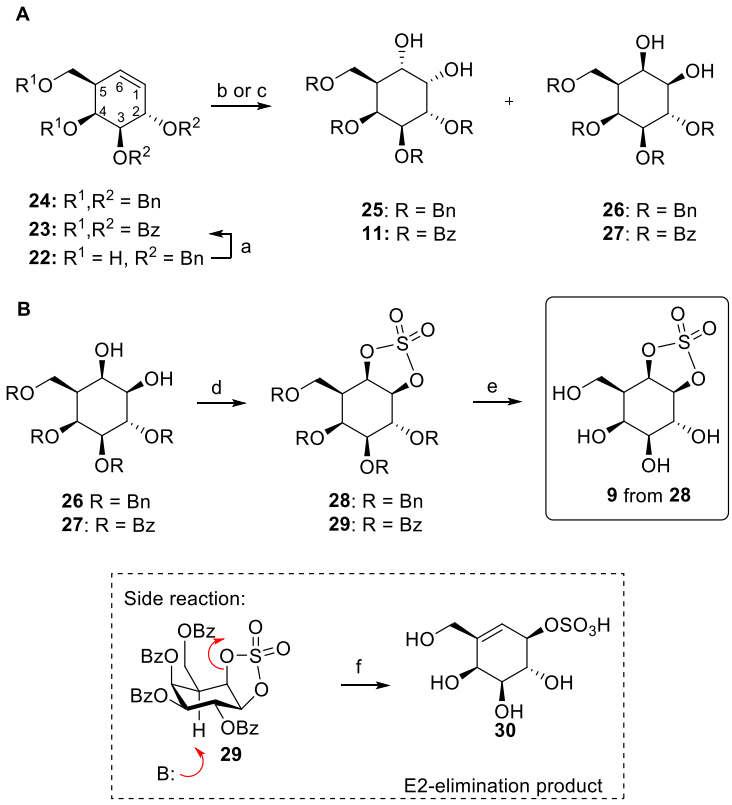
4.1. General Experimental Details

Unless stated otherwise, starting materials, reagents and solvents were purchased as high-grade commercial products from Sigma-Aldrich or ABCR and were used without further purification. Dichloromethane (DCM), tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were stored over 4 Å molecular sieves, which were dried *in vacuo* before use. All reactions were performed under an argon atmosphere unless stated otherwise. Solvents used for flash column chromatography were of pro analysis quality. Reactions were monitored by analytical thin-layer chromatography (TLC) using Merck aluminum sheets pre-coated with silica gel 60 with detection by UV absorption (254 nm) and by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot H_2O$ (10 g/L) in 10% sulfuric acid followed by charring at ~150 ˚C or by spraying with an aqueous solution of $KMnO_4$ (7%) and K_2CO_3 (2%) followed by charring at ~150 °C. Column chromatography was performed manually using either Baker or Screening Device silica gel 60 (0.04 - 0.063 mm), or with a Biotage Isolera™ flash purification system using silica gel cartridges (Screening devices SiliaSep HP, particle size 15-40 µm, 60A) in the indicated solvents. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV-500 (500/125 MHz), and Bruker AV-400 (400/100 MHz) spectrometer in the given solvent. Chemical shifts are given in ppm relative to the chloroform, methanol, or dimethylsulfoxide residual solvent peak or tetramethylsilane (TMS) as internal standard. Coupling constants are given in Hz. All given ^{13}C spectra are proton decoupled. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), qt (quintet), m (multiplet), br (broad), ar (aromatic), app (apparent). 2D NMR experiments (HSQC, COSY and NOESY) were carried out to assign protons and carbons of the new structures and assignation follows the general numbering shown in cyclohexene **24**. High-resolution mass spectra (HRMS) of intermediates were recorded with an LTQ Orbitrap (Thermo Finnigan), and final compounds were recorded with an apex-QE instrument (Bruker). Optical rotations were measured on an Anton Paar MCP automatic polarimeter (Sodium D-line, λ = 589 nm). LC/MS analysis was performed on an LCQ Advantage Max (Thermo Finnigan) ion-trap spectrometer (ESI+) coupled to a Surveyor HPLC system (Thermo Finnigan) equipped with a C18 column (Gemini, 4.6 mm x 50 mm, 3 µm particle size, Phenomenex) equipped with buffers A: H_2O, B: acetonitrile (MeCN) and C: 1% aqueous TFA, or an Agilent Technologies 1260 Infinity LCMS with a 6120 Quadrupole MS system equipped with buffers A: H_2O, B: acetonitrile (MeCN) and C: 100 mM NH_4OAc.

4.2. Synthesis and Characterization Data of Compounds

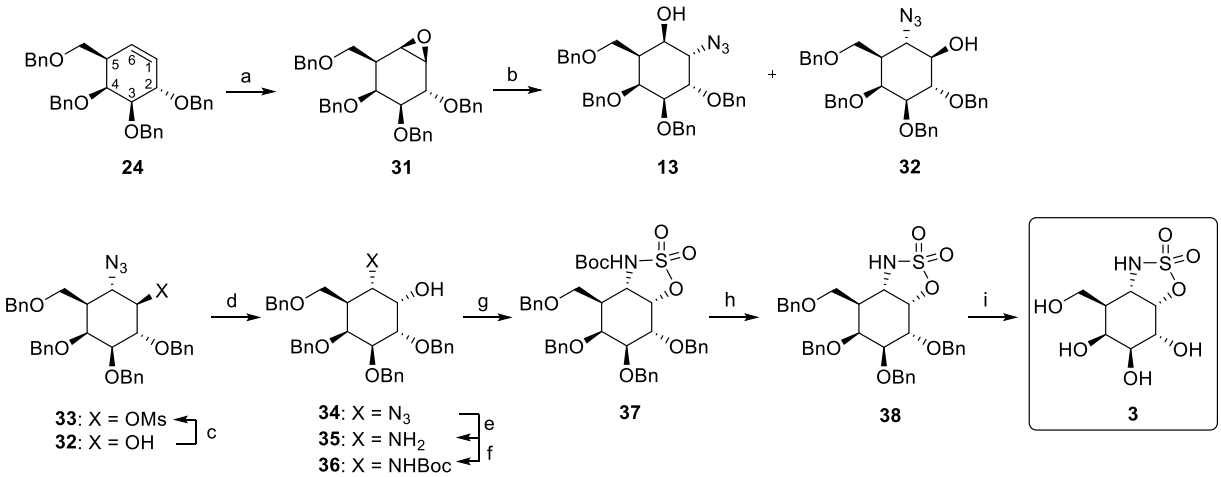
First, for the synthesis of the cyclosulfates **2** and **9,** perbenzylation of starting cyclohexene **24** (synthesized from D-xylose following the procedure described by Llebaria and co-workers[32]) and subsequent oxidation with OsO_4 gave diols **25** and **26** as a non-separable mixture of isomers with a 1:4 ratio (**Scheme S1A**). In parallel, oxidation with $RuCl_3$ and sodium periodate by *in situ* formation of RuO_4 exclusively afforded β-diol **26**. In order to synthesize an α-diol

intermediate, we explored the oxidation reaction in different protected cyclohexenes. Oxidation reactions on acetylated cyclohexene (following either OsO_4 or RuO_4 protocol) yielded a mixture of multiple side products probably due to acetyl migration. Interestingly, oxidation on perbenzoylated cyclohexene **23** with OsO_4 afforded a separable mixture of diols **11** and **27** in a 1:0.6 ratio, whereas $RuCl_3$ and sodium periodate conditions yielded a 0.5:1 ratio of α- and β- diols, which could be separated after column chromatography. Benzoylated diols **11** and **27** were then treated with thionyl chloride and subsequently oxidized to the cyclic sulfate to afford the protected cyclosulfates **12** and **29**. Deprotection of β-analogue **29** with different mild/basic conditions (i.e. NH_3 in MeOH, KCN or Et_3N/H_2O under reflux) resulted in the E2-elimination product **30**. We envisioned that elimination would be less likely to occur in α-cyclosulfate **12** where the corresponding C-OSO_3 bond is equatorial. Indeed, α-*gal*-cyclosulfate **2** was obtained after benzoyl removal in methanolic ammonia (Scheme 1). β-*Gal*-cyclosulfate **9** was instead synthesized from the perbenzylated β-cyclosulfate **28** after hydrogenation in the presence of Pearlman's catalyst.



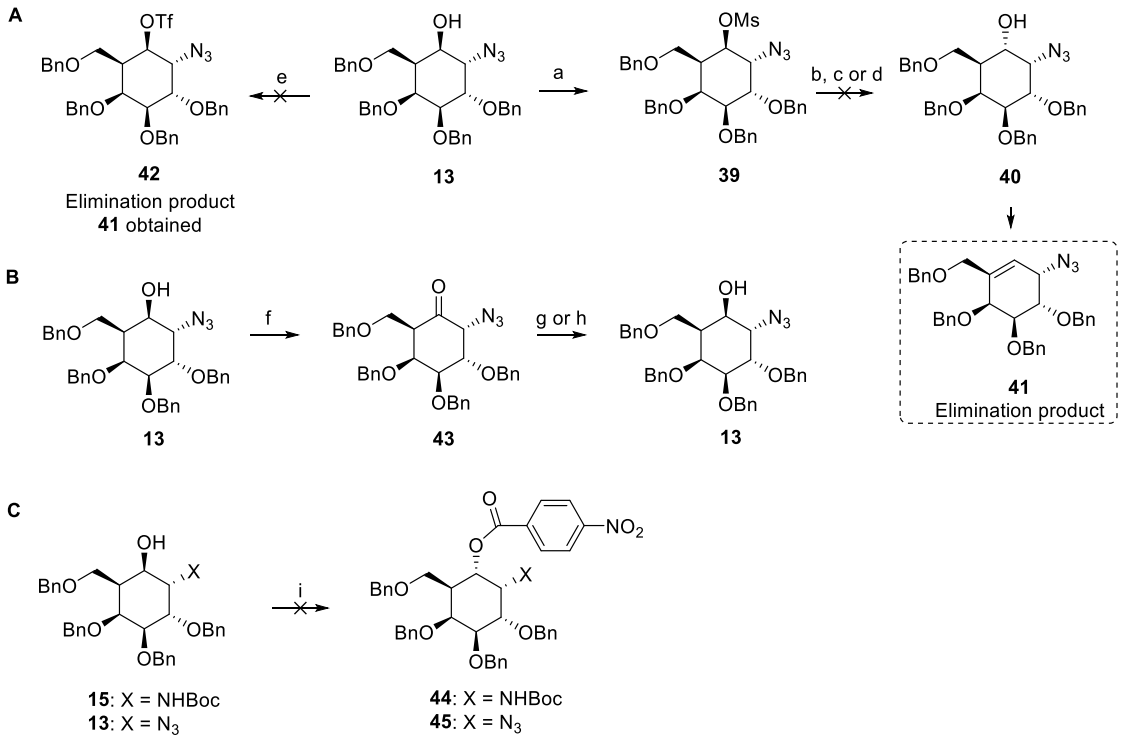
Scheme S1. Synthesis of D-galactose configured cyclosulfate analogues 2 and 9. Synthesis of protected diols **11** and **25**-**27** (A), and β-*gal*-cyclosulfate **9** (B). Reagents and conditions: a) (i) BCl_3, DCM, -78 °C, 3.5 h; (ii) BzCl, pyridine, rt, 18 h, 79%; b) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, EtOAc, MeCN, 0 °C, 2 h, **25**: 0% and **26**: 78%; c) OsO_4, NMO, H_2O, acetone, rt, 3 days, **11**: 44% and **27**: 34%; d) (i) $SOCl_2$, Et_3N, imidazole, DCM, 0 °C; (ii) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, 0 °C, 3 h, **28**: 69%, **29**: 82%; e) H_2, $Pd(OH)_2$, MeOH, rt, 18 h, 90%; f) NH_3, MeOH, rt, 3 h.

The synthesis of cyclosulfamidate **3** was achieved from *cis*-1-hydroxy-6-azido cyclohexene **34**, which was obtained by first nucleophilic addition of sodium azide to β-cyclophellitol **31** followed by mesylation and subsequent inversion of the stereochemistry of the secondary alcohol (**Scheme S2**). Azido intermediate **34** was reduced and ensuing Boc protection afforded intermediate **36**, which was treated with thionyl chloride under basic conditions to form a mixture of sulfite stereoisomers that were further oxidized to the Boc-protected cyclosulfamidate **37**. Cyclosulfamidate **37** was deprotected with TFA, and intermediate **38** was directly deprotected by hydrogenolysis to afford the desired final cyclosulfamidate **3**.



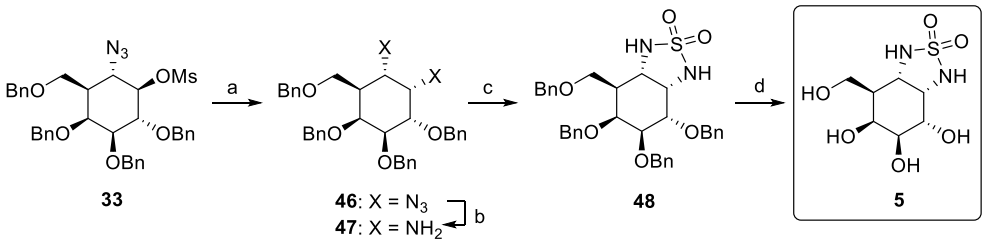
Scheme S2. Synthesis of α-D-galactose configured cyclosulfamidate 3. Reagents and conditions: a) *m*-CPBA, DCM, rt, 18 h, 76%; b) NaN_3, $LiClO_4$, DMF, 80-100 °C, 18 h, **13**: 40% and **32**: 38%; c) MsCl, Et_3N, DCM, rt, 4 h, 92%; d) H_2O, DMF, 140 °C, 3 days, 67%; e) PtO_2, H_2, THF, rt, 4 h, 80%; f) Boc_2O, Et_3N, DCM, rt, 18 h, 99%; (g) (i) $SOCl_2$, Et_3N, imidazole, DCM, 0 °C; (ii) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, 0°C, 3 h, 62%; h) TFA, DCM, rt, 8 h, 99%; i) H_2, $Pd(OH)_2$, MeOH, rt, 18 h, 92% .

Synthesis of sulfamidate **4** was to some extent a challenge (**Scheme S3** and **Scheme 1**). Mesylation of hydroxyl **13** and nucleophilic inversion of stereochemistry resulted in elimination product **41**, and the use of triflate as leaving group ensued *in situ* elimination as well. Oxidation with Dess-Martin periodinane and subsequent reduction (with sodium borohydride or a bulkier hydride reagent such as K-selectride) yielded exclusively the undesired *trans*-1-azido-6-hydroxy-cyclohexene **13**. A third attempt by means of a sterically hindered Mitsunobu inversion with *para*-nitrobenzoate described on azido-cyclohexene **13** or Boc-protected amino derivative **45** also failed.



Scheme S3. Attempted synthesis of D-galactose configured 1-amino-6-hydroxy-cyclohexane 18. Reagents and conditions: a) MsCl, Et_3N, Me-Imidazole, $CHCl_3$, rt 1.5 h, 95%; (b) H_2O, DMF, 140 °C, 3 days; (c) $NaNO_2$, DMF, 120 °C, 18 h; (d) 1 M NaOH, 1,4-dioxane, reflux, 18 h; Tf_2O, pyridine, DCM, 0 °C; (f) Dess-Martin periodinane, DCM, rt, 1.5 h, quant; (g) $NaBH_4$, THF, MeOH, 0 °C, 30 min; (h) K-selectride, THF, -78 °C, 2 h; (i) *p*-NO_2-$C_6H_4CO_2H$, DEAD, PPh_3, THF, rt, 18 h.

Cis-diamino **47** was synthesized by nucleophilic addition of sodium azide to mesylated intermediate **33** and subsequent reduction with H_2/Pt_2O in excellent yields. Then, treatment with $SO_2(NH_2)_2$ in pyridine under reflux to create the cyclic sulfate and benzyl removal by hydrogenation afforded final cyclosulfamide **5 (Scheme S4)**.



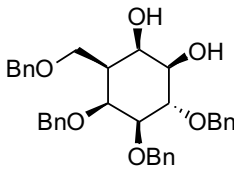
Scheme S4. Synthesis of α-D-galactose configured cyclosulfamide 5. Reagents and conditions: a) NaN_3, $LiClO_4$, DMF, 80-100 °C, 18 h, 69%; b) Pt_2O, H_2, THF, 2 h, 88%; c) $SO_2(NH_2)_2$, pyridine, reflux, 18 h, 61%; d) H_2, $Pd(OH)_2$, MeOH, rt, 18 h, 94%.

4.3. Synthesis and Characterization Data of Compounds

4.3.1. Synthesis and Characterization Data of 2 and 9.

Synthesis of D-Galactose Configured *Cis*-Diols **11**, **26** and **27**.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)cyclohexane-1,2-diol (**26**)

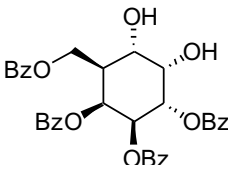


Compound **24** (507 mg, 0.97 mmol) was dissolved in EtOAc:MeCN (1:1, 30 mL) and cooled to 0 °C. A solution of $NaIO_4$ (302 mg, 1.4 mmol) and a catalytic amount of $RuCl_3 \cdot 3H_2O$ (0.027 mg, 0.13 mmol) in H_2O (8 mL) was added and the reaction mixture was stirred for 2 h at 0°C. The reaction was then quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) and the different phases were separated. The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (EtOAc from 10% to 70% in pentane) gave pure β-diol **26** (420 mg, 0.76 mmol, 78%). $[\alpha]_D^{20}$ = +16.8 (*c* = 1, MeOH). IR (neat, cm^{-1}) 3446, 3030, 2914, 2862, 1452, 1084, 1059. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 7.42 – 7.20 (m, 20H, CH Ar), 4.99 – 4.88 (m, 3H, CH_2Ph, C*H*HPh), 4.81 – 4.72 (m, 2H, CH_2Ph), 4.52 – 4.41 (m, 3H, CH_2Ph, C*H*HPh), 4.26 (s, 1H, CH-4), 3.99 – 3.87 (m, 2H, CH-2, CH-6), 3.77 (t, *J* = 9.1 Hz, 1H, C*H*HOBn), 3.66 (dd, *J* = 9.2, 5.5 Hz, 1H, CH*H*OBn), 3.54 (d, *J* = 10.3 Hz, 1H, CH-1), 3.48 – 3.43 (m, 1H, CH-3), 2.71 (s, 1H, OH-1), 1.82 – 1.75 (m, 1H, CH-5), 1.62 (br s, 1H, OH-6). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 138.9, 138.5, 138.0, 137.9 (4 C_q Ph), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5 (20 CH Ar) 83.9 (C-3), 80.9 (C-2), 77.6 (C-4), 76.0, 75.9 (2 CH_2Ph), 75.7 (C-1), 73.6, 73.3 (2 CH_2Ph), 72.1 (C-6), 68.1 (C-7), 40.9 (C-5).

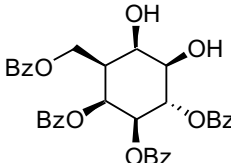
HRMS: calcd. for $[C_{35}H_{39}O_6]^+$ 555.27466; found 555.27412. HRMS: calcd. for $[C_{35}H_{38}NaO_6]^+$ 577.25661; found 577.25569; in agreement with literature.[32]

(1*S*,2*S*,3*S*,4*S*,5*R*,6*R*)-4-((Benzoyloxy)methyl)-5,6-dihydroxycyclohexane-1,2,3-triyl tribenzoate (**11**) and (1*S*,2*S*,3*S*,4*S*,5*S*,6*S*)-4-((benzoyloxy)methyl)-5,6-dihydroxycyclohexane-1,2,3-triyl tribenzoate (**27**)

Compound **23** (3.77 g, 6.54 mmol) was dissolved in acetone:H_2O (6:1, 58 mL), and NMO (1.53 g, 13.1 mmol) and a catalytic amount of OsO_4 (2.5 wt% in H_2O, 4.99 g, 6.16 mL, 0.49 mmol) were added. The reaction mixture was stirred for 72 h at room temperature. The reaction was then quenched with saturated aqueous Na_2SO_3 (50 mL), diluted with H_2O (20 mL), and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture gave a ratio of **11**/**27**: 1/0.6. Purification by column chromatography with silica gel from Fisher Scientific (60 Å, particle size 20-45 micron, toluene to 15% EtOAc in toluene) gave β-diol **27** as a white foam (1.36 g, 2.23 mmol, 34%), a mixture of β-diol **27** and α-diol **11** as a white foam (0.95 g, 1.55 mmol, 24%, ratio α/β: 1/0.1), and α-diol **11** as a white foam (0.81 g, 1.33 mmol, 20%).



α-Diol 11: $[\alpha]_D^{20}$ = +65.2 (*c* = 1, MeOH). IR (neat, cm^{-1}) 1720, 1601, 1450, 1265, 1109, 1094, 1069, 1026. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 8.01 – 7.89 (m, 6H, CH Ar), 7.71 (dd, *J* = 8.3, 1.2 Hz, 2H, CH Ar), 7.61 – 7.55 (m, 1H, CH Ar 7.51 – 7.36 (m, 5H, CH Ar), 7.33 – 7.15 (m, 6H, CH Ar), 6.16 (t, *J* = 2.7 Hz, 1H, CH-4), 5.99 (dd, *J* = 10.6, 3.2 Hz, 1H, CH-3), 5.75 (dd, *J* = 10.6, 2.7 Hz, 1H, CH-2), 4.85 (dd, *J* = 11.5, 3.9 Hz, 1H, C*H*HOBz), 4.66 (d, *J* = 2.3 Hz, 1H, CH-1), 4.47 (dd, *J* = 11.5, 8.6 Hz, 1H, CH*H*OBz), 4.27 – 4.19 (m, 1H, CH-6), 3.45 (d, *J* = 9.2 Hz, 1H, OH-6), 3.37 (d, *J* = 1.9 Hz, 1H, OH-1), 3.02 – 2.94 (m, 1H, CH-5). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 167.3, 166.1, 165.9, 165.5, (4 C=O), 133.5, 133.2, 129.9, 129.8, 129.2, 128.8, 128.5, 128.4, 128.3 (20 CH Ar), 129.6, 129.5, 129.3, 129.2 (4 C_q Bz), 71.6 (C-1/C-2), 71.3 (C-1/C-2), 70.5 (C-3), 69.1 (C-4), 67.8 (C-6), 63.0 (C-7), 40.0 (C-5). HRMS: calcd. for $[C_{35}H_{31}O_{10}]^+$ 611.19172; found 611.19139.



β-Diol 27: $[\alpha]_D^{20}$ = +51.4 (*c* = 1, MeOH). IR (neat, cm^{-1}) 1720, 1601, 1450, 1267, 1109, 1096, 1070, 1026. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.09 (m, 2H, CH Ar), 8.06 – 7.99 (m, 2H, CH Ar), 7.97 – 7.92 (m, 2H, CH Ar), 7.79 – 7.74 (m, 2H, CH Ar), 7.59 – 7.50 (m, 2H, CH Ar), 7.48 – 7.36 (m, 7H, CH Ar), 7.34 – 7.12 (m, 3H, CH Ar), 6.12 – 6.05 (m, 2H, CH-2, CH-4), 5.52 (dd, *J* = 10.5, 3.3 Hz, 1H, CH-3), 4.79 (dd, *J* = 11.3, 7.6 Hz, 1H, C*H*HOBz), 4.48 (dd, *J* = 11.3, 7.4 Hz, 1H, CH*H*OBz), 4.30 (dd, *J* = 6.4, 3.4 Hz, 1H, CH-6), 3.96 – 3.89 (m, 1H, CH-1), 3.56 (d, *J* = 7.4 Hz, 1H, OH-1), 3.43 (d, *J* = 4.2 Hz, 1H, OH-6), 2.49 – 2.42 (m, 1H, CH-5). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 167.3, 166.8, 165.9, 165.8 (4 C=O), 133.5, 133.4, 133.3, 130.1, 129.8, 129.1, 129.0, 128.6, 128.4, 128.3 (20 CH Ar), 129.5, 129.4 129.3, 128.7 (4 C_q Bz), 73.3 (C-1), 72.1 (C-3), 71.8 (C-2/C-4), 69.5 (C-6),

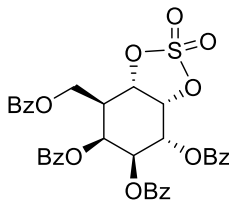
68.93(C-2/C-4), 61.9 (C-7), 39.7 (C-5). HRMS: calcd. for $[C_{35}H_{31}O_{10}]^+$ 611.19172; found 611.19127.

General Procedure for the Synthesis of Cyclosulfates **12**, **28** and **29**.

Thionyl chloride (3.5 eq. for *cis*- and 7 eq. for *trans*-diol) was added over 5 min to a solution of diol (1 eq.) and triethylamine (4 eq.) in DCM (50 mL/mmol) at 0 °C and the reaction was kept at neutral pH. The reaction mixture was then diluted with cold diethyl ether and washed with cold water and brine. The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure, co-evaporated with toluene (3 x 10 mL), and the residual triethylamine was removed under high vacuum (1 h).

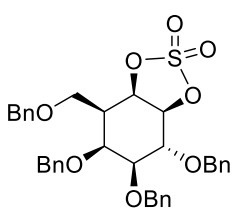
The resulting oil was dissolved in CCl_4 (40 mL/mmol) and MeCN (40 mL/mmol), and the solution was cooled to 0 °C in an ice-bath. A solution of catalytic amount of $RuCl_3 \cdot 3H_2O$ (0.1 eq.) and $NaIO_4$ (2 eq.) in water (40 mL/mmol) was added, and the reaction mixture was stirred at 0 °C for 3 h. Diethyl ether was added, and the two layers were separated. The aqueous phase was extracted again with diethyl ether and the combined organic extracts were washed with brine and dried over $MgSO_4$. The crude was concentrated under reduced pressure and purified by silica column chromatography (from Pentane to Pentane/EtOAc 8:2) to afford the desired intermediates.

(3a*R*,4*R*,5*S*,6*S*,7*R*,7a*S*)-7-((Benzoyloxy)methyl)-2,2-dioxidohexahydrobenzo[*d*][1,3,2] dioxathiole-4,5,6-triyl tribenzoate (**12**)



Obtained as a white solid from **11** (100 mg, 0.16 mmol) in 56% yield (62 mg, 0.09 mmol). $[\alpha]_D^{20}$ = +86.5 (*c* = 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.05 – 7.97 (m, 2H, CH Ar), 7.97 – 7.87 (m, 4H, CH Ar), 7.80 (d, 2H, CH Ar), 7.66 – 7.51 (m, 2H, CH Ar), 7.51 – 7.35 (m, 6H, CH Ar), 7.35 – 7.23 (m, 4H, CH Ar), 6.27 (t, *J* = 2.5 Hz, 1H, CH-4), 6.07 (dd, *J* = 10.6, 3.8 Hz, 1H, CH-2), 5.93 (dd, *J* = 10.6, 2.7 Hz, 1H, CH-3), 5.80 (t, *J* = 4.1 Hz, 1H, CH-1), 5.34 (dd, *J* = 10.4, 4.4 Hz, 1H, CH-6), 4.72 (dd, *J* = 11.6, 4.5 Hz, 1H, C*H*HOBz), 4.53 (dd, *J* = 11.6, 7.4 Hz, 1H, CH*H*OBz), 3.31 – 3.23 (m, 1H, CH-5). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 166.1, 165.6, 165.4, 164.9 (4 C=O), 134.2, 134.1, 133.7, 133.4, 130.2, 129.9, 129.8 129.7 (12 CH Ar), 129.1 (C_q Bz), 128.9, 128.8 (4 CH Ar), 128.6 (C_q-Bz), 128.54, 128.51 (4 CH Ar), 128.1 (C_q-Bz), 81.3 (C-6), 80.4 (C-1), 69.6 (C3), 68.5 (C-4), 67.0 (C-2), 61.1 (CH_2), 39.8 (C-5). HRMS: calcd. for $[C_{35}H_{29}O_{12}S]^+$ 673.13797; found 673.13794; HRMS: calcd. for $[C_{35}H_{32}NO_{12}S]^+$ 690.16452; found 690.16436; HRMS: calcd. for $[C_{35}H_{28}NaO_{12}S]^+$ 695.11992; found 695.11936.

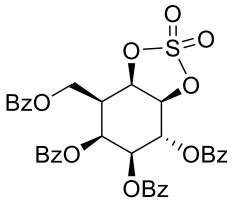
(3a*S*,4*R*,5*S*,6*S*,7*R*,7a*R*)-4,5,6-Tris(benzyloxy)-7-((benzyloxy)methyl)hexahydrobenzo[*d*] [1,2,3]dioxathiole 2,2-dioxide (**28**)



Obtained as an oil from **26** (200 mg, 0.36 mmol) in 69% yield (153 mg, 0.25 mmol). $[\alpha]_D^{20}$ = -1.7 (*c* = 1, MeOH). IR (neat, cm^{-1}) 1724, 1454, 1384, 1207, 1091. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 7.36 – 7.23 (m, 20H, CH Ar), 5.21 – 5.18 (m, 1H, CH-6), 5.03 (d, *J* = 12.1 Hz, 1H, CH*H*Ph), 4.87 – 4.62 (m, 6H, 2

CH_2Ph, CH-1, CH-2), 4.59 – 4.53 (m, 1H, CH*H*Ph), 4.45 – 4.37 (m, 2H, CH_2Ph), 4.06 (t, *J* = 2.2 Hz, 1H, CH-4), 3.69 – 3.54 (m, 2H, CH_2OBn), 3.36 (dd, *J* = 10.3, 2.1 Hz, 1H, CH-3), 2.07 – 2.00 (m, 1H, CH-5). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.6, 138.0, 137.9, 137.6 (4 C_q Bn), 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 127.3 (20 CH Ar), 87.3 (C-3), 81.5 (C-1), 81.1 (C-4), 77.8 (C-2), 76.1, 74.7 (2 CH_2Ph), 73.9 (C-6), 73.8, 73.5 (2 CH_2Ph), 67.1 (C-7), 40.7 (C-5). HRMS: calcd. for $[C_{35}H_{37}O_8S]^+$ 617.22091; found 617.22083. HRMS: calcd. for $[C_{35}H_{36}NaO_8S]^+$ 639.20286; found 639.20223.

(3a*S*,4*R*,5*S*,6*S*,7*R*,7a*R*)-7-((Benzoyloxy)methyl)-2,2-dioxidohexahydrobenzo[*d*][1,3,2] dioxathiole-4,5,6-triyl tribenzoate (**29**)

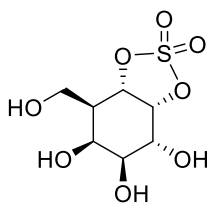


Obtained as a white solid from **27** (45 mg, 0.08 mmol) in 82% yield (41 mg, 0.07 mmol). $[\alpha]_D^{20}$ = +56.1 (*c* = 1, MeOH). IR (neat, cm^{-1}) 1722, 1601, 1450, 1397, 1258, 1211, 1090, 1069. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 8.18 (d, *J* = 7.3 Hz, 2H, CH Ar), 8.03 (d, *J* = 7.3 Hz, 2H, CH Ar), 7.94 (d, *J* = 7.3 Hz, 2H, CH Ar), 7.76 (d, *J* = 7.3 Hz, 2H, CH Ar), 7.68 – 7.41 (m, 8H, CH Ar), 7.36 (t, *J* = 7.8 Hz, 2H, CH Ar), 7.29 – 7.23 (m, 2H, CH Ar), 6.62 (dd, *J* = 11.0, 8.6 Hz, 1H, CH-2), 6.19 (t, *J* = 2.4 Hz, 1H, CH-4), 5.56 (t, *J* = 4.3 Hz, 1H, CH-6), 5.50 (dd, *J* = 11.1, 2.5 Hz, 1H, CH-3), 5.28 (dd, *J* = 8.6, 5.1 Hz, 1H, CH-1), 4.68 – 4.55 (m, 2H, CH_2OBz), 3.04 – 2.97 (m, 1H, CH-5). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 166.2, 165.6, 165.5, 165.0 (4 C=O), 134.1, 133.8, 130.4, 130.0, 129.9, 129.0, 128.8, 128.6 (20 CH Ar), 128.5, 128.3 (4 C_q Bz), 83.7 (C-1), 79.8 (C-6), 70.8 (C-3), 68.8 (C-2), 67.0 (C-4), 60.6 (C-7), 38.5 (C-5),. HRMS: calcd. for $[C_{35}H_{29}O_{12}S]^+$ 673.13797; found 673.13784. HRMS: calcd. for $[C_{35}H_{28}NaO_{12}S]^+$ 695.11992; found 695.11973.

General Procedure for the Deprotection of Cyclosulfates **12** and **29**.

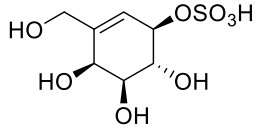
7N methanolic ammonia (0.4 eq.) was added to a solution of intermediates **12** and **29** (1 eq.) in MeOH (40 mL/mmol) under argon atmosphere. The reaction mixture was stirred at room temperature and under argon atmosphere for 2 h. Then, the reaction mixture was concentrated under reduced pressure and the crude was purified by chromatography (from DCM to DCM/MeOH 9:1) to afford the desired final products **2** and side product **30**.

(3a*R*,4*R*,5*S*,6*S*,7*R*,7a*S*)-4,5,6-Trihydroxy-7-(hydroxymethyl)hexahydrobenzo[*d*][1,3,2] dioxathiole 2,2-dioxide (**2**)



Obtained as a white solid from **12** (46 mg, 0.07 mmol) in 34% yield (5.9 mg, 0.02 mmol). $[\alpha]_D^{20}$ = -9.0 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, Methanol-d_4): *δ* 5.32 (t, *J* = 4.1 Hz, 1H, CH-1), 4.97 (dd, *J* = 10.6, 4.4 Hz, 1H, CH-6), 4.18 (t, *J* = 2.4 Hz, 1H, CH-4), 4.14 (dd, *J* = 10.0, 3.9 Hz, 1H, CH-2), 3.88 – 3.75 (m, 2H, CH_2), 3.69 (dd, *J* = 10.0, 2.5 Hz, 1H, CH-3), 2.31 – 2.23 (m, 1H, CH-5). ^{13}C NMR (101 MHz, Methanol-d_4): *δ* 86.3 (C-1), 85.2 (C-6), 72.6 (C-3), 70.3 (C-4), 68.5 (C-2), 60.2 (CH_2), 44.9 (C-5). HRMS: calcd. for $[C_7H_{12}NaO_8S]$ 279.01506; found 279.01436.

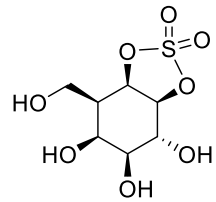
(1*S*,4*S*,5*S*,6*R*)-4,5,6Trihydroxy-3-(hydroxymethyl)cyclohex-2-en-1-yl hydrogen sulfite (**30**)



Obtained as a white solid from **29** (16 mg, 0.024 mmol) in 70% yield (4.0 mg, 0.017 mmol). ^{1}H NMR (400 MHz, Methanol-d_4): δ 5.90 (dd, J = 2.6, 1.3 Hz, 1H, CH-6), 4.75 (dt, J = 7.6, 2.1 Hz, 1H, CH-1), 4.17 (d, J = 4.0 Hz, 1H, CH-4), 4.13 (t, J = 1.7 Hz, 2H, CH_2), 3.89 (dd, J = 10.6, 7.6 Hz, 1H, CH-2), 3.50 (dd, J = 10.7, 4.1 Hz, 1H, CH-3). ^{13}C NMR (101 MHz, Methanol-d_4): δ 141.6 (C_q-5), 124.9 (C-6), 81.1 (C-1), 72.6 (C-3), 72.2 (C-2), 67.8 (C-4), 63.6 (CH_2).

Deprotection of Cyclosulfate **28**

(3a*S*,4*R*,5*S*,6*S*,7*R*,7a*R*)-4,5,6-Trihydroxy-7-(hydroxymethyl)hexahydrobenzo[*d*][1,3,2] dioxathiole 2,2-dioxide (**9**)

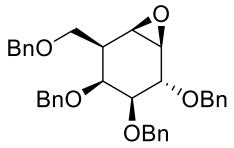


Compound **28** (133 mg, 0.216 mmol) was dissolved in dry MeOH (10 mL). The solution was bubbled through with argon and a catalytic amount of palladium hydroxide on carbon (20%, 61 mg, 0.086 mmol, 0.4 eq.) was added. The reaction mixture was hydrogenated with a hydrogen balloon and stirred under a hydrogen atmosphere overnight at room temperature. The reaction mixture was filtered over Celite® and concentrated *in vacuo*. Purification by column chromatography (DCM to 20% MeOH in DCM) gave deprotected β-cyclosulfate **9** as a colorless oil in 63% yield (35 mg, 0.137 mmol). $[\alpha]_D^{20}$ = -17.7 (c = 1, MeOH). IR (neat, cm^{-1}) 3350, 1373, 1206, 1049. ^{1}H-NMR (400 MHz, Methanol-d_4): δ 5.28 (t, J = 4.3 Hz, 1H, CH-6), 4.78 (dd, J = 8.6, 5.0 Hz, 1H, CH-1), 4.31 (dd, J = 10.3, 8.6 Hz, 1H, CH-2), 4.01 (t, J = 2.7 Hz, 1H, CH-4), 3.87 – 3.78 (m, 2H, CH_2), 3.35 (dd, J = 10.4, 2.7 Hz, 1H, CH-3), 2.11 – 2.04 (m, 1H, CH-5). ^{13}C-NMR (100 MHz, Methanol-d_4): δ 89.7 (C-1), 83.5 (C-6), 73.7 (C-3), 70.4 (C-2), 70.0 (C-4), 60.3 (CH_2), 43.0 (C-5). HRMS: calcd. for $[C_7H_{13}O_8S]^+$ 257.03311; found 257.03254. HRMS: calcd. for $[C_7H_{12}NaO_8S]^+$ 279.01506; found 279.01475.

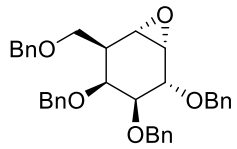
4.3.2. Synthesis and Characterization Data of Compound 3.

(1*R*,2*R*,3*S*,4*S*,5*R*,6*R*)-2,3,4-Tris(benzyloxy)-5-((benzyloxy)methyl)-7-oxabicyclo[4.1.0] heptane (**31**) and (1*S*,2*R*,3*S*,4*S*,5*R*,6*S*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)-7-oxabicyclo[4.1.0] heptane (**α-epoxide**)

The perbenzylated cyclohexene **24** (0.517 g, 0.99 mmol) was dissolved in dry DCM (10 mL). *m*-CPBA (≤77%, 0.565 g, 2.5 mmol, 2.5 eq.) was added at 0 °C. The reaction mixture was stirred at rt overnight. The reaction was quenched with sat. aq. Na_2SO_3. The aqueous phase was extracted with DCM (x3) and the resulting organic phase was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 50:1 → 20:1 → 10:1 → 6:1) to give a mixture of isomers (0.509 g, 0.95 mmol, 95%, 1:4 mixture of **α-epoxide** and **31** (β-epoxide) as colorless oils. The isomers were almost completely separated.



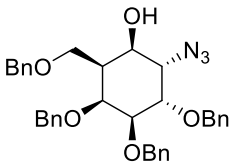
31: R_f 0.31 (Pentane/EtOAc 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.21 (m, 20H, CH Ar), 4.86 (d, J_{gem} = 12.0 Hz, 1H, C*H*HPh), 4.81 (d, J_{gem} = 11.4 Hz, 1H, C*H*HPh), 4.76 (d, J_{gem} = 11.4 Hz, 1H, CH*H*Ph), 4.72 (d, J_{gem} = 12.0 Hz, 1H, C*H*HPh), 4.70 (d, J_{gem} = 12.0 Hz, 1H, CH*H*Ph), 4.56 (d, J_{gem} = 12.0 Hz, 1H, CH*H*Ph), 4.45 (s, 2H, CH_2Ph), 4.14 (d, $J_{2,3}$ = 8.7 Hz, 1H, CH-2), 3.94 (dd, $J_{4,5}$ = 4.5 Hz, $J_{4,3}$ = 2.1 Hz, 1H, CH-4), 3.72 (dd, J_{gem} = 8.9 Hz, $J_{CHH,5}$ = 6.9 Hz, 1H, C*H*HOBn), 3.64 (dd, $J_{CHH,5}$ = 7.5 Hz, 1H, CH*H*OBn), 3.46 (dd, 1H, CH-3), 3.24 (d, $J_{1,6}$ = 3.8 Hz, 1H, CH-1), 3.17 (t, $J_{6,5}$ = 2.9 Hz, 1H, CH-6), 2.32 (tdd, 1H, CH-5). The spectroscopic data are in agreement with those previously reported.[32]



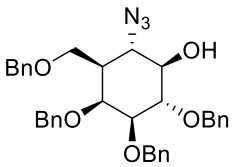
α-epoxide: R_f 0.48 (Pentane/EtOAc 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.21 (m, 20H, CH Ar), 4.89 (d, J_{gem} = 11.4 Hz, 1H, C*H*HPh), 4.85 (d, J_{gem} = 11.9 Hz, 1H, C*H*HPh), 4.81 (d, J_{gem} = 11.9 Hz, 1H, CH*H*Ph), 4.72 (d, J_{gem} = 11.9 Hz, 1H, C*H*HPh), 4.68 (d, J_{gem} = 11.4 Hz, 1H, CH*H*Ph), 4.51 (d app, 2H, C*H*HPh, CH*H*Ph), 4.47 (d, J_{gem} = 11.9 Hz, 1H, CH*H*Ph), 4.25 (dd, $J_{2,3}$ = 8.5 Hz, $J_{2,1}$ = 2.4 Hz, 1H, CH-2), 3.93-3.91 (m, 1H, CH-4), 3.62 (dd, $J_{3,4}$ = 1.3 Hz, 1H, CH-3), 3.59 (d, $J_{CH2,5}$ = 8.0 Hz, 2H, CH_2OBn), 3.37 (dd, $J_{1,6}$ = 3.9 Hz, 1H, CH-1), 2.96 (dd, $J_{6,5}$ = 1.5 Hz, 1H, CH-6), 2.30 (td, $J_{5,4}$ = 3.5 Hz, 1H, CH-5).

(1*R*,2*S*,3*S*,4*S*,5*S*,6*S*)-2-Azido-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)cyclohexan-1-ol (**13**) and (1*R*,2*S*,3*R*,4*S*,5*S*,6*S*)-2-azido-4,5,6-tris(benzyloxy)-3-((benzyloxy)methyl)cyclo-hexan-1-ol **32**)

Epoxide **31** (0.960 g, 1.8 mmol) was dissolved in dry DMF (50 mL). $LiClO_4$ (3.81 g, 36 mmol, 20 eq.) and NaN_3 (1.61 g, 25 mmol, 14 eq.) were added. The reaction mixture was stirred at 80 °C overnight. H_2O was added and the aqueous phase was extracted with EtOAc (x3). The resulting organic phase was washed with H_2O (x3) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 20:1 → 7:1) to give **13** (0.413 g, 0.71 mmol, 40 %) and **32** (0.397 g, 0.69 mmol, 38 %) as colorless oils.

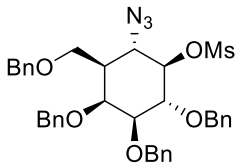


Cyclohexane 13: R_f 0.42 (Pentane/EtOAc 9:1). $[\alpha]_D^{20}$ +16.1 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}) 3474, 3030, 2918, 2102, 1454, 1273, 1055, 735, 696. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.24 (m, 18H, CH Ar), 7.21-7.15 (m, 2H, CH Ar), 4.94 (d, J_{gem} = 11.0 Hz, 1H, C*H*HPh), 4.87-4.69 (m, 4H, 2 x C*H*HPh, 2 x CH*H*Ph) 4.46 (d, J_{gem} = 12.1 Hz, 1H, C*H*HPh), 4.44 (d, J_{gem} = 12.1 Hz, 1H, CH*H*Ph), 4.40 (d, J_{gem} = 12.1 Hz, 1H, CH*H*Ph), 4.29 (dd, $J_{2,3}$ = 9.9 Hz, $J_{2,1}$ = 3.0 Hz, 1H, CH-2), 4.25 (bs, 1H, CH-4), 4.09 (t, $J_{1,2/6}$ = 3.0 Hz, 1H, CH-1), 3.89 (d, $J_{OH,6}$ = 10.1 Hz, 1H, O*H*), 3.82-3.75 (m, 1H, CH-6), 3.77 (dd, 1H, CH-3), 3.67 (t, $J_{gem/CHH,5}$ = 9.2 Hz, 1H, C*H*HOBn), 3.54 (dd, $J_{CHH,5}$ = 5.4 Hz, 1H, CH*H*OBn), 2.06-1.98 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.2, 138.1, 137.9 (C_q Ar), 128.5-127.5 (CH Ar), 80.8 (C-3), 78.4 (C-4), 76.7 (C-2), 75.9, 73.6, 73.4, 73.4 (CH_2Ph), 71.6 (C-6), 67.8 (CH_2OBn), 64.9 (C-1), 38.7 (C-5). HRMS: Calcd. for $C_{35}H_{38}N_3O_5^+$ m/z 580.28060, found m/z 580.28048.

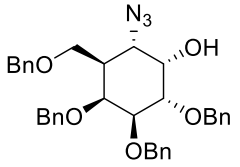


Cyclohexane 32: R_f 0.26 (Pentane/EtOAc 9:1). $[\alpha]_D^{20}$ -29.7 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}) 3431, 3030, 2916, 2102, 1454, 1057, 733, 696. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.39-7.24 (m, 20H, CH Ar), 5.00 (d, J_{gem} = 11.1 Hz, 1H, C*H*HPh), 4.98 (d, J_{gem} = 11.1 Hz, 1H, C*H*HPh), 4.77 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.69 (d, J_{gem} = 11.1 Hz, 1H, CH*H*Ph), 4.68 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.49 (d app, 2H, C*H*HPh, CH*H*Ph), 4.41 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.22 (t, $J_{4,3/5}$ = 2.3 Hz, 1H, CH-4), 3.89 (t, $J_{2,1/3}$ = 9.3 Hz, 1H, CH-2), 3.68 (dd, J_{gem} = 8.8 Hz, $J_{CHH,5}$ = 4.1 Hz, 1H, C*H*HOBn), 3.60 (dd, $J_{CHH,5}$ = 10.2 Hz, 1H, CH*H*OBn), 3.52 (bt, $J_{1,6}$ = 9.3 Hz, 1H, CH-1), 3.45 (dd, $J_{6,5}$ = 11.5 Hz, 1H, CH-6), 3.42 (dd, 1H, CH-3), 2.59 (d, $J_{OH,1}$ = 1.5 Hz, 1H, OH), 1.66 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 138.9, 138.6, 138.3, 138.1 (C_q Ar), 128.7-127.6 (CH Ar), 83.7 (C-3), 81.4 (C-2), 77.1 (C-1), 75.7, 75.2 (CH_2Ph), 73.6 (C-4), 73.5, 72.6 (CH_2Ph), 67.9 (CH_2OBn), 61.7 (C-6), 42.5 (C-5). HRMS: Calcd. for $C_{35}H_{38}N_3O_5^+$ m/z 580.28060, found m/z 580.28030.

(1*R*,2*S*,3*R*,4*S*,5*S*,6*R*)-2-Azido-4,5,6-tris(benzyloxy)-3-((benzyloxy)methyl)cyclohexyl methanesulfonate (**33**)



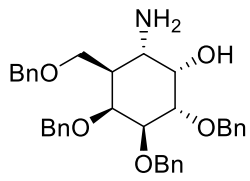
The azido alcohol **32** (0.390 g, 0.67 mmol) was dissolved in dry DCM (7 mL). The solution was cooled to 0 °C and Et_3N (0.47 mL, 3.4 mmol, 5 eq.) and MsCl (0.26 mL, 3.4 mmol, 5 eq.) were added. The reaction mixture was stirred at rt for 4 h. The reaction was quenched by the addition of 1 M aq. HCl. The aqueous phase was then extracted with DCM (x3) and the resulting organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 20:1 → 3:1) to give **33** (0.407 g, 0.62 mmol, 92%) as a colorless oil. R_f 0.48 (Pentane/EtOAc 5:1). $[\alpha]_D^{20}$ -21.4 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3030, 2868, 2106, 1454, 1350, 1175, 735, 696. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.39-7.24 (m, 20H, CH Ar), 4.97 (d, J_{gem} = 11.0 Hz, 1H, C*H*HPh), 4.95 (d, J_{gem} = 10.6 Hz, 1H, C*H*HPh), 4.76 (d, J_{gem} = 10.6 Hz, 1H, CH*H*Ph), 4.74 (d, J_{gem} = 11.6 Hz, 1H, C*H*HPh), 4.68 (d, J_{gem} = 11.6 Hz, 1H, CH*H*Ph), 4.53-4.47 (m, 3H, CH-1, C*H*HPh, CH*H*Ph), 4.44 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.21 (t, $J_{4,3/5}$ = 1.8 Hz, 1H, CH-4), 4.06 (t, $J_{2,1/3}$ = 9.6 Hz, 1H, CH-2), 3.70 (dd, J_{gem} = 8.8 Hz, $J_{CHH,5}$ = 4.2 Hz, 1H, C*H*HOBn), 3.63 (t, $J_{CHH,5}$ = 9.7 Hz, 1H, CH*H*OBn), 3.58 (dd, $J_{6,5}$ = 11.9 Hz, $J_{6,1}$ = 9.9 Hz, 1H, CH-6), 3.47 (dd, 1H, CH-3), 2.96 (s, 3H, CH_3), 1.77 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 138.6, 137.9, 137.8 (C_q Ar), 128.6-127.7 (CH Ar), 84.5 (C-1), 83.8 (C-3), 78.6 (C-2), 75.6, 75.3, 73.6 (CH_2Ph), 73.3 (C-4), 73.2 (CH_2Ph), 67.7 (CH_2OBn), 61.2 (C-6), 42.4 (C-5), 39.1 (CH_3). HRMS: Calcd. for $C_{36}H_{39}N_3O_7SNH_4^+$ m/z 675.28470, found m/z 675.28452.



Mesylate **33** (0.618 g, 0.94 mmol) was dissolved in dry DMF (12 mL) and H_2O (3 mL) was added. The reaction mixture was stirred at 140 °C for 3 days in a sealed microwave vial. The reaction mixture was allowed to reach rt and diluted with EtOAc. The solution was washed with water (x2) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 20:1 → 8:1) to give **34** (0.363 g, 0.63 mmol, 67%) as a colorless oil. R_f 0.57 (Pentane/EtOAc 5:1). $[\alpha]_D^{20}$ -17.7 (*c* = 1, $CHCl_3$). IR

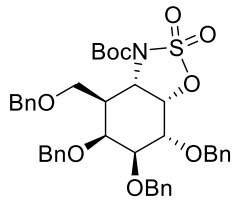
(neat, cm^{-1}): 3422, 3030, 2866, 2097, 1454, 1086, 1074, 733, 696. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.40-7.20 (m, 20H, CH Ar), 4.95 (d, J_{gem} = 10.8 Hz, 1H, C*H*HPh), 4.77 (m, 3H, C*H*HPh, CH_2Ph), 4.69 (d, J_{gem} = 11.5 Hz, 1H, CH*H*Ph), 4.52 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.47 (d, J_{gem} = 10.8 Hz, 1H, CH*H*Ph), 4.44 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.28 (t, $J_{1,2/6}$ = 2.8 Hz, 1H, CH-1), 4.24 (t, $J_{4,3/5}$ = 2.2 Hz, 1H, CH-4), 3.89 (dd, $J_{2,3}$ = 9.7 Hz, 1H, CH-2), 3.80 (dd, 1H, CH-3), 3.63 (d, $J_{CH2,5}$ 7.3 Hz, 2H, CH_2OBn), 3.29 (dd, $J_{6,5}$ 12.0 Hz, 1H, CH-6), 2.63 (s, 1H, OH), 2.46 (dtd, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.1, 138.8, 138.2, 138.2 (C_q Ar), 128.6-127.6 (CH Ar), 80.5 (C-3), 78.6 (C-2), 75.3 (CH_2Ph), 74.5 (C-4), 73.5, 73.2, 73.2 (CH_2Ph), 70.7 (C-1), 68.1 (CH_2OBn), 58.6 (C-6), 39.1 (C-5). HRMS: Calcd. for $C_{35}H_{38}N_3O_5^+$ m/z 580.28060, found m/z 580.28029.

(1*S*,2*S*,3*R*,4*S*,5*S*,6*S*)-2-Amino-4,5,6-tris(benzyloxy)-3-((benzyloxy)methyl)cyclohexan-1-ol (**35**)



The azide **34** (0.316 g, 0.54 mmol) was dissolved in dry THF (20 mL). PtO_2 (0.039 g, 0.17 mmol, 0.3 eq.) was added. The reaction was stirred under an H_2 atmosphere for 4 h at rt. The mixture was filtered through celite and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (DCM/MeOH 100:1 → 10:1) to give **35** (0.242 g, 0.44 mmol, 80%) as a colorless oil. R_f 0.46 (DCM/MeOH 10:1). $[\alpha]_D^{20}$ -1.7 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3400, 3030, 2918, 1452, 1063, 731, 694. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.41-7.21 (m, 20H, CH Ar), 4.96 (d, J_{gem} = 11.2 Hz, 1H, C*H*HPh), 4.78 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.77 (d, J_{gem} = 11.5 Hz, 1H, C*H*HPh), 4.75 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.70 (d, J_{gem} = 11.5 Hz, 1H, CH*H*Ph), 4.48 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.47 (d, J_{gem} = 11.2 Hz, 1H, CH*H*Ph), 4.42 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.10 (t, $J_{4,3/5}$ = 2.4 Hz, 1H, CH-4), 3.99 (t, $J_{1,2/6}$ = 3.0 Hz, 1H, CH-1), 3.92 (dd, $J_{2,3}$ = 9.8 Hz, 1H, CH-2), 3.80 (dd, 1H, CH-3), 3.73 (dd, J_{gem} = 9.0 Hz, $J_{C\underline{H}H,5}$ = 5.5 Hz, 1H, C*H*HOBn), 3.57 (t, $J_{CH\underline{H},5}$ = 9.0 Hz, 1H, CH*H*OBn), 2.99 (dd, $J_{6,5}$ = 11.3 Hz, 1H, CH-6), 2.22 (br s, 3H, OH, NH_2), 2.12-2.02 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.4, 139.1, 138.6, 138.3 (C_q Ar), 128.5-127.4 (CH Ar), 80.9 (C-3), 79.1 (C-2), 75.6 (C-4), 74.9, 73.4, 73.1, 72.9 (4 x CH_2Ph), 72.0 (C-1), 70.2 (CH_2Ph), 50.1 (C-6), 41.3 (C-5). HRMS: Calcd. for $C_{35}H_{40}NO_5^+$ m/z 554.29010, found m/z 554.28981.

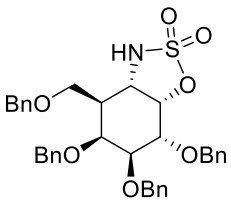
tert-Butyl (3a*S*,4*R*,5*S*,6*S*,7*R*,7a*S*)-5,6,7-tris(benzyloxy)-4-((benzyloxy)methyl)hexahydro-3*H*-benzo[*d*][1,2,3]oxathiazole-3-carboxylate 2,2-dioxide (**37**)



35 (0.122 g, 0.22 mmol) was dissolved in dry DCM (4 mL). Et_3N (0.15 mL, 1.08 mmol, 5 eq.) and Boc_2O (0.059 g, 0.27 mmol, 1.2 eq.) were added at 0 °C. The reaction mixture was stirred at rt overnight before the addition of sat. aq. NH_4Cl. The aqueous phase was extracted with DCM (x3). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue **36** was dissolved in dry DCM (5 mL). Imidazole (0.078 g, 1.15 mmol, 5 eq.), Et_3N (0.15 mL, 1.08 mmol, 5 eq.) and $SOCl_2$ (0.16 mL, 2.19 mmol, 10 eq.) were added at 0 °C. The reaction mixture was stirred at this temperature for 1 h before the addition

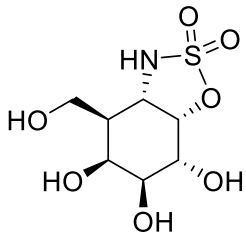
of H_2O. The aqueous phase was extracted with DCM (x3) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was dissolved in a 1:1:1 mixture of MeCN, CCl_4, and H_2O (12 mL). $RuCl_3 \cdot 3H_2O$ (0.010 g, 0.048 mmol, 0.2 eq.) and $NaIO_4$ (0.114 g, 0.53 mmol, 2.4 eq.) were added at 0 °C. The reaction mixture was stirred at this temperature for 1.5 h. H_2O and sat. aq. $Na_2S_2O_3$ were added and the aqueous phase was extracted with EtOAc (x3). The resulting organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 50:1 → 10:1) to give **37** (98 mg, 0.14 mmol, 62% over 3 steps) as a colorless oil. R_f 0.53 (Pentane/EtOAc 5:1). $[\alpha]_D^{20}$ -5.8 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3030, 2924, 1732, 1454, 1369, 1317, 1105, 1088, 844, 735, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.23 (m, 18H, CH Ar), 7.20-7.16 (m, 2H, CH Ar), 5.00 (t, $J_{1,2/6}$ = 3.9 Hz, 1H, CH-1), 4.90 (d, J_{gem} = 11.0 Hz, 1H, C*H*HPh), 4.82 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.81 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.76 (d app, J_{gem} = 11.7 Hz, 1H, 2 x CH*H*Ph), 4.45 (d, J_{gem} = 11.0 Hz, 1H, CH*H*Ph), 4.44 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.38 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.29-4.24 (m, 2H, CH-6, CH-4), 4.20 (dd, $J_{2,3}$ = 10.0 Hz, $J_{2,1}$ = 3.9 Hz, 1H, CH-2), 3.84 (dd, $J_{3,4}$ = 1.9 Hz, 1H, CH-3), 3.57 (t, $J_{gem/C\underline{H}H,5}$ = 9.8 Hz, 1H, C*H*HOBn), 3.43 (dd, $J_{CH\underline{H},5}$ = 4.5 Hz, 1H, CH*H*OBn), 2.40-2.31 (m, 1H, CH-5), 1.46 (s, 9H, $(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (C=O), 138.5, 138.4, 137.9, 137.5 (C_q Ar), 128.7-127.6 (CH Ar), 85.7 (*C*$(CH_3)_3$), 81.0 (C-1), 80.5 (C-3), 75.2 (CH_2Ph), 74.4 (C-2), 74.2 (C-4), 73.6, 73.6, 73.4 (CH_2Ph), 67.4 (CH_2OBn), 57.4 (C-6), 43.2 (C-5), 27.8 (C(*C*$H_3)_3$). HRMS: Calcd. for $C_{40}H_{45}NO_9SNa^+$ m/z 738.27072, found m/z 738.27015.

(3a*S*,4*R*,5*S*,6*S*,7*R*,7a*S*)-5,6,7-Tris(benzyloxy)-4-((benzyloxy)methyl)hexahydro-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (**38**)



Boc-protected sulfamidate **37** (0.098 g, 0.14 mmol) was dissolved in DCM (2 mL) and TFA (0.2 mL) was added. The reaction mixture was stirred at rt for 8 h. The mixture was then concentrated *in vacuo* and remaining volatiles were co-evaporated with toluene (x3) to give **38** (0.087 g, 0.14 mmol, 100%) as a colorless oil. R_f 0.41 (Pentane/EtOAc 3:1). $[\alpha]_D^{20}$ -2.1 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3030, 2868, 1454, 1339, 1190, 1083, 737, 696. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.22 (m, 18H, CH Ar), 7.19-7.11 (m, 2H, CH Ar), 5.36 (d, $J_{N\underline{H},6}$ = 3.0 Hz, 1H, NH), 5.04 (t, $J_{1,2/6}$ = 4.0 Hz, 1H, CH-1), 4.88 (d, J_{gem} = 11.1 Hz, 1H, C*H*HPh), 4.82 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.77 (s, 2H, CH_2Ph), 4.71 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.45 (s, 2H, CH_2Ph), 4.43 (d, J_{gem} = 11.1 Hz, 1H, CH*H*Ph), 4.16 (dd, $J_{2,3}$ = 9.4, 1H, CH-2), 3.96 (t, $J_{4,3/5}$ = 2.1 Hz, 1H, CH-4), 3.86 (dd, 1H, CH-3), 3.68 (dt, $J_{6,5}$ = 10.6 Hz, 1H, CH-6), 3.61 (dd, J_{gem} = 8.8 Hz, $J_{C\underline{H}H,5}$ = 8.0 Hz, 1H, C*H*HOBn), 3.49 (dd, $J_{CH\underline{H},5}$ = 6.5 Hz, 1H, CH*H*OBn), 2.44-2.36 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.2, 137.6, 137.4 (C_q Ar), 128.7-127.6 (CH Ar), 83.0 (C-1), 80.4 (C-3), 75.1 (C-4), 75.0 (C-2), 74.9, 73.7, 73.6, 73.5 (CH_2Ph), 70.4 (CH_2OBn), 58.6 (C-6), 41.0 (C-5). HRMS: Calcd. for $C_{35}H_{38}NO_7S^+$ m/z 616.23635, found m/z 616.23619.

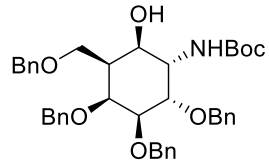
(3a*S*,4*R*,5*S*,6*S*,7*R*,7a*S*)-5,6,7-Trihydroxy-4-(hydroxymethyl)hexahydro-3*H*-benzo[*d*][1,2,3] oxathiazole 2,2-dioxide (**3**)



Perbenzylated **38** (0.042 g, 0.068 mmol) was dissolved in MeOH (3 mL), purged with Argon, and $Pd(OH)_2$ on carbon (20 wt. %, 0.032 g, 0.046 mmol, 0.7 eq.) was added. The reaction mixture was stirred vigorously at rt under a H_2 atmosphere for 8 h. The mixture was filtered through a celite plug and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (from DCM to DCM/MeOH 9:1) to give final compound **3** (0.016 g, 0.063 mmol, 92%) as a colorless oil. R_f 0.55 (DCM/MeOH 7:3 + 1% Et_3N). $[\alpha]_D^{20}$ -10.7 (*c* = 0.5, MeOH). IR (neat, cm^{-1}): 3271, 2970, 1327, 1180, 1080, 1028. ^1H NMR (400 MHz, CD_3OD): δ 4.98 (t, $J_{1,2/6}$ = 3.9 Hz, 1H, CH-1), 4.17 (t, $J_{4,3/5}$ = 2.3 Hz, 1H, CH-4), 4.06 (dd, $J_{2,3}$ = 10.1 Hz, 1H, CH-2), 3.79-3.70 (m, 2H, C*H*$_2$OH), 3.68 (dd, $J_{6,5}$ = 11.5 Hz, 1H, CH-6), 3.67 (dd, 1H, CH-3), 2.16-2.07 (m, 1H, CH-5). ^{13}C NMR (100 MHz, CD_3OD): δ 88.8 (C-1), 72.7 (C-3), 70.7 (C-4), 69.2 (C-2), 61.0 (CH_2), 57.2 (C-6), 44.0 (C-5).

3.3.3. Synthesis and Characterization Data of 4

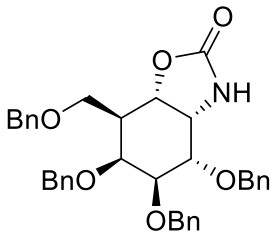
tert-Butyl ((1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)-6-hydroxy-cyclohexyl)carbamate (**15**)



Azide **13** (1.475 g, 2.54 mmol) was dissolved in dry THF (25 mL) and PtO_2 (0.175 g, 0.77 mmol, 0.3 eq.) was added. The reaction was stirred vigorously for 1.5 h while being bubbled through with H_2. The mixture was then filtered over celite and concentrated *in vacuo*. The crude residue **14** was redissolved in dry DCM (25 mL), and Et_3N (1.8 mL, 12.9 mmol, 5 eq.) and Boc_2O (0.623 g, 2.86 mmol, 1.1 eq.) were added at 0 °C. The reaction mixture was stirred overnight at rt before the addition of sat. aq. NH_4Cl. The aqueous phase was extracted with DCM (x3) and the resulting organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 9:1 → 5:1 →3:1) to give Boc-protected **15** (1.521 g, 2.33 mmol, 91%) as a colorless oil. R_f 0.64 (Pentane/EtOAc 3:1). $[\alpha]_D^{20}$ +15.1 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3485, 3340, 3030, 2922, 1713, 1497, 1454, 1366, 1169, 1098, 735, 696. ^1H NMR (500 MHz, DMSO-d_6, 373 K): δ 7.37-7.19 (m, 20H, CH Ar), 6.13 (s, 1H, NH), 4.74 (d, J_{gem} = 11.5 Hz, 1H, C*H*HPh), 4.70 (d, J_{gem} = 12.1 Hz, 1H, C*H*HPh), 4.67 (d, J_{gem} = 12.1 Hz, 1H, CH*H*Ph), 4.60 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.52 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.48 (d, J_{gem} = 11.5 Hz, 1H, CH*H*Ph), 4.46 (d, J_{gem} = 12.1 Hz, 1H, C*H*HPh), 4.41 (d, J_{gem} = 12.1 Hz, 1H, CH*H*Ph), 4.13-4.02 (m, 3H, CH-1, CH-2, CH-4), 3.90 (dd, $J_{3,2}$ = 8.6 Hz, $J_{3,4}$ 2.9 Hz, 1H, CH-3), 3.83 (bs, 1H, OH), 3.73 (dd, J_{gem} = 9.4 Hz, $J_{C\underline{H}H,5}$ = 6.9 Hz, 1H, C*H*HOBn), 3.68 (br s, 1H, CH-6), 3.65 (dd, $J_{CH\underline{H},5}$ = 6.4 Hz, 1H, CH*H*OBn), 2.28 (br s, 1H, CH-5), 1.38 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): δ 155.1 (C=O), 138.7, 138.3, 138.2 (C_q Ar), 127.6-126.5 (20 x CH Ar), 78.6 (C-3), 77.5 (*C*$(CH_3)_3$), 77.1 (C-4), 74.5 (C-2), 73.3, 72.0, 71.8, 71.0

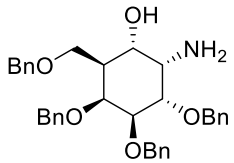
(4 x CH_2Ph), 69.9 (C-6), 67.5 (CH_2OBn), 52.9 (C-1), 40.0 (C-5), 27.8 ($C(CH_3)_3$). Calcd. for $C_{40}H_{48}NO_7^+$ m/z 654.34308, found m/z 654.34265.

(3a*S*,4*S*,5*S*,6*S*,7*S*,7a*S*)-4,5,6-Tris(benzyloxy)-7-((benzyloxy)methyl)hexahydrobenzo[*d*]-oxazol-2(3*H*)-one (**17**)



Boc-protected **15** (1.488 g, 2.28 mmol) was dissolved in dry $CHCl_3$ (20 mL) and Et_3N (1.6 mL, 11.5 mmol, 5 eq.), 1-methylimidazole (1.8 mL, 22.6 mmol, 10 eq.) and MsCl (0.9 mL, 11.6 mmol, 5 eq.) were added at 0 °C. The reaction mixture was stirred at rt overnight. EtOAc was added and the mixture was washed with 1 M aq. HCl (x3), H_2O and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mesylated residue **16** was dissolved in dry DMF and stirred at 120 °C for 2 days. The mixture was then diluted with EtOAc and washed with H_2O (x2) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 9:1 → 5:1 → 3:1) to give **17** (0.616 g, 1.1 mmol, 47% over 2 steps) as a colorless oil. R_f 0.51 (Pentane/EtOAc 2:1). $[\alpha]_D^{20}$ -13.1 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3267, 3030, 2866, 1759, 1452, 1074, 1016, 732, 694. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.27 (m, 18H, CH Ar), 7.23-7.18 (m, 2H, CH Ar), 5.23 (s, 1H, NH), 4.90 (d, J_{gem} = 11.2 Hz, 1H, C*H*HPh), 4.86 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.79 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.74 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.67 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.49 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.47 (d, J_{gem} = 11.2 Hz, 1H, CH*H*Ph), 4.40 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.27-4.20 (m, 3H, CH-1, CH-4, CH-6), 4.08 (dd, $J_{2,3}$ = 9.6 Hz, $J_{(2,1)/(3,4)}$ = 4.7 Hz, 1H, CH-2/CH-3), 3.75 (dd, $J_{(2,1/3,4)}$ 1.8 Hz, 1H, CH-2/CH-3), 3.66-3.59 (m, 2H, CH_2OBn), 2.17-2.07 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4 (C=O), 138.6, 138.4, 138.1, 138.0 (C_q Ar), 128.7-127.6 (CH Ar), 81.5 (C-2/C-3), 76.0 (C-2/C-3), 75.7 (C-4/C-6), 74.9, 74.3, 73.5 (CH_2Ph), 73.5 (C-4/C-6), 72.9 (CH_2Ph), 67.5 (CH_2OBn), 55.5 (C-1), 43.5 (C-5). Calcd. for $C_{36}H_{38}NO_6^+$ m/z 580.26994, found m/z 580.26959; Calcd. for $C_{36}H_{41}N_2O_6^+$ m/z 597.29646, found m/z 597.29573; Calcd. for $C_{36}H_{37}NaNO_6^+$ m/z 602.25186, found m/z 602.25074.

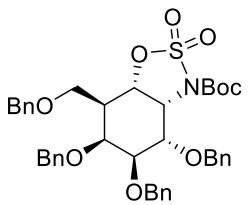
(1*S*,2*S*,3*S*,4*S*,5*S*,6*S*)-2-Amino-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)cyclohexan-1-ol (**18**)



Intermediate **17** (0.589 g, 1.0 mmol) was dissolved in EtOH (60 mL) and 1 M aq. NaOH (15 mL) was added. The reaction mixture was stirred at 70 °C for 3 h and then at rt overnight. EtOH was removed under reduced pressure. Afterwards, H_2O was added, and the aqueous mixture was extracted with EtOAc (x3). The resulting organic phase was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (DCM/MeOH 100:1 →25:1) to give **18** (0.461 g, 0.83 mmol, 82%) as a white solid. R_f 0.66 (DCM/MeOH 10:1). $[\alpha]_D^{20}$ +5.5 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3331, 3026,

2920, 1450, 1092, 1022, 719, 696. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.21 (m, 20H, CH Ar), 4.93 (d, J_{gem} = 11.4 Hz, 1H, C*H*HPh), 4.80 (d, J_{gem} = 11.9 Hz, 1H, C*H*HPh), 4.74 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.73 (d, J_{gem} = 11.9 Hz, 1H, CH*H*Ph),4.67 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.49 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.45 (d, J_{gem} = 11.4 Hz, 1H, CH*H*Ph), 4.44 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 3.96 (t, $J_{4,3/5}$ = 2.5 Hz, 1H, CH-4), 3.96-3.92 (m, 1H, CH-2), 3.90-3.85 (m, 2H, CH-3, CH-6), 3.80 (dd, J_{gem} = 9.0 Hz, $J_{C\underline{H}H,5}$ = 7.6 Hz, 1H, C*H*HOBn), 3.60 (dd, $J_{CH\underline{H},5}$ = 6.7 Hz, 1H, CH*H*OBn), 3.53 (t, $J_{1,2/6}$ = 3.7 Hz, 1H, CH-1), 2.30-2.19 (m, 1H, CH-5), 2.13-1.40 (br s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 139.1, 138.9, 137.9 (C_q Ar), 128.5-127.5 (20 x CH Ar), 80.5 (C-3), 78.6 (C-2), 75.7 (C-4), 74.9, 73.5, 73.3, 72.7 (4 x CH_2Ph), 71.2 (CH_2OBn), 70.0 (C-6), 53.2 (C-1), 41.2 (C-5). HRMS: Calcd. for $C_{35}H_{40}NO_5^+$ m/z 554.29010, found m/z 554.28981.

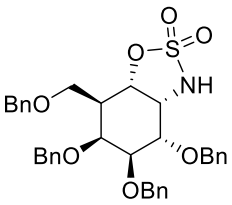
tert-Butyl (3a*R*,4*S*,5*S*,6*S*,7*R*,7a*S*)-4,5,6-tris(benzyloxy)-7-((benzyloxy)methyl)hexahydro-3*H*-benzo[*d*][1,2,3]oxathiazole-3-carboxylate 2,2-dioxide (**20**)



The amino alcohol **18** (0.151 g, 0.27 mmol) was dissolved in dry DCM (5 mL). Et_3N (0.19 mL, 1.4 mmol, 5 eq.) and Boc_2O (0.074 g, 0.34 mmol, 1.2 eq.) were added at 0 °C and the reaction mixture was stirred at rt overnight. The reaction was quenched with sat. aq. NH_4Cl and the aqueous phase was extracted with DCM (x3). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude **19** was dissolved in dry DCM (5 mL), and Et_3N (0.4 mL, 2.9 mmol, 11 eq.), imidazole (0.102 g, 1.5 mmol, 5.5 eq.) and $SOCl_2$ (0.2 mL, 2.7 mmol, 10 eq.) were added at 0 °C. The reaction mixture was stirred at this temperature for 30 min before the addition of H_2O. The aqueous phase was extracted with DCM (x3). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in MeCN (4 mL), CCl_4 (4 mL) and H_2O (4 mL). $RuCl_3 \cdot xH_2O$ (0.014 g, 0.067 mmol, 0.25 eq.) and $NaIO_4$ (0.146 g, 0.68 mmol, 2.5 eq.) were added at 0 °C and the reaction mixture was stirred at this temperature for 1 h. Afterwards, sat. aq. $Na_2S_2O_3$ was added and the aqueous phase was extracted with EtOAc (x3). The resulting organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude residue was finally purified by flash column chromatography (Pentane/EtOAc 50:1 → 15:1) to give **20** (0.115 g, 0.16 mmol, 59% over 3 steps) as a colorless oil. R_f 0.44 (Pentane/EtOAc 10:1). $[\alpha]_D^{20}$ +8.8 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3049, 2976, 1732, 1379, 1329, 1194, 1150, 837. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 16H, CH Ar), 7.22-7.16 (m, 4H, CH Ar), 4.94 (t, $J_{6,1/5}$ = 5.1 Hz, 1H, CH-6), 4.65 (d, J_{gem} = 12.1 Hz, 1H, C*H*HPh), 4.58 (d, J_{gem} = 11.5 Hz, 1H, C*H*HPh), 4.51 (dd, $J_{1,2}$ = 4.0 Hz, 1H, CH-1) 4.44 (d, J_{gem} = 12.0 Hz, 1H, C*H*HPh), 4.44-4.37 (m, 4H, C*H*HPh, 3 x CH*H*Ph), 4.35 (d, J_{gem} = 12.1 Hz, 1H, CH*H*Ph), 4.19 (t, $J_{4,3/5}$ = 3.8 Hz, 1H, CH-4), 4.09 (t, $J_{2,3}$ = 3.0 Hz, 1H, CH-2), 3.76 (dd, J_{gem} = 9.9 Hz, $J_{C\underline{H}H,5}$ = 6.2 Hz, 1H, C*H*HOBn), 3.69 (t, 1H, CH-3), 3.61 (dd, $J_{CH\underline{H},5}$ = 8.1 Hz, 1H, CH*H*OBn), 2.73 (ddt, 1H, CH-5), 1.55 (s, 9H, (CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (C=O), 138.3, 137.9, 137.8, 137.5 (C_q Ar), 128.6-127.7 (20 x CH Ar), 85.3 (C(CH_3)$_3$), 79.1 (C-6), 77.5 (C-3), 73.9 (CH_2Ph), 73.8 (C-2), 73.3 (2 x CH_2Ph), 72.4 (CH_2Ph), 72.2 (C-4), 66.6 (CH_2OBn), 56.7 (C-1), 39.8 (C-5), 28.1 ((CH_3)$_3$).

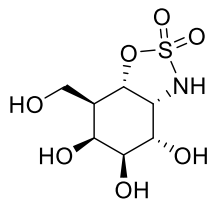
HRMS: Calcd. for $C_{40}H_{49}N_2O_9S^+$ m/z 733.31588, found m/z 733.31588; Calcd. for $C_{40}H_{45}NO_9SNa^+$ m/z 738.27072, found m/z 738.27063.

(3a*R*,4*S*,5*S*,6*S*,7*R*,7a*S*)-4,5,6-Tris(benzyloxy)-7-((benzyloxy)methyl)hexahydro-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (**21**)



Boc-protected **20** (0.092 g, 0.13 mmol) was dissolved in DCM (5 mL), TFA (0.5 mL) was added and the reaction was stirred at rt for 16 h. The reaction mixture was concentrated, and the remaining volatiles were co-evaporated with toluene (x3). The crude residue was purified by flash column chromatography to give **21** (0.057 g, 0.092 mmol, 71%) as a colorless oil. R_f 0.40 (Pentane/EtOAc 9:1). $[\alpha]_D^{20}$ -19.8 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3030, 2866, 1497, 1454, 1339, 1184, 1069, 748, 735, 696. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.38 – 7.25 (m, 18H, CH Ar), 7.17 (dd, *J* = 7.1, 2.5 Hz, 2H, CH Ar), 4.96 (d, *J* = 3.5 Hz, 1H, NH), 4.87 (d, *J* = 11.0 Hz, 1H, C*H*HPh), 4.81 (d, *J* = 11.6 Hz, 1H, C*H*HPh), 4.76 – 4.65 (m, 3H¸ C*H*$_2$Ph, C*H*HPh), 4.55 – 4.47 (m, 2H, C*H*HPh, CH-6), 4.47 – 4.36 (m, 3H, C*H*$_2$Ph, CH-1), 4.24 (t, *J* = 2.1 Hz, 1H, CH-4), 4.11 (dd, *J* = 9.5, 4.8 Hz, 1H, CH-2), 3.84 (dd, *J* = 9.6, 2.0 Hz, 1H, CH-3), 3.66 – 3.56 (m, 2H, CH_2OBn), 2.61 (tdd, *J* = 9.3, 4.8, 2.0 Hz, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 138.4, 138.3, 137.9, 137.7 (4 x C_q Ar), 128.7, 128.6, 128.4, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6 (20 x CH Ar), 82.4 (C-6), 80.8 (C-3), 75.4 (C-2), 75.2, 74.1 (2 x CH_2Ph), 73.9 (C-4), 73.4, 73.1 (2 x CH_2Ph), 66.8 (CH_2OBn), 58.2 (C-1), 41.9 (C-5). HRMS: Calcd. for $C_{35}H_{41}N_2O_7S^+$ m/z 633.26345, found m/z 633.26306; Calcd. for $C_{35}H_{37}NNaO_7S^+$ m/z 638.21584, found m/z 638.21823.

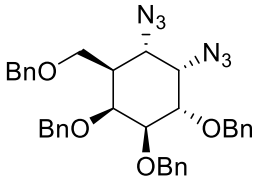
(3a*R*,4*S*,5*S*,6*S*,7*R*,7a*S*)-4,5,6-trihydroxy-7-(hydroxymethyl)hexahydro-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (**4**)



Perbenzylated **21** (0.049 g, 0.08 mmol) was dissolved in MeOH (3 mL), purged with Argon and $Pd(OH)_2$ on carbon (20 wt. %, 0.022 g, 0.032 mmol, 0.4 eq.) was added. The reaction mixture was stirred vigorously at rt under a H_2 atmosphere for 18 h. The mixture was filtered through a celite plug and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (from DCM to DCM/MeOH 9:1) to give final compound **4** (0.009 g, 0.035 mmol, 44%) as a colorless oil. R_f 0.45 (DCM/MeOH 8:2 + 1% Et_3N). $[\alpha]_D^{20}$ -14.5 (*c* = 0.2, MeOH). ^{1}H NMR (400 MHz, CD_3OD): *δ* 4.73 (dd, *J* = 10.6, 5.3 Hz, 1H, CH-6), 4.40 (t, *J* = 5.1 Hz, 1H, CH-1), 4.16 (t, *J* = 2.4 Hz, 1H, CH-4), 4.06 (dd, *J* = 9.8, 4.9 Hz, 1H, CH-2), 3.85 – 3.76 (m, 2H, C*H*$_2$OH), 3.72 (dd, *J* = 9.8, 2.5 Hz, 1H, CH-3), 2.28 (dddd, *J* = 10.4, 8.0, 4.3, 2.2 Hz, 1H, CH-5). ^{13}C NMR (100 MHz, CD_3OD): *δ* 83.8 (C-6), 72.6 (C-3), 70.6 (C-4), 69.0 (C-2), 61.2 (C-1), 60.4 (CH_2), 44.8 (C-5).

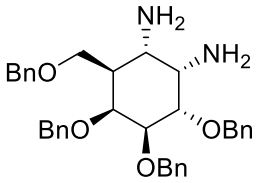
3.3.4 Synthesis and Characterization Data of Compound 5

((((1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-4,5-Diazido-6-((benzyloxy)methyl)cyclohexane-1,2,3-triyl)-tris(oxy))tris(methylene))tribenzene (**46**)



NaN_3 (0.297 g, 4.5 mmol, 10 eq.) was added to a solution of mesylate **33** (0.289 g, 0.44 mmol) in dry DMF (7 mL) and the reaction mixture was stirred at 100 °C overnight. The mixture was allowed to cool to rt and diluted with EtOAc and H_2O. The aqueous phase was extracted with EtOAc (x2), and the combined organic phases were washed with H_2O (x2) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Pentane/EtOAc 50:1 → 25:1) to give **46** (0.184 g, 0.31 mmol, 69%) as a colorless oil. R_f 0.44 (Pentane/EtOAc 20:1). $[\alpha]_D^{20}$ -1.7 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3030, 2920, 2099, 1454, 1086, 733, 696. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.39-7.19 (m, 20H, CH Ar), 4.95 (d, J_{gem} = 10.9 Hz, 1H, C*H*HPh), 4.82 (d app, 2H, 2 x C*H*HPh), 4.74 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.73 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.50 (d, J_{gem} = 11.8 Hz, 1H, C*H*HPh), 4.45 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.43 (d, J_{gem} = 11.8 Hz, 1H, CH*H*Ph), 4.18 (t, $J_{4,3/5}$ = 2.3 Hz, 1H, CH-4), 4.10 (t, $J_{1,2/6}$ = 3.2 Hz, 1H, CH-1), 4.03 (dd, $J_{2,3}$ = 9.8 Hz, 1H, CH-2), 3.78 (dd, 1H, CH-3), 3.61-3.55 (m, 2H, CH_2OBn), 3.38 (dd, $J_{6,5}$ = 11.8 Hz, 1H, CH-6), 2.28-2.18 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 138.9, 138.7, 138.1, 138.0 (4 x C_q Ar), 128.6-127.6 (20 x CH Ar), 80.8 (C-3), 78.1 (C-2), 75.5 (CH_2Ph), 74.6 (C-4), 73.6, 73.5, 73.5 (3 x CH_2Ph), 67.8 (CH_2OBn), 64.9 (C-1), 57.8 (C-6), 40.1 (C-5). HRMS: Calcd. for $C_{35}H_{37}N_6O_4^+$ m/z 605.28708, found m/z 605.28670.

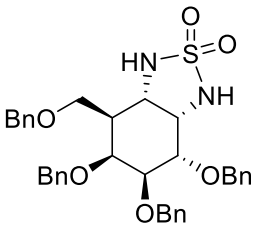
(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)cyclohexane-1,2-diamine (**47**)



Pt_2O (0.005 g, 0.022 mmol, 0.4 eq.) was added to a solution of **46** (0.035 g, 0.058 mmol) in dry THF (2 mL) and the reaction mixture was stirred vigorously under an atmosphere of H_2 for 2 h. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (DCM/MeOH 100:1 → 20:1) to give **47** (0.028 g, 0.051 mmol, 88%) as a colorless oil. R_f 0.56 (DCM/MeOH 9:1 + 1% Et_3N). $[\alpha]_D^{20}$ +5.3 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3300, 3030, 2922, 1452, 1362, 1090, 733, 696. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.41-7.22 (m, 20H, CH Ar), 4.96 (d, J_{gem} = 10.8 Hz, 1H, C*H*HPh), 4.80 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.74 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.72 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.67 (d, J_{gem} = 11.7 Hz, 1H, CH*H*Ph), 4.48 (d, J_{gem} = 11.7 Hz, 1H, C*H*HPh), 4.47 (d, J_{gem} = 10.7 Hz, 1H, CH*H*Ph), 4.42 (d, J_{gem} = 11.9 Hz, 1H, CH*H*Ph), 4.07 (t, $J_{4,3/5}$ = 2.4 Hz, 1H, CH-4), 3.97 (dd, $J_{2,3}$ = 9.7 Hz, $J_{2,1}$ = 4.0 Hz, 1H, CH-2), 3.83 (dd, 1H, CH-3), 3.69 (dd, J_{gem} = 9.0 Hz, $J_{C\underline{H}H,5}$ = 5.9 Hz, 1H, C*H*HOBn), 3.56 (t, $J_{C\underline{H}H,5}$ = 8.5 Hz, 1H, CH*H*OBn), 3.44 (t, $J_{1,6}$ = 3.3 Hz, 1H, CH-1), 3.07 (dd, $J_{6,5}$ = 11.1 Hz, 1H, CH-6), 2.25-2.04 (m, 5H, CH-5, 2 x NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.4, 139.1, 138.9, 138.2 (4 x C_q Ar), 128.5-127.4 (20 x CH Ar), 80.3 (C-3), 78.8 (C-2), 75.9 (C-4), 74.9, 73.4, 73.2, 72.5 (4 x CH_2Ph), 70.3 (CH_2OBn), 54.0 (C-1), 50.2 (C-6), 40.9

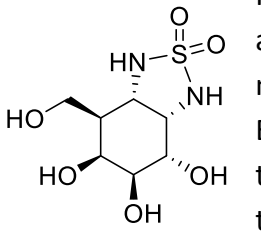
(C-5). Note: broad ^{13}C NMR signals are observed. HRMS: Calcd. for $C_{35}H_{40}N_2O_4H^+$ m/z 553.30608, found m/z 553.30592.

(3a*S*,4*S*,5*S*,6*S*,7*R*,7a*S*)-4,5,6-Tris(benzyloxy)-7-((benzyloxy)methyl)octahydrobenzo[*c*]-[1,2,5] thiadiazole 2,2-dioxide (**48**)



Sulfamide (0.106 g, 1.1 mmol, 20 eq.) was added to a solution of **47** (0.030 g, 0.054 mmol) in dry pyridine (5 mL). The reaction mixture was stirred at reflux temperature overnight before it was concentrated *in vacuo* and the remaining solvent was coevaporated with toluene (x3). Water was added, and the aqueous solution was extracted with DCM (x3). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (Pentane/EtOAc 9:1 → 1:1 + 1% Et_3N) to give **48** (0.033 g, 0.054 mmol, 99 %) as a colorless oil. $[\alpha]_D^{20}$ +9.0 (*c* = 1, $CHCl_3$). IR (neat, cm^{-1}): 3254, 3030, 2922, 1454, 1304, 1260, 1111, 737, 698. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.40 – 7.23 (m, 18H, CH Ar), 7.19 – 7.09 (m, 2H, CH Ar), 5.39 (d, *J* = 1.9 Hz, 1H, NH), 4.89 (d, *J* = 11.3 Hz, 1H, C*H*HPh), 4.81 (d, *J* = 11.6 Hz, 1H, C*H*HPh), 4.79 – 4.67 (m, 3H, C*H*HPh, CH_2Ph), 4.54 (d, *J* = 3.5 Hz, 1H, NH), 4.50 – 4.40 (m, 3H, C*H*HPh, CH_2Ph), 4.33 (q, *J* = 4.4 Hz, 1H, CH-1), 4.11 (dd, *J* = 9.4, 4.5 Hz, 1H, CH-2), 3.92 – 3.82 (m, 2H, CH-3, CH-4), 3.69 – 3.60 (m, 2H, CH-6, C*H*HOBn), 3.49 (dd, *J* = 9.0, 5.5 Hz, 1H, C*H*HOBn), 2.54 – 2.43 (m, 1H, CH-5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 138.4, 138.4, 137.9, 137.4 (4 x C_q Ar), 128.7, 128.7, 128.6, 128.5, 128.2, 128.1, 128.1, 128.0, 127.98, 127.95, 127.88, 127.6 (20 x CH Ar), 80.9 (C-3), 76.2 (C-2), 75.8 (C-4), 74.8, 73.9, 73.7, 73.4 (4 x CH_2Ph), 71.6 (CH_2OBn), 58.5 (C-1), 57.7 (C-6), 41.1 (C-5). HRMS: Calcd. for $C_{35}H_{39}N_2O_6S^+$ m/z 615.25288, found m/z 615.25222; Calcd. for $C_{35}H_{42}N_3O_6S^+$ m/z 632.27943, found m/z 632.27814; Calcd. for $C_{35}H_{38}N_2NaO_6S^+$ m/z 637.23346, found m/z 637.23483.

(3a*S*,4*S*,5*S*,6*S*,7*R*,7a*S*)-4,5,6-Trihydroxy-7-(hydroxymethyl)octahydrobenzo[*c*]-[1,2,5] thiadiazole 2,2-dioxide (**5**)

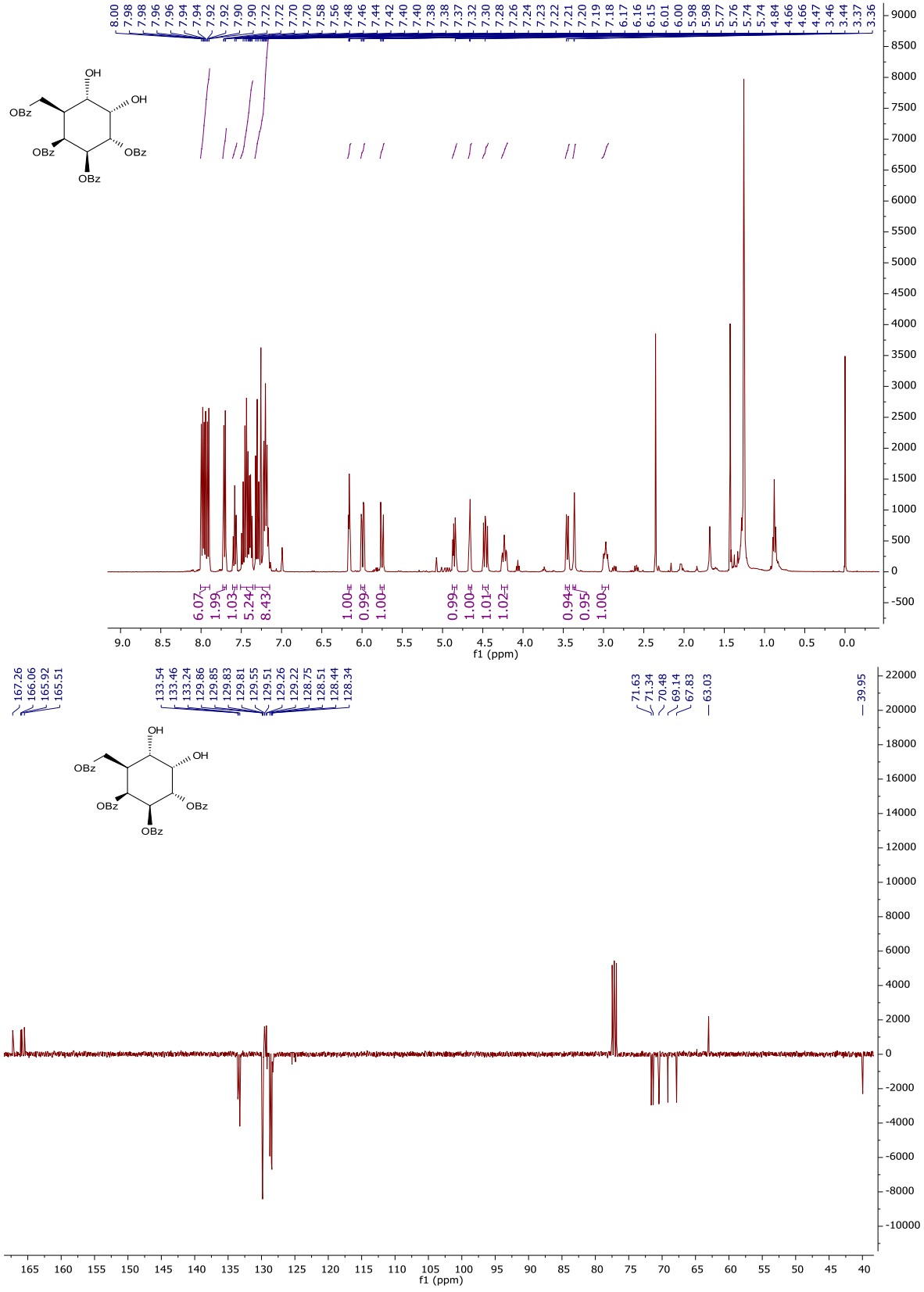


$Pd(OH)_2$ on carbon (20 wt. %, 0.013 g, 0.019 mmol, 0.6 eq.) was added to a solution of **48** (0.018 g, 0.029 mmol) in MeOH (3 mL). The reaction mixture was stirred vigorously at rt under an atmosphere of H_2 for 6 h. Extra $Pd(OH)_2$ on carbon (0.015 g, 0.021 mmol, 0.7 eq.) was added and the reaction mixture was stirred at rt overnight. The mixture was filtered through celite and concentrated *in vacuo* to give final compound **5** (0.007 g, 0.028 mmol, 94%) as a colorless oil. R_f 0.31 (DCM/MeOH 7:3 + 1% Et_3N). $[\alpha]_D^{20}$ -8.7 (*c* = 0.5, MeOH). IR (neat, cm^{-1}): 3262, 2926, 1728, 1271, 1130. ^1H NMR (400 MHz, CD_3OD): *δ* 4.17 (t, $J_{1,2/6}$ = 4.8 Hz, 1H, CH-1), 4.11 (t, $J_{4,3/5}$ = 2.2. Hz, 1H, CH-4), 4.01 (dd, $J_{2,3}$ 9.9 Hz, 1H, CH-2), 3.78 (dd, J_{gem} 10.5 Hz, $J_{CHH,5}$ = 5.4 Hz, 1H, C*H*HOH), 3.76-3.68 (m, 2H, CH*H*OH, CH-3), 3.55 (dd, $J_{6,5}$ =

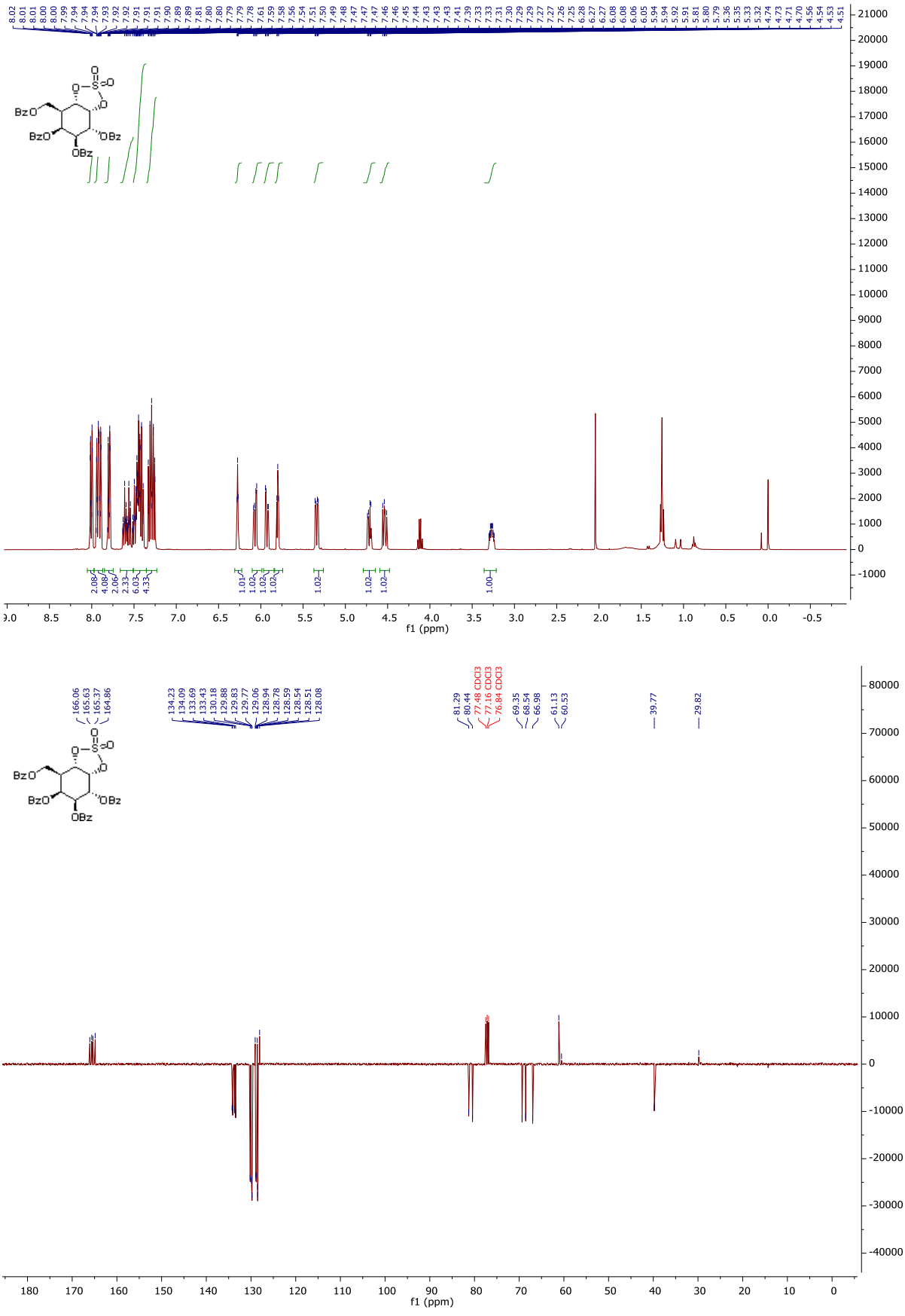
11.3 Hz, 1H, CH-6), 2.18-2.08 (m, 1H, CH-5). ^{13}C-NMR (100 MHz, CD_3OD): δ 72.7 (C-3), 71.1 (C-4), 69.6 (C-2), 63.7 (C-1), 61.7 (CH_2OH), 56.7 (C-6), 44.1 (C-5).

5. NMR Spectra

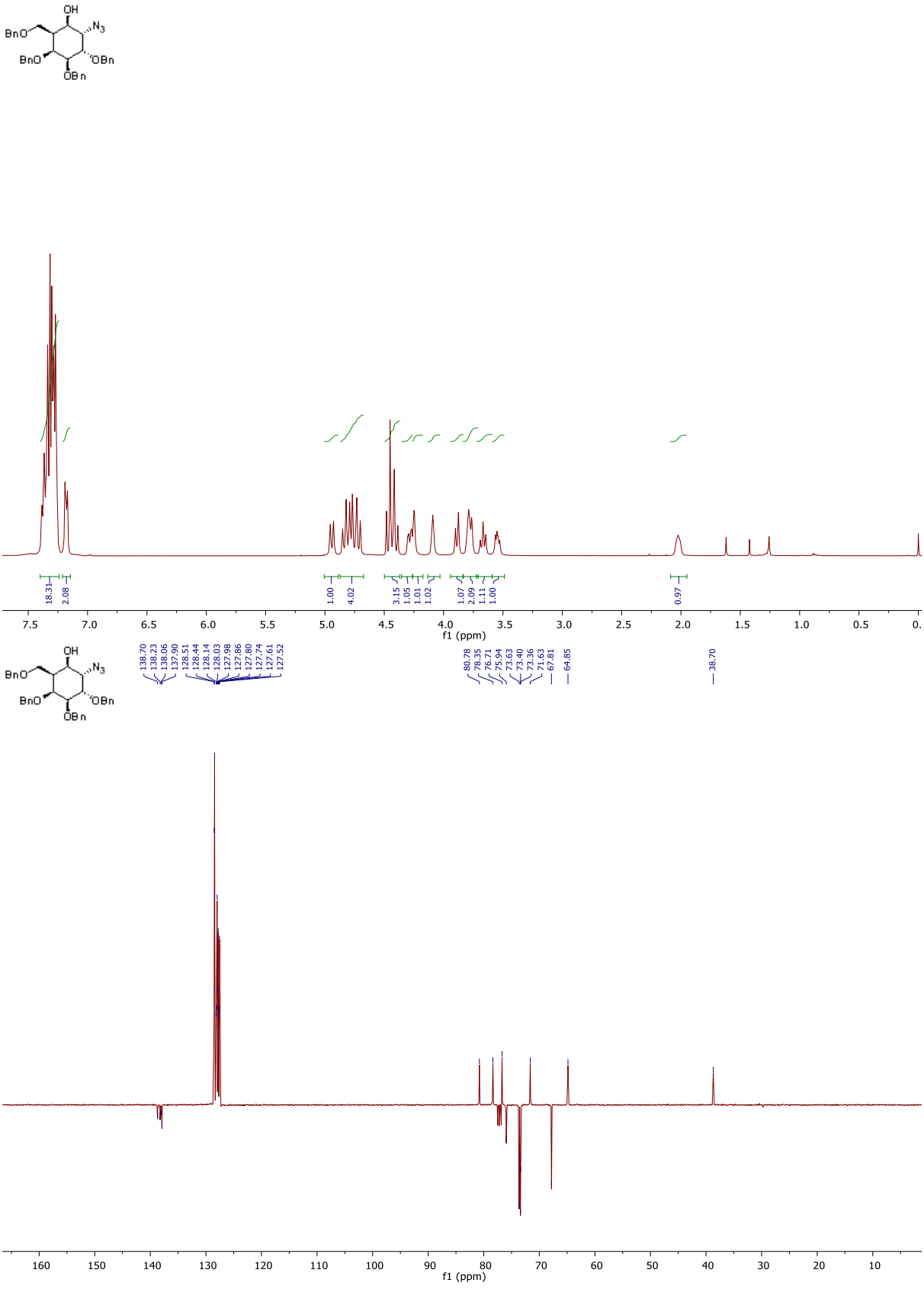
^{1}H-NMR and ^{13}C-NMR spectra of **11** in $CDCl_3$



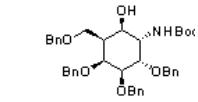
^{1}H-NMR and ^{13}C-NMR spectra of **12** in $CDCl_3$

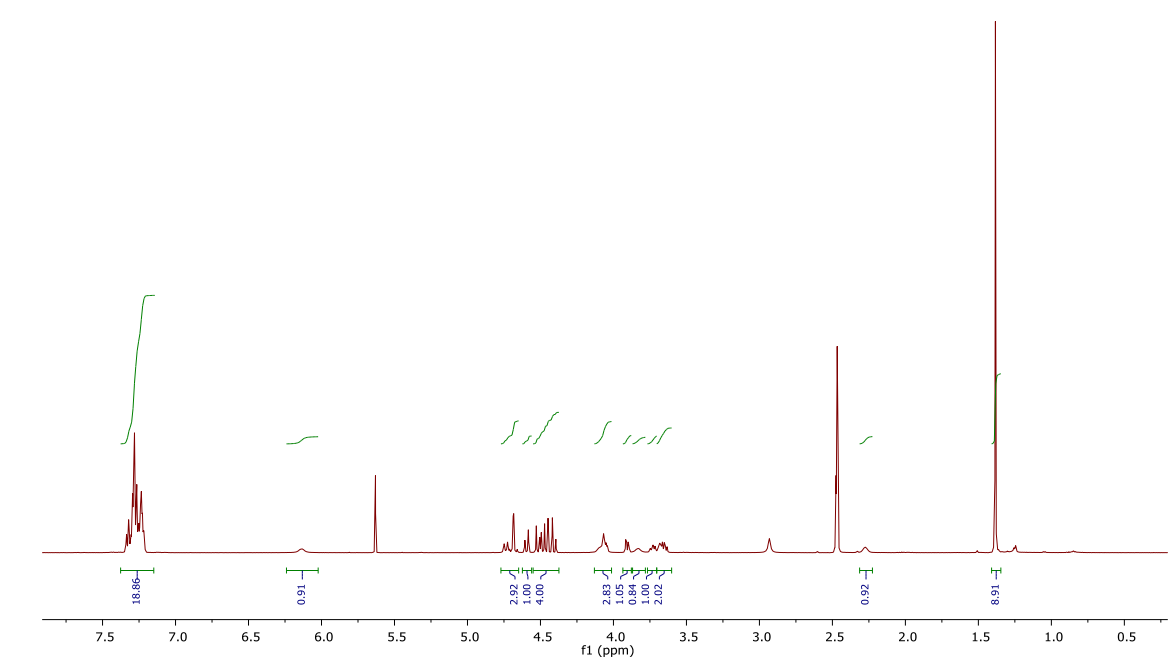


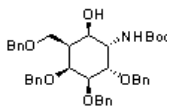
^{1}H-NMR and ^{13}C-NMR spectra of **13** in $CDCl_3$

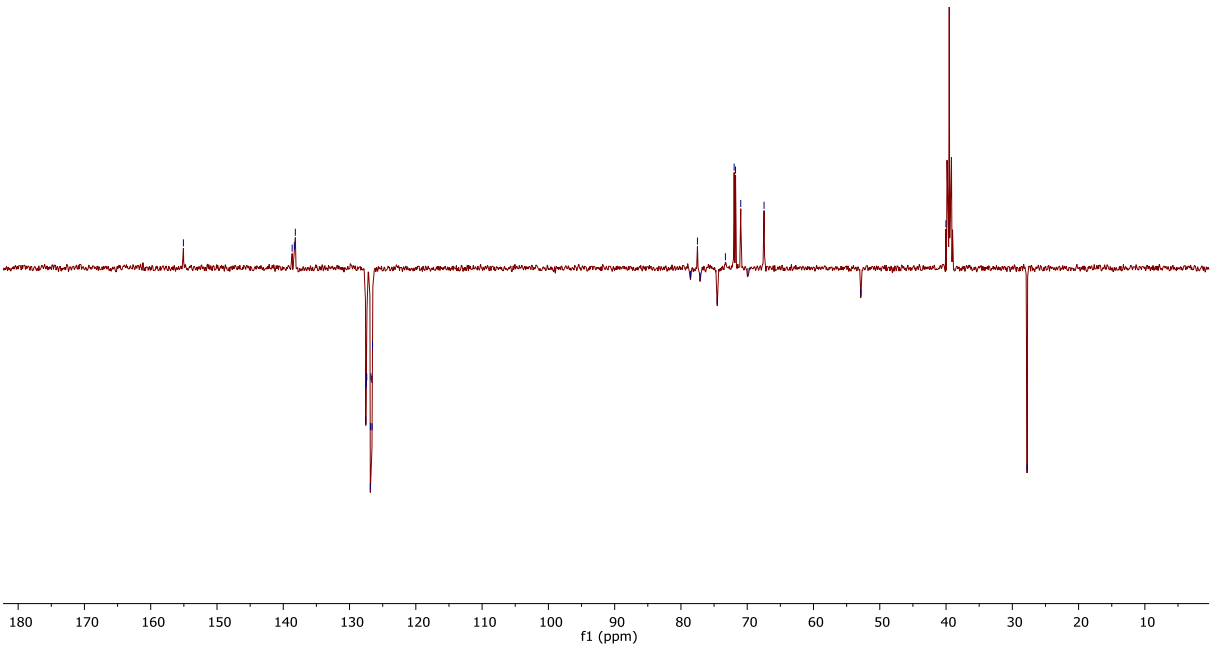


^{1}H-NMR and ^{13}C-NMR spectra of **15** in DMSO-d_6

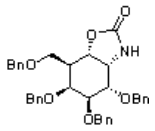


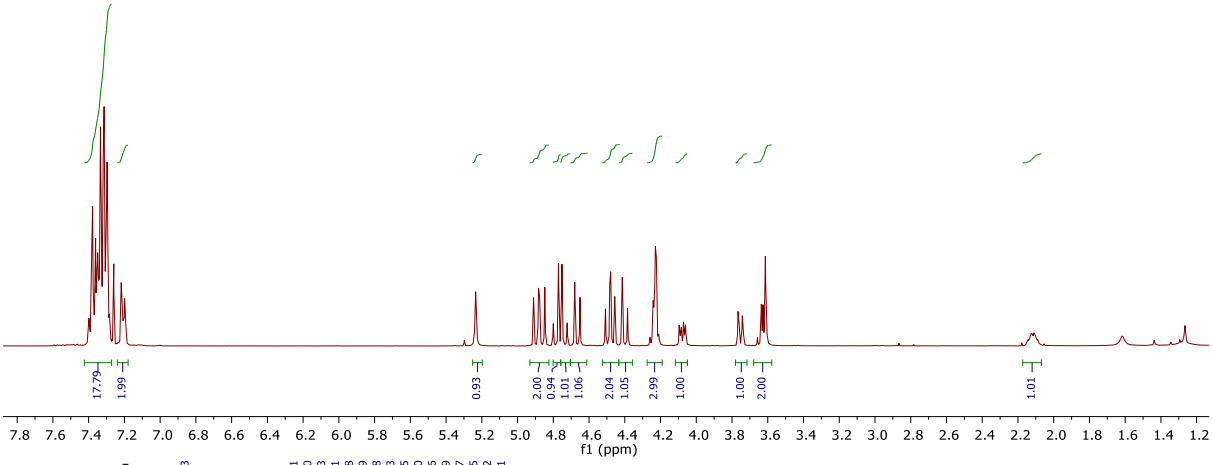


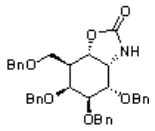




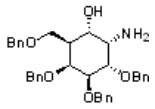
^{1}H-NMR and ^{13}C-NMR spectra of **17** in $CDCl_3$

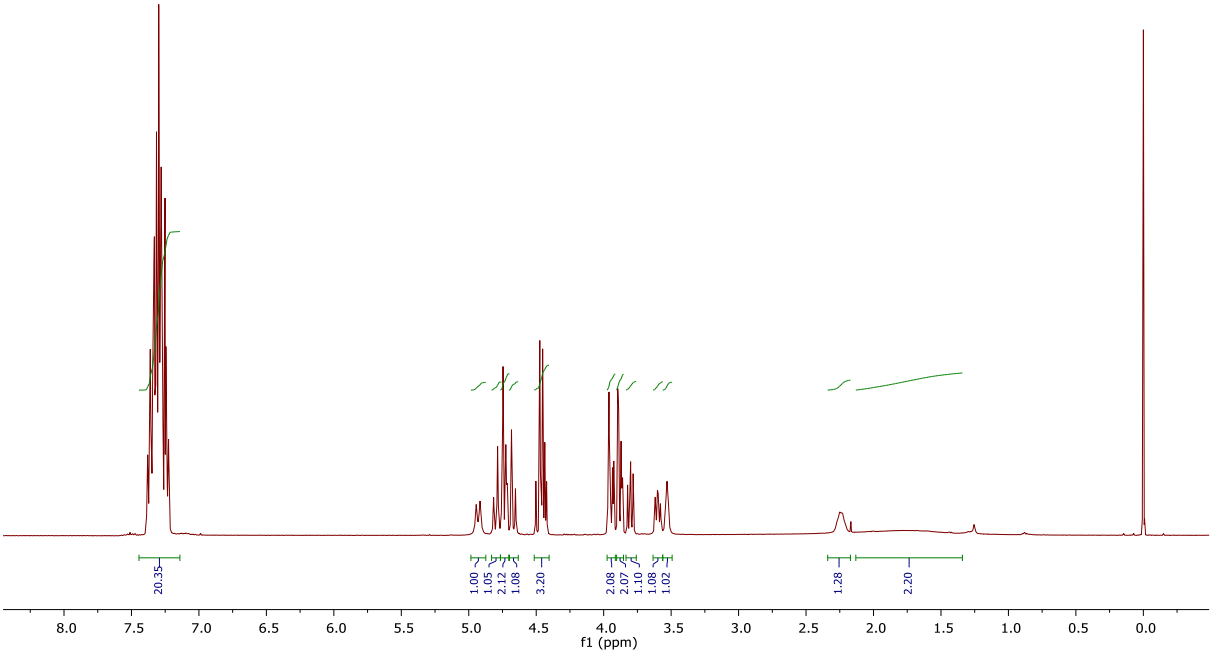


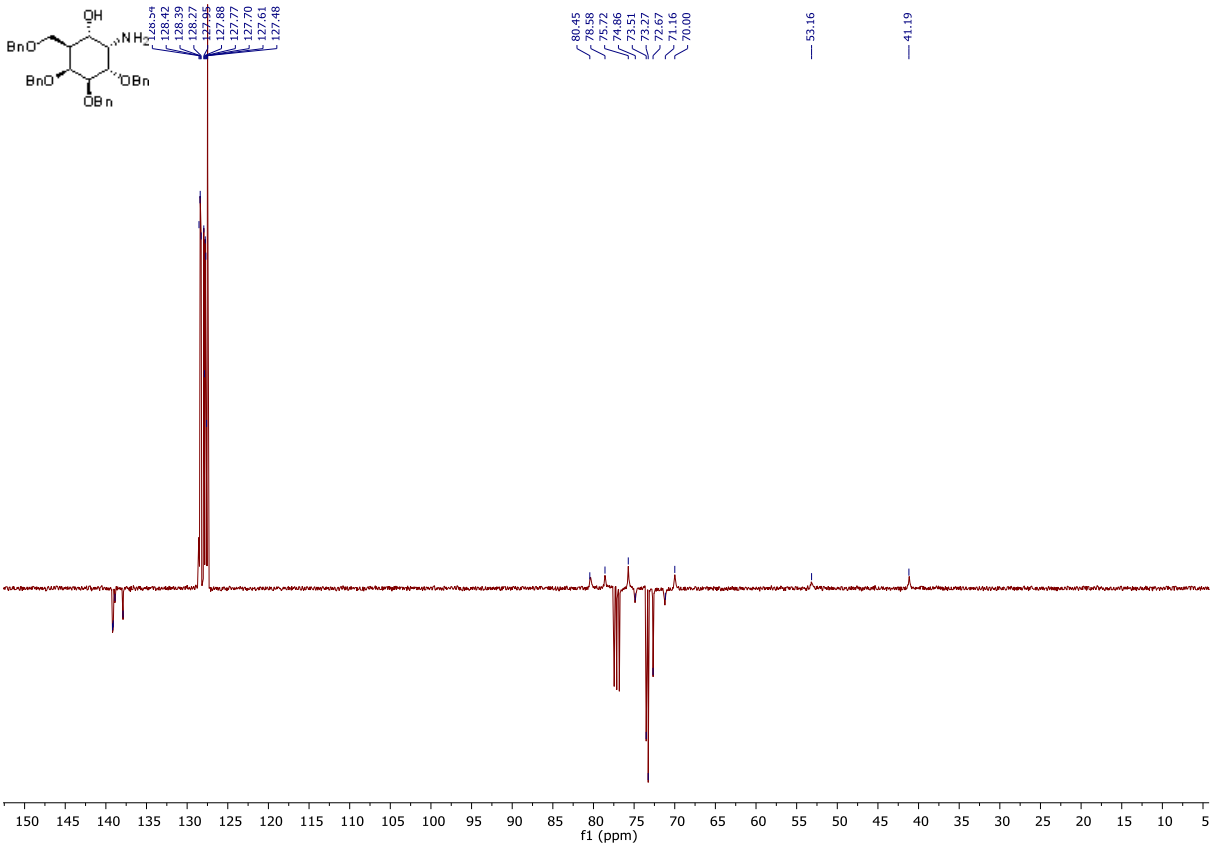




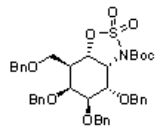
^{1}H-NMR and ^{13}C-NMR spectra of **18** in $CDCl_3$

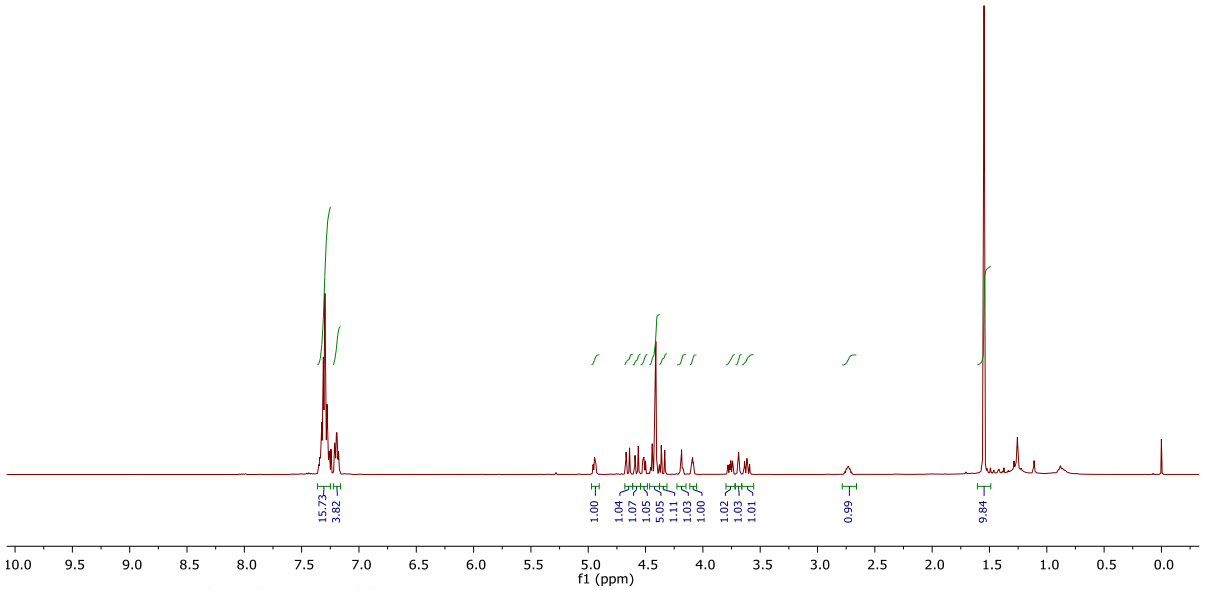


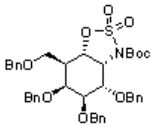




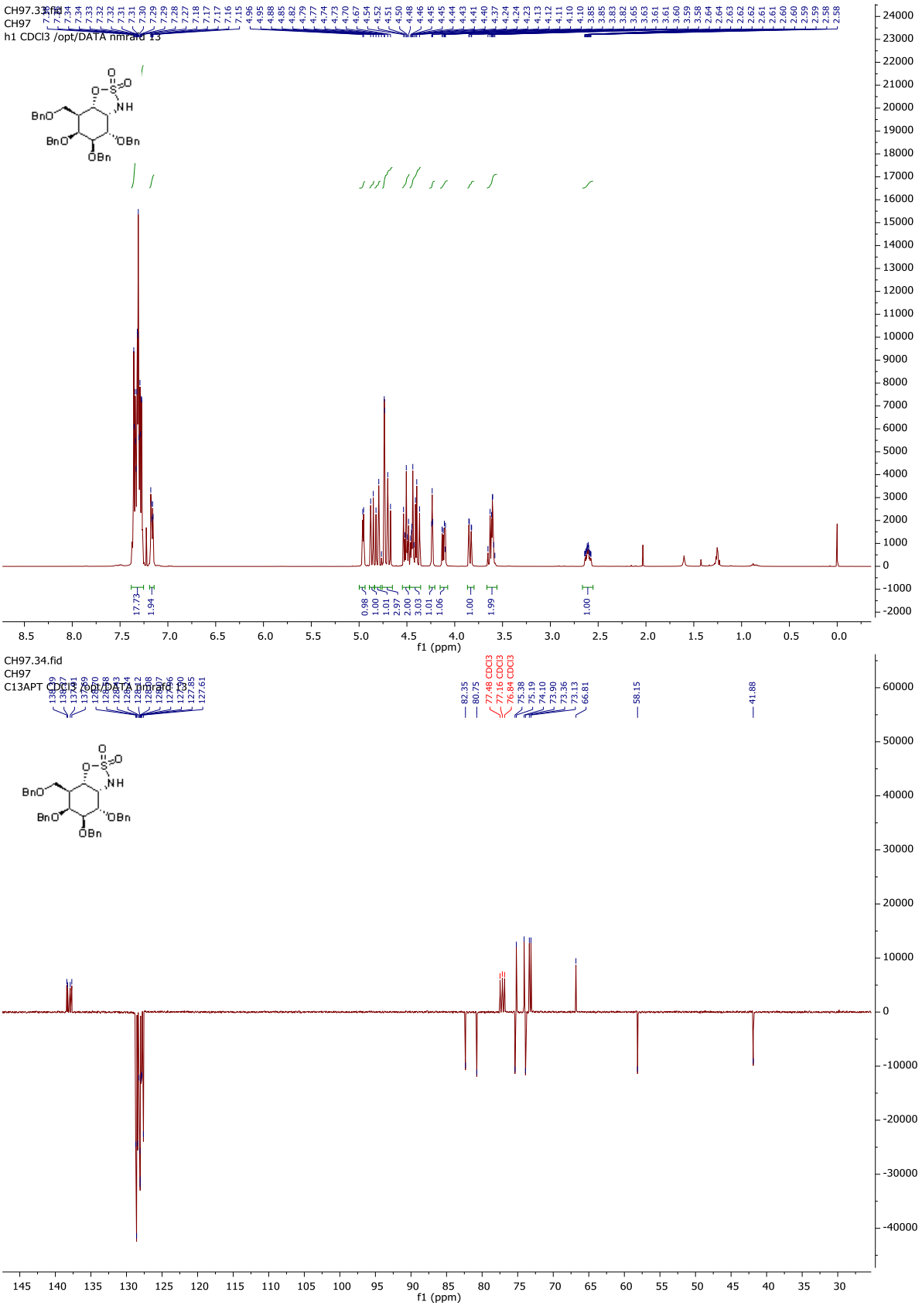
^{1}H-NMR and ^{13}C-NMR spectra of **20** in $CDCl_3$



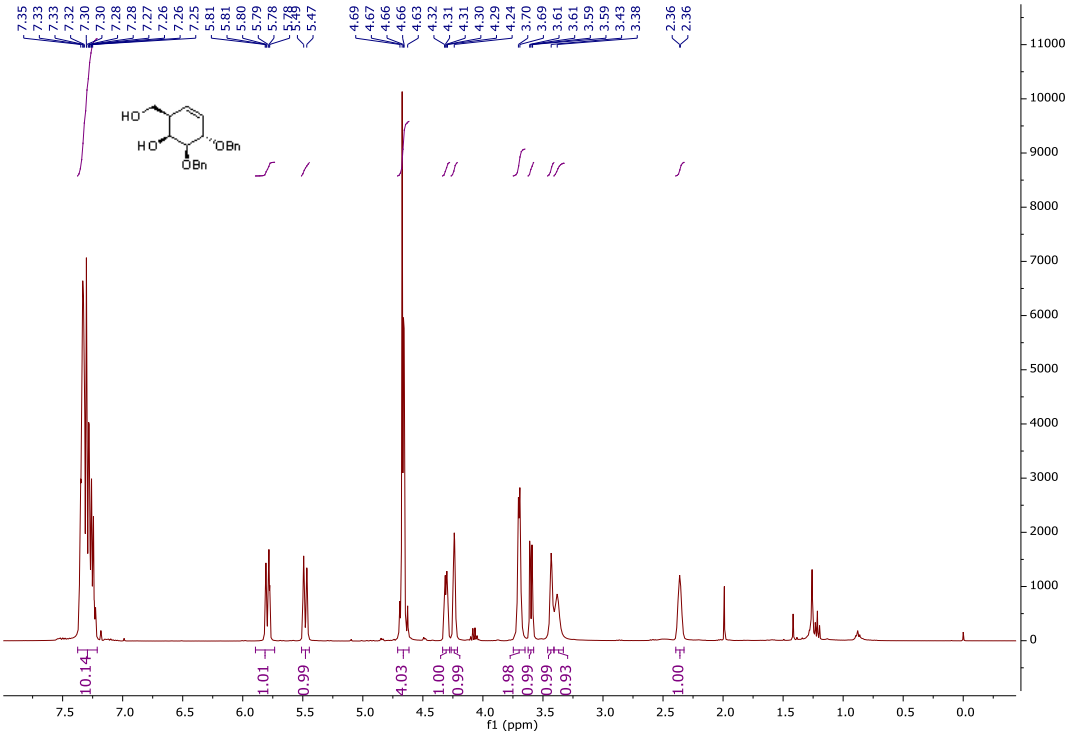




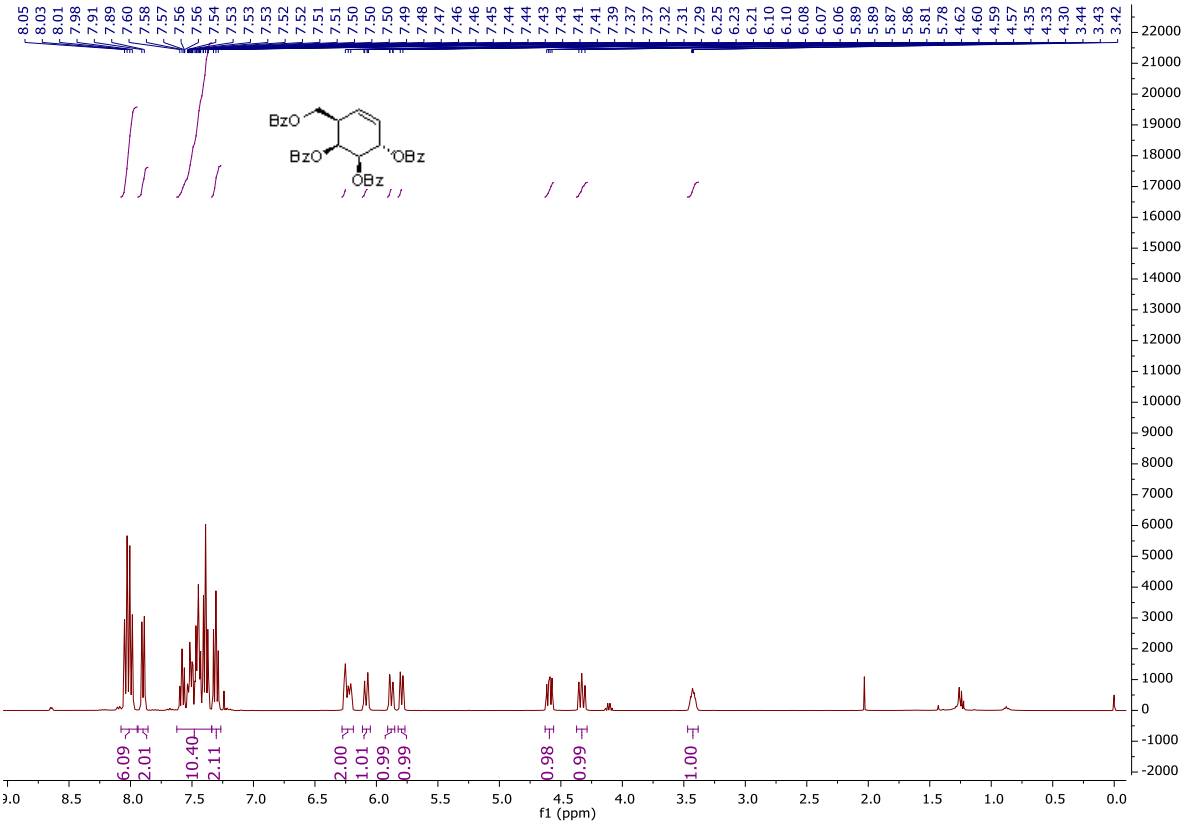
^{41}H-NMR and ^{13}C-NMR spectra of **21** in $CDCl_3$



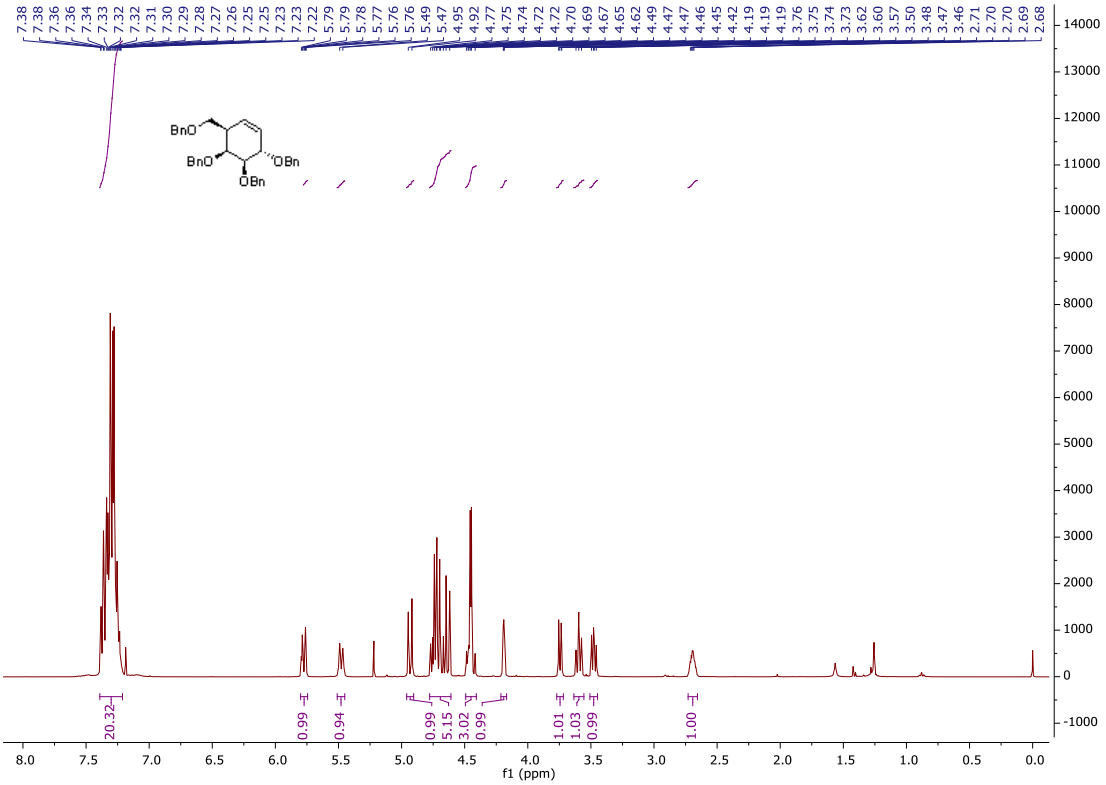
^{1}H-NMR spectra of **22** in $CDCl_3$



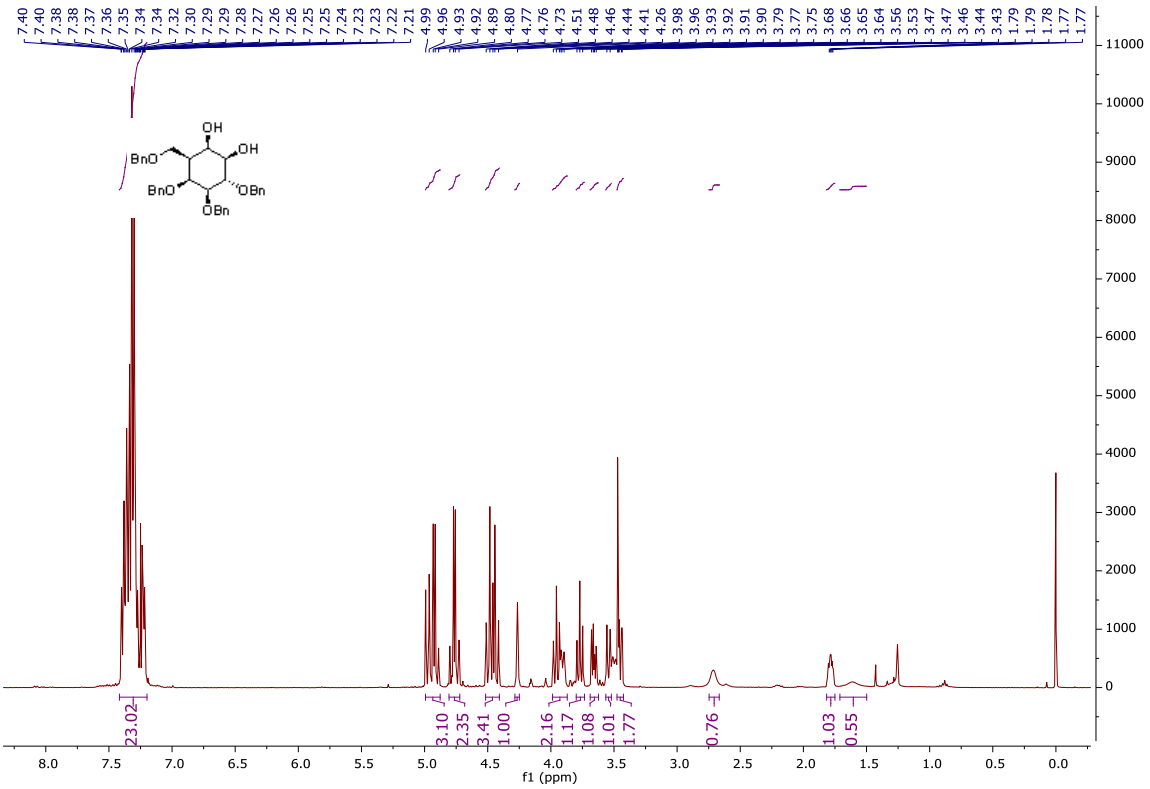
^{1}H-NMR spectra of **23** in $CDCl_3$

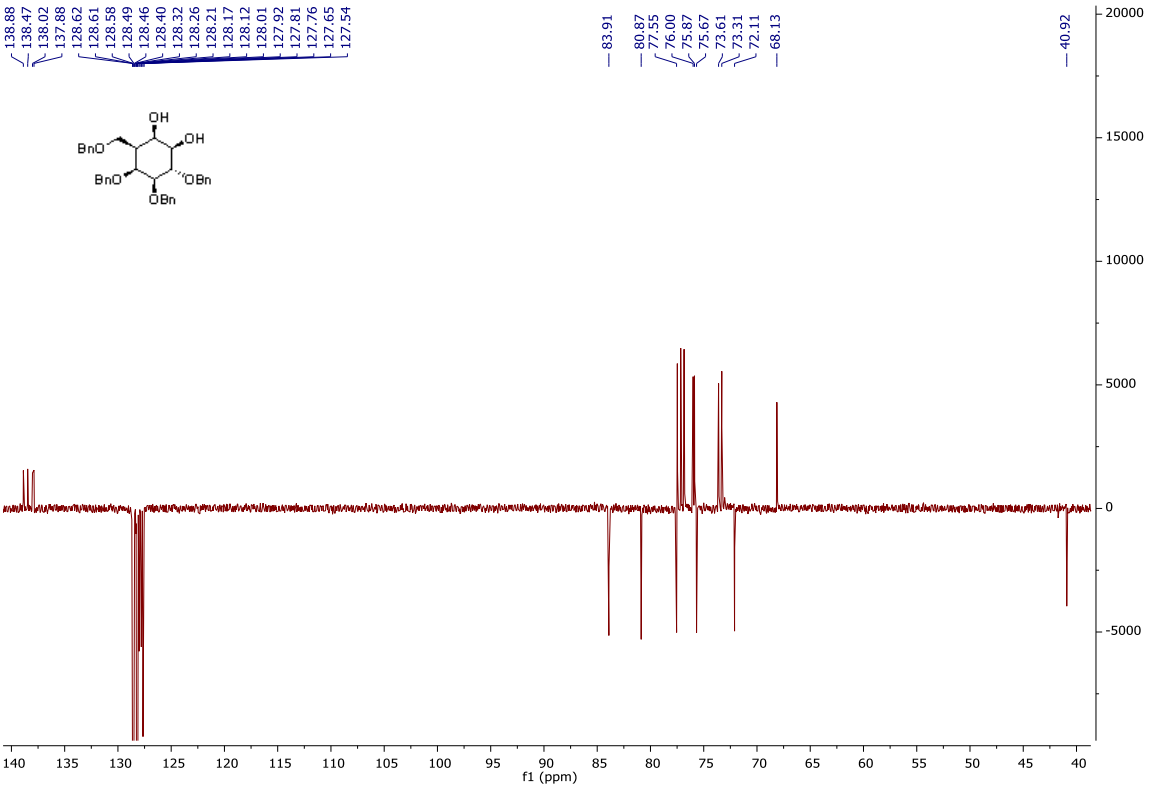


^{1}H-NMR spectra of **24** in $CDCl_3$

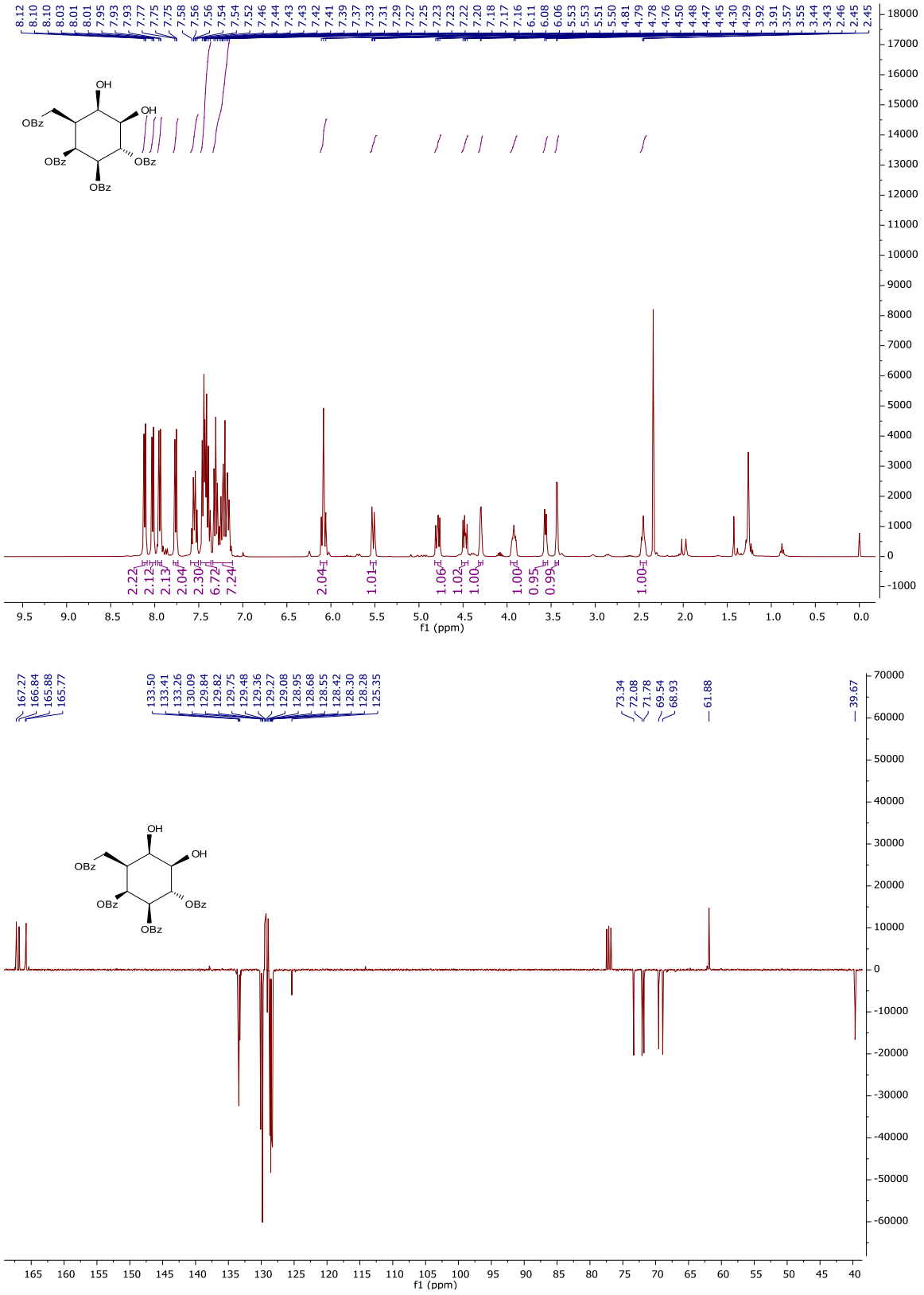


^{1}H-NMR and ^{13}C-NMR spectra of **26** in $CDCl_3$

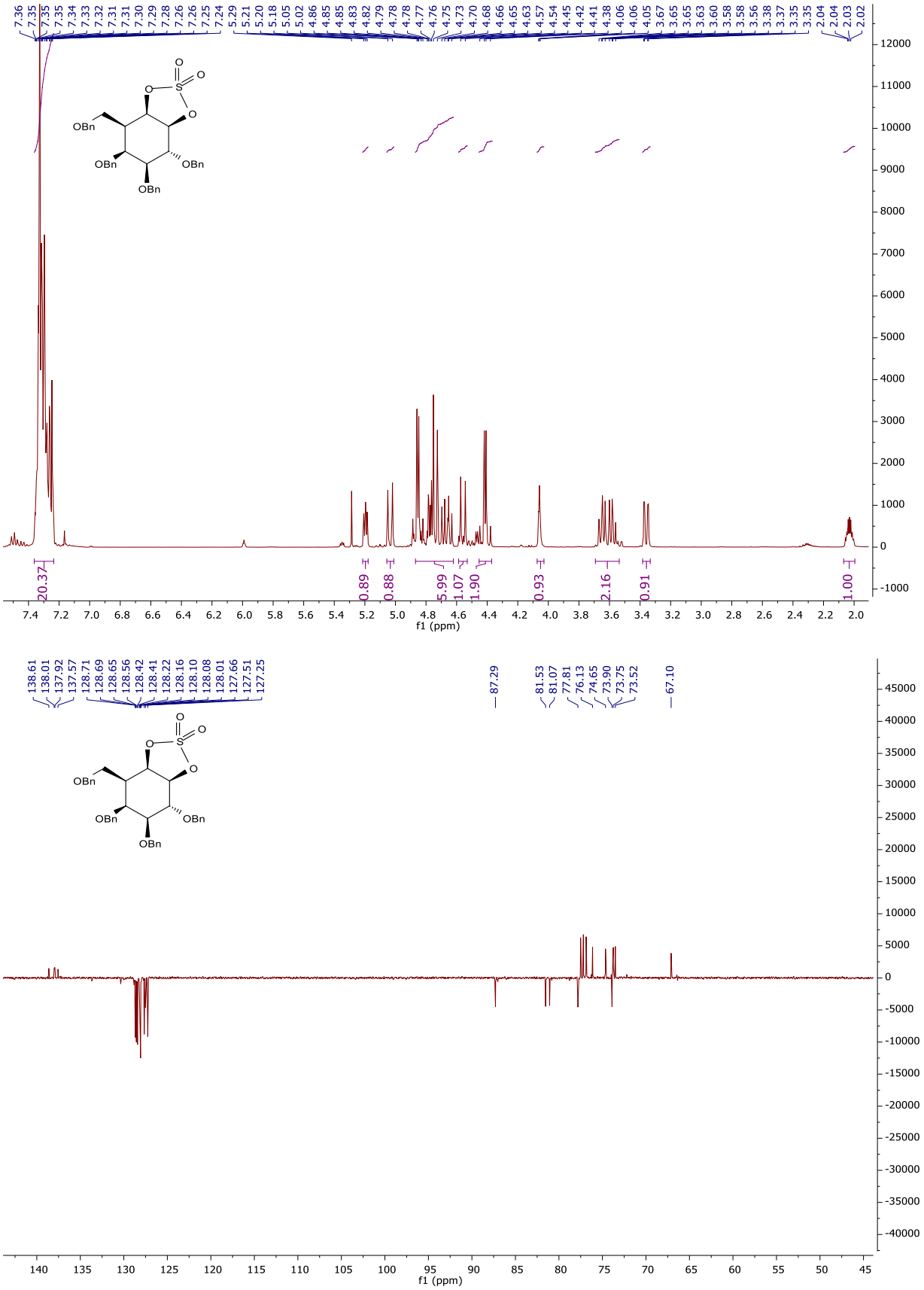




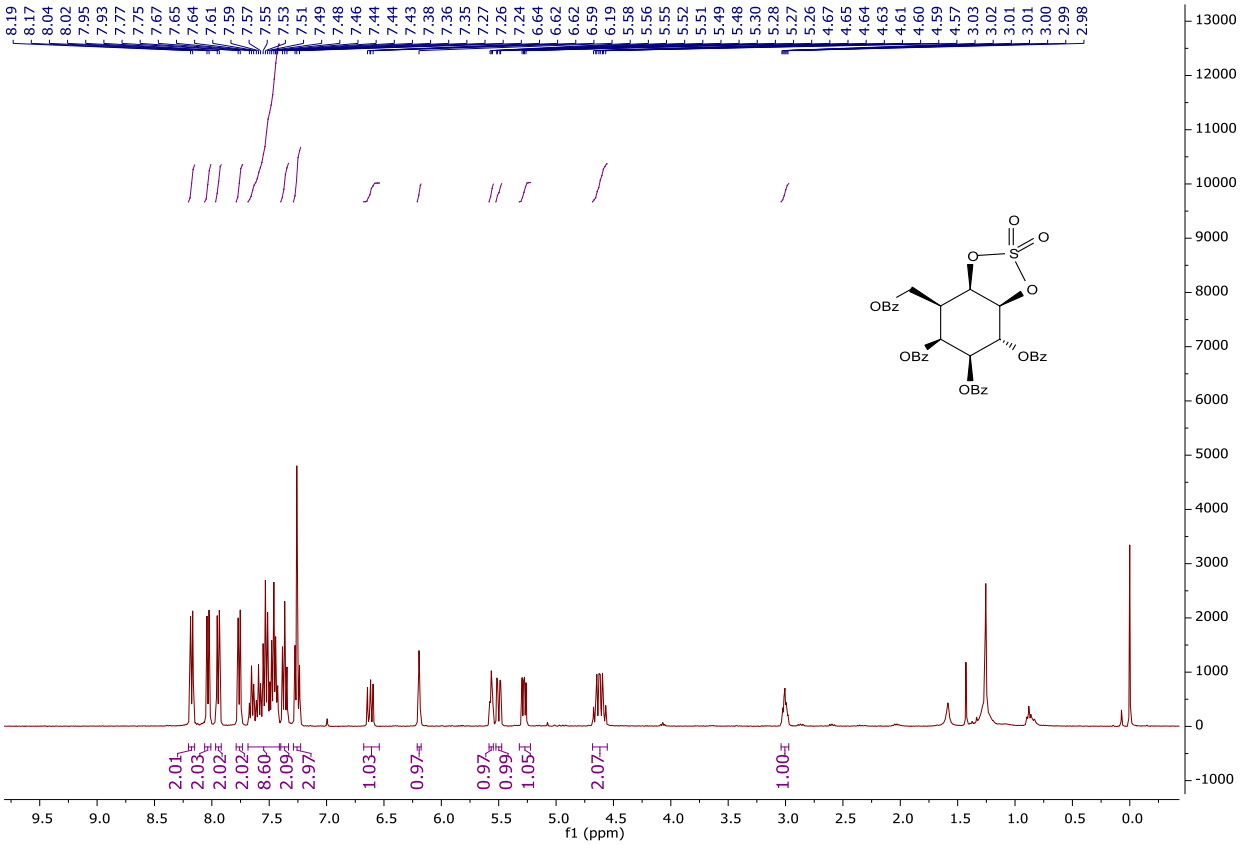
^{1}H-NMR and ^{13}C-NMR spectra of **27** in $CDCl_3$

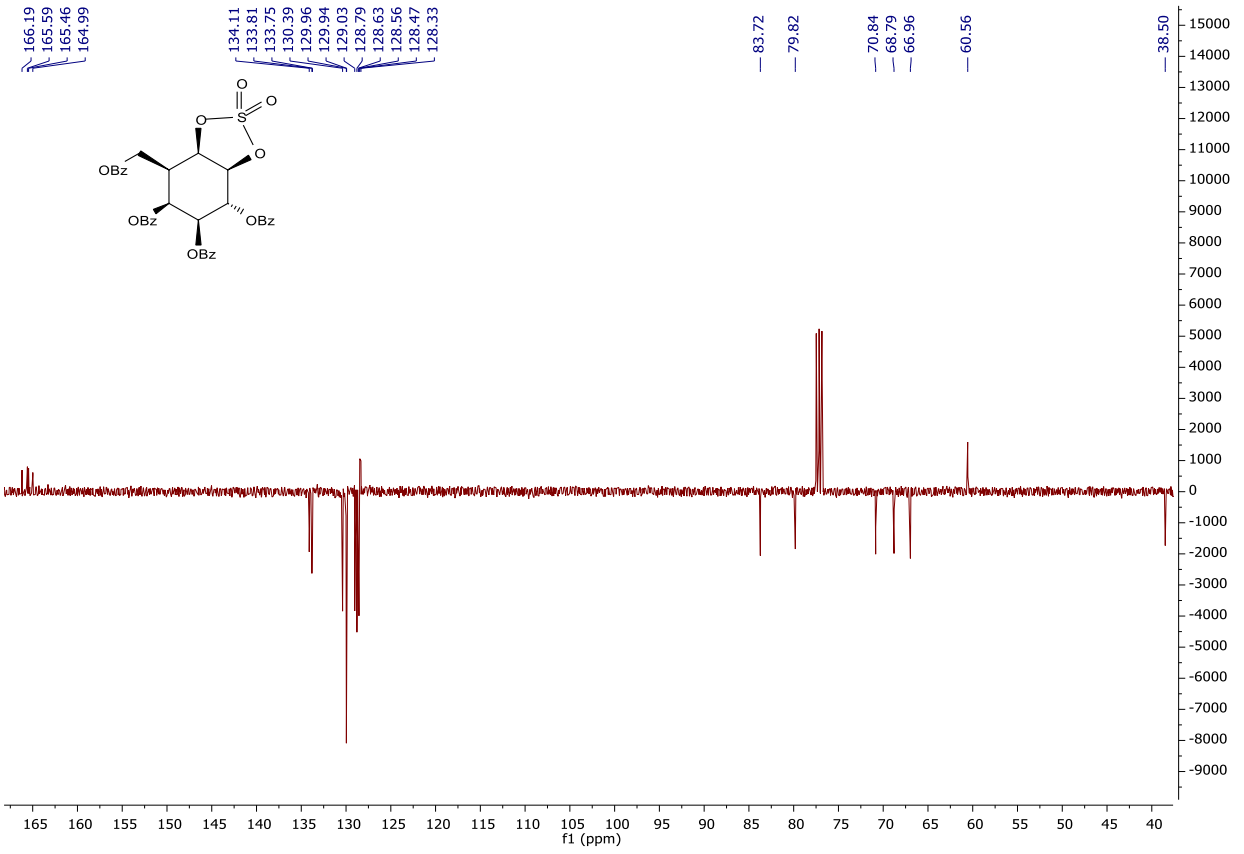


^{1}H-NMR and ^{13}C-NMR spectra of **28** in $CDCl_3$

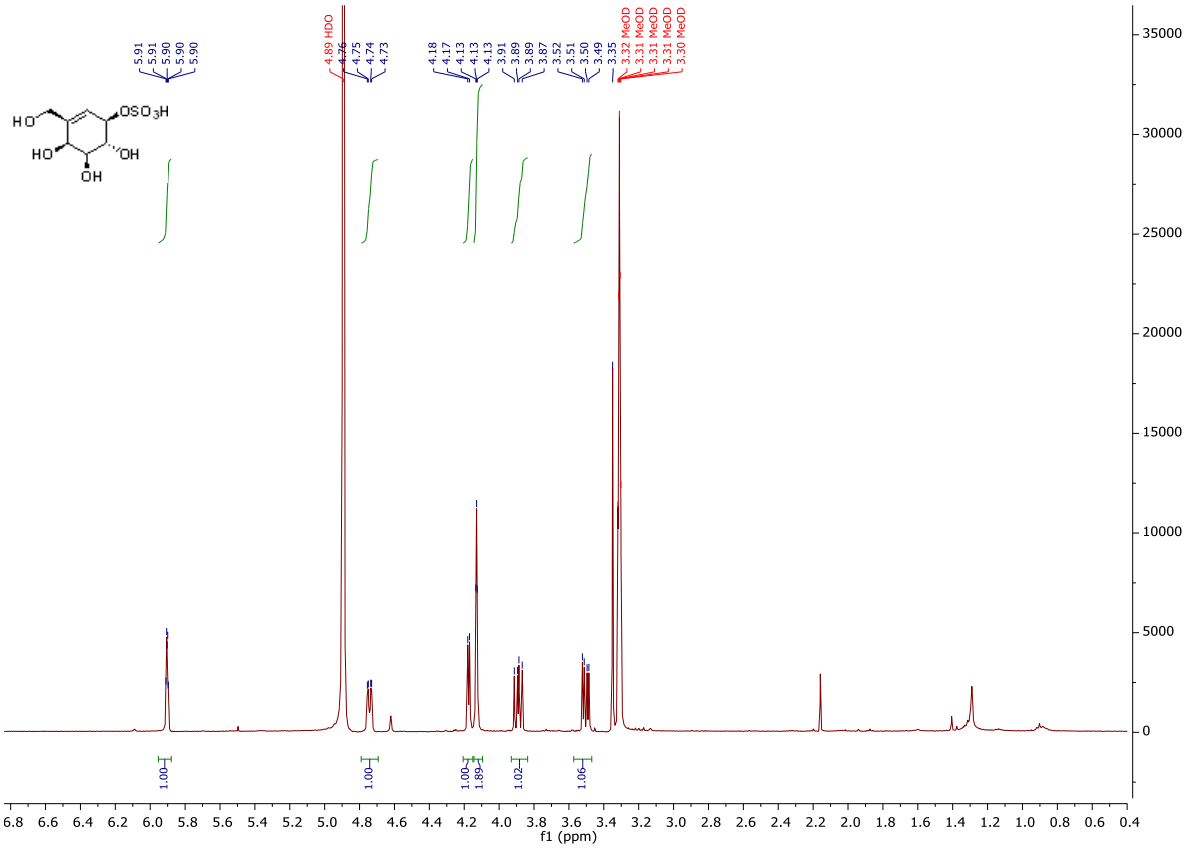


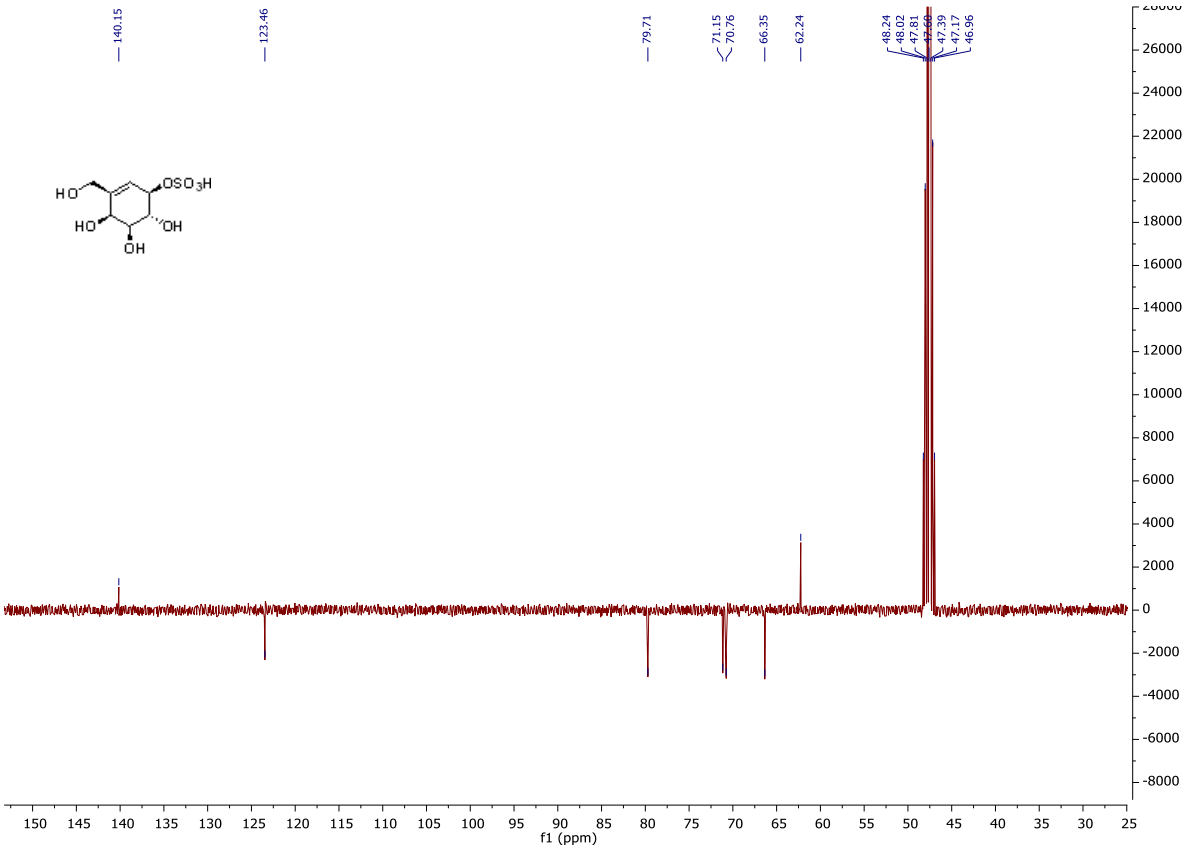
^{1}H-NMR and ^{13}C-NMR spectra of **29** in $CDCl_3$



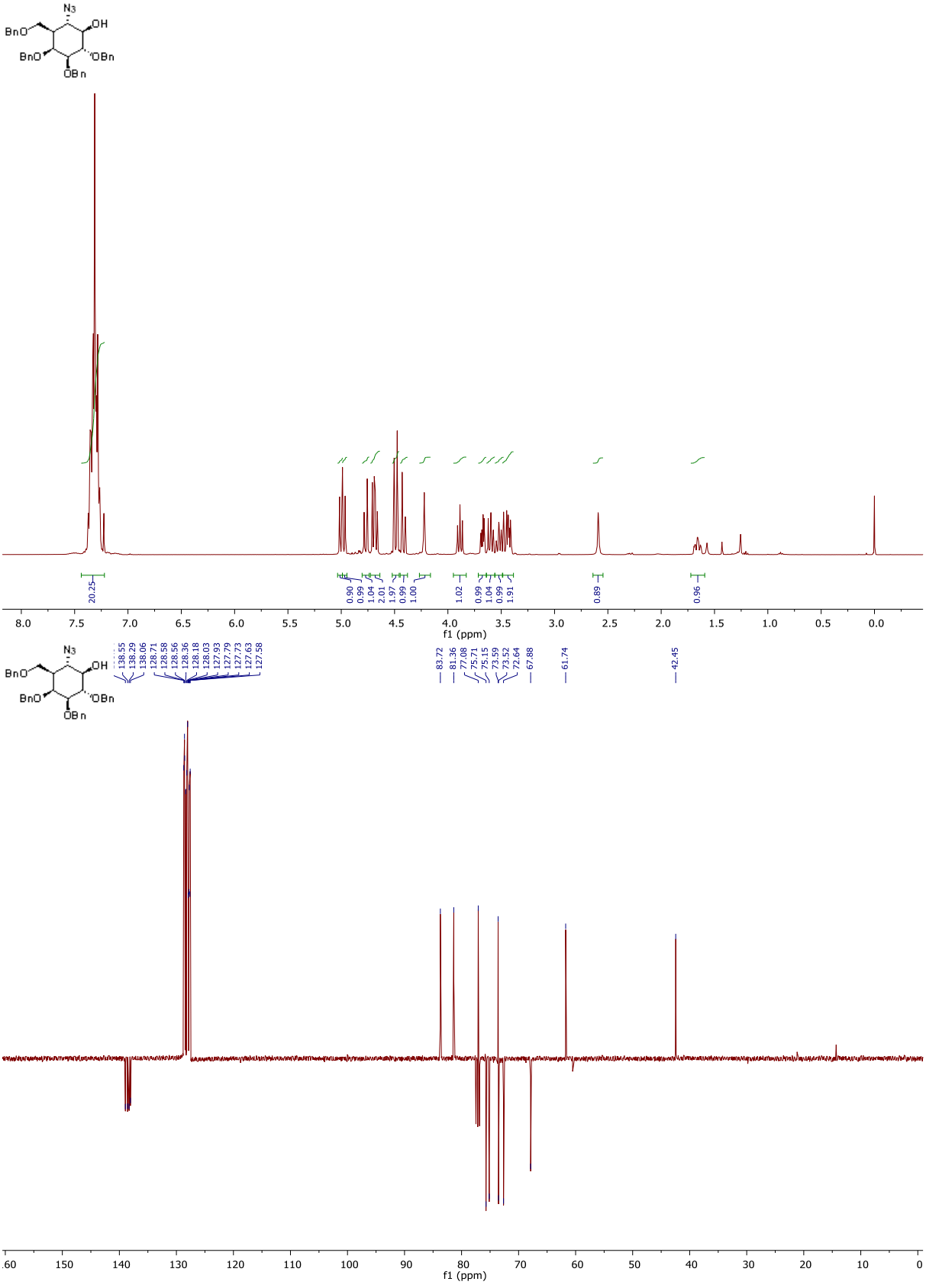


^{1}H-NMR and ^{13}C-NMR spectra of **30** in $CDCl_3$

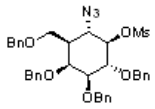


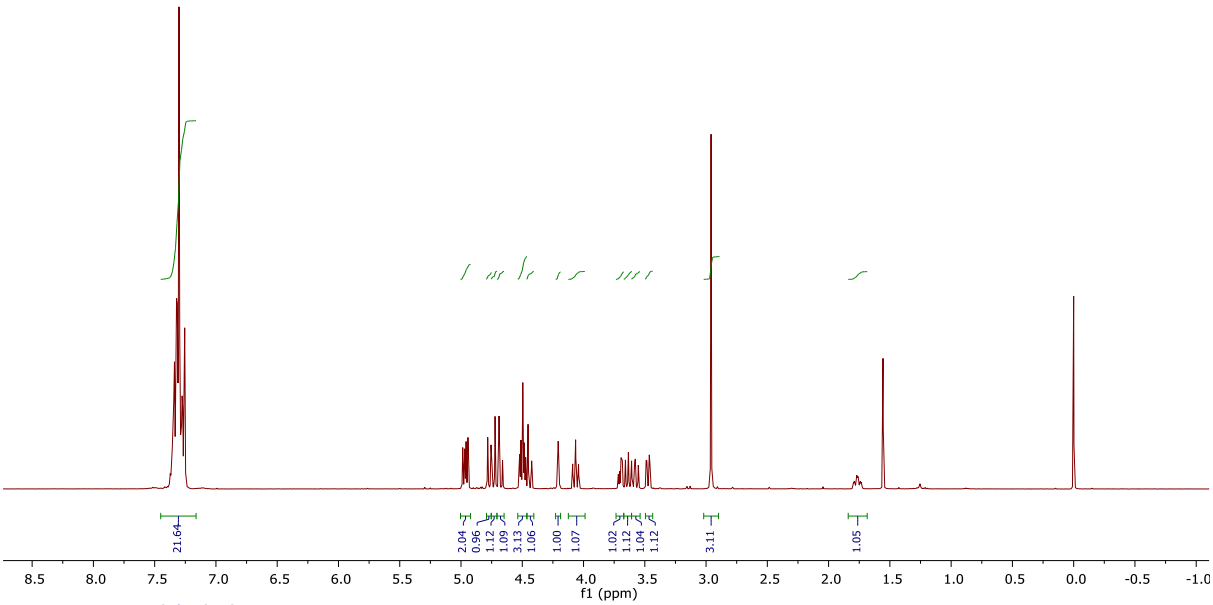


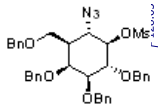
^{1}H-NMR and ^{13}C-NMR spectra of **32** in $CDCl_3$

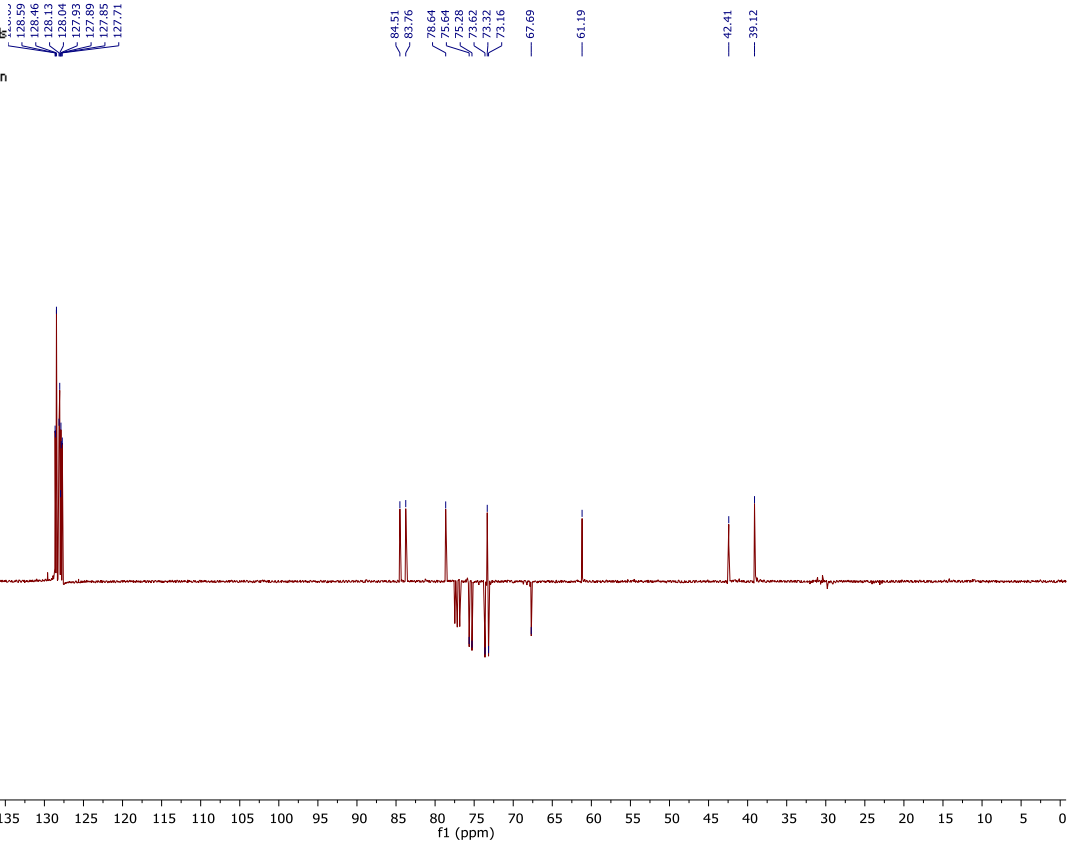


^{1}H-NMR and ^{13}C-NMR spectra of **33** in $CDCl_3$

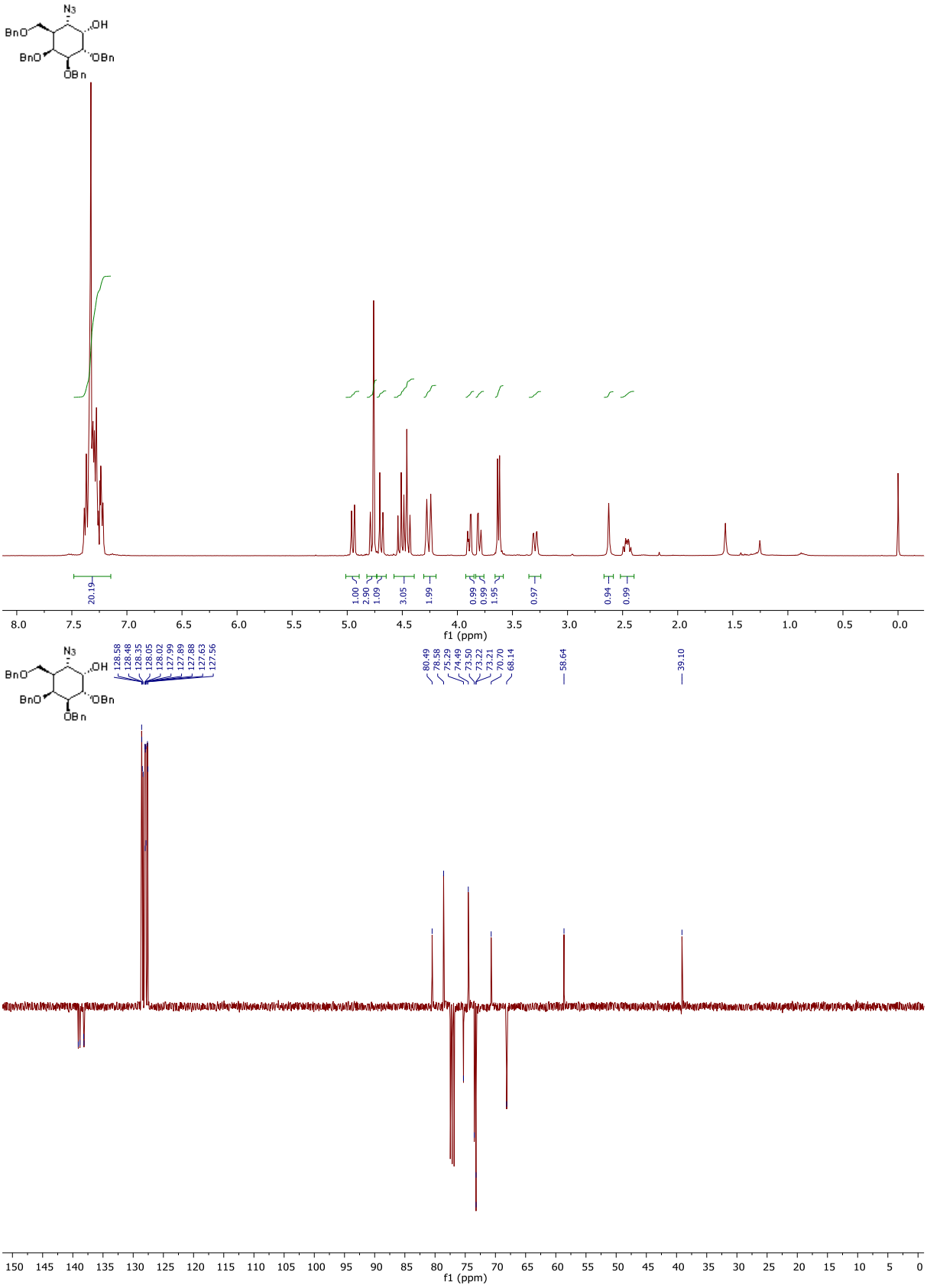




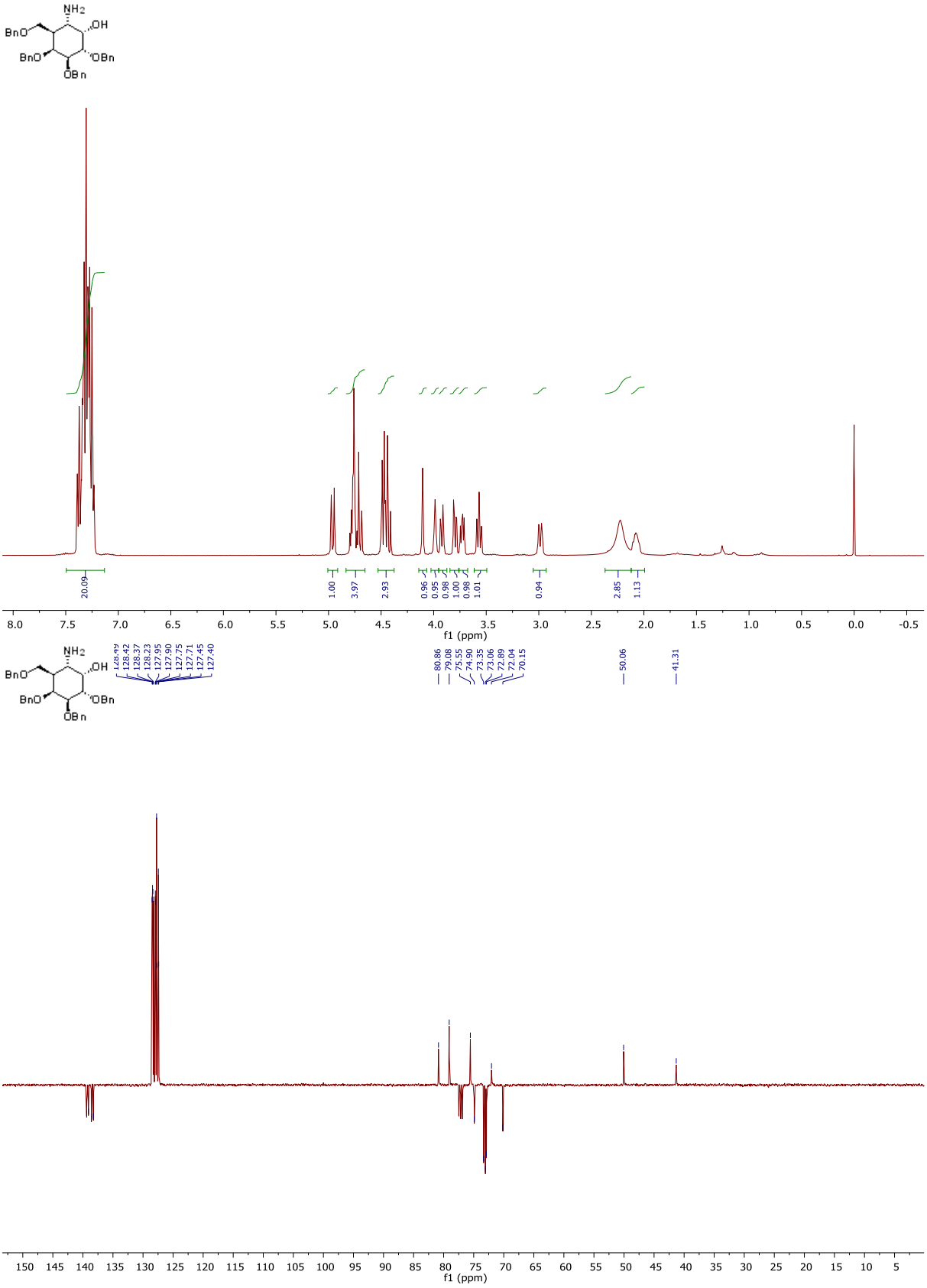




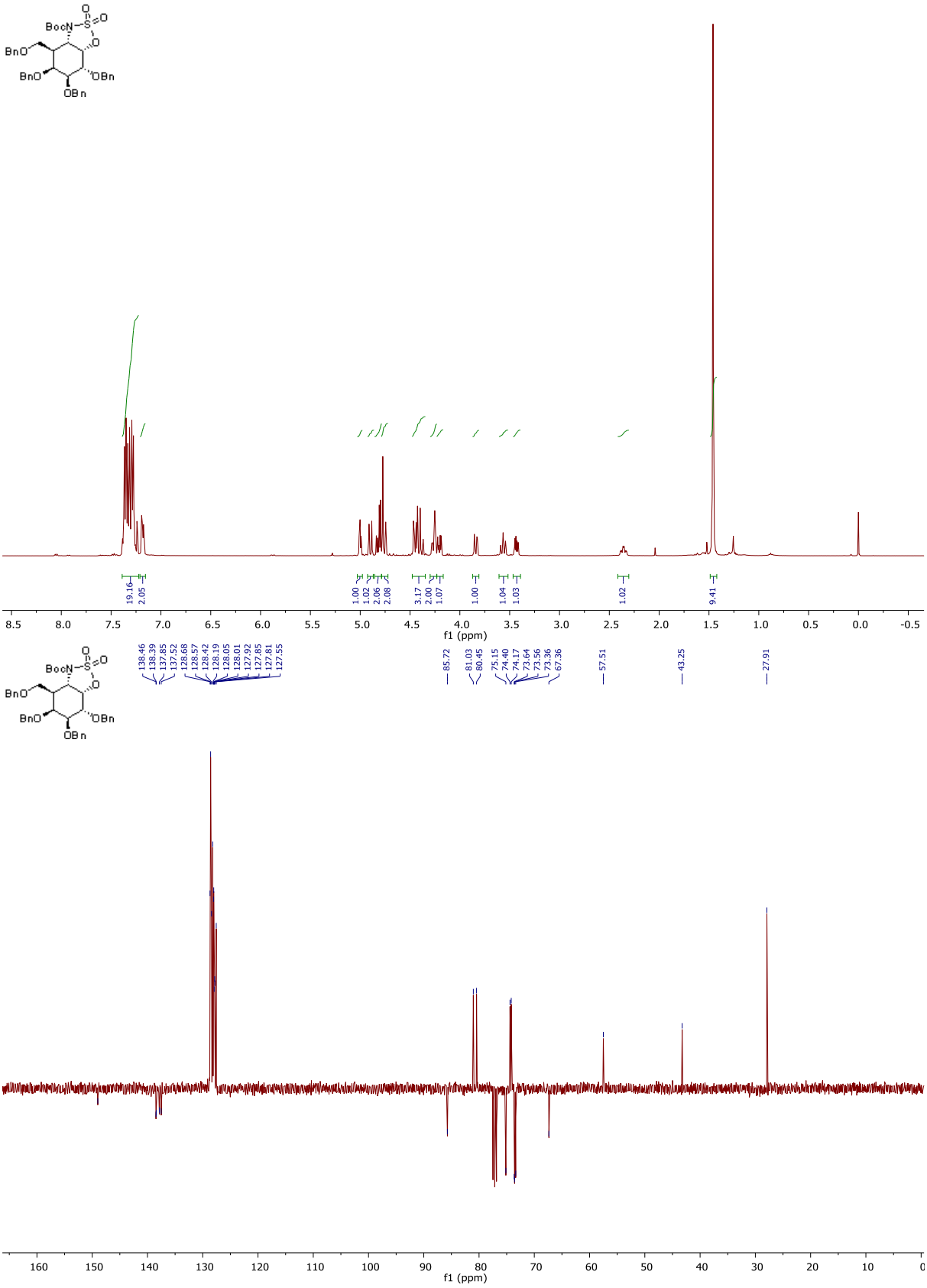
^{1}H-NMR and ^{13}C-NMR spectra of **34** in $CDCl_3$



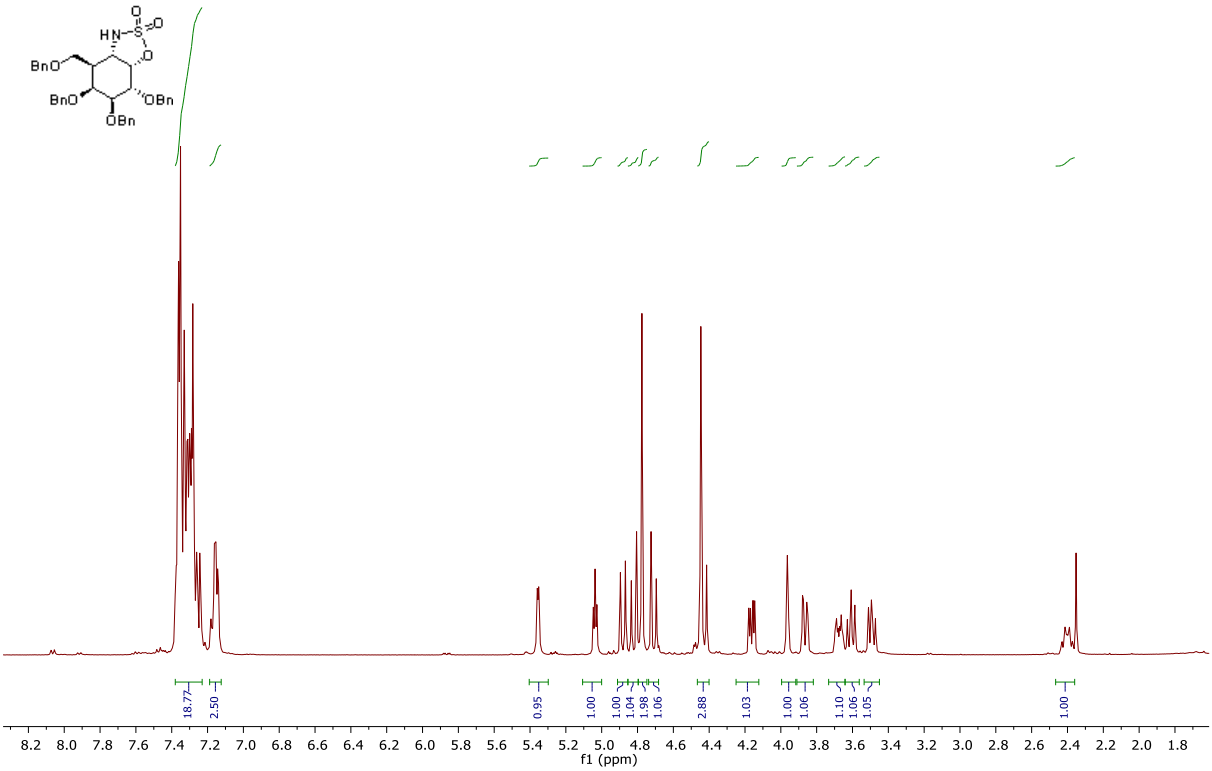
^{1}H-NMR and ^{13}C-NMR spectra of **35** in $CDCl_3$

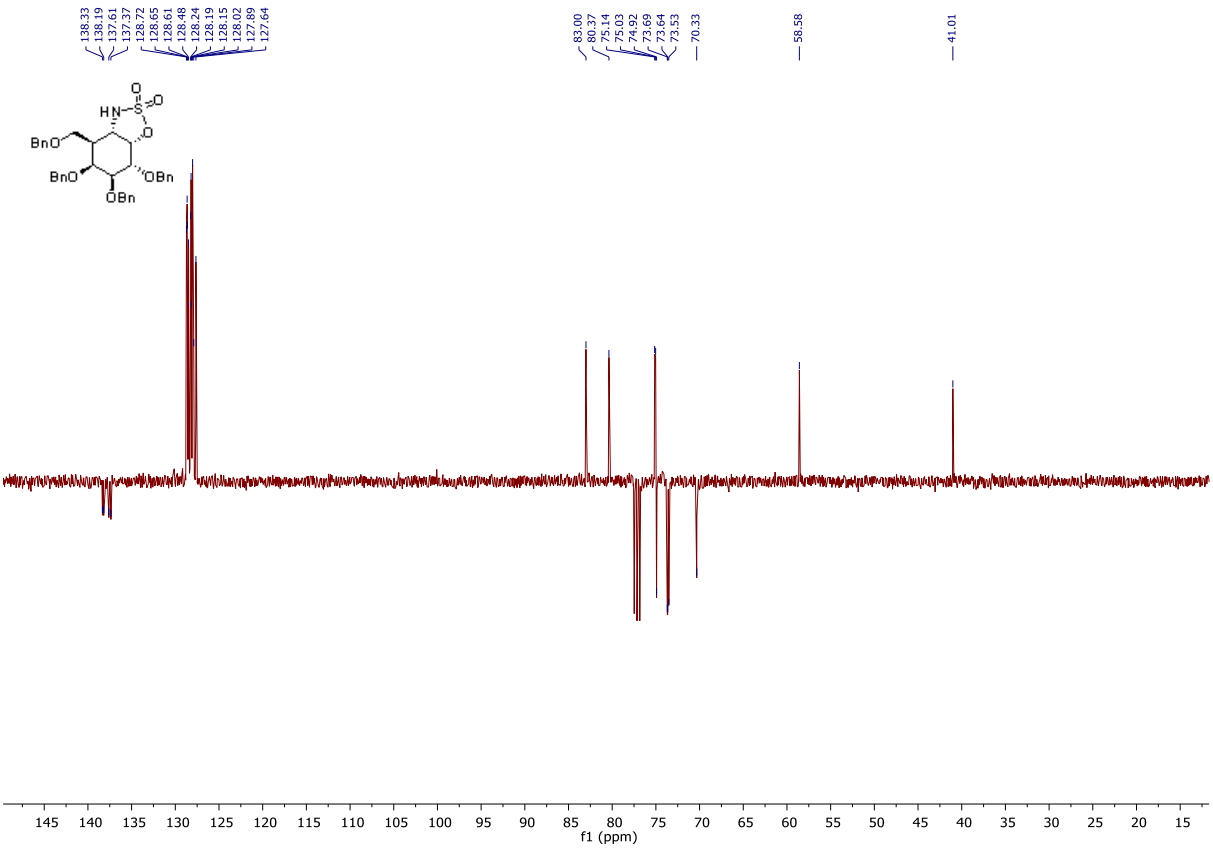


^{1}H-NMR and ^{13}C-NMR spectra of **37** in $CDCl_3$

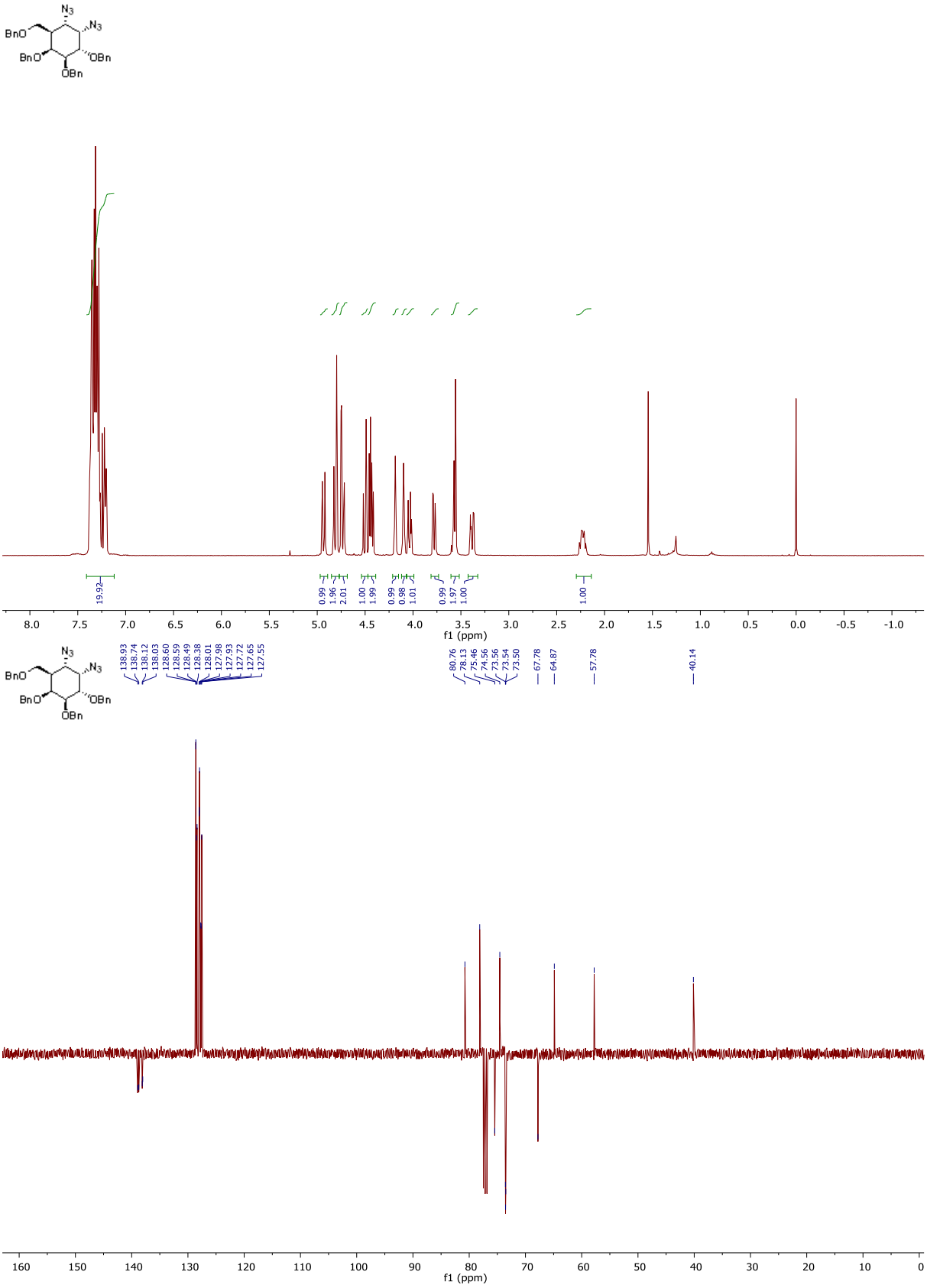


^{1}H-NMR and ^{13}C-NMR spectra of **38** in $CDCl_3$

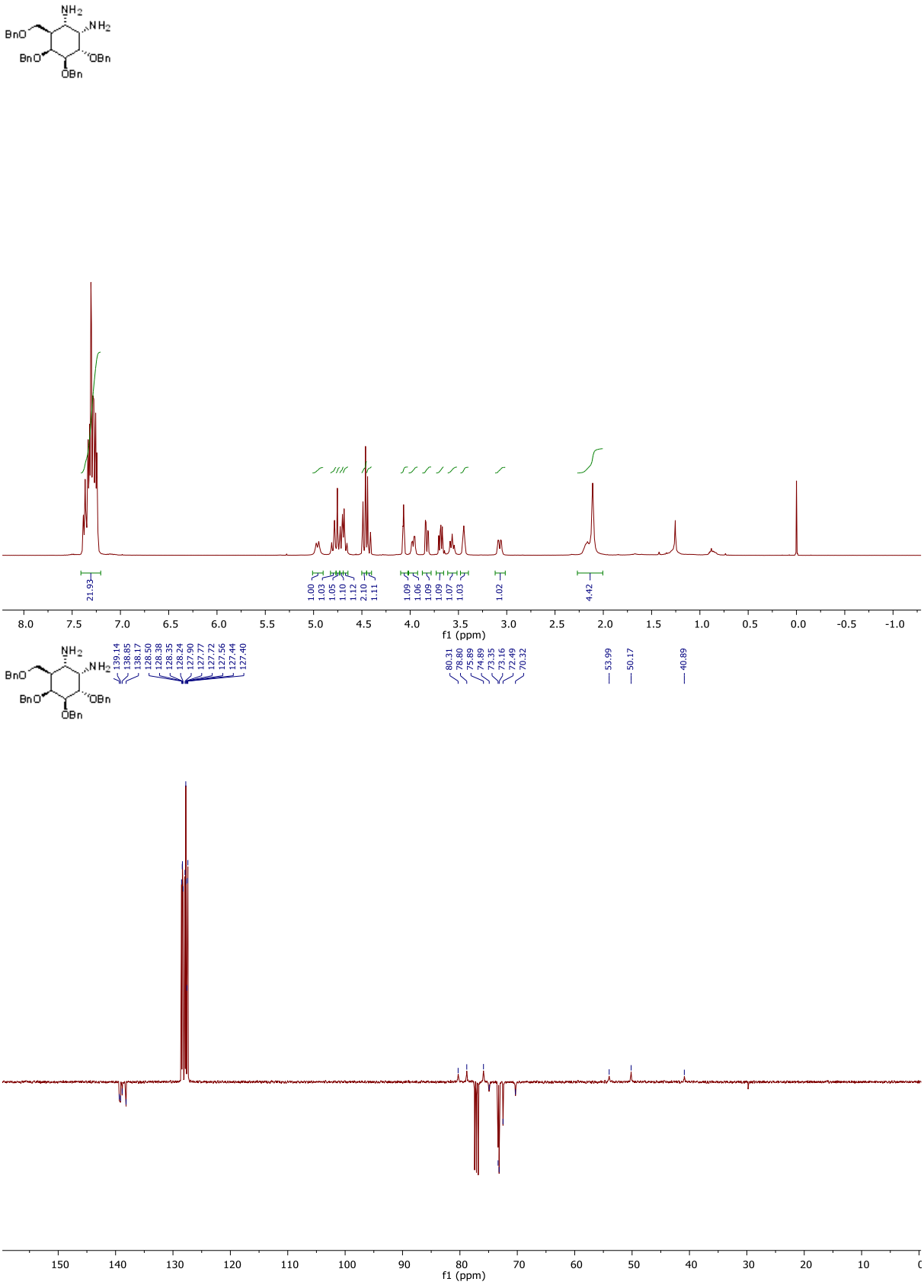




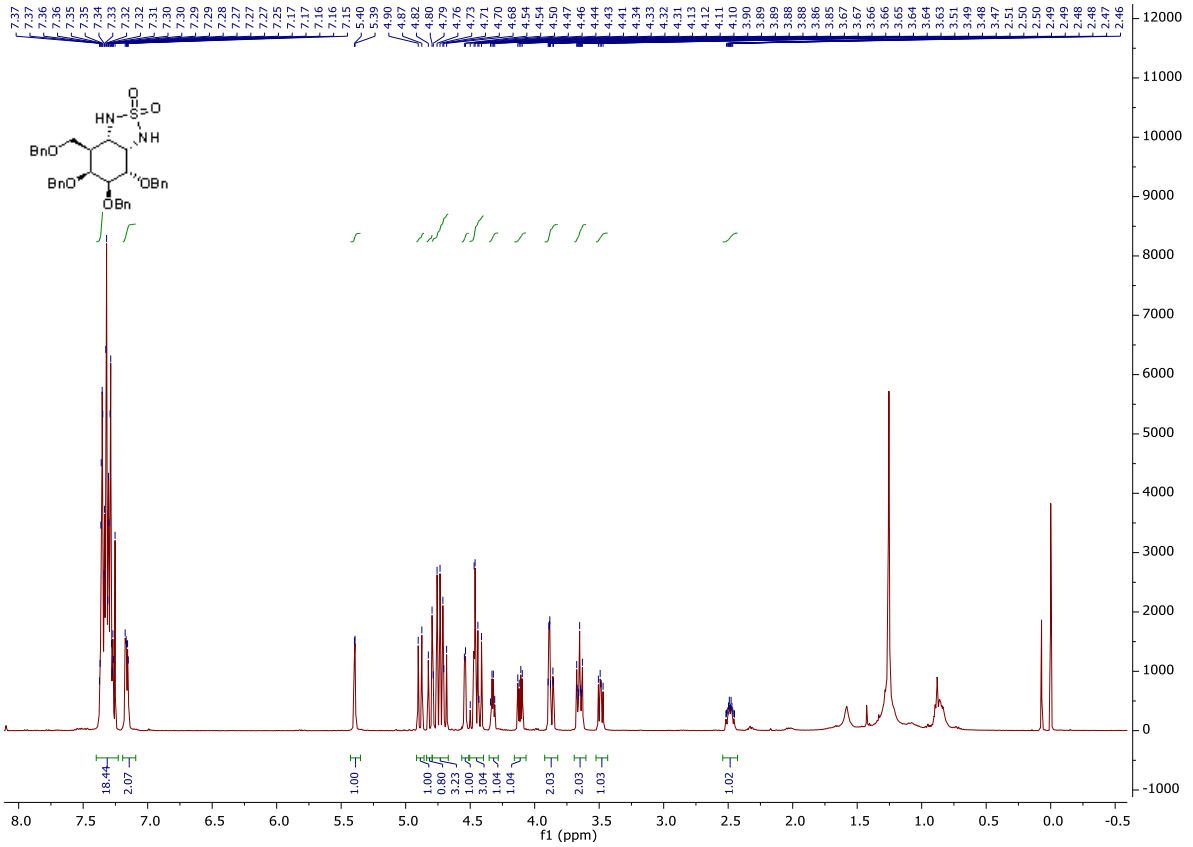
^{1}H-NMR and ^{13}C-NMR spectra of **46** in $CDCl_3$

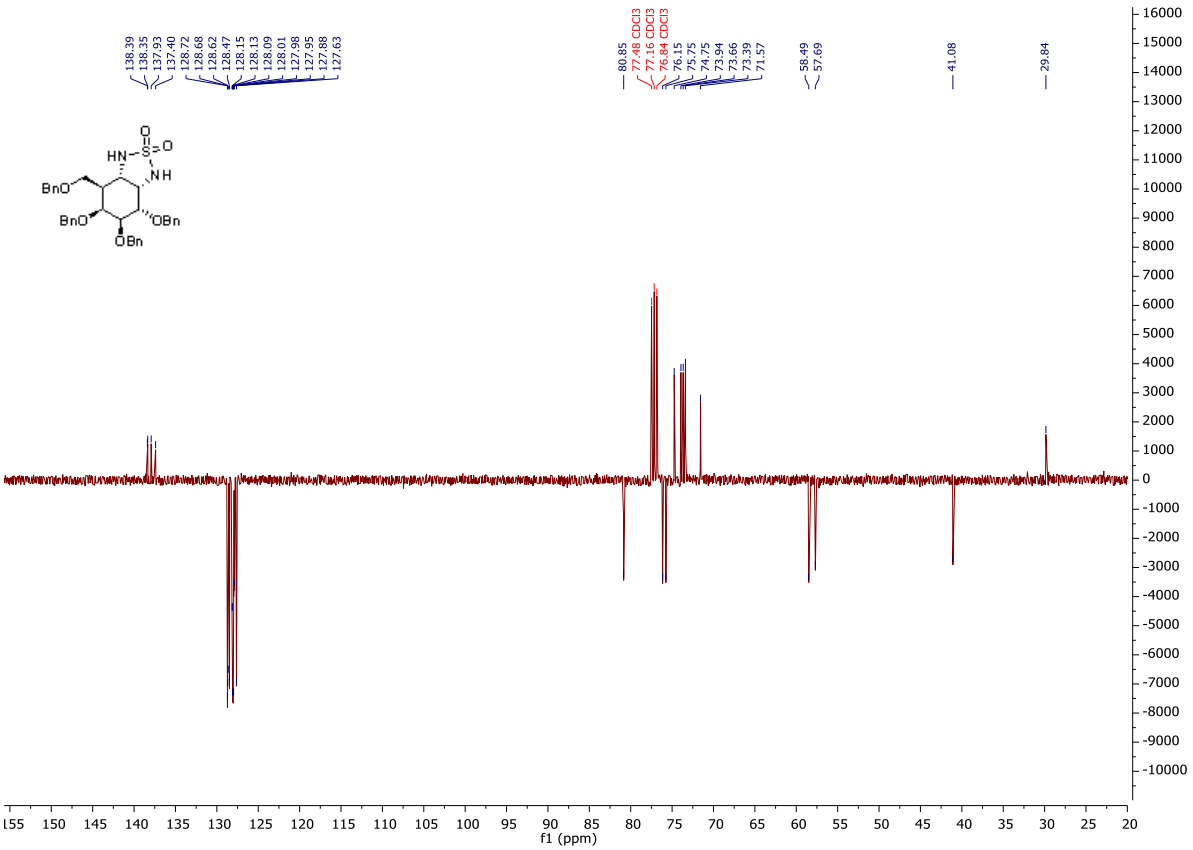


^{1}H-NMR and ^{13}C-NMR spectra of **47** in $CDCl_3$



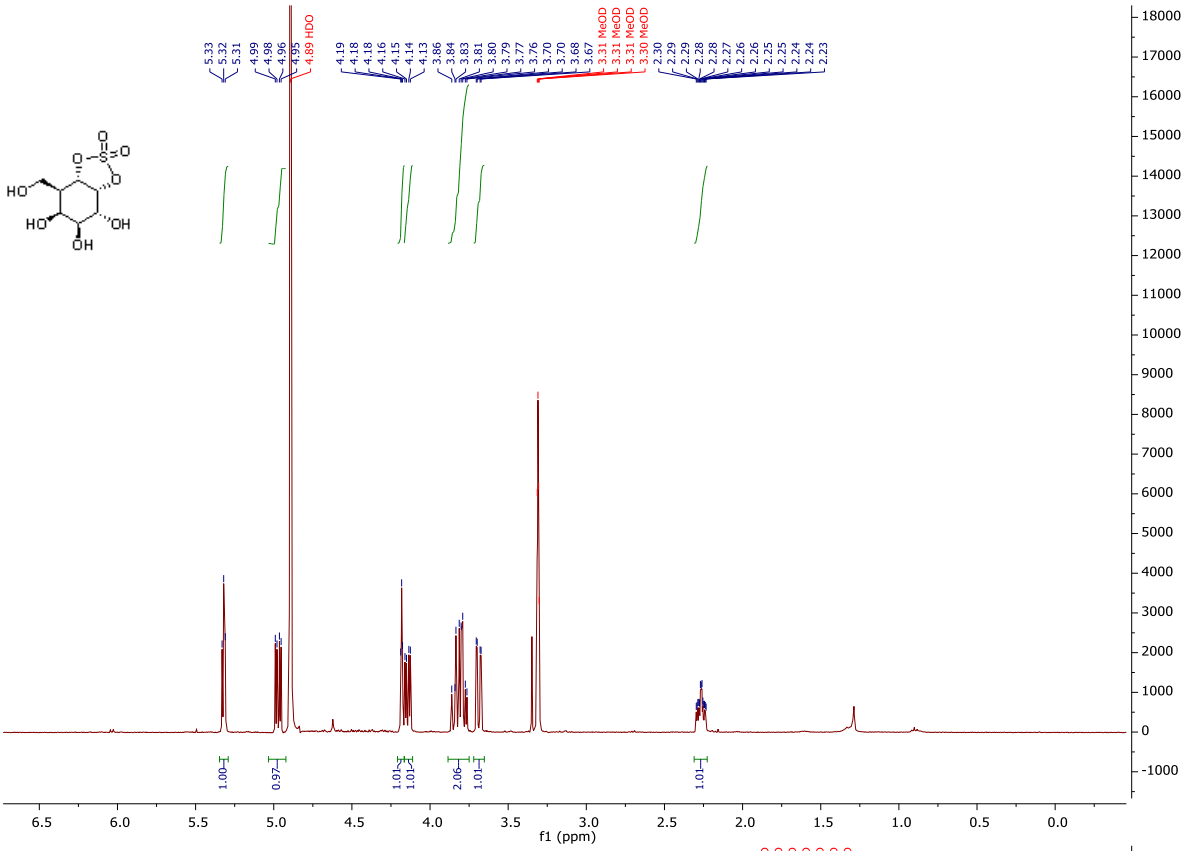
^{1}H-NMR and ^{13}C-NMR spectra of **48** in $CDCl_3$

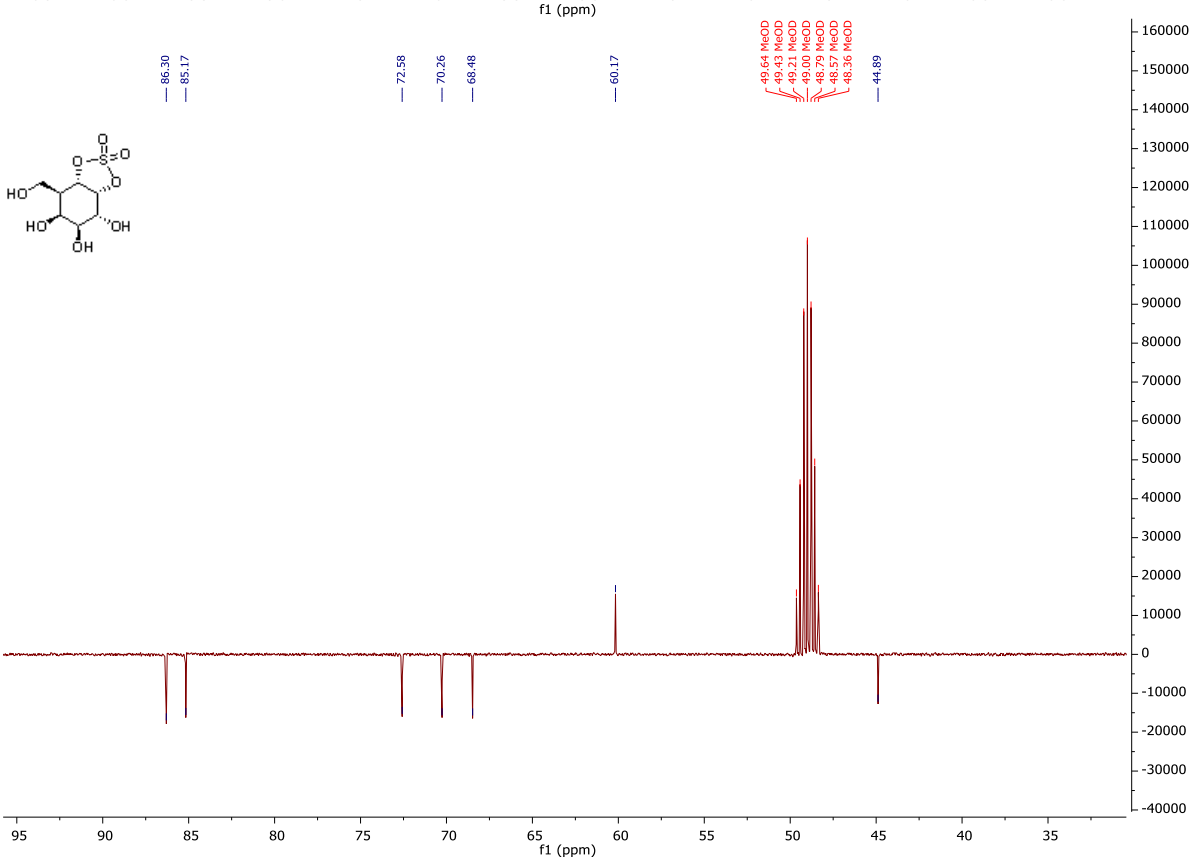




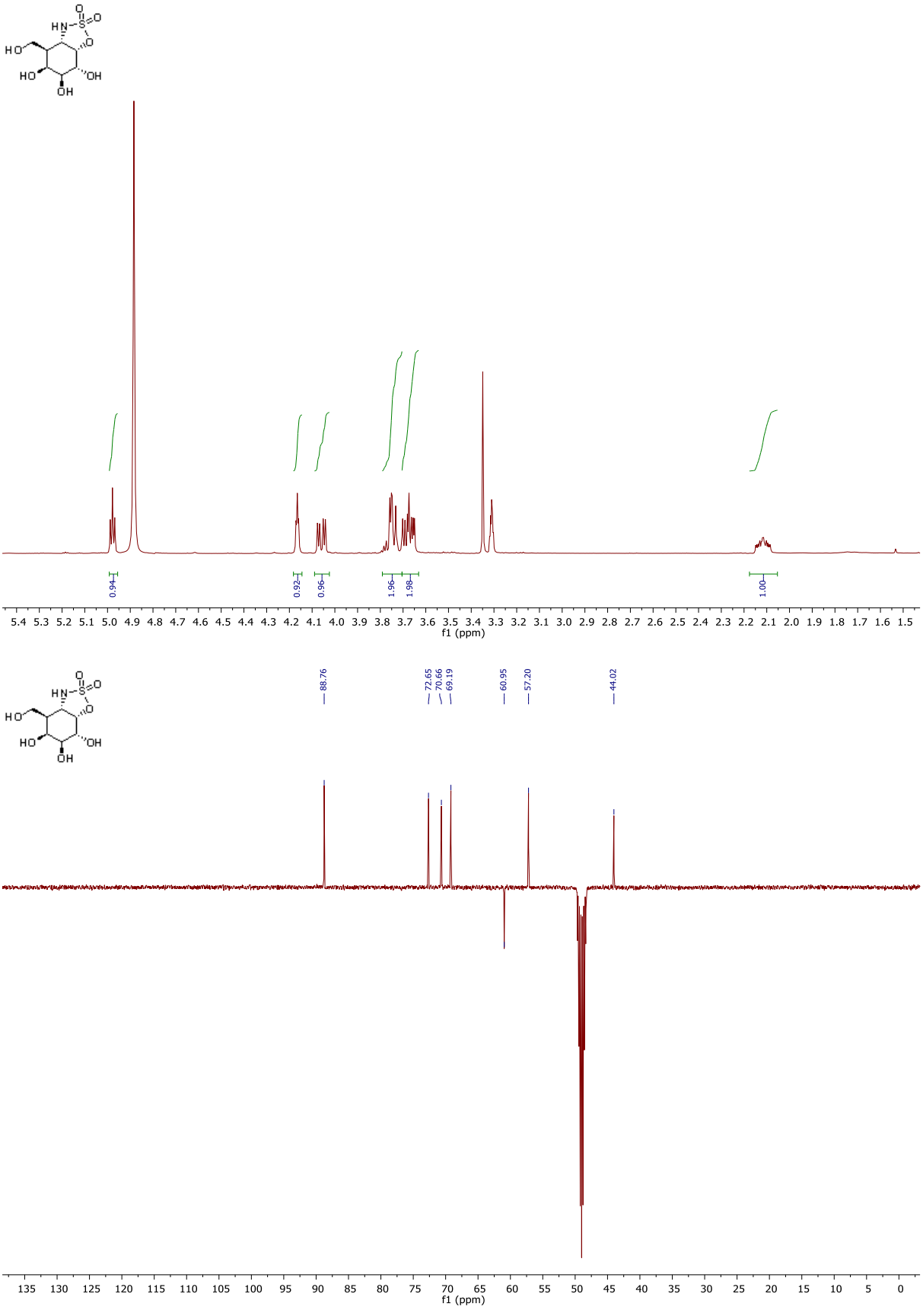
Final Compounds

^{1}H-NMR and ^{13}C-NMR spectra of **2** in CD_3OD

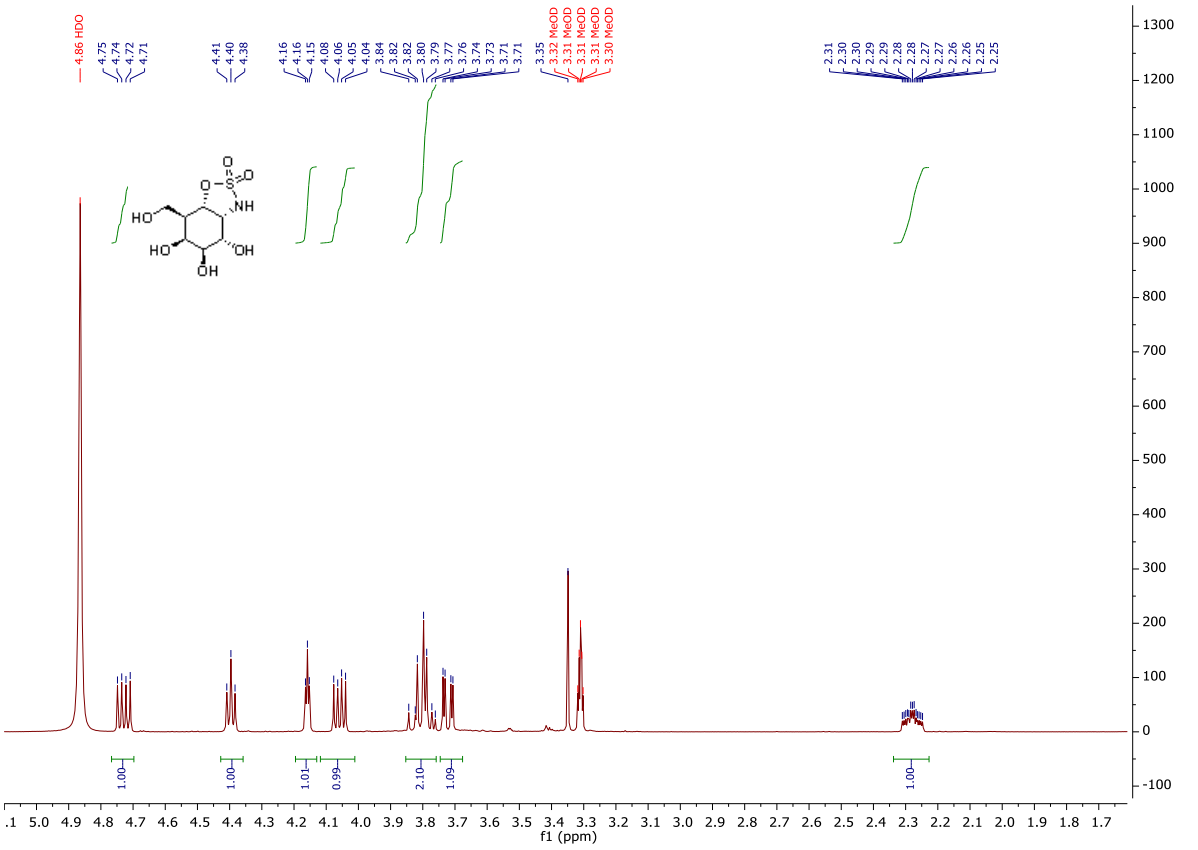


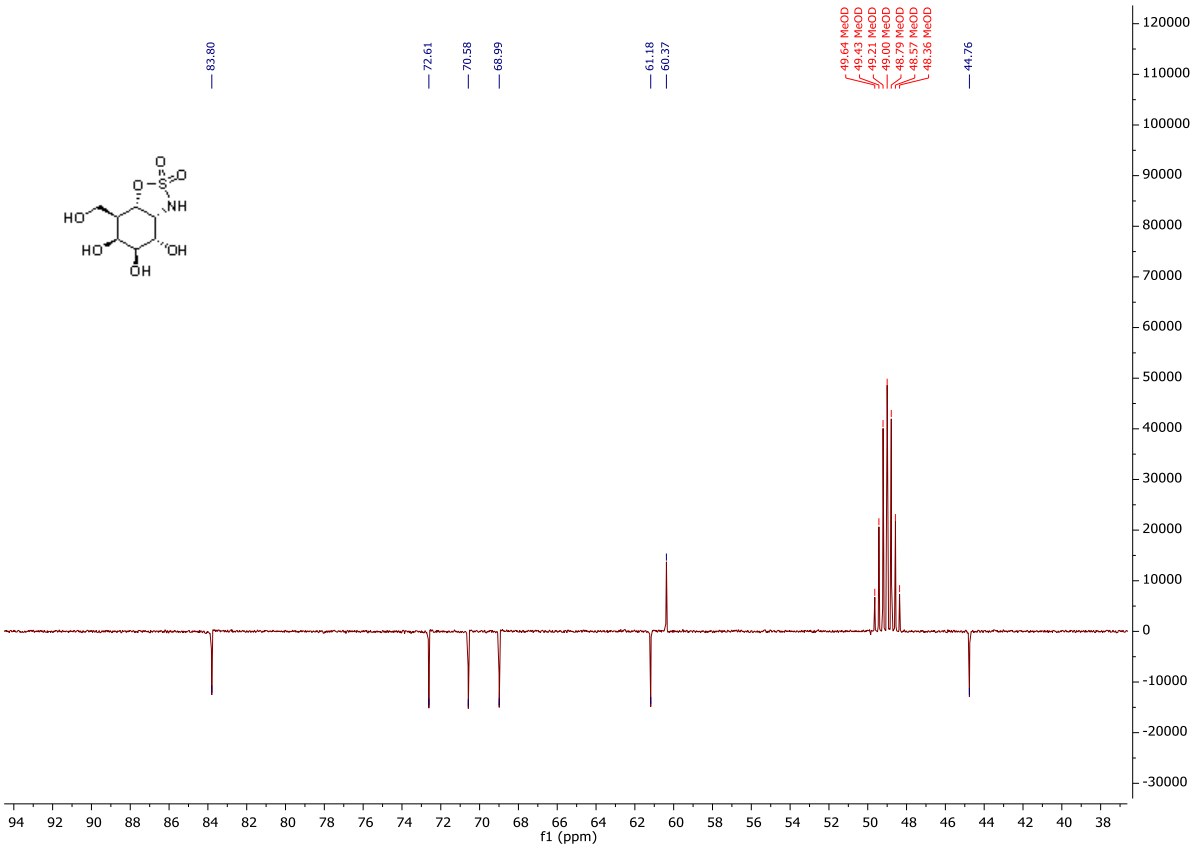


^{1}H-NMR and ^{13}C-NMR spectra of **3** in CD_3OD

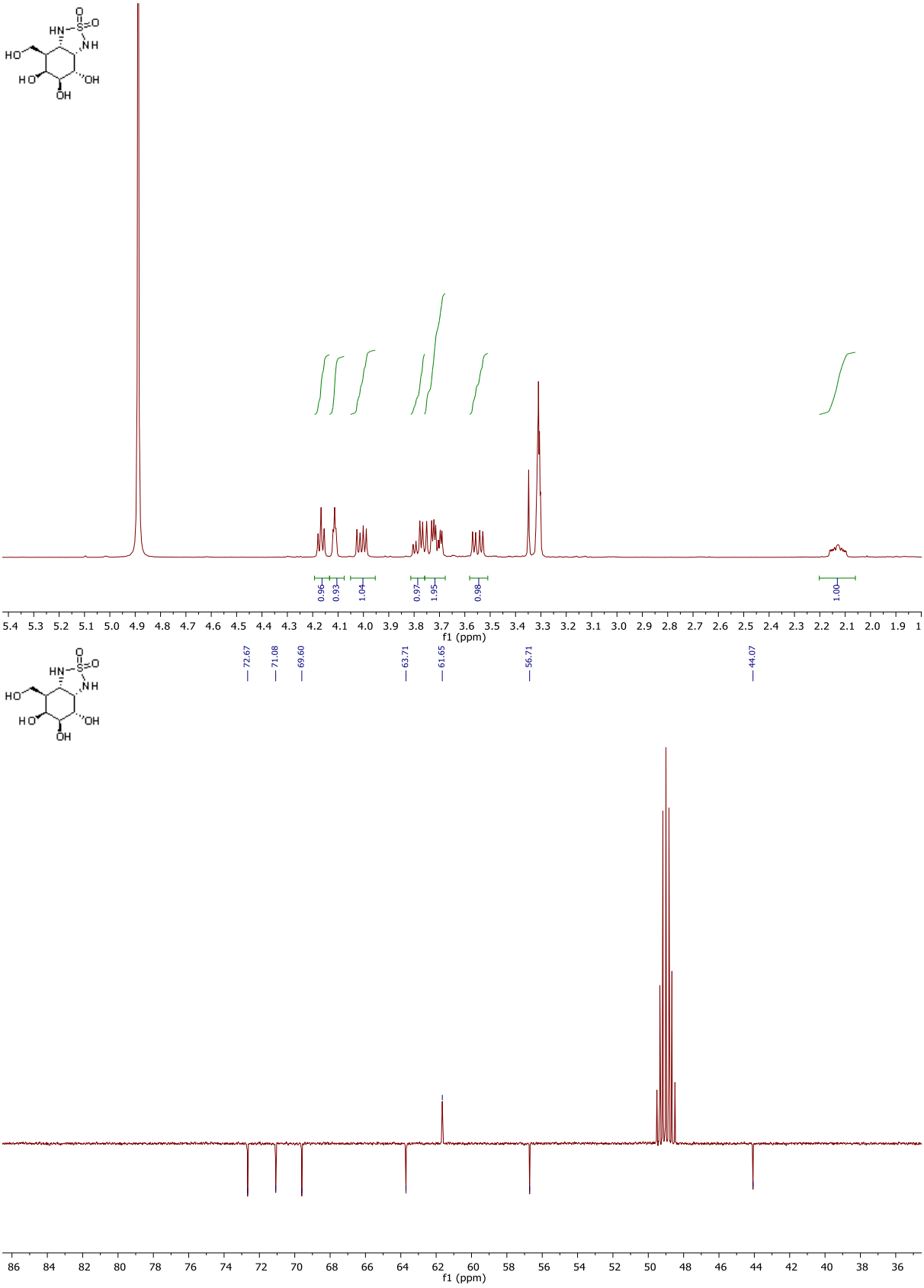


^{1}H-NMR and ^{13}C-NMR spectra of **4** in CD_3OD

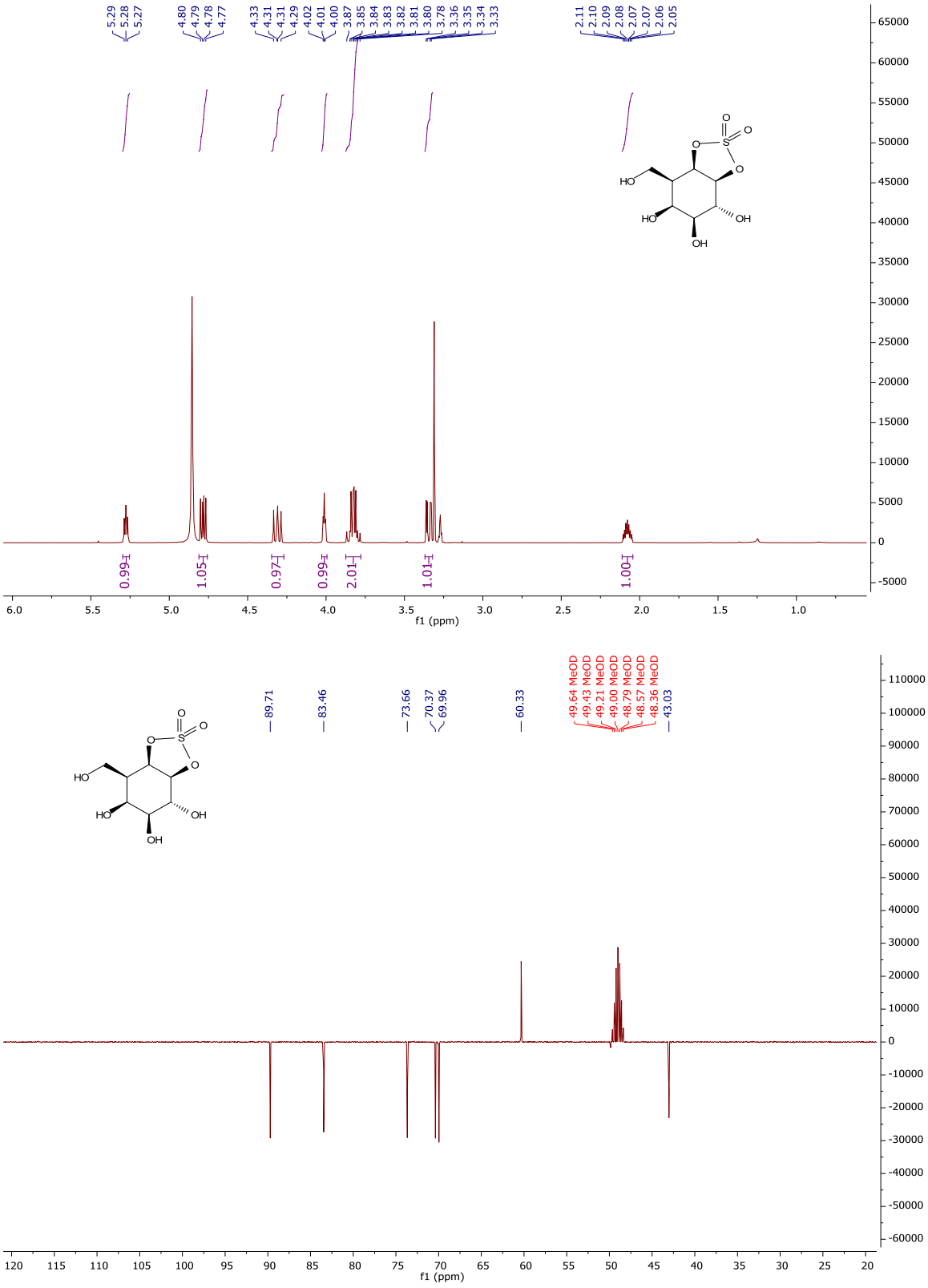




^{1}H-NMR and ^{13}C-NMR spectra of **5** in CD_3OD



^{1}H-NMR and ^{13}C-NMR spectra of **9** in CD_3OD



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