Supporting Information

Structure-Guided Design of C3-Branched Swainsonine as Potent and Selective Human Golgi α-Mannosidase (GMII) Inhibitor

Tony S. Koemans, Megan Bennett, Maria J. Ferraz, Zachary Armstrong, Marta Artola, Johannes M. F. G. Aerts, Jeroen Codée, Herman S. Overkleeft, Gideon J. Davies

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Protein expression and purification

Drosophila Golgi α-mannosidase (dGMII) and human Golgi α-mannosidase (hGMII) were expressed in *Trichoplusia ni* cells (Invitrogen) and purified as previously reported[1], stored at -80 °C and thawed prior to use. Human GH38 α-mannosidases MAN2A1, MAN2A2, MAN2B1, MAN2B2 and MAN2C1 were overexpressed in HEK293T cells as previously reported.[1]

Binding affinity assay

Initial screening to assess binding affinity was carried out using a Nano-DSF melting temperature (T_m) assay. Purified dGMII and hGMII were diluted to a final concentration of 1 mg.mL^{-1} in a buffer containing 20 mM HEPES, 20 mM NaCl and 1 mM DTT pH 7.4, and incubated for 2-3 hrs at room temperature with final concentrations of 1 mM of inhibitors **1**, **4** or **5**. A sample without any inhibitor was included as a reference for the T_m of the apo dGMII/hGMII protein. Capillaries were then used to load the complexes into a Prometheus (NanoTemper) Nano-DSF machine to assess protein stability by monitoring the fluorescence of tryptophan and tyrosine residues. The temperature ramp was set from 20-95 ºC with a change of 1 ºC/min and an excitation power of 27%. T_m values were calculated from the melting curves detailed in Figure S1 and S2 and Table S1. Two repeats were performed for each data set.

***K*ᵢ determination**

The K_i values of inhibitors for both dGMII and hGMII were determined by monitoring concentration-dependent decrease in accumulation of the fluorophore 4-methylumbelliferone when incubating 4-methylumbelliferyl-α-D-mannopyranoside with either of the two enzymes. Reactions were carried out in a buffer containing 50 mM MES pH 5.5, 1 mM $ZnSO_4$ and 0.1% (w/v) BSA in FluoroNunc™ 96-well plates (ThermoFisher). Inhibitor concentrations varied from 0-300 nM (swainsonine **1**), 0-200 µM (**4**) or 0-400 µM (**5**). Inhibitors were incubated, at room temperature, for approximately 30 minutes, with either dGMII or hGMII at final concentrations of 10 nM. 4-Methylumbelliferyl-α-D-mannopyranoside (Sigma Aldrich) was added to the reaction mixture to initiate the reaction at a fixed concentration of either 1 mM or 1.5 mM for dGMII or 750 µM or 1 mM for hGMII. Fluorescent intensity measurements were recorded using a BMG Labtech Clariostar plate reader in a continuous fashion with a top optic reader and a focal height of 5 mm. RFU were recorded at λ_{ex} = 320-360 nm and λ_{em} = 430-450 nm wavelengths with readings every 36 s for 120 cycles. The gain was set to 500 and reactions recorded at 25 ºC, and reactions were incubated at 500 rpm for 10 s before the first cycle was recorded. RFUs for each inhibitor concentration were plotted against time to work out the velocities. The inverse of the initial velocities ($1/V_o$) for each set of inhibitor concentrations were plotted in a set of Dixon plots at both 4-methylumbelliferyl-α-D-mannopyranoside concentrations for each protein. OriginPro (OriginLab®) was used to perform linear regression and extrapolation to obtain the intercept of the lines which correspond to the K_i values for each inhibitor and protein complex. All fluorescence units were normalised to samples containing no inhibitors. Dixon plots are detailed in SI Figure 3.

Selectivity determination

HEK293T cells overexpressing human GH38 α-mannosidases MAN2A1, MAN2A2, MAN2B1, MAN2B2 and MAN2C1 were cultured in DMEM with 10% FCS (v/v), 0.1% penicillin/streptomycin (w/v) and 1% Glutamax (v/v) under 5% CO_2 at 37 °C in the presence of 100 µg/mL Zeocin to promote selection. Once confluent, cells were washed 3x with PBS, aliquoted and pellets were stored at -80 °C until use. Cell pellets were homogenised (Sonics VibraCell, 5s at 20% amplitude) in 150 mM McIlvaine buffer at pH 5.5 (MAN2A1, MAN2A2), pH 4.5 (MAN2B1, MAN2B2) or pH 6.7 (MAN2C1) containing either 2 mM $ZnCl_2$ (MAN2A1, MAN2A2, MAN2B1, MAN2B2) or 2 mM $CoCl_2$ (MAN2C1). For IC_{50} measurements, 12.5 µL of homogenate (50 µg MAN2A1 or MAN2A2, 12.5 µg MAN2B1 or MAN2B2, MAN2C1 2.5 µg) was pre-incubated with 12.5 µL of compound (up to a concentration of 100 µM, final DMSO concentration 0.5%) at 37 °C for 30 min. Then, 100 µL 4-methylumbelliferyl-α-D-mannopyranoside (Glycosynth) substrate mix containing 0.1% (w/v) bovine serum albumin and 1 mM $ZnCl_2$ or $CoCl_2$ in 150 mM McIlvaine buffer at the corresponding pH (10 mM for MAN2A1, MAN2A2 and MAN2B1, 4mM for MAN2B2, 2 mM for MAN2C1) was then added, and further incubated for 30 min at 37 °C. After stopping the reaction with 200 µL excess 1 M NaOH-glycine (pH 10.3), liberated 4-MU fluorescence was measured with a fluorimeter LS55 (Perkin Elmer) at λ_{Ex} 366 nm and λ_{Em} 445 nm. Measurements were performed in 3 biological replicates with technical duplos. Results were processed and analysed using GraphPad Prism 9.0.

X-ray crystallography and structural refinement

Crystals were grown in screens optimised from previous conditions[1]. Crystals were set up in 48-well MAXI plates in a sitting drop vapour diffusion method. The best crystals grew in conditions containing 100 mM succinate pH 7.0 and 6-12% (w/v) PEG 3350 at a protein concentration of 10 $mg.mL^{-1}$ and seeded in a ratio of 200:100:400 nL of protein:seed:mother liquor. Crystals were soaked for 3-4 hr or overnight with final inhibitor concentrations of 10 mM. Crystals were then either cryoprotected with either 15 % (w/v) 2-methyl-2,4-pentanediol (MPD) or 25 % (w/v) ethylene glycol and fished and flash cooled in liquid nitrogen. Crystals were tested in-house for diffraction using a Rigaku XtaLAB Synergy-R diffractometer equipped with a microfocus MicroMax 007HF rotating anode generator with a specialised confocal MaxFlux optic. The best crystals were then sent to the Diamond Light Source synchrotron. Data was processed using the Xia2-DIALS pipeline. Structure generation and refinement was carried out using either CCP4i2 (V.8.0.011) or the CCP4 cloud interface. The atomic model that was used for molecular replacement was previously reported (PDB: 6RQZ)[1]. Iterative cycles of REFMAC, followed by manual buildings in COOT was used to generate the final structural outcome. Omit maps for inhibitors were calculated in the CCP4i2 interface. Refinement statistics are outlined in SI Table 3. Structures were deposited in the Protein Data Base (PDB) under accession codes 9FTR and 9FTQ for the dGMII:**4** and dGMII:**5** complexes, respectively.

Supplementary Table 1. T_m for dGMII in complex with various ligands

Sample Name	Onset T_m (°C)	T_m (°C)
Apo dGMII	36.6 ± 3.89	50.9 ± 1.74

dGMII:**1**	63.1 ± 5.70	74.1 ± 4.32
dGMII:**4**	49.5 ± 4.21	61.1 ± 2.02
dGMII:**5**	57.0 ± 1.20	65.7 ± 0.20
Apo hGMII	44.9 ± 0.04	54.5 ± 0.01
hGMII:**1**	47.0 ± 0.46	72.8 ± 0.22
hGMII:**4**	49.6 ± 0.31	61.7 ± 0.22
hGMII:**5**	48.4 ± 0.08	60.8 ± 0.16

Supplementary Table 2. K_i-values for compounds **1**, **4** and **5** as dGMII and hGMII inhibitors

Compound	**dGMII** (K_i, μM)	**hGMII** (K_i, μM)
1	0.0847 ± 0.008	0.0441 ± 0.009
4	5.63 ± 1.00	14.9 ± 5.04
5	167 ± 13.2	308 ± 6.57

Supplementary Table 3. X-ray data collection and refinement statistics for dGMII in complex with inhibitors

	dGMII:4	**dGMII:5**
Beamline	Diamond i03	Diamond i03
Wavelength (Å)	0.9762	0.9763
Resolution (Å)	57.68-2.14 (2.20-2.14)	74.98-2.47 (2.57-2.47)
Space Group	$P2_12_12_1$	$P2_12_12_1$
Unit cell (Å)	a = 89.11; b = 91.94; c = 133.24 α = β = γ = 90°	a = 88.91; b = 90.91; c = 132.60 α = β = γ = 90°
Number of molecules in the asymmetric unit	1	1
Unique reflections	61056 (4448)	39207 (4329)
Completeness (%)	100.0 (100.0)	99.9 (100.0)
R_{merge} (%)	0.045 (0.352)	0.037 (0.215)
$R_{p.i.m.}$	0.045 (0.352)	0.037 (0.215)
Multiplicity	1.9 (1.9)	1.9 (1.9)
$<I/\sigma(I)$	9.6 (1.0)	8.0 (0.9)
Overall B from Wilson plot (Å$_2$)	32	41
$CC_{1/2}$	0.997 (0.682)	0.998 (0.94)
R_{cryst}/R_{free} (%)	17.9/25.9	20.8/29.8
r.m.s.d. 1-2 bonds (Å)	0.0144	0.0074
r.m.s.d. 1-3 angles (°)	2.5800	2.0720
Avge main chain B (Å^2)	37	52
Avge side chain B (Å^2)	38	52

Avge water B (Å^2)	37	38
Avge ligand B (Å^2)	28	39
Avge Zinc B (Å^2)	27	43

Figure S1. Melting point curves for dGMII against a range of designed and known ligands. T_m values calculated from a series of nanoDSF assays where the recorded 350:330nm fluorescence ratio (*y*) is plotted against temperature values in Celsius, °C, (*x*). Colours denote different ligands complexed, which is indicated in the legend. Curves and first derivatives are a representation of one repeat.

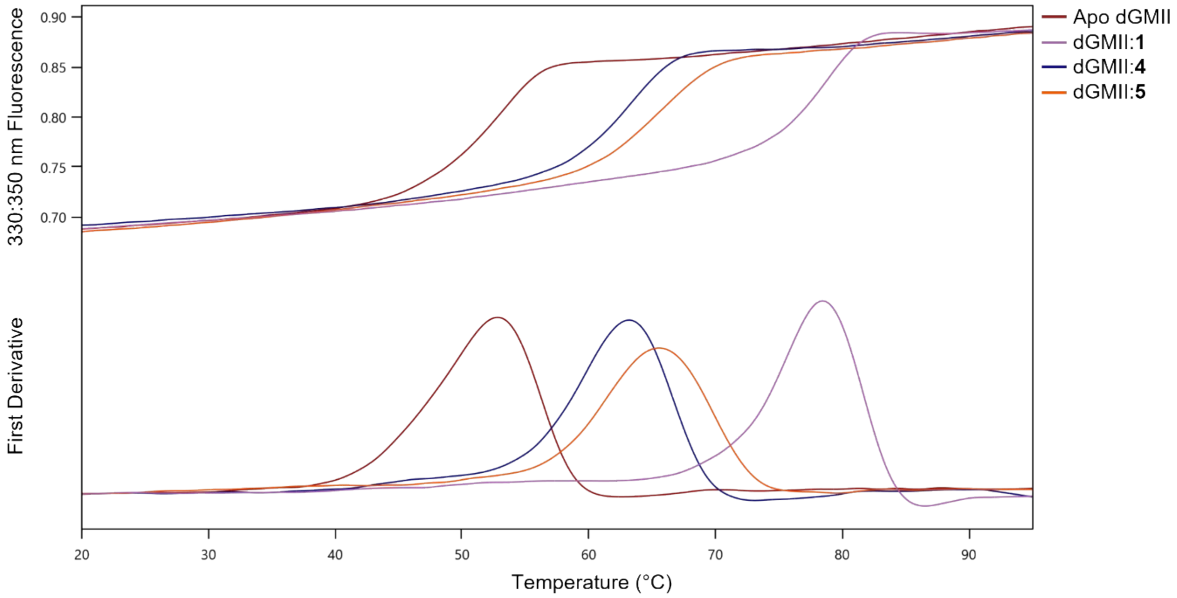


Figure S2. Melting point curves for hGMII against a range of designed and known ligands. T_m values calculated from a series of nanoDSF assays where the recorded 350:330nm fluorescence ratio (*y*) is plotted against temperature values in Celsius, °C, (*x*). Colours denote different ligands complexed, which is indicated in the legend. Curves and first derivatives are a representation of one repeat.

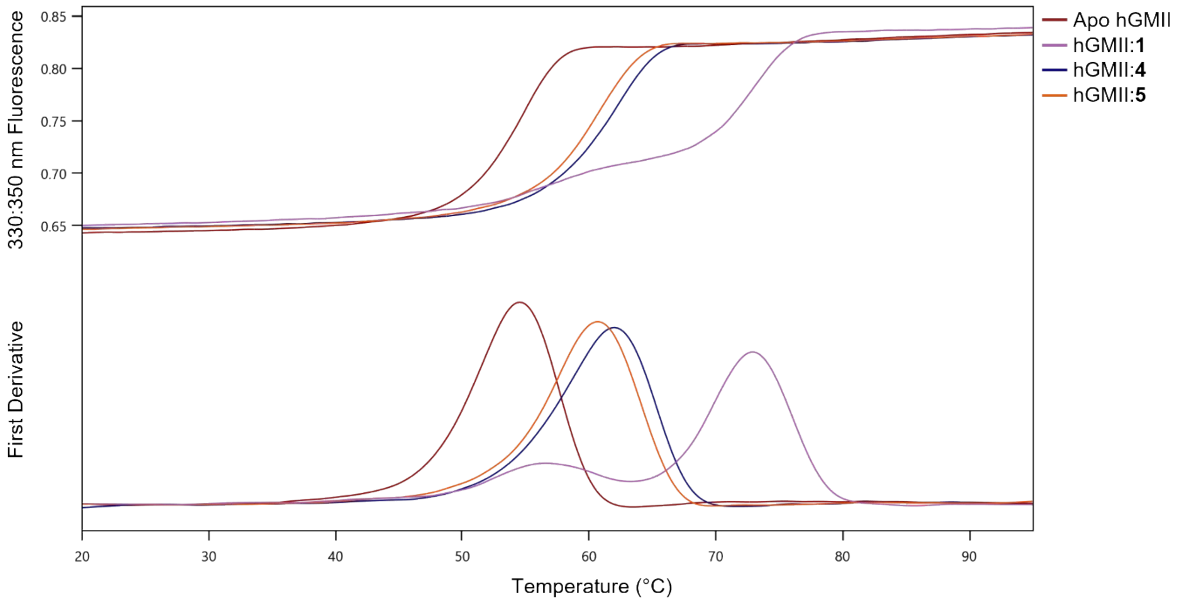


Figure S3. Dixon plots for calculating inhibitory constants for dGMII and hGMII with designed ligands and swainsonine. Dixon plots for dGMII (left panels) in complex with various ligands were calculated from two standard concentrations of 4-Methylumbelliferyl *α*-D-mannopyranoside, 1.5 mM (green) and 1 mM (black), for hGMII (right panels) standard concentrations of 4-methylumbelliferyl *α*-D-mannopyranoside at 0.75 mM (blue) and 1 mM (black) were used. **A** dGMII in complex with **1** and calculated reciprocal initial velocity values (s. μM^{-1}) against inhibitor concentration (μM). **B** dGMII in complex with **4** and calculated reciprocal initial velocity values (s. μM^{-1}) against inhibitor concentration (μM). **C** dGMII in complex with **5** and calculated reciprocal initial velocity values (s. μM^{-1}) against inhibitor concentration (μM). **D** hGMII in complex with **1** and calculated reciprocal initial velocity values (s. μM^{-1}) against inhibitor concentration (μM). **E** hGMII in complex with **4** and calculated reciprocal initial velocity values (s. μM^{-1}) against inhibitor concentration (μM). **F** hGMII in complex with **5** and calculated reciprocal initial velocity values (s. μM^{-1}) against inhibitor concentration (μM).

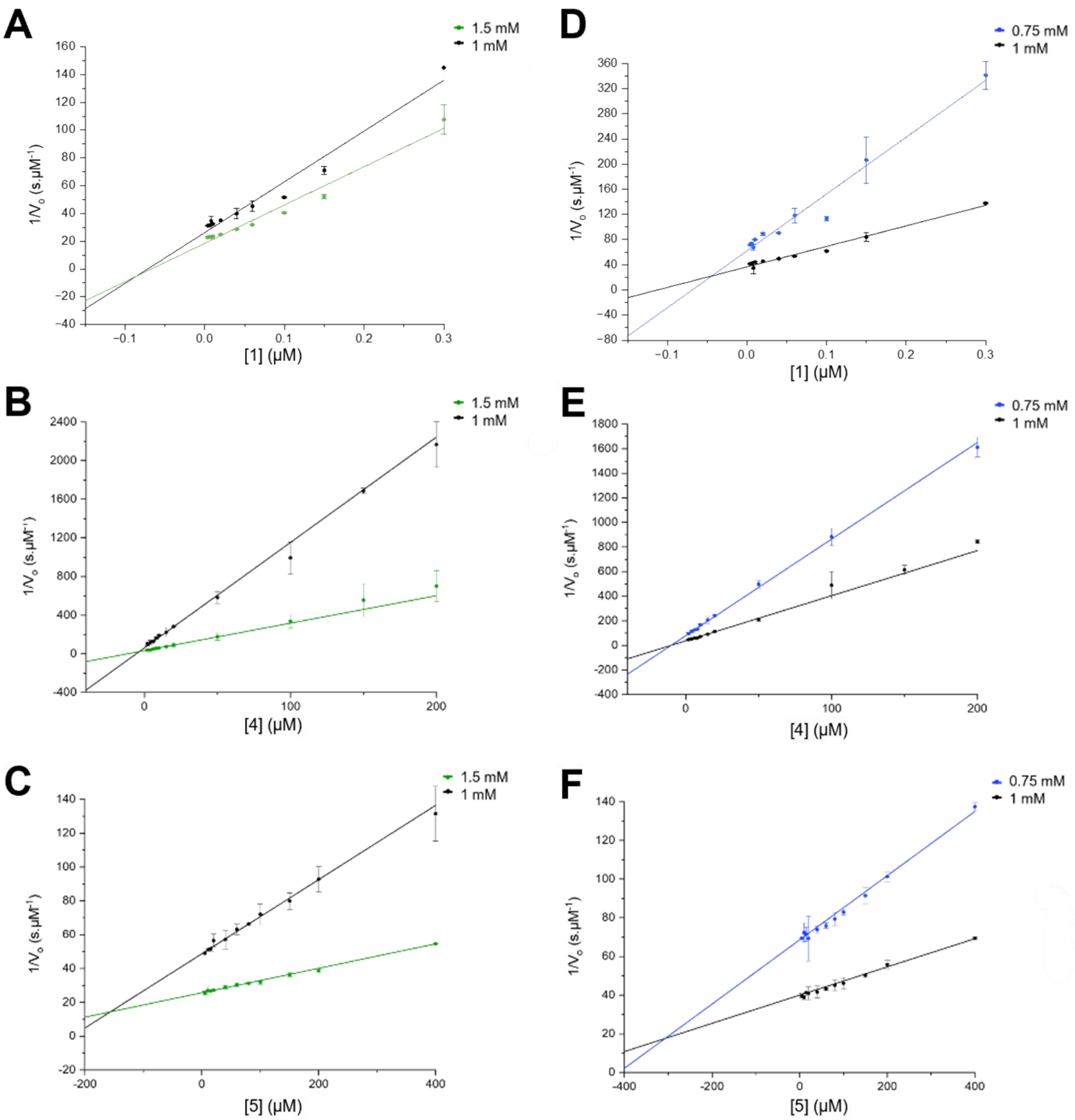


Figure S4. Ligand densities from the complexed crystal structures with designed inhibitors **4** and **5**. Images were created and visualised in CCP4mg (v. 2.10.11). Active site zincs are displayed in grey spheres throughout, and ligands are displayed in green cylinder form. All omit maps were calculated in the CCP4i2 interface or obtained from the PDB and are displayed in grey chickenwire. F_o-F_c maps are all contoured at 3 σ except for **5** (**B**) which is contoured at 2.5 σ. **A** Omit map for **4** in the dGMII active site. **B** Omit map for **5** in the dGMII active site.

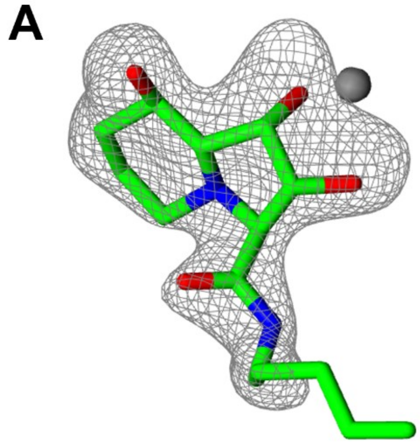


Figure S5. Octahedral coordination of the active site zinc in the active sites of complexed dGMII structures with designed inhibitors **4** and **5**. Images were created and visualised in CCP4mg (v. 2.10.11). Active site zincs are displayed in grey spheres throughout, and ligands are displayed in blue cylinder form. All bonds are indicated by blue dashed lines with all distances being displayed in angstroms (σ). **A** Binding pocket of dGMII:**4** with active site residues (yellow) and **4** forming a bonding network to the active site zinc. **B** Binding pocket of dGMII:**5** with active site residues (grey) and **5** forming a bonding network to the active site zinc.

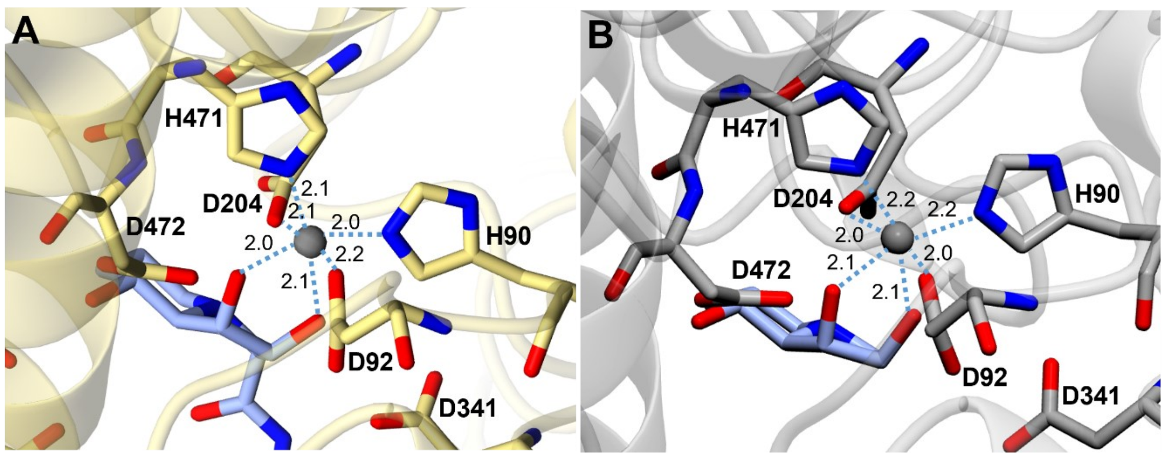
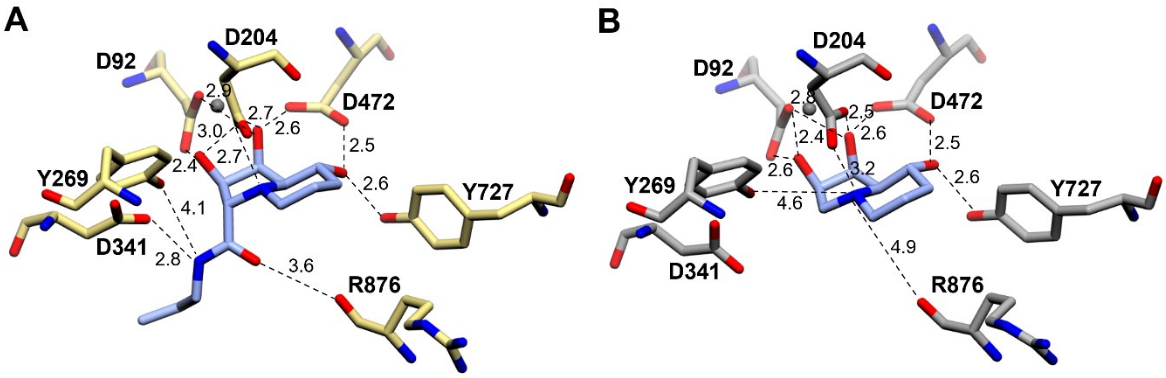


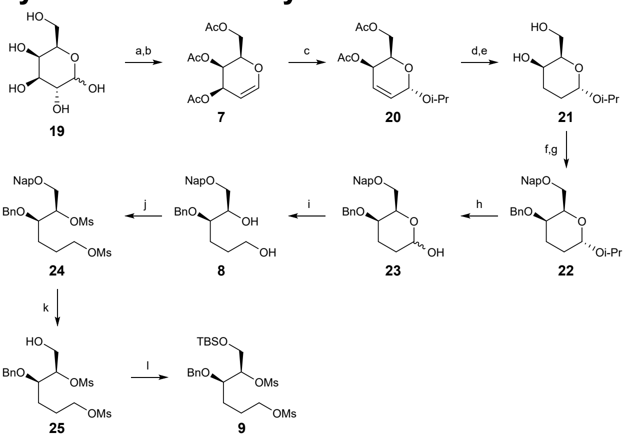
Figure S6. Binding pockets and secondary coordination spheres of dGMII in complex with **4** and **5**. Images were created and visualised in CCP4mg (v. 2.10.11). All ligands are displayed in blue cylinder form throughout. All bonds are indicated by black dashed lines with all distances being displayed in angstroms (σ). Water molecules are displayed in red spheres and zinc in grey sphere form. **A** Binding pocket of dGMII:**4** with active site residues (yellow) and **4** forming a series of hydrogen bonding networks. **B** Binding pocket of dGMII:**5** with active site residues (grey) and **5** forming a series of hydrogen bonding networks**.**



Chemical synthesis

General information: All moisture and oxygen sensitive reactions were carried out dry and under an argon atmosphere. Dry solvents were obtained by storage on flame dried molecular sieves 3 Å or 4 Å. All commercially available chemicals were used as received without further purification. All reactions were followed by thin layer chromatography using Merck Silica gel 60 F_{254} aluminum sheets. Detection was done by UV (254 nm), staining with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L), $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid in water, a solution of $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in water, or a solution of ninhydrin (1 g/L) in 0.5% acetic acid in acetone, followed by heating at 150 °C. Flash column chromatography was performed with Screening Devices BV silica gel (particle size of 40-63 µm, pore diameter of 60 Å) with indicated eluents. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 and 101 MHz respectively), a Bruker AV-500 (500 and 126 MHz respectively) and a Bruker DMX 850 (850 and 214 MHz respectively). Chemical shifts are given in ppm (δ) relative to tetramethyl silane (TMS) or the residual solvent peak as internal standard and coupling constants are given in Hz. Reversed phase HPLC purification was performed on a Thermo Finnigan Surveyor HPLC system with a Phenomenex Gemini C_{18} column (4.6 mm x 50 mm, 5 µm particle size). High resolution mass spectrometry analysis was performed with a Thermo Finnigan LTQ Orbitrap mass spectrometer equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at *m/z* 400 (mass range *m/z* 150 - 2000) and dioctyl phthalate (*m/z* = 301.28428) as lock mass. The high-resolution mass spectrometer was calibrated before measurements with a calibration mixture (Thermo Finnigan).

Synthesis of bismesylate 9



Scheme 1. *Reagents and conditions*: a) Ac_2O, $HClO_4$, 0 °C, 1 h, then HBr in AcOH, r.t., 16 h; b) Zn, NH_4Cl, EtOAc, r.t., 16 h, 70% (over 2 steps); c) $SnCl_4$, *i*PrOH, DCM, r.t., 16 h, 62%; d) H_2, Pd/C, EtOH, r.t., 3 h, 90%; e) NaOMe, MeOH, r.t., 2 h, 99%; f) NapBr, 2-APB, KI, K_2CO_3, MeCN, 65 °C, 3 h, 89%; g) BnBr, NaH, TBAI, DMF, r.t., 16 h, 94%; h) 4:1 AcOH/1 M HCl, 60 °C, 16 h, quant.; i), $NaBH_4$, EtOH, r.t., 3 h, 98%; j) MsCl, pyr, 0 °C, 2 h, quant.; k) DDQ, 3:1 DCM/H_2O, r.t., 3 h, quant; l) TBSCl, imidazole, DCM, 0 °C, 2 h, 96%.

Compound 7: A suspension of galactose (60.0 g, 333 mmol) in acetic anhydride (240 mL) was cooled to 0 °C with an ice bath. A catalytic amount of perchloric acid (20 drops) was slowed added, after which the ice bath was removed, and the suspension was stirred for 1 hour at room temperature. The reaction was cooled to 0 °C, a solution of HBr in acetic acid (33 wt.%, 480 mL, 2.67 mol, 8 eq.) was added dropwise and the reaction was stirred at room temperature overnight. The mixture was then poured into ice water (1 L) and extracted with DCM (3x). The organic layers were washed with water (1x) and concentrated *in vacuo*. The residue was redissolved in EtOAc (666 mL, 0.50 M) followed by the addition of zinc (130 g, 2.00 mol, 6 eq.) and NH_4Cl (107 g, 2.00 mol, 6 eq.) and the reaction was stirred overnight. The reaction was then filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (30% → 50% Et_2O/pentane) gave compound **7** (63.8 g, 234 mmol) in 70% yield as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 6.3, 1.7 Hz, 1H), 5.61 – 5.48 (m, 0H), 5.43 (dt, *J* = 4.5, 1.6 Hz, 1H), 4.73 (ddd, *J* = 6.3, 2.7, 1.5 Hz, 1H), 4.36 – 4.30 (m, 1H), 4.30 – 4.18 (m, 2H), 2.13 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 170.5, 170.3, 145.6, 99.0, 72.9, 64.0, 63.9, 62.1, 21.0, 20.9, 20.8. HRMS: $[M+Na]^+$ calculated for $[C_{12}H_{16}O_7Na]^+$: 297.07882, found 295.07856.

Compound 20: To a solution of compound **7** (50.6 g, 186 mmol) in DCM (929 mL) at 0 °C was added isopropanol (28.4 mL, 372 mmol, 2 eq.). A solution of $SnCl_4$ (1 M in DCM, 18.6 mL, 18.6 mmol, 0.1 eq.) was added dropwise at 0 °C and the reaction was stirred at room temperature overnight. The reaction was neutralized with sat. aq. $NaHCO_3$, diluted with EtOAc and the mixture was washed with H_2O (1x). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% → 40% Et_2O/pentane) gave compound **20** (33.5 g, 123 mmol) in 66% yield as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (ddd, *J* = 10.0, 5.4, 0.9 Hz, 1H), 6.04 – 5.94 (m, 1H), 5.17 (d, *J* = 2.8 Hz, 1H), 5.01 (dd, *J* = 5.4, 2.3 Hz, 1H), 4.43 – 4.35 (m, 1H), 4.25 – 4.19 (m, 2H), 4.00 (hept, *J* = 6.1 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 131.3, 125.1, 92.5, 70.7, 66.8, 63.2, 63.1, 23.6, 22.1, 21.0, 20.9. HRMS: $[M+Na]^+$ calculated for $[C_{13}H_{20}O_6Na]^+$: 295.11521, found 295.11485.

Compound 26: Compound **20** (34.9 g, 128 mmol) was co-evaporated with toluene under argon (3x) and dissolved in ethanol (341 mL). The solution was purged for 45 min with argon after which, palladium on carbon (10% wt. loading, 4.11 g) was added and the mixture was purged with argon for another 15 minutes. The mixture was then purged with hydrogen gas for 15 min and the reaction was stirred at room temperature for 3 hours under hydrogen atmosphere. The reaction was filtered over celite and concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (20% → 40% Et_2O/pentane) to afford compound **26** (31.8 g, 116 mmol) in 90% yield as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (d, *J* = 3.1 Hz, 1H), 4.92 (s, 1H), 4.19 – 4.14 (m, 1H), 4.14 – 4.01 (m, 2H), 3.91 (hept, *J* = 6.2 Hz, 1H), 2.10 (s, 3H), 2.08 – 2.02 (m, 4H), 1.94 (tt, *J* = 13.6, 3.7 Hz, 1H), 1.81 (dq, *J* = 13.5, 3.2 Hz, 1H), 1.57 – 1.48 (m, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 170.7, 94.9, 68.9, 67.1, 67.0, 63.8, 24.9, 23.4, 22.6, 21.8, 21.3, 20.9. HRMS: $[M+Na]^+$ calculated for $[C_{13}H_{22}O_6Na]^+$: 297.13086, found 297.13054.

Compound 21: To a solution of compound **26** (28.3 g, 103 mmol) in MeOH (275 mL, 0.375 M) was added NaOMe (4.37 M in MeOH, 7.09 mL, 0.3 eq.). After stirring for 2 hours at room temperature, the reaction was quenched with Amberlite H^+ (pH ≈ 5), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (2% → 4% MeOH/DCM) gave compound **21** (19.4 g, 102 mmol) in 99% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, *J* = 2.8 Hz, 1H), 3.99 – 3.77 (m, 5H), 3.07 (s, 1H), 2.61 (s, 1H), 2.14 – 1.91 (m, 2H), 1.75 – 1.64 (m, 1H), 1.55 – 1.44 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 95.0, 69.4, 68.2, 67.1, 64.9, 25.5, 24.1, 23.5, 21.5. HRMS: $[M+Na]^+$ calculated for $[C_9H_{18}O_4Na]^+$: 213.10979, found 213.10973.

Compound 27: Compound **21** (18.0 g, 94.4 mmol) was co-evaporated with toluene under argon (3x) and dissolved in dry MeCN (315 mL). Potassium iodide (12.0 g, 104 mmol, 1.1 eq.), K_2CO_3 (14.3 g, 104 mmol, 1.1 eq.), 2-aminoethyl diphenylborinate (6.37 g, 28.3 mmol, 0.3 eq.) and 2-(bromomethyl)naphthalene (31.3 g, 142 mmol, 1.5 eq.) were added sequentially and the reaction was heated to 65 °C and stirred for 3 hours. The reaction mixture was concentrated and redissolved in EtOAc. The organic phase was washed with H_2O (2x) and brine (1x), and the aqueous layers extracted with EtOAc (1x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% → 40% EtOAc/PE) gave **27** (27.8 g, 84.2 mmol) as a colourless oil in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.71 (m, 4H), 7.52 – 7.42 (m, 3H), 5.02 (d, *J* = 3.2 Hz, 1H), 4.80 – 4.66 (m, 2H), 4.02 – 3.98 (m, 1H), 3.98 – 3.92 (m, 1H), 3.90 (s, 1H), 3.76 – 3.68 (m, 2H), 3.23 (s, 1H), 2.13 (tt, *J* = 13.4, 4.1 Hz, 1H), 2.07 – 1.93 (m, 1H), 1.78 – 1.67 (m, 1H), 1.53 – 1.43 (m, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.2, 133.0, 128.2, 127.8, 127.7, 126.5, 126.1, 125.9, 125.6, 95.0, 73.7, 71.7, 68.7, 68.0, 66.1, 25.4, 24.0, 23.4, 21.4. HRMS: $[M+Na]^+$ calculated for $[C_{20}H_{26}O_4Na]^+$: 353.17233, found 353.17197.

Compound 22: Compound **27** (53.7 g, 163 mmol) was dissolved in DMF (1.00 L) and cooled to 0 °C and NaH (13.0 g, 325 mmol, 2 eq.) was slowly added. The reaction was stirred for 15 min at 0 °C after which BnBr (38.7 mL, 325 mmol, 2 eq.) and TBAI (3.95 g, 16.3 mmol, 0.1 eq.) were added. The reaction was stirred overnight at room temperature and subsequently quenched with MeOH. Most of the solvent was removed *in vacuo* and Et_2O and H_2O were added. The two phases were separated, and the aqueous layers were extracted with Et_2O (1x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (10% → 30% Et_2O/pentane) to obtain compound **22** (64.4 g, 153 mmol) as a colourless oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.71 (m, 5H), 7.49 – 7.38 (m, 3H), 7.32 – 7.19 (m, 5H), 5.00 (d, *J* = 3.2 Hz, 1H), 4.72 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.11 (td, *J* = 6.3, 1.3 Hz, 1H), 3.97 (hept, *J* = 6.2 Hz, 1H), 3.74 – 3.60 (m, 2H), 3.60 – 3.54 (m, 1H), 2.15 – 2.00 (m, 1H), 1.97 – 1.83 (m, 2H), 1.50 (dt, *J* = 13.2, 3.0 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 136.0, 133.3, 133.0, 128.3, 128.1, 127.9, 127.9, 127.7, 127.6, 126.4, 126.1, 125.8, 125.8, 94.5, 73.5, 71.1, 70.9, 70.4, 69.7, 67.9, 24.8, 23.5, 21.5, 20.9. HRMS: $[M+Na]^+$ calculated for $[C_{27}H_{32}O_4Na]^+$: 443.21928, found 443.21872.

Compound 23: A solution of compound **22** (11.8 g, 28.0 mmol) in a mixture of AcOH/1M HCl (280 mL, 4:1) was stirred overnight at 60 °C. After cooling the reaction to room temperature, it was slowly poured into sat. aq. $NaHCO_3$ (1.12 L) at 0°C. The aqueous phase was extracted with EtOAc (3x) and combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification by silica gel column chromatography (30% → 60% EtOAc/PE) compound **23** (10.6 g, 28.0 mmol) was obtained in quantitative yield as a colourless oil as a mixture of isomers (3:2, α:β). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.66 (m, 5H), 7.49 – 7.36 (m, 4H), 7.33 – 7.17 (m, 5H), 5.37 (d, *J* = 2.5 Hz, 1H), 4.79 (d, *J* = 7.2 Hz, 0H), 4.76 – 4.70 (m, 1H), 4.65 – 4.59 (m, 2H), 4.40 – 4.33 (m, 1H), 4.31 – 4.23 (m, 1H), 3.79 – 3.75 (m, 0H), 3.75 – 3.63 (m, 1H), 3.59 – 3.53 (m, 1H), 3.50 (s, 1H), 3.46 (s, 0H), 3.20 (s, 0H), 2.82 (s, 1H), 2.18 – 1.99 (m, 1H), 1.99 – 1.82 (m, 1H), 1.82 – 1.67 (m, 1H), 1.66 – 1.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 135.7, 133.4, 133.1, 128.4, 128.3, 128.3, 128.0, 128.0, 128.0, 127.8, 127.7, 126.8, 126.8, 126.2, 126.0, 126.0, 126.0, 96.3, 91.7, 77.2, 73.8, 73.7, 71.2, 71.0, 70.9, 70.8, 70.1, 70.0, 69.8, 27.9, 25.1, 24.3, 20.3. HRMS: $[M+Na]^+$ calculated for $[C_{24}H_{26}O_4Na]^+$: 401.17233, found 401.17193.

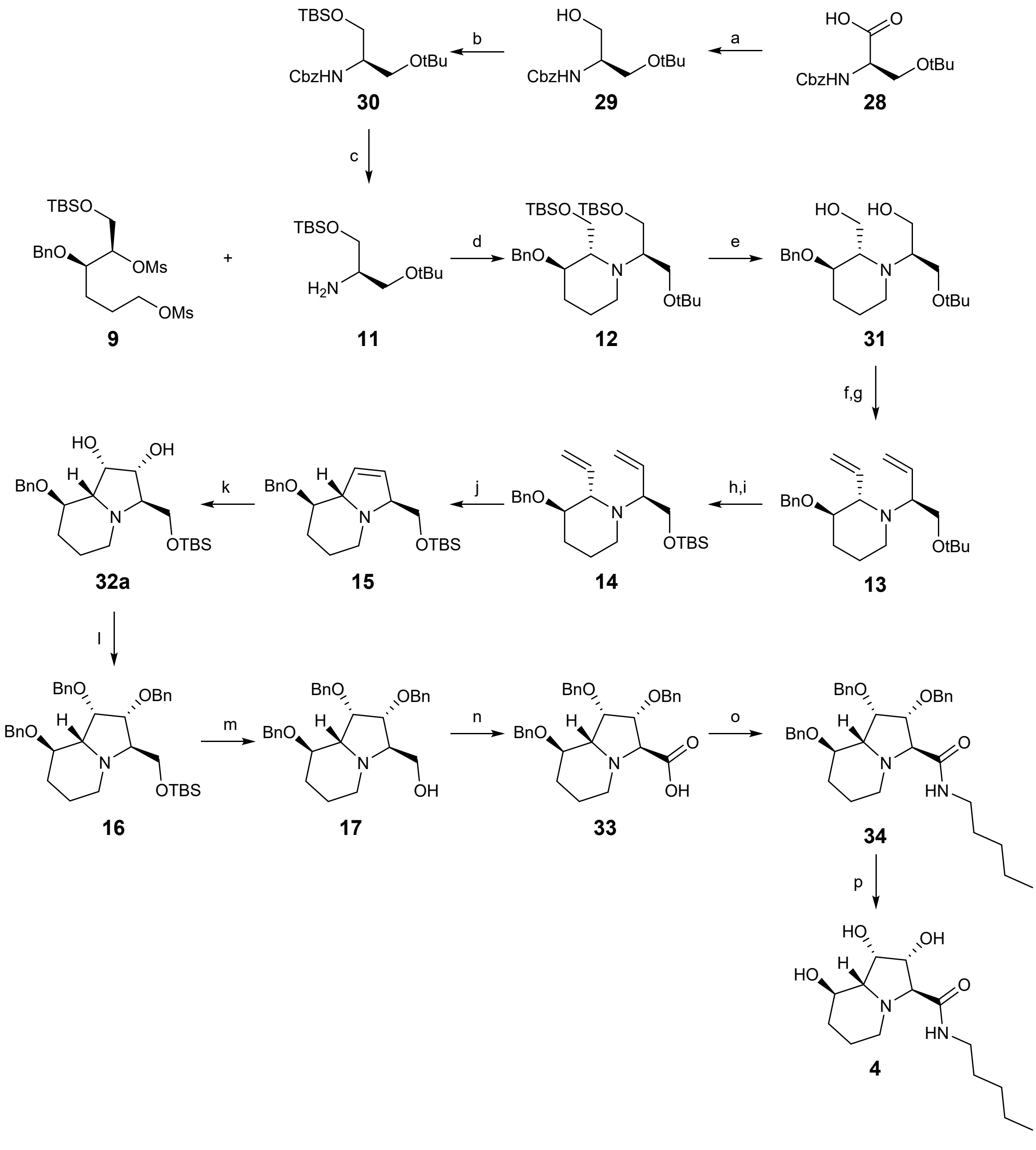
Compound 8: Compound **23** (10.3 g, 27.1 mmol, 1 eq.) was dissolved in EtOH (136 mL, 0.2 M) and $NaBH_4$ (1.03 g, 27.1 mmol, 1 eq.) was slowly added. After stirring for 3 hours at room temperature, the reaction was quenched with H_2O at 0 °C. Additional H_2O was added and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel column chromatography (2% → 10% MeOH/DCM) purification gave compound **8** (10.1 g, 26.5 mmol) as a colourless oil in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.71 (m, 4H), 7.56 – 7.40 (m, 3H), 7.35 – 7.20 (m, 5H), 4.70 (s, 2H), 4.66 – 4.46 (m, 2H), 3.89 (p, *J* = 10.2, 4.9 Hz, 1H), 3.69 – 3.49 (m, 6H), 2.59 (d, *J* = 5.4 Hz, 1H), 1.79 – 1.56 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 135.5, 133.3, 133.1, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 126.8, 126.3, 126.1, 126.0, 79.1, 73.7, 72.8, 71.7, 71.2, 62.9, 28.7, 26.7. HRMS: $[M+Na]^+$ calculated for $[C_{24}H_{28}O_4Na]^+$: 403.18798, found 403.18766.

Compound 24: A solution of compound **8** (7.6 g, 20 mmol) in pyridine (80 mL) was cooled to 0 °C. Methanesulfonyl chloride (3.9 mL, 50 mmol, 2.5 eq.) was added slowly and the reaction was stirred for 2 hours at 0 °C. The reaction was quenched with H_2O and additional H_2O was added. The aqueous phase was extracted with EtOAc and the organic layer was washed with 1M HCL (1x), sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% → 50% EtOAc/PE) gave compound **24** (11 g, 20 mmol) in quantitative yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.67 (m, 4H), 7.57 – 7.37 (m, 3H), 7.37 – 7.11 (m, 5H), 4.93 – 4.85 (m, 1H), 4.77 – 4.65 (m, 2H), 4.65 – 4.52 (m, 2H), 4.21 – 4.09 (m, 2H), 3.86 – 3.74 (m, 2H), 3.74 – 3.65 (m, 1H), 3.03 (s, 3H), 2.93 (s, 3H), 1.90 – 1.65 (m, 3H), 1.63 – 1.47 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 134.8, 133.3, 133.2, 129.2, 128.7, 128.6, 128.4, 128.3, 128.3, 128.0, 127.9, 127.0, 126.5, 126.3, 125.8, 125.4, 81.7, 77.5, 73.8, 73.0, 69.6, 68.7, 38.6, 37.4, 25.8, 25.4. HRMS: $[M+Na]^+$ calculated for $[C_{26}H_{32}O_8S_2Na]^+$: 559.14308, found 559.14320.

Compound 25: Compound **24** (1.61 g, 3.00 mmol) was dissolved in a mixture of DCM/H_2O (3:1, 40 mL) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (2.04 g, 9.00 mmol, 3 eq.) was added. The reaction was stirred at room temperature for 3 hours and subsequently quenched with sat. aq. $Na_2S_2O_3$. Additional H_2O was added, and the mixture was extracted with DCM (2x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (1% → 3% MeOH/DCM) furnished compound **25** (1.19 g, 3.00 mmol) as pale-yellow oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 4.82 – 4.71 (m, 1H), 4.68 – 4.55 (m, 2H), 4.23 – 4.12 (m, 2H), 4.01 – 3.78 (m, 2H), 3.74 (q, *J* = 4.4 Hz, 1H), 3.07 (s, 3H), 2.99 (s, 3H), 1.92 – 1.72 (m, 3H), 1.68 – 1.55 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 128.8, 128.4, 128.3, 83.0, 77.2, 73.0, 69.6, 61.8, 38.5, 37.5, 25.9, 25.2. HRMS: $[M+Na]^+$ calculated for $[C_{15}H_{24}O_8S_2Na]^+$: 419.108048, found 419.08050.

Compound 9: A solution of compound **25** (1.8 g, 4.6 mmol) and imidazole (0.40 g, 5.9 mmol, 1.3 eq.) in DCM (11 mL) was cooled to 0 °C. *tert*-butyldimethylsilyl chloride (0.82 g, 5.5 mmol, 1.2 eq.) was added and the reaction was stirred for 2 hours at 0 °C. The reaction was quenched by the addition of MeOH, and the mixture was washed with H_2O. The aqueous layer was extracted with DCM (2x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. After silica gel column chromatography (20% → 40% EtOAc/PE) compound **9** (2.2 g, 4.4 mmol) was obtained in 96% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 4.71 – 4.54 (m, 3H), 4.22 – 4.14 (m, 2H), 3.95 – 3.77 (m, 1H), 3.71 (p, *J* = 8.5, 4.0 Hz, 1H), 3.04 (s, 2H), 2.98 (s, 2H), 1.91 – 1.68 (m, 3H), 1.63 – 1.47 (m, 2H), 0.90 (s, 7H), 0.08 (d, *J* = 5.0 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 128.7, 128.4, 128.3, 83.8, 77.4, 73.1, 69.6, 62.0, 38.5, 37.5, 26.0, 25.9, 25.5, 18.4, -5.3. HRMS: $[M+Na]^+$ calculated for $[C_{21}H_{39}O_8S_2Si_1]^+$: 511.18501, found 511.18512.

Synthesis of indolizidine 4



Scheme 2. *Reagents and conditions*: a) isobutyl chloroformate, N-methylmorpholine, $NaBH_4$, DCM, -15 °C, 2 h, quant; b) TBSCl, imidazole, DCM, 0 °C to r.t., 2 h, 89%; c) Pd/C, H_2, EtOH, r.t., 16 h, 98%; d) DIPEA, MeCN, 50 °C to 70 °C, 4 days, 77%; e) TBAF, THF, r.t., 16 h, 94%; f) oxalyl chloride, DMSO, Et_3N, DCM, -78 °C to 0 °C, 5 h; g) $MeP(Ph)_3Br$, NaHMDS, THF, -78 °C to 0 °C, 16 h, 36% (over 2 steps); h) TFA, H_2O, 0 °C to r.t., 2 h, 89%; i) TBSCl, imidazole, DCM, 0 °C, 2 h, 96%; j) Schrock-Hoveyda catalyst, benzene, r.t., 16 h, 50%; k) OsO_4, TMEDA, DCM, -78 °C then ethylenediamine, r.t., 16 h, **32a**: 48% and **32b**: 16%; l) BnBr, NaH, DMF, r.t., 4 h, 70%; m) TBAF, THF, r.t., 2 h, 82%; n) CrO_3, H_2SO_4, H_2O, acetone, 60 °C to 0 °C, 30 min, 42%; o) amylamine, HATU, DIPEA, r.t., 16 h, 92%; p) Pd/C, H_2, HCl, dioxane, r.t., 16 h, 89%.

Compound 29: Z-D-ser(OtBu)-OH (1.48 g, 5.00 mmol) was dissolved in DME (10 mL) and cooled to -15 °C. N-methylmorpholine (0.55 mL, 5.00 mmol, 1 eq.) and isobutyl chloroformate (1.14 mL, 5.00 mmol, 1 eq.) were added dropwise and the mixture was stirred for 1 hour at -15 °C. The resulting suspension was filtered, and the filtrate was cooled to -15 °C. A solution of $NaBH_4$ (3 M in H_2O, 2.5 mL, 7.5 mmol, 1.5 eq.) was added followed by the addition of H_2O (125 mL) and the mixture was stirred for 2 hours at room temperature. The reaction was extracted with DCM (3x) and the organic layers were washed with 1 M HCl (1x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (30% → 40% EtOAc/PE) gave compound **29** (1.25 g, 4.44 mmol) as a white solid in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 5.52 (d, *J* = 8.1 Hz, 1H), 5.11 (s, 2H), 3.89 – 3.83 (m, 1H), 3.83 – 3.76 (m, 1H), 3.76 – 3.67 (m, 1H), 3.59 (d, *J* = 3.4 Hz, 2H), 1.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 128.7, 128.3, 77.5, 77.2, 76.8, 74.0, 67.0, 64.9, 63.8, 51.7, 27.4. HRMS: $[M+Na]^+$ calculated for $[C_{15}H_{23}NO_4Na]^+$: 304.15193, found 304.15163.

Compound 30: Compound **29** (12.3 g, 43.9 mmol) was co-evaporated with toluene under argon (3x) and dissolved in DCM (43.9 mL). Imidazole (3.59 g, 52.7 mmol, 1.2 eq.) was added and the solution was cooled to 0 °C. TBSCl (7.60 g, 50.5 mmol, 1.15 eq.) was added slowly and the reaction was stirred for 2 hours at room temperature. The mixture was poured into sat. aq. $NaHCO_3$ and extracted with DCM (3x). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. After silica gel column chromatography, compound **30** (15.6 g, 39.5 mmol) was obtained in 89% yield as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 5.14 (d, *J* = 7.7 Hz, 1H), 5.10 (s, 2H), 3.82 – 3.61 (m, 2H), 3.61 – 3.54 (m, 1H), 3.51 (dd, *J* = 8.9, 3.3 Hz, 1H), 3.33 (dd, *J* = 8.6, 6.0 Hz, 1H), 1.15 (s, 9H), 0.88 (s, 9H), 0.07 – 0.02 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 136.7, 128.7, 128.4, 128.3, 77.5, 77.2, 76.8, 73.0, 66.8, 61.3, 59.3, 52.3, 27.6, 26.0, 18.4, -5.4. HRMS: $[M+H]^+$ calculated for $[C_{21}H_{38}NO_4Si]^+$: 396.25646, found 396.25611.

Compound 11: After co-evaporation with toluene (3x), compound **30** (0.79 g, 2.0 mmol) was dissolved in dry EtOH (5.3 mL) under an argon atmosphere. The solution was purged with argon for 15 minutes and palladium on carbon (10% wt. loading, 64 mg) was added followed by purging with argon for another 15 minutes. The mixture was then purged with hydrogen for 15 min and stirred under a hydrogen atmosphere overnight at room temperature. The reaction was filtered over celite and concentrated *in vacuo* and purified by silica gel column chromatography (2% → 10% MeOH/DCM) to obtain compound **11** (0.51 g, 1.95) in 98% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.50 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.36 (dd, *J* = 8.7, 5.0 Hz, 1H), 3.22 (dd, *J* = 8.7, 6.4 Hz, 1H), 2.97 – 2.87 (m, 1H), 1.60 (s, 2H), 1.17 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.8, 65.3, 63.7, 53.2, 27.7, 26.0, 18.4, -5.3. HRMS: $[M+H]^+$ calculated for $[C_{13}H_{32}NO_2Si]^+$: 262.21968, found 262.21952.

Compound 12: Compound **9** (2.87 g, 5.61 mmol) and compound **11** (3.80 g, 14.5 mmol, 2.6 eq.) were dissolved in MeCN (11 mL). DIPEA (5.85 mL, 33.6 mmol, 6 eq.) was added and the mixture was stirred at 50 °C for 3 days. After full consumption of the starting material, the reaction was stirred overnight to 70 °C. The reaction was concentrated *in vacuo* and purified by silica gel column chromatography (2% → 10% Et_2O/pentane) to give compound **12** (2.56 g, 4.41 mmol) in 79% yield as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H), 4.67 – 4.44 (m, 2H), 3.99 – 3.85 (m, 2H), 3.80 – 3.66 (m, 2H), 3.50 – 3.45 (m, 1H), 3.45 – 3.38 (m, 1H), 3.36 – 3.30 (m, 1H), 3.20 – 3.12 (m, 1H), 2.87 – 2.79 (m, 1H), 2.67 (dt, *J* = 7.4, 3.8 Hz, 1H), 2.54 – 2.43 (m, 1H), 2.09 – 1.97 (m, 1H), 1.73 – 1.57 (m, 1H), 1.45 – 1.32 (m, 2H), 1.15 (s, 9H), 0.90 – 0.86 (m, 18H), 0.05 – 0.01 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 128.4, 127.8, 127.4, 75.1, 72.4, 71.0, 66.1, 61.9, 60.9, 60.2, 59.6, 46.8, 29.2, 27.7, 26.1, 26.1, 23.8, 18.4, -5.4. HRMS: $[M+H]^+$ calculated for $[C_{32}H_{62}NO_4Si_2]^+$: 580.42119, found 580.41971.

Compound 31: To a solution of compound **12** (0.64 g, 1.1 mmol, 1 eq.) in THF (5.1 mL, 0.2 M) was added TBAF (1 M in THF, 3.3 mL, 3.3 mmol, 3 eq.) and the mixture was stirred at room temperature overnight. The reaction was diluted with DCM and washed with H_2O (1x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (2% → 10% MeOH/DCM) gave compound **31** (0.31 g, 0.89 mmol) in 88% yield as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 5H), 5.00 (s, 1H), 4.67 – 4.48 (m, 2H), 3.98 (dd, *J* = 11.9, 10.2 Hz, 1H), 3.44 – 3.37 (m, 1H), 3.34 – 3.11 (m, 7H), 2.86 (td, *J* = 12.6, 2.7 Hz, 1H), 2.71 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.71 (m, 1H), 1.46 – 1.32 (m, 2H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 128.5, 127.8, 127.7, 74.5, 73.8, 70.5, 67.3, 65.8, 60.8, 60.0, 59.1, 36.4, 27.4, 25.5, 21.1. HRMS: $[M+H]^+$ calculated for $[C_{20}H_{34}NO_4]^+$: 352.24824, found 352.24795.

Compound 13: A solution of oxalyl chloride (0.69 mL, 8.0 mmol) in DCM (8.0 mL) was cooled to -78 °C. Next, DMSO (0.71 mL, 10 mmol, 5 eq.) was dissolved in DCM (5.0 mL, 2 M) and added dropwise to the oxalyl chloride solution at -78 °C. After stirring for 40 minutes, a solution of compound **31** (0.70 g, 2.0 mmol, 1 eq.) in DCM (4.0 mL, 0.5 M) was added dropwise to the reaction mixture and the reaction was stirred for 2 hours at -78 °C. Triethylamine (3.4 mL, 24 mmol, 12 eq.) was added and the mixture was allowed to warm to 0 °C while stirring over 2 hours. The off-white suspension was diluted with DCM and washed H_2O (1x) and the aqueous layer was extracted with DCM (1x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used in the next step without purification. Methyltriphenylphosphonium bromide (1.4 g, 4.2 mmol, 2 eq.) was suspended in dry THF (12 mL, 0.33 M) and cooled to -78 °C. Sodium bis(trimethylsilyl)amide (1 M in THF, 4.2 mL, 4.2 mmol, 2.1 eq.) was added dropwise and the reaction was stirred for 2 hours while warming to 0 °C. The bright yellow suspension was cooled back to -78 °C and a solution of the aldehyde from the previous step in dry THF (2.7 mL, 0.75 M) was added dropwise. The reaction mixture was stirred overnight while warming to room temperature and quenched with sat. aq. NH_4Cl. The mixture was diluted with DCM and washed with H_2O (1x). The aqueous layer was extracted with DCM (2x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification by silica gel column chromatography (20% → 50% Et_2O/pentane) compound **13** was obtained as a pale-yellow oil. To remove trace impurities, the compound was redissolved in Et_2O and extracted with 1 M HCl (2x). The combined aqueous layers were basified with 3M NaOH and extracted with DCM (2x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Another purification by silica gel column chromatography (20% → 50% Et_2O/pentane) gave compound **13** (230 mg, 0.894 mmol) as a colourless and odourless oil in 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 5.84 – 5.59 (m, 2H), 5.35 – 5.05 (m, 4H), 4.60 – 4.40 (m, 2H), 3.60 – 3.50 (m, 1H), 3.51 – 3.40 (m, 2H), 3.21 – 3.10 (m, 1H), 2.87 (t, J = 8.7 Hz, 1H), 2.78 (dt, J = 11.2, 1.3 Hz, 1H), 2.22 (td, J = 11.5, 2.6 Hz, 1H), 2.15 – 2.02 (m, 1H), 1.68 (dp, J = 13.4, 3.5 Hz, 1H), 1.50 – 1.34 (m, 1H), 1.32 – 1.18 (m, 1H), 1.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.9, 134.1, 128.3, 127.9, 127.5, 119.5, 119.0, 78.6, 72.9, 71.7, 69.4, 64.6, 61.7, 46.4, 30.2, 27.7, 23.8. HRMS: $[M+H]^+$ calculated for $[C_{22}H_{34}NO_2]^+$: 344.25841, found 344.25827.

Compound 35: Compound **13** (0.34 g, 0.99 mmol) was dissolved in TFA (5.9 mL) and cooled to 0 °C. 10 drops of H_2O were added, and the solution was stirred at room temperature for 2 hours. The reaction was diluted with DCM (100 mL) and the organic phase was washed with 1 M NaOH (2x). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (2% → 5% MeOH/DCM) gave compound **35** (0.25 g, 0.89 mmol) as a colourless oil in 89% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 6H), 5.75 – 5.53 (m, 2H), 5.40 – 5.04 (m, 4H), 4.53 (q, J = 11.6 Hz, 2H), 3.79 – 3.66 (m, 1H), 3.51 (t, J = 10.5 Hz, 1H), 3.41 (dd, J = 10.3, 5.7 Hz, 1H), 3.21 – 3.10 (m, 1H), 2.97 (t, J = 8.7 Hz, 1H), 2.86 – 2.76 (m, 1H), 2.22 – 2.04 (m, 2H), 1.74 (dp, J = 12.5, 3.2 Hz, 1H), 1.51 – 1.34 (m, 1H), 1.34 – 1.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.5, 132.0, 128.4, 127.9, 127.6, 120.2, 120.0, 78.7, 71.7, 69.1, 61.5, 60.1, 43.9, 30.3, 23.8. HRMS: $[M+H]^+$ calculated for $[C_{18}H_{26}NO_2]^+$: 288.19581, found 288.19571.

Compound 14: A solution of compound **35** (0.13 g, 0.46 mmol, 1 eq.) and imidazole (47 mg, 0.70 mmol) in DCM (1.1 mL) was cooled to 0 °C. TBSCl (84 mg, 0.56 mmol, 1.2 eq.) was added and the mixture was stirred at 0 °C for 2 hours. The reaction was quenched by addition of MeOH and washed with H_2O (1x). The organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (5% → 20% Et_2O/pentane) gave compound **14** (0.18 g, 0.44 mmol) in 96% yield as a colourless oil. ^1H NMR (850 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 4H), 7.26 – 7.23 (m, 1H), 5.79 – 5.73 (m, 1H), 5.68 – 5.62 (m, 1H), 5.36 – 5.04 (m, 4H), 4.57 – 4.45 (m, 2H), 3.71 – 3.65 (m, 2H), 3.55 – 3.50 (m, 1H), 3.16 – 3.12 (m, 1H), 2.85 (t, J = 8.7 Hz, 1H), 2.80 (dt, J = 11.3, 2.9 Hz, 1H), 2.21 (td, J = 11.6, 2.5 Hz, 1H), 2.10 (dq, J = 11.6, 3.5 Hz, 1H), 1.68 (dq, J = 13.2, 3.4 Hz, 1H), 1.46 – 1.38 (m, 1H), 1.27 – 1.19 (m, 1H), 0.87 (s, 9H), 0.04 – 0.01 (m, 6H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 139.1, 139.1, 133.8, 128.3, 127.9, 127.5, 119.4, 119.3, 78.7, 71.6, 69.5, 65.7, 63.4, 46.3, 30.2, 26.1, 23.8, 18.5, -5.1, -5.1. HRMS: $[M+H]^+$ calculated for $[C_{24}H_{40}NO_2Si]^+$: 402.28228, found 402.28181.

Compound 15: This reaction was carried out under Schlenk conditions with flame-dried glassware. Compound **14** (583 mg, 1.45 mmol) was dissolved in dry benzene (14.5 mL) and added to a flask containing (341 mg, 0.436 mmol, 0.3 eq.) under argon atmosphere, and the dark red/brown solution was stirred overnight at room temperature. The reaction was quenched by exposing to air for 1 hour and used as solution for silica gel column chromatography (5% → 20% Et_2P/pentane) to obtain starting material **14** (0.241 mg, 0.600 mmol) in 41% yield and the product compound **15** (270 mg, 0.722 mmol) as a pale-yellow oil in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 6.19 (dt, *J* = 6.1, 1.7 Hz, 1H), 5.85 (dt, *J* = 6.2, 1.6 Hz, 1H), 4.66 – 4.43 (m, 2H), 3.87 – 3.77 (m, 1H), 3.72 – 3.64 (m, 1H), 3.55 – 3.50 (m, 1H), 3.50 – 3.45 (m, 1H), 3.15 – 3.04 (m, 1H), 2.80 – 2.68 (m, 1H), 2.26 – 2.11 (m, 1H), 1.70 (s, 0H), 1.63 – 1.45 (m, 1H), 1.37 – 1.20 (m, 1H), 0.89 (s, 9H), 0.06 – 0.03 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 132.9, 130.8, 128.5, 127.8, 127.7, 79.6, 71.0, 70.1, 68.1, 65.1, 45.9, 30.0, 26.0, 22.8, 18.4, -5.2, -5.3.

Compound 32a and 32b: Compound **15** (0.27 g, 0.72 mmol, 1 eq.) and N,N,N',N'-tetramethylethylenediamine (0.12 mL, 0.79 mmol) were dissolved in DCM (34 mL, 0.021 M) and the solution was cooled to -78 °C. A solution of OsO_4 (0.020 M in DCM, 39 mL, 0.76 mmol, 1.05 eq.) was slowly added and the solution was stirred at -78 °C for 1 hour. Ethylenediamine (0.96 mL, 14 mmol, 20 eq.) was added and the mixture was stirred overnight while warming to room temperature. The reaction was concentrated *in vacuo* and purified by silica gel column chromatography (2% → 10% MeOH/DCM) to give compound **32a** (0.14 g, 0.34 mmol) in 48% yield and **32b** (47 mg, 0.12 mmol) in 16% yield. Data for **32a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.22 (m, 5H), 4.75 – 4.48 (m, 1H), 4.23 – 4.12 (m, 2H), 3.75 (ddd, *J* = 37.4, 10.8, 3.5 Hz, 2H), 3.61 – 3.50 (m, 1H), 3.00 (q, *J* = 3.5 Hz, 1H), 2.91 (d, *J* = 10.4 Hz, 1H), 2.80 (dd, *J* = 9.2, 3.4 Hz, 1H), 2.56 (td, *J* = 11.8, 2.9 Hz, 1H), 2.28 – 2.17 (m, 1H), 1.73 – 1.63 (m, 1H), 1.60 – 1.44 (m, 1H), 1.27 – 1.11 (m, 1H), 0.89 (s, 9H), 0.05 (d, *J* = 1.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 128.7, 128.1, 128.0, 74.0, 73.4, 71.2, 70.7, 68.5, 68.2, 62.3, 45.6, 29.8, 26.0, 23.3, 18.2, -5.4. HRMS: $[M+Na]^+$ calculated for $[C_{22}H_{38}NO_4Si]^+$: 408.25646, found 408.25634. Data for **32b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 5H), 4.74 – 4.44 (m, 2H), 4.30 – 4.20 (m, 1H), 4.07 – 3.97 (m, 1H), 3.75 (d, *J* = 3.2 Hz, 2H), 3.32 – 3.08 (m, 3H), 3.05 – 2.94 (m, 1H), 2.90 – 2.77 (m, 2H), 2.63 (td, *J* = 12.3, 2.9 Hz, 1H), 2.26 – 2.17 (m, 1H), 1.67 – 1.52 (m, 4H), 1.52 – 1.37 (m, 1H), 1.35 – 1.14 (m, 2H), 0.98 – 0.80 (m, 10H), 0.12 – 0.09 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.6, 127.9, 127.8, 76.0, 73.2, 71.9, 70.5, 70.4, 62.7, 60.9, 46.1, 30.2, 26.0, 22.2.

Compound 16: Compound **32a** (0.12 g, 0.29 mmol) was co-evaporated with toluene (3x) and dissolved in DMF (2.9 mL) under argon. NaH (24 mg, 0.60 mmol, 2.1 eq.) was added and the mixture was stirred for 15 minutes at room temperature followed by addition of benzyl bromide (0.15 mL, 0.63 mmol, 4.4 eq.). The reaction was stirred for 4 hours at room temperature and subsequently quenched with MeOH. The reaction was diluted with DCM and washed with H_2O (1x). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (30% → 60% Et_2O/pentane) gave compound **16** (0.12 g, 0.20 mmol) as a colourless oil in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 15H), 4.86 – 4.69 (m, 2H), 4.67 – 4.37 (m, 4H), 4.24 – 4.18 (m, 1H), 4.03 (d, *J* = 5.2 Hz, 1H), 3.82 – 3.70 (m, 2H), 3.63 – 3.56 (m, 1H), 3.25 (dt, *J* = 5.8, 3.2 Hz, 1H), 2.98 – 2.91 (m, 1H), 2.76 (dd, *J* = 8.9, 3.1 Hz, 1H), 2.54 (td, *J* = 11.4, 3.4 Hz, 1H), 2.30 – 2.21 (m, 1H), 1.69 – 1.51 (m, 4H), 1.23 – 1.08 (m, 1H), 0.90 – 0.88 (m, 1H), 0.84 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H). ^{13}C NMR

(101 MHz, $CDCl_3$) δ 139.2, 139.2, 138.8, 128.4, 128.3, 128.3, 127.9, 127.7, 127.6, 127.6, 127.5, 80.3, 76.9, 74.7, 73.8, 72.1, 70.5, 68.5, 65.3, 61.9, 45.8, 30.0, 26.0, 23.5, 18.2, -5.4, -5.5. HRMS: $[M+H]^+$ calculated for $[C_{36}H_{50}NO_4Si]^+$: 588.35036, found 588.35011.

Compound 17: To a solution of compound **16** (0.12 g, 0.20 mmol) in THF (1.0 mL) was added TBAF (1 M in THF, 0.60 mL, 0.60 mmol, 3 eq.). After stirring for 2 hours at room temperature, the reaction was diluted with DCM and the organic phase was washed with H_2O (1x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (2% → 5% MeOH/DCM) to obtain compound **17** (78 mg, 0.16 mmol) as a colourless oil in 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.16 (m, 15H), 4.83 – 4.44 (m, 6H), 4.07 (t, *J* = 4.8 Hz, 1H), 4.01 (t, *J* = 4.7 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.71 – 3.63 (m, 1H), 3.59 – 3.51 (m, 1H), 3.23 (q, *J* = 3.4 Hz, 1H), 3.09 (dd, *J* = 8.9, 4.3 Hz, 1H), 2.87 (dt, *J* = 12.4, 3.5 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.22 – 2.12 (m, 1H), 1.67 – 1.55 (m, 2H), 1.38 – 1.22 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.9, 138.7, 128.5, 128.4, 128.0, 127.8, 127.7, 127.5, 127.5, 80.9, 79.1, 73.5, 73.3, 72.9, 71.1, 66.3, 65.8, 60.7, 45.8, 29.8, 20.9. HRMS: $[M+Na]^+$ calculated for $[C_{30}H_{36}N_1O_4]^+$: 474.26389, found 474.26354.

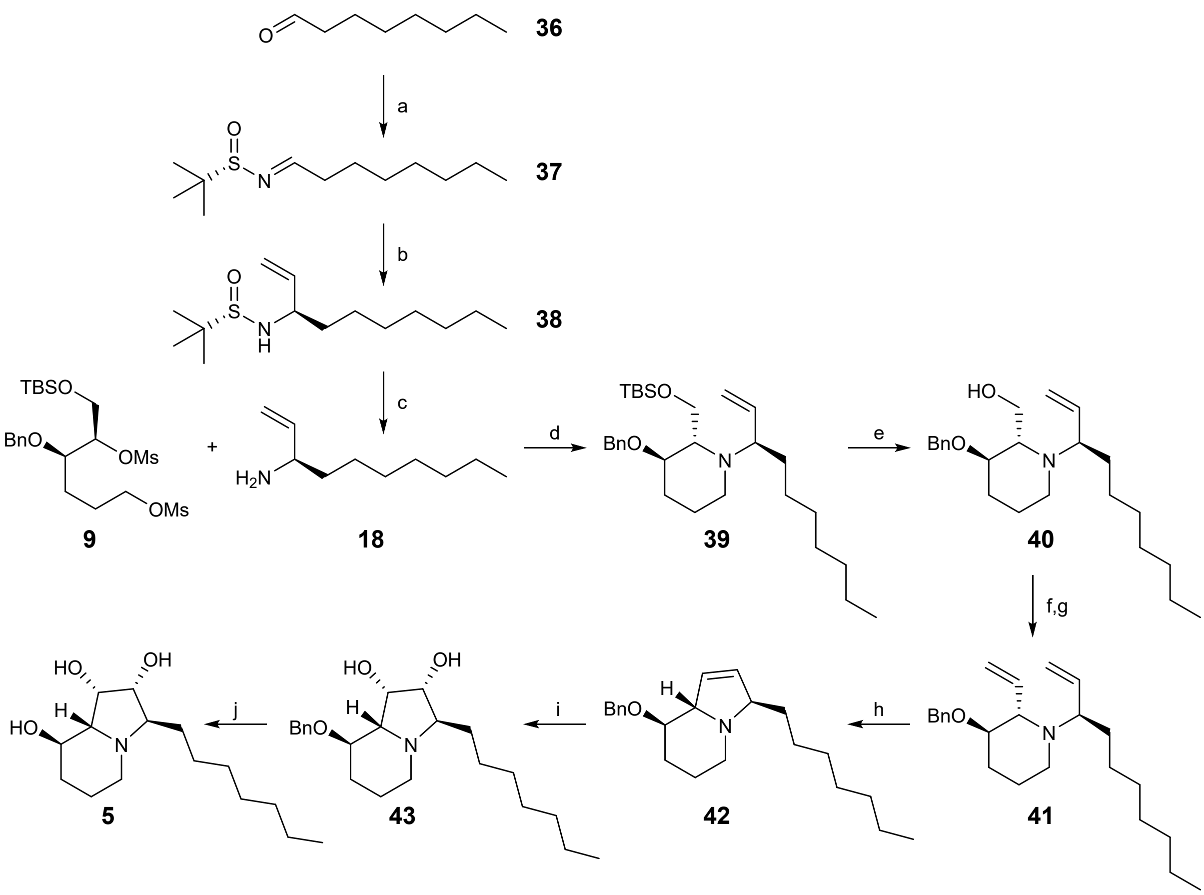
Compound 33: A stock solution of $HCrO_4^-$ (Jones reagent) was prepared by dissolving conc. H_2SO_4 (8.7 mL, 0.16 mol) in H_2O (30 mL) followed by the addition of CrO_3 (2.1 g, 21 mmol). Compound **17** (77.8 mg, 0.164 mmol) was dissolved in mixture of acetone/H_2O (3:2, 4.11 mL) and the pH was adjusted to pH ≈ 4 with 1 M H_2SO_4 aq. The solution was heated to 60 °C and the stock solution of Jones reagent (1.46 mL) was slowly added. The reaction was then stirred for 30 minutes at 60 °C and subsequently cooled to 0 °C, quenched with $Na_2S_2O_3$ sat. aq. and neutralized with $NaHCO_3$ sat. aq. The aqueous phase was extracted with DCM (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (3% → 8% MeOH/DCM) gave compound **33** (33.7 mg, 69.1 μmol) in 42% yield as a light brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.13 (m, 15H), 4.90 – 4.64 (m, 4H), 4.57 – 4.39 (m, 4H), 4.16 (s, 1H), 3.89 (d, *J* = 10.3 Hz, 2H), 3.64 (s, 1H), 3.17 (s, 2H), 2.09 – 1.95 (m, 1H), 1.88 (s, 1H), 1.64 – 1.43 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 138.2, 138.0, 137.9, 128.5, 128.5, 128.5, 128.1, 128.1, 127.9, 127.8, 127.7, 81.6, 78.4, 74.1, 72.7, 72.4, 71.7, 71.0, 49.4, 26.8, 19.1. HRMS: $[M+Na]^+$ calculated for $[C_{30}H_{34}NO_5]^+$: 488.24315, found 488.24310.

Compound 34: Compound **33** (18 mg, 36 μmol) was dissolved in DMF (1.0 mL) and DIPEA (13 μL, 72 μmol, 2 eq.) and HATU (14 mg, 38 μmol, 1.05 eq.) were subsequently added. The mixture was stirred for 5 minutes at room temperature followed by the addition of amylamine (42 μL, 0.36 mmol, 10 eq.). The reaction was stirred overnight at room temperature and diluted with DCM. The organic phase was washed with H_2O (1x) and the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (10% → 30% EtOAc/PE) gave compound **34** (18 mg, 33 μmol) in 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.15 (m, 15H), 6.88 (t, *J* = 5.9 Hz, 1H), 4.88 – 4.59 (m, 4H), 4.56 – 4.46 (m, 2H), 4.11 (dd, *J* = 5.4, 2.5 Hz, 1H), 4.04 – 3.93 (m, 2H), 3.59 (d, *J* = 2.5 Hz, 1H), 3.32 – 3.10 (m, 3H), 2.77 – 2.60 (m, 2H), 2.17 – 2.05 (m, 1H), 1.77 (s, 1H), 1.62 –

1.38 (m, 4H), 1.38 – 1.19 (m, 6H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 139.2, 138.7, 138.6, 128.4, 128.4, 128.3, 128.2, 127.8, 127.6, 127.4, 82.6, 79.6, 73.7, 72.7, 72.2, 71.4, 70.2, 64.7, 47.1, 39.1, 30.6, 29.4, 29.1, 22.4, 20.6, 14.1. HRMS: $[M+Na]^+$ calculated for $[C_{35}H_{45}N_2O_4]^+$: 557.33738, found 557.33709.

Compound 4: Compound **33** (5.0 mg, 9.0 μmol) was co-evaporated with toluene under argon (3x) and dissolved in dioxane (0.50 mL, 18 mM). H_2O (0.2 mL) was added followed by the addition of 1 M HCl aq. (0.2 mL). the solution was purged with argon for 15 minutes and a catalytic amount of palladium on carbon was added. The mixture was then purged with argon for another 15 minutes and subsequently purged with hydrogen for 15 minutes and stirred overnight under hydrogen atmosphere at room temperature. The reaction was then filtered over a Whatman filter and purified by HPLC to obtain compound **4** (2.3 mg, 8.0 μmol) in 89% yield. ^1H NMR (850 MHz, D_2O + 2 eq. NaOD) δ 4.41 (t, J = 4.9 Hz, 1H), 4.29 (dd, J = 5.2, 3.4 Hz, 1H), 3.77 – 3.71 (m, 1H), 3.48 (d, J = 4.4 Hz, 1H), 3.32 – 3.27 (m, 1H), 3.17 (dt, J = 13.7, 7.0 Hz, 1H), 2.77 (dd, J = 9.3, 3.4 Hz, 1H), 2.76 – 2.73 (m, 1H), 2.31 (td, J = 11.9, 2.8 Hz, 1H), 2.06 – 2.03 (m, 1H), 1.72 – 1.68 (m, 1H), 1.57 – 1.48 (m, 4H), 1.36 – 1.27 (m, 5H), 1.26 – 1.19 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (214 MHz, D_2O) δ 173.0, 74.1, 70.6, 70.0, 69.4, 66.2, 45.6, 39.2, 31.8, 28.3, 28.0, 22.5, 21.6, 13.2. HRMS: $[M+Na]^+$ calculated for $[C_{14}H_{27}N_2O_4]^+$: 287.19653, found 287.19624.

Synthesis of indolizidine 5



Scheme 3. *Reagents and conditions*: a) (*S*)-*tert*-butylsulfinamide, pyridinium *p*-toluenesulfonate, $MgSO_4$, DCM, r.t., 16 h, 80%; b) vinylMgBr, toluene, r.t., 16 h, 77%; c) 4M HCl in dioxane, MeOH, 0 °C to r.t., 1 h, 98%; d) DIPEA, MeCN, 50 °C, 3 days, 55%; e) TBAF, THF, r.t., 16h, 98%; f) oxalyl chloride, DMSO, Et_3N, DCM, -78 °C to 0 °C, 5 h; g) $MeP(Ph)_3Br$, NaHMDS, THF, -78 °C to 0 °C, 16 h, 37% (over 2 steps); h) Schrock-Hoveyda catalyst, benzene, r.t., 16 h, 87%; i) OsO_4, TMEDA, DCM, -78 °C then ethylenediamine, r.t., 16 h, 39%; j) Pd/C, H_2, HCl, dioxane/H_2O, r.t., 16 h, 90%.

Compound 37: To a solution of (*S*)-*tert*-butylsulfinamide (0.61 g, 5.0 mmol) in DCM (10 mL) was added pyridinium *p*-toluenesulfonate (62 mg, 0.25 mmol, 0.05 eq.), $MgSO_4$ (3.0 g, 25 mmol, 5 eq.) and octanal (0.78 mL, 5.0 mmol, 1 eq.). The resulting mixture was stirred overnight at room temperature and subsequently filtered over Celite and concentrated *in vacuo*. Purification by silica gel column chromatography (10% → 20% Et_2O/pentane) gave compound **37** (0.92 g, 4.0 mmol) in 80% yield as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, *J* = 4.8 Hz, 1H), 2.55 – 2.46 (m, 2H), 1.61 (p, *J* = 7.4 Hz, 3H), 1.38 – 1.23 (m, 8H), 1.19 (s, 9H), 0.91 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 56.6, 36.3, 31.8, 29.3, 29.2, 28.2, 25.7, 24.8, 22.7, 22.5, 14.2. HRMS: $[M+H]^+$ calculated for $[C_{36}H_{50}NO_4Si]^+$: 232.17296, found 232.17283.

Compound 38: Compound **37** (0.92 g, 4.0 mmol) was co-evaporated with toluene (3x) under an argon atmosphere. The residue was dissolved in dry toluene (400 mL) followed by the addition of vinylmagnesium bromide (1 M in THF, 8 mL, 8 mmol, 2 eq.). The resulting solution was stirred overnight at room temperature and subsequently quenched with H_2O and concentrated *in vacuo*. The residue was redissolved in Et_2O and washed with 1M HCL (1x), sat. aq. $NaHCO_3$ (1x) and brine (1x). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% → 50% EtOAc/PE) gave compound **38** (0.84 g, 3.1 mmol) in 77% yield as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.75 (m, 1H), 5.27 – 5.13 (m, 2H), 3.78 – 3.66 (m, 1H), 3.07 (d, *J* = 6.3 Hz, 1H), 1.69 – 1.57 (m, 1H), 1.54 – 1.40 (m, 1H), 1.37 – 1.23 (m, 10H), 1.21 (s, 9H), 0.91 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 116.5, 58.9, 55.9, 35.4, 31.9, 29.5, 29.3, 25.6, 22.8, 22.7, 14.2. HRMS: $[M+H]^+$ calculated for $[C_{14}H_{30}NOS]^+$: 260.20426, found 260.20412.

Compound 18: A solution of compound **38** (1.77 g, 6.47 mmol) in MeOH (64.7 mL) was cooled to 0 °C. HCl (4M in dioxane, 3.24 mL, 12.9 mmol, 2 eq.) was added and mixture was stirred for 1 hour while warming to room temperature. The reaction was concentrated *in vacuo* and the residue was redissolved in DCM and washed with 1 M HCl (1x). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (2% → 10% MeOH/DCM) gave the hydrochloride salt of compound **38** which was neutralized by dissolving in DCM and washing with 1 M NaOH (1 x) to obtain compound **41** (0.983 g, 6.33 mmol) in 98% yield as a colourless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.71 (m, 1H), 5.17 – 4.95 (m, 2H), 3.32 – 3.22 (m, 1H), 1.45 – 1.37 (m, 1H), 1.35 – 1.19 (m, 11H), 0.91 – 0.82 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 113.5, 54.7, 37.7, 32.0, 29.7, 29.4, 26.2, 22.8, 14.2. HRMS: $[M+H]^+$ calculated for $[C_{10}H_{22}N]^+$: 156.17468, found 156.17463.

Compound 39: Compound **9** (1.7 g, 3.3 mmol) was dissolved in dry MeCN (6.5 mL) and compound **18** (0.983 g, 6.33 mmol, 2 eq.) and DIPEA (1.7 mL, 9.8 mmol, 3 eq.) were added. The resulting mixture was stirred for 3 days at 50 °C and subsequently concentrated *in vacuo*. Purification by silica gel column chromatography (5% → 40% EtOAc/PE) gave compound **39** (0.85 g, 1.8 mmol) in 55% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H), 5.89 – 5.74 (m, 1H), 5.17 – 5.05 (m, 2H), 4.64 – 4.43 (m, 2H), 3.91 – 3.78 (m, 2H), 3.49 – 3.38 (m, 2H), 2.74 – 2.64 (m, 2H), 2.38 – 2.27 (m, 1H), 2.08 – 1.97 (m, 1H), 1.79 – 1.51 (m, 2H), 1.45 – 1.10 (m, 14H), 0.93 – 0.82 (m, 10H), 0.04 – 0.02 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 139.2, 128.4, 127.9, 127.5, 115.5, 74.9, 70.9, 64.4, 61.7, 60.8, 45.0, 32.1, 30.2, 29.5, 28.7, 27.5, 27.1, 26.1, 22.8, 18.5, 14.3, -5.2. HRMS: $[M+H]^+$ calculated for $[C_{29}H_{52}NO_2Si]^+$: 474.37618, found 474.37570.

Compound 40: To a solution of compound **39** (0.85 g, 1.8 mmol) in THF (3.6 mL) was added TBAF (1 M in THF, 2.7 mL, 2.7 mmol, 1.5 eq.) and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM and washed with H_2O (1x). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (0% → 6% MeOH/DCM) gave compound **40** (0.63 g, 1.8 mmol) in 98% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 5.85 – 5.72 (m, 1H), 5.22 – 5.07 (m, 2H), 4.66 – 4.48 (m, 2H), 3.93 – 3.82 (m, 1H), 3.75 – 3.67 (m, 1H), 3.52 – 3.40 (m, 2H), 2.89 – 2.80 (m, 1H), 2.72 (s, 1H), 2.40 (t, *J* = 10.3 Hz, 1H), 2.16 – 2.05 (m, 1H), 1.79 – 1.64 (m, 1H), 1.64 – 1.52 (m, 1H), 1.49 – 1.09 (m, 12H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 138.7, 128.5, 127.9, 127.7, 116.5, 75.1, 71.3, 62.2, 60.3, 58.1, 44.1, 32.0, 30.0, 29.4, 29.2, 27.1, 27.1, 22.8, 21.8, 14.2. HRMS: $[M+H]^+$ calculated for $[C_{23}H_{38}NO_2]^+$: 360.28971, found 360.28931.

Compound 41: Oxalyl chloride (0.26 mL, 3.1 mmol) was dissolved in DCM (3.1 mL) and the solution was cooled to -78 °C. A solution of DMSO (0.28 mL, 3.9 mmol, 5 eq.) in DCM (2.0 mL, 2 M) was added dropwise to the oxalyl chloride solution at -78 °C and the mixture was stirred for 40 minutes at -78 °C. A solution of compound **40** (0.28 g, 0.76 mmol, 1 eq.) in DCM (1.6 mL, 0.5 M) was added dropwise to the reaction mixture and the reaction was stirred for 2 hours at -78 °C. Triethylamine (1.3 mL, 3.9 mmol, 12 eq.) was added and the mixture was allowed to warm to 0 °C while stirring over 2 hours. The off-white suspension was diluted with DCM and washed H_2O (1x) and the aqueous layer was extracted with DCM (1x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used in the next step without purification. To a suspension of methyltriphenylphosphonium bromide (0.56 g, 1.6 mmol, 2 eq.) in dry THF (4.7 mL, 0.33 M) at -78 °C was added sodium bis(trimethylsilyl)amide (1 M in THF, 1.6 mL, 1.6 mmol, 2.1 eq.) dropwise and the reaction was stirred for 2 hours while warming to 0 °C. The bright yellow suspension was cooled back to -78 °C and a solution of the aldehyde from the previous step in dry THF (1.0 mL, 0.75 M) was added dropwise. The reaction was stirred overnight while warming to room temperature and quenched with sat. aq. NH_4Cl. The mixture was diluted with DCM and washed with H_2O (1x). The aqueous layer was extracted with DCM (2x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (5% → 20% Et_2O/pentane) compound **41** (0.24 g, 0.67 mmol) was obtained as a pale-yellow oil in 86% yield. To remove trace impurities, compound **41** (90 mg, 0.25 mmol) was purified by HPLC followed by another purification by silica gel column chromatography (5% → 20% Et_2O/pentane) to give compound **41** (33 mg, 93 µmol) as a colourless and odourless oil in 37% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H), 5.86 – 5.65 (m, 2H), 5.37 – 5.25 (m, 2H), 5.14 – 5.04 (m, 2H), 4.59 – 4.45 (m, 2H), 3.39 – 3.29 (m, 1H), 3.26 – 3.15 (m, 1H), 3.01 (t, *J* = 8.5 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.20 – 2.04 (m, 2H), 1.72 – 1.63 (m, 2H), 1.61 – 1.50 (m, 1H), 1.47 – 1.34 (m, 1H), 1.34 – 1.17 (m, 11H), 1.07 (s, 1H), 0.88 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 139.1, 138.8, 128.3, 127.9, 127.5, 118.9, 115.8, 78.7, 71.6, 69.0, 61.6, 45.1, 32.0, 30.2, 30.0, 29.4, 27.0, 25.0, 23.7, 22.8, 14.3. HRMS: $[M+H]^+$ calculated for $[C_{24}H_{38}NO]^+$: 356.29479, found 356.29444.

Compound 42: This reaction was performed under Schlenk-conditions under argon with flame dried glassware. Compound **41** (33 mg, 93 µmol) was dissolved in dry benzene (1.0 mL) and added to a flask containing 2,6-Diisopropylphenylimidoneophylidene[racemic-BIPHEN]molybdenum (21 mg, 28 µmol). The mixture was stirred overnight at room temperature overnight and subsequently quenched by exposure to air. Purification by silica gel column chromatography (5% → 20% Et_2O/pentane) gave compound **42** (27 mg, 81 µmol) as a colourless oil in 87%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 6.14 (d, *J* = 6.1 Hz, 1H), 5.87 – 5.80 (m, 1H), 4.71 – 4.52 (m, 2H), 3.31 (td, *J* = 9.9, 4.3 Hz, 1H), 3.24 – 3.12 (m, 1H), 3.00 – 2.88 (m, 2H), 2.25 – 2.11 (m, 2H), 1.80 – 1.48 (m, 5H), 1.46 – 1.05 (m, 15H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 133.3, 129.8, 128.5, 127.7, 127.6, 125.7, 78.7, 74.3, 71.2, 68.4, 47.2, 32.9, 32.0, 31.0, 30.5, 30.1, 29.9, 29.4, 26.3, 25.4, 22.8, 14.3. HRMS: $[M+H]^+$ calculated for $[C_{22}H_{34}NO]^+$: 328.26349, found 328.26312.

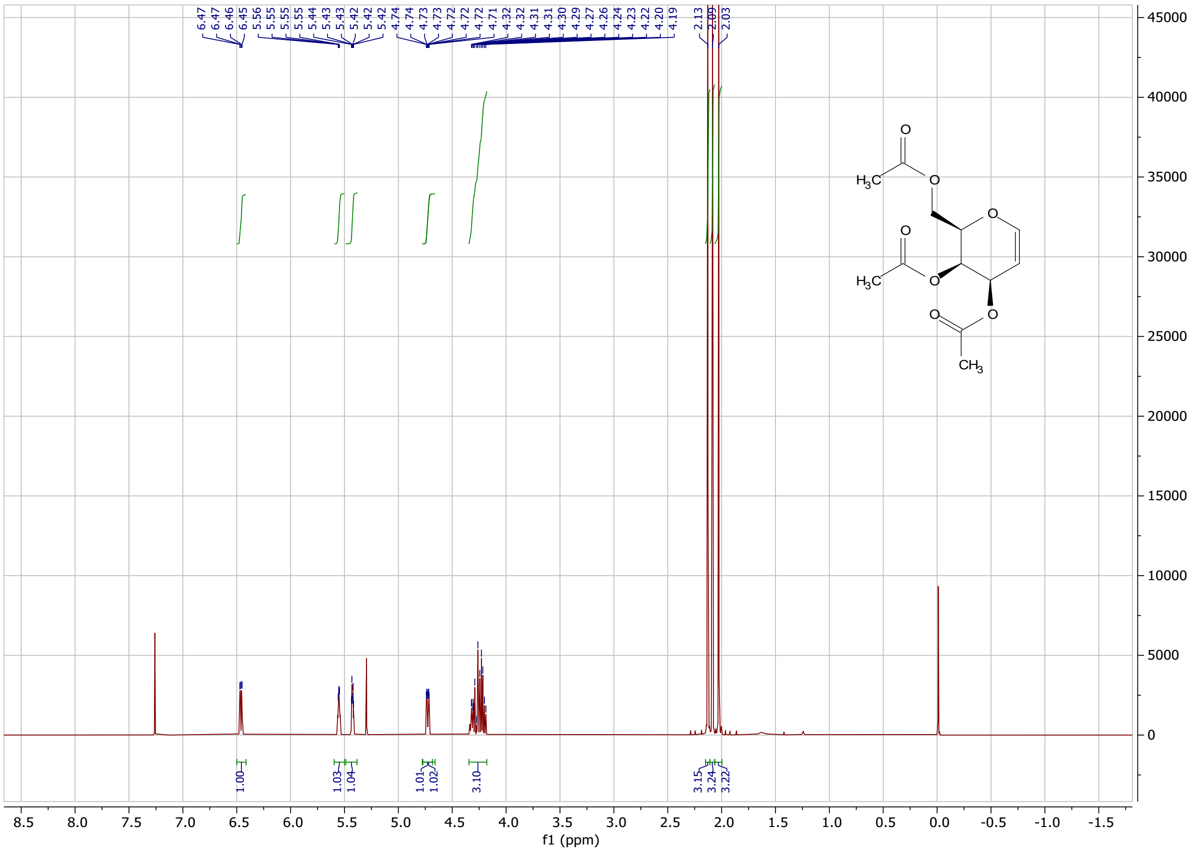
Compound 43: A solution of compound **42** (18 mg, 55 µmol) and N,N,N',N'-tetramethylethylenediamine (9.1 µL, 61 µmol, 1.1 eq.) in DCM (2.5 mL) was cooled to -78 °C. A solution of OsO_4 (0.020 M in DCM, 3.0 mL, 58 µmol, 1.05 eq.) was slowly added and the solution was stirred at -78 °C for 1 hour. Ethylenediamine (37 µL, 0.55 mmol, 10 eq.) was added and the mixture was stirred overnight while warming to room temperature. The reaction was concentrated *in vacuo* and purified by silica gel column chromatography (2% → 5% MeOH/DCM) to give compound **43** (7.8 mg, 22 µmol) in 39% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 4.73 – 4.52 (m, 1H), 4.26 (dd, *J* = 6.0, 4.1 Hz, 1H), 4.13 (t, *J* = 6.4 Hz, 1H), 3.60 (td, *J* = 10.5, 4.5 Hz, 1H), 3.05 – 3.00 (m, 1H), 2.28 – 2.21 (m, 1H), 2.12 – 2.05 (m, 1H), 1.88 (dd, *J* = 9.2, 4.0 Hz, 1H), 1.76 – 1.69 (m, 2H), 1.61 – 1.38 (m, 4H), 1.38 – 1.15 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.9, 128.6, 128.0, 127.9, 73.6, 71.9, 71.0, 70.5, 69.6, 69.4, 50.9, 32.0, 30.4, 30.2, 29.4, 27.3, 26.8, 23.7, 22.8, 14.3. HRMS: $[M+H]^+$ calculated for $[C_{22}H_{36}NO_3]^+$: 362.26897, found 362.26870.

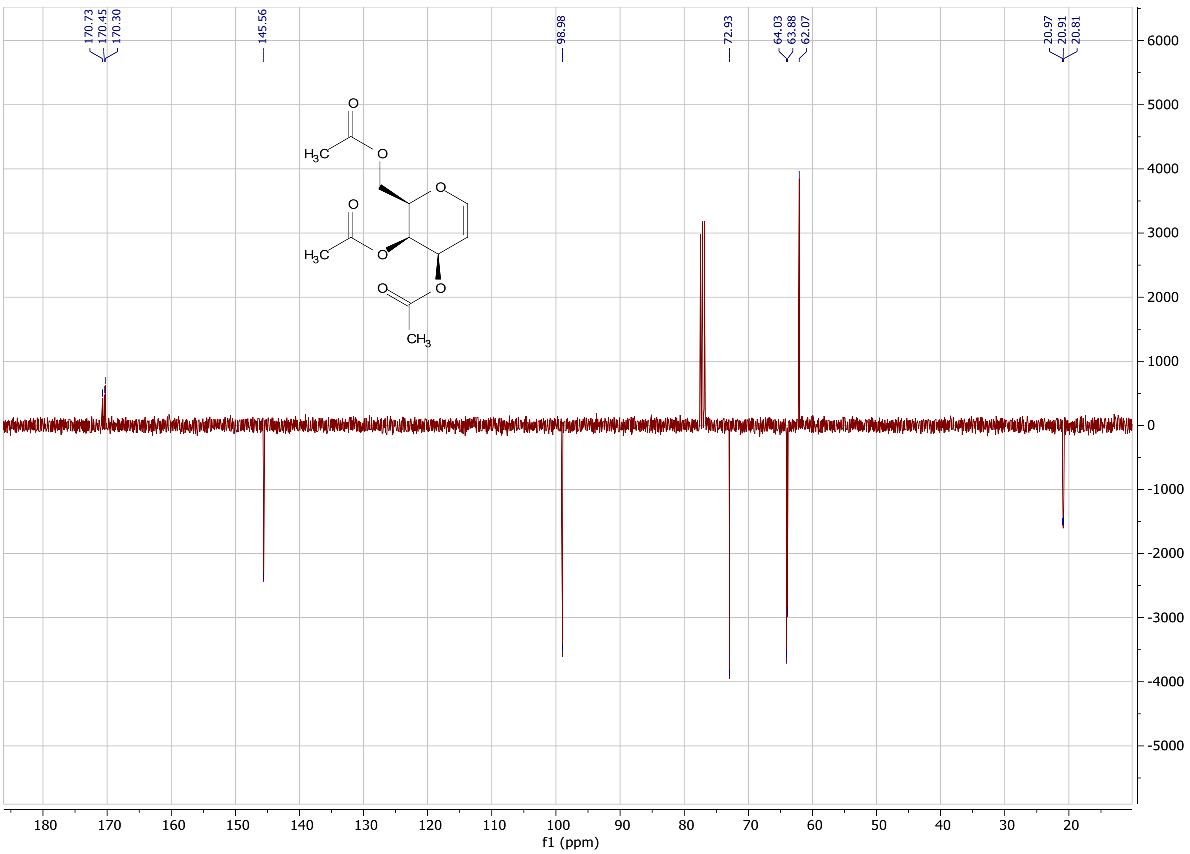
Compound 5: Compound **43** (7.2 mg, 20 µmol) was dissolved in dioxane/H_2O (1: 1, 1.0 mL) and HCl (1 M, 40 µL, 40 µmol, 2 eq.) was added. The solution was purged with argon for 15 minutes followed by the addition of palladium on carbon (10% wt. loading, catalytic) and the mixture was purged with argon for another 15 minutes. The reaction was purged with hydrogen for 15 minutes and stirred under hydrogen atmosphere overnight at room temperature. The mixture was filtered over a Whatman filter and concentrated *in vacuo*. Purification by silica gel column chromatography (2% → 10% H_2O/MeCN) gave compound **5** (4.9 mg, 18 μmol) in 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (dd, *J* = 7.8, 5.5 Hz, 1H), 4.45 – 4.41 (m, 1H), 3.99 (td, *J* = 11.0, 4.5 Hz, 1H), 3.56 (dd, *J* = 11.9, 3.2 Hz, 1H), 3.30 – 3.26 (m, 1H), 2.88 (dd, *J* = 10.1, 3.0 Hz, 1H), 2.80 (td, *J* = 12.9, 3.3 Hz, 1H), 2.17 (dq, *J* = 11.8, 3.4 Hz, 1H), 1.99 (d, *J* = 15.1 Hz, 1H), 1.91 (dp, *J* = 16.2, 5.3 Hz, 1H), 1.85 – 1.71 (m, 1H), 1.71 – 1.63 (m, 1H), 1.58 (tt, *J* = 11.8, 5.4 Hz, 1H), 1.54 – 1.44 (m, 1H), 1.44 – 1.22 (m, 10H), 0.97 – 0.85 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 73.2, 71.5, 69.3, 68.9, 64.7, 51.6, 49.5, 49.3, 49.2, 49.0, 48.8, 48.7, 48.5, 32.9, 32.9, 30.7, 30.2, 27.4, 26.3, 23.7, 22.2, 14.4. HRMS: $[M+H]^+$ calculated for $[C_{15}H_{30}NO_3]^+$: 272.22202, found 272.22180.

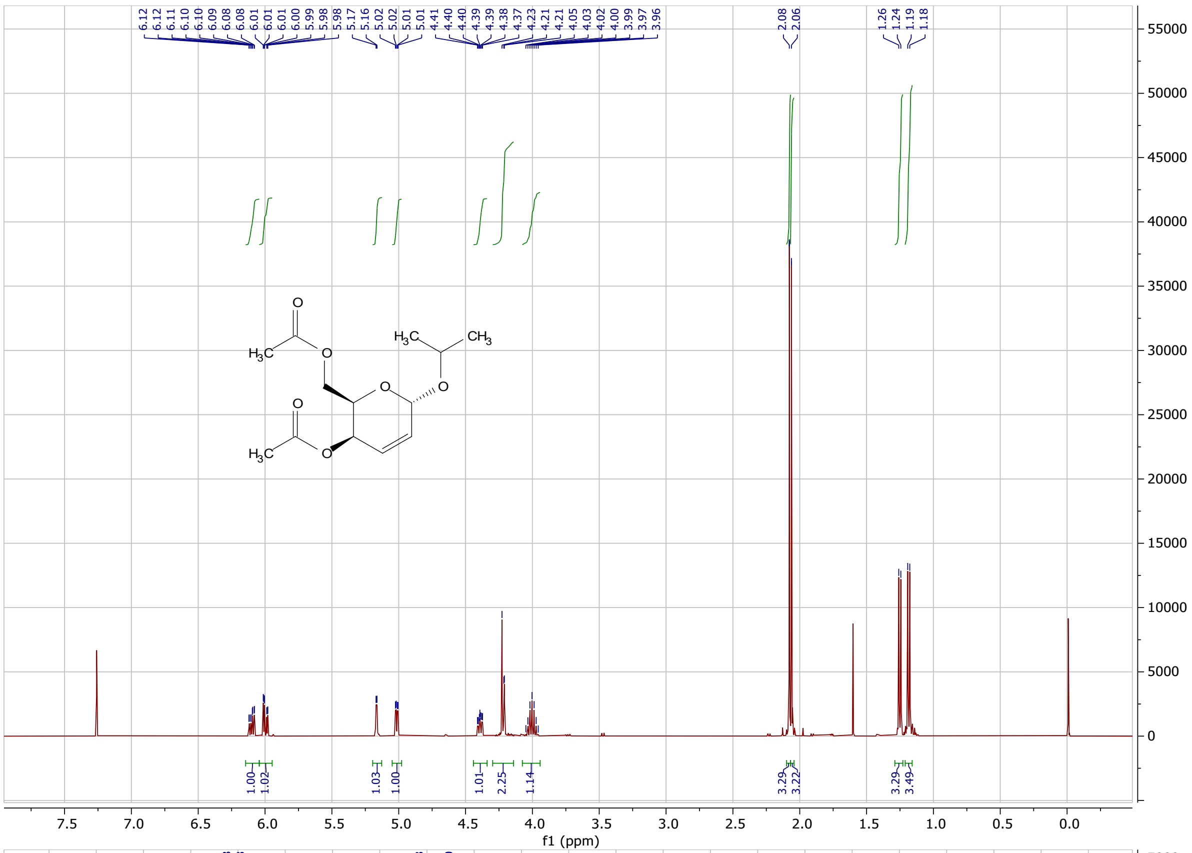
Reference

1. Z. Armstrong, C.-L. Kuo, D. Lahav, B. Liu, R. Johnson, T. J. M. Beenakker, C. de Boer, C.-S. Wong, E. R. van Rijssel, M. F. Debets, B. I. Florea, C. Hissink, R. G. Boot, P. P. Geurink, H. Ovaa, M. van der Stelt, G. M. van der Marel, J. D. C. Codée, J. M. F. G. Aerts, L. Wu, H. S. Overkleeft and G. J. Davies, *J. Am. Chem. Soc.*, 2020, **142**, 13021-13029.

NMR Spectra



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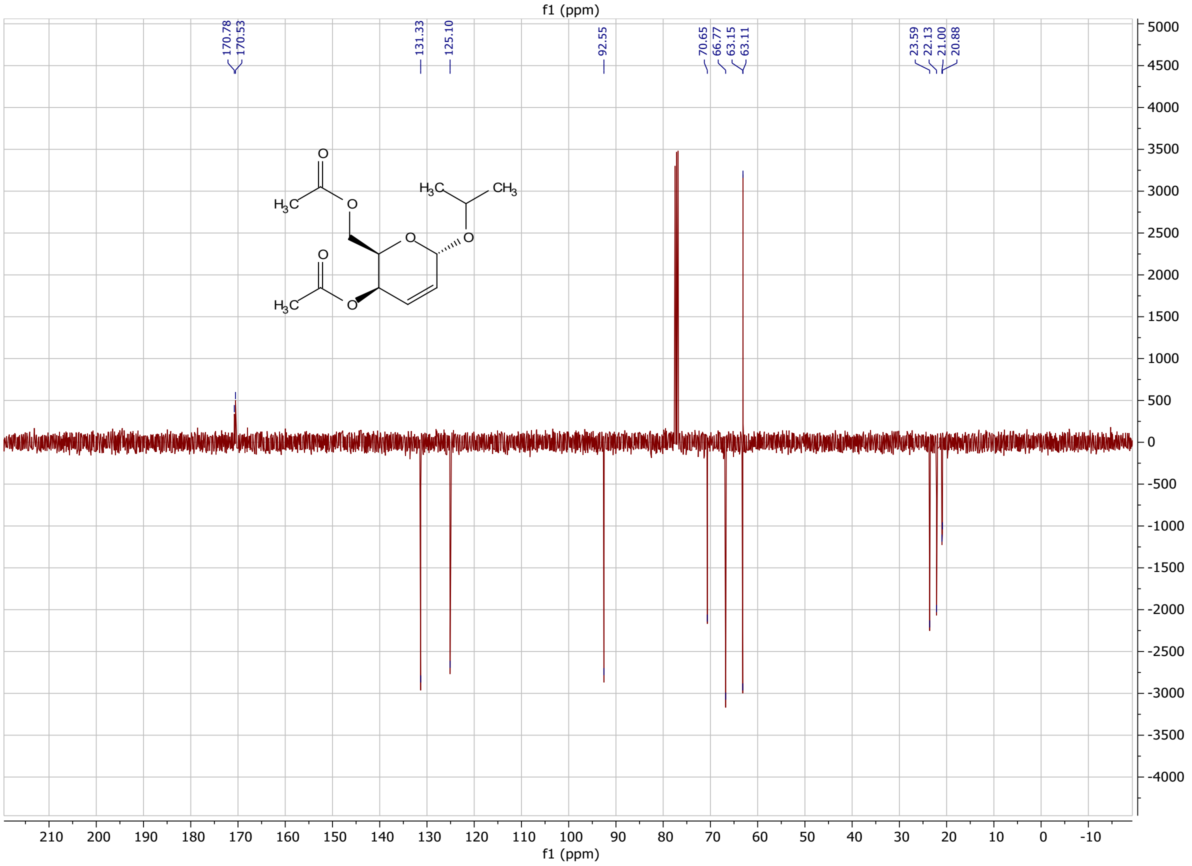
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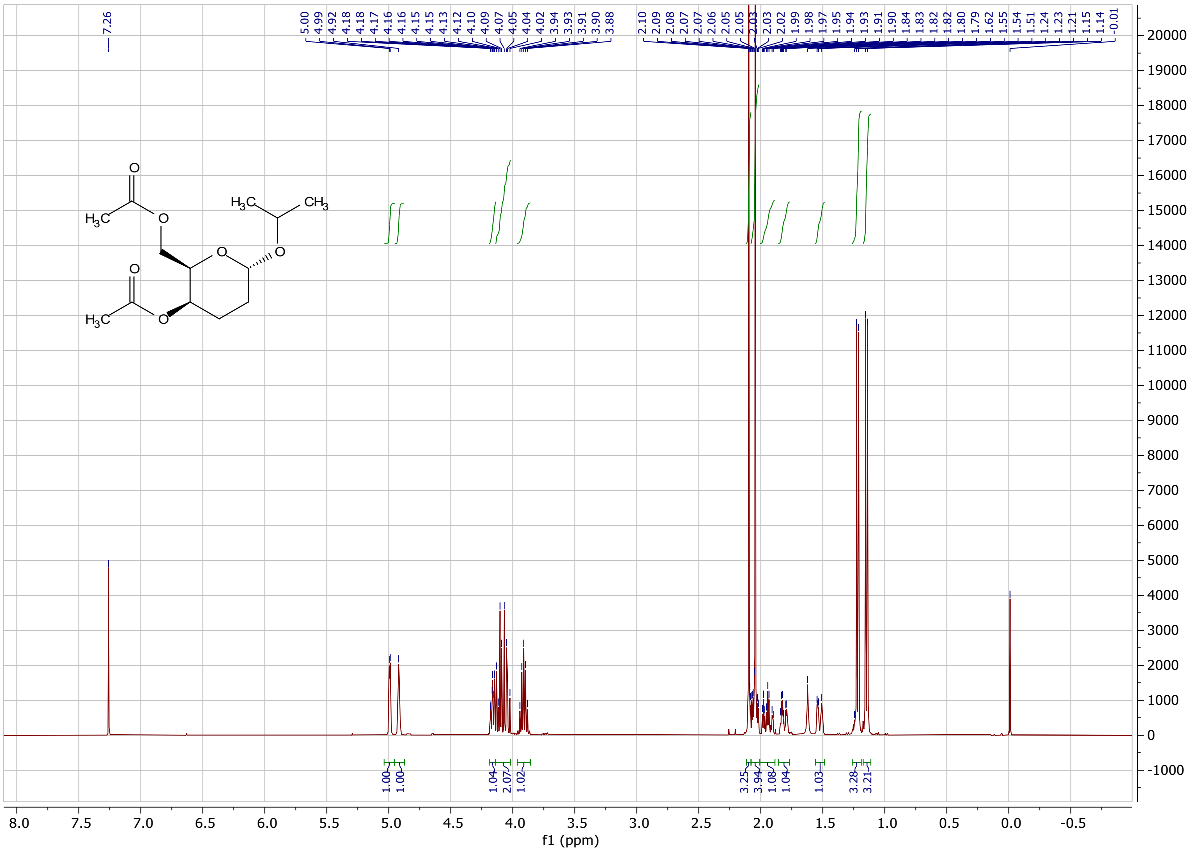

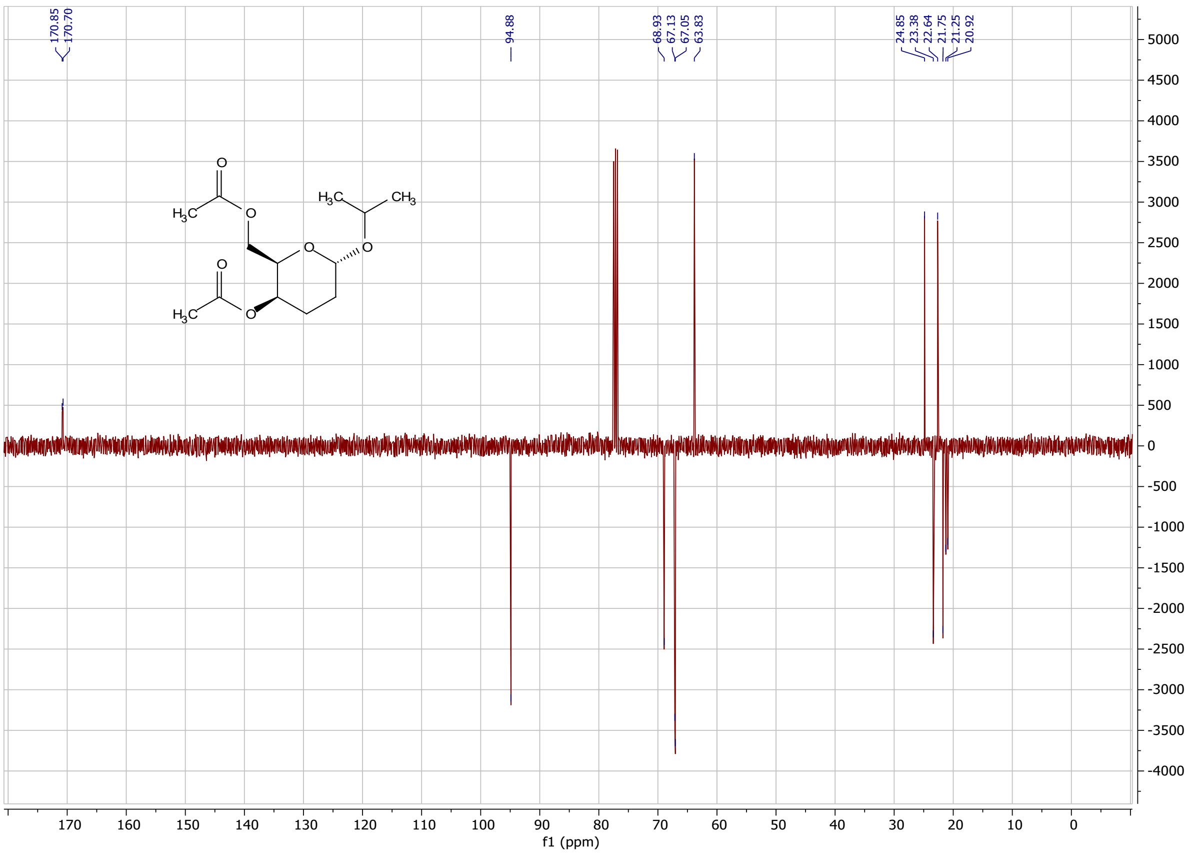

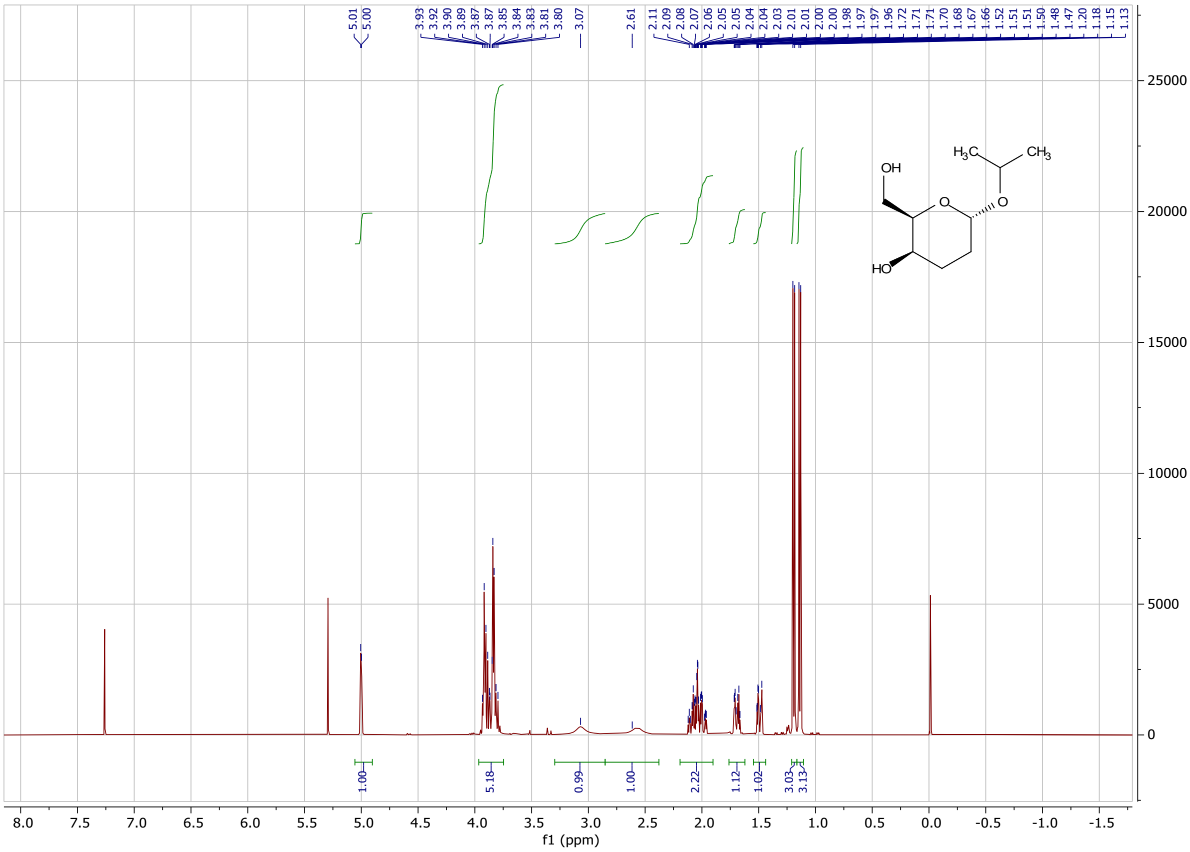
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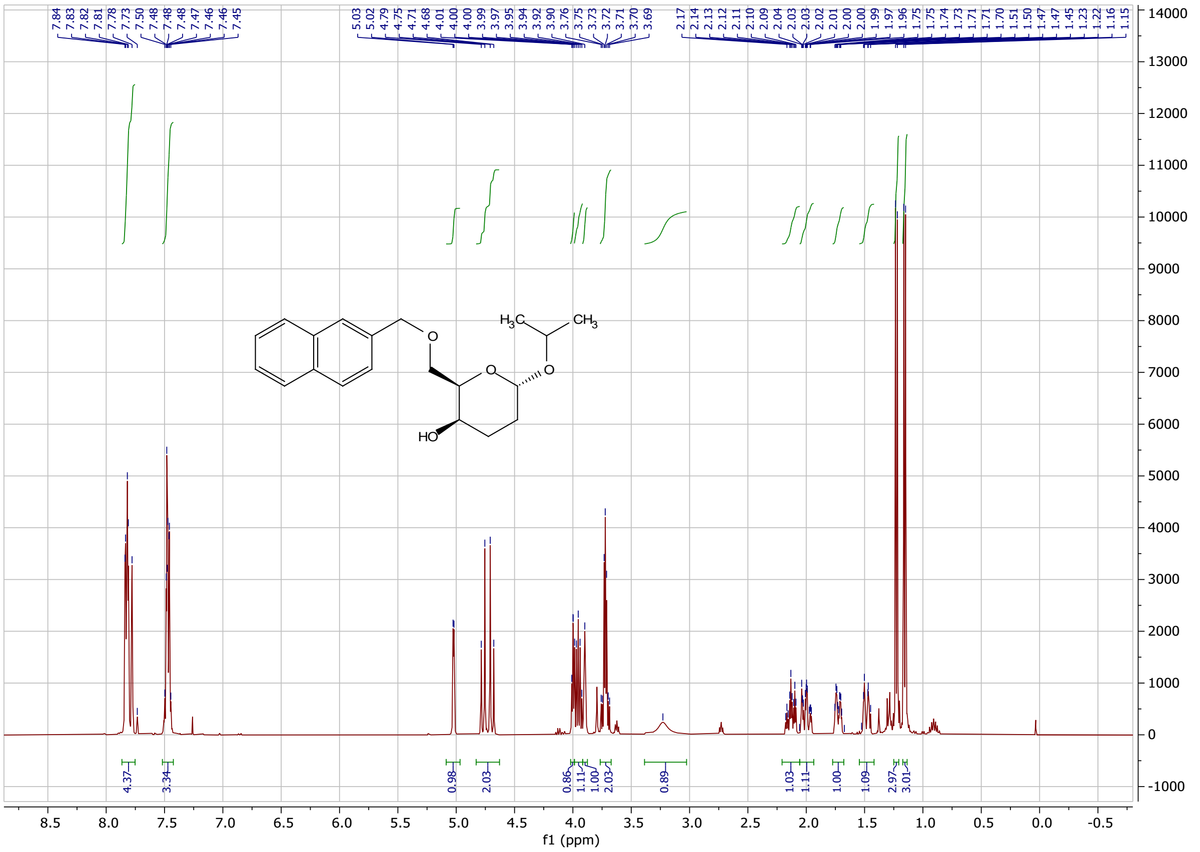

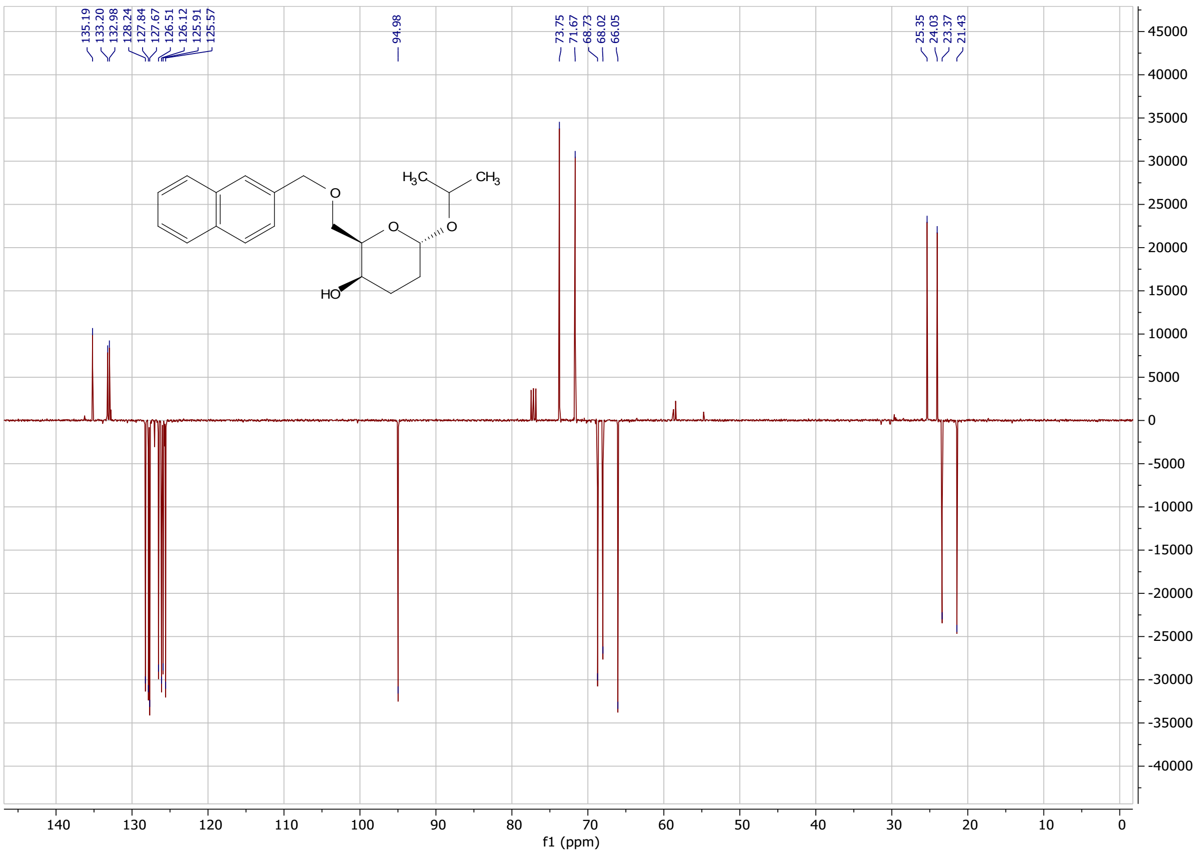

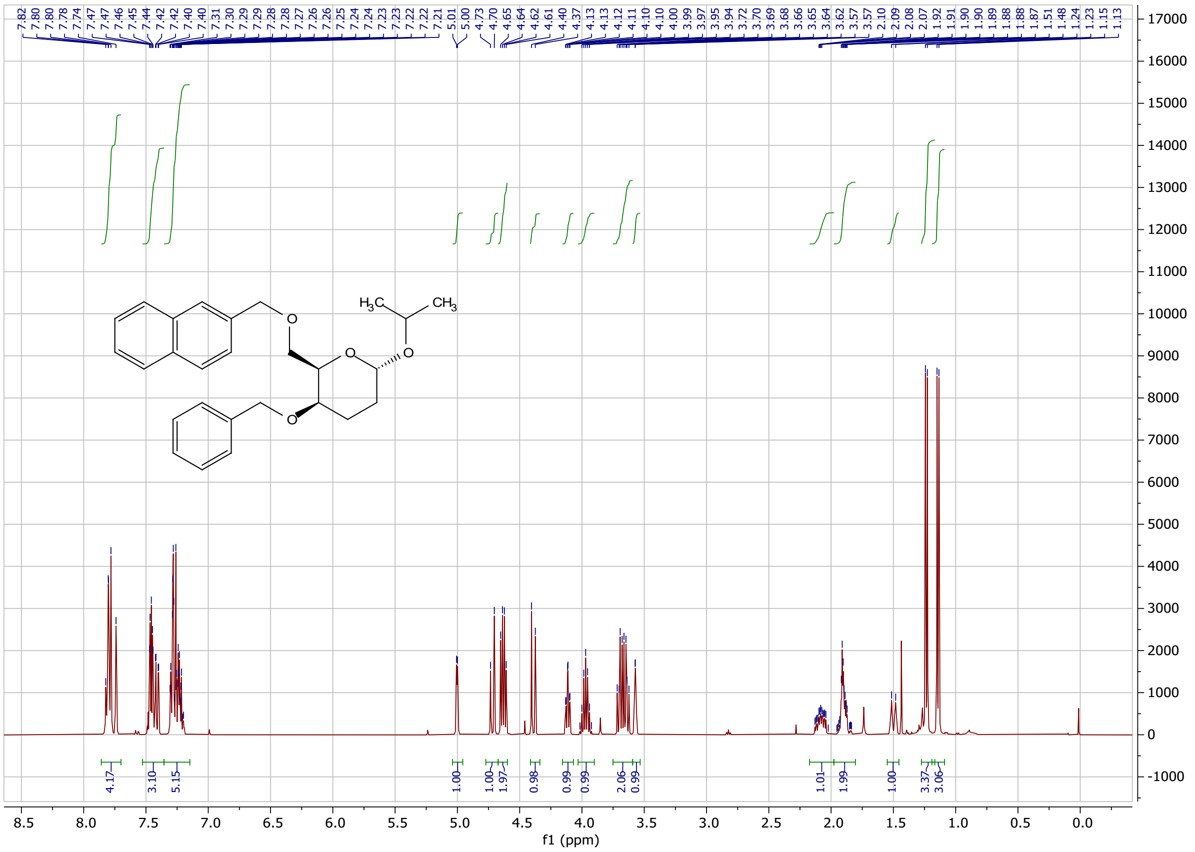

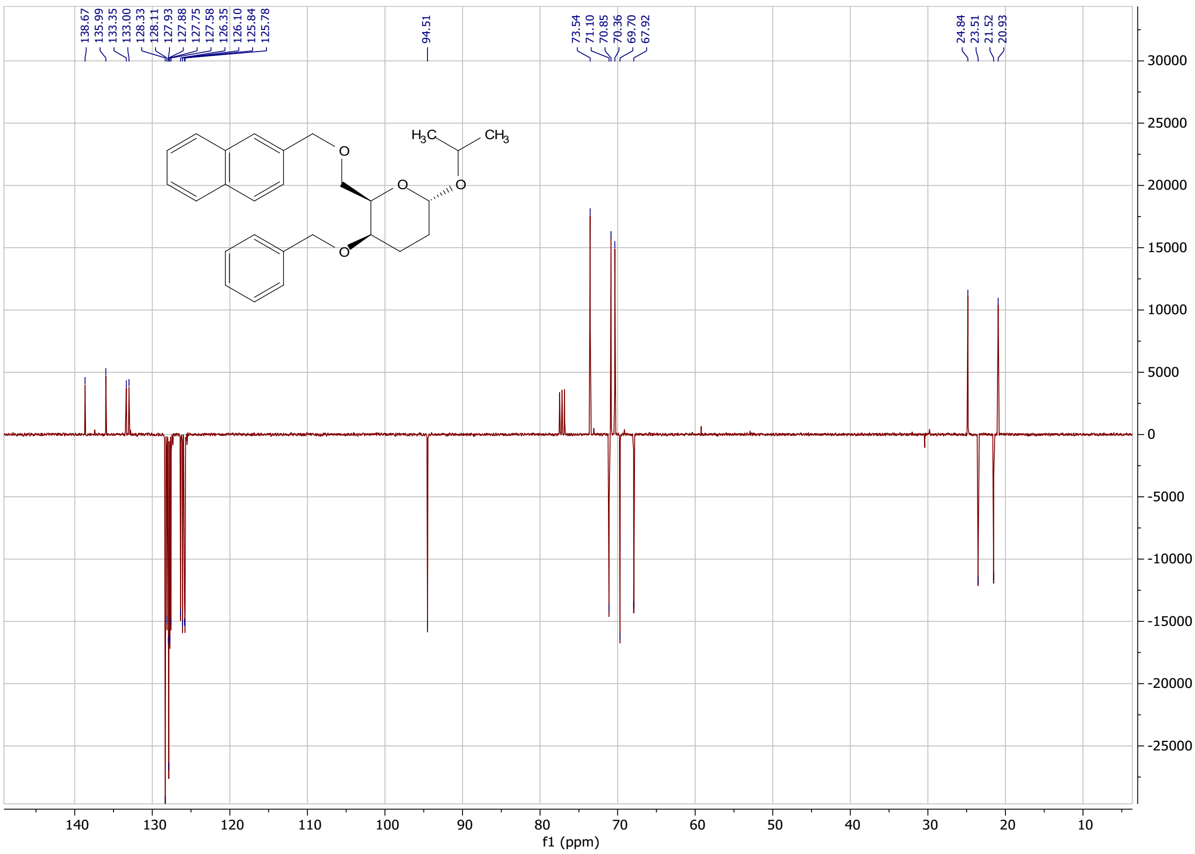

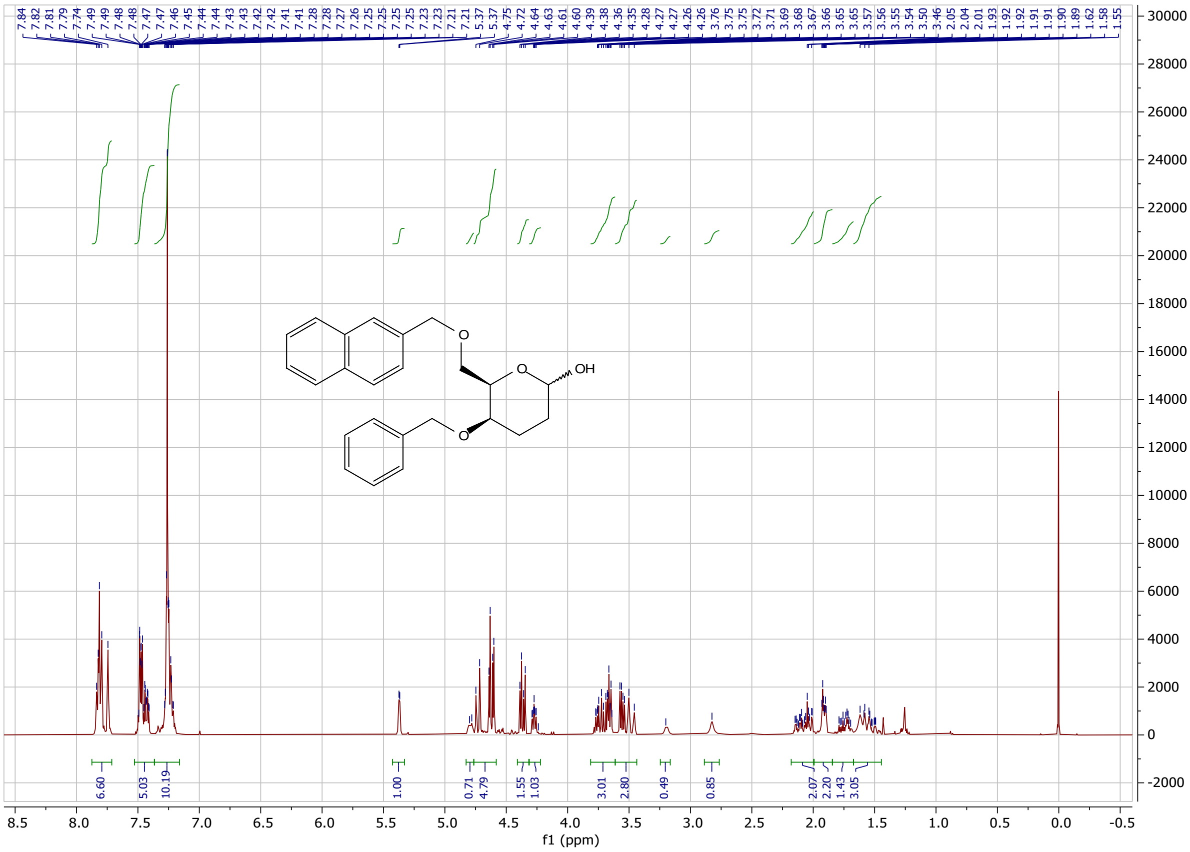

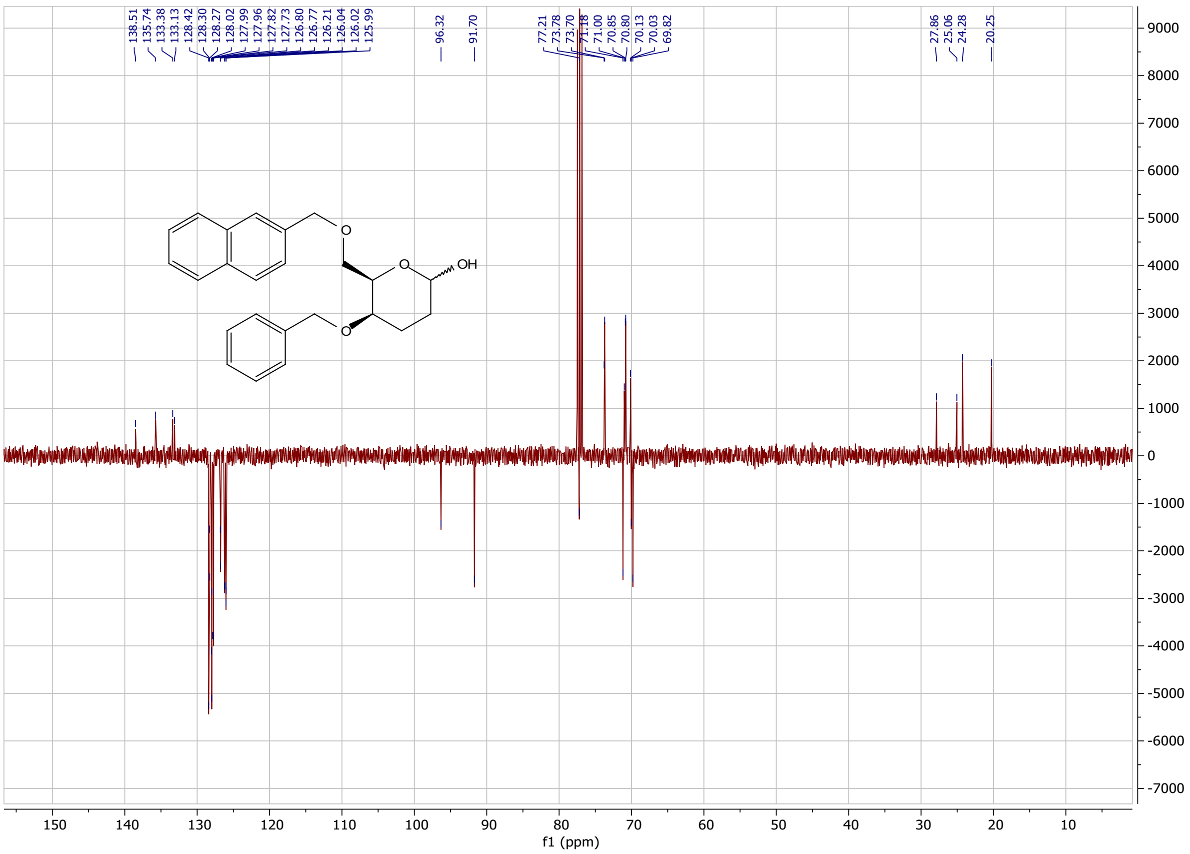

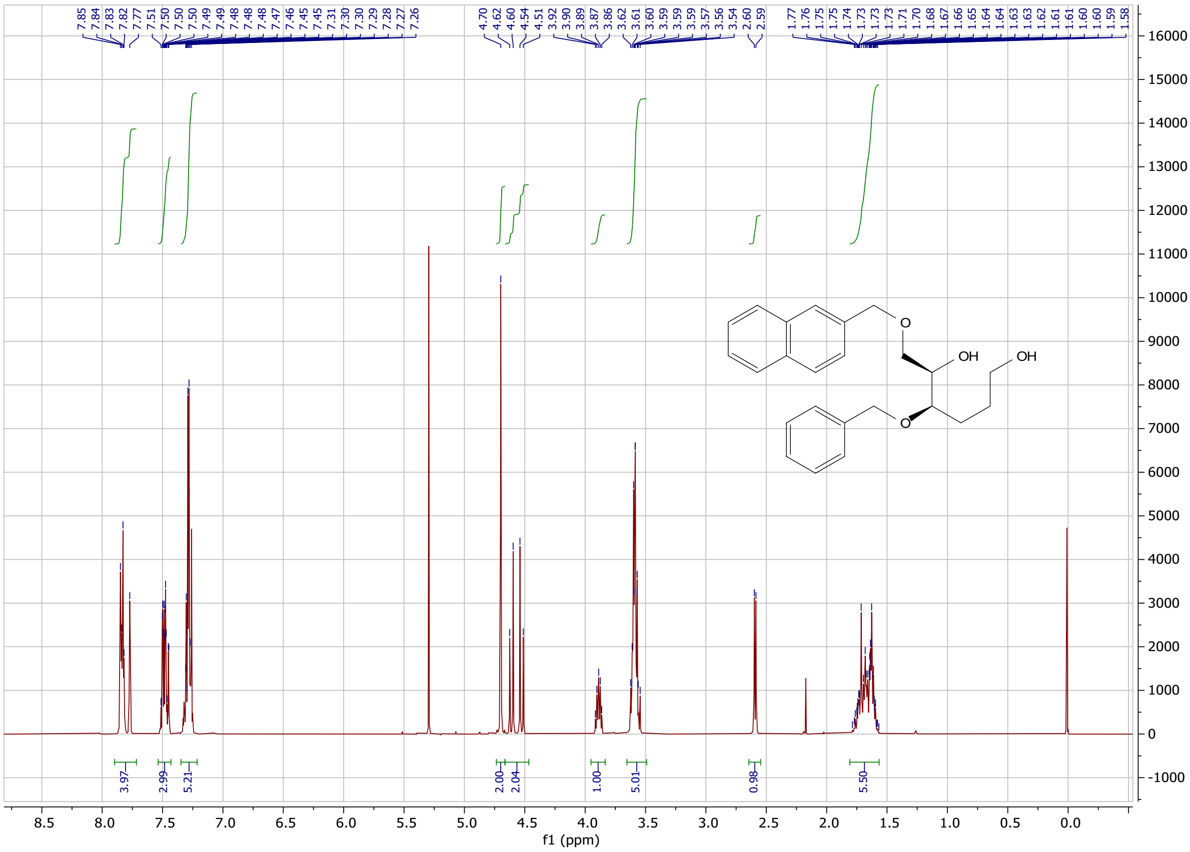
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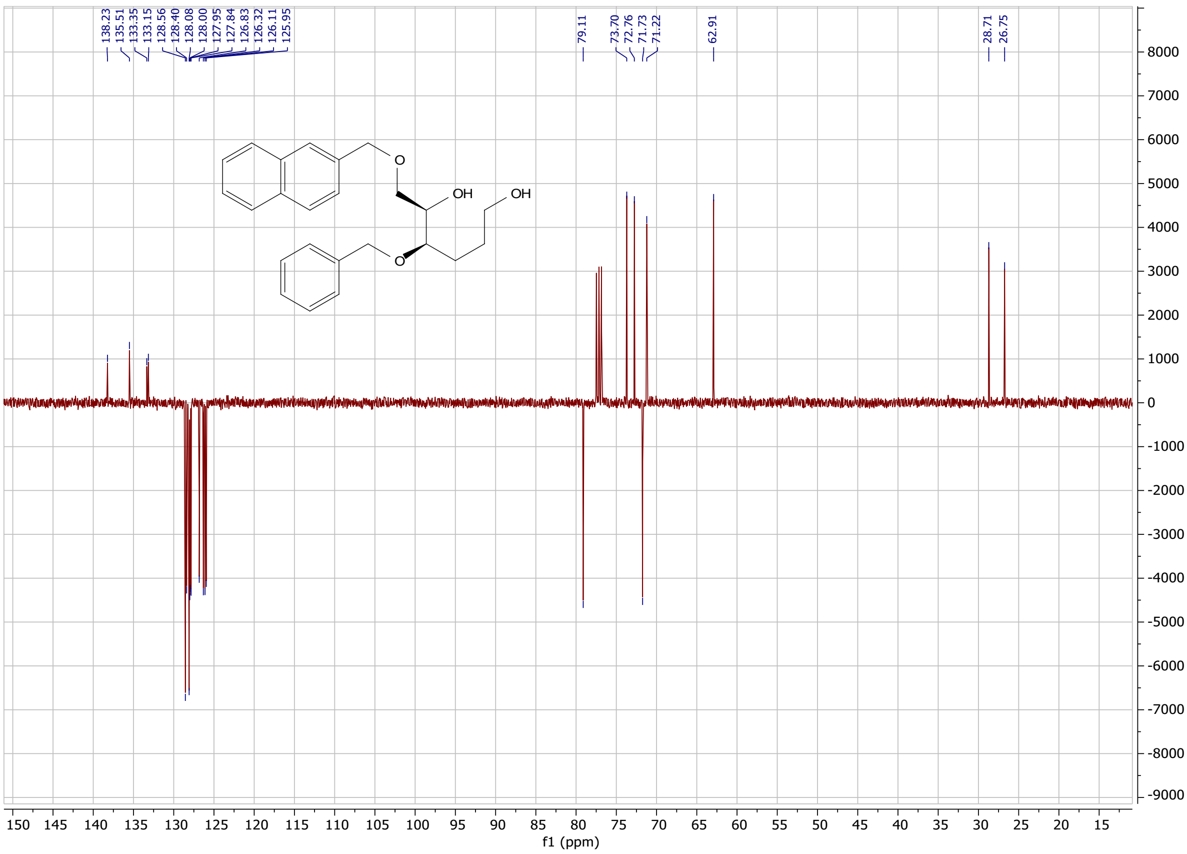
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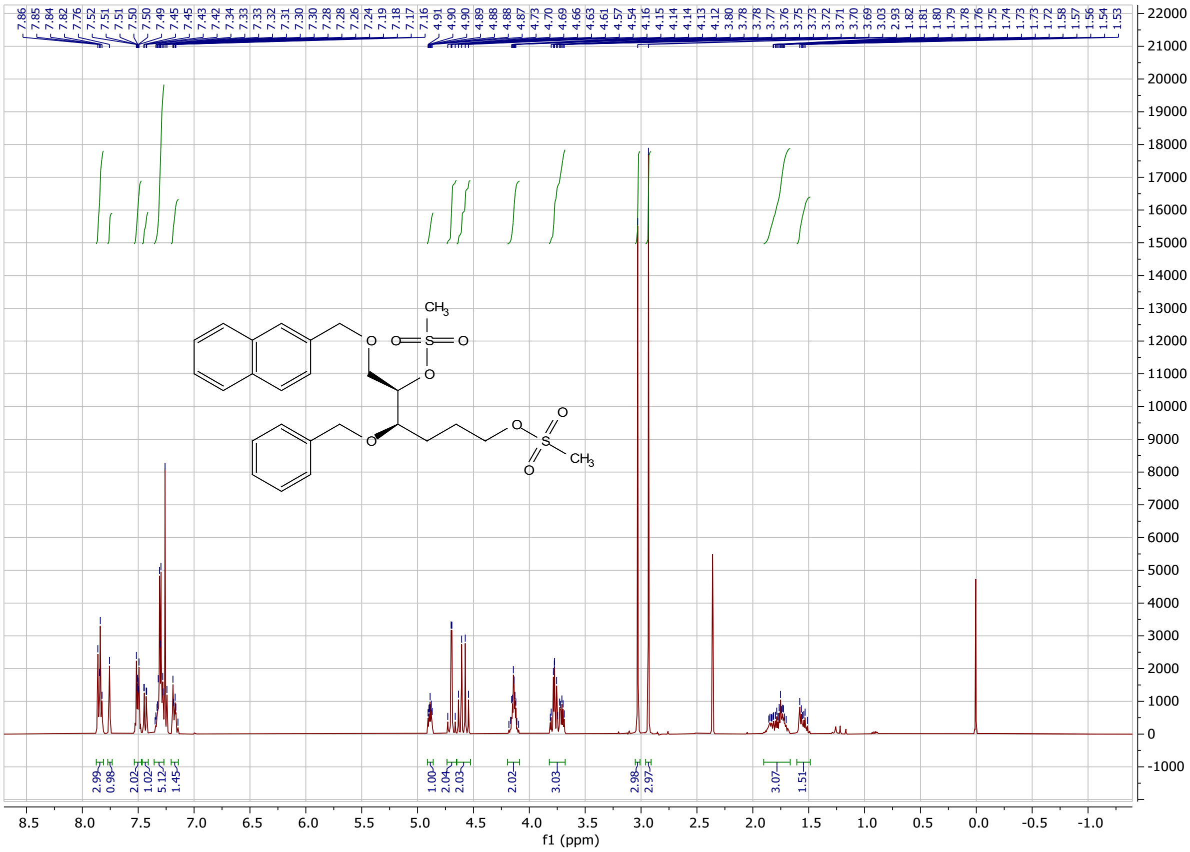

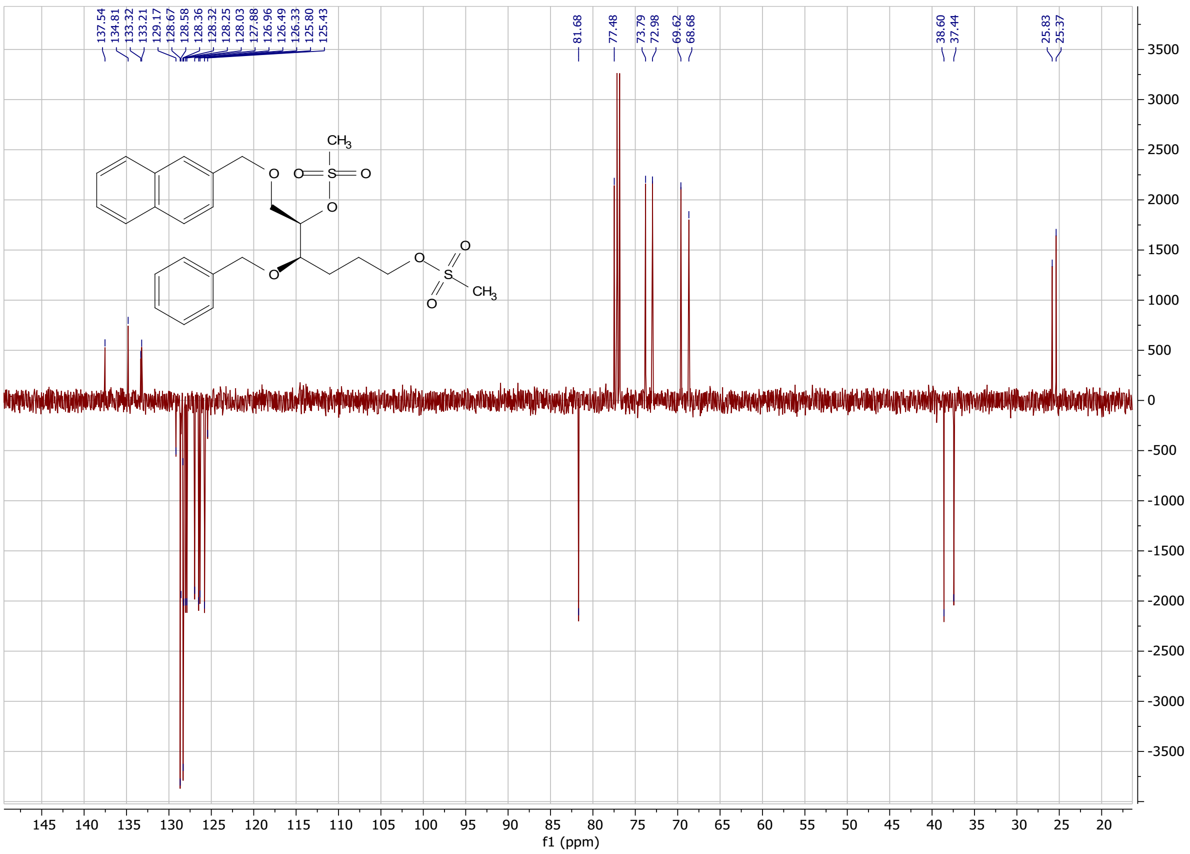

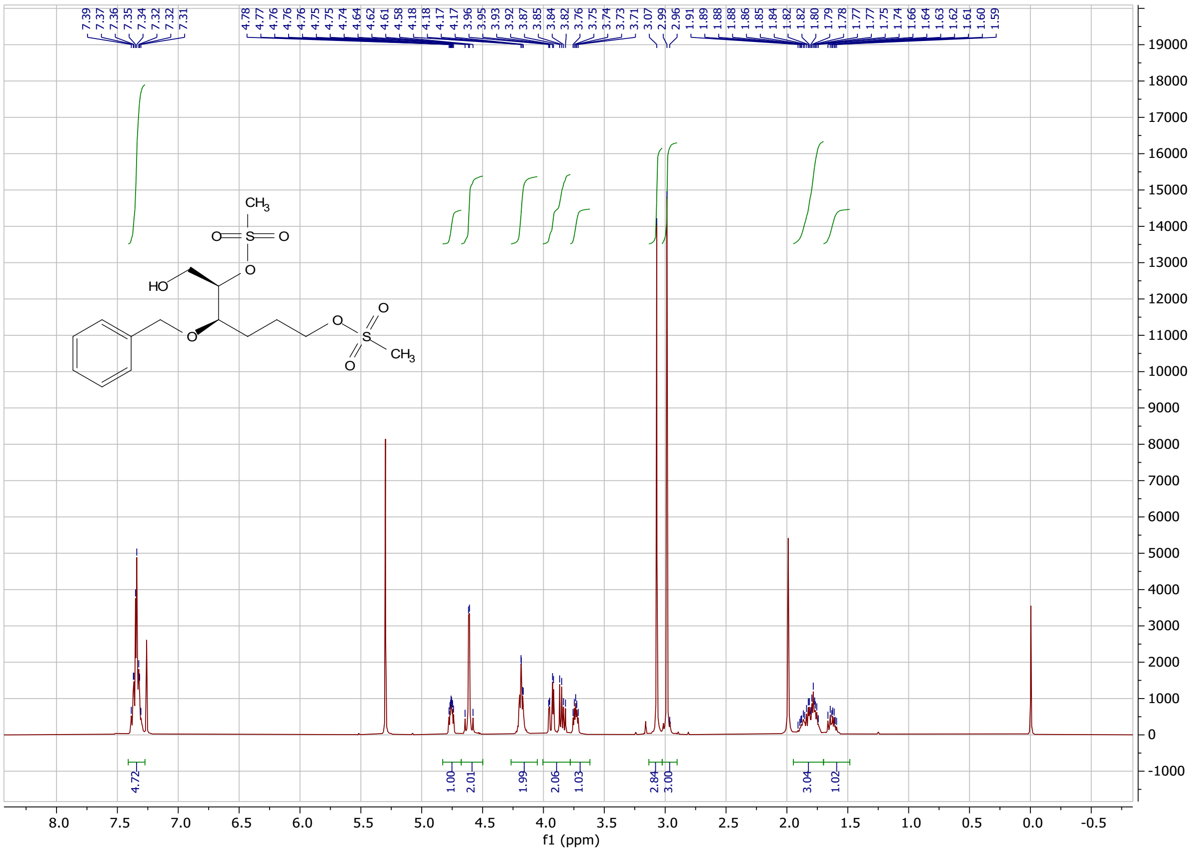
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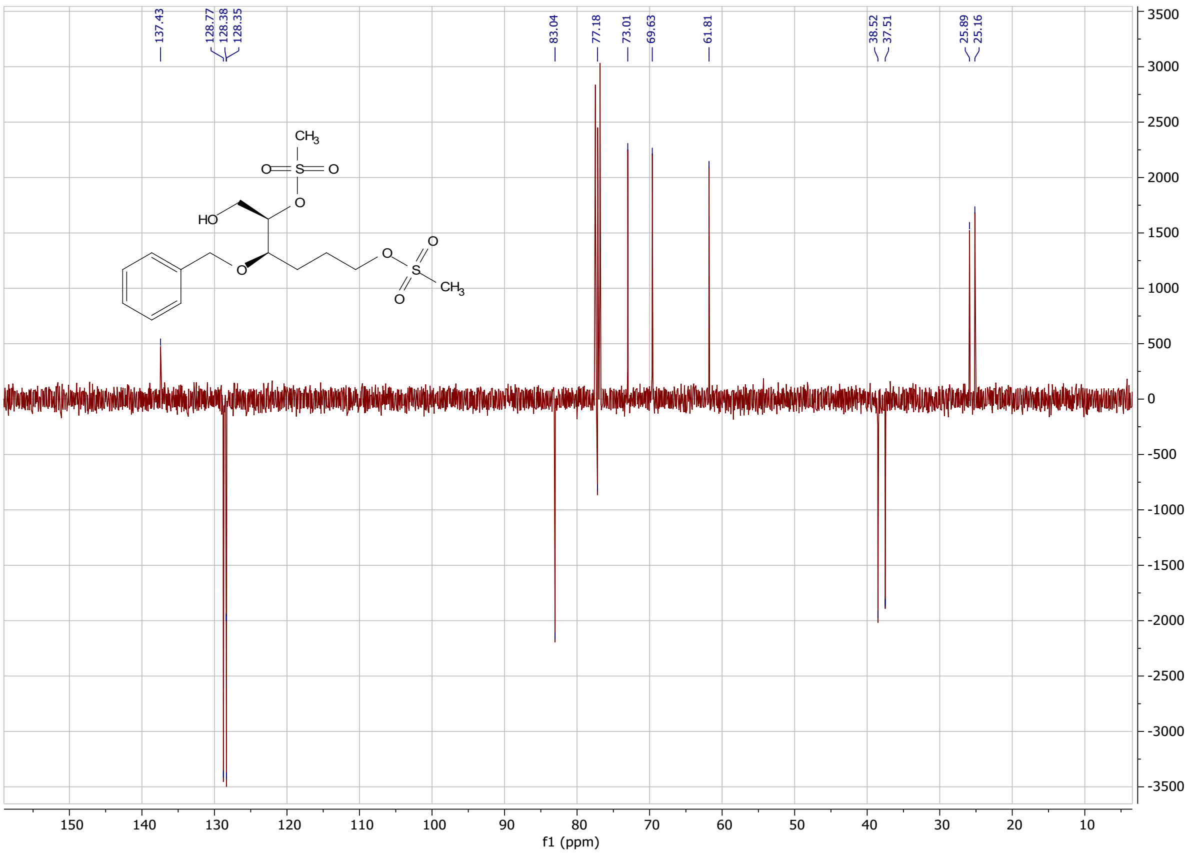
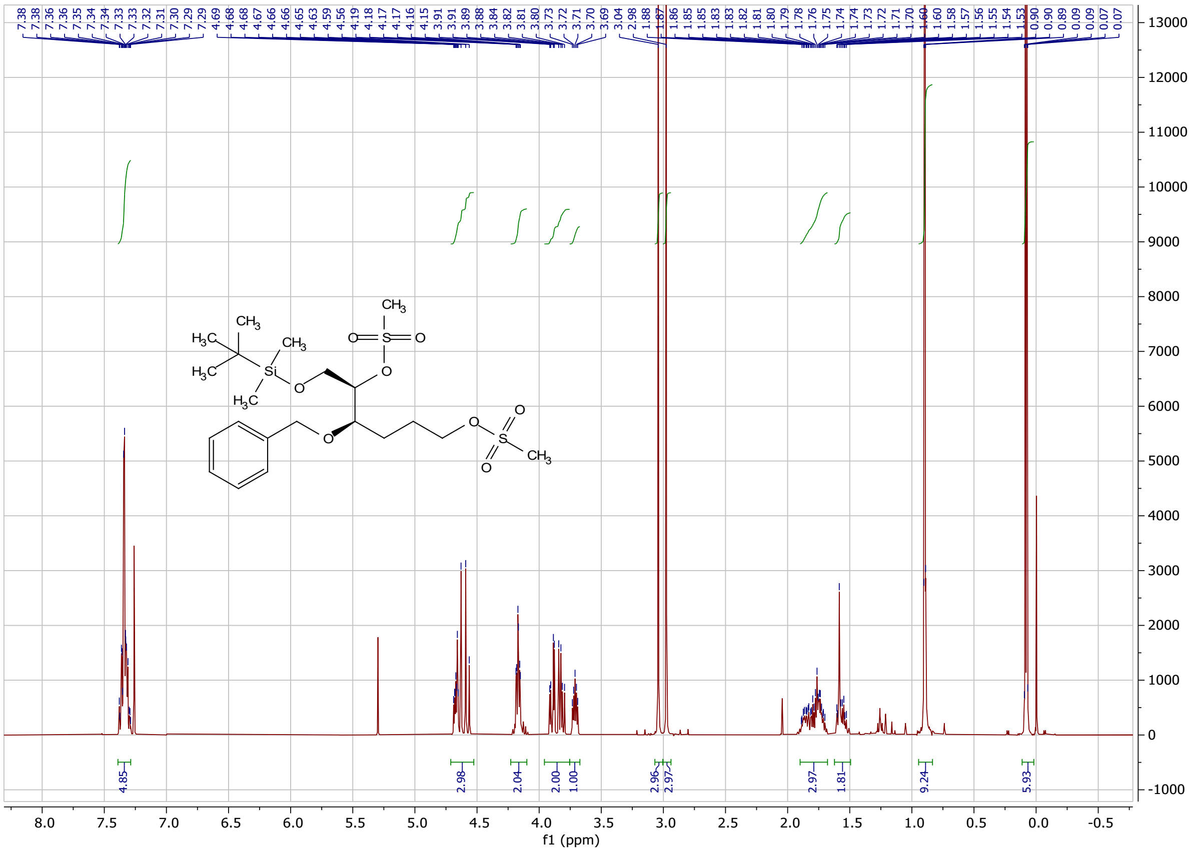
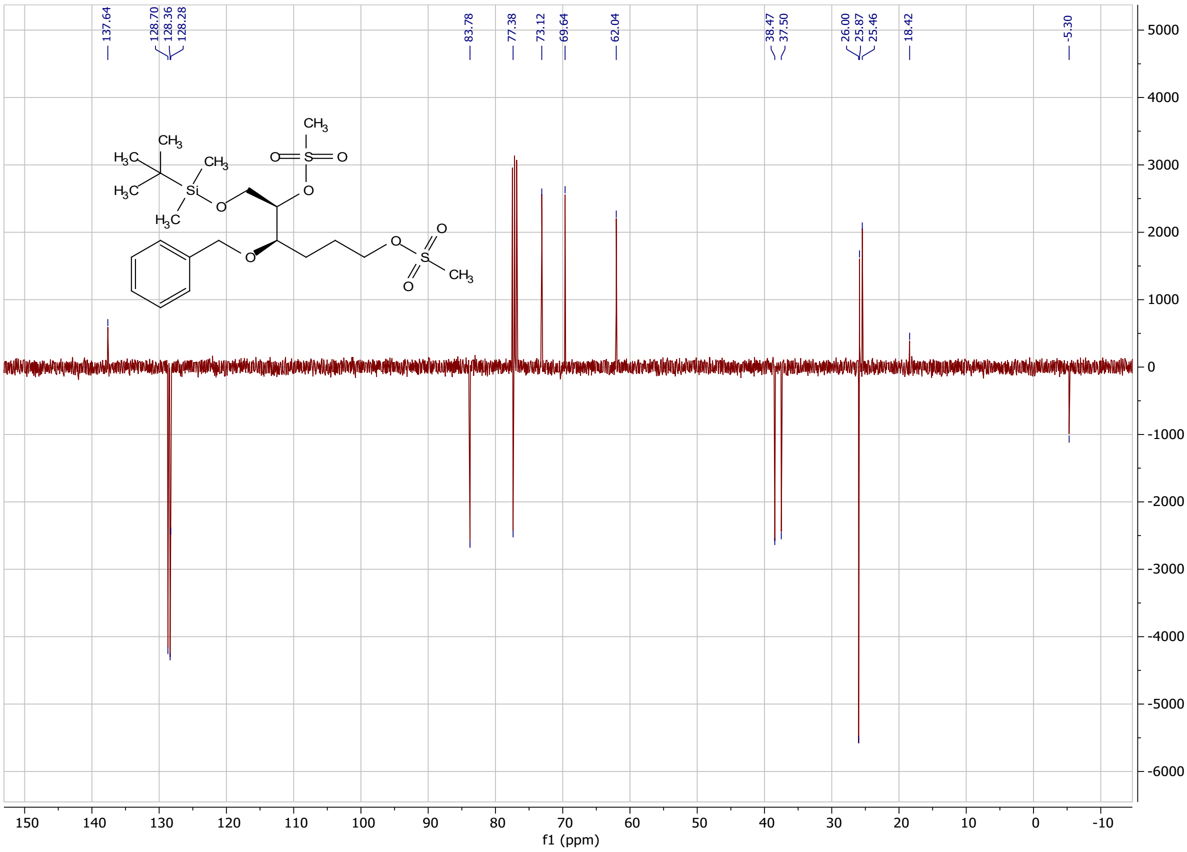
f1 (ppm)

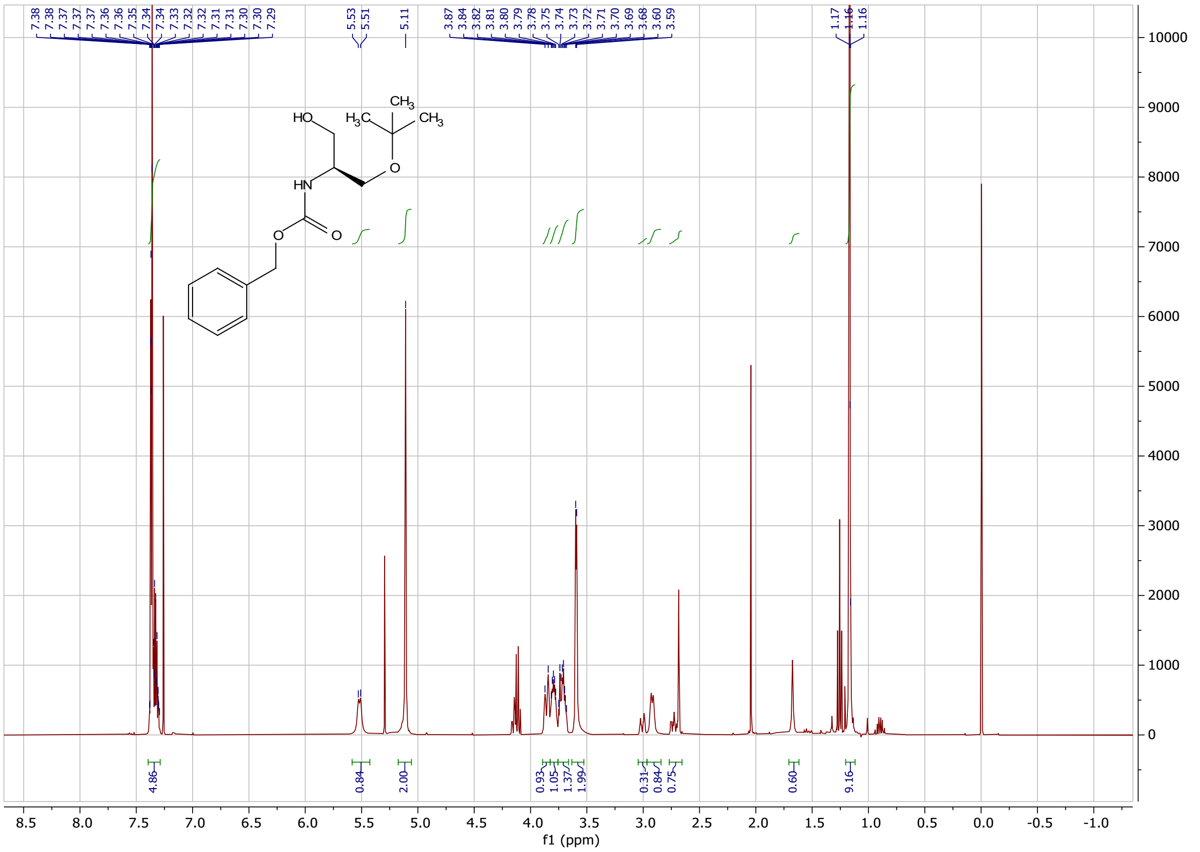

137.43 128.77 128.38 128.35 83.04 77.18 73.01 69.63 61.81 38.52 37.51 25.89 25.16
f1 (ppm)

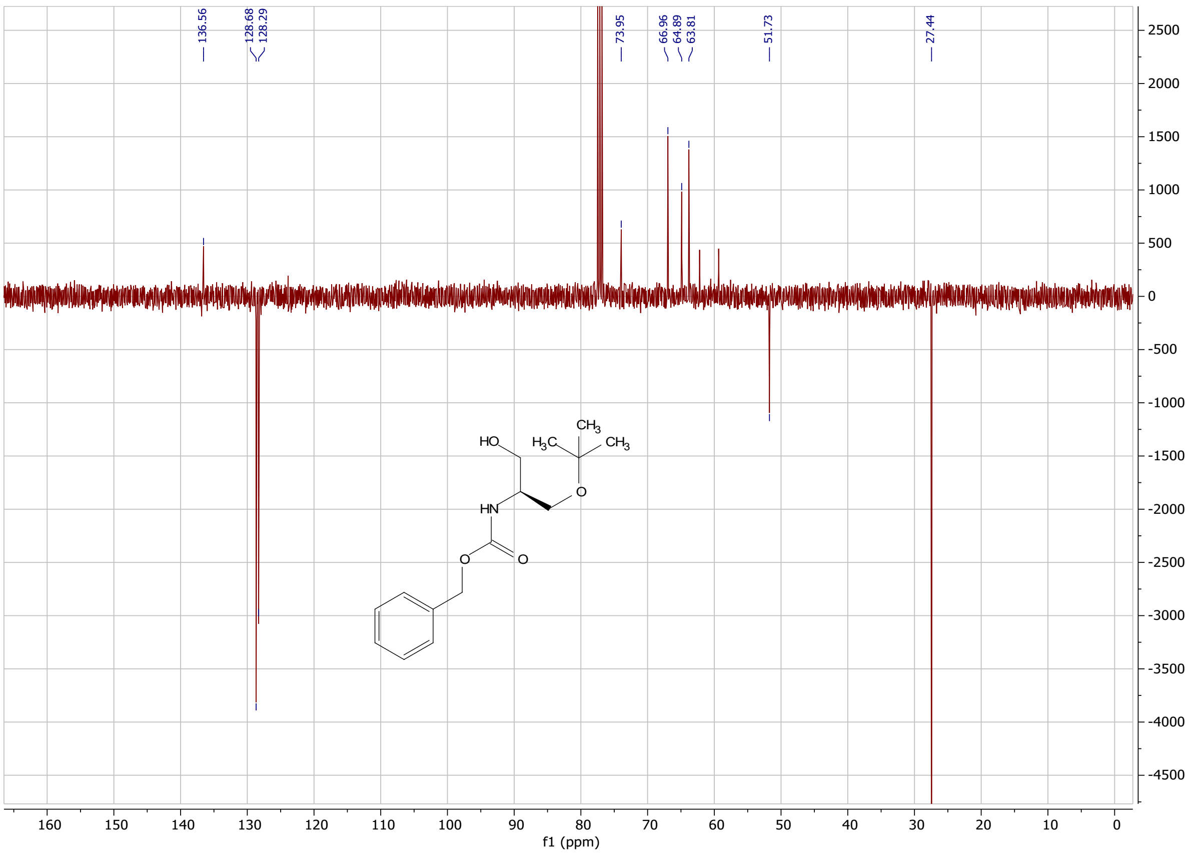


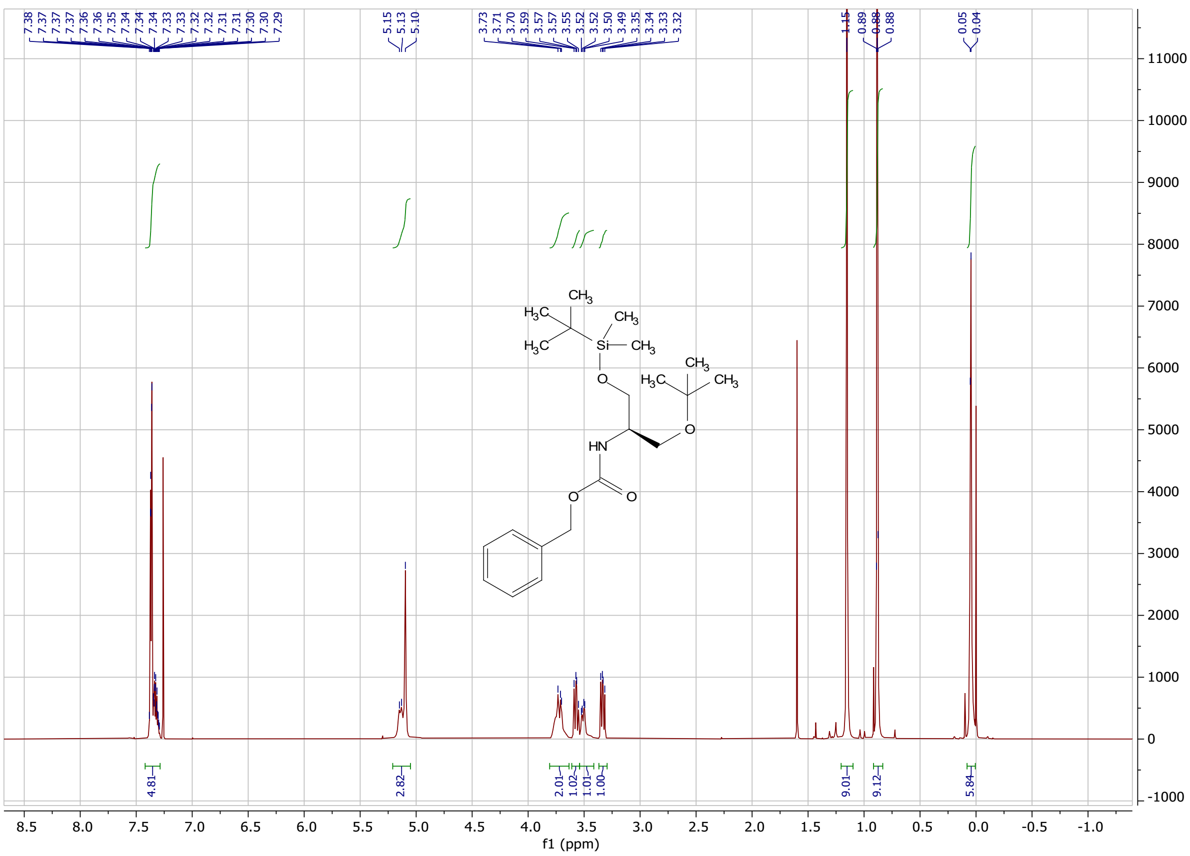
7.38 7.38 7.36 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.30 7.29 7.29 4.69 4.68 4.67 4.66 4.66 4.65 4.63 4.59 4.56 4.19 4.18 4.17 4.17 4.16 4.15 3.91 3.91 3.89 3.88 3.84 3.82 3.81 3.80 3.73 3.72 3.71 3.70 3.69 3.04 2.98 1.88 1.87 1.86 1.85 1.85 1.83 1.83 1.82 1.81 1.80 1.79 1.78 1.76 1.75 1.74 1.74 1.73 1.72 1.71 1.70 1.60 1.60 1.58 1.57 1.56 1.55 1.55 1.54 1.53 0.90 0.90 0.89 0.09 0.09 0.07 0.07
4.85 2.98 2.04 2.00 1.00 2.96 2.97 2.97 1.81 9.24 5.93
f1 (ppm)

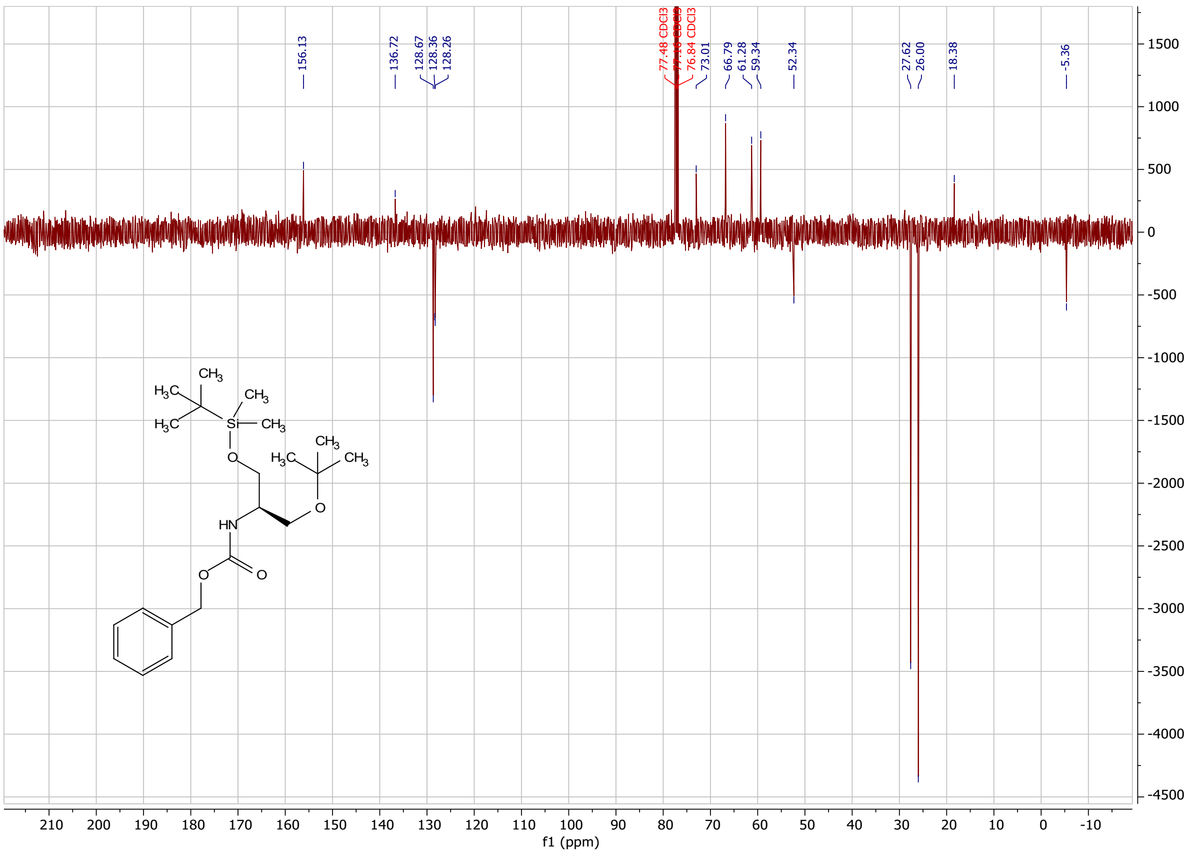


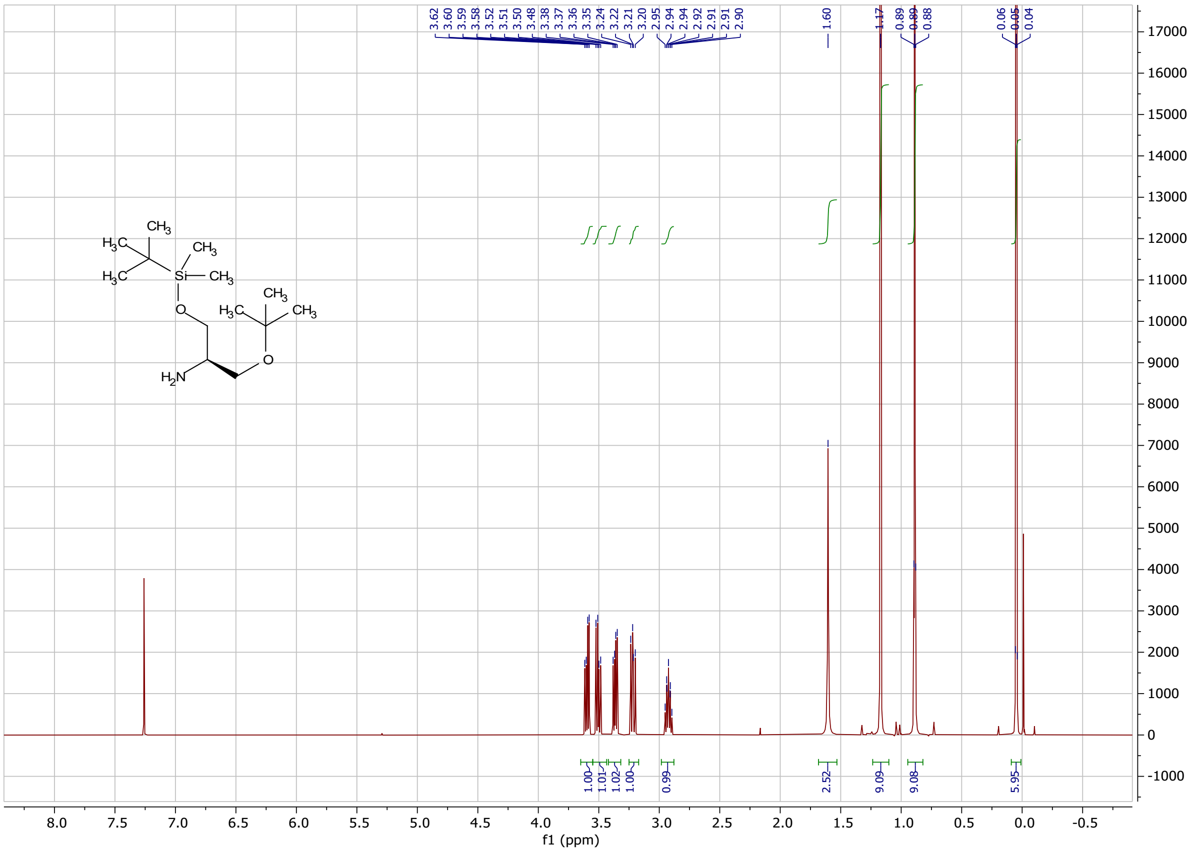
137.64 128.70 128.36 128.28 83.78 77.38 73.12 69.64 62.04 38.47 37.50 26.00 25.87 25.46 18.42 -5.30
f1 (ppm)

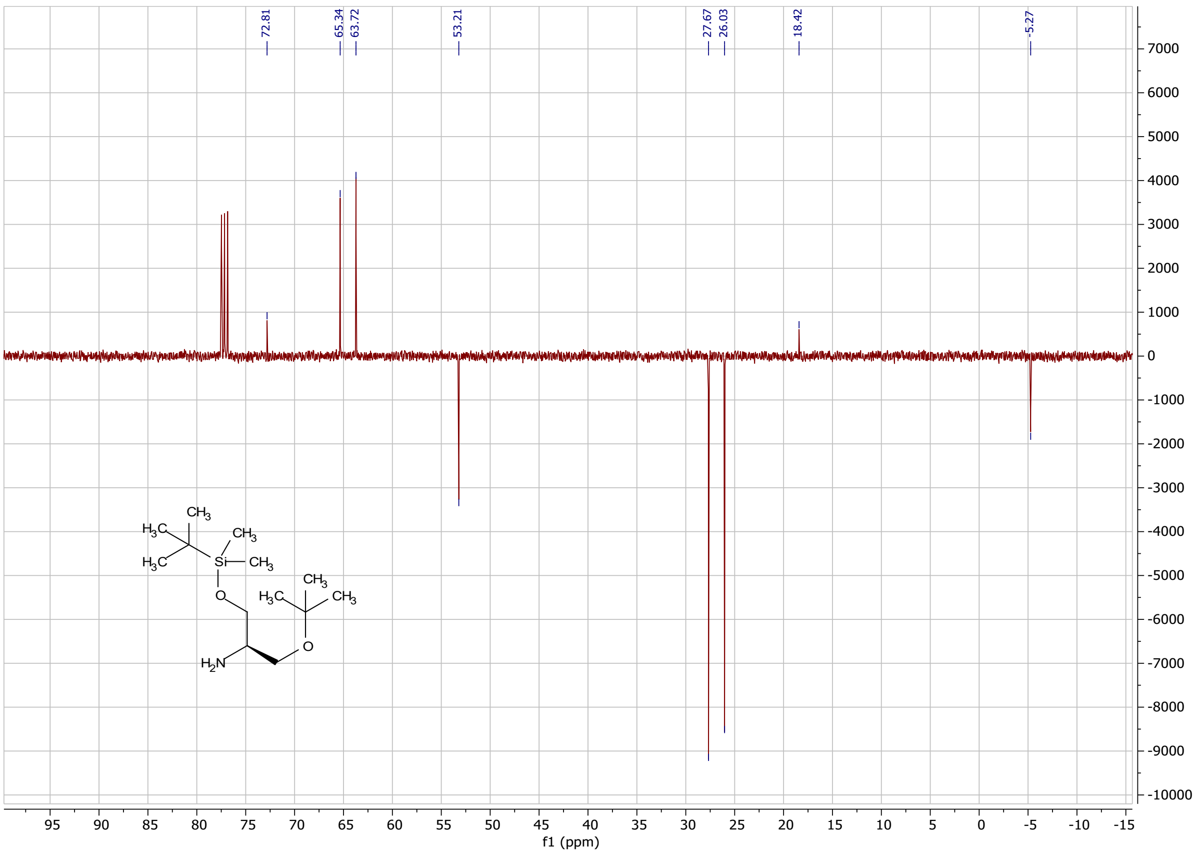


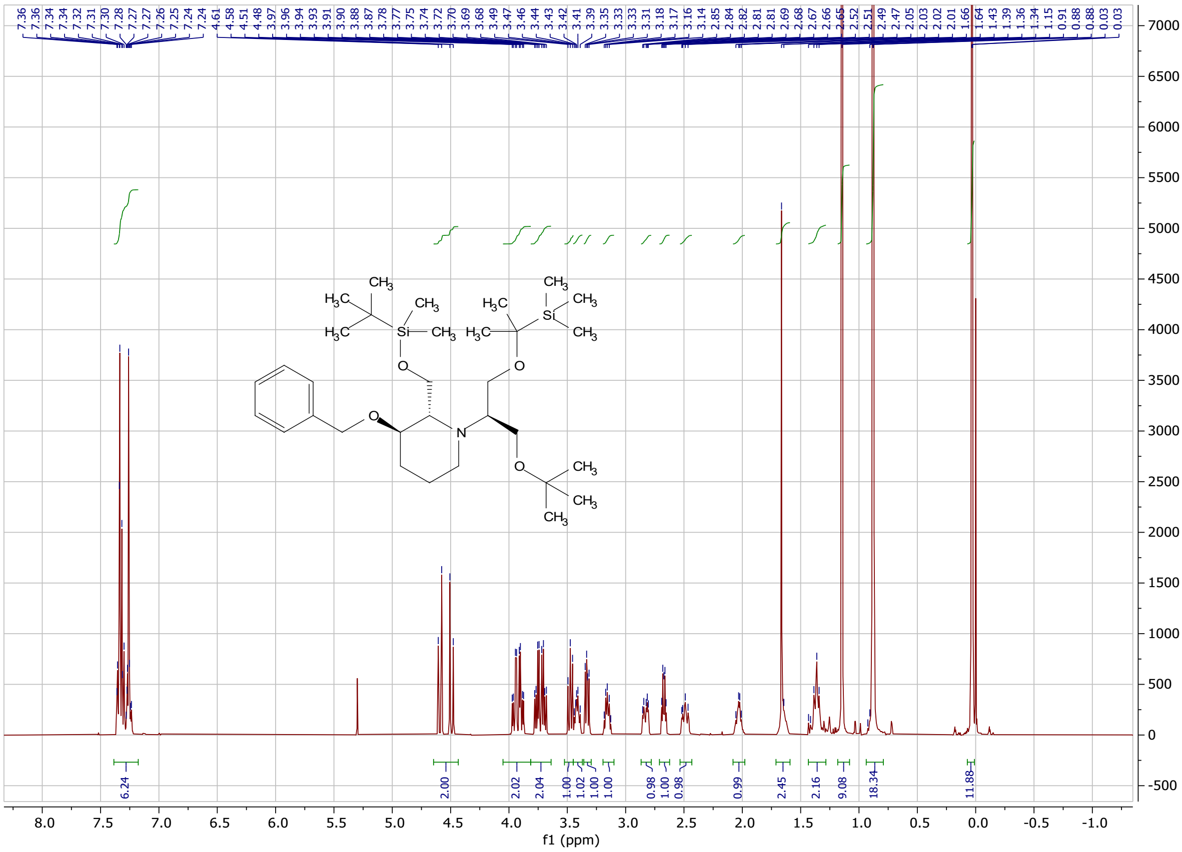


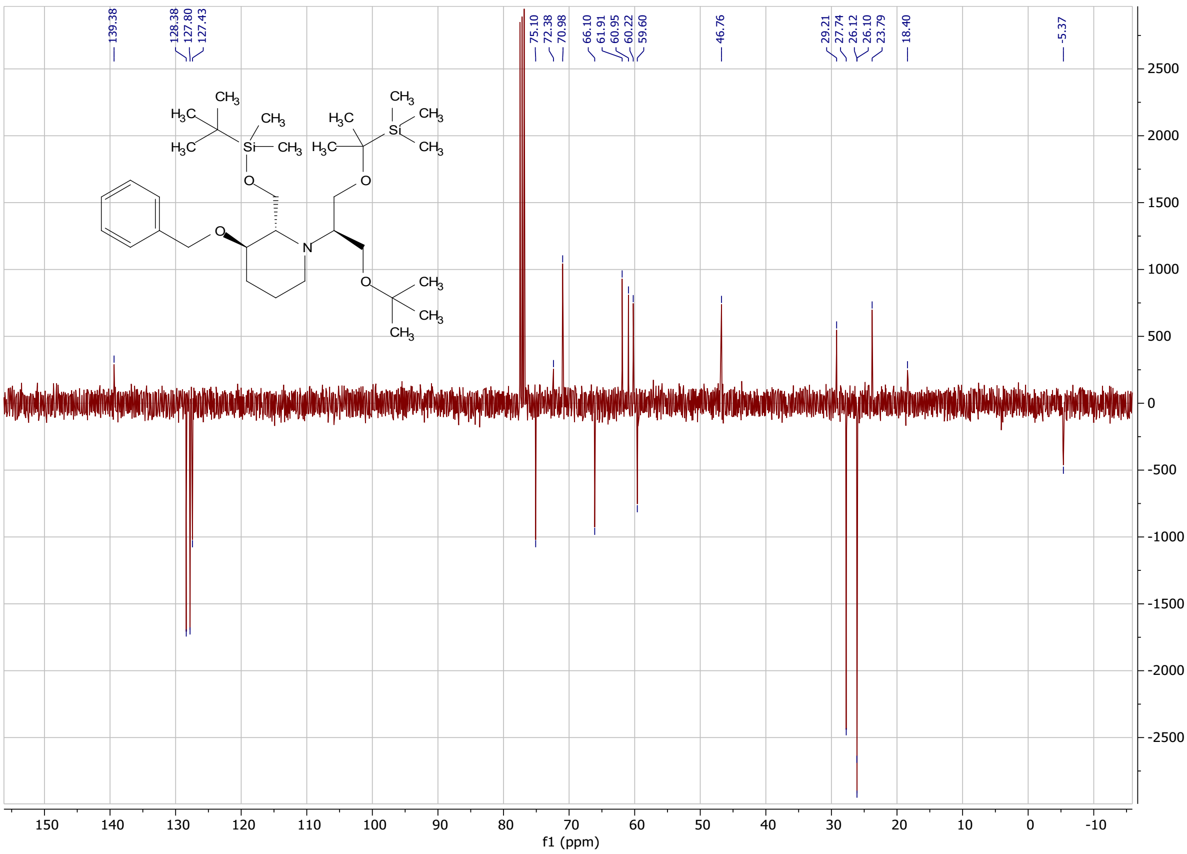

7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
5.15
5.13
5.10
3.73
3.71
3.70
3.59
3.57
3.57
3.55
3.52
3.52
3.50
3.49
3.35
3.34
3.33
3.32
1.15
0.89
0.88
0.88
0.05
0.04
4.81
2.82
2.01
1.02
1.01
1.00
9.01
9.12
5.84
f1 (ppm)

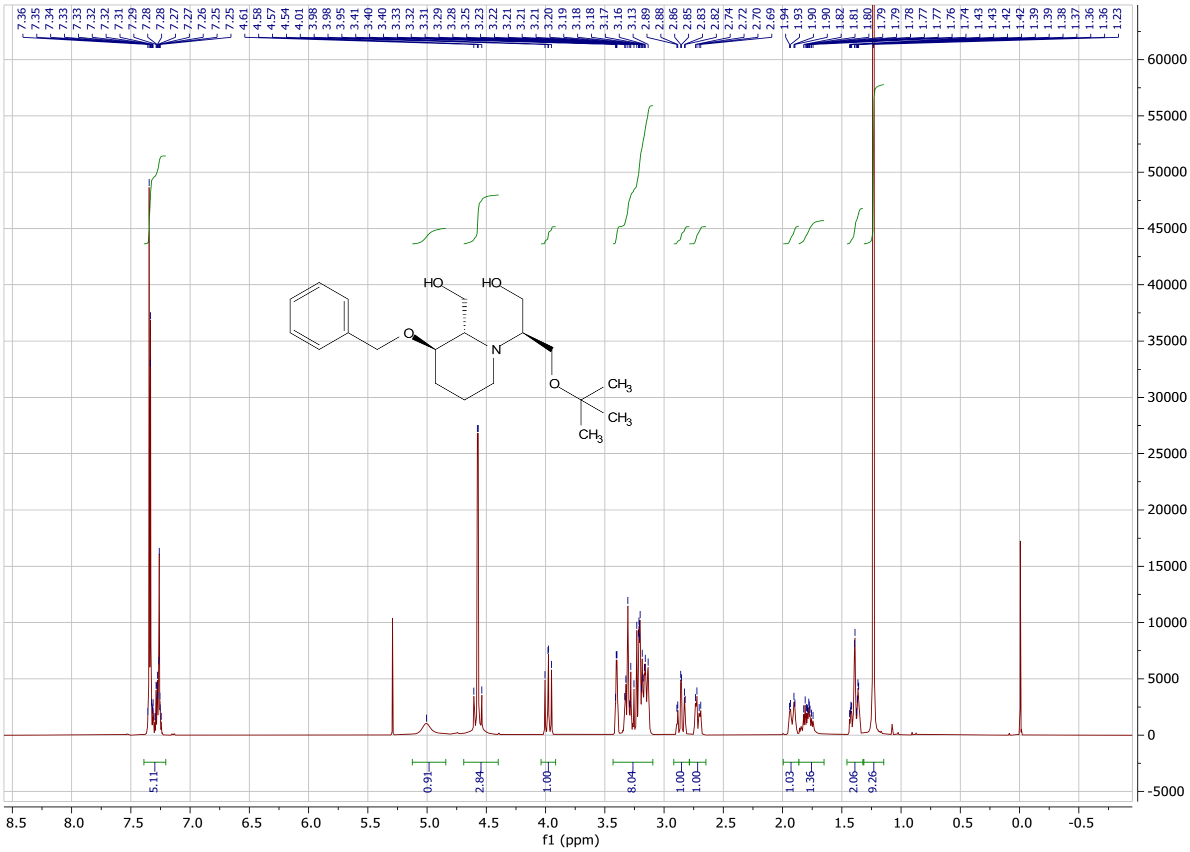

156.13
136.72
128.67
128.36
128.26
77.48 CDCl3
76.84 CDCl3
73.01
66.79
61.28
59.34
52.34
27.62
26.00
18.38
-5.36
f1 (ppm)

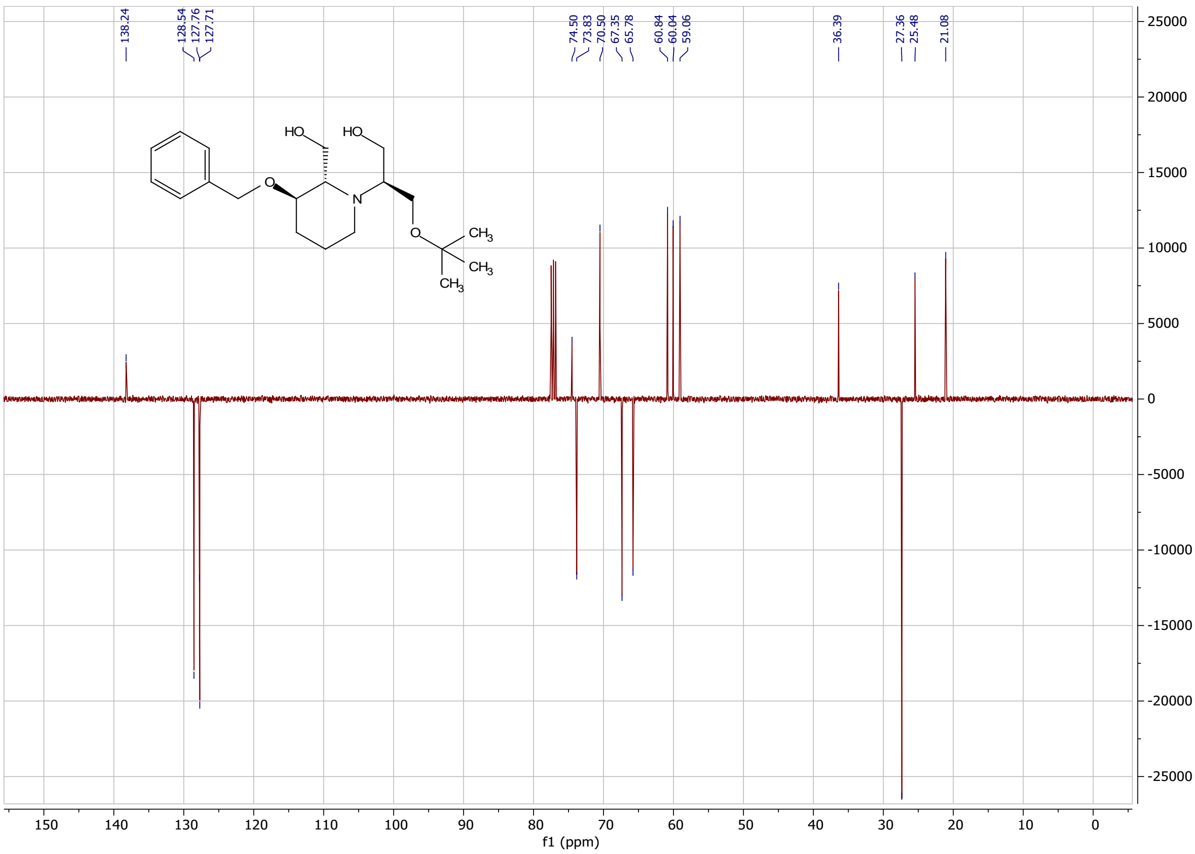

3.62
3.60
3.59
3.58
3.52
3.51
3.50
3.48
3.38
3.37
3.36
3.35
3.24
3.22
3.21
3.20
2.95
2.94
2.94
2.92
2.91
2.91
2.90
1.60
1.17
0.89
0.89
0.88
0.06
0.05
0.04
1.00
1.01
1.02
1.00
0.99
2.52
9.09
9.08
5.95
f1 (ppm)

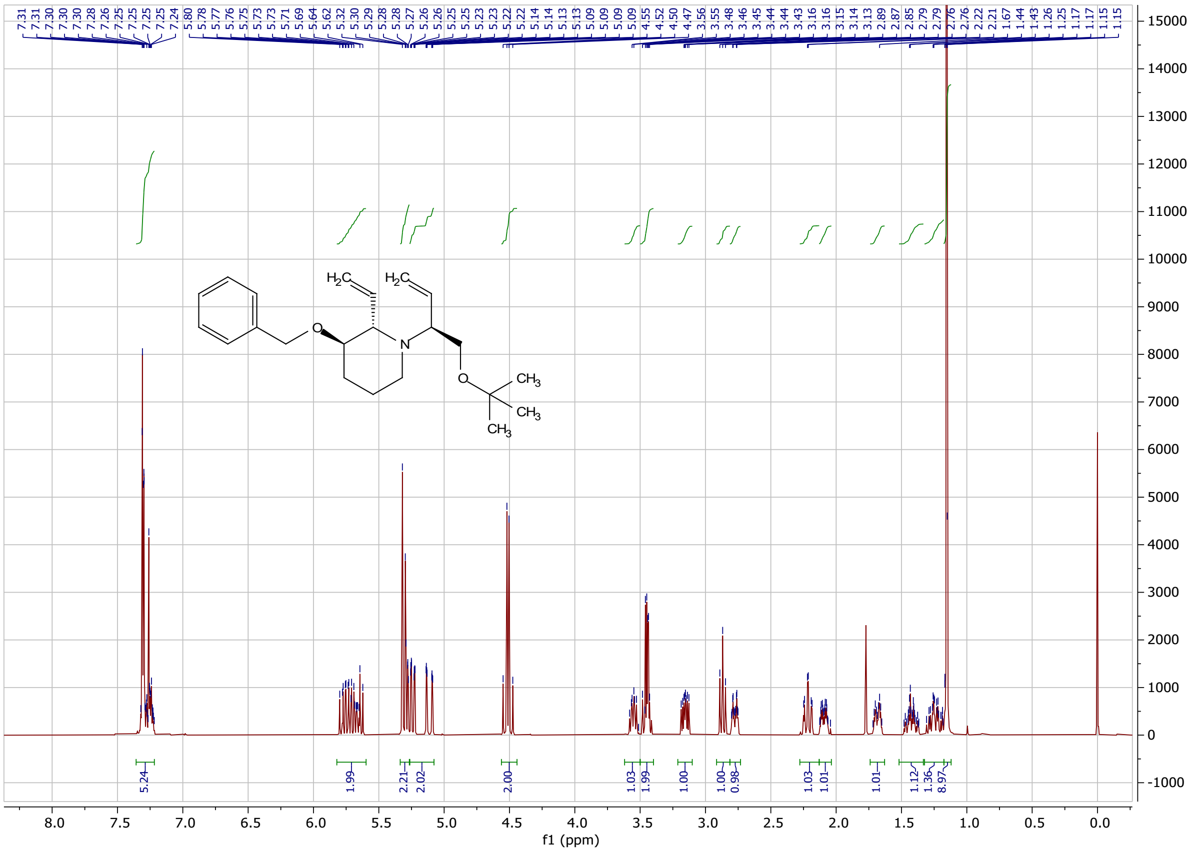

72.81
65.34
63.72
53.21
27.67
26.03
18.42
-5.27
f1 (ppm)



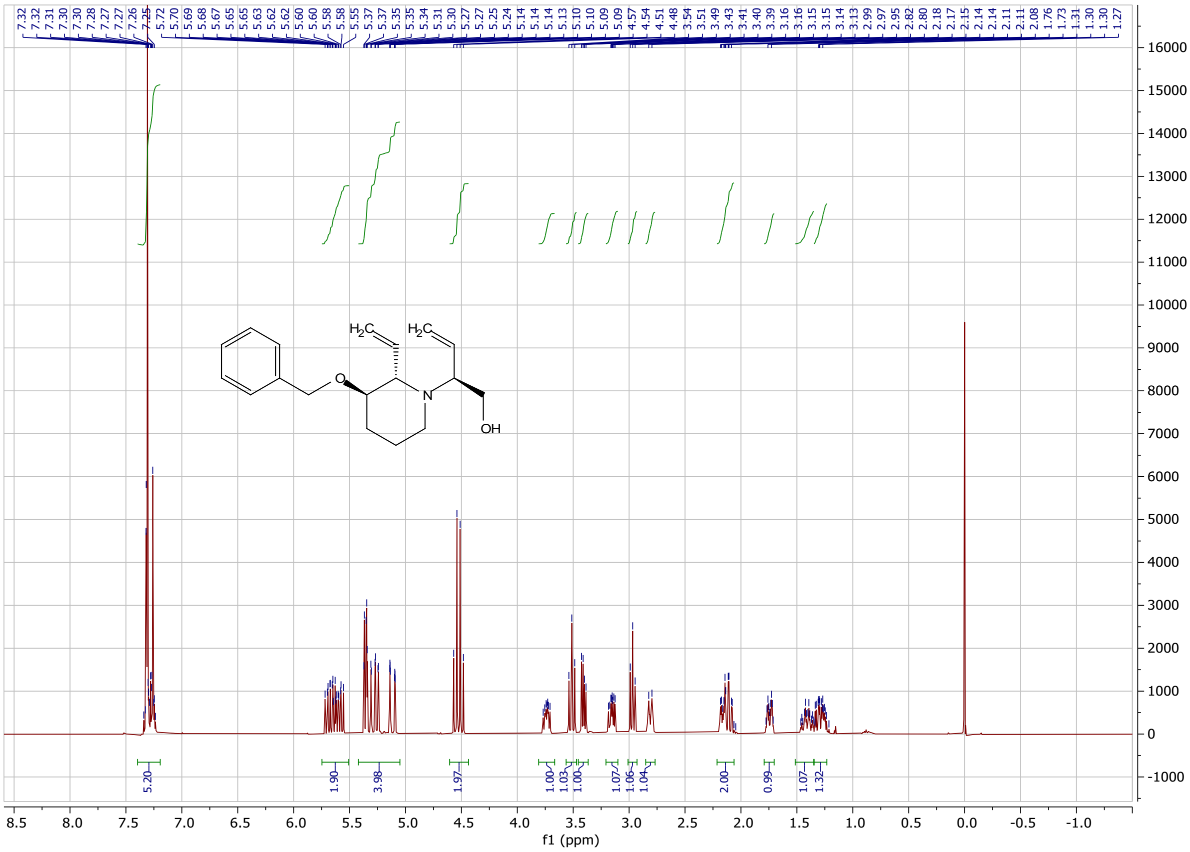


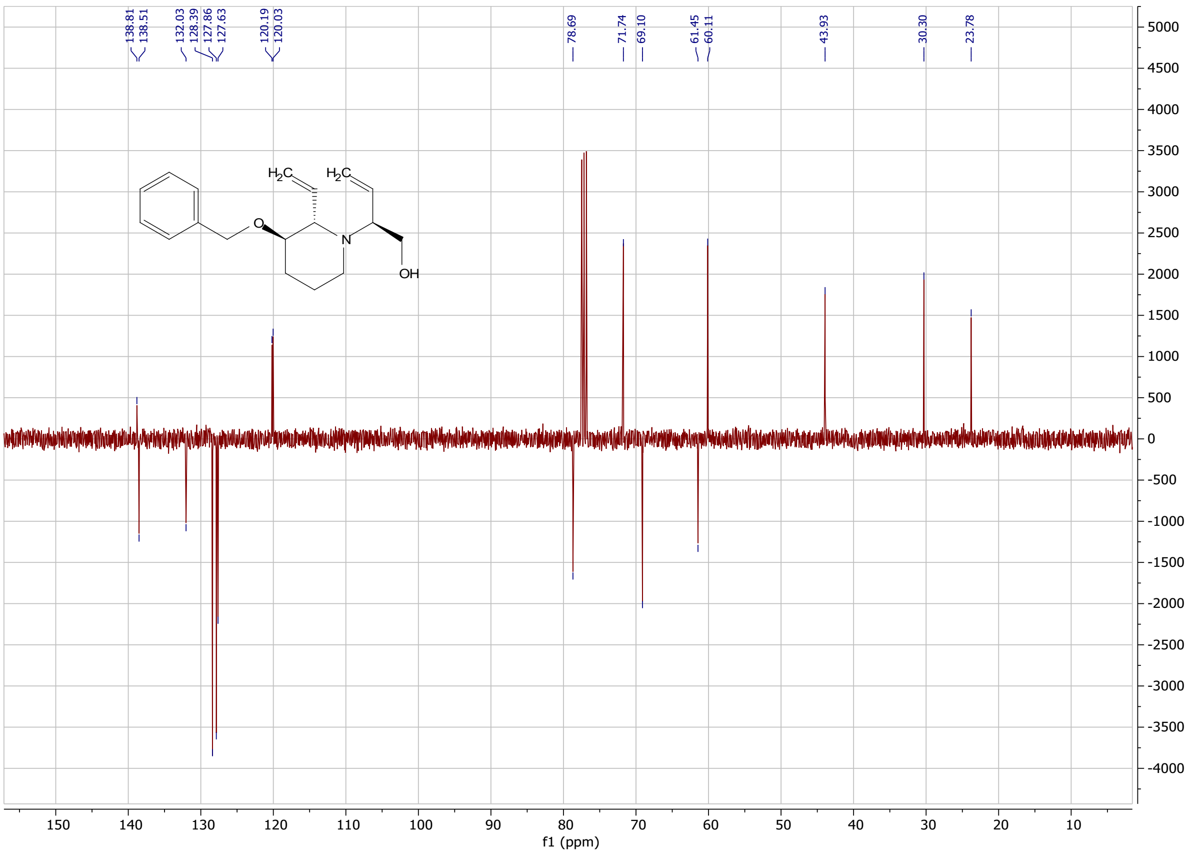


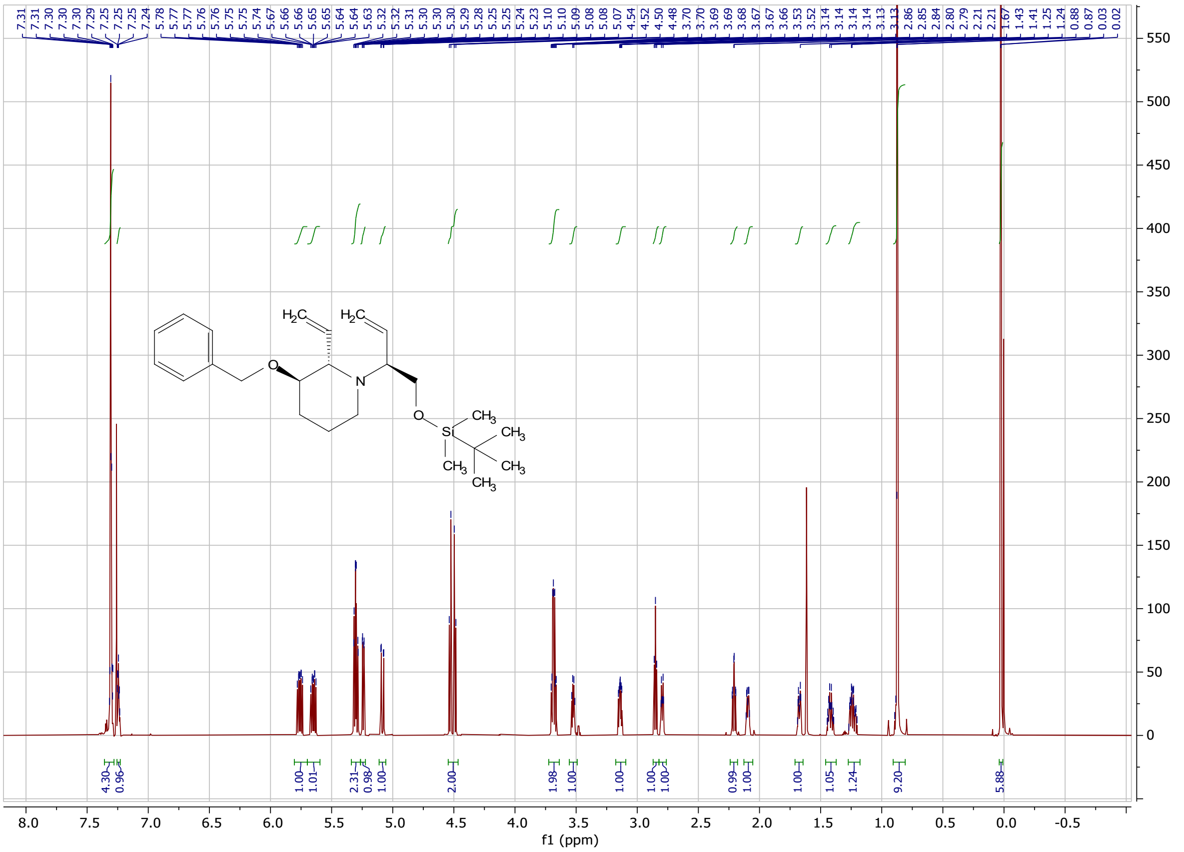



f1 (ppm)

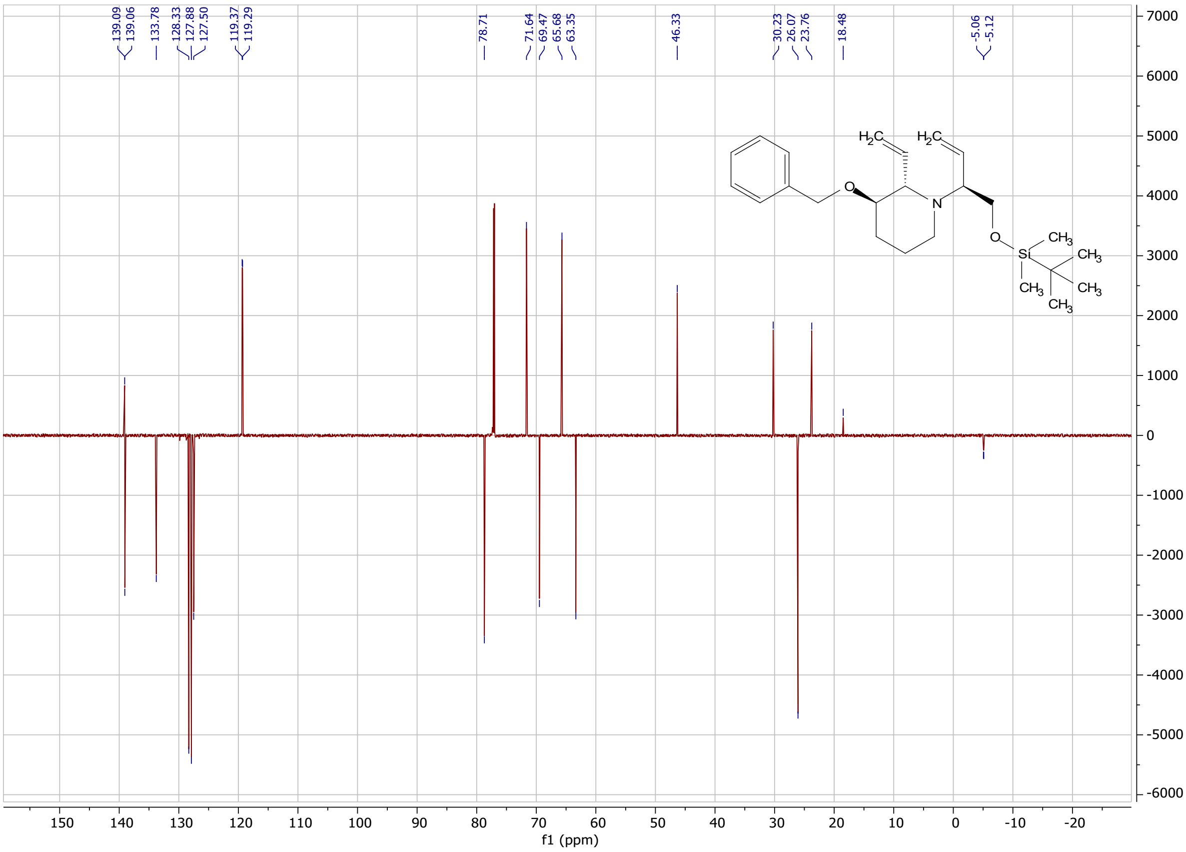

f1 (ppm)



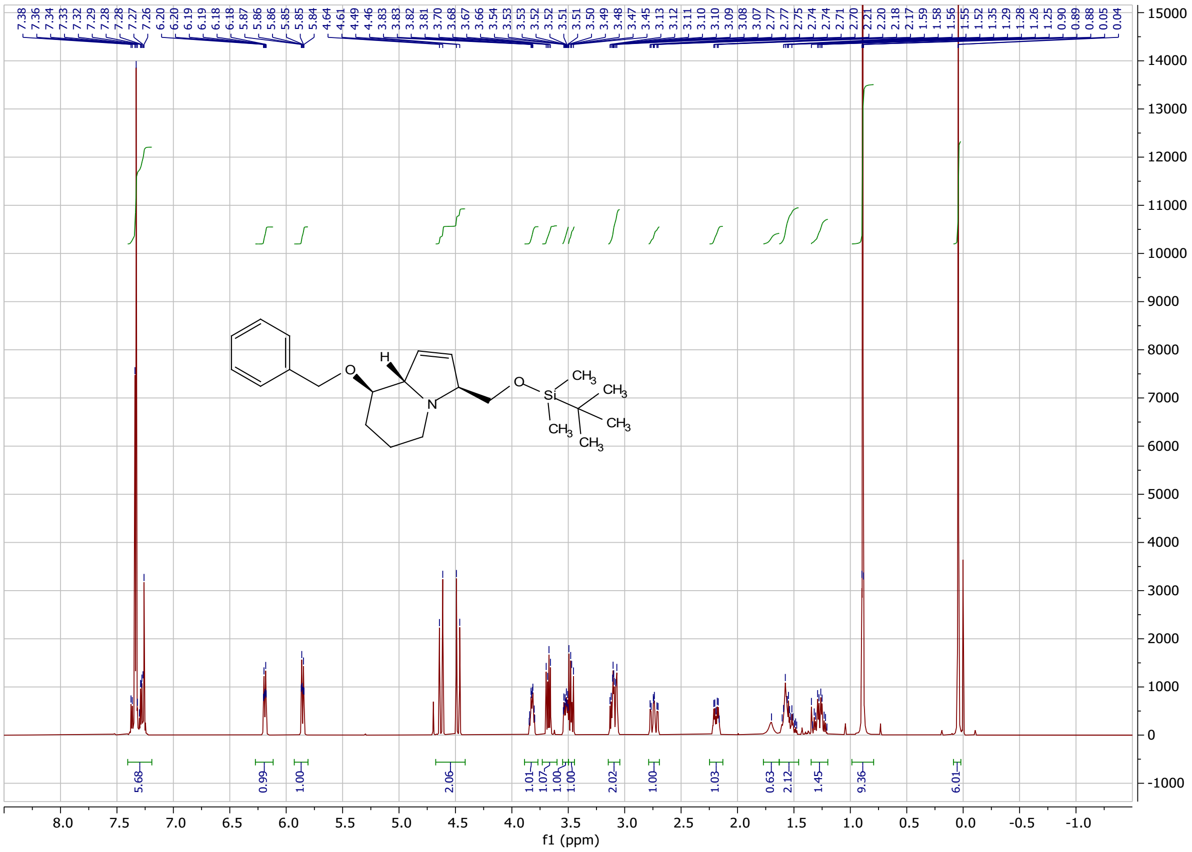


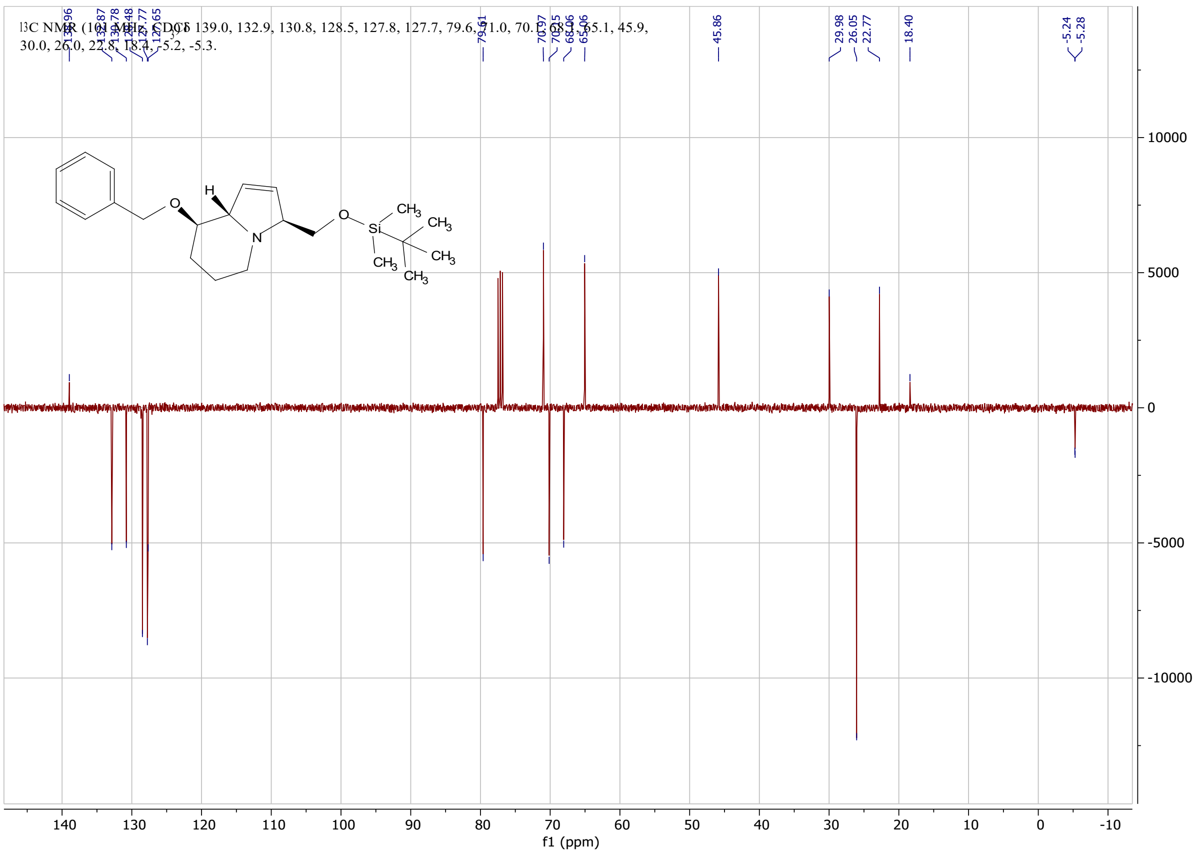


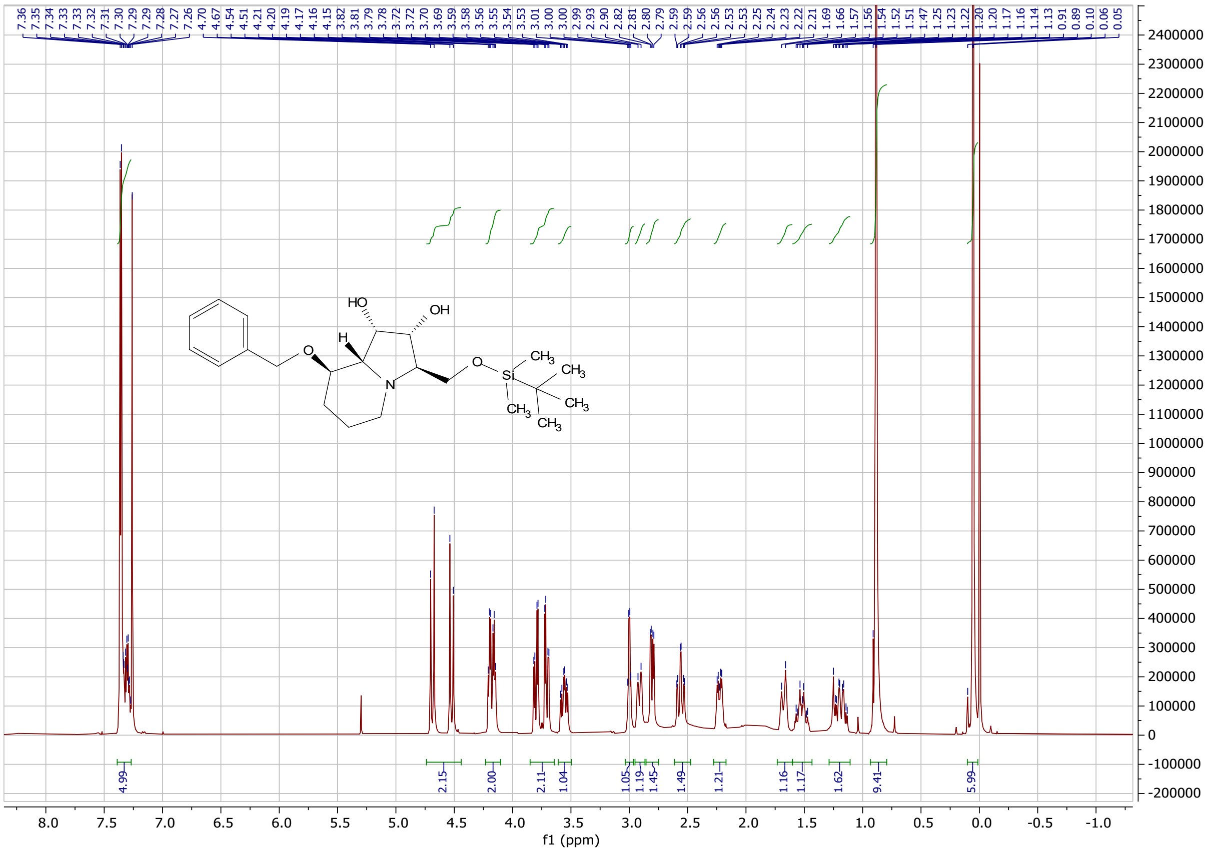
H2C
H2C
O
N
O
Si
CH3
CH3
CH3
CH3
CH3
f1 (ppm)

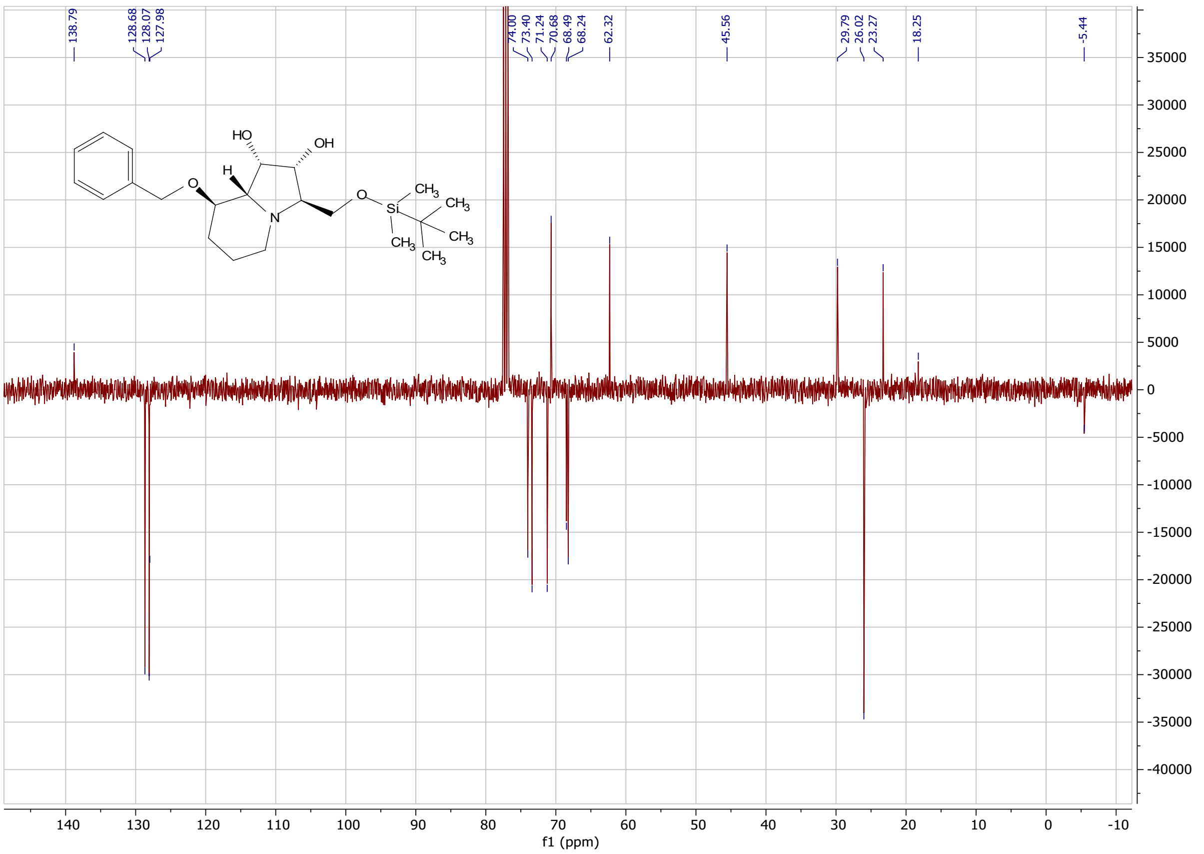


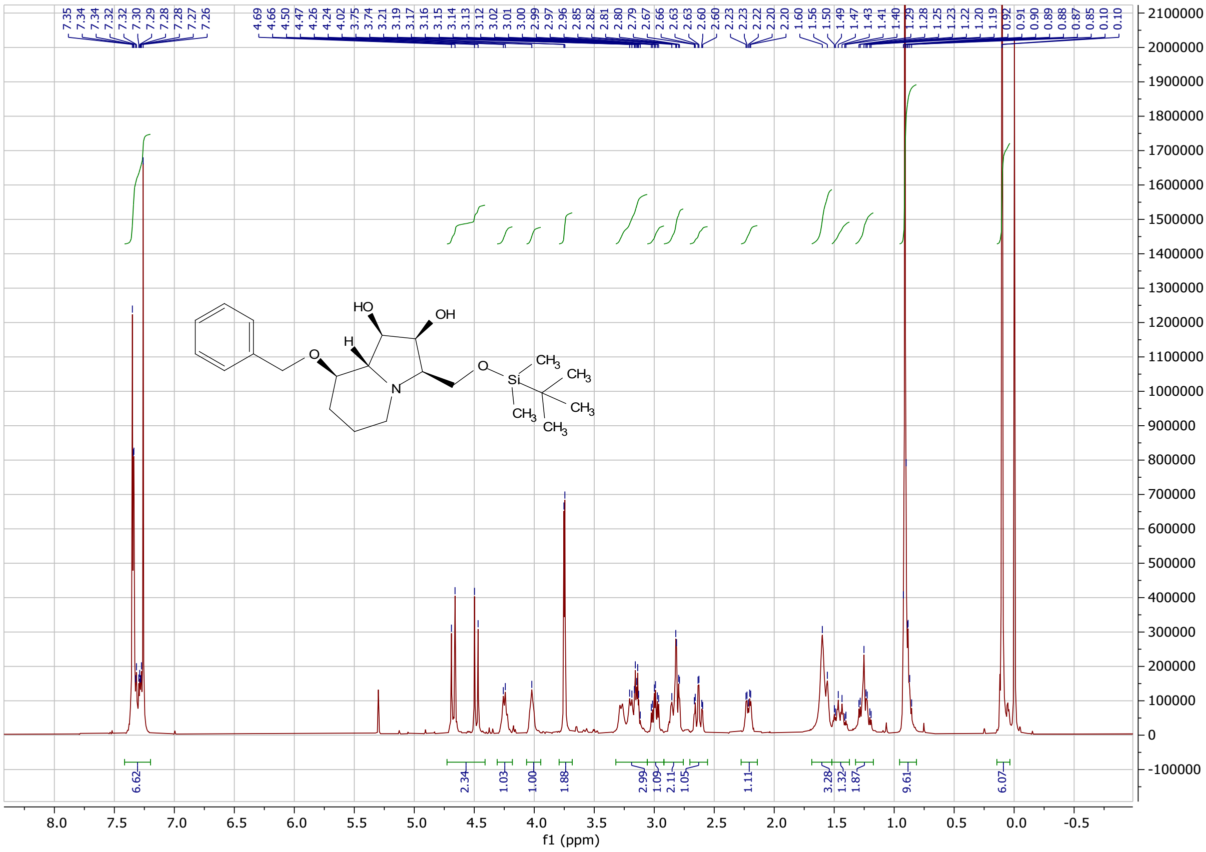
139.09
139.06
133.78
128.33
127.88
127.50
119.37
119.29
78.71
71.64
69.47
65.68
63.35
46.33
30.23
26.07
23.76
18.48
-5.06
-5.12
H2C
H2C
O
N
O
Si
CH3
CH3
CH3
CH3
CH3
f1 (ppm)

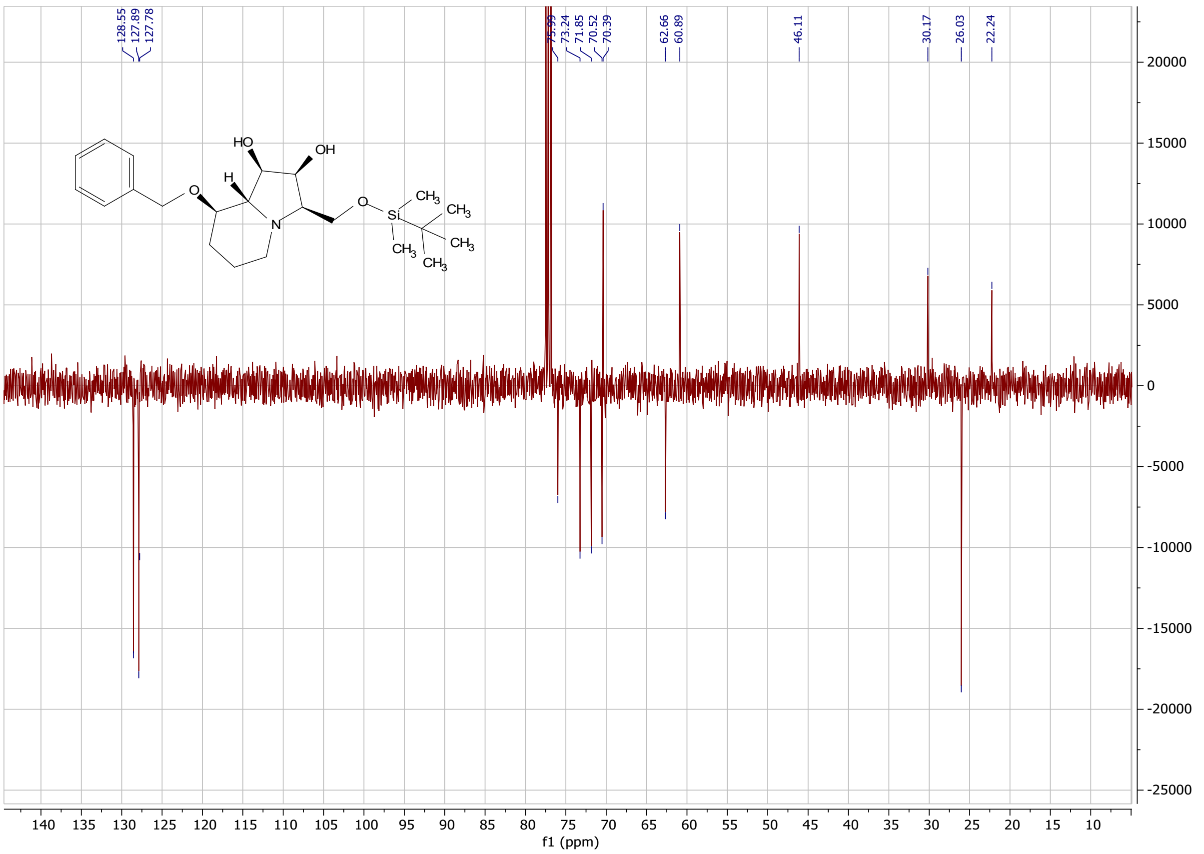


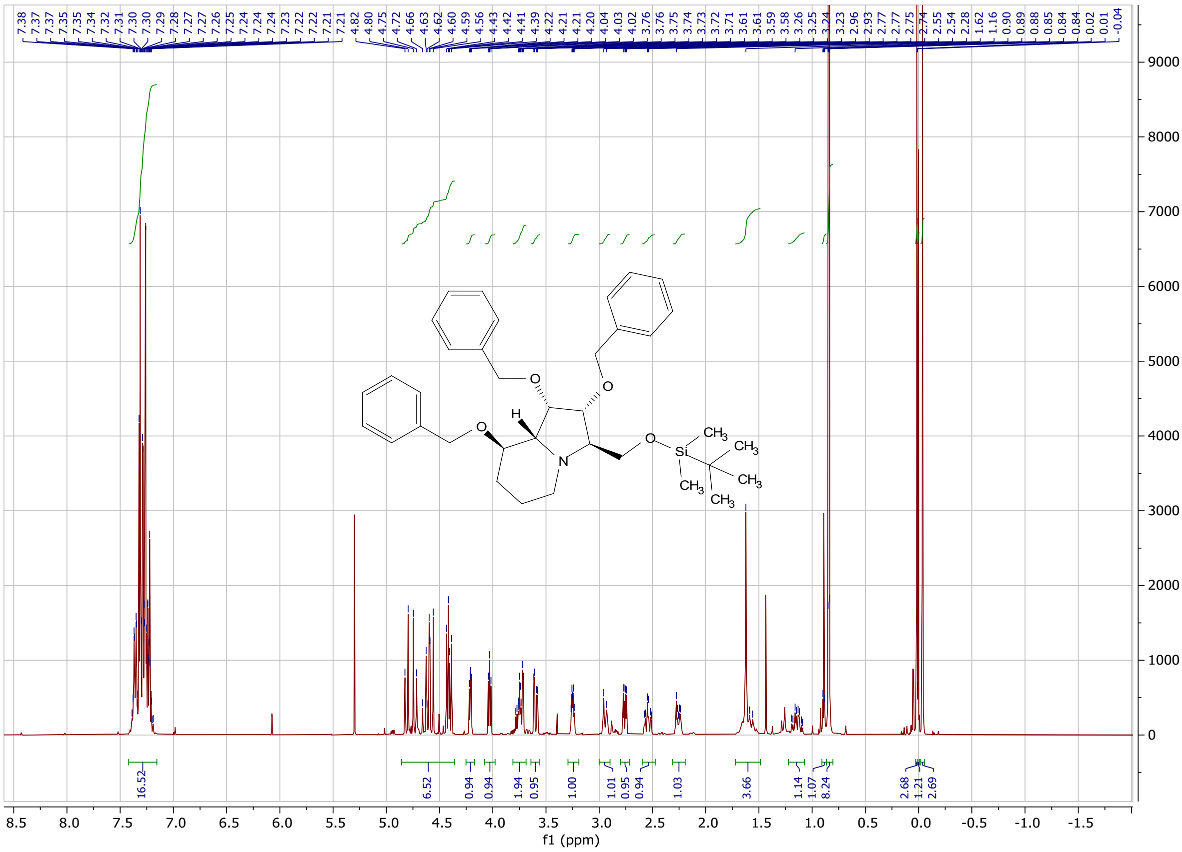

13C NMR (101 MHz, CDCl3 δ 139.0, 132.9, 130.8, 128.5, 127.8, 127.7, 79.6, 71.0, 70.1, 68.5, 65.1, 45.9,
30.0, 26.0, 22.8, 18.4, -5.2, -5.3.

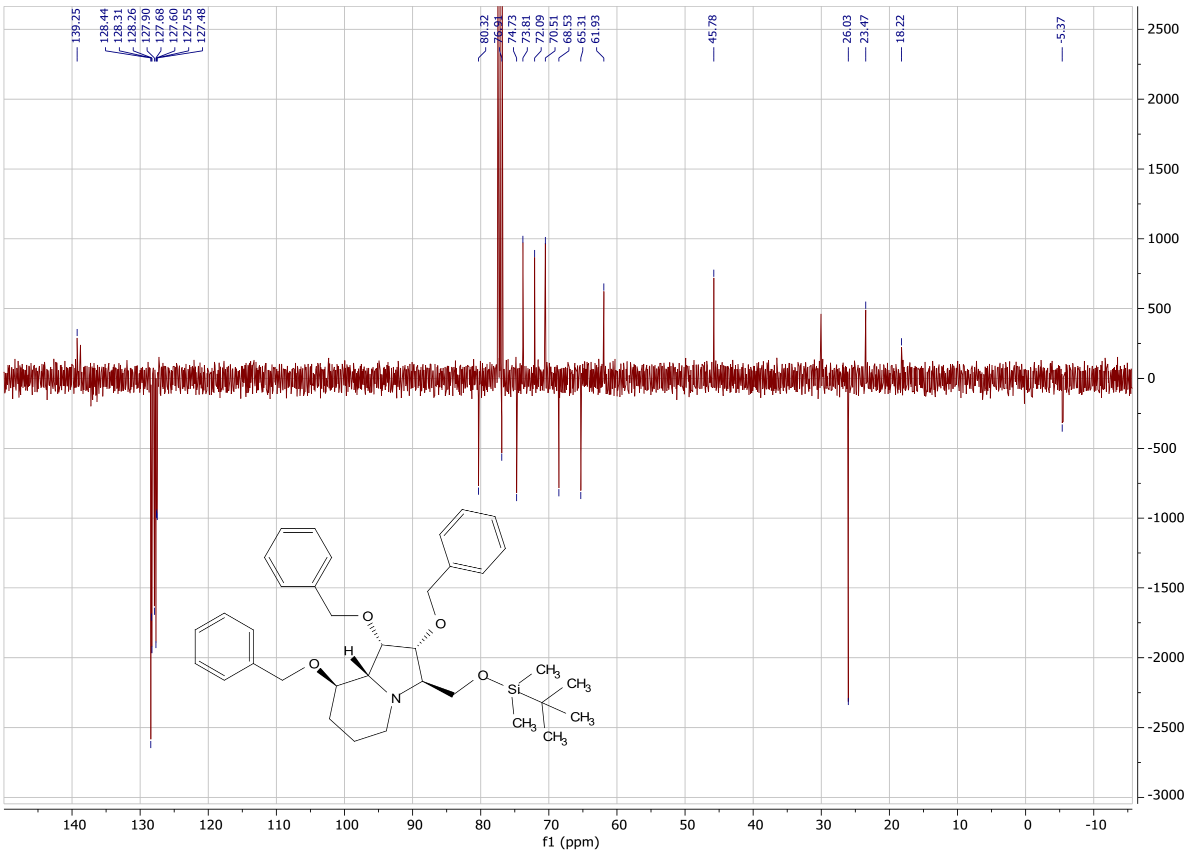

f1 (ppm)

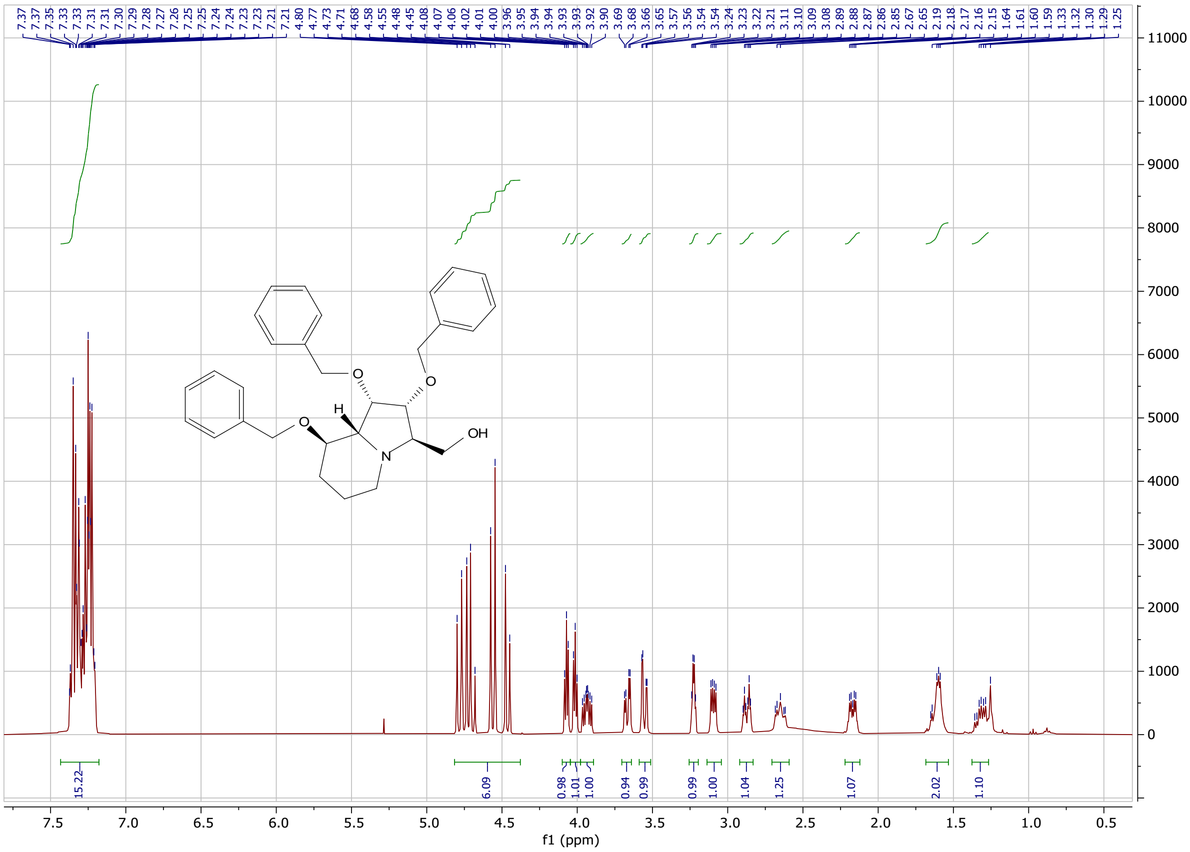

f1 (ppm)

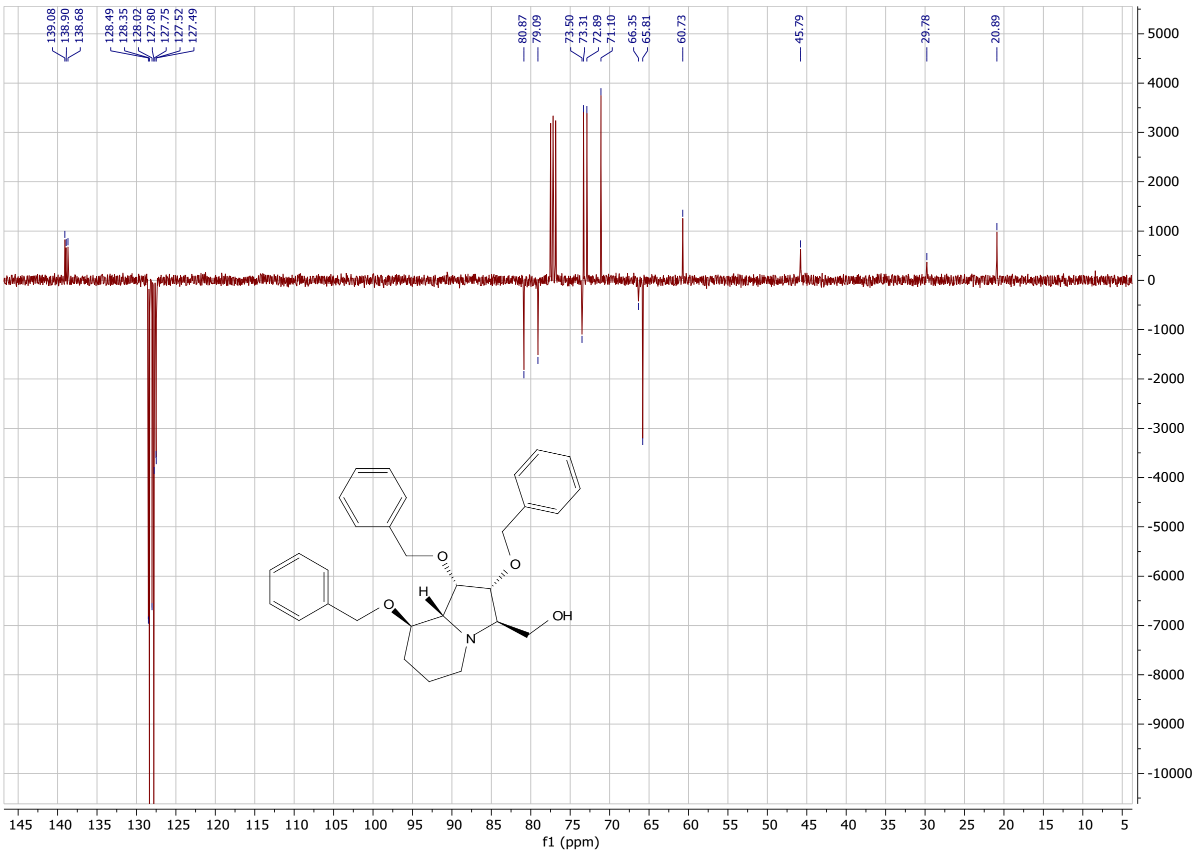

HO
OH
H
O
N
O
Si
CH3
CH3
CH3
CH3
CH3
f1 (ppm)

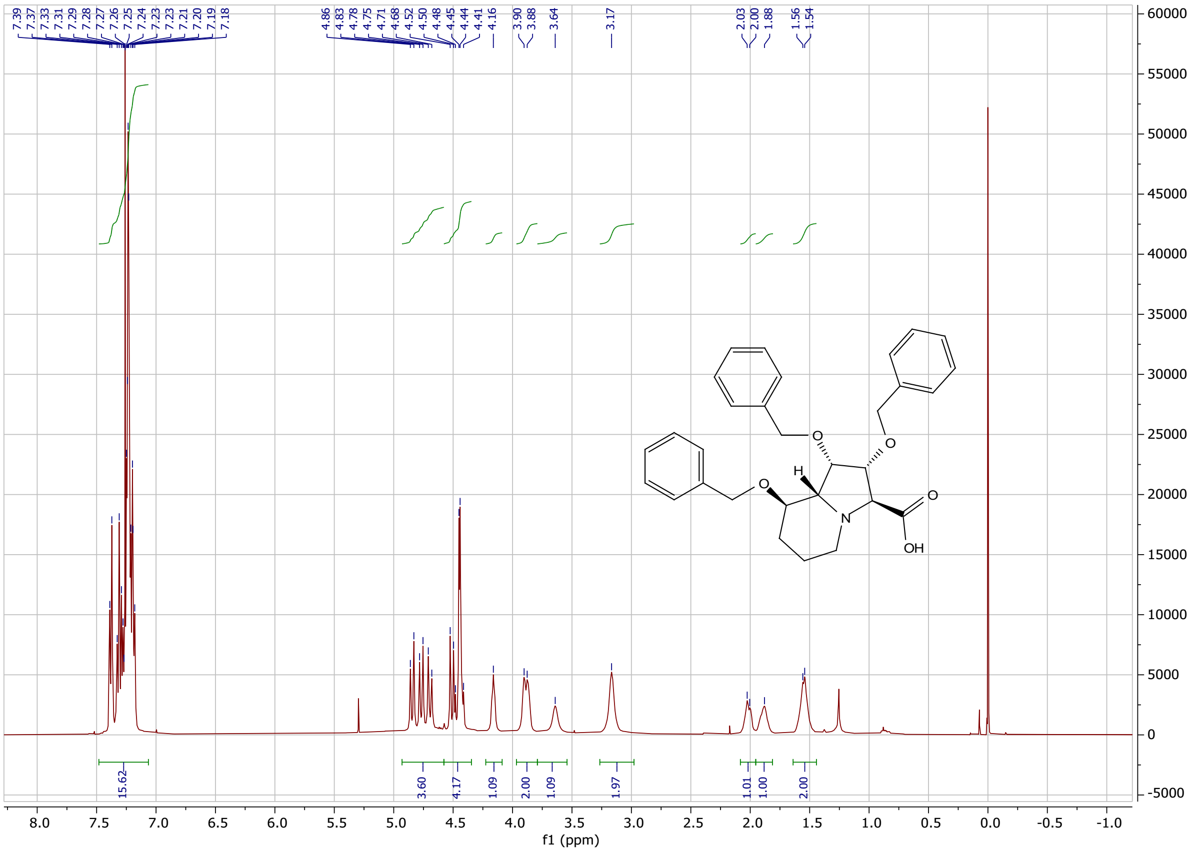

128.55
127.89
127.78
75.99
73.24
71.85
70.52
70.39
62.66
60.89
46.11
30.17
26.03
22.24
f1 (ppm)



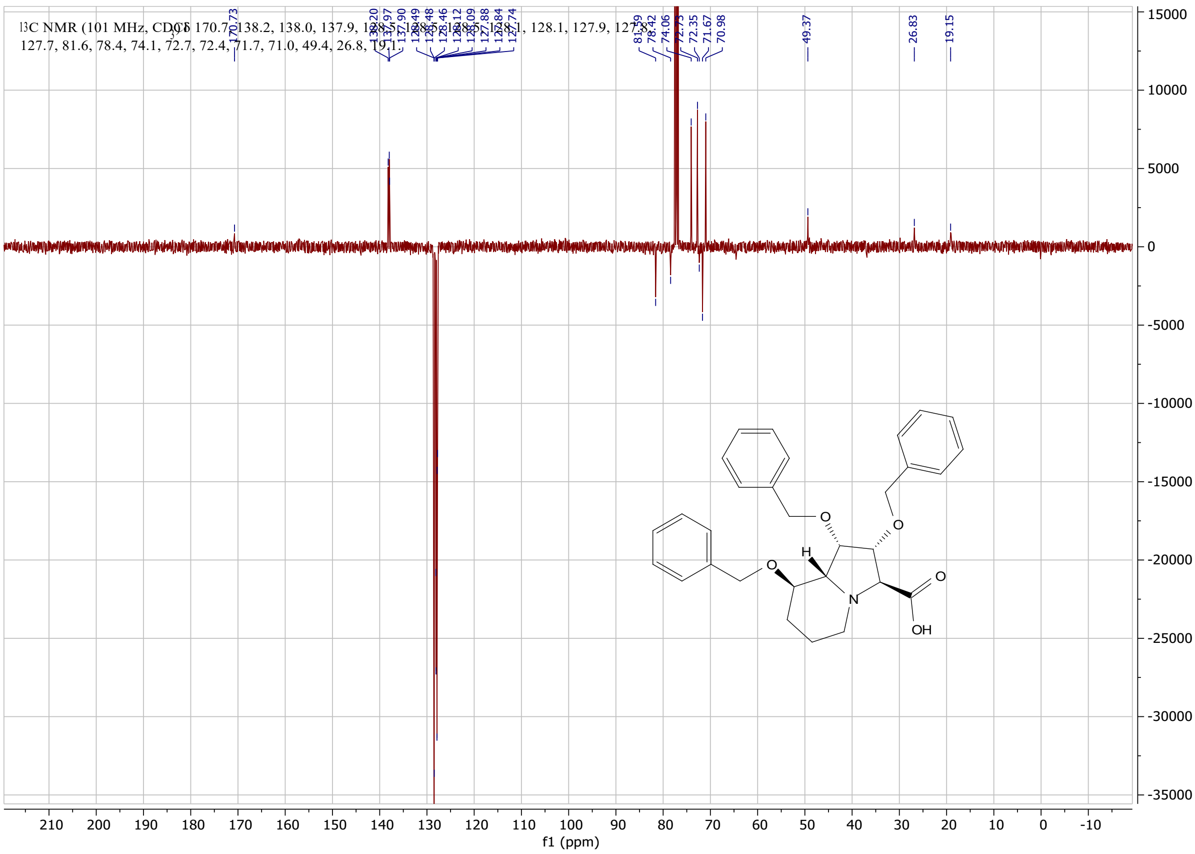



7.37 7.37 7.35 7.33 7.33 7.31 7.31 7.30 7.29 7.28 7.27 7.26 7.25 7.25 7.24 7.24 7.23 7.23 7.21 7.21 4.80 4.77 4.73 4.71 4.68 4.58 4.55 4.48 4.45 4.08 4.07 4.06 4.02 4.01 4.00 3.96 3.95 3.94 3.94 3.93 3.93 3.92 3.90 3.69 3.68 3.66 3.65 3.57 3.56 3.54 3.54 3.24 3.23 3.22 3.21 3.11 3.10 3.09 3.08 2.89 2.88 2.87 2.86 2.85 2.67 2.65 2.19 2.18 2.17 2.16 2.15 1.64 1.61 1.60 1.59 1.33 1.32 1.30 1.29 1.25
15.22 6.09 0.98 1.01 1.00 0.94 0.99 0.99 1.00 1.04 1.25 1.07 2.02 1.10
O O H O OH N
f1 (ppm)

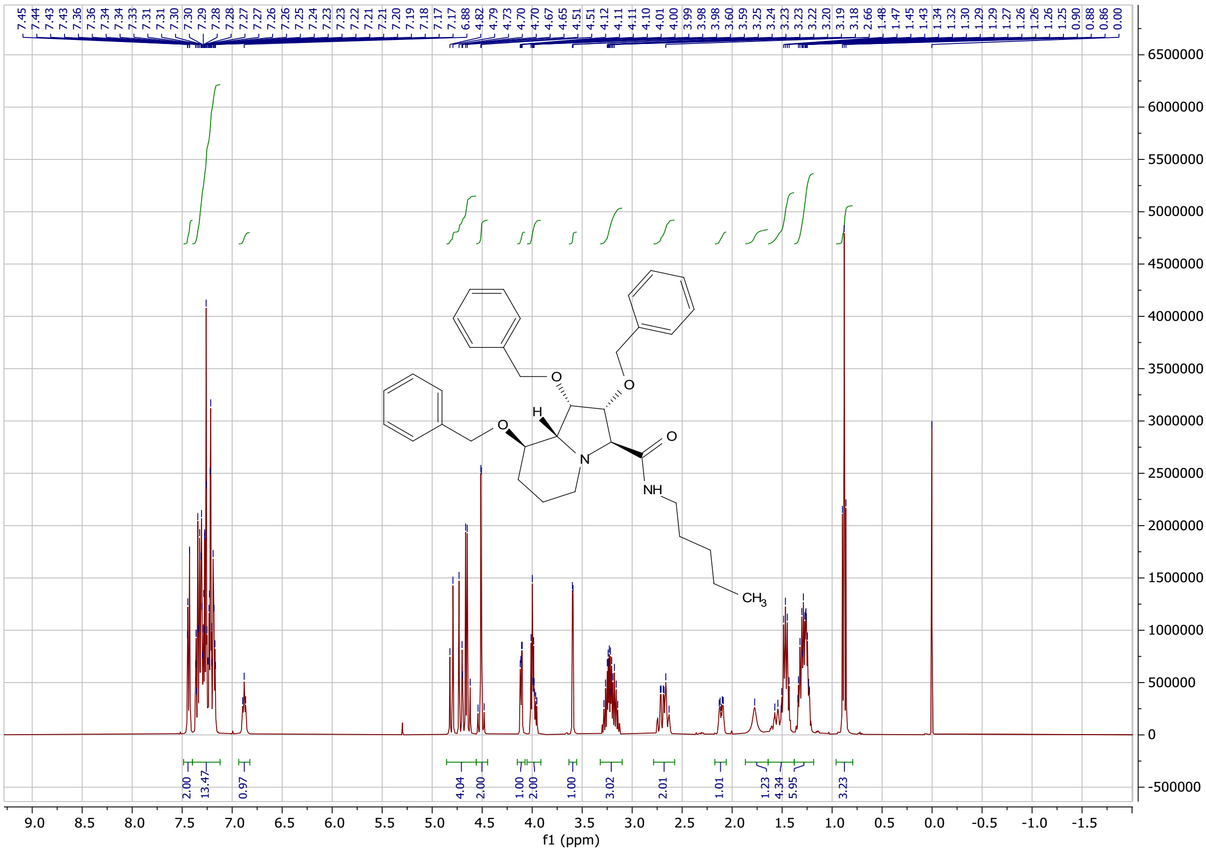

139.08 138.90 138.68 128.49 128.35 128.02 127.80 127.75 127.52 127.49 80.87 79.09 73.50 73.31 72.89 71.10 66.35 65.81 60.73 45.79 29.78 20.89
O O H O OH N
f1 (ppm)

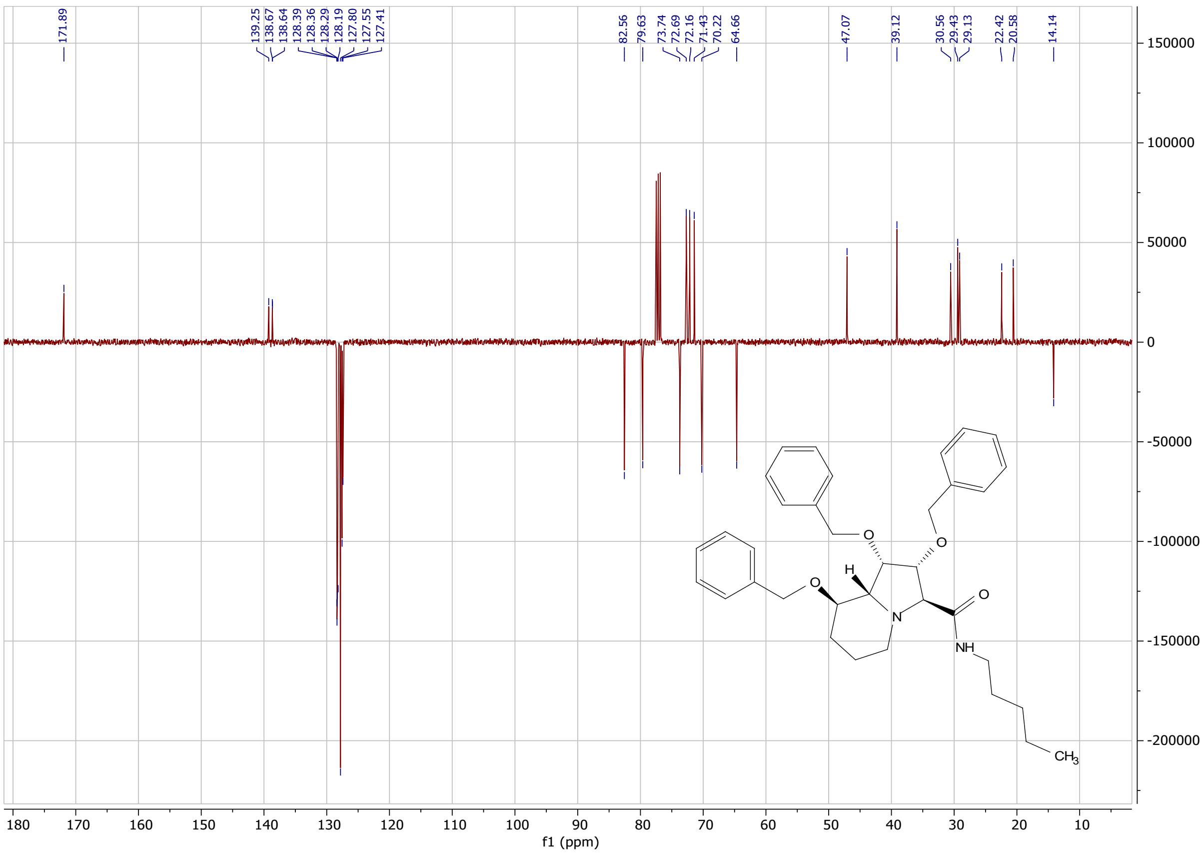


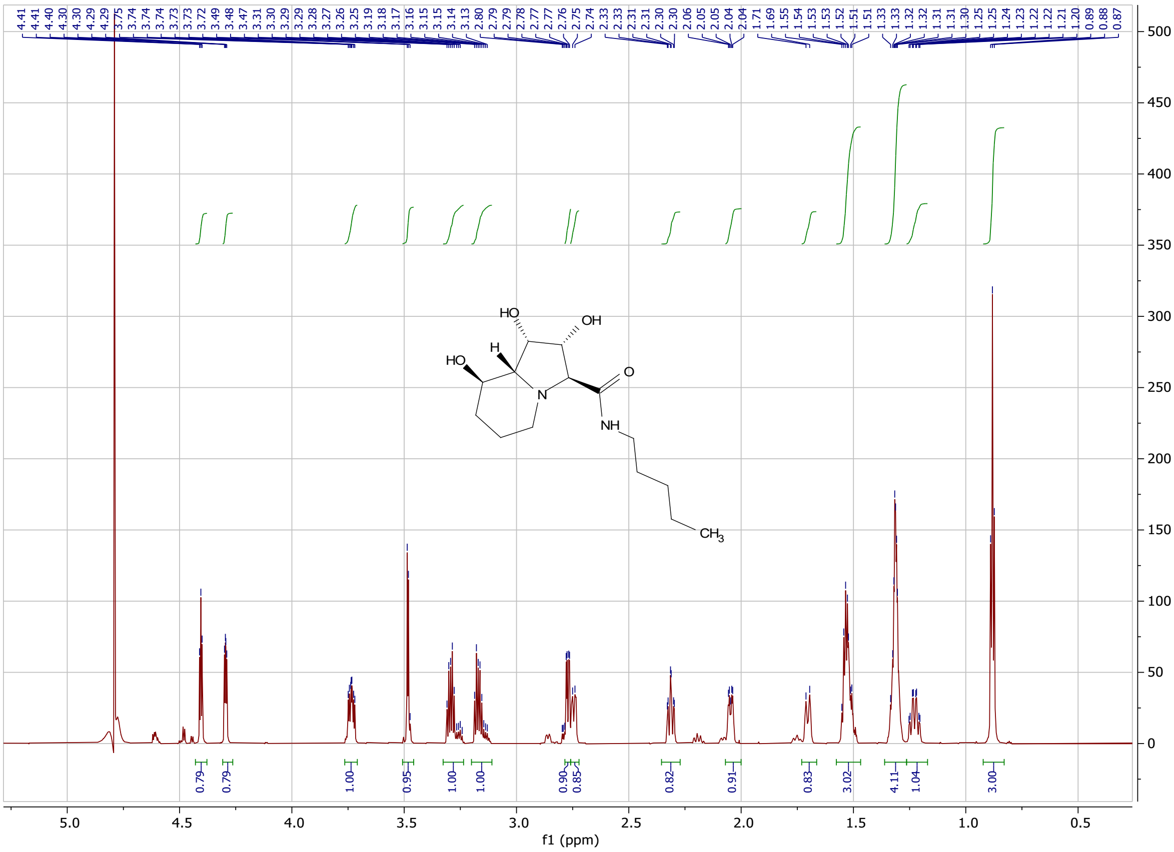
7.39 7.37 7.33 7.31 7.29 7.28 7.27 7.26 7.25 7.24 7.23 7.23 7.21 7.20 7.19 7.18
4.86 4.83 4.78 4.75 4.71 4.68 4.52 4.50 4.48 4.45 4.44 4.41 4.16 3.90 3.88 3.64 3.17
2.03 2.00 1.88 1.56 1.54
15.62 3.60 4.17 1.09 2.00 1.09 1.97 1.01 1.00 2.00
O
O
O
H
N
O
OH
f1 (ppm)

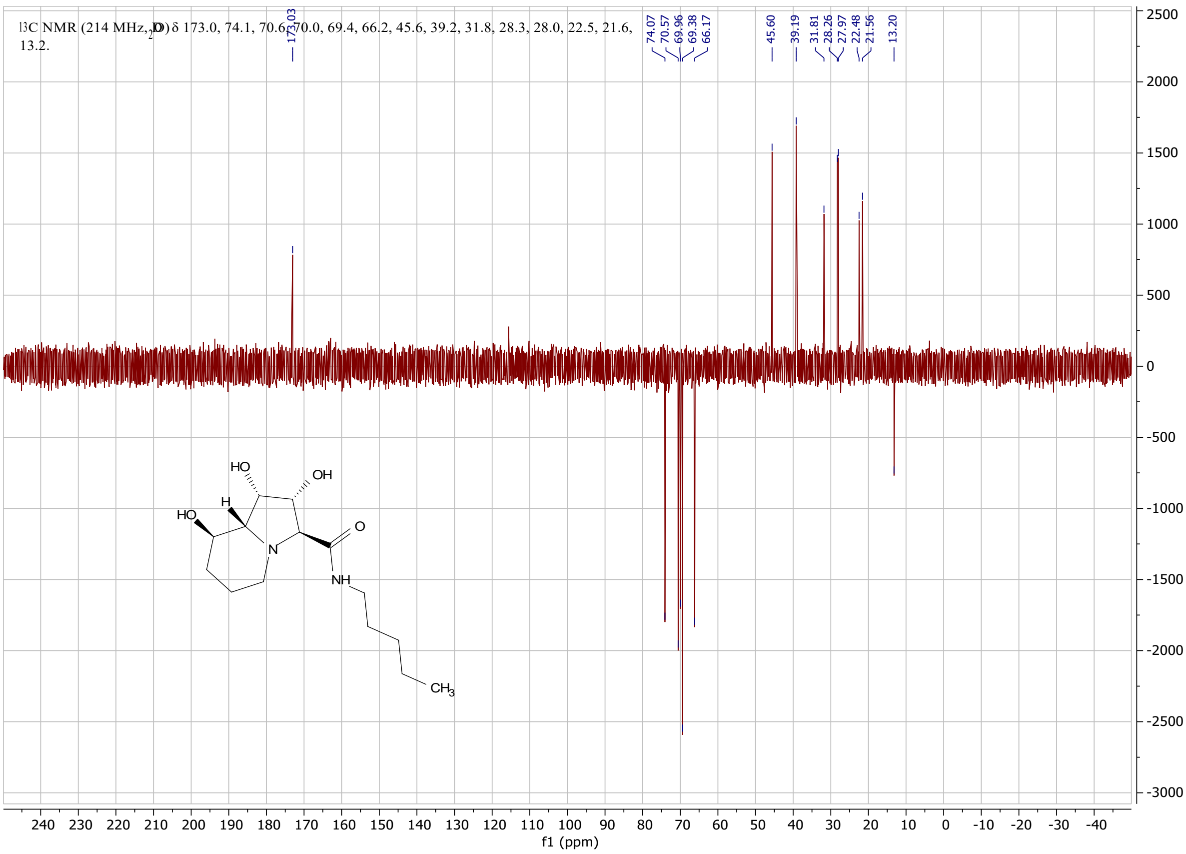


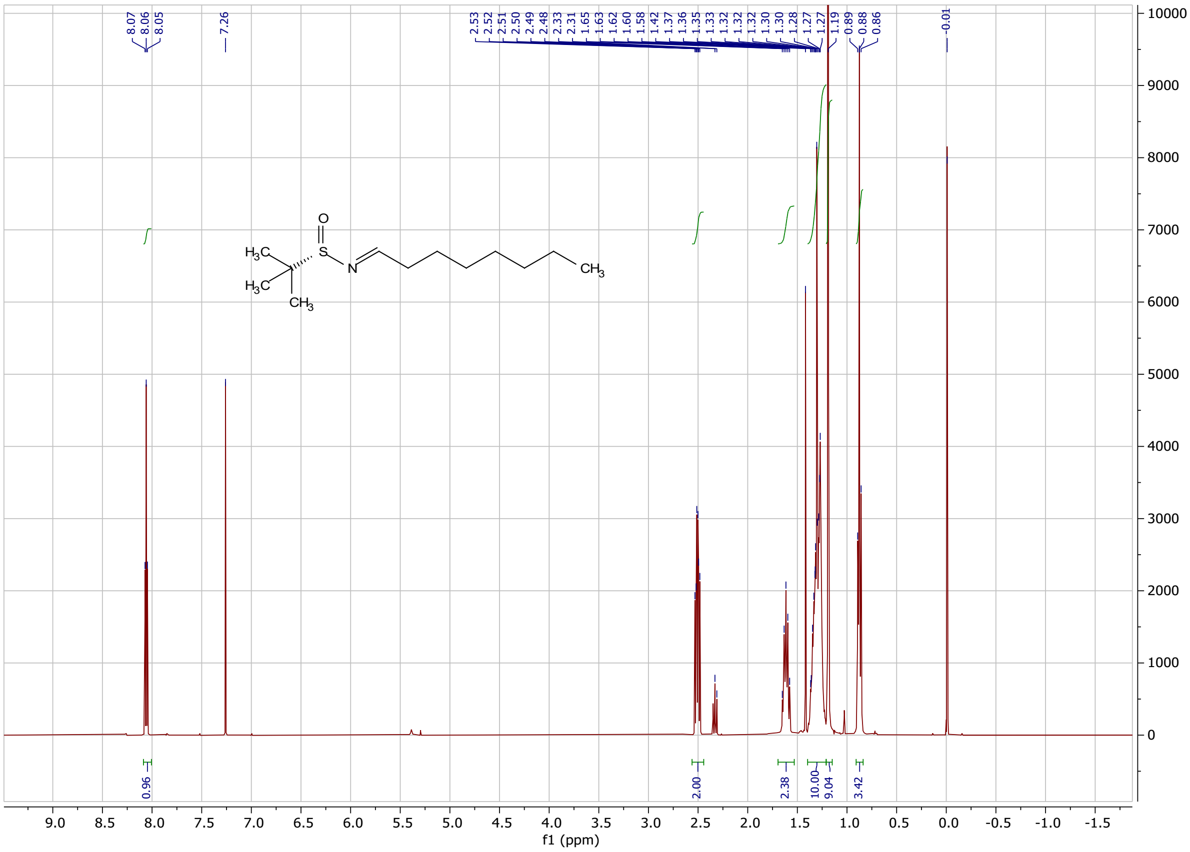
13C NMR (101 MHz, CDCl3) δ 170.7, 138.2, 138.0, 137.9, 128.5, 128.5, 128.5, 128.1, 128.1, 127.9, 127.8, 127.7, 81.6, 78.4, 74.1, 72.7, 72.4, 71.7, 71.0, 49.4, 26.8, 19.1.
170.73
138.20 137.97 137.90 128.49 128.48 128.46 128.12 128.09 127.88 127.84 127.74
81.59 78.42 74.06 72.73 72.35 71.67 70.98
49.37 26.83 19.15
O
O
O
H
N
O
OH
f1 (ppm)


f1 (ppm)
O
O
O
H
N
O
NH
CH3

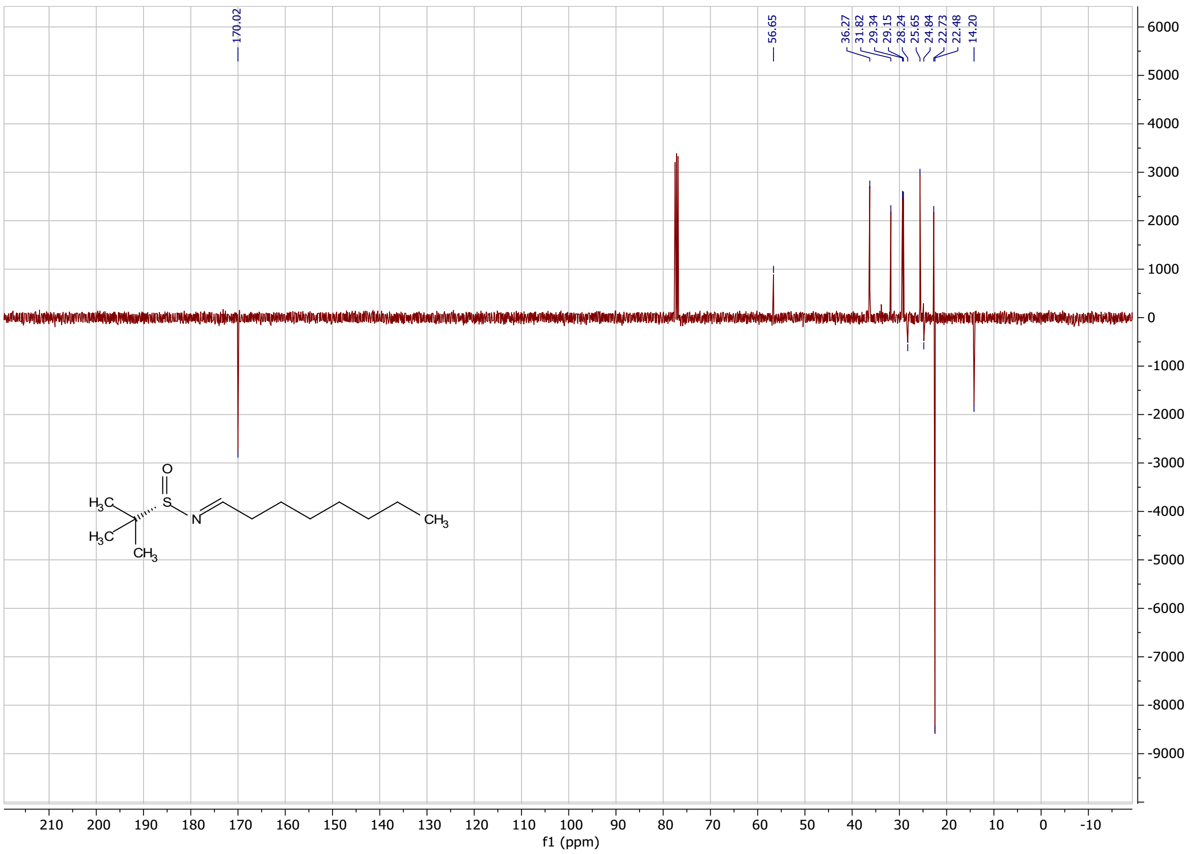

f1 (ppm)
O
O
O
H
N
O
NH
CH3


HO
OH
H
HO
N
O
NH
CH3
f1 (ppm)

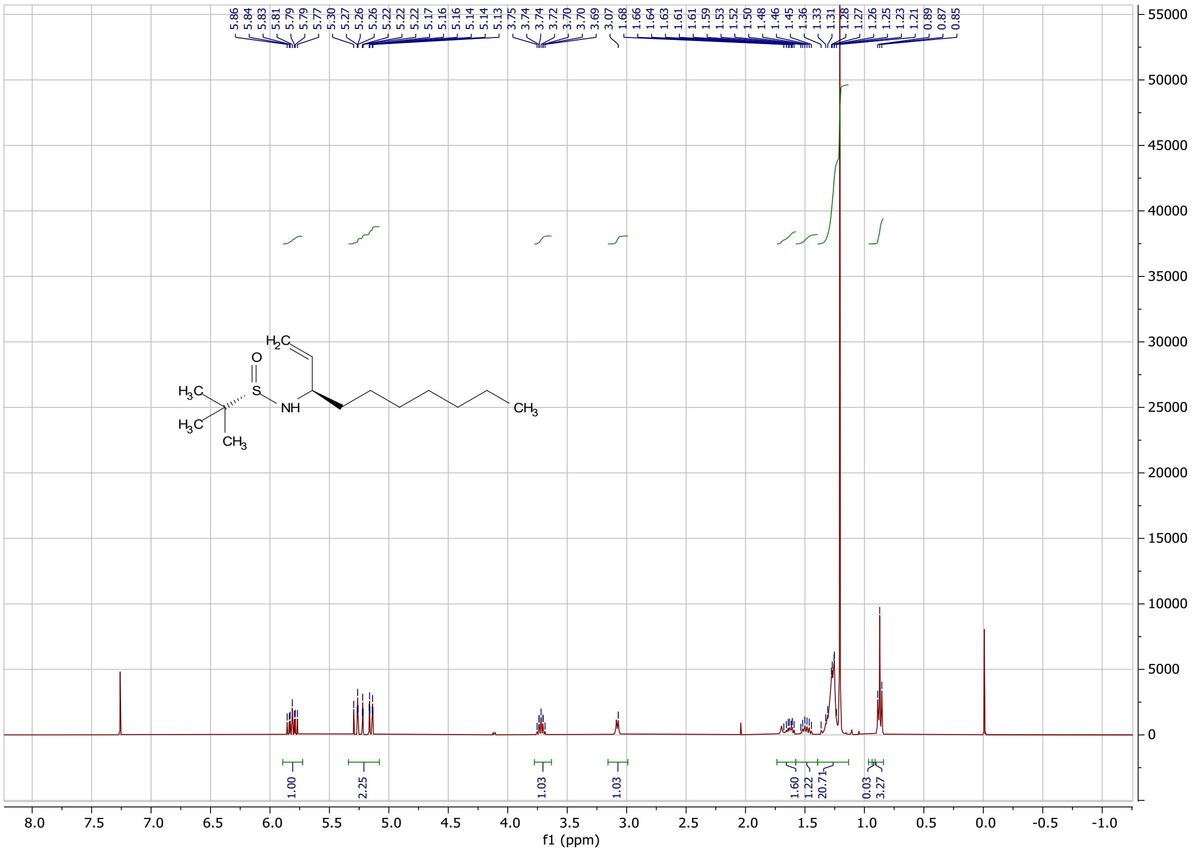

13C NMR (214 MHz, D2O) δ 173.0, 74.1, 70.6, 70.0, 69.4, 66.2, 45.6, 39.2, 31.8, 28.3, 28.0, 22.5, 21.6, 13.2.
HO
OH
H
HO
N
O
NH
CH3
f1 (ppm)

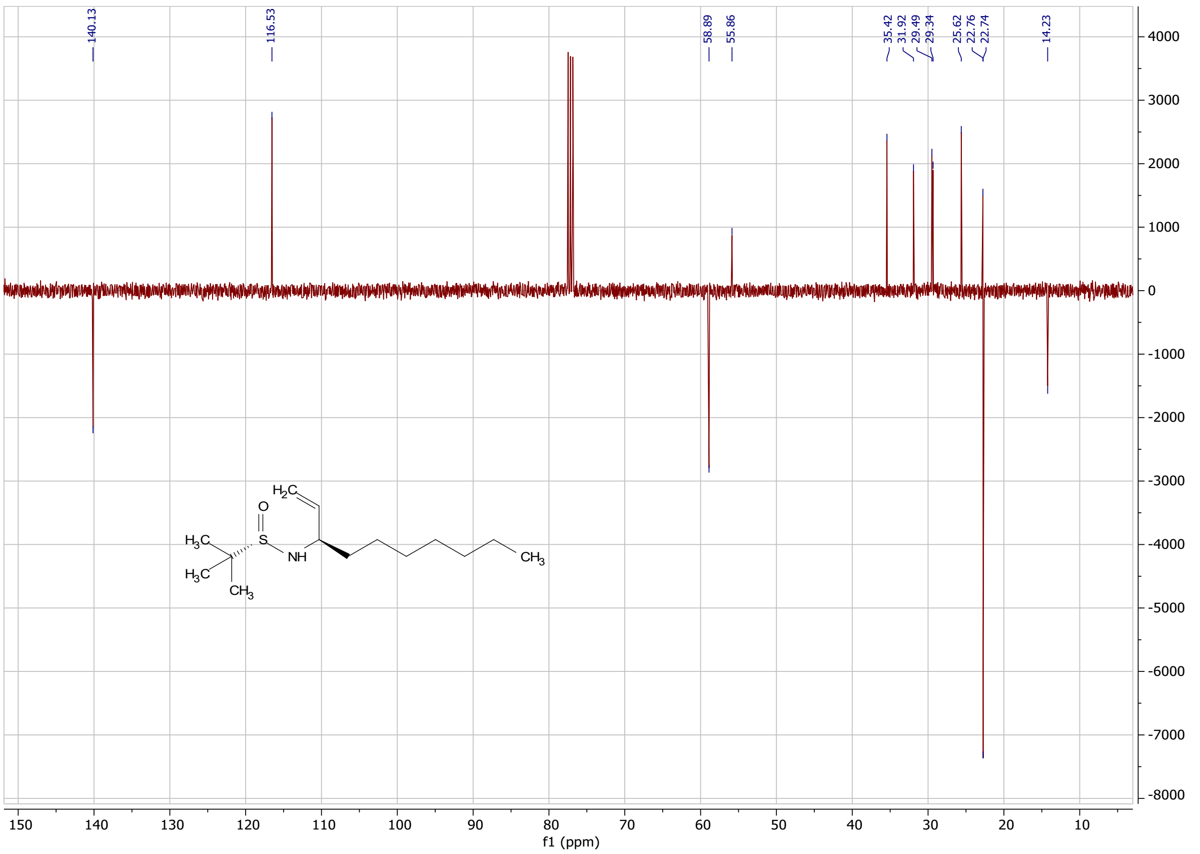


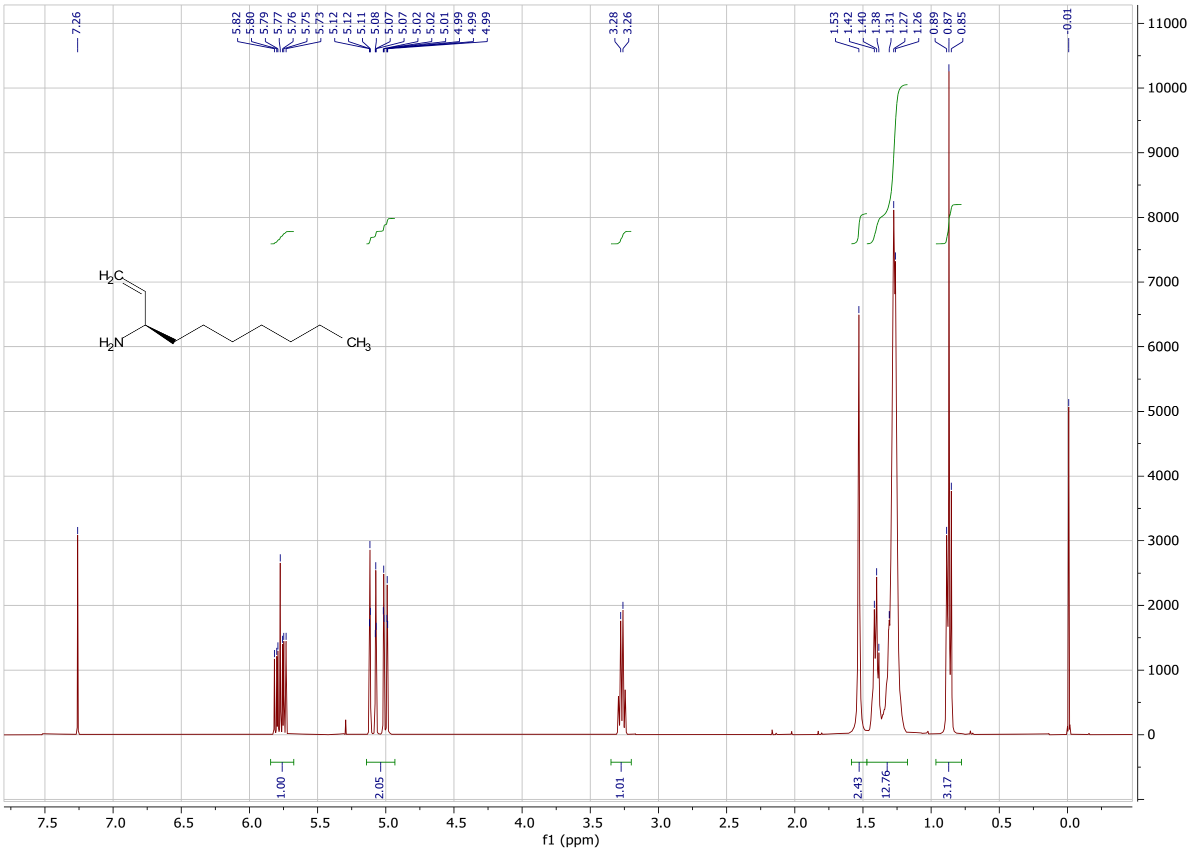
8.07
8.06
8.05
7.26
2.53
2.52
2.51
2.50
2.49
2.48
2.33
2.31
1.65
1.63
1.62
1.60
1.58
1.42
1.37
1.36
1.35
1.33
1.32
1.32
1.32
1.30
1.30
1.28
1.27
1.27
1.19
0.89
0.88
0.86
-0.01
0.96
2.00
2.38
10.00
9.04
3.42
f1 (ppm)

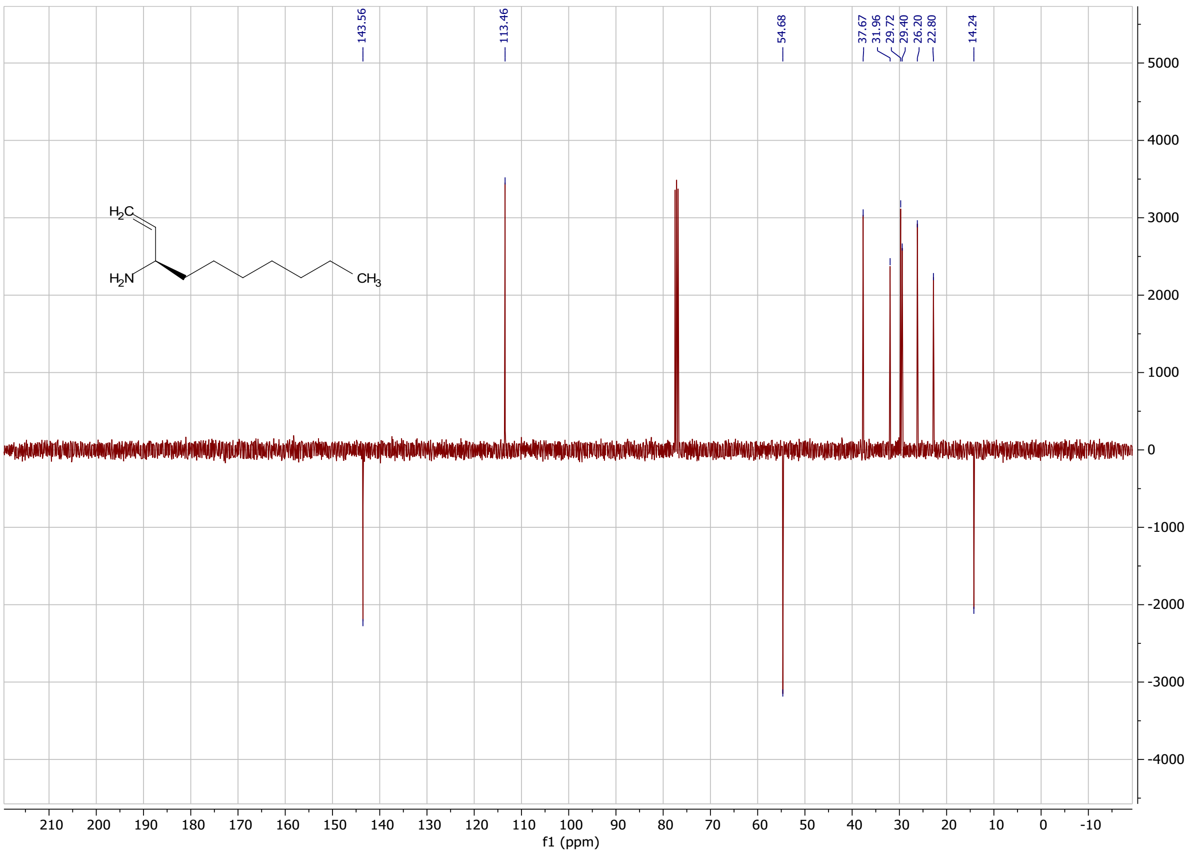


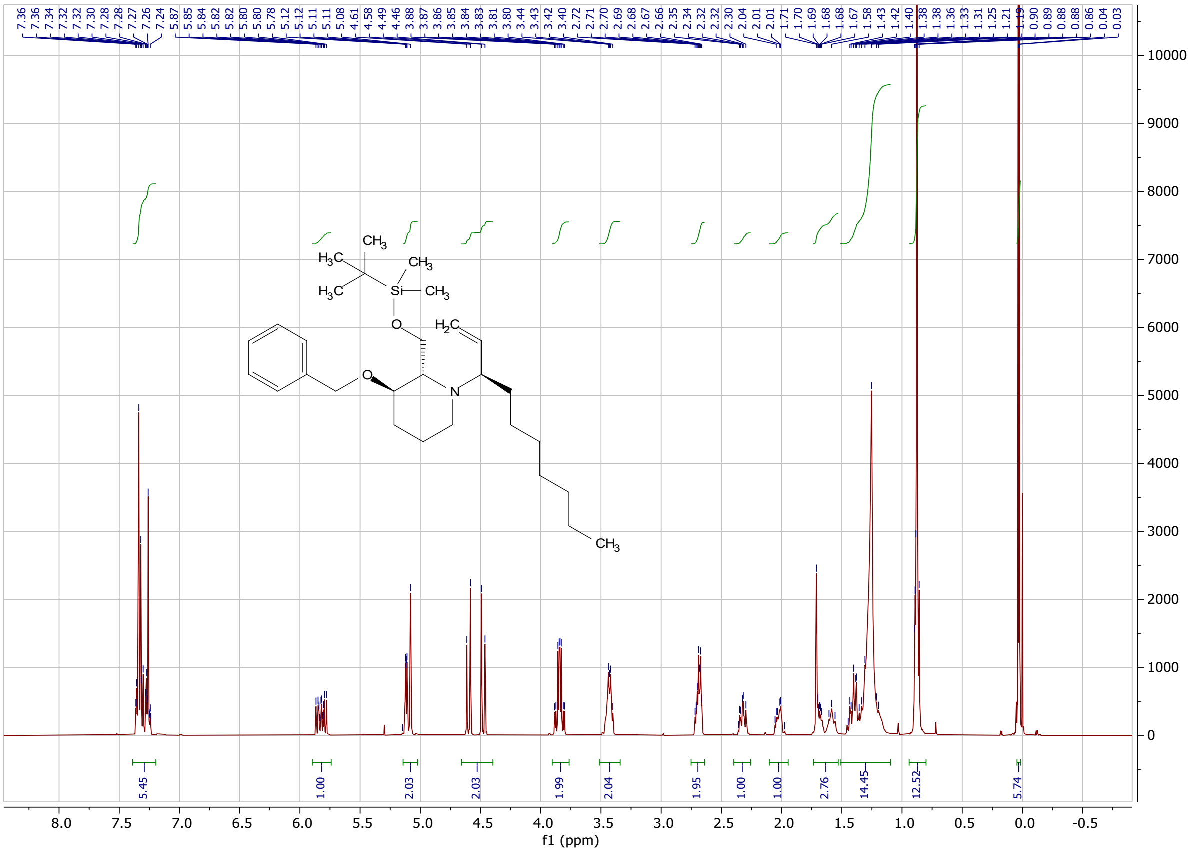
170.02
56.65
36.27
31.82
29.34
29.15
28.24
25.65
24.84
22.73
22.48
14.20
f1 (ppm)

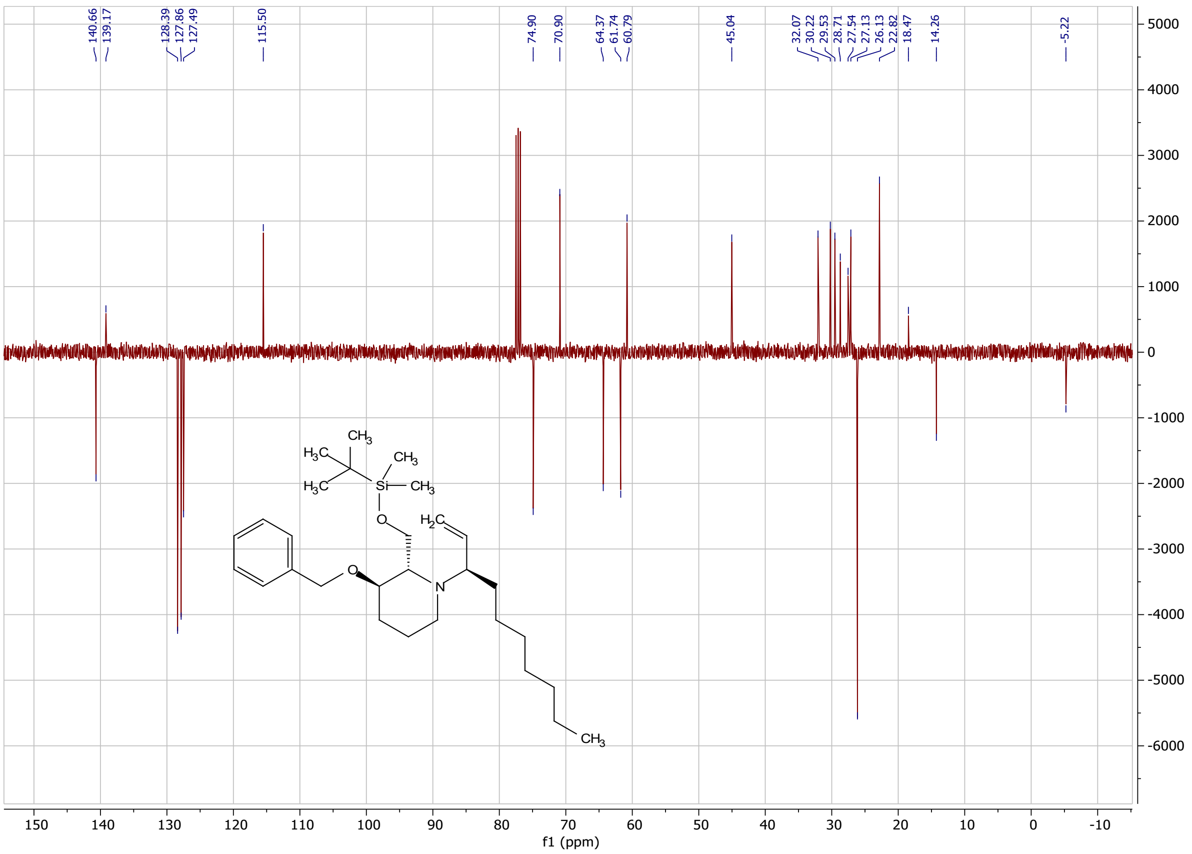

f1 (ppm)
1.00
2.25
1.03
1.03
1.60
1.22
20.71
0.03
3.27

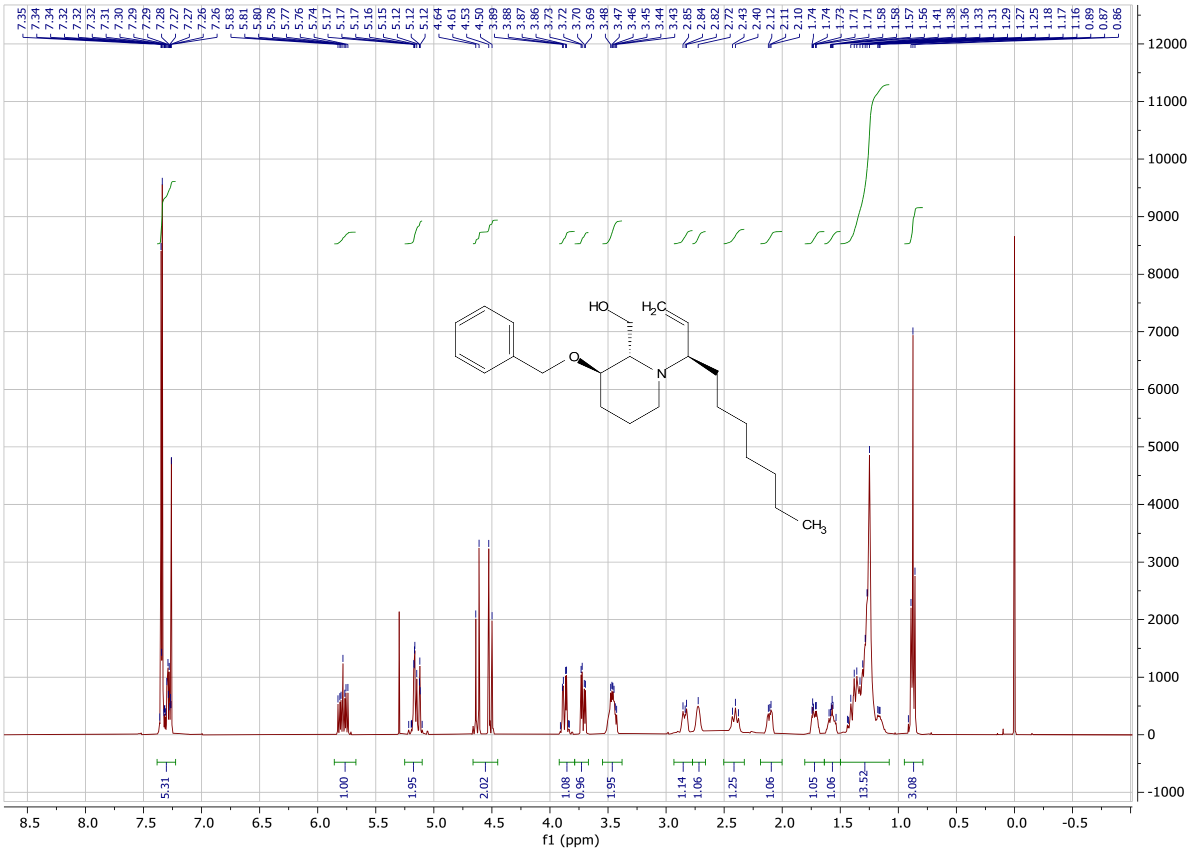

140.13
116.53
58.89
55.86
35.42
31.92
29.49
29.34
25.62
22.76
22.74
14.23
f1 (ppm)

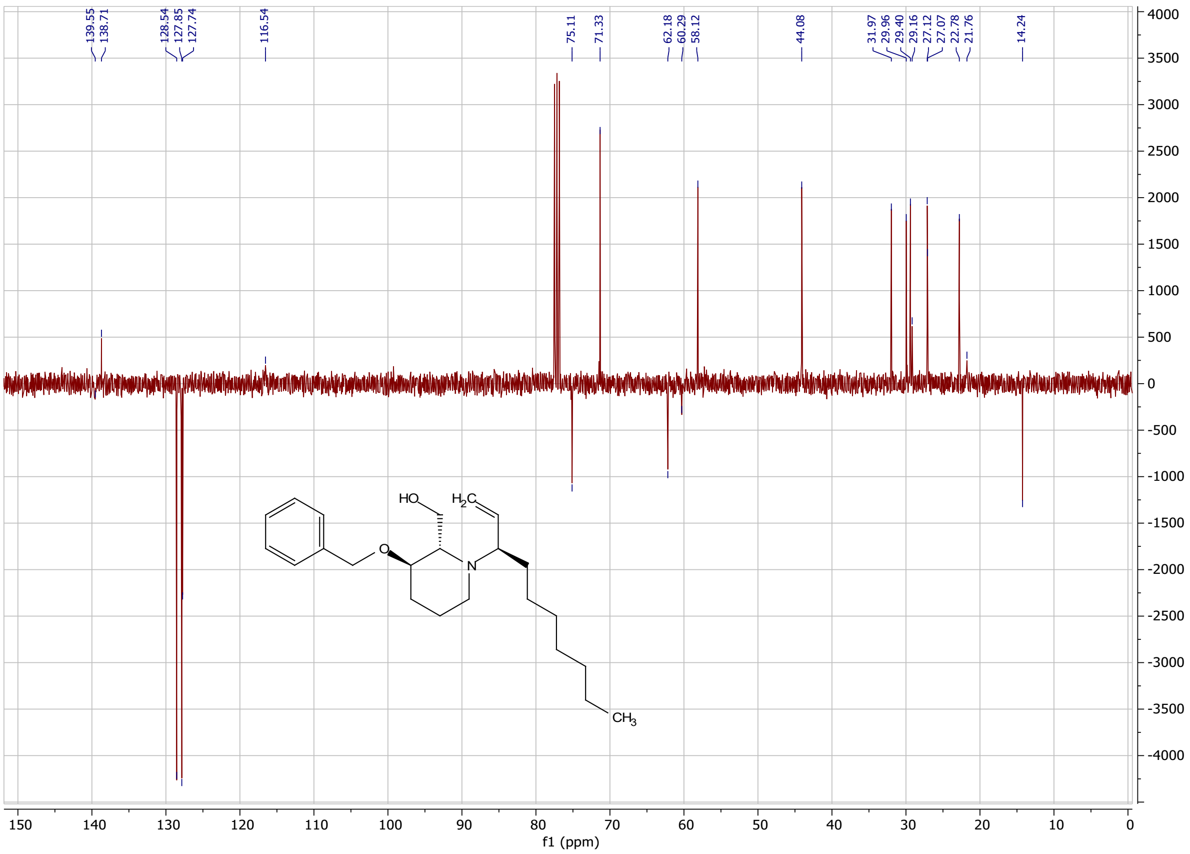

7.26
5.82
5.80
5.79
5.77
5.76
5.75
5.73
5.12
5.11
5.08
5.07
5.07
5.02
5.02
5.01
4.99
4.99
4.99
3.28
3.26
1.53
1.42
1.40
1.38
1.31
1.27
1.26
0.89
0.87
0.85
-0.01
H2C
H2N
CH3
1.00
2.05
1.01
2.43
12.76
3.17
f1 (ppm)

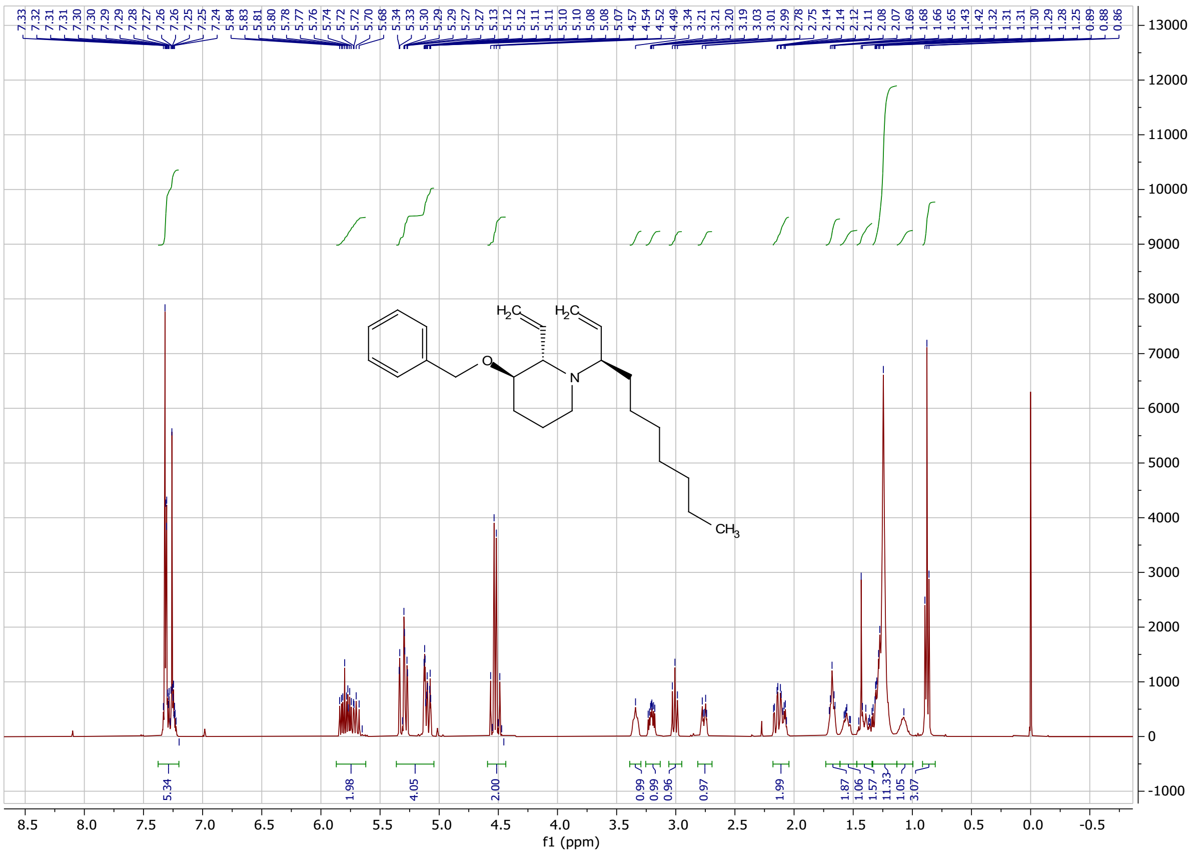

143.56
113.46
54.68
37.67
31.96
29.72
29.40
26.20
22.80
14.24
H2C
H2N
CH3
f1 (ppm)

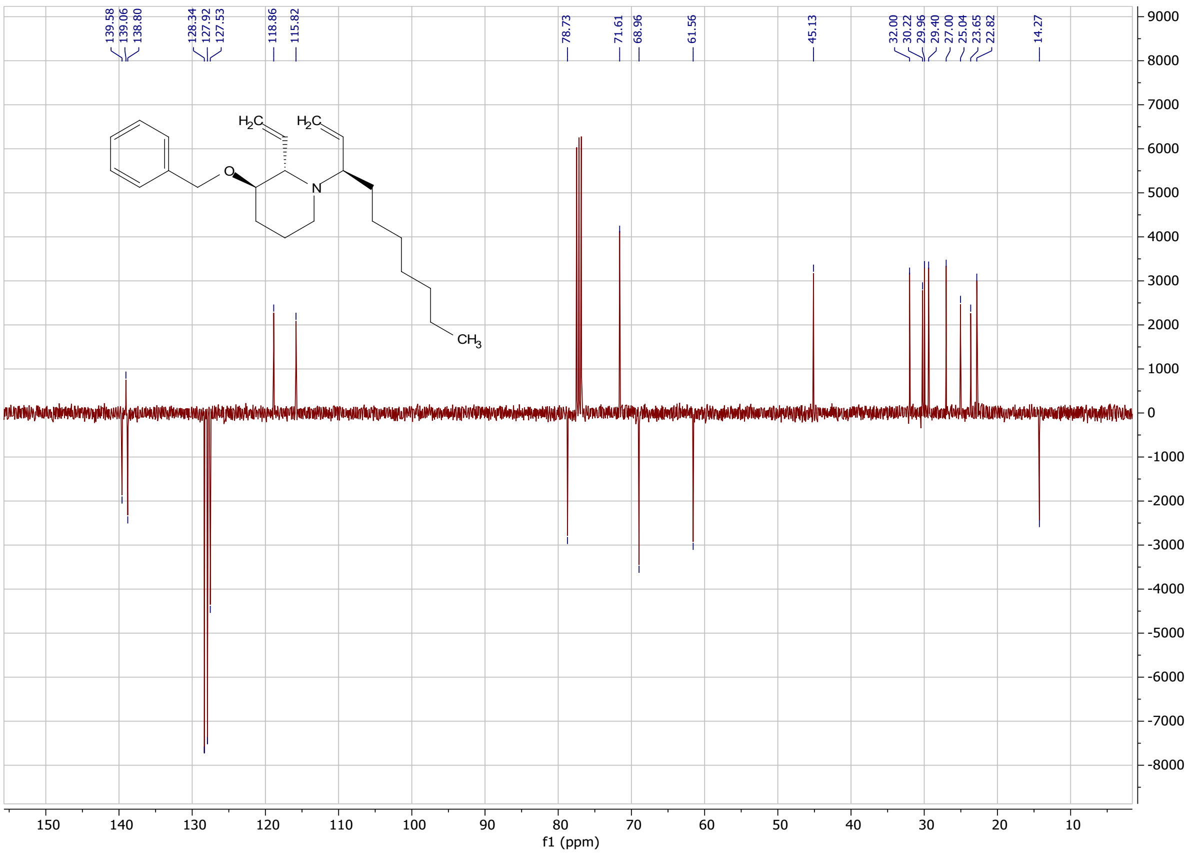

5.45
1.00
2.03
2.03
1.99
2.04
1.95
1.00
1.00
2.76
14.45
12.52
5.74
f1 (ppm)

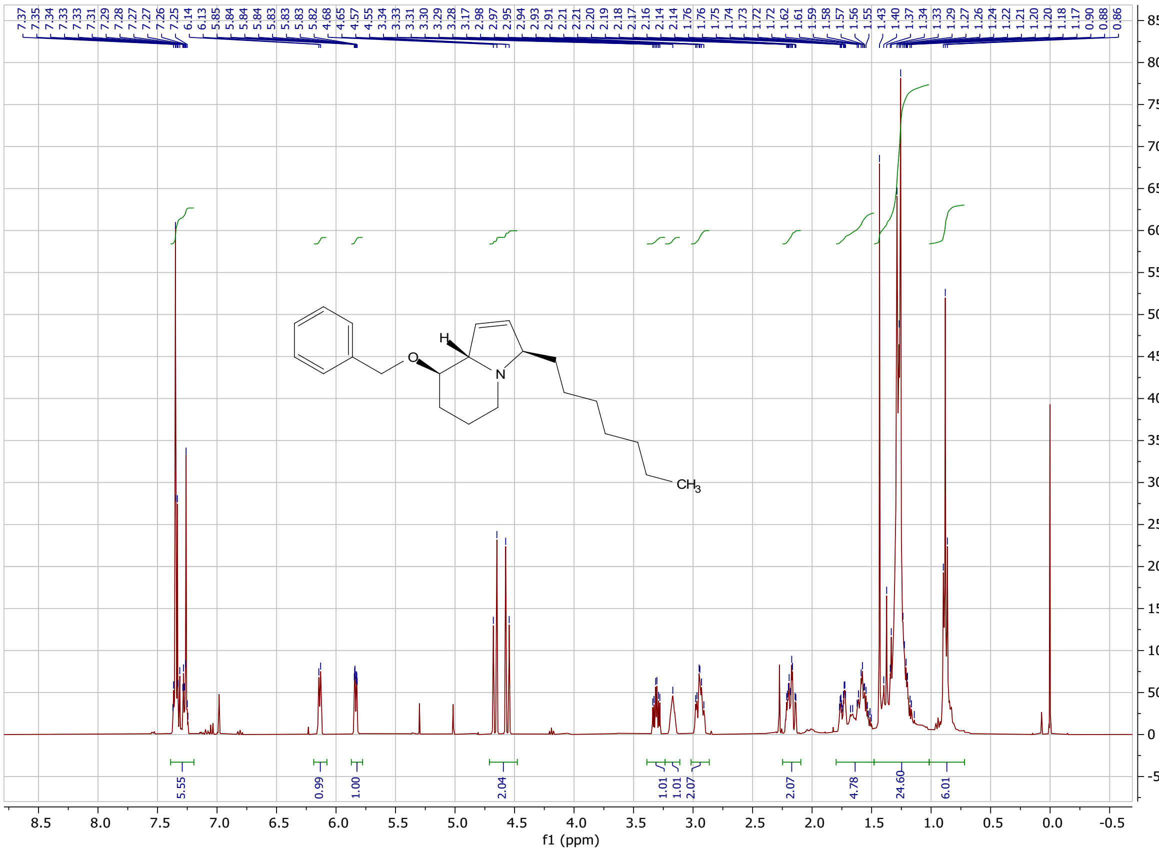

140.66
139.17
128.39
127.86
127.49
115.50
74.90
70.90
64.37
61.74
60.79
45.04
32.07
30.22
29.53
28.71
27.54
27.13
26.13
22.82
18.47
14.26
-5.22
f1 (ppm)

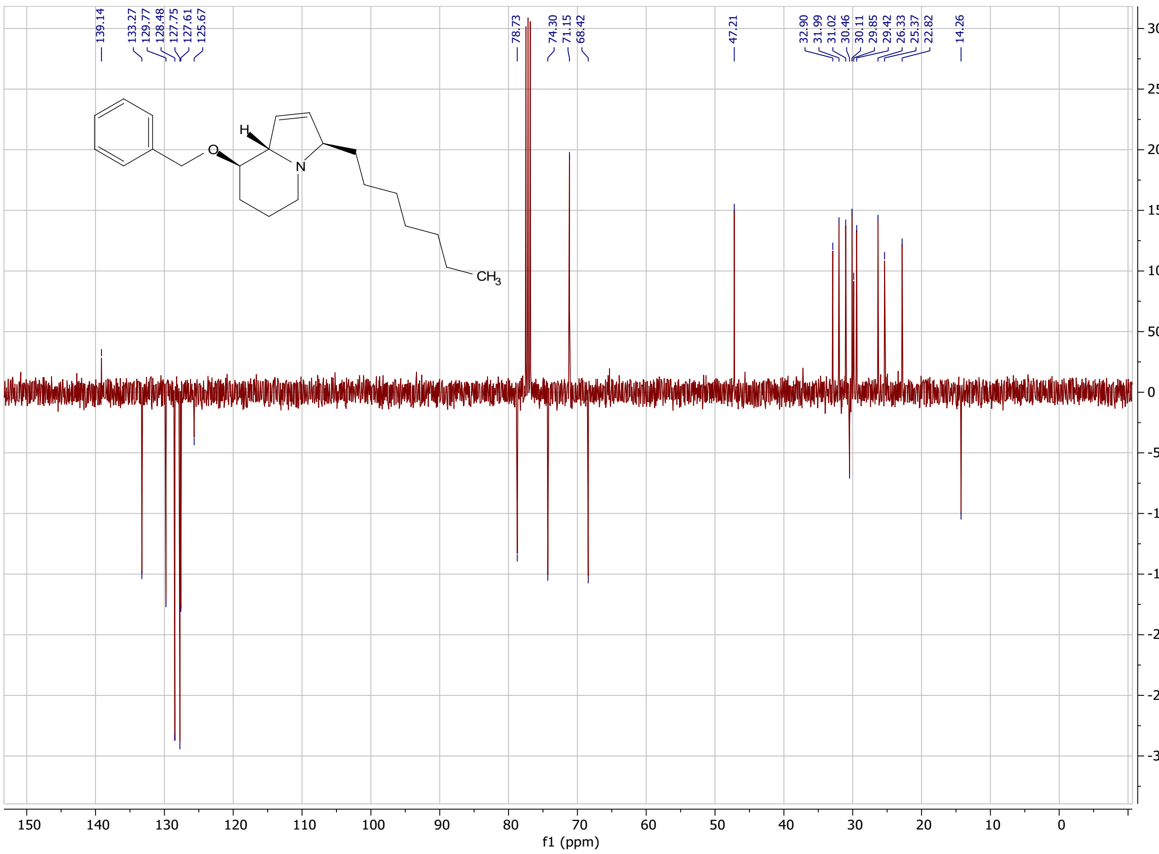


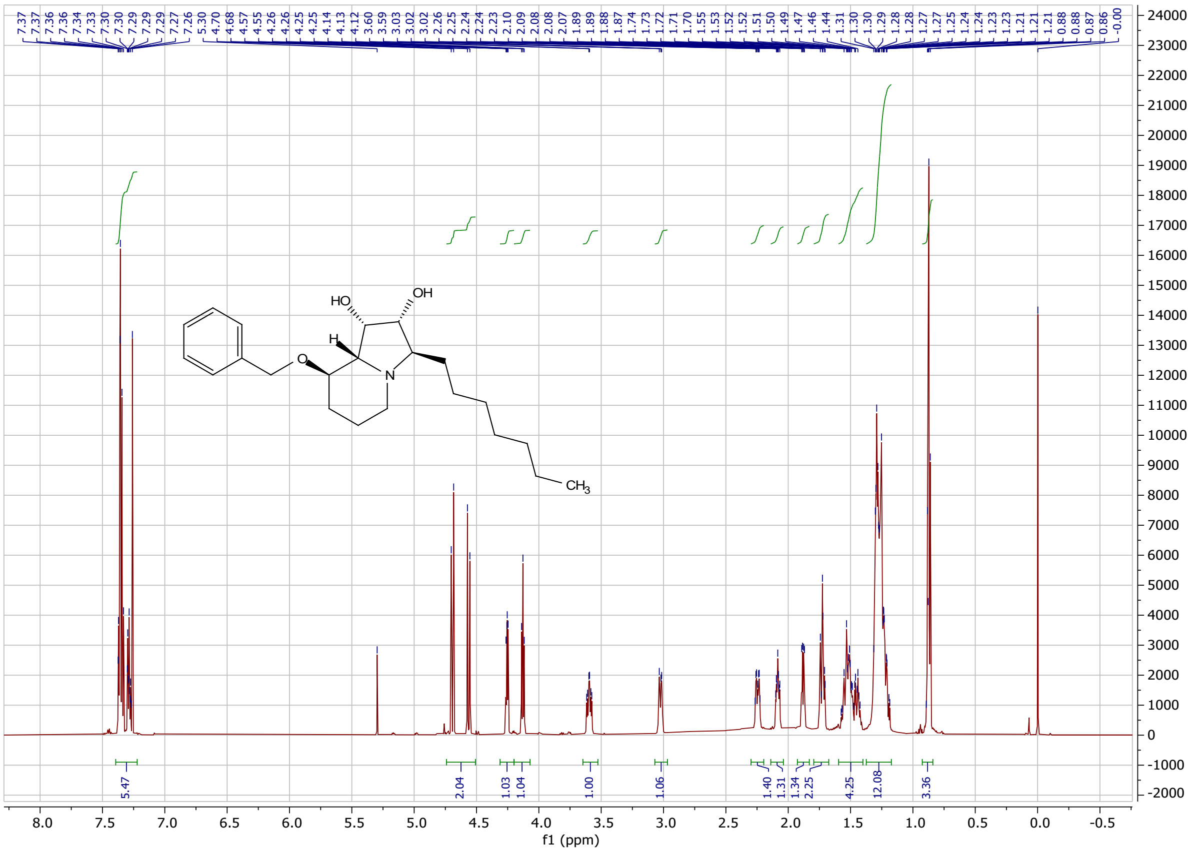


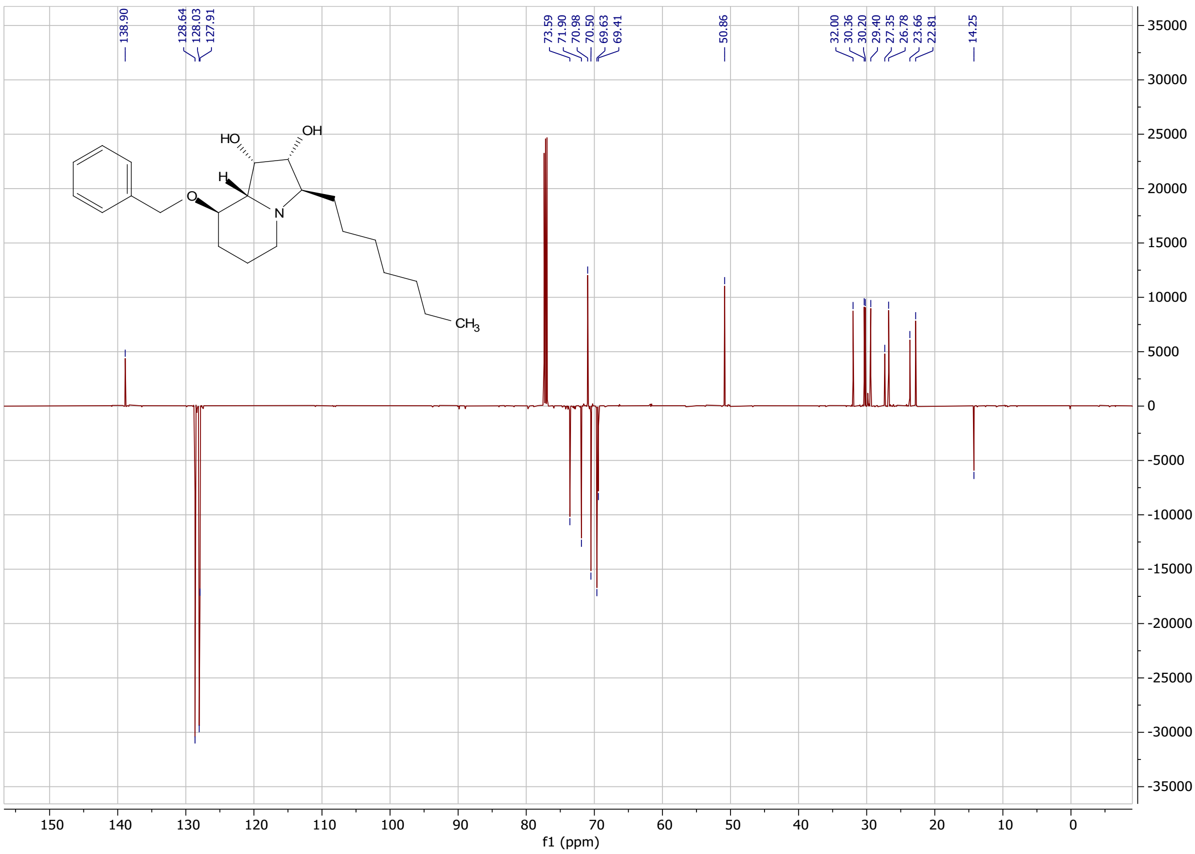


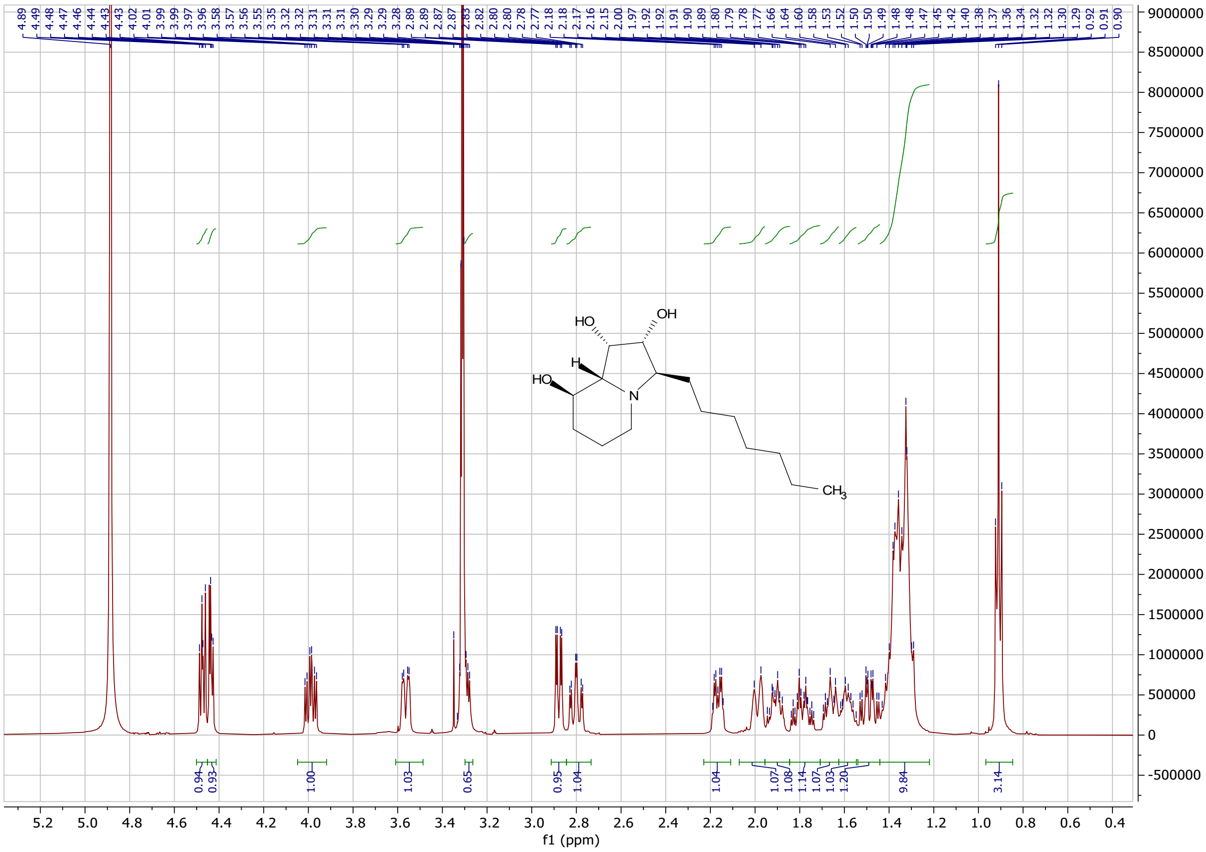


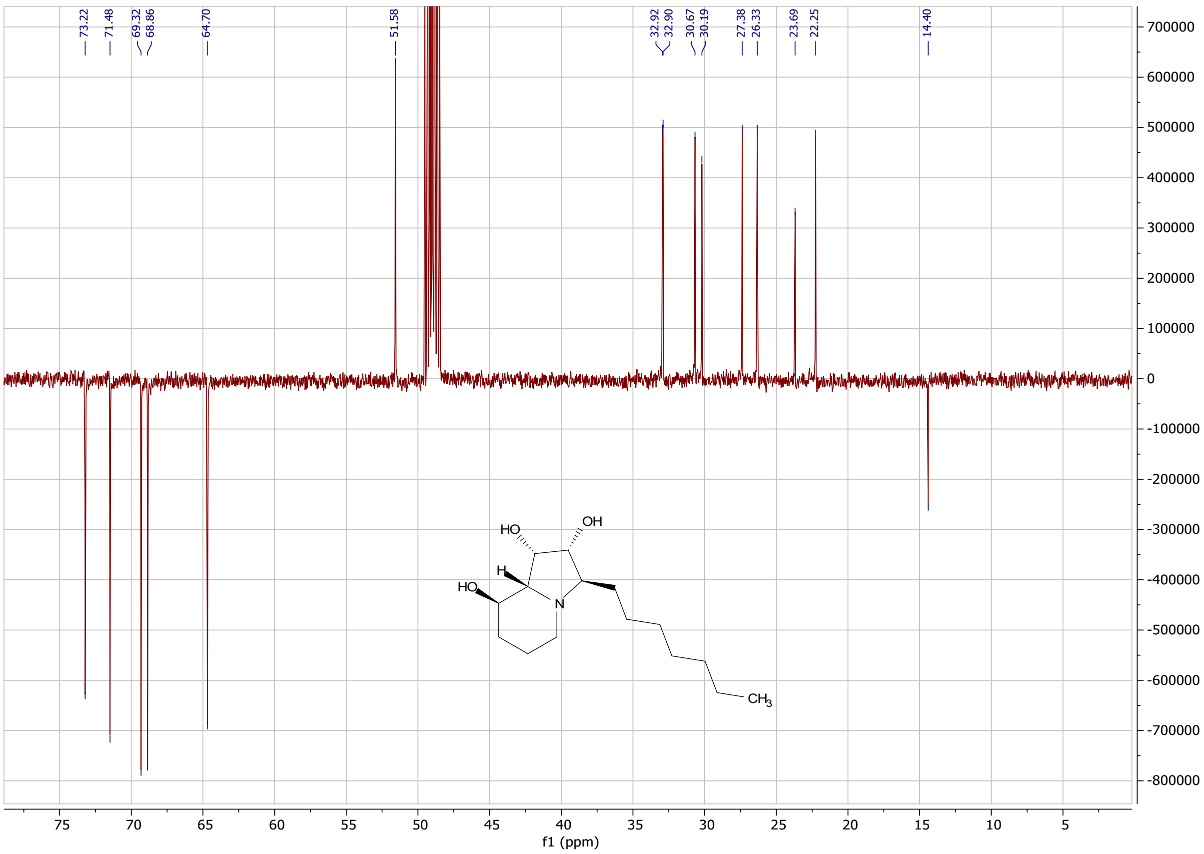

7.37 7.35 7.34 7.33 7.33 7.31 7.29 7.28 7.27 7.27 7.26 7.25 6.14 6.13 5.85 5.84 5.84 5.84 5.83 5.83 5.83 5.82 4.68 4.65 4.57 4.55 3.34 3.33 3.31 3.30 3.29 3.28 3.17 2.98 2.97 2.97 2.95 2.94 2.93 2.93 2.91 2.21 2.21 2.20 2.19 2.18 2.17 2.16 2.14 2.14 2.14 1.76 1.76 1.75 1.74 1.73 1.72 1.72 1.62 1.61 1.59 1.58 1.57 1.56 1.55 1.43 1.40 1.37 1.34 1.33 1.29 1.27 1.26 1.24 1.22 1.21 1.20 1.20 1.18 1.17 0.90 0.88 0.86
5.55 0.99 1.00 2.04 1.01 1.01 2.07 2.07 4.78 24.60 6.01
H
O
N
CH3
f1 (ppm)


139.14 133.27 129.77 128.48 127.75 127.61 125.67 78.73 74.30 71.15 68.42 47.21 32.90 31.99 31.02 30.46 30.11 29.85 29.42 26.33 25.37 22.82 14.26
H
O
N
CH3
f1 (ppm)


HO
OH
H
O
N
CH3
5.47
2.04
1.03
1.04
1.00
1.06
1.40
1.31
1.34
2.25
4.25
12.08
3.36
f1 (ppm)


138.90
128.64
128.03
127.91
73.59
71.90
70.98
70.50
69.63
69.41
50.86
32.00
30.36
30.20
29.40
27.35
26.78
23.66
22.81
14.25
HO
OH
H
O
N
CH3
f1 (ppm)


HO
OH
H
HO
N
CH3
f1 (ppm)


73.22
71.48
69.32
68.86
64.70
51.58
32.92
32.90
30.67
30.19
27.38
26.33
23.69
22.25
14.40
HO
OH
H
HO
N
CH3
f1 (ppm)

References

1. Z. Armstrong, C. L. Kuo, D. Lahav, B. Liu, R. Johnson, T. J. M. Beenakker, C. de Boer, C. Wong, E. R. van Rijssel, M. F. Debets, B. I. Florea, C. Hissink, R. G. Boot, P. P. Geurink. H. Ovaa, M. van der Stelt, G. M. van der Marel, J. D. C. Codée, J. M. F. G. Aerts, L. Wu, H. S. Overkleeft, G. J. Davies, *J. Am. Chem. Soc.* 2020, **142**, 13021-13029.