

SUPPLEMENTARY MATERIAL

Synthetic Access to the Mandelalide Family of Macrolides: Development of an Anion Relay Chemistry Strategy

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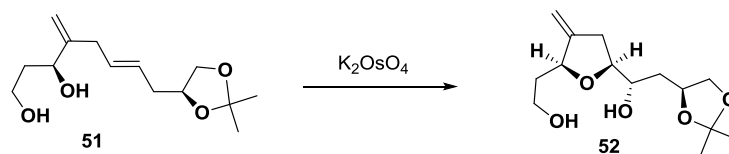
*smithab@sas.upenn.edu

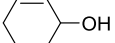
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Table S1. Conditions screened for osmium-mediated oxidative cyclization of diol 51

(conditions that provided the best results are highlighted)



Solvent mixture: acetone:H ₂ O	Acid: Cu(OTf)₂	Oxidant: pyridine-N-Oxide (PNO)	Temp.: room temp.
acetone:pH 5 buffer	Zn(OTf) ₂	4-nitropyridine-N-Oxide	40°C
acetone:pH 6.5 buffer	Sc(OTf) ₃		60°C
MeCN:H ₂ O	Al(OTf) ₃		90°C
MeCN:pH 4 buffer	CSA	Additive: citric acid	Conc.: 0.1M
MeCN:pH 5 buffer	TFA		0.04 M
MeCN:pH 6.5 buffer			0.02 M

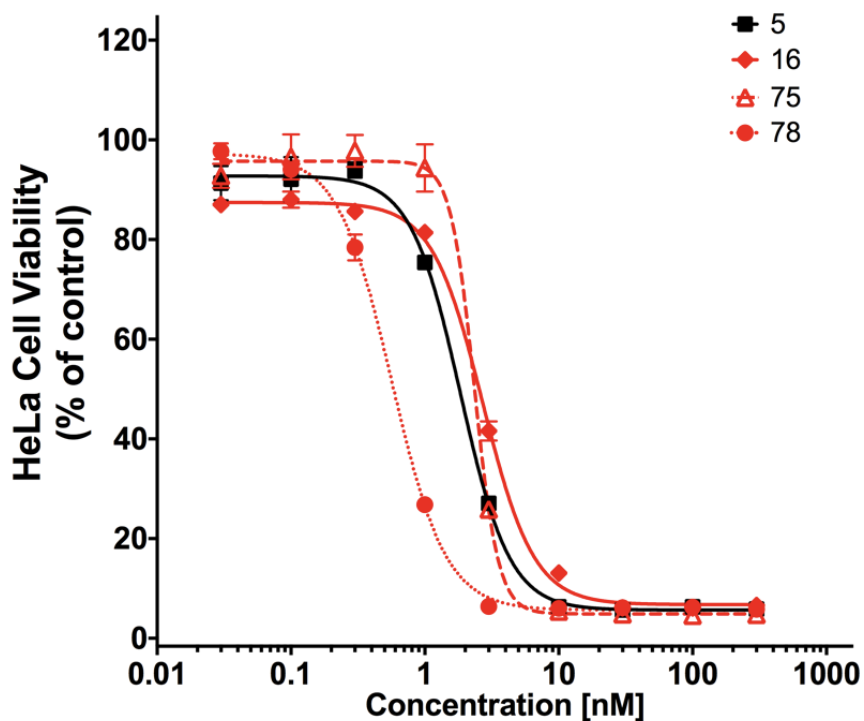


Figure S1. Comparative analysis of HeLa cell viability in response to synthetic compounds.

Concentration-response profiles for synthetic mandelalide compounds against human HeLa cervical cells. Cells were seeded at 10,000 cells per well and exposed to increasing concentrations (0.03–300 nM) of each compound or vehicle (0.1% DMSO) in triplicate for 72 h. Cell viability was determined by MTT assay with the viability of vehicle-treated cells defined as 100%. Graphs represent mean viability \pm SE (n = 3 wells per treatment) from a representative comparison that was repeated in at least three independent experiments.

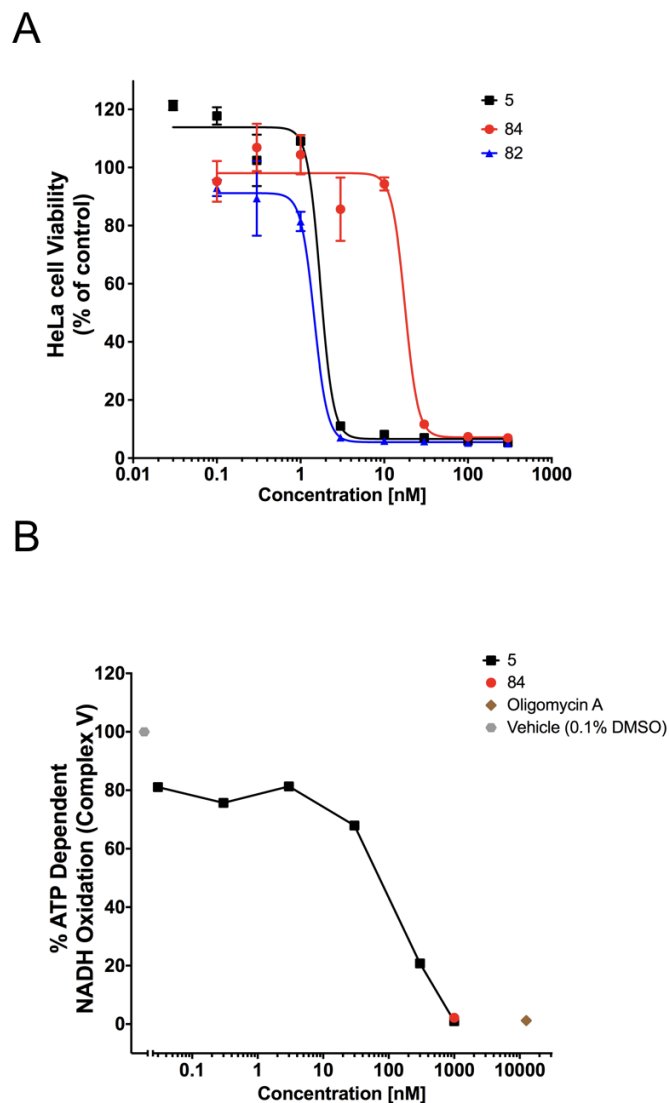


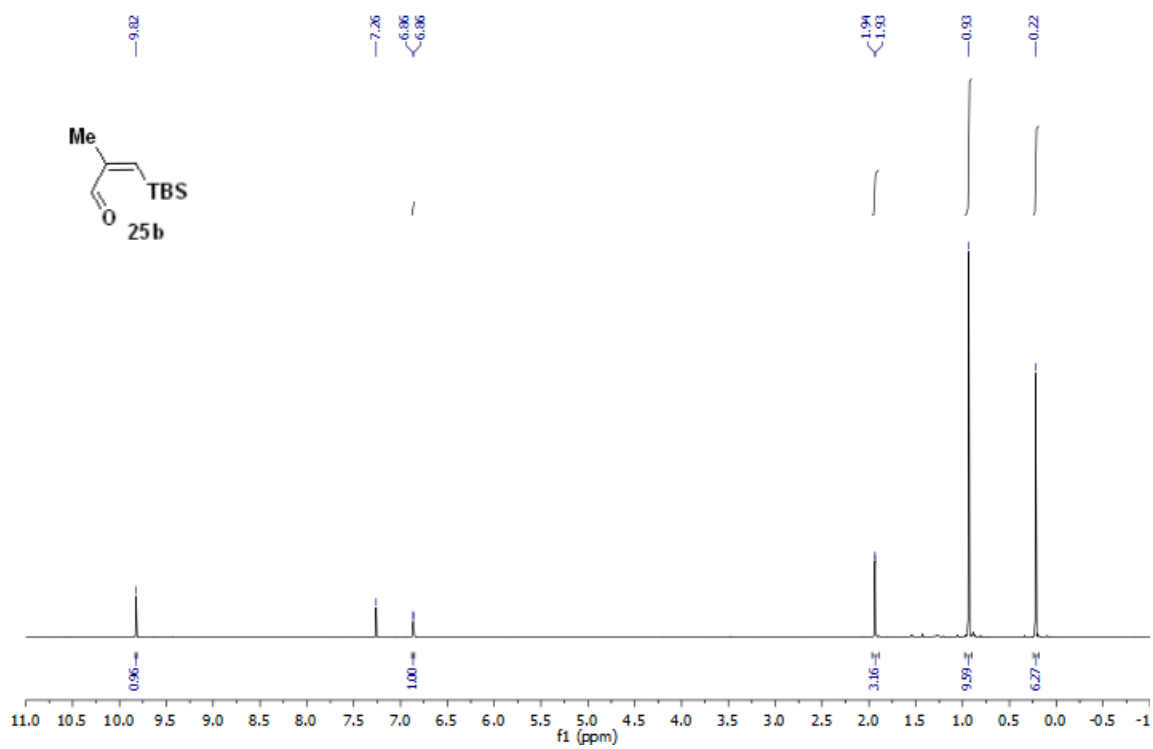
Figure S2. Analysis of the biological activity of alkyne-tagged and biotin-tagged mandelalide A analogs.

(A) Concentration-response profiles for (–)- mandelalide A (**5**), with alkyne (**82**) or biotin (**84**) tag at C₂₄ against human HeLa cervical cells. Cells were seeded at 10,000 cells per well and exposed to increasing concentrations of each compound or vehicle (0.1% DMSO) in triplicate for 72 h. Cell viability was determined by MTT assay with the viability of vehicle-treated cells defined as 100%.

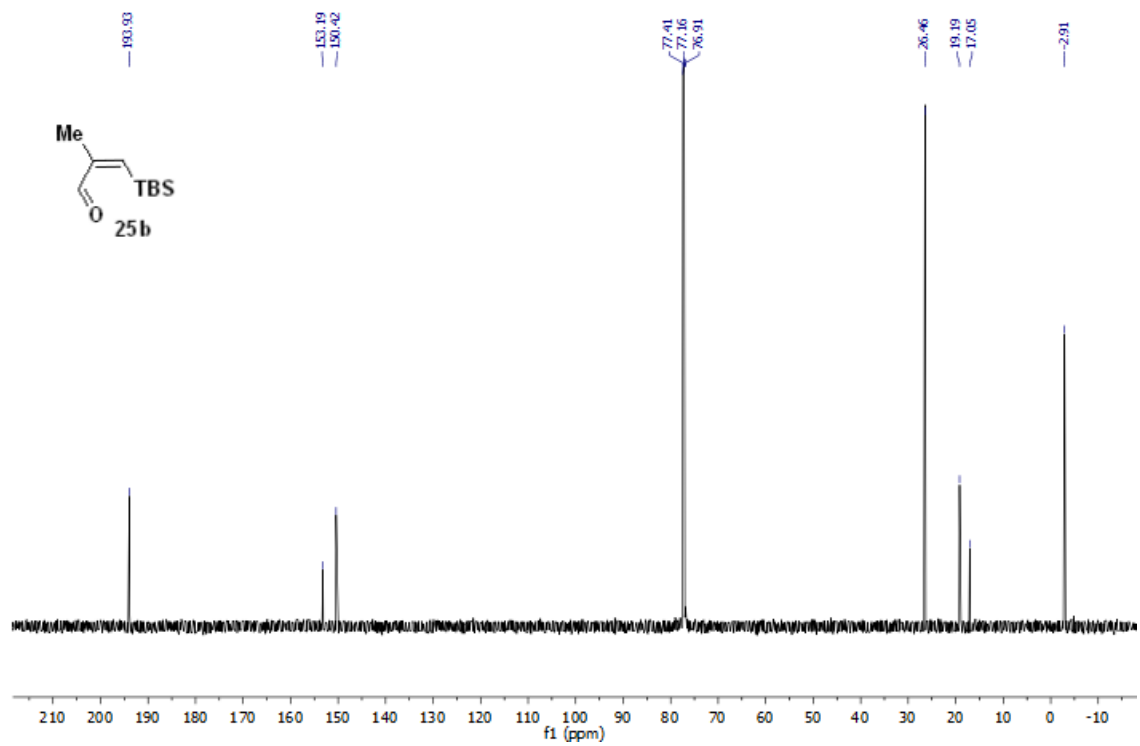
(B) Biotin-tagged mandelalide A (**84**) inhibits complex V activity in isolated mitochondria. The % rate of ATP-dependent NADH oxidation was calculated from a series of time- dependent reactions carried out in the presence of **84** or increasing concentrations of **5** using isolated mitochondria from bovine heart as the source of complex V ATP synthase activity. A saturating concentration of oligomycin A (12.5 μ M) was used as a control inhibitor of complex V.

^1H -NMR and ^{13}C -NMR spectra of synthetic compounds

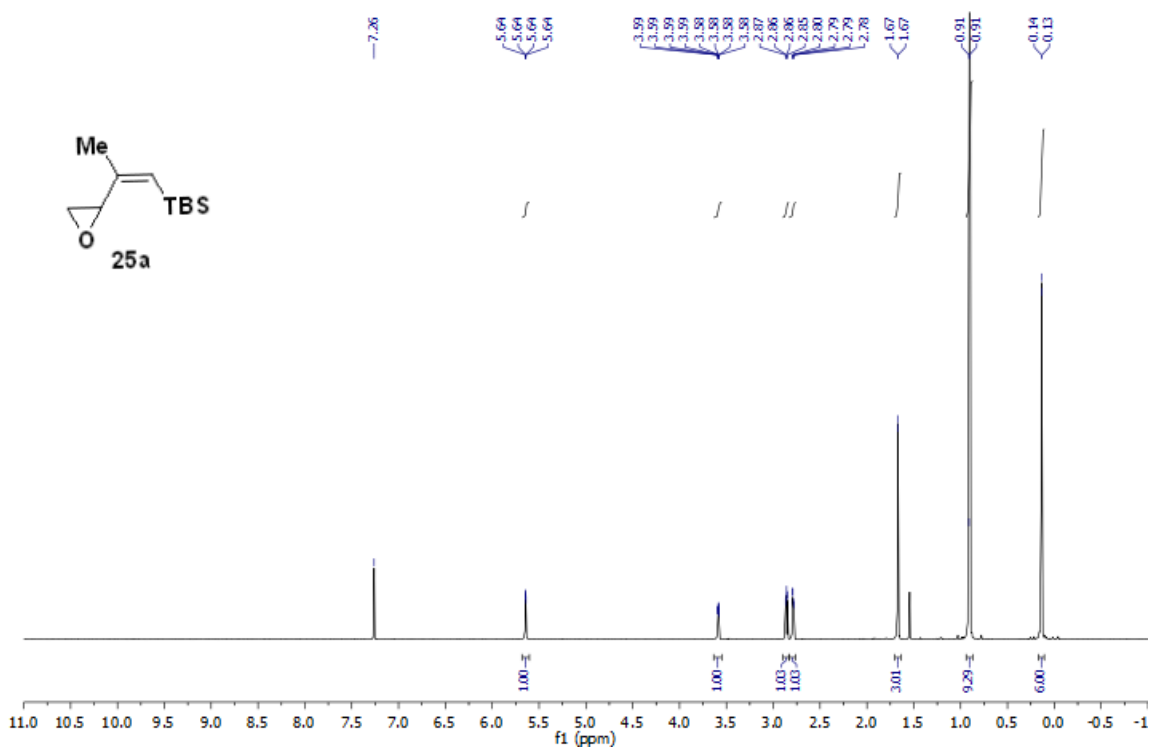
The 500 MHz $^1\text{H-NMR}$ Spectrum of Compound **25b** in CDCl_3



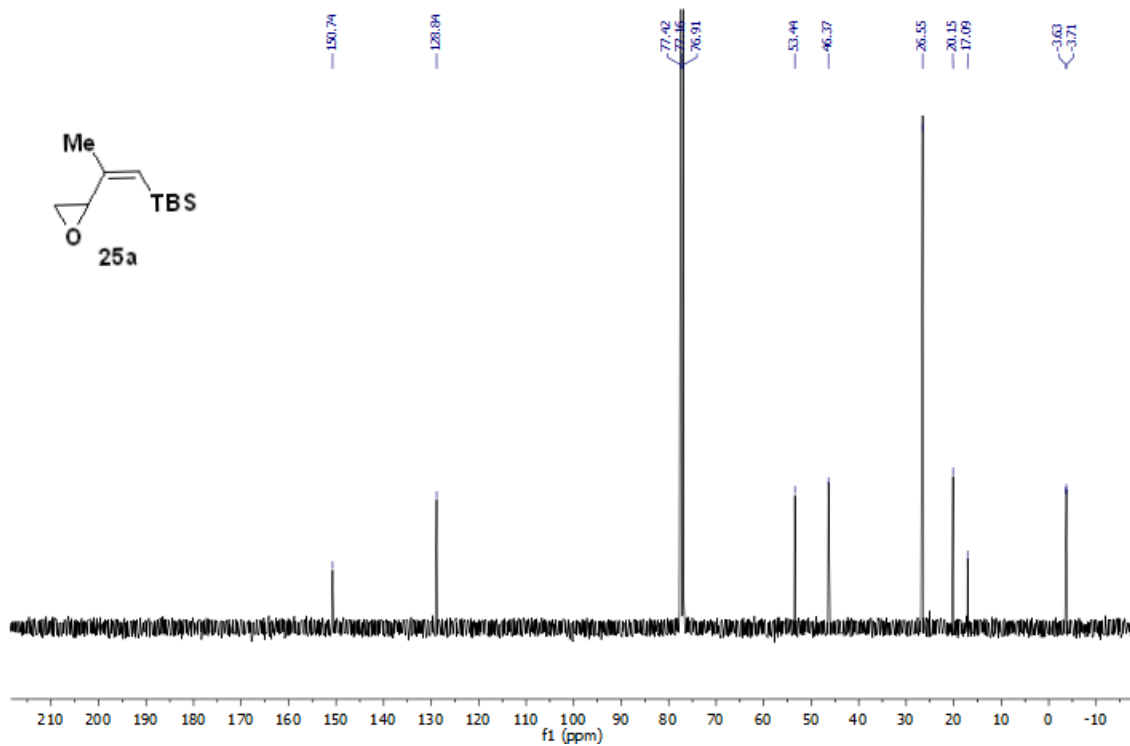
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound **25b** in CDCl_3



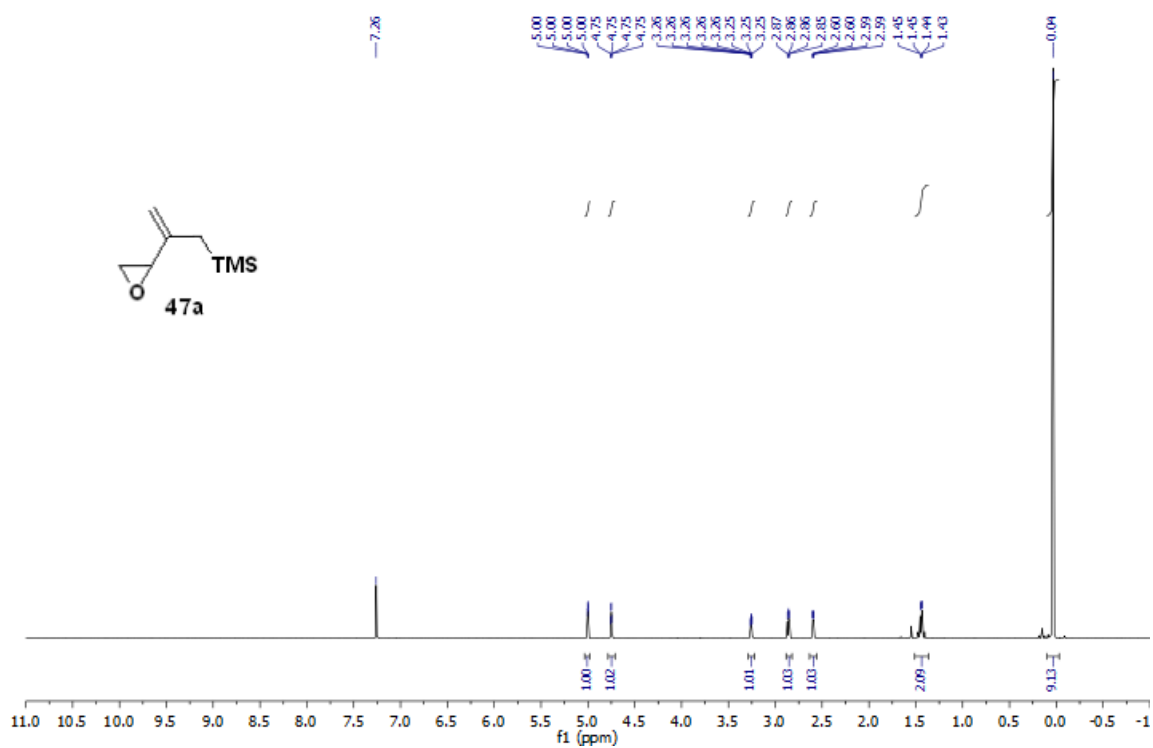
The 500 MHz $^1\text{H-NMR}$ Spectrum of Compound **25a** in CDCl_3



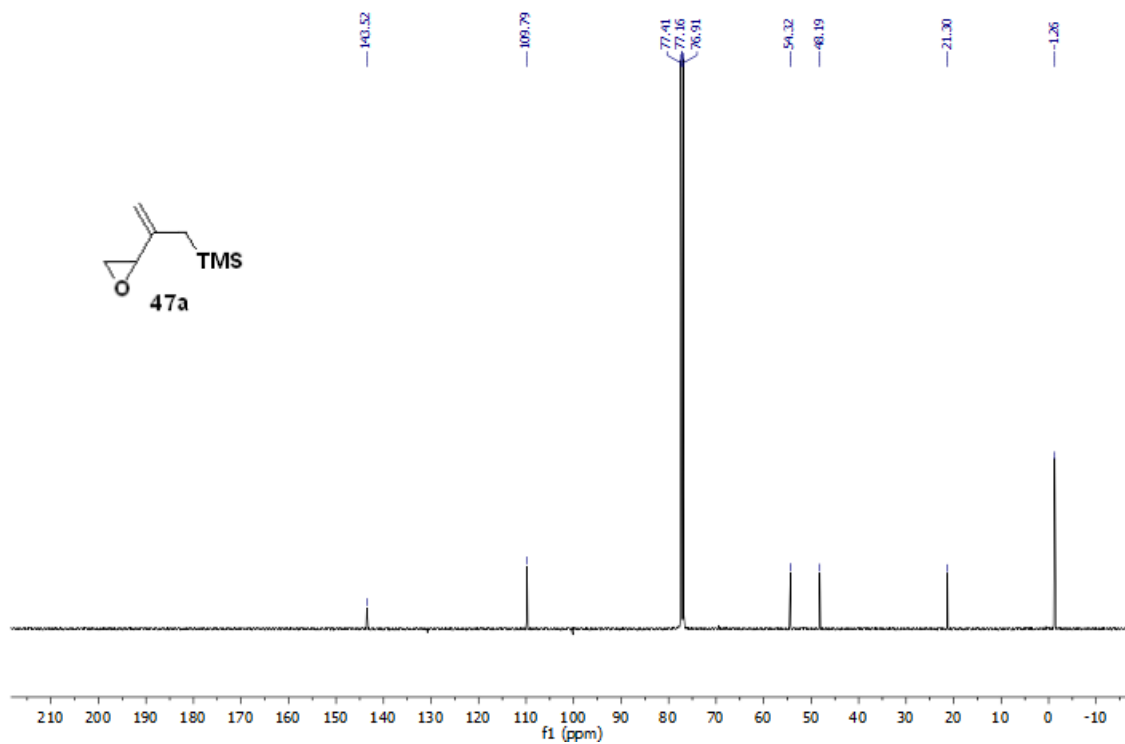
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound **25a** in CDCl_3



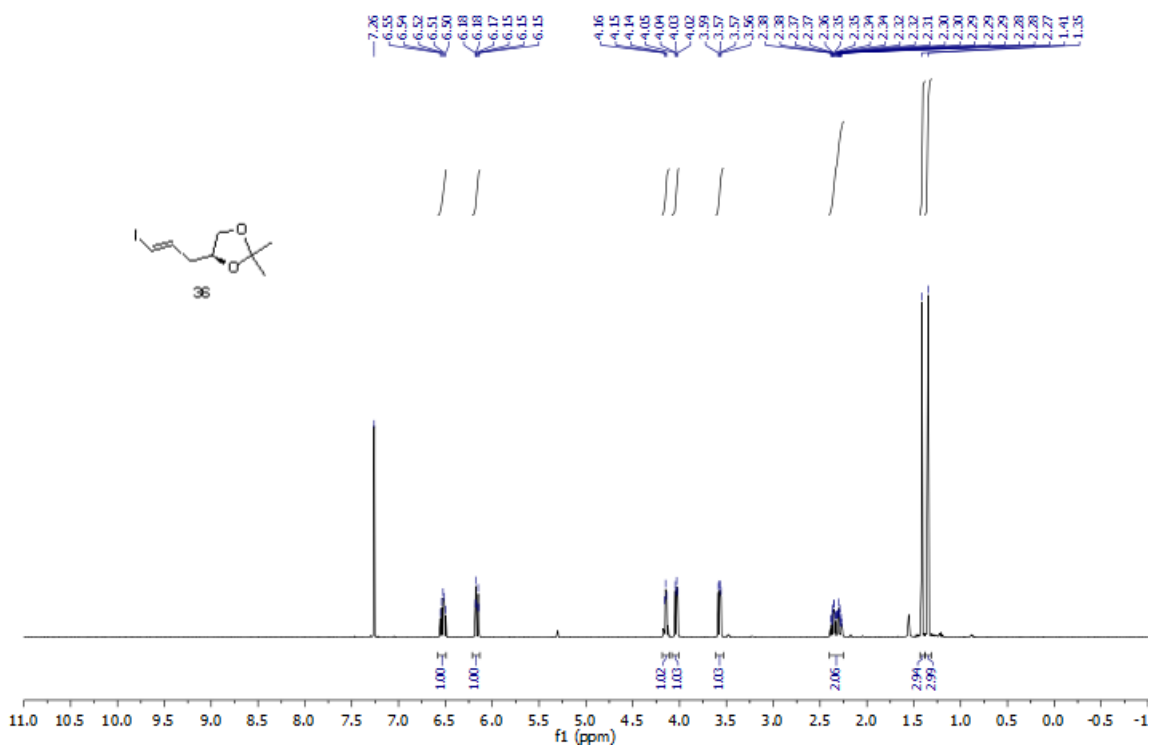
The 500 MHz ^1H -NMR Spectrum of Compound **47a** in CDCl_3



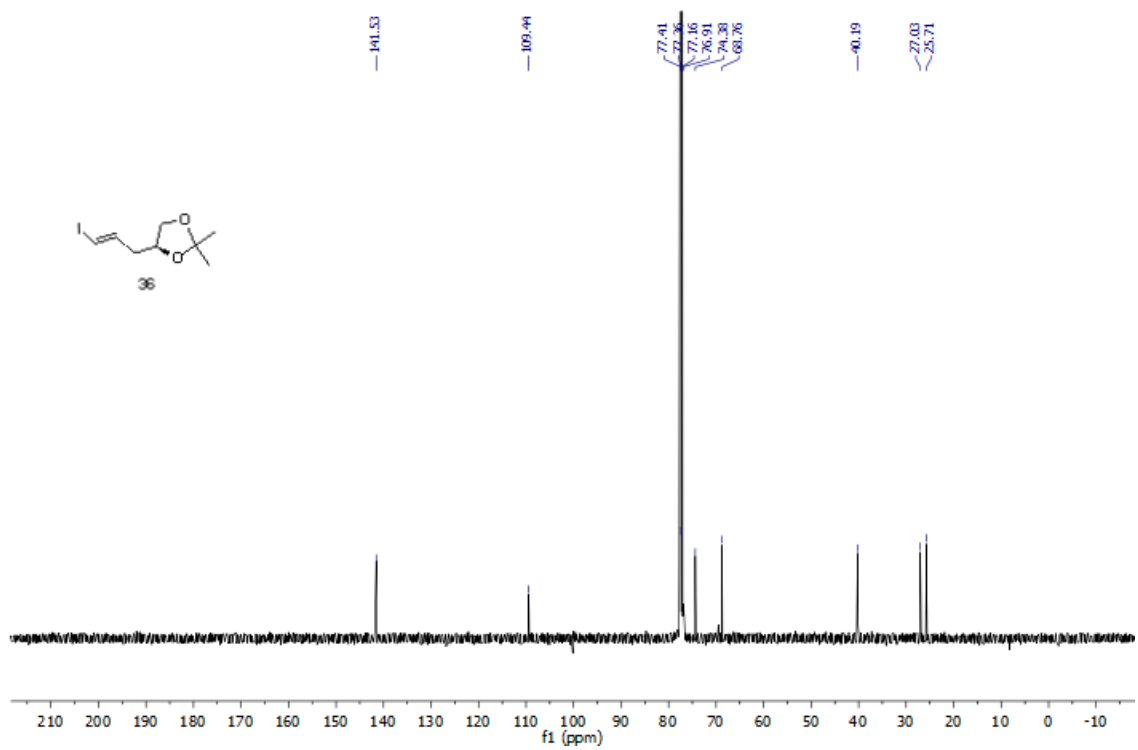
The 125 MHz ^{13}C -NMR Spectrum of Compound **47a** in CDCl_3



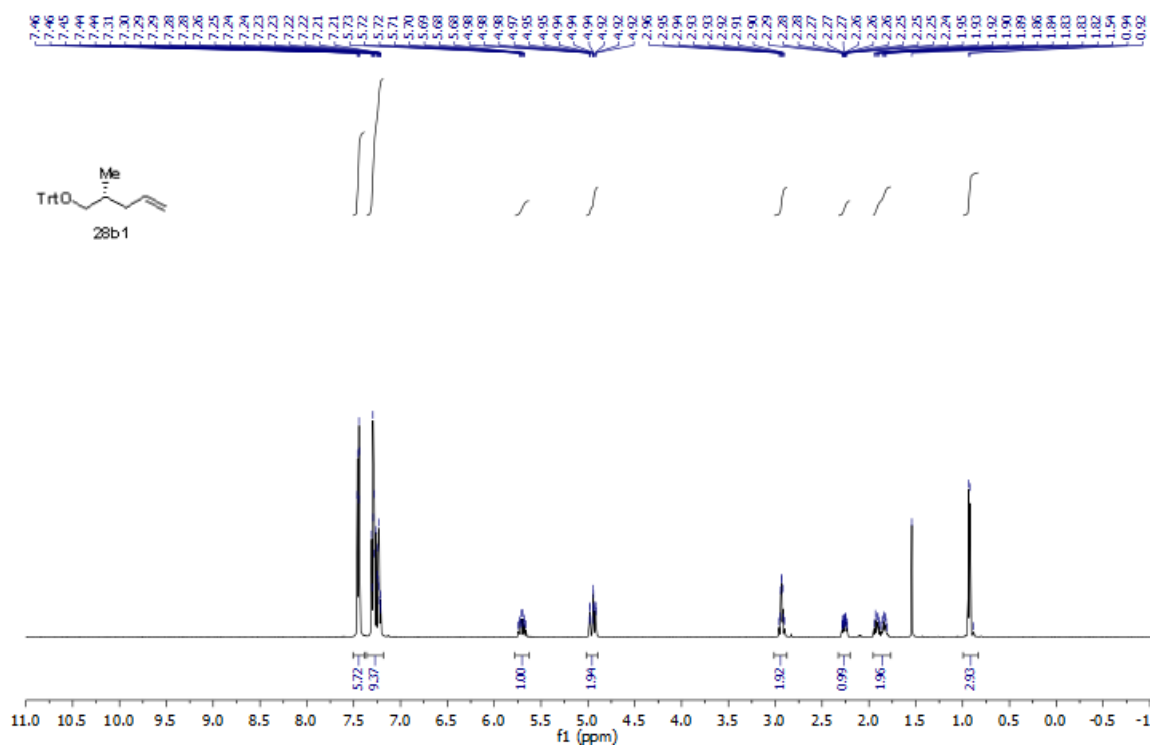
The 500 MHz ^1H -NMR Spectrum of Compound **36** in CDCl_3



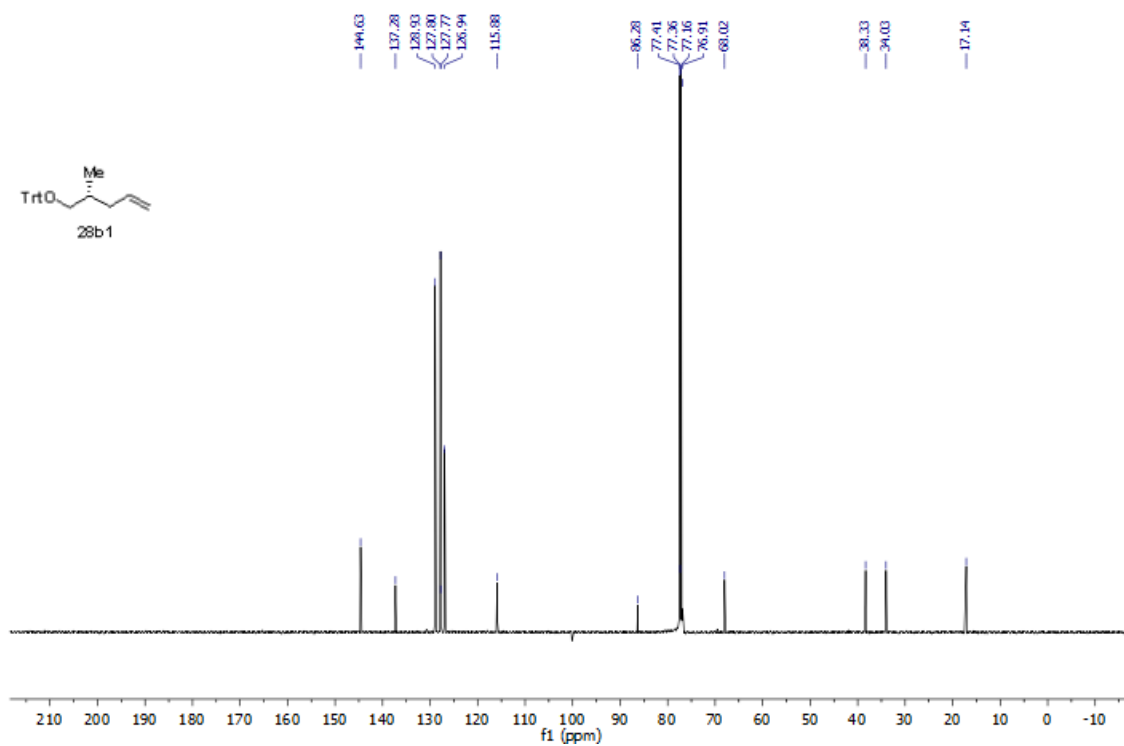
The 125 MHz ^{13}C -NMR Spectrum of Compound **36** in CDCl_3



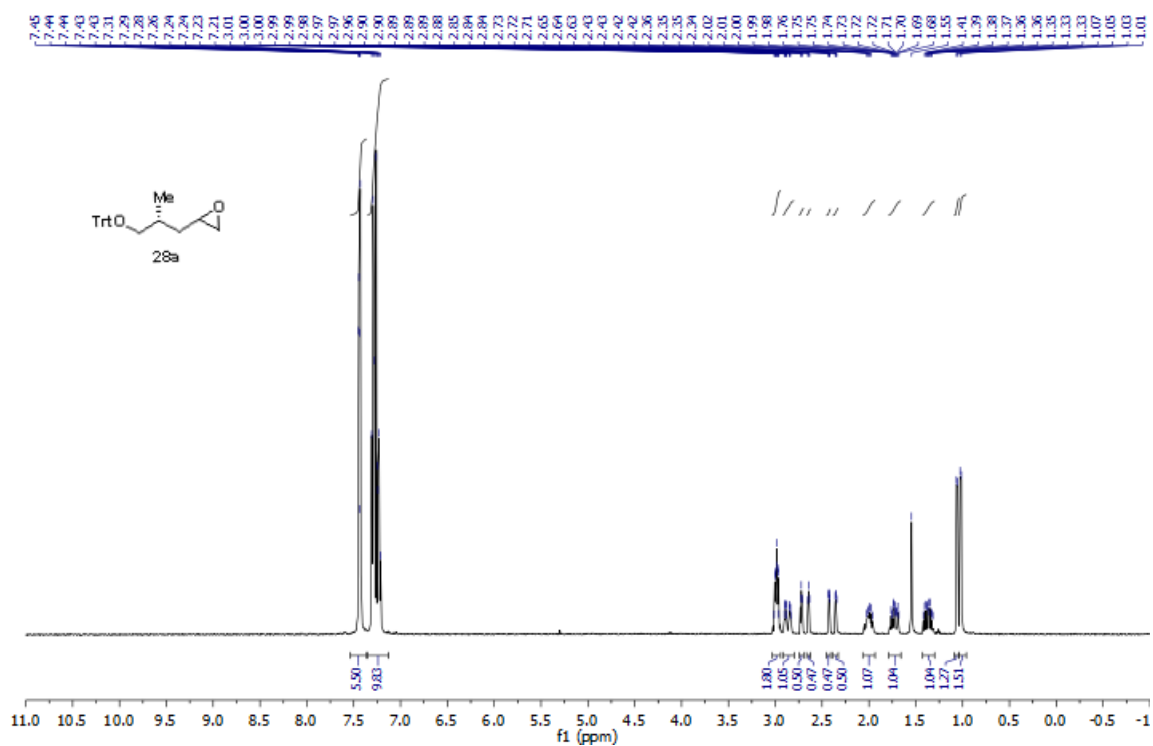
The 500 MHz ¹H-NMR Spectrum of Compound **28b1** in CDCl₃



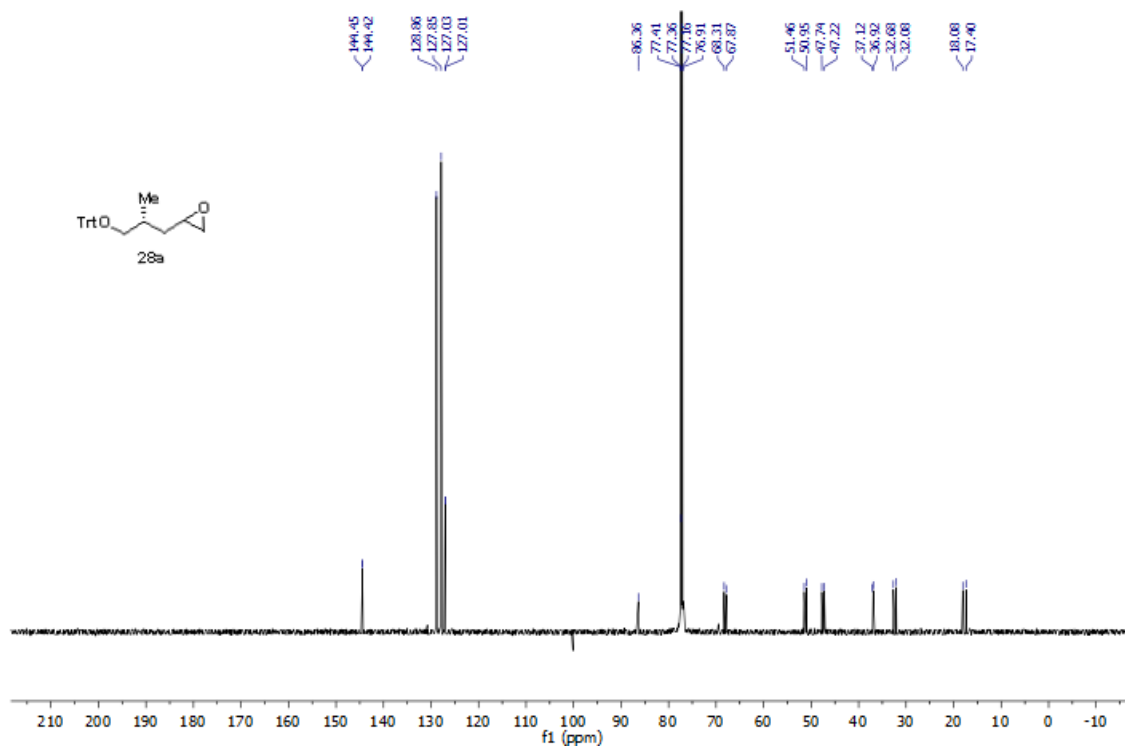
The 125 MHz ¹³C-NMR Spectrum of Compound **28b1** in CDCl₃



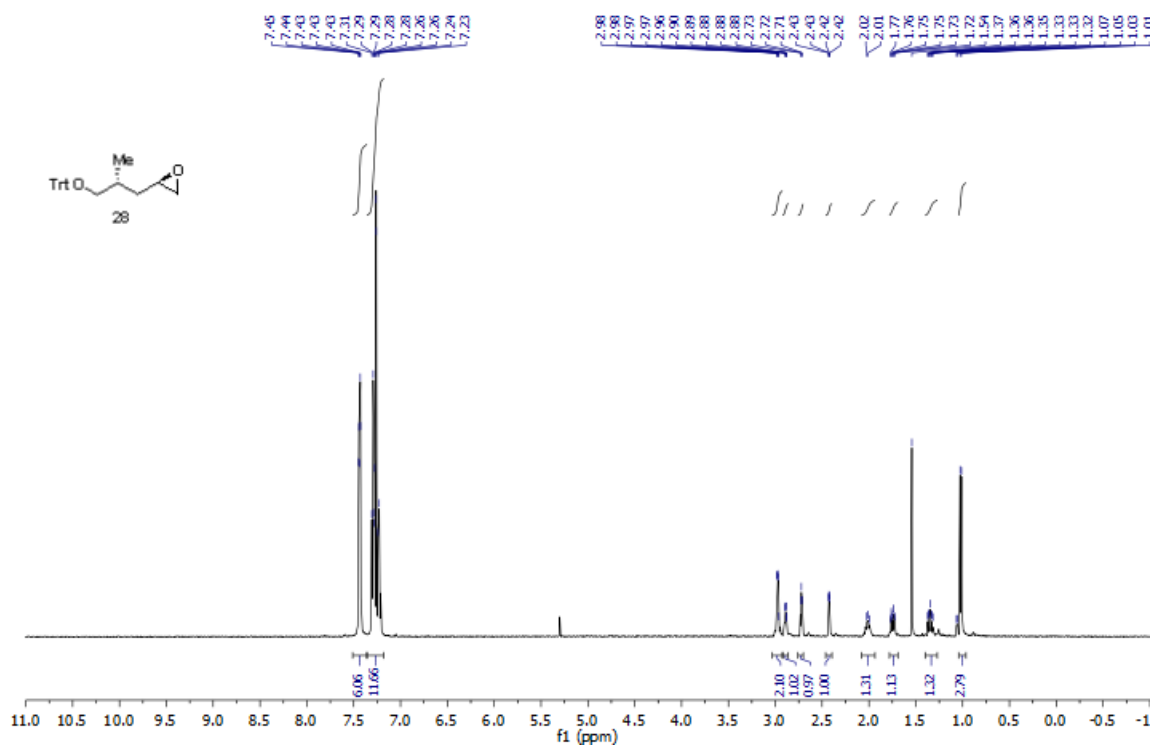
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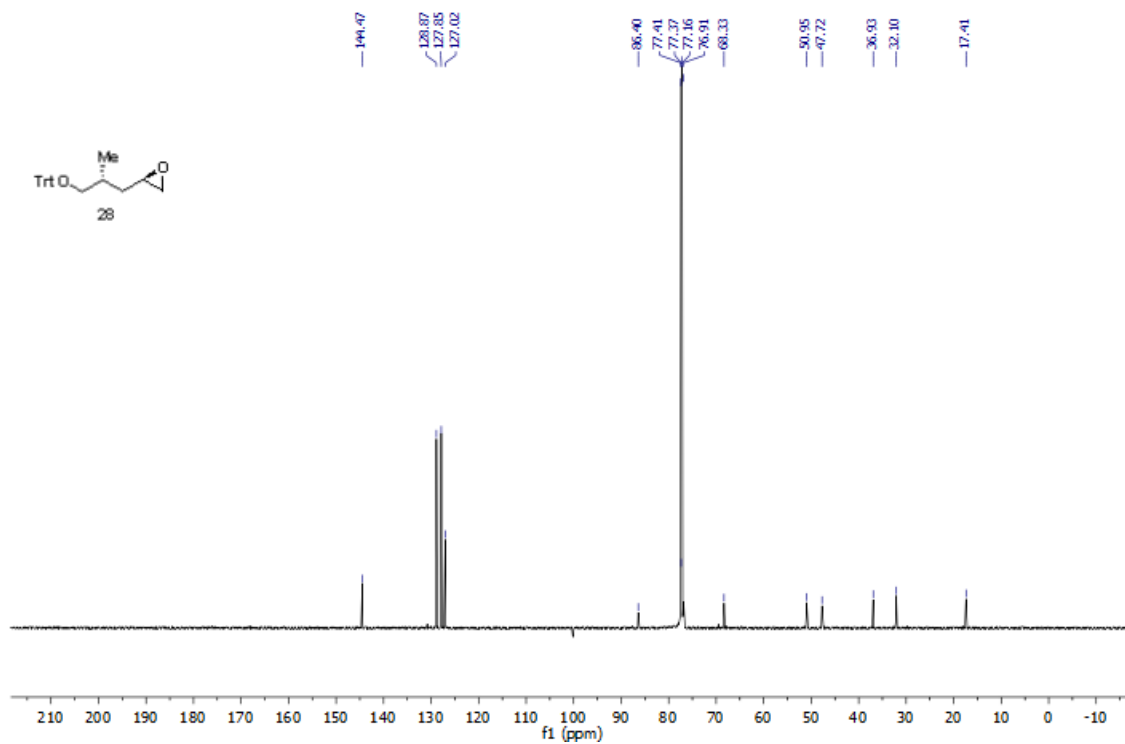
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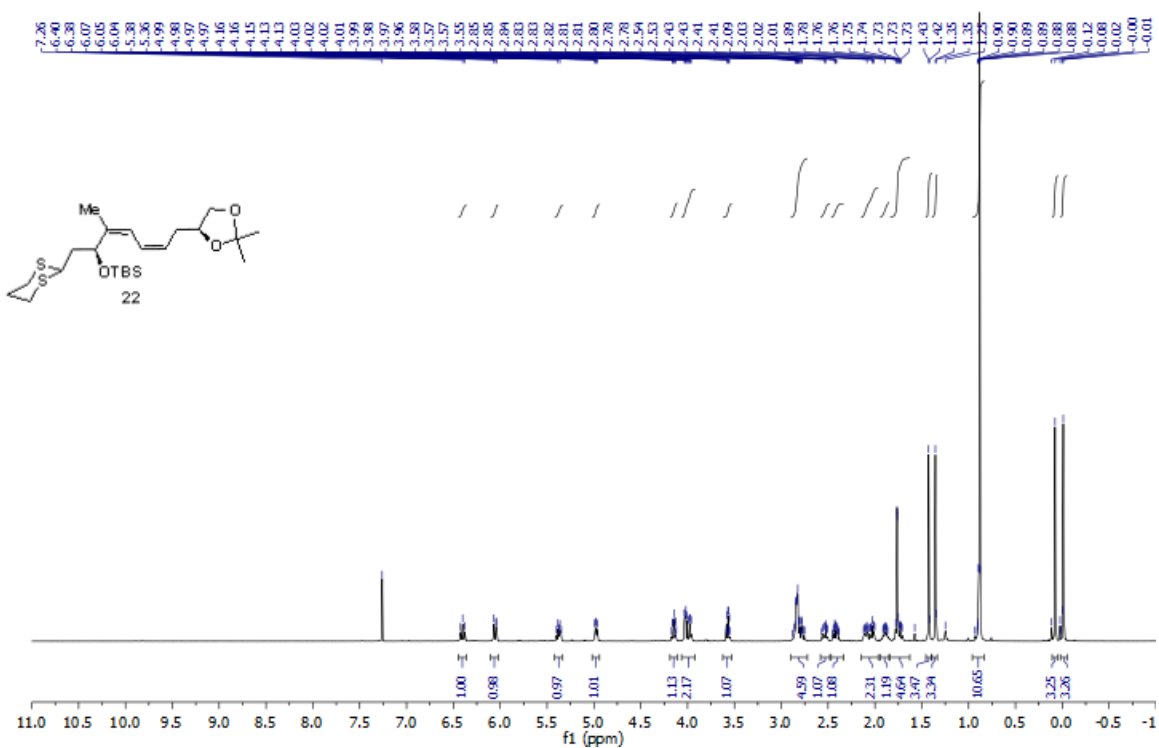
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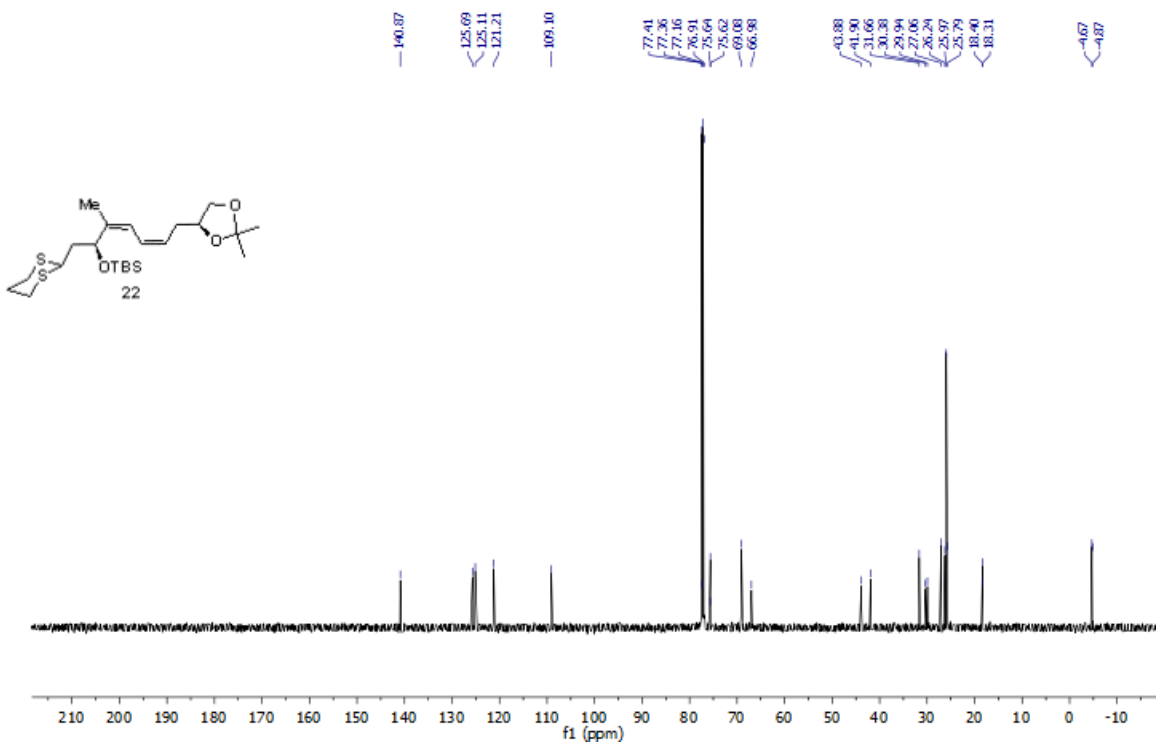
The 125 MHz ^{13}C -NMR Spectrum of Compound **28** in CDCl_3



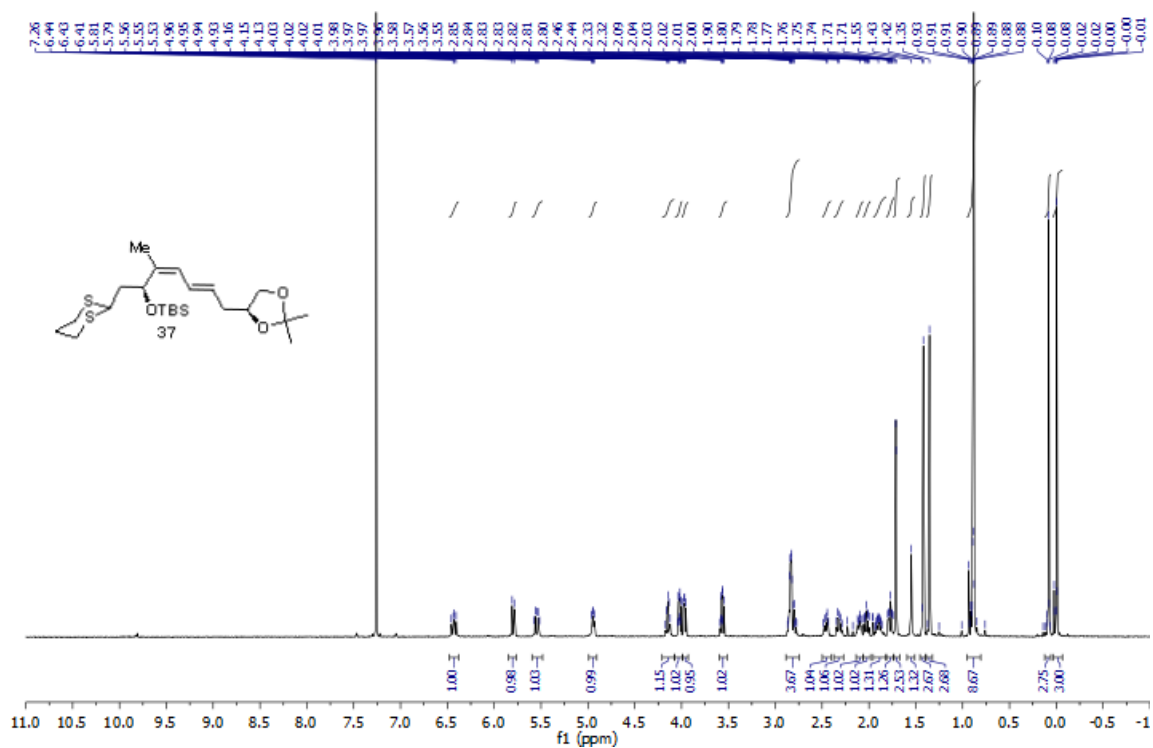
The 500 MHz $^1\text{H-NMR}$ Spectrum of Compound **22** in CDCl_3



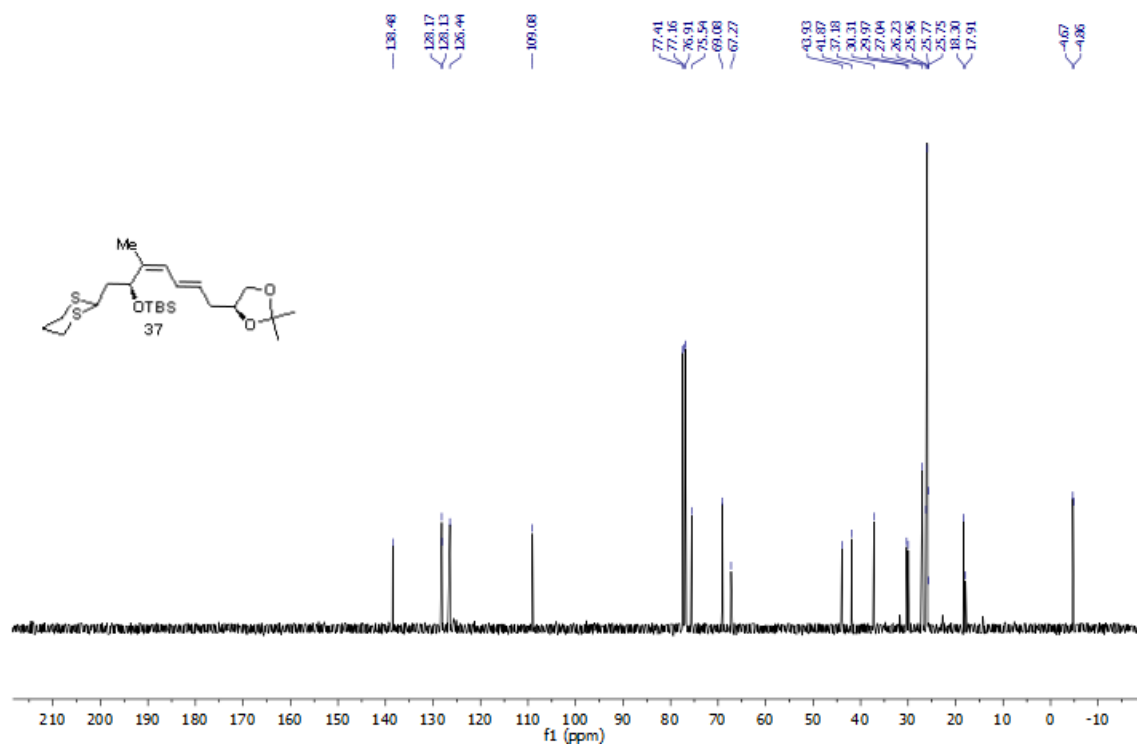
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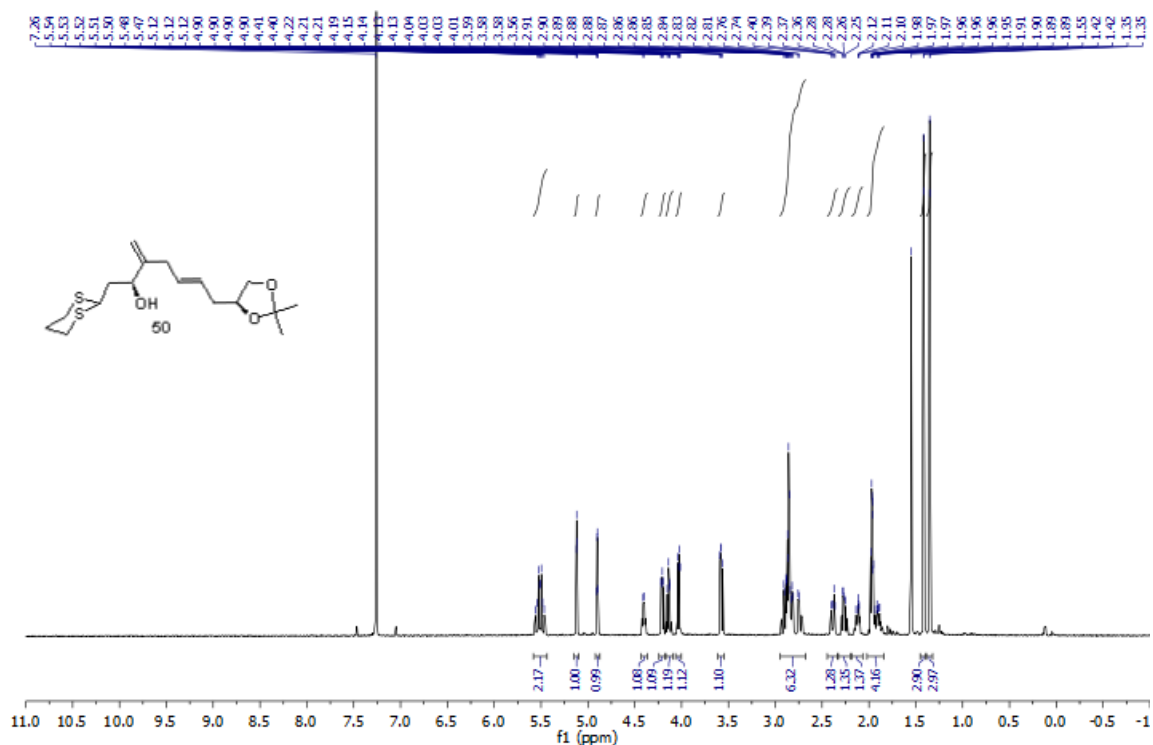
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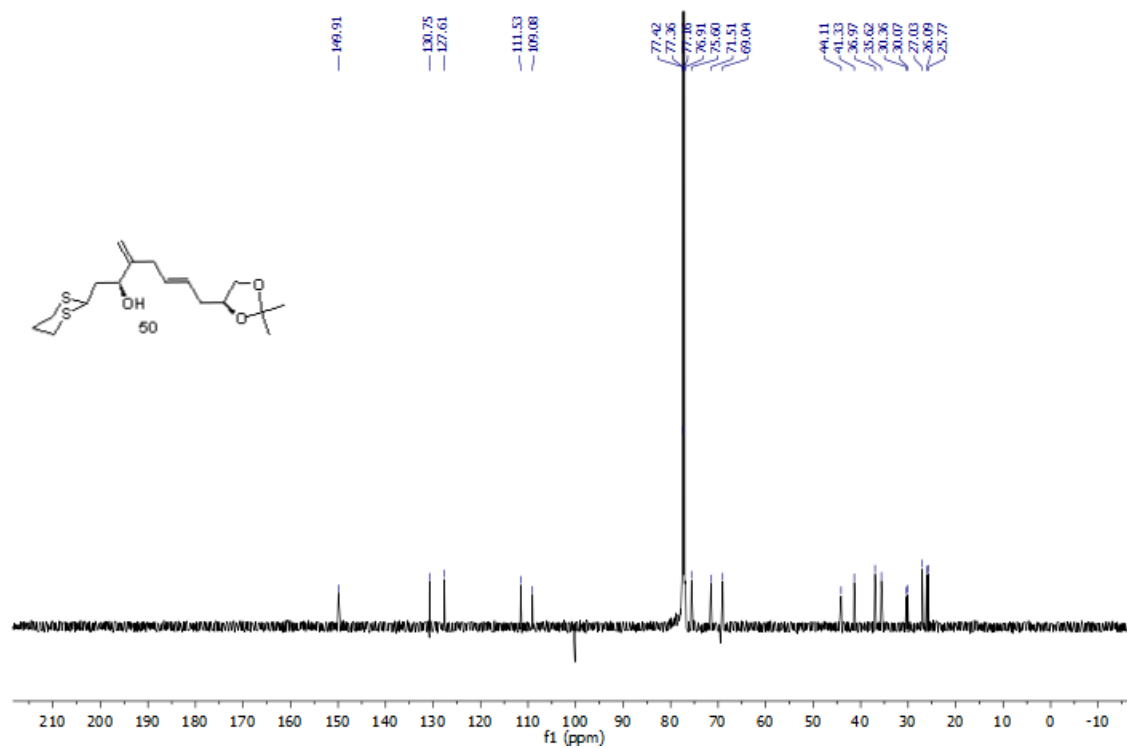
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound **37** in CDCl_3



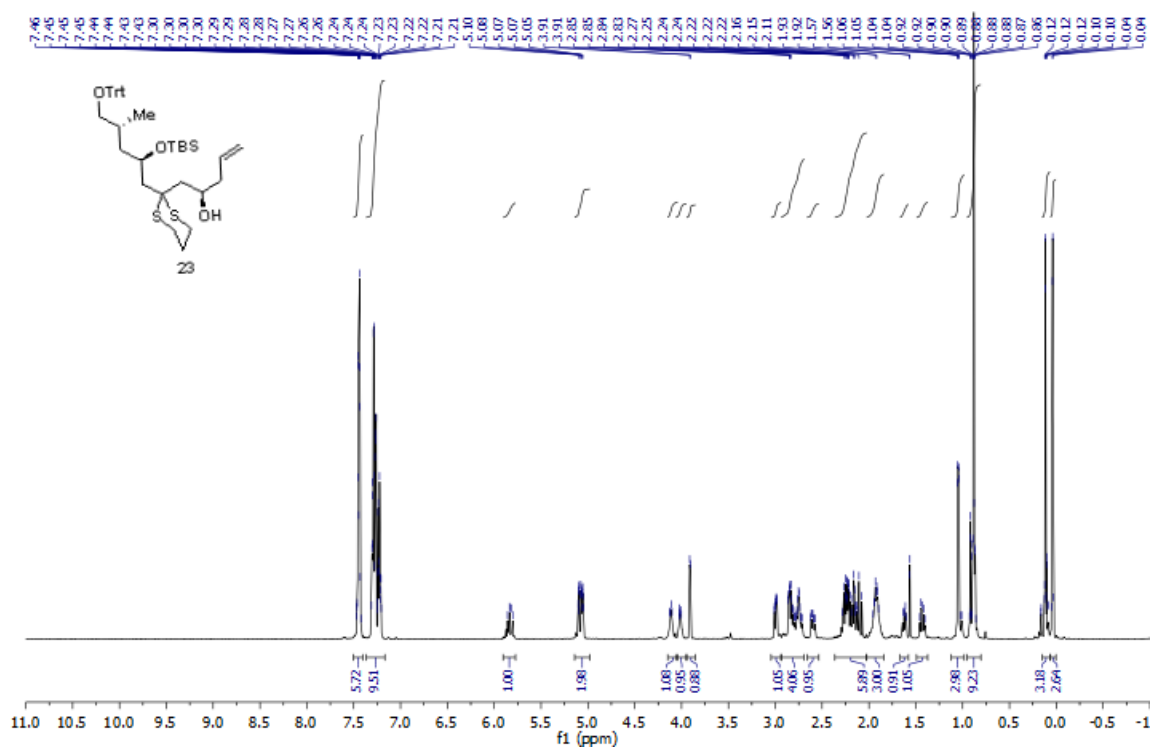
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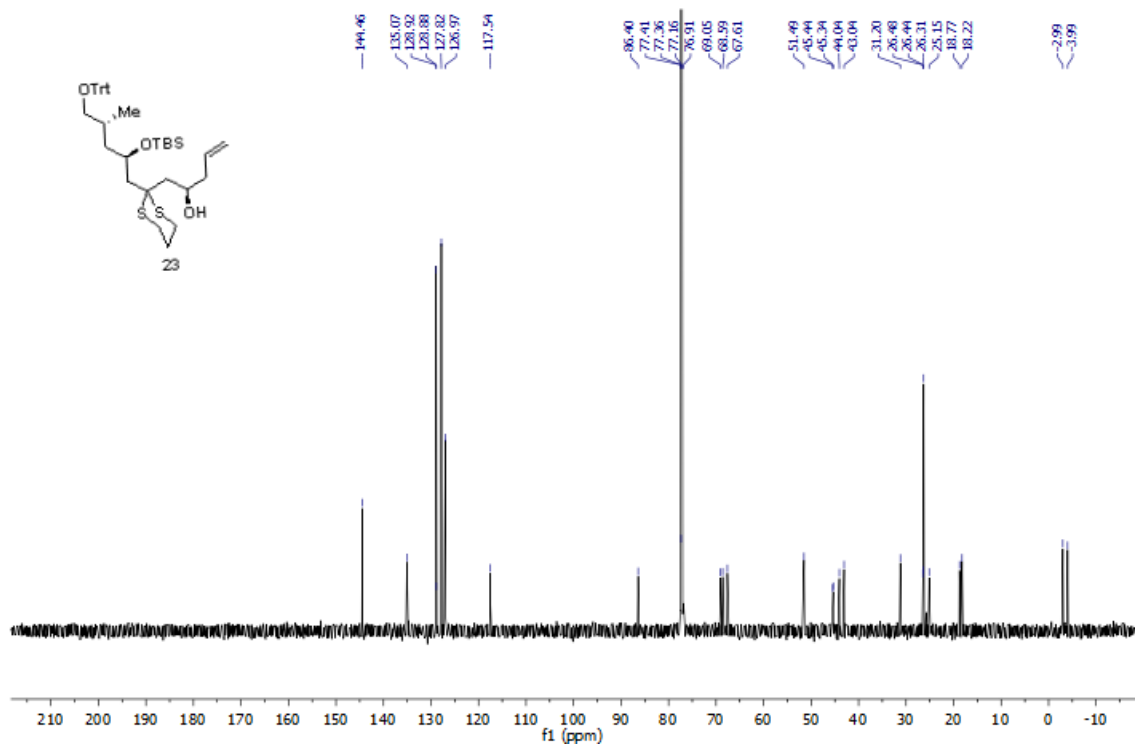
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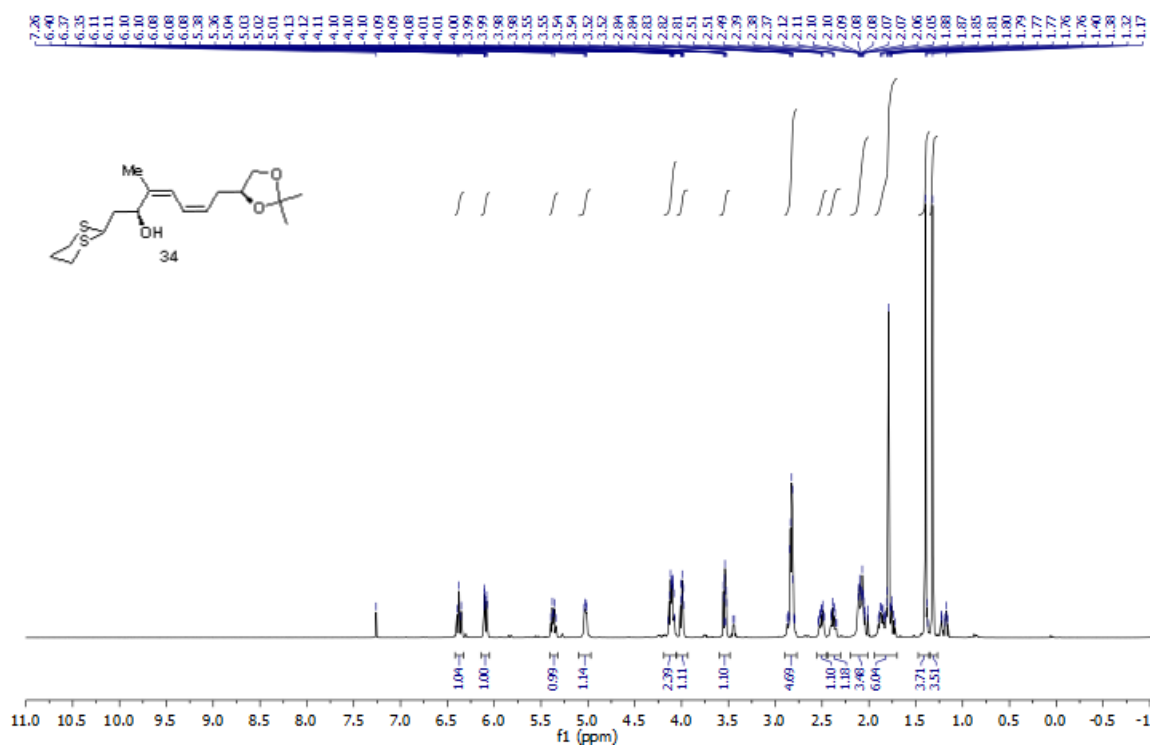
The 500 MHz ¹H-NMR Spectrum of Compound **23** in CDCl₃



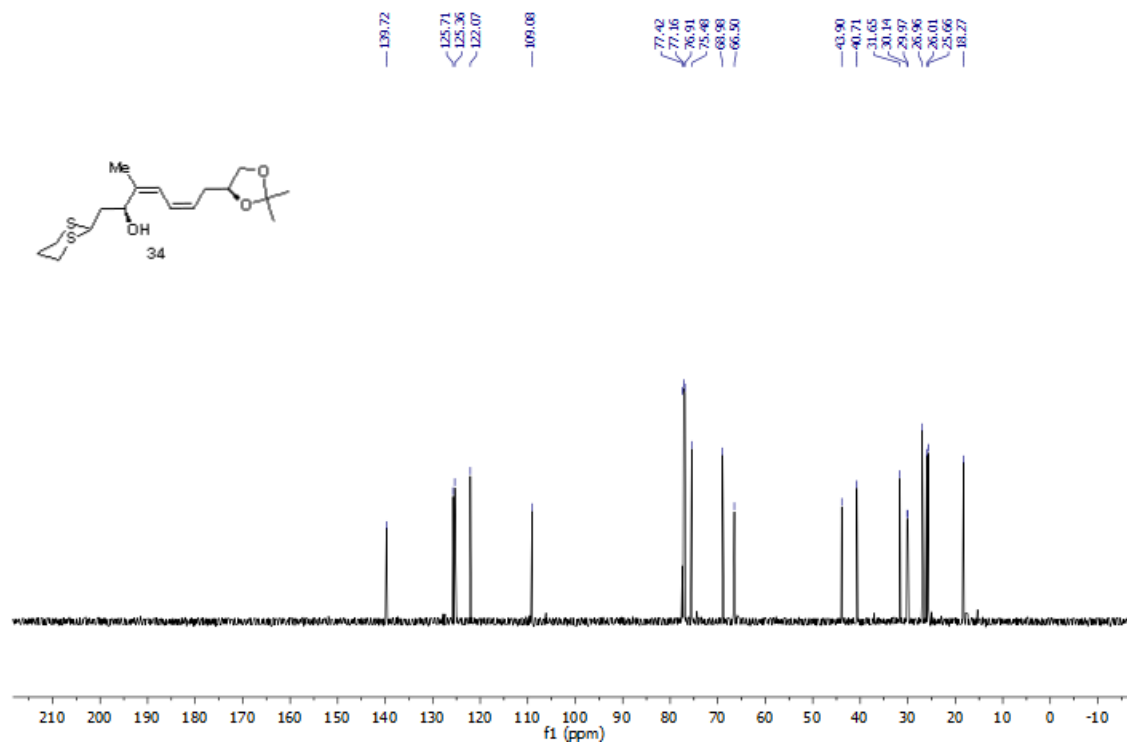
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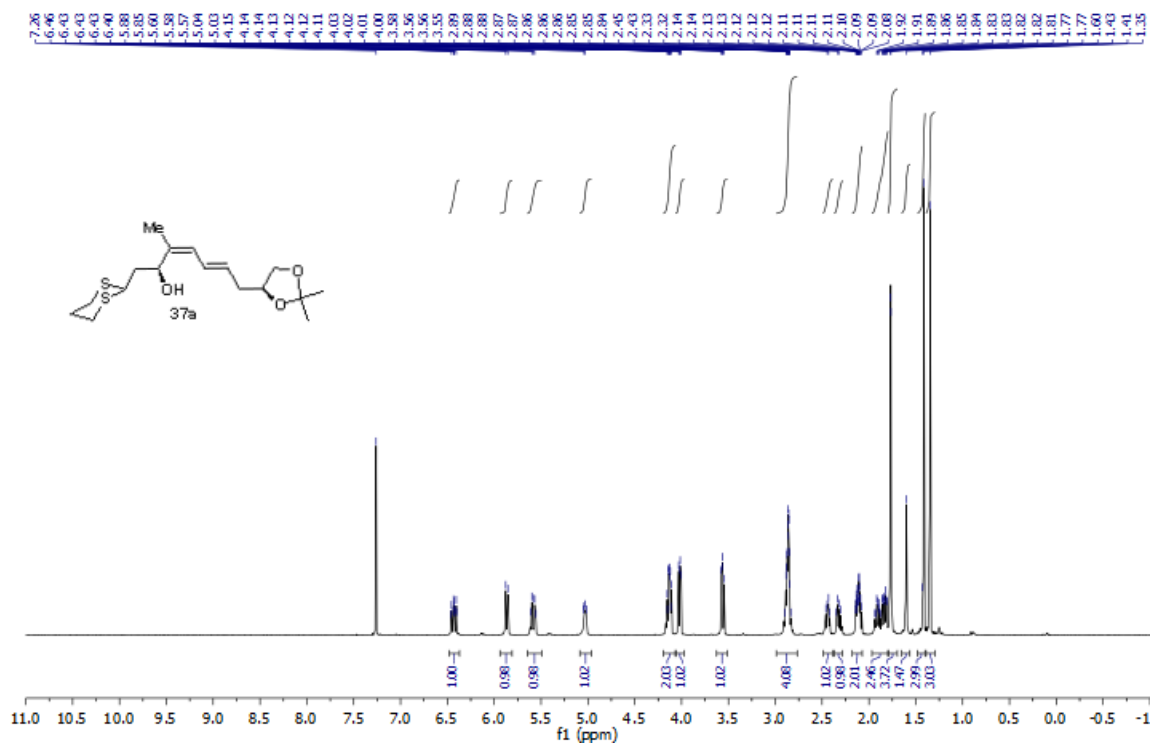
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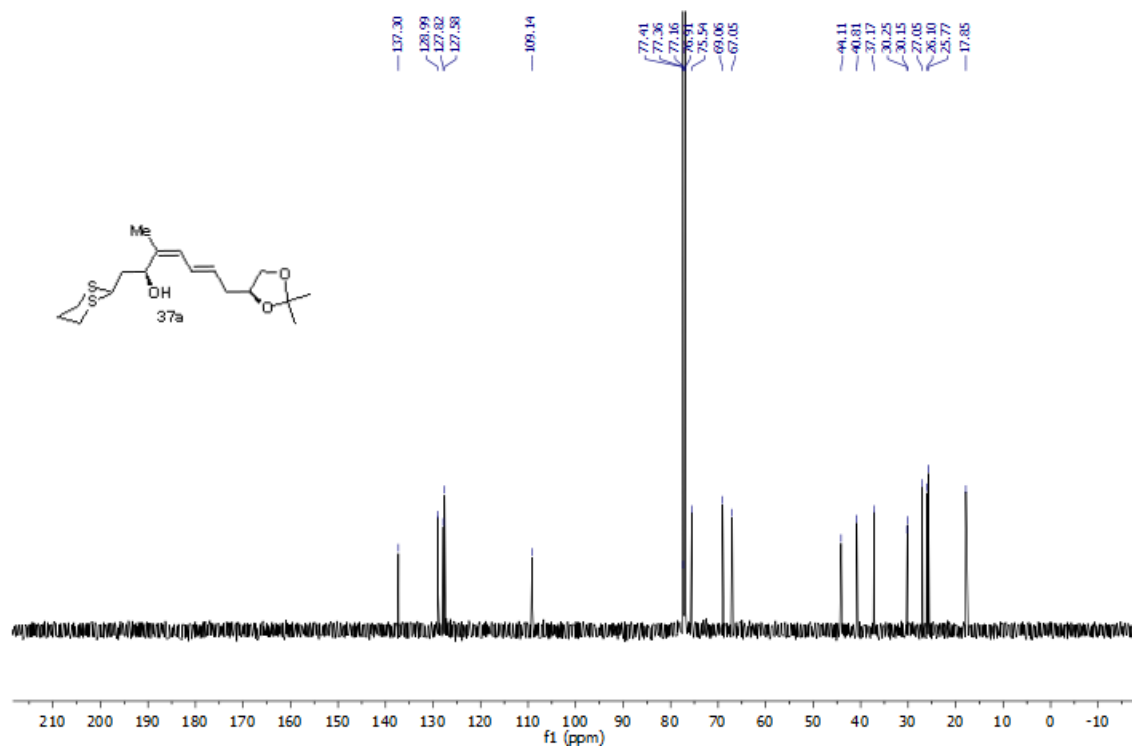
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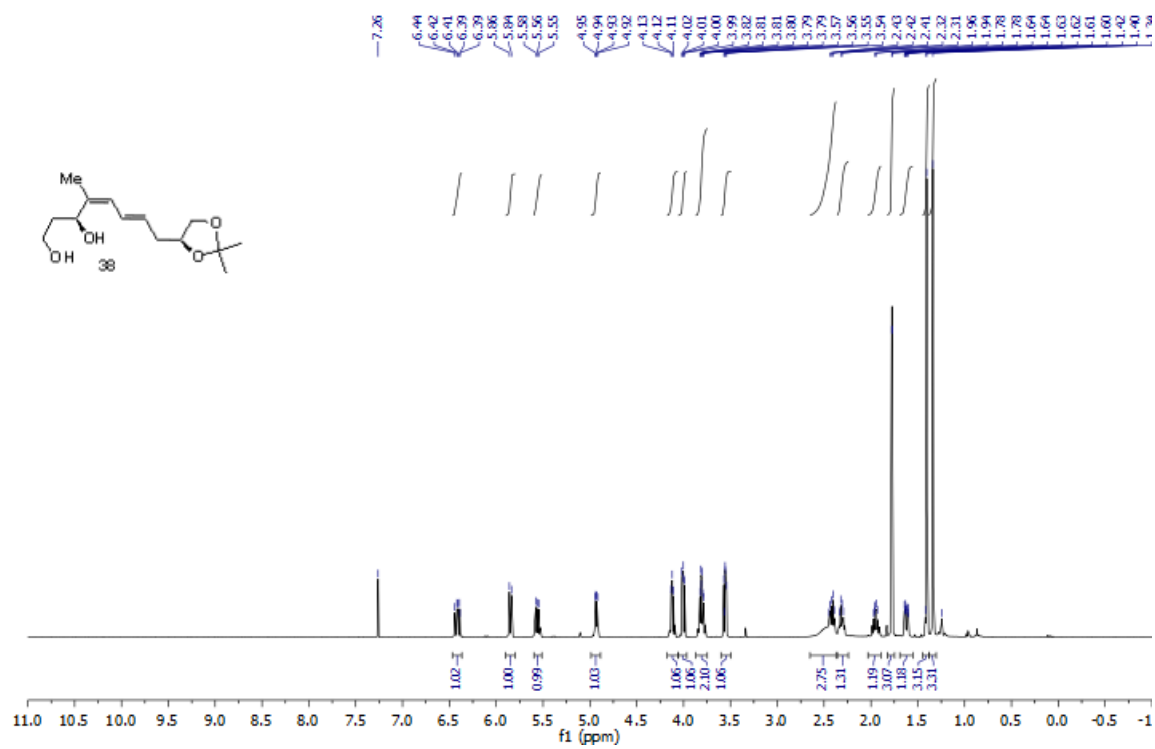
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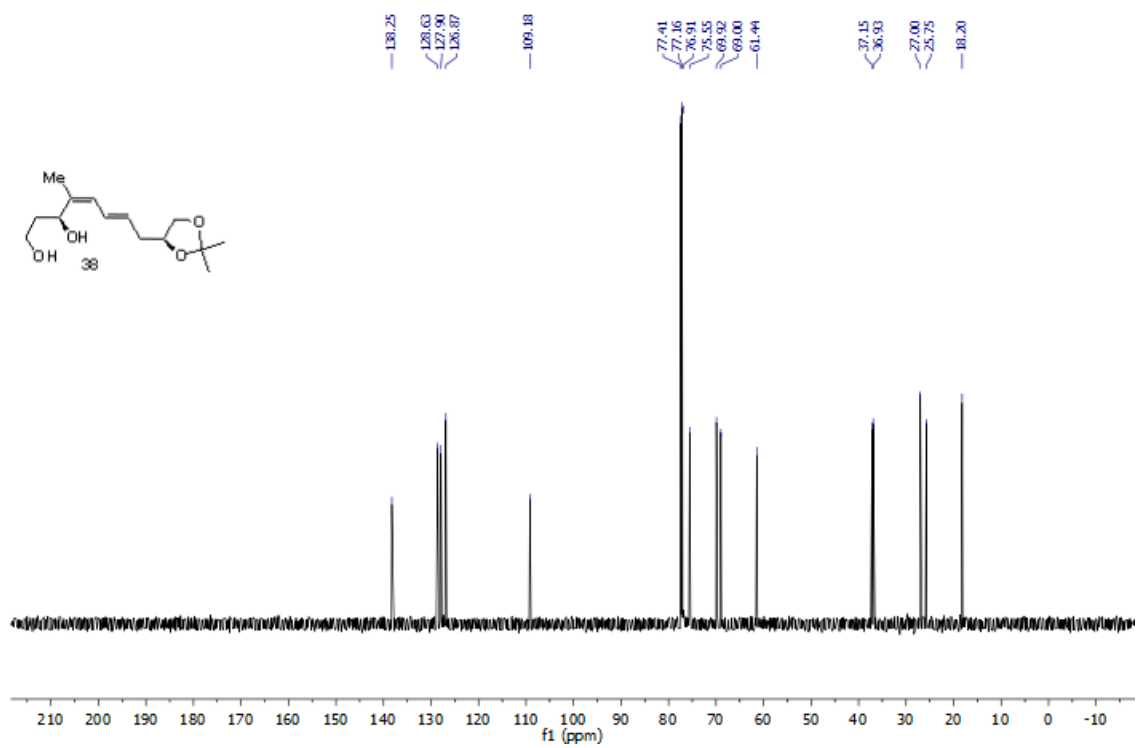
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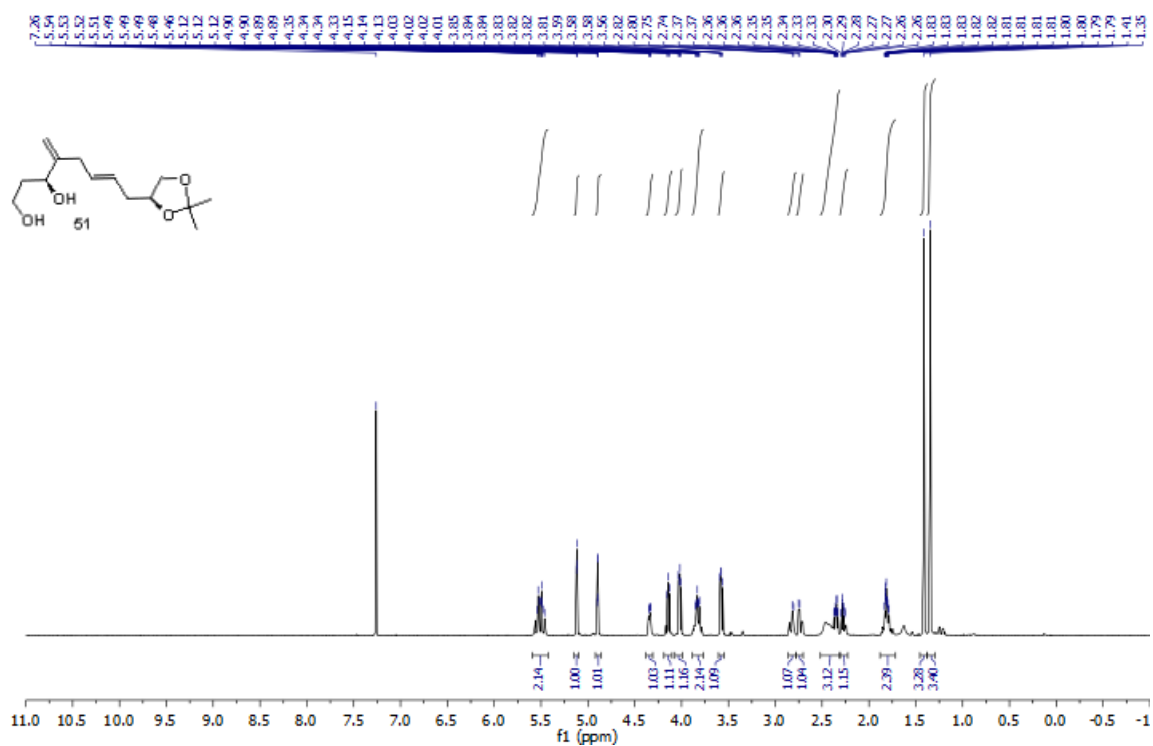
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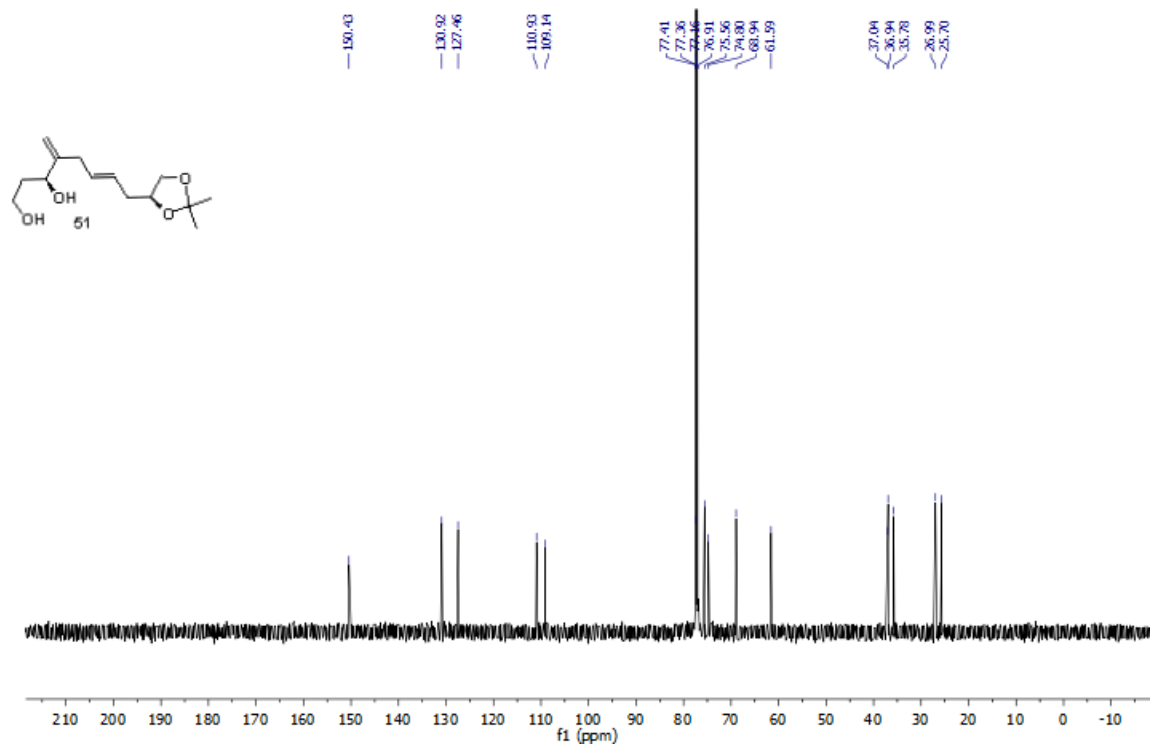
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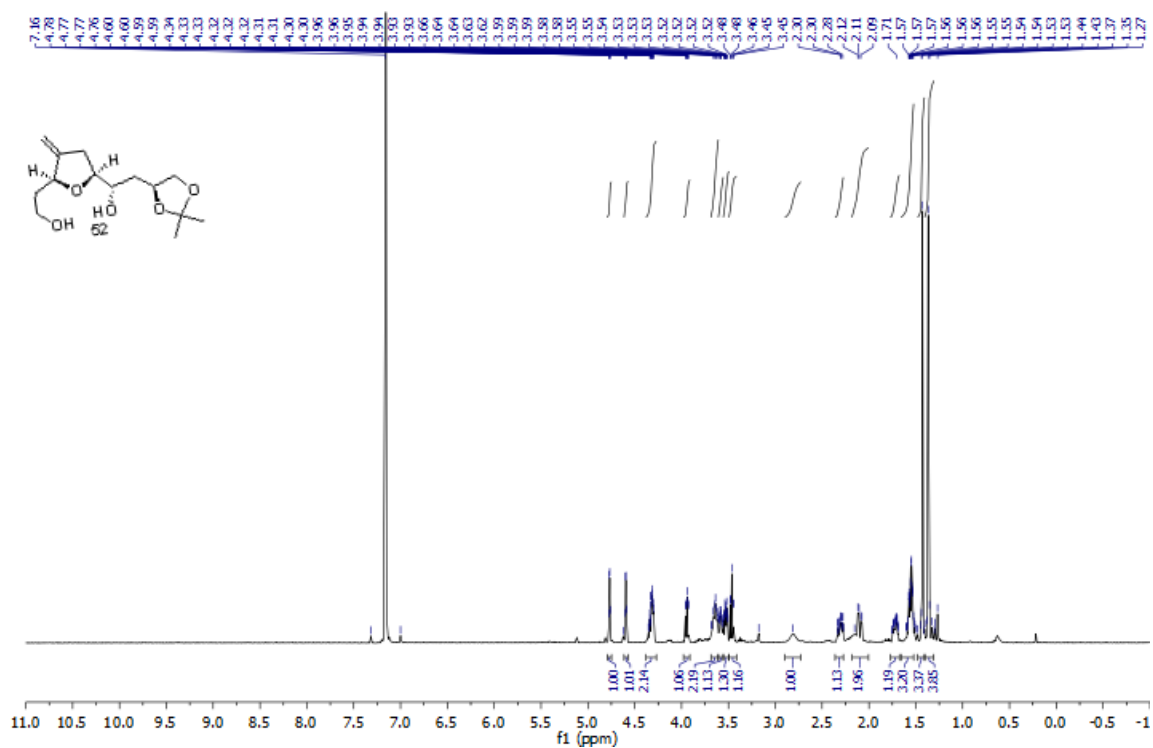
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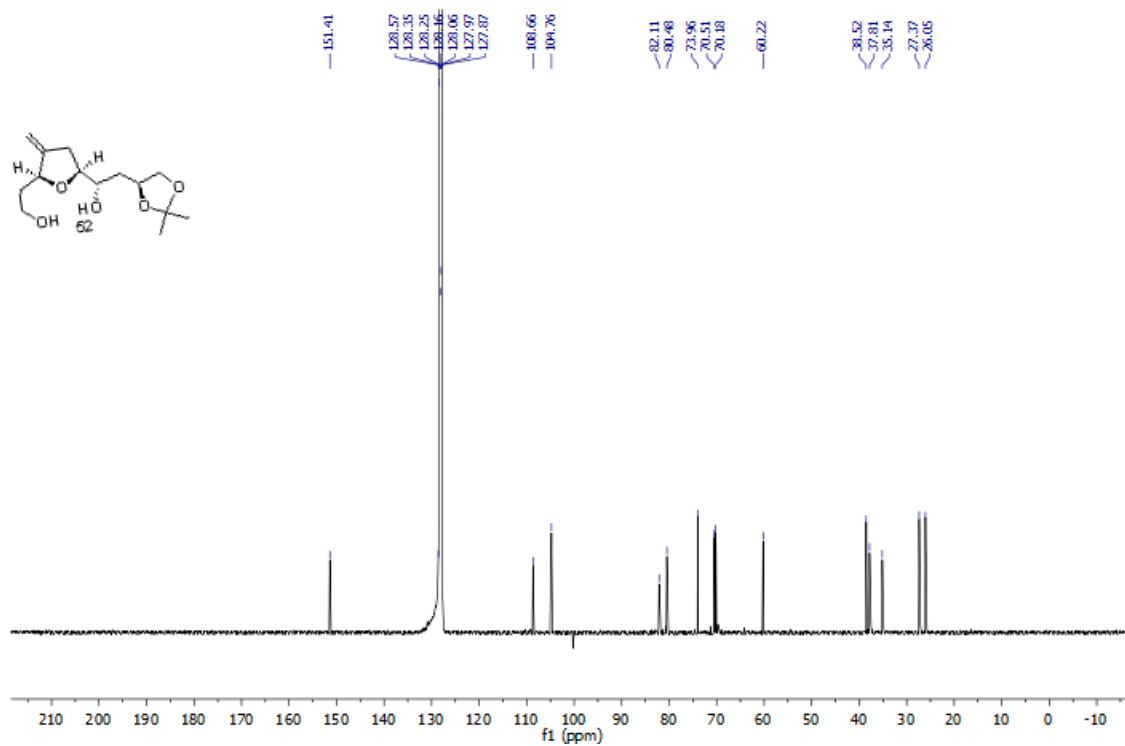
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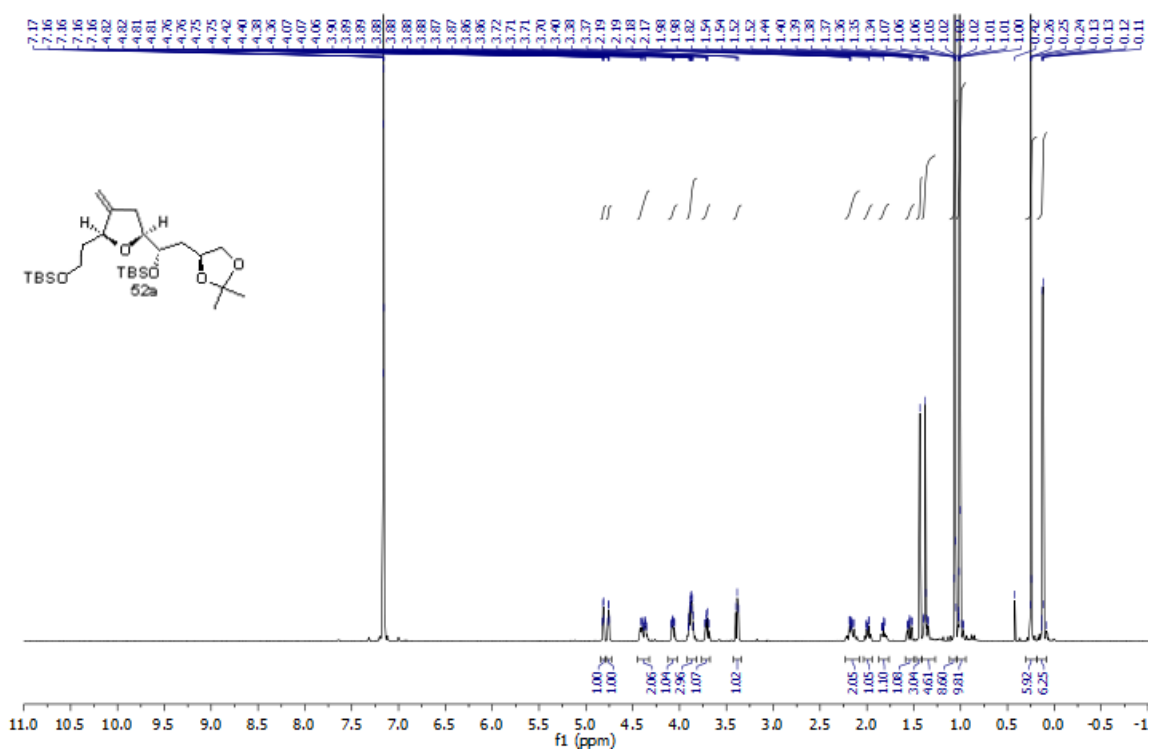
The 500 MHz ^1H -NMR Spectrum of Compound **52** in C_6D_6



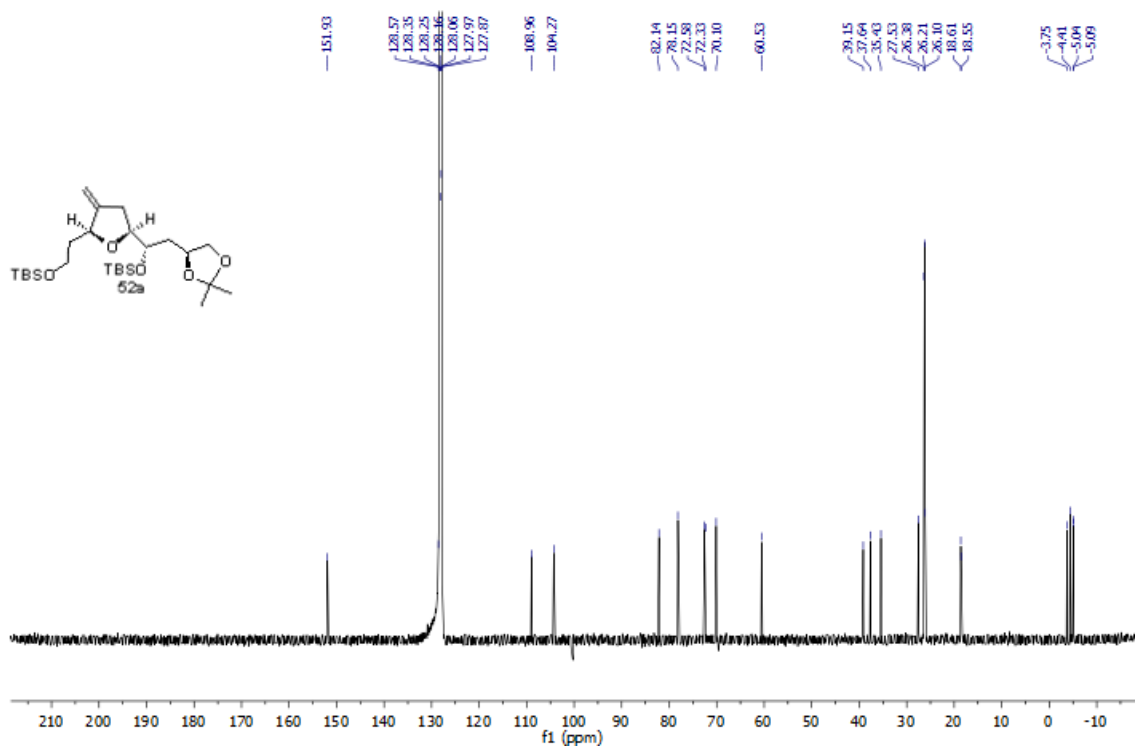
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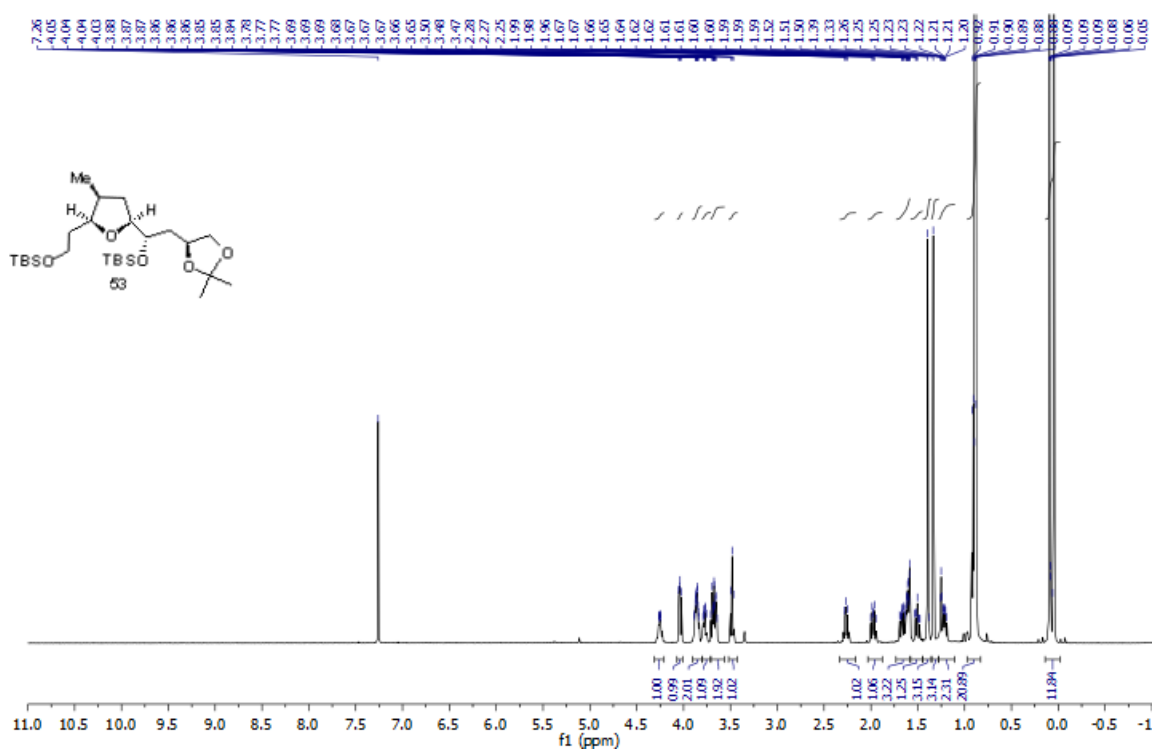
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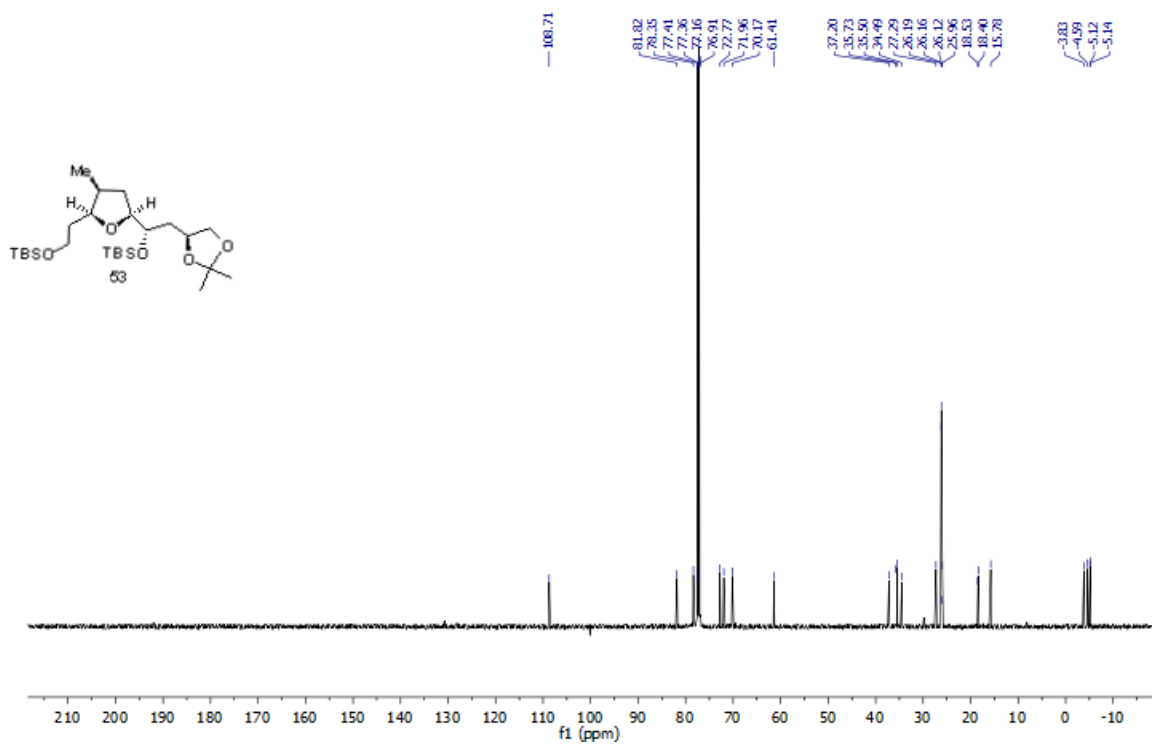
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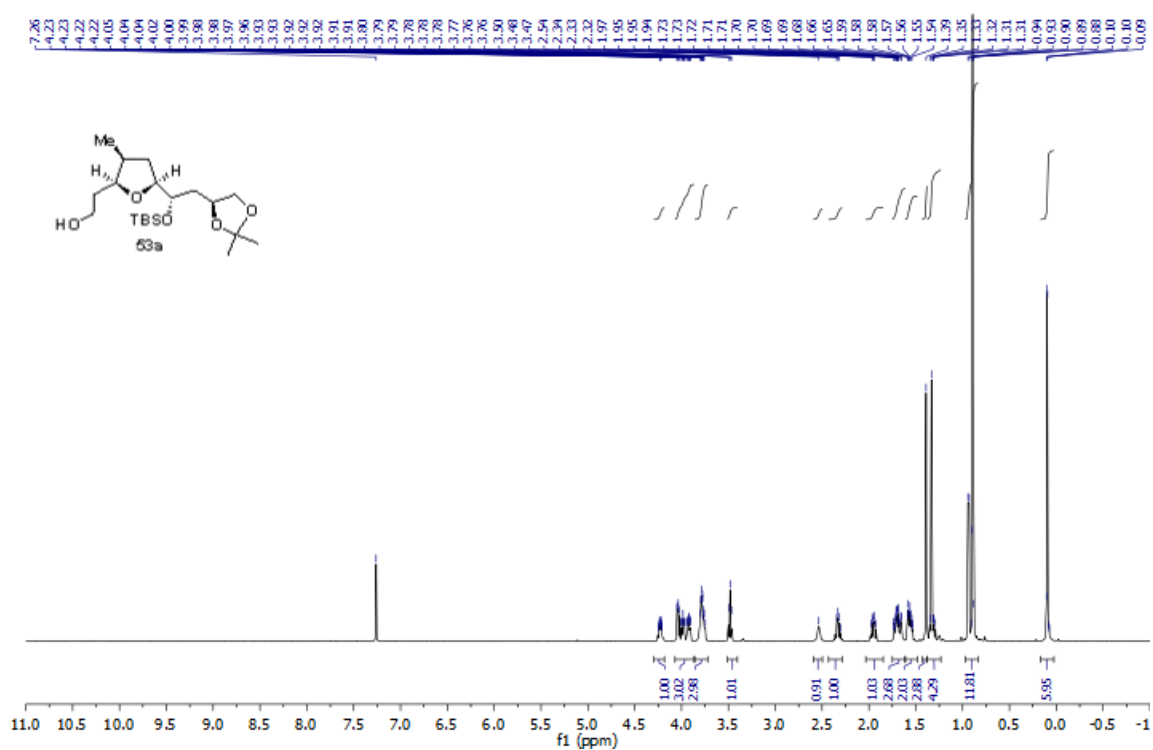
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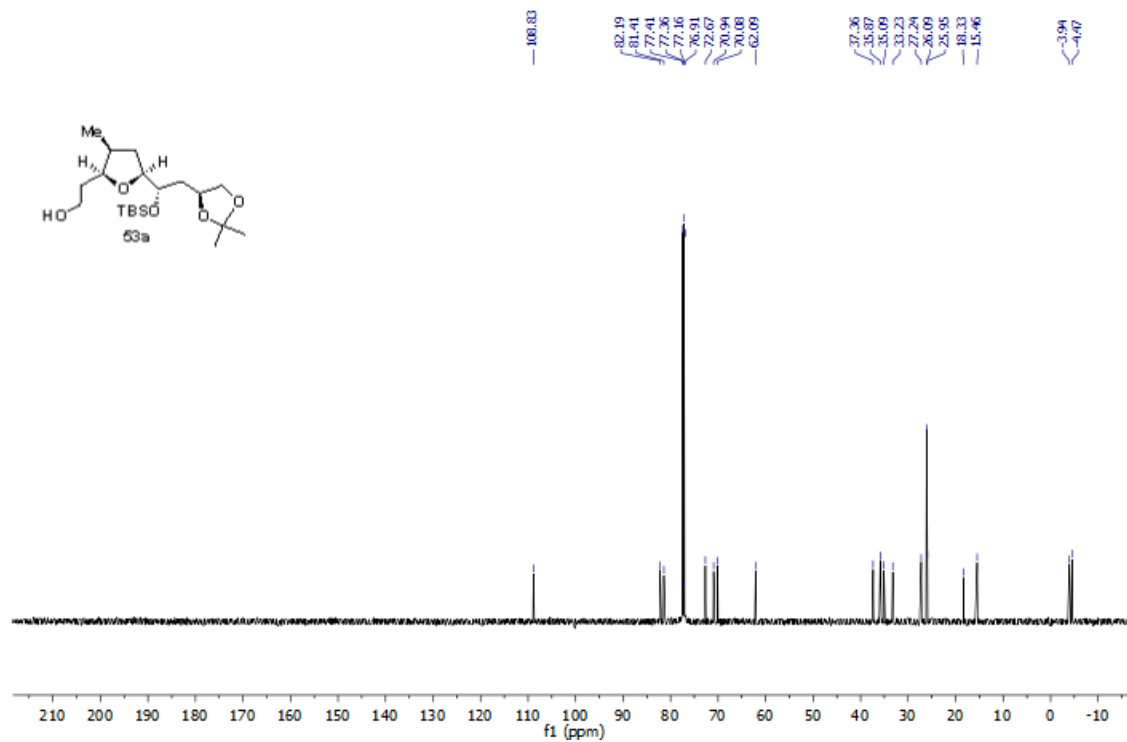
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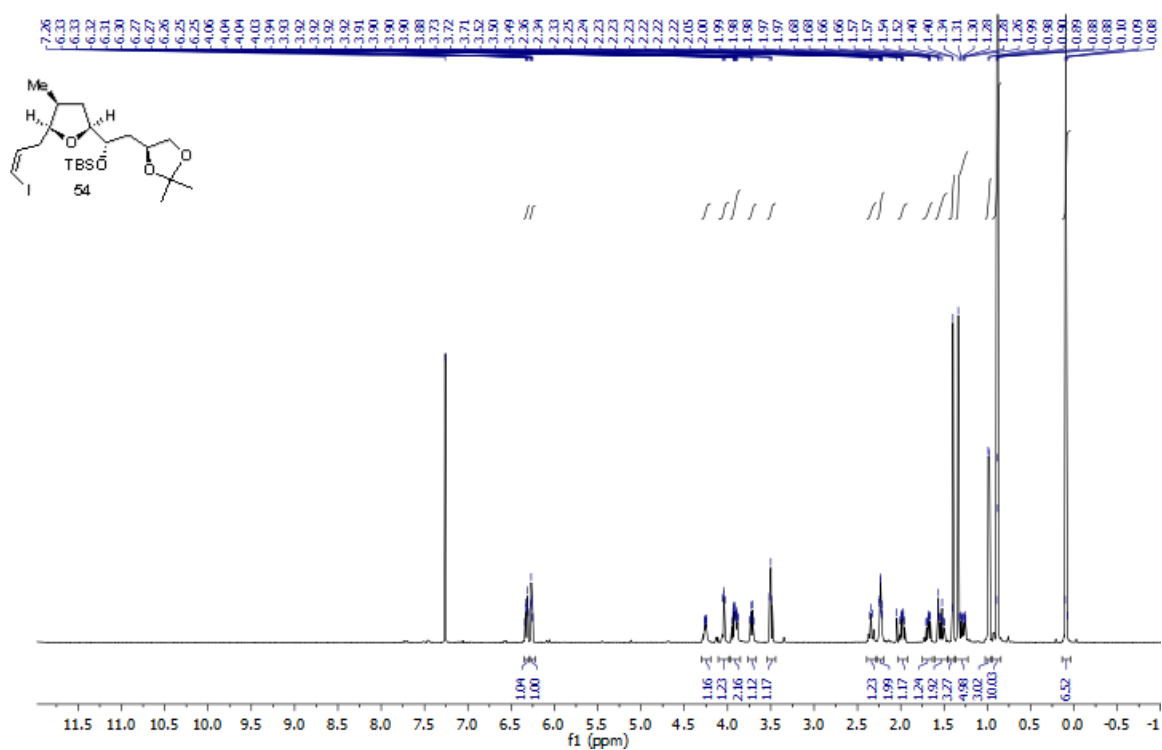
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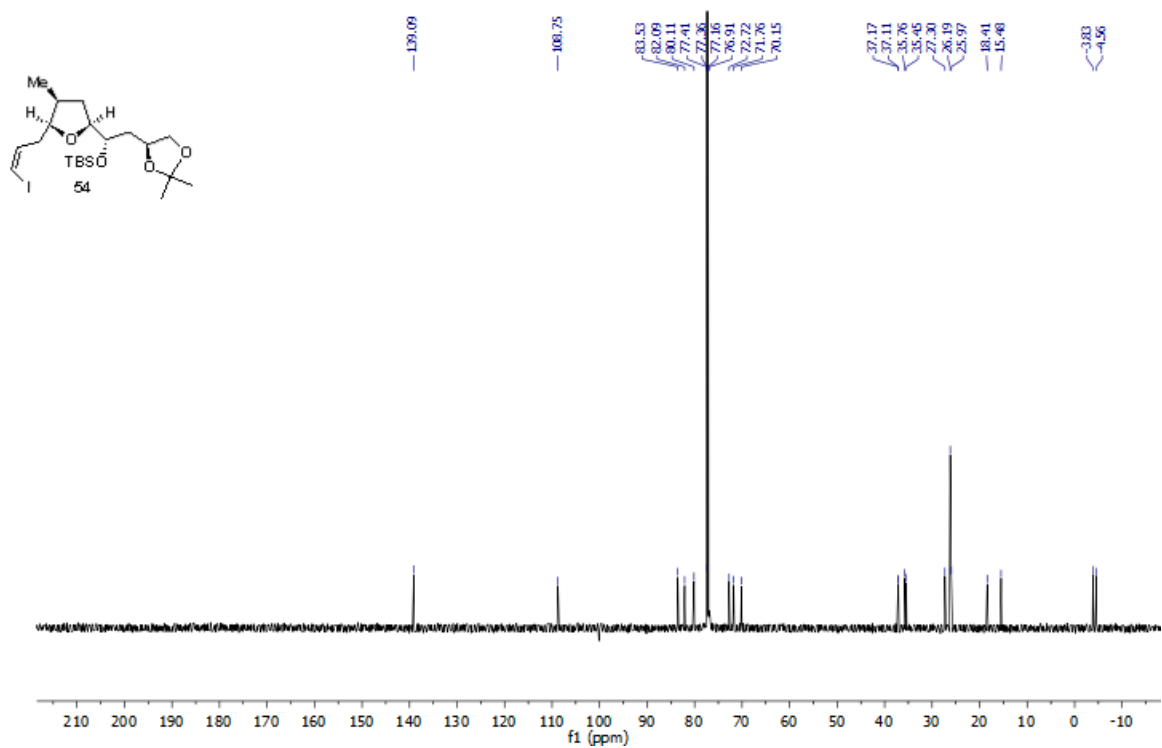
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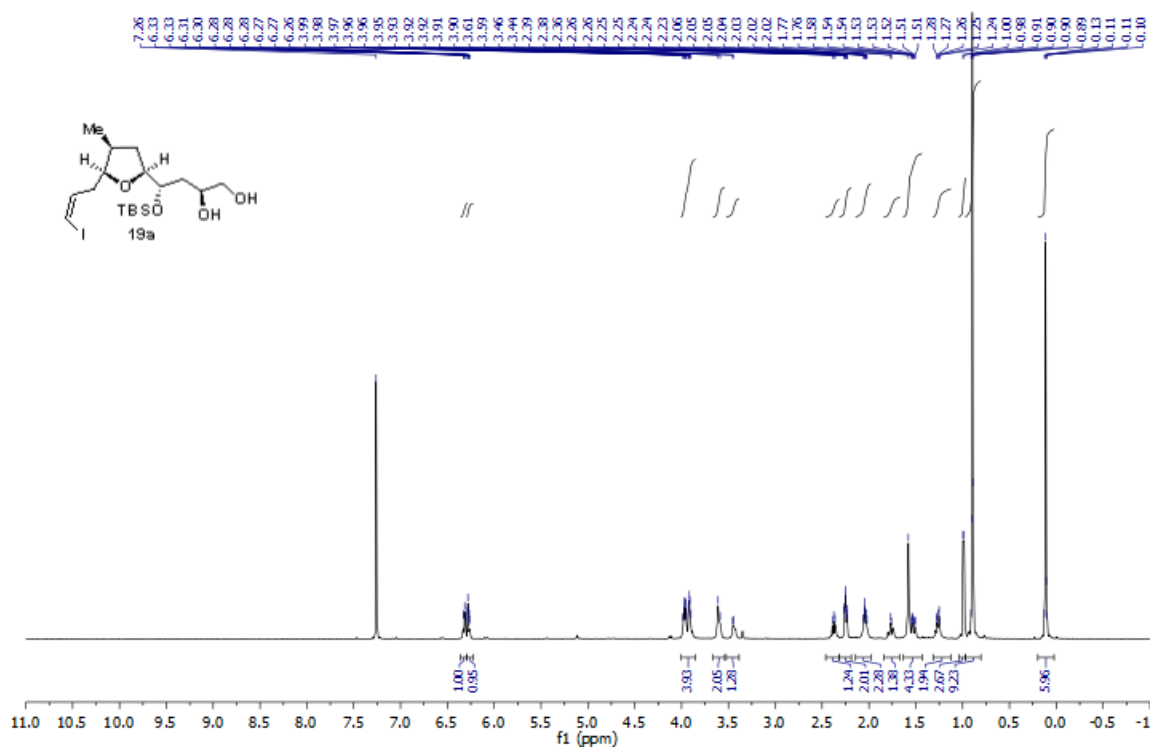
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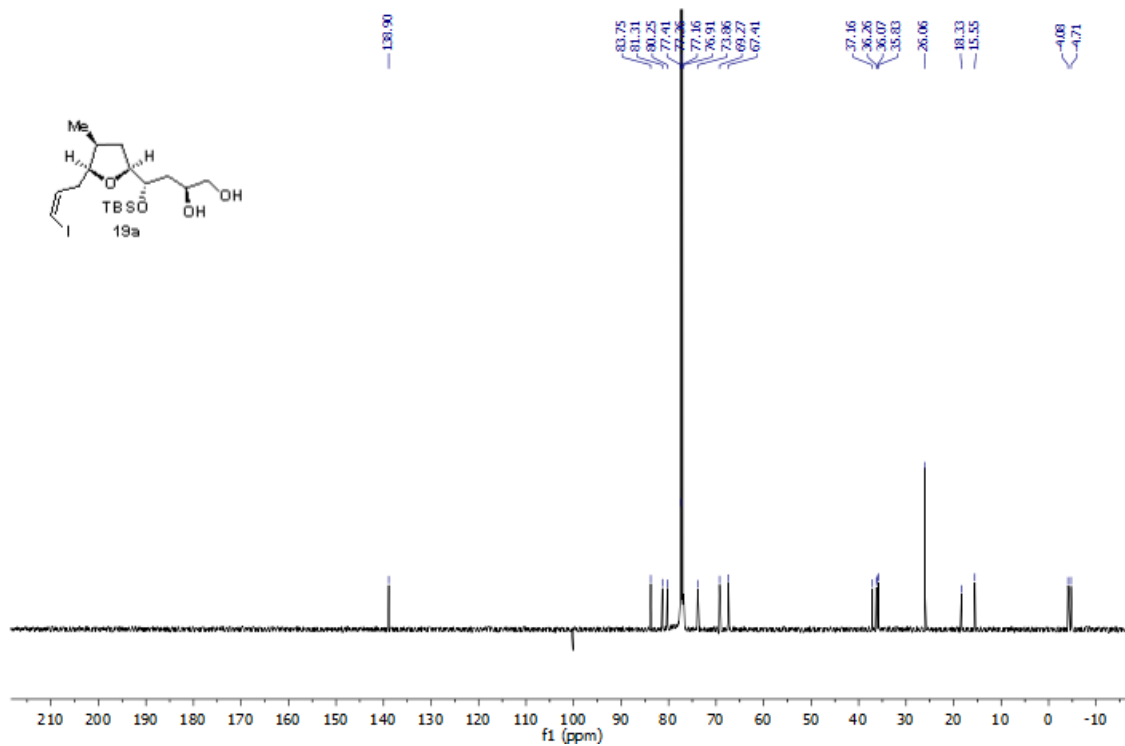
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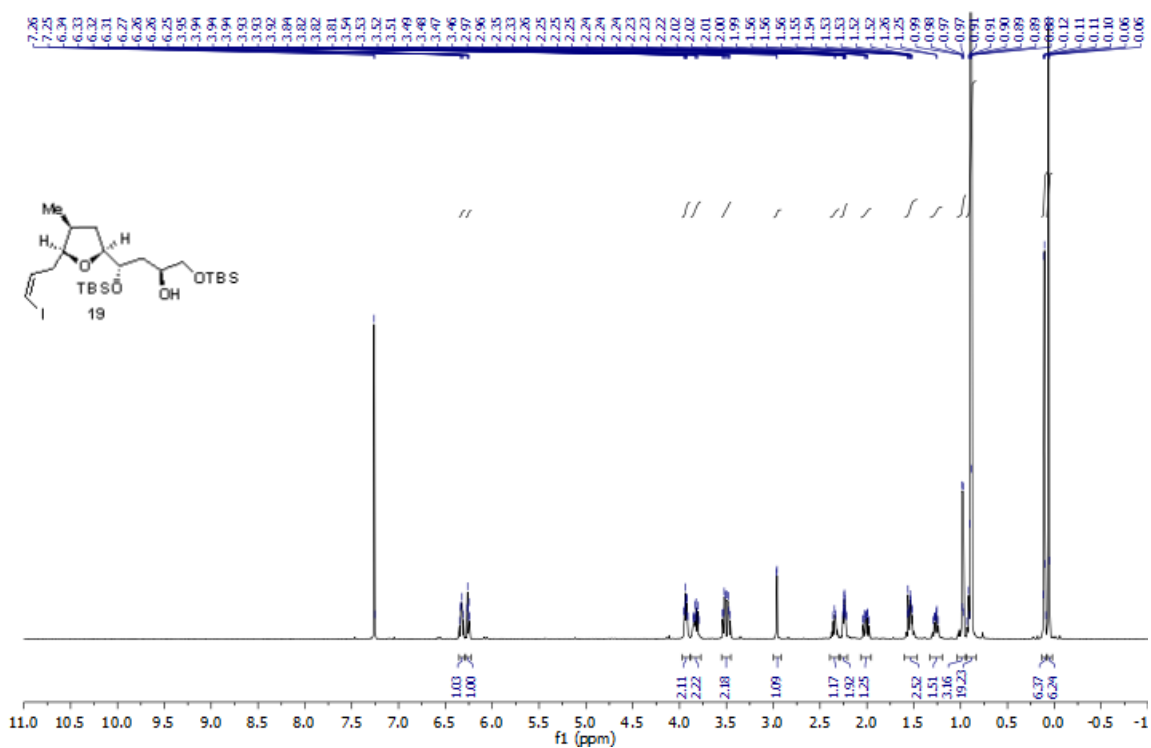
The 500 MHz ^1H -NMR Spectrum of Compound **19a** in CDCl_3



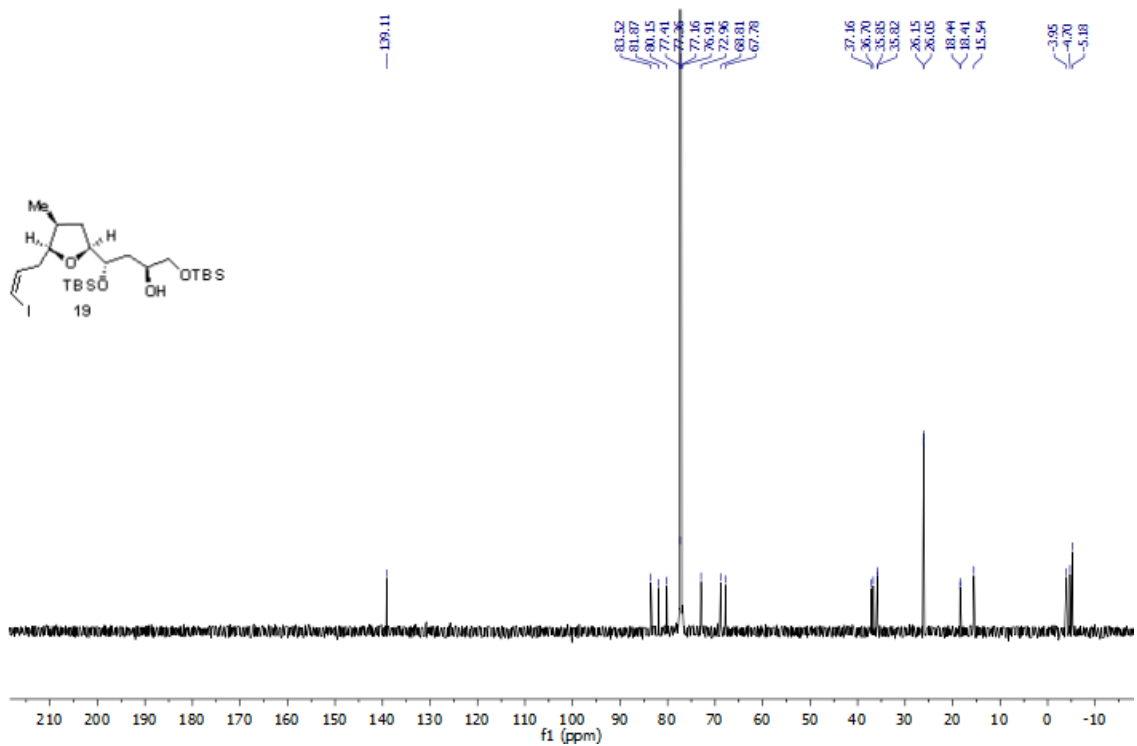
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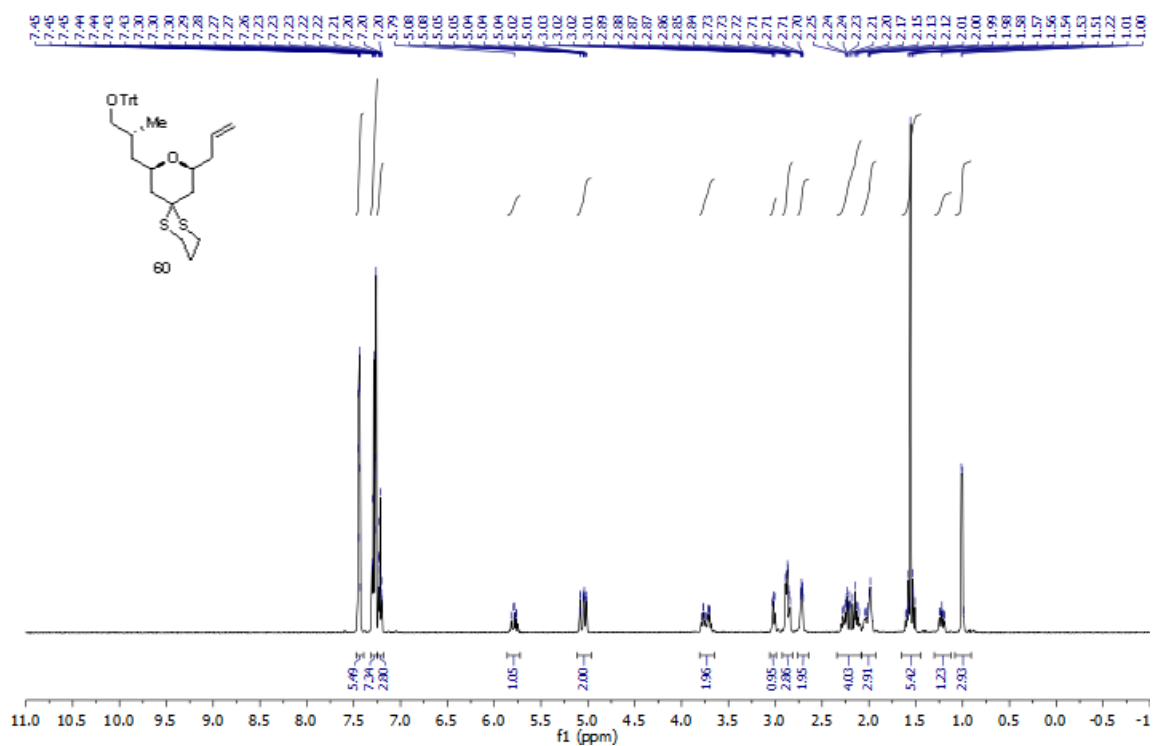
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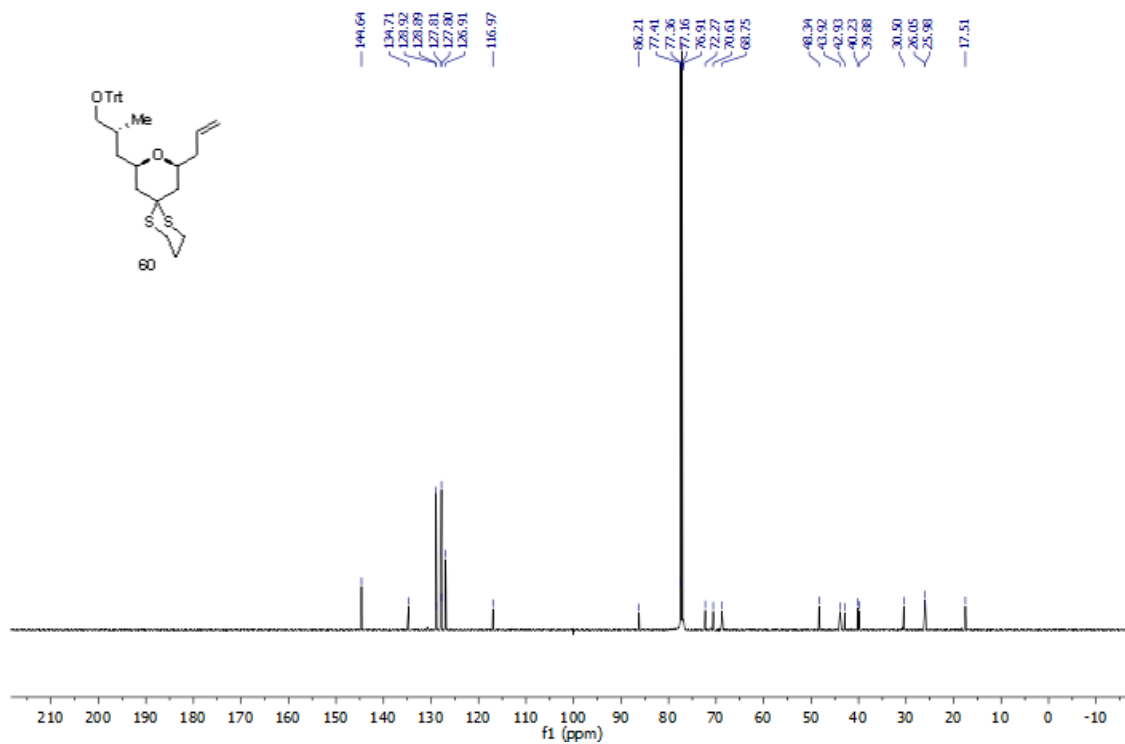
The 125 MHz ^{13}C -NMR Spectrum of Compound **19** in CDCl_3



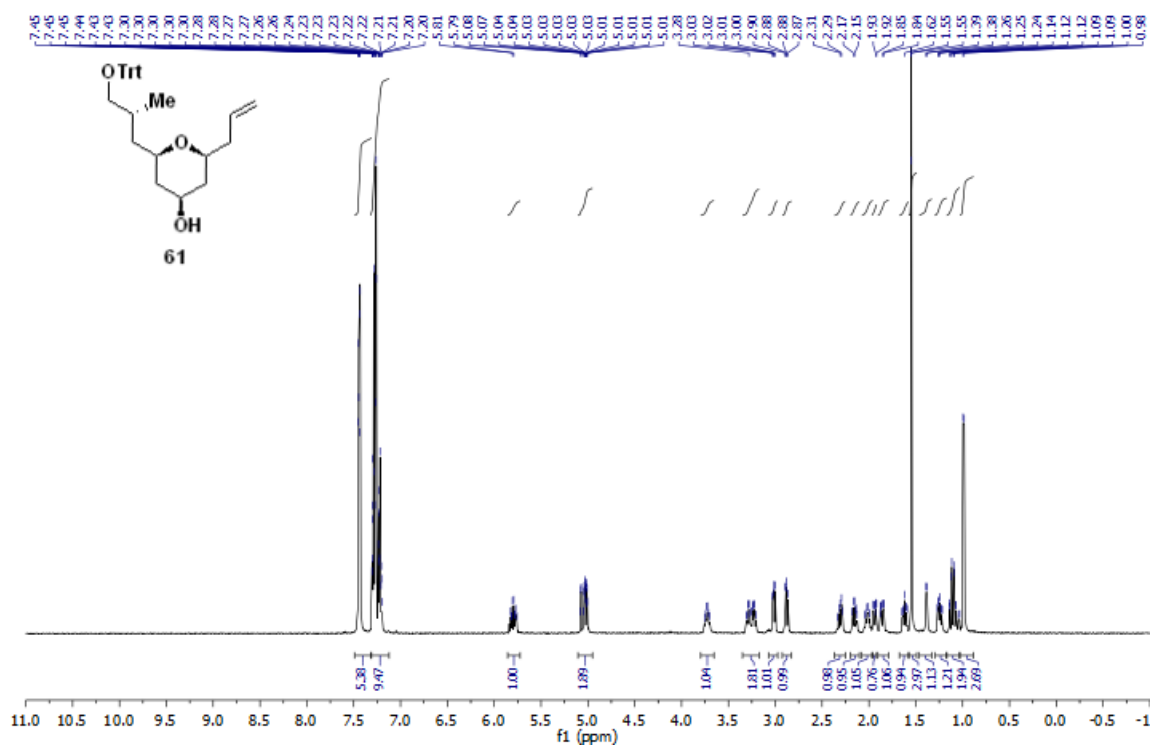
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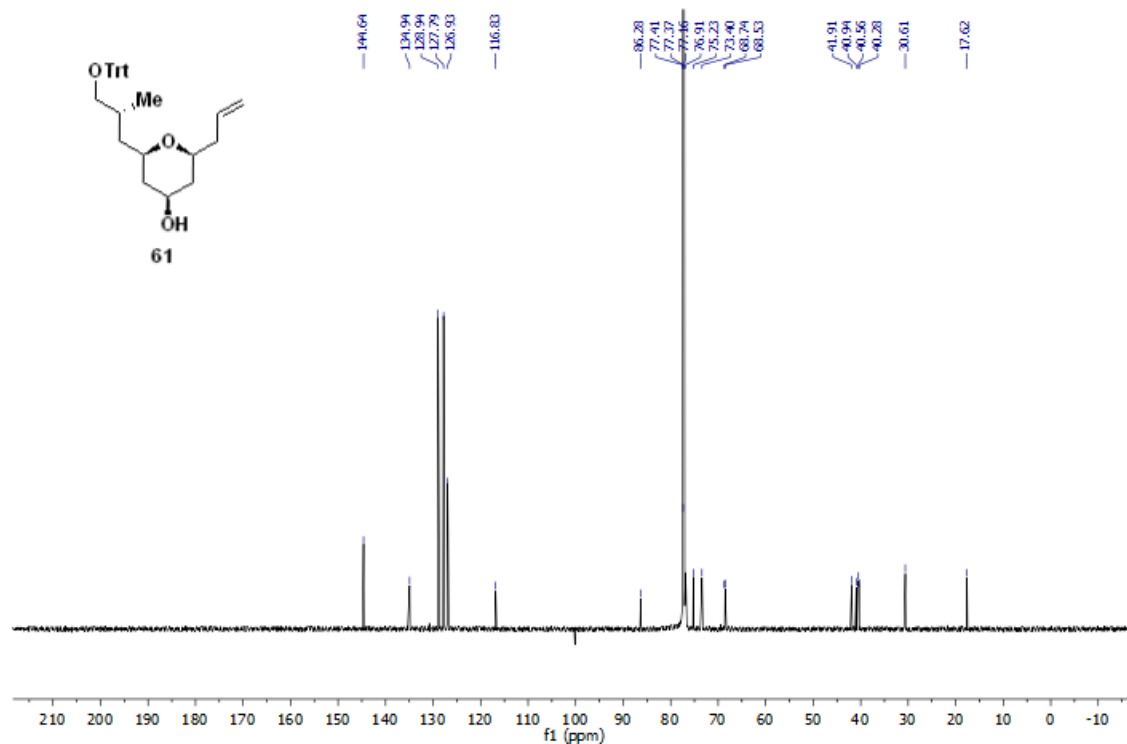
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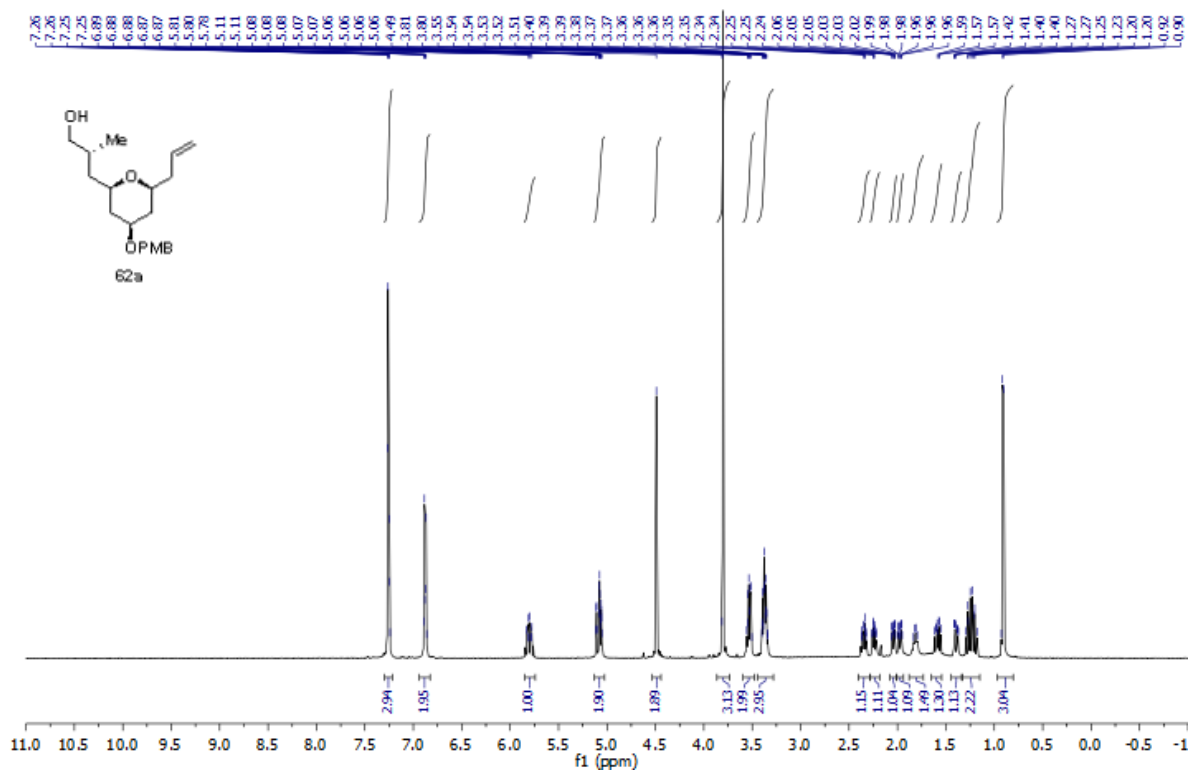
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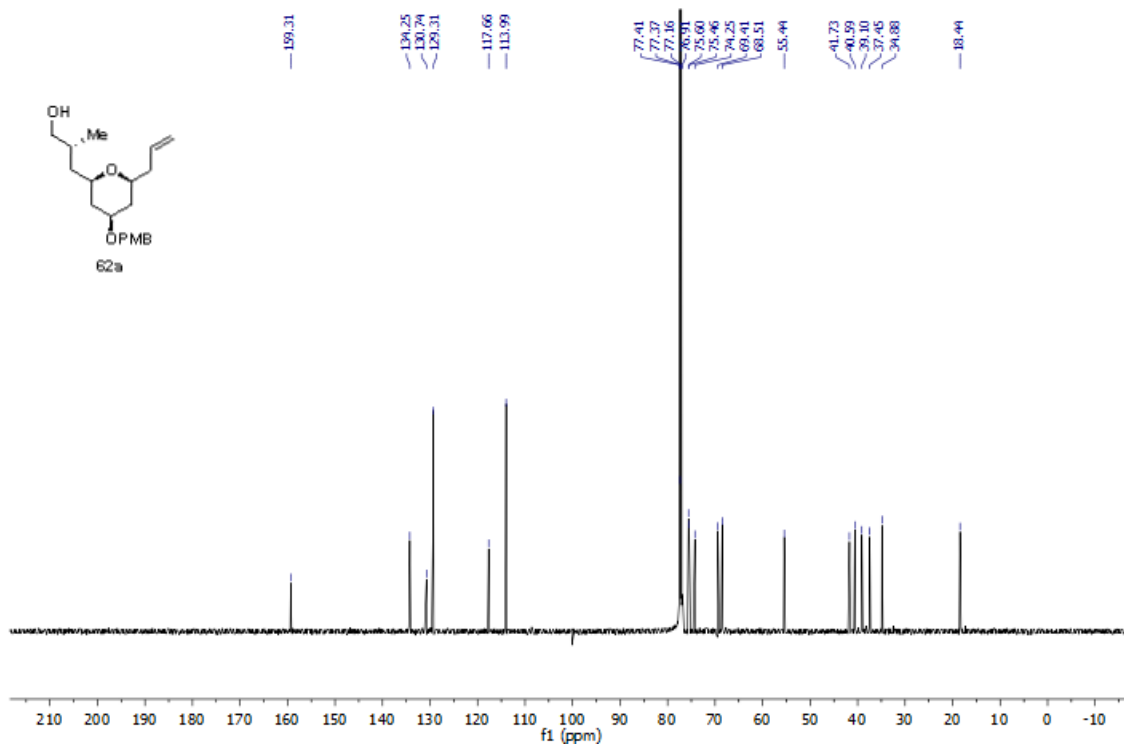
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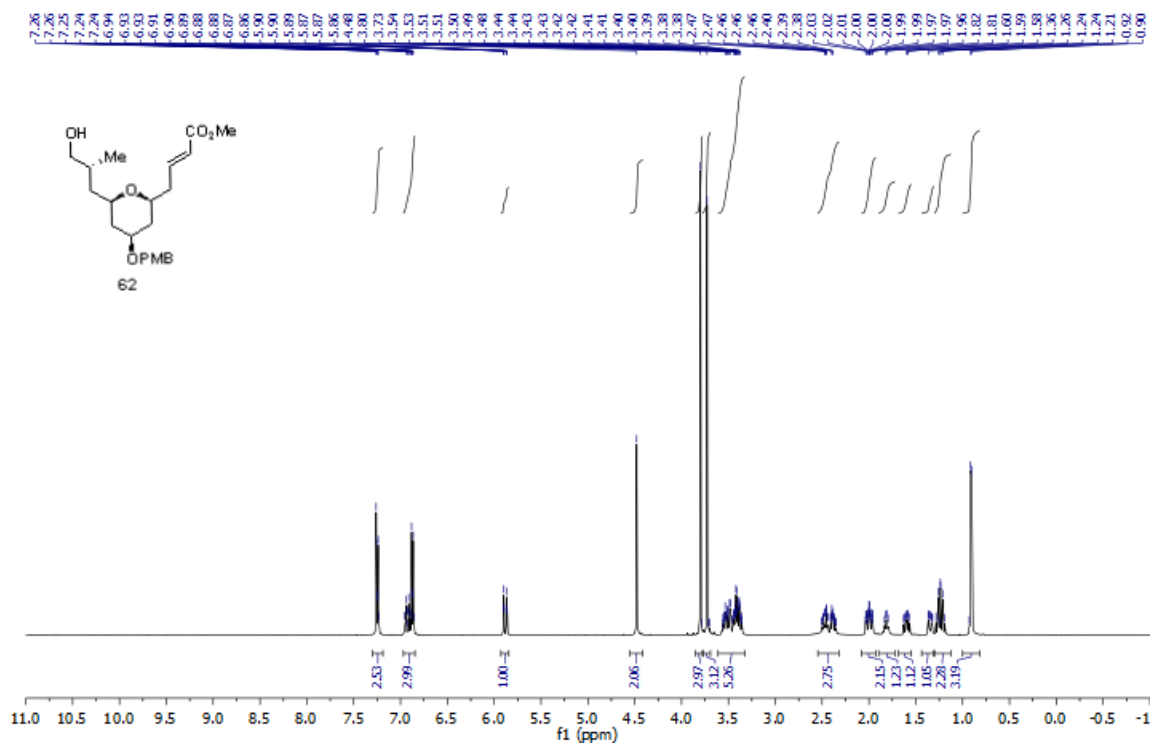
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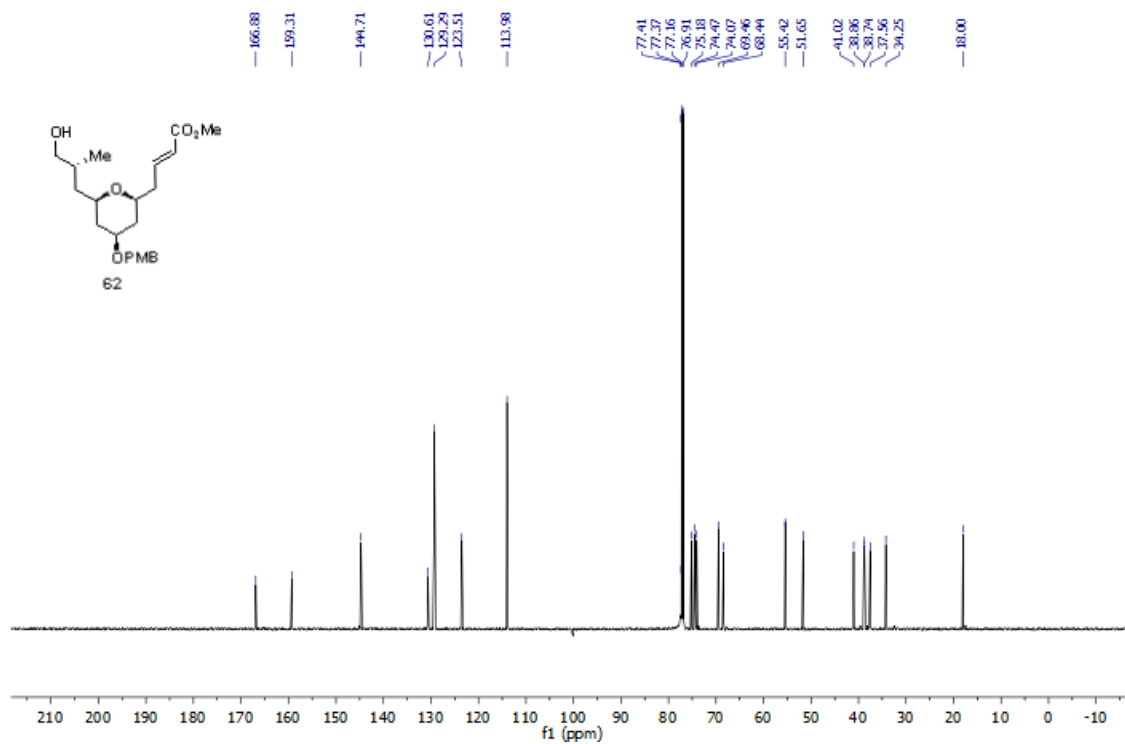
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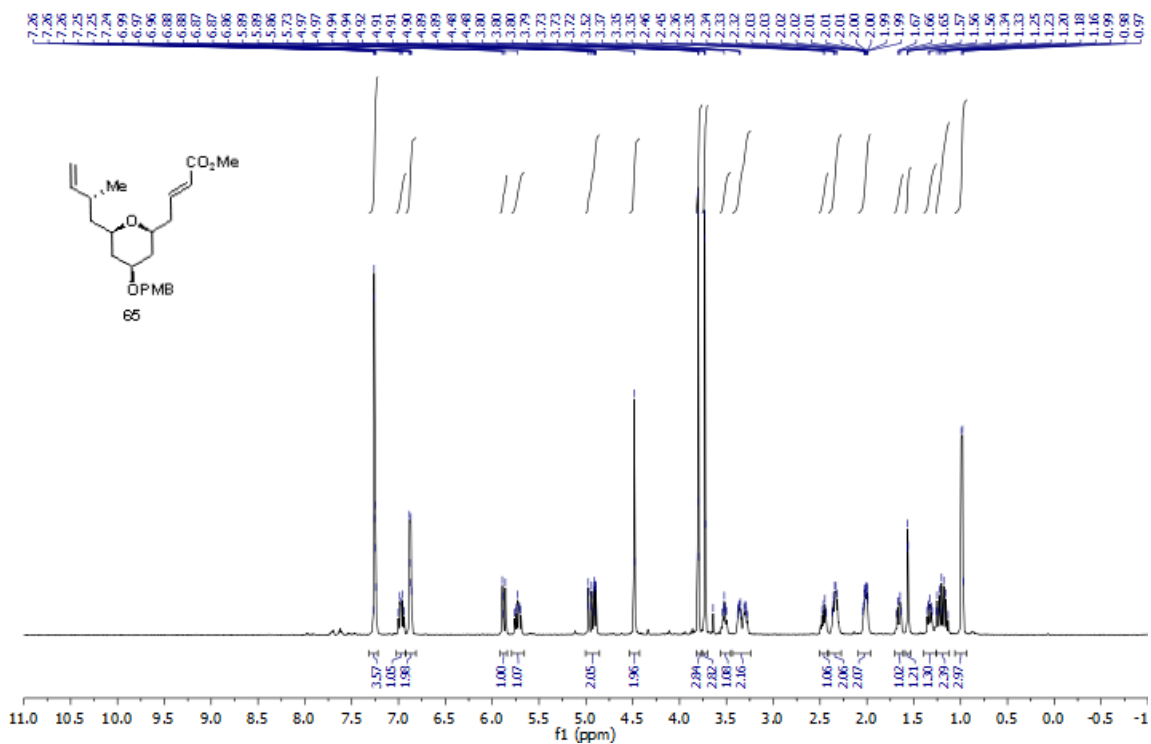
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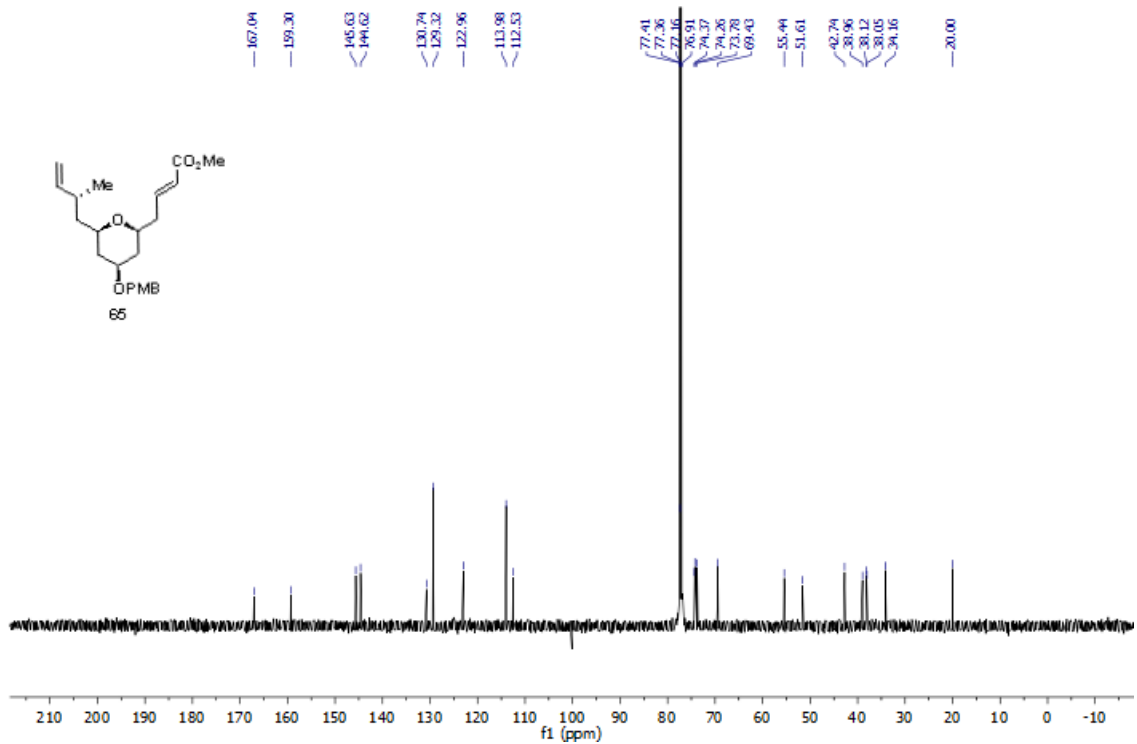
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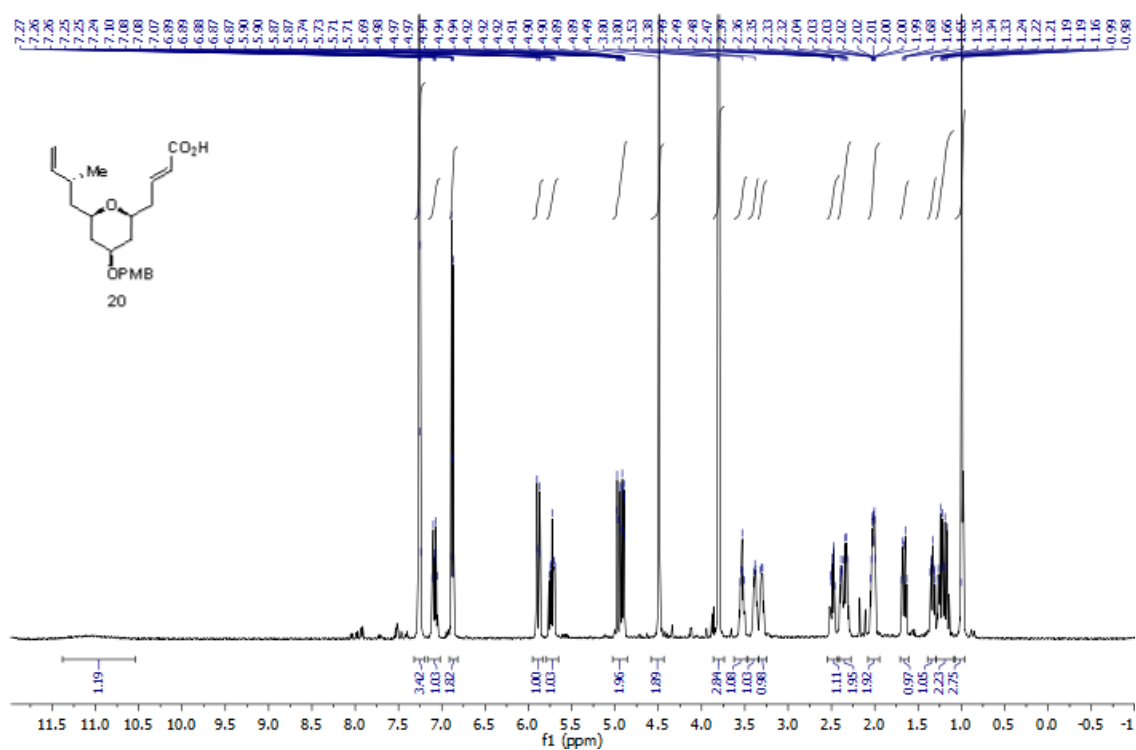
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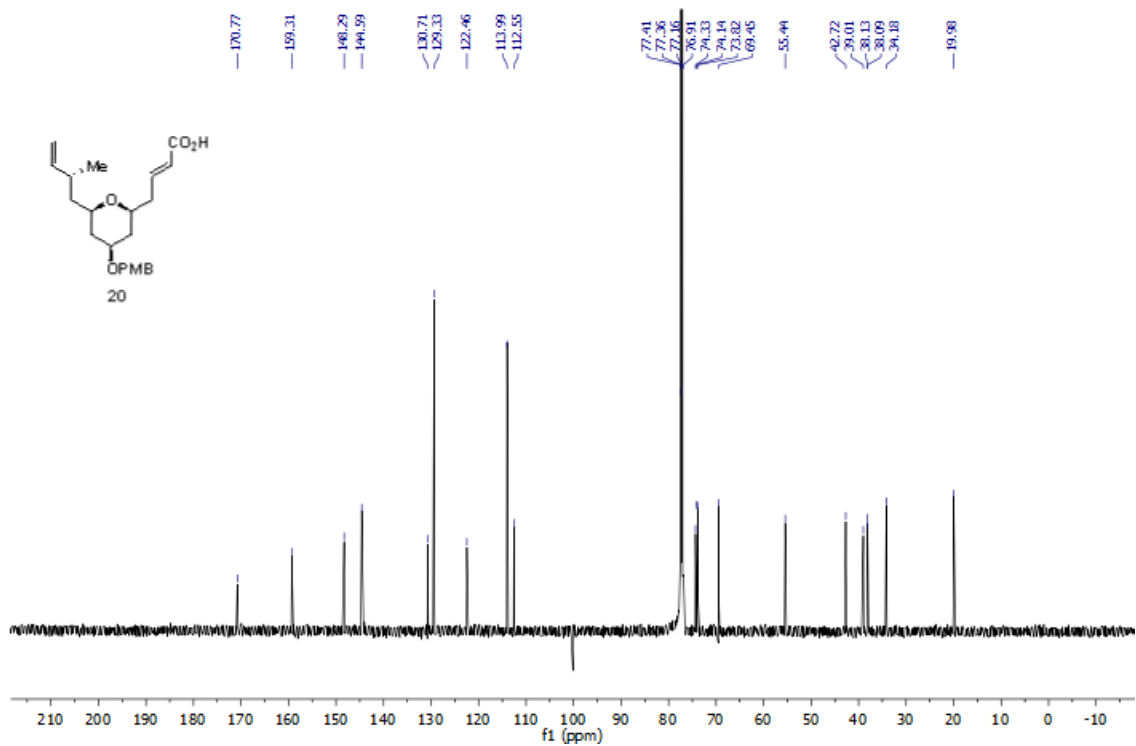
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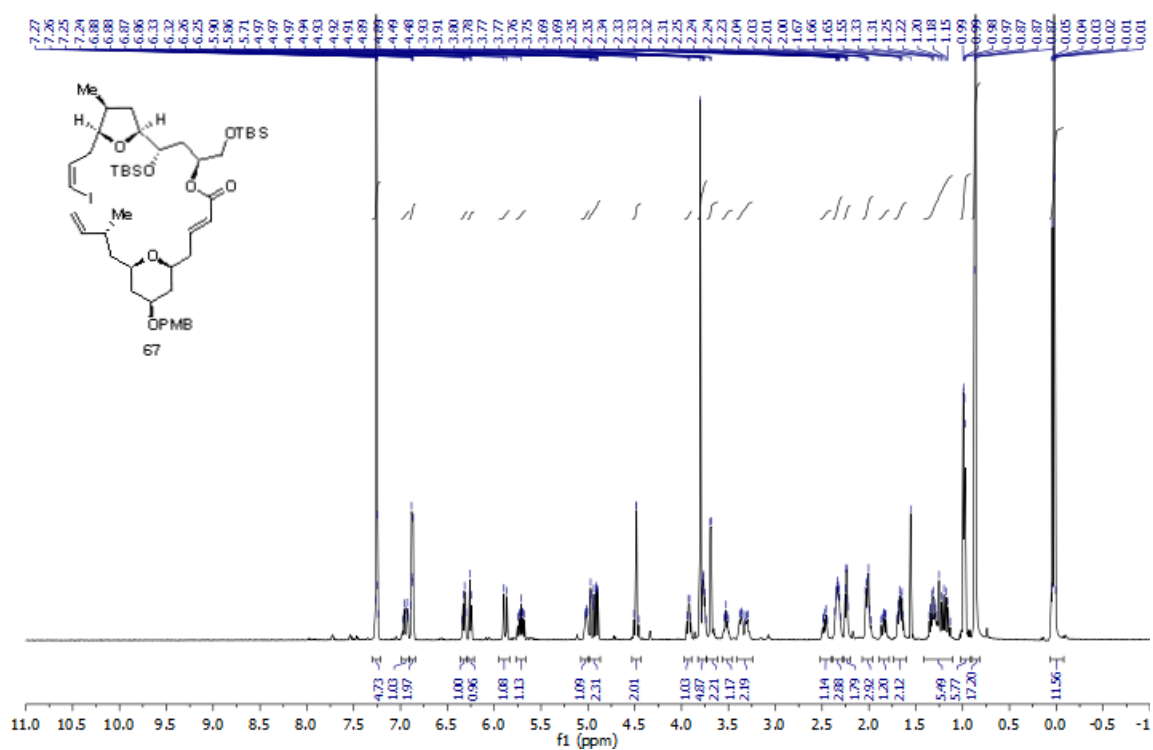
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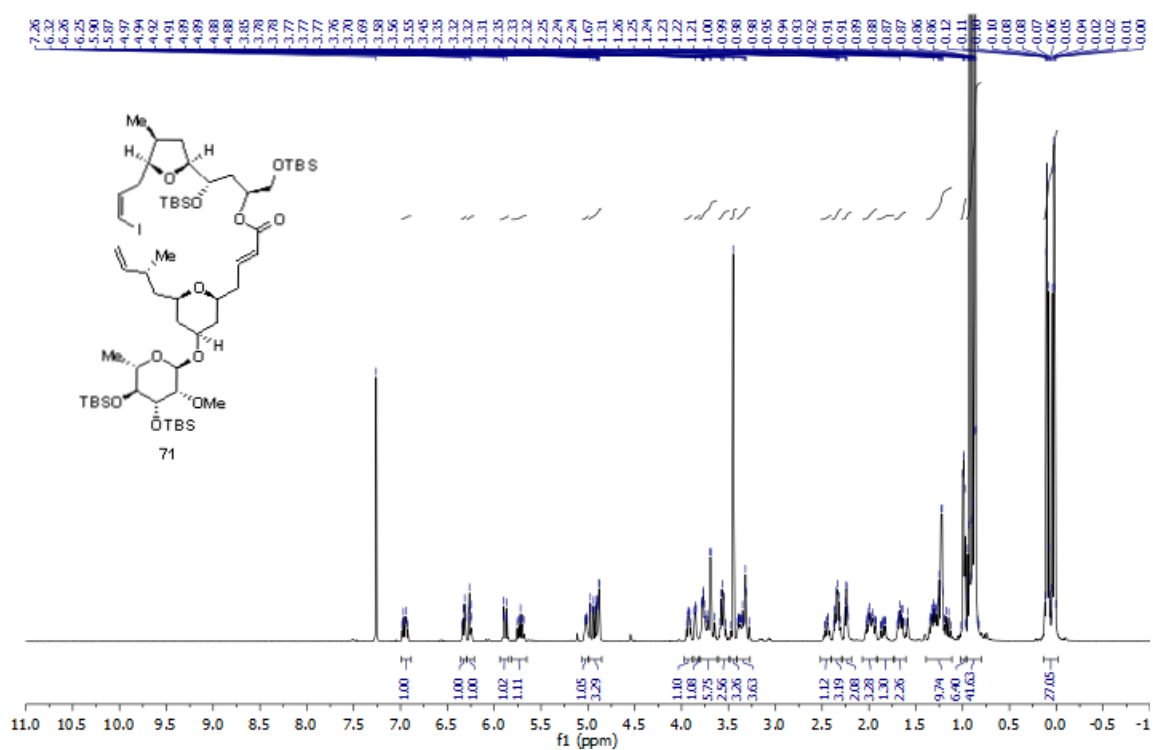
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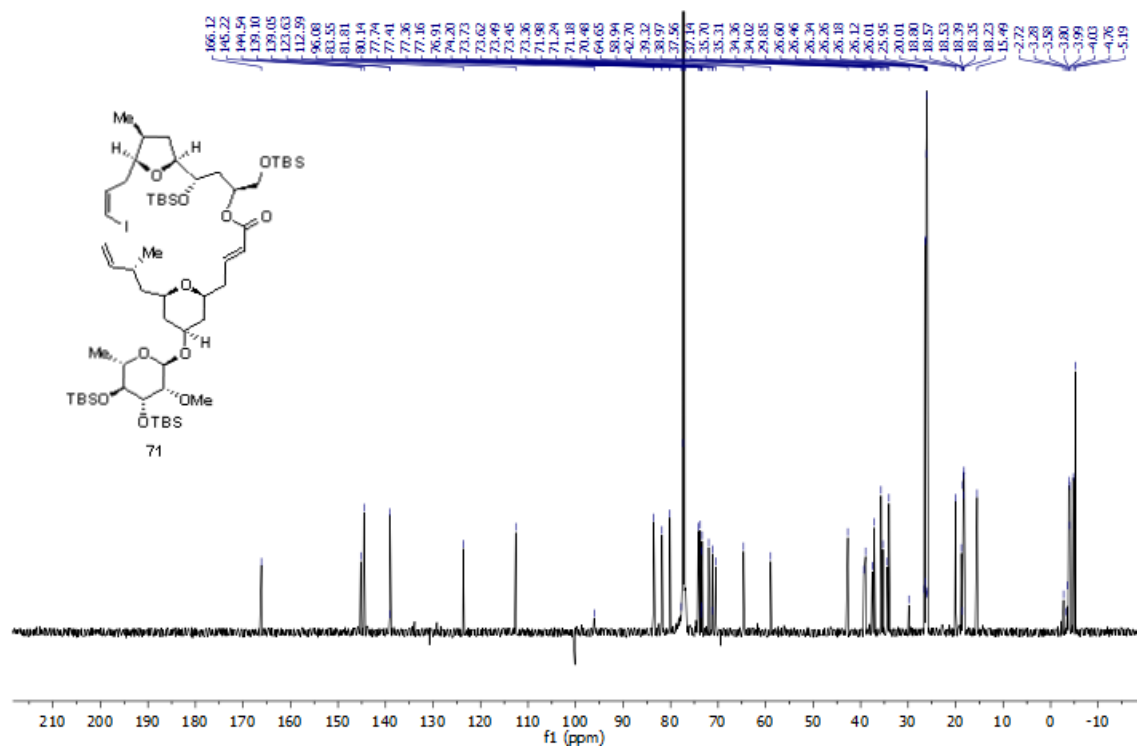
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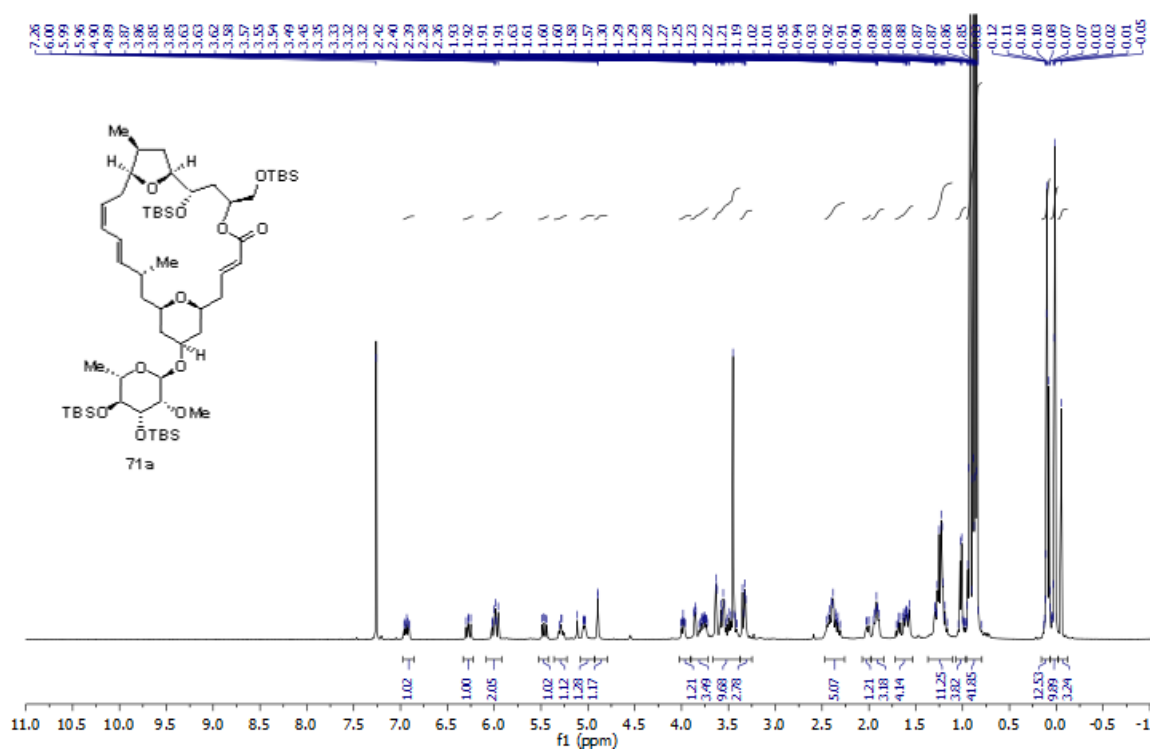
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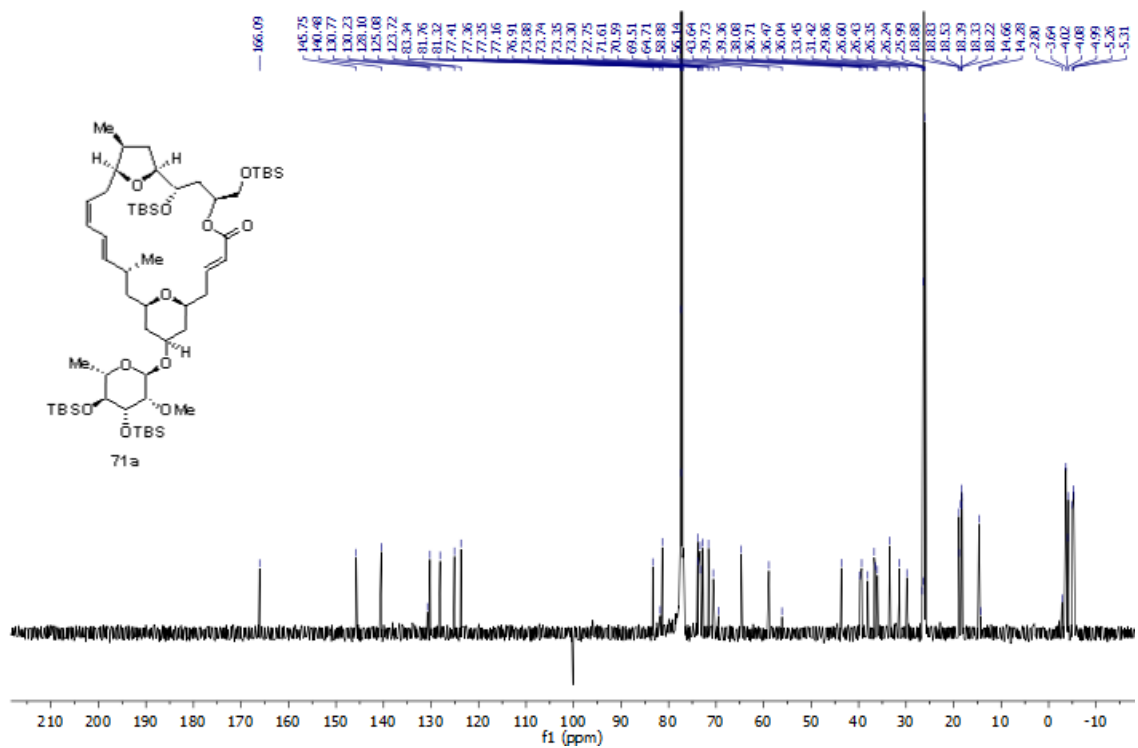
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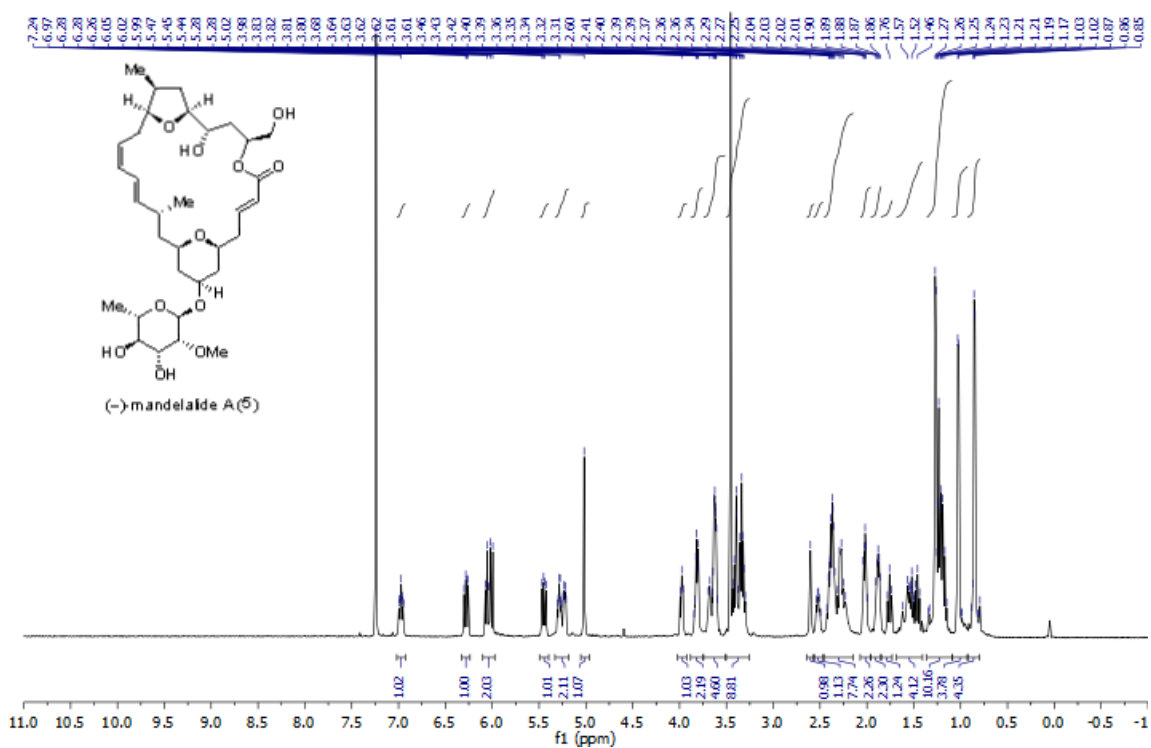
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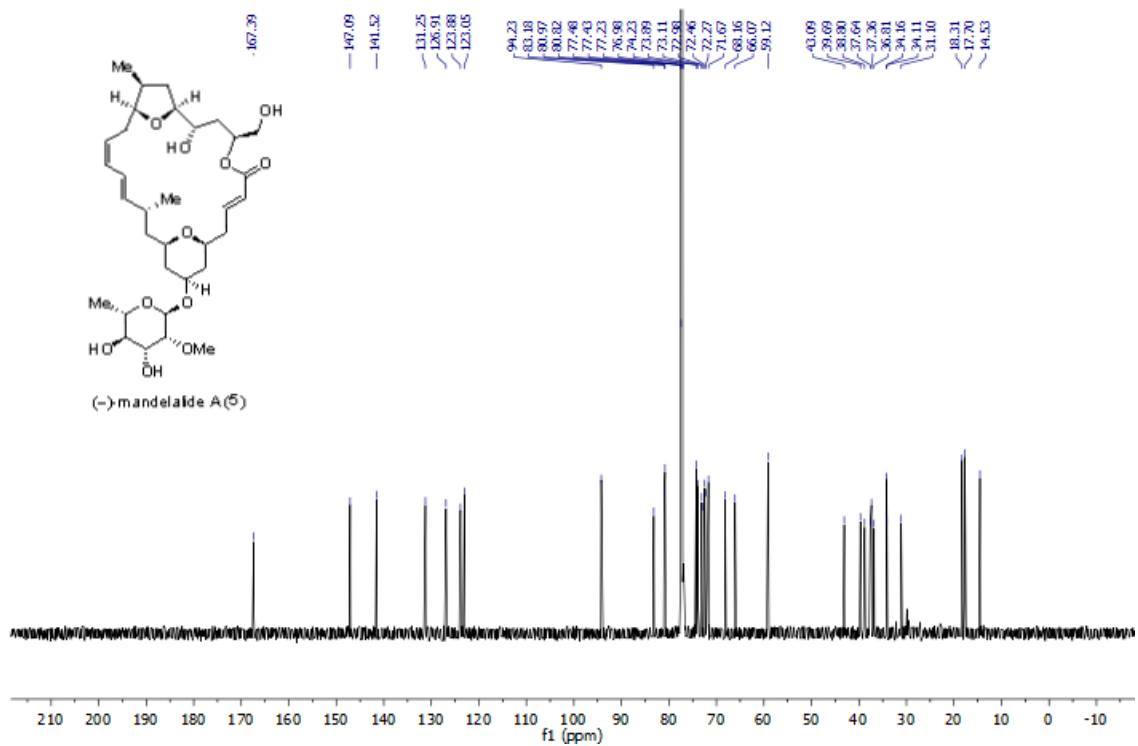
The 125 MHz ¹³C-NMR Spectrum of Compound **71a** in CDCl₃



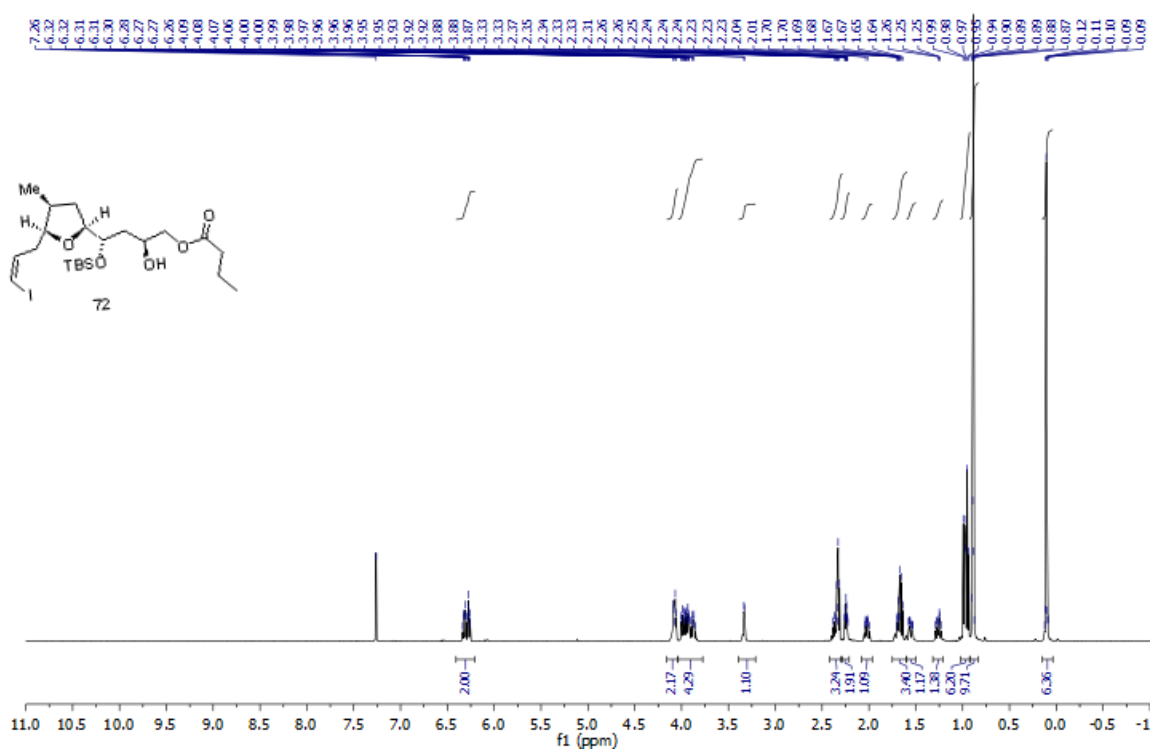
The 600 MHz $^1\text{H-NMR}$ Spectrum of Compound 5 in CDCl_3



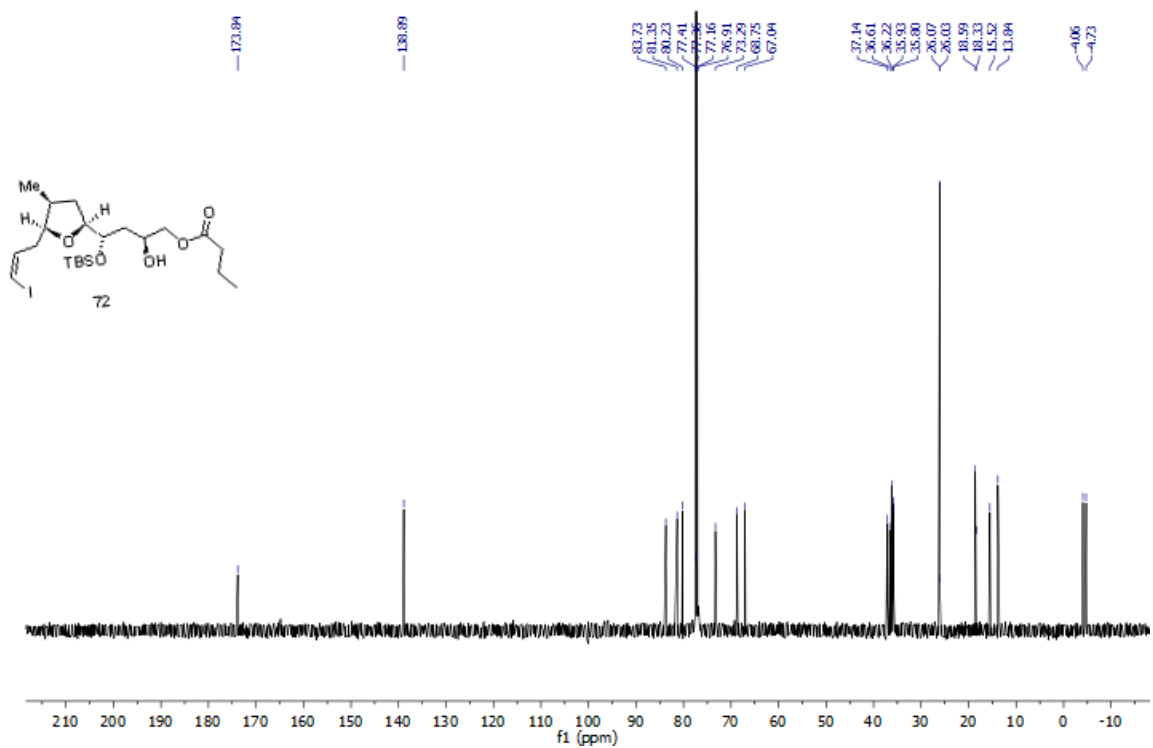
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound 5 in CDCl_3



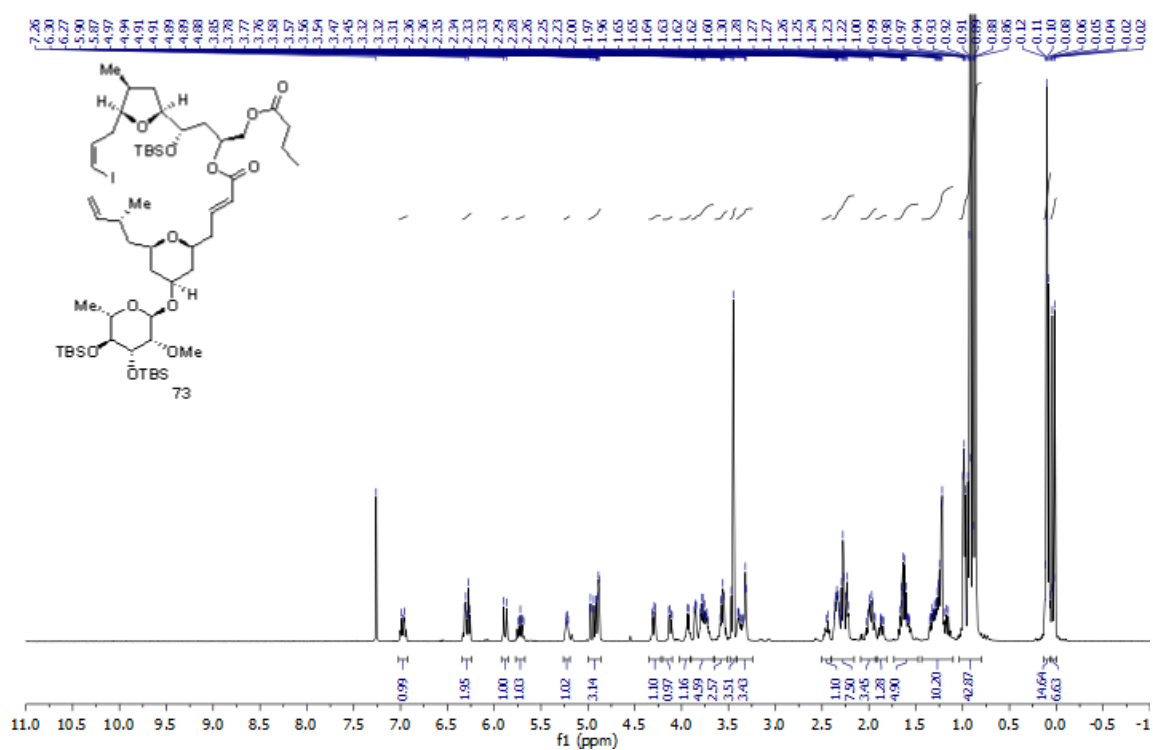
The 500 MHz ^1H -NMR Spectrum of Compound **72** in CDCl_3



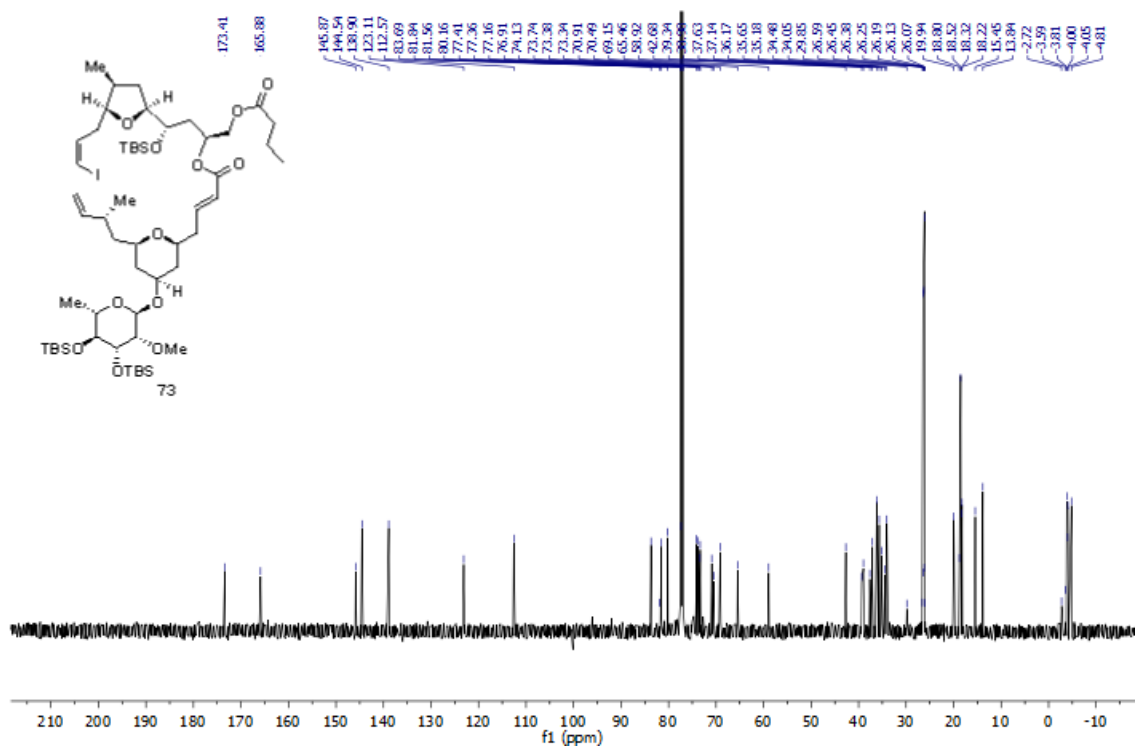
The 125 MHz ^{13}C -NMR Spectrum of Compound **72** in CDCl_3



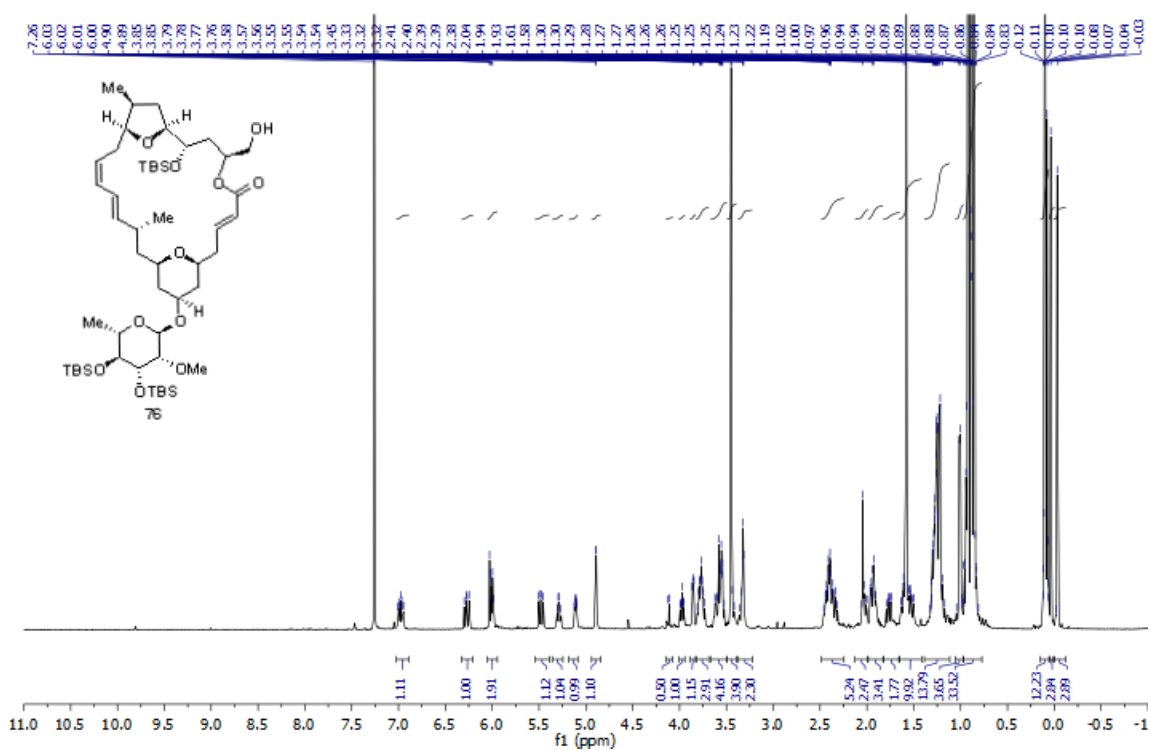
The 500 MHz ^1H -NMR Spectrum of Compound **73** in CDCl_3



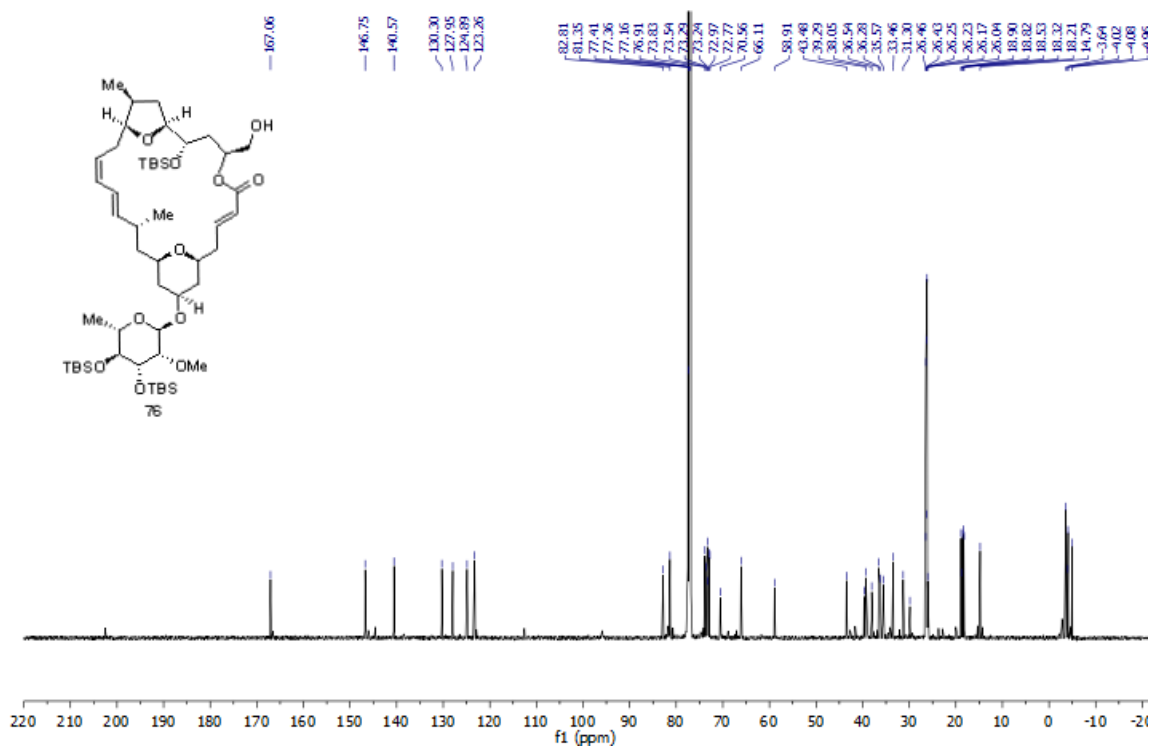
The 125 MHz ^{13}C -NMR Spectrum of Compound **73** in CDCl_3



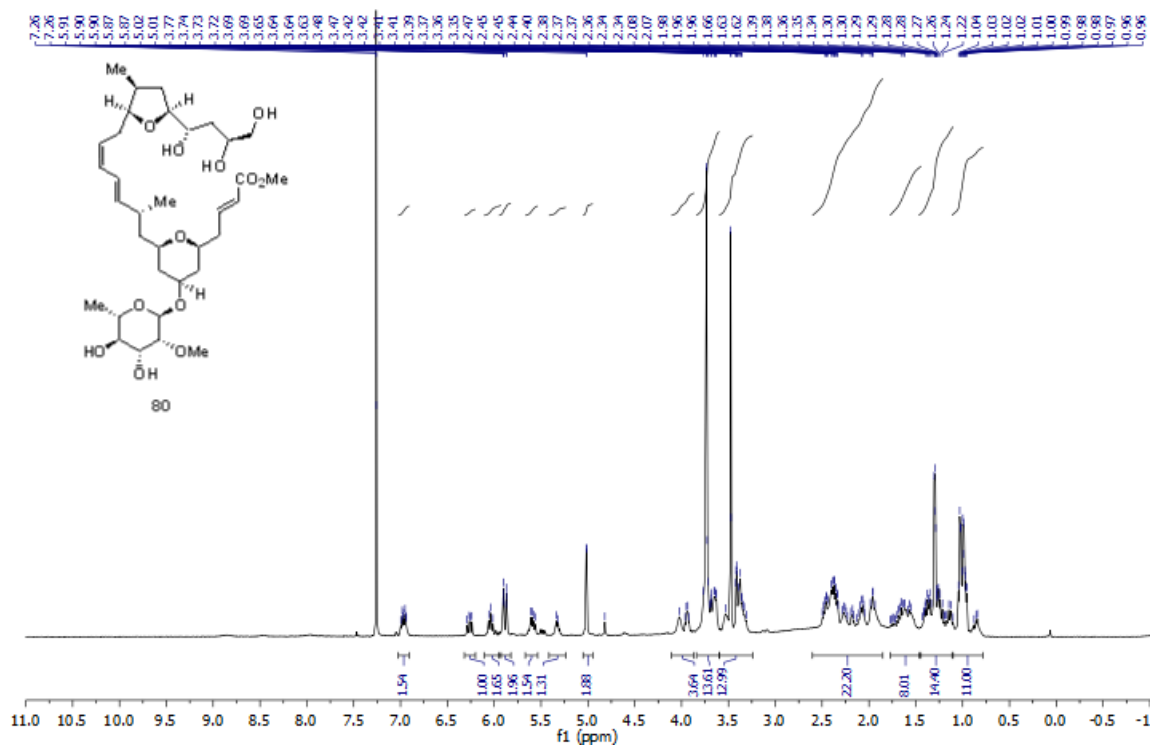
The 500 MHz $^1\text{H-NMR}$ Spectrum of Compound **76** in CDCl_3



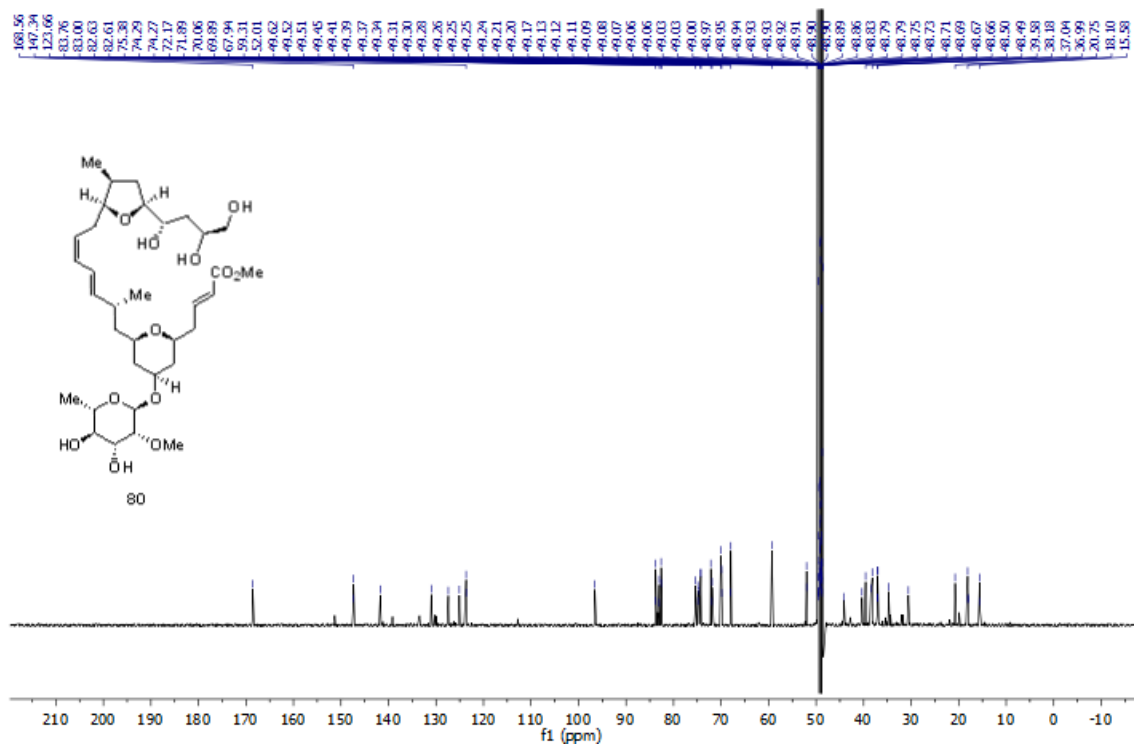
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound **76** in CDCl_3



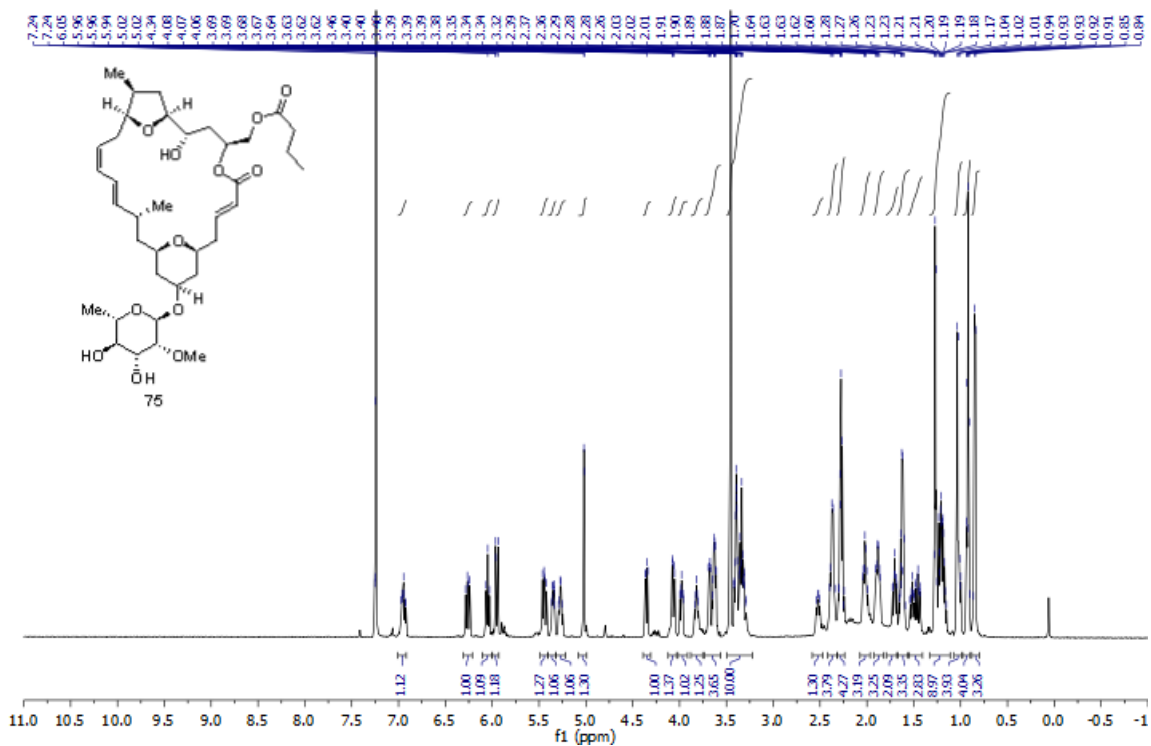
The 500 MHz $^1\text{H-NMR}$ Spectrum of Compound **80** in CDCl_3



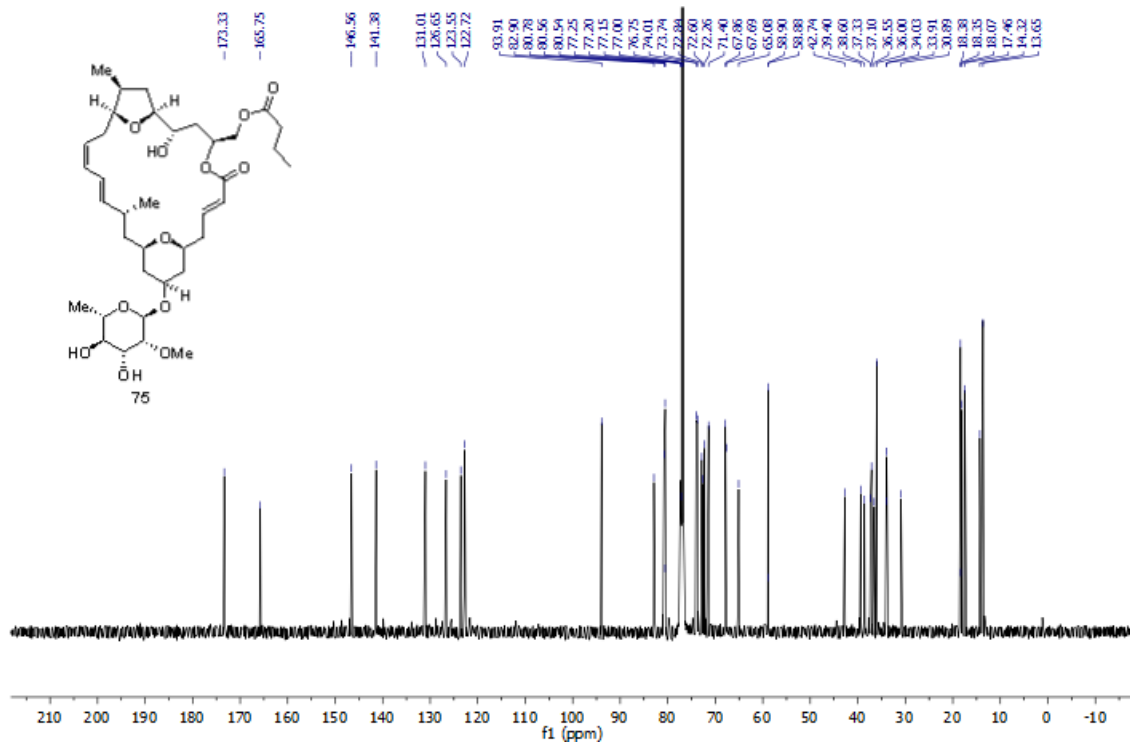
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound **80** in CD_3OD



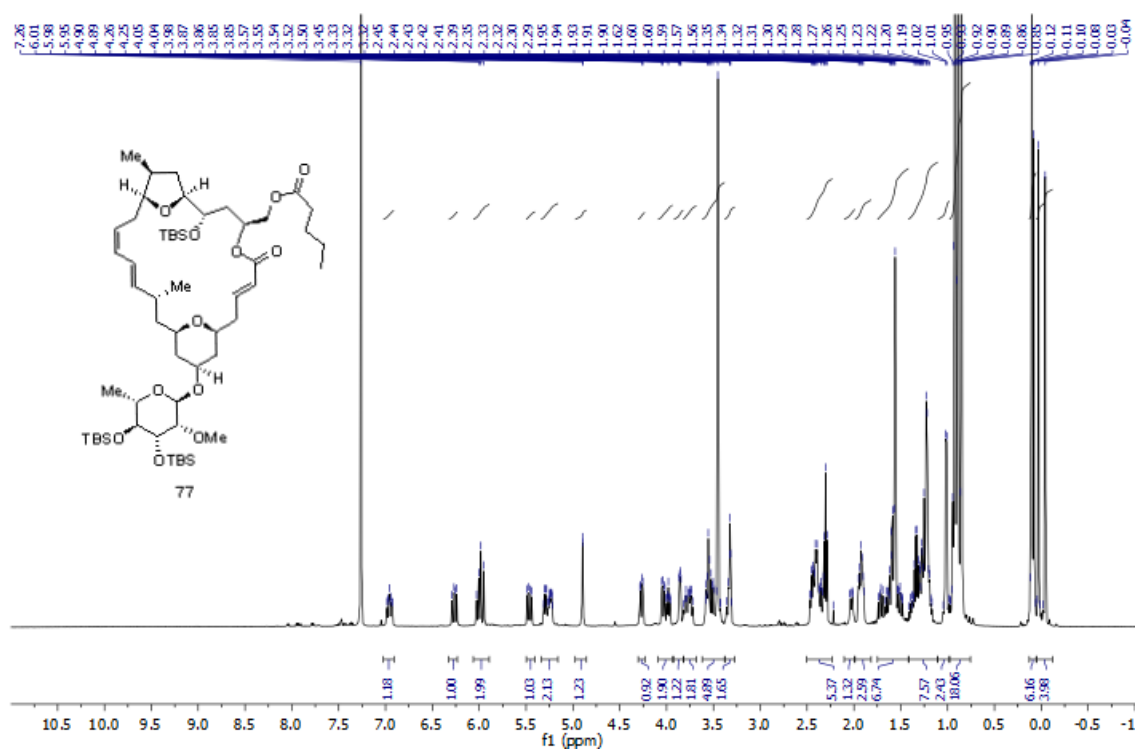
The 600 MHz $^1\text{H-NMR}$ Spectrum of Compound **75** in CDCl_3



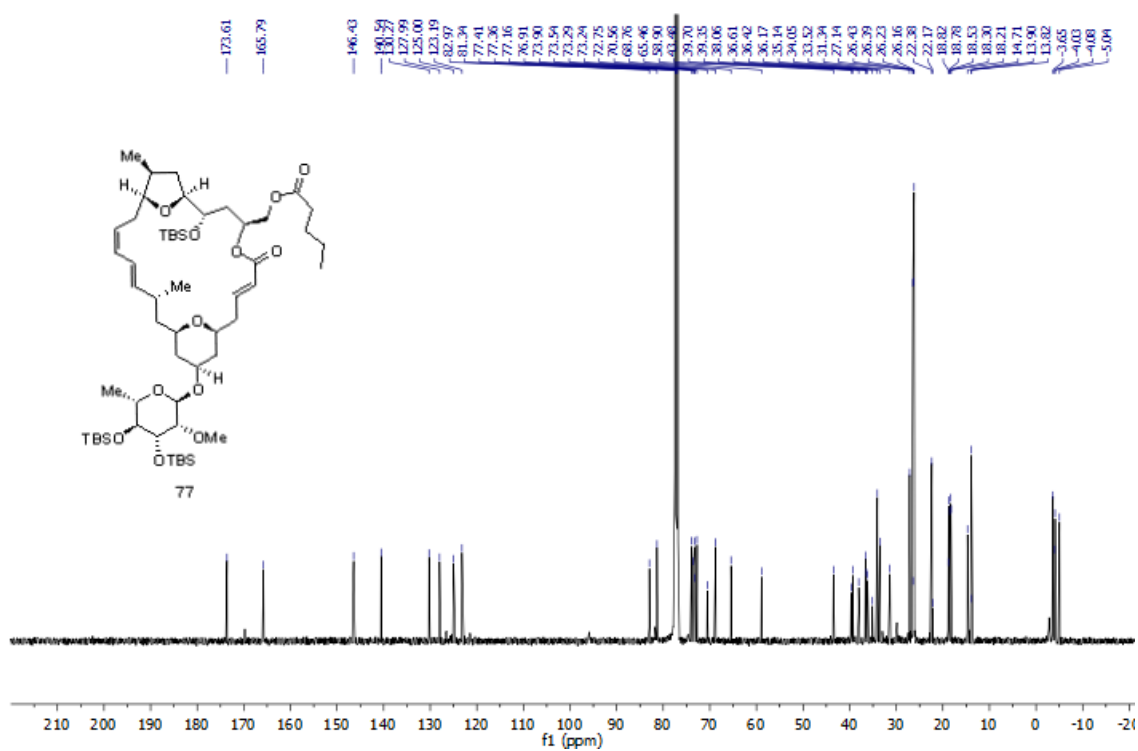
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound **75** in CDCl_3



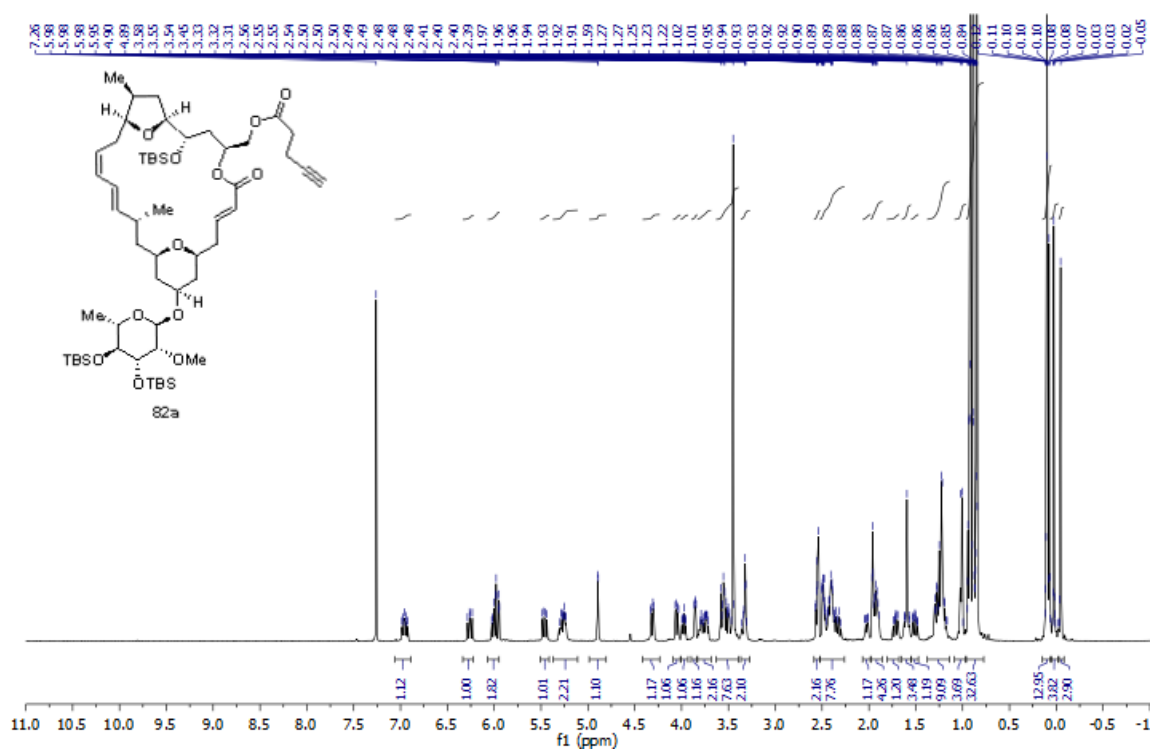
The 600 MHz $^1\text{H-NMR}$ Spectrum of Compound **77** in CDCl_3



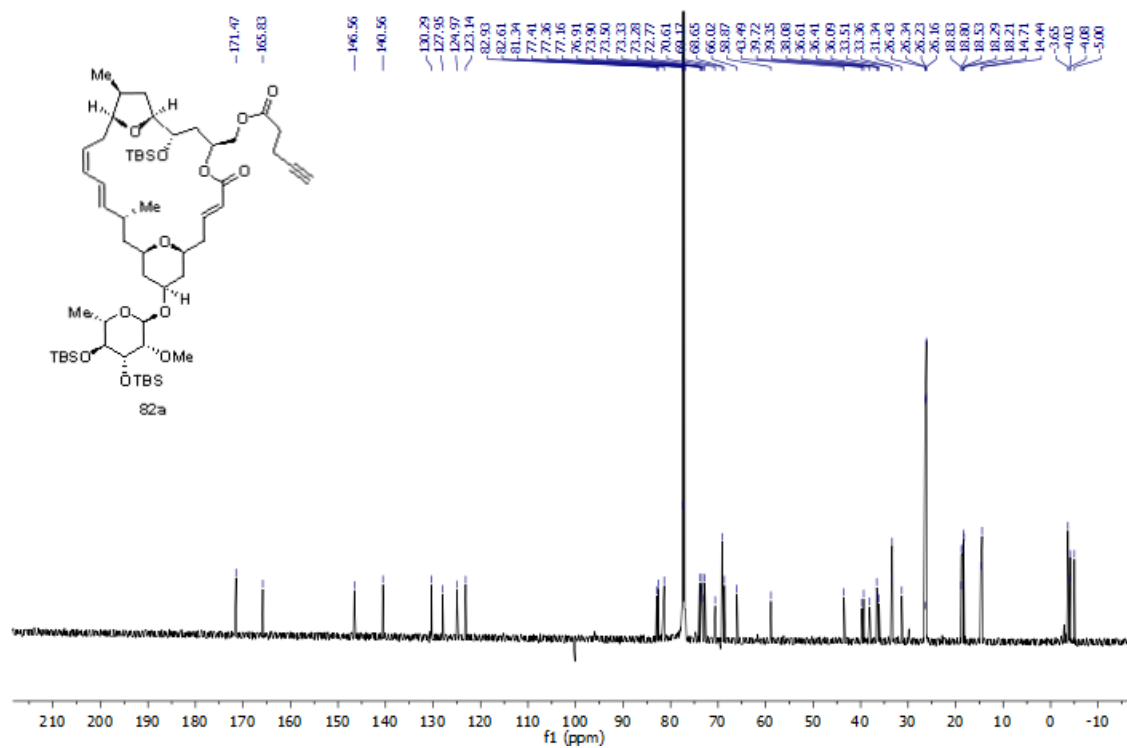
The 125 MHz $^{13}\text{C-NMR}$ Spectrum of Compound **77** in CDCl_3



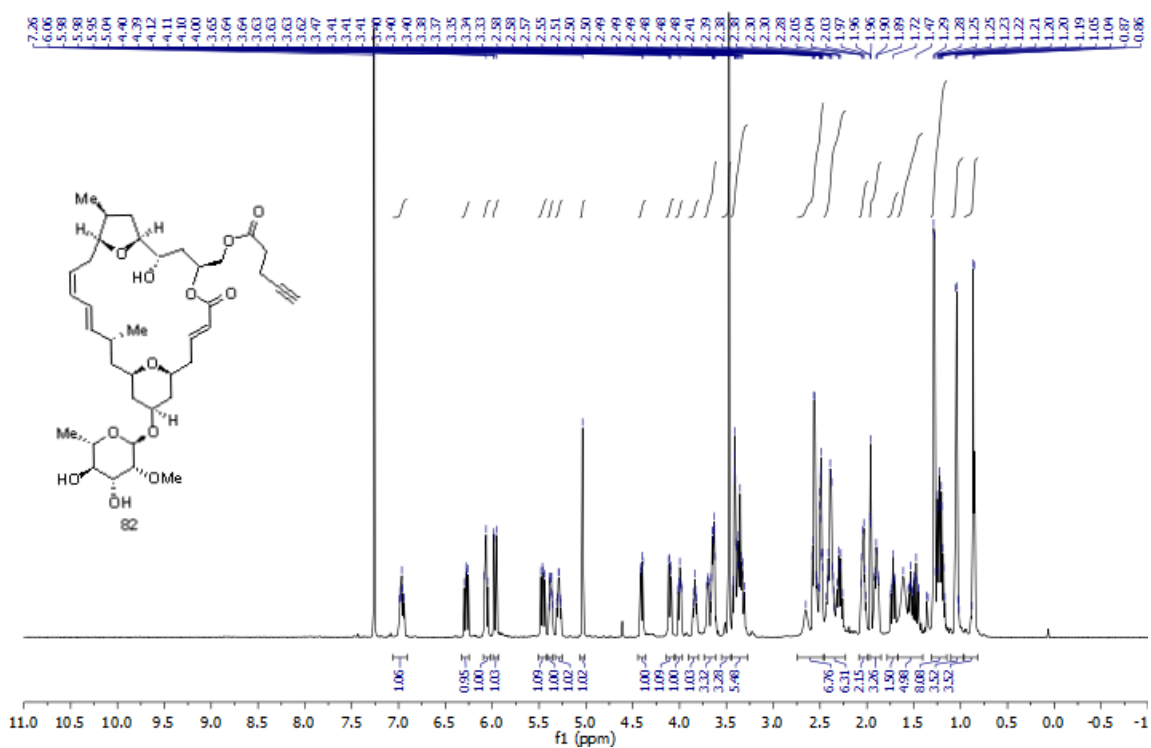
The 500 MHz ¹H-NMR Spectrum of Compound **82a** in CDCl₃



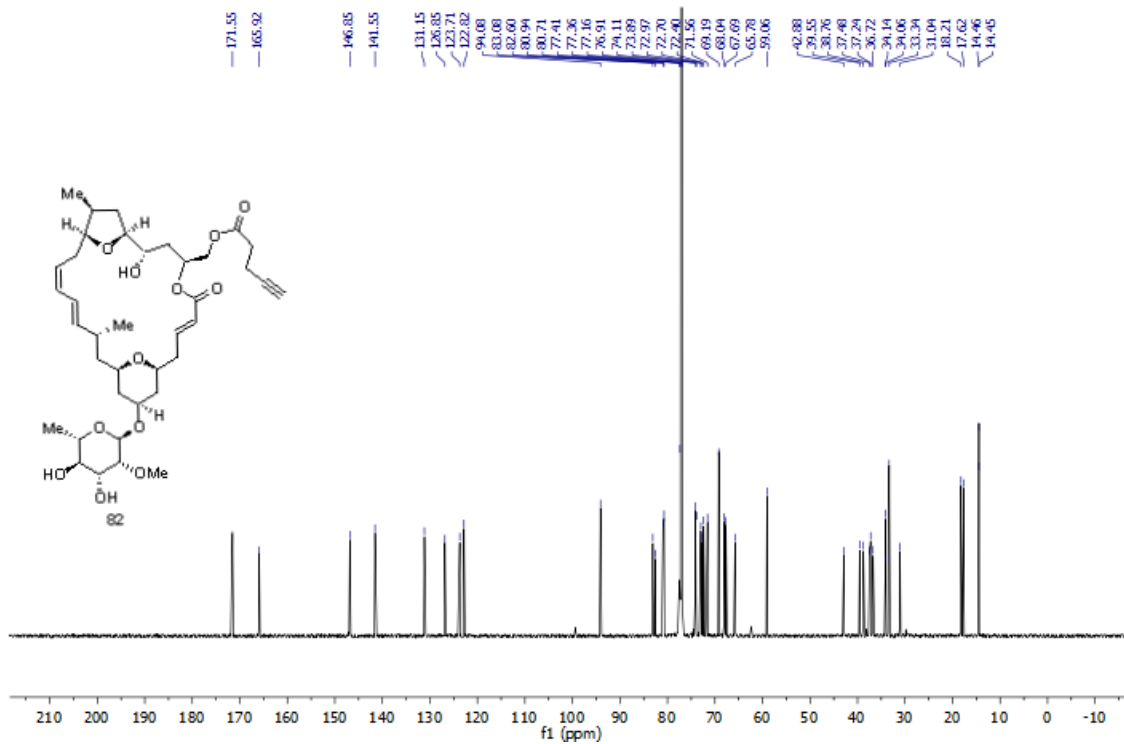
The 125 MHz ¹³C-NMR Spectrum of Compound **82a** in CDCl₃



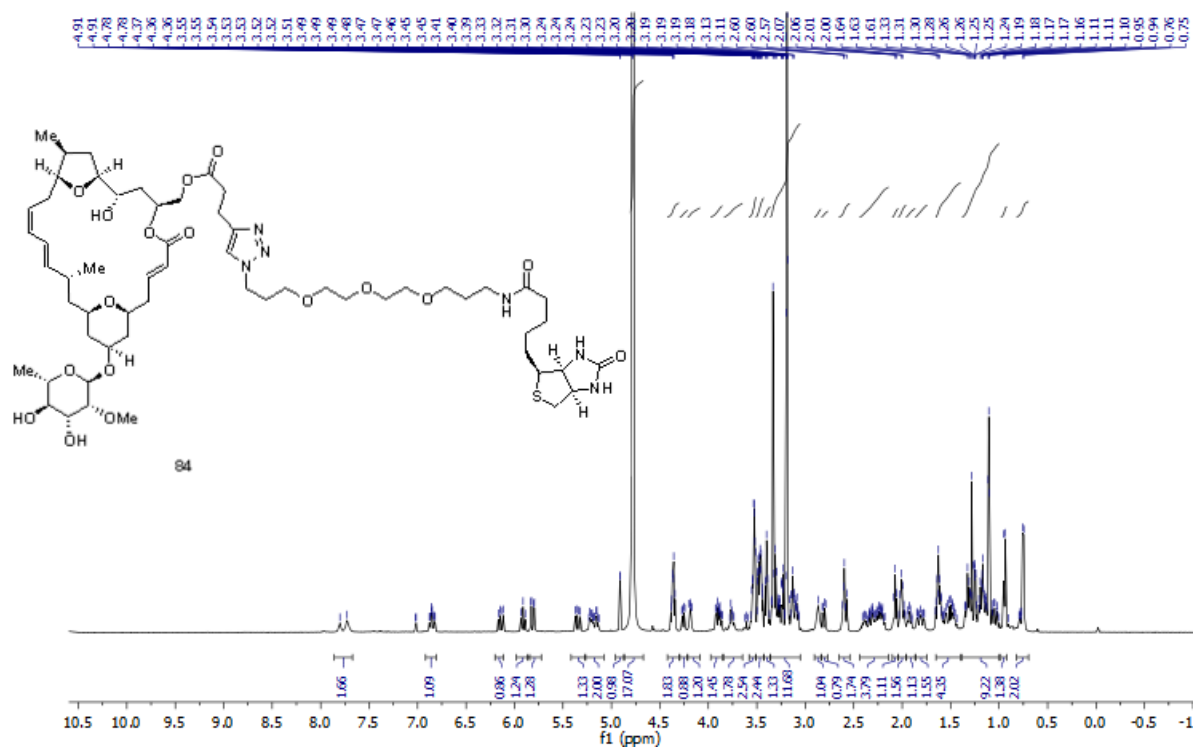
The 600 MHz ¹H-NMR Spectrum of Compound **82** in CDCl₃



The 125 MHz ¹³C-NMR Spectrum of Compound **82** in CDCl₃



The 600 MHz ¹H-NMR Spectrum of Compound **84** in CD₃OD



The 125 MHz ¹³C-NMR Spectrum of Compound **84** in CD₃OD

