

Total Synthesis, Stereochemical Assignment, and Biological Activity of All Known (–)-Trigonoliimines

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General Procedures. All reactions were performed in oven-dried or flame-dried round-bottomed flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Where necessary (so noted), solutions were deoxygenated by argon purging for a minimum of 10 min. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 40–63 µm, 4–6% H₂O content).¹ Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an aqueous solution of ceric ammonium molybdate (CAM) on a hot plate (~250 °C). Organic solutions were concentrated at 29–33 °C on rotary evaporators capable of achieving a minimum pressure of ~2 torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, tetrahydrofuran, acetonitrile, toluene, methanol, and dimethylformamide were purified by the method of Grubbs et al. under positive argon pressure.²

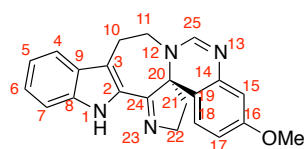
Instrumentation. Proton (¹H) and carbon (¹³C) nuclear magnetic resonance spectra were recorded with 500 MHz NMR spectrometers. Proton nuclear magnetic resonance (¹H NMR) spectra are reported in parts per million on the δ scale and are referenced from the residual protium in the NMR solvent (CDCl₃: δ 7.24 (CHCl₃), CD₃OD: δ 3.31 (CHD₂OD), DMSO-*d*₆: δ 2.50 (DMSO-*d*₅)). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment].

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

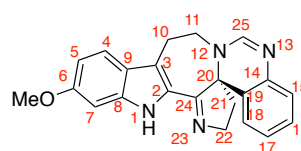
² Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million on the δ scale and are referenced from the carbon resonances of the solvent (CDCl_3 : δ 77.23, CD_3OD : δ 49.15, $\text{DMSO}-d_6$: δ 39.51). Data is reported as follows: chemical shift or chemical shift (assignment). Infrared data (IR) are reported as follows: [frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad)]. Specific rotations are reported as follows: [wavelength of light, temperature ($^{\circ}\text{C}$), specific rotation, concentration in grams/100 mL of solution, solvent]. High-resolution mass spectrometric data (HRMS) were recorded using electrospray ionization (ESI) source or direct analysis in real time (DART) ionization source.

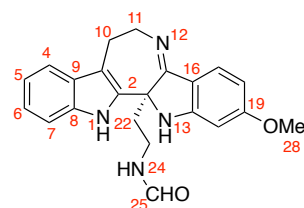
Positional Numbering System. In assigning the ^1H and ^{13}C NMR data of all intermediates en route to our total synthesis of (–)-1, (–)-2, (–)-3, and (–)-4, we have employed a uniform numbering system consistent with that of the final targets.



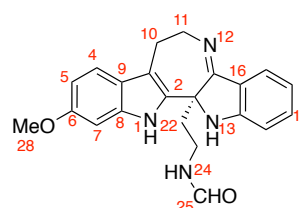
(–)-trigonoliimine A (1)



(–)-trigonoliimine B (2)

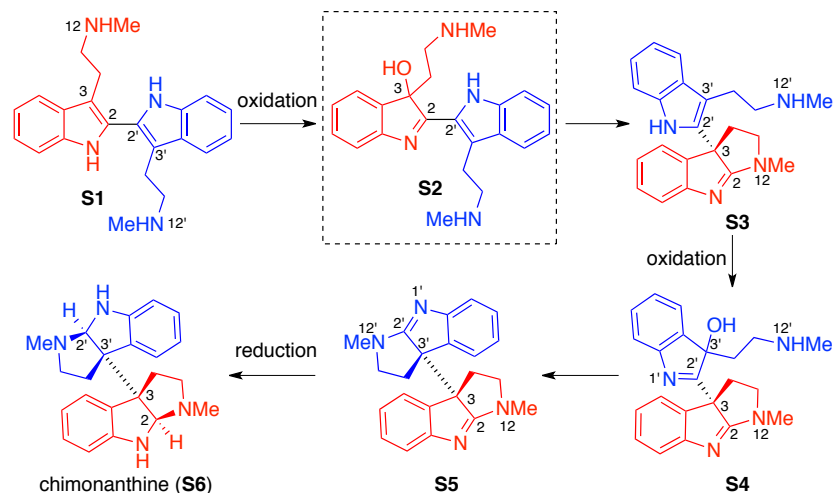


(–)-trigonoliimine C (3)



(–)-isotrigonoliimine C (4)

Inspiration for the oxidation and rearrangement approach.

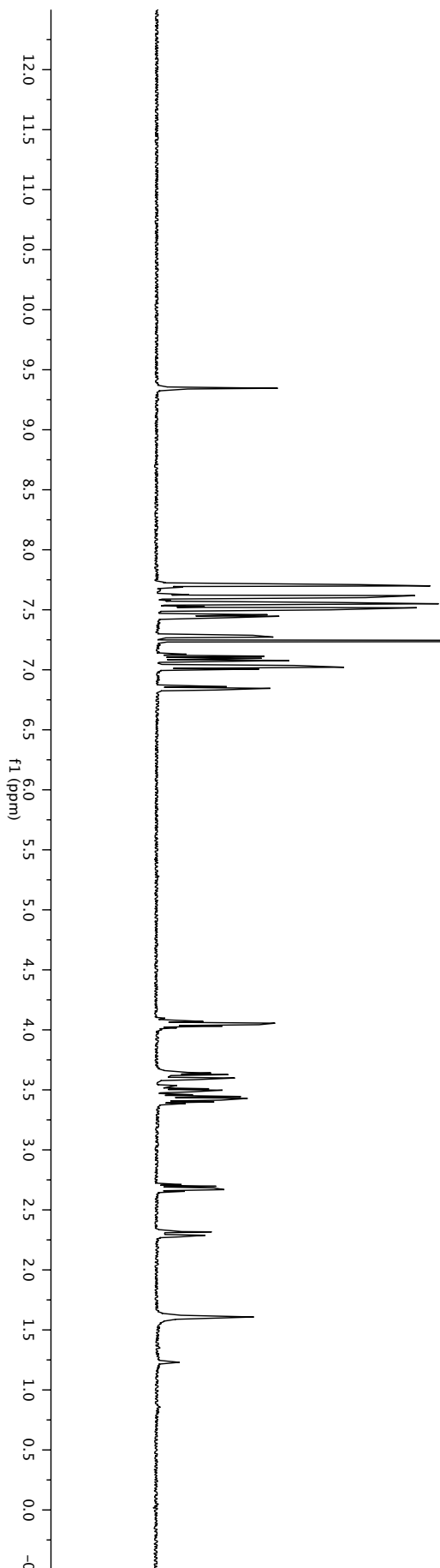
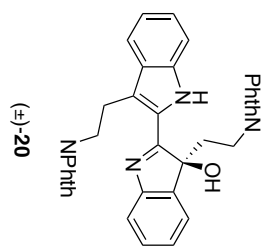


Scheme S1. Our original hypothesis for the oxidation and rearrangement of bistryptamine **S1** to access the calycanthaceous alkaloids.

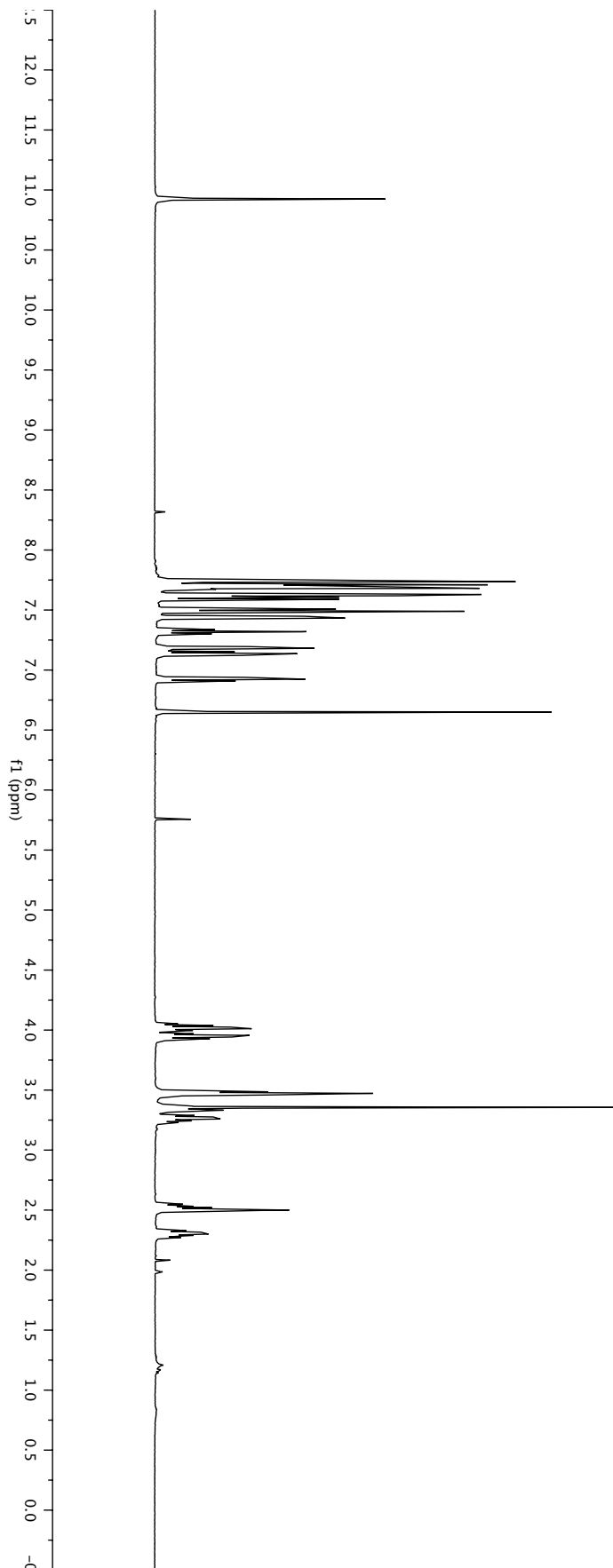
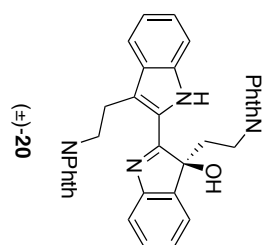
In 2008, our laboratory provided a hypothesis for a strategy toward the calycanthaceous alkaloids from oxidation and rearrangement of a 2,2'-bistryptamine derivative (Scheme S1).³ We expected that the oxidation of 2,2'-bistryptamine **S1** would afford mono-oxidized hydroxyindolenine **S2**, which after 1,2-aryl shift followed by cyclization of the amine moiety to the carbonyl group of the resulting oxindole intermediate would give imine **S3**. After another round of oxidation and rearrangement followed by reduction step, we envisioned the formation of chimonanthine (**S6**). Interestingly, at the time we envisioned this approach the trigonoliimine alkaloids were not known; however, their isolation prompted our reinvestigation of this approach in their context enabling the program discussed in this report.

³ Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313–324.

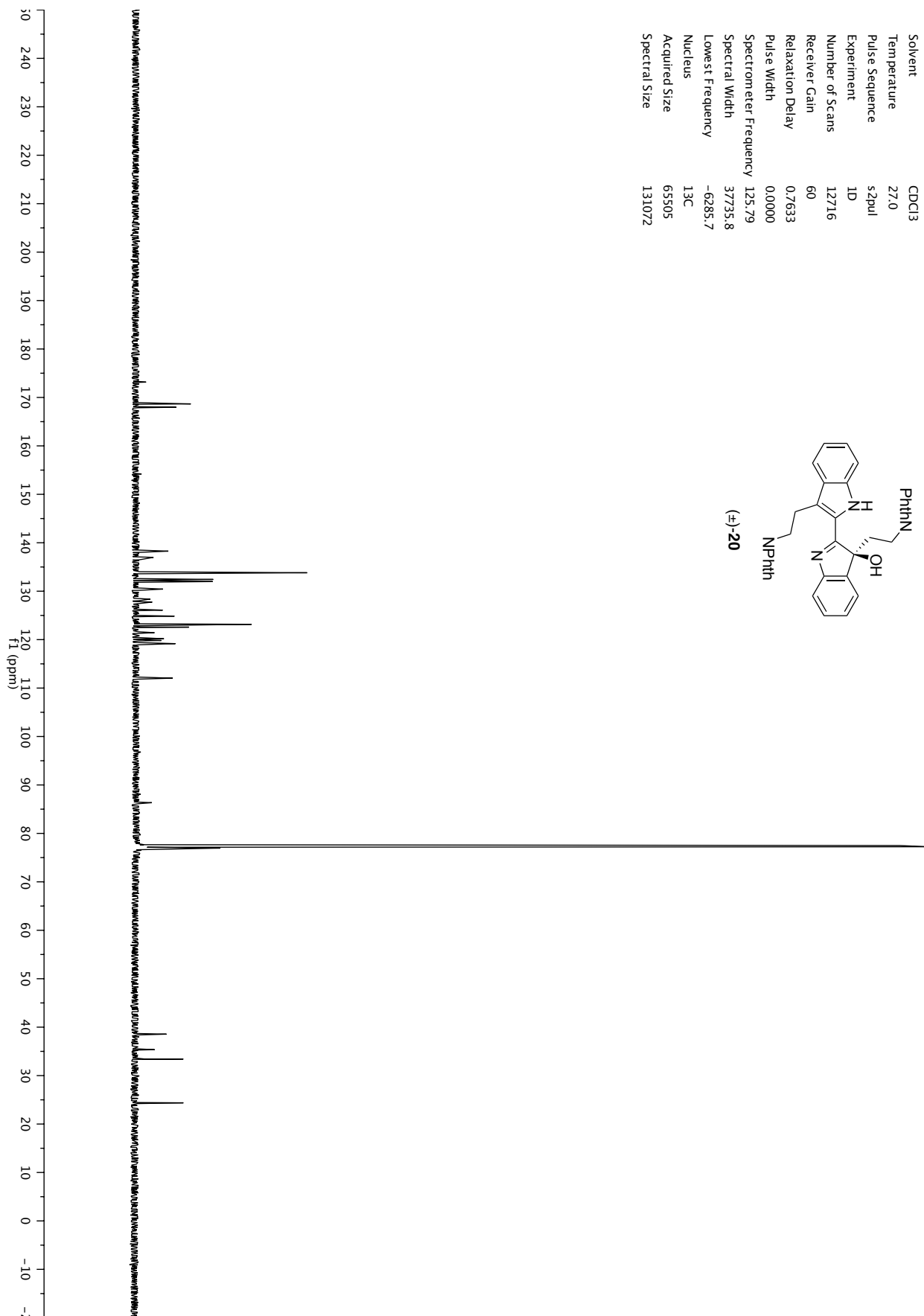
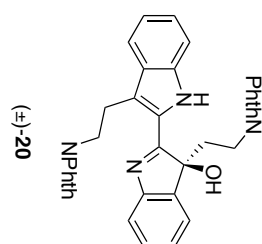
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Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	30.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	8
Receiver Gain	40
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	–524.3
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072

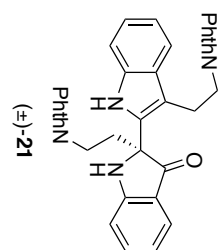


Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	DMSO
Temperature	30.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	20
Receiver Gain	22
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	–504.9
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072

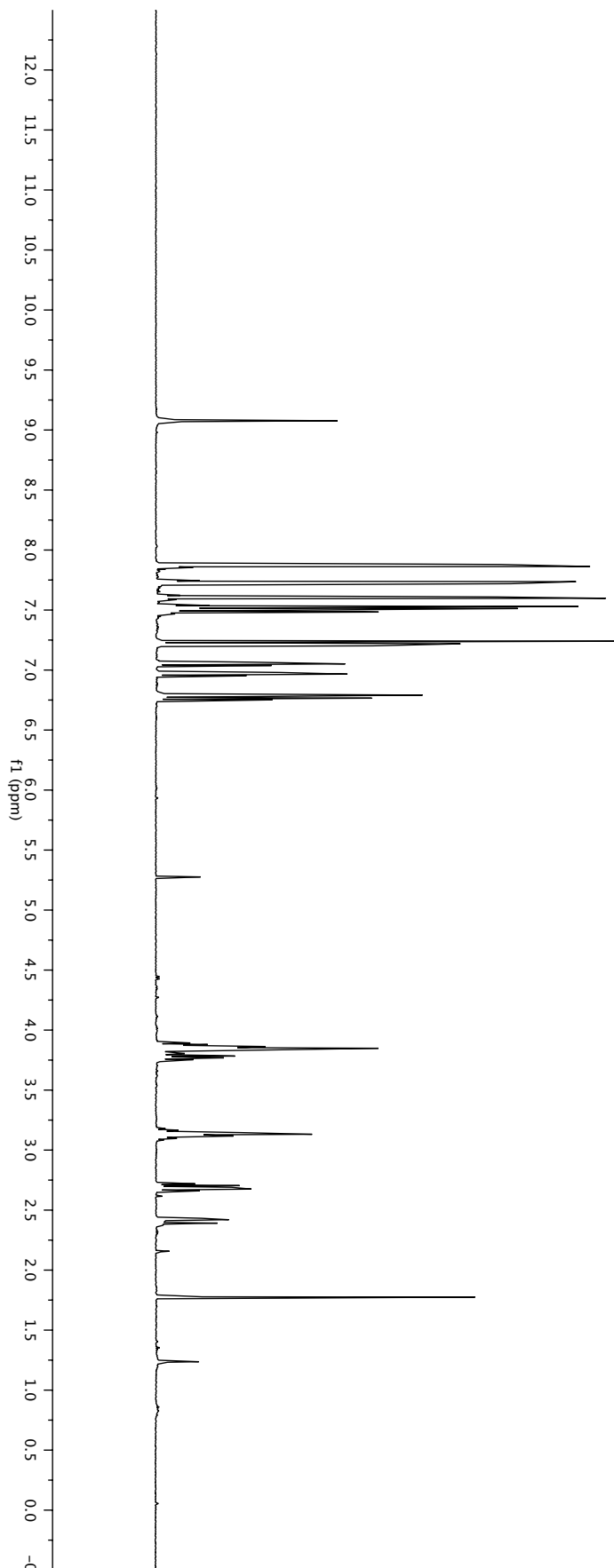


Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	27.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	12716
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
Spectrometer Frequency	125.79
Spectral Width	37735.8
Lowest Frequency	–6285.7
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072

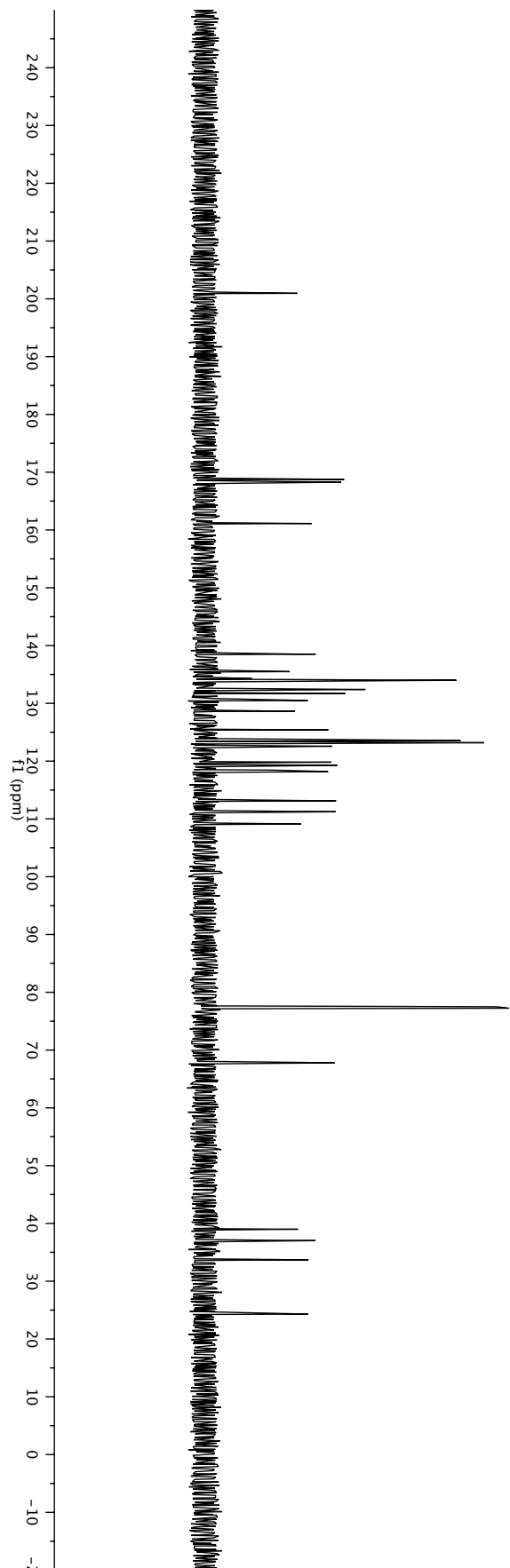
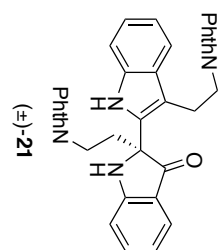




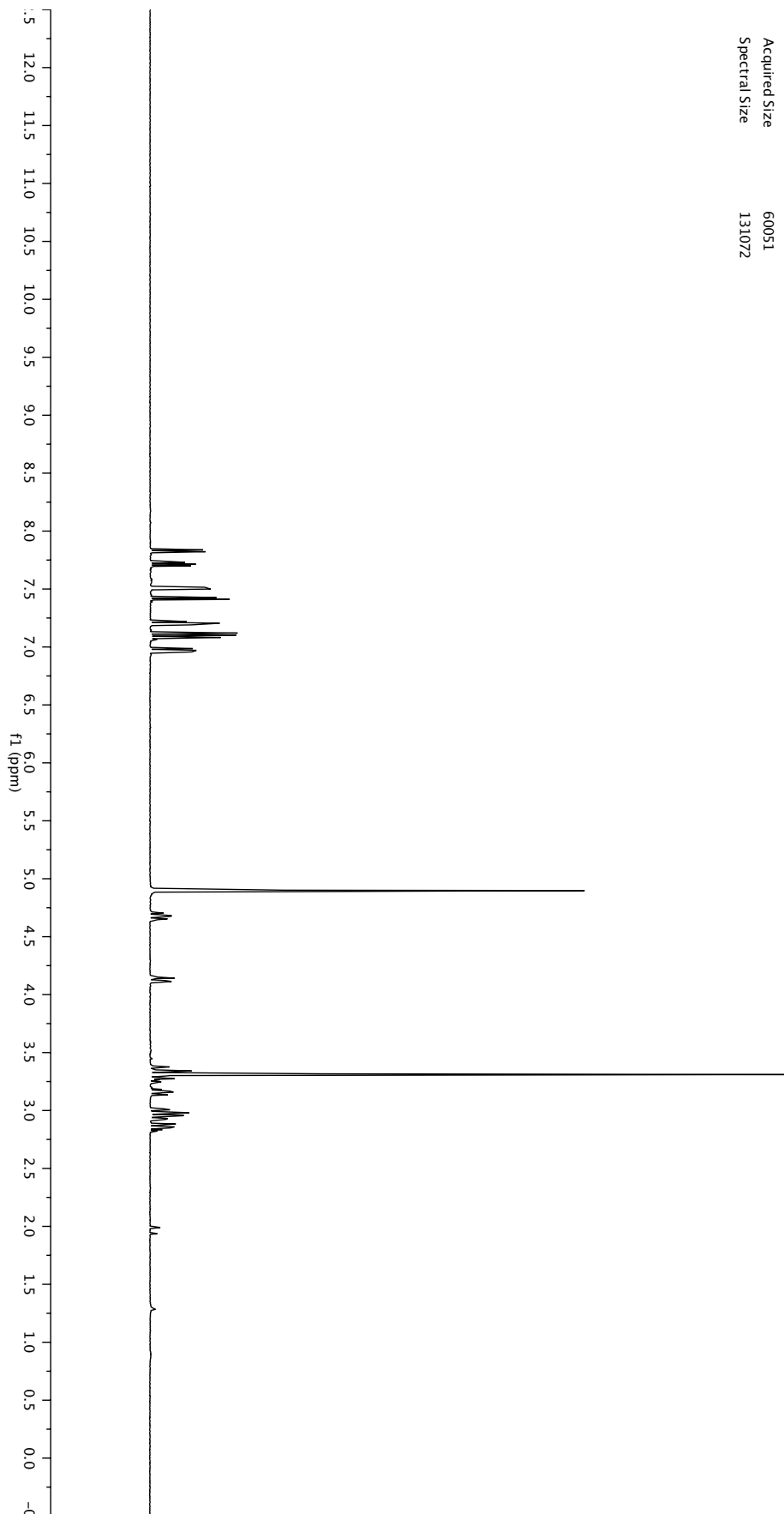
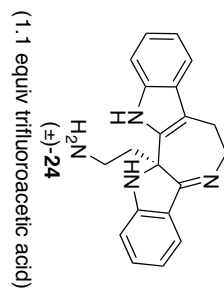
Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	30.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	10
Receiver Gain	28
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	–524.3
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072



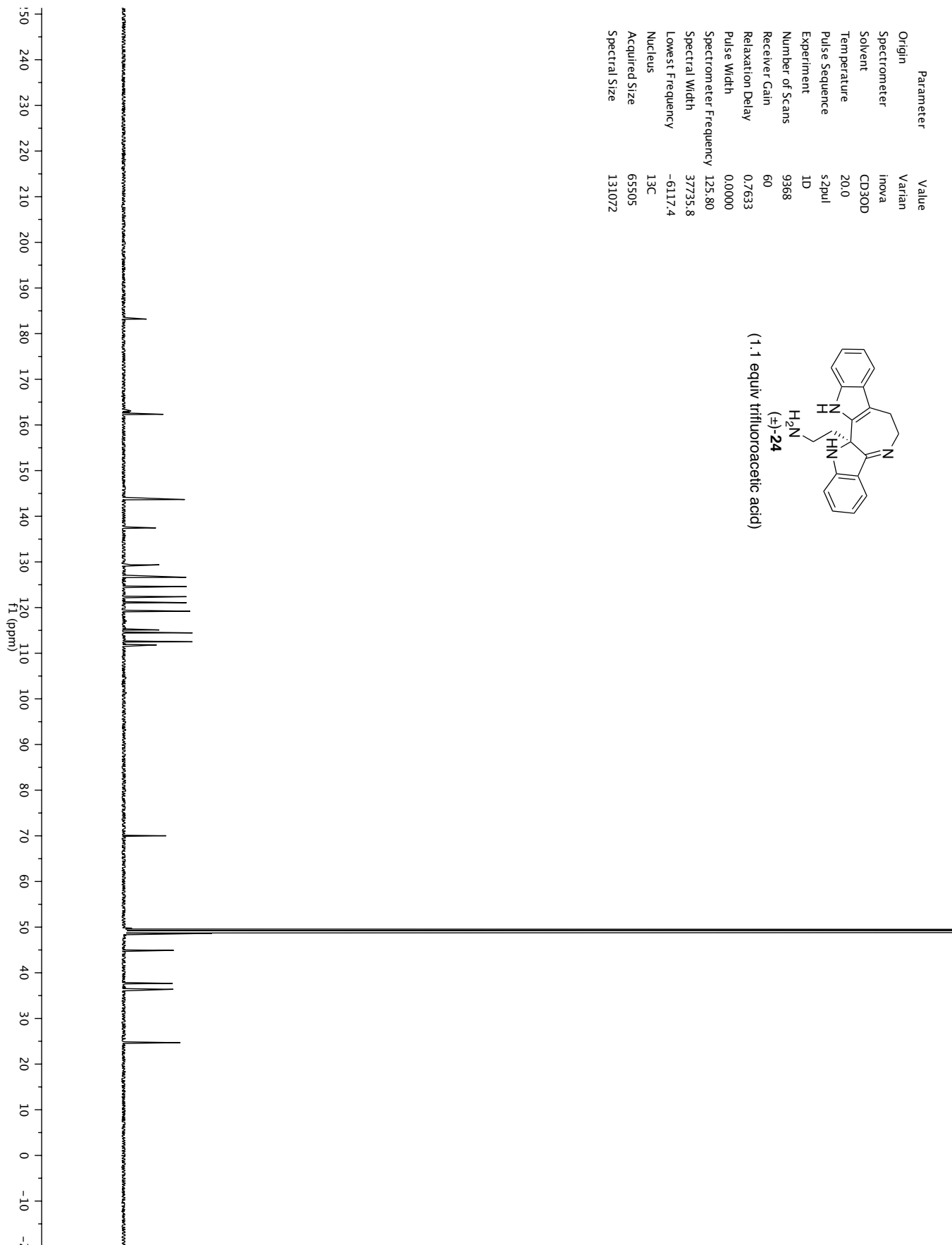
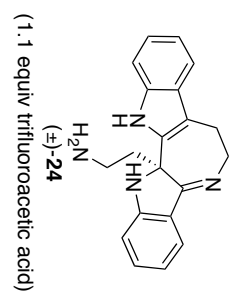
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Solvent	CDCl ₃
Temperature	15.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	80
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
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Spectral Width	37735.8
Lowest Frequency	–6289.1
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072

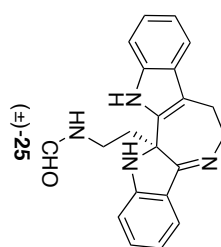


Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CD3OD
Temperature	30.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	8
Receiver Gain	34
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	–512.8
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072

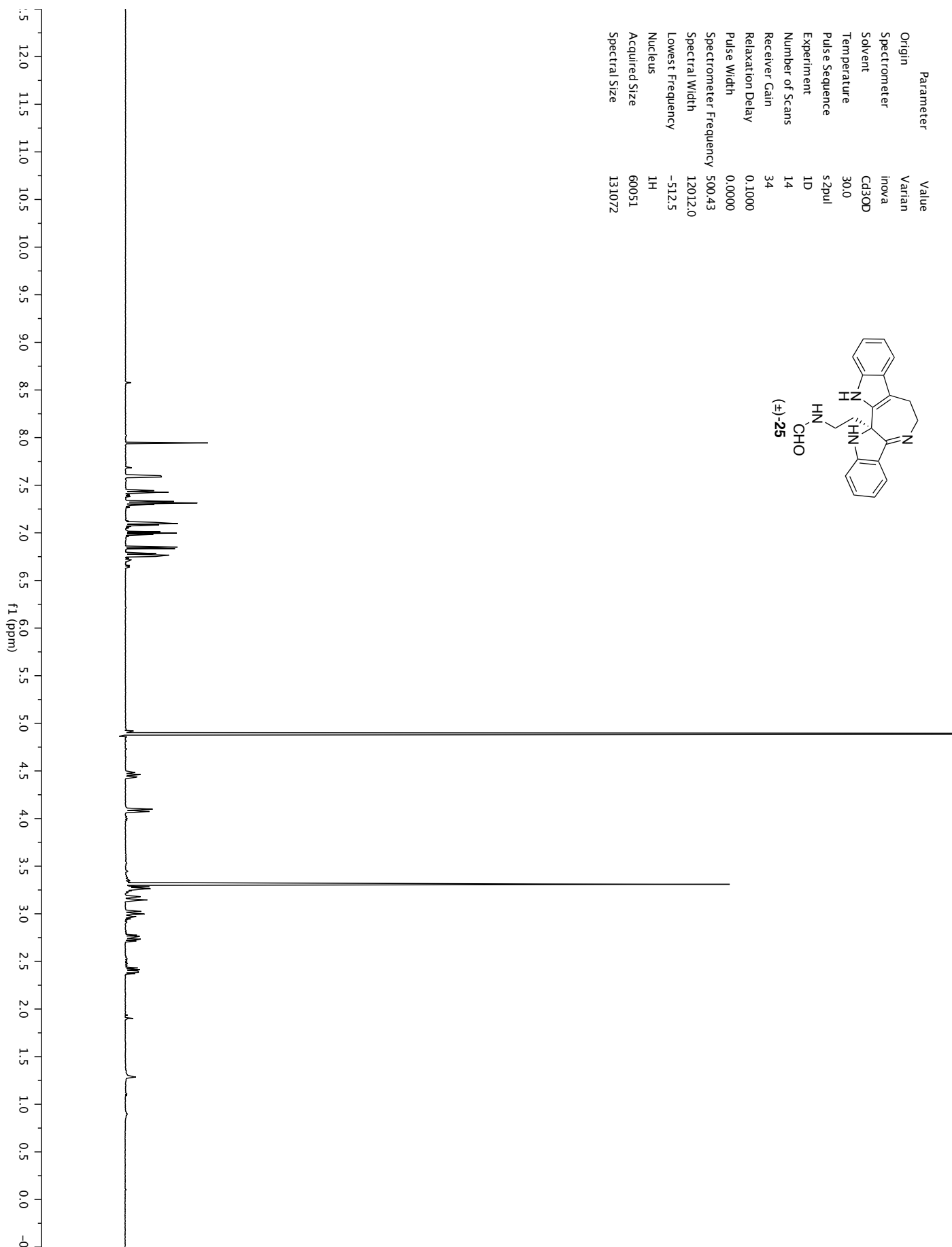


Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CD3OD
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	9368
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
Spectrometer Frequency	125.80
Spectral Width	37735.8
Lowest Frequency	–6117.4
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072

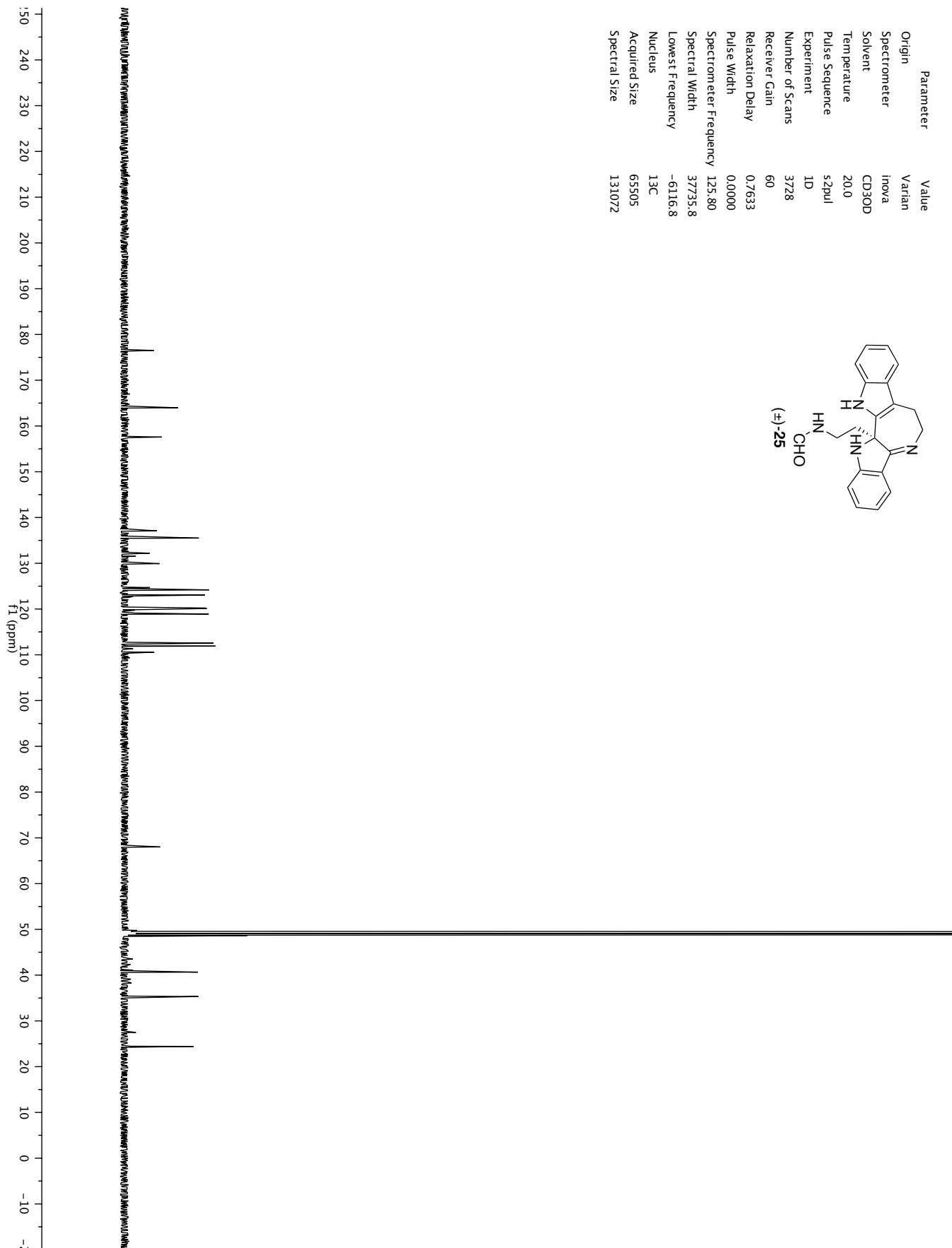
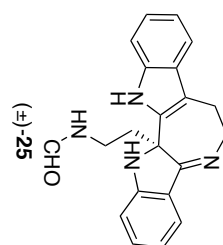




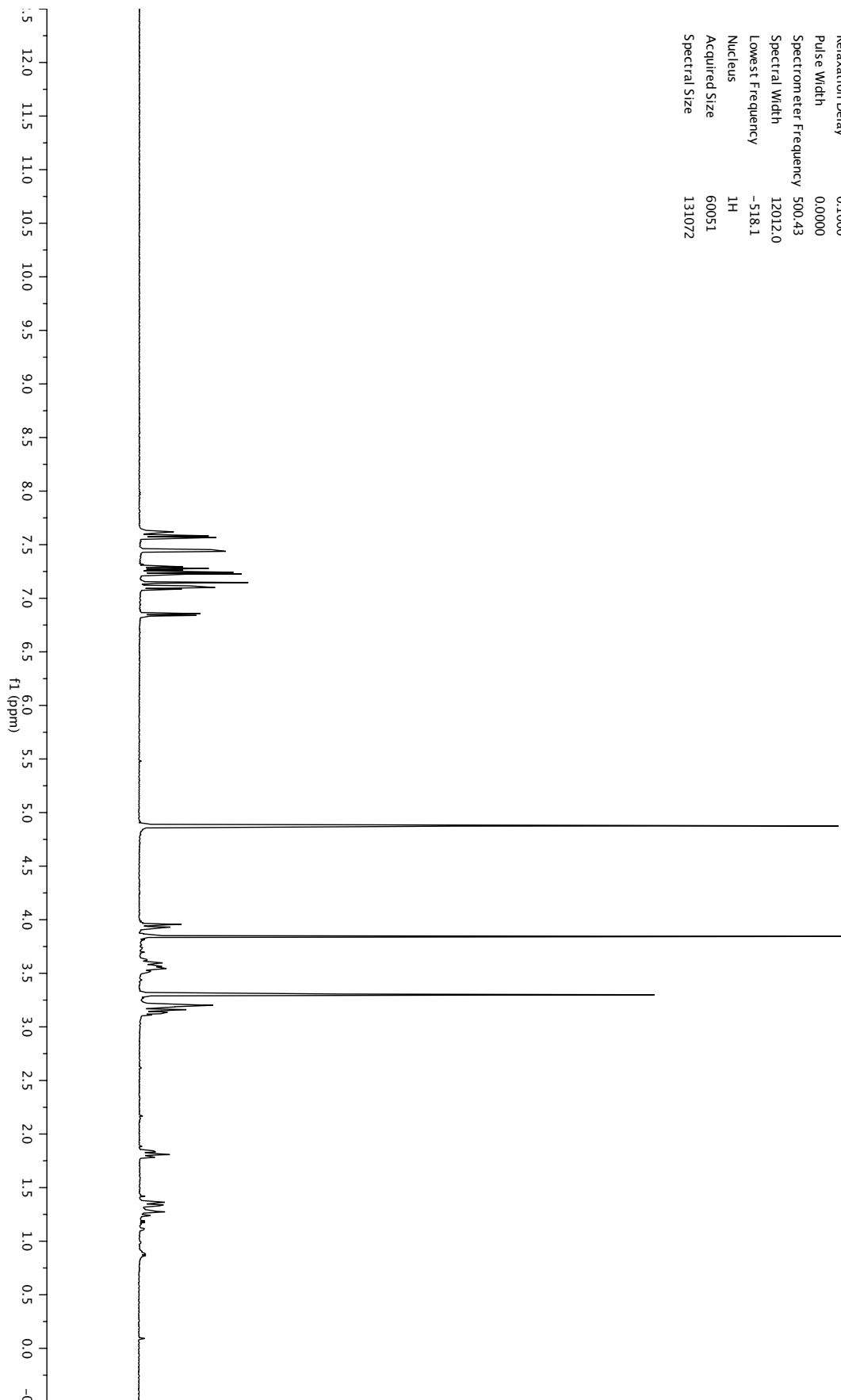
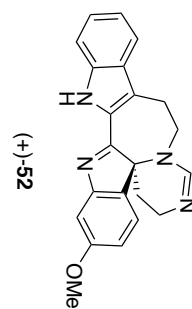
Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CD3OD
Temperature	30.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	14
Receiver Gain	34
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	-512.5
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072



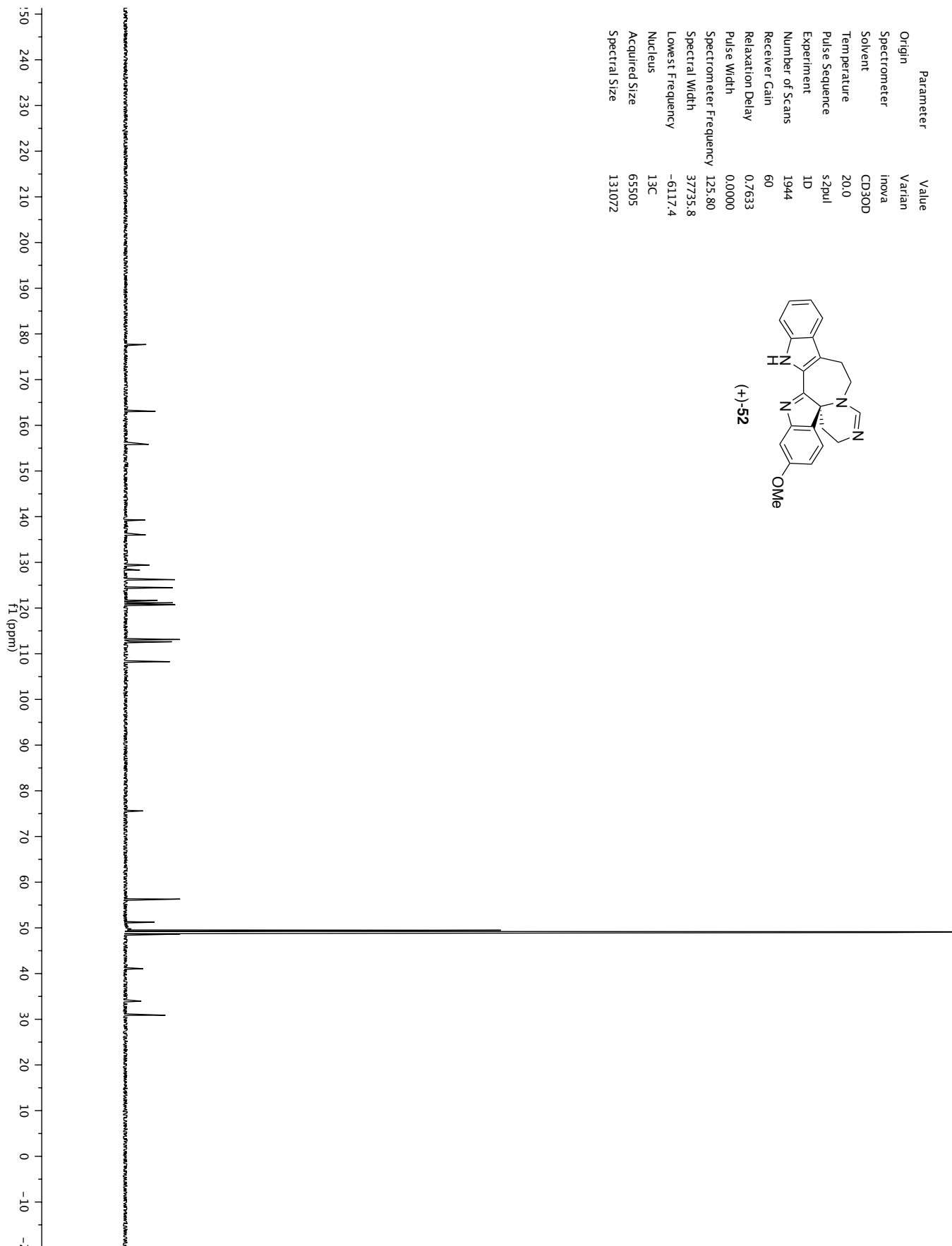
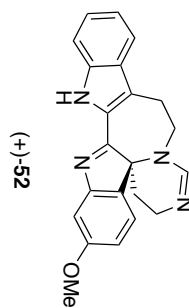
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Spectrometer	inova
Solvent	CD3OD
Temperature	20.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	3728
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
Spectrometer Frequency	125.80
Spectral Width	37735.8
Lowest Frequency	–6116.8
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072



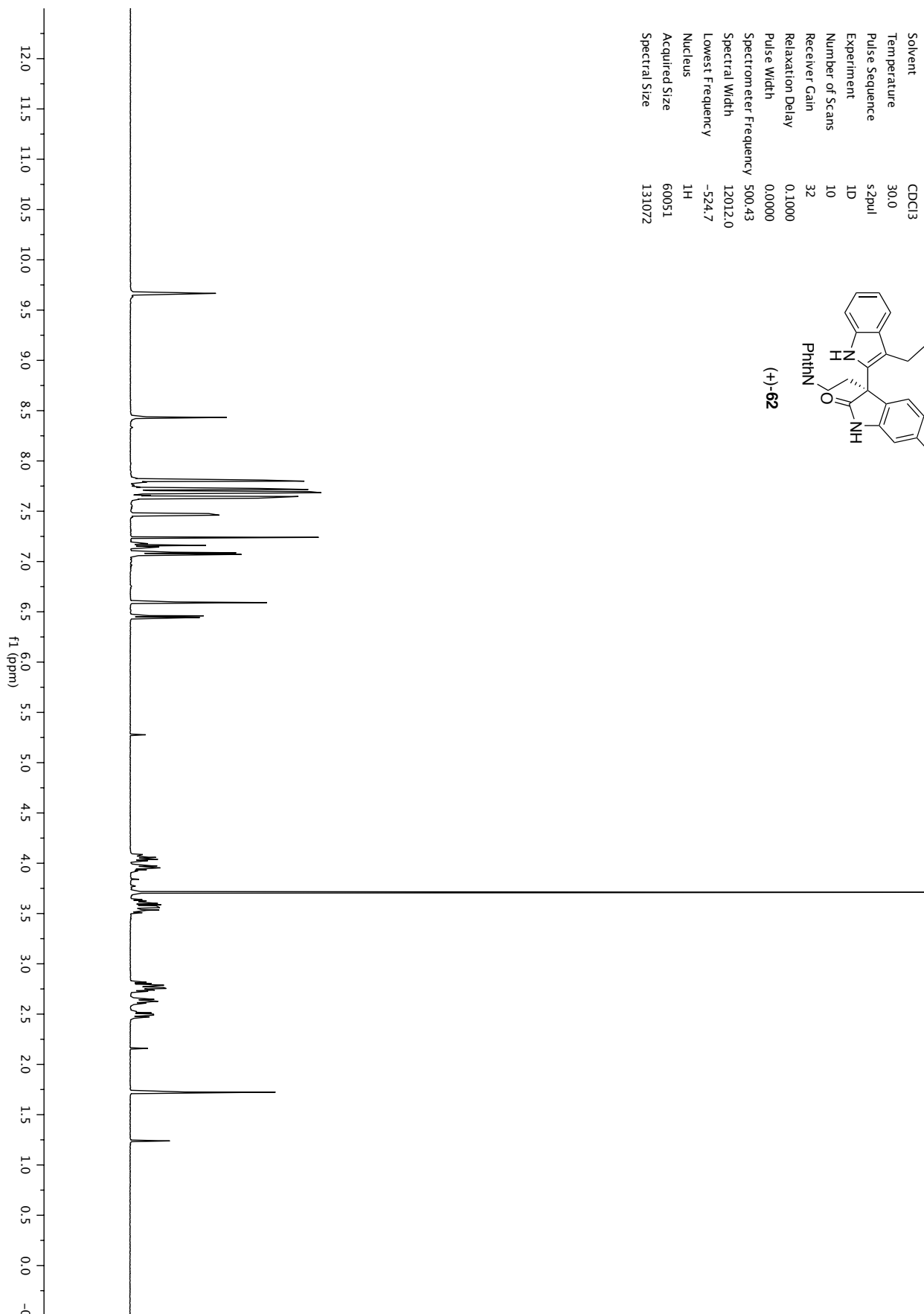
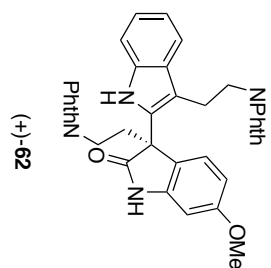
Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CD3OD
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	10
Receiver Gain	32
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	–518.1
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072



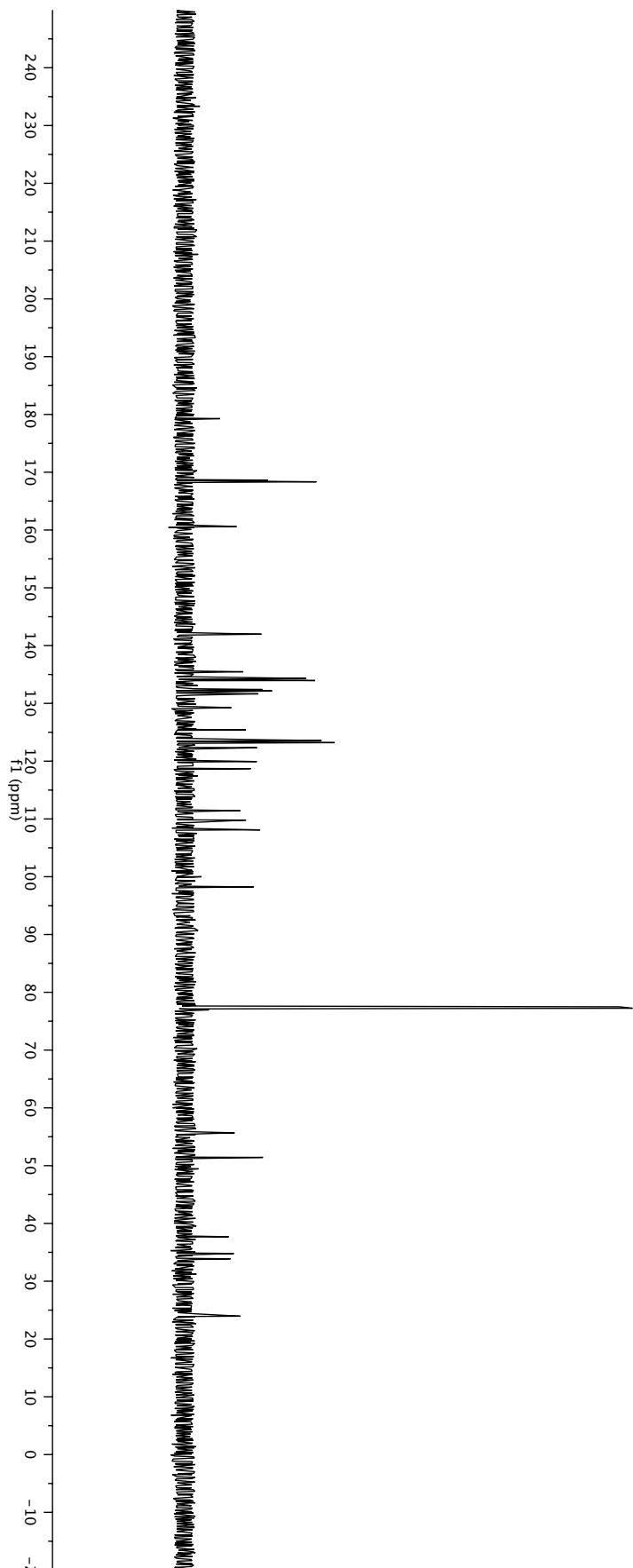
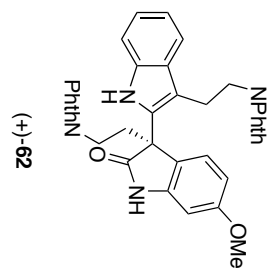
Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CD3OD
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	1944
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
Spectrometer Frequency	125.80
Spectral Width	37735.8
Lowest Frequency	-6117.4
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072

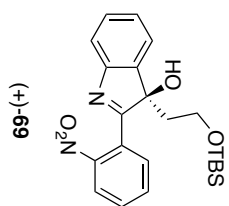


Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	30.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	10
Receiver Gain	32
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	–524.7
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072

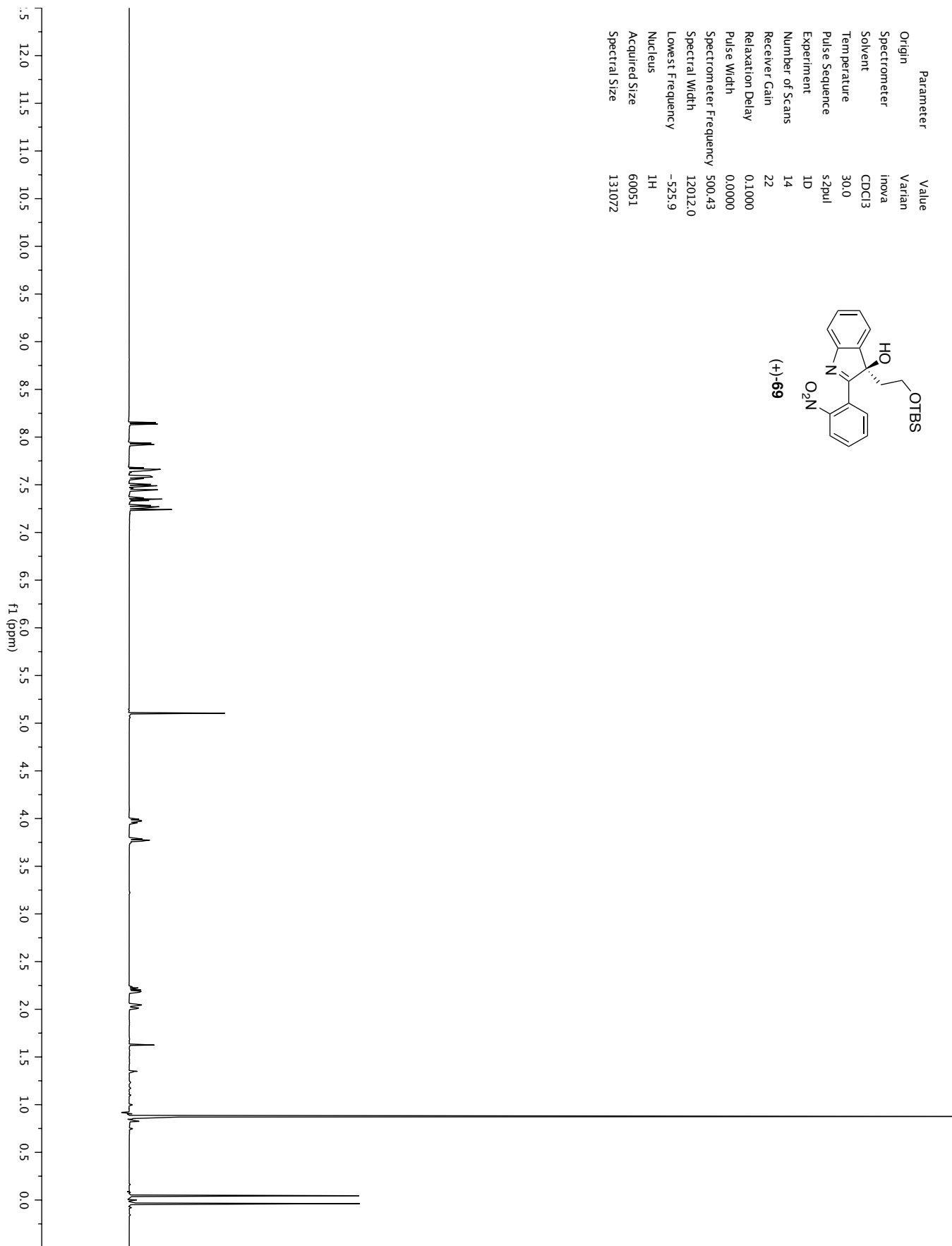


Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	186
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
Spectrometer Frequency	125.79
Spectral Width	37735.8
Lowest Frequency	–6288.0
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072

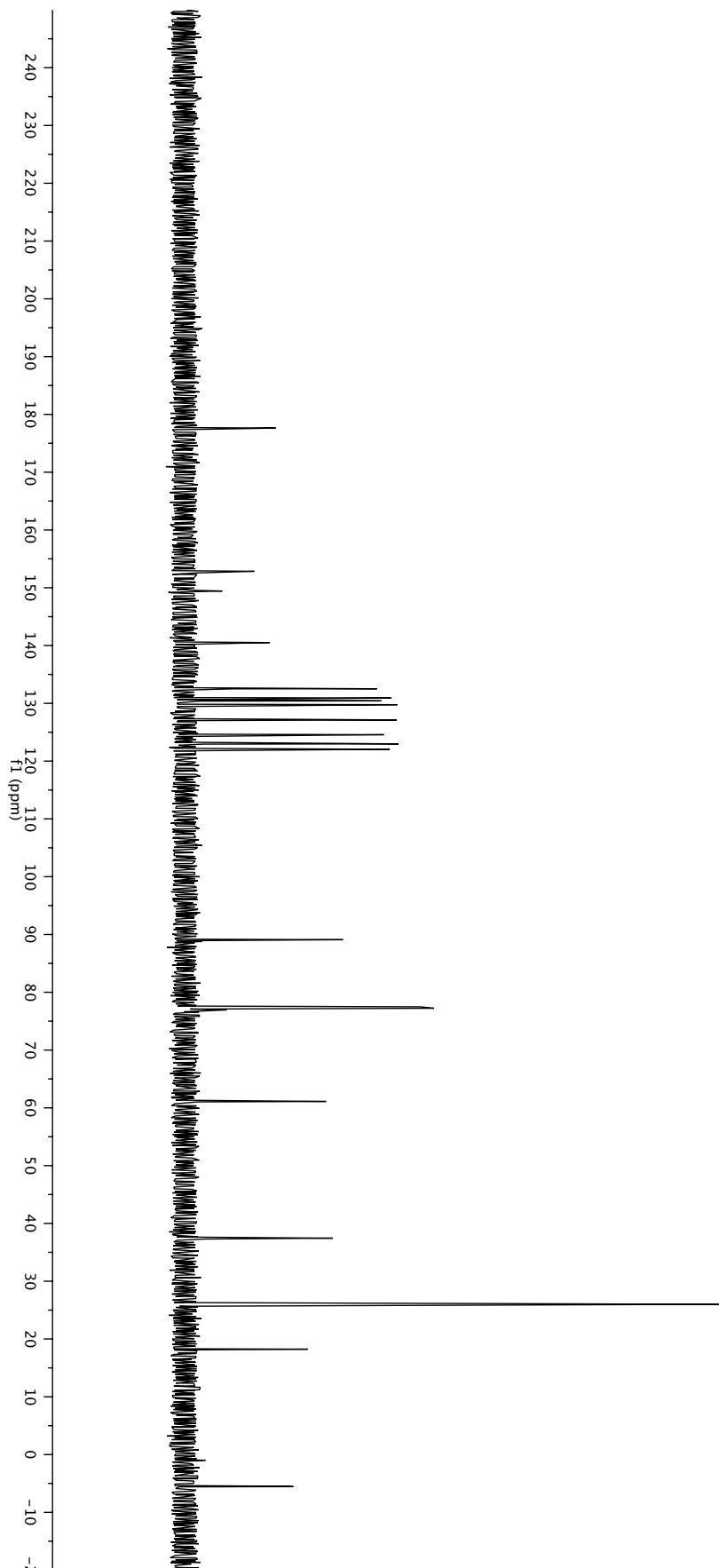
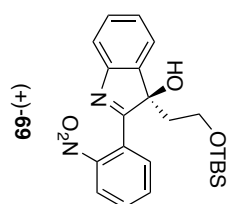




Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	30.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	14
Receiver Gain	22
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	-525.9
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072



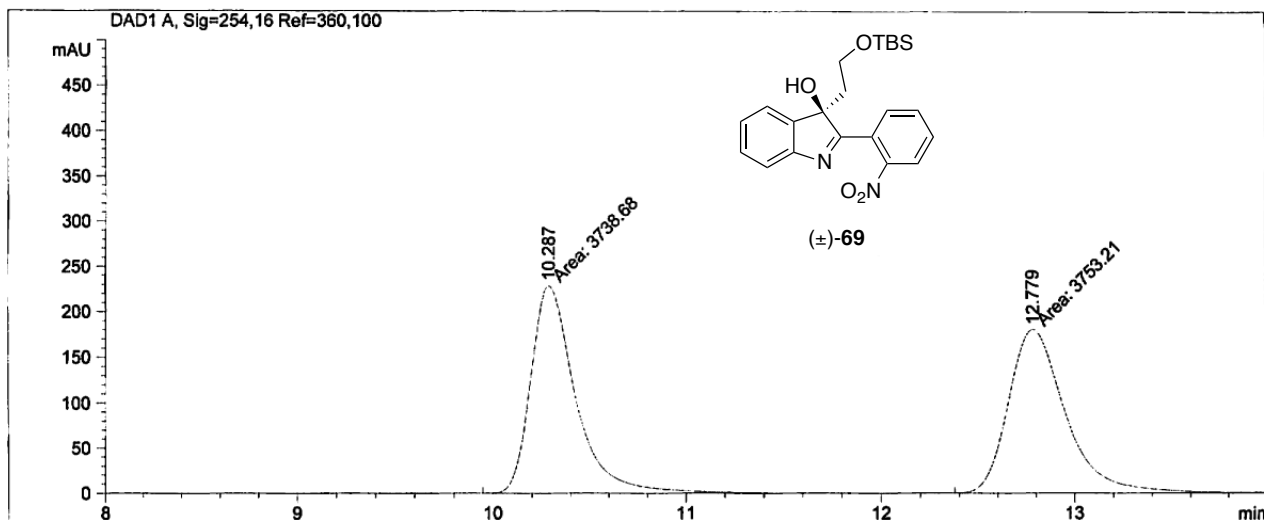
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Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	30.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	112
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
Spectrometer Frequency	125.79
Spectral Width	37735.8
Lowest Frequency	–6289.2
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072



```

Injection Date   :                               Seq. Line :    3
Sample Name     :                               Location  : Vial 91
Acq. Operator   : SH                               Inj         :    1
                                                    Inj Volume  : 0 µl
Different Inj Volume from Sequence !      Actual Inj Volume : 5 µl
Acq. Method     :
Last changed    :
Analysis Method :
Last changed    :

```



```
Sorted By      :      Signal
Multiplier    :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.287	MM	0.2718	3738.68066	229.28889	49.9031
2	12.779	MM	0.3450	3753.20703	181.29138	50.0969

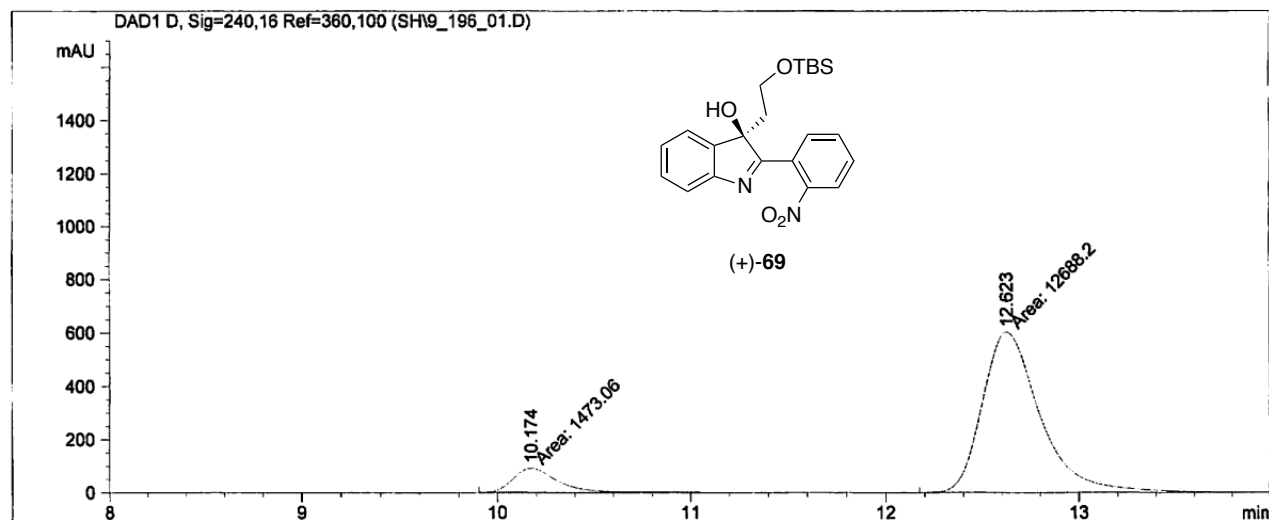
Results obtained with enhanced integrator!

Signal 1: DAD1 A, Sig=254,16 Ref=360,100

Signal 1: DAD1 A, Sig=254,16 Ref=360,100

chiralpak IC 80:20=Hx:IPA 0.5 mL/min

```
=====
Injection Date   :                               Seq. Line :    1
Sample Name     :                               Location  : Vial 91
Acq. Operator   : SH                           Inj         :    1
                                           Inj Volume  : 0 µl
Different Inj Volume from Sequence !   Actual Inj Volume : 5 µl
Acq. Method     :
Last changed    :
Analysis Method :
Last changed    :
=====
```



Area Percent Report

```
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 D, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.174	MM	0.2661	1473.06104	92.25103	10.4020
2	12.623	MM	0.3503	1.26882e4	603.61407	89.5980

Totals : 1.41613e4 695.86510

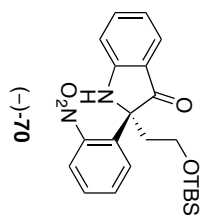
Results obtained with enhanced integrator!

Summed Peaks Report

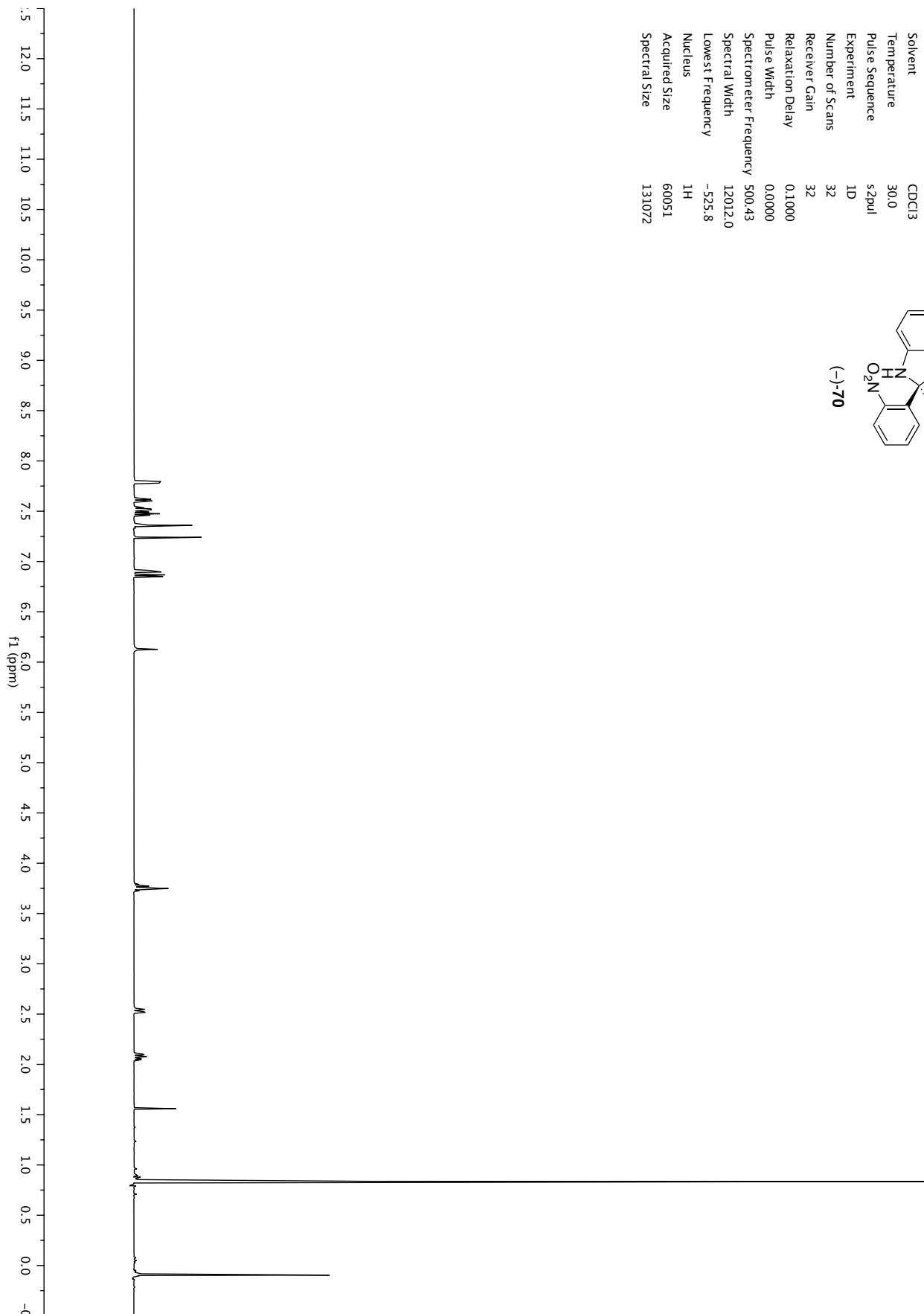
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Final Summed Peaks Report

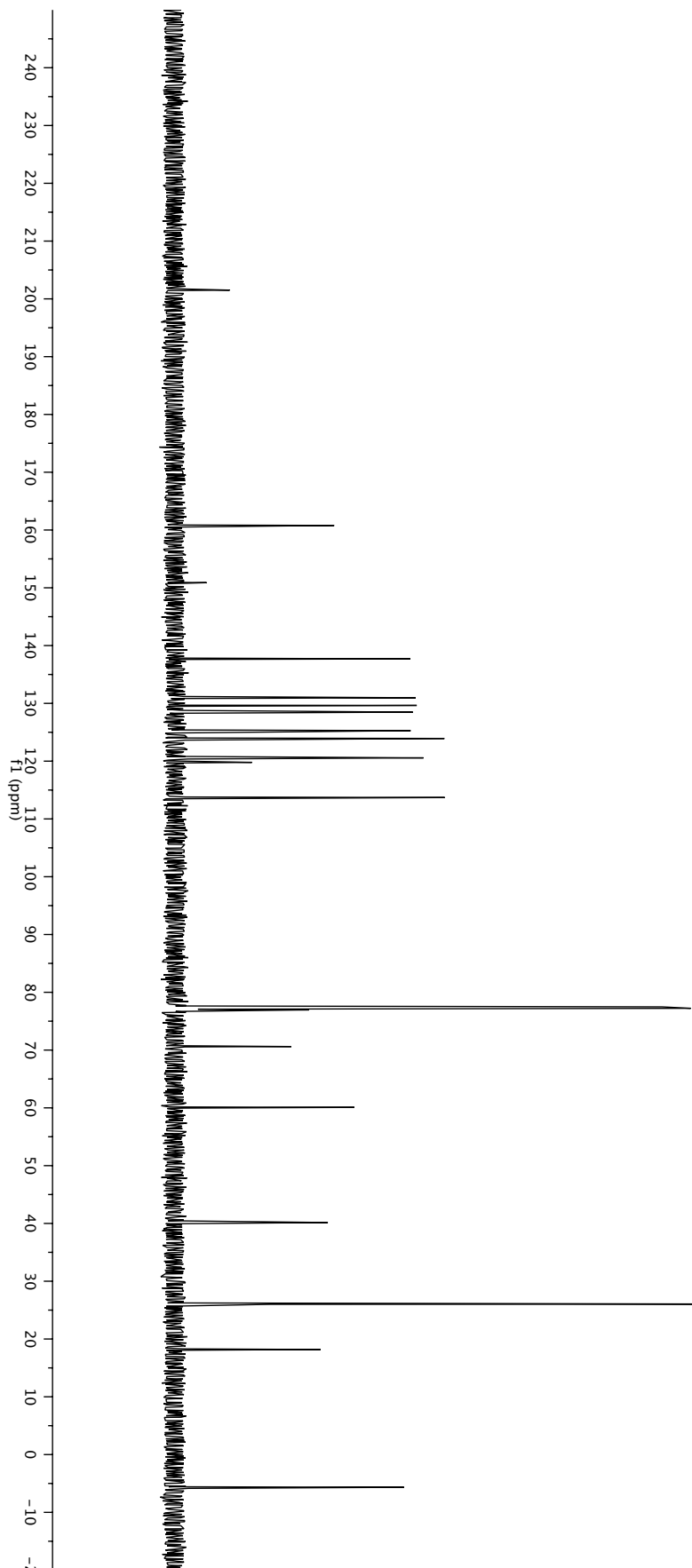
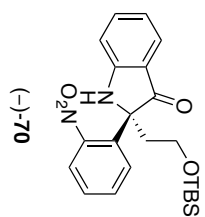
Signal 1: DAD1 D, Sig=240,16 Ref=360,100



Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	30.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	32
Receiver Gain	32
Relaxation Delay	0.1000
Pulse Width	0.0000
Spectrometer Frequency	500.43
Spectral Width	12012.0
Lowest Frequency	–525.8
Nucleus	¹ H
Acquired Size	60051
Spectral Size	131072



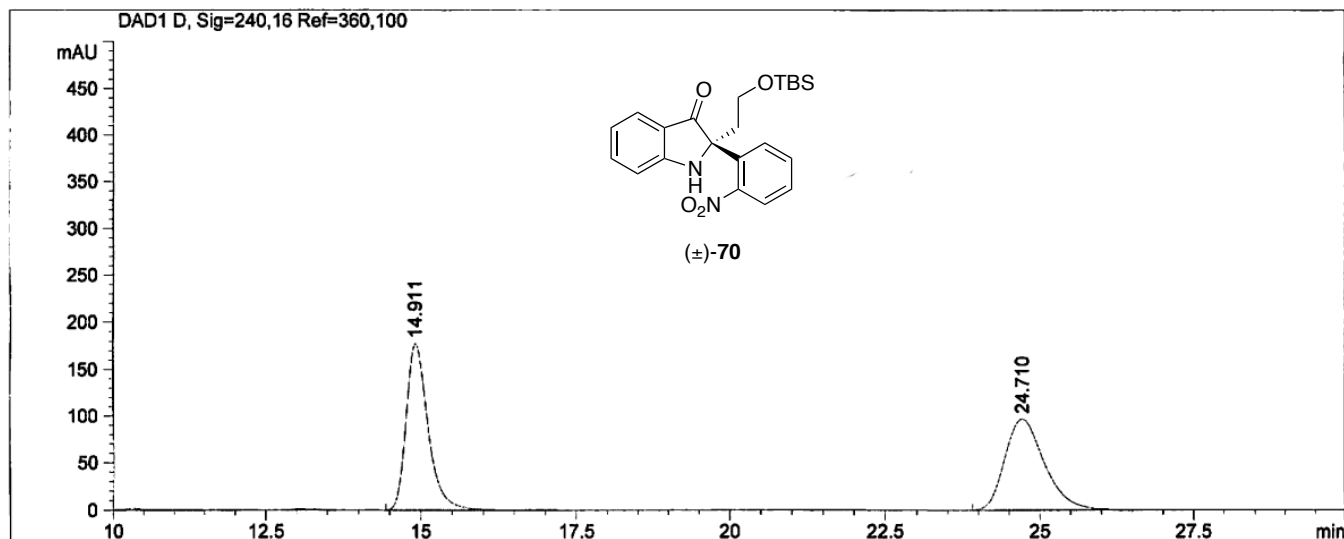
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Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	30.0
Pulse Sequence	s 2pul
Experiment	1D
Number of Scans	986
Receiver Gain	60
Relaxation Delay	0.7633
Pulse Width	0.0000
Spectrometer Frequency	125.79
Spectral Width	37735.8
Lowest Frequency	–6288.1
Nucleus	¹³ C
Acquired Size	65505
Spectral Size	131072



chiralpak IC 80:20=Hx:IPA 0.5 mL/min

```
=====
Injection Date   :                               Seq. Line :    1
Sample Name     :                               Location  : Vial 91
Acq. Operator   : SH                           Inj         :    1
                                                Inj Volume  : 0 µl
Different Inj Volume from Sequence !      Actual Inj Volume : 5 µl
Acq. Method     :
Last changed    :

Analysis Method :
Last changed    :
=====
```



Area Percent Report

```
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 D, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.911	BB	0.3701	4303.46680	177.35651	50.1508
2	24.710	BB	0.6603	4277.58594	96.65764	49.8492

Totals : 8581.05273 274.01414

Results obtained with enhanced integrator!

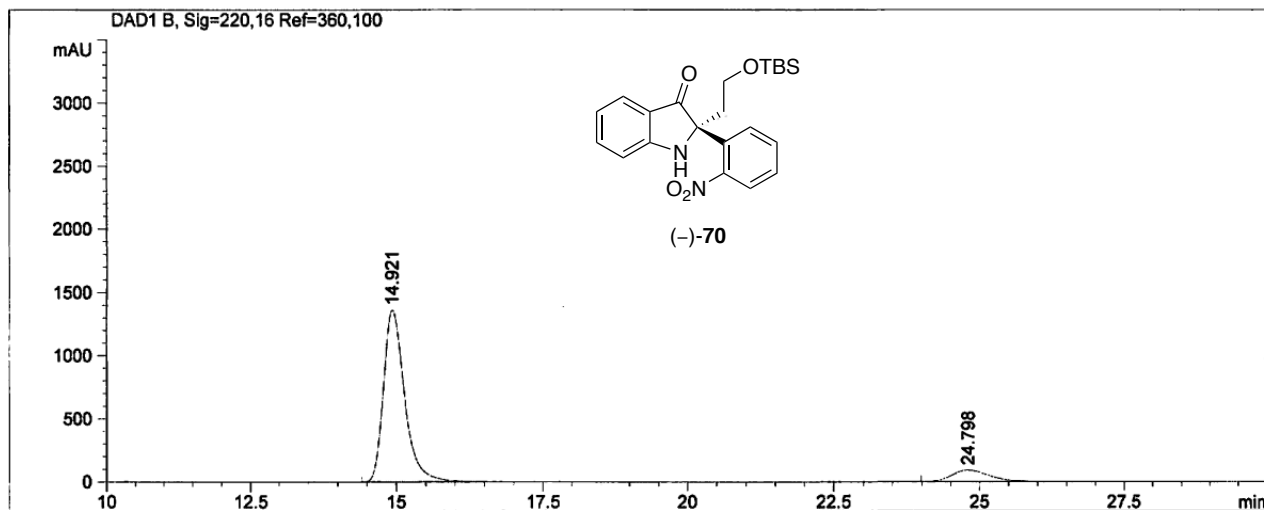
Summed Peaks Report

Signal 1: DAD1 D, Sig=240,16 Ref=360,100

chiralpak IC 83:17=Hx:IPA 0.5 mL/min

```
=====
Injection Date   :                               Seq. Line :    2
Sample Name     :                               Location  : Vial 92
Acq. Operator   : SH                           Inj          :    1
                                                Inj Volume   : 0 µl
Different Inj Volume from Sequence !      Actual Inj Volume : 5 µl
Acq. Method     :
Last changed    :

Analysis Method :
Last changed    :
=====
```



Area Percent Report

```
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 B, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.921	BB	0.3776	3.41137e4	1364.64807	89.3473
2	24.798	BB	0.6212	4067.29736	91.39735	10.6527

Totals : 3.81810e4 1456.04542

Results obtained with enhanced integrator!

Summed Peaks Report

Signal 1: DAD1 B, Sig=220,16 Ref=360,100