TOTAL SYNTHESIS OF LUPIN ALKALOIDS, DITERPENOID ALKALOIDS, AND PROGRESS TOWARDS THE MYRSINANE DITERPENES.

Thesis by

Jeff K. Kerkovius

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2023

(Defended May 31, 2023)

Jeffrey Kevan Kerkovius

ORCID: 0000-0001-5692-0285

To Miranda, Aelin, Kevan, Jenny, Mike, and Sushi

ACKNOWLEDGEMENTS

First and foremost, I want to thank my family for their unwavering support during my degree. Miranda, you are the support structure in my life. You have been there through all my ups and downs and have helped me through it all. You are the best. I love our family with Aelin and I look forward to what the future will bring! Aelin, you can't talk yet, but you are so darn cute. I know you will grow up to be an awesome human one day! Just don't forget about your old man! Mom and Dad, thank you so much for providing me with advice, money, and food over the years. The help you have provided has been instrumental in my success to date. Mike, you have been a great younger brother and whether you liked it or not. It's always fun to try out food stuff and play video games together.

To the Reisman lab, you all are an awesome bunch and I have enjoyed hanging out with all of you at various times. I may have made my passion for sushi well known, and I hoped that I can pass that onto other members of the Reisman Lab. I starting in the early days of the lab with Sean Feng where we would travel around Pasadena testing the various sushi places then rating them on a graph of price versus quality (the answer is always sushi gen). Karaoke has been a really fun pastime in the Reisman lab where it's a blast to sing your heart out to random songs, what a good time (go to Pharoah Karaoke Lounge in Korea town). I have also loved going on hiking trips into the san Gabriel mountains, which has been a blast. The wilderness has tons of exploration, discovery, and tranquility to offer and is a really nice escape from the busy life of graduate school.

I also want to thank the PI's I have had over the years. Fred Menard was instrumental in starting my research journey, teaching me how to operate as an

independent scientist. Mike Kerr helped to fine tune my abilities as a scientist, and I am super grateful for his guidance during my master's degree. Sarah Reisman has helped me to become a highly rigorous scientist, which has helped me to solve really challenging synthetic problems that I am proud of. I look forward to where my next steps will bring me and what I can learn!

ABSTRACT

The interplay between total synthesis and methodology is a driver of innovation in organic synthesis. Challenging bond formations in complex systems necessitate the development ever more robust new reactions, which intern can enable more efficient syntheses. The need for powerful synthetic organic chemistry can't be understated because of its utility in applications such as medicine, petrochemicals, plastics, and agrichemicals.

Herein, we present how total synthesis drives innovation in organic chemistry. First, a novel cyclization reaction between pyridine and glutaryl chloride is discussed, which has enabled the synthesis of seven lupin alkaloids. Next, the development of a convergent fragment coupling tactic based upon the semi-pinacol rearrangement is evaluated for its generality inspired by the total synthesis of several C19 diterpenoid alkaloids. Lastly, a convergent fragment coupling approach is applied to the total synthesis of falcatin A based upon a Mukaiyama Michael tandem Mukaiyama aldol reaction.

PUBLISHED CONTENT AND CONTRIBUTIONS

Portions of the work described herein were disclosed in the following publications:

1. Wong, A. R.; Fastuca, N. J.; Mak, V. W.; Kerkovius, J. K.; Stevenson, S. M.; Reisman, S. E. Total Synthesis of the C19 Diterpenoid Alkaloids (–)-Talatisamine, (–)-Liljestrandisine, and (–)-Liljestrandinine by a Fragment Coupling Approach. *ACS. Cent. Sci.* **2021**, *7*, 1311–1316.

DOI: 10.1021/acscentsci.1c00540

J. K. K. contributed to route optimization of the bicyclo[3.2.1]octane and scale up efforts.

2. Kerkovius, J. K.; Stegner, A.; Turlik, A.; Lam, P. H.; Houk, K. N.; Reisman, S. E. A Pyridine Dearomatization Approach to the Matrine-Type Lupin Alkaloids. *J. Am. Chem. Soc.* **2022**, *144*, 15938–15943.

DOI: 10.1021/jacs.2c06584

J. K. K. conceived the synthetic strategy, conducted experiments, and participated in preparation of the supporting data and writing of the manuscript.

3. Kerkovius, J. K.; Wong, A. R.; Mak, V. W.; Reisman, S. E. A convergent fragment coupling strategy to access quaternary stereogenic centers. *Chem. Sci.* **2023**, Accepted.

DOI: 10.1039/D2SC07023E

J. K. K. conducted experiments and participated in preparation of the supporting data and writing of the manuscript.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

[list the abbreviations used in your thesis, in alphabetical order, examples below]

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
^{i}Bu	*iso*-butyl
^{n}Bu	butyl or *norm*-butyl
^{s}Bu	*sec*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope

°C	degrees Celsius
ca.	circa
calc'd	calculated
CAM	cerium ammonium molybdate
cat.	catalyst
Cbz	benzyloxycarbonyl
cis	on the same side
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
conc.	concentrated
conv.	conversion
Cp	cyclopentadienyl
Cy	cyclohexyl
Cyp	cyclopentyl
Δ	heat or difference
δ	chemical shift in ppm
d	doublet
d	deutero or dextrorotatory
D	deuterium
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIPEA	*N*,*N*-diisopropylethylamine; Hunig's base
DIBAL	diisobutylaluminum hydride

DFT	density functional theory
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropylene urea
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile
E	trans (entgegen) olefin geometry
ee	enantiomeric excess
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
epi	epimeric
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)

^{1}H	proton
[H]	reduction
HAT	hydrogen atom transfer
hex	hexyl
HMDS	hexamethyldisilazane
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
in situ	in the reaction mixture
IPA	isopropanol
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LC/MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide

LED	light-emitting diode
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves or mass spectrometry
m/z	mass-to-charge ratio
NBS	*N*-bromosuccinimide
ND	not determined
NHC	*N*-heterocyclic carbene
NHK	Nozaki-Hiyama-Kishi
NHP	*N*-hydroxyphthalimide
nm	nanometer(s)

NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
[O]	oxidation
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Piv	pivaloyl
pK_a	acid dissociation constant
Pr	propyl
^{i}Pr	isopropyl
^{n}Pr	propyl or *norm*-propyl
py	pyridine
q	quartet
quant.	quantitative
R	alkyl group
R_L	large group
R	rectus
RCM	ring-closing metathesis
recry.	recrystallization
ref	reference
R_f	retention factor
rt	room temperature

s	singlet or seconds
S	sinister
sat.	saturated
SET	single-electron transfer
SFC	supercritical fluid chromatography
SM	starting material
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
temp	temperature
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	toluene
trans	on the opposite side
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
vide infra	see below

v/v	volume per volume
w/v	weight per volume
X	halide
xs	excess
Z	cis (zusammen) olefin geometry

Chapter 1

Total Synthesis as a Driver of Innovation†

1.1 INTRODUCTION

Total synthesis has been an important and impactful field of organic chemistry ever since its conception in the mid-1800s, where Wohler's synthesis of urea and Kolbe's synthesis of acetic led to the downfall of vitalism.[1–3] Often the targets of total synthesis are natural products, which frequently have potent biological activity. Structure activity relationship (SAR) studies of natural products can be enabled through total synthesis because it might not be possible to modify the natural product directly.[4] In addition, total synthesis can be used to help validate biosynthetic hypotheses, which often results in a concise and elegant approach towards a natural product.[5] As a core area of organic chemistry, total synthesis acts as a driver of innovation where it inspires the development of new reactions and reagents.[6] Highlighted in this chapter are examples of the innovation that total synthesis

---

J. K. K. was supported by an NSERC PGS-D fellowship (PGSD3-532535-2019).

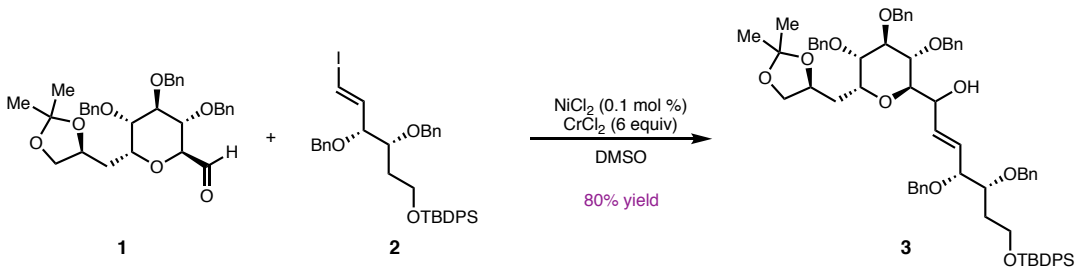
has inspired and how it relates to the work presented in this thesis.

1.2 TOTAL SYNTHESIS AND INNOVATION

1.2.1 The Nozaki-Hiyama-Kishi Reaction

Kishi encountered difficulty in the total synthesis of palytoxin when attempts to couple **1** to **2** using traditional methodologies failed.[7] Inspiration for solving the problem was derived from a paper that reported alkenyl chromium species could undergo 1,2-addition into aldehydes.[8] However, the batch of chromium (II) chloride greatly influenced the yield of the reaction, what Kishi referred to as a technical difficulty. It was eventually found that traces of other metals in the chromium (II) chloride were required for success. Through the addition of nickel or palladium salts the reproducibility issues were solved and the reaction was rendered reproducible (Scheme 1.1).[9] This reaction is now known as the Nozaki-Hiyama-Kishi (NHK) reaction and is a powerful tool regularly utilized in natural product synthesis.[10]

Scheme 1.1. *Application of NHK reaction to the synthesis of palytoxin.*

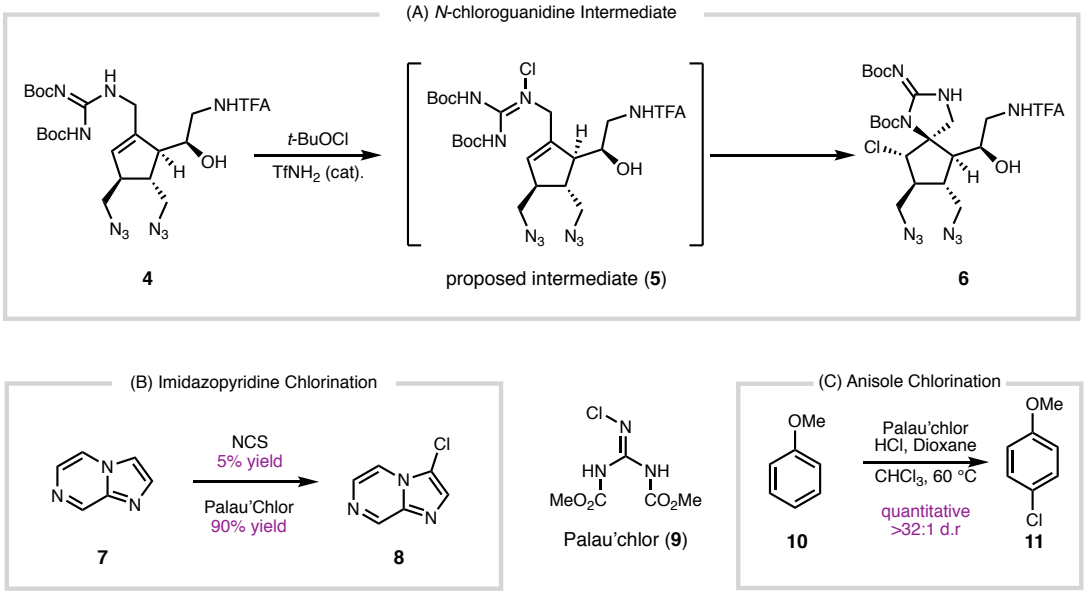


1.2.2 Palau'chlor

The development of new reagents can also be inspired by total synthesis efforts. During a mechanistic investigation of the chlorospirocyclization of **4** to **6** in the total synthesis of

axinellamines, Baran hypothesized that *N*-chloroguanidine formation could be key for the success of the reaction (Scheme 1.2A).[11] Inspired by this hypothesis, Baran synthesized *N*-chlorobis(Boc)guanidine and found that it was a highly effective chlorinating reagent in the chlorospirocyclization of a model substrate. Optimization of this novel guanidinium based chlorinating agent led to the discovery of Palau'chlor (**9**), which is a bench-stable, commercially available chlorinating agent that showed improved yields when compared to other known chlorinating agents. For example, imidazopyridine **7** underwent chlorination in 5% yield with NCS while Palau'Chlor formed **8** in 90% yield under identical conditions (Scheme 1.2B). In addition, the chlorination of arenes such as anisole (**10**) by Palau'chlor was found to be high yielding and regioselective for para-chlorination (Scheme 1.2C).[12]

Scheme 1.2. *Development of Palau'chlor during the total synthesis of the axinellamine alkaloids.*

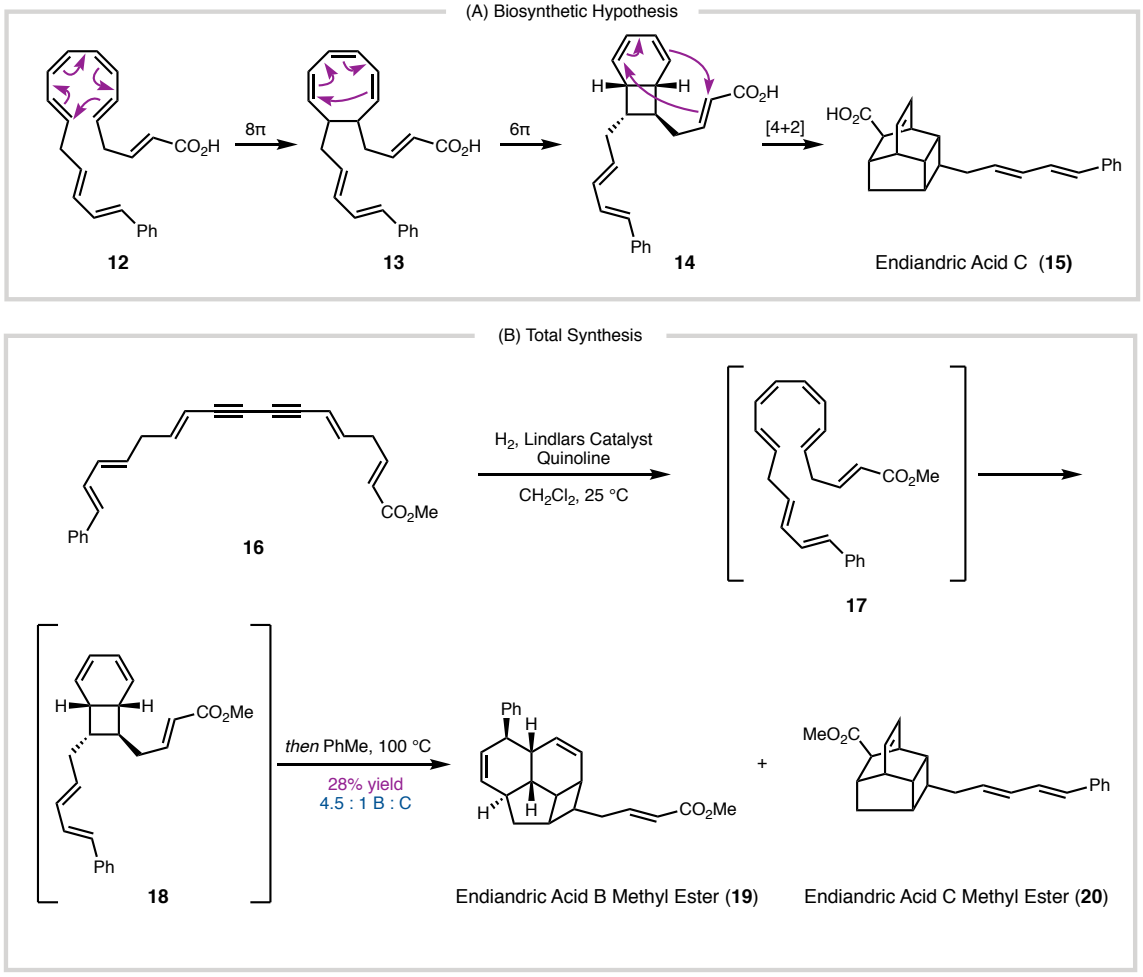


1.2.3 Biomimetic Synthesis

While total synthesis can inspire the development of novel methods and reagents,

total synthesis strategies can alternatively be inspired by biosynthetic hypotheses. Bioinspired or biomimetic total synthesis can be used to validate biosynthetic hypotheses, providing evidence that specific transformations can occur in biological systems. Bioinspired syntheses can be highly efficient due to following the innate reactivity of a natural product. A highlighted example of total synthesis being used to validate a biosynthetic hypothesis is in the synthesis of the endiandric acids by Nicolaou (Scheme 1.3B)[13]. Endiandric acid (**15**) is a potent antimicrobial compound that is formed as a racemate.[14] It was hypothesized that instead of an enzymatic cyclization, polyene **12** could first undergo an 8π conrotatory electrocyclic cyclization to yield **13**, which could undergo a 6π disrotatory electrocyclic cyclization to form **14**, followed by a [4+2] cycloaddition to reach endiandric acid C (**15**) (Scheme 1.3A)[15]. Nicolaou synthesized ene-yne **16**, and performed a partial hydrogenation using Lindlar's catalyst.[13] Presumably polyene **17** was produced from the hydrogenation, which spontaneously underwent an 8π conrotatory and 6π disrotatory cyclization cascade to yield diene **18**. While diene **18** could be isolated, direct heating of the reaction mixture promoted the [4+2] cycloaddition to yield a mixture of endiandric acid methyl esters B (**19**) and C (**20**) in a 4.5 : 1 ratio in 28% yield. The production of a natural product scaffold from a linear precursor (**16**) in a single step is an elegant approach towards these natural products and helped to validate the biosynthetic hypothesis for their formation.

Scheme 1.3. *Bio- and total synthesis of the endiandric acids.*



1.2.4 Summary

As highlighted in the previous examples, the innovation that total synthesis inspires is a central theme in organic chemistry and to the work presented in this thesis. The biosynthesis of the lupin alkaloids inspired our retrosynthetic analysis, which led to the discovery of a novel cascade cyclization reaction between pyridine and glutaryl chloride to form the entire carbocyclic scaffold of the natural products in a single step. We developed a 1,2-addition semi-pinacol rearrangement sequence to form quaternary stereocenters via a convergent fragment coupling approach motivated by our total synthesis of the C19 diterpenoid alkaloids. Progress towards the total synthesis of falcatin A has been

enabled by methodologies such as the TASF(Me) mediated Mukaiyama-Michael addition, and NHK reaction, showcasing that innovative methods and reagents can help to produce innovative syntheses.

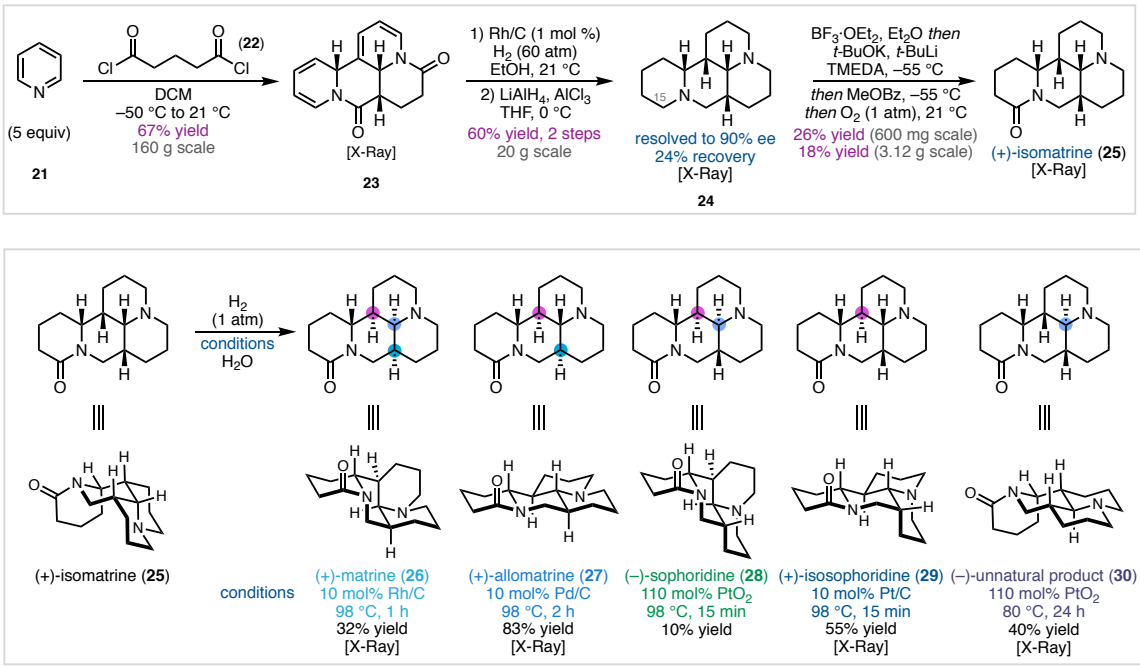
1.3 THESIS OUTLINE

1.3.1 Total Synthesis of Lupin Alkaloids

The second chapter of this thesis is focused on the total synthesis of the matrine-type lupin alkaloids (**25**–**29**) (Scheme 1.4).[16] Select members from this family of alkaloids have been shown to possess anti-cancer activity (matrine (**26**), sophoridine (**28**)),[17–19] while other members of these alkaloids (isomatrine (**25**), isosophoridine (**29**)) have not yet had their biological activity evaluated because they are not readily available from natural sources. The lack of availability of all the matrine-type lupin alkaloids motivated us to synthesize previously inaccessible members of this family of natural products.[17,18]

Our proposed synthesis was inspired by the biosynthesis of the lupin alkaloids leading us to design a cascade cyclization between glutaryl chloride (**22**) and pyridine (**21**). We found that this cyclization occurred in good yields to produce the entire carbon scaffold of isomatrine (**23**), including three of the four stereocenters present in the natural product. We were able to synthesize isomatrine (**25**) with this route, and isomerize isomatrine into an additional five alkaloids, four of which are known natural products. In summary, the biosynthesis of the matrine type-lupin alkaloids inspired us to develop novel chemistry to access this family of natural products, including isomatrine (**25**) and sophoridine (**28**), which have not yet been synthesized to date.

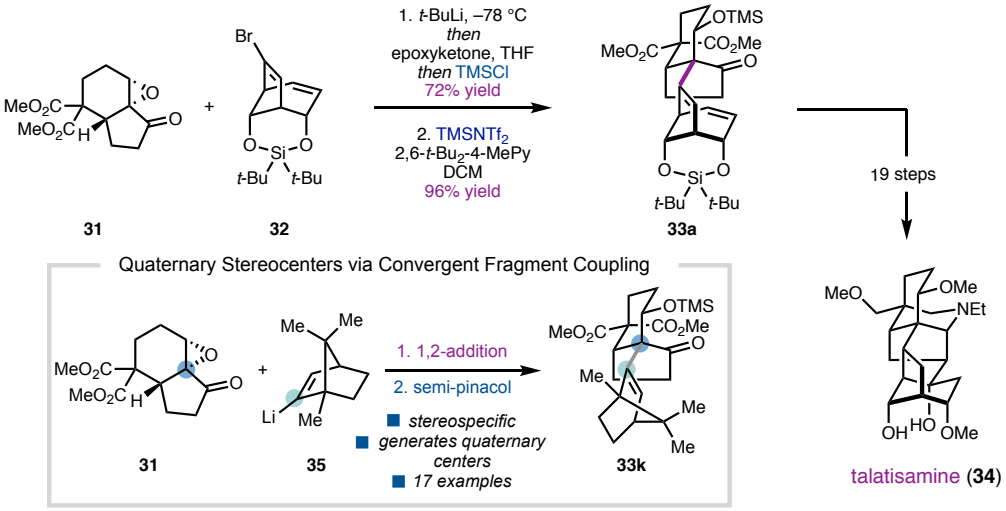
Scheme 1.4. *Total synthesis of matrine-type lupin alkaloids.*



1.3.2 Convergent Fragment Coupling via the Semi-Pinacol Rearrangement

The third chapter of this thesis focuses on the development of the semi-pinacol reaction in the context of our C19 diterpenoid alkaloid syntheses (Scheme 1.5).[20] In our key strategic disconnection, we coupled **31** and **32** by a 1,2-addition semi-pinacol rearrangement sequence to convergently form a quaternary stereocenter (**33**) in high yield. Our total synthesis inspired us to investigate the generality of this transformation towards forming quaternary stereocenters in polycyclic systems.[21] We found that the reaction could tolerate a variety of functional groups including enol ethers, allylic silyl ethers, alkenyl and aryl bromides, esters, and aryl triflates. The yields for the semi-pinacol rearrangement were uniformly high and this strategy is currently being leveraged for the total synthesis of additional diterpenoid alkaloids in our lab.

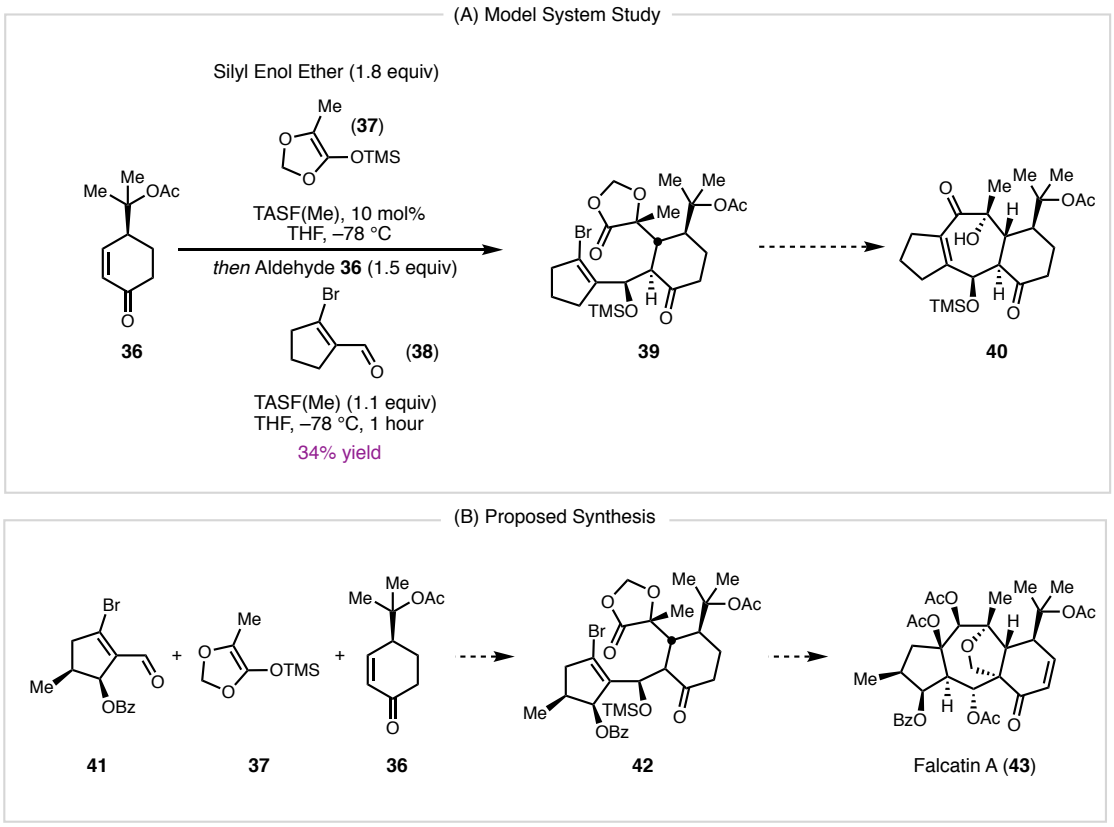
Scheme 1.5. *Convergent fragment coupling approach to quaternary stereocenters.*



1.3.3 Progress Towards the Total Synthesis of Falcatin A.

The fourth chapter of this thesis focuses on work towards the total synthesis of falcatin A (**43**), a highly oxygenated myrsinane diterpene (Scheme 1.6B).[22] The central seven-membered ring was a key strategic challenge and major focus for our proposed synthesis. We found that a three-component coupling between enone **37**, silyl enol ether **38**, and aldehyde **39** could rapidly incorporate all the required carbons for the natural product. These precursor building blocks are all readily accessible in two steps or less from commercial materials allowing us to rapidly generate molecular complexity. Focus has now shifted towards the formation of the central seven membered ring through an NHK reaction or lithiation 1,2-addition. Enabling methodologies such as the NHK reaction and Mukaiyama aldol addition are helping to create an efficient synthesis of falcatin A, which showcases the importance that new methodologies hold in synthesis.

Figure 1.6. *Progress towards the total synthesis of falcatin A.*



1.4 CONCLUDING REMARKS

The desire to synthesize complex molecules ever more efficiently has driven innovation in organic chemistry. The NHK reaction was borne out of a need to perform a 1,2-addition into a complex aldehyde in the synthesis of palytoxin when standard reactions failed.[7] Since the NHK reaction was first showcased as a high yielding and selective reaction in complex molecules, it has found use in total synthesis, especially in the synthesis of medium-sized rings.[23] A mechanistic investigation of a key step in the total synthesis of axinellamines led to the discovery of Palau'Chlor, which is a first in class guanidinium-based chlorinating reagent.[12] Palau'Chlor has been shown to chlorinate arenes selectively in high yields, and has been used in the total synthesis of natural products.[24] Innovative syntheses have also been driven by biosynthetic hypotheses. The total synthesis of

endiandric acids represent a landmark accomplishment where an entire natural product could be synthesized concisely from an acyclic precursor.[13] The unique 8π, 6π, [4+2] cyclization cascade helped to validate the biosynthetic hypothesis as well as provide strong support for the Woodward-Hoffman rules.

The theme of total synthesis driving innovation in organic chemistry underlies the topics presented in this thesis. The need for a concise route to the lupin alkaloids led to the development of a novel cyclization cascade between pyridine and glutaryl chloride to efficiently construct the carbon scaffold of these natural products in a single step. The cyclization product was then concisely transformed into five alkaloids in five steps or less. The total synthesis of the C19 diterpenoid alkaloids motivated the development of a convergent fragment coupling methodology to form quaternary centers. It was found that this strategy could form a variety of hindered quaternary stereocenters selectively in complex substrates while tolerating a variety of different functional groups. The development of more efficient synthetic methods has proven useful on route towards the total synthesis of falcatin A. The NHK reaction and Mukaiyama-Michael addition are examples of where practical robust methods help to create more efficient syntheses. In summary, total synthesis is a driver of innovation and a critical aspect of modern organic chemistry where it inspires reaction development, reagent invention, and can prove as a testing ground for biosynthetic hypotheses.

1.5 NOTES AND REFERENCES

(1) *Newton's Apple and Other Myths about Science*; Harvard University Press, 2015.
(2) Ramberg, P. J. The Death of Vitalism and The Birth of Organic Chemistry: Wohler's Urea Synthesis and the Disciplinary Identity of Organic Chemistry. *Ambix* **2000**, *47*, 170–195.

(3) Wöhler, F. Ueber Künstliche Bildung Des Harnstoffs. *Ann. Phys. Chem.* **1828**, *88*, 253–256.
(4) Truax, N. J.; Romo, D. Bridging the Gap between Natural Product Synthesis and Drug Discovery. *Nat. Prod. Rep.* **2020**, *37*, 1436–1453.
(5) Bulger, P. G.; Bagal, S. K.; Marquez, R. Recent Advances in Biomimetic Natural Product Synthesis. *Nat. Prod. Rep.* **2008**, *25*, 254–297.
(6) Armaly, A. M.; DePorre, Y. C.; Groso, E. J.; Riehl, P. S.; Schindler, C. S. Discovery of Novel Synthetic Methodologies and Reagents during Natural Product Synthesis in the Post-Palytoxin Era. *Chem. Rev.* **2015**, *115*, 9232–9276.
(7) Kishi, Y. Natural Products Synthesis: Palytoxin. *Pure Appl. Chem.* **1989**, *61*, 313–324.
(8) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. Selective Grignard-Type Carbonyl Addition of Alkenyl Halides Mediated by Chromium(II) Chloride. *Tetrahedron Lett.* **1983**, *24*, 5281–5284.
(9) Jin, Haolun.; Uenishi, Junichi.; Christ, W. J.; Kishi, Yoshito. Catalytic Effect of Nickel(II) Chloride and Palladium(II) Acetate on Chromium(II)-Mediated Coupling Reaction of Iodo Olefins with Aldehydes. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646.
(10) Hargaden, G. C.; Guiry, P. J. The Development of the Asymmetric Nozaki–Hiyama–Kishi Reaction. *Adv. Synth. Catal.* **2007**, *349*, 2407–2424.
(11) Su, S.; Rodriguez, R. A.; Baran, P. S. Scalable, Stereocontrolled Total Syntheses of (±)-Axinellamines A and B. *J. Am. Chem. Soc.* **2011**, *133*, 13922–13925.
(12) Rodriguez, R. A.; Pan, C.-M.; Yabe, Y.; Kawamata, Y.; Eastgate, M. D.; Baran, P. S. Palau'chlor: A Practical and Reactive Chlorinating Reagent. *J. Am. Chem. Soc.* **2014**, *136*, 6908–6911.
(13) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. The Endiandric Acid Cascade. Electrocyclizations in Organic Synthesis. 4. Biomimetic Approach to Endiandric Acids A-G. Total Synthesis and Thermal Studies. *J. Am. Chem. Soc.* **1982**, *104*, 5560–5562.
(14) Lenta, B. N.; Chouna, J. R.; Nkeng-Efouet, P. A.; Sewald, N. Endiandric Acid Derivatives and Other Constituents of Plants from the Genera Beilschmiedia and Endiandra (Lauraceae). *Biomolecules* **2015**, *5*, 910–942.
(15) Bandaranayake, W. M.; Banfield, J. E.; Black, D. S. C. Postulated Electrocyclic Reactions Leading to Endiandric Acid and Related Natural Products. *J. Chem. Soc. Chem. Commun.* **1980**, No. 19, 902–903.
(16) Kerkovius, J. K.; Stegner, A.; Turlik, A.; Lam, P. H.; Houk, K. N.; Reisman, S. E. A Pyridine Dearomatization Approach to the Matrine-Type Lupin Alkaloids. *J. Am. Chem. Soc.* **2022**, *144*, 15938–15943.
(17) Zhang, H.; Chen, L.; Sun, X.; Yang, Q.; Wan, L.; Guo, C. Matrine: A Promising Natural Product With Various Pharmacological Activities. *Front. Pharmacol.* **2020**, *11*.
(18) You, L.; Yang, C.; Du, Y.; Wang, W.; Sun, M.; Liu, J.; Ma, B.; Pang, L.; Zeng, Y.; Zhang, Z.; Dong, X.; Yin, X.; Ni, J. A Systematic Review of the Pharmacology, Toxicology and Pharmacokinetics of Matrine. *Front. Pharmacol.* **2020**, *11*.
(19) Wang, Q.; Li, Y.; Li, K.-W.; Zhou, C.-Z. Sophoridine: A Review of Its Pharmacology, Pharmacokinetics and Toxicity. *Phytomedicine* **2022**, *95*, 153756.

(20) Wong, A. R.; Fastuca, N. J.; Mak, V. W.; Kerkovius, J. K.; Stevenson, S. M.; Reisman, S. E. Total Syntheses of the C19 Diterpenoid Alkaloids (−)-Talatisamine, (−)-Liljestrandisine, and (−)-Liljestrandinine by a Fragment Coupling Approach. *ACS Cent. Sci.* **2021**, *7*, 1311–1316.
(21) Kerkovius, J.; Wong, A.; Mak, V.; Reisman, S. E. A Convergent Fragment Coupling Strategy to Access Quaternary Stereogenic Centers. *Chem. Sci.* **2023**.
(22) Vasas, A.; Forgo, P.; Orvos, P.; Tálosi, L.; Csorba, A.; Pinke, G.; Hohmann, J. Myrsinane, Premyrsinane, and Cyclomyrsinane Diterpenes from Euphorbia Falcata as Potassium Ion Channel Inhibitors with Selective G Protein-Activated Inwardly Rectifying Ion Channel (GIRK) Blocking Effects. *J. Nat. Prod.* **2016**, *79*, 1990–2004.
(23) MacMillan, D. W. C.; Overman, L. E. Enantioselective Total Synthesis of (-)-7-Deacetoxyalcyonin Acetate. First Synthesis of a Eunicellin Diterpene. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392.
(24) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. Total Synthesis of Gukulenin B via Sequential Tropolone Functionalizations. *J. Am. Chem. Soc.* **2022**, *144*, 5190–5196.

Chapter 2

A Pyridine Dearomatization Approach to the Matrine-type Lupin Alkaloids[1]

2.1 INTRODUCTION

(+)-Matrine and (+)-isomatrine are tetracyclic alkaloids isolated from the plant *Sophora flavescens*, the roots of which are used in traditional Chinese medicine. Biosynthetically, these alkaloids are proposed to derive from three molecules of (–)-lysine via the intermediacy of the unstable cyclic imine Δ^1-piperidine. Inspired by the

---

Portions of this chapter have been reproduced from a published manuscript.[1] J. K. K was supported by an NSERC PGS-D fellowship (PGSD3-532535-2019). A. R. W and V. W. M were supported by an NSF Graduate Research Fellowship (DGE-1144469). S. E. R. acknowledges financial support from the NIH (R35GM118191).

biosynthesis, a new dearomative annulation reaction has been developed that leverages pyridine as a stable surrogate for Δ^1-piperidine. In this key transformation, two molecules of pyridine are joined with a molecule of glutaryl chloride to give the complete tetracyclic framework of the matrine alkaloids in a single step. Using this dearomative annulation, isomatrine is synthesized in four steps from inexpensive commercially available chemicals. Isomatrine then serves as the precursor to additional lupin alkaloids, including matrine, allomatrine, isosophoridine, and sophoridine.

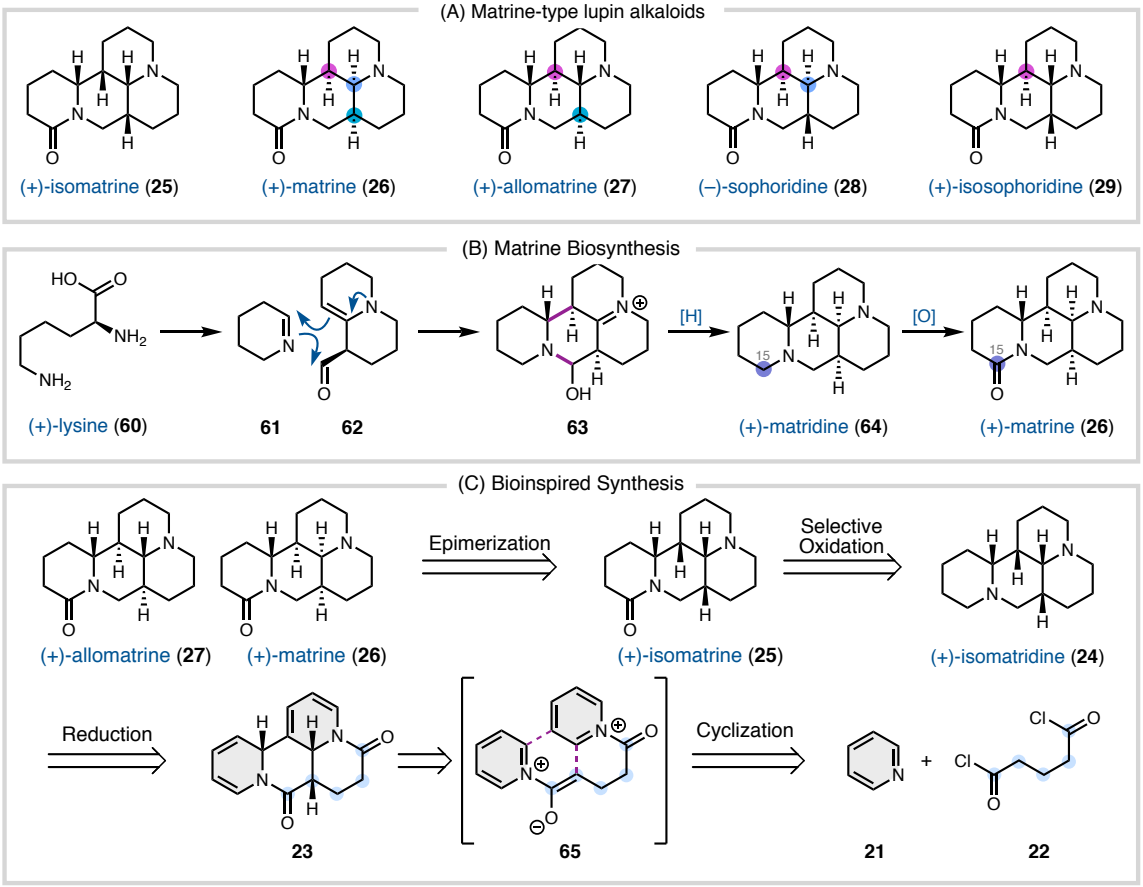
2.2 MATRINE TYPE LUPIN ALKALOIDS

2.2.1 Biosynthesis and Bioinspired Synthesis

The lupin alkaloids are a structurally diverse class of quinolizidine-containing natural products isolated from plants in the Lupinus genus (Figure 2.1A).[2] (+)-Matrine (**26**), the primary component of Chinese *Kushen* injection, inhibits proliferation in metastatic cancer cell lines and has also been investigated as a therapeutic agent against encephalomyelitis, asthma, arthritis, and osteoporosis.[3,4] (–)-Sophoridine (**28**) is an approved chemotherapeutic in China, which has also demonstrated antibiotic activity.[5] Little is known about the pharmacological properties of (+)-isomatrine (**25**) and (+)-isosophoridine (**29**), which likely reflects their limited accessibility from commercial vendors.[5] Although the detailed enzymatic pathway has not been fully annotated, the biosynthesis of matrine is proposed to initiate with the enzymatic conversion of (–)-lysine (**60**) to Δ^1-piperidine (**61**) (Figure 2.1B).[6,7] Subsequent dimerization of **61** followed by oxidation and isomerization is proposed to yield quinolizidine **62**, a shared biosynthetic precursor to several lupin alkaloids.[8,9] Mannich addition of **62** to a third equivalent of **61**

and cyclization with the pendant aldehyde is proposed to generate the oxidized tetracycle **63**, which upon reduction gives (+)-matridine (**64**). Seminal studies by Abdusalamov demonstrated that feeding ^{14}C-labeled (+)-**64** to *Goebelia Pachycarpa* resulted in the isolation of radio-labelled (+)-**26**, suggesting that the final step in the biosynthesis of **26** is a site-selective C–H oxidation.[10,11]

Figure 2.1. *(A) Chemical structures of matrine-type lupin alkaloids. (B) Proposed biosynthesis of matrine (C) Retrosynthetic analysis of isomatrine.*



We sought to devise a unified synthesis that could provide access to the series of matrine-type alkaloids shown in Figure 2.1A. Inspired by the proposed biosynthesis, it was envisioned that pyridine (**21**) could serve as a stable, inexpensive synthon for Δ^1-piperidine

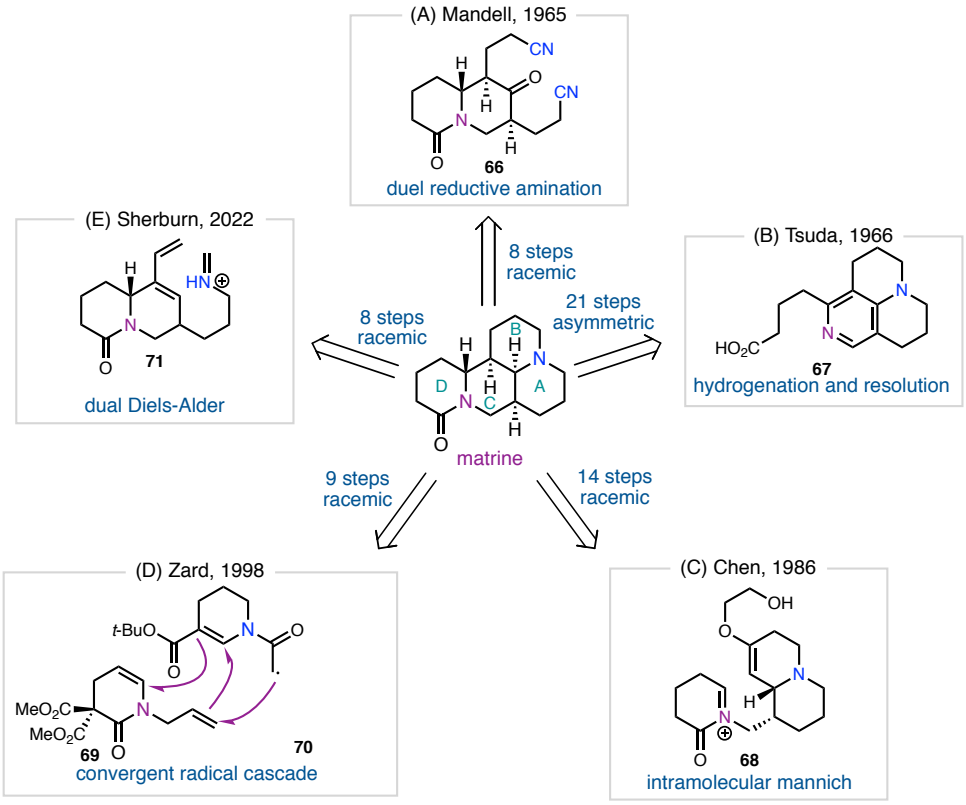
(**61**), and the remaining five carbons of the tetracyclic matrine framework could derive from glutaryl chloride (**22**, Figure 2.1C). In the key step, we proposed a dearomative annulation via bis-acyl pyridinium salt **65** to form tetracycle **23**, a molecule that contains all the carbon and nitrogen atoms of **25**.[12] Tetracycle **23** could be elaborated to **25** by global reduction followed by a site-selective oxidation of isomatridine (**24**) reminiscent of the proposed biosynthesis of matrine (**26**). Isomatrine (**25**) is the least thermodynamically stable lupin alkaloid and its isomerization to both **26** and **27** has been previously reported.[13] We therefore anticipated that access to **25** could enable the synthesis of additional lupin alkaloids.[14] This type of late-stage isomerization strategy was also deployed in the 2022 Sherburn synthesis of several matrine alkaloids.[15]

2.2.2 Previous Syntheses

Synthetically, most of the work prior to 2022 had focused on matrine (**26**), with four reported total syntheses (Figure 2.2). The first total synthesis of matinre was accomplished by Mandell in 1963 utilizing a key dual reductive amination approach of **66** to access both the A and B rings of matrine stereoselectively in a single step.[16,17] Subsequently, Tsuda published a lengthy route to the matrine alkaloids dependant upon hydrogenation of pyridine **67** and classical resolution.[18] In 1986 Chen demonstrated that a biomimetic intramolecular Mannich approach of **68** to forge the C ring of matrine was a viable strategy.[19] Zard designed an intriguing radical cascade cyclization between enamide **69** and xanthate **70** to forge both the A and C rings of matrine simultaneously.[20] While these syntheses all targeted matrine, synthetic access to the minor congeners is far more limited with only two syntheses of allomatrine appearing, until a recent report by Sherburn and coworkers, which outlined a diene-transmissive Diels-Alder based approach to the

lupin alkaloids.[15,17–20] In addition, there was a single total synthesis each of allomatrine (**27**) and isosophoridine (**29**), and no reported total syntheses of isomatrine (**25**) or sophoridine (**28**).[21,22]

Figure 2.2. *Previous total syntheses of the matrine-type lupin alkaloids.*



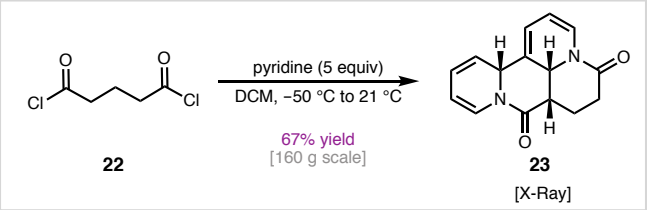
2.3 KEY CYCLIZATION STEP

2.3.1 Initial Reaction Hit

Our studies commenced with the investigation of the dearomative annulation (Scheme 2.1). Addition of glutaryl chloride (**22**) to pyridine (**21**) in dichloromethane at –50 °C followed by warming to 20 °C resulted in clean formation of (±)-tetracycle **23** in

62% yield (10 g scale). The reaction was highly robust and could be carried out on one mole scale to produce over 160 grams (67% yield) of (±)-tetracycle **23** in a single batch.

Scheme 2.1. *Cyclization of pyridine and glutaryl chloride.*



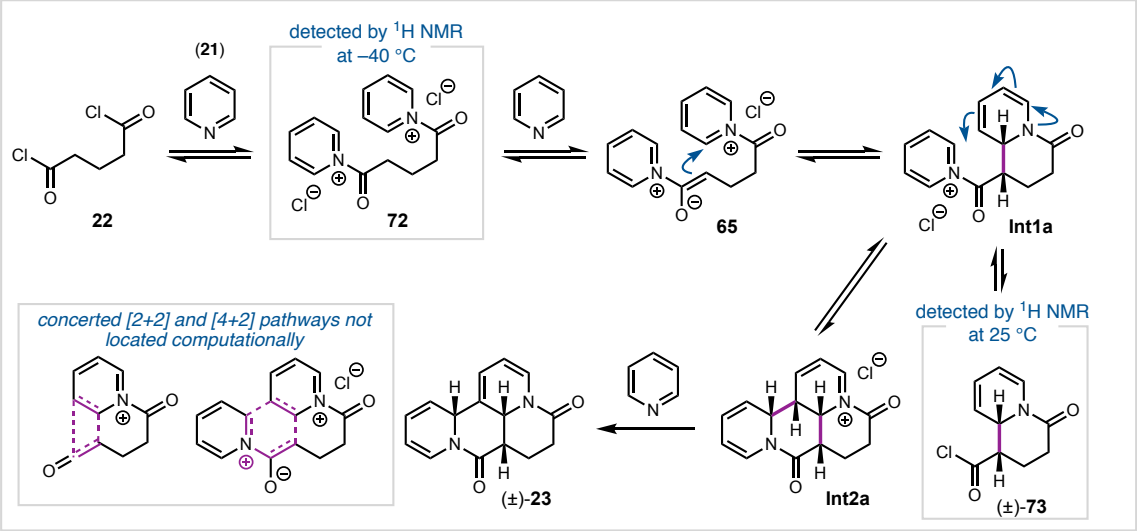
The product was isolated by precipitation from the crude reaction mixture, alleviating the need for a workup or column chromatography. Given the cost of pyridine ($7/mol, Millipore-Sigma, 2022), glutaryl chloride ($211/mol, Oakwood Chemical, 2022), and all solvents ($31/mol, Fischer Scientific, 2022), the raw materials cost $398/mol of product formed. Recrystallization of (±)-**23** enabled single crystal X-ray diffraction, which confirmed the *syn-syn* relative stereochemistry.

2.3.2 Mechanistic Investigation of the Cyclization Cascade

To elucidate the reaction pathway, mechanistic and computational studies were undertaken. Monitoring the reaction between **21** and **22** by ^{1}H NMR determined that the initially formed species at –40 °C was bis-acyl pyridinium salt **72** (Scheme 2.2). After warming to 25 °C, acid chloride **73** resulting from mono-cyclization was observed. Presumably the acyl pyridinium salt **Int1a** and acyl chloride **73** are in equilibrium, but the acyl chloride is the major species at 25 °C. A second, minor species assigned as the acid chloride resulting from **Int1b** (vide infra, same as **Int1a** with trans stereochemistry) was also observed; this species was consumed as the reaction progressed to full conversion.

Although deprotonation and elimination of acyl pyridinium salts or acyl chlorides can give rise to ketene intermediates,[23] no such species was detected by ^{1}H NMR or by reactIR. Attempts to calculate a pathway involving ketene intermediates failed to locate a transition state (TS) for a concerted [2+2] cycloaddition. Similarly, no TS for the concerted [4+2] cycloaddition of bis-acyl pyridinium salt **65** could be located.

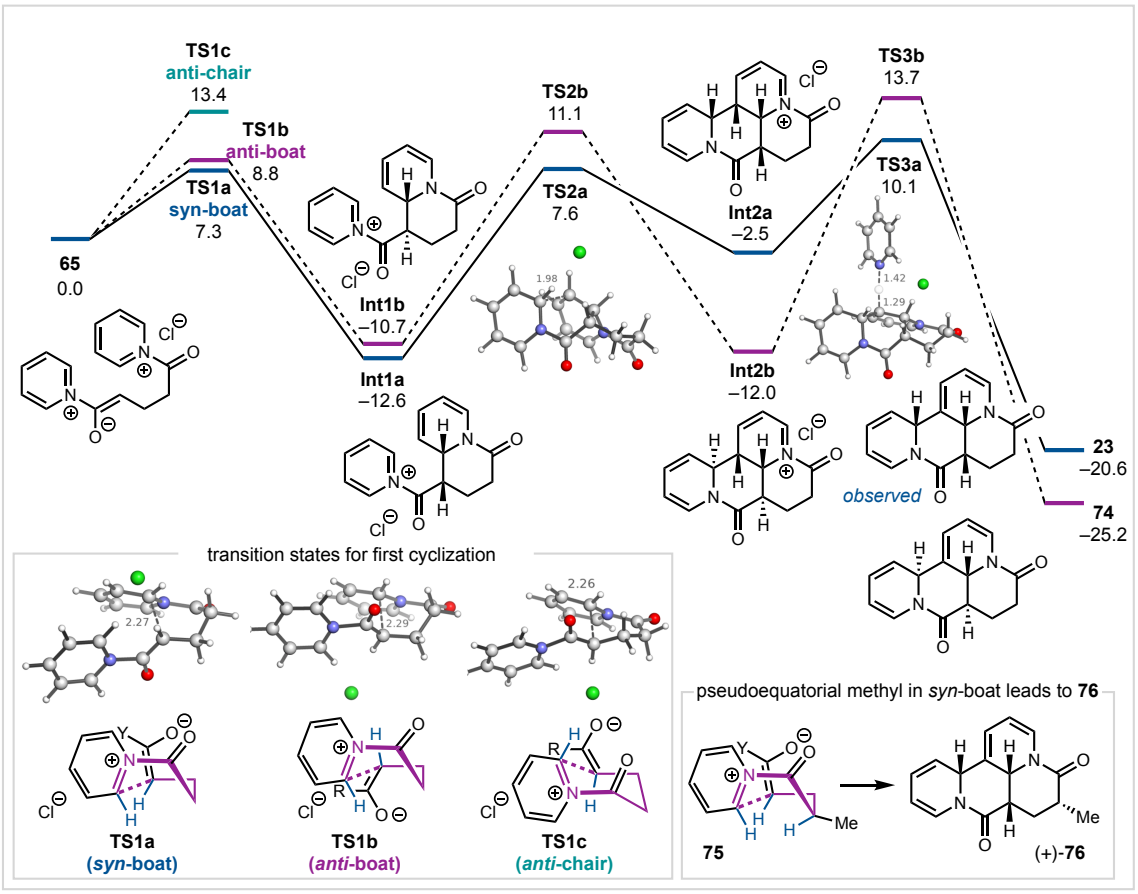
Scheme 2.2. *Mechanistic proposal for the cyclization of pyridine and glutaryl chloride.*



Investigation of a stepwise pathway determined that the lowest-energy TS for the first cyclization involves a boat-like conformation to form the *syn* product (**TS1a**, ΔG_{TS} = 7.3 kcal/mol) (Figure 2.3). Attempts to find the analogous chair-like TS were unsuccessful and led instead to conversion to the boat-like TS. The pathways leading to the *anti* mono-cyclization product (**Int1b**) are higher in energy (see **TS1b** and **TS1c**). The preference for the *syn* boat compared to the *anti* boat TS is likely due to favorable dispersive interactions between the heteroaryl ring and the oxygen-bearing carbon of the enolate, as well as minimization of the dipole moment in the *syn* TS. In order to test the importance of

dispersive interactions in these TSs, the TSs were recomputed with B3LYP, a functional known to lack dispersion. Indeed, with this functional, the difference between the two transition states was only 0.1 kcal/mol, insufficient to account for the observed selectivity. Inclusion of dispersion with Grimme's D3 correction restored the energy difference to 1.4 kcal/mol in favor of the *syn* boat transition state.[24] These TSs lead to two intermediates: *syn* intermediate **Int1a** (–12.6 kcal/mol) and *anti* intermediate **Int1b** (–10.7 kcal/mol). The TS for the second C–C bond formation (**TS2a**) is most favorable for the *syn-syn* intermediate (**Int2a**), with a barrier of 20.2 kcal/mol. The second lowest-energy pathway proceeds via **TS2b** leading to **Int2b**, which gives rise to the *anti-syn-anti* configuration at the ring fusions. The transition states leading to the other four potential diastereomers are higher in energy. Formation of **Int2a** and **Int2b** is followed by deprotonation by pyridine. While **Int2b** is lower in energy than **Int2a**, the deprotonation of **Int2a** to give *syn-syn* (±)-**23** follows the lowest-energy pathway. Thus, the selectivity-determining step is the final deprotonation (**TS3a**) and *syn-syn* (±)-**23** is favored, even though it is thermodynamically less stable than *anti-anti* **74**. These results are consistent with the experimentally observed formation of product (±)-**23** as a single diastereomer, despite the initial mixture of monocyclization products.

Figure 2.3. *Computational investigation of the cyclization of pyridine and glutaryl chloride.*

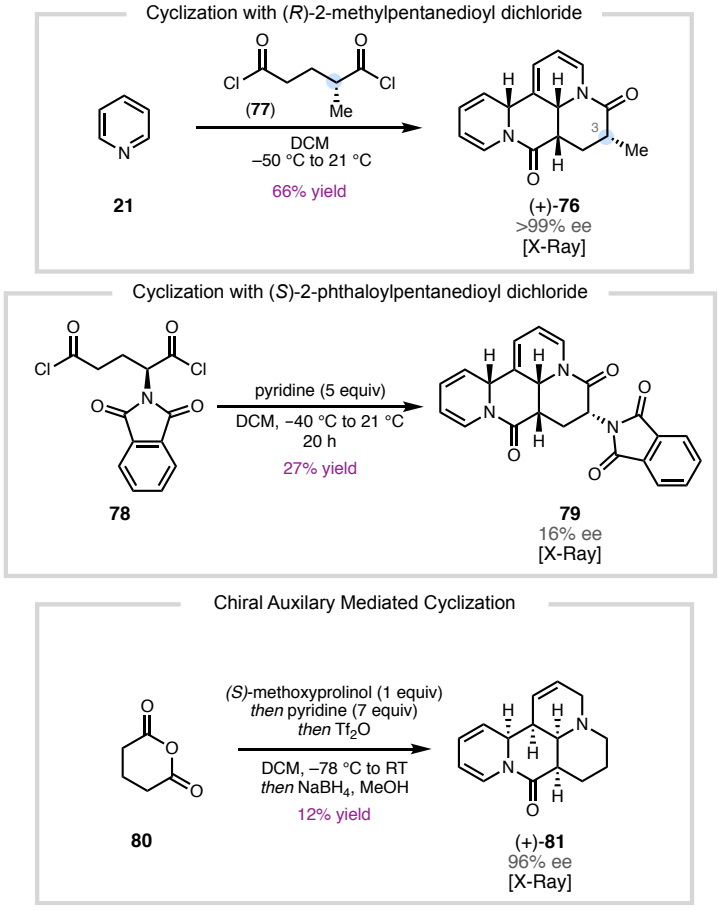


2.3.3 Attempted Enantioselective Cyclization

Attempts to render the cyclization reaction between pyridine and glutaryl chloride enantioselective were met without success. Various additives for the cyclization reaction including PyBOX ligands, chiral bases, and anion binding catalysts all exerted no effect. Interestingly, when enantiopure (*R*)-2-methylpentandioyl chloride was employed, C3-methyl tetracycle (+)-**76** was obtained in 66% yield as a single diastereomer and in >99% ee (Figure 2.4). This stereochemical outcome is consistent with the calculations, where the pathway initiating with a *syn* boat transition state bearing the methyl group in a pseudo-

equatorial position is favored. When (*S*)-2-phthaloyl glutaryl chloride was employed, product was formed in a 27% yield; however, significant erosion of the enantiomeric excess occurred. Attempts to use methoxyprolinol to ring open glutaric anhydride (**80**) *in situ* followed by amide and carboxylic acid activation with triflic anhydride allowed the cyclization to occur in 94% ee, but extensive optimization efforts were never able to help improve the yield of **81** above 12%. The 24% material recovery from the resolution of isomatridine (**24**) led us to favor the classical resolution approach.

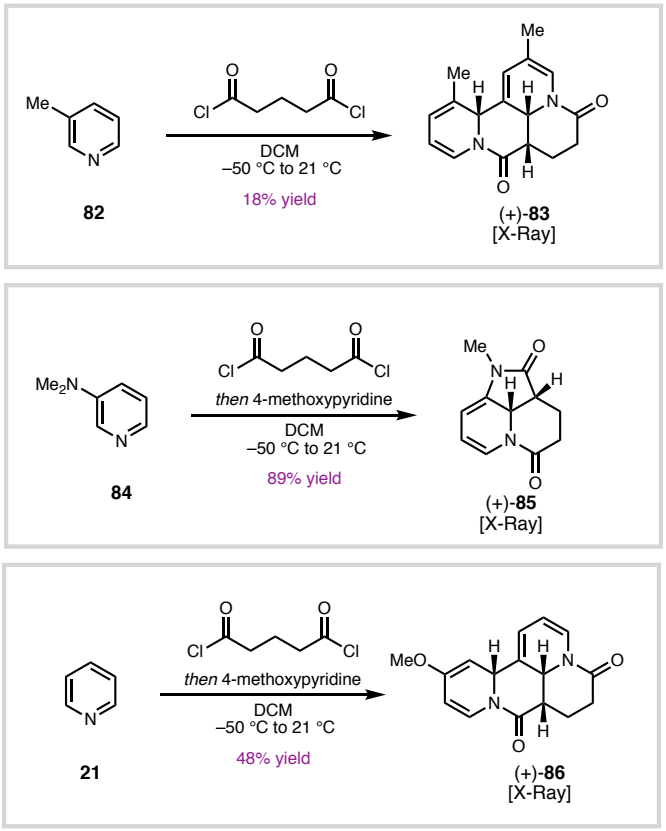
Figure 2.4. *Attempted enantioselective cyclizations.*



2.3.4 Cyclization of Pyridine Derivatives

Several pyridine analogues were tested in the cyclization reaction with limited success. The cyclization of 3-methylpyridine gave **83** in a modest 18% yield and was isolated as a single isomer (Figure 2.5). 4-Methylpyridine produced a mixture of isomers, which were unstable and inseparable. DMAP failed to provide any products in the reaction, and 4-methoxypyridine yielded a product that was too unstable to isolate. With 3-dimethylaminopyridine (**84**), monocycle **85** was produced in 89% yield. It is suspected that the first cyclization takes place, then the dimethylamino group is acylated by the adjacent carboxy group, and lastly demethylation takes place to yield **85**. It was found that the cyclization could be interrupted with 4-methoxypyridine to produce the mixed cyclization product **86**. Interestingly, the mixed pyridine cyclization was quite high yielding. It is hypothesized that pyridine substituents interefere with the first cyclization, but not the second cyclization explaining the significantly higher yield in the mixed cyclization example.

Figure 2.5. *Pyridine derivative cyclizations.*



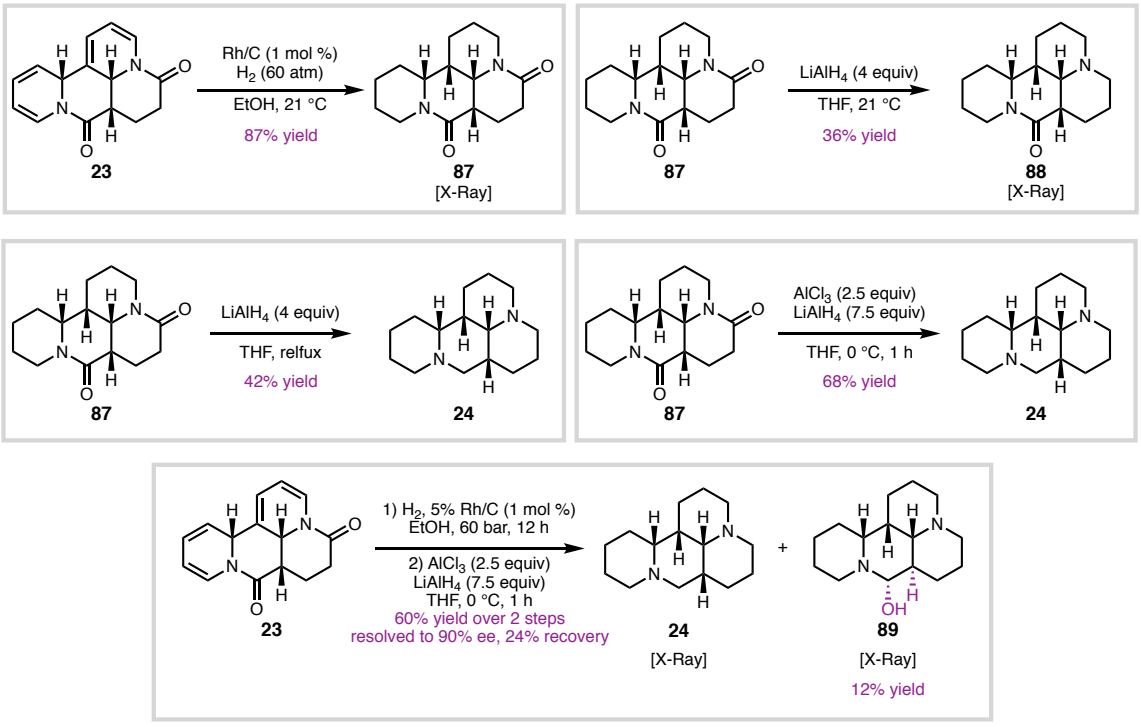
2.4 COMPLETION OF THE SYNTHESIS

2.4.1 Global Reduction

At this stage, attention turned to elaborating (±)-**23** to isomatrine (**25**). Hydrogenation of tetraene **23** proceeded smoothly to yield bis-amide **87** (Figure 2.6). Initial attempts to perform the reduction of **87** with lithium aluminum hydride led to partial reduction to yield monoamide **88**. Refluxing the reaction in LAH provided isomatridine (**24**) in a modest yield. Switching to aluminum hydride gave isomatridine (**24**) in 68% yield, or in a 60% yield over two steps alleviating the need to purify the intermediate bis-amide **87**. Purification of isomatridine (**24**) was readily accomplished by generating its hydrogen

oxalate salt followed by trituration in acetone, obviating the need for column chromatography. Small quantities of hemi-aminal **89** were also produced during the alane reduction of bis-amide **87**. At this stage, resolution of isomatridine (±)-**24** can be achieved by recrystallization of the di-*p*-toluoyl tartaric acid salt to give 24% recovery (46% theoretical yield) of (+)-isomatridine **24** in 90% ee.

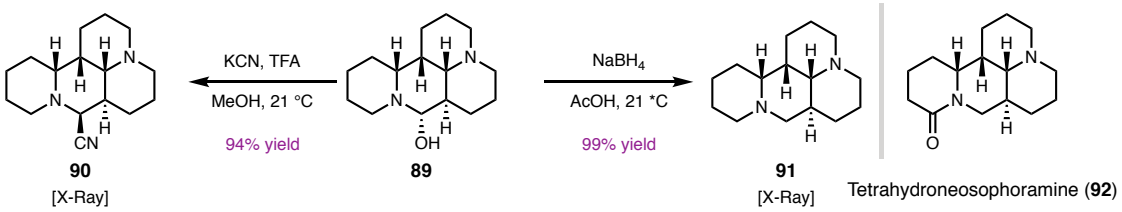
Figure 2.6. *Reduction of tetracycle **23** to isomatridine (**24**).*



Hemi-aminal **89** could be reduced with sodium borohydride in acetic acid to quantitatively yield diamine **91**, which contains the stereochemistry of tetrahydroneosoporamine (**92**) (THNS) (Scheme 2.2). Current efforts in collaboration with the Narayan lab are underway to oxidize diamine **91** into THNS (**92**), the final lupin alkaloid that has not yet been synthesized. Hemi-aminal **89** could also be transformed into

α-cyanoamine **90** in 94% yield by treatment with a mixture of potassium cyanide and trifluoroacetic acid in methanol.

Scheme 2.2. *Access to other diamine diastereomers.*



2.4.2 Isomatridine as a Ligand

It was hypothesized that isomatridine (**24**) could act as a novel bidendate ligand if the scaffold could access a conformation in which both nitrogen atoms were pointed into the concave face of the molecule. Gratifyingly, it was found that treatment of isomatridine with anhydrous copper (II) chloride yielded the copper complex in 72% yield (Scheme 2.3). It was hypothesized that this novel complex might possess catalytic activity; to that end it was screened in the Henry reaction between benzaldehyde and nitromethane (Table 2.1).[25] Modest yields and conversions were observed, likely due to the low solubility of copper complex **93** in methanol. Future efforts will be directed towards studying the reaction using enantiopure copper complex **93** and optimizing the reaction for both yield and ee.

Scheme 2.3. *Synthesis of the copper (II) chloride complex of isomatridine.*

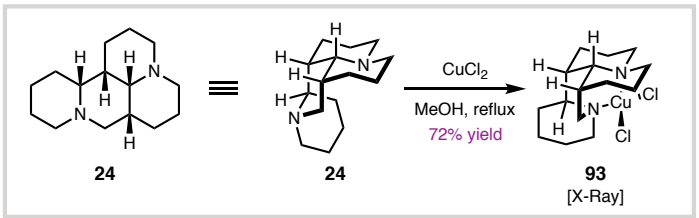
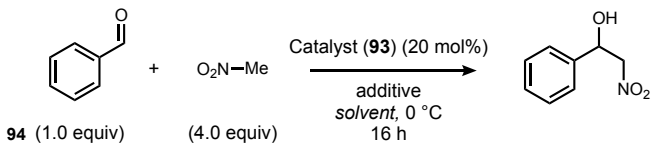


Table 2.1. *Catalytic activity of copper complex* ***93****.*

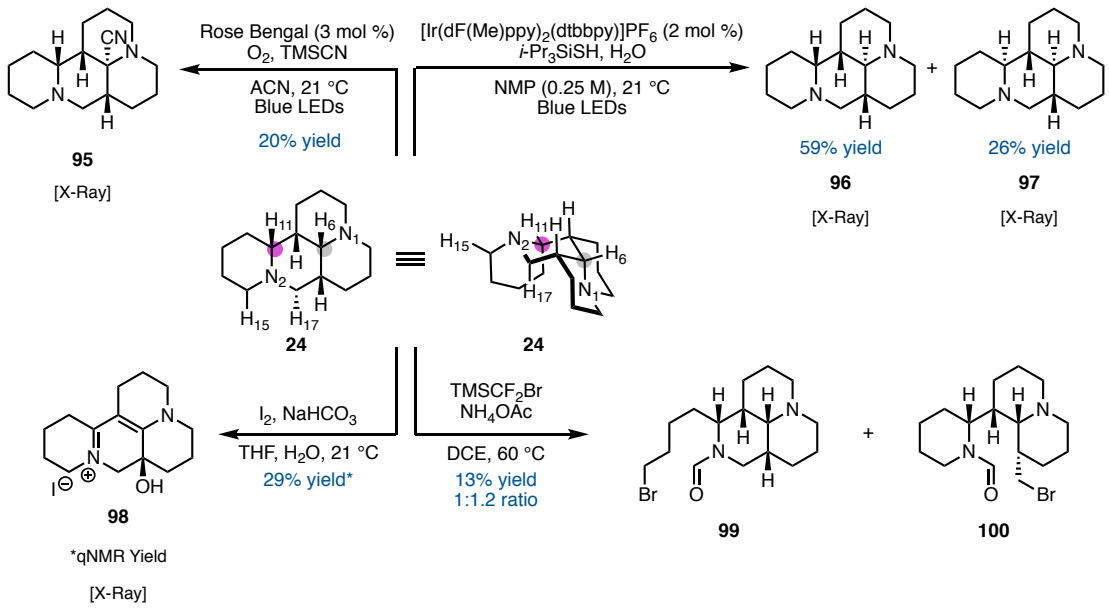


Entry	solvent	additive	conversion **94**	yield
1	MeOH	NEt_3 (3 mol%)	10%	5%
2	MeOH	none	9%	4%
3	THF	none	10%	7%
4	DMF	none	14%	9%
5	DCM	none	22%	14%

2.4.3 C15 Selective Oxidation

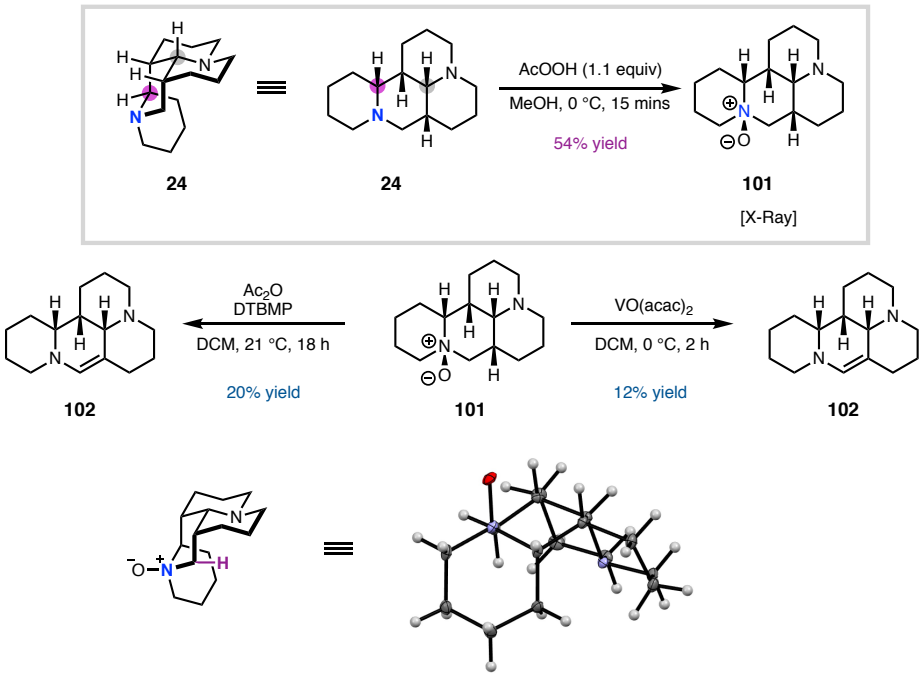
Inspired by the proposed biosynthesis,[26] we initially investigated the enzymatic oxidation of (+)-**24** to give (+)-**25**. Unfortunately, a screen of >180 bacterially derived P450 enzymes (both wild type and mutants) failed to produce any promising leads. As a result, our focus turned towards non-enzymatic methods for the selective oxidation of C15. It was hypothesized that the oxidation of isomatridine (**24**) may be an aerobic oxidation, and not an enzymatic process. Treatment of **24** with singlet oxygen in the presence of trimethylsilyl cyanide led to α-aminonitrile **95** in 20% yield (Scheme 2.4).[27] Analysis of the X-ray structure of **24** revealed that N1 points into the cavity of the molecule while the N2 lone pair points outwards. Photoredox conditions were attempted to oxidize the less hindered lone pair, but led instead to epimerization of the stereocenters adjacent to the nitrogen atoms to produce **96** and **97**.[28] An attempt at a direct oxidation of isomatridine with molecular iodine under basic conditions produced conjugated iminium ion **98** in 29% yield.[29] Recently reported conditions for the cleavage of C-N bonds was found to be unselective and low yielding, producing an inseparable mixture of **99** and **100**.[30]

Scheme 2.4. *C15 oxidation attempts on isomatridine.*



Utilizing peracetic acid, the selective oxidation of N_2 was achieved to yield the expected *N*-oxide **101** in a 54% yield (Scheme 2.5). However, attempts to advance **101** via Polonovski reaction (acetic anhydride/di-*tert*-butyl-4-methyl pyridine (DTBMP)) led to formation of the undesired enamine **102**.[31] In addition, the application of recently reported conditions for a *syn*-Polonovski reaction also provided undesired enamine **102**.[32] Analysis of the X-ray structure of **101** confirmed that antiperiplanar alignment of H17 with the N–O bond is ideally suited to regioselectively form the undesired elimination product **102**.

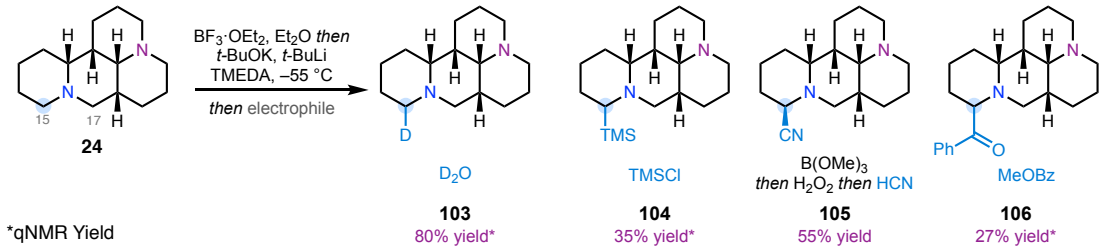
Scheme 2.5. *Attempted Polonovski oxidation of isomatridine.*



We became interested in a report by Kessar and coworkers demonstrating that amine–BF_3 adducts could undergo deprotonation using mixtures of *tert*-butyl lithium (*t*-BuLi) and potassium *tert*-butoxide (*t*-BuOK).[33] Consistent with the selectivity in the *N*-oxide formation, treatment of diamine (+)-**24** with $BF_3{\cdot}OEt_2$ quantitatively formed the Lewis acid-base complex. Deprotonation of the BF_3 complex of (+)-**24** with a mixture of *t*-BuLi and *t*-BuOK in *N,N,N,N*-tetramethylethylenediamine (TMEDA) occurred with good selectivity for the less sterically encumbered C15 over C17 (10:1), as determined by trapping with deuterated methanol (**103**, Scheme 2.6).[28] Unfortunately, trapping of this anion with other electrophiles proved challenging. For example, deprotonation followed by quenching with TMSCl provided silylated diamine **104** in only 35% yield, while trapping with methyl benzoate gave unstable phenyl ketone **106** in 27% yield. The best yield of C15-functionalized product was obtained when **24** was deprotonated and then

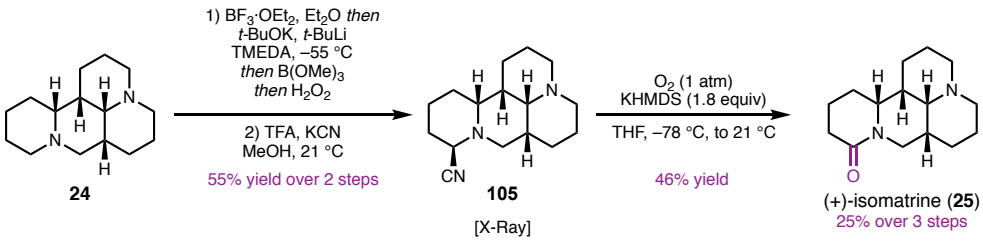
trapped with trimethyl borate; oxidation with hydrogen peroxide and trapping of the resultant enamine with HCN to give aminonitrile **105** in 55% yield.

Scheme 2.6. *C15 selective functionalization.*

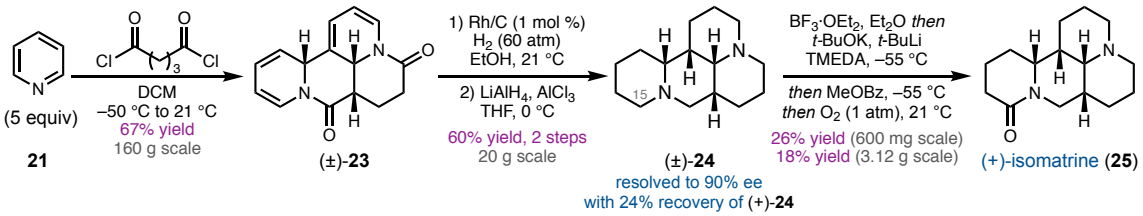


Aerobic oxidation of **105** provided isomatrine in 46% yield (25% yield over three steps from **24**, Scheme 2.7).[34] Alternatively, deprotonation of (+)-**24**, trapping with methyl benzoate, and aerobic oxidation could be carried out in a single reaction flask to give (+)-**25** directly in 18–26% yield, depending on the scale (Scheme 2.8).[35] This route provides access to (±)-isomatrine in four steps, and (+)-isomatrine can be easily accessed by incorporating the resolution of diamine **24**. To date, >1 gram of (+)-isomatrine has been prepared via this route.

Scheme 2.7. *Conversion of isomatridine into isomatrine via α-aminonitrile* ***105****.*



Scheme 2.8. *Completion of the synthesis of isomatrine.*



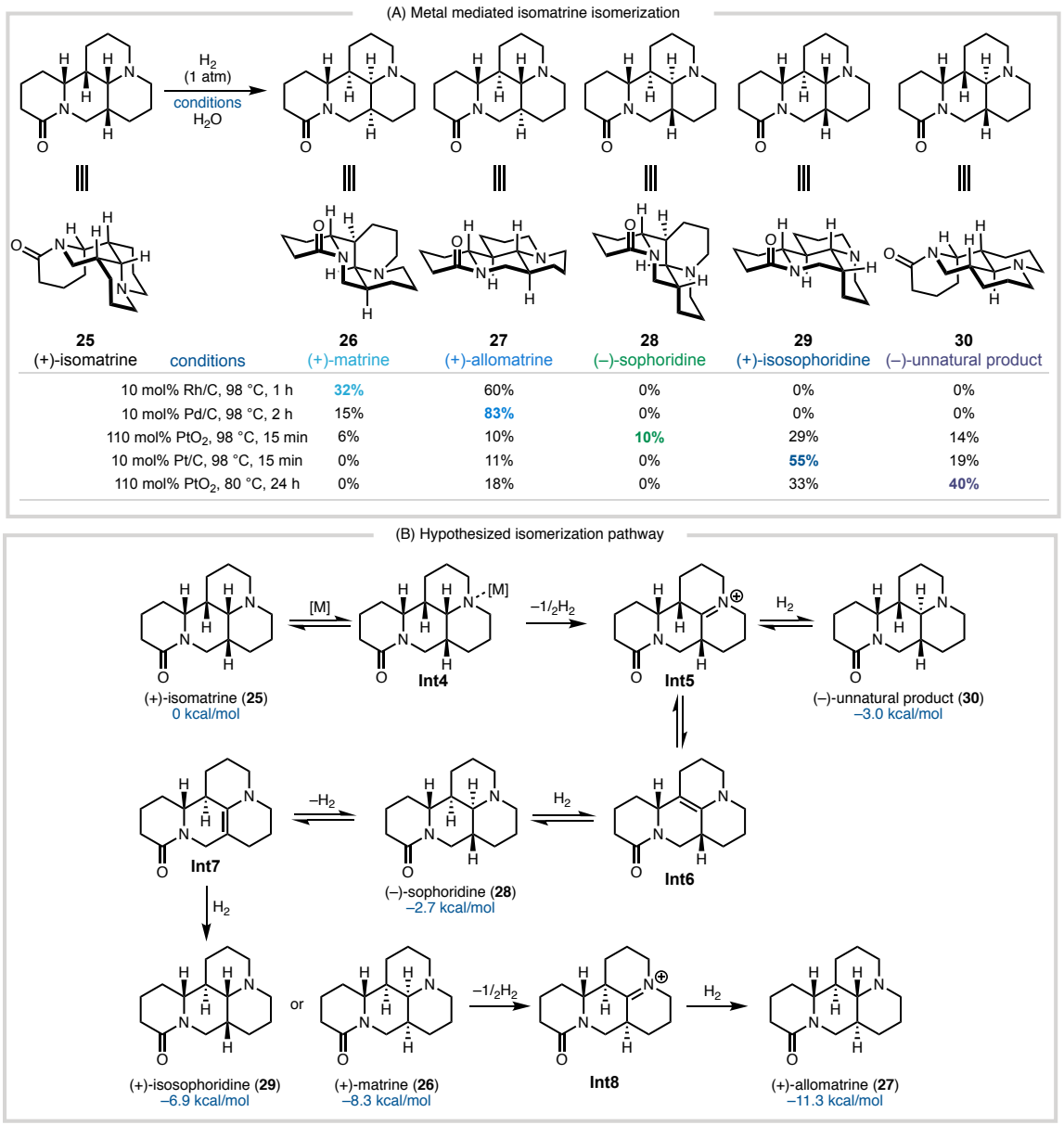
2.4.4 Isomatrine Isomerization

Initial attempts to reproduce Okuda's Pt-catalyzed isomerization of (+)-isomatrine failed to provide the reported yields of (+)-matrine (**26**) and (+)-allomatrine (**27**), and instead produced a mixture of five compounds in our hands.[13] To improve the yield of **26** and **27**, while also broadening the synthetic access to other congeners, an investigation of several isomerization catalysts was carried out. Use of Rh/C provided the best yields of (+)-**26** (32% yield, Figure 2.6), while (+)-**27** could be obtained in 83% yield when Pd/C was used. Isomerization with Pt/C provided (+)-isosophoridine (**29**) in 55% yield. Finally, use of PtO_2 at 98 °C for 15 minutes furnished (–)-sophoridine (**28**) in 10% yield, together with the other isomers.[36] When the reaction with PtO_2 was conducted at 80 °C for 24 hours, (–)-isomer **30** was isolated in 40% yield. To our knowledge, **30** has not yet been isolated from natural sources.

The hypothesized mechanism is thought to occur via a series of metal mediated dehydrogenations, and hydrogenations guided by the relative thermodynamic stabilities of the natural products.[14] First (+)-isomatrine can coordinate to the metal (**Int4**) followed by dehydrogenation to yield iminium ion **Int5**, hydrogenation of which can yield (–)-unnatural product **30**. Isomerization if iminium ion **Int5** can yield enamine **Int6**, hydrogenation of

which provides (–)-sophoridine (**28**). A subsequent dehydrogenation and isomerization give rise to enamine **Int7**, which depending upon the face of hydrogenation can provide either (+)-isosophoridine (**29**) or (+)-matrine (**26**). A final dehydrogenation can provide **Int8**, which upon hydrogenation gives the thermodynamically most stable diastereomer (+)-allomatrine (**27**).

Figure 2.6. *Isomerization of isomatrine into other matrine-type lupin alkaloids.*

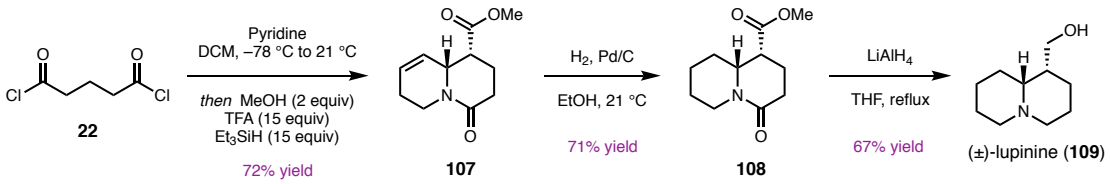


2.5 SPARTEINE AND LUPININE

2.5.1 Total Synthesis of Lupinine

The cyclization reaction between pyridine and glutaryl chloride goes through intermediate monocyclized acid chloride **73**, which we envisioned could be intercepted and utilized to access additional lupin alkaloids. Methanol reacted with intermediate acid chloride **73** to form the methyl ester, which had the enamide bond reduced with TFA and triethylsilane allowing for the isolation of **107** (Scheme 2.9). Hydrogenation of **107** produced **108**, which was reduced with $LiAlH_4$ to provide the natural product lupinine (**109**) in a total of three steps in a 35% overall yield from glutaryl chloride.[37]

Scheme 2.9. *Total synthesis of lupinine (**109**).*

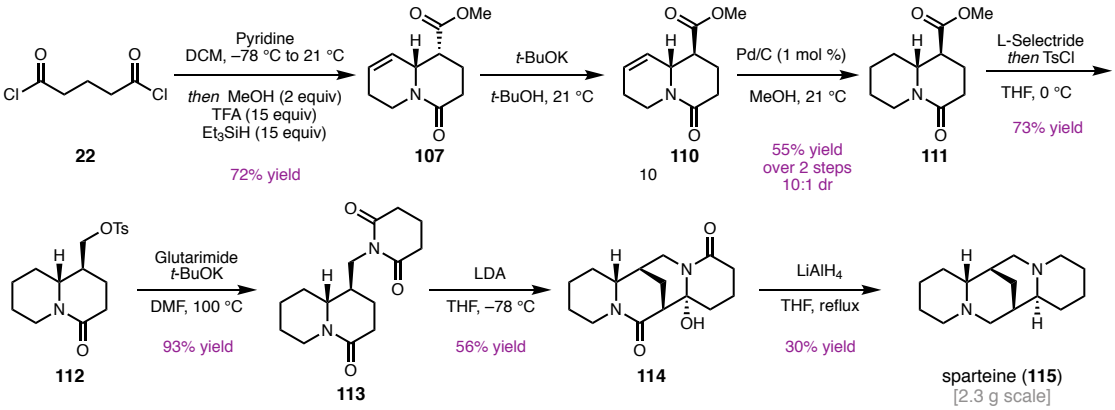


2.5.2 Total Synthesis of Sparteine

We reasoned that it could be possible to access sparteine (**115**) by taking advantage of monocyclized compound **107**. Epimerization of **107** was accomplished with potassium *t*-butoxide to provide **110** as a 10:1 mixture of diastereomers, which was carried forward as a mixture. Hydrogenation proceeded smoothly to yield **111** in 55% yield over 2 steps. L-selectride was found to selectively reduce the methyl ester, which was trapped with tosyl chloride to yield alkyl tosylate **112**. An S_N2 reaction between tosylate **112** and glutarimide occurred in high yields to produce **113**. An intramolecular cyclization was accomplished

by treatment of **113** with LDA to yield the carbon scaffold of sparteine.[38] Lastly, $LiAlH_4$ reduction of **114** yielded sparteine in 30% yield.

Scheme 2.10. *Total synthesis of sparteine.*



2.6 CONCLUDING REMARKS

The bioinspired dearomative annulation between pyridine and glutaryl chloride developed here has enabled the first total synthesis of the lupin alkaloid (–)-sophoridine, and the shortest syntheses of (+)-isomatrine, (+)-matrine, (+)-allomatrine, and (+)-isosophoridine reported to date. The power of the pyridine dearomative cascade reaction allows these syntheses to be highly concise due to forming the carbocyclic scaffold of these natural products in a single step. The initially formed heterocycle can be hydrogenated and reduced with alane to yield isomatridine, which has found use as a novel ligand and can be prepared on gram scale. Efforts towards the discovery of the C15 selective oxidation have led to the development of reactions that can functionalize a variety of positions on isomatridine, which could be useful towards potential SAR studies that were not previously possible starting from the natural product. The selective deprotonation, electrophile

trapping, oxidation cascade sequence to synthesize isomatrine enabled its total synthesis in a total of four steps from pyridine and has allowed us to prepare over a gram of isomatrine to date.

The total syntheses of lupinine and sparteine have also been achieved using this route. Based upon a mechanistic investigation of the cyclization reaction, it was discovered that the dearomative pyridine cyclization proceeds through two distinct stages at substantially different rates. The first product of the cyclization can be selectively accessed by quenching the reaction before the second cyclization takes place with methanol. Global reduction of the obtained quinolizidine has resulted in the preparation of lupinine in a total of three steps and 35% overall yield. The five-step transformation of the obtained quinolizidine **107** into sparteine has been realized on gram scale, providing a supply of this challenging to source natural product. The diversity of lupin alkaloids and related structures prepared from commodity chemicals is anticipated to support future pharmacological investigations.

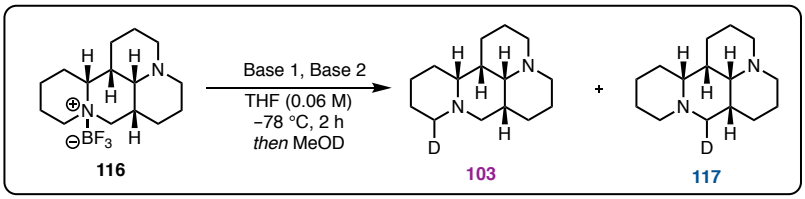
2.7 EXPERIMENTAL SECTION

Unless otherwise stated, reactions were performed under an inert atmosphere (dry N_2) using freshly dried solvents and standard Schlenk techniques. Glassware was oven-dried at 120 °C for a minimum of four hours. Tetrahydrofuran (THF), methylene chloride (DCM), acetonitrile (ACN), methanol (MeOH), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. CH_2Cl_2 (D150-4), benzene (PhH, OmniSolv, BX0212-1), acetonitrile (A998-4), pentane (P399-4), acetone (A18-20), hexanes (H292-20), and *n*-butanol (A399-4) were purchased from Fisher and used as

received. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from VWR (EM-DX1727-6) and used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV or by staining with *p*-anisaldehyde or potassium permanganate ($KMnO_4$). Flash column chromatography was performed as described by Still et al.[39] using silica gel (particle size 0.032–0.063) purchased from MilliporeSigma. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), a Bruker 400 MHz Spectrometer with broadband iProbe, or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CDCl_3$ (^1H, $\delta = 7.26$; ^{13}C, $\delta = 77.16$) or CD_2Cl_2 ^1H, $\delta = 5.32$; ^{13}C, $\delta = 53.84$). $CDCl_3$ was stored over anhydrous potassium carbonate (K_2CO_3). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS data were acquired using an Agilent 6230 Series time-of-flight (TOF) mass spectrometer with an Agilent G1978A ion trap or by LC-MS using a Waters LCT Premier XE Electrospray TOF mass spectrometer interfaced with Waters UPLC chromatography, or by GC-MS interfaced with a JEOL JMS-T2000 GC AccuTOF GC-Alpha with Field Ionization. Molecular formulas of the compounds [M] are given, with the observed ion fragment in brackets, e.g. $[M+H]^+$. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Melting points were determined using a Büchi B-545 capillary melting

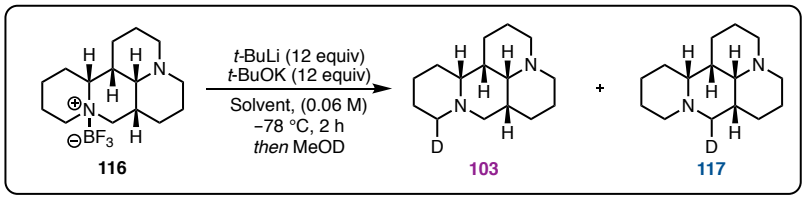
point apparatus, and the values reported are uncorrected. Photochemical experiments were performed using a 34 W Kessil H150 Blue LED light. Unless otherwise stated, chemicals and reagents were used as received. Reagents were purchased from commercial vendors as follows: Solid potassium *tert*-butoxide was purchased from STREM Chemicals Inc., stored in a glovebox, and used as received. TMEDA and trimethylborate were purchased from MilliporeSigma and were distilled over CaH_2 under N_2 prior to use. Glutaryl chloride was purchased from Oakwood Chemicals Inc. and was used as received. Anhydrous pyridine, rhodium on carbon (5%), palladium on carbon (10%), platinum dioxide, platinum on carbon (5%), trimethylsilyl cyanide, lithium aluminum hydride, aluminum trichloride, *tert*-butyl lithium solution in pentanes, rose bengal, peracetic acid, hydrogen peroxide, oxalyl chloride, $Rh(PPh_3)_3(CO)(H)$, sodium borohydride, $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$, triisopropylsilanethiol, (fluorodibromo)trimethylsilane, and *N*-phthaloyl-L-glutamic acid were purchased from MilliporeSigma and were used as received. Di-*p*-toluoyl-L-tartaric acid was purchased from Ambeed Inc. and was used as received. (*R*)-2-methylglutaric acid and racemic 2-methylglutaric acid were purchased from Combi-Blocks Inc. and used as received. ^1H qNMR standards trimethylphenyl silane (99% purity) and pyrazine (≥99% purity) were purchased from MilliporeSigma and used as received.

Table 2.2. *Deprotonation – solvent screen.*



Entry	Base 1 (equiv)	Base 2 (equiv)	Ratio 103:117	% Yield 103	% Yield 107	Total Conversion
1	$Zn(TMP)_2$•LiCl (12 equiv)	/	/	0%	0%	0%
2	$(i\text{-}Pr)_2NMgCl$•LiCl (12 equiv)	/	/	0%	0%	0%
3	TMPMgCl•LiCl (12 equiv)	/	/	0%	0%	0%
4	*t*-BuLi (12 equiv)	/	/	0%	0%	0%
5	*n*-BuLi (12 equiv)	*t*-BuOK (12 equiv)	0.4 : 1.0	21%	54%	75%
6	*s*-BuLi (12 equiv)	*t*-BuOK (12 equiv)	1.5 : 1.0	25%	17%	42%
7	*t*-BuLi (12 equiv)	*t*-BuOK (12 equiv)	2.0 : 1.0	26%	13%	39%
8	*t*-BuLi (12 equiv)	*t*-BuOK (6 equiv)	2.0 : 1.0	6%	3%	9%
9	*t*-BuLi (12 equiv)	*t*-BuOK (24 equiv)	1.4 : 1.0	46%	33%	79%
10	*t*-BuLi (6 equiv)	*t*-BuOK (24 equiv)	1.2 : 1.0	31%	26%	57%
11	*t*-BuLi (12 equiv)	*t*-BuONa (12 equiv)	0.3 : 1.0	5%	16%	21%
12	*t*-BuLi (12 equiv)	*t*-BuOCs (12 equiv)	0.5 : 1.0	25%	55%	80%

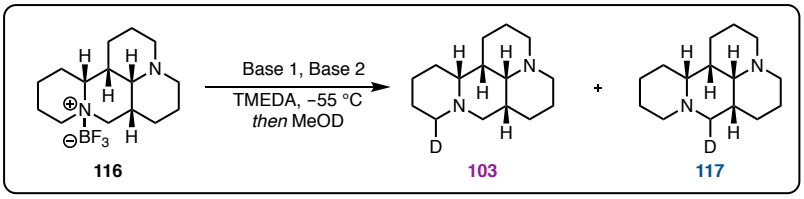
Table 2.3. *Deprotonation – optimization in TMEDA.*



Entry	Solvent	Ratio 103:117	% Yield 103	% Yield 107	Total Conversion
1	Hexanes	/	0%	0%	0%
2	Et_2O	0.4 : 1.0	26%	63%	88%
3	2-MeTHF	0.8 : 1.0	4%	5%	9%
4	THF	2.0 : 1.0	26%	13%	39%
5	TBME	0.2 : 1.0	10%	45%	55%
6	CPME	0.3 : 1.0	20%	62%	82%
7	THP[a]	2.4 : 1.0	31%	13%	44%
8	50% THF/50% THP	1.8 : 1.0	22%	12%	34%
9	THF-d_8	2.0 : 1.0	44%	37%	81%
10	THF/TMEDA (12 equiv)	1.8 : 1.0	39%	22%	61%
11	Et_2O/TMEDA (12 equiv)	1.3 : 1.0	50%	40%	90%
12	CPME/TMEDA (12 equiv)	1.1 : 1.0	34%	31%	65%
13	50% Hexanes/50%TMEDA	1.2 : 1.0	14%	12%	26%
14	TMEDA[b]	5.0 : 1.0	45%	9%	54%
15	*N*-methylpyrrolidine	1.0 : 1.0	29%	30%	59%

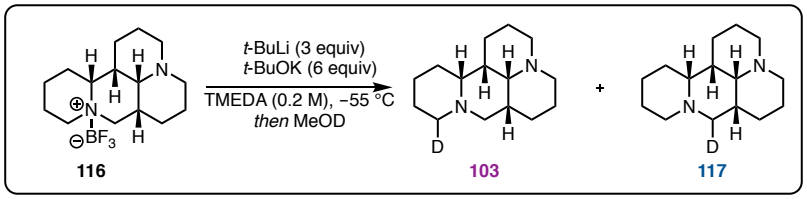
[a]run at –40°C.
[b]run at –50°C.

Table 2.4. *Deprotonation – optimization of base and equivalents.*



Entry	Base 1 (equiv)	Base 2 (equiv)	Concentration	Ratio 103:117	% Yield 103	% Yield 107	Total Conversion
1	*n*-BuLi (12 equiv)	*t*-BuOK (12 equiv)	0.06 M	0.2 : 1.0	12%	55%	67%
2	*t*-BuLi (6 equiv)	*t*-BuOK (12 equiv)	0.06 M	10.0 : 1.0	80%	8%	88%
3	*t*-BuLi (12 equiv)	*t*-BuOK (24 equiv)	0.06 M	3.7 : 1.0	70%	19%	89%
4	*t*-BuLi (12 equiv)	*t*-PeOK (24 equiv)	0.06 M	3.2 : 1.0	64%	20%	84%
5	*t*-BuLi (2 equiv)	*t*-BuOK (4 equiv)	0.06 M	> 20.0 : 1.0	62%	1%	63%
6	*t*-BuLi (3 equiv)	*t*-BuOK (4 equiv)	0.06 M	11.0 : 1.0	72%	7%	79%
7	*t*-BuLi (3 equiv)	*t*-BuOK (5 equiv)	0.06 M	8.8 : 1.0	73%	8%	81%
8	*t*-BuLi (3 equiv)	*t*-BuOK (6 equiv)	0.06 M	7.1 : 1.0	73%	10%	83%
9	*t*-BuLi (3 equiv)	*t*-BuOK (9 equiv)	0.06 M	> 20.0 : 1.0	71%	2%	73%
10	*t*-BuLi (4 equiv)	*t*-BuOK (8 equiv)	0.06 M	5.8 : 1.0	60%	10%	70%
11	*t*-BuLi (3 equiv)	*t*-BuOK (6 equiv)	0.1 M	7.7 : 1.0	72%	9%	81%
12	*t*-BuLi (3 equiv)	*t*-BuOK (6 equiv)	0.2 M	11.6 : 1.0	76%	7%	83%
13	*t*-BuLi (3 equiv)	*t*-BuOK (6 equiv)	0.3 M	5.9 : 1.0	74%	12%	86%
14	*t*-BuLi (3 equiv)	*t*-BuOK (6 equiv)	0.4 M	18.5 : 1.0	69%	4%	73%

Table 2.5. *Deprotonation – optimization of time.*



Entry	Deprotonation Time	*t*-BuLi Addn. Time	Ratio 103:117	% Yield 103	% Yield 117	Total Conversion
1	0.5 h	60 s	4.9 : 1.0	73%	15%	88%
2	0.5 h	10 s	6.2 : 1.0	74%	12%	86%
3	1 h	60 s	9.5 : 1.0	69%	7%	76%
4	2 h	60 s	11.6 : 1.0	76%	7%	83%
5	3 h	60 s	10.3 : 1.0	78%	8%	86%
6	4 h	60 s	4.2 : 1.0	69%	17%	86%

Figure 2.7. *Deprotonation – electrophile trapping – oxidation screen.*

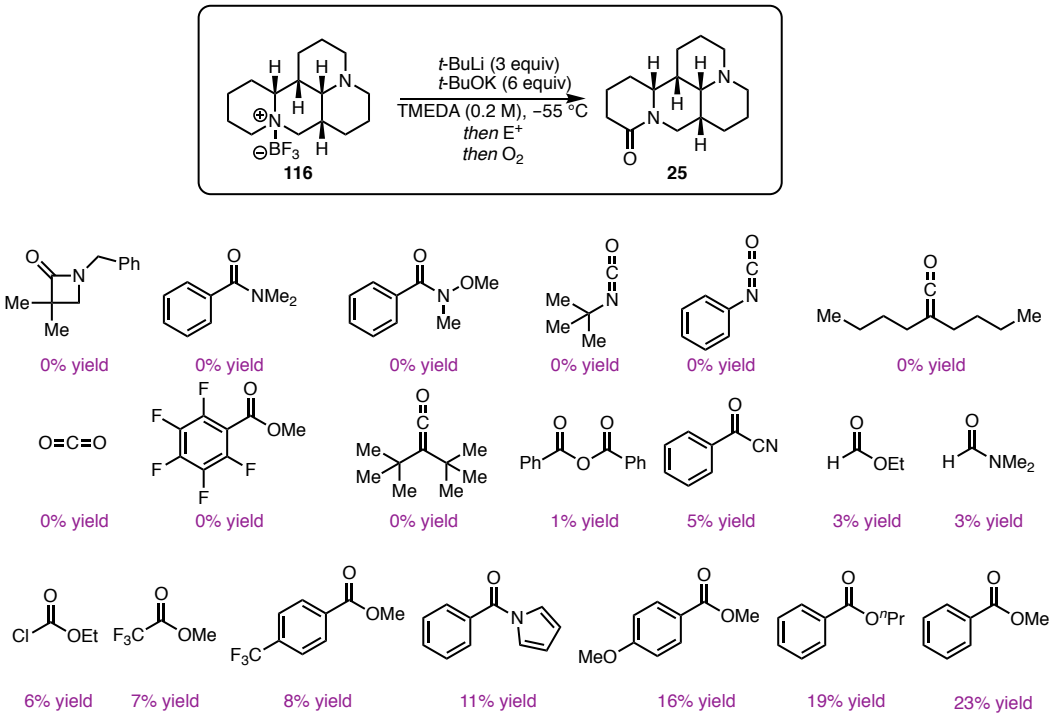
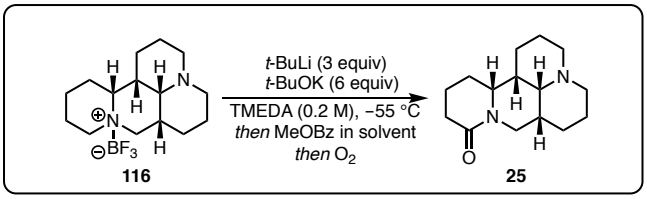
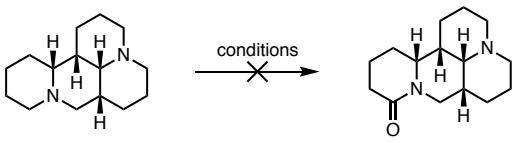


Table 2.6. *Deprotonation – methyl benzoate trapping – oxidation screen.*



Entry	MeOBz Equiv	Solvent	% Yield
1	25	TMEDA	15
2	4	Hexanes	26
3	4	Et_2O	26
4	4	PhMe	29
5	4	CPME	28
6	8	CPME	32
7	12	CPME	28

Table 2.7. *Unsuccesful oxidation reactions.*



24 **25**

Entry	Conditions	Result
1	2 Equiv. $KMnO_4$, H_2O, 90 °C, 5 min	Recovered SM
2	30 Equiv. $KMnO_4$, H_2O, 90 °C, 30 min	Complex Mixture
3	PhIO, H_2O, 21 °C, 24 h	Recovered SM
4	IBX, H_2O, 21 °C, 24 h	Recovered SM
5	$FeCl_3$•$6H_2O$, 2-picolinic acid, $PhCO_3t$-Bu, H_2O, Pyridine, 70 °C, 24 h	Recovered SM
6	AgCN (2.1 equiv), ACN, 80 °C, 48 h	Recovered SM
7	Ru(bpy)3(PF6)2 (2 mol %), TMSCN, DMF, 20 °C, Blue LEDs, 22 h	Recovered SM
8	$Cu(CH_3CN)_4PF_6$, ABNO, NMI, 4,4'-dimethoxy-2,2'-bpy, O_2 (1 atm)	Recovered SM

Figure 2.8. *Unsuccesful oxidation reactions.*

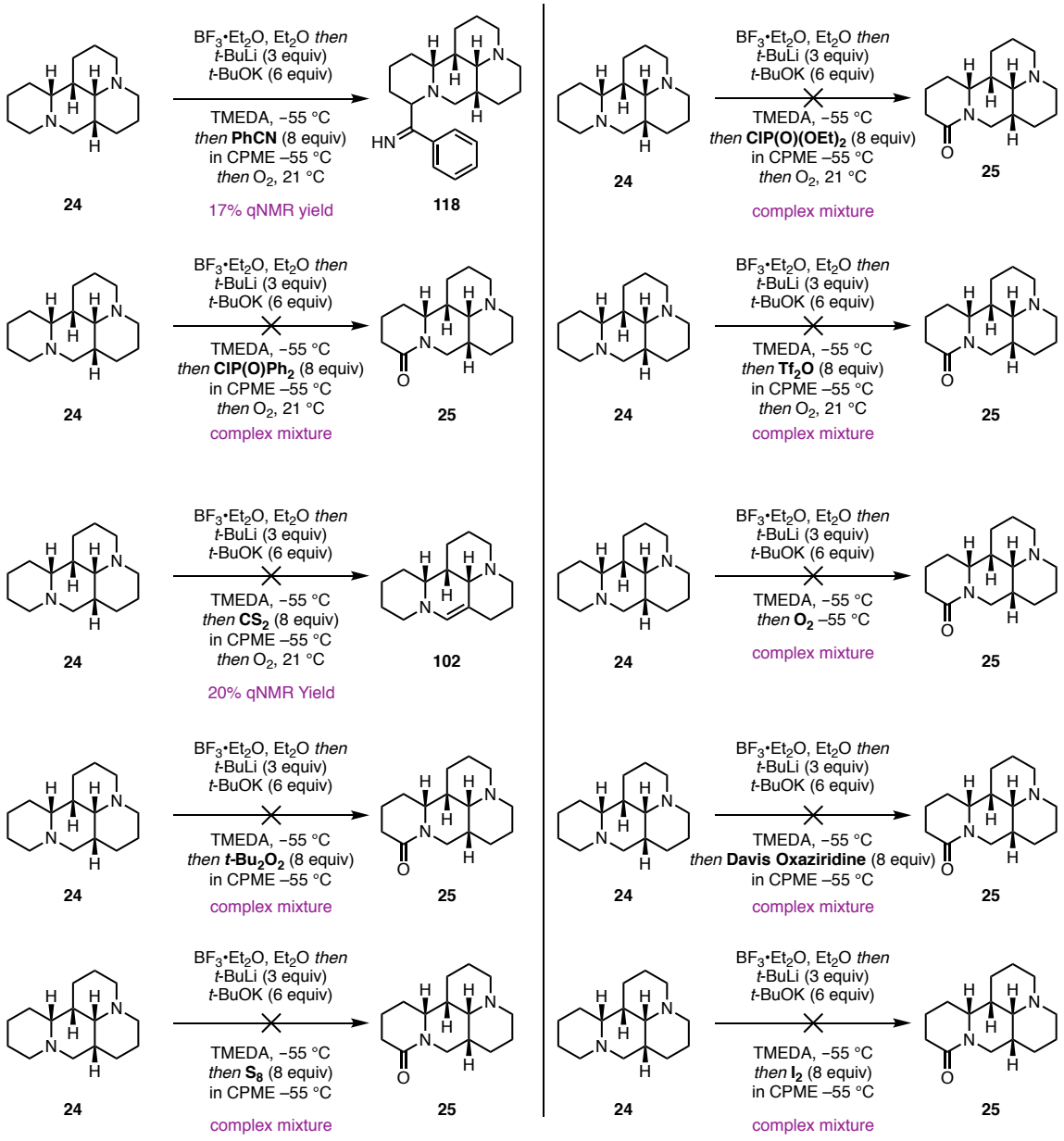


Figure 2.9. *Unsuccesful oxidation reactions.*

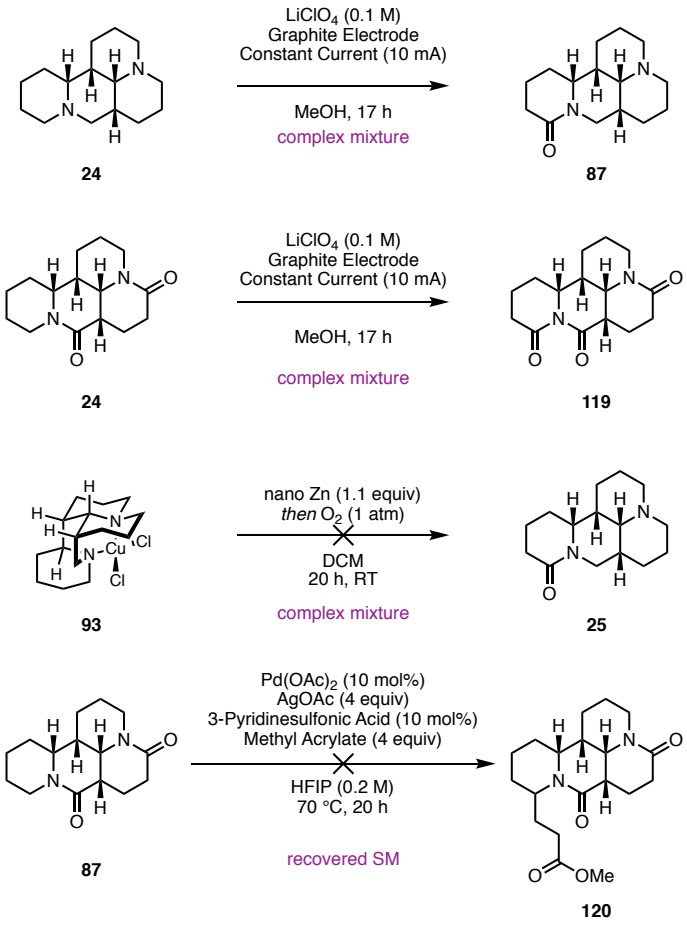
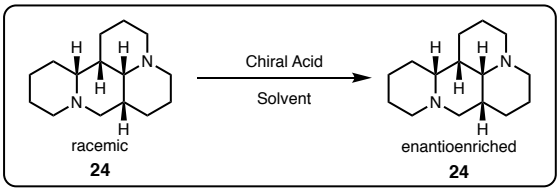


Table 2.8. *Resolution crystallization optimization initial screening.*



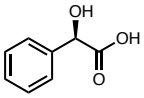
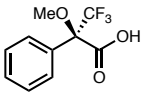
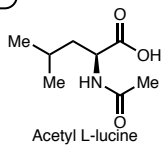
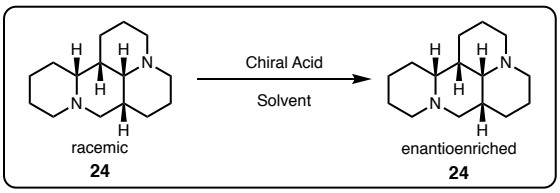
Solvent (0.2 M) \ Acid	 (*R*)-Mandelic Acid **121** (2 equiv)	 (*R*)-Moshers Acid **122** (2 equiv)	 Acetyl L-lucine **123** (2 equiv)
i-PrOH	No Crystals	No Crystals	No Crystals
2-BuOH	No Crystals	No Crystals	No Crystals
Acetone	No Crystals	No Crystals	No Crystals

Table 2.9. *Resolution crystallization optimization tartrate hit.*



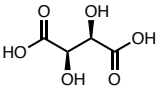
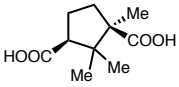
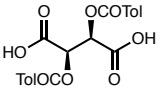
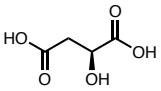
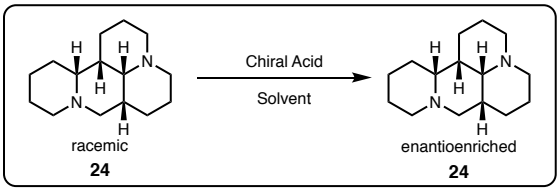
Acid (1 equiv) / Solvent (0.4 M)	 **124** D-tartaric acid	 **125** (+)-camphoric acid	 **126** (+)-di-*p*-toluoyl tartaric acid	 **127** L-malic acid
H_2O	No Crystals	No Crystals	No Crystals	No Crystals
MeOH	No Crystals	No Crystals	No Crystals	No Crystals
EtOH	22% recovery 2% ee	No Crystals	48% recovery 5% ee	No Crystals
i-PrOH	29% recovery 15% ee	No Crystals	61% recovery 58% ee	No Crystals
n-BuOH	21% recovery 30% ee	No Crystals	Insoluble @ 0.4 M	No Crystals
s-BuOH	Insoluble at 0.4 M	No Crystals	Insoluble @ 0.4 M	No Crystals
CH_3CN	No Crystals	No Crystals	No Crystals	No Crystals
HFIP	No Crystals	No Crystals	No Crystals	No Crystals

Table 2.10. *Optimization of a tartrate resolution.*



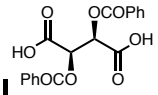
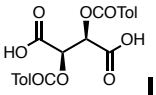
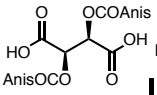
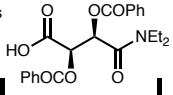
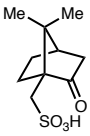
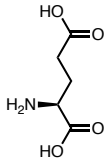
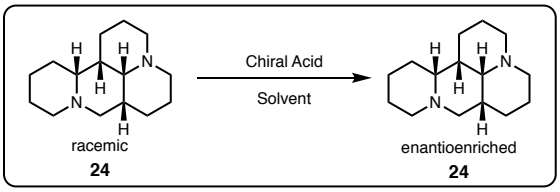
Solvent (0.4 M) \ Acid (1 equiv)	 **128** (–)-di-benzoyl tartaric acid	 **126** (–)-di-*p*-toluoyl tartaric acid	 **129** (+)-di-anisoyl tartaric acid	 **130** (–)-di-benzoyl-monodiethylamine tartaric acid	 **131** (*R*)-Camphor-Sulfonic Acid	 **132** L-Glutamic Acid
EtOH	No Crystals	10% recovery –14% ee	No Crystals	No Crystals	No Crystals	Insoluble at 0.4 M
i-PrOH	25% recovery –20% ee	23% recovery +47% ee	17% recovery 0% ee	No Crystals	No Crystals	Insoluble at 0.4 M
t-BuOH	18% recovery –17% ee	No Crystals	57% recovery 0% ee	No Crystals	No Crystals	Insoluble at 0.4 M
n-PrOH	17% recovery –10% ee	10% recovery –10% ee	No Crystals	No Crystals	No Crystals	Insoluble at 0.4 M
n-BuOH	44% recovery –8% ee	21% recovery –37% ee	38% recovery 0% ee	No Crystals	No Crystals	Insoluble at 0.4 M
s-BuOH	50% recovery +21% ee	Inoluble at 0.4 M	44% recovery 0% ee	No Crystals	No Crystals	Insoluble at 0.4 M

Table 2.11. *Optimization of tartrate equivalents for the resolution.*



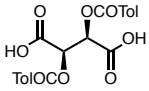
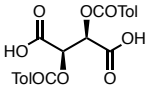
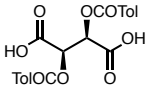
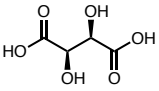
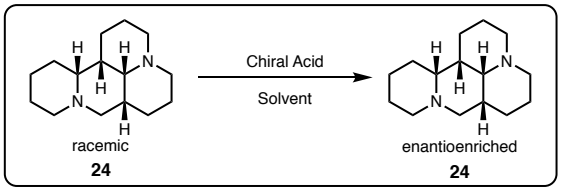
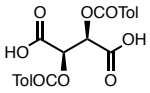
Solvent (0.4 M) \ Acid	 **126** (–)-di-*p*-toluoyl tartaric acid 0.50 equiv	 **126** (–)-di-*p*-toluoyl tartaric acid 0.75 equiv	 **126** (–)-di-*p*-toluoyl tartaric acid 1.0 equiv	 **124** D-tartaric acid 1.0 equiv
i-PrOH	No Crystals	31% recovery 68% ee	39% recovery 63% ee	Insoluble at 0.4 M
s-BuOH	Insoluble at 0.4 M	Insoluble at 0.4 M	Insoluble at 0.4 M	16% recovery 8% ee

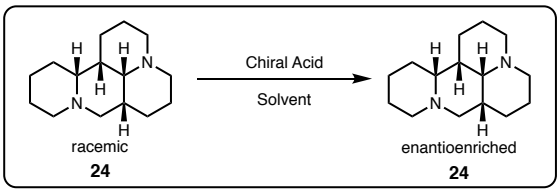
Table 2.12. *Optimization of solvent for the tartrate resolution.*

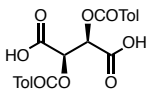
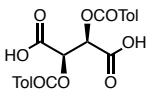
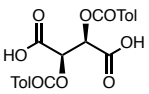
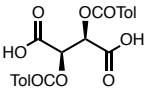




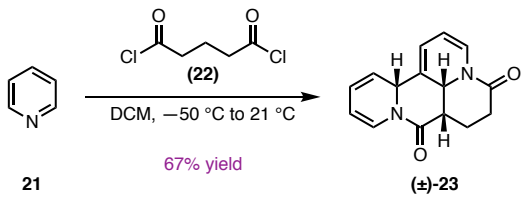
Solvent (0.2 M) \ Acid (1 equiv)	**126** di-*p*-toluoyl tartaric acid (1 equiv)
i-PrOH	56% recovery 65% ee
s-BuOH	52% recovery 77% ee
Acetone	72% recovery –15% ee
CPME	No Crystals
DCE	No Crystals
t-AmylOH	No Crystals

Table 2.12. *Optimization of solvent and concentration for the resolution.*



Solvent \ Conc.	 **126** 0.2 M	 **126** 0.15 M	 **126** 0.10 M	 **126** 0.05 M
i-PrOH	59% recovery 63% ee	55% recovery 68% ee	49% recovery 74% ee	49% recovery 49% ee
2-BuOH	68% recovery 47% ee	51% recovery 72% ee	37% recovery 91% ee	3% recovery 63% ee
2-pentanol	59% recovery 64% ee	59% recovery 56% ee	54% recovery 70% ee	19% recovery 89% ee
2-hexanol	39% recovery 72% ee	37% recovery 76 % ee	27% recovery 76% ee	No Crystals
3-pentanol	53% recovery 67% ee	55% recovery 62% ee	39% recovery 79% ee	2% recovery 76% ee

Preparation of (±)-tetracycle 23:



Large-Scale Procedure:

A 12 L oven-dried, N_2-flushed 3-neck flask equipped with an overhead stirrer, thermocouple, and rubber septum was charged with anhydrous DCM (8.0 L, 0.12 M) followed by glutaryl chloride (**22**) (126 mL, 980 mmol, 1.0 equiv). The solution was cooled to –50 °C on an acetone/dry ice bath. Pyridine (**21**) (396 mL, 4.90 mol, 5.0 equiv) was added via cannula at such a rate as to prevent the temperature from rising above –40 °C (*ca*. 1 hour). Following pyridine addition, the reaction was stirred at –50 °C for 15 minutes and then at 21 °C until complete, as judged by ^{1}H NMR in CD_2Cl_2 (*ca*. 24–36 hours). Upon completion, the reaction was concentrated under reduced pressure to yield a brown solid which was suspended in MeOH (800 mL). The solids were isolated via suction filtration, washed with MeOH (3 x 150 mL), and dried *in vacuo* to yield (±)-tetracycle **23** as a tan crystalline solid (165.9 g, 67% yield).

Medium-Scale Procedure:

A 3 L oven-dried, N_2-flushed 3-neck flask equipped with an overhead stirrer, thermocouple, and rubber septum was charged with anhydrous DCM (1.8 L, 0.1 M) followed by glutaryl chloride (**22**) (23 mL, 179 mmol, 1.0 equiv). The solution was cooled to –50 °C on an acetone/dry ice bath. Pyridine (**21**) (72 mL, 895 mmol, 5.0 equiv) was added via cannula at such a rate as to prevent the temperature from rising above –40 °C

(*ca*. 30 minutes). Following pyridine addition, the reaction was stirred at –50 °C for 15 minutes then at 21 °C until complete, as judged by ^{1}H NMR in CD_2Cl_2 (*ca*. 24–36 hours). Upon completion, the reaction was concentrated under reduced pressure to yield a brown solid which was suspended in MeOH (200 mL). The solids were isolated via suction filtration, washed with MeOH (3 x 100 mL), and dried *in vacuo* to yield (±)-tetracycle **23** as a tan crystalline solid (31.1 g, 68% yield).

Small-Scale Procedure:

A 1 L oven-dried, N_2-flushed flask with a 36 mm x 18 mm x 18 mm egg-shaped stir bar was charged with anhydrous DCM (296 mL, 0.1 M) followed by glutaryl chloride (**22**) (3.78 mL, 29.6 mmol, 1.0 equiv). The solution was cooled to –50 °C on an acetone/dry ice bath. Pyridine (**21**) (12 mL, 148 mmol, 5.0 equiv) was added dropwise via syringe over the course of 10 minutes. Following pyridine addition, the reaction was stirred at –50 °C for 15 minutes then at 21 °C until complete, as judged by ^{1}H NMR in CD_2Cl_2 (*ca*. 24–36 hours). Upon completion, the reaction was concentrated under reduced pressure to yield a brown solid which was suspended in MeOH (40 mL). The solids were isolated via suction filtration, washed with MeOH (3 x 50 mL), and dried *in vacuo* to yield (±)-tetracycle **23** as a tan crystalline solid (4.67 g, 62% yield).

(±)-Tetracycle 23:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 7.7 Hz, 1H), 7.03 (dq, *J* = 8.0, 1.0 Hz, 1H), 6.00 (dddd, *J* = 10.1, 5.8, 2.2, 1.0 Hz, 1H), 5.87 (dddd, *J* = 5.0, 2.4, 1.5, 0.6 Hz, 1H), 5.67 (dd, *J* = 7.7, 5.4 Hz, 1H), 5.61 (ddt, *J* = 10.1, 3.3, 1.2 Hz, 1H), 5.39 (t, *J* = 2.8 Hz, 1H), 5.15 (ddd, *J* = 8.0, 5.7, 1.1 Hz, 1H), 4.72 – 4.66 (m, 1H), 2.94 (ddd, *J* = 18.7, 13.3, 6.0 Hz,

1H), 2.86 (dt, J = 6.7, 3.4 Hz, 1H), 2.63 (ddt, J = 13.7, 5.8, 2.7 Hz, 1H), 2.47 (dddd, J = 18.1, 5.3, 2.4, 1.3 Hz, 1H), 2.00 (dddt, J = 18.5, 13.4, 9.9, 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 168.0, 130.8, 126.1, 123.3, 122.4, 121.2, 118.0, 109.7, 102.8, 53.7, 53.2, 36.9, 28.6, 19.5.

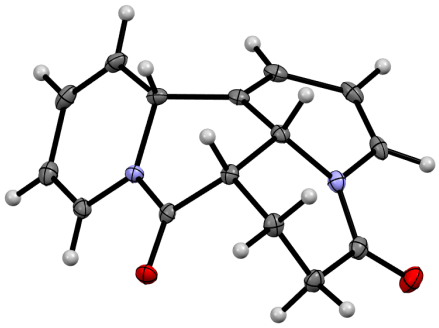
FTIR (NaCl, thin film): 3087, 2960, 2365, 1668, 1655, 1583, 1407, 1287, 1266, 1244, 1184, 733 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{14}N_2O_2$ $[M^{\bullet}]^+$ 254.1050, found 254.1038.

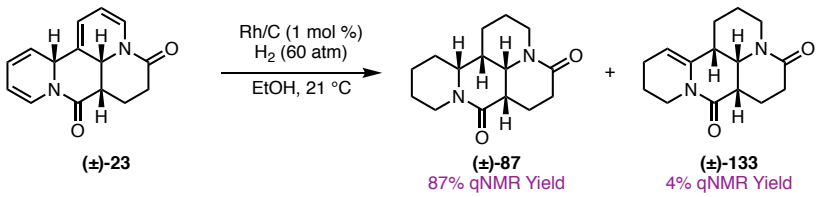
TLC (10% MeOH/90% PhH), **R_f:** 0.32 ($KMnO_4$).

M.P. 184.2 °C – 186.9 °C.

Figure 2.10. *X-Ray structure of (±)-**23**. CCDC number: 2159766*



Preparation of (±)-bis-amide 87:



A Parr Instrument Company pressure vessel (600 mL volume, model 4760) containing a 50 mm x 6 mm x 6 mm rectangular stir bar was charged with (±)-tetracycle **23**, (22.0 g, 39.7 mmol, 1.0 equiv), 5% rhodium on carbon (817 mg, 0.397 mmol, 1 mol %), and EtOH (200 mL, 0.4 M). The vessel was flushed with argon then pressurized and vented with H_2 (3 x 7 atm). The vessel was pressurized with H_2 to 60 atm and stirred at 1200 rpm at 21 °C for 20 hours. Upon completion, the reaction was carefully depressurized and filtered through celite that was subsequently washed with DCM. The solution was concentrated under reduced pressure to yield a yellow oil that solidified slowly on standing. (±)-Bis-amide **S1** was obtained as a pale yellow, crystalline solid and was used directly in the next step without additional purification. Purity was measured via ^{1}H qNMR against pyrazine as an internal standard. An analytically pure sample was prepared via SiO_2 column chromatography [1 g of crude material, 120 g SiO_2, 50 mm column diameter, 10% MeOH/90% ACN] to yield (±)-bis-amide **87** as a white crystalline solid.

(±)-Enamide **133** was produced in 4% qNMR yield (against pyrazine) during the reaction and an analytically pure sample was obtained via SiO_2 column chromatography of the crude reaction mixture [1 g of crude material, 120 g SiO_2, 50 mm column diameter, 10% MeOH/90% ACN] to yield (±)-enamide **133** as a white crystalline solid.

(±)-Bis-amide 87:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.81 (ddt, *J* = 12.8, 4.2, 2.1 Hz, 1H), 4.71 (dq, *J* = 12.3, 2.4, 1.4 Hz, 1H), 3.74 (dd, *J* = 7.6, 3.5 Hz, 1H), 3.39 (ddd, *J* = 12.5, 6.6, 2.4 Hz, 1H), 2.83 (qt, *J* = 4.1, 2.0 Hz, 1H), 2.64 (ddt, *J* = 13.1, 5.2, 2.7 Hz, 1H), 2.55 (td, *J* = 11.9, 3.3 Hz, 1H), 2.42 (td, *J* = 12.5, 2.3 Hz, 1H), 2.38 – 2.30 (m, 2H), 2.07 (ddd, *J* = 17.8, 14.2, 4.6 Hz,

1H), 1.92 (ddt, *J* = 15.1, 5.3, 2.9 Hz, 1H), 1.89 – 1.75 (m, 4H), 1.73 – 1.59 (m, 3H), 1.42 (qt, *J* = 12.4, 3.6 Hz, 1H), 1.37 – 1.25.

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 167.2, 61.5, 56.8, 45.6, 42.1, 38.1, 34.0, 32.1, 29.9, 26.1, 25.9, 25.1, 22.3, 21.6.

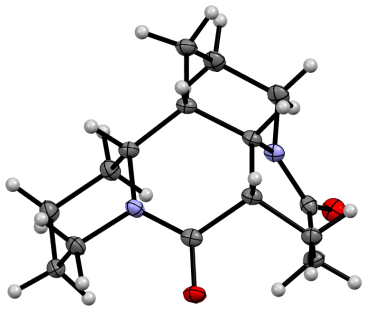
FTIR (NaCl, thin film): 2932, 2855, 1636, 1472, 750 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{22}N_2O_2Na$ $[M+Na]^+$ 285.1573, found 285.1573

TLC (15% MeOH/85% ACN), **R_f:** 0.26 ($KMnO_4$).

M.P. 147.1 °C – 150.5 °C.

Figure 2.11. *X-Ray structure of (±)-**87**. CCDC number:not publication quality.*



(±)-Enamide 133:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 (td, *J* = 4.1, 1.9 Hz, 1H), 4.76 (ddt, *J* = 13.3, 4.9, 1.9 Hz, 1H), 4.34 – 4.25 (m, 1H), 3.71 (dd, *J* = 6.1, 3.1 Hz, 1H), 3.21 (dddd, *J* = 13.1, 10.5, 3.2, 1.0 Hz, 1H), 2.92 (qd, *J* = 5.2, 4.6, 2.3 Hz, 1H), 2.65 (dh, *J* = 5.4, 2.7 Hz, 1H), 2.57 (dddd, *J* = 13.1, 5.4, 3.3, 2.2 Hz, 1H), 2.48 (td, *J* = 13.1, 3.5 Hz, 1H), 2.32 (ddtd, *J* = 17.5, 4.2, 2.1, 0.7 Hz, 1H), 2.23 (ddd, *J* = 16.9, 5.3, 2.8 Hz, 1H), 2.17 (dd, *J* = 13.9, 4.9 Hz, 1H),

2.11 (dddd, J = 9.5, 7.1, 6.1, 3.3 Hz, 2H), 1.91 – 1.79 (m, 2H), 1.79 – 1.63 (m, 4H), 1.53 (dq, J = 13.3, 3.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 166.8, 133.1, 106.8, 57.0, 42.3, 41.0, 39.8, 36.5, 29.4, 25.9, 22.6, 22.6, 21.6, 20.1.

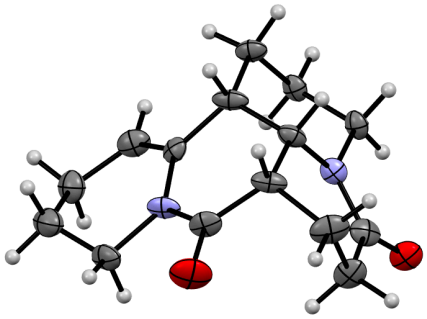
FTIR (NaCl, thin film): 3052, 2985, 2974, 2954, 2874, 1633, 1414, 1264 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$ 261.1603, found 261.1593.

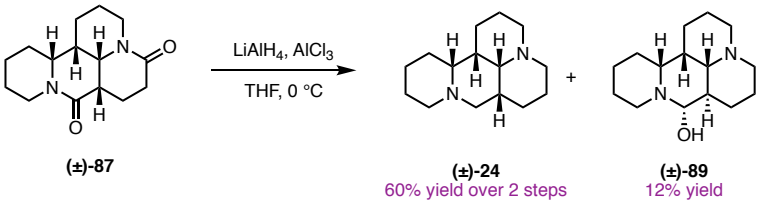
TLC (15% MeOH/85% ACN), **R_f:** 0.37 ($KMnO_4$).

M.P. 76.6 °C – 83.1 °C.

Figure 2.12. *X-Ray structure of (±)-**133**. CCDC number: not publication quality.*



Preparation of (±)-diamine 24:

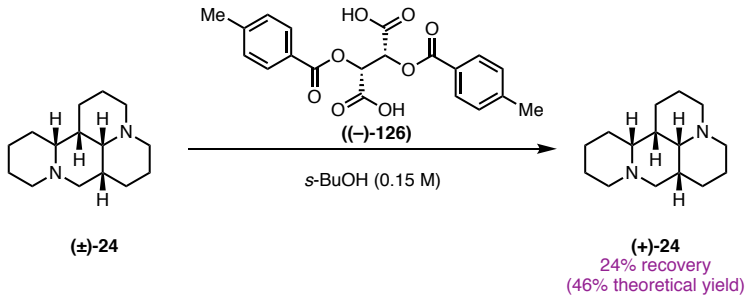


A 3 L oven-dried, N_2-flushed flask equipped with a thermocouple and a mechanical stirrer was charged with THF (856 mL, 0.1 M). The THF was cooled to 0 °C on an ice bath,

then $AlCl_3$ (29.7 g, 223 mmol, 2.6 equiv) was added in a single portion, causing the solution to heat up to 30 °C. Upon dissolution of $AlCl_3$, lithium aluminum hydride (25.6 g, 642 mmol, 7.5 equiv) was added in portions at such a rate as to keep the internal temperature below 21 °C. Upon completion of the addition (*ca*. 10 minutes), the reaction was allowed to stir for 30 minutes while cooling to 0 °C on an ice bath. A solution of unpurified (±)-bis-amide **87** (*ca.* 22.5 g, 85.6 mmol, 1.0 equiv) in THF (449 mL, 0.2 M) was added via cannula into the reaction flask at such a rate as to keep the internal temperature below 10 °C (*ca.* 30 minutes). Upon completion, the reaction was stirred for 1 hour at 0 °C. A 6 L Erlenmeyer flask in an ice bath was equipped with a mechanical stirrer and charged with ice (1500 g), water (500 mL), and Rochelle's salt (200 g). The reaction was quenched by addition via cannula into the ice slurry (*ca*. 10 minutes). Liquid nitrogen was periodically added to purge hydrogen gas from the Erlenmeyer flask. Upon completion of the quench, 3 M NaOH (1 L) was added to the reaction mixture, which was then stirred at 21 °C until the aluminum salts transformed from a grey sediment into a white slurry (*ca.* 30 minutes). The organic layer was separated, and the aqueous layer was extracted with DCM (5 x 400 mL). The combined organic layers were concentrated under reduced pressure without drying. To the crude residue was added enough 12 M HCl (*ca.* 20–30 mL) to make the mixture acidic followed by enough 3 M NaOH (*ca*. 200 mL) to make the mixture basic. The resulting milky white suspension was extracted with DCM (5 x 120 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in Et_2O (400 mL) and was concentrated under reduced pressure until crystallization of (±)-hemi-aminal **89** began. The mixture was diluted in Et_2O (total volume *ca.* 200–300 mL), and the solids

were isolated via suction filtration. The solids were washed with Et_2O (3 x 30 mL) to yield (±)-hemi-aminal **89** as a white crystalline solid (2.49 g, 12% yield). The filtrate was concentrated under reduced pressure to yield crude (±)-diamine **24** as a yellow oil, which was allowed to crystallize under vacuum (0.3 torr) on a Schlenk line (13.55 g). To crude (±)-diamine **24** was added anhydrous oxalic acid (6.76 g, 75.1 mmol, 1.0 equiv based on the mass of the obtained crude diamine) and MeOH (214 mL, 0.4 M). The mixture was heated to boiling, cooled to 21 °C, and concentrated under reduced pressure. The obtained solids were concentrated under reduced pressure from acetone (2 x 100 mL) and dried under vacuum (0.3 torr) on a Schlenk line on a warm water bath (40 °C). The solids were suspended in acetone with the aid of sonication and isolated by suction filtration. The solids were washed with acetone (3 x 60 mL) and dried by pulling air through. The obtained crystals were dissolved in water (100 mL) and made basic with 3 M NaOH (*ca*. 50 mL), and the aqueous layer was extracted with DCM (5 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was concentrated under reduced pressure from Et_2O (3 x 100 mL) and suction filtered to remove precipitates. The obtained solution was concentrated under reduced pressure and allowed to crystallize under vacuum (0.3 torr) on a Schlenk line to yield (±)-diamine **24** as a white crystalline solid (11.97 g, 60%).

Resolution of (+)-diamine 24



A 500 mL flask equipped with a 40 mm x 15 mm x 15 mm egg-shaped stir bar was charged with (±)-diamine **24** (11.97 g, 51.1 mmol, 1.0 equiv), (–)-di-*O,O'*-*p*-toluyl-L-tartaric acid (**126**) (19.7 g, 51.1 mmol, 1.0 equiv), and *s*-BuOH (341 mL, 0.15 M). The mixture was heated, with stirring, under N_2 until a homogenous solution was obtained. The mixture was cooled to 21 °C and stirred at 300 rpm. Crystallization progress was monitored by ^{1}H NMR. Aliquots of the supernatant (250 μL), obtained by stopping stirring and allowing the solids to settle out of solution (*ca.* 10 minutes), were concentrated under vacuum (0.3 torr) on a Schlenk line and then dissolved in $CDCl_3$. Crystallization was allowed to progress until 45% of diamine **24** had crystallized (*ca*. 25–45 hours), as measured relative to an aliquot taken before crystallization had begun. The crystals were isolated via suction filtration and washed with *s*-BuOH (3 x 20 mL) then acetone (1 x 20 mL). The obtained crystalline solid was transferred into a separatory funnel with water (500 mL) and DCM (100 mL). The suspension was made basic with 3 M NaOH (*ca.* 50 mL) and then the aqueous layer was extracted with DCM (4 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was concentrated under reduced pressure from Et_2O (3 x 50 mL), suction filtered, and concentrated under reduced pressure. The resolution procedure was repeated a second time on the obtained diamine **24** (*ca*. 50-70% ee) to yield enantioenriched

(+)-diamine **24** (2.82 g, 46% recovery of (+)-**24**, >90% ee) as a white to pale yellow crystalline solid. The optical activity of (+)-diamine **24** was assessed via ^{1}H NMR of its mono-(–)-di-*O,O'*-*p*-toluyl-L-tartaric acid salt (prepared in MeOH followed by concentration under vacuum (0.3 torr) on a Schlenk line for 30 minutes) in $CDCl_3$.

(+)-Diamine 24:

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.40 (t, *J* = 11.5 Hz, 1H), 3.01 – 2.91 (m, 2H), 2.83 (ddd, *J* = 12.4, 5.7, 2.8 Hz, 1H), 2.80 – 2.70 (m, 2H), 2.10 (qd, *J* = 13.5, 3.3 Hz, 1H), 2.04 (dd, *J* = 11.0, 4.2 Hz, 1H), 1.96 – 1.78 (m, 6H), 1.78 – 1.66 (m, 3H), 1.65 – 1.48 (m, 4H), 1.44 – 1.31 (m, 4H), 1.11 (d, *J* = 14.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 63.1, 61.1, 58.0, 57.7, 55.5, 46.1, 38.6, 36.9, 29.0, 27.0, 26.3, 24.3, 23.0, 22.4, 19.2.

FTIR (NaCl, thin film): 2922, 2848, 2806, 2765, 2745, 2693, 2674, 2612, 2550, 2442, 1441, 1353, 1165, 1122, 1091, 1054 cm^{-1}.

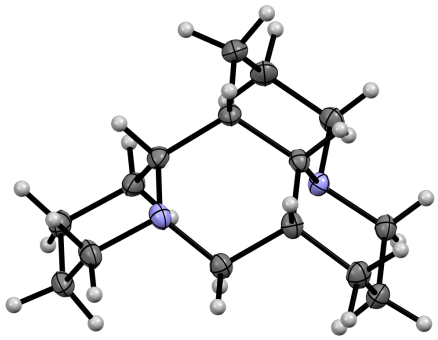
HRMS: (ESI-TOF) calc'd for $C_{15}H_{27}N_2$ $[M+H]^+$ 235.2169, found 235.2164.

TLC (40% 2 M NH_3 in MeOH/60% ACN), **R_f:** 0.37 ($KMnO_4$).

M.P. 64.1 °C – 66.7 °C.

Specific Optical Rotation: $[\alpha]\frac{21}{D} =$ +22.3 (c 1.0, $CHCl_3$).

Figure 2.13. *X-Ray structure of (+)-**24**. CCDC number: 2159767.*



(±)-Hemi-aminal 89:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.83 (d, *J* = 11.8 Hz, 1H), 3.72 (d, *J* = 11.3 Hz, 1H), 3.01 (dd, *J* = 11.4, 8.8 Hz, 1H), 2.95 – 2.85 (m, 3H), 2.66 (dd, *J* = 11.3, 4.3 Hz, 1H), 2.49 (dt, *J* = 10.6, 2.9 Hz, 1H), 2.28 (dq, *J* = 13.2, 3.5 Hz, 1H), 2.07 (dt, *J* = 10.8, 3.0 Hz, 1H), 1.99 (s, 1H), 1.87 (tdd, *J* = 11.9, 8.9, 3.6 Hz, 1H), 1.81 – 1.36 (m, 11H), 1.35 – 1.21 (m, 2H), 1.14 (tdd, *J* = 13.2, 11.5, 4.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 92.8, 63.2, 60.8, 54.2, 52.9, 45.9, 40.8, 33.9, 29.8, 29.1, 26.1, 25.0, 25.0, 19.8, 18.8.

FTIR (NaCl, thin film): 2941, 2861, 2832, 1456, 1436, 1118, 1032 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{27}N_2O$ $[M+H]^+$ 251.2123, found 251.2122.

TLC (40% 2 M NH_3 in MeOH/60% ACN), **R_f:** 0.35 ($KMnO_4$).

M.P. 149.5 °C – 151.1 °C.

Figure 2.14. *X-Ray structure of (±)-**89**. CCDC number: 2159770.*

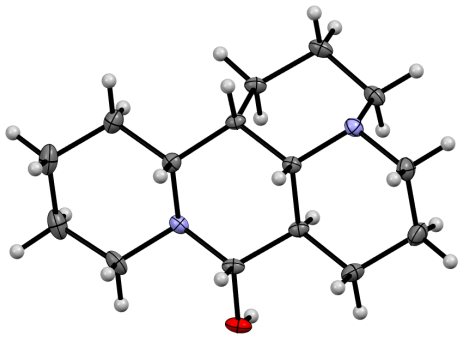


Figure 2.15. ^{1}H *NMR assay for determining enantiomeric excess.*

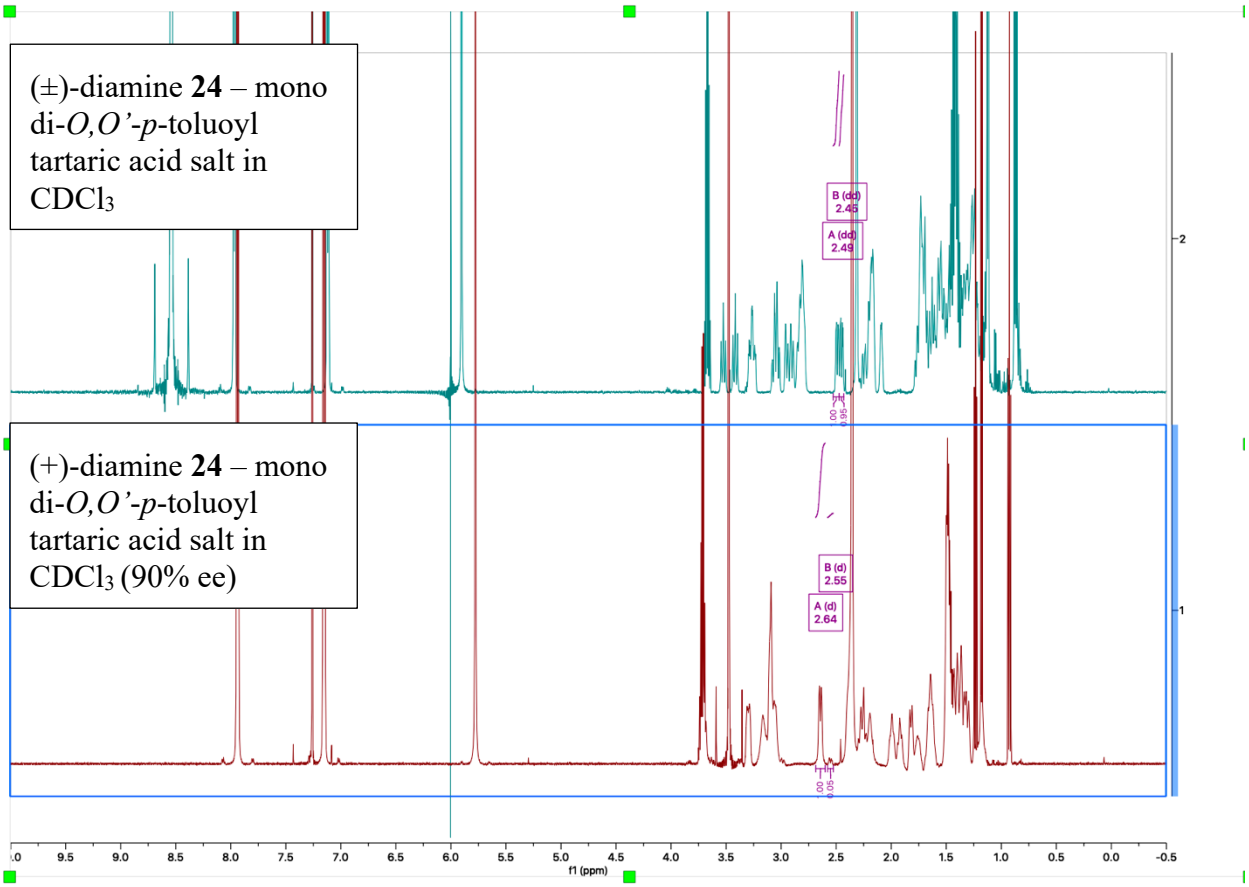
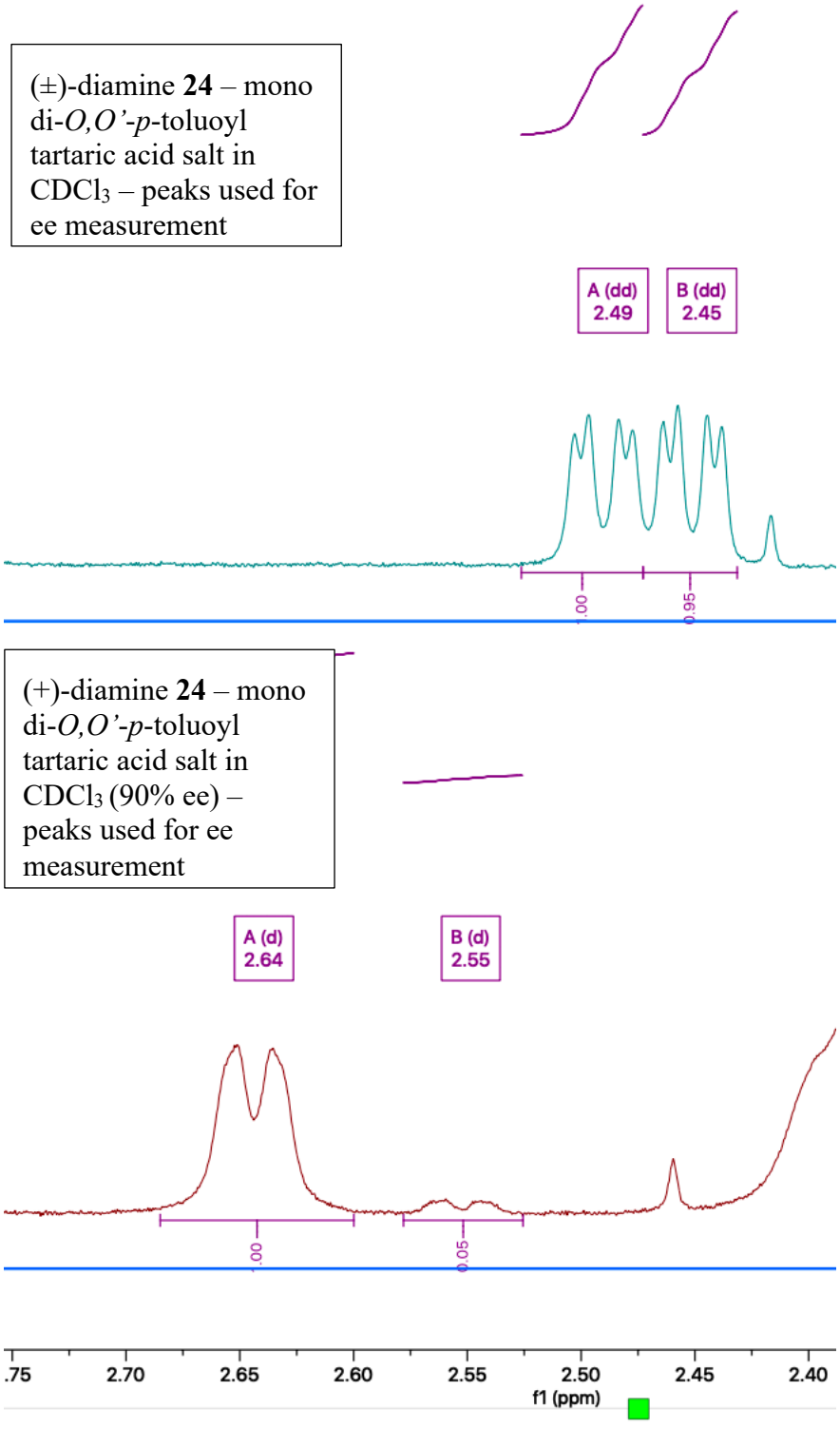
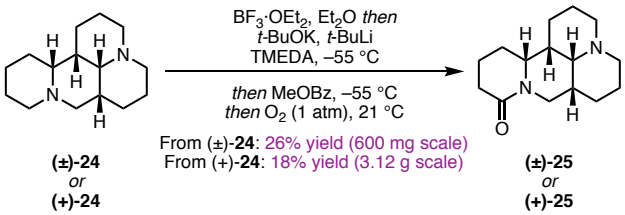


Figure 2.16. ^{1}H *NMR assay for determining enantiomeric excess close up.*



Preparation of (±)-isomatrine (25) and (+)-isomatrine (25):



Small scale racemic procedure:

A 250 mL oven-dried flask equipped with a 40 mm x 15 mm x 15 mm egg-shaped stir bar was charged with (±)-diamine **24** (600 mg, 2.56 mmol, 1.0 equiv), then the flask was evacuated and backfilled three times with N_2. Diethyl ether (2.6 mL, 1 M) was added, resulting in a clear, colorless solution. To the solution at 21 °C was added boron trifluoride diethyl etherate (319 uL, 2.59 mmol, 1.01 equiv). The resulting white slurry was stirred at 21 °C for five minutes followed by removal of the diethyl ether under vacuum (0.3 torr) on a Schlenk line; the solids were allowed to dry for an additional 30 minutes. After backfilling the flask with N_2, a thermocouple was introduced into the flask through the rubber septum. The flask was cooled to –60 °C and maintained at this temperature using an acetone/dry ice bath. A solution of potassium *tert*-butoxide (1.72 g, 15.4 mmol, 6.0 equiv) in tetramethylethylenediamine (TMEDA) (12.8 mL, 0.2 M), prepared by dissolving potassium *tert*-butoxide in TMEDA in an inert atmosphere followed by clarification of the suspension via syringe filtration, was added via syringe, allowing the solution to flow down the side of the flask to pre-cool it before it encountered the solids. To the resulting suspension between –55 °C to –60 °C was added *tert*-butyl lithium (1.6 M in pentane, 4.8 mL, 7.68 mmol, 3.0 equiv) via syringe at such a rate as to prevent the internal reaction temperature from increasing above –40 °C (*ca.* 2 to 4 minutes). Once the addition was

complete, the reaction was stirred for 30 minutes at –55 °C to –60 °C. Subsequently, a solution of methyl benzoate (2.56 mL, 20.5 mmol, 8.0 equiv) in cyclopentyl methyl ether (10.2 mL, 0.25 M) was added at such a rate as to prevent the internal reaction temperature from increasing above –40 °C (*ca*. 4 to 8 minutes). Once the addition was complete, the reaction was allowed to stir at –55 °C to –60 °C for 30 minutes, then methanol (311 uL, 7.68 mmol, 3.0 equiv) was added. The thermocouple was removed, and the rubber septum was replaced with a new rubber septum. **Caution!** Traces of solid *tert*-butyl lithium tend to get stuck on the inside of the rubber septum, and it should be replaced before oxygen is introduced into the flask. The flask was purged with O_2 (balloon) at –55 °C and then allowed to warm to 21 °C. The resulting orange suspension was stirred vigorously (1500 rpm) for 2 hours. Upon completion, the yellow suspension was diluted in water (50 mL) and treated with sat. aq. $Na_2S_2O_3$ (15 mL) and 3 M NaOH (15 mL). The reaction mixture was extracted with DCM (4 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via SiO_2 column chromatography (30 g SiO_2, 30 mm column diameter, 3% 2 M NH_3 in MeOH/97% $CHCl_3$ containing 0.75% EtOH as a stabilizer). The obtained product underwent a final purification by crystallization from boiling hexanes (*ca*. 5 mL). After dissolution in boiling hexanes, the solution was allowed to slowly cool to 21 °C then –20 °C. The supernatant was decanted and the crystals washed with cold hexanes (3 x 1 mL). The obtained crystals were dried *in vacuo* to yield (±)-isomatrine (**25**) as white crystalline needles (167 mg, 26% yield).

Large Scale Enantiopure Procedure:

A 1 L oven-dried, N_2-flushed flask equipped with a 40 mm x 15 mm x 15 mm egg-shaped stir bar was charged with (+)-diamine **24** (3.12 g, 13.3 mmol, 1.0 equiv), then the flask was evacuated and backfilled three times with N_2. Diethyl ether (14 mL, 1 M) was added, which created a clear pale yellow solution. To the solution at 21 °C was added boron trifluoride diethyl etherate (1.66 mL, 13.4 mmol, 1.01 equiv). The resulting white slurry was stirred at 21 °C for five minutes followed by removal of the diethyl ether under vacuum (0.3 torr) on a Schlenk line; the solids were allowed to dry for an additional 30 minutes. After backfilling the flask with N_2, a thermocouple was introduced into the flask through the rubber septum. The flask was cooled to –60 °C and maintained at this temperature using an acetone/dry ice bath. A solution of potassium *tert*-butoxide (8.96 g, 79.9 mmol, 6.0 equiv) in TMEDA (67 mL, 0.2 M), prepared by dissolving potassium *tert*-butoxide in TMEDA in an inert atmosphere followed by clarification of the suspension via syringe filtration, was added via syringe, allowing the solution to flow down the side of the flask to pre-cool it before it encountered the solids. To the resulting suspension at –55 °C to –60 °C was added *tert*-butyl lithium (1.6 M in pentane, 25 mL, 39.9 mmol, 3.0 equiv) via cannula at such a rate as to prevent the reaction temperature from increasing above –40 °C (*ca.* 5 to 10 minutes). Once the addition was complete, the reaction was stirred for 30 minutes at –55 °C to –60 °C. Subsequently, a solution of methyl benzoate (13.3 mL, 106 mmol, 8.0 equiv) in cyclopentyl methyl ether (53 mL, 0.25 M) was added at such a rate as to prevent the reaction temperature from increasing above –40 °C (*ca*. 5 to 12 minutes). Once the addition was complete, the reaction was allowed to stir at –55 °C for 30 minutes, then methanol (1.62 mL, 39.9 mmol, 3.0 equiv) was added. The thermocouple was removed, and the rubber septum was replaced with a new rubber septum. **Caution!** Traces

of solid *tert*-butyl lithium tend to get stuck on the inside of the rubber septum, and it should be replaced before oxygen is introduced. The flask was purged with O_2 (balloon) at –55 °C then was allowed to warm to 21 °C. The resulting orange suspension was stirred vigorously (1500 rpm) for 2 hours. Upon completion, the yellow suspension was diluted in water (150 mL) and treated with sat. aq. $Na_2S_2O_3$ (50 mL) and 3 M NaOH (50 mL). The reaction mixture was extracted with DCM (4 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via SiO_2 column chromatography (120 g SiO_2, 50 mm column diameter, eluting with 3% 2 M NH_3 in MeOH/97% $CHCl_3$ containing 0.75% EtOH as a stabilizer). The product underwent a final purification by crystallization from boiling hexanes (*ca*. 15 mL). After dissolution in boiling hexanes, the solution was allowed to slowly cool to 21 °C then to –20 °C. The supernatant was decanted and the crystals washed with cold hexanes (3 x 2 mL). The obtained crystals were dried *in vacuo* to yield (+)-isomatrine (**25**) as white crystalline needles (589 mg, 18% yield, >99% ee). An X-ray structure was acquired directly from the obtained crystals.

(+)-Isomatrine (25):

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.77 (p, *J* = 4.4 Hz, 1H), 3.62 (t, *J* = 13.0 Hz, 1H), 3.52 (dd, *J* = 12.8, 4.1 Hz, 1H), 2.71 (d, *J* = 9.2 Hz, 1H), 2.67 (td, *J* = 11.2, 2.6 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.35 – 2.26 (m, 2H), 2.22 – 2.15 (m, 1H), 2.05 (dt, *J* = 11.5, 8.0 Hz, 1H), 1.99 – 1.90 (m, 2H), 1.90 – 1.81 (m, 2H), 1.75 – 1.59 (m, 5H), 1.56 (dt, *J* = 13.4, 5.4 Hz, 1H), 1.53 – 1.47 (m, 1H), 1.47 – 1.36 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 61.3, 55.9, 52.8, 52.1, 43.2, 39.3, 32.8, 30.8, 27.4, 26.8, 21.6, 21.4, 20.3, 18.2.

FTIR (NaCl, thin film): 2983, 2952, 2887, 2795, 2684, 1618, 1421, 1276, 1265, 1170 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{15}H_{24}N_2O$ $[M]^+$ 248.1883, found 248.1886.

TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), **R_f:** 0.36 ($KMnO_4$).

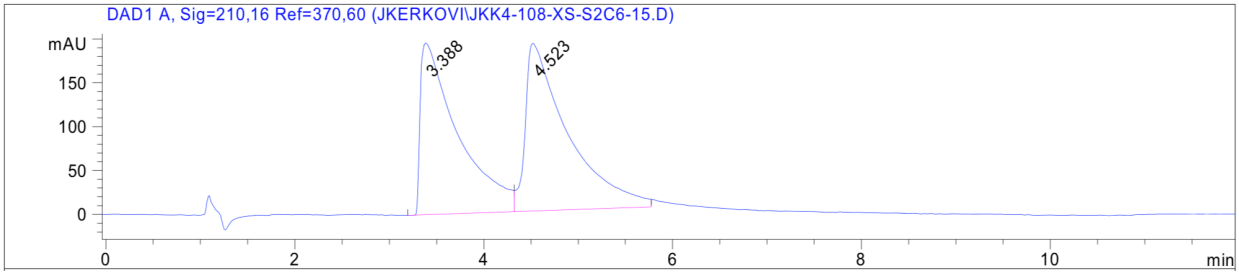
M.P. 99.1 °C – 100.3 °C.

Specific Optical Rotation: $[\alpha]\frac{21}{D} = +35.5$ (c 1.0, $CHCl_3$).

Literature Specific Optical Rotation: $[\alpha]\frac{21}{D} = +44$ (c 1.0, $CHCl_3$).[14]

Chiral SFC: (OB-H, 2.5 mL/min, 15% IPA in CO_2, λ = 210 nm): t_R (major) = 3.388 min, t_R (minor) = 4.523 min.

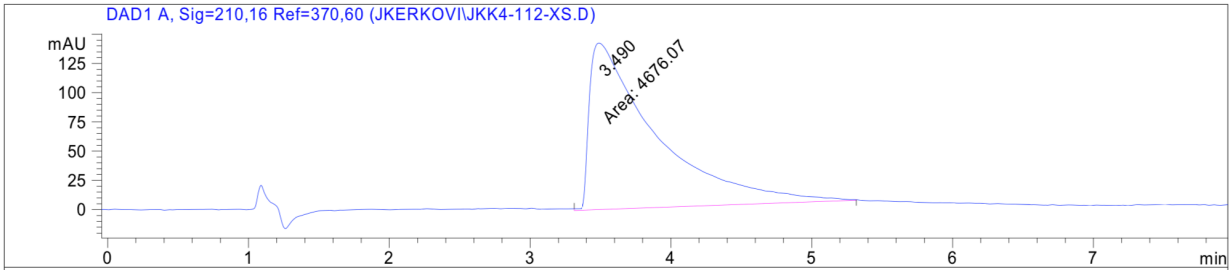
Figure 2.17. *SFC trace of racemic isomatrine.*



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.388	BV	0.3695	5387.90967	195.53056	47.3900
2	4.523	VB	0.4174	5981.39648	190.98810	52.6100

Figure 2.18. *SFC trace of enantiopure isomatrine.*



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.490	MM	0.5466	4676.07227	142.58051	100.0000

Figure 2.19. *X-Ray structure of (+)-isomatrine ((+)-**25**). CCDC number: 2159771.*

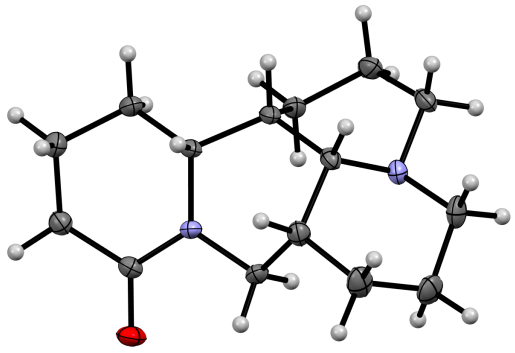
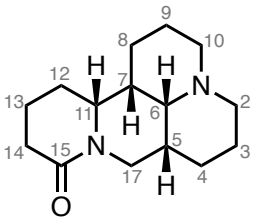


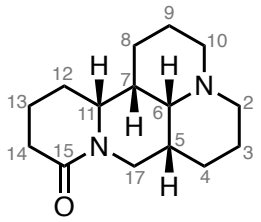
Table 2.13. *^{1}H NMR data for authentic vs synthetic (+)-isomatrine.*

The X-ray structure of (+)-isomatrine has been previously published.[13]



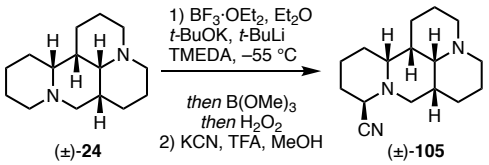
Isomatrine Literature ^{1}H δ ppm (220 MHz, $CDCl_3$)[13]	Isomatrine Recorded ^{1}H δ ppm (600 MHz, $CDCl_3$)
3.78 (m, 1H)	3.77, (p, *J* = 4.4 Hz, 1H)
3.63 (dd, *J* = 13.5, 12.8 Hz, 1 H)	3.62 (t, *J* = 13.0 Hz, 1H)
3.51 (dd, 13.5, 4.6 Hz, 1H)	3.52 (dd, *J* = 12.8, 4.1 Hz, 1H)
2.93 – 2.64 (m, 2H)	2.71 (d, *J* = 9.2 Hz, 1H)
	2.67 (td, *J* = 11.2, 2.6 Hz, 1H)
2.50 – 1.30 (m, 19H)	2.45 – 2.39 (m, 1H)
	2.35 – 2.26 (m, 2H)
	2.22 – 2.15 (m, 1H)
	2.05 (dt, *J* = 11.5, 8.0 Hz, 1H)
	1.99 – 1.90 (m, 2H)
	1.90 – 1.81 (m, 2H)
	1.75 – 1.59 (m, 5H)
	1.56 (dt, *J* = 13.4, 5.4 Hz, 1H)
	1.53 – 1.45 (m, 1H)
	1.45 – 1.36 (m, 3H)

Table 2.14. *^{13}C NMR data for authentic vs synthetic (+)-isomatrine.*



Carbon No. isomatrine	Isomatrine Literature ^{13}C δ ppm (75 MHz, $CDCl_3$)[13]	Isomatrine Recorded ^{13}C δ ppm (101 MHz, $CDCl_3$)	Δ δ
2	55.7	55.9	0.2
3	21.2	21.4	0.2
4	21.2	21.6	0.3
5	30.6	30.8	0.2
6	61.0	61.3	0.3
7	39.1	39.3	0.2
8	26.7	26.8	0.1
9	20.2	20.3	0.1
10	51.9	52.1	0.2
11	52.6	52.8	0.2
12	27.1	27.4	0.3
13	18.2	18.2	0.0
14	32.6	32.8	0.2
15	170.4	170.6	0.2
17	43.1	43.2	0.1

Preparation of (±)-aminonitrile 105:



A 50 mL flask was charged with (±)-diamine **24** (200 mg, 0.66 mmol, 1.0 equiv). The flask was evacuated and backfilled three times with N_2. Diethyl ether (0.9 mL, 1 M) was added, resulting in a clear, colorless solution. To the solution at 21 °C was added boron trifluoride diethyl etherate (106 uL, 0.86 mmol, 1.01 equiv). The resulting white suspension was stirred at 21 °C for five minutes followed by removal of the diethyl ether under vacuum (0.3 torr) on a Schlenk line; the solids were allowed to dry for an additional 30 minutes. The flask was backfilled with N_2, and a thermocouple was introduced into the flask through the septum. The flask was cooled to –60 °C and maintained at this temperature using an acetone/dry ice bath. A solution of potassium *tert*-butoxide (446 mg, 3.97 mmol, 6.0 equiv) in TMEDA (3.3 mL, 0.2 M), prepared by dissolving potassium *tert*-butoxide in TMEDA in an inert atmosphere followed by clarification of the suspension via syringe filtration, was added via syringe by allowing the solution to flow down the side of the flask to pre-cool it before it encountered the solids. To the resulting suspension at –55 °C to –60 °C was added *tert*-butyl lithium (1.6 M in pentane, 1.24 mL, 1.99 mmol, 3.0 equiv) via syringe at such a rate as to prevent the reaction temperature from increasing above –40 °C (*ca.* 1 to 2 minutes). Once the addition was complete, the reaction was stirred for 30 minutes at –55 °C to –60 °C. After 30 minutes, trimethylborate (0.59 mL, 5.29 mmol, 8.0 equiv) was added at such a rate as to prevent the reaction temperature from increasing above –40 °C

(*ca*. 5 to 8 minutes). Once the addition was complete, the reaction was allowed to stir at –55 °C for 30 minutes. Subsequently, 30% aqueous hydrogen peroxide (0.68 mL, 6.62 mmol, 10.0 equiv) was added at –55 °C, then the reaction was allowed to warm to 21 °C and stir for one hour. After one hour, the reaction was treated with 3 M NaOH (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield a yellow oil. A 25 mL flask was charged with the crude reaction mixture, potassium cyanide (302 mg, 4.63 mmol, 7.0 equiv), and methanol (6.6 mL, 0.1 M). The flask was capped with a rubber septum, and trifluoroacetic acid (1.0 mL, 13.2 mmol, 20.0 equiv) was added (**Caution!** HCN vapors are produced!) The reaction was stirred until complete consumption of the starting material, as judged by TLC (*ca*. 2 hours). Upon completion, the reaction was quenched with 3 M NaOH (50 mL). The aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction was purified via SiO_2 column chromatography (20 g SiO_2, 20 mm column diameter, 4% 2 M NH_3 in MeOH/96% $CHCl_3$ containing 0.75% EtOH) to yield (±)-aminonitrile **105** as a white crystalline solid (94.5 mg, 55% yield). X-ray-quality crystals were grown by allowing a solution of (±)-aminonitrile **105** in diethyl ether to slowly evaporate at 21 °C.

(±)-Aminonitrile 105:

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.93 (dt, *J* = 3.5, 1.7 Hz, 1H), 3.34 (dd, *J* = 11.9, 10.6 Hz, 1H), 3.19 (ddd, *J* = 12.5, 5.6, 2.9 Hz, 1H), 2.73 (ddd, *J* = 9.3, 7.4, 4.9 Hz, 2H), 2.10 (qd, *J* = 13.1, 4.1 Hz, 1H), 2.03 (dd, *J* = 10.5, 4.3 Hz, 1H), 1.97 (dt, *J* = 13.7, 4.5 Hz, 1H), 1.94 –

1.90 (m, 2H), 1.90 – 1.83 (m, 2H), 1.82 – 1.71 (m, 3H), 1.70 – 1.58 (m, 3H), 1.53 (dt, J = 12.9, 4.5 Hz, 2H), 1.49 (h, J = 1.4 Hz, 1H), 1.48 – 1.45 (m, 1H), 1.45 – 1.38 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 120.0, 62.8, 57.8, 57.6, 57.1, 54.7, 46.9, 38.0, 36.4, 28.6, 26.7, 23.5, 22.9, 22.3, 22.2, 21.8.

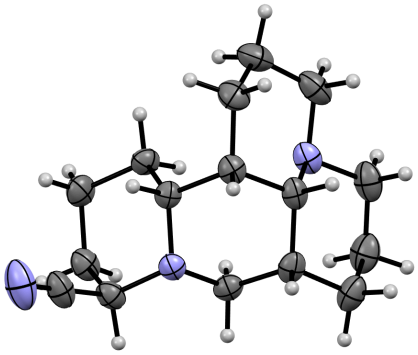
FTIR (NaCl, thin film): 2928, 2858, 2804, 2762, 2676, 2240, 1462, 1359, 1123 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{26}N_3$ $[M+H]^+$ 260.2121, found 260.2122.

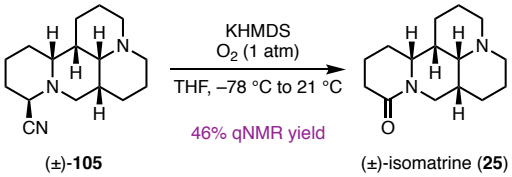
TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ containing 0.75% EtOH), **R_f:** 0.42 ($KMnO_4$).

M.P. 134.5 – 138.3 °C.

Table 2.20. *X-Ray structure of (±)-**105**. CCDC number: 2159774.*



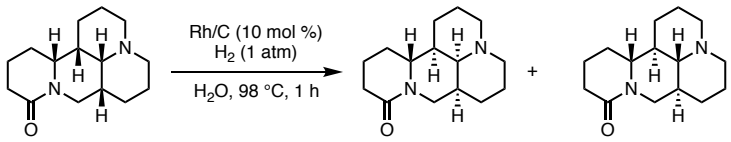
Preparation of (±)-isomatrine (25) from (±)-aminonitrile 105:



An oven-dried, N_2-flushed 10 mL flask was charged with (±)-aminonitrile **105** (20 mg, 77 μmol, 1.0 equiv), and THF (0.77 mL, 0.1 M). The solution was cooled to –78 °C,

then potassium hexamethyldisilazide (0.5 M in PhMe, 278 µL, 139 µmol, 1.8 equiv) was added dropwise. The yellow solution was stirred at –78 °C for 30 minutes, then the flask was purged with dry O_2 (balloon) at –78 °C. The solution was stirred vigorously (1500 rpm) and was allowed to warm to 21 °C then stirred for an additional 30 minutes. Upon completion, the reaction was treated with 3 M NaOH (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with DCM (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The yield of (±)-isomatrine (**25**) was measured by ^{1}H qNMR (46% yield, pyazine internal standard).

Preparation of (+)-matrine (26):



(+)-isomatrine **25**

(+)-matrine **26** 32% yield

(+)-allomatrine **27** 60% yield

A 50 mL flask with a 20 mm x 8 mm x 8 mm egg-shaped stir bar was charged with (+)-isomatrine (50.0 mg, 201 µmol, 1.0 equiv), 5% rhodium on carbon (41.4 mg, 20.1 µmol, 10 mol %), and water (5 mL, 0.04 M). The reaction was purged with N_2 (balloon) followed by H_2 (balloon). The reaction was not stirred during the gas purge. Once the flask was under an atmosphere of H_2, it was placed into a preheated oil bath at 98 °C, and the mixture was stirred at 1500 rpm for 1 hour. Upon completion, the flask was removed from the oil bath and cooled to 21 °C. The catalyst was removed via filtration through a syringe filter, then the filter was washed with water (3 x 5 mL). The obtained aqueous solution was concentrated under reduced pressure. The crude product was purified by SiO_2 column

chromatography (20 g SiO_2, 20 mm column diameter, 3% 2 M NH_3 in MeOH/97% $CHCl_3$ containing 0.75% EtOH as a stabilizer) to yield (+)-matrine (**26**) as a white crystalline solid (16.1 mg, 32% yield) along with (+)-allomatrine (**27**) as a white crystalline solid (29.8 mg, 60% yield).

(+)-Matrine (26):

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.40 (dd, *J* = 12.8, 4.4 Hz, 1H), 3.81 (td, *J* = 9.8, 5.8 Hz, 1H), 3.04 (t, *J* = 12.7 Hz, 1H), 2.83 (ddt, *J* = 11.4, 4.3, 2.2 Hz, 1H), 2.78 (dp, *J* = 11.6, 2.1 Hz, 1H), 2.42 (dtd, *J* = 17.1, 4.7, 1.8 Hz, 1H), 2.24 (ddd, *J* = 16.9, 11.0, 5.5 Hz, 1H), 2.12 – 2.04 (m, 2H), 1.99 – 1.91 (m, 2H), 1.89 (dt, *J* = 14.3, 2.5 Hz, 1H), 1.84 – 1.77 (m, 1H), 1.77 – 1.55 (m, 5H), 1.51 (tt, *J* = 13.6, 4.9 Hz, 1H), 1.47 – 1.34 (m, 5H).

^{1}H NMR (600 MHz, C_6D_6): δ 4.76 (dd, *J* = 12.5, 4.4 Hz, 1H), 3.57 (q, *J* = 7.8 Hz, 1H), 3.05 (t, *J* = 12.6 Hz, 1H), 2.58 (d, *J* = 10.9 Hz, 1H), 2.52 (d, *J* = 11.3 Hz, 1H), 2.39 (dtd, *J* = 16.8, 4.7, 1.9 Hz, 1H), 2.09 (ddd, *J* = 16.6, 10.9, 5.5 Hz, 1H), 1.74 – 1.61 (m, 3H), 1.61 – 1.45 (m, 4H), 1.45 – 1.31 (m, 2H), 1.33 – 1.19 (m, 2H), 1.18 – 0.97 (m, 5H), 0.88 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 63.9, 57.5, 57.4, 53.3, 43.4, 41.6, 35.5, 33.0, 27.9, 27.3, 26.6, 21.3, 20.9, 19.2.

^{13}C NMR (101 MHz, C_6D_6): δ 168.0, 63.9, 57.5, 57.5 53.0, 43.5, 41.6, 35.9, 33.3, 28.2, 27.3, 26.7, 21.5, 21.0, 19.3.

FTIR (NaCl, thin film): 2985, 2944, 2683, 1624, 1464, 1420, 1263, 1168 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{25}N_2O$ $[M+H]^+$ 249.1961, found 249.1961.

TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), **R*f*:** 0.46 ($KMnO_4$).

M.P. 69.6 – 71.4 °C.

Specific Optical Rotation: $[\alpha]\frac{21}{D} = +42.8$ (c 1.0, $CHCl_3$).

Literature Specific Optical Rotation: $[\alpha]\frac{21}{D} = +38$ (c 1.0, H_2O).[14]

Figure 2.21. *X-Ray structure of the monohydrate of (+)-matrine ((+)-**26**). CCDC number: not publication quality.*

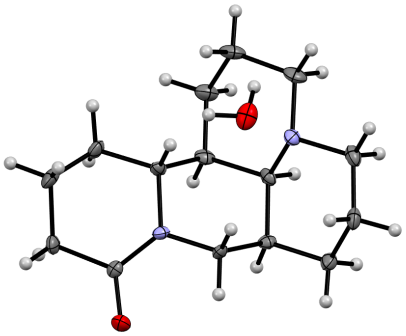
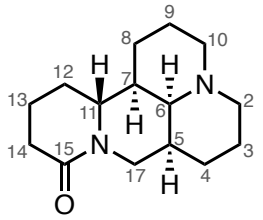


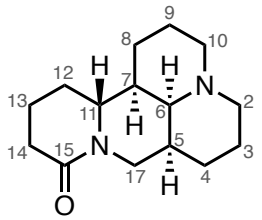
Table 2.15. *^{1}H NMR data for authentic vs synthetic (+)-matrine.*

The X-ray structure of matrine has been previously published (CCDC: 1209643).[40]



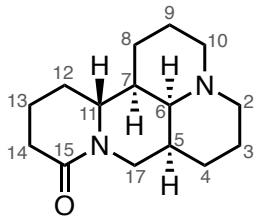
Matrine Literature ^{1}H δ ppm (400 MHz, $CDCl_3$)[41]	Matrine Recorded ^{1}H δ ppm (600 MHz $CDCl_3$)
4.40 (dd, *J* = 12.7, 4.3 Hz, 1H)	4.40 (dd, *J* = 12.8, 4.4 Hz, 1H)
3.82 (dt, *J* = 10.1, 7.7 Hz, 1H)	3.81 (td, *J* = 9.8, 5.8 Hz, 1H)
3.05 (t, *J* = 12.7 Hz, 1H)	3.04 (t, *J* = 12.7 Hz, 1H)
2.80 (m, 2H)	2.83 (ddt, *J* = 11.4, 4.3, 2.2 Hz, 1H)
	2.78 (dp, *J* = 11.6, 2.1 Hz)
2.43 (m, 1H)	2.42 (dtd, *J* = 17.1, 4.7, 1.8 Hz, 1H)
2.25 (m, 1H)	2.24 (ddd, *J* = 16.9, 11.0, 5.5 Hz, 1H)
2.09 (m, 3H)	2.12 – 2.04 (m, 2H)
	1.99 – 1.91 (m, 2H)
1.94 (m, 4H)	1.89 (dt, *J* = 17.1, 4.7, 1.8 Hz, 1H)
1.87 (m, 1H)	1.84 – 1.77 (m, 1H)
1.85 – 1.50 (m, 9H)	1.77 – 1.55 (m, 5 H)
	1.51 (tt, *J* = 13.6, 4.9 Hz, 1H)
	1.47 – 1.34 (m, 5H)

Table 2.16. *^{13}C NMR data for authentic vs synthetic (+)-matrine.*



Carbon No. matrine	Matrine Literature ^{13}C δ ppm (101 MHz, $CDCl_3$)	Matrine Recorded ^{13}C δ ppm (101 MHz, $CDCl_3$)	Δ δ
2	57.6	57.5	–0.1
3	21.4	21.3	–0.1
4	27.9	27.9	0.0
5	35.6	35.5	–0.1
6	64.0	63.9	–0.1
7	43.4	43.4	0.0
8	26.6	26.6	0.0
9	21.0	20.9	–0.1
10	57.4	57.4	0.0
11	53.4	53.3	–0.1
12	27.4	27.3	–0.1
13	19.2	19.2	0.0
14	33.0	33.0	0.0
15	169.7	169.5	–0.2
17	41.7	41.6	–0.1

Table 2.17. *^{1}H NMR data for authentic vs synthetic (+)-matrine in C_6D_6.*

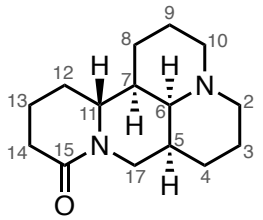


Matrine Literature ^{1}H δ ppm (500 MHz, C_6D_6)[42*]	Matrine Recorded ^{1}H δ ppm (600 MHz, C_6D_6)
4.73 (dd, *J* = 12.6, 4.4 Hz, 1H)	4.76 (dd, *J* = 12.5, 4.4 Hz, 1H)
3.57 (ddd, *J* = 9.5, 9.2, 5.8 Hz, 1H)	3.57 (q, *J* = 7.8 Hz, 1H)
3.03 (dd, *J* = 12.6, 12.4 Hz, 1H)	3.05 (t, *J* = 12.6 Hz, 1H)
2.57 (ddd, *J* = 11.1, 4.2, 2.1 Hz, 1H)	2.58 (d, *J* = 10.9 Hz, 1H)
2.52 (dd, *J* = 11.0, 4.0, 2.1 Hz, 1H)	2.52 (d, *J* = 11.3 Hz, 1H)
2.38 (ddd, *J* = 17.0, 4.8, 2.0 Hz, 1H)	2.39 (dtd, *J* = 16.8, 4.7, 1.9 Hz, 1H)
2.08 (dd, *J* = 17.0, 10.7, 5.5 Hz, 1H)	2.09 (ddd, *J* = 16.6, 10.9, 5.5 Hz, 1H)
1.71 (m, 1H)	1.74 – 1.61 (m, 3H)
1.70 (ddd, *J* = 11.9, 11.1, 2.8, 1H)	
1.67 (ddd, *J* = 12.9, 11.0, 2.8 Hz, 1H)	
1.55 (dddt, *J* = 13.6, 13.3, 12.9, 4.0 4.0 Hz, 1H)	1.61 – 1.45 (m, 4H)
1.50 (d, *J* = 11.4 Hz, 1H)	
1.49 (ddd, *J* = 12.4, 4.9, 4.4 Hz, 1H)	
1.49 (m, 1H)	
1.42 (d, *J* = 13.7 Hz, 1H)	1.45 – 1.31 (m, 2H)
1.36 (dtt, *J* = 12.7, 11.9, 4.3, 4.2 Hz, 1H)	
1.28 (d, *J* = 12.7 Hz, 1H)	1.33 – 1.19 (m, 2H)
1.22 (dddd, *J* = 13.7, 13.6, 4.9, 4.7 Hz, 1H)	

1.13 (ddddd, J = 13.4, 12.7, 10.7, 4.8, 3.0 Hz, 1H)	1.18 – 0.97 (m, 5H)
1.09 (d, J = 13.3 Hz, 1H)	
1.07 (d, J = 12.7 Hz, 1H)	
1.02 (m, 1H)	
1.02 (m, 1H)	
0.88 (dddd, J = 13.4, 11.4, 9.2, 3.2 Hz, 1H)	0.88 (q, J = 11.6 Hz, 1H)

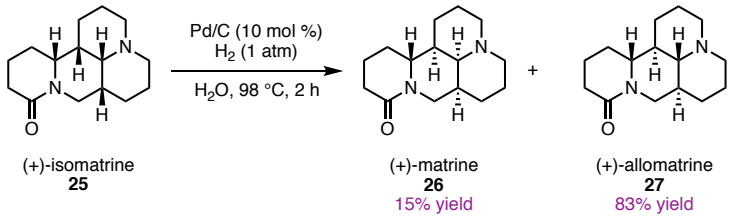
*The literature report of the ^{1}H NMR of matrine in C_6D_6 utilized HMQC, HMQC-TOCSY, and MAXY to measure the coupling constants of overlapping multiplets.

Table 2.18. *^{13}C NMR data for authentic vs synthetic (+)-matrine in C_6D_6.*



Carbon No. matrine	Matrine Literature ^{13}C δ ppm (126 MHz, C_6D_6)	Matrine Recorded ^{13}C δ ppm (101 MHz, C_6D_6)	Δ δ
2	57.0	57.5	0.5
3	21.0	21.5	0.5
4	27.7	28.2	0.5
5	35.4	35.9	0.5
6	63.4	63.9	0.5
7	43.0	43.5	0.5
8	26.2	26.7	0.5
9	20.5	21.0	0.5
10	57.0	57.5	0.5
11	52.5	53.0	0.5
12	26.7	26.7	0.0
13	18.8	19.3	0.5
14	32.8	33.3	0.5
15	167.6	168.0	0.4
17	41.1	41.6	0.5

Preparation of (+)-allomatrine (27):



A 50 mL flask with a 20 mm x 8 mm x 8 mm egg-shaped stir bar was charged with (+)-isomatrine (50.0 mg, 201 μmol, 1.0 equiv), 10% palladium on carbon (21.4 mg, 20.1 μmol, 10 mol %), and water (5 mL, 0.04 M). The reaction was purged with N_2 (balloon) followed by H_2 (balloon). The reaction was not stirred during the gas purge. Once the flask was under an atmosphere of H_2, it was placed into a preheated oil bath at 98 °C, and the mixture was stirred at 1500 rpm for 2 hours. Upon completion, the flask was removed from the oil bath and cooled to 21 °C. The catalyst was removed via filtration through a syringe filter, then the filter was washed with water (3 x 5 mL). The obtained aqueous solution was concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (20 g SiO_2, 20 mm column diameter, 3% 2 M NH_3 in MeOH/97% $CHCl_3$ containing 0.75% EtOH as a stabilizer) to yield (+)-allomatrine (**27**) as a white crystalline solid (41.5 mg, 83% yield) along with (+)-matrine (**26**) as a white crystalline solid (7.3 mg, 15% yield).

(+)-Allomatrine (27):

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.68 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.98 (td, *J* = 9.5, 5.4 Hz, 1H), 2.87 – 2.77 (m, 2H), 2.40 (dtd, *J* = 17.3, 4.6, 1.9 Hz, 1H), 2.26 (ddd, *J* = 17.1, 11.3, 5.6 Hz, 1H), 2.15 (t, *J* = 12.4 Hz, 1H), 2.06 (dtt, *J* = 13.6, 5.4, 2.5 Hz, 1H), 2.00 – 1.90 (m,

2H), 1.86 – 1.77 (m, 2H), 1.73 – 1.61 (m, 5H), 1.57 (dddd, J = 23.5, 11.9, 4.8, 2.8 Hz, 1H), 1.49 – 1.37 (m, 2H), 1.42 – 1.36 (m, 1H), 1.32 (t, J = 9.6 Hz, 1H), 1.27 – 1.19 (m, 1H), 0.98 – 0.82 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): 169.3, 70.8, 60.3, 56.6, 55.9, 46.3, 46.2, 39.1, 32.9, 28.4, 27.5, 26.9, 24.8, 24.8, 19.4.

FTIR (NaCl, thin film): 2986, 1628, 1422, 1260 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{25}N_2O$ $[M+H]^+$ 249.1961, found 249.1961.

TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), **R_f:** 0.34 ($KMnO_4$).

M.P. 88.5 – 94.8 °C.

Specific Optical Rotation: $[\alpha]_D^{21} = +40.5$ (c 1.0, $CHCl_3$).

Literature Specific Optical Rotation: $[\alpha]_D^{21} = +51.2$ (c 1.07, $CHCl_3$).[21]

Figure 2.22. *X-Ray structure of (+)-allomatrine ((+)-**27**). CCDC number: 2159773.*

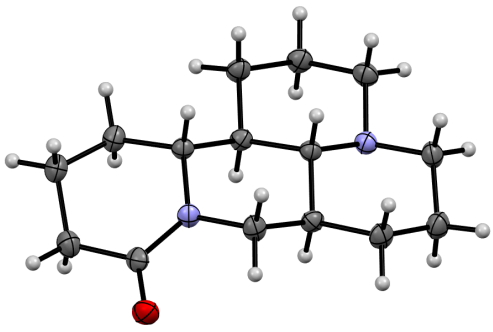
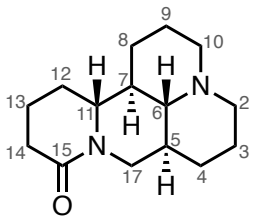


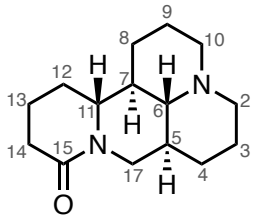
Table 2.19. *^{1}H NMR data for authentic vs synthetic (+)-allomatrine.*

The X-ray structure of allomatrine has been previously published (CCDC: 1102291).[43]



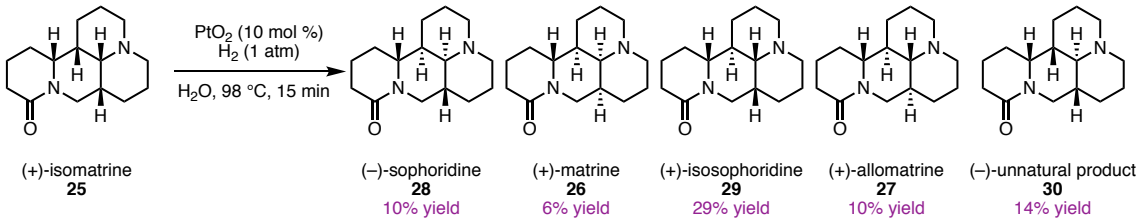
Allomatrine Literature ^{1}H δ ppm (400 MHz, $CDCl_3$)[43]	Allomatrine Recorded ^{1}H δ ppm (600 MHz, $CDCl_3$)
4.69 (dd, *J* = 12.9, 3.9 Hz, 1H)	4.68 (dd, *J* = 13.3, 3.9 Hz, 1H)
3.00 (td, *J* = 9.4, 5.4 Hz, 1H)	2.98 (td, *J* = 9.5, 5.4 Hz, 1H)
2.85 (m, 2H)	2.87 – 2.77 (m, 2H)
2.42 (m, 1H)	2.40 (dtd, *J* = 17.3, 4.6, 1.9 Hz, 1H)
2.27 (ddd, *J* = 17.0, 11.1, 5.5 Hz, 1H)	2.26 (ddd, *J* = 17.1, 11.3, 5.6 Hz, 1H)
2.17 (t, *J* = 12.9 Hz, 1H)	2.15 (t, *J* = 12.4 Hz, 1H)
2.11 – 1.92 (m, 3H)	2.06 (dtt, *J* = 13.6, 5.4, 2.5 Hz, 1H)
	2.00 – 1.90 (m, 2H)
1.89 – 1.78 (m, 2H)	1.86 – 1.77 (m, 2H)
1.75 – 1.58 (m, 5H)	1.73 – 1.61 (m, 5H)
1.58 (m, 1H)	1.57 (dddd, *J* = 23.5, 11.9, 4.8, 2.8 Hz, 1H)
1.52 – 1.39 (m, 2H)	1.49 – 1.37 (m, 2H)
1.35 (t, *J* = 9.4 Hz, 1H)	1.32 (t, *J* = 9.6 Hz, 1H)
1.27 (m, 1H)	1.27 – 1.19 (m, 1H)
1.03 – 0.83 (m, 2H)	0.98 – 0.82 (m, 2H)

Table 2.20. *^{13}C NMR data for authentic vs synthetic (+)-allomatrine.*



Carbon No. allomatrine	Allomatrine Literature ^{13}C δ ppm (101 MHz, $CDCl_3$)[43]	Allomatrine Recorded ^{13}C δ ppm (101 MHz, $CDCl_3$)	Δ δ
2	55.8	55.9	0.1
3	24.5	24.8	0.3
4	27.4	27.6	0.2
5	38.9	39.1	0.2
6	70.7	70.9	0.2
7	46.0	46.3	0.3
8	26.7	26.9	0.2
9	24.5	24.8	0.3
10	56.4	56.6	0.2
11	60.1	60.3	0.2
12	28.2	28.4	0.2
13	19.3	19.5	0.2
14	32.7	32.9	0.2
15	169.1	169.3	0.2
17	46.1	46.3	0.2

Preparation of (–)-sophoridine (28):



A 50 mL flask with a 20 mm x 8 mm x 8 mm egg-shaped stir bar was charged with (+)-isomatrine (50.0 mg, 201 μmol, 1.0 equiv), PtO_2 (4.6 mg, 20.1 μmol, 10 mol %) and water (5 mL, 0.04 M). The reaction was purged with N_2 (balloon) followed by H_2 (balloon). The reaction was not stirred during the gas purge. Once the flask was under an atmosphere of H_2, it was put into a preheated oil bath at 98 °C, and the mixture was stirred at 1500 rpm for 15 minutes. Upon completion, the flask was removed from the oil bath and cooled to 21 °C. The catalyst was removed via filtration through a syringe filter, then the filter was washed with water (3 x 5 mL). The obtained aqueous solution was concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (20 g SiO_2, 20 mm column diameter, 3% 2 M NH_3 in MeOH/97% $CHCl_3$ containing 0.75% EtOH as a stabilizer to 15% 2 M NH_3 in MeOH/85% $CHCl_3$ containing 0.75% EtOH as a stabilizer in 2% increments) to yield (–)-sophoridine (**28**) as a white crystalline solid (5.0 mg, 10% yield), (+)-isosophoridine (**29**) as a white crystalline solid (14.6 mg, 29% yield); a mixture of (+)-allomatrine (**27**) and (–)-unnatural product **30** in a 40:60 ratio (12.1 mg, 24% combined yield) as a clear, colorless oil; and a mixture of (+)-isomatrine (**25**) and (+)-matrine (**26**) in a 80:20 ratio (15.5 mg, 31% combined yield) as a white crystalline solid.

(–)-Sophoridine (28):

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (t, *J* = 11.6 Hz, 1H), 3.34 (t, *J* = 10.0 Hz, 1H), 3.26 (t, *J* = 12.6 Hz, 1H), 2.86 (d, *J* = 12.1 Hz, 1H), 2.76 (t, *J* = 10.8 Hz, 1H), 2.39 (dt, *J* = 17.6,

5.6 Hz, 1H), 2.31 (ddd, *J* = 17.5, 9.2, 5.7 Hz, 1H), 2.25 – 2.09 (m, 2H), 2.08 – 1.37 (m, 14H), 1.05 (qd, *J* = 12.8, 3.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 63.5, 56.0, 55.8, 50.4, 47.7, 41.1, 32.6, 30.9, 30.3, 28.2, 23.8, 21.9, 21.6, 19.0.

FTIR (NaCl, thin film): 2986, 2938, 1622, 1420, 1272, 1263 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{25}N_2O$ $[M+H]^+$ 249.1961, found 249.1960.

TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), **R_f:** 0.24 ($KMnO_4$).

M.P. 61.2 – 64.2 °C.

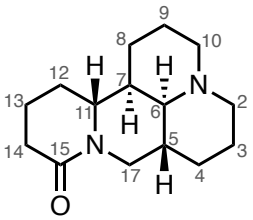
Specific Optical Rotation: $[\alpha]\frac{21}{D} =$ –57.3 (c 1.0, $CHCl_3$).

Specific Optical Rotation: $[\alpha]\frac{21}{D} =$ –60.9 (c 1.0, H_2O).

Literature Specific Optical Rotation: $[\alpha]\frac{21}{D} =$ –64 (c 1.0, H_2O).[14]

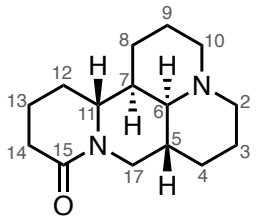
Table 2.21. *^{1}H NMR data for authentic vs synthetic (+)-sophoridine.*

The X-ray structure of sophoridine has been previously published (CCDC: 1261174).[36]



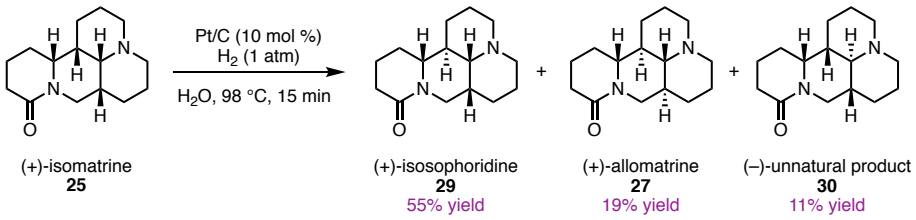
Sophoridine Literature ^{1}H δ ppm	Sophoridine Recorded ^{1}H δ ppm (600 MHz, $CDCl_3$)
unpublished	3.42 (dd, *J* = 11.6 Hz, 1H)
	3.34 (br t, *J* = 10.0 Hz, 1H)
	3.26 (t, *J* = 12.6 Hz, 1H)
	2.86 (d, *J* = 12.1 Hz, 1H)
	2.76 (t, *J* = 10.8 Hz, 1H)
	2.39 (dt, *J* = 17.6, 5.6 Hz, 1H)
	2.31 (ddd, *J* = 17.5, 9.2, 5.7 Hz, 1H)
	2.25 – 2.09 (m, 2H)
	2.08 – 1.37 (m, 14H)
	1.05 (qd, *J* = 12.8, 3.8 Hz, 1H)

Table 2.22. *^{13}C NMR data for authentic vs synthetic (+)-sophoridine.*



Carbon No. sohporidine	Sophoridine Literature ^{13}C δ ppm (101 MHz, $CDCl_3$)[44]	Sophoridine Recorded ^{13}C δ ppm (101 MHz, $CDCl_3$)	Δ δ
2	50.2	50.4	0.2
3	21.6	21.9	0.3
4	23.5	23.8	0.3
5	30.6	31.0	0.4
6	63.2	63.5	0.3
7	40.8	41.1	0.3
8	30.1	30.3	0.2
9	21.5	21.6	0.1
10	55.8	56.0	0.2
11	55.7	55.8	0.1
12	28.0	28.2	0.2
13	18.8	19.0	0.2
14	32.5	32.6	0.1
15	169.9	170.1	0.2
17	47.4	47.7	0.3

Preparation of (+)-isosophoridine (29):



A 50 mL flask with a 20 mm x 8 mm x 8 mm egg-shaped stir bar was charged with (+)-isomatrine (50.0 mg, 201 μmol, 1.0 equiv), 10% platinum on carbon (78.5 mg, 20.1 μmol, 10 mol %), and water (5 mL, 0.04 M). The reaction was purged with N_2 (balloon) followed by H_2 (balloon). The reaction was not stirred during the gas purge. Once the flask was under an atmosphere of H_2, it was put into a preheated oil bath at 98 °C, and the mixture was stirred at 1500 rpm for 15 minutes. Upon completion, the flask was removed from the oil bath and cooled to 21 °C. The catalyst was removed via filtration through a syringe filter, then the filter was washed with water (3 x 5 mL). The obtained aqueous solution was concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (20 g SiO_2, 20 mm column diameter, 3% 2 M NH_3 in MeOH/97% $CHCl_3$ with 0.75% EtOH stabilizer to 15% 2 M NH_3 in MeOH/85% $CHCl_3$ with 0.75% EtOH stabilizer as a gradient in 2% increments) to yield (+)-isosophoridine (**29**) as a white crystalline solid (27.5 mg, 55% yield) along with a mixture of (+)-allomatrine (**27**) and (–)-unnatural product **30** in a 36:64 ratio (14.9 mg, 30% combined yield).

(+)-Isosophoridine (29):

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.67 (dd, *J* = 13.3, 1.9 Hz, 1H), 3.00 – 2.82 (m, 4H), 2.75 (dd, *J* = 10.8, 4.7 Hz, 1H), 2.63 (dd, *J* = 13.4, 3.6 Hz, 1H), 2.46 (dt, *J* = 11.6, 3.6 Hz, 1H),

2.40 (dtd, *J* = 17.3, 5.2, 1.7 Hz, 1H), 2.28 (ddd, *J* = 17.2, 9.8, 5.4 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.93 – 1.70 (m, 5H), 1.86 – 1.75 (m, 3H), 1.73 (ddt, *J* = 15.9, 6.1, 3.6 Hz, 1H), 1.66 – 1.55 (m, 2H), 1.55 – 1.48 (m, 2H), 1.38 – 1.28 (m, 2H), 1.04 (qd, *J* = 12.7, 4.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 62.4, 60.1, 54.2, 46.9, 45.2, 36.1, 33.4, 33.0, 28.1, 26.7, 26.0, 23.1, 19.3, 19.2.

FTIR (NaCl, thin film): 2934, 2856, 1632, 1265, 1168 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{25}N_2O$ $[M+H]^+$ 249.1961, found 249.1963.

TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), **R_f:** 0.24 ($KMnO_4$).

M.P. 111.0 – 114.1 °C.

Specific Optical Rotation: $[\alpha]_D^{21} = +94.0$ (c 1.0, $CHCl_3$).

Specific Optical Rotation: $[\alpha]_D^{21} = +98.7$ (c 1.0, EtOH).

Literature Specific Optical Rotation: $[\alpha]_D^{21} = +101$ (c 1.0, EtOH).[14]

Figure 2.23. *X-Ray structure of (±)-isosophoridine ((±)-**29**). CCDC number 2159772.*

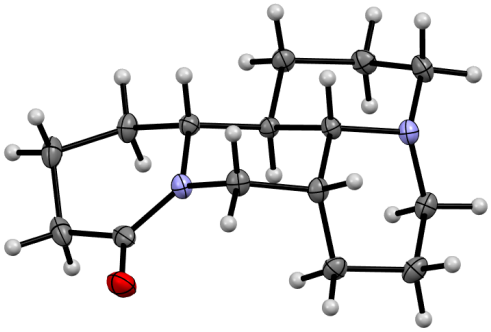
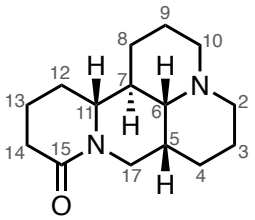


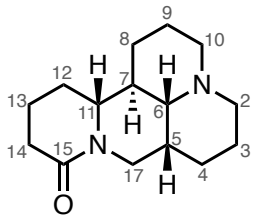
Table 2.23. *^{1}H NMR data for authentic vs synthetic (+)-isosophoridine.*

The X-ray structure of isosophoridine has been previously published (CCDC: 1180978 and 1180979).[45,46]



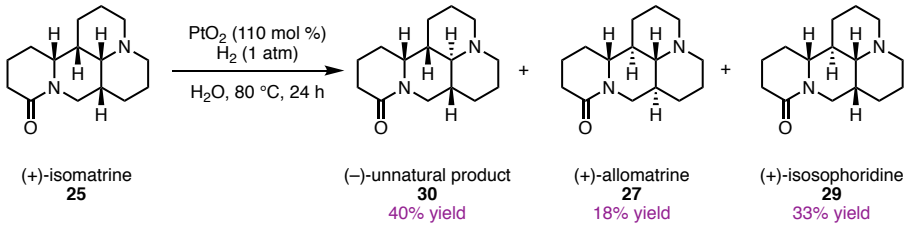
Isosophoridine Literature ^{1}H δ ppm (400 MHz, $CDCl_3$)[22]	Isosophoridine Recorded ^{1}H δ ppm (600 MHz, $CDCl_3$)
4.69 (dd, *J* = 13.4, 1.9 Hz, 1H)	4.67 (dd, *J* = 13.3, 1.9 Hz, 1H)
3.02 – 2.85 (m, 4H)	3.00 – 2.82 (m, 4H)
2.77 (dd, *J* = 10.6, 4.7, Hz, 1H)	2.75, (dd, *J* = 10.8, 4.7 Hz, 1H)
2.65 (dd, *J* = 13.4, 3.5 Hz, 1H)	2.63 (dd, *J* = 13.4, 3.6 Hz, 1H)
2.52 – 2.37 (m, 2H)	2.46 (dt, *J* = 11.6, 3.6 Hz, 1H)
	2.40 (dtd, *J* = 17.3, 5.2, 1.7 Hz, 1H)
2.35 –2.24 (m, 1H)	2.28 (ddd, *J* = 17.2, 9.8, 5.4 Hz, 1H)
2.09 – 1.99 (m, 1H)	2.07 – 1.95 (m, 1H)
1.95 – 1.71 (m, 5H)	1.93 – 1.70 (m, 6H)
1.71 – 1.49 (m, 4H)	1.66 – 1.47 (m, 4H)
1.41 – 1.23 (m, 3H)	1.38 – 1.29 (m, 2H)
1.05 (qd, *J* = 12.4, 4.2 Hz, 1H)	1.04 (qd, *J* = 12.7, 4.2 Hz, 1H)

Table 2.24. *^{13}C NMR data for authentic vs synthetic (+)-isosophoridine.*



Carbon No. isosohporidine	Isosophoridine Literature ^{13}C δ ppm (101 MHz, $CDCl_3$)[22]	Isosophoridine Recorded ^{13}C δ ppm (101 MHz, $CDCl_3$)	Δ δ
2	45.0	45.2	0.2
3	25.6	26.0	0.4
4	22.7	23.1	0.4
5	35.8	36.1	0.3
6	62.1	62.4	0.3
7	33.3	33.4	0.1
8	26.6	26.7	0.1
9	19.0	19.3	0.3
10	53.9	54.2	0.3
11	59.9	60.2	0.3
12	27.8	28.1	0.3
13	18.9	19.2	0.3
14	32.8	33.0	0.2
15	169.9	169.9	0.0
17	46.6	46.9	0.3

Preparation of (–)-unnatural product 30:



A 50 mL flask with a 20 mm x 8 mm x 8 mm egg-shaped stir bar was charged with (+)-isomatrine (30.0 mg, 121 μmol, 1.0 equiv.), PtO_2 (30.2 mg, 133 μmol, 110 mol %), and water (3 mL, 0.04 M). The reaction was purged with N_2 (balloon) followed by H_2 (balloon). The reaction was not stirred during the gas purge. Once the flask was under an atmosphere of H_2, it was put into a preheated oil bath at 80 °C, and the mixture was stirred at 1500 rpm for 24 hours. Upon completion, the flask was removed from the oil bath and cooled to 21 °C. The catalyst was removed via filtration through a syringe filter, then the filter was washed with water (3 x 5 mL). The obtained aqueous solution was concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (5 g SiO_2, 10 mm column diameter, 5% 2 M NH_3 in MeOH/95% $CHCl_3$ containing 0.75% EtOH to 10% 2 M NH_3 in MeOH/90% $CHCl_3$ containing 0.75% EtOH as a gradient in 1% increments) to yield (+)-isosophoridine (**29**) as a white crystalline solid (9.9 mg, 33% yield) along with a mixture of (+)-allomatrine (**3**) and (–)-unnatural product **30**. The separation of the (–)-unnatural product was carried out via HPLC reverse phase chromatography (Eclipse XDB-C8 – 9.4 mm x 250 mm column, 8% ACN/92% H_2O with 0.2% TFA, flow rate: 5 mL/min, t_r ((–)-unnatural product **30**) = 5.06 min, t_r ((+)-allomatrine (**27**)) = 6.29 min) to yield (–)-unnatural product **30** as a white crystalline solid (12.0 mg, 40% yield) along with (+)-allomatrine (**27**) as a white crystalline solid (5.4 mg, 18% yield). X-ray-

quality crystals of (–)-unnatural product **30** were prepared via slow evaporation of a hexanes solution at –20 °C open to air.

(–)-Unnatural Product 30:

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (ddd, *J* = 9.5, 8.2, 4.6 Hz, 1H), 3.47 (dd, *J* = 13.5, 6.9 Hz, 1H), 3.35 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.83 (d, *J* = 10.6 Hz, 2H), 2.45 – 2.24 (m, 2H), 2.10 – 1.96 (m, 2H), 1.88 – 1.52 (m, 11H), 1.38 (t, *J* = 10.2 Hz, 1H), 1.30 (dd, *J* = 12.7, 5.1 Hz, 1H), 1.24 (dd, *J* = 12.5, 3.4 Hz, 1H), 1.13 – 0.98 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 65.4, 56.1, 55.9, 54.5, 46.7, 42.4, 35.8, 32.1, 30.3, 27.3, 25.8, 24.8, 24.4, 19.3.

FTIR (NaCl, thin film): 2922, 2798, 2740, 1638, 1179, 1142, 1126 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{25}N_2O$ $[M+H]^+$ 249.1961, found 249.1960.

TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), $\mathbf{R_f}$**:** 0.34 ($KMnO_4$).

M.P. 63.2 – 66.5 °C.

Specific Optical Rotation: $[\alpha]\frac{21}{D} =$ –53.0 (c 1.0, $CHCl_3$).

Figure 2.24. *X-Ray structure of (–)-unnatural product ((–)-**30**). CCDC number: 2163777.*

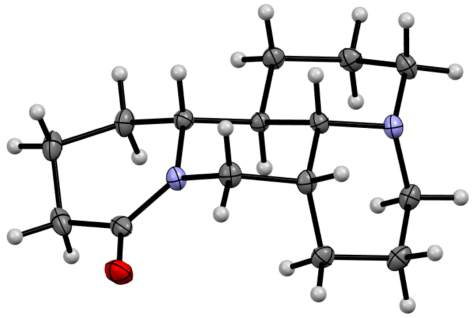
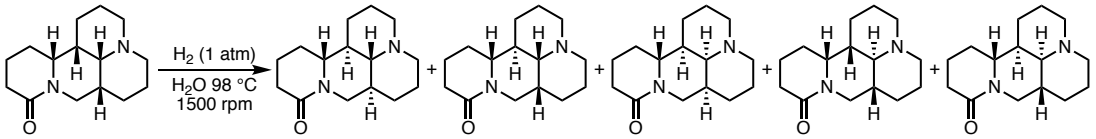


Table 2.25. *Isomatrine isomerization optimization.*

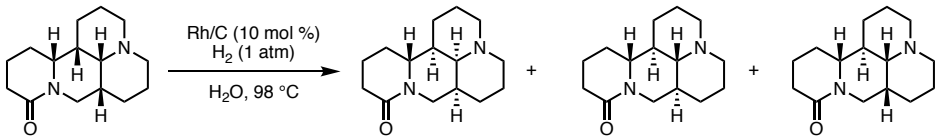


(+)-isomatrine **25** | (+)-allomatrine **27** | (+)-isosophoridine **29** | (+)-matrine **26** | (–)-unnatural product **30** | (–)-sophoridine **28**

Entry	Catalyst (loading)	Time	Recovered SM	allomatrine	isosophoridine	matrine	unnatural isomer	sophoridine
1	PtO_2 (10 mol%)	0.25 h	57%	6%	15%	3%	9%	10%
2[a]	PtO_2 (10 mol %)	0.25 h	100%	0%	0%	0%	0%	0%
3[b]	PtO_2 (10 mol %)	0.25 h	87%	3%	5%	2%	0%	2%
4[c]	PtO_2 (10 mol%)	0.25 h	95%	1%	1%	0%	1%	1%
5	Rh/C (10 mol%)	0.25 h	35%	30%	5%	26%	2%	1%
6	Pd/C (10 mol%)	0.25 h	10%	42%	6%	28%	12%	2%
7	Ru/C (10 mol%)	0.25 h	100%	0%	0%	0%	0%	0%
8	Ir/C (10 mol%)	0.25 h	7%	10%	59%	2%	11%	11%
9	RuO_2 (10 mol%)	0.25 h	100%	0%	0%	0%	0%	0%
10	Pt/C (10 mol%)	0.25 h	0%	12%	67%	0%	21%	0%
11[d]	PtO_2 (10 mol%)	0.25 h	100%	0%	0%	0%	0%	0%
12	PtO_2 (5 mol%)	24 h	100%	0%	0%	0%	0%	0%
13[c]	PtO_2 (5 mol%)	24 h	73%	10%	5%	11%	0%	0%
14[c]	PtO_2 (110 mol%)	24 h	5%	36%	9%	3%	48%	0%
15[c]	PtO_2 (5 mol%)	0.25 h	99%	0%	1%	0%	0%	0%
16	PtO_2 (110 mol%)	0.25 h	0%	20%	55%	2%	21%	1%

reported yields are qNMR yields against a pyrazine internal standard

Table 2.26. *Isomatrine isomerization optimization with Rh/C.*

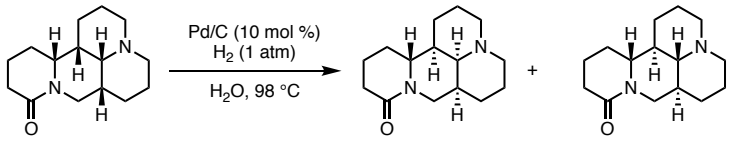


(+)-isomatrine **25** | (+)-matrine **26** | (+)-allomatrine **27** | (+)-isosophoridine **29**

Entry	Time	Recovered SM	allomatrine	isosophoridine	matrine	unnatural product	sophoridine
1	0.5 h	35	30%	5%	26%	2%	1%
2	0.75 h	39	23%	10%	28%	0%	0%
3	1 h	18	30%	10%	42%	0%	0%
4	1.5 h	8	35%	9%	48%	0%	0%
5	2 h	0	57%	0%	42%	0%	0%
6	6 h	0	70%	0%	30%	0%	0%
7	24 h	0	76%	0%	24%	0%	0%

all yields are qNMR yields against pyrazine internal standard

Table 2.27. *Isomatrine isomerization optimization with Pd/C.*

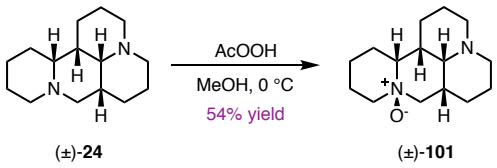


(+)-isomatrine **25** (+)-matrine **26** (+)-allomatrine **27**

Entry	Time	Recovered SM	allomatrine	isosophoridine	matrine	unnatural product	sophoridine
1	0.25 h	10	42%	6%	28%	0%	2%
2	0.75 h	0	64%	6%	36%	0%	2%
3	1 h	0	87%	0%	13%	0%	0%
4	1.5 h	0	78%	0%	22%	0%	0%
5	2 h	0	82%	0%	18%	0%	0%
6	6 h	0	92%	0%	8%	0%	0%
7	24 h	0	88%	0%	12%	0%	0%

all yields are qNMR yields against pyrazine internal standard

Preparation of (±)-*N*-oxide 101:



(±)-**24** (±)-**101**

A 1 L flask was charged with (±)-diamine **24** (2.50 g, 10.7 mmol, 1.0 equiv) and methanol (323 mL, 0.033 M). The solution was cooled to 0 °C, then peracetic acid (32% wt. % in dilute acetic acid, 2.42 mL, 11.7 mmol, 1.1 equiv) was added dropwise. The reaction was stirred for 15 minutes at 0 °C followed by removal of the solvent under reduced pressure. The residue was diluted in DCM (200 mL) and the organic layer washed with 3 M NaOH (50 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by crystallization from boiling hexanes (15 mL) and enough chloroform to ensure complete dissolution. The solution was allowed to cool to 21 °C then to –20 °C. The solution was decanted from the crystals, and the crystals were washed with a 5:1 mixture of hexanes/chloroform followed by drying *in vacuo* to yield (±)-*N*-oxide **101** as a white crystalline solid (1.44 g, 54% yield).

(±)-*N*-oxide 101:

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (dd, *J* = 12.7, 11.0 Hz, 1H), 3.47 (ddtd, *J* = 13.2, 4.0, 2.3, 0.3 Hz, 1H), 3.37 (td, *J* = 13.2, 4.4 Hz, 1H), 3.17 (dtd, *J* = 7.8, 6.0, 4.9, 2.8 Hz, 1H), 3.14 – 3.06 (m, 1H), 3.02 (dddd, *J* = 13.2, 5.4, 3.8, 1.3 Hz, 1H), 2.81 – 2.66 (m, 2H), 2.40 – 2.26 (m, 2H), 2.01 (t, *J* = 3.9 Hz, 1H), 1.98 – 1.32 (m, 15H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 77.0, 72.2, 61.0, 57.6, 57.5, 57.4, 31.1, 29.2, 29.1, 27.3, 25.5, 23.8, 23.1, 22.6, 22.2.

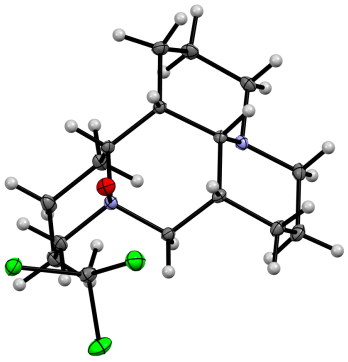
FTIR (NaCl, thin film): 2985, 1420, 1268 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{27}N_2O$ $[M+H]^+$ 251.2118, found 251.2116.

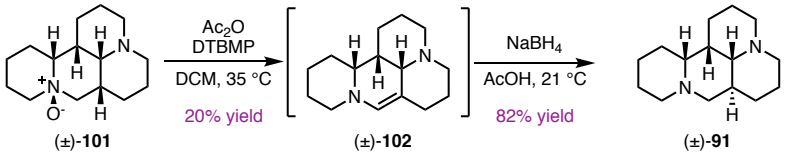
TLC (40% 2 M NH_3 in MeOH/60% ACN), **R*f*:** 0.31 ($KMnO_4$).

M.P. 202.9 – 208.1 °C.

Figure 2.25. *X-Ray structure of the mono-chloroform adduct of (±)-**101**. CCDC number 2159764.*



Preparation of (±)-diamine 91



N-oxide elimination:

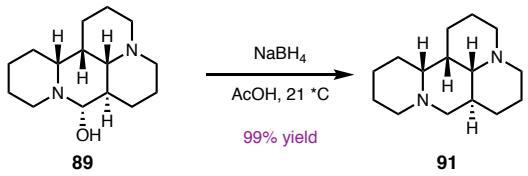
A 25 mL oven-dried, N_2-flushed flask was charged with (±)-*N*-oxide **101** (100 mg, 0.399 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (147 mg, 0.718 mmol, 1.8

equiv), DCM (10 mL, 0.04 M), and acetic anhydride (0.38 mL, 3.99 mmol, 10.0 equiv). The reaction was stirred at 35 °C until complete consumption of the starting material, as judged by TLC (*ca.* 24 hours). The reaction was concentrated under reduced pressure and then the crude product was partially purified via SiO_2 column chromatography (20 g SiO_2, 20 mm column diameter, 40% 2 M NH_3 in MeOH/60% can) to yield (±)-enamine **102** as a brown oil (18.4 mg, 20% yield) which was unstable to storage and was immediately subjected to reduction.

Sodium borohydride reduction:

A 25 mL flask was charged with partially purified (±)-enamine **102** (107 mg, 0.46 mmol, 1.0 equiv), sodium borohydride (34.8 mg, 0.92 mmol, 2.0 equiv), and acetic acid (4.6 mL, 0.1 M). The reaction stirred at 21 ºC until complete consumption of the starting material, as judged by TLC (*ca.* 20 minutes). Upon completion, the reaction was diluted in DCM (50 mL) and was neutralized with 3 M NaOH (50 mL). The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via SiO_2 column chromatography (20 g SiO_2, 20 mm column diameter, 40% 2 M NH_3 in MeOH/60% can) to yield (±)-diamine **91** as a white crystalline solid (88.3 mg, 82% yield). X-ray-quality crystals were grown by allowing a solution of **91** in acetonitrile to slowly evaporate at 21 °C.

Sodium borohydride reduction of hemi-aminal **89**:



To a 250 mL flask was added the hemi-aminal **89** (500 mg, 2.00 mmol, 1.0 equiv), sodium borohydride (151 mg, 3.99 mmol, 2.0 equiv) and AcOH (10 mL, 0.2 M) at 21 °C. The reaction was stirred for 24 hours at 21 °C and was quenched with 3 M NaOH until basic by pH paper. The crude reaction mixture was extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was allowed to crystallize under vacuum on a Schlenk line (0.3 torr, 30 minutes). The solids were dissolved in Et2O (30 mL) and the cloudy suspension was vacuum filtered. The clear colorless solution was concentrated under reduced pressure to yield the product diamine **91** as a white crystalline solid (468 mg, 99% yield) which did not require additional purification.

(±)-Diamine 91:

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.99 – 2.91 (m, 3H), 2.83 (ddt, *J* = 11.5, 4.2, 2.0 Hz, 1H), 2.61 (dd, *J* = 11.3, 3.9 Hz, 1H), 2.52 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.46 (dddd, *J* = 11.3, 4.0, 2.5, 1.2 Hz, 1H), 2.16 (qt, *J* = 11.3, 3.8 Hz, 1H), 1.87 – 1.79 (m, 3H), 1.79 – 1.70 (m, 2H), 1.70 – 1.53 (m, 5H), 1.54 – 1.40 (m, 4H), 1.37 (ddq, *J* = 13.0, 5.5, 2.8 Hz, 1H), 1.27 – 1.17 (m, 2H), 1.05 (tdd, *J* = 13.0, 11.7, 4.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 66.2, 64.0, 63.3, 57.2, 54.7, 45.8, 41.2, 30.2, 29.7, 26.3, 26.2, 26.0, 24.8, 20.1, 19.1.

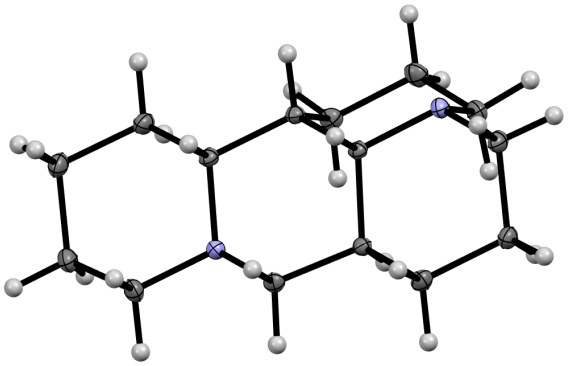
FTIR (NaCl, thin film): 2927, 2850, 2750, 1440, 1131, 1110 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{27}N_2$ $[M+H]^+$ 235.2169, found 235.2167.

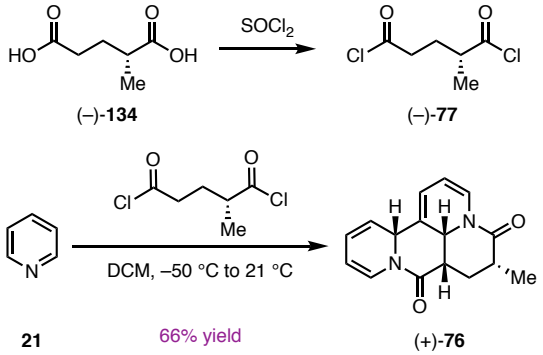
TLC (40% 2 M NH_3 in MeOH/60% ACN), **R*f*:** 0.32 ($KMnO_4$).

M.P. 82.3 – 83.3 °C.

Figure 2.26. *X-Ray structure of (±)-**91**.CCDC number: 2159765.*



Preparation of (+)-3-methyltetracycle 76:



A 25 mL oven-dried, N_2 flushed flask was charged with (*R*)-2-methyl glutaric acid (1.00 g, 6.84 mmol, 1.0 equiv) and thionyl chloride (4.0 mL, 54.7 mmol, 8.0 equiv). The suspension was stirred for 24 hours at 21 °C under N_2, after which point it became a homogenous solution. The thionyl chloride was removed under vacuum (0.3 torr) on a

Schlenk line at 21 °C to yield (*R*)-2-methylglutaryl chloride (**77**) as a clear, colorless liquid, which was used directly in the subsequent cyclization reaction.

A 100 mL oven-dried, N_2-flushed flask with a 36 mm x 18 mm x 18 mm egg-shaped stir bar was charged with DCM (26.4 mL, 0.125 M) and (*R*)-2-methylglutaryl chloride (605 mg, 3.31 mmol, 1.0 equiv). The solution was cooled to –50 °C, then pyridine (1.34 mL, 16.5 mmol, 5.0 equiv) was added dropwise over the course of 5 minutes. The reaction was allowed to warm to 21 °C and stirred for 24 hours. The reaction was concentrated under reduced pressure and diluted in MeOH (20 mL). The solids were isolated by suction filtration, washed with MeOH (2 x 10 mL), and dried *in vacuo* to yield (+)-3-methyltetracycle **76** as a light orange crystalline solid (0.589 g, 66% yield).

(+)-3-methyltetracycle 76:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dt, *J* = 8.0, 1.0 Hz, 1H), 6.99 (dq, *J* = 8.1, 0.9 Hz, 1H), 6.04 (dddd, *J* = 10.1, 5.8, 2.2, 1.0 Hz, 1H), 5.78 (ddt, *J* = 5.8, 2.8, 1.0 Hz, 1H), 5.50 (ddt, *J* = 10.1, 3.4, 1.2 Hz, 1H), 5.32 (dd, *J* = 7.9, 5.7 Hz, 1H), 5.14 (ddd, *J* = 8.1, 5.7, 1.1 Hz, 1H), 5.09 (t, *J* = 2.9 Hz, 1H), 4.95 (ddt, *J* = 9.5, 2.6, 1.2 Hz, 1H), 2.96 (q, *J* = 9.5 Hz, 1H), 2.31 – 2.19 (m, 1H), 2.16 (dt, *J* = 9.3, 4.6 Hz, 1H), 2.03 (td, *J* = 13.8, 9.9 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 168.9, 129.6, 124.4, 123.7, 122.2, 120.9, 117.9, 103.7, 102.7, 54.0, 51.9, 41.5, 34.8, 25.5, 15.4.

FTIR (NaCl, thin film): 2946, 2835, 1652, 1456, 1113, 1033 cm^{-1}.

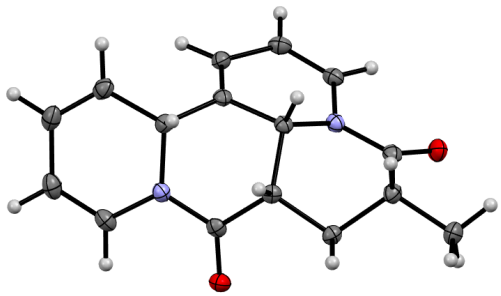
HRMS: (ESI-TOF) calc'd for $C_{16}H_{17}N_2O_2$ $[M+H]^+$ 269.1290, found 269.1278.

TLC (50% EtOAc /50% hexanes), **R_f:** 0.37 ($KMnO_4$).

M.P. 192.5 – 196.4 °C.

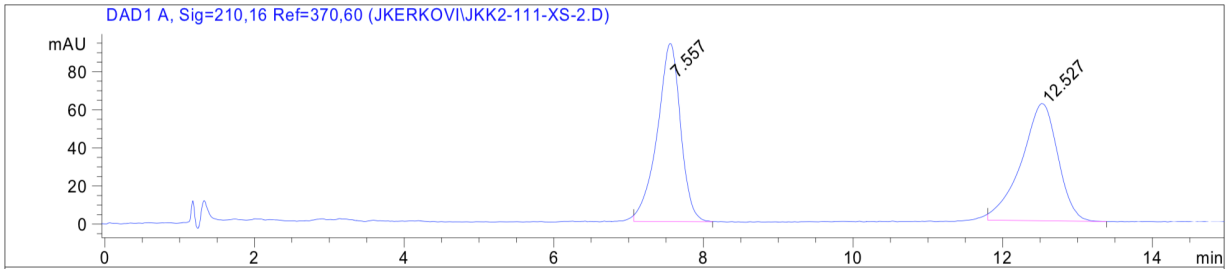
Specific Optical Rotation: $[\alpha]\frac{21}{D} = -1115$ (c 1.0, $CHCl_3$).

Figure 2.27. *X-Ray structure of (±)-**76**. CCDC number: 2159768.*



Chiral SFC: (IC, 2.5 mL/min, 45% IPA in CO_2, λ = 210 nm): t_R (major) = 7.6 min, t_R (minor) = 12.5 min.

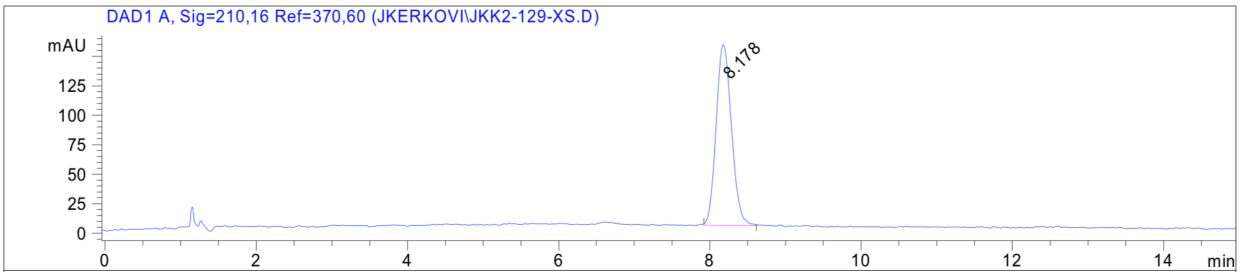
Figure 2.28. *SFC trace of racemic **76***



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.557	BB	0.3214	2030.30872	93.47500	49.3078
2	12.527	BB	0.5080	2087.31201	61.50079	50.6922

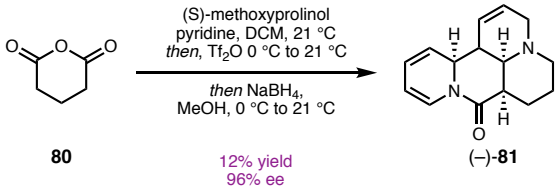
Figure 2.29. *SFC trace of enantiopure* ***76****.*



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.178	BB	0.2207	2161.24438	153.12198	100.0000

Preparation of tetracycle (–)-81:



To a 100 mL flask in a glovebox was added the glutaric anhydride (100 mg, 876 umol, 1.0 equiv), pyridine (496 uL, 6.13 mmol, 7.0 equiv), DCM (8.76 mL, 0.1 M), and (*S*)-(+)-2-(methoxymethyl)pyrrolidine (108 uL, 876 umol, 1.0 equiv). The reaction was stirred for 30 minutes at 21 °C then cooled to –78 °C. To the solution was added trifluoromethanesulfonic anhydride (302 uL, 1.80 mmol, 2.05 equiv). The reaction was then allowed to warm to 21 °C, and stirred for 4 hours. Then, the MeOH (8.76 mL, 0.1 M) was added and the solution cooled to 0 °C. The sodium borohydride (497 mg, 13.1 mmol, 15 equiv) was added next in portions. Once the addition was finished, the

reaction was warmed to 21 °C and stirred for 30 minutes. The crude reaction mixture was concentrated under reduced pressure, made basic with sat. Na_2CO_3 (20 mL) and water (20 mL). The reaction mixture was extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. In a glovebox the crude material was treated with Et_2O (20 mL), which caused the product to crash out as an tan solid. The product was isolated via suction filtration in the glovebox to yield the product (–)-**81** as a light tan crystalline solid (25.5 mg, 12% yield, 96% ee).

(+)-tetracycle 81:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.02 (ddt, *J* = 10.5, 5.7, 2.3 Hz, 1H), 5.94 (dddd, *J* = 10.0, 5.7, 2.3, 1.1 Hz, 1H), 5.90 (dtd, *J* = 10.2, 2.9, 0.9 Hz, 1H), 5.50 (ddt, *J* = 10.0, 3.5, 1.2 Hz, 1H), 5.01 (ddd, *J* = 7.9, 5.7, 1.1 Hz, 1H), 4.84 (dt, *J* = 5.8, 2.8 Hz, 1H), 3.09 (dd, *J* = 15.9, 5.9 Hz, 1H), 2.93 (ddt, *J* = 11.1, 3.8, 1.7 Hz, 1H), 2.83 (dd, *J* = 8.6, 3.6 Hz, 1H), 2.71 (dtd, *J* = 8.6, 4.5, 4.1, 1.8 Hz, 1H), 2.58 (ddt, *J* = 15.9, 3.9, 2.1 Hz, 1H), 2.42 (dtd, *J* = 12.6, 4.2, 2.3 Hz, 1H), 2.33 (q, *J* = 3.6 Hz, 1H), 2.24 – 2.05 (m, 2H), 1.55 – 1.45 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 128.5, 123.7, 123.4, 122.3, 121.3, 101.8, 58.1, 56.8, 55.7, 52.3, 41.0, 39.7, 24.2, 21.4.

FTIR (NaCl, thin film): 3054, 2986, 2339, 1675, 1655, 1420, 1265, 896, 738 cm^{-1}.

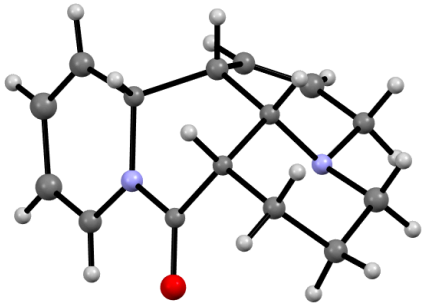
HRMS: (ESI-TOF) calc'd for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1497, found 243.1509.

TLC (3% MeOH/97% $CHCl_3$ with 0.75% EtOH stabilizer), **R_f:** 0.27 ($KMnO_4$).

M.P. 175.7 °C – 178.1 °C.

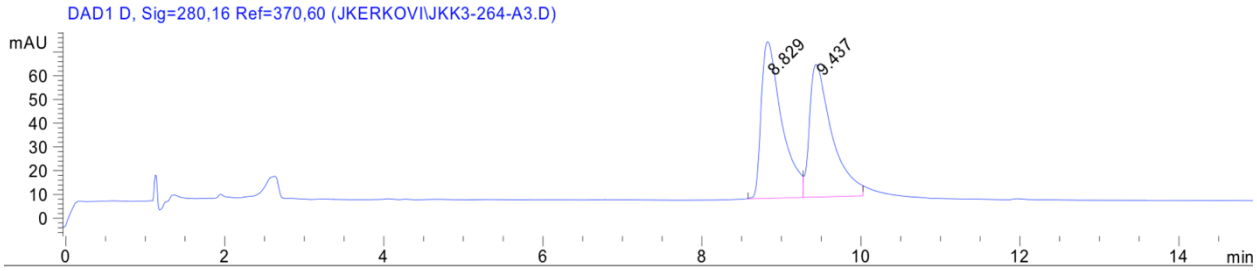
Specific Optical Rotation: $[\alpha]_D^{21}$ = –94.0 (c 1.0, $CHCl_3$).

Figure 2.30. *X-Ray structure of (+)-**81**. CCDC number: not publication quality.*



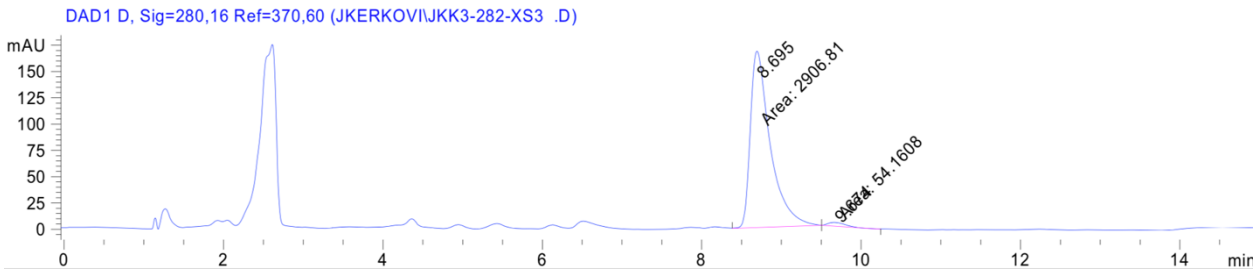
Chiral SFC: (IC, 2.5 mL/min, 30% IPA in CO_2, λ = 280 nm): t_R (major) = 8.829 min, t_R (minor) = 9.437 min.

Figure 2.31. *SFC trace of racemic **81**.*



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.829	BV	0.2651	1182.97705	65.99975	51.8590
2	9.437	VB	0.2855	1098.16357	55.83330	48.1410

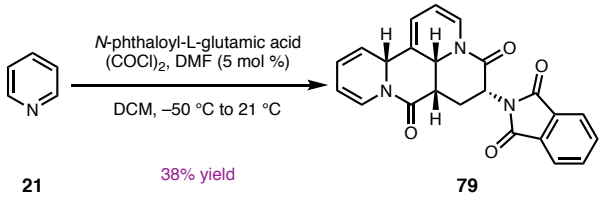
Figure 2.32. *SFC trace of enantioenriched* ***81****.*



Signal 3: DAD1 D, Sig=280,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.695	MM	0.2889	2906.81177	167.67546	98.1708
2	9.674	MM	0.2538	54.16077	3.55604	1.8292

Preparation of 8-phthaloyltetracycle 79:



A 500 mL oven dried flask was charged with *N*-phthaloyl-L-glutamic acid (5.00 g, 18.0 mmol, 1.0 equiv), DMF (70 µL, 0.90 mmol, 5 mol %), and DCM (18 mL, 1 M). The flask was equipped with a scrubber to remove HCl vapors, and to the suspension in the flask was added oxalyl chloride (3.36 mL, 39.7 mmol, 2.2 equiv). The reaction was stirred at ambient temperature for 5 hours which resulted in the formation of a clear colorless solution, and progress of the reaction was monitored by NMR aliquots. The solution was diluted in DCM (180 mL, 0.1 M) and was cooled to –50 °C. To the solution was added pyridine (7.29 mL, 90.2 mmol, 5 equiv) over the course of 5 minutes. The

slurry was stirred at –50 °C for 15 minutes then at ambient temperature for 15 hours. The reaction was concentrated under reduced pressure and suspended in MeOH (50 mL). The solids were isolated by suction filtration and dried in vacuo to yield the product as a brown powder (2.72 g, 38% yield). Using enantiopure *N*-phthaloyl-L-glutamic acid provided the product **79** with 16% ee.

8-phthaloyltetracycle 79:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 – 7.85 (m, 2H), 7.76 – 7.70 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.01 (dt, *J* = 7.9, 1.0 Hz, 1H), 6.06 (dddd, *J* = 10.0, 5.8, 2.2, 0.9 Hz, 1H), 5.83 (ddt, *J* = 5.7, 2.7, 0.9 Hz, 1H), 5.53 (ddt, *J* = 10.1, 3.4, 1.2 Hz, 1H), 5.43 (dd, *J* = 7.9, 5.8 Hz, 1H), 5.17 (dd, *J* = 8.0, 5.8 Hz, 1H), 5.14 (t, *J* = 2.3 Hz, 1H), 5.12 (dd, *J* = 9.9, 2.8 Hz, 1H), 4.78 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.33 (td, *J* = 13.7, 10.2 Hz, 1H), 3.12 (q, *J* = 9.6 Hz, 1H), 2.33 (ddd, *J* = 13.8, 9.1, 4.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 166.9, 134.4, 134.0, 131.7, 129.3, 124.0, 123.7, 123.6, 122.2, 120.6, 117.5, 105.0, 102.8, 53.7, 51.6, 48.8, 40.3, 22.0.

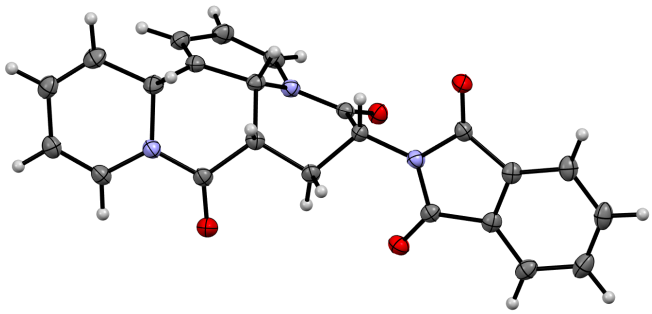
FTIR (NaCl, thin film): 3053, 2986, 1720, 1672, 1610, 1421, 1390, 1266 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{23}H_{17}N_3O_4$ $[M+H]^+$ 400.1297, found 400.1292

TLC (60% EtOAc /40% ACN), $\mathbf{R_f}$**:** 0.50 ($KMnO_4$).

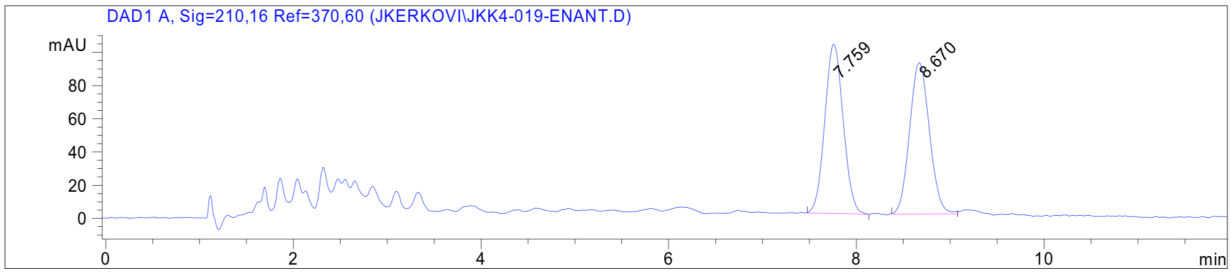
M.P. decomposed at 180 °C.

Figure 2.33. *X-Ray structure of (+)-**79**. CCDC 2159769.*



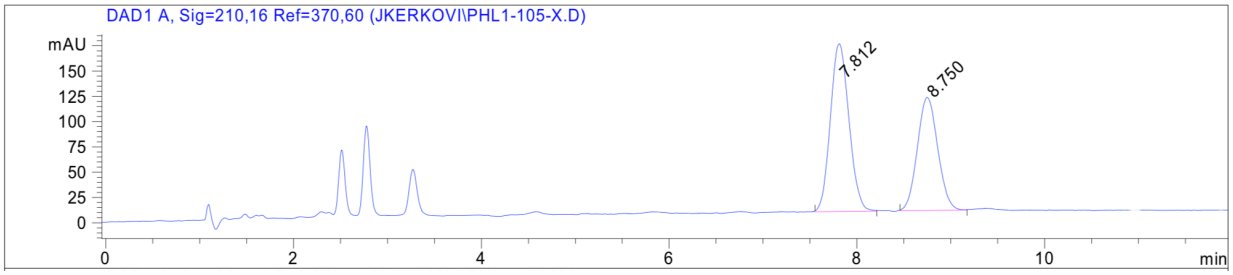
Chiral SFC: (AD-H, 2.5 mL/min, 45% IPA in CO2, λ = 210 nm): tR (major) = 7.8 min, tR (minor) = 8.7 min.

Figure 2.34. *SFC trace of racemic **79**.*



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.759	BB	0.2153	1390.96790	101.88776	50.9158
2	8.670	BB	0.2316	1340.93018	91.18265	49.0842

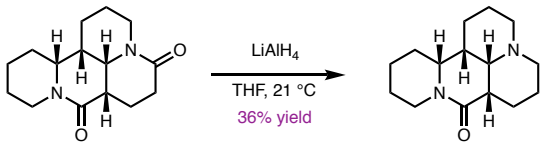
Figure 2.35. *SFC trace of scalemic* ***79****.*



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.812	BB	0.2122	2275.86987	165.71790	57.3807
2	8.750	BB	0.2364	1690.39539	111.81298	42.6193

Preparation of mono-amide 88:



87 **88**

A 100 mL N_2 flushed flask was charged with bis-amide **87** (498 mg, 1.90 mmol, 1.0 equiv.), and THF (9.5 mL, 0.2 M). The solution was cooled to 0 °C, then $LiAlH_4$ (144 mg, 3.80 mmol, 2.0 equiv) was added to the flask in a single portion. The reaction was stirred at 0 °C for 5 minutes, then at ambient temperature until complete by TLC (*ca.* 18 hours). Upon completion the reaction was quenched with sat. Rochelles salt (20 mL). The reaction mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via SiO_2 column chromatography [40 g SiO_2, 30 mm

column diameter, and eluted with 20% MeOH/80% ACN] to yield mono amide **88** as a white crystalline solid (171 mg, 36% yield).

mono-amide 88:

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.81 (ddq, *J* = 12.7, 3.6, 2.1 Hz, 1H), 3.39 (ddd, *J* = 11.3, 7.9, 2.5 Hz, 1H), 2.86 – 2.74 (m, 2H), 2.66 (ddt, *J* = 13.1, 4.0, 2.1 Hz, 1H), 2.43 – 2.29 (m, 2H), 2.27 – 2.16 (m, 2H), 2.07 (qd, *J* = 12.5, 3.7 Hz, 1H), 2.00 – 1.88 (m, 3H), 1.81 – 1.62 (m, 4H), 1.62 – 1.56 (m, 1H), 1.50 – 1.35 (m, 5H), 1.20 (dddd, *J* = 19.9, 8.1, 6.6, 3.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 63.4, 62.5, 57.5, 57.0, 45.2, 40.8, 34.9, 33.1, 26.5, 25.9, 25.8, 25.7, 22.9, 22.6.

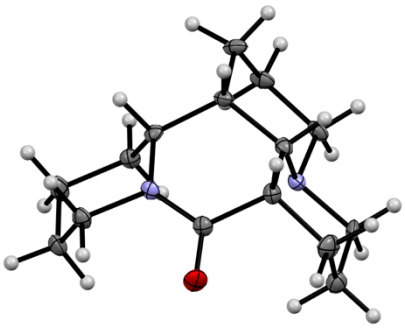
FTIR (NaCl, thin film): 2921, 2854, 2762, 2805, 1634, 1434, 1243, 1134 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{24}N_2O$ $[M+H]^+$ 249.1961, found 249.1958.

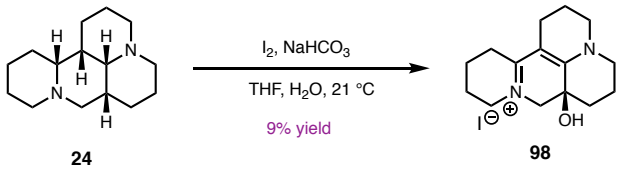
TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), **R_f:** 0.42 ($KMnO_4$).

M.P. 97.6 – 103.3 °C.

Figure 2.36. *X-Ray structure of (±)-**88**. CCDC number: not publication quality.*



Preparation of conjugated iminium ion **98**:



24 **98**

A 100 mL flask was charged with diamine **24** (200 mg, 0.85 mmol, 1 equiv), sodium bicarbonate (717 mg, 8.53 mmol, 10 equiv), THF (24 mL, 0.025 M), water (10 mL, 0.025 M), and iodine (1.62 g, 6.40 mmol, 7.5 equiv) and was stirred at ambient temperature for 20 hours. Upon completion the reaction was diluted in water (200 mL), and the reaction mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. A QNMR of the crude reaction revealed a 29% yield of iminium ion **98**. An analytically pure sample was prepared by purification of the crude reaction mixture by SiO_2 column chromatography [20 g SiO_2, 20 mm column diameter, 10% 2 M NH_3 in MeOH/90% $CHCl_3$ containing 0.75% EtOH as a stabilizer to 20% 2 M NH_3 in MeOH/90% $CHCl_3$ containing 0.75% EtOH in 2% increments] to yield a yellow oil. Trituration of the yellow oil from acetone yielded the iminium ion **98** as a pale yellow crystalline solid (18.7 mg, 9% yield). X-ray quality crystals were grown by slow evaporation from acetone under an atmosphere of N_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (s, 1H), 3.93 (dt, *J* = 13.1, 6.1 Hz, 1H), 3.77 (d, *J* = 14.5 Hz, 1H), 3.52 – 3.34 (m, 5H), 3.24 (ddd, *J* = 13.4, 6.6, 4.3 Hz, 1H), 2.80 (dt, *J* = 18.8, 6.1 Hz, 1H), 2.65 – 2.39 (m, 3H), 2.27 – 1.70 (m, 9H), 1.51 (td, *J* = 13.6, 3.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 157.3, 95.5, 63.7, 60.1, 52.2, 51.3, 50.5, 29.1, 28.0, 21.8, 21.1, 20.4, 18.5, 17.2.

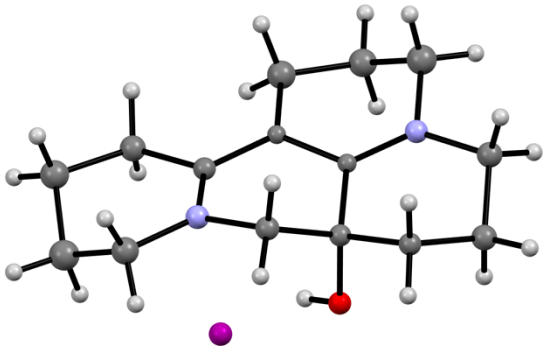
FTIR (NaCl, thin film): 3053, 2986, 2685, 1605, 1554, 1422, 1273, 1261 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{23}N_2O$ $[M]^+$ 247.1805, found 247.1805.

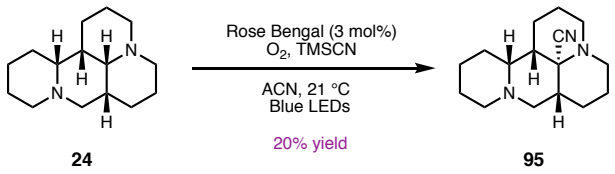
TLC (10% 2 M NH_3 in MeOH/90% $CHCl_3$ with 0.75% EtOH stabilizer), **R_f:** 0.19 ($KMnO_4$).

M.P. 178.9 – 181.6 °C.

Figure 2.37. *X-Ray structure of (±)-**98**. CCDC number: not publication quality.*



Preparation of α-aminonitrile 24:



To a 4 mL vial was added the diamine **24** (50.5 mg, 0.22 mmol, 1.0 equiv), rose bengal (6.58 mg, 6.46 µmol, 3 mol %), trimethylsilyl cyanide 98 % (108 uL, 0.86 mmol, 4.0 equiv), and acetonitrile (2.15 mL, 0.1 M) The reaction was stirred vigorously under

dry air while being The reaction was irradiated with a 34 W Kessil H150 Blue LED setup for 3 hours. Once the reaction was complete, K_2CO_3 was added, and the reaction was stirred for 10 minutes. The crude product was purified via SiO_2 column chromatography [5 g SiO_2, 10 mm column, 18% 2 M NH_3 in MeOH acetonitrile] to yield **95** as a light pink oil (11.0 mg, 20% yield).

α-aminonitrile 24:

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.10 (t, *J* = 11.8 Hz, 1H), 3.01 – 2.91 (m, 3H), 2.67 (ddd, *J* = 12.2, 5.2, 2.1 Hz, 2H), 2.49 – 2.34 (m, 3H), 2.15 (qd, *J* = 13.2, 3.9 Hz, 1H), 1.97 (ddd, *J* = 12.5, 5.4, 3.3 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.85 (dt, *J* = 11.8, 3.4 Hz, 1H), 1.76 – 1.60 (m, 4H), 1.60 – 1.51 (m, 2H), 1.51 – 1.41 (m, 2H), 1.35 (tt, *J* = 12.7, 3.7 Hz, 1H), 1.32 – 1.24 (m, 2H), 1.19 (d, *J* = 13.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 117.4, 64.2, 60.8, 54.9, 52.1, 51.5, 49.0, 45.5, 43.3, 25.5, 25.0, 25.0, 24.9, 24.5, 20.3, 20.0.

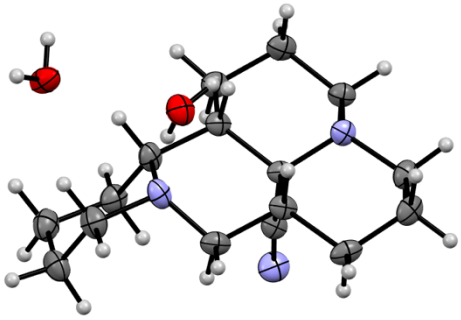
FTIR (NaCl, thin film): 2984, 2930, 2852, 2304, 1459, 1441, 1421, 1266 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{16}H_{25}N_3$ $[M+H]^+$ 260.2121, found 260.2120.

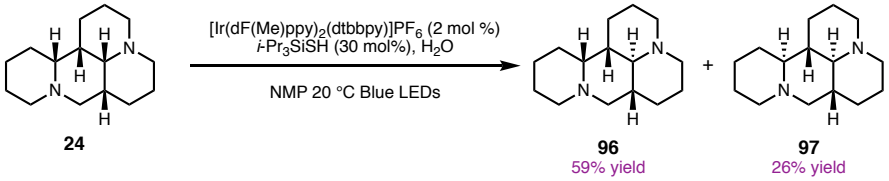
TLC (40% 2 M NH_3 in MeOH/60% ACN), **R_f:** 0.20 ($KMnO_4$).

M.P. 66.8 – 67.9 °C.

Figure 2.38. *X-Ray structure of the dihydrate of (±)-**95**. CCDC number: not publication quality.*



Preparation of diamine 96 and diamine 97:



A one dram vial was charged with $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ (8.7 mg, 8.53 µmol, 2 mol %), diamine **24** (100 mg, 427 µmol, 1 equiv), NMP (1.7 mL, 0.25 M), triisopropylsilanethiol (27.5 µL, 128 µmol, 30 mol %), and water (77 µL, 50 equiv) sequentially, then the vial was sparged with N_2 for 20 minutes. The reaction was irradiated with a 34 W Kessil H150 Blue LED setup for 24 hours. The reaction mixture was passed through a SiO_2 plug with DCM to elute the NMP then 2 M NH_3 in MeOH to elute the products. The crude product mixture was purified via SiO_2 column chromatography [5 g SiO_2, 10 mm column, eluted with 40% 2 M NH_3 in MeOH/60% ACN] to yield the diamine **96** as a white crystalline solid (58.6 mg, 59% yield) and

diamine **97** as a white crystalline solid (26.2 mg, 26% yield). X-Ray quality crystals were grown from slow evaporation of a solution of each diamine in ACN.

Diamine 96:

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 – 2.73 (m, 6H), 2.38 (dd, *J* = 11.4, 3.9 Hz, 1H), 1.99 (td, *J* = 11.7, 3.3 Hz, 1H), 1.95 – 1.88 (m, 1H), 1.88 – 1.82 (m, 1H), 1.79 – 1.52 (m, 9H), 1.51 – 1.32 (m, 3H), 1.27 – 1.18 (m, 1H), 1.17 – 1.07 (m, 2H), 1.02 (qd, *J* = 12.9, 4.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 65.7, 60.6, 56.8, 56.5, 54.8, 51.0, 43.2, 41.3, 29.0, 27.7, 26.0, 25.5, 25.2, 19.2, 18.8.

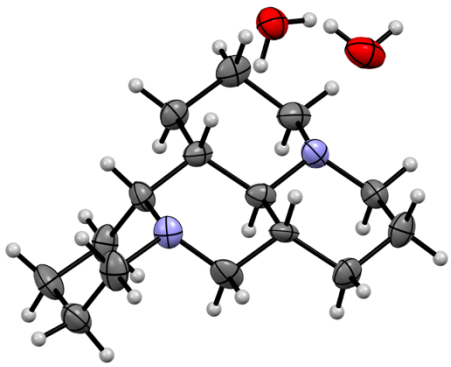
FTIR (NaCl, thin film): 2930, 2856, 2802, 2750, 1265 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{15}H_{26}N_2$ $[M]^+$ 234.20905, found 234.20943.

TLC (40% 2 M NH_3 in MeOH/60% ACN), **R_f:** 0.11 ($KMnO_4$).

M.P. 57.1 – 58.8 °C.

Figure 2.39. *X-Ray structure of (±)-**96**. CCDC number: not publication quality.*



Diamine 97:

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 – 2.75 (m, 3H), 2.68 (dd, *J* = 11.3, 3.5 Hz, 1H), 2.02 – 1.89 (m, 3H), 1.90 – 1.80 (m, 3H), 1.80 – 1.54 (m, 6H), 1.51 (td, *J* = 10.1, 2.2 Hz, 1H), 1.23 – 1.04 (m, 5H), 0.94 (qd, *J* = 12.5, 4.5 Hz, 1H), 0.88 – 0.74 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 71.3, 66.7, 61.8, 56.8, 56.6, 56.2, 44.6, 39.3, 29.9, 29.5, 29.1, 27.0, 25.7, 25.1, 24.6.

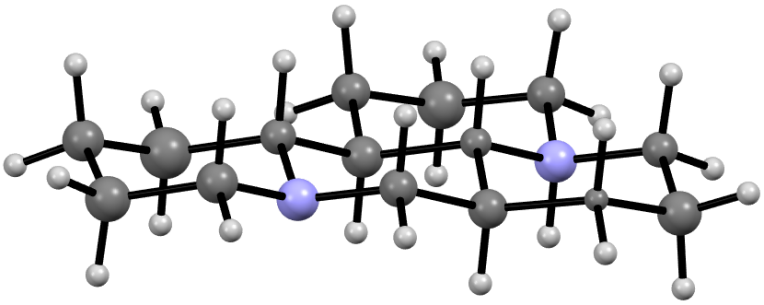
FTIR (NaCl, thin film): 2935, 2854, 2802, 2754, 1264 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{15}H_{26}N_2$ $[M]^+$ 234.20905, found 234.20976.

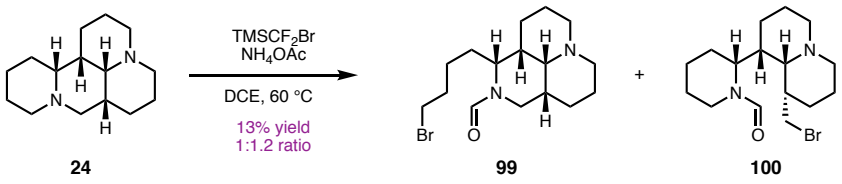
TLC (40% 2 M NH_3 in MeOH/60% ACN), **R_f:** 0.32 ($KMnO_4$).

M.P. 46.8 – 49.1 °C.

Figure 2.40. *X-Ray structure of (±)-**97**. CCDC number: not publication quality.*



Preparation of alkyl bromides 99 and 100:



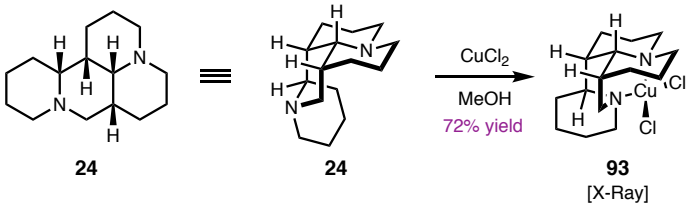
A 1-dram vial in a glovebox was charged with diamine **24** (46.9 mg, 200 μmol, 1 equiv), ammonium acetate (61.7 mg, 800 μmol, 4 equiv), dichloroethane (0.5 mL, 0.4 M), and lastly (bromodifluoromethyl)trimethylsilane (124 μL, 800 μmol, 4 equiv). The reaction was sealed and stirred at 60 °C for 12 hours. Upon completion the mixture was filtered through a pad of celite which was washed with EtOAc (3 x 10 mL). The solution was concentrated under reduced pressure and purified via SiO_2 column chromatography on SiO_2 [5 g SiO_2, 10 mm column diameter, eluted with 5% 2 M NH_3 in MeOH/95% $CHCl_3$ containing 0.75% EtOH] to yield the mixture of products **99** and **100** as a clear colorless oil (11.8 mg, 13% yield).

alkyl bromides 99 and 100:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.03 (s, 1H), 4.39 (dt, *J* = 12.3, 5.1 Hz, 1H), 3.90 (dd, *J* = 12.7, 4.3 Hz, 1H), 3.49 (t, *J* = 12.8 Hz, 1H), 3.45 – 3.31 (m, 6H), 2.98 – 2.89 (m, 2H), 2.81 – 2.73 (m, 5H), 2.37 (dtd, *J* = 13.6, 11.4, 4.8 Hz, 1H), 2.29 (dddd, *J* = 13.8, 12.5, 10.2, 4.9 Hz, 1H), 2.08 (q, *J* = 3.3 Hz, 2H), 2.01 – 1.93 (m, 1H), 1.93 – 1.79 (m, 10H), 1.76 (ddt, *J* = 14.5, 11.4, 3.0 Hz, 3H), 1.72 – 1.58 (m, 10H), 1.58 – 1.49 (m, 3H), 1.45 (dddd, *J* = 13.1, 9.9, 5.1, 2.6 Hz, 4H), 1.41 – 1.31 (m, 2H), 1.31 – 1.23 (m, 2H), 1.23 – 1.14 (m, 1H).

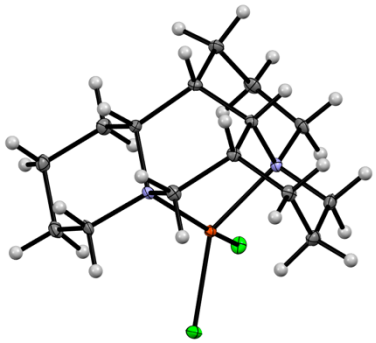
^{13}C NMR (101 MHz, $CDCl_3$): δ 161.2, 160.8, 63.9, 63.8, 59.3, 57.7, 57.6, 57.5, 57.5, 51.6, 42.3, 39.1, 37.8, 37.2, 35.9, 35.8, 34.1, 33.6, 32.7, 32.7, 30.2, 30.0, 28.1, 28.1, 26.6, 26.5, 25.9, 25.3, 22.7, 22.6, 21.7, 21.6.

Preparation of copper complex 93:

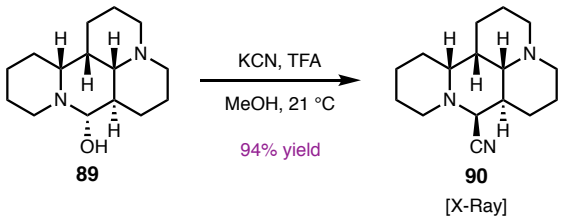


A 1-dram vial in a glovebox was charged anhydrous copper (II) chloride (57.7 mg, 429 umol, 1.0 equiv) and anhydrous MeOH (0.85 mL, 0.5 M) and was stirred until a homogenous solution was obtained. A separate 2-dram vial in a glovebox was charged with isomatridine (**24**) and MeOH (0.85 mL, 0.5 M) and was stirred until a homogenous solution was obtained. The two solutions were mixed, which initially produced a mixed blue/yellow precipitate. The mixture was heated to reflux for one minute, and then cooled to 21 °C at which point green crystals formed in a cloudy suspension. The supernatant was decanted, and the crystals were washed with MeOH (2 x 0.3 mL) and dried under vacuum (0.3 torr, 30 minutes) to yield the product **93** as a bright green crystalline solid (114 mg, 72% yield). The copper complex was found to be air stable but decomposed in aqueous solution. The copper complex could also be reduced to a copper (I) complex with zinc dust. The obtained crystals were directly used to obtain an X-ray structure.

Figure 2.41. *X-Ray structure of (±)-**93**. CCDC number: not publication quality.*



Preparation of α-aminonitrile 90:



A 10 mL flask was charged with potassium cyanide (91.0 mg, 1.40 mmol, 7.0 equiv), hemi-aminal **89** (50.0 mg, 200 umol, 1.0 equiv), and MeOH (2.00 mL, 0.1 M). The flask was capped with a septa, then trifluoroacetic acid (153 uL, 2.00 mmol, 10 equiv) was added. The reaction was stirred while sealed at 21 °C for 1 hour. Upon completion the reaction was made basic with 3 M NaOH. The reaction mixture was extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product **90** was obtained as a white crystalline solid (48.7 mg, 94% yield) and did not require additional purification.

α-aminonitrile 90:

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.60 (d, *J* = 4.5 Hz, 1H), 3.02 – 2.91 (m, 3H), 2.89 (td, *J* = 12.0, 2.9 Hz, 1H), 2.71 (d, *J* = 11.0 Hz, 1H), 2.51 – 2.40 (m, 3H), 2.38 (tt, *J* = 11.9, 4.7 Hz, 1H), 1.88 (qt, *J* = 13.2, 4.3 Hz, 1H), 1.80 – 1.57 (m, 7H), 1.57 – 1.40 (m, 4H), 1.35 (qd, *J* = 13.9, 13.5, 4.3 Hz, 1H), 1.31 – 1.21 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 115.9, 62.5, 59.8, 59.1, 54.3, 54.2, 45.6, 40.3, 29.3, 28.7, 27.7, 25.9, 25.8, 24.0, 19.8, 18.4.

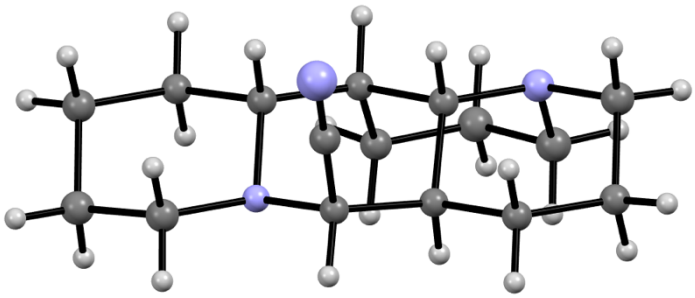
FTIR (NaCl, thin film): 3052, 2984, 2941, 2304, 1420, 1268, 895 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{16}H_{25}N_3$ $[M+H]^+$ 260.2121, found 260.2120.

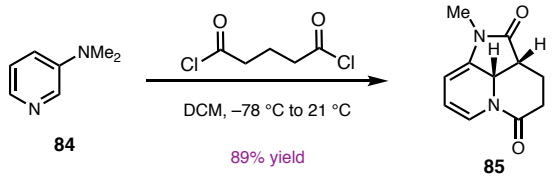
TLC (10% 2 M NH_3 in MeOH /90% $CHCl_3$ stabilized with 0.75% EtOH), **R_f:** 0.35 ($KMnO_4$).

M.P. 180.2 °C – 181.1 °C

Figure 2.42. *X-Ray structure of (±)-**90**. CCDC number: not publication quality.*



Preparation of monocycle 85:



A 50 mL flask under N_2 was charged with glutaryl chloride (0.21 mL, 1.64 mmol, 1.0 equiv) and DCM (16.4 mL, 0.1 M). The solution was cooled to –78 °C then 3-dimethylaminopyridine (**84**) (1.00 g, 8.19 mmol, 5.0 equiv) was added dropwise. The mixture was stirred for 5 minutes after which it was warmed to 21 °C and stirred for 2 hours at this temperature. The reaction was then quenched with TFA (1 mL) and washed with water (30 mL). The organic layer was then washed with sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained as an orange crystalline solid (289 mg, 89% yield). The product **85** formed X-ray quality crystals directly, and the product did not need any additional purification. The product was found to undergo slow aerobic oxidation in solution.

monocycle 85:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.02 (d, *J* = 7.5 Hz, 1H), 5.78 (dd, *J* = 7.5, 5.6 Hz, 1H), 5.34 (dd, *J* = 5.6, 2.3 Hz, 1H), 4.43 (dd, *J* = 9.8, 2.3 Hz, 1H), 3.05 (s, 4H), 2.64 (dt, *J* = 16.3, 2.7 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.39 – 2.32 (m, 1H), 1.69 – 1.57 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 168.4, 135.8, 121.2, 111.5, 94.6, 52.1, 40.0, 32.1, 26.8, 20.3.

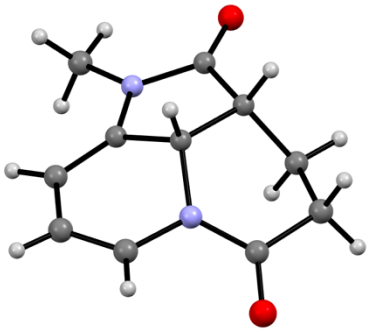
FTIR (NaCl, thin film): 3054, 2985, 2305, 1730, 1718, 1660, 1420, 1273, 1264, 896 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{11}H_{12}N_2O_2$ $[M+H]^+$ 205.0977, found 205.0977

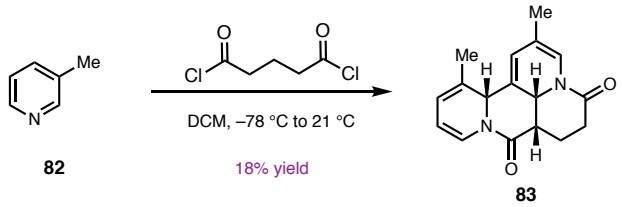
TLC (90% EtOAc /10% Hexanes), **R_f:** 0.23 ($KMnO_4$).

M.P. 133.4 °C – 135.2 °C.

Figure 2.43. *X-Ray structure of (±)-**85**. CCDC number: not publication quality.*



Preparation of dimethyltetracycle 83:



A 500 mL flask under N2 was charged with glutaryl chloride (1.37 mL, 10.7 mmol, 1.0 equiv), and DCM (107 mL, 0.1 M). The solution was cooled to –78 °C then 3-methylpyridine (**82**) (5.22 mL, 53.7 mmol, 5.0 equiv) was added. The solution was stirred at –78 °C for 30 minutes and then was allowed to warm to 21 °C and stir for 24 hours. Upon completion, the reaction was concentrated under reduced pressure, and then under vacuum on a Schlenk line (0.3 torr, 30 minutes). The residue was suspended in MeOH (30 mL) and is collected by suction filtration. The product was washed with MeOH (2 x 10 mL) and Et_2O (2 x 10 mL). The obtained solids were dried under vacuum to yield the

product **83** as a tan crystalline solid (552 mg, 18% yield). The product underwent aerobic oxidation in solution in air.

dimethyltetracycle 83:

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.93 – 6.83 (m, 2H), 5.84 (d, *J* = 5.9 Hz, 1H), 5.65 (d, *J* = 2.6 Hz, 1H), 5.15 – 5.06 (m, 2H), 4.68 (dd, *J* = 7.5, 2.8 Hz, 1H), 3.05 – 2.92 (m, 2H), 2.59 (ddt, *J* = 13.6, 5.9, 2.7 Hz, 1H), 2.44 (dd, *J* = 17.8, 5.0 Hz, 1H), 2.00 (tt, *J* = 13.4, 5.1 Hz, 1H), 1.85 (s, 3H), 1.83 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 167.9, 129.1, 126.4, 123.6, 121.0, 120.9, 119.9, 118.6, 102.9, 57.6, 53.2, 37.1, 28.5, 21.2, 19.4, 18.1.

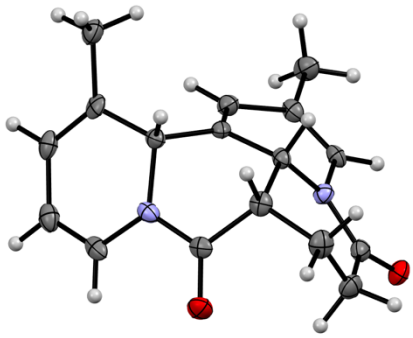
FTIR (NaCl, thin film): 3053, 2986, 1712, 1420, 1266, 896 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{17}H_{18}N_2O_2$ $[M+H]^+$ 283.1447, found 283.1434

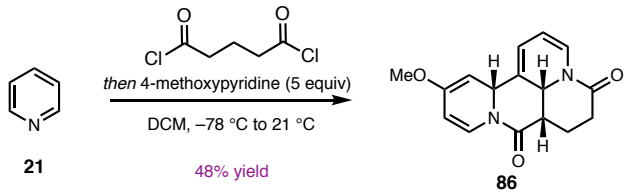
TLC (60% EtOAc /40% Hexanes), **R_f:** 0.20 ($KMnO_4$).

M.P. 197.8 °C – 201.7 °C.

Figure 2.44. *X-Ray structure of (±)-**83**. CCDC number: not publication quality.*



Preparation of enol ether 86:



A 500 mL flask under N_2 was charged with glutaryl chloride (3.78 mL, 29.6 mmol, 1.0 equiv) and DCM (296 mL, 0.1 M). The solution was cooled to –78 °C then pyridine (12.0 mL, 148 mmol, 5.0 equiv) was added over the course of one minute. The slurry was stirred at –78 °C for 15 minutes after which it was allowed to warm to 21 °C and stir until the mixture became homogenous. Upon reaching homogeneity the 4-methoxypyridine (15.0 mL, 29.6 mmol, 5.0 equiv) was added immediately all at once. The reaction was then stirred at 21 °C for 24 hours. Upon completion, the reaction was concentrated under reduced pressure, and then under vacuum on a Schlenk line (0.3 torr, 30 minutes). The residue was suspended in MeOH (10 mL), and the solids were isolated by suction filtration. The solids were washed with MeOH (2 x 5 mL) and Et_2O (2 x 15 mL). The solids were dried under vacuum (0.3 torr, 30 minutes) to yield the product **86** as a tan crystalline solid.

enol ether 86:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.9 Hz, 1H), 7.03 (dq, *J* = 7.9, 1.0 Hz, 1H), 6.03 (ddt, *J* = 10.2, 3.7, 1.2 Hz, 1H), 5.79 (dddd, *J* = 10.2, 5.7, 2.5, 1.0 Hz, 1H), 5.56 (d, *J* = 8.1 Hz, 1H), 5.35 (t, *J* = 3.0 Hz, 1H), 5.16 (ddt, *J* = 7.6, 5.7, 0.9 Hz, 1H), 4.71 (d, *J* = 7.3 Hz, 1H), 3.50 (s, 3H), 2.98 (ddd, *J* = 18.6, 13.0, 6.0 Hz, 1H), 2.72 (dt, *J* = 7.2, 3.6 Hz, 1H), 2.59 (dddd, *J* = 13.7, 6.0, 3.4, 2.5 Hz, 1H), 2.46 (dddd, *J* = 18.3, 5.3, 2.5, 1.3 Hz, 1H), 1.94 (dddd, *J* = 13.8, 13.1, 5.3, 4.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3, 167.9, 149.1, 129.8, 122.4, 121.5, 118.2, 109.0, 106.8, 103.5, 58.5, 54.4, 53.4, 36.9, 28.7, 19.9.

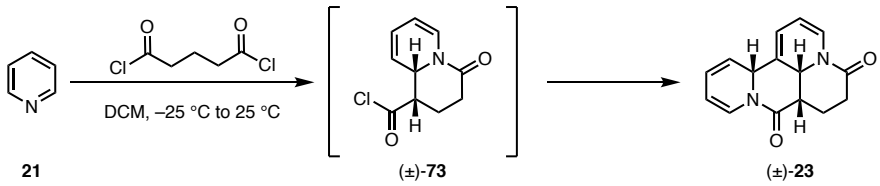
FTIR (NaCl, thin film): 3053, 2986, 2932, 1831, 2300, 1674, 1653, 1591, 1414, 1266, 1166 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{16}H_{16}N_2O_3$ $[M+H]^+$ 285.1239, found 285.1231.

TLC (4% MeOH /96% DCM), **R_f:** 0.39 ($KMnO_4$).

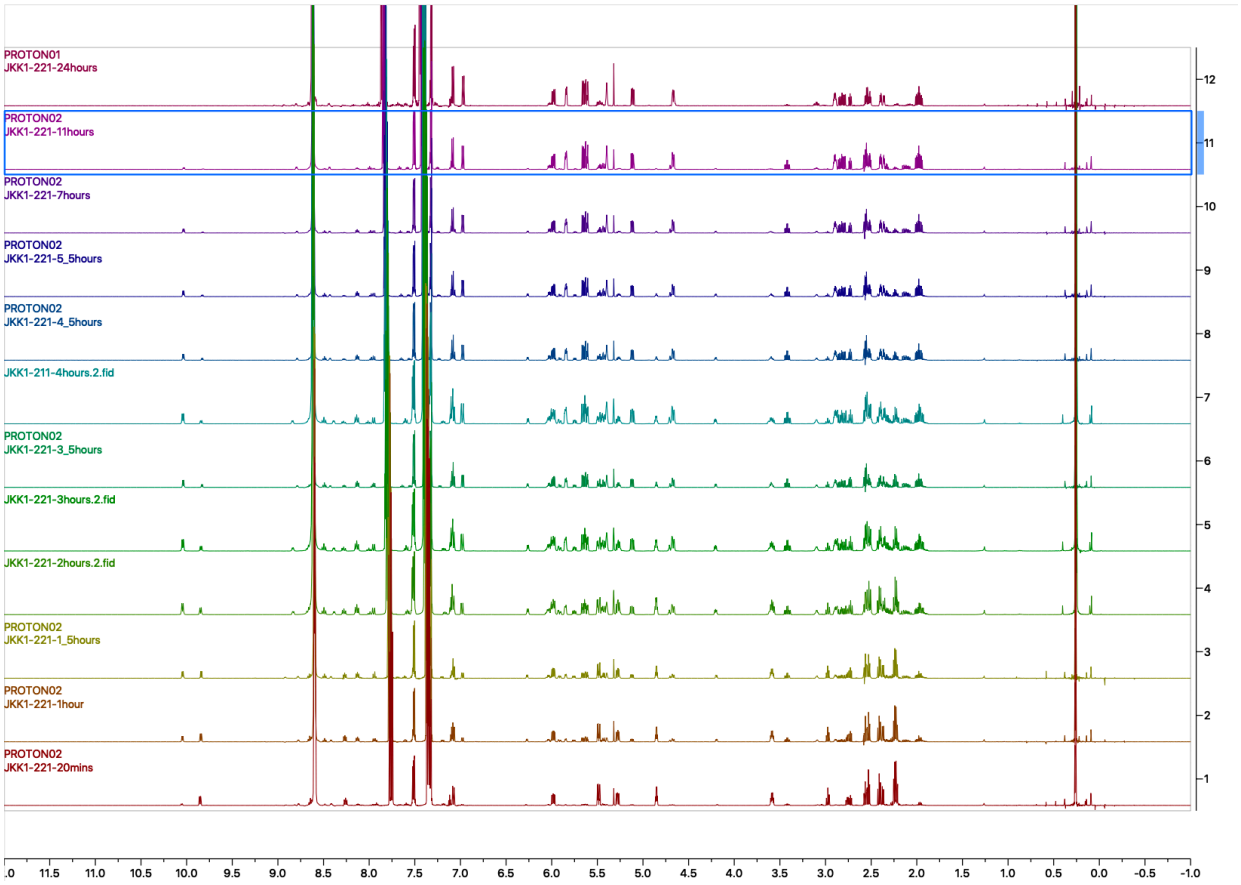
M.P. 182.0 °C – 184.3 °C.

Cyclization NMR Study:



In a glovebox, an NMR tube was charged with CD_2Cl_2 (0.75 mL, 0.045 M), pyridine (34 μL, 0.42 mmol, 12.0 equiv), and $PhSiMe_3$ (5.1 mg, 0.034 mmol, 0.97 equiv). The solution was cooled in the glovebox freezer (–25 °C) for 15 minutes. To the cold solution was rapidly added glutaryl chloride (4.5 μL, 0.035 mmol, 1.0 equiv). The tube was capped and inverted to mix. Initially, a precipitate formed which dissolved after one minute of mixing. The reaction was then monitored by ^{1}H qNMR over the course of 24 hours ($PhSiMe_3$ internal standard).

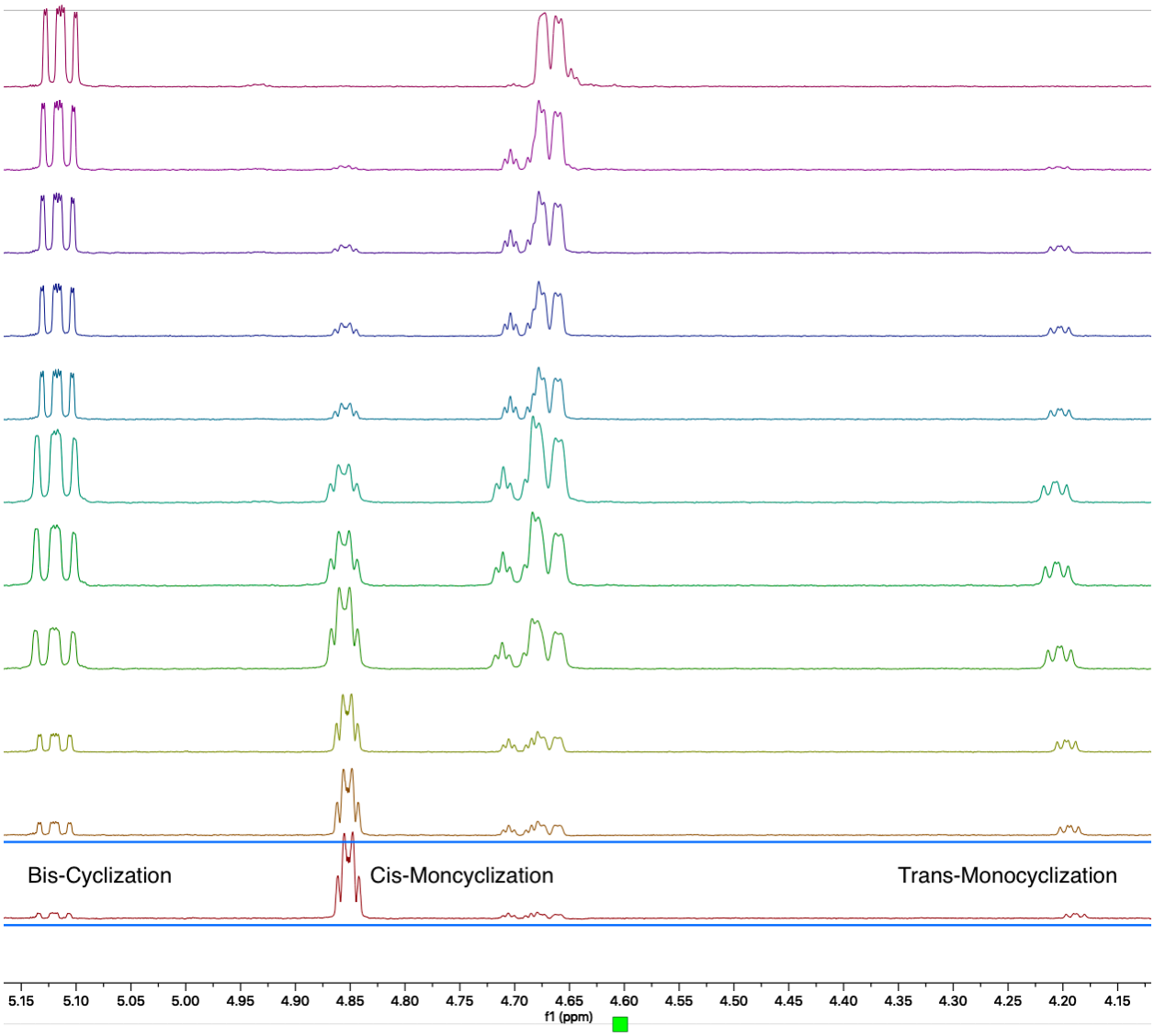
Figure 2.45. *Cyclization of glutaryl chloride and pyridine ^{1}H NMR time-course study.*



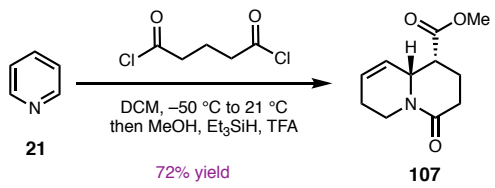
(±)-Acid chloride 73:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.08 (dt, *J* = 8.1, 0.9 Hz, 1H), 5.98 (dddd, *J* = 9.7, 5.6, 2.6, 1.0 Hz, 1H), 5.49 (ddt, *J* = 9.7, 2.9, 1.1 Hz, 1H), 5.28 (ddd, *J* = 7.7, 4.9, 1.0 Hz, 1H), 4.85 (dt, *J* = 5.0, 2.8 Hz, 1H), 3.59 (dt, *J* = 6.5, 4.8 Hz, 1H), 2.76 (td, *J* = 7.5, 4.8 Hz, 1H), 2.55 (dt, *J* = 17.1, 7.0 Hz, 1H), 2.40 (dt, *J* = 17.2, 7.2 Hz, 1H), 2.27 – 2.19 (m, 1H).

Figure 2.46. *Cyclization of glutaryl chloride and pyridine ^{1}H NMR time-course study trans isomer inset.*



Preparation of alkenyl ester 107:



A 500 mL oven dried N_2 flushed flask was charged with glutaryl chloride (0.76 mL, 5.92 mmol, 1 equiv) and DCM (59 mL, 0.1 M). The solution was cooled to –50 °C, then pyridine (2.4 mL, 29.6 mmol, 5 equiv) was added dropwise. The thick slurry was stirred at –50 °C for 15 minutes and then allowed to warm to ambient temperature. Once the reaction become homogenous (ca. 30-60 minutes) the methanol (0.48 mL, 11.8 mmol, 2 equiv) was added. The solution was cooled to 0 °C then triethylsilane (14.2 mL, 88.8 mmol, 15 equiv) was added followed by a dropwise addition trifluoroacetic acid (6.8 mL, 88.8 mmol, 15 equiv). The reaction was allowed to warm to ambient temperature and stirred for 18 hours. Once complete, the reaction was made basic with sat. Na_2CO_3, and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via SiO_2 column chromatography [160 g SiO_2, 55 mm diameter column, eluted with 60% Acetone/40% Hexanes] to yield the alkenyl methyl ester **107** as a pale yellow crystalline solid (895 mg, 72% yield).

Alkenyl Ester 107:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 – 5.89 (m, 1H), 5.50 (ddt, *J* = 10.1, 2.9, 1.4 Hz, 1H), 4.76 (ddt, *J* = 12.8, 5.8, 1.3 Hz, 1H), 4.37 (ddt, *J* = 6.9, 4.9, 2.4 Hz, 1H), 3.69 (s, 3H), 3.01 (dt, *J* = 6.6, 4.9 Hz, 1H), 2.73 (td, *J* = 12.2, 4.2 Hz, 1H), 2.61 (ddd, *J* = 17.7, 7.8, 6.7 Hz, 1H), 2.43 (dt, *J* = 17.6, 6.5 Hz, 1H), 2.33 (ddtd, *J* = 20.3, 11.9, 6.0, 2.5 Hz, 1H), 2.10 – 1.96 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 169.1, 129.1, 125.9, 55.8, 52.0, 43.1, 39.8, 30.4, 24.7, 21.6.

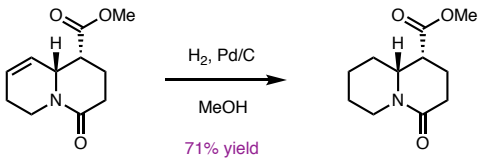
FTIR (NaCl, thin film): 3031, 2951, 2841, 1736, 1642, 1459, 1436, 1417, 1280, 1263, 1233, 1193, 1163, 1014, 988, 917 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{11}H_{15}NO_3$ $[M]^+$ 209.10464, found 209.10482.

TLC (50% acetone/50% hexanes), **R_f:** 0.23 ($KMnO_4$).

M.P. 38.4 – 40.6 °C.

Preparation of methyl ester 108:



107 **108**

A 25 mL flask was charged with alkenyl methyl ester **107** (100 mg, 0.478 mmol, 1 equiv), 10% palladium on carbon (25.4 mg, 23.9 μmol, 5 mol %) and methanol (4.78 mL, 0.1 M). The flask was purged with N_2 (balloon) then with H_2 (balloon). The reaction was stirred vigorously (1500 rpm) until complete consumption of the starting material was observed by TLC (*ca.* 3 hours). Upon completion the reaction was filtered over celite, concentrated under reduced pressure, and purified via SiO_2 column chromatography [20 g SiO_2, 20 mm column diameter, eluted with 25% acetone/75% hexanes] to yield the methyl ester **108** as a white crystalline solid (72.2 mg, 71% yield).

Methyl Ester 108:

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.76 (ddt, *J* = 12.8, 4.3, 2.0 Hz, 1H), 3.73 (s, 3H), 3.74 – 3.67 (m, 1H), 2.98 (dt, *J* = 11.0, 5.8 Hz, 1H), 2.60 – 2.44 (m, 2H), 2.40 – 2.28 (m, 1H), 2.09 – 1.98 (m, 2H), 1.95 (d, *J* = 13.6 Hz, 1H), 1.64 (ddd, *J* = 10.7, 8.4, 5.5 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.51 – 1.36 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 167.9, 58.1, 52.2, 44.7, 43.5, 31.5, 28.4, 25.5, 25.0, 19.6.

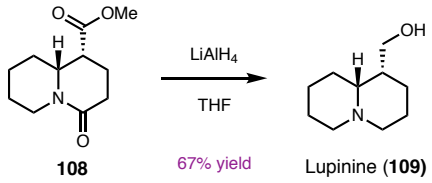
FTIR (NaCl, thin film): 2985, 2952, 1738, 1635, 1439, 1420, 1275, 1262, 1168 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{11}H_{17}NO_3$ $[M]^+$ 211.12029, found 211.12066.

TLC (25% acetone/75% hexanes), **R_f:** 0.22 ($KMnO_4$).

M.P. 74.6 – 75.9 °C.

Preparation of lupinine (109):



108 Lupinine (**109**)

An oven dried N_2 flushed 25 mL flask was charged with methyl ester **108** (50.0 mg, 237 μmol, 1 equiv) and THF (2.4 mL, 0.1 M) after which the flask was equipped with a reflux condenser which had been purged with N_2. The solution was heated to reflux, then lithium aluminum hydride (1.0 M in THF, 1.32 mL, 1.32 mmol, 5.6 equiv) was added dropwise. The solution was refluxed for 3 hours under N_2. Upon completion, the reaction was cooled to ambient temperature, and was quenched by a dropwise addition of a saturated solution of rochelles salt (10 mL). The reaction mixture was extracted with DCM (5 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via SiO_2 column chromatography [20 g SiO_2, 20 mm column diameter, eluted with 35% 2 M NH_3 in MeOH/65% ACN] to yield lupinine as a white crystalline solid (26.9 mg, 67% yield).

Lupinine (109):

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.43 (s, 1H), 4.16 (ddd, *J* = 10.7, 4.7, 1.7 Hz, 1H), 3.69 (d, *J* = 10.7 Hz, 1H), 2.86 – 2.78 (m, 2H), 2.23 – 2.08 (m, 2H), 2.01 (td, *J* = 12.8, 3.0 Hz, 1H), 1.90 – 1.69 (m, 4H), 1.65 – 1.49 (m, 6H), 1.26 (qt, *J* = 13.5, 4.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 66.2, 65.2, 57.3, 57.2, 38.2, 31.6, 29.9, 25.8, 24.8, 23.1.

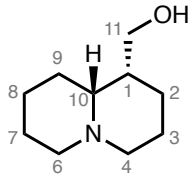
FTIR (NaCl, thin film): 2985, 2941, 2859, 1466, 1445, 1421, 1268, 1262 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{10}H_{19}NO$ $[M]^+$ 169.14612, found 169.14620.

TLC (35% 2 M NH_3 in MeOH/65% ACN), **R_f:** 0.39 ($KMnO_4$).

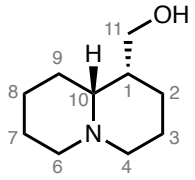
M.P. 47.9 – 51.1 °C.

Table 2.28. *^{1}H NMR data for authentic vs synthetic (±)-lupinine.*



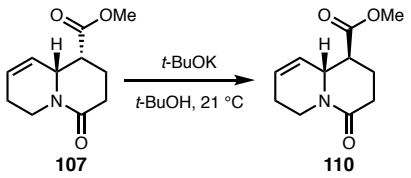
Lupinine literature δ ppm[47] (300 MHz, $CDCl_3$)	Lupinine recorded δ ppm (500 MHz, $CDCl_3$)
4.75 (br s, 1H)	5.43 (br s, 1H)
4.09 - 4.14, (m, 1H)	4.16 (ddd, *J* = 10.7, 4.7, 1.7 Hz, 1H)
3.67 (d, *J* = 10.8 Hz, 1H)	3.69 (d, *J* = 10.7, 1H)
2.81 - 2.77 (m, 2H)	2.86 - 2.78 (m, 2H)
2.14 - 1.99 (m, 3H)	2.23 - 2.08 (m, 2H)
–	2.01 (td, *J* = 12.8, 3.0 Hz, 1H)
1.74 - 1.80 (m, 4H)	1.90 - 1.69 (m, 4H)
1.58 - 1.52 (m, 6H)	1.65 - 1.49 (m, 6H)
1.30 - 1.15 (m, 1H)	1.26 (qt, *J* = 13.5, 4.5 Hz, 1H)

Table 2.29. *^{13}C NMR data for authentic vs synthetic (±)-lupinine.*



Carbon No. lupinine	Lupinine literature δ ppm (75 MHz, $CDCl_3$)	Lupinine recorded δ ppm (101 MHz, $CDCl_3$)	Δ δ
1	38.3	38.2	-0.1
2	31.3	31.6	0.3
3	23.0	23.1	0.1
4	57.0	57.2	0.2
5	57.2	57.3	0.1
6	24.5	24.8	0.3
7	25.7	25.8	0.1
8	29.8	29.9	0.1
9	65.0	65.2	0.2
10	65.9	66.2	0.3

Preparation of trans methyl ester 110:



A 1 L N_2 -flushed flask was charged with **107** (21.6 g, 103 mmol, 1.0 equiv) and *t*-BuOH (413 mL, 0.25 M). Next, potassium *t*-BuOK (4.63 g, 41.3 mmol, 0.4 equiv) was added in a single portion, and the solution was stirred at 21 °C until a 10:1 ratio of **110**:**107** was reached as judged by ^{1}H NMR aliquots (*ca.* 4 hours). Upon completion, the reaction was quenched with acetic acid (2.36 mL, 41.3 mmol, 0.4 equiv). The reaction was concentrated under reduced pressure. The residue was diluted with sat. aq. $NaHCO_3$ and was extracted with DCM (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step without additional purification. An analytically pure sample was obtained by SiO_2 column chromatography (20 g SiO_2, 20 mm column, 40% Acetone/60% Hexanes) to provide **110** as a white crystalline solid.

(±)-methyl ester epimer 110:

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94-5.90 (m, 1H), δ5.56-5.50 (m, 1H), 4.83 (ddt, *J* = 12.9, 5.8, 1.4 Hz, 1H), 4.31 (dq, *J* = 10.6, 2.1 Hz, 1H), 3.76 (s, 3H), 2.64 (td, *J* = 12.4, 4.1 Hz, 1H), 2.56 (ddd, *J* = 17.7, 5.5, 2.5 Hz, 1H), 2.47 (ddd, *J* = 12.3, 10.6, 3.2 Hz, 1H), 2.40 (ddd, *J* = 18.1, 12.6, 6.3 Hz, 1H), 2.25 (dddq, *J* = 17.7, 11.9, 5.9, 2.6 Hz, 1H), 2.11 – 2.00 (m, 2H), 1.94 (qd, *J* = 12.6, 5.4 Hz, 1H).

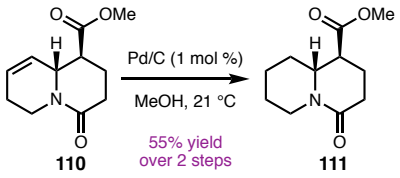
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 168.1, 127.9, 127.1, 56.6, 52.7, 46.4, 39.0, 31.8, 25.3, 24.2

FTIR (NaCl, thin film): 3052, 2953, 1728, 1639, 1434 cm^{-1}.

HMRS: (ESI-TOF) calc'd for $C_{11}H_{15}O_3N$ $[M+H]^+$ 210.1124, found 210.1124.

TLC: 50% acetone in 50% hexane, $\mathbf{R_f}$ = 0.44 ($KMnO_4$).

Preparation of methyl ester 111:



A 1 L flask was charged with all the trans methyl ester **110** from the previous step (*ca.* 21.6 g, 103 mmol, 1.0 equiv), 10% palladium on carbon (971 mg, 0.91 mmol, 1 mol %), and MeOH (456 mL, 0.2 M). The flask was purged with N_2 followed by H_2, then the reaction was stirred at 1500 RPM at 21 °C until full consumption of the starting material was observed by TLC (*ca.* 2 hours). Upon completion, the solution was then filtered through celite with DCM, concentrated under reduced pressure, and purified via SiO_2 column chromatography (1900 g SiO_2, 120 mm column, 40:60 acetone/hexane) to provide **111** as a white crystalline solid (10.6 g, 55% yield).

(±)-methyl ester 111:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80 (ddt, *J* = 13.2, 4.2, 2.1 Hz, 1H), 3.73 (s, 3H), 3.58 (ddd, *J* = 11.0, 8.2, 2.5 Hz, 1H), 2.59 – 2.40 (m, 3H), 2.34 (ddd, *J* = 17.2, 11.1, 5.5 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.92 (dtd, *J* = 13.2, 11.0, 4.8 Hz, 1H), 1.87 – 1.77 (m, 2H), 1.69

(ddq, J = 13.4, 4.0, 2.1 Hz, 1H), 1.48 (qt, J = 12.2, 3.4 Hz, 1H), 1.43 – 1.32 (m, 1H), 1.25 (tdd, J = 13.1, 11.3, 3.5 Hz, 1H).

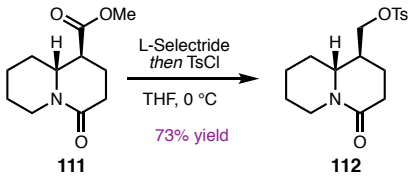
^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 168.4, 58.4, 52.7, 47.1, 43.1, 33.8, 31.8, 25.5, 24.7, 23.5

FTIR (NaCl, thin film): 3050, 2856, 1732, 1645, 1454 cm^{-1}.

HMRS: (ESI-TOF) calc'd for $C_{11}H_{17}O_3N$ $[M+H]^+$ 212.1281, found 212.1281.

TLC: 50% acetone in 50% hexane, $\mathbf{R_f}$ = 0.48 (Seebach's "Magic" Stain)

Preparation of (±)-tosylate 112:



111 **112**

A 1 L N_2 flushed flask was charged with **111** (10.6 g, 50.2 mmol, 1.0 equiv) and THF (201 mL, 0.25 M). The solution was cooled to 0 °C then L-Selectride (1 M in THF, 105 mL, 105 mmol, 2.1 equiv) was added over the course of 5 minutes. The reaction was allowed to stir for 10 mins at 0 °C after which *p*-toluenesulfonyl chloride (16.3 g, 85.3 mmol, 1.7 equiv) as a solution in THF (25 mL, 1 M) was added at such a rate as to prevent the temperature from increasing above 10 °C (*ca.* 10 minutes). The clear solution was stirred for 15 minutes, after which it was quenched by the dropwise addition of a mixture of hydrogen peroxide (30% in water, 9.2 mL, 90.1 mmol, 1.8 equiv) and sodium hydroxide (4.0 g, 100 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 1 hour. Upon the completion, the reaction mixture was concentrated under reduced pressure, diluted with sat. NH_4Cl (50 mL), and extracted with DCM (3 x 75 mL). The

combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via column chromatography (1500 g SiO_2, 120 mm column, 40:60 Acetone/Hexane) to yield **112** in a white crystalline solid (12.4 g, 73% yield).

(±)-tosylate 112:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.75 (ddt, *J* = 13.1, 4.2, 2.2 Hz, 1H), 4.30 – 3.74 (m, 2H), 3.04 (ddd, *J* = 11.5, 7.3, 2.5 Hz, 1H), 2.46 (s, 3H) 2.24 (ddd, *J* = 17.4, 10.3, 5.4 Hz, 2H), 2.24 (ddd, *J* = 17.4, 10.3, 5.4 Hz, 1H), 1.88 – 1.74 (m, 4H), 1.61 (dddd, *J* = 20.4, 15.2, 10.2, 3.7 Hz, 2H), 1.46 – 1.30 (m, 2H), 1.27 – 1.16 (m, 1H).

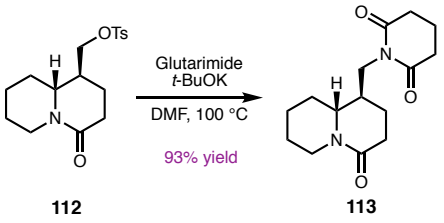
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 145.7, 133.0, 130.5, 128.4, 71.1, 58.3, 43.5, 40.0, 33.5, 31.1, 25.5, 24.9, 22.1.

FTIR (NaCl, thin film): 3053, 2942, 1633, 1362, 1265 cm^{-1}.

HMRS: (ESI-TOF) calc'd for $C_{17}H_{23}SO_4N$ $[M+H]^+$ 338.1424, found 338.1421.

TLC: 50% acetone in 50% hexane, $\mathbf{R_f}$ = 0.36 ($KMnO_4$).

Preparation of (±)-imide 113:



112 **113**

An oven dried N_2 flushed 250 mL flask was charged with glutarimide (9.56 g, 84.5 mmol, 2.3 equiv) and DMF (184 mL, 0.2 M). To the solution was added *t*-BuOK

(5.77 g, 51.4 mmol, 1.4 equiv) after which the mixture was allowed to stir for 15 minutes. A separate oven dried N_2 flushed 500 mL flask was charged with tosylate **112** (12.4 g, 36.7 mmol, 1.0 equiv) and DMF (92 mL, 0.4 M). The glutarimide solution was cannulated into the tosylate solution over the course of 5 minutes. The reaction mixture was then heated at 100 °C until complete consumption of the starting material was observed by TLC (*ca.* 3 hours). Upon completion, the reaction mixture was cooled to 21 °C. The flask was equipped with a shortpath distillation head, and the majority of the DMF was removed by distillation (35 °C, 0.3 torr). The residue was diluted in sat. $NaHCO_3$ (100 mL) and was extracted with DCM (3 x 75 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (500 g SiO_2, 80 mm column, 50% Acetone/50% Hexanes) to yield the product **113** as a white crystalline solid (9.50 g, 93% yield).

(±)-glutarimide 113:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.81 (ddt, *J* = 13.2, 4.3, 2.2 Hz, 1H), 4.15 – 3.55 (m, 2H), 3.00 (ddd, *J* = 10.5, 7.5, 2.4 Hz, 1H), 2.69 (t, *J* = 6.5 Hz, 4H), 2.48 (dt, *J* = 17.3, 5.0 Hz, 1H), 2.38 (td, *J* = 12.9, 2.8 Hz, 1H), 2.18 (ddd, *J* = 16.8, 10.7, 5.3 Hz, 1H), 2.03 – 1.92 (m, 3H), 1.90 – 1.80 (m, 2H), 1.65 (ddt, *J* = 13.7, 9.3, 4.6 Hz, 2H), 1.55 – 1.34 (m, 3H), 1.29 (qd, *J* = 12.7, 3.6 Hz, 1H).

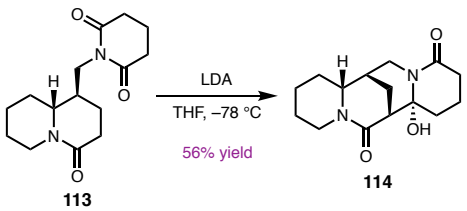
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2, 169.1, 60.9, 43.5, 42.3, 39.4, 33.8, 33.6, 31.5, 25.7, 25.2, 23.2, 17.6.

FTIR (NaCl, thin film): 3053, 2943, 1679, 1631, 1264 cm^{-1}.

HMRS: (ESI-TOF) calc'd for $C_{15}H_{22}O_3N_2$ $[M+H]^+$ 279.1705, found 279.1703.

TLC: 50% acetone in 50% hexane, $\mathbf{R_f}$ = 0.48 (Seebach's "Magic" Stain).

Preparation of (±)-tetracycle 114:



A 250 mL oven dried N_2 flushed flask was charged with diisopropylamine (8.61 mL, 61.4 mmol, 1.8 equiv) and THF (68 mL, 1.0 M). The solution was cooled to 0 °C then *n*-buthyllithium (2.5 M in hexanes, 24.6 mL, 61.4 mmol, 1.8 equiv) was added dropwise after which the reaction was allowed to stir for 15 minutes at 0 °C. A separate 500 mL oven dried N_2 flushed flask was charged with glutarimide **113** (9.50 g, 34.1 mmol, 1.0 equiv) and THF (341 mL, 0.1 M) and was then cooled to –78 °C. The LDA solution was cannulated into the glutarimide solution at –78 °C rapidly over the course of 2 minutes. The reaction was stirred for an additional 2 minutes at –78 °C and then quenched with acetic acid (9.8 mL, 171 mmol, 5.0 equiv) at –78 °C. The reaction mixture was removed from the cooling bath and concentrated under reduced pressure. The crude reaction mixture was diluted in sat. NH_4Cl (100 mL) and extracted with DCM (3 x 75 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via SiO_2 column chromatography (500 g SiO_2, 80 mm column, 15% MeOH/85% EtOAc) to yield the product **114** as a white crystalline solid (5.30 g, 56% yield).

(±)-tetracycle 17:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.74 (ddt, *J* = 13.1, 4.2, 1.9 Hz, 1H), 4.07 (s, 1H), 3.02 – 2.97 (m, 1H), 2.72 (dt, *J* = 4.1, 2.0 Hz, 1H), 2.57 – 2.46 (m, 3H), 2.33 (ddd, *J* = 17.6, 12.6, 6.7 Hz, 1H), 2.23 (pq, *J* = 9.2, 3.2 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.88 – 1.79 (m, 2H), 1.76 – 1.66 (m, 2H), 1.66 – 1.51 (m, 3H), 1.48 – 1.36 (m, 2H).

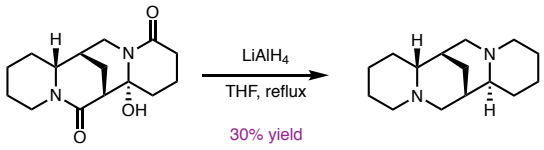
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 168.9, 84.6, 62.9, 49.1, 44.4, 38.7, 38.5, 32.3, 31.8, 31.2, 26.1, 25.2, 20.4, 16.4.

FTIR (NaCl, thin film): 3053, 1641, 1615, 1269, 1407 cm^{-1}.

HMRS: (ESI-TOF) calc'd for $C_{15}H_{22}O_3N_2$ $[M+H]^+$ 212.1705, found 212.1703.

TLC: 15% methanol in 85% ethyl acetate, $\mathbf{R_f}$ = 0.26 (Seebach's "Magic" Stain)

Preparation of sparteine (115):



An N_2 flushed oven dried 1L round bottom flask was charged with bis-amide **114** (5.00 g, 18.0 mmol, 1.0 equiv) and THF (180 mL, 0.1 M). To the solution at 21 °C was added $LiAlH_4$ (1.0 M solution in THF, 341 mL, 341 mmol, 19 equiv). The solution was heated to reflux for 16 hours. Upon completion, the solution was cooled to 21 °C then poured into a solution of sat. aq. Rochelles salt (500 mL) and ice (500 g). After quenching, 3 M NaOH (100 mL) was added, and the mixture was stirred for 15 minutes to break apart the aluminum solids into a white slurry. The mixture was concentrated

under reduced pressure to remove the THF. Subsequently the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified via distillation under reduced pressure (300 mTorr, 80.0 °C – 82.1 °C, 120 °C oil bath temperature) (2.30 g, 80% purity by qNMR in $CDCl_3$, pyrazine standard). The obtained pale-yellow oil was treated with 2 M H_2SO_4 (8 mL, 16 mmol, 2.1 equiv) followed by freezing and water removal through lyophilization. The obtained solids were dissolved in boiling EtOH, cooled to 0 °C, and the crystals were isolated by vacuum filtration to provide sparteine bis-sulfate pentahydrate as a white crystalline solid (2.50 g, 30% yield).

(±)-sparteine (115):

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.93 (dd, *J* = 14.2, 10.7 Hz, 1H), 4.74 (ddt, *J* = 13.1, 4.2, 1.9 Hz, 1H), 4.07 (s, 1H), 3.02 – 2.97 (m, 1H), 2.72 (dt, *J* = 4.1, 2.0 Hz, 1H), 2.57 – 2.46 (m, 3H), 2.33 (ddd, *J* = 17.6, 12.6, 6.7 Hz, 1H), 2.23 (pq, *J* = 9.2, 3.2 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.88 – 1.79 (m, 2H), 1.76 – 1.66 (m, 2H), 1.66 – 1.51 (m, 3H), 1.48 – 1.36 (m, 2H).

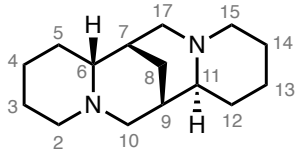
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 168.9, 84.6, 62.9, 49.1, 44.4, 38.7, 38.5, 32.3, 31.8, 31.2, 26.1, 25.2, 20.4, 16.4.

FTIR (NaCl, thin film): 2985, 2933, 1421, 1268 cm^{-1}.

HMRS: (ESI-TOF) calc'd for $C_{15}H_{27}N_2$ $[M+H]^+$ 235.2169, found 235.2177.

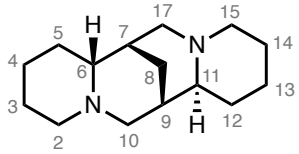
TLC: 15% methanol in 85% ethyl acetate, $\mathbf{R_f}$ = 0.26 (Seebach's "Magic" Stain)

Table 2.30. *^{1}H NMR data for authentic vs synthetic (±)-sparteine bis-sulfate (D_2O).*



Sparteine literature δ ppm (400 MHz, D_2O)[48]	Sparteine recorded δ ppm (600 MHz, D_2O)
3.59 (br t, *J* = 13.0 Hz, 1H)	3.66 (dd, *J* = 14.5, 11.3 Hz, 1H)
3.48–3.31 (m, 4H)	3.52 – 3.45 (m, 3H)
–	3.41 (dt, *J* = 12.1, 3.3 Hz, 1H)
3.24 (br d, *J* = 11.0 Hz, 1H)	3.31 (dd, *J* = 11.9, 2.5 Hz, 1H)
3.17–2.96 (m, 4H)	3.20 – 3.14 (m, 2H)
–	3.11 (td, *J* = 12.7, 3.5 Hz, 2H)
2.55 (br d, *J* = 10.0 Hz, 1H)	2.62 (d, *J* = 11.3 Hz, 1H)
2.22 (br s, 1H)	2.30 (s, 1H)
–	2.15 (dq, *J* = 15.3, 4.1 Hz, 1H)
2.08 (br d, *J* = 15.0 Hz, 1H)	2.04 (d, *J* = 14.7 Hz, 1H)
2.01–1.44 (m, 13H)	1.98 – 1.86 (m, 6H)
–	1.86 – 1.71 (m, 3H)
–	1.71 – 1.56 (m, 3H)

Table 2.31. *^{13}C NMR data for authentic vs synthetic (±)-sparteine bis-sulfate (D_2O).*



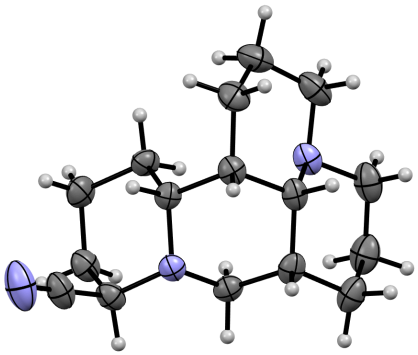
Carbon Number	Sparteine literature δ ppm (101 MHz, D_2O)	Sparteine literature δ ppm (101 MHz, D_2O)	Δ δ
6	66.5	66.5	0.0
11	63.2	63.2	0.0
10	57.2	57.1	–0.1
2	56.5	56.5	0.0
15	55.0	55.0	0.0
17	49.0	48.9	–0.1
9	32.0	32.0	0.0
12	31.3	31.3	0.0
7	29.1	29.1	0.0
5	26.8	26.8	0.0
3	22.7	22.7	0.0
4	22.5	22.5	0.0
14	22.4	22.4	0.0
8	21.9	21.9	0.0
13	21.5	21.5	0.0

2.8 X-RAY CRYSTALLOGRAPHY REPORTS

Low-temperature diffraction data (φ- and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to either a PHOTON 100 CMOS detector with Mo-Kα radiation (λ = 0.71073 Å) or a PHOTON II CPAD detector with either Mo-Kα radiation (λ = 0.71073 Å) or Cu-Kα radiation (λ = 1.54178 Å) from a fine-focus sealed X-ray tube. All diffractometer manipulations, including data collection integration and scaling, were carried out using the Bruker APEXII software.[49] Absorption corrections were applied using SADABS.[50] The structure was solved by intrinsic phasing using SHELXT[51] and refined against F2 on all data by full-matrix least squares with SHELXL-2014[52] using established refinement techniques.[53] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl and hydroxyl groups). Absolute configuration was determined by anomalous dispersion[54] and confirmed by Bayesian statistical analysis using the program PLATON.[55] Graphical representation of the structure with 50% probability thermal ellipsoids was generated using Mercury visualization software.[56]

Crystallographic Analysis of (±)-105.

Special Refinement Details



Compound (±)-**105** crystallizes in the triclinic space group P-1 with two molecules in the asymmetric unit. CCDC number: 2159774.

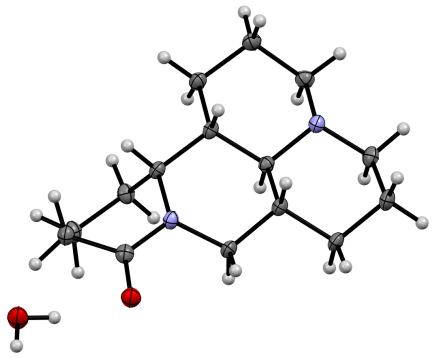
Table 2.32. *Crystal data and structure refinement for (±)-**105**.*

Identification code	V22048
Empirical formula	$C_{16}H_{25}N_3$
Formula weight	259.39
Temperature/K	200.0
Crystal system	triclinic
Space group	P-1
a/Å	10.3418(10)
b/Å	11.0488(9)
c/Å	13.5340(12)
α/°	71.002(5)
β/°	75.301(7)
γ/°	89.676(5)
Volume/Å^3	1409.4(2)
Z	4
ρ_{calc}g/cm^3	1.222
μ/mm^{-1}	0.560

F(000)	568.0
Crystal size/mm^3	0.3 × 0.15 × 0.15
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.166 to 150.084
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -16 ≤ l ≤ 16
Reflections collected	32777
Independent reflections	5743 [R_{int} = 0.0603, R_{sigma} = 0.0397]
Data/restraints/parameters	5743/0/343
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0497, wR_2 = 0.1416
Final R indexes [all data]	R_1 = 0.0579, wR_2 = 0.1522
Largest diff. peak/hole / e Å^{-3}	0.34/-0.22

Crystallographic Analysis of (–)-30 monohydrate.

Special Refinement Details



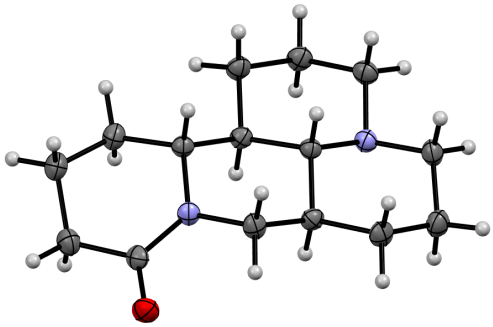
Compound (–)-**30** monohydrate crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = 0.09(15). Bayesian statistics further confirm the absolute stereochemistry: P2(true) = 1.000, P3(true) = 0.992, P3(rac-twin) = 0.008, and P3(false) = 0.1x10^{-10}. CCDC number: 2163777.

Table 2.33. *Crystal data and structure refinement for (–)-**30** monohydrate.*

Identification code	V22047
Empirical formula	$C_{15}H_{28}N_2O_3$
Formula weight	266.38
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.5987(12)
b/Å	14.549(5)
c/Å	7.3792(15)
α/°	90
β/°	99.85(2)
γ/°	90
Volume/Å^3	698.0(3)
Z	2
ρ_{calc}g/cm^3	1.267
μ/mm^{-1}	0.665
F(000)	292.0
Crystal size/mm^3	0.15 × 0.1 × 0.05
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	12.166 to 148.87
Index ranges	$-7 \leq h \leq 8$, $-18 \leq k \leq 17$, $-9 \leq l \leq 9$
Reflections collected	10516
Independent reflections	2832 [R_{int} = 0.0508, R_{sigma} = 0.0415]
Data/restraints/parameters	2832/1/175
Goodness-of-fit on F^2	0.895
Final R indexes [I>=2σ (I)]	R_1 = 0.0357, wR_2 = 0.1073
Final R indexes [all data]	R_1 = 0.0396, wR_2 = 0.1131
Largest diff. peak/hole / e Å^{-3}	0.22/-0.18
Flack parameter	0.09(15)

Crystallographic Analysis of (+)-27.

Special Refinement Details



Compound (+)-**27** crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = -0.16(18). Bayesian statistics further confirm the absolute stereochemistry: P2(true) = 1.000, P3(true) = 0.988, P3(rac-twin) = 0.012, and P3(false) = 0.2×10^{-8}. CCDC number: 2159773.

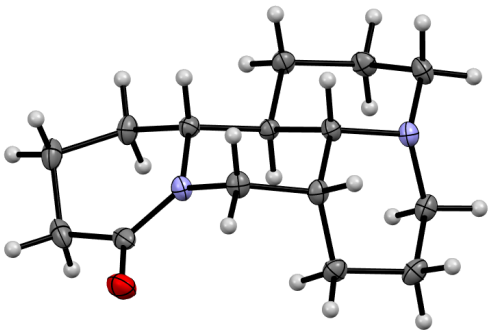
Table 2.34. *Crystal data and structure refinement for (+)-**27**.*

Identification code	V22044
Empirical formula	$C_{15}H_{24}N_2O$
Formula weight	248.36
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.6233(8)
b/Å	8.0886(11)
c/Å	12.9022(19)
α/°	90
β/°	103.235(9)
γ/°	90
Volume/Å^3	672.85(16)
Z	2

ρ_{calc}g/cm^3	1.226
μ/mm^{-1}	0.599
F(000)	272.0
Crystal size/mm^3	0.3 × 0.15 × 0.15
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.038 to 159.11
Index ranges	$-8 \leq h \leq 8$, $-10 \leq k \leq 10$, $-16 \leq l \leq 14$
Reflections collected	11330
Independent reflections	2847 [R_{int} = 0.0738, R_{sigma} = 0.0617]
Data/restraints/parameters	2847/1/163
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0485, wR_2 = 0.1361
Final R indexes [all data]	R_1 = 0.0527, wR_2 = 0.1420
Largest diff. peak/hole / e Å^{-3}	0.36/-0.25
Flack parameter	-0.16(18)

Crystallographic Analysis of (±)-29.

Special Refinement Details



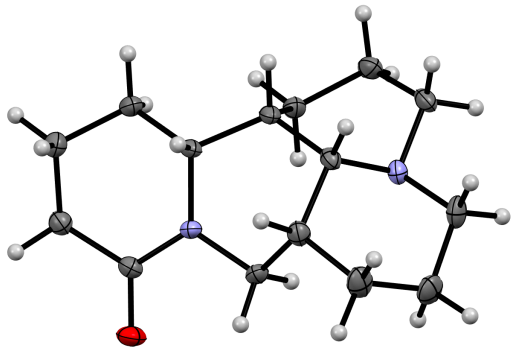
Compound (±)-**29** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. CCDC number: 2159772.

Table 2.35. *Crystal data and structure refinement for (±)-**29**.*

Identification code	V22037
Empirical formula	$C_{15}H_{24}N_2O$
Formula weight	248.36
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.700(3)
b/Å	22.520(9)
c/Å	8.384(2)
α/°	90
β/°	116.574(15)
γ/°	90
Volume/Å^3	1300.4(8)
Z	4
ρ_{calc}g/cm^3	1.269
μ/mm^{-1}	0.620
F(000)	544.0
Crystal size/mm^3	0.3 × 0.2 × 0.1
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.852 to 148.692
Index ranges	$-8 \leq h \leq 9$, $-22 \leq k \leq 27$, $-8 \leq l \leq 10$
Reflections collected	9620
Independent reflections	2589 [R_{int} = 0.0383, R_{sigma} = 0.0318]
Data/restraints/parameters	2589/0/163
Goodness-of-fit on F^2	0.971
Final R indexes [I>=2σ (I)]	R_1 = 0.0368, wR_2 = 0.1194
Final R indexes [all data]	R_1 = 0.0462, wR_2 = 0.1291
Largest diff. peak/hole / e Å^{-3}	0.25/-0.18

Crystallographic Analysis of (+)-25.

Special Refinement Details



Compound (+)-**25** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = -0.11(11). Bayesian statistics further confirm the absolute stereochemistry: P2(true) = 1.000, P3(true) = 1.000, P3(rac-twin) = $0.1x10^{-8}$, and P3(false) = $0.4x10^{-30}$. CCDC number: 2159771.

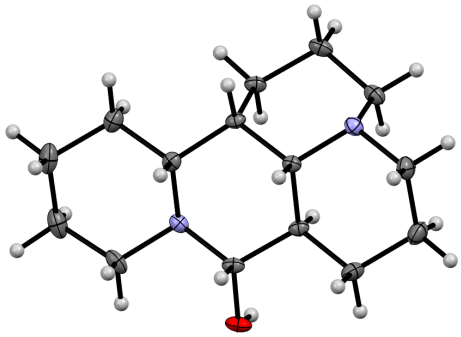
Table 2.36. *Crystal data and structure refinement for (+)-**25**.*

Identification code	V22027
Empirical formula	$C_{15}H_{24}N_2O$
Formula weight	248.36
Temperature/K	100.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.4690(6)
b/Å	11.4564(13)
c/Å	15.6304(13)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1337.5(2)
Z	4
ρ_{calc}g/cm^3	1.233
μ/mm^{-1}	0.602

F(000)	544.0
Crystal size/mm^3	0.4 × 0.15 × 0.15
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	9.572 to 149.208
Index ranges	-8 ≤ h ≤ 9, -14 ≤ k ≤ 13, -19 ≤ l ≤ 19
Reflections collected	19281
Independent reflections	2724 [R_{int} = 0.0440, R_{sigma} = 0.0240]
Data/restraints/parameters	2724/0/163
Goodness-of-fit on F^2	0.973
Final R indexes [I>=2σ (I)]	R_1 = 0.0341, wR_2 = 0.1044
Final R indexes [all data]	R_1 = 0.0346, wR_2 = 0.1052
Largest diff. peak/hole / e Å^{-3}	0.18/-0.24
Flack parameter	-0.11(11)

Crystallographic Analysis of (±)-89.

Special Refinement Details



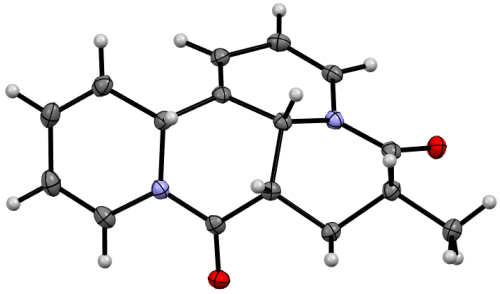
Compound (±)-**89** crystallizes in the triclinic space group P-1 with two molecules in the asymmetric unit. CCDC number: 2159770.

Table 2.37. *Crystal data and structure refinement for (±)-**89**.*

Identification code	V21098
Empirical formula	$C_{15}H_{26}N_2O$
Formula weight	250.38
Temperature/K	100.0
Crystal system	triclinic
Space group	P-1
a/Å	10.6426(13)
b/Å	10.6776(12)
c/Å	13.7940(13)
α/°	107.937(7)
β/°	108.100(5)
γ/°	101.232(6)
Volume/Å^3	1342.4(3)
Z	4
ρ_{calc}g/cm^3	1.239
μ/mm^{-1}	0.601
F(000)	552.0
Crystal size/mm^3	0.2 × 0.15 × 0.15
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.34 to 149.188
Index ranges	-12 ≤ h ≤ 13, -13 ≤ k ≤ 13, -17 ≤ l ≤ 17
Reflections collected	14327
Independent reflections	5244 [R_{int} = 0.0274, R_{sigma} = 0.0317]
Data/restraints/parameters	5244/0/327
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0379, wR_2 = 0.1033
Final R indexes [all data]	R_1 = 0.0395, wR_2 = 0.1047
Largest diff. peak/hole / e Å^{-3}	0.26/-0.26

Crystallographic Analysis of (+)-76.

Special Refinement Details



Compound (+)-**76** crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = 0.13(8). Bayesian statistics further confirm the absolute stereochemistry: P2(true) = 1.000, P3(true) = 1.000, P3(rac-twin) = $0.7x10^{-5}$, and P3(false) = $0.4x10^{-34}$. CCDC number: 2159768.

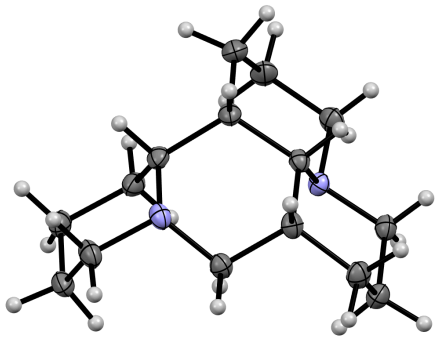
Table 2.38. *Crystal data and structure refinement for (+)-**76**.*

Identification code	V19453
Empirical formula	$C_{16}H_{16}N_2O_2$
Formula weight	268.31
Temperature/K	100.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.8059(15)
b/Å	11.451(2)
c/Å	12.474(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1257.9(4)
Z	4
ρ_{calc}g/cm^3	1.417
μ/mm^{-1}	0.764

F(000)	568.0
Crystal size/mm^3	? × ? × ?
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	12.302 to 149.394
Index ranges	-11 ≤ h ≤ 10, -14 ≤ k ≤ 14, -15 ≤ l ≤ 15
Reflections collected	23931
Independent reflections	2557 [R_{int} = 0.0554, R_{sigma} = 0.0245]
Data/restraints/parameters	2557/0/182
Goodness-of-fit on F^2	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0329, wR_2 = 0.1071
Final R indexes [all data]	R_1 = 0.0339, wR_2 = 0.1113
Largest diff. peak/hole / e Å^{-3}	0.17/-0.20
Flack parameter	0.13(8)

Crystallographic Analysis of (±)-24.

Special Refinement Details



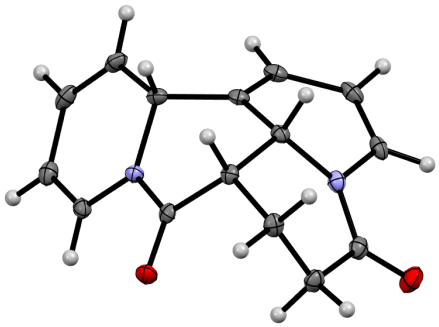
Compound (±)-**24** crystallizes in the monoclinic space group $P2_1/c$ with two molecules in the asymmetric unit. CCDC number: 2159767.

Table. 2.39. *Crystal data and structure refinement for (±)-**24**.*

Identification code	V19355
Empirical formula	$C_{15}H_{26}N_2$
Formula weight	234.38
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.738(2)
b/Å	17.591(4)
c/Å	14.316(3)
α/°	90
β/°	103.629(10)
γ/°	90
Volume/Å^3	2627.8(9)
Z	8
ρ_{calc}g/cm^3	1.185
μ/mm^{-1}	0.521
F(000)	1040.0
Crystal size/mm^3	0.22 × 0.08 × 0.03
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.102 to 161.38
Index ranges	$-13 \leq h \leq 12$, $-21 \leq k \leq 22$, $-17 \leq l \leq 17$
Reflections collected	38183
Independent reflections	5498 [R_{int} = 0.0594, R_{sigma} = 0.0296]
Data/restraints/parameters	5498/0/307
Goodness-of-fit on F^2	1.029
Final R indexes [I>=2σ (I)]	R_1 = 0.0455, wR_2 = 0.1109
Final R indexes [all data]	R_1 = 0.0542, wR_2 = 0.1175
Largest diff. peak/hole / e Å^{-3}	0.27/-0.26

Crystallographic Analysis of (±)-23.

Special Refinement Details



Compound (±)-**23** crystallizes in the monoclinic space group $P2_1/c$ with two molecules in the asymmetric unit. CCDC number: 2159766.

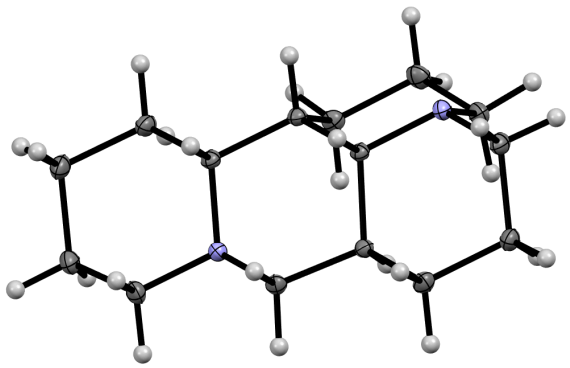
Table 2.40. *Crystal data and structure refinement for (±)-**23**.*

Identification code	V18405 a
Empirical formula	$C_{15}H_{14}N_2O_2$
Formula weight	254.24
Temperature/K	99.97
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.0167(3)
b/Å	15.8509(6)
c/Å	20.6888(9)
α/°	90
β/°	91.261(2)
γ/°	90
Volume/Å^3	2300.47(17)
Z	46
ρ_{calc}g/cm^3	1.468
μ/mm^{-1}	0.099
F(000)	1072.5
Crystal size/mm^3	0.51 × 0.41 × 0.32

Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.7 to 55.02
Index ranges	$-9 \leq h \leq 9$, $-20 \leq k \leq 20$, $-26 \leq l \leq 26$
Reflections collected	40432
Independent reflections	5233 [R_{int} = 0.0603, R_{sigma} = 0.0348]
Data/restraints/parameters	5233/0/343
Goodness-of-fit on F^2	1.049
Final R indexes [I>=2σ (I)]	R_1 = 0.0463, wR_2 = 0.0897
Final R indexes [all data]	R_1 = 0.0608, wR_2 = 0.0929
Largest diff. peak/hole / e $Å^{-3}$	0.48/-0.51

Crystallographic Analysis of (±)-91.

Special Refinement Details



Compound (±)-**91** crystallizes in the triclinic space group P-1 with one molecule in the asymmetric unit. CCDC number: 2159765.

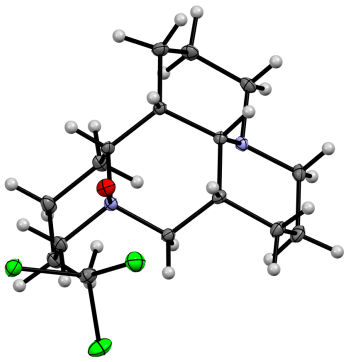
Table 2.41. *Crystal data and structure refinement for (±)-**91**.*

Identification code	d20015

Empirical formula	$C_{15}H_{26}N_2$
Formula weight	234.38
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	5.129(5)
b/Å	9.175(10)
c/Å	14.500(7)
α/°	106.65(3)
β/°	93.82(3)
γ/°	92.81(6)
Volume/Å^3	650.7(10)
Z	2
ρ_{calc}g/cm^3	1.196
μ/mm^{-1}	0.070
F(000)	260.0
Crystal size/mm^3	0.47 × 0.18 × 0.05
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	2.942 to 74.252
Index ranges	$-8 \leq h \leq 8$, $-15 \leq k \leq 15$, $-24 \leq l \leq 24$
Reflections collected	41718
Independent reflections	6408 [R_{int} = 0.0428, R_{sigma} = 0.0339]
Data/restraints/parameters	6408/0/155
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0465, wR_2 = 0.1095
Final R indexes [all data]	R_1 = 0.0753, wR_2 = 0.1238
Largest diff. peak/hole / e Å^{-3}	0.41/-0.24

Crystallographic Analysis of (±)-101 mono-chloroform adduct.

Special Refinement Details



Compound (±)-**101** mono-chloroform adduct crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. CCDC number: 2159764.

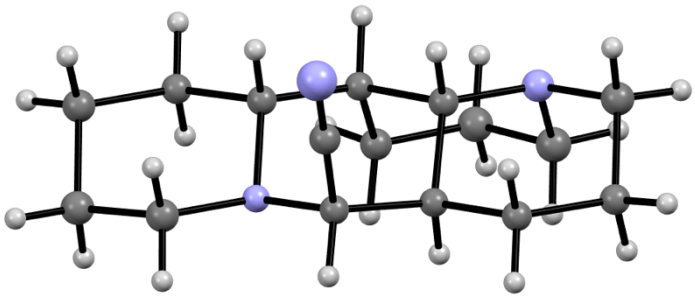
Table 2.42. *Crystal data and structure refinement for (±)-**101** mono-chloroform adduct.*

Identification code	D20014
Empirical formula	$C_{16}H_{27}Cl_3N_2O$
Formula weight	369.74
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.771(4)
b/Å	13.008(10)
c/Å	23.438(6)
α/°	90
β/°	96.271(16)
γ/°	90
Volume/Å^3	1748.9(17)
Z	4
ρ_{calc}g/cm^3	1.404
μ/mm^{-1}	0.528
F(000)	784.0
Crystal size/mm^3	0.45 × 0.4 × 0.32
Radiation	MoKα (λ = 0.71073)

2Θ range for data collection/°	3.496 to 79.03
Index ranges	$-10 \leq h \leq 10$, $-23 \leq k \leq 23$, $-39 \leq l \leq 41$
Reflections collected	113231
Independent reflections	10352 [R_{int} = 0.0335, R_{sigma} = 0.0183]
Data/restraints/parameters	10352/0/199
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0342, wR_2 = 0.0843
Final R indexes [all data]	R_1 = 0.0442, wR_2 = 0.0886
Largest diff. peak/hole / e $Å^{-3}$	0.95/-0.85

Crystallographic Analysis of (±)-90.

Special Refinement Details



Compound (±)-**90** mono-chloroform adduct crystallizes in the triclinic space group P-1 with one molecule in the asymmetric unit. CCDC number: not publication quality.

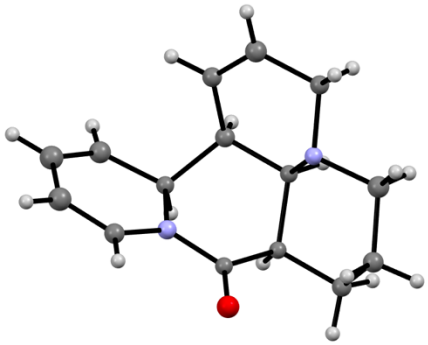
Table 2.43. *Crystal data and structure refinement for (±)-**90**.*

Identification code	V22045
Empirical formula	$C_{16}H_{25}N_3$
Formula weight	259.39
Temperature/K	100.0
Crystal system	triclinic
Space group	P-1

a/Å	5.0835(7)
b/Å	11.3220(13)
c/Å	12.058(2)
α/°	94.182(7)
β/°	94.487(11)
γ/°	95.227(12)
Volume/Å^3	686.75(18)
Z	2
ρ_{calc}g/cm^3	1.254
μ/mm^{-1}	0.575
F(000)	284.0
Crystal size/mm^3	0.4 × 0.1 × 0.1
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.866 to 99.416
Index ranges	$-4 \leq h \leq 2$, $-4 \leq k \leq 10$, $-2 \leq l \leq 11$
Reflections collected	475
Independent reflections	474 [R_{int} = 0.0376, R_{sigma} = 0.0211]
Data/restraints/parameters	474/0/77
Goodness-of-fit on F^2	1.113
Final R indexes [I>=2σ (I)]	R_1 = 0.0377, wR_2 = 0.1220
Final R indexes [all data]	R_1 = 0.0488, wR_2 = 0.1389
Largest diff. peak/hole / e Å^{-3}	0.07/-0.08

Crystallographic Analysis of (–)-81.

Special Refinement Details



Compound (–)-**81** crystallizes in the monoclinic space group Cc with one molecule in the asymmetric unit. Absolute configuration was determined by anomalous dispersion (Flack = -2.3(10). Bayesian statistics further supports the absolute stereochemistry: P2(true) = -0.630, P3(true) = 0.422, P3(rac-twin) = 0.330, and P3(false) = 0.248. CCDC number: not publication quality.

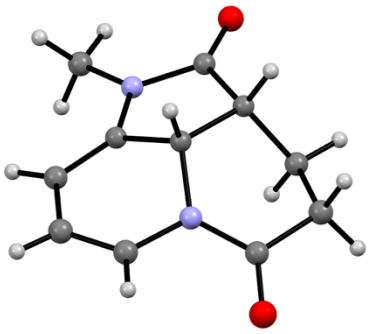
Table 2.44. *Crystal data and structure refinement for (–)-**81**.*

Identification code	D21063
Empirical formula	$C_{17}H_{19}N_3O$
Formula weight	281.35
Temperature/K	296.15
Crystal system	monoclinic
Space group	Cc
a/Å	5.201(3)
b/Å	14.167(7)
c/Å	16.404(18)
α/°	90
β/°	98.21(3)
γ/°	90
Volume/Å^3	1196.4(16)
Z	4
ρ_{calc}g/cm^3	1.562
μ/mm^{-1}	0.100

F(000)	600.0
Crystal size/mm^3	0.4 × 0.25 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.018 to 53.262
Index ranges	-5 ≤ h ≤ 5, -15 ≤ k ≤ 15, -19 ≤ l ≤ 19
Reflections collected	3029
Independent reflections	1770 [R_{int} = 0.0862, R_{sigma} = 0.1507]
Data/restraints/parameters	1770/2/163
Goodness-of-fit on F^2	0.978
Final R indexes [I>=2σ (I)]	R_1 = 0.0563, wR_2 = 0.0893
Final R indexes [all data]	R_1 = 0.1330, wR_2 = 0.1092
Largest diff. peak/hole / e Å^{-3}	0.22/-0.26
Flack parameter	-2.3(10)

Crystallographic Analysis of (±)-85.

Special Refinement Details



Compound (±)-**85** crystallizes in the orthorhombic space group Pbca with one molecule in the asymmetric unit. CCDC number: not publication quality.

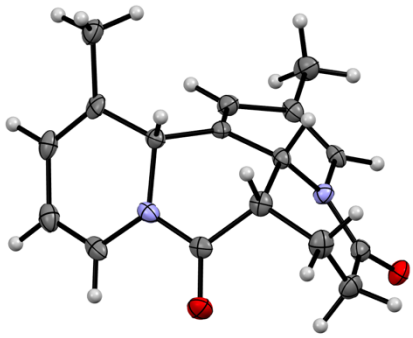
Table 2.45. *Crystal data and structure refinement for (±)-**85**.*

Identification code	V21213
Empirical formula	$C_{19}H_{24}N_2O_4$

Formula weight	344.413
Temperature/K	100.0
Crystal system	orthorhombic
Space group	Pbca
a/Å	13.504(4)
b/Å	9.889(2)
c/Å	14.150(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1889.5(11)
Z	4
ρ_{calc}g/cm^3	1.211
μ/mm^{-1}	0.085
F(000)	736.4
Crystal size/mm^3	0.4 × 0.35 × 0.35
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.76 to 71.94
Index ranges	-18 ≤ h ≤ 16, -12 ≤ k ≤ 13, -18 ≤ l ≤ 22
Reflections collected	12367
Independent reflections	2452 [R_{int} = 0.0700, R_{sigma} = 0.0588]
Data/restraints/parameters	2452/0/62
Goodness-of-fit on F^2	1.049
Final R indexes [I>=2σ (I)]	R_1 = 0.0675, wR_2 = 0.1607
Final R indexes [all data]	R_1 = 0.1149, wR_2 = 0.1894
Largest diff. peak/hole / e Å^{-3}	0.72/-0.74

Crystallographic Analysis of (±)-83.

Special Refinement Details



Compound (±)-**83** crystallizes in the monoclinic space group C2/c with one molecule in the asymmetric unit. CCDC number: not publication quality.

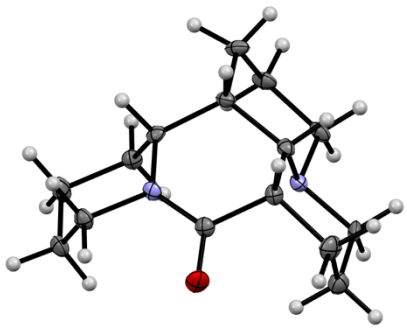
Table 2.46. *Crystal data and structure refinement for (±)-**83**.*

Identification code	V21215
Empirical formula	$C_{17}H_{18}N_2O_2$
Formula weight	282.345
Temperature/K	100.0
Crystal system	monoclinic
Space group	C2/c
a/Å	23.208(15)
b/Å	9.265(3)
c/Å	16.238(16)
α/°	90
β/°	127.920(18)
γ/°	90
Volume/Å^3	2754(3)
Z	8
ρ_{calc}g/cm^3	1.362
μ/mm^{-1}	0.090
F(000)	1200.5
Crystal size/mm^3	0.38 × 0.32 × 0.185
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.44 to 59.14
Index ranges	-27 ≤ h ≤ 29, -10 ≤ k ≤ 12, -22 ≤ l ≤ 22

Reflections collected	9241
Independent reflections	3236 [R_{int} = 0.1607, R_{sigma} = 0.2114]
Data/restraints/parameters	3236/0/192
Goodness-of-fit on F^2	0.958
Final R indexes [I>=2σ (I)]	R_1 = 0.0770, wR_2 = 0.1696
Final R indexes [all data]	R_1 = 0.1798, wR_2 = 0.2363
Largest diff. peak/hole / e $Å^{-3}$	1.00/-0.95

Crystallographic Analysis of (±)-88.

Special Refinement Details



Compound (±)-**88** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. CCDC number: not publication quality.

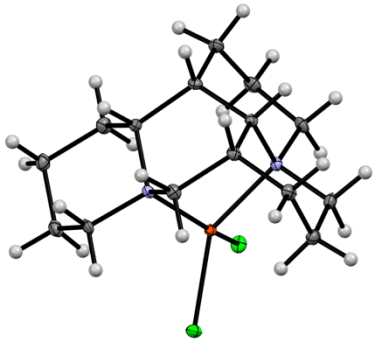
Table 2.47. *Crystal data and structure refinement for (±)-**88**.*

Identification code	V20006
Empirical formula	$C_{16}H_{24}NO$
Formula weight	246.36
Temperature/K	99.99
Crystal system	monoclinic
Space group	$P2_1/n$

a/Å	5.4330(11)
b/Å	13.383(4)
c/Å	18.052(2)
α/°	90
β/°	90.171(11)
γ/°	90
Volume/Å^3	1312.6(5)
Z	4
ρ_{calc}g/cm^3	1.247
μ/mm^{-1}	0.077
F(000)	540.0
Crystal size/mm^3	? × ? × ?
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.444 to 72.732
Index ranges	$-9 \leq h \leq 9$, $-22 \leq k \leq 22$, $-30 \leq l \leq 30$
Reflections collected	34154
Independent reflections	6337 [R_{int} = 0.0685, R_{sigma} = 0.0544]
Data/restraints/parameters	6337/0/163
Goodness-of-fit on F^2	1.123
Final R indexes [I>=2σ (I)]	R_1 = 0.2513, wR_2 = 0.5841
Final R indexes [all data]	R_1 = 0.2577, wR_2 = 0.5904
Largest diff. peak/hole / e Å^{-3}	1.01/-1.12

Crystallographic Analysis of (±)-93.

Special Refinement Details



Compound (±)-**93** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. CCDC number: not publication quality.

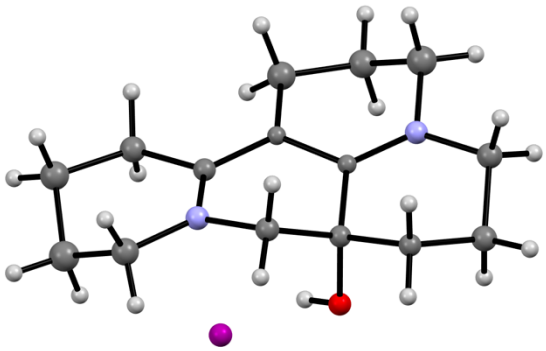
Table 2.48. *Crystal data and structure refinement for (±)-**93**.*

Identification code	d19147
Empirical formula	$C_{15}H_{26}Cl_2CuN_2$
Formula weight	368.82
Temperature/K	99.98
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	8.918(4)
b/Å	13.094(9)
c/Å	13.774(9)
α/°	90
β/°	105.34(5)
γ/°	90
Volume/Å^3	1551.1(17)
Z	4
ρ_{calc}g/cm^3	1.579
μ/mm^{-1}	1.744
F(000)	772.0
Crystal size/mm^3	0.44 × 0.2 × 0.08
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.368 to 75.22
Index ranges	$-15 \leq h \leq 15$, $-22 \leq k \leq 22$, $-23 \leq l \leq 23$

Reflections collected	69103
Independent reflections	7997 [R_{int} = 0.0372, R_{sigma} = 0.0240]
Data/restraints/parameters	7997/0/182
Goodness-of-fit on F^2	1.013
Final R indexes [I>=2σ (I)]	R_1 = 0.0244, wR_2 = 0.0512
Final R indexes [all data]	R_1 = 0.0361, wR_2 = 0.0543
Largest diff. peak/hole / e $Å^{-3}$	0.49/-0.49

Crystallographic Analysis of (±)-98.

Special Refinement Details



Compound (±)-**98** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. CCDC number: not publication quality.

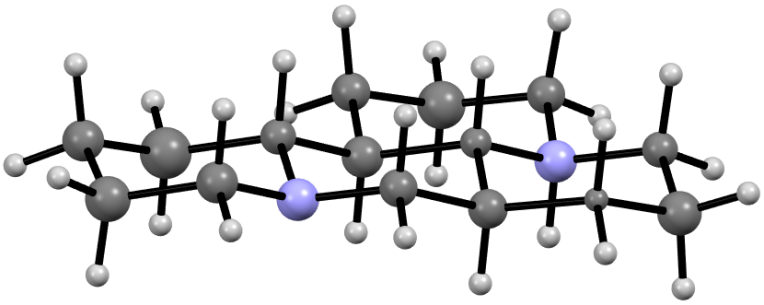
Table 2.49. *Crystal data and structure refinement for (±)-**98**.*

Identification code	V22009
Empirical formula	$C_{15}H_{24}N_2OI$
Formula weight	280.42
Temperature/K	100.0

Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	12.8228(19)
b/Å	8.3093(12)
c/Å	14.078(2)
α/°	90
β/°	95.136(13)
γ/°	90
Volume/Å^3	1494.0(4)
Z	4
ρ_{calc}g/cm^3	1.247
μ/mm^{-1}	1.870
F(000)	608.0
Crystal size/mm^3	? × ? × 0.15
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.938 to 148.562
Index ranges	$-14 \leq h \leq 14$, $-10 \leq k \leq 9$, $-15 \leq l \leq 8$
Reflections collected	4460
Independent reflections	1887 [R_{int} = 0.0649, R_{sigma} = 0.0726]
Data/restraints/parameters	1887/0/78
Goodness-of-fit on F^2	1.075
Final R indexes [I>=2σ (I)]	R_1 = 0.0738, wR_2 = 0.2057
Final R indexes [all data]	R_1 = 0.0886, wR_2 = 0.2214
Largest diff. peak/hole / e Å^{-3}	3.40/-4.19

Crystallographic Analysis of (±)-97.

Special Refinement Details



Compound (±)-**97** crystallizes in the triclinic space group P1 with two molecules in the asymmetric unit. CCDC number: not publication quality.

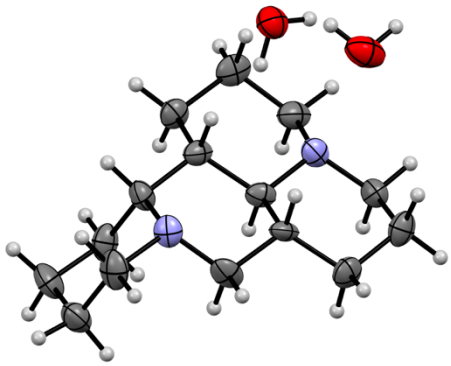
Table 2.50. *Crystal data and structure refinement for (±)-**97**.*

Identification code	V20119
Empirical formula	$C_{15}H_{26}N_2$
Formula weight	234.38
Temperature/K	100.0
Crystal system	triclinic
Space group	P1
a/Å	4.6048(5)
b/Å	10.8544(11)
c/Å	13.5496(16)
α/°	91.728(14)
β/°	90.179(10)
γ/°	102.239(8)
Volume/Å^3	661.52(13)
Z	2
ρ_{calc}g/cm^3	1.177
μ/mm^{-1}	0.517
F(000)	260.0
Crystal size/mm^3	0.2 × 0.08 × 0.07
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.526 to 159.182
Index ranges	$-5 \leq h \leq 5$, $-13 \leq k \leq 13$, $-16 \leq l \leq 16$

Reflections collected	14702
Independent reflections	4817 [R_{int} = 0.0688, R_{sigma} = 0.0680]
Data/restraints/parameters	4817/3/134
Goodness-of-fit on F^2	3.790
Final R indexes [I>=2σ (I)]	R_1 = 0.2362, wR_2 = 0.5409
Final R indexes [all data]	R_1 = 0.2639, wR_2 = 0.5655
Largest diff. peak/hole / e $Å^{-3}$	2.67/-0.95
Flack parameter	0.4(4)

Crystallographic Analysis of (±)-96 dihydrate.

Special Refinement Details



Compound (±)-**96** dihydrate crystallizes in the orthorhombic space group Pbcn with one molecule in the asymmetric unit. CCDC number: not publication quality.

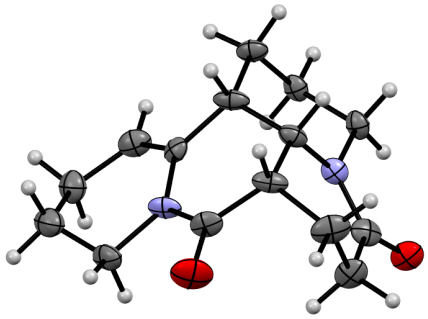
Table 2.51. *Crystal data and structure refinement for (±)-**96** dihydrate.*

Identification code	v20120
Empirical formula	$C_{15}H_{26}N_2O_{0.13}$
Formula weight	236.38
Temperature/K	100.0
Crystal system	orthorhombic

Space group	Pbcn
a/Å	22.990(9)
b/Å	6.991(2)
c/Å	19.007(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3054.8(18)
Z	8
ρ_{calc}g/cm^3	1.028
μ/mm^{-1}	0.458
F(000)	1048.0
Crystal size/mm^3	? × ? × ?
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	9.306 to 99.616
Index ranges	$-14 \leq h \leq 22$, $-2 \leq k \leq 6$, $-18 \leq l \leq 12$
Reflections collected	3454
Independent reflections	1343 [R_{int} = 0.0459, R_{sigma} = 0.0553]
Data/restraints/parameters	1343/0/178
Goodness-of-fit on F^2	1.239
Final R indexes [I>=2σ (I)]	R_1 = 0.1127, wR_2 = 0.2674
Final R indexes [all data]	R_1 = 0.1385, wR_2 = 0.2786
Largest diff. peak/hole / e Å^{-3}	0.33/-0.28

Crystallographic Analysis of (±)-133.

Special Refinement Details



Compound (±)-**133** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. CCDC number: not publication quality.

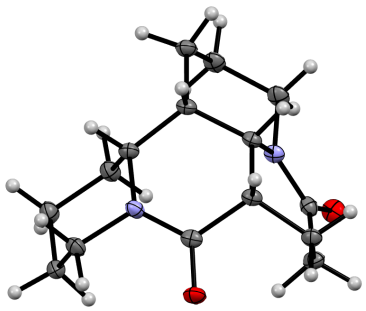
Table 2.52. *Crystal data and structure refinement for (±)-**133**.*

Identification code	V21317
Empirical formula	$C_{15}H_{20}N_3O_2$
Formula weight	274.34
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	12.249(11)
b/Å	8.778(6)
c/Å	12.919(13)
α/°	90
β/°	98.75(3)
γ/°	90
Volume/Å^3	1373(2)
Z	4
ρ_{calc}g/cm^3	1.327
μ/mm^{-1}	0.090
F(000)	588.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	MoKα (λ = 0.71073)

2Θ range for data collection/°	4.976 to 72.256
Index ranges	$-13 \leq h \leq 16$, $-11 \leq k \leq 14$, $-18 \leq l \leq 15$
Reflections collected	9867
Independent reflections	3365 [R_{int} = 0.1918, R_{sigma} = 0.2293]
Data/restraints/parameters	3365/0/176
Goodness-of-fit on F^2	1.682
Final R indexes [I>=2σ (I)]	R_1 = 0.2035, wR_2 = 0.5010
Final R indexes [all data]	R_1 = 0.3340, wR_2 = 0.5603
Largest diff. peak/hole / e $Å^{-3}$	4.93/-0.56

Crystallographic Analysis of (±)-87.

Special Refinement Details



Compound (±)-**87** crystallizes in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit. CCDC number: not publication quality.

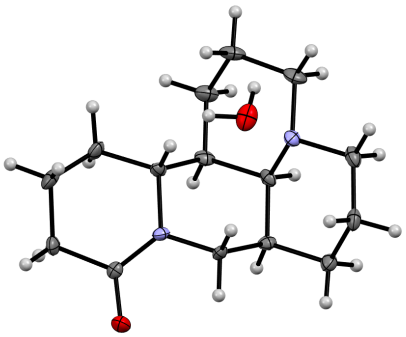
Table 2.53. *Crystal data and structure refinement for (±)-**87**.*

Identification code	V19018
Empirical formula	$C_{15}H_{22}N_2O_2$
Formula weight	262.34
Temperature/K	99.99

Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	13.8942(11)
b/Å	9.0952(9)
c/Å	10.4946(9)
α/°	90
β/°	105.846(4)
γ/°	90
Volume/Å^3	1275.8(2)
Z	4
ρ_{calc}g/cm^3	1.366
μ/mm^{-1}	0.726
F(000)	568.0
Crystal size/mm^3	? × ? × ?
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.612 to 148.632
Index ranges	$-13 \leq h \leq 15$, $-10 \leq k \leq 11$, $-10 \leq l \leq 12$
Reflections collected	4850
Independent reflections	2197 [R_{int} = 0.0557, R_{sigma} = 0.0566]
Data/restraints/parameters	2197/0/77
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0745, wR_2 = 0.1975
Final R indexes [all data]	R_1 = 0.0771, wR_2 = 0.2008
Largest diff. peak/hole / e Å^{-3}	0.51/-0.67

Crystallographic Analysis of (±)-26 monohydrate.

Special Refinement Details



Compound (±)-**26** monohydrate crystallizes in the tetragonal space group $P4_32_12$ with one molecule in the asymmetric unit. CCDC number: not publication quality.

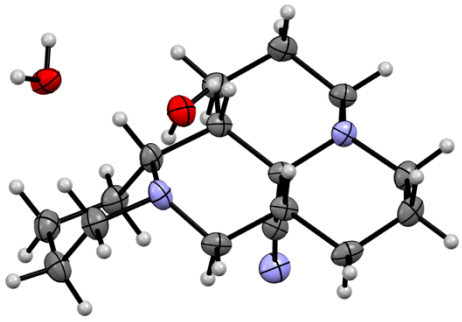
Table 2.54. *Crystal data and structure refinement for (±)-**26** monohydrate.*

Identification code	V22034
Empirical formula	$C_{15}H_{24}N_2O$
Formula weight	248.36
Temperature/K	100.0
Crystal system	tetragonal
Space group	$P4_32_12$
a/Å	11.6747(9)
b/Å	11.6747(9)
c/Å	21.878(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2981.9(8)
Z	8
ρ_{calc}g/cm^3	1.106
μ/mm^{-1}	0.540
F(000)	1088.0
Crystal size/mm^3	0.45 × 0.4 × 0.3
Radiation	CuKα (λ = 1.54178)

2Θ range for data collection/°	8.584 to 148.596
Index ranges	$-10 \leq h \leq 8$, $-7 \leq k \leq 13$, $-23 \leq l \leq 14$
Reflections collected	7045
Independent reflections	2250 [R_{int} = 0.0371, R_{sigma} = 0.0286]
Data/restraints/parameters	2250/0/175
Goodness-of-fit on F^2	2.458
Final R indexes [I>=2σ (I)]	R_1 = 0.0896, wR_2 = 0.2715
Final R indexes [all data]	R_1 = 0.0939, wR_2 = 0.2742
Largest diff. peak/hole / e $Å^{-3}$	2.50/-0.40
Flack parameter	0.10(15)

Crystallographic Analysis of (±)-95 dihydrate.

Special Refinement Details



Compound (±)-**95** dihydrate crystallizes in the monoclinic space group C2/c with one molecule in the asymmetric unit. CCDC number: not publication quality.

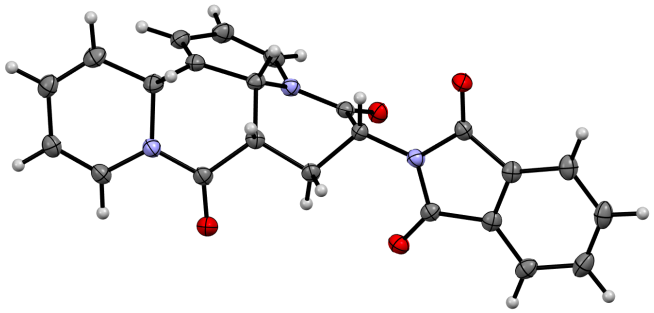
Table 2.55. *Crystal data and structure refinement for (±)-**95** dihydrate.*

Identification code	V21361
Empirical formula	$C_{16}H_{25}N_3O_{0.13}$
Formula weight	261.39

Temperature/K	100.0
Crystal system	monoclinic
Space group	C2/c
a/Å	23.605(6)
b/Å	7.0420(12)
c/Å	19.453(5)
α/°	90
β/°	97.767(14)
γ/°	90
Volume/Å^3	3203.9(13)
Z	8
ρ_{calc}g/cm^3	1.084
μ/mm^{-1}	0.502
F(000)	1144.0
Crystal size/mm^3	0.25 × 0.05 × 0.05
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.56 to 148.54
Index ranges	-21 ≤ h ≤ 24, -6 ≤ k ≤ 8, -13 ≤ l ≤ 17
Reflections collected	3621
Independent reflections	1967 [R_{int} = 0.0441, R_{sigma} = 0.0533]
Data/restraints/parameters	1967/0/196
Goodness-of-fit on F^2	1.214
Final R indexes [I>=2σ (I)]	R_1 = 0.0638, wR_2 = 0.1738
Final R indexes [all data]	R_1 = 0.0893, wR_2 = 0.1877
Largest diff. peak/hole / e Å^{-3}	0.46/-0.25

Crystallographic Analysis of (±)-79.

Special Refinement Details



Compound (±)-**79** crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. CCDC number: 2159769.

Table 2.56. *Crystal data and structure refinement for (±)-**79**.*

Identification code	V19479
Empirical formula	$C_{23}H_{17}N_3O_4$
Formula weight	399.39
Temperature/K	99.99
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.1166(7)
b/Å	15.6750(16)
c/Å	11.2761(15)
α/°	90
β/°	102.567(9)
γ/°	90
Volume/Å^3	882.71(19)
Z	2
ρ_{calc}g/cm^3	1.503
μ/mm^{-1}	0.864
F(000)	416.0
Crystal size/mm^3	0.15 × 0.1 × 0.05
Radiation	CuKα (λ = 1.54178)

2Θ range for data collection/°	8.032 to 149.378
Index ranges	$-6 \leq h \leq 6$, $-19 \leq k \leq 19$, $-14 \leq l \leq 14$
Reflections collected	9371
Independent reflections	3529 [R_{int} = 0.0436, R_{sigma} = 0.0431]
Data/restraints/parameters	3529/1/271
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0325, wR_2 = 0.0787
Final R indexes [all data]	R_1 = 0.0355, wR_2 = 0.0804
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.17
Flack parameter	0.23(11)

2.9 COMPUTATIONAL METHODS

Density functional theory (DFT) calculations were performed with Gaussian 16.[57] A comprehensive conformer search was performed for each intermediate and transition state using the CREST program.[24] Geometry optimizations, frequency calculations, and energy calculations were performed using the ωB97XD[58] functional and def2-TZVP basis set.[59,60] Dichloromethane solvation was modeled using the SMD solvation model.[61] A chloride anion was included when necessary to create a neutral species. Frequency calculations confirmed the optimized structures as minima (zero imaginary frequencies) or transition state structures (one imaginary frequency) on the potential energy surface. A quasi-harmonic correction was applied using the GoodVibes program.[62] PyMOL was used to render visualizations of structures.[63] Initial structures were made using GaussView.[64] For calculations analyzing the effects of dispersion on the transition states, the B3LYP-D3/def2-TZVP/SMD(DCM) and B3LYP/def2-TZVP/SMD(DCM) levels of theory were used.

Figure 2.47. *Second C–C Bond Formation Energies.*

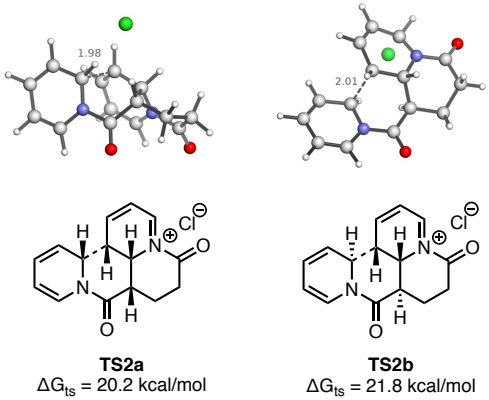


Figure 2.48. *Deprotonation of Int2a with Pyridine Energies.*

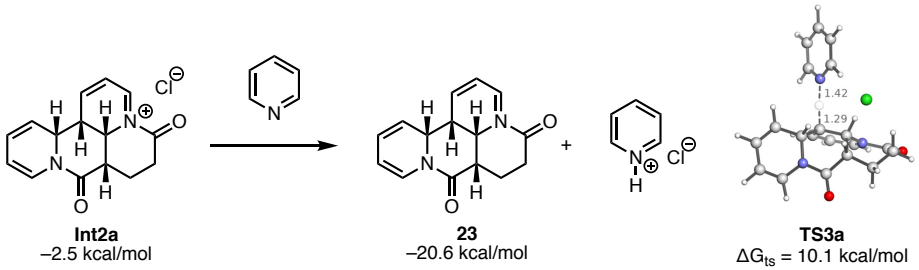


Figure 2.49. *Initial C–C Bond Formation with an acyl-Cl/acyl-pyridinium Starting Material.*

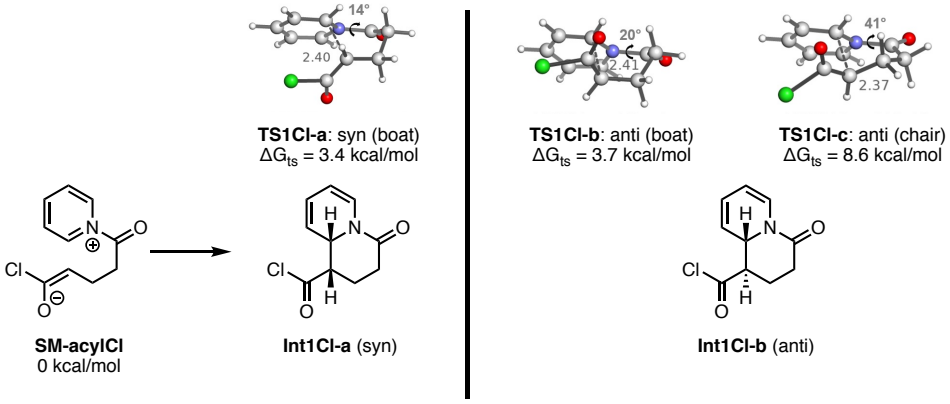


Figure 2.50. *C–C Bond Formation with a Ketene Starting Material Resulting in the Formation of a Cyclobutanone Intermediate.*

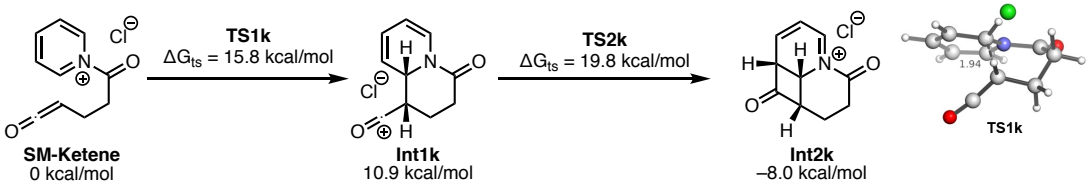


Figure 2.51. *Relative Energy of Starting Material Species.*

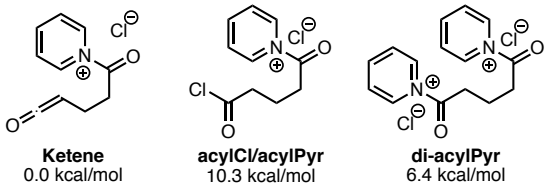


Table 2.57. *Summary of Energies.*

Structure	E (au)	qh-H (au)	qh-S (au)	qh-G(T) (au)	qh-G(T) (kcal/mol)	ΔG relative to SM (kcal/mol)
Figure 2.						
1. 65	-1300.829	-1300.542	0.064877	-1300.606	-816142.2	0.0
2. TS1a	-1300.820	-1300.532	0.062761	-1300.595	-816134.9	7.3
3. TS1b	-1300.816	-1300.529	0.063230	-1300.592	-816133.4	8.8
4. TS1c	-1300.809	-1300.519	0.066721	-1300.586	-816129.2	13.0
5. Int1a	-1300.853	-1300.563	0.062907	-1300.626	-816154.8	-12.6
6. Int1b	-1300.849	-1300.560	0.063824	-1300.623	-816152.9	-10.7
7. TS2a	-1300.823	-1300.534	0.060381	-1300.594	-816134.6	7.6
8. TS2b	-1300.820	-1300.530	0.058511	-1300.589	-816131.1	11.1
9. Int2a	-1300.851	-1300.553	0.057899	-1300.610	-816144.7	-2.5
10. Int2b	-1300.859	-1300.567	0.058893	-1300.626	-816154.2	-12.0
11. TS3a	-1549.130	-1548.752	0.073312	-1548.825	-971901.5	10.1
12. TS3b	-1549.125	-1548.746	0.073075	-1548.819	-971897.9	13.7
13. Int3a	-840.012	-839.736	0.055476	-839.791	-526976.5	-20.6
14. Int3b	-840.020	-839.743	0.055101	-839.798	-526981.1	-25.2
15. Pyr	-248.294	-248.202	0.032670	-248.235	-155769.4	
16. Pyr·HCl	-709.151	-709.044	0.039009	-709.083	-444955.7	
SI						
17. SM-acylCl	-1052.506	-1052.313	0.053085	-1052.366	-660369.2	0.0
18. TS1Cl-a	-1052.502	-1052.310	0.051096	-1052.361	-660365.8	3.4
19. TS1Cl-b	-1052.501	-1052.309	0.051295	-1052.360	-660365.5	3.7
20. TS1Cl-c	-1052.492	-1052.301	0.051695	-1052.352	-660360.6	8.6
21. SM-ketene	-1052.514	-1052.321	0.056199	-1052.378	-660376.4	0.0

22. TS1k	-1052.491	-1052.300	0.052884	-1052.352	-660360.7	15.8
23. Int1k	-1052.499	-1052.307	0.053175	-1052.360	-660365.5	10.9
24. TS2k	-1052.485	-1052.294	0.052200	-1052.346	-660356.6	19.8
25. Int2k	-1052.537	-1052.341	0.049466	-1052.390	-660384.4	-8.0
SM species						
26. di-acylPyr	-2009.980	-2009.586	0.084118	-2009.670	-1261086.0	6.4
27. acylCl/acylPyr	-2009.971	-2009.579	0.085215	-2009.664	-1261082.1	10.3
28. ketene	-2009.984	-2009.592	0.087969	-2009.680	-1261092.4	0.0

Table 2.58. *Coordinates.*

1			
C	4.241804	-0.634410	0.109065
C	3.688490	-1.777624	-0.447706
C	2.395767	-1.735813	-0.913047
N	1.679201	-0.606082	-0.849794
C	2.187084	0.505890	-0.299249
C	3.475550	0.516688	0.186345
H	3.855962	1.425019	0.631595
H	1.539952	1.375440	-0.225545
C	0.246192	-0.667665	-1.377307
C	-0.198668	0.478885	-1.948167
C	-1.602848	0.566770	-2.450576
H	-1.673252	1.340472	-3.215910
H	-1.910565	-0.374284	-2.914120
C	-2.674652	0.939926	-1.385415
C	-2.930778	-0.180457	-0.436496
O	-3.799951	-0.987369	-0.550315

N	-2.016018	-0.344090	0.728848
C	-1.133729	0.605773	1.086228
C	-0.277851	0.395257	2.143310
C	-0.331500	-0.801107	2.833221
C	-1.255398	-1.768014	2.451870
C	-2.083311	-1.516970	1.393619
H	-2.811344	-2.222896	1.026827
H	-1.326928	-2.716355	2.963574
H	0.336807	-0.984056	3.664458
H	0.411799	1.187375	2.397192
H	-1.103624	1.538158	0.542790
Cl	0.564792	3.540088	0.616096
H	-2.389871	1.858833	-0.877126
H	-3.627096	1.109665	-1.885869
H	0.431524	1.351535	-2.021092
O	-0.305276	-1.769418	-1.200954
H	1.883731	-2.583965	-1.342729
H	4.248509	-2.698586	-0.522547
H	5.255553	-0.645123	0.487474

2

C	4.267561	-0.697170	0.058179
C	3.568186	0.491891	0.179673
C	2.274329	0.569424	-0.279421
N	1.685644	-0.498367	-0.845175
C	2.346432	-1.661597	-0.962186
C	3.640909	-1.788773	-0.522173
C	0.251226	-0.489595	-1.355875

C	-0.424308	0.720658	-1.285486
C	-1.110646	0.461671	0.866266
C	-0.073093	0.149509	1.777280
C	-1.751713	0.827168	-1.978595
C	-2.997817	1.018098	-1.069379
C	-3.210914	-0.161917	-0.185934
N	-2.113019	-0.456669	0.693185
C	-2.023818	-1.716474	1.232741
C	-0.990557	-2.058491	2.028902
C	0.002656	-1.089550	2.327196
O	-4.156391	-0.902702	-0.216378
O	-0.168008	-1.582892	-1.708201
H	5.286523	-0.773905	0.414137
H	4.008670	1.368130	0.633325
H	1.703333	1.485636	-0.169012
H	1.785195	-2.461989	-1.419214
H	4.145154	-2.737292	-0.636660
H	0.097654	1.644379	-1.090643
H	-1.348426	1.500150	0.713311
H	0.625436	0.939396	2.013768
H	-1.735420	1.690928	-2.644661
H	-1.920081	-0.057705	-2.593480
H	-3.887324	1.117447	-1.686940
H	-2.894426	1.930635	-0.479691
H	-2.828592	-2.383756	0.966917
H	-0.943717	-3.055128	2.441984
H	0.797220	-1.331050	3.021434
Cl	0.710884	3.543824	0.705226

3

C	4.302610	0.418756	-0.601979
C	4.056378	-0.902940	-0.942663
C	2.903867	-1.503525	-0.500635
N	2.015849	-0.829208	0.248533
C	2.239670	0.448457	0.597732
C	3.379996	1.094547	0.178126
C	0.759246	-1.590272	0.649824
C	-0.332857	-0.811317	0.996101
C	-1.048406	-0.494707	-1.159738
C	-0.143437	0.318341	-1.874353
C	-1.536193	-1.486154	1.589505
C	-2.645547	-1.934500	0.595469
C	-3.233296	-0.770273	-0.121882
N	-2.276064	0.024923	-0.852232
C	-2.546957	1.356006	-1.031904
C	-1.646907	2.173958	-1.620294
C	-0.422485	1.633784	-2.077346
O	-4.372583	-0.399635	-0.059350
O	0.832172	-2.803807	0.505707
H	5.204394	0.913303	-0.938503
H	4.749049	-1.470781	-1.546793
H	2.639366	-2.527817	-0.714284
H	1.507840	0.961247	1.215295
H	3.529611	2.122346	0.476766
H	-0.228453	0.248654	1.176443
H	-0.989427	-1.566909	-1.250131

H	0.770908	-0.130938	-2.235064
H	-1.232341	-2.389812	2.119761
H	-1.993933	-0.817563	2.320008
H	-3.455085	-2.416124	1.138818
H	-2.238525	-2.660116	-0.110635
H	-3.509619	1.681147	-0.669379
H	-1.878923	3.221213	-1.742754
H	0.281270	2.266384	-2.602271
Cl	0.145562	2.713079	2.115411

4

C	-4.205066	-1.070480	0.044850
C	-2.969470	-1.504960	0.494098
C	-1.925442	-0.613877	0.582838
N	-2.096472	0.674570	0.239034
C	-3.287750	1.111669	-0.200170
C	-4.361273	0.261652	-0.304878
C	-0.975128	1.710350	0.277398
C	0.245454	1.257766	0.737967
C	1.012873	0.576880	-1.268333
C	0.062071	-0.105233	-2.059039
C	1.373269	2.233396	0.906695
C	2.747434	1.561086	0.935995
C	3.148278	0.527943	-0.083422
N	2.106400	-0.128466	-0.846344
C	2.195901	-1.482296	-1.009507
C	1.245119	-2.164876	-1.687703
C	0.159566	-1.450486	-2.241231

O	4.271081	0.135751	-0.211430
O	-1.271578	2.793599	-0.213295
H	-5.036054	-1.759529	-0.030652
H	-2.796732	-2.531931	0.782802
H	-0.956259	-0.935435	0.948737
H	-3.322773	2.159245	-0.457047
H	-5.306513	0.648031	-0.657511
H	0.334449	0.324518	1.278095
H	1.153856	1.638272	-1.405160
H	-0.738838	0.471757	-2.499029
H	1.337737	2.992939	0.122022
H	1.275718	2.779283	1.849846
H	3.542024	2.306907	0.947791
H	2.846176	0.999182	1.873213
H	3.061487	-1.946197	-0.563146
H	1.333623	-3.234796	-1.799824
H	-0.583116	-1.972684	-2.830734
Cl	0.764392	-2.016958	2.313895

5

C	-3.745491	-1.648673	0.203284
C	-3.537248	-0.299075	-0.023961
C	-2.330493	0.265979	0.311767
N	-1.370984	-0.490876	0.875609
C	-1.557791	-1.803463	1.122063
C	-2.738064	-2.408771	0.783847
H	-2.862686	-3.464660	0.974027
H	-0.731012	-2.326016	1.578154

C	-0.045302	0.075192	1.243725
O	0.496693	-0.409299	2.185363
C	0.515801	1.118199	0.328335
C	1.677239	1.878352	0.991240
H	1.527949	2.944501	0.827807
H	1.663989	1.709363	2.066148
C	3.056776	1.483141	0.434746
C	3.182849	0.012141	0.147739
O	4.107595	-0.681144	0.522706
N	2.129990	-0.496870	-0.589330
C	2.024542	-1.867909	-0.791571
C	1.013510	-2.410171	-1.474451
C	-0.003651	-1.548150	-2.053937
C	0.011758	-0.237387	-1.825036
C	1.049293	0.422651	-0.967662
H	1.473728	1.246080	-1.547119
H	-0.723988	0.428264	-2.258602
H	-0.768108	-1.982354	-2.686281
H	0.972384	-3.481010	-1.610105
H	2.826402	-2.441047	-0.350725
H	3.848808	1.761589	1.125356
H	3.239415	2.014629	-0.504193
H	-0.262435	1.820736	0.017201
H	-2.127784	1.322645	0.138490
H	-4.297800	0.328638	-0.465231
H	-4.685970	-2.109648	-0.068612
Cl	-1.922507	3.510219	-0.675623

6

C	-4.857986	0.466590	-0.175803
C	-4.677088	-0.894401	0.036356
C	-3.410199	-1.378132	0.218048
N	-2.347791	-0.546190	0.184096
C	-2.499041	0.777098	-0.021578
C	-3.755602	1.303363	-0.200653
C	-1.003206	-1.161691	0.393207
C	0.164845	-0.358346	-0.071714
C	1.485961	-0.991582	0.422116
C	1.635276	-0.881643	1.913493
C	0.129001	-0.250659	-1.624452
C	1.341110	-0.933881	-2.256311
C	2.612722	-0.389519	-1.667093
N	2.607085	-0.353519	-0.290932
C	3.646424	0.285390	0.378266
C	3.703633	0.357277	1.707630
C	2.651595	-0.256196	2.499781
O	3.545411	0.018976	-2.332271
O	-0.981157	-2.258065	0.853248
H	-5.852726	0.868042	-0.318021
H	-5.511363	-1.580062	0.060844
H	-3.191933	-2.420457	0.391828
H	-1.619653	1.421969	-0.012532
H	-3.851547	2.368760	-0.352705
H	0.112977	0.653788	0.341556
H	1.469758	-2.052890	0.155124
H	0.856748	-1.352071	2.499792

H	-0.778636	-0.692828	-2.036127
H	0.121315	0.806517	-1.889706
H	1.364021	-0.764484	-3.330263
H	1.300513	-2.014027	-2.086686
H	4.383909	0.722423	-0.277663
H	4.522585	0.877199	2.182532
H	2.704983	-0.203251	3.580114
Cl	-0.080278	3.141767	0.256717

7

C	-3.767925	-0.993200	-0.038669
C	-3.095201	-1.945482	0.788089
C	-1.896272	-1.637303	1.316089
N	-1.288982	-0.431096	1.036466
C	-1.795519	0.399564	0.050407
C	-3.142264	0.148615	-0.383756
C	0.001519	-0.172682	1.569234
C	0.761564	0.892602	0.828566
C	0.857915	0.510899	-0.684578
C	-0.459273	0.283766	-1.409477
C	2.165855	1.128569	1.404634
C	3.291355	0.800310	0.412381
C	3.066263	-0.513571	-0.268541
N	1.762850	-0.648182	-0.790847
C	1.344626	-1.851310	-1.235161
C	0.118115	-2.051152	-1.795948
C	-0.722029	-0.947582	-1.982540
O	3.872459	-1.405378	-0.362075

O	0.423677	-0.843280	2.475012
H	-4.781225	-1.188820	-0.364528
H	-3.552746	-2.893554	1.030073
H	-1.345348	-2.283221	1.982063
H	-1.531849	1.452399	0.132670
H	-3.611258	0.905955	-0.996454
H	0.192859	1.825624	0.853399
H	1.343536	1.360672	-1.161199
H	-0.856697	1.168183	-1.893668
H	2.263392	2.170562	1.703318
H	2.294342	0.518585	2.297214
H	4.255898	0.761609	0.912309
H	3.350467	1.571577	-0.361587
H	2.071575	-2.646085	-1.134409
H	-0.152420	-3.035417	-2.146030
H	-1.625855	-1.059561	-2.569625
Cl	-0.963130	3.682556	-0.490044

8

C	-3.964636	-1.480477	0.080184
C	-4.417582	-0.109300	-0.026496
C	-3.543100	0.890485	0.113174
N	-2.189332	0.658689	0.355252
C	-1.673254	-0.676493	0.390688
C	-2.670835	-1.738853	0.294007
C	-1.312723	1.731762	0.281415
C	0.145805	1.350110	0.303601
C	0.546923	0.410920	-0.875055

C	-0.438959	-0.689620	-1.194519
C	1.085299	2.557552	0.323561
C	2.403541	2.284102	-0.423033
C	2.873033	0.859244	-0.299474
N	1.897315	-0.078645	-0.569206
C	2.171996	-1.429765	-0.284959
C	1.289948	-2.397669	-0.970360
C	0.087190	-2.030708	-1.403513
O	4.003782	0.542605	0.013267
O	-1.713923	2.874548	0.180973
H	-4.683312	-2.286559	0.005506
H	-5.458755	0.116439	-0.206394
H	-3.808964	1.933875	0.047978
H	-0.942383	-0.836028	1.177764
H	-2.302908	-2.750762	0.403236
H	0.302599	0.757476	1.207910
H	0.629604	1.035212	-1.766997
H	-1.161235	-0.377820	-1.942490
H	0.591113	3.411936	-0.135947
H	1.299460	2.828645	1.356971
H	3.200574	2.930703	-0.064576
H	2.271944	2.490451	-1.489080
H	3.228154	-1.623682	-0.426014
H	1.657849	-3.410008	-1.066425
H	-0.555686	-2.750753	-1.895700
Cl	1.997725	-1.767905	1.581335

9

C	2.735216	1.173874	1.868249
C	3.889893	0.833559	1.046585
C	3.702411	0.286072	-0.163828
N	2.392512	0.191710	-0.651262
C	1.510357	1.263082	-0.202598
C	1.532765	1.312371	1.300689
C	1.933704	-0.975721	-1.201786
C	0.483306	-1.342783	-0.924969
C	-0.528429	-0.177539	-0.865556
C	0.179150	1.177575	-0.940268
C	0.546327	-2.144040	0.384243
C	-0.846738	-2.543611	0.811026
C	-1.733986	-1.356080	1.029402
N	-1.452528	-0.228636	0.285003
C	-2.408889	0.814394	0.357231
C	-1.893266	2.153746	-0.011870
C	-0.705902	2.320017	-0.568984
O	-2.656075	-1.376654	1.822428
O	2.680868	-1.771956	-1.736397
H	2.867069	1.255645	2.940292
H	4.890488	0.912461	1.448627
H	4.485318	-0.160779	-0.759525
H	1.982841	2.190928	-0.557212
H	0.629610	1.501586	1.866882
H	0.183832	-2.027045	-1.717233
H	-1.154404	-0.244579	-1.758611
H	0.438802	1.304280	-1.996736
H	1.165802	-3.026588	0.230210

H	1.014483	-1.543199	1.168351
H	-0.840279	-3.120535	1.734324
H	-1.319908	-3.162062	0.041053
H	-2.872329	0.806888	1.336169
H	-2.540007	2.990916	0.216200
H	-0.336735	3.317532	-0.780126
Cl	-3.867548	0.451907	-0.767205

10

C	3.985624	-1.682300	-0.428108
C	4.485129	-0.543943	0.324597
C	3.694954	0.513043	0.511481
N	2.391699	0.562189	0.024629
C	1.758583	-0.585430	-0.656919
C	2.736605	-1.699799	-0.885836
C	1.602439	1.644595	0.328628
C	0.191366	1.502729	-0.181582
C	-0.445823	0.208728	0.339488
C	0.523860	-0.992446	0.188672
C	-0.712238	2.673797	0.125399
C	-1.995853	2.483996	-0.665384
C	-2.552195	1.080014	-0.706730
N	-1.738529	0.021173	-0.340093
C	-2.361064	-1.245989	-0.274902
C	-1.431850	-2.388472	-0.423317
C	-0.127143	-2.258006	-0.255520
O	-3.687742	0.886268	-1.096968
O	2.008661	2.615475	0.937638

H	4.651294	-2.511434	-0.633779
H	5.490948	-0.538917	0.718475
H	3.995853	1.399279	1.049539
H	1.399774	-0.258489	-1.639165
H	2.378649	-2.527567	-1.483286
H	0.273425	1.407435	-1.271516
H	-0.648700	0.338807	1.406018
H	0.927959	-1.193410	1.186062
H	-0.915667	2.712127	1.197599
H	-0.238378	3.614887	-0.149764
H	-1.831616	2.757730	-1.712262
H	-2.800250	3.122037	-0.301126
H	-3.176835	-1.277332	-0.985879
H	-1.881751	-3.342252	-0.666496
H	0.511681	-3.124295	-0.375629
Cl	-3.258253	-1.467010	1.359076

11

C	0.237787	4.103224	-0.394699
C	1.687977	4.156135	-0.313066
C	2.399864	3.037553	-0.466354
N	1.804567	1.803378	-0.699750
C	0.337947	1.634775	-0.669749
C	-0.387456	2.941213	-0.562230
C	2.585544	0.668449	-0.729341
C	1.802730	-0.621869	-0.848866
C	0.618322	-0.718386	0.150590
C	0.014561	0.654064	0.462143

C	2.697691	-1.858592	-0.780381
C	1.943165	-3.053093	-0.193673
C	1.567020	-2.748346	1.218913
N	1.010574	-1.446467	1.376777
C	0.840563	-0.953164	2.602342
C	0.363512	0.311547	2.858123
C	0.073283	1.130817	1.780673
O	1.735386	-3.464415	2.170891
O	3.799445	0.715490	-0.673053
H	-0.328696	5.023953	-0.330043
H	2.196487	5.093309	-0.139747
H	3.477861	3.004951	-0.418143
H	0.028123	1.156316	-1.603927
H	-1.465921	2.880346	-0.641949
H	1.313564	-0.605262	-1.828369
H	-0.133273	-1.330832	-0.351432
H	-1.259592	0.462876	0.366292
H	3.055436	-2.112072	-1.776696
H	3.575768	-1.646626	-0.169260
H	2.548814	-3.956168	-0.191955
H	1.036674	-3.243993	-0.779595
H	1.141553	-1.619130	3.401159
H	0.290002	0.655479	3.877896
H	-0.174755	2.173951	1.953451
C	-5.351113	-0.208741	0.062401
C	-4.516300	-0.787218	-0.880302
C	-3.152429	-0.576855	-0.784785
C	-3.431435	0.727773	1.104121

C	-4.801855	0.563752	1.075526
H	-6.422048	-0.358515	0.010046
H	-4.909013	-1.396887	-1.682377
H	-2.446595	-1.010802	-1.490538
H	-2.938228	1.320260	1.867899
H	-5.420817	1.030587	1.829099
N	-2.641235	0.167592	0.193868
Cl	-0.696331	-2.212946	-2.831124

12

C	-2.340245	2.746351	0.974425
C	-2.354254	3.128932	-0.427939
C	-1.355009	2.746004	-1.222430
N	-0.288820	1.974785	-0.763270
C	-0.141646	1.610143	0.662680
C	-1.326719	2.046049	1.474118
C	0.702195	1.618031	-1.648523
C	1.740952	0.694696	-1.044185
C	0.941504	-0.448727	-0.388729
C	0.145156	0.099147	0.797834
C	2.772127	0.179180	-2.049340
C	2.619263	-1.320402	-2.313389
C	2.659457	-2.096753	-1.032212
N	1.836719	-1.558074	-0.024627
C	1.851486	-2.100868	1.209888
C	1.156436	-1.587239	2.258188
C	0.443199	-0.396651	2.066046
O	3.328820	-3.081695	-0.835796

O	0.695799	1.966091	-2.813442
H	-3.160482	3.048694	1.613400
H	-3.162865	3.720415	-0.832057
H	-1.300370	2.988760	-2.272668
H	0.749882	2.111016	1.061238
H	-1.300674	1.785748	2.524097
H	2.246023	1.231937	-0.235031
H	0.241480	-0.847896	-1.130518
H	-1.024553	-0.463965	0.643985
H	2.670446	0.720812	-2.988007
H	3.774389	0.367976	-1.665991
H	3.410184	-1.696445	-2.957924
H	1.662748	-1.522486	-2.806082
H	2.499742	-2.960686	1.312230
H	1.250121	-2.034679	3.235077
H	0.032133	0.103238	2.933794
C	-4.616293	-2.264282	-0.363869
C	-4.192267	-1.151898	-1.074970
C	-2.984989	-0.572162	-0.737623
C	-2.630001	-2.123614	0.936776
C	-3.824206	-2.760321	0.660186
H	-5.557862	-2.740757	-0.605235
H	-4.784989	-0.736065	-1.877775
H	-2.603823	0.302561	-1.250107
H	-1.966655	-2.458503	1.725646
H	-4.122951	-3.624756	1.236571
N	-2.233258	-1.059124	0.245970
Cl	2.791281	1.638418	2.523597

13		.com	
C	3.245896	1.162020	1.416122
C	4.002511	0.299044	0.522034
C	3.345878	-0.470762	-0.354889
N	1.955542	-0.341393	-0.477247
C	1.465081	1.017483	-0.232777
C	1.984460	1.471837	1.112970
C	1.201169	-1.441175	-0.763603
C	-0.295485	-1.346014	-0.575665
C	-0.885101	0.028107	-0.858560
C	-0.012130	1.186347	-0.442601
C	-0.646216	-1.815884	0.836925
C	-2.154355	-1.944267	0.932187
C	-2.885563	-0.689230	0.538058
N	-2.213669	0.207357	-0.254430
C	-2.796639	1.455794	-0.505714
C	-2.009516	2.529373	-0.634643
C	-0.582300	2.394204	-0.413026
O	-4.021193	-0.462403	0.918480
O	1.714267	-2.504294	-1.066836
H	3.704088	1.497633	2.338372
H	5.073707	0.198068	0.626747
H	3.807573	-1.248945	-0.944126
H	1.966467	1.638719	-0.990449
H	1.345555	2.061087	1.757810
H	-0.721515	-2.063201	-1.278250
H	-1.031824	0.109228	-1.944615

H	-0.172947	-2.776642	1.037392
H	-0.273624	-1.098633	1.573702
H	-2.479041	-2.191829	1.942153
H	-2.504464	-2.746822	0.275759
H	-3.875667	1.488378	-0.516594
H	-2.445507	3.500363	-0.822808
H	0.003360	3.283156	-0.207416

14

C	3.897890	1.166846	-0.302606
C	4.149551	-0.123847	0.318559
C	3.158823	-1.009378	0.421002
N	1.871051	-0.744959	-0.038341
C	1.523341	0.533750	-0.707613
C	2.692388	1.472685	-0.771374
C	0.896244	-1.704088	0.106538
C	-0.481671	-1.238682	-0.312613
C	-0.731850	0.098022	0.377582
C	0.289152	1.121069	-0.060971
C	-1.592995	-2.209430	0.018876
C	-2.899588	-1.641712	-0.514035
C	-3.161663	-0.188934	-0.191889
N	-2.087709	0.601171	0.149994
C	-2.309965	1.921362	0.551291
C	-1.299706	2.795305	0.611964
C	0.018438	2.410479	0.131195
O	-4.284210	0.277686	-0.262938
O	1.118447	-2.807928	0.564539

H	4.710573	1.877310	-0.389742
H	5.129928	-0.371262	0.698821
H	3.271745	-1.983527	0.872294
H	1.243470	0.290312	-1.742723
H	2.506295	2.419136	-1.261397
H	-0.463057	-1.071476	-1.396878
H	-0.618444	-0.059342	1.461686
H	-1.400733	-3.186142	-0.422937
H	-1.647650	-2.347383	1.101284
H	-3.761104	-2.200493	-0.150066
H	-2.920400	-1.711810	-1.606345
H	-3.336701	2.173128	0.769923
H	-1.490275	3.809982	0.931493
H	0.728735	3.189337	-0.115226

15

C	1.404367	0.000028	0.000000
C	0.711314	1.202450	-0.000003
C	-0.662196	1.177712	-0.000002
C	-0.662147	-1.177737	0.000002
C	0.711370	-1.202419	0.000002
H	2.486537	0.000057	-0.000001
H	1.226688	2.151364	-0.000005
H	-1.282237	2.061832	-0.000004
H	-1.282142	-2.061889	0.000004
H	1.226776	-2.151315	0.000004
N	-1.297291	-0.000030	0.000001
H	-2.310834	-0.000050	0.000001

16

C	-2.622139	0.000083	0.000080
C	-1.927526	1.201096	0.000008
C	-0.551697	1.170062	-0.000017
C	-0.551845	-1.170138	-0.000019
C	-1.927674	-1.201022	0.000012
H	-3.704419	0.000163	-0.000033
H	-2.442262	2.150711	-0.000021
H	0.069207	2.054928	0.000012
H	0.068971	-2.055060	0.000004
H	-2.442525	-2.150573	-0.000020
N	0.088106	-0.000065	-0.000074
H	1.155017	-0.000189	-0.000300
Cl	3.068504	-0.000001	0.000029

17

C	1.524973	0.672122	-0.548227
C	1.376658	1.567821	0.461239
C	0.293776	2.598766	0.361342
H	0.556647	3.468347	0.965870
H	0.185253	2.950529	-0.668083
C	-1.127189	2.177768	0.849798
C	-1.743979	1.143180	-0.025880
O	-2.513813	1.358740	-0.909364
N	-1.342838	-0.277776	0.181864
C	-0.607787	-0.664227	1.241045
C	-0.214788	-1.975703	1.374361
C	-0.579096	-2.892808	0.406870

C	-1.345105	-2.476953	-0.676676
C	-1.709201	-1.163184	-0.769155
H	-2.282711	-0.760379	-1.588762
H	-1.645526	-3.163504	-1.454123
H	-0.272256	-3.926860	0.492171
H	0.374982	-2.259314	2.233279
H	-0.360685	0.078922	1.976657
H	-1.091626	1.862790	1.891136
H	-1.791136	3.038683	0.783846
H	2.028817	1.545243	1.319297
O	0.936019	0.447174	-1.587458
Cl	3.006523	-0.544590	-0.194004

18

C	-1.349532	-0.985439	-0.605617
C	-0.647112	-1.571458	0.434124
C	0.310441	0.507842	1.155634
C	-0.641851	1.531469	1.285877
C	0.624901	-2.305987	0.130060
C	1.947667	-1.699350	0.690218
C	2.274523	-0.402402	0.038070
N	1.287556	0.637450	0.212669
C	1.283617	1.682686	-0.673932
C	0.344226	2.650356	-0.598303
C	-0.641701	2.576256	0.411960
O	3.217187	-0.193737	-0.675302
O	-1.063991	-0.719346	-1.745583
H	-1.170997	-1.789458	1.351968

H	0.509158	-0.150440	1.979346
H	-1.363052	1.457744	2.085924
H	0.570681	-3.313667	0.546230
H	0.743698	-2.414039	-0.949431
H	2.773898	-2.372669	0.473242
H	1.882286	-1.590591	1.774036
H	2.067873	1.657372	-1.414107
H	0.359517	3.464149	-1.307967
H	-1.379055	3.363050	0.503264
Cl	-3.074325	-0.433693	-0.045451

19

C	2.081258	-0.726876	-0.005772
C	0.948504	-0.760497	0.786676
C	-0.378466	0.476404	-0.796527
C	0.007691	1.825594	-0.823910
C	0.131441	-2.021063	0.824277
C	-0.920008	-2.223962	-0.309268
C	-2.017918	-1.228441	-0.203862
N	-1.586900	0.153221	-0.257484
C	-2.335148	1.083440	0.409668
C	-1.935626	2.374813	0.474856
C	-0.746370	2.760776	-0.180404
O	-3.170752	-1.463012	0.029468
O	2.473412	-1.427378	-0.905307
H	0.852139	-0.044839	1.587601
H	0.050594	-0.225331	-1.490335
H	0.914020	2.086084	-1.349142

H	0.784102	-2.894633	0.765358
H	-0.392590	-2.082951	1.779561
H	-1.376041	-3.206993	-0.215483
H	-0.427364	-2.175750	-1.281296
H	-3.240262	0.708184	0.861535
H	-2.541033	3.092515	1.008495
H	-0.444926	3.800005	-0.181418
Cl	3.146837	0.801950	0.368813

20

C	-2.067551	-0.824881	0.121624
C	-0.862228	-1.119170	-0.475966
C	0.400263	0.345183	0.893386
C	-0.215854	1.590109	1.094253
C	-0.051268	-2.286253	0.016728
C	1.439623	-2.189664	-0.315909
C	2.251049	-0.953336	-0.036332
N	1.549949	0.304780	0.166783
C	2.012986	1.399474	-0.503081
C	1.374489	2.590381	-0.404391
C	0.244526	2.690805	0.433863
O	3.444150	-0.921522	-0.096522
O	-2.608656	-1.187993	1.137068
H	-0.641943	-0.697100	-1.445447
H	0.232286	-0.467979	1.580543
H	-1.066252	1.637765	1.758119
H	-0.185489	-2.406849	1.095090
H	-0.394640	-3.227367	-0.424958

H	1.986956	-3.018970	0.132401
H	1.567235	-2.300925	-1.400445
H	2.900723	1.241905	-1.096593
H	1.752241	3.444538	-0.946289
H	-0.245111	3.647103	0.563974
Cl	-2.976225	0.554979	-0.838429

21

C	3.429695	-1.032600	0.374830
O	3.271354	-2.123448	0.744326
C	3.604092	0.187344	-0.052530
C	2.600179	1.306749	0.098455
C	1.205195	0.864498	0.511055
C	0.467220	0.168492	-0.585557
O	0.790421	0.089619	-1.725257
N	-0.807804	-0.500997	-0.196529
C	-1.420558	-0.224377	0.968618
C	-2.602198	-0.845006	1.293223
C	-3.161959	-1.744032	0.402382
C	-2.521269	-2.004176	-0.802395
C	-1.343845	-1.364905	-1.081169
H	-0.788560	-1.510491	-1.994331
H	-2.929205	-2.697341	-1.523132
H	-4.093616	-2.239864	0.641308
H	-3.077656	-0.605997	2.232879
H	-0.958617	0.501104	1.614620
H	1.227308	0.231735	1.402102
H	0.593414	1.742179	0.755138

H	2.956998	2.014369	0.849443
H	2.542010	1.853952	-0.843315
H	4.560271	0.378632	-0.525490
Cl	-1.671249	2.837494	-0.008679

22

C	-0.209404	-1.381284	1.723882
C	-0.879176	-0.438611	1.036751
C	0.091812	-0.306925	-0.642725
C	0.605525	-1.576906	-1.091817
C	-0.957098	0.984337	1.576920
C	-0.810005	2.028171	0.453134
C	0.581285	2.004585	-0.097981
N	1.028899	0.704349	-0.463399
C	2.380571	0.427870	-0.403915
C	2.848852	-0.800479	-0.679549
C	1.930636	-1.821603	-1.080567
O	1.334909	2.939331	-0.142887
O	0.435065	-2.209520	2.161695
H	-1.817063	-0.824170	0.599356
H	-0.845103	0.002668	-1.099304
H	-0.116545	-2.313942	-1.414997
H	-1.929337	1.120260	2.046863
H	-0.191608	1.150507	2.334591
H	-0.989093	3.024289	0.850068
H	-1.547690	1.833919	-0.329947
H	3.002854	1.266916	-0.132373
H	3.909849	-0.994089	-0.627139

H	2.310177	-2.781358	-1.406677
Cl	-3.332147	-0.409933	-1.087759

23

C	0.744234	-0.731256	-1.648078
C	0.888986	0.116748	-0.561922
C	-0.081457	-0.291140	0.622289
C	-0.151570	-1.765311	0.857712
C	0.768852	1.621000	-0.927407
C	-0.091177	2.342794	0.115840
C	-1.443948	1.694271	0.237139
N	-1.385768	0.321004	0.418690
C	-2.528884	-0.449242	0.222153
C	-2.514321	-1.778550	0.332866
C	-1.282330	-2.451167	0.702641
O	-2.495330	2.285767	0.122532
O	0.658790	-1.452860	-2.503643
H	1.958470	-0.090569	-0.156671
H	0.413440	0.178025	1.474662
H	0.775075	-2.236558	1.159248
H	1.770128	2.045232	-0.947126
H	0.323786	1.747642	-1.913131
H	-0.236903	3.378396	-0.180850
H	0.411326	2.338454	1.086238
H	-3.408413	0.124397	-0.028310
H	-3.421145	-2.340570	0.165529
H	-1.295951	-3.519591	0.877049
Cl	3.603093	-0.022589	0.874237

24

C	0.698443	0.931322	1.384832
C	0.864082	-0.185122	0.482605
C	-0.063852	0.225710	-0.659648
C	-0.026111	1.723888	-0.538844
C	0.617272	-1.575265	1.093476
C	-0.248204	-2.368003	0.111539
C	-1.553782	-1.661121	-0.144125
N	-1.412920	-0.306313	-0.419876
C	-2.528220	0.501507	-0.514004
C	-2.444325	1.840501	-0.549269
C	-1.150166	2.461777	-0.483146
O	-2.639489	-2.191710	-0.072436
O	0.740531	1.572934	2.311001
H	1.931723	-0.076896	0.106296
H	0.326957	-0.140590	-1.611118
H	0.951200	2.182825	-0.648739
H	1.572422	-2.072196	1.247213
H	0.112838	-1.502484	2.056555
H	-0.470609	-3.356644	0.505073
H	0.284047	-2.492014	-0.836375
H	-3.467316	-0.032606	-0.506804
H	-3.343177	2.436359	-0.590790
H	-1.080796	3.537810	-0.381667
Cl	3.722000	-0.162372	-0.906443

25

C	2.129317	-1.089080	0.022144

C	1.924846	0.226309	0.763776
C	0.442847	-0.197033	0.946111
C	0.795639	-1.645535	0.543480
C	2.177341	1.549615	0.055260
C	0.940588	2.433784	0.205008
C	-0.289169	1.764668	-0.354091
N	-0.405661	0.424792	-0.058814
C	-1.510081	-0.298726	-0.565025
C	-1.220403	-1.733394	-0.841899
C	-0.143113	-2.343408	-0.369704
O	-1.106653	2.344183	-1.042178
O	2.943698	-1.481887	-0.757396
H	2.431720	0.168938	1.729136
H	0.024309	-0.068889	1.943163
H	1.002296	-2.245234	1.433786
H	3.049868	2.054447	0.466487
H	2.373540	1.377082	-1.005083
H	1.057210	3.384264	-0.311418
H	0.760471	2.648018	1.263351
H	-1.892412	0.213765	-1.440554
H	-1.936292	-2.247582	-1.469896
H	0.065555	-3.374151	-0.628874
Cl	-2.957640	-0.222692	0.611637

26

C	0.167617	0.622901	0.074598
C	-0.564210	1.686746	0.377092
C	-2.962518	-0.388146	0.840838

C	-2.839966	-1.519425	1.611049
C	-1.323759	2.459308	-0.653236
C	-2.822020	2.094261	-0.752868
C	-3.016211	0.745063	-1.370030
N	-2.857487	-0.461258	-0.496847
C	-2.653269	-1.638709	-1.115508
C	-2.533811	-2.795801	-0.391962
C	-2.630408	-2.739303	0.991944
O	-3.175618	0.541377	-2.529645
O	0.240472	0.030387	-1.107880
H	-0.626953	1.997686	1.411421
H	-3.154816	0.577457	1.271717
H	-2.932003	-1.434254	2.683576
H	-1.278273	3.519130	-0.401360
H	-0.860626	2.336946	-1.633037
H	-3.311704	2.788809	-1.432704
H	-3.316469	2.180296	0.210475
H	-2.592543	-1.600751	-2.191856
H	-2.370590	-3.728248	-0.911846
H	-2.543726	-3.642508	1.581521
Cl	3.049711	3.549372	0.720273
H	1.217259	-0.240546	-1.318082
C	0.794295	-1.386279	1.252011
C	1.477170	-2.056282	2.231357
C	2.313450	-1.342511	3.082013
C	2.449173	0.023473	2.914654
C	1.746376	0.657952	1.914593
N	0.927128	-0.051126	1.120838

H	2.862895	-1.855212	3.860413
H	0.132089	-1.870321	0.550010
H	1.352216	-3.125043	2.326095
H	3.110959	0.609443	3.535824
H	1.866957	1.713976	1.677877
Cl	-5.899091	0.602838	0.085231
C	3.161715	-1.760615	-1.962456
C	4.503002	-2.077993	-2.064980
C	5.439179	-1.138442	-1.659976
C	4.999652	0.080477	-1.170512
C	3.638195	0.317839	-1.103784
N	2.738805	-0.587750	-1.491654
H	6.497979	-1.355350	-1.725845
H	2.393836	-2.462682	-2.266086
H	4.803819	-3.041051	-2.454398
H	5.692904	0.843104	-0.842728
H	3.256391	1.261285	-0.719760

27

C	-1.859240	2.417850	0.492574
C	-0.779964	3.174522	0.652239
C	0.464757	0.486030	-0.814784
C	0.167585	-0.197703	-1.970496
C	0.155453	3.000353	1.812601
C	1.272165	1.952416	1.590613
C	0.747041	0.555534	1.655174
N	0.435949	-0.147523	0.371416
C	0.151778	-1.464110	0.452498

C	-0.123916	-2.188511	-0.674150
C	-0.128640	-1.546764	-1.906918
O	0.524949	-0.047184	2.656434
O	-2.271686	1.491179	1.340179
H	-0.553093	3.924051	-0.091651
H	0.770720	1.523836	-0.848630
H	0.197293	0.338214	-2.907746
H	0.660019	3.947590	2.001633
H	-0.393664	2.739155	2.718757
H	1.975528	2.015652	2.420437
H	1.817082	2.160974	0.670168
H	0.164079	-1.887552	1.444356
H	-0.339386	-3.242806	-0.583602
H	-0.352652	-2.101182	-2.808765
Cl	-2.893123	2.646461	-0.920406
H	-2.675892	0.678988	0.881759
C	-3.136918	-1.772459	1.201979
C	-3.410502	-3.083022	0.854408
C	-3.718513	-3.366736	-0.466661
C	-3.743653	-2.330690	-1.386215
C	-3.459011	-1.049024	-0.948808
N	-3.159310	-0.774312	0.318801
H	-3.937129	-4.381430	-0.774703
H	-2.886005	-1.505438	2.222345
H	-3.381989	-3.859903	1.606363
H	-3.981324	-2.506181	-2.426632
H	-3.466177	-0.210133	-1.634670
Cl	2.459744	3.019986	-1.791850

C	3.659557	-0.335074	-0.376381
C	4.079398	-1.349131	-1.223890
C	4.253755	-2.620916	-0.702835
C	4.004312	-2.827686	0.644875
C	3.584476	-1.752134	1.411154
N	3.408880	-0.527588	0.918395
H	4.579819	-3.437404	-1.335409
H	3.500353	0.671643	-0.757263
H	4.262655	-1.137769	-2.269217
H	4.130271	-3.802372	1.097798
H	3.372675	-1.880014	2.467977

28

C	5.604905	-1.261563	-0.255488
O	6.186759	-2.201250	-0.607473
C	4.963611	-0.195110	0.139634
C	3.789715	0.388975	-0.608227
H	3.785504	0.047616	-1.643372
C	2.443808	0.079596	0.037992
C	2.035538	-1.339720	-0.161871
O	2.646751	-2.193368	-0.717346
N	0.701592	-1.720829	0.390618
C	0.103616	-2.797067	-0.151099
C	-1.116657	-3.217856	0.309324
C	-1.727310	-2.519881	1.340768
C	-1.096951	-1.410045	1.879066
C	0.121612	-1.020749	1.381164
H	0.647308	-0.161587	1.782339

H	-1.539497	-0.837027	2.680594
H	-2.692686	-2.834050	1.715151
H	-1.584283	-4.077621	-0.147066
H	0.638094	-3.281797	-0.952821
Cl	0.085672	-0.163617	-2.555358
H	1.648768	0.679404	-0.414005
H	2.466989	0.319752	1.104559
H	3.902368	1.473368	-0.633800
H	5.294584	0.237539	1.076351
Cl	1.272091	1.810659	3.133342
H	0.425961	2.521796	1.489201
N	-0.004001	2.879362	0.596469
C	-1.296357	2.641927	0.364939
C	-1.878907	3.100668	-0.794053
C	-1.099084	3.796392	-1.704871
C	0.243930	4.022164	-1.436764
C	0.772732	3.547825	-0.259973
H	1.805015	3.678826	0.031929
H	0.876403	4.555324	-2.131261
H	-1.534951	4.157684	-2.626944
H	-2.924089	2.898932	-0.977146
H	-1.834430	2.076564	1.112829
C	-4.716529	-0.267095	0.940064
N	-3.668906	0.310821	0.353852
C	-3.205506	-0.240180	-0.767210
C	-3.763785	-1.370346	-1.345032
C	-4.852921	-1.962646	-0.728413
C	-5.338900	-1.401060	0.442519

H	-6.186740	-1.828088	0.962070
H	-5.314802	-2.847038	-1.149885
H	-3.339176	-1.772766	-2.255393
H	-2.334320	0.221170	-1.223954
H	-5.076232	0.198394	1.852077

2.10 NOTES AND REFERENCES

(1) Kerkovius, J. K.; Stegner, A.; Turlik, A.; Lam, P. H.; Houk, K. N.; Reisman, S. E. A Pyridine Dearomatization Approach to the Matrine-Type Lupin Alkaloids. *J. Am. Chem. Soc.* **2022**, *144* (35), 15938–15943.

(2) Ohmiya, S.; Saito, K.; Murakoshi, I. *Chapter 1 Lupine Alkaloids. In The Alkaloids: Chemistry and Pharmacology.*, Cordell, G. A., Ed.; Academic Press, 1995.

(3) Zhang, H.; Chen, L.; Sun, X.; Yang, Q.; Wan, L.; Guo, C. Matrine: A Promising Natural Product With Various Pharmacological Activities. *Front. Pharmacol.* **2020**, *11*.

(4) You, L.; Yang, C.; Du, Y.; Wang, W.; Sun, M.; Liu, J.; Ma, B.; Pang, L.; Zeng, Y.; Zhang, Z.; Dong, X.; Yin, X.; Ni, J. A Systematic Review of the Pharmacology, Toxicology and Pharmacokinetics of Matrine. *Front. Pharmacol.* **2020**, *11*.

(5) Wang, Q.; Li, Y.; Li, K.-W.; Zhou, C.-Z. Sophoridine: A Review of Its Pharmacology, Pharmacokinetics and Toxicity. *Phytomedicine* **2022**, *95*, 153756.

(6) Bunsupa, S.; Katayama, K.; Ikeura, E.; Oikawa, A.; Toyooka, K.; Saito, K.; Yamazaki, M. Lysine Decarboxylase Catalyzes the First Step of Quinolizidine Alkaloid Biosynthesis and Coevolved with Alkaloid Production in Leguminosae. *Plant Cell* **2012**, *24* (3), 1202–1216.

(7) Yang, T.; Nagy, I.; Mancinotti, D.; Otterbach, S. L.; Andersen, T. B.; Motawia, M. S.; Asp, T.; Geu-Flores, F. Transcript Profiling of a Bitter Variety of Narrow-Leafed Lupin to Discover Alkaloid Biosynthetic Genes. *J. Exp. Bot.* **2017**, *68* (20), 5527–5537.

(8) Golebiewski, W. M.; Spenser, I. D. Biosynthesis of the Lupine Alkaloids. II. Sparteine and Lupanine. *Can. J. Chem.* **1988**, *66* (7), 1734–1748.

(9) Mancinotti, D.; Frick, K. M.; Geu-Flores, F. Biosynthesis of Quinolizidine Alkaloids in Lupins: Mechanistic Considerations and Prospects for Pathway Elucidation. *Nat. Prod. Rep.* **2022**, *39* (7), 1423–1437.

(10) Abdusalamov, B. A. Biosynthesis and Metabolism of Some Matrine Alkaloids InGoebelia Pachycarpa. *Chem. Nat. Compd.* **1984**, *20* (1), 1–9.

(11) Leeper, F. J.; Grue-Sørensen, G.; Spenser, I. D. Biosynthesis of the Quinolizidine Alkaloids. Incorporation of Δ1-Piperideine into Matrine. *Can. J. Chem.* **1981**, *59* (1), 106–115.

(12) Warneke, J.; Plaumann, M.; Wang, Z.; Böhler, E.; Kemken, D.; Kelm, S.; Leibfritz, D.; Azov, V. A. New Insights into the Old Reaction between Acryloyl Chlorides and Pyridine. *Tetrahedron Lett.* **2015**, *56* (9), 1124–1127.

(13) Ueno, A.; Morinaga, K.; Fukushima, S.; Iitaka, Y.; Koiso, Y.; Okuda, S. Studies on Lupin Alkaloids. VI. Isolation and Structure of (+)-Isomatrine. *Chem. Pharm. Bull. (Tokyo)* **1975**, *23* (11), 2560–2566.

(14) Galasso, V.; Asaro, F.; Berti, F.; Pergolese, B.; Kovač, B.; Pichierri, F. On the Molecular and Electronic Structure of Matrine-Type Alkaloids. *Chem. Phys.* **2006**, *330* (3), 457–468.

(15) Magann, N. L.; Westley, E.; Sowden, M. J.; Gardiner, M. G.; Sherburn, M. S. Total Synthesis of Matrine Alkaloids. *J. Am. Chem. Soc.* **2022**, *144* (43), 19695–19699.

(16) Mandell, Leon.; Singh, K. P.; Gresham, J. T.; Freeman, Walter. Total Synthesis of d,l-Matrine. *J. Am. Chem. Soc.* **1963**, *85* (17), 2682–2683.

(17) Mandell, L.; Singh, K. P.; Gresham, J. T.; Freeman, W. J. The Total Syntheses of d,l-Matrine and d,l-Leontine1. *J. Am. Chem. Soc.* **1965**, *87* (22), 5234–5236.

(18) Okuda, S.; Yoshimoto, M.; Tsuda, K. Studies on Lupin Alkaloids. IV. Total Syntheses of Optically Active Matrine and Allomatrine. *Chem. Pharm. Bull. (Tokyo)* **1966**, *14* (3), 275–279.

(19) Chen, J.; Browne, L. J.; Gonnela, N. C. Total Synthesis of (±)-Matrine. *J. Chem. Soc. Chem. Commun.* **1986**, No. 12, 905–907.

(20) Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z. A Short Synthesis of (±)-Matrine. *Angew. Chem. Int. Ed.* **1998**, *37* (8), 1128–1131.

(21) Watkin, S. V.; Camp, N. P.; Brown, R. C. D. Total Synthesis of the Tetracyclic Lupin Alkaloid (+)-Allomatrine. *Org. Lett.* **2013**, *15* (17), 4596–4599.

(22) Lyu, X. Stereoselective Total Synthesis of Lupin Alkaloids. phd, University of Southampton, 2018. https://eprints.soton.ac.uk/429608/ (accessed 2023-03-16).

(23) Paull, D. H.; Weatherwax, A.; Lectka, T. Catalytic, Asymmetric Reactions of Ketenes and Ketene Enolates. *Tetrahedron* **2009**, *65* (34), 6771–6803.

(24) Pracht, P.; Bohle, F.; Grimme, S. Automated Exploration of the Low-Energy Chemical Space with Fast Quantum Chemical Methods. *Phys. Chem. Chem. Phys.* **2020**, *22* (14), 7169–7192.

(25) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. Enantioselective Nitroaldol (Henry) Reaction Using Copper(II) Complexes of (−)-Sparteine. *Chem. Commun.* **2006**, No. 39, 4066–4068.

(26) Wink, M.; Hartmann, T.; Witte, L. Enzymatic Synthesis of Quinolizidine Alkaloids in Lupin Chloroplasts. *Z. Für Naturforschung C* **1980**, *35* (1–2), 93–97.

(27) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. Highly Efficient Oxidation of Amines to Imines by Singlet Oxygen and Its Application in Ugi-Type Reactions. *Org. Lett.* **2009**, *11* (20), 4568–4571.

(28) Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. Photoredox-Catalyzed Deuteration and Tritiation of Pharmaceutical Compounds. *Science* **2017**, *358* (6367), 1182–1187.

(29) Griffiths, R. J.; Burley, G. A.; Talbot, E. P. A. Transition-Metal-Free Amine Oxidation: A Chemoselective Strategy for the Late-Stage Formation of Lactams. *Org. Lett.* **2017**, *19* (4), 870–873.

(30) Su, J.; Ma, X.; Ou, Z.; Song, Q. Deconstructive Functionalizations of Unstrained Carbon–Nitrogen Cleavage Enabled by Difluorocarbene. *ACS Cent. Sci.* **2020**, *6* (10), 1819–1826.

(31) Grierson, D. The Polonovski Reaction. In *Organic Reactions*; John Wiley & Sons, Ltd, 2004; pp 85–295.

(32) Lee, S.; Kang, G.; Chung, G.; Kim, D.; Lee, H.-Y.; Han, S. Biosynthetically Inspired Syntheses of Secu′amamine A and Fluvirosaones A and B. *Angew. Chem. Int. Ed.* **2020**, *59* (17), 6894–6901.

(33) Kessar, S. V.; Singh, P.; Singh, K. N.; Singh, S. K. Facile α-Deprotonation–Electrophilic Substitution of Quinuclidine and DABCO. *Chem. Commun.* **1999**, No. 19, 1927–1928.

(34) Chuang, T.-H.; Yang, C.-C.; Chang, C.-J.; Fang, J.-M. Base-Catalyzed Autoxidation of α-Aminonitriles. An Efficient Method for Conversion of Aldehydes to Amides and 2-Amino-2-Sulfenylacetonitrile to Carbamates. *Synlett* **1990**, *1990* (12), 733–734.

(35) García-Valverde, M.; Pedrosa, R.; Vicente, M. A Novel and Efficient Oxidation of 1,2-Amino Alcohols to Dialkylamides. *Synlett* **2002**, *2002* (12), 2092–2094.

(36) Ibragimov, B. T.; Tishchenko, G. N.; Kushmuradov, Yu. K.; Aripov, T. F.; Sadykov, A. S. Molecular and Crystal Structure of Sophoridine. *Chem. Nat. Compd.* **1979**, *15* (3), 308–314.

(37) Wink, M.; Meißner, C.; Witte, L. Patterns of Quinolizidine Alkaloids in 56 Species of the Genus Lupinus. *Phytochemistry* **1995**, *38* (1), 139–153.

(38) Gray, D.; Gallagher, T. A Flexible Strategy for the Synthesis of Tri- and Tetracyclic Lupin Alkaloids: Synthesis of (+)-Cytisine, (±)-Anagyrine, and (±)-Thermopsine. *Angew. Chem. Int. Ed.* **2006**, *45* (15), 2419–2423.

(39) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43* (14), 2923–2925.

(40) Ibragimov, B. T.; Talipov, S. A.; Tischenko, G. N.; Kushmuradov, Y. K.; Aripov, T. F. Molecular and Crystal-Structure of Matrine. *Kristallografiya* **1978**, *23*, 1189–1195.

(41) Ling, J. Y.; Zhang, G. Y.; Cui, Z. J.; Zhang, C. K. Supercritical Fluid Extraction of Quinolizidine Alkaloids from Sophora Flavescens Ait. and Purification by High-

Speed Counter-Current Chromatography. *J. Chromatogr. A* **2007**, *1145* (1), 123–127.

(42) Bai, G.-Y.; Wang, D.-Q.; Ye, C.-H.; Liu, M.-L. 1H And13C Chemical Shift Assignments and Stereochemistry of Matrine and Oxymatrine. *Appl. Magn. Reson.* **2002**, *23* (2), 113–121.

(43) Ibragimov, B. T.; Tishchenko, G. N.; Kushmuradov, Yu. K.; Aripov, T. F.; Sadykov, A. S. X-Ray Structural Investigation of Allomatrine and Its N-Oxide. *Chem. Nat. Compd.* **1979**, *15* (3), 368–369.

(44) Qiao, L.; Huang, L.; Gao, C.; Zhao, Y.; Yang, X.; Zhang, L. NMR Studies of the Matrine Alkaloids. *J Peking Univ Health Sci* **1994**, *26*, 485–486.

(45) Ibragimov, B. T.; Tishchenko, G. N.; Talipov, S. A.; Kushmuradov, Y. K.; Aripov, T. F. Structure of Isosophoridine. *Khimiia Prir. Soedin.* **1981**, 460–465.

(46) Ibragimov, B. T.; Talipov, S. A.; Tishchenko, G. N.; Kushmuradov, Y. K.; Aripov, T. F. Molecular and Crystal Structure of Isosophoridine. *Khimiia Prir. Soedin.* **1979**, 586–588.

(47) Santos, L. S.; Mirabal-Gallardo, Y.; Shankaraiah, N.; Simirgiotis, M. J. Short Total Synthesis of (-)-Lupinine and (-)-Epiquinamide by Double Mitsunobu Reaction. *Synthesis* **2011**, *2011* (1), 51–56.

(48) Firth, J. D.; Canipa, S. J.; Ferris, L.; O'Brien, P. Gram-Scale Synthesis of the (−)-Sparteine Surrogate and (−)-Sparteine. *Angew. Chem. Int. Ed.* **2018**, *57* (1), 223–226.

(49) *APEX2, Version 2 User Manual, M86-E01078, Bruker Analytical X-Ray Systems, Madison, WI, 2006.*

(50) *Sheldrick, G.M. SADABS (Version 2008/1): Program for Absorption Correction for Data from Area Detector Frames, University of Göttingen, 2008.*

(51) *Sheldrick, G. Acta Crystallogr., Sect. A: Found. Crystallogr. 2008, 64, 112.*

(52) *Sheldrick, G. M. Acta Crystallogr., Sect. C: Struct. Chem. 2015, C71, 3.*

(53) *Müller, P. Crystallogr. Rev. 2009, 15, 57.*

(54) Parsons, S.; Flack, H. D.; Wagner, T. Use of Intensity Quotients and Differences in Absolute Structure Refinement. *Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater.* **2013**, *69* (3), 249–259.

(55) Van Der Sluis, P.; Spek, A. L. BYPASS: An Effective Method for the Refinement of Crystal Structures Containing Disordered Solvent Regions. *Acta Crystallogr. Sect. A* **1990**, *46* (3), 194–201.

(56) Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T. A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M.; Wood, P. A. Mercury 4.0: From Visualization to Analysis, Design and Prediction. *J. Appl. Crystallogr.* **2020**, *53* (1), 226–235.

(57) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 16 Rev. A.03, 2016.

(58) Chai, J.-D.; Head-Gordon, M. Long-Range Corrected Hybrid Density Functionals with Damped Atom–Atom Dispersion Corrections. *Phys. Chem. Chem. Phys.* **2008**, *10* (44), 6615–6620.

(59) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7* (18), 3297–3305.

(60) Weigend, F. Accurate Coulomb-Fitting Basis Sets for H to Rn. *Phys. Chem. Chem. Phys.* **2006**, *8* (9), 1057–1065.

(61) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113* (18), 6378–6396.

(62) Luchini, G.; Alegre-Requena, J. V.; Funes-Ardoiz, I.; Paton, R. S. GoodVibes: Automated Thermochemistry for Heterogeneous Computational Chemistry Data. F1000Research April 24, 2020.

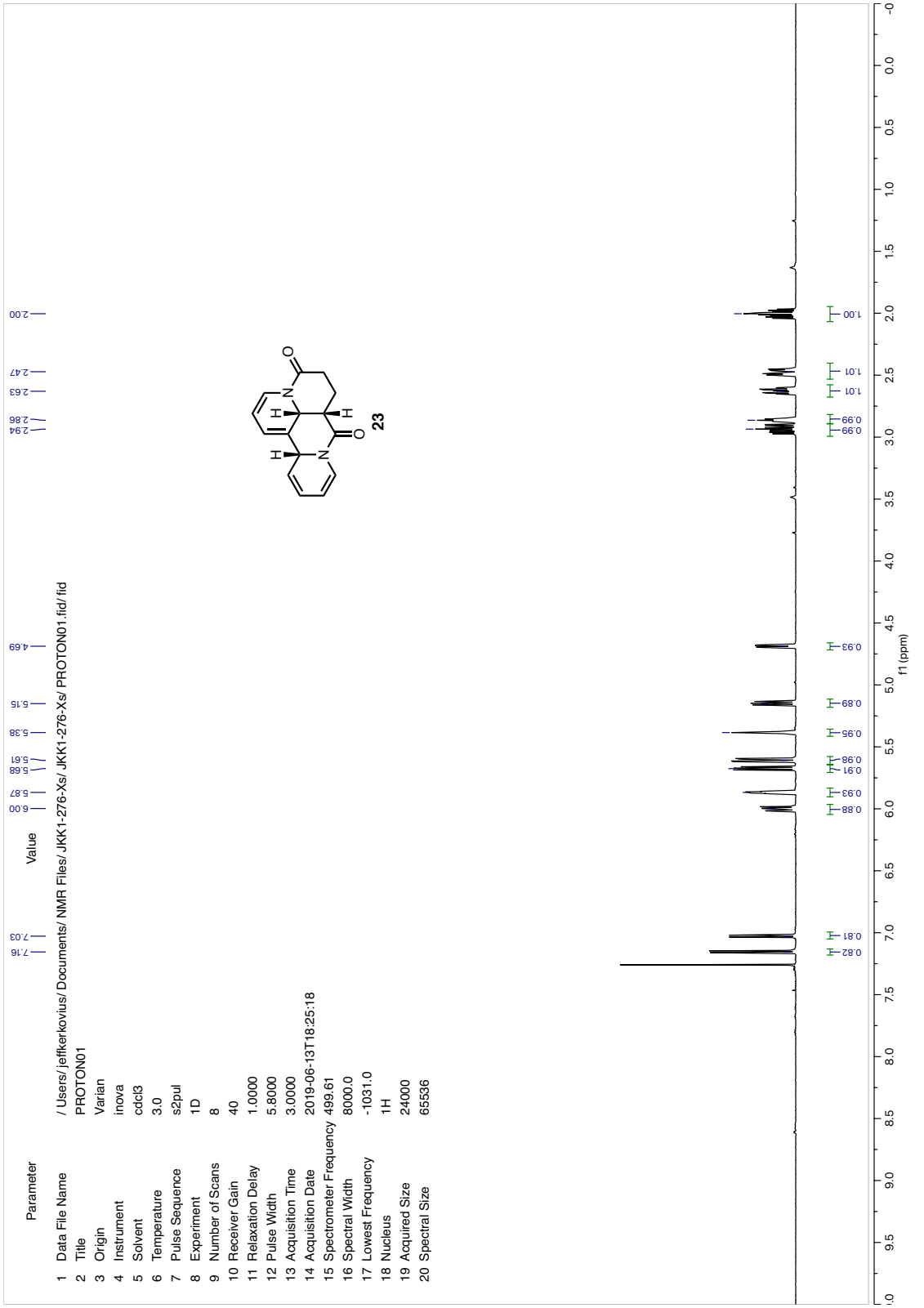
(63) The PyMOL Molecular Graphics System.

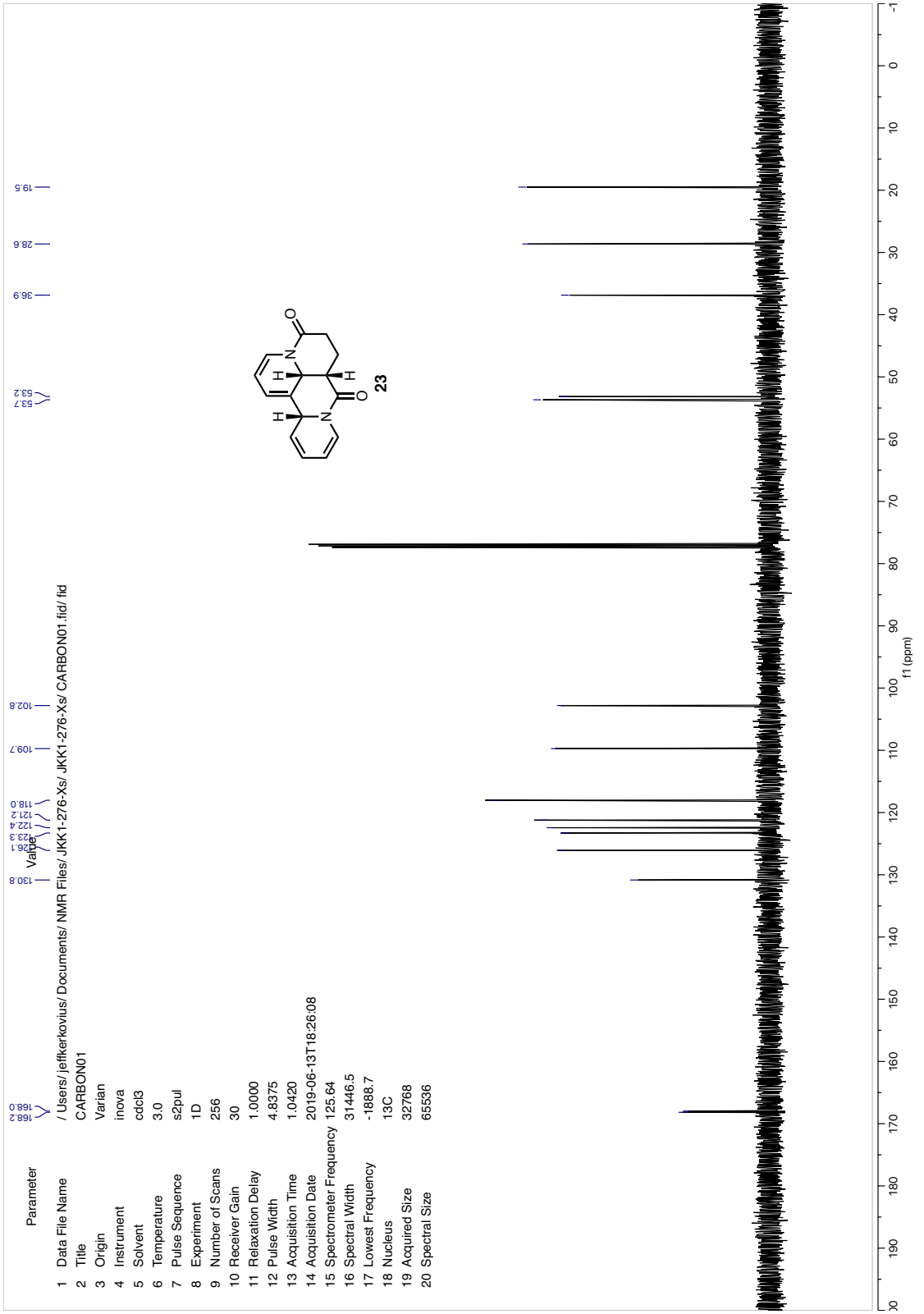
(64) Dennington, R.; Keith, T. A.; Millam, J. M. GaussView, 2016.

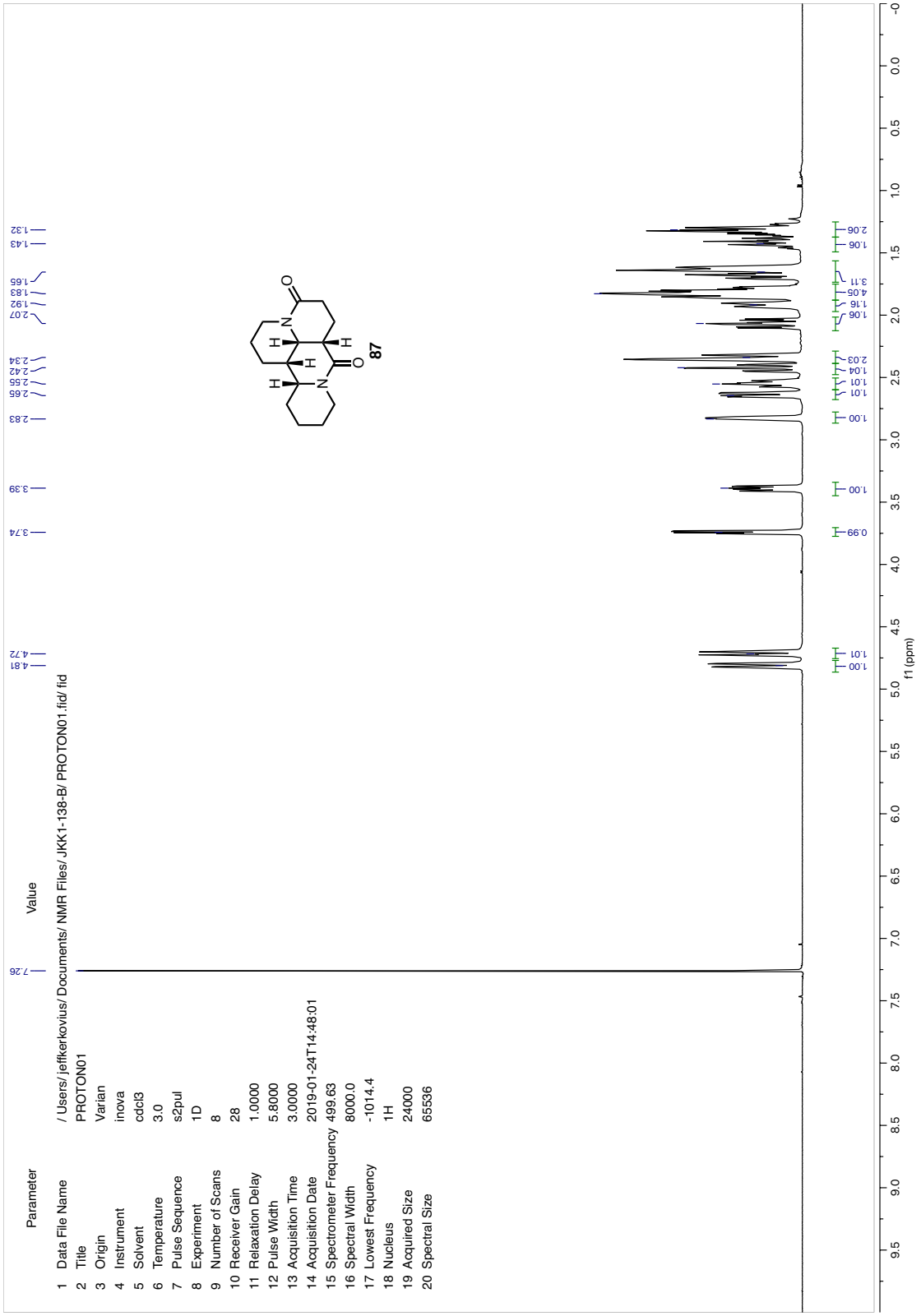
Appendix 1

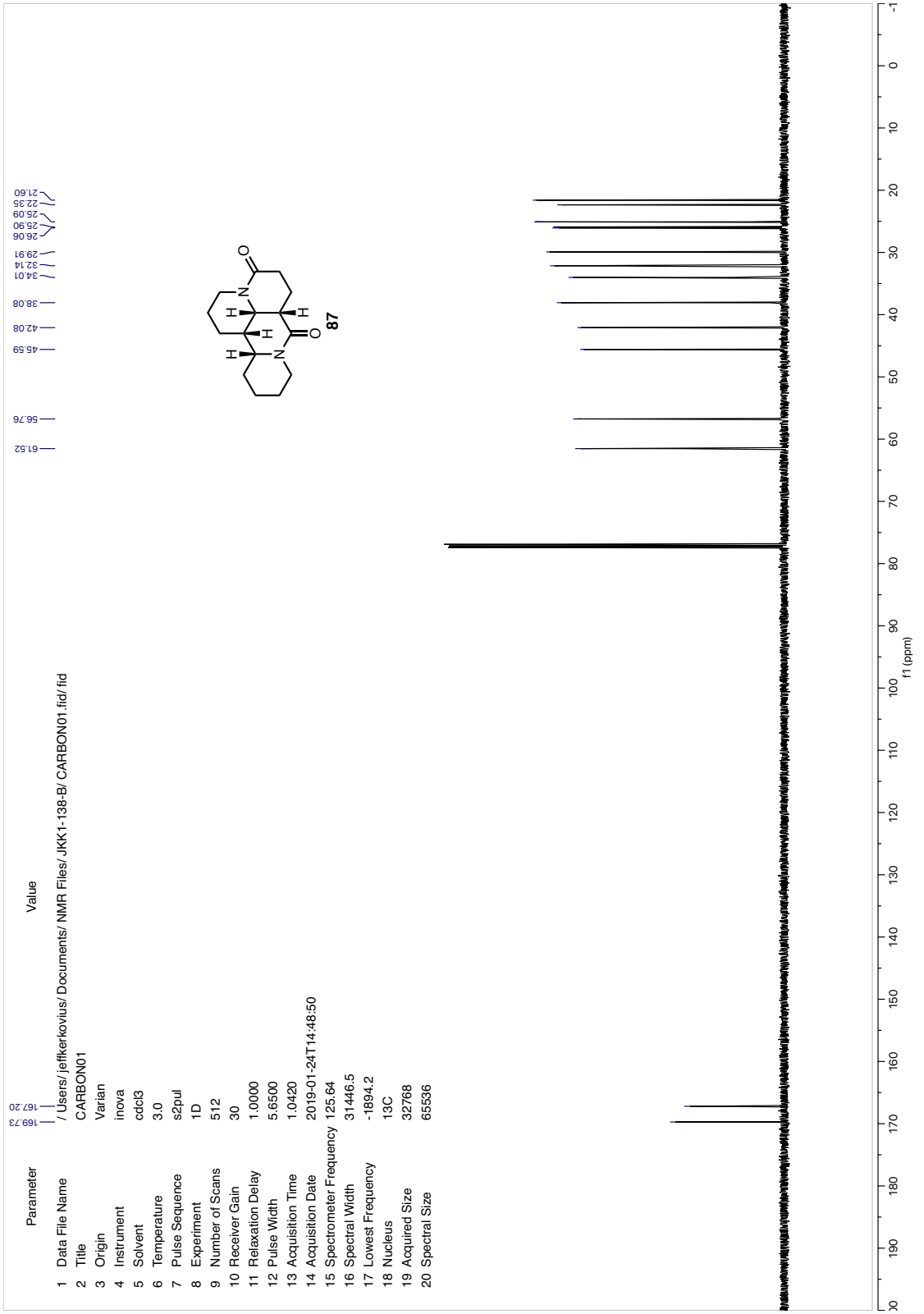
Spectra Relevant to Chapter 2:

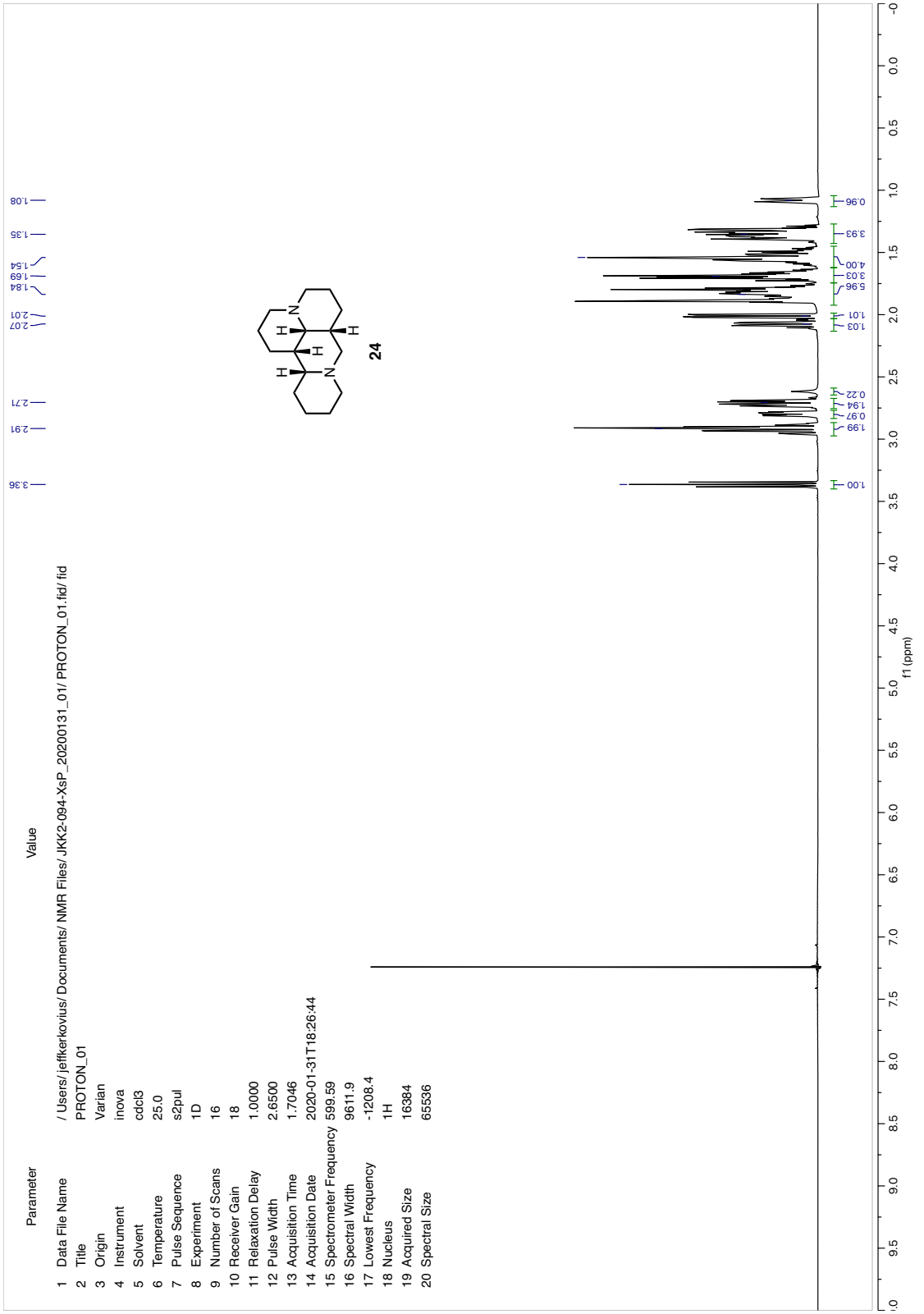
A Pyridine Dearomatization Approach to the Matrine-Type Lupin Alkaloids

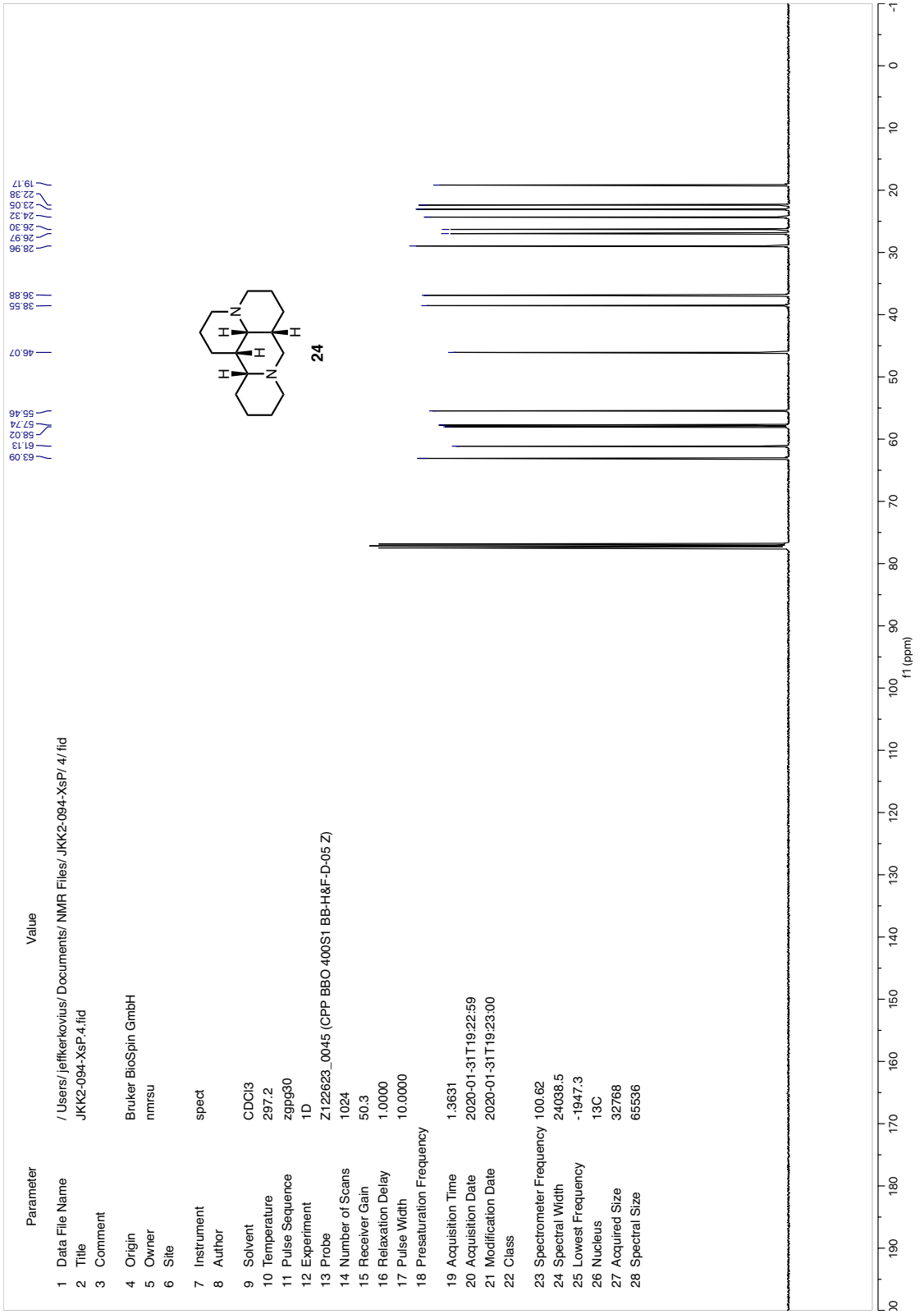

Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK1-276-Xs/ JKK1-276-Xs/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 40
11 Relaxation Delay 1.0000
12 Pulse Width 5.8000
13 Acquisition Time 3.0000
14 Acquisition Date 2019-06-13T18:25:18
15 Spectrometer Frequency 499.61
16 Spectral Width 8000.0
17 Lowest Frequency -1031.0
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
7.16
7.03
6.00
5.87
5.68
5.61
5.38
5.15
4.69
2.94
2.86
2.63
2.47
2.00
0.82
0.81
0.88
0.93
0.91
0.98
0.96
0.89
0.93
0.99
0.99
1.01
1.01
1.00
23
f1 (ppm)

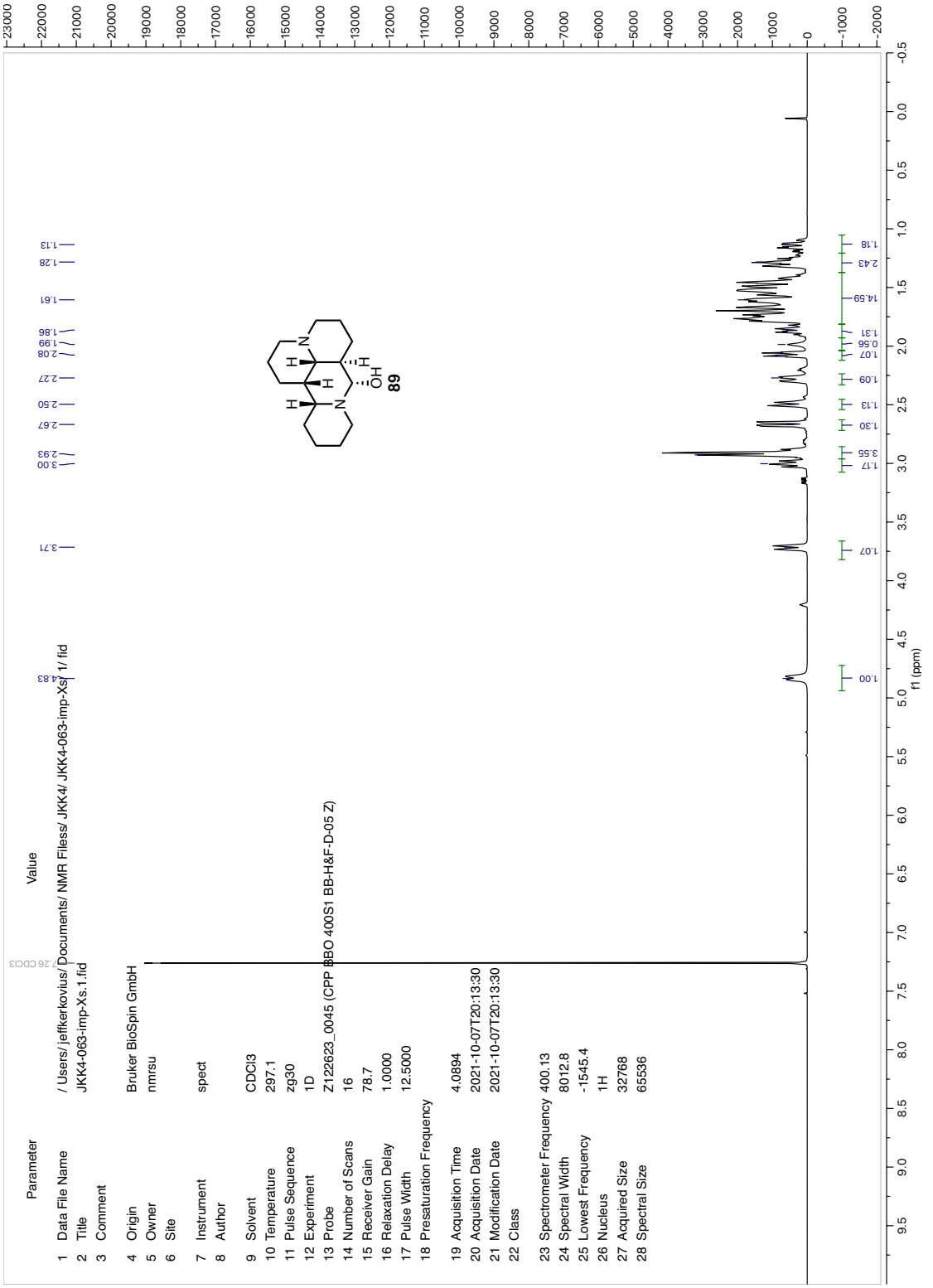

Parameter
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK1-276-Xs/ JKK1-276-Xs/ CARBON01.fid/ fid
2 Title CARBON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 256
10 Receiver Gain 30
11 Relaxation Delay 1.0000
12 Pulse Width 4.8375
13 Acquisition Time 1.0420
14 Acquisition Date 2019-06-13T18:26:08
15 Spectrometer Frequency 125.64
16 Spectral Width 31446.5
17 Lowest Frequency -1888.7
18 Nucleus 13C
19 Acquired Size 32768
20 Spectral Size 65536
Value
168.2
168.0
130.8
126.1
123.3
122.4
121.2
118.0
109.7
102.8
53.7
53.2
36.9
28.6
19.5
23
f1 (ppm)

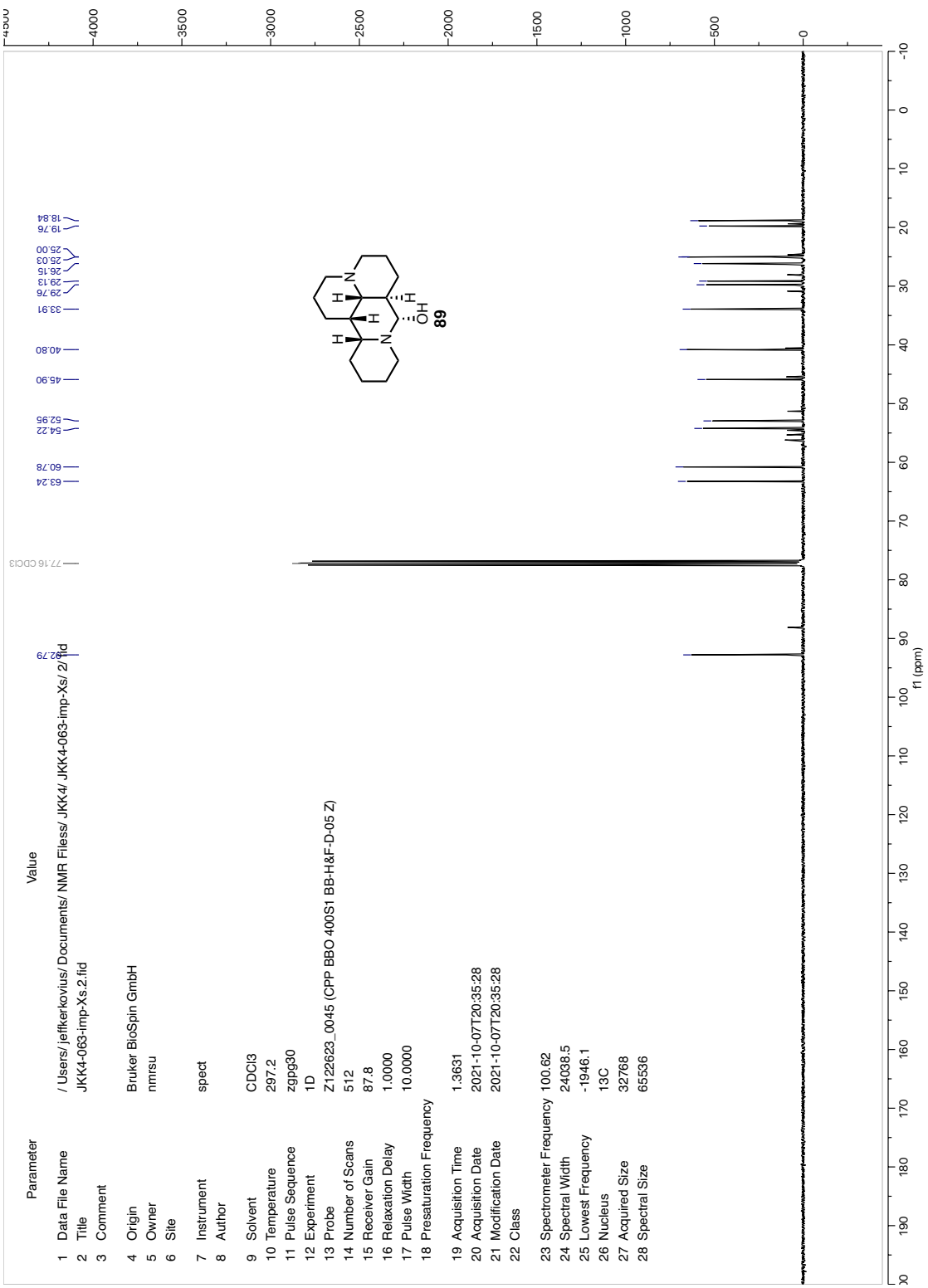

Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK1-138-B/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 28
11 Relaxation Delay 1.0000
12 Pulse Width 5.8000
13 Acquisition Time 3.0000
14 Acquisition Date 2019-01-24T14:48:01
15 Spectrometer Frequency 499.63
16 Spectral Width 8000.0
17 Lowest Frequency -1014.4
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
87
f1 (ppm)

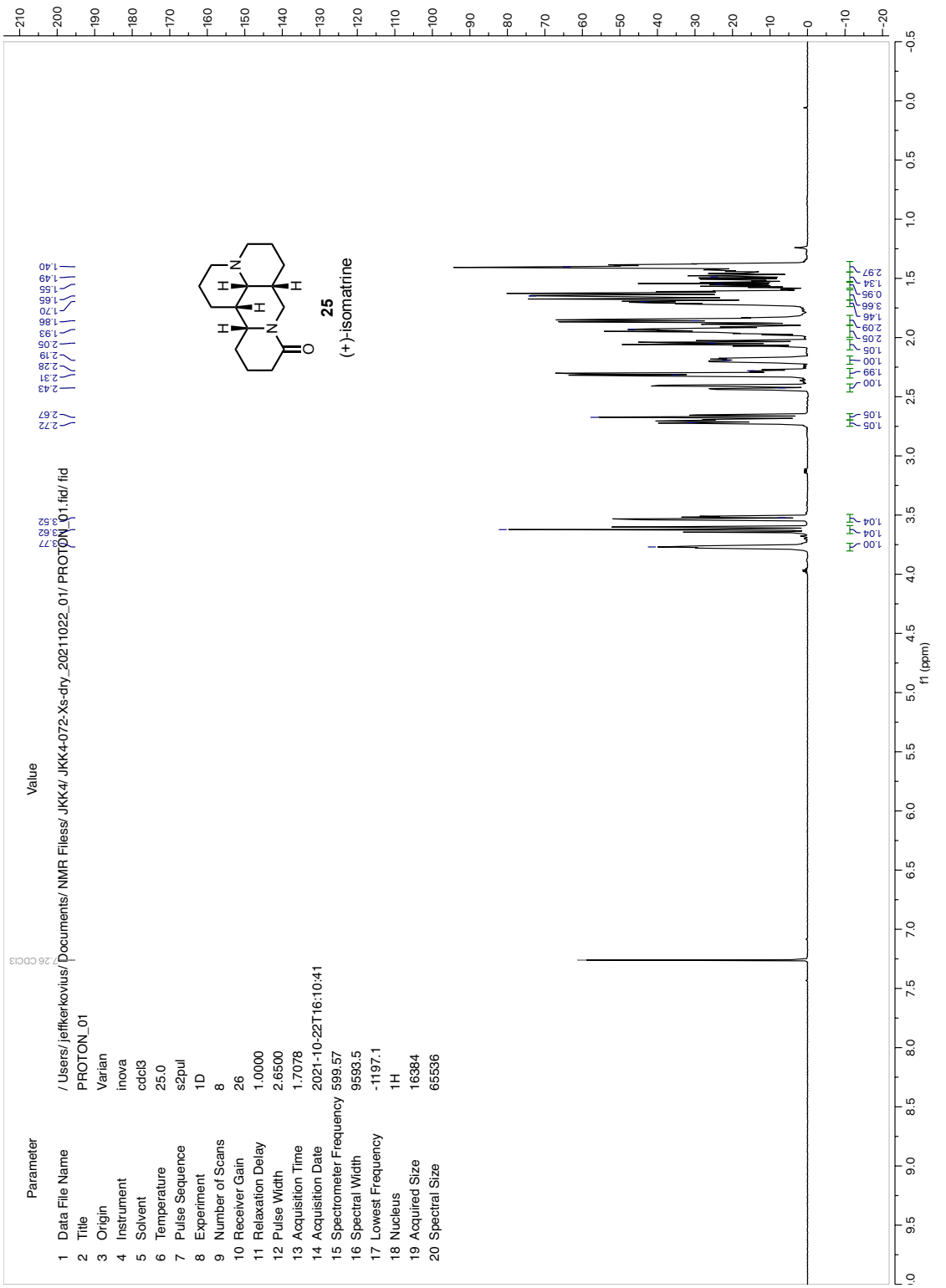

Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK1-138-B/ CARBON01.fid/ fid
2 Title CARBON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 512
10 Receiver Gain 30
11 Relaxation Delay 1.0000
12 Pulse Width 5.6500
13 Acquisition Time 1.0420
14 Acquisition Date 2019-01-24T14:48:50
15 Spectrometer Frequency 125.64
16 Spectral Width 31446.5
17 Lowest Frequency -1894.2
18 Nucleus 13C
19 Acquired Size 32768
20 Spectral Size 65536
169.73
167.20
61.52
56.76
45.59
42.08
38.08
34.01
32.14
29.91
26.06
25.90
25.09
22.35
21.60
87
f1 (ppm)

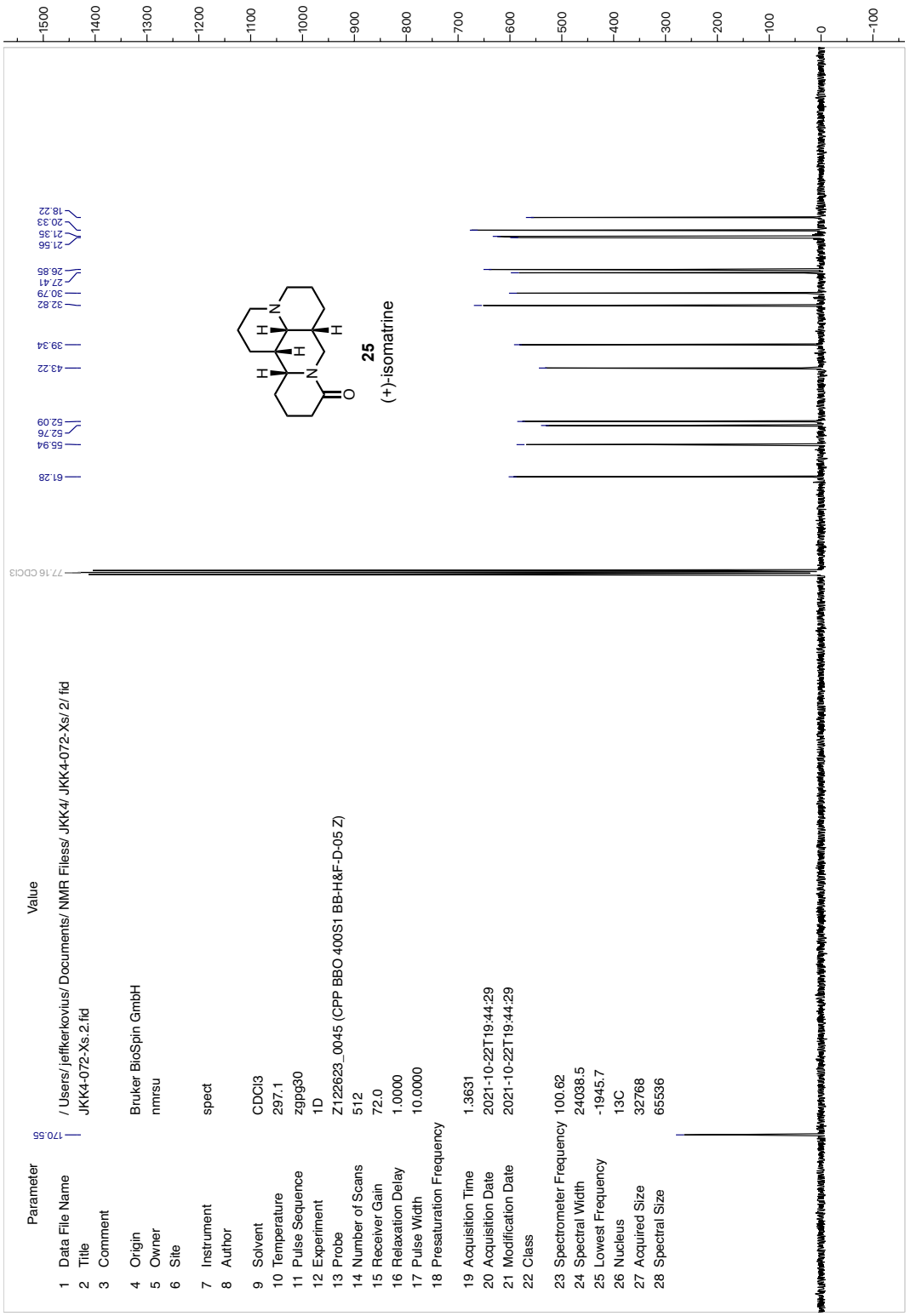

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2-094-XsP_20200131_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 16
10 Receiver Gain 18
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7046
14 Acquisition Date 2020-01-31T18:26:44
15 Spectrometer Frequency 599.59
16 Spectral Width 9611.9
17 Lowest Frequency -1208.4
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
24
f1 (ppm)

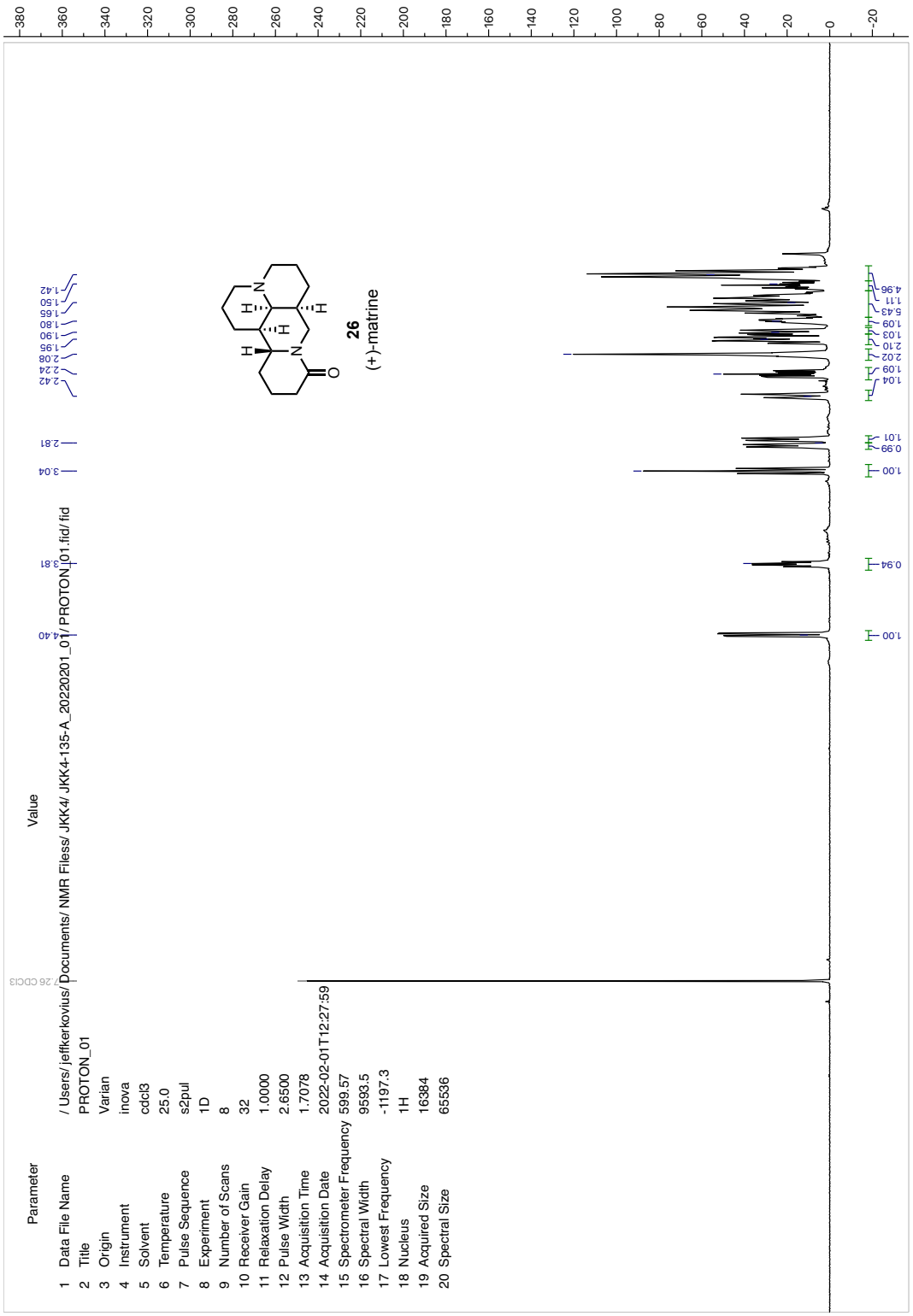

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2-094-XsP/ 4/ fid
2 Title JKK2-094-XsP.4.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 50.3
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2020-01-31T19:22:59
21 Modification Date 2020-01-31T19:23:00
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1947.3
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
63.09
61.13
58.02
57.74
55.46
46.07
38.55
36.88
28.96
26.97
26.30
24.32
23.05
22.38
19.17
24
f1 (ppm)

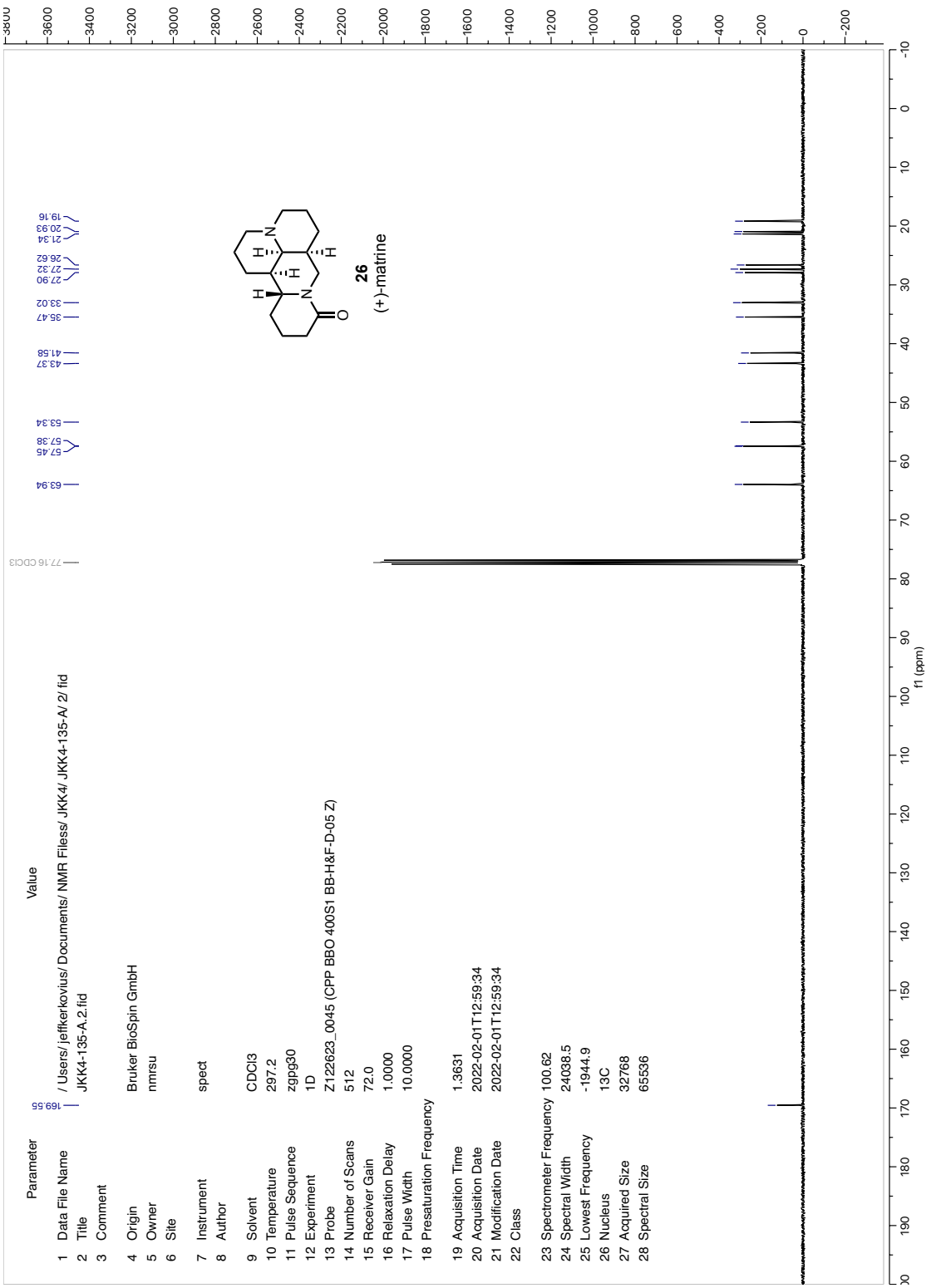

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-063-imp-Xs/ 1/ fid
2 Title JKK4-063-imp-Xs.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 16
15 Receiver Gain 78.7
16 Relaxation Delay 1.0000
17 Pulse Width 12.5000
18 Presaturation Frequency
19 Acquisition Time 4.0894
20 Acquisition Date 2021-10-07T20:13:30
21 Modification Date 2021-10-07T20:13:30
22 Class
23 Spectrometer Frequency 400.13
24 Spectral Width 8012.8
25 Lowest Frequency -1545.4
26 Nucleus 1H
27 Acquired Size 32768
28 Spectral Size 65536
CDCl3
7.26
4.83
3.71
3.00
2.93
2.67
2.50
2.27
2.08
1.99
1.86
1.61
1.28
1.13
1.00
1.07
3.55
1.17
1.30
1.13
1.09
1.07
0.56
1.31
14.59
2.43
1.18
89
f1 (ppm)

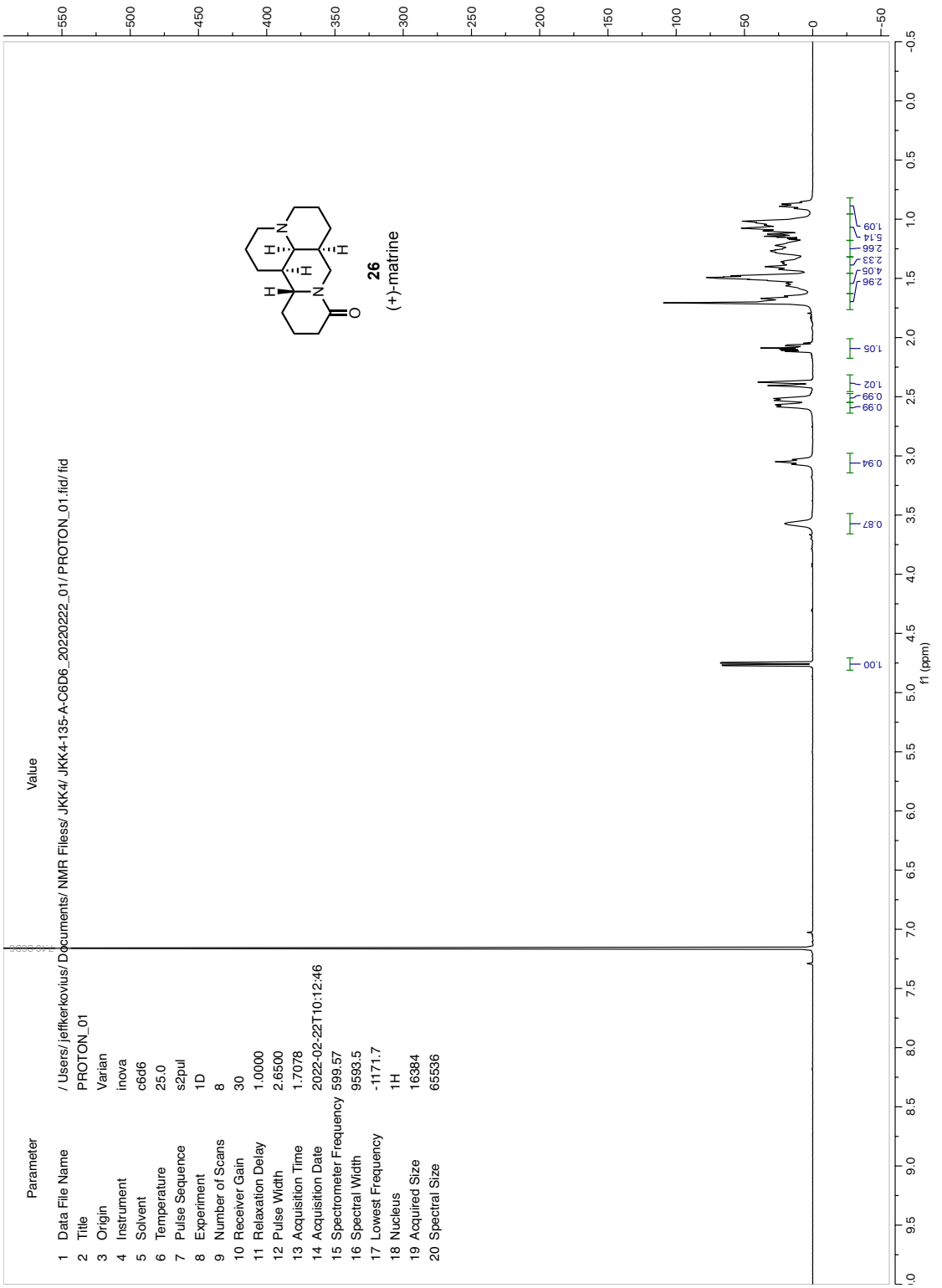

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Filess/ JKK4/ JKK4-063-imp-Xs/ 2/fid
2 Title JKK4-063-imp-Xs.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 87.8
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-07T20:35:28
21 Modification Date 2021-10-07T20:35:28
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1946.1
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
82.79
77.16 CDCl3
63.24
60.78
54.22
52.95
45.90
40.80
33.91
29.76
29.13
26.15
26.03
25.00
19.76
18.84
89
f1 (ppm)

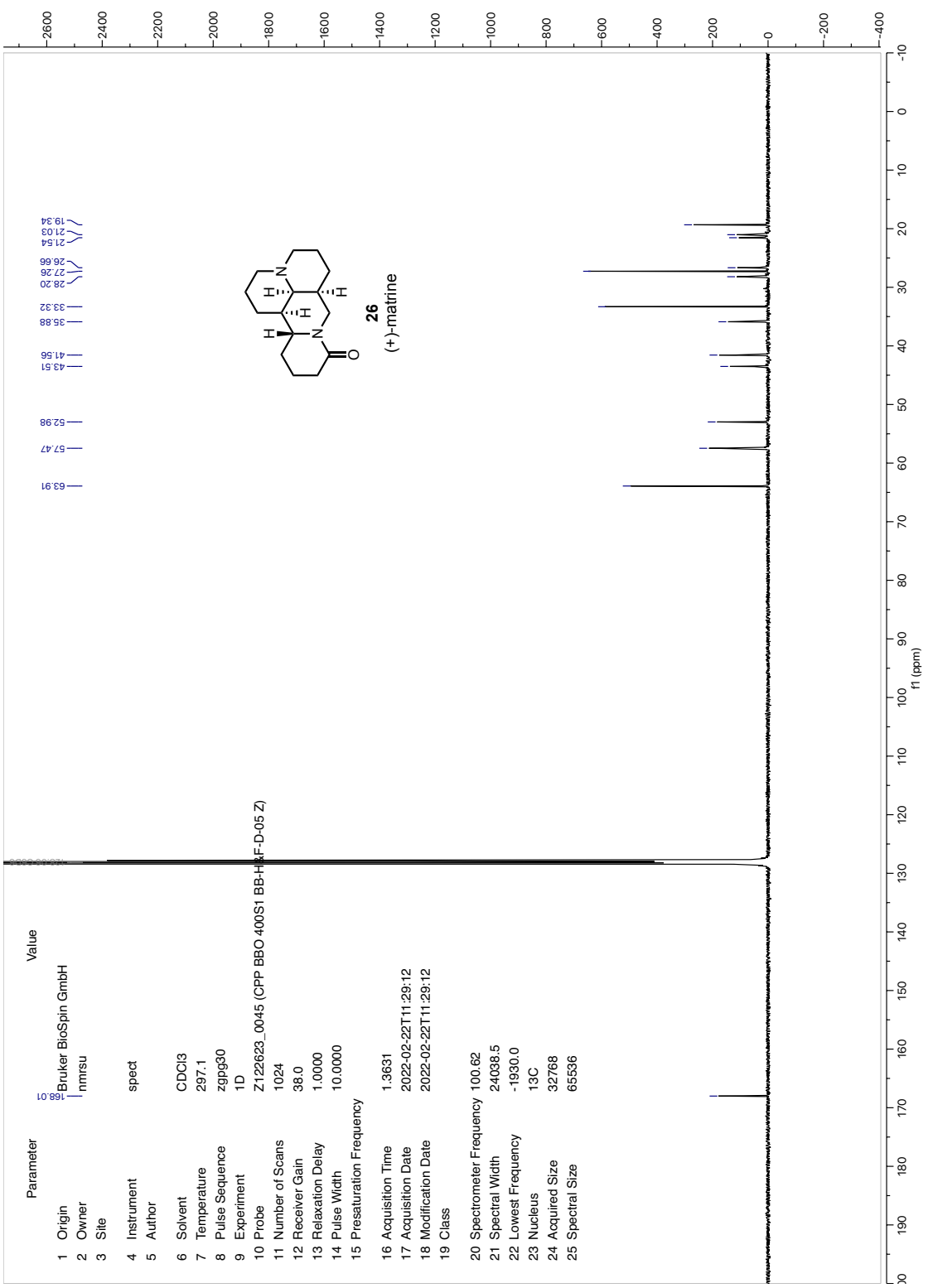

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Filess/ JKK4/ JKK4-072-Xs-dry_20211022_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 26
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2021-10-22T16:10:41
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1197.1
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
CDCl3
7.26
7.77
3.62
3.52
2.72
2.67
2.43
2.31
2.28
2.19
2.05
1.93
1.86
1.70
1.65
1.55
1.49
1.40
25
(+)-isomatrine
1.00
1.04
1.04
1.05
1.05
1.00
1.00
1.99
1.05
2.09
2.05
1.46
0.95
3.66
1.34
2.97
f1 (ppm)


Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-072-Xs/ 2/ fid
2 Title JKK4-072-Xs_2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-22T19:44:29
21 Modification Date 2021-10-22T19:44:29
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1945.7
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
170.55
77.16 CDCl3
61.28
55.94
52.76
52.09
43.22
39.34
32.82
30.79
27.41
26.85
21.56
21.35
20.33
18.22
25
(+)-isomatrine
f1 (ppm)

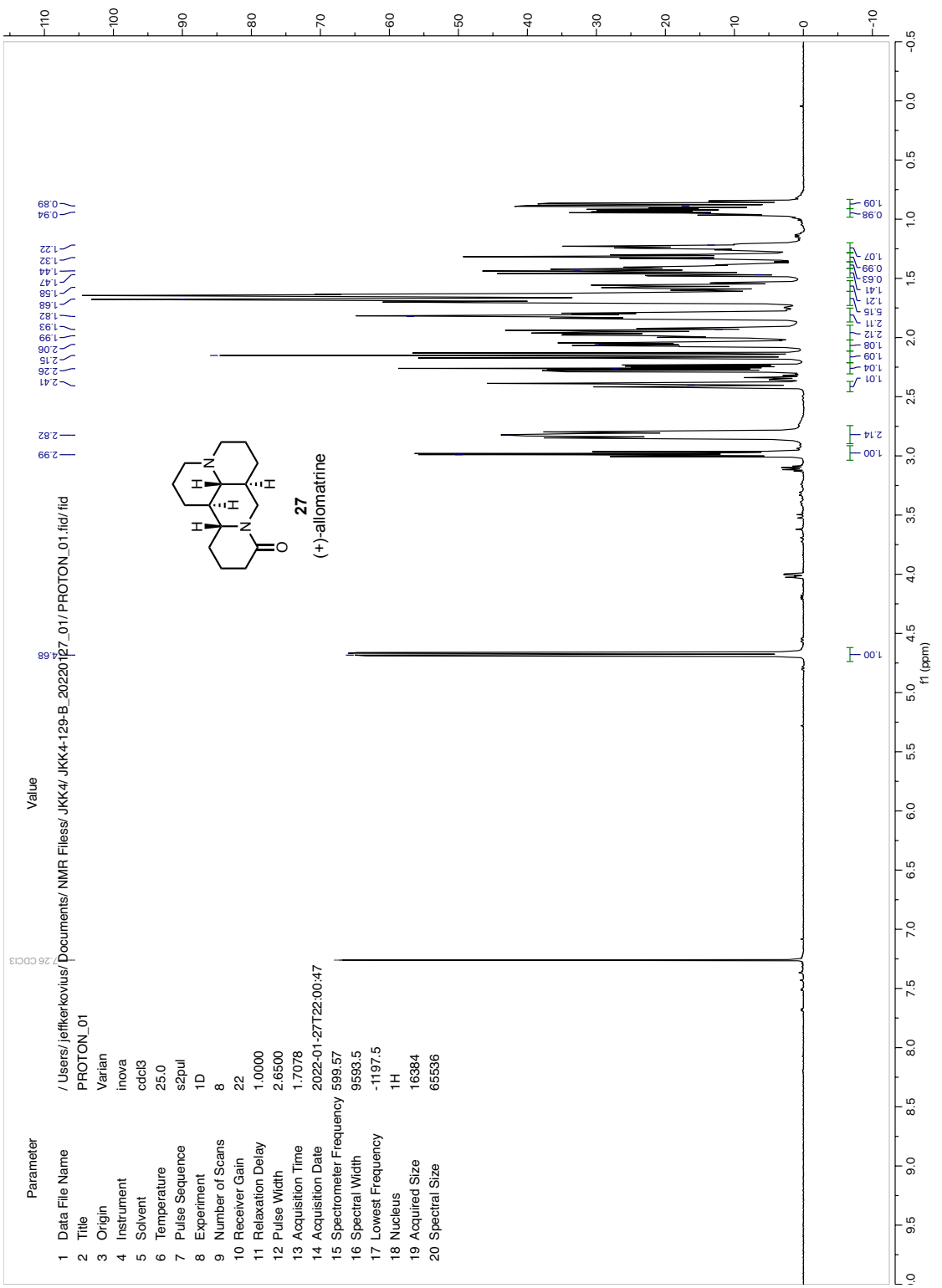

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-135-A_20220201_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 32
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2022-02-01T12:27:59
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1197.3
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
26
(+)-matrine
f1 (ppm)

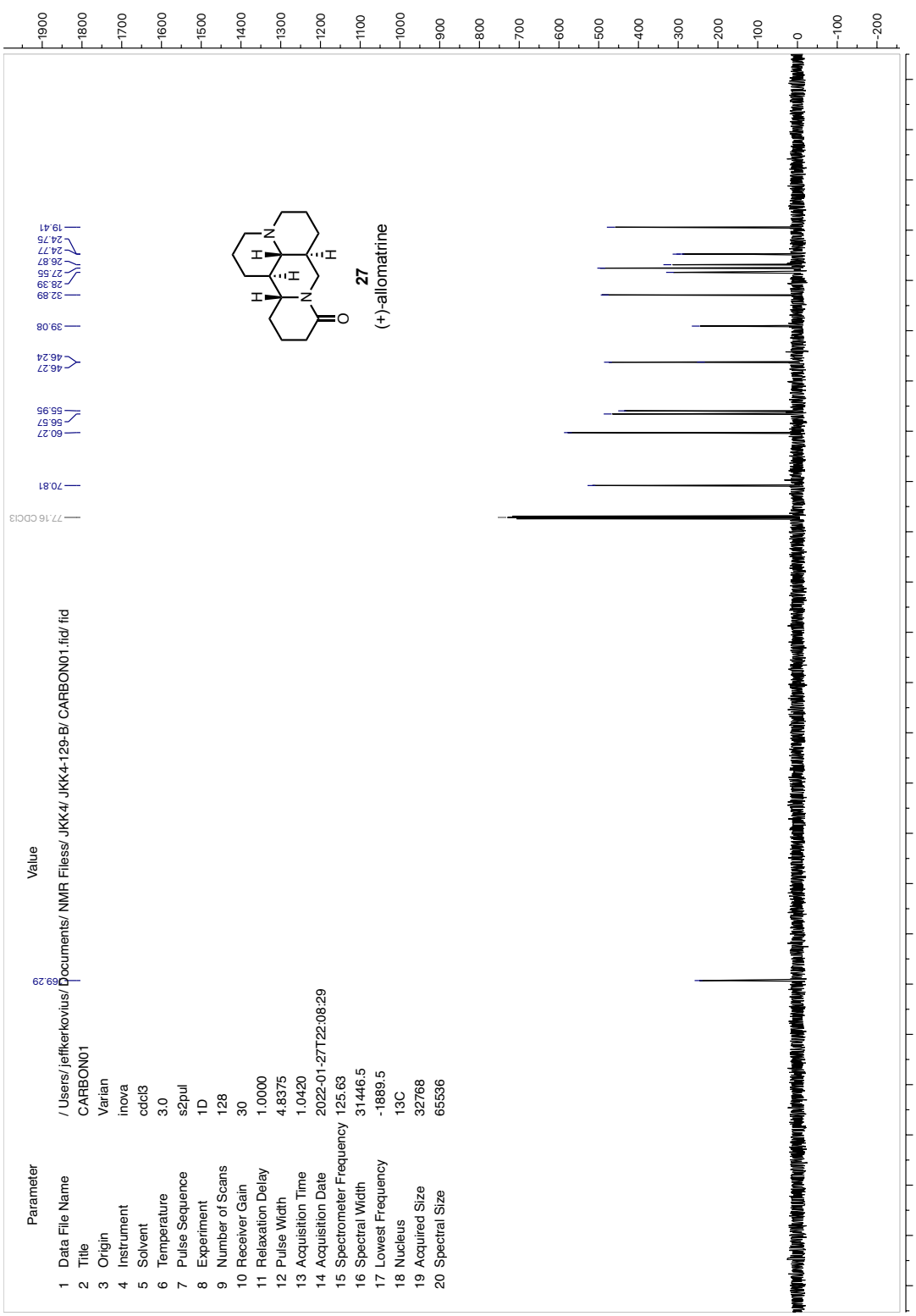

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-135-A/ 2/ fid
2 Title JKK4-135-A.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2022-02-01T12:59:34
21 Modification Date 2022-02-01T12:59:34
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1944.9
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
169.55
77.16 CDCl3
63.94
57.45
57.38
53.34
43.37
41.58
35.47
33.02
27.90
27.32
26.62
21.34
20.93
19.16
26
(+)-matrine
f1 (ppm)

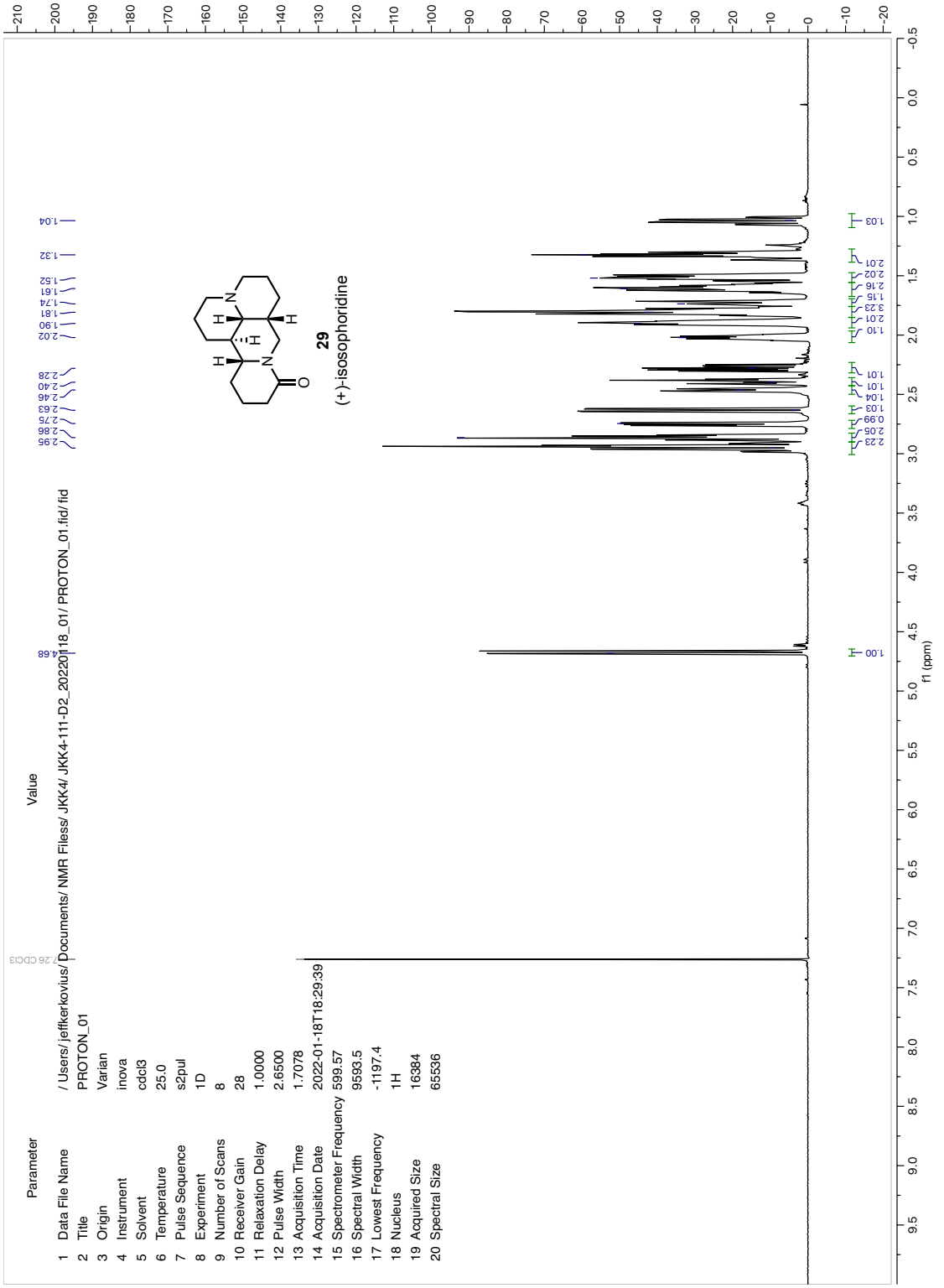

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-135-A-C6D6_20220222_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent c6d6
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 30
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2022-02-22T10:12:46
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1171.7
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
26
(+)-matrine
1.00
0.87
0.94
1.05
1.02
0.99
0.99
2.96
4.05
2.33
2.66
5.14
1.09
f1 (ppm)

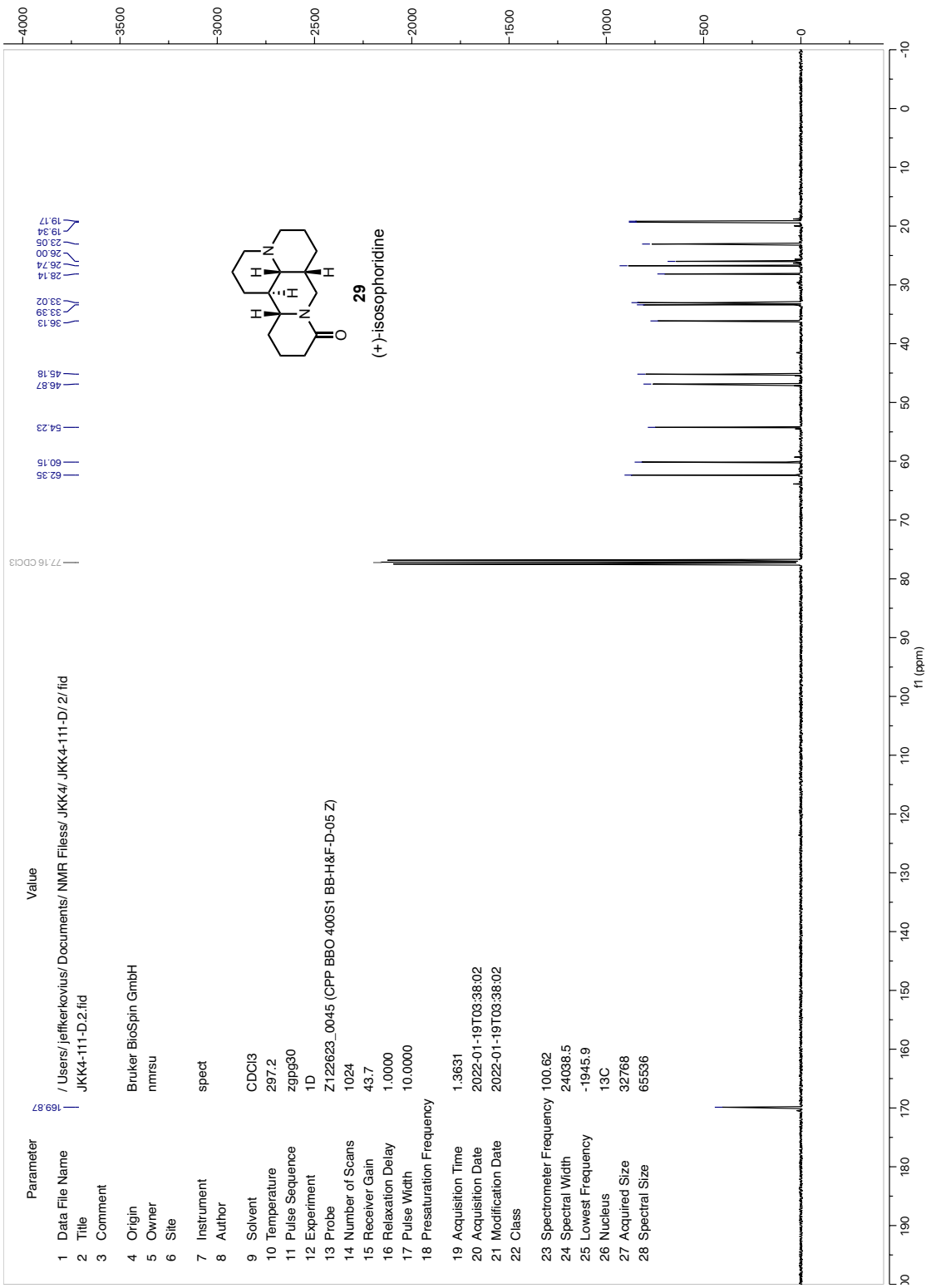


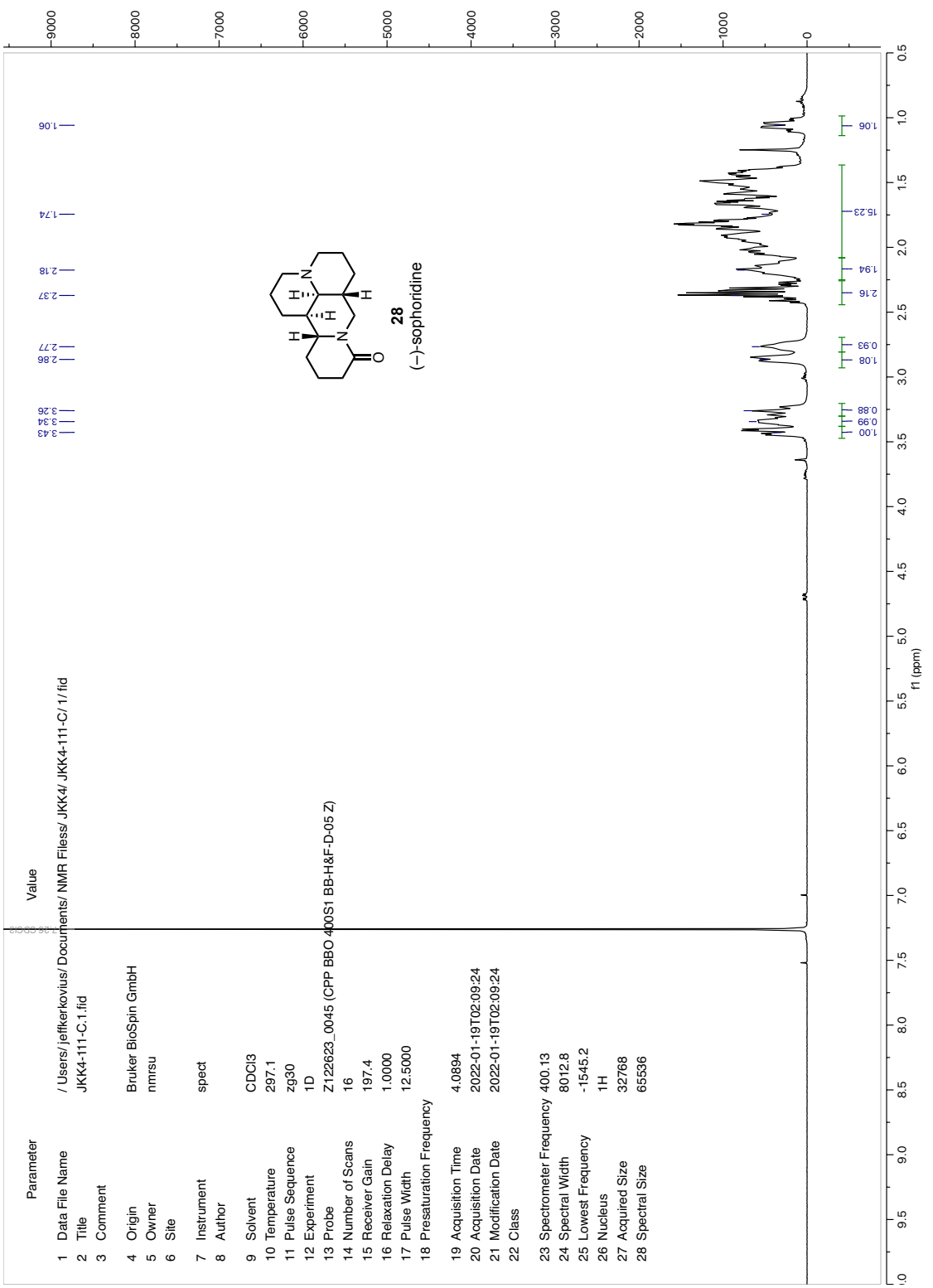
	Parameter	Value
1	Origin	Bruker BioSpin GmbH
2	Owner	nmrsu
3	Site	
4	Instrument	spect
5	Author	
6	Solvent	CDCl3
7	Temperature	297.1
8	Pulse Sequence	zgpg30
9	Experiment	1D
10	Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
11	Number of Scans	1024
12	Receiver Gain	38.0
13	Relaxation Delay	1.0000
14	Pulse Width	10.0000
15	Presaturation Frequency	
16	Acquisition Time	1.3631
17	Acquisition Date	2022-02-22T11:29:12
18	Modification Date	2022-02-22T11:29:12
19	Class	
20	Spectrometer Frequency	100.62
21	Spectral Width	24038.5
22	Lowest Frequency	-1930.0
23	Nucleus	13C
24	Acquired Size	32768
25	Spectral Size	65536

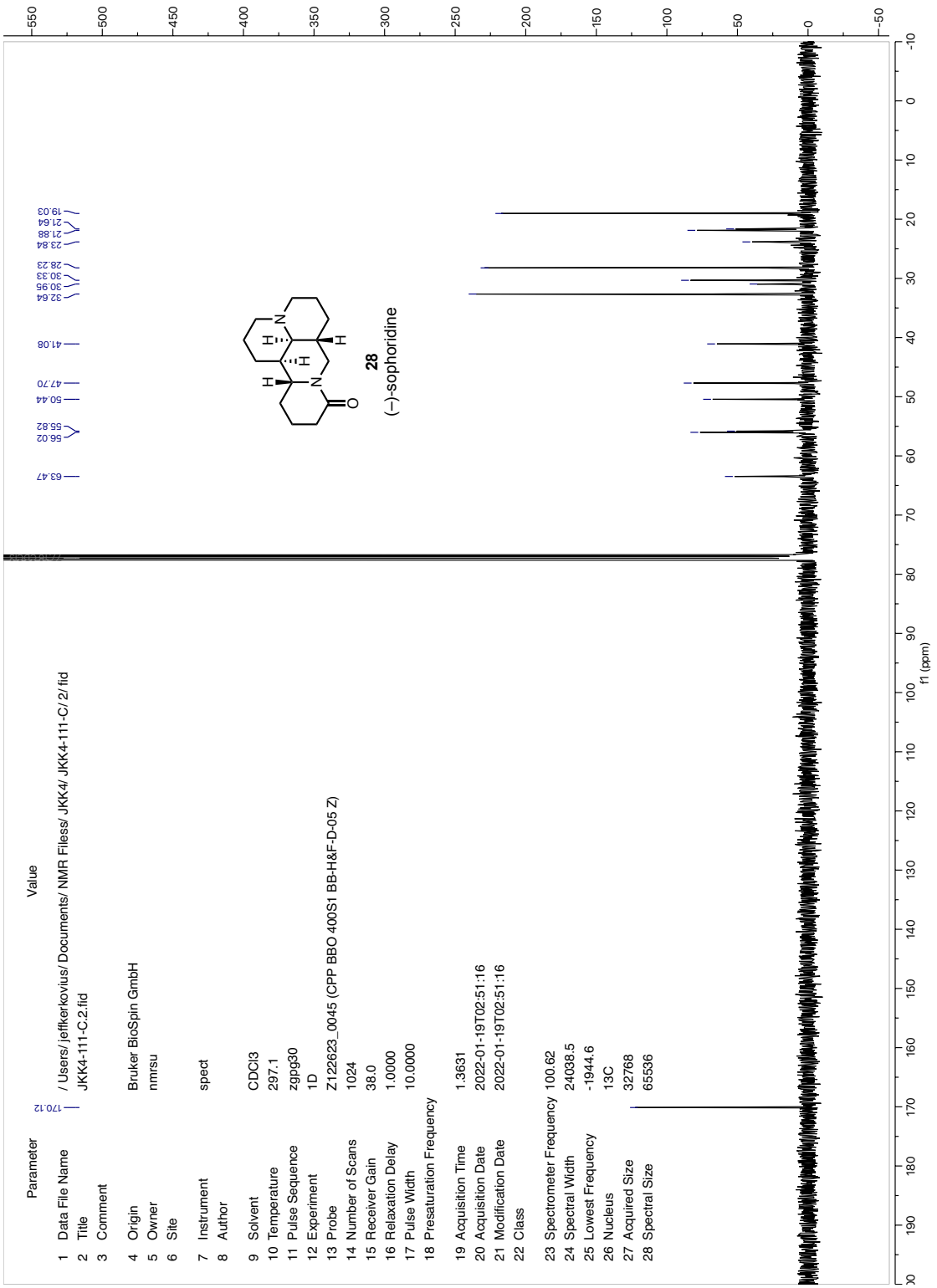

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-129-B_20220127_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 22
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2022-01-27T22:00:47
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1197.5
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
27
(+)-allomatrine
f1 (ppm)

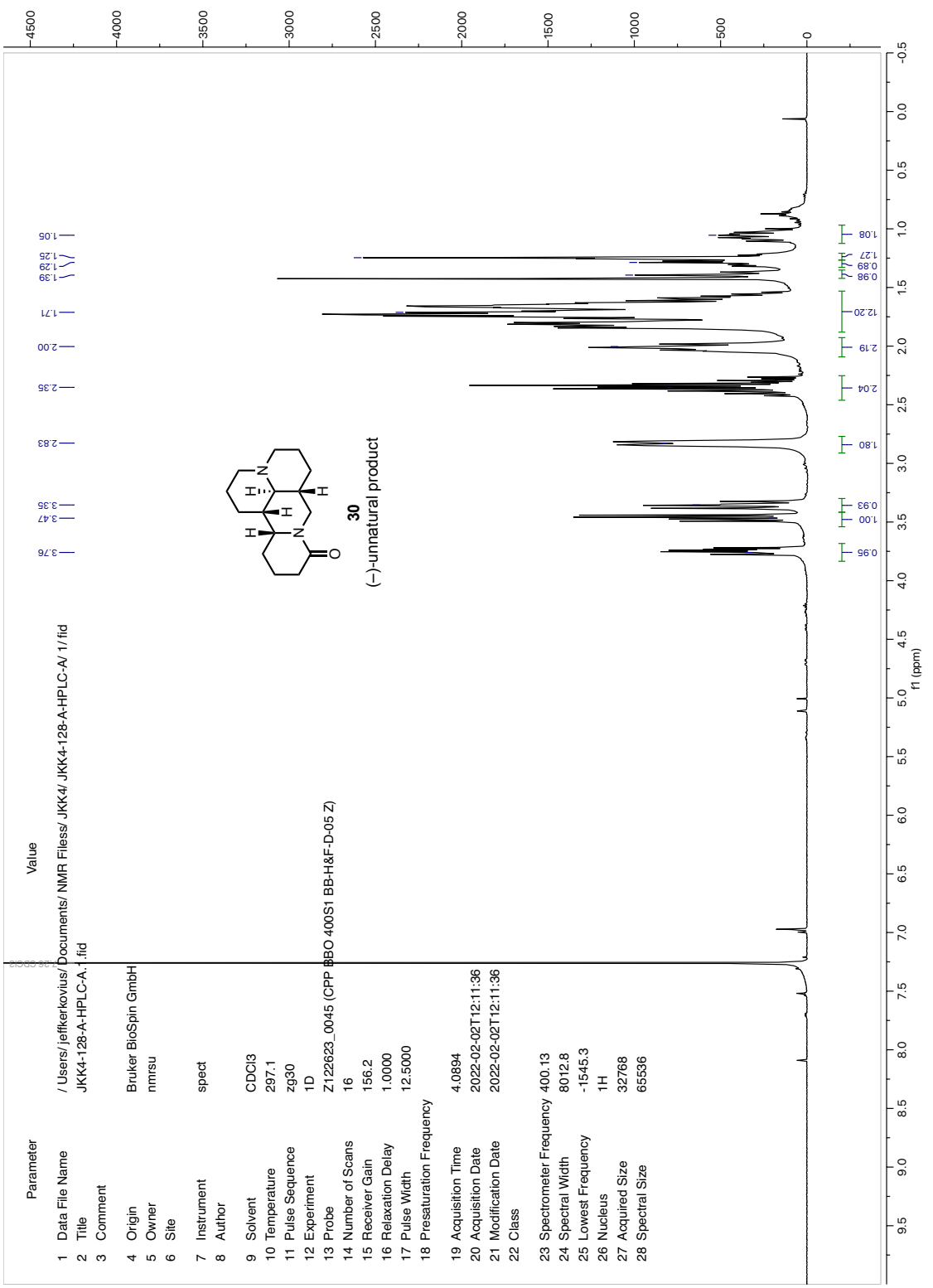

Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-129-B/ CARBON01.fid/ fid
2 Title CARBON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 128
10 Receiver Gain 30
11 Relaxation Delay 1.0000
12 Pulse Width 4.8375
13 Acquisition Time 1.0420
14 Acquisition Date 2022-01-27T22:08:29
15 Spectrometer Frequency 125.63
16 Spectral Width 31446.5
17 Lowest Frequency -1889.5
18 Nucleus 13C
19 Acquired Size 32768
20 Spectral Size 65536
169.29
77.16 CDCl3
70.81
60.27
56.57
55.95
46.27
46.24
39.08
32.89
28.39
27.55
26.87
24.77
24.75
19.41
27
(+)-allomatrine
f1 (ppm)

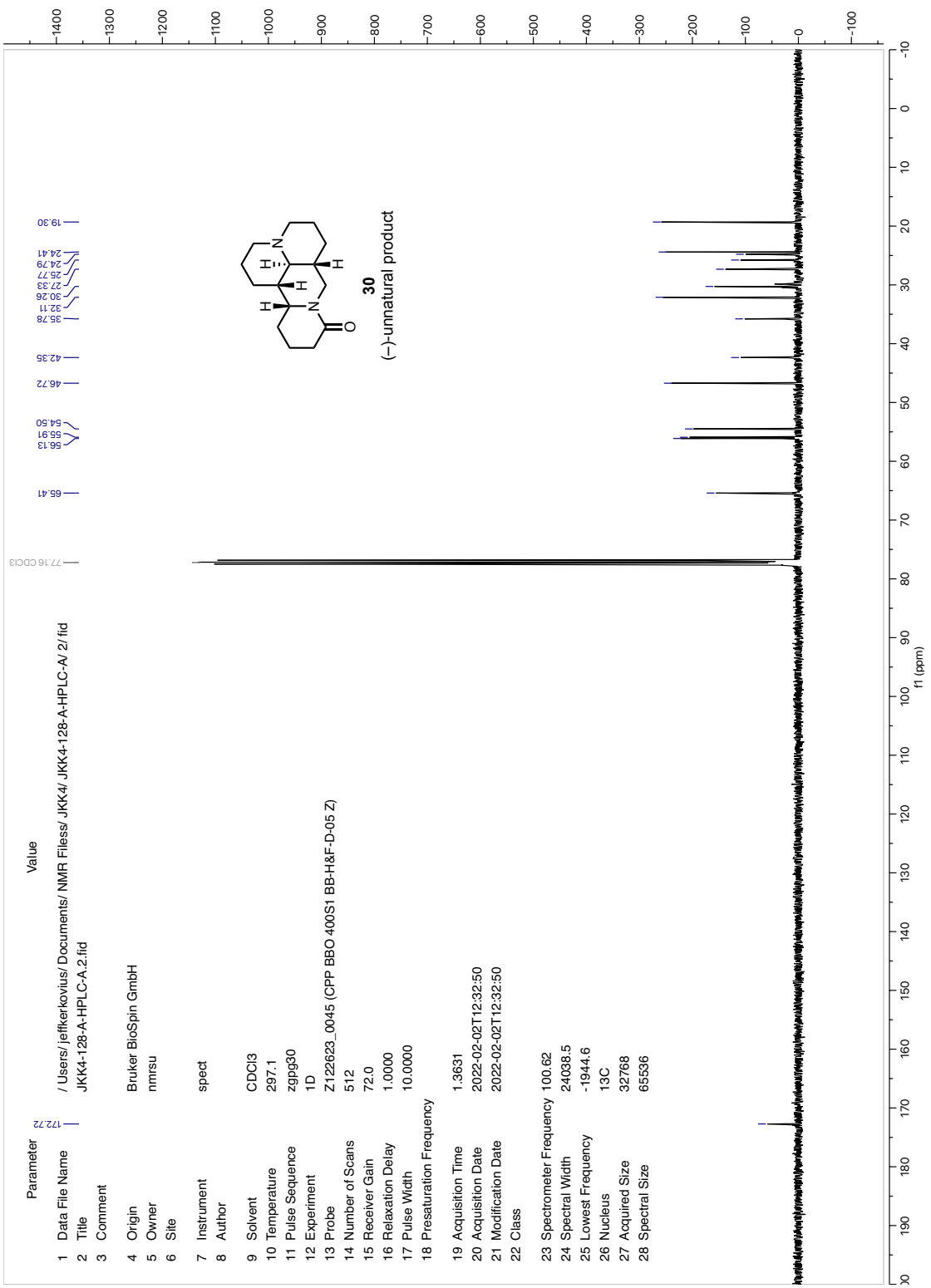

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-111-D2_20220118_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 28
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2022-01-18T18:29:39
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1197.4
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
29
(+)-isosophoridine
f1 (ppm)

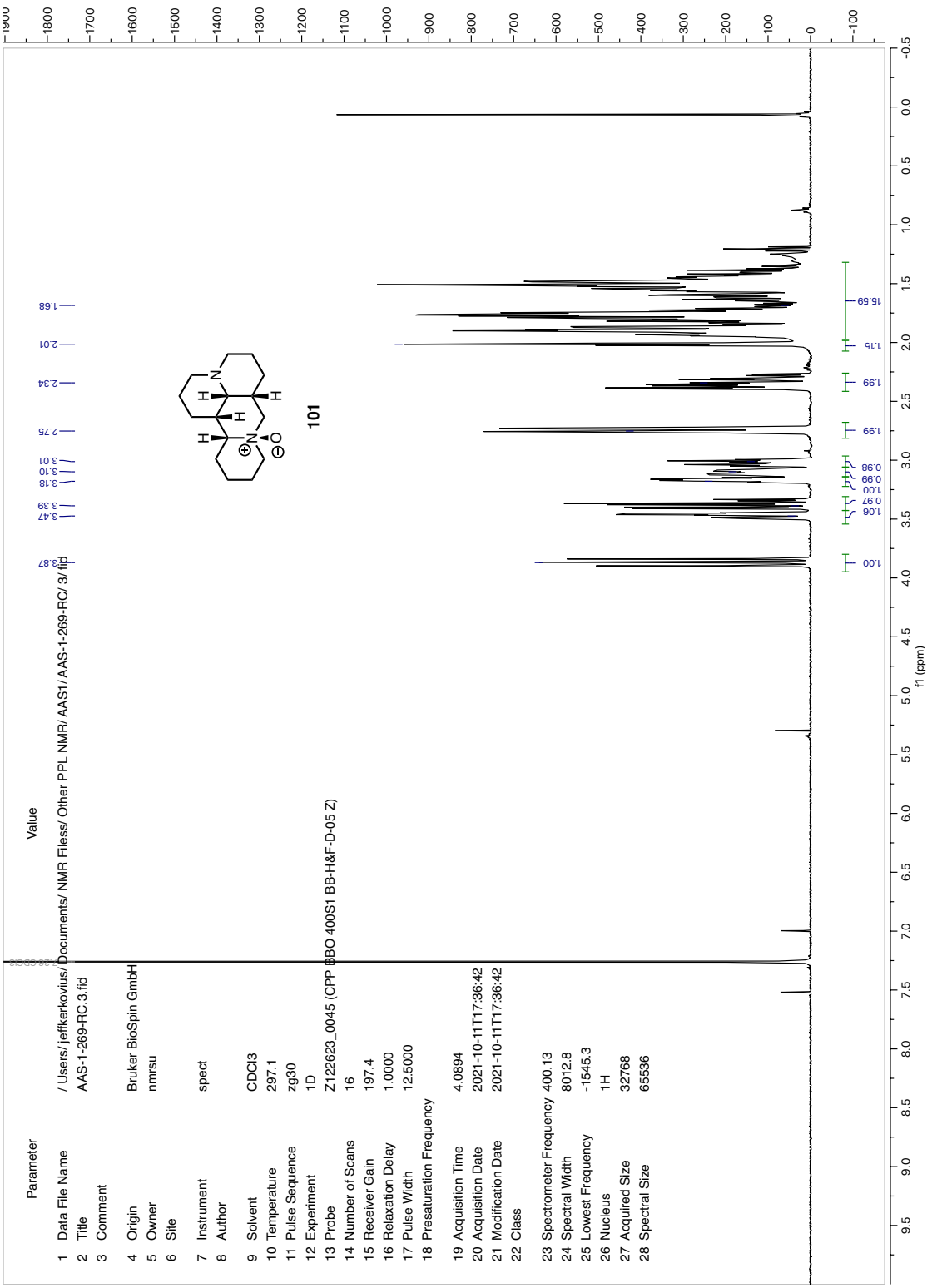

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-111-D/ 2/ fid
2 Title JKK4-111-D.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 43.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2022-01-19T03:38:02
21 Modification Date 2022-01-19T03:38:02
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1945.9
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
169.87
77.16 CDCl3
62.35
60.15
54.23
46.87
45.18
36.13
33.39
33.02
28.14
26.74
26.00
23.05
19.34
19.17
29
(+)-isosophoridine
f1 (ppm)

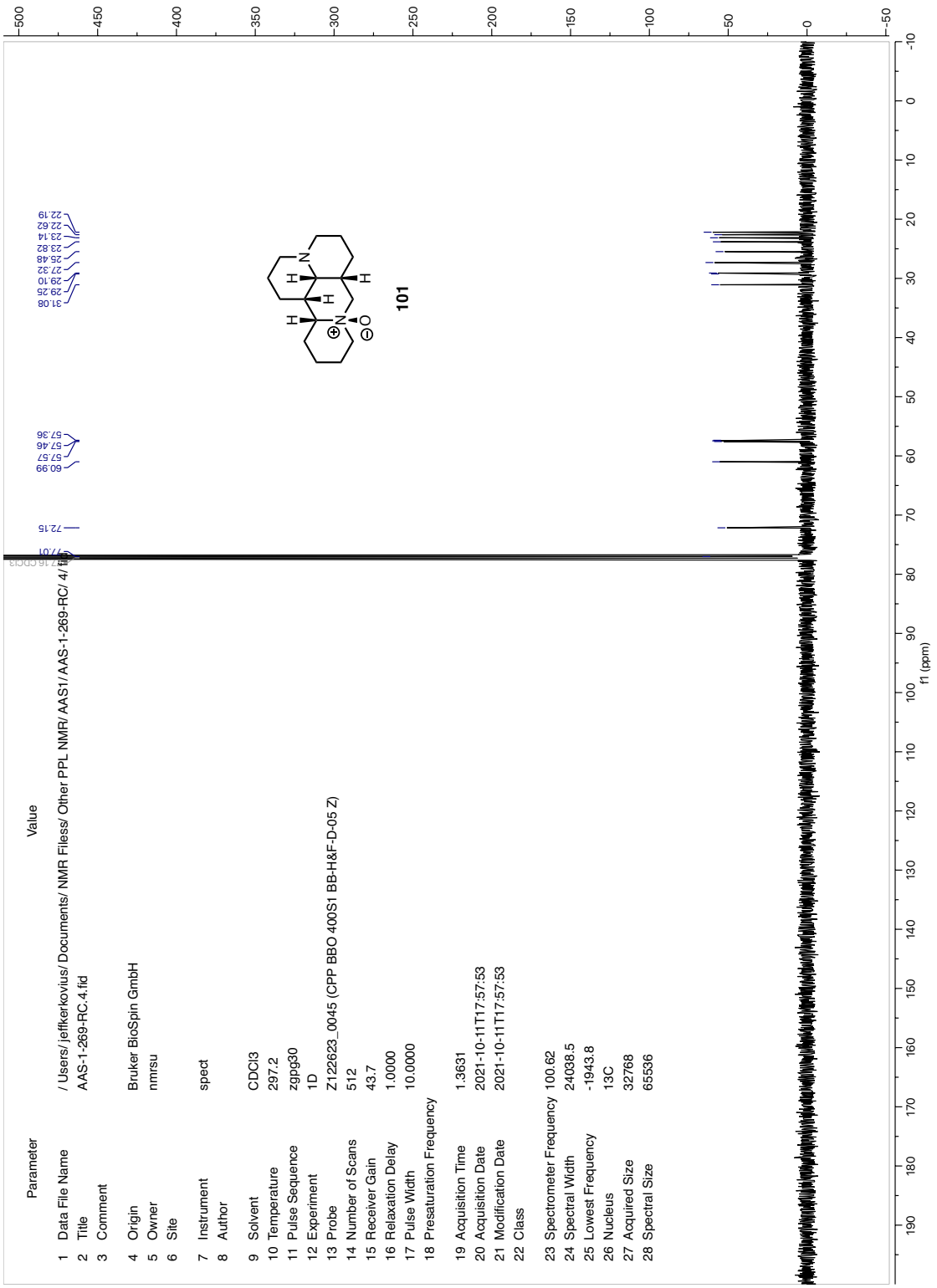

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-111-C/ 1/ fid
2 Title JKK4-111-C.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 16
15 Receiver Gain 197.4
16 Relaxation Delay 1.0000
17 Pulse Width 12.5000
18 Presaturation Frequency
19 Acquisition Time 4.0894
20 Acquisition Date 2022-01-19T02:09:24
21 Modification Date 2022-01-19T02:09:24
22 Class
23 Spectrometer Frequency 400.13
24 Spectral Width 8012.8
25 Lowest Frequency -1545.2
26 Nucleus 1H
27 Acquired Size 32768
28 Spectral Size 65536
28
(−)-sophoridine
f1 (ppm)

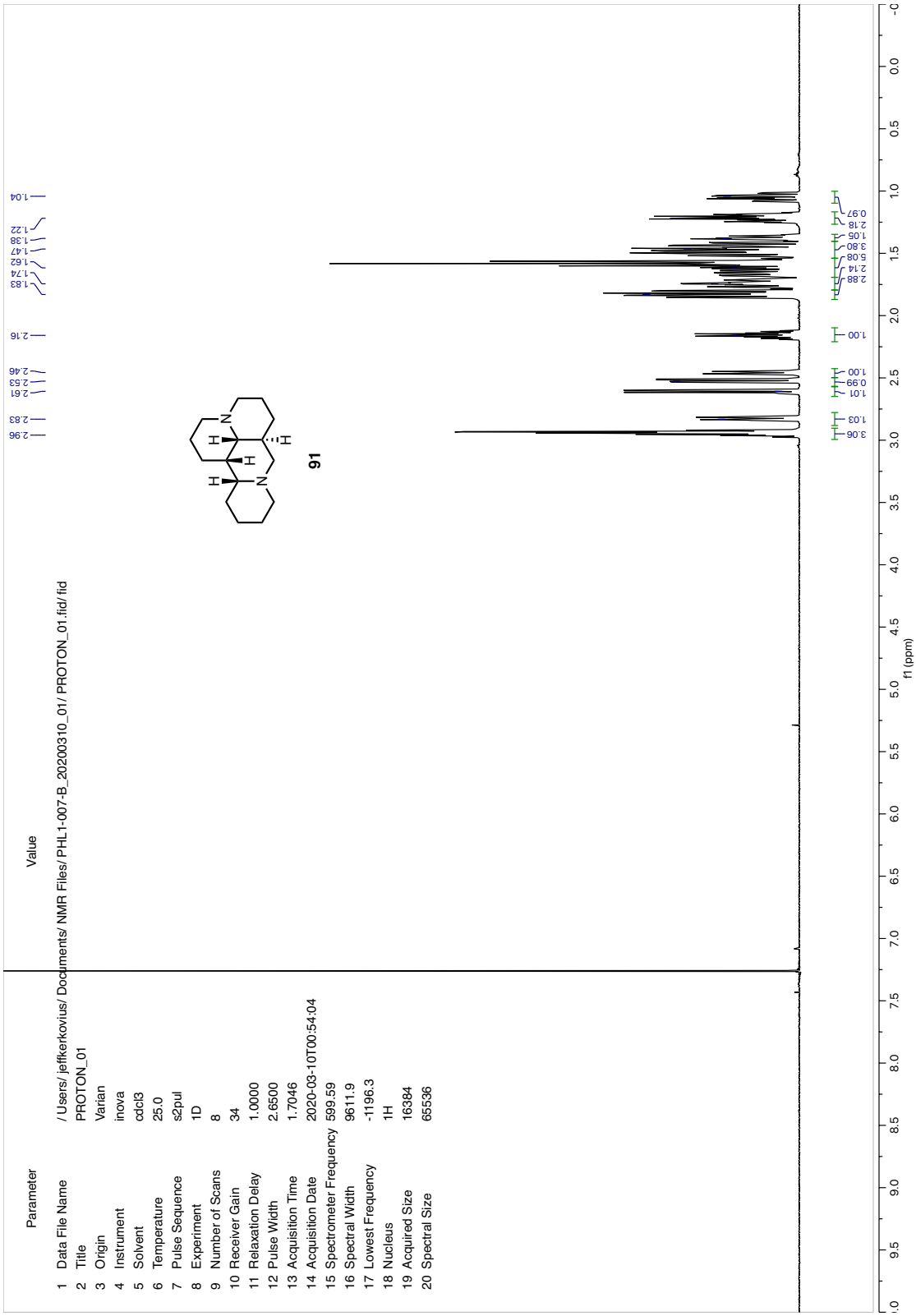

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Filess/ JKK4/ JKK4-111-C/ 2/ fid
2 Title JKK4-111-C.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 38.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2022-01-19T02:51:16
21 Modification Date 2022-01-19T02:51:16
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1944.6
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
170.12
63.47
56.02
55.82
50.44
47.70
41.08
32.64
30.95
30.33
28.23
23.84
21.88
21.64
19.03
28
(−)-sophoridine
f1 (ppm)

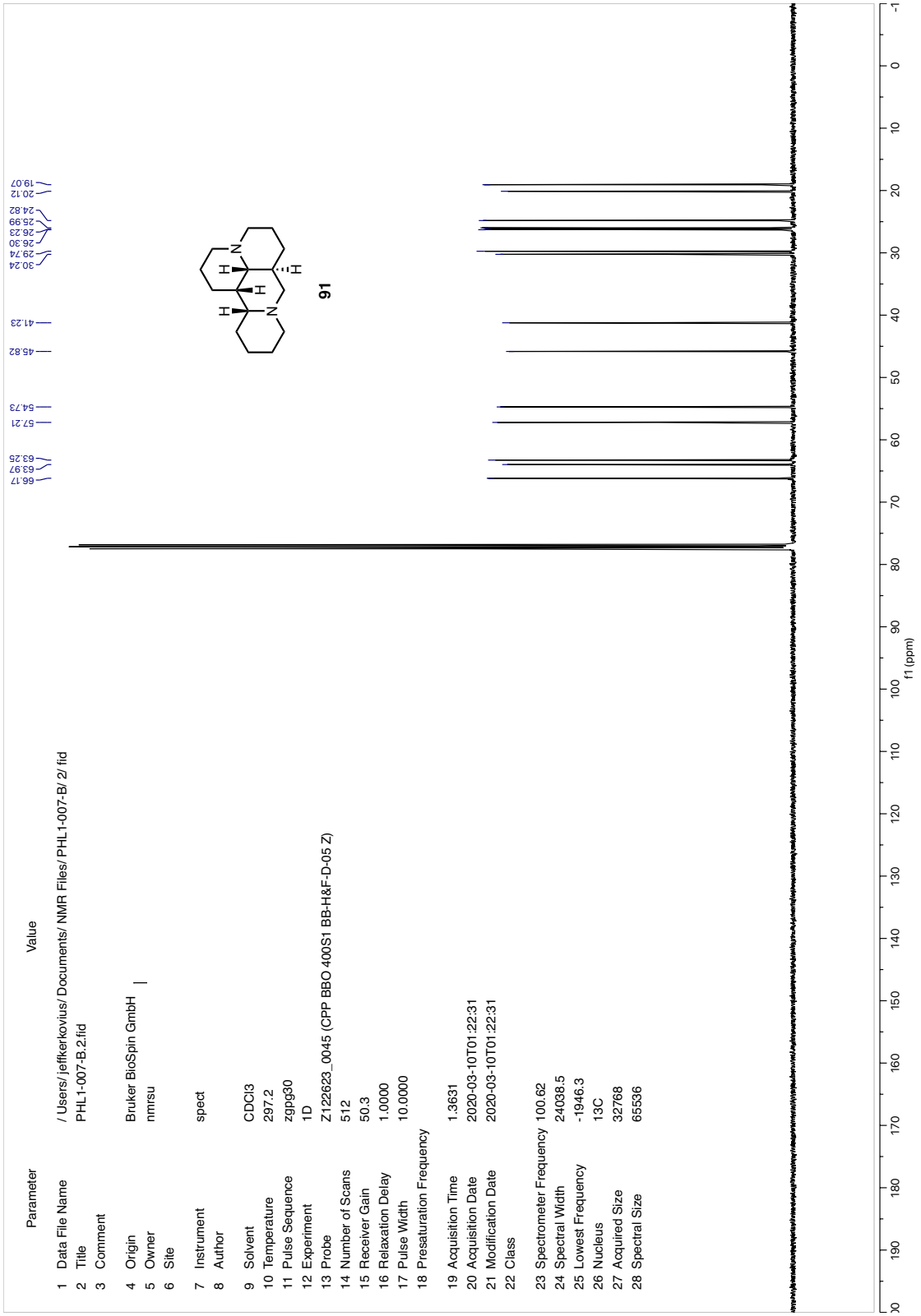

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-128-A-HPLC-A/ 1/ fid
2 Title JKK4-128-A-HPLC-A.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 16
15 Receiver Gain 156.2
16 Relaxation Delay 1.0000
17 Pulse Width 12.5000
18 Presaturation Frequency
19 Acquisition Time 4.0894
20 Acquisition Date 2022-02-02T12:11:36
21 Modification Date 2022-02-02T12:11:36
22 Class
23 Spectrometer Frequency 400.13
24 Spectral Width 8012.8
25 Lowest Frequency -1545.3
26 Nucleus 1H
27 Acquired Size 32768
28 Spectral Size 65536
30
(−)-unnatural product
f1 (ppm)

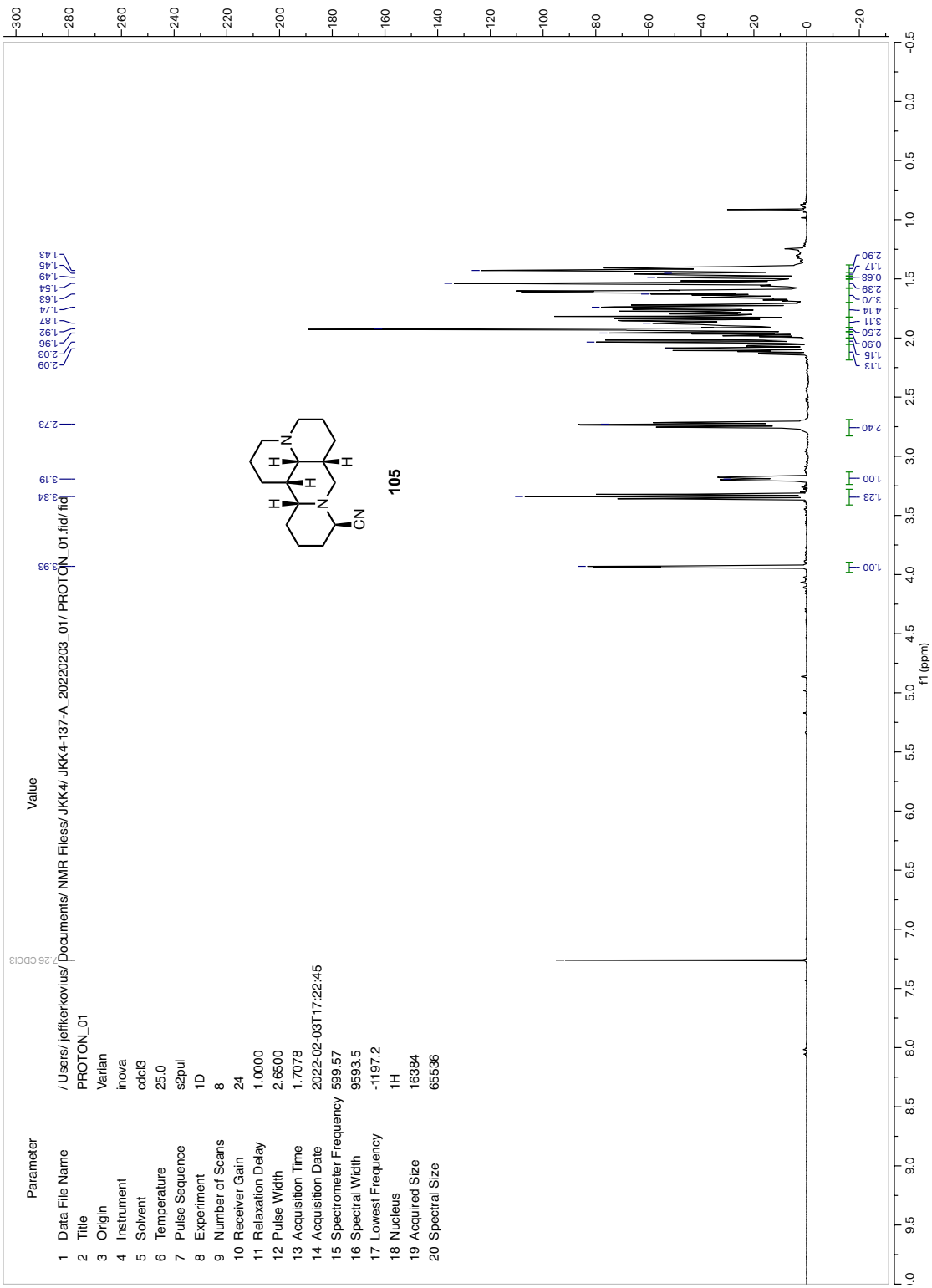

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-128-A-HPLC-A/ 2/ fid
2 Title JKK4-128-A-HPLC-A.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2022-02-02T12:32:50
21 Modification Date 2022-02-02T12:32:50
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1944.6
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
172.72
77.16 CDCl3
65.41
56.13
55.91
54.50
46.72
42.35
35.78
32.11
30.26
27.33
25.77
24.79
24.41
19.30
30
(−)-unnatural product
f1 (ppm)

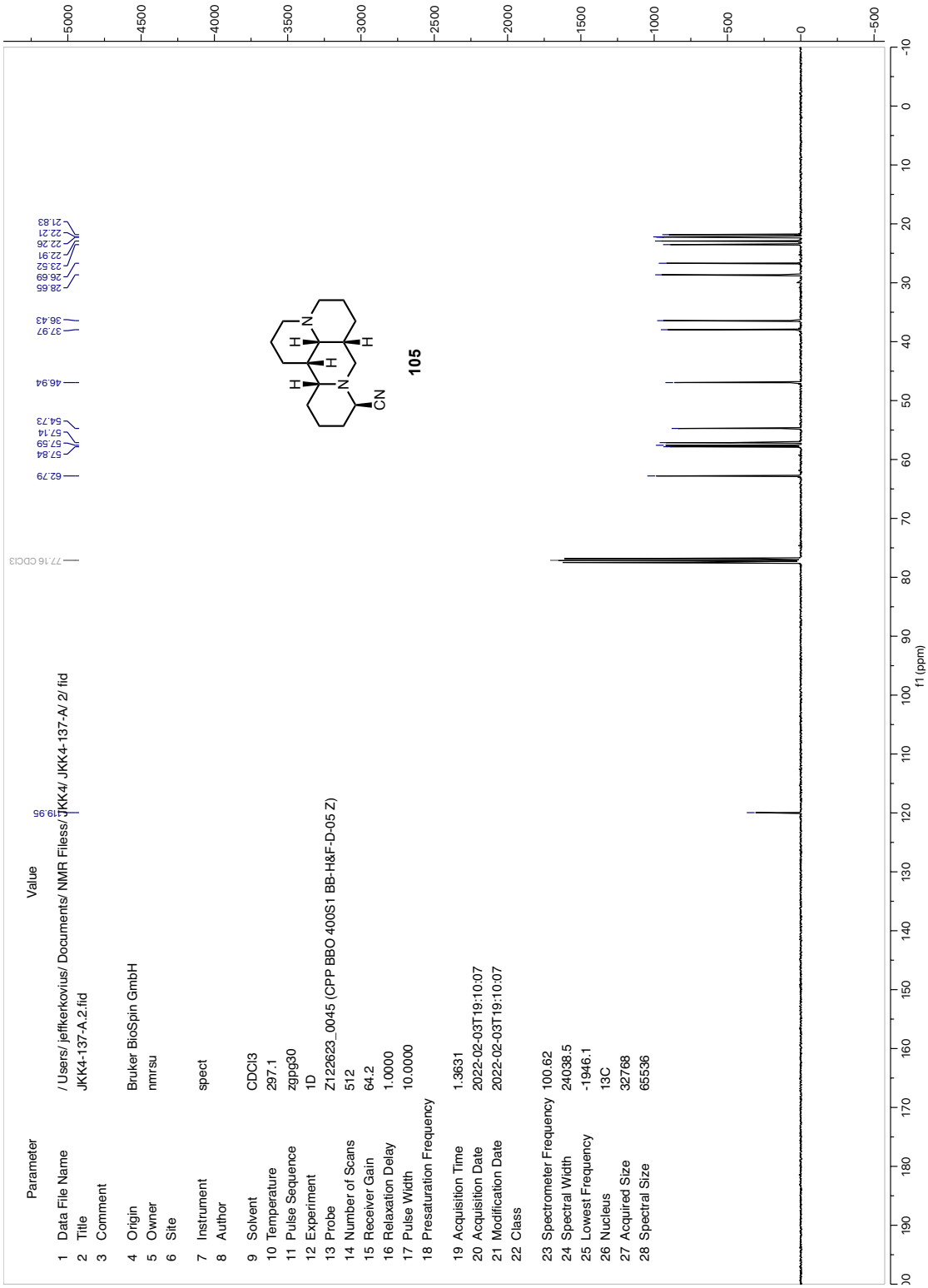

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Filess/ Other PPL NMR/ AAS1/ AAS-1-269-RC/ 3/ fid
2 Title AAS-1-269-RC.3.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 16
15 Receiver Gain 197.4
16 Relaxation Delay 1.0000
17 Pulse Width 12.5000
18 Presaturation Frequency
19 Acquisition Time 4.0894
20 Acquisition Date 2021-10-11T17:36:42
21 Modification Date 2021-10-11T17:36:42
22 Class
23 Spectrometer Frequency 400.13
24 Spectral Width 8012.8
25 Lowest Frequency -1545.3
26 Nucleus 1H
27 Acquired Size 32768
28 Spectral Size 65536
101
1.68
2.01
2.34
2.75
3.01
3.10
3.18
3.39
3.47
3.87
15.59
1.15
1.99
1.99
0.98
0.99
1.00
0.97
1.06
1.00
f1 (ppm)

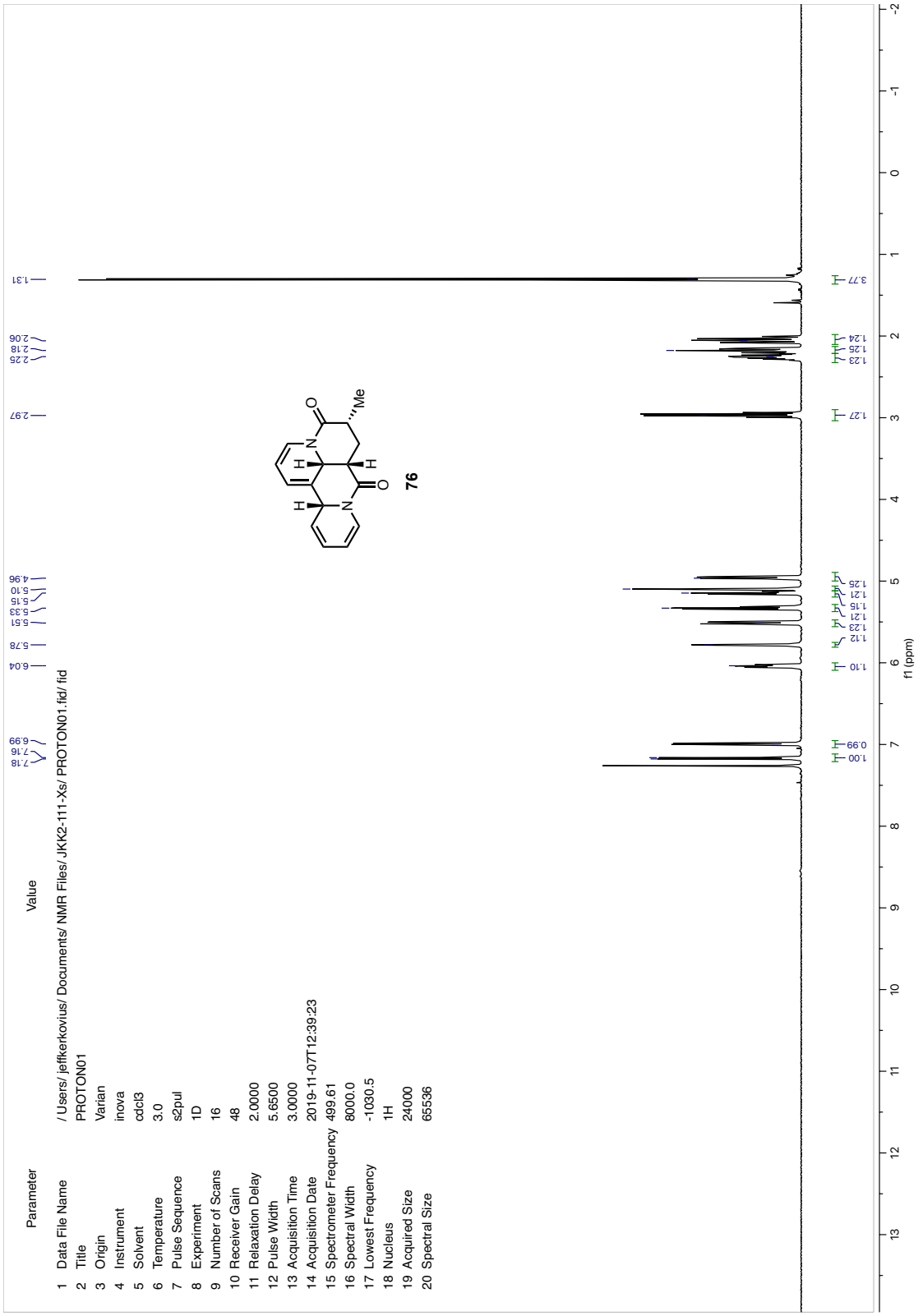

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ AAS1/ AAS-1-269-RC/ 4/
2 Title AAS-1-269-RC.4.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 43.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-11T17:57:53
21 Modification Date 2021-10-11T17:57:53
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1943.8
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
77.01
72.15
60.99
57.57
57.46
57.36
31.08
29.25
29.10
27.32
25.48
23.82
23.14
22.62
22.19
101
f1 (ppm)

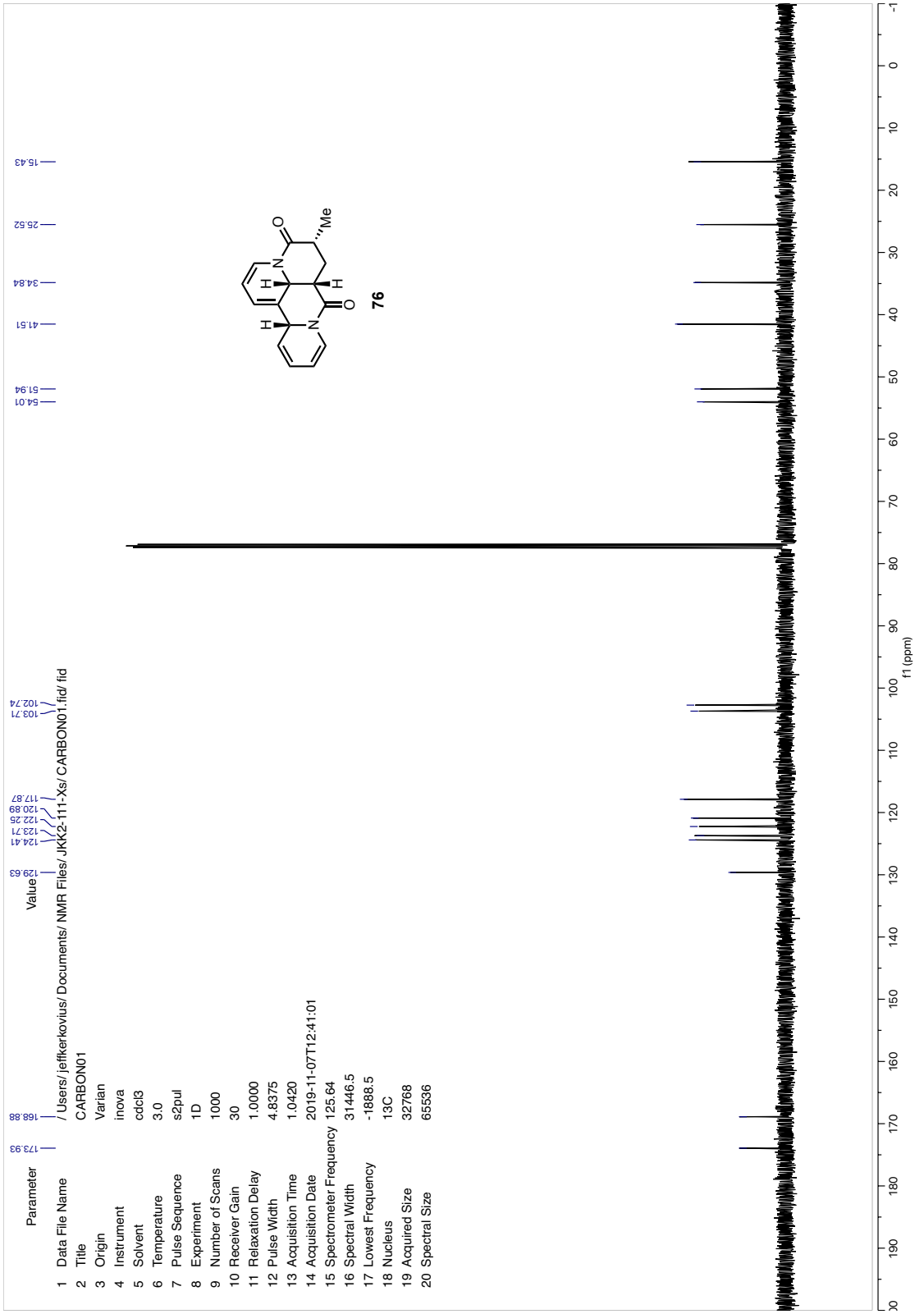

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ PHL1-007-B_20200310_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 34
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7046
14 Acquisition Date 2020-03-10T00:54:04
15 Spectrometer Frequency 599.59
16 Spectral Width 9611.9
17 Lowest Frequency -1196.3
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
91
f1 (ppm)

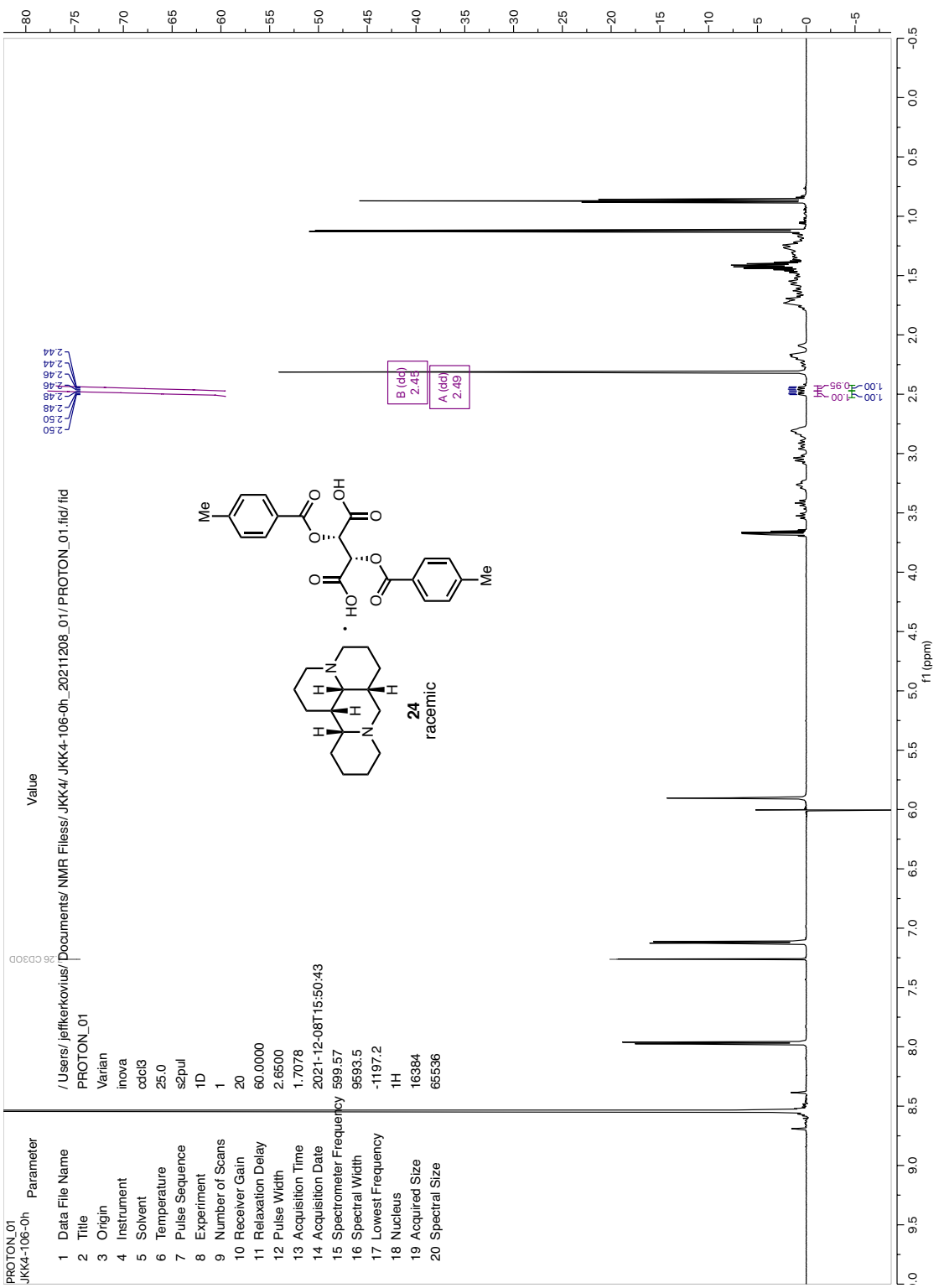

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ PHL1-007-B/ 2/ fid
2 Title PHL1-007-B.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 50.3
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2020-03-10T01:22:31
21 Modification Date 2020-03-10T01:22:31
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1946.3
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
19.07
20.12
24.82
25.99
26.23
26.30
29.74
30.24
41.23
45.82
54.73
57.21
63.25
63.97
66.17
91
f1 (ppm)

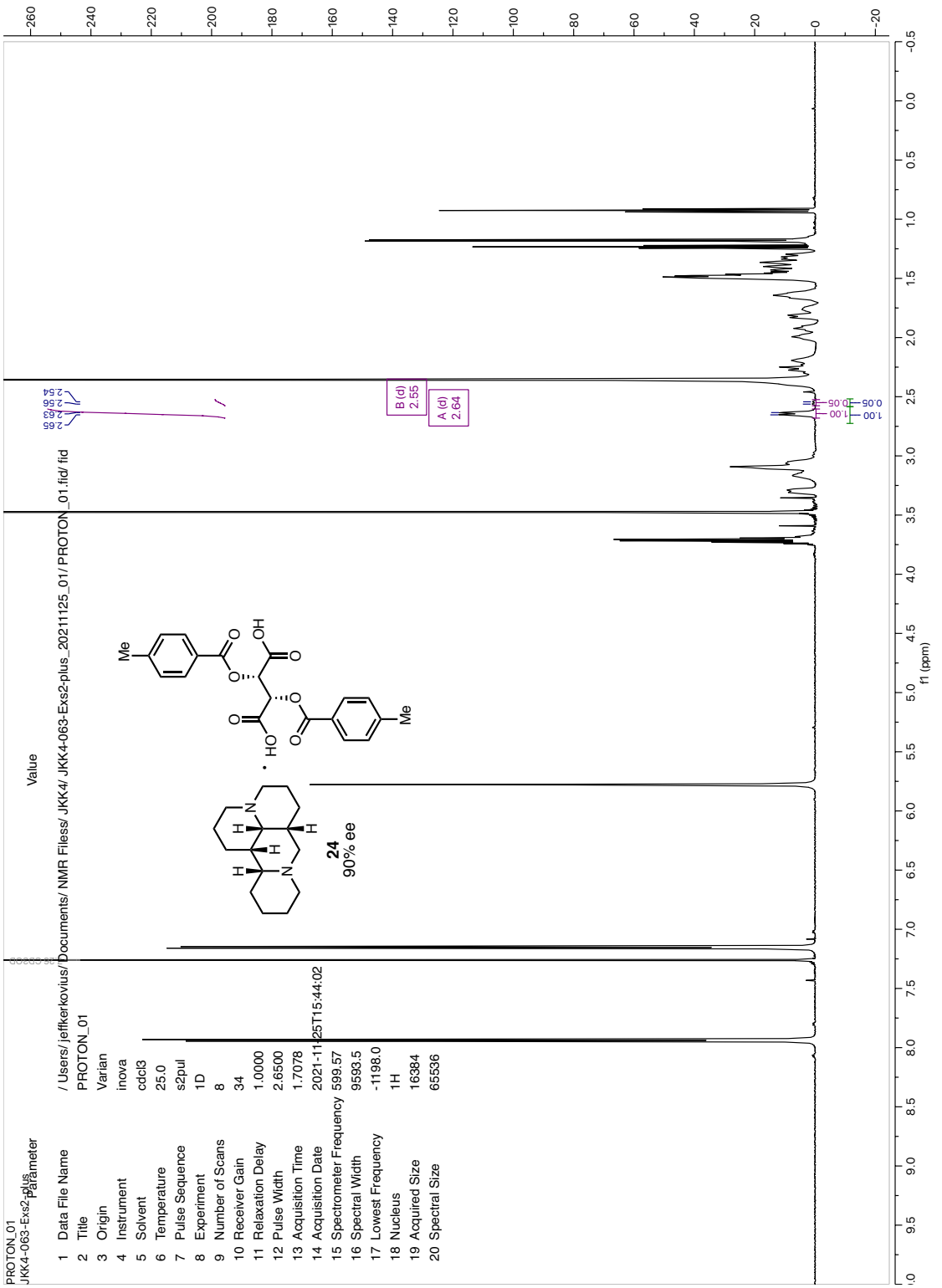

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-137-A_20220203_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 24
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2022-02-03T17:22:45
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1197.2
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
105
f1 (ppm)

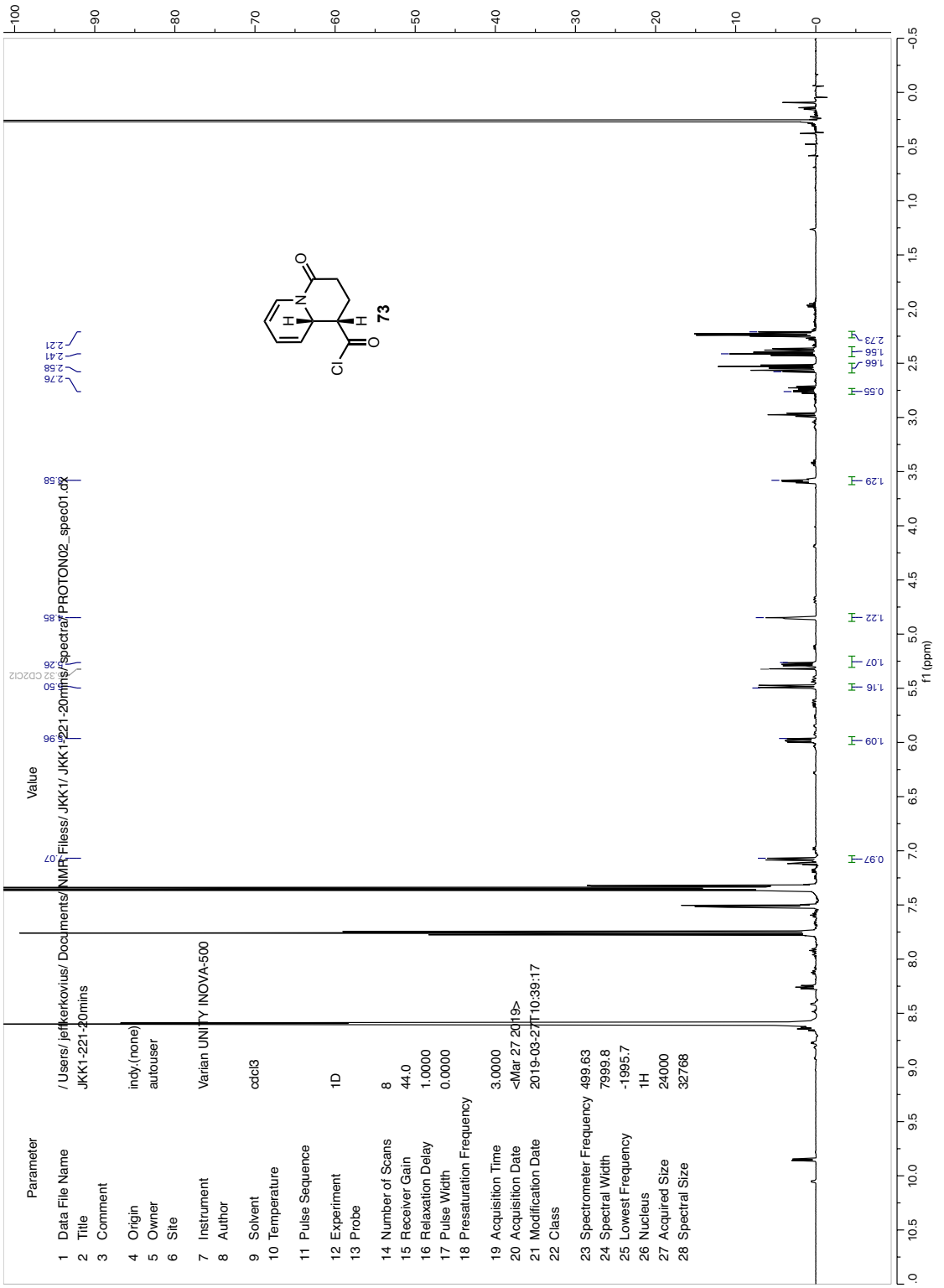

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-137-A/ 2/ fid
2 Title JKK4-137-A.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 64.2
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2022-02-03T19:10:07
21 Modification Date 2022-02-03T19:10:07
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1946.1
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
119.95
77.16 CDCl3
62.79
57.84
57.59
57.14
54.73
46.94
36.43
37.97
28.65
26.69
23.52
22.91
22.26
22.21
21.83
105
f1 (ppm)

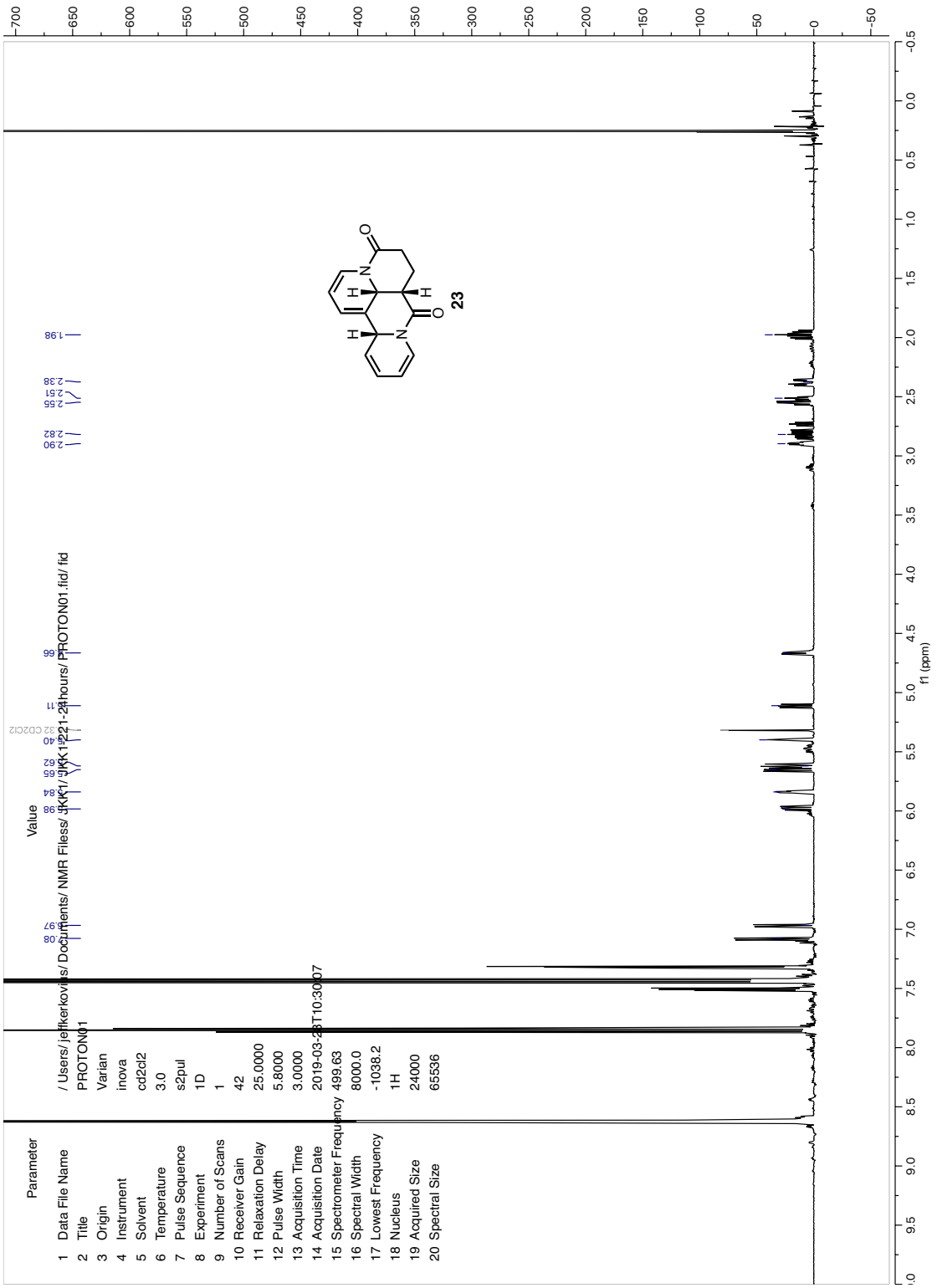

Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2-111-Xs/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 16
10 Receiver Gain 48
11 Relaxation Delay 2.0000
12 Pulse Width 5.6500
13 Acquisition Time 3.0000
14 Acquisition Date 2019-11-07T12:39:23
15 Spectrometer Frequency 499.61
16 Spectral Width 8000.0
17 Lowest Frequency -1030.5
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
7.18
7.16
6.99
6.04
5.78
5.51
5.33
5.15
5.10
4.96
2.97
2.25
2.18
2.06
1.31
Me
O
N
H
H
O
N
H
76
0.99
1.00
1.10
1.12
1.23
1.21
1.16
1.21
1.25
1.27
1.23
1.25
1.24
3.77
f1 (ppm)

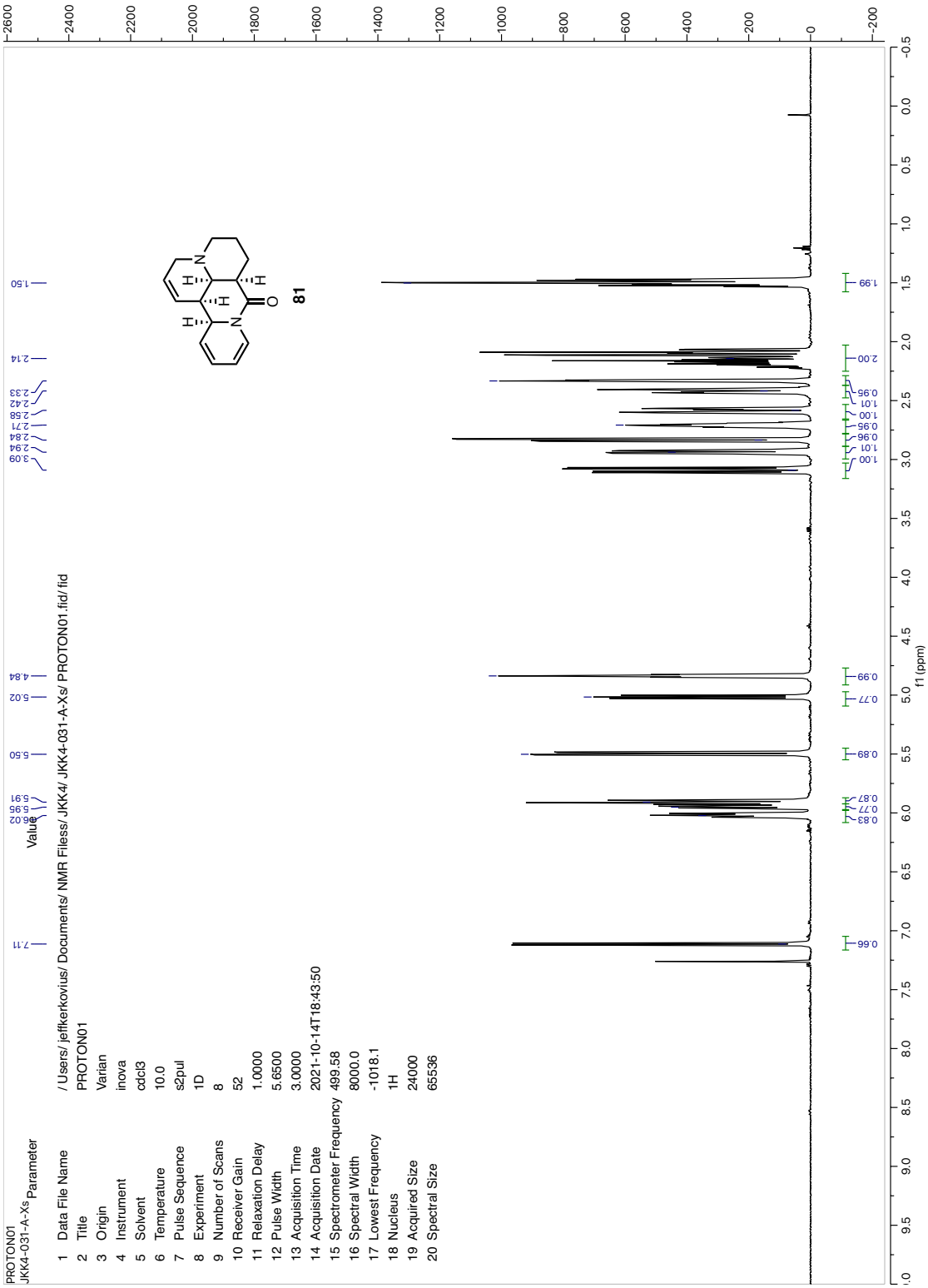

Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2-111-Xs/ CARBON01.fid/ fid
2 Title CARBON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 1000
10 Receiver Gain 30
11 Relaxation Delay 1.0000
12 Pulse Width 4.8375
13 Acquisition Time 1.0420
14 Acquisition Date 2019-11-07T12:41:01
15 Spectrometer Frequency 125.64
16 Spectral Width 31446.5
17 Lowest Frequency -1888.5
18 Nucleus 13C
19 Acquired Size 32768
20 Spectral Size 65536
173.93
168.88
129.63
124.41
123.71
122.25
120.89
117.87
103.71
102.74
54.01
51.94
41.51
34.84
25.52
15.43
Me
76
f1 (ppm)

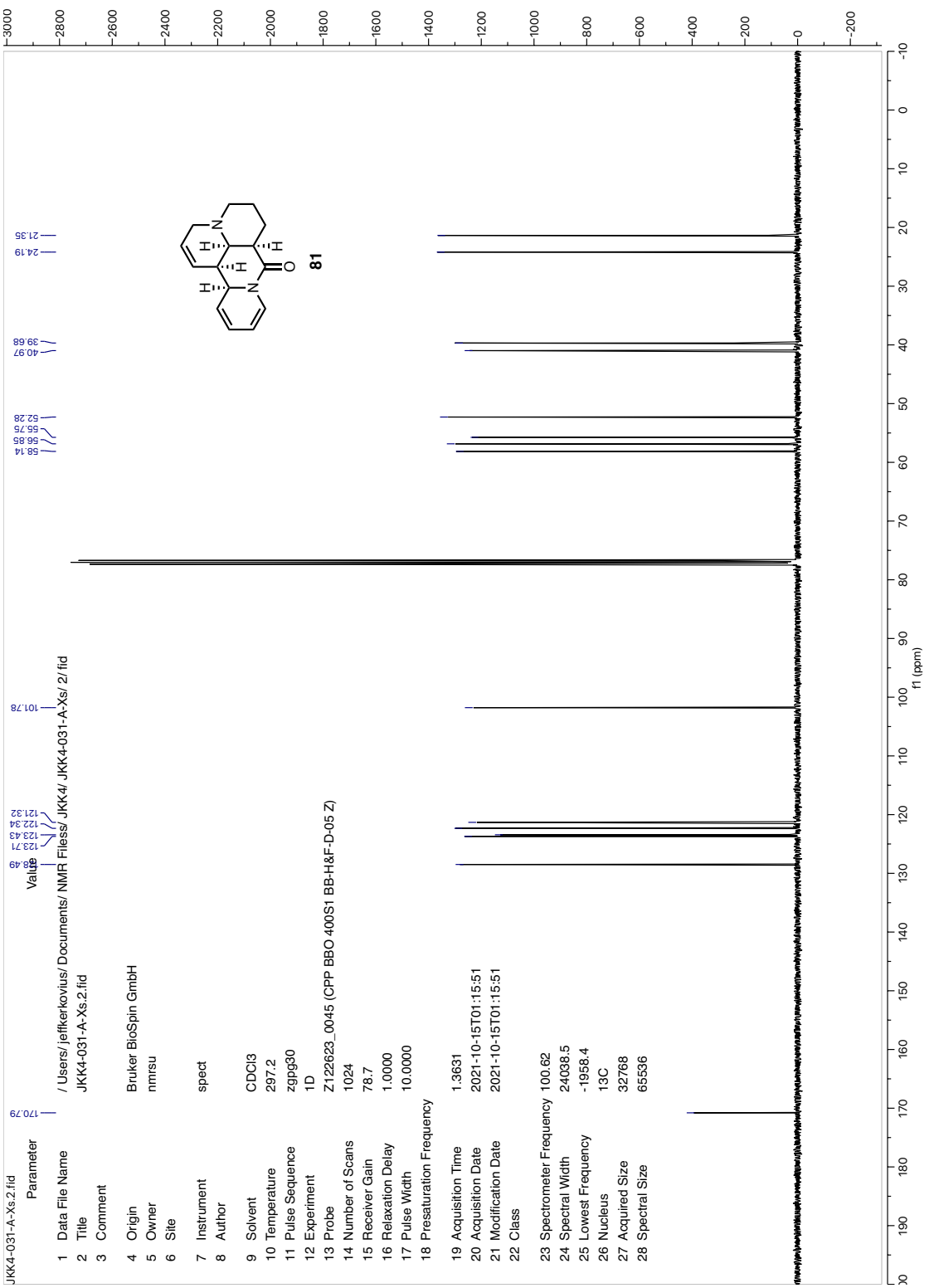

PROTON_01
JKK4-106-0h
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-106-0h_20211208_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 1
10 Receiver Gain 20
11 Relaxation Delay 60.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2021-12-08T15:50:43
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1197.2
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
26 CD3OD
B (dd) 2.45
A (dd) 2.49
1.00
1.00
0.95
24
racemic
f1 (ppm)

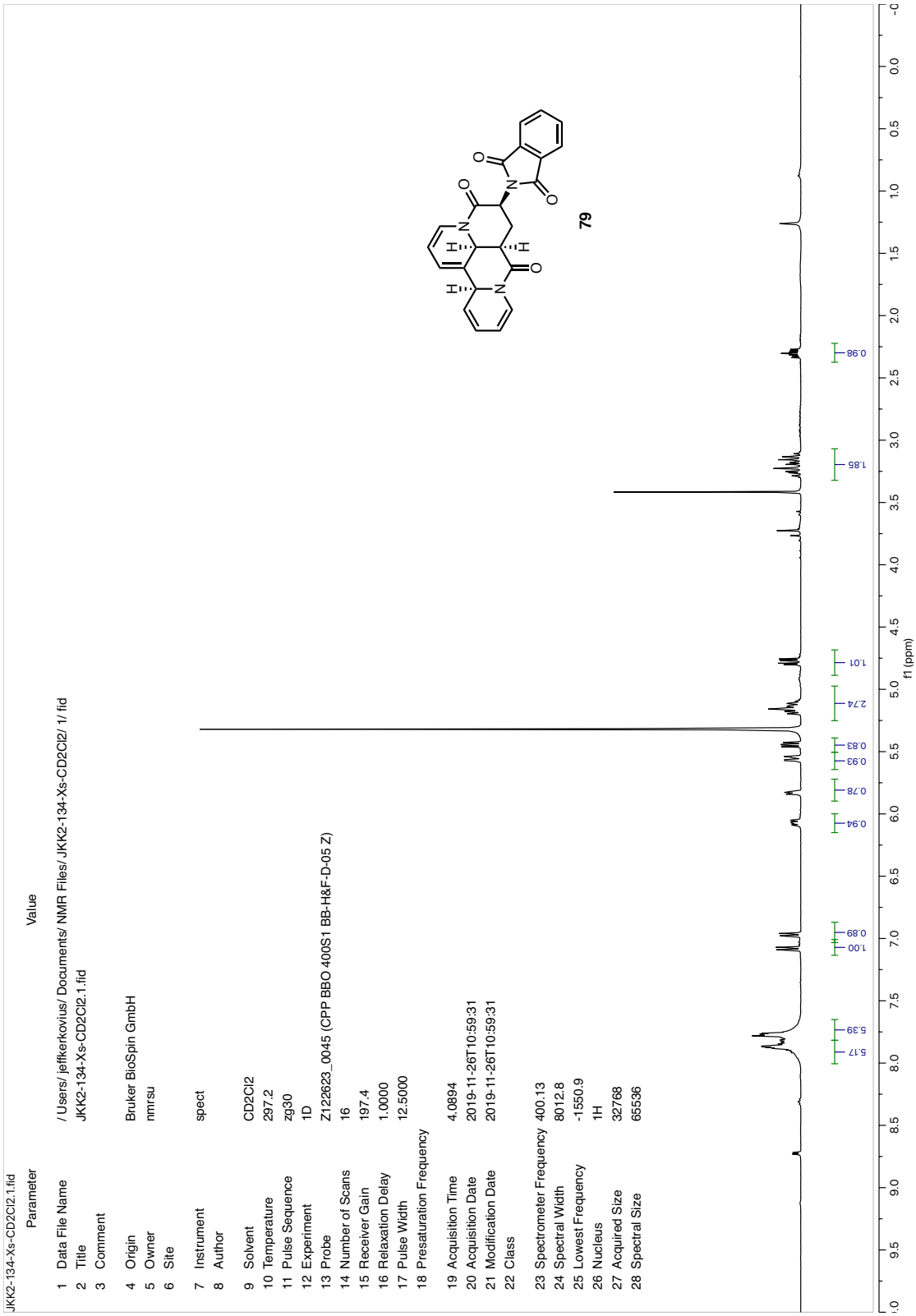

PROTON_01
JKK4-063-Exs2-plus
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-063-Exs2-plus_20211125_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 34
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2021-11-25T15:44:02
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1198.0
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
Me
OH
HO
Me
24
90% ee
B (d)
2.55
A (d)
2.64
2.65
2.63
2.56
2.54
1.00
0.05
f1 (ppm)

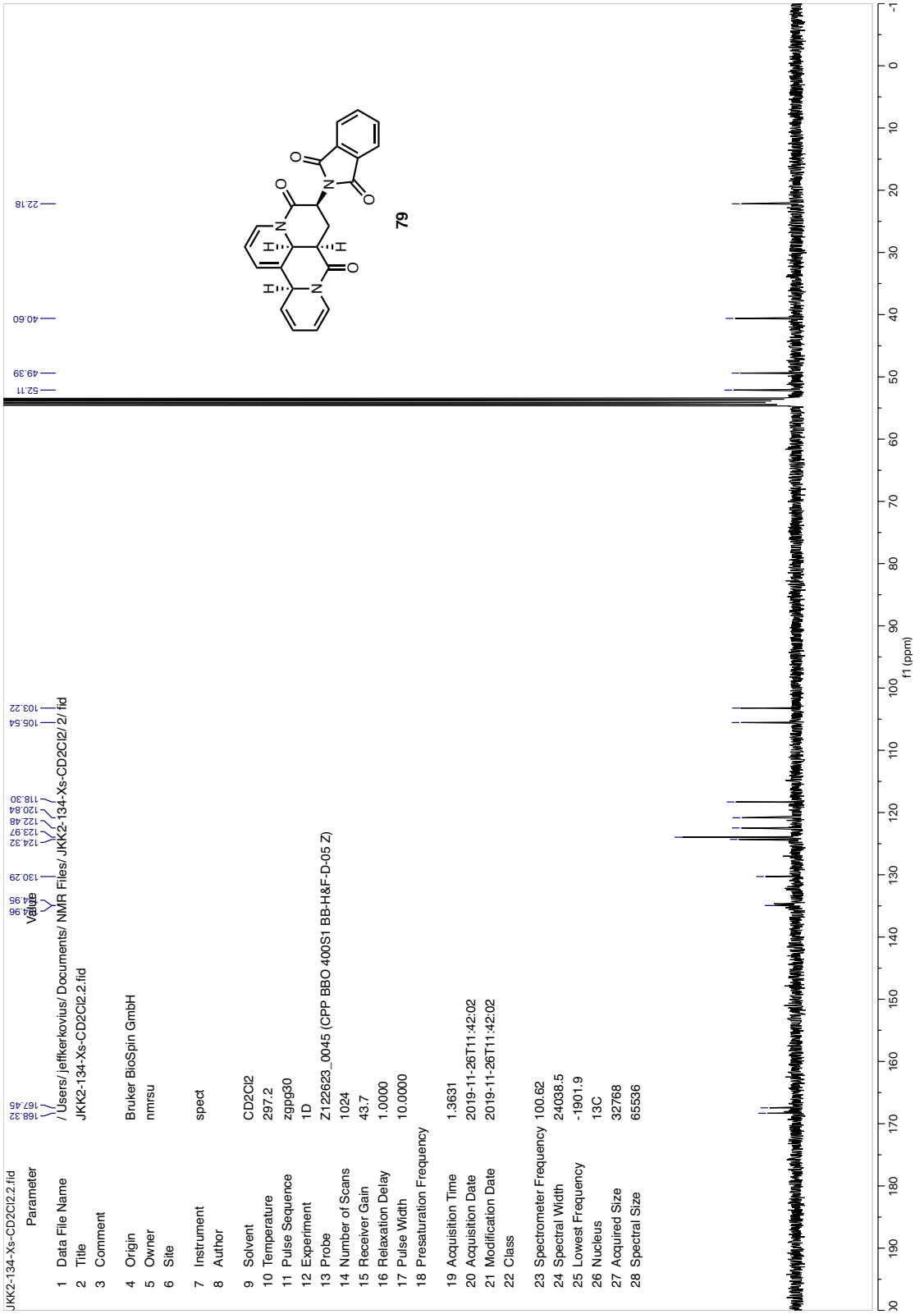

Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK1/ JKK1-221-20mins/ spectra/ PROTON02_spec01.dx
2 Title JKK1-221-20mins
3 Comment
4 Origin indy (none)
5 Owner autouser
6 Site
7 Instrument Varian UNITY INOVA-500
8 Author
9 Solvent cdcl3
10 Temperature
11 Pulse Sequence
12 Experiment 1D
13 Probe
14 Number of Scans 8
15 Receiver Gain 44.0
16 Relaxation Delay 1.0000
17 Pulse Width 0.0000
18 Presaturation Frequency
19 Acquisition Time 3.0000
20 Acquisition Date <Mar 27 2019>
21 Modification Date 2019-03-27T10:39:17
22 Class
23 Spectrometer Frequency 499.63
24 Spectral Width 7999.8
25 Lowest Frequency -1995.7
26 Nucleus 1H
27 Acquired Size 24000
28 Spectral Size 32768
2.76
2.58
2.41
2.21
7.58
7.50
7.26
7.07
CDCl3
7.85
7.96
0.97
1.09
1.16
1.07
1.22
1.29
0.55
1.66
1.56
2.73
73
f1 (ppm)

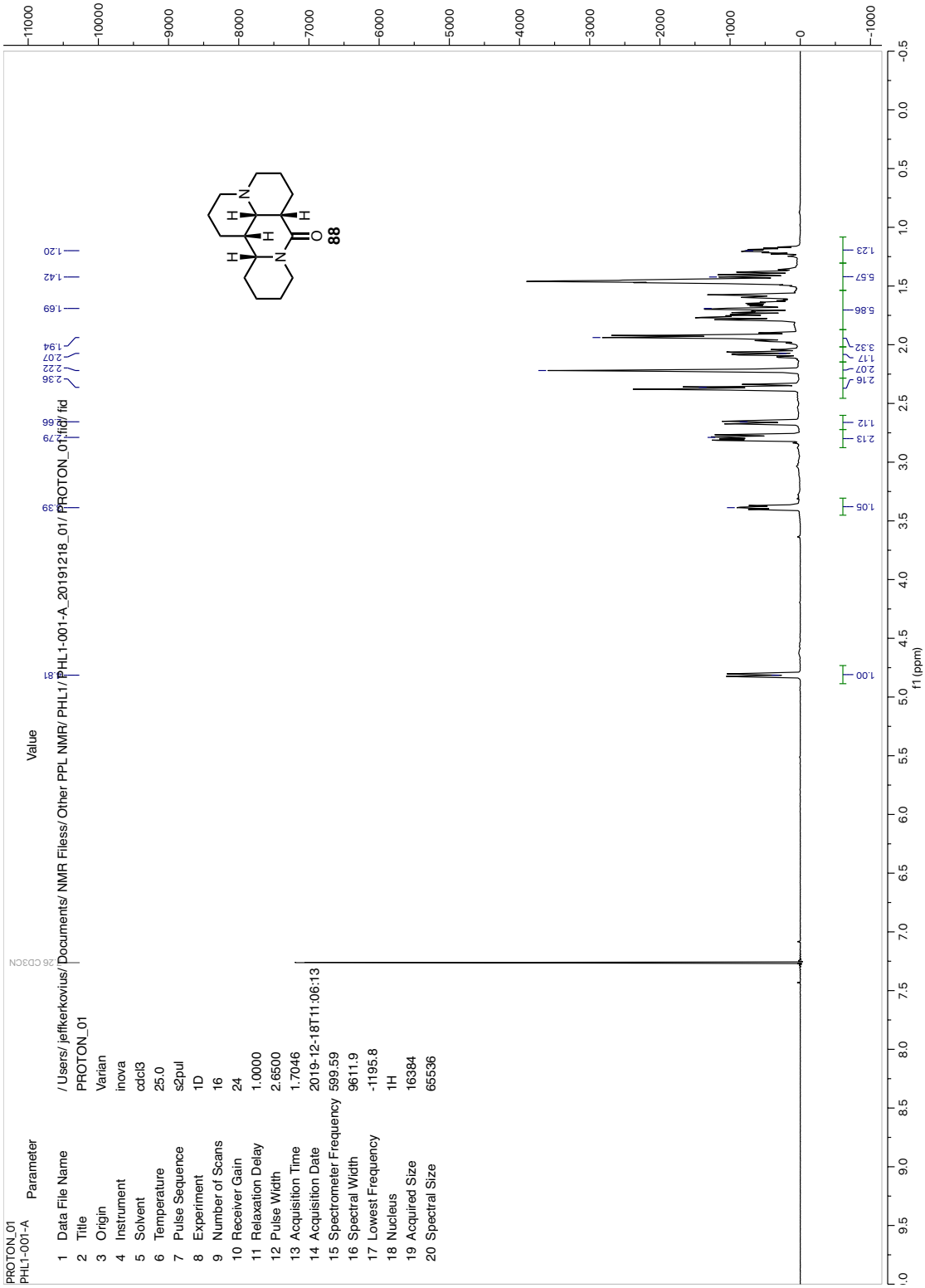

23
f1 (ppm)
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Filess/ JKK1/ JKK1-221-24hours/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cd2cl2
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 1
10 Receiver Gain 42
11 Relaxation Delay 25.0000
12 Pulse Width 5.8000
13 Acquisition Time 3.0000
14 Acquisition Date 2019-03-28T10:30:07
15 Spectrometer Frequency 499.63
16 Spectral Width 8000.0
17 Lowest Frequency -1038.2
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536

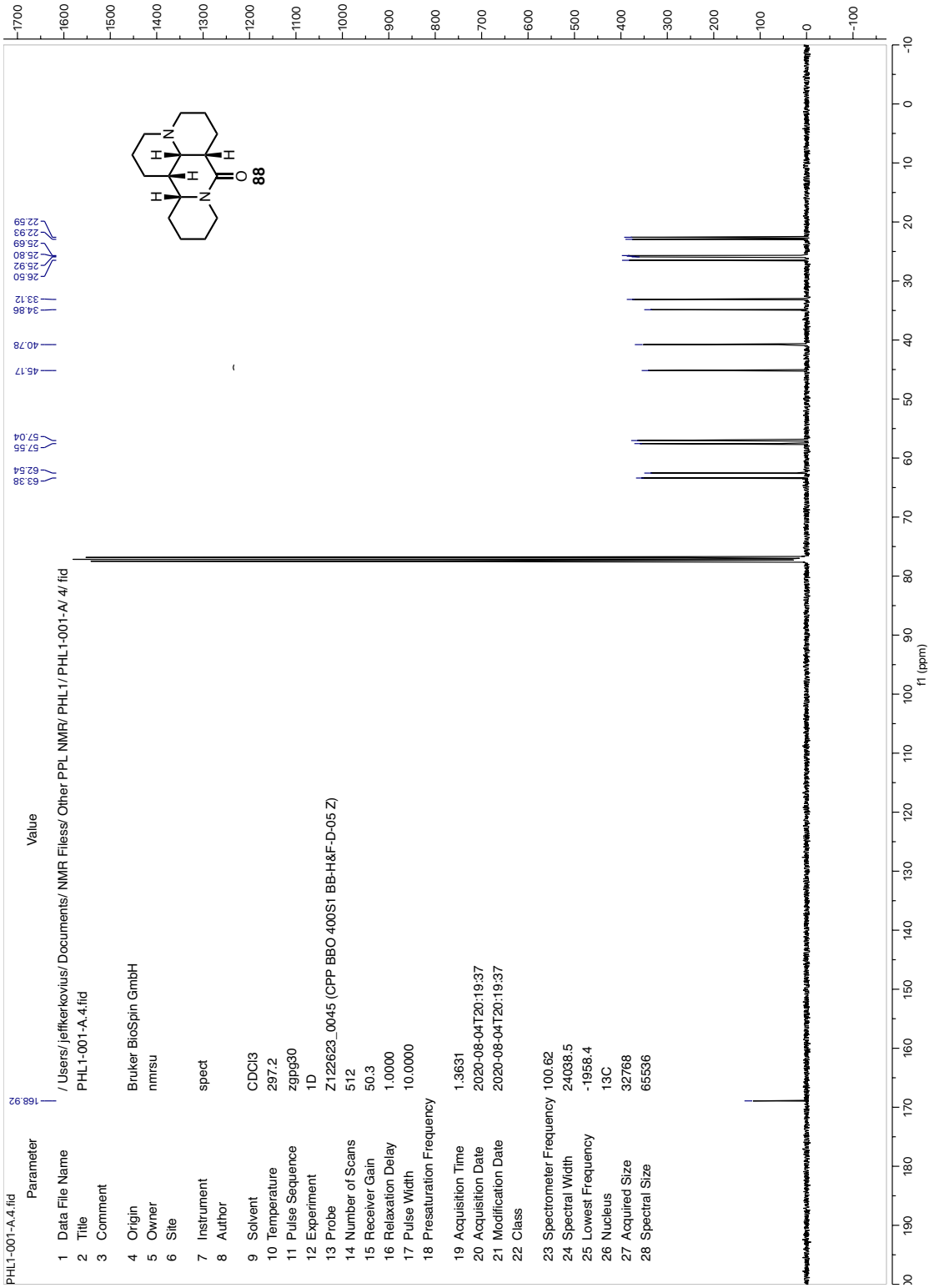

PROTON01
JKK4-031-A-Xs
Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-031-A-Xs/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 10.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 52
11 Relaxation Delay 1.0000
12 Pulse Width 5.6500
13 Acquisition Time 3.0000
14 Acquisition Date 2021-10-14T18:43:50
15 Spectrometer Frequency 499.58
16 Spectral Width 8000.0
17 Lowest Frequency -1018.1
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
81
f1 (ppm)


JKK4-031-A-Xs.2.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-031-A-Xs/ 2/ fid
2 Title JKK4-031-A-Xs.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 78.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-15T01:15:51
21 Modification Date 2021-10-15T01:15:51
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1958.4
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
170.79
101.78
83.49
123.71
123.43
122.34
121.32
58.14
56.85
55.75
52.28
40.97
39.68
24.19
21.35
81
f1 (ppm)

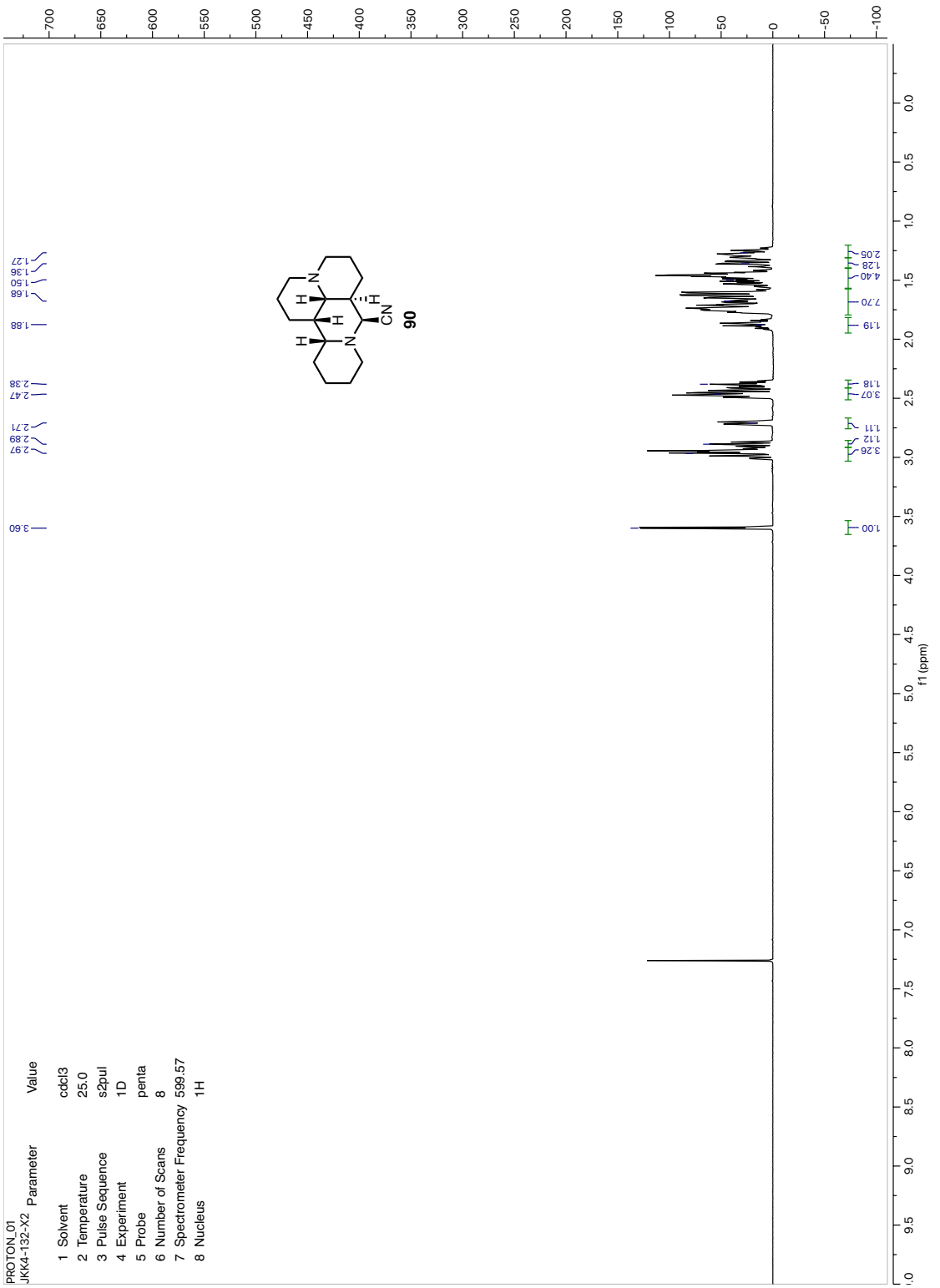

JKK2-134-Xs-CD2Cl2.1.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2-134-Xs-CD2Cl2/ 1/ fid
2 Title JKK2-134-Xs-CD2Cl2.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CD2Cl2
10 Temperature 297.2
11 Pulse Sequence zg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 16
15 Receiver Gain 197.4
16 Relaxation Delay 1.0000
17 Pulse Width 12.5000
18 Presaturation Frequency
19 Acquisition Time 4.0894
20 Acquisition Date 2019-11-26T10:59:31
21 Modification Date 2019-11-26T10:59:31
22 Class
23 Spectrometer Frequency 400.13
24 Spectral Width 8012.8
25 Lowest Frequency -1550.9
26 Nucleus 1H
27 Acquired Size 32768
28 Spectral Size 65536
79
5.39
5.17
1.00
0.89
0.94
0.78
0.93
0.83
2.74
1.01
1.85
0.98
f1 (ppm)

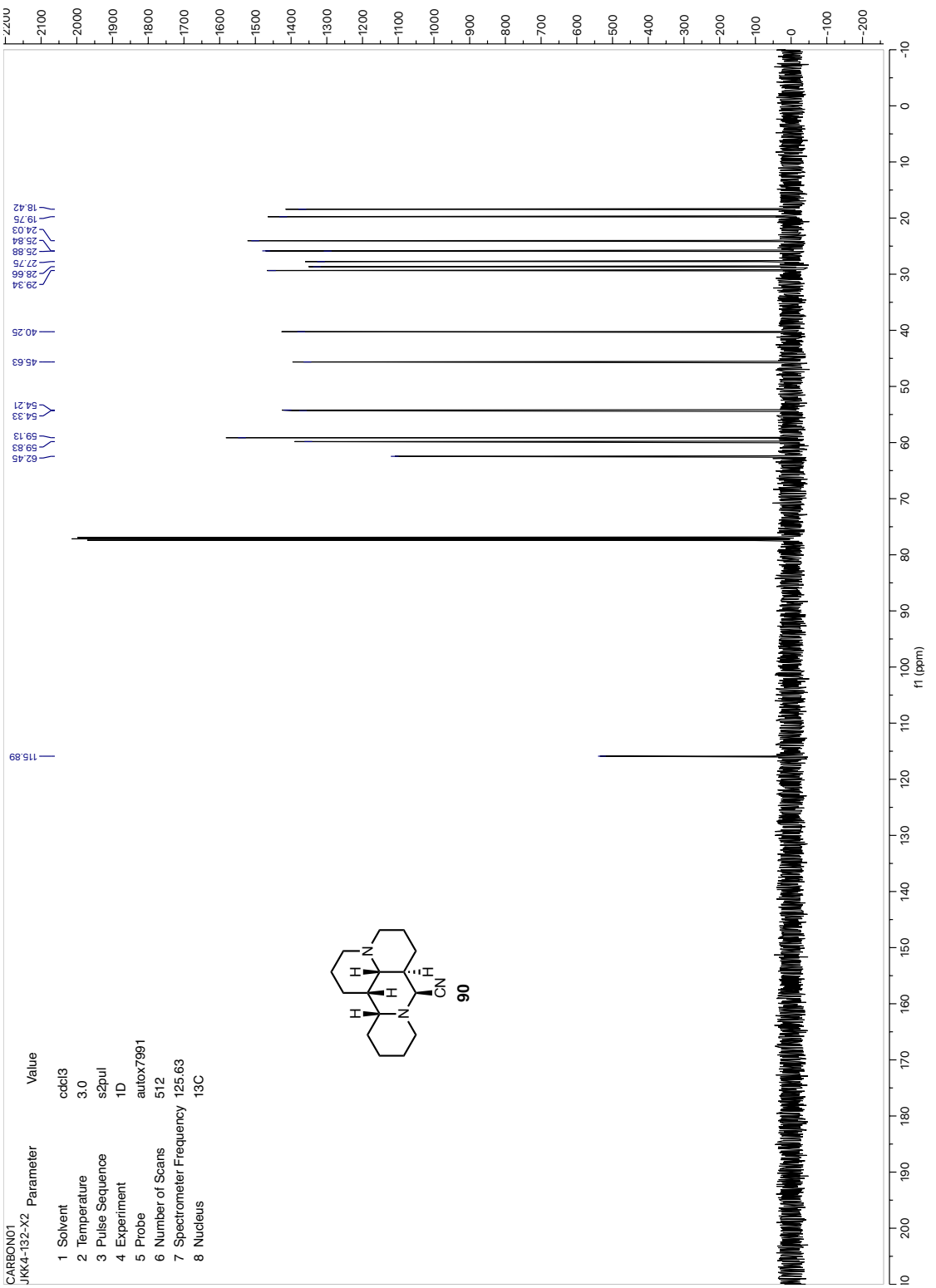

JKK2-134-Xs-CD2Cl2.2.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2-134-Xs-CD2Cl2/ 2/ fid
2 Title JKK2-134-Xs-CD2Cl2.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CD2Cl2
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 43.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2019-11-26T11:42:02
21 Modification Date 2019-11-26T11:42:02
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1901.9
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
168.32
167.45
130.29
124.96
124.95
124.32
123.97
122.48
120.84
118.30
105.54
103.22
52.11
49.39
40.60
22.18
79
f1 (ppm)

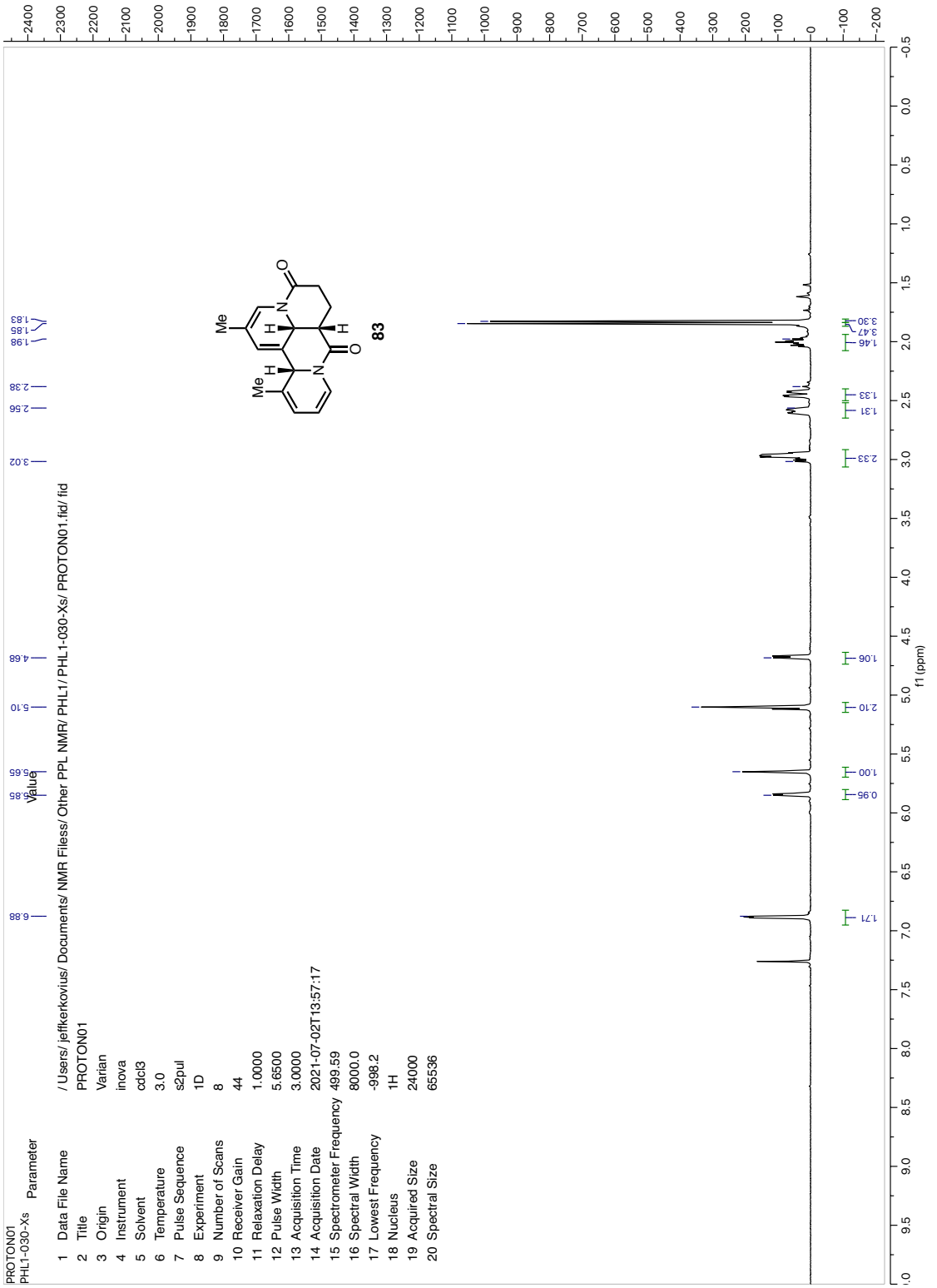

PROTON_01
PHL1-001-A
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-001-A_20191218_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 16
10 Receiver Gain 24
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7046
14 Acquisition Date 2019-12-18T11:06:13
15 Spectrometer Frequency 599.59
16 Spectral Width 9611.9
17 Lowest Frequency -1195.8
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
26 CD3CN
88
f1 (ppm)

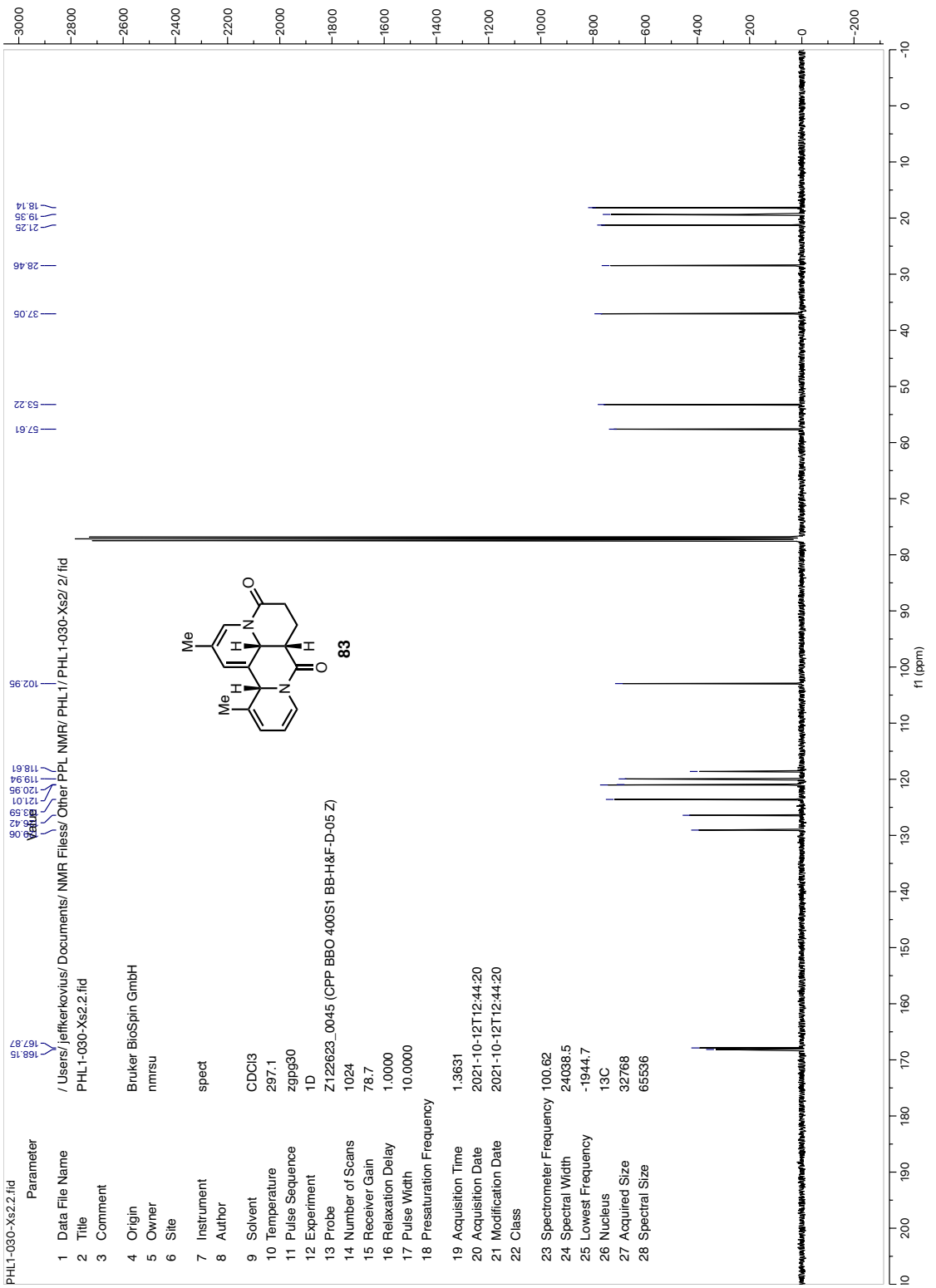


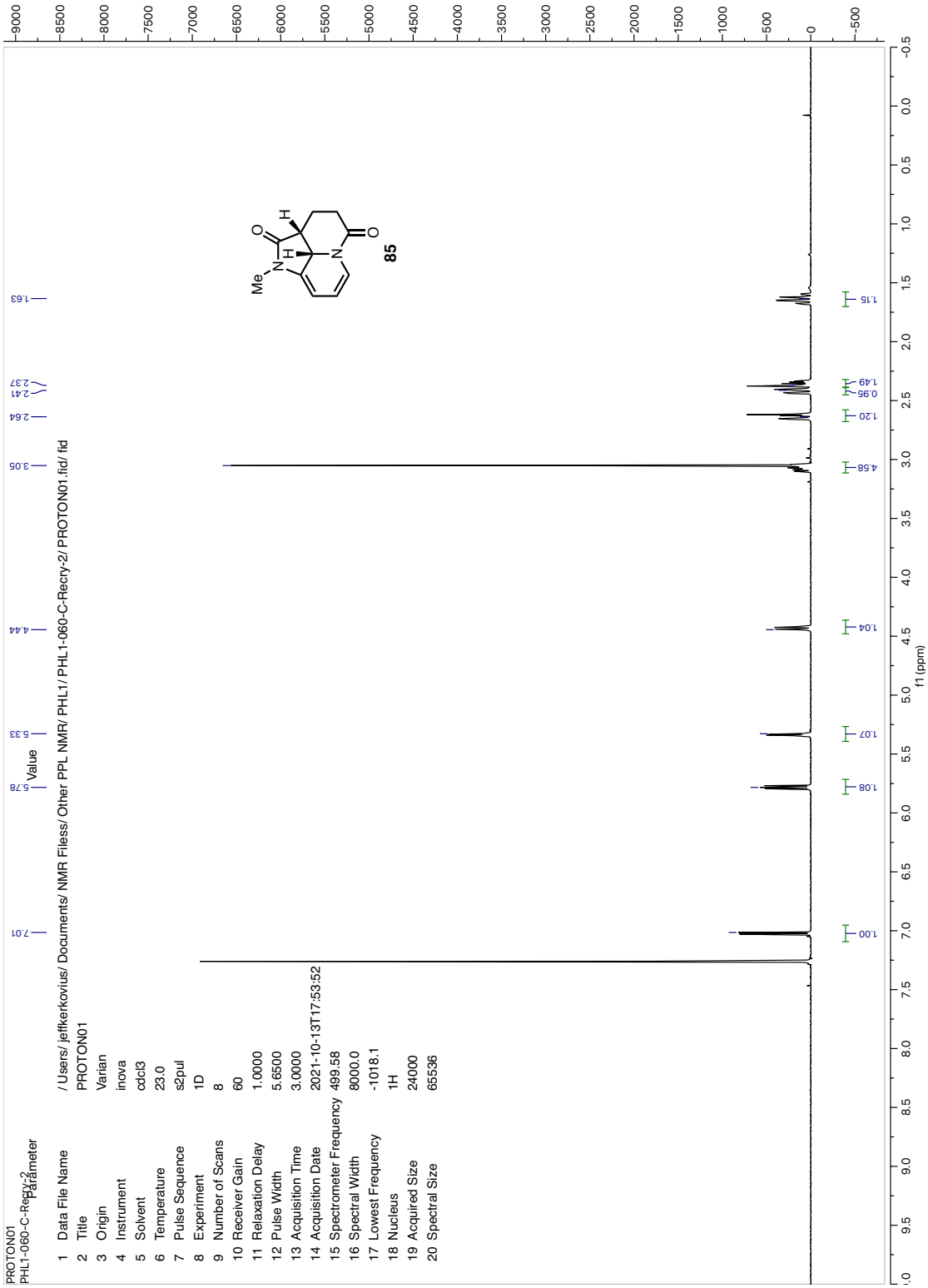
Parameter	Value
1 Data File Name	/ Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-001-A/ 4/ fid
2 Title	PHL1-001-A.4.fid
3 Comment	
4 Origin	Bruker BioSpin GmbH
5 Owner	nmrsu
6 Site	
7 Instrument	spect
8 Author	
9 Solvent	CDCl3
10 Temperature	297.2
11 Pulse Sequence	zgpg30
12 Experiment	1D
13 Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans	512
15 Receiver Gain	50.3
16 Relaxation Delay	1.0000
17 Pulse Width	10.0000
18 Presaturation Frequency	
19 Acquisition Time	1.3631
20 Acquisition Date	2020-08-04T20:19:37
21 Modification Date	2020-08-04T20:19:37
22 Class	
23 Spectrometer Frequency	100.62
24 Spectral Width	24038.5
25 Lowest Frequency	-1958.4
26 Nucleus	13C
27 Acquired Size	32768
28 Spectral Size	65536

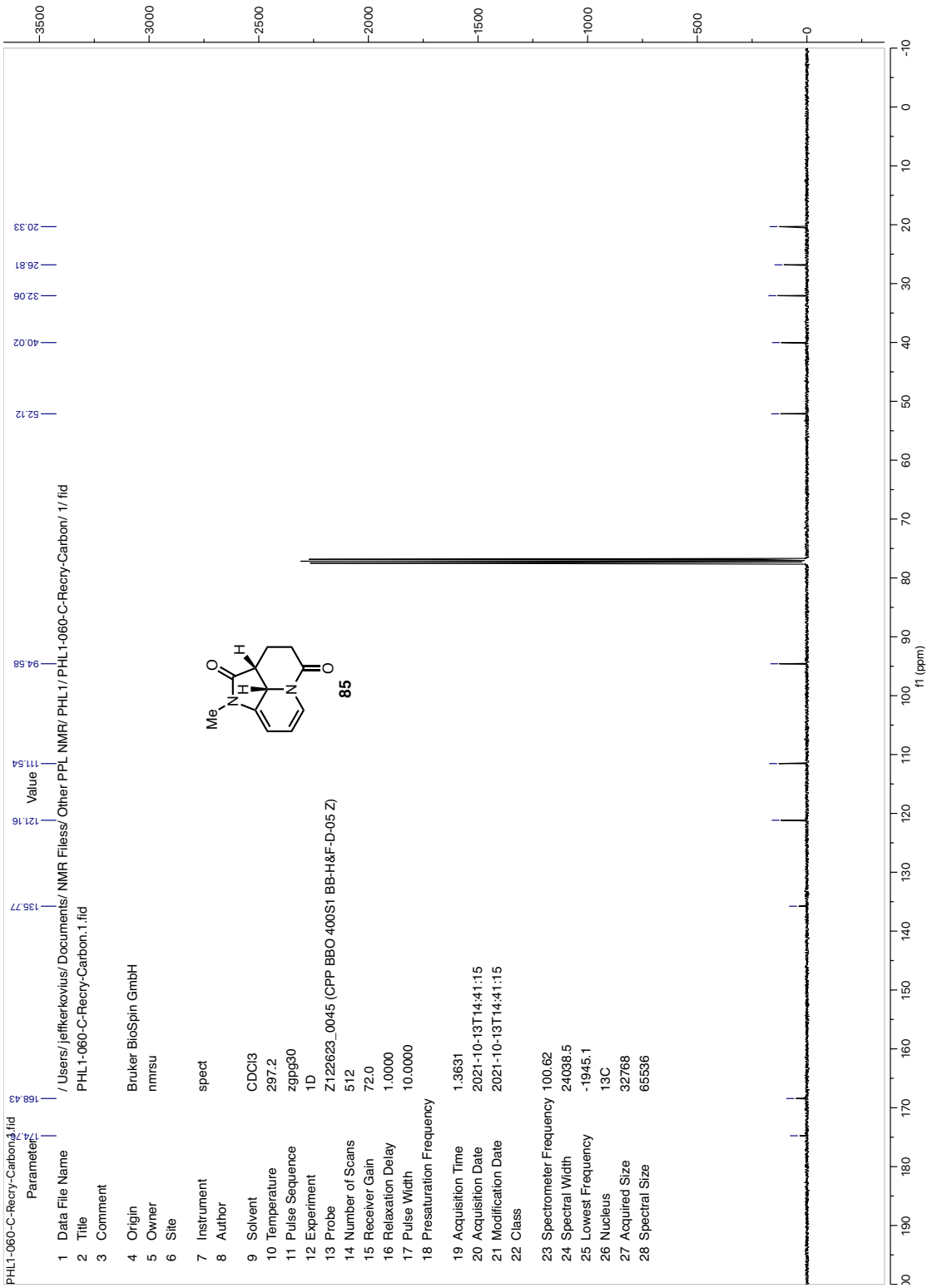

PROTON_01
JKK4-132-X2
Parameter Value
1 Solvent cdcl3
2 Temperature 25.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe penta
6 Number of Scans 8
7 Spectrometer Frequency 599.57
8 Nucleus 1H
90
f1 (ppm)

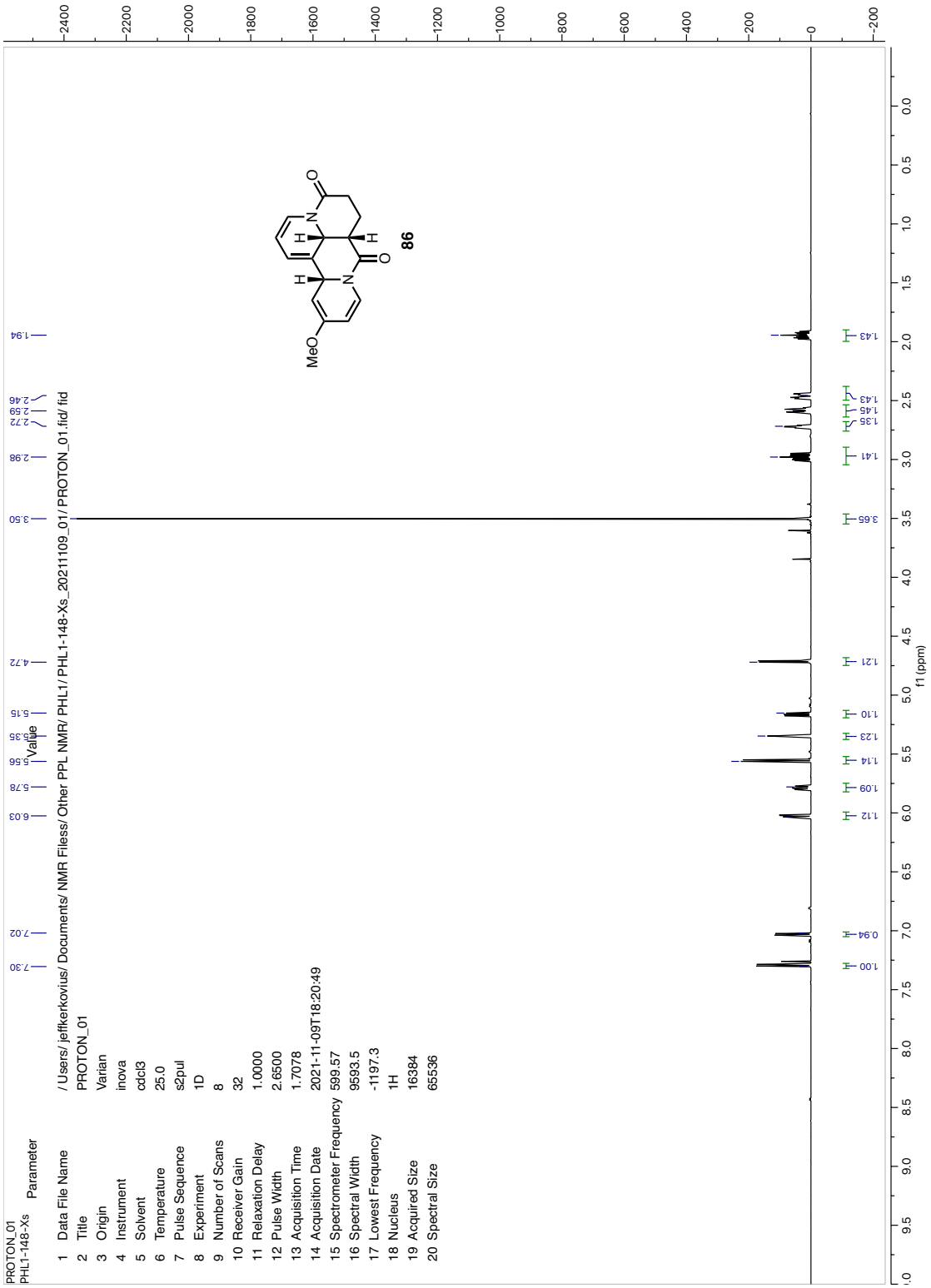

CARBON01
JKK4-132-X2
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.63
8 Nucleus 13C
18.42
19.75
24.03
25.84
25.88
27.75
28.66
29.34
40.25
45.63
54.21
54.33
59.13
59.83
62.45
115.89
90
f1 (ppm)

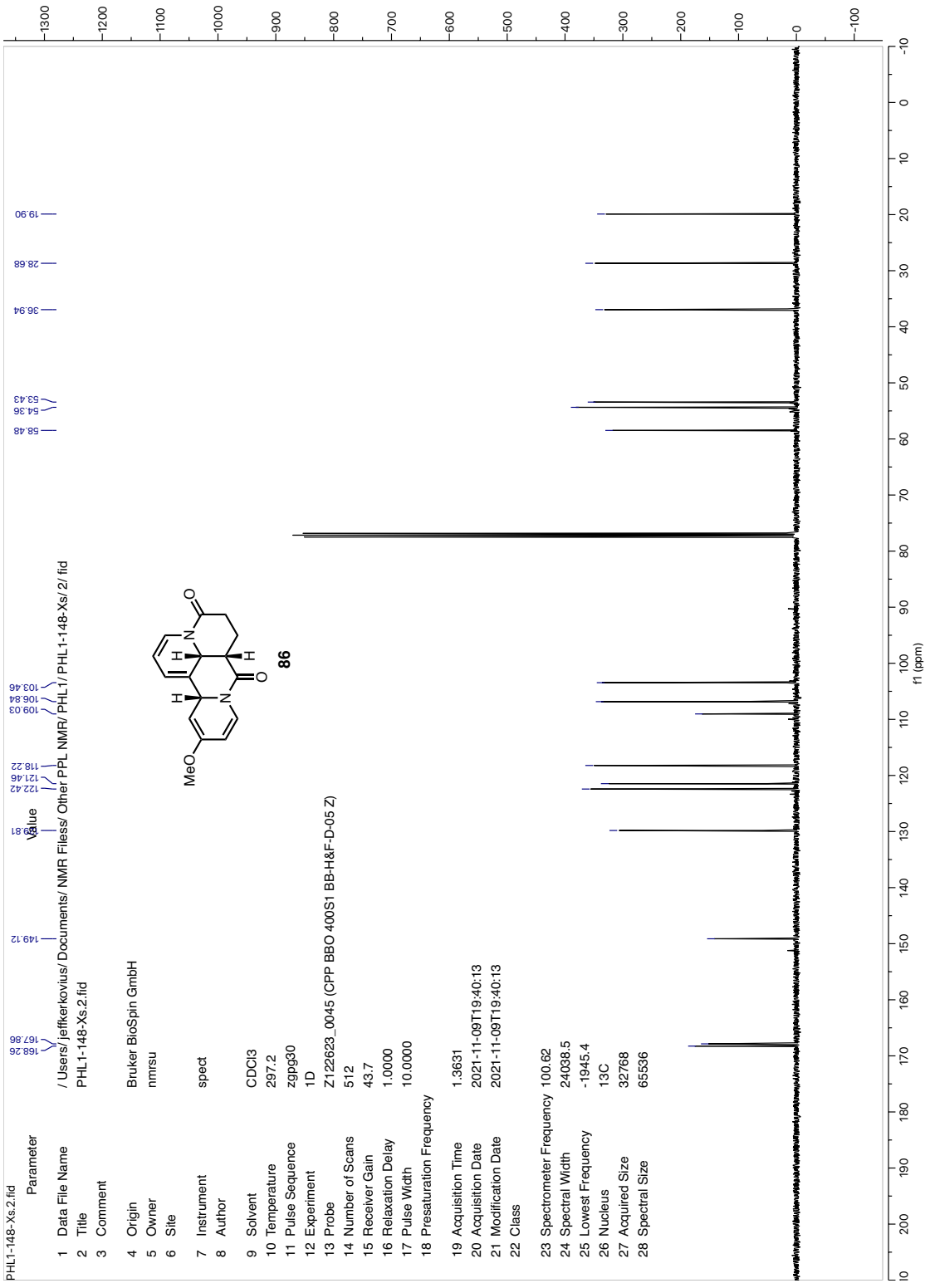

PROTON01
PHL1-030-Xs
Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Filess/ Other PPL NMR/ PHL1/ PHL1-030-Xs/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 44
11 Relaxation Delay 1.0000
12 Pulse Width 5.6500
13 Acquisition Time 3.0000
14 Acquisition Date 2021-07-02T13:57:17
15 Spectrometer Frequency 499.59
16 Spectral Width 8000.0
17 Lowest Frequency -998.2
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
6.88
5.85
5.65
5.10
4.68
3.02
2.56
2.38
1.98
1.85
1.83
Me
H
N
O
83
1.71
0.96
1.00
2.10
1.06
2.33
1.31
1.33
1.46
3.47
3.30
f1 (ppm)

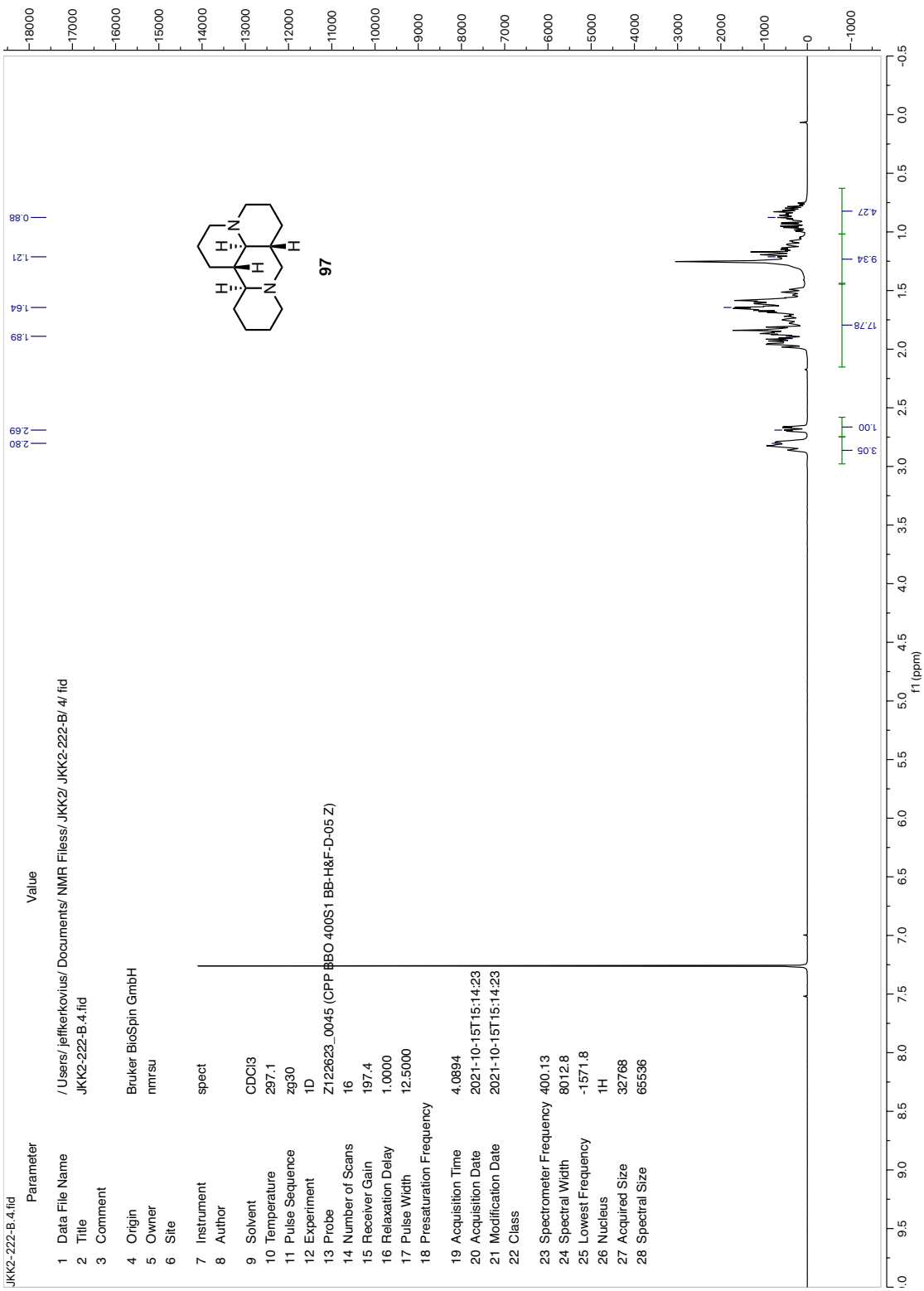

PHL1-030-Xs2.2.fid
Parameter
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-030-Xs2/ 2/ fid
2 Title PHL1-030-Xs2.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 78.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-12T12:44:20
21 Modification Date 2021-10-12T12:44:20
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1944.7
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
168.15
167.87
118.61
119.94
120.95
121.01
133.59
136.42
139.06
102.95
57.61
53.22
37.05
28.46
21.25
19.35
18.14
Me
Me
H
H
O
O
N
N
83
f1 (ppm)

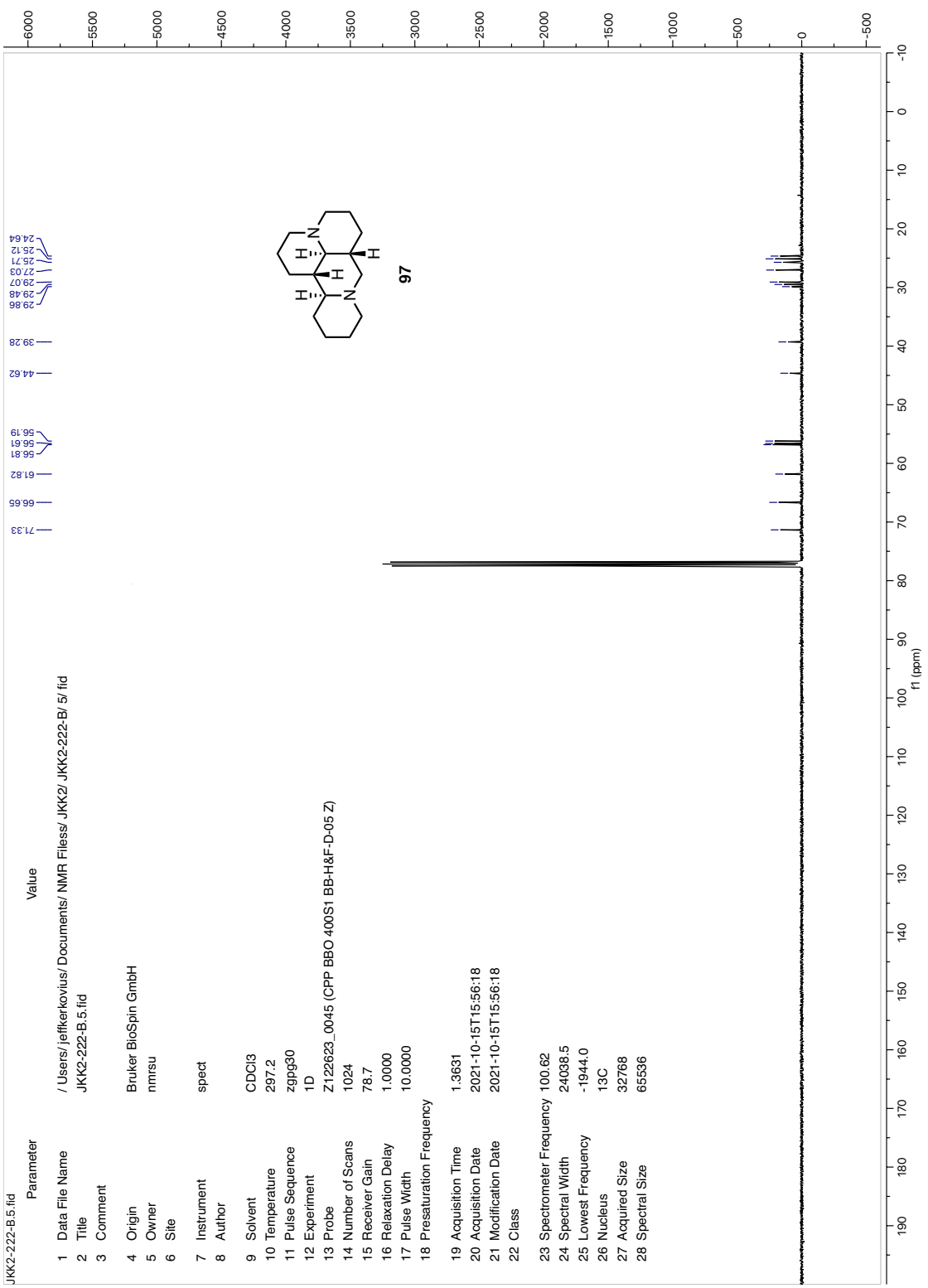

PROTON01
PHL1-060-C-Recry-2
Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-060-C-Recry-2/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 23.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 60
11 Relaxation Delay 1.0000
12 Pulse Width 5.6500
13 Acquisition Time 3.0000
14 Acquisition Date 2021-10-13T17:53:52
15 Spectrometer Frequency 499.58
16 Spectral Width 8000.0
17 Lowest Frequency -1018.1
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
7.01
5.78
5.33
4.44
3.05
2.64
2.41
2.37
1.63
1.00
1.08
1.07
1.04
4.58
1.20
0.95
1.49
1.15
Me
85
f1 (ppm)

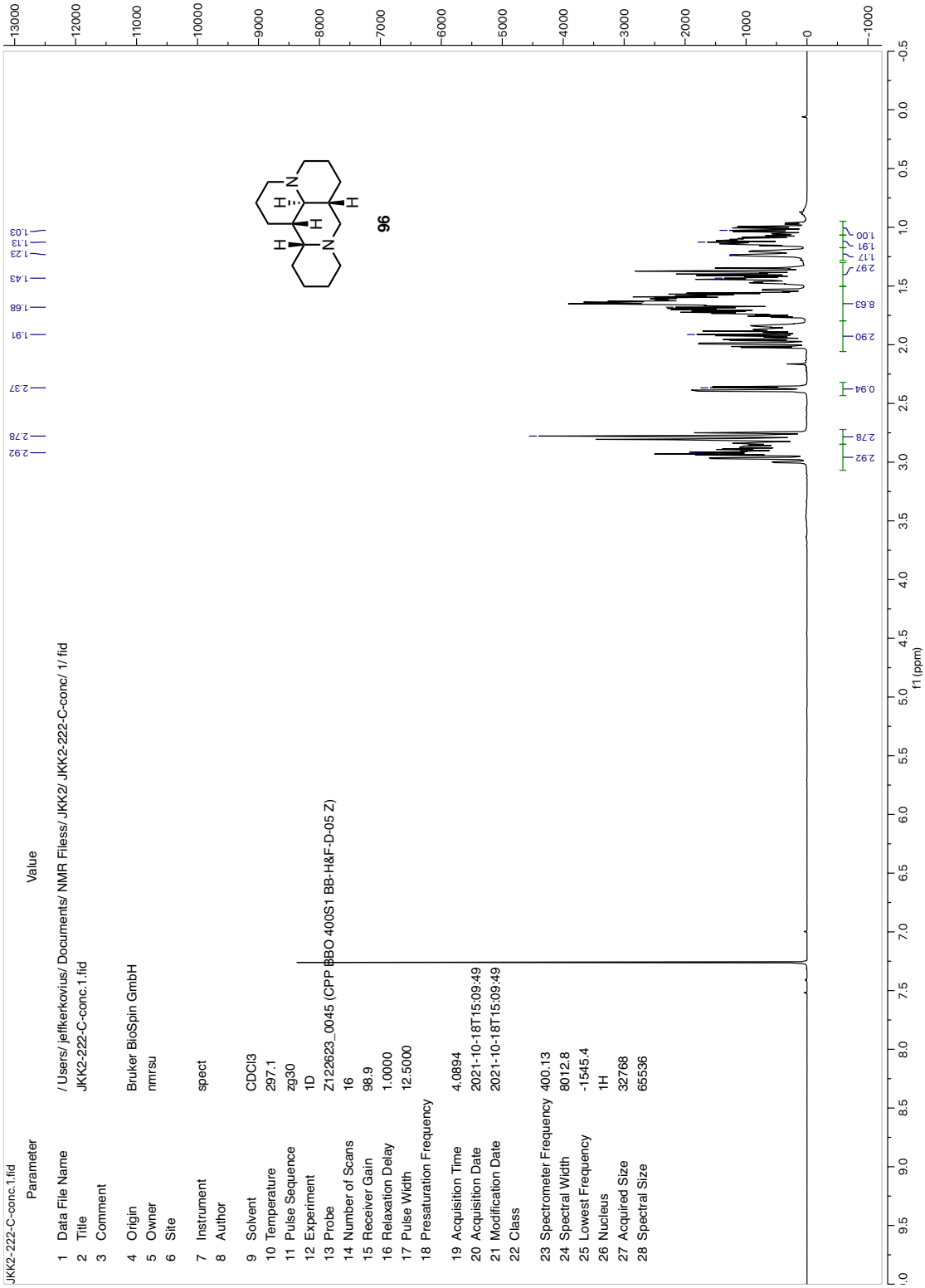

PHL1-060-C-Recry-Carbon.1.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-060-C-Recry-Carbon/ 1/ fid
2 Title PHL1-060-C-Recry-Carbon.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-13T14:41:15
21 Modification Date 2021-10-13T14:41:15
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1945.1
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
174.27
168.43
135.77
121.16
111.54
94.58
52.12
40.02
32.06
26.81
20.33
Me
85
f1 (ppm)

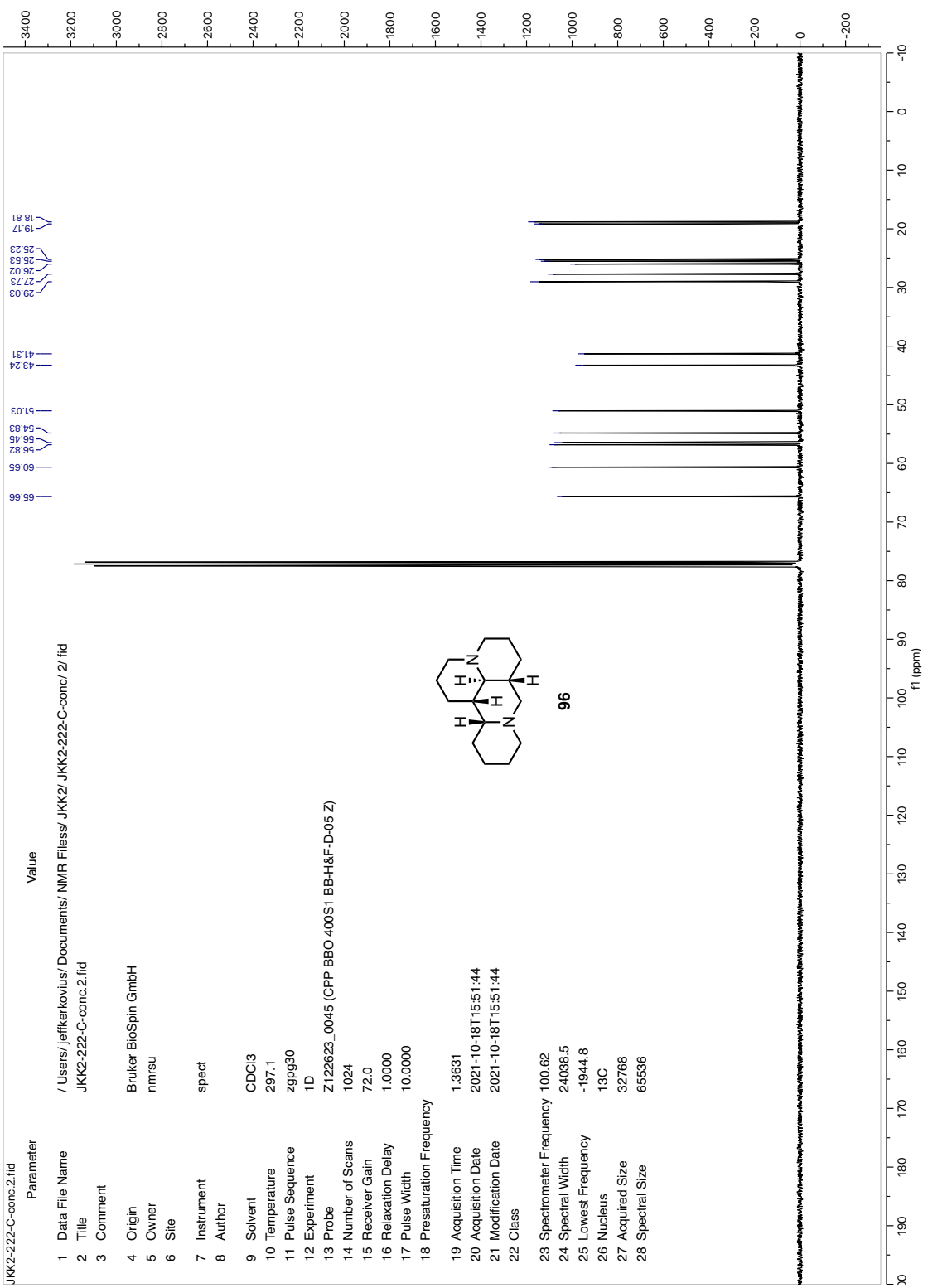

PROTON_01
PHL1-148-Xs
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-148-Xs_20211109_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 32
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2021-11-09T18:20:49
15 Spectrometer Frequency 599.57
16 Spectral Width 9593.5
17 Lowest Frequency -1197.3
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
7.30
7.02
6.03
5.78
5.56
5.35
5.15
4.72
3.50
2.98
2.72
2.59
2.46
1.94
1.00
0.94
1.12
1.09
1.14
1.23
1.10
1.21
3.65
1.41
1.35
1.45
1.43
1.43
MeO
86
f1 (ppm)

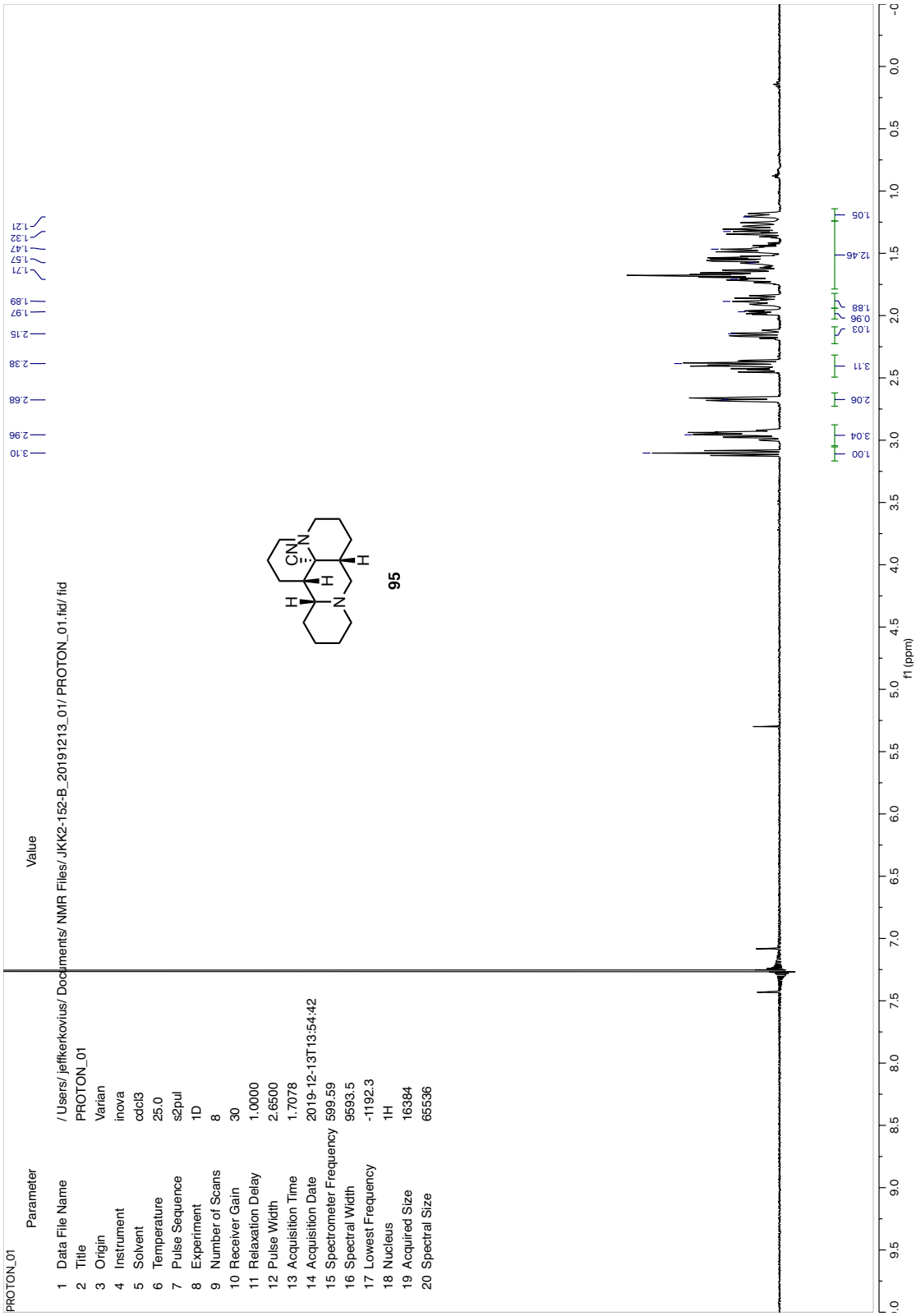

PHL1-148-Xs.2.fid
Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-148-Xs/ 2/ fid
2 Title PHL1-148-Xs.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 43.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-11-09T19:40:13
21 Modification Date 2021-11-09T19:40:13
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1945.4
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
168.26
167.86
149.12
129.81
122.42
121.46
118.22
109.03
106.84
103.46
86
MeO
58.48
54.36
53.43
36.94
28.68
19.90
f1 (ppm)


JKK2-222-B.4.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2/ JKK2-222-B/ 4/ fid
2 Title JKK2-222-B.4.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 16
15 Receiver Gain 197.4
16 Relaxation Delay 1.0000
17 Pulse Width 12.5000
18 Presaturation Frequency
19 Acquisition Time 4.0894
20 Acquisition Date 2021-10-15T15:14:23
21 Modification Date 2021-10-15T15:14:23
22 Class
23 Spectrometer Frequency 400.13
24 Spectral Width 8012.8
25 Lowest Frequency -1571.8
26 Nucleus 1H
27 Acquired Size 32768
28 Spectral Size 65536
97
0.88
1.21
1.64
1.89
2.69
2.80
4.27
9.34
17.78
1.00
3.05
f1 (ppm)

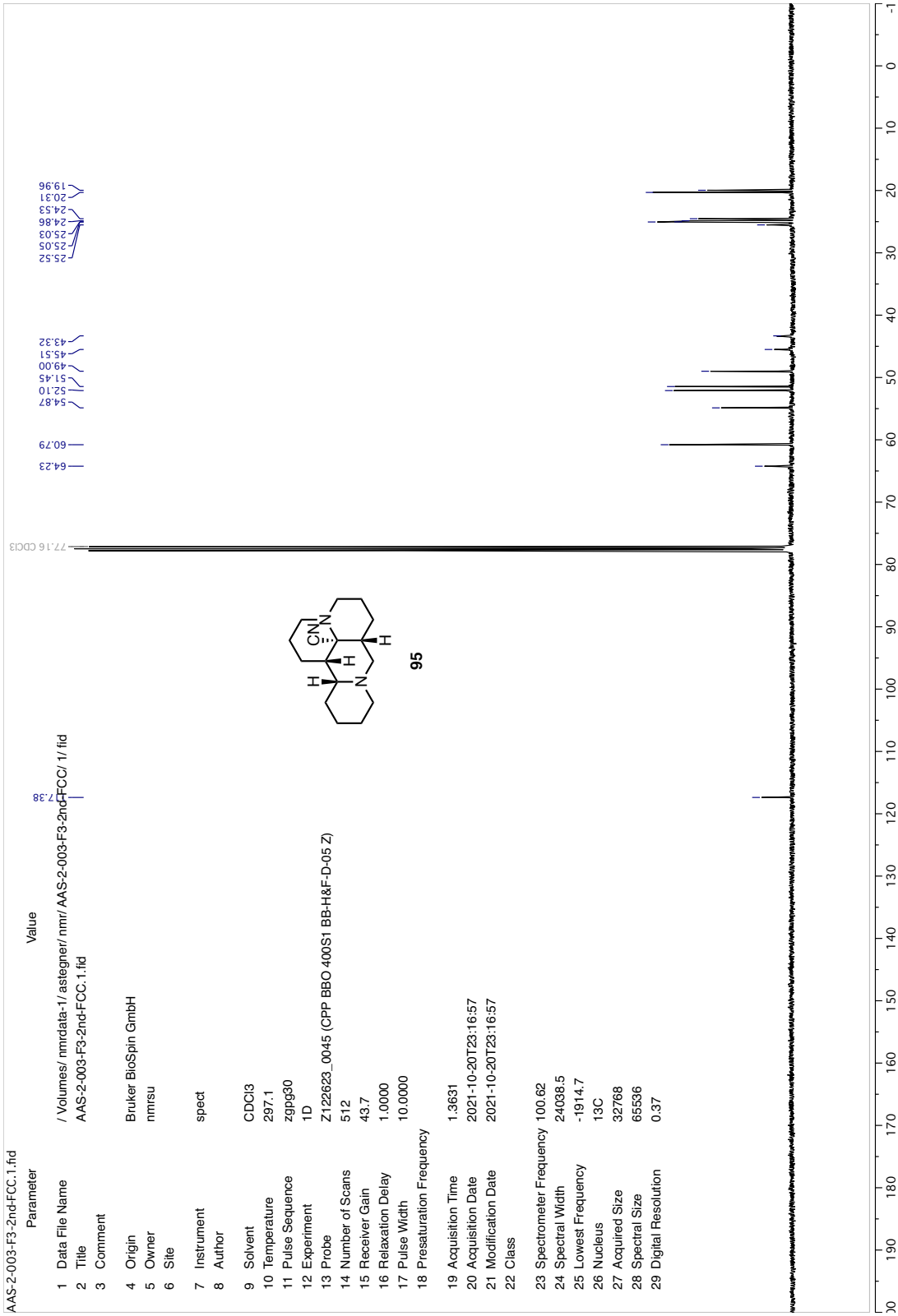

JKK2-222-B.5.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2/ JKK2-222-B/ 5/ fid
2 Title JKK2-222-B.5.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 78.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-15T15:56:18
21 Modification Date 2021-10-15T15:56:18
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1944.0
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
71.33
66.65
61.82
56.81
56.61
56.19
44.62
39.28
29.86
29.48
29.07
27.03
25.71
25.12
24.64
97
f1 (ppm)

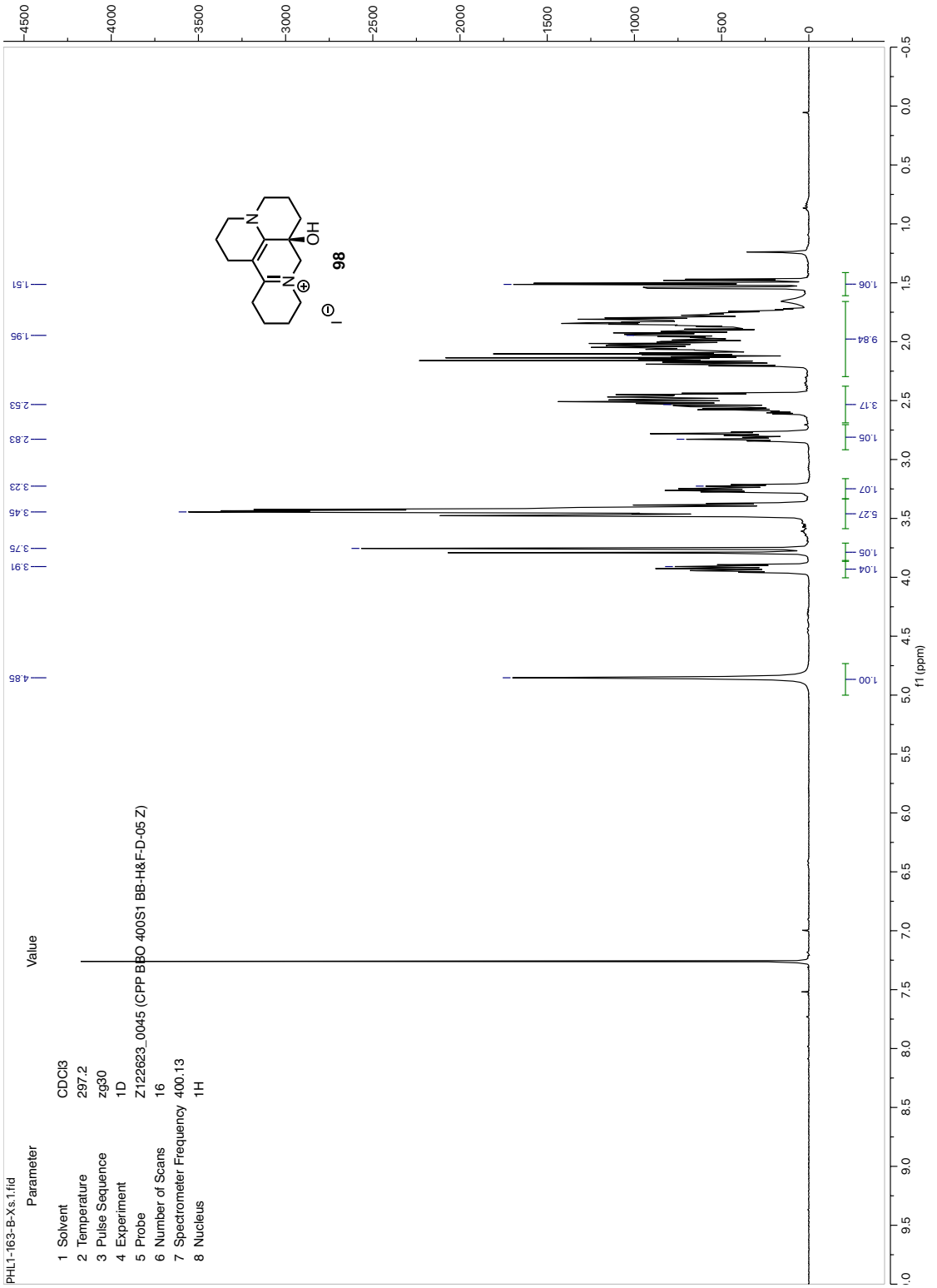

JKK2-222-C-conc.1.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2/ JKK2-222-C-conc/ 1/ fid
2 Title JKK2-222-C-conc.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 16
15 Receiver Gain 98.9
16 Relaxation Delay 1.0000
17 Pulse Width 12.5000
18 Presaturation Frequency
19 Acquisition Time 4.0894
20 Acquisition Date 2021-10-18T15:09:49
21 Modification Date 2021-10-18T15:09:49
22 Class
23 Spectrometer Frequency 400.13
24 Spectral Width 8012.8
25 Lowest Frequency -1545.4
26 Nucleus 1H
27 Acquired Size 32768
28 Spectral Size 65536
96
f1 (ppm)

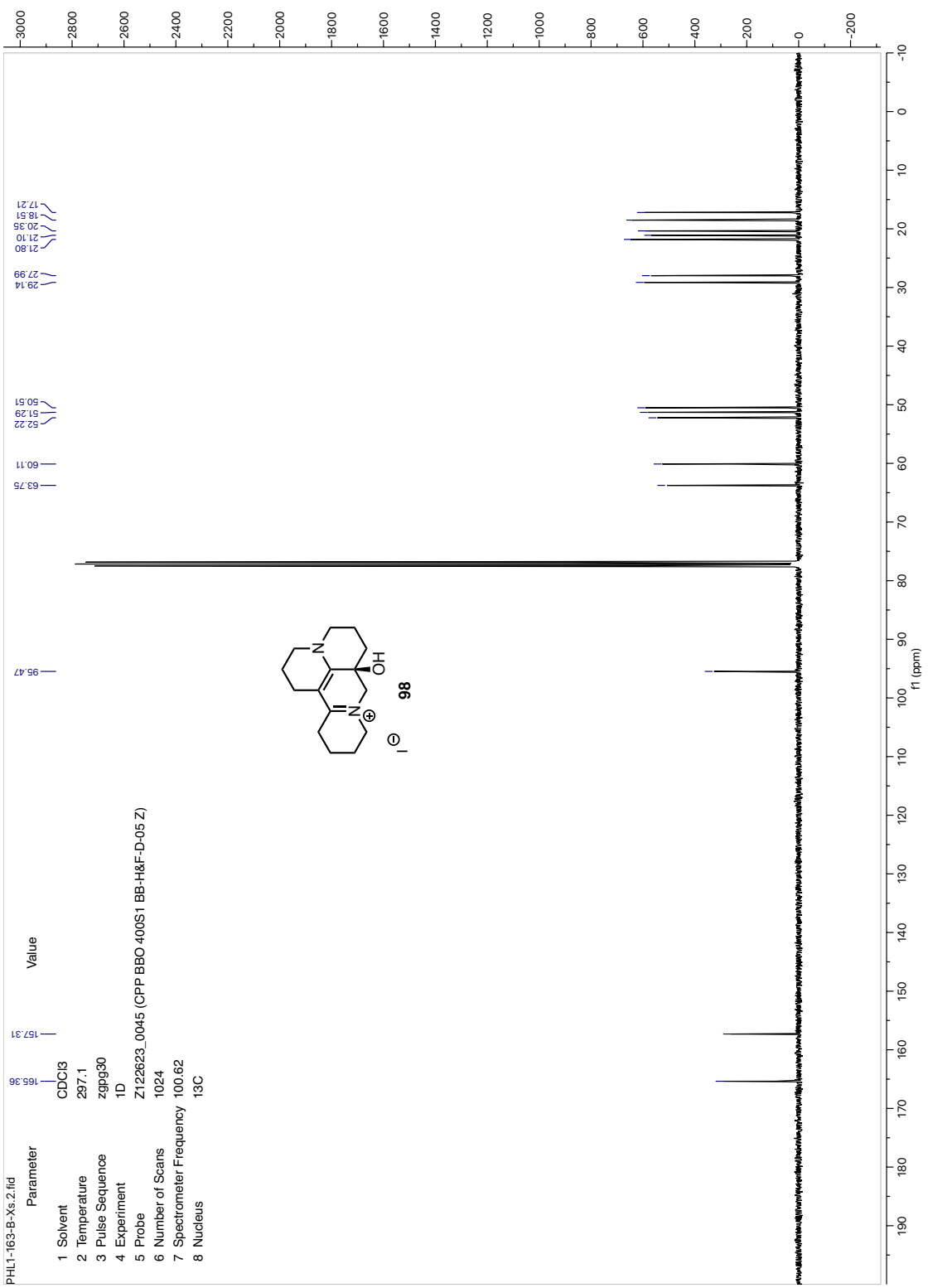

JKK2-222-C-conc.2.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2/ JKK2-222-C-conc/ 2/ fid
2 Title JKK2-222-C-conc.2.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 1024
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-18T15:51:44
21 Modification Date 2021-10-18T15:51:44
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1944.8
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
18.81
19.17
25.23
26.53
26.02
27.73
29.03
41.31
43.24
51.03
54.83
56.45
56.82
60.65
65.66
96
f1 (ppm)

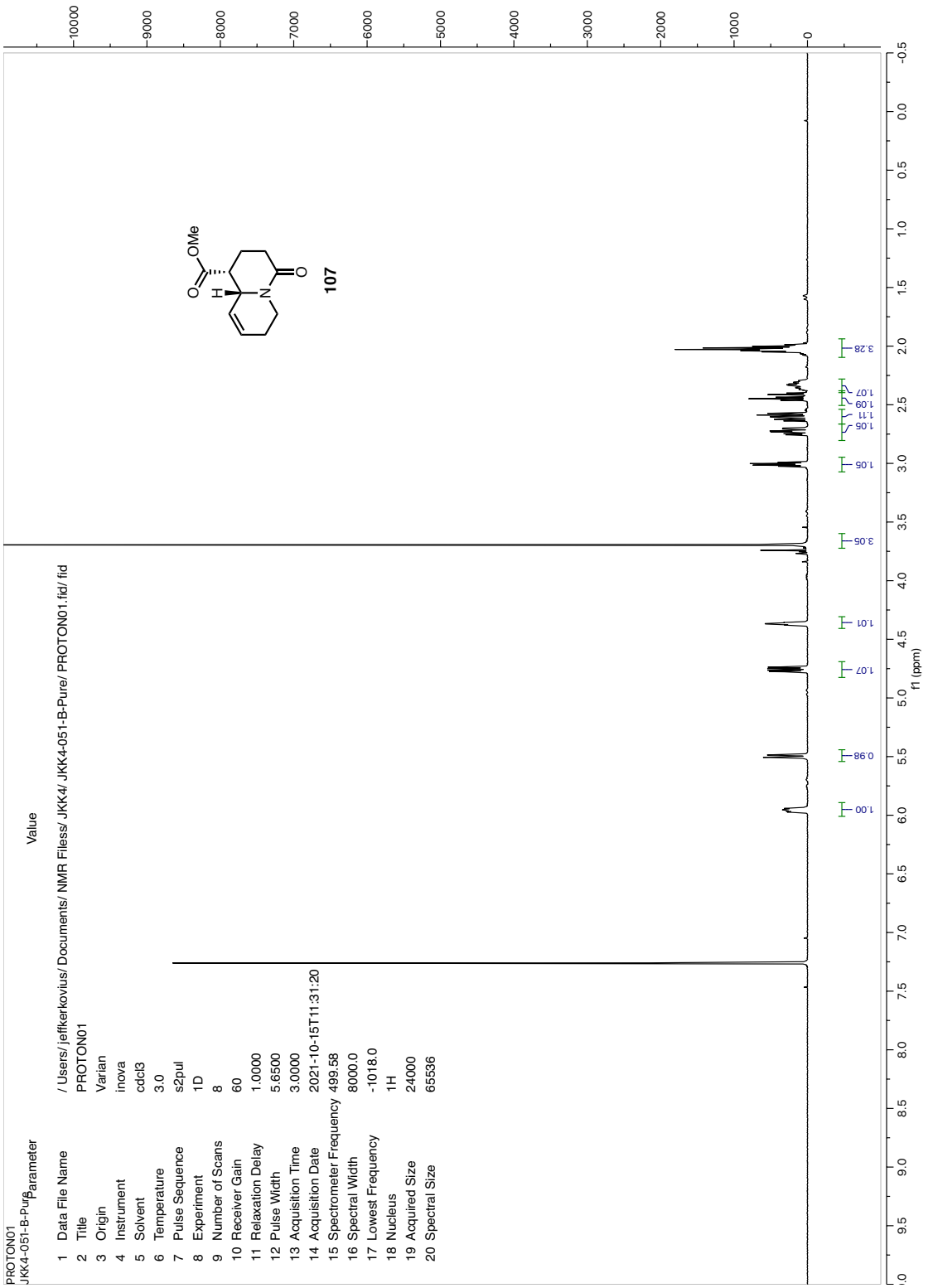

PROTON_01
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK2-152-B_20191213_01/ PROTON_01.fid/ fid
2 Title PROTON_01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 25.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 30
11 Relaxation Delay 1.0000
12 Pulse Width 2.6500
13 Acquisition Time 1.7078
14 Acquisition Date 2019-12-13T13:54:42
15 Spectrometer Frequency 599.59
16 Spectral Width 9593.5
17 Lowest Frequency -1192.3
18 Nucleus 1H
19 Acquired Size 16384
20 Spectral Size 65536
3.10
2.96
2.68
2.38
2.15
1.97
1.89
1.71
1.57
1.47
1.32
1.21
1.00
3.04
2.06
3.11
1.03
0.96
1.88
12.46
1.05
f1 (ppm)

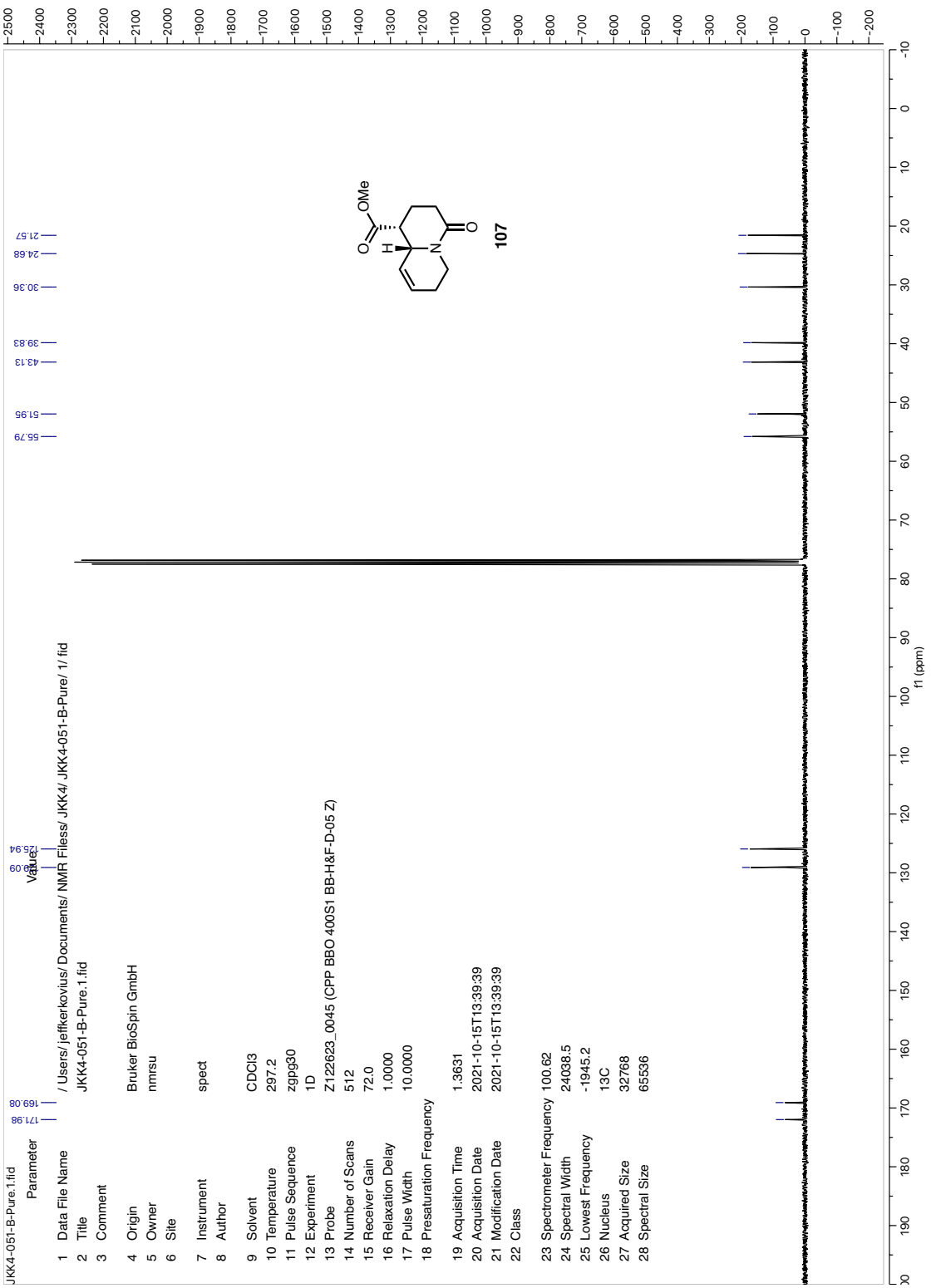
95

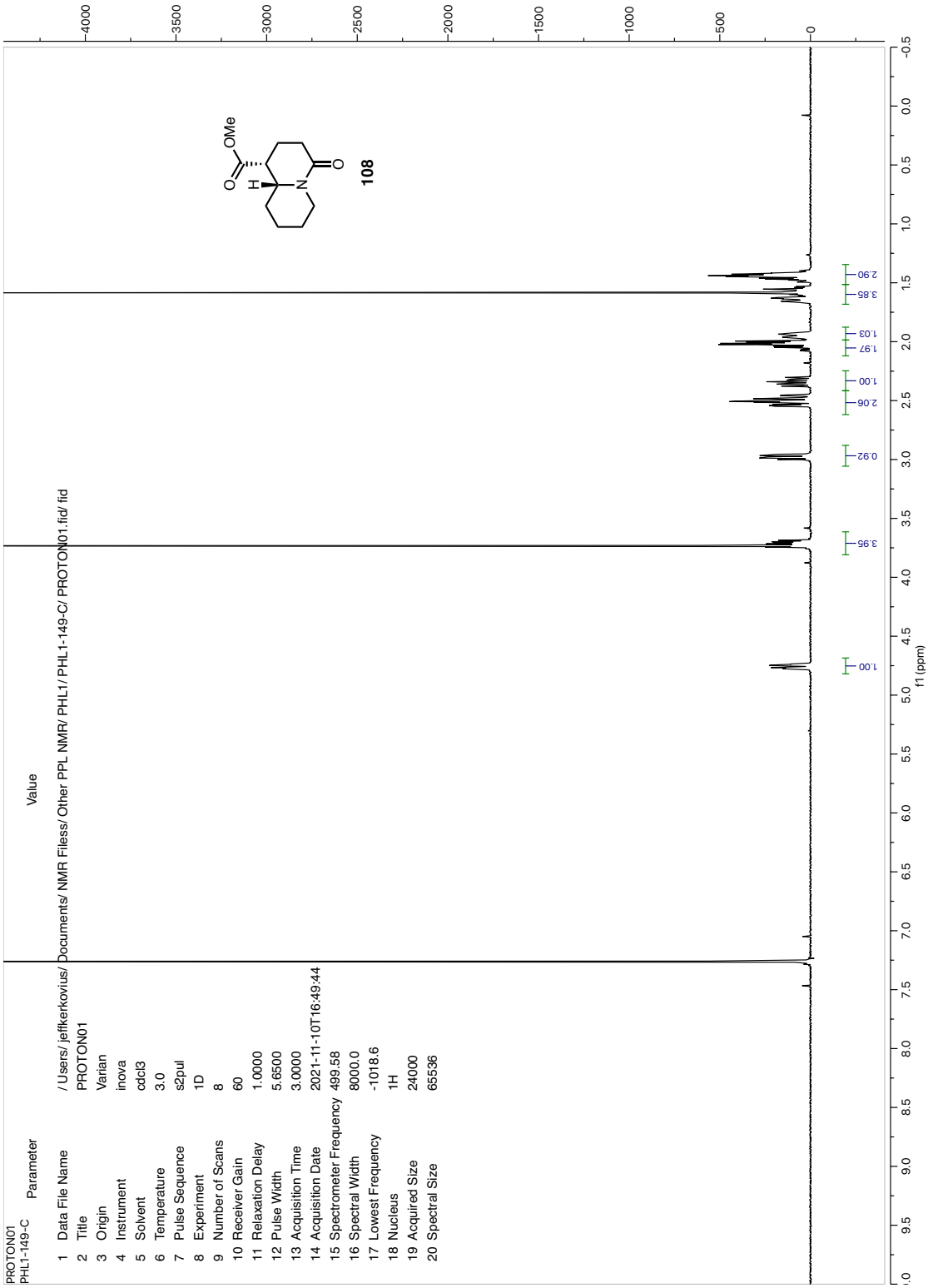

AAS-2-003-F3-2nd-FCC.1.fid
Parameter
Value
1 Data File Name / Volumes/ nmrdata-1/ astegner/ nmr/ AAS-2-003-F3-2nd-FCC/ 1/ fid
2 Title AAS-2-003-F3-2nd-FCC.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 43.7
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-20T23:16:57
21 Modification Date 2021-10-20T23:16:57
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1914.7
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
29 Digital Resolution 0.37
7.38
77.16 CDCl3
64.23
60.79
54.87
52.10
51.45
49.00
45.51
43.32
25.52
25.05
25.03
24.86
24.53
20.31
19.96
95
f1 (ppm)

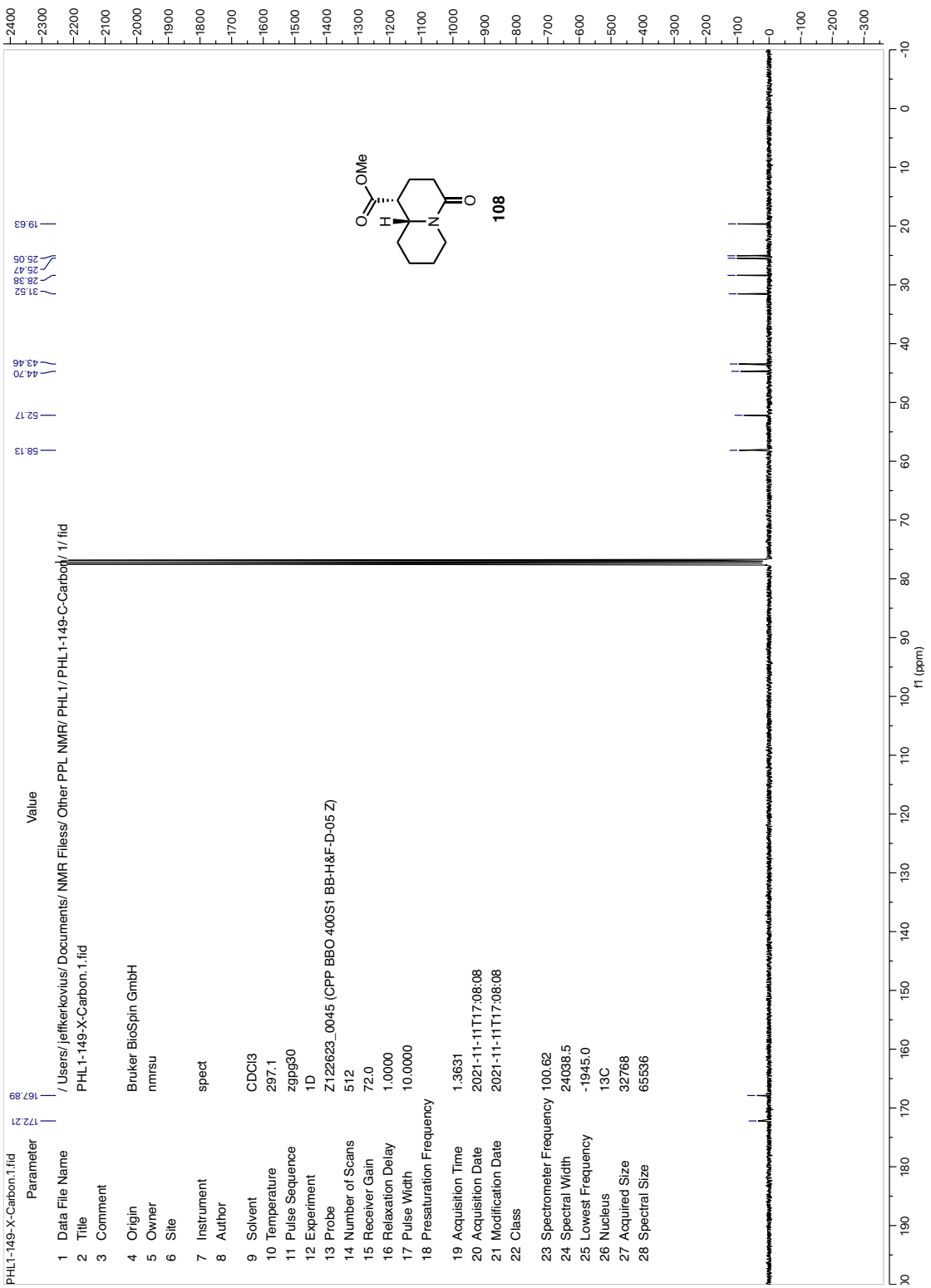

PHL1-163-B-Xs.1.fid
Parameter Value
1 Solvent CDCl3
2 Temperature 297.2
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
98
f1 (ppm)

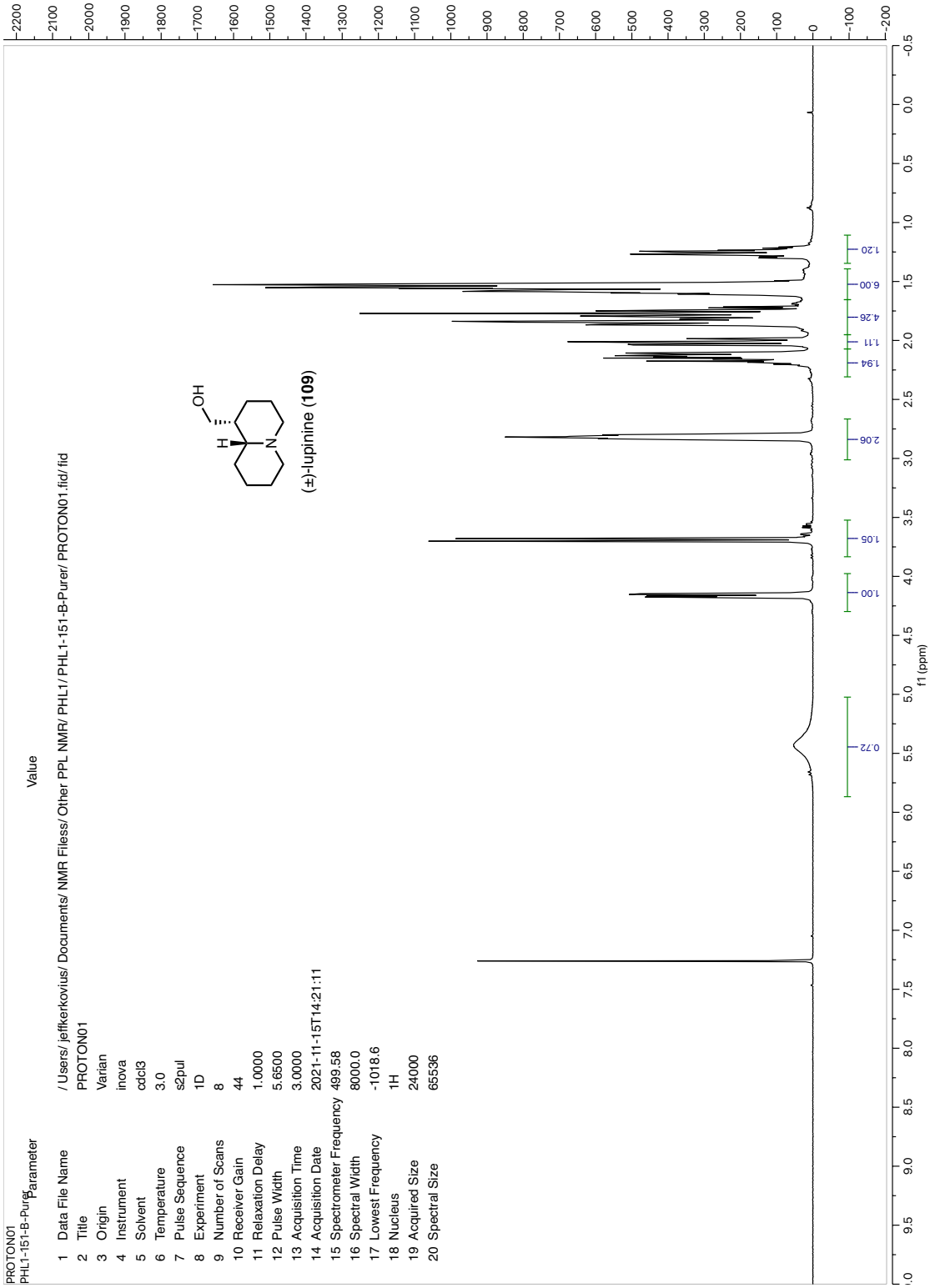

PHL1-163-B-Xs.2.fid
Parameter Value
1 Solvent CDCl3
2 Temperature 297.1
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 1024
7 Spectrometer Frequency 100.62
8 Nucleus 13C
165.36
157.31
95.47
63.75
60.11
52.22
51.29
50.51
29.14
27.99
21.80
21.10
20.35
18.51
17.21
98
f1 (ppm)

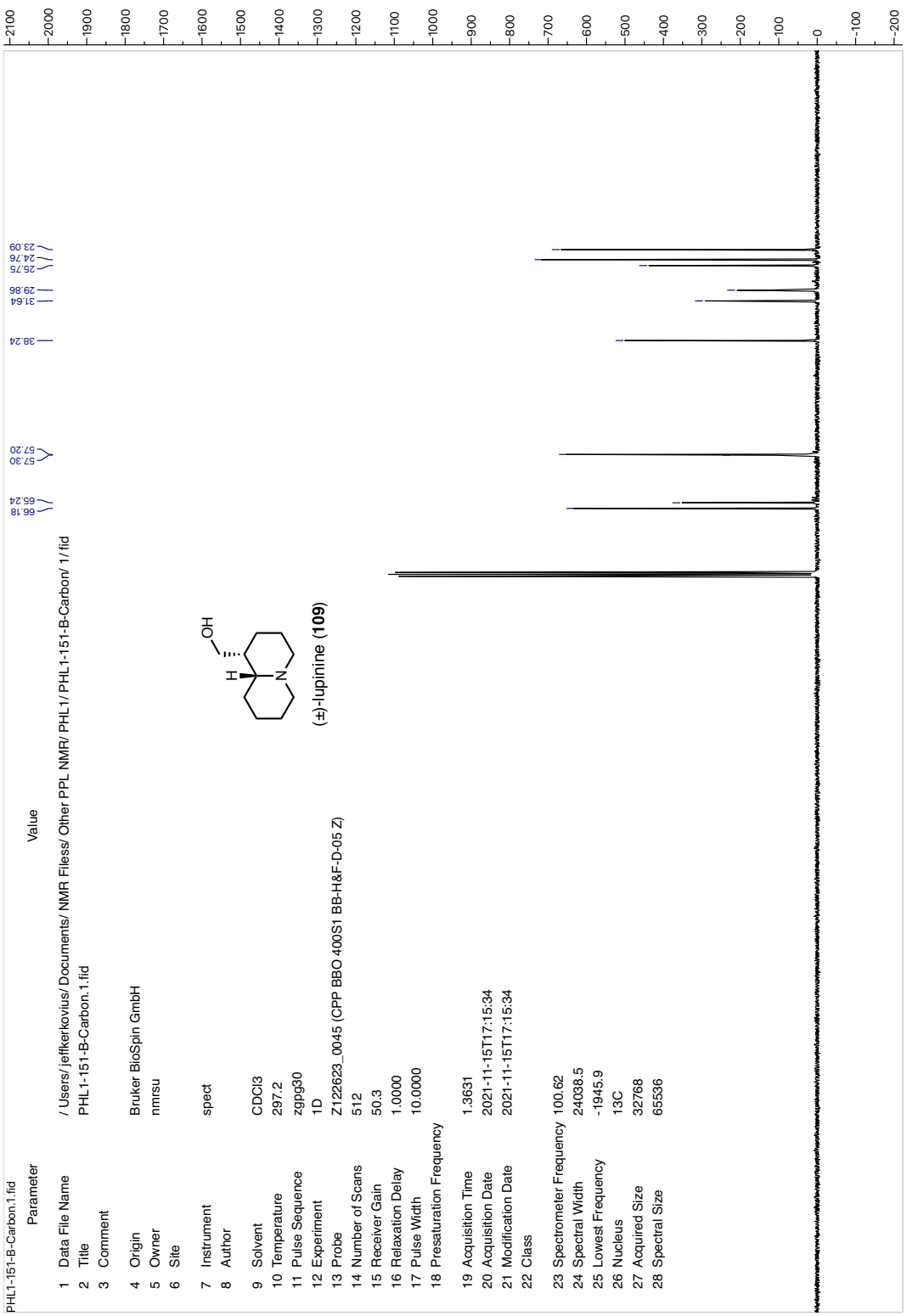

PROTON01
JKK4-051-B-Pure
Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-051-B-Pure/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 60
11 Relaxation Delay 1.0000
12 Pulse Width 5.6500
13 Acquisition Time 3.0000
14 Acquisition Date 2021-10-15T11:31:20
15 Spectrometer Frequency 499.58
16 Spectral Width 8000.0
17 Lowest Frequency -1018.0
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
OMe
O
H
N
O
107
3.28
1.07
1.09
1.11
1.05
1.06
3.05
1.01
1.07
0.98
1.00
f1 (ppm)

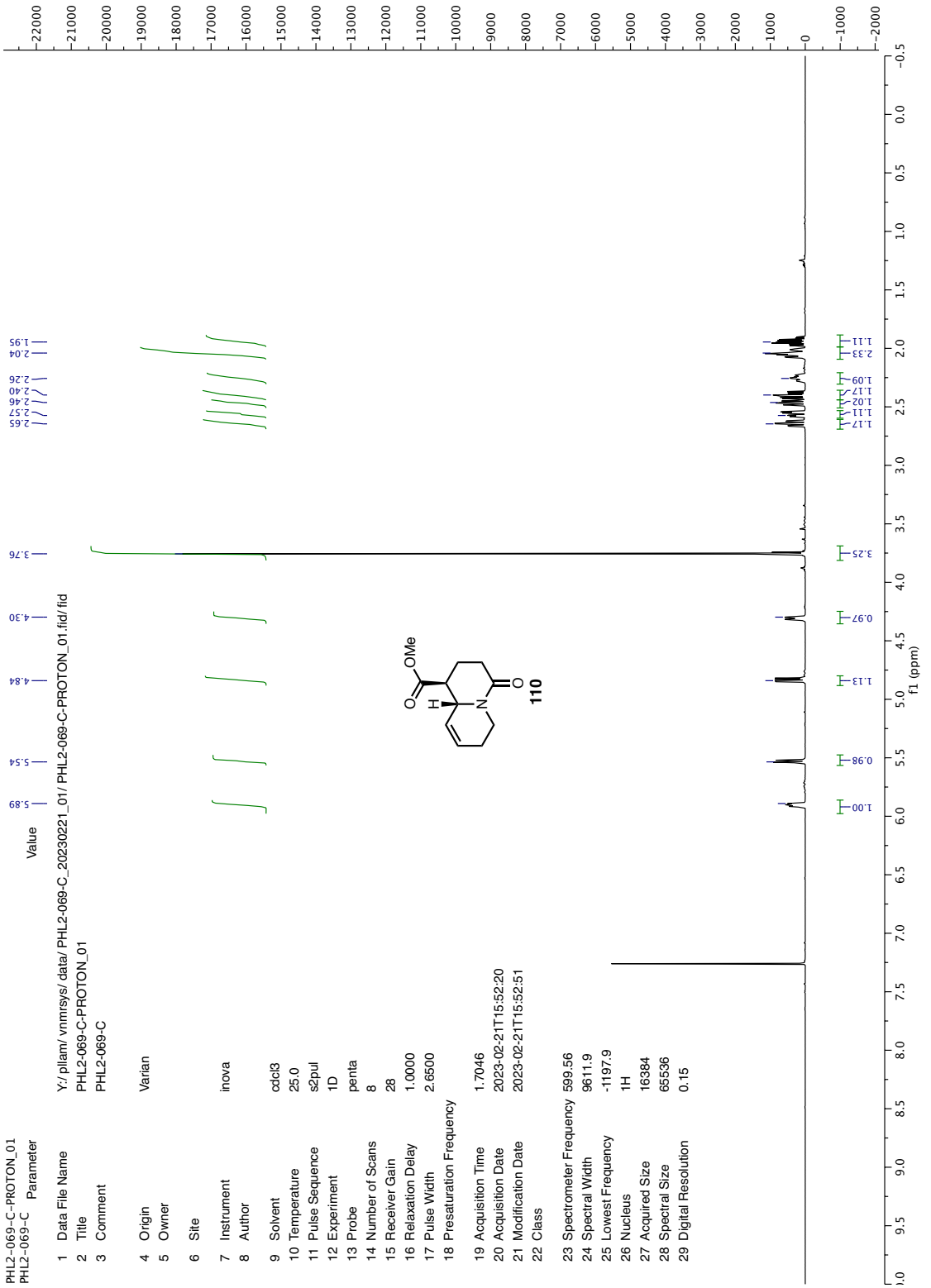

JKK4-051-B-Pure.1.fid
Parameter Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ JKK4/ JKK4-051-B-Pure/ 1/ fid
2 Title JKK4-051-B-Pure.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-10-15T13:39:39
21 Modification Date 2021-10-15T13:39:39
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1945.2
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
171.98
169.08
125.94
120.09
55.79
51.95
43.13
39.83
30.36
24.68
21.57
OMe
O
O
H
N
107
f1 (ppm)

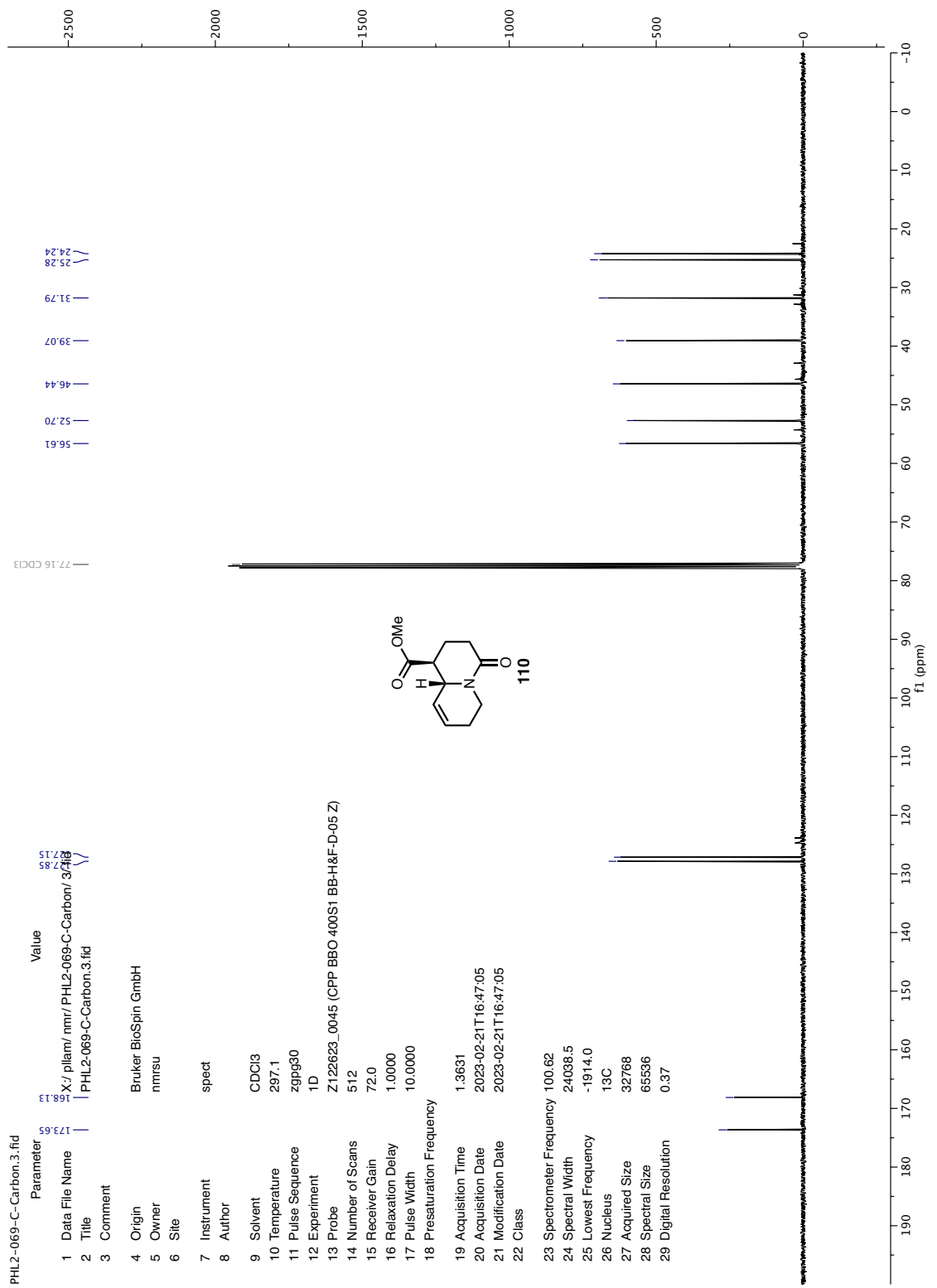

PROTON01
PHL1-149-C
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Filess/ Other PPL NMR/ PHL1/ PHL1-149-C/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 60
11 Relaxation Delay 1.0000
12 Pulse Width 5.6500
13 Acquisition Time 3.0000
14 Acquisition Date 2021-11-10T16:49:44
15 Spectrometer Frequency 499.58
16 Spectral Width 8000.0
17 Lowest Frequency -1018.6
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
OMe
O
H
N
O
108
2.90
3.85
1.03
1.97
1.00
2.06
0.92
3.96
1.00
f1 (ppm)

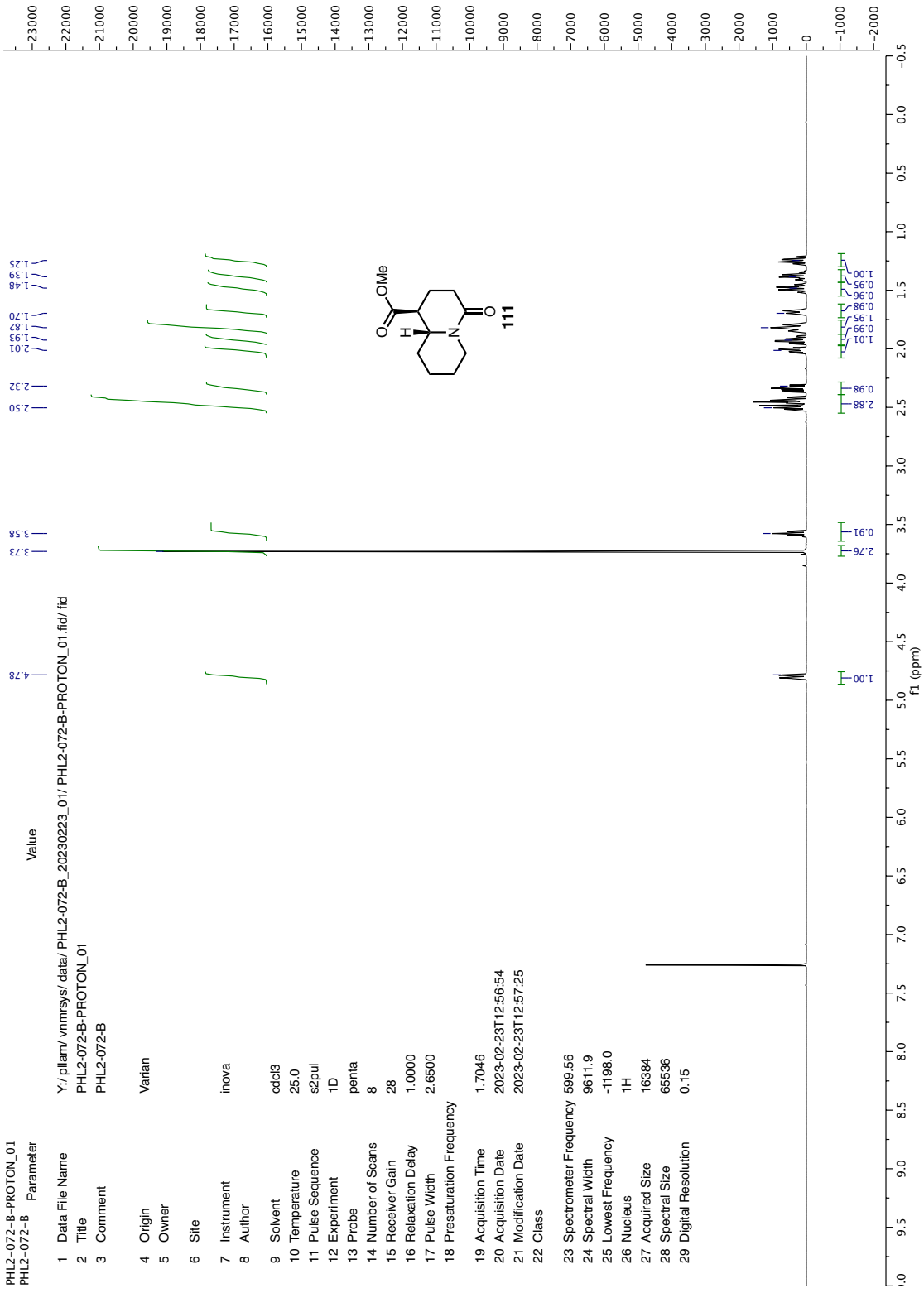

PHL1-149-X-Carbon.1.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-149-C-Carbon/ 1/ fid
2 Title PHL1-149-X-Carbon.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-11-11T17:08:08
21 Modification Date 2021-11-11T17:08:08
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1945.0
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
172.21
167.89
58.13
52.17
44.70
43.46
31.52
28.38
28.47
26.05
19.63
OMe
O
O
H
N
O
108
f1 (ppm)

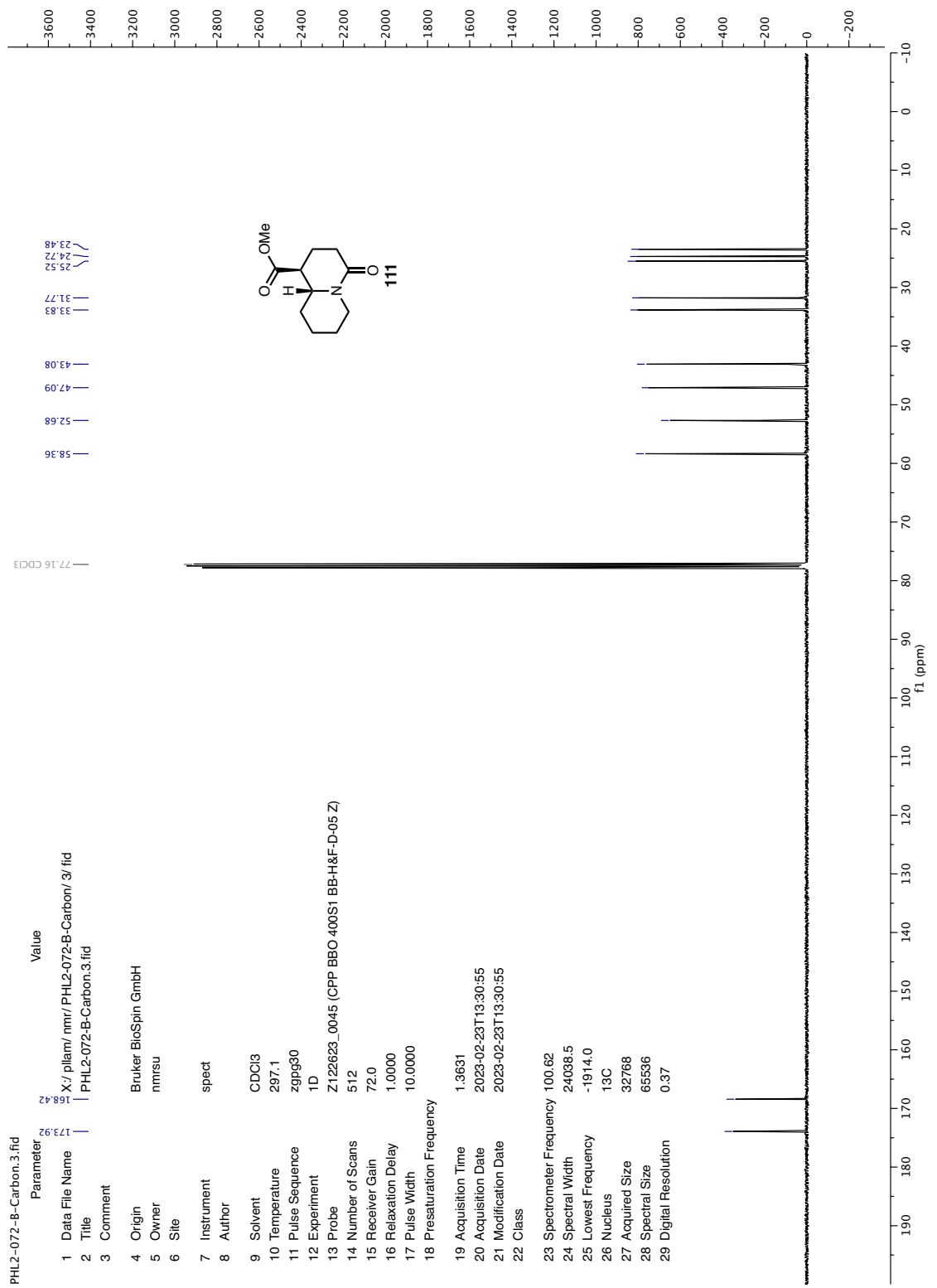

PROTON01
PHL1-151-B-Purer
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-151-B-Purer/ PROTON01.fid/ fid
2 Title PROTON01
3 Origin Varian
4 Instrument inova
5 Solvent cdcl3
6 Temperature 3.0
7 Pulse Sequence s2pul
8 Experiment 1D
9 Number of Scans 8
10 Receiver Gain 44
11 Relaxation Delay 1.0000
12 Pulse Width 5.6500
13 Acquisition Time 3.0000
14 Acquisition Date 2021-11-15T14:21:11
15 Spectrometer Frequency 499.58
16 Spectral Width 8000.0
17 Lowest Frequency -1018.6
18 Nucleus 1H
19 Acquired Size 24000
20 Spectral Size 65536
OH
H
N
(±)-lupinine (109)
0.72
1.00
1.05
2.06
1.94
1.11
4.26
6.00
1.20
f1 (ppm)

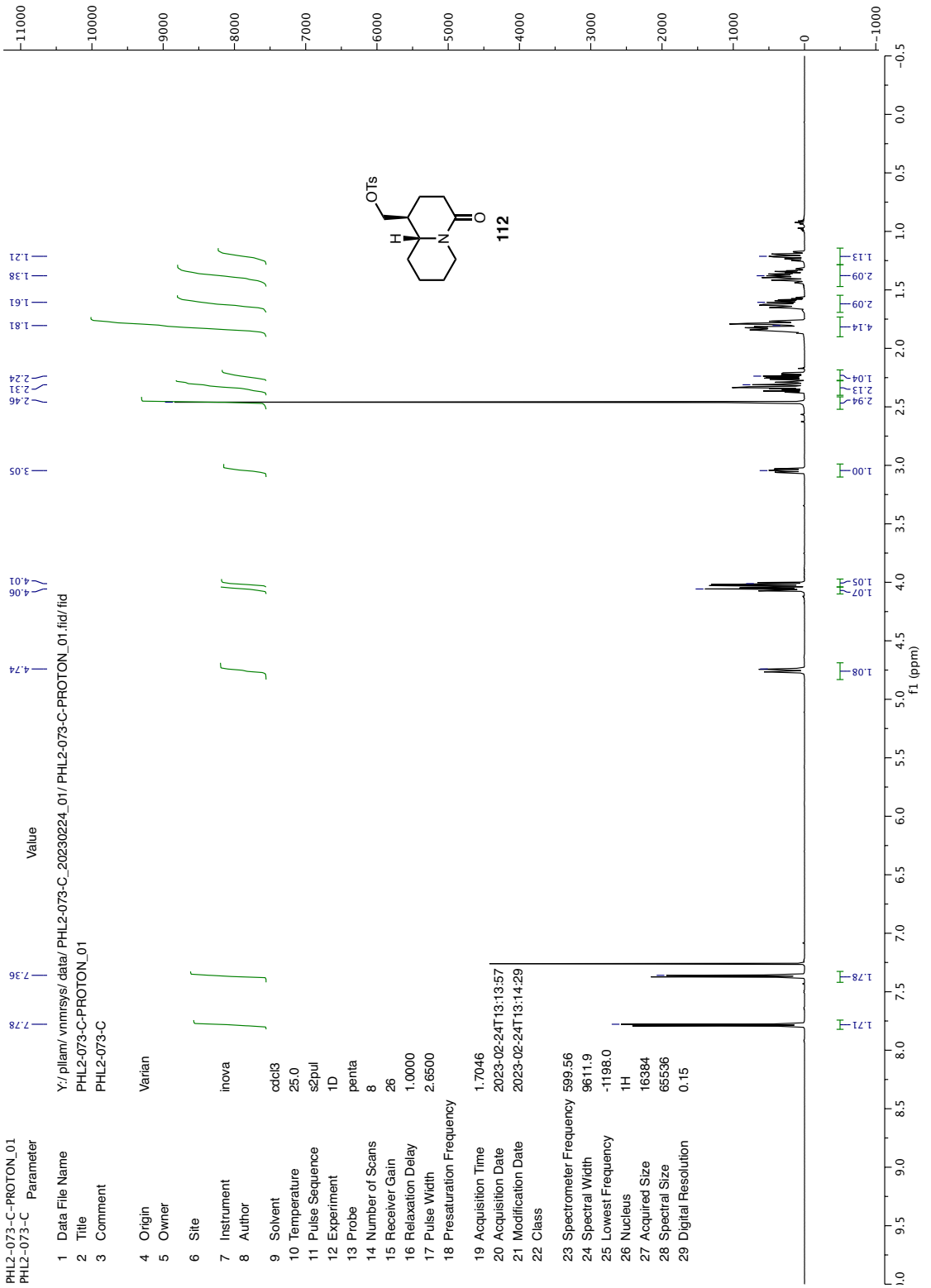

PHL1-151-B-Carbon.1.fid
Parameter
Value
1 Data File Name / Users/ jeffkerkovius/ Documents/ NMR Files/ Other PPL NMR/ PHL1/ PHL1-151-B-Carbon/ 1/ fid
2 Title PHL1-151-B-Carbon.1.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 50.3
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2021-11-15T17:15:34
21 Modification Date 2021-11-15T17:15:34
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1945.9
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
OH
H
N
(±)-lupinine (109)
66.18
65.24
57.30
57.20
38.24
31.64
29.86
25.75
24.76
23.09
f1 (ppm)

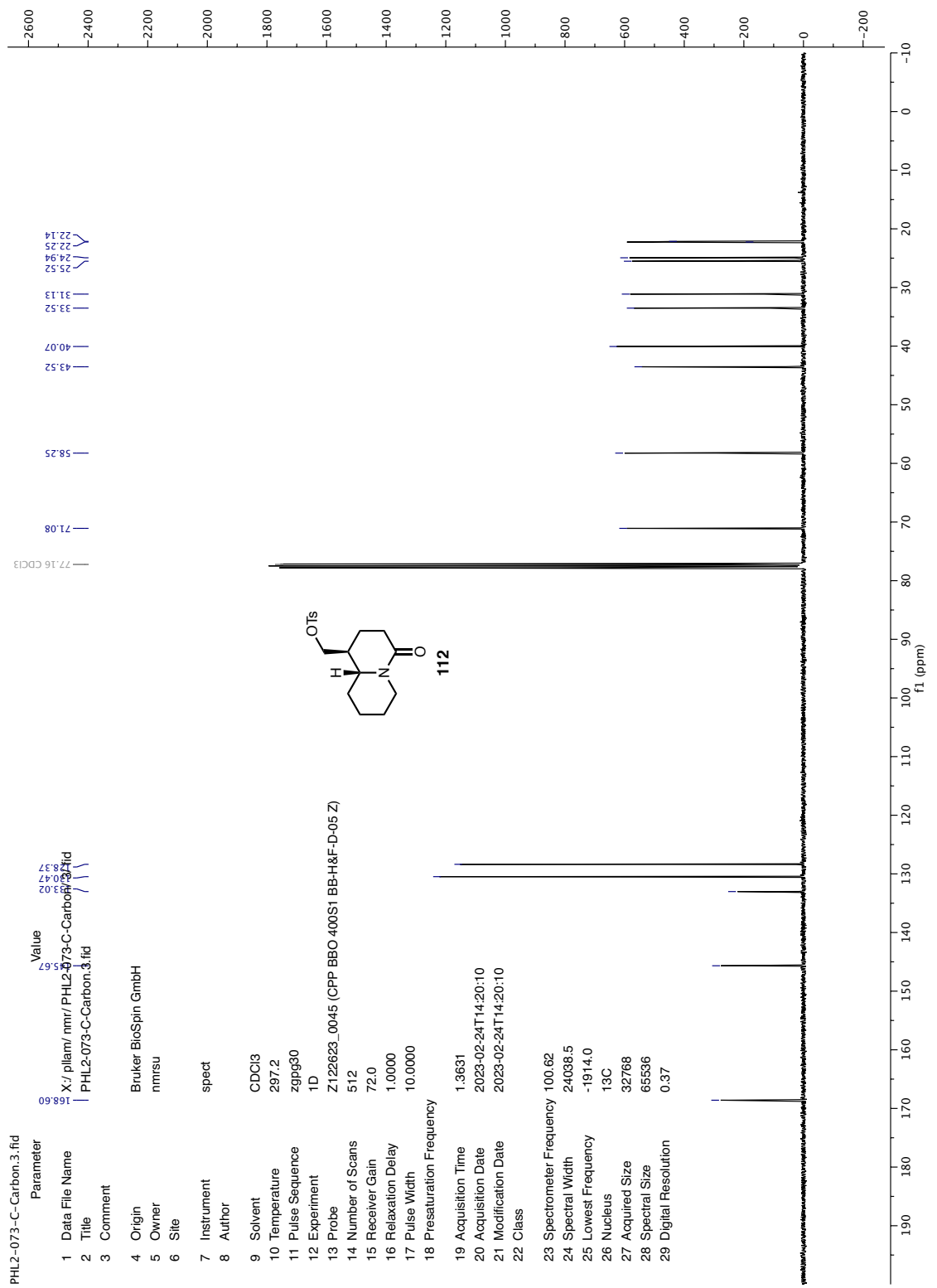

PHL2-069-C-PROTON_01
PHL2-069-C
Parameter
Value
1 Data File Name Y:/ pllam/ vnmrsys/ data/ PHL2-069-C_20230221_01/ PHL2-069-C-PROTON_01.fid/ fid
2 Title PHL2-069-C-PROTON_01
3 Comment PHL2-069-C
4 Origin Varian
5 Owner
6 Site
7 Instrument inova
8 Author
9 Solvent cdcl3
10 Temperature 25.0
11 Pulse Sequence s2pul
12 Experiment 1D
13 Probe penta
14 Number of Scans 8
15 Receiver Gain 28
16 Relaxation Delay 1.0000
17 Pulse Width 2.6500
18 Presaturation Frequency
19 Acquisition Time 1.7046
20 Acquisition Date 2023-02-21T15:52:20
21 Modification Date 2023-02-21T15:52:51
22 Class
23 Spectrometer Frequency 599.56
24 Spectral Width 9611.9
25 Lowest Frequency -1197.9
26 Nucleus 1H
27 Acquired Size 16384
28 Spectral Size 65536
29 Digital Resolution 0.15
5.89
5.54
4.84
4.30
3.76
2.65
2.57
2.46
2.40
2.26
2.04
1.95
1.00
0.98
1.13
0.97
3.25
1.17
1.11
1.02
1.17
1.09
2.33
1.11
OMe
O
O
H
N
O
110
f1 (ppm)

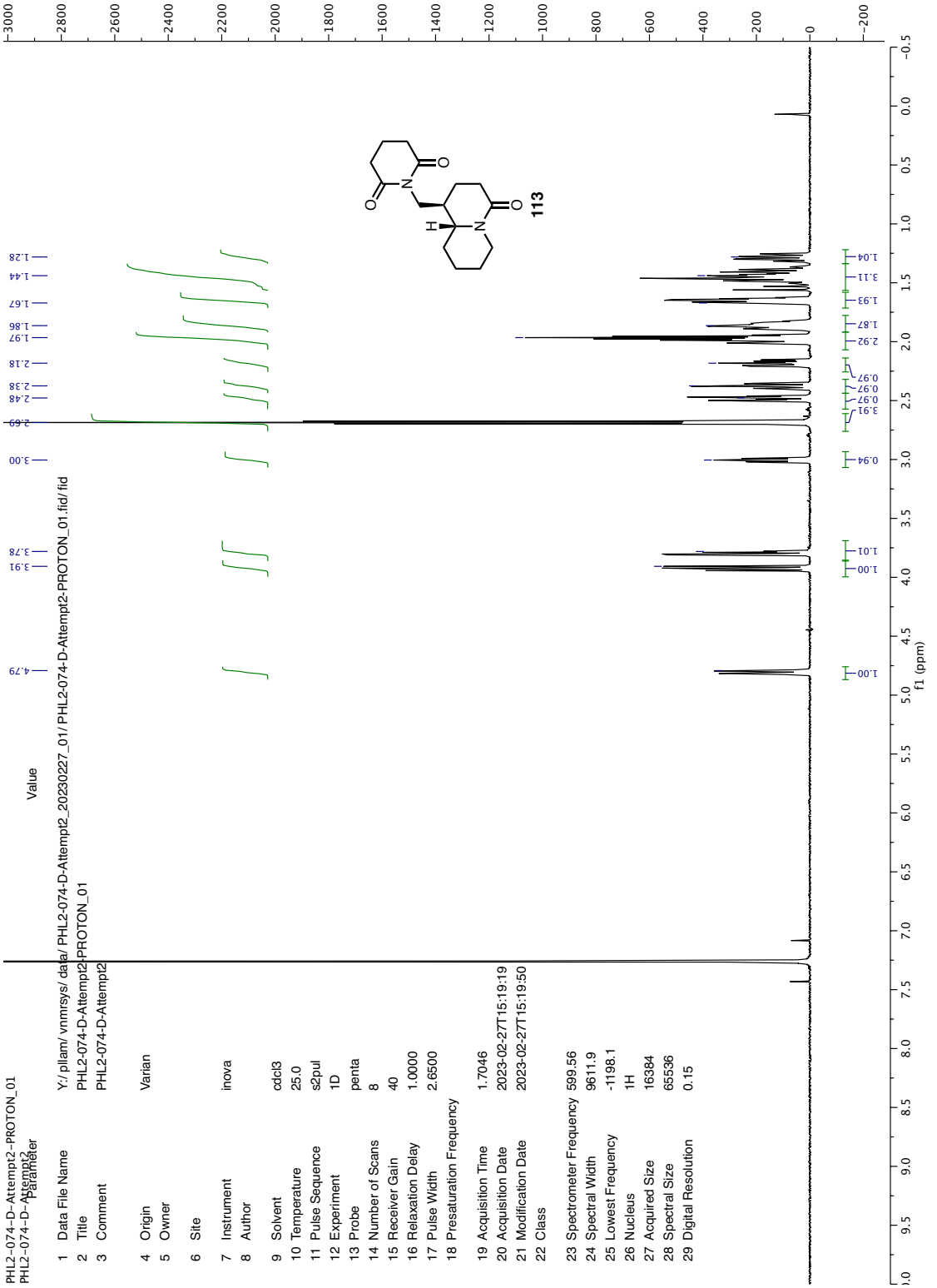

PHL2-069-C-Carbon.3.fid
Parameter
Value
1 Data File Name X:/ pllam/ nmr/ PHL2-069-C-Carbon/ 3/fid
2 Title PHL2-069-C-Carbon.3.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2023-02-21T16:47:05
21 Modification Date 2023-02-21T16:47:05
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1914.0
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
29 Digital Resolution 0.37
173.65
168.13
127.85
127.15
77.16 CDCl3
56.61
52.70
46.44
39.07
31.79
25.28
24.24
OMe
O
H
N
O
110
f1 (ppm)

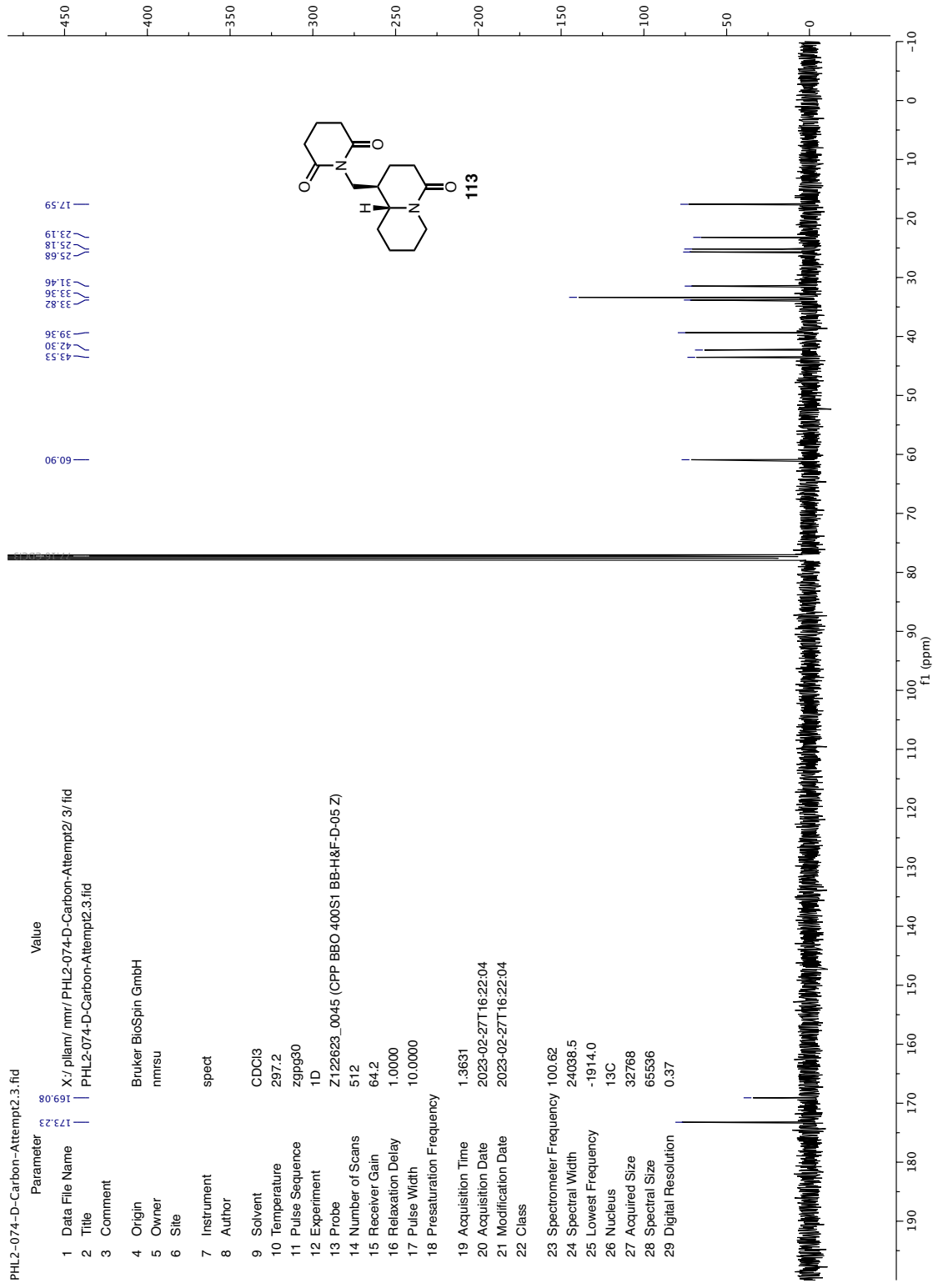

PHL2-072-B-PROTON_01
PHL2-072-B
Parameter Value
1 Data File Name Y:/ pllam/ vnmrsys/ data/ PHL2-072-B_20230223_01/ PHL2-072-B-PROTON_01.fid/ fid
2 Title PHL2-072-B-PROTON_01
3 Comment PHL2-072-B
4 Origin Varian
5 Owner
6 Site
7 Instrument inova
8 Author
9 Solvent cdcl3
10 Temperature 25.0
11 Pulse Sequence s2pul
12 Experiment 1D
13 Probe penta
14 Number of Scans 8
15 Receiver Gain 28
16 Relaxation Delay 1.0000
17 Pulse Width 2.6500
18 Presaturation Frequency
19 Acquisition Time 1.7046
20 Acquisition Date 2023-02-23T12:56:54
21 Modification Date 2023-02-23T12:57:25
22 Class
23 Spectrometer Frequency 599.56
24 Spectral Width 9611.9
25 Lowest Frequency -1198.0
26 Nucleus 1H
27 Acquired Size 16384
28 Spectral Size 65536
29 Digital Resolution 0.15
4.78
3.73
3.58
2.50
2.32
2.01
1.93
1.82
1.70
1.48
1.39
1.25
1.00
2.76
0.91
2.88
0.98
1.01
0.99
1.95
0.98
0.96
0.95
1.00
OMe
O
O
H
N
O
111
f1 (ppm)

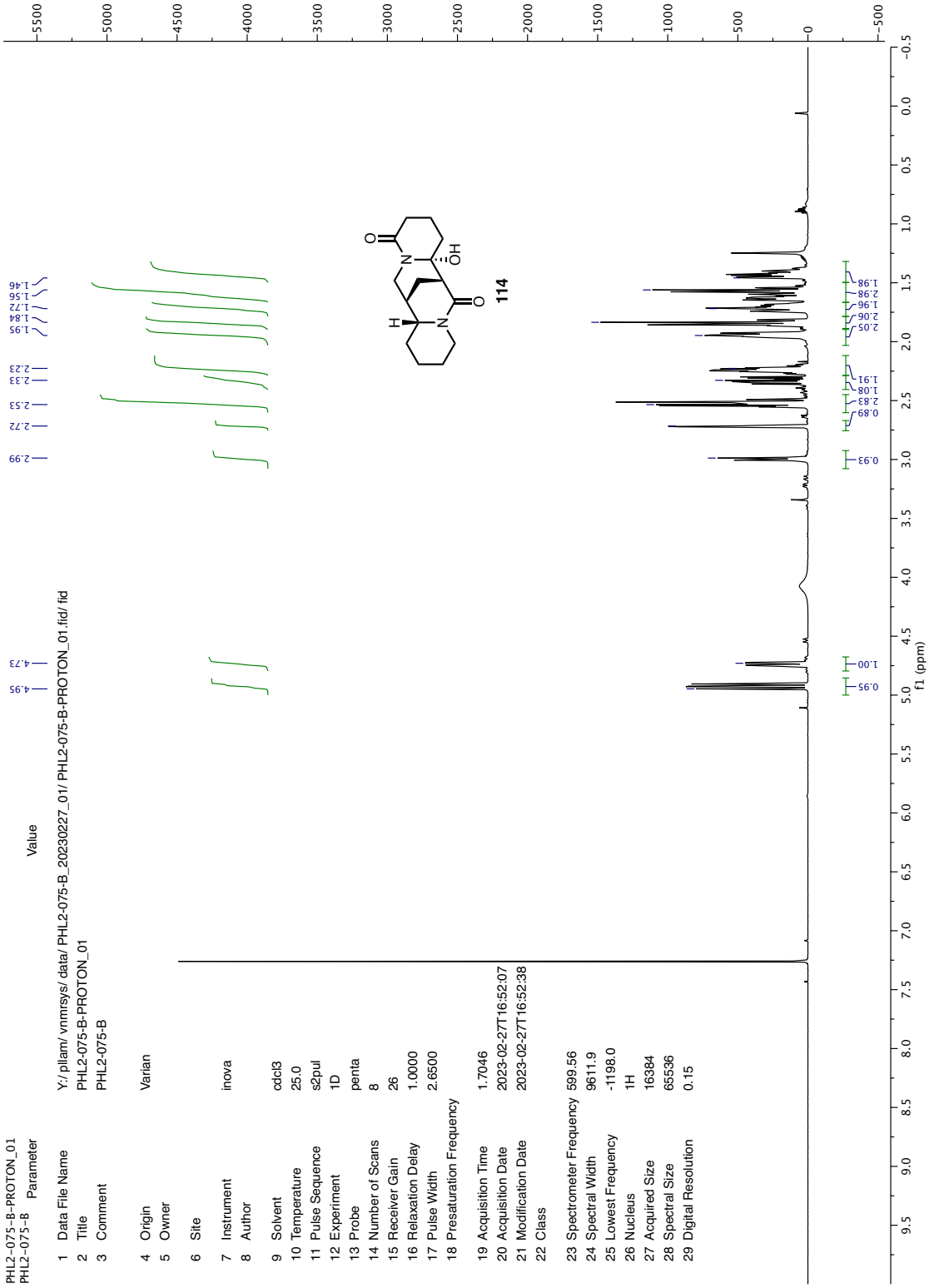

PHL2-072-B-Carbon.3.fid
Parameter Value
1 Data File Name X:/ pllam/ nmr/ PHL2-072-B-Carbon/ 3/ fid
2 Title PHL2-072-B-Carbon.3.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.1
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2023-02-23T13:30:55
21 Modification Date 2023-02-23T13:30:55
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1914.0
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
29 Digital Resolution 0.37
168.42
173.92
77.16 CDCl3
58.36
52.68
47.09
43.08
33.83
31.77
25.52
24.72
23.48
OMe
O
H
N
O
111
f1 (ppm)

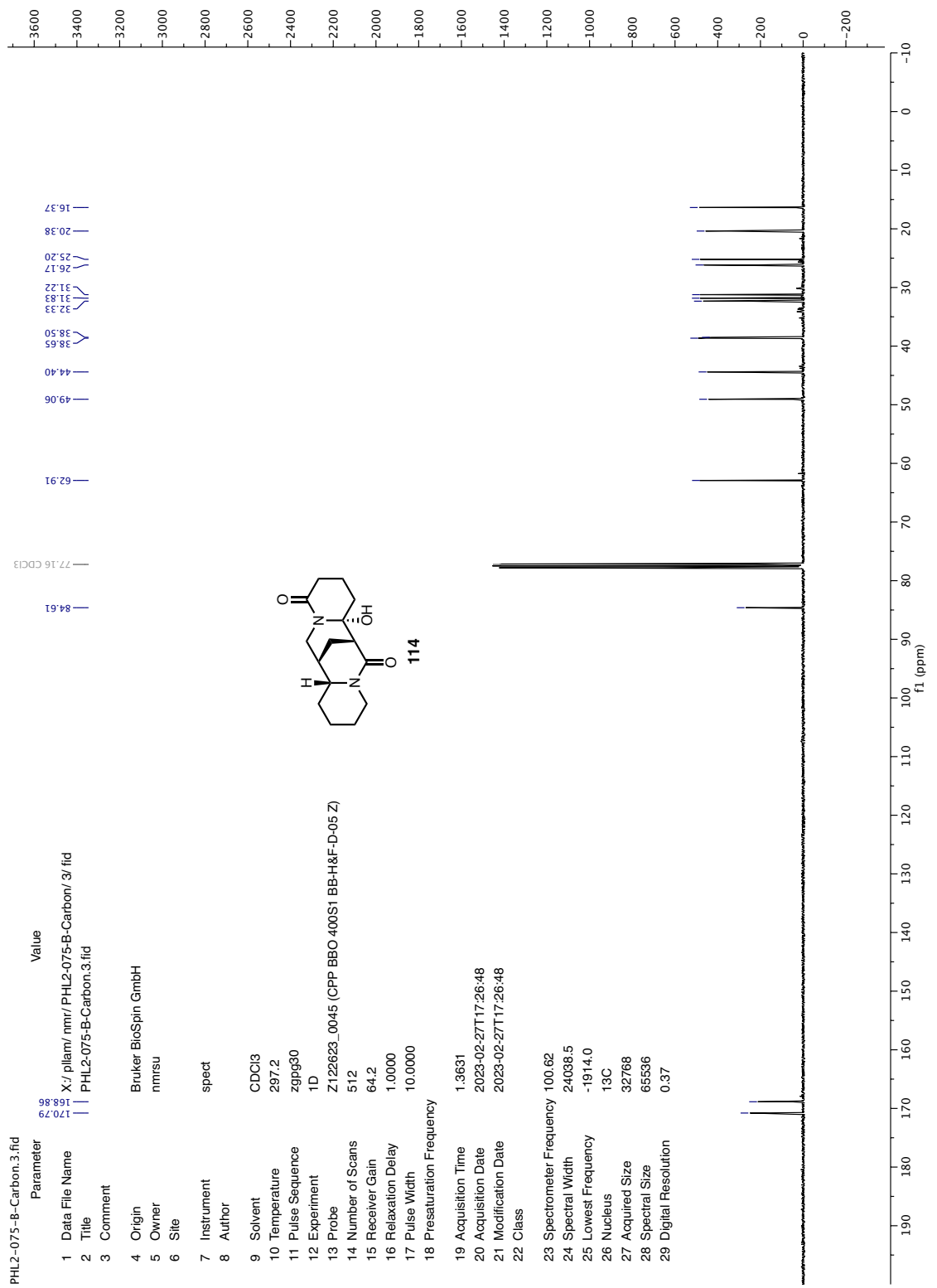

PHL2-073-C-PROTON_01
PHL2-073-C Parameter Value
1 Data File Name Y:/ pllam/ vnmrsys/ data/ PHL2-073-C_20230224_01/ PHL2-073-C-PROTON_01.fid/ fid
2 Title PHL2-073-C-PROTON_01
3 Comment PHL2-073-C
4 Origin Varian
5 Owner
6 Site
7 Instrument inova
8 Author
9 Solvent cdcl3
10 Temperature 25.0
11 Pulse Sequence s2pul
12 Experiment 1D
13 Probe penta
14 Number of Scans 8
15 Receiver Gain 26
16 Relaxation Delay 1.0000
17 Pulse Width 2.6500
18 Presaturation Frequency
19 Acquisition Time 1.7046
20 Acquisition Date 2023-02-24T13:13:57
21 Modification Date 2023-02-24T13:14:29
22 Class
23 Spectrometer Frequency 599.56
24 Spectral Width 9611.9
25 Lowest Frequency -1198.0
26 Nucleus 1H
27 Acquired Size 16384
28 Spectral Size 65536
29 Digital Resolution 0.15
7.78
7.36
4.74
4.06
4.01
3.05
2.46
2.31
2.24
1.81
1.61
1.38
1.21
OTs
H
N
O
112
1.71
1.78
1.08
1.07
1.05
1.00
2.94
2.13
1.04
4.14
2.09
2.09
1.13
f1 (ppm)

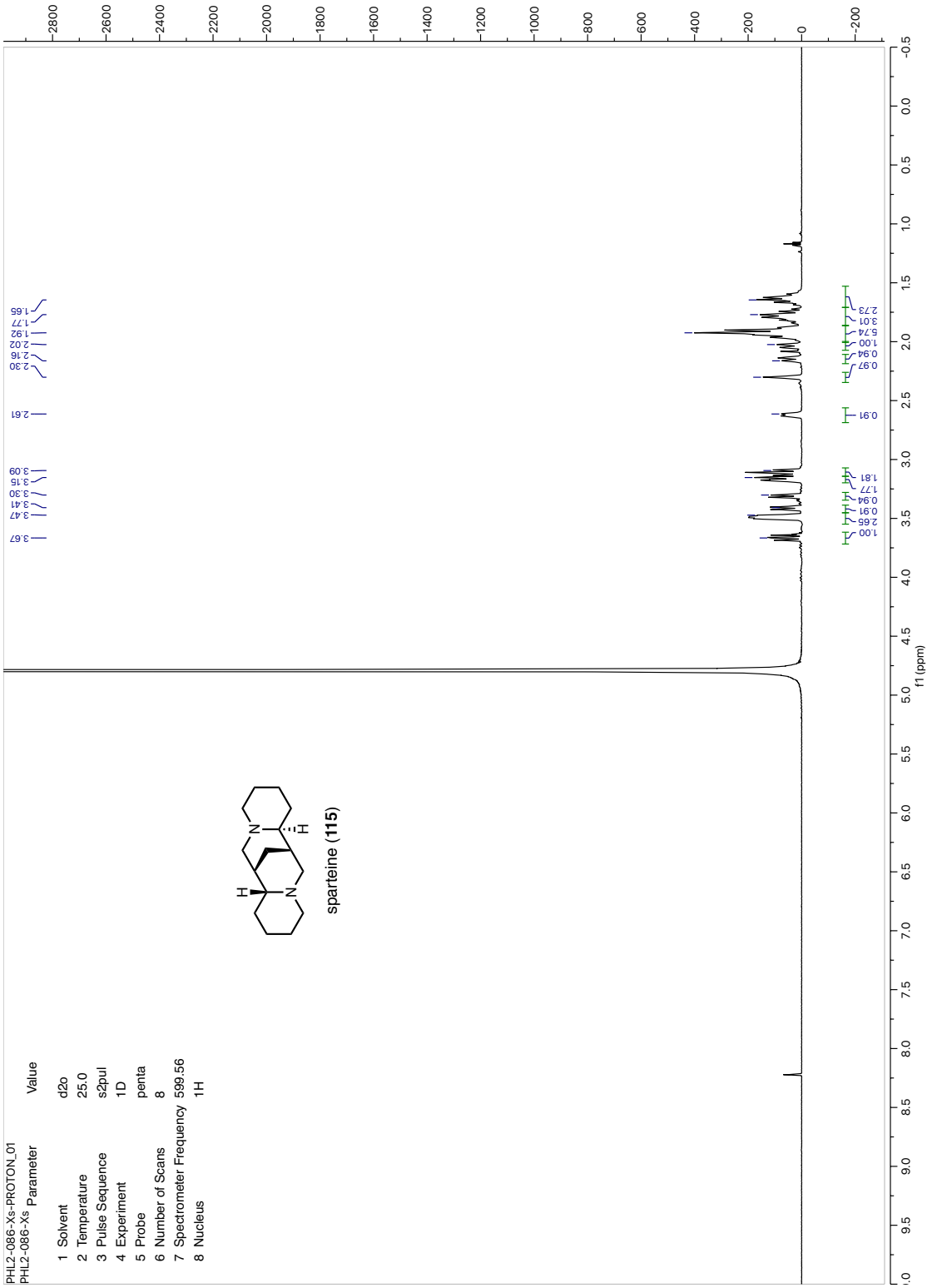

PHL2-073-C-Carbon.3.fid
Parameter Value
1 Data File Name X:/ pllam/ nmr/ PHL2-073-C-Carbon.3.fid
2 Title PHL2-073-C-Carbon.3.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 72.0
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2023-02-24T14:20:10
21 Modification Date 2023-02-24T14:20:10
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1914.0
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
29 Digital Resolution 0.37
168.60
135.67
130.02
128.47
128.37
77.16 CDCl3
71.08
58.25
43.52
40.07
33.52
31.13
25.52
24.94
22.25
22.14
OTs
H
N
O
112
f1 (ppm)

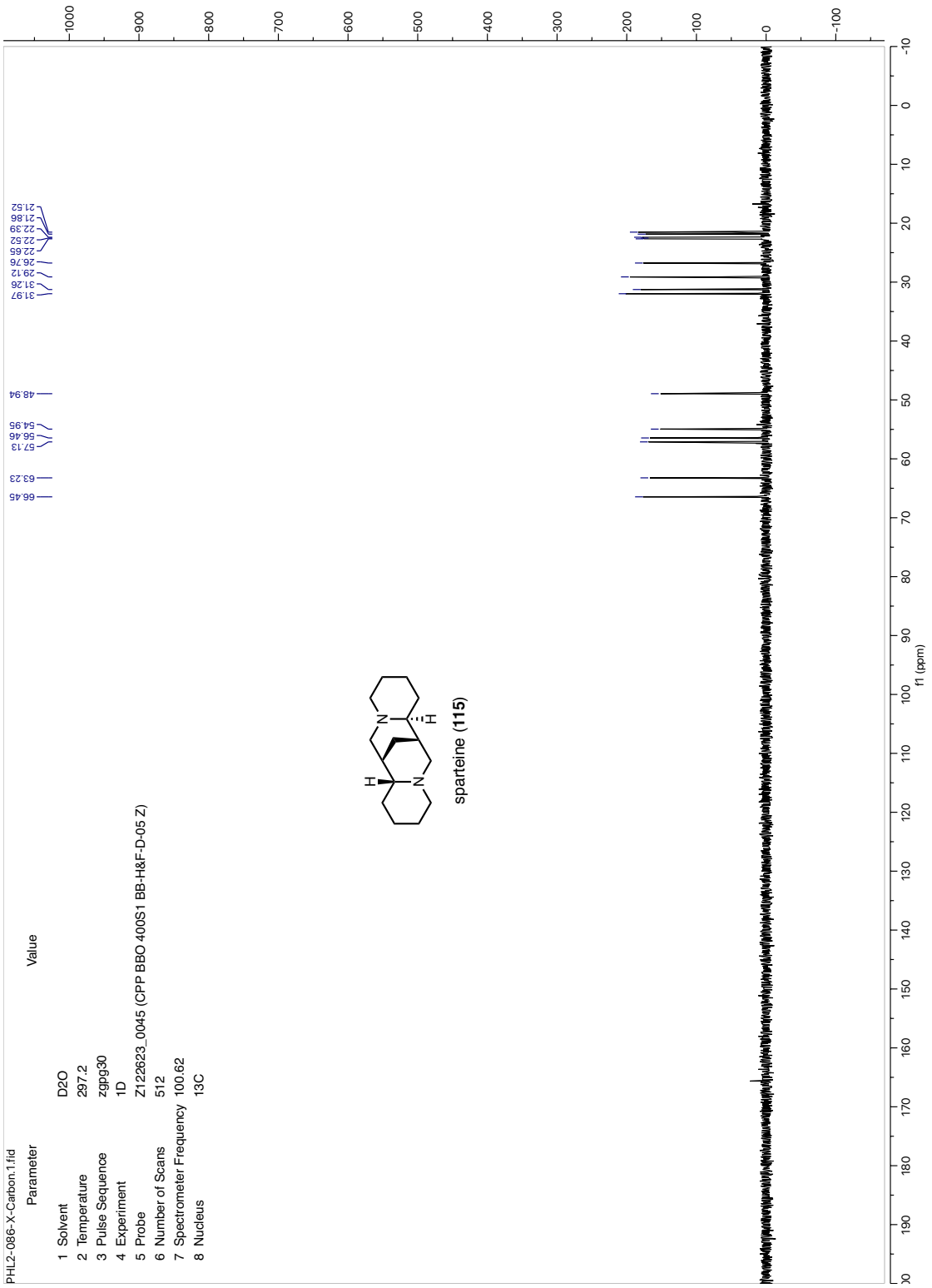

PHL2-074-D-Attempt2-PROTON_01
PHL2-074-D-Attempt2
Parameter Value
1 Data File Name Y:/ pllam/ vnmrsys/ data/ PHL2-074-D-Attempt2_20230227_01/ PHL2-074-D-Attempt2-PROTON_01.fid/ fid
2 Title PHL2-074-D-Attempt2-PROTON_01
3 Comment PHL2-074-D-Attempt2
4 Origin Varian
5 Owner
6 Site
7 Instrument inova
8 Author
9 Solvent cdcl3
10 Temperature 25.0
11 Pulse Sequence s2pul
12 Experiment 1D
13 Probe penta
14 Number of Scans 8
15 Receiver Gain 40
16 Relaxation Delay 1.0000
17 Pulse Width 2.6500
18 Presaturation Frequency
19 Acquisition Time 1.7046
20 Acquisition Date 2023-02-27T15:19:19
21 Modification Date 2023-02-27T15:19:50
22 Class
23 Spectrometer Frequency 599.56
24 Spectral Width 9611.9
25 Lowest Frequency -1198.1
26 Nucleus 1H
27 Acquired Size 16384
28 Spectral Size 65536
29 Digital Resolution 0.15
113
f1 (ppm)


PHL2-074-D-Carbon-Attempt2.3.fid
Parameter Value
1 Data File Name X:/ pllam/ nmr/ PHL2-074-D-Carbon-Attempt2/ 3/ fid
2 Title PHL2-074-D-Carbon-Attempt2.3.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 64.2
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2023-02-27T16:22:04
21 Modification Date 2023-02-27T16:22:04
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1914.0
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
29 Digital Resolution 0.37
173.23
169.08
77.59
60.90
43.53
42.30
39.36
33.82
33.36
31.46
25.68
25.18
23.19
17.59
113
f1 (ppm)


PHL2-075-B-PROTON_01
PHL2-075-B Parameter Value
1 Data File Name Y:/ pllam/ vnmrsys/ data/ PHL2-075-B_20230227_01/ PHL2-075-B-PROTON_01.fid/ fid
2 Title PHL2-075-B-PROTON_01
3 Comment PHL2-075-B
4 Origin Varian
5 Owner
6 Site
7 Instrument inova
8 Author
9 Solvent cdcl3
10 Temperature 25.0
11 Pulse Sequence s2pul
12 Experiment 1D
13 Probe penta
14 Number of Scans 8
15 Receiver Gain 26
16 Relaxation Delay 1.0000
17 Pulse Width 2.6500
18 Presaturation Frequency
19 Acquisition Time 1.7046
20 Acquisition Date 2023-02-27T16:52:07
21 Modification Date 2023-02-27T16:52:38
22 Class
23 Spectrometer Frequency 599.56
24 Spectral Width 9611.9
25 Lowest Frequency -1198.0
26 Nucleus 1H
27 Acquired Size 16384
28 Spectral Size 65536
29 Digital Resolution 0.15
4.95
4.73
2.99
2.72
2.53
2.33
2.23
1.95
1.84
1.72
1.56
1.46
114
1.00
0.95
0.93
0.89
2.83
1.91
1.08
2.98
1.96
2.06
2.05
1.98
f1 (ppm)


PHL2-075-B-Carbon.3.fid
Parameter Value
1 Data File Name X:/ pllam/ nmr/ PHL2-075-B-Carbon/ 3/ fid
2 Title PHL2-075-B-Carbon.3.fid
3 Comment
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Site
7 Instrument spect
8 Author
9 Solvent CDCl3
10 Temperature 297.2
11 Pulse Sequence zgpg30
12 Experiment 1D
13 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
14 Number of Scans 512
15 Receiver Gain 64.2
16 Relaxation Delay 1.0000
17 Pulse Width 10.0000
18 Presaturation Frequency
19 Acquisition Time 1.3631
20 Acquisition Date 2023-02-27T17:26:48
21 Modification Date 2023-02-27T17:26:48
22 Class
23 Spectrometer Frequency 100.62
24 Spectral Width 24038.5
25 Lowest Frequency -1914.0
26 Nucleus 13C
27 Acquired Size 32768
28 Spectral Size 65536
29 Digital Resolution 0.37
170.79
168.86
84.61
77.16 CDCl3
62.91
49.06
44.40
38.65
38.50
32.33
31.83
31.22
26.17
25.20
20.38
16.37
OH
114
f1 (ppm)


PHL2-086-Xs-PROTON_01
PHL2-086-Xs
Parameter Value
1 Solvent d2o
2 Temperature 25.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe penta
6 Number of Scans 8
7 Spectrometer Frequency 599.56
8 Nucleus 1H
sparteine (115)
f1 (ppm)


PHL2-086-X-Carbon.1.fid
Parameter Value
1 Solvent D2O
2 Temperature 297.2
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 512
7 Spectrometer Frequency 100.62
8 Nucleus 13C
21.52
21.86
22.39
22.52
22.65
26.76
29.12
31.26
31.97
48.94
54.95
56.46
57.13
63.23
66.45
sparteine (115)
f1 (ppm)

Chapter 3

A Convergent Fragment Coupling Strategy to Access Quaternary Stereogenic Centers[†]

3.1 INTRODUCTION

The formation of quaternary stereogenic centers via convergent fragment coupling is a longstanding challenge in organic synthesis.[2] Here, we report a strategy for the formation of quaternary stereogenic centers in polycyclic systems based upon the semipinacol reaction. In the key transformation, two fragments of a similar size and complexity are joined by a 1,2-addition of an alkenyl lithium to an epoxy ketone, and the resulting epoxy silyl ether undergoes a semi-pinacol rearrangement catalyzed by *N*-(trimethylsilyl)bis(trifluoromethanesulfonyl)imide ($TMSNTf_2$) or trimethylsilyl

[†] This chapter has been reproduced from a published manuscript.[1] J. K. K was supported by an NSERC PGS-D fellowship (PGSD3-532535-2019). A. R. W and V. W. M were supported by an NSF Graduate Research Fellowship (DGE-1144469). S. E. R. acknowledges financial support from the NIH (R35GM118191).

trifluoromethanesulfonate (TMSOTf). Polycyclic scaffolds were generated in high yields and the reaction conditions tolerated a variety of functional groups including esters, silyl ethers, enol ethers, and aryl triflates. This method provides a useful strategy for the synthesis of complex polycyclic natural product-like scaffolds with quaternary stereogenic centers from simplified fragments.

3.2 CONVERGENT FRAGMENT COUPLING USING A 1,2-ADDITION SEMI-PINACOL REARRANGEMENT SEQUENCE

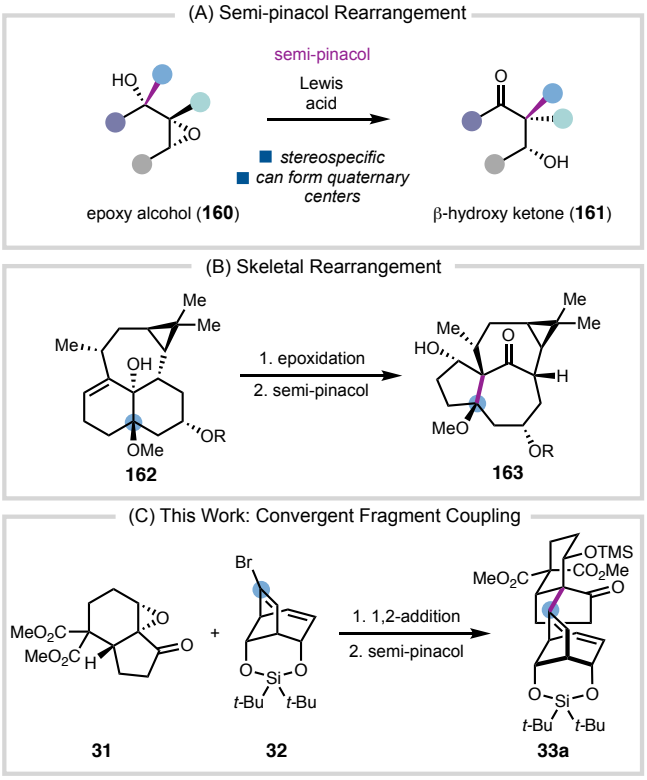
3.2.1 Challenges with Quaternary Stereocenter Formation

Convergent fragment coupling is a strategic approach that can rapidly generate complex molecules by joining fragments of a similar size and complexity.[3–5] The independent synthesis of each fragment can be completed in parallel and this approach reduces the potential for competitive functional group reactivity. Many elegant syntheses have been developed utilizing a fragment coupling as a key strategic disconnection, often employing well established chemistry such as the Michael addition, the Diels–Alder reaction, transition metal-catalyzed cross-coupling, and 1,2-nucleophilic addition.[6,7] A major limitation to these approaches is the challenge of accessing stereogenic quaternary carbons, which are common motifs in natural products.[2] Stereocontrol at attached-ring quaternary centers represents an especially difficult task due to the lack of well-defined stereocontrol elements, in contrast to the more rigid ring topologies of bridging, spirocyclic, and fused ring systems.[8,9]

A powerful method to form quaternary stereogenic centers is the semi-pinacol rearrangement, a stereospecific reaction that can convert epoxy alcohols to α-quaternary

ketones (Figure 3.1A).[10–32] The strategic application of the semi-pinacol rearrangement in total synthesis has predominately focused on skeletal rearrangement (for example, Figure 3.1B) rather than as part of a fragment coupling tactic.[33–38] There have been relatively few applications of the semi-pinacol rearrangement as fragment coupling strategies in total synthesis,[39,40] which motivated us to develop a general set of conditions based upon our work towards the C19 diterpenoid alkaloids (Figure 3.1C).[40]

Figure 3.1. *Synthetic Strategies Using the Semi-Pinacol Rearrangement.*



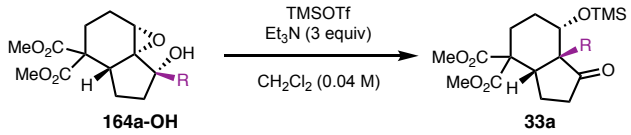
3.2.2 Reaction Optimization

Our initial studies began with the investigation of the semi-pinacol rearrangement of epoxide **164a-OH**, an intermediate in our synthesis of the diterpenoid alkaloid (–)-talatisamine (**34**).[40] Treatment alcohol **164a–OH** with 1.2 equiv of TMSOTf at –10 °C

resulted only in silylation of the tertiary alcohol to give **164a** in 97% isolated yield (Table 3.1A, entry 1). However, performing the reaction with 1.5 equiv of TMSOTf at 21 °C provided β-silyoxyketone **33a** in 33% yield along with several other side products (entry 2). Although the yield of **33a** was low, this result did confirm the feasibility of migrating the bicyclic fragment. Since migration occurred after silyl ether formation when excess TMSOTf was used, we posited that use of **164a** as a substrate in conjunction with a stronger Lewis acid could allow the reaction to be conducted at low temperature, and could potentially improve the yield of **33a** (Table 3.1B).[41] When **164a** was treated with 1.0 equiv of $TMSNTf_2$ at –78 °C for 45 minutes, starting material was consumed, but low yields of **33a** were again observed (entry 1). Close monitoring of the reaction at early timepoints revealed that the reaction was very fast; indeed, stopping the reaction after 60 seconds improved the yield to 50% (entry 2). Further improvement was obtained by lowering the reaction temperature to –94 °C and quenching 10 seconds after addition of $TMSNTf_2$ (entry 3). Although we were pleased with this discovery, it was not well suited for up-scaling.

Table 3.1. *Synthetic Strategies Using the Semi-Pinacol Rearrangement.*

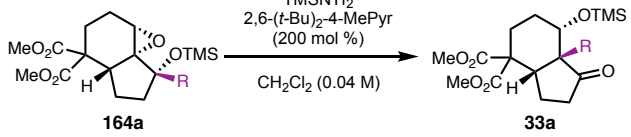
a



164a-OH **33a**

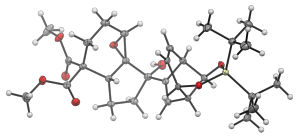
Entry	Lewis Acid (Equiv)	Temperature	Product	Yield (%)
1	TMSOTf (1.2)	–10 °C	**164a**	97
2	TMSOTf (1.5)	21 °C	**33a**	33

b



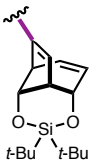
164a **33a**

Entry	Equiv LA	Temperature	Time	Yield (%)
1	1.0	–78 °C	45 min	25
2	1.0	–78 °C	60 sec	50
3	1.0	–94 °C	10 sec	90
4[a]	0.1	–78 °C to 0 °C	2.5 h	99
5[b]	0.1	–78 °C	15 min	97



164a-OH

R=

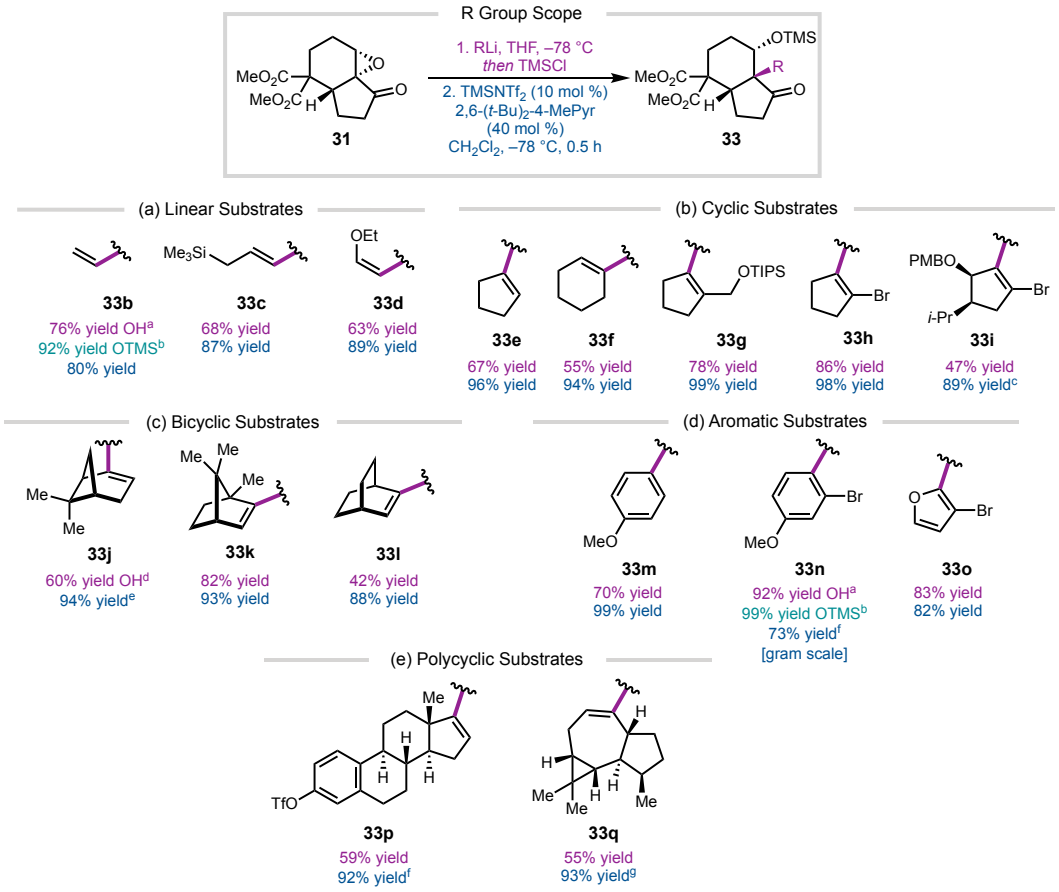


[a] 110 mol % of 2,6-(*t*-Bu)$_2$-4-MePyr. [b] 110 mol % of 2,6-(*t*-Bu)$_2$-4-MePyr on 4.3 g scale

Given that the use of silyl ether **164a** negated the need for stoichiometric $TMSNTf_2$, we evaluated using this Lewis acid catalytically. Gratifyingly, treatment of **164a** with 10 mol % $TMSNTf_2$ at –78 °C and then warming to 0 °C over 2.5 hours gave **33a** in 99% yield (entry 4). The optimal conditions for gram scale were treatment of **164a** with 10 mol % $TMSNTf_2$ at –78 °C for 15 minutes without warming, which provided semi-pinacol product **33a** in a 97% yield (entry 5). To our knowledge, $TMSNTf_2$ has not previously been used as a catalyst for the semi-pinacol reaction.

3.2.3 Substrate Scope

Figure 3.2. *Scope of the Migrating Group.*

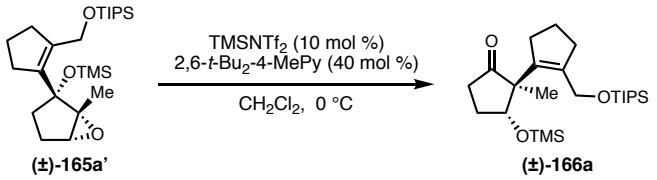


Isolated yields of 1,2-addition product in purple, isolated yield of silylation (if separate step) in teal, isolated yields of semipinacol product in blue.
[a] Yield of 1,2-addition from Grignard reagent without TMSCl trapping. [b] Yield of TMS protection. [c] 50 mol % $TMSNTf_2$, 110 mol % 2,6-(*t*-Bu)$_2$-4-MePyr, –78 °C, 4 h.
[d] Yield of 1,2-addition from alkenyl lithium without TMSCl trapping. [e] TMSOTf (5 equiv), Et_3N (6 equiv), 0 °C to 21 °C, 1 h.
[f] 50 mol % $TMSNTf_2$, 110 mol % 2,6-(*t*-Bu)$_2$-4-MePyr, 0 °C, 0.5 h. [g] 30 mol % $TMSNTf_2$, 100 mol % 2,6-(*t*-Bu)$_2$-4-MePyr, –78 °C, 4 h.

With optimized conditions in hand, we examined the scope of the convergent fragment coupling strategy (Figure 3.2). Although the yields of the alkenyl lithium 1,2-addition were substrate dependent, the semi-pinacol rearrangement gave consistently high yields. Simple linear alkenes, including an allylic silane and enol ether, migrated with high yields (**33c**, **33d**). Cyclic and bicyclic alkenyl substrates also provided the rearrangement products (**33e–33l**) in excellent yields, showcasing the ability for this reaction to form attached-ring motifs bearing hindered quaternary centers. The fragment coupling tolerated substrates bearing TIPS- and PMB-protected alcohols (**33g**, **33i**), functional groups that

could be useful in natural product synthesis applications. Aromatic substrates were also found to be viable in this reaction, with products **33m–33o** obtained in high yields. In addition to the gram scale synthesis of **33a**, the semi-pinacol rearrangement to yield aryl bromide **33n** was carried out on gram scale in 73% yield. We were able to effect the migration of large polycyclic alkenes (**33p–33q**) in yields greater than 90%. Notably, these conditions are relatively mild and tolerated allyl ethers and enol ethers (**33d**, **33g**, **33i**), which are often reactive under common semi-pinacol rearrangement conditions.[12] A small additive screen found that the reaction tolerates acetal (Table 3.2, entry 2) and ester (entry 3) functional groups, while an *N*-*t*-butyl-carboxylate-protected amine (entry 4) inhibited product formation.

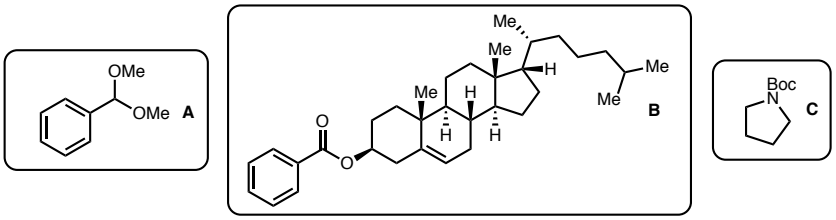
Table 3.2. *Protecting Group Compatibility Additive Screen.*



(±)-165a' **(±)-166a**

Entry	Additive	Reaction Yield	Recovered **165a'**	Mass Balance	Additive Recovery
1	none	93%	0%	93%	N/A
2	**A**	86%	0%	86%	76% recovery
3	**B**	92%	0%	92%	93% recovery
4	**C**	20%	71%	91%	87% recovery

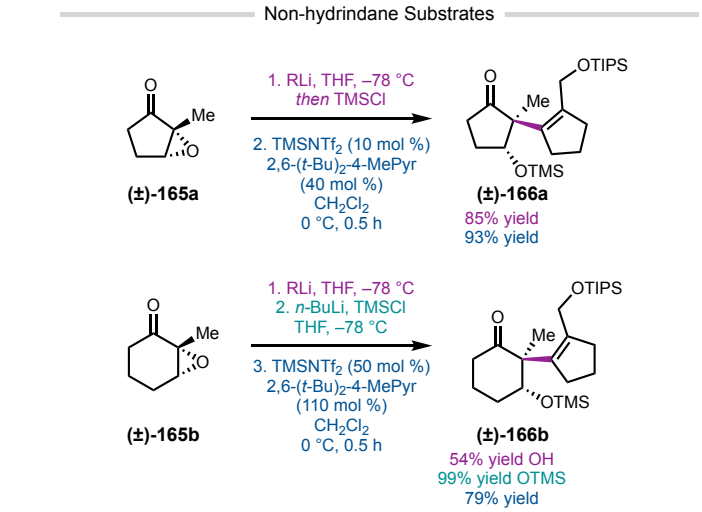
all yields in table are qNMR yields with pyrazine internal standard in $CDCl_3$



We also investigated simpler monocyclic ketones for their ability to rearrange using $TMSNTf_2$ as the Lewis acid (Figure 3.3). Using 10 mol % $TMSNTf_2$, cyclopentanone **(±)-**

166a was prepared in 93% yield. Although the cyclohexyl substrate was less reactive, by increasing the catalyst loading to 50 mol %, the semi-pinacol product **(±)-166b** was obtained in 79% yield.

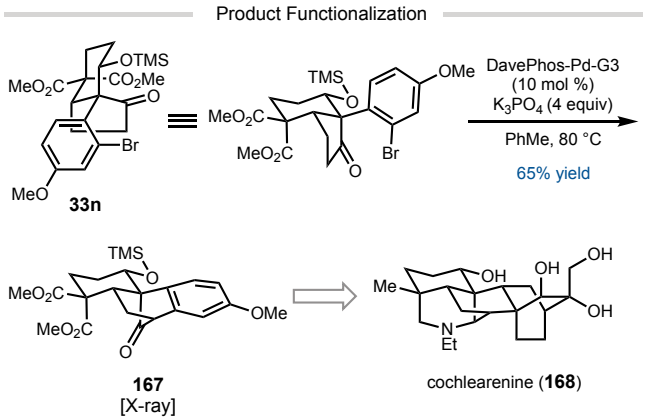
Figure 3.3. *Substrates Derived from Monocyclic Epoxyketones.*



3.2.4 Product Derivatization

Several of the products prepared by this method contained alkenyl or aryl bromide substituents (e.g. **33h**, **33i**, **33n**, and **33o**), which can allow for further functionalization of the product. For example, treatment of ketone **33n** with DavePhos-Pd-G3 in the presence of K_3PO_4 at 80 °C resulted in clean enolate arylation to give tetracycle **167** (Scheme 3.1).[42] We anticipate that tetracycle **167** could serve as an intermediate for the synthesis of the denudatine-type diterpenoid alkaloids such as cochlearnine (**168**).[43,44]

Scheme 3.1. *Intramolecular Enolate Arylation of* ***33n****.*



3.3 CONCLUDING REMARKS

The method disclosed in this chapter was inspired by work on the total synthesis of the C19 diterpenoid alkaloids.[40] Strategically it was envisioned in the total synthesis of talatisamine that two fragments of a similar size and complexity could be joined via the central B ring of the natural product. This strategy was successfully accomplished by performing a 1,2-addition semi-pinacol rearrangement sequence to join two fragments, which created an all-carbon quaternary center stereospecifically. It was envisioned that this innovative strategy could be applicable to the synthesis of additional natural products, which motivated us to explore the generality of this approach. It was found that a variety of different functional groups were tolerated in this transformation sequence including enol ethers, allylic silyl ethers, esters, allyl silanes, aryl triflates, and sterically congested terpenes. *N*-Boc pyrrolidine was found to inhibit the semi-pinacol rearrangement, and some degradation of acetals was also observed. The resulting semi-pinacol products could be transformed into tetracyclic precursors to additional diterpenoid alkaloids, the total synthesis of which are currently under investigation in our lab. In addition, this sequence also works on simpler epoxyketone substrates demonstrating the applicability of this

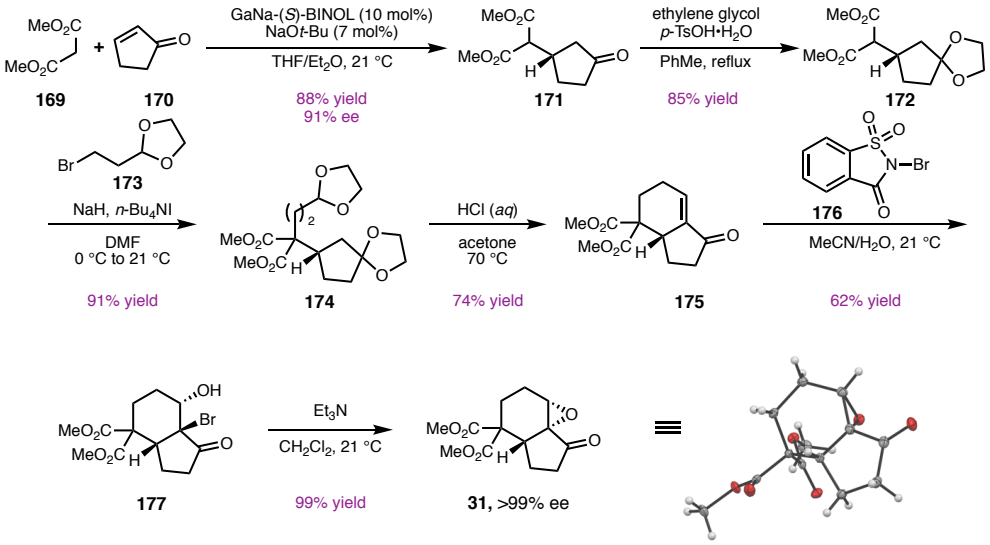
approach to form a variety of different quaternary stereocenters. In summary, we have developed a convergent fragment coupling approach to access a variety of quaternary centers in polycyclic systems in high yields with potential applications in natural product total synthesis.

3.4 EXPERIMENTAL SECTION

Unless otherwise stated, reactions were performed under an inert atmosphere (dry N_2) using freshly dried solvents and standard Schlenk techniques. Glassware was oven-dried at 120 °C for a minimum of four hours. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (ACN), methanol (MeOH), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. CH_2Cl_2 (D150-4), benzene (PhH, OmniSolv, BX0212-1), acetonitrile (A998-4), pentane (P399-4), acetone (A18-20), hexanes (H292-20), and *n*-butanol (A399-4) were purchased from Fisher and used as received. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from VWR (EM-DX1727-6) and used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV or by staining with p-anisaldehyde or potassium permanganate ($KMnO_4$). Flash column chromatography was performed as described by Still et al.[45] using silica gel (particle size 0.032–0.063) purchased from MilliporeSigma. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), a Bruker 400 MHz Spectrometer with broadband iProbe, or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CDCl_3$ (1H, δ = 7.26; 13C, δ = 77.16), CD_2Cl_2 (^1H, δ = 5.32; ^{13}C, δ = 53.84) or CD_3CN (^1H, δ = 1.94; ^{13}C,

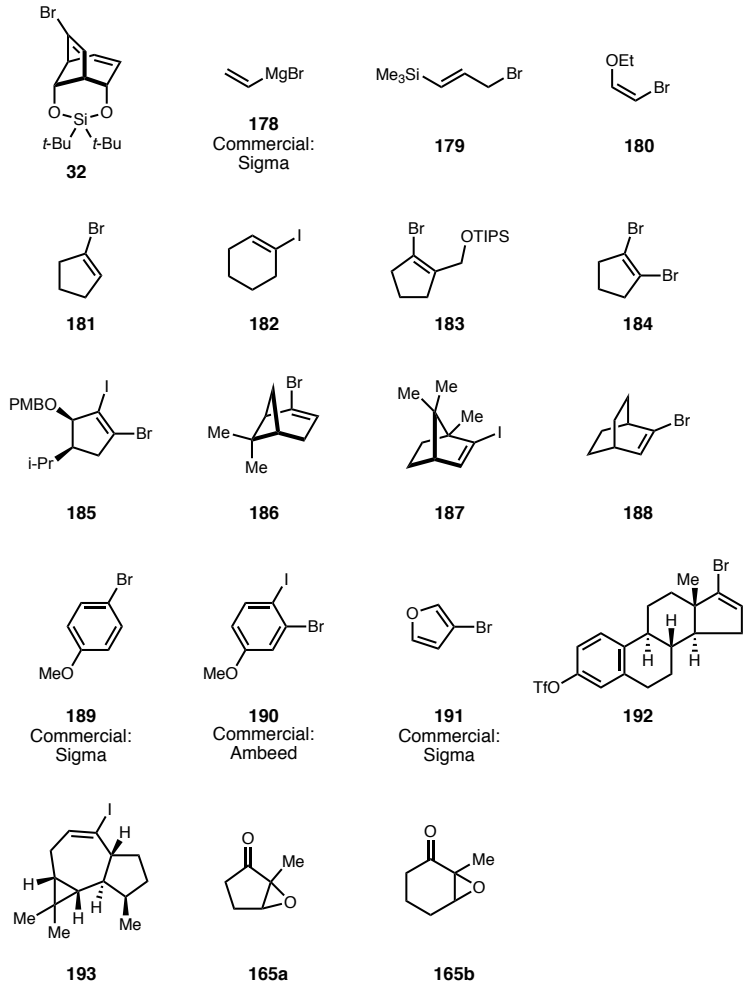
δ = 118.3). $CDCl_3$ was stored over anhydrous potassium carbonate (K_2CO_3). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS data were acquired using an Agilent 6230 Series time-of-flight (TOF) mass spectrometer with an Agilent G1978A ion trap or by LC-MS using a Waters LCT Premier XE Electrospray TOF mass spectrometer interfaced with Waters UPLC chromatography, or by GC-MS interfaced with a JEOL JMS-T2000 GC AccuTOF GC-Alpha with Field Ionization. Molecular formulas of the compounds [M] are given, with the observed ion fragment in brackets, e.g. $[M+H]^+$. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Melting points were determined using a Büchi B-545 capillary melting point apparatus, and the values reported are uncorrected. Unless otherwise stated, chemicals and reagents were used as received. Stereochemistry of products was assigned analogous to compounds **164a-OH** (CCDC # 2083859) and **167** (CCDC # 2224814), both of which have had their absolute configuration confirmed via X-ray crystallography. The X-ray structure of **164a-OH** has been previously reported by Reisman and appears as **S11** in their SI.[40]

Scheme 3.2. *Preparation of enantiopure epoxyketone* ***(+)-31****.*

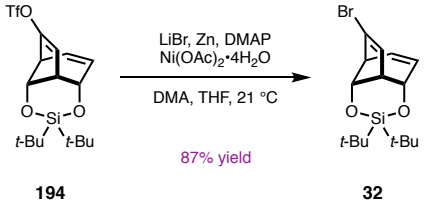


31 was prepared according to a six step procedure reported by Reisman, and ^{1}H NMR data matched their report.[40]

Figure 3.4. *Preparation of alkenyl halides for 1,2-additions.*



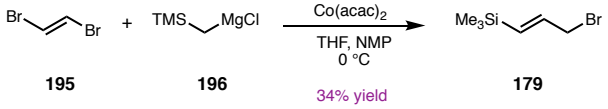
Preparation of 32:



Alkenyl triflate **194** was prepared in 11 steps according to a procedure reported by Reisman,[40] and ^{1}H NMR characterization data matched their report.

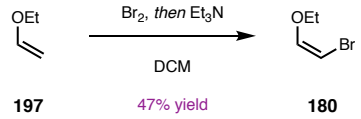
Alkenyl bromide **32** were prepared according to a procedure reported by Reisman,[40] and ^{1}H NMR characterization data matched their report.

Preparation of 179:



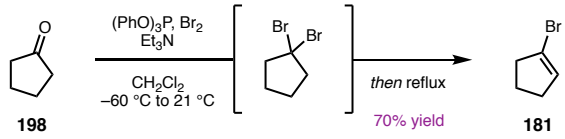
Allyl bromide **179** was prepared according to a procedure reported by Okamoto.[46] ^{1}H NMR characterization data matched a report by Clayden.[47]

Preparation of 180:



Bromoethoxy ethene **180** was prepared according a procedure reported by Valentí.[48] ^{1}H NMR characterization data matched a report by Stalick.[49]

Preparation of alkenyl bromide 181:

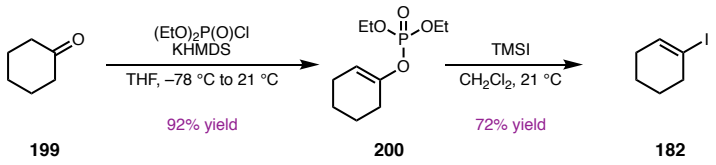


A 500 mL round bottom flask was charged with triphenyl phosphite (27.6 mL, 105 mmol, 1.1 equiv), CH_2Cl_2 (300 mL), and was cooled to –60 °C. Br_2 (5.9 mL, 115.5 mmol, 1.2 equiv) was added followed by Et_3N (17.6 mL, 126 mmol, 1.3 equiv). Cyclopentanone (**198**, 8.53 mL, 96 mmol, 1.0 equiv) was added and the reaction was allowed to warm to ambient temperature. The reaction mixture was stirred until complete consumption of the starting material was observed by TLC (100% hexanes, $KMnO_4$ stain, *ca*. 6 hours). Upon

completion, the flask was equipped with a reflux condenser and the reaction mixture was heated to reflux until complete consumption of the starting material was observed by TLC (100% hexanes, $KMnO_4$ stain, *ca*. 1 hour). The reaction was cooled to ambient temperature and the mixture was transferred to a separatory funnel. The organic layer was washed with aqueous 2 M HCl (2 x 300 mL), and the combined aqueous washes were extracted with pentane (2 x 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure on an ice bath due to the volatility of the product. Purification of the crude residue by column chromatography (silica, 100% pentane) provided alkenyl bromide **181** (10 g, 67.2 mmol, 70% yield) as a clear oil contaminated with some residual pentane.

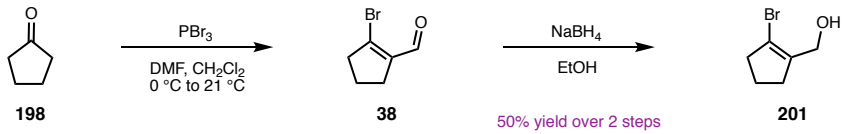
^{1}H NMR data agrees with characterization data reported by Hayashi.[50] This procedure was adapted from a procedure reported by Liang.[51]

Preparation of cyclohexenyl iodide 182:



Cyclohexenyl iodide **182** was prepared according to a procedure by Wiemer.[52] ^{1}H NMR data agrees with characterization data reported by Prabhu.[53]

Preparation of allylic alcohol 201:



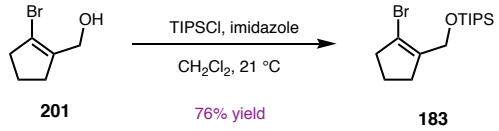
A 1 L round bottom flask was charged with DMF (14.0 mL, 181 mmol, 3.2 equiv) and CH_2Cl_2 (80 mL). The solution was cooled to 0 °C, then PBr_3 (14.3 mL, 153 mmol, 2.7 equiv) was added dropwise via syringe. The reaction mixture was allowed to stir for 1 hour at 0 °C. A solution of cyclopentanone (**198**, 5.0 mL, 56.5 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added dropwise via syringe. The reaction was allowed to warm to 21 °C and was stirred for an additional 21 h. The reaction was cooled to 0 °C and quenched *carefully* with sat. $NaHCO_3$ (500 mL). Solid $NaHCO_3$ was added periodically as needed until bubbling ceased and the aqueous layer tested to be slightly basic with pH paper. The resulting mixture was extracted with Et_2O (3 x 250 mL), and the combined organic extracts were washed with H_2O (2 x 500 mL) then brine (500 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica, 15% EtOAc:85% hexanes) to afford bromoenal **38** (*ca*. 5.8 g), which was used in the next step without rigorous removal of solvent. Spectroscopic data for bromoenal **38** matched that reported in the literature.[54]

A 500 mL round bottom flask was charged with bromoenal **38** (*ca.* 5.8 g) and EtOH (33 mL) followed by cooling the reaction to 0 °C. $NaBH_4$ (1.5 g, 39.8 mmol, 1.2 equiv) was added and the reaction was stirred for 1 hour at 0 °C. The reaction was quenched with H_2O (200 mL) and the mixture was partially concentrated under reduced pressure to remove ethanol. The resulting aqueous solution was extracted with Et_2O (3 x 200 mL), and the combined organic extracts were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (silica, 15% EtOAc in hexanes) afforded allylic alcohol **201** (5.05 g, 28.5

mmol, 50% yield over two steps) as a clear colorless oil. Allylic alcohol **201** matched characterization reported in the literature.[55]

Caution: Bromoenal **38** was found to decompose exothermically upon standing for several hours at 21 °C, or several days at –20 °C. It was found to be stable to storage at –78 °C at which temperature it solidifies into a crystalline solid. It was also found to be stable to storage as a 10% solution in diethyl ether at –20 °C for months.

Preparation of TIPS ether 183:



A 200 mL round bottom flask was charged with allylic alcohol **201** (5.05 g, 28.5 mmol, 1.0 equiv), imidazole (4.66 g, 68.5 mmol, 2.4 equiv), DMF (57 mL), and TIPSCl (7.32 mL, 34.2 mmol, 1.2 equiv) sequentially. The reaction was stirred at 21 °C until complete consumption of the starting material was observed by TLC (*ca*. 12 hours). The reaction was quenched with sat. $NaHCO_3$ (100 mL) and H_2O (100 mL) then the reaction mixture was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with H_2O (200 mL), brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by column chromatography (5% EtOAc:95% hexanes) to afford TIPS ether **183** (7.27 g, 21.8 mmol, 76% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (tq, *J* = 1.7, 0.9 Hz, 2H), 2.68 – 2.62 (m, 2H), 2.52 – 2.45 (m, 2H), 1.99 – 1.91 (m, 2H), 1.18 – 1.10 (m, 3H), 1.10 – 1.04 (m, 18H).

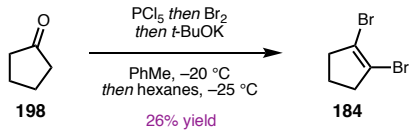
^{13}C NMR (126 MHz, $CDCl_3$): δ 140.7, 115.2, 61.4, 40.2, 32.3, 21.5, 18.0, 12.0.

FTIR (NaCl, thin film): 2960, 2941, 2892, 2866, 1657, 1463, 1383, 1369, 1104, 1066 cm^{-1}.

HRMS: (FAB) calc'd for $C_{15}H_{28}BrOSi$ $[M+H-H_2]^+$ 331.1093, found 331.1089.

TLC (10% EtOAc:90% Hexanes), R_f: 0.77 ($KMnO_4$ stain).

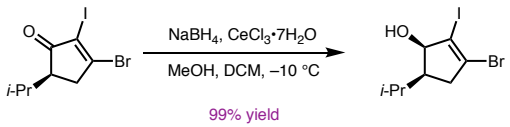
Preparation of 184:



198 184

Cyclopentenyl dibromide **184** was prepared according to a procedure reported by Feringa.[56] ^1H NMR data agrees with characterization data in their report.

Preparation of 202:



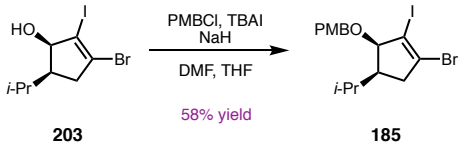
202 203

Ketone **202** was prepared according to a five step procedure reported by Reisman, and ^1H NMR data matched their report.[57] Alcohol **203** was prepared via a Luche reduction.

A 100 mL flask was charged with ketone **202** (0.517 g, 1.57 mmol, 1.0 equiv), MeOH (15.7 mL), and CH_2Cl_2 (15.7 mL). The solution was cooled to –10 °C and then cerium chloride heptahydrate (1.76 g, 4.71 mmol, 3.0 equiv) was added, followed by $NaBH_4$ (89.2 mg, 2.36 mmol, 2.0 equiv). The mixture was stirred at –10 °C until complete consumption of the starting material was observed by TLC (*ca*. 30 minutes). The reaction was quenched with 1 M NaOH (30 mL) and diluted with Et_2O (100 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined

organic extracts were washed with brine (1 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica, 10–20% Et_2O in hexanes gradient) afforded the product as a pale yellow crystalline solid (0.515 g, 99% yield). ^1H NMR characterization data matched the data in Reisman's report with the exception that alcohol **203** had the opposite optical rotation sign. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$= +3.4° (c = 1.00, $CHCl_3$).

Preparation of 185:

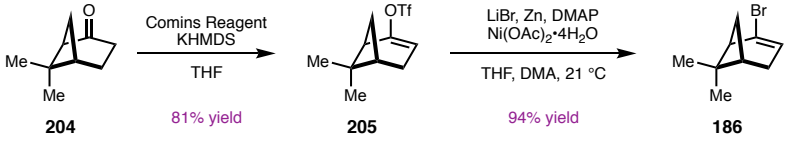


203 **185**

PMB ether **185** was prepared via a procedure reported by Reisman.[57] A 25 mL flask in a glovebox was charged with NaH (dry 95%, 71.4 mg, 2.83 mmol, 2.0 equiv) and DMF (3.54 mL) (Note 1). The flask was sealed with a rubber septum removed from the glovebox, put under N_2 on a Schlenk line, and cooled to 0 °C. A solution of alcohol **203** (468 mg, 1.41 mmol, 1.0 equiv) in THF (3.54 mL) was cannulated into the NaH suspension. The reaction was stirred for 45 minutes, then 4-methoxybenzyl chloride (249 uL, 1.84 mmol, 1.3 equiv) was added dropwise. The reaction was warmed to 21 °C, then tetrabutylammonium iodide (157 mg, 0.42 mmol, 0.30 equiv) was added in a single portion. The reaction was stirred at 21 °C until complete consumption of the starting material was observed by TLC (*ca.* 16 hours). The reaction was quenched by a dropwise addition of sat. NH_4Cl (15 mL) at 0 °C. The reaction mixture was diluted in Et_2O (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with water (1 x 20 mL), brine (1 x 20

mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica, 50% CH_2Cl_2:50% hexanes followed by a second column using a 7.5% EtOAc in hexanes to 15% EtOAc in hexanes gradient) afforded the product as a clear colorless oil (0.368 g, 58% yield). ^1H NMR characterization data matched the data in Reisman's report with the exception that PMB ether **185** had the opposite optical rotation sign. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +20.4° (c = 1.00, $CHCl_3$). Note 1. Hazards have been found with the use of NaH in DMF.[58] Scaling up the reaction is strongly not recommended for this reason.

Preparation of 186:



205 was prepared from (+)-nopinone (**204**) according to a procedure reported by Fallis,[59] ^1H NMR characterization data matched their report.

186 was prepared via a procedure adapted from Reisman.[60] A 25 mL flask equipped with a stir bar was brought into a glovebox. The flask was charged with nickel (II) acetate tetrahydrate (8.98 mg, 0.036 mmol, 0.05 equiv), 4-dimethylaminopyridine (8.81 mg, 0.072 mmol, 0.10 equiv), and lithium bromide (94.0 mg, 1.08 mmol, 1.5 equiv). Anhydrous THF (2.2 mL), and DMA (0.7 mL) were added. The alkenyl triflate **205** (250 mg of a 78% solution in PhMe, 0.72 mmol, 1.0 equiv) was added. The flask was stirred at 600 RPM for 16 hours at 21 °C. The reaction was quenched with sat. NH_4Cl (10 mL), and water (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over

anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure (**Caution!** The product is volatile!). The crude product was purified by column chromatography (silica, 100% pentane) to yield **186** as a clear colorless oil (145 mg, 94% yield).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.83 (tdd, *J* = 3.2, 1.8, 1.1 Hz, 1H), 2.47 (dt, *J* = 8.9, 5.7 Hz, 1H), 2.41 (td, *J* = 5.6, 1.9 Hz, 1H), 2.34 (dt, *J* = 17.5, 3.2 Hz, 1H), 2.25 (dt, *J* = 17.5, 3.0 Hz, 1H), 2.14 (ttd, *J* = 5.7, 2.8, 1.1 Hz, 1H), 1.37 (d, *J* = 8.9 Hz, 1H), 1.30 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 126.7, 123.5, 52.7, 40.2, 33.3, 32.8, 26.1, 20.8.

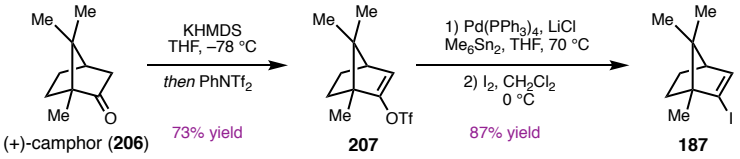
FTIR (NaCl, thin film): 3036, 2924, 2930, 2341, 2357, 1627, 1471, 1308, 1048, 1048, 971, 881 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_9H_{13}Br$ $[M]^+$ 200.0195, found 200.0199.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +53.9 (*c* = 1.00, $CHCl_3$).

TLC (100% Hexanes), R*f*: 0.77, ($KMnO_4$ stain).

Preparation of 187:



Preparation of enol triflate 207:

A 500 mL oven dried N_2 flushed flask was charged with (+)-camphor (**206**) (4.58 g, 30 mmol, 1.0 equiv) and THF (250 mL). The solution was cooled to –78 °C and then KHMDS (63 mL, 0.5 M in toluene, 31.5 mmol, 1.05 equiv) was added dropwise. The reaction was stirred for 45 minutes at –78 °C. A 100 mL oven dried N_2 flushed flask was charged with $PhNTf_2$ (11.25 g, 31.5 mmol, 1.05 equiv) and THF (50 mL). The $PhNTf_2$

solution was transferred via cannula into the enolate solution over the course of 30 minutes. The resulting mixture was allowed to warm to 21 °C and allowed to react until complete consumption of the starting material was observed by TLC (*ca*. 12 hours). The reaction was quenched with sat. NH_4Cl (100 mL). The reaction mixture was extracted with Et_2O (3 x 200 mL), then the combined organic extracts were washed with aqueous 1 M NaOH (4 x 100 mL), brine (1 x 100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by filtration through silica gel (eluting with hexanes) afforded alkenyl triflate **207** (6.20 g, 21.9 mmol, 73% yield) as a clear colorless oil. ^1H NMR data matches a report by Fallis.[61]

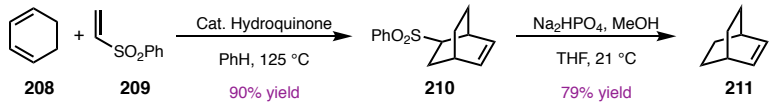
Preparation of alkenyl iodide 187:

A 100 mL flask in a glovebox was charged with alkenyl triflate **207** (1.00 g, 3.52 mmol, 1.0 equiv), LiCl (447 mg, 10.55 mmol, 3.0 equiv), and $Pd(PPh_3)_4$ (163 mg, 0.141 mmol, 0.04 equiv). THF (35 mL) was added, and once the contents dissolved Me_6Sn_2 (1.15 g, 3.52 mmol, 1.0 equiv) was added. The flask was sealed with a reflux condenser containing a septum, brought out of the glovebox, put under N_2 on a Schlenk line, and was heated to reflux (bath temperature set to 70 °C) with vigorous stirring for 3 h. The reaction mixture was cooled to 21 °C then was diluted with hexanes (75 mL) and H_2O (25 mL). The reaction mixture was extracted with hexanes (3 x 75 mL). The combined organic extracts were washed with H_2O (25 mL), 10% NH_4OH (25 mL), H_2O (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

A 100 mL oven dried N_2 flushed flask was charged with the crude alkenyl stannane, CH_2Cl_2 (25 mL), then the solution was cooled to 0 °C. To the stannane was cannulated a solution of I_2 (0.938 g, 3.70 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL). After stirring for 30

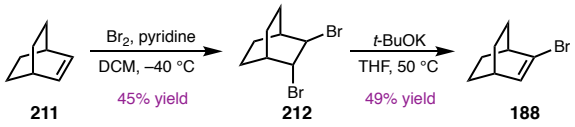
min at 0 °C the reaction was quenched with sat. $Na_2S_2O_3$ (50 mL) and diluted with H_2O (25 mL) and CH_2Cl_2 (25 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue via filtration through silica gel (eluting with hexanes) provided alkenyl iodide **187** (800 mg, 3.06 mmol, 87% yield) as a clear oil. **Note**: alkenyl iodide **187** is slightly volatile, and it should not be left under vacuum for extended periods of time. ^{1}H NMR data matched a report by Kollàr.[62]

Preparation of 211:



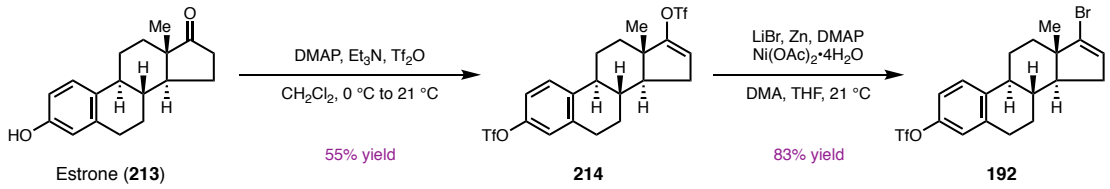
211 was prepared according to a procedure reported by Paquette,[63] ^{1}H NMR characterization data matched their report.

Preparation of 188:



188 was prepared from **211** according to a procedure reported by Takeuchi,[64] ^{1}H NMR characterization data matched their report.

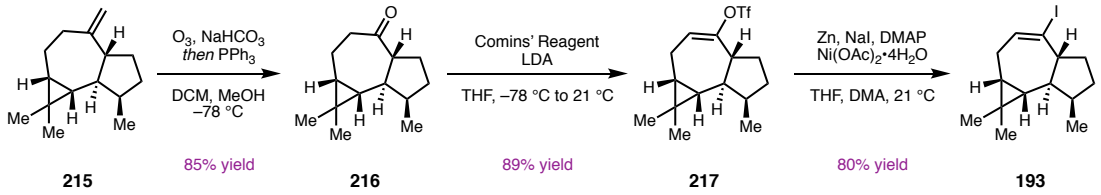
Preparation of 192:



Alkenyl triflate **214** was prepared according to a procedure reported by Wang,[65] and ^{1}H NMR characterization data matched their report.

Alkenyl bromide **192** was prepared according to a procedure reported by Reisman,[60] and ^{1}H NMR characterization data matched their report.

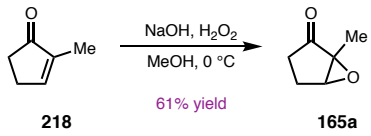
Preparation of 193:



Ketone **216** was prepared according to a procedure reported by Barker,[66] and ^{1}H NMR characterization data matched their report.

Alkenyl triflate **217** and alkenyl iodide **193** were prepared according to a procedure reported by Reisman,[60] and ^{1}H NMR characterization data matched their report.

Preparation of 165a:



Epoxide **165a** was prepared according to a literature procedure by Berthold.[67]

^{1}H NMR (400 MHz, Chloroform-*d*): δ 3.77 (dt, *J* = 1.7, 0.8 Hz, 1H), 2.35 (dddd, *J* = 17.1, 9.0, 7.4, 0.9 Hz, 1H), 2.32 – 2.22 (m, 1H), 2.16 – 2.04 (m, 1H), 2.03 – 1.94 (m, 1H), 1.44 (s, 3H).

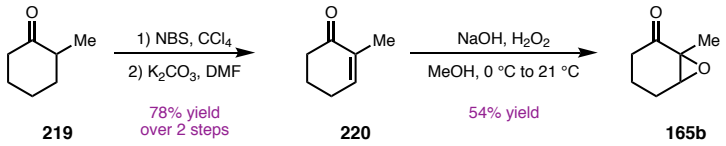
^{13}C NMR (101 MHz, $CDCl_3$): δ 211.0, 64.2, 61.1, 31.3, 22.4, 10.1.

FTIR (NaCl, thin film): 2973, 2936, 1746, 1446, 1072, 844 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_6H_8O_2$ $[M]^+$ 112.0519, found 112.0519.

TLC (20% EtOAc:80% Hexanes), R_f: 0.33 ($KMnO_4$ stain).

Preparation of 4b:



Enone **220** was prepared according to a literature report by Maddaluno,[68] and ^{1}H NMR characterization data matched their report.

Epoxide **165b** was prepared according to a literature report by Berthold,[67] and ^{1}H NMR characterization data matched their report.

Preparative procedures for 1,2-additions followed by TMS trapping:

General Procedure A (Regular Addition)

A 50 mL round bottom flask was charged with epoxyketone **31** (0.30 mmol) and was dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 5 mL at 45 °C water bath temperature, 30 mbar pressure), followed by drying under vacuum on a Schlenk line (0.3 mbar) for 30 minutes. An oven

dried 10 mL flask under N_2, sealed with a rubber septum, was charged with the alkenyl or aryl halide (0.36 mmol, 1.2 equiv) via syringe followed by THF (0.12 M). The alkenyl or aryl halide solution was cooled to –78 °C followed by a rapid addition of *t*-BuLi (1.7 M in pentane, 2.4–2.7 equiv) and was stirred for 20 minutes at this temperature. Epoxyketone **31** was dissolved in THF (0.05 M) and was cooled to –94 °C in an acetone/liq. N_2 bath. The alkenyl or aryl lithium solution was added via cannula to the epoxyketone solution over the course of 5 minutes then the solution was stirred at –94 °C for 20 minutes. The reaction was warmed to –78 °C on an acetone/CO_2 bath for 5 minutes, then TMSCl (2.4 equiv) was added. The cooling bath was removed, and the reaction was warmed to 21 °C. Upon reaching 21 °C the flask was stirred for an additional 10 minutes then the reaction was concentrated under reduced pressure and purified immediately by SiO_2 column chromatography.

General Procedure B (Inverse Addition)

A 25 mL round bottom flask was charged with epoxyketone **31** (0.30 mmol) and dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 5 mL at 45 °C water bath temperature, 30 mbar pressure) followed by drying on a Schlenk line (0.3 mbar) for 30 minutes. An oven dried 10 mL flask under N_2, sealed with a rubber septum, was charged with the alkenyl or aryl halide (0.36 mmol, 1.2 equiv) via syringe followed by THF (0.12 M). The alkenyl or aryl halide solution was cooled to –78 °C followed by a rapid addition of *t*-BuLi (1.7 M in pentane, 2.4–2.7 equiv) and stirred for 20 minutes at this temperature. The alkenyl or aryl lithium solution was cooled to –94 °C in an acetone/liq. N_2 bath. Epoxyketone **31** was dissolved in THF (6 mL, 0.05 M) and cannulated into the alkenyl or aryl lithium solution over the course of 5

minutes. The flask was rinsed with THF (2 x 1 mL), then the solution was stirred at this temperature for 20 minutes. The reaction was warmed to –78 °C on an acetone/CO_2 bath for 5 minutes, then TMSCl (2.4 equiv) was added. The cooling bath was removed, and the reaction was warmed to 21 °C. Upon reaching 21 °C the flask was stirred for an additional 10 minutes, and then the reaction was concentrated under reduced pressure and purified immediately by SiO_2 column chromatography.

Procedure C (LDA Lithiation of furan)

A 25 mL round bottom flask was charged with epoxyketone **31** (0.30 mmol) and dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 5 mL at 45 °C water bath temperature, 30 mbar pressure) followed by drying on a Schlenk line (0.3 mbar) for 30 minutes. A 50 mL flask under N_2 was charged with *i*-Pr_2NH (1.25 equiv) and THF (0.13 M). The solution was cooled to –78 °C, followed by the addition of *n*-BuLi (1.25 equiv). The solution was stirred at –78 °C for 30 minutes. A 25 mL oven dried N_2 flushed round bottom flask was charged with 3-bromofuran (**191**) (1.2 equiv) and THF (0.21 M). The bromofuran solution was cannulated into the LDA solution over the course of 5 minutes. The flask containing the bromofuran solution was rinsed into the reaction flask with THF (2 x 1 mL) to ensure quantitative reagent transfer. The resulting solution was stirred at –78 °C for 30 minutes followed by cooling the solution to –94 °C. Epoxyketone **31** was dissolved in THF (0.075 M) and was cannulated into the furan solution over the course of 5 minutes. The flask containing the epoxy ketone solution was rinsed into the reaction flask with THF (2 x 1 mL) to ensure quantitative reagent transfer. Once the addition was complete, the reaction was stirred at –94 °C for 20 minutes

followed by warming the reaction to –78 °C with an acetone/CO_2 bath. The reaction was stirred at –78 °C for 5 minutes, followed by adding TMSCl (2.4 equiv). The reaction was allowed to warm to 21 °C and was stirred for 15 minutes. The reaction was concentrated under reduced pressure and purified immediately by SiO_2 chromatography.

Procedure D (Grignard Addition)

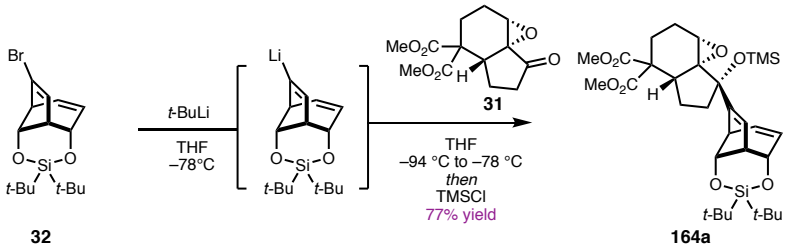
A 50 mL round bottom flask was charged with epoxyketone **31** (0.30 mmol) and dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 5 mL at 45 °C water bath temperature, 30 mbar pressure) followed by drying on a Schlenk line (0.3 mbar) for 30 minutes. The epoxyketone was dissolved in THF (0.075 M) and was cooled to –94 °C. To the epoxyketone solution was added a solution of the Grignard reagent (1.2 equiv) dropwise over the course of 5 minutes. The reaction was stirred at –94 °C for 20 minutes then –78 °C for 5 minutes. The reaction was quenched with sat. NH_4Cl at –78 °C. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The reaction was purified immediately by SiO_2 chromatography.

Notes

1. It is extremely important for this reaction to be rigorously dry. Trace water significantly diminishes the yield.
2. Before use, the alkenyl halides were dried by eluting them through a SiO_2 plug with pentane followed by concentration under reduced pressure. The purity of the alkenyl halides was quantified using qNMR (pyrazine internal standard).

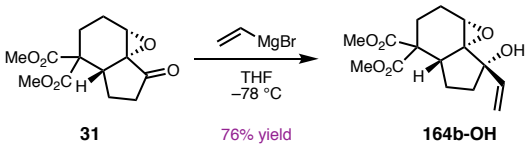
3. It is important to run an SiO_2 column immediately following the concentration of the reaction because the product is unstable in the crude reaction mixture.
4. Scales larger than 0.30 mmol were quenched with sat. $NaHCO_3$, and an aqueous workup was performed. Specific details can be found in their respective procedures.

Preparation of 1,2-addition product 164a:



Prepared from **1** (2.13 g, 7.93 mmol, 1.3 equiv), and alkenyl bromide **S11** (2.18 g, 6.10 mmol, 1.0 equiv) according to method reported by Reisman, and ^{1}H NMR characterization data matched their report.[40]

Preparation of 1,2-addition product 164b-OH:



Prepared via General Procedure D, 76% yield.

Prepared from **31** (81.2 mg, 0.30 mmol, 1.0 equiv), and vinylmagnesium bromide (1.0 M in THF, 0.36 mL, 0.36 mmol, 1.2 equiv) according to method **D**. The crude

reaction was purified by column chromatography (silica, 40% EtOAc:60% Hexanes) to yield **164b-OH** (68.6 mg, 76% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.89 (dd, *J* = 17.1, 10.6 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.13 (dd, *J* = 10.7, 1.4 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.29 (d, *J* = 4.0 Hz, 1H), 2.75 (dd, *J* = 10.8, 7.4 Hz, 1H), 2.52 (s, 1H), 2.51 – 2.43 (m, 1H), 2.40 – 2.27 (m, 2H), 2.09 – 1.90 (m, 4H), 1.59 – 1.50 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 170.4, 140.2, 113.7, 75.8, 72.1, 56.4, 55.2, 53.1, 52.3, 44.0, 38.5, 29.5, 23.6, 21.7.

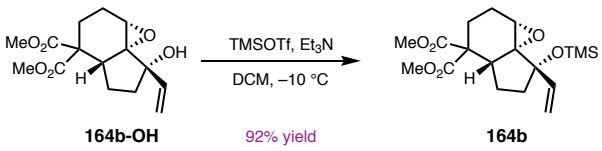
FTIR (NaCl, thin film): 3508, 3092, 2998, 2953, 1731, 1433, 1243, 1213, 1060 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{15}H_{21}O_6$ $[M+H]^+$, 297.1333 found 297.1327.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +21.4° (*c* = 0.50, $CHCl_3$).

TLC (40% EtOAc:60% Hexanes), R_f: 0.39, (dark blue in *p*-anisaldehyde stain).

Preparation of silyl ether 164b:



164b-OH 92% yield **164b**

A 25 mL oven dried N_2 flushed round bottom flask was charged with alcohol **164b-OH** (68.6 mg, 0.23 mmol, 1.0 equiv) and CH_2Cl_2 (6 mL, 0.04 M). The solution was cooled to –10 °C then triethylamine (120 μL, 0.87 mmol, 3.8 equiv) was added followed by TMSOTf (50 μL, 0.28 mmol, 1.2 equiv). The reaction was stirred for 15 minutes at –10 °C followed by a quench with sat. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over

anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 15% EtOAc:85% Hexanes) to yield the product **164b** (78.2 mg, 92% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.93 (ddd, *J* = 17.2, 10.6, 0.7 Hz, 1H), 5.28 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.13 (dd, *J* = 10.6, 1.2 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.20 (d, *J* = 3.7 Hz, 1H), 2.74 (t, *J* = 9.4 Hz, 1H), 2.59 (dddd, *J* = 12.8, 10.7, 9.5, 5.1 Hz, 1H), 2.43 – 2.24 (m, 2H), 2.16 – 1.98 (m, 2H), 1.97 – 1.82 (m, 2H), 1.53 – 1.44 (m, 1H), 0.08 (s, 8H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 170.6, 141.9, 113.7, 78.9, 71.0, 55.2, 53.7, 52.9, 52.2, 42.3, 35.7, 29.9, 22.5, 21.5, 2.4.

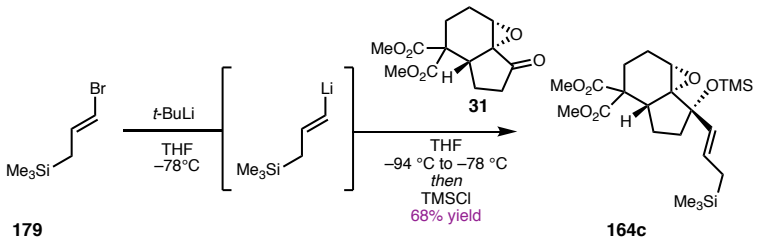
FTIR (NaCl, thin film): 3084, 2952, 1734, 1639, 1451, 1434, 1249, 1059, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{18}H_{28}O_6SiNa$ $[M+Na]^+$, 391.1547 found 391.1547.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +17.5° (*c* = 1.00, $CHCl_3$).

TLC (15% EtOAc:85% Hexanes), R_f: 0.33, (turquoise in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164:



Prepared via General Procedure B, 68% yield.

Prepared from **31** (80.9, 0.30 mmol, 1.0 equiv), **179** (77.2 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.45 mL, 0.74 mmol, 2.4 equiv), and TMSCl (90 μL, 0.71 mmol, 2.4 equiv) according to method **B**. The reaction was directly subjected to

column chromatography (silica, 10% Acetone:90% Hexanes) to yield **164c** (92.6 mg, 68% yield) as a white crystalline solid.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.67 (dt, *J* = 15.5, 8.2 Hz, 1H), 5.36 (dq, *J* = 15.5, 1.2 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.22 (dd, *J* = 3.6, 0.8 Hz, 1H), 2.78 (dd, *J* = 9.8, 9.0 Hz, 1H), 2.59 (dddd, *J* = 13.0, 11.2, 9.0, 4.0 Hz, 1H), 2.38 – 2.24 (m, 2H), 2.08 (ddd, *J* = 12.8, 8.8, 4.0 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.95 – 1.87 (m, 1H), 1.81 (dddd, *J* = 13.0, 9.9, 8.8, 7.4 Hz, 1H), 1.51 (dd, *J* = 8.2, 1.3 Hz, 2H), 1.49 – 1.41 (m, 1H), 0.06 (s, 9H), 0.03 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 170.6, 132.0, 127.0, 78.3, 71.3, 55.2, 53.6, 52.8, 52.2, 41.8, 35.6, 30.2, 23.0, 22.0, 21.6, 2.4, –1.7.

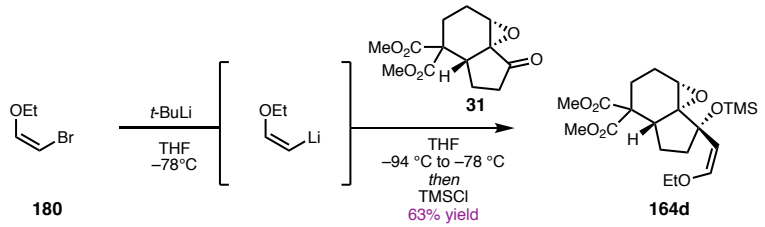
FTIR (NaCl, thin film): 2993, 2952, 2898, 1734, 1654, 1450, 1434, 1248, 888, 857, 841 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{22}H_{38}O_6Si_2Na$ $[M+Na]^+$, 477.2099 found 477.2098.

$[\alpha]_D^{25}$ = +36.7° (*c* = 1.00, $CHCl_3$).

TLC (10% Acetone:90% Hexanes), R_f: 0.30, (blue in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164d:



Prepared via General Procedure B, 63% yield.

Prepared from **31** (81.0 mg, 0.30 mmol, 1.0 equiv), **180** (54.4 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.48 mL, 0.82 mmol, 2.7 equiv), and TMSCl (90 µL, 0.71 mmol, 2.4 equiv) according to method **B**. The reaction was directly subjected to column chromatography (silica, 20% EtOAc:80% Hexanes) to yield **164d** (79.0 mg, 63% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.90 (d, *J* = 7.1 Hz, 1H), 4.34 (dd, *J* = 7.1, 0.6 Hz, 1H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.68 (s, 3H), 3.33 (d, *J* = 3.6 Hz, 1H), 2.88 (dd, *J* = 9.9, 8.6 Hz, 1H), 2.49 (dddd, *J* = 12.6, 10.4, 8.5, 3.8 Hz, 1H), 2.34 – 2.25 (m, 2H), 2.12 (ddd, *J* = 12.1, 8.3, 3.8 Hz, 1H), 2.01 – 1.96 (m, 1H), 1.95 – 1.87 (m, 1H), 1.86 – 1.80 (m, 1H), 1.57 – 1.49 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.08 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.5, 170.7, 146.0, 109.6, 76.7, 70.9, 68.6, 55.3, 55.2, 52.6, 51.9, 42.1, 38.5, 29.8, 21.6, 21.5, 15.4, 2.3.

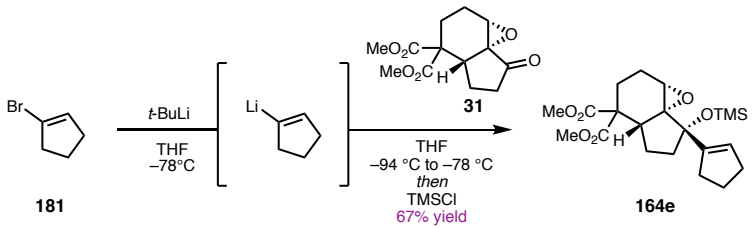
FTIR (NaCl, thin film): 2952, 1733, 1659, 1433, 1248, 1101, 841 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{20}H_{33}O_7Si$ $[M+H]^+$ 413.1990, found 413.2000.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +57.5° (*c* = 1.00, $CHCl_3$).

TLC (20% EtOAc:80% Hexanes), R_f: 0.30, (pink in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164e:



Prepared via General Procedure A, 67% yield.

Prepared from **31** (81.3 mg, 0.30 mmol, 1.0 equiv), *t*-BuLi (1.7 M in pentane, 0.44 mL, 0.74 mmol, 2.5 equiv), TMSCl (90 µL, 0.63 mmol, 2.4 equiv), and **181** (51.9 mg, 0.36 mmol, 1.2 equiv) according to method **A**. The reaction was directly subjected to column chromatography (silica, 10% EtOAc:90% Hexanes) to yield **164e** (82.8 mg, 67% yield) as a white crystalline solid.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.67 (p, *J* = 2.0 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.28 (dd, *J* = 3.6, 0.8 Hz, 1H), 2.65 – 2.55 (m, 2H), 2.43 – 2.18 (m, 7H), 2.04 – 1.79 (m, 5H), 1.54 – 1.44 (m, 1H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 170.4, 146.1, 126.4, 77.5, 70.3, 55.0, 54.3, 52.7, 52.0, 41.7, 35.3, 32.4, 31.3, 29.8, 23.2, 22.0, 21.2, 1.9.

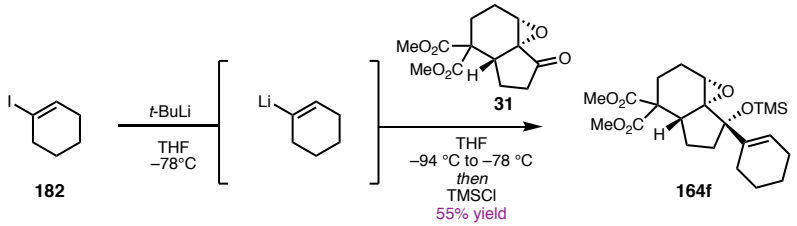
FTIR (NaCl, thin film): 2952, 2847, 1733, 1449, 1433, 1248, 840 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{21}H_{33}O_6Si$ $[M+H]^+$ 409.2041, found 409.2059.

$[\alpha]_D^{25}$ = +32.7° (*c* = 1.00, $CHCl_3$).

TLC (10% EtOAc:90% Hexanes), R*f*: 0.12, (navy blue in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164f:



Prepared via General Procedure A, 55% yield.

Prepared from **31** (80.5 mg, 0.30 mmol, 1.0 equiv), **182** (77.3 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.47 mL, 0.80 mmol, 2.7 equiv), and TMSCl (90 µL,

0.71 mmol, 2.4 equiv) according to method **A**. The reaction was directly subjected to column chromatography (silica, 10% EtOAc:90% Hexanes) to yield **164f** (70.1 mg, 55% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.76 – 5.73 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.31 (d, *J* = 3.8 Hz, 1H), 2.63 (dd, *J* = 9.7, 8.2 Hz, 1H), 2.55 (dddd, *J* = 12.7, 10.5, 8.2, 3.2 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.21 (ddd, *J* = 12.7, 8.2, 3.2 Hz, 1H), 2.16 – 2.00 (m, 3H), 1.98 – 1.85 (m, 3H), 1.82 – 1.75 (m, 1H), 1.75 – 1.68 (m, 1H), 1.67 – 1.60 (m, 1H), 1.59 – 1.45 (m, 3H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 170.5, 138.1, 122.5, 80.5, 70.3, 55.1, 55.0, 52.7, 52.0, 41.7, 34.1, 29.8, 25.3, 24.0, 22.8, 22.2, 21.9, 21.2, 2.0.

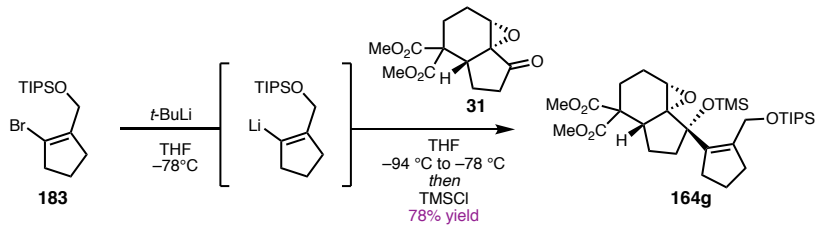
FTIR (NaCl, thin film): 2950, 2859, 1733, 1449, 1434, 1248, 841 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{22}H_{35}O_6Si$ $[M+H]^+$ 423.2197, found 423.2189.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +11.1° (*c* = 1.00, $CHCl_3$).

TLC (10% EtOAc:90% Hexanes), R_f: 0.40, (navy blue in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164g:



Prepared via General Procedure A, 78% yield.

Prepared from **31** (80.5 mg, 0.30 mmol, 1.0 equiv), **183** (141.0 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.48 mL, 0.82 mmol, 2.7 equiv), and TMSCl (90

μL, 0.71 mmol, 2.4 equiv) according to Method **A**. The reaction was directly subjected to column chromatography (silica, 10% EtOAc:90% Hexanes) to yield **164g** (140.1 mg, 78% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 4.58 (dt, *J* = 13.4, 1.6 Hz, 1H), 4.47 (dt, *J* = 13.9, 2.0 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.27 (d, *J* = 3.7 Hz, 1H), 2.67 (dd, *J* = 10.4, 8.5 Hz, 1H), 2.58 – 2.46 (m, 4H), 2.46 – 2.40 (m, 1H), 2.39 – 2.33 (m, 1H), 2.32 – 2.26 (m, 1H), 2.18 (ddd, *J* = 13.2, 8.2, 6.6 Hz, 1H), 2.03 (ddd, *J* = 13.3, 10.0, 5.4 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.77 (p, *J* = 7.5 Hz, 2H), 1.50 (ddd, *J* = 13.3, 10.3, 8.4 Hz, 1H), 1.10 – 1.05 (m, 21H), 0.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 170.4, 140.3, 137.6, 79.3, 71.2, 61.3, 55.2, 55.1, 52.8, 52.1, 43.7, 38.0, 35.5, 35.1, 29.6, 23.1, 21.8, 21.4, 18.1, 12.0, 2.2.

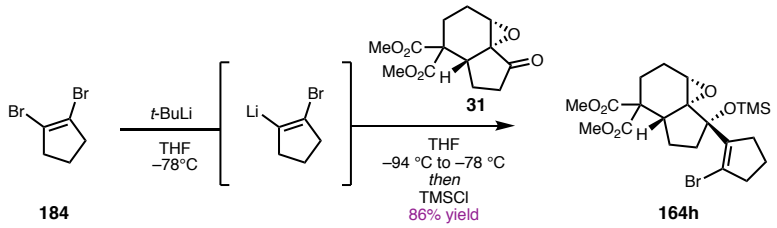
FTIR (NaCl, thin film): 2949, 2866, 1738, 1463, 1434, 1248, 1219, 881, 841 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{31}H_{58}O_7Si_2N$ $[M+NH_4]^+$ 612.3746, found 612.3751.

$[\alpha]_D^{25}$ = +17.8° (*c* = 1.00, $CHCl_3$).

TLC (10% EtOAc:90% Hexanes), R_f: 0.30, (navy blue in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164h:



Prepared via General Procedure A, 86% yield.

Prepared from **31** (80.1 mg, 0.30 mmol, 1.0 equiv), **184** (81.3 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.44 mL, 0.74 mmol, 2.5 equiv), and TMSCl (90 µL, 0.63 mmol, 2.4 equiv) according to method **A**. The reaction was directly subjected to column chromatography (silica, 20% EtOAc:80% Hexanes) to yield **164h** (125.5 mg, 86% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 3.75 (s, 3H), 3.69 (s, 3H), 3.42 (d, *J* = 3.6 Hz, 1H), 2.82 (t, *J* = 9.1 Hz, 1H), 2.78 – 2.62 (m, 2H), 2.55 – 2.39 (m, 4H), 2.36 – 2.26 (m, 2H), 2.04 – 1.96 (m, 2H), 1.94 – 1.83 (m, 3H), 1.62 – 1.54 (m, 1H), 0.08 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 170.5, 141.1, 115.3, 78.9, 70.1, 56.5, 55.2, 52.8, 52.0, 43.3, 42.9, 36.8, 34.3, 29.4, 22.4, 21.5, 21.3, 2.0.

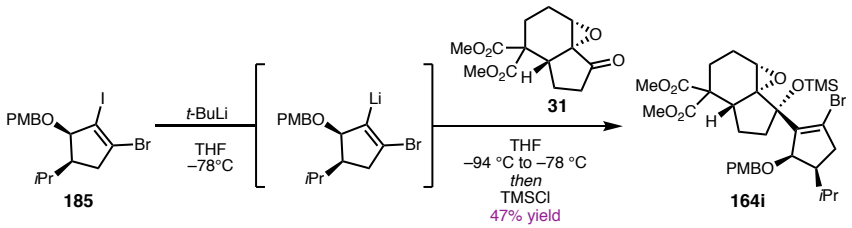
FTIR (NaCl, thin film): 2952, 2851, 1733, 1448, 1433, 1248, 840 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{21}H_{32}O_6SiBr$ $[M+H]^+$ 487.1146, found 487.1145.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +52.6° (*c* = 1.00, $CHCl_3$).

TLC (15% EtOAc:85% Hexanes), R*f*: 0.17, (dark blue in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164i:



Prepared via General Procedure B, 47% yield.

Prepared from **31** (81.1 mg, 0.30 mmol, 1.0 equiv), **185** (164.0 mg, 0.36 mmol, 1.2 equiv), *n*-BuLi (2.6 M in hexanes, 0.45 mL, 0.38 mmol, 1.3 equiv), and TMSCl (90

μL, 0.71 mmol, 2.4 equiv) according to method **B**. The reaction was directly subjected to column chromatography (silica, 15% EtOAc:85% Hexanes) to yield **164i** (95.1 mg, 47% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.27 – 7.22 (m, 2H), 6.89 – 6.84 (m, 2H), 4.79 (d, *J* = 10.4 Hz, 1H), 4.51 (dd, *J* = 5.5, 1.0 Hz, 1H), 4.45 (d, *J* = 10.4 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.24 (d, *J* = 3.3 Hz, 1H), 3.15 (dd, *J* = 12.7, 5.4 Hz, 1H), 2.73 (ddd, *J* = 16.0, 9.3, 1.1 Hz, 1H), 2.55 (dd, *J* = 15.9, 7.3 Hz, 1H), 2.43 – 2.19 (m, 4H), 2.11 – 1.92 (m, 4H), 1.77 – 1.60 (m, 2H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.12 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 170.8, 159.2, 146.7, 131.3, 129.3, 121.2, 113.9, 84.5, 81.1, 72.7, 71.1, 58.6, 55.4, 52.9, 52.3, 51.2, 46.6, 46.1, 43.8, 28.6, 26.9, 25.3, 22.1, 22.0, 21.3, 2.9.

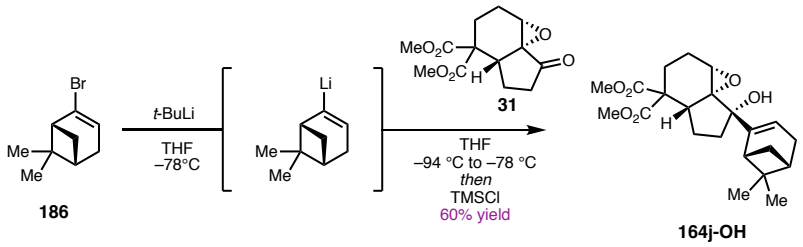
FTIR (NaCl, thin film): 2954, 2867, 1732, 1614, 1514, 1248, 835, 758, 752 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{32}H_{49}O_8SiBrN$ $[M+NH_4]^+$, 682.2405 found 682.2385.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +63.9° (*c* = 1.00, $CHCl_3$).

TLC (15% EtOAc:85% Hexanes), R_f: 0.32, (forest green in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164j-OH:



Prepared via General Procedure A, 60% yield.

Prepared from **31** (80.5 mg, 0.30 mmol, 1.0 equiv), **186** (79.7 mg, 0.40 mmol, 1.3 equiv), *t*-BuLi (1.7 M in pentane, 0.44 mL, 0.72 mmol, 2.4 equiv) according to method **A**. The reaction was quenched with sat. NH_4Cl and was allowed to warm to 21 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 30% EtOAc:70% Hexanes) to yield **164j-OH** (70.0 mg, 60% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.51 (tt, *J* = 3.1, 1.5 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.38 (d, *J* = 3.8 Hz, 1H), 2.78 (dd, *J* = 10.5, 8.1 Hz, 1H), 2.51 – 2.30 (m, 7H), 2.26 (dt, *J* = 17.8, 2.8 Hz, 1H), 2.11 (ttd, *J* = 5.6, 2.7, 1.2 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.90 (dtd, *J* = 12.4, 7.9, 4.8 Hz, 1H), 1.82 (ddd, *J* = 13.4, 9.4, 4.8 Hz, 1H), 1.64 – 1.51 (m, 1H), 1.30 (s, 3H), 1.14 (d, *J* = 8.6 Hz, 1H), 0.85 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 170.5, 148.7, 117.3, 77.2, 71.1, 56.8, 55.3, 53.0, 52.2, 44.8, 42.9, 40.9, 37.8, 37.3, 31.9, 31.4, 29.6, 26.4, 23.2, 21.6, 21.6.

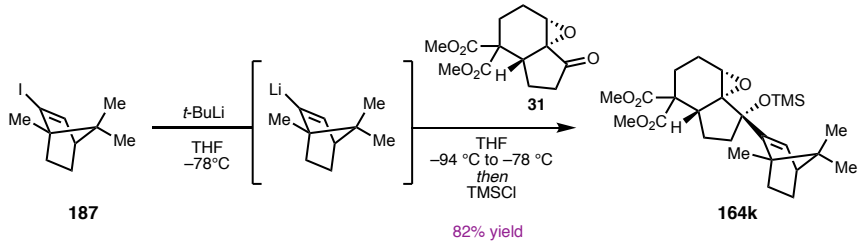
FTIR (NaCl, thin film): 3504, 2949, 2917, 1734, 1458, 1450, 1432, 1239, 1220, 1174 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{22}H_{31}O_6$ $[M+H]^+$, 391.2115 found 391.2113.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +29.4° (*c* = 1.00, $CHCl_3$).

TLC (30% EtOAc:70% Hexanes), R_f: 0.37, (purple in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164k:



Prepared via General Procedure B, 82% yield.

Prepared from **31** (81.1 mg, 0.30 mmol, 1.0 equiv), **187** (94.6 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.45 mL, 0.74 mmol, 2.5 equiv), and TMSCl (90 µL, 0.63 mmol, 2.4 equiv) according to method **B**. The crude reaction mixture was purified by column chromatography (silica, 10% EtOAc:90% Hexanes) to yield **164k** (118.7 mg, 82% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.71 (d, *J* = 3.4 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.34 (d, *J* = 3.6 Hz, 1H), 2.78 (t, *J* = 9.3 Hz, 1H), 2.52 (dddd, *J* = 12.8, 10.8, 9.0, 4.6 Hz, 1H), 2.41 – 2.28 (m, 2H), 2.25 (t, *J* = 3.5 Hz, 1H), 2.19 (ddd, *J* = 13.0, 8.6, 4.6 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.87 – 1.79 (m, 2H), 1.56 – 1.44 (m, 2H), 1.23 (ddd, *J* = 12.2, 9.2, 3.6 Hz, 1H), 1.10 (s, 3H), 1.01 (ddd, *J* = 11.6, 9.2, 3.7 Hz, 1H), 0.77 (s, 3H), 0.74 (s, 3H), 0.06 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 170.6, 150.0, 128.7, 79.3, 70.1, 57.1, 55.3, 55.2, 55.0, 52.7, 51.9, 51.2, 42.4, 36.1, 32.9, 29.8, 25.4, 22.7, 21.2, 19.7, 19.5, 13.5, 2.4.

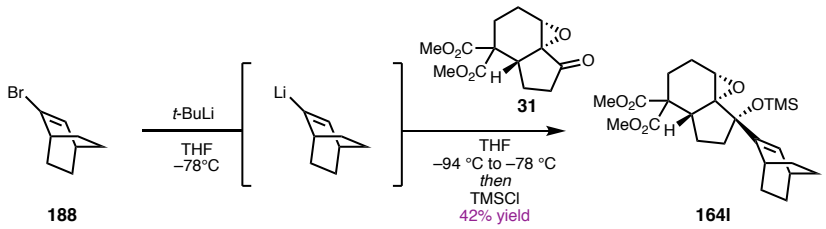
FTIR (NaCl, thin film): 2952, 2873, 1734, 1450, 1434, 1247, 839, 887 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{26}H_{41}O_6Si$ $[M+H]^+$ 477.2667, found 477.2673.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –11.8° (*c* = 1.00, $CHCl_3$).

TLC (10% EtOAc:90% Hexanes), R_f: 0.29, (navy blue in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164l:



Prepared via General Procedure A, 42% yield.

Prepared from **31** (80.8, 0.30 mmol, 1.0 equiv), **188** (67.6 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.45 mL, 0.74 mmol, 2.4 equiv), and TMSCl (90 μL, 0.71 mmol, 2.4 equiv) according to method **A**. The reaction was directly subjected to column chromatography (silica, 15% EtOAc:85% Hexanes) to yield **164l** (56.5 mg, 42% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 6.14 (dd, *J* = 6.8, 1.7 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.36 (d, *J* = 3.6 Hz, 1H), 2.70 (br s, 1H), 2.67 (t, *J* = 9.4 Hz, 1H), 2.64 – 2.53 (m, 2H), 2.39 – 2.26 (m, 2H), 2.23 (ddd, *J* = 12.6, 8.6, 3.9 Hz, 1H), 2.01 (ddd, *J* = 12.7, 10.9, 7.4 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.62 – 1.49 (m, 4H), 1.48 – 1.39 (m, 1H), 1.32 – 1.22 (m, 3H), 1.10 (ddt, *J* = 14.4, 8.8, 3.1 Hz, 1H), 0.06 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 170.7, 147.5, 127.2, 79.6, 70.4, 55.2, 54.6, 52.9, 52.1, 42.3, 34.3, 30.6, 30.3, 30.0, 26.9, 26.4, 26.4, 26.1, 22.5, 21.5, 2.3.

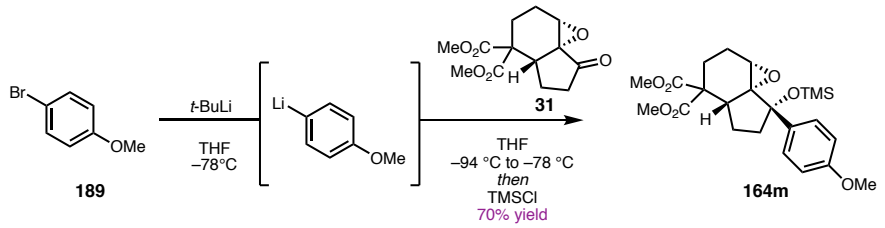
FTIR (NaCl, thin film): 2945, 2862, 1734, 1450, 1433, 1247, 841 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{24}H_{36}O_6SiK$ $[M+K]^+$, 487.1913 found 487.1921.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +16.8° (*c* = 1.00, $CHCl_3$).

TLC (15% EtOAc:85% Hexanes), R_f: 0.54, (purple in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164m:



Prepared via General Procedure A, 70% yield.

Prepared from **31** (81.2 mg, 0.30 mmol, 1.0 equiv), **189** (67.3 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.48 mL, 0.82 mmol, 2.7 equiv), and TMSCl (90 μL, 0.71 mmol, 2.4 equiv) according to method **A**. The reaction was directly subjected to column chromatography (silica, 20% EtOAc:80% Hexanes) to yield **164m** (95.6 mg, 70% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.35 – 7.31 (m, 2H), 6.88 – 6.85 (m, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.65 (s, 3H), 3.47 (d, *J* = 4.1 Hz, 1H), 2.73 (dddd, *J* = 13.1, 11.0, 8.7, 3.6 Hz, 1H), 2.55 (dd, *J* = 9.9, 8.8 Hz, 1H), 2.46 (ddd, *J* = 13.0, 8.4, 3.7 Hz, 1H), 2.33 (dddd, *J* = 15.4, 10.2, 8.1, 0.7 Hz, 1H), 2.27 – 2.17 (m, 2H), 1.98 – 1.87 (m, 2H), 1.35 (ddd, *J* = 13.3, 10.3, 8.5 Hz, 1H), –0.08 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 170.4, 158.9, 136.7, 127.2, 113.6, 79.4, 72.2, 55.2, 55.0, 54.8, 52.7, 52.1, 41.7, 36.4, 29.6, 22.2, 21.3, 1.9.

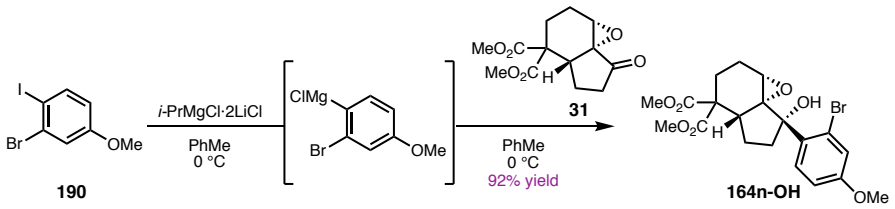
FTIR (NaCl, thin film): 2998, 2952, 2838, 1732, 1609, 1511, 1250, 887, 841 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{23}H_{33}O_7Si$ $[M+H]^+$ 449.1990, found 449.1998.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +37.5° (*c* = 1.00, $CHCl_3$).

TLC (20% EtOAc:80% Hexanes), R*f*: 0.24, (dark blue in *p*-anisaldehyde stain).

Preparation of epoxy-alcohol 164n-OH:



A 250 mL round bottom flask was charged with aryl iodide **190** (4.85 g, 15.49 mmol, 1.7 equiv), PhMe (27 mL, 0.54 M), and was cooled to 0 °C. To the solution was added *i*-PrMgCl·2LiCl (1.3 M in THF, 11.9 mL, 15.49 mmol, 1.7 equiv) dropwise via syringe, which was then allowed to stir at 0 °C for 1 hour. A separate 100 mL flask was charged with epoxyketone **31** (2.54 g, 9.45 mmol, 1 equiv) and PhMe (48 mL, 0.2 M) under N_2 (to get the epoxyketone to dissolve, the PhMe solution was heated slightly in a warm water bath). To the aryl Grignard solution at 0 °C was added the epoxyketone solution dropwise via cannula. The epoxyketone flask was rinsed with PhMe (1 x 20 mL) to ensure quantitative transfer then the reaction was stirred for 30 minutes at 0 °C. **Caution**: the epoxyketone may crash out of solution, gentle heating will re-dissolve the epoxyketone. The reaction was quenched with H_2O (30 mL) and the reaction mixture was allowed to warm to 21 °C. The biphasic mixture was transferred to a 1 L Erlenmeyer flask, and aqueous sat. Rochelle's salt solution (150 mL) and Et_2O were added (150 mL). The biphasic mixture was allowed to vigorously stir for 30 minutes. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (4 x 150 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica, 30% Ethyl

acetate:70% Hexanes) to yield epoxy alcohol **164n-OH** (3.95 g, 8.70 mmol, 92% yield) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.74 (d, *J* = 8.9 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.78 (s, 6H), 3.73 (s, 3H), 3.43 (dd, *J* = 12.8, 6.1 Hz, 1H), 3.25 – 3.19 (m, 1H), 3.07 (d, *J* = 1.3 Hz, 1H), 2.67 – 2.52 (m, 1H), 2.42 – 2.30 (m, 2H), 2.25 (dtd, *J* = 15.7, 8.7, 1.2 Hz, 1H), 2.13 – 2.00 (m, 3H), 1.78 (dt, *J* = 13.4, 8.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 170.8, 159.1, 134.1, 129.9, 120.5, 119.7, 112.7, 78.1, 72.8, 61.1, 55.5, 55.2, 52.9, 52.0, 45.7, 40.1, 28.2, 25.7, 21.7.

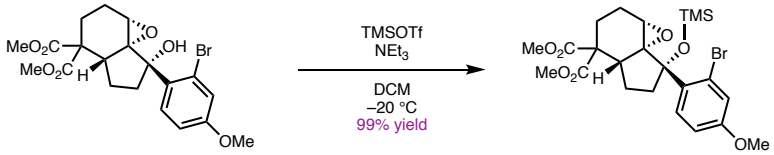
FTIR (NaCl, thin film): 3491, 2995, 2952, 2838, 2255, 1731, 1602, 1487, 1291, 1234, 1031, 917, 731 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{20}H_{25}O_8Br$ $[M+H_2O]^+$ 472.0727, found 472.0750.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +58.1° (*c* = 1.35, $CHCl_3$).

TLC (30% EtOAc:70% Hexanes), R_f: 0.40 (blue in *p*-anisaldehyde)

Preparation of silyl ether 164n:



164n-OH **164n**

A 500 mL round bottom flask was charged with epoxy alcohol **164n-OH** (3.95 g, 8.67 mmol, 1.0 equiv) and was dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 10 mL at 45 °C water bath temperature) followed by drying under vacuum on a Schlenk line (0.2 torr) for 30 minutes. The epoxy alcohol was dissolved in CH_2Cl_2 (87 mL, 0.1 M) and was cooled to –20 °C on

an acetone/dry ice bath. Et_3N (3.63 mL, 26.0 mmol, 3.0 equiv) was added followed by TMSOTf (1.49 mL, 10.4 mmol, 1.2 equiv). The reaction was stirred for 30 minutes then was warmed to 0 °C on an ice bath. An additional portion of TMSOTf was added if needed (0.63 mL, 3.47 mmol, 0.4 equiv) to ensure complete consumption of starting material by TLC. The reaction was quenched with sat. $NaHCO_3$ (150 mL) and was allowed to warm to 21 °C. The biphasic mixture was transferred to a separatory funnel, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 10% to 15% to 20% ethyl acetate in hexanes) to afford silyl ether **164n** (4.52 g, 8.59 mmol, 99% yield) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.30 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 2.7 Hz, 1H), 6.79 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 3.47 (d, *J* = 3.5 Hz, 1H), 2.93 (dd, *J* = 10.9, 7.7 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.50 – 2.27 (m, 4H), 2.14 – 2.07 (m, 1H), 1.97 – 1.88 (m, 1H), 1.65 – 1.53 (m, 1H), 0.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 170.4, 158.8, 135.7, 128.1, 122.7, 121.0, 112.3, 82.1, 70.6, 56.7, 55.5, 55.2, 52.8, 52.1, 43.8, 40.3, 29.2, 24.1, 21.4, 2.4.

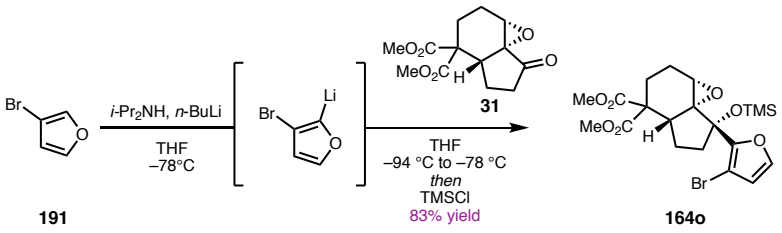
FTIR (NaCl, thin film): 2952, 2389, 1731, 1601, 1488, 1434, 1239, 1032, 883, 842, 734 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{23}H_{35}O_7BrN$ $[M+NH_4]^+$ 544.1361, found 544.1359.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +34.4° (*c* = 1.30, $CHCl_3$).

TLC (20% EtOAc:80% Hexanes), R*f*: 0.40 (blue in *p*-anisaldehyde)

Preparation of 1,2-addition product 164o:



Prepared via General Procedure C, 83% yield.

Prepared from **31** (81.2 mg, 0.30 mmol, 1.0 equiv), *n*-BuLi (2.6 M in hexanes, 140 µL, 0.36 mmol, 1.3 equiv), *i*-Pr_2NH (60 µL, 0.43 mmol, 1.4 equiv), **191** (52.9 mg, 0.36 mmol, 1.2 equiv) and TMSCl (90 µL, 0.87 mmol, 2.4 equiv) according to method **C**. The reaction was directly subjected to column chromatography (silica, 15% EtOAc:85% Hexanes) to yield **164o** (122.0 mg, 83% yield) as a pale yellow crystalline solid.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.34 (d, *J* = 1.9 Hz, 1H), 6.42 (d, *J* = 1.9 Hz, 1H), 3.76 (s, 3H), 3.68 (d, *J* = 3.7 Hz, 1H), 3.66 (s, 3H), 2.79 (ddd, *J* = 12.3, 8.2, 2.4 Hz, 1H), 2.65 (dddd, *J* = 12.4, 10.1, 7.8, 2.4 Hz, 1H), 2.57 (dd, *J* = 10.0, 7.8 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.13 – 2.05 (m, 1H), 2.03 – 1.97 (m, 1H), 1.90 – 1.79 (m, 1H), 1.58 – 1.45 (m, 1H), –0.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 170.4, 150.9, 141.6, 116.0, 97.3, 76.6, 70.0, 56.2, 55.1, 52.7, 52.1, 41.4, 35.1, 29.7, 21.3, 21.1, 1.1.

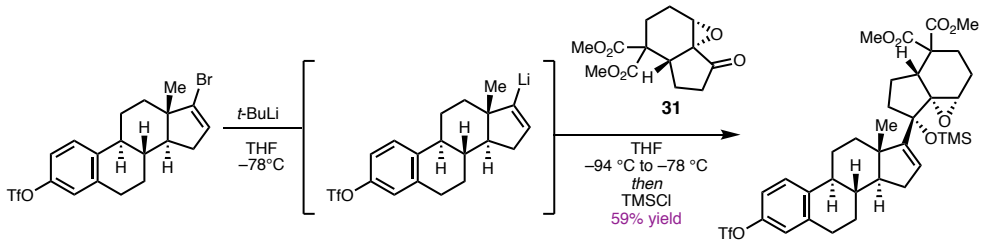
FTIR (NaCl, thin film): 3151, 2993, 2952, 2847, 1733, 1567, 1432, 1250, 873, 843 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{20}H_{28}O_7SiBr$ $[M+H]^+$ 487.0782, found 487.0780.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +57.4° (*c* = 1.00, $CHCl_3$).

TLC (15% EtOAc:85% Hexanes), R_f: 0.29, (light brown in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164p:



192 **164p**

Prepared via General Procedure B, 59% yield.

Prepared from **31** (80.5 mg, 0.30 mmol, 1.0 equiv), **192** (187.0 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.46 mL, 0.75 mmol, 2.4 equiv), and TMSCl (90 µL, 0.71 mmol, 2.4 equiv) according to method **B**. The reaction was directly subjected to repeated column chromatography (silica, 10% EtOAc:90% Hexanes) to yield **164p** (131.0 mg, 59% yield) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.31 (d, *J* = 8.5 Hz, 1H), 7.01 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.97 (d, *J* = 2.6 Hz, 1H), 5.67 (dd, *J* = 3.3, 1.5 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.36 (d, *J* = 3.8 Hz, 1H), 2.96 – 2.90 (m, 2H), 2.83 (dd, *J* = 10.1, 8.2 Hz, 1H), 2.59 (dddd, *J* = 13.1, 11.2, 8.2, 3.3 Hz, 1H), 2.43 – 2.18 (m, 6H), 2.18 – 2.07 (m, 2H), 2.04 – 1.92 (m, 3H), 1.87 (ddt, *J* = 13.1, 10.2, 8.4 Hz, 1H), 1.67 – 1.38 (m, 6H), 1.00 (s, 3H), 0.10 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 170.8, 158.0, 147.6, 141.4, 139.7, 127.0, 125.8, 121.3, 120.2, 118.2, 117.7, 80.3, 70.9, 57.2, 55.8, 55.5, 52.9, 52.1, 48.0, 44.3, 41.9, 37.5, 36.8, 36.6, 31.1, 30.0, 29.6, 27.3, 26.6, 22.5, 21.3, 17.9, 2.7.

*Note: The peaks at 120.2 ppm, and 118.2 ppm are split due to C-F coupling. ^{1}J=320.8 Hz.

^{19}F NMR (376 MHz, $CDCl_3$): δ 73.0.

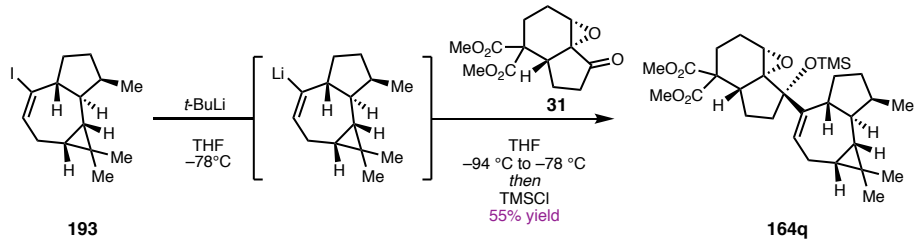
FTIR (NaCl, thin film): 2949, 2850, 1734, 1420, 1249, 1214, 1143, 919, 882, 839, 758 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{35}H_{46}F_3O_9SSi$ $[M+H]^+$, 727.2578 found 727.2582.

$[\alpha]_D^{25}$ = +22.5° (*c* = 1.00, $CHCl_3$).

TLC (10% EtOAc:90% Hexanes), R_f: 0.46, (turquoise in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 164q:



Prepared via General Procedure B, 55% yield.

Prepared from **31** (80.5 mg, 0.30 mmol, 1.0 equiv), **193** (127.0 mg, 0.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 0.45 mL, 0.74 mmol, 2.4 equiv), and TMSCl (90 µL, 0.71 mmol, 2.4 equiv) according to method **B**. The reaction was directly subjected to column chromatography (silica, 100% Pentane) to yield **164q** (88.5 mg, 55% yield) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.67 (ddd, *J* = 8.9, 4.2, 1.6 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.29 (d, *J* = 3.7 Hz, 1H), 2.63 (dd, *J* = 10.3, 7.8 Hz, 1H), 2.49 – 2.29 (m, 4H), 2.20 – 1.94 (m, 7H), 1.94 – 1.74 (m, 3H), 1.62 – 1.49 (m, 1H), 1.26 (tt, *J* = 12.0, 9.6 Hz, 1H), 1.07 (s, 3H), 1.02 (s, 3H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.85 (td, *J* = 10.2, 9.5, 6.7 Hz, 1H), 0.52 (dd, *J* = 11.4, 9.4 Hz, 1H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 170.6, 145.6, 123.1, 83.9, 72.3, 56.6, 55.3, 52.8, 52.1, 46.4, 45.1, 42.8, 41.1, 33.1, 32.9, 32.3, 29.8, 28.6, 26.8, 25.4, 24.1, 23.0, 21.7, 18.8, 18.6, 15.4, 2.4.

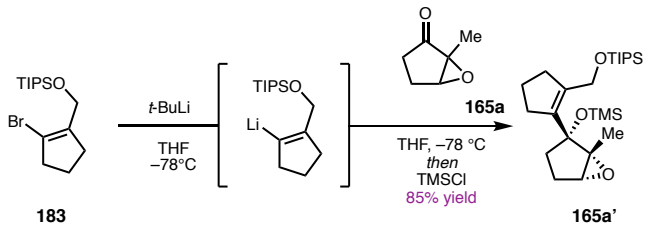
FTIR (NaCl, thin film): 2951, 2868, 1734, 1456, 1433, 1247, 1221, 838, 758 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{30}H_{50}O_6SiN$ $[M+NH_4]^+$, 548.3402 found 548.3398.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –40.0° (*c* = 1.00, $CHCl_3$).

TLC (10% EtOAc:90% Hexanes), R_f: 0.54, (blue in *p*-anisaldehyde stain).

Preparation of 1,2-addition product 165a':



Prepared via General Procedure A, 85% yield.

Prepared from **165a** (235 mg, 1.97 mmol, 1.0 equiv), **183** (788 mg, 2.36 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 2.84 mL, 4.83 mmol, 2.45 equiv) and TMSCl (0.60 mL, 2.4 equiv) according to method **A**. The reaction was quenched with sat. $NaHCO_3$, and the reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 1% EtOAc: 99% Hexanes) to yield the product **165a'** (737.4 mg, 85% yield) as a white crystalline solid.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 4.80 (dt, *J* = 14.0, 1.6 Hz, 1H), 4.60 (dt, *J* = 13.9, 2.0 Hz, 1H), 3.29 (s, 1H), 2.71 – 2.57 (m, 1H), 2.55 – 2.44 (m, 1H), 2.36 (dddt, *J* = 15.3, 8.8, 6.7, 2.2 Hz, 1H), 2.19 (dddd, *J* = 16.6, 9.0, 4.8, 2.0 Hz, 1H), 2.00 (td, *J* = 10.1, 3.4 Hz, 1H), 1.85 – 1.65 (m, 5H), 1.34 (s, 3H), 1.21 – 1.00 (m, 21H), 0.19 (s, 9H).

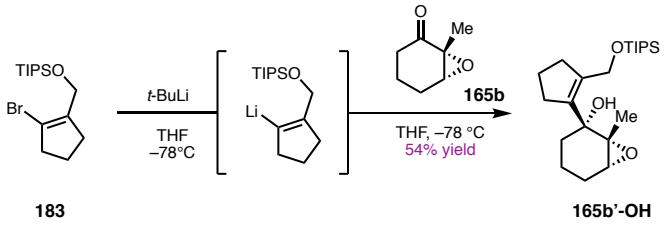
^{13}C NMR (126 MHz, $CDCl_3$): δ 139.3, 136.0, 86.1, 67.4, 63.7, 61.7, 35.1, 34.9, 34.4, 26.5, 22.1, 18.3, 18.3, 13.4, 12.2, 2.4.

FTIR (NaCl, thin film): 2934, 2866, 1652, 1463, 1248, 1098, 1056, 989, 839 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{24}H_{46}O_3Si_2$ $[M]^+$ 438.2980, found 438.2985.

TLC (10% EtOAc:90% Hexanes), R_f: 0.67 (grey in *p*-anisaldehyde)

Preparation of 1,2-addition product 165b'-OH:



Prepared via General Procedure A, 54% yield.

Prepared from **165b** (229 mg, 1.82 mmol, 1.0 equiv), **183** (726 mg, 2.18 mmol, 1.2 equiv), *t*-BuLi (1.7 M in pentane, 2.62 mL, 4.45 mmol, 2.45 equiv) according to method **A**. The reaction was quenched with MeOH (1 mL) and sat. NH_4Cl (5 mL) at –78 °C. The reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 15%

EtOAc:85% Hexanes) then a second column (silica, 1% – 5% gradient of Et_2O in CH_2Cl_2) to yield the product **165b'-OH** (372.8 mg, 54% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 4.49 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 12.5 Hz, 1H), 3.24 (t, *J* = 2.2 Hz, 1H), 3.05 (s, 1H), 2.62 – 2.38 (m, 4H), 2.02 (dt, *J* = 13.0, 6.0 Hz, 1H), 1.89 – 1.61 (m, 4H), 1.58 – 1.42 (m, 2H), 1.40 – 1.33 (m, 1H), 1.32 (s, 3H), 1.17 – 1.05 (m, 21H).

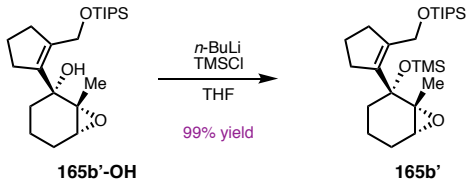
^{13}C NMR (126 MHz, $CDCl_3$): δ 139.4, 137.5, 74.9, 64.0, 63.0, 61.2, 36.2, 36.0, 30.4, 23.9, 22.3, 19.2, 18.2, 16.4, 12.1.

FTIR (NaCl, thin film): 3485, 2940, 2893, 2965, 1463, 1381, 1086, 996, 882 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{22}H_{41}O_3Si$ $[M+H]^+$ 381.2825, found 381.2808.

TLC (5% Et_2O:95% CH_2Cl_2), R_f: 0.47 (purple in *p*-anisaldehyde)

Preparation of silyl ether 165b':



A 25 mL oven dried N_2 flushed flask was charged with epoxy alcohol **165b'-OH** (100 mg, 0.26 mmol, 1.0 equiv) and THF (2.6 mL). The solution was cooled to –78 °C then *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.32 mmol, 1.2 equiv) was added and the reaction stirred for 20 minutes. Next, to the solution was added trimethylsilyl chloride (67 μL, 0.53 mmol, 2.0 equiv). The reaction was allowed to warm to 21 °C and stir at this temperature for 15 minutes. The reaction was quenched with sat. $NaHCO_3$, and the reaction mixture

was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 2% EtOAc:98% Hexanes) to yield the product **165b'** (117.5 mg, 99% yield) as a clear colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.54 (dt, *J* = 12.7, 1.2 Hz, 1H), 4.35 (ddd, *J* = 12.6, 2.5, 1.2 Hz, 1H), 3.11 (d, *J* = 4.2 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.59 – 2.34 (m, 3H), 1.95 – 1.59 (m, 5H), 1.50 (dt, *J* = 11.6, 3.3 Hz, 1H), 1.47 – 1.38 (m, 1H), 1.35 (dq, *J* = 10.5, 2.9 Hz, 1H), 1.31 (s, 3H), 1.18 – 1.00 (m, 21H), 0.17 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.1, 137.6, 80.1, 63.8, 62.5, 61.4, 36.7, 35.9, 32.9, 22.7, 21.8, 18.8, 18.5, 18.2, 12.2, 2.8.

FTIR (NaCl, thin film): 2934, 2863, 1463, 1378, 1250, 1100, 1013, 964, 883, 840 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{25}H_{48}O_3Si_2$ $[M]^+$ 452.3137, found 452.3143.

TLC (10% EtOAc:90% Hexanes), R_f: 0.72 (dark purple in *p*-anisaldehyde)

Preparative procedures for semi-pinacol rearrangements:

General Procedure A:

A 25 mL round bottom flask was charged with the epoxide (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (0.40 equiv). The mixture was dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 5 mL, 45 °C water bath temperature) followed by drying under vacuum on a Schlenk line (0.3 torr) for 30 minutes. The flask was backfilled with N_2 and was charged CH_2Cl_2 (0.04 M). The resulting solution was cooled to –78 °C then *N*-

(Trimethylsilyl)bis(trifluoromethanesulfonyl)imide ($TMSNTf_2$) (0.10 equiv) was added, which was weighed out in a glovebox in a 25 μL syringe. The reaction was stirred for 30 minutes at –78 °C and was then quenched with MeOH (0.1 mL) at this temperature. The reaction was warmed to 21 °C then the reaction concentrated under reduced pressure. The crude product was purified directly by SiO_2 column chromatography.

General Procedure B:

A 25 mL round bottom flask was charged with the epoxide (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.1 equiv). The mixture was dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 5 mL, 45 °C water bath temperature) followed by drying under vacuum on a Schlenk line (0.3 torr) for 30 minutes. The flask was backfilled with N_2 and was charged CH_2Cl_2 (0.04 M). The resulting solution was cooled to –78 °C and then *N*-(Trimethylsilyl)bis(trifluoromethanesulfonyl)imide ($TMSNTf_2$) (0.50 equiv) was added, which was weighed out in a glovebox in a 25 μL syringe. The reaction was stirred for 4 hours at –78 °C and was then quenched with MeOH (0.1 mL) at this temperature. The reaction was warmed to 21 °C then the reaction was concentrated under reduced pressure. The crude product was purified directly by SiO_2 column chromatography.

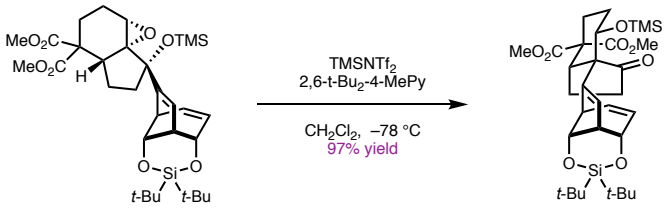
General Procedure C

A 25 mL round bottom flask was charged with the epoxide (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.0 equiv). The mixture was dried via azeotropic removal of trace water by concentration under reduced pressure from anhydrous toluene (3 x 5 mL, 45 °C water bath temperature) followed by drying under vacuum on a Schlenk line (0.3 torr) for 30 minutes. The flask was backfilled with N_2 and charged with CH_2Cl_2 (0.04 M). The resulting solution was cooled to –78 °C, then *N*-(Trimethylsilyl)bis(trifluoromethanesulfonyl)imide ($TMSNTf_2$) (0.30 equiv) was added, which was weighed out in a glovebox in a 25 μL syringe. The reaction was stirred for 4 hours at –78 °C and was then quenched with MeOH (0.1 mL) at this temperature. The reaction was warmed to 21 °C then the reaction was concentrated under reduced pressure. The crude product was purified directly by SiO_2 column chromatography.

General Procedure D:

A 25 mL round bottom flask was charged with the epoxy alcohol (1.0 equiv), triethylamine (6.0 equiv), and CH_2Cl_2 (0.1 M). The solution was cooled to 0 °C then TMSOTf (5.0 equiv) was added, and the reaction was stirred for 1 hour at this temperature. The reaction was quenched with sat. NH_4Cl (5 mL), and 1 M HCl (1 mL) and was stirred vigorously for 1 hour at 21 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography.

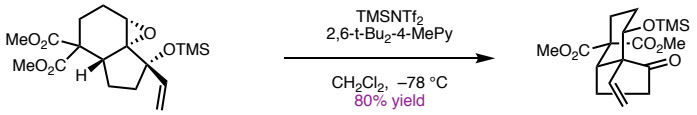
Preparation of semi-pinacol product 33a:



164a **33a**

Prepared from **164a** (4.27 g, 7.93 mmol, 1.0 equiv), according to method reported by Reisman, and ^{1}H NMR characterization data matched their report.[40]

Preparation of semi-pinacol product 33b:



164b **33b**

Prepared via General Procedure A, 80% yield.

Prepared from **164b** (79.1 mg, 0.22 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (17.6 mg, 0.086 mmol, 0.4 equiv), and $TMSNTf_2$ (7.6 mg, 0.022 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33b** (63.5 mg, 80% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.66 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.21 (dd, *J* = 11.2, 0.6 Hz, 1H), 5.08 (dt, *J* = 17.8, 0.4 Hz, 1H), 4.19 (t, *J* = 2.9 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.18 (dd, *J* = 12.4, 7.2 Hz, 1H), 2.46 (td, *J* = 13.8, 4.0 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.23 – 2.07 (m, 3H), 1.78 – 1.68 (m, 1H), 1.64 – 1.50 (m, 2H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 218.2, 171.0, 170.9, 138.7, 116.1, 70.5, 58.1, 56.3, 52.8, 52.8, 45.6, 38.6, 27.0, 23.6, 19.4, 0.1.

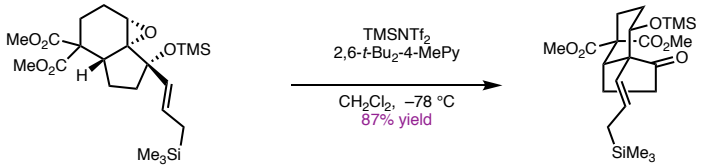
FTIR (NaCl, thin film): 3086, 2954, 1738, 1681, 1434, 1253, 1172, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{18}H_{28}O_6SiNa$ $[M+Na]^+$ 391.1547, found 391.1553.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +143.8° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R*f*: 0.34 (turquoise in *p*-anisaldehyde).

Preparation of semi-pinacol product 33c:



164c **33c**

Prepared via General Procedure A, 87% yield.

Prepared from **164c** (92.6 mg, 0.20 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (16.7 mg, 0.082 mmol, 0.4 equiv), and $TMSNTf_2$ (7.2 mg, 0.020 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 10% Acetone:90% Hexanes) to yield **33c** (80.2 mg, 87% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.59 (dt, *J* = 16.0, 8.1 Hz, 1H), 5.14 (dt, *J* = 15.9, 1.3 Hz, 1H), 4.07 (t, *J* = 2.7 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.16 (dd, *J* = 12.5, 6.8 Hz, 1H), 2.51 – 2.41 (m, 1H), 2.34 – 2.24 (m, 1H), 2.19 – 2.03 (m, 3H), 1.73 – 1.65 (m, 1H), 1.59 – 1.52 (m, 2H), 1.48 – 1.42 (m, 2H), 0.05 (s, 9H), –0.01 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 218.6, 171.1, 129.2, 128.3, 72.4, 57.4, 56.5, 52.8, 52.7, 45.6, 38.5, 26.9, 23.8, 23.6, 19.4, 0.1, –1.7.

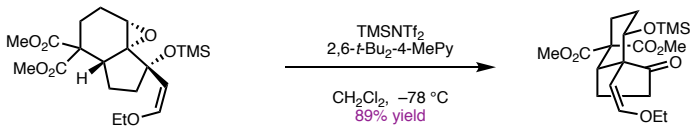
FTIR (NaCl, thin film): 2953, 1741, 1434, 1404, 1251, 1170, 844 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{22}H_{38}O_6Si_2Na$ $[M+Na]^+$ 477.2099, found 477.2098.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +130.6° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R*f*: 0.40 (navy blue in *p*-anisaldehyde).

Preparation of semi-pinacol product 33d:



164d **33d**

Prepared via General Procedure A, 89% yield.

Prepared from **164d** (67.4 mg, 0.16 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (13.4 mg, 0.065 mmol, 0.4 equiv), and $TMSNTf_2$ (6.0 mg, 0.016 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33d** (60.9 mg, 89% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.92 (d, *J* = 6.1 Hz, 1H), 4.04 (d, *J* = 6.1 Hz, 1H), 3.93 (t, *J* = 2.8 Hz, 1H), 3.78 (dq, *J* = 9.9, 7.1 Hz, 1H), 3.73 (s, 3H), 3.74 – 3.67 (m, 1H), 3.68 (s, 3H), 3.52 (dd, *J* = 13.0, 7.0 Hz, 1H), 2.41 (td, *J* = 13.8, 3.8 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.26 (ddd, *J* = 18.4, 8.7, 1.0 Hz, 1H), 2.17 – 2.01 (m, 2H), 1.79 (dddd, *J* = 11.4,

8.6, 7.0, 1.3 Hz, 1H), 1.67 (dddd, *J* = 14.4, 13.6, 3.2, 2.0 Hz, 1H), 1.60 (dq, *J* = 14.4, 3.7 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.04 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 220.6, 171.3, 145.1, 107.2, 72.1, 68.0, 56.2, 54.8, 52.7, 52.5, 43.7, 38.4, 26.6, 24.0, 19.4, 15.3, 0.1.

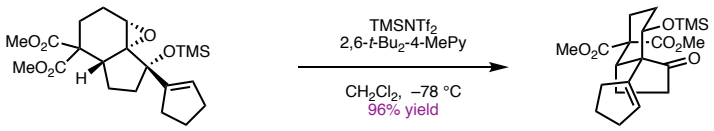
FTIR (NaCl, thin film): 2954, 2898, 1742, 1659, 1435, 1252, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{20}H_{32}O_7SiNa$ $[M+Na]^+$ 435.1810, found 435.1818.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +89.9° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R_f: 0.23 (brown in *p*-anisaldehyde).

Preparation of semi-pinacol product 33e:



164e **33e**

Prepared via General Procedure A, 96% yield.

Prepared from **164e** (77.9 mg, 0.19 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (15.7 mg, 0.076 mmol, 0.4 equiv), and $TMSNTf_2$ (6.7 mg, 0.019 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33e** (74.4 mg, 96% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.38 (p, *J* = 2.1 Hz, 1H), 4.33 (t, *J* = 2.9 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.37 (dd, *J* = 12.5, 6.9 Hz, 1H), 2.53 (dddd, *J* = 16.9, 9.6, 4.7, 2.0 Hz, 1H), 2.46 (td, *J* = 13.9, 3.9 Hz, 1H), 2.42 – 2.24 (m, 3H), 2.24 – 2.07 (m, 3H), 1.98

– 1.89 (m, 1H), 1.89 – 1.81 (m, 2H), 1.81 – 1.72 (m, 2H), 1.68 (dq, *J* = 14.3, 3.6 Hz, 1H), 0.06 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 219.4, 171.0, 170.7, 143.1, 127.5, 70.5, 58.0, 56.3, 52.7, 42.1, 39.3, 33.1, 32.9, 28.0, 23.7, 23.0, 19.7, 0.1.

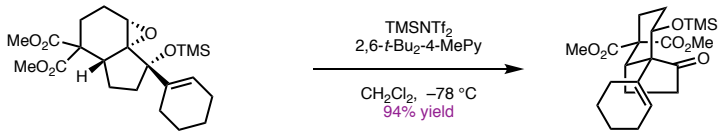
FTIR (NaCl, thin film): 2953, 2849, 1741, 1434, 1252, 1169, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{21}H_{32}O_6SiNa$ $[M+Na]^+$ 431.1860, found 431.1861.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +100.5° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R_f: 0.33 (dark green in *p*-anisaldehyde).

Preparation of semi-pinacol product 33f:



164f **33f**

Prepared via General Procedure A, 94% yield.

Prepared from **164f** (54.1 mg, 0.13 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (10.5 mg, 0.051 mmol, 0.4 equiv), and $TMSNTf_2$ (4.5 mg, 0.013 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33f** (50.9 mg, 94% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.32 (t, *J* = 3.8 Hz, 1H), 4.34 (s, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.46 (dd, *J* = 12.5, 7.2 Hz, 1H), 2.44 (td, *J* = 13.8, 4.0 Hz, 1H), 2.32 (dd, *J* =

17.8, 8.0 Hz, 1H), 2.27 – 2.03 (m, 5H), 2.03 – 1.93 (m, 1H), 1.80 – 1.69 (m, 2H), 1.69 – 1.54 (m, 4H), 1.54 – 1.42 (m, 2H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 220.5, 171.0, 170.7, 136.4, 124.3, 69.9, 60.6, 56.3, 52.8, 41.4, 39.9, 28.2, 26.9, 25.7, 23.6, 23.0, 22.1, 19.7, 0.2.

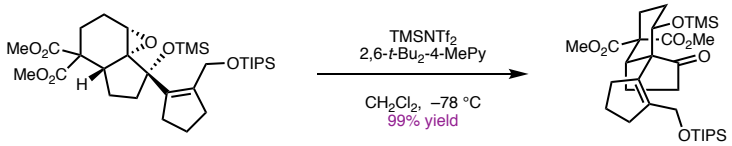
FTIR (NaCl, thin film): 2950, 2933, 2858, 2839, 1740, 1682, 1434, 1251, 1060, 1020, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{22}H_{34}O_6SiNa$ $[M+Na]^+$ 445.2017, found 445.2023.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +102.6° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R_f: 0.37 (pistachio in *p*-anisaldehyde).

Preparation of semi-pinacol product 33g:



164g **33g**

Prepared via General Procedure A, 99% yield.

Prepared from **164g** (132.0 mg, 0.22 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (18.2 mg, 0.89 mmol, 0.4 equiv), and $TMSNTf_2$ (7.8 mg, 0.022 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33g** (130.0 mg, 99% yield) as a clear colorless oil.

^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 4.27 (t, *J* = 2.9 Hz, 1H), 4.22 (d, *J* = 12.2 Hz, 1H), 4.05 (d, *J* = 12.7 Hz, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.40 (dd, *J* = 12.6, 7.5 Hz, 1H),

2.63 – 2.51 (m, 1H), 2.51 – 2.39 (m, 2H), 2.38 – 2.30 (m, 1H), 2.30 – 2.16 (m, 3H), 2.15 – 2.03 (m, 2H), 1.90 – 1.77 (m, 2H), 1.77 – 1.67 (m, 3H), 1.20 – 1.04 (m, 21H), 0.05 (s, 9H).

^{13}C NMR (101 MHz, CD_3CN): δ 218.6, 170.8, 170.7, 138.4, 136.0, 70.5, 61.6, 57.5, 56.4, 52.0, 51.9, 45.2, 38.5, 36.5, 34.8, 28.2, 23.3, 21.4, 19.2, 17.4, 11.9, –1.1.

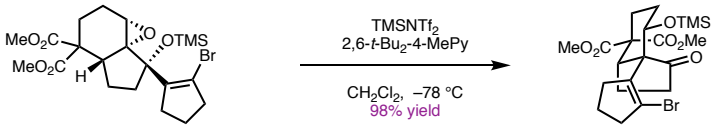
FTIR (NaCl, thin film): 2948, 2865, 1743, 1447, 1252, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{31}H_{54}O_7Si_2Na$ $[M+Na]^+$ 617.3300, found 617.3309.

$[\alpha]_D^{25}$ = +26.9° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R_f: 0.49 (dark purple in *p*-anisaldehyde).

Preparation of semi-pinacol product 33h:



164h **33h**

Prepared via General Procedure A, 98% yield.

Prepared from **164h** (82.0 mg, 0.17 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (13.8 mg, 0.067 mmol, 0.4 equiv), and $TMSNTf_2$ (5.9 mg, 0.017 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33h** (80.1 mg, 98% yield) as a clear colorless oil.

^{1}H NMR (400 MHz, CD_3CN): δ 4.23 (s, 1H), 3.84 – 3.74 (m, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 2.62 (dddd, *J* = 11.7, 7.8, 5.1, 2.4 Hz, 2H), 2.52 – 2.32 (m, 3H), 2.25 (dddd, *J* = 18.6,

9.2, 1.3, 0.7 Hz, 2H), 2.13 – 1.99 (m, 2H), 1.90 – 1.78 (m, 3H), 1.76 – 1.61 (m, 2H), 0.03 (s, 9H).

^{13}C NMR (101 MHz, CD_3CN): δ 217.3, 171.0, 170.7, 140.1, 116.8, 70.2, 57.2, 56.5, 52.1, 52.0, 42.2, 41.5, 39.3, 35.0, 28.2, 23.6, 21.7, 19.2, –1.0. *run at 70 °C to converge atropisomers.

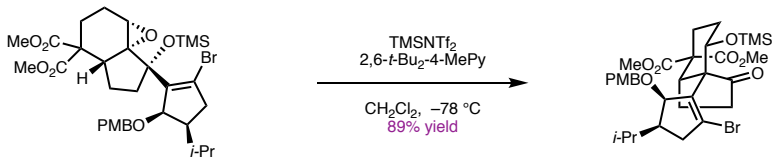
FTIR (NaCl, thin film): 2952, 2911, 2858, 1740, 1622, 1433, 1252, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{21}H_{31}O_6SiBrNa$ $[M+Na]^+$ 509.0965, found 509.0950.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +20.0° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R_f: 0.31 (dark pistachio in *p*-anisaldehyde).

Preparation of semi-pinacol product 33i:



164i **33i**

Prepared via General Procedure B, 89% yield.

Prepared from **164i** (78.2 mg, 0.12 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (26.5 mg, 0.13 mmol, 1.1 equiv), and $TMSNTf_2$ (20.8 mg, 0.059 mmol, 0.5 equiv) at –78 °C for 4 hours according to method **B**. The reaction was purified by column chromatography (silica, 10 to 20% EtOAc gradient in hexanes) to yield **33i** (69.4 mg, 89% yield) as a white foam.

^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.40 – 7.32 (m, 2H), 6.89 – 6.80 (m, 2H), 5.17 (d, *J* = 10.3 Hz, 1H), 4.78 – 4.72 (m, 1H), 4.47 (d, *J* = 5.7 Hz, 1H), 4.23 (d, *J* = 10.3 Hz, 1H),

3.78 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 2.68 (d, *J* = 8.2 Hz, 2H), 2.61 (ddd, *J* = 18.6, 10.8, 9.6 Hz, 1H), 2.48 (ddd, *J* = 14.0, 12.5, 5.1 Hz, 1H), 2.33 (ddt, *J* = 18.5, 9.3, 1.0 Hz, 1H), 2.13 (tdd, *J* = 12.5, 10.8, 9.6 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.98 – 1.87 (m, 2H), 1.83 (dddd, *J* = 11.9, 9.5, 7.7, 1.2 Hz, 1H), 1.76 – 1.65 (m, 2H), 1.11 (d, *J* = 5.8 Hz, 3H), 0.96 (d, *J* = 6.0 Hz, 3H), –0.06 (d, *J* = 0.8 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 218.8, 171.4, 171.0, 159.0, 140.8, 131.5, 129.5, 125.6, 113.7, 81.9, 67.9, 66.0, 57.5, 56.7, 55.4, 52.8, 52.7, 50.3, 46.1, 43.1, 39.7, 29.1, 27.7, 24.1, 22.1, 21.7, 19.1, 0.2.

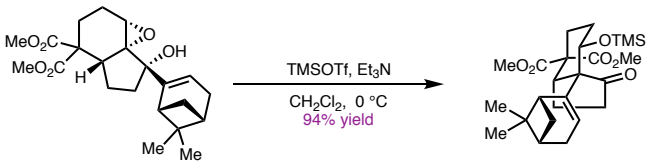
FTIR (NaCl, thin film): 2954, 1738, 1614, 1514, 1251, 1172, 1059, 866, 840 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{32}H_{49}O_8SiBrN$ $[M+NH_4]^+$ 682.2405, found 682.2403.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +12.3° (*c* = 1.00, $CHCl_3$).

TLC (20% EtOAc:80% Hexanes), R_f: 0.42 (dark blue in *p*-anisaldehyde).

Preparation of semi-pinacol product 33j:



164j-OH **33j**

Prepared via General Procedure D, 94% yield.

Prepared from **164j-OH** (60.0 mg, 0.15 mmol, 1.0 equiv), triethylamine (129 µL, 0.92 mmol, 6.0 equiv), and TMSOTf (139 µL, 0.77 mmol, 5.0 equiv) at 0 °C for 1 hour according to method **D**. The reaction was quenched with sat. NH_4Cl (5 mL), and 1 M HCl (1 mL) and was stirred vigorously for 1 hour. The layers were separated, and the

aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 100% CH_2Cl_2 to 10% Et_2O in CH_2Cl_2 gradient) to yield **33j** (66.9 mg, 94% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.18 (dq, *J* = 3.1, 1.6 Hz, 1H), 4.35 (t, *J* = 2.8 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.31 (dd, *J* = 11.9, 7.1 Hz, 1H), 2.45 (td, *J* = 13.9, 3.6 Hz, 1H), 2.39 (dt, *J* = 8.8, 5.7 Hz, 1H), 2.27 – 2.14 (m, 4H), 2.12 – 1.98 (m, 2H), 1.96 (dtd, *J* = 5.6, 2.8, 1.1 Hz, 1H), 1.88 (td, *J* = 5.6, 1.8 Hz, 1H), 1.85 – 1.72 (m, 2H), 1.69 (dq, *J* = 14.2, 3.6 Hz, 1H), 1.39 (d, *J* = 8.8 Hz, 1H), 1.22 (s, 3H), 0.88 (s, 3H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 217.8, 171.1, 170.7, 145.8, 119.7, 69.8, 60.0, 56.5, 53.0, 52.7, 45.8, 41.9, 40.3, 39.7, 38.7, 32.3, 31.4, 28.4, 26.7, 24.0, 21.2, 19.4, 0.2.

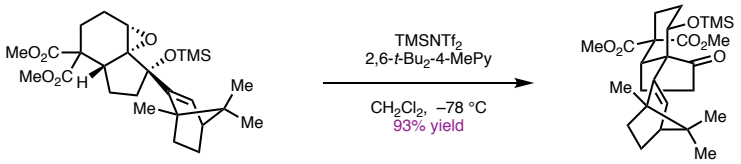
FTIR (NaCl, thin film): 2952, 2916, 2930, 1742, 1459, 1432, 1250, 1169, 1057, 844 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{25}H_{39}O_6Si$ $[M+H]^+$ 463.2510, found 463.2527.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +69.8° (*c* = 1.00, $CHCl_3$).

TLC (100% CH_2Cl_2), R_f: 0.54 (dark blue in *p*-anisaldehyde).

Preparation of semi-pinacol product 33k:



164k **33k**

Prepared via General Procedure A, 93% yield.

Prepared from **164k** (82.9 mg, 0.17 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (14.3 mg, 0.070 mmol, 0.4 equiv), and $TMSNTf_2$ (6.1 mg, 0.017 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 6% Acetone:94% Hexanes) to yield **33k** (77.2 mg, 93% yield) as a white crystalline solid.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.70 (d, *J* = 3.7 Hz, 1H), 4.31 (s, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 3.27 (dd, *J* = 11.8, 8.1 Hz, 1H), 2.39 (td, *J* = 13.9, 3.4 Hz, 1H), 2.34 – 2.19 (m, 2H), 2.17 (t, *J* = 3.7 Hz, 1H), 2.12 (dt, *J* = 14.0, 3.1 Hz, 1H), 2.07 – 1.91 (m, 3H), 1.78 (ddt, *J* = 11.6, 9.0, 3.6 Hz, 1H), 1.69 (dq, *J* = 14.1, 3.5 Hz, 1H), 1.59 (ddd, *J* = 12.1, 9.2, 3.3 Hz, 1H), 1.37 (ddd, *J* = 11.9, 8.9, 4.0 Hz, 1H), 0.91 (d, *J* = 3.6 Hz, 6H), 0.71 (s, 3H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 219.9, 171.3, 170.7, 146.9, 133.4, 71.1, 59.0, 57.2, 56.5, 55.7, 52.7, 52.7, 51.5, 42.1, 38.9, 31.6, 28.5, 25.2, 24.6, 20.1, 19.9, 19.5, 14.3, 0.2.

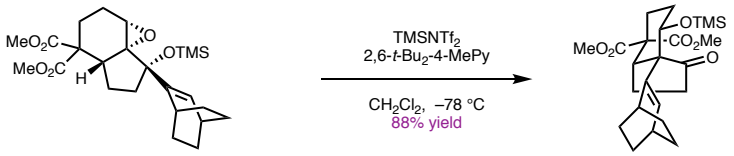
FTIR (NaCl, thin film): 3062, 2951, 2874, 1742, 1434, 1250, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{26}H_{40}O_6SiK$ $[M+K]^+$ 515.2226, found 515.2231.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +1.8° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R*f*: 0.41 (vibrant purple in *p*-anisaldehyde).

Preparation of semi-pinacol product 33l:



164l 33l

Prepared via General Procedure A, 88% yield.

Prepared from **164l** (53.0 mg, 0.12 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (9.7 mg, 0.047 mmol, 0.4 equiv), and $TMSNTf_2$ (4.2 mg, 0.012 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 10% Acetone:90% Hexanes) to yield **33l** (50.7 mg, 88% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.85 (dd, *J* = 7.0, 1.9 Hz, 1H), 4.34 (t, *J* = 2.8 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.35 (dd, *J* = 12.3, 7.0 Hz, 1H), 2.50 – 2.41 (m, 2H), 2.29 (dd, *J* = 17.9, 8.1 Hz, 1H), 2.22 – 2.01 (m, 4H), 1.88 – 1.79 (m, 1H), 1.79 – 1.66 (m, 3H), 1.55 – 1.24 (m, 6H), 1.18 (dddd, *J* = 11.8, 9.1, 5.8, 2.5 Hz, 1H), 0.05 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 218.7, 171.2, 170.6, 143.8, 129.7, 69.9, 59.8, 56.5, 52.8, 52.7, 42.7, 39.5, 33.8, 30.7, 28.5, 27.4, 26.8, 26.4, 25.1, 24.1, 19.4, 0.2.

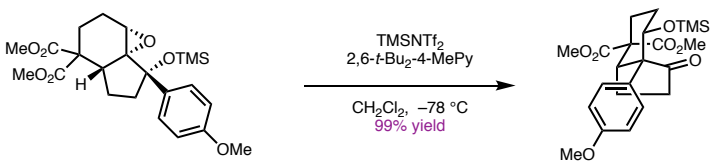
FTIR (NaCl, thin film): 2948, 2863, 1732, 1434, 1252, 860, 844 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{24}H_{36}O_6SiNa$ $[M+Na]^+$ 471.2173, found 471.2155.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +35.6° (*c* = 1.00, $CHCl_3$).

TLC (10% Acetone:90% Hexanes), R_f: 0.29 (bright red in *p*-anisaldehyde).

Preparation of semi-pinacol product 33m:



164m **33m**

Prepared via General Procedure A, 99% yield.

Prepared from **164m** (95.4 mg, 0.21 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (17.5 mg, 0.085 mmol, 0.4 equiv), and $TMSNTf_2$ (7.5 mg, 0.021 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33m** (94.5 mg, 99% yield) as a clear colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 6.99 – 6.94 (m, 2H), 6.85 – 6.79 (m, 2H), 4.64 (t, *J* = 3.1 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.57 (dd, *J* = 12.7, 6.6 Hz, 1H), 3.04 (s, 3H), 2.54 – 2.41 (m, 2H), 2.41 – 2.28 (m, 2H), 2.25 (dtd, *J* = 13.8, 3.5, 1.1 Hz, 1H), 2.02 (tdd, *J* = 13.9, 3.6, 2.2 Hz, 1H), 1.97 – 1.90 (m, 1H), 1.84 (dq, *J* = 14.5, 3.5 Hz, 1H), 0.09 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 220.7, 170.9, 170.2, 158.0, 134.2, 128.9, 113.7, 69.4, 58.8, 56.1, 55.4, 52.8, 52.3, 48.1, 39.6, 28.2, 23.7, 19.4, 0.1.

FTIR (NaCl, thin film): 2952, 2901, 2836, 2794, 1742, 1611, 1514, 1253, 1172, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{23}H_{32}O_7SiNa$ $[M+Na]^+$ 471.1810, found 471.1811.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +72.7° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R_f: 0.15 (yellow in *p*-anisaldehyde).

Preparation of rearrangement product 33n:

164n **33n**

A 500 mL flask was charged with silyl ether **164n** (4.52 g, 8.59 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.94 g, 9.45 mmol, 1.1 equiv) and CH_2Cl_2 (172 mL,

0.05 M), and the solution was cooled to 0 °C. To the flask was added *N*-(Trimethylsilyl)bis(trifluoromethanesulfonyl)imide ($TMSNTf_2$) (1.52, 4.30 mmol, 0.50 equiv) which had being weighed out in a glovebox in a 1 mL syringe. After stirring for an additional 30 minutes at 0 °C the reaction was quenched with sat. $NaHCO_3$ (200 mL) and the solution was allowed to warm to 21 °C. The biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 10% to 12.5% to 15% acetone in hexanes gradient) to afford ketone **33n** (3.32 g, 6.27 mmol, 73% yield) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.17 (d, *J* = 2.8 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 1H), 6.77 (dd, *J* = 8.9, 2.8 Hz, 1H), 4.55 – 4.53 (m, 1H), 4.32 (dd, *J* = 12.0, 8.1 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.07 (s, 3H), 2.75 (dt, *J* = 18.1, 9.6 Hz, 1H), 2.47 (td, *J* = 13.8, 3.8 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.32 – 2.18 (m, 2H), 2.05 – 1.95 (m, 2H), 1.84 (dq, *J* = 14.6, 3.5 Hz, 1H), 0.08 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 219.3, 170.7, 170.3, 158.3, 132.5, 130.1, 123.7, 120.6, 112.4, 70.6, 58.5, 56.1, 55.5, 52.7, 52.2, 41.7, 39.3, 28.4, 23.6, 19.1, –0.1.

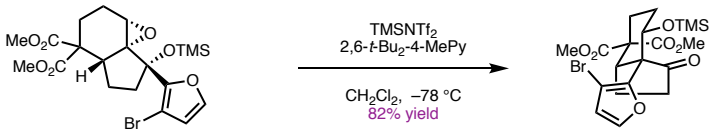
FTIR (NaCl, thin film): 3470, 3083, 2254, 1745, 1732, 1602, 1493, 1456, 1253, 1213, 1173, 1047, 1026, 869, 840, 731 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{23}H_{32}O_7SiBr$ $[M+H]^+$ 527.1095, found 527.1093.

$[\alpha]_D^{25}$ = +52.6° (*c* = 1.40, $CHCl_3$).

TLC (20% EtOAc:80% Hexanes), R_f: 0.35 (yellow in *p*-anisaldehyde).

Preparation of semi-pinacol product 33o:



164o **33o**

Prepared via General Procedure A, 82% yield.

Prepared from **164o** (84.9 mg, 0.17 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (14.3 mg, 0.070 mmol, 0.4 equiv), and $TMSNTf_2$ (6.2 mg, 0.017 mmol, 0.1 equiv) at –78 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 15% Acetone:85% Hexanes) to yield **33o** (69.2 mg, 82% yield) as a clear colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.24 (d, *J* = 2.0 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 4.65 (t, *J* = 2.7 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, *J* = 12.9, 7.4 Hz, 1H), 3.43 (s, 3H), 2.62 – 2.35 (m, 4H), 2.32 – 2.11 (m, 3H), 1.98 (tdd, *J* = 14.4, 3.4, 2.1 Hz, 1H), 1.87 – 1.74 (m, 2H), 0.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 215.5, 170.8, 170.7, 150.6, 141.1, 115.1, 96.4, 68.9, 56.3, 56.2, 53.1, 52.8, 43.4, 39.0, 28.6, 23.8, 19.4, 0.1.

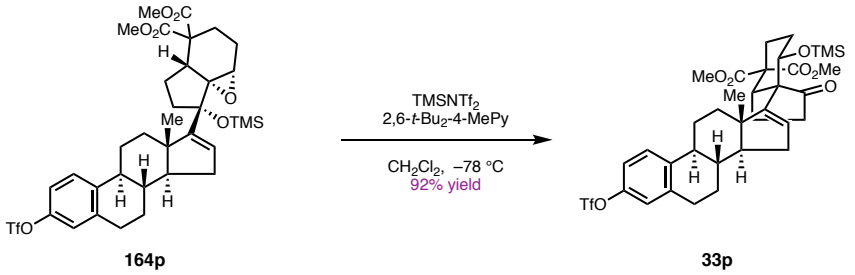
FTIR (NaCl, thin film): 3126, 2954, 1748, 1572, 1434, 1253, 1059, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{20}H_{28}O_7SiBr$ $[M+H]^+$ 487.0782, found 487.0798.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +16.7° (*c* = 1.00, $CHCl_3$).

TLC (15% Acetone:85% Hexanes), R_f: 0.27 (purple in *p*-anisaldehyde).

Preparation of semi-pinacol product 33p:



164p **33p**

Prepared via General Procedure B, 92% yield.

Prepared from **164p** (66.3 mg, 0.091 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (20.6 mg, 0.10 mmol, 1.1 equiv), and $TMSNTf_2$ (16.1 mg, 0.046 mmol, 0.5 equiv) at –78 °C for 4 hours according to method **B**. The reaction was purified by column chromatography (silica, 15% EtOAc:85% Hexanes) to yield **33p** (60.8 mg, 92% yield) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.27 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.96 (d, *J* = 2.7 Hz, 1H), 5.56 (dd, *J* = 3.6, 1.6 Hz, 1H), 4.40 (s, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.34 (t, *J* = 9.9 Hz, 1H), 2.93 – 2.87 (m, 2H), 2.44 – 2.36 (m, 1H), 2.35 – 2.29 (m, 2H), 2.29 – 2.18 (m, 3H), 2.18 – 2.03 (m, 4H), 1.99 – 1.89 (m, 2H), 1.76 (d, *J* = 10.6 Hz, 1H), 1.74 – 1.67 (m, 1H), 1.67 – 1.51 (m, 4H), 1.48 – 1.37 (m, 1H), 1.03 (s, 3H), 0.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 219.8, 171.3, 171.0, 154.1, 147.7, 141.2, 139.7, 129.4, 126.9, 121.3, 118.2, 70.6, 58.7, 56.5, 56.3, 52.6, 52.5, 48.5, 43.8, 43.7, 39.0, 36.8, 36.2, 31.2, 29.6, 28.1, 27.1, 26.5, 24.5, 20.0, 17.9, 0.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ 73.0.

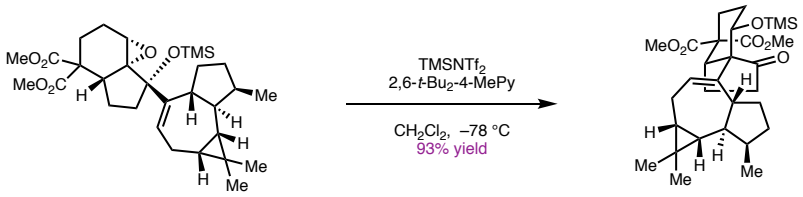
FTIR (NaCl, thin film): 2952, 1741, 1605, 1490, 1423, 1250, 1211, 1143, 919, 843, 756 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{35}H_{46}F_3O_9SSi$ $[M+H]^+$ 727.2578, found 727.2581.

$[\alpha]_D^{25}$ = +51.4° (*c* = 1.00, $CHCl_3$).

TLC (15% EtOAc:85% Hexanes), R_f: 0.31 (dark blue in *p*-anisaldehyde).

Preparation of semi-pinacol product 33q:



164q **33q**

Prepared via General Procedure C, 93% yield.

Prepared from **164q** (62.4 mg, 0.12 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (24.1 mg, 0.12 mmol, 1.0 equiv), and $TMSNTf_2$ (12.5 mg, 0.035 mmol, 0.3 equiv) at –78 °C for 4 hours according to method **C**. The reaction was directly subjected to column chromatography (silica, 100% CH_2Cl_2) to yield **33q** (58.2 mg, 93% yield) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 5.35 (dt, *J* = 9.2, 2.9 Hz, 1H), 4.20 (s, 1H), 3.72 (s, 3H), 3.72 (dd, *J* = 12.1, 8.2 Hz, 1H), 3.63 (s, 3H), 2.55 – 2.45 (m, 0H), 2.43 – 2.08 (m, 6H), 2.07 – 1.96 (m, 3H), 1.93 – 1.80 (m, 3H), 1.73 (dq, *J* = 14.6, 3.4 Hz, 1H), 1.70 – 1.65 (m, 1H), 1.61 (dt, *J* = 11.4, 4.1 Hz, 1H), 1.02 (s, 3H), 1.01 (s, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.63 (dd, *J* = 11.5, 9.3 Hz, 1H), 0.06 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 219.8, 171.2, 170.6, 141.9, 127.1, 72.2, 61.2, 56.1, 52.8, 52.5, 49.7, 42.8, 42.5, 39.3, 33.8, 33.5, 33.2, 30.0, 28.4, 27.5, 26.2, 24.2, 23.2, 19.4, 19.0, 18.4, 15.5, 0.3.

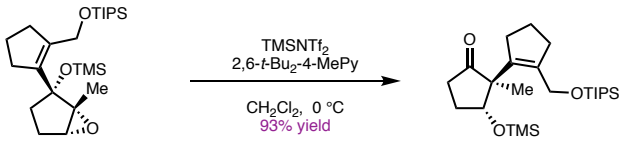
FTIR (NaCl, thin film): 2952, 2870, 1736, 1457, 1251, 1056, 836, 750 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{30}H_{46}O_6SiNa$ $[M+Na]^+$ 553.2956, found 553.2948.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –43.1° (*c* = 1.00, $CHCl_3$).

TLC (10% EtOAc:90% Hexanes), R_f: 0.31 (navy blue in *p*-anisaldehyde).

Preparation of semi-pinacol product 166a:



165a' **166a**

Prepared via General Procedure A, 93% yield.

Prepared from **165a'** (52.7 mg, 0.12 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (9.9 mg, 0.048 mmol, 0.4 equiv), and $TMSNTf_2$ (4.2 mg, 0.012 mmol, 0.1 equiv) at 0 °C for 30 minutes according to method **A**. The reaction was purified by column chromatography (silica, 1.5% Acetone:98.5% Hexanes) to yield **166a** (48.8 mg, 93% yield) as a clear colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.32 (t, *J* = 5.2 Hz, 1H), 4.22 – 4.07 (m, 2H), 2.64 – 2.52 (m, 1H), 2.52 – 2.21 (m, 5H), 2.04 (dddd, *J* = 13.0, 9.4, 6.6, 4.9 Hz, 1H), 1.86 – 1.67 (m, 3H), 1.10 (s, 3H), 1.09 – 1.02 (m, 21H), 0.10 (s, 9H).

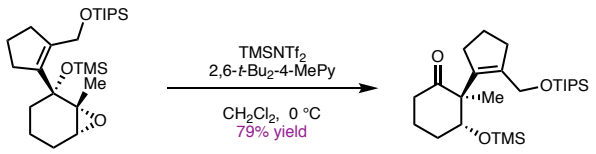
^{13}C NMR (101 MHz, $CDCl_3$): δ 219.6, 138.3, 136.1, 78.4, 60.8, 56.4, 36.2, 35.5, 35.1, 28.6, 21.4, 18.2, 15.6, 12.1, 0.1.

FTIR (NaCl, thin film): 2939, 2865, 1746, 1652, 1462, 1251, 1094, 1064, 880, 848, 842 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{24}H_{47}O_3Si_2$ $[M+H]^+$ 439.3064, found 439.3079.

TLC (10% EtOAc:90% Hexanes), R_f: 0.58 (dark blue in *p*-anisaldehyde).

Preparation of semi-pinacol product 166b:



165b' **166b**

Prepared via General Procedure B, 79% yield.

Prepared from **165b'** (57.2 mg, 0.125 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (28.2 mg, 0.138 mmol, 1.1 equiv), and $TMSNTf_2$ (22.1 mg, 0.0625 mmol, 0.5 equiv) at 0 °C for 30 minutes according to method **B**. The reaction was purified by column chromatography (silica, 1.5% Acetone:98.5% Hexanes) to yield **166b** (44.7 mg, 79% yield) as a clear colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.17 (dt, *J* = 4.7, 1.5 Hz, 1H), 4.10 (dt, *J* = 12.6, 1.2 Hz, 1H), 4.00 (ddd, *J* = 12.5, 2.2, 1.1 Hz, 1H), 2.67 (ddd, *J* = 13.4, 12.0, 6.5 Hz, 1H), 2.61 – 2.31 (m, 4H), 2.26 (dddd, *J* = 13.4, 4.9, 3.5, 1.5 Hz, 1H), 2.04 (ddt, *J* = 24.1, 11.9, 4.8, 3.7 Hz, 1H), 1.90 (tdd, *J* = 12.1, 4.0, 1.8 Hz, 1H), 1.82 – 1.70 (m, 2H), 1.66 (dtt, *J* = 13.5, 5.3, 2.7 Hz, 1H), 1.08 (s, 3H), 1.06 – 0.99 (m, 21H), 0.19 – 0.11 (m, 1H), 0.06 (s, 9H).

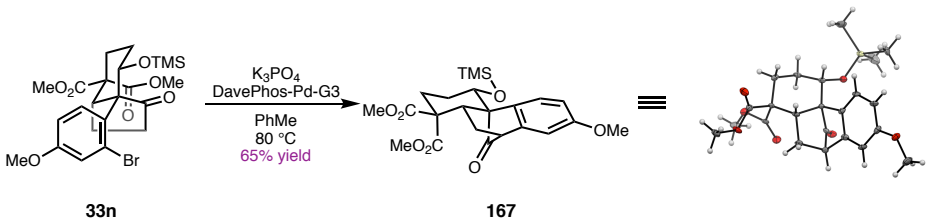
^{13}C NMR (101 MHz, $CDCl_3$): δ 214.5, 138.1, 137.3, 77.9, 60.0, 57.5, 39.3, 35.4, 34.9, 29.9, 21.6, 21.4, 19.4, 18.1, 12.1, 0.2.

FTIR (NaCl, thin film): 2943, 2893, 2867, 1714, 1660, 1463, 1251, 1103, 1079, 1067, 986, 840 cm^{-1}.

HRMS: (FI-TOF) calc'd for $C_{25}H_{48}O_3Si_2$ $[M]^+$ 452.3137, found 452.3137.

TLC (10% EtOAc:90% Hexanes), R_f: 0.58 (dark pink in *p*-anisaldehyde).

Preparation of aromatic intermediate 167:



A 40 mL vial was charged with aryl bromide **33n** (480 mg, 0.910 mmol, 1.0 equiv) and was brought into a glovebox. The vial was charged with K_3PO_4 (882 mg, 3.64 mmol, 4.0 equiv), DavePhos-Pd-G3 (69.5 mg, 0.091 mmol, 10 mol %), and lastly PhMe (23 mL, 0.04 M). The vial was sealed, brought out of the glovebox, and placed inside an 80 °C oil bath. The reaction was allowed to stir for 15 hours. **Note**: it is extremely important to maintain vigorous stirring. A cross-shaped stir bar was used in this reaction. When the stirring was not vigorous incomplete conversion was observed. The reaction was cooled to 21 °C and filtered through a plug of silica gel that had pre-saturated with Et_2O. The crude product was purified by column chromatography (silica, 15% to 18% to 20% EtOAc in hexanes gradient) to afford **167** (264 mg, 0.592 mmol, 65% yield) as a white solid.

The material was recrystallized from Et_2O to afford crystals suitable for X-ray diffraction analysis.

Note: This reaction was initially developed and performed on racemic material and the X-ray structure was obtained was on racemic material. The route was repeated and fully characterized using enantiopure epoxyketone **31**.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.12 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.5 Hz, 1H), 4.53 (dd, *J* = 10.0, 5.8 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 3.36 (d, *J* = 4.4 Hz, 1H), 2.58 (dt, *J* = 12.6, 4.6 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.05 – 1.89 (m, 4H), 1.53 (dd, *J* = 12.4, 11.1 Hz, 1H), 0.11 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 199.5, 171.8, 170.4, 158.8, 142.4, 133.5, 121.5, 112.3, 107.1, 67.9, 56.8, 55.4 (two ^{13}C signals), 52.7, 52.3, 49.0, 43.1, 30.3, 28.7, 28.5, 0.7.

FTIR (NaCl, thin film): 2954, 1790, 1779, 1738, 1732, 1609, 1484, 1455, 1251, 1121, 1043, 908, 875, 842, 732 cm^{-1}.

HRMS: (ESI-TOF) calc'd for $C_{23}H_{31}O_7Si$ $[M+H]^+$ 447.1834, found 447.1824.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +51.7° (*c* = 0.78, $CHCl_3$).

TLC (20% EtOAc:80% Hexanes), R*f*: 0.35 (UV, brown in I_2 stain) Note: does not appear in *p*-anisaldehyde or CAM.

X-Ray Crystallographic Data

Low-temperature diffraction data (*ϕ*- and *ω*-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to either a PHOTON 100 CMOS detector with Mo-*Kα* radiation (*λ* = 0.71073 Å) or a PHOTON II CPAD detector with either Mo-*Kα* radiation (*λ* = 0.71073 Å) or Cu-*Kα* radiation (*λ* = 1.54178 Å) from a fine-focus sealed X-ray tube. All diffractometer manipulations, including data collection integration, and scaling were carried out using the Bruker APEXII software.[69] Absorption

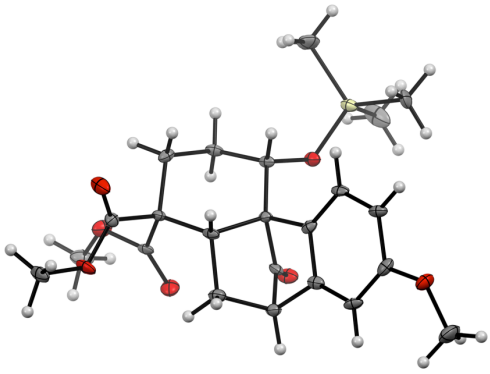
corrections were applied using SADABS.[70] The structure was solved by intrinsic phasing using SHELXT[71] and refined against F^2 on all data by full-matrix least squares with SHELXL-2014[72] using established refinement techniques.[73] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl and hydroxyl groups). Absolute configuration was determined by anomalous dispersion[74] and confirmed by Bayesian statistical analysis using the program PLATON.[75] Graphical representation of the structure with 50% probability thermal ellipsoids was generated using Mercury visualization software.

CRYSTALLOGRAPHIC ANALYSIS OF **167**

Special Refinement Details

Rendering of **167**.

Figure 3.4. *X-Ray structure of* ***167****.*



Compound **167** crystallizes in the orthorhombic space group *P*bca with one molecule in the asymmetric unit. CCDC 2224814.

Table 3.3. *Crystal data and structure refinement for* ***167****.*

Identification code	P16149	
Empirical formula	$C_{23}H_{30}O_7Si$	
Formula weight	446.56	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 18.2041(15) Å	α = 90°.
	b = 12.7693(13) Å	β = 90°.
	c = 19.5076(18) Å	γ = 90°.
Volume	4534.6(7) $Å^3$	
Z	8	
Density (calculated)	1.308 Mg/m^3	
Absorption coefficient	0.145 mm^{-1}	
F(000)	1904	
Crystal size	0.188 x 0.151 x 0.05 mm^3	
Theta range for data collection	2.210 to 32.037°.	
Index ranges	-27<=h<=27, -17<=k<=18, -29<=l<=26	
Reflections collected	135898	
Independent reflections	7877 [R(int) = 0.0810]	
Completeness to theta = 26.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7468 and 0.6970	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7877 / 0 / 287	
Goodness-of-fit on F^2	1.090	
Final R indices [I>2sigma(I)]	R1 = 0.0443, wR2 = 0.0997	
R indices (all data)	R1 = 0.0621, wR2 = 0.1053	
Extinction coefficient	0.0014(3)	
Largest diff. peak and hole	0.412 and -0.287 $e.Å^{-3}$	

3.5 NOTES AND REFERENCES

(1) Kerkovius, J.; Wong, A.; Mak, V.; Reisman, S. E. A Convergent Fragment Coupling Strategy to Access Quaternary Stereogenic Centers. *Chem. Sci.* **2023**.

(2) Peterson, E. A.; Overman, L. E. Contiguous Stereogenic Quaternary Carbons: A Daunting Challenge in Natural Products Synthesis. *Proc. Natl. Acad. Sci.* **2004**, *101*, 11943–11948.

(3) Hendrickson, J. B. Systematic Synthesis Design. 6. Yield Analysis and Convergency. *J. Am. Chem. Soc.* **1977**, *99*, 5439–5450.

(4) Bertz, S. H. Convergence, Molecular Complexity, and Synthetic Analysis. *J. Am. Chem. Soc.* **1982**, *104*, 5801–5803.

(5) Velluz, L.; Valls, J.; Nominé, G. Recent Advances in the Total Synthesis of Steroids. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 181–200.

(6) Urabe, D.; Asaba, T.; Inoue, M. Convergent Strategies in Total Syntheses of Complex Terpenoids. *Chem. Rev.* **2015**, *115*, 9207–9231.

(7) Tomanik, M.; Hsu, I. T.; Herzon, S. B. Fragment Coupling Reactions in Total Synthesis That Form Carbon–Carbon Bonds via Carbanionic or Free Radical Intermediates. *Angew. Chem. Int. Ed.* **2021**, *60*, 1116–1150.

(8) Huffman, B. J.; Chu, T.; Hanaki, Y.; Wong, J. J.; Chen, S.; Houk, K. N.; Shenvi, R. A. Stereodivergent Attached-Ring Synthesis via Non-Covalent Interactions: A Short Formal Synthesis of Merrilactone A. *Angew. Chem. Int. Ed.* **2022**, *61*, e202114514.

(9) E. J. Corey, X.-M. C. *The Logic of Chemical Synthesis*; Wiley: New York, 1995.

(10) Li, D. R.; Xia, W. J.; Tu, Y. Q.; Zhang, F. M.; Shi, L. A Novel AlEt3-Promoted Tandem Reductive Rearrangement of 1-Benzyloxy-2,3-Epoxides: New Route to 2-Quaternary 1,3-Diol Units. *Chem. Commun.* **2003**, No. 6, 798–799.

(11) Lee, S.; Kim, K.; Cha, J. A Semi-Pinacol Rearrangement Approach to Bicyclo[3.2.1]Octan-2-Ones and Bicyclo[3.2.1]Octan-3-Ones. *Synlett* **2008**, *2008*, 2155–2157.

(12) Hu, X.-D.; Fan, C.-A.; Zhang, F.-M.; Tu, Y. Q. A Tandem Semipinacol Rearrangement/Alkylation of α-Epoxy Alcohols: An Efficient and Stereoselective Approach to Multifunctional 1,3-Diols. *Angew. Chem. Int. Ed.* **2004**, *43*, 1702–1705.

(13) Liu, Y.; Tse, Y.-L. S.; Kwong, F. Y.; Yeung, Y.-Y. Accessing Axially Chiral Biaryls via Organocatalytic Enantioselective Dynamic-Kinetic Resolution-Semipinacol Rearrangement. *ACS Catal.* **2017**, *7*, 4435–4440.

(14) Li, X.; Wu, B.; Zhao, X. Z.; Jia, Y. X.; Tu, Y. Q.; Li, D. R. An Interesting AlEt3-Promoted Stereoselective Tandem Rearrangement/Reduction of α-Hydroxy (or Amino) Heterocyclopropane. *Synlett* **2003**, *2003*, 623–626.

(15) Snape, T. J. Application of the Semi-Pinacol Rearrangement towards the Generation of Alkenyl-Substituted Quaternary Carbon Centres. *Org. Biomol. Chem.* **2006**, *4*, 4144–4148.

(16) Wu, H.; Wang, Q.; Zhu, J. Catalytic Enantioselective Pinacol and Meinwald Rearrangements for the Construction of Quaternary Stereocenters. *J. Am. Chem. Soc.* **2019**, *141*, 11372–11377.
(17) Marson, C. M.; Khan, A.; Porter, R. A.; Cobb, A. J. A. Construction of Functionalised Medium Rings by Stereospecific Expansions of 2,3-Epoxy Alcohols under Mild Conditions. *Tetrahedron Lett.* **2002**, *43*, 6637–6640.
(18) Liu, M.; Huang, H.; Chen, Y. Cyclic Iodine Reagents Enable Allylic Alcohols for Alkyl Boronate Addition/Rearrangement by Photoredox Catalysis. *Chin. J. Chem.* **2018**, *36*, 1209–1212.
(19) Chen, C.; Kang, J.-C.; Mao, C.; Dong, J.-W.; Xie, Y.-Y.; Ding, T.-M.; Tu, Y.-Q.; Chen, Z.-M.; Zhang, S.-Y. Electrochemical Halogenation/Semi-Pinacol Rearrangement of Allylic Alcohols Using Inorganic Halide Salt: An Eco-Friendly Route to the Synthesis of β-Halocarbonyls. *Green Chem.* **2019**, *21*, 4014–4019.
(20) Lukamto, D. H.; Gaunt, M. J. Enantioselective Copper-Catalyzed Arylation-Driven Semipinacol Rearrangement of Tertiary Allylic Alcohols with Diaryliodonium Salts. *J. Am. Chem. Soc.* **2017**, *139*, 9160–9163.
(21) Romanov-Michailidis, F.; Pupier, M.; Guénée, L.; Alexakis, A. Enantioselective Halogenative Semi-Pinacol Rearrangement: A Stereodivergent Reaction on a Racemic Mixture. *Chem. Commun.* **2014**, *50*, 13461–13464.
(22) Namba, K.; Kanaki, M.; Suto, H.; Nishizawa, M.; Tanino, K. Hg(OTf)2-Catalyzed Vinylogous Semi-Pinacol Rearrangement Leading to 1,4-Dihydroquinolines. *Org. Lett.* **2012**, *14*, 1222–1225.
(23) Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Shi, Y. Lewis Acid Promoted Highly Stereoselective Rearrangement of 2,3-Aziridino Alcohols: A New Efficient Approach to β-Amino Carbonyl Compounds. *Org. Lett.* **2002**, *4*, 363–366.
(24) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. On the Use of Epoxy Alcohol-Aldol Rearrangement for Stereoselective Construction of Quarternary Carbon Centers. *Tetrahedron Lett.* **1987**, *28*, 5891–5894.
(25) Yao, S.; Zhang, K.; Zhou, Q.-Q.; Zhao, Y.; Shi, D.-Q.; Xiao, W.-J. Photoredox-Promoted Alkyl Radical Addition/Semipinacol Rearrangement Sequences of Alkenylcyclobutanols: Rapid Access to Cyclic Ketones. *Chem. Commun.* **2018**, *54*, 8096–8099.
(26) Fan, C.-A.; Hu, X.-D.; Tu, Y.-Q.; Wang, B.-M.; Song, Z.-L. Progressive Studies on the Novel Samarium-Catalyzed Diastereoselective Tandem Semipinacol Rearrangement/Tishchenko Reduction of Secondary α-Hydroxy Epoxides. *Chem. – Eur. J.* **2003**, *9*, 4301–4310.
(27) Cheer, C. J.; Johnson, C. R. Stereoselective Rearrangements of Conformationally Mobile Epoxides. *J. Am. Chem. Soc.* **1968**, *90*, 178–183.
(28) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. Stereoselective Reductive Rearrangement of α-Hydroxy Epoxides: A New Method for Synthesis of 1,3-Diols1. *J. Org. Chem.* **1999**, *64*, 629–633.
(29) Hirama, N.; Sakamoto, R.; Maruoka, K. Synthesis of α-Quaternary Aldehydes via a Stereoselective Semi-Pinacol Rearrangement of Optically Active Epoxy Alcohols. *Asian J. Org. Chem.* **2019**, *8*, 1390–1393.

(30) Gu, P.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y.; Zhang, F. Tandem Semipinacol/Schmidt Reaction Leading to a Versatile and Efficient Approach to Azaquaternary Alkaloid Skeletons. *Org. Lett.* **2006**, *8*, 5271–5273.
(31) Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. Zinc Bromide as Catalyst for the Stereoselective Construction of Quaternary Carbon: Improved Synthesis of Diastereomerically Enriched Spirocyclic Diols. *J. Chem. Soc. Perkin 1* **2000**, No. 22, 3791–3794.
(32) Yang, M.; Wang, L.; He, Z.-H.; Wang, S.-H.; Zhang, S.-Y.; Tu, Y.-Q.; Zhang, F.-M. Tandem Semipinacol-Type 1,2-Carbon Migration/Aldol Reaction toward the Construction of [5–6–7] All-Carbon Tricyclic Core of Calyciphylline A-Type Alkaloids. *Org. Lett.* **2012**, *14*, 5114–5117.
(33) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. Total Synthesis of Ingenol. *J. Am. Chem. Soc.* **2003**, *125*, 1498–1500.
(34) J. Snape, T. Recent Advances in the Semi-Pinacol Rearrangement of α-Hydroxy Epoxides and Related Compounds. *Chem. Soc. Rev.* **2007**, *36*, 1823–1842.
(35) Wang, B.; Tu, Y. Q. Stereoselective Construction of Quaternary Carbon Stereocenters via a Semipinacol Rearrangement Strategy. *Acc. Chem. Res.* **2011**, *44*, 1207–1222.
(36) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. Semipinacol Rearrangement in Natural Product Synthesis. *Chem. Rev.* **2011**, *111*, 7523–7556.
(37) Zhang, X.-M.; Tu, Y.-Q.; Zhang, F.-M.; Chen, Z.-H.; Wang, S.-H. Recent Applications of the 1,2-Carbon Atom Migration Strategy in Complex Natural Product Total Synthesis. *Chem. Soc. Rev.* **2017**, *46*, 2272–2305.
(38) Zhang, X.-M.; Li, B.-S.; Wang, S.-H.; Zhang, K.; Zhang, F.-M.; Tu, Y.-Q. Recent Development and Applications of Semipinacol Rearrangement Reactions. *Chem. Sci.* **2021**, *12*, 9262–9274.
(39) Cernijenko, A.; Risgaard, R.; Baran, P. S. 11-Step Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* **2016**, *138*, 9425–9428.
(40) Wong, A. R.; Fastuca, N. J.; Mak, V. W.; Kerkovius, J. K.; Stevenson, S. M.; Reisman, S. E. Total Syntheses of the C19 Diterpenoid Alkaloids (−)-Talatisamine, (−)-Liljestrandisine, and (−)-Liljestrandinine by a Fragment Coupling Approach. *ACS Cent. Sci.* **2021**, *7*, 1311–1316.
(41) Mathieu, B.; Ghosez, L. Trimethylsilyl Bis(Trifluoromethanesulfonyl)Imide as a Tolerant and Environmentally Benign Lewis Acid Catalyst of the Diels–Alder Reaction. *Tetrahedron* **2002**, *58*, 8219–8226.
(42) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. Highly Active and Selective Catalysts for the Formation of α-Aryl Ketones. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.
(43) Dank, C.; Sanichar, R.; Choo, K.-L.; Olsen, M.; Lautens, M. Recent Advances Towards Syntheses of Diterpenoid Alkaloids. *Synthesis* **2019**, *51*, 3915–3946.
(44) Kou, K. G. M.; Li, B. X.; Lee, J. C.; Gallego, G. M.; Lebold, T. P.; DiPasquale, A. G.; Sarpong, R. Syntheses of Denudatine Diterpenoid Alkaloids: Cochlearenine, N-Ethyl-1α-Hydroxy-17-Veratroyldictyzine, and Paniculamine. *J. Am. Chem. Soc.* **2016**, *138*, 10830–10833.

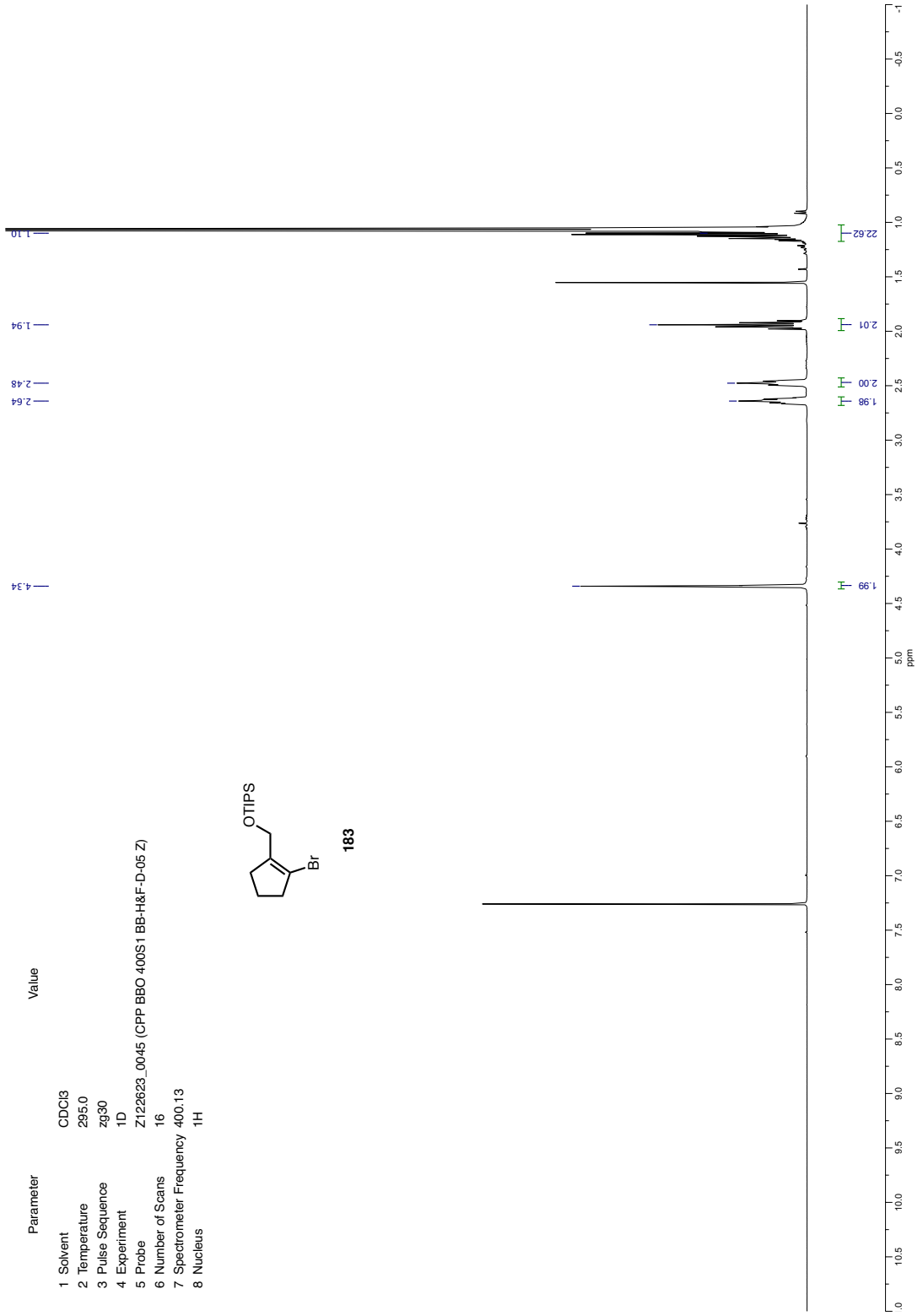
(45) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(46) Kamachi, T.; Kuno, A.; Matsuno, C.; Okamoto, S. Cobalt-Catalyzed Mono-Coupling of R3SiCH2MgCl with 1,2-Dihalogenoethylene: A General Route to γ-Substituted (E)-Allylsilanes. *Tetrahedron Lett.* **2004**, *45*, 4677–4679.
(47) Amer, M. M.; Olaizola, O.; Carter, J.; Abas, H.; Clayden, J. An Aliphatic Bischler–Napieralski Reaction: Dihydropyridones by Cyclocarbonylation of 3-Allylimidazolidin-4-Ones. *Org. Lett.* **2020**, *22*, 253–256.
(48) Pericàs, M. A.; Serratosa, F.; Valentí, E. An Efficient Synthesis of Tert-Alkoxyethynes. *Tetrahedron* **1987**, *43*, 2311–2316.
(49) Stalick, W. M.; Khorrami, A.; Hatton, K. S. Dehydrobromination of 1,2-Dibromoethyoxyethane Using Various Amine Bases. *J. Org. Chem.* **1986**, *51*, 3577–3581.
(50) Shirakawa, E.; Imazaki, Y.; Hayashi, T. Ruthenium-Catalyzed Transformation of Alkenyl Triflates to Alkenyl Halides. *Chem. Commun.* **2009**, No. 34, 5088.
(51) Zhan, F.; Liang, G. Formation of Enehydrazine Intermediates through Coupling of Phenylhydrazines with Vinyl Halides: Entry into the Fischer Indole Synthesis. *Angew. Chem. Int. Ed.* **2013**, *52*, 1266–1269.
(52) Lee, K.; Wiemer, D. F. The Reaction of Vinyl Phosphates with Iodotrimethylsilane: Synthesis of Vinyl Iodides from Ketones. *Tetrahedron Lett.* **1993**, *34*, 2433–2436.
(53) Ojha, D. P.; Prabhu, K. R. Regioselective Synthesis of Vinyl Halides, Vinyl Sulfones, and Alkynes: A Tandem Intermolecular Nucleophilic and Electrophilic Vinylation of Tosylhydrazones. *Org. Lett.* **2015**, *17*, 18–21.
(54) Despotopoulou, C.; Bauer, R. C.; Krasovskiy, A.; Mayer, P.; Stryker, J. M.; Knochel, P. Selective Mono- and 1,2-Difunctionalisation of Cyclopentene Derivatives via Mg and Cu Intermediates. *Chem. – Eur. J.* **2008**, *14*, 2499–2506.
(55) Harrowven, D. C.; Pascoe, D. D.; Guy, I. L. Thermally Induced Cyclobutenone Rearrangements and Domino Reactions. *Angew. Chem. Int. Ed.* **2007**, *46*, 425–428.
(56) Pijper, T. C.; Kudernac, T.; Browne, W. R.; Feringa, B. L. Effect of Immobilization on Gold on the Temperature Dependence of Photochromic Switching of Dithienylethenes. *J. Phys. Chem. C* **2013**, *117*, 17623–17632.
(57) Han, A.; Tao, Y.; Reisman, S. E. A 16-Step Synthesis of the Isoryanodane Diterpene (+)-Perseanol. *Nature* **2019**, *573*, 563–567.
(58) Yang, Q.; Sheng, M.; Henkelis, J. J.; Tu, S.; Wiensch, E.; Zhang, H.; Zhang, Y.; Tucker, C.; Ejeh, D. E. Explosion Hazards of Sodium Hydride in Dimethyl Sulfoxide, N,N-Dimethylformamide, and N,N-Dimethylacetamide. *Org. Process Res. Dev.* **2019**, *23*, 2210–2217.
(59) Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. Aryl Annulation of Cyclic Ketones via a Magnesium Carbometalation−6-π- Electrocyclization Protocol. *Org. Lett.* **2005**, *7*, 767–770.

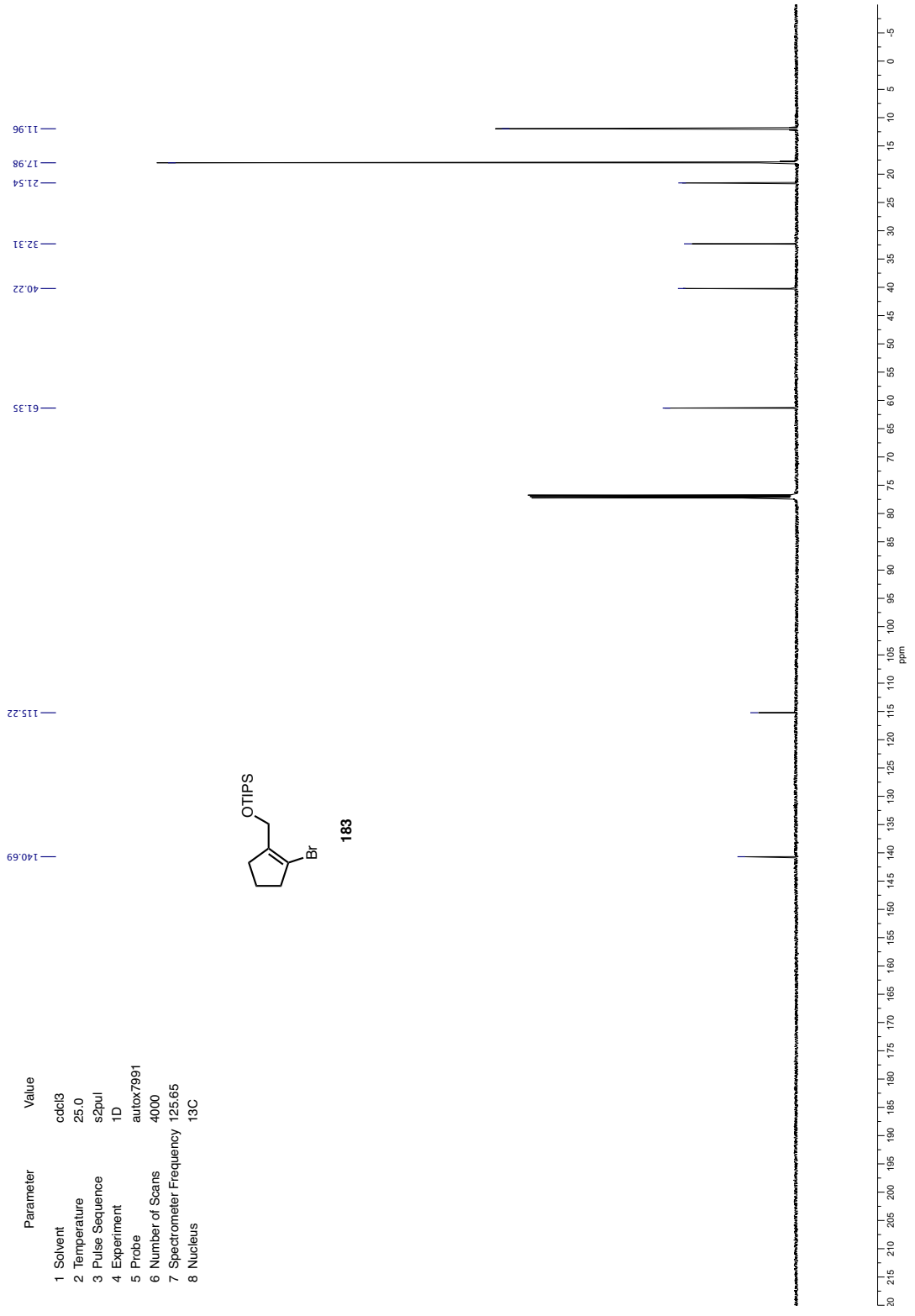
(60) Hofstra, J. L.; Poremba, K. E.; Shimozono, A. M.; Reisman, S. E. Nickel-Catalyzed Conversion of Enol Triflates into Alkenyl Halides. *Angew. Chem. Int. Ed.* **2019**, *58*, 14901–14905.
(61) Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. Aryl Annulation of Cyclic Ketones via a Magnesium Carbometalation−6-π- Electrocyclization Protocol. *Org. Lett.* **2005**, *7*, 767–770.
(62) Mikle, G.; Boros, B.; Kollár, L. Synthesis of Bornene-2,2′-Diamino-1,1′-Binaphthalene Conjugates in Palladium-Catalysed Aminocarbonylations. *Tetrahedron Asymmetry* **2016**, *27*, 377–383.
(63) Carr, R. V. C.; Williams, R. V.; Paquette, L. A. Dienophilic Properties of Phenyl Vinyl Sulfone and Trans-1-(Phenylsulfonyl)-2-(Trimethylsilyl)Ethylene. Their Utilization as Synthons for Ethylene, 1-Alkenes, Acetylene, and Monosubstituted Alkynes in the Construction of Functionalized Six-Membered Rings via [4 + 2] .Pi. Cycloaddition Methodology. *J. Org. Chem.* **1983**, *48*, 4976–4986.
(64) Komatsu, K.; Aonuma, S.; Jinbu, Y.; Tsuji, R.; Hirosawa, C.; Takeuchi, K. Generation and Oligomerization of Bicyclo[2.2.2]Octyne and Properties of Tris(Bicyclo[2.2.2]Octeno)Benzene Obtained from the Linear Trimer. *J. Org. Chem.* **1991**, *56*, 195–203.
(65) Sun, Q.; Jiang, C.; Xu, H.; Zhang, Z.; Liu, L.; Wang, C. Pd(PPh3)4/AgOAc-Catalyzed Coupling of 17-Steroidal Triflates and Alkynes: Highly Efficient Synthesis of D-Ring Unsaturated 17-Alkynylsteroids. *Steroids* **2010**, *75*, 936–943.
(66) Duhamel, N.; Martin, D.; Larcher, R.; Fedrizzi, B.; Barker, D. Convenient Synthesis of Deuterium Labelled Sesquiterpenes. *Tetrahedron Lett.* **2016**, *57*, 4496–4499.
(67) Kraft, P.; Berthold, C. (4E,8Z)-12-Methyloxacyclotetradeca-4,8-Dien-2-One and Its 7a-Homologue: Conformationally Constrained Double-Unsaturated Macrocyclic Musks by Ring-Closing Alkyne Metathesis. *Synthesis* **2008**, *2008*, 543–550.
(68) Lhermet, R.; Durandetti, M.; Maddaluno, J. Intramolecular Carbonickelation of Alkenes. *Beilstein J. Org. Chem.* **2013**, *9*, 710–716.
(69) *APEX2, Version 2 User Manual, M86-E01078, Bruker Analytical X-Ray Systems, Madison, WI, 2006.*
(70) *Sheldrick, G.M. SADABS (Version 2008/1): Program for Absorption Correction for Data from Area Detector Frames, University of Göttingen, 2008.*
(71) *Sheldrick, G. Acta Crystallogr., Sect. A: Found. Crystallogr. 2008, 64, 112.*
(72) *Sheldrick, G. M. Acta Crystallogr., Sect. C: Struct. Chem. 2015, C71, 3.*
(73) *Müller, P. Crystallogr. Rev. 2009, 15, 57.*
(74) *Parsons, S.; Flack, H. D.; Wagner, T. Acta Crystallogr., Sect. B: Struct. Sci. Cryst. Eng. Mater. 2013, B69, 249.*
(75) *Spek, A. L. Acta Crystallogr., Sect. D: Struct. Biol. 2009, D65, 148.*

Appendix 2

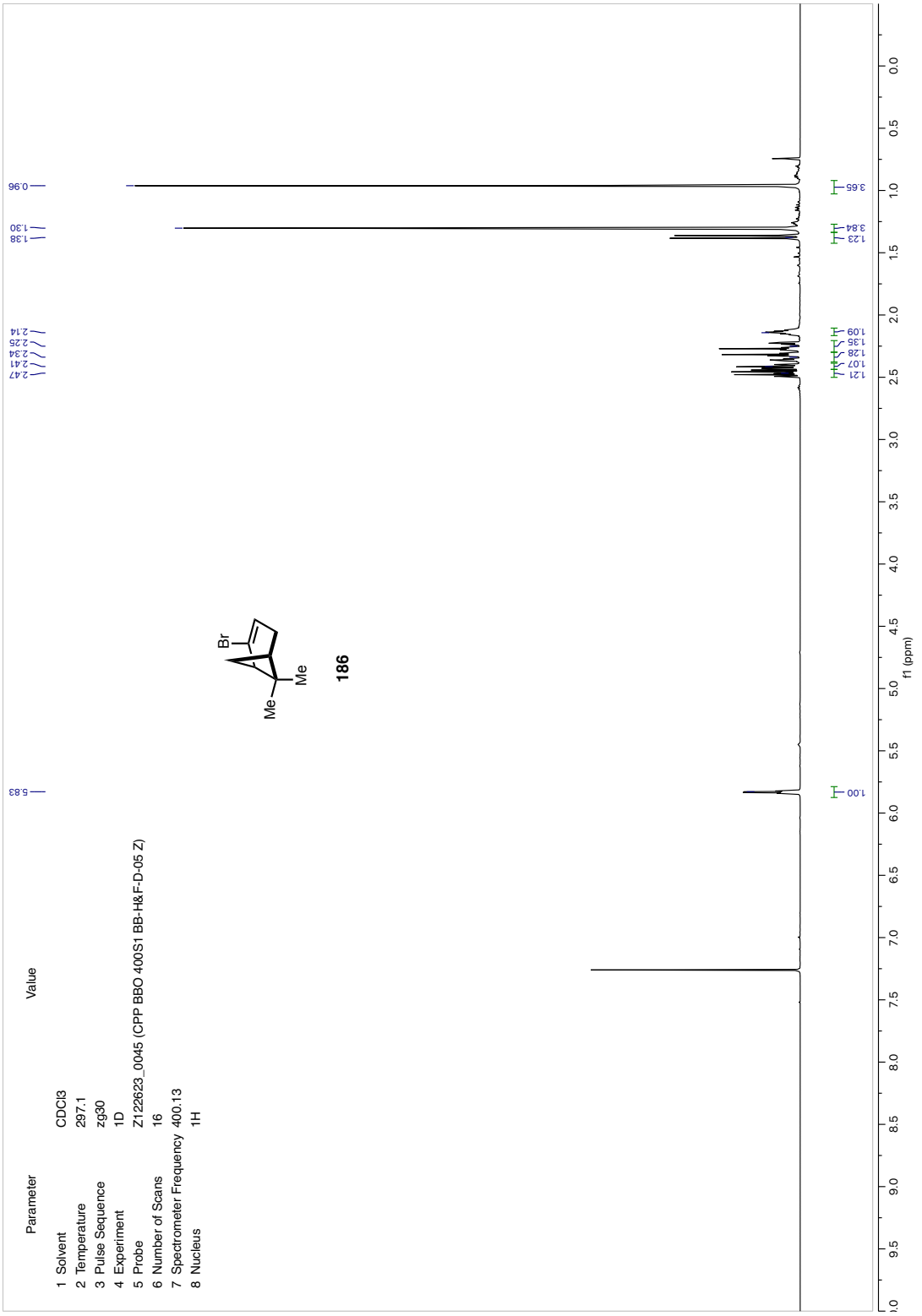
Spectra Relevant to Chapter 3:

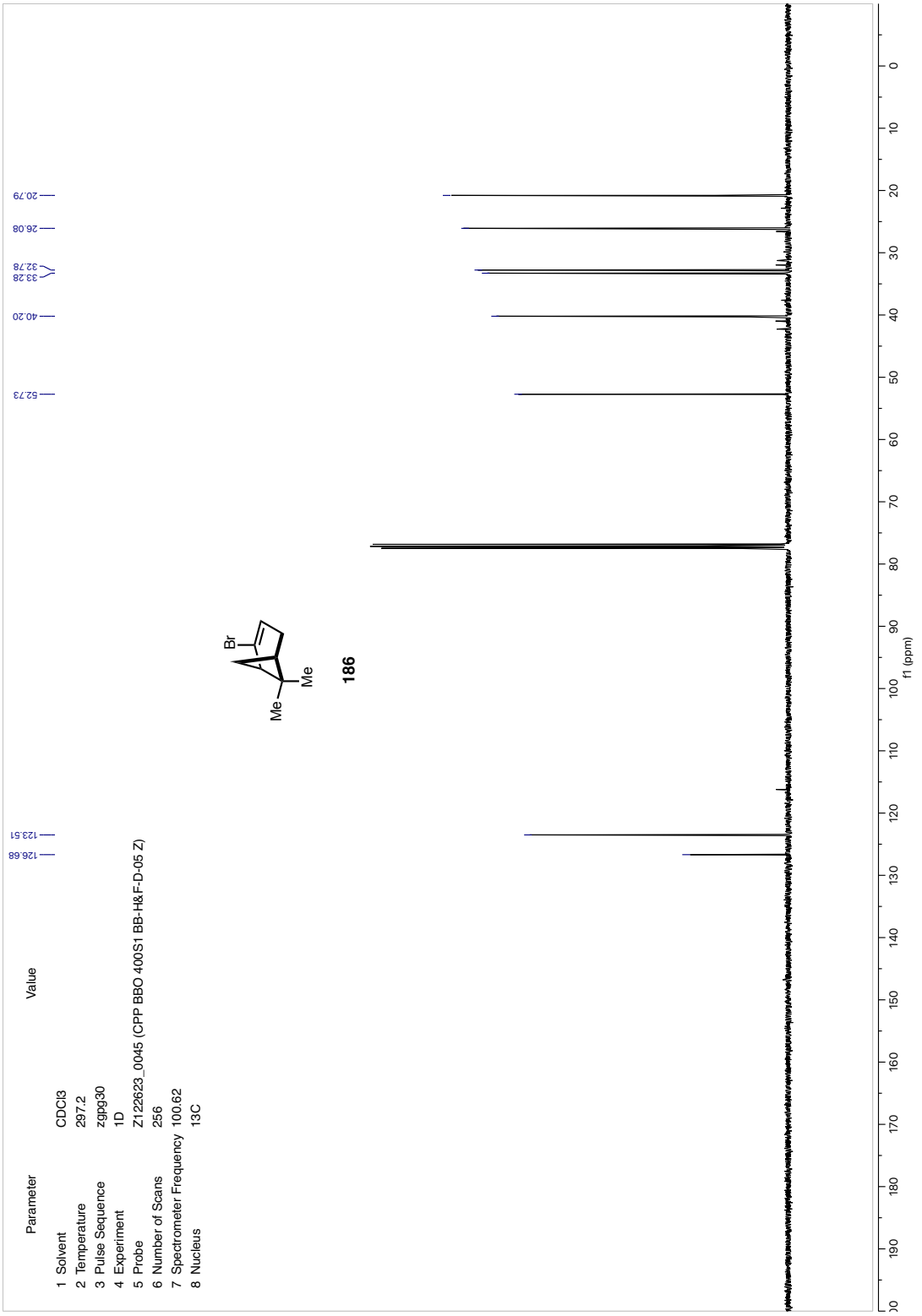
A convergent fragment coupling strategy to access quaternary stereogenic centers

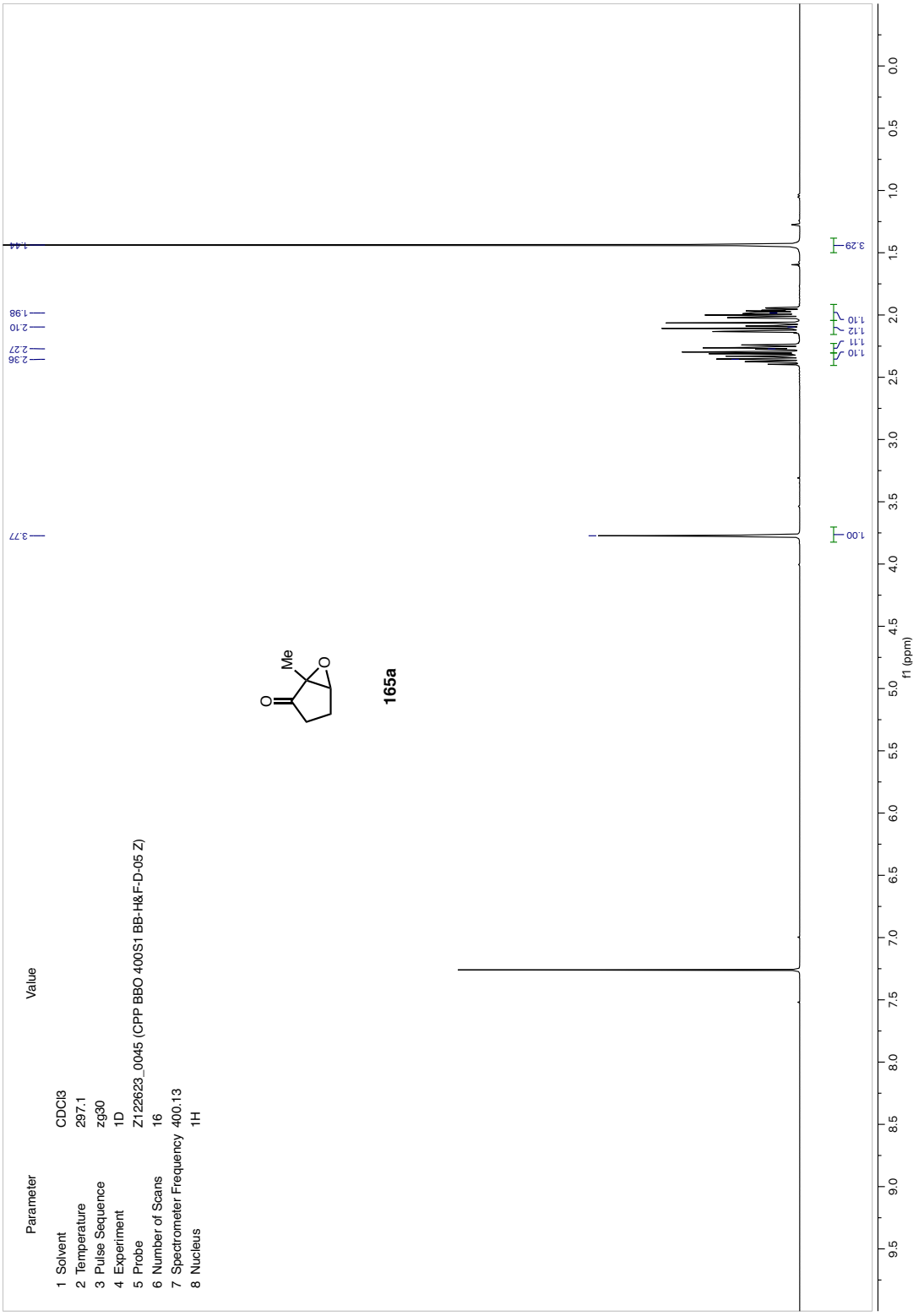

OTIPS
Br
183
Parameter Value
1 Solvent CDCl3
2 Temperature 295.0
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
1.10
1.94
2.48
2.64
4.34
22.62
2.01
2.00
1.98
1.99
ppm

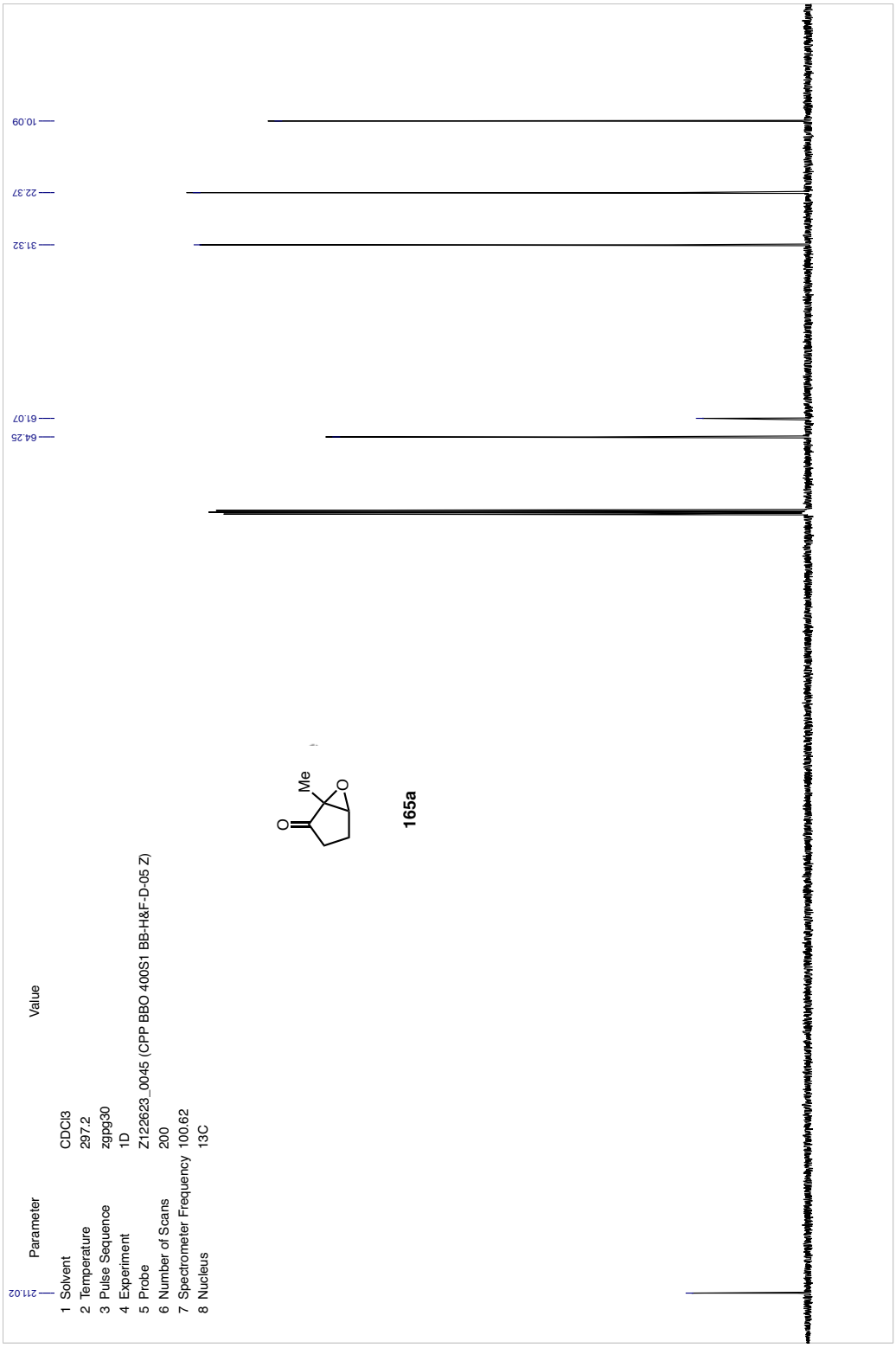


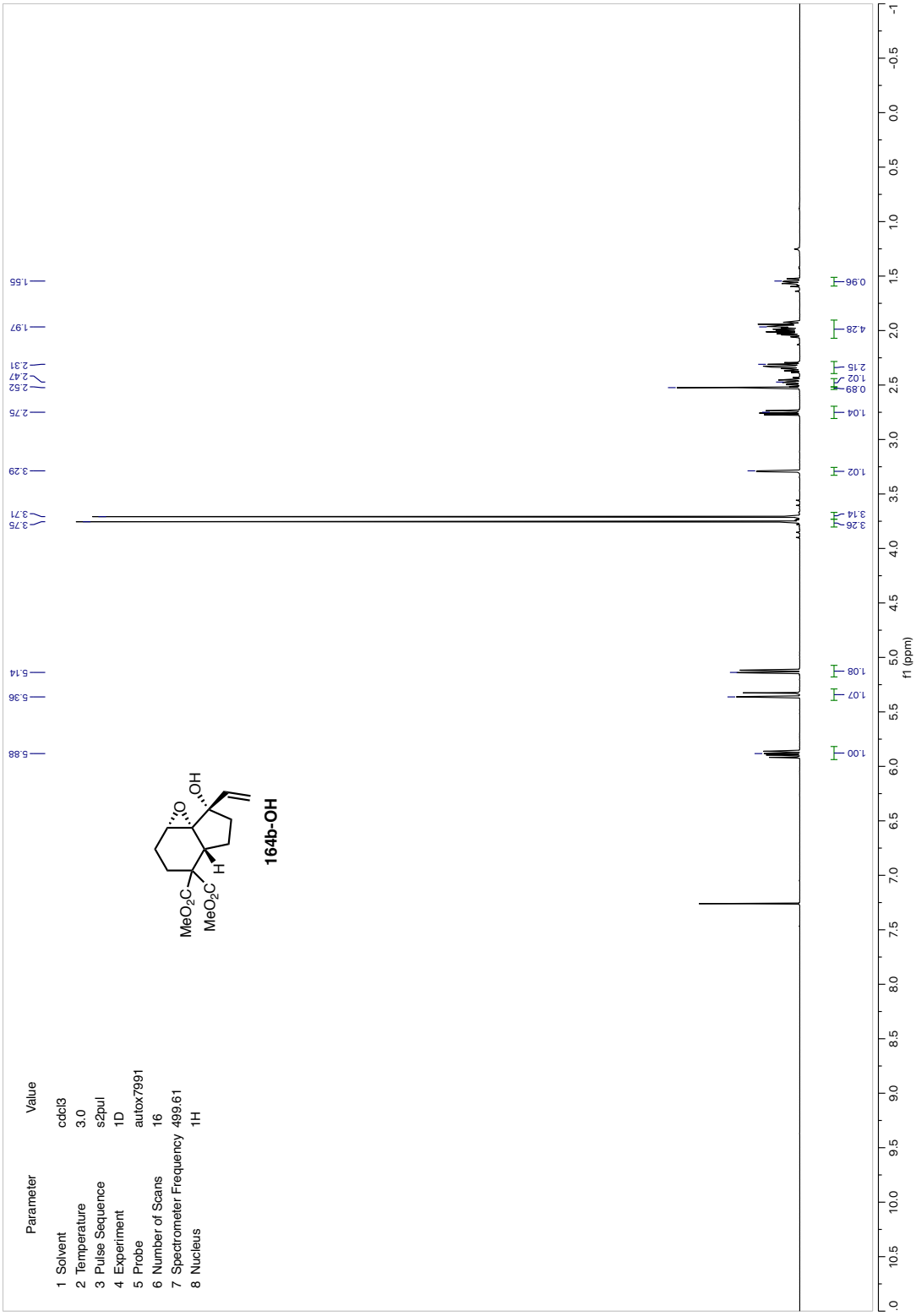
	Parameter	Value
1	Solvent	cdcl3
2	Temperature	25.0
3	Pulse Sequence	s2pul
4	Experiment	1D
5	Probe	autox7991
6	Number of Scans	4000
7	Spectrometer Frequency	125.65
8	Nucleus	13C

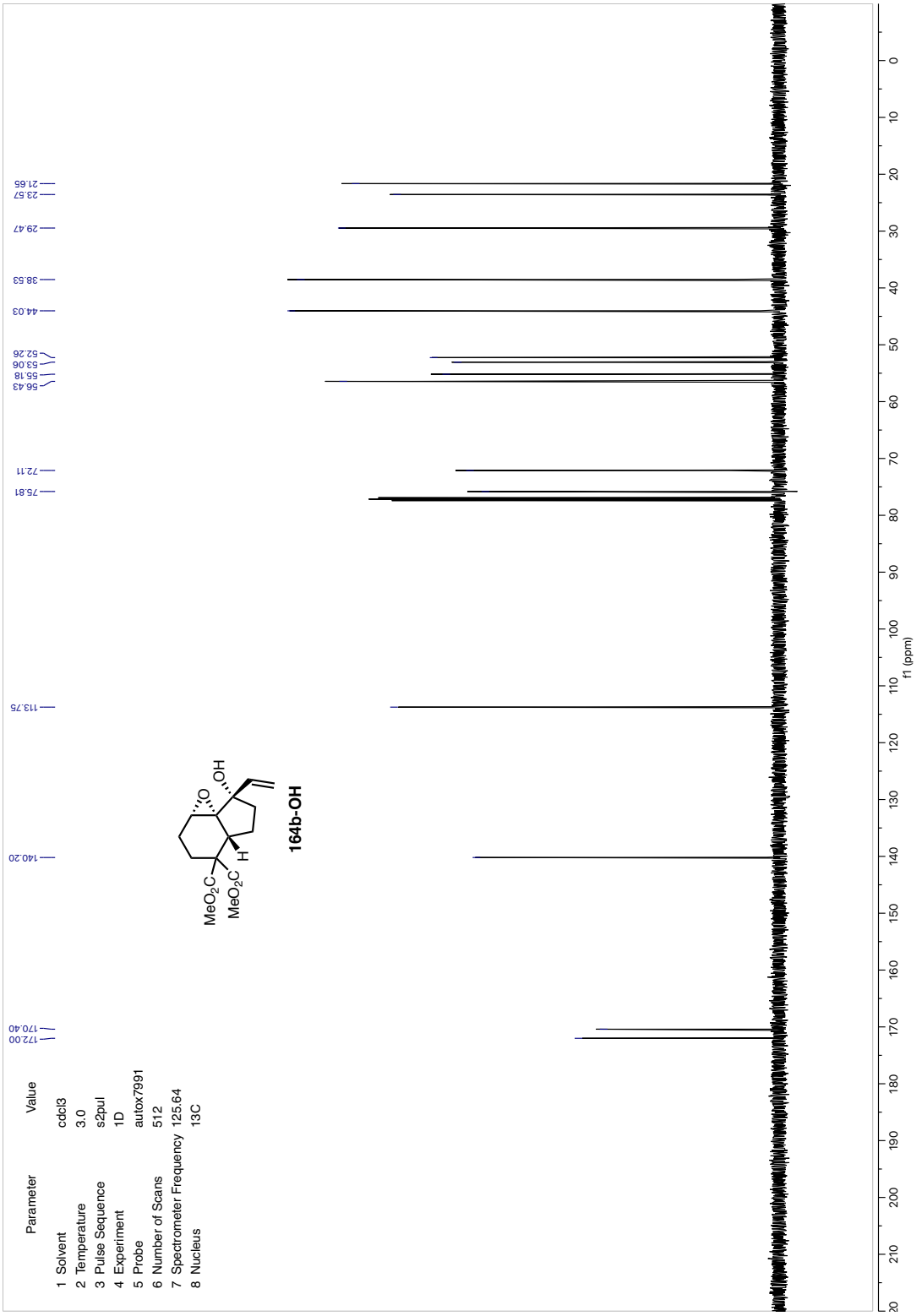

Parameter Value
1 Solvent CDCl3
2 Temperature 297.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
Br
Me
Me
186
f1 (ppm)

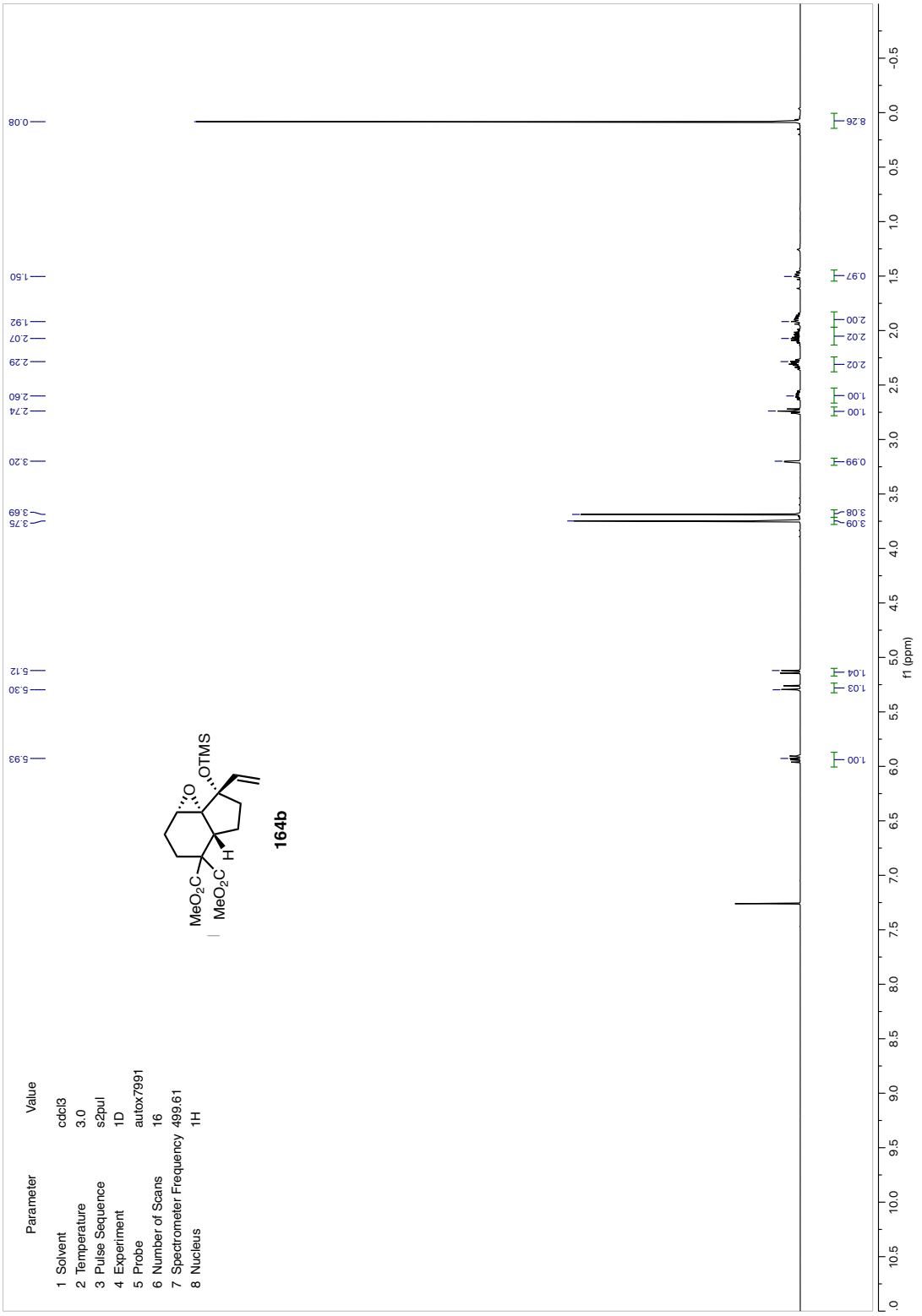

Parameter
Value
1 Solvent CDCl3
2 Temperature 297.2
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 256
7 Spectrometer Frequency 100.62
8 Nucleus 13C
Br
Me
Me
186
20.79
26.08
32.78
33.28
40.20
52.73
123.51
126.68
f1 (ppm)

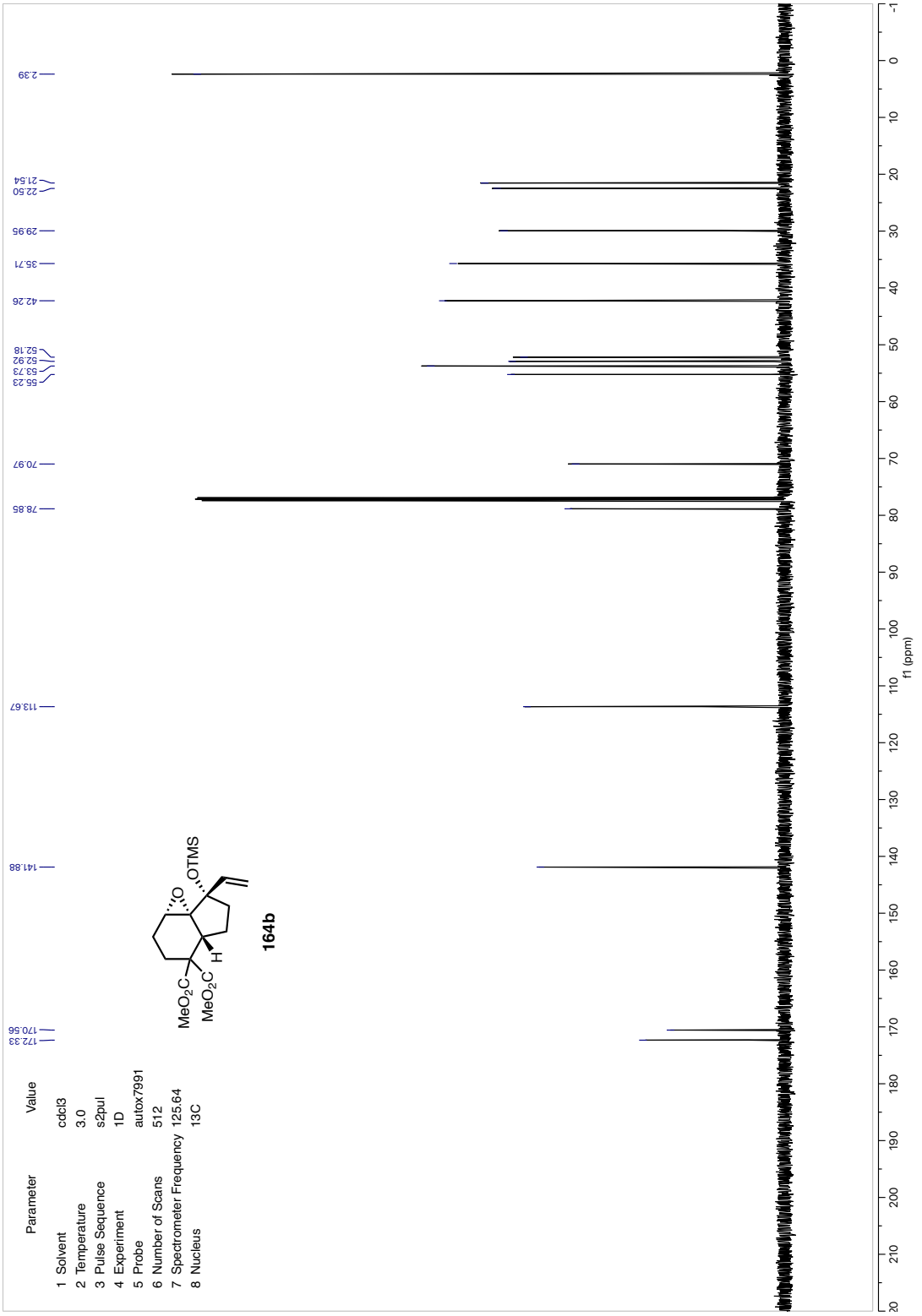

Parameter Value
1 Solvent CDCl3
2 Temperature 297.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
Me
O
O
165a
1.44
1.98
2.10
2.27
2.36
3.77
3.29
1.10
1.12
1.11
1.10
1.00
f1 (ppm)

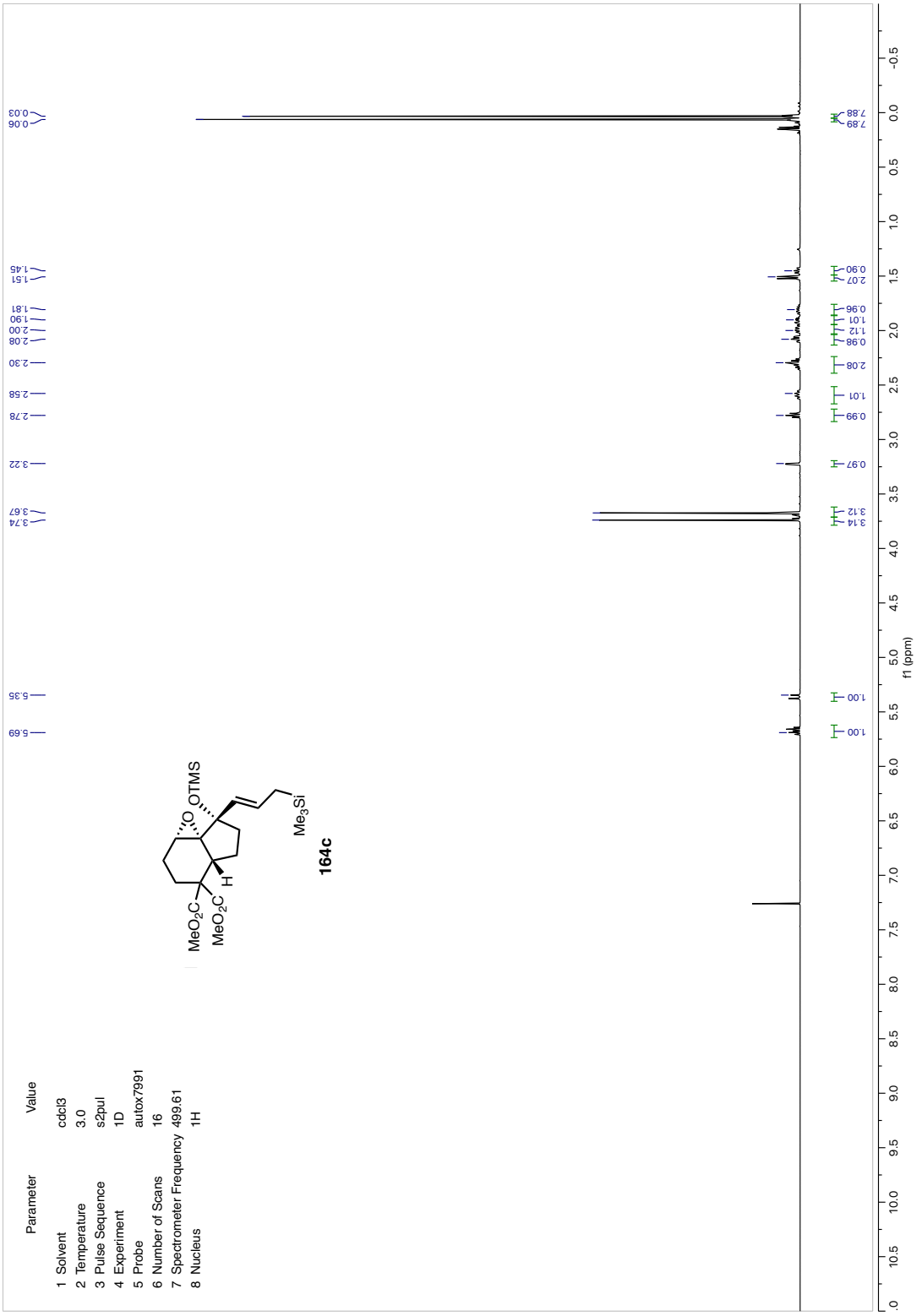

Parameter Value
1 Solvent CDCl3
2 Temperature 297.2
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 200
7 Spectrometer Frequency 100.62
8 Nucleus 13C
Me
O
O
165a
211.02
64.25
61.07
31.32
22.37
10.09
f1 (ppm)

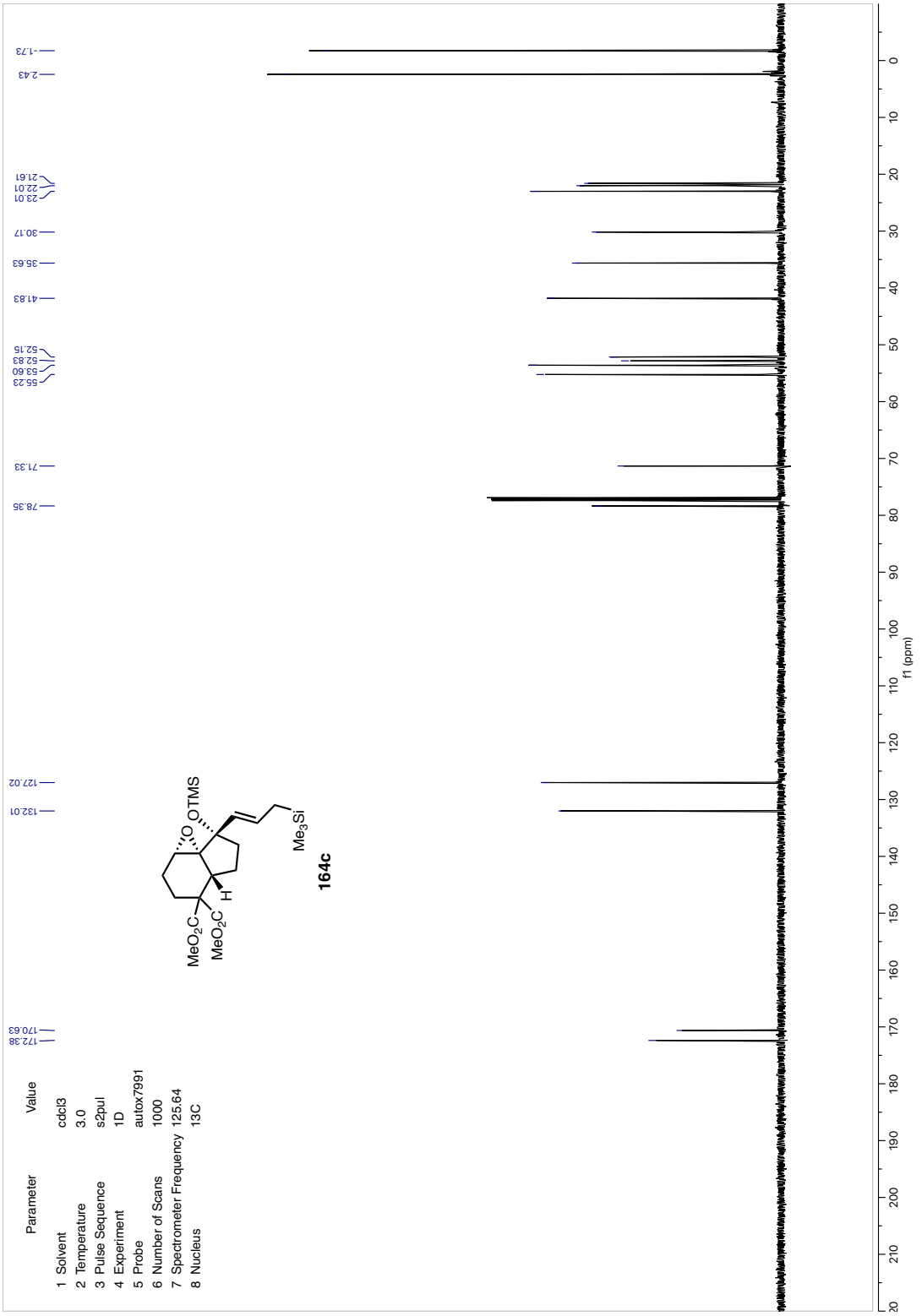

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
164b-OH
f1 (ppm)

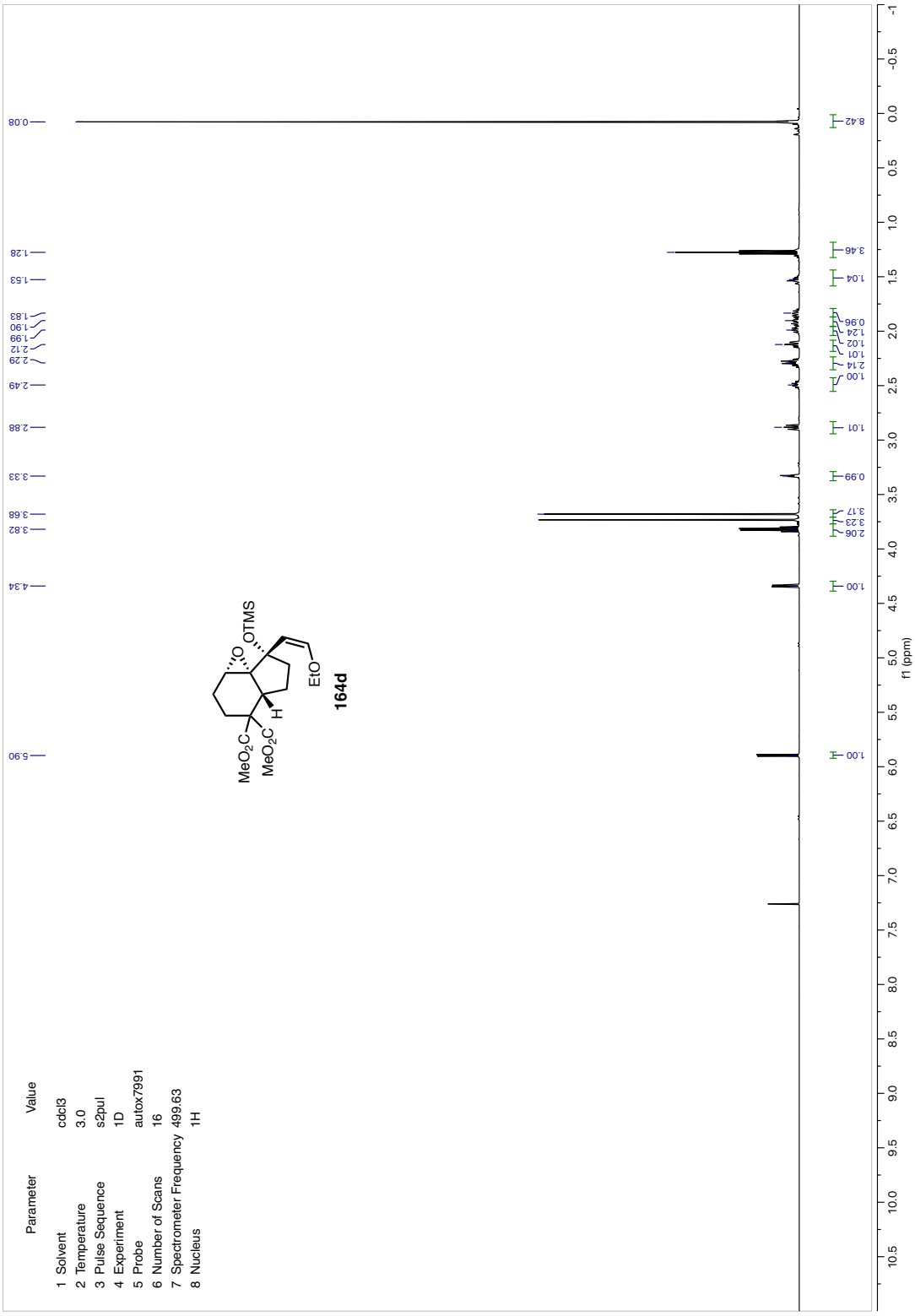

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
172.00
170.40
140.20
113.75
75.81
72.11
56.43
55.18
53.06
52.26
44.03
38.53
29.47
23.57
21.65
MeO2C
MeO2C
O
OH
H
164b-OH
f1 (ppm)

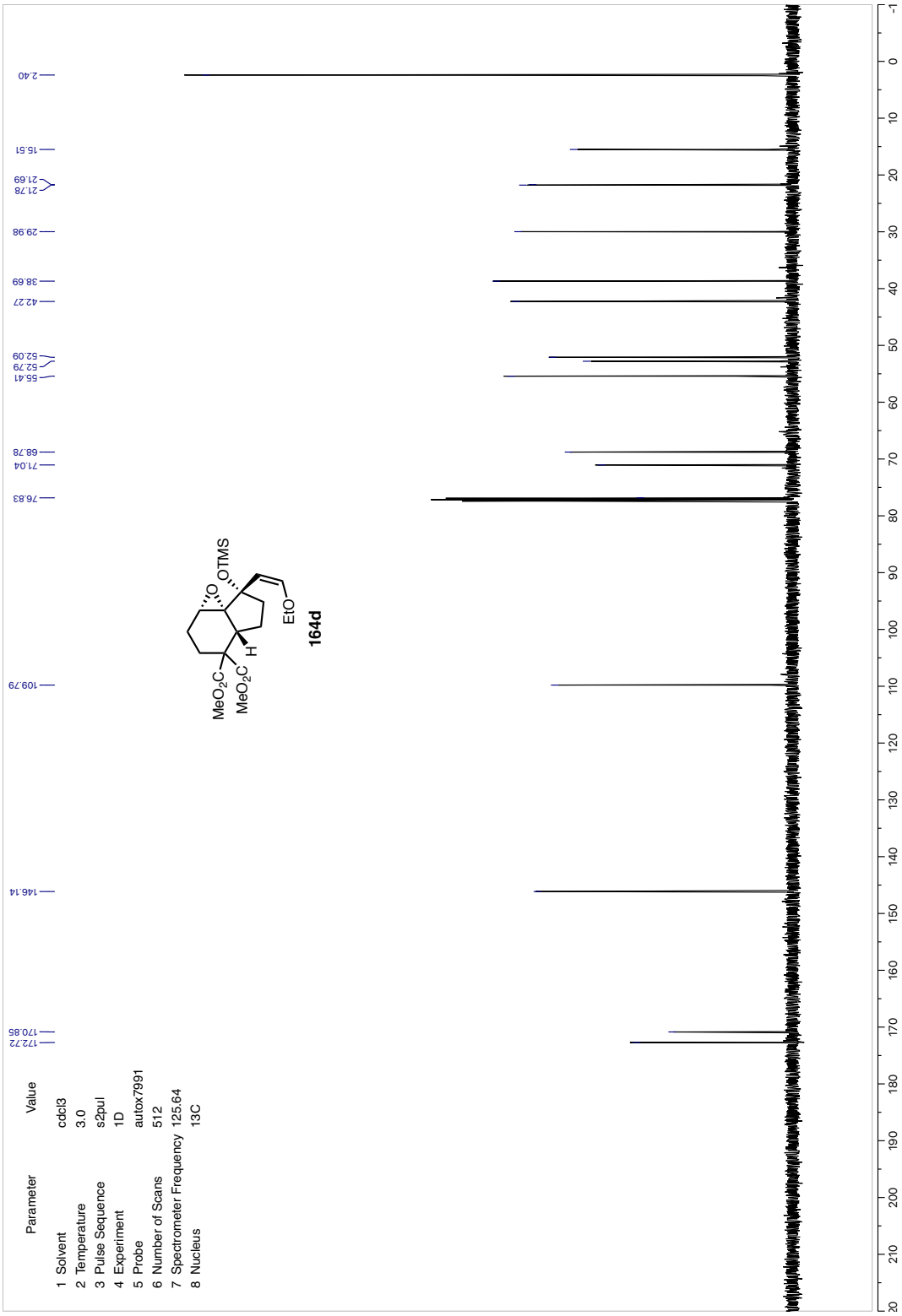

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
O
H
MeO2C
MeO2C
164b
f1 (ppm)

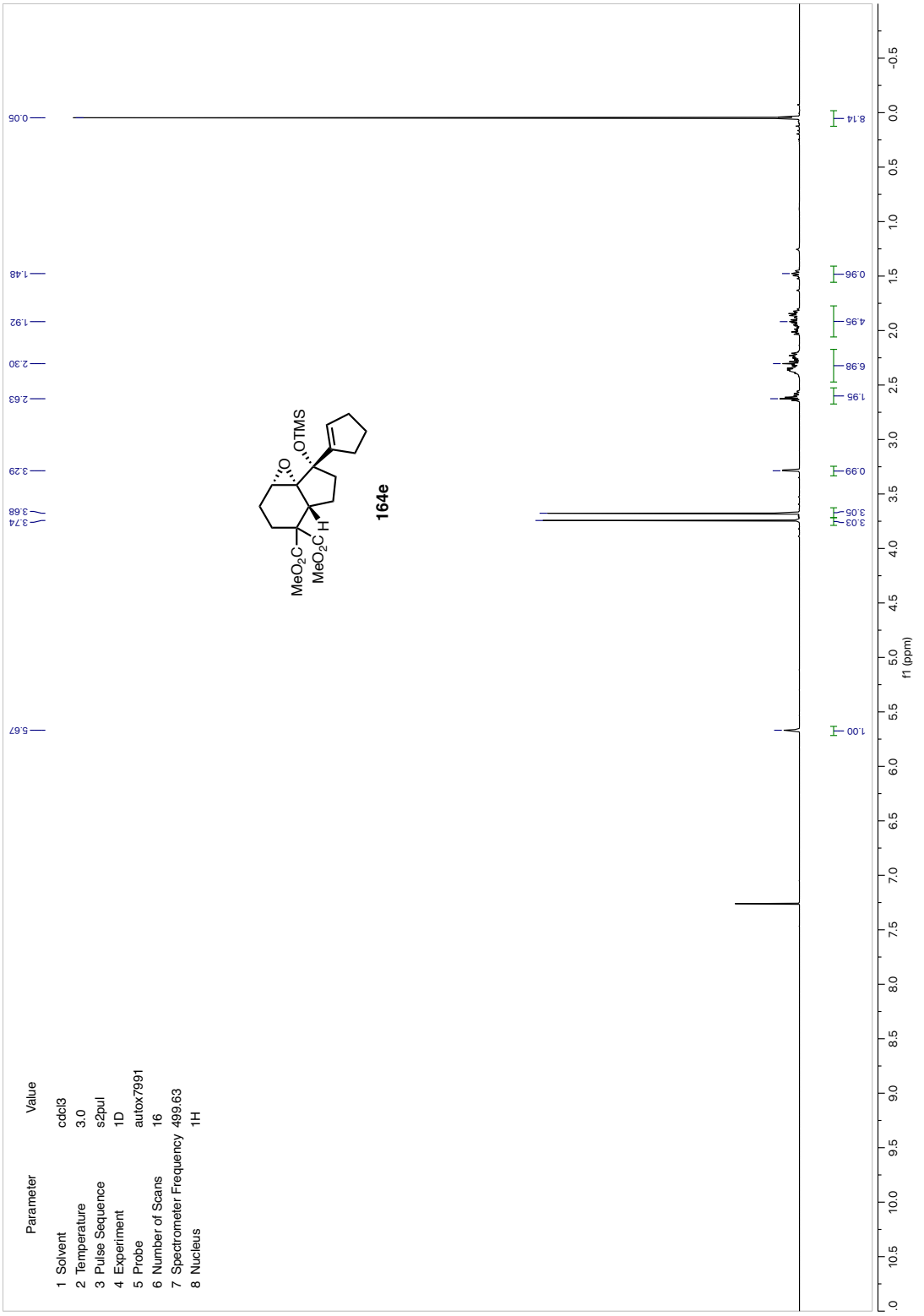

2.39
21.54
22.50
29.95
35.71
42.26
52.18
52.92
53.73
55.23
70.97
78.85
113.67
141.88
170.56
172.33
OTMS
O
H
MeO2C
MeO2C
164b
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

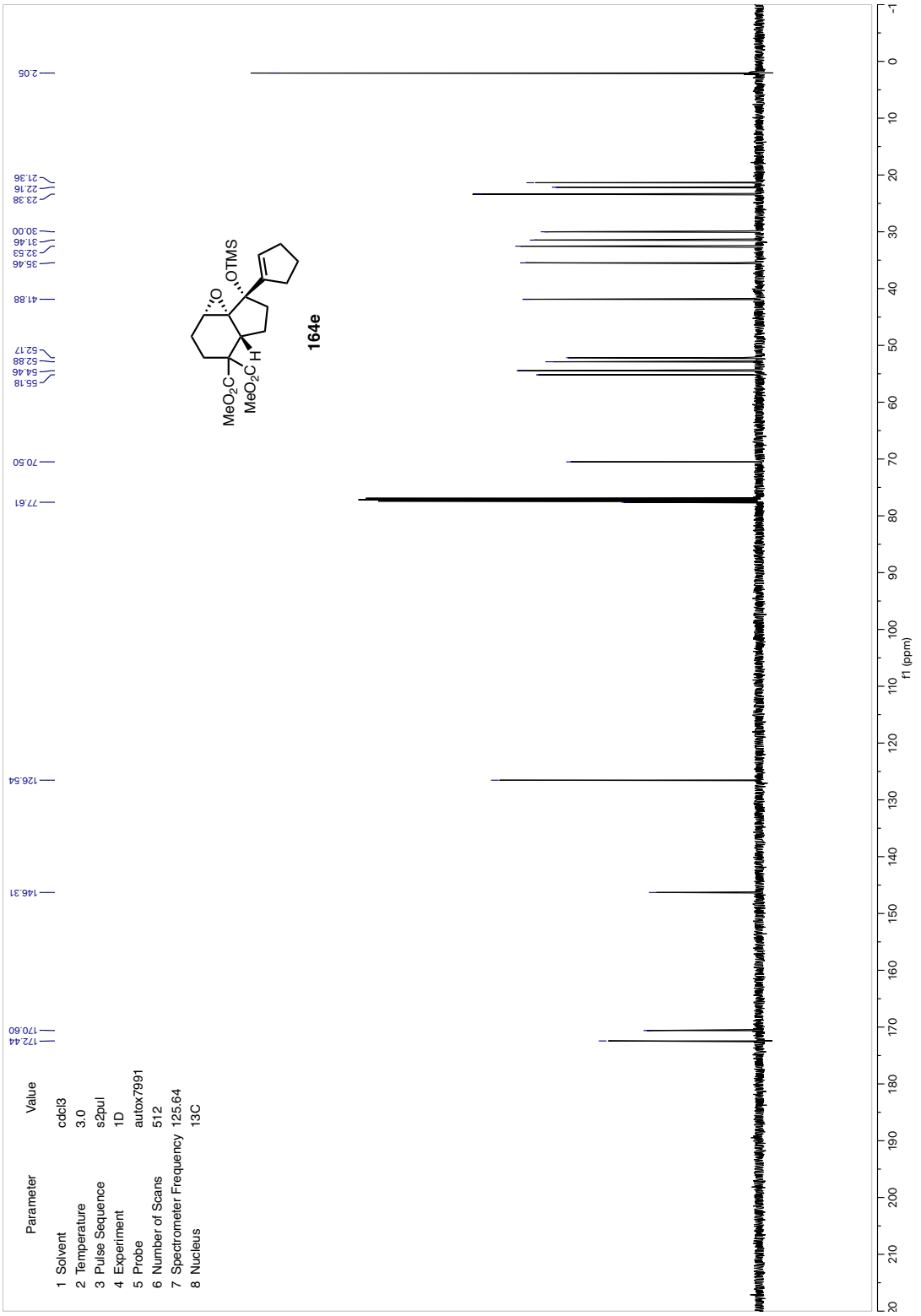

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
MeO2C
MeO2C
H
O OTMS
Me3Si
164c
f1 (ppm)

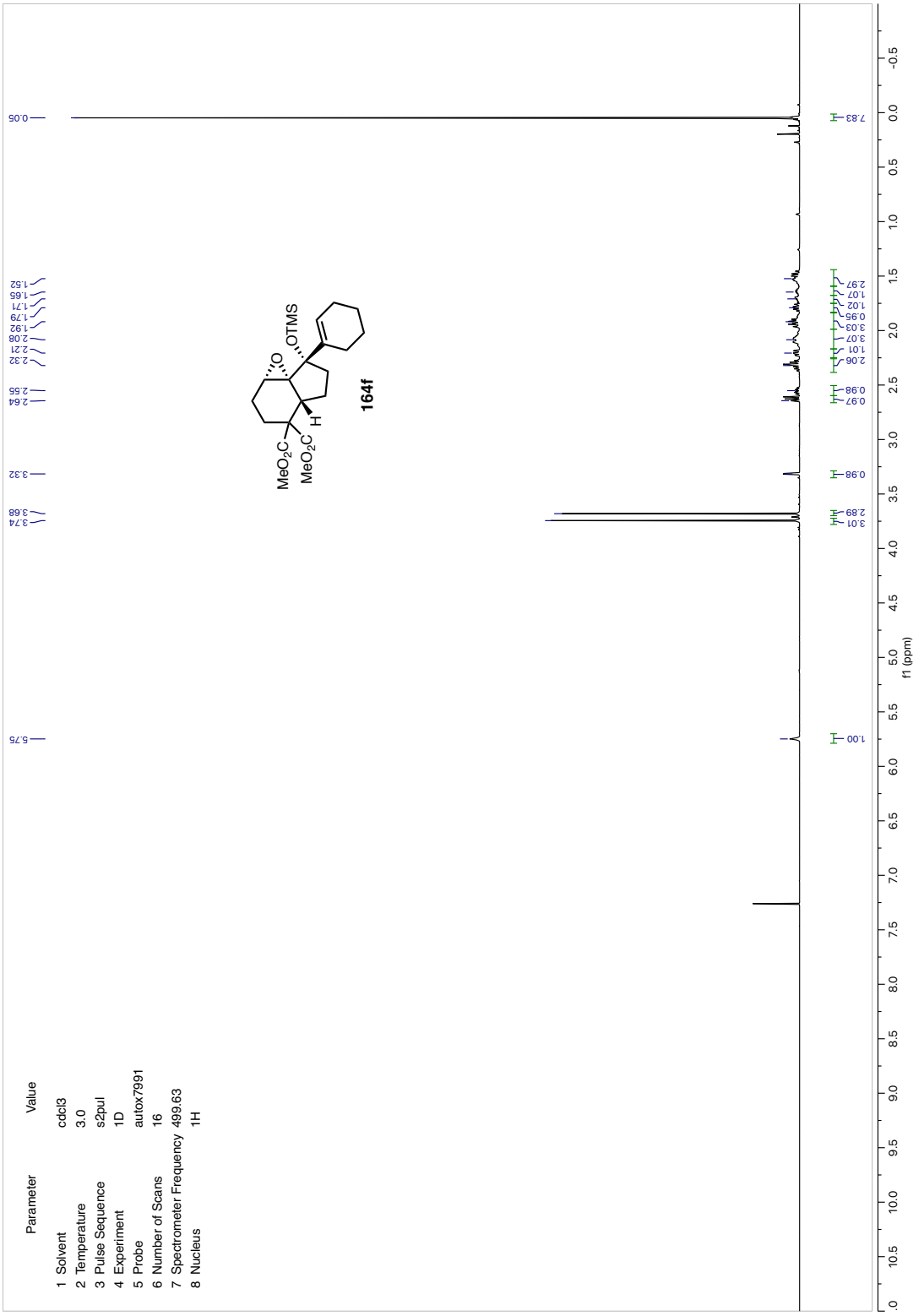

-1.73
2.43
21.61
22.01
23.01
30.17
35.63
41.83
52.15
52.83
53.60
55.23
71.33
78.35
127.02
132.01
170.63
172.38
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
MeO2C
MeO2C
OTMS
H
Me3Si
164c
f1 (ppm)

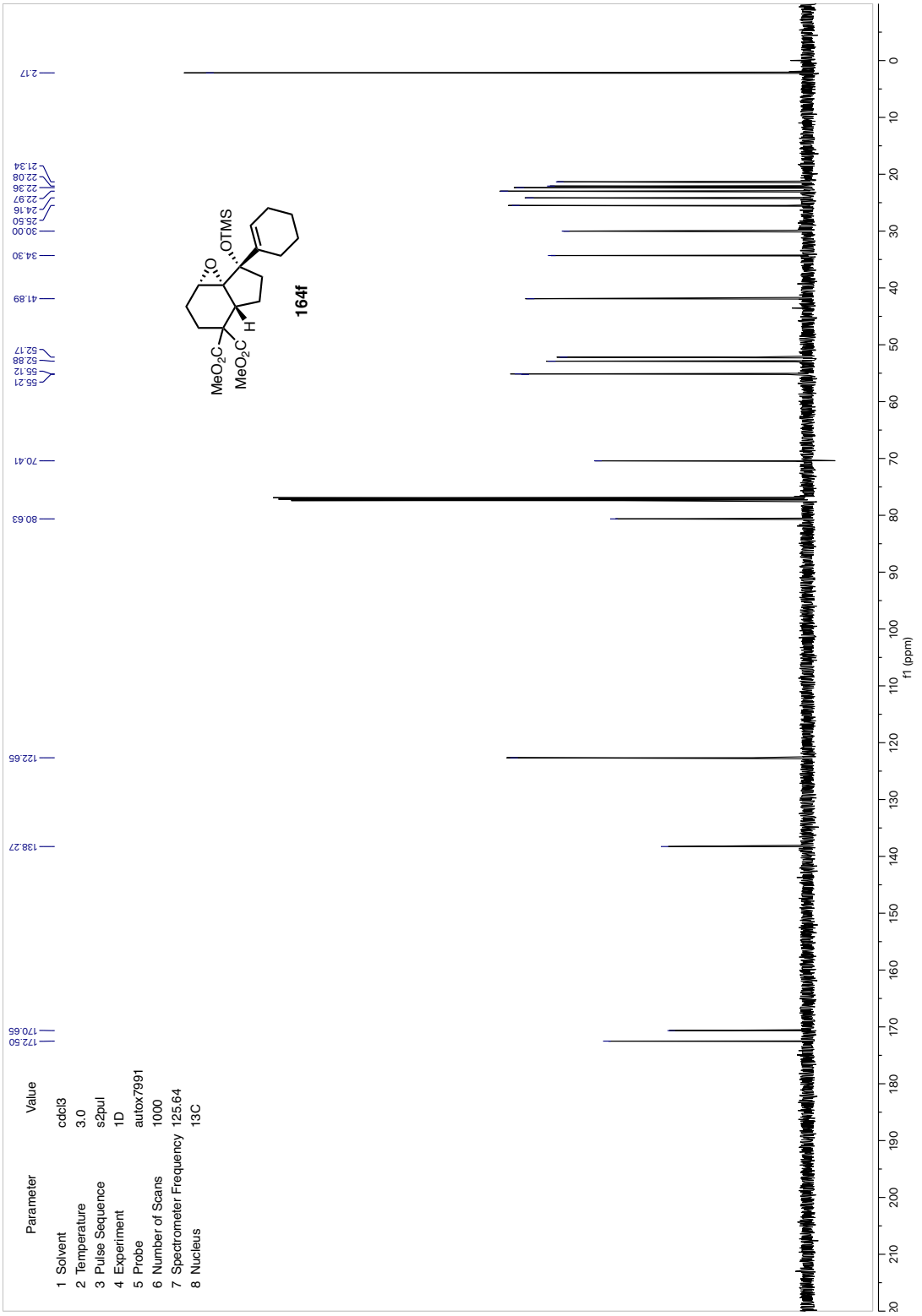

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.63
8 Nucleus 1H
MeO2C
MeO2C
OTMS
EtO
H
164d
f1 (ppm)

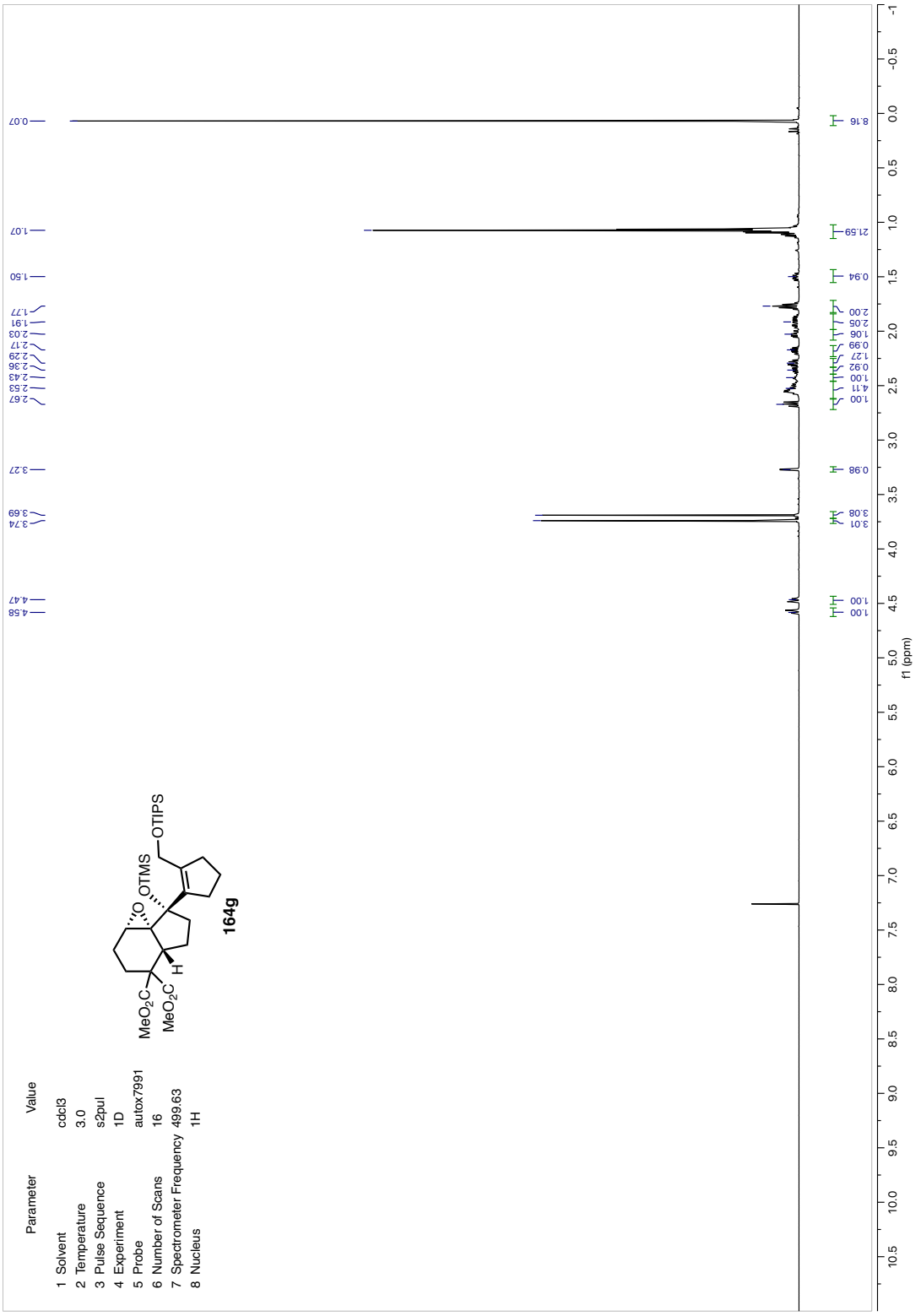

2.40
15.51
21.69
21.78
29.98
38.69
42.27
52.09
52.79
55.41
68.78
71.04
76.83
109.79
146.14
170.85
172.72
OTMS
EtO
H
MeO2C
MeO2C
164d
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

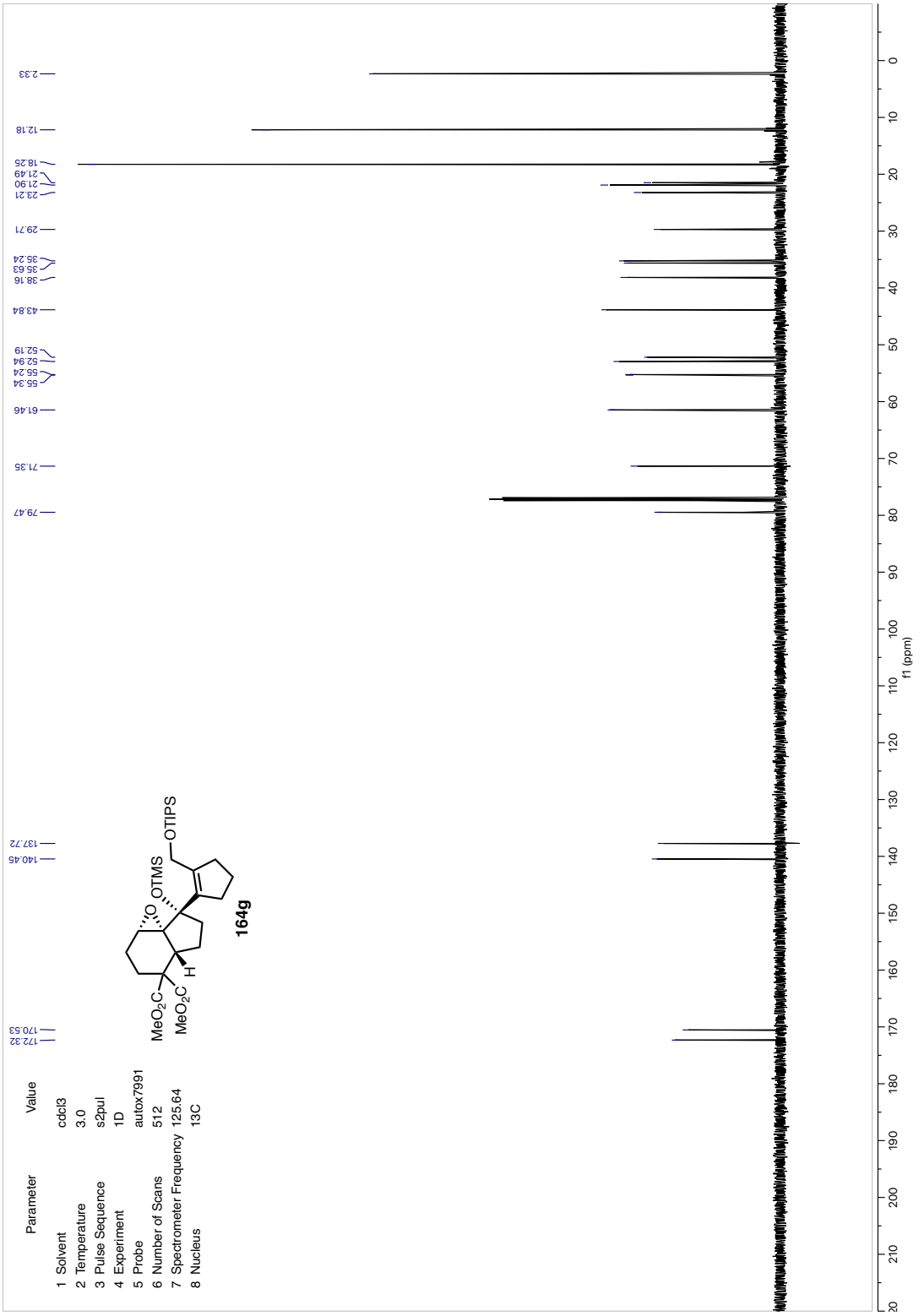

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.63
8 Nucleus 1H
OTMS
MeO2C
MeO2C
H
164e
f1 (ppm)

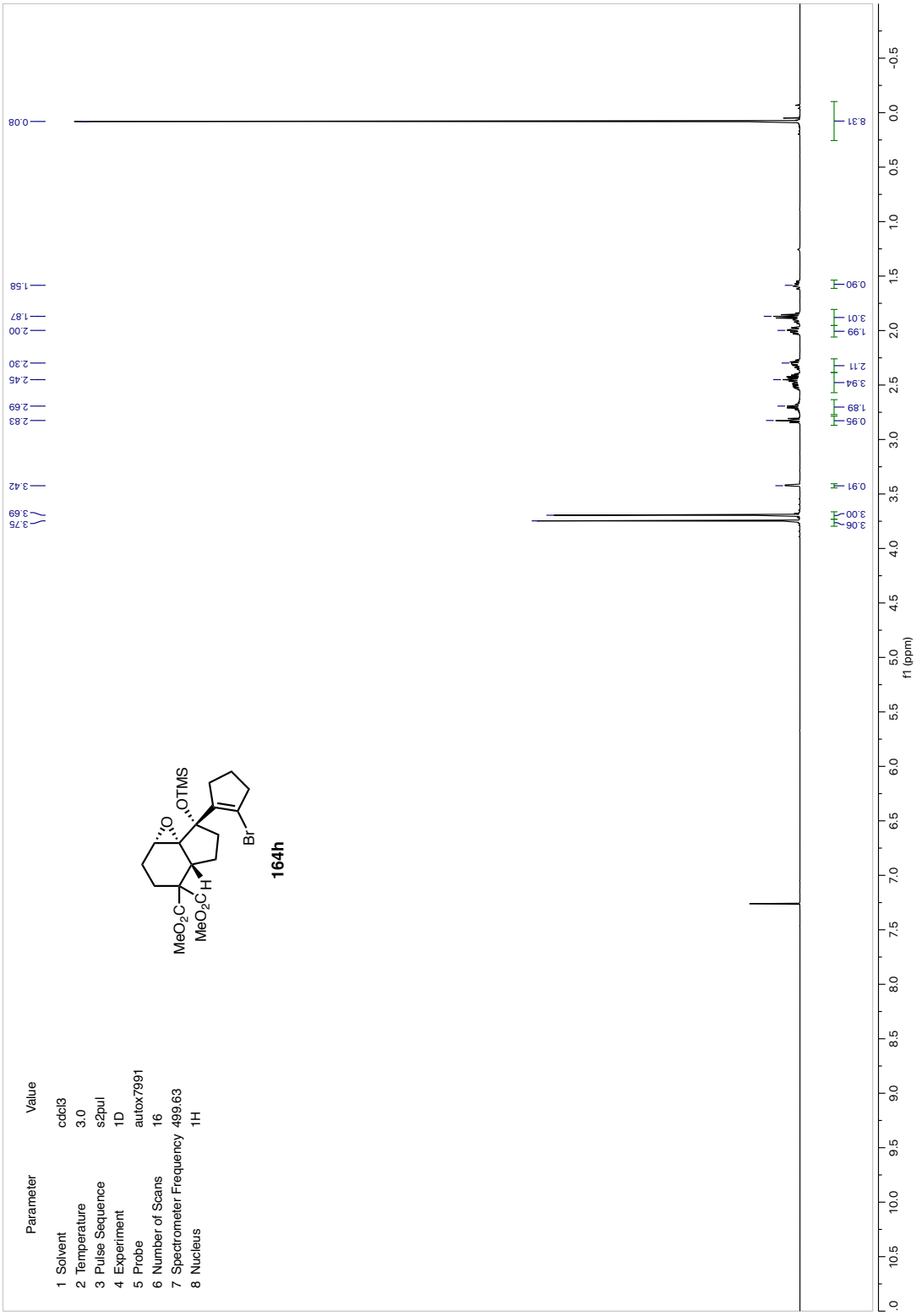

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
172.44
170.60
146.31
126.54
77.61
70.50
55.18
54.46
52.88
52.17
41.88
35.46
32.53
31.46
30.00
23.38
22.16
21.36
2.05
OTMS
O
H
MeO_2C
MeO_2C
164e
f1 (ppm)

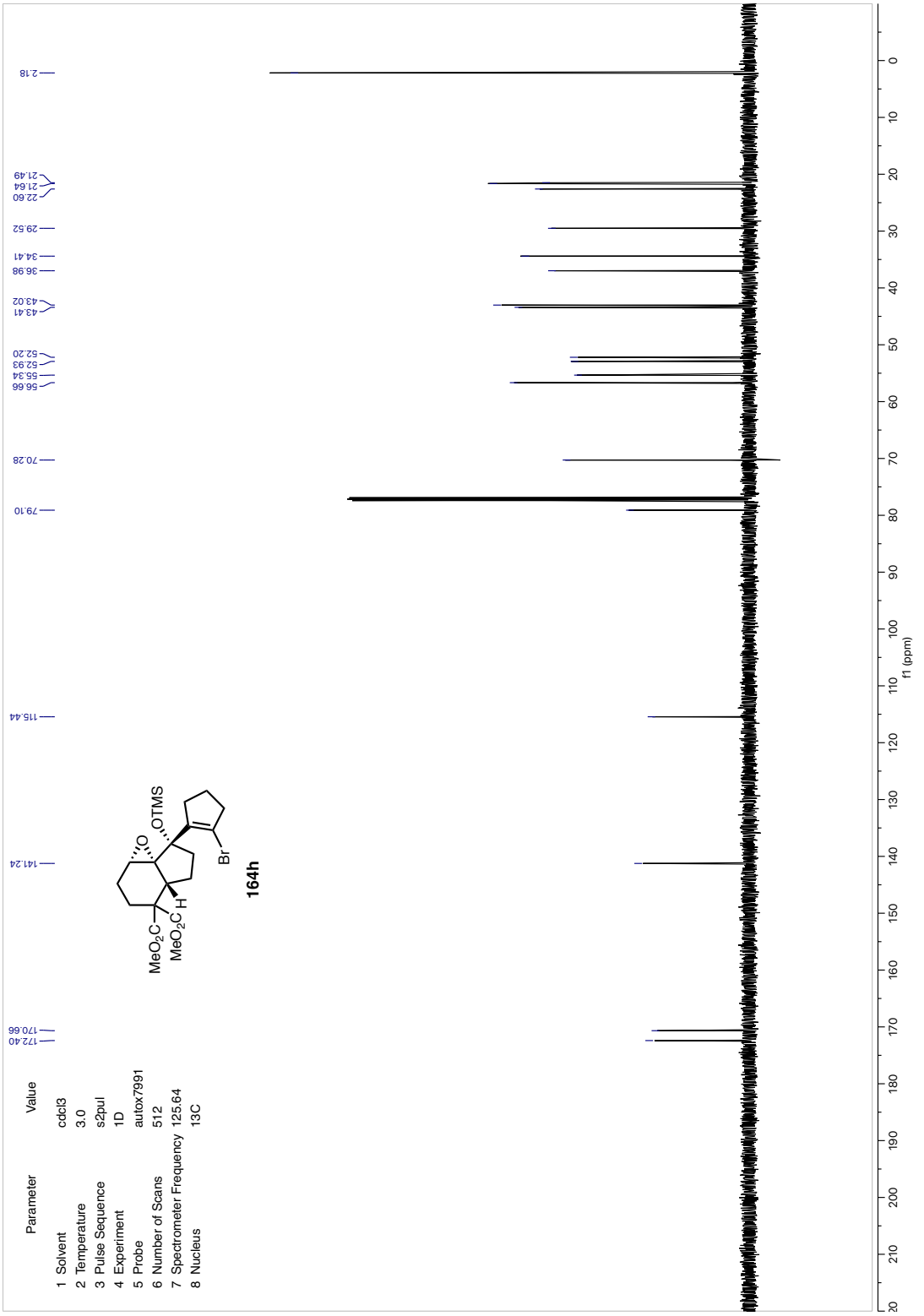

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.63
8 Nucleus 1H
OTMS
MeO2C
MeO2C
H
164f
f1 (ppm)

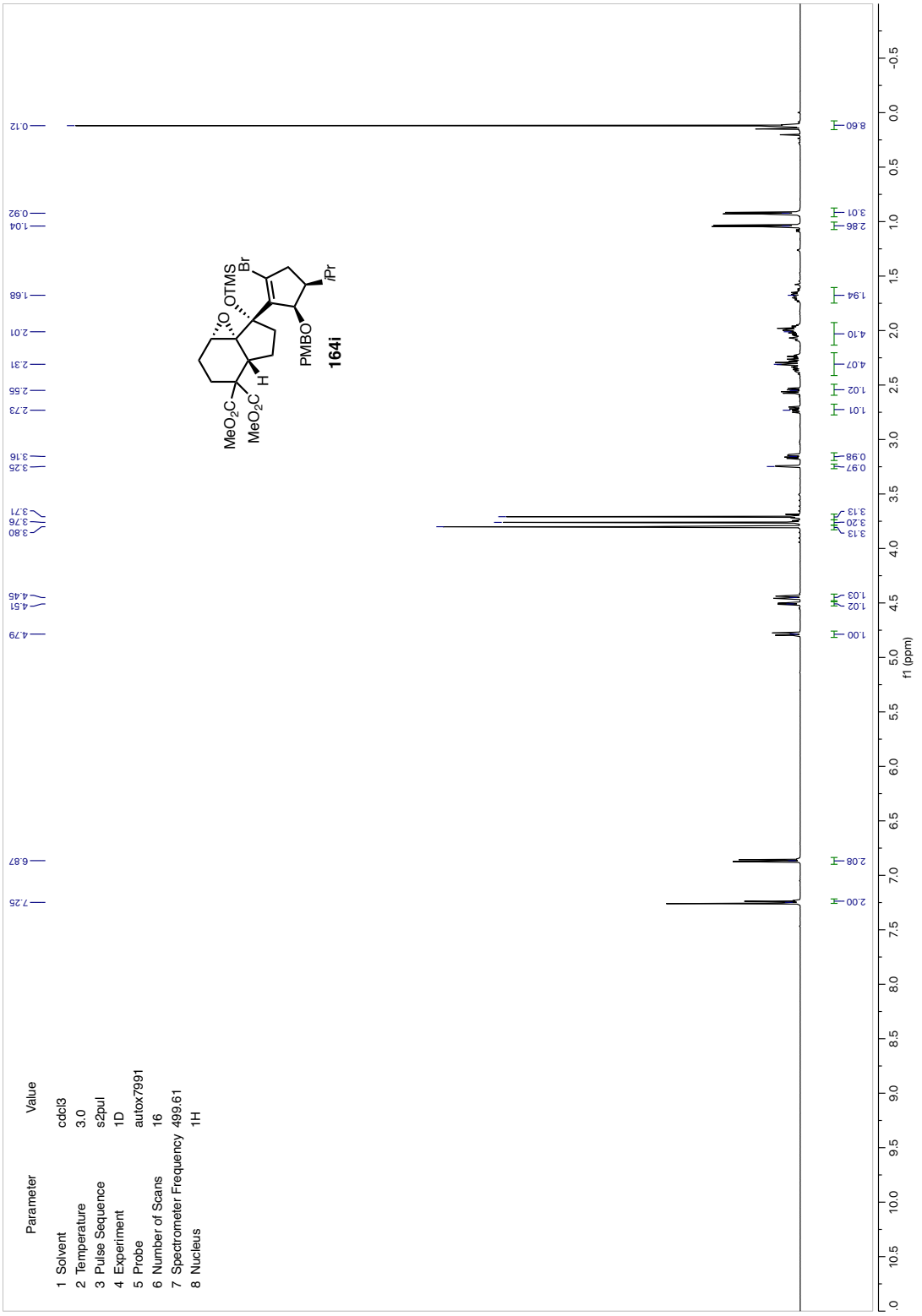

OTMS
O
H
MeO2C
MeO2C
164f
2.17
21.34
22.08
22.36
22.97
24.16
25.50
30.00
34.30
41.89
52.17
52.88
55.12
55.21
70.41
80.63
122.65
138.27
170.65
172.50
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

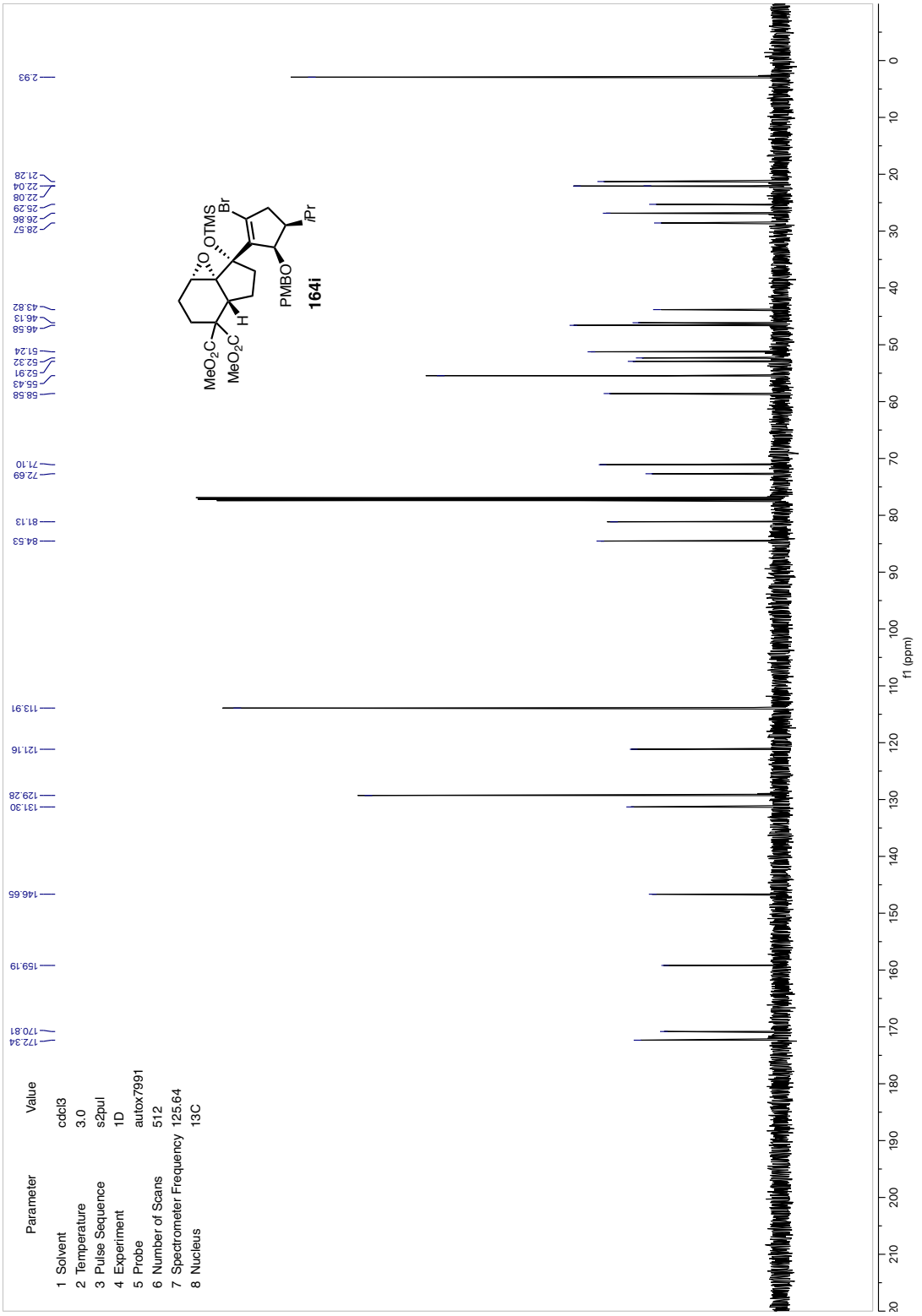

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.63
8 Nucleus 1H
OTMS
OTIPS
MeO2C
MeO2C
H
164g
f1 (ppm)

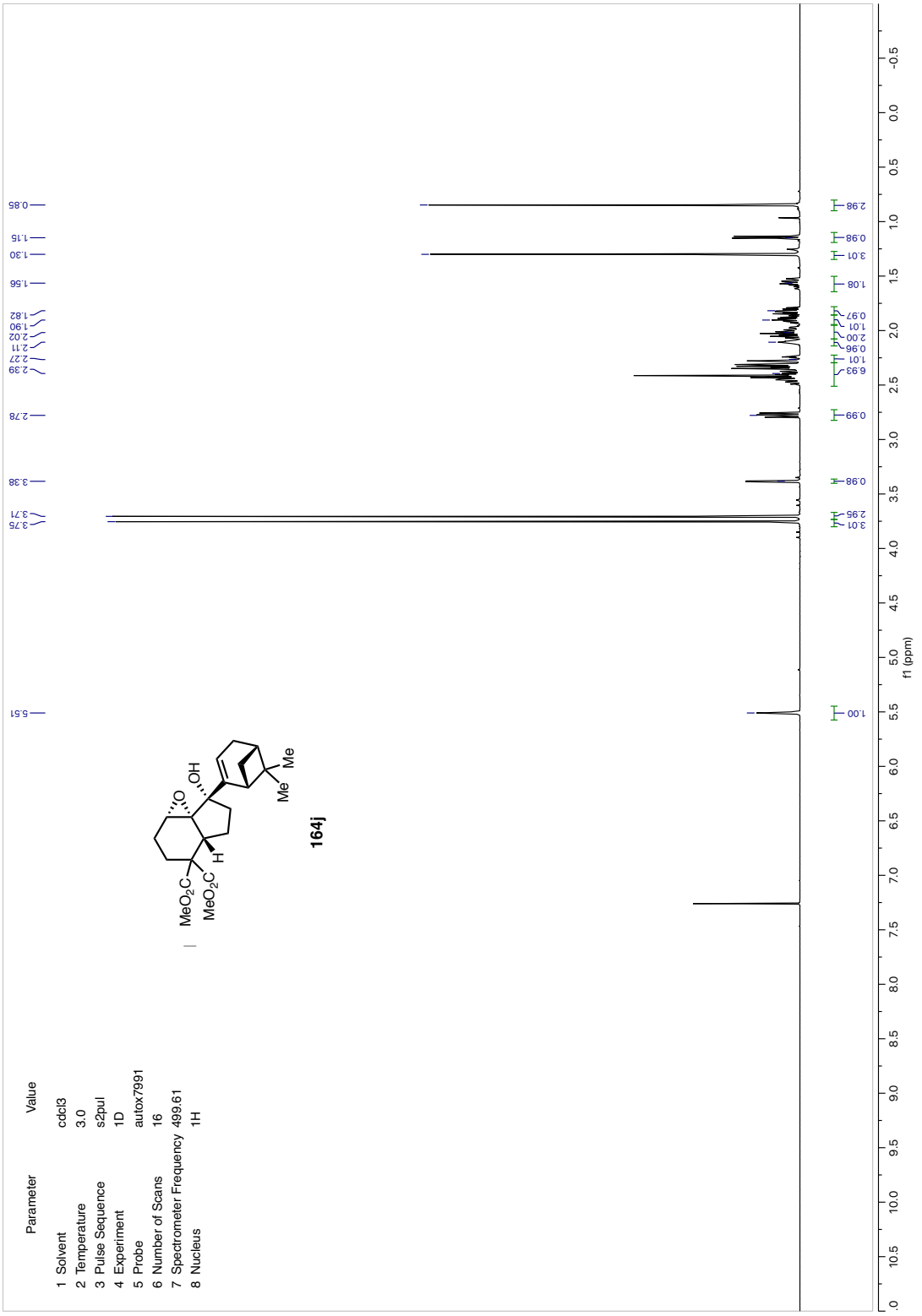

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
OTMS
OTIPS
MeO2C
MeO2C
H
164g
2.33
12.18
18.25
21.49
21.90
23.21
29.71
35.24
35.63
38.16
43.84
52.19
52.94
55.24
55.34
61.46
71.35
79.47
137.72
140.45
170.53
172.32
f1 (ppm)

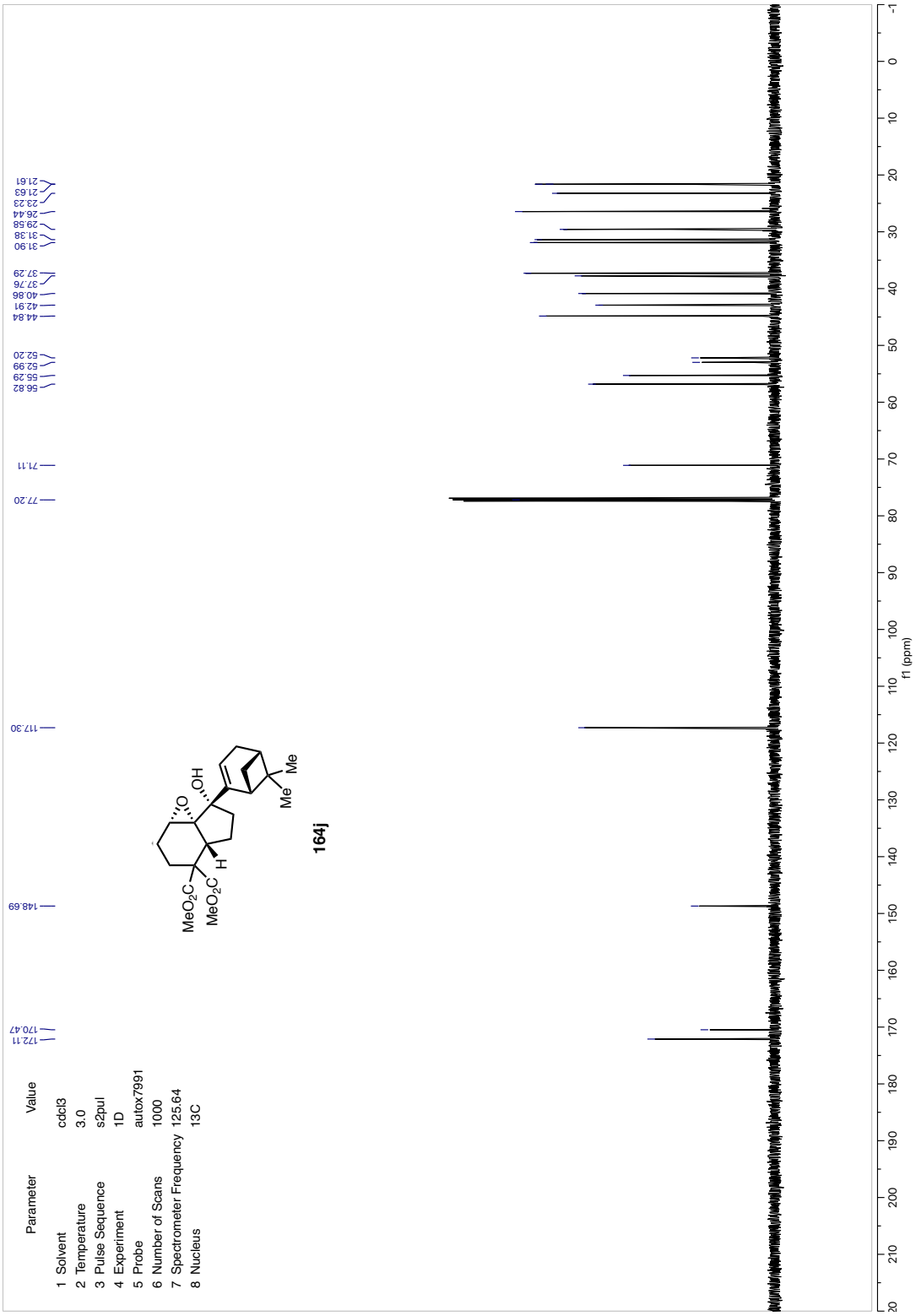

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.63
8 Nucleus 1H
MeO2C
MeO2C
O
OTMS
Br
164h
f1 (ppm)

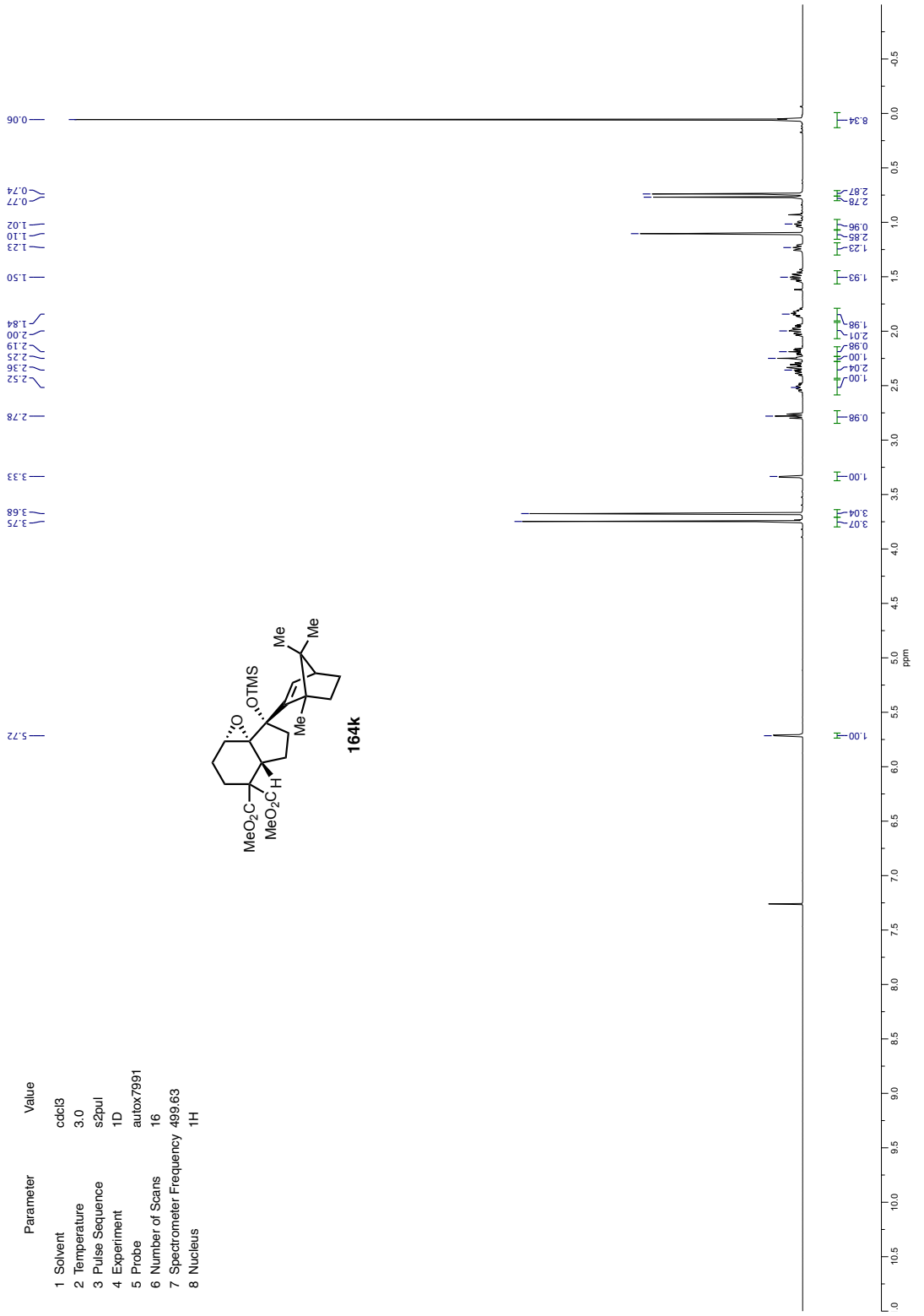

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
172.40
170.66
141.24
115.44
79.10
70.28
56.66
55.34
52.93
52.20
43.41
43.02
36.98
34.41
29.52
22.60
21.64
21.49
2.18
MeO2C
MeO2C
H
OTMS
O
Br
164h
f1 (ppm)

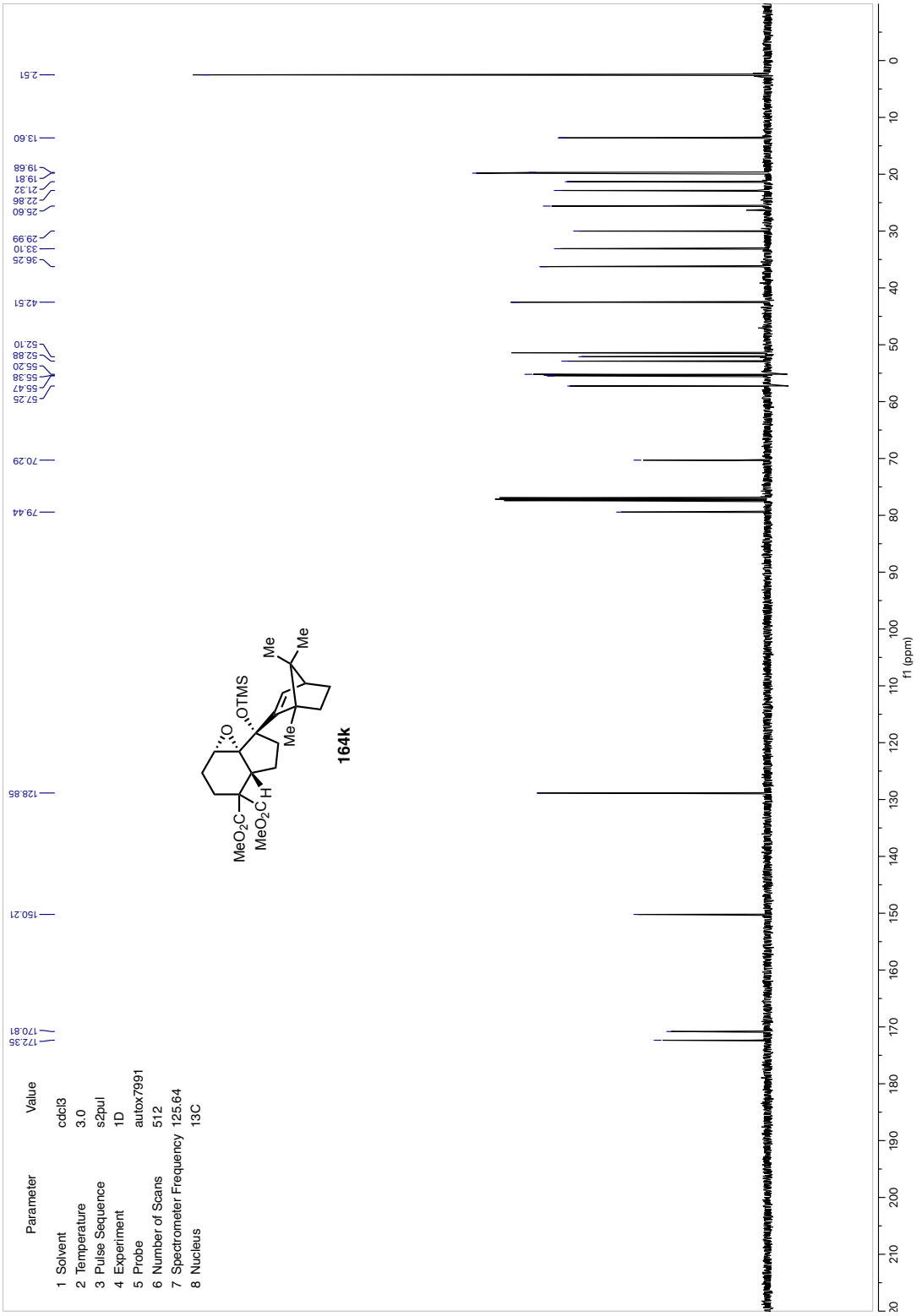

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
Br
iPr
PMBO
H
MeO2C
MeO2C
164i
f1 (ppm)

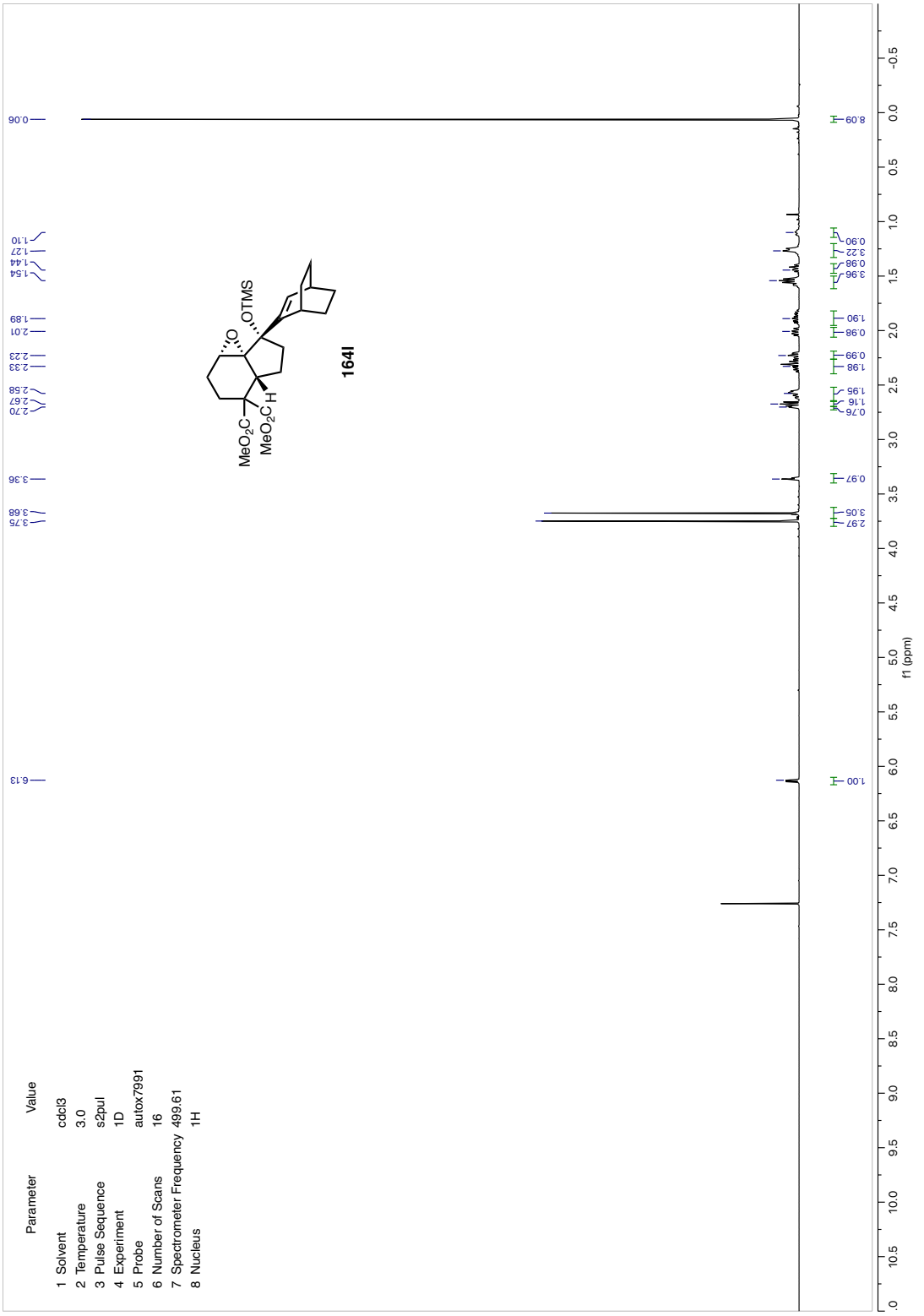

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
172.34
170.81
159.19
146.65
131.30
129.28
121.16
113.91
84.53
81.13
72.69
71.10
58.58
55.43
52.91
52.32
51.24
46.58
46.13
43.82
28.57
26.86
25.29
22.08
22.04
21.28
2.93
MeO2C
MeO2C
H
O
OTMS
Br
PMBO
iPr
164i
f1 (ppm)

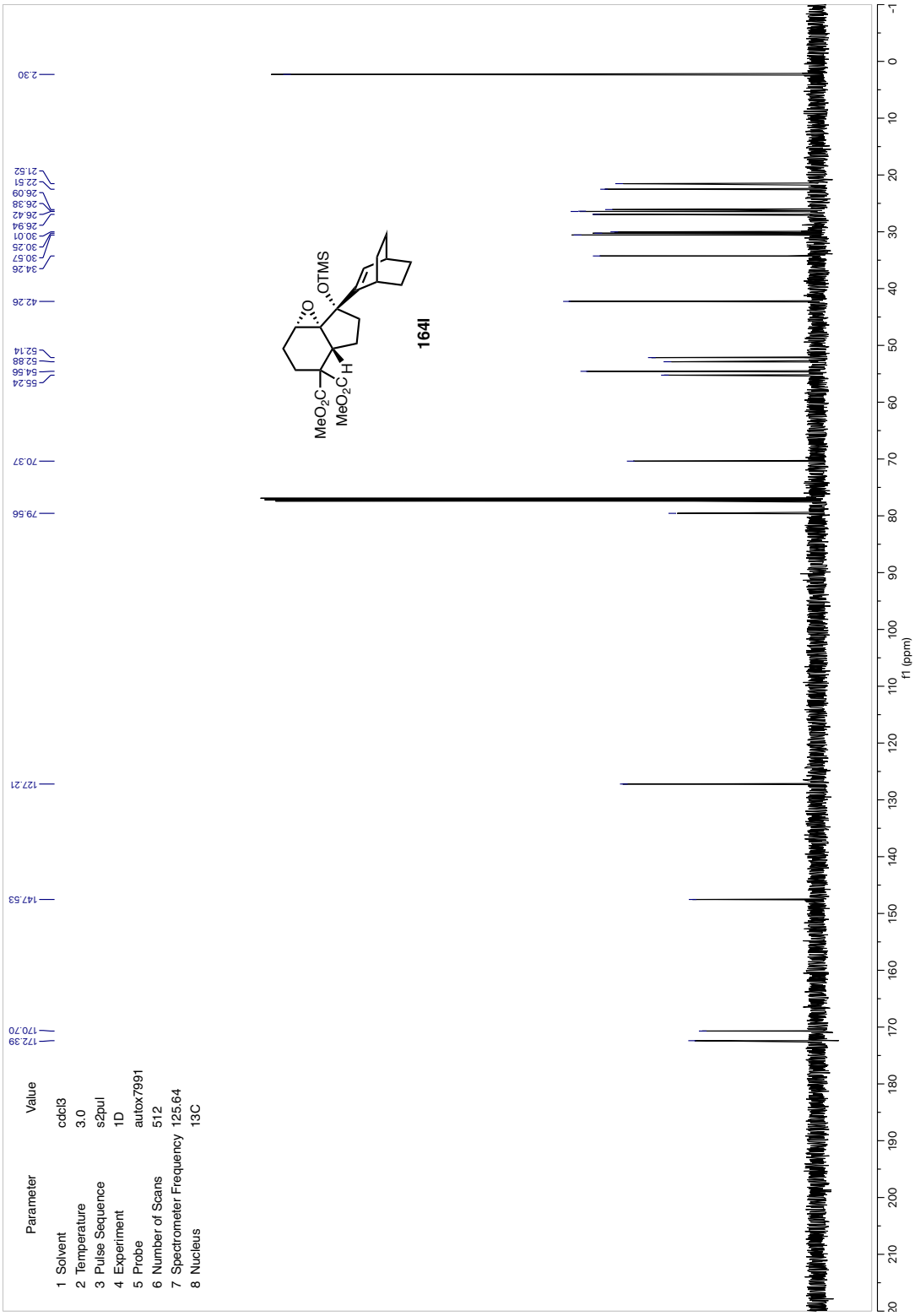

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
MeO2C
MeO2C
O
OH
H
Me
Me
164j
f1 (ppm)


Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
172.11
170.47
148.69
117.30
77.20
71.11
56.82
55.29
52.99
52.20
44.84
42.91
40.86
37.76
37.29
31.90
31.38
29.58
26.44
23.23
21.63
21.61
MeO2C
MeO2C
O
OH
H
Me
Me
164j
f1 (ppm)

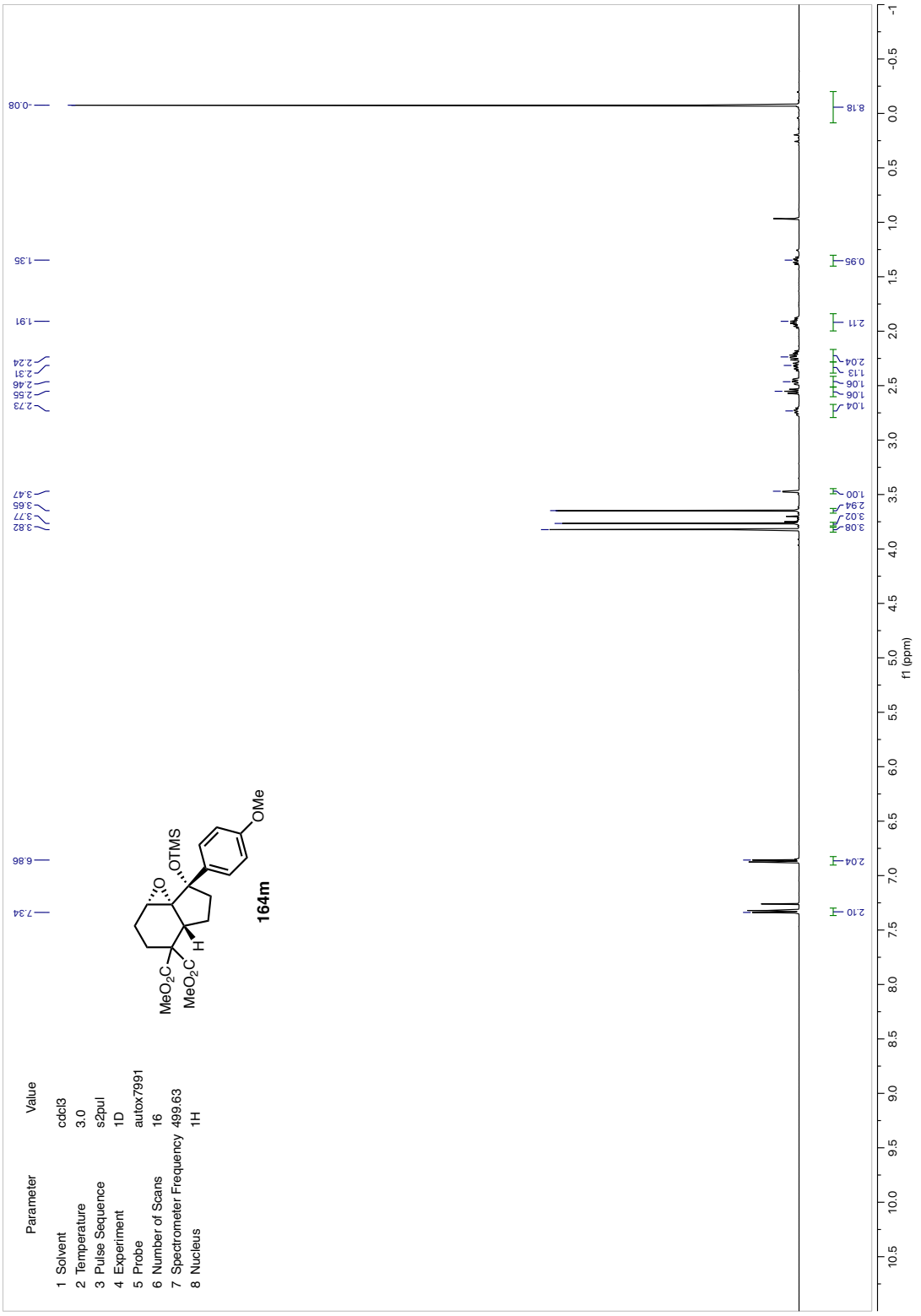

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.63
8 Nucleus 1H
MeO2C
MeO2C
H
O
OTMS
Me
Me
Me
164k
ppm

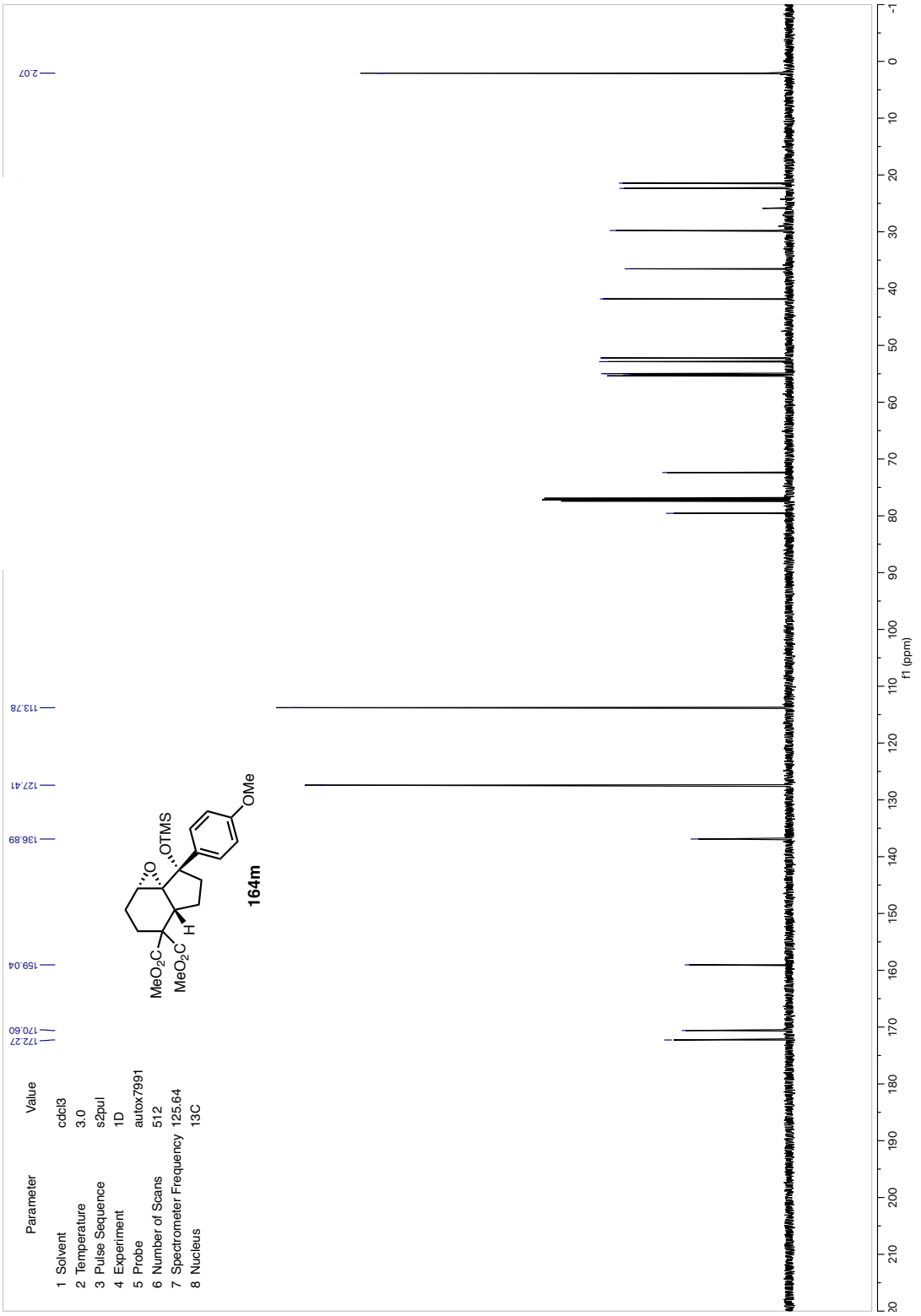

2.51
13.60
19.68
19.81
21.32
22.86
25.60
29.99
33.10
36.25
42.51
52.10
52.88
55.20
55.38
55.47
57.25
70.29
79.44
128.85
150.21
170.81
172.35
Me
Me
OTMS
O
Me
MeO2C
MeO2C
H
164k
f1 (ppm)

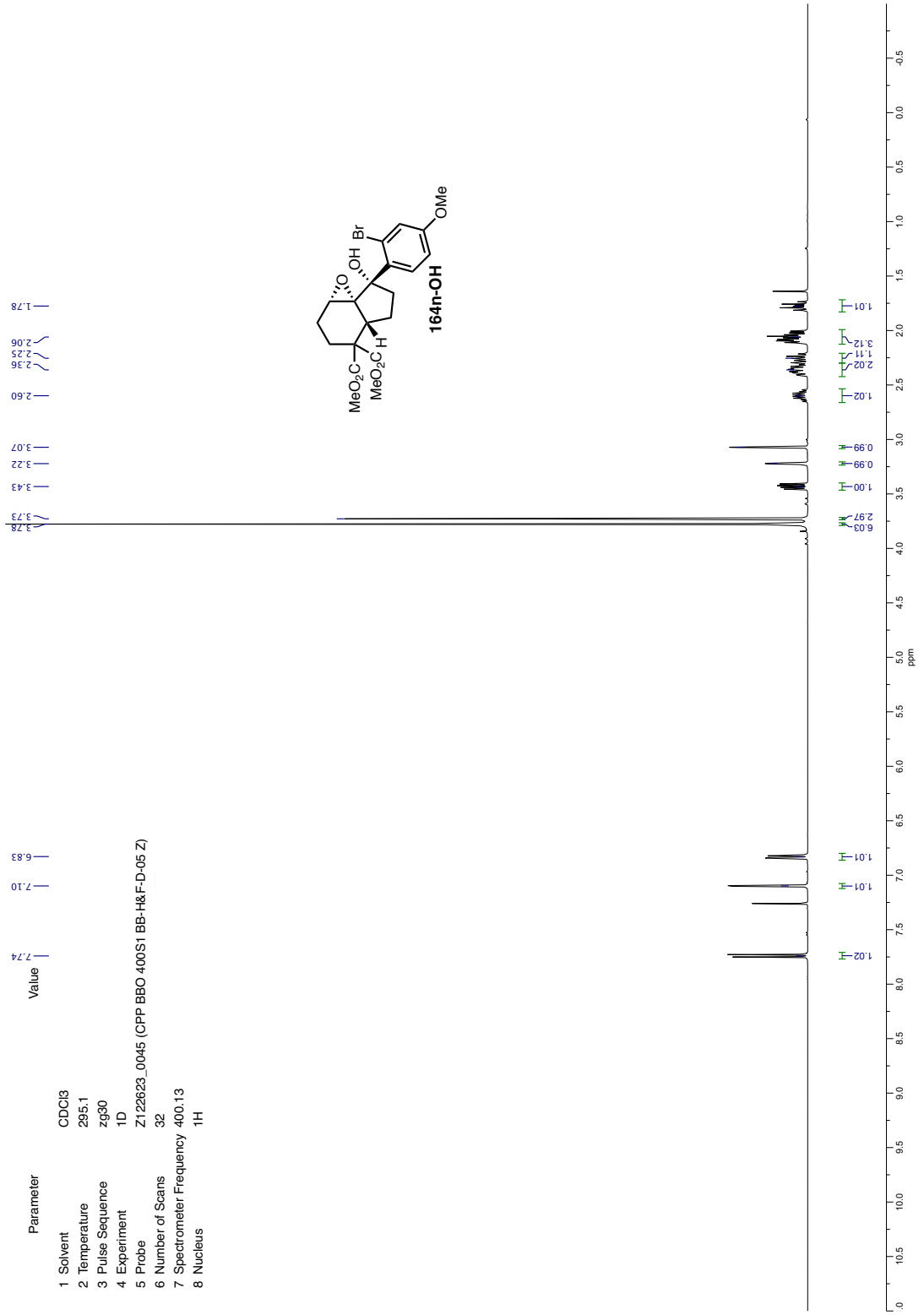

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
O
MeO2C
MeO2C
H
164l
f1 (ppm)

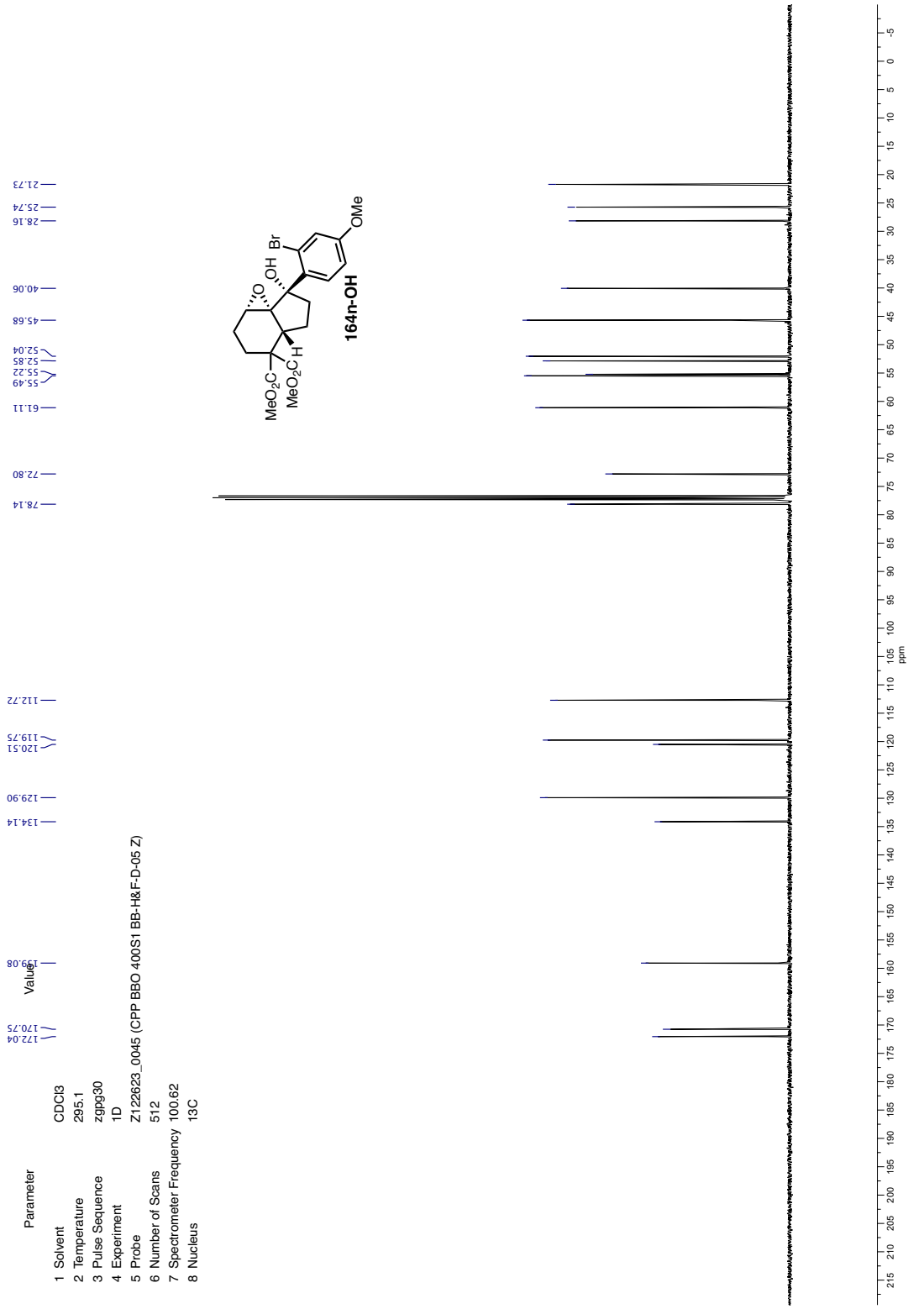


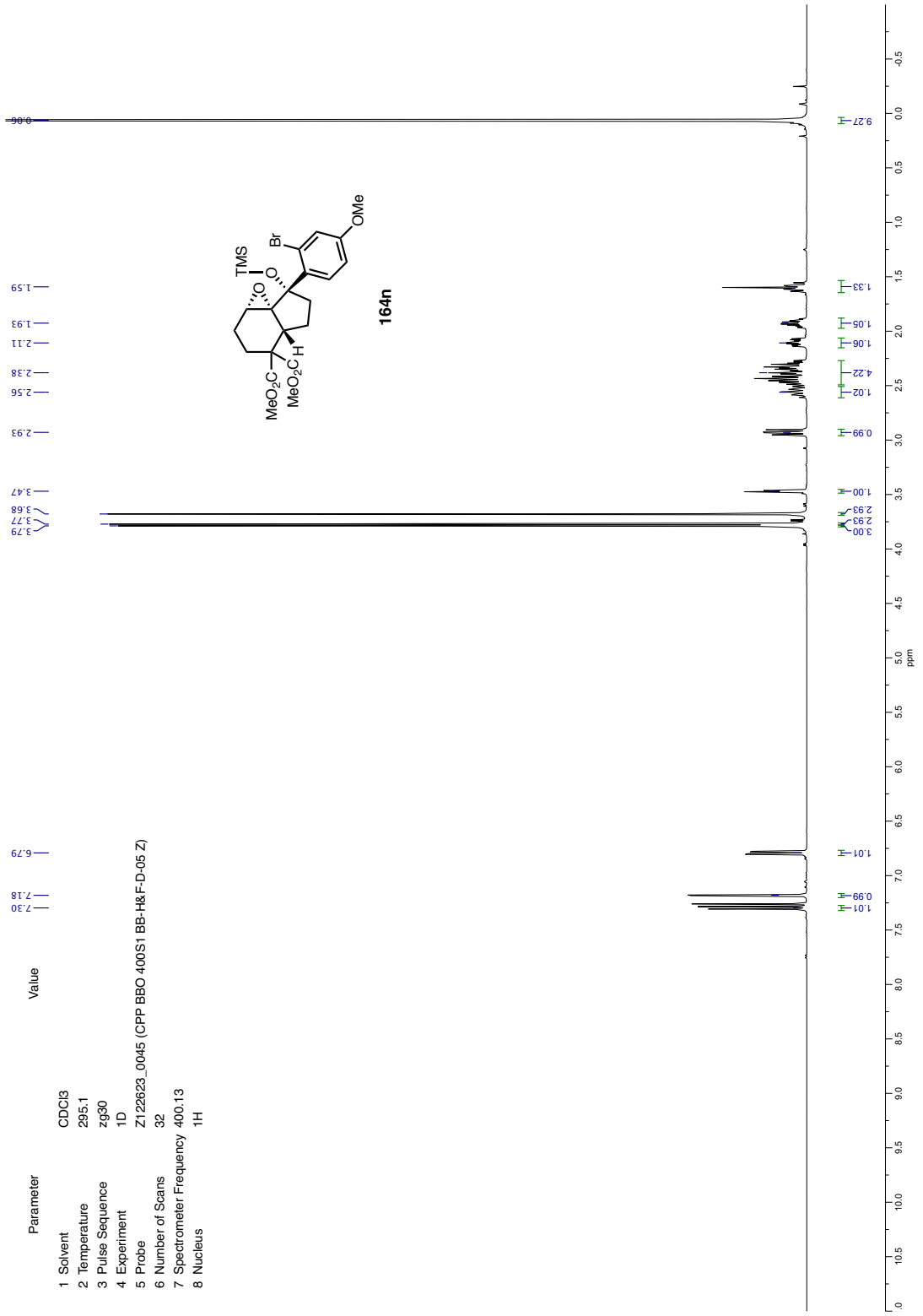
	Parameter	Value
1	Solvent	cdcl3
2	Temperature	3.0
3	Pulse Sequence	s2pul
4	Experiment	1D
5	Probe	autox7991
6	Number of Scans	512
7	Spectrometer Frequency	125.64
8	Nucleus	13C

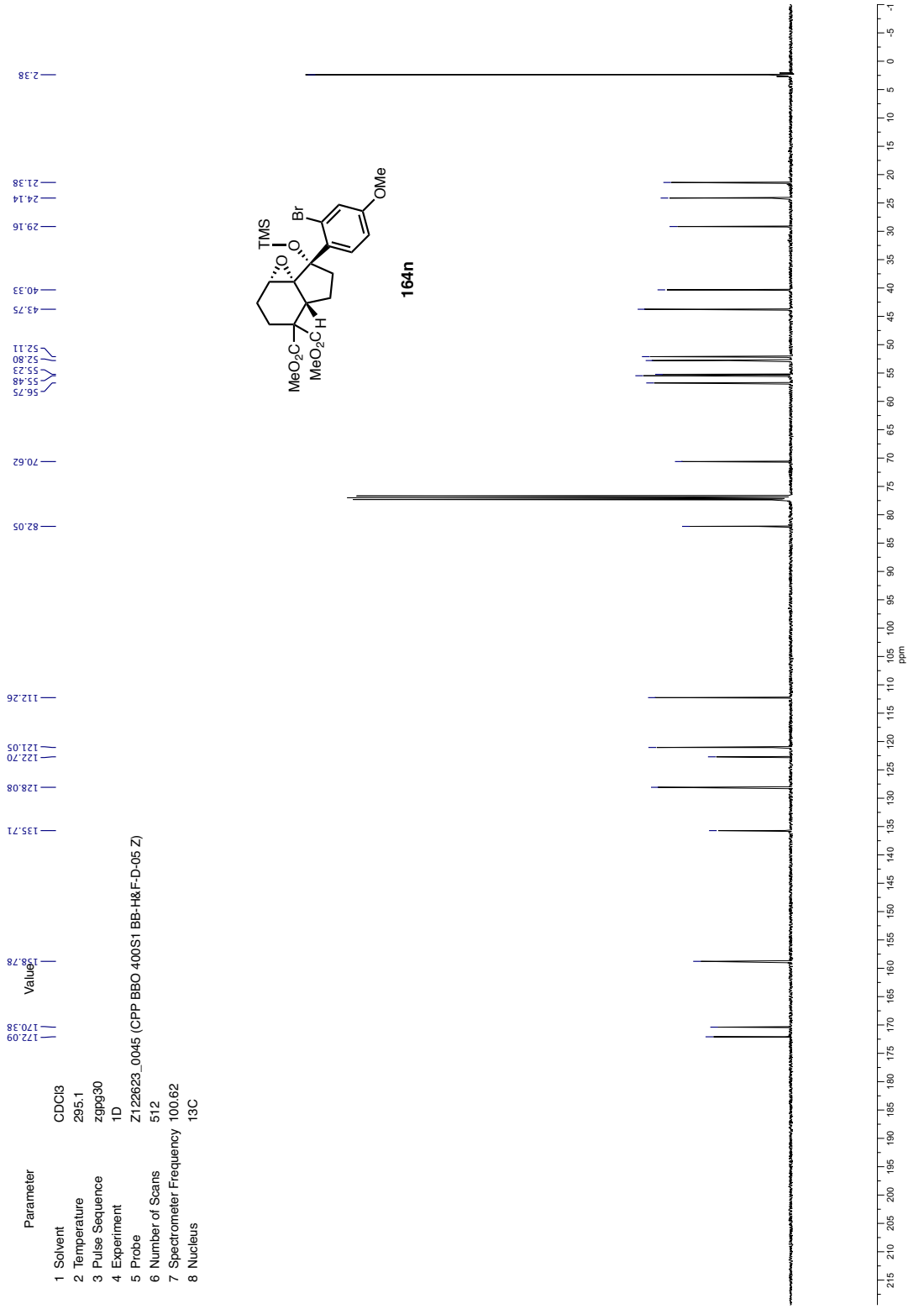

-0.08
1.35
1.91
2.24
2.31
2.46
2.55
2.73
3.47
3.65
3.77
3.82
6.86
7.34
8.18
0.95
2.11
2.04
1.13
1.06
1.06
1.04
1.00
2.94
3.02
3.08
2.04
2.10
f1 (ppm)
OMe
OTMS
O
H
MeO2C
MeO2C
164m
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.63
8 Nucleus 1H

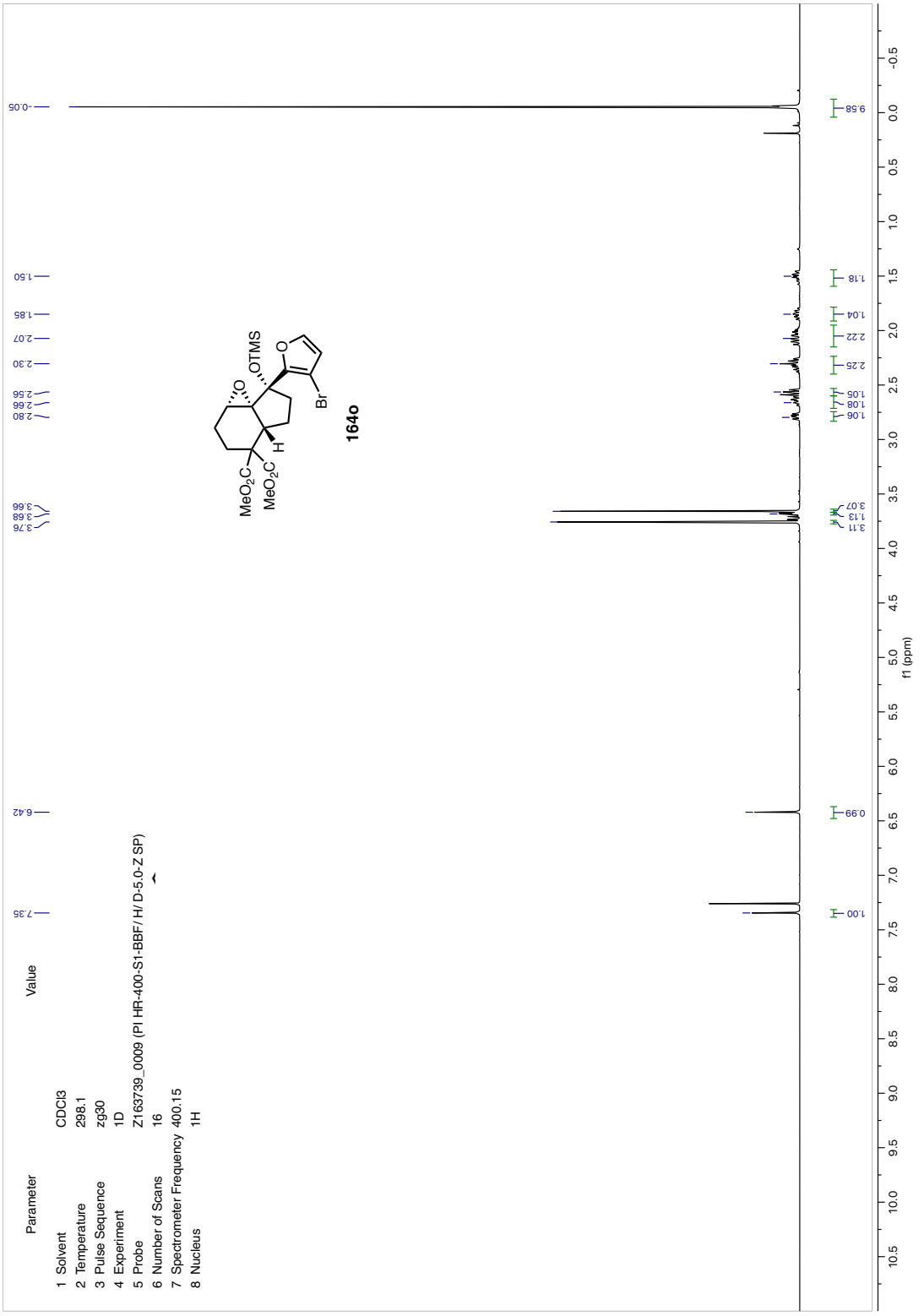

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
172.27
170.60
159.04
136.89
127.41
113.78
2.07
OTMS
OMe
MeO_2C
MeO_2C
H
O
164m
f1 (ppm)

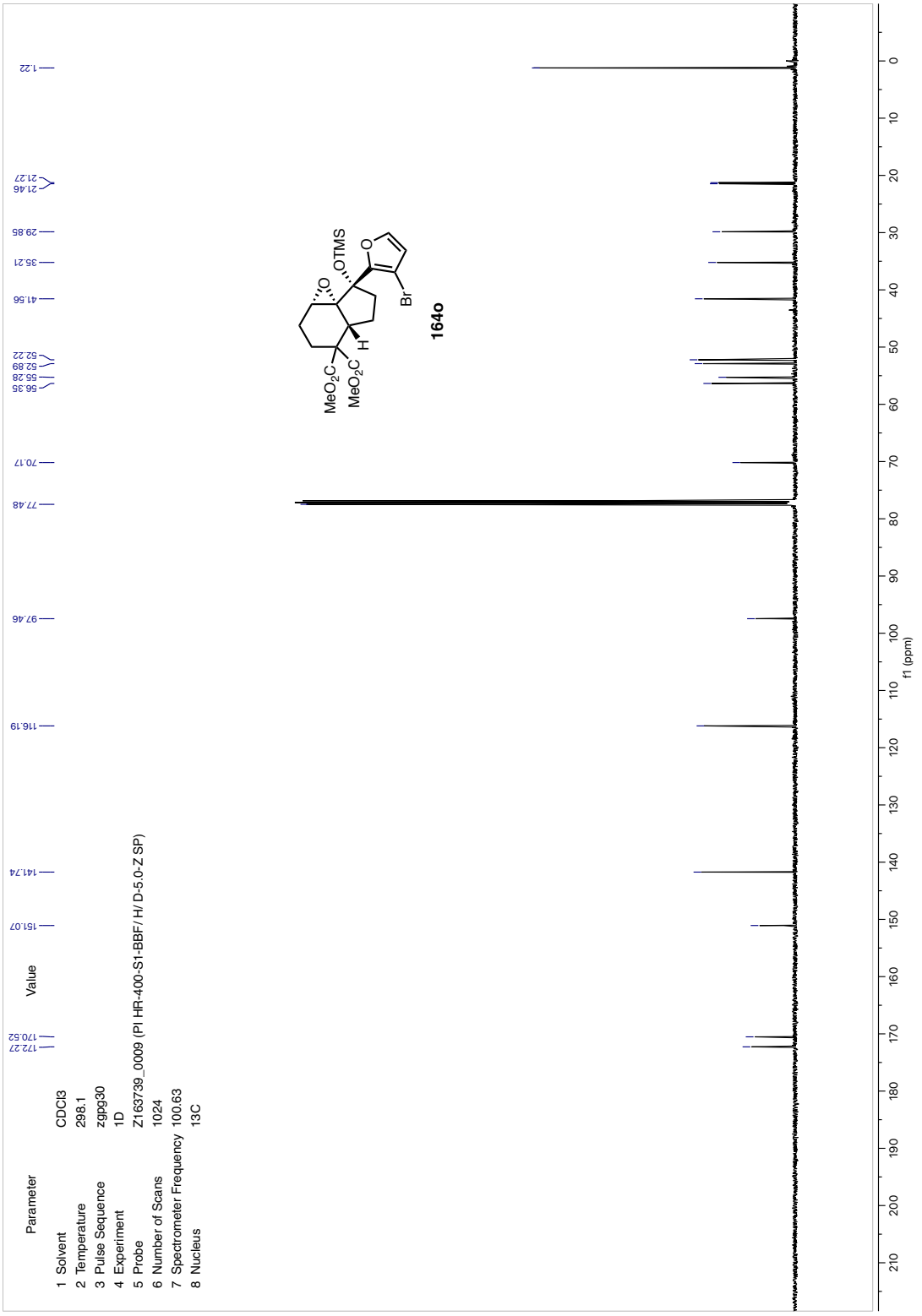

Parameter Value
1 Solvent CDCl3
2 Temperature 295.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 32
7 Spectrometer Frequency 400.13
8 Nucleus 1H
164n-OH
OMe
Br
OH
O
MeO2C
MeO2C
H
7.74
7.10
6.83
3.78
3.73
3.43
3.22
3.07
2.60
2.36
2.25
2.06
1.78
1.02
1.01
1.01
2.97
1.00
0.99
0.99
1.02
3.12
1.11
2.02
1.01
ppm

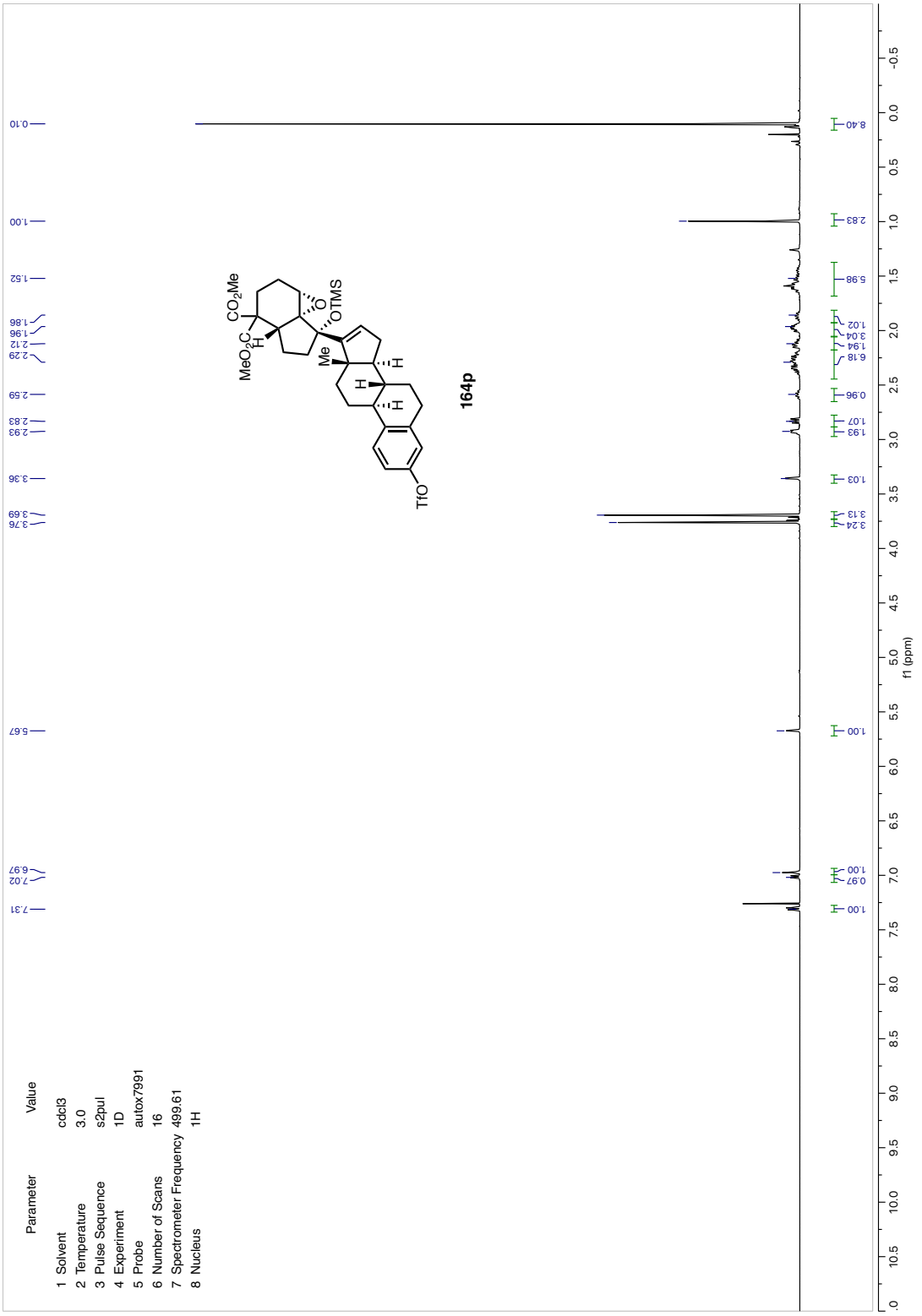

Parameter Value
1 Solvent CDCl3
2 Temperature 295.1
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 512
7 Spectrometer Frequency 100.62
8 Nucleus 13C
21.73
25.74
28.16
40.06
45.68
52.04
52.85
55.22
55.49
61.11
72.80
78.14
112.72
119.75
120.51
129.90
134.14
170.75
172.04
179.08
OMe
Br
OH
O
MeO2C
MeO2C
H
164n-OH
ppm

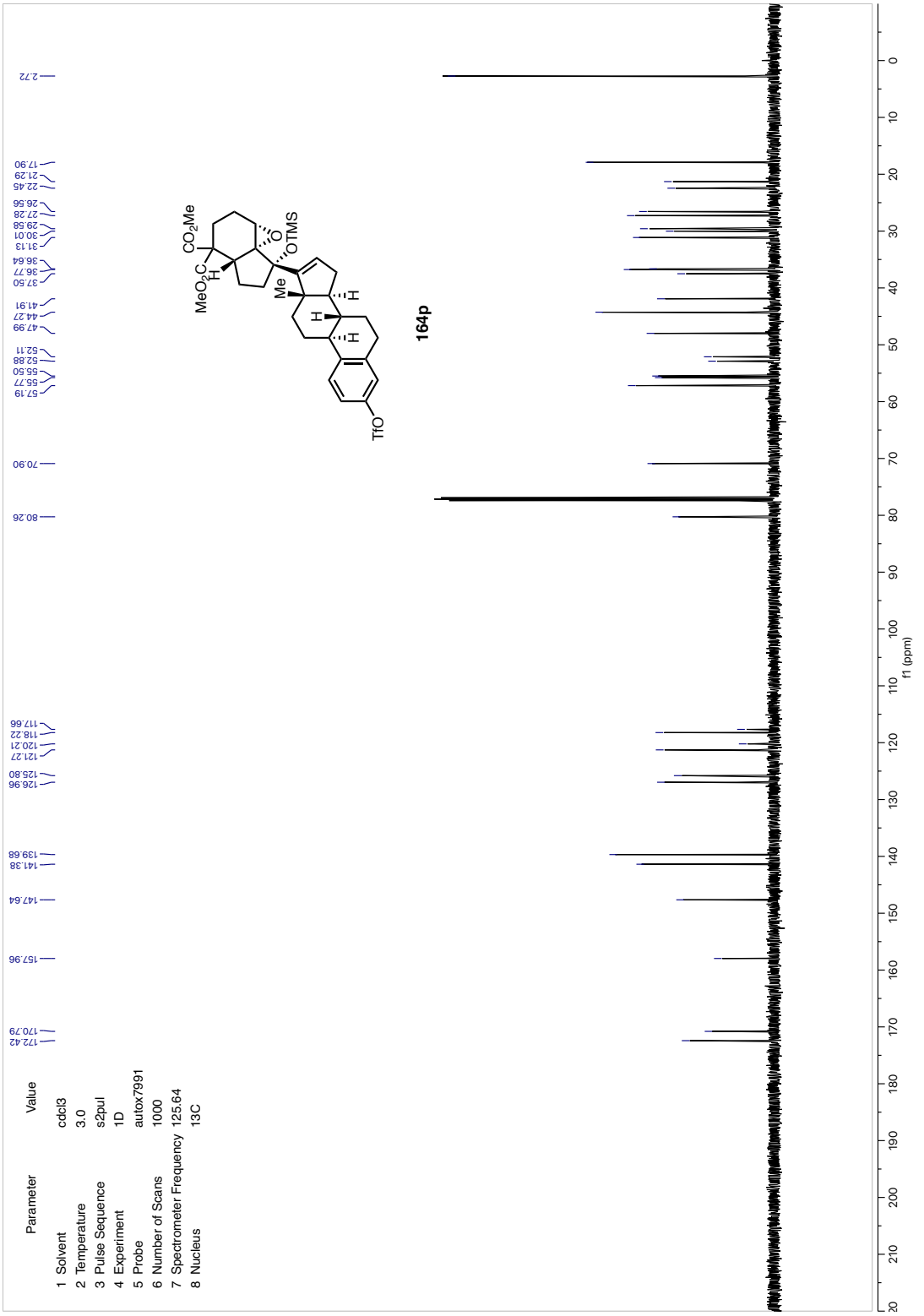

TMS
Br
OMe
O
O
MeO2C
MeO2C
H
164n
Parameter Value
1 Solvent CDCl3
2 Temperature 295.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 32
7 Spectrometer Frequency 400.13
8 Nucleus 1H
ppm

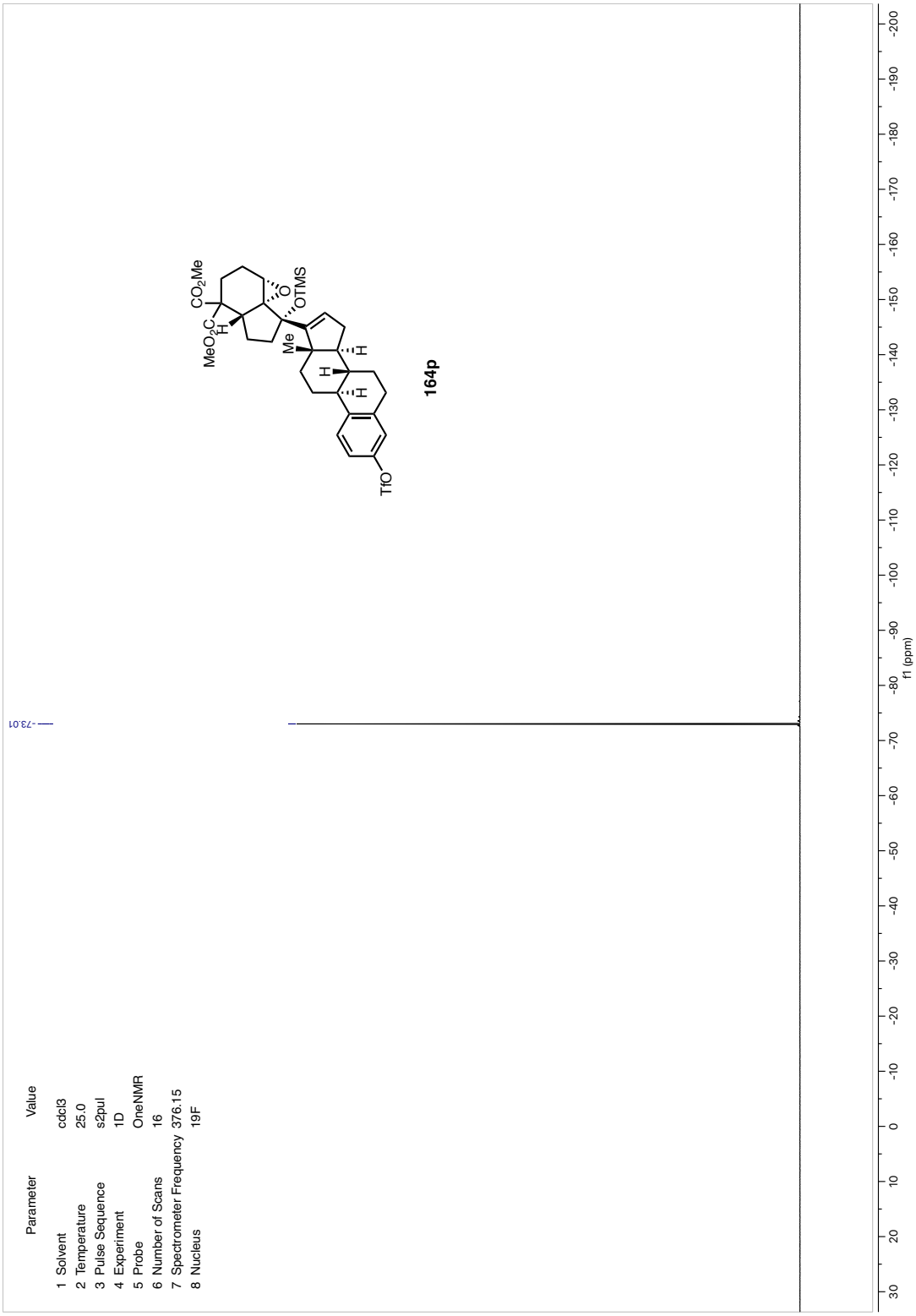

Parameter Value
1 Solvent CDCl3
2 Temperature 295.1
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 512
7 Spectrometer Frequency 100.62
8 Nucleus 13C
2.38
21.38
24.14
29.16
40.33
43.75
52.11
52.80
55.23
55.48
56.75
70.62
82.05
112.26
121.05
122.70
128.08
135.71
138.78
170.38
172.09
TMS
Br
OMe
MeO2C
MeO2C
H
164n
ppm

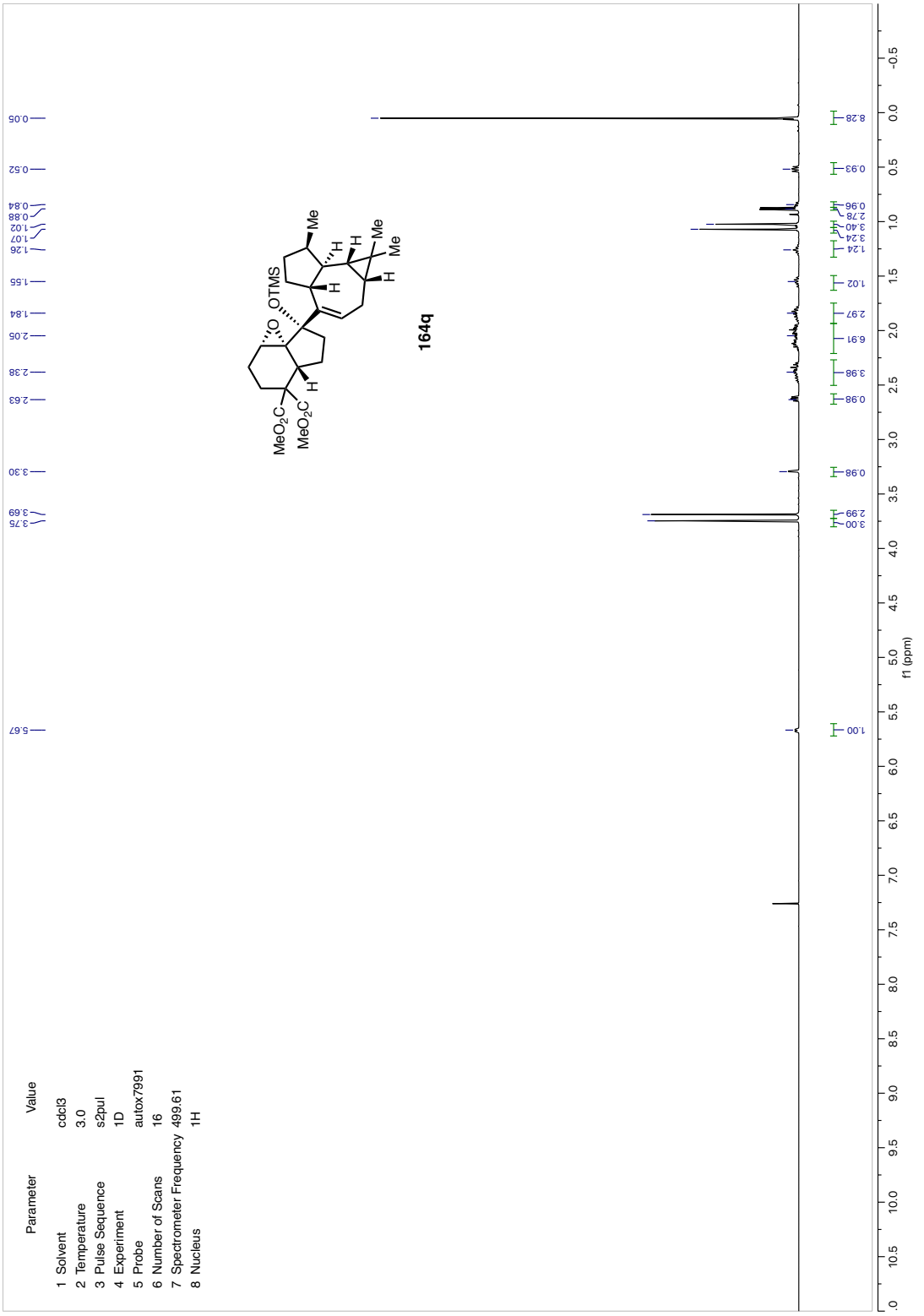

Parameter Value
1 Solvent CDCl3
2 Temperature 298.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
6 Number of Scans 16
7 Spectrometer Frequency 400.15
8 Nucleus 1H
MeO2C
MeO2C
OTMS
Br
164o
f1 (ppm)

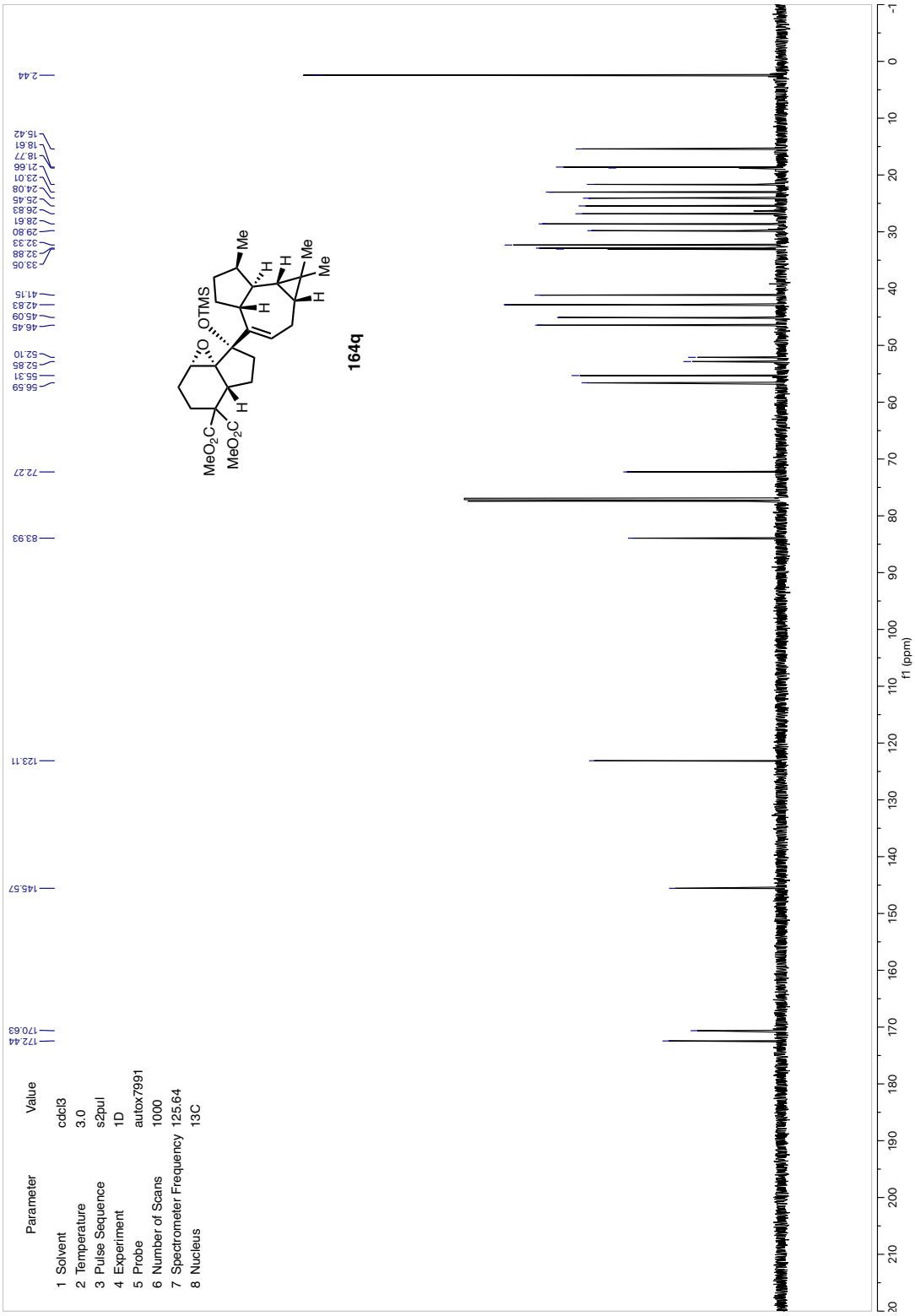

Parameter Value
1 Solvent CDCl3
2 Temperature 298.1
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
6 Number of Scans 1024
7 Spectrometer Frequency 100.63
8 Nucleus 13C
172.27
170.52
151.07
141.74
116.19
97.46
77.48
70.17
56.35
55.28
52.89
52.22
41.56
35.21
29.85
21.46
21.27
1.22
MeO2C
MeO2C
H
O
OTMS
O
Br
164o
f1 (ppm)

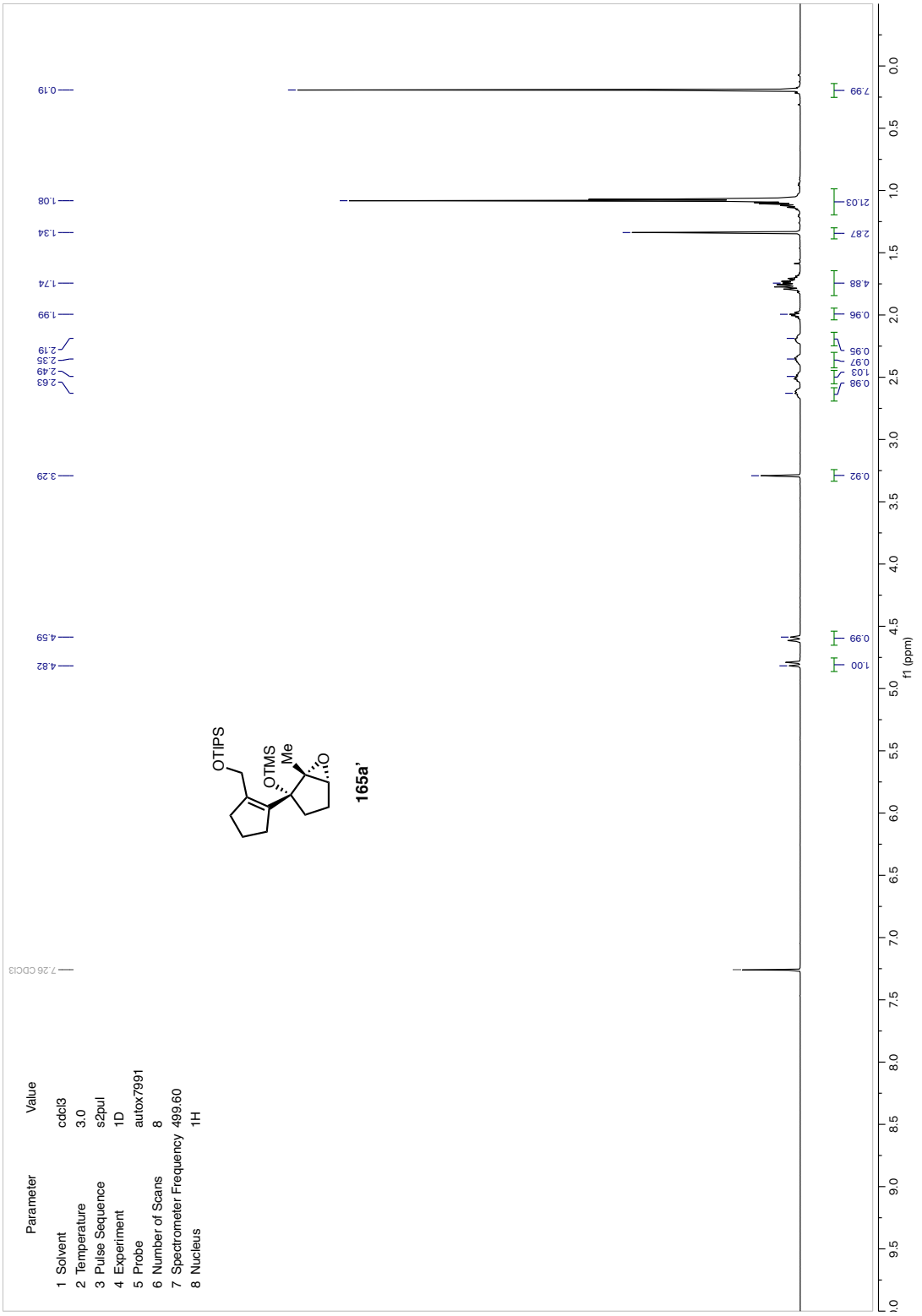

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
CO2Me
MeO2C
O
OTMS
Me
H
H
H
TfO
164p
f1 (ppm)

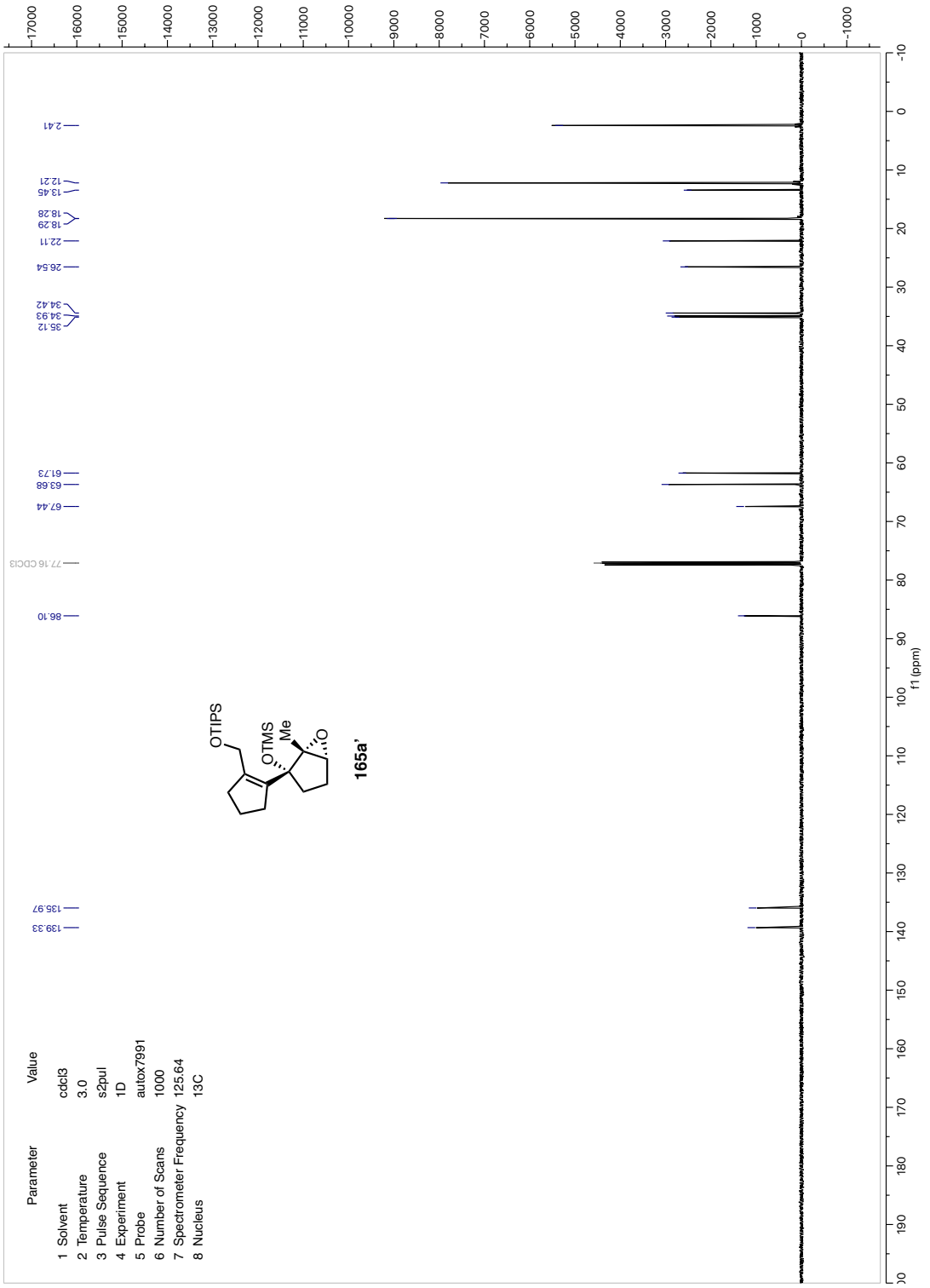

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
2.72
17.90
22.45
21.29
26.56
27.28
29.58
30.01
31.13
36.64
36.77
37.50
41.91
44.27
47.99
52.11
52.88
55.50
55.77
57.19
70.90
80.26
117.66
118.22
120.21
121.27
125.80
126.96
139.68
141.38
147.64
157.96
170.79
172.42
CO2Me
MeO2C
H
O
OTMS
Me
H
H
H
TfO
164p
f1 (ppm)

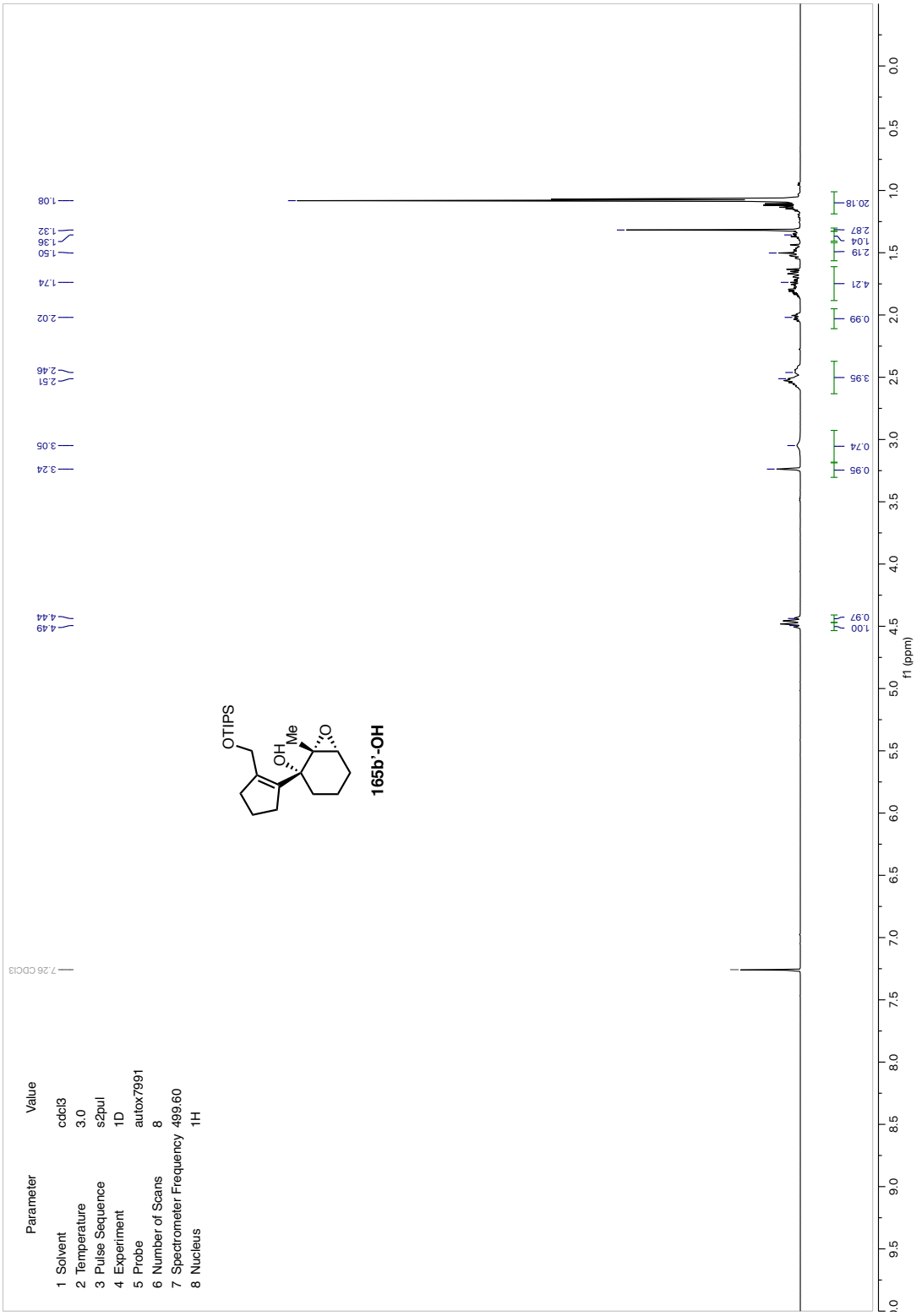

Parameter Value
1 Solvent cdcl3
2 Temperature 25.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe OneNMR
6 Number of Scans 16
7 Spectrometer Frequency 376.15
8 Nucleus 19F
-73.01
CO2Me
MeO2C
H
O
OTMS
Me
H
H
H
TfO
164p
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

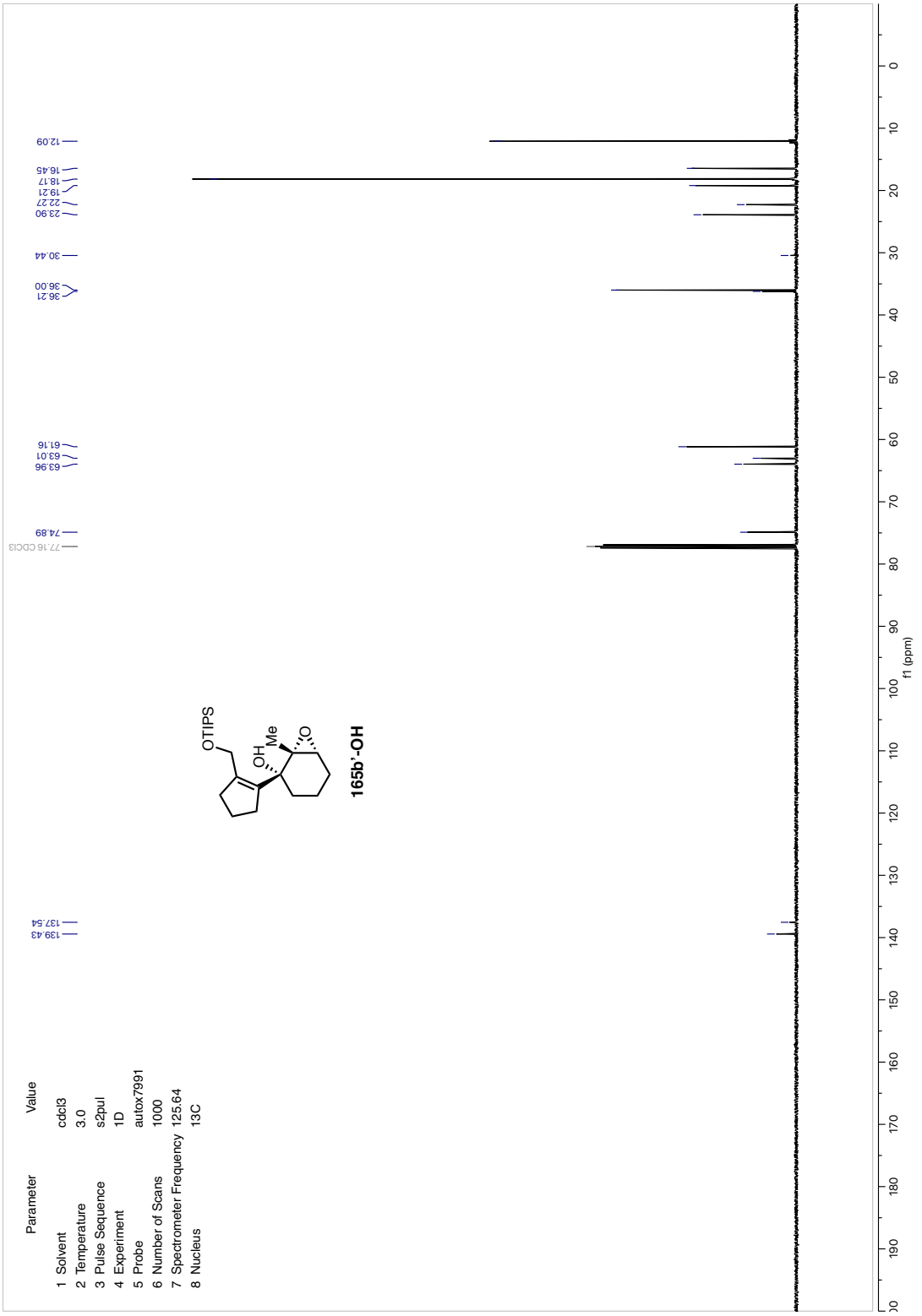

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
Me
Me
Me
H
H
H
H
MeO2C
MeO2C
164q
f1 (ppm)

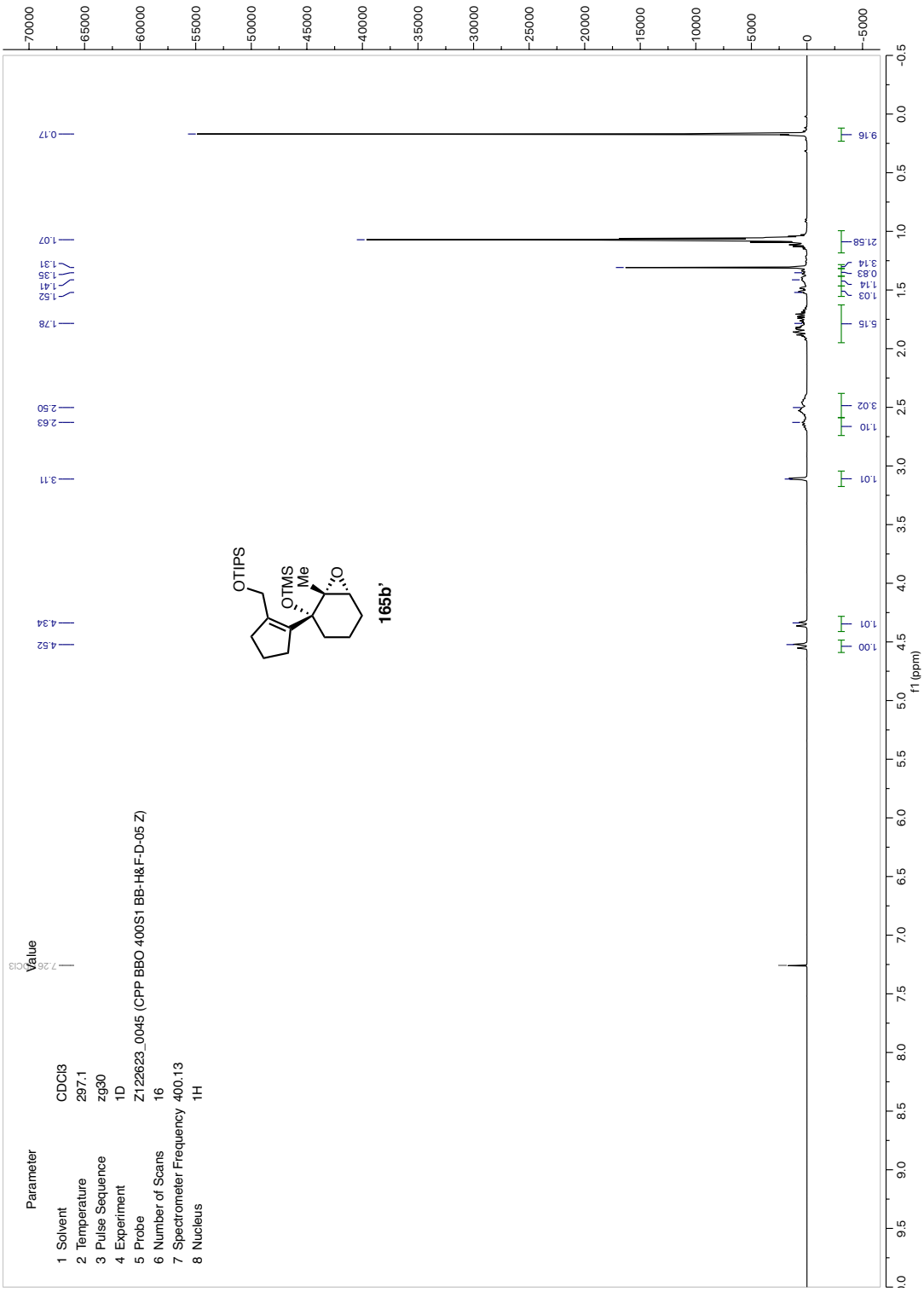

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
2.44
15.42
18.61
18.77
21.66
23.01
24.08
25.45
26.83
28.61
29.80
32.33
32.88
33.05
41.15
42.83
45.09
46.45
52.10
52.85
55.31
56.59
72.27
83.93
123.11
145.57
170.63
172.44
OTMS
O
MeO2C
MeO2C
Me
Me
Me
H
H
H
H
164q
f1 (ppm)

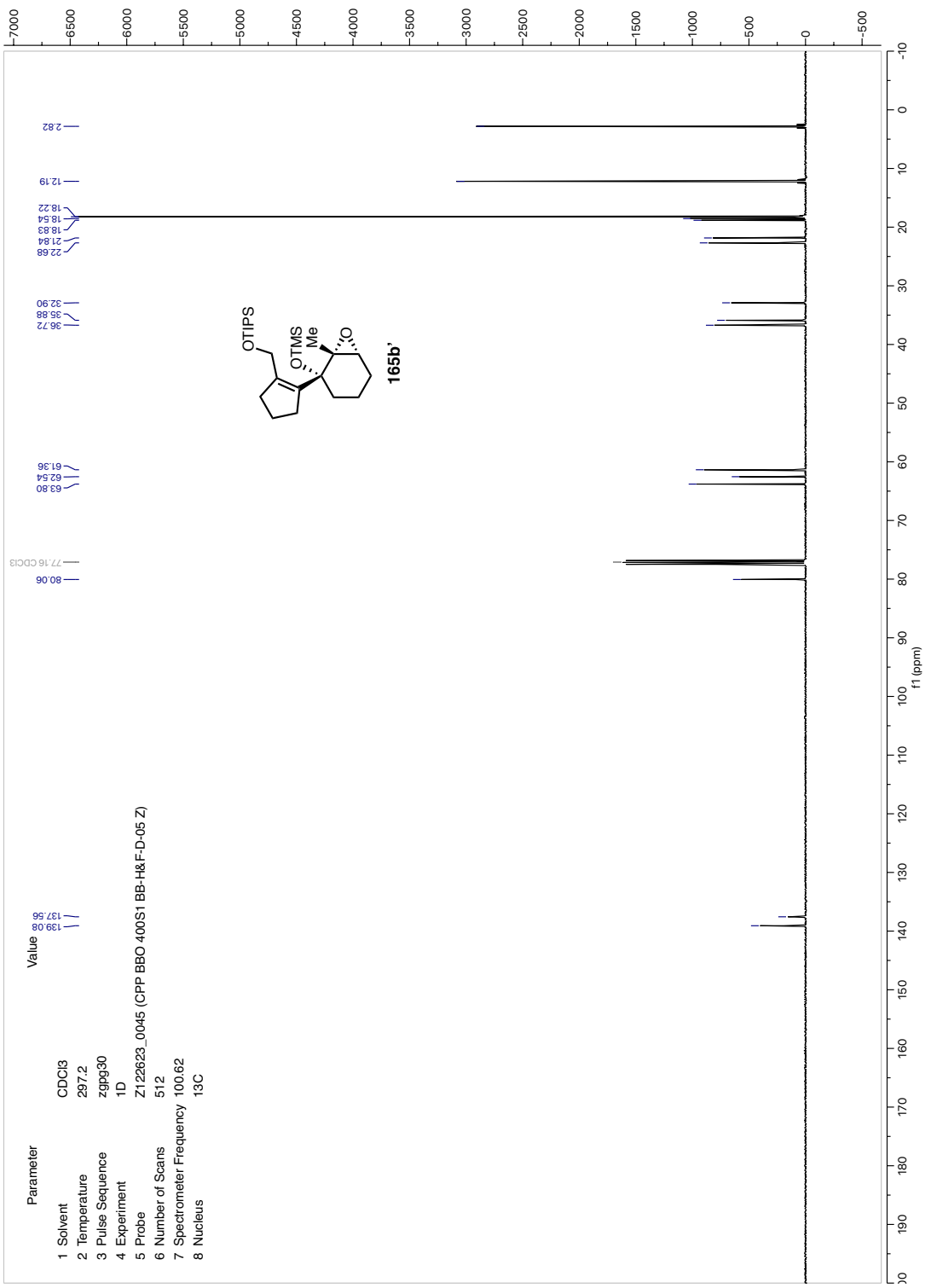

OTIPS
OTMS
Me
O
165a'
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 8
7 Spectrometer Frequency 499.60
8 Nucleus 1H
0.19
1.08
1.34
1.74
1.99
2.19
2.35
2.49
2.63
3.29
4.59
4.82
7.26 CDCl3
7.99
21.03
2.87
4.88
0.96
0.95
0.97
1.03
0.98
0.92
0.99
1.00
f1 (ppm)

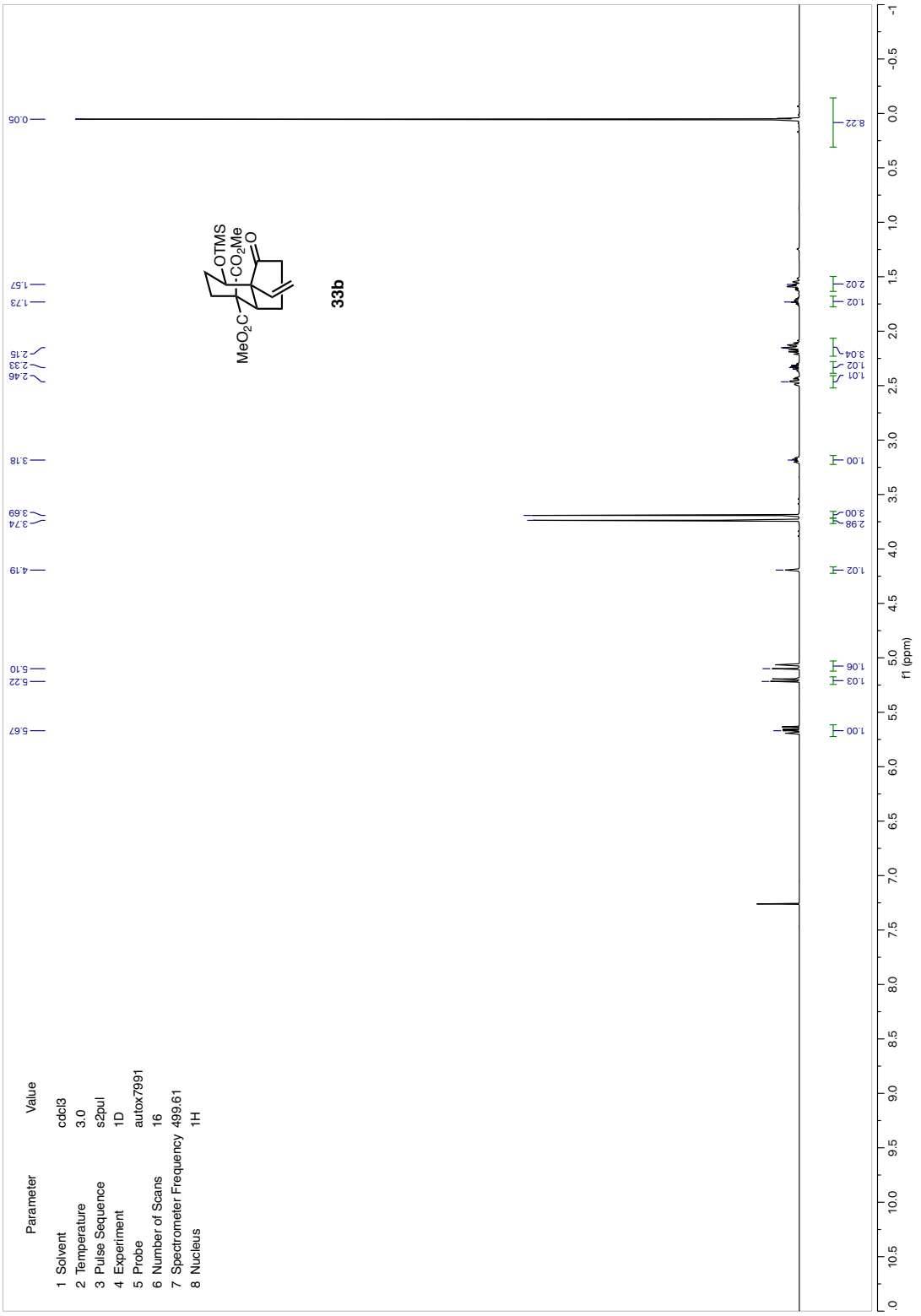

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
2.41
12.21
13.45
18.28
18.29
22.11
26.54
34.42
34.93
35.12
61.73
63.58
67.44
77.16 CDCl3
86.10
135.97
139.33
OTIPS
OTMS
Me
O
165a'
f1 (ppm)

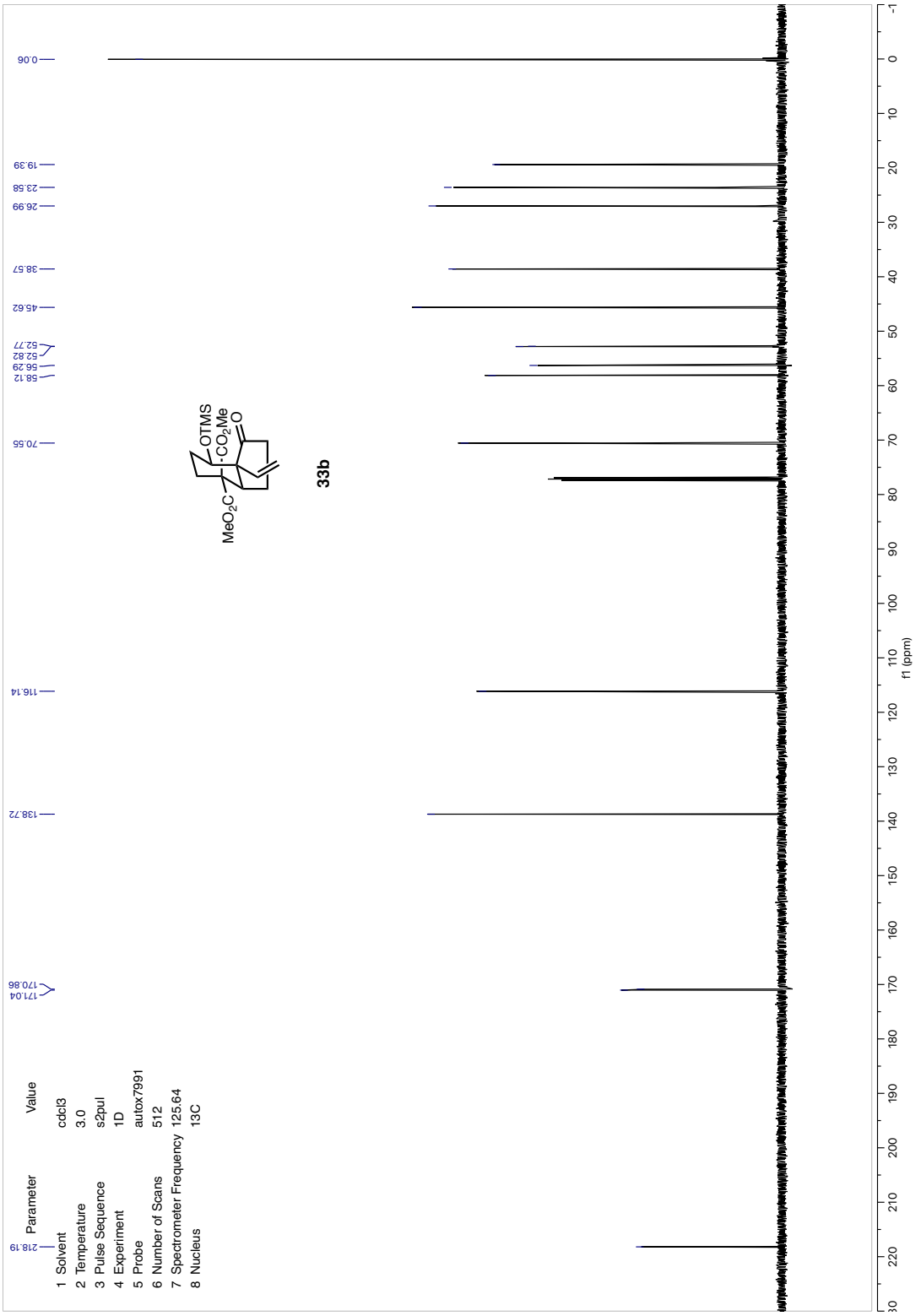

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 8
7 Spectrometer Frequency 499.60
8 Nucleus 1H
OTIPS
OH
Me
O
165b'-OH
7.26 CDCl3
4.49
4.44
3.24
3.05
2.51
2.46
2.02
1.74
1.50
1.36
1.32
1.08
0.97
1.00
0.95
0.74
3.95
0.99
4.21
2.19
1.04
2.87
20.18
f1 (ppm)

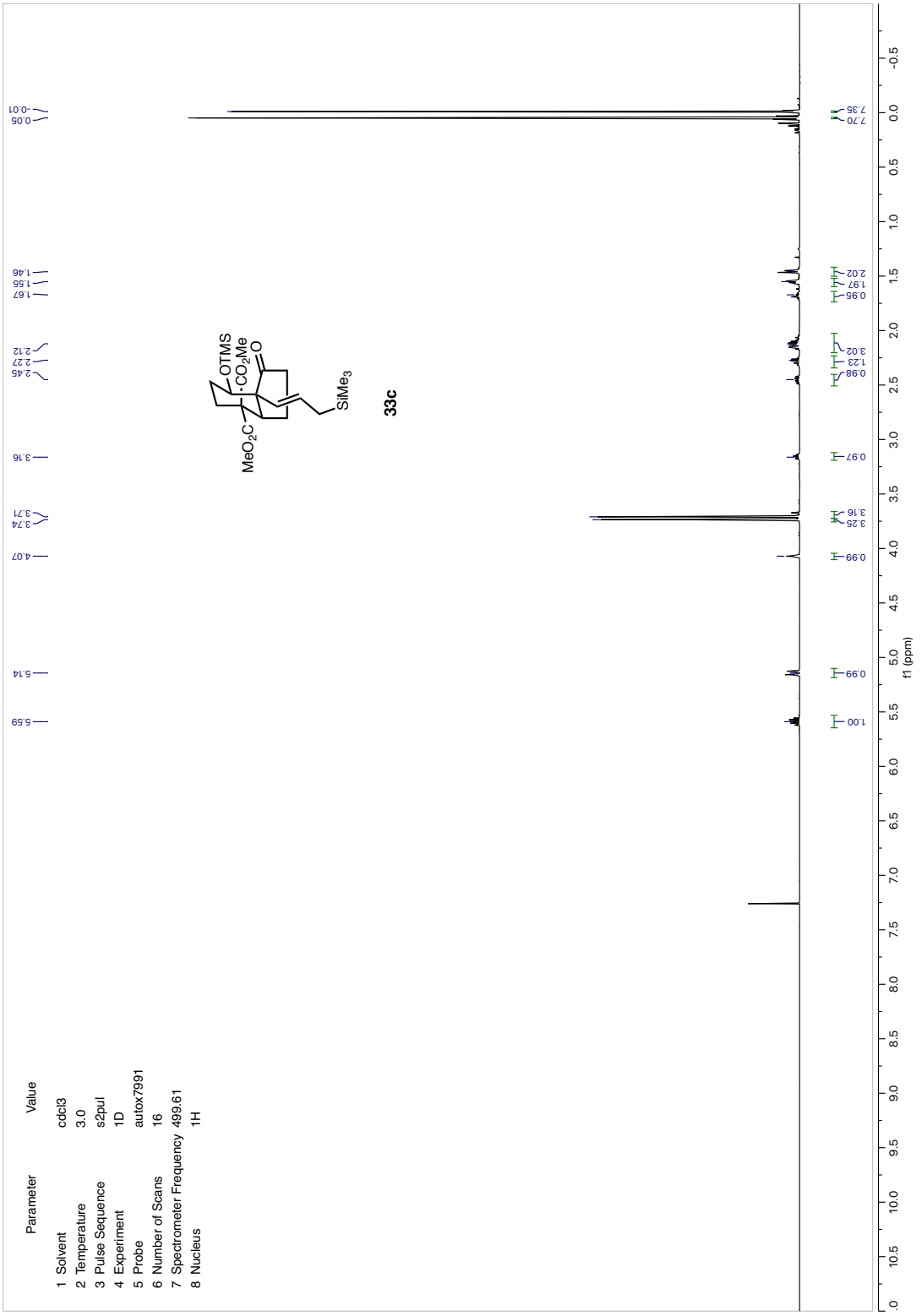

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
12.09
16.45
18.17
19.21
22.27
23.90
30.44
36.21
36.00
61.16
63.01
63.96
74.89
77.16 CDCl3
137.54
139.43
OTIPS
OH
Me
O
165b'-OH
f1 (ppm)

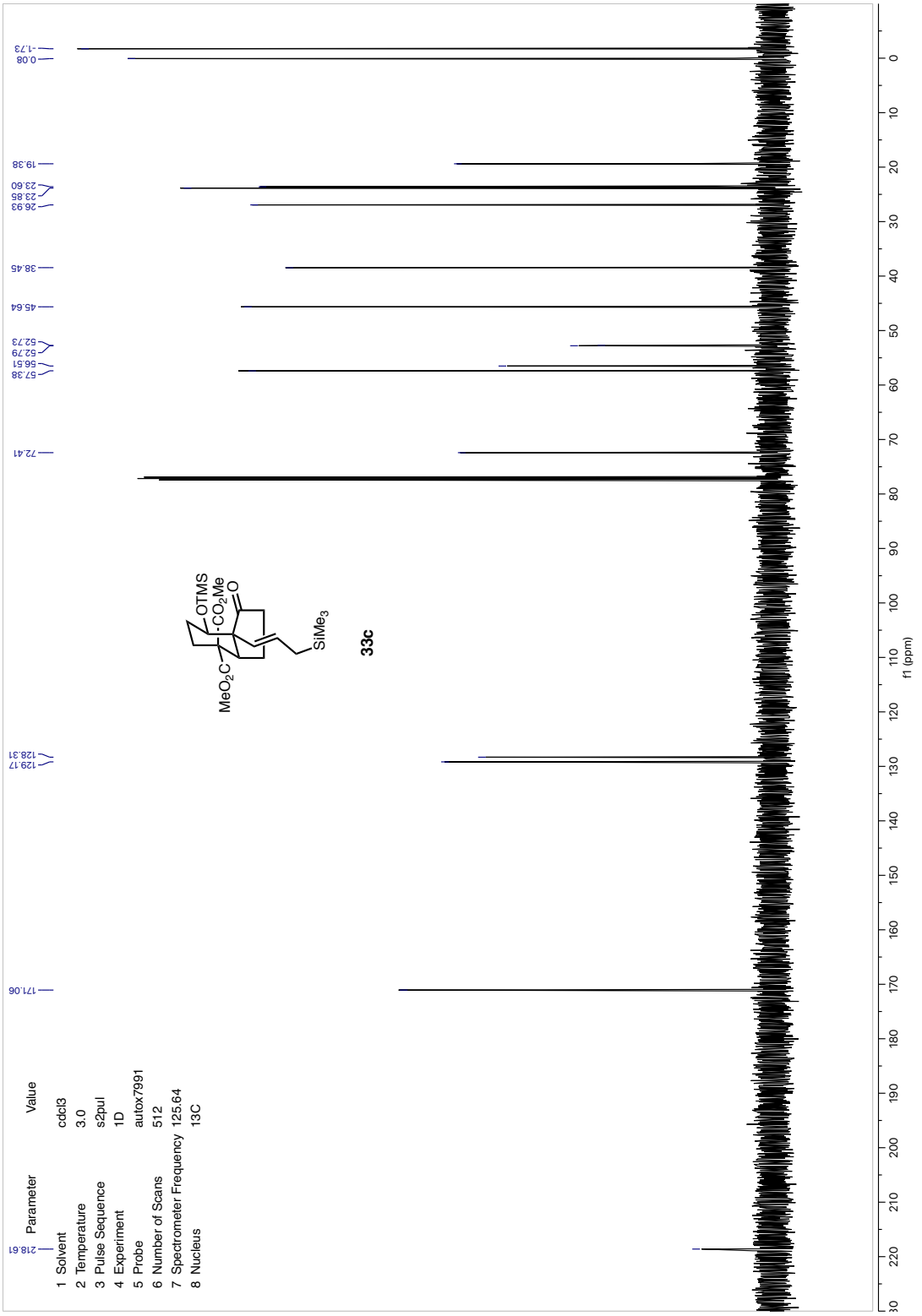

OTIPS
OTMS
Me
O
165b'
Parameter Value
1 Solvent CDCl3
2 Temperature 297.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
f1 (ppm)

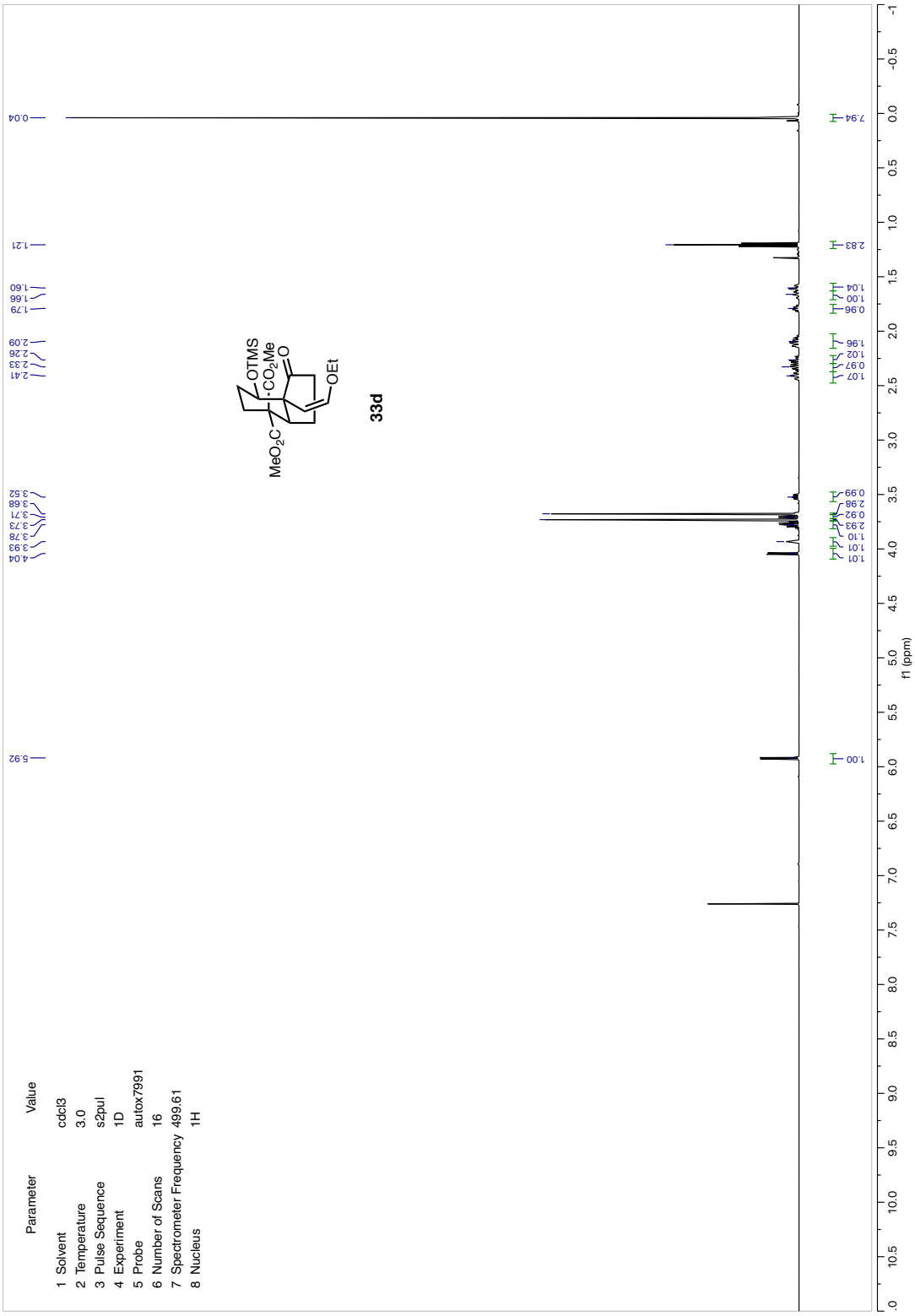

OTIPS
OTMS
Me
O
165b'
2.82
12.19
18.22
18.54
18.83
21.84
22.68
32.90
35.88
36.72
61.36
62.54
63.80
77.16 CDCl3
80.06
137.56
139.08
Parameter
1 Solvent CDCl3
2 Temperature 297.2
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 512
7 Spectrometer Frequency 100.62
8 Nucleus 13C
Value
f1 (ppm)

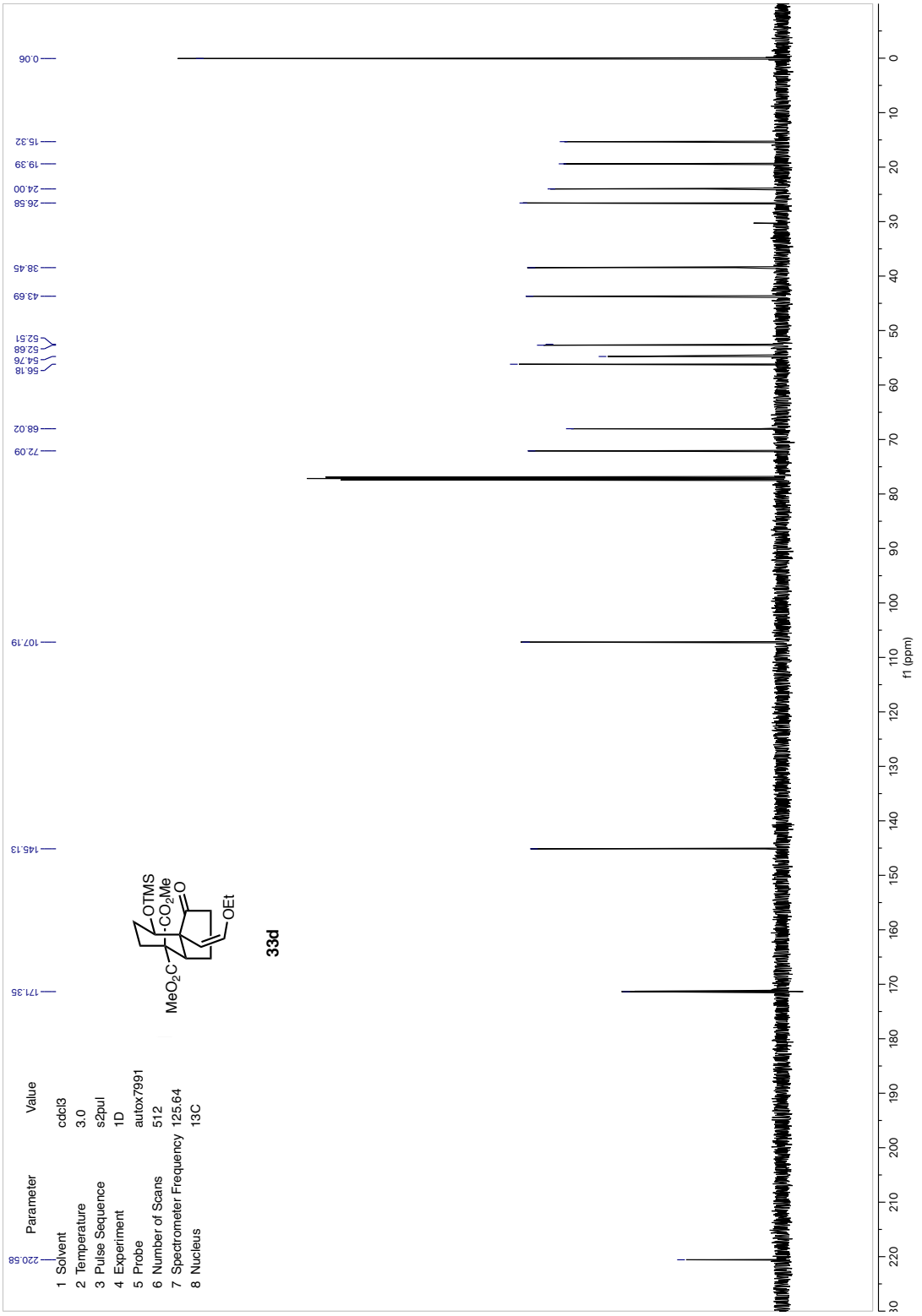

OTMS
CO2Me
O
MeO2C
33b
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
0.05
1.57
1.73
2.15
2.33
2.46
3.18
3.69
3.74
4.19
5.10
5.22
5.67
8.22
2.02
1.02
3.04
1.01
1.02
1.00
3.00
2.98
1.02
1.06
1.03
1.00
f1 (ppm)

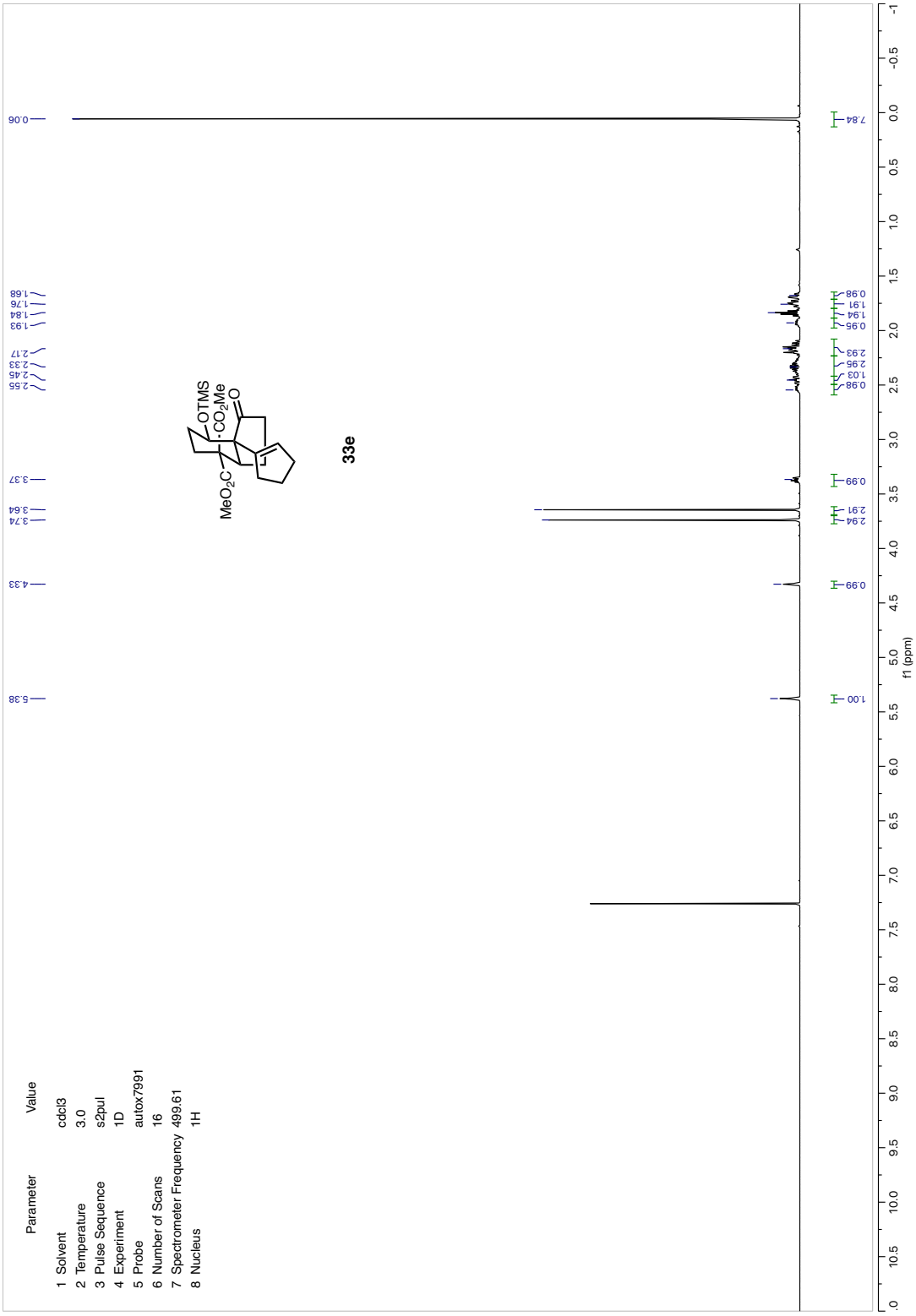

0.06
19.39
23.58
26.99
38.57
45.62
52.77
52.82
56.29
58.12
70.55
116.14
138.72
171.04
170.86
218.19
OTMS
CO2Me
O
MeO2C
33b
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

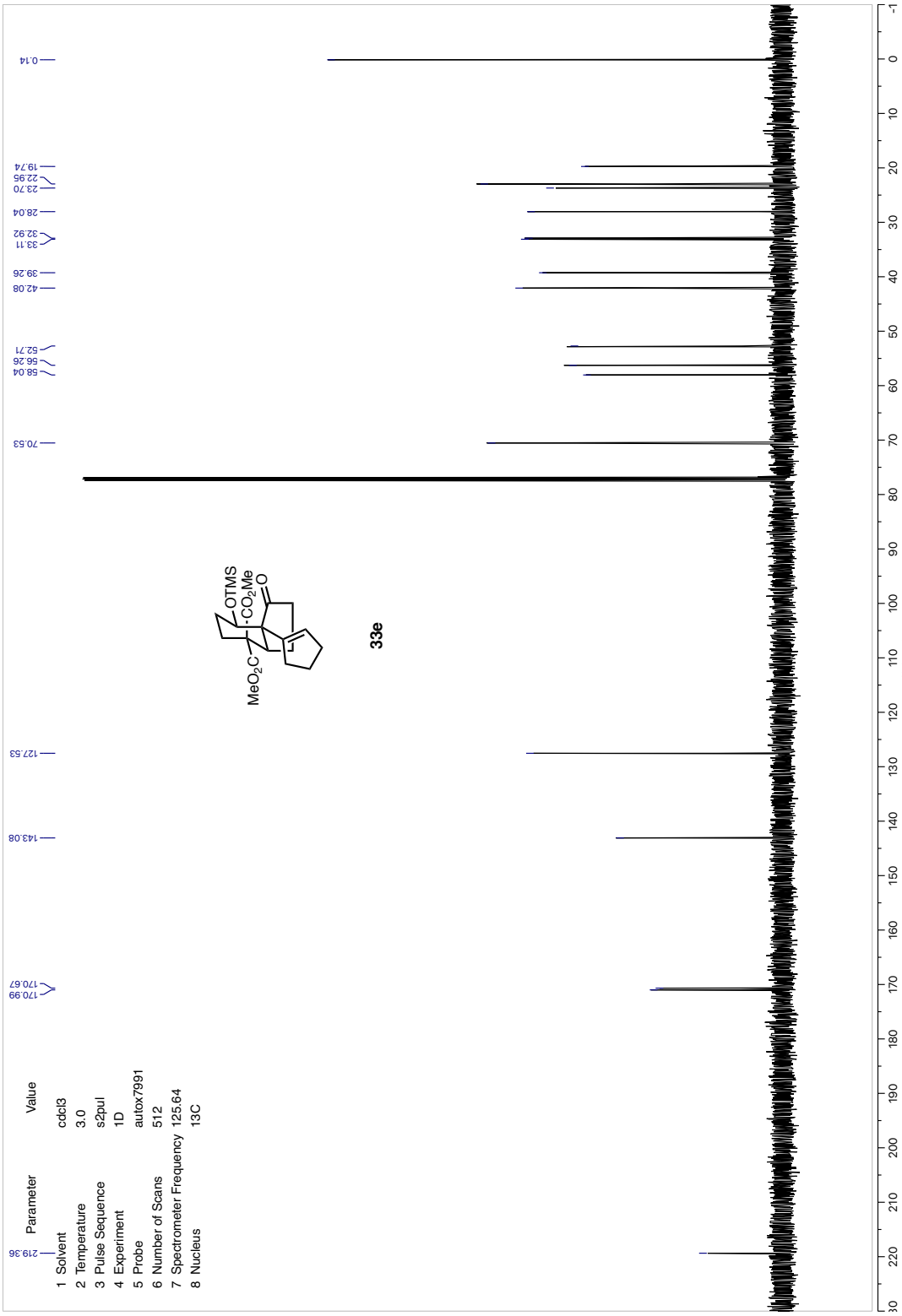

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
CO2Me
O
MeO2C
SiMe3
33c
f1 (ppm)

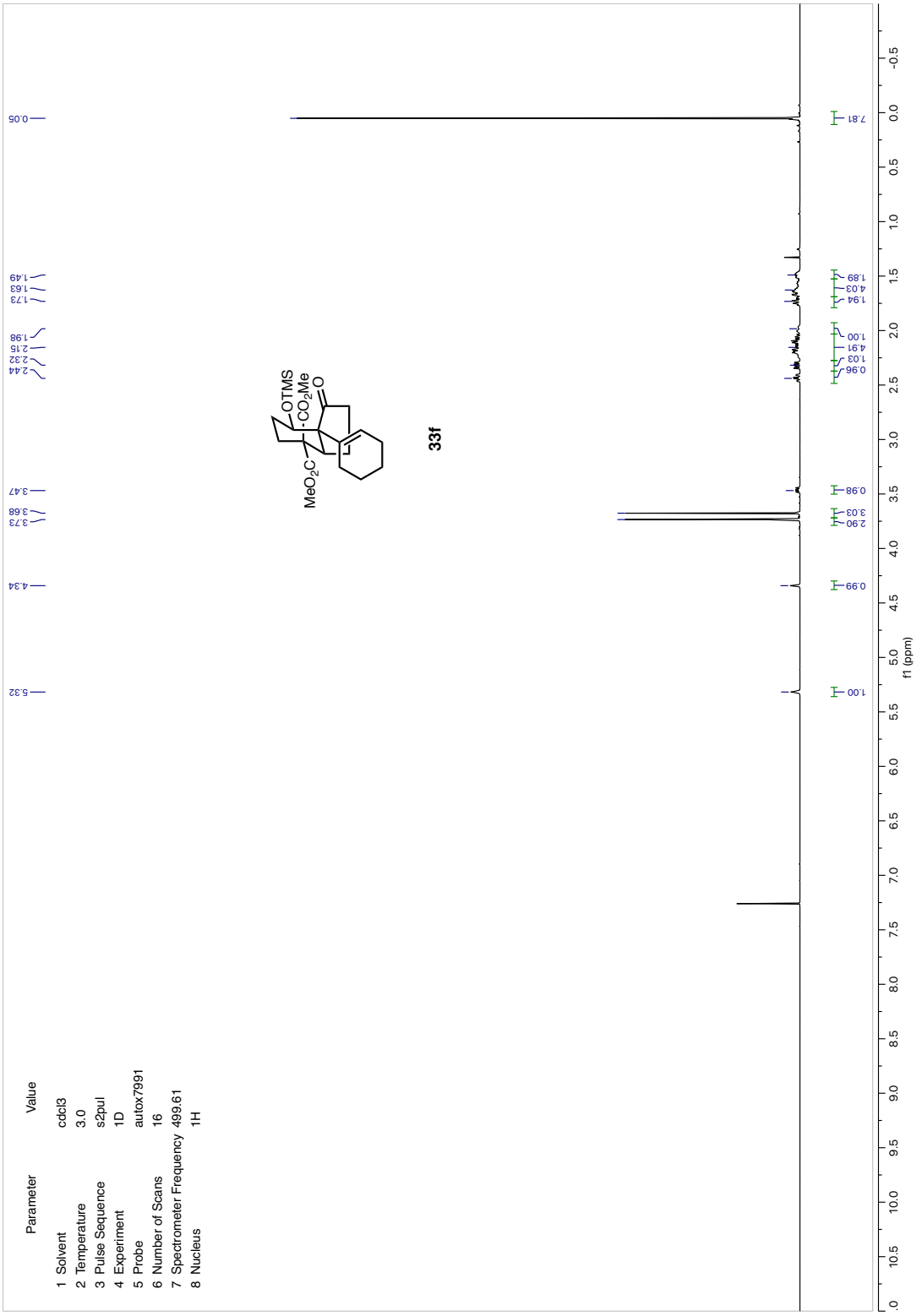

-1.73
0.08
19.38
23.60
23.85
26.93
38.45
45.64
52.73
52.79
56.51
57.38
72.41
128.31
129.17
171.06
218.61
OTMS
CO2Me
O
MeO2C
SiMe3
33c
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

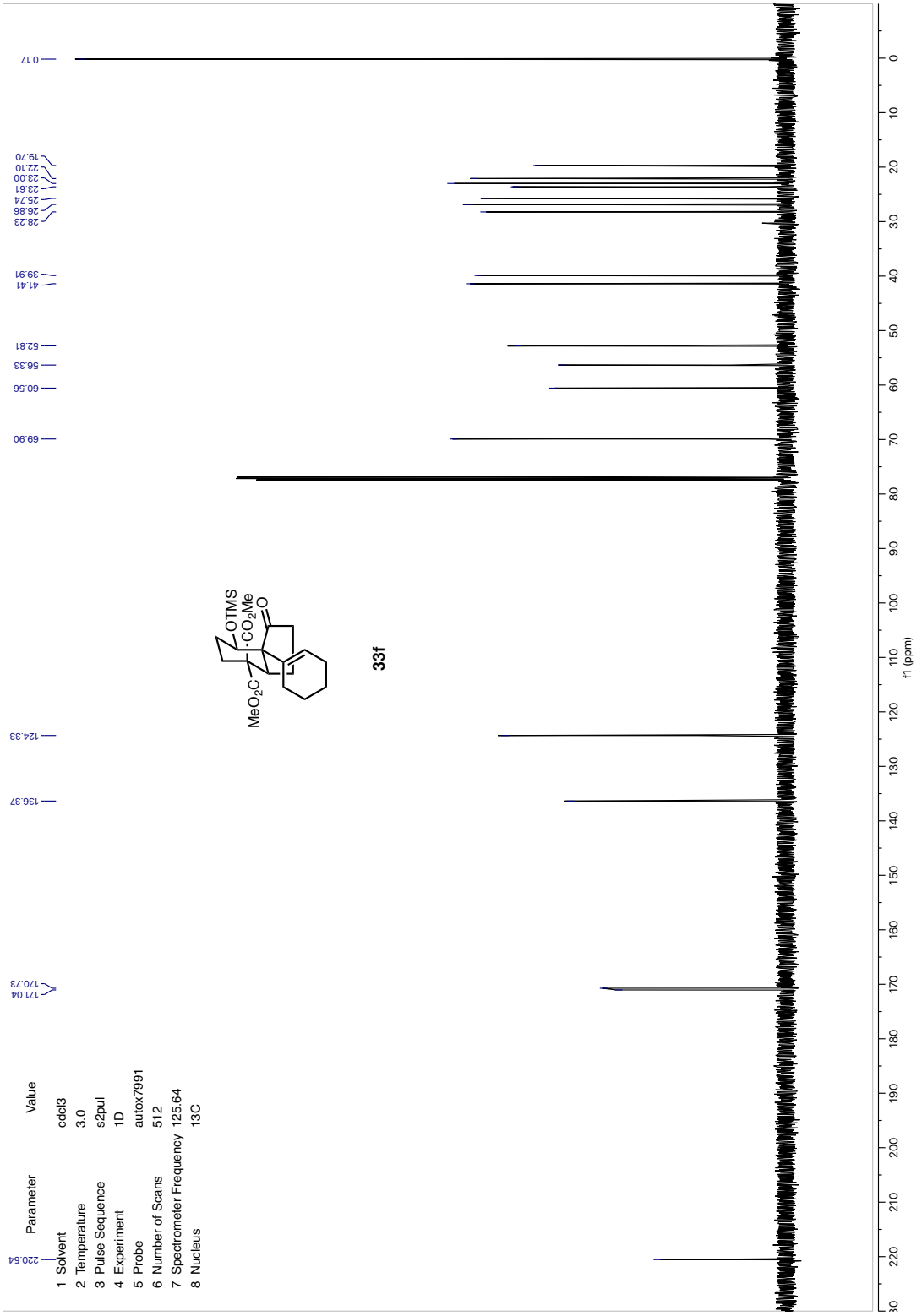

OTMS
CO2Me
O
OEt
MeO2C
33d
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
f1 (ppm)

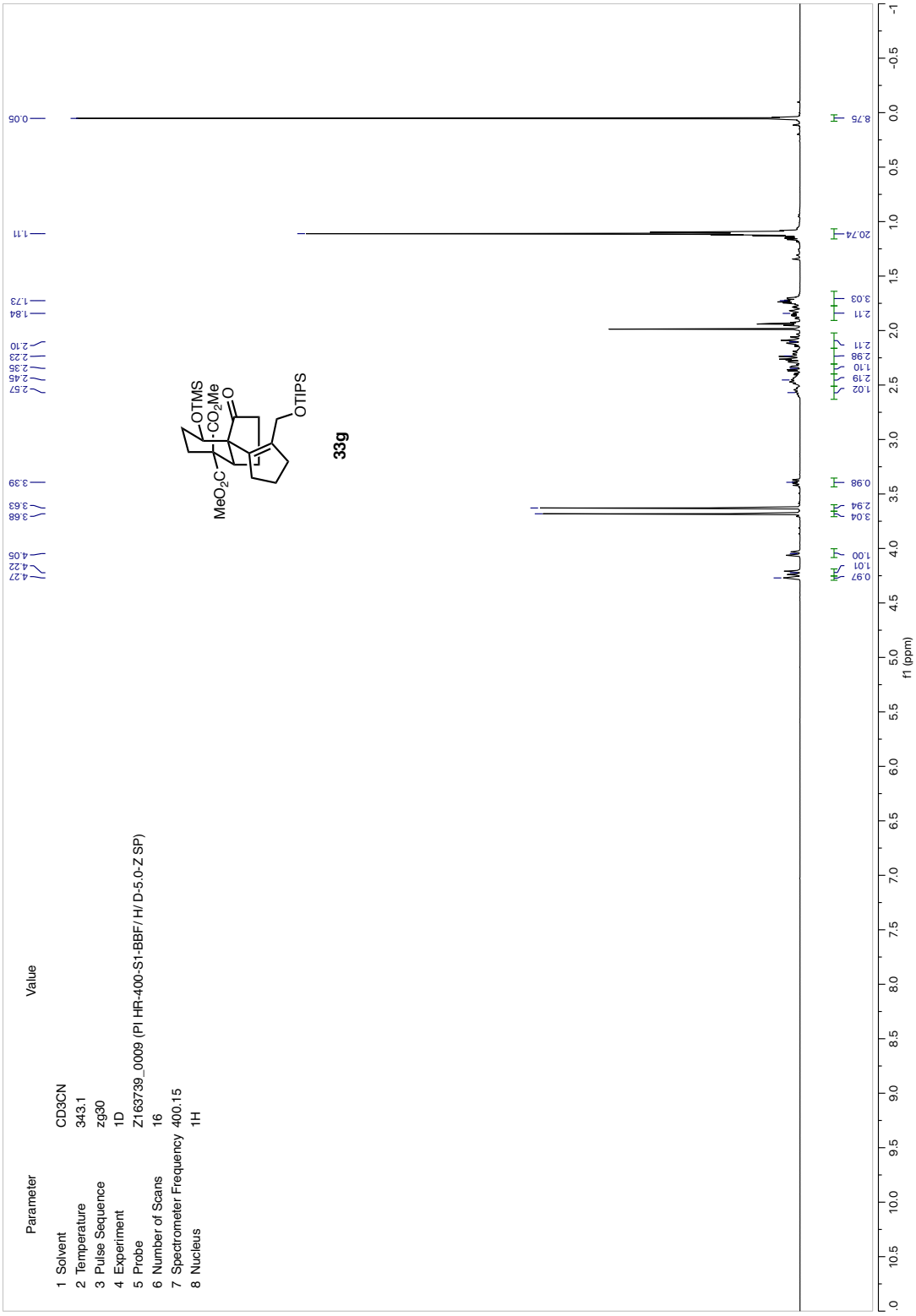

0.06
15.32
19.39
24.00
26.58
38.45
43.69
52.51
52.68
54.76
56.18
68.02
72.09
107.19
145.13
171.35
220.58
OTMS
CO2Me
O
OEt
MeO2C
33d
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

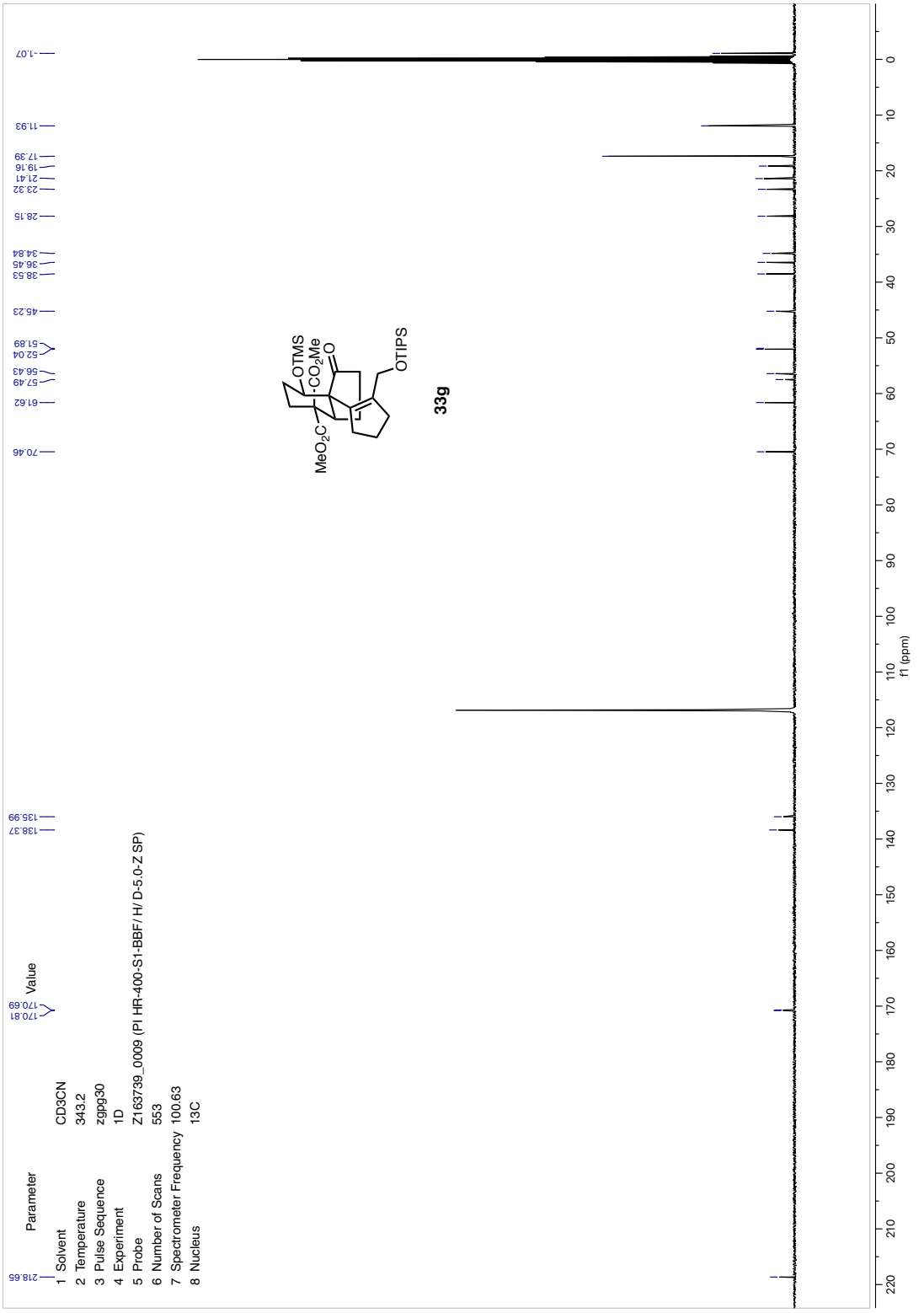

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
CO2Me
MeO2C
O
33e
f1 (ppm)

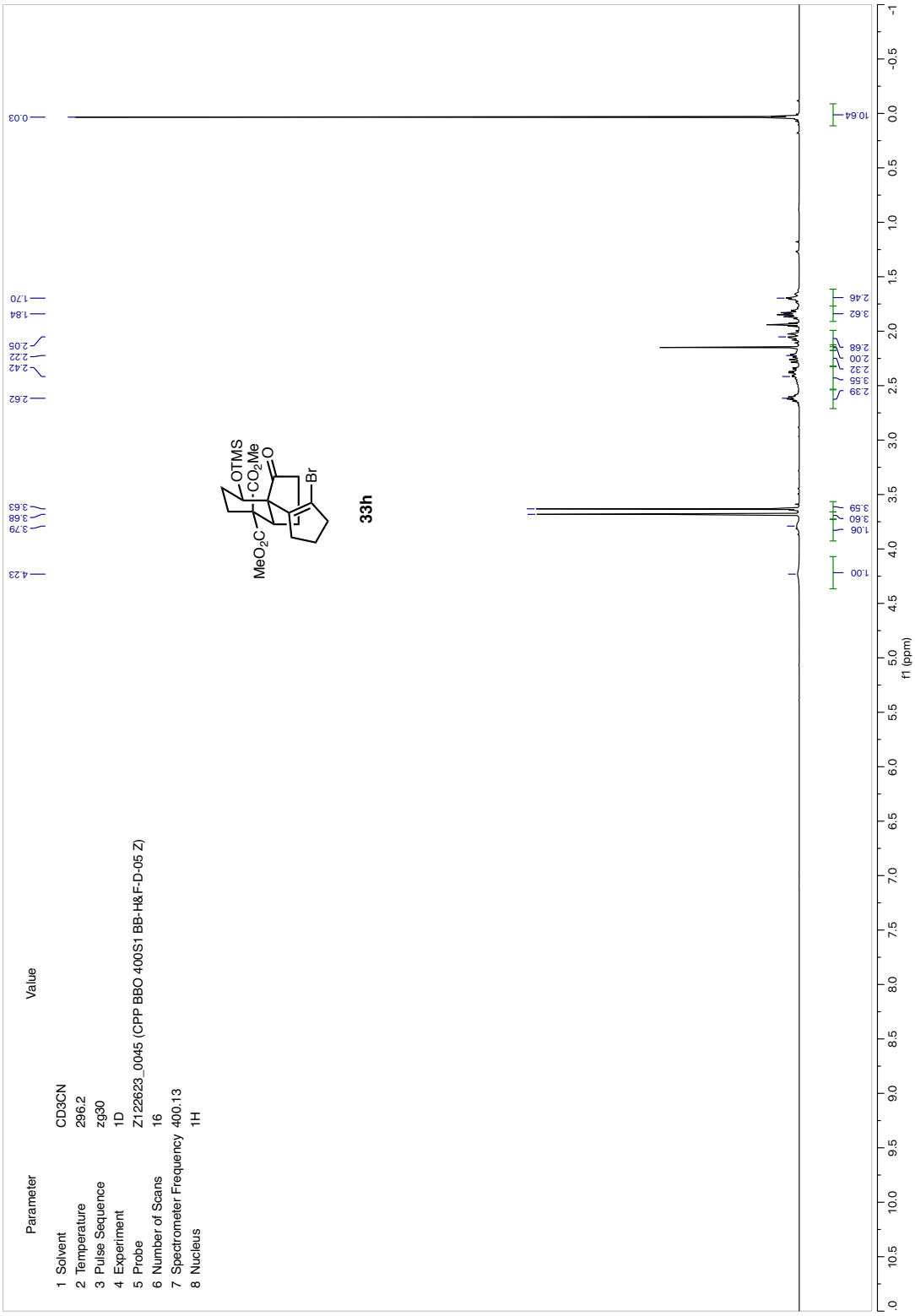

0.14
19.74
22.95
23.70
28.04
32.92
33.11
39.26
42.08
52.71
56.26
58.04
70.53
127.53
143.08
170.67
170.99
219.36
OTMS
CO2Me
O
MeO2C
33e
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

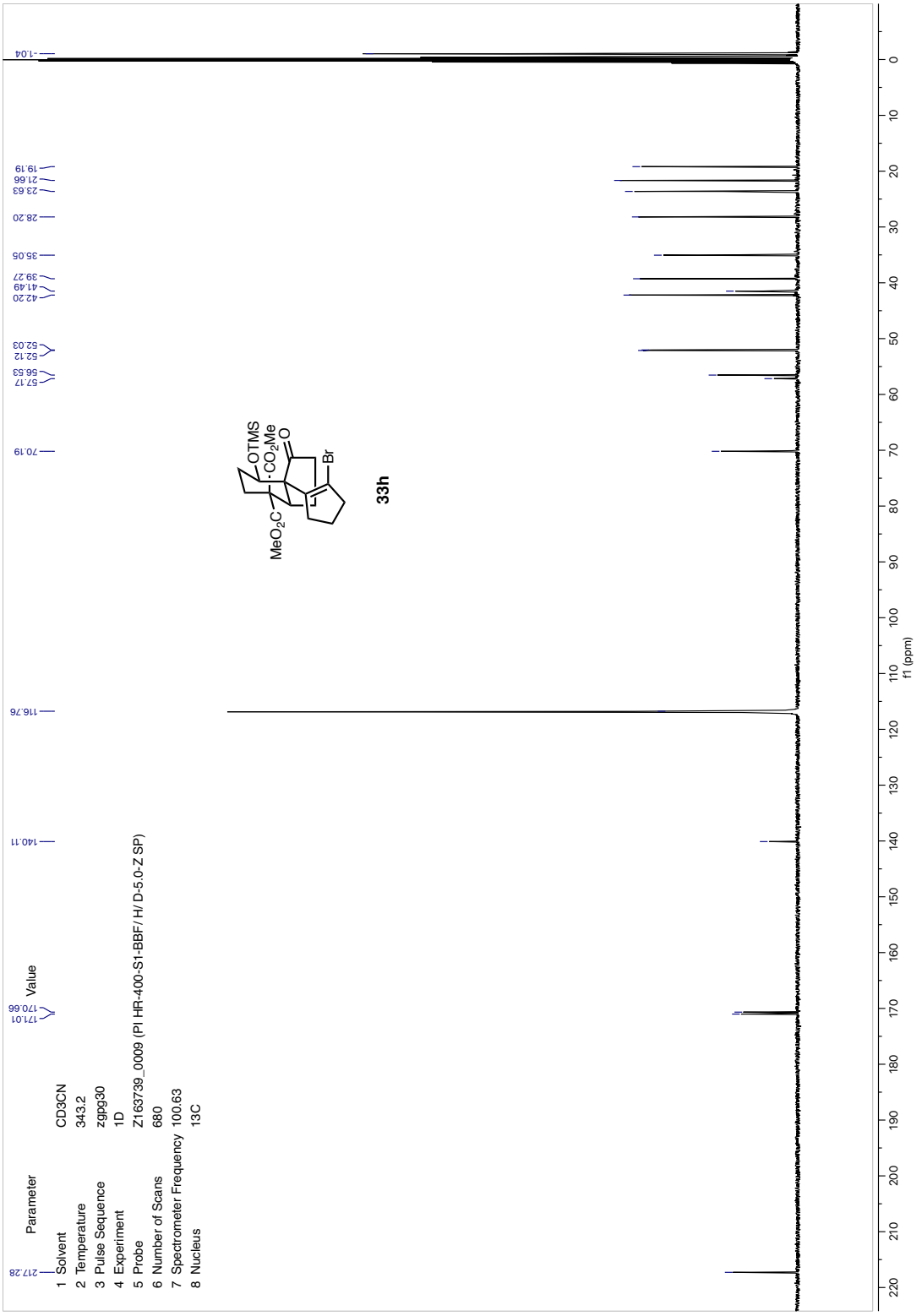

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
CO2Me
MeO2C
33f
f1 (ppm)

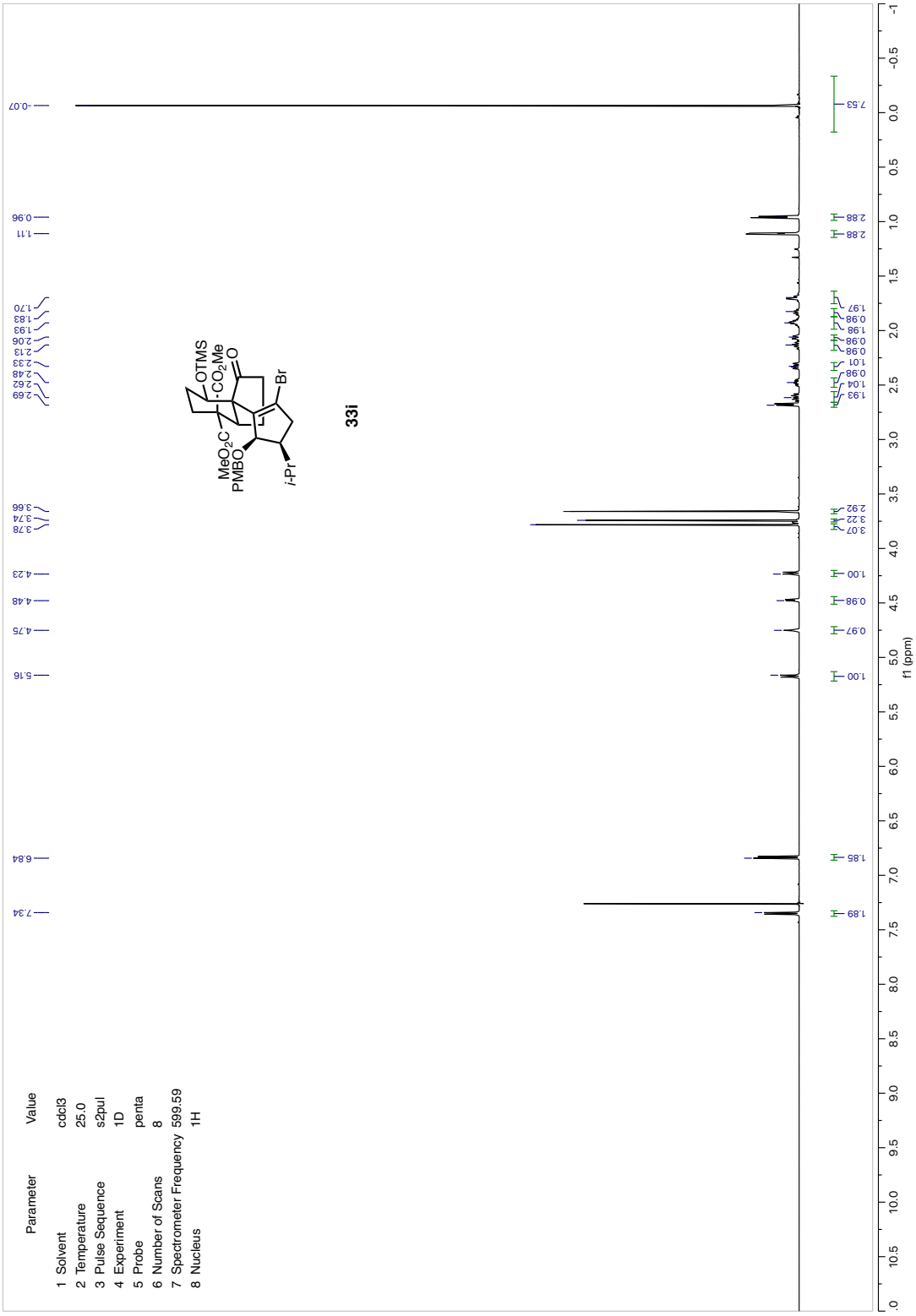

0.17
19.70
22.10
23.00
23.61
25.74
26.86
28.23
39.91
41.41
52.81
56.33
60.56
69.90
124.33
136.37
171.04
170.73
220.54
OTMS
CO2Me
O
MeO2C
33f
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

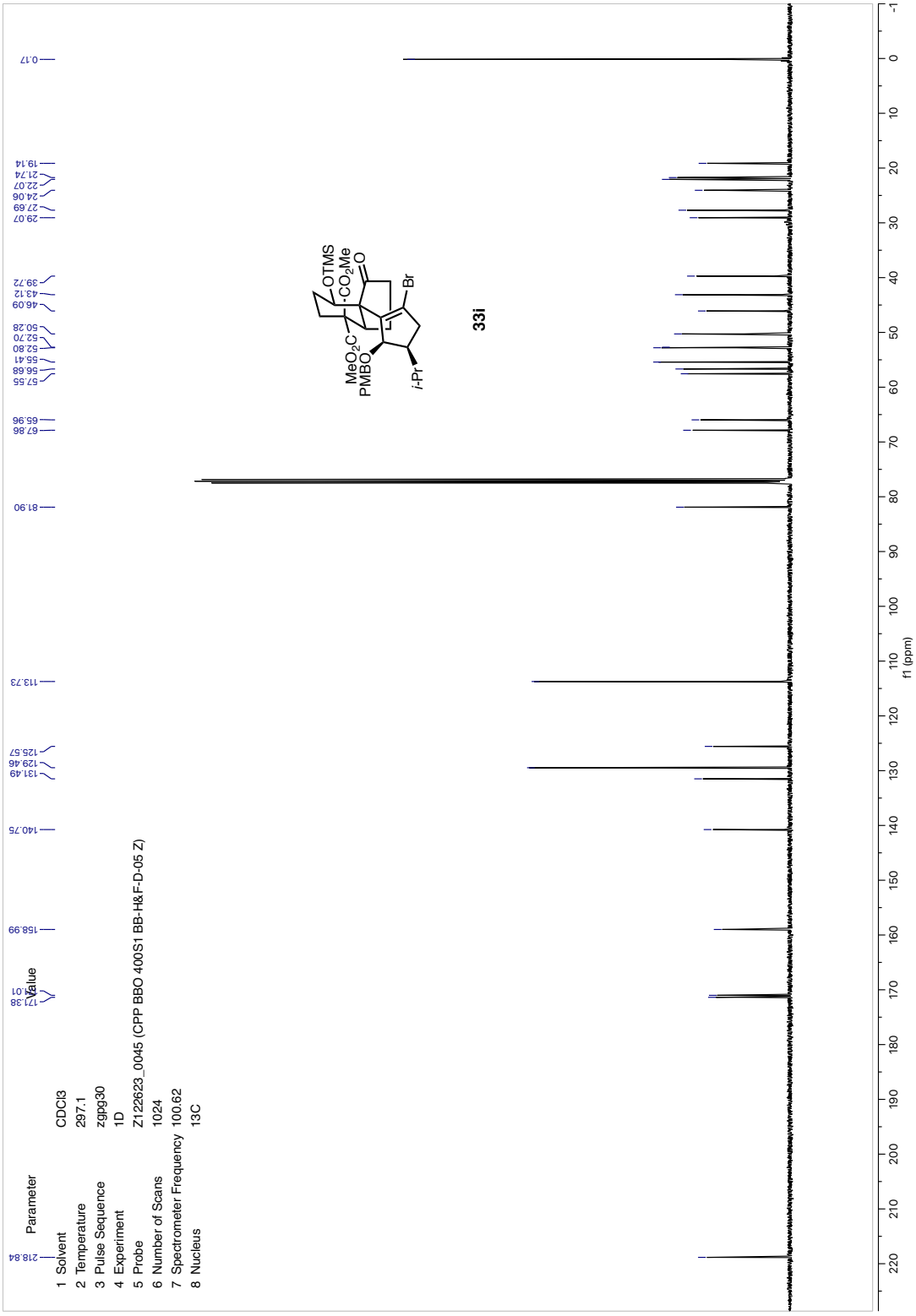

Parameter Value
1 Solvent CD3CN
2 Temperature 343.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
6 Number of Scans 16
7 Spectrometer Frequency 400.15
8 Nucleus 1H
OTMS
CO2Me
MeO2C
OTIPS
33g
f1 (ppm)

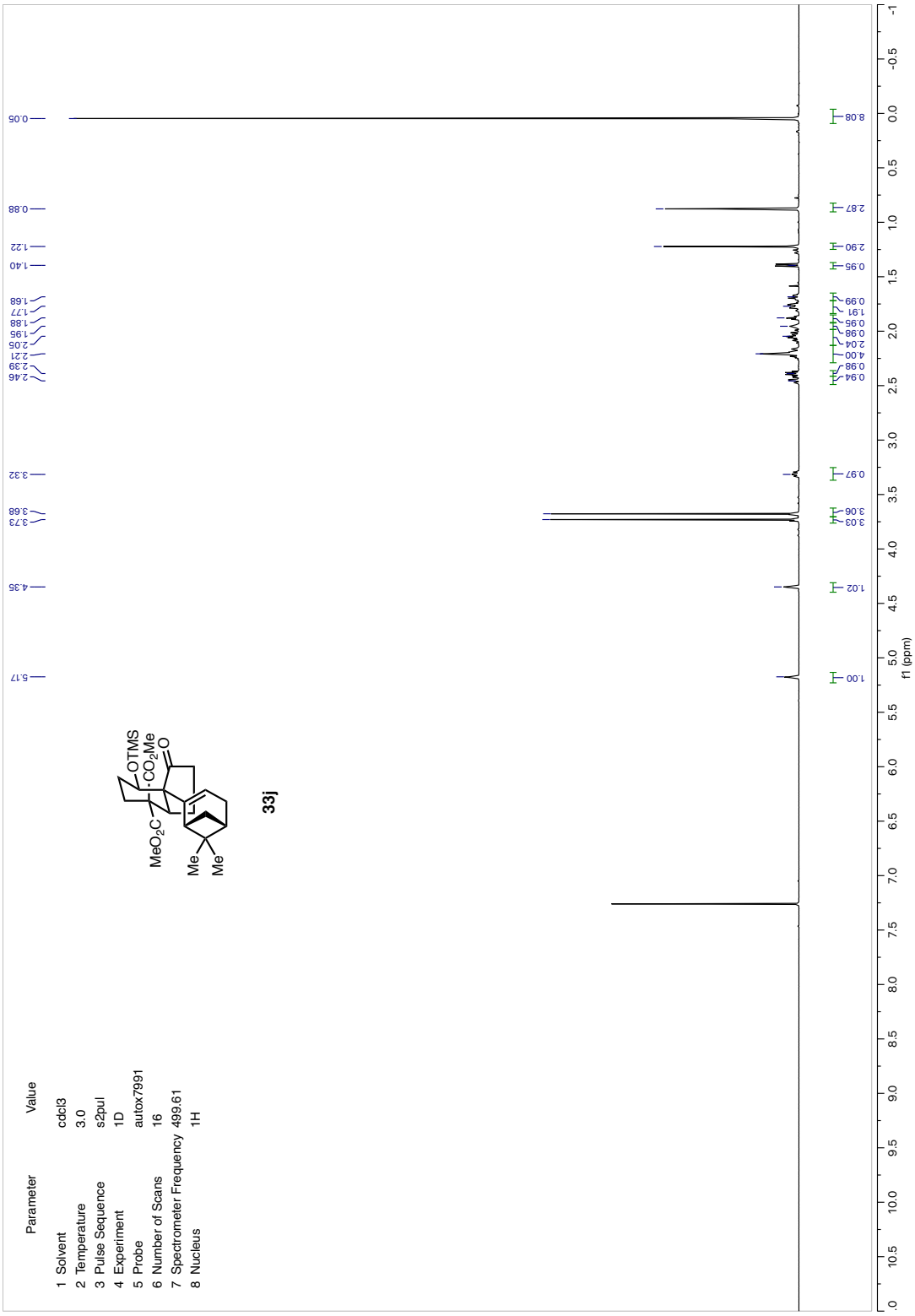

OTMS
CO2Me
O
MeO2C
OTIPS
33g
Parameter Value
1 Solvent CD3CN
2 Temperature 343.2
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
6 Number of Scans 553
7 Spectrometer Frequency 100.63
8 Nucleus 13C
-1.07
11.93
17.39
19.16
21.41
23.32
28.15
34.84
36.45
38.53
45.23
51.89
52.04
56.43
57.49
61.62
70.46
135.99
138.37
170.81
170.69
218.65
f1 (ppm)

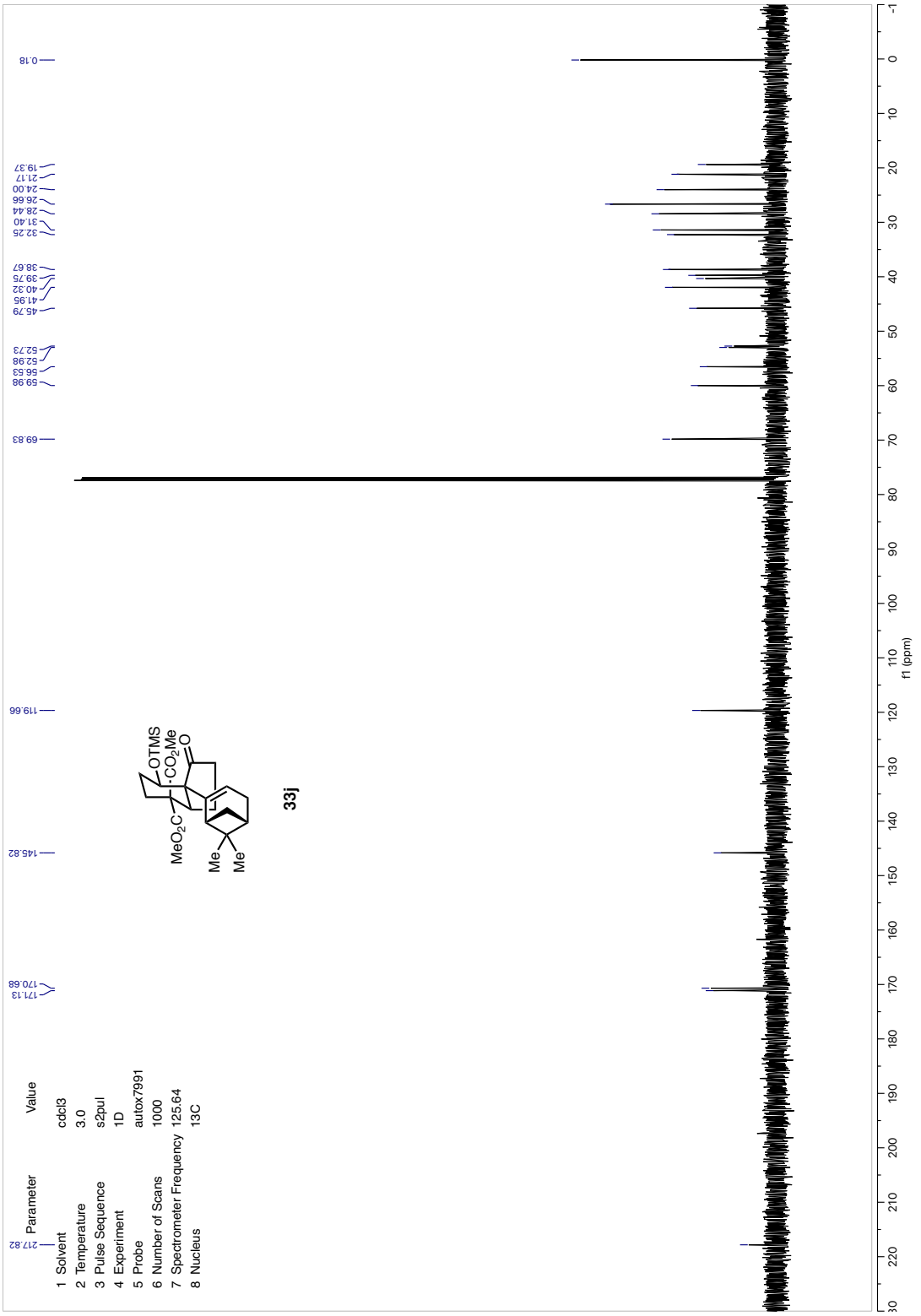

Parameter Value
1 Solvent CD3CN
2 Temperature 296.2
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
OTMS
CO2Me
O
Br
MeO2C
33h
0.03
1.70
1.84
2.05
2.22
2.42
2.62
3.63
3.68
3.79
4.23
10.64
2.46
3.62
2.68
2.00
2.32
3.55
2.39
3.59
3.60
1.06
1.00
f1 (ppm)

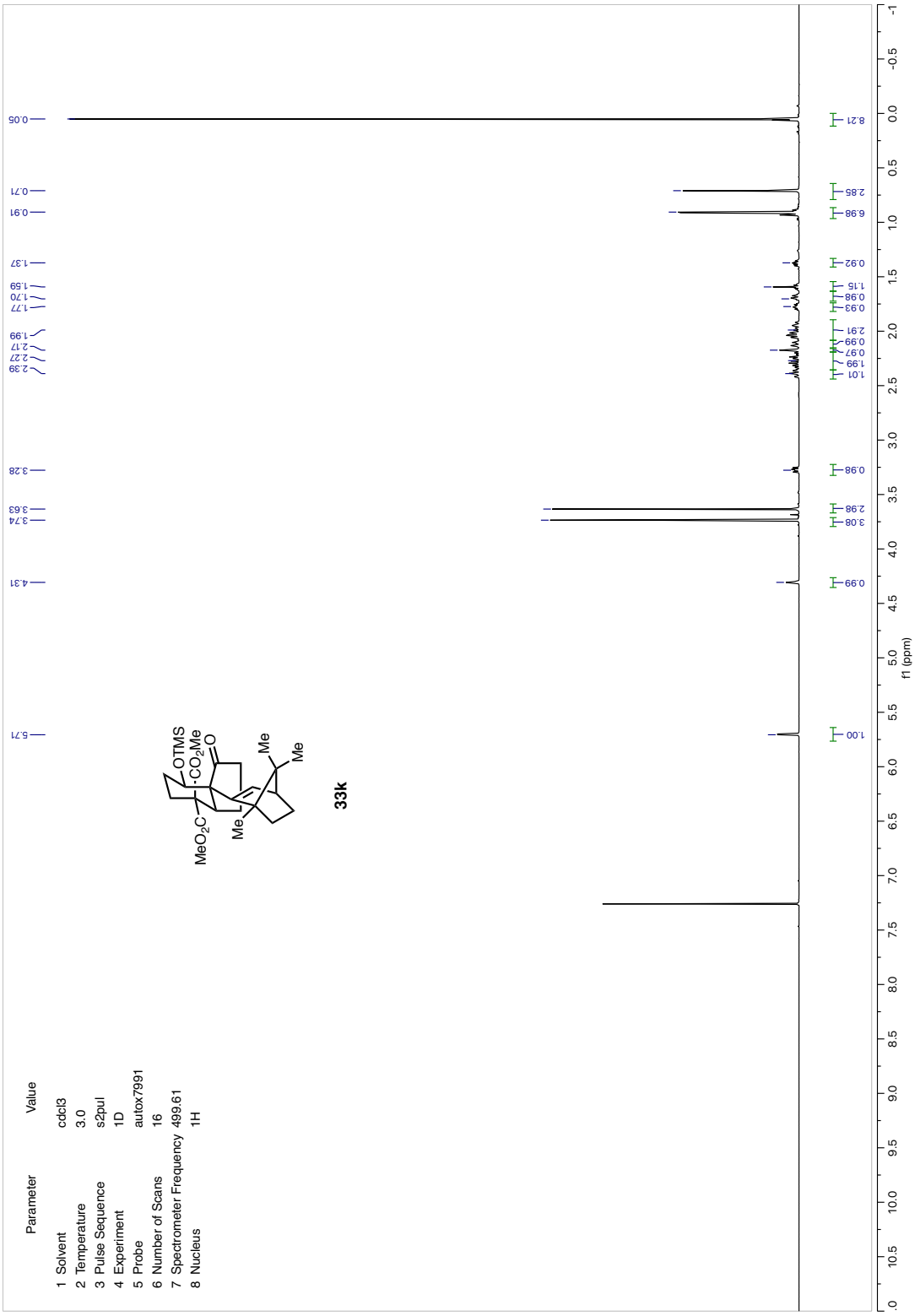

-1.04
19.19
21.66
23.63
28.20
35.05
39.27
41.49
42.20
52.03
52.12
56.53
57.17
70.19
116.76
140.11
170.66
171.01
217.28
OTMS
CO2Me
O
Br
MeO2C
33h
Parameter Value
1 Solvent CD3CN
2 Temperature 343.2
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z163739_0009 (PI HR-400-S1-BBF/ H/ D-5.0-Z SP)
6 Number of Scans 680
7 Spectrometer Frequency 100.63
8 Nucleus 13C
f1 (ppm)

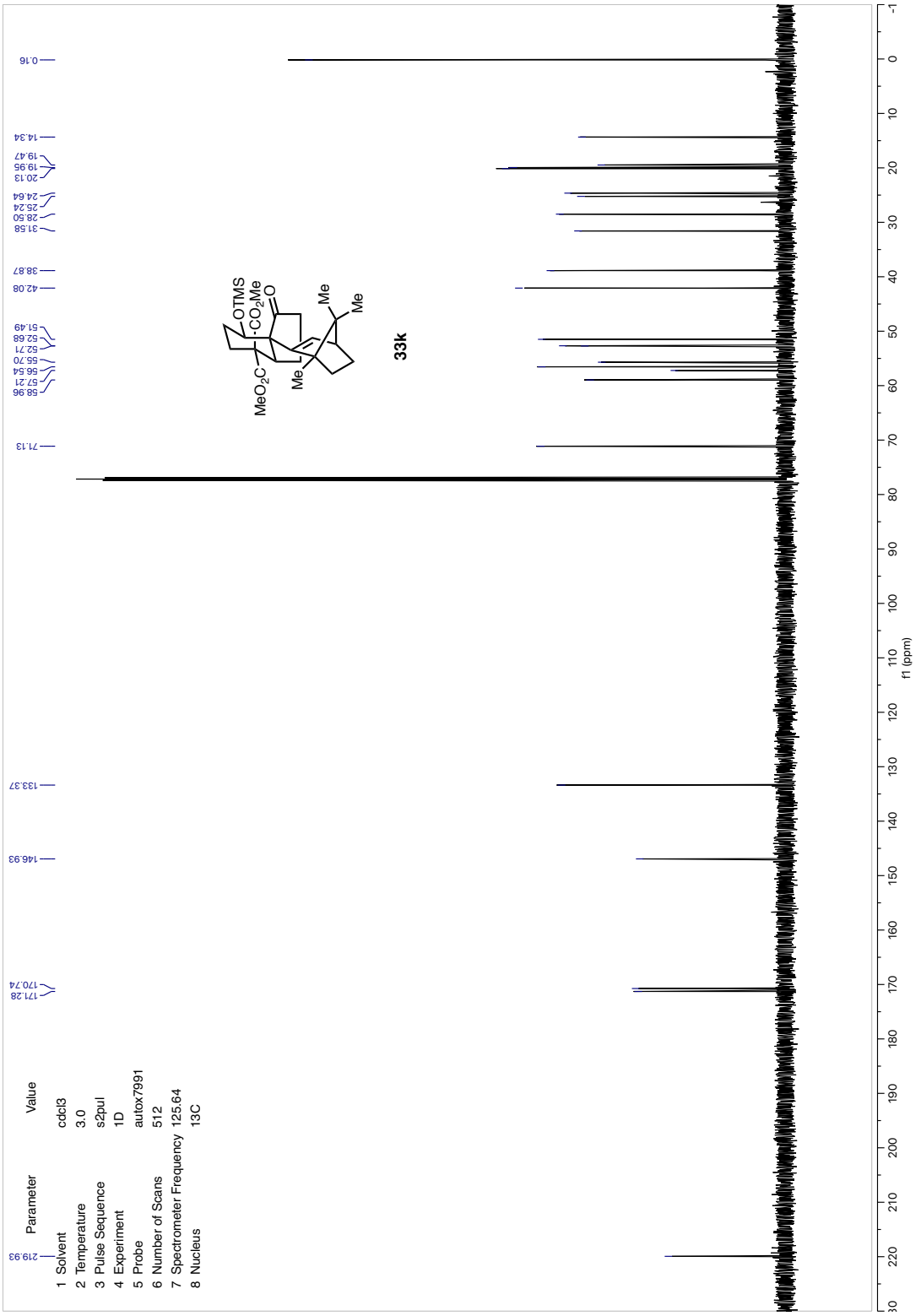

OTMS
CO2Me
O
Br
MeO2C
PMBO
i-Pr
33i
Parameter Value
1 Solvent cdcl3
2 Temperature 25.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe penta
6 Number of Scans 8
7 Spectrometer Frequency 599.59
8 Nucleus 1H
f1 (ppm)

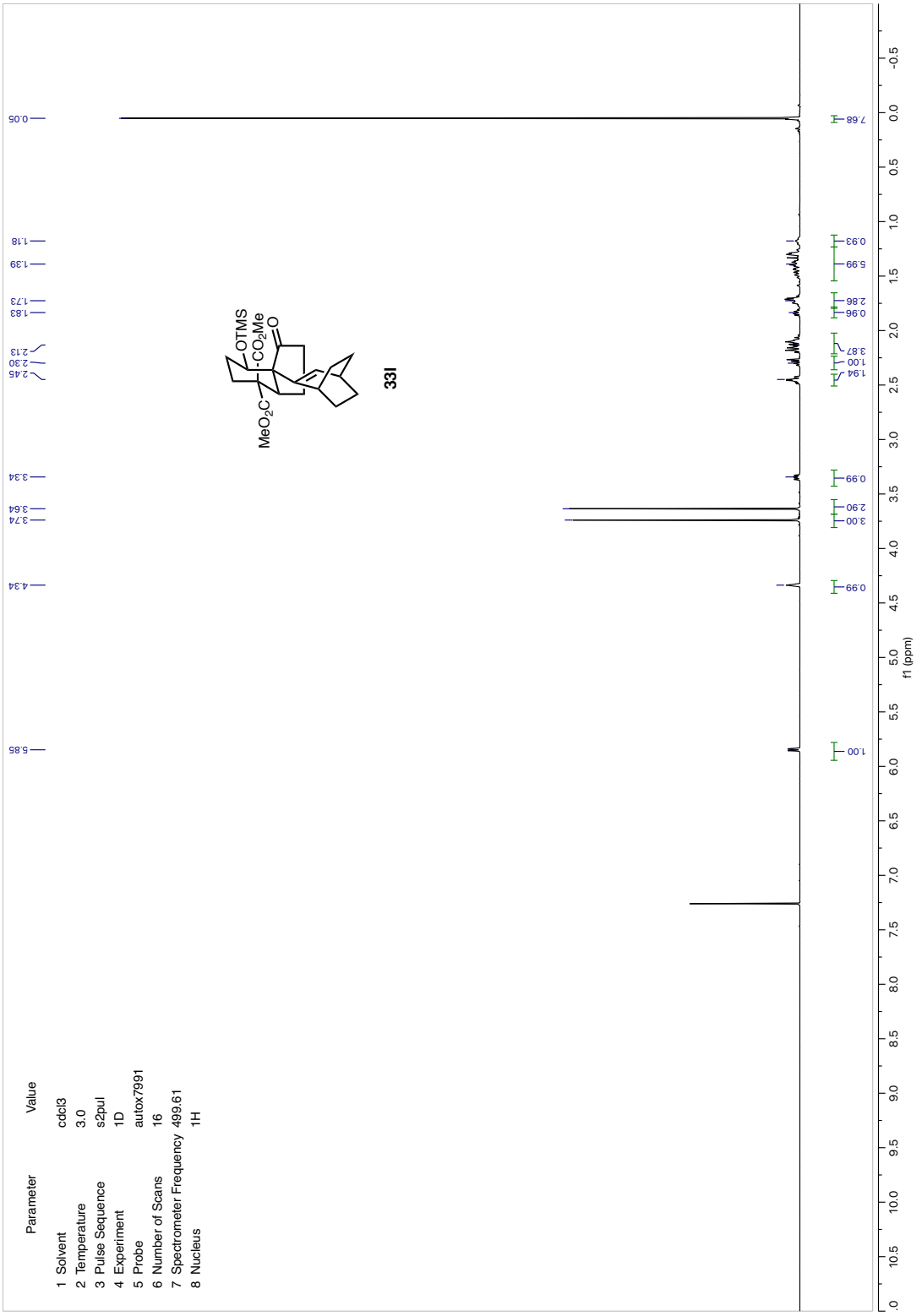

Parameter Value
1 Solvent CDCl3
2 Temperature 297.1
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 1024
7 Spectrometer Frequency 100.62
8 Nucleus 13C
218.84
171.38
158.99
140.75
131.49
129.46
125.57
113.73
81.90
67.86
65.96
57.55
56.68
55.41
52.80
52.70
50.28
46.09
43.12
39.72
29.07
27.69
24.06
22.07
21.74
19.14
0.17
OTMS
CO2Me
O
Br
MeO2C
PMBO
i-Pr
33i
f1 (ppm)

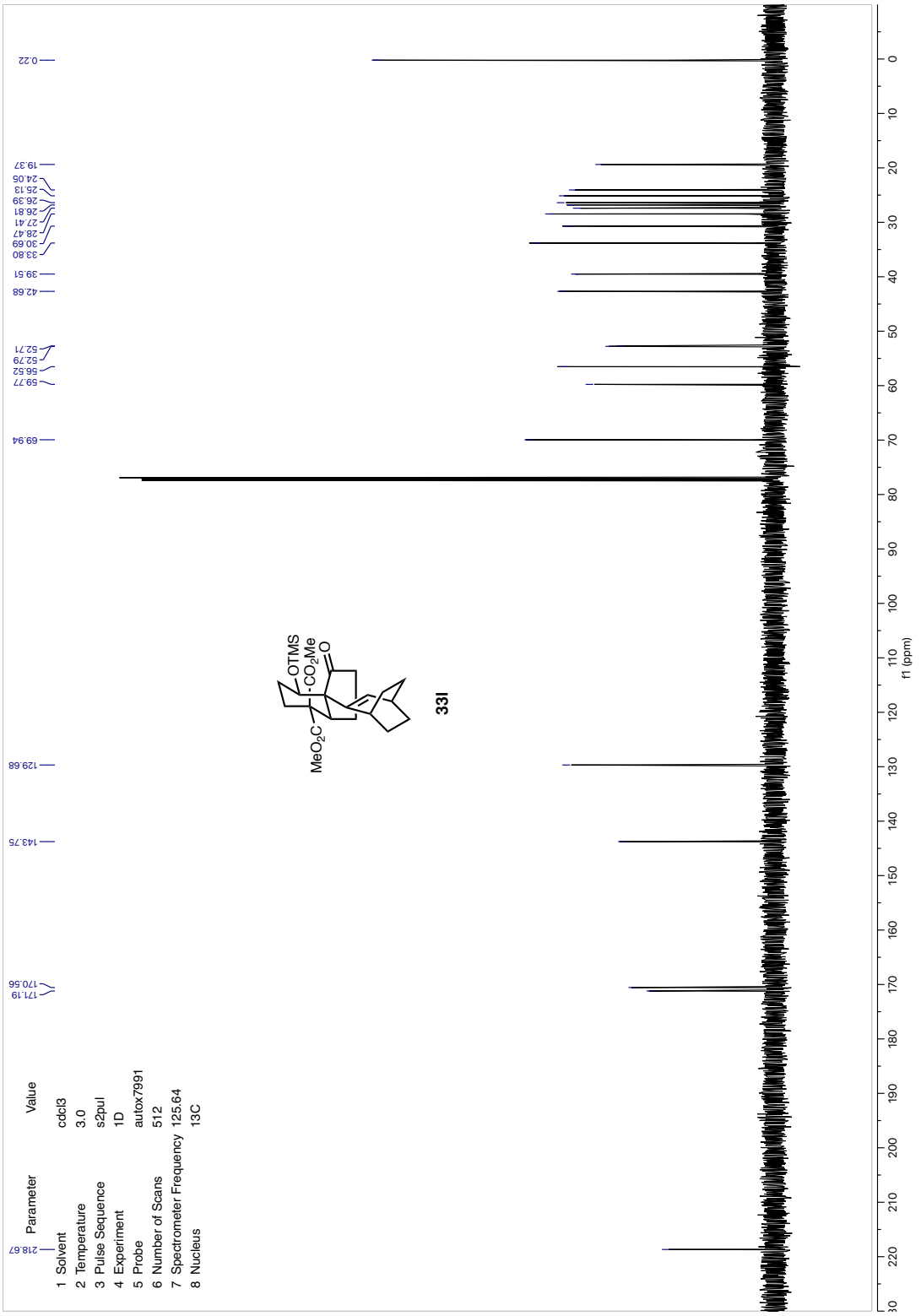

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
CO2Me
O
MeO2C
Me
Me
33j
f1 (ppm)

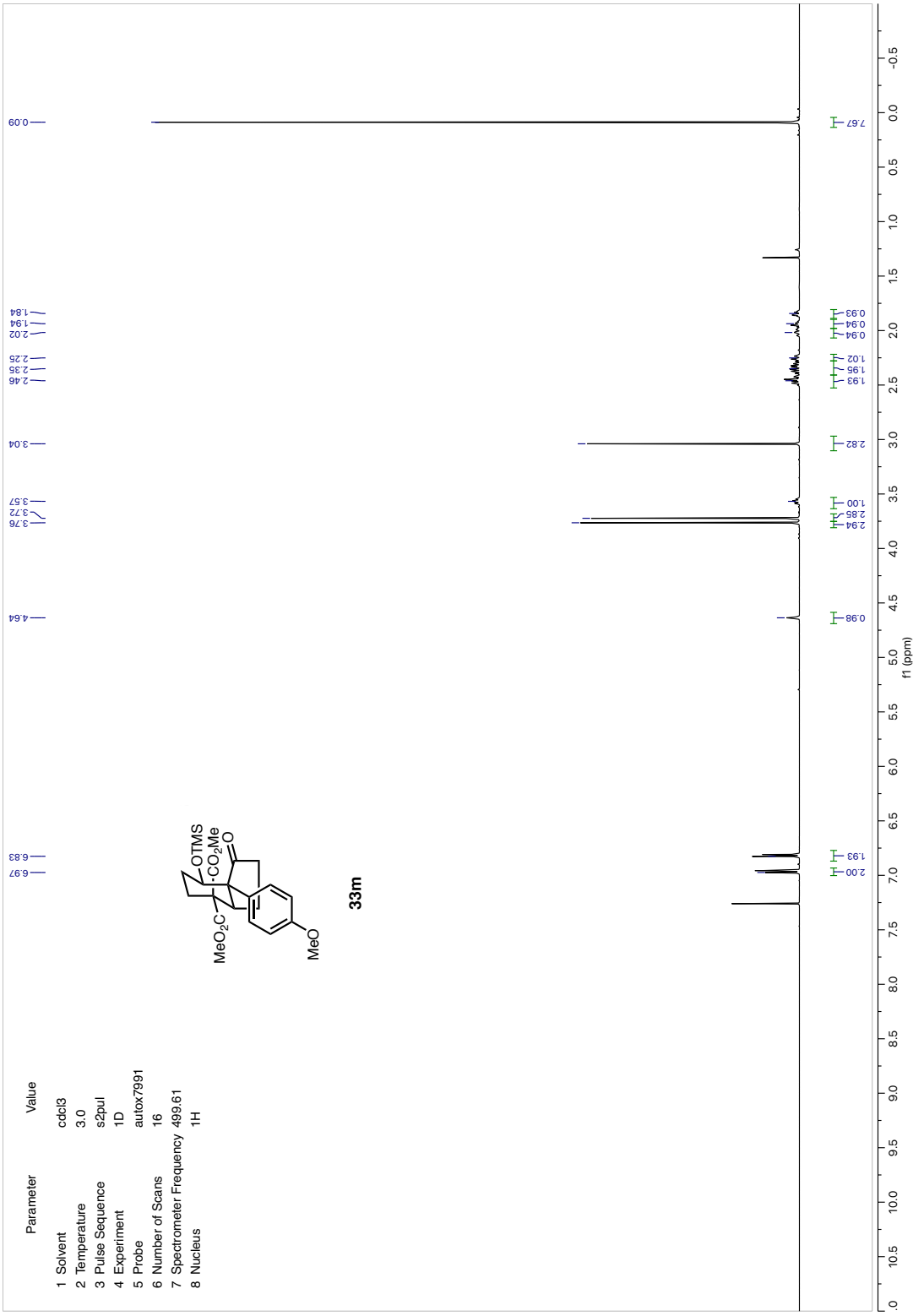

217.82
171.13
170.68
145.82
119.66
69.83
59.98
56.53
52.98
52.73
45.79
41.95
40.32
39.75
38.67
32.25
31.40
28.44
26.66
24.00
21.17
19.37
0.18
OTMS
MeO2C
CO2Me
O
Me
Me
33j
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

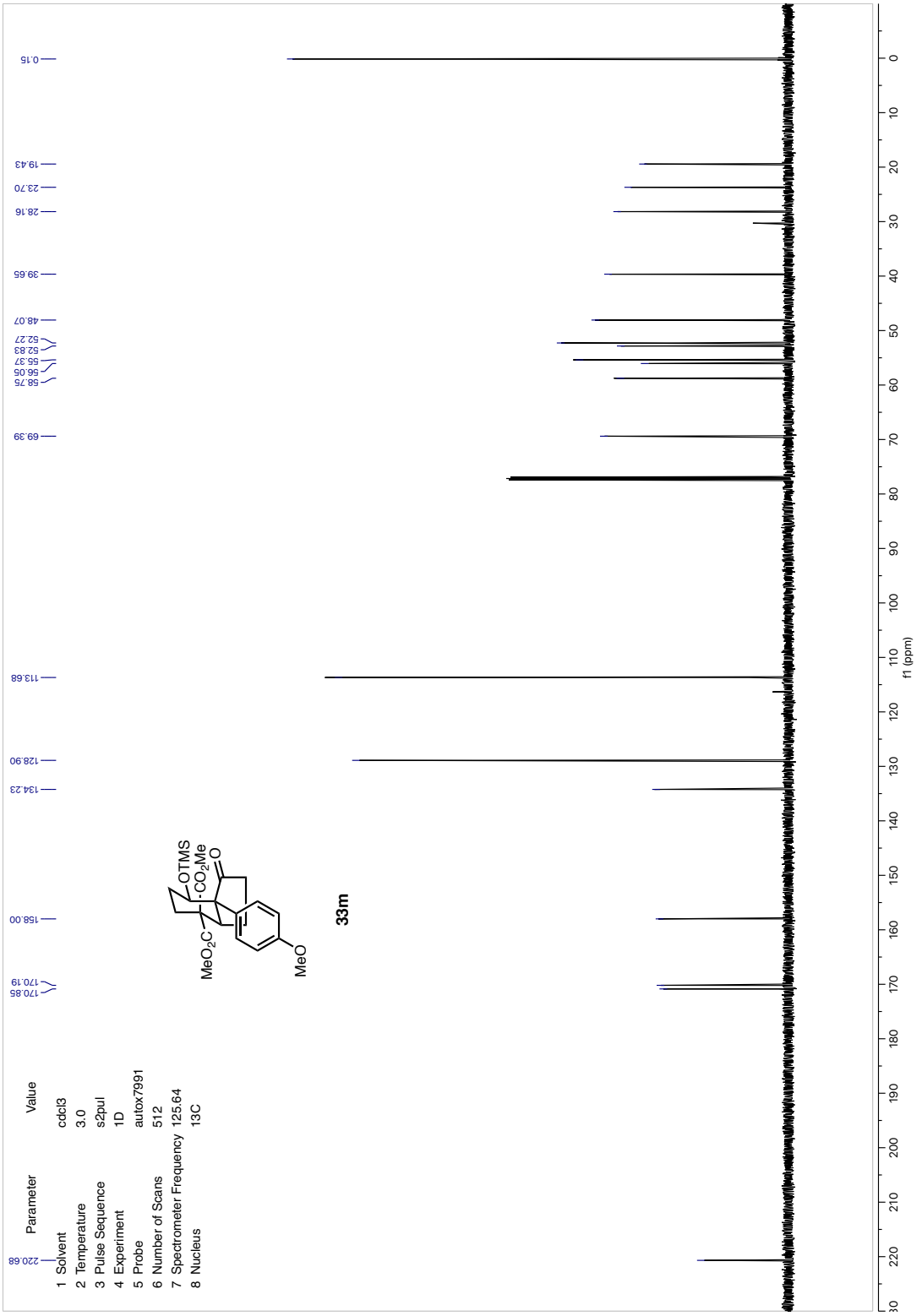

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
CO2Me
O
MeO2C
Me
Me
Me
33k
f1 (ppm)

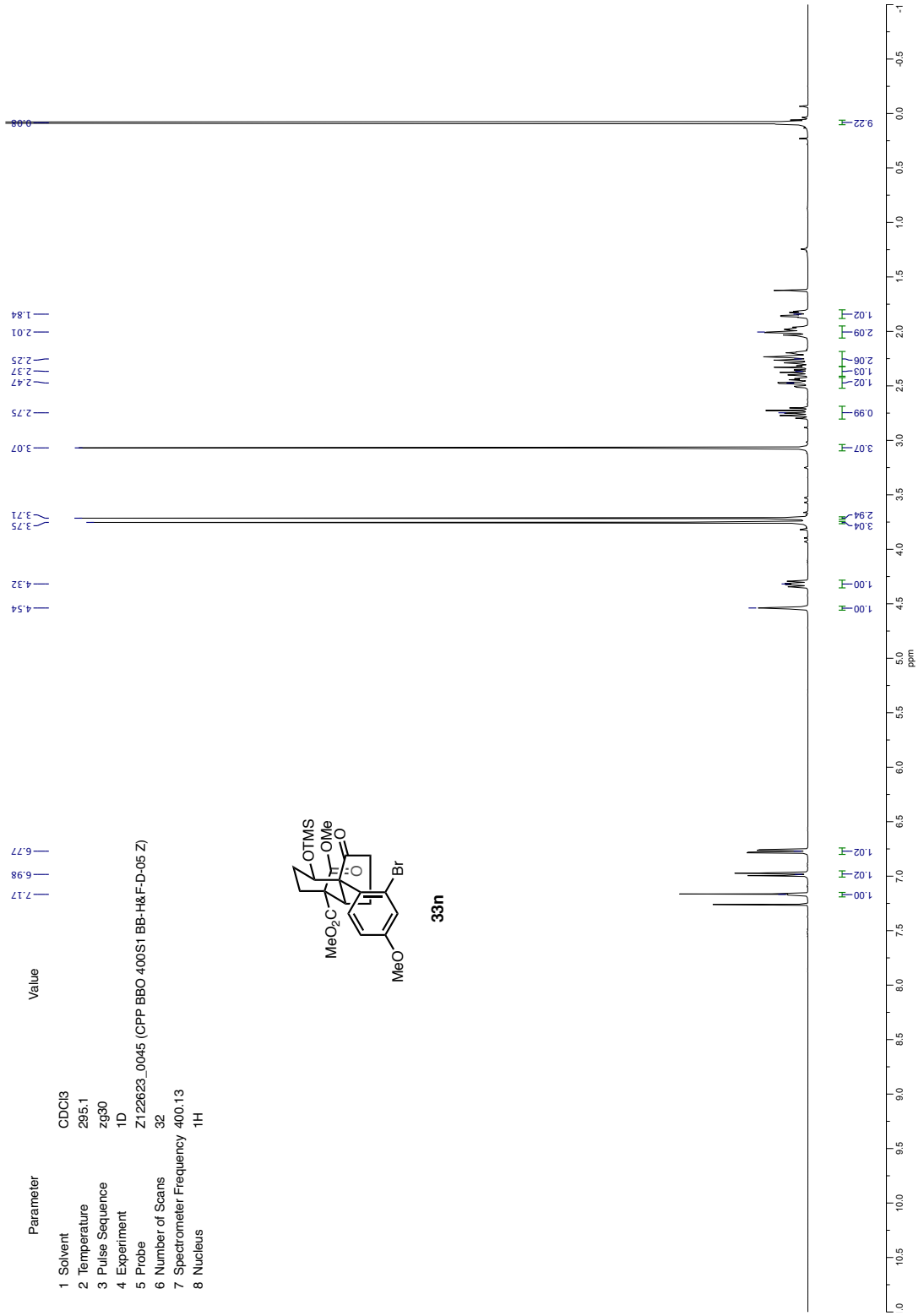

0.16
14.34
19.47
19.95
20.13
24.64
25.24
28.50
31.58
38.87
42.08
51.49
52.68
52.71
55.70
56.54
57.21
58.96
71.13
133.37
146.93
171.28
170.74
219.93
OTMS
CO2Me
O
MeO2C
Me
Me
Me
33k
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

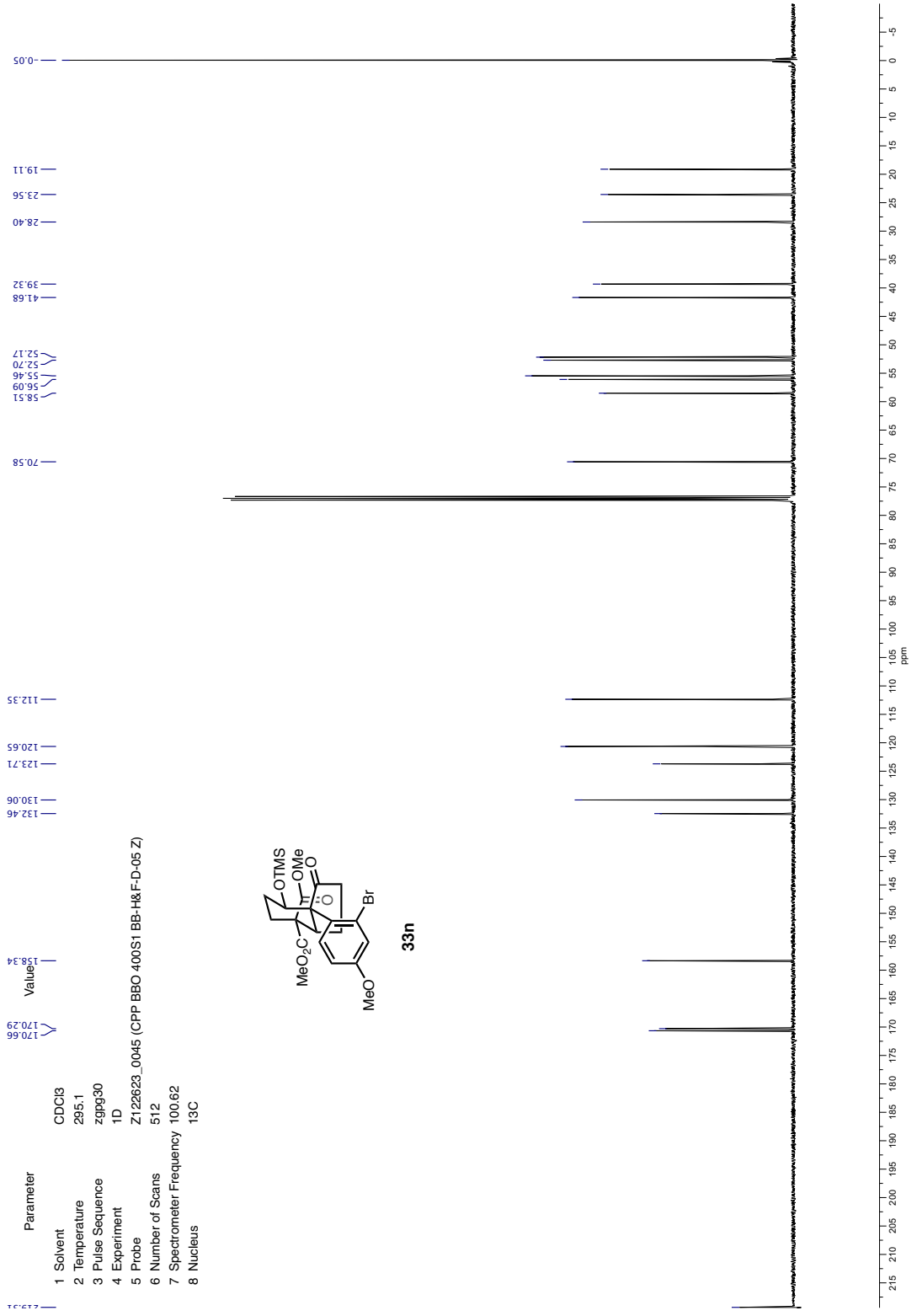

OTMS
CO2Me
O
MeO2C
33l
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
0.05
1.18
1.39
1.73
1.83
2.13
2.30
2.45
3.34
3.64
3.74
4.34
5.85
7.68
0.93
5.99
2.86
0.96
3.87
1.00
1.94
0.99
2.90
3.00
0.99
1.00
f1 (ppm)

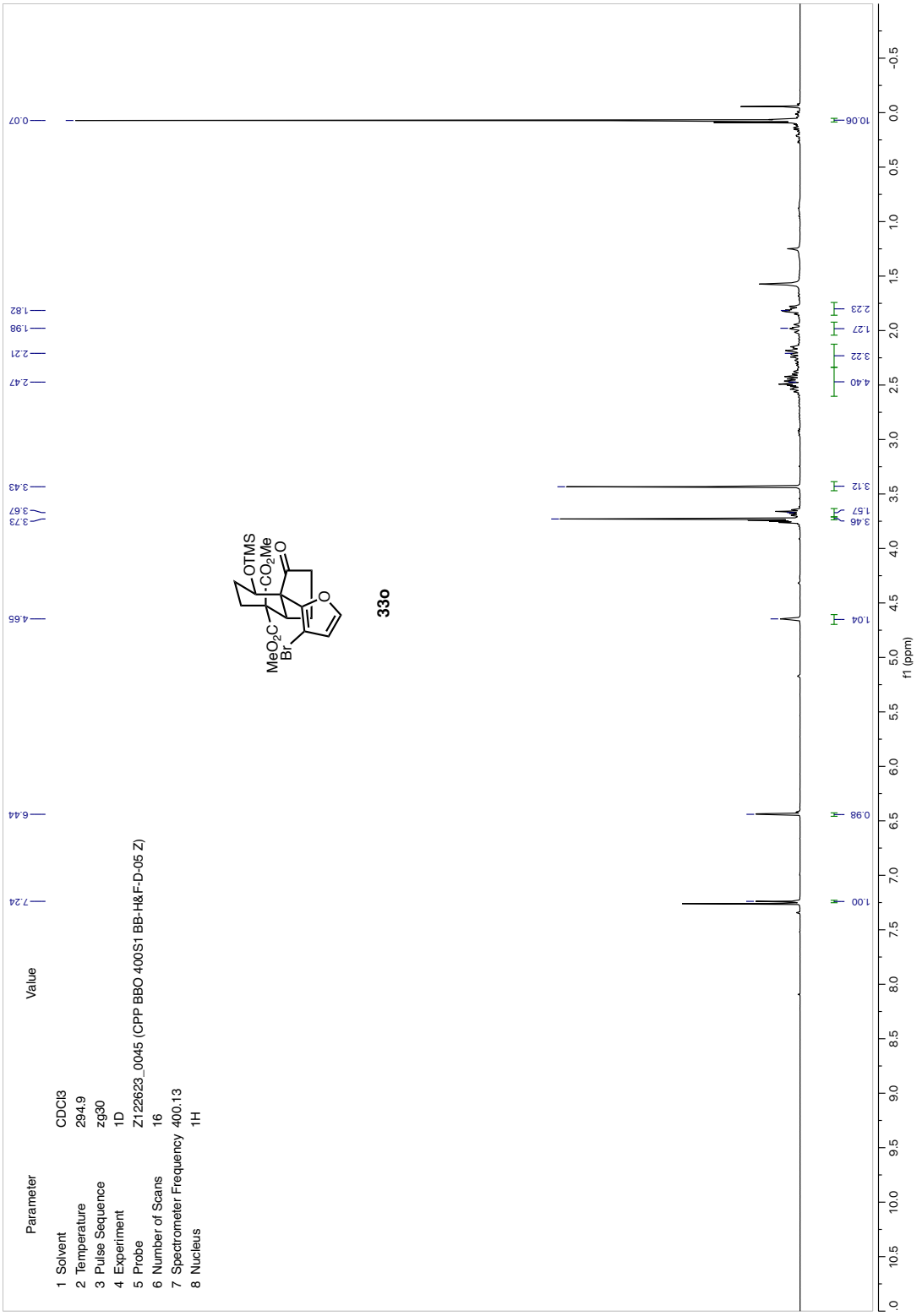

0.22
19.37
24.05
25.13
26.39
26.81
27.41
28.47
30.69
33.80
39.51
42.68
52.71
52.79
56.52
59.77
69.94
129.68
143.75
170.56
171.19
218.67
OTMS
CO2Me
O
MeO2C
33l
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

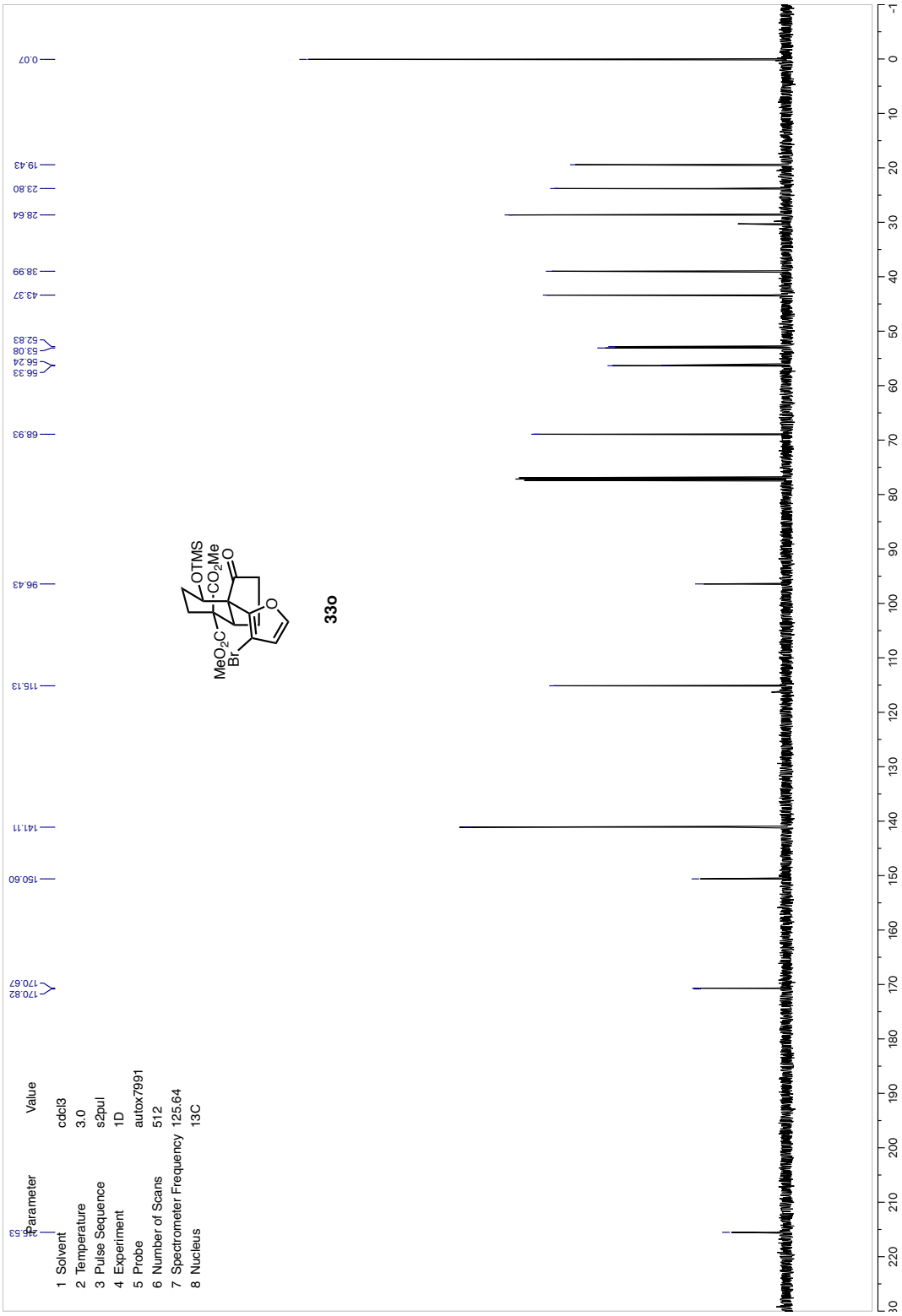

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
CO2Me
MeO2C
MeO
33m
f1 (ppm)

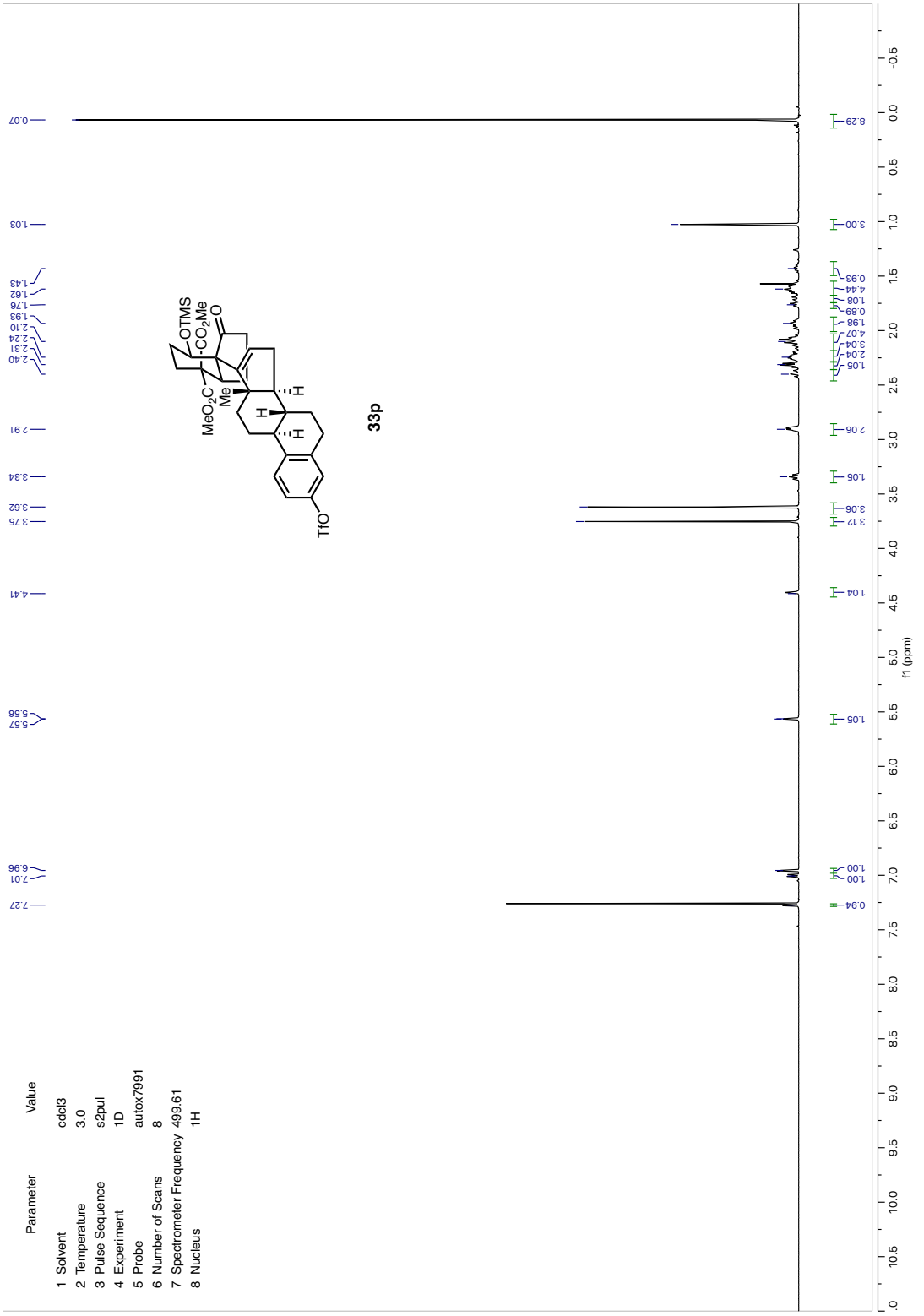

0.15
19.43
23.70
28.16
39.65
48.07
52.27
52.83
55.37
56.05
58.75
69.39
113.68
128.90
134.23
158.00
170.85
170.19
220.68
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
OTMS
CO2Me
O
MeO2C
MeO
33m
f1 (ppm)

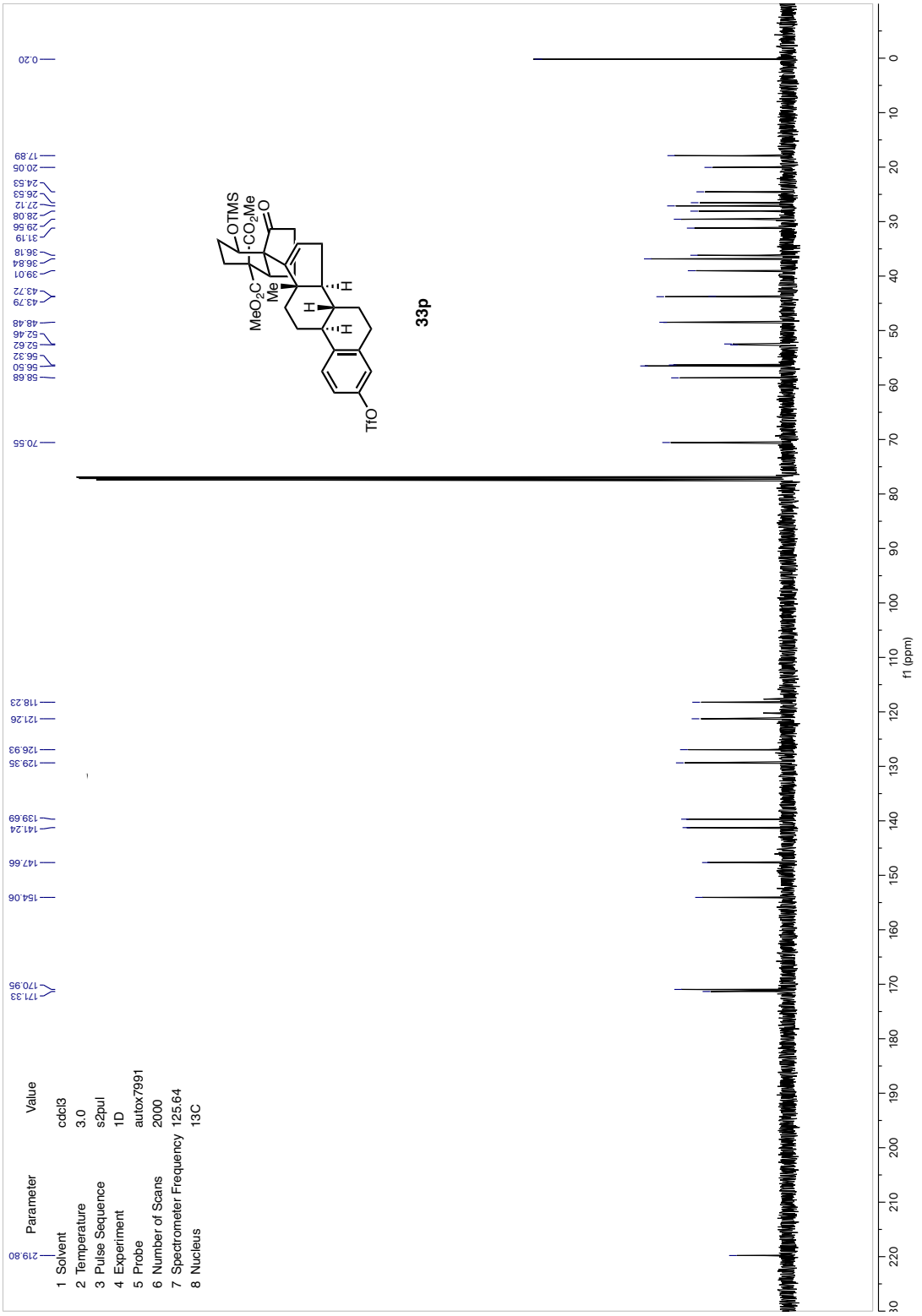

Parameter
Value
1 Solvent CDCl3
2 Temperature 295.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 32
7 Spectrometer Frequency 400.13
8 Nucleus 1H
OTMS
OMe
O
O
Br
MeO
MeO2C
33n
ppm

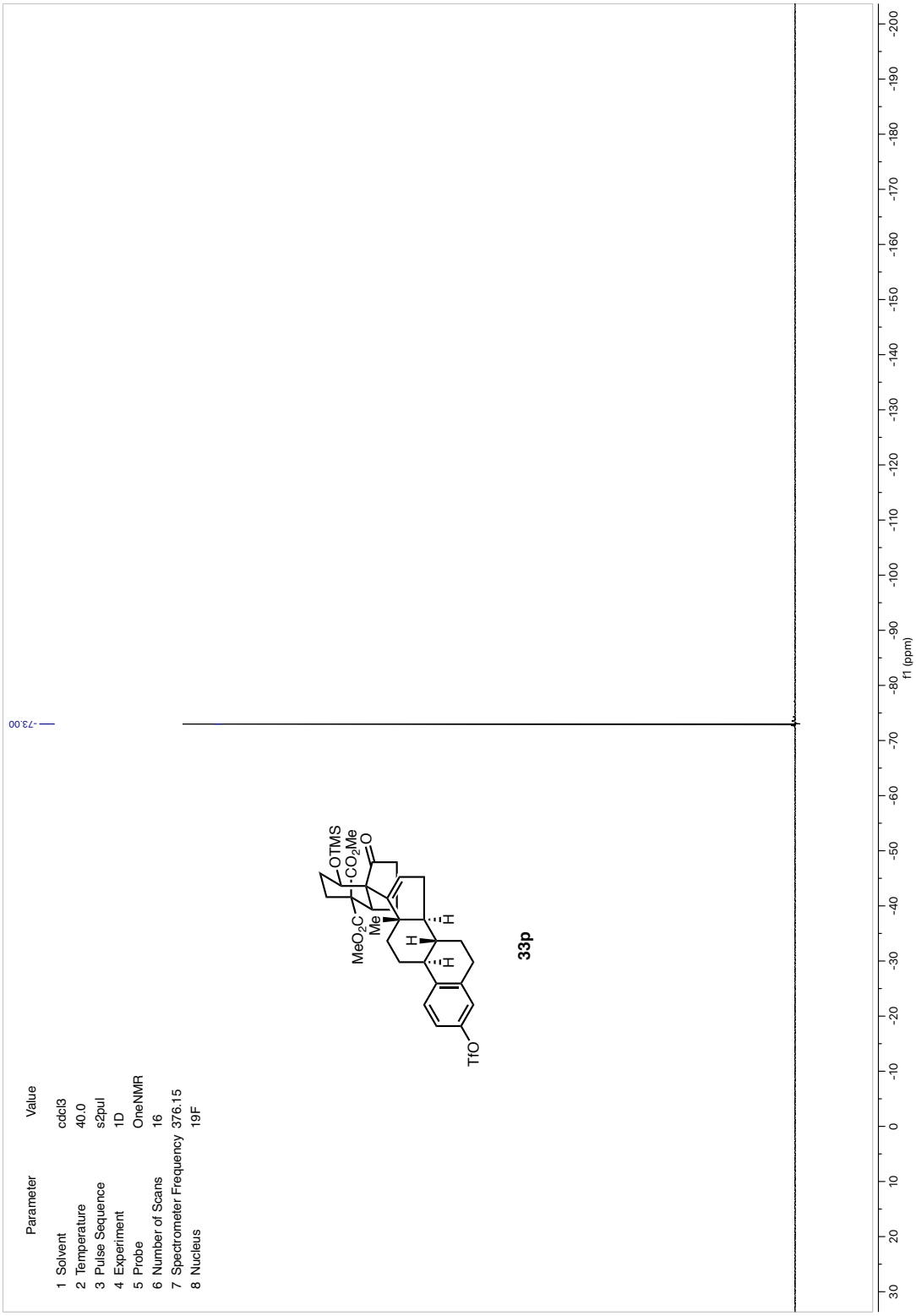

Parameter Value
1 Solvent CDCl3
2 Temperature 295.1
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 512
7 Spectrometer Frequency 100.62
8 Nucleus 13C
-0.05
19.11
23.56
28.40
39.32
41.68
52.17
52.70
55.46
56.09
58.51
70.58
112.35
120.65
123.71
130.06
132.46
158.34
170.29
170.66
OTMS
OMe
O
H
O
Br
MeO
MeO2C
33n
ppm

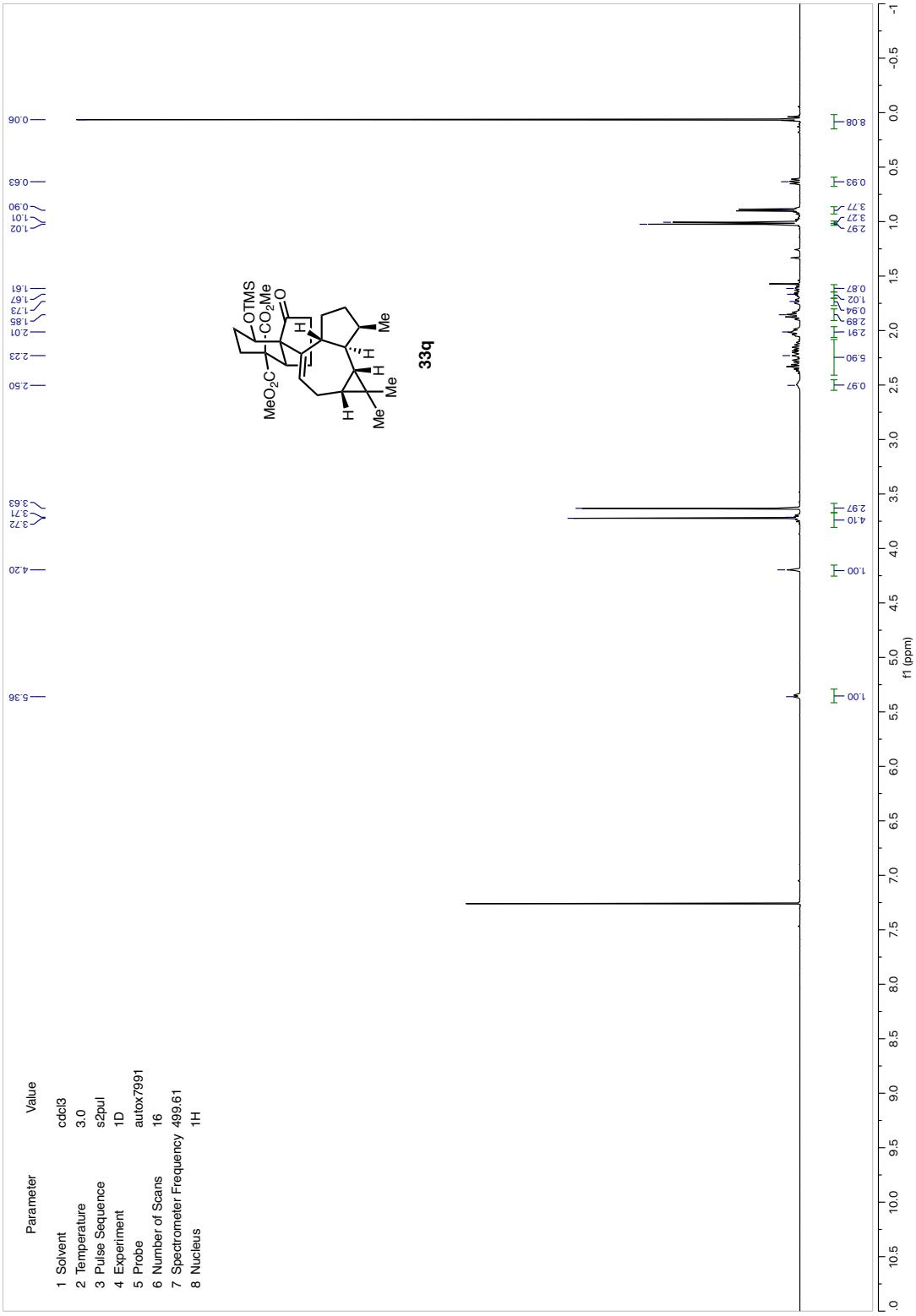

Parameter Value
1 Solvent CDCl3
2 Temperature 294.9
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
OTMS
CO2Me
O
MeO2C
Br
O
33o
0.07
1.82
1.98
2.21
2.47
3.43
3.67
3.73
4.65
6.44
7.24
10.06
2.23
1.27
3.22
4.40
3.12
1.57
3.46
1.04
0.98
1.00
f1 (ppm)

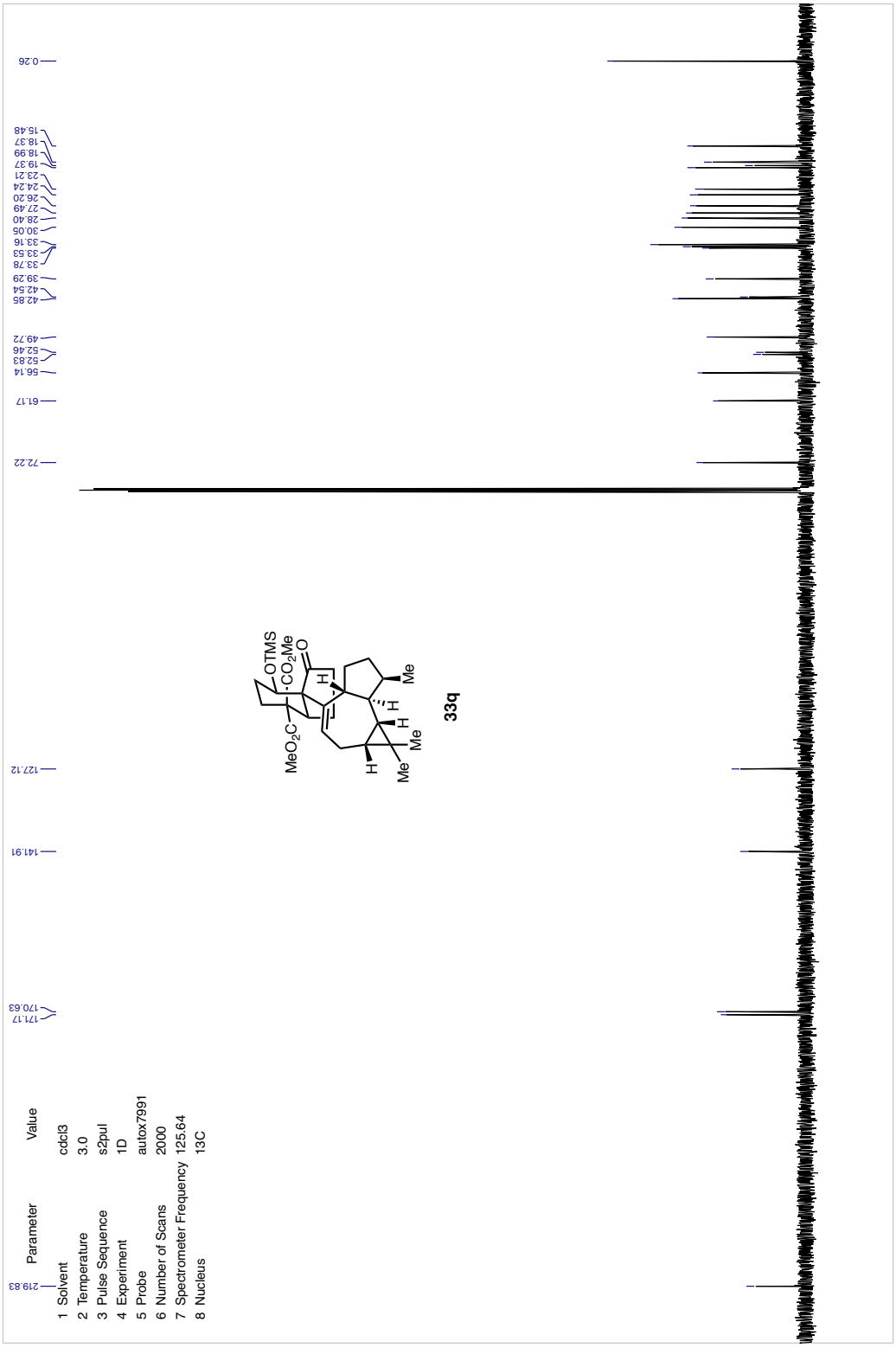

0.07
19.43
23.80
28.64
38.99
43.37
52.83
53.08
56.24
56.33
68.93
96.43
115.13
141.11
150.60
170.67
170.82
214.53
OTMS
CO2Me
O
MeO2C
Br
O
33o
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 512
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

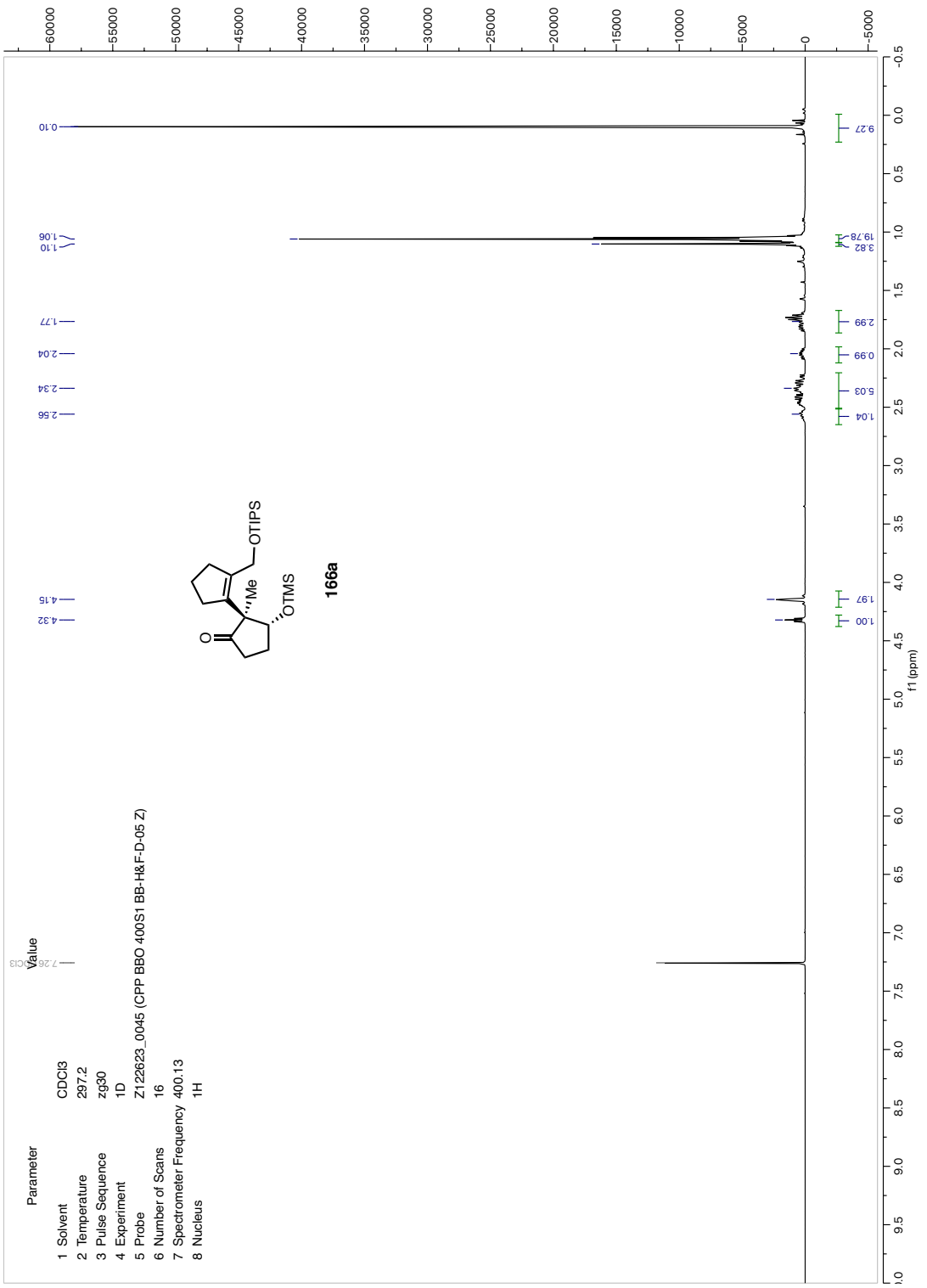

Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 8
7 Spectrometer Frequency 499.61
8 Nucleus 1H
OTMS
CO2Me
O
MeO2C
Me
H
H
H
TfO
33p
f1 (ppm)

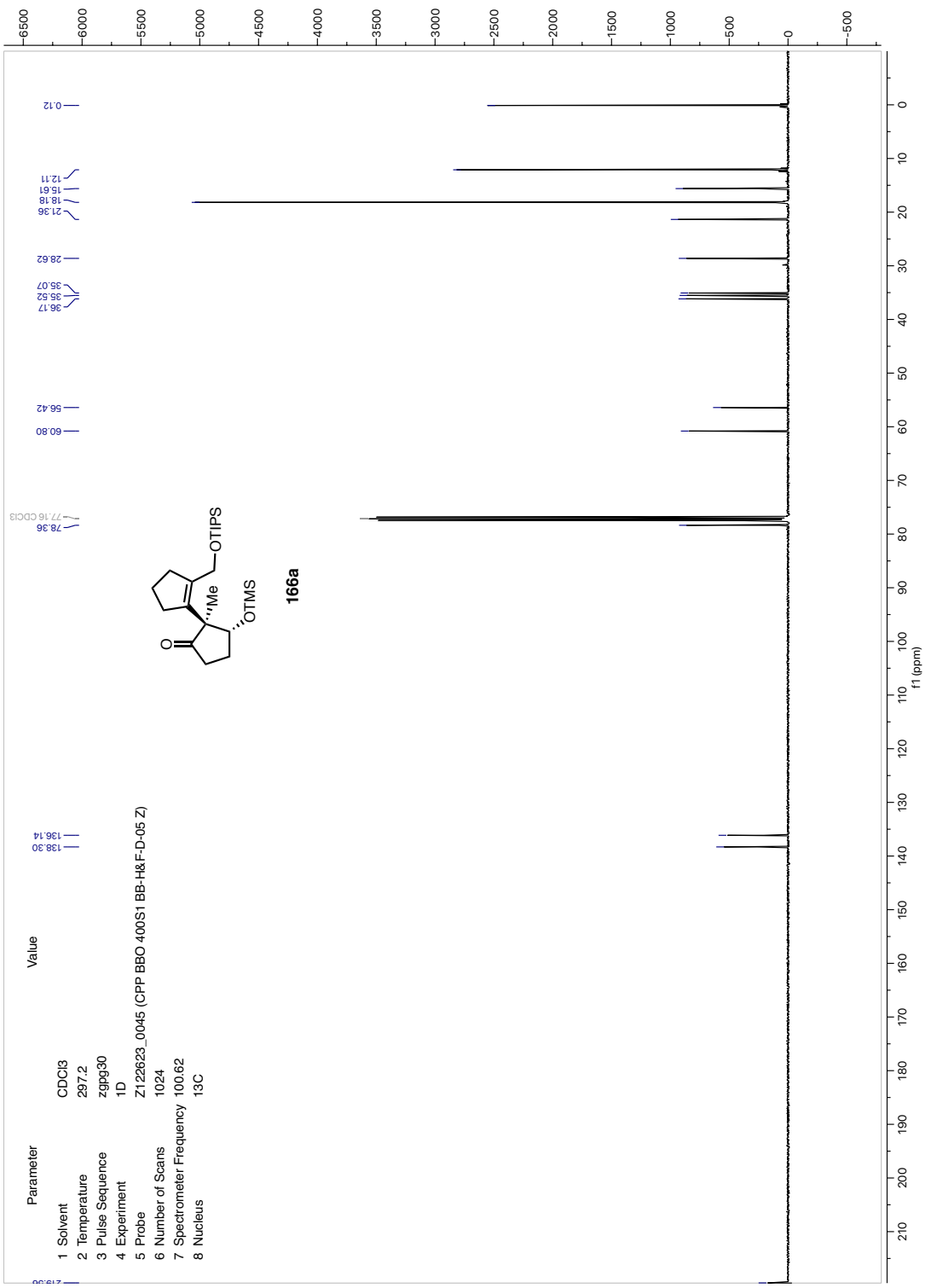

OTMS
CO2Me
O
MeO2C
Me
H
H
H
H
TfO
33p
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 2000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
219.80
171.33
170.95
154.06
147.66
141.24
139.69
129.35
126.93
121.26
118.23
70.55
58.68
56.50
56.32
52.62
52.46
48.48
43.72
43.79
39.01
36.84
36.18
31.19
29.56
28.08
27.12
26.53
24.53
20.05
17.89
0.20
f1 (ppm)

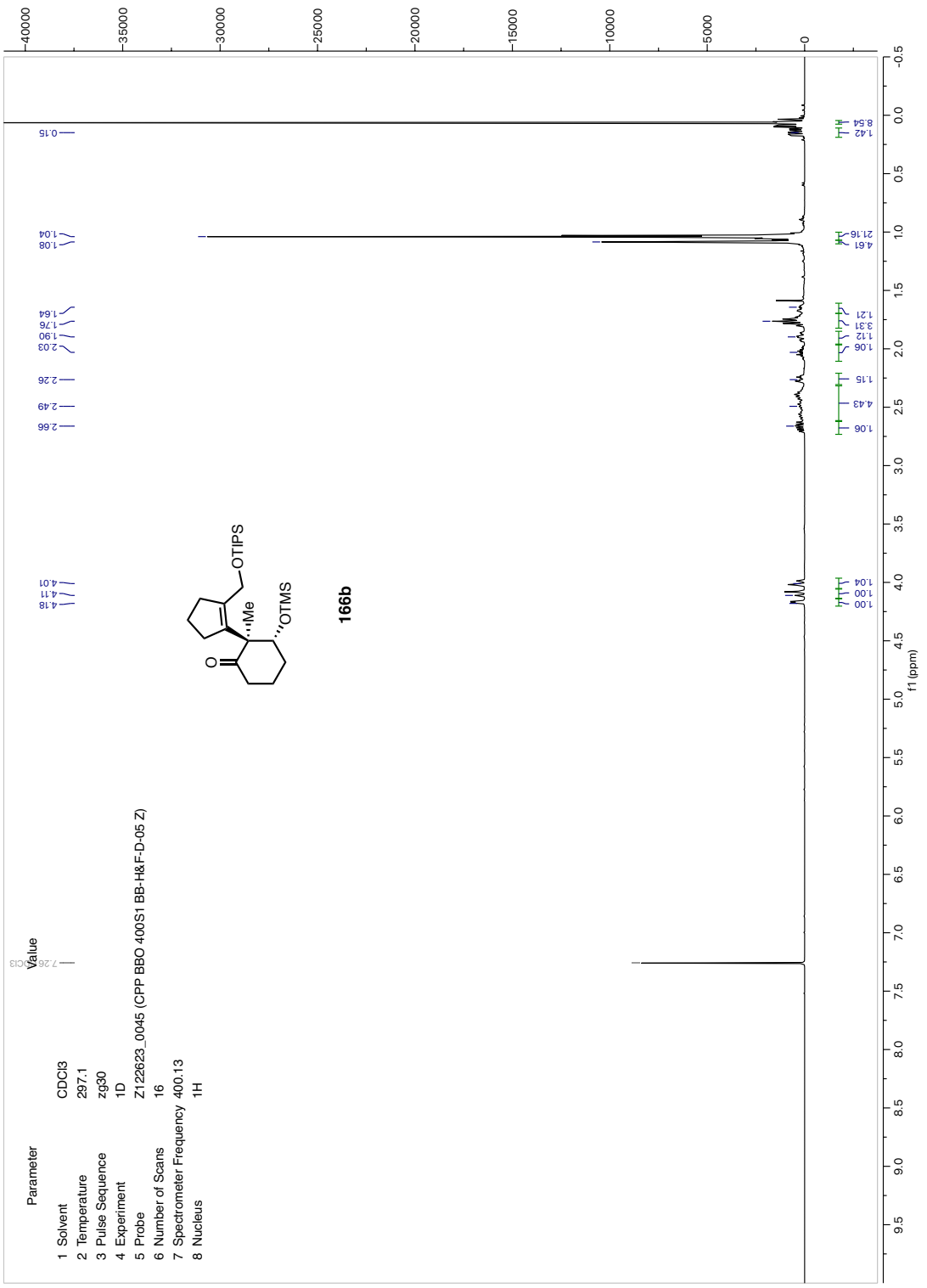

Parameter Value
1 Solvent cdcl3
2 Temperature 40.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe OneNMR
6 Number of Scans 16
7 Spectrometer Frequency 376.15
8 Nucleus 19F
-73.00
OTMS
CO2Me
O
MeO2C
Me
H
H
H
TfO
33p
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

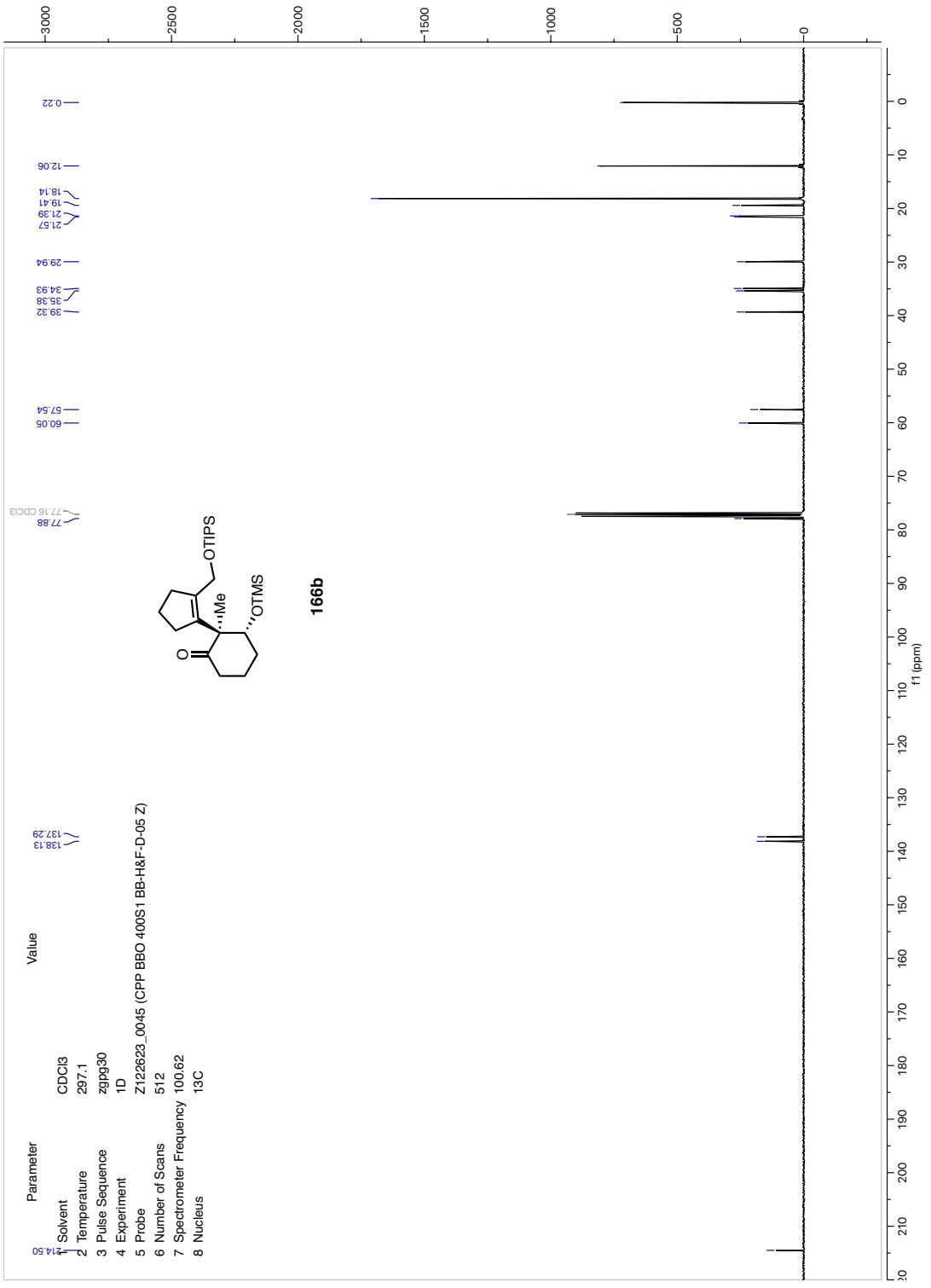

OTMS
CO2Me
MeO2C
O
H
H
H
Me
Me
Me
H
33q
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 16
7 Spectrometer Frequency 499.61
8 Nucleus 1H
f1 (ppm)

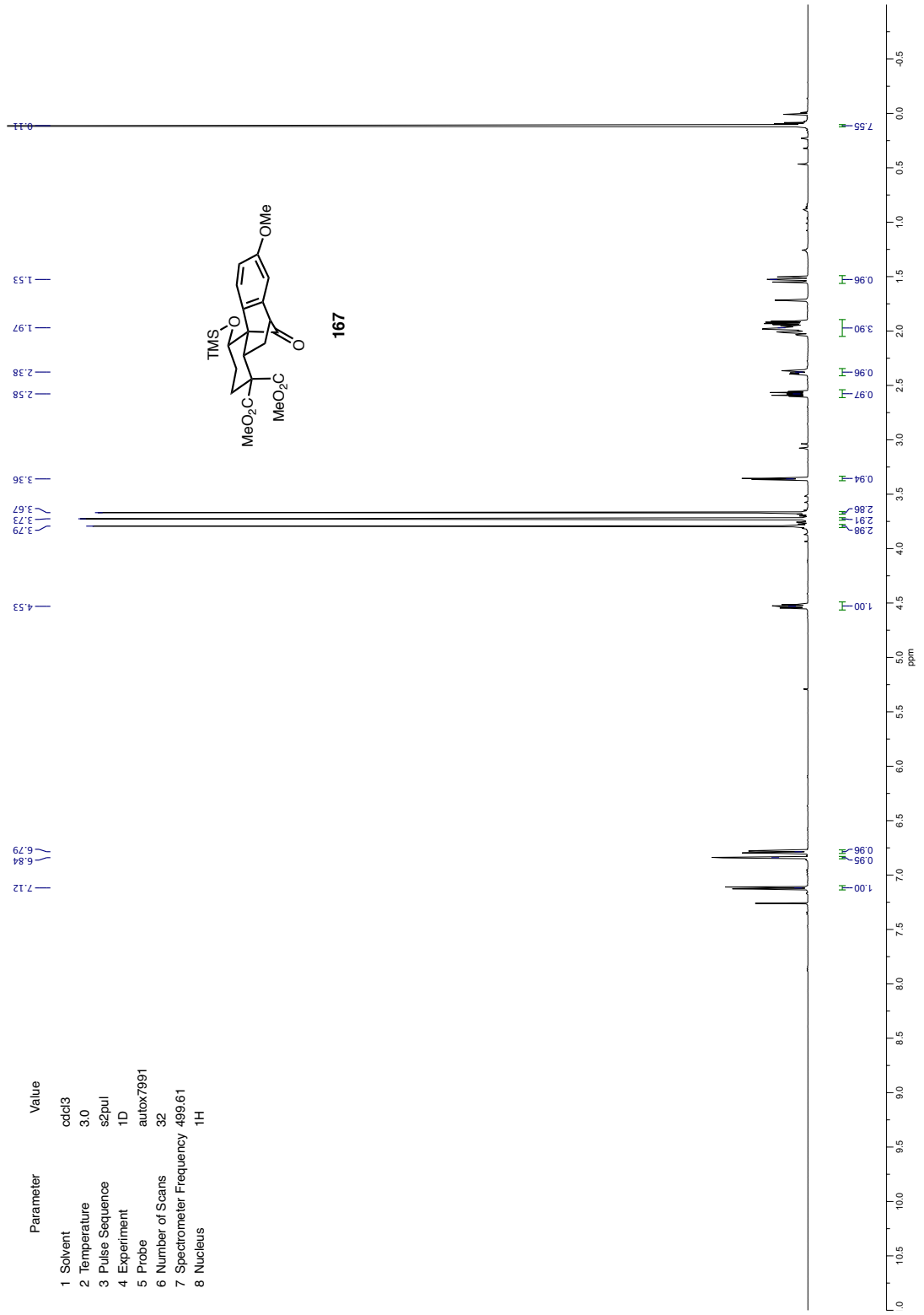

0.26
15.48
18.37
18.99
19.37
23.21
24.24
26.20
27.49
28.40
30.05
33.16
33.59
33.78
39.29
42.54
42.85
49.72
52.46
52.83
56.14
61.17
72.22
127.12
141.91
170.63
171.17
219.83
OTMS
CO2Me
O
MeO2C
H
H
H
Me
Me
Me
33q
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 2000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
f1 (ppm)

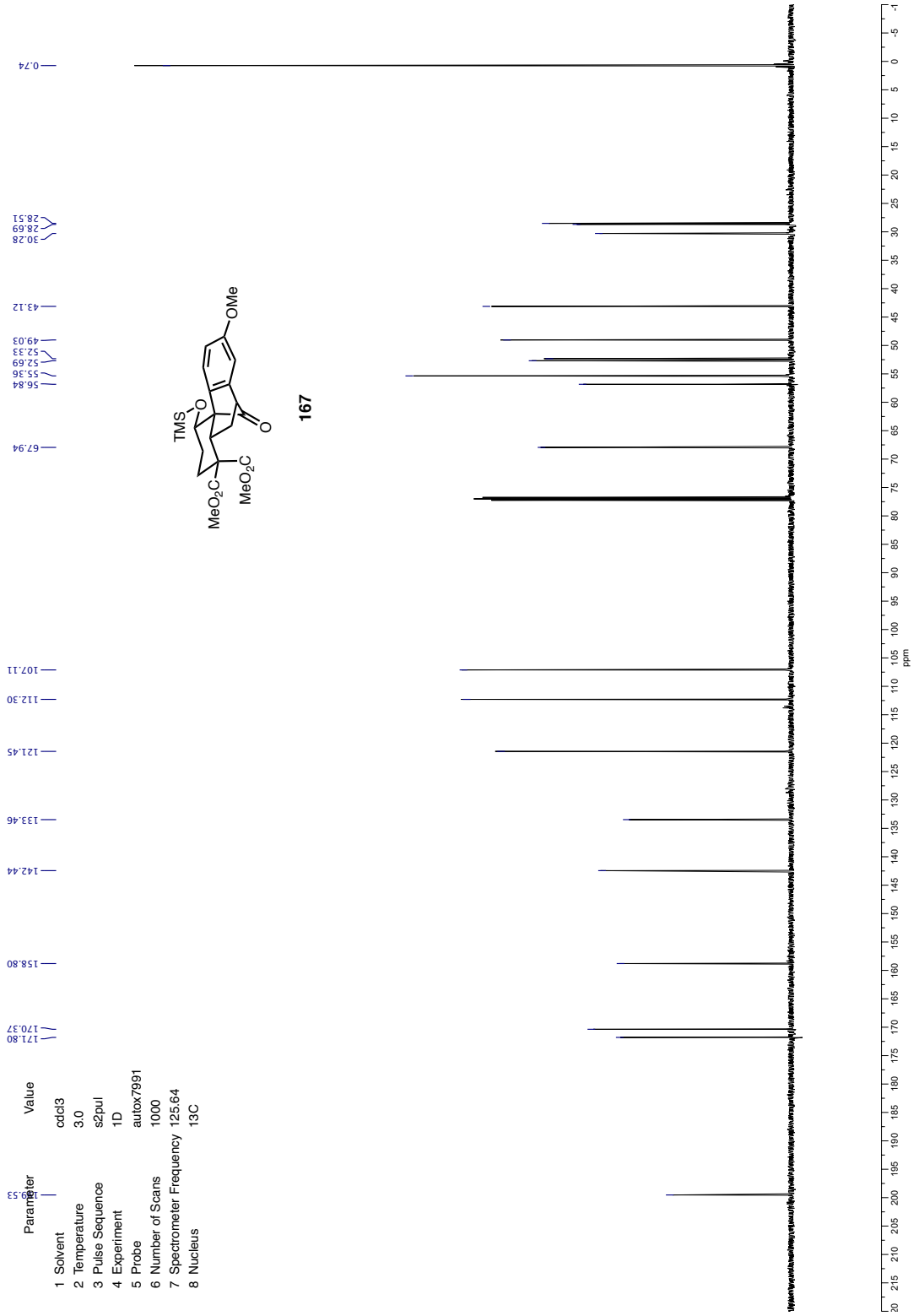

OTIPS
Me
OTMS
O
166a
Parameter Value
1 Solvent CDCl3
2 Temperature 297.2
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 297.2
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 1024
7 Spectrometer Frequency 100.62
8 Nucleus 13C
0.12
12.11
15.61
18.18
21.36
28.62
35.07
35.52
36.17
56.42
60.80
77.16 CDCl3
78.36
136.14
138.30
OTIPS
Me
OTMS
O
166a
f1 (ppm)


OTIPS
Me
OTMS
O
166b
Parameter Value
1 Solvent CDCl3
2 Temperature 297.1
3 Pulse Sequence zg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 16
7 Spectrometer Frequency 400.13
8 Nucleus 1H
f1 (ppm)


Parameter
Value
1 Solvent CDCl3
2 Temperature 297.1
3 Pulse Sequence zgpg30
4 Experiment 1D
5 Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
6 Number of Scans 512
7 Spectrometer Frequency 100.62
8 Nucleus 13C
-0.22
12.06
18.14
19.41
21.39
21.57
29.94
34.93
35.38
39.32
57.54
60.05
77.16 CDCl3
77.88
138.13
137.29
214.50
OTIPS
Me
OTMS
O
166b
f1 (ppm)


OMe
TMS
O
O
MeO2C
MeO2C
167
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 32
7 Spectrometer Frequency 499.61
8 Nucleus 1H
ppm


0.74
28.51
28.69
30.28
43.12
49.03
52.33
52.69
55.36
56.84
67.94
107.11
112.30
121.45
133.46
142.44
158.80
170.37
171.80
13.53
Parameter Value
1 Solvent cdcl3
2 Temperature 3.0
3 Pulse Sequence s2pul
4 Experiment 1D
5 Probe autox7991
6 Number of Scans 1000
7 Spectrometer Frequency 125.64
8 Nucleus 13C
TMS
O
OMe
O
MeO2C
MeO2C
167
ppm

[This chapter is temporarily embargoed.]

ABOUT THE AUTHOR

Jeffrey Kevan Kerkovius was born on June 14th, 1992 to Kevan Springford and Jenny Kerkovius in Kelowna, BC, Canada. He grew up on the outskirts of West Kelowna, graduating from Mount Boucherie high school in 2010. Jeff had an innate passion for chemistry, going as far as setting up a lab in his parent's workshop, which included a fully functioning fumehood and Schlenk line. Jeff then attended the University of British Columbia Okanagan (UBCO) in Kelowna to pursue his undergraduate studies. Jeff took a year off university after his first year to pursue cross country skiing professionally, where he achieved a personal best 2nd place finish at the Canadian national championships. Jeff then returned to UBCO to complete his undergraduate studies where he performed undergraduate research under the supervision of Prof. Fred Menard working on the synthesis of fluorescent labelled voltage gated calcium channel probes. After receiving his B.Sc. in chemistry, he then moved to London, Ontario, Canada to pursue his M.Sc. in chemistry under the supervision of Prof. Michael Kerr. He successfully completed the total synthesis of three indole alkaloids via a divergent synthetic route. Upon graduating with his M.Sc. Jeff moved to Pasadena, CA, USA to pursue his Ph.D. with Prof. Sarah Reisman. In her laboratory Jeff worked on the total synthesis of several alkaloids and diterpenes and developed methods inspired by the total synthesis work. Upon completion of his Ph.D. Jeff will move to Neurocrine Biosciences as a medicinal chemist.